[4+2] CYCLOADDITIONS OF IMINOACETONITRILES: A GENERAL STRATEGY FOR THE SYNTHESIS OF QUINOLIZIDINES, INDOLIZIDINES, AND PIPERIDINES

By

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By

Kevin Matthew Maloney

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ABSTRACT

Iminoacetonitriles participate as reactive dienophiles in intermolecular and intramolecular Diels-Alder cycloadditions leading to quinolizidines, indolizidines, and piperidines. The resultant α-amino nitrile cycloadducts are versatile synthetic intermediates which can be further elaborated by stereoselective alkylation, reduction, reductive cyclization, and Bruylants reactions. The first part of this thesis describes the full details of our studies on the synthesis of iminoacetonitriles, the scope of their Diels-Alder reactions, and the synthetic elaboration of the α-amino nitrile cycloadducts to provide access to a variety of substituted quinolizidine and indolizidine derivatives. The second part of this thesis reports on the total synthesis of quinolizidine (–)-217A and our efforts directed toward the total synthesis of indolizidine (–)-235B′.

Thesis Supervisor: Rick L. Danheiser

Title: Professor of Chemistry

Acknowledgments

All acknowledgments must begin with my thesis advisor Rick Danheiser. I will forever be grateful to Rick for allowing me to join his laboratory and helping me become a better chemist. I continue to be amazed not only be the extent of his knowledge, but also by his ability to explain complex topics in a simple and straightforward manner. Besides being a great advisor, Rick has also been a great friend. I will definitely miss our weekly (sometimes daily) discussions about the Red Sox and Patriots. Also, I would like to thank Rick for being an amazing pitcher the past three years on Toxic Waste. Without his consistent domination on the mound, we never would have won three straight MIT softball championships.

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I owe a debt of gratitude to my parents for their unending support and encouragement. Thank you so much! You are wonderful parents and I wouldn't be where I am today without your love and support.

Last, but not least, I would like to thank Venda, Coors, and Coconut for their friendship and love. Coors has been my best friend for the past seven years and I would not have survived graduate school without his companionship. Most importantly, I would like to thank my girlfriend, Venda, for her love and support, and I am looking forward to starting a new life with her in New Jersey.

Table of Contents

Part I

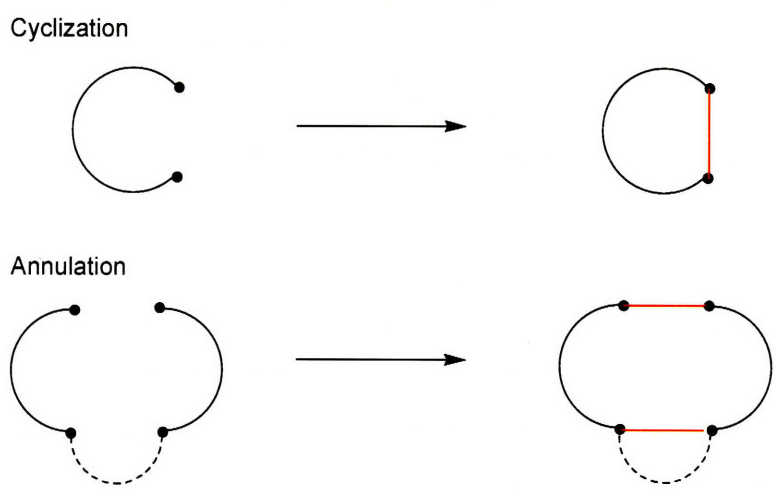
Introduction and Background

Chapter 1 – Introduction

Cyclization and Annulation Strategies

The vast number of natural products and pharmaceutical agents that contain a ring system has motivated our research group's interest in developing practical, reliable, and efficient methods for the preparation of cyclic and polycyclic molecules. Cyclizations and annulations[1] represent the two general strategies for constructing cyclic systems (Scheme 1). A cyclization strategy involves the intramolecular formation of *one new bond* whereas an annulation strategy involves the formation of *two new bonds* in either an intramolecular or intermolecular fashion to form the cyclic structure. With the formation of two new bonds, annulations provide a more convergent and powerful strategy than cyclizations for the synthesis of cyclic compounds. Annulation strategies also provide the possibility of creating multiple stereocenters in a single step, and intramolecular versions allow for the efficient and rapid assembly of *polycyclic* systems.

Scheme 1

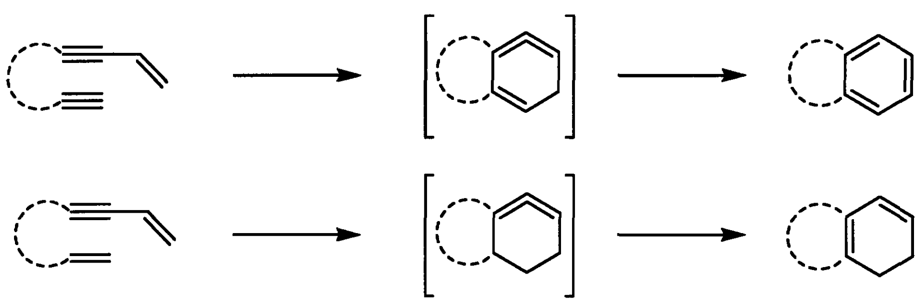


[1] For the definition of an annulation, see Danheiser, R. L.; Gee, S. K.; Sard, H. *J. Am. Chem. Soc.* **1982**, *104*, 7670.

Cycloadditions of Conjugated Enynes

Cycloaddition reactions comprise the most common type of annulation and rank among the most powerful transformations available to synthetic chemists.[2] The Diels-Alder cycloaddition, first reported in 1928 by Otto Diels and Kurt Alder,[3] is perhaps the most important of all six-membered ring-forming reactions and has been widely employed as the pivotal step in numerous natural product syntheses.[4] The [4+2] cycloaddition reaction of dienes and "dienophiles," each of which can incorporate a wide range of functionality, allows access to a diverse range of carbocyclic and heterocyclic molecules. In recent years, our laboratory has explored the possibility of reacting an enyne with an enynophile, in a process akin to the Diels-Alder cycloaddition, to form new aromatic and dihydroaromatic systems (Scheme 2).

Scheme 2



Despite a few scattered reports in the literature describing intramolecular [4+2] cycloadditions of conjugated enynes, the generality and scope of this fascinating reaction remained undefined until our laboratory began to investigate this transformation as an efficient route to highly substituted aromatic and heteroaromatic compounds. In 1994, our laboratory was the first to report studies that established the feasibility of these cycloadditions as a practical

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[2] Carruthers, W. *Cycloaddition Reactions in Organic Synthesis*; Pergamon Press: New York, 1990.
[3] Diels, O.; Alder, K. *Liebigs Ann. Chem.* **1928**, *460*, 98.
[4] For reviews of the Diels-Alder reaction, see: (a) Fringuelli, F.; Taticchi, A. *The Diels-Alder Reaction: Selected Practical Methods*; John Wiley & Sons: New York, 2002. (b) Fringuelli, F.; Taticchi, A. *Dienes in the Diels-Alder Reaction*; John Wiley & Sons: New York, 1990. (c) Oppolzer, W. In *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I. Eds.; Pergamon Press: Oxford, 1991, Vol. 5, pp 315-399.

method for organic synthesis and discussed possible mechanisms for these reactions.[5] Subsequent work in our group has demonstrated that enyne cycloadditions can be conducted under thermal conditions, as well in the presence of protic and Lewis acids, with a variety of substituents on the enyne, enynophile, and connecting tether.[6]

Our laboratory has also investigated the possibility of incorporating a heteroatom into the enyne or enynophile in variants of the cycloaddition leading to heterocyclic molecules. Initially, we explored the feasibility of replacing a carbon atom in the enyne with an oxygen atom as shown in eq 1. Melanie Wills discovered that the [4+2] cycloaddition of conjugated alkynyl carbonyl compounds provides access to dihydroisobenzofurans with a variety of functionality (eq 1).[7]

(1)

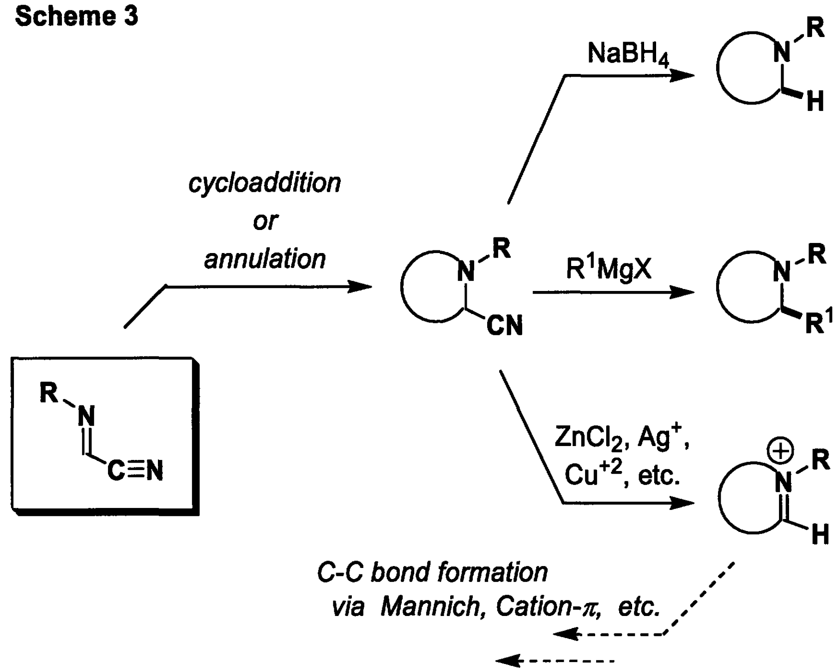
Next, we became interested in the development of new types of activated imine derivatives with the ability to function as reactive 2π components. For example, the ability to use an imine as a reactive 2π component would allow access to substituted nitrogen heterocycles and would provide a powerful extension of the scope of the enyne cycloaddition.

Examination of the literature on activated imines that participate in related cycloadditions revealed that none of the conventional imine derivatives were ideal for the enyne cycloadditions we envisioned.[8] We consequently turned our attention to *iminoacetonitriles*, a class of electron-deficient imines whose cycloaddition chemistry had not previously been examined. Our interest

[5] Danheiser, R. L.; Gould, A. E.; Fernandez de la Pradilla, R.; Helgason, A. L. *J. Org. Chem.* **1994**, *59*, 5514.
[6] (a) Dunetz, J. R.; Danheiser, R. L. *J. Am. Chem. Soc.* **2005**, *127*, 5776. (e) Hayes, M. E.; Shinokubo, H.; Danheiser, R. L. *Org. Lett.* **2005**, *7*, 3917.
[7] For a discussion regarding the scope and mechanism of this cycloaddition, see Wills, M. S. B.; Danheiser, R. L. *J. Am. Chem. Soc.* **1998**, *120*, 9378.
[8] For a discussion of [4+2] cycloadditions of imines, see Chapter 2.

in this class of imines derived from the expectation that they should function as reactive partners in a variety of cycloaddition and annulation processes, providing access to cyclic α-amino nitriles of diverse ring size (Scheme 3). α-Amino nitriles are exceptionally versatile intermediates for the synthesis of nitrogen heterocycles. Metalation provides opportunities for alkylation and other carbon-carbon bond-forming processes, while exposure to Lewis acids furnishes iminium ions which can be intercepted with Grignard reagents (Bruylants reaction) and organosilanes, or engaged in Mannich reactions and other useful "cation-π"-type cyclization processes.[9]

Scheme 3



In fact, it appeared to us that iminoacetonitriles would be a valuable 2π component in a variety of different annulation and cycloaddition processes including, in particular, the hetero Diels-Alder reaction. To place our work in perspective, the next chapter provides a brief

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[9] For reviews on the chemistry of α-amino nitriles, see: (a) Ender, D.; Shilvock, J. P. *Chem. Soc. Rev.* **2000**, *29*, 359. (b) Husson, H.-P.; Royer, J. *Chem. Soc. Rev.* **1999**, *28*, 383. (c) Shafran, Y. M.; Bakulev, V. A.; Mokrushin, V. S. *Russ. Chem. Rev.* **1989**, *58*, 148. (d) Rubiralta, M.; Giralt, E.; Diez, A. In *Piperidine: Structure, Preparation, Reactivity, and Synthetic Applications of Piperidine and its Derivatives*; Elsevier: Amsterdam, 1991; pp 225-312.

overview on the *state of the art* with regard to imino dienophiles in intramolecular and intermolecular aza Diels-Alder cycloadditions.

Chapter 2 – Diels-Alder Reactions of Imino Dienophiles

The development of imine derivatives as 2π components in aza Diels-Alder reactions has greatly facilitated the ease with which nitrogen heterocycles can be synthesized in an efficient manner.[10] This chapter provides a brief overview of the most commonly used imino dienophiles in intermolecular and intramolecular Diels-Alder cycloadditions. This discussion will emphasize the reactions of "activated" imines, since these imines tend to be the most reactive in hetero [4+2] cycloadditions. Although simple unactivated imines can participate as 2π components in Diels-Alder cycloadditions, these reactions often require harsh conditions and tend to be limited in substrate scope. The two general approaches employed to activate imine derivatives involve (a) attaching an electron-withdrawing group to the carbon and/or nitrogen of the imine, and (b) the use of the iminium ions as dienophiles.

Intermolecular Diels-Alder Reaction of Imino Dienophiles

The use of activated imines as dienophiles in the intermolecular Diels-Alder reaction has attracted considerable attention.[10] Among the most important classes of activated imino dienophiles are *N*-sulfonylimines (e.g., **1**),[11,12] *N*-acylimines (e.g., **2** and **3**),[13,14] *C*-acylimines

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[10] For reviews on the hetero Diels-Alder reaction of imino dienophiles, see: (a) Heintzelman, G. R.; Meigh, I. R.; Mahajan, Y. R.; Weinreb, S. M. *Org. React.* **2005**, *65*, 141. (b) Buonora, P.; Olsen, J.-C.; Oh, T. *Tetrahedron* **2001**, *57*, 6099. (c) Jørgensen, K. A. *Angew. Chem. Int. Ed.* **2000**, *39*, 3558.

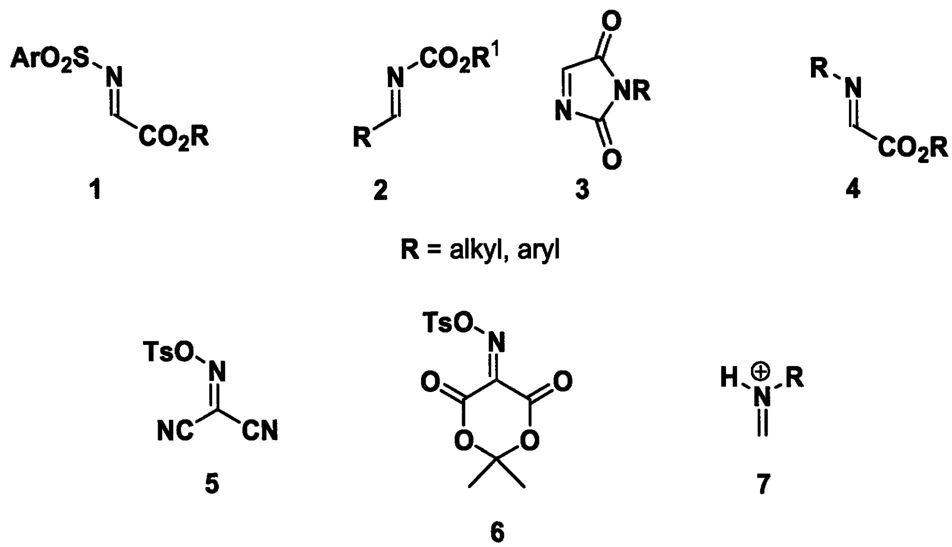
[11] (a) Kresze, G.; Albrecht, R. *Chem. Ber.* **1964**, *97*, 490. (b) Kresze, G.; Wagner, U. *Liebigs Ann. Chem.* **1972**, 762, *106*. (c) Albrecht, R.; Kresze, G. *Chem. Ber.* **1965**, *98*, 1431.

[12] For examples in total synthesis, see: (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.

[13] For examples of acyclic *N*-acylimines, see: (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.

[14] For examples of cyclic *N*-acylimines, see: (a) Goldstein, E.; Ben-Ishai, D. *Tetrahedron Lett.* **1969**, 2631. (b) Ben-Ishai, D.; Goldstein, E. *Tetrahedron* **1971**, *27*, 3119.

(e.g., **4**), oximino ester derivatives (e.g., **5**[15] and **6**[16]), and iminium ions (e.g., **7**).[17,18] Although several types of imino dienophiles exist for the aza Diels-Alder reaction, the most useful are the *C*-acylimines developed by Bailey and coworkers and these imines will be the focus of this section.



Bailey and coworkers have shown that the *C*-acylimine **9** represents the state of the art for imino dienophiles in terms of ease of synthesis, substrate scope, stereocontrol, and synthetic utility of the resulting Diels-Alder cycloadducts.[19] Imine **9** was synthesized in 94% yield as a stable white solid by simply stirring ethyl glyoxylate hydrate with benzhydrylamine (eq 2). Reaction of imine **9** with a variety of dienes in the presence of 1 equiv of TFA in trifluoroethanol delivers the desired cycloadducts **10-14** in 42-95% yield. In the case of acyclic dienes, the *endo*

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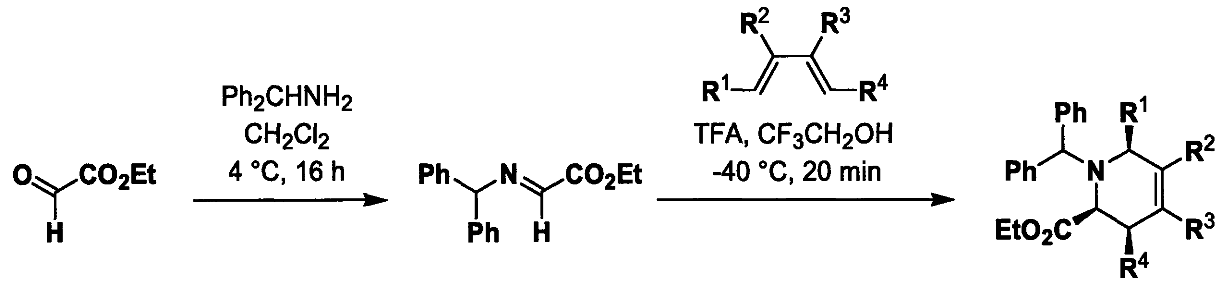
[15] (a) Biehler, J.-M.; Perchais, J.; Fleury, J.-P. *Bull. Soc. Chim. Fr.* **1971**, 2711. (b) Biehler, J.-M.; Fleury, J.-P. *J. Heterocycl. Chem.* **1971**, *8*, 431. (c) Perchais, J.; Fleury, J.-P. *Tetrahedron* **1972**, *28*, 2267. (d) Fleury, J.-P.; Desbois, M.; See, J. *Bull. Soc. Chim. Fr.* **1978**, II-147.
[16] (a) Renslo, A. R.; Danheiser, R. L. *J. Org. Chem.* **1998**, *63*, 7840. (b) Danheiser, R. L.; Renslo, A. R.; Amos, D. T.; Wright, G. T. *Org. Synth.* **2003**, *80*, 133.
[17] (b) Parker, D. T. In *Organic Synthesis in Water*; Grieco, P. A., Ed.; Blackie Academic & Professional: London, 1998; pp 47-81. (b) Larsen, S. D.; Grieco, P. A. *J. Am. Chem. Soc.* **1985**, *107*, 1768. (c) Grieco, P. A.; Larsen, S. D.; Fobare, W. F. *Tetrahedron Lett.* **1986**, *27*, 1975.
[18] For the use lanthanide(III) triflates as catalysts, see: (a) Yu, L.; Chen, D.; Wang, P.-G. *Tetrahedron Lett.* **1996**, *37*, 2169. (b) Zhang, W.; Xie, W.; Fang, J.; Wang, P. G. *Tetrahedron Lett.* **1999**, *40*, 7929. (c) Yu, L.-B.; Chen, D.; Li, J.; Ramirez, J.; Wang, P. G.; Bott, S. G. *J. Org. Chem.* **1997**, *62*, 208.
[19] Bailey, P. D.; Smith, P. D.; Pederson, F.; Clegg, W.; Rosair, G. M.; Teat, S. J. *Tetrahedron Lett.* **2002**, *43*, 1067.

cycloadduct is formed exclusively with complete regiocontrol. However, in the case of cyclic dienes (e.g., cyclopentadiene and cyclohexadiene), the *exo* cycloadduct is formed predominantly (>97:3). Also, reaction of imine **14** with *trans*-2,4-hexadiene occurs with suprafacial addition to give the *cis*-substitued cycloadduct **14** consistent with the Woodward-Hoffmann rules.[20]



(2)

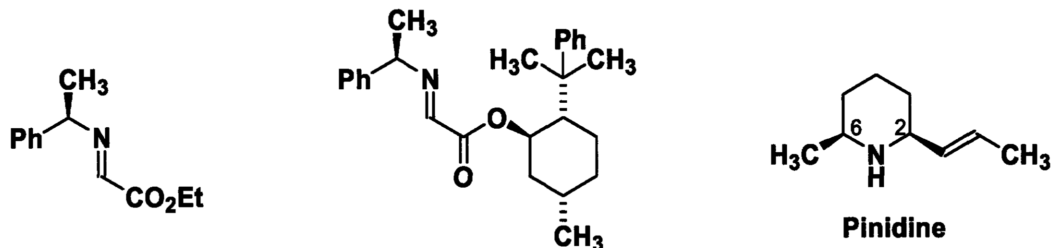
8 **9**

10 $R^2, R^3 = CH_3$ 95%
11 $R^3 = CH_3$ 87%
12 $R^1 = CH_3$ 62%
13 $R^1, R^2 = CH_3$ 42%
14 $R^1, R^4 = CH_3$ 60%
(other R = H)

Bailey and coworkers have extended this chemistry to include asymmetric reactions by using imines such as **15** with a 1-phenylethyl auxiliary on nitrogen; both enantiomeric forms of this imine are readily available. Cycloadditions of chiral imine **15** with cyclic dienes provide products with good asymmetric induction (84-100% de), but reactions with acyclic dienes produce products with varying levels of selectivity (26-68% de).[21] However, Bailey has shown that excellent asymmetric induction for acyclic dienes can be achieved if a second matched chiral auxiliary is introduced into the ester functionality (e.g., **16**).[22] Finally, Bailey and coworkers have demonstrated the synthetic utility of the cycloadducts of these reactions by applications to the efficient total synthesis of pinidine[23] and the asymmetric synthesis of pipecolic acid

[20] Woodward, R. B.; Hoffmann, R. *The Conversation of Orbital Symmetry*; Verlag Chemie: Weinheim, 1970.
[21] (a) Bailey, P. D.; Wilson, R. D.; Brown, G. R. *J. Chem. Soc., Perkin Trans. 1* **1991**, 1337. (b) Bailey, P. D.; Wilson, R. D.; Brown, G. R.; Korber, F.; Reid, A.; Wilson, R. D. *Tetrahedron: Asymmetry* **1991**, *2*, 1263.
[22] Bailey, P. D.; Londesbrough, D. J.; Hancock, T. C.; Heffernan, J. D.; Holmes, A. B. *Chem. Commun.* **1994**, 2543.
[23] Bailey, P. D.; Smith, P. D.; Morgan, K. M.; Rosair, G. M. *Tetrahedron Lett.* **2002**, *43*, 1071.

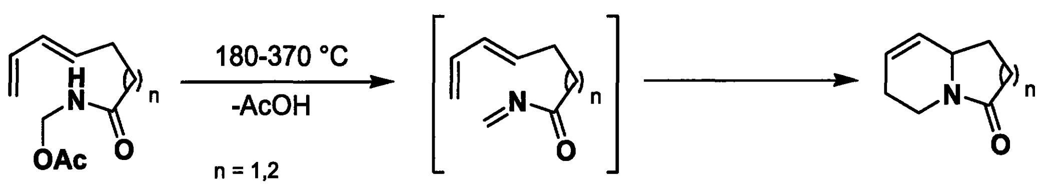
derivatives.[21b] However, it is important to note that Bailey's methodology only provides access to *cis*-2,6-disubstituted piperidines. Several important natural products possess a *trans*-2,6-disubstituted piperidine, and thus a method that would allow access to both diastereomers would be a valuable addition to synthetic methodology.[24]



15 16 Pinidine

Intramolecular Diels-Alder Reactions of Imino Dienophiles

The most extensive investigations of the intramolecular imino Diels-Alder reaction have been carried out by Weinreb and Grieco using *N*-acylimines and iminium ions, respectively. Weinreb's strategy employs the thermolysis of *N*-acetoxymethyl amides **17** to generate *N*-acylimines **18** as reactive dienophiles which then undergo cycloaddition in situ (eq 3). By varying the length of the tether, Weinreb and coworkers have synthesized both indolizidines (n = 1) and quinolizidines (n = 2) **19** using this approach.[25]



(3)

17 **18** **19**

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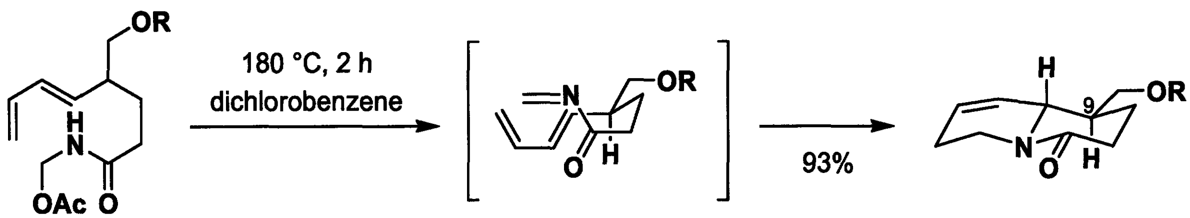
[24] For recent examples on the stereoselective synthesis of 2,6-dialkylpiperidines, see: (a) Agami, C.; Couty, F.; Mathieu, H. *Tetrahedron Lett.* 1998, *39*, 3505. (b) Felpin, F. X.; Lebreton, J. *Eur. J. Org. Chem.* **2003**, 3693. (c) Kuethe, J. T.; Comins, D. L. *Org. Lett.* **2000**, *2*, 855. (d) Carbonnel, S.; Troin, Y. *Heterocycles* **2002**, 10, 1807. (e) Monfray, J.; Gelas-Mailhe, Y.; Gramain, J. C.; Remuson, G. *Tetrahedron: Asymmetry* **2005**, *16*, 1025.

