I. New Cycloadditions for the Synthesis of Nitrogen Heterocycles
II. Organic Synthesis in Supercritical Carbon Dioxide

by
Adam Robert Renslo

B. A., Chemistry
Saint Olaf College, 1993

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 1998

Signature of Author.....
Department of Chemistry
May 8, 1998

Certified by.....
Rick L. Danheiser
Professor of Chemistry
Thesis Supervisor

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

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

Professor Timothy M. Swager .....
Chairman

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

Professor Peter H. Seeberger.....

Acknowledgments

I would like to begin by thanking Professor Rick L. Danheiser for providing me with the opportunity to perform research and learn new chemistry as a member of his research group. Rick is a superb teacher and has contributed significantly to my intellectual growth over the past five years. He has also been a valuable resource of knowledge and advice in the various research projects I have been a part of. I am especially grateful for the editorial contributions Rick made during the writing of this thesis. Finally, I thank Professor Danheiser and the Chemistry Department for funding in the form of teaching and research assistantships and tuition scholarships.

I would also like to acknowledge the profound influence that Professors Robert M. Hanson and John P. Walters have had on my life and on my decision to pursue a career in science. Bob's enthusiasm for chemistry was infectious and I feel fortunate that my first experience with college chemistry occurred in his class. I also thank him for introducing me to the excitement (and frustration) of performing original research. Professor John "Doc" Walters has provided me with inspiration and good advice for as long as I have known him. I would be surprised if there is anyone else in the world who can make learning analytical chemistry more exciting and enjoyable than Doc does. I thank both Bob and Doc for their support and for encouraging me to pursue a Ph.D.

I sincerely thank all of the current and former members of the Danheiser group for making my graduate school experience vastly more enjoyable than it might otherwise have been. I especially enjoyed the breaks from lab provided by summer softball and volleyball games. Special thanks to Sandy Gould, Mike Lawlor, Matt Martin, Kevin Shea, and Greg Dudley for organizing and leading the various incarnations of *Toxic Waste* and *The Cuzins*. I thank Melanie Bartow Wills for her friendship, support, and for numerous cathartic trips to Toscis' during the sometimes-difficult "early years." I wish her the very best in her future, confident that she will be successful. Brenda Palucki was a fine baymate and friend who offered many helpful suggestions over the years. I am especially grateful to Brenda for teaching me her excellent laboratory technique. Rob Niger has been a never-ending source of comic relief over the years, even if his comments occasionally gave the lab the sound and feel of an automotive repair shop! I thank Rob for his friendship and for introducing me to *The Allman Brothers Band.* I wish Rob the best and sincerely hope that some time soon he will be making enough money to buy a new car. I have enjoyed many discussions with Matt Martin on topics ranging from the Red Sox to computer games to, of course, Star Wars. I look forward to hearing what kind of negative spin he will manage to put on the Red Sox World Series victory this fall! I have enjoyed playing softball and volleyball with Dawn Bennett and getting to know her great little dog Wile E. Dawn deserves special thanks for her very careful proofreading of parts of this thesis. Kevin Shea has been a good friend as well as a standout softball and volleyball player (thanks for all the sets). I admire his passion and aptitude for teaching and wish him the best in the future. Greg Dudley is very bright guy with a great sense of humor who's also not a shabby athlete (although at 6'4" he should be able to dunk a basketball!). I have enjoyed getting to know Jason Diffendal and wish him the best of luck with the supercritical fluid project. Our most recent group of post-docs (Jari Yli-Kauhaluoma, Chris Mellon, and Kazuya Matsunaga) have been great people to get to know and are also among the most helpful and knowledgeable post-docs we have had in the group. I am especially grateful to Chris Mellon for helpful discussions about my chemistry and the job search. Finally, I thank Dawn Bennett, Matt Martin, Kevin Shea, and Greg Dudley for proofreading parts of my thesis.

I am grateful for the support of many friends from St. Olaf and MIT, including Adam Boskovic, Rob Walker, Dave Vasconez, Julie Espelien, Mike Amendola and Diego Hoic. I am especially grateful for the friendship, love, and support of Miho Kubota. Her companionship has been a continuous source of strength for me and I thank her for that. My family has also been a great source of strength and encouragement throughout graduate school. I am especially grateful to Mom and Dad who always emphasized the importance of a good education but never tried to influence where that education might lead me. This thesis is dedicated to them and to my late uncle, Dr. Douglas Anderson whom I always admired and who is greatly missed.

for Mom and Dad

and

in memory of uncle Doug

I. New Cycloadditions for the Synthesis of Nitrogen Heterocycles

II. Organic Synthesis in Supercritical Carbon Dioxide

by

Adam Robert Renslo

Submitted to the Department of Chemistry
on May 8, 1998 in partial fulfillment of the
requirements for the Degree of Doctor of Philosophy

ABSTRACT

Alkyliminoacetonitrile derivatives were investigated as dienophiles in the Diels-Alder reaction. These activated imines react with dienes in intramolecular [4+2] cycloadditions to provide products with either the quinolizidine or indolizidine ring system, depending on the length of the tether connecting diene and dienophile. Quinolizidine cycloadducts are formed in good yield and with high stereoselectivity whereas indolizidine cycloadducts are formed in only modest yields.

A new oximinosulfonate dienophile derived from Meldrum's acid reacts in efficient and regioselective [4+2] cycloadditions with substituted dienes under Lewis acid promotion. The cycloadducts obtained from these reactions can be converted into substituted pyridine derivatives in high yields. This two-step pyridine annulation was successfully applied to the total synthesis of the pyridine alkaloids fusaric acid and *S*-(+)-fusarinolic acid. Some of the cycloadducts obtained in the reactions of this new dienophile are prone to undergo Stieglitz rearrangement, thereby producing pyrrolines.

The rate and selectivity of the Diels-Alder reaction in supercritical carbon dioxide ($scCO_2$) was investigated as a function of pressure and density. The rate of the reaction can be correlated to the density of the supercritical solution and increases from 2.8 to 4.0 x 10^{-5} L/mmol h upon increasing the density from 0.33 to 0.858 g/mL. The regioselectivity of several Diels-Alder reactions was found not to be significantly influenced by the solution density. The *endo* stereoselectivity of the Diels-Alder reaction between acrylonitrile and cyclopentadiene was found to increase by ca. 3% upon increasing the CO_2 pressure from 103 to 300 bar or upon *decreasing* the pressure from 103 to 82 bar. The use of silica (SiO_2) as a reaction promoter in $scCO_2$ leads to improvements in the yield and selectivity of Diels-Alder reactions.

Thesis Supervisor: Rick L. Danheiser

Title: Professor of Chemistry

Table of Contents

Part I

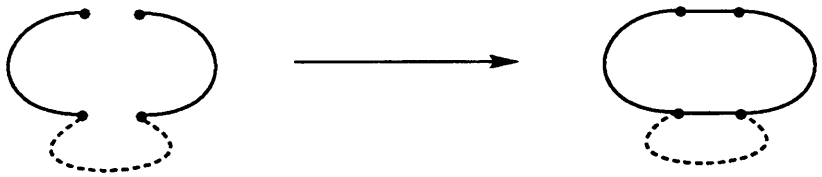
Synthetic Approaches to Nitrogen Heterocycles Based on Cycloadditions of Activated Imines

Chapter 1
Background and Introduction

Our research group has been involved for some time in the development of new methods for the synthesis of cyclic and polycyclic molecules. The construction of cyclic structures is generally accomplished using either cyclization or annulation reactions. As illustrated below, cyclization strategies rely on an *intramolecular* reaction of some kind to generate a cyclic system from an acyclic precursor. Annulation strategies involve the formation of *two* new bonds to produce the cyclic system and are generally regarded to be more convergent processes. Also, because two new bonds are formed in an annulation, the possibility exists for the simultaneous creation of several stereocenters in a single step. For these reasons, our group has generally focused on annulation strategies in developing new synthetic methods.

Cyclization Strategy

Annulation Strategy



The Diels-Alder reaction exemplifies the power of annulation strategies for the synthesis of cyclic molecules.[1] The generally high regio- and stereoselectivity of this

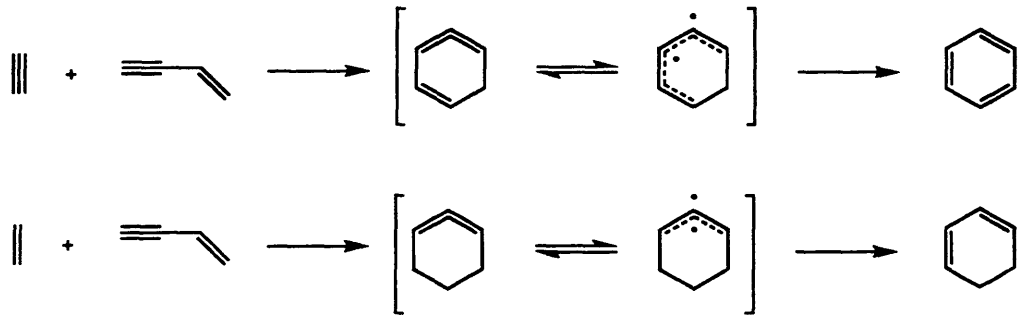
[1] For a review of the Diels-Alder reaction, see: (a) Fringuelli, F.; Taticchi, A. *Dienes in the Diels-Alder Reaction*; Wiley: New York, 1990. (b) Oppolzer, W. In *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I., Eds.; Pergamon Press: Oxford, 1991, Vol. 5, pp 315-399.

reaction allows the creation and control of up to four stereocenters in a single synthetic step. Intramolecular versions[2] of the reaction can be particularly powerful for the construction of *polycyclic* systems. For these reasons, the Diels-Alder reaction has found widespread application in the synthesis of natural products and commercially valuable organic chemicals.

A New Cycloaddition Strategy

Our group has recently become interested in new cycloaddition strategies employing highly unsaturated, conjugated compounds. In particular, we wondered whether the [4+2] cycloaddition of *enynes* with alkynes or alkenes would constitute a *general* method for the preparation of aromatic and dihydroaromatic molecules (Scheme 1). To our delight, these

Scheme 1



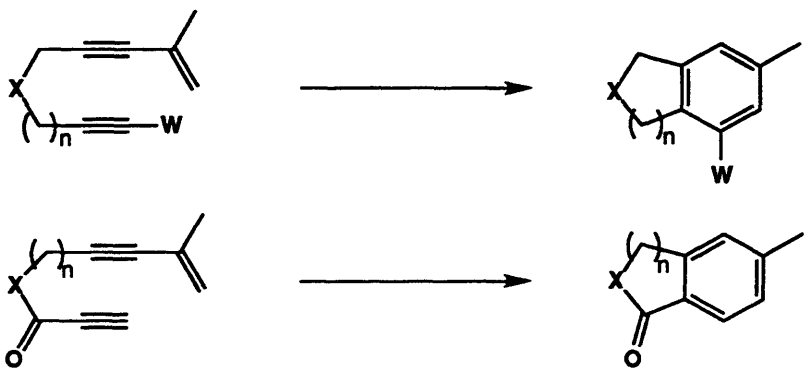
reactions have proven to be of considerable synthetic value. In 1994, our laboratory reported the first systematic investigation of the scope of the *intramolecular* [4+2] cycloadditions of conjugated enynes.[3] As shown below, a variety of different polycyclic

---

[2] For reviews of intramolecular Diels-Alder reactions, see: (a) Roush, W. R. In *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I., Eds.; Pergamon Press: Oxford, 1991, Vol. 5, pp 513-550. (b) Ciganek, E. In *Organic Reactions*; Dauben, W. G., Ed.; John Wiley & Sons: New York, 1984, Vol. 32, pp 1-374.

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

aromatic compounds can be prepared using this methodology. For example, the tether that connects the enyne to the enynophile may be aliphatic,[4] aromatic,[5] or may include



X = CH_2, NR, O

W = C(O)R, CHO, CO_2Me, SO_2Ph,

n = 1, 2

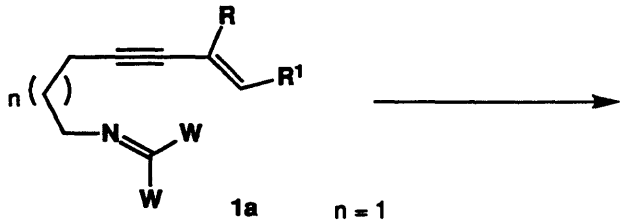
heteroatoms,[6] thereby allowing the preparation of a variety of heterocycles. The length of the tether may also be varied to produce polycyclic products with ring systems of different sizes. Finally, the use of *alkynyl carbonyl* compounds as the 4π component in the reaction has recently been shown to provide access to polycyclic furans[7] via a cycloaddition-rearrangement mechanism.

Heteroatom Dienophiles and Enynophiles

The original goal of my project was the development of new, activated imines that might serve as the 2π component in intramolecular Diels-Alder and enyne cycloaddition reactions. As illustrated below for the enyne cycloaddition (eq 1), the use of an imine enynophile would produce products with the important indolizidine (**2a**) and quinolizidine (**2b**) ring systems.

---

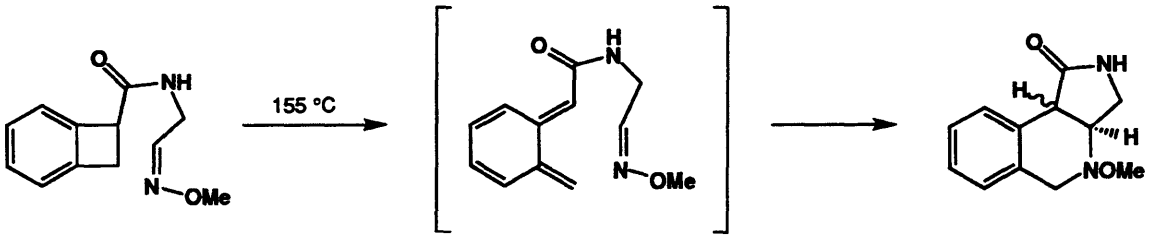
[4] Gould, A. E. Ph.D. Thesis, Massachusetts Institute of Technology, June 1996.
[5] Helgason, A. L. Ph.D. Thesis, Massachusetts Institute of Technology, May 1994.
[6] Palucki, B. L. Ph.D. Thesis, Massachusetts Institute of Technology, June 1997.
[7] Wills, M. S. B. Ph.D. Thesis, Massachusetts Institute of Technology, June 1998.



(1)

The use of imines as dienophiles in the Diels-Alder reaction has attracted a considerable amount of attention.[8] Indeed, these reactions comprise a powerful strategy for the synthesis of nitrogen heterocycles. Chapter 1 in Part II of this thesis will provide a thorough review of the various imine derivatives that have been employed in *inter*molecular Diels-Alder reactions. The scope of the current discussion will therefore be limited to examples of *intra*molecular[9] imino Diels-Alder reactions that serve to demonstrate the power of this strategy for the synthesis of complex polycyclic natural products.

The first example of an intramolecular imino Diels-Alder reaction was reported by Oppolzer[10] in 1972. As shown below, heating a solution of oxime **3** in bromobenzene



3 **4** **5**

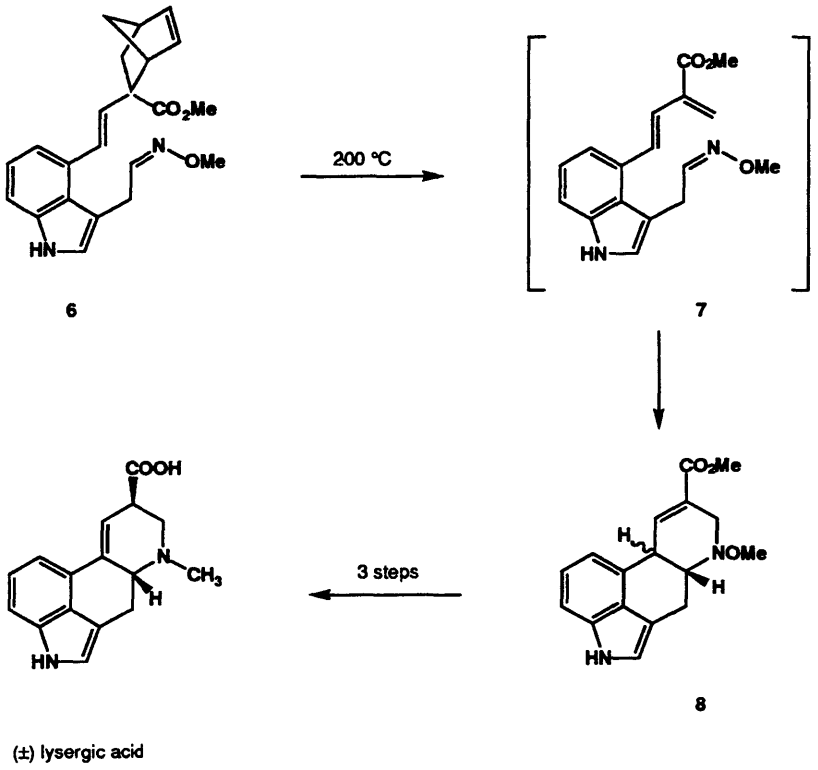
[8] For reviews of imino dienophiles in the Diels-Alder reaction, see: (a) Weinreb, S. M. In *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I., Eds.; Pergamon Press: Oxford, 1991, Vol. 5, pp 401-413. (b) Weinreb, S. M.; Levin, J. I. *Heterocycles*, **1979**, *7*, 949. (c) Weinreb, S. M.; Staib, R. R. *Tetrahedron*, **1982**, *38*, 3087. (d) Boger, D. L.; Weinreb, S. M. *Hetero Diels-Alder Methodology in Organic Synthesis*; Academic: San Diego, 1987; Chapter 2.

[9] For a review of intramolecular imino Diels-Alder reactions, see ref. 8d, pp 61-67.

[10] Oppolzer, W. *Angew. Chem., Int. Ed. Engl.* **1972**, *11*, 1031.

generates a highly reactive *o*-quinodimethane species (**4**) which undergoes an intramolecular Diels-Alder reaction to provide a mixture of diastereomeric products **5** in 68% yield. Oppolzer used a similar strategy to construct the tetracyclic ring system of (±)-lysergic acid (Scheme 2).[11] The key step in the synthesis involves the retro-Diels-Alder

Scheme 2

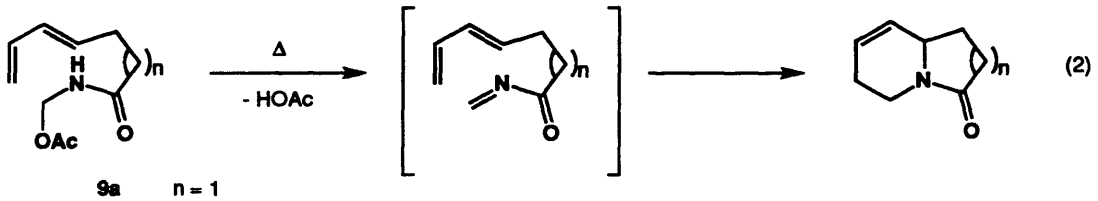


reaction of compound **6** to generate the diene intermediate **7**. Subsequent reaction of this species in an intramolecular imino Diels-Alder reaction provides the cycloadduct **8** as a mixture of diastereomers in 67% yield. With the required tetracyclic ring system in place, the cycloadduct **8** was readily converted in three steps to (±)-lysergic acid. In considering these Diels-Alder reactions, it is interesting to note that even unactivated dienophiles (*O*-methyloximes) are reactive in the intramolecular Diels-Alder reaction. This fact is no doubt

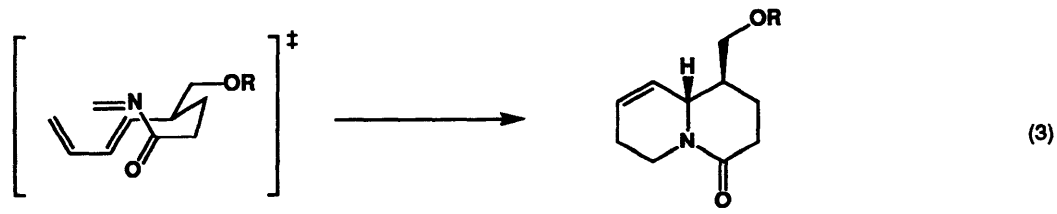
[11] Oppolzer, W.; Francotte, E.; Bättig, K. *Helv. Chim. Acta* **1981**, *64*, 478.

a consequence of the entropic advantages enjoyed by intramolecular reactions as compared to intermolecular ones.

The most extensive investigations of the intramolecular imino Diels-Alder reaction have been those carried out by Weinreb[12] and Grieco[13] with *N*-acylimines and iminium ions respectively. The Weinreb strategy (eq 2) relies on the thermolysis of an *N*-acetoxymethyl amide (**9**), thereby generating an *N*-acylimine (**10**) which serves as the dienophile in an



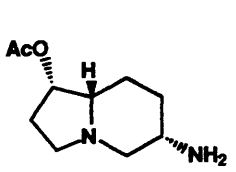
intramolecular Diels-Alder reaction to provide indolizidine (**11a**) or quinolizidine (**11b**) cycloadducts. The preferred transition state for these reactions is one in which the *N*-acylimine moiety adopts an endo orientation relative to the diene (eq 3). For this reason, the products **11** are often obtained with excellent stereoselectivity (particularly in the case of quinolizidine products **11b**).



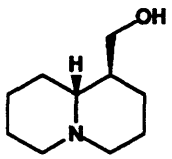
[12] (a) Weinreb, S. M. *Acc. Chem. Res.* **1985**, *18*, 16. (b) Weinreb, S. M.; Khatri, N. A.; Shringarpure, J. *J. Am. Chem. Soc.* **1979**, *101*, 5073. (c) Gobao, R. A.; Bremmer, M. L.; Weinreb, S. M. *J. Am. Chem. Soc.* **1982**, *104*, 7065. (d) Bremmer, M. L.; Khatri, N. A.; Weinreb, S. M. *J. Org. Chem.* **1983**, *48*, 3661. (e) Bailey, T. R.; Garigipati, R. S.; Morton, J. A.; Weinreb, S. M. *J. Am. Chem. Soc.* **1984**, *106*, 3240.

[13] (a) Larsen, S. D.; Grieco, P. A. *J. Am. Chem. Soc.* **1985**, *107*, 1768. (b) Grieco, P. A.; Larsen, S. D.; Fobare, W. F. *Tetrahedron Lett.* **1986**, *27*, 1975. (c) Grieco, P. A.; Parker, D. T. *J. Org. Chem.* **1988**, *53*, 3325. (d) Grieco, P. A.; Parker, D. T. *J. Org. Chem.* **1988**, *53*, 3658.

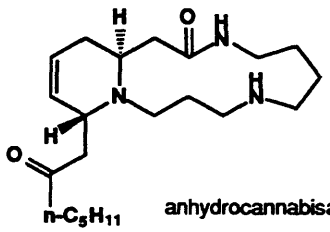
The Weinreb group has applied the imino Diels-Alder reaction of *N*-acylimines to the total synthesis of a variety of natural products, including slaframine,[12c] *epi*-lupinine,[12d] and anhydrocannabisativene.[12e]



slaframine

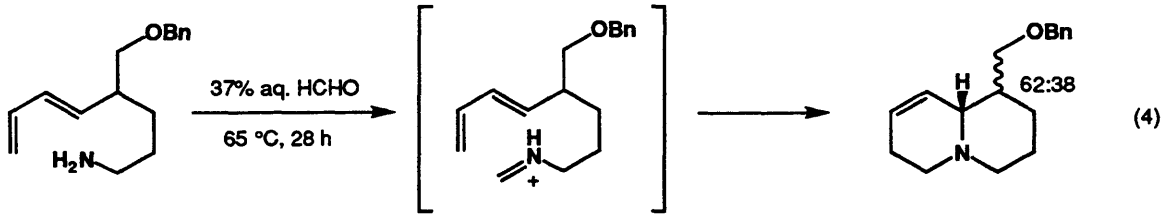


epi-lupinine



anhydrocannabisativine

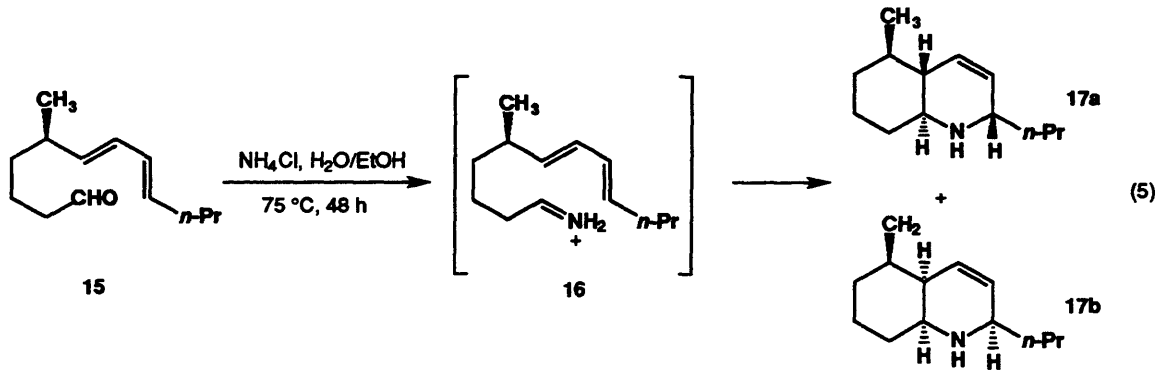
The Grieco strategy also relies on the *in situ* generation of a reactive imine species, in this case an iminium ion formed under Mannich-like conditions. The example below illustrates the application of this strategy in the synthesis of **14**, an intermediate for the



12 **13** **14** (4)

synthesis of lupinine and *epi*lupinine.[13c] Treatment of the hydrochloride salt of amine **12** with an aqueous formaldehyde solution leads to the formation of the iminium ion **13** which reacts in an intramolecular Diels-Alder reaction to provide a mixture (62:38) of cycloadducts **14** in 82% yield. The diastereomeric cycloadducts **14** were readily separated and hydrogenated (Pd/C) to provide synthetic (±)-lupinine and (±)-*epi*lupinine. The stereoselectivity of the reaction is unfortunately quite low, especially when compared to the selectivity obtained by the Weinreb group in their synthesis of (±)-*epi*lupinine.[12d]

An interesting advantage of the Grieco strategy is that the method is not limited to the synthesis of heterocycles in which the nitrogen atom is a part of the ring junction. This point is illustrated below for the preparation of **17**, an intermediate in the synthesis of



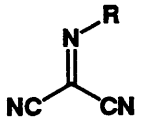
(5)

(-)-8a-*epi*pumiliotoxin C.[13d] Reaction of the *aldehyde* **15** with an ammonium chloride solution results in the formation of iminium ion **16** in which the nitrogen atom is in the terminal position (as opposed to the internal position as in **13**). Subsequent intramolecular cycloaddition then produces heterocyclic products (**17**) with an all-carbon ring junction. Unfortunately, as in the synthesis of (±)-lupinine and (±)-*epi*lupinine (eq 4), the stereoselectivity of the reaction is rather poor (69:31 favoring **17a**). Unlike *N*-acylimine dienophiles (eq 3), iminium ions display little endo/exo selectivity and therefore generally give mixtures of products. Although neither of the products **17** had the correct stereochemistry for conversion to (-)-pumiliotoxin C, the major diastereomer was nevertheless converted to (-)-8a-*epi*pumiliotoxin C in one step by hydrogenation over Pd/C.

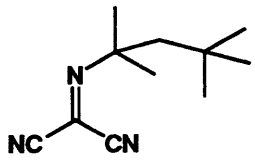
The examples presented above illustrate the power of intramolecular imino Diels-Alder strategies for the construction of complicated polycyclic molecules from relatively simple acyclic precursors. These reactions are especially powerful in cases where the

stereoselectivity can be controlled, thereby allowing the configuration of several stereogenic centers to be fixed in a single step.

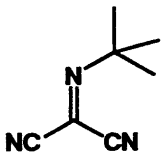
The goal of my project, as outlined previously, was the development of new, activated imines for application in our group's intramolecular enyne cycloaddition chemistry and in traditional intramolecular imino Diels-Alder reactions. At the outset of the project, we chose to examine *doubly activated* imines. This choice was based on our belief that these systems would possess superior reactivity in the cycloaddition reaction, could be relatively easily prepared, and would provide cycloadducts amenable to further synthetic transformation. In particular, we were attracted to alkyliminomalonitrile derivatives (**18**) in which the imine is activated by two nitriles. Surprisingly, this class of imines has scarcely



18



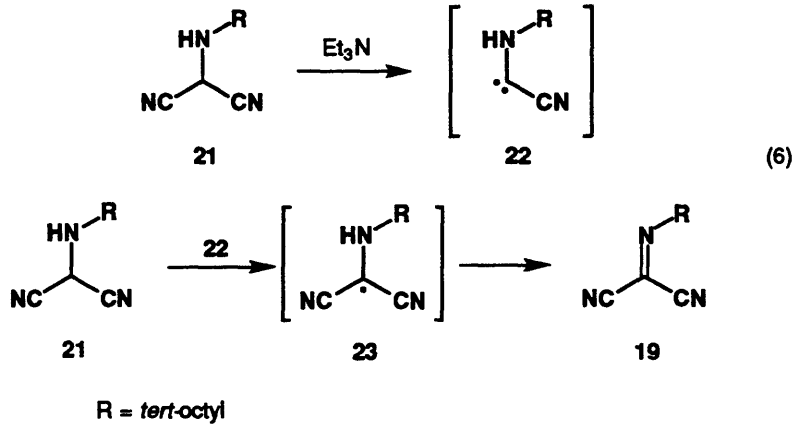
19



20

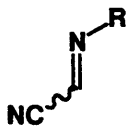
been studied by chemists, and no investigation of the reactivity of these species in cycloaddition reactions has been described. In fact, the only reported examples of these compounds are the *tert*-octyl and *tert*-butyl derivatives **19** and **20**. The *tert*-octyl derivative **19** was *one of many* products isolated in studies of the base-promoted decomposition of *tert*-octylaminomalonitrile (**21**) by DeVries.[14] The formation of **19** was attributed to the reaction sequence presented in equation 6. Deprotonation of **21** is followed by α-elimination of cyanide to give a carbene (**22**). This species abstracts a hydrogen atom from another molecule of **21** to give the radical **23** which undergoes disproportionation to produce **19** (and the reduced species). Compound **19** was identified by comparison to an authentic sample that was prepared from *tert*-octylamine in a rather long, five-step

[14] DeVries, L. *J. Org. Chem.* **1973**, *38*, 2604.



synthesis. The *tert*-butyl derivative **20** has not been isolated but rather was suggested as a possible intermediate in the dimerization of *tert*-butyliminoacetonitrile.[15] Although the use of alkyliminomalonitriles (**18**) in the Diels-Alder reaction is unknown, a considerable body of literature does exist describing the successful use of other electron-deficient imines[8] in these reactions. For this reason, we were confident that the imines **18**, if rendered synthetically available, would be excellent partners in [4+2] cycloadditions of dienes and enynes.

In addition to the doubly-activated imines discussed above, we also became interested in a related class of imines, the alkyliminoacetonitriles (**24**). Although



24

presumably less reactive than the alkyliminomalonitrile derivatives (**18**), we felt that the imines **24** would be sufficiently reactive to participate in *intramolecular* cycloaddition reactions with dienes or enynes. In addition, these imines were anticipated to be more synthetically accessible than the doubly activated imines **18**. Indeed, a number of

[15] Dabek, H.; Selvarajan, R.; Boyer, J. H. *J. Chem. Soc., Chem Commun.* **1972**, 244.

derivatives of **24** have been prepared,[16] although their use in [4+2] cycloadditions has not been reported.

The following two chapters describe studies directed toward the synthesis of alkyliminomalonitrile (**18**) and alkyliminoacetonitrile (**24**) derivatives, respectively. In addition, the synthesis of diene- and enyne-based cycloaddition substrates and their utility in the synthesis of nitrogen heterocycles will be discussed.

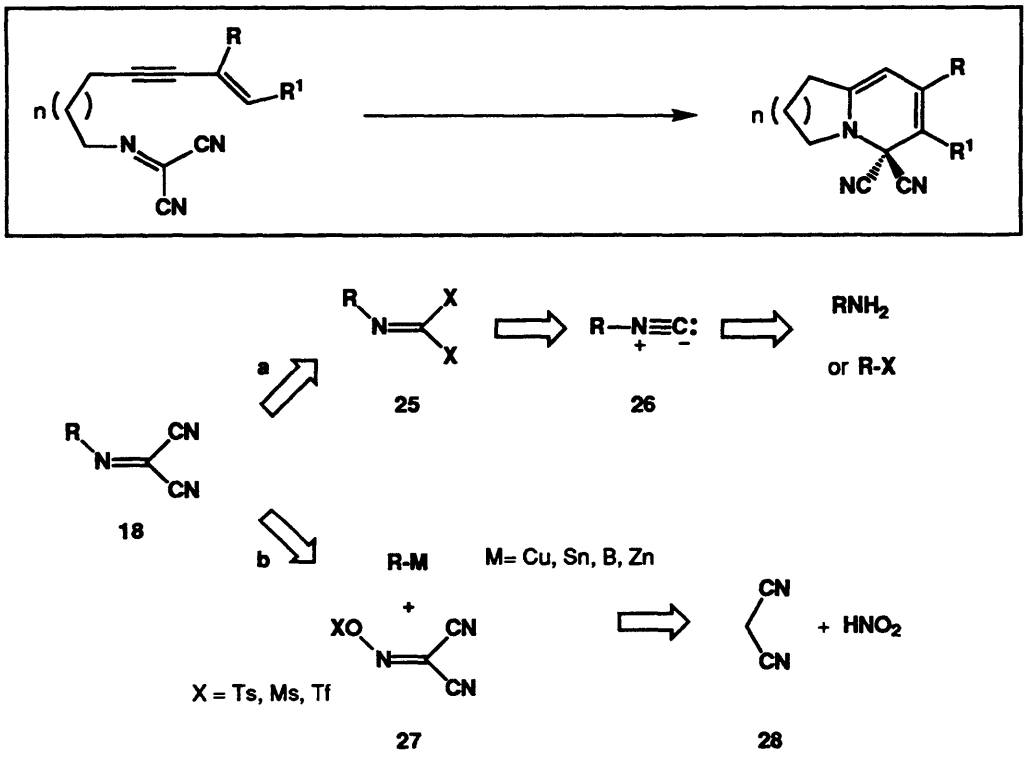
[16] (a) Boyer, J. H.; Dabek, H. *J. Chem. Soc., Chem. Commun.* **1970**, 1204. (b) Boyer, J. H.; Kooi, J. *J. Am. Chem. Soc.* **1976**, *98*, 1099 (c) see also ref. 14.

Chapter 2

Synthetic Approaches to Electron-Deficient Imine Derivatives

The original goal of my project, as outlined in Chapter 1, was the development of new, activated imine derivatives that might serve as the 2π component in intramolecular Diels-Alder and enyne cycloaddition reactions. This chapter describes studies directed toward the preparation of alkyliminomalonitrile and related electron-deficient imines. Scheme 3 illustrates the desired cycloaddition reaction for an enyne substrate, and includes our retrosynthetic analysis of the key alkyliminomalonitrile derivatives (**18**).

Scheme 3



Our retrosynthetic analysis of **18** revealed two possible disconnections, **a** and **b** (Scheme 3). Following disconnection **a**, we felt that the desired imines **18** could be produced from the addition of two equivalents of cyanide anion to an imidoyl dihalide (**25**,

X = Cl, Br, I). Imidoyl dihalides, in turn, can be prepared from the corresponding isonitrile derivatives (**26**) by the addition of halogen.[17] A variety of methods exist for the preparation of isonitriles from the corresponding primary amines or alkyl iodides.[18] Following disconnection **b**, we wondered whether it would be possible to effect a cuprate addition-elimination reaction on the known[19] oxime tosylate **27** (X = Ts). Alternatively, we thought a transition-metal mediated coupling reaction of the corresponding triflate **27** (X = Tf) with an alkyl organometallic reagent might be feasible. The required oxime derivatives **27** would be readily available from the nitrosation of malonitrile (**28**).

The Isonitrile Route

The first strategy we investigated was route **a** (Scheme 3), which required the synthesis of isonitrile derivatives (**26**). We decided to prepare a *diene* substrate first in order to evaluate the reactivity of imines **18** as dienophiles in intramolecular Diels-Alder reactions. If successful in diene substrates, the synthesis of the corresponding *enyne* substrate would then be attempted. Scheme 4 presents our synthesis of the dienyl *isonitrile* **33** that would serve as a precursor to the desired alkyliminomalonitrile cycloaddition substrate.

Our synthetic route to iodide **32** is based on those reported previously by other workers.[20] The synthesis begins with a Johnson-Claisen[21] reaction of commercially available penta-1,4-diene-3-ol (**29**) to provide, stereoselectively, the *E*-1,3-dienyl ester

---

[17] For a review on the preparation of imidoyl dihalides, see: Kühle, E.; Anders, B.; Zumach, G. *Angew. Chem., Int. Ed. Engl.* **1967**, *6*, 649.

[18] For reviews on the preparation of isonitriles, see: (a) Ugi, I.; Fetzer, U.; Eholzer, U.; Knupfer, H.; Offermann, K. *Angew. Chem., Int. Ed. Engl.* **1965**, *4*, 472. (b) Sandler, S. R.; Karo, W. *Organic Functional Group Preparations, 2nd ed.*; Academic: San Diego, 1989; Vol. 3, Chapter 5.

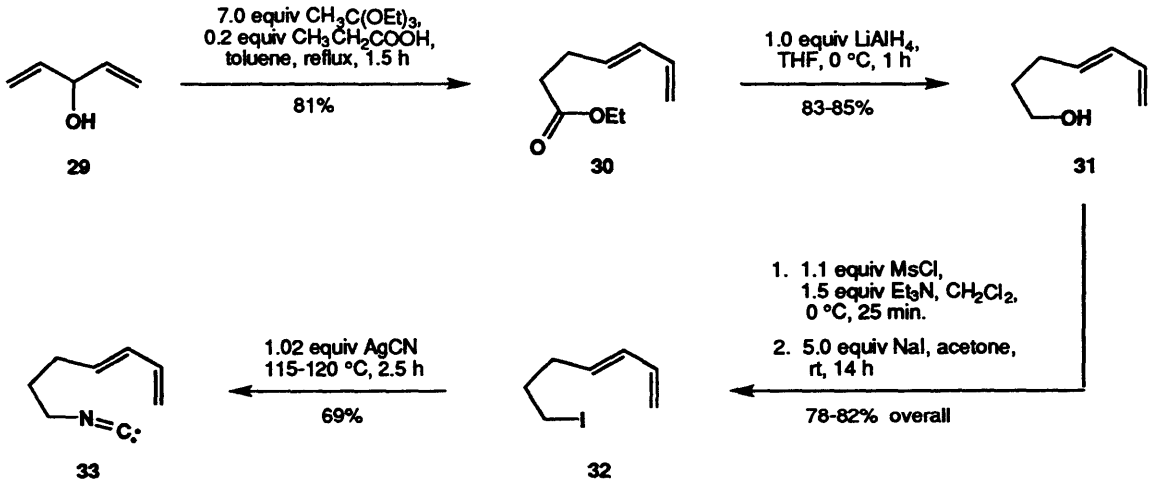
[19] Biehler, J.-M.; Perchais, J.; Fleury, J.-P. *Bull. Soc. Chim. Fr.* **1971**, 2711(B).

[20] (a) Hudlicky, T.; Koszyk, F. J.; Kutchan, T. M.; Sheth, J. P. *J. Org. Chem.* **1980**, *45*, 5020. (b) Roush, W. R.; Gillis, H. R.; Ko, A. I. *J. Am. Chem. Soc.* **1982**, *104*, 2269. (c) Vedejs, E.; Eberlein, T. H.; Wilde, R. G. *J. Org. Chem.* **1988**, *53*, 2220.

[21] Johnson, W. S.; Wertheman, L.; Bartlett, W. R.; Brocksom, T. J.; Li, T. T.; Faulkner, D. J.; Petersen, M. R. *J. Am. Chem. Soc.* **1970**, *92*, 741.

30[20a,b] in high yield. This ester was then converted to the alcohol **31**[20b] in 83-85% yield by reduction with $LiAlH_4$ in THF. The conversion of alcohol **31** to iodide **32** was accomplished using a modification of the procedure described previously by Vedejs.[20c] The alcohol **31** was converted to the mesylate using the Crossland[22] procedure and the crude mesylate was used directly in the preparation of iodide **32** (NaI in acetone). In this way, the iodide could be obtained in 78-82% overall yield following column chromatography. The conversion of iodide **32** to the desired isonitrile **33** was accomplished by heating the iodide in the presence of silver cyanide without solvent for 2.5 hours at 115-120 °C.[23] This reaction must be monitored carefully since prolonged heating results in much lower yields. The offensive-smelling isonitrile **33** proved quite stable and could be purified by column chromatography (in the hood!). The identity of isonitrile **33**

Scheme 4



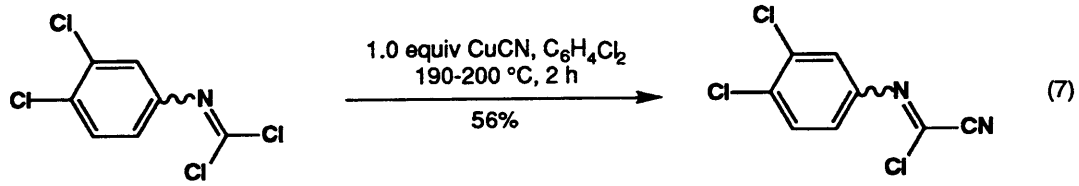
was confirmed by the observation of a characteristic isonitrile stretching band at 2150 cm^{-1} in the IR spectrum, and by the presence of ^{13}C-^{14}N coupling in the ^{13}C NMR spectrum. With the isonitrile **33** in hand, the conversion to imidoyl dihalide and then to

[22] Crossland, R. K.; Servis, K. L. *J. Org. Chem.* **1970**, *35*, 3195.
[23] This procedure was based on that reported in ref. 18b, p 209.

iminomalonitrile could be attempted. Before this work is discussed, however, a brief review of the synthesis and reactivity of imidoyl dihalides may be helpful.

The reaction of isonitriles with chlorine or bromine takes place at, or below, room temperature to provide the corresponding imidoyl dichlorides or dibromides.[17] The reaction is applicable to both alkyl and aryl isonitriles, although long-chain alkyl isonitriles undergo competing chlorination of the alkyl chain.

Imidoyl dihalides react readily in nucleophilic displacement reactions with a variety of nucleophiles, including amines, alkoxides, and thiolates. [24] Either one or both halogen atoms can undergo displacement by nucleophiles, depending on the reaction stoichiometry. Nucleophilic displacement with cyanide, on the other hand, has scarcely been examined. The lone example (eq 7) involves the reaction of an aryl imidoyl dichloride (**34**) with copper cyanide (1 equivalent) in dichlorobenzene at 190-200 °C for 2 hours. The resulting



34 **35** (7)

mono-substitution product **35** was obtained in 56% yield after purification by distillation.[25] Attempts to prepare the *iminomalonitrile* using *two* equivalents of metal cyanide reportedly gave only traces of the desired product, while the major product was described as "a very stable, black copper complex, which [was] not investigated further." Reaction of the mononitrile **35** with a second equivalent of CuCN did provide the dinitrile, although the yields were low (<30%) and no experimental details were provided.[26]

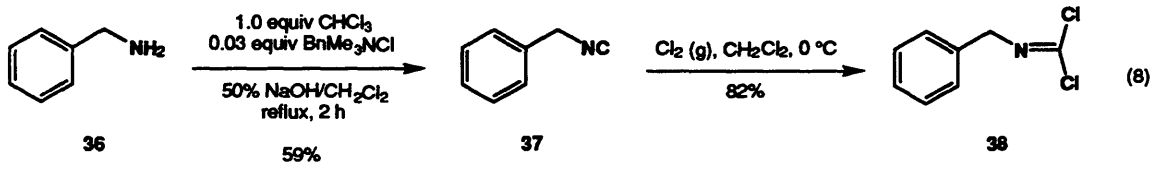
---

[24] For a review of the chemistry of imidoyl dihalides, see: Kühle, E. *Angew Chem., Int. Ed. Engl.* **1969**, *8*, 20.

[25] Kühle, E.; Anders, B. *Chem. Abstr.* **1966**, *65*, 18536g.

[26] These results were reported in a review, with no experimental detail provided; see ref. 24, p 28.

Despite this seemingly inauspicious literature precedence, we felt that if an imidoyl *diiodide* could be prepared (or generated *in situ* from the dichloride), the displacement reaction with cyanide would be greatly facilitated. To examine this possibility, we prepared benzylimidoyl dichloride (**38**) as a model compound (eq 8). Compound **38** was prepared



36 **37** **38** (8)

by bubbling chlorine gas[27] into a CH_2Cl_2 solution of benzyl isocyanide (**37**) at 0 °C until the reaction was complete (as judged by tlc). The formation of **38** was confirmed by the observation of prominent R-N=C and C-Cl stretching bands at 1645 cm^{-1} and 880 cm^{-1} respectively in the IR spectrum.[28] The isonitrile **37** was prepared by the addition of dichlorocarbene to benzylamine (**36**) under phase-transfer catalysis conditions as described by Weber.[29]

Our initial model studies were aimed at the preparation of benzyliminomalonitrile *directly* from benzyl isocyanide (**37**). We hoped that the addition of iodine (1 equivalent) to a mixture of **37** and a cyanide source (2 equivalents) would lead to imidoyl diiodide formation, followed by rapid nucleophilic displacement by cyanide to form the desired iminomalonitrile derivative. Unfortunately, when this experiment was attempted with I_2 and CuCN in either dichloromethane or acetonitrile, only polar baseline material was observed by tlc. Furthermore, the IR spectrum of the product(s) failed to show the expected nitrile and imine stretching bands around 2210 and 1595 cm^{-1} respectively.[30] An isonitrile stretching band was observed at 2195 cm^{-1}, as compared to the band at 2140 cm^{-1}

---

[27] Chlorine was generated by the addition of aqueous HCl to $KMnO_4$ as described in: Casey, M.; Leonard, J.; Lygo, B.; Proctor, G. *Advanced Practical Organic Chemistry*; Blackie: London, 1990; p 87.

[28] The expected ranges for these stretching bands are 1645-1660 cm^{-1} and 850-910 cm^{-1}, see ref. 17, p 661.

[29] Weber, W. P.; Gokel, G. *Tetrahedron Lett.* **1972**, 1637.

[30] The imine **19** was reported to have IR stretching bands at 2210 and 1595 cm-1, see ref. 14.

observed for benzyl isocyanide (**37**). This suggested that an isonitrile-copper complex of some type may in fact be the major product in these reactions.[31] For example, the copper complex *t*-butyl-NC•CuCN has been reported[32] to have an isonitrile stretching band at 2182 cm^{-1} (*t*-butyl isonitrile has a band at 2140 cm^{-1}).

In order to avoid the formation of isonitrile-metal complexes, we investigated the use of NaCN in reactions with benzyl isocyanide (**37**) and iodine. Unfortunately, this change led to the complete decomposition of **37** (as judged by tlc). The reaction of **37** with iodine alone gave similar results, suggesting that reaction with iodine is responsible for the observed decomposition. Having had no success with these more direct strategies for the synthesis of iminomalonitrile derivatives, we turned our attention to reactions of the imidoyl dichloride **38** (eq 8).

In our model studies with **38**, we hoped to effect nucleophilic displacement with cyanide under milder conditions than had been reported previously (eq 7). For example, we heated the imidoyl dichloride **38** in refluxing dichloromethane or dichloroethane with CuCN (2.2-4.0 equiv) and NaI (0.4-1.0 equiv) in the hope that initial displacement by iodide ion would generate a more reactive imidoyl diiodide which might then undergo displacement by cyanide. Analysis of these reaction mixtures by tlc, however, revealed only slow conversion of the starting materials to polar baseline material.

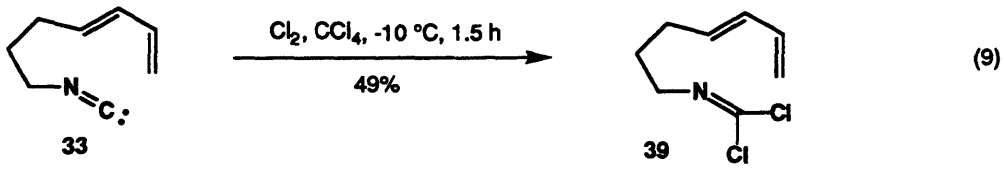
The reaction of imidoyl dichlorides with iodide *has* been reported to provide imidoyl diiodides.[33] However, the diiodides are themselves subject to a facile α-elimination reaction to give iodine and the isonitrile. It is possible that in our model studies with **38**, the desired imidoyl diiodide is indeed formed but undergoes α-elimination faster than the desired displacement with cyanide. This would be consistent with the observed

---

[31] Isonitrile-metal complexes are well known, see: Malatesta, L.; Bonati, F. *Isocyanide Complexes of Metals*; Wiley: London, 1969.
[32] Otsuka, S.; Mori, K.; Yamagami, K. *J. Org. Chem.* **1966**, *31*, 4170.
[33] Petrov, K. A.; Neimysheva, A. A. *J. Gen. Chem. USSR* **1959**, 2131.

darkening of reaction mixtures (elimination of I_2) and formation of polar baseline material (isonitrile-copper complexes).

Despite having had little success in our model studies with **38**, we turned our attention back to the isonitrile **33** and its conversion to the corresponding imidoyl dichloride **39** (eq 9). This was accomplished by the slow addition of chlorine (as a solution



(9)

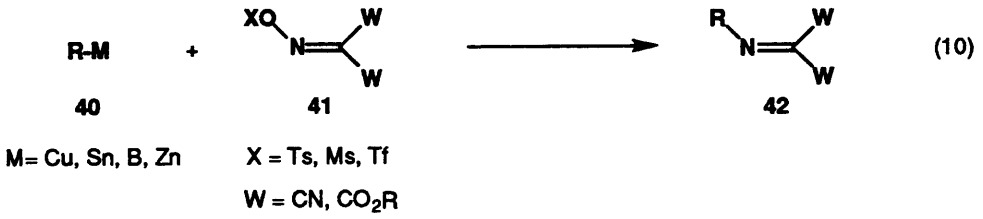
in CCl_4) to a CCl_4 solution of **33** at -10 °C until the reaction was complete (as judged by tlc). The product **39** was isolated in 49% yield after purification by column chromatography on deactivated silica gel. The modest yield is attributed to the formation of several byproducts, presumably resulting from undesired chlorination reactions of **33**.

Unfortunately, all attempts to effect cycloaddition reactions with **39** were unsuccessful. For example, reaction of **39** in toluene at 180 °C in the presence of BHT (3 equiv) for 24 h returned primarily (>90%) starting material as judged by tlc and NMR analysis. Longer reaction times led to the complete decomposition of **39**. When CuCN (2 equivalents) was included in the reaction mixture, similar decomposition was observed. These discouraging results and our inability to prepare iminomalonitrile derivatives with model compound **38** led us to investigate our second synthetic plan for the synthesis of iminomalonitrile derivatives, disconnection **b** (Scheme 3).

The Oximinosulfonate Route

The strategy based on disconnection **b** (Scheme 3) involves the addition-elimination or, alternatively, transition-metal mediated coupling reactions of oxime derivatives **41** (eq 10) with alkyl copper, tin, zinc, or boron reagents (**40**). The prepartion of doubly

activated oxime derivatives (**41**) was first reported by Fleury and co-workers[19] in the early 1970s. This seminal work included the synthesis of derivatives with nitrile, ester, and amide groups on carbon and tosyl, mesyl and *p*-nitrobenzyl groups on oxygen. Some of these oximes were later found to participate in intermolecular Diels-Alder reactions with



dienes.[34] Not surprisingly, the most reactive oxime dienophiles were those activated by two nitrile groups (**41**, W = CN). Oximes activated by two *esters* were found to be completely unreactive in cycloadditions, even with cyclopentadiene at elevated temperatures.

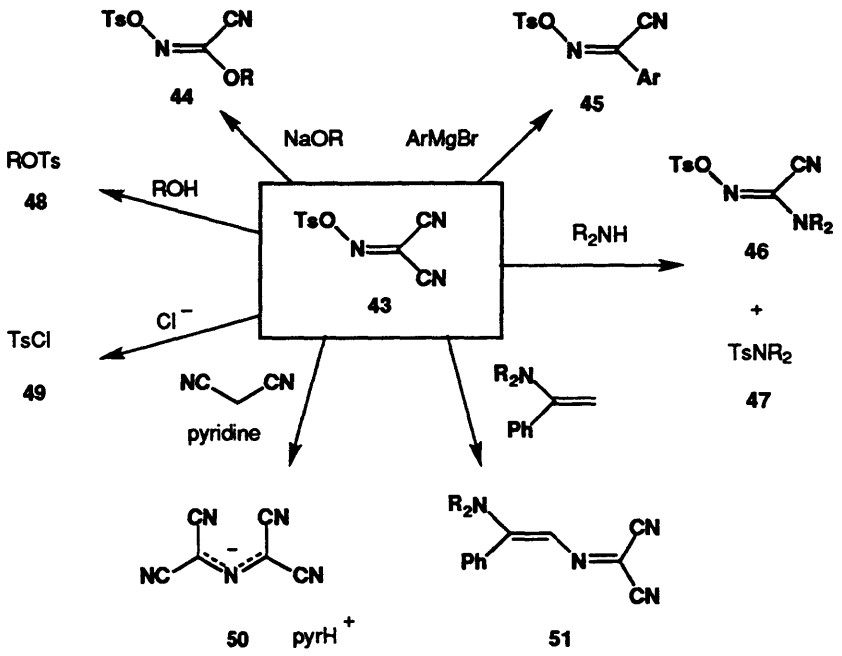
An understanding of the inherent reactivity of oximes **41** in nucleophilic addition reactions would be helpful in evaluating the feasibility of the desired transformation (eq 10). In 1972, Fleury and co-workers published a paper[35] describing the reactivity of oximinotosylate **43** towards a variety of nucleophiles. As shown in Scheme 5, these oxime derivatives can undergo nucleophilic substitution reactions at either carbon, nitrogen, or sulfur. Reactions with "hard" nucleophiles such as alkoxides and Grignard reagents give products of C-alkylation (**44** and **45**). Stirring oxime **43** in alcoholic solvents for a period of days results in reaction at *sulfur* to produce alkyltosylates (**48**). Similar reactivity is observed when **43** is treated with halide nucleophiles (F^-, Cl^-, Br^-). Reaction with secondary amines gives mixtures of C-alkylation (**46**) and sulfonylation (sulfonamide **47**) products. Finally, the addition of "soft" carbon nucleophiles such as enamines[36] and the

---

[34] Biehler, J.-M.; Fleury, J.-P. *J. Heterocycl. Chem.* **1971**, *8*, 431.
[35] Perchais, J.; Fleury, J.-P. *Tetrahedron* **1972**, *28*, 2267.
[36] Lang, M.; Schoeni, J.-P.; Pont, C.; Fleury, J.-P. *Helv. Chim. Acta* **1986**, *69*, 793.

carbanion derived from malonitrile[37] provides the *N-addition* products **50** and **51**. This result is encouraging since the desired cuprate addition to **43** (eq 10) also involves reaction

Scheme 5

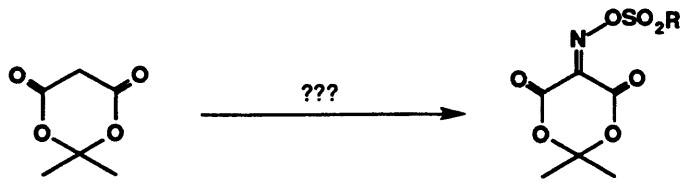


at nitrogen. Furthermore, the reactivity of cuprate reagents is often akin to that of "soft" carbon nucleophiles. For example, both cuprate reagents and malonate enolates undergo 1,4-addition to enones.

Synthesis of New Oximinosulfonates and Phosphates

In addition to malonitrile-derived oximes, we considered whether it would be possible to prepare oximinosulfonates derived from Meldrum's acid (**52**, eq 11). We expected that these compounds (**53**) would be less susceptible to C-alkylation reactions than the iminomalonitriles **43** (Scheme 5). The use of a *cyclic* diester was expected to

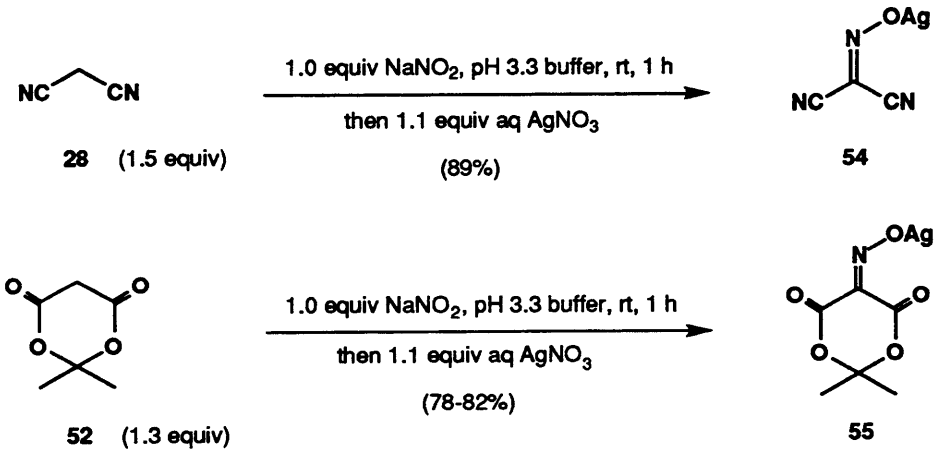
[37] Perchais, J.; Fleury, J.-P. *Tetrahedron* **1974**, *30*, 999.



52 53 (11)

render the resulting oxime and imine derivatives much more reactive in cycloadditions than the corresponding *acyclic* diesters.[38]

Our procedure for the preparation of oximinosulfonates is based on those reported by Fleury[39] and Williams.[40] The first step (eq 12) involves the nitrosation of malonitrile (or Meldrum's acid) with sodium nitrite in a pH 3.3 acetate buffer. The reaction mixture is then treated with an aqueous $AgNO_3$ solution to effect precipitation of the oxime as its silver salt. The oxime salts (**54** and **55**) are then collected by filtration, placed in a vacuum desiccator, and thoroughly dried.[41]



(12)

[38] Meldrum's acid (MA) is a significantly stronger acid than the corresponding acyclic malonate esters (by around 10 pKa units!). Likewise, methylene derivatives of MA are more reactive than the corresponding acyclic compounds. This enhanced reactivity may be attributed to the acyclic structure in which the π orbitals of the ester carbonyls are held in the ideal orientation for overlap with a carbanion or methylene double bond. For a review of Meldrum's acid, see: McNab, H. *Chem. Soc. Rev.* **1978**, *7*, 345.

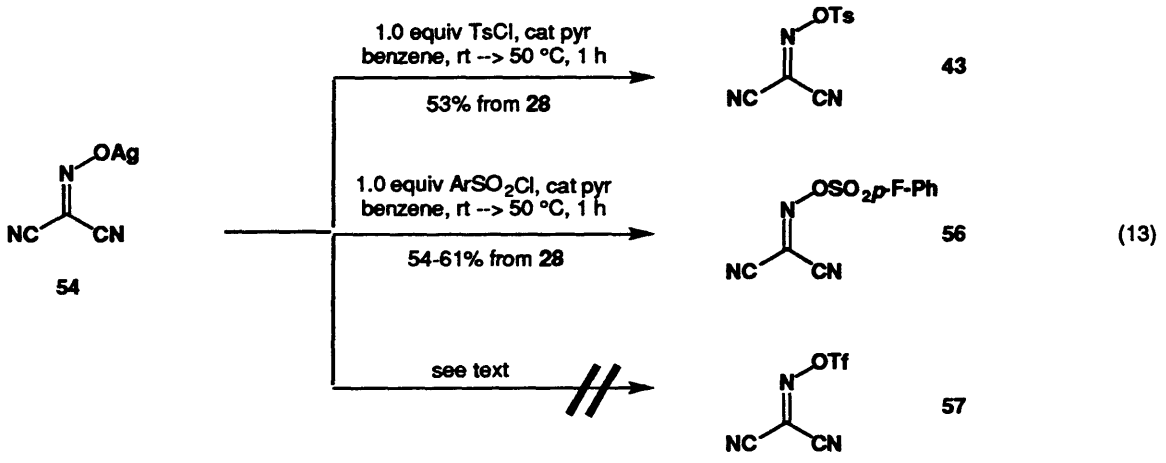
[39] Perrocheau, J.; Carrié, R.; Fleury, J.-P. *Can. J. Chem.* **1994**, *72*, 2458.

[40] Iglesias, E.; Williams, L. H. *J. Chem. Soc., Perkin Trans. 2* **1989**, 343.

[41] The orange (**54**) and red (**55**) solids are not purified further, but used directly in subsequent reactions.

The oxime salts **54** and **55** serve as convenient intermediates for the synthesis of a variety of oximino esters. In addition to the tosylates reported by Fleury, we were interested in more reactive derivatives for possible application in transition-metal mediated coupling reactions. We therefore attempted the preparation of triflate,[42] *p*-fluorobenzenesulfonate,[43] and diphenylphosphate[44] derivatives.

Equation 13 presents the synthesis of tosylate **43** and *p*-fluorobenzenesulfonate **56** from the malonitrile oxime salt **54**. These sulfonylation reactions are conducted under heterogeneous reaction conditions by treatment of a benzene suspension of **54** with the appropriate sulfonyl chloride and a catalytic amount of pyridine. Interestingly, the conversion of silver salt **54** to the desired products **43** and **56** is accompanied by a color change from orange to gray as the colored oxime salt is converted to colorless AgCl. Removal of insoluble AgCl by filtration, and concentration of the filtrate provides the crude products. Although sensitive to hydrolysis, **43** and **56** can be purified by column chromatography using deactivated silica gel.



(13)

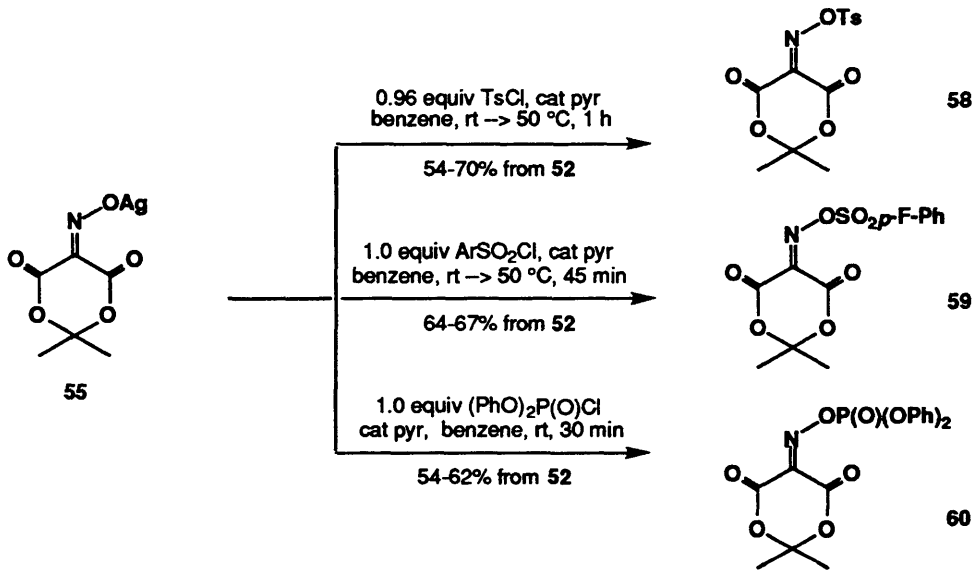
[42] For a review of the preparation and coupling reactions of *vinyl* and *aryl* triflates, see: Ritter, K. *Synthesis*, **1993**, 735.

[43] For examples of coupling reactions of *aryl* arenesulfonates, see: Badone, D.; Cecchi, R.; Guzzi, U. *J. Org. Chem.* **1992**, *57*, 6321.

[44] For examples of coupling reactions of *ketene acetal* phosphates, see: Nicolaou, K. C.; Shi, G.-Q.; Gunzer, J. L.; Gärtner, P.; Yang, Z. *J. Am. Chem. Soc.* **1997**, *119*, 5467.

Attempts to prepare the triflate **57** from the free oxime[45] using triflic anhydride or the Comins[46] reagent were unsuccessful (in CH_2Cl_2 with DMAP or Et_3N). Monitoring the progress of these reactions proved challenging, and it is therefore difficult to say why they were unsuccessful. If the desired triflate was formed, it is possible that it was unstable to the work-up conditions or may have been lost during attempted isolation due to its volatility.

Equation 14 presents the synthesis of oxime derivatives **58**, **59**, and **60** from the Meldrum's acid-derived oxime salt **55**. These reactions were carried out as described



(14)

above for the corresponding malonitrile derivatives (eq 13). In addition to the tosylate **58** and *p*-fluorobenzenesulfonate **59**, the phosphate **60** was prepared by the phosphorylation of **55** with diphenylphosphoryl chloride. As with the malonitrile derivatives (eq 13), the oximes **58-60** could be purified by column chromatography on deactivated silica gel. The phosphate **60** was especially sensitive to hydrolysis, however, so chromatographic

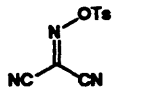
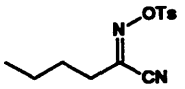
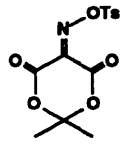
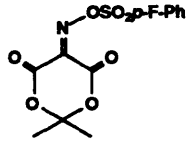
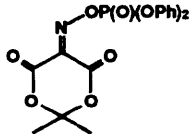
[45] Prepared from the salt **54** by reaction with 30% aqueous HNO_3 and extration with ether (followed by the usual work up).
[46] Comins, D. L.; Dehghani, A. *Tetrahedron Lett.* **1992**, *33*, 6299.

purification was conducted at 0 °C. With a number of oxime derivatives (eqs 13 and 14) in hand, the stage was set for attempts at the desired cuprate and coupling reactions.

Cuprate Additions

The results of cuprate addition reactions are summarized below in Table 1. A variety of reagents were examined, including lower- and higher-order cuprates, phenylthio(alkyl)cuprates,[47] and a phenylacetylene cuprate[48] reagent that has recently been shown to add to oximinosulfonates. The addition of these cuprate reagents to solutions of

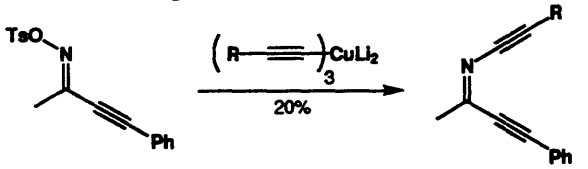
Table 1. Attempted Cuprate Addition Reactions

Oxime Derivative	Bu_2CuLi[a]	$R_2CuCNLi_2$[b]	Bu(SPh)CuLi[c]	BuLi[d]	Ph—≡—)$_3$CuLi$_2$[e]
43 	Decomposition	Decomposition (R = Me) (R = Bu)	Decomposition	 61	53%
58 					Starting material and unidentified aromatic products.
59 		Decomposition (R = Bu)			
60 		Decomposition (R = Bu)			

[a] 1 equiv in THF at -78 °C. [b] 1.1 equiv in THF at -78 °C. Additives such as TMSCl and BF_3•Et_2O were also tried in reactions of 43. [c] 1.1 equiv in THF at -100 °C to rt. [d] 0.95 equiv in THF at -78 °C. [e] 1.0 equiv in THF at -78 °C to -30 °C.

[47] Posner, G. H.; Brunelle, D. J.; Sinoway, L. *Synthesis* **1974**, 662.

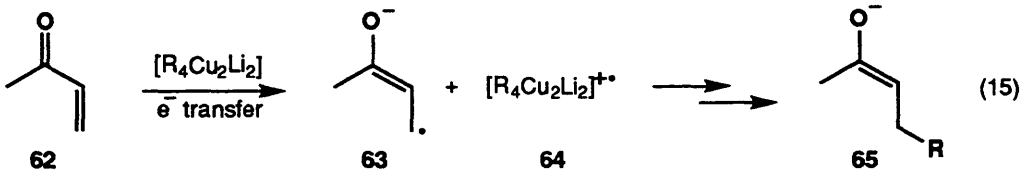
[48] The following addition-elimination reaction proceeded in low yield.



David, W. M.; Kerwin, S. M. *J. Am. Chem. Soc.* **1997**, *119*, 1464.

the oxime derivatives at -78 °C produced thick black reaction mixtures almost immediately. In all cases, the mass balance of products following work-up was very low, suggesting that considerable decomposition had occurred. The use of additives such as trimethylsilyl chloride[49] and $BF_3 \cdot Et_2O$[50] in reactions of **43** gave similar results. In contrast, reaction of **43** with *n*-BuLi produced the C-alkylation product **61** in 53% yield. This result is not surprising considering the tendency of oximinotosylate **43** to undergo C-alkylation in reaction with Grignard reagents and alkoxides (Scheme 5).

A possible explanation for the failure of these cuprate additions might be the involvement of electron transfer processes. Single electron transfer has in fact been suggested as a possible first step in the mechanism of cuprate additions.[51] According to



62 63 64 65 (15)

this proposal (eq 15), reduction of an enone (**62**) by the cuprate reagent generates a radical anion (**63**) and a cationic cuprate radical (**64**). Coupling of these radicals and transfer of an alkyl group from copper then produces the observed 1,4-addition products (**65**).[52]

In the case of the oxime derivatives in Table 1, single electron transfer would be expected to produce the radical anions **66** and **67**. Radicals situated between electron

---

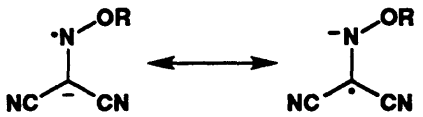
[49] Alexakis, A.; Berlan, J.; Besace, Y. *Tetrahedron Lett.* **1986**, *27*, 1047.

[50] (a) Lipshutz, B. H.; Parker, D. A.; Kozlowski, J. A.; Nguyen, S. L. *Tetrahedron Lett.* **1984**, *25*, 5959. For additions to aldimines, see: (b) Wada, M.; Sakurai, Y.; Akiba, K. *Tetrahedron Lett.* **1984**, *25*, 1079.

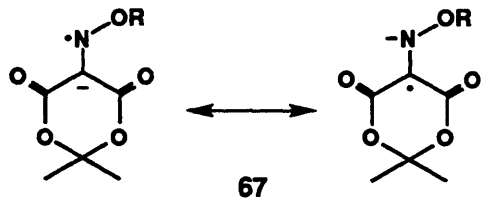
[51] House, H. O. *Acc. Chem. Res.* **1976**, *9*, 59.

[52] The oxidation and reduction potentials of cuprates and enones can be used to predict whether or not addition reactions are likely to occur. When the reduction potential of the enone becomes too negative, insufficient concentrations of the required radical intermediates will be produced and conjugate addition does not occur. Alternatively, if the reduction potential of the enone is too positive, a two electron reduction may occur, resulting in the reduction of the enone.

withdrawing *and* electron donating groups are especially stable species.[53] The oxime derivatives in question would therefore be expected to be good oxidizing agents (that is,



66



67

easily reducible). Indeed, in their work with oximinosulfonates, Fleury and co-workers reported that tosylate **43** can undergo both one and *two* electron reduction.[35] These reduced species were quite unstable, however, and their corresponding oxidation could not be observed. The failure of the cuprate addition reactions in Table 1 is most probably due to reduction of the oxime derivatives by the cuprate reagents, thereby generating stabilized radical anions (or dianions) that are slow to couple with cuprate radicals and instead undergo undesired coupling and/or fragmentation reactions.

Transition-Metal Mediated Coupling Reactions

As mentioned previously, we were intrigued by the possibility that oximinosulfonate derivatives such as **56** and **59** might serve as electrophiles in transition-metal mediated coupling reactions with organometallic nucleophiles. Since our goal was the preparation of diene and enyne substrates for intramolecular cycloaddition reactions, we were primarily interested in coupling reactions of *alkyl* organometallic reagents. Organozinc reagents[54] were of particular interest due to their ready availability from alkyl halides and their superior reactivity as compared to alkylstannanes. Organozinc compounds have been shown to participate in coupling reactions[55] with a variety of

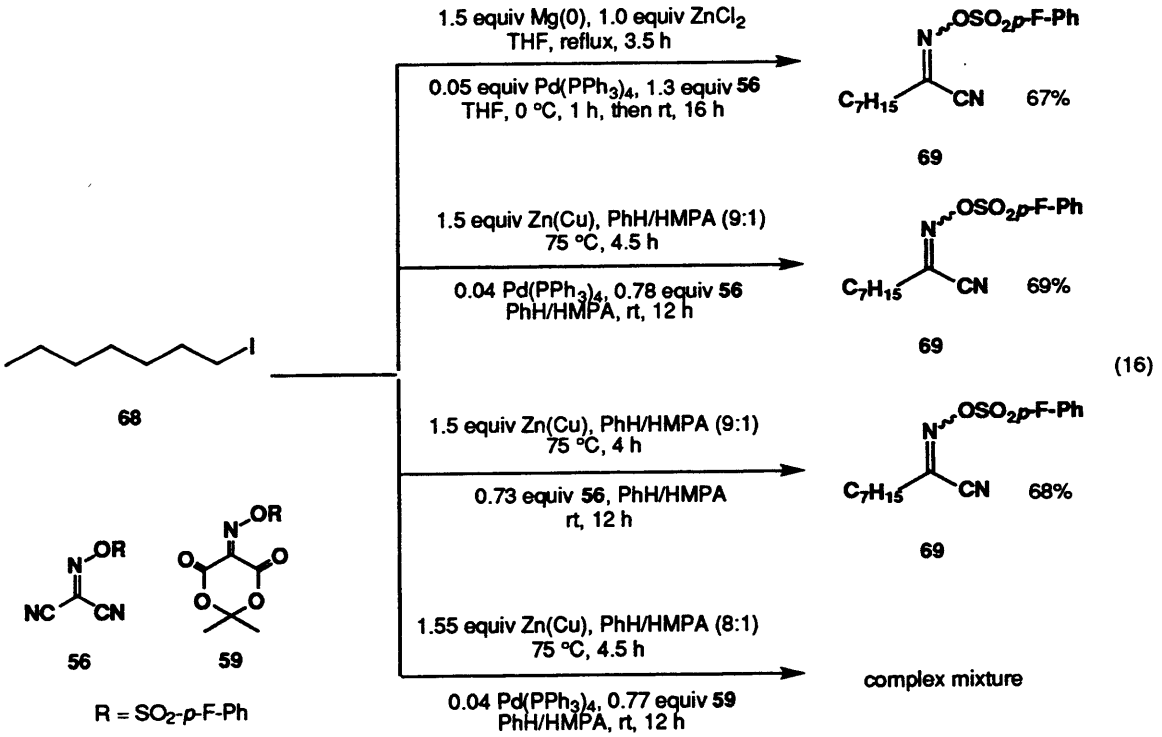
[53] They possess capto-dative stabilization, see: Viehe, H. G.; Merényl, R.; Stella, L.; Janousek, Z. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 917.

[54] Erdik, E. *Organozinc Reagents in Organic Synthesis*; CRC: Boca Raton, 1996.

[55] (a) Erdik, E. *Tetrahedron* **1992**, *48*, 9577. (b) Negishi, E.-I.; Valente, L. F.; Kobayashi, M. *J. Am. Chem. Soc.* **1980**, *102*, 3298. (c) Kobayashi, M.; Negishi, E.-I. *J. Org. Chem.* **1980**, *45*, 5223. (d)

electrophiles, including vinyl bromides,[55b] β-bromo-substituted α,β-unsaturated carbonyl compounds,[55c] aryl and vinyl iodides[55d] and triflates,[55f] acid chlorides,[55e] and allylic chlorides.[55f] These reactions typically occur under mild reaction conditions (near room temperature) and are compatible with functional groups such as esters and ketones (due to the lower reactivity of organozinc compounds as compared to Grignard or alkyllithium reagents in nucleophilic addition to carbonyl groups).

A summary of our investigation of coupling reactions between organozinc reagents and oximinosulfonates is shown in equation 16. The organozinc reagent derived from iodoheptane (**68**) was selected as a model compound for these initial attempts at coupling reactions. Preparation of the organozinc reagent was initially accomplished using the Negishi[55b] protocol (Mg(0), $ZnCl_2$, refluxing THF). Reaction of this organozinc reagent



(16)

Tamaru, Y.; Ochiai, H.; Nakamura, T.; Yoshida, Z. *Tetrahedron Lett.* **1986**, *27*, 955. (e) Tamaru, Y.; Ochiai, H.; Nakamura, T.; Tsubaki, K.; Yoshida, Z. *Tetrahedron Lett.* **1985**, *26*, 5559. (f) Tamaru, Y.; Ochiai, H.; Nakamura, T.; Yoshida, Z. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 1157.

with oximinosulfonate **56** at 0 °C in the presence of $Pd(PPh_3)_4$ led to immediate consumption of **56** and the formation of a new product (as judged by tlc). Isolation of this product and NMR analysis suggested that it was the C-alkylation product **69**. This assignment was further supported by the observation of a molecular ion at 326.11005 (for $C_{15}H_{19}N_2O_3SF$) in the HRMS spectrum of the product. Since the Negishi protocol involves the intermediacy of a Grignard reagent, we were concerned that the formation of **69** was perhaps due to reaction with the Grignard reagent rather than coupling with the desired organozinc species. For this reason, we prepared the organozinc reagent *directly*, by the reaction of iodide **68** with zinc-copper couple.[55f] When this organozinc reagent was reacted with oximinosulfonate **56**, however, the same C-alkylated product (**69**) was formed in essentially identical yield! When the reaction was conducted *without* $Pd(PPh_3)_4$, **69** was again formed in high yield, confirming that the catalyst plays no role in this addition-elimination reaction. Despite the lower reactivity of organozinc compounds as compared to Grignard and alkyllithium reagents, it appears that C-alkylation of **56** is a favorable process. The use of the Meldrum's acid derivative **59**, which we expected to be less prone to C-alkylation, unfortunately led to the formation of a complex mixture of products as judged by tlc and NMR spectroscopy.

In addition to coupling reactions with organozinc reagents, we also briefly examined reactions with organoboron compounds (Suzuki reactions) and alkylstannanes (Stille reactions). Unfortunately, control experiments indicated that the basic reaction conditions employed in the Suzuki coupling reaction are not compatible with oximinosulfonate derivatives.[56] Attempted Stille coupling reactions of **56** and **59** with tetrabutyltin resulted in the decomposition of the oximinosulfonate derivatives without formation of the desired coupled products. Attempts to couple oximino*phosphate* **58** with 2-(tributylstannyl)-thiophene similarly resulted in decomposition.

---

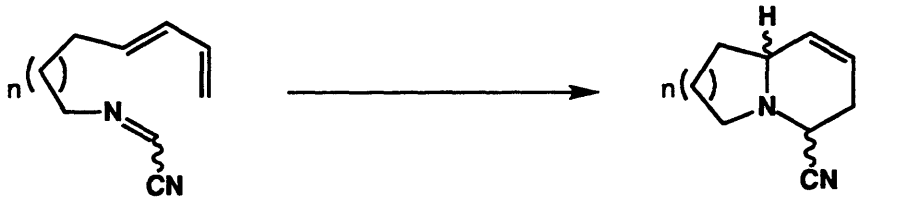
[56] Even less basic conditions employing K_3PO_4 as base led to decomposition of **56** in control experiments.

Summary

This chapter described two strategies we hoped would lead to the efficient preparation of electron-deficient imine derivatives. Although both were ultimately unsuccessful, a variety of new oximinosulfonate derivatives based on Meldrum's acid were prepared for the first time. In subsequent studies of these compounds, the tosylate **58** was shown to react efficiently and regioselectively in *inter*molecular cycloaddition reactions with dienes. These reactions and their application in new pyridine annulation methodology are the subject of Part II of this thesis.

Chapter 3
Synthetic Approaches to Nitrogen Heterocycles via Alkyliminoacetonitrile Derivatives

This chapter details our investigation of intramolecular Diels-Alder and enyne cycloadditions in which an *alkyliminoacetonitrile* derivative serves as the 2π component in the reaction. In contrast to the iminomalonitrile derivatives discussed in Chapter 2, the iminoacetonitriles are substituted with a single nitrile group on carbon. Although these species are presumably less reactive, we felt they would possess sufficient reactivity for use in *intramolecular* cycloaddition reactions. We also expected that these imines would be more synthetically accessible than the iminomalonitriles. The proposed intramolecular cycloaddition of an iminoacetonitrile dienophile with a diene is illustrated below.



70 n = 1
71 n = 2

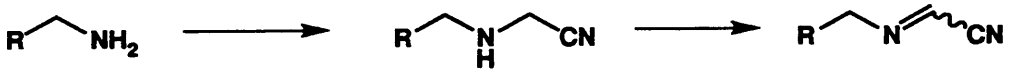
72 n = 1
73 n = 2

A number of alkyliminoacetonitriles[14, 16] have been reported in the literature, although their use in cycloaddition reactions has not previously been described. For this reason, we chose to first investigate diene-containing substrates so that the relative reactivity of the iminoacetonitriles could be assessed. In particular, we investigated substrates with either three carbons (**70**) or four carbons (**71**) in the connecting chain between the diene and iminoacetonitrile dienophile. Successful intramolecular Diels-Alder

reaction of these substrates would provide products with either the indolizidine (**72**) or quinolizidine (**73**) ring systems.

Synthesis of Cycloaddition Substrates

Previously reported synthetic routes to alkyliminoacetonitrile derivatives (**76**) have relied on a two-step procedure (eq 17) starting with a primary amine (**74**) and involving the intermediacy of an *amino*acetonitrile (**75**). The alkylation step (**74** → **75**) has typically



(17)

74 **75** **76**

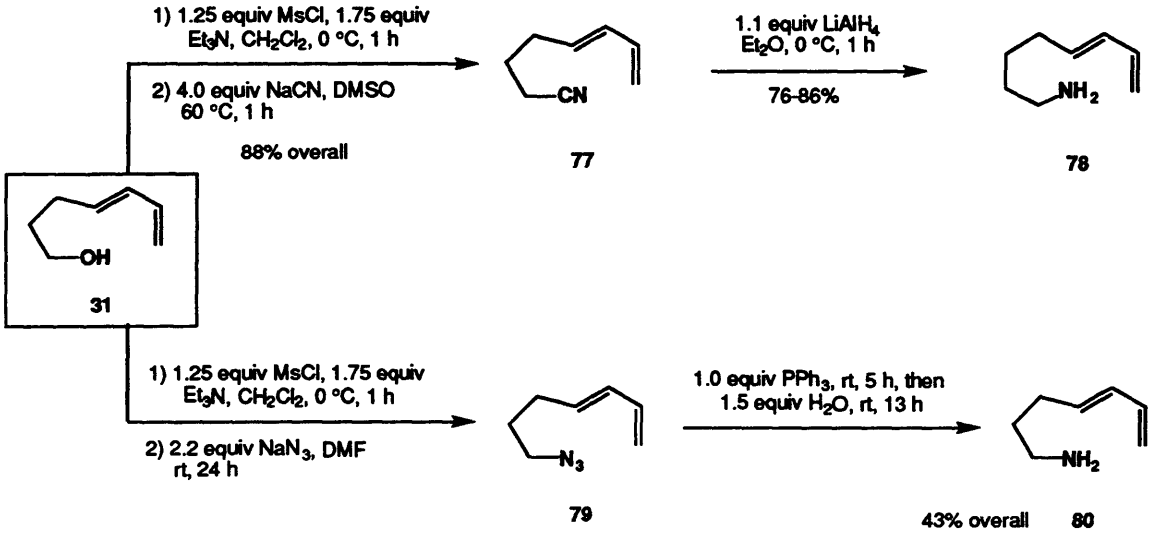
been accomplished with hydroxyacetonitrile in refluxing H_2O/ethanol.[57] The subsequent dehydrogenation step (**75** → **76**) is usually accomplished by electrophilic chlorination (of **75**) followed by elimination of HCl with base to provide **76**.[14, 16] The application of this strategy to the synthesis of **70** and **71** therefore requires the preparation of amines **78** and **80**.

Scheme 6 presents our synthesis of the key dienylamines **78** and **80** starting from the alcohol **31** (prepared as described previously, Scheme 4). The conversion of **31** to the nitrile **77** was accomplished using a modification of the route described by Roush.[20b] Conversion of **31** to the corresponding mesylate[22] was followed by nucleophilic displacement with cyanide ion (NaCN in DMSO). In this fashion, the nitrile **77**[20b] could be obtained in excellent overall yield (88%) following purification by column chromatography. Reduction of **77** with $LiAlH_4$ in Et_2O proceeded smoothly to provide the desired amine **78**[13a] in high yield after purification by Kugelrohr distillation. The synthesis

---

[57] Luskin, L. S.; Culver, M. J.; Gantert, G. E.; Craig, W. E.; Cook, R. S. *J. Am. Chem. Soc.* **1956**, *78*, 4042.

Scheme 6



of the amine **80**[58] followed a strategy analogous to that used for **78**. Nucleophilic displacement of the mesylate derived from **31** with *azide* ion (NaN_3 in DMF) provided the dienyl azide **79**. This compound was not purified but was reduced directly to the primary amine using PPh_3[59] to provide amine **80** in 43% overall yield (3 steps) after purification by Kugelrohr distillation.

The synthesis of the *enyne* **84** (Scheme 7) parallels the routes to dienes **78** and **80** (Scheme 6). Homopropargylic alcohol **82**[60] was prepared from 3-butyn-1-ol (**81**) and 2-bromopropene using a modification of the Castro-Stephens reaction.[61] This alcohol was then converted to the nitrile **83** by displacement of the corresponding mesylate[22] with cyanide (NaCN, DMSO). Finally, reduction of the nitrile with $LiAlH_4$ provided the amine **84** in 90% yield after purification by Kugelrohr distillation.

---

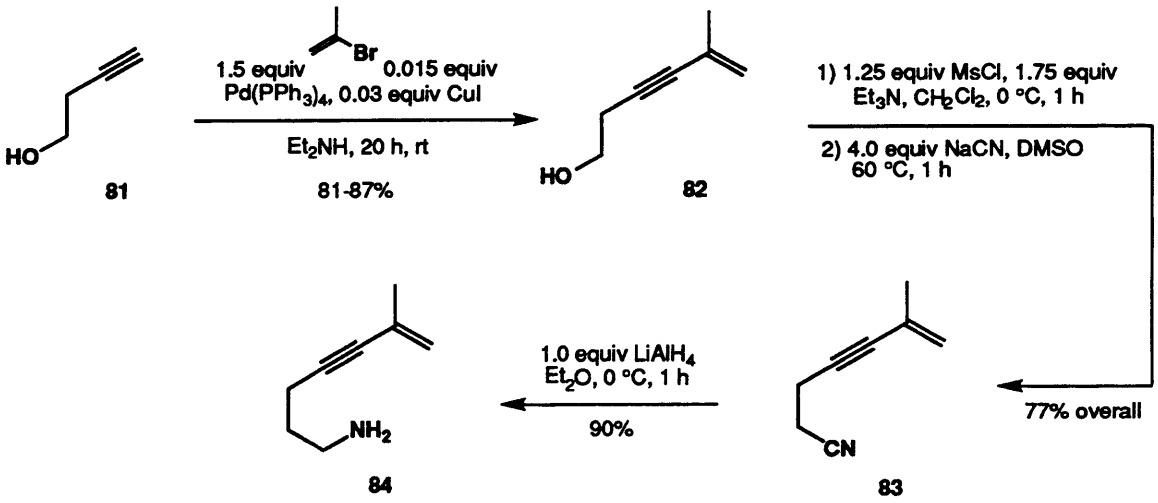
[58] This compound has been prepared previously using a different route; see: Grieco, P. A.; Galatsis, P.; Spohn, R. F. *Tetrahedron* **1986**, *42*, 2847.

[59] Vaultier, M.; Knouzi, N.; Carrié, R. *Tetrahedron Lett.* **1983**, *24*, 763.

[60] This alcohol is commercially available.

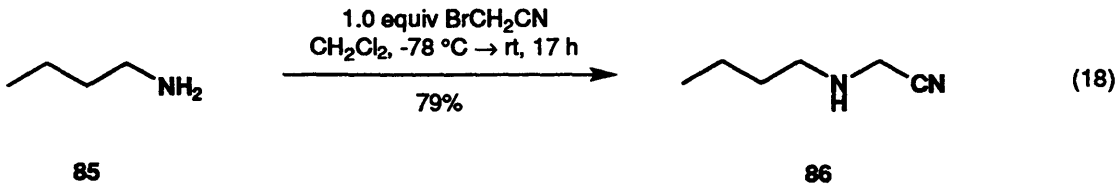
[61] Takahashi, S.; Kuroyama, Y.; Sonogashira, K.; Hagihara, N. *Synthesis* **1980**, 627.

Scheme 7



Preparation of Alkyliminoacetonitriles from Primary Amines - Model Studies

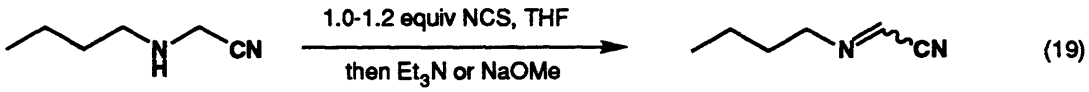
With the amines **78**, **80** and **84** in hand, the stage was set for their conversion to iminoacetonitrile derivatives. Our initial investigation of this conversion was carried out with *n*-butylamine (**85**) as a model compound. The first step in the synthetic sequence involves the cyanomethylation of a primary amine to provide an alkylaminoacetonitrile (**74** → **75**, eq 17). This alkylation had previously been effected by reaction of the amine with hydroxyacetonitrile in refluxing ethanol/H_2O.[57] We thought that the use of bromoacetonitrile as alkylating agent might allow the use of milder reaction conditions that would in turn be compatible with a wider array of functional groups. Indeed, reaction of three equivalents of *n*-butylamine with bromoacetonitrile in CH_2Cl_2 at *room temperature* provided the desired product **86** in nearly quantitative yield. Since the use of excess amine would be undesirable in the alkylation of **78**, **80**, and **84**, we investigated the alkylation of **85** (1 equivalent) with bromoacetonitrile in the presence of triethylamine (2.5 equivalents). Under these conditions however, low yields of **86** (ca. 20%) were obtained. Surprisingly, a 79% yield of **86** was obtained when equimolar amounts of *n*-butylamine and bromoacetonitrile were reacted *without* additional base present (eq 18).