[25] Khatri, N. K.; Schmitthenner, H. F.; Shringarpure, J.; Weinreb, S. M. *J. Am. Chem. Soc.* **1981**, *103*, 6387.

In some cases, Weinreb obtained cycloadducts with excellent stereoselectivity as illustrated with the example shown in eq 4. This cycloaddition apparently proceeds via a transition state where the carbonyl group adopts an *endo* orientation and the benzyloxymethyl group is pseudoequatorial on the developing six-membered ring.[26] However, in cycloadditions leading to indolizidines, the level of stereoselectivity drops significantly with respect to the allylic substituent.[27]



(4)

Weinreb and coworkers extended their method to include imine dienophiles bearing acyl groups on both carbon and nitrogen.[28] For example, thermolysis of **20** affords imine **21** which then undergoes Diels-Alder cycloaddition to afford the bicyclic carbamate **22** as a single diastereomer in 83% yield. It was suggested that the *N*-acyl group, rather than the *C*-acyl group, occupies an *endo* orientation with the alkyl substituent in a pseudoequatorial position in the transition state. Weinreb and coworkers have applied this elegant methodology to the total of synthesis of several natural products including *epi*-lupinine,[26] slaframine,[27] and anhydrocannabiasativene.[29]

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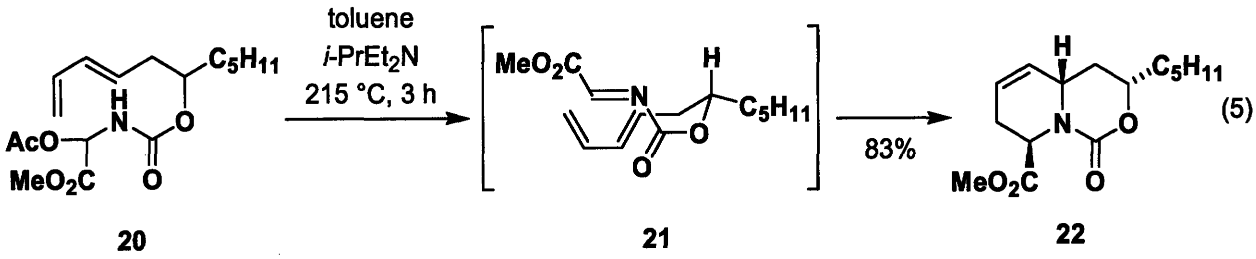
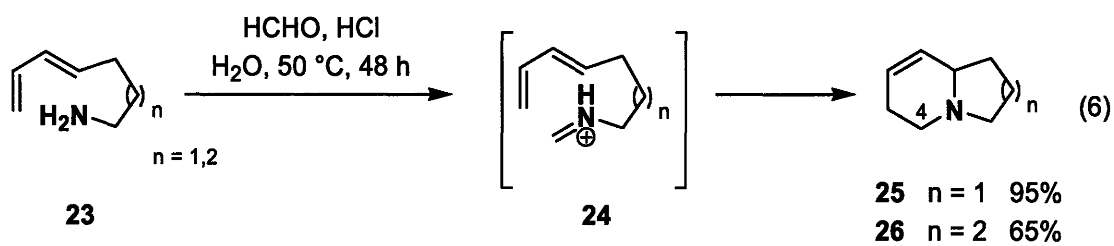
[26] (a) Bremmer, M. L.; Weinreb, S. M. *Tetrahedron Lett.* **1983**, *24*, 261. (b) Bremmer, M. L.; Khatri, N. A.; Weinreb, S. M. *J. Org. Chem.* **1983**, *48*, 3661.
[27] Gobao, R. A.; Bremmer, M. L.; Weinreb, S. M. *J. Am. Chem. Soc.* **1982**, *104*, 7065.
[28] (a) Bland, D. C.; Raudenbush, B. C.; Weinreb, S. M. *Org. Lett.* **2000**, *2*, 4007. (b) Nader, B.; Franck, R. W.; Weinreb, S. M. *J. Am. Chem. Soc.* **1980**, *102*, 1153. (c) Nader, B.; Bailey, T. R.; Franck, R. W.; Weinreb, S. M. *J. Am. Chem. Soc.* **1981**, *103*, 7573.
[29] Bailey, T. R.; Garigipati, R. S.; Morton, J. A.; Weinreb, S. M. *J. Am. Chem. Soc.* **1984**, *106*, 3240.



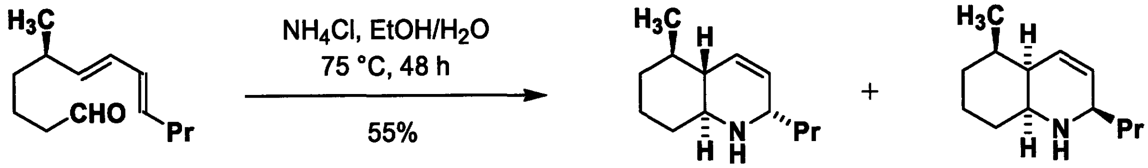
Grieco and coworkers have shown that simple iminium ions generated *in situ* undergo smooth Diels-Alder cycloadditions to give nitrogen heterocycles.[30] For example, addition of dienyl amines **23** to aqueous HCl and formaldehyde leads to the expected indolizidine **25** or quinolizidine **26** in good to excellent yield via cycloaddition of the corresponding iminium ions **24**. Unfortunately, Grieco reports that utilizing other aldehydes in place of formaldehyde (such as acetaldehyde) lead to low yields and a complex mixture of products. Consequently, this method does not provide access to C-4 substituted quinolizidines or indolizidines. Although Wang and coworkers have shown that lanthanide triflates catalyze intermolecular cycloadditions of simple iminium ions,[18] the use of lanthanide triflates for related *intra*molecular cycloadditions has not been reported.



Unlike Weinreb's *N*-acylimines, iminium ions do not react with good stereocontrol in Diels-Alder reactions. For example, treatment of dienyl aldehyde **27** with aqueous ammonium chloride delivers cycloadducts **28a** and **28b** as a 69:31 mixture of diastereomers in 55% yield (eq 7).[31] It is also important to note that by using a dienyl aldehyde such as **27** instead of a dienyl

[30] (a) reference 17 (b) Grieco, P. A.; Larsen, S. D. *J. Org. Chem.* **1986**, *51*, 3553. (c) Grieco, P. A.; Parker, D. T. *J. Org. Chem.* **1988**, *53*, 3325.
[31] Grieco, P. A.; Parker, D. T. *J. Org. Chem.* **1988**, *53*, 3658.

amine, Grieco has extended the methodology to the synthesis of nitrogen heterocycles in which the nitrogen atom is not located at the ring juncture of the new bicyclic system.



(7)

27 28a 69:31 28b

Summary

Although elegant methodology exists for the intermolecular and intramolecular Diels-Alder cycloaddition of imino dienophiles, we believed that iminoacetonitriles would have several advantages as 2π components in [4+2] cycloadditions and would provide access to substituted nitrogen heterocycles not easily obtained via previous methodology.[32] This thesis describes the full details of our studies on the synthesis of iminoacetonitriles, the scope of their Diels-Alder reactions, and the synthetic elaboration of the α-amino nitrile cycloadducts to provide access to a variety of substituted quinolizidine and indolizidine derivatives. Part III also reports on the total synthesis of quinolizidine (–)-217A and our efforts directed toward the total synthesis of indolizidine (–)-235B′.

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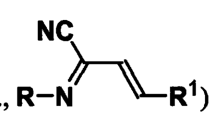
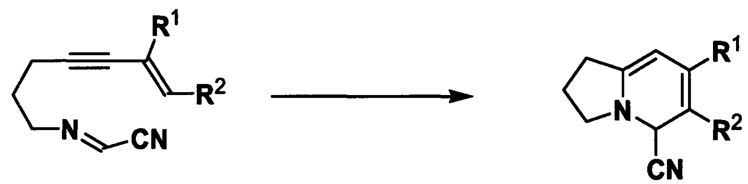
[32] It should be mentioned that the related 1-aza-2-cyanodienes (e.g., ) have been utilized in both intermolecular and intramolecular Diels-Alder cycloadditions by Fowler and coworkers. See: (a) Sisti, N. J.; Zeller, E.; Grierson, D. S.; Fowler, F. W. *J. Org. Chem.* **1997**, *62*, 2093. (b) Motorina, I. A.; Fowler, F. W.; Grierson, D. S. *J. Org. Chem.* **1997**, *62*, 2098. (c) Teng, M.; Fowler, F. W. *Tetrahedron Lett.* **1989**, *30*, 2481. (d) Teng, M.; Fowler, F. W. *J. Org. Chem.* **1990**, *55*, 5646. (e) Trione, C.; Toledo, L. M.; Kuduk, S. D.; Fowler, F. W.; Grierson, D. S. *J. Org. Chem.* **1993**, *58*, 2075.

Part II

Diels-Alder Cycloadditions of Iminoacetonitriles

Chapter 3 – Preparation of Iminoacetonitriles

The limitations associated with the Diels-Alder reactions of known imine derivatives motivated us to explore the cycloadditions and annulations of a new class of activated imines: *iminoacetonitriles*. Initial studies by Adam Renslo focused on the application of iminoacetonitriles in intramolecular enyne cycloadditions (eq 8); however, subsequently we decided to undertake the systematic investigation of a wide range of cycloadditions involving these species, beginning with the Diels-Alder reaction. In order for iminoacetonitriles to serve as useful building blocks, however, it was first necessary to develop effective procedures for the synthesis of this novel class of activated imines. This chapter describes the development and implementation of a Mitsunobu reaction as a key step in the synthesis of iminoacetonitriles, and it also reviews the literature procedures that existed for the preparation of this class of imines prior to our work.



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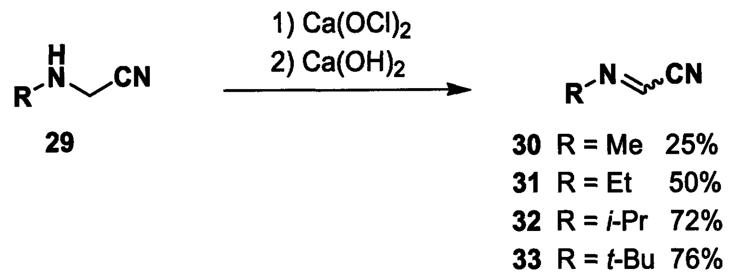
Previous Approaches to the Preparation of Iminoacetonitriles

At the outset of the investigations in our laboratory, iminoacetonitriles were relatively unknown compounds. In 1970, Boyer and Dabek had reported the first synthesis of an iminoacetonitrile, demonstrating that chlorination of *N*-*t*-butylaminoacetonitrile (prepared via the Strecker reaction) with *t*-butyl hypochlorite followed by elimination of HCl with triethylamine afforded **33** in 46% yield.[33] In a subsequent report, Boyer and Dabek found that using calcium

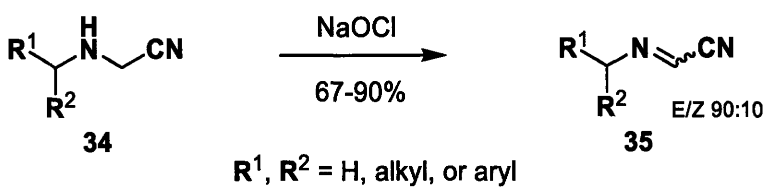
[33] Boyer, J. H.; Dabek, H. *J. Chem. Soc., Chem. Commun.* **1970**, 1204.

hypochlorite and calcium hydroxide led to increased yields and improved substrate scope (eq 9).[34]



(9)

After we began our investigations on the synthesis of iminoacetonitriles, a modification of Boyer's protocol, involving a one-pot procedure, was reported by Selva and coworkers.[35] Selva discovered that treatment of several α-amino nitriles with 1.5 equiv of aqueous NaOCl at 10 °C afforded the expected iminoacetonitriles in good yield (67-90%) with preference for the *E* isomer (eq 10).



(10)

Initially, we focused on extending this approach to the synthesis of iminoacetonitrile Diels-Alder substrates such as **38**. Since we were concerned about the stability of the dienyl portion of **38** to hypochlorite reagents, we decided to employ the mild chlorinating reagent *N*-chlorosuccinimide in our studies. As shown in Scheme 4, Adam Renslo developed a "one-flask" procedure for conversion of α-amino nitriles (e.g., **37**) to the desired iminoacetonitriles. Treatment of **37** with 1 equiv of NCS followed by addition of 1 equiv of sodium methoxide delivered iminoacetonitrile **38** as a mixture of *E* and *Z* isomers in 66% yield.[36]

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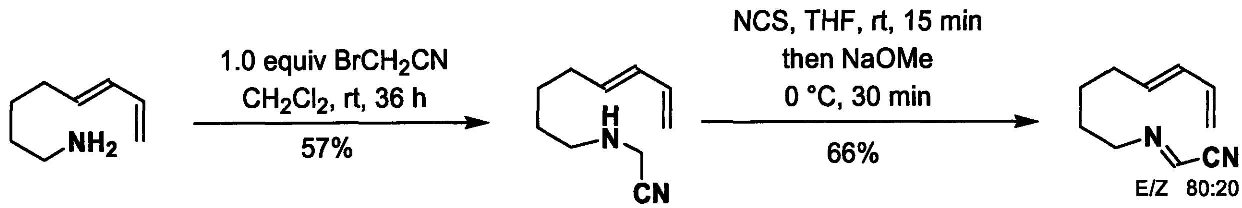
[34] Boyer, J. H.; Kooi, J. *J. Am. Chem. Soc.* **1976**, *98*, 1099.
[35] Perosa, A.; Selva, M.; Tundo, P. *Tetrahedron Lett.* **1999**, *40*, 7573.
[36] Amos, D. T.; Renslo, A. R.; Danheiser, R. L. *J. Am. Chem. Soc.* **2003**, *125*, 4970.

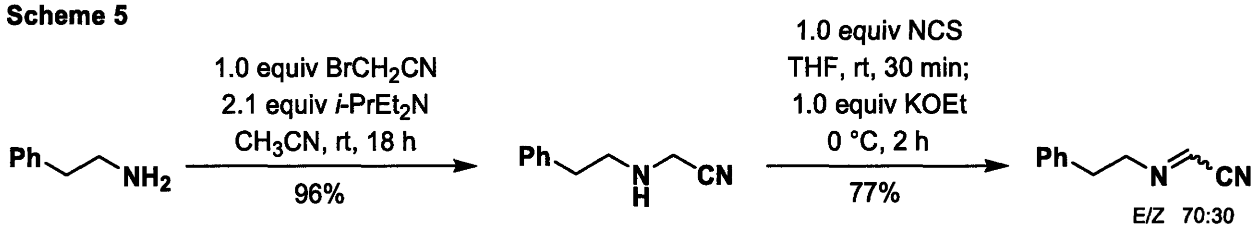
Scheme 4



36 37 38

Recently, we discovered that a slightly modified procedure leads to improved yields of iminoacetonitriles (Scheme 5). For example, alkylation of phenethylamine **39** with 1 equiv of bromoacetonitrile delivered α-amino nitrile **40** in 96% yield. Reaction of **40** with NCS followed by elimination by treatment with 1 equiv of potassium ethoxide at 0 °C for 2 h then afforded iminoacetonitrile **41** in 77% yield. This modified procedure is superior to our previous procedure in that the elimination is extremely clean (by tlc analysis), which allows for a simple purification by column chromatography.

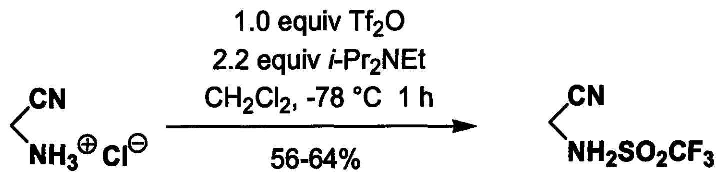
Scheme 5



39 40 41

Mitsunobu Approach to the Preparation of Iminoacetonitriles

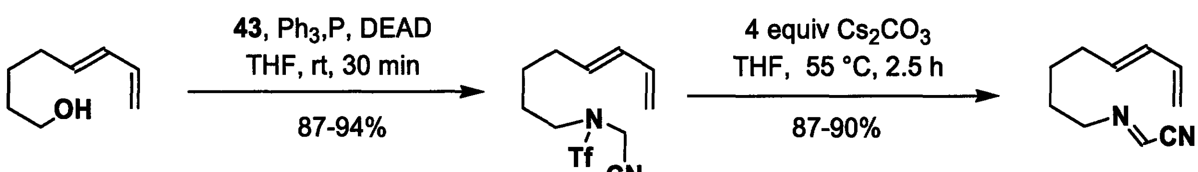
Although the method described above reliably furnished access to the desired iminoacetonitriles, for the preparation of our cycloaddition substrates we were not satisfied with employing amines such as **36** as starting materials. Even though amines are fairly simple to synthesize, all of the synthetic sequences we envisioned for the preparation of our cycloaddition substrates would involve the preparation of the amine from an alcohol derivative via substitution with azide or cyanide, followed by reduction. Consequently, a more expeditious route was developed by David Amos that begins with readily available alcohols and utilizes the previously unknown sulfonamide **43**.[36] Sulfonamide **43** is easily prepared by treating the commercially available hydrochloride salt of aminoacetonitrile **42** with one equiv of triflic anhydride in the presence of Hünig's base (eq 11). This simple procedure provides muti-gram quantities of **43** in high purity as a low-melting solid that is stable for months when stored under argon at ca. 4 °C.



42 **43** (11)

A typical example of the application of this approach developed by David Amos is shown in Scheme 6. Mitsunobu coupling reaction of alcohol **44** with sulfonamide **43,** followed by elimination of trifluoromethanesulfinate, provides the desired iminoacetonitrile via a simple two-step protocol in excellent yield.

Scheme 6



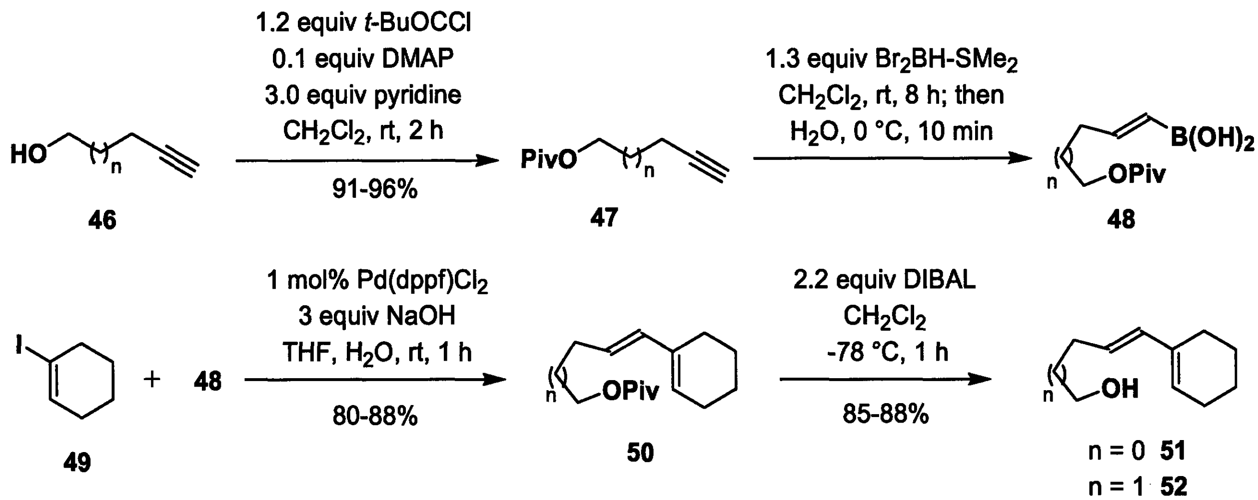
44 **45** **38** E/Z 80:20

Preparation of Iminoacetonitriles

As discussed previously, the method outlined in Scheme 6 was applied by David Amos to the synthesis of a variety of iminoacetonitrile cycloaddition substrates. This section details the preparation of several new cycloaddition substrates that were required in my further studies on the scope of the iminoacetonitrile cycloaddition reaction. The first target molecules I examined were the indolizidine (n = 1) and quinolizidine (n = 2) precursors **58, 60,** and **62** shown in Table

1. The requisite alcohols **51** and **52** were prepared utilizing a Suzuki cross-coupling reaction between 1-iodocyclohexene[37] and the vinyl boronic acids **48**. To prepare the requisite boronic acids (**48**), commercially available alkynols **46** were protected as the corresponding pivalate esters and then hydroborated with dibromoborane and converted to the boronic acid via the method of Brown.[38] The coupling of vinyl iodide **49** and boronic acids **48** (used without purification) under standard Suzuki cross-coupling conditions[39] afforded the desired dienes **50** in 80-88% yield. DIBAL reduction then cleaved the pivalate group to provide alcohols **51** and **52** in 85-88% yield.

Scheme 7



Next, we turned our attention to synthesizing an alcohol substrate of type **56** with a C-6 methyl substituent. Compound **55** was prepared according to the method of Noyori. Thus, allylation of dihydropyran **53** via in situ generation of 2-methoxytetrahydropyran (**54**) afforded tetrahydropyran **55** in 71% yield.[40] Exposing **55** to Schlosser's base then provided dienyl

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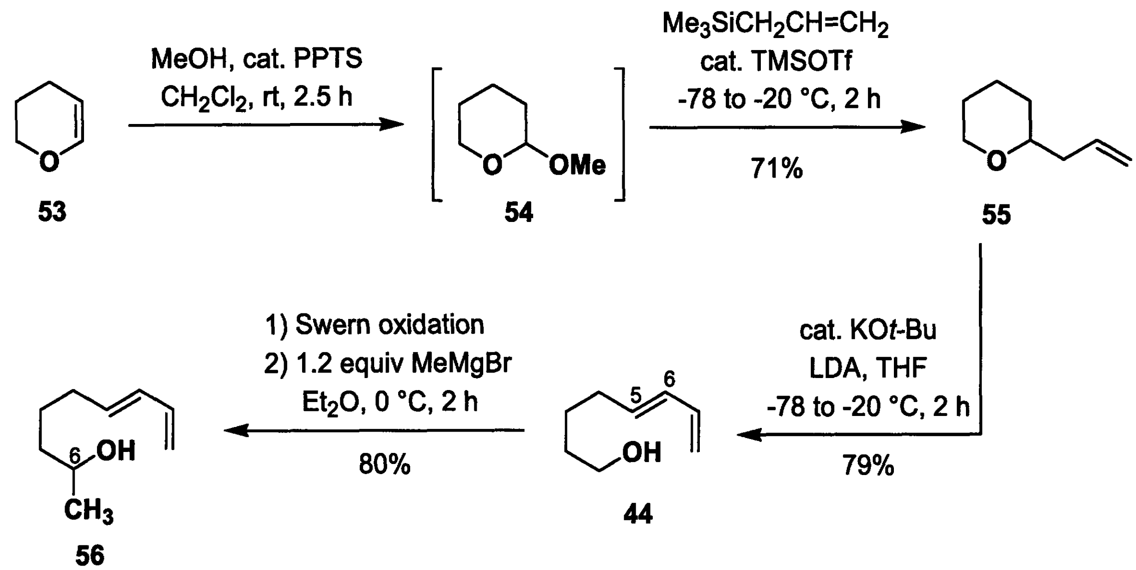
[37] 1-Iodocyclohexene was prepared by treating the hydrazone derivative of cyclohexanone with iodine according to Pross, A.; Sternhell, S. *Aust. J. Chem.* **1970**, *23*, 989.
[38] (a) Brown, H. C.; Campbell Jr., J. B. *J. Org. Chem.* **1980**, *45*, 389. (b) Brown, H. C.; Bhat, N. G.; Somayaji, V. *Organometallics* **1983**, *2*, 1311.
[39] For reviews on the Suzuki cross-coupling, see: (a) Bellina, F.; Carpita, A.; Rossi, R. *Synthesis* **2004**, *15*, 2419. (b) Miyaura, N. In *Metal-Catalyzed Cross-Coupling Reactions*, 2nd ed; Diederich, F., de Meijere, A.; Wiley-VCH: New York, 2004; Chapter 2.
[40] Tsunoda, T.; Suzuki, M.; Noyori, R. *Tetrahedron Lett.* **1980**, *21*, 71.

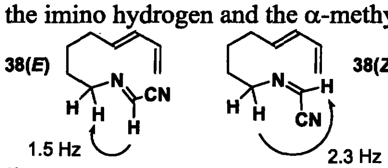
alcohol **44** as a single isomer (Scheme 8).[41] The large coupling constant (J = 17.5 Hz) observed between the protons on C-5 and C-6 indicated the presence of an E-olefin. Swern oxidation of **44** followed by addition of methylmagnesium bromide afforded the desired secondary alcohol **56** in 80% yield.