(18)

85 **86**

The conversion of **86** to butyliminoacetonitrile formally requires a dehydrogenation reaction. This transformation was accomplished previously by *N*-chlorination of the alkylaminoacetonitrile with *tert*-butyl hypochlorite followed by dehydrochlorination with triethylamine.[14] In model studies with **86**, we used *N*-chlorosuccinimide for the chlorination reaction and either triethylamine or sodium methoxide for the elimination (eq



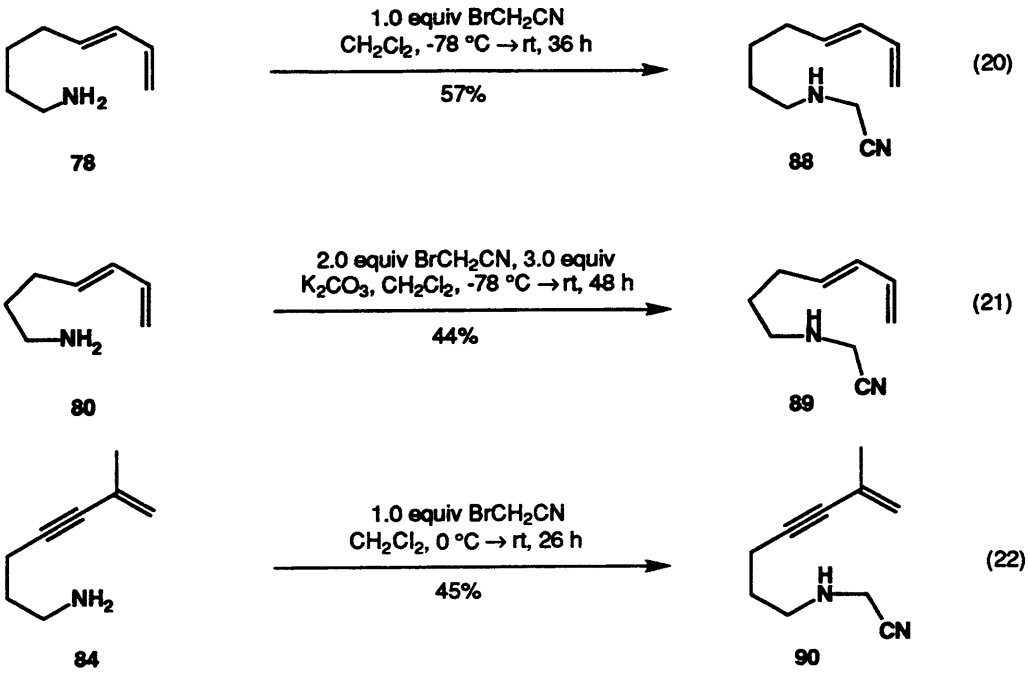
(19)

86 **87**

19). Both procedures gave the desired imine **87** in acceptable yields (ca. 50-70%). The reaction with sodium methoxide gave a cleaner product, however, so its use was favored in these reactions. Other bases were not examined, and it is possible that the use of hindered bases such as KO*t*-Bu and *i*-Pr_2EtN might lead to further improvements.

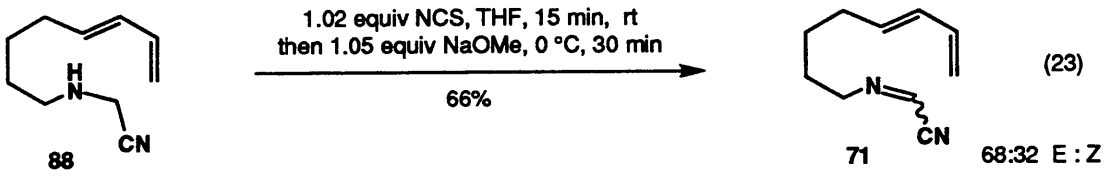
Preparation of Alkyliminoacetonitriles from Amines 78, 80, and 84

The conversion of amines **78**, **80**, and **84** to cycloaddition substrates **71**, **70**, and **91** was accomplished using the synthetic procedures developed in our model studies with **85** (*vide supra*). The results of the alkylation of amines **78**, **80**, and **84** with bromoacetonitrile are illustrated in equations 20-22. In all cases, these reactions did not

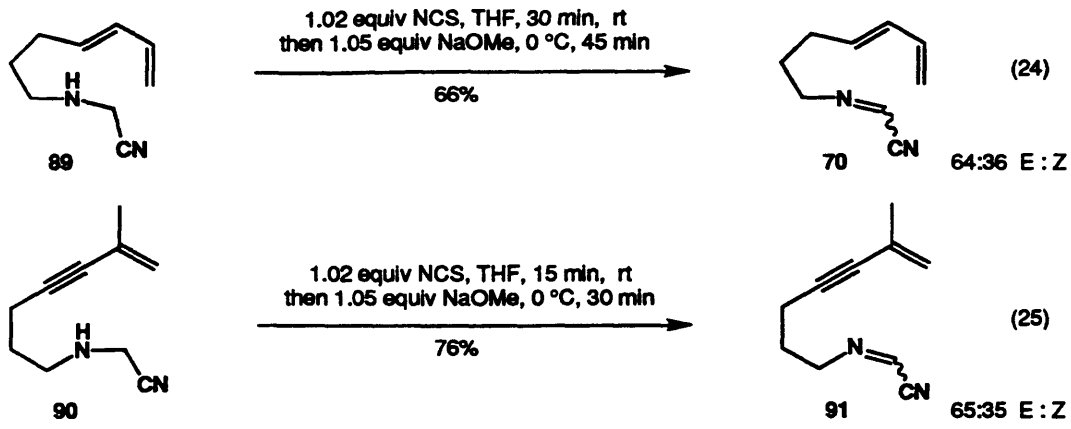


proceed to completion, and modest yields of the desired alkylation products were obtained. The low conversion is presumably a result of proton transfer from the alkylated amine hydrobromide salt to the (more basic) unreacted amine. The use of excess alkylating agent and additional base (K_2CO_3) did not lead to improved conversions, however (eq 21). No additional optimization of the reaction was attempted, although there is clearly room for improvement.

The conversion of aminonitriles **88-90** to the corresponding imines was accomplished using the NCS/NaOMe protocol developed in our model studies. This procedure worked quite well, providing the desired imines **71**, **70**, and **91** in good yield (eq 23-25) after purification by column chromatography.[62] In all cases, a mixture of *E* and

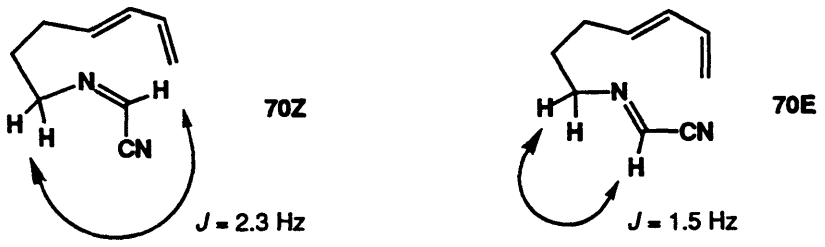


[62] Chromatography was carried out with 1% triethylamine in the eluent to neutralize acidic sites on the silica gel.



Z imine isomers were obtained with modest selectivity for the *E* isomer (eq 23-25). This assignment is based on the following observations. As shown below for **70**, the methylene signals for the two isomers are well separated in the ^{1}H NMR spectrum, with the minor product having the more downfield signal. The signal for the *Z* isomer (**70Z**) is

expected to be further downfield since it lies within the deshielding cone of the nitrile π bonds. More conclusive evidence comes from the *four-bond* coupling[63] observed between the imine hydrogen and the α-methylene signal as shown below. The minor product displays a larger coupling constant, suggesting a *transoid* relationship between the imine



[63] The magnitude of this coupling in E and Z aldimines has been described: Yeh, H. J. C.; Ziffer, H.; Jerina, D. M. *J. Am. Chem. Soc.* **1973**, *95*, 2741.

hydrogen and methylene groups (as in **70Z**). The major product displays a smaller four-bond coupling constant, suggesting a cisoid relationship (as in **70E**). The magnitude of these coupling constants are in excellent agreement with those reported for other *E* and *Z* aldimine systems.[64] With cycloaddition substrates **71, 70,** and **91** in hand, the stage was set for an investigation of the reactivity of these compounds in intramolecular [4+2] cycloaddition reactions.

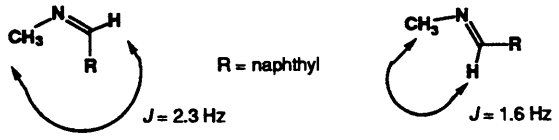
Intramolecular [4+2] Cycloadditions of Alkyliminoacetonitriles

In our studies of the cycloadditions of alkyliminoacetonitriles **70, 71,** and **91,** we were interested in addressing a number of issues. The first was whether this particular imine functionality is reactive enough to participate in cycloaddition reactions with dienes and enynes. Since the iminoacetonitrile substrates are obtained as mixtures of *E* and *Z* isomers, the stereoselectivity of the reaction was also recognized to be an important issue. Finally, the reactions of substrates **70** and **71** (which differ only in the length of the tether) were studied to obtain information about the importance of this variable in the reaction.

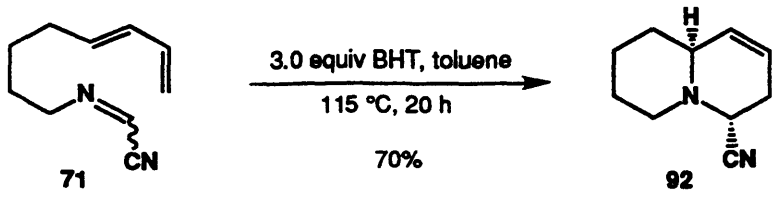
The first substrate examined was the diene **71.** A mixture of *E* and *Z* imine isomers (68:32) of **71** was heated in toluene in a sealed tube (with three equivalents of BHT). After 20 hours at 115 °C, the tube was cooled to room temperature and the products isolated. To our delight, we obtained the cycloadduct **92** as a *single diastereomer* in 70% yield following purification by column chromatography (eq 26). The diastereomeric purity was confirmed by inspection of the ^{1}H and ^{13}C NMR spectra of the product.[65] The *cis*

---

[64] From ref. 63:



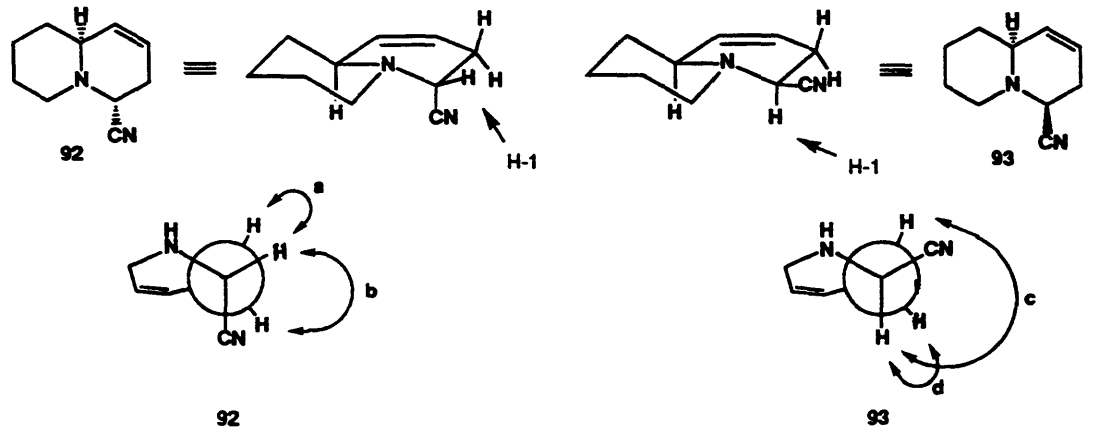
[65] Only 10 peaks were observed in the ^{13}C NMR spectra of product. Analysis by ^{1}H NMR was also consistent with the presence of a single diastereomer.



(26)

stereochemistry assigned for cycloadduct **92** is based on analysis of the ^{1}H NMR spectrum as described below. The signal for H-1 in **92** falls at 3.79 ppm and is a *doublet* with a coupling constant of 6.3 Hz. In the two possible diastereomeric products **92** and **93** (Scheme 8), only the H-1 (indicated by arrow) signal of **92** could be a simple doublet.

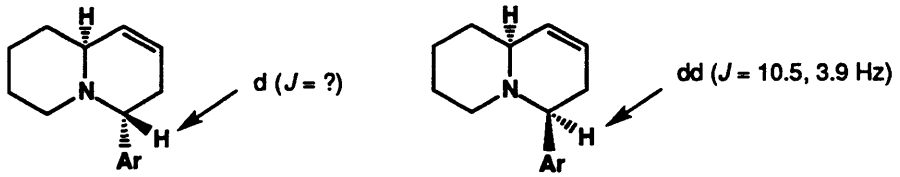
Scheme 8



For **92**, the coupling constant **a** would be expected to fall between 4 and 8 Hz while that for **b** should be quite small (0 to 2 Hz). In **93**, however, the coupling constant **c** must be very large (8 to 15 Hz) while that for **d** should still fall between 4 and 8 Hz. The signal for H-1 in **93** should therefore be a *doublet of doublets*. The observation in the product of a doublet with a coupling constant around 6 Hz is therefore consistent only with **92**.

Further support for the above analysis comes from the coupling reported in the quinolizidine compounds **94** and **95**, shown below.[66] As expected, the signal for H-1 in the *cis* quinolizidine **94** is a doublet (no coupling constant was given) while that for the

[66] Quick, J.; Khandelwal, Y.; Meltzer, P. C.; Weinberg, J. S. *J. Org. Chem.* **1983**, *48*, 5199.

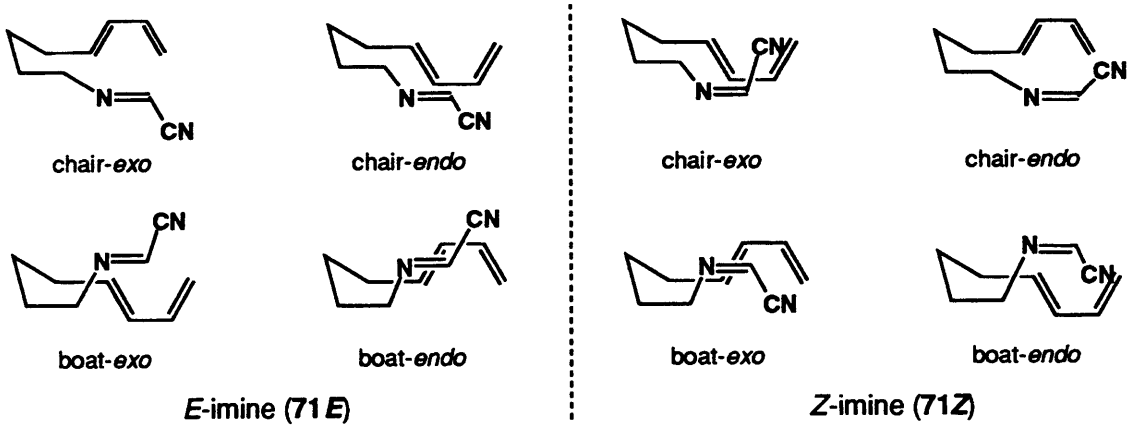


94 95

trans quinolizidine **95** is a doublet of doublets (J = 10.5, 3.9 Hz).

In addition to the product **92**, a small amount (<10%) of unreacted starting material was also isolated in the reaction of **71** (eq 26). Interestingly, the ratio of E and Z isomers in this material was essentially unchanged, suggesting that the two imine isomers react with similar rates. The formation of a single diastereomeric product cannot, therefore, be attributed to a failure of one of the isomers to react. Considering this fact, it was at first surprising that only a single diastereomer (**92**) was formed. In order to explain the high stereoselectivity obtained in this reaction, it will be helpful to examine the various transition states available to the substrate **71** in its conversion to **92**. Scheme 9 presents these transition states for both the E and Z isomers of **71**. Each isomer has four diastereomeric

Scheme 9

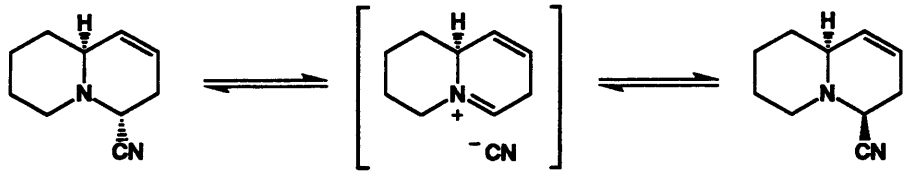


transition states through which it may react. The connecting chain may adopt either chair-like or boat-like conformations, while the iminoacetonitrile group may adopt either an *endo* or *exo* orientation with respect to the diene. Inspection of Scheme 9 reveals that the *exo* transition states all provide *cis* quinolizidine products (**92**) while the *endo* transition states all lead to *trans* quinolizidine products (**93**). Chair and boat transition states give different products only in substrates with substitution on the connecting chain, and therefore give the same product in the case of **71**. The stereochemistry of the imine dienophile determines whether a *cis* or *trans* ring junction is formed. This is of little consequence with **71**, however, due to the low energetic barrier for inversion of the nitrogen atom in the products. *All four* of the *exo* transition states in Scheme 9 would therefore be predicted to give the observed *cis* quinolizidine product **92**. Although the preference for an *exo* transition state is apparently high, it is impossible to determine the relative importance of the chair and boat conformations in reactions of **71**. This question could be addressed, however, using a cycloaddition substrate with a stereogenic center in the connecting chain.[67]

Although the analysis above explains the observed stereochemistry of the product **92**, it is not entirely clear why iminoacetonitrile dienophiles should demonstrate such high selectivity for an *exo* transition state. This is especially puzzling when one considers that *N*-acylimines[12] display high *endo* selectivity while iminium ions[13] are generally not selective at all. Another possible explanation for the observed stereoselectivity is that both isomers **92** and **93** are formed in the reaction and then undergo equilibration under the reaction conditions. In principle, the equilibration of **92** and **93** could occur if the Diels-Alder reaction is reversible under the reaction conditions. Alternatively, epimerization of the cycloadducts via the iminium ion **96** should also be possible. Indeed, the epimerization

[67] The *relative* stereochemistry between this stereocenter and the newly formed stereocenters is determined by the relative stability of chair and boat transition states.

of *N*-substituted *cis*-2,6-dicyanopiperidines to the corresponding *trans* derivatives by refluxing in ethanol solvent has been reported.[68]



92 96 93

Assuming that equilibration of **92** and **93** is facile under the reaction conditions (toluene, 115 °C), the exclusive formation of diastereomer **92** requires that it be considerably lower in energy than **93**. In fact, the related α-cyanopiperidines are known to exist almost exclusively in conformations where the cyano group is in an *axial* position.[69] This preference is attributed to an *anomeric effect*[70] between the nitrile and the neighboring nitrogen atom. As illustrated below for **92** and **93**, the axial orientation of the nitrile group

92 93

in **92** allows for a favorable dipole-dipole interaction. In molecular orbital terms, the anomeric effect is attributed to an interaction between the lone pair electrons on the heteroatom and the σ* orbital of the neighboring C-X bond (X = OR, Cl, CN, etc). Similar interactions in **92** between the lone pair on nitrogen and the σ* orbital of the C-CN bond would be expected to lower the energy of **92** relative to **93**. The formation of a single diastereomeric product in cycloaddition reactions of **71** is therefore consistent with

---

[68] Bonin, M.; Chiaroni, A.; Riche, C.; Beloeil, J.-C., Grierson, D. S.; Husson, H.-P. *J. Org. Chem.* **1987**, *52*, 382.

[69] For an excellent review of α-cyanopiperidines, see: *Piperidine. Structure, Preparation, Reactivity, and Synthetic Applications of Piperidine and its Derivatives*; Elsevier: Amsterdam, 1991; Chapter 8.

[70] For a review of the anomeric effect, see: Kirby, A. J. *The Anomeric Effect and Related Stereoelectronic Effects at Oxygen*; Springer-Verlag: Berlin, 1983.

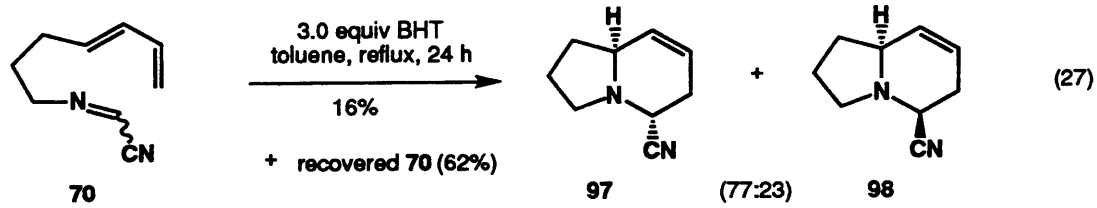
the initial formation of mixtures of products, followed by equilibration to form exclusively the lower-energy diastereomer **92**.

In our studies with **71**, we briefly examined the possibility of promoting the cycloaddition reaction using metal salts. In particular, we wondered whether reaction with silver (I) salts would generate a nitrilium ion intermediate that might then undergo Diels-Alder reaction under mild conditions. When **71** was reacted with silver triflate (1.05 equiv) in dichloromethane at -20 °C, however, a complex mixture of products was formed (as judged by tlc and NMR analysis). Reaction of **71** with silver nitrate (1.5 equiv) in dichloromethane at 0 °C resulted in the formation of polar baseline material (as judged by tlc). Although these initial studies were unsuccessful, further work in this area is warranted.

In summary, the alkyliminoacetonitrile substrate **71** reacts as desired in an intramolecular imino Diels-Alder reaction to provide cycloadduct **92** in good yield as a single diastereomer. The stereoselectivity of the reaction is attributed to either a highly *exo*-selective cycloaddition or, more likely, equilibration of diastereomers **92** and **93** under the reaction conditions to form the lower energy species **92**.

The next iminoacetonitrile substrate investigated was the diene **70**. This substrate differs from **71** only in the length of the connecting chain (three carbons vs. four carbons). Imine **70** was therefore expected to provide cycloadducts with the *indolizidine* ring system. When imine **70** was heated for 24 h in toluene (with 3 equiv of BHT) at reflux, two new products were observed. Although the tlc characteristics of these new spots were consistent with the desired product, the conversion was judged to be quite low (ca. 10-20% by tlc). When the reaction mixture was heated for another 24 h, however, a complex mixture was observed by tlc and a considerable amount of insoluble tar had covered the inside of the reaction flask. Similar results were obtained when the reaction was carried out in a sealed tube at 150 °C for 15 h. If the reaction was stopped after only 24 h at reflux

(toluene), a 16% yield of cycloadducts **97** and **98** could be obtained, along with 62% of unreacted **70** (eq 27). The stereochemical assignments shown below are based on the



coupling observed for H-1 in **97** and **98** (as in the assignment of **92**, Scheme 8). The signal for H-1 in the major product of the reaction is a doublet of doublets at 4.01 ppm with coupling constants of 7.0 and 1.3 Hz and is therefore most consistent with the *cis* indolizidine **97**. The signal for H-1 in the minor product is a doublet of doublets at 3.91 ppm with coupling constants of 8.1 and 4.9 Hz and is therefore most consistent with **98**.

The results of our preliminary studies with three-carbon substrate **70** suggest that its rate of cycloaddition is significantly lower than that of the homologous four-carbon substrate **71**.[71] This rather dramatic difference in reactivity was unexpected considering the seemingly minor differences between **70** and **71**. Furthermore, in their studies with iminium ion dienophiles, Grieco and co-workers observed *similar* rates for cycloadditions of substrates with three and four carbons in the connecting chain.[72] A comparison of three- and four-carbon substrates in reactions of *N*-acylimines[12a] is more difficult. The generation and subsequent reaction of these species was effected either by heating in a high-boiling solvent or by passage through a hot tube (pyrolysis) in the gas phase. The best method for *N*-acylimine formation varied by substrate, but no generalizations with respect to the length

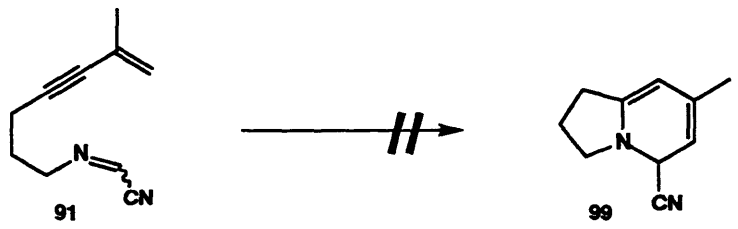
[71] After ca. 24 h in toluene at 115 °C, the cycloaddition of **71** is complete while the reaction of **70** has proceeded to only about 10-20% conversion.

[72] The three-carbon substrate gave a higher yield (95%) than the four-carbon substrate (65%) when each was reacted for 48 h at 50 °C, see: ref 13a.

of the connecting chain can be drawn.[73] In any event, no significant differences in rate were observed in three- and four-carbon *N*-acylimine substrates.

Whatever the reason for the sluggish reactivity of **70**, its instability to higher reaction temperatures and longer reaction times seriously limits the yield of cycloadduct that may be obtained under standard thermal reaction conditions. The reaction of this substrate at very high temperatures for very short time periods (as in hot-tube pyrolysis) might be a more promising approach to effecting cycloadditions in these substrates. Investigation of this possibility and further work with various acid and metal promoters is clearly needed.

The final substrate investigated was the *enyne* **91**. When this substrate was heated to 120 °C in a sealed tube in toluene (with 3 equiv of BHT) for 3 h, only starting material was observed by tlc. When the tube was heated to 150 °C for 24 h, a significant amount of insoluble tar was deposited on the inside of the sealed tube and a complex mixture of products was formed (as judged by tlc). Similar results were obtained when the reaction was conducted at 115 °C for 8 days. Analysis of these reaction mixtures by tlc and NMR

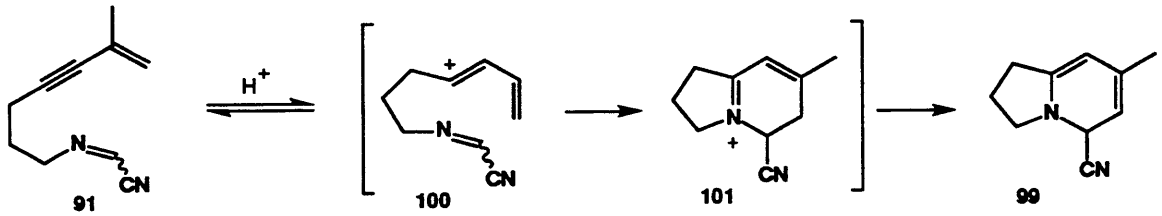


spectroscopy revealed small amounts of starting material along with other unidentified products, none of which were the desired cycloadduct **99**. Although the structure of these products could not be rigorously assigned, it appears that a majority of them possess an intact enyne moiety. It therefore seems that instability of the iminoacetonitrile group to prolonged reaction times and high reaction temperatures is responsible for the observed

[73] The only generalization made was that lower-molecular weight species tend to give better results with hot-tube pyrolysis.

decomposition. Since cycloaddition of the three-carbon *enyne* substrate **91** presumably has a higher activation energy than the three-carbon *diene* substrate **70**, it seems quite unlikely that the reaction of **91** could be activated thermally without destruction of the iminoacetonitrile dienophile.[74] Considering the greater reactivity of the four-carbon diene **71** (as compared to **70**), the investigation of a four-carbon *enyne* substrate is a high priority for future work.

In addition to thermal reactions of **91**, we briefly investigated the promotion of the desired cycloaddition reaction using protic acids. Methanesulfonic acid has been shown to promote a variety of enyne cycloaddition reactions.[4, 6] The likely mechanism of these reactions involves protonation of the enyne to generate a high energy vinyl cation which then reacts in a charge accelerated [4+2] cycloaddition reaction.[6] If a cationic diene (**100**)



were formed by reaction of **91** with acid, the subsequent cycloaddition should be facile since a much more stable iminium ion (**101**) is formed in the process. When a dichloromethane solution of **91** was treated with 2.5 equivalents of methanesulfonic acid, only polar baseline material was observed by tlc. NMR analysis of the reaction products showed oligomeric material, suggesting that cationic polymerization was occuring. It should be noted, however, that the reaction conditions employed in this preliminary work were quite harsh. Further investigation of other (milder) reaction conditions is needed.

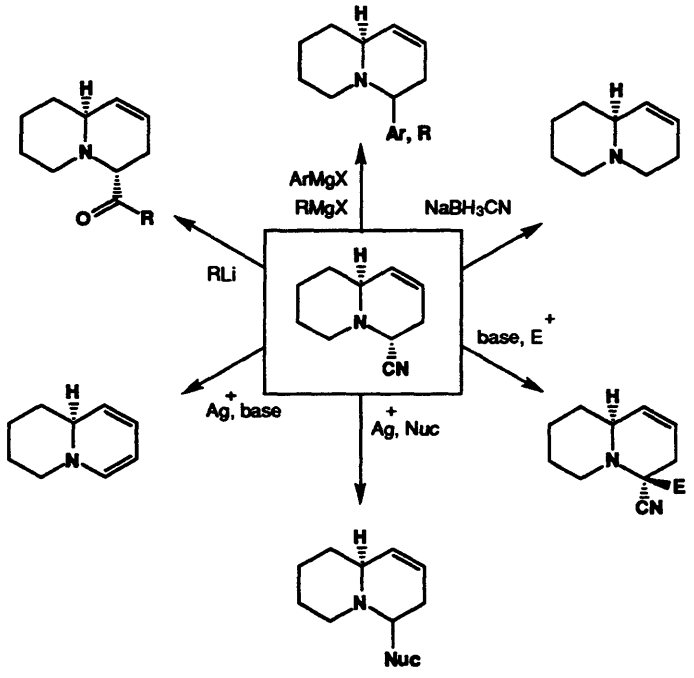
---

[74] The flash vacuum pyrolysis (FVP) of enyne **91** warrants investigation. Cycloadditions of all-carbon enynes using FVP has recently been demonstrated, see: Burrell, R. C.; Daoust, K. J.; Bradley, A. Z.; DiRico, K. J.; Johnson, R. P. *J. Am. Chem. Soc.* **1996**, *118*, 4218.

Conclusions

Alkyliminoacetonitriles have been shown to participate in intramolecular [4+2] cycloaddition reactions with dienes. Preliminary work suggests that this imine functional group has limited stability at temperatures much above 115 °C or in reactions that require prolonged heating. Nonetheless, these dienophiles show considerable promise for application in the synthesis of the quinolizidine ring system. The key iminoacetonitrile function is readily constructed in two steps from a primary amine and the quinolizidine products are obtained in good yield and with excellent diastereoselectivity. A significant advantage of these reactions as compared to cycloadditions of *N*-acylimines[12] and iminium[13] ions is the presence of an *α-cyanoamine* in the products. These iminium ion precursors have been shown to possess considerable synthetic utility.[69] Cycloadducts such as **92** should therefore be quite amenable to further synthetic elaboration (Scheme 10).

Scheme 10



In contrast, cycloaddition strategies involving iminium ion dienophiles appear to be quite limited with regard to the introduction of functionality at C-1. In *inter*molecular

cycloadditions, the use of acetaldehyde (in place of formaldehyde) for iminium ion formation gave low yields and produced undesired by-products in reaction with cyclopentadiene.[13a] The iminium species formed from acetone was completely unreactive in cycloadditions.[13a] To date, all of the reported *intra*molecular cycloadditions have involved unsubstituted iminium ion dienophiles derived from formaldehyde.

Reactions of *N*-acylimine[12] dienophiles result in products with lactam functionality. An *N*-acylimine possessing a carbomethoxy group at the imine carbon was used in the total synthesis of anhydrocannabisativene.[12e] It is therefore possible to introduce C-1 substitution in the products of these reactions. The generality of this approach with regard to alkyl or aryl substituents is unknown, however.

Iminoacetonitrile dienophiles show considerable promise in organic synthesis, although further investigation of these cycloaddition reactions is required. The identification of reaction conditions for the efficient cycloaddition of three-carbon-tethered diene and enyne substrates would be especially valuble. Further work will also be required to delineate the scope of the cycloaddition in more substituted derivatives. In particular, the stereoselectivity of the reaction with regard to substitution in the connecting chain should be addressed. Finally, it would be interesting to determine whether the use of *di*chloro- (or *di*alkoxy) acetonitrile[75] could provide direct access to iminoacetonitrile dienophiles. In principle, reaction of a primary amine with these compounds would generate the desired dienophiles in a single step, furthering the synthetic utility of these new cycloadditions.

---

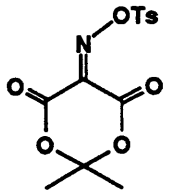
[75] These materials are commercially available although their use in iminoacetonitrile preparation has not been reported.

Part II

Synthesis of Nitrogen Heterocycles via Regiocontrolled [4+2] Cycloadditions of Oximinosulfonates

Chapter 1
Background and Introduction

Part II of this thesis details our investigation of *intermolecular* Diels-Alder reactions of oximinosulfonate **58**. We have found that this Meldrum's acid derivative reacts in a regioselective manner with a number of dienes to provide [4+2] cycloadducts that can be readily converted to substituted pyridines (Chapter 2). The application of this two-step annulation to the total synthesis of pyridine alkaloids is the subject of Chapter 3. Finally, Chapter 4 presents our studies of Steglitz-type rearrangements in [4+2] cycloadducts of **58**.



58

Chapter 1 of Part I reviewed the use of imino dienophiles in *intramolecular* Diels-Alder reactions. Here we present a survey of the literature pertaining to the use of imines and oximes as dienophiles in *intermolecular* Diels-Alder reactions. This discussion will not be comprehensive but will focus on the most synthetically useful methods that have been developed. For a discussion of more esoteric reactions and those that have very limited scope, the reader is directed to one of the many reviews that have been published.[8]

The body of literature describing pyridine synthesis is immense.[76] Of the various methods available for constructing pyridines, those based on cycloaddition reactions are particularly attractive due to their convergent nature. The review presented here will

[76] For a review of pyridine synthesis, see: Jones, G. In *Comprehensive Heterocyclic Chemistry*; Boulton, A. J., McKillop, A., Eds.; Pergamon: New York, 1984; Vol. 2, Part 2A, pp 395-510.

therefore focus only on methods involving the [4+2] cycloadditions of azadienes and azadienophiles.

Imino Dienophiles in the Diels-Alder Reaction

The use of imines as dienophiles in the Diels-Alder reaction has attracted considerable attention.[8] The most important classes of imino dienophiles are the *N*-sulfonylimines, *N*-acylimines, neutral imines activated by Lewis acids, and iminium ions. Each of these types of imino dienophiles will be discussed here separately, with a special emphasis on the scope of application and the regioselectivity of their reactions.

As in the more common Diels-Alder reactions of alkene and alkyne dienophiles, reactions of imino dienophiles involve the $HOMO_{diene}$ and $LUMO_{dienophile}$ frontier molecular orbitals (FMO).[77] The regioselectivity of these reactions is controlled by the FMO coefficients as shown below (Scheme 11).[78] The strongest interactions are predicted to be between the centers on the FMO that have the largest atomic coefficient. In Scheme 11, the shaded and unshaded circles represent the terminal FMO while the size of the circles corresponds to the relative size of the atomic coefficients. A larger atomic coefficient on carbon in the dienophile (as in **A**) would predict substitution patterns as in **102**, while a larger coefficient on nitrogen (**B**) would predict substitution as in **103** (Scheme 11). The great majority of imino dienophiles react to provide products with the substitution pattern corresponding to **102**.[79] Only in imines with *two* withdrawing groups on carbon does the alternate substitution pattern emerge (product **103**).

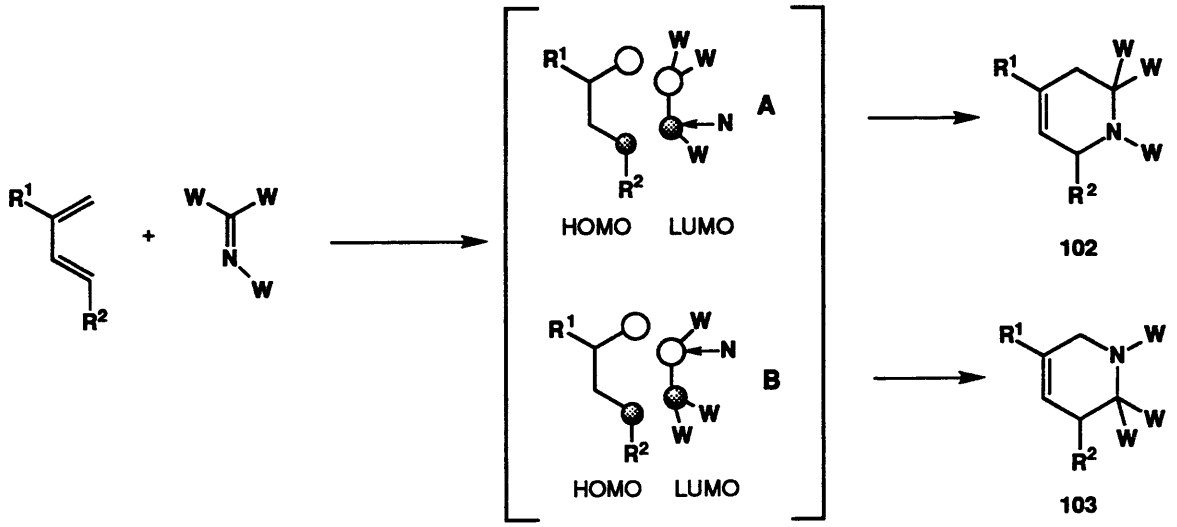
---

[77] (a) Desimoni, G.; Tacconi, G.; Barco, A.; Pollini, G. P. *Natural Products Synthesis Through Pericyclic Reactions*; ACS Monograph 180; American Chemical Society: Washington, D.C., 1983; pp 229-236. (b) FMO theory: Fukui, K. *Acc. Chem. Res.* **1971**, *4*, 57.

[78] (a) Houk, K. N. *J. Am. Chem. Soc.* **1973**, *95*, 4092. (b) Eisenstein, O.; Lefour, J. M.; Anh, N. T. *Tetrahedron* **1977**, *33*, 523.

[79] The atomic coefficients in the LUMO of imines have been calculated. The larger coefficient is found on carbon as expected from experimental results, see: (a) Lucchini, V.; Prato, M.; Scorrano, G.; Tecilla, P. *J. Org. Chem.* **1988**, *53*, 2251. (b) Jursic, B. S.; Zdravkovski, Z. *J. Chem. Soc., Perkin Trans. 2* **1994**, 1877.

Scheme 11

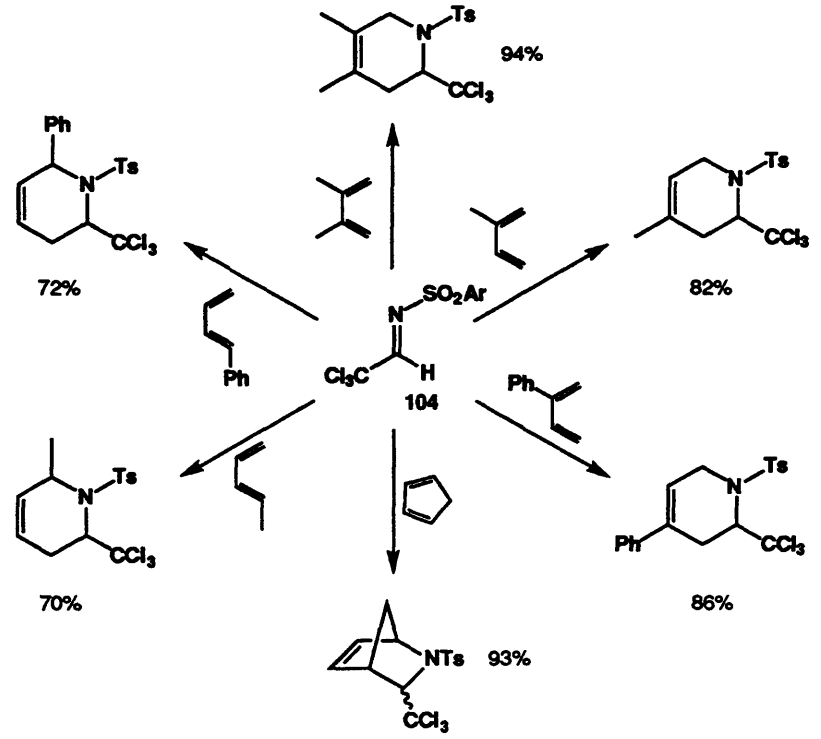


N-Sulfonylimines

Kresze and Albrecht's work on *N*-sulfonylimines represents one of the first systematic investigations of imino dienophiles.[80] The trichloromethyl (**104**) and trifluoromethyl derivatives described in this study were prepared by the condensation of an arylsulfonamide with chloral (or fluoral). These imines react with cyclic and acyclic dienes (in refluxing benzene) to provide cycloadducts in high yields and with excellent regioselectivity (Scheme 12). The major limitation of these dienophiles with regard to natural products synthesis appears to be the necessary incorporation of a trichloromethyl or trifluoromethyl group in the dienophile and consequently in the cyclic products. The conversion of these groups into more synthetically useful functionality can be tedious. For example, Speckamp[81] has reported a three-step sequence for the conversion of the trichloromethyl to a hydroxymethyl group. This sequence proceeds in unspecified overall

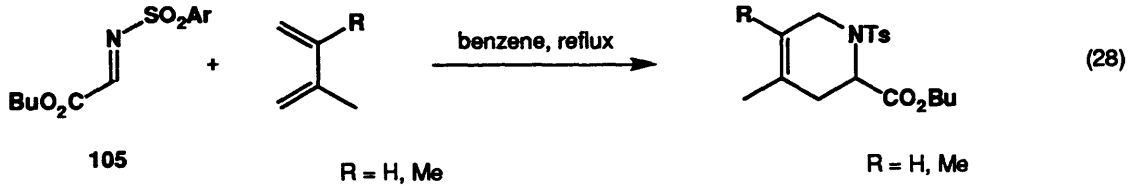
[80] (a) Kresze, G.; Albrecht, R. *Chem. Ber.* **1964**, *97*, 490. (b) Kresze, G.; Wagner, U. *Liebigs Ann. Chem.* **1972**, *762*, 106.
[81] Rijsenbrij, P. P. M.; Loven, R.; Wijnberg, J. B. P. A.; Speckamp, W. N.; Huisman, H. O. *Tetrahedron Lett.* **1972**, 1425.

Scheme 12



yield and involves a hydrogenation step that results in the reduction of the olefin as well as the trichloromethyl group.

Kresze and Albrecht also described the glyoxal-derived *N*-sulfonylimines **105**, a more synthetically useful class of imino dienophiles (eq 28).[82] The reactions of these



(28)

doubly-activated dienophiles proceed in refluxing benzene to give cycloadducts in good yields and with high regioselectivity.[83] Asymmetric versions of the reaction have recently

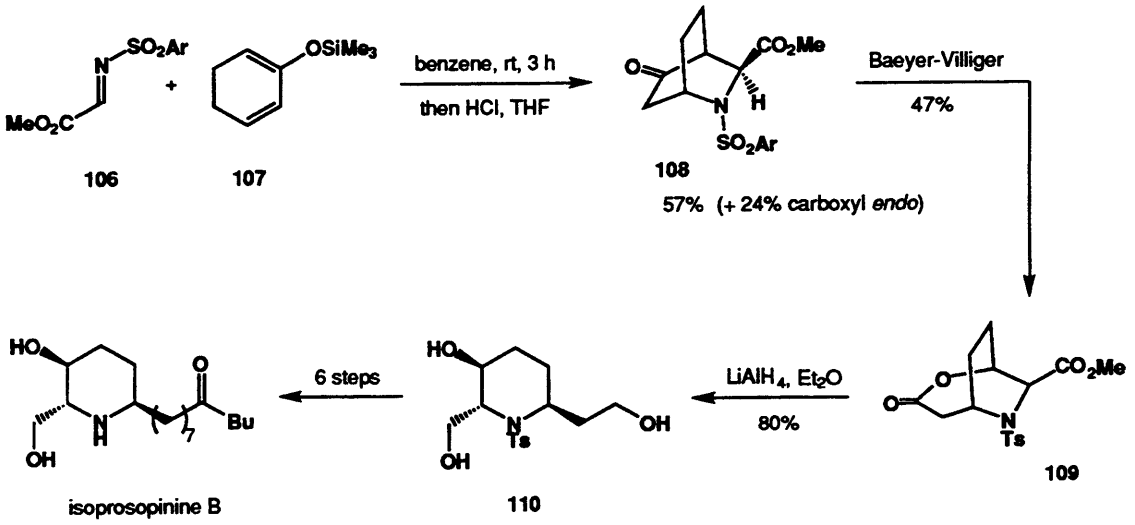
[82] Albrecht, R.; Kresze, G. *Chem. Ber.* **1965**, *98*, 1431.

[83] The chemistry of *N*-sulfonyl imines (including cycloadditions) has been recently reviewed, see: Weinreb, S. M. *Top. Curr. Chem.* **1997**, *190*, 131.

been reported using dienophiles derived from chiral amine[84] or glyoxylate[85] starting materials.

Diels-Alder reactions of *N*-sulfonylimines (**105**) have been used in the total synthesis of a number of natural products. [86] A particularly nice example of this work is Holmes' clever synthetic route to the natural product (±)-isoprosopinine B (Scheme 13).[86a] The key Diels-Alder reaction between imine **106** and the activated cyclohexadiene **107** proceeded at *room temperature* to give, after hydrolysis, the bridged cycloadduct **108** as a single regioisomer but as a 70:30 mixture of *exo* and *endo* stereoisomers. Baeyer-Villiger oxidation of the major stereoisomer provided the ring-expanded product **109**. Reduction of both carbonyl groups in **109** produced the key triol **110** which possesses the complete cyclic skeleton and correct relative stereochemistry of isoprosopinine B. The Diels-Alder

Scheme 13



[84] (a) Stella, L.; Abraham, H. *Tetrahedron Lett.* **1990**, *31*, 2603. (b) Bailey, P. D.; Wilson, R. D.; Brown, G. R. *J. Chem. Soc., Perkin Trans. 1* **1991**, 1337.

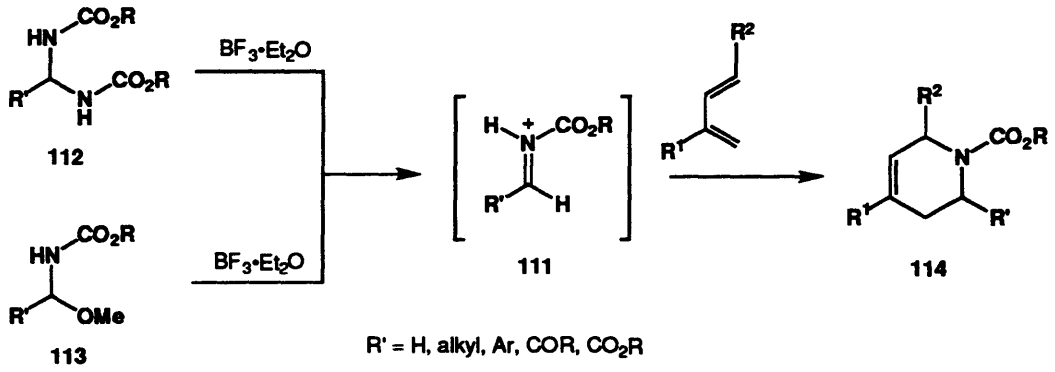
[85] Hamley, P. H.; Helmchen, G.; Holmes, A. B.; Marshall, D. R.; MacKinnon, J. W. M.; Smith, D. F.; Ziller, J. W. *J. Chem. Soc., Chem. Commun.* **1992**, 786.

[86] (a) Holmes, A. B.; Thompson, J.; Baxter, A. J. G.; Dixon, J. *J. Chem. Soc., Chem. Commun.* **1985**, 37. (b) Maggini, M.; Prato, M.; Scorrano, G. *Tetrahedron Lett.* **1990**, *31*, 6243. (c) Hamada, T.; Zenkoh, T.; Sato, H.; Yonemitsu, O. *Tetrahedron Lett.* **1991**, *32*, 1649.

reaction of **106** with **107** served to install the piperidine ring of isoprosopinine B while simultaneously setting the correct relative stereochemistry at three stereocenters (albeit with modest selectivity at one stereocenter). This example nicely illustrates the power of imino Diels-Alder reactions for the synthesis of complex heterocyclic structures.

N-Acylimines

A variety of imines activated on nitrogen by ketone and ester groups have been shown to react as dienophiles in Diels-Alder reactions. Both neutral *N*-acylimines and *N*-



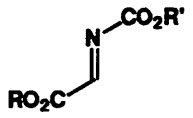
acyliminium ions have been reported. The iminium species (**111**) are generated *in situ* from biscarbamates (**112**) or α-alkoxycarbamates (**113**) by reaction with BF_3•Et_2O in refluxing benzene or diethyl ether.[87] As with *N*-sulfonylimines, the reactions of *N*-acylimines generally display high regioselectivity for products (**114**) possessing substitution patterns analogous to **102** (Scheme 11).

In addition to *N*-acyliminium species, a variety of *neutral N*-acylimines (**115-117**) have also been shown to participate in Diels-Alder reactions.[88] These imines are prepared

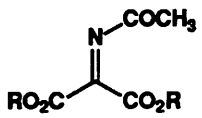
[87] (a) Merten, R.; Muller, G. *Angew. Chem.* **1962**, *74*, 866. (b) Merten, R.; Muller, G. *Chem. Ber.* **1964**, *97*, 682. (c) Baldwin, J. E.; Forrest, A. K.; Monaco, S.; Young, R. J. *J. Chem. Soc., Chem. Commun.* **1985**, 1586. (d) Fischer, G.; Frits, H.; Prinzbach, H. *Tetrahedron Lett.* **1986**, *27*, 1269.

[88] (a) Jung, M. E.; Shishido, K.; Light, L.; Davis, L. *Tetrahedron Lett.* **1981**, *22*, 4607. (b) von der Brück, D.; Bühler, R.; Plieninger, H. *Tetrahedron* **1972**, *28*, 791.

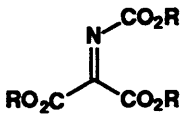
from glyoxylates (for **115**) or oxomalonates (**116** and **117**) using aza-Wittig methodology. As one might expect, imines **115-117** are generally less reactive than



115



116



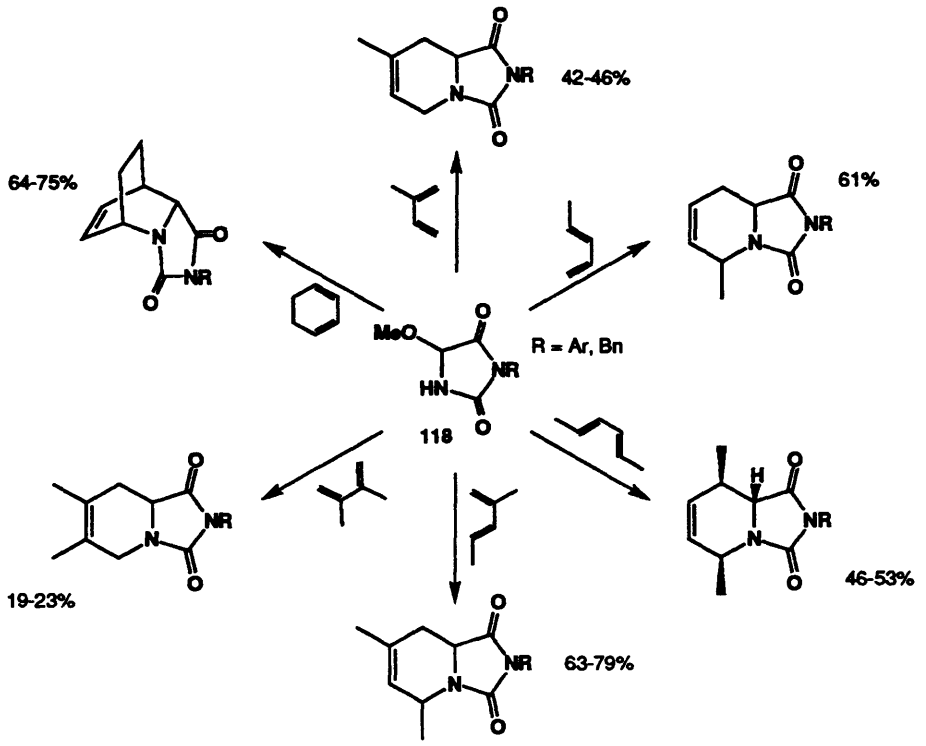
117

N-acyliminium ions. For example, imine **115** was reactive only with Danishefsky's diene and other electron-rich dienes.[88a] The triply-activated diene **116** also shows poor reactivity and gives a mixture of regioisomeric products in reactions with Danishefsky's diene.[88a] This regiochemical ambiguity presumably arises from atomic coefficients of similar magnitude on carbon and nitrogen in the LUMO of these dienophiles (**116**). Finally the triester **117** was also a rather poor dienophile in Diels-Alder reactions, requiring high temperatures and high pressure in reactions with acyclic dienes.[88b]

In addition to the *N*-acylimines discussed above, a number of *cyclic N*-acylimines have been described. The most extensive studies have been carried out with imino dienophiles derived from 5-methoxyhydantoins (**118**).[89] Reaction of **118** with dienes in toluene at 170 °C results in the formation of cycloadducts in modest to good yields and with high regioselectivity (Scheme 14). The reactive dienophile in these cycloadditions is presumably the dehydrohydantoin, formed *in situ* from **118** by elimination of methanol. The stereoselectivity of the reaction is of some interest since high selectivity for the *exo* product is often observed. This selectivity most likely results from thermodynamic control since *endo* selectivity is observed at lower reaction temperatures. These reactions can also be performed in refluxing benzene in the presence of naphthalenesulfonic acid, though yields are considerably lower under these conditions. Although four equivalents of diene

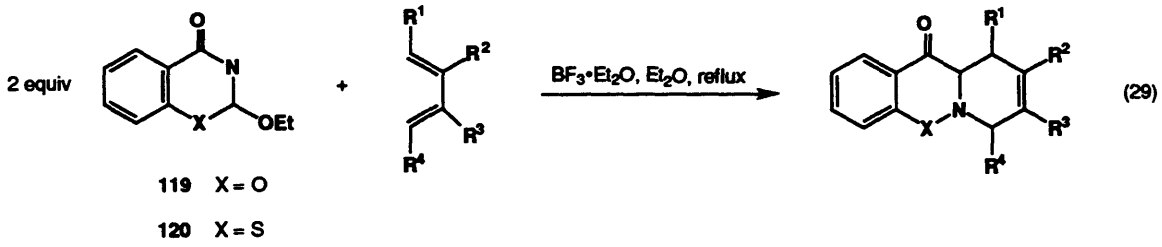
[89] (a) Goldstein, E.; Ben-Ishai, D. *Tetrahedron Lett.* **1969**, 2631. (b) Ben-Ishai, D.; Goldstein, E. *Tetrahedron* **1971**, *27*, 3119.

Scheme 14



were used in reactions with **118** (Scheme 14), it is unclear whether this is *required.* Obviously, the utility of any reaction is greatly diminished if the use of a large excess of one (potentially complex) reactant is required.

Other cyclic *N*-acylimines that have been employed in Diels-Alder reactions include the benzoxazinone **119** and the benzothiazinone **120**.[90] In the case of **119** and **120**, an *N*-acyliminium species is generated by reaction with $BF_3{\cdot}Et_2O$ in refluxing diethyl ether (eq 29). Unlike the hydantoin **118**, reactions of **119** and **120** under *thermal* conditions

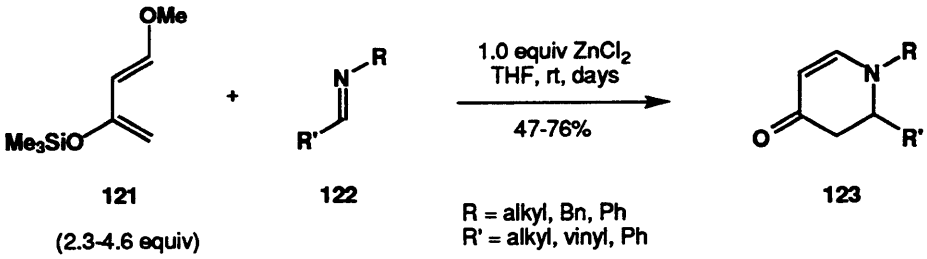


[90] (a) Ben-Ishai, D.; Warshawsky, A. *J. Heterocycl. Chem.* **1971**, *8*, 865. (b) Ben-Ishai, D.; Gillon, I.; Warshawsky, A. *J. Heterocycl. Chem.* **1973**, *10*, 149.

returned only complex mixtures. Reaction of **119** or **120** with highly substituted dienes provides good to excellent yields of cycloadducts with excellent regioselectivity (substitution patterns corresponding to **102** are observed). Unfortunately, reaction of **119** and **120** with less substituted dienes like isoprene and penta-1,3-diene gave only complex mixtures. The scope of these reactions is therefore quite limited.

Neutral Imines

In 1982, Kerwin and Danishefsky reported that simple alkyl and aryl-substituted imines (**122**) react with Danishefsky's diene (**121**) at *room temperature* in the presence of $ZnCl_2$ (1 equiv).[91] As shown in equation 30, the products of the reaction are vinylogous amides (**123**), formed by hydrolysis of the initial cycloadducts (presumably during the work-up or upon purification by column chromatography). The yields are modest to good and the regioselectivity is excellent. A disadvantage of this method is the requirement that excess (2.3-4.6 equiv) diene be used to obtain optimal yields in the reaction.[92] Also,



(30)

neutral imines **122** react only with highly activated dienes (such as **121**). The use of *cyclic* imines in the reaction was subsequently reported by Vacca[93] and Danishefsky,[94] and allows the construction of polyheterocyclic systems (eq 31).

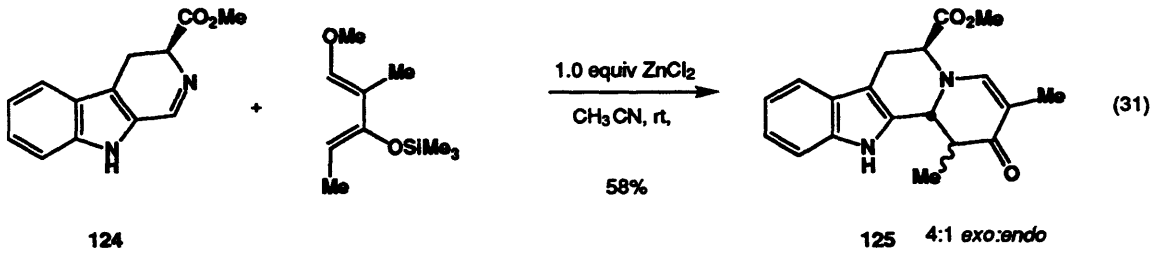
---

[91] Kerwin, J. F.; Danishefsky, S. *Tetrahedron Lett.* **1982**, *23*, 3739.

[92] For example, the use of 1.1 equivalents of diene **121** led to yields 15-30% lower than those obtained when a larger excess was used (eq 30).

[93] Vacca, J. P. *Tetrahedron Lett.* **1985**, *26*, 1277.

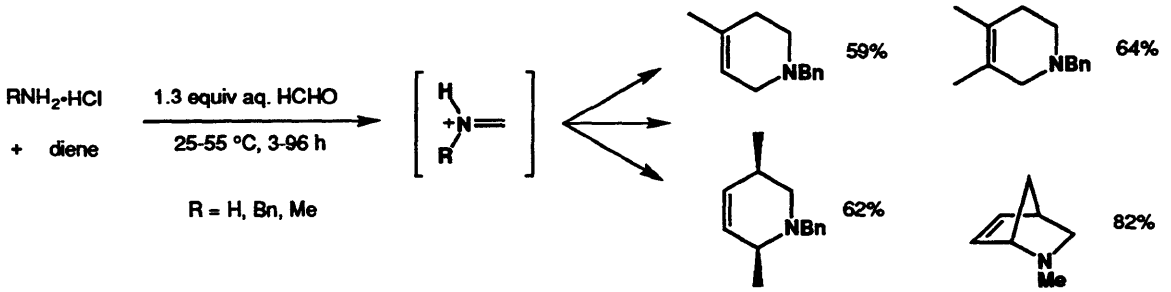
[94] Danishefsky, S.; Langer, M.; Vogel, C. *Tetrahedron Lett.* **1985**, *26*, 5983.



124 125 4:1 *exo:endo*

Iminium Ions

Grieco and co-workers have demonstrated that iminium ions, generated in aqueous solution under Mannich-like conditions, react with dienes in Diels-Alder reactions.[95] The iminium ion dienophile is generated by the reaction of a primary amine with aqueous formaldehyde, or alternatively, by reaction of an aldehyde with ammonium chloride solution. As shown below, the reaction is successful with cyclic and acyclic dienes and the yields are good. The regioselectivity of the reaction is high, favoring products with substitution patterns analogous to **102**. Unfortunately, iminium ions derived from higher aldehydes are generally much less reactive in Diels-Alder reactions.[96] As discussed in Chapter 1 of Part I, the *intramolecular* version of this reaction has been used to prepare polycyclic heterocycles, including several natural products.[13]



[95] (a) Larsen, S. D.; Grieco, P. A. *J. Am. Chem. Soc.* **1985**, *107*, 1768. (b) Grieco, P. A.; Larsen, S. D.; Fobare, W. F. *Tetrahedron Lett.* **1986**, *27*, 1975.

[96] Iminium ions derived from acetaldehyde gave low yields while those derived from acetone were completely unreactive. However, the use of lanthanide(III) trifluoromethanesulfonates as catalysts in these reactions has recently been shown to significantly increase the reactivity of alkyl-substituted iminium ion dienophiles, see: Yu, L.; Chen, D.; Wang, P.-G. *Tetrahedron Lett.* **1996**, *37*, 2169.

In summary, a variety of imino dienophiles have been used in the Diels-Alder reaction. Simple alkyl and aryl imines must be activated by Lewis acids or by the formation of an iminium ion species. Imines activated by acyl or sulfonyl groups are often reactive enough to participate in Diels-Alder reactions with thermal activation (no Lewis or protic acids required). In some cases, however, even these activated imines react only with the more reactive classes of electron-rich dienes. In essentially all cases, the regioselectivity of the reaction is high and favors products with substitution "ortho" and "para" to nitrogen (**102**, Scheme 11). This regioselectivity can be understood in molecular orbital terms by assuming a larger atomic coefficient on *carbon* in the LUMO of imino dienophiles (**A**, Scheme 11).[79] As we shall see, doubly-activated *oximino* dienophiles react to provide the opposite substitution pattern (**103**, Scheme 11) and are therefore complementary to imino dienophiles for use in the Diels-Alder reaction.

Oximino Dienophiles in the Diels-Alder Reaction

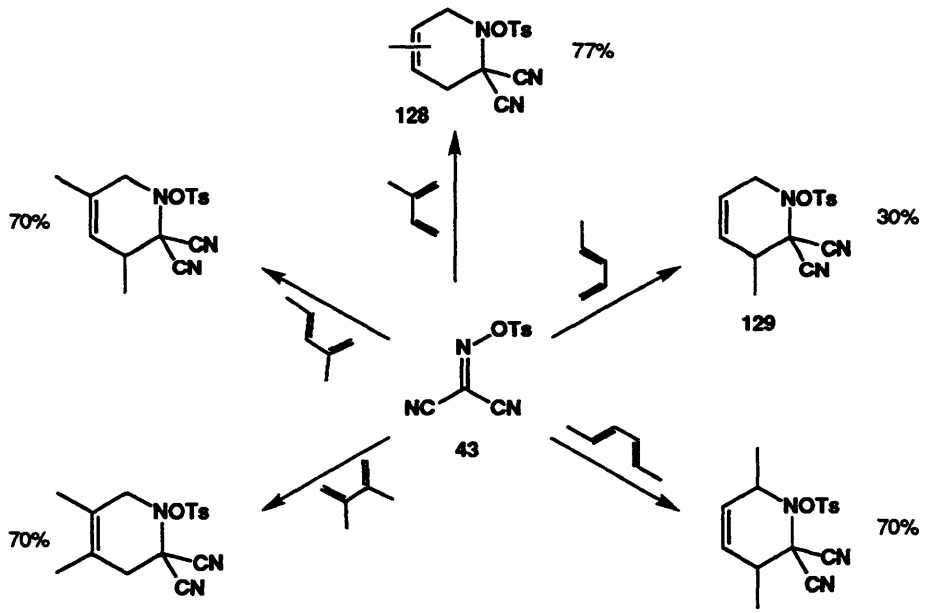
In comparison to imines, oximes have attracted far less attention as dienophiles in the Diels-Alder reaction. In fact, nearly all the work in this area has been reported by a single research group. In the early 1970s, Fleury and co-workers described the synthesis of a variety of oximino esters from the corresponding malonate derivatives.[19] As shown below, a number of these oximes were found to react with cyclopentadiene in Diels-Alder

126 127

R^1	R^2	R^3	conditions	Yield (%)
CN	CN	Ts	ether, 20 °C	88
CN	CN	Bz	ether, 20 °C	80
CN	CO_2Et	Ts	ether, 20 °C	61
CO_2Et	CO_2Et	Ts	acetone, 60 °C	0

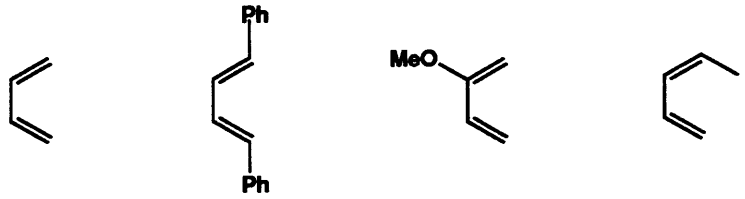
reactions.[34] The most reactive dienophiles are those substituted with two nitrile groups on carbon. Following these studies with cyclopentadiene, the Fleury group reported on the reactivity of oximino*tosylate* **43** (i.e., **126**, R^1, R^2 = CN; R^3 = Ts) in Diels-Alder reactions with *acyclic* dienes.[97] As shown in Scheme 15, this dienophile (**43**) reacts with a number of dienes in refluxing benzene to provide the expected cycloadducts. The yield in many cases is quite good, although the reaction with 1,3-pentadiene provides cycloadduct **129** in only 30% yield. Significantly, the regioselectivity of the reaction is opposite to that obtained with imine dienophiles. Substitution patterns corresponding to **103** (Scheme 11) are observed, suggesting that the larger atomic coefficient lies on *nitrogen* in the LUMO of oximino dienophiles such as **126**. It should be noted, however, that the reaction of **43** with isoprene produces a mixture of regioisomeric products **128**. Since reactions with other 2-substituted dienes were not reported, the regioselectivity of oximinosulfonate **43** in Diels-Alder reactions remains somewhat dubious.

Scheme 15

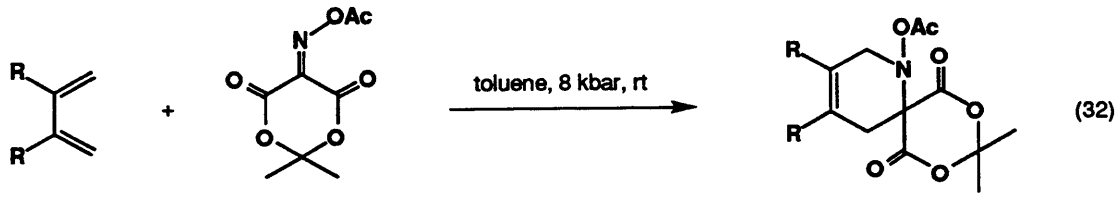


[97] Fleury, J.-P.; Desbois, M.; See, *J. Bull. Soc. Chim. Fr.* **1978**, II-147.

All of the reactions in Scheme 15 were carried out using three equivalents of diene, except for the reaction with isoprene (ca. 10 equiv of diene was used). This represents a potential limitation of the method, although it is unclear whether the use of excess diene is required. Another serious limitation is the instability of dienophile **43** above 90 °C. This instability precludes the use of forcing reaction conditions and consequently limits the scope of the cycloaddition to include only those dienes that react below 90 °C. The dienes shown below, for example, were unreactive with **43** in refluxing benzene (ca. 80 °C).



The first example of an oximino dienophile derived from Meldrum's acid was the acetate **132** reported by Katagiri in 1994.[98] The only Diels-Alder cycloadditions reported for this oxime were those with 2,3-dimethylbutadiene (**130**), 2,3-dimethoxybutadiene (**131**), and cyclopentadiene (eq 32). The reaction with cyclopentadiene was carried out at



(32)

130 R = Me

131 R = MeO

132

133 R = Me 68%

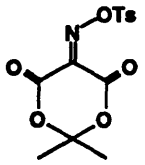
134 R = MeO 62%

room temperature in benzene or with no solvent. Reaction of this oxime with dienes **130** and **131** required high pressure (8 kbar, toluene, rt), providing cycloadducts **133** and **134**

[98] Katagiri, N.; Nochi, H.; Kurimoto, A.; Sato, H.; Kaneko, C. *Chem. Pharm. Bull.* **1994**, *42*, 1251.

in 68% and 62% yield, respectively. The regioselectivity of the reaction is uncertain since no unsymmetrical dienes were studied.

The work of Fleury and Katagiri represented the state of the art for oximino dienophiles when we began our investigations with the oximinosulfonate **58**. We expected



58

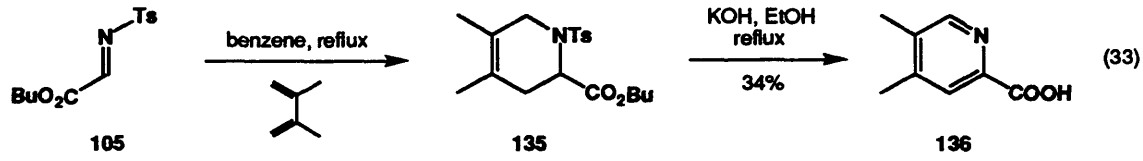
this doubly-activated oximino dienophile to provide access to [4+2] cycloadducts with regiochemistry opposite (and complementary) to that of cycloadducts prepared from imine dienophiles. We also expected that **58** would be subject to Lewis-acid promotion and might therefore have advantages over other oximino dienophiles (**43** and **132**) with regard to reactivity and regioselectivity.

[4+2] Cycloadditions in Pyridine Synthesis

Herein we present a brief overview of the existing [4+2] cycloaddition strategies for pyridine synthesis. The purpose of this review is to provide a context within which the pyridine annulation described in Chapter 2 may be evaluated. The review will be presented in two sections covering, respectively, those strategies that employ an azadienophile in the cycloaddition, and those that employ an azadiene.

Azadienophiles

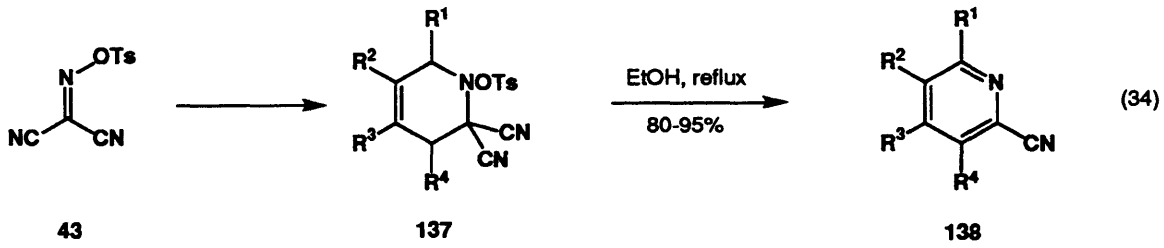
The first example of pyridine synthesis involving the cycloaddition of an azadienophile was reported by Kresze with the *N*-tosylimine **105**.[82] Reaction of **105** with 2,3-dimethylbutadiene provided the cycloadduct **135** in unspecified yield (eq 33). Aromatization of this tetrahydropyridine was accomplished by treatment with KOH in



(33)

refluxing ethanol to provide the picolinic acid derivative **136** in low yield. The mechanism of this conversion presumably involves the elimination of sulfinic acid from **135** to provide a dihydropyridine which then undergoes disproportionation to give the observed pyridine **136**. It is likely that the yield of this reaction could be improved by the use of an oxidizing agent in the aromatization step.

In their work with oximinosulfonate **43**, Fleury and co-workers found that the cycloadducts obtained from **43** could be easily converted to pyridines (eq 34). Simply

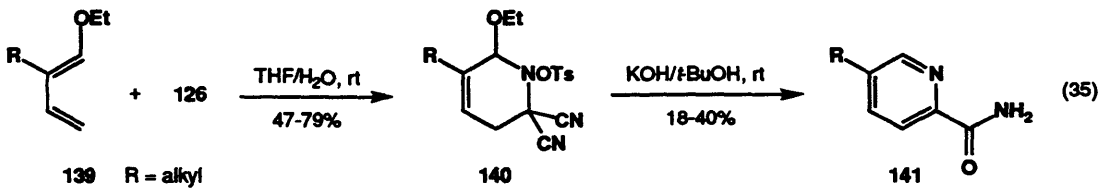


(34)

refluxing cycloadducts **137** in ethanol induces elimination of HCN and TsOH to provide the pyridines **138** in excellent yields.[97]

Breitmaier reported the reaction of alkoxy dienes **139** with the oximinotosylate **43** developed by Fleury (*vide supra*).[99] The Diels-Alder reaction was carried out in THF/H_2O at room temperature to give the products **140** in modest to good yield (eq 35). These cycloadducts were then converted to pyridines **141** in low yield by treatment with KOH in *t*-BuOH. The basic conditions used in this step are also responsible for hydrolysis of the nitrile substituent to an amide (**141**). The utility of this method is seriously limited by the

[99] Dormagen, W.; Rotscheidt, K.; Breitmaier, E. *Synthesis* **1988**, 636.



low yields obtained in the aromatization step, and the rather long synthetic sequence required to prepare dienes **139**.

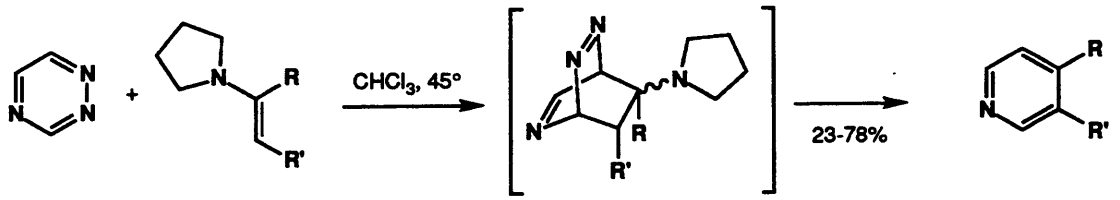
Of these three pyridine annulations, that reported by Fleury is clearly the most attractive. The most serious limitations of this method stem from the rather low reactivity and dubious regioselectivity observed in reactions of the dinitrile **43** with dienes.

Azadienes

The use of azadiene cycloadditions in pyridine synthesis has been investigated to a much greater extent than have reactions of aza-dienophiles. Both cyclic and acyclic azadienes have been used in various types of Diels-Alder reactions to provide pyridine or tetrahydropyridine products. A complete review of these reactions is beyond the scope of the discussion here. We will therefore focus on reactions of the cyclic 1,2,4-triazine system, and some important reactions utilizing acyclic azadienes. For a comprehensive review of heterocyclic azadienes in pyridine synthesis, the reader is directed to several excellent review articles.[100]

Among the various heterocyclic azadienes that have been used for pyridine synthesis, the 1,2,4-triazines[101] are perhaps the most useful. These heterocycles react in inverse electron demand Diels-Alder cycloadditions with a variety of electron rich alkenes. The reaction of 1,2,4-triazine (**142**) with a variety of different *enamines* (**143**) is illustrated below.[101f] The initially formed bridged cycloadduct **144** undergoes a retro Diels-Alder

[100] (a) Boger, D. L. *Chem. Rev.* **1986**, *86*, 781. (b) Boger, D. L. *Bull. Soc. Chim. Belg.* **1990**, *90*, 599.
[101] (a) Dittmar, W.; Sauer, J.; Steigel, A. *Tetrahedron Lett.* **1969**, 5171. (b) Burg, B.; Dittmar, W.; Reim, H. Steigel, A.; Sauer, J. *Tetrahedron Lett.* **1975**, 2897. (c) Muller, K.; Sauer, J. *Tetrahedron Lett.* **1984**, *25*, 2541. (d) Neunhoeffer, H.; Frühauf, H.-W.; *Liebigs Ann. Chem.* **1972**, *758*, 120. (e) Neunhoeffer, H.; Werner, G. *Liebigs Ann. Chem.* **1973**, 1955. (f) Boger, D. L.; Panek, J. S. *J. Org. Chem.* **1981**, *46*, 2179.



142 143 R, R' = alkyl, cycloalkyl 144 145

reaction (loss of nitrogen), followed by elimination of pyrrolidine to provide the pyridine products (**145**). The yields are quite good in most cases and the regioselectivity is excellent. Because enamines are available from simple ketones, a wide variety of different pyridines, including polycyclic systems, can be constructed using this methodology. The use of *unsymmetrical* ketones would of course require the selective formation of one enamine in order to avoid the formation of mixtures of pyridine products.

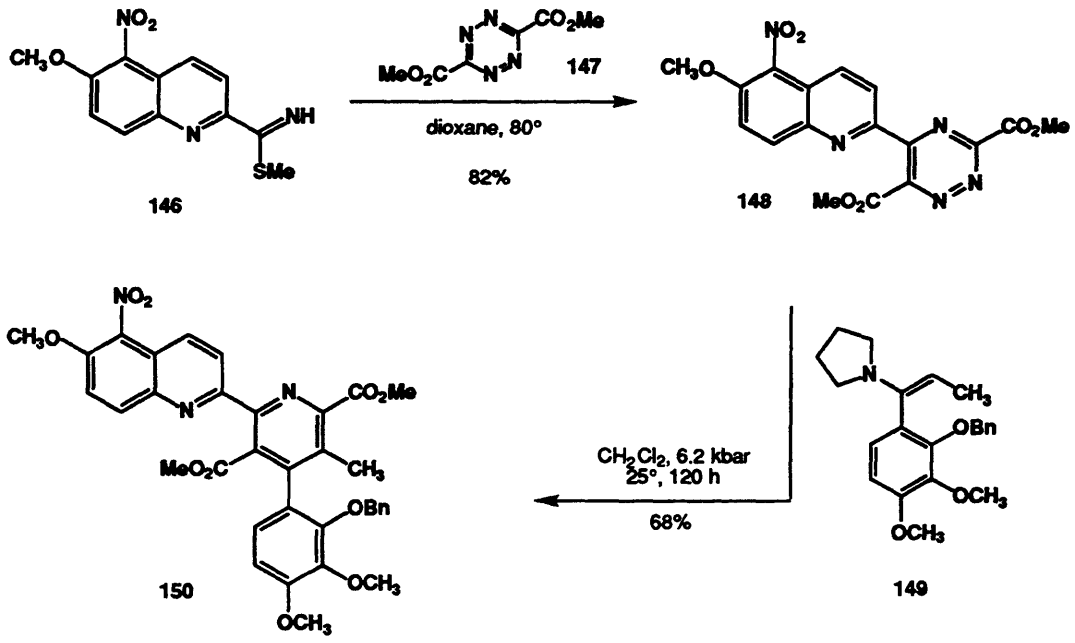
Boger and co-workers have used 1,2,4-triazines[102] for the construction of pyridine rings in complex, highly-substituted natural products.[103] A particularly elegant example of this work is found in Boger's formal synthesis of streptonigrin (Scheme 16).[103a] An inverse electron demand Diels-Alder reaction between the thioimidate **146** and a 1,2,4,5-*tetrazine* (**147**) provides the 1,2,4-triazine **148**. A second Diels-Alder reaction between the triazine **148** and enamine **149** then produces the pyridine **150**, an advanced streptonigrin intermediate. This synthetic sequence is noteworthy for its convergency. Two successive azadiene Diels-Alder reactions serve to join **146** and **149** to form the central pyridine ring of **150**. The Diels-Alder reaction of 1,2,4-triazines is clearly a powerful strategy for the construction of highly substituted pyridines.

---

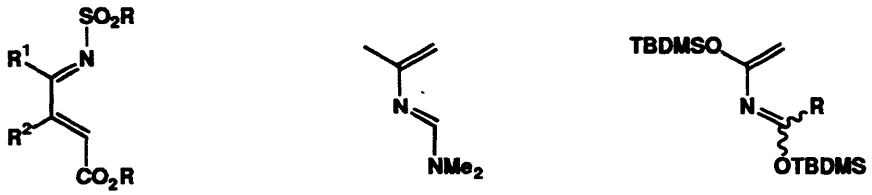
[102] Substituted 1,2,4-triazenes are most commonly prepared by the condensation of a diketone or glyoxylate with an amidrazone. Alkyl, aryl, and heteroaryl-substituted 1,2,4-triazenes can be prepared in this fashion although mixtures of products are obtained when unsymmetrical diketones are employed. For a review of the preparation of 1,2,4-triazenes, see: Neunhoeffer, H.; Wiley, P. F. *Chem. Heterocycl. Compound.* **1978**, *33*, 189.

[103] (a) Boger, D. L.; Panek, J. S. *J. Am. Chem. Soc.* **1985**, *107*, 5745. (b) Boger, D. L.; Duff, S. R.; Panek, J. S.; Yasuda, M. *J. Org. Chem.* **1985**, *50*, 5782. (c) see also ref 100b and references cited therein.

Scheme 16



Compared to cyclic azadienes, the *acyclic* derivatives represent a more recent development in organic synthesis. Progress in this area has been slowed by the tendency of azadienes to undergo tautomerization to enamines or nucleophilic addition. These problems have been partially resolved in the α,β-unsaturated imines shown below. The

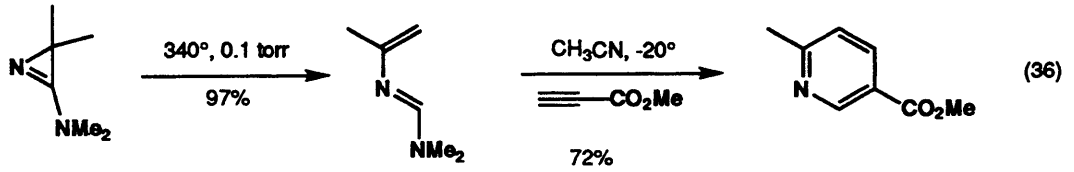


introduction of electron withdrawing groups (as in **151**) activates the azadiene for reaction with electron-rich alkenes and disfavors tautomerization to the enamine.[104] The addition of

[104] (a) Boger, D. L.; Curran, T. T. *J. Org. Chem.* **1990**, *55*, 5439. (b) Boger, D. L.; Corbett, W. L.; Curran, T. T.; Kasper, A. M. *J. Am. Chem. Soc.* **1991**, *113*, 1713. (c) Boger, D. L.; Nakahara, S. *J. Org. Chem.* **1991**, *56*, 880.

electron-donating groups (as in **152** and **153**) serves to activate the azadiene for reaction with electron-deficient alkenes while deactivating the imine toward nucleophilic attack.[105]

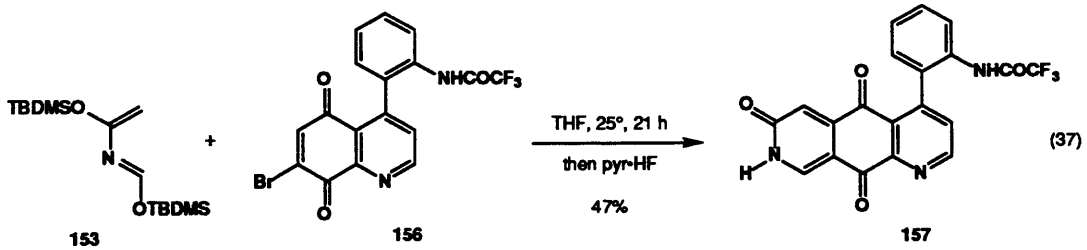
The azadiene **152** is generated in excellent yield from the azirine **154** by vacuum thermolysis (eq 36).[105a] The reaction of **152** with methyl propiolate generates a dihydropyridine cycloadduct which then undergoes elimination of dimethylamine to afford the pyridine **155** in good yield. The dimethylamino group in **152** therefore serves to both activate the azadiene and then, after cycloaddition, to facilitate aromatization. Although



154 152 155 (36)

152 displays good reactivity and regioselectivity, this method is limited by the need to prepare the azirine precursor **154** (a four-step synthesis). Furthermore, the preparation of azirines **154** possessing two *different* alkyl groups would presumably give mixtures of azadienes **152**.

The more readily available siloxy-substituted azadiene **153**, also introduced by Ghosez, reacts regioselectively with acetylenic dienophiles to provide, after hydrolysis, pyridone products.[105c] This diene was used by Stille in the synthesis of amphimedine, as shown below (eq 37).[105d] The cycloaddition of **153** with bromoquinone **156** proceeded at

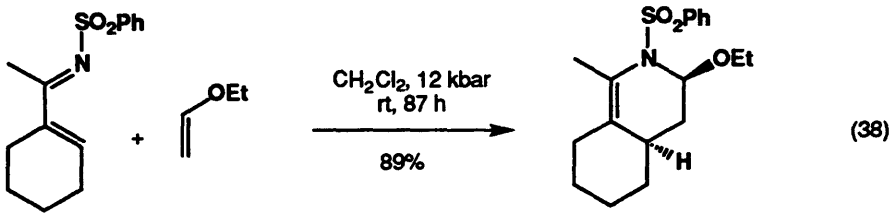


153 156 157 (37)

[105] (a) Demoulin, A.; Gorissen, H.; Hesbain-Frisque, A.-M.; Ghosez, L. *J. Am. Chem. Soc.* **1975**, *97*, 4409. (b) Sainte, F.; Serckx-Poncin, B.; Hesbain-Frisque, A.-M.; Ghosez, L. *J. Am. Chem. Soc.* **1982**, *104*, 1428. (c) Bayard, P.; Ghosez, L. *Tetrahedron Lett.* **1988**, *29*, 6115. (d) Echavarren, A. M.; Stille, J. K. *J. Am. Chem. Soc.* **1988**, *110*, 4051.

room temperature to afford the pyridone **157** which was converted to amphimedine in two steps. The scope of these reactions has been expanded to include azadienes **153** in which the terminal siloxy substituent is replaced by a *t*-butyl or phenyl group. The use of simple alkyl groups in these positions has not been reported, however. Most likely, these azadienes would be subject to enamine tautomerization.

The *N*-sulfonyl azadienes developed by Boger (**151**) react regio- and stereoselectively in Diels-Alder reactions with electron-rich dienophiles. The reaction of **158** with ethyl vinyl ether (eq 38) illustrates several attractive features of this chemistry.[104b] When the reaction was carried out in dichloromethane at room temperature and high pressure,[106] the cycloadduct **159** was formed in 89% yield and with >20:1 stereoselectivity for the *endo* isomer. Also noteworthy is the fact that the azadiene does not suffer from



158 159 (38)

competing enamine tautomerization. Finally, the cycloadduct **159** possesses two leaving groups and could presumably be converted to the corresponding pyridine. Indeed, this methodology was used to prepare the pyridine ring of streptonigrone C. The conversion of the tetrahydropyridine cycloadduct to a fully aromatized pyridine was accomplished by reaction with *t*-BuOK in THF followed by treatment with DDQ in dichloromethane.[104c]

Summary

The Diels-Alder reaction of imino and oximino dienophiles with dienes represents a powerful strategy for the synthesis of nitrogen heterocycles. Significantly, these two

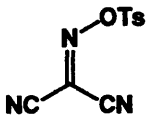
[106] The reaction can also be carried out at ambient pressure in refluxing toluene (79% yield, >20:1 endo).

classes of azadienophiles display complementary regioselectivity in their reactions with dienes. The *oximino* dienophiles have been much less investigated, however, and those systems that have been studied suffer from low reactivity and sometimes dubious regiochemistry. In the following chapter, we describe Lewis acid-promoted cycloadditions of oximinosulfonate **58** that are in many respects superior to existing synthetic methodology. The aromatization of these cycloadducts to substituted pyridines is also described. This two-step annulation comprises one of the few azadienophile-based strategies for pyridine synthesis.

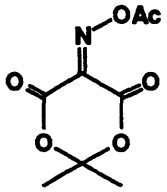
Chapter 2

Synthesis of Substituted Pyridines via Regiocontrolled Cycloadditions of Oximinosulfonates

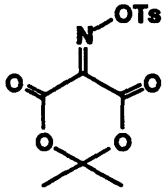
The use of imino and oximino dienophiles in the Diels-Alder reaction comprises a powerful strategy for the synthesis of nitrogen heterocycles. We became interested in investigating the reactivity of the previously unknown oximinosulfonate **58** as a dienophile in the Diels-Alder reaction. In these studies, we hoped to address the problems of low reactivity and dubious regioselectivity that plague the existing methodology (reactions of **43** and **132**).



43



132



58

We were optimistic that many of the drawbacks associated with the use of **43** and **132** could be eliminated by using the oximino dienophile **58**. This optimism was rooted in the following expectations regarding oximinosulfonate **58** and the cycloadducts formed from it:

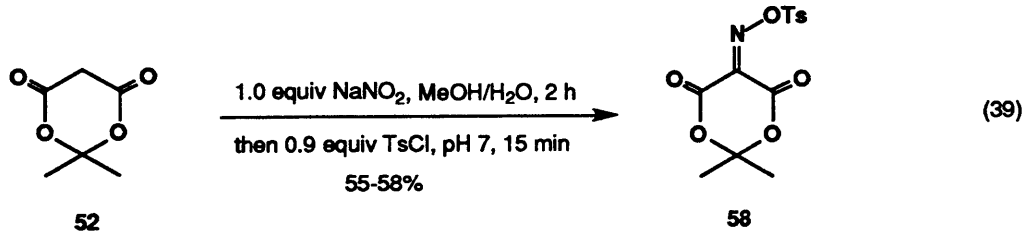
- Enhanced reactivity as compared to acyclic diesters
- Subject to Lewis acid promotion, thus providing a basis for high regioselectivity
- Cycloadducts amenable to further synthetic elaboration

Here we report our studies of the scope and regiochemical course of Diels-Alder reactions between oximinosulfonate **58** and dienes. These cycloadditions constitute the

first step of a new two-step annulation for the synthesis of substituted pyridines from dienes.

Synthesis of Oximinosulfonate 58

Our original studies with oximinosulfonate **58** involved its use as an electrophile in unsuccessful cuprate coupling reactions (Part I, Chapter 2). In these early studies, **58** was prepared from Meldrum's acid via the corresponding oxime silver salt **55**. During the course of our subsequent *cycloaddition* studies with **58**, a more convenient and economically attractive method for its preparation was sought. After some experimentation, we found that the preparation of **58** from Meldrum's acid (**52**) could be



52 **58** (39)

accomplished in *one step* (eq 39) without the involvement of a silver salt intermediate. The nitrosation[107] of Meldrum's acid (**52**) is carried out with $NaNO_2$ in methanol/H_2O for two hours at room temperature. The solution is neutralized[108] by the addition of pH 7 phosphate buffer and then treated with TsCl (0.9 eq). The sulfonylation occurs almost immediately, resulting in the precipitation of insoluble **58** from solution. The solid **58** is then collected by filtration, washed with cold methanol, and dried in a desiccator over P_2O_5. This simple procedure provides multi-gram quantities of **58** in good yield and high purity (no further purification is required). Oximinosulfonate **58** is an easily handled white solid (mp 155-156 °C) that can be weighed out in air and is stable for months when stored under argon in a refrigerator.