Scheme 8



As summarized in Table 1, our Mitsunobu-elimination protocol allowed for the efficient conversion of the alcohols described above to the desired iminoacetonitriles in excellent yield. In each case, the iminoacetonitriles were produced as a mixture of E and Z isomers.[42,43] Thus, subjecting alcohols **51** and **52** to our standard Mitsunobu reaction conditions afforded triflamides **57** and **59** in 83-90% yield. The subsequent elimination reactions proceeded uneventfully on exposure of these intermediates to Cs_2CO_3 to give iminoacetonitriles **58** and **60**, each in 86%

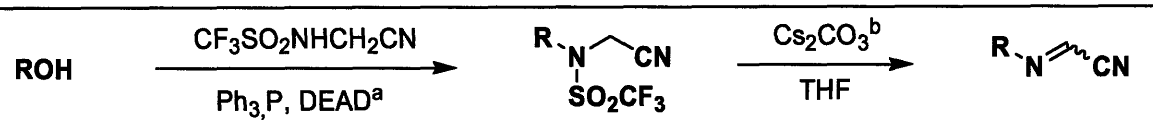
[41] Margot, C.; Rizzolio, M.; Schlosser, M. *Tetrahedron* **1990**, *46*, 2411.
[42] The stereochemical assignment of the imine isomers was obtained from the four-bond coupling observed between the imino hydrogen and the α-methylene hydrogen atoms. For example,

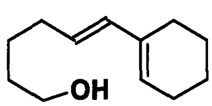
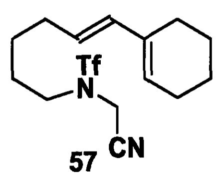
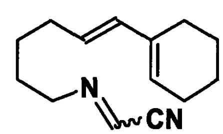
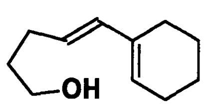
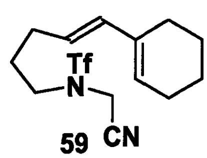
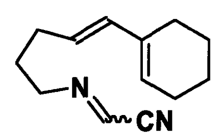
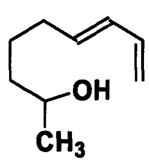
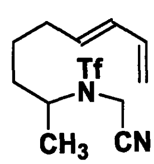
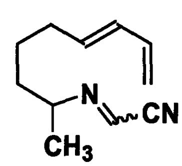


[43] The stereochemistry of the iminoacetonitrile (e.g., **38**) is not crucial, as we will demonstrate in chapter 4 that iminoacetonitrile isomers interconvert under the conditions of the [4+2] cycloaddition.

yield. Under our standard conditions, however, the Mitsunobu reaction of secondary alcohol **56** was extremely sluggish at room temperature and delivered a low yield of the desired triflamide **61**. Fortunately, we found that by switching the solvent to benzene and heating at 55 °C for 4 h, triflamide **61** could be obtained in 78% yield. The slow rate of this reaction was not unexpected as Mitsunobu reactions proceed via a S_N2 mechanism and therefore are greatly affected by the steric environment of the reacting carbon.

Table 1. Synthesis of Iminoacetonitriles



entry	alcohol	triflamide	yield (%)[c]	iminoacetonitrile	yield (%)[c] (*E/Z* ratio)
1	 **52**	 **57**	83-85	 **58**	86 (78:22)
2	 **51**	 **59**	90	 **60**	86 (70:30)
3	 **56**	 **61**	78	 **62**	90-95 (79:21)

[a] 1.05 equiv $TfNHCH_2CN$, 1.2 equiv Ph_3P, 1.2 equiv DEAD, THF-toluene, rt, 0.5-4 h (entry 3: benzene, rt, 12 h then 55 °C, 4 h). [b] 3-4 equiv Cs_2CO_3, THF, 45-55 °C, 2-4 h. [c] Isolated yield of products purified by column chromatography.

Optimization studies on the trifluoromethanesulfinate elimination step showed that cesium carbonate and potassium carbonate both furnish the desired product. However, by using cesium carbonate the reaction proceeds faster and leads to fewer side products and higher yields (by ca. 20%) of the desired imine. Although 4 equiv of cesium carbonate were used in every case, the reaction does proceed with 1 equiv although at a slower reaction rate. Also, the optimal temperature for the elimination proved to be 55 °C; however, the reaction does proceed fairly efficiently at room temperature if carried out over ca. 24 h.

In general, iminoacetonitriles are susceptible to hydrolysis under slightly acidic conditions and tend to slowly decompose at room temperature (ca. 30% decomposition after two weeks). Therefore, we do not usually store iminoacetonitriles for extended periods of time. However, iminoacetonitriles are easily purified by column chromatography as long as the silica gel is pretreated with one percent triethylamine to avoid acidic hydrolysis.

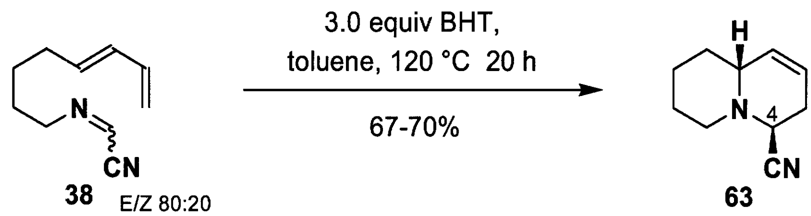
Chapter 4 – Intramolecular [4+2] Cycloadditions of Iminoacetonitriles

Although the Diels-Alder cycloaddition of a number of iminoacetonitriles had previously been studied by David Amos,[36] we felt there were several aspects of this chemistry that required further investigation. This chapter describes the details of our studies aimed at examining the mechanism of the iminoacetonitrile cycloaddition, expanding the scope of the cycloaddition to include the synthesis of tricyclic systems, and our investigation of the feasibility of promoting the cycloaddition under mild conditions with either Lewis or Brønsted acids.

Thermal Iminoacetonitrile Cycloadditions

In our original study, David Amos had discovered that simply heating the appropriate iminoacetonitriles in toluene leads to the formation of the desired Diels-Alder cycloadducts, usually as a single diastereomer. For example, heating a toluene solution of **38** (80:20 mixture of *E* and *Z* imine isomers) at 120 °C in the presence of 3 equiv of BHT in a sealed tube affords cycloadduct **63** in 67-70% yield after purification by column chromatography (eq 12). Interestingly, in this and other cases the cycloadduct with an *exo*-oriented axial cyano group is obtained as the exclusive product of the reaction.[36] Experiments carried out by David Amos[44] suggest that the initially formed epimeric cycloadducts equilibrate through an iminium ion to afford the axial cyano isomer which is favored as a consequence of the "α-amino nitrile anomeric effect."[45]

[44] Amos, D. T. Ph. D. Thesis, Massachusetts Institute of Technology, June 2003, pp 109-116.
[45] Bonin, M.; Romero, J. R.; Grierson, D. S.; Husson, H.-P. *J. Org. Chem.* **1984**, *49*, 2392.

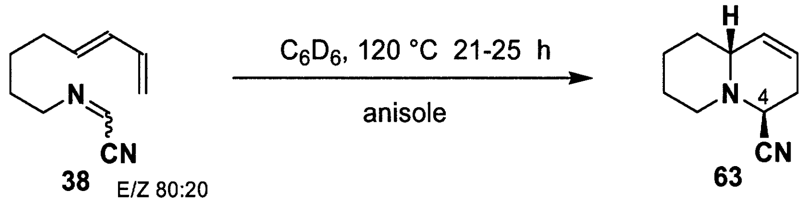


(12)

In order to better understand the mechanism of the iminoacetonitrile cycloaddition, I carried experiments to carefully monitor the cycloaddition of iminoacetonitrile **38** by ^{1}H NMR. These experiments were conducted in sealed NMR tubes by dissolving iminoacetonitrile **38**, 3 equiv of BHT, and a known amount of anisole (as internal standard) in 1 mL of benzene-d_6 (ca. concentration of 0.05 M). A ^{1}H NMR spectrum was taken at time zero and then the tube was heated at 120 °C for 21-25 h. At several points during the cycloaddition, the reaction tube was removed from the heating bath, and a ^{1}H NMR spectrum was recorded. With the assumption that the amount of internal standard did not change during the course of the experiment, the amount of iminoacetonitrile **38** and cycloadduct **63** was calculated.

As can be seen in Figure 1, the cycloaddition follows first order kinetics with respect to iminoacetonitrile **38**. As expected, the rate of disappearance of iminoacetonitrile **38** was unaffected by the addition of BHT; however, BHT did significantly increase the yield of the reaction by ca. 40%. In an attempt to reduce the amount of BHT used in the cycloaddition, we screened the reaction using various concentrations of this additive. Unfortunately, we discovered that 3 or more equiv of BHT gave the best results. Based on the result that BHT does not affect the rate of disappearance of iminoacetonitrile **38**, we hypothesized that BHT is in fact inhibiting decomposition of the cycloadduct, presumably through radical pathways. This is not unreasonable, as one might envision the possibility of loss of a hydrogen atom generating a captodatively stabilized radical at C-4. In order to confirm this hypothesis, we subjected cycloadduct **63** to our standard cycloaddition conditions (toluene, 120 °C) with and without

BHT. After 12 h, the cycloadduct in the absence of BHT had decomposed by 20% relative to the cycloadduct with BHT (3 equiv).



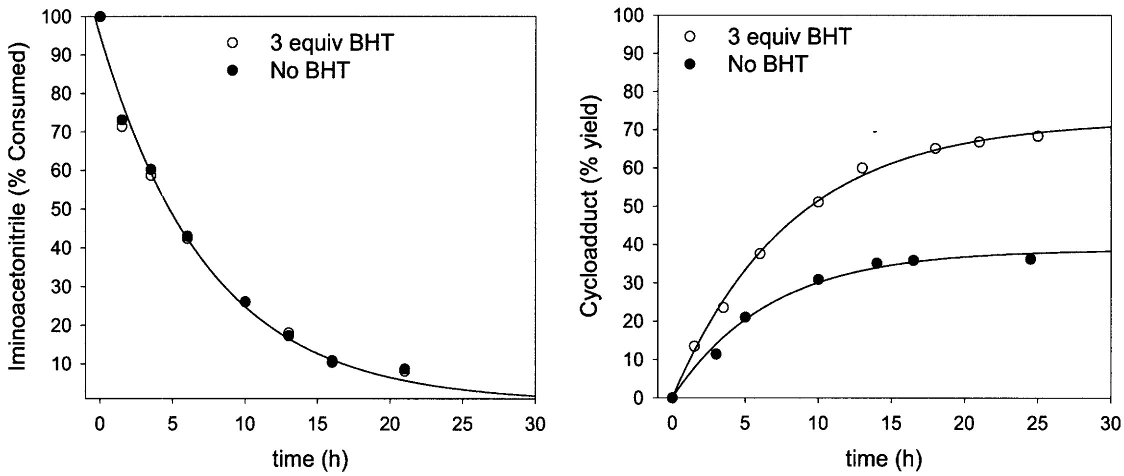


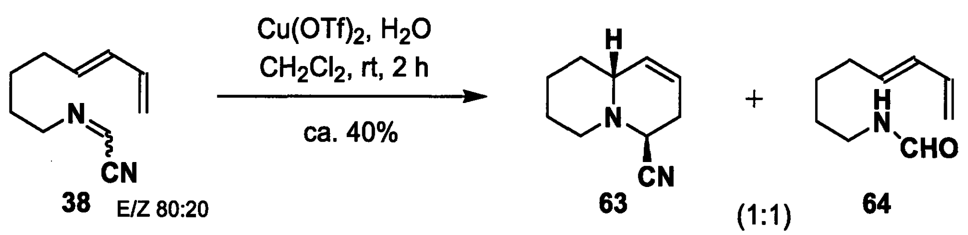
Figure 1. Effect of BHT on the Rate of the Iminoacetonitrile Diels-Alder Cycloaddition

In addition to studying the effect that BHT has on the rate of the cycloaddition, we were also interested in monitoring the relative reactivity of the *E* and *Z* iminoacetonitrile isomers in the cycloaddition. Interestingly, we discovered that the initial ratio (80:20) of *E* and *Z* isomers of iminoacetonitrile **38** equilibrates to a thermodynamic ratio (60:40) of *E* and *Z* isomers before any cycloadduct is formed, and this ratio then remains constant throughout the course of the cycloaddition. This observation suggests that either the imine isomers undergo cycloaddition at the same rate, or one isomer is reacting faster but interconversion occurs rapidly and maintains the thermodynamic ratio. Unfortunately, this provides little insight into the reactivity of each imine isomer, and further studies are required.

Acid-Promoted Iminoacetonitrile Cycloadditions

In an effort to expand the scope of the iminoacetonitrile cycloaddition, particularly to substrates that react sluggishly or are completely unreactive under thermal conditions, we next shifted our focus to the development of an acid-promoted cycloaddition. Examples have been reported in the literature of acid-promoted Diels-Alder cycloadditions of related imino dienophiles, and it therefore appeared possible that our reactions might be accelerated by acid.[10]

At first, we investigated the use of Lewis acids with a known affinity for cyano groups, such as copper, silver, and zinc salts. In this case we hypothesized that ionization of cyanide might produce a nitrilium ion that could undergo an accelerated Diels-Alder reaction. We also explored Lewis acids known to catalyze related imine cycloadditions,[10] such as Yb(OTf)$_3$, Sc(OTf)$_3$, and $BF_3 \cdot OEt_2$. Surprisingly, under completely anhydrous conditions, attempted cycloaddition of imine **38** in the presence of these additives led to recovery of unreacted starting material (**38**) in 95% yield. It is important to recall that iminoacetonitriles are extremely susceptible to hydrolysis under slightly acid conditions and therefore it is crucial to run acid-catalyzed reactions under completely anhydrous conditions. Interestingly, in one experiment we noticed that cycloaddition of **38** with Cu(OTf)$_2$ in the presence of a trace of H_2O delivered a 1:1 mixture of **63** and the hydrolysis byproduct **64** in 40% yield (eq 11).

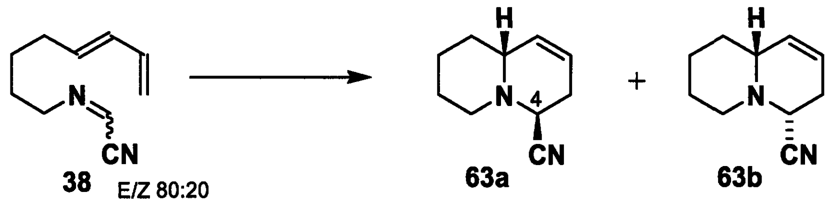


(13)

Encouraged by the possibility that the reaction in the above experiment was actually being promoted by trifluoromethanesulfonic acid generated *in situ*, we investigated the use of several Brønsted acids, such as TsOH, CSA, TFA, AcOH, and H_3PO_4. We discovered that acids with pKa values less than -1 are effective promoters of the cycloaddition, whereas reaction in the presence of weaker acids such as TFA and AcOH afford the cycloadduct in low yields (less than 15%) accompanied by extensive decomposition. Presumably, decomposition is initiated by acid-catalyzed hydrolysis or nucleophilic addition to the iminoacetonitrile moiety.

Optimization studies revealed that methanesulfonic acid in CH_2Cl_2 (0.1 M) is the most effective promoter of the iminoacetonitrile cycloaddition. For example, treatment of iminoacetonitrile **38** with 1 equiv of MsOH in CH_2Cl_2 under anhydrous conditions delivers the desired α-amino nitriles **63a** and **63b** in 80% yield as a 55:45 mixture of epimers (Scheme 9). The mixture of epimers at C-4 is inconsequential due to the fact that further transformations at the C-4 carbon are controlled by stereoelectronic effects independent of the C-4 cyano group stereochemistry (for a discussion, see Part III). If desired, heating the mixture in CH_3CN equilibrates the isomers to afford exclusively the thermodynamically favored axial oriented nitrile (Scheme 9). It is important to note that the addition of 4Å molecular sieves (ca. 10 mg of 4 Å molecular sieves per 1 mL CH_2Cl_2) is crucial to the success of the cycloaddition. Sieves presumably serve to completely inhibit hydrolysis of the iminoacetonitrile which otherwise significantly reduces the yield of the cycloaddition. Also, 1 equiv of MsOH is required for complete consumption of the starting material; this is not unexpected as the nitrogen atom in the cycloadduct is more basic than the nitrogen atom in the imine.

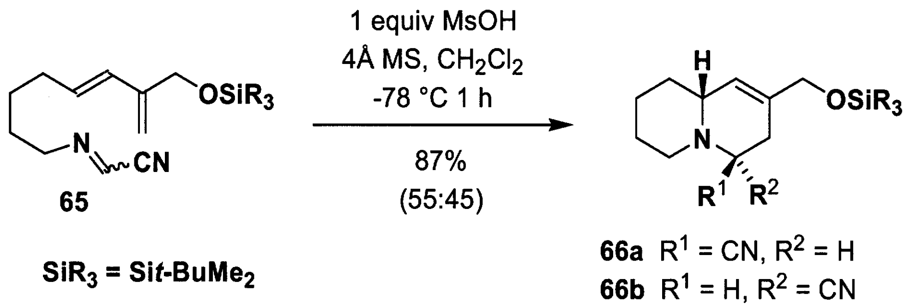
Scheme 9



Conditions	Yield	63a : 63b
3.0 equiv BHT, toluene, 120 °C, 20 h	67-70%	100 : 0
1 equiv MsOH, 4Å MS CH_2Cl_2, rt, 30 min	80%	55 : 45
1 equiv MsOH, 4Å MS CH_2Cl_2, rt 30 min; CH_3CN, 45 °C, 1.5 h	80%	100 : 0

Mechanism of the Acid-Promoted Cycloaddition of Iminoacetonitriles

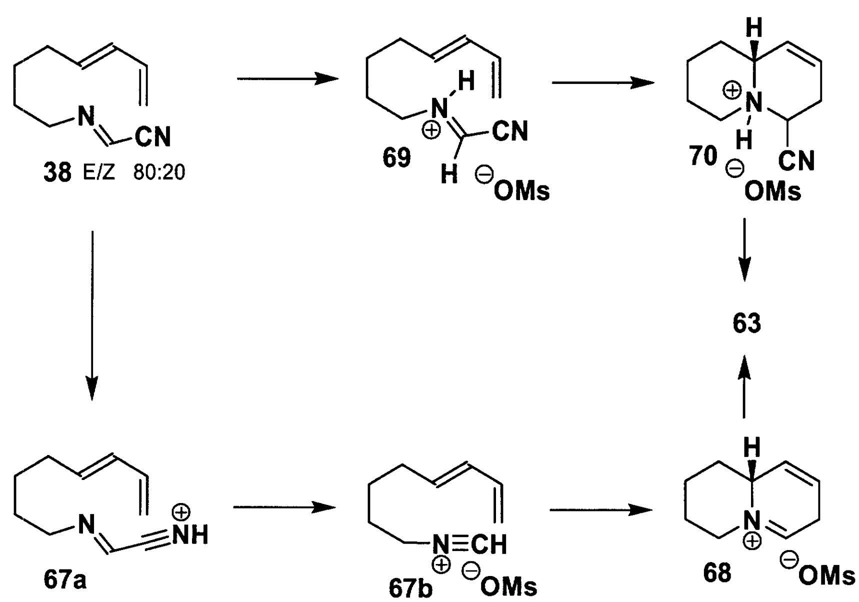
Analysis of the mechanism and stereochemical course of the iminoacetonitrile cycloaddition is challenging due to the possibility for isomerization of the isomeric imine substrates as well as the α-amino nitrile cycloadducts under the conditions of the reaction. As mentioned above, axial nitriles are the major or exclusive products of the reaction, and several observations suggest that this is the result of thermodynamic control. In the case of acid-promoted cycloadditions, treatment of iminoacetonitrile **65** with 1 equiv of MsOH at -78 °C for 1 h followed by quenching with aqueous sodium bicarbonate at -78 °C furnishes **66b** (equatorial nitrile) as a single diastereomer. However, all attempts to purify this compound by column chromatography led to a mixture (ca. 55:45) of **66a** and **66b**. This experiment demonstrates that the kinetic product of the cycloaddition is the equatorial nitrile and the cycloadducts equilibrate through an iminium ion to afford the thermodynamic product (axial nitrile). Also, α-amino nitrile cycloadducts (e.g., **81** in Scheme 14) with electron-withdrawing groups in the connecting tether have been found to equilibrate more slowly due to inductive destabilization of the intermediate iminium ion.



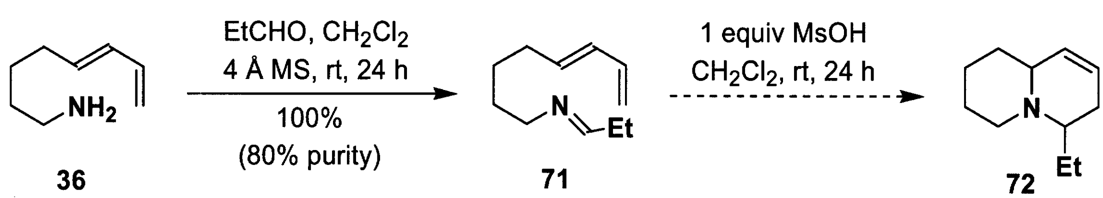
(14)

The facility of the acid-promoted cycloaddition of iminoacetonitriles is remarkable and of great synthetic importance. With regard to mechanism, in iminoacetonitriles such as **38** there are two possible sites of protonation. Protonation of the cyano group could lead to ionization to form nitrilium ion **67** which could then undergo [4+2] cycloaddition. Alternatively, protonation of the imine could generate the iminium ion **69** which might then be the intermediate undergoing Diels-Alder cycloaddition (Scheme 10).

Scheme 10



It will be recalled that the intramolecular Diels-Alder reaction investigated by Grieco and coworkers involved the *in situ* generation of a reactive iminium ion as a dienophile (see p 18). Cycloadditions involving iminium **69** (Scheme 10) should be more facile than the iminium ions studied by Grieco because the cyano group should destabilize the adjacent carbocation thereby increasing the reactivity of the dienophile. In order to test this hypothesis, we examined the reactivity of imine **71** lacking the cyano group. As shown in eq 15, treatment of imine **71** (*E* isomer by ^{1}H NMR analysis) with 1 equiv of MsOH led to recovered starting material with no sign of the desired cycloadduct. Although this experiment seems to support the hypothesis that the increased reactivity of **69** is a result of destabilization of the adjacent carbocation by the cyano group, the increased reactivity of imine **38** versus imine **71** could also be the result of steric hindrance in the transition state (cyano versus ethyl) or increased reactivity of the *Z*-imine isomer versus the *E*-isomer. As previously discussed, the *E* and *Z* isomers of iminoacetonitriles such as **38** equilibrate under the Diels-Alder reaction conditions whereas the *E* and *Z* isomers of imines such as **71** do not equilibrate. Therefore, if the *Z* isomer is the reactive imine isomer in the cycloaddition, then this could account for the difference in Diels-Alder reactivity between imines **38** and **71**.



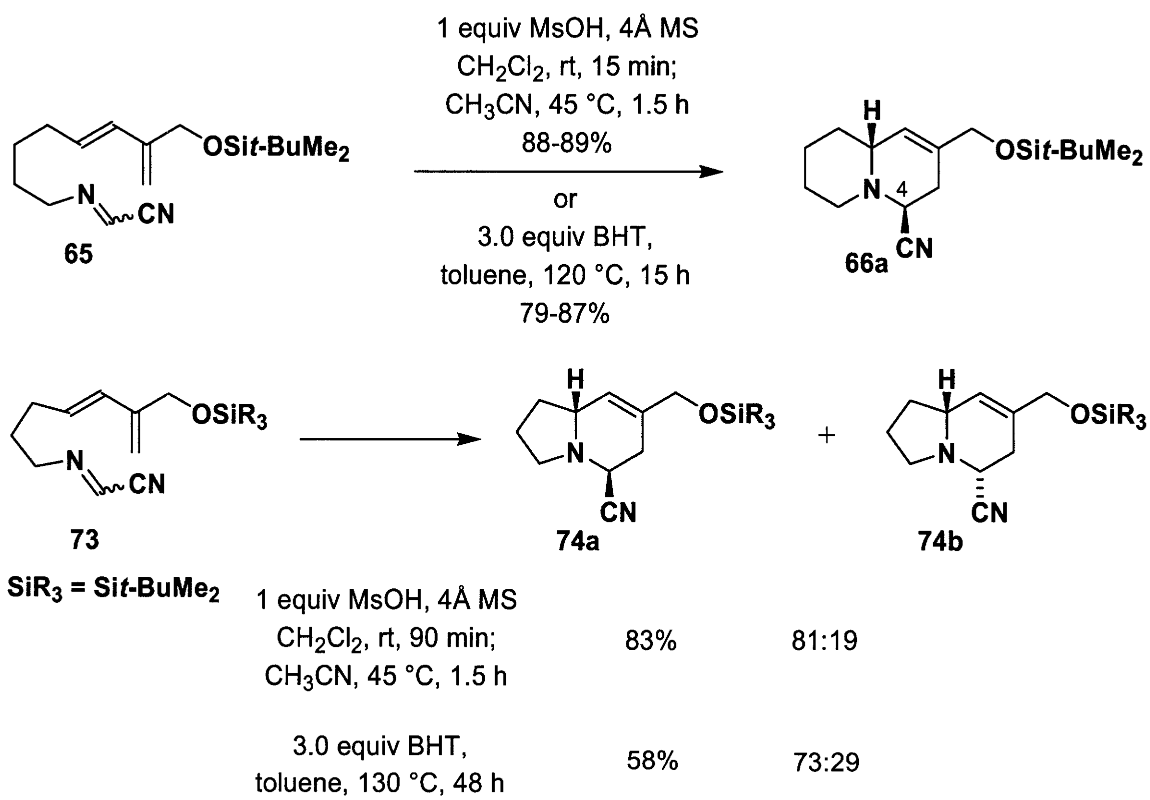
(15)

Scope of the Intramolecular [4+2] Cycloadditions of Iminoacetonitriles

Having developed conditions for acid-promoted cycloadditions of iminoacetonitriles, we turned our attention to investigating the scope of this process. This section begins with the results of an examination of the acid-promoted cycloaddition of several iminoacetonitriles previously prepared by David Amos.[36] Of particular interest were iminoacetonitriles that Amos discovered were either sluggish or unreactive under the original thermal cycloaddition conditions. The second part of this section explores the application of the iminoacetonitrile cycloaddition to the synthesis of tricyclic systems which had not previously been investigated.

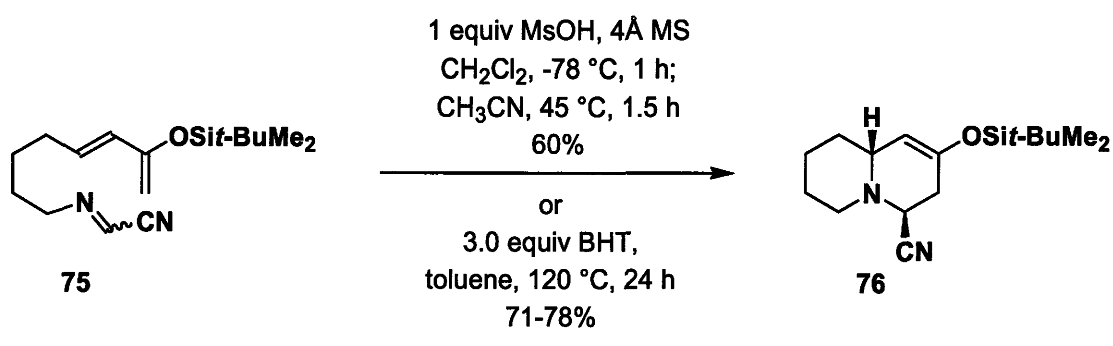
Initially, we decided to investigate the acid-promoted Diels-Alder cycloaddition of iminoacetonitrile **65** (Scheme 11). In the event, cycloaddition of imine **65** with 1 equiv of MsOH afforded **66a** in 88-89% yield as a single diastereomer after heating the crude product in CH_3CN at 45 °C for 1.5 h.

Scheme 11



Next, we explored the preparation of indolizidine **74** via the acid-promoted cycloaddition of iminoacetonitrile **73**. As shown in Scheme 11, cycloaddition of imine **73** in the presence of MsOH furnishes indolizidines **74a** and **74b** as a 30:70 mixture of C-5 isomers. In this case, heating the mixture of cycloadducts (**74**) in CH_3CN at 45 °C for 1.5 h affords an 81:19 mixture of **74a** and **74b** which represents the thermodynamic ratio. Interestingly, the rate of the cycloaddition of imine **73** (3-carbon tether) is significantly slower than imine **50** (4-carbon tether) under thermal conditions. However, the acid-promoted cycloadditions of imines **65** and **73** are extremely facile at room temperature and produce the desired cycloadducts in consistently higher yields as compared to the thermal reactions.

Our attention was next focused on the feasibility of using silyl enol ethers as part of the diene component. These experiments were aimed at laying the groundwork for applications of the cycloaddition in the total synthesis of certain alkaloid natural products. As shown in eq 16, thermal cycloaddition of imine **75** affords **76** in 71-78% yield as a single diastereomer. Initial investigations of the acid-promoted cycloaddition of imine **75** were completely unsuccessful due to decomposition of the silyl enol ether under the acidic reaction conditions. However, by conducting the reaction at -78 °C with dropwise addition of MsOH, we were able to obtain cycloadduct **76** in 60% yield with only a trace of decomposition. It should be emphasized that for the cases shown in Scheme 11 and eq 16 exactly 1 equiv of MsOH was used to avoid competing desilylation reactions.

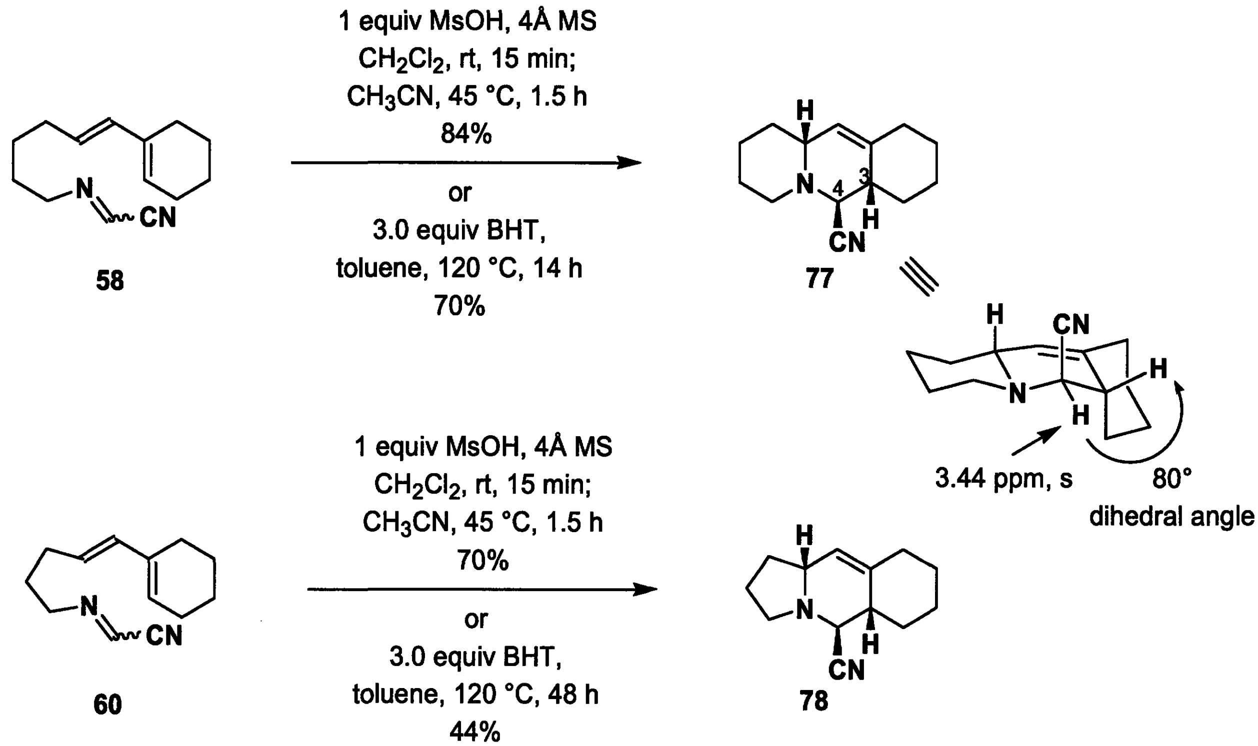


75 **76** (16)

The next stage of our investigation of the scope of the iminoacetonitrile cycloaddition involved the synthesis of the tricyclic systems **77**, **78**, and **80** (Scheme 12 and eq 17). The first two cases we examined involved vinylcyclohexenes as diene components. Subjecting imines **58** and **60** to thermal and acid-promoted cycloadditions afforded cycloadducts **77** and **78**, in each case as a single diastereomer. To assign the stereochemistry of the cyano group at C-4, we first calculated the dihedral angles for both epimers and then used the Karplus curve to predict coupling constants for the proton at C-4. For an axial cyano group (calculated dihedral angle of 80°), the coupling constant would be expected to fall between 0 and 1 Hz. On the other hand, for an equatorial cyano group (calculated dihedral angle of 45°), the coupling constant would be expected to fall between 4 and 8 Hz.[46,47] The proton at C-4 of cycloadduct **77** appeared as a singlet in the ^{1}H NMR spectrum and thus is consistent with an axially disposed cyano group *cis* to the C-3 proton (Scheme 12).[48]

[46] Dihedral angles calculated with Chem3D, version 7.0.1; CambridgeSoft: Cambridge, MA, 2002.
[47] Friebolin, H. Basic One- and Two-Dimensional NMR Spectroscopy, 2nd ed.; VCH: New York, 1993, pp 88-91; translated by J. K. Becconsall.
[48] The stereochemistry of indolizidine **78** was established by comparing its NMR spectra to that of quinolizidine **77**.

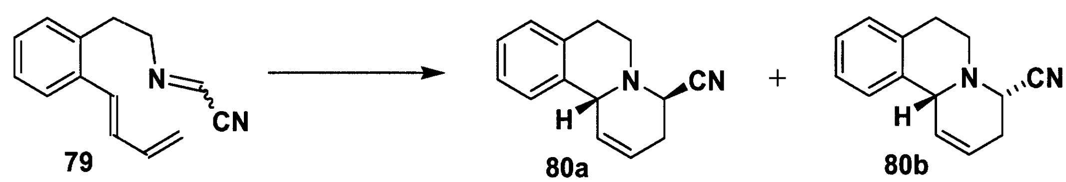
Scheme 12



Once again, the acid-promoted cycloadditions proceeded in consistently higher yield as compared to thermal reactions. As expected, suprafacial cycloaddition leads to a single product in which the two ring junction hydrogens are *cis*. As expected from previous results, the rate of the thermal cycloaddition leading to **78** was considerably slower than the homologous case leading to **77**. An important trend to point out is that thermal cycloadditions of imines such as **60** and **73** leading to indolizidines are relatively sluggish and generally proceed in modest yield.

The final tricyclic case we studied involved the preparation of benzoquinolizidine **80** (Scheme 13). As previously reported by Amos, cycloaddition of imine **79** under thermal conditions afforded cycloadducts **80a** and **80b** in 44-45% yield as a 79:21 mixture of epimers.[36] However, acid-promoted cycloaddition of this imine produced cycloadducts **80a** and **80b** in improved yield (60%). It should be mentioned that at elevated temperatures, especially in polar solvents such as CH_3CN, cycloadducts **80a** and **80b** suffered from instability, which most likely contributed to the relatively low yield observed in this case.[49]

Scheme 13



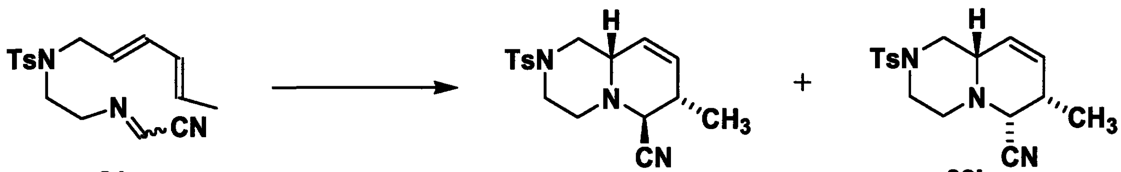
1 equiv MsOH, 4Å MS CH_2Cl_2, rt, 1 h; CH_3CN, 45 °C, 1.5 h	60% (79:21)
3.0 equiv BHT, toluene, 120 °C, 36 h	44-45% (79:21)

Our next goal was to investigate the acid-promoted cycloaddition of iminoacetonitrile **81**. We were particularly interested in the reactivity of imine **81** due to the presence of the electron-withdrawing sulfonamide nitrogen in the connecting tether. As previously reported by Amos, thermal cycloaddition of **81** in toluene afforded **82a** and **82b** in 90-95% yield as a 37:63 mixture of C-4 isomers. Interestingly, Amos had found that conducting the reaction in a more polar solvent such as CH_3CN afforded cycloadduct **82a** in 61-64% yield as a single diastereomer, albeit in lower yield. The relatively slow equilibration rate of cyano isomers **82a** and **82b** compared to other quinolizidine cycloadducts is a result of inductive destabilization of the intermediate iminium ion by the electron-withdrawing sulfonamide group. As expected from these results, the acid-promoted cycloaddition of imine **81** at room temperature affords cycloadduct **82b** (kinetic product) in 71% yield as a single diastereomer. Once again, heating

[49] For the stereochemical assignment of **80a** and **80b**, see reference 44 (pp 103-104).

82b in CH_3CN equilibrates the C-4 cyano group to afford exclusively the thermodynamically favored axial oriented nitrile. It should be mentioned that cycloadducts **82a** and **82b** both possess a *cis*-relationship between the methyl group and ring junction hydrogen atom consistent with suprafacial cycloaddition to the diene.

Scheme 14



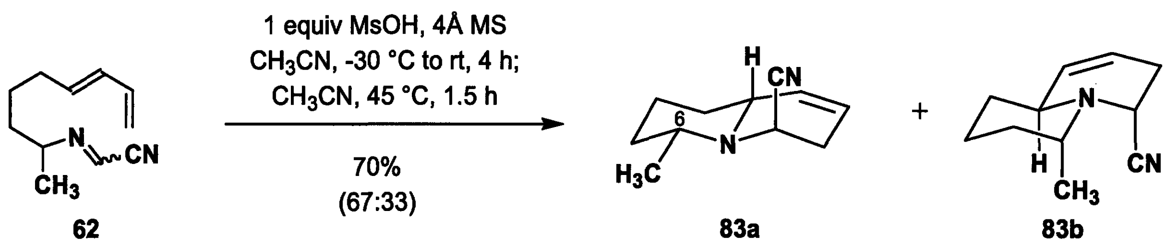
81 82a 82b

3.0 equiv BHT, toluene, 120 °C, 36 h	90-95% (37:63)
3.0 equiv BHT, CH_3CN, reflux, 24 h	61-64% (100:0)
1 equiv MsOH, 4Å MS CH_2Cl_2, rt, 1 h	71% (0:100)
1 equiv MsOH, 4Å MS CH_2Cl_2, rt, 1 h; CH_3CN, 45 °C, 18 h	71% (100:0)

At this stage, we decided to examine the feasibility of preparing cycloadducts with substituents at the C-6 position such as **83**. These cycloadducts are of particular importance due to the abundance of biologically active 4,6-disubstituted quinolizidine natural products.[50] Amos had found in our previous studies that iminoacetonitriles with substituents alpha to the imine such as **62** are completely unreactive under thermal conditions.[36] Unfortunately, the acid-

[50] For a recent review of the chemistry and biology of quinolizidine alkaloids, see: Daly, J. W.; Garraffo, H. M.; Spande, T. F. In *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Pergamon: New York, 1999; Vol. 13, pp 1-161.

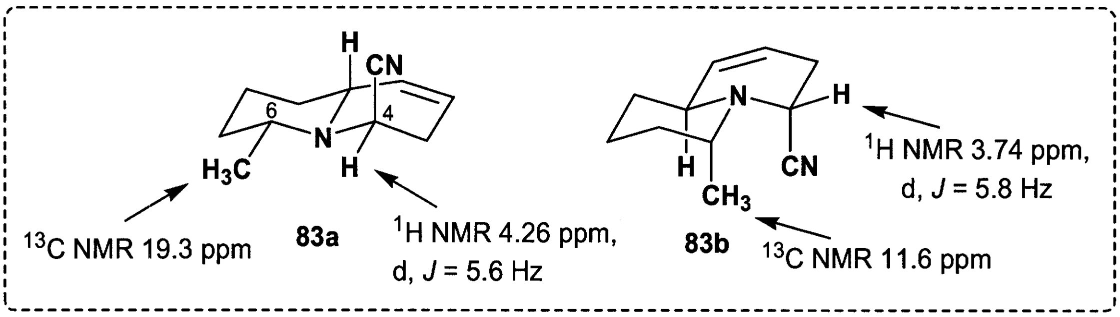
promoted cycloaddition of iminoacetonitrile **62** (1 equiv MsOH, CH_2Cl_2, rt) also failed to produce the desired cycloadduct **83** (unreacted **62** was recovered in ca. 90% yield). However, we discovered that reaction in a more polar solvent (CH_3CN instead of CH_2Cl_2) affords cycloadducts **83a** and **83b** in 70% yield as a 67:33 mixture. One possible explanation for this solvent effect is that protonation of **62** to form either the key iminium ion of type **69** (see Scheme 10) or nitrilium ion of type **67b** is much more favorable in acetonitrile. Alternatively, perhaps the nitrilium ion of type **67b** is the species undergoing cycloaddition and its formation is much faster in the more polar solvent. Finally, it is possible that the rate of cycloaddition of the intermediate carbocation (either of type **67b** or **69**) is faster in the more polar solvent, perhaps due to the formation of a more reactive solvent-separated ion pair.



(17)

The stereochemistry of cycloadducts **83a** and **83b** was established by NMR analysis. The protons at C-4 of **83a** and **83b** appeared as doublets and therefore were assigned as equatorial. The carbon of the methyl group in **83a** is shifted downfield (19.3 ppm vs 11.6 ppm) relative to the carbon of the methyl group in **83b**. The equatorial methyl group lies in the deshielding cone of a C-C bond of the ring skeleton and therefore is expected to appear further downfield than the axial methyl group.[51]

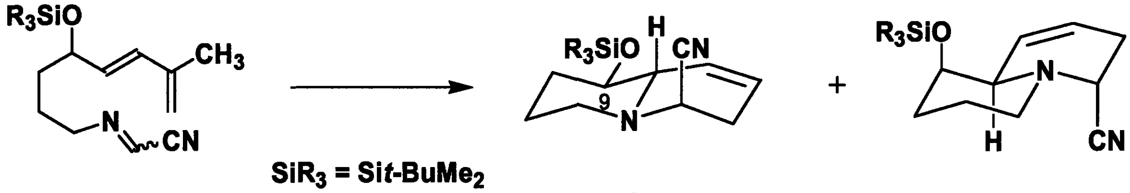
[51] Silverstein, R. M.; Webster, F. X. Spectrometric Identification of Organic Compounds, 6th ed.; John Wiley & Sons, Inc.: New York, 1998; pp 155-156.



Next, we were interested in exploring the acid-promoted cycloaddition of iminoacetonitrile **84** (Scheme 15). Previous work by David Amos showed that under thermal conditions cycloadducts **85a** and **85b** are obtained in 73% yield as a 55:45 mixture of isomers at C-9.[36,52] Acid-promoted cycloaddition of imine **84** under standard conditions (1 equiv MsOH, CH_2Cl_2, rt) also furnishes **85a** and **85b** as a 55:45 mixture, albeit in slightly improved yield. However, we discovered that conducting the reaction at -78 °C afforded cycloadduct **85a** in 81% yield as a single diastereomer after heating the crude product in CH_3CN at 45 °C for 1.5 h. This is an exciting result as it provides the opportunity to use a C-9 stereogenic center as a directing group in a diastereoselective cycloaddition.

[52] For the stereochemical assignment of **85a** and **85b**, see reference 36 (pp 106-107).

Scheme 15



84 | 85a | 85b

Conditions	Yield	85a:85b
3.0 equiv BHT, toluene, 120 °C, 22 h	73%	55:45
1 equiv MsOH, 4Å MS CH_2Cl_2, rt, 1 h; CH_3CN, 45 °C, 1.5 h	81%	50:50
1 equiv MsOH, 4Å MS CH_2Cl_2, -78 °C, 1 h; CH_3CN, 45 °C, 1.5 h	81%	100:0

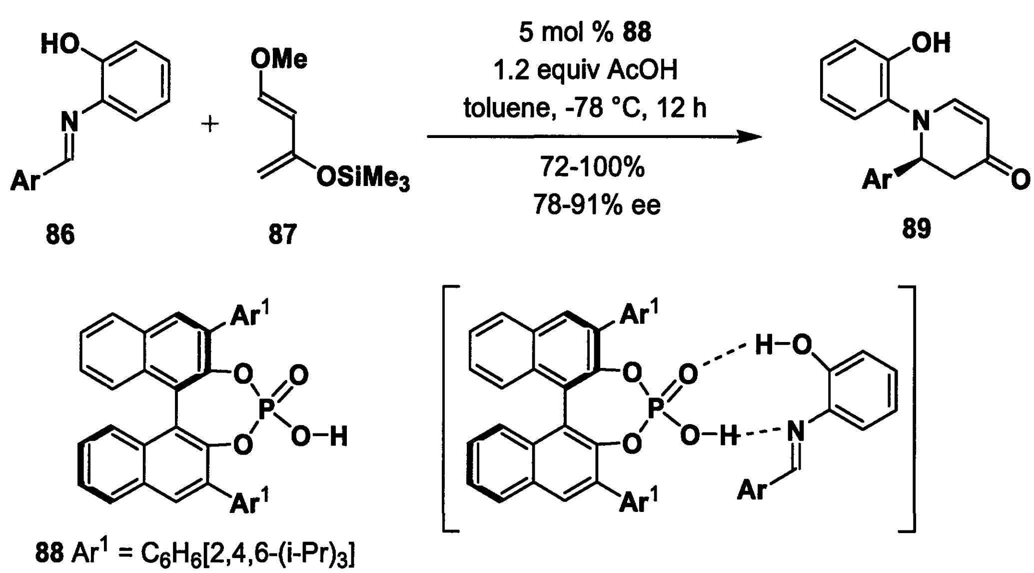
Enantioselective Intramolecular [4+2] Cycloadditions of Iminoacetonitriles

Having investigated the scope of the acid-promoted iminoacetonitrile cycloaddition, we turned our attention to the possibility of using chiral Brønsted acids for an enantioselective version. Recently, several laboratories have shown that chiral phosphoric acids (e.g., **88**) function as powerful organocatalysts for activation of imine functional groups which then participate in a number of useful asymmetric reactions.[53] Of particular relevance to our work, the laboratories of Akiyama[54] and Gong[55] have developed enantioselective aza Diels-Alder reactions catalyzed by chiral phosphoric acids.

[53] For a review of chiral phosphoric acids, see: Connon, S. J. *Angew. Chem. Int. Ed.* **2006**, *45*, 3909.
[54] (a) Akiyama, T.; Tamura, Y.; Itoh, J.; Morita, H.; Fuchibe, K. *Synlett* **2006**, 141. (b) Itoh, J.; Fuchibe, K.; Akiyama, T. *Angew. Chem. Int. Ed.* **2006**, *45*, 4796. (c) Akiyama, T.; Morita, H.; Fuchibe, K. *J. Am. Chem. Soc.* **2006**, *128*, 13070.
[55] Liu, H.; Cun, L. F.; Mi, A. Q.; Jiang, Y. Z.; Gong, L. Z. *Org. Lett.* **2006**, *8*, 6023.