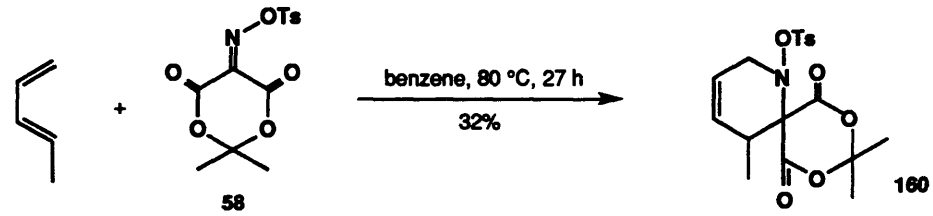
---

[107] Meldrum's acid (MA) is itself sufficiently acidic to catalyze the nitrosation reaction. For the first report of the nitrosation of MA, see: Eistert, B.; Geiss, F.; *Chem. Ber.* **1961**, *94*, 929.

[108] Neutralization before the addition of TsCl helps prevent the acid-promoted addition of methanol to **58** (a 35% yield is obtained without buffer).

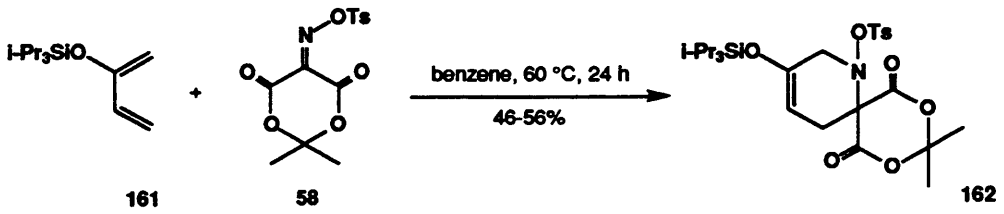
Cycloadditions of Oximinosulfonate 58 Under Thermal Conditions

We began our investigation by examining the reactivity of **58** with dienes under thermal conditions. When **58** was heated with penta-1,3-diene in refluxing benzene for 27 hours, the cycloadduct **160** was obtained in 32% yield as a single regioisomer (eq 40).



(40)

While we were pleased to find that oximinosulfonate **58** could indeed participate in Diels-Alder reactions, our enthusiasm was tempered by the low yield obtained. Furthermore, analysis of the reaction mixture by tlc indicated the formation of several side products, while NMR analysis of the crude reaction mixture suggested incomplete (ca. 60%) conversion of starting material. When longer reaction times or higher temperatures (refluxing toluene) were employed, however, a complex mixture of products was formed and none of the desired cycloadduct could be isolated. We therefore concluded that either oximinosulfonate **58** or the cycloadduct **160** was unstable under the reaction conditions. Indeed, when a purified sample of **160** was heated at reflux in benzene, a number of new compounds were produced (as judged by tlc) and a brown tar formed on the inside of the reaction flask. In contrast, no decomposition of the dienophile **58** was observed upon heating in refluxing benzene for 24 hours (tlc and NMR analysis). Believing that adventitious acid might be responsible for the instability of **160**, we investigated the use of acid scavengers such as collidine and polyvinylpyridine. Unfortunately, the use of polyvinylpyridine appeared to retard the rate of reaction while the use of collidine led to complex mixtures of products. The best results we obtained in *thermal* cycloadditions of **58** were in reactions with the siloxydiene **161** (eq 41). The higher yields obtained in this



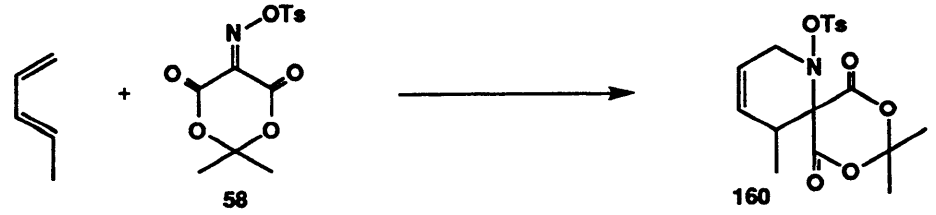
161 58 162 (41)

case are presumably due to the more reactive nature of **161** and the lower reaction temperatures employed.

Cycloadditions of Oximinosulfonate 58 With Protic and Lewis Acid Promotion

We next investigated the use of protic and Lewis acids in reactions of **58**, remembering that iminium ions and Lewis acid-coordinated imines are generally more reactive than the corresponding neutral imines (Chapter 1). Table 2 summarizes our initial studies of protic and Lewis acid-promoted reactions of **58** with penta-1,3-diene. Our familiarity with this reaction under thermal conditions (eq 40) facilitated the analysis (tlc and NMR) of these reaction mixtures (Table 2). When the reaction was carried out in

Table 2. Protic and Lewis acid Promoters in Reactions of 58.

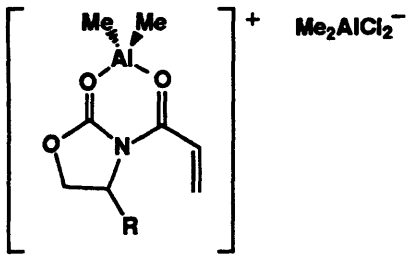


58 160

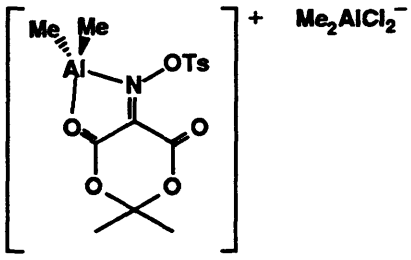
Promoter	Conditions	Results/Yields
Methanesulfonic acid	1.0 equiv, CH_2Cl_2, rt	no reaction, diene decomposition
Camphorsulfonic acid	1.0 equiv, CH_2Cl_2, rt	background reaction
$AlCl_3$	1.0 equiv, CH_2Cl_2, -50 °C to rt	no reaction, diene decomposition
$ZnCl_2$	1.0 equiv, THF, rt to 70 °C	complex mixture
$TiCl_4$	1.0 equiv, CH_2Cl_2, -78 °C to rt	no reaction at -78 °C, then decomposition
Me_2AlCl	1.4 equiv, CH_2Cl_2, -78 °C to 0 °C	39% isolated yield (incomplete conversion)
Me_2AlCl	**2.0 equiv, CH_2Cl_2, -78 °C, 2-4 h**	**75-78% isolated yield**

dichloromethane with one equivalent of methanesulfonic acid, only diene polymerization was observed by tlc. The use of camphorsulfonic acid led to the slow formation of **160** but the rate was probably not greater than that of the background reaction.[109] Use of the Lewis acids $AlCl_3$, $TiCl_4$, and $ZnCl_2$ led either to complex mixtures or to diene polymerization.

Evans[110] has reported that α,β-unsaturated *N*-acyloxazolidinones form highly reactive, cationic Lewis acid complexes (**163**) with dialkylaluminum chlorides when *more than one equivalent* of the Lewis acid is used. We felt that **58** might also be capable of the bidentate coordination required for the formation of a cationic Lewis acid complex (such as **164**). We therefore investigated the use of dialkylaluminum chlorides in reactions of **58**.



163



164

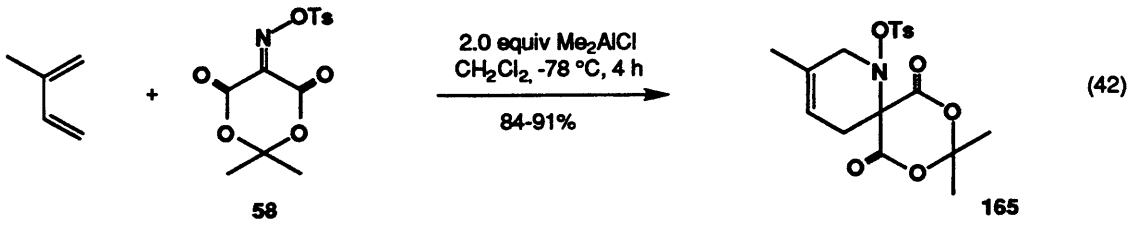
As shown in Table 2, the reaction between **58** and penta-1,3-diene in dichloromethane at -78 °C with 1.4 equivalents of Me_2AlCl provided the desired cycloadduct **160** in 39% yield as a single regioisomer. Although the yield was modest, we were encouraged by this result and the observation that **160** was the only product formed in significant quantities (as judged by tlc analysis). It was also clear from tlc and NMR analysis that the conversion of starting material was incomplete. We therefore increased the amount of Me_2AlCl used in the reaction to 2.0 equivalents and were delighted to find that a 75-78% isolated yield of cycloadduct **160** could be obtained after 2 to 4 hours at -78 °C.

---

[109] ca. 7% conversion after 24 h.

[110] (a) Evans, D. A.; Chapman, K. T.; Bisaha, J. *J. Am. Chem. Soc.* **1984**, *106*, 4261. (b) Evans, D. A.; Chapman, K. T.; Bisaha, J. *J. Am. Chem. Soc.* **1988**, *110*, 1238.

When the reaction of **58** with *isoprene* was attempted under these conditions, even higher yields (84-91%) of cycloadduct (**165**) were obtained (eq 42). Significantly, both cycloadducts **160** and **165** are formed with excellent regioselectivity. No evidence of



58 **165** (42)

other regioisomers can be detected in the ^{1}H NMR spectra of cycloadducts **160** and **165**. The efficiency and regioselectivity of these reactions compares favorably to the equivalent reactions of the biscyano oximinosulfonate **43**. As shown in Scheme 15 (Chapter 1), this dienophile reacts with penta-1,3-diene in refluxing benzene to provide cycloadduct **129** in only 30% yield. Reaction of bisnitrile **43** with isoprene provides cycloadduct **128** as a *mixture* of regioisomers in 77% overall yield. Neither cycloadditions of **43** nor the Meldrum's acid-derived oxime acetate **132** described by Katagiri are subject to Lewis acid promotion. We observed only decomposition when these dienophiles were subjected to the reaction conditions used with **58** (2.0 equivalents Me_2AlCl in CH_2Cl_2 at -78 °C).

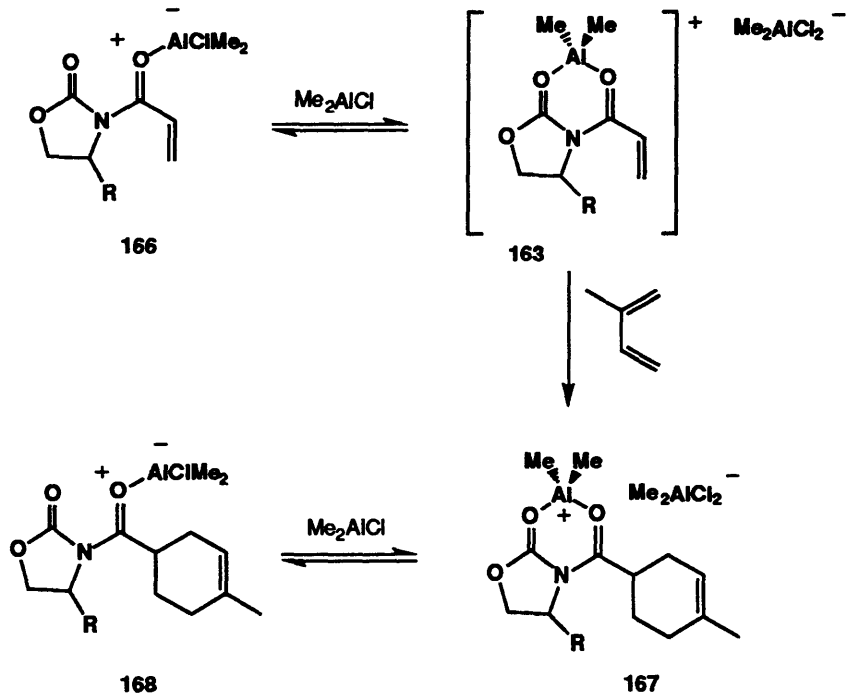
The importance of Lewis acid stoichiometry in reactions of **58** was revealed by the following experiments. The reaction of **58** with penta-1,3-diene was carried out under the standard conditions (CH_2Cl_2, -78 °C) while the amount of Me_2AlCl was varied from 0.1 to 2.0 equivalents. The reactions were stopped after exactly 4 h and the yields of cycloadduct **160** determined by NMR analysis using an internal standard (see below). The fact that no

Equiv Me_2AlCl	Yield of **160**
0.1	0%
1.0	15%
1.4	33%
2.0	78%

cycloadduct is produced in reactions with 0.1 equivalents of Me_2AlCl suggests that a neutral 1:1 Lewis acid-**58** complex is not an active dienophile under the reaction conditions. As the amount of Me_2AlCl is increased from 1.0 to 2.0 equivalents, the yields of **160** increase in rough correlation to the excess Me_2AlCl added. These results support the proposition that the active dienophile in these reactions is a cationic 2:1 Lewis acid-**58** complex such as **164**.

Whereas a full 2.0 equivalents of Me_2AlCl is required for complete conversion in reactions of **58**, Evans and co-workers[110] found that even a small excess (1.1 equiv) of Me_2AlCl is sufficient to promote Diels-Alder reactions of α,β-unsaturated *N*-acyloxazolidinones. Scheme 17 illustrates the Lewis acid-promoted Diels-Alder reaction of Evans' oxazolidinone dienophile with isoprene. The initial 1:1 complex **166** is proposed[110] to be in equilibrium with the cationic 2:1 complex **163**. Reaction of the latter species with isoprene then provides cycloadduct **167**. This 2:1 complex may then undergo equilibration with the 1:1 complex **168** to regenerate free Me_2AlCl. This final equilibrium

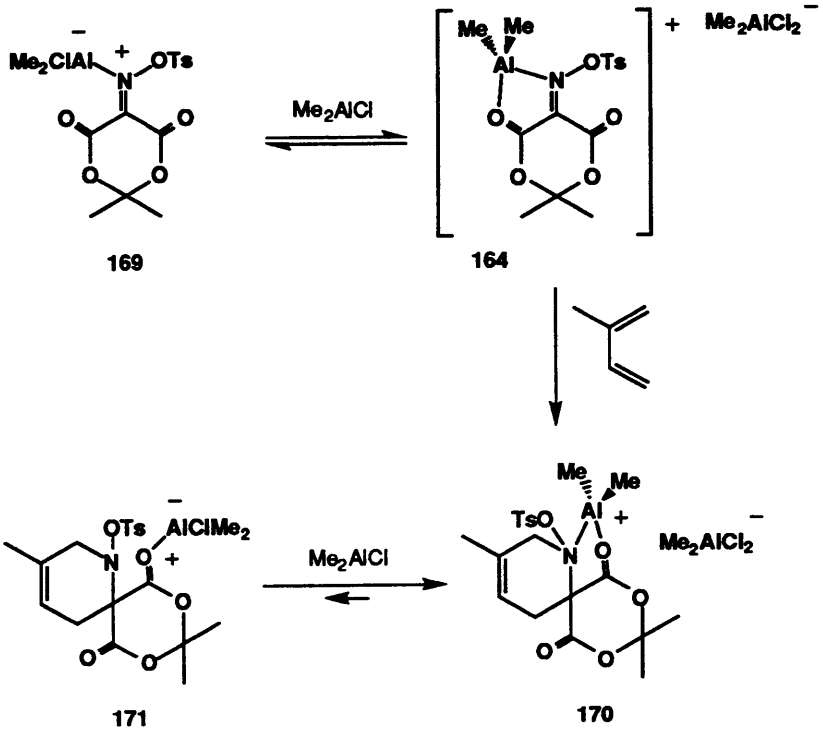
Scheme 17



and the regeneration of free Me_2AlCl provides a rational for the success of these reactions when only a small excess of Lewis acid is used.

Now consider the Lewis acid-promoted reaction of **58** with dienes (Scheme 18).

Scheme 18

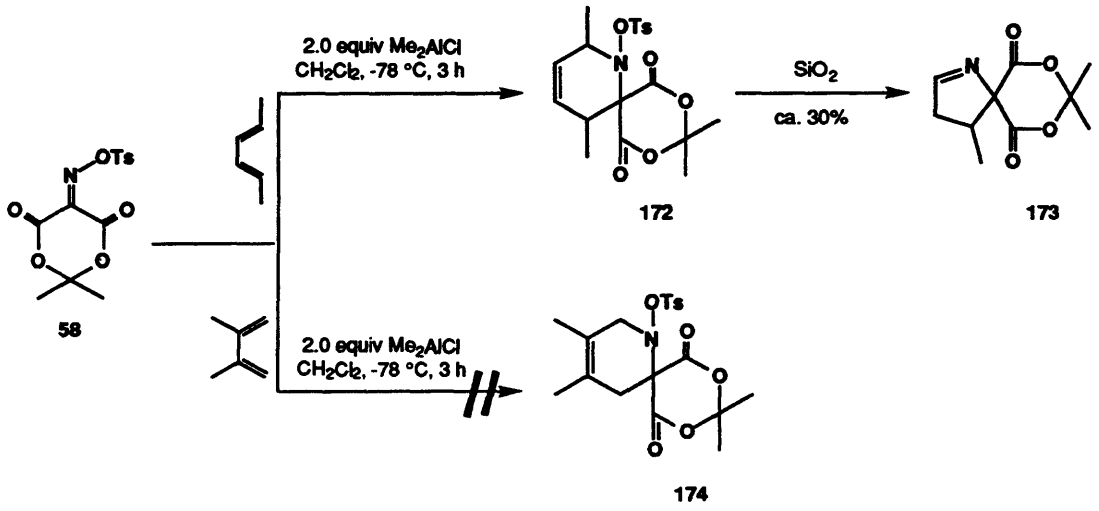


As with oxazolidinone dienophiles, an equilibrium between a 1:1 complex (**169**) and the cationic 2:1 complex **164** is assumed. Significantly, the reaction of **164** with a diene involves *reaction at one of the atoms involved in coordination to the metal* (the nitrogen of the oxime). This results in the formation of a cycloadduct (**170**) with a more basic sp^3 hybridized nitrogen atom. The coordination in **170** should be significantly stronger than that in **167**, and **170** should therefore predominate over **171** in the indicated equilibrium. The 2:1 complex **170** therefore acts as a thermodynamic sink, precluding the release of Me_2AlCl and making necessary the use of 2.0 equivalents of Lewis acid in reactions of **58**.

The Diels-Alder reactions of **58** with isoprene and penta-1,3-diene are efficient and highly regioselective processes (*vide supra*). We were therefore surprised to observe very

different results when **58** was reacted with more substituted dienes. The reactions of **58** with hexa-2,4-diene and 2,3-dimethylbutadiene are shown in Scheme 19. Although the expected cycloadduct (**172**) from reaction with hexa-2,4-diene was observed in the crude

Scheme 19



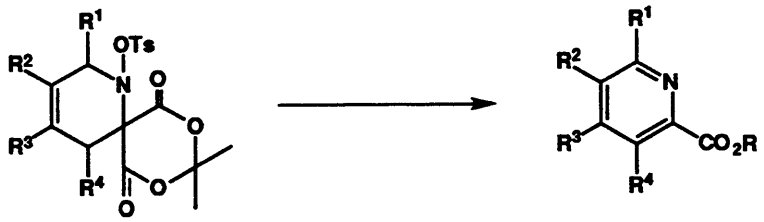
product mixture (NMR analysis), attempted purification of this material by column chromatography produced only the rearranged pyrroline **173** in low yield. Further difficulties were encountered when reaction with 2,3-dimethylbutadiene was attempted. In this case, none of the expected cycloadduct **174** was observed, even in the crude reaction mixture. Instead, a mixture of products was formed in low yield, suggesting that rearrangement processes were at work. The formation of pyrroline products in these reactions is attributed to Stieglitz-type rearrangement of the initially formed cycloadducts **172** and **174**. A complete discussion of our synthetic and mechanistic studies of these rearrangements will be presented in Chapter 4.

In view of the results presented in Scheme 19, it might appear that the utility of dienophile **58** is limited to reactions with monosubstituted dienes. However, if cycloadducts such as **172** could be converted directly, without purification, to more stable species, the reaction of **58** with more substituted dienes might still be of value. We

therefore sought out reaction conditions for the conversion of the tetrahydropyridine cycloadducts to substituted pyridines.

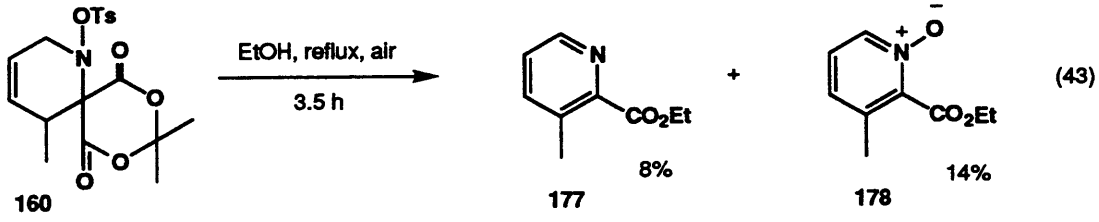
Synthesis of Substituted Pyridines

In considering the conversion of cycloadducts **175** to the substituted pyridines **176**, we anticipated the following requirements. First, a suitable nucleophile would be needed for cleavage of the dioxadione ring. Second, an oxidizing agent of some type



175 176

would be required to effect the oxidation of a dihydropyridine to a pyridine. Fleury and co-workers reported the aromatization of cycloadducts **137** by treatment in refluxing ethanol (Chapter 1, eq 34). However, only elimination reactions (of HCN and TsOH) are required to convert these cycloadducts (**137**) to pyridines, and consequently no oxidizing agent is required. We considered whether heating cycloadducts **175** in refluxing ethanol open to the air (as an oxidant) might provide pyridines **176**. When this was attempted with cycloadduct **160**, we did indeed obtain the expected pyridine **177**, albeit in only 8% yield



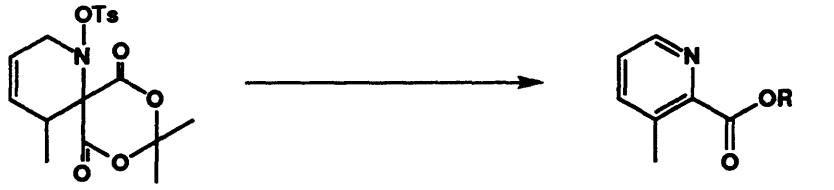
160 177 178 (43)

and accompanied by the over-oxidized pyridine *N*-oxide **178** (14% yield, eq 43). Although far from an optimal result, this initial experiment represents the starting point

from which evolved an efficient protocol for the conversion of cycloadducts **175** to pyridines.

Chart 1 summarizes our studies of cycloadduct **160** and its conversion to pyridine **179**. The use of NaOMe for the nucleophilic opening of the dioxadione ring proved most effective, allowing the reaction to be carried out at 0 °C. The subsequent elimination of acetone and decarboxylation occur spontaneously under the reaction conditions. A mixed solvent system of methanol and THF (1:1) was found to be optimal with regard to yield

Chart 1. Optimization Studies of the Aromatization Reaction



160 **179** R = Me, Et

Oxidizing Reagent:

DDQ is ineffective

O_2 and air led to complex mixtures

NCS is effective

NCS is superior to NBS

1.0 equiv NCS is superior to 1.2 or 3.0 equiv

Nucleophile:

Alkoxide at low temperature is superior to heating in alcohol

NaOMe is superior to NaOEt

3.0 equiv alkoxide is optimal

Solvent System:

THF alone leads to complex mixtures

160 is insoluble in MeOH alone

THF/MeOH (1:1) is effective

Order of Addition:

Addition of methoxide before NCS is more effective

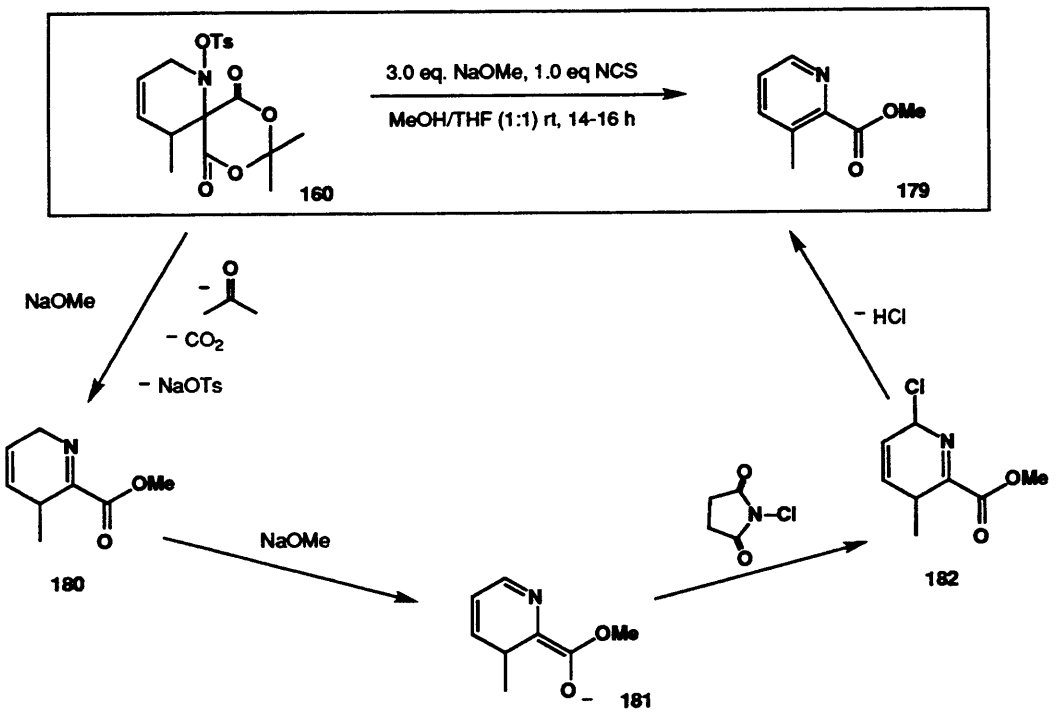
and solubility considerations. Of the various oxidizing agents examined, the most effective was *N*-chlorosuccinimide (NCS). In fact, the use of this reagent in conjunction with NaOMe has recently been reported in the oxidation of cyclic imines to pyridines.[111] The

[111] De Kimpe, N.; Keppens, M.; Fonck, G. *J. Chem. Soc., Chem. Commun.* **1996**, 635.

optimized conditions for the conversion of cycloadducts **175** to pyridines **176** can be summarized as follows. A solution of the cycloadduct in methanol-THF (1:1) is cooled at 0 °C and treated with 3.0 equivalents of NaOMe solution, followed by the addition of 1.0 equivalent of NCS. The reaction mixture is then stirred overnight at room temperature and the pyridine products isolated[112] and purified in the normal way. The yields obtained using this procedure are ca. 70% for cycloadduct **160**, and are typically higher with other cycloadducts (in some cases nearly quantitative).

One possible mechanism for this aromatization reaction is shown in Scheme 20 (for the conversion of cycloadduct **160** to pyridine **179**). Nucleophilic addition of NaOMe to

Scheme 20



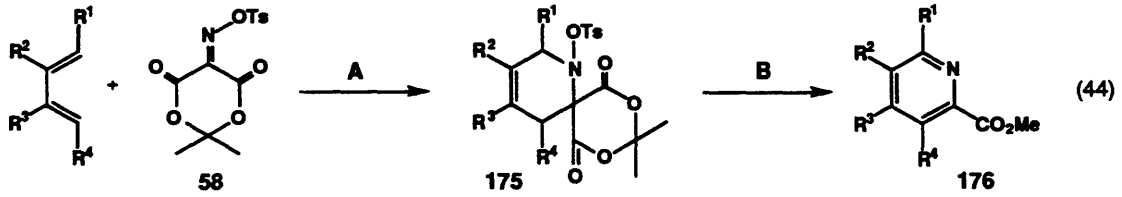
the dioxadione is followed by elimination of acetone and decarboxylation. The resulting ester enolate likely undergoes β-elimination of tosylate anion to produce dihydropyridine

[112] Care must be exercised to insure that strongly basic work-up conditions are avoided since the pyridine esters are sensitive to hydrolysis. This difficulty was circumvented by performing a neutral work-up with pH 7 phosphate buffer.

180. Chlorination (NCS) of this species via the enolate **181** affords **182**. Finally, elimination of HCl from **182** provides the pyridine **179**. It should be emphasized that no experimental inquiry into the actual mechanism of the reaction has been attempted. The mechanistic proposition in Scheme 20 simply serves to illustrate one possible pathway.

Pyridine Annulation Utilizing Oximinosulfonate 58 - Scope and Limitations

The Lewis acid-promoted reaction of **58** with dienes, and the conversion of the resulting cycloadducts to pyridines, together comprise a new annulation method for the synthesis of substituted pyridines from 1,3-dienes (eq 44). This annulation is best accomplished using the cycloadducts **175** directly, without purification, in the subsequent aromatization reaction. In addition to providing the best overall yields, this procedure allows the formation of pyridines from cycloadducts that are prone to rearrangement upon purification by column chromatography (Scheme 19).



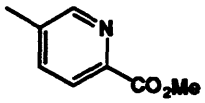
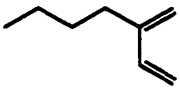
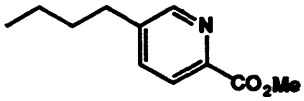
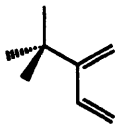
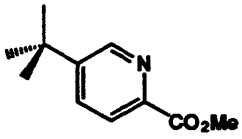
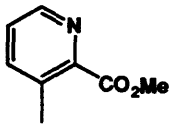
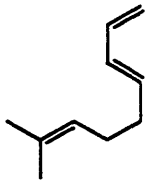
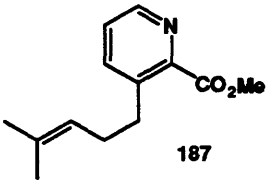
58 175 176 (44)

A 2.0 equiv Me_2AlCl, CH_2Cl_2, -78 °C

B 3.0 equiv NaOMe, 1.0 equiv NCS, MeOH/THF (1:1), rt

With both steps of the pyridine annulation optimized, we initiated an investigation of the scope of this process for the synthesis of substituted pyridines. Table 3 presents the results of annulation reactions of *monosubstituted* dienes. Very good overall yields (73-77%) are obtained in reactions of 2-substituted dienes (entries 1-3), providing the methyl-, *n*-butyl-, and *t*-butyl-substituted pyridines **183-185**. Reactions with 1-substituted dienes

Table 3. Pyridine Annulations with Monosubstituted Dienes

Entry	Diene	Equiv (Diene)	Pyridine	Overall Yield (%)[a]
1		3.0	 **183**	77
2		1.5	 **184**	72
3		1.5	 **185**	73
4		3.0	 **179**	56-57
5	 **186**	1.5	 **187**	60

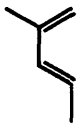
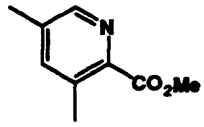
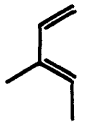
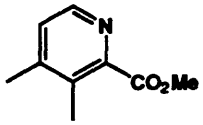
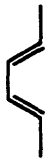
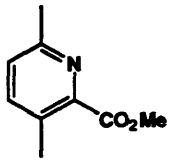
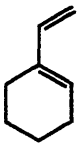
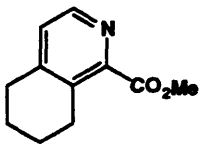
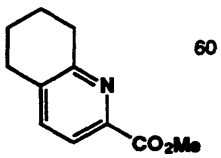
[a] Isolated overall yield for two steps.

provide slightly lower overall yields (56-60%) of the substituted pyridines **179**[113] and **187**. The reaction of diene **186** (to provide **187**) demonstrates the compatibility of a reactive olefin functionality with the cycloaddition and chlorination conditions. Also noteworthy are the excellent results obtained when a relatively small excess (1.5 equiv) of diene is used. This bodes well for application of the annulation in total synthesis (Chapter 3). All the annulations in Table 3 provided regioisomericaly pure products as judged by

[113] (a) Hromatka, O.; Binder, D.; Stanetty, P.; Marischler, G. *Monatsh. Chem.* **1976**, *107*, 233. (b) Subramanyam, C.; Chattarjee, S.; Mallamo, J. P. *Tetrahedron Lett.* **1996**, *37*, 459.

NMR analysis. As discussed previously, the annulation provides products with the opposite regiochemistry as would be obtained from cycloadditions of *imine* dienophiles.

Table 4. Pyridine Annulations with Disubstituted Dienes

Entry	Diene	Equiv Diene	Pyridine	Overall Yield (%)[a]
6		3.0	 **188**	70
7		3.0	 **189**	40
8[b]		3.0	 **190**	40
9		1.5	 **191** **83 : 17**  **192**	60

[a] Isolated overall yield over two steps. [b] 5.0 Equiv MeONa,and 4.0 equiv NCS were used.

The spectral characteristics (^{1}H and ^{13}C NMR, IR, EA) of the pyridines in Table 3 were fully consistent with the assigned structures. Furthermore, the known compounds **183**[114]

[114] The ^{1}H NMR spectrum of this pyridine was consistent with that reported previously, see: Deady. L. W.; Harrison, P. M.; Topsom, R. D. *Org. Magn. Reson.* **1975**, *7*, 41.

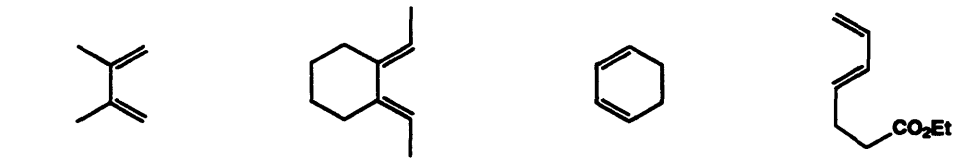
and **184**[115] showed spectral characteristics consistent with those reported previously for these compounds.

Table 4 presents the results of annulation reactions with *disubstituted* dienes. The most efficient reactions are those with 1,3-substituted dienes (entry 6), providing 3,5-substituted pyridines such as **188** in good overall yields (70%). The annulation is somewhat less effective for the preparation of the 3,4- and 3,6-substituted pyridines **189** and **190** (40% overall yield, entries 7 and 8). The lower yields obtained in these cases are undoubtedly due to competing rearrangement processes of the type outlined in Scheme 19 and described in detail later (Chapter 4). The use of dienes such as 1-vinylcyclohexene (entry 9) in the annulation provides access to bicyclic pyridines (regioisomers **191** and **192**) in acceptable overall yields (60%). The regiochemical ambiguity in this case can be attributed to the opposing directing effects of substituents at the 1 and 2 positions in 1,3-dienes. The spectral characteristics (^{1}H and ^{13}C NMR, IR, EA) of the pyridines in Table 4 were fully consistent with the assigned structures. The known pyridine **188** had a melting point of 42-43 °C as compared to 39-41 °C reported previously for this compound.[116]

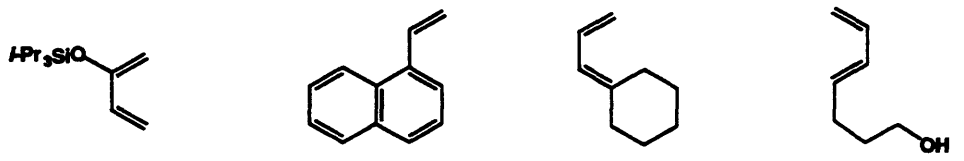
Reactions of the dienes shown below did not produce pyridines, either because of low reactivity/stability in the cycloaddition step, or because the cycloadducts, once formed, are prone to rearrangement. The reaction of 2,3-dimethylbutadiene or the tetrasubstituted diene **193** with **58** produced mixtures of products, the structures of which suggested rearrangement of the initially formed cycloadducts (as in Scheme 19). In general, dienes with substitution at both the 2 and 3 positions produce cycloadducts that are extremely susceptible to rearrangement. The presence of ester (**30**) or alcohol (**31**) functionality inhibits the cycloaddition reaction, even when three or more equivalents of Lewis acid are employed. These reactive functional groups would therefore need to be protected for use in

---

[115] The ^{1}H NMR spectrum of this pyridine was consistent with that reported previously, see: Capasso, R.; Evidente, A.; Cutignano, A.; Vurro, M.; Zonno, M. C.; Bottalico, A. *Phytochemistry* **1996**, *41*, 1035.
[116] Blank, B.; DiTullio, N. W.; Krog, A. J.; Saunders, H. L. *J. Med. Chem.* **1979**, *22*, 840.



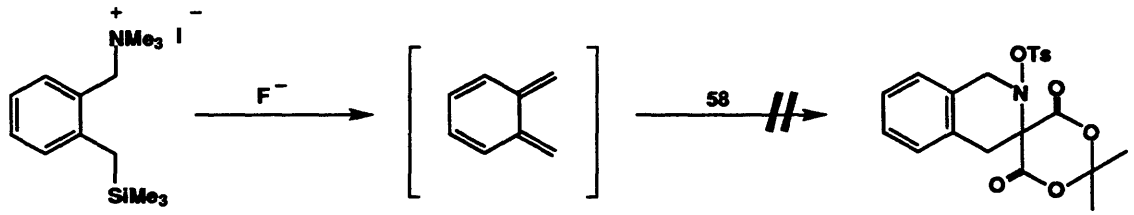
193 30



161 194 195 31

the annulation. The siloxydiene **161**, which reacted under thermal conditions (eq 41), was unreactive under Lewis acid promotion. This result is most likely due to instability of the silyl enol ether to the Lewis acidic conditions. Dienes **194** and **195** were likewise unreactive with **58**. The failure of **195** to react is, perhaps, not surprising since the expected cycloadduct from its reaction with **58** would possess two contiguous quaternary centers. It is puzzling, however, that cyclohexadiene failed to react. A possible explanation might be unfavorable steric interactions between the diene and the Lewis acid-complexed dienophile.

We also examined the possibility of reacting **58** with an *o*-quinodimethane (**197**), generated in situ by the addition of fluoride anion to the quaternary ammonium salt **196**.[117]



196 197 198

[117] Prepared in four steps from N,N-dimethylbenzylamine, see: Ito, Y.; Nakatsuka, M.; Saegusa, T. *J. Am. Chem. Soc.* **1982**, *104*, 7609.

Although cycloadducts from 2,3-substituted dienes are usually prone to rearrangement, we thought the *aromatic* product **198** might be stable to rearrangement. When the above reaction was attempted using either Bu_4NF or CsF, only decomposition was observed. In contrast, reaction of **196** with methyl acrylate as dienophile produced the expected cycloadduct in 61% yield along with a 24% yield of the *o*-quinodimethane dimer. The most likely explanation for the failure of **58** to react is the instability of this species to fluoride anion. For example, the related oximinosulfonate **43** undergoes reaction at sulfur in the presence of fluoride anion (Scheme 5, Part I).[35] The fact that very little, if any, *o*-quinodimethane *dimer* formed in reactions with **58** suggests that **197** was not generated in significant quantities (presumably because of fluoride addition to **58** rather than **196**). The reaction of **58** with **197** might still be feasible if the *o*-quinodimethane species is generated under reaction conditions compatible with **58**.

The new pyridine annulation presented in this chapter possesses a number of advantages when compared with the method described by Fleury using biscyano oximinosulfonate **43**. Whereas reactions of **43** sometimes display low regioselectivity (reaction with isoprene), cycloadditions with **58** appear to be uniformly regioselective. Reaction of **58** with monosubstituted dienes provides consistently high yields of cycloadducts whereas reactions of **43** are sometimes inefficient (30% yield with penta-1,3-diene). The rather mediocre reactivity of **43** is compounded by its poor thermal stability (which precludes the use of forcing conditions). In contrast, reactions of **58** occur under Lewis acid promotion at -78 °C and are successful with less reactive dienes. Finally, pyridine annulation with **58** can be accomplished using only a small excess (1.5 equiv) of diene whereas at least 3 and as many as 10 equivalents were required in reactions with **43**.

In other respects, the two methods are complementary. For example, annulations of **58** provide pyridine products with an *ester* substituent whereas annulations with **43** provide pyridines with a *nitrile* group. While reactions of **43** can provide access to 4,5-

substituted pyridines, the corresponding cycloadducts of **58** are unstable and undergo rearrangement.

Summary

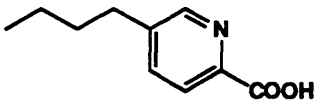
The Lewis acid-promoted reaction of oximinosulfonate **58** with dienes is an efficient and regioselective process. The cycloadducts obtained in these reactions are readily converted to substituted pyridines, thereby providing a new method for the synthesis of pyridines from 1,3-dienes. Pyridines prepared in this manner possess a carbomethoxy group at the 2 position, and as such, are derivatives of picolinic acid. The annulation is most effective for the preparation of pyridines with substitution at the 3 and/or 5 positions. The corresponding 3,4- and 3,6-substituted pyridine derivatives are formed in modest yields while 4,5-substituted pyridines cannot be prepared using this annulation. While dienes possessing reactive olefin functionality (**186**) are compatible with the reaction conditions, those with ester or alcohol groups (**30** and **31**) are not and would need to be protected for use in the annulation.

This new pyridine annulation is especially effective for the construction of 5-alkylpicolinic acid derivatives, an important class of biologically active pyridines. We therefore decided to test the utility of this new method in the total synthesis of pyridine alkaloids. The following chapter describes the successful application of this new annulation to the total synthesis of the natural products fusaric acid and *S*-(+)-fusarinolic acid.

Chapter 3

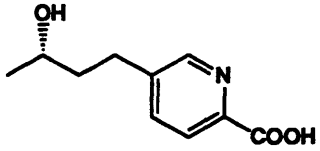
Total Synthesis of Fusaric Acid and *S*-(+)-Fusarinolic Acid

The previous chapter described a new pyridine annulation based on the [4+2] cycloadditions of oximinosulfonate **58**. This annulation provides a particularly powerful method for the construction of 5-alkylpicolinic acid derivatives, an important class of biologically active pyridines. An important test for any new methodology is its utility in total synthesis, where the complexity of the starting materials is typically greater than those used in method development. Therefore, to further test and refine this new pyridine annulation, we have investigated its application to the total synthesis of the pyridine alkaloids fusaric acid (**199**) and *S*-(+)-fusarinolic acid (**200**). The synthesis of **200** was expected to be particularly informative with regard to the types of functionality that can be introduced using the annulation (i.e., the oxygenated side chain).



fusaric acid

199



S-(+)-fusarinolic acid

200

Fusaric Acid

Isolation and Biological Activity

The phytotoxin fusaric acid is produced by several species of plant-pathogenic fungi belonging to the genus *Fusarium*.[118] In nature, fusaric acid acts as a plant growth

[118] (a) Yabuta, T.; Kambe, K.; Hayashi, T. *J. Agric. Chem. Soc. Jpn.* **1934**, *10*, 1059. (b) Grove, J. F.; Jeffs, P. W.; Mulholland, T. P. C. *J. Chem. Soc.* **1958**, 1236. (c) Hidaka, H.; Nagatsu, T.; Takeya, K. *J. Antibiot.* **1969**, *22*, 228. (d) Nagatsu, T.; Hidaka, H.; Kuzuya, H.; Takeya, K.; Umezawa, H.; Takeuchi, T.; Suda, H. *Biochem. Pharmacol.* **1970**, *19*, 35. (e) Suda, H.; Takeuchi, T.; Nagatsu, T.; Matsuzaki, M.; Matsumoto, I.; Umezawa, H. *Chem. Pharm. Bull.* **1969**, *17*, 2377. (f) Claydon, N.; Grove, J. F.; Pople, M. *Phytochemistry* **1977**, *16*, 603. (g) Abraham, W.-R.; Hanssen, H.-P. *Tetrahedron* **1992**, *48*, 10559. (h) Capasso, R.; Evidente, A.; Cutignano, A.; Vurro, M.; Zonno, M. C.; Bottalico, A. *Phytochemistry* **1996**, *41*, 1035.

inhibitor causing leaf and stem necrosis and inhibiting root elongation. Fusaric acid is one of the major phytotoxins isolated from cultures of *Fusarium nygamai*, a fungus that is pathogenic to the parasitic weed *Striga hermonthica* (witchweed). It has therefore been suggested that fusaric acid could be used as a herbicide for the control of these weeds.[118h] Fusaric acid is also pathogenic to invertebrates and its use as an insecticide has been suggested.[118f]

In addition to its phytotoxicity, fusaric acid possesses significant hypotensive activity in mammals.[118c,e] For example, injecting rabbits with 50 mg/kg of fusaric acid produced up to 30% reductions in their blood pressure.[113e] The hypotensive activity of this compound arises from its potent inhibition of dopamine β-hydroxylase.[119] Inhibition of this enzyme results in the lowering of norepinephrine levels in the cardiovascular system, causing a hypotensive effect. The inhibition is non-competitive, suggesting that fusaric acid interacts with the enzyme-substrate complex.[118d]

Previously Reported Syntheses of Fusaric Acid

A number of syntheses of fusaric acid have been reported.[120] Despite the rather simple structure of this alkaloid, most of the reported routes require between five and seven synthetic steps.[120a,b,d,e] More recently, shorter routes (3-4 steps) have been described.[120f,g] The majority of the syntheses rely upon the synthetic elaboration of an existing pyridine ring, although two of these routes utilize cycloadditions of azadienes.[120e,f] The synthesis of fusaric acid using an *azadienophile*-based strategy has not been reported. Scheme 21 summarizes some of the earlier synthetic routes to fusaric acid.

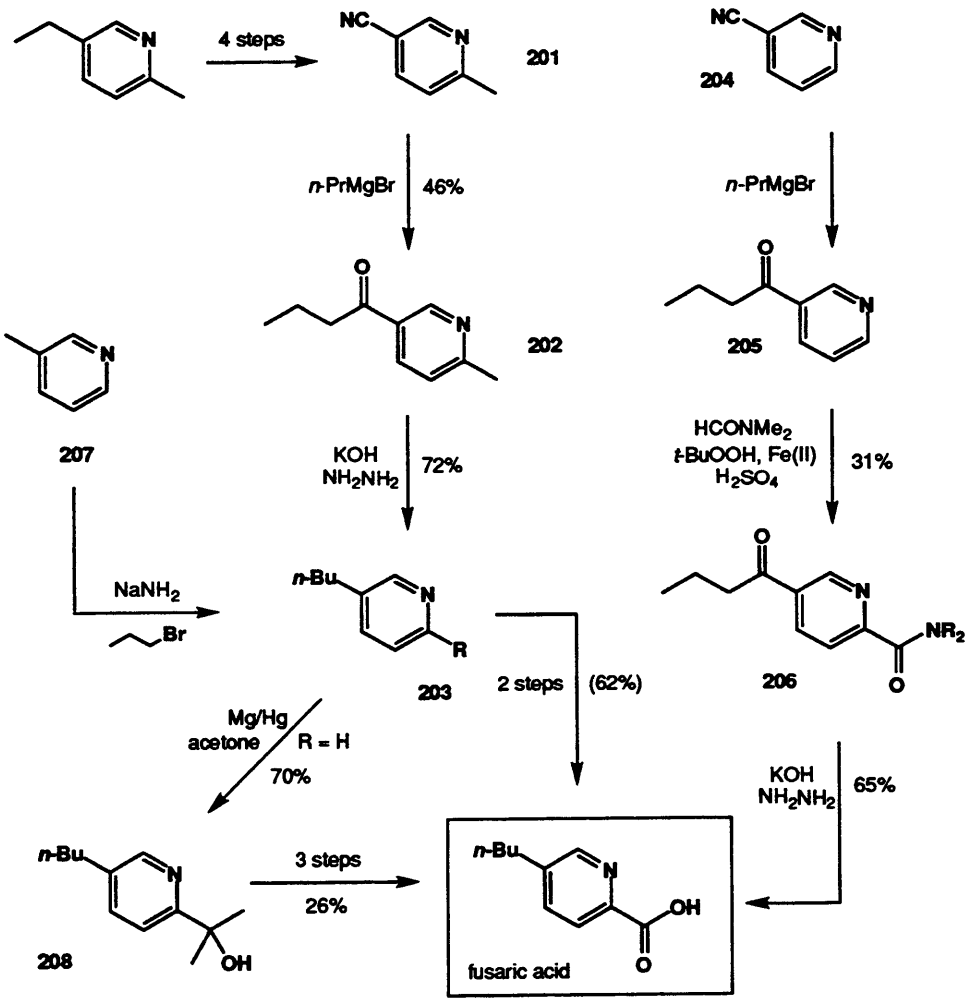
---

[119] Fusaric acid is a nanomolar inhibitor of dopamine β-hydroxylase ($IC_{50} = 3.0 \times 10^{-8}$ M), see : ref. 118d.

[120] (a) Plattner, Pl. A.; Keller, W.; Boller, A. *Helv. Chim. Acta* **1954**, *37*, 1379. (b) Hardegger, E.; Nikles, E. *Helv. Chim. Acta* **1957**, *40*, 1016 (c) Vogt, H.; Mayer, H. *Tetrahedron Lett.* **1966**, 5887. (d) Tschesche, R.; Führer, W. *Chem. Ber.* **1978**, *111*, 3502. (e) Sagi, M.; Amano, M.; Konno, S.; Yamanaka, H. *Heterocycles* **1989**, *29*, 2249. (f) Waldner, A. *Synth. Commun.* **1989**, *19*, 2371. (g) Langhals, E.; Langhals, H.; Rüchardt, C. *Liebigs Ann. Chem.* **1982**, 930.

The addition of a Grignard reagent to a cyanopyridine has commonly been used to introduce the *n*-butyl side chain of fusaric acid. For example, reaction of the pyridine **201** (prepared from 5-ethyl-2-methylpyridine in 4 steps) with *n*-propylmagnesium bromide provided the ketone **202**; Wolff-Kishner reduction then afforded **203** (R = CH_3) which was converted to fusaric acid in two steps.[120a] The oxidation of the methyl group in **203** to form fusaric acid has also been accomplished in a single step by reaction with SeO_2.[120b] A second and much shorter synthesis of fusaric acid starts with commercially available 3-cyanopyridine (**204**).[120g] Grignard addition to the nitrile provides the ketone **205**, and

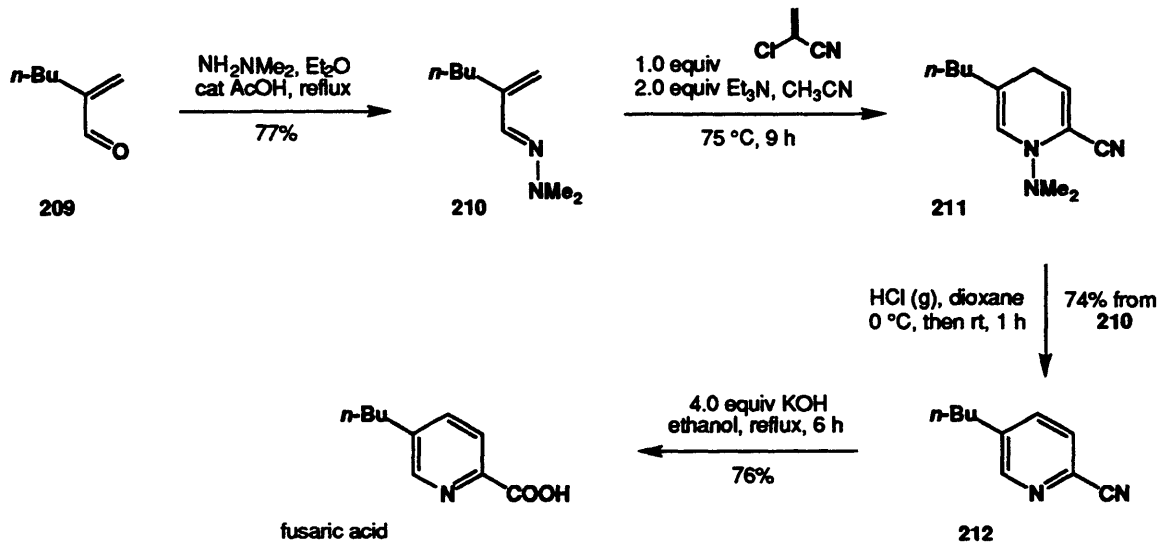
Scheme 21



Minisci[121] reaction with DMF then forms the amide **206** regioselectively, albeit in poor yield. Reaction of **206** under Wolff-Kishner conditions both reduces the ketone and hydrolyses the amide to generate fusaric acid. An alternative method for introduction of the *n*-butyl group involves the alkylation of 3-methylpyridine (**207**) with bromopropane to provide *n*-butylpyridine (**203**, R = H, unspecified yield).[120d] Reaction of this pyridine with acetone in the presence of magnesium amalgam provides the tertiary alcohol **208** which can be converted to fusaric acid in three steps.

Waldner employed a hetero Diels-Alder strategy in what is probably the most efficient synthesis of fusaric acid yet reported (Scheme 22).[120f] The key azadiene **210** is

Scheme 22



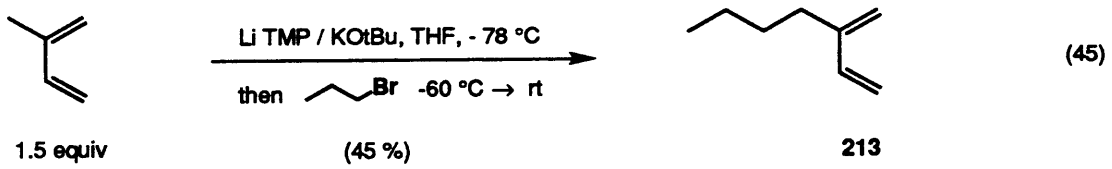
prepared in one step from the commercially available unsaturated aldehyde **209**. The Diels-Alder reaction of **210** with 2-chloroacrylonitrile provides, after cycloaddition and elimination of HCl, the dihydropyridine **211**. Elimination of dimethylamine from this intermediate is effected with HCl in dioxane to give the cyanopyridine **212** in 74% overall yield from **210**. Hydrolysis of the nitrile in **212** completes the synthesis. This synthesis

[121] (a) Minisci, F.; Gardini, G. P.; Galli, R.; Bertini, F. *Tetrahedron Lett.* **1970**, 15. (b) Gardini, G. P.; Minisci, F.; Palla, G.; Arnone, A.; Galli, R. *Tetrahedron Lett.* **1971**, 59.

illustrates the convergency and efficiency of annulation strategies for the synthesis of aromatic heterocycles.

A New Synthesis of Fusaric Acid

Here we present the total synthesis of fusaric acid based on the two-step pyridine annulation described in Chapter 2. Application of this annulation strategy to the total synthesis of fusaric acid required the preparation of the *n*-butyl-substituted diene **213** (eq 45). This diene had been prepared previously using multi-step reaction sequences.[122] We considered the possibility of preparing **213** in one step by the alkylation of isoprene with bromopropane. The metallation-alkylation of isoprene was first reported by Brandsma for alkylations with bromoheptane and oxirane.[123] The use of a more basic potassium dialkylamide (generated from a lithium dialkylamide and KO*t*-Bu) is required to generate sufficient concentrations of the metallated isoprene species.[124] As shown in equation 45,



(45)

metallation of isoprene and alkylation with bromopropane provided the desired diene **213** in 45% yield (ca. 90% purity) following column chromatography. Further purification of this compound by distillation gave much lower yields and did not improve the purity significantly. Fortunately, we found that the material obtained after chromatography could be used directly (without further purification) in the annulation reaction.

---

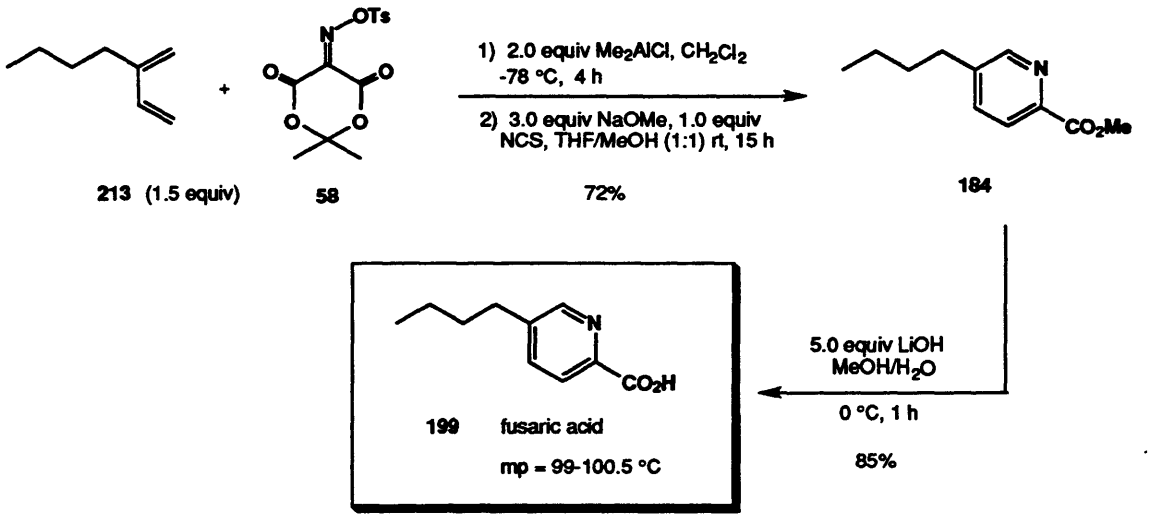
[122] (a) Korobova, L. M.; Livshits, I. A. *Zh. Obshch. Khim.* **1964**, *34*, 3419. (b) Ueno, Y.; Sano, H.; Aoki, S.; Okawara, M. *Tetrahedron Lett.* **1981**, *28*, 2675. (c) Dzhemilev, U. M.; Ibragimov, A. G. *J. Organomet. Chem.* **1994**, *466*, 1.

[123] (a) Klusener, P. A. A.; Hommes, H. H.; Verkruijsse, H. D.; Brandsma, L. *J. Chem. Soc., Chem. Commun.* **1985**, 1677. (b) Brandsma, L. *Preparative Polar Organometallic Chemistry*; Springer-Verlag: Berlin, 1987; Vol. 2, pp 43-44.

[124] The use of the amide derived from tetramethypiperidine (TMP) gave higher yields than that derived from diisopropylamine.

The reaction of oximinosulfonate **58** with 1.5 equivalents of diene **213** using the standard annulation conditions provided methyl fusarate[125] (**184**) in good overall yield (72%) as a single regioisomer (Scheme 23). Hydrolysis of this ester (LiOH in $MeOH/H_2O$) provided synthetic fusaric acid in 85% yield following purification by sublimation (0.1 mmHg, 110 °C). Synthetic fusaric acid had a melting point of 99-100.5 °C as compared to 100-101 °C reported for the natural product.[118b] The spectral data (^1H and ^{13}C NMR, IR, EA) for synthetic fusaric acid was consistent with that reported

Scheme 23



previously for fusaric acid isolated from natural sources.[118g] This new synthesis of fusaric acid compares quite favorably with previously reported syntheses and proceeds in four steps and 35% overall yield from Meldrum's acid (**52**).

[125] Synthetic methyl fusarate had spectral characteristics consistent with that reported previously for the natural product, see: 118h.

S-(+)-Fusarinolic Acid

Isolation and Total Synthesis

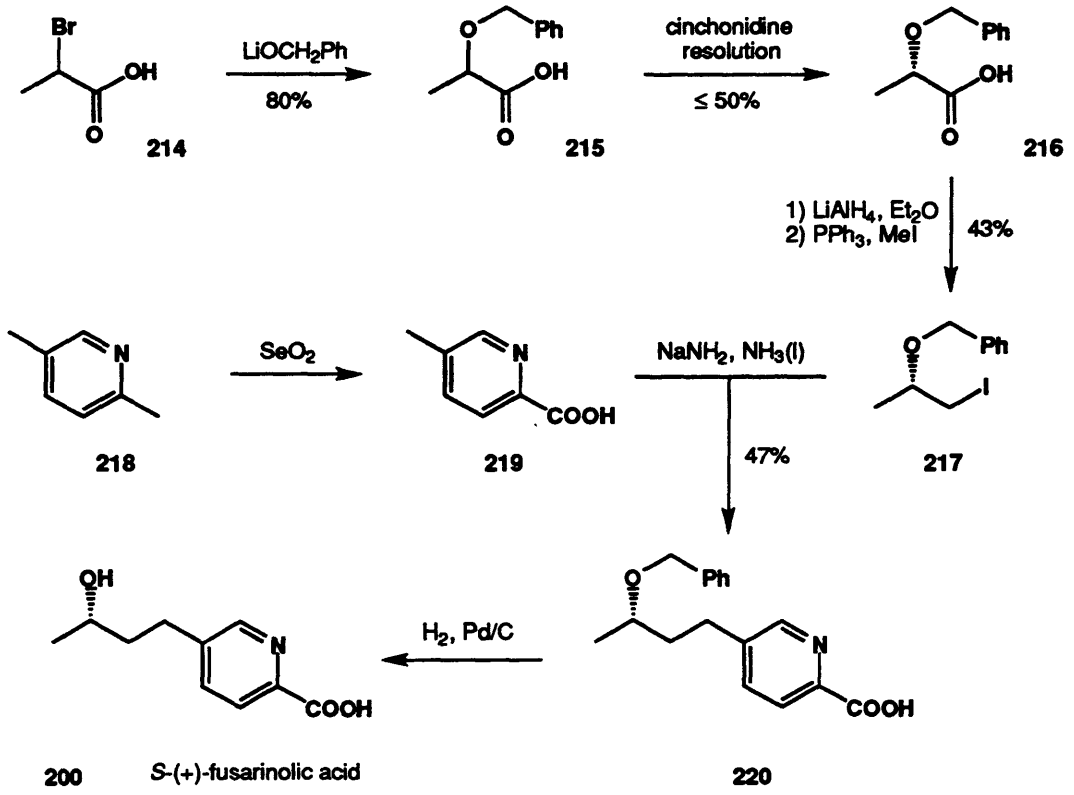
In comparison to fusaric acid, much less is known about the oxygenated derivative *S*-(+)-fusarinolic acid (**200**). This alkaloid was isolated[126] from *Gibberella fujikuroi*, the same species of fungus from which fusaric and dehydrofusaric acid had previously been extracted.[118b] The structure of *S*-(+)-fusarinolic acid was assigned on the basis of UV, NMR, and combustion analysis and then confirmed by total synthesis, which also allowed the correct absolute stereochemistry to be assigned.[126] The phytotoxicity of *S*-(+)-fusarinolic acid was found to be much lower than that of fusaric acid in tomato plant assays.[126] No other reports on the biological activity of **200** have appeared, however.

The first total synthesis of *S*-(+)-fusarinolic acid was reported concurrent with its isolation.[126] The synthesis was accomplished in six steps but in an overall yield of less than 8%. Three additional synthetic routes to (±)-fusarinolic acid were subsequently reported, although these were considerably longer and less efficient (8-10 steps, 2-5% overall yield).[127] All of these syntheses rely on the synthetic elaboration of 5-methylpyridine-2-carboxylic acid (**219**). The first synthesis is the shortest and most efficient and is presented in Scheme 24.[126] The key step in the route involves the alkylation of pyridine **219** with the iodide **217** (prepared in four steps from **214**) to give the benzyl-protected fusarinolic acid derivative **220**. Hydrogenolysis of this species then gives synthetic *S*-(+)-fusarinolic acid in unspecified yield. The specific rotation of synthetic *S*-(+)-fusarinolic acid was consistent with that of the natural product while the anilide derivatives of synthetic and natural *S*-(+)-fusarinolic acid had similar melting points. No additional spectral data was provided for either the synthetic or natural material.

---

[126] Steiner, K.; Graf, U.; Hardegger, E. *Helv. Chim. Acta* **1971**, *54*, 845.
[127] Büyük, G.; Hardegger, E. *Helv. Chim. Acta* **1975**, *58*, 682.

Scheme 24

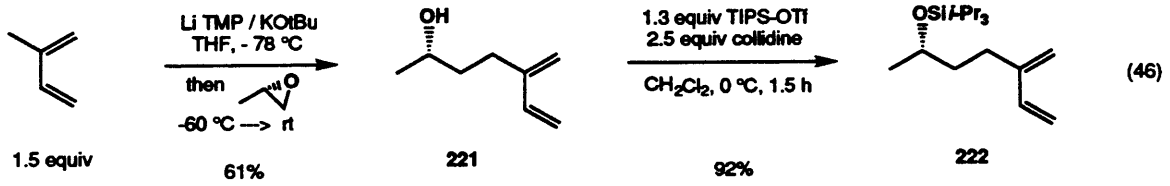


A New Synthesis of S-(+)-Fusarinolic Acid

Here we present a new synthesis of *S*-(+)-fusarinolic acid using the pyridine annulation described in Chapter 2. Both *S*-(+)-fusarinolic acid and the racemate were prepared. The yields reported below are for the optically active compounds although the synthetic route was initially optimized using the racemic material.

We were optimistic that our new pyridine annulation would provide a significantly improved synthesis of *S*-(+)-fusarinolic acid (**200**). The application of this annulation strategy to the synthesis of **200** requires a diene with an alcohol substituent. The use of dienes with alcohol functionality had previously led to sluggish reaction rates in the Lewis acid-promoted cycloaddition (Chapter 2). We therefore anticipated that a protected alcohol

would be required for use in the annulation. Our synthesis of the requisite diene **222** is shown in eq 46. Metallation[123] of isoprene with LiTMP/KO*t*-Bu and alkylation with *S*-(-)-

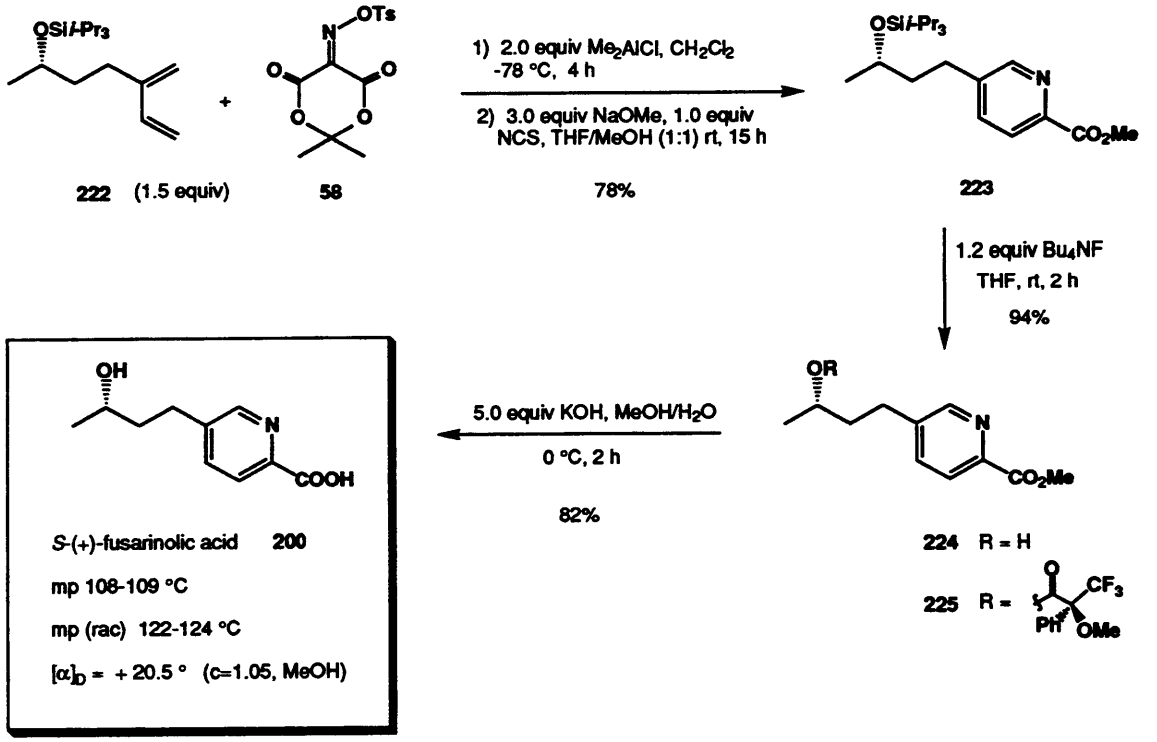


(46)

propylene oxide provided the alcohol **221** in 61% yield following purification by column chromatography. This alcohol was then protected as the triisopropylsilyl ether **222**.[128]

Scheme 25 illustrates the use of diene **222** in the total synthesis of *S*-(+)-fusarinolic acid. The reaction of oximinosulfonate **58** with 1.5 equivalents of diene **222** using the standard annulation conditions provided the desired pyridine **223** in high overall yield

Scheme 25



[128] The corresponding *trimethylsilyl* ether was also prepared but this diene was unreactive in the Lewis acid-promoted cycloaddition reaction.

(78%) following purification by column chromatography. Additionally, the unreacted diene **222** could be recovered essentially quantitatively. The use of less than 1.5 equivalents of diene in the annulation should also be effective, although this was never attempted. The yield of pyridine **223** (78%) is the highest yet obtained using this new pyridine annulation. Removal of the silyl protecting group in **223** was accomplished in 94% yield by reaction with tetrabutylammonium fluoride in THF to provide *S*-(+)-methyl fusarinolate (**224**). At this stage, the enantiomeric purity of the material was assessed by conversion of alcohol **224** to the Mosher ester **225**. Analysis of **225** by ^{1}H and ^{19}F NMR revealed only one diastereomer within the detection limits of the spectrometer.[129] The synthesis of *S*-(+)-fusarinolic acid was completed by hydrolysis of the methyl ester **224** with KOH in methanol/H_2O. The isolation of *S*-(+)-fusarinolic acid was complicated by its high solubility in aqueous solutions. Standard extraction techniques proved unsatisfactory, even when polar organic phases such as ethyl acetate-dichloromethane were used. Fortunately, *S*-(+)-fusarinolic acid could be recovered from an appropriately buffered (pH 2.5) aqueous solution by continuous liquid-liquid extraction with dichloromethane for two days. Attempted crystallization (dichloromethane-methanol) of the crude product gave an oil that subsequently crystallized, providing synthetic *S*-(+)-fusarinolic acid in 82% yield. The spectral data (^{1}H and ^{13}C NMR, IR, EA) obtained for **200** was fully consistent with the structure of *S*-(+)-fusarinolic acid. The (+)-camphorsulfonate salt of synthetic **200** had a melting point of 188-189 °C as compared to 187-188 °C reported for the same derivative prepared from authentic **200**.[126]

Melting point data for natural and synthetic fusarinolic acid is presented in the Table below. When we prepared *racemic* fusarinolic acid by a route analogous to that shown in Scheme 25, the melting point (122-124 °C) was consistent with that reported previously for synthetic (±)-fusarinolic acid.[126,127] Our synthetic *S* enantiomer, however, had a melting

[129] The Mosher ester of *racemic* **225** was also prepared and the diastereomers were found to be well resolved by both ^{1}H and ^{19}F NMR spectroscopy.

point of 108-109 °C as compared to 122-124 °C reported previously[122] for synthetic material obtained by resolution of the racemate. Melting point depression is quite common in chiral compounds that form true racemic solids (in which the two enantiomers co-exist in the same unit cell).[130] Therefore, the depressed melting point we observed for synthetic *S*-(+)-fusarinolic acid does not necessarily imply that it is impure. Indeed, this material displays a sharp melting point, appears pure by spectroscopic analysis, and passed elemental analysis. A more likely explanation for the discrepancy in melting points is that the *S*-enantiomer obtained previously[127] (by resolution) in fact contained a significant amount of the racemic solid (which melts at 122-124 °C). This would be consistent with the lower specific rotation observed for this resolved material as compared to that recorded for the authentic natural product.[126]

Melting Point Data for Fusarinolic Acid and Derivatives

	natural[126]	synthetic (this work)	synthetic[126]	synthetic[127]
free acid-(±)		122-124 °C	122-123 °C	121-123 °C
free acid-*S*-(+)	oil	108-109 °C		122-124 °C
anilide	99-100 °C		101-102 °C	
(+)-CSA salt	187-188 °C	188-189 °C		
Cu complex	278-281 °C			

The Table below presents the specific rotation data for synthetic and natural *S*-(+)-fusarinolic acid. The specific rotation of our synthetic material was ***higher*** than that reported for natural *S*-(+)-fusarinolic acid (+ 20.5° vs + 7.5°). There are several possible explanations for this discrepancy. It is conceivable that our synthetic material contains a minor impurity that possesses an extremely high rotation, thereby affecting the overall

[130] Eliel, E. L.; Wilen, S. H. *Stereochemistry of Organic Compounds*; Wiley: New York, 1994; pp 162-173.

rotation observed. Alternatively, it is possible that *S*-(+)-fusarinolic acid isolated from natural sources was not entirely pure and gave a rotation lower than what would be observed for the pure material. Considering that natural **200** was isolated as an oil while pure synthetic material is a solid, it seems reasonable to suggest that the *S*-(+)-fusarinolic acid isolated from natural sources may have been somewhat impure.

Specific Rotation for Synthetic and Natural *S*-(+)-Fusarinolic Acid

natural[126]	synthetic (this work)	synthetic[126]	synthetic[127]
$[\alpha]_D = +7.5°$ (MeOH, c = 1)	$[\alpha]^{25}_D = +20.5°$ (MeOH, c = 1.05)	$[\alpha]_D = +7.66°$ (MeOH, c = 2)	$[\alpha]_D = +4.8°$ (EtOH, c = 1.3)

The new synthesis of *S*-(+)-fusarinolic acid presented here compares quite favorably to the previously reported routes (*vide supra*). Although the necessary protection of alcohol **221** adds two steps to the synthesis (for a total of six), the overall yield (33%) is more than four times higher than the best route previously reported. This synthesis illustrates the efficiency of annulation methods for the construction of aromatic heterocycles.

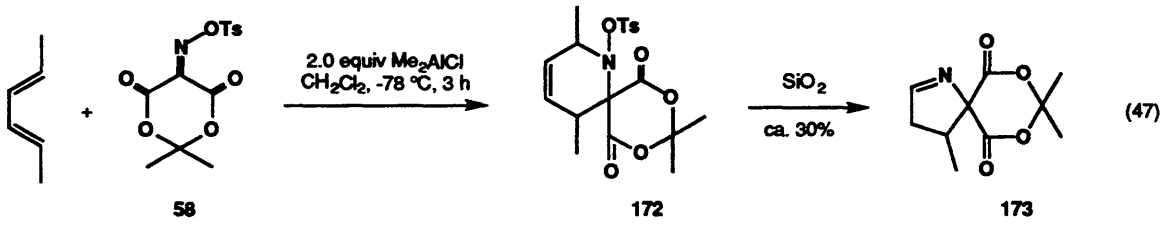
Summary

A new pyridine annulation has been employed for the total synthesis of fusaric acid and *S*-(+)-fusarinolic acid in four and six steps, respectively. The high efficiency of the synthetic routes suggests that this new annulation will be useful for the construction of other substituted picolinic acid derivatives.

Chapter 4
Rearrangement of Oximinosulfonate Cycloadducts to Pyrrolines

This chapter describes rearrangement reactions we have observed in some of the cycloadducts derived from oximinosulfonate **58**. In addition, we present synthetic and mechanistic studies that shed light on the mechanism of these rearrangements.

The first indication that cycloadducts of **58** could undergo rearrangement occurred when we attempted to react 2,4-hexadiene with oximinosulfonate **58** (eq 47). Instead of



58 172 173 (47)

the expected cycloadduct **172**, we observed only the pyrroline **173** after purification by column chromatography. The structure assigned for **173** is fully consistent with its spectral data (^{1}H and ^{13}C NMR, IR).[131] We were intrigued by the rearrangement of **172** to **173** since this transformation involves a ring contraction with concurrent loss of a carbon atom from **172**. In considering possible mechanisms for this rearrangement, it seemed possible that vinyl migration to nitrogen in **172** might be involved in its conversion to **173**. The migration of alkyl, aryl, and vinyl groups to nitrogen is in fact well known. A brief discussion of the literature pertaining to this chemistry will be helpful in understanding the rearrangements of cycloadducts such as **172**.

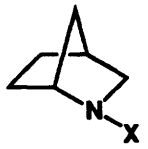
The Stieglitz Rearrangement

In the early part of this century, Stieglitz and co-workers observed that trityl-*N*-chloramines and tritylhydroxylamines rearrange to give, after hydrolysis, aniline and

[131] A more thorough structural analysis of these pyrrolines will be presented later in this chapter.

benzophenone.[132] This rearrangement involves the migration an aryl group to nitrogen, generating an iminium ion. Hydrolysis of this species produces the observed products. Today, the migration of aryl, alkyl, or vinyl groups to *N*-chloroamines or hydroxylamine derivatives (N-OSO_2Ar, N-OC(O)R, etc.) is referred to as the Stieglitz rearrangement.

There has been a considerable amount of interest in the Stieglitz rearrangements of bridged bicyclic systems such as **226**. The *N*-chloro derivatives undergo Stieglitz

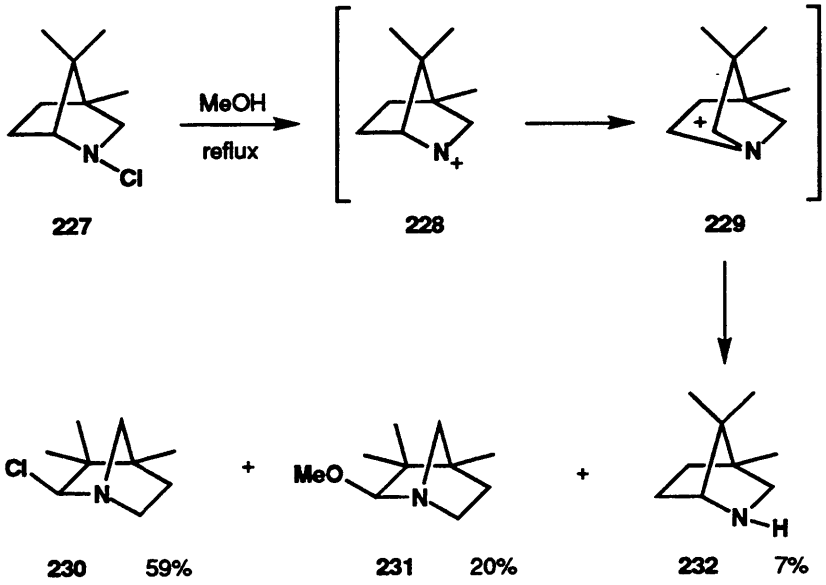


226 X = Cl, OSO_2Ar

rearrangement upon solvolysis in refluxing methanol whereas the sulfonyloxy derivatives often rearrange spontaneously at or below room temperature. The mechanism of these rearrangements has been of particular interest, especially with regard to the nature of the nitrogen species involved in the reaction. Gassman[133] and co-workers have suggested that an electron-deficient divalent nitrogen species (a nitrenium ion) is a discrete intermediate in these reactions. As shown in Scheme 26, solvolysis of **227** in refluxing methanol leads to nitrenium ion formation (**228**) and subsequent alkyl migration to give **229**. Reaction of this iminium ion with chloride ion or solvent produces the products **230** and **231**, respectively. The formation of reduced products (the amine **232**) was suggested to arise from intersystem crossing of the nitrenium ion **228** to the triplet species. The triplet diradical would then abstract hydrogen atoms from the solvent to give an ammonium salt and then, after neutralization, the amine **232**. When the solvolysis was conducted in mixtures of methanol and chloroform or bromoform, the reduced species (**232**) was formed in much greater amounts. This result seems to support the existence of a discrete

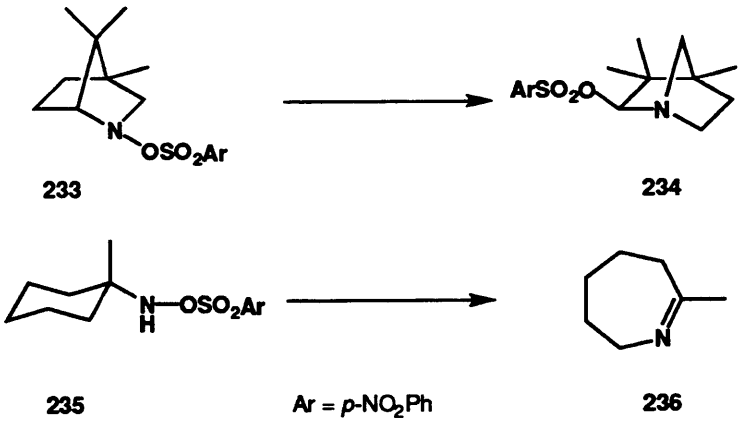
[132] (a) Stieglitz, J.; Leech, P. N. *Chem. Ber.* **1913**, *46*, 2147. (b) Stieglitz, J.; Leech, P. N. *J. Am. Chem. Soc.* **1914**, *36*, 272.
[133] (a) Gassman, P. G. *Acc. Chem. Res.* **1970**, *3*, 26 and references cited therein. (b) Gassman, P. G.; Hartman, G. D. *J. Am. Chem. Soc.* **1973**, *95*, 449.

Scheme 26



nitrenium ion in the rearrangement since increased intersystem crossing (due to a heavy-atom effect) could explain the increased yield of **232**.

Hoffman[134] has shown that *N*-arylsulfonyloxyamines are particularly prone to Stieglitz rearrangement. As shown below, rearrangement of the nosylates **233** and **235** produced the products **234** and **236** but none of the corresponding reduced compounds

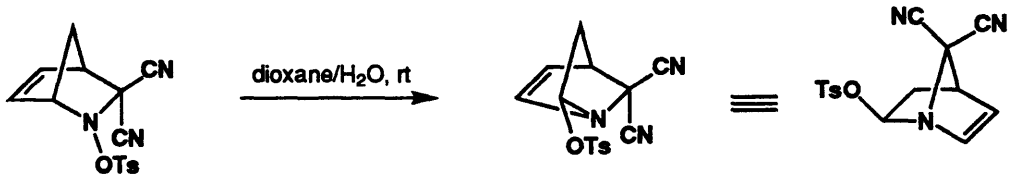


(even when heavy atom solvents were used).[135] When the rearrangments were effected under high dilution conditions in methanol, no products of methanol capture were

[134] Hoffman, R. V.; Kumar, A. K.; Buntain, G. A. *J. Am. Chem. Soc.* **1985**, *107*, 4731.

observed. Based on these results and those of other workers, Hoffman concluded that "rearrangement is concerted with leaving group loss, and that products result from the collapse of intimate ion pairs".[134] These workers also outlined the factors that govern the ease with which Stieglitz rearrangement can occur. The leaving group plays an important role, with the order of reactivity being N-OSO_2Ar > N-Cl > N-OC(O)R. Another important factor is the structural arrangement of the migrating and leaving groups. In particular, the migrating group must be antiperiplanar to the leaving group in order for rearrangement to occur.[134]

Fleury and co-workers reported Stieglitz rearrangements in bicyclic cycloadducts of oximinosulfonate dienophiles.[136] For instance, the cyclopentadiene cycloadduct **237** rearranged to the bicycle **238** upon treatment with dioxane/H_2O at room temperature (eq 48). As in the systems studied by Hoffman, the rearrangement of **237** was stereospecific,



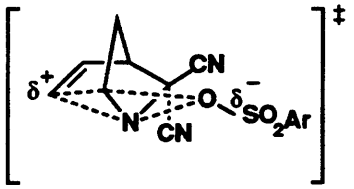
237 **238** (48)

producing exclusively the *exo* product **238**. This selectivity was taken as evidence for a concerted reaction with internal return of ions from an intimate ion pair. The transition state **239** was proposed for the rearrangement.[136c] The rearrangement of **237** to **238** is different from the systems studied by Hoffman and Gassman in that the migrating group is *vinyl* rather than alkyl. In fact, Fleury found that this unsaturation facilitates the

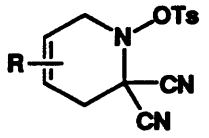
---

[135] These results have cast doubt on the existence of triplet nitrenium ions in these reactions. Hoffman has suggested that the formation of reduced products (such as **232**) is due to protonated or metallated nitrogen radical cations, formed by homolytic cleavage of the N-X bond in the protonated (or metallated) starting materials.

[136](a) Fleury, J.-P.; Biehler, J.-M.; Desbois, M. *Tetrahedron Lett.* **1969**, 4091. (b) Biehler, J.-M.; Fleury, J.-P. *Tetrahedron* **1971**, *27*, 3171. (c) Fleury, J.-P.; Desbois, M. *J. Heterocycl. Chem.* **1978**, *15*, 1005.



239



240

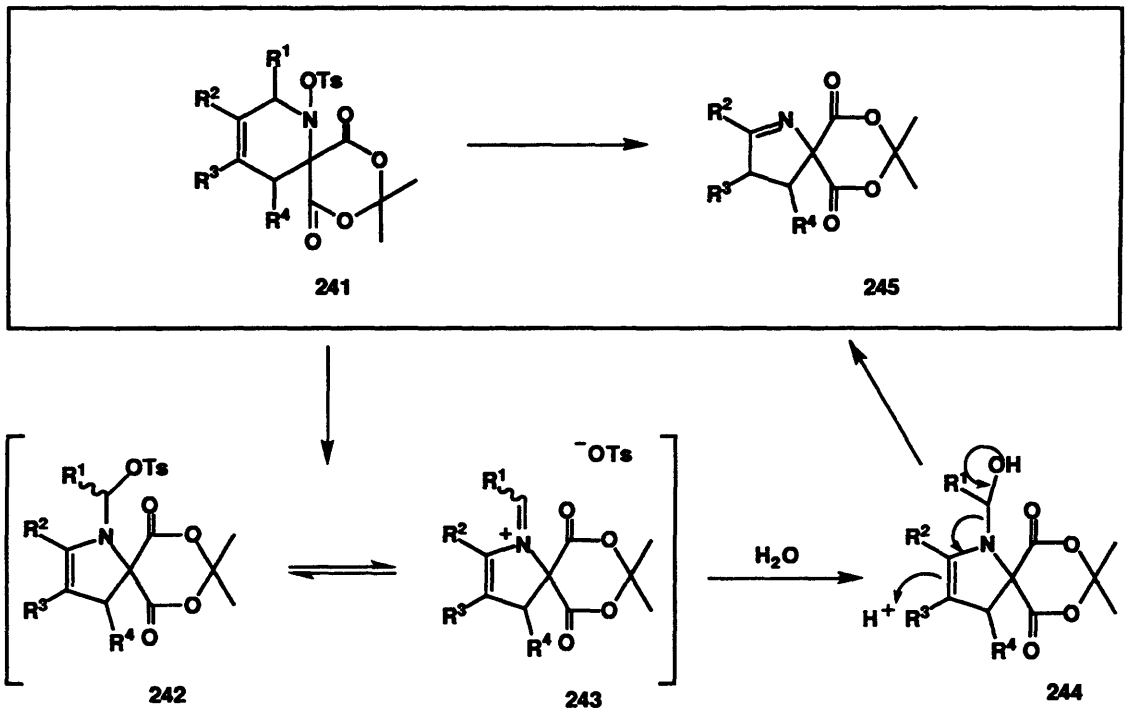
rearrangement.[137] When **237** was hydrogenated, the resulting bicycle required more forcing conditions to effect rearrangement. While the rearrangement was facile in bridged cycloadducts such as **237**, Fleury observed no such rearrangement in comparable monocyclic adducts such as **240**.

Stieglitz Rearrangment of Cycloadducts Derived from Oximinosulfonate 58

We now turn our attention back to the rearrangement of cycloadducts such as **172**. As mentioned in Chapter 2, reaction of oximinosulfonate **58** with 1,4- and 2,3-substituted dienes produces cycloadducts that are especially susceptible to rearrangement. Based on these empirical observations and the work of Gassman, Hoffman, and Fleury, we propose the following mechanism for rearrangements of cycloadducts **241** (Scheme 27). Vinyl migration to nitrogen in **241** is most likely concerted with leaving group loss to give an iminium salt (**243**) or, alternatively, the product of ion pair collapse (**242**). Hydrolysis (in the work-up or during purification) would then be expected to generate the hemiaminal **244**. This species would then fragment as shown to provide the observed pyrroline products **245**. This mechanistic proposal is consistent with the empirical observation that R^1-substitution in **241** facilitates rearrangement (iminium salt **243** would be stabilized by alkyl substituents at R^1). We briefly examined the possibility of trapping the putative iminium species **243** with an external nucleophile. We felt cyanide ion was the ideal nucleophile for this purpose since it would be reactive toward **243** but would not lead to

[137] This effect has also been observed in norbornyl systems and was attributed to anchimeric assistance of ionization by the π electron cloud, see: Winstein, S.; Shatavsky, M.; Norton, C.; Woodward, R. B. *J. Am. Chem. Soc.* **1955**, *77*, 4183.

Scheme 27



fragmentation of the addition product (as occurs in the conversion of **244** to **245**). A variety of cyanide sources and solvents were examined in these experiments.[138] Unfortunately, the only identifiable product formed was the pyrroline (**245**). [139] No products of the desired cyanide addition reaction could be isolated.[140]

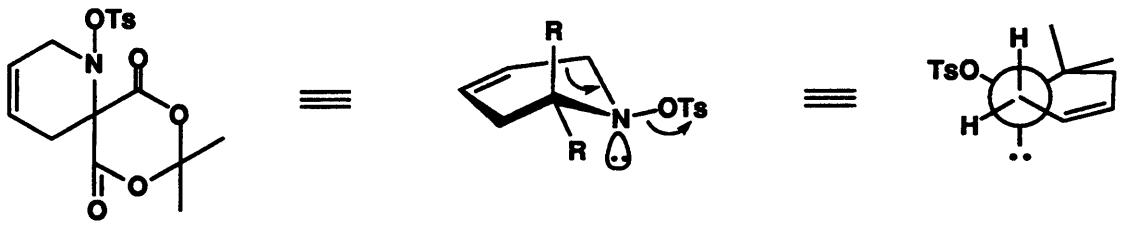
Hoffman has emphasized the importance of stereoelectronic factors in the Stieglitz rearrangement, in particular, the requirement that the migrating group be antiperiplanar with respect to the leaving group.[134] As shown below, cycloadducts **241** do indeed meet this

---

[138] When the isoprene cycloadduct **165** was heated in acetonitrile or benzene in the presence of 3.0 equivalents of alkali cyanide salts (NaCN or KCN), only the normal pyrroline product was observed. The use of a more soluble cyanide source (Me_4NAgCN_2) gave similar results. A switch to DMSO or methanol led to complex mixtures and methanolysis of the dioxadione, respectively.

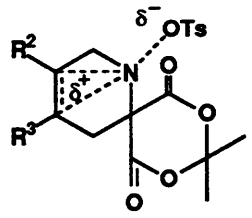
[139] It is unclear how pyrroline formation could have occurred in these experiments since they were conducted in NMR tubes (no work-up) using dried and distilled solvents (no water present). It is possible that attack of cyanide anion on the sulfonyl group in intermediate **242** is responsible for pyrroline formation.

[140] The Fleury group was likewise unable to trap reaction intermediates in their studies with **237**, see ref 136a.



requirement when the leaving group (OTs) is in an equatorial position. A direct vinyl migration to nitrogen in cycloadducts **241** is therefore mechanistically viable with regard to stereoelectronic considerations.