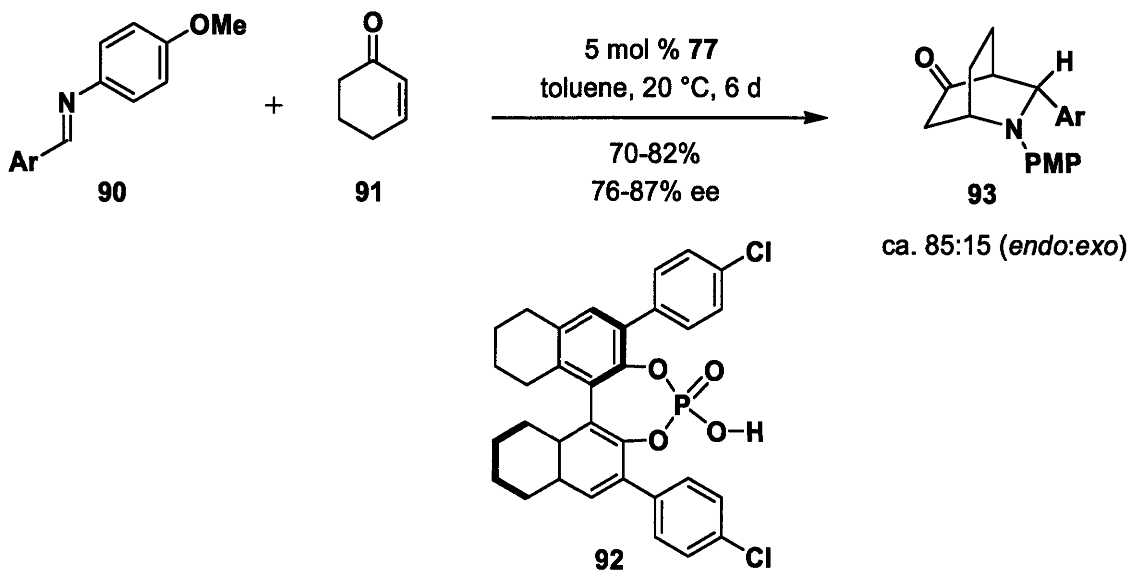
As shown in Scheme 16, Akiyama and coworkers discovered that chiral phosphoric acid **88**, derived from (*R*)-BINOL, catalyzes the Diels-Alder cycloaddition of aryl imines (e.g., **86**) with Danishefsky's diene to give piperidinone derivatives **89** in 72-100% yield and 78-91% ee. Akiyama and coworkers attribute the good levels of enantioselectivity to a nine-membered transition state in which one face of the imine is blocked by the acid catalyst. Akiyama and coworkers have also shown that the steric bulk of the aryl groups at the 3 and 3′ positions are crucial for high levels of enantioselectivity.[54]

Scheme 16



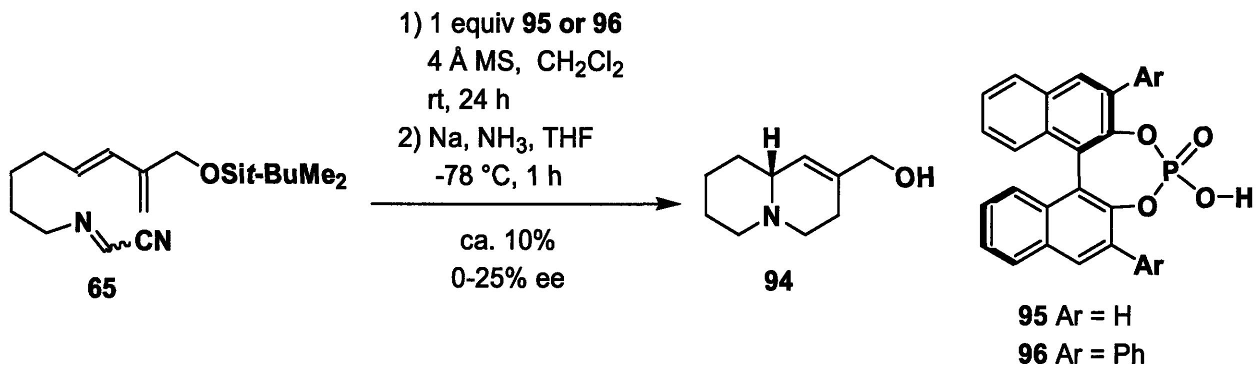
Gong and coworkers developed a direct asymmetric aza Diels-Alder reaction catalyzed by chiral phosphoric acid **92**, which involves the in situ generation of the diene (Scheme 14). Gong reasoned that under the acidic reaction conditions cyclohexenone (**91**) would enolize and the resulting dienol would behave as a 4π component in the cycloaddition. In the event, treatment of aldimine **90** with cyclohexenone and **92** afforded cycloadduct **93** with good enantioselectivity. Although substitution at the 3 and 3′ positions of the catalyst is important for high levels of enantioselectivity, Gong noticed that sterically congested aryl groups, such as 4-*t*-BuC_6H_6, actually had a deleterious effect on enantioselectivity. Gong and coworkers also found that H_8-BINOL-derived phosphoric acids (e.g., **92**) lead to higher selectivity than the corresponding BINOL-derived acids.[55]

Scheme 17



Encouraged by this work, our efforts were directed toward the development of an enantioselective Diels-Alder cycloaddition of iminoacetonitriles. Our initial efforts focused on the cycloaddition of imine **65** with commercially available phosphoric acid **95** (Scheme 18). Treatment of imine **65** with 1 equiv of **95** in CH_2Cl_2 for 24 h afforded the desired cycloadduct, which upon reductive decyanation afforded **94** as racemic mixture. Although this reaction was not enantioselective, we were glad to see that phosphoric acids of type **95** do promote the iminoacetonitrile cycloaddition. Therefore, we decided to try the bulkier phosphoric acid **96**, which is readily accessible from commercially available (*R*)-BINOL.[56] In this case, quinolizidine **94** was obtained in ca. 25% ee, albeit in low yield (ca. 10%). It should be mentioned that the cycloaddition step in both cases is extremely sluggish and affords several by-products. In order to increase the rate and success of the cycloaddition, the acidity of the phosphoric acid needs to be increased as discussed in the section on acid-promoted cycloadditions.[57] Although the overall yield (ca. 10%) and enantiomeric excess are low, we are confident that manipulation of the steric bulk and electronic properties of the 3 and 3′ aryl groups will lead to an effective chiral phosphoric acid for our iminoacetonitrile cycloaddition.

Scheme 18



Summary

In conclusion, iminoacetonitriles participate in acid-promoted intramolecular [4+2] cycloadditions affording quinolizidine and indolizidine ring systems. In comparison to thermal cycloadditions, acid-promoted cycloadditions of iminoacetonitriles generally afford cycloadducts in higher yields, with better selectivity, with faster reaction rates, and under milder reaction conditions.

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[56] For the synthesis of **80**, see: (a) Simonsen, K. B.; Gothelf, K. V.; Jørgensen, K. A. *J. Org. Chem.* **1998**, *63*, 7536. (b) Wipf, P.; Jung, J. K. *J. Org. Chem.* **2000**, *65*, 6319.

[57] Acids **79** and **80** have pka values of ca. -1 to 0.

Chapter 5 – Intermolecular [4+2] Cycloadditions of Iminoacetonitriles

Introduction

The piperidine substructure is one of the most common motifs found in natural products and pharmaceutical compounds. According to Watson and coworkers, the piperidine substructure was mentioned in over 12,000 compounds in clinical or pre-clinical studies from July 1988 through December 1998.[58] The important biological activities of piperidines have thus stimulated the development of new methods, and considerable synthetic effort has been invested in this area.[59]

One of the most important methods for the synthesis of six-membered rings is the Diels-Alder reaction. Therefore, the development of imine derivatives as 2π components in aza Diels-Alder reactions has greatly facilitated the ease with which piperidines can be synthesized in an efficient manner. Although several types of imino dienophiles exist for the aza Diels-Alder reaction, the most useful are the *C*-acylimines developed by Bailey and coworkers. As discussed in chapter 2, Bailey and coworkers have demonstrated that imine **9** represents the state of the art for imino dienophiles. As shown in eq 18, cycloadditions of imine **9** with a variety of dienes afford piperidine cycloadducts (**10-14**) in good yield with excellent diastereoselectivity. It is important to note that Bailey's methodology only provides access to *cis*-2,6-disubstituted piperidines. Since a number of important natural products possess a *trans*-2,6-disubstituted piperidine structure, a method that would allow access to both diastereomers would be a valuable addition to synthetic methodology.

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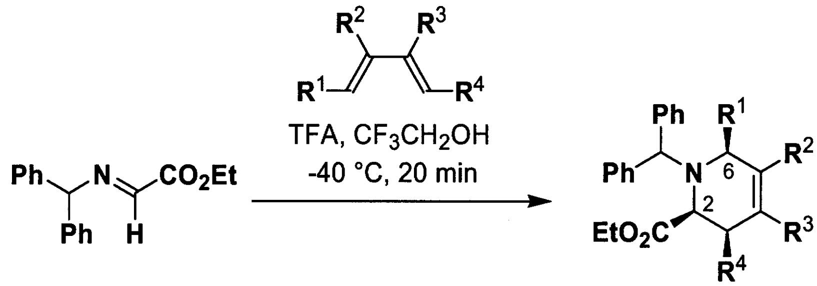
[58] Watson, P. S.; Jiang, B.; Scott, B. *Org. Lett.* **2000**, *23*, 3679.

[59] For reviews on the synthesis of piperidines, see: (a) Bailey, P. D.; Millwood, P. A.; Smith, P. D. *J. Chem. Soc., Chem. Commun.* **1998**, 633. (b) Laschat, S.; Dickner, T. *Synthesis* **2000**, 1781. (c) Weintraub, P. M.; Sabol, J. S.; Kane, J. M.; Borcherding, D. R. *Tetrahedron* **2003**, *59*, 2953. (d) Buffat, M. G. P. *Tetrahedron* **2004**, *60*, 1701.

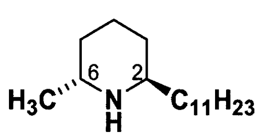


9

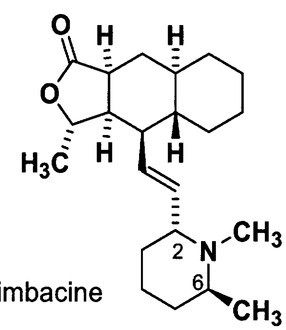
10 R^2, R^3 = CH_3 95%
11 R^3 = CH_3 87%
12 R^1 = CH_3 62%
13 R^1, R^2 = CH_3 42%
14 R^1, R^4 = CH_3 60%
(other R = H)

(18)

2,6-Disubstituted piperidines represent a subclass of naturally occurring piperidines that have stimulated considerable synthetic interest due to their wide range of pharmacological activities.[60] Two prominent examples are (–)-solenopsin A, a constituent of the venom of the *Solenopsis* species,[61] and (+)-himbacine, a piperidine alkaloid isolated from the bark of *Galbulimina baccata* of the magnolia family.[62] These two natural products have appeared as novel drug candidates for the treatment of Alzheimer's disease.[63]



(–)-Solenopsin A

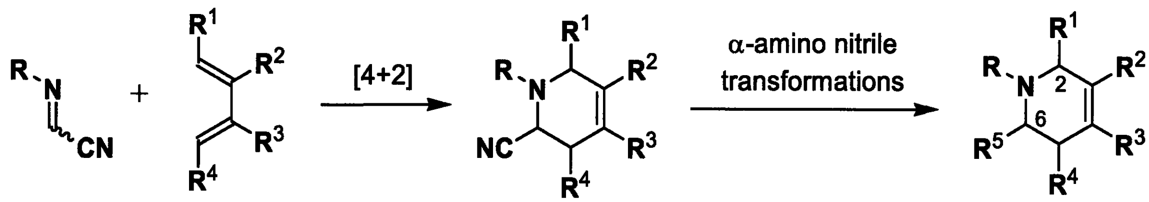


(+)-Himbacine

The importance of piperidines, specifically 2,6-disubstituted piperidines, encouraged us to explore the feasibility of *intermolecular* [4+2] cycloadditions of iminoacetonitriles. As shown in eq 19, the ability to use an iminoacetonitrile as a reactive 2π component in intermolecular

[60] Schneider, M. In *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Pergamon: Oxford, 1996; Vol. 10, pp 155-299.
[61] Jones, T. H.; Blum, M. S.; Fales, H. M. *Tetrahedron* **1982**, *38*, 1949.
[62] Pinhey, J. T.; Ritchie, E.; Taylor, W. C. *Aust. J. Chem.* **1961**, *14*, 106.
[63] Takadoi, M.; Yamaguchi, K.; Terashima, S. *Bioorg. Med. Chem.* **2003**, *11*, 1169.

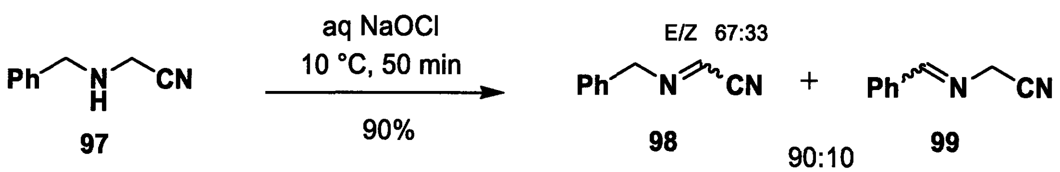
hetero Diels-Alder cycloadditions would provide access to substituted piperidines in a highly convergent fashion. The synthetically versatile α-amino nitrile moiety of the resulting cycloadduct would then allow for the synthesis of a variety of both *cis*- and *trans*-2,6-disubstituted piperidines in contrast to Bailey's methodology.



(19)

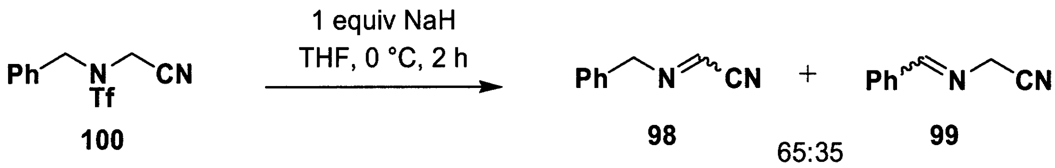
Synthesis of Benzyliminoacetonitrile

For our initial studies, we decided to focus on iminoacetonitrile **98** with the expectation that a benzyl group would be readily removable from the cycloadducts. Iminoacetonitrile **98** was previously synthesized by Selva and coworkers as shown in eq 20.[35] Selva discovered that treatment of amino nitrile **97** with aqueous NaOCl at 10 °C affords imines **98** and **99** as a 90:10 mixture in 90% yield. Unfortunately, we found that separation of the desired iminoacetonitrile **98** from **99** was extremely difficult and not practical for large scale applications. Therefore, we decided to explore alternative methods for the synthesis of iminoacetonitrile **98**.



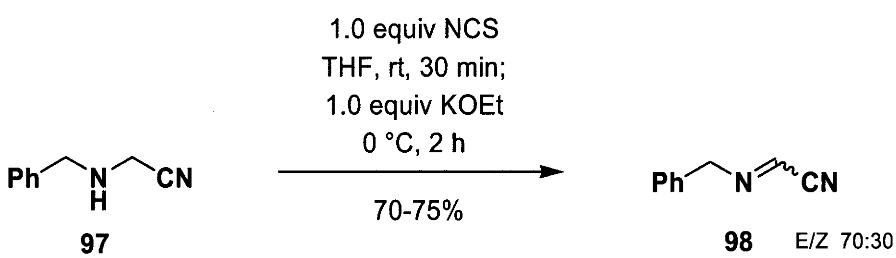
(20)

We next investigated the synthesis of **98** via elimination of trifluoromethanesulfinate from triflamide **100** which was synthesized from the corresponding alcohol via our Mitsunobu strategy. Disappointingly, under standard elimination conditions (Cs_2CO_3) the regioisomeric imine **99** was isolated in 85% yield with no sign of the desired iminoacetonitrile **98**. After screening a variety of bases, however, NaH was found to provide the best ratio of imines **98** and **99**, but still as a mixture (65:35 ratio) (eq 21).



(21)

Discouraged by these results, we next examined the use of our original elimination protocol (NCS, base). Treating amine **97** with NCS followed by KOEt afforded the desired iminoacetonitrile **98** in 70-75% yield (eq 22). The crude ^{1}H NMR spectrum indicated less than 1% of the conjugated imine **99** had formed under these conditions. However, immediate purification on acetone-deactivated silica gel was crucial to avoid isomerization to the alternative imine. Also, benzyliminoacetonitrile **98** is fairly unstable at room temperature and can only be stored for a few weeks in CH_2Cl_2 solution at 4 °C before isomerization takes place.

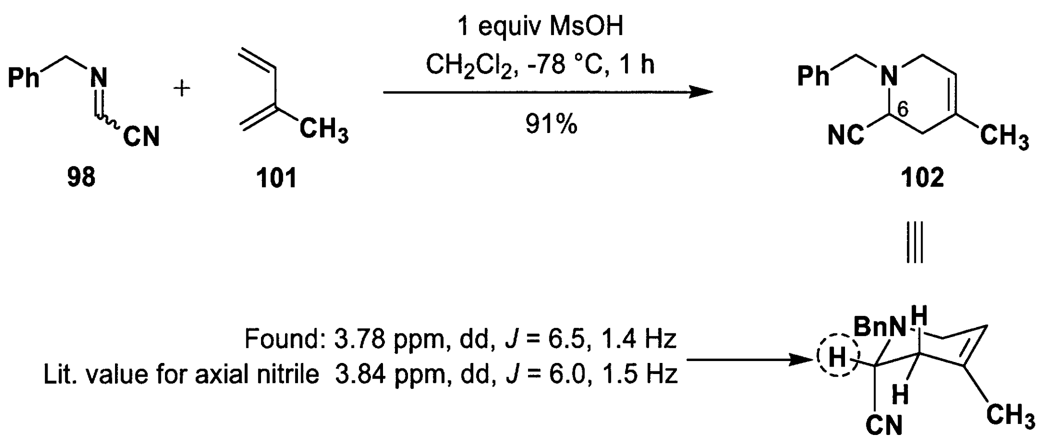


(22)

Scope of the Intermolecular Iminoacetonitrile Cycloaddition

With an effective method for preparation of benzyliminoacetonitrile **98** in hand, our efforts were next directed at exploring the reactivity of **98** as a 2π component in hetero Diels-Alder cycloadditions. Heating imine **98** with isoprene and 3 equiv of BHT in toluene at 120 °C led to recovered imine with no sign of the desired cycloadduct. Notably, however, none of the isomerized imine was formed under these conditions. Undeterred by these results, we shifted our focus to acid-promoted cycloadditions. As shown in Scheme 19, reaction of imine **98** with 3 equiv of isoprene and 1 equiv of MsOH in CH_2Cl_2 at -78 °C for 1 h followed by a basic workup afforded the known cycloadduct **102**[64] in 91% yield as a single regioisomer. Comparison of the coupling constants for the indicated proton at C-6 to literature values confirmed the presence of an axial oriented nitrile.[65] Optimization studies demonstrated that the number of equiv of isoprene could be reduced to 1.5 equiv without a decrease in the yield. As expected from our intramolecular cycloaddition studies, 1 equiv of MsOH was required for complete consumption of iminoacetonitrile **98**.

Scheme 19



In order to rationalize the observed regiochemistry of the intermolecular iminoacetonitrile cycloaddition, one must invoke frontier molecular orbital theory. As is the case with more conventional Diels-Alder reactions, the $HOMO_{diene}$ and $LUMO_{dienophile}$ frontier molecular orbitals (FMOs) control the regiochemistry of aza Diels-Alder reactions.[66] As shown below, in the case of imino dienophiles, a larger atomic coefficient on the carbon atom of the C=N bond (**A**) leads to a preference for product **I**, while a larger coefficient on the nitrogen atom (**B**) favors the

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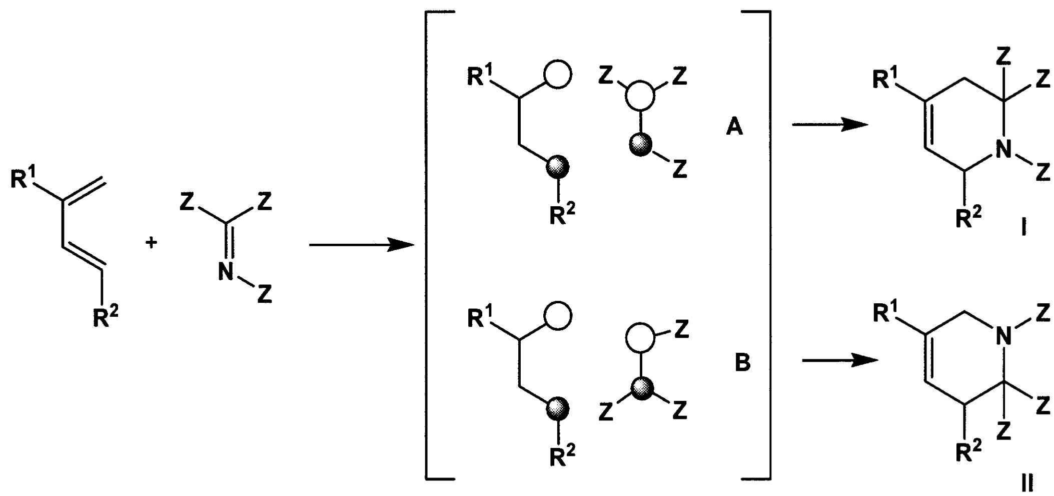
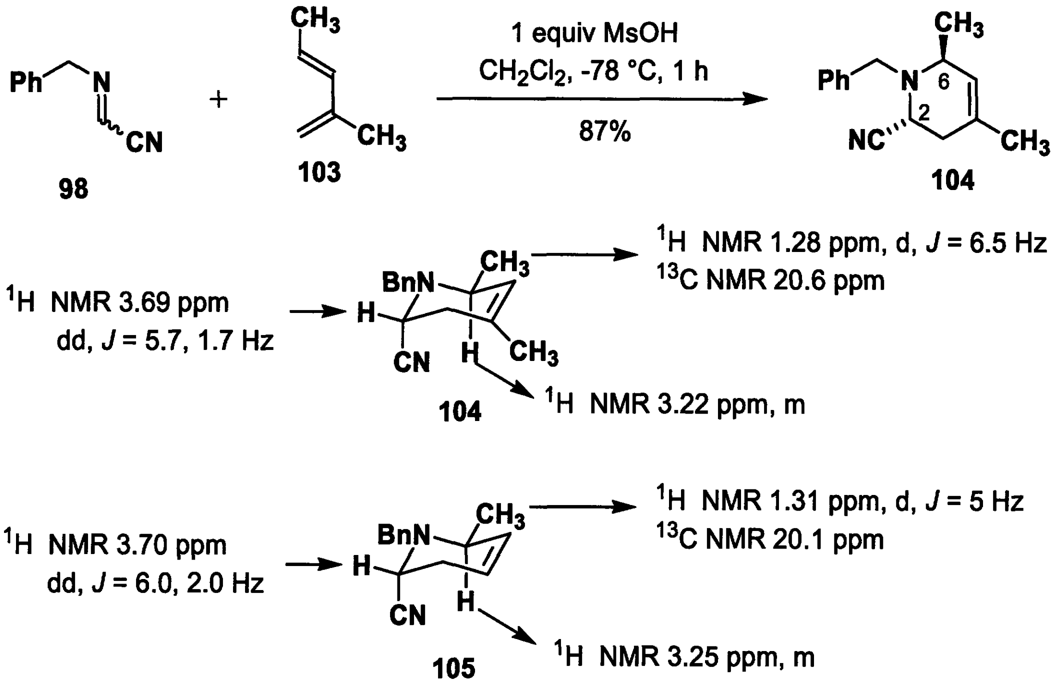
[64] Bonin, M.; Romero, J. R.; Grierson, D. S., and Husson, H.-P. *J. Org. Chem.* **1984**, *49*, 2392.
[65] Husson and coworkers assigned the nitrile as axial due to the lack of a large coupling constant (axial-axial) for the proton at C-2.
[66] Fleming, I. *Frontier Orbitals and Organic Chemical Reactions*; John Wiley & Sons: New York, 1976.

regioisomeric product **II**. The majority of imino dienophiles react to provide products with the substitution pattern of **I**.[10] However, imines with two electron-withdrawing groups on the carbon atom tend to afford products with substitution pattern **II**. The observation that iminoacetonitrile **98** affords cycloadduct **102**, consistent with substitution pattern **I**, suggests that the largest atomic coefficient in the LUMO is located on the carbon atom of the C=N bond as is the case with simple imines baring only alkyl and aryl substituents.



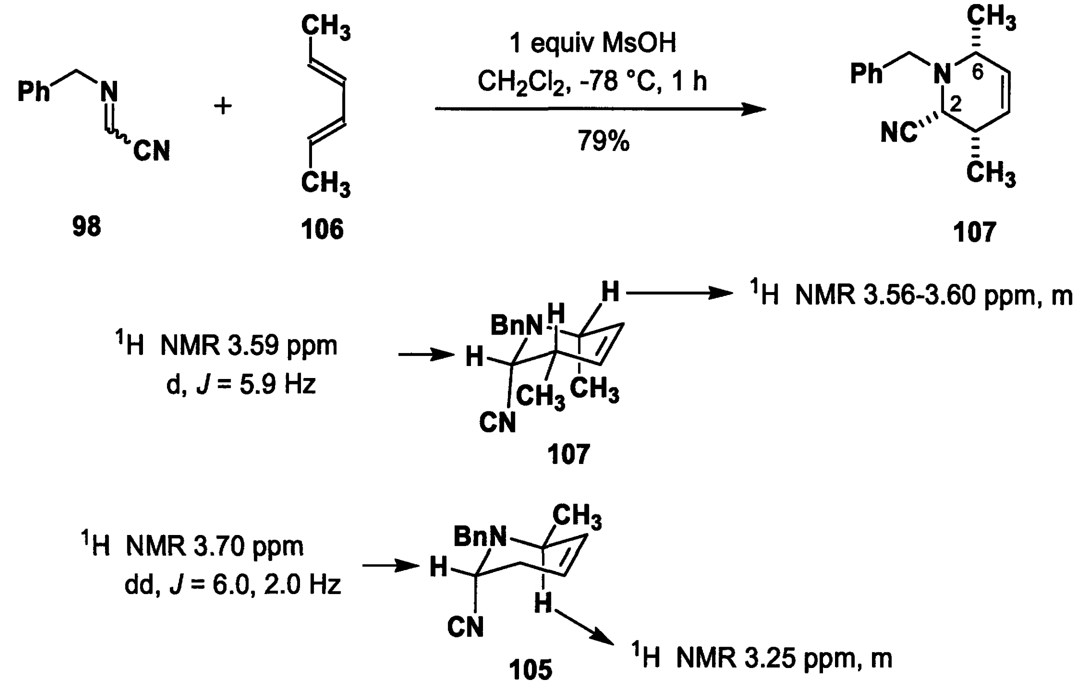
With conditions for the intermolecular cycloaddition of iminoacetonitriles in hand, efforts were directed toward exploring the scope of the cycloaddition. As shown in Scheme 20, the cycloaddition of imine **98** with 2-methyl-1,3-pentadiene afforded cycloadduct **104** in 87% yield as a single diastereomer with an axial oriented cyano group. As shown below, the structure and stereochemical assignment of cycloadduct **104** were confirmed by comparison to the known piperidine **105**.[64]

Scheme 20



Next, cycloaddition of imine **98** and 2,4-hexadiene was examined and was found to produce cycloadduct **107** as a single diastereomer in 79% yield (Scheme 21). The *cis*-relationship between the C-3 and C-6 methyl groups is consistent with suprafacial addition of the diene to the imine. Comparison of the chemical shifts and coupling constants in **107** to the known piperidine **105** established the stereochemistry at C-2, C-3, and C-6. The absence of an equatorial-equatorial *J*-coupling of ca. 2.0 Hz for the C-2 proton in compound **107** indicated that the C-3 methyl group occupies an equatorial orientation. Based on the observed difference in chemical shift between the C-6 protons of **107** and **105**, we concluded that the C-6 proton of **107** was equatorial.