Substitution at R^3 in cycloadducts **241** (Scheme 27) was also observed to promote the rearrangement. This effect is probably related to the role the olefin plays in anchimerically assisting the ionization of the N-OTs bond. As mentioned previously, the presence of unsaturation in bicyclic systems (**237**) was found to facilitate Stieglitz rearrangement.[136c] With cycloadducts **241**, this effect can be understood by considering the relative importance of a species such as **246**. When both R^2 and R^3 are alkyl groups (as is the case when 2,3-substituted dienes are used in the cycloaddition), the resulting

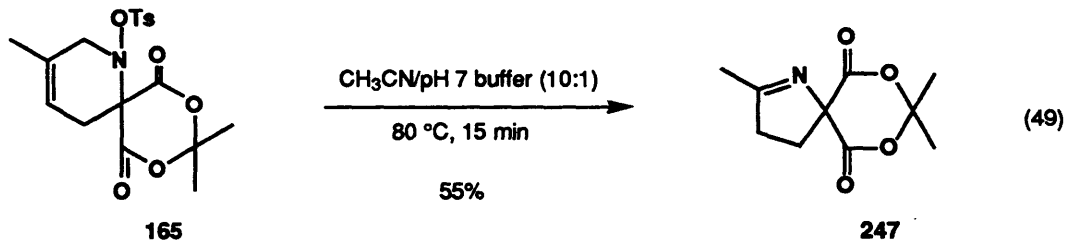


246

anchimeric assistance should be greater due to increased stabilization of the partial positive charge. This increased anchimeric assistance should in turn favor ionization of the N-OTs bond, thereby promoting rearrangement.

Promotion of Stieglitz Rearrangements in Cycloadducts of 58

The rearrangement of cycloadducts **241** most likely is triggered by ionization of the N-OTs bond (Scheme 27). Considering this, we thought it would be possible to promote these rearrangements by subjecting the cycloadducts **241** to reaction conditions that promote ionization and stabilize charge separation. It was our hope that under the appropriate reaction conditions, a variety of cycloadducts **241** could be converted to pyrrolines **245** (including those cycloadducts that are not normally prone to rearrangement). To examine this possibility, we conducted experiments with cycloadduct **165** (which does not rearrange under normal circumstances). After some experimentation, we found that heating this cycloadduct in a mixture of acetonitrile and pH 7 phosphate buffer produced the rearranged pyrroline **247** in 55% yield (eq 49).[141] The modest yield

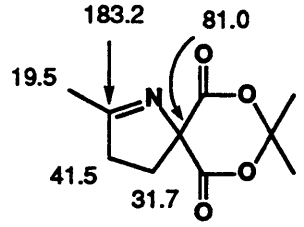


165 247 (49)

of **247** is due in part to the sensitivity of this compound to purification on silica gel (the mass balance of products before chromatography was as high as 89%). The use of a buffered solution in the above reaction (eq 49) results in significantly higher yields (by ca. 30%) than are obtained with unbuffered solutions. The role of the buffer is to neutralize the TsOH produced in the rearrangement. The use of K_2CO_3 or NaOAc in these reactions led to much lower mass balance of products and increased formation of elimination products. The use of THF or DMSO in place of acetonitrile led to complex mixtures and decomposition, respectively.

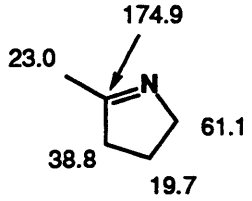
[141] This was accompanied by a small amount (<10%) of another product that was not fully characterized but is believed to be a dihydropyridine, formed by elimination of TsOH from **165**.

The structural assignment for **247** was fully consistent with the spectral data (^{1}H and ^{13}C NMR, IR, GC/MS). The assignment of ^{1}H and ^{13}C NMR signals in **247** is shown below along with the signals for the known pyrroline **248**.[142] Additional evidence



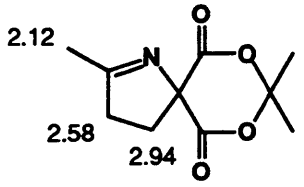
IR: 1640 cm^{-1} (C=N)

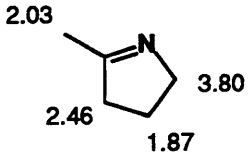
247



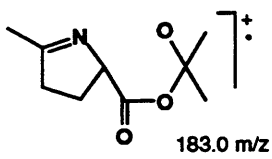
IR: 1645 cm^{-1} (C=N)

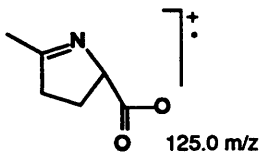
248

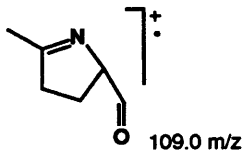


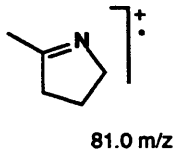


for the structure of **247** was provided by the fragmentation pattern observed by GC/MS analysis. In addition to a molecular ion at 211.0 m/z, a peak is observed at 196.0 m/z for the $(M - CH_3)^+$ fragment and several other peaks corresponding to the fragments shown









above are also observed. This data confirms that a carbon atom is indeed lost during the rearrangement of cycloadduct **165**.

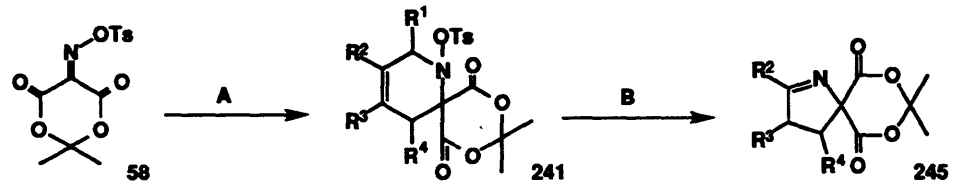
The conditions that were developed for the conversion of cycloadduct **165** to pyrroline **247** (eq 49) were subsequently employed in the synthesis of other pyrrolines.

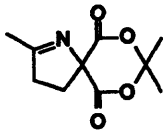
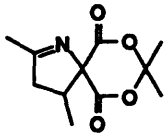
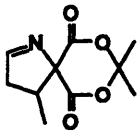
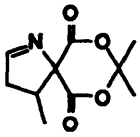
---

[142] (a) ^{13}C and IR data: Vaultier, M.; Lambert, P. H.; Carrié, R. *Bull. Soc. Chim. Fr.* **1986**, 83. (b) ^{1}H NMR data: Hua, D. H.; Miao, S. W.; Bharathi, S. N.; Katsuhira, T.; Bravo, A. A. *J. Org. Chem.* **1990**, *55*, 3682.

The results of these studies are shown in Table 5. For purposes of comparison, it is necessary to report the overall yields for the two step cycloaddition-rearrangement reaction sequence. The overall yields of pyrroline products are modest to low. Ketimines (**247** and **249**) are formed in higher yield than the aldimine **173**, presumably due to the higher stability of the former species. Significantly, reaction with either 1,3-pentadiene or 2,4-

Table 5. Synthesis of Substituted Pyrrolines From 1,3-Dienes



Diene	Reaction Time (B)	Product	Overall Yield
	15 min	 247	42%
	45 min	 249	45%
	2 h	 173	24%
	< 5 min	 173	35%

Conditions: **A**: 3.0 equiv diene, 2.0 equiv Me_2AlCl, 1.0 equiv **58**, CH_2Cl_2, -78 °C
B: CH_3CN/pH 7 phosphate buffer (10:1), 80 °C

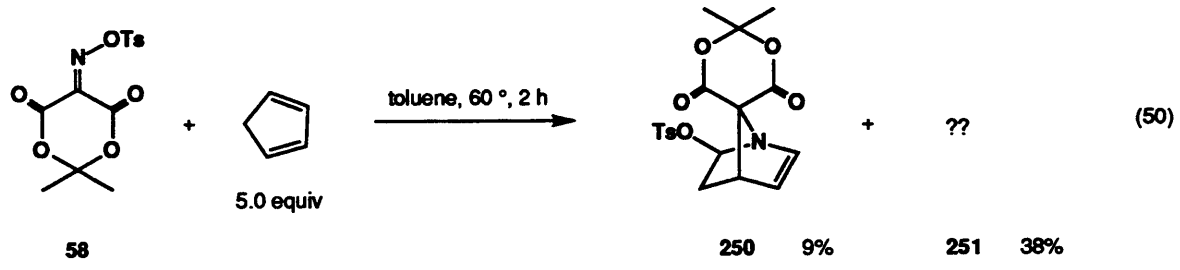
hexadiene gives the same pyrroline product **173**, as would be expected since the carbon α to nitrogen in the cycloadducts (**241**) is lost during rearrangement. The higher reactivity of the hexadiene cycloadduct in the rearrangement (<5 min vs. 2 h) was also anticipated since this cycloadduct is substituted at R^1 (**241**, R^1, R^4 = Me) and should therefore stabilize iminium ion intermediates such as **243** (Scheme 27). In addition to pyrrolines, small

amounts (<10%) of other products are sometimes formed in the above reactions (Table 5). Although not fully characterized, these products appear to be tetrahydropyridines, formed by the elimination of TsOH from cycloadducts **241**.

The Stieglitz rearrangements of cycloadducts **241** are believed to be the first examples of vinyl migration in simple nonbridged cyclic systems. It remains unclear why cycloadducts **241** undergo Stieglitz rearrangements while the corresponding cycloadducts **240** (*vide supra*) reported by Fleury do not. Perhaps the dioxaspiro ring system in **241** affects the conformation of the tetrahydropyridine ring in such a way that rearrangement is facilitated. Alternatively, unfavorable steric interactions between the dioxadione ring of **241** and the large tosyl group may help promote ionization of the N-OTs bond.

Novel Rearrangements in the Reaction of Oximinosulfonate 58 with Cyclopentadiene

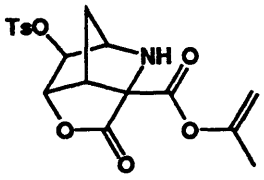
The reaction of oximinosulfonate **58** with cyclopentadiene is presented separately because of the novel rearranged products formed in this reaction. When **58** was heated in toluene (sealed tube) with cyclopentadiene for 2 h at 60 °C, two products were isolated following column chromatography, neither of which was the expected cycloadduct (eq 50). The minor product (**250**, 9% yield) was that resulting from Stieglitz rearrangement, analogous in structure to the bicycle **238** (eq 48) reported by Fleury.[136]



The major product of the reaction (**251**, 38% yield) was not so easily identified. It was clear by inspection of the ^{1}H and ^{13}C NMR spectra that **251** possessed all the hydrogen (19) and carbon (18) atoms expected for the cycloadduct of **58** and

cyclopentadiene. It was also clear, however, that major structural rearrangements had occurred. Although **251** possessed a tosyl group, it was apparently bound to *carbon* in **251** since the IR and ^{1}H NMR data strongly suggested the presence of a secondary amine.[143] Also puzzling was the observation that compound **251** had only 2 methyl groups (one of which belonged to the tosyl group). This suggested that the acetonide of the dioxadione ring had been altered in some fashion.

We also performed more advanced NMR experiments (DEPT and TOCSY) to assist in assigning the structure of **251**. The DEPT experiment indicated the presence of 2 methyl, 2 methylene, 8 methine, and 6 quaternary carbons in **251**. The TOCSY (TOtal Correlation SpectroscopY) experiment helped identify the different spin systems present in **251** and their relative proximity. With this new data in hand, we were eventually able to assign the structure shown below for **251**. This interesting tricyclic structure is fully

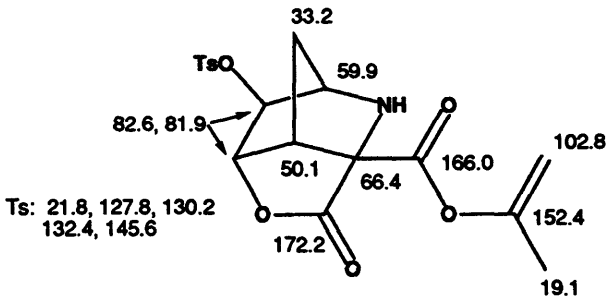


251

consistent with the spectral data obtained for product **251**. The complete data from the ^{13}C NMR and DEPT experiments is tabulated below, along with the assignments for **251**.

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

δ 19.9	CH_3	δ 102.8	CH_2
21.8	CH_3	127.8	CH
33.2	CH_2	130.2	CH
50.1	CH	132.4	quat
59.9	CH	145.6	quat
66.4	quat	152.4	quat
81.9	CH	166.0	quat
82.6	CH	172.2	quat

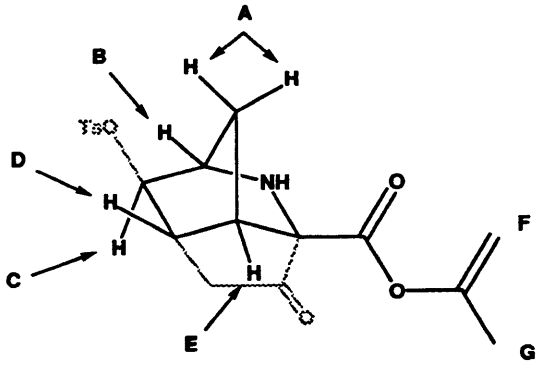


[143] IR: 3345 cm^{-1}; ^{1}H NMR: δ 2.63 (br s) that was not observed in the presence of D_2O.

The ^{1}H NMR and data for **251** was consistent with the assigned structure, and supports an *exo* orientation for the tosylate group. The information gleaned from the TOCSY experiment is tabulated below. In examining this data, it is equally important to consider those ^{1}H NMR signals that *do not* correlate strongly as it is to consider those that do. For example, strong correlation was observed between the signals for **A** and the two bridgehead protons **B** and **E**. Correlation was also observed between **A** and **C**, but not between **A** and **D**. These observations allow the assignment of proton **C** to be made since W-coupling might be expected between **C** and **A** (but not between **D** and **A**). In similar fashion, the TOCSY correlation data allowed all of the ^{1}H NMR signals in **251** to be assigned.

TOCSY

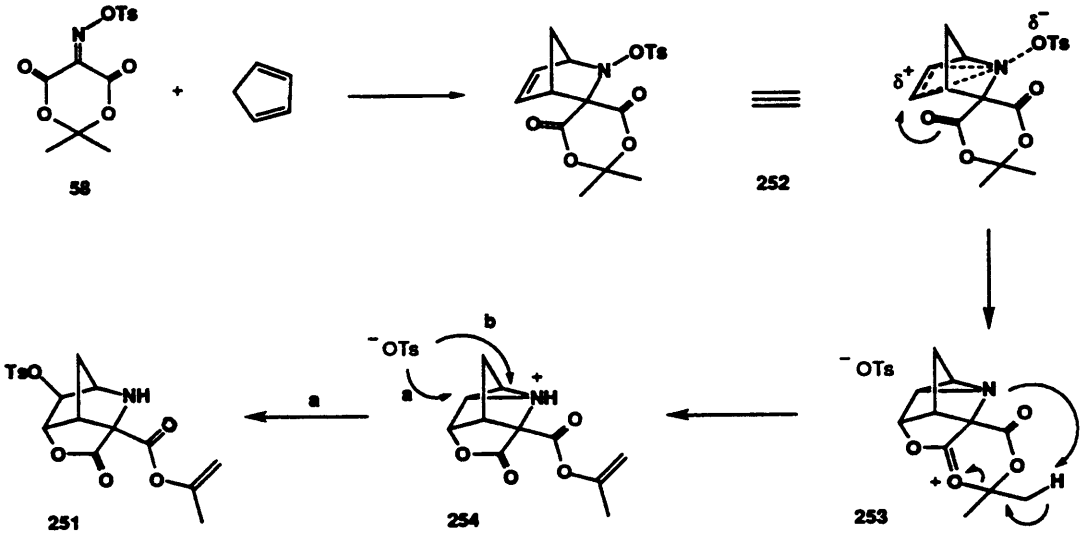
strong correlation		weak or no correlation	
A-B	B-D	A-D	F-(A-E)
A-C	C-D	B-E	G-(A-E)
A-E	D-E	C-E	
B-C	F-G	D-A	



Scheme 28 presents a possible mechanistic pathway for the rearrangement of the initially formed cycloadduct **252** to the observed product **251**. Ionization of the N-OTs bond in **252** should be assisted anchimerically by the olefin, as shown. Nucleophilic attack of the *endo* carbonyl on this electrophilic π bond would generate the aziridine intermediate **253**. Deprotonation of this species at one of the acetonide methyl groups opens the dioxadione ring system to give an aziridinium ion (**254**). The collapse of this ion pair by attack of tosylate at the aziridinium ion would then generate the observed product **251**. In principle, this tosylate addition could occur at either carbon of the aziridinium ion **254** (path **a** or **b**, Scheme 28). Since the only product isolated is **251**, it

seems there is a strong preference for attack via path **a**. [144] It was not obvious from inspection of a computer-minimized model of **254** why attack via path **a** should be favored, although one of the methylene-bridge hydrogens in **254** does partially block nucleophilic attack via path **b**.

Scheme 28

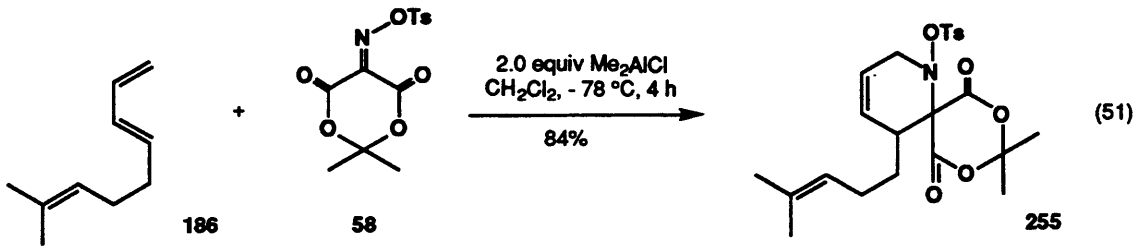


This departure from normal Stieglitz-rearrangement chemistry is novel and results from the presence of an auspiciously situated nucleophile in **252** (the *endo* carbonyl). Although the yield of **251** is modest (38%), it is nonetheless striking that a product of such structural complexity is formed in a single step from relatively simple starting materials. We therefore considered whether an analogous reaction could be observed in simple *unbridged* cycloadducts.

To investigate this possibility, we prepared the cycloadduct **255** by reaction of oximinosulfonate **58** with the diene **186**[145] (eq 51). This reaction proceeded smoothly

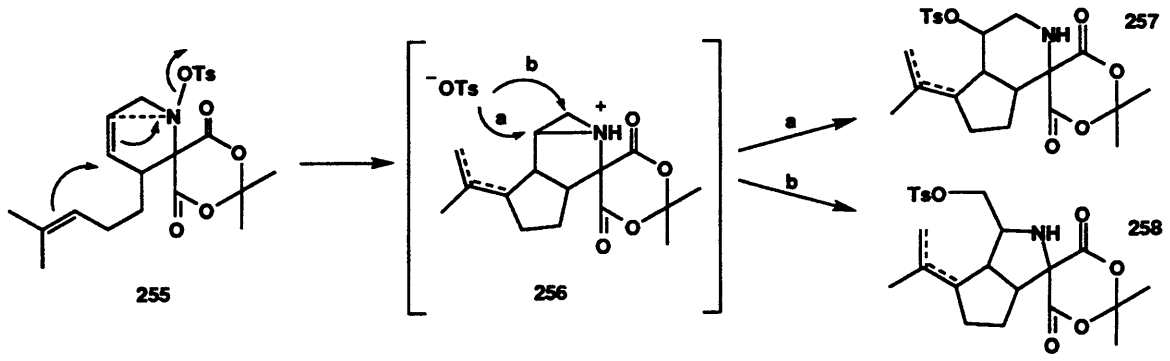
[144] Since the yield of **251** is modest, it is also possible that both modes of attack occur but the product from attack via path **b** is for some reason unstable and not isolable.

[145] Diene **186** was prepared from the ester **30** (Scheme 4) by (a) reduction to the aldehyde with DIBAL, and (b) reaction with the Wittig reagent derived from triphenylisopropylphosphonium iodide.



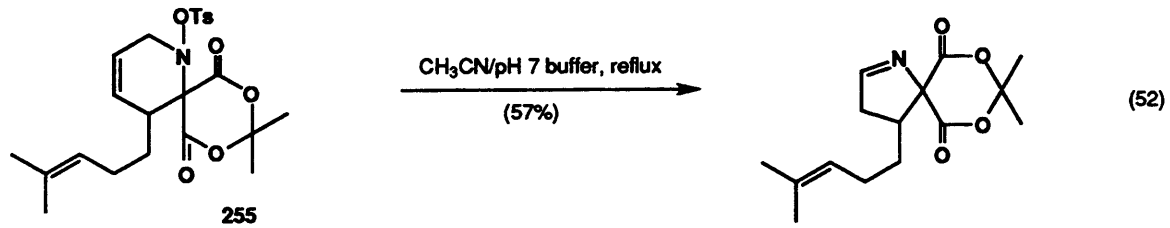
186 58 255 (51)

under the standard conditions to provide **255** in high yield (84%). This cycloadduct has a reactive olefin substituent that we hoped would serve as nucleophile in a cationic cyclization reaction as shown below. Participation of this π bond in the ionization of the N-OTs bond in **255** would generate, after elimination, the aziridinium species **256**. Opening of the aziridine by addition of tosylate would then produce **257** and/or **258**.



255 256

When we heated a benzene solution of **255** to 80 °C in an NMR tube for 1 h, only starting material was observed by ^{1}H NMR. When the same experiment was conducted in DMSO or acetonitrile, complex mixtures of products were formed. When **255** was heated in acetonitrile-pH 7 buffer (10:1), the normal rearranged pyrroline was formed in ca. 57%



255 (52)

yield (eq 52). No evidence for the formation of **257** or **258** could be found. In unbridged cycloadducts such as **255**, migration of the vinyl group to nitrogen is apparently much faster than reaction with the olefin substituent.

Summary

Cycloadducts **241** with substitution at R^1 or R^3 undergo facile Stieglitz rearrangements to give pyrroline products. These rearrangements can be promoted by heating the cycloadducts in a buffered solution of acetonitrile. The cyclopentadiene cycloadduct **252** undergoes a novel rearrangement in which the *endo* carbonyl of the dioxadione ring adds into the π bond of the cycloadduct, generating a product with a bridged tricyclic skeleton.

Part III

Organic Synthesis in Supercritical Carbon Dioxide

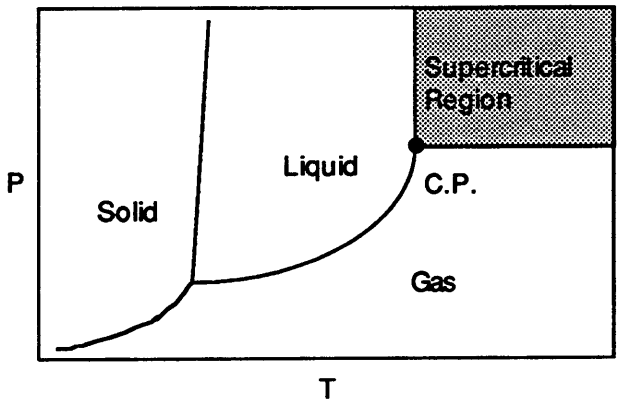
Chapter 1
Background and Introduction

In 1994 our research group began a collaboration with the laboratories of Jefferson W. Tester in the Department of Chemical Engineering to explore the use of supercritical fluids as novel reaction media for organic synthesis. The specific aims of this multidisciplinary research effort included:

- The investigation of the applicability of supercritical carbon dioxide ($scCO_2$) as a solvent for several important classes of organic reactions.
- The investigation of pressure and density effects on the rate and selectivity of organic reactions in $scCO_2$.
- The identification of environmentally benign catalysts and promoters for use in $scCO_2$.
- The invention of new synthetic processes that involve CO_2 as a reactant as well as a solvent.

This chapter reviews the literature pertaining to the use of $scCO_2$ as a reaction solvent for organic synthesis. In addition, we discuss here the unique properties of supercritical fluids which endow them with certain advantages (and disadvantages) when compared to traditional liquid solvents. Chapters 2 and 3 describe studies directed towards the first three research aims listed above. To date, we have made little progress toward achieving the fourth goal - identifying new synthetic methods that involve CO_2 as a reactant. This remains an area of high priority for future work, however.

The critical point of a pure fluid marks the temperature (T_c) and pressure (P_c) above which a liquid and vapor phase can no longer co-exist. Above its critical temperature and



pressure, a pure fluid is said to be "supercritical." Supercritical fluids have properties intermediate between those of liquids and gases. For example, the density of a supercritical fluid is typically between 0.1 and 1.0 g/cm^3. Similarly, the viscosity and diffusivity of a supercritical fluid falls between those of liquids and gases. The critical constants for some common fluids are presented in the table below. Supercritical carbon dioxide is noteworthy in that its critical temperature is quite low (T_c = 31 °C).

Fluid	T_c (°C)	P_c (bar)
xenon	17	58
CHF_3	26	49
CO_2	31	74
hexane	234	30
methanol	239	81
water	374	220

There has been considerable interest recently in the use of supercritical carbon dioxide ($scCO_2$) as a reaction medium for organic synthesis.[146] Much of this interest has

[146] Reviews: (a) Subramaniam, B.; McHugh, M. A. *Ind. Eng. Chem. Process Des. Dev.* **1986**, *25*, 1. (b) Savage, P. E.; Gopalan, S.; Mizan, T. I.; Martino, C. J.; Brock, E. E. *AIChE J.* **1995**, *47*, 1723. (c)

been fueled by environmental and health concerns regarding the use of traditional organic solvents. By comparison, CO_2 is cheap, relatively nontoxic, and poses minimal problems with regard to waste disposal. Aside from these practical advantages, supercritical fluids (and $scCO_2$ in particular) possess many unique properties that could, in principle, be used to influence the rates and selectivities of organic reactions. Some of these properties and their effects are listed below (for $scCO_2$).

- Low viscosity - enhanced diffusion effects
- High compressibility - enhanced thermodynamic pressure/density effects
- Solute/solvent "clustering" effects
- High solubility of gases
- High solubility of fluorinated compounds

The following discussion addresses each of the properties listed above separately. Selected examples of experimental work will also be presented in order to demonstrate the effect of the various properties on actual reactions. In this way, a review of the literature and a discussion of the properties of supercritical fluids will be presented concurrently. For a comprehensive treatment, the reader is directed to the more extensive review articles.[146a-c]

Low Viscosity - Diffusion Effects

Because supercritical fluids (SCF) are less dense and more gas-like than liquids, they also have lower viscosities and greater diffusivities. The rates of diffusion-controlled

---

Morgenstern, D. A.; LeLacheur, R. M.; Morita, D. K.; Borkowsky, S. L.; Feng, S.; Brown, G. H.; Luan, L.; Gross, M. F.; Burk, M. J.; Tumas, W. *ACS Symp. Ser.* **1996**, *626*, 132. (d) Brennecke, J. F. In *Supercritical Fluid Engineering Science: Fundamentals and Applications*; Kiran, E. and Brennecke, J. F., Eds.; ACS Symposium Series 514; American Chemical Society: Washington, DC, 1993; Chapter 16. (e) Poliakoff, M.; Howdle, S. *Chem. Br.* **1995**, *31*, 118. (f) Kaupp, G. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1452 (g) Clifford, T.; Bartle, K. *Chem. & Ind.* **1996**, 449. (h) Phelps, C. L.; Smart, N. G.; Wai, C. M. *J. Chem. Educ.* **1996**, *73*, 1163. (i) Black, H. *Environ. Sci. Technol.* **1996**, *30*, 124A.

reactions are therefore expected to be higher in supercritical fluids. In addition, the rates of these reactions should *increase* as the pressure (and density) of the SCF is *decreased.* This effect should be more pronounced in the near-supercritical region where the fluid is more compressible and the density varies significantly with pressure.

Bright and co-workers studied the effect of density on the rate of pyrene eximer formation in $scCO_2$.[147] The rate of this diffusion-controlled reaction was found to be two orders of magnitude higher in $scCO_2$ than in cyclohexane. This dramatic rate acceleration was attributed to the lower viscosity of the supercritical fluid solvent. In addition, the rate constant was found to increase (from 0.9 to 2.6 x 10^{-11} $M^{-1}s^{-1}$) as the pressure was lowered from 90 to 75 bar (at 32 °C). This is precisely what one would expect for a diffusion-controlled reaction where the diffusivity of the solvent has a dominant effect on the rate of reaction. Brennecke and co-workers reported similar density effects in their studies of benzophenone triplet annihilation and benzyl radical recombination.[148] In this study, a wider range of pressures (ca. 70-300 bar) was examined and, as expected, the most dramatic rate effects were in the near-supercritical region (< 100 bar).

High Compressibility - Enhanced Thermodynamic Pressure/Density Effects

Pressure or density effects on rate are generally small for reactions in liquid solvents since liquids are essentially incompressible.[149] For supercritical fluids, on the other hand, pressure/density effects can be more significant, especially in the highly-compressible region near the critical point. These effects can be understood by considering the pressure dependence of the transition state theory-derived reaction rate constant.[146d] This rate equation (below) includes a term for the activation volume ($\Delta V^{\ddagger}$) of the reaction. The activation volume is the difference in partial molar volumes between the transition state

---

[147] Zagrobelny, J.; Betts, T. A.; Bright, F. V. *J. Am. Chem. Soc.* **1992**, *114*, 5249.
[148] Roberts, C. B.; Zhang, J.; Brennecke, J. F.; Chateauneuf, J. E. *J. Am. Chem. Soc.* **1993**, *97*, 5618.
[149] The use of very high pressure (thousands of atm) to accelerate cycloadditions in liquid solvents is well known, see: Matsumoto, K.; Sera, A.; Uchida, T. *Synthesis* **1985**, 1; 999.

$$\left(\frac{\partial \ln k_x}{\partial P}\right)_T = -\frac{\Delta V^{\ddagger}}{RT}$$

complex and the reactants. Therefore, reactions with a negative activation volume should experience an *increase* in rate with increasing pressure (and density). The reader will note that this trend is opposite to that predicted for diffusion-controlled reactions (*vide supra*) where the diffusivity of the solvent is the dominant factor affecting rate.

Paulaitis and Alexander studied the Diels-Alder reaction of maleic anhydride with isoprene in $scCO_2$.[150] Rate constants for the reaction were determined at three temperatures (35, 45, and 65 °C) and a at range of pressures. The reaction rate was found to increase by a factor of ca. 2 as the pressure was increased from 81 to 435 bar, with the effect being more pronounced in the near-supercritical region (between 81 and 100 bar). The researchers attributed these results to the thermodynamic pressure effect on the rate constant.

Reaction *selectivities* could also be influenced by density or pressure if the competing reaction pathways have different activation volumes. This effect was demonstrated by Kim and Johnston in their studies of the stereoselectivity of the Diels-Alder reaction of cyclopentadiene and methyl acrylate in $scCO_2$.[151] A small increase in the ratio of *endo* to *exo* products from 73.8% *endo* to 74.4% *endo* was observed upon increasing the pressure from 100 to 300 bar. The increase in selectivity was attributed to a smaller partial molar volume for the *endo* transition state as compared to the *exo* transition state.

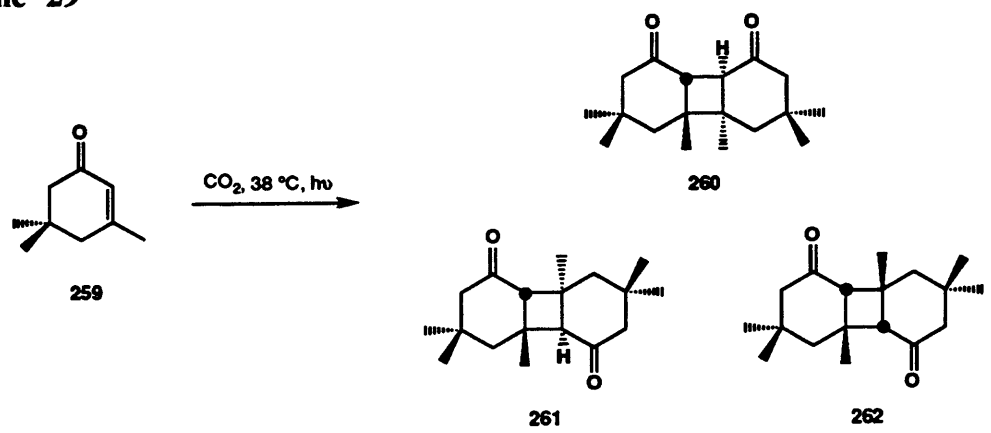
A more pronounced selectivity effect was observed by Johnston and co-workers in their studies of the photodimerization of isophorone (Scheme 29).[152] This reaction was studied in $scCO_2$ and $scCHF_3$ at pressures ranging from 50 to 500 bar. The regioselectivity of the reaction (**260**:(**261**+**262**)) was not affected significantly by pressure, although the

---

[150] Paulaitis, M. E.; Alexander, G. C. *Pure Appl. Chem.* **1987**, *59*, 61.
[151] Kim, S.; Johnston, K. P. *Chem. Eng. Commun.* **1988**, *63*, 49.
[152] Hrnjez, B. J.; Mehta, A. J.; Fox, M. A.; Johnston, K. P. *J. Am. Chem. Soc.* **1989**, *111*, 2662.

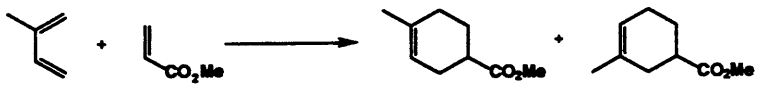
stereoselectivity (**260**:**261**) displayed a rather pronounced pressure effect. The ratio of **261** to **262** increased from 67:33 to 80:20 in $scCO_2$ over the pressure range examined. This increased selectivity was attributed to a thermodynamic pressure effect on the

Scheme 29



competing rate constants, favoring the formation of **261** (the transition state of which was proposed to have the smaller partial molar volume).

Ikushima and co-workers have studied rate and selectivity effects in the Diels-Alder reaction of isoprene and methyl acrylate in $scCO_2$.[153] As in previous Diels-Alder studies,[143] the reaction rate was found to increase with increasing pressure. More striking, however, was the observation that the regioselectivity of the reaction varied significantly with pressure. As shown below, a *reversal* of the normal regiochemical course of the Diels-



CO_2, 49.5 bar, 50 °C	67.1	32.9
CO_2, 74.5 bar, 50 °C	*38.9*	*61.1*
CO_2, 117 bar, 50 °C	71.3	28.7
CO_2,156.9 bar, 50 °C	75.5	24.5

[153] (a) Ikushima, Y.; Ito, S.; Asano, T.; Yokoyama, T.; Saito, N.; Hatakeda, K.; Goto, T. *J. Chem. Eng. Jpn.* **1990**, *23*, 96. (b) Ikushima, Y.; Saito, N.; Arai, M. *J. Phys. Chem.* **1992**, *96*, 2293.

Alder reaction was observed near the critical pressure of pure CO_2 at 50 °C. Ikushima and co-workers attributed this result to steric effects, suggesting that aggregation of solvent molecules around the transition state in the near-critical region in some fashion disfavors the more "sterically stable" para isomer.[153b] Although the aggregation (or "clustering") of solvent molecules around solutes in supercritical fluids has some theoretical and experimental basis (*vide infra*), it is unclear how these effects could alter the regioselectivity of a Diels-Alder reaction so drastically.

Solute/Solvent "Clustering" Effects

There is considerable spectroscopic and theoretical evidence to suggest that the local density of supercritical solvent molecules around a solute can be significantly greater than the bulk density, especially near the critical point of the solution.[154] The presence of higher local density around a solute could, in principle, affect reaction rates and selectivities. This might occur through a change in solvent properties (density, viscosity, and dielectric) near the solute, or by the formation of a solvent cage that prevents the entrance or escape of reactive species. A theoretical study[155] of these solvent "clusters" suggested that the integrity of the cluster is maintained only for a few picoseconds. Therefore, in order for solvent "clustering" to affect a reaction, the reaction must occur within the lifetime of the integrity of the cluster. Experimental evidence that "clustering" effects can affect rates and selectivities has only recently begun to accumulate.

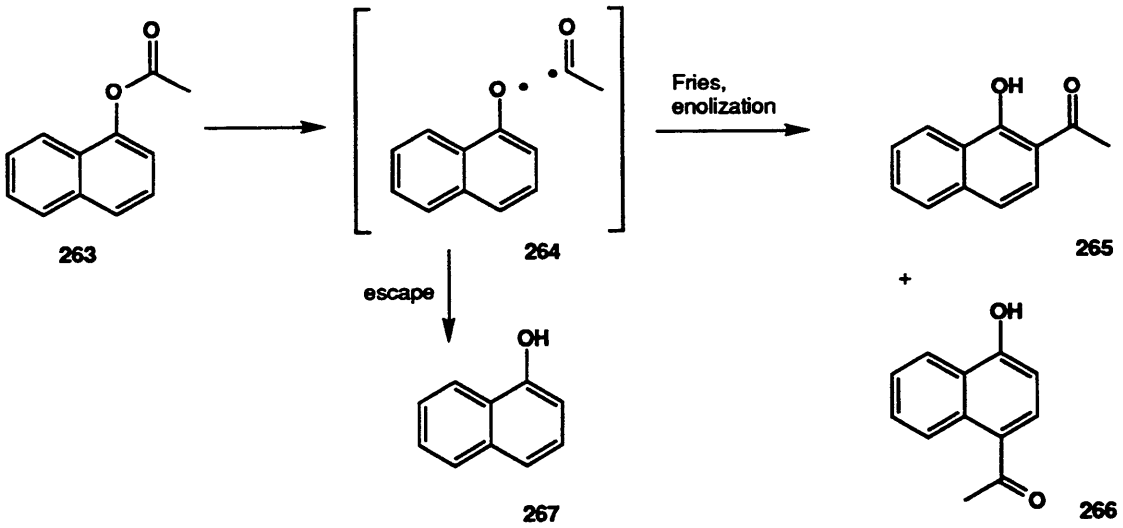
Randolf and Carlier[156] studied Heisenberg spin-exchange between di-*tert*-butyl nitroxide radicals in sc-ethane and found the that the rate of reaction increased with decreasing pressure, as would be expected for a diffusion-controlled reaction. Interestingly, the rates measured in the low density regime near the critical point were *greater* than those predicted from diffusion control. This remarkable observation was

[154] reference 146d, pp 205-215 and references therein.
[155] Petsche, I. B.; Debenedetti, P. G. *J. Chem. Phys.* **1989**, *91*, 7075.
[156] Randolph, T. W.; Carlier, C. *J. Phys. Chem.* **1992**, *96*, 5146.

attributed to solvent cage effects of clustering around the reacting species, resulting in longer collision times and higher reaction rates. The time scale of these collisions is on the order of 0.01 ps while the time between collisions is much longer (10 - 100 ns). The researchers therefore suggest that solvent clustering can affect reaction probabilities but not collision frequency.[156] Finally, it is worth noting that evidence of solvent clustering was *not* found in studies of other diffusion-controlled reactions (*vide supra*).[147,148]

Perhaps the most convincing experimental evidence for the existence of solvent clusters is the recent report by Weedon and co-workers on the photo-Fries rearrangement of naphthyl acetate in $scCO_2$ (Scheme 30).[157] In this work, the ratio of Fries-rearrangement products (**265** and **266**) to cage-escape product (**267**) was measured as a function of pressure in $scCO_2$. This ratio was found to be constant at ca. 4 over much of the pressure range investigated (100 to 340 bar). In the near-supercritical regime (80 to 100 bar), however, the ratio increased dramatically to more than 12, favoring the Fries products

Scheme 30

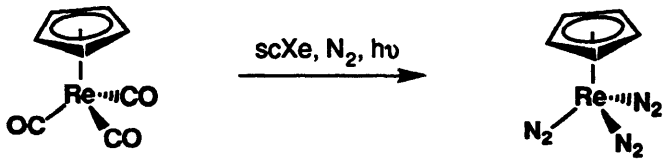


[157] Andrew, D.; Des Islet, B. T.; Margaritis, A.; Weedon, A. C. *J. Am. Chem. Soc.* **1995**, *117*, 6132

(**265** and **266**). This effect was interpreted as resulting from the formation of supercritical solvent clusters around the radical pair **264**, increasing the yield of Fries products while disfavoring radical escape and the formation of **267**. It therefore seems that clustering effects can indeed influence the outcome of chemical reactions, provided they are fast and occur within the statistical lifetime of the solvent cluster.

High Solubility of Gases

A significant advantage of supercritical fluid (SCF) solvents as compared to conventional liquid solvents is the much higher solubility of gases in the former reaction media. Chemical reactions that involve gaseous reagents (H_2, CO, etc.) might therefore be expected to be accelerated when conducted in a SCF solvent. Indeed, the use of SCF solvents for homogeneous catalysis and in the preparation of novel coordination compounds has attracted a considerable amount of attention.[158] For example, Poliakoff and Howdle have generated a variety of previously unknown dinitrogen and dihydrogen transition metal complexes using sc-Xe as solvent (eq 53).[159] The formation of these



(53)

highly labile complexes was possible because of the high concentrations of H_2 and N_2 present in the SCF solvent. The use of sc-Xe offers the additional advantage that the products can be observed spectroscopically during the reaction (sc-Xe is spectroscopically transparent from vacuum UV through the far IR).

---

[158] For reviews, see: (a) Jessop, P. G.; Ikariya, T.; Noyori, R. *Science*, **1995**, *269*, 1065. (b) ref 146e.
[159] see ref 146e and references cited therein.

In 1994, Noyori and co-workers reported the catalytic hydrogenation of $scCO_2$ to produce formic acid.[160] The hydrogenation reaction was catalyzed by $RuH_2(PMe_3)_4$ and was found to be 18 times faster in $scCO_2$ than in THF. The observed rate acceleration was not simply a result of higher CO_2 concentration since the reaction was very slow in *liquid* CO_2. Rather, the accelerated reaction rate in $scCO_2$ can be attributed to the high miscibility of H_2 gas in the supercritical phase and to the excellent mass-transfer capabilities of this solvent. Other examples of homogeneous catalysis in $scCO_2$ using gaseous reagents include the asymmetric hydrogenation[161] of α-enamides, the hydroformylation[162] of terminal alkenes, and Pauson-Khand[163] reactions. In these cases, rates and selectivities were similar to those reported in traditional organic solvents.

High Solubility of Fluorinated Compounds

The solvating ability of $scCO_2$ is often compared to that of non-polar organic solvents (e.g., heptane, carbon tetrachloride) or to fluorocarbon solvents.[146e] As these comparisons suggest, in $scCO_2$ the solubility of polar organic molecules, let alone inorganic reagents and catalysts, is very low. A striking exception are the fluorocarbons which display very high solubility in $scCO_2$. This may be due to the poor solvating properties (low polarizability, small dielectric) of both fluorinated compounds and $scCO_2$, or to favorable electrostatic interactions[164] between CO_2 and the fluorocarbons.

A common strategy for the solubilization of insoluble catalysts and reagents has been the preparation of special fluorinated derivatives. For example, a number of organometallic complexes for homogeneous catalysis have been rendered soluble in $scCO_2$

---

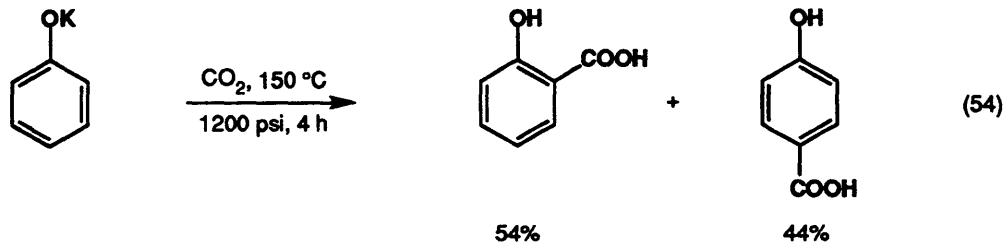
[160] (a) Jessop, P. G.; Ikariya, T.; Noyori, R. Nature 1994, 368, 231. (b) Jessop, P. G.; Hsiao, Y.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1996**, *118*, 344.
[161] Burk, M. J.; Feng, S.; Gross, M. F.; Tumas, W. *J. Am. Chem. Soc.* **1995**, *117*, 8277.
[162] (a) Rathke, J. W.; Klingler, R. J.; Krause, T. R. *Organometallics* **1991**, *10*, 1350. (b) Kainz, S.; Koch, D.; Baumann, W.; Leitner, W. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1628.
[163] Jeong, N.; Hwang, S. H.; Lee, Y. W.; Lim, J. S. *J. Am. Chem. Soc.* **1997**, *119*, 10549.
[164] Cece, A.; Jureller, S. H.; Kerschner, J. L.; Moschner, K. F. *J. Phys. Chem.* **1996**, *100*, 7435.

by the use of fluorinated ligands[165] or counter ions.[161] Curran and co-workers have described the synthesis of fluorinated alkylstannanes for use in the mediation of radical cyclization, coupling, and reduction reactions in $scCO_2$.[166]

DeSimone and co-workers have used the solubility characteristics of $scCO_2$ to advantage, demonstrating that this supercritical fluid is an ideal medium for the synthesis of fluorocarbon polymers.[167] For example, the polymerization of fluorinated acrylate monomers in $scCO_2$ (initiated with AIBN) produced polymers identical to those formed in the chlorofluorocarbon (CFC) solvents traditionally used for these polymerizations.

Additional Advantages of $scCO_2$ as a Reaction Medium for Organic Synthesis

The possibility that carbon dioxide could be used as a reactant as well as a solvent is another attractive feature of $scCO_2$ as reaction media. The Kolbe-Schmitt[168] reaction is a classical example of just this type of CO_2 fixation (eq 54). This reaction involves the addition of carbon dioxide at elevated temperatures and pressure to a metal phenolate salt, or alternatively, the corresponding phenol, in the presence of a base such as potassium

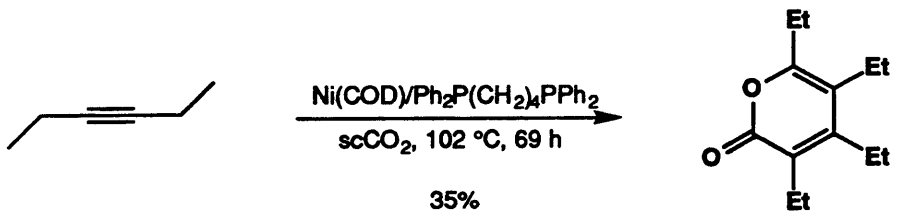


(54)

carbonate. The most recent example of a reaction involving carbon dioxide as a reactant is the ruthenium-catalyzed hydrogenation of $scCO_2$ described by Noyori (*vide supra*).[160] A

[165] (a) Fürstner, A.; Koch, D.; Langemann, K.; Leitner, W.; Six, C. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2466. (b) ref 162b.
[166] Hadida, S.; Super, M. S.; Beckman, E. J.; Curran, D. P. *J. Am. Chem. Soc.* **1997**, *119*, 7406.
[167] DeSimone, J. M.; Guan, Z.; Elsbernd, C. S. *Science* **1992**, *257*, 945.
[168] Lindsey, A. S.; Jeskey, H. *Chem. Rev.* **1957**, *57*, 583.

final example of this type is the nickel-catalyzed reaction of hex-3-yne with carbon dioxide in $scCO_2$, described by Reetz (eq 55).[169] This reaction proved rather sluggish and a large

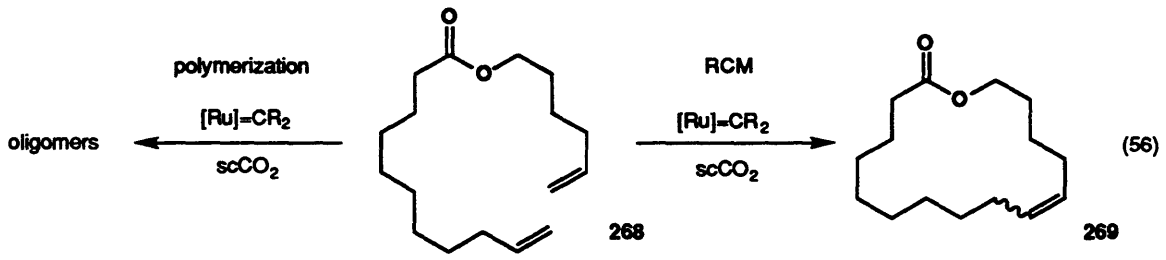


(55)

amount (59%) of the starting material was recovered unreacted. The relative scarcity of reactions using carbon dioxide as a C-1 building block identifies this area as fertile ground for additional research.

Another area in which SCF solvents might find application is in intramolecular ring-forming reactions, particularly those in which large cyclic systems are desired. The formation of large rings is complicated by unfavorable entropic factors, and products of undesired intermolecular reactions are often formed. In liquid solvents, these reactions are typically carried out under high dilution so as to favor the intramolecular process. As the pressure of a SCF solvent is increased, the number of solvent molecules per unit volume (i.e., the density) increases significantly. On the other hand, the number of *solute* molecules per unit volume remains constant as the SCF solvent pressure is increased. Therefore, it should be possible to create greater *effective dilution* simply by increasing the pressure (and hence the density) of a supercritical fluid solvent. This is in fact the case, as has been demonstrated by Fürstner in the ring-closing metathesis (RCM) of the ester **268** (eq 56).[165a] The intramolecular reaction (RCM) of **268** produces the macro lactone **269** whereas the corresponding intermolecular reaction produces oligomers of **268**. The product ratio of lactone to oligomers was found to correlate strongly with the density of the $scCO_2$ reaction media. At densities below 0.65 g/mL, the oligomers were the major product, while at densities above 0.65 g/mL the macro lactone was formed as the major

[169] Reetz, M. T.; Könen, W.; Strack, T. *Chimia* **1993**, *47*, 493.



product (85% yield at ρ = 0.85 g/mL). This result was attributed to greater effective dilution of **268** at higher $scCO_2$ densities, thus favoring the intramolecular RCM reaction over polymerization.

Summary

Supercritical fluids possess many unique properties that could potentially be used to alter the course of organic reactions. However, with a few exceptions, the rate and selectivity effects reported thus far have been rather modest. A significant disadvantage of $scCO_2$ for use as a reaction media is its rather poor solvating properties. In the next chapter, we present our studies of pressure and density effects on the rate and selectivity of Diels-Alder reactions in $scCO_2$. Finally, Chapter 3 presents work aimed at identifying environmentally benign catalysts and promoters for use in $scCO_2$.

Chapter 2
Rates and Selectivities of Diels-Alder Reactions in $scCO_2$

Supercritical fluid solvents possess several unique properties that can, in principle, be used to alter the rates and selectivities of organic reactions. We were especially intrigued by previous reports (Chapter 1) that the regio and stereoselectivity of reactions could be influenced (sometimes dramatically) by changes in the pressure and density of a supercritical reaction medium. If fully realized, this novel mode of selectivity control would represent a significant advance for organic synthesis. We therefore initiated an investigation of pressure/density effects on the rate and selectivity of Diels-Alder reactions in supercritical carbon dioxide ($scCO_2$). The Diels-Alder reaction was selected because of our group's familiarity with this cycloaddition and because a considerable body of literature exists regarding the rate and selectivity of the reaction in normal liquid phase solvents.

The high pressure reactors and related apparatus used in these studies were designed and assembled by Randy D. Weinstein, our collaborator and a chemical engineering graduate student in the research group of Jefferson W. Tester. Mr. Weinstein was also responsible for the maintenance and operation of these reactors during our investigations. Our initial rate studies were conducted in a 1-L stirred stainless steel autoclave manufactured by Autoclave Engineers. The reactor used in our studies of regio- and stereoselectivity was a custom-made stainless steel reactor (ca. 25 mL working volume) incorporating a sapphire window for visual monitoring of phase behavior.

Pressure and Density Effects on the Rate of the Diels-Alder Reaction in $scCO_2$[170]

Several studies of the Diels-Alder reaction in $scCO_2$ have been reported (Chapter 1).[171] In many of these studies, the concept of an activation volume has been used to

[170] Weinstein, R. D.; Renslo, A. R.; Danheiser, R. L.; Harris, J. G.; Tester, J. W. *J. Phys. Chem.* **1996**, *100*, 12337.

explain the pressure dependence of the rate constants in $scCO_2$. It has also been shown that reaction rates can be correlated to solvent parameters such as E_T (the transition energy of phenol blue).[171d,e-g] Unfortunately, these treatments do not allow predictions of reaction rates based on simple properties of the fluid (e.g., the density or pressure). As an initial study, we decided to examine the rate of the Diels-Alder reaction between cyclopentadiene and ethyl acrylate (eq 57). In this study, we hoped to determine which solvent parameters

(57)

(pressure or density) were most important in determining reaction rates in $scCO_2$. In addition, we expected to become familiar with the more practical aspects of performing organic reactions in $scCO_2$.

The rate of the Diels-Alder reaction between ethyl acrylate and cyclopentadiene was studied at 38 °C and pressures from 80 to 210 bar. Rate data was acquired by following the formation of products. For each pressure investigated, $scCO_2$ samples were removed from the reactor at six different times during the course of the reaction (typically 2 days). The amount of product formed at each time was determined by ^1H NMR analysis using an internal standard, and a bimolecular rate constant was then calculated. Figure 1 presents rate constants for the Diels-Alder reaction of cyclopentadiene and ethyl acrylate plotted as a function of CO_2 pressure. Figure 2 presents the same data as a function of density.

---

[171] (a) Hayatt, J. A. *J. Org. Chem.* **1984**, *49*, 5097. (b) Paulaitis, M. E.; Alexander, G. C. *Pure Appl. Chem.* **1987**, *59*, 61. (c) Kim, S.; Johnston, K. P. *ACS Symp. Ser.* **1987**, *329*, 42. (d) Kim, S.; Johnston, K. P. *Chem. Eng. Commun.* **1988**, *63*, 49. (e) Ikushima, Y.; Ito, S.; Asano, T.; Yokoyama, T.; Saito, N.; Hatakeda, K.; Goto, T. *J. Chem. Eng. Jpn.* **1990**, *23*, 96. (f) Ikushima, Y.; Saito, N.; Arai, M. *Bull. Chem. Soc. Jpn.* **1991**, *64*, 282. (g) Ikushima, Y.; Saito, N.; Arai, M. *J. Phys. Chem.* **1992**, *96*, 2293. (h) Isaacs, N. S.; Keating, N. *J. Chem. Soc., Chem. Commun.* **1992**, 876. (i) Clifford, A. A.; Pople, K.; Gaskill, W. J.; Bartle, K. D.; Rayner, C. M. *J. Chem. Soc., Chem. Commun.* **1997**, 595.

The rate of the reaction increases with pressure, as expected based on previous studies[171] of Diels-Alder reactions in $scCO_2$ and as would be expected for a thermodynamic

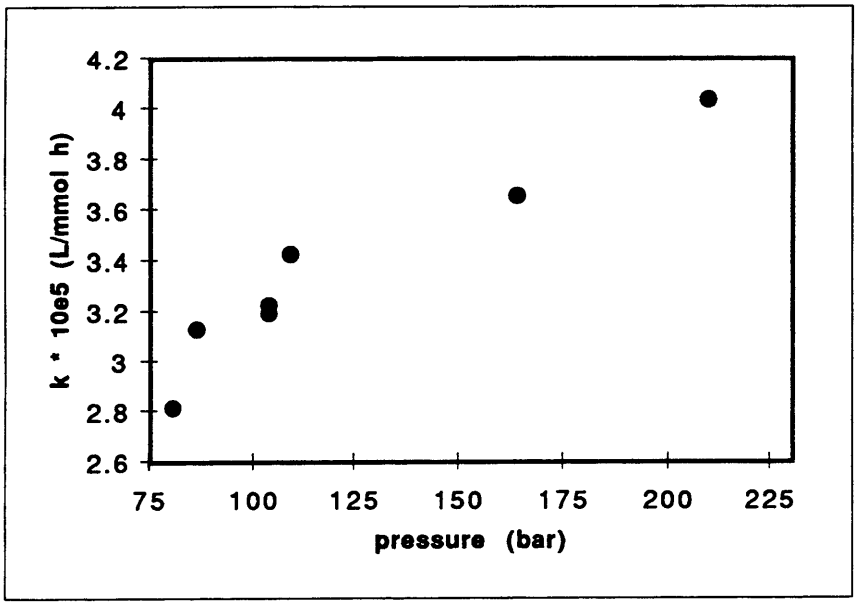


Figure 1. Effect of pressure on the Diels-Alder reaction of cyclopentadiene and ethyl acrylate in $scCO_2$ at 38 °C.

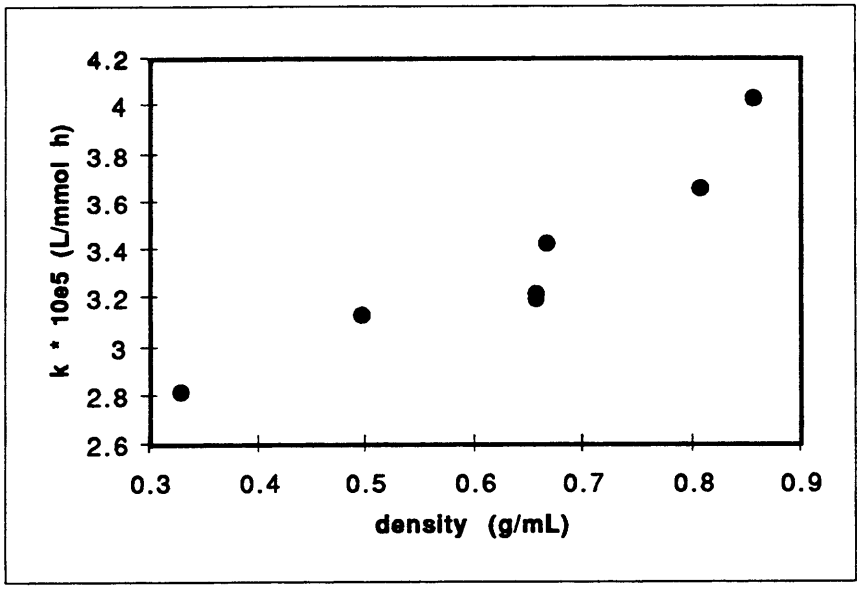


Figure 2. Effect of density on the Diels-Alder reaction of cyclopentadiene and ethyl acrylate in $scCO_2$ at 38 °C.

pressure effect on the rate constant (Chapter 1). As reported previously, the pressure effect appears to be more pronounced in the near-supercritical region (80 to 110 bar, Figure 1). This augmented pressure effect may simply reflect the greater compressibility of the supercritical fluid near the critical point (i.e., the effect of pressure on density is greatest near the critical point). When the rate data are plotted as a function of density (Figure 2), the effect appears to be more linear in nature, with no augmentation near the critical point. These observations seem to suggest that density, not pressure, is the most important solvent property affecting the rate of these reactions (*vide infra*).

The rate of the Diels-Alder reaction between cyclopentadiene and ethyl acrylate was also investigated at *constant density* (0.5 g/mL) and at temperatures from 38 to 88 °C. When these rate constants are plotted as a function of temperature (an Arrhenius plot, Figure 3), an activation energy for the reaction can be determined (E_A = 40 ± 2 kJ/ mol). Whereas other workers have calculated constant-pressure activation energies, we have shown that density is the independent property in these reactions.[170] This is borne out in

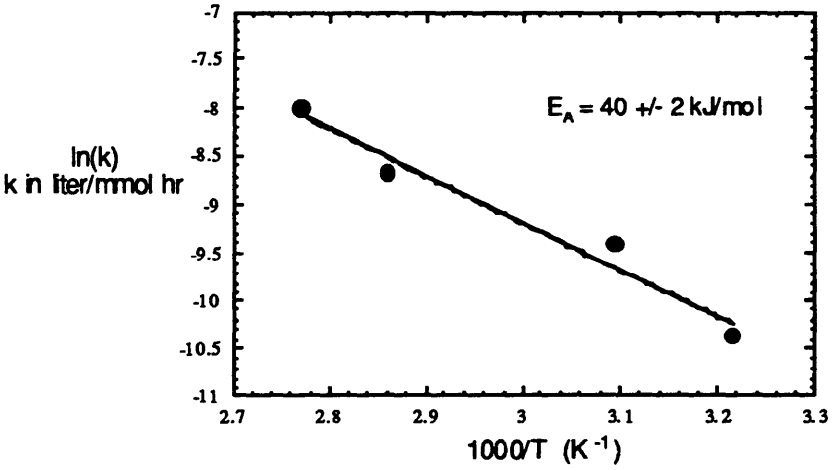


Figure 3. Arrhenius plot of the Diels-Alder reaction of cyclopentadiene and ethyl acryalte at a constant density of 0.5 g/mL.

the density dependence of our empirically-determined rate law for the reaction. The rate law fits the form $k = A(\rho)\ e^{-E_A/RT}$ where $A(\rho)$ is approximately linear in density ($A(\rho) = 138 + 133\rho$ (L/mmol h) when ρ has units of g/mL). Therefore, once an activation energy has been determined experimentally, the rate of reaction can be predicted based solely on the density of the supercritical solution.

It can be demonstrated that density effects on the reaction rate are independent of temperature effects. For example, Figure 4 presents temperature-normalized rate constants, $k(T,\rho)/k(T,\rho_o)$, for the cycloaddition of ethyl acrylate and cyclopentadiene (eq 57) at temperatures from 38 to 88 °C. The density of normalization (ρ_o) was 0.5 g/mL and so all the data sets have a point at $\rho = \rho_o = 0.5$ g/mL and $\ln(k/k_o) = 0$. When plotted in this way, the temperature effects on reaction rate are essentially removed. As shown in Figure 4, all the $\ln[k(T,\rho)/k(T,\rho_o]$ vs ρ data collapse onto a single line, demonstrating that the density effect on the rate constant can be separated from temperature effects.

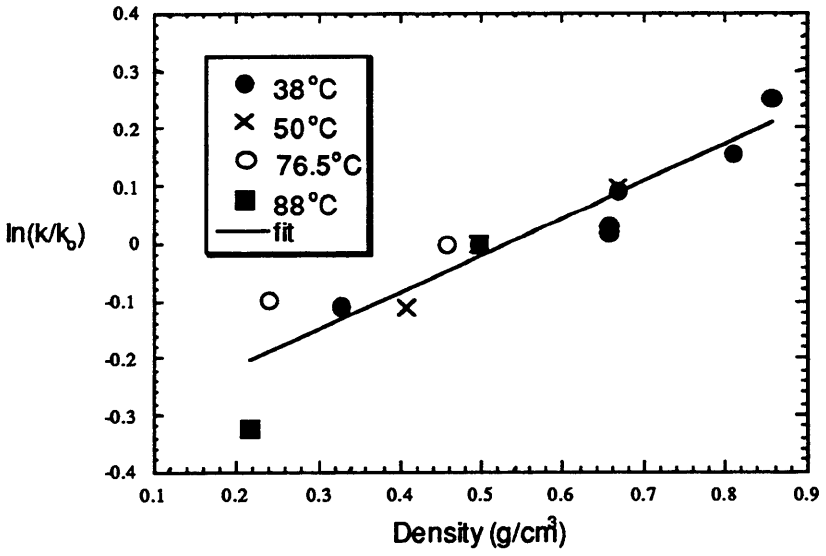


Figure 4. Diels-Alder (cyclopentadiene and ethyl acrylate) rate constants at various temperatures normalized to the rate constant at the same temperature and a fixed density of 0.5 g/mL.

In summary, the rate of the Diels-Alder reaction between cyclopentadiene and ethyl acrylate was studied at pressures from 80 to 210 bar and at temperatures from 38 to 88 °C. An activation energy of 40 ± 2 kJ/mol was determined at a constant density of 0.5 g/mL. The reaction rate increases with increasing pressure (and density) and can be predicted from the density of the supercritical solution and an experimentally determined activation energy. The magnitude of the density effect on the rate constant is rather small and is consistent with the effects reported in other studies[171] of Diels-Alder reactions in $scCO_2$. The rate of the cycloaddition in $scCO_2$ at 38 °C was somewhat lower than that in methylene chloride (4.6×10^{-5} L/mmol h), tetrahydrofuran (3.1×10^{-5} L/mmol h), or hexane (2.3×10^{-5} L/mmol h) at 25 °C and 1 bar.

The Regiochemical Course of the Diels-Alder Reaction in $scCO_2$[172]

Ikushima and co-workers[171e,g] have noted a striking pressure effect on the regiochemistry of the Diels-Alder reaction in $scCO_2$ (Chapter 1). When the reaction of isoprene with methyl acrylate was conducted near the critical pressure of CO_2 at 50 °C, a *reversal* of the normal regiochemical course of the reaction was observed. We were intrigued by the prospect that Diels-Alder regiochemistry could be significantly altered simply by varying reaction conditions in a supercritical reaction medium. This novel mode of regiocontrol would represent a significant advance for organic synthesis, and so we initiated a systematic investigation of the effects of $scCO_2$ pressure and density on the regiochemical course of the Diels-Alder reaction.

The view-cell reactor used in these studies has a working volume of ca. 25 mL and incorporates a sapphire window for visual verification of phase behavior in supercritical fluid (SCF) solutions. This ability to monitor phase behavior is important since the critical locus of a SCF can change significantly in the presence of solutes (e.g., reactants and

[172] Renslo, A. R.; Weinstein, R. D.; Tester, J. W.; Danheiser, R. L. *J. Org. Chem.* **1997**, *62*, 4530.

products).[173] In our studies, we chose to sample the entire reaction mixture in order to eliminate any errors associated with partial sampling of (possibly non-homogeneous) SCF solutions. Sampling was accomplished by the slow release of reactor pressure through a long tube immersed in diethyl ether and by thorough rinsing of the reactor and sampling lines.

Table 6 summarizes the results of our systematic investigation of the regiochemical course of the Diels-Alder reaction in $scCO_2$. The first reaction examined was that between isoprene and methyl acrylate, for which a dramatic reversal in regiochemistry had been previously reported.[171e,g] We began by examining this reaction under the identical conditions of pressure, temperature and concentration (Table 6, entries 3, 4, 6) as had been used in the previous study. Entry 4 represents the conditions under which a dramatic reversal in regiochemistry had been observed (74.5 bar and 50 °C). When the reaction was conducted under these conditions, we were surprised to observe a *two-phase* mixture through the reactor window. Analysis of the reaction mixture after 4 days at 50 °C revealed the formation of cycloadducts[174] **270** and **271** in a ratio very similar to that obtained in toluene (entries 1 and 2); i.e., no deviation from normal Diels-Alder regioselectivity had occurred. Similar regioselectivity was observed when the reaction was conducted at 50 °C and 95.2 bar (entry 5), the pressure at which we first observed the formation of a homogeneous supercritical phase. In fact, under all conditions examined, the dramatic selectivity effects reported by Ikushima and co-workers were not observed.

In light of these results, it is possible that the previously reported reactions[171e,g] may have been conducted in a two-phase region below the critical point of the mixture. Although pure CO_2 exists as a homogeneous supercritical phase at 74.5 bar and 50 °C, a two-phase mixture may be obtained when solutes (reactants and/or products) are present.

---

[173] (a) McHugh, M.A.; Krukonis, V. J. *Supercritical Fluid Extraction, 2nd ed.*; Butterworth-Heinemann: Boston, MA, 1994; Chapters 3 and 5. (b) Adrian, T.; Hasse, H.; Maurer, G. *J. Supercritical Fluids* **1996**, *9*, 19. (c) Wendland, M., Hasse, H.; Maurer, G. *J. Supercritical Fluids* **1994**, *7*, 245.

[174] The ^1H NMR spectrum was consistent with that previously reported, see: Devine, P. N.; Oh, T. *J. Org. Chem.* **1992**, *57*, 396.

Since Ikushima and co-workers sampled *aliquots* of reaction mixtures, it seems likely that the results obtained were not representative of the reaction mixture as a whole. We believe that these results highlight the importance of verifying phase-behavior when sampling a CO_2 reaction mixture. Partial sampling techniques are reliable only if the phase behavior is known with certainty (e.g., if it can be monitored visually).

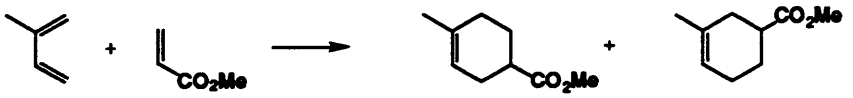
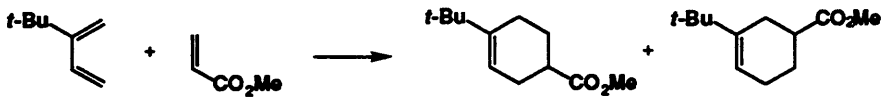
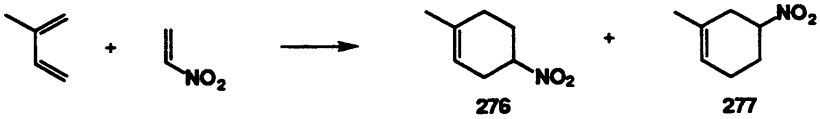
Ikushima and co-workers rationalized the regiochemical results of their study on the basis of *steric effects*, suggesting that the aggregation of solvent molecules around the activated complex in the near supercritical region in some fashion disfavors the "more sterically stable" para isomer, resulting in the preferential formation of the meta isomer.[171g] Although the aggregation of solvent molecules around solutes in supercritical fluids has some theoretical and experimental basis (Chapter 1), it is unclear how this solvent aggregation could have such a dramatic effect on the regioselectivity of the reaction. Furthermore, the stereo- and regiochemical outcome of cycloadditions is generally predicted by considering interactions between frontier molecular orbitals[175] on the reacting partners, rather than by steric factors. Nonetheless, we next designed a series of experiments to determine whether unusual selectivity effects might emerge in reactions involving more sterically and more electronically biased dienes and dienophiles.

Table 6 summarizes the results of our study of steric and electronic substituent effects on the regiochemical course of the Diels-Alder reaction in $scCO_2$. All of these experiments were conducted under single-phase supercritical conditions as verified by visual inspection of reaction mixtures. For each case, at least one experiment was conducted in the near-supercritical region (entries 9, 13, 17), and for comparison, all cases were also evaluated at 117 bar and 50 °C (entries 10, 14, 18). In addition, higher

---

[175] A number of molecular orbital methods have been described. FMO theory: Fleming, I. *Frontier Orbitals and Organic Chemical Reactions*; John Wiley & Sons: London, 1976; pp 121-142. PMO theory: (a) Bonati, L.; Moro, G.; Pitea, D.; Gatti, C. *J. Mol. Struct.: Theochem* **1990**, *208*, 235. (b) Craig, S. L.; Stone, A. J. *J. Chem. Soc., Faraday Trans.* **1994**, *90*, 1663. Complementary reactivity surfaces: Kahn, S. D.; Pau, C. F.; Overman, L. E.; Hehre, W. J. *J. Am. Chem. Soc.* **1986**, *108*, 7381.

Table 6. Regioselectivity of Diels-Alder Reactions in Carbon Dioxide and Conventional Solvents

Entry	Conditions	Yield (%)[a]	Ratio[b]
			
		270	271
1	$PhCH_3$, 145 °, 15 h	78	71:29 (71:29)
2	$PhCH_3$, 50 °, 3 d	(7)	69:31 (72:28)
3[c]	CO_2, 49.5 bar, 50 °, 4 d	(11)	69:31 (73:27)
4[c]	CO_2, 74.5 bar, 50 °, 4 d	(5)	67:33 (73:27)
5	CO_2, 95.2 bar, 50 °, 7 d	(4)	71:29 (73:27)
6	CO_2, 117 bar, 50 °, 3 d	(3)	70:30 (72:28)
			
		272	273
7	neat, 185 °, 16 h	78	63:37 (63:37)
8	$PhCH_3$, 50 °, 3 d	(19)	69:31 (68:32)
9	CO_2, 87 bar, 50 °, 3 d	(5)	71:29 (68:32)
10	CO_2, 117 bar, 50 °, 3 d	(4)	69:31 (68:32)
11	CO_2, 117 bar, 150 °, 24 h	54	65:35 (64:36)
			
		274	275
12	$PhCH_3$, 110 °, 45 h	48	87:13
13	CO_2, 90 bar, 50 °, 3 d	trace[d]	
14	CO_2, 117 bar, 50 °, 3 d	(<1)	92:8[e]
15	CO_2, 117 bar, 150 °, 24 h	(31)	85:15
			
		276	277
16	PhH, BHT, 60 °, 5 h	77	81:19 (81:19)
17	CO_2, 86 bar, 50 °, 3 d	(31)	84:16 (84:16)
18	CO_2, 117 bar, 50 °, 3 d	(14)	84:16 (84:16)

[a] Isolated yield or (estimated by ^1H NMR). [b] Ratio of isomers determined by ^1H NMR and (GC) analysis. [c] Two-phase reaction mixture observed. [d] Ratio could not be determined. [e] Appoximate ratio due to low conversion.

temperature runs were used to determine regioselectivity under conditions that provide cycloadducts in synthetically useful yields (entries 11, 15).

The reaction of 2-*t*-butylbutadiene[176] (entries 7-11) with methyl acrylate was selected in order to test the proposition[171e,g] that steric effects are important in determining the regiochemical course of Diels-Alder reactions in $scCO_2$. We reasoned that the ratio of isomers produced in the reaction of this diene in CO_2 would be more sensitive to reaction conditions as compared to isoprene if steric interactions dominate in determining Diels-Alder regioselectivity. Under all conditions examined, however, the cycloadducts[177] **272** and **273** were formed with little variation in regioselectivity (a small temperature effect on selectivity was noted). In particular, no dramatic reversal in the regiochemical course of the reaction was observed near the critical point of CO_2 (entry 9).

We next turned our attention to varying the electronic character of the diene and dienophile substituents. The reaction of 2-trimethylsiloxybutadiene with methyl acrylate in toluene (reflux, 45 h, entry 12) provided an 87:13 ratio of cycloadducts **274** and **275** (48% yield) as determined by ^1H NMR analysis. [178] In carbon dioxide, this reaction proved very sluggish, affording only traces of **274** and **275** after 3 days at 50 °C (entries 13, 14). At 150 °C, higher conversions were obtained (entry 15) with selectivity similar to that observed in toluene (entry 12). The last system examined involved the reaction of nitroethylene with isoprene. Under standard conditions (benzene, BHT, 60 °C, entry 16) the expected Diels-Alder adducts **276** and **277** were obtained in a ratio of 81:19 and in 77% yield.[179] When the reaction was conducted in $scCO_2$, very similar regioselectivity (84:16) was observed (entries 17, 18). In these reactions the low yields obtained are most

---

[176] Kugatova-Shemyakina, G. P.; Berzin, V. B. *Zh. Org. Khim.* **1971**, *7*, 290.

[177] The ^1H NMR spectrum was consistent with that previously reported, see: Ayral-Kaloustian, S.; Agosta, W. C. *J. Org. Chem.* **1981**, *46*, 4880.

[178] This reaction has previously been reported to give the cycloadducts in a 98:2 ratio, see: Jung, M. E.; McCombs, C. A.; Takeda, Y.; Pan, Y.-G. *J. Am. Chem. Soc.* **1981**, *103*, 6677.

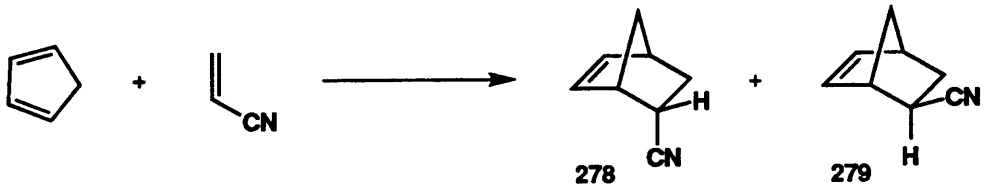
[179] In contrast, a ratio of 95:5 was reported previously under identical conditions, see: Ono, N.; Miyake, H.; Kamimura, A.; Kaji, A. *J. Chem. Soc., Perkin Trans. 1* **1987**, 1929.

likely due to polymerization of the dienophile, since the reactions in CO_2 were performed in the absence of a radical inhibitor (such as BHT).

In summary, the regiochemical course of the Diels-Alder reaction was investigated in $scCO_2$ and conventional reaction media. The reactions of a number of dienes and dienophiles with different steric and electronic attributes were examined in the near-supercritical regime. ^1H NMR and GC analyses of these reactions in CO_2 have failed to confirm the previously reported dramatic effect of varying reaction conditions on Diels-Alder regiochemistry. It seems clear from our studies that careful monitoring of phase behavior is crucial for meaningful analysis of reactions in supercritical media, particularly when sampling small portions of the reactor volume. It is possible that a combination of unknown phase behavior and partial sampling of reaction mixtures may have led to erroneous results in the earlier study[171e,g] of the regiochemical course of the Diels-Alder reaction in supercritical CO_2.

Pressure Effects on the Stereoselectivity of a Diels-Alder Reaction in $scCO_2$

Here we describe our studies regarding the stereoselectivity of the Diels-Alder reaction between acrylonitrile and cyclopentadiene in $scCO_2$ (eq 58). Kim and Johnston[171d] had previously reported a very small (ca. 1%) pressure effect on the *endo/exo* ratio of a



(58)

related reaction in $scCO_2$ (that between methyl acrylate and cyclopentadiene). In this work, the selectivity for the *endo* cycloadduct was observed to increase as the pressure was raised from 100 to 300 bar. Pressures in the near supercritical region (<100 bar) were not

investigated. We were therefore especially interested in examining pressure effects on stereoselectivity near the critical point of the solution.

The same view-cell reactor used in our regiochemical studies (*vide supra*) was used for our investigation of stereoselectivity in $scCO_2$. All reactions were conducted under single-phase supercritical conditions as verified by visual inspection of reaction mixtures. All reactions were carried out at 50 °C for 24 h, and sampling of the entire reaction mixture was achieved as described above for the regiochemical studies. The *endo-exo* ratio of cycloadducts[180] (**278**:**279**) was then determined by GC analysis.[181]

Figure 5 presents the *endo* selectivity observed at various pressures for the Diels-Alder reaction of cyclopentadiene and acrylonitrile in $scCO_2$. The selectivity for the *endo* product **278** increases as the pressure is raised from 100 to 300 bar. This pressure effect is similar to that observed previously by Kim and Johnston, although the magnitude is somewhat greater (ca. 3% increase in *endo* vs. only ca. 1%). Kim and Johnston attributed this trend to a thermodynamic pressure effect on the rate constants of the two competing reaction pathways. For example, the increase in *endo* selectivity with pressure can be understood by assuming that the transition state leading to the *endo* product has a smaller partial molar volume. Another explanation for this pressure effect is provided by considering the dipole moments of the competing *endo* and *exo* transition states. Berson and co-workers[182] have discussed solvent effects on Diels-Alder *endo/exo* selectivity in terms of the relative solvation of transition states with differing dipolar character. The selectivity for *endo* cycloadducts was found to increase as the "solvent strength" (e.g. polarity, dielectric, etc.) of the reaction media increased.[183] Berson attributed this effect to

---

[180] The ^1H NMR spectrum was consistent with that previously reported, see: Nakagawa, K.; Ishii, Y.; Ogawa, M. *Tetrahedron*, **1976**, *32*, 1427.

[181] The accuracy of the GC analysis was confirmed by comparison to ratios determined by ^1H NMR.

[182] Berson, J. A.; Hamlet, Z.; Mueller, W. A. *J. Am. Chem. Soc.* **1962**, *84*, 297.

[183] The solvent parameter Ω (introduced by Berson) is defined as the logarithm of the *endo:exo* ratio (log N/X) for the Diels-Alder reaction of cyclopentadiene with methyl acrylate.

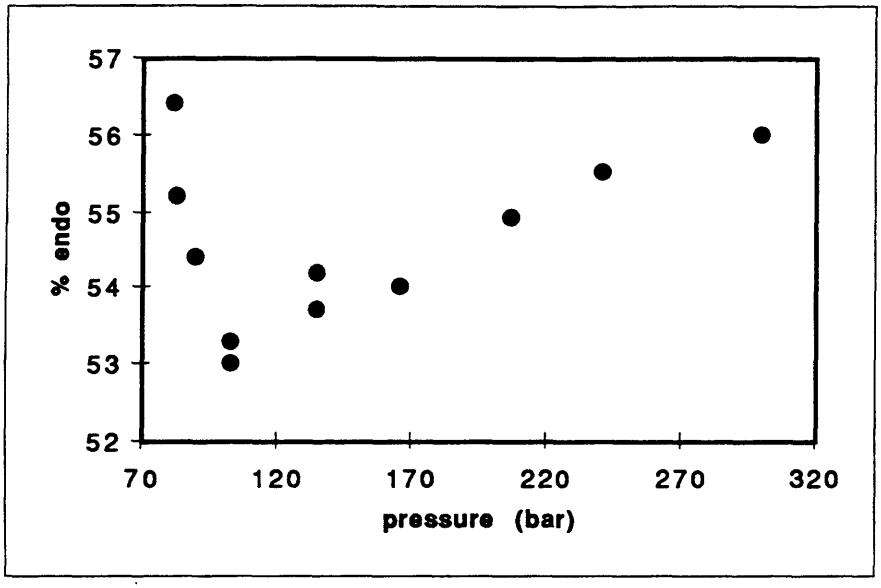
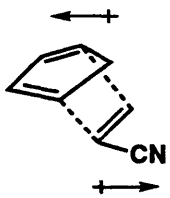


Figure 5. Effect of pressure on the stereoselectivity of the Diels-Alder reaction of cyclopentadiene and acrylonitrile at 50 °C in $scCO_2$.

greater solvation of the *endo* transition state, which has a larger dipole moment. Since the "solvent strength" of $scCO_2$ increases with pressure, a corresponding increase in the *endo*:*exo* ratio of cycloadducts would be expected (the *endo* transition state **278‡** has the larger dipole moment, as shown below).

278‡



279‡

A more unusual selectivity effect was observed when the reaction of cyclopentadiene and acrylonitrile was carried out at pressures *below* 100 bar in $scCO_2$ (Figure 5). In this regime, the *endo* selectivity was found to increase with *decreasing* pressure - exactly the opposite trend as was observed above 100 bar. Kim and Johnston did not investigate this low pressure regime in their studies with methyl acrylate and

cyclopentadiene, but predicted that the *endo* selectivity would continue to decrease with decreasing pressure below 100 bar. Our results defy this prediction and seem to indicate that other effects dominate near the critical pressure. Conceivably, this unusual selectivity effect could be related to the aggregation (or "clustering") phenomena sometimes observed in supercritical fluids near the critical point (Chapter 1). One way that solvent aggregation could affect reaction selectivities would be through changes in the local solvent properties (density, dielectric, etc.) around a solute (e.g., a transition state). Higher solvent density and dielectric around the transition states in question would be predicted to result in higher *endo*:*exo* ratios for the reasons mentioned previously.[184] The pressure effects observed below 100 bar (Figure 5) are therefore consistent with higher local solvent density around the transition states near the critical pressure in $scCO_2$.

Summary

We have observed only modest pressure and density effects in our studies of Diels-Alder reactions in supercritical carbon dioxide. The rate of the reaction between cyclopentadiene and ethyl acrylate was found to increase by a factor of ca. 2 upon increasing the solution density from 0.3 to 0.9 g/mL. With an empirical rate law, the reaction rate could be predicted from the density of the solution and an empirically determined activation energy. The regiochemical course of the Diels-Alder reaction was investigated with several dienes and dienophiles at pressures near the critical pressure (*Pc*) of carbon dioxide. The previously reported dramatic effect of pressure on regioselectivity could not be duplicated. Finally, the *endo*:*exo* of a Diels-Alder reaction was shown to increase (by ca. 3%) with increasing pressure above 100 bar and with decreasing pressure below 100 bar.

---

[184] The *endo* transition state has a greater dipole moment and a smaller partial molar volume as compared to the *exo* transition state.

Chapter 3
Catalysts and Promoters for Organic Synthesis in Supercritical Carbon Dioxide

Here we present the results of our preliminary investigation of the use of solid-phase catalysts and promoters to increase reaction rates and selectivities in supercritical carbon dioxide ($scCO_2$). Our interest in this area stems from what we have found to be one of the major limitations of $scCO_2$ as reaction solvent, namely, the sluggish rates observed for many reactions in this media (Chapter 2). We have attempted to address this problem through the use of silica (SiO_2) as a solid-phase promoter for reactions in $scCO_2$. Among the many attractive features of this material are its low cost, minimal environmental impact, easy separation from $scCO_2$ reaction mixtures, and potential for reuse. We have also examined the possibility that $scCO_2$ could be used to extract reaction products from the silica surface (a necessary step that is usually accomplished with organic solvents). Finally, we show that the utility of these solid promoters can be expanded by "doping" the silica surface with protic or Lewis acids.

The use of silica to promote reactions in organic solvents (or in the absence of solvent) is well known. A variety of silica-promoted reactions have been reported, including ozonoylses, alkylations, acylations, cycloadditions, halogenations, oxidations, and reductions.[185] In all cases, the products of the reaction must be extracted from the silica surface using an organic solvent. The use of "doped" silica and alumina to promote reactions in organic solvents has also been reported. For example, Kropp and co-workers have used silica in combination with protic acids to promote a variety of reactions in solvents such as dichloromethane.[186] A solid-phase promoter composed of silica-

[185] For a recent review , see: Basiuk, V. A. *Russ. Chem. Rev. (Engl. Transl.)* **1995**, *64*, 1003.
[186] Kropp, P. J.; Breton, G. W.; Craig, S. L.; Crawford, S. D.; Durland, W. F.; Jones, J. E.; Raleigh, J. S. *J. Org. Chem.* **1995**, *60*, 4246.

supported $ZnCl_2$ and alumina-supported K_2CO_3 has recently been employed for Friedel-Crafts allylation of aromatic rings in dichloroethane.[187]

Despite this considerable body of literature, the use of silica or alumina to promote reactions in $scCO_2$ has not been reported. Very recently, Poliakoff and co-workers reported Friedel-Crafts[188] and hydrogenation[189] reactions in $scCO_2$ using sulfonylated polysiloxane and polysiloxane-supported palladium promoters, respectively. These reactions involved the use of gaseous reagents (propene and H_2), thereby taking advantage of the high solubility of gases in $scCO_2$. Compared to the polysiloxane polymers used in this work, silica is significantly less expensive and more readily available.

Silica-Promoted Diels-Alder Reactions in $scCO_2$

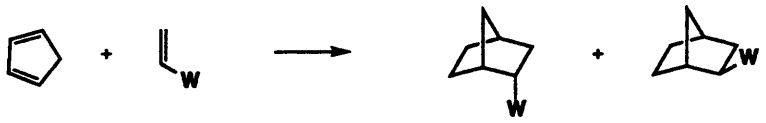
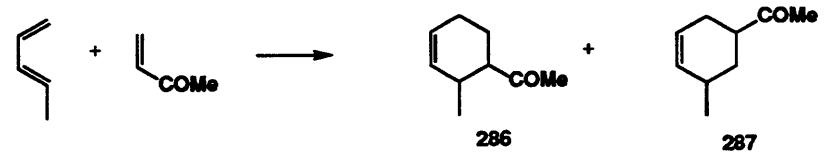
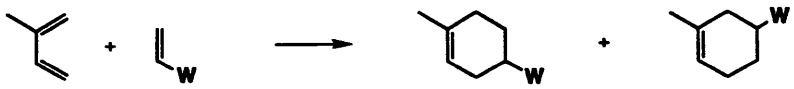
As an initial test case for the use of solid promoters in $scCO_2$, we examined the Diels-Alder reaction. This choice reflects the significant body of literature (including our work, Chapter 2) that exists regarding the rate of this reaction in $scCO_2$ *without* promoters and catalysts. Furthermore, the Diels-Alder reaction has already been shown to be promoted by silica when the diene and dienophile are deposited on the suface of the solid.[190]

Table 7 summarizes the results of our initial investigations of silica-promoted Diels-Alder reactions in $scCO_2$. All of these experiments were conducted under supercritical reaction conditions at a pressure of 1500 psi (103 bar). Dried[191] silica with an average particle size of ca. 1 μm was used in a ratio of ca. 1:1 (w:w) with respect to the starting materials. All the reactions with cyclopentadiene were conducted at 50 °C for 4 h, while

---

[187] Kodomari, M.; Nawa, S.; Miyoshi, T.; *J. Chem. Soc., Chem. Commun.* **1995**, 1895.
[188] Hitzler, M. G.; Smail, F. R.; Ross, S. K.; Poliakoff, M. *J. Chem. Soc., Chem. Commun.* **1998**, 259.
[189] Hitzler, M. G.; Poliakoff, M. *J. Chem. Soc., Chem. Commun.* **1997**, 1667.
[190] (a) Parlar, H.; Baumann, R. *Angew. Chem. Int. Ed. Engl.* **1981**, *20*, 1014. (b) Veselovskii, V. V.; Lozanova, A. V.; Moiseenko, A. M.; Gybin, A. S.; Smit, V. A. *Bull. Acad. Sci. USSR* **1987**, 887. (c) Veselovskii, V. V.; Gybin, A. S.; Lozanova, A. V.; Moiseenko, A. M.; Smit, V. A. *Tetrahedron Lett.* **1988**, *29*, 175. (d) Veselovskii, V. V.; Gybin, A. S.; Lozanova, A. V.; Moiseenko, A. M.; Smit, V. A *Bull. Acad. Sci. USSR* **1990**, 94.
[191] The silica was dried by heating at 180-200 °C (1 atm) to constant weight.

Table 7. Silica Promoted Diels-Alder Reactions in $scCO_2$

Entry	Conditions[a]	Promoter[b]	Yield (%)[c]	Selectivity[d]
				
W = COMe			**280**	**281**
1	CO_2, 50 °C, 4 h	No	29	82:18
2	CO_2, 50 °C, 4 h	Yes	82	92:8
W = CN			**282**	**283**
3	CO_2, 50 °C, 4 h	No	5	57:43
4	CO_2, 50 °C, 4 h	Yes	14	59:41
W = CO_2Me			**284**	**285**
5	CO_2, 50 °C, 4 h	No	5	72:28
6	CO_2, 50 °C, 4 h	Yes	21	85:15
				
			286	**287**
7	CO_2, 80 °C, 24 h	No	3	81:19
8	CO_2, 80 °C, 24 h	Yes	31	94:6
				
W = COMe			**288**	**289**
9	CO_2, 80 °C, 24 h	No	5	67:33
10	CO_2, 80 °C, 24 h	Yes	35	73:27
W = CO_2Me			**290**	**291**
11	CO_2, 80 °C, 24 h	No	2	68:32
12	CO_2, 80 °C, 24 h	Yes	3	73:27

[a] All reactions were conducted at 103 bar in CO_2. [b] 1 μm silica in ca. 1:1 (w:w) ratio. [c] Yield estimated by ^{1}H NMR using an internal standard. [d] Ratio of isomers determined by ^{1}H NMR analysis except for entries 3 and 4 (GC analysis).

reactions of acyclic dienes were carried out at 80 °C for 24 h. These standardized reaction conditions were chosen to facilitate comparisons of yield and selectivity; no attempt was made to find the optimal conditions for each case.

As shown in Table 7, the use of silica in $scCO_2$ led to increased yields and selectivities in a number of Diels-Alder reactions. The most pronounced effects were observed in reactions of methyl vinyl ketone (MVK). For example, the yield of the reaction between MVK and cyclopentadiene increased from 29% to 82% in the presence of silica (entries 1 and 2).[192] Likewise, the *endo* selectivity of the reaction increased from 82% to 92%. Similar increases in yield and selectivity were observed for the reaction of MVK with acyclic dienes (isoprene and penta-1,3-diene) in the presence of silica (entries 7-10).[193] The beneficial effects of silica were less evident for reactions of ester- and nitrile-substituted dienophiles (entries 3-6, 11, 12). Encouraged by these initial results, we selected the reaction of MVK with penta-1,3-diene (entries 7 and 8) as a test case for further investigation.

Pressure Effects on Silica-Promoted Cycloadditions in $scCO_2$

The mechanism of silica promotion has not been firmly established, although it is clear that promotion occurs at the surface of the solid. Silica promotion of the Diels-Alder reaction (Table 7) most likely results from hydrogen bonding to (or protonation of) the dienophile by acidic SiOH groups on the silica surface, thereby lowering the energy of the $LUMO_{dienophile}$ and facilitating the cycloaddition. The adsorption of reactants to the silica surface may also facilitate and/or stabilize formation of the prereaction complex by bringing the reactants into close proximity.[185]

---

[192] The ^1H NMR spectrum of the products was consistent with that reported previously, see: Kaptein, B.; Monaco, V.; Broxterman, Q. B.; Schoemaker, H. E.; Kamphuis, *J. Recl. Trav. Chim. Pays-Bas* **1995**, *114*, 231.

[193] The ^1H NMR spectrum of the products was consistent with that reported previously, see: Wright, M. W.; Smalley, T. L.; Welker, M. E.; Rheingold, A. L. *J. Am. Chem. Soc.* **1994**, *116*, 6777.

The rates of these Diels-Alder reactions in $scCO_2/SiO_2$ are expected to be lower in $scCO_2$ *solution* than on the surface of the SiO_2 promoter. Any variable that influences the distribution of reactants between the solid and solution phase could therefore influence the rate of the reaction. The solubilities of organic compounds in $scCO_2$ are a strong function of pressure/density, with the solvating power of $scCO_2$ being greater at higher density.[194] Reactions in $scCO_2$ under heterogeneous conditions (i.e., with silica promotion) might therefore be expected to exhibit a pressure effect on reaction rates (and yields).

The Diels-Alder cycloaddition of MVK and penta-1,3-diene was investigated at 80 °C and at CO_2 pressures from 0 to 310 bar (Figure 6). The yield of cycloadduct increased sharply as the pressure was lowered below 100 bar and continued to increase as the

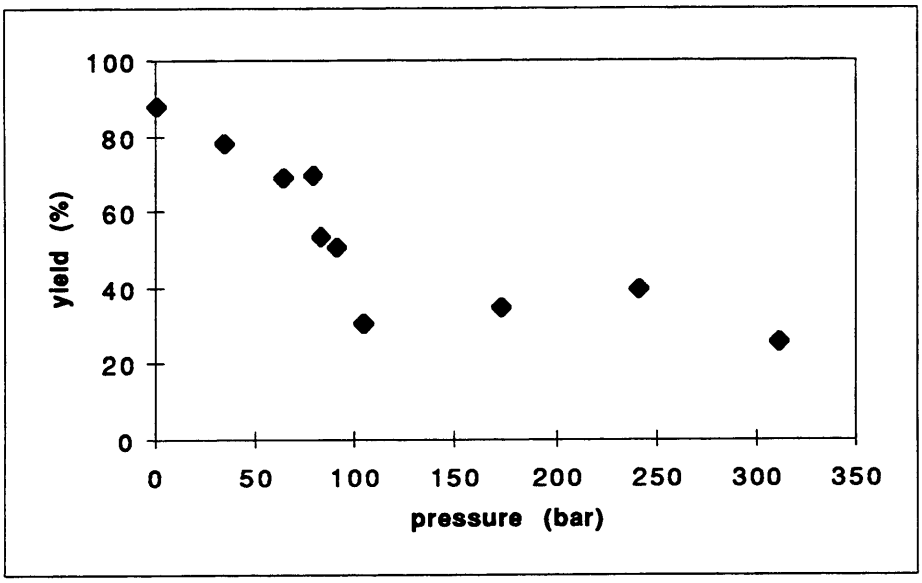


Figure 6. Effect of pressure on the silica-promoted cycloaddition of methyl vinyl ketone and penta-1,3-diene at 80 °C in CO_2.

pressure was lowered below the critical pressure of pure CO_2 (i.e., experiments conducted below 74 bar involved gaseous CO_2). This pressure effect is consistent with an increased concentration of reactants on the silica surface at low CO_2 pressures (< 100 bar) where the

[194] Brogle, H. *Chem. Ind. (London)* **1982**, *12*, 385.

solubility of organic compounds in CO_2 is low (probably near zero in gaseous CO_2).[195] In order to test this hypothesis, we designed a series of experiments to examine the distribution of reactants and products between the solution and solid phases in these reactions.

Distribution of Solutes Between the Solution and Solid Phase in SiO_2/CO_2 Mixtures

We examined the partitioning of MVK, penta-1,3-diene, and cycloadduct (**286** and **287**) between the solution and solid phases in SiO_2/CO_2 mixtures at 80 °C and pressures from 33 to 310 bar. The results of this study are presented in Figure 7 as a percentage of

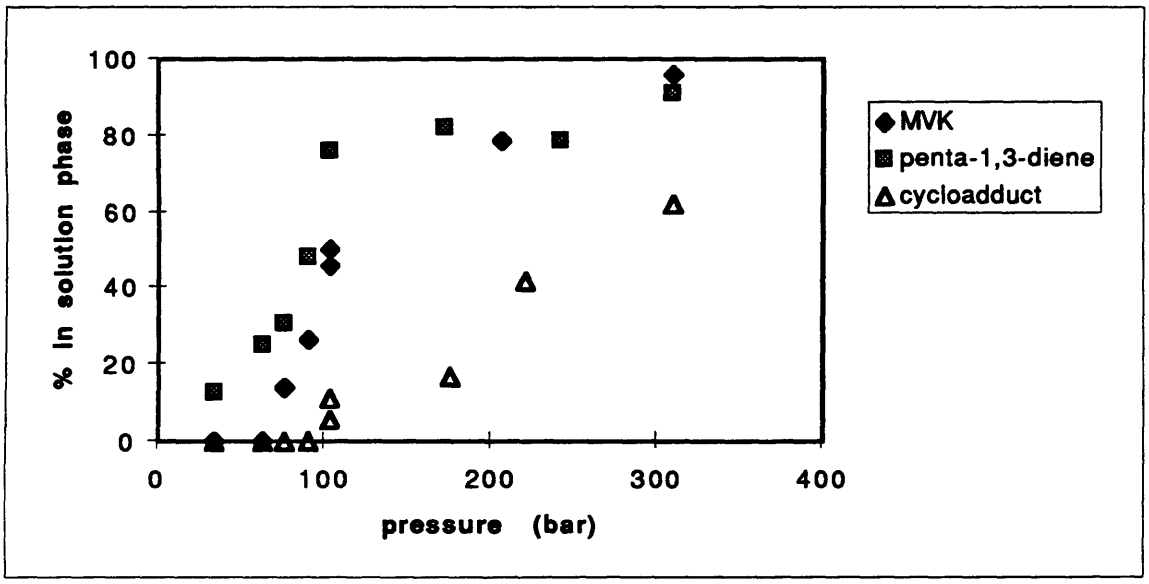


Figure 7. Distribution of reactants and products in SiO_2/CO_2 mixtures at 80 °C.

solute in CO_2 solution at different pressures. Each experiment was conducted with 2.5 mmol of solute (diene, dienophile, or cycloadduct) and 0.50 g of silica in CO_2 at 80 °C, the same conditions of temperature, concentration, and silica loading as were used in the

[195] A similar pressure effect was observed in the absence of silica. At pressures near or below the critical point, the reactants are no longer soluble and a two-phase reaction mixture is formed. The higher yields at low pressure are attributed to the much higher reactant concentrations for the two-phase (liquid organic and gaseous CO_2) reaction mixture.

cycloaddition studies (Figure 6). As shown in Figure 7, the amount of MVK and penta-1,3-diene in CO_2 solution drops significantly as the pressure is lowered below 100 bar. The reader will note that this is the exactly the same pressure/density regime where the yield of cycloadduct begins to *increase* significantly (Figure 6). We therefore conclude that as the pressure (and density) of the CO_2 solution is lowered, the solute (diene and dienophile) distribution is shifted from the CO_2 solution phase to the solid silica phase. Reaction rates on the surface of silica are greater than in solution, so the yield increases with decreasing CO_2 pressure.

The partitioning data in Figure 7 was acquired by varying CO_2 pressure/density at constant solute concentrations. It is also possible to vary the relative amounts of solute and silica while keeping the density constant. This data can then be used to determine the maximum amount of a solute that can be adsorbed to a given amount of silica under particular reaction conditions. The results of these studies (isotherms) is presented below for MVK (Figure 8) and the cycloadducts **286** and **287** (Figure 9).

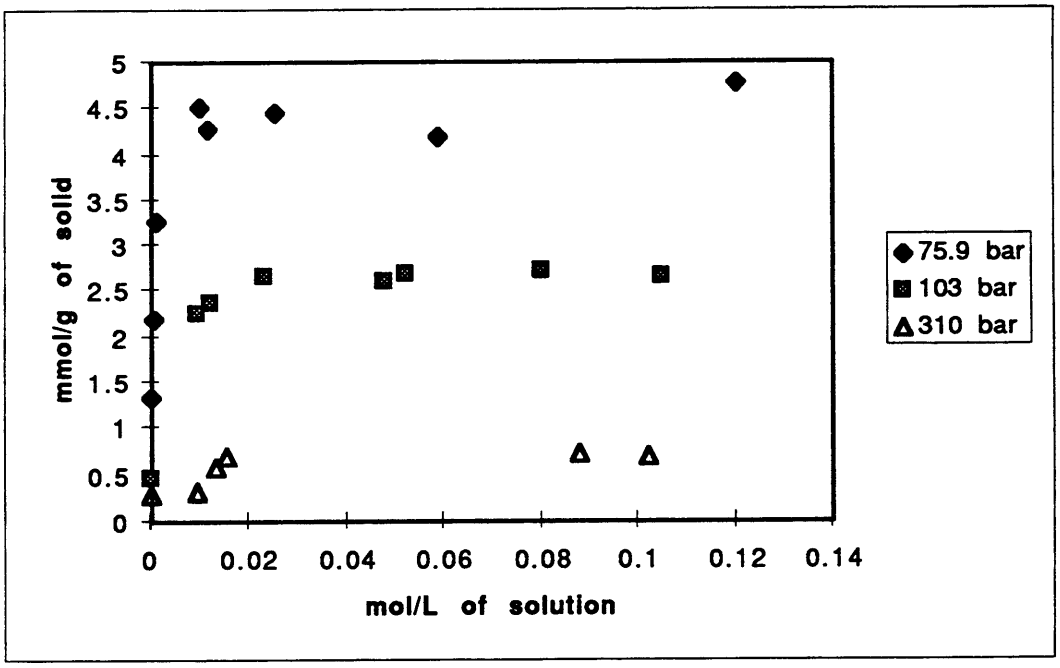


Figure 8. Isotherm for MVK in SiO_2/CO_2 mixtures at 80 °C and three different pressures.

The X-axis in these figures plots the concentration (in mol/L) of solute in CO_2 solution while the Y-axis plots the amount of solute adsorbed to silica (in mmol/g). As shown in Figure 8, the amount of MVK adsorbed to the silica surface reaches a maximum, above which the addition of more MVK only increases its concentration in the solution phase. As expected, these maxima depend strongly upon pressure/density, with nearly 5 times more MVK adsorbed to silica at 75.9 bar as at 310 bar. The data in Figure 8 could be used to determine optimal reactant to promoter ratios for silica-promoted reactions in $scCO_2$ at different pressures.

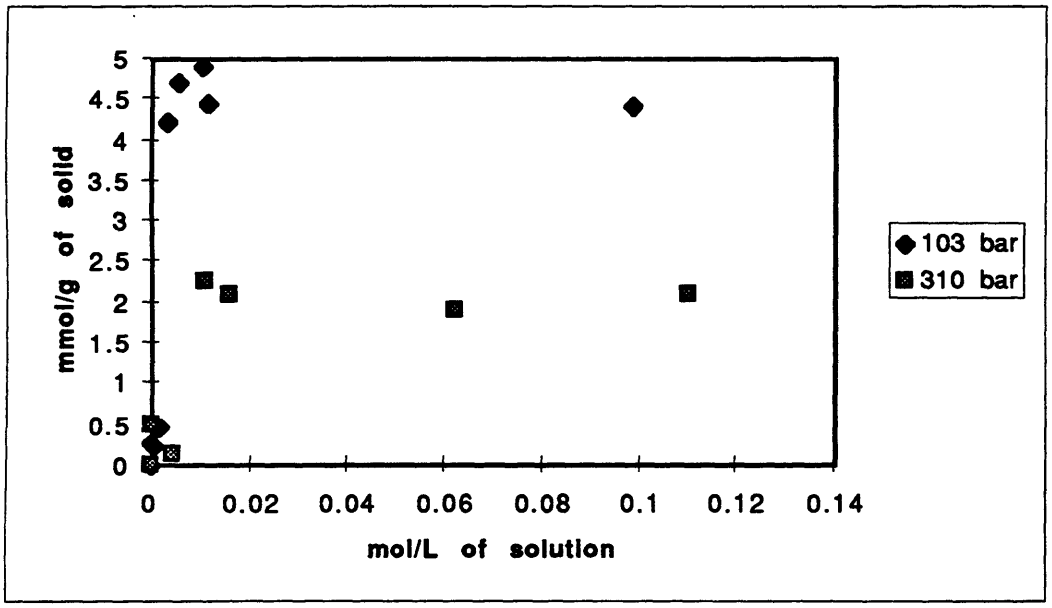


Figure 9. Isotherm for Cycloadducts 286 and 287 in SiO_2/CO_2 mixtures at 80 ℃ and two different pressures.

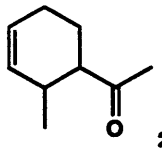
The data for cycloadducts **286** and **287** also shows maxima that are dependent upon pressure (Figure 9). These compounds appear to have a greater affinity for silica than does MVK. For example, only ca. 0.7 mmol/g of MVK is adsorbed to silica at 310 bar whereas ca. 2.0 mmol/g of cycloadduct is adsorbed to silica under the same conditions.

Finally, the data in Figures 8 and 9 could be used to identify optimal extraction conditions for the removal of reaction products from silica surfaces (*vide infra*).

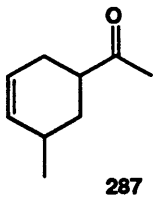
*Extraction of Cycloadducts **286** and **287** from Silica using $scCO_2$*

The use of solids to promote organic reactions makes necessary the subsequent extraction of the reaction products from the solid promoter. This extraction is typically accomplished using organic solvents, but it should be possible to use $scCO_2$ for the extraction, thereby furthering the environmental benefits of this solvent. Indeed, $scCO_2$ has found widespread application in the extraction of natural products (including caffeine), specialty chemicals, and hazardous organic and inorganic wastes.[196]

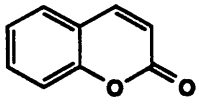
The reactor used in these studies was designed and constructed by Randy D. Weinstein and consists of a vertical tube (ca. 25 mL working volume) with 0.2 μm filters at either end. During extraction, the tube is pressurized with carbon dioxide through a valve in the base of the reactor and can then be depressurized through a valve at the top, thereby insuring that $scCO_2$ passes directly through the silica during extractions. The data presented in Figures 7-9 indicate that high CO_2 pressures/densities should be most effective for extracting the cycloadducts **286** and **287** from the silica promoter. In model studies, we found that three semi-batch extractions[197] at 207 bar were sufficient to recover 92% of cycloadducts **286** and **287** from silica gel. Even *solids* such as coumarin (**292**) could be



286



287

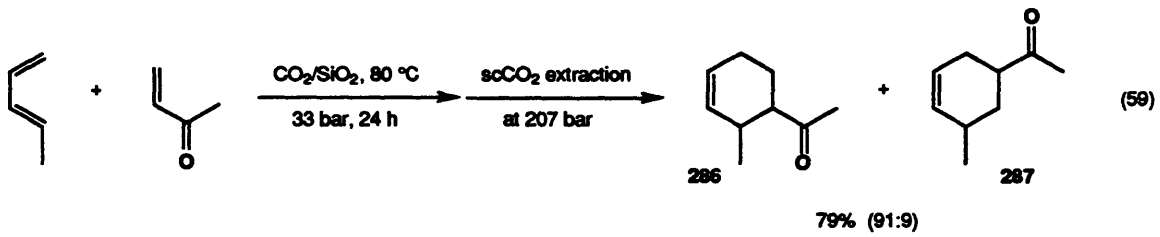


292

[196] (a) McHugh, M. A.; Krukonis, V. J. *Supercritical Fluid Extraction: Principles and Practice*; Butterworths: Boston, 1986. (b) Bevan, C. D.; Marshall, P. S. *Nat. Prod. Rep.* **1994**, *11*, 451. (c) Phelps, C. L.; Smart, N. G.; Wai, C. M. *J. Chem. Educ.* **1996**, *73*, 1163. (d) ref 194.

[197] The reactor-extractor was pressurized to 207 bar and three high-pressure samples were isolated and depressurized through a long tube immersed in Et_2O. This extraction was repeated three times.

recovered almost quantitatively (93%), although in this case several extractions were required (10 extractions at 310 bar). Equation 59 summarizes an optimized silica-promoted



(59)

promoted cycloaddition - extraction procedure for the reaction of MVK and penta-1,3-diene in $scCO_2$. The cycloaddition was conducted for 24 h at 80 °C and 33 bar in $scCO_2$. Semi-batch extraction with $scCO_2$ at 207 bar then provided cycloadducts **286** and **287** in 79% yield as a 91:9 mixture of regioisomers and as an 84:16 and 73:27 mixture of stereoisomers, respectively. The yield (79%) is nearly identical to that obtained using standard extraction techniques, suggesting that the $scCO_2$ extraction was essentially quantitative.

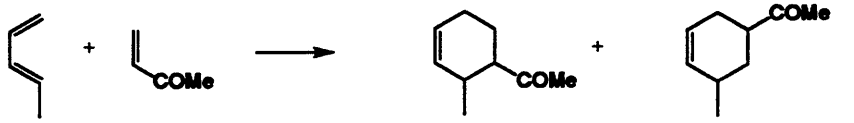
Protic and Lewis Acid-Doped Silica Promoters in $scCO_2$

Here we present our preliminary results regarding the use of protic and Lewis acid-doped silica to promote reactions in $scCO_2$. As discussed in the introduction, the use of protic acids in conjunction with silica and alumina has been shown to facilitate a number of acid-promoted reactions in traditional organic solvents.[186] We have found the activation provided by untreated silica gel promoters to be only modest. For example, MVK reacts with penta-1,3-diene in 5 days at 100 °C in toluene, whereas the same reaction in $SiO_2/scCO_2$ requires 24 h at 80 °C (eq 59). By comparison, Lewis acid-promoted Diels-Alder reactions typically proceed at or below room temperature. The identification of highly activated solid-phase promoters with reactivity comparable to Lewis acids is therefore desirable.

With this goal in mind, we initiated an investigation of the reactivity of protic and Lewis acid-doped silica gel promoters. These materials are prepared by the addition of a known amount of protic or Lewis acid to a dichloromethane suspension of silica gel.[198] The solvent is then removed in vacuo to give a free-flowing powder with a known amount of acid per gram of solid (typically between 0.9 and 1.3 mmol/g). Using this procedure, it is possible to tune the activity of a given promoter by increasing or decreasing the amount of acid used in its preparation.

To date, we have prepared silica doped with H_2SO_4, H_3PO_4, $AlCl_3$, and $TiCl_4$. The reaction of MVK and penta-1,3-diene was selected as a test case to evaluate the reactivity of these new acid-doped promoters. We decided to first investigate reactions under solid phase reaction conditions (no solvent) and then, if successful, attempt the reactions in $scCO_2$. The results of our initial studies are summarized in Table 8. Phosphoric acid-

Table 8. Silica-Promoted Diels-Alder Reactions in $scCO_2$

Entry	Conditions	Promoter	Yield (%)[a]	Regio/(Stereo)[b]
				
			286	**287**
1	toluene, 100 °C, 5 d	none	77%	82:18 / (69:31; 60:40)
2	no solvent, rt, 0.5 h	SiO_2-H_3PO_4	83%	99:1 / (93:7; N. D.)
3	no solvent, rt	SiO_2-H_2SO_4	*c*	
4	no solvent, rt	SiO_2-$AlCl_3$	*c*	
5	no solvent, rt	SiO_2-$TiCl_4$	*c*	
6	CO_2, 33 bar, 80 °C, 24 h	SiO_2	78%	92:8 / (87:13; 76:24)
7	CO_2, 103 bar, 80 °C, 24 h	SiO_2	(31%)	94:6/ (89:11; N.D.)
8	CO_2, 103 bar, 40 °C, 4 h	SiO_2-H_3PO_4	57%	98:2 / (84:16, N.D.)

[a] Isolated yields. [b]Regio- (**286**:**287**) and stereoselectivity (*endo/exo* **286** ; *endo/exo* **287**) were determined by ^1H NMR analysis. [c]Diene polymerization predominated.

[198] Dried (150-200 °C) chromatography-grade silica gel is used.

doped silica was found to be an exceptionally effective promoter, producing an 83% isolated yield of cycloadduct after only 30 min at *room temperature* in the absence of solvent (entry 2). Furthermore, the regio- and stereoselectivity of the reaction was excellent. When other doped promoters were used in the reaction, violent exotherms developed, and the starting materials decomposed almost immediately (entries 3-5). Presumably, cationic diene polymerization is a favorable process under these highly acidic reaction conditions. Apparently the phosphoric acid-promoted cycloaddition is sufficiently accelerated as to be competitive with diene polymerization. In $scCO_2$, the use of SiO_2-H_3PO_4 provides acceptable yields (57%) of Diels-Alder cycloadduct after 4 h at 40 °C.[199] By comparison, the use of untreated silica requires longer reaction times and higher temperatures (24 h and 80 °C, entries 6-7).

Summary

Diels-Alder reactions in $scCO_2$ are promoted in the presence of silica gel. The most dramatic rate enhancement is observed at low CO_2 pressures where the concentration of the reactants in solution is low. Extraction of the cycloadducts from the silica surface can be accomplished at high CO_2 pressure/density where organic compounds are more soluble in $scCO_2$. Acid-doping of silica promoters has been shown to greatly enhance their activating effect. The initial studies with these promoters lay the groundwork for their application to a wide range of other acid and Lewis-acid promoted reactions in $scCO_2$.

[199] Longer reaction times or higher temperatures did not improve the yield of this reaction.

Part IV

Experimental Section

Experimental Section

General Procedures

All reactions were performed in flame-dried glassware under a positive pressure of argon. Reaction mixtures were stirred magnetically unless otherwise indicated. Air- and moisture-sensitive liquids and solutions were transferred via syringe or cannula and were introduced into reaction vessels through rubber septa. Reaction product solutions were concentrated by using a Büchi rotary evaporator at 15-20 mmHg. 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 argon or vacuum from calcium hydride: methanol, toluene, benzene, dichloromethane, acetonitrile, collidine, 2,2,6,6-tetramethylpiperidine, dimethyl sulfoxide, triethylamine, diethylamine, diisopropylamine, and triisopropylsilyl trifluoromethanesulfonate.

Distilled under argon or vacuum from phosphorus pentoxide: methanesulfonyl chloride.

Distilled under argon or vacuum from sodium benzophenone ketyl: tetrahydrofuran and diethyl ether.

Distilled under argon or vacuum: isoprene, acrylonitrile, methyl vinyl ketone, and methyl acrylate.

Purification of other reagents was accomplished in the following manner: *N*-chlorosuccinimide was recrystallized from acetic acid, meldrum's acid was recrystallized from acetone-water, tosyl chloride was recrystallized from diethyl ether at -78 °C, and sodium iodide, sodium cyanide, and silver cyanide were dried at 100 °C (0.1 mmHg) for 12-16 h.

Nitroethylene[200] and 2-(trimethylsiloxy)butadiene[201] were prepared according to literature procedures. 2-*tert*-Butylbuta-1,3-diene and 1-vinylcyclohex-1-ene were prepared as described by Korotkov and Roguleva[202] except that the dehydration was effected according to the general method of Traynelis et al. Cyclopentadiene was prepared by heating the dimer (ca. 180 °C) under a Vigreux column and collecting the distillate in a flask cooled at -78 °C. Cyclopentadiene was then stored at -60 °C until needed. Sodium methoxide solution was freshly prepared before use by the addition of sodium to methanol at 0 °C.

Chromatography

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

---

200 Ranganathan, D.; Rao, C. B.; Ranganathan, S.; Mehrotra, A. K.; Iyengar, R. *J. Org. Chem.* **1980**, *45*, 1185.
201 Jung, M. E.; McCombs, C. A.; Takeda, Y.; Pan, Y.-G.; *J. Am. Chem. Soc.* **1981**, *103*, 6677.
202 Korotkov, A. A.; Roguleva, L. F. *Zh. Org. Khim.* **1965**, *1*, 1180.

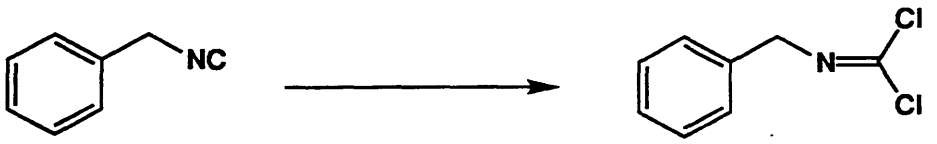
Column chromatography was performed on ICN silica gel (32-60 μm) or EM Science silica gel 60 (35-75 μm). Deactivated silica gel was obtained via rinsing the silica with copious amounts of acetone through a glass fritte and then drying in an oven for 5-12 h.

Instrumentation.

Melting points (mp) were determined with a Fisher-Johns melting point apparatus and are uncorrected. Boiling points are uncorrected. Infrared spectra (IR) were recorded using a Perkin Elmer 1320 grating spectrophotometer. ^{1}H NMR spectra were measured with Varian XL-300 (300 MHz), Varian Unity-300 (300 MHz), and Varian Unity-500 (500 MHz) spectrophotometers. Chemical shifts are expressed in parts per million (δ) downfield from tetramethylsilane. ^{13}C NMR spectra were measured with Varian XL-300 (75 MHz) and Varian Unity-500 (500 MHz) spectrophotometers. Chemical shifts are expressed in parts per million (δ), relative to tetramethylsilane (with the central peak of $CDCl_3$ at 77.0 ppm used as a standard). 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.

Benzyl isocyanide (37).

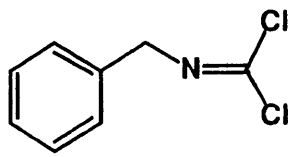
A 100-mL, one-neck, round-bottomed flask equipped with an argon inlet adapter and reflux condenser was charged with benzylamine (5.36 g, 50 mmol), chloroform (5.97 g, 4.0 mL, 50 mmol), benzyltrimethylammonium chloride (0.297 g, 1.5 mmol), and 15 mL of dichloromethane. The solution was stirred vigorously and 15 mL of a 50% aqueous NaOH solution was added in one portion. The mixture began to reflux spontaneously, becoming red in color. After 1.5 h, the solution stopped refluxing and was then heated to reflux with an oil bath for an additional hour. The solution was then allowed to cool to room temperature and stirred for 2 h and 50 mL of dichloromethane and 50 mL of water was added. The aqueous phase was separated and extracted with two 50-mL portions of dichloromethane and the combined organic phases were washed with 50 mL of H_2O, 50 mL of a saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated to provide 5.95 g of a deep red oil. Column chromatography on 100 g of silica gel (elution with 15% ethyl acetate-hexane) afforded 3.48 g (59%) of benzyl isocyanide as a yellow oil with spectral characteristics identical to that of commercially available benzyl isocyanide.



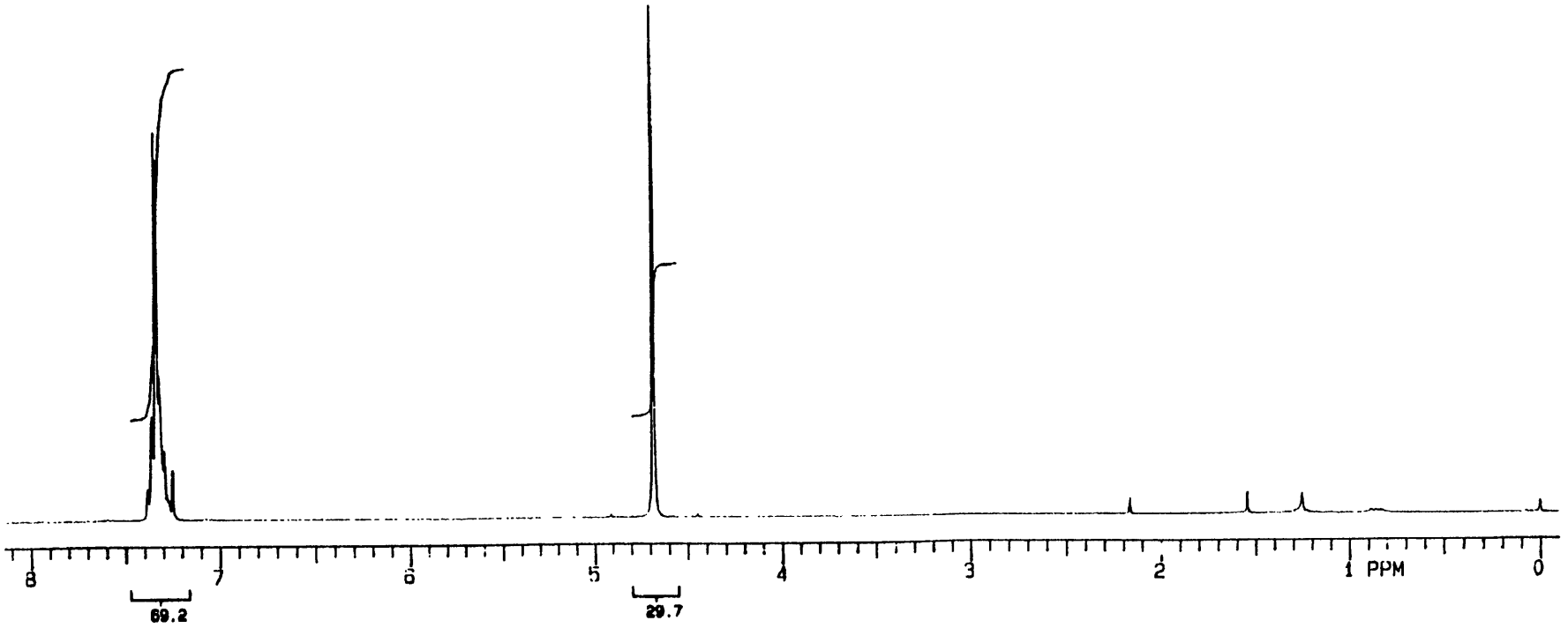
Benzylimidoyl dichloride (38).

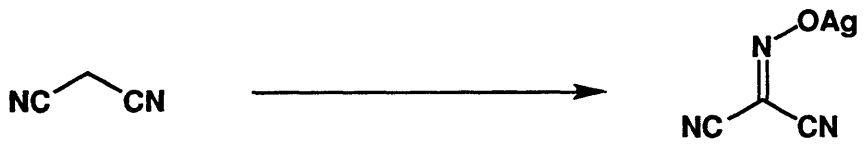
A 50-mL, three-necked, round-bottomed flask equipped with a glass pipette inlet, septum, and a glass stopper was charged with benzyl isocyanide (0.897 g, 7.66 mmol) and 16 mL of dichloromethane. The solution was cooled at 0 °C while chlorine gas was bubbled slowly into the solution via the pipette inlet. The excess gas was allowed to leave the flask through a cannula which led into a solution of H_2O. The reaction was monitored by tlc. After 20 min, the reaction was complete (as judged by tlc) and the chlorine addition was stopped. The solution was stirred for 30 min at room temperature and then dried over Na_2SO_4, filtered, and concentrated to afford 1.27 g of a yellow oil. Purification by Kugelrohr distillation (80 °C, 0.2 mmHg) provided 1.18 g (82%) of the imidoyl dichloride **38** as a colorless oil.

IR ($CHCl_3$)	3000, 1645, 1455, 1350, 990, 880 cm^{-1}
^1H NMR (300 MHz, $CDCl_3$)	δ 4.68 (s, 2 H), 7.27-7.39 (m, 5 H)
^{13}C NMR (75 MHz, $CDCl_3$)	δ 58.4, 125.4, 127.6, 127.8, 128.7, 136.4



38



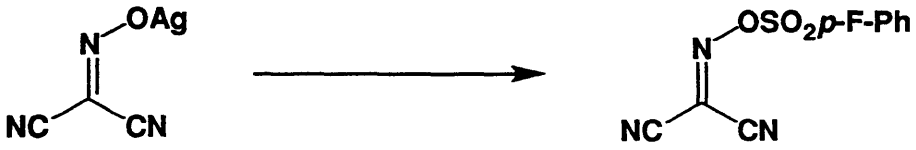


Oxime Salt 54.

A 25-mL, one-necked, round-bottomed flask equipped with a solid addition funnel was charged with malonitrile (0.941 g, 14.2 mmol) and 10 mL of a pH 3 acetate buffer. This solution was stirred at room temperature and treated with $NaNO_2$ (0.655 g, 9.50 mmol) slowly via the addition funnel over 15 min to give an orange solution. After stirring at room temperature for 10 min, the deep orange solution was treated with a saturated aqueous solution of $AgNO_3$ (1.77 g, 10.4 mmol) in one portion. The resulting thick yellow suspension was stirred for 10 min and then filtered with the aid of 50 mL of cold H_2O. The yellow-orange solid was washed with 20 mL of Et_2O and then dried in a desiccator over dry-rite (ca. 3 h, 0.1 mmHg) and then P_2O_5 (ca. 15 h, 0.1 mmHg) to provide 1.708 g (89% crude) of the silver salt **54** as a yellow-orange solid. This material was used directly in subsequent sulfonylation reactions.

Tosyloxyiminomalonitrile (43).

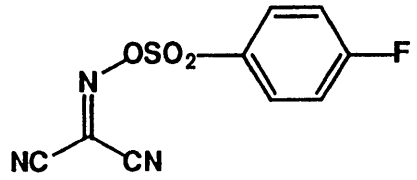
A 50-mL, one-necked, round-bottomed flask equipped with a reflux condenser and argon inlet adapter was charged with tosyl chloride (0.944 g, 4.95 mmol) and 30 mL of benzene. The solution was stirred at room temperature and then treated with the silver salt **54** (1.00 g, 4.95 mmol) to give an orange-yellow suspension. To this suspension was added pyridine (0.25 g, 0.25 mL, 3.1 mmol) in three portions over 15 min which caused the suspension to become gray. The reaction mixture was then heated at 45 °C for 10 min to give a gray suspension. After cooling to room temperature, the mixture was filtered with the aid of 10 mL of benzene. The combined filtrate was then concentrated to afford a brown oil. Column chromatography on 30 g of deactivated silica gel (elution with 10% ethyl acetate-hexane) provided 0.714 g (52% overall) of the oxime **43** as a white solid (mp 114-115 °C) with physical and spectral characteristics identical to those reported by Fleury.[19]



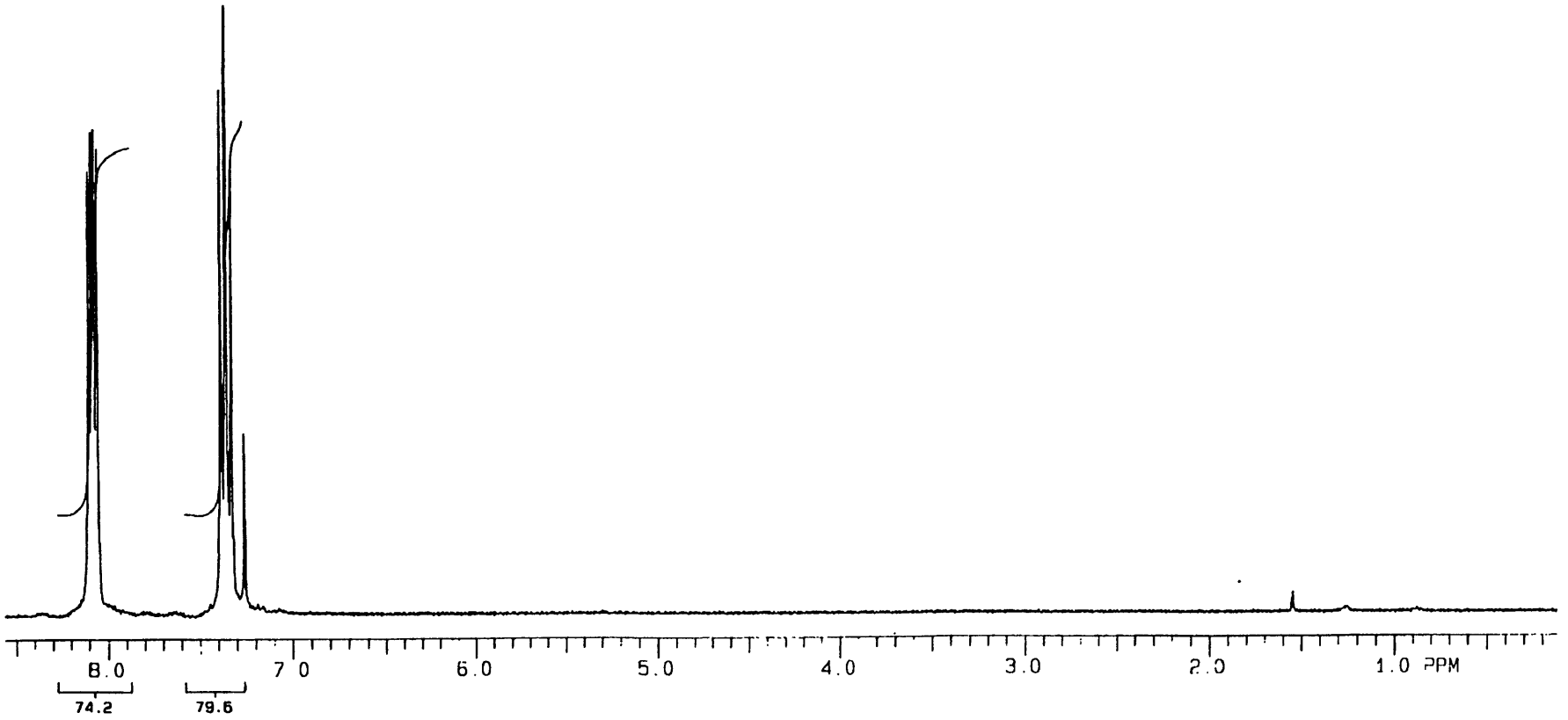
p-Fluorobenzenesulfonyloxyiminomalonitrile (56).

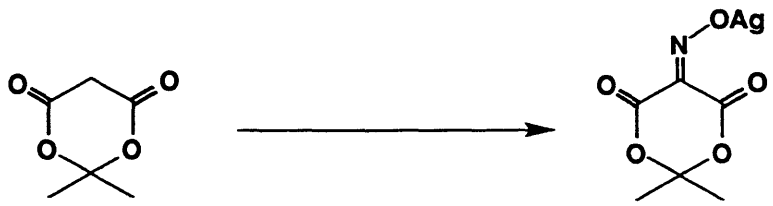
A 250-mL, one-necked, round-bottomed flask equipped with a reflux condenser and argon inlet adapter was charged with 4-fluorophenylsulfonyl chloride (3.15 g, 16.2 mmol) and 90 mL of benzene. The solution was stirred at room temperature and then treated with the silver salt **54** (3.27 g, 16.2 mmol) in one portion to give an orange-yellow suspension. To this reaction mixture was added five drops of pyridine which caused the suspension to become gray. The mixture was then heated at 45 °C for 10 min. After cooling to room temperature, the gray suspension was filtered with the aid of 10 mL of benzene. The combined filtrate was then concentrated to afford an orange oil. Column chromatography on 60 g of deactivated silica gel (elution with 12% ethyl acetate-hexane) provided 2.78 g (61% overall) of the oxime **56** as a white solid: mp 82-84 °C.

IR ($CHCl_3$)	3020, 2240, 1590, 1490, 1415, 1240, 1200, 970 cm^{-1}
^1H NMR (300 MHz, $CDCl_3$)	δ 7.36 (ddd, J = 2.8, 8.3, 8.3 Hz, 2 H), 8.08 (ddd, J = 3.3, 5.3, 10.1 Hz, 2 H)
^{13}C NMR (75 MHz, $CDCl_3$)	δ 104.2, 107.4, 114.8, 117.6 ($J_{C\text{-}F}$ = 23 Hz), 128.2 ($J_{C\text{-}F}$ = 2.9 Hz), 132.9 ($J_{C\text{-}F}$ = 10.5 Hz), 167.4 ($J_{C\text{-}F}$ = 261 Hz)



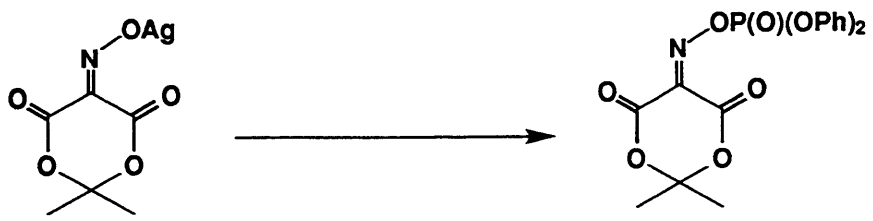
56





Oxime Salt 55.

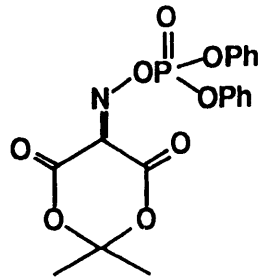
A 100-mL, one-necked, round-bottomed flask equipped with a solid addition funnel was charged with Meldrum's acid (10.0 g, 69.4 mmol) and 60 mL of a pH 3 acetate buffer. This white suspension was stirred at room temperature and treated with $NaNO_2$ (3.68 g, 53.4 mmol) slowly via the addition funnel over 45 min to give a deep red solution. After stirring at room temperature for 15 min, the deep red solution was treated with a saturated aqueous solution of $AgNO_3$ (9.98 g, 58.7 mmol) in one portion. The resulting thick pink suspension was stirred for 15 min and then filtered with the aid of 100 mL of cold H_2O. The pink solid was washed with 20 mL of Et_2O and then dried in a desiccator over dry-rite (ca. 3 h, 0.1 mmHg) and then P_2O_5 (ca. 15 h, 0.1 mmHg) to provide 12.16 g (81% crude) of the silver salt **55** as a pink solid.



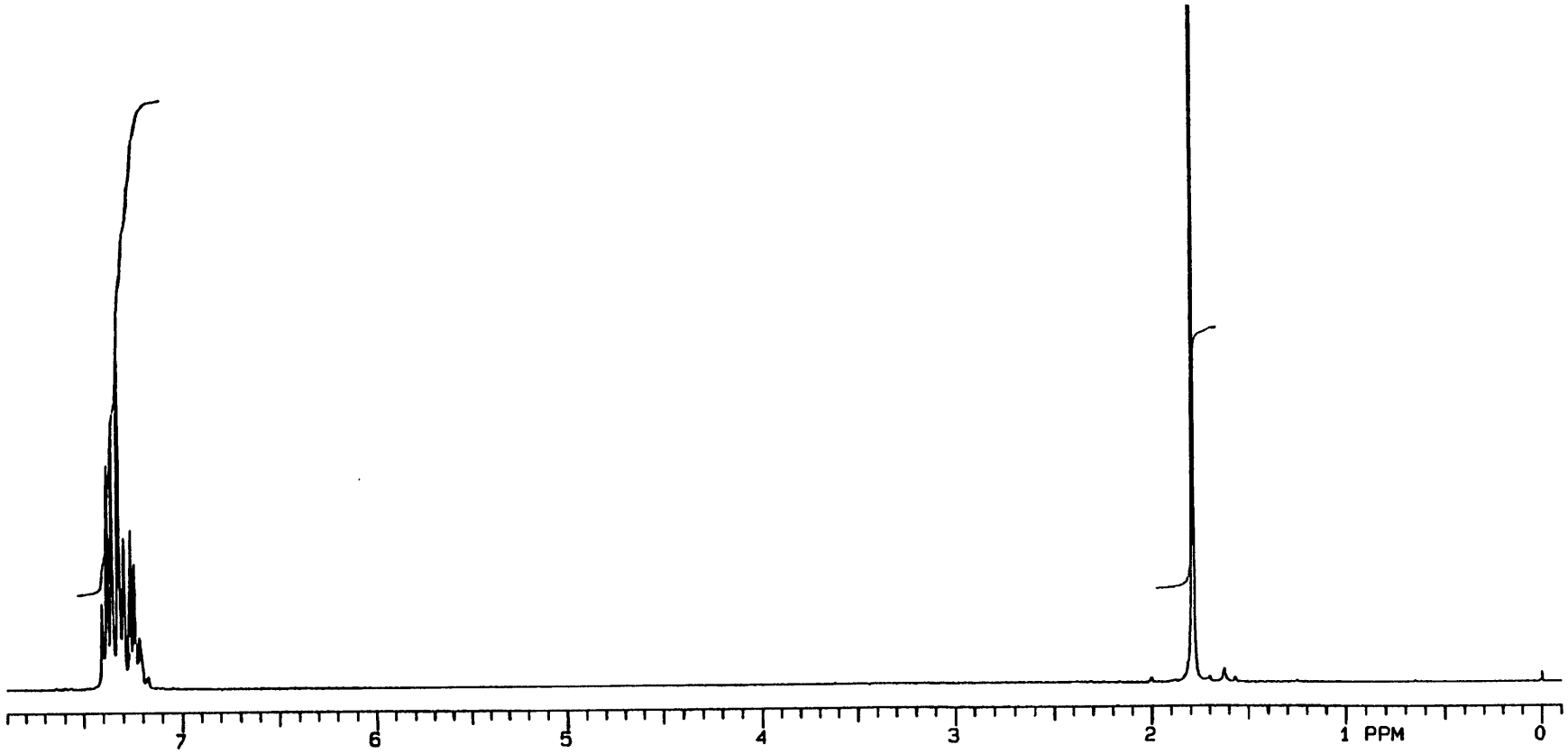
Diphenylphosphoryloxyimino-2,2-dimethyl-1,3-dioxane-4,6-dione (60).

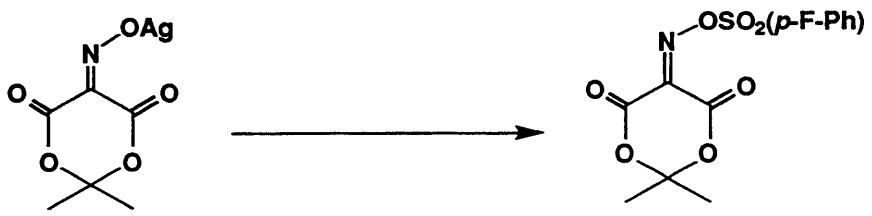
A 25-mL, one-necked, round-bottomed flask equipped with argon inlet adapter was charged with $(PhO)_2P(O)Cl$ (0.53 mL, 0.68 g, 2.54 mmol) and 13 mL of toluene. The solution was stirred at room temperature and then treated with the silver salt **55** (0.750 g, 2.68 mmol) in one portion to give a deep red suspension. To this reaction mixture was added five drops of pyridine which caused the suspension to become pink, then orange, and then yellow. After 30 min, the mixture was filtered with the aid of 10 mL of toluene. The combined filtrate was then concentrated and the residue passed through a column of deactivated silica gel cooled to 0 °C (elution with dichloromethane) to provide 0.772 g (61% overall) of the oxime **60** as a viscous, pale yellow oil.

IR ($CHCl_3$)	3020, 1795, 1765, 1590, 1490, 1390, 1290, 1185, 1160, 1015, 985, 935 cm^{-1}
^1H NMR (300 MHz, $CDCl_3$)	δ 1.79 (s, 6 H), 7.24 (t, J = 6 Hz, 2 H), 7.30 (d, J = 8, 4 H), 7.38 (dd, J = 7, 8 Hz, 4 H)
^{13}C NMR (75 MHz, $CDCl_3$)	δ 27.9, 106.6, 119.9 (d, J = 5.1 Hz), 125.9, 129.7, 142.0 (d, J = 13.2 Hz), 149.2, 149.7 (d, J = 7.6 Hz), 154.3



60

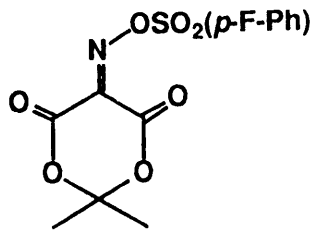




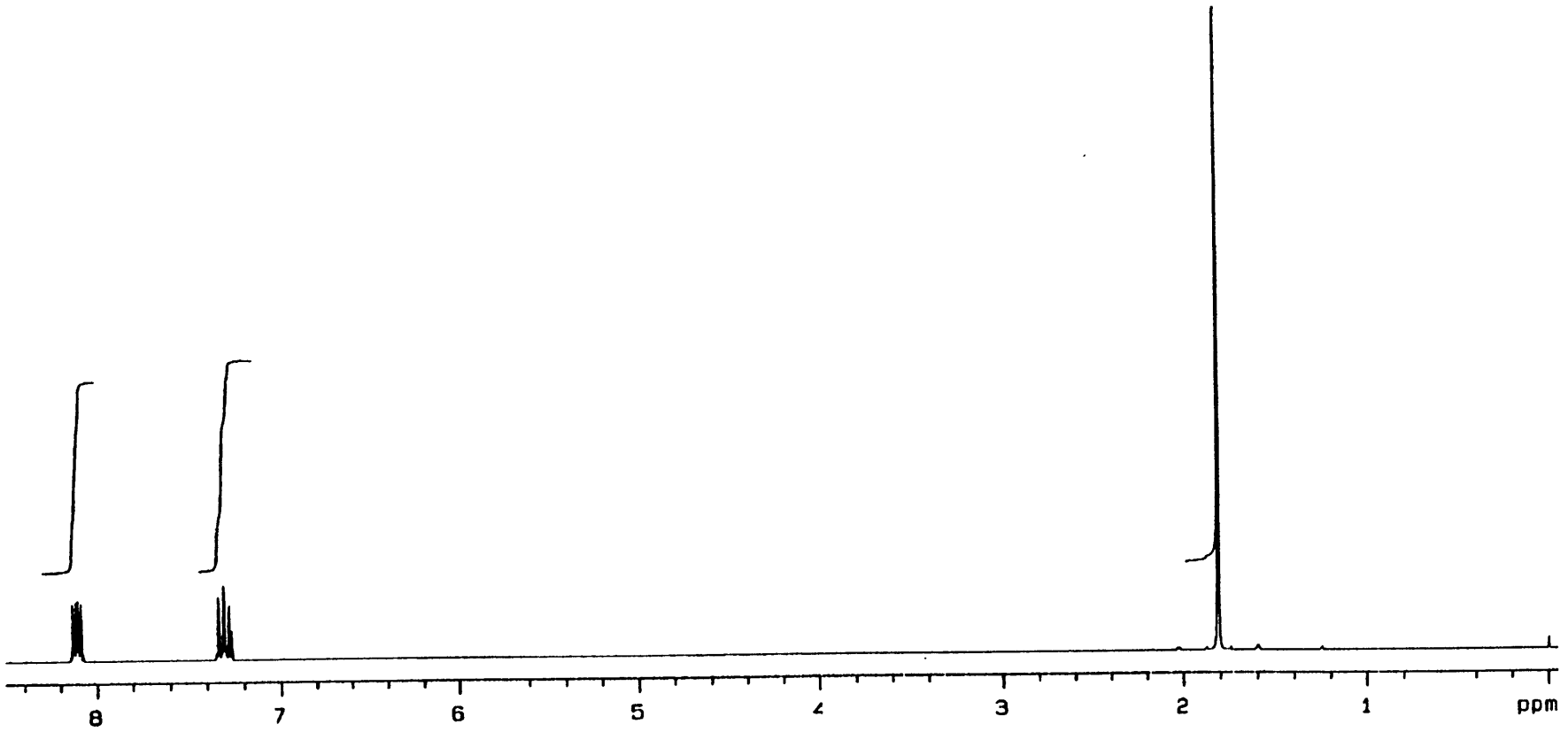
5-*p*-Fluorobenzenesulfonyloxyimino-2,2-dimethyl-1,3-dioxane-4,6-dione (59).

A 25-mL, one-necked, round-bottomed flask equipped with a reflux condenser and argon inlet adapter was charged with 4-fluorophenylsulfonyl chloride (0.340 g, 1.75 mmol) and 11 mL of benzene. The solution was stirred at room temperature and then treated with the silver salt **55** (0.489 g, 1.75 mmol) in one portion to give a deep red suspension. The reaction mixture was then treated with five drops of pyridine which caused the suspension to become pink. The mixture was then heated at 45 °C for 10 min to give a peach-pink suspension. After cooling to room temperature, the mixture was filtered with the aid of 10 mL of benzene. The combined filtrate was then concentrated to afford 0.555 g of an off-white solid. Column chromatography on 20 g of deactivated silica gel (elution with 50% ethyl acetate-hexane) provided 0.474 g (66% overall) of the oxime **59** as a white solid: mp 154-156 °C.

IR ($CHCl_3$)	3010, 1790, 1760, 1590, 1490, 1400, 1290, 1195, 920cm^{-1}
^1H NMR (300 MHz, $CDCl_3$)	δ 1.81 (s, 6 H), 7.31 (ddd, J = 2, 8, 9 Hz, 2 H), 8.11 (ddd, J = 2, 5, 9 Hz, 2 H)
^{13}C NMR (75 MHz, $CDCl_3$)	δ 28.2, 107.0, 117.1 ($J_{C\text{-}F}$ = 52 Hz), 129.1 ($J_{C\text{-}F}$ = 3 Hz), 132.7 ($J_{C\text{-}F}$ = 10 Hz), 139.1, 149.5, 154.5, 166.9 ($J_{C\text{-}F}$ = 258 Hz)



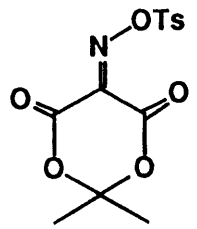
59



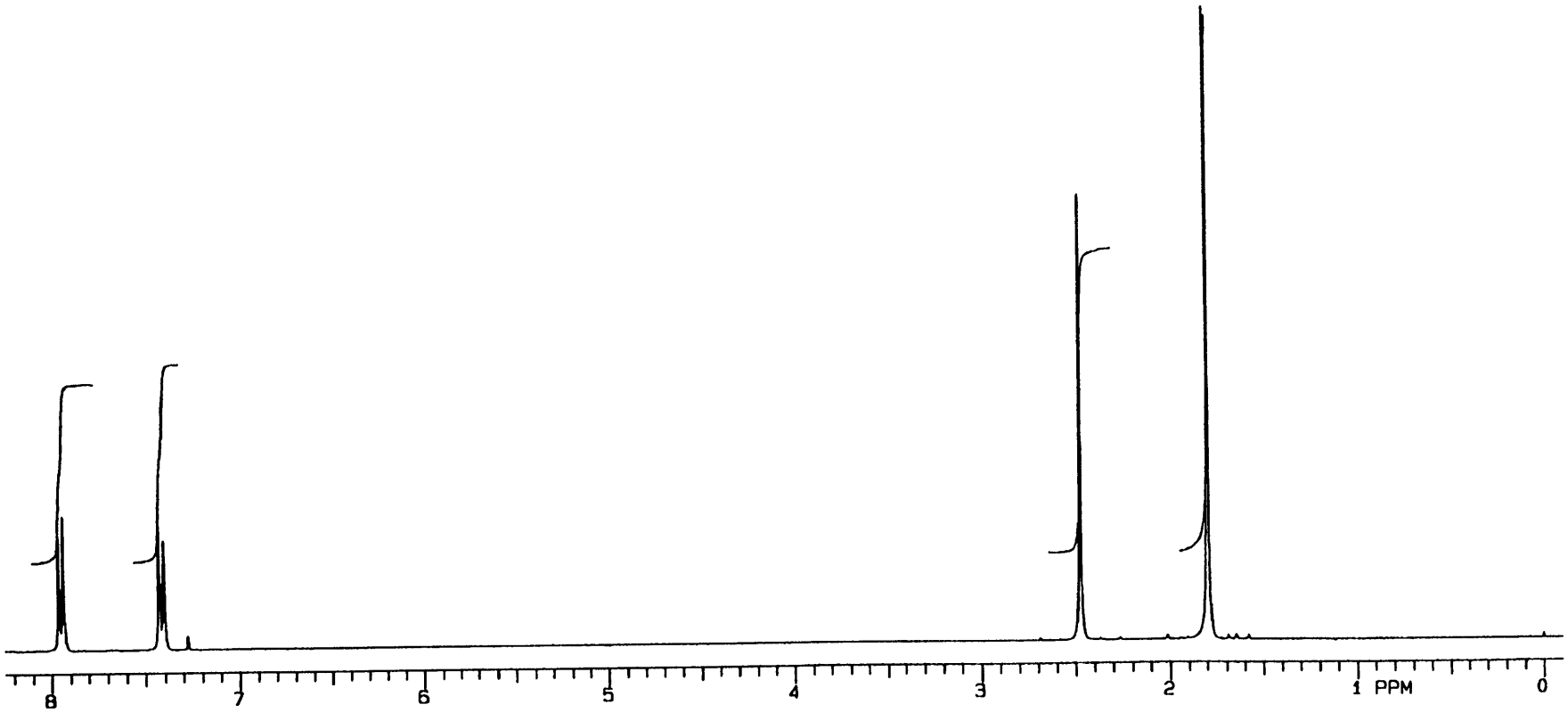
5-Tosyloxyimino-2,2-dimethyl-1,3-dioxane-4,6-dione (58).

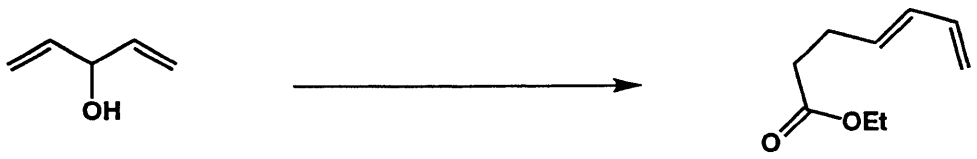
A 25-mL, round-bottomed flask equipped with an argon inlet adapter and solid addition funnel was charged with Meldrum's acid (2.61 g, 18.1 mmol) and 13 mL of methanol. To this suspension was added in one portion a solution of sodium nitrite (1.25 g, 18.1 mmol) in 10 mL of water. The reaction mixture was stirred for 2 h at room temperature to give a deep red solution which was treated with 2.5 mL of pH 7 phosphate buffer and then cooled to 0 °C. Tosyl chloride (3.11 g, 16.9 mmol) was added over 3 min via the solid addition funnel, the cooling bath was removed, and the resulting peach colored mixture was stirred for 30 min and then filtered with the aid of 30 mL of cold methanol. The resulting solid was dried at 0.2 mmHg over P_2O_5 for 2 h to provide 3.02 g (57% based on TsCl) of (**58**) as a white solid: mp 155-156 °C.

IR ($CHCl_3$)	3020, 1790, 1765, 1596, 1400, 1290 cm^{-1}	
^1H NMR (300 MHz, $CDCl_3$)	δ 1.78 (s, 6 H), 2.46 (s, 3 H), 7.40 (d, J = 8.4 Hz, 2 H), 7.93 (d, J = 8.4 Hz, 2 H)	
^{13}C NMR (75 MHz, $CDCl_3$)	δ 21.8, 28.1, 106.8, 129.5, 130.1, 130.2, 138.8, 147.1, 149.6, 154.7.	
Elemental Analysis	Calcd for $C_{13}H_{13}NO_7S$:	C, 47.70; H, 4.00; N, 4.28
	Found:	C, 47.76; H, 4.02; N, 4.22



58

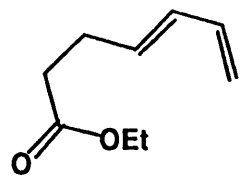




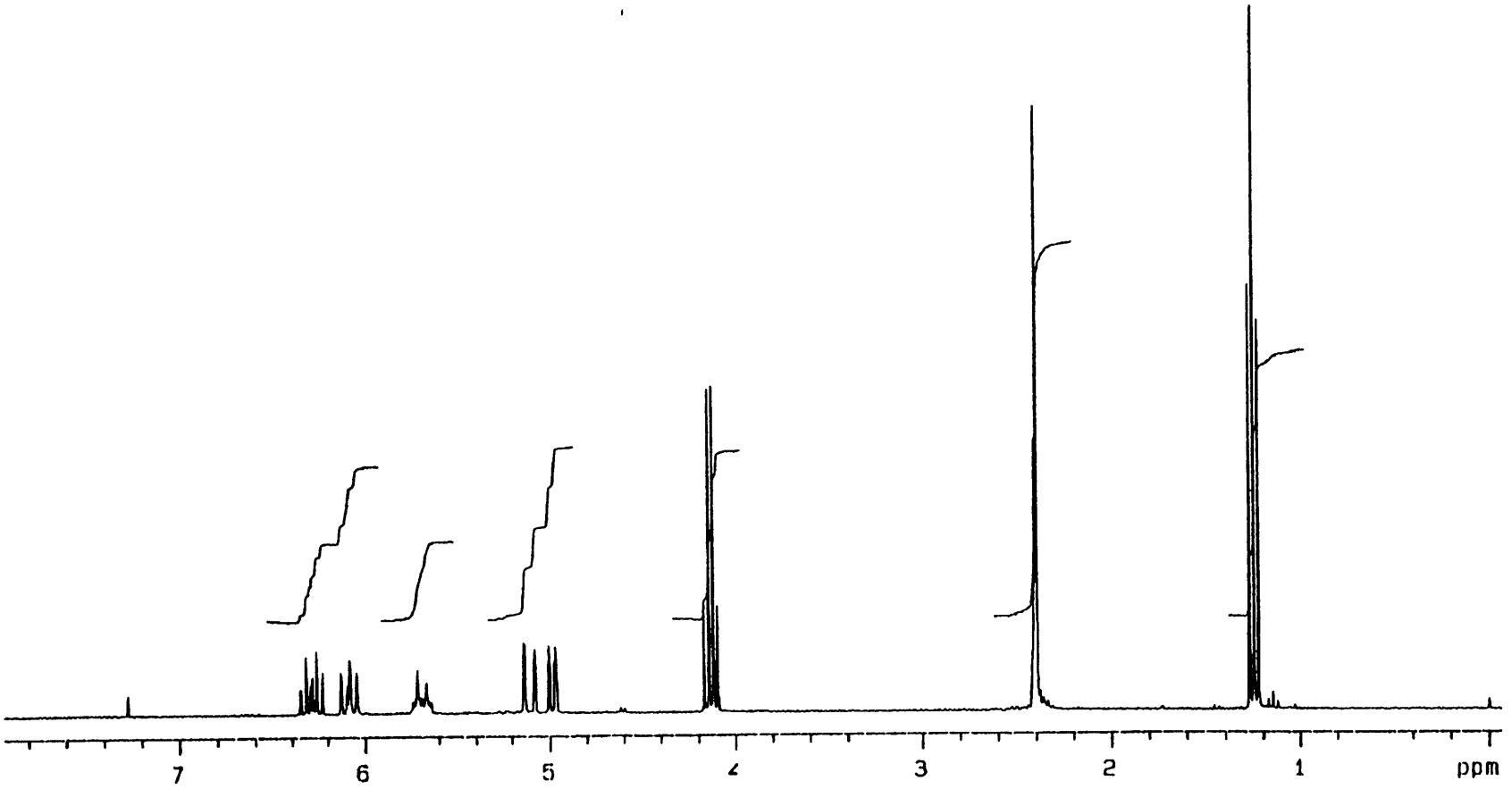
Ethyl hepta-4(*E*),6-dienoate (30).

A 250-mL, one-necked, round-bottomed flask equipped with a reflux condenser and argon inlet adapter was charged with penta-1,4-diene-3-ol (2.32 g, 27.6 mmol), triethyl orthoacetate (35.4 mL, 31.0 g, 193 mmol), propionic acid (0.41 mL, 0.41 g, 5.5 mmol), and 100 mL of toluene. The pale yellow solution was heated at reflux for 1.5 h and then allowed to cool to room temperature. The solution was transferred to a separatory funnel with the aid of 60 mL of Et_2O and washed with two 150-mL portions of 1 N HCl solution, 100 mL of H_2O, 100 mL of saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated to afford 6.25 g of the crude ester as an orange oil. Column chromatography on 20 g of silica gel (elution with 5% ethyl acetate-hexane) provided 3.74 g (81%) of the ester **30** as a colorless oil with spectral data consistent with that previously reported.[20b]

IR (thin film)	2980, 1735, 1445, 1372, 1248, 1180, 1005, 901 cm^{-1}
^1H NMR (300 MHz, $CDCl_3$)	δ 1.25 (t, J = 7 Hz, 3 H), 2.40 (m, 4 H), 4.13 (q, J = 7 Hz, 2 H), 4.98 (dd, J = 2, 10 Hz, 1 H), 5.12 (dd, J = 2, 17 Hz, 1 H), 5.60-5.67 (m, 1 H), 6.08 (dd, J = 10, 15 Hz, 1 H), 6.29 (ddd, J = 10, 10, 17 Hz, 1 H)
^{13}C NMR (75 MHz, $CDCl_3$)	δ 14.2, 27.8, 33.8, 60.3, 115.6, 131.9, 132.6, 136.8, 172.8



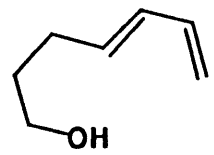
30



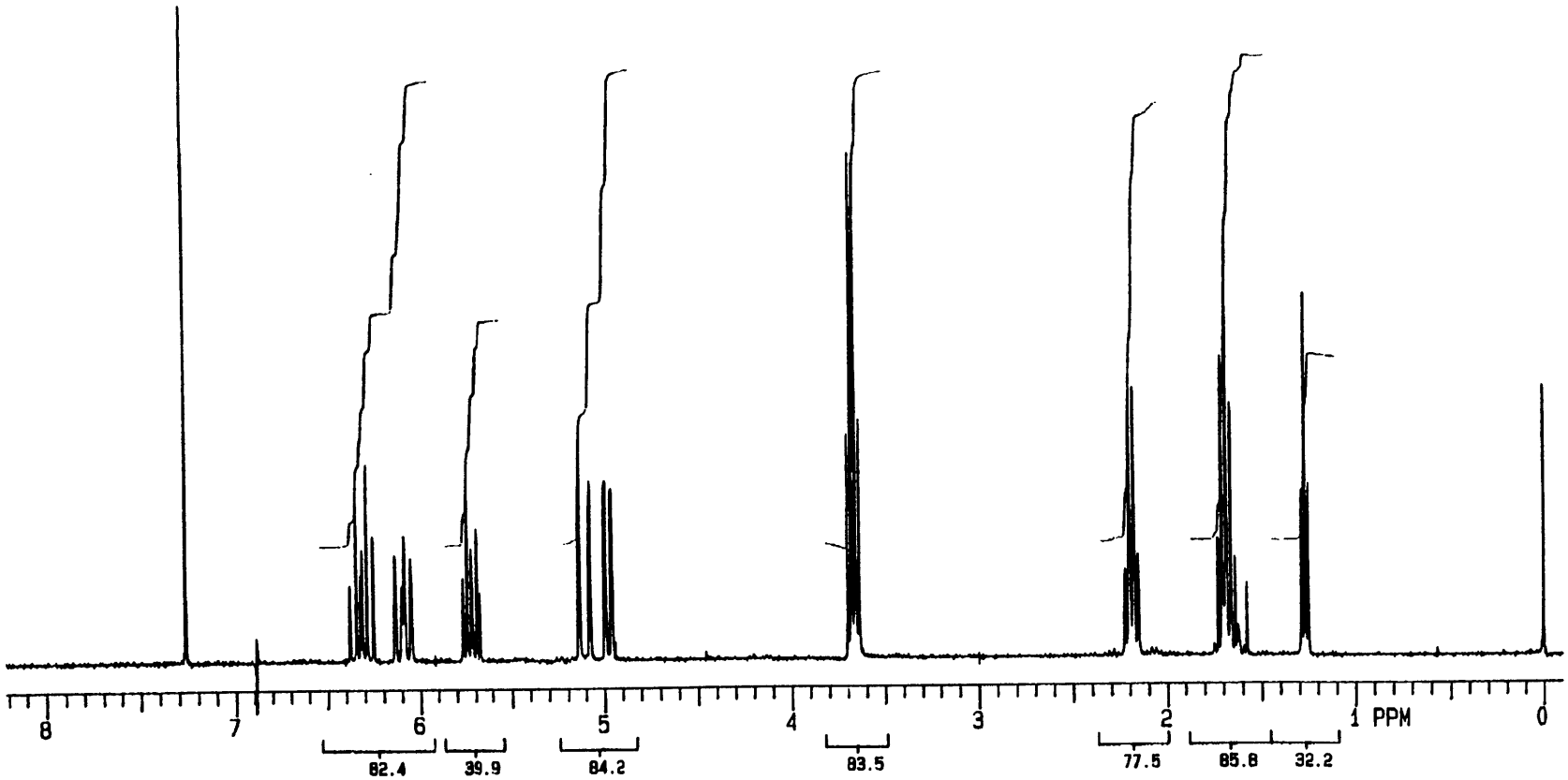
Hepta-4(*E*),6-dien-1-ol (31).

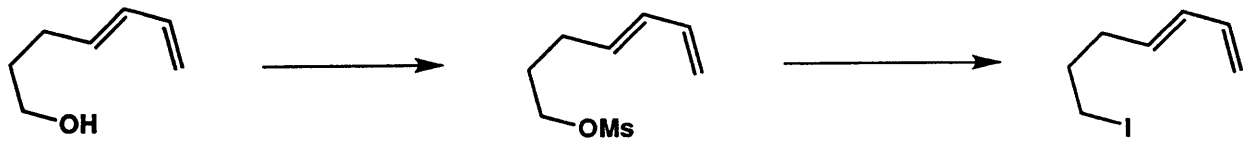
A 100-mL, one-necked, round-bottomed flask equipped with an argon inlet needle and septum was charged with $LiAlH_4$ (0.455 g, 12.0 mmol) and 40 mL of THF. The resulting gray suspension was cooled at 0 °C while a solution of ester **30** (1.849 g, 12.0 mmol) in 10 mL of THF was added dropwise via cannula over 5 min. The gray suspension was stirred at 0 °C for 1 h and then quenched by the slow addition of 10 mL of water and then 20 mL of 1 N HCl solution. The resulting mixture was stirred at room temperature for 45 min and then diluted with 20 mL of water and 75 mL of Et_2O. The layers were separated and the aqueous phase extracted with two 75-mL portions of Et_2O. The combined organic phases were washed with 30 mL of saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated to afford 1.171 g of a pale yellow oil. Column chromatography on 15 g of silica gel (elution with 25% ethyl acetate-hexane) provided 1.139 g (85%) of diene **31** as a colorless oil with spectral data consistent with that previously reported.[20b,c]

IR (thin film)	3335, 2935, 1650, 1600, 1005, 898 cm^{-1}
^1H NMR (300 MHz, $CDCl_3$)	δ 1.27 (t, *J* = 5 Hz, 1 H), 1.68 (m, 2 H), 2.19 (app q, *J* = 7 Hz, 2 H), 3.67 (app q, *J* = 6 Hz, 2 H), 4.98 (d, *J* = 10 Hz, 1 H), 5.10 (d, *J* = 17 Hz, 1 H), 5.71 (dt, *J* = 7, 15 Hz, 1 H), 6.09 (dd, *J* = 10, 15 Hz, 1 H), 6.32 (ddd, *J* = 10, 10, 15 Hz, 1 H)
^{13}C NMR (75 MHz, $CDCl_3$)	δ 28.7, 31.9, 62.1, 115.0, 131.4, 134.3, 137.0



31





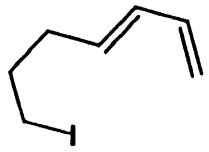
7-Iodohepta-1,3(*E*)-diene (32).

A 250-mL, one-necked, round-bottomed flask equipped with an argon inlet needle and septum was charged with the alcohol **31** (1.22 g, 10.9 mmol) and 100 mL of dichloromethane. The colorless solution was cooled at 0 °C while triethylamine (2.28 mL, 1.65 g, 16.4 mmol) was added via syringe in one portion followed by mesyl chloride (0.93 mL, 1.37 g, 12.0 mmol) dropwise via syringe over 10 min. After stirring for 25 min at 0 °C, the solution was diluted with 30 mL dichloromethane and washed with 100 mL of cold H_2O, 100-mL of cold 1 N HCl, 100-mL of saturated $NaHCO_3$, and 50-mL of saturated NaCl solution. The organic phase was then dried over $MgSO_4$, filtered, and concentrated to provide 2.011 g of the mesylate as a pale yellow oil. This material was used in the next step without purification.

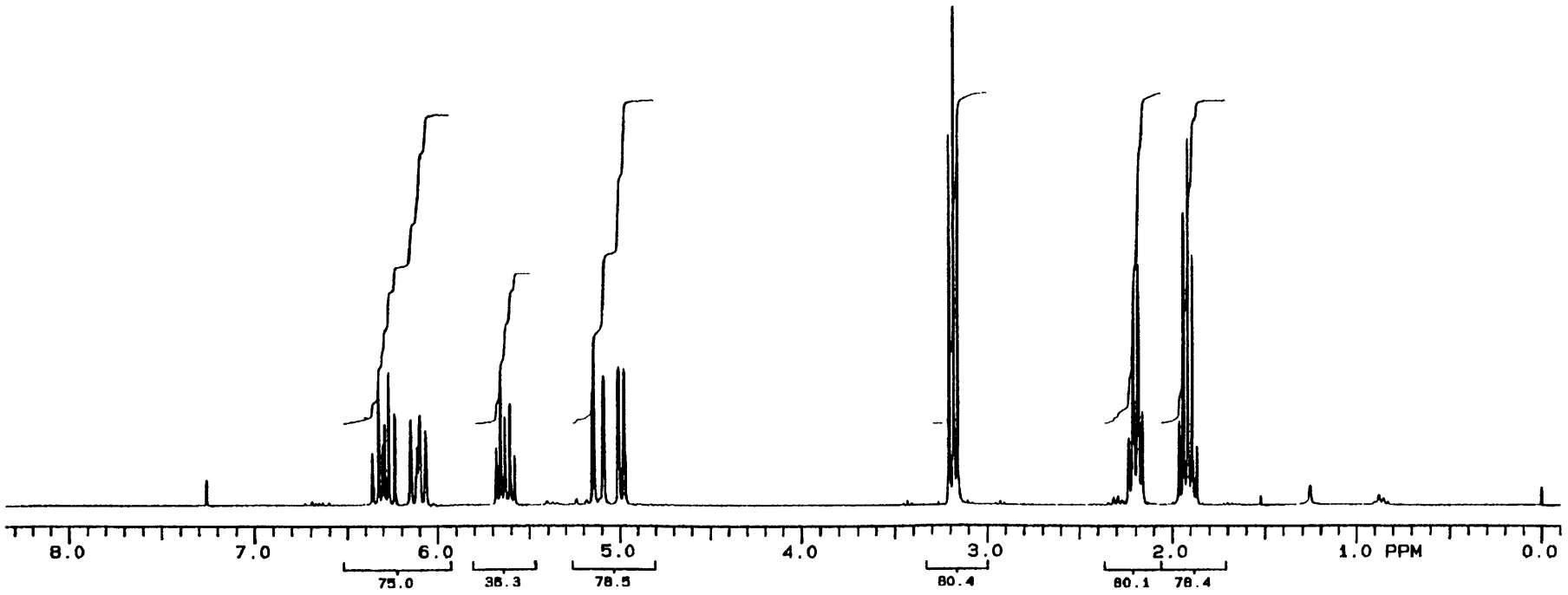
A 50-mL, one-necked, round-bottomed flask equipped with an argon inlet needle and septum was charged with the crude mesylate and 20 mL of acetone and the flask was wrapped in aluminum foil. Sodium iodide (8.20 g, 54.5 mmol) was added in one portion and the resulting solution was stirred at room temperature for 4 h. The resulting mixture was diluted with 40 mL of H_2O and the aqueous phase was extracted with four 25-mL portions of Et_2O. The combined organic phases were washed with saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated to provide a pale yellow oil. Column chromatography on 35 g of silica gel (elution with 2% ethyl acetate-hexane) provided 2.014 g (82% overall) of the iodide **32** as a clear, colorless oil with spectral data consistent with that previously reported.[20c]

IR (thin film)	2930, 1650, 1602, 1430, 1214, 1005, 950, 900 cm^{-1}
^1H NMR (300 MHz, $CDCl_3$)	δ 1.92 (app quint, J = 7 Hz, 2 H), 2.20 (app q, J = 7 Hz, 2 H), 3.19 (t, J = 7 Hz, 2 H), 4.99 (d, J = 10 Hz, 1 H), 5.12 (d, J = 17 Hz, 1 H), 5.63 (dt , J = 7, 14 Hz, 1 H), 6.10

	(dd, J = 10, 16 Hz, 1 H), 6.29 (ddd, J = 10, 10, 17 Hz, 1 H)
^{13}C NMR (75 MHz, $CDCl_3$)	δ 6.2, 32.7, 33.1, 115.6, 132.3, 132.5, 136.9



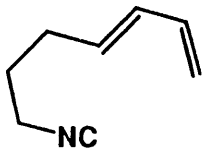
32



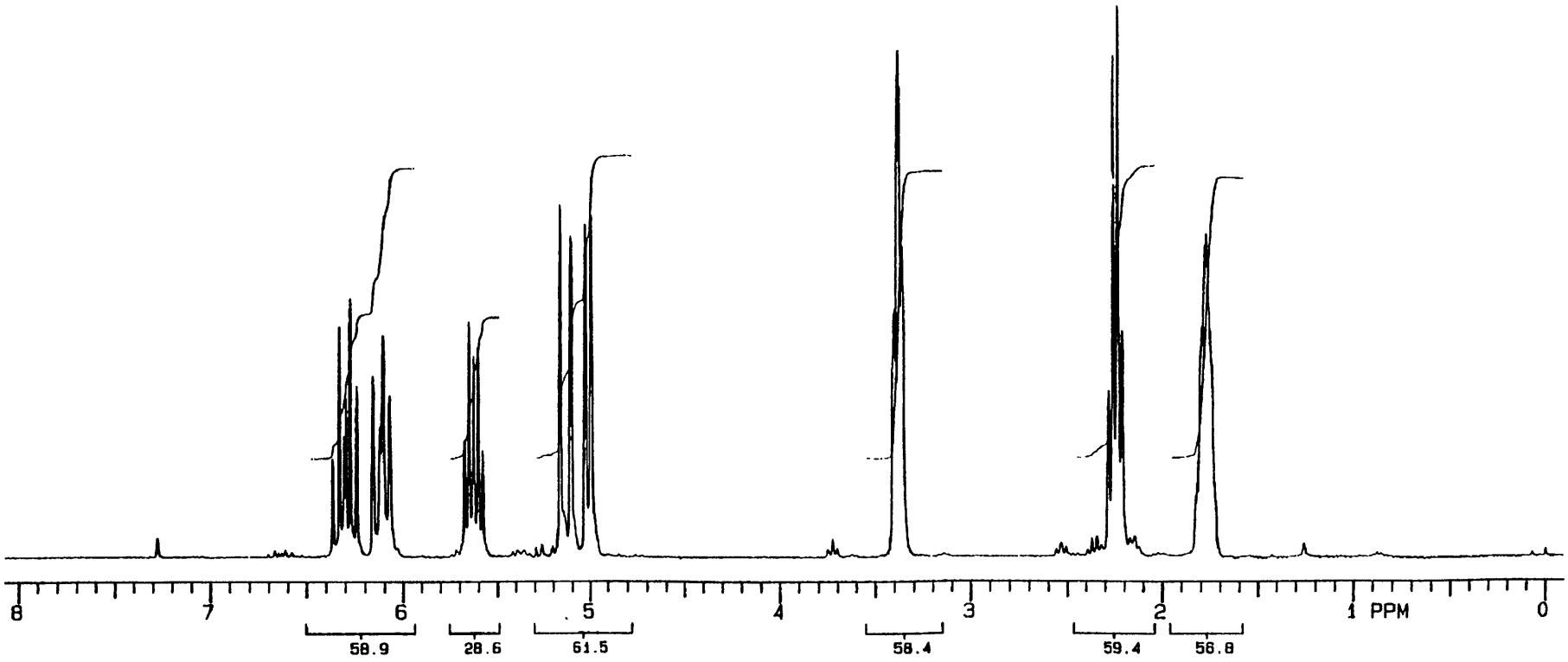
7-Isocyanohepta-1,3(*E*)-diene (33).

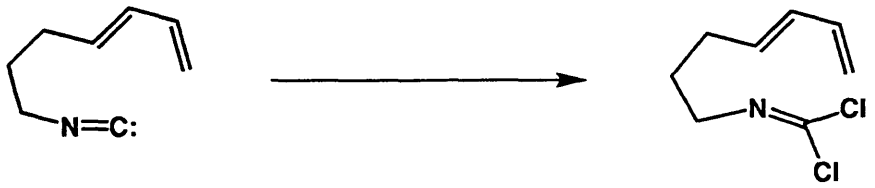
A 10-mL, one-necked, round-bottomed flask equipped with a reflux condenser and argon inlet adapter was charged with the iodide **32** (1.22 g, 5.4 mmol) and AgCN (0.740 g, 5.5 mmol). The resulting yellow suspension, was heated to 115-120 °C for 2.5 h to give a very thick brown substance. After being cooled to room temperature, the brown material was dissolved in ca. 20 mL of dichloromethane and ca. 20 mL of aqueous KCN solution was added. This mixture was stirred for 16 h and an additional 20 mL of dichloromethane was then added. The organic layer was separated washed with 20 mL of saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by column chromatography on 50 g of silica gel (elution with 5% ethyl acetate-hexane) to provide 0.449 g (69%) of the isonitrile **33** as a yellow oil.

IR (thin film)	3000, 2945, 2150, 1645, 1600, 1450, 1005, 955, 905 cm^{-1}
^1H NMR (300 MHz, $CDCl_3$)	δ 1.73-1.82 (m, 2 H), 2.24 (app q, J = 7 Hz, 2 H), 3.38 (d tr, J = 2, 7 Hz, 2 H), 5.01 (d, J = 10 Hz, 1 H), 5.14 (d, J = 17 Hz, 1 H), 5.63 (d tr, J = 7, 15 Hz, 1 H), 6.11 (dd, J = 10, 15 Hz, 1 H), 6.30 (ddd, J = 10, 10, 17, 1 H)
^{13}C NMR (75 MHz, $CDCl_3$)	δ 28.3, 28.8, 40.6 (t, J_{C-N} = 6 Hz), 115.8, 131.7, 132.6, 136.5, 155.97 (d, J_{C-N}= 6 Hz)



33

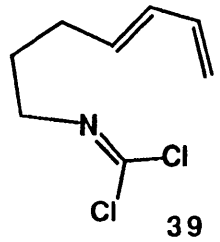




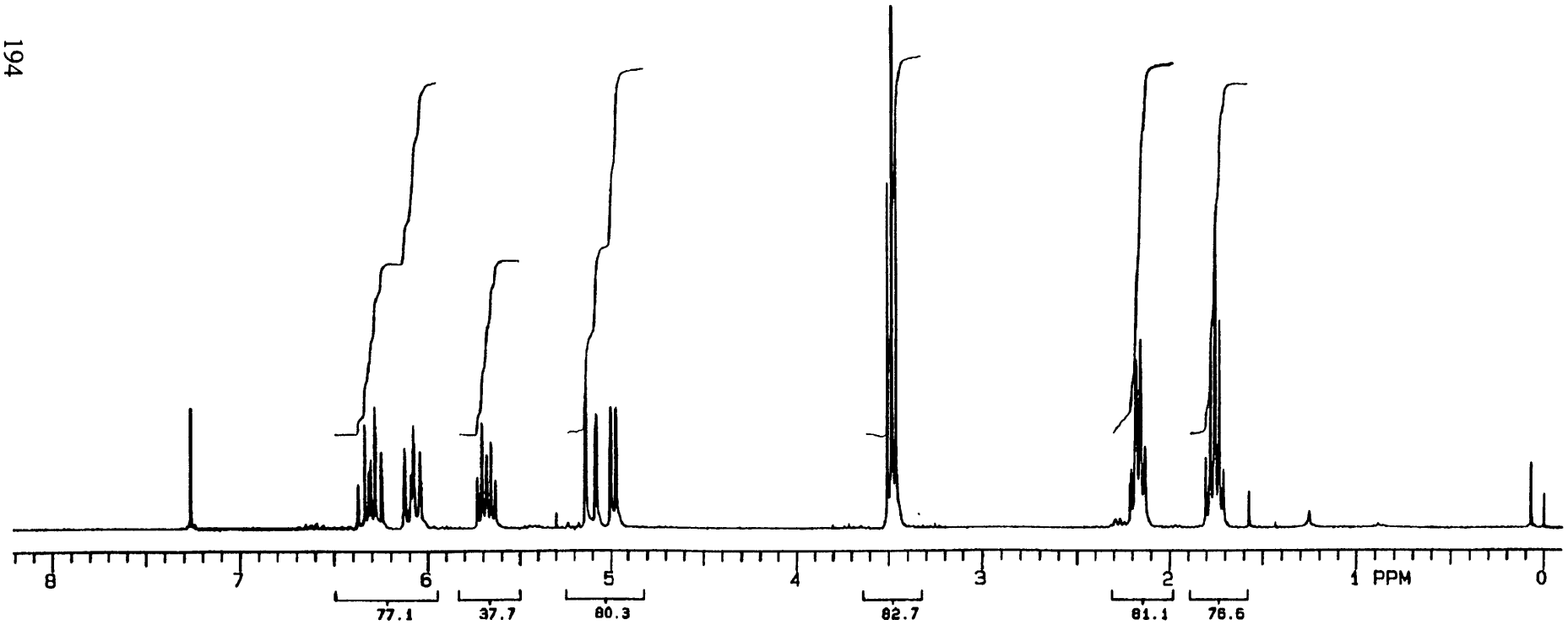
Imidoyl dichloride 39.

A 10-mL, one-necked, round-bottomed flask wrapped in aluminum foil and equipped with an argon inlet needle and septum was charged with isonitrile **33** (0.046 g, 0.38 mmol) and 2 mL of CCl_4. The solution was cooled at -10 °C and a solution of chlorine (ca. 2.8 M in CCl_4) was added in five portions (0.91 mL total, 2.55 mmol) over 1.5 h until tlc analysis indicated complete reaction of the starting material. The solution was then concentrated and the residue was purified by column chromatography on 4 g of deactivated silica gel (elution with 2% ethyl acetate-hexane) to provide 0.036 g (49%) of the imidoyl dichloride **39** as a pale yellow oil.

IR ($CHCl_3$)	3000, 2940, 1645, 900, 885 cm^{-1}
^1H NMR (300 MHz, $CDCl_3$)	δ 1.76 (app quint, J = 7 Hz, 2 H), 2.17 (app q, J = 7 Hz, 2 H), 3.49 (t, J = 7, 2 H), 4.98 (dd, J = 2, 10 Hz, 1 H), 5.11 (d, J = 17 Hz, 1 H), 5.69 (d tr, J = 7, 14 Hz, 1 H), 6.08 (dd, J = 10, 15 Hz, 1 H), 6.31 (ddd, J = 10, 10, 17 Hz, 1 H)
^{13}C NMR (75 MHz, $CDCl_3$)	δ 28.7, 30.0, 54.2, 115.4, 124.0, 131.9, 133.6, 137.0



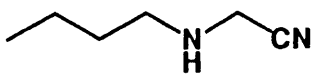
39



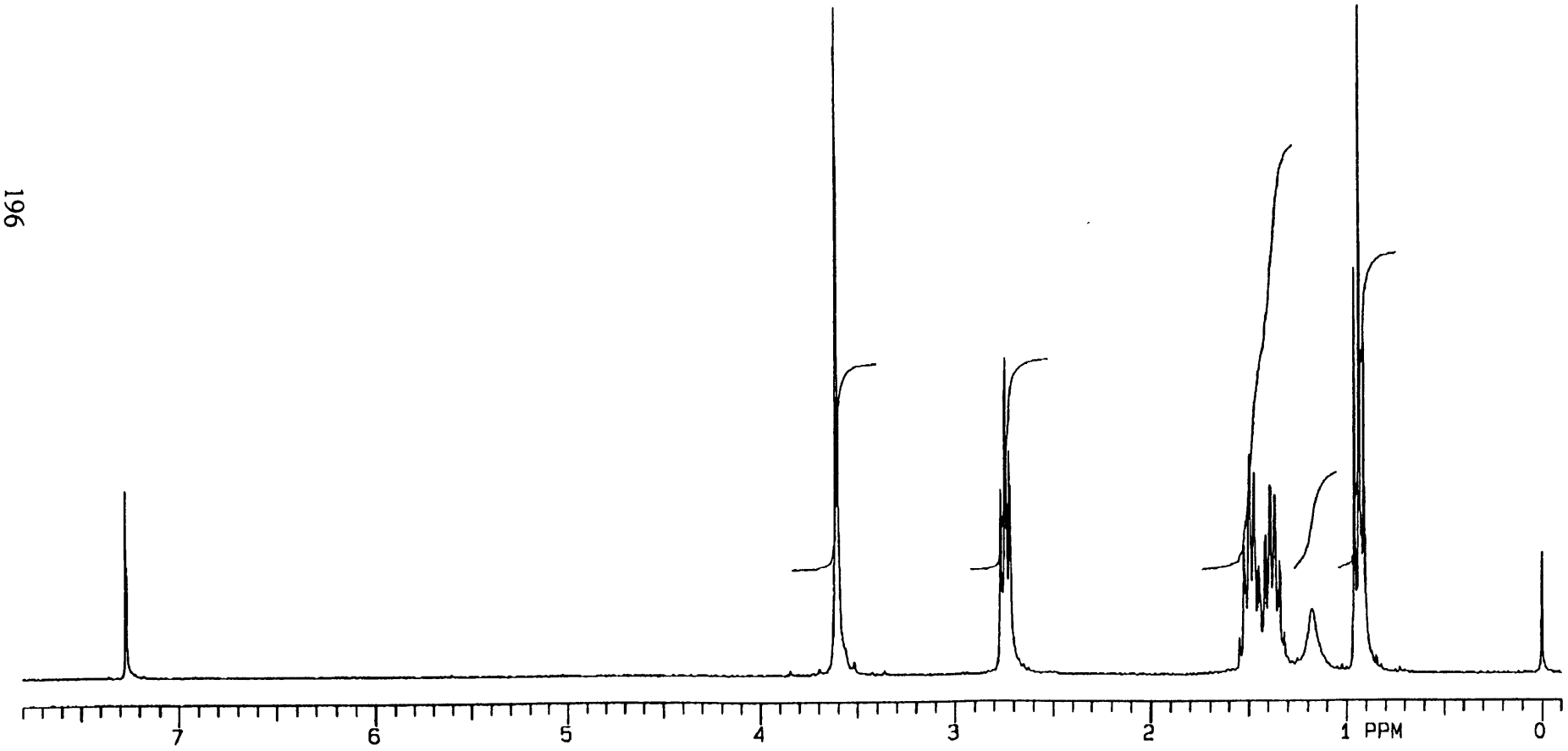
_n_-Butylaminoacetonitrile (86).