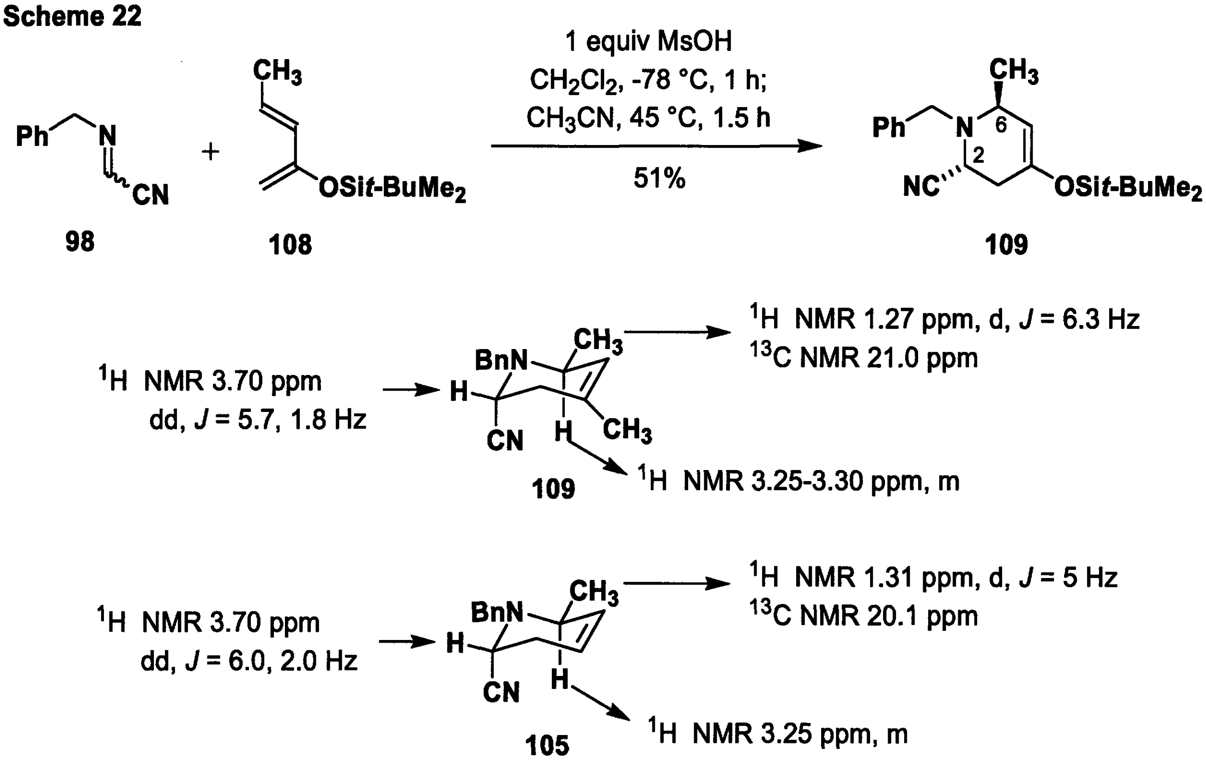
Scheme 21



The last case we explored involved the cycloaddition of imine **98** and silyl enol ether **108**[67] to provide cycloadduct **109** in 51% yield as a single diastereomer (Scheme 22). As shown in Scheme 22, comparison of the chemical shift and coupling constant values for cycloadduct **109** and the known piperidine **105**[64] elucidated the stereochemistry of the key stereocenters, at C-6 and C-2. The lower yield in this case is most likely a result of competing decomposition of silyl enol ether **108** under the acidic conditions of the reaction. In contrast to **104** and **107,** cycloadduct **109** was initially isolated as a mixture of nitrile isomers. However, simply heating the mixture at 45 °C in CH_3CN for 1.5 h affords the thermodynamically favored product with an axial cyano group. Cycloadduct **109** should be a useful intermediate as it should be possible to selectively install substituents at C-2, C-5, and C-6 utilizing the α-amino nitrile moiety and the masked carbonyl at C-4.

[67] For the synthesis of silyl enol ether **91**, see: Jacobi, P. A.; Cai, G. *Heterocycles* **1993,** *35,* 1103.

Scheme 22



Summary

In conclusion, benzyliminoacetonitrile participates in acid-promoted intermolecular [4+2] cycloadditions with a variety of dienes affording piperidine ring systems. The cycloadducts are obtained as single regioisomers and diastereomers with axial oriented cyano groups in good yield.

Part III

Synthetic Utility of

α-Amino Nitrile Cycloadducts

Chapter 6 – Transformations of α-Amino Nitrile Cycloadducts

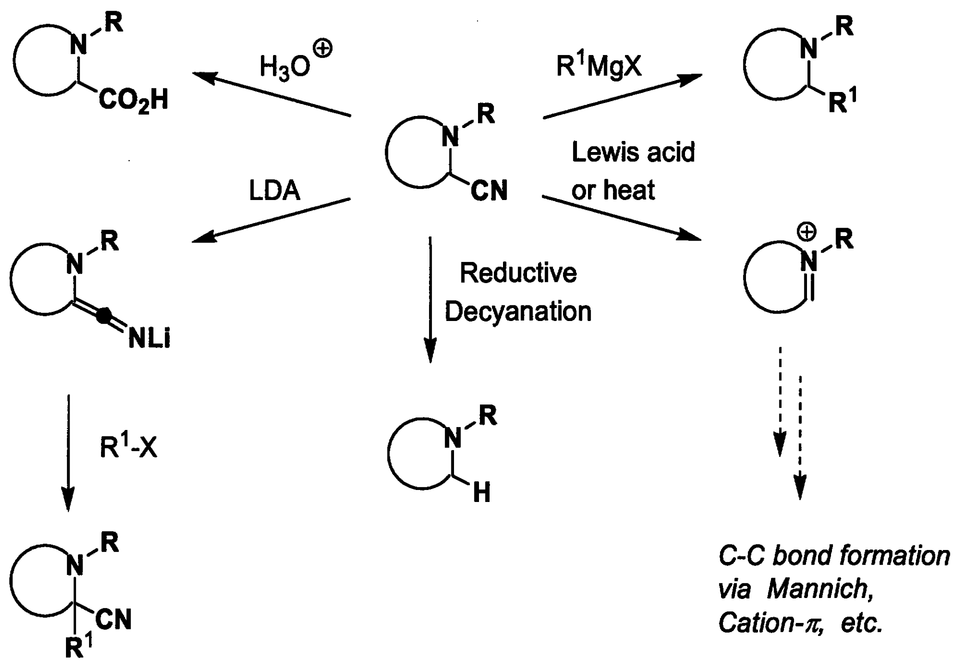
As discussed in Chapter 1, one of our primary reasons for exploring iminoacetonitriles as 2π components in aza Diels-Alder cycloadditions was our expectation that the α-amino nitrile cycloadducts would serve as versatile synthetic intermediates amenable to further elaboration. This chapter begins with a brief overview of previous studies on α-amino nitrile transformations and then provides details of our work involving the synthetic elaboration of α-amino nitrile cycloadducts to give substituted quinolizidines and indolizidines.

Introduction and Background

As shown in Scheme 23, α-amino nitriles are exceptionally versatile intermediates for the synthesis of nitrogen heterocycles.[9] The simplest and most well-known reaction of α-amino nitriles is hydrolysis to produce amino acids, as demonstrated by Strecker in 1850.[68] Several other useful transformations such as reduction and nucleophilic addition are possible based on the nitrile moiety, but the focus of this chapter will be on the application of α-amino nitriles as *latent iminium ions*.

[68] Strecker, A. *Liebigs. Ann. Chem.* **1850**, *75*, 27.

Scheme 23

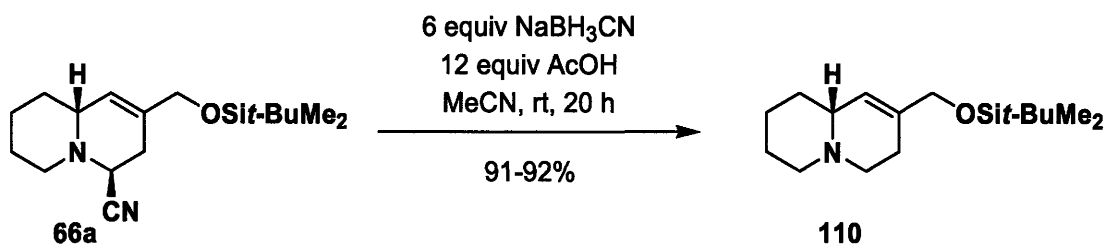


The ability of α-amino nitriles to function as stable precursors to iminium ions and the ease with which ionization of the cyano group occurs provides for a wide range of further reactions, such as Mannich condensations, cation-π type cyclizations, and Bruylants reactions.[9] A complementary mode of reactivity involves metallation of the nitrile to afford stabilized lithium derivatives that can then undergo a variety of carbon-carbon bond-forming reactions. Thus, by proper choice of reaction conditions, the carbon atom of the α-amino nitrile can function as either a nucleophilic or electrophilic species.

The simplest transformation in which α-amino nitriles function as latent iminium ion precursors is reductive decyanation (Scheme 23). This type of reduction is usually carried with $NaBH_4$ in EtOH, with either heat or a large excess of reducing agent (10 equiv).[69] However, a variety of other reagents have been reported for the reductive decyanation of α-amino nitriles,

[69] For a review on reductive decyanations, see Mattalia, J. M.; Marchi-Delapierra, C.; Hazimeh, H.; Chanon, M. *Arkivoc* **2006**, *4*, 90.

including $LiAlH_4$,[70] BH_3,[71] $Zn(BH)_4$,[72] $NaBH_3CN$,[73] KBH_4,[74] and alkali metals in liquid NH_3.[75] Although several methods are well known for this transformation, David Amos found that consistently superior yields (ca. 10% higher) are obtained using $NaBH_3CN$ in AcOH. For example, Amos found that treatment of **66a** with $NaBH_3CN$ and AcOH in CH_3CN delivered quinolizidine **110** in 91-92% yield (eq 23), while with $NaBH_4$ in refluxing EtOH **110** was obtained in 83% yield.[36]



(23)

A unique mode of reactivity of α-amino nitriles that deserves special mention is the Bruylants reaction.[76] Typically, organometallic species such as alkyllithium compounds react with nitriles via a 1,2-addition pathway. However, reaction of an α-amino nitrile with a Grignard reagent usually leads to ionization of the cyano group to generate an iminium ion due to the Lewis acidic nature of the magnesium species present in the Grignard reagent. The iminium ion is then trapped by organomagnesium compounds to give the *substitution* product rather than the "normal" addition product (eq 24). Several types of Grignard reagents have been utilized in the Bruylants reaction including alkyl, vinyl, aryl, and alkynyl magnesium halides.[77,9] A modification of the Bruylants reaction involves reaction with Grignard reagents in the

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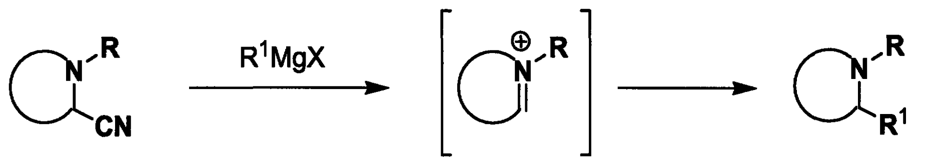
[70] Froelich, O.; Desos, P.; Bonin, M.; Quirion, J.-C.; Husson, H.-P. *J. Org. Chem.* **1996**, *61*, 6700.
[71] Ogura, K.; Shimamura, Y.; Fujita, M. *J. Org. Chem.* **1991**, *56*, 2920.
[72] Zhu, J.; Quiron, J.-C.; Husson, H.-P. *Tetrahedron Lett.* **1989**, *30*, 5137.
[73] Mitch, C. H. *Tetrahedron Lett.* **1988**, *29*, 6831.
[74] Kuehne, M. J.; Xu, F. *J. Org. Chem.* **1997**, *62*, 7950.
[75] Arseniyadis, S.; Huange, P. Q.; Husson, H.-P. *Tetrahedron Lett.* **1988**, *29*, 1391.
[76] Bruylants, P. *Bull. Soc. Chem. Belg.* **1924**, *33*, 467.
[77] For examples of the Bruylants reaction, see: (a) Albrecht, H.; Dollinger, H. *Synthesis* **1985**, 743. (b) Agami, C.; Couty, F.; Evano, G. *Org. Lett.* **2000**, *2*, 2085.

presence of a Lewis acid which enables the reaction to be conducted at low temperatures (-78 °C).[77] In addition to Grignard reagents, silyl enol ethers,[78] ketones,[79] malonates,[9a] indoles,[9a] and organozinc compounds[80] also react with these latent iminium ions to afford substitution products analogous to those formed in the Bruylants reaction.



(24)

The chemistry discussed above has been elegantly utilized in the laboratories of Husson and Polniaszek, among others. Husson and coworkers have exploited the reactivity of the α-amino nitrile moiety of non-racemic *N*-(cyanomethyl)oxazolidines (e.g., **111**) for the synthesis of several natural products.[81] As shown in Scheme 24, metallation of **111** with LDA followed by alkylation with propyl bromide afforded **112** in 98% yield. Reduction of **112** with $NaBH_4$ followed by removal of the chiral auxiliary afforded (*S*)-(+)-coniine in good yield and excellent enantiomeric purity. To access (*R*)-(–)-coniine, Husson and coworkers used the electrophilic nature of the α-amino nitrile moiety. Ionization of the cyano group upon treatment of **111** with silver tetrafluoroborate afforded an intermediate iminium ion, which upon addition of propylmagnesium bromide provided the overall substitution product **113**. Subsequent removal of the chiral auxiliary afforded (*R*)-(–)-coniine in good yield with excellent stereochemical purity.[82]

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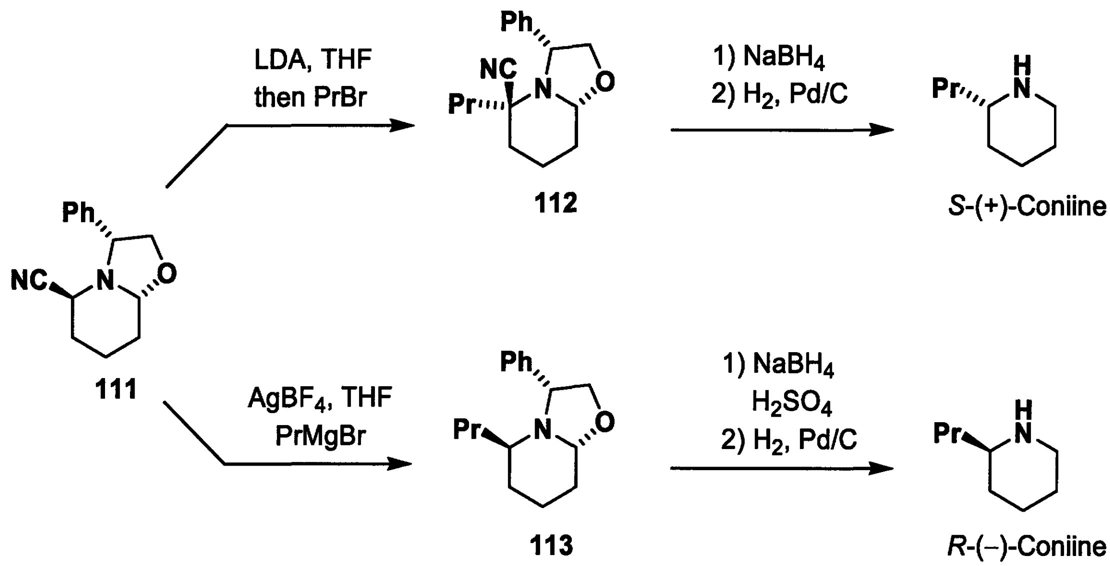
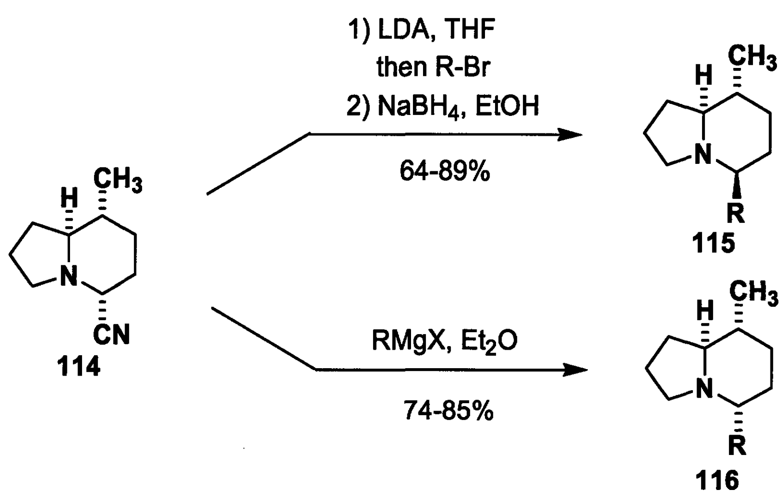
[78] (a) Koskinen, A.; Lounasmaa, M. *J. Chem. Soc., Chem. Commun.* **1983**, 821. (b) Grierson, D. S.; Bettiol, J.-L.; Buck, I.; Husson, H.-P. *J. Org. Chem.* **1992**, *57*, 6414.
[79] Bonjoch, J.; Casamitjana, N.; Gracia, J.; Bosch, J. *Tetrahedron Lett.* **1989**, *30*, 5655.
[80] Bernardi, L.; Bonini, B. F.; Capito, E.; Dessole, G. Fochi, M.; Comes-Franchini, M.; Ricci, A. *Synlett* **2003**, 1778.
[81] For a review of Husson's CN(*R,S*) method, see: Husson, H.-P.; Royer, J. *Chem. Soc. Rev.* **1999**, *28*, 383.
[82] Guerrier, L.; Royer, J.; Grierson, D. S.; Husson, H.-P. *J. Am. Chem. Soc.* **1983**, *105*, 7754.

Scheme 24



Polniaszek and Belmont utilized α-amino nitrile **114** in the total synthesis of several indolizidine alkaloids.[83] As shown in Scheme 25, alkylation of the metalated nitrile with alkyl bromides followed by reductive decyanation furnished indolizidine **115** in good yield as a single diastereomer. Alternately, Bruylants reaction of α-amino nitrile **114** with Grignard reagents delivered the stereocomplementary product **116**, again as a single diastereomer.

Scheme 25



[83] (a) Polniaszek, R. P.; Belmont, S. E. *J. Org. Chem.* **1990**, *55*, 4688. (b) Polniaszek, R. P.; Belmont, S. E. *J. Org. Chem.* **1991**, *56*, 4868.

In summary, α-amino nitriles are extremely versatile intermediates for the synthesis of nitrogen heterocycles. Our iminoacetonitrile cycloaddition methodology provides a general and efficient route to polycyclic α-amino nitriles, and we were excited to investigate the elaboration of these cycloadducts to demonstrate their utility as synthetic intermediates.

Transformations of α-Amino Nitrile Cycloadducts

Our early studies on the transformations of α-amino nitrile cycloadducts focused on reactions involving quinolizidine **66a** and indolizidine **74** as prototype systems. These cycloadducts are readily accessible on a multigram scale, stable to long term storage, and easy to handle. The first part of this chapter discusses the reductive decyanation, alkylation, and Bruylants reaction of α-amino nitriles **66a** and **74**. The second part of this chapter then describes our efforts toward the synthesis of quinolizidines and indolizidines incorporating quaternary centers, including spiroquinolizidines.

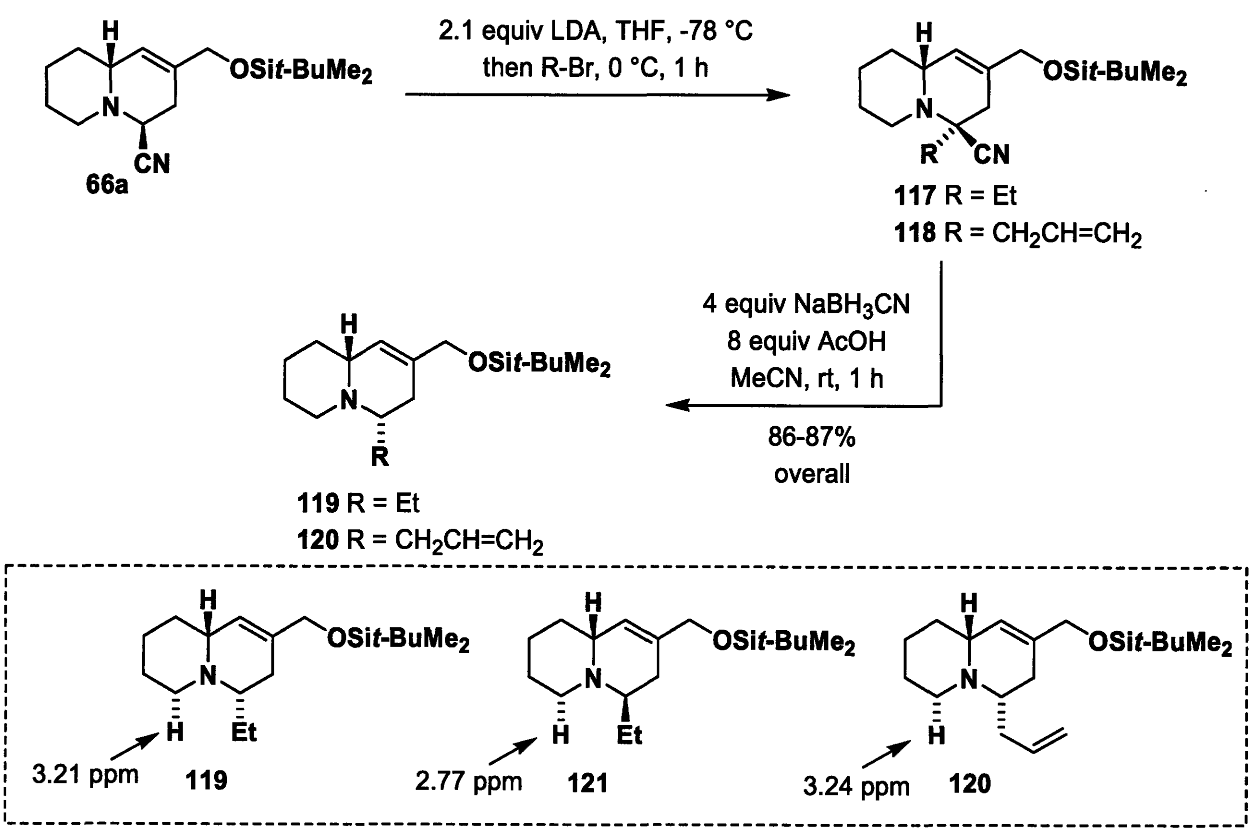
Alkylation/Reductive Decyanation

Previous studies by David Amos had established conditions for the tandem alkylation-reductive decyanation of our α-amino nitrile cycloadducts. For example, as illustrated in Scheme 26, treatment of **66a** with 2.1 equiv of LDA[84] at -78 °C followed by quenching with ethyl iodide afforded the tertiary α-amino nitrile **117** in quantitative yield, though with only 90% purity. Further purification was not attempted as tertiary α-amino nitriles such as **117** decompose upon purification by silica gel chromatography. Therefore, treatment of **117** without prior purification with $NaBH_3CN$ under our standard reductive decyanation conditions delivered

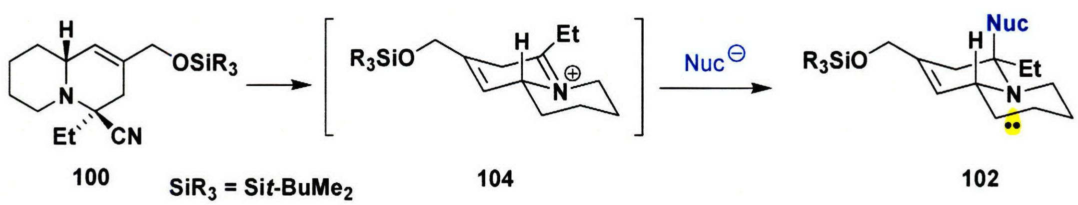
[84] Employing less LDA led to the recovery of starting material.

quinolizidine **119** in 87% yield (overall from **66a**) as a single diastereomer.[36] As expected, the reductive decyanation of the tertiary α-amino nitrile **117** was considerably faster than the reduction of the secondary α-amino nitrile **66a** due to the increased stability of the tetrasubstituted iminium ion intermediate. Using similar conditions, I extended the tandem alkylation-reductive decyanation protocol developed by Amos to the synthesis of **120**. Thus, alkylation of **66a** with allyl bromide followed by reductive decyanation afforded quinolizidine **120** in 86% overall yield as a single diastereomer. The allyl group of **120** was assigned as equatorial (*endo*) based on NMR analysis and comparison with the spectra previously reported by Amos[36] for the related compounds **119** and **121** as shown below.

Scheme 26



The stereochemical control observed in the reductive decyanation step is of particular significance. As shown in eq 25, the stereochemistry of the tertiary α-amino nitrile **117** is irrelevant as the first step in the reductive decyanation involves ionization of the cyano group to generate iminium ion **122**. This carbocation is then trapped via *exo* (axial) addition of a nucleophile (hydride in this case) which is predicted by stereoelectronic considerations to occur such that approach of the nucleophile maintains maximum orbital overlap with the developing lone pair on nitrogen.[85]

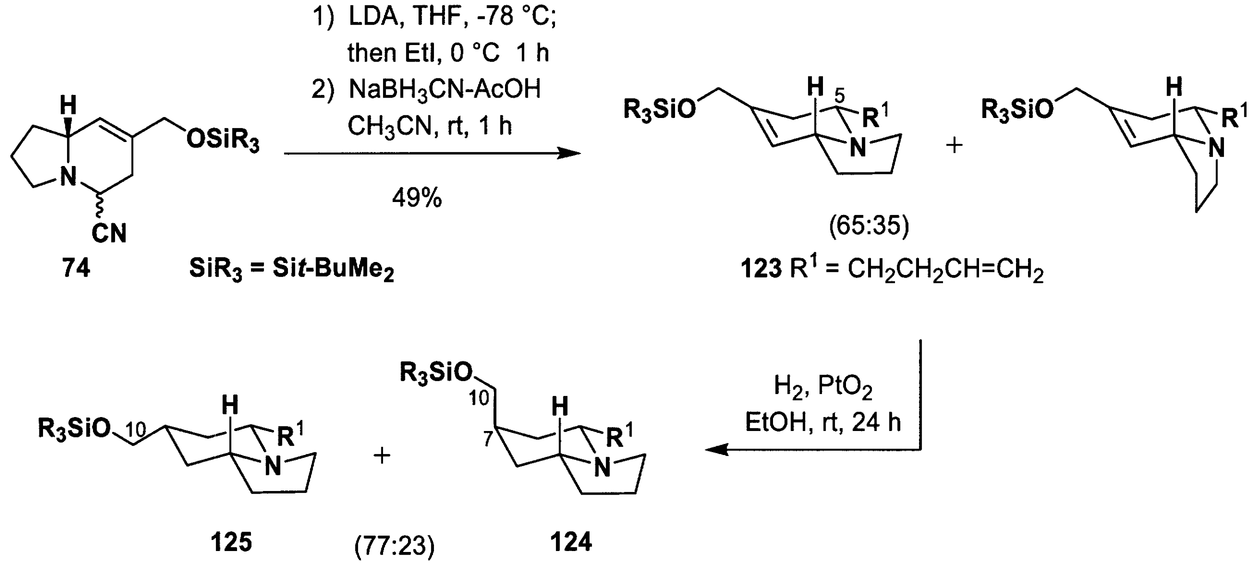


(21)

As mentioned previously, several biologically active indolizidine alkaloids are substituted at the C-5 carbon. Therefore, our efforts were next directed at applying the tandem alkylation-reductive decyanation to the synthesis of indolizidine **123** (Scheme 27). In the event, treatment of α-amino nitrile **74** with 2.1 equiv of LDA followed by quenching the metalated nitrile with 4-bromobutene afforded the tertiary α-amino nitrile in quantitative yield (85% purity) as a single diastereomer. Subjecting the unpurified tertiary α-amino nitrile to our standard reductive decyanation conditions then delivered indolizidine **123** in 49% yield as a 65:35 mixture of isomers. As discussed below, spectroscopic studies (vide infra) confirmed that both isomers possess an equatorial butenyl substituent, *trans* to the ring junction hydrogen, and that the two isomers in fact differ as *conformational isomers*, with *trans* and *cis* azaindane systems, respectively.

[85] (a) Deslongchamps, P. *Stereoelectronic Effects in Organic Chemistry*; Pergamon: New York, 1983, pp 211-221. (b) Stevens, R. V. *Acc. Chem. Res.* **1984**, *17*, 289.

Scheme 27



In order to confirm the structure of indolizidine **123**, we hydrogenated the mixture to afford indolizidines **124** and **125** in quantitative yield as a 77:23 mixture of isomers which were shown to differ only by the configuration at the new C-7 center determined in the hydrogenation. This finding indicates that the original indolizidine isomers **123** must both have the same configuration at C-5, and thus must be conformational isomers differing with regard to having a *cis* or *trans* azabicyclic skeleton. The assignment of the C-7 stereocenter was established by comparison of the chemical shifts of the protons at C-10 of **124** and **125** to related compounds.[86] As shown below, the butenyl group (R^1) in **124** was assigned as equatorial (*endo*) based on NMR analysis and comparison of the H_{3a} chemical shift in each compound with the spectra previously reported by Polniaszek and coworkers[83a] for the related compounds **126** and **127**.

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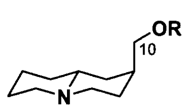
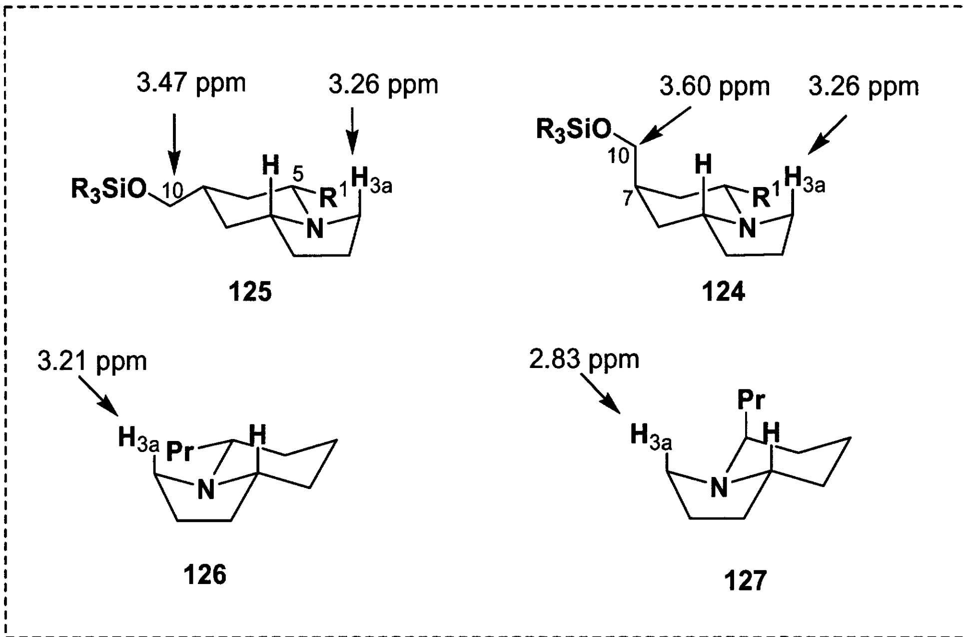
[86] Wyman and coworkers found that the C-10 protons of  are deshielded by ca. 0.15 ppm relative to the equatorial (CH_2OR) isomer, see Wyman, P. A.; Gaster, L. M.; King, F. D.; Sutton, J. M.; Ellis, E. S.; Wardle, K. A.; Young, T. J. *Bioorg. Med. Chem.* **1996**, *4*, 255.



In order to obtain further support for our assignment for **123**, we investigated the energy difference between *cis*- and *trans*-fused indolizidines **I** and **II** using *ab initio* methods. As can be seen in Figure 2, the *trans*-fused saturated indolizidine (**Ia**) was calculated to be 2.5 kcal/mol more stable than the *cis*-fused saturated indolizidine (**Ib**), consistent with literature values.[87] In contrast, calculation of the energy difference between the *trans*- and *cis*-fused *unsaturated* indolizidines **II** revealed that *trans*-fused form **IIa** is only 0.1 kcal/mol more stable than the *cis*-fused form **IIb**. This is in accordance with our observation that the related unsaturated indolizidine **123** exists as a mixture of *trans*- and *cis*-fused indolizidines whereas the hydrogenation products are observed to be only *trans*-fused systems.

[87] The *trans*-fused indolizidine is 2.4 kcal/mol more stable than the *cis*-fused indolizidine, see Aaron, H. S.; Ferguson, C. P. *Tetrahedron Lett.* **1968**, *9*, 6191.

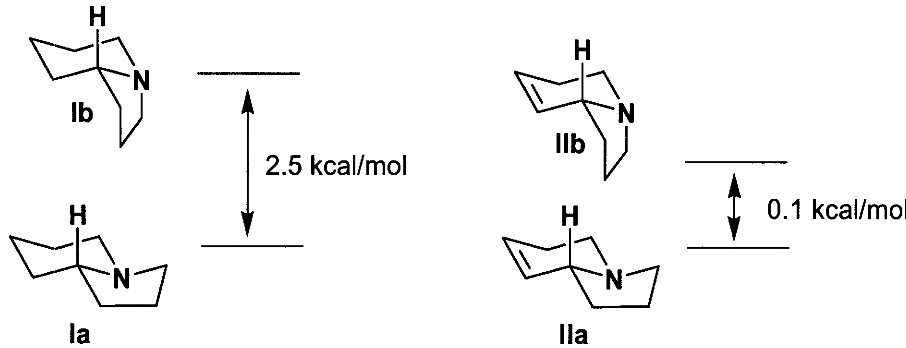
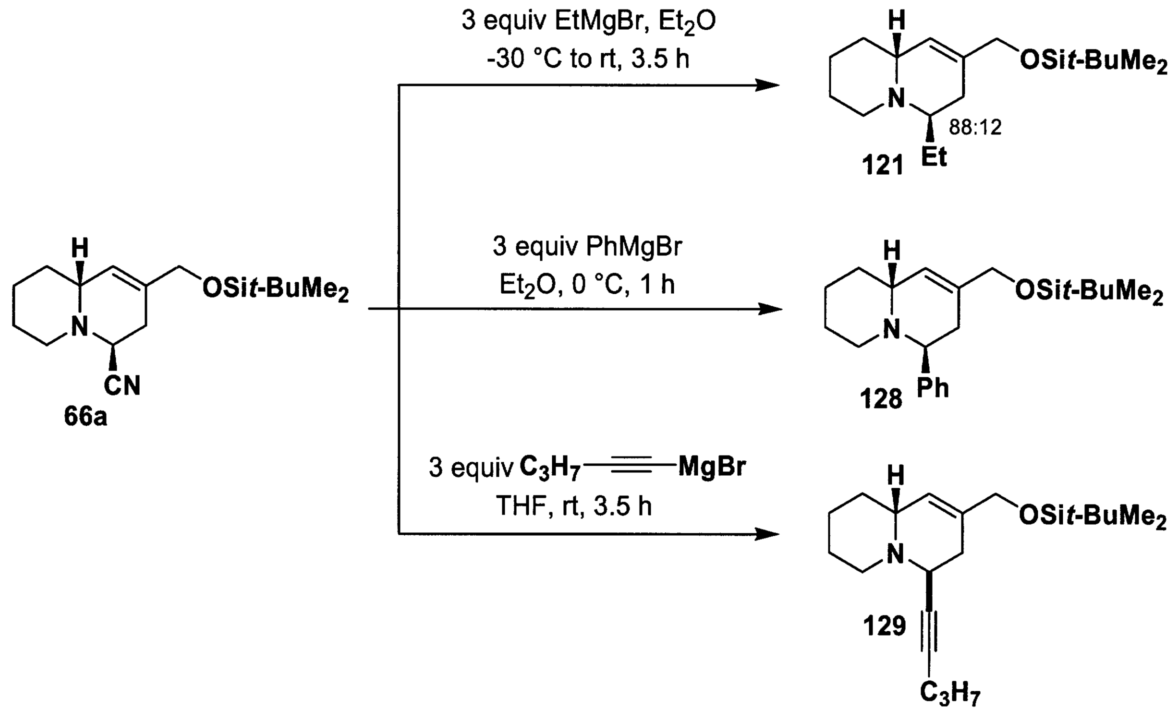


Figure 2. Relative energies for saturated and unsaturated indolizidines calculated using MacSpartan '04 (*ab initio* HF-6-311+G**) (Wavefunctions, Irvine, CA).

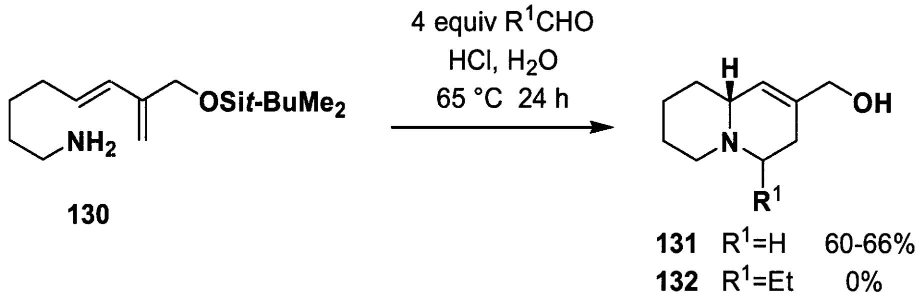
Bruylants Reaction

We next turned our attention to the Bruylants reaction of α-amino nitrile **66a**. Some of the earlier results obtained by David Amos are shown in Scheme 27. Thus, Amos had found that treatment of **66a** with 3 equiv of ethylmagnesium bromide in Et_2O affords quinolizidine **121** in 85% yield as an 88:12 mixture of β and α ethyl stereoisomers.[36] As predicted by stereoelectronic principles (vida supra), the intermediate iminium ion is trapped via axial addition of the Grignard reagent to give the major diastereomer **121**. Interested in exploring the scope of this process with respect to different types of Grignard reagents, Amos found that aryl and alkynyl Grignard reagents deliver the expected quinolizidines **128** and **129** in excellent yield as a single diastereomer in each case (Scheme 27). Of particular importance is the stereocomplementary nature of transformations **66a→119** (Scheme 26) and **66a→121,** in which the C-4 stereocenter can be controlled to provide either diastereomer depending on the protocol employed.

Scheme 27



It should be noted that the ability of our strategy to provide efficient access to substituted quinolizidines and indolizidines such as **119** and **121** is of particular importance, since nitrogen heterocycles of this type are not available via the intramolecular Diels-Alder reactions of iminium ions described by Grieco. As discussed in Chapter 2, Grieco reported that iminium ions derived from formaldehyde readily undergo the desired cycloaddition, but in the case of iminium ions derived from acetaldehyde "the reaction rate was substantially retarded and the number of byproducts was significantly increased."[30] To obtain more specific data on the scope of the Grieco iminium ion Diels-Alder reaction, David Amos investigated the reactions shown in eq 26.[36] As expected, the formiminium ion derived from **130** and HCHO afforded the expected cycloadduct **131** in good yield; however, the analogous reaction of **130** with propionaldehyde failed to deliver the expected cycloadduct **132** and instead resulted in the formation of a complex mixture of products. In contrast, as discussed above, our iminoacetonitrile cycloaddition strategy not only provides access to substituted quinolizidines and indolizidines such as **132**, but also allows us to selectively generate either of the two stereoisomers.



(26)

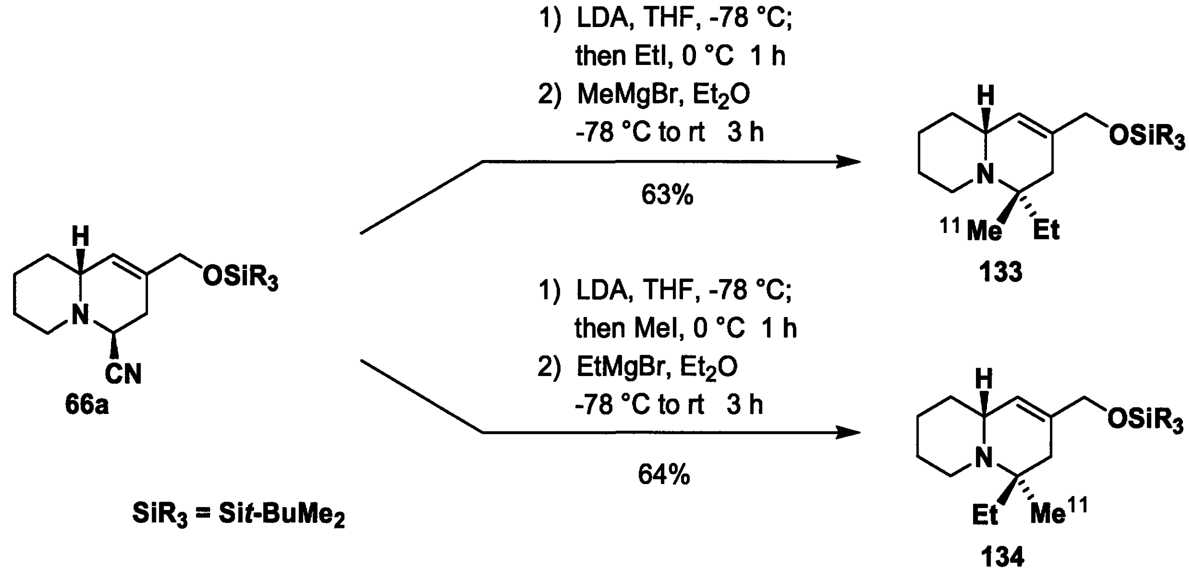
Synthesis of Quinolizidines and Indolizidines with Quaternary Centers

Next, we turned our attention to the application of this chemistry for the synthesis of quinolizidines and indolizidines incorporating quaternary centers.[88] The diastereoselective installation of quaternary centers has always been a challenging problem in organic synthesis. We envisioned that by using a combination of alkylation reactions and stereocontrolled additions to iminium ions, stereoisomeric quinolizidines and indolizidines with quaternary centers would be available with a high degree of stereocontrol. As illustrated in Scheme 28, this has indeed turned out to be the case. Thus, alkylation of **66a** with ethyl iodide followed by Bruylants reaction with methylmagnesium bromide affords quinolizidine **133** as a single diastereomer. The diastereomeric quinolizidine **134** was prepared by reaction of the metalated nitrile with methyl iodide and subsequent reaction with ethylmagnesium bromide. It is crucial to the success of the Bruylants reaction that upon scaling up the reaction (>100 mg) the Grignard reagent is pre-cooled to 0 °C before addition to the alkylated α-amino nitrile. If the Grignard reagent is not pre-cooled to 0 °C, the yield of the reaction is decreased (ca. 30-40%) because the alkylated α-

[88] See reference 9 and Husson, H.-P.; Royer, J.; Yue, C. *J. Org. Chem.* **1992**, *57*, 4211.

amino nitrile (obtained from the first step) rapidly decomposes upon addition of the Grignard reagent.

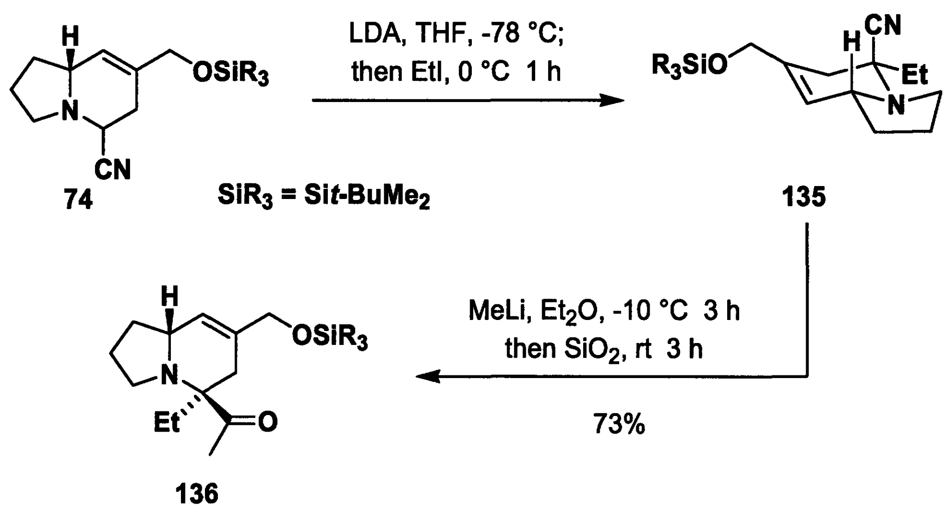
Scheme 28



The stereochemical assignments of the quaternary centers in **133** and **134** are based on the observed resonances for the C-11 methyl groups in the ^{1}H NMR spectrum. The protons of the C-11 methyl group in quinolizidine **134** are shifted downfield (1.10 ppm vs 0.88 ppm) relative to the protons in the C-11 methyl group of **133**. The equatorial methyl group lies in the deshielding cone of a C-C bond of the ring skeleton and therefore is expected to appear further downfield than the axial methyl group.[51] This assignment is consistent with axial delivery of the Grignard nucleophile to the iminium ion as previously discussed.

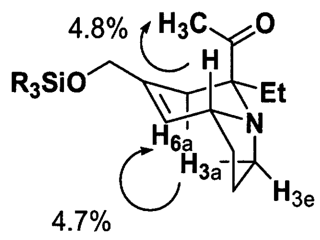
A second strategy for installing quaternary centers exploits the nucleophilic character of a metalated α-amino nitrile and the electrophilic character of the nitrile group itself. Alkylation of **74** with ethyl iodide followed by addition of methyllithium provided the expected imine, which upon hydrolysis by added silica gel afforded **136** in 73% yield (overall from **74**) as a single diastereomer (Scheme 29). The cyano group of the alkylated α-amino nitrile **135** was anticipated to be axially disposed due to the anomeric effect, and thus ketone **136** is predicted to have the stereochemistry shown.

Scheme 29

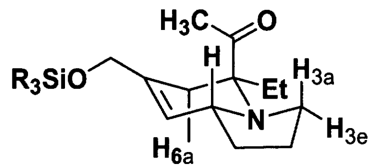


The stereochemistry of the quaternary center in **136** was established using NOE difference experiments. Irradiation of the ring junction hydrogen produced an NOE enhancement at the acetyl methyl group confirming the equatorial disposition of the ethyl group. Interestingly, irradiation of H_{3a}[89] produced an NOE enhancement at the C-6 axial hydrogen (H_{6a}) and not at the ring junction hydrogen leading to the conclusion that **136** exists as the *cis*-azaindane conformational isomer as shown below.

[89] The chemical shifts of the C-3 protons are well resolved in the ^1H NMR spectrum of **136**. The more deshielded proton (2.98 ppm vs 2.55 ppm) was assigned as the equatorial proton (H_{3e}) due to the fact that it lies in the deshielding cone of a C-C bond of the ring skeleton.



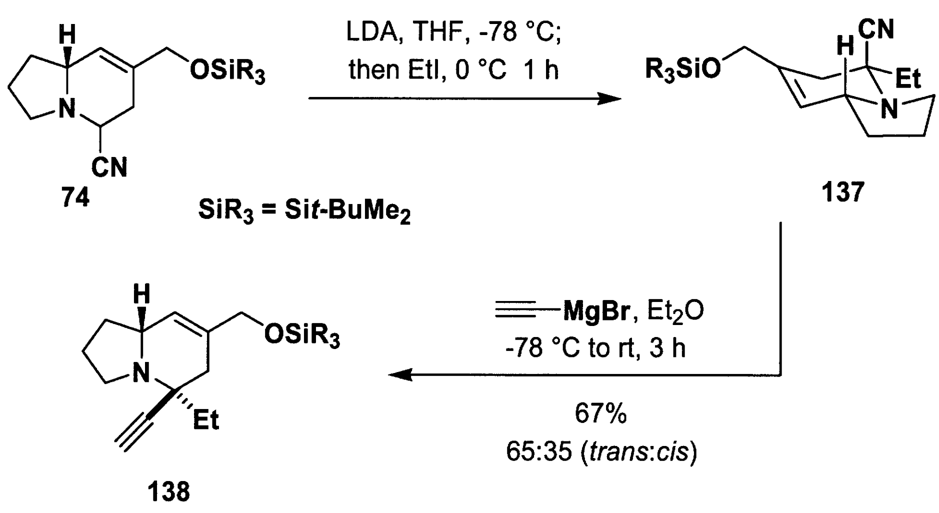
NOE enhancements
for *cis*-**136**



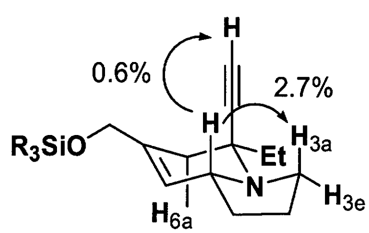
trans-**136**

Next, indolizidine **138** was prepared in 67% yield by reacting the metalated α-amino nitrile with ethyl iodide to give tertiary α-amino nitrile **137** which was immediately treated with ethynylmagnesium bromide. Again, as predicted on the basis of stereoelectronic considerations, diastereomer **138** was obtained as the exclusive product of the reaction (Scheme 30). However, in this case, we isolated a 65:35 mixture of *trans*- and *cis*-fused indolizidine conformational isomers which could be separated by column chromatography.

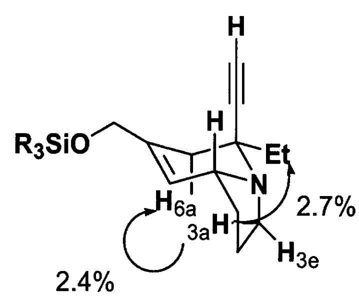
Scheme 30



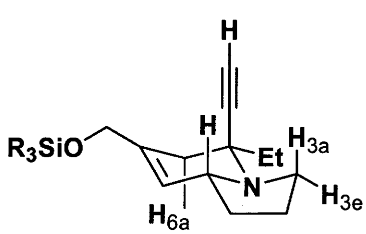
Unambiguous assignment of the *trans*- and *cis*-fused indolizidine ring systems was accomplished by employing difference NOE experiments. First, identification of H_{3e} and H_{3a} in the spectra of the major and minor isomers was made by NMR analysis. The chemical shifts of the C-3 protons are well resolved in the ^{1}H NMR spectra of both isomers. The more deshielded proton (for major-**138** 2.91 ppm vs 2.39 ppm and for minor-**138** 3.14 ppm vs 2.82 ppm) was assigned as (H_{3e}) due to the fact that it lies in the deshielding cone of a C-C bond of the ring skeleton.[51] Irradiation of the ring junction hydrogen in the major ring system produced NOE enhancements at H_{3a} and the acetylene hydrogen. These results rule out the possibility of the structure of the major isomer being *trans*-**139**. However, irradiation of the H_{6a} proton did not produce an NOE enhancement at H_{3a}. Therefore, we concluded that the major isomer is *trans*-**138**. Next, irradiation of H_{3a} of the minor product produced NOE enhancements at the C-6 axial hydrogen (H_{6a}) and the ethyl group which supports the assignment of the minor isomer as *cis*-**138** instead of *cis*-**139**.