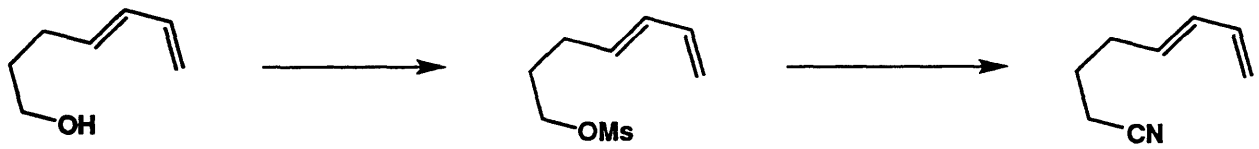
A 10-mL, one-neck, round-bottomed flask equipped with argon inlet needle and septum was charged with _n_-butylamine (0.140 g, 1.91 mmol) and 5 mL of dichloromethane. The solution was cooled at -78 °C and treated with bromoacetonitrile (0.13 mL, 0.23 g, 1.91 mmol) dropwise via syringe over 3 min. The reaction mixture was allowed to warm to room temperature and stirred for 18 h. The reaction mixture was then diluted with 10 mL of dichloromethane and washed with 10 mL of saturated $NaHCO_3$ solution. The $NaHCO_3$ solution was back-extracted with 10 mL of dichloromethane and the combined organic phases were washed with 10 mL of saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated to afford 0.204 g of the crude product as a pale yellow oil. Kugelrohr distillation (ca. 0.2 mmHg, 100 °C) provided 0.169 g (79%) of the nitrile **86** as a colorless oil.

IR (thin film)	3340, 2970, 2940, 2240, 1470, 1035, 875 cm^{-1}
^1H NMR (300 MHz, $CDCl_3$)	δ 0.94 (t, J = 7.2 Hz, 3 H), 1.18 (br s, 1 H), 1.32-1.55 (m, 4 H), 2.74 (t, J = 6.9 Hz, 2 H), 3.60 (s, 2 H)
^{13}C NMR (75 MHz, $CDCl_3$)	δ 13.9, 20.2, 31.5, 37.4, 48.5, 117.9



86





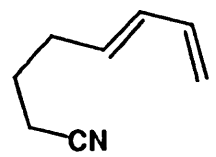
Octa-5(*E*),7-dienenitrile (77).

A 100-mL, one-necked, round-bottomed flask equipped with an argon inlet needle and septum was charged with the alcohol **31** (1.00 g, 8.92 mmol) and 50 mL of dichloromethane. The colorless solution was cooled at 0 °C while triethylamine (2.2 mL, 1.58 g, 15.6 mmol) was added via syringe in one portion followed by mesyl chloride (0.86 mL, 1.28 g, 11.2 mmol) dropwise via syringe over 5 min. After stirring for 1 h at 0 °C, the solution was diluted with 30 mL of dichloromethane and washed with 100 mL of cold H_2O, 100-mL of cold 1 N HCl, 100-mL of saturated $NaHCO_3$, and 50-mL of saturated NaCl solution. The organic phase was then dried over $MgSO_4$, filtered, and concentrated to provide 1.748 g of the mesylate as a pale yellow oil. This material was used in the next step without purification.

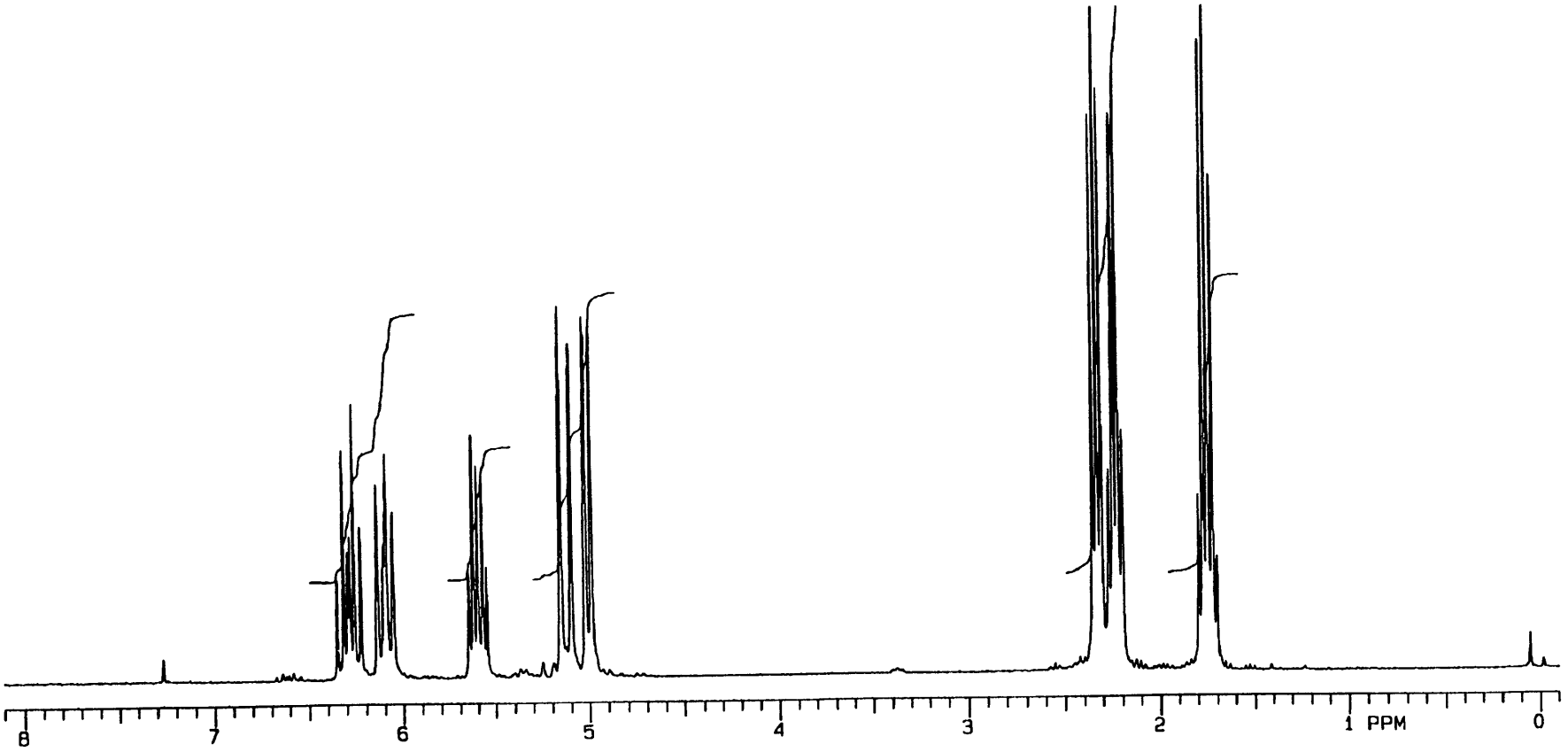
A 50-mL, one-necked, round-bottomed flask equipped with an argon inlet needle and septum was charged with the crude mesylate and 18 mL of DMSO. To the resulting pale yellow solution was added NaCN (1.75 g, 35.7 mmol) to give a deep yellow suspension that was then heated at 60 °C for 1 h. The resulting brown suspension was cooled to room temperature and diluted with 100 mL of H_2O. The solution was extracted with three 50-mL portions of Et_2O and the combined organic phases were washed with 50 mL of saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated to afford 1.012 g of a brown oil. Column chromatography on 20 g of silica gel (elution with 25% ethyl acetate-hexane) provided 0.948 g (88% overall) of the nitrile **77** as a pale yellow oil with spectral data consistent with that previously reported.[20b]

IR (thin film)	3020, 2950, 2255, 1425, 1005, 965, 905 cm^{-1}
^1H NMR (300 MHz, $CDCl_3$)	δ 1.75 (app quint, J = 7 Hz, 2 H), 2.23 (app q, J = 7, 2 H), 2.33 (t, J = 7 Hz, 2 H), 4.99 (d, J = 10 Hz, 1 H), 5.12 (d, J

	= 17 Hz, 1 H), 5.59 (dt, J = 7, 15 Hz, 1 H), 6.09 (dd, J = 10, 15 Hz, 1 H), 6.28 (ddd, J = 10, 10, 17 Hz, 1 H)
^{13}C NMR (75 MHz, $CDCl_3$)	δ 16.2, 24.6, 31.0, 116.0, 119.4, 131.7, 132.7, 136.4



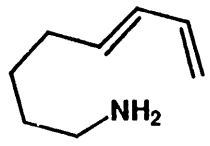
77



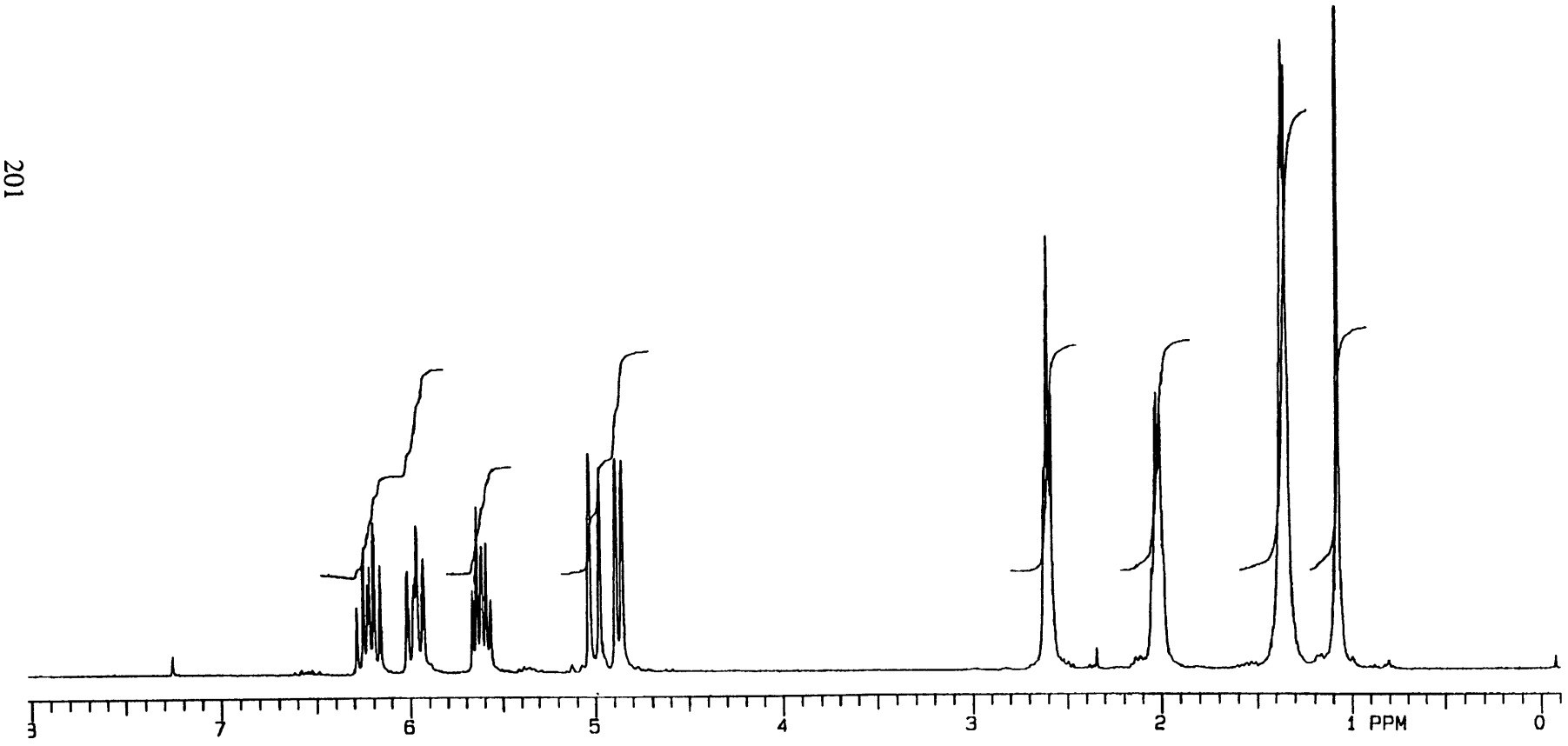
Octa-5(*E*),7-diene-1-amine (78).

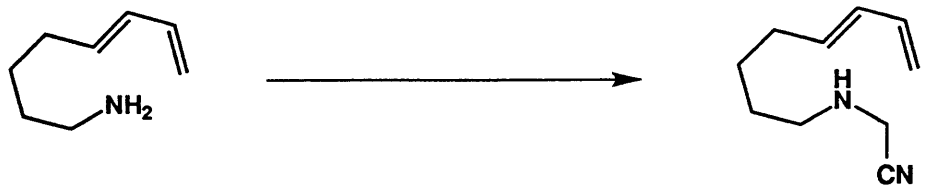
A 100-mL, three-necked, round-bottomed flask equipped with an argon inlet adapter, septum, and glass stopper was charged with $LiAlH_4$ (0.276 g , 7.26 mmol) and 50 mL of Et_2O. This gray suspension was stirred at 0 °C while a solution of the nitrile **77** (0.800 g, 6.6 mmol) in 15 mL of Et_2O was added dropwise via cannula over 10 min. The suspension was stirred at 0 °C for 1 h and then quenched by the slow addition of 8 mL of 1 N NaOH solution followed by 20 mL of H_2O and another 5 mL of 1 N NaOH solution. The resulting two-phase solution was stirred at room temperature for 45 min and then the layers were separated and the aqueous phase extracted with three 40-mL portions of Et_2O. The combined organic phases were washed with 50 mL of saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated to afford a pale yellow oil. Kugelrohr distillation (ca. 0.2 mmHg, 50 °C) provided 0.713 g (86%) of the amine **78** as a colorless oil.

IR (thin film)	3370, 3290, 2930, 2850, 1600, 1000, 955, 895 cm^{-1}
^1H NMR (300 MHz, $CDCl_3$)	δ 1.08 (s, 2H), 1.31-1.41 (m, 4H), 2.01-2.05 (m, 2H), 2.61 (app t, J = 7 Hz, 2 H), 4.88 (d, J = 10 Hz, 1 H), 5.00 (d, J = 17 Hz, 1 H), 5.62 (dtr, J = 7, 15 Hz, 1 H), 5.97 (dd, J = 10, 15 Hz, 1 H), 6.23 (ddd, J = 10, 10, 17 Hz, 1 H)
^{13}C NMR (75 MHz, $CDCl_3$)	δ 26.2, 32.1, 33.2, 41.9, 114.6, 130.9, 134.9, 137.0



78

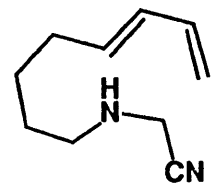




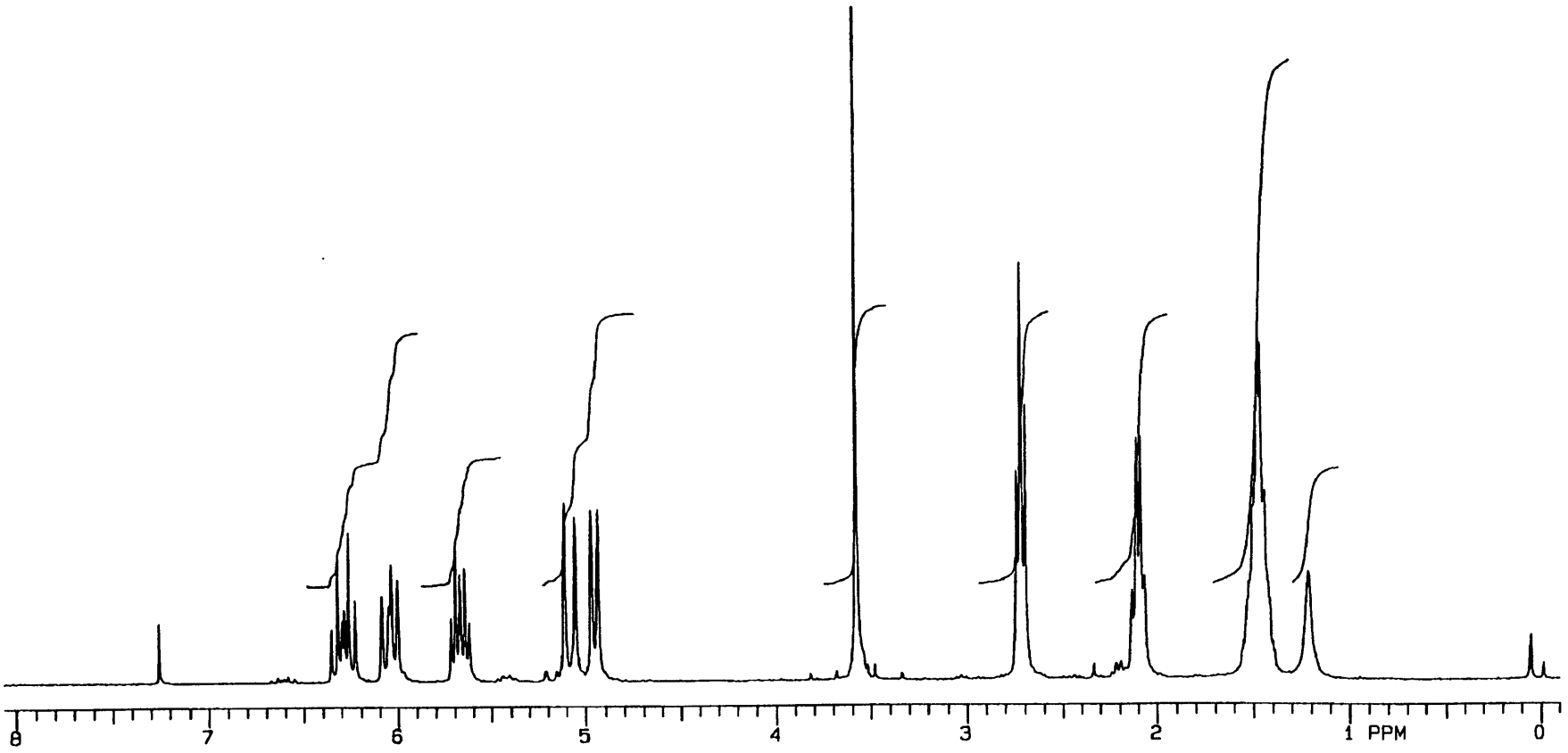
Octa-5(*E*),7-dienylaminoacetonitrile (88).

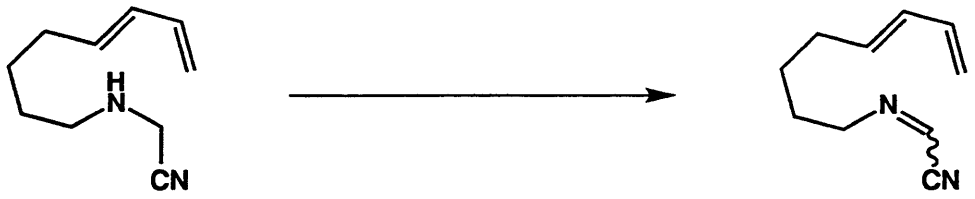
A 100-mL, one-necked, round-bottomed flask equipped with an argon inlet needle and septum was charged with the amine **78** (0.655 g, 5.32 mmol) and 35 mL of dichloromethane. The colorless solution was cooled at -78 °C while bromoacetonitrile (0.37 mL, 0.637 g, 5.31 mmol) was added dropwise over 2 min. The solution was allowed to warm to room temperature and was stirred in the dark for 1.5 days. The resulting cloudy white solution was then diluted with 20 mL of dichloromethane and extracted with 30 mL of saturated $NaHCO_3$ solution. The $NaHCO_3$ phase was back-extracted with 15 mL of dichloromethane, and the combined organic phases were then washed with 30 mL of saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated to afford 1.09 g of a oily solid. Two Kugelrohr distillations (ca. 0.2 mmHg, 100-150 °C) provided 0.500 g (57%) of the amine **88** as a colorless oil.

IR (thin film)	3340, 2930, 1650, 1605, 1130, 1005, 955, 905 cm^{-1}
^1H NMR (300 MHz, $CDCl_3$)	δ 1.21 (br s, 1 H), 1.40-1.57 (br m, 4 H), 2.10 (app q, J = 7 Hz, 2 H), 2.72 (t, J = 7 Hz, 2 H), 3.58 (s, 2 H), 4.96 (d, J = 10 Hz, 1 H), 5.09 (d, J = 16 Hz, 1 H), 5.67 (d tr, J = 7, 14 Hz, 1 H), 6.05 (dd, J = 10, 15 Hz, 1 H), 6.29 (ddd, J = 10, 10, 17 Hz, 1 H)
^{13}C NMR (75 MHz, $CDCl_3$)	δ 26.5, 28.9, 32.1, 37.3, 48.6, 115.0, 117.8, 131.3, 134.6, 137.1



88

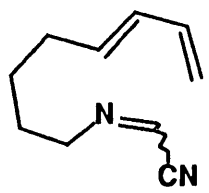




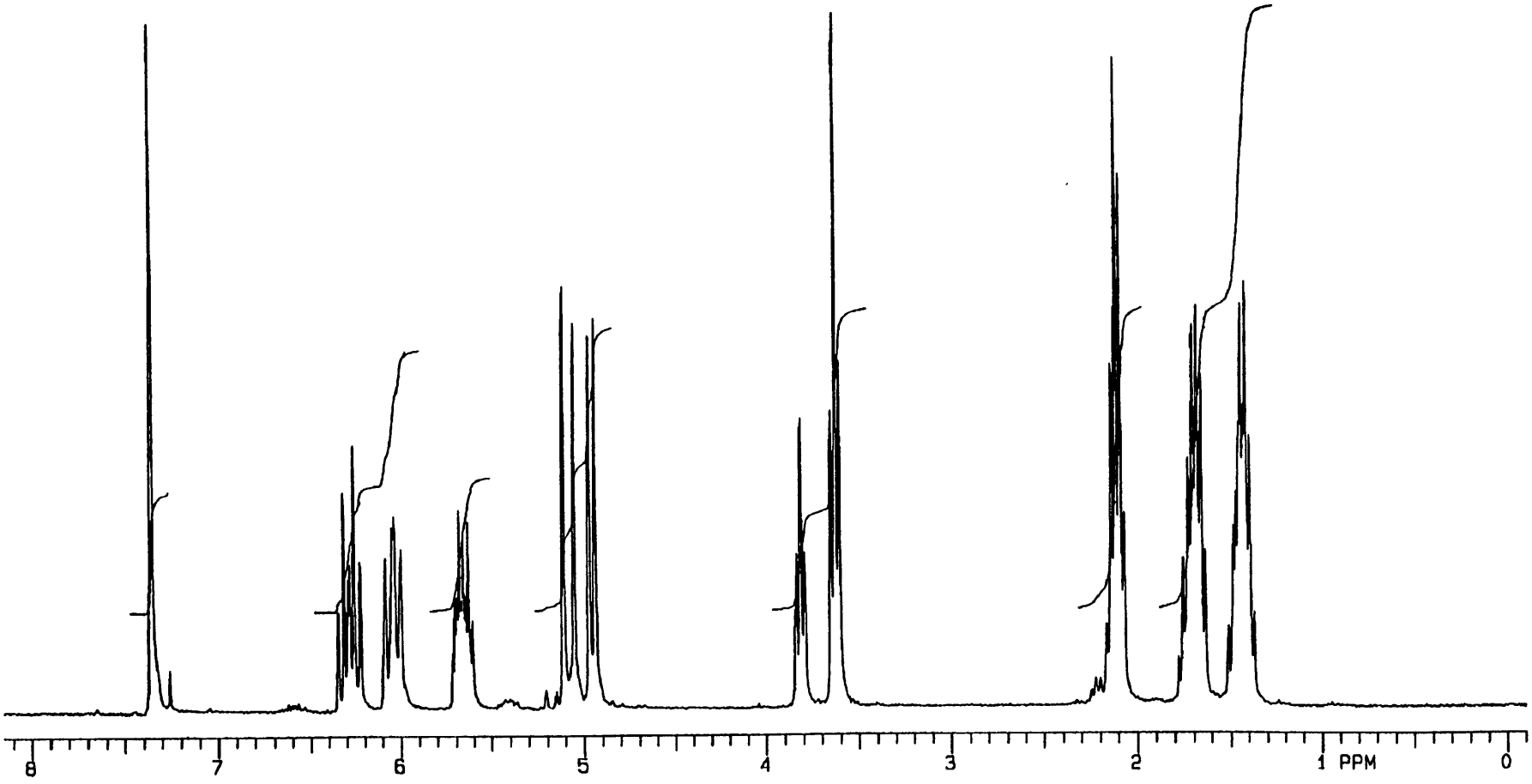
Octa-5(*E*),7-dienyliminoacetonitrile (71).

A 25-mL, one-necked, round-bottomed flask equipped with an argon inlet needle and septum was charged with the amine **88** (0.308 g, 1.875 mmol) and 18 mL of THF. The solution was stirred at room temperature and *N*-chlorosuccinimide (0.255 g, 1.91 mmol) was added in one portion to give a clear colorless solution. After stirring for 15 min at room temperature, the flask was cooled to 0 °C and NaOMe solution (1.16 mL, 1.64 M in methanol, 1.91 mmol) was added dropwise via syringe over 2 min to give a cloudy solution. The reaction mixture was stirred for 30 min at 0 °C and then poured into 30 mL of saturated $NaHCO_3$ solution with the aid of 10 mL of H_2O. The aqueous phase was extracted with three 40-mL portions of Et_2O and the combined organic phases were washed with 40 mL of saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated to afford 0.312 g of a yellow oil. Column chromatography on 15 g of silica gel (5% ethyl acetate-1% triethylamine-hexane) provided 0.202 g (66%) of the imine **71** (68:32, *E* : *Z*) as a colorless oil.

IR (thin film)	2925, 2845, 1620, 1600, 1440, 1450, 1005, 955, 900 cm^{-1}
^1H NMR (300 MHz, $CDCl_3$)	δ 1.37-1.51 (m, 2 H, both isomers), 1.64-1.78 (m, 2 H, both isomers), 2.12 (app quint, *J* = 7 Hz, 2 H, both isomers), 3.63 (dt, *J* = 6.9, 1.5 Hz, 2 H, *E* isomer), 3.82 (dt, *J* = 6.9, 2.3 Hz, 2 H, *Z* isomer), 4.95 (d, *J* = 10 Hz, 1 H, both isomers), 5.08 (d, *J* = 17 Hz, 1 H, both isomers), 5.61-5.71 (m, 2 H, both isomers), 6.04 (dd, *J* = 11, 15 Hz, 1 H, both isomers), 6.22-6.35 (m, 1 H, both isomers), 7.35 (s, 1 H, both isomers)
^{13}C NMR (75 MHz, $CDCl_3$)	δ 26.4, 29.2, 31.9, 59.6, 62.7, 109.2, 114.3, 115.0, 115.1, 131.3, 131.4, 134.2, 134.3, 135.7, 136.9, 137.0



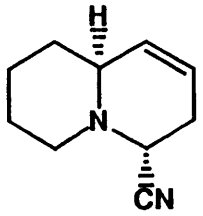
71



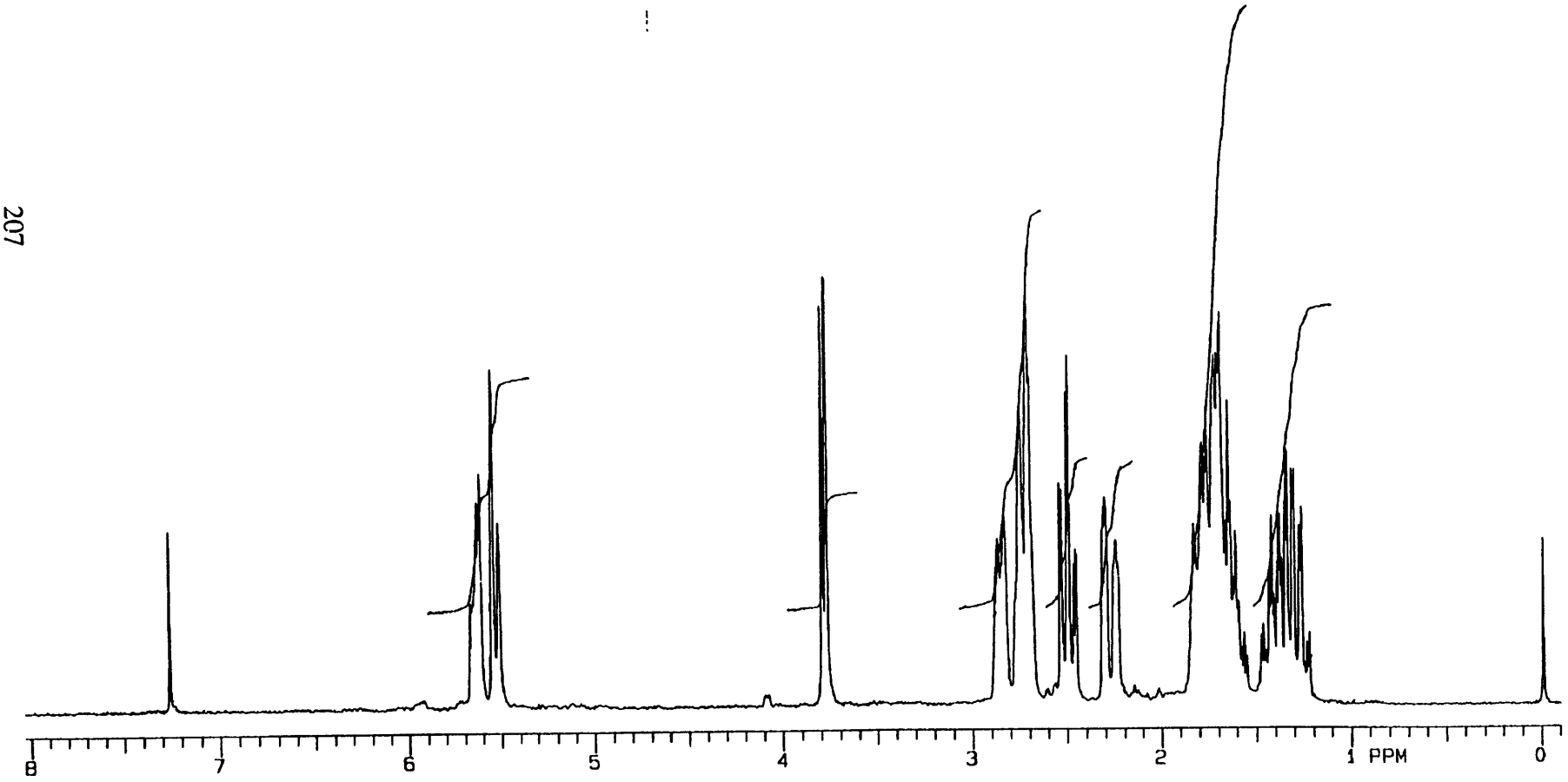
***cis*-3,4-Didehydro-1-cyanoquinolizidine (92).**

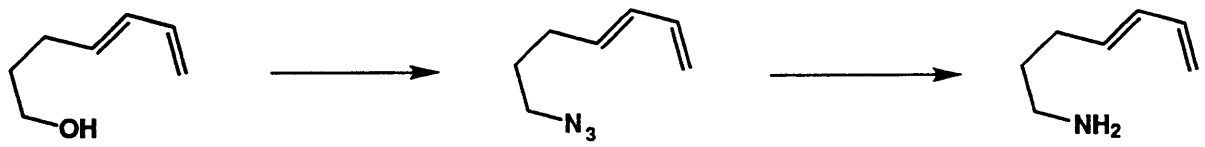
A threaded Pyrex tube (ca. 50 mL capacity) was charged with the imine **71** (0.127 g, 0.78 mmol), 15 mL of toluene, and 4-methyl-2,6-di-tert-butylphenol (0.516 g, 2.34 mmol). Argon was bubbled through the solution for 5 min and the tube was sealed with a threaded Teflon cap. The reaction mixture was heated at 115 °C for 20 h and then allowed to cool to room temperature. Concentration of the solution gave an orange oil that was purified by column chromatography on 12 g of silica gel (elution with 25% ethyl acetate-1% triethylamine-hexane) to afford 0.089 g (70%) of the cycloadduct **92** as a pale yellow oil.

IR (thin film)	3030, 2940, 2225, 2250, 1440, 1330, 1290, 1130, 1120, 850, 795 cm^{-1}
^1H NMR (300 MHz, $CDCl_3$)	δ 1.23-1.49 (m, 2 H), 1.57-1.84 (m, 4 H), 2.28 (br d, J = 18 Hz, 1 H), 2.50 (d tr, J = 3, 11 Hz, 1 H), 2.74 (br d, J = 11 Hz, 2 H), 2.86 (br d, J = 11 Hz, 1 H), 3.79 (d, J = 6 Hz, 1 H), 5.54 (δ , J = 10 Hz, 1 H), 5.62-5.67 (m, 1 H)
^{13}C NMR (75 MHz, $CDCl_3$)	δ 24.5, 25.7, 29.5, 31.7, 51.9, 54.0, 56.7, 116.9, 120.4, 130.5



92





Hepta-4(*E*),6-diene-1-amine (80).

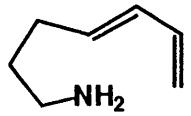
A 100-mL, one-necked, round-bottomed flask equipped with an argon inlet needle and septum was charged with the alcohol **31** (0.995 g, 8.88 mmol) and 50 mL of dichloromethane. The colorless solution was cooled at 0 °C while triethylamine (2.2 mL, 1.52 g, 15.5 mmol) was added via syringe in one portion followed by mesyl chloride (0.86 mL, 1.27 g, 11.1 mmol) dropwise via syringe over 5 min. After stirring for 1 h at 0 °C, the solution was diluted with 30 mL of dichloromethane and washed with 100 mL of cold H_2O, 100 mL of cold 1 N HCl, 100 mL of saturated $NaHCO_3$, and 50 mL of saturated NaCl solution. The organic phase was then dried over $MgSO_4$, filtered, and concentrated to provide 1.68 g of the mesylate as a pale yellow oil. This material was used in the next step without purification.

A 100-mL, one-necked, round-bottomed flask equipped with an argon inlet needle and septum was charged with the crude mesylate and 25 mL of DMF. To the resulting pale yellow solution was added NaN_3 (1.27 g, 19.53 mmol) to give a deep yellow suspension that was stirred at room temperature for 24 h. The resulting white suspension was then diluted with 100 mL of H_2O and extracted with three 50-mL portions of Et_2O. The combined organic phases were washed with 50 mL of saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated to afford 1.307 g of the azide **79** as a pale yellow oil. This material was used in the next step without purification.

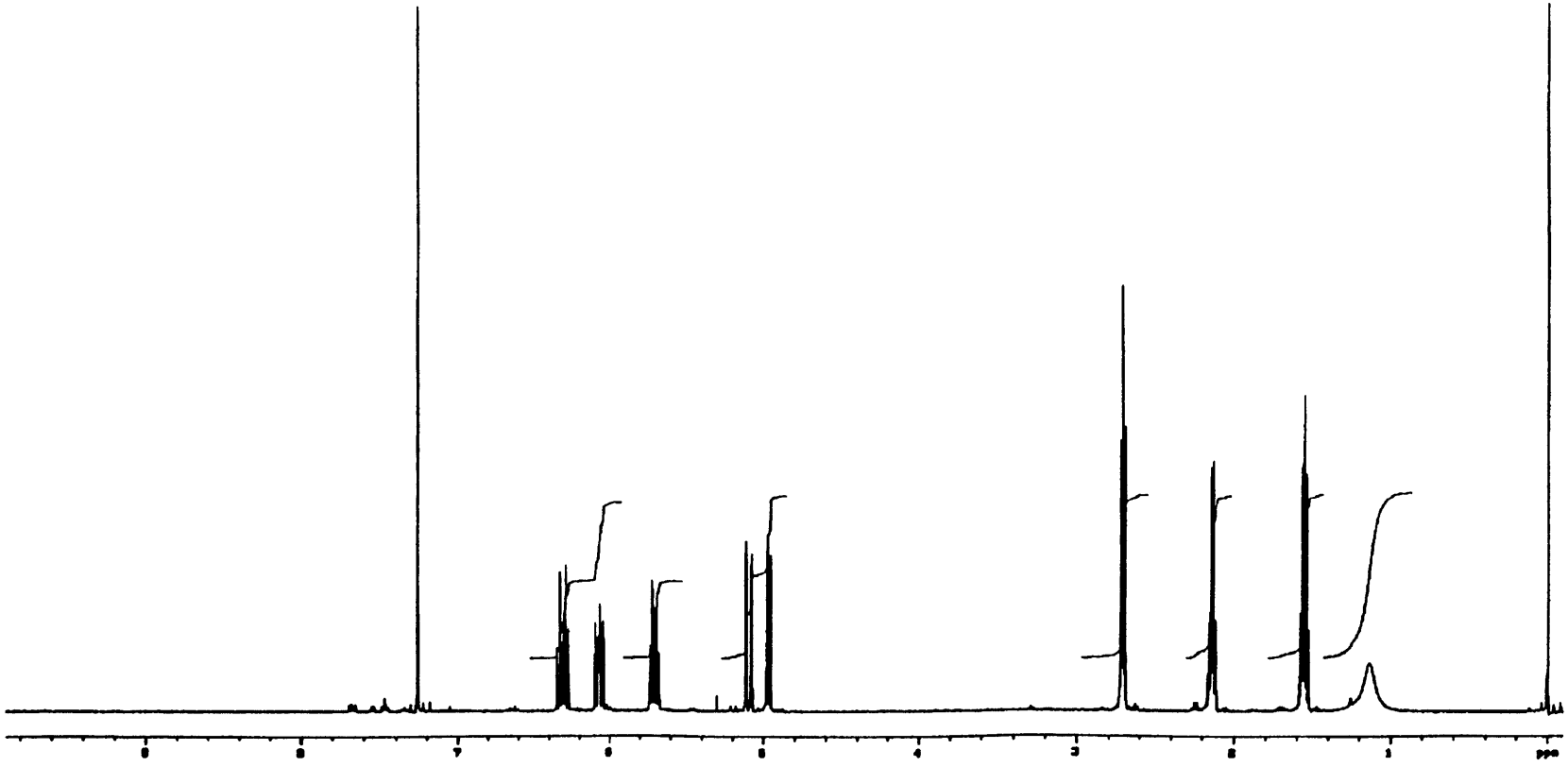
A 100-mL, one-necked, round-bottomed flask equipped with an argon inlet needle and septum was charged with the crude azide **79** (8.88 mmol) and 30 mL of THF. This pale yellow solution was stirred at room temperature while triphenylphosphine (2.33 g, 8.88 mmol) was added in one portion. The resulting deep yellow solution was stirred at room temperature for 5 h and then treated with H_2O (0.24 mL, 0.24 g, 13 mmol) and stirred for another 13 h at room

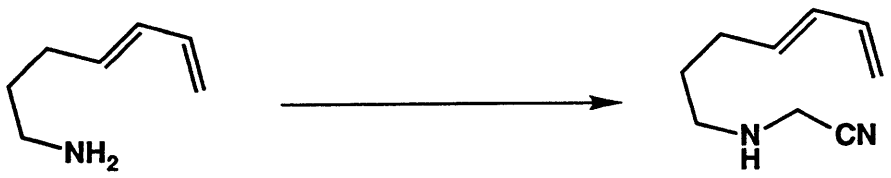
temperature. The clear yellow reaction mixture was then concentrated to ca. 10 mL and diluted with 70 mL of H_2O and 10 mL of 1 N NaOH solution. The aqueous phase was extracted with four 30-mL portions of Et_2O and the combined organic phases were washed with 40 mL of saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated to a volume of ca. 10 mL which led to precipitation of triphenylphosphine oxide. The yellow solution was separated from the solid precipitate and the precipitate was washed with three 10-mL portions of Et_2O. The combined organic extracts were then concentrated to give a yellow oil with a suspended white solid. Kugelrohr distillation (ca. 15 mmHg, 70 °C) provided 0.411 g (42% over three steps) of the amine **80** as a colorless oil with spectral data consistent with that previously reported.[58]

IR (thin film)	3360, 2920, 2850, 2090, 1650, 1600, 1005, 950, 900 cm^{-1}
^1H NMR (300 MHz, $CDCl_3$)	δ 1.26 (s, 2 H), 1.55 (app quint, J = 7 Hz, 2 H), 2.13 (app q, J = 7 Hz, 2 H), 2.70 (t, J = 7 Hz, 2 H), 4.96 (d, J = 10 Hz, 1 H), 5.09 (d, J = 17 Hz, 1 H), 5.70 (d tr, J = 7, 14 Hz, 1 H), 6.06 (dd, J = 11, 15 Hz, 1 H), 6.31 (ddd, J = 10, 10, 17 Hz, 1 H)
^{13}C NMR (75 MHz, $CDCl_3$)	δ 29.8, 33.0, 41.6, 114.9, 131.2, 134.6, 137.1



80

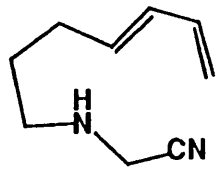




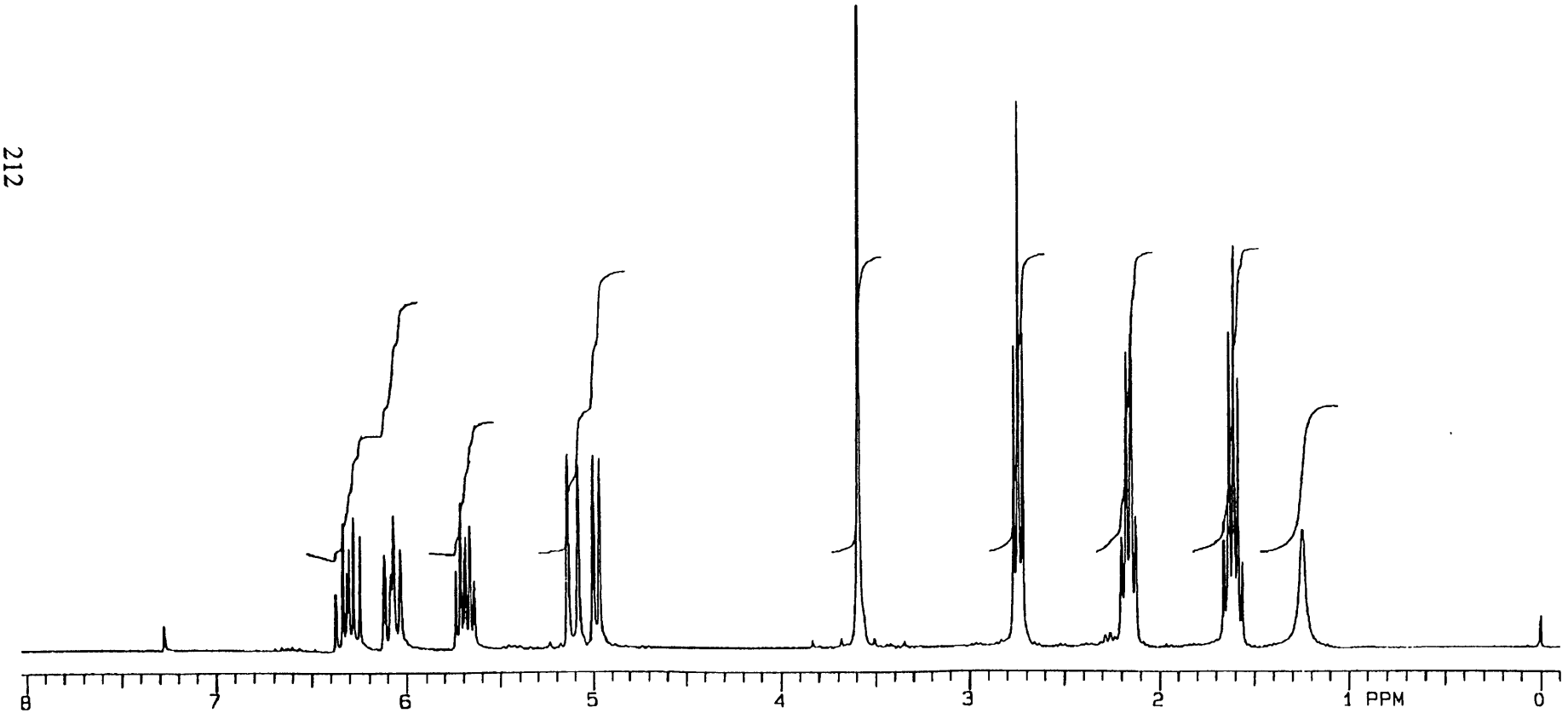
Hepta-4(*E*),6-dienylaminoacetonitrile (89).

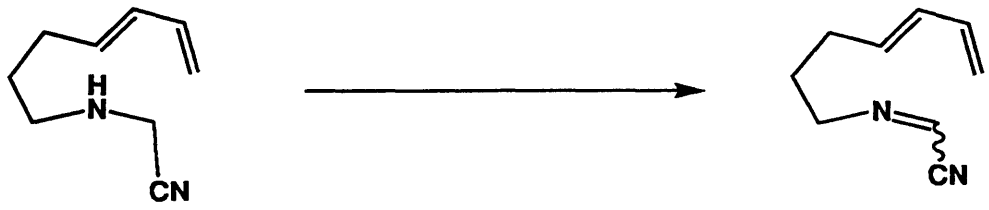
A 100-mL, one-necked, round-bottomed flask equipped with an argon inlet needle and septum was charged with the amine **80** (0.411 g, 3.7 mmol) and 12 mL of dichloromethane. The colorless solution was cooled at -78 °C while bromoacetonitrile (0.26 mL, 0.444 g, 3.7 mmol) was added dropwise over 2 min. The solution was allowed to warm to room temperature and was stirred for 24 h. The clear colorless solution was then treated with K_2CO_3 (1.534 g, 11.1 mmol) and stirred for 5 h before the addition of a second equivalent of bromoacetonitrile (0.26 mL, 0.444 g, 3.7 mmol). The reaction mixture was stirred for an additional 24 h and then filtered with the aid of three 10-mL portions of dichloromethane. The combined organic phases were then concentrated onto 1.5 g of silica gel to give a free-flowing powder. This powder was added to a column of 15 g of silica gel and eluted with 25% ethyl acetate-1% triethylamine-hexane to provide 0.242 g (44%) of the amine **89** as a colorless oil.

IR (thin film)	3330, 2930, 2250, 2230, 1650, 1600, 1465, 1130, 1005, 950, 900 cm^{-1}
^1H NMR (300 MHz, $CDCl_3$)	δ 1.24 (br s, 1 H), 1.60 (app quint, *J* = 7 Hz, 2 H), 2.15 (app q, *J* = 7 Hz, 2 H), 2.73 (t, *J* = 7 Hz, 2 H), 3.58 (s, 2 H), 4.98 (d, *J* = 10 Hz, 1 H), 5.10 (d, *J* = 17 Hz, 1 H), 5.68 (d tr, *J* = 7, 14 Hz, 1 H), 6.06 (dd, *J* = 10, 15 Hz, 1 H), 6.30 (ddd, *J* = 10, 10, 17 Hz, 1 H)
^{13}C NMR (75 MHz, $CDCl_3$)	δ 28.8, 29.9, 37.2, 48.2, 115.2, 117.8, 131.5, 133.9, 136.9



89

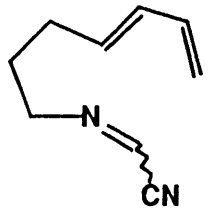




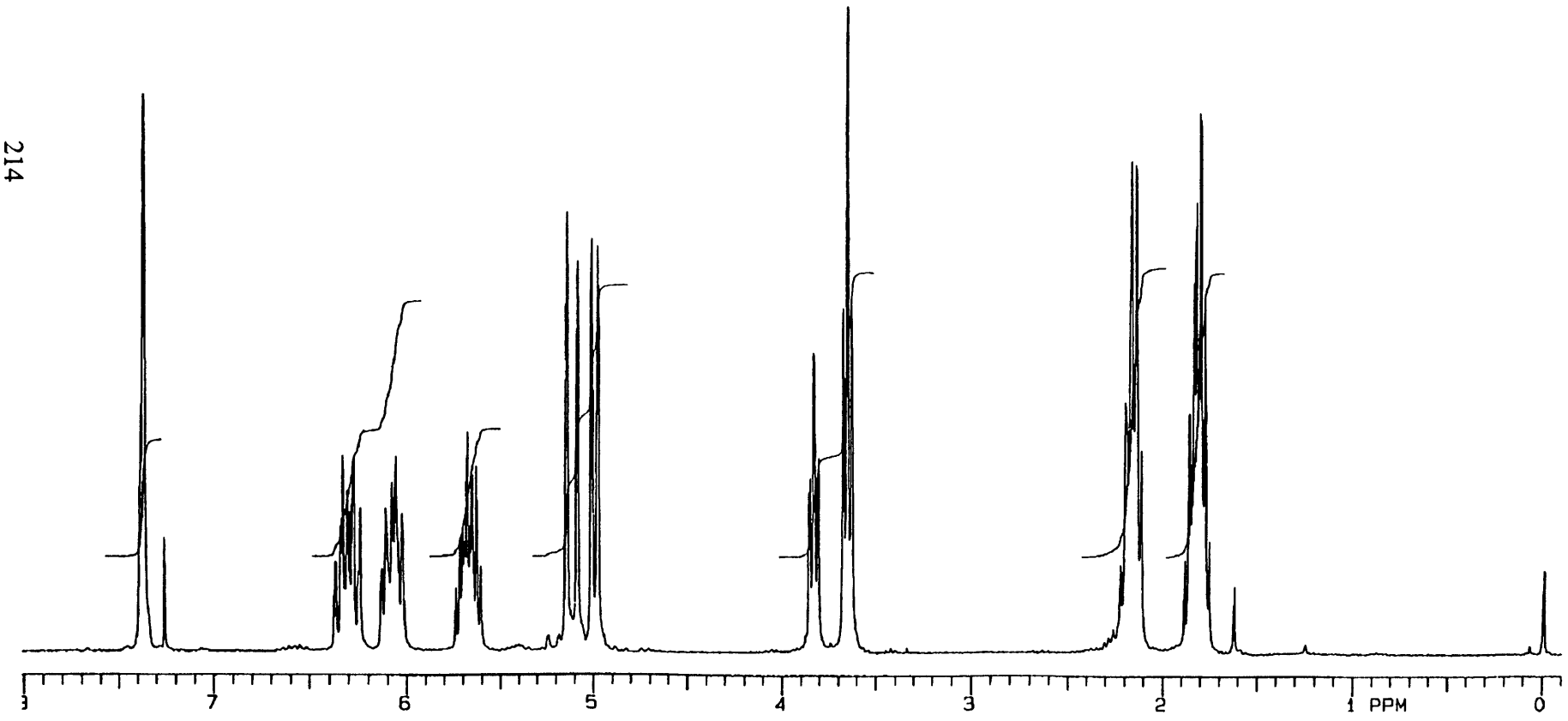
Hepta-4(*E*),6-dienyliminoacetonitrile (70).

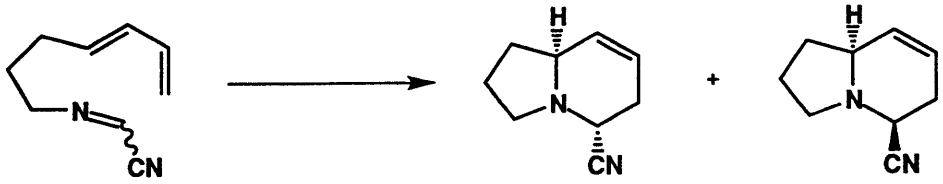
A 25-mL, one-necked, round-bottomed flask equipped with an argon inlet needle and septum was charged with the amine **89** (0.236 g, 1.57 mmol) and 16 mL of THF. The solution was stirred at room temperature and *N*-chlorosuccinimide (0.214 g, 1.60 mmol) was added in one portion to give a clear colorless solution. After stirring for 30 min at room temperature, the flask was cooled to 0 °C and NaOMe solution (1.00 mL, 1.64 M in methanol, 1.65 mmol) was added dropwise via syringe over 2 min to give a cloudy solution. The reaction mixture was stirred for 45 min at 0 °C and then poured into 30 mL of saturated $NaHCO_3$ solution with the aid of 10 mL of H_2O. The aqueous phase was extracted with three 30-mL portions of Et_2O and the combined organic phases were washed with 30 mL of saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated to afford 0.262 g of a yellow oil. Column chromatography on 15 g of silica gel (5% ethyl acetate-1% triethylamine-hexane) provided 0.154 g (66%) of the imine **70** (64:36, *E* : *Z*) as a colorless oil.

IR (thin film)	2930, 2840, 1600, 1620, 1440, 1005, 955, 900 cm^{-1}
^1H NMR (300 MHz, $CDCl_3$)	δ 1.75-1.88 (m, 2 H, both isomers), 2.11-2.22 (m, 2 H, both isomers), 3.65 (dt, *J* = 7, 1.5 Hz, 2 H, *E* isomer), 3.83 (dt, *J* = 8, 2.3 Hz, 2 H, *Z* isomer), 4.99 (d, *J* = 10 Hz, 1 H, both isomers), 5.11 (d, *J* = 17 Hz, 1 H, both isomers), 5.60-5.74 (m, 1 H, both isomers), 6.02-6.13 (m, 1 H, both isomers), 6.23-6.37 (m, 1 H, both isomers), 7.37 (s, 1 H, both isomers)
^{13}C NMR (125 MHz, $CDCl_3$)	δ 29.1, 29.3, 29.7, 29.9, 59.0, 62.2, 109.3, 114.4, 115.5, 155.6, 131.5, 132.0, 132.1, 133.2, 133.3, 135.9, 136.8, 136.9



70





3,4-Didehydro-1-cyanoindolizidine (97 and 98).

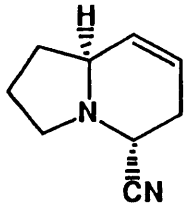
A 25-ml, one-neck, round-bottomed flask equipped with a reflux condenser and argon inlet adapter was charged with the imine **70** (0.034 g, 0.23 mmol), 5 mL of toluene, and 4-methyl-2,6-di-*tert*-butylphenol (0.151 g, 0.687 mmol). The reaction mixture was heated at reflux for 24 h and then allowed to cool to room temperature. The yellow solution was concentrated and the residue purified by column chromatography on 2 g of silica gel (elution with 25% ethyl acetate-1% triethylamine-hexane) to afford 0.168 g of a mixture of imine **70** and BHT (18.5 mg of **70**) along with 9 mg of a mixture of the cycloadducts and imine **70** (3 mg of imine **70**). Purification of the latter material on 1.5 g of silica-gel (elution with 25% ethyl acetate-1% triethylamine-hexane) provided 4.1 mg of a 91:9 (**97**:**98**) mixture of cycloadducts and 1.2 mg of a 31:69 (**97**:**98**) mixture of cycloadducts. The overall yield of cycloadducts **97** and **98** was 16% in an overall ratio of 77:23. The total amount of recovered imine **70** was 21 mg (62%).

Indolizidine **97**:

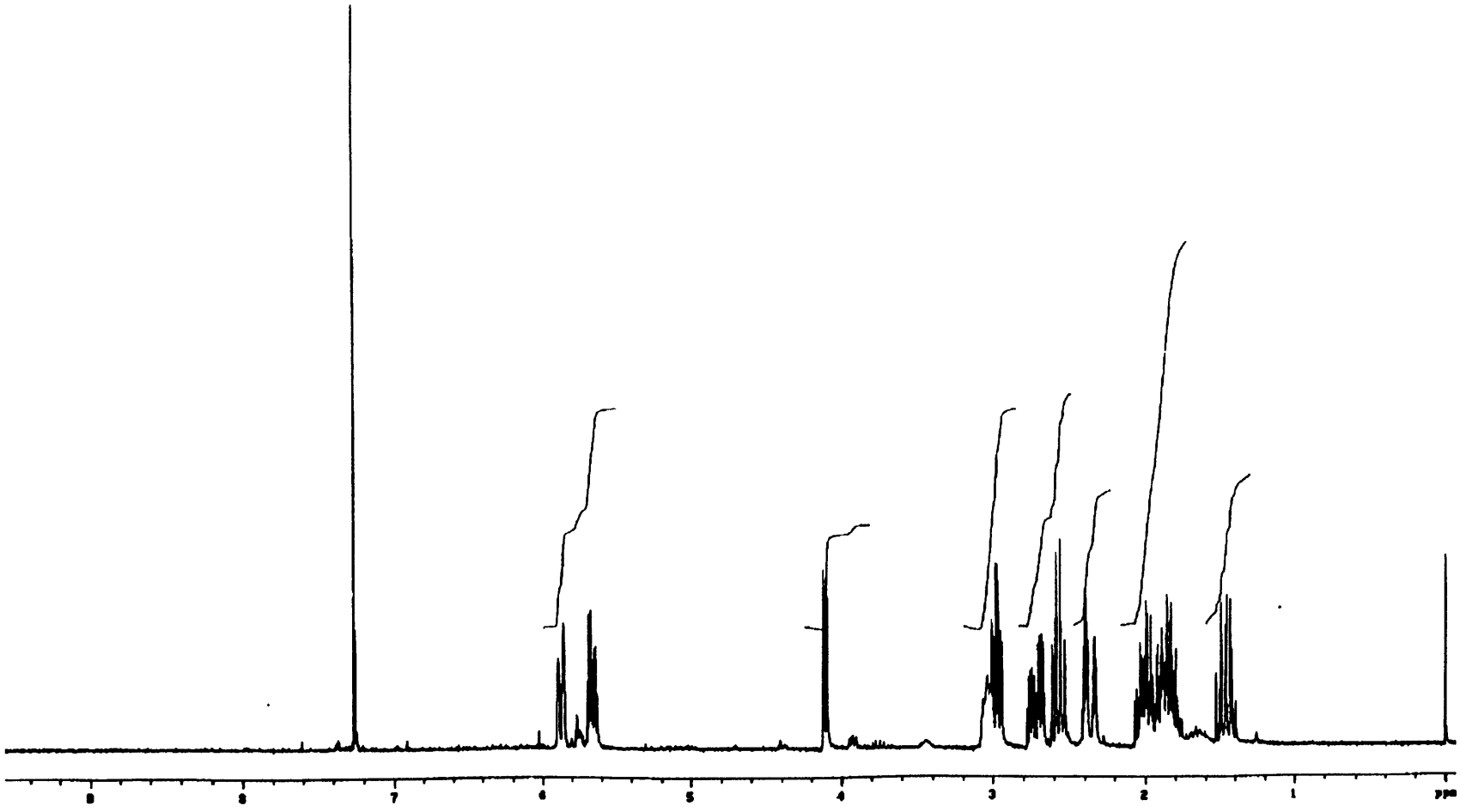
IR ($CHCl_3$)	2960, 2820. 1460, 1430, 1330, 1230, 1200, 1160, 1120 cm^{-1}
^1H NMR (300 MHz, $CDCl_3$)	δ 1.39-1.52 (m, 1 H), 1.79-2.06 (m, 3 H), 2.31-2.41 (dm, 1 H), 2.52-2.61 (m, 1 H), 2.66-2.77 (dm, 1 H), 2.92-3.06 (m, 2 H), 4.10 (dd, J = 7.0, 1.3 Hz, 1 H), 5.62-5.69 (dm, 1 H), 5.85-5.89 (dm, 1 H)
^{13}C NMR (125 MHz, $CDCl_3$)	δ 21.2, 28.6, 29.1, 47.8, 49.8, 56.3, 117.1, 121.4, 128.5

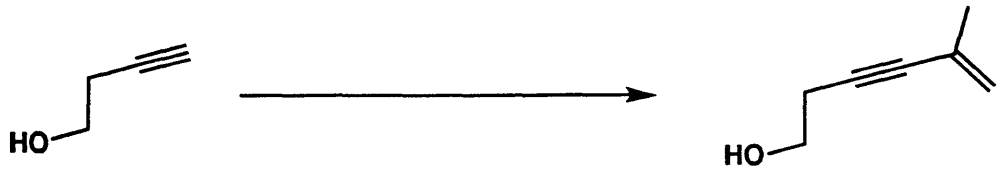
Indolizidine **98**:

^1H NMR (300 MHz, $CDCl_3$)	δ 1.5-3.1 (m, 8 H), 3.40-3.49 (m, 1 H), 3.91 (dd, J = 8.1, 4.9 Hz, 1 H), 5.7-5.8 (m, 2 H)



97

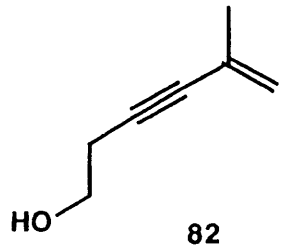




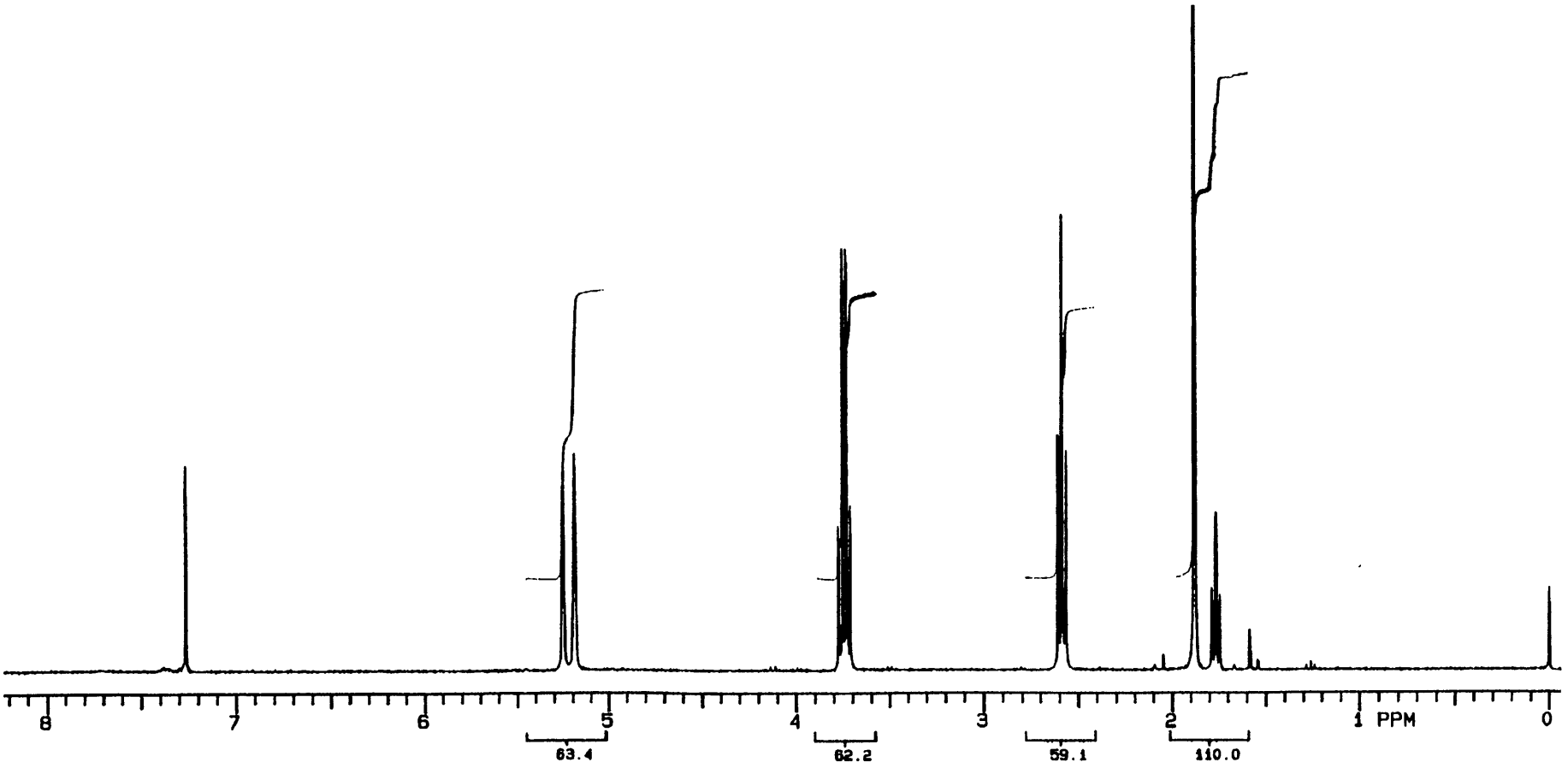
5-Methyl-hex-5-en-3-yn-1-ol (82).

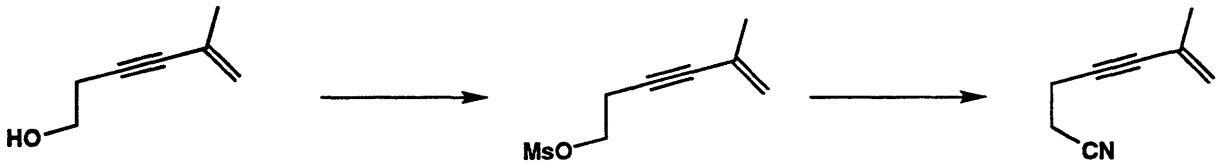
A 250-mL, one-necked, round-bottomed flask equipped with an argon inlet needle and rubber septum was charged with 80 mL of diethylamine, 2-bromopropene (2.50 mL, 3.40 g, 28.1 mmol), 3-butyn-1-ol (1.40 mL, 1.31 g, 18.8 mmol), copper (I) iodide (0.054 g, 0.280 mmol), and tetrakis(triphenylphosphine) palladium (0) (0.650 g, 0.565 mmol). The resulting yellow mixture was stirred at 25 °C for 20 h. The reaction mixture was then filtered, concentrated, and the yellow residue was dissolved in 50 mL of Et_2O. An aqueous NH_4Cl solution (25 g of NH_4Cl in 125 mL of H_2O) was then added, the layers separated, and the aqueous phase extracted with two 50-mL portions of Et_2O. The combined organic phases were washed with saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated onto 4 g of silica gel. Column chromatography on 50 g of silica gel (20% ethyl acetate-hexane) provided 1.68 g (81%) of alcohol **81** as a yellow-orange oil with spectral characteristics consistent with the commercially available material.

IR (thin film)	3350, 2950, 2920, 2225, 1610, 1435, 1375, 1295, 1245, 1045, 895 cm^{-1}
^1H NMR (300 MHz, $CDCl_3$)	δ 1.77 (t, J = 7 Hz, 1 H), 1.88 (d, J = 0.6 Hz, 3 Hz), 2.59 (t, J = 6 Hz, 2 H), 3.74 (app q, J = 6 Hz, 2 H), 5.19 (app tr, J = 1.6 Hz, 1 H), 5.25 (s, 1 H)
^{13}C NMR (75 MHz, $CDCl_3$)	δ 23.3, 23.5, 60.8, 83.2, 85.4, 121.0, 126.7



82





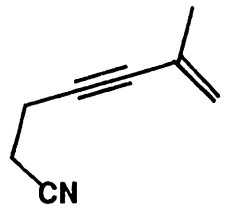
6-Methyl-hept-6-en-4-ynenitrile (83).

A 100-mL, one-necked, round-bottomed flask equipped with an argon inlet needle and septum was charged with the alcohol **82** (1.18 g, 10.7 mmol) and 60 mL of dichloromethane. The colorless solution was cooled at 0 °C while triethylamine (2.60 mL, 1.90 g, 18.7 mmol) was added via syringe in one portion followed by mesyl chloride (1.03 mL, 1.53 g, 13.4 mmol) dropwise via syringe over 5 min. After stirring for 1 h at 0 °C, the solution was diluted with 30 mL dichloromethane and washed with 100 mL of cold H_2O, 100 mL of cold 1 N HCl, 100 mL of saturated $NaHCO_3$, and 50 mL of saturated NaCl solution. The organic phase was then dried over $MgSO_4$, filtered, and concentrated to provide the crude mesylate as an orange-yellow oil. This material was used in the next step without purification.

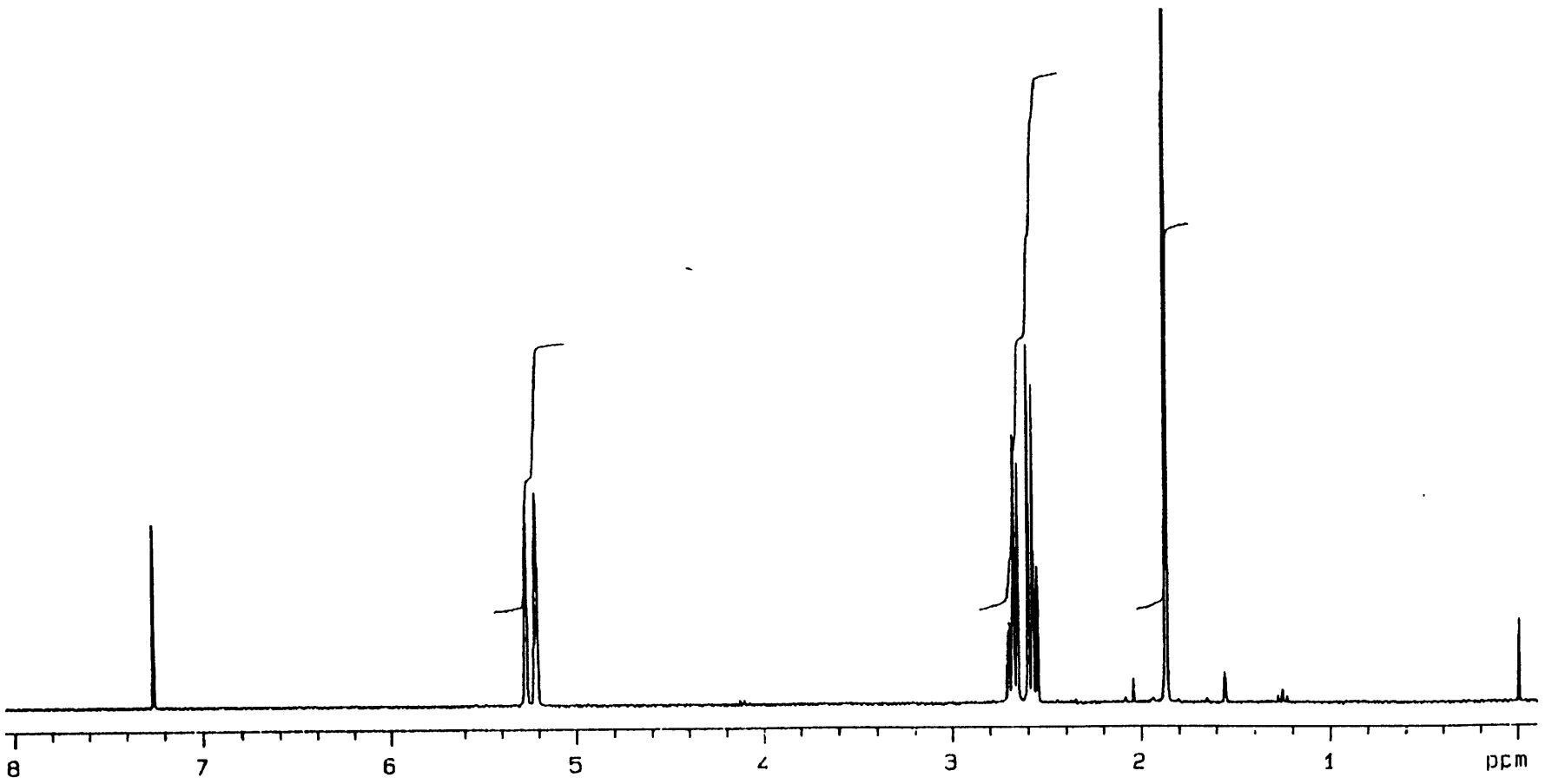
A 50-mL, one-necked, round-bottomed flask equipped with an argon inlet needle and septum was charged with the crude mesylate and 13 mL of DMSO. To the resulting pale yellow solution was added NaCN (2.10 g, 42.8 mmol) to give a deep yellow suspension which was then heated at 60 °C for 1 h. The resulting orange suspension was cooled to room temperature and diluted with 50 mL of H_2O. The solution was extracted with three 50-mL portions of Et_2O and the combined organic phases were washed with 50 mL of saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated to afford 1.117 g of a brown oil. Column chromatography on 30 g of silica gel (elution with 25% ethyl acetate-hexane) provided 0.988 g (77% overall) of the nitrile **83** as a colorless oil.

IR (thin film)	2970, 2950, 2920, 2245, 1610, 1430, 1375, 1345, 1290, 905 cm^{-1}
^1H NMR (300 MHz, $CDCl_3$)	δ 1.87 (app q, J = 1 Hz, 3 H), 2.55-2.60 (m, 2 H), 2.68 (dtr, J = 2, 7 Hz, 2 H), 5.22 (app tr, J = 1.7 Hz, 1 H), 5.27-5.28 (m, 1 H)

^{13}C NMR (75 MHz, $CDCl_3$)	δ 16.5, 17.5, 23.4, 84.0, 84.2, 118.2, 122.0, 126.3



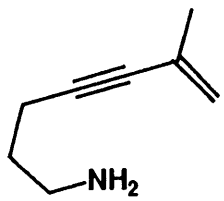
83



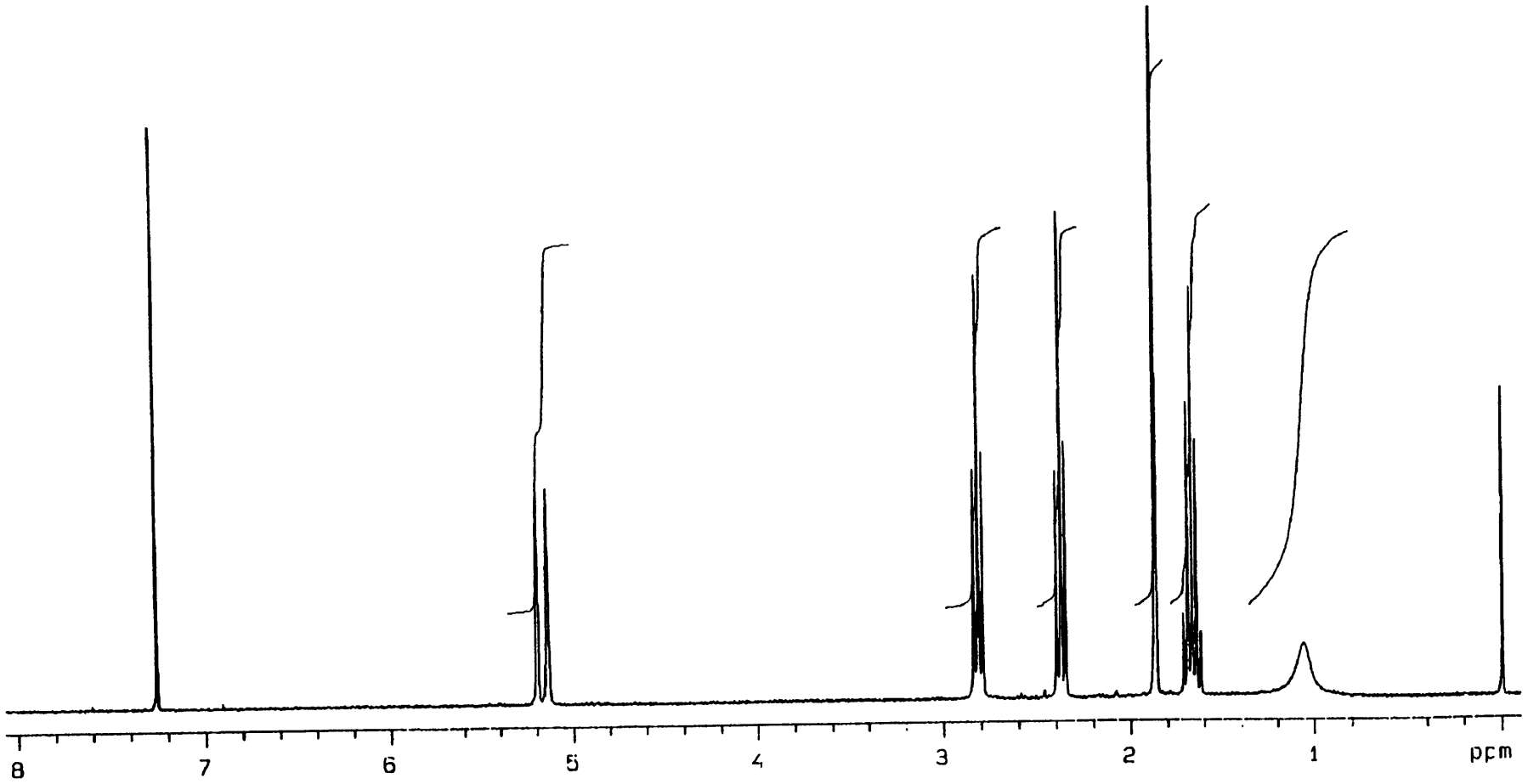
6-Methyl-hept-6-en-4-yn-1-amine (84).

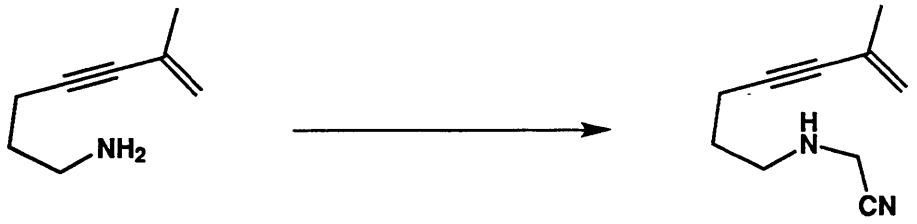
A 100-mL, one-necked, round-bottomed flask equipped with an argon inlet needle and septum was charged with $LiAlH_4$ (0.315 g , 8.30 mmol) and 50 mL of Et_2O. This gray suspension was stirred at 0 °C while a solution of the nitrile **83** (0.900 g, 7.55 mmol) in 15 mL of Et_2O was added dropwise via cannula over 10 min. The suspension was stirred at 0 °C for 1 h and then quenched by the slow addition of 6 mL of 1 N NaOH solution followed by 20 mL of H_2O and another 6 mL of 1 N NaOH solution. The resulting two-phase solution was stirred at room temperature for 15 min and then the layers were separated and the aqueous phase extracted with three 30-mL portions of Et_2O. The combined organic phases were washed with 40 mL of saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated to afford a pale yellow oil. Kugelrohr distillation (ca. 0.2 mmHg, 60 °C) provided 0.838 g (90%) of the amine **84** as a colorless oil.

IR (thin film)	3370, 3290, 2940, 2855, 2220, 1610, 1435, 1375, 1335, 1295, 895 cm^{-1}
^1H NMR (300 MHz, $CDCl_3$)	δ 1.07 (br s, 2 H), 1.67 (app quint, J = 7 Hz, 2 H), 1,87 (app q, J = 1 Hz, 3 H), 2.37 (t, J = 7 Hz, 2 H), 2.81 (app tr, J = 7 Hz, 2 H), 5.13-5.15 (m, 1 H), 5.19-5.20 (m, 1 H)
^{13}C NMR (75 MHz, $CDCl_3$)	δ 16.6, 23.7, 32.4, 41.2, 82.1, 88.5, 120.4, 127.1



84

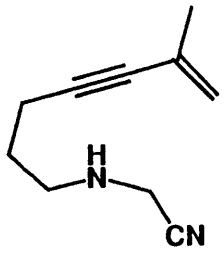




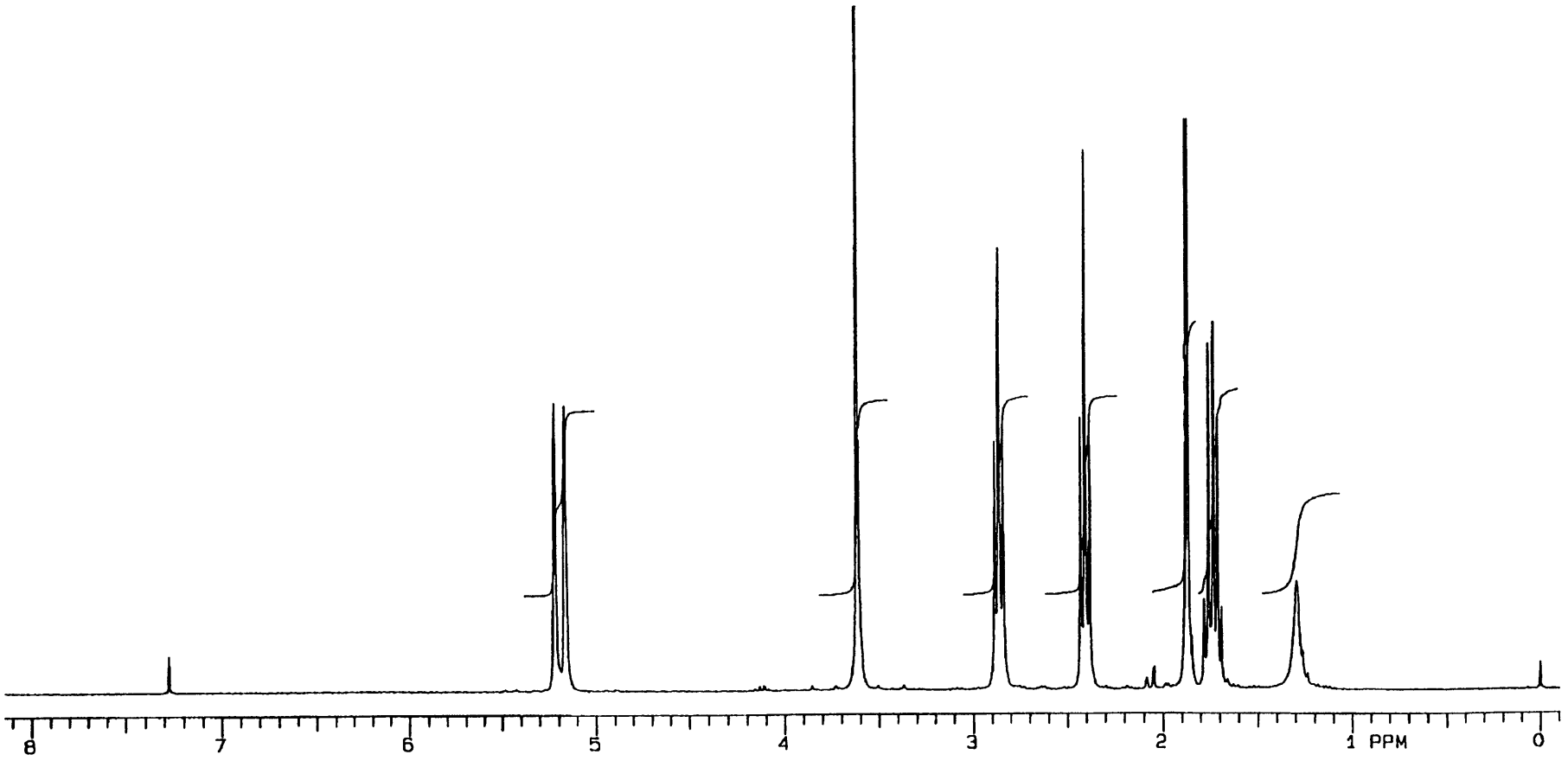
6-Methyl-hept-6-en-4-ynylaminoacetonitrile (90).

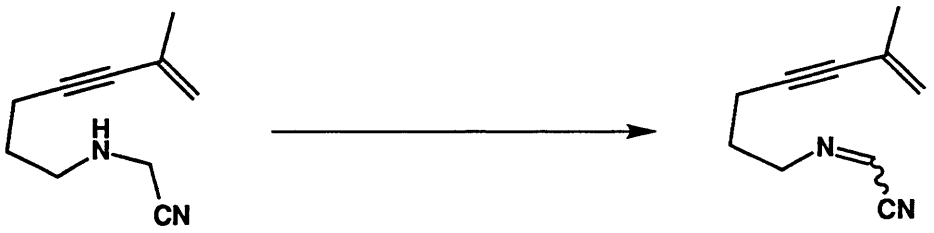
A 25-mL, one-necked, round-bottomed flask equipped with an argon inlet needle and septum was charged with the amine **84** (0.501 g, 4.07 mmol) and 10 mL of dichloromethane. The colorless solution was cooled at 0 °C while bromoacetonitrile (0.28 mL, 0.488 g, 4.07 mmol) was added dropwise over 2 min. The solution was allowed to warm to room temperature and was stirred for 26 h. The reaction mixture was then concentrated onto 2 g of silica gel to give a free-flowing powder. This powder was added to a column of 15 g of silica gel and eluted with 25% ethyl acetate-1% triethylamine-hexane to provide 0.298 g (45%) of the amine **90** as a colorless oil.

IR (thin film)	3340, 1960, 2850, 2235, 1615, 1440, 1380, 1335, 1290, 1140, 900 cm^{-1}
^1H NMR (300 MHz, $CDCl_3$)	δ 1.29 (br s, 1 H), 1.74 (app quint, J = 7 Hz, 2 H), 1.87 (s, 3 H), 2.41 (t, J = 7 Hz, 2 H), 2.86 (t, J = 7 Hz, 2 H), 3.61 (s, 2 H), 5.16 (s, 1 H), 5.21 (s, 1 H)
^{13}C NMR (75 MHz, $CDCl_3$)	δ 16.9, 23.7, 28.2, 37.3, 47.6, 82.5, 88.0, 117.7, 120.7, 127.0



90

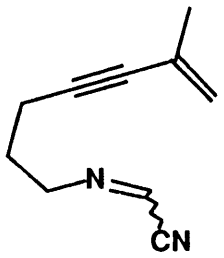




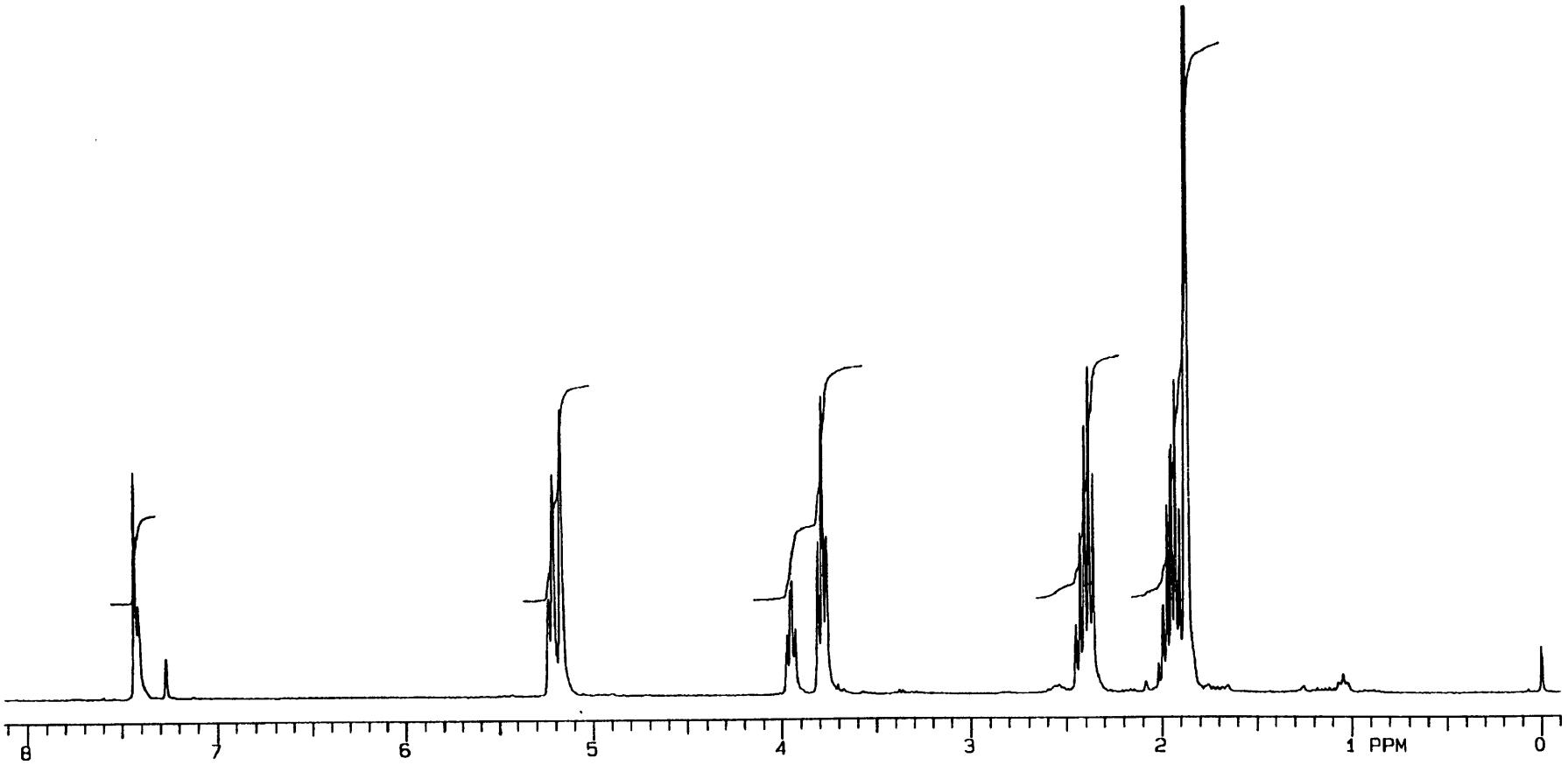
6-Methyl-hept-6-en-4-ynyliminoacetonitrile (91).

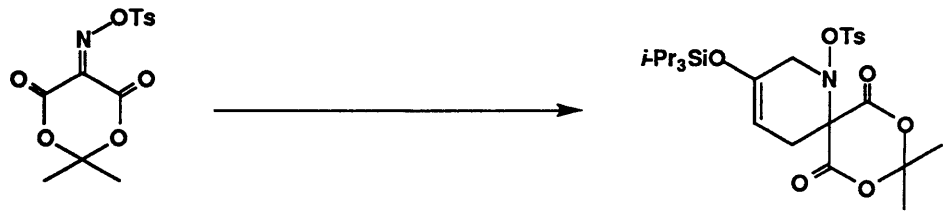
A 50-mL, one-necked, round-bottomed flask equipped with an argon inlet needle and septum was charged with the amine **90** (0.281 g, 1.73 mmol) and 18 mL of THF. The solution was stirred at room temperature and *N*-chlorosuccinimide (0.236 g, 1.77 mmol) was added in one portion to give a clear colorless solution. After stirring for 15 min at room temperature, the flask was cooled to 0 °C and NaOMe solution (1.10 mL, 1.64 M in methanol, 1.82 mmol) was added dropwise via syringe over 2 min to give a cloudy solution. The reaction mixture was stirred for 30 min at 0 °C and then poured into 20 mL of saturated $NaHCO_3$ solution with the aid of 10 mL of H_2O. The aqueous phase was extracted with three 25-mL portions of Et_2O and the combined organic phases were washed with 20 mL of saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated to give a yellow oil. Column chromatography on 12 g of silica gel (5% ethyl acetate-1% triethylamine-hexane) provided 0.211 g (76%) of the imine **91** (65:35, *E* : *Z*) as a colorless oil.

IR (thin film)	2900, 2800, 2160, 1585, 1410, 1345, 1305, 1260, 870cm^{-1}
^{1}H NMR (300 MHz, $CDCl_3$)	δ 1.87 (s, 3 H, both isomers), 1.91-2.00 (m, 2 H, both isomers), 2.36-2.45 (m, 2 H, both isomers), 3.79 (dt, *J* = 6.7, 1.5 Hz, 2 H, *E* isomer), 3.95 (dt, *J* = 6.7, 2.3 Hz, 2 H, *Z* isomer), 5.17 (s, 1 H, both isomers), 5.22 (d, *J* = 7 Hz, 1 H, both isomers), 7.41 (s, 1 H, *Z* isomer), 7.43 (s, 1 H, *E* isomer)
^{13}C NMR (125 MHz, $CDCl_3$)	δ 16.6, 16.8, 23.86, 23.72, 28.2, 28.7, 58.1, 61.2, 83.0, 83.1, 87.0, 87.2, 109.2, 114.3, 120.88, 120.94, 126.8, 126.9, 131.9, 136.4



91

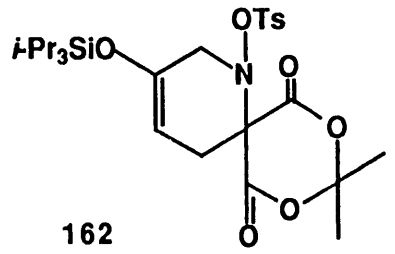




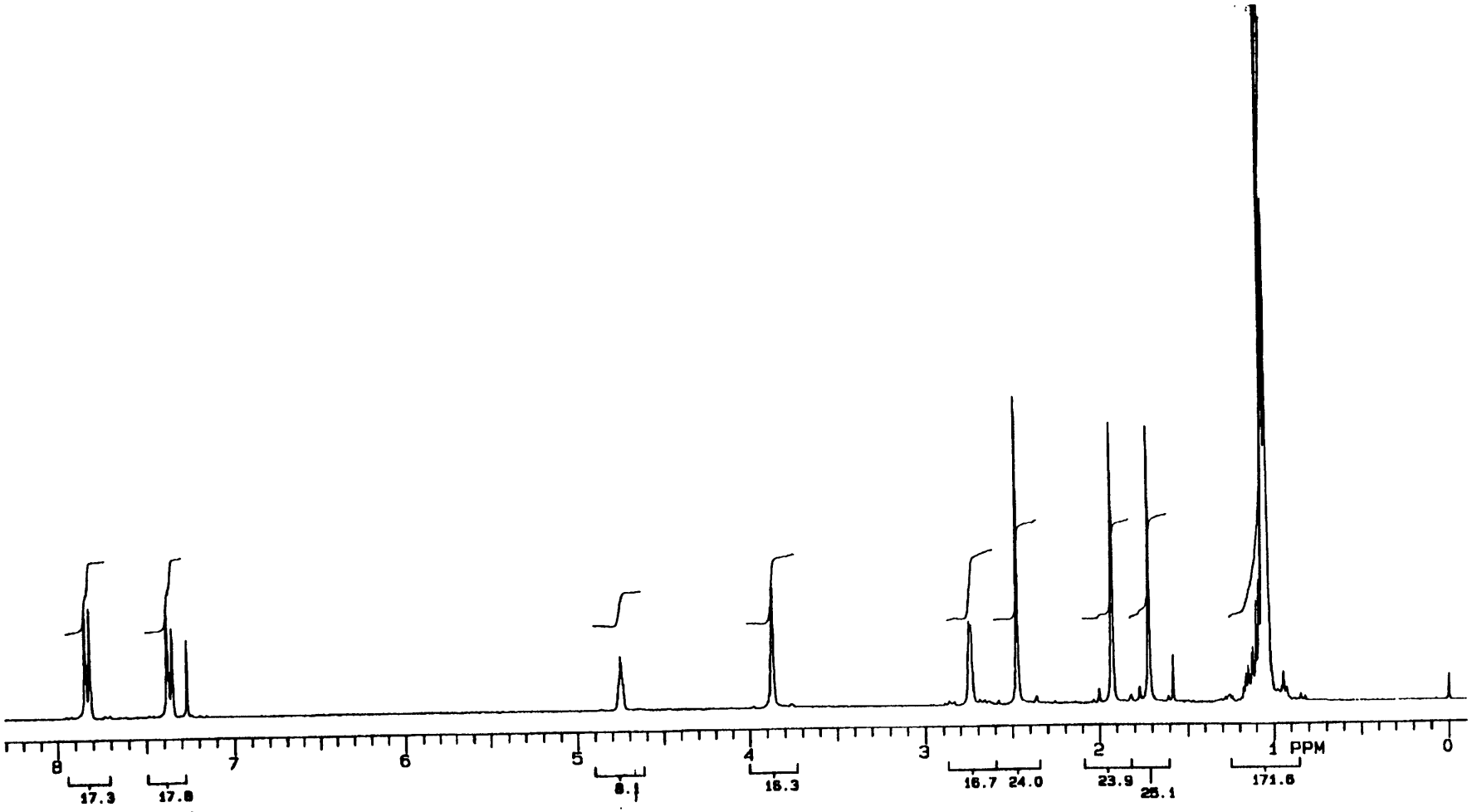
9-Triisopropylsiloxy-3,3-dimethyl-1,5-dioxo-7-tosyloxy-7-aza-2,4-dioxaspiro [5.5]undec-9-ene (162).

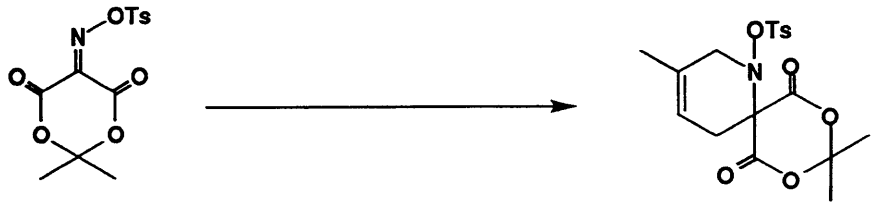
A 25-mL, round-bottomed flask equipped with an argon inlet adapter and a reflux condenser was charged with a solution of 2-triisopropylsiloxybuta-1,3-diene (0.366 g, 1.37 mmol) and oximinosulfonate (**58**) (0.150 g, 0.458 mmol) in 8.0 mL of benzene. The solution was heated at 55-60 °C for 24 h, cooled to room temperature, and then concentrated to give a brown oil. Purification by column chromatography on 10 g of deactivated silica (elution with 0-25% ethyl acetate-hexane) afforded 0.142 g (56%) of **162** as a yellow oil.

IR ($CHCl_3$)	2950, 2370, 1755, 1390, 1310 cm^{-1}
^1H NMR (300 MHz, $CDCl_3$)	δ 1.04 (d, J = 5.7 Hz, 18 H), 1.05-1.15 (m, 3 H), 1.72 (s, 3 H), 1.93 (s, 3 H), 2.47 (s, 3 H), 2.74 (m, 2 H), 3.87 (d, J = 1.5 Hz, 2 H), 4.75 (m, 1 H), 7.36 (d, J = 8.1 Hz, 2 H), 7.81 (d, J = 8.4 Hz, 2 H)
^{13}C NMR (75 MHz, $CDCl_3$)	δ 12.4, 17.7, 21.7, 28.6, 29.2, 30.5, 56.2, 66.7, 95.3, 106.4, 129.3, 129.7, 131.2, 144.5, 146.0, 163.8.


OTs
i-Pr3SiO
N
O
O
O
O

162

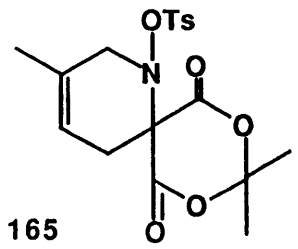

8
7
6
5
4
3
2
1 PPM
0
17.3
17.8
8.1
16.3
16.7 24.0
23.9
25.1
171.6



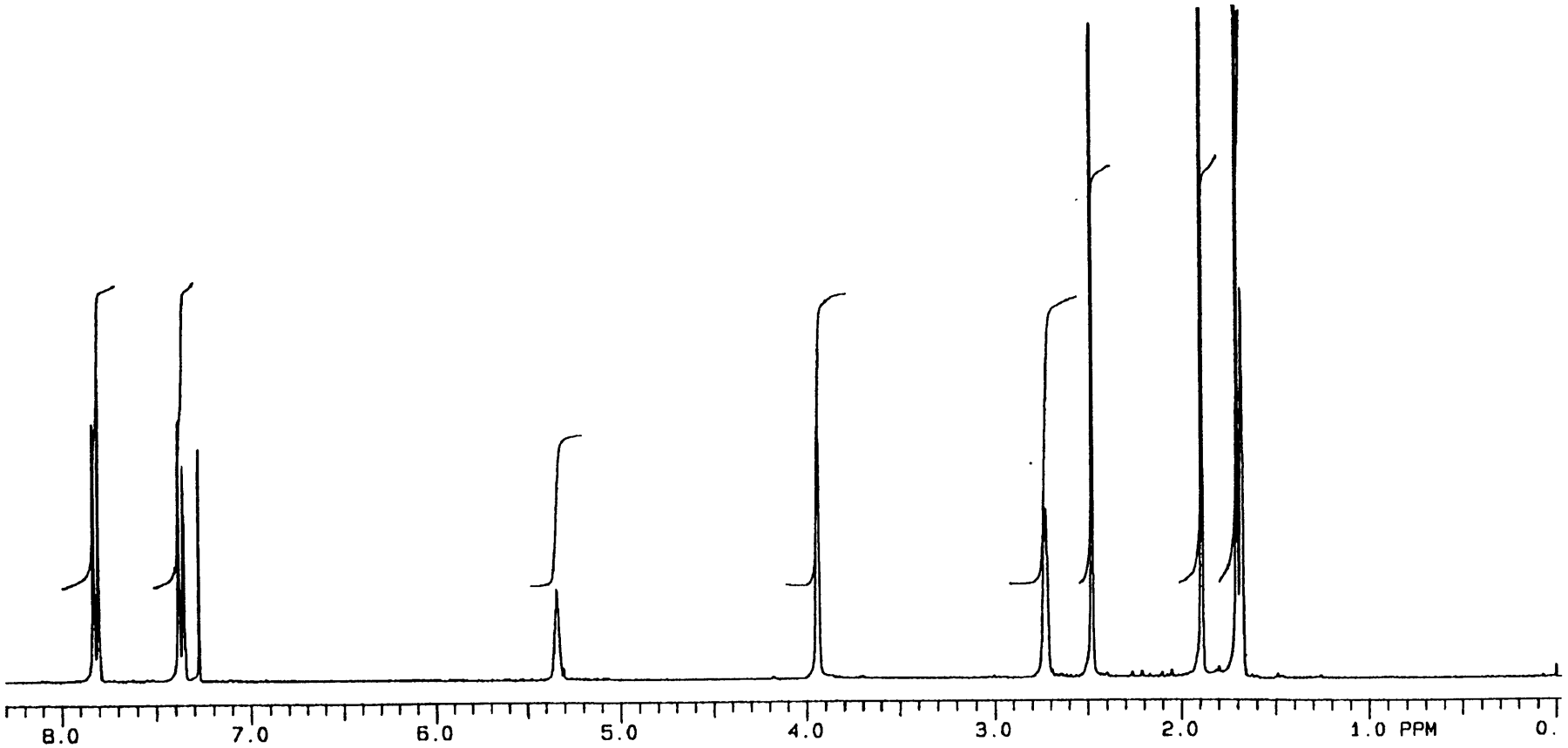
General Procedure for Lewis Acid Promoted Reaction of Oximinosulfonate 58 with Dienes. Preparation of 3,3,9-trimethyl-1,5-dioxo-7-tosyloxy-7-aza-2,4-dioxaspiro[5.5]undec-9-ene (165).

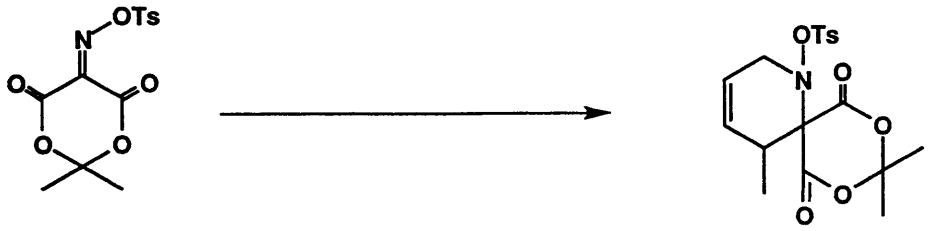
A 50-mL, three-necked, round-bottomed flask equipped with an argon inlet adapter, glass stopper, and rubber septum was charged with a solution of oximinosulfonate (**58**) (0.327 g, 1.00 mmol) and isoprene (0.204 g, 3.00 mmol) in 14 mL of dichloromethane. The solution was cooled at -78 °C while Me_2AlCl solution (1.0 M in hexane, 2.0 mL, 2.0 mmol) was added dropwise via syringe over 4 min. The resulting orange solution was stirred for 4 h at -78 °C to give a yellow solution, and then quenched by the addition of 3 mL of saturated sodium potassium tartrate solution. The resulting mixture was allowed to warm to 0 °C, 15 mL of dichloromethane and 15 mL of water were added, and the aqueous phase was separated and extracted with three 20-mL portions of dichloromethane. The combined organic phases were washed with 30 mL of saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated to provide an orange oil. Column chromatography on silica gel (elution with 1% methanol-dichloromethane) provided 0.354 g (90%) of the cycloadduct (**165**) as a white foam.

IR ($CHCl_3$)	3020, 1780, 1750, 1385, 1300 cm^{-1}
^1H NMR (300 MHz, $CDCl_3$)	δ 1.67 (s, 3 H), 1.69 (s, 3 H), 1.88 (s, 3 H), 2.48 (s, 3 H), 2.72 (br dd, J = 1.2, 3.3 Hz, 2 H), 3.93 (s, 2 H), 5.33 (br dd, J = 1.2, 3.6 Hz, 1 H), 7.36 (d, J = 8.7 Hz, 2 H), 7.81 (d, J = 8.4 Hz, 2 H)
^{13}C NMR (75 MHz, $CDCl_3$)	δ 20.3, 21.7, 28.5, 29.3, 32.8, 57.4, 66.3, 106.2, 113.9, 129.2, 129.55, 129.62, 131.2, 145.9, 164.0.



165

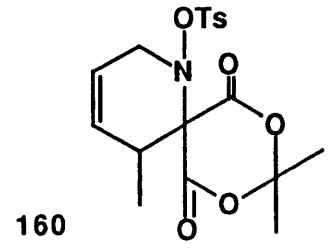




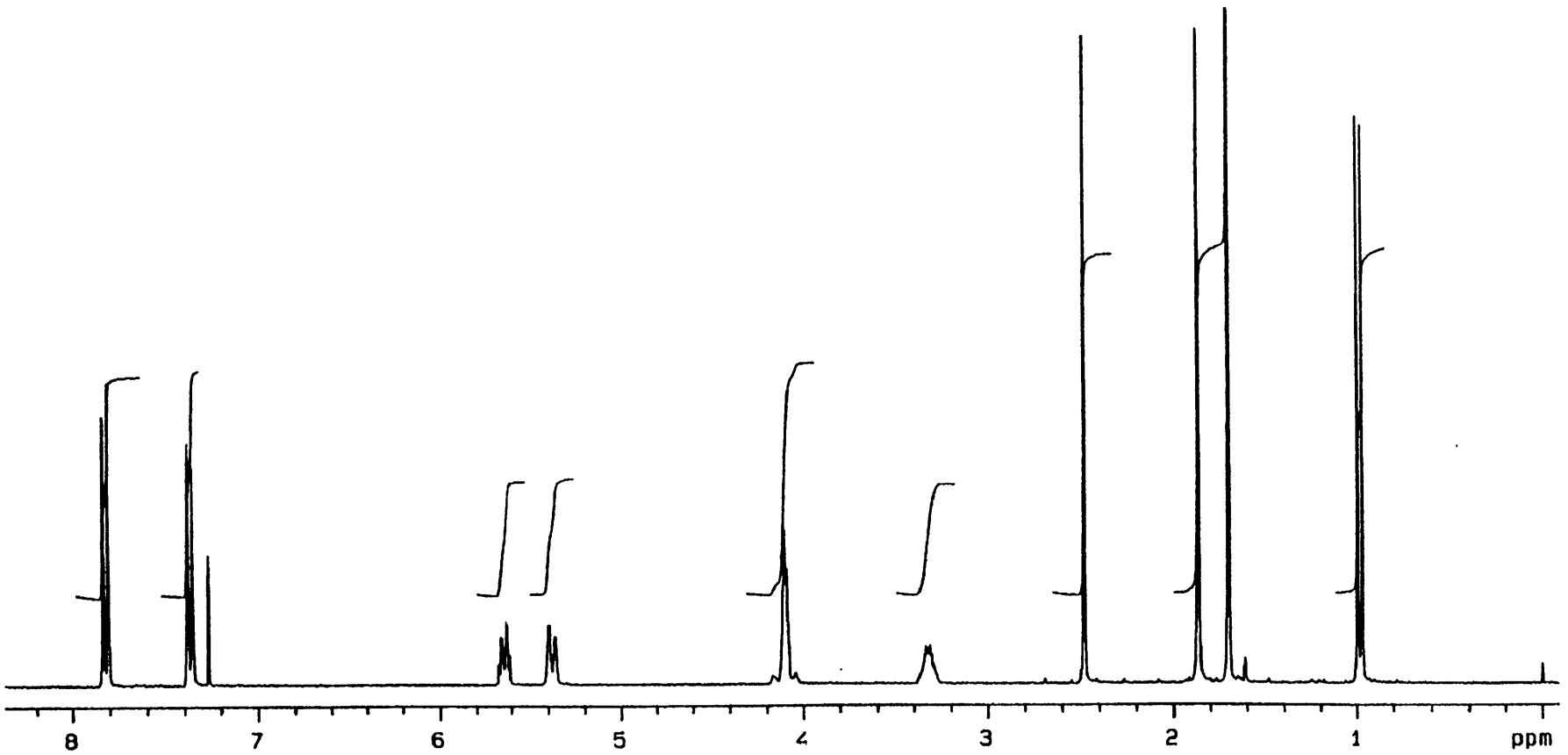
3,3,11-Trimethyl-1,5-dioxo-7-tosyloxy-7-aza-2,4-dioxaspiro[5.5]undec-9-ene (160).

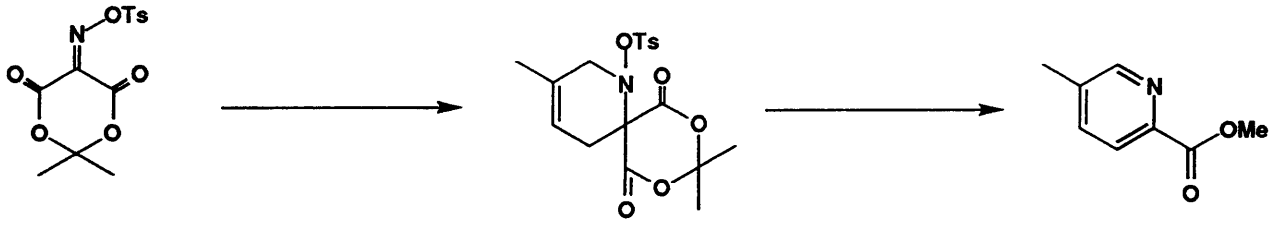
Reaction of oximinosulfonate (**58**) (1.22 g, 3.73 mmol) with *trans*-penta-1,3-diene (0.761 g, 11.2 mmol) and Me_2AlCl (1.0 M in hexane, 7.5 mL, 7.5 mmol) in 37 mL of dichloromethane at -78 °C for 4 h according to the general procedure furnished 1.15 g (78%) of cycloadduct **160** as a white solid: mp (dec) 133-145 °C.

IR ($CHCl_3$)	3005, 1780, 1750, 1380, 1290 cm^{-1}
^1H NMR (300 MHz, $CDCl_3$)	δ 0.98 (d, *J* = 7.5 Hz, 3 H), 1.70 (s, 3 H), 1.86 (s, 3 H), 2.47 (s, 3 H), 3.28-3.34 (m, 1 H), 4.03-4.09 (m, 2 H), 5.35-5.39 (dm, *J* = 10.3 Hz, 1 H), 5.60-5.65 (dm, *J* = 10.1 Hz, 1 H), 7.36 (d, *J* = 8.0 Hz, 2 H), 7.81 (d, *J* = 8.3 Hz, 2 H)
^{13}C NMR (75 MHz, $CDCl_3$)	δ 14.9, 21.8, 29.2, 29.5, 40.5(br), 54.3, 71.6, 106.5, 122.0, 125.5, 129.4, 129.6, 131.1, 146.0, 161.6, 164.9.



160





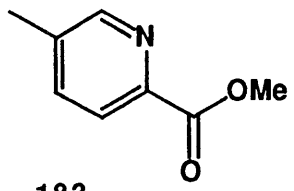
General Procedure for Two-Step Pyridine Annulation. Preparation of Methyl 5-methylpyridine-2-carboxylate (183).

A 50-mL, three-necked, round-bottomed flask equipped with an argon inlet adapter, glass stopper, and rubber septum was charged with oximinosulfonate (**58**) (0.450 g, 1.37 mmol), isoprene (0.281 g, 4.13 mmol), and 19 mL of dichloromethane. The solution was cooled at -78 °C while Me_2AlCl solution (1.0 M in hexane, 2.7 mL, 2.7 mmol) was added dropwise via syringe over 4 min. The orange solution was stirred for 3 h at -78 °C, and the resulting yellow solution was quenched by the addition of 4 mL of saturated sodium potassium tartrate solution. The resulting mixture was allowed to warm to 0 °C, 20 mL of dichloromethane and 20 mL of water were added, and the aqueous phase was separated and extracted with three 25-mL portions of dichloromethane. The combined organic phases were washed with 30 mL of saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated to provide the crude cycloadduct as an orange foam.

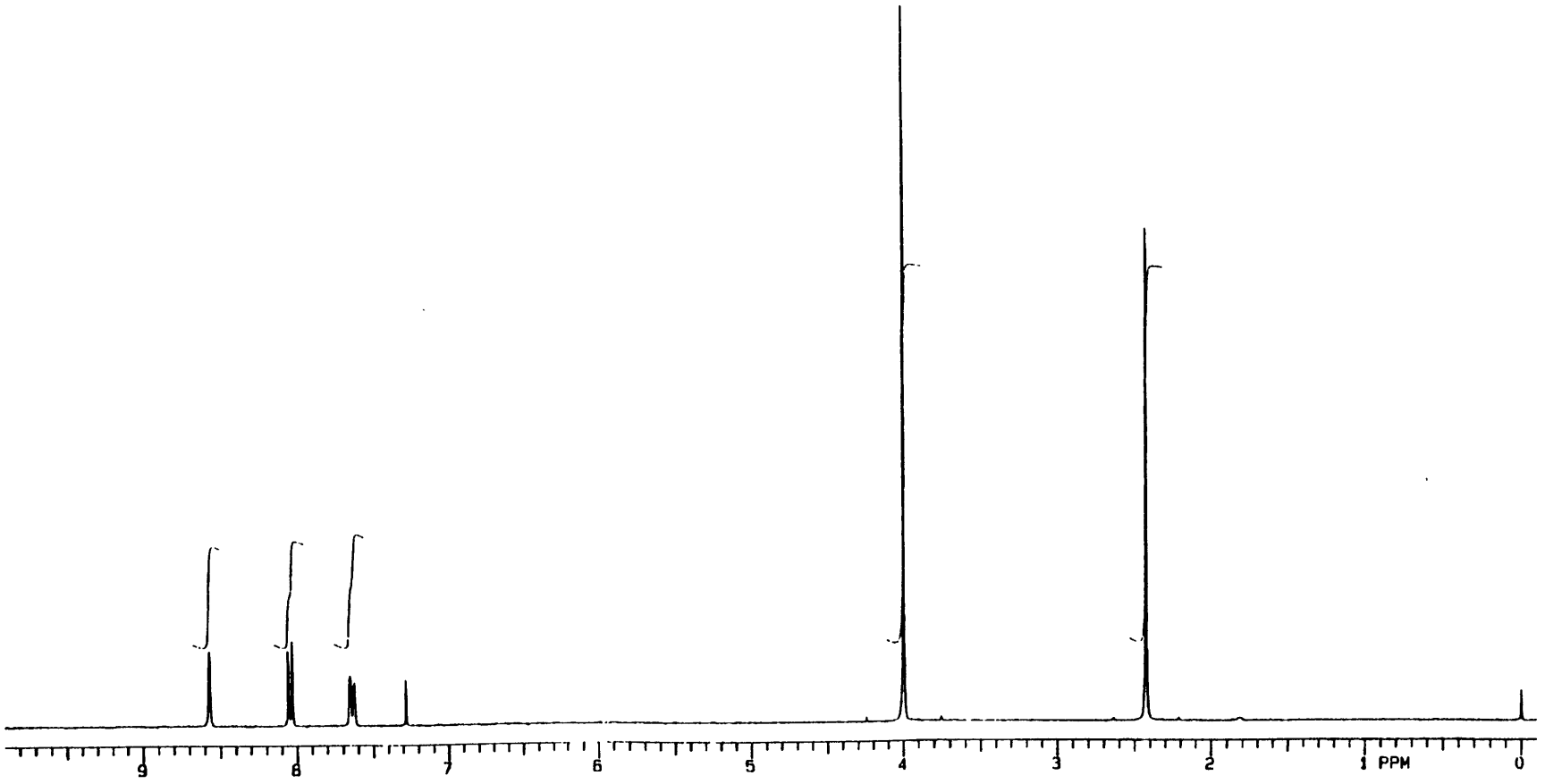
A 100-mL, round-bottomed flask equipped with an argon inlet adapter was charged with a solution of the crude cycloadduct in 13 mL of tetrahydrofuran and 13 mL of methanol. The solution was cooled at 0 °C while NaOMe solution (1.51 M in methanol, 2.7 mL, 4.1 mmol) was added via syringe over 1 min, followed by the addition of *N*-chlorosuccinimide (0.183 g, 1.37 mmol) in one portion. The cooling bath was removed and the solution was stirred in the dark for 16 h. The reaction mixture was then concentrated to ca. 5 mL and diluted with 30 mL of ethyl acetate and 30 mL of pH 7 phosphate buffer. The aqueous phase was separated and extracted with two 25-mL portions of ethyl acetate and the combined organic phases were extracted with three 25-mL portions of 1.0 N HCl. The combined acidic extracts were neutralized by the slow addition of

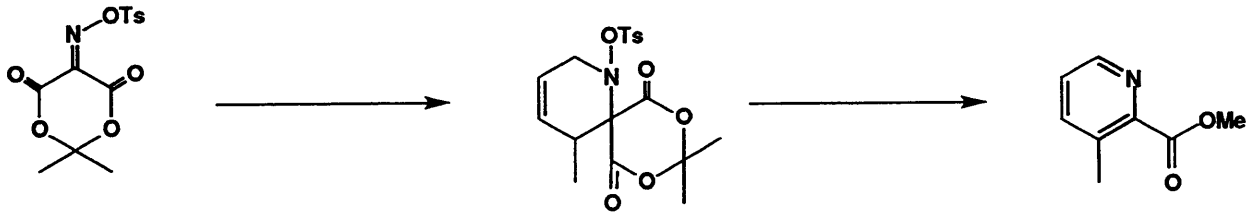
solid $NaHCO_3$ and then extracted with three 30-mL portions of ethyl acetate. The combined organic phases were washed with 20 mL of saturated NaCl solution, dried over Na_2SO_4, filtered, and concentrated onto 1 g of silica gel. Column chromatography on 10 g of silica gel (25% ethyl acetate-1% triethylamine-hexane) provided 0.159 g (77%) of pyridine **183** a colorless solid: mp 54-55 °C (pet ether). The spectral data was consistent with that previously reported for this pyridine.[114]

IR ($CHCl_3$)	2950, 1695, 1420, 1295, 1107 cm^{-1}	
^1H NMR (300 MHz, $CDCl_3$)	δ 2.43 (s, 3 H), 4.00 (s, 3H), 7.64 (dd, J = 7.8, 2.0 Hz, 1 H), 8.05 (d, J = 8.3 Hz, 1 H), 8.57 (d, J = 2.0 Hz, 1 H)	
^{13}C NMR (75 MHz, $CDCl_3$)	δ 18.5, 52.6, 124.6, 137.1, 137.3, 145.2, 150.2, 165.6.	
Elemental Analysis	Calcd for $C_8H_9NO_2$:	C, 63.56; H, 6.00; N, 9.27
	Found:	C, 63.57; H, 6.24; N, 9.20



183

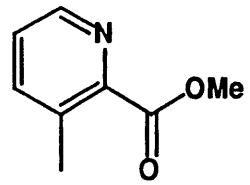




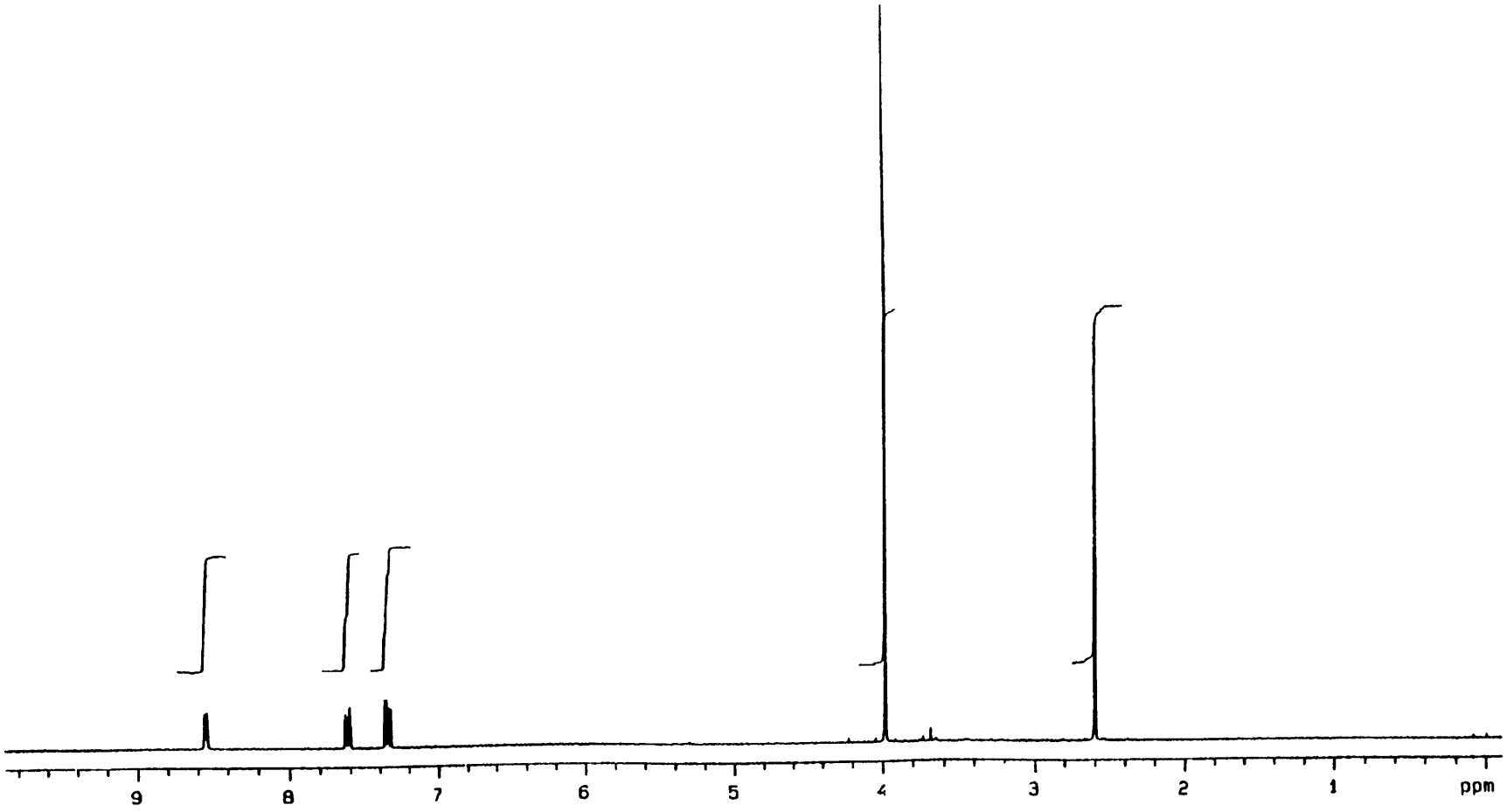
Methyl-3-methylpyridine-2-carboxylate (179).

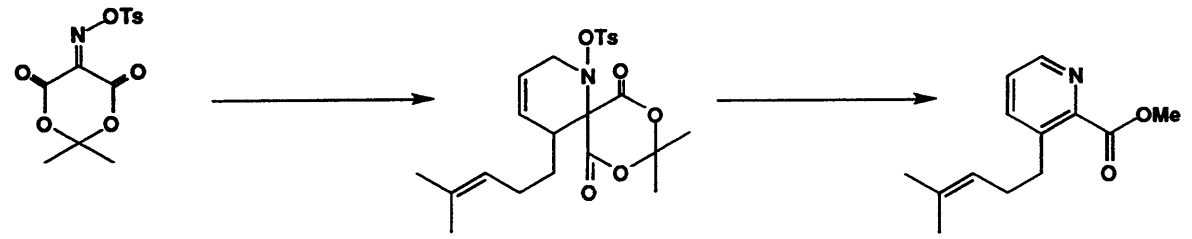
Reaction of oximinosulfonate (**58**) (0.45 g, 1.37 mmol) with *trans*-penta-1,3-diene (0.280 g, 4.12 mmol) and Me_2AlCl (1.0 M in hexane, 2.7 mL, 2.7 mmol) in 20 mL of dichloromethane at -78 °C for 3 h according to the general procedure provided the crude cycloadduct as a pink solid. Reaction of the crude cycloadduct with NaOMe (1.53 M in methanol, 2.7 mL, 4.1 mmol) and *N*-chlorosuccinimide (0.183 g, 1.37 mmol) in 13 mL of tetrahydrofuran and 13 mL of methanol at room temperature for 16 h according to the general procedure furnished 0.117 g (57%) of pyridine **179**[113] as a clear colorless oil.

IR (film)	2975, 1725, 1440, 1310, 1105 cm^{-1}
^1H NMR (300 MHz, $CDCl_3$)	δ 2.60 (s, 3H), 3.99 (s, 3 H), 7.31 (dd, J = 7.8, 3.9 Hz, 1 H), 7.58 (dd, J = 7.8, 2.9 Hz, 1 H), 8.51 (dd, J = 4.4, 1.5 Hz, 1 H)
^{13}C NMR (75 MHz, $CDCl_3$)	δ 19.8, 52.3, 125.8, 135.4, 139.7, 146.7, 146.8, 166.3.



179

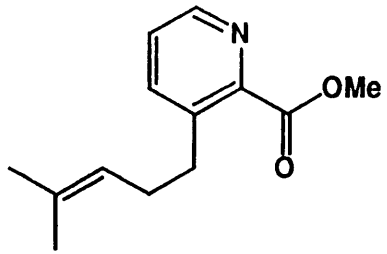




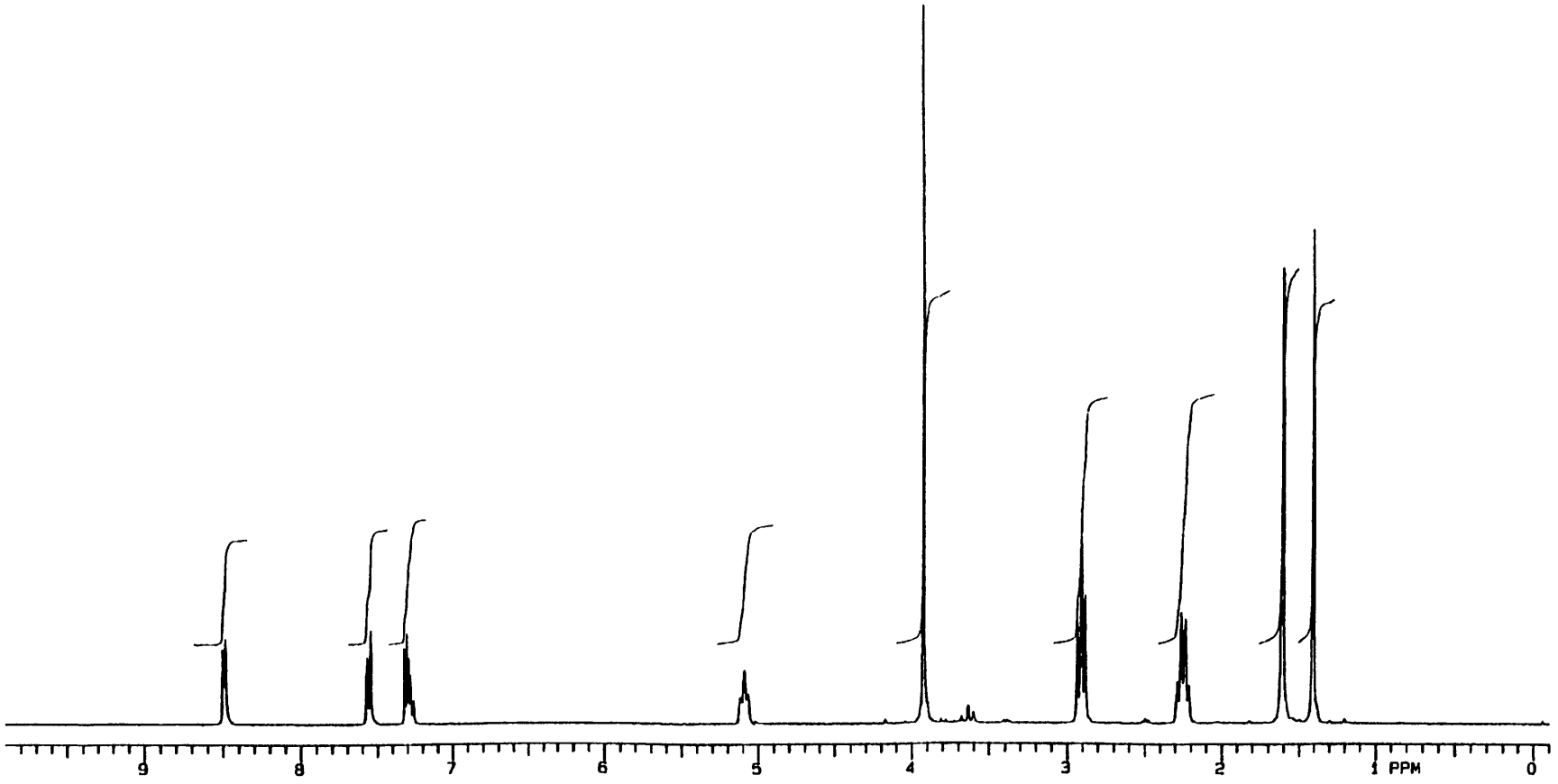
Methyl-3-(4-methylpent-3-enyl)pyridine-2-carboxylate (187).

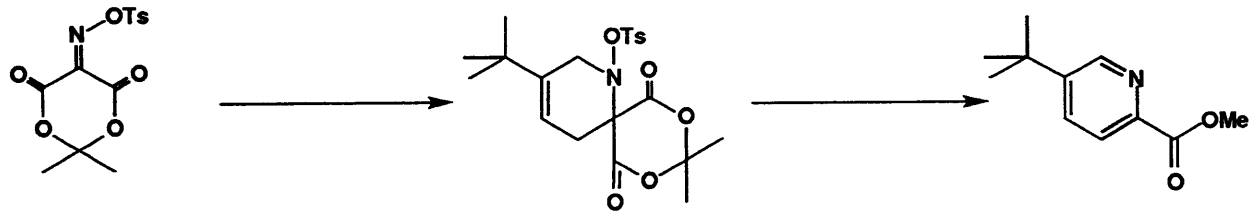
Reaction of oximinosulfonate (**58**) (0.384 g, 1.17 mmol) with diene **186** (0.240 g, 1.76 mmol) and Me_2AlCl (1.0 M in hexane, 2.3 mL, 2.34 mmol) in 16 mL of dichloromethane at -78 °C for 3 h according to the general procedure provided the crude cycloadduct as an orange oil. Reaction of the crude cycloadduct with NaOMe (1.40 M in methanol, 2.5 mL, 3.51 mmol) and *N*-chlorosuccinimide (0.156 g, 1.17 mmol) in 11 mL of tetrahydrofuran and 11 mL of methanol at room temperature for 20 h according to the general procedure furnished 0.139 g (54%) of pyridine **187** as a clear colorless oil.

IR (thin film)	2960, 2930, 1730, 1450, 1430, 1305, 1200, 1135, 1110, 1090 cm^{-1}
^1H NMR (300 MHz, $CDCl_3$)	δ 1.41 (s, 3 H), 1.61 (s, 3 H), 2.25 (app q, J = 8 Hz, 2 H), 2.91 (t, J = 8 Hz, 2 H), 3.93 (s, 3 H), 5.09 (t, J = 7 Hz, 1 H), 7.30 (dd, J = 5, 8 Hz, 1 H), 7.55 (d, J = 7 Hz, 1 H), 8.49 (d, J = 5 Hz, 1 H)
^{13}C NMR (75 MHz, $CDCl_3$)	δ 17.4, 25.5, 29.4, 32.7, 52.5, 122.7, 125.7, 132.9, 139.0, 139.1, 146.7, 147.2, 166.4



187

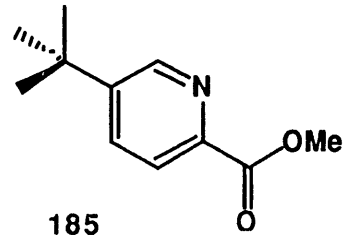




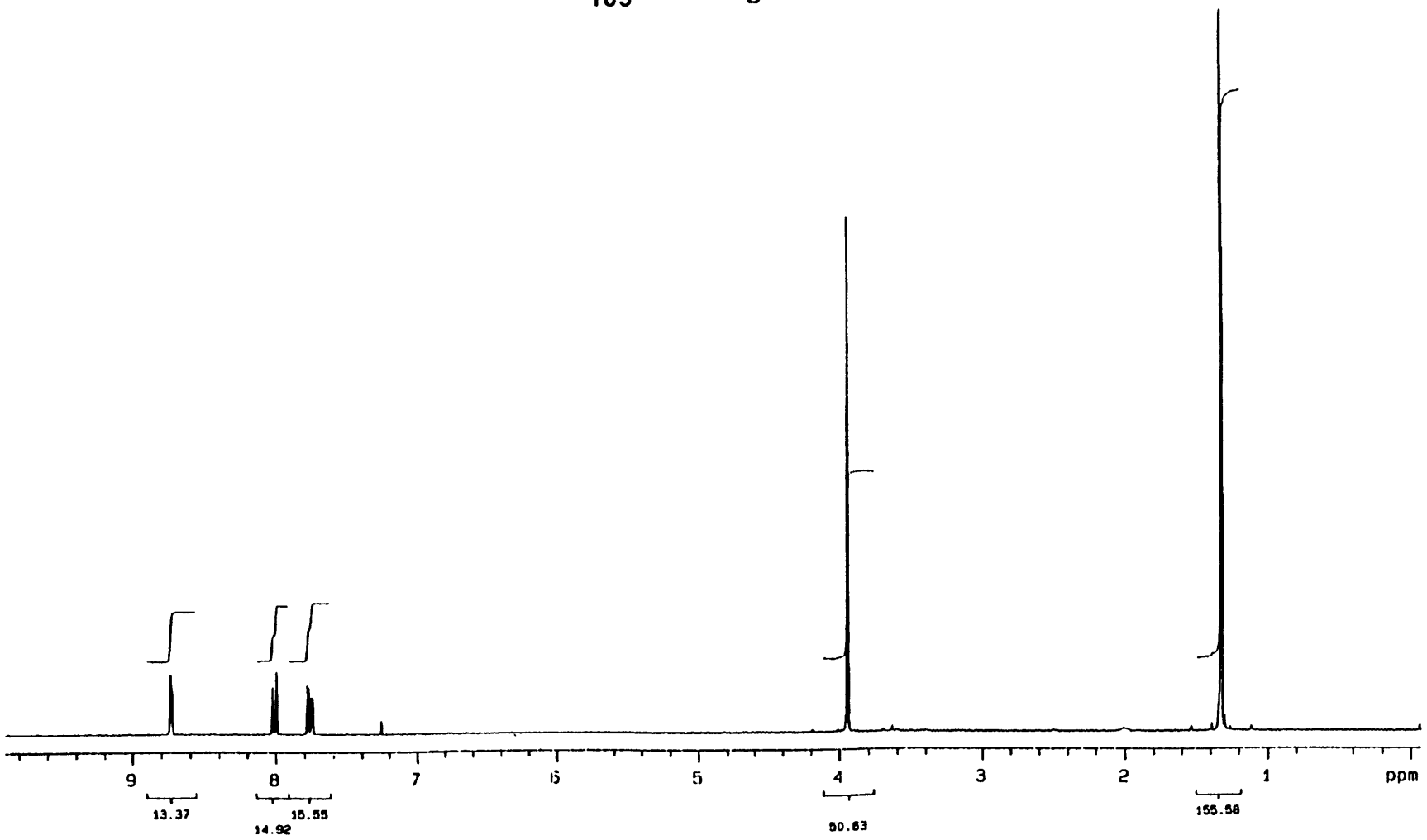
Methyl-5-*tert*-butylpyridine-2-carboxylate (185).

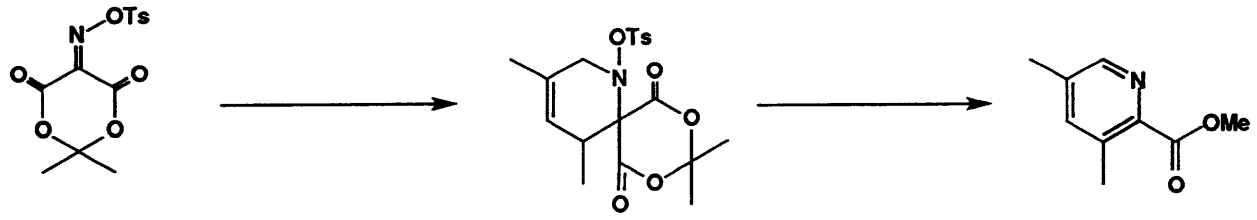
Reaction of oximinosulfonate (**58**) (0.545 g, 1.66 mmol) with 2-*tert*-butylbuta-1,3-diene (0.275 g, 2.49 mmol) and Me_2AlCl (1.0 M in hexane, 3.3 mL, 3.3 mmol) in 14 mL of dichloromethane at -78 °C for 3.5 h according to the general procedure provided the crude cycloadduct as a pink foam. Reaction of the crude cycloadduct with NaOMe (1.52 M in methanol, 3.3 mL, 5.0 mmol) and *N*-chlorosuccinimide (0.222 g, 1.66 mmol) in 15 mL of tetrahydrofuran and 15 mL of methanol at room temperature for 14 h according to the general procedure furnished 0.234 g (73%) of pyridine **185** as a pale yellow oil.

IR (film)	2960, 1740, 1720, 1435, 1315, 1125 cm^{-1}
^1H NMR (300 MHz, $CDCl_3$)	δ 1.38 (s, 9 H), 4.01 (s, 3 H), 7.82 (dd, J = 8.1, 2.4 Hz, 1 H), 8.07 (d, J = 8.1 Hz, 1 H), 8.79 (d, J = 2.4 Hz, 1 H)
^{13}C NMR (75 MHz, $CDCl_3$)	δ 30.7, 33.9, 52.6, 124.5, 133.8, 145.1, 147.7, 149.9, 165.7.



185

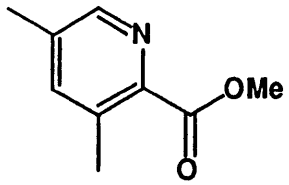




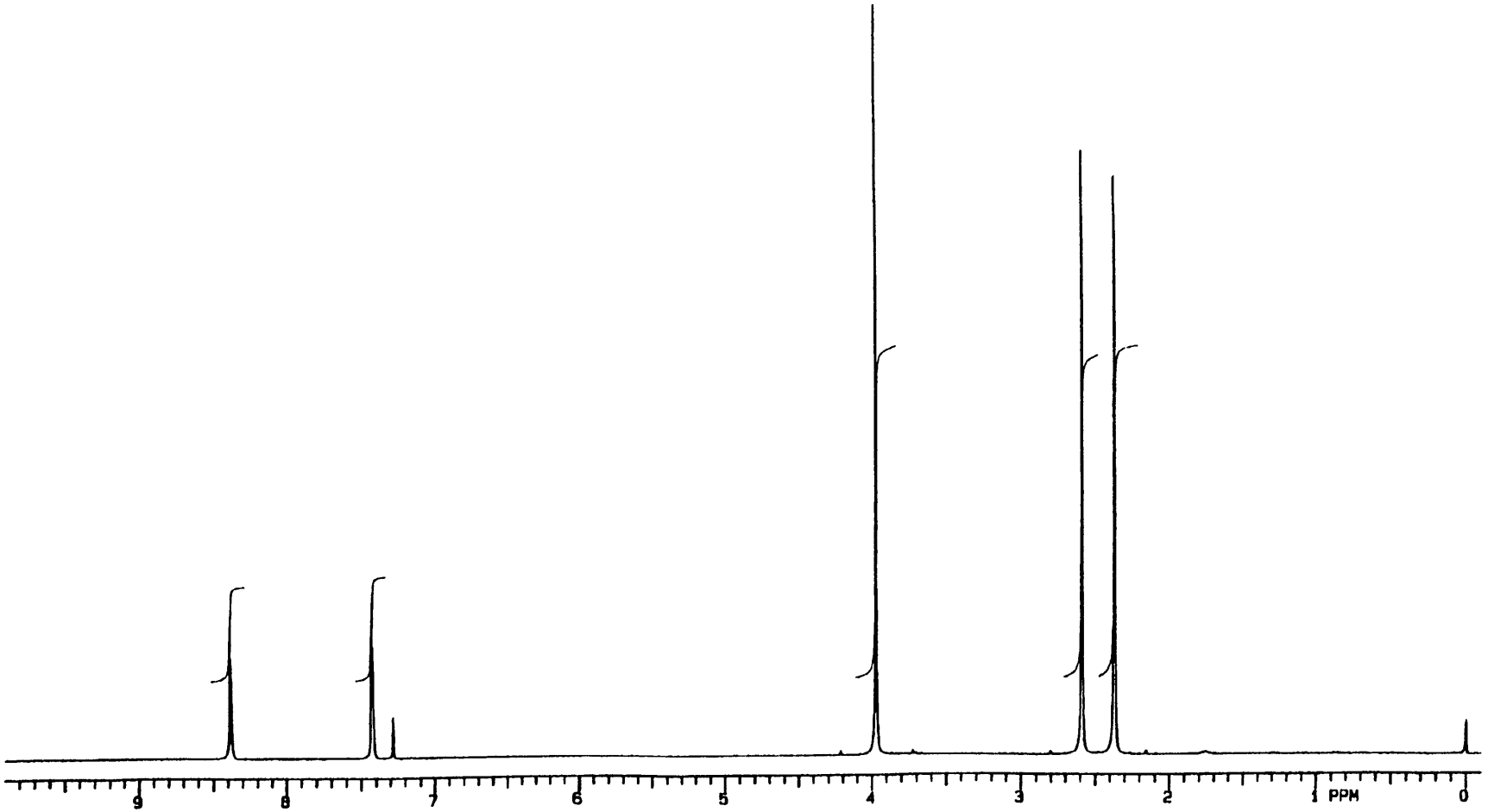
Methyl-3,5-dimethylpyridine-2-carboxylate (188).

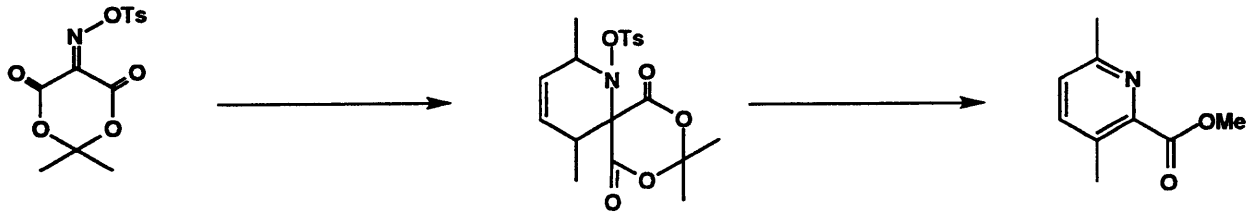
Reaction of oximinosulfonate (**58**) (0.450 g, 1.37 mmol) with a 70:30 mixture of *trans*-2-methylpenta-1,3-diene and 4-methylpenta-1,3-diene (0.452 g, 5.5 mmol) and Me_2AlCl (1.0 M in hexane, 2.7 mL, 2.7 mmol) in 20 mL of dichloromethane at -78 °C for 1 h according to the general procedure provided the crude cycloadduct as a yellow foam. Reaction of the crude cycloadduct with NaOMe (1.53 M in methanol, 2.7 mL, 4.4 mmol) and *N*-chlorosuccinimide (0.183 g, 1.37 mmol) in 15 mL of tetrahydrofuran and 15 mL of methanol at room temperature for 16 h according to the general procedure furnished 0.159 g (70%) of pyridine **188** as a colorless solid: mp 42-43 °C (pet ether). This pyridine was previously reported to have a mp of 39-41 °C.[116]

IR ($CHCl_3$)	2960, 1710, 1440, 1305, 1095 cm^{-1}	
^1H NMR (300 MHz, $CDCl_3$)	δ 2.34 (s, 3 H), 2.56 (s, 3 H), 3.94 (s, 3 H), 7.39 (s, 1 H), 8.35 (s, 1 H)	
^{13}C NMR (75 MHz, $CDCl_3$)	δ 18.2, 20.0, 52.4, 135.6, 136.4, 140.4, 144.1, 147.4, 166.5.	
Elemental Analysis	Calcd for $C_9H_{11}NO_2$:	C, 65.44; H, 6.71; N, 8.48
	Found:	C, 64.59; H, 6.80; N, 8.40



188

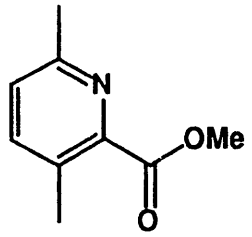




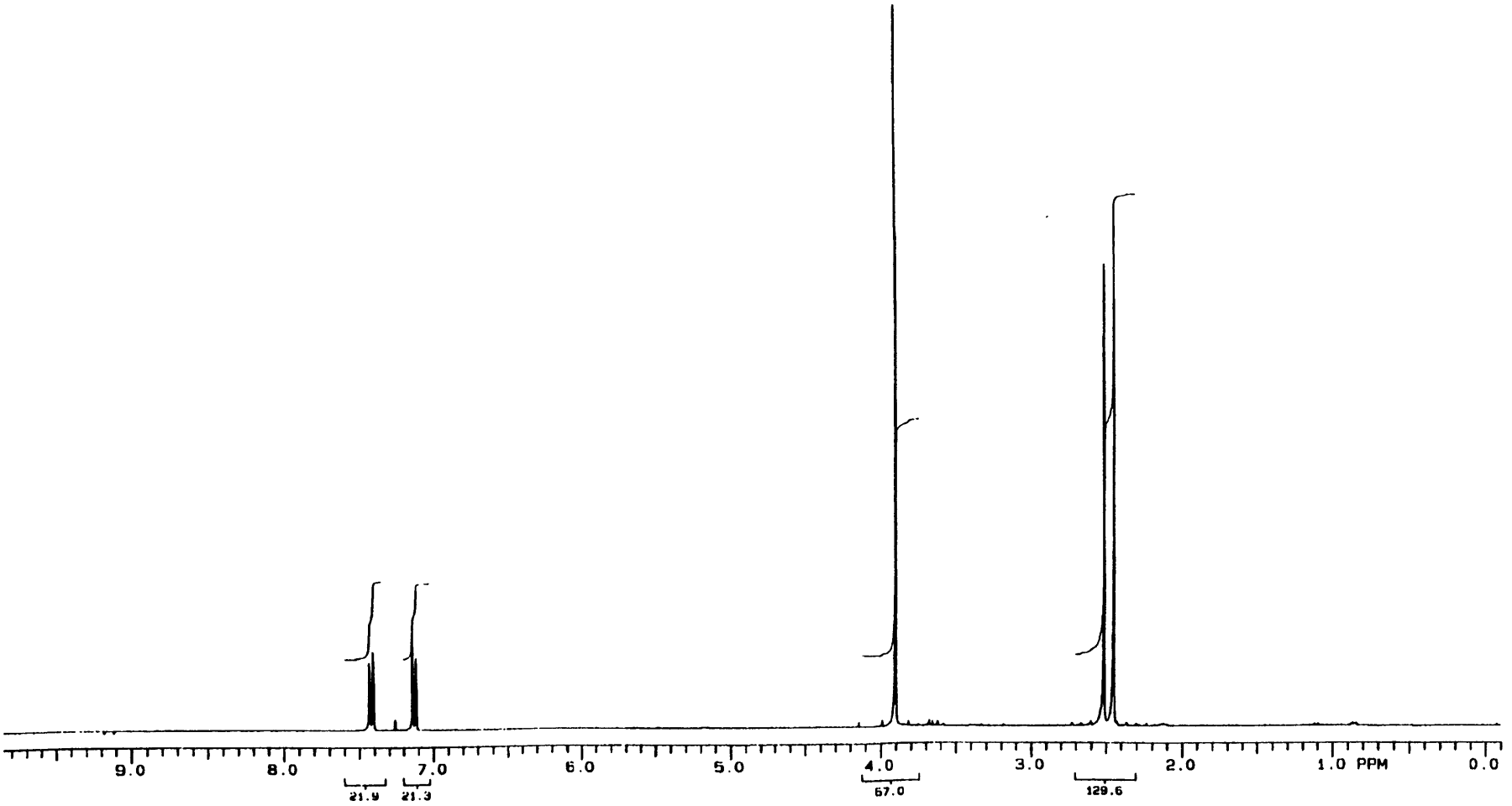
Methyl-3,6-dimethylpyridine-2-carboxylate (190).

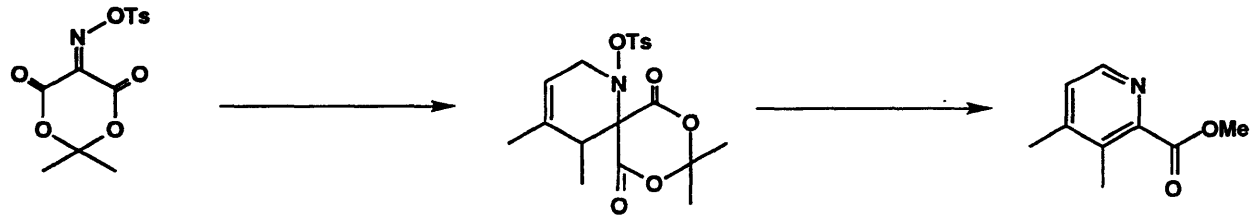
Reaction of oximinosulfonate (**58**) (0.600 g, 1.83 mmol) with *trans,trans*-hexa-2,4-diene (0.451 g, 5.49 mmol) and Me_2AlCl (1.0 M in hexane, 3.7 mL, 3.7 mmol) in 25 mL of dichloromethane at -78 °C for 1.5 h according to the general procedure provided the crude cycloadduct as a pink foam. Reaction of the crude cycloadduct in 20 mL of tetrahydrofuran and 20 mL of methanol at room temperature with NaOMe in *three portions* (1.51 M in methanol, 6.0 mL total, 9.2 mmol, *5.0 equiv*) and *N*-chlorosuccinimide in *two portions* (0.489 g, 7.3 mmol, *4.0 equiv*) for 13 h according to the general procedure furnished 0.120 g (40%) of pyridine **190** as a clear colorless oil.

IR (film)	2950, 1725, 1435, 1320, 1100 cm^{-1}
^1H NMR (300 MHz, $CDCl_3$)	δ 2.53 (s, 3 H), 2.59 (s, 3 H), 3.97 (s, 3H), 7.20 (d, J = 8.0 Hz, 1 H), 7.49 (d, J = 7.8 Hz, 1 H)
^{13}C NMR (75 MHz, $CDCl_3$)	δ 19.3, 23.9, 52.4, 125.6, 131.8, 140.0, 146.5, 155.6, 166.7.



190

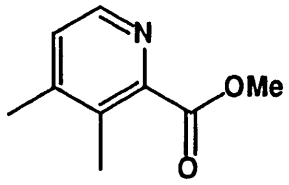




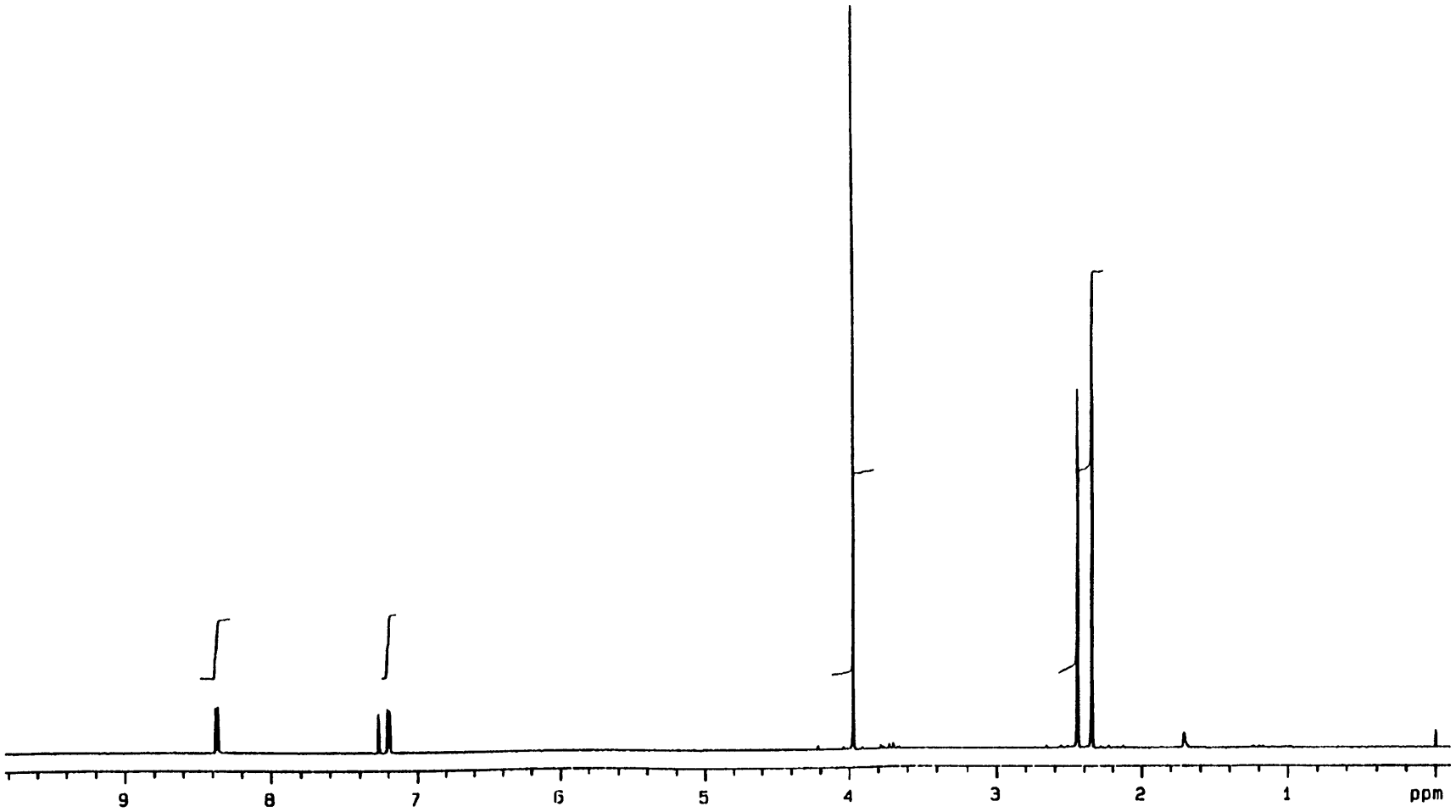
Methyl-3,4-dimethylpyridine-2-carboxylate (189).

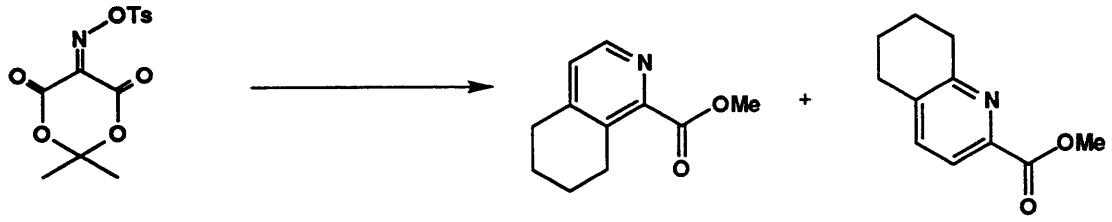
Reaction of oximinosulfonate (**58**) (0.452 g, 1.38 mmol) with 3-methylpenta-1,3-diene (0.340 g, 4.14 mmol) and Me_2AlCl (1.0 M in hexane, 2.8 mL, 2.8 mmol) in 19 mL of dichloromethane at -78 °C for 2.5 h according to the general procedure provided the crude cycloadduct as a orange foam. Reaction of the crude cycloadduct with NaOMe (1.52 M in methanol, 2.7 mL, 4.1 mmol) and *N*-chlorosuccinimide (0.184 g, 1.38 mmol) in 12 mL of tetrahydrofuran and 12 mL of methanol at room temperature for 14 h according to the general procedure furnished 0.091 g (40%) of pyridine **189** as a pale yellow oil.

IR ($CHCl_3$)	2900, 1725, 1440, 1300, 1190, 1055 cm^{-1}
^1H NMR (300 MHz, $CDCl_3$)	δ 2.33 (s, 3 H), 2.43 (s, 3 H), 3.96 (s, 3 H), 7.19 (d, J = 4.9 Hz, 1 H), 8.36 (d, J = 4.9 Hz, 1 H)
^{13}C NMR (75 MHz, $CDCl_3$)	δ 14.9, 19.9, 52.5, 127.0, 133.1, 146.3, 147.8, 148.8, 167.3.



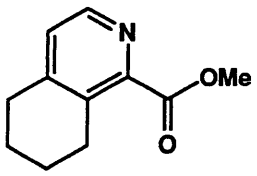
189





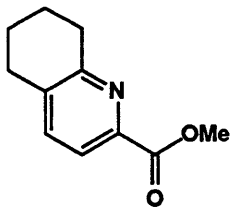
Methyl-5,6,7,8-tetrahydroisoquinoline-1-carboxylate (191) and methyl-5,6,7,8-tetrahydroquinoline-2-carboxylate (192).

Reaction of oximinosulfonate (**58**) (0.635 g, 1.94 mmol) with 1-vinylcyclohex-1-ene (0.315 g, 2.91 mmol) and Me_2AlCl (1.0 M in hexane, 3.9 mL, 3.9 mmol) in 16 mL of dichloromethane at -78 °C for 4 h according to the general procedure provided the crude cycloadduct as an orange foam. Reaction of the crude cycloadduct with NaOMe (1.51 M in methanol, 3.9 mL, 5.8 mmol) and *N*-chlorosuccinimide (0.259 g, 1.94 mmol) in 18 mL of tetrahydrofuran and 18 mL of methanol at room temperature for 16 h according to the general procedure furnished 0.184 g (50%) of pyridine **191** as a pale yellow solid and 0.039 g (11%) of pyridine **192** as a pale yellow oil.



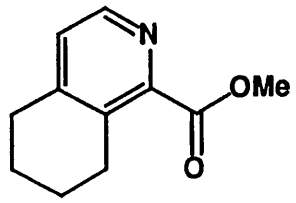
pyridine **191**: mp 68-69 °C (pet ether)

IR ($CHCl_3$)	3020, 2970, 1720, 1435, 1210 cm^{-1}	
^1H NMR (300 MHz, $CDCl_3$)	δ 1.79-1.82 (m, 4 H), 2.80-2.84 (m, 2 H), 3.02-3.06 (m, 2 H), 3.96 (s, 3 H), 7.13 (d, J = 4.8 Hz, 1 H), 8.36 (d, J = 4.8 Hz, 1 H)	
^{13}C NMR (75 MHz, $CDCl_3$)	δ 21.6, 22.4, 25.9, 29.5, 52.4, 126.6, 134.5, 145.6, 147.5, 148.2, 166.8.	
Elemental Analysis	Calcd for $C_{11}H_{13}NO_2$:	C, 69.09; H, 6.85; N, 7.32
	Found:	C, 69.10; H, 6.98; N, 7.23

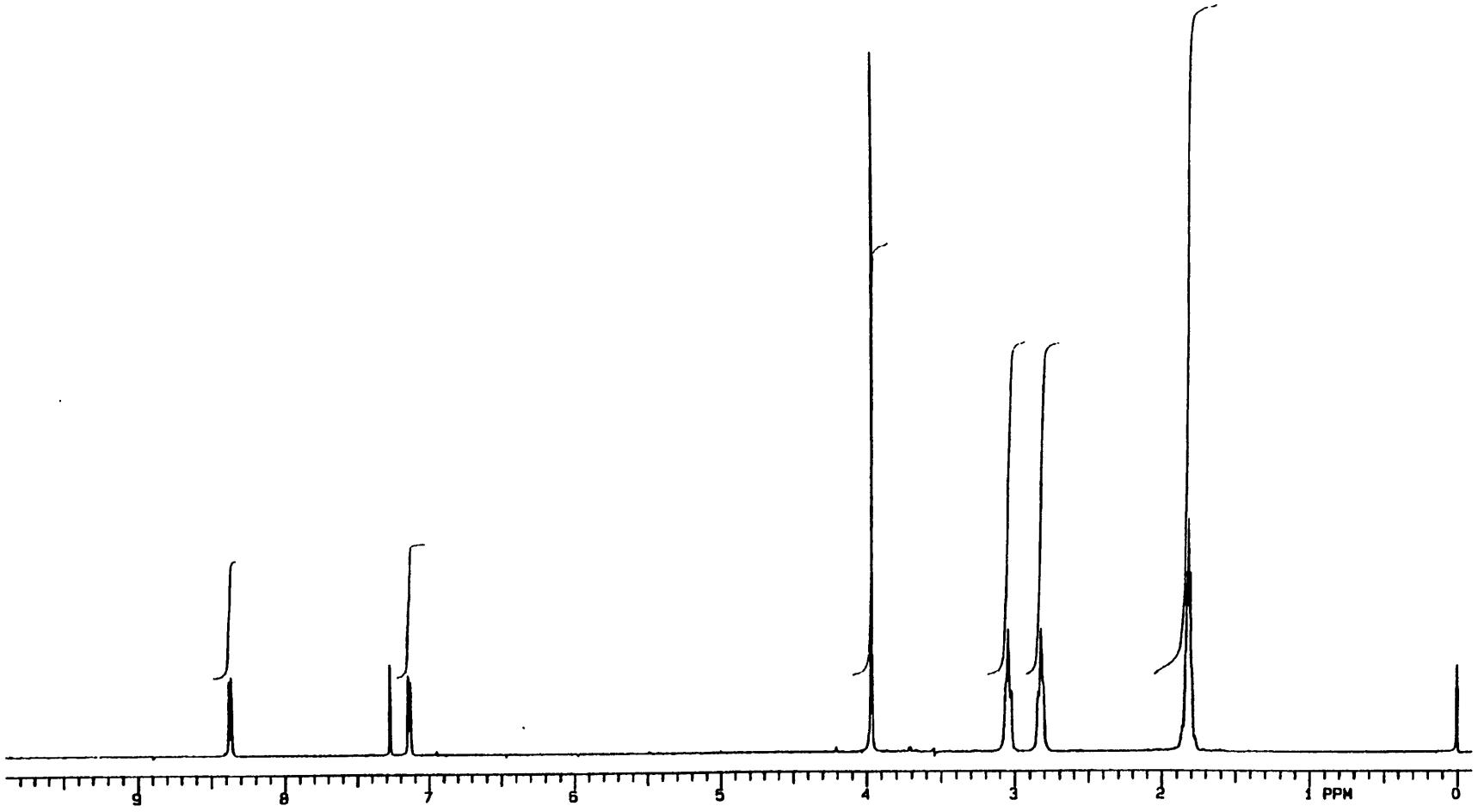


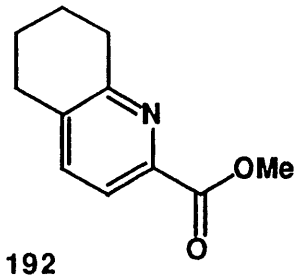
pyridine **192**:

IR ($CHCl_3$)	2940, 1720, 1435, 1320, 1130 cm^{-1}
^1H NMR (300 MHz, $CDCl_3$)	δ 1.82-1.94 (m, 4 H), 2.84 (tr, J = 6.4 Hz, 2 H), 3.03 (tr, J = 6.7 Hz, 2 H), 3.98 (s, 3 H), 7.49 (d, J = 7.8 Hz, 1 H), 7.88 (d, J = 7.8 Hz, 1 H)
^{13}C NMR (75 MHz, $CDCl_3$)	δ 22.3, 22.8, 29.0, 32.7, 52.7, 122.5, 136.7, 137.4, 145.1, 158.0, 166.1.

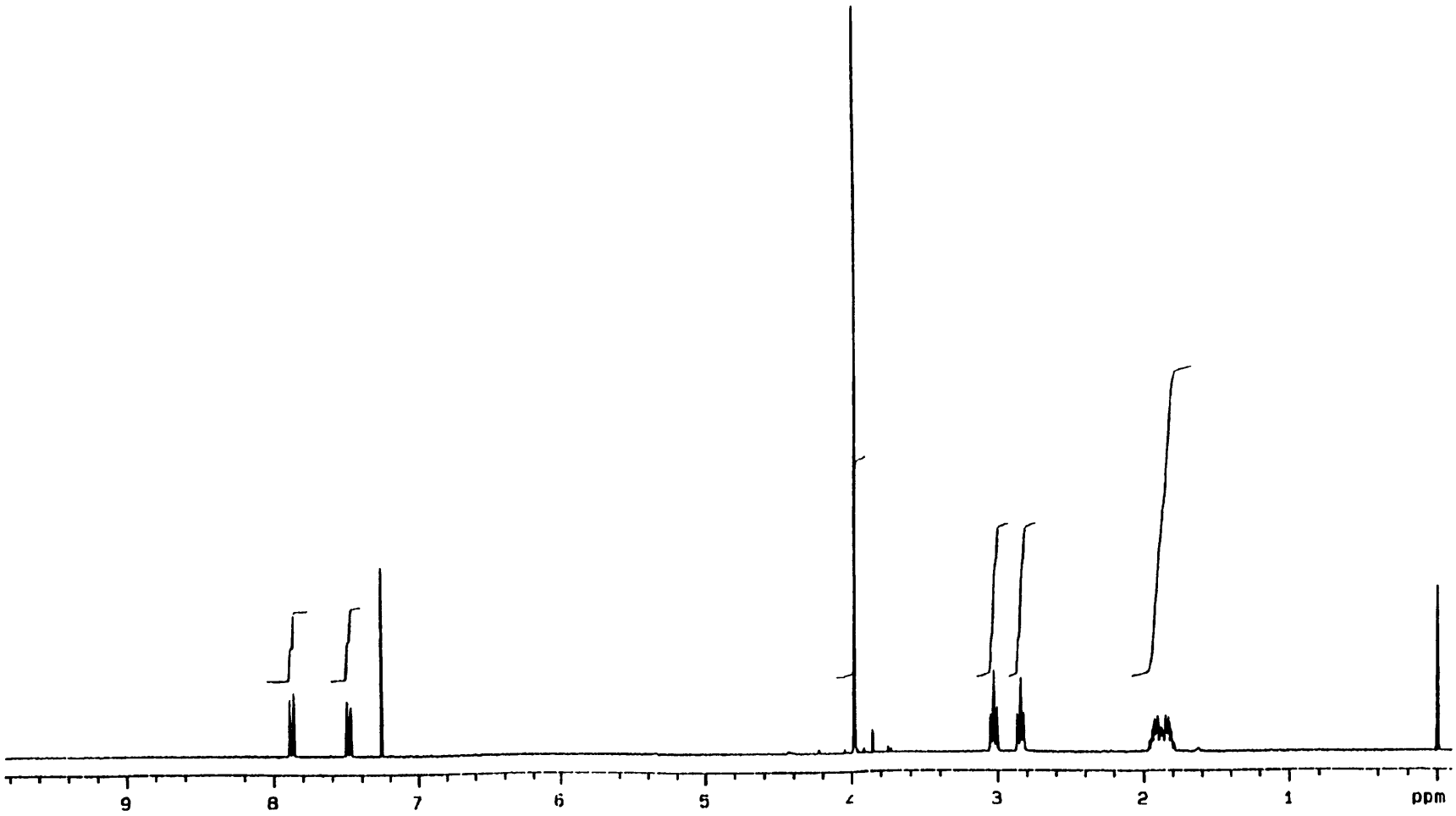


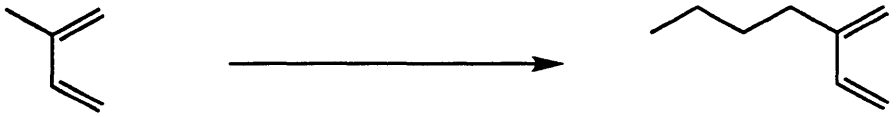
191





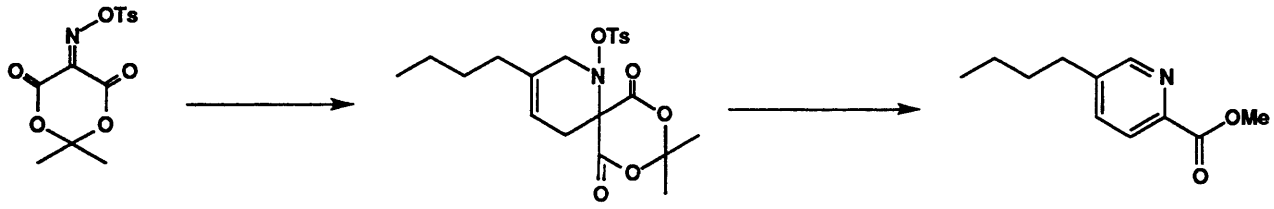
192





3-Methylenehept-1-ene (213).

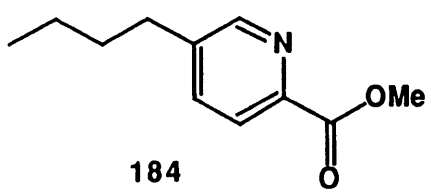
A 50-mL, three-necked, round-bottomed flask equipped with argon inlet adapter and septum was charged with KO*t*-Bu (1.65 g, 14.7 mmol), 12 mL of tetrahydrofuran, and 2,2,6,6-tetramethylpiperidine (2.08 g, 14.7 mmol). This solution was cooled at -65 °C while *n*-BuLi solution (2.5 M in hexane, 5.9 mL, 14.7 mmol) was added dropwise via syringe over 2 min. The resulting orange solution was cooled at -78 °C while isoprene (1.50 g, 22.1 mmol) was added dropwise via syringe over 10 min. The resulting red solution was stirred for 10 min at -78 °C and then a solution of 1-bromopropane (2.72 g, 22.1 mmol) in 3 mL of tetrahydrofuran was added dropwise via cannula over 30 sec. The resulting yellow suspension was stirred for 20 min at -50 °C, the cooling bath was removed, and the solution allowed to warm to 0 °C. The yellow suspension was then quenched by addition of 40 mL of water and the solution extracted with three 25-mL portions of ether. The combined organic phases were washed with two 20-mL portions of 1 N HCl solution and 30 mL of saturated NaCl solution. The organic phase was dried over $MgSO_4$, filtered, and then the solvent was removed by distillation at ambient pressure. The pale yellow residue was purified by column chromatography (elution with pentane). Pentane was removed from the collected fractions by distillation (1 atm) to give 0.687 g (45%, ca. 90% pure) of the diene **213** as a clear colorless oil.[122] This material was used in the next step without further purification.



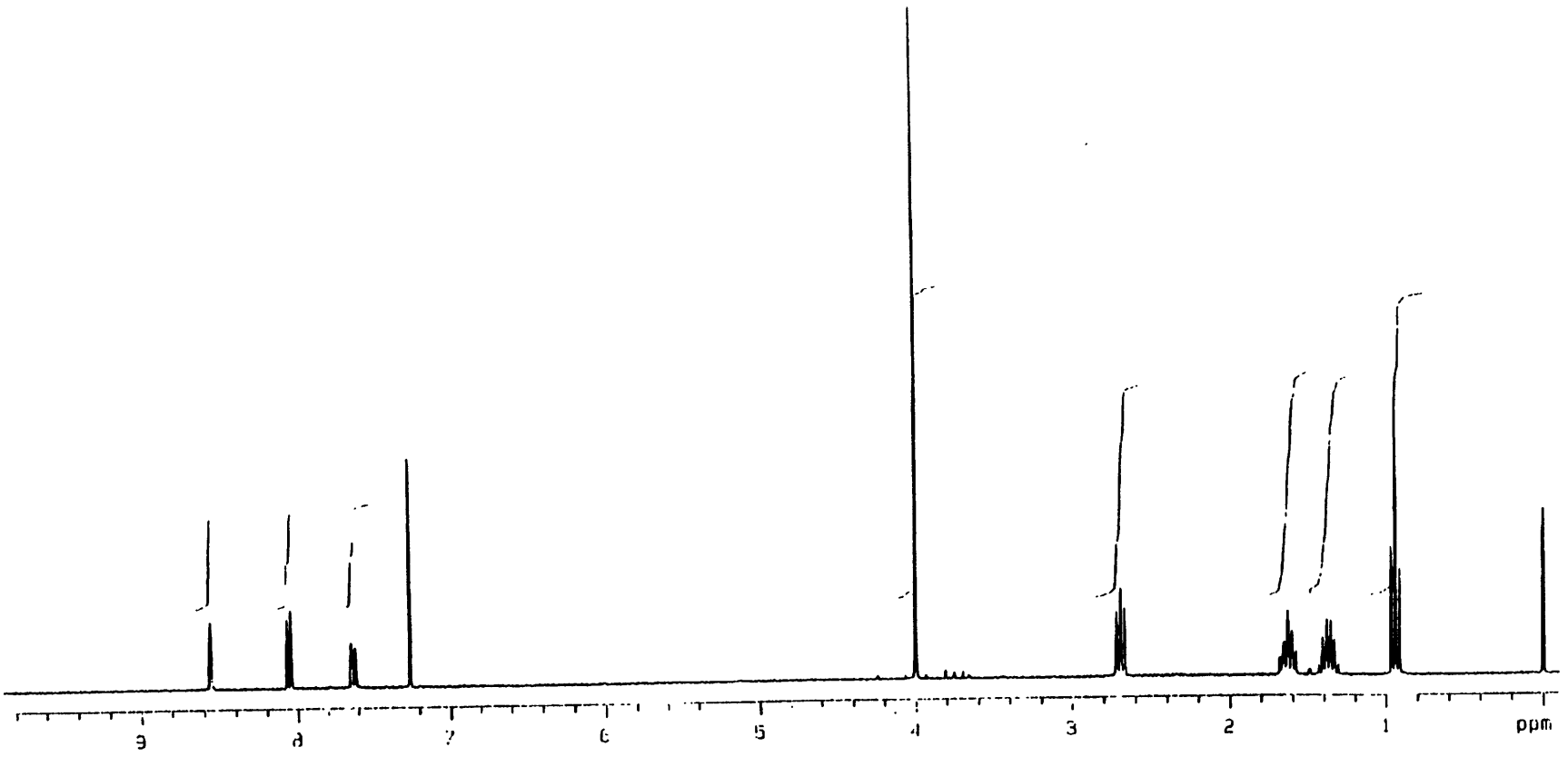
Methyl-5-*n*-butylpyridine-2-carboxylate (methyl fusarate) (184).

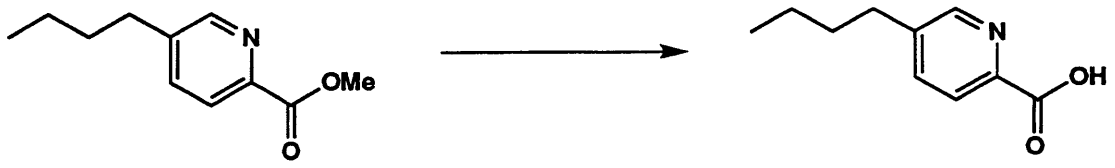
Reaction of oximinosulfonate (**58**) (0.419 g, 1.28 mmol) with 3-methylenehept-1-ene (0.200 g, 1.92 mmol) and Me_2AlCl (1.0 M in hexane, 2.6 mL, 2.6 mmol) in 11 mL of dichloromethane at -78 °C for 4 h according to the general procedure provided the crude cycloadduct as an orange foam. Reaction of the crude cycloadduct with NaOMe (1.42 M in methanol, 2.7 mL, 3.8 mmol) and *N*-chlorosuccinimide (0.171 g, 1.28 mmol) in 12 mL of tetrahydrofuran and 12 mL of methanol at room temperature for 15 h according to the general procedure furnished 0.179 g (72%) of pyridine **184** as a pale yellow oil with spectral data consistent with that previously reported.[118h]

IR (film)	2990, 1725, 1440, 1310, 1120 cm^{-1}
^1H NMR (300 MHz, $CDCl_3$)	δ 0.92 (tr, J = 7.5 Hz, 3 H), 1.31-1.35 (app hex, 2 H), 1.56-1.66 (app quint, 2 H), 2.65-2.70 (tr, J = 7.5 Hz, 2 H), 3.98 (s, 3 H), 7.62 (dd, J = 8.1, 1.9 Hz, 1 H), 8.04 (d, J = 7.8 Hz, 1 H), 8.54 (d, J = 1.8 Hz, 1 H)
^{13}C NMR (75 MHz, $CDCl_3$)	δ 13.6, 22.1, 32.6, 32.8, 52.6, 124.8, 136.5, 142.1, 145.4, 149.9, 165.7.



184

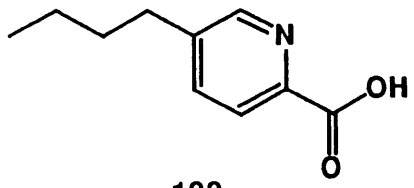




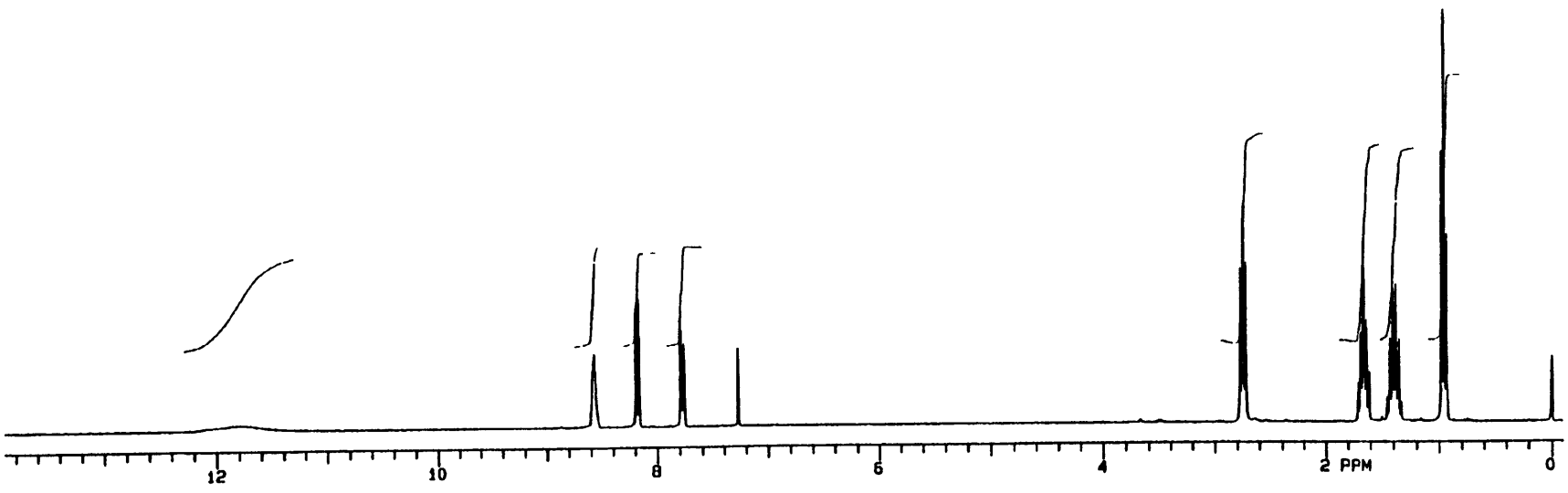
5-*n*-Butylpyridine-2-carboxylic acid (Fusaric Acid) (199).

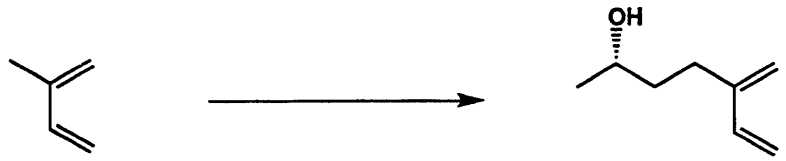
A 10-mL, one-necked, round-bottomed flask equipped with an argon inlet adapter was charged with methyl fusarate (**184**) (0.126 g, 0.652 mmol), 2 mL of methanol, and 0.5 mL of water. The solution was cooled at 0 °C and treated with LiOH-H_2O (0.239 g , 3.26 mmol) in one portion. The resulting mixture was stirred for 1 h at 0 °C, the cooling bath removed, and the solution was diluted with 2 mL of water. The resulting mixture was acidified to pH 2 by the slow addition of 1.0 N HCl solution and then extracted with eight 10-mL portions of ethyl acetate. The combined organic phases were dried over $MgSO_4$, filtered, and concentrated to provide a white solid. Sublimation at 0.1 mmHg and ca. 100 °C provided 0.099 g (85%) of fusaric acid as a white solid: mp 99-100.5 °C (lit.[113b] mp 100-101 °C). The spectral data for synthetic fusaric acid was consistent with that reported for fusaric acid isolated from natural sources.[118b, g]

IR ($CHCl_3$)	2960, 2930, 1765, 1410, 1355, 1295 cm^{-1}
^1H NMR (300 MHz, $CDCl_3$)	δ 0.95 (tr, J = 7.3 Hz, 3 H), 1.35-1.45 (app hex, J = 7.3 Hz 2 H), 1.60-1.70 (m, 2 H), 2.73 (tr, J = 7.6 Hz, 2 H), 7.75 (dd, J = 8.0, 2.1 Hz, 1 H), 8.14 (d, J = 8.0, 1 H), 8.44 (d, J = 1.5 Hz, 1 H), 11.8 (br s, 1 H)
^{13}C NMR (75 MHz, $CDCl_3$)	δ 13.7, 22.2, 32.7, 32.8, 124.5, 138.5, 143.0, 145.0, 147.6, 165.3.
Elemental Analysis	Calcd for $C_{10}H_{13}NO_2$: C, 67.02; H, 7.31; N, 7.82 Found: C, 67.10; H, 7.27; N, 7.66



199



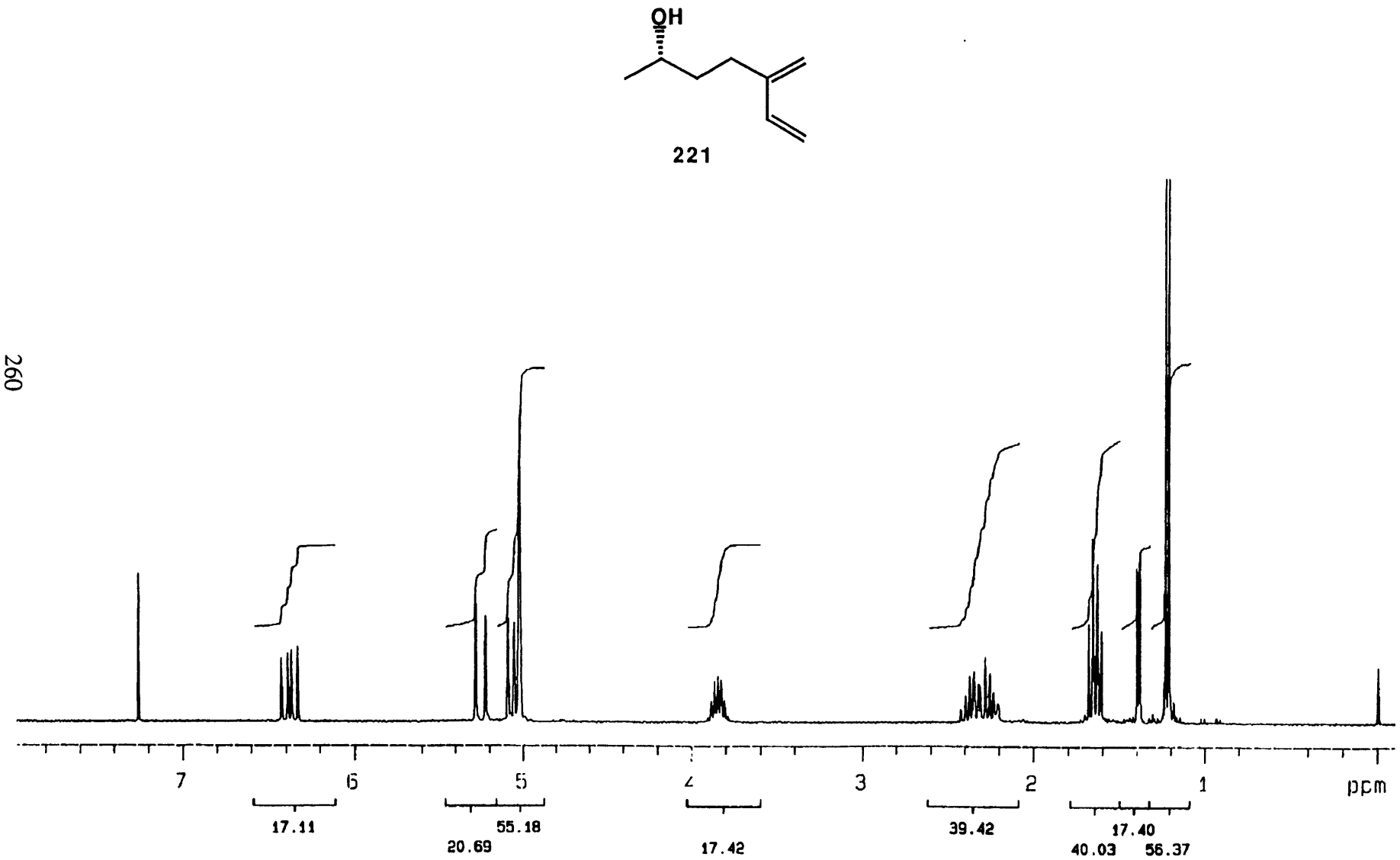


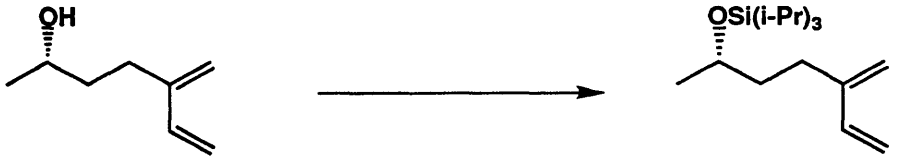
(*S*)-5-Methylenehept-6-en-2-ol (221).

A 25-mL, two-necked, round-bottomed flask equipped with argon inlet adapter and septum was charged with KO*t*-Bu (0.310 g, 2.75 mmol), 3 mL of tetrahydrofuran, and 2,2,6,6-tetramethylpiperidine (0.388 g, 2.75 mmol). This solution was cooled at -60 °C while *n*-BuLi solution (2.55 M in hexane, 1.1 mL, 2.8 mmol) was added dropwise via syringe over 2 min. The resulting orange solution was then cooled at -78 °C while isoprene (0.28 g, 0.41 mL, 4.1 mmol) was added dropwise via syringe over 5 min. The resulting red solution was stirred for 10 min at -60 to -70 °C and then a solution of (*S*)-propylene oxide (0.240 g, 4.13 mmol) in 1 mL of tetrahydrofuran was added dropwise via cannula over 2 min. The resulting deep red solution was stirred for 10 min at -50 °C, the cooling bath was removed, and the solution was allowed to warm to room temperature. The resulting pale yellow solution was quenched by the addition of 10 mL of water and the solution was extracted with six 10-mL portions of ether. The combined organic phases were washed with two 10-mL portions of 0.5 N HCl solution and the combined acidic phases were back-extracted with two 10-mL portions of ether. The combined organic phases were dried over $MgSO_4$, filtered, and concentrated onto 1.4 g of silica gel. The free-flowing powder was placed atop a column of 16 g of silica gel and eluted with 25% ethyl acetate-0.1% methanol hexane to provide 0.212 g (61%) of the diene **221** as a clear, pale yellow oil: $[a]^{25}_D$ +16° ($CHCl_3$, c = 2.70).

IR (film)	3340, 2960, 2925, 1595, 1080 cm^{-1}
^1H NMR (300 MHz, $CDCl_3$)	δ 1.23 (d, *J* = 6.3 Hz, 3 H), 1.43 (br s, 1H), 1.62-1.69 (app quart, *J* = 7.8 Hz, 2 H), 2.24-2.40 (m, 2 H), 3.82-3.88 (app hex, *J* = 6.0 Hz, 2 H), 5.03 (s, 2 H), 5.08 (d, *J* = 10.8 Hz, 1 H), 5.26 (d, *J* = 17.4 Hz, 1 H), 6.38 (dd, *J* = 17.7, 11.1 Hz, 1 H)

^{13}C NMR (75 MHz, $CDCl_3$)	δ 23.5, 27.5, 37.6, 67.8, 113.3, 115.7, 138.7, 146.1.

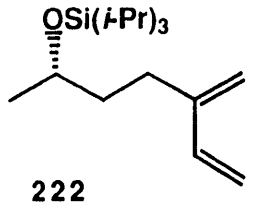

OH
221
260
7
6
5
4
3
2
1
ppm
17.11
20.69
55.18
17.42
39.42
17.40
40.03
56.37



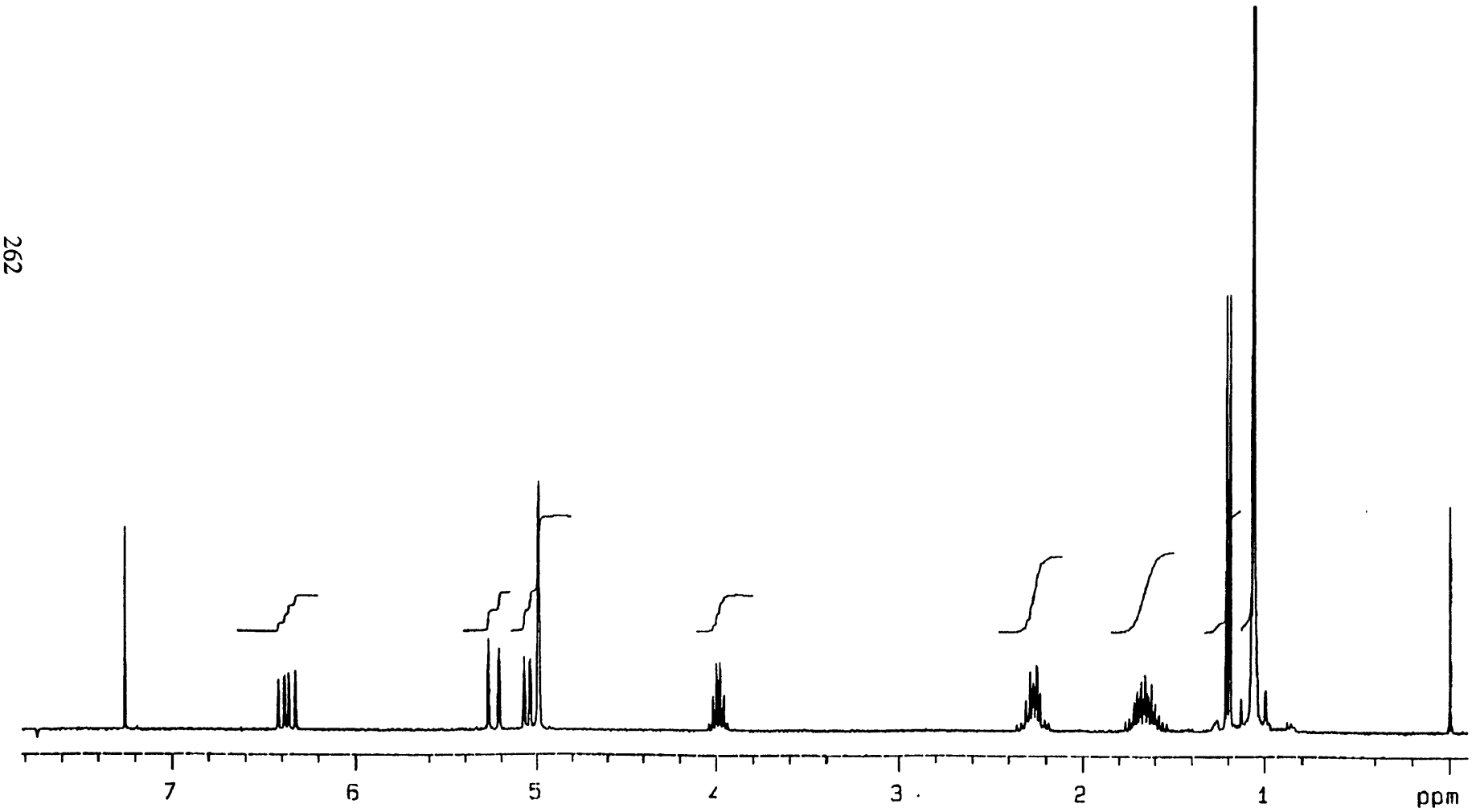
(*S*)-2-triisopropylsiloxy-5-methylenehept-6-ene (222).

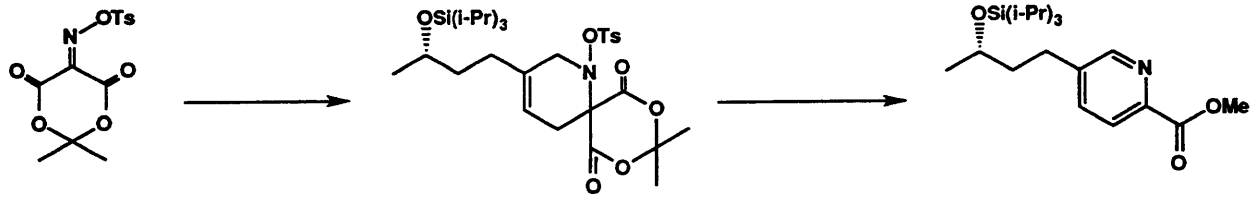
A 25-mL, one-necked, round-bottomed flask equipped with an argon inlet adapter was charged with diene **221** (0.349 g, 2.76 mmol) and 4 mL of dichloromethane. This solution was cooled at 0 °C while collidine (0.836 g, 6.90 mmol) was added via syringe in one portion, followed by the addition of triisopropylsilyl trifluoromethanesulfonate (1.1 g, 0.97 mL, 3.6 mmol) dropwise via syringe over 10 min. The reaction mixture was stirred for 1.5 h at 0 °C and then diluted with 20 mL of dichloromethane. The solution was washed with one 20-mL portion of 1.0 N HCl solution and the acidic solution was back-extracted with 10-mL of dichloromethane. The combined organic phases were then washed with 15 mL of saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated to give a clear, colorless oil. Purification by column chromatography on 15 g of silica gel (elution with 1% triethylamine-hexane) provided 0.720 g (92%) of the diene **222** as a clear colorless oil: $[a]^{25}_D$ +2.6° ($CHCl_3$, c = 2.8).

IR (film)	2940, 1595, 1460, 1095 cm^{-1}
^1H NMR (300 MHz, $CDCl_3$)	δ 1.07 (s, 21 H), 1.20 (d, *J* = 6.0 Hz, 3 H), 1.58-1.72 (m, 2 H), 2.23-2.31 (m, 2 H), 3.96-4.02 (app hex, *J* = 5.9 Hz, 1H), 5.00 (s, 2 H), 5.06 (d, *J* = 10.8 Hz, 1 H), 5.24 (d, *J* = 17.7 Hz, 1 H), 6.37 (dd, *J* = 17.7, 10.8 Hz, 1 H)
^{13}C NMR (75 MHz, $CDCl_3$)	δ 12.5, 18.1, 18.2, 23.5, 27.1, 38.5, 68.4, 113.2, 115.4, 138.9, 146.6.



222

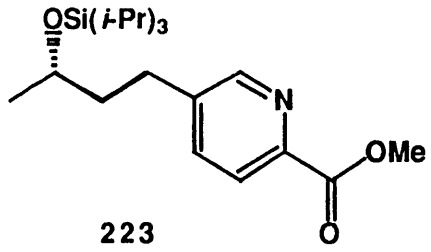




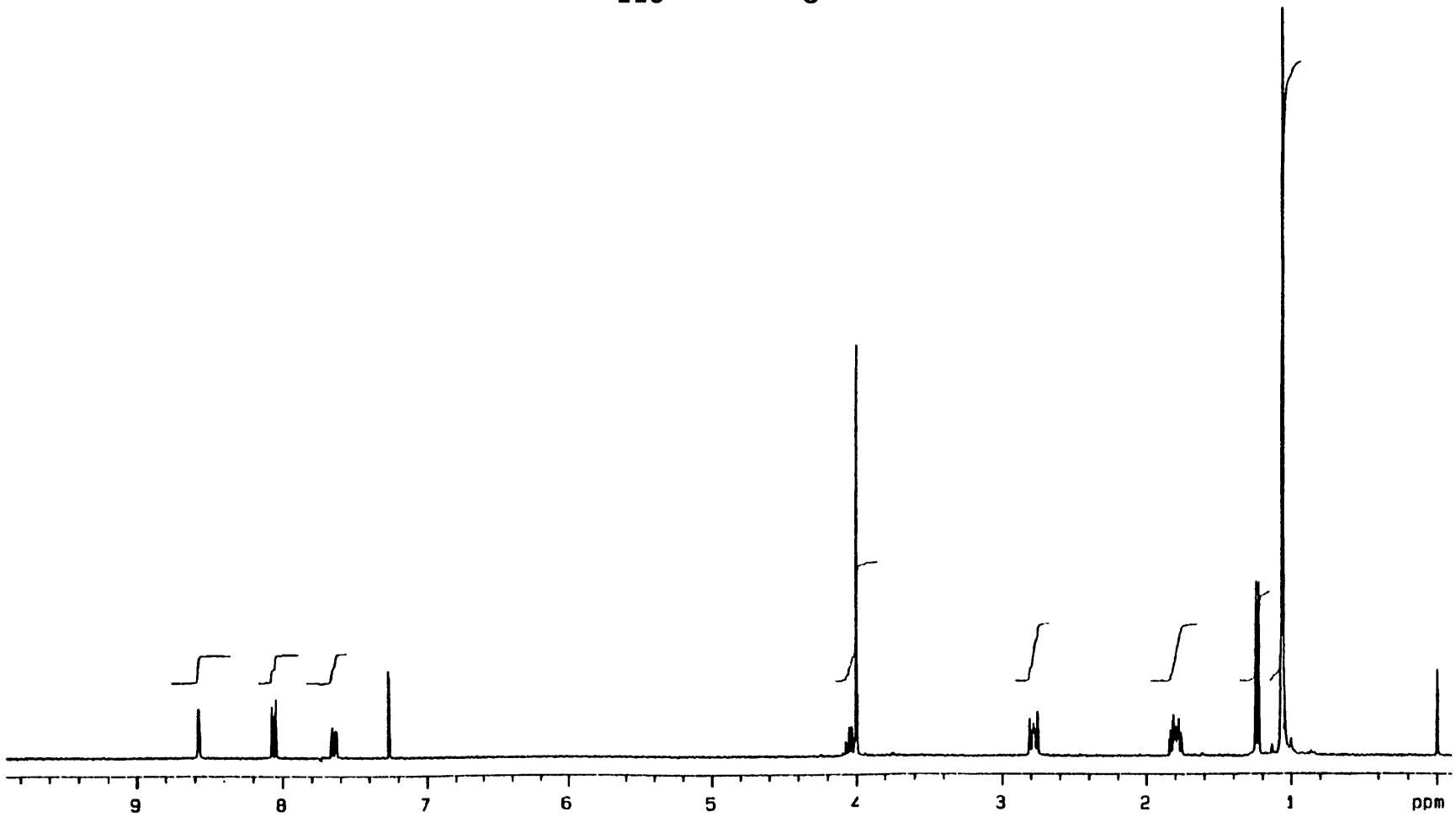
(*S*)-Methyl-5-(3-triisopropylsiloxybutyl)pyridine-2-carboxylate (223).

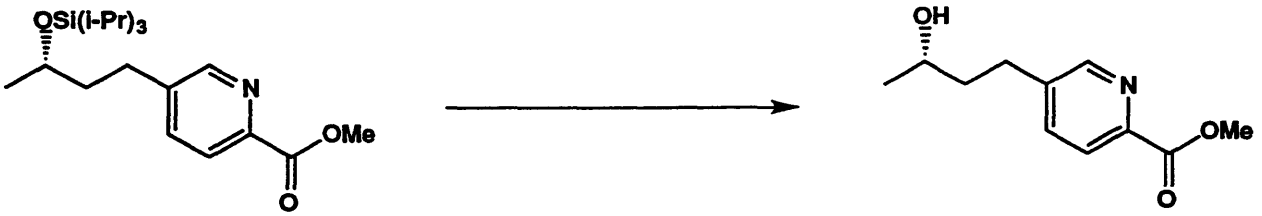
Reaction of oximinosulfonate (**58**) (0.494 g, 1.51 mmol) with diene **222** (0.640 g, 2.27 mmol) and Me_2AlCl (1.0 M in hexane, 3.0 mL, 3.0 mmol) in 13 mL of dichloromethane at -78 °C for 3 h according to the general procedure provided the crude cycloadduct as an orange oil. Reaction of the crude cycloadduct with a NaOMe (1.44 M in methanol, 3.1 mL, 4.5 mmol) and *N*-chlorosuccinimide (0.202 g, 1.51 mmol) in 15 mL of tetrahydrofuran and 15 mL of methanol at room temperature for 16 h according to the general procedure furnished 0.428 g (78%) of pyridine **223** as a pale yellow oil: $[a]^{25}_D$ +0.86° ($CHCl_3$, c = 1.97).

IR (film)	2940, 1745, 1720, 1310 cm^{-1}
^1H NMR (300 MHz, $CDCl_3$)	δ 1.07 (s, 21 H), 1.24 (d, 6.0 Hz, 3 H), 1.76-1.83 (m, 2 H), 2.76-2.81 (m, 2 H), 4.00 (s, 3 H), 4.04 (app hex, *J* = 5.9 Hz, 1 H), 7.65 (dd, *J* = 8.0, 1.7 Hz, 1 H), 8.06 (d, *J* = 8.0 Hz, 1 H), 8.57 (d, *J* = 2.1 Hz, 1 H)
^{13}C NMR (75 MHz, $CDCl_3$)	δ 12.4, 18.11, 18.07, 23.3, 28.5, 40.9, 52.7, 67.6, 124.9, 136.5, 142.3, 145.5, 150.0, 165.8.



223

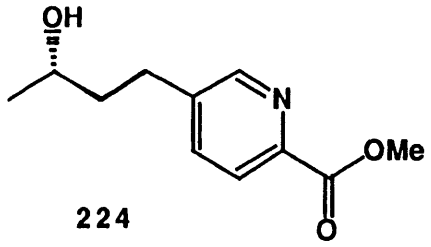




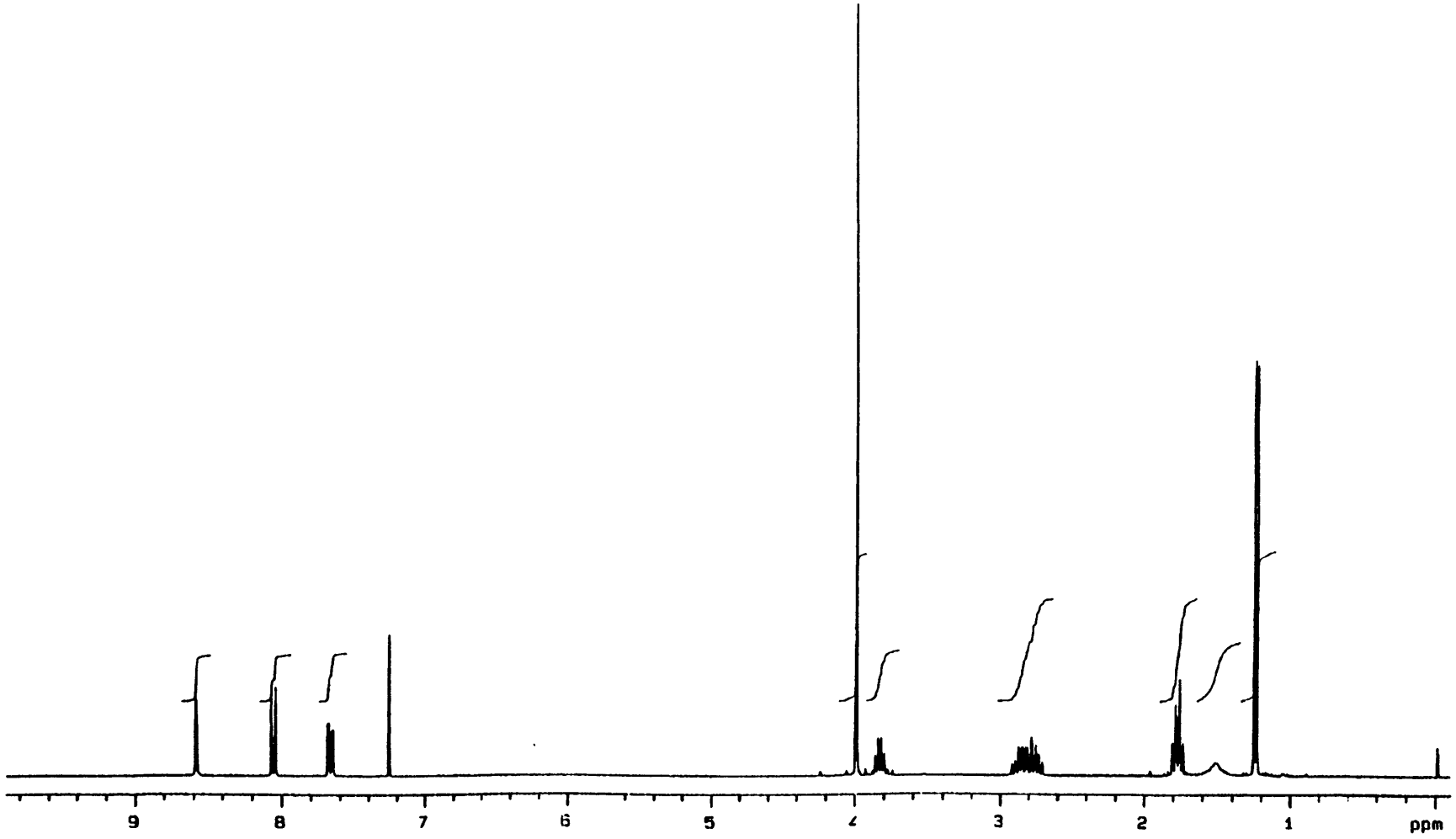
(*S*)-Methyl-5-(3-hydroxybutyl)pyridine-2-carboxylate ((*S*)-methyl fusarinolate) (224).

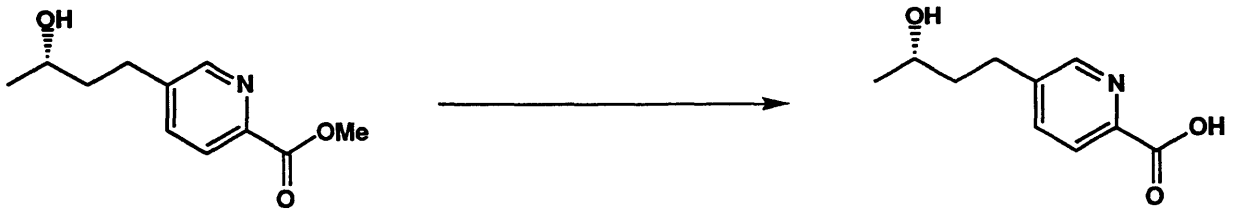
A 10-mL, one-necked, round-bottomed flask equipped with septum and argon inlet needle was charged with pyridine **223** (0.079 g, 0.22 mmol) and 2.2 mL of tetrahydrofuran. This solution was stirred at room temperature and treated with tetrabutylammonium fluoride solution (1.0 M in THF, 0.24 mL, 0.24 mmol) dropwise via syringe over 1 min. The resulting orange solution was stirred for 2 h at room temperature and then quenched by the addition of 2 mL of saturated NH_4Cl solution. The resulting mixture was stirred for 15 min, diluted with 10 mL of water, and extracted with eight 5-mL portions of ethyl acetate. The combined organic phases were dried over $MgSO_4$, filtered, and concentrated onto 0.4 g of silica gel. The free-flowing powder was placed atop a column of 5 g of silica gel and eluted with 1% triethylamine-0.1% methanol-ethyl acetate to furnish 0.042 g (93%) of (*S*)-methyl fusarinolate (**224**) as a clear colorless oil: $[a]^{25}_D$ +17.9° ($CHCl_3$, c = 1.13).

IR (film)	3370, 2960, 1725, 1570, 1310 cm^{-1}
^1H NMR (300MHz, $CDCl_3$)	δ 1.25 (d, *J* = 6.2 Hz, 3 H), 1.52 (br s, 1 H), 1.74-1.82 (m, 2 H), 2.72-2.93 (m, 2 H), 3.80-3.86 (app hex, *J* = 6.2 Hz, 1 H), 3.99 (s, 3 H), 7.67 (dd, *J* = 8.0, 2.3 Hz, 1 H), 8.06 (d, *J* = 8.0 Hz, 1 H), 8.59 (d, *J* = 2.0 Hz, 1 H)
^{13}C NMR (75 MHz, $CDCl_3$)	δ 23.7, 29.2, 39.9, 52.6, 66.9, 124.9, 136.6, 141.6, 145.7, 150.0, 165.7.



224

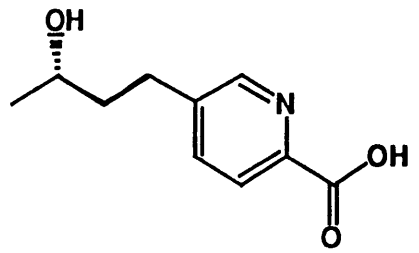




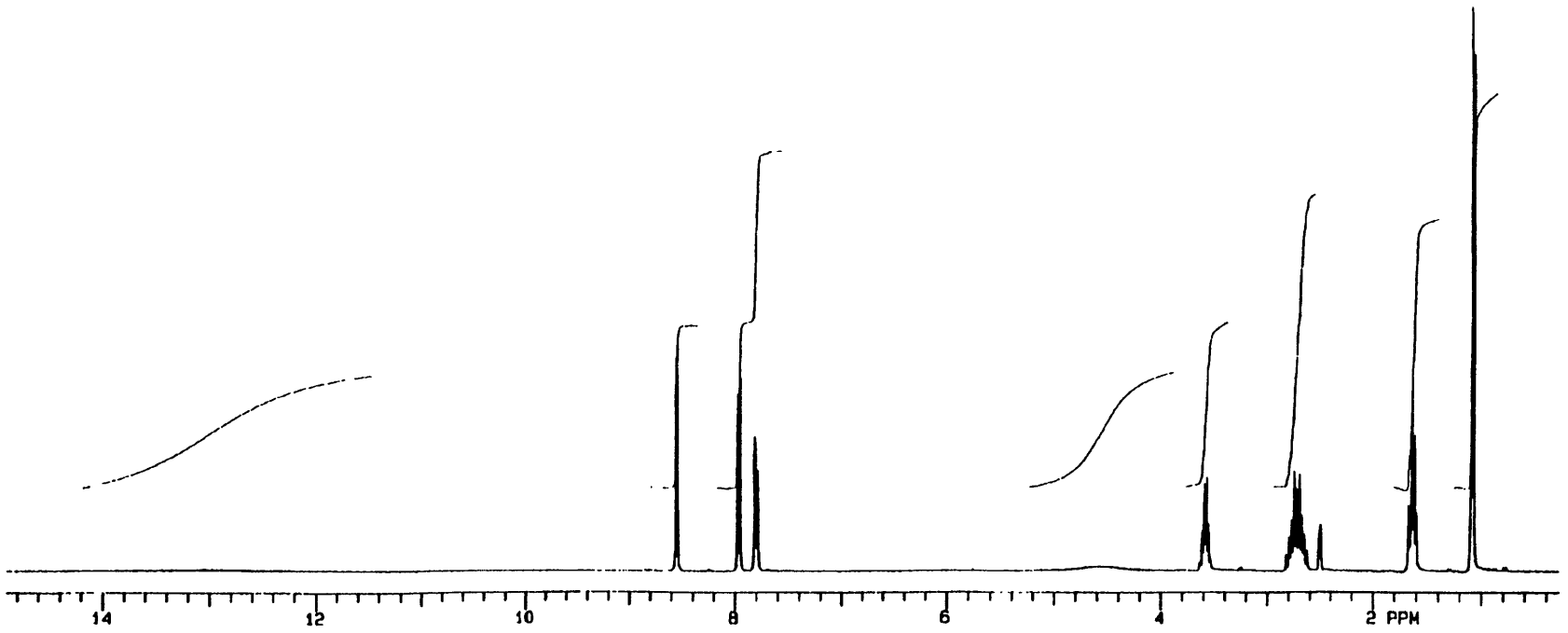
(*S*)-5-(3-hydroxybutyl)pyridine carboxylic acid ((*S*)-fusarinolic acid) (200).

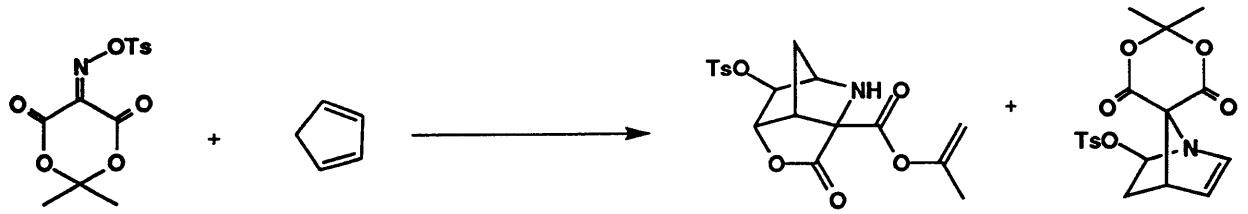
A 25-ml, round-bottomed flask equipped with an argon inlet adapter was charged with (*S*)-methyl fusarinolate **224** (0.128 g, 0.610 mmol). The flask was cooled at 0 °C while KOH solution (1.0 M in methanol, 4.6 mL, 4.6 mmol) was added in one portion via syringe, followed by the addition of 1.2 mL of water in one portion. The resulting solution was stirred for 2 h at 0 °C and then concentrated to ca. 1 mL. The residue was then treated with 10 mL of pH 2.5 phosphate buffer and the resulting solution subjected to a continuous liquid-liquid extraction with 20 mL of dichloromethane for 2 days. The resulting dichloromethane solution was dried over Na_2SO_4, filtered, and concentrated to give 0.120 g of a colorless oil. Attempted recrystallization from dichloromethane-methanol gave an oil which solidified under vacuum (0.1 mmHg) to provide 0.097 g (82%) of (*S*)-fusarinolic acid[126,127] as a colorless crystalline solid: mp 108-109 °C ; mp ((+) CSA salt) 188-189 °C; $[a]^{25}_D$ +20.5° (MeOH, c = 1.05).

IR (KBr)	3265, 2870, 2420, 1660 cm^{-1}	
^1H NMR (300 MHz, DMSO-*d6*)	δ 1.08 (d, *J* = 6.0 Hz, 3 H), 1.60-1.67 (app quart, *J* = 6.2 Hz, 2 H), 2.62-2.82 (m, 2 H), 3.53-3.61 (app hex, *J* = 6.0 Hz, 1 H), 4.2-4.8 (br s, 1 H), 7.79 (dd, *J* = 8.1, 1.9 Hz, 1 H), 7.95 (d, *J* = 8.1 Hz, 1 H), 8.54 (d, *J* = 1.7, 1 H), 11.8-13.2 (br s, 1 H)	
^{13}C NMR (75 MHz, CD_3OD)	δ 23.7, 30.3, 41.2, 67.7, 126.4, 140.1, 144.4, 146.9, 149.6, 167.2.	
Elemental Analysis	Calcd. for $C_{10}H_{13}NO_3$:	C, 61.53; H, 6.71; N, 7.18
	Found:	C, 61.24; H, 6.71; N, 7.03



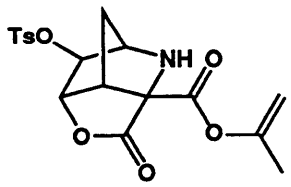
200





7-oxo-1-(propenoxycarbonyl)-4-tosyloxy-3,8-methano-2-aza-6-oxabicyclo[3.2.1] octane (251) and 3,3-dimethyl-1,5-dioxo-8-tosyloxy-7,10-etheno-7-aza-2,4-dioxaspiro[5.4]decane (250).

A threaded Pyrex tube (ca. 50 mL capacity) equipped with a rubber septum and argon inlet needle was charged with oximinosulfonate (**58**) (0.198 g, 0.605 mmol), cyclopentadiene (0.200 g, 3.02 mmol), and 20 mL of toluene. The tube was then sealed with a Teflon cap and heated at 60 °C for 2 h to give an orange solution. After cooling to room temperature, the solution was concentrated, and the resulting orange oil purified by column chromatography on 12 g of silica gel (elution with 25% ethyl acetate-hexane) to provide 0.090g (38%) of 7-oxo-1-(propenoxycarbonyl)-4-tosyloxy-3,8-methano-2-aza-6-oxabicyclo[3.2.1]octane (**251**) and 0.021 g (9%) of 3,3-dimethyl-1,5-dioxo-8-tosyloxy-7,10-etheno-7-aza-2,4-dioxaspiro[5.4]decane (**250**).



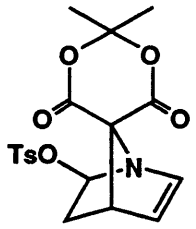
7-oxo-1-(propenoxycarbonyl)-4-tosyloxy-3,8-methano-2-aza-6-oxabicyclo[3.2.1] octane (251):

white solid mp: 135-137 °C

IR ($CHCl_3$) 3345, 3030, 1800, 1755, 1375, 1175, 995 cm^{-1}

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.75 (dq, *J* = 12.1, 1.8 Hz, 1H), 1.94 (s, 3 H), 2.17 (d, *J* = 12.9 Hz, 1 H), 2.48 (s, 3 H), 2.5-2.7 (br s, 1 H), 3.61 (dq, *J* = 5.1, 1.4 Hz, 1 H), 3.76 (s, 1 H), 4.31 (app tr, *J* = 1.7 Hz, 1 H), 4.68 (dd, *J* = 5.1, 1.4 Hz, 1 H), 4.77 (s, 2 H), 7.39 (d, *J* = 7.8 Hz, 2 H), 7.81 (d, *J* = 8.3 Hz, 2 H)

^{13}C NMR (75 MHz, $CDCl_3$) δ 19.1, 21.8, 33.2, 50.1, 59.9, 66.4, 81.9, 82.6, 102.8, 127.8, 130.2, 132.4, 145.6, 152.4, 166.0, 172.2.



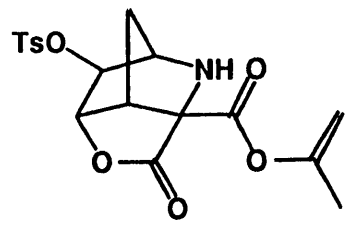
3,3-dimethyl-1,5-dioxo-8-tosyloxy-7,10-etheno-7-aza-2,4-dioxaspiro[5.4] decane (250):

colorless oil

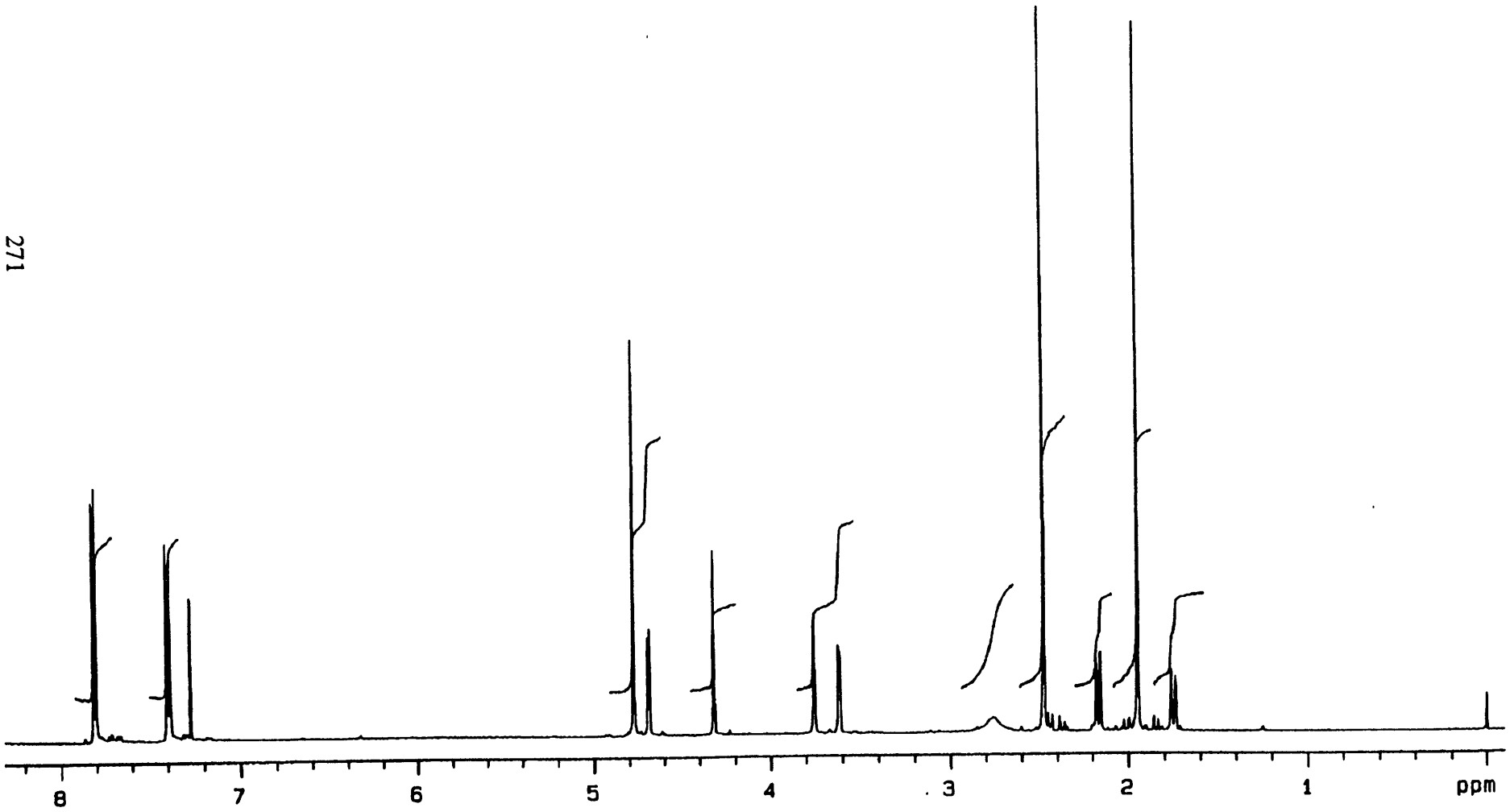
IR ($CHCl_3$) 3020, 1780, 1740, 1380, 1320, 1180, 1055 cm^{-1}

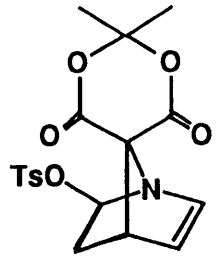
^{1}H NMR (300MHz, $CDCl_3$) δ 1.71 (s, 3 H), 1.94 (dd, *J* = 12.9, 6.7 Hz, 1 H), 2.21 (s, 3 H), 2.45 (s, 3 H), 2.66 (dtr, *J* = 12.9, 2.6 Hz, 1 H), 3.43 (tr, *J* = 3.0 Hz, 1 H), 5.23 (dd, *J* = 6.7, 2.4 Hz, 1 H), 6.04 (d, *J* = 3.8 Hz, 1 H), 6.65 (dd, *J* = 3.8, 3.0 Hz, 1 H), 7.34 (d, *J* = 7.9 Hz, 2 H), 7.76 (d, *J* = 8.3 Hz, 2 H)

^{13}C NMR (125 MHz, $CDCl_3$) δ 21.6, 26.7, 30.0, 30.5, 44.5, 82.3, 93.9, 108.3, 127.5, 129.8, 133.9, 134.5, 140.1, 145.1, 162.34, 162.32.

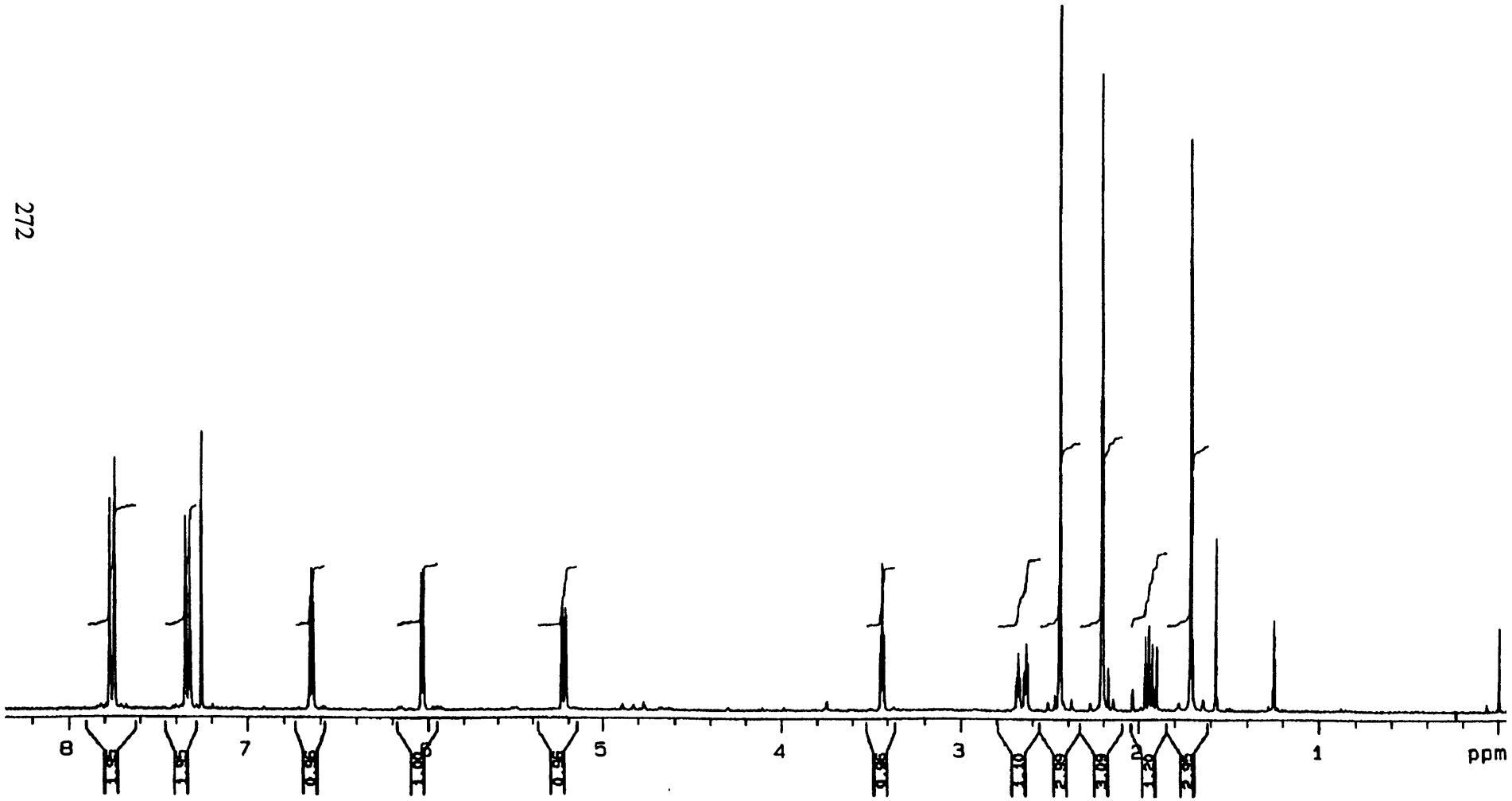


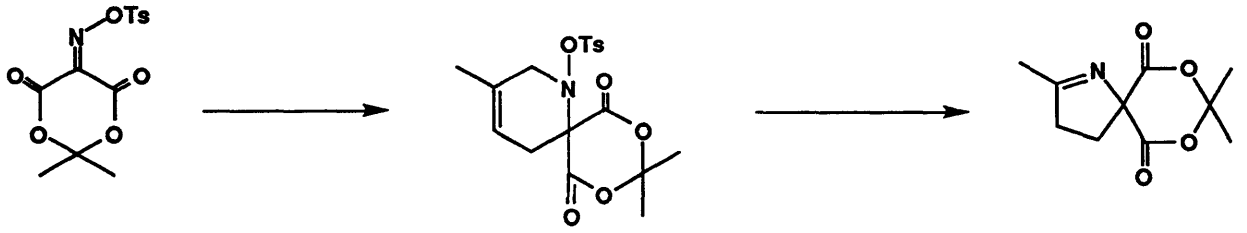
251





250





General Procedure for Two-Step Pyrroline Annulation. Preparation of 2,8,8-Trimethyl-6,10-dioxo-1-aza-7,9-dioxaspiro[4.5]dec-1-ene (247).

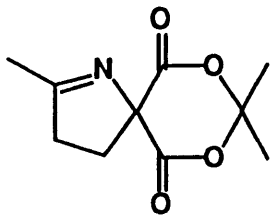
A 50-mL, three-necked, round-bottomed flask equipped with an argon inlet adapter, glass stopper, and rubber septum was charged with a solution of oximinosulfonate (**58**) (0.328 g, 1.00 mmol) and isoprene (0.204 g, 0.30 mL, 3.00 mmol) in 12 mL of dichloromethane. The solution was cooled at -78 °C while Me_2AlCl solution (1.0 M in hexane, 2.0 mL, 2.0 mmol) was added dropwise via syringe over 4 min. The resulting orange solution was stirred for 3 h at -78 °C to give a yellow solution and then quenched by the addition of 3 mL of saturated sodium potassium tartrate solution. The resulting mixture was allowed to warm to 0 °C, 20 mL of dichloromethane and 20 mL of water were added, and the aqueous phase was separated and extracted with three 20-mL portions of dichloromethane. The combined organic phases were washed with 30 mL of saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated to provide the crude cycloadduct as a yellow foam.

A 100-ml, one-necked, round-bottomed flask equipped with an argon inlet adapter and reflux condenser was charged with a solution of the crude cycloadduct in 21 mL of acetonitrile and 2.5 mL of pH 7 phosphate buffer (NaH_2PO_4/Na_2HPO_4). The resulting solution was heated at 80 °C for 30 min, allowed to cool to room temperature, and concentrated to a volume of ca. 2 mL. The resulting residue was diluted with 15 mL of dichloromethane and 15 mL of water, and the aqueous phase was separated and extracted with three 20-mL portions of dichloromethane. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated onto 1 g of deactivated silica gel. The free-flowing powder was placed on a column of 10 g of deactivated

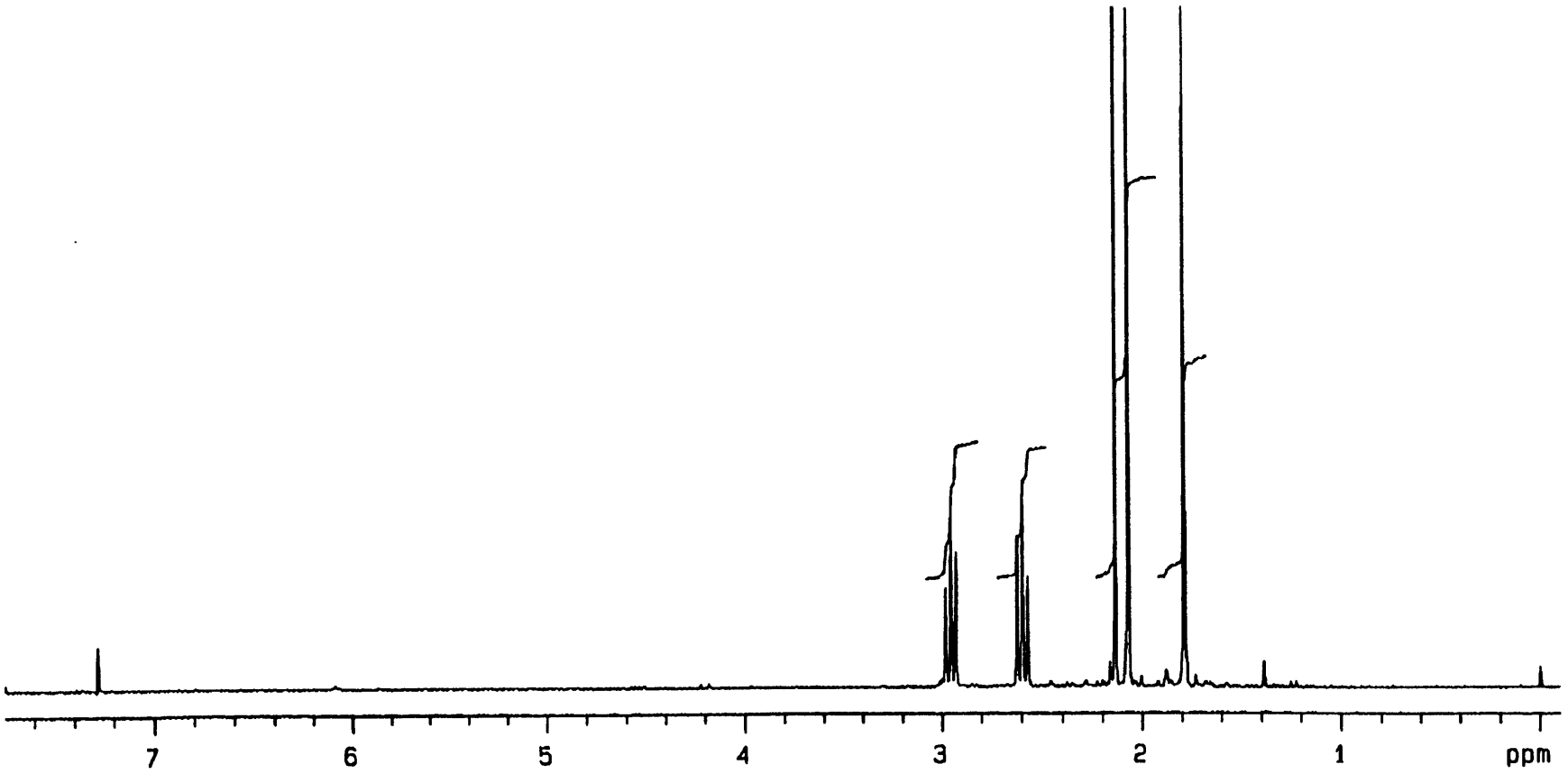
silica gel and eluted with 0-25% ethyl acetate-hexane to provide 0.089 g (42%) of the pyrroline **247** as a colorless oil.

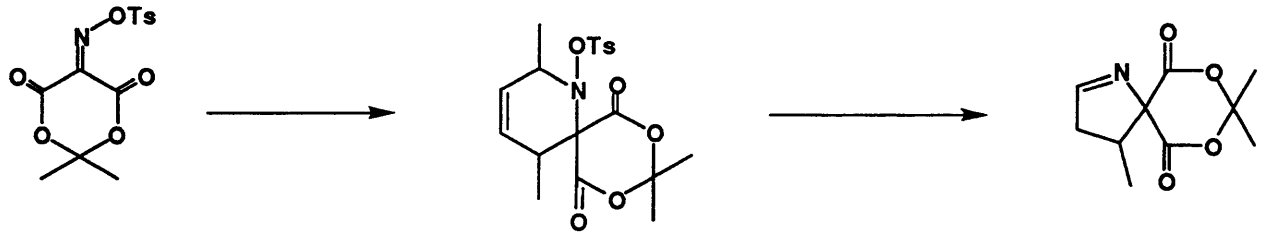
pyrroline 247:

IR ($CHCl_3$)	3015, 1745, 1635, 1300 cm^{-1}
^1H NMR (300 MHz, $CDCl_3$)	δ 1.78 (s, 3 H), 2.05 (s, 3 H), 2.12 (s, 3 H), 2.58 (tr, J = 7.5 Hz, 2 H), 2.94 (tr, J = 7.5 Hz, 2 H)
^{13}C NMR (75 MHz, $CDCl_3$)	δ 19.5, 28.5, 28.8, 31.7, 41.5, 81.0, 106.4, 167.7, 183.2.



247

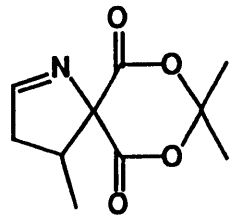




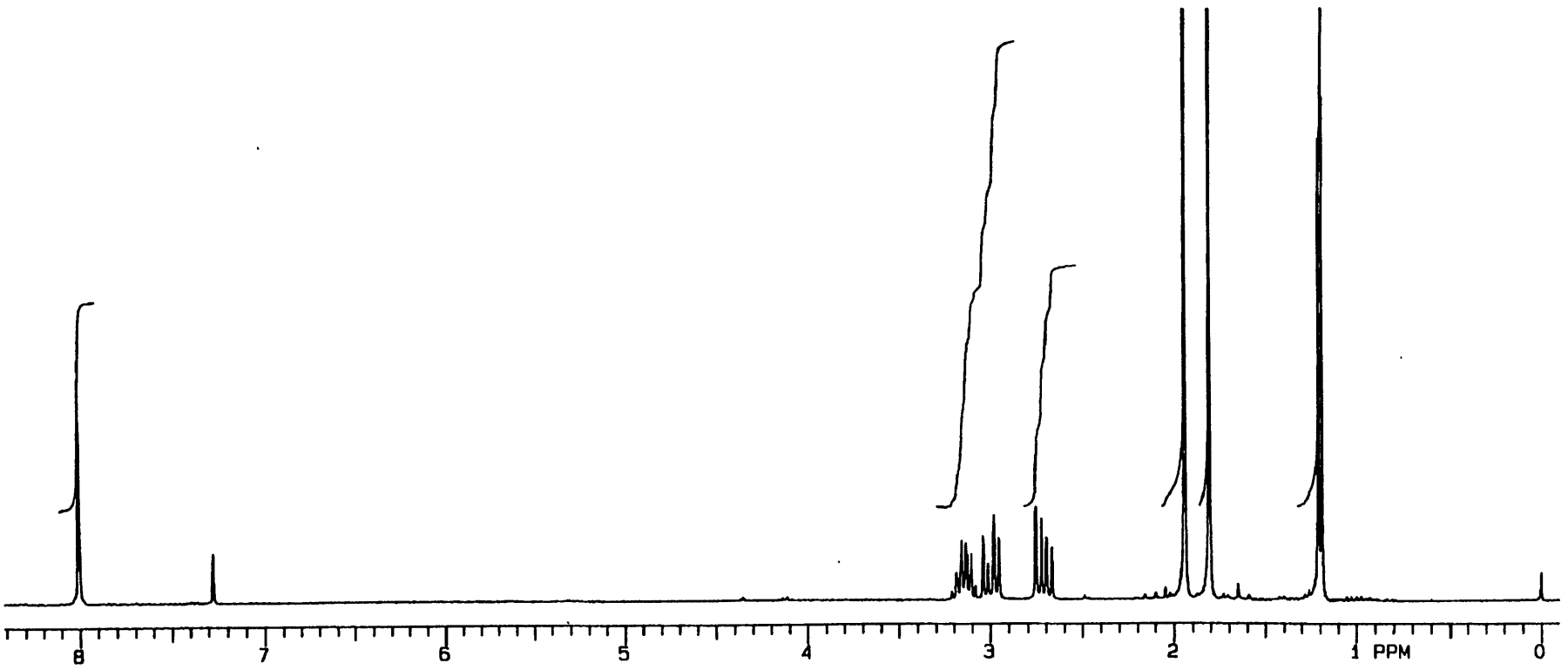
4,8,8-Trimethyl-6,10-dioxo-1-aza-7,9-dioxaspiro[4.5]dec-1-ene (173).

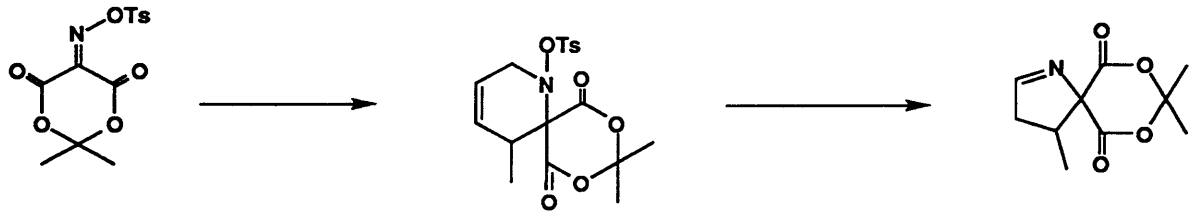
Reaction of oximinosulfonate (**58**) (0.328 g, 1.00 mmol) with *trans*-hexa-2,4-diene (0.246 g, 3.00 mmol) and Me_2AlCl (1.0 M in hexane, 2.0 mL, 2.0 mmol) in 12 mL of dichloromethane at -78 °C for 3 h according to the general procedure provided the crude cycloadduct as a yellow foam. Reaction of the crude cycloadduct with 20 mL of acetonitrile and 2.5 mL of pH 7 phosphate buffer at 80 °C for 10 min according to the general procedure furnished 0.073 g (35%) of pyrroline **173** as a white solid: mp 102-106 °C.

IR ($CHCl_3$)	2990, 1780, 1745, 1620 cm^{-1}
^1H NMR (300 MHz, $CDCl_3$)	δ 1.18 (d, J = 7.2 Hz, 3 H), 1.79 (s, 3 H), 1.93 (s, 3H), 2.69 (dd, J = 17.4, 9.0 Hz, 1 H), 2.98 (dd, J = 18.6, 8.7 Hz, 1 H), 3.12 (m, 1 H), 7.99 (s, 1 H)
^{13}C NMR (75 MHz, $CDCl_3$)	δ 14.1, 27.8, 29.8, 42.5, 45.6, 83.1, 106.0, 165.1, 168.2, 175.5.



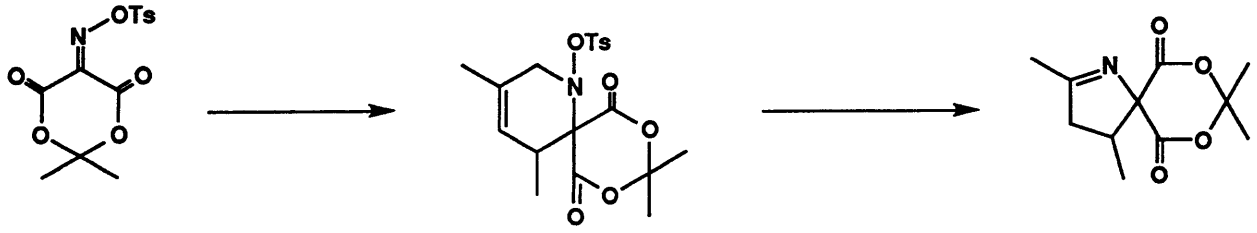
173





4,8,8-Trimethyl-6,10-dioxo-1-aza-7,9-dioxaspiro[4.5]dec-1-ene (173).

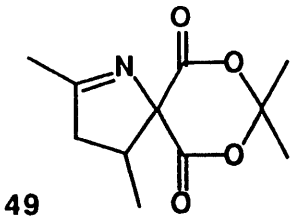
Reaction of oximinosulfonate (**58**) (1.22 g, 3.73 mmol) with penta-1,3-diene (0.761 g, 11.2 mmol) and Me_2AlCl (1.0 M in hexane, 7.5 mL, 7.5 mmol) in 37 mL of dichloromethane at -78 °C for 3 h according to the general procedure provided 1.15 g (78%) of the cycloadduct **160** as a white foam after purification by column chromatography. Reaction of cycloadduct **160** (0.337 g, 0.85 mmol) with 19 mL of acetonitrile and 2.0 mL of pH 7 phosphate buffer at 80 °C for 2 h according to the general procedure furnished 0.053 g (24% overall from **58**) of pyrroline **173** as a white solid with spectral characteristics identical to **173** obtained from pyrroline annulation with *trans,trans*-hexa-2,4-diene.



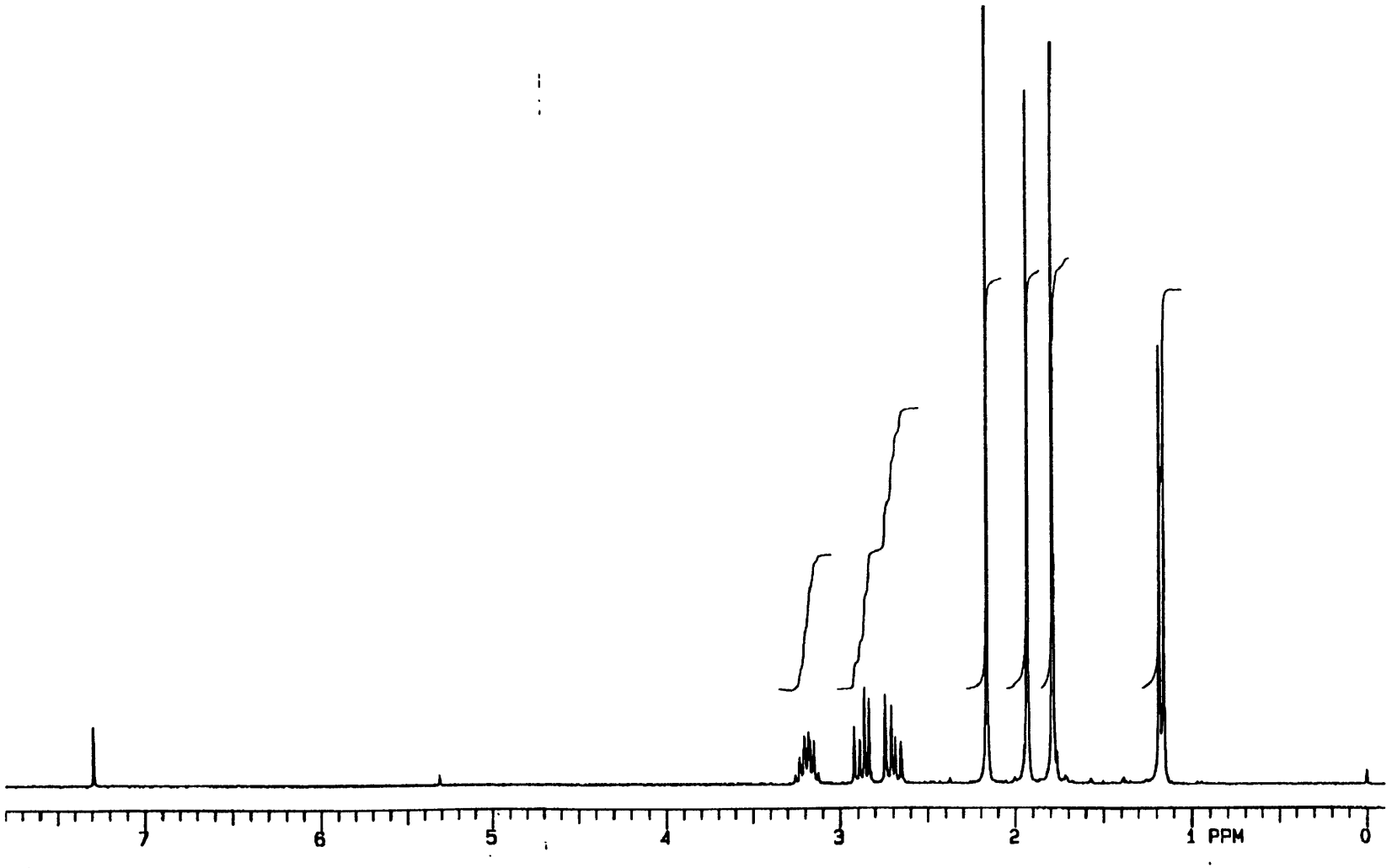
2,4,8,8-Tetramethyl-6,10-dioxo-1-aza-7,9-dioxaspiro[4.5]dec-1-ene (249).

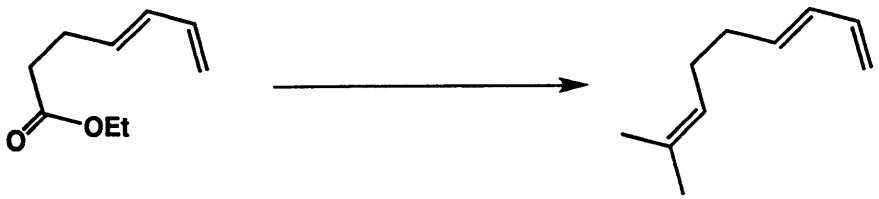
Reaction of oximinosulfonate (**58**) (0.328 g, 1.00 mmol) with a 70:30 mixture of *trans*-2-methylpenta-1,3-diene and 4-methylpenta-1,3-diene (0.329 g, 4.00 mmol) and Me_2AlCl (1.0 M in hexane, 2.0 mL, 2.0 mmol) in 12 mL of dichloromethane at -78 °C for 1 h according to the general procedure provided the crude cycloadduct as an orange foam. Reaction of the crude cycloadduct with 21 mL of acetonitrile and 2.5 mL of pH 7 phosphate buffer at 80 °C for 45 min according to the general procedure furnished 0.102 g (45%) of pyrroline **249** as a white solid: mp 108-109 °C.

IR ($CHCl_3$)	2990, 1780, 1750, 1630 cm^{-1}	
^1H NMR (300 MHz, $CDCl_3$)	δ 1.14 (d, J = 6.9 Hz, 3 H), 1.76 (s, 3 H), 1.90 (s, 3 H), 2.14 (s, 3 H), 2.76 (dd, J = 16.8, 9.6 Hz, 1 H), 2.85 (dd, J = 16.8, 8.4 Hz, 1 H), 3.16 (m, 1H)	
^{13}C NMR (75 MHz, $CDCl_3$)	δ 14.2, 20.1, 27.8, 29.9, 44.1, 47.4, 83.1, 105.8, 165.9, 168.8, 184.9.	
Elemental Analysis	Calcd for $C_{11}H_{15}NO_4$:	C, 58.66; H, 6.71; N, 6.22
	Found:	C, 58.79; H, 6.68; N, 6.02



249





8-Methyl-nona-1,3(*E*),7-triene (186).

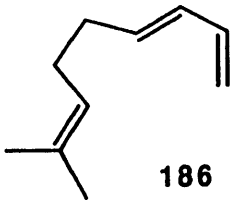
A 250-mL, three-necked, round-bottomed flask equipped with argon inlet adapter, septum, and glass stopper was charged with isopropyltriphenylphosphonium iodide (2.49 g, 5.76 mmol) and 50 mL of THF. The resulting yellow suspension was cooled at 0 °C while n-BuLi (2.4 mL, 2.35 M in hexanes, 5.55 mmol) solution was added dropwise via syringe over 10 min. The resulting red solution of the ylide was then stirred at 0 °C for 2 h.

A 50-mL, three-necked, round-bottomed flask equipped with argon inlet adapter, septum, and glass stopper was charged with the ester X (0.883 g, 5.76 mmol) and 10 mL of toluene. The solution was cooled at -78 °C while diisobutylaluminum hydride (5.80 mL, 1.0 M in hexanes, 5.76 mmol) solution was added slowly via syringe along the inside of the reaction flask. The reaction mixture was stirred at -78 °C for 20 min and then quenched by the addition of 5 mL of saturated sodium potassium tartrate solution. After warming to ca. 0 °C, the mixture was filtered through celite with the aid of 30 mL of Et_2O. The combined solution was then diluted with 10 mL H_2O, the layers separated, and the aqueous phase extracted with two 40-mL portions of Et_2O. The combined organic phases were washed with 30 mL of saturated NaCl solution, dried over $MgSO_4$, filtered and concentrated to afford 1.03 g of the crude aldehyde intermediate.

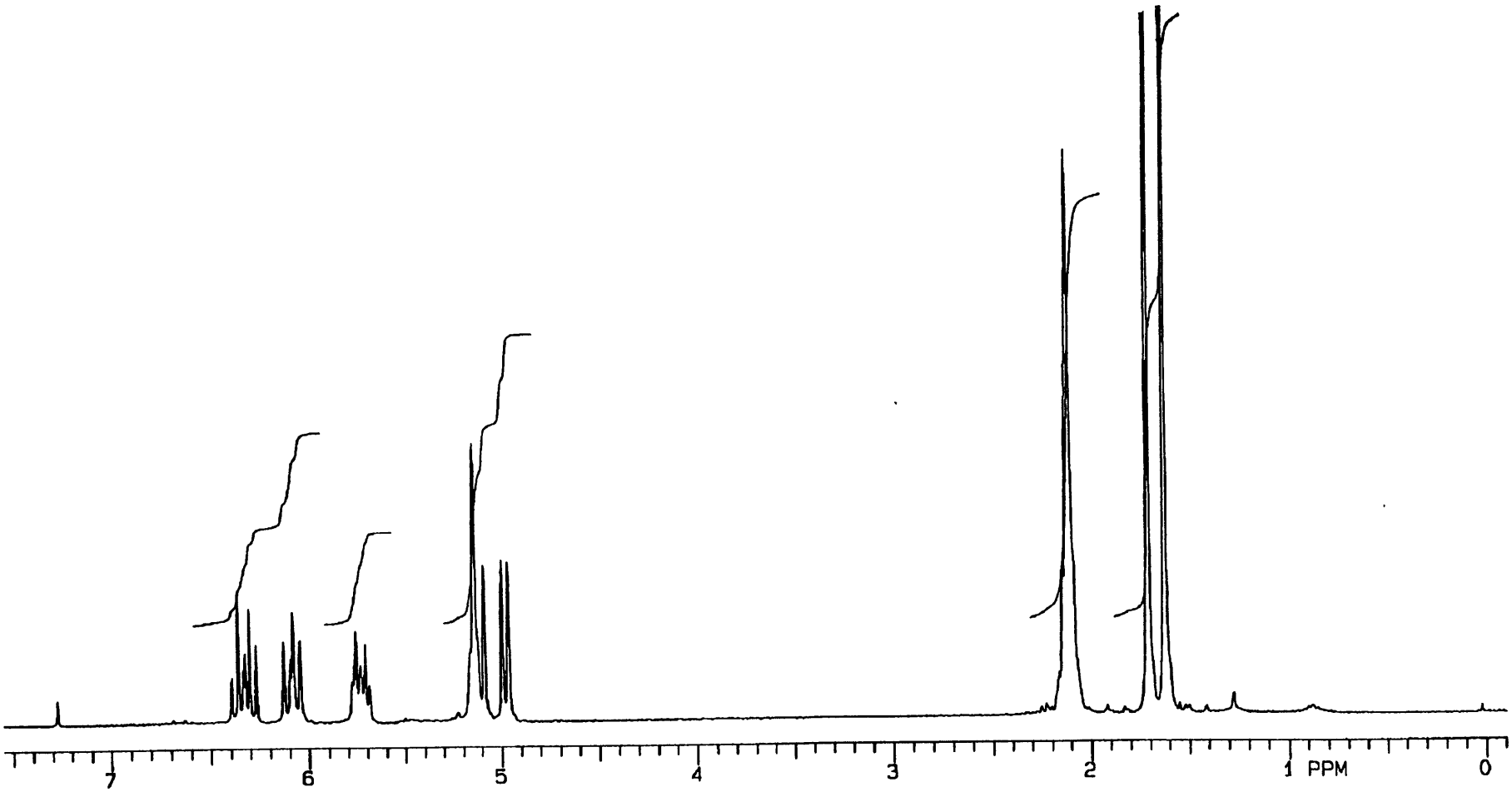
A 50-mL, one-neck, round-bottomed flask equipped with and argon inlet needle and septum was charged with the crude aldehyde and 30 mL of THF. The solution was then added dropwise via cannula to the ylide solution over 10 min to give a red-orange suspension. After stirring for 30 min at 0°C and 1 h at room temperature, the reaction mixture was quenched by the addition of 30 mL of a saturated NH_4Cl solution to give a white suspension. 30 mL of H_2O was then added and the aqueous phase extracted with three 50-mL portions of Et_2O. The combined organic phases were washed with 50 mL of H_2O, 50 mL of saturated NaCl solution, dried over

$MgSO_4$, filtered, and concentrated to give a mixture of a white solid and a pale yellow oil. The oil was separated from the solid with the aid of several 5-mL portions of pentane and the combined pentane phases were concentrated. Two chromatographic separations with 20 g and 12 g of silica gel respectively (elution with pentane) provided 0.467 g (62% overall) of the diene **186** as a colorless oil.

IR (thin film)	2965, 2920, 1600, 1445, 1380, 1005, 955, 900 cm^{-1}
^1H NMR (300 MHz, $CDCl_3$)	δ 1.63 (s, 3 H), 1.71 (s, 3 H), 2.06-2.15 (m, 4 H), 4.98 (d, J = 10.2 Hz, 1 H), 5.11 (d, J = 17.0 Hz, 1 H), 5.14 (br s, 1 H), 5.68-5.76 (m, 1 H), 6.09 (dd, J = 10.4, 15.0 Hz, 1 H), 6.33 (ddd, J = 10.0, 10.2, 16.9 Hz, 1 H)
^{13}C NMR (75 MHz, $CDCl_3$)	δ 17.7, 25.7, 27.8, 32.8, 114.7, 123.8, 131.0, 131.9, 135.1, 137.3



186



Density and pressure effects on the rate of the Diels-Alder reaction of ethyl acrylate and cyclopentadiene in scCO$_2$.

All reactions were performed in a 1-L, stirred stainless-steel (33-316) autoclave (Autoclave Engineers model HT-60771(316) with MagneDriveII agitation). The reactant feed and sampling techniques were designed on the basis of methods reported by other investigators.[203] Cyclopentadiene was freshly prepared before use by thermal cracking of the dimer. Ethyl acrylate was distilled (1 atm) before each run. *p*-Dimethoxybenzene was used as an internal standard.

In a typical experiment, cyclopentadiene (6.65 g, 101 mmol) and ethyl acrylate (9.24 g, 92.3 mmol) were placed in separate feed lines isolated from the system. *p*-Dimethoxybenzene (1.68g, 12.2 mmol) was placed directly in the autoclave which was sealed and flushed with CO_2. The vessel was preheated and brought up to pressure, the reactants being introduced a few (5-10) minutes before the desired pressure was attained. Samples were taken by isolating 10 mL of the reaction mixture in a sample line and slowly releasing pressure by bubbling through acetone. The sample line was then flushed with acetone and low pressure CO_2. Control experiments established the accuracy and reliability of this sampling procedure.

Generally, 12 samples were collected at 6 times during a kinetics run that typically spanned 2 days. The second sample taken at each time was taken to be most representative of the reaction mixture and was analyzed. Analysis of the products was carried out as follows. The acetone solution of products was filtered through a fritted funnel and volatiles removed by rotary evaporation (5-20 mmHg). The residue was taken into $CDCl_3$ and analyzed by ^1H NMR (300 MHz, Varian XL-300). Comparison of the integrated signals of product and internal standard

---

203 (a) Kim, S.; Johnston, K. P. *Chem. Eng. Commun.* **1988**, *63*, 49. (b) McHugh, M.; Paulaitis, M. E. *J. Chem. Eng. Data* **1980**, *25*, 326.

allowed for the calculation of the amount of product formed at the time of sampling. A bimolecular rate constant was then calculated as shown below.

$$\frac{d[P]}{dt} = k[A][B] \qquad A = \text{cyclopentadiene};\ B = \text{ethyl acrylate}$$

$$\xi = \frac{[B]_0 - [B]_t}{[B]_0} \qquad r = \frac{[A]_0}{[B]_0}$$

$$[A]_t = [B]_0(r-\xi) \qquad [B]_t = [B]_0(1-\xi) \qquad [P]_t = [B]_0\xi$$

so

$$\frac{d\xi[B]_0}{dt} = k[B]_0(r-\xi)[B]_0(1-\xi) \qquad \text{or} \qquad \frac{d\xi}{(r-\xi)(1-\xi)} = k[B]_0 dt$$

which can be converted to

$$d\xi\left[\frac{1}{r-1}\right]\left[\frac{1}{1-\xi} - \frac{1}{r-\xi}\right] = k[B]_0 dt$$

integration of which gives...

$$\left[\frac{1}{r-1}\right]\left[\ln\frac{r-\xi}{1-\xi} - \ln r\right] = k[B]_0 t \quad \text{or} \quad \ln\frac{r-\xi}{1-\xi} = (r-1)k[B]_0 t + \ln r$$

which is of the form $y = mx + b$ and can be used to calculate the rate constant k.

rate data

rate vs pressure

pressure (bar)	k * 10^5 (L/mmol h)
80.7	2.81
86.9	3.13
104.1	3.19
104.1	3.22
108.9	3.42
164.1	3.65
210.2	4.03

rate vs density

density (g/mL	k * 10^5 (L/mmol h)
0.330	2.81
0.497	3.13
0.657	3.19
0.657	3.22
0.667	3.42
0.809	3.66
0.858	4.03

Arrhenius data

1000/T (K^{-1})	ln(k)
2.77	-8.01
2.86	-8.67
3.09	-9.41
3.21	-10.4

normalized rate constants

38 °C

density (g/mL)	$\ln(k/k_0)$
0.330	-0.108
0.497	0
0.657	0.0198
0.657	0.0297
0.667	0.0902
0.809	0.157
0.858	0.254

50 °C

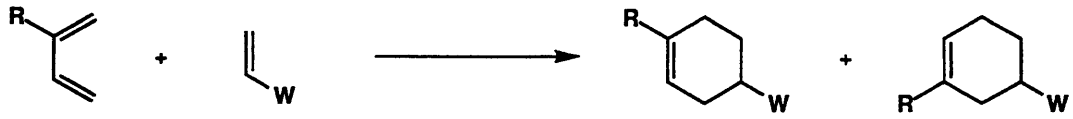
density (g/mL)	$\ln(k/k_0)$
0.408	-0.109
0.497	0
0.667	0.0998

76.5 °C

density (g/mL)	$\ln(k/k_0)$
0.239	-0.0989
0.458	0

88°C

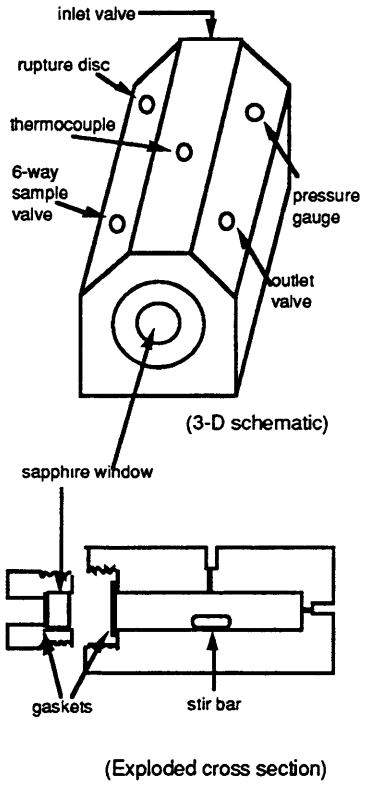
density (g/mL)	$\ln(k/k_0)$
0.215	-0.323
0.499	



R = Me, *t*-Bu, Me_3SiO
W = CO_2Me, NO_2

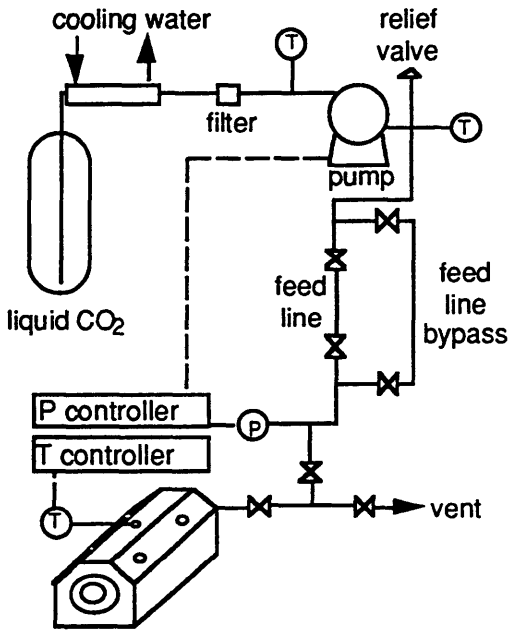
Studies of the regiochemical course of Diels-Alder reactions in $scCO_2$.

Reactor Design. The reactor (see below) has a working volume of 25 mL and is constructed of 316 stainless steel with a design similar to that in use at Los Alamos National Laboratory.[204] The temperature limits of our reactor have been increased by substituting copper gaskets for polymeric ones in the window seals and using taper seals (High Pressure Equipment Company) in the body of the reactor. These improvements have allowed for reaction temperatures up to 250 °C and pressures to 250 bar (or as high as 350 bar at ambient temperature).



[204] Morgenstern, D. A.; LeLacheur, R. M.; Morita, D. K.; Borkowsky, S. L.; Feng, S.; Brown, G. H.; Luan, L.; Gross, M. F.; Burk, M. J.; Tumas, W. *ACS Symp. Ser.* **1996**, *626*, 132.

Sample Introduction. A flow diagram for our system is shown below. Reactants are sealed in oven-dried glass ampoules and placed in the reactor along with a magnetic stirbar. After heating to the desired temperature, pressurization of the vessel with CO_2 causes the ampoules to rupture while the stirbar ensures efficient mixing of the reactants. Alternatively, reactants may be placed directly in the reactor or in feed lines, isolated from the system. Upon pressurization, CO_2 passes though the feed lines and into the reactor. All three feed methods were shown to give reliable results. Representative procedures for the three methods used are given below.

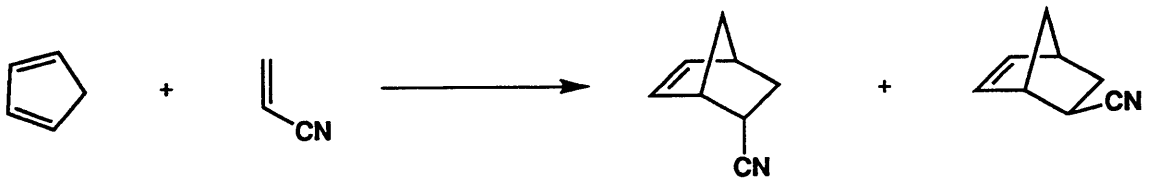


Representative Procedure (Ampoules Method). This procedure was used for entries 9, 10, 13, 14, 17 and 18 (Table 6). Methyl acrylate (0.344 g, 4.0 mmol) and 2-*t*-butyl-1,3-butadiene (0.440 g, 4.0 mmol) were placed in separate oven-dried ampoules and sealed under argon. The ampoules were placed in the reactor (predried at 120 °C under positive argon pressure) along with a magnetic stirbar. The reactor was sealed, placed on a stirplate, and wrapped with heating tape. Low pressure CO_2 was passed through the system while the temperature was raised to 50 °C over 8 min. The reactor was then pressurized causing the ampoules to burst. After 3 days at 50 °C and 117 bar, the pressure in the reactor was slowly released through a long narrow tube, the end of

which was immersed in ca. 70 mL of diethyl ether. Additional ether (ca. 30 mL) was used to rinse the inside of the reactor and the sampling tube. The combined ether solutions were dried over $MgSO_4$, filtered, and concentrated at ca. 20 mmHg to provide 0.031 g (4%) of a colorless oil. ^1H NMR and GC analyses revealed cycloadducts **272** and **273** in ratios of 69:31 and 68:32, respectively.

Representative Procedure (Direct Feed Method). This procedure was used for large scale reactions (entries 3-6). Methyl acrylate (1.26 g, 14.6 mmol) and isoprene (1.99 g, 29.2 mmol) were placed in the predried reactor along with a stirbar. The system was sealed, briefly flushed with CO_2, and then heated to 50 °C. The reactor was then pressurized, the reaction was carried out for the required time, and the products were then isolated and analyzed as described above.

Representative Procedure (Feed Line Method). This method was used (entries 11, 15) when significant polymerization or degradation of the reactants took place during the reactor heat up period. Methyl acrylate (0.344 g, 4.0 mmol) and 2-*t*-butyl-1,3-butadiene (0.440 g, 4.0 mmol) were placed in a feed line connected to the predried reactor (see Figure 2). Low pressure CO_2 was flushed through the system via the feed line bypass, while the temperature was raised to 150 °C. The reactor was then pressurized by directing the CO_2 through the feed line. The reaction was carried out for the desired time and the products were then isolated and analyzed as described above.



Studies of pressure and density effects on the stereoselectivity of the Diels-Alder reaction of acrylonitrile and cyclopentadiene in $scCO_2$.

In these studies, we used the same view-cell reactor as was used in our studies of the regiochemical course of Diels-Alder reactions in $scCO_2$. Acrylonitrile (0.132 g, 0.16 mL, 2.5 mmol) and cyclopentadiene (0.248 g, 0.31 mL, 3.8 mmol) were placed in separate oven-dried ampoules and sealed under argon. The ampoules were placed in the reactor (predried at 120 °C under positive argon pressure) along with a magnetic stirbar. The reactor was sealed, placed on a stirplate, and wrapped with heating tape. Low pressure CO_2 was passed through the system while the temperature was raised to 50 °C over 8 min. The reactor was then pressurized causing the ampoules to burst. After 24 h at 50 °C, the pressure in the reactor was slowly released through a long narrow tube, the end of which was immersed in ca. 70 mL of dichloromethane. Additional dichloromethane (ca. 30 mL) was used to rinse the inside of the reactor and the sampling tube. The *endo*:*exo* ratio (**278**:**279**) was then determined by GC analysis.

selectivity data

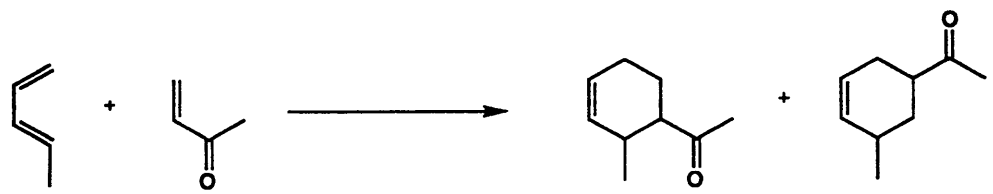
pressure (bar)	*% endo*
82.1	56.4
82.8	55.2
89.7	54.4
103.4	53.3
103.4	53.0
135.2	54.2

135.2	53.7
165.5	54.0
206.7	54.9
241.4	55.5
300.0	56.0

Representative procedure for silica-promoted reactions in $scCO_2$. Reaction of methyl vinyl ketone and penta-1,3-diene. This procedure was used for the Diels-Alder reactions presented in Tables 7 and 8. Methyl vinyl ketone (0.175 g, 2.5 mmol) and penta-1,3-diene (0.225 g, 3.75 mmol) were placed in separate oven-dried ampoules and sealed under argon. The ampoules were placed in the reactor (predried at 120 °C under positive argon pressure) along with silica (0.50 g), *p*-dimethoxybenzene (an internal standard), and a magnetic stirbar. The reactor was sealed, placed on a stirplate, and wrapped with heating tape. Low pressure CO_2 was passed through the system while the temperature was raised to 50 °C over 8 min. The reactor was then pressurized causing the ampoules to burst and the temperature increased to 80 °C. After 24 h at 80 °C and 103 bar, the pressure in the reactor was slowly released through a long narrow tube, the end of which was immersed in ca. 70 mL of ethyl acetate. Additional ethyl acetate (ca. 30 mL) was used to rinse the inside of the reactor and the sampling tube. Ca. 30 mL of this ethyl acetate solution was passed through a 0.2 μm filter, dried over $MgSO_4$, filtered, and concentrated. Comparison of the integrated ^1H NMR signals for cycloadduct and internal standard allowed a yield to be calculated.

General procedure for the preparation of protic and Lewis acid-doped silica promoters. Preparation of H_3PO_4-SiO_2.

A 200-mL one-necked, round-bottomed flask was charged with silica (25 g, dried) and 70 mL of dichloromethane. The resulting suspension was stirred at room temperature while phosphoric acid (85%, 4.6 g, 2.7 mL, 15 M, 40 mmol) was added dropwise over 2 min. The suspension was stirred for 30 min and then concentrated (on the rotary and then at 0.1 mmHg for 2 h) to give ca. 30 g a free-flowing powder with ca. 1.35 mmol of H_3PO_4 per gram of solid.



General procedure for Diels-Alder reactions on the surface of doped promoters. Preparation of 286 and 287.

A threaded Pyrex tube (ca. 10 mL volume) was charged with methyl vinyl ketone (0.11 g, 0.13 mL, 1.5 mmol) and penta-1,3-diene (0.15 g, 0.22 mL, 2.25 mL). To this solution at room temperature was added H_3PO_4-SiO_2 (1.10 g, 1.35 mmol/g, 1.5 mmol) and the tube was sealed and shaken for ca. 2 min to give a free-flowing powder. After 30 min at room temperature, the tube was opened and the orange solid placed directly onto a column of 10 g silica gel and eluted with 5% Et_2O-1%Et_3N hexane to provide 0.172 g (83%) of **286** and **287** (99:1) as a colorless oil with spectral characteristics consistent with those reported previously.[193]