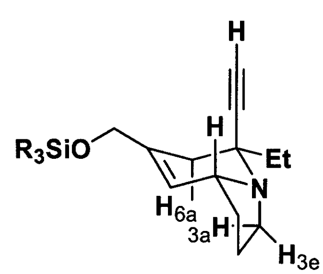
NOE enhancements
for *trans*-**138**



NOE enhancements
for *cis*-**138**



trans-**139**



cis-**139**

The preceding reaction sequences for the installation of quaternary centers take advantage of all three reactive characteristics of the α-amino nitrile moiety. The alkylation employs the nucleophilic character of metalated nitriles, while the formation of the ketone demonstrates the electrophilic nature of the cyano group, and the Bruylants reaction exploits the latent iminium ion character present in this functional group. Therefore, implementing the appropriate tactics allows the incorporation of different functional groups with complementary stereochemistry.

Synthesis of Spiroquinolizidines

Our attention was next focused on utilizing α-amino nitrile cycloadducts for the synthesis of spiro-fused azatricyclic systems. Besides being structurally intriguing molecules, these systems are also found in biologically active natural products such as halichlorine. Halichlorine, a marine alkaloid isolated from the sponge *Halichondria okadai Kadota*, inhibits the expression of VCAM-1 (Vascular Cell Adhesion Molecule-1) and therefore has been identified as a lead compound for the development of antiinflammatory drugs.[90,91] Initially, we envisioned using ring closing metathesis as shown in Scheme 31 to form the spirocyclic system of molecules such as **141**.[92]

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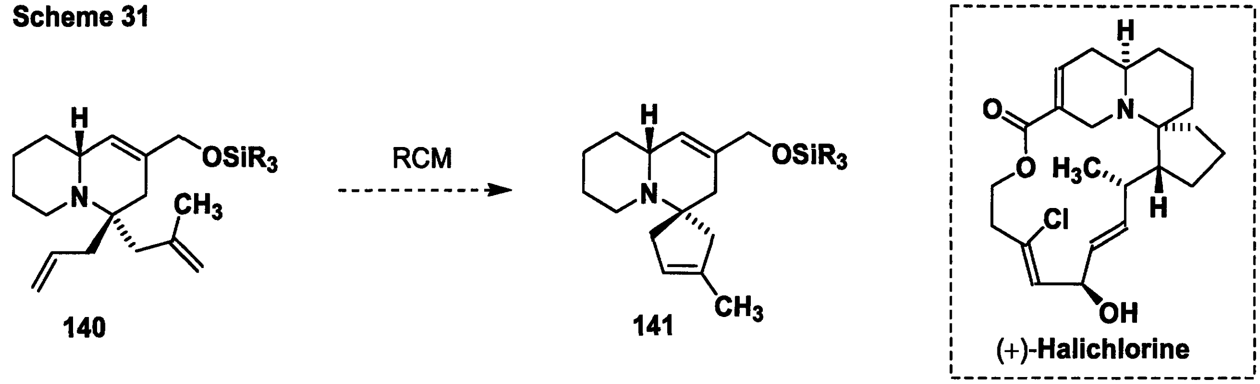
[90] Isolation and activity as inhibitor of VCAM-1: Kuramoto, M.; Tong, C.; Yamada, K.; Chiba, T.; Hayashi, Y.; Uemura, D. *Tetrahedron Lett.* **1996**, *37*, 3867

[91] Synthetic studies: (a) Trauner, D.; Schwarz, J. B.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **1999**, *38*, 3542. (b) Matsumura, Y.; Aoyagi S.; Kibayashi, C. *Org. Lett.* **2004**, *6*, 965.

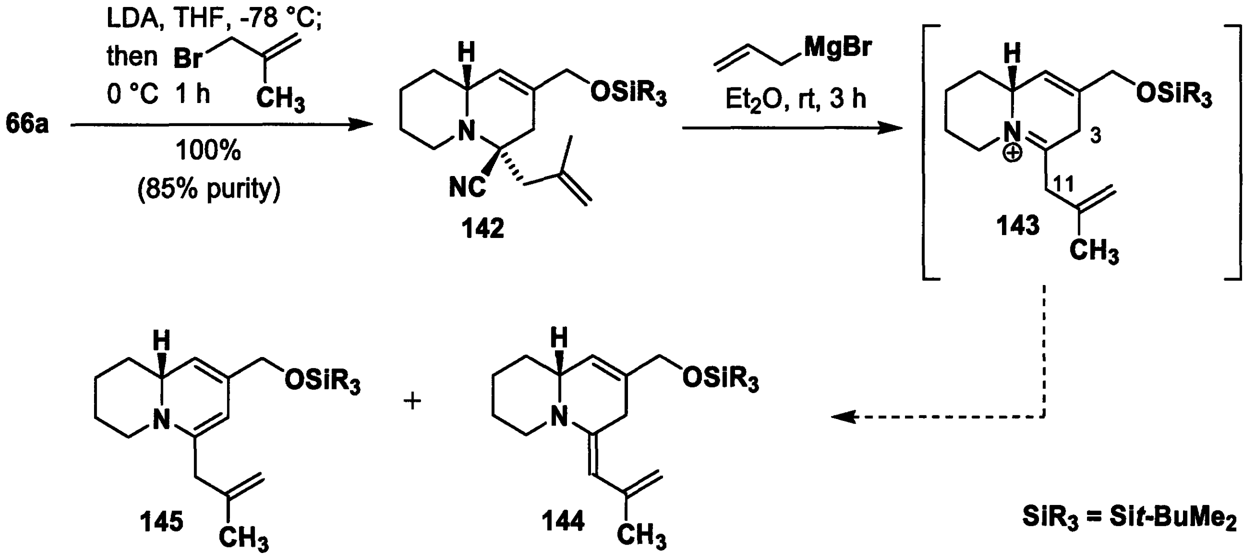
[92] For a review on metathesis reactions in organic synthesis, see Grubbs, R. H. *Handbook of Metathesis*; Wiley-VCH: Germany, 2003; vol. 2.

Scheme 31



Unfortunately, attempts to synthesize the RCM quinolizidine substrate **140** were unsuccessful (Scheme 32). Alkylation of cycloadduct **66a** proceeded normally, but the resulting tertiary α-amino nitrile **142** decomposed upon addition of the alkyl Grignard reagent (precooled to 0 °C) to give a mixture of several products, two of which we have been tentatively assigned as **144** and **145**. The Grignard reagent appears to deprotonate the iminium ion **143** at C-3 or C-11 to give the dienamine byproducts. It also appears that the rate of deprotonation of **143**, probably at the activated allylic C-11 position, occurs at a much faster rate than nucleophilic addition to the iminium ion in this case. Unfortunately, we did not try any other Grignard reagents in the Bruylants reaction of **142** and therefore we cannot say with certainly that it is the substrate structure that is solely responsible for the failure of the Bruylants reaction.

Scheme 32



A second approach we explored is shown in Scheme 33 and involves an enyne ring closing metathesis strategy to deliver the spiroquinolizidine.[93] Thus, alkylation of the metalated nitrile with 4-bromobutene followed by addition of ethynylmagnesium bromide afforded quinolizidine **146** in 65% yield as a single diastereomer.[94] The success of the Bruylants reaction in this case is attributable to two factors which we believe suppress the rate of deprotonation. First, ethynylmagnesium bromide is less basic than allylmagnesium bromide. Second, the side chain does not have a double-bond located so as to allow formation of a conjugated dienamine similar to **144**. With **146** in hand, we investigated the enyne ring closing metathesis reaction and found that treatment of **146** with 5 mol % of **147** in toluene at 85 °C for 2 h affords spiroquinolizidine **148** in 82% yield. Efforts to employ less catalyst led to incomplete conversion and low yields.

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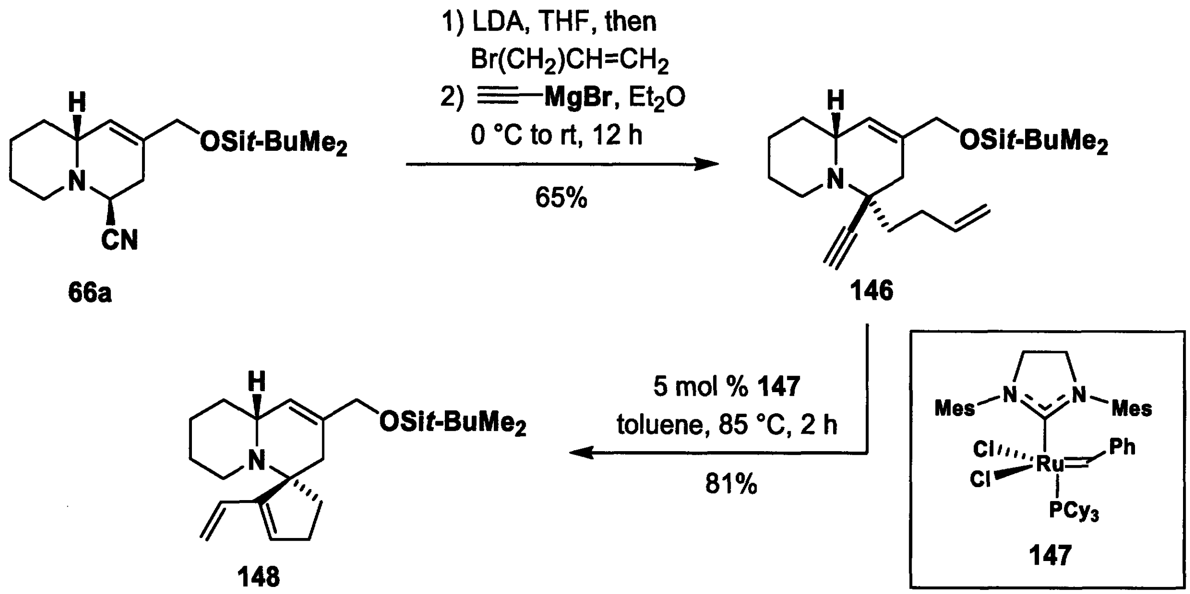
[93] For reviews on enyne metathesis, see: (a) Diver, S. T.; Giessert, A. J. *Chem. Rev.* **2004**, *104*, 1317. (b) Poulsen, C. S.; Madsen, R. *Synthesis* **2003**, 1. (c) Villar, H.; Frings, M.; Bolm, C. *Chem. Soc. Rev.* **2007**, *36*, 55.
[94] The assignment of the quaternary center in **146** was confirmed by a NOE enhancement produced at the acetylenic proton upon irradiation of the ring junction hydrogen.

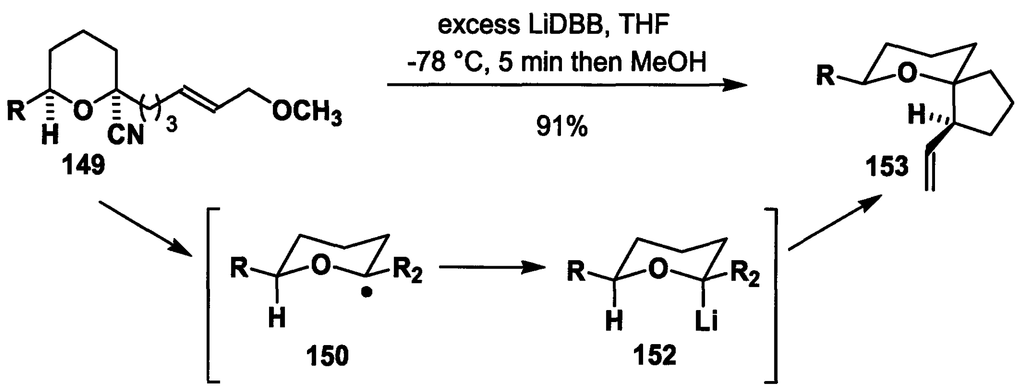
Scheme 33



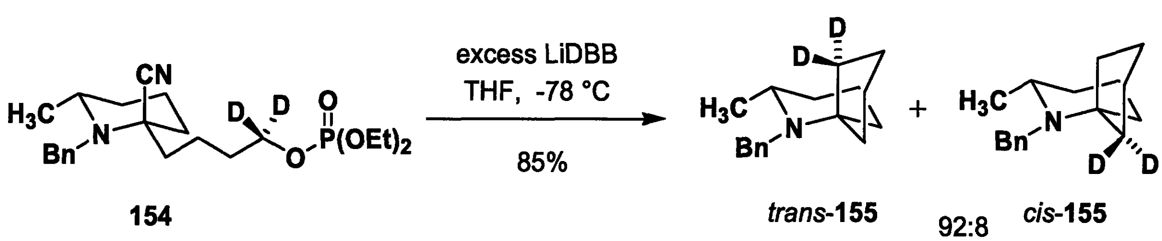
Finally, we explored the feasibility of using a reductive cyclization to form the spirocyclic system. Our interest in reductive cyclization of nitriles originated from consideration of the elegant work of Rychnovsky and coworkers. As shown in Scheme 34, Rychnovsky has shown that exposure of cyanohydrin **149** to 4,4'-di-*t*-butylbiphenylide (LiDBB) affords spirocycle **153** in excellent yield as a single diastereomer.[95] Mechanistic studies of the reductive lithiation of cyanohydrins showed that the stereochemistry of the organolithium intermediate is controlled by the preference of the unpaired electron in **150** to occupy an orbital with axial orientation due to anomeric stabilization. Following a second electron transfer, the lithium compound **152** cyclizes to deliver spirocycle **153**.[96]

[95] (a) Rychnovsky, S. D.; Takaoka, L. R. *Angew. Chem. Int. Ed.* **2003**, *42*, 818. (b) La Cruz, T. E.; Rychnovsky, S. D. *J. Org. Chem.* **2006**, *71*, 1068.
[96] Rychnovsky, S. D.; Powers, J. P.; LePage, T. J. *J. Am. Chem. Soc.* **1992**, *114*, 8375.

Scheme 34



Rychnovsky and coworkers have also extended this methodology to α-amino nitriles with pendant phosphate leaving groups (e.g., eq 27). Reductive lithiation of **154** with LiDBB and subsequent cyclization affords spirocycle **155** in 85% yield. Consistent with previous cyanohydrin reductive cyclization studies, this reductive spiroannulation is highly stereoselective and produces a 92:8 mixture of *trans*- and *cis*-**155**.[97]



(27)

Inspired by this work, we decided to explore the reductive spiroannulation of α-amino nitrile cycloadducts. As shown in Scheme 35, alkylation of the metalated nitrile with 1-chloro-5-iodopentane afforded tertiary α-amino nitrile **156,** which without purification underwent reductive cyclization with LiDBB to deliver spiroquinolizidine **157** in 51% overall yield from **66a**. Although this is a fairly simple example, it does demonstrate that the reductive cyclization of α-amino nitrile cycloadducts is a powerful method for the stereocontrolled synthesis of spirocyclic systems.

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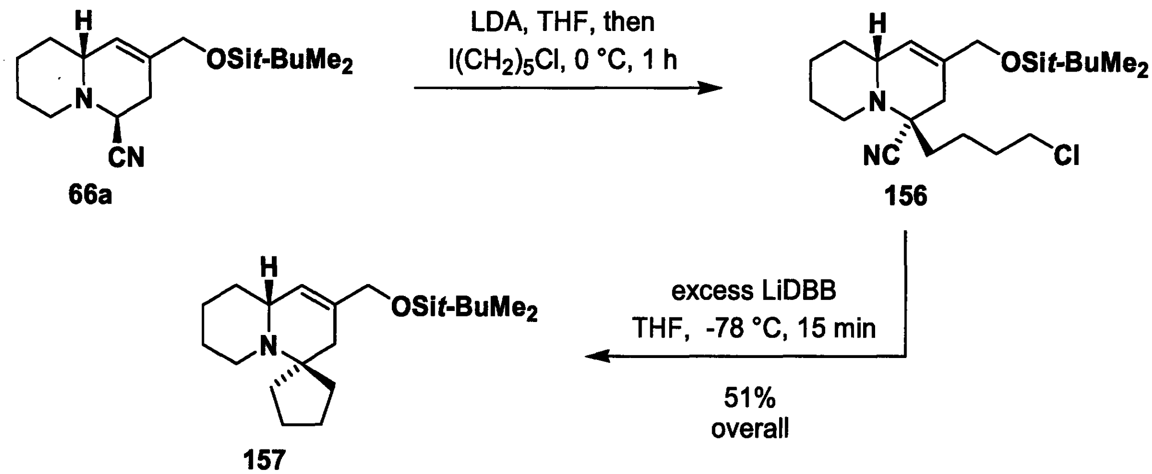
[97] (a) Wolckenhauer, S. A.; Rychnovsky, S. D. *Tetrahedron* **2005**, *61*, 3371. (b) Wolckenhauer, S. A.; Rychnovsky, S. D. *Org. Lett.* **2004**, *6*, 2745.

Scheme 35



Summary

In conclusion, our α-amino nitrile cycloadducts undergo a variety of useful synthetic transformations leading to a variety of substituted quinolizidines and indolizidines. These transformations take advantage of the latent iminium ion character of α-amino nitriles, along with the reactivity of the cyano group. These studies provided a better understanding of the reactivity of our α-amino nitrile cycloadducts, enabling us to apply this methodology to the total synthesis of quinolizidine and indolizidine natural products as described in the following two chapters.

Chapter 7 – Total Synthesis of Quinolizidine (–)-217A

As discussed in the previous chapter, the intramolecular [4+2] cycloaddition of iminoacetonitriles provides access to α-amino nitrile cycloadducts that are versatile synthetic intermediates for the synthesis of quinolizidines and other nitrogen heterocyclic systems. This chapter describes the total synthesis of the natural product quinolizidine (–)-217A utilizing an iminoacetonitrile cycloaddition as the key step.

Introduction

The importance of substituted quinolizidines and indolizidines as synthetic targets is well established. The skeletons of a number of bioactive natural products incorporate these structures, and many of these compounds are available in very limited amounts from their natural source.[98] Highly toxic quinolizidine and indolizidine alkaloids isolated from the skin of poisonous amphibians have attracted much interest as research tools for neurophysiological investigations, and recently quinolizidine alkaloids obtained from marine sources have been identified as lead compounds for the development of anticancer, anti-inflammatory, and cardiovascular drugs. A number of ingenious methods have been developed in response to the synthetic challenge posed by these molecules, and these alkaloids have served as a popular testing ground for methods for the construction of pyrrolidines, piperidines, and various azabicyclic systems.[99]

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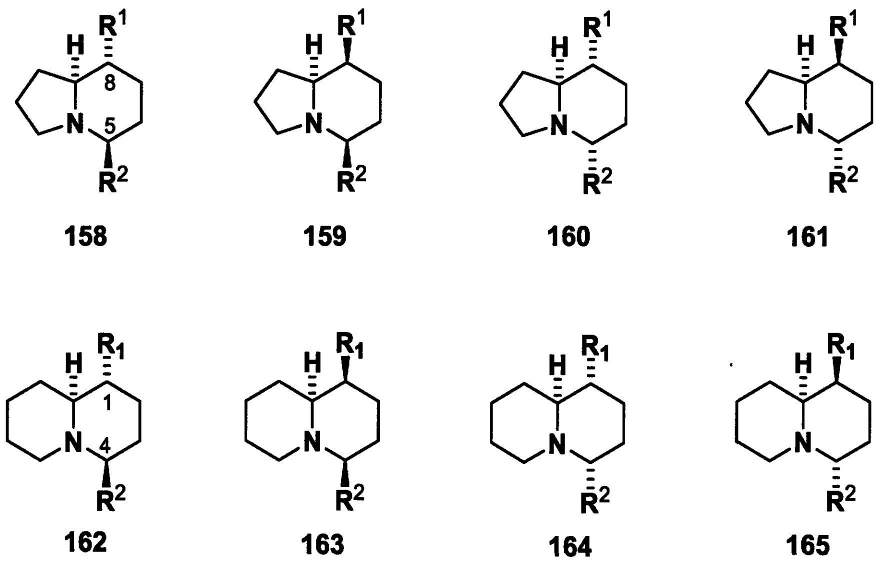
[98] For a recent review of the chemistry and biology of indolizidine and quinolizidine alkaloids, see Daly, J. W.; Garraffo, H. M.; Spande, T. F. In *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Pergamon: New York, 1999; Vol. 13, pp 1-161.

[99] Reviews: (a) Michael, J. P. In *The Alkaloids*; Cordell, G. A., Ed.; Academic Press: New York, 2001; Vol. 55, pp 91-258. (b) Michael, J. P. *Nat. Prod. Rep.* **2004**, *21*, 625 and references therein.

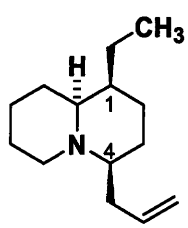
A majority of these "izidine" type alkaloids can be classified as either 1,4-disbustituted quinolizidines or 5,8-disubstituted indolizidines. As shown in Scheme 36, there are four possible diastereomers for each class and currently there are known examples of each type of alkaloid except **159**, **164**, and **165**.[100] Even though elegant methods exist for the synthesis of these types of alkaloids,[101] we felt that our iminoacetonitrile cycloaddition chemistry would be a valuable addition to the synthetic methodology because we should be able to access all possible stereoisomers from a few common α-amino nitrile cycloadducts. As discussed in Chapter 6, the stereochemistry at C-4 of quinolizidines (and C-5 of indolizidines) can be controlled by employing the proper choice of reagents in the synthetic elaboration of α-amino nitriles. For example, the tandem alkylation-reductive decyanation affords the equatorial oriented side chain (R^2), whereas the Bruylants reaction produces the axial oriented side chain. On the other hand, the stereochemistry at C-1 of quinolizidines and C-8 of indolizidines can be manipulated by the proper application of thermodynamic or kinetic control. For example, thermodynamic control can provide routes to systems such as **158**, **160**, **162**, and **164** where R^1 is an equatorial side chain. Alternatively, hydrogenation of a C1-C2 (quinolizidine) or C7-C8 (indolizidine) alkene double bond is expected to occur from the less hindered *exo* face of the azabicyclic system to afford the axial R^1 side chain.

[100] For a review of quinolizidines and indolizidines isolated from nature, see Daly, J. W.; Spande, T. F.; Garraffo, H. M. *J. Nat. Prod.* **2005**, **68**, 1556.
[101] For reviews on the synthesis of 1,4-disubstituted quinolizidines and 5,8-disubstituted indolizidines, see: (a) Michael, J. P. In *The Alkaloids*; Cordell, G. A., Ed; Academic Press: New York, 2001; Vol. 55, pp 91-258. (b) Michael, J. P. *Nat. Prod. Rep.* **2007**, *1*, 191 and references cited therein.

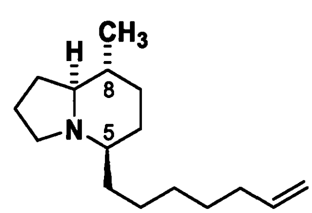
Scheme 36



In order to further test and refine our iminoacetonitrile cycloaddition methodology, we have undertaken the synthesis of several bioactive quinolizidine and indolizidine alkaloids such as 217A,[102] 207I,[102b] and 235B′.[103] By employing an intramolecular Diels-Alder cycloaddition of iminoacetonitriles, we expected to be able to efficiently access the bicyclic core of these quinolizidine and indolizidine alkaloids in only 5-6 steps. With an α-amino nitrile handle, we would then be able to elaborate the aforementioned cycloadducts into the fully adorned natural products.



Quinolizidine (–)-207I



Indolzidine (–)-235B'

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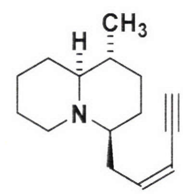
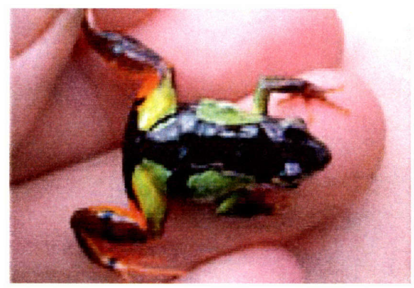
[102] (a) Garrafo, H. M.; Caceres, J.; Daly, J. W.; Spande, T. F.; Andriamaharavo, N. R.; Andriantsiferana, M. *J. Nat. Prod.* **1993**, *56*, 1016. (b) Jain, P.; Garraffo, H. M.; Yeh, H. J. C.; Spande, T. F.; Daly, J. W.; Andriamaharavo, N. R. *J. Nat. Prod.* **1996**, *59*, 1174.

[103] Edwards, M. W.; Daly, J. W. *J. Nat. Prod.* **1988**, *51*, 1188.

This chapter describes the application of the iminoacetonitrile cycloaddition as a key step in the total synthesis of quinolizidine (–)-217A, an amphibian alkaloid isolated in minute quantities by Daly in 1993 from skin extracts of the Madagascan frog *Mantella baroni*. Alkaloid (–)-217A, along with several other 1,4-disubstituted quinolizidines and 5,8-disubstituted indolizidines, is believed to be dietary in origin based on the fact that many of the "izidine" type alkaloids have also been detected in ants, which the Mantelline and Dendrobates frogs are known to eat.[104] Our goal was the development of an efficient approach to the synthesis of quinolizidine 217A capable of supporting the preparation of significant quantities of the target alkaloid.



Quinolizidine (–)- 217A



Previous Total Syntheses of 217A

Pearson and coworkers published the first total synthesis of 217A in 1998, producing racemic 217A in 20 steps.[105] As shown in Scheme 37, Pearson's synthesis commences with the preparation of lactone **167**. Addition of allyltrimethylsilane to aldehyde **166**[106] followed by cyclization of the resultant hydroxy ester gave lactone **167** in 73% yield. Methylation of **167** followed by oxidation and protection afforded lactone **168** as a 1:1 mixture of diastereomers

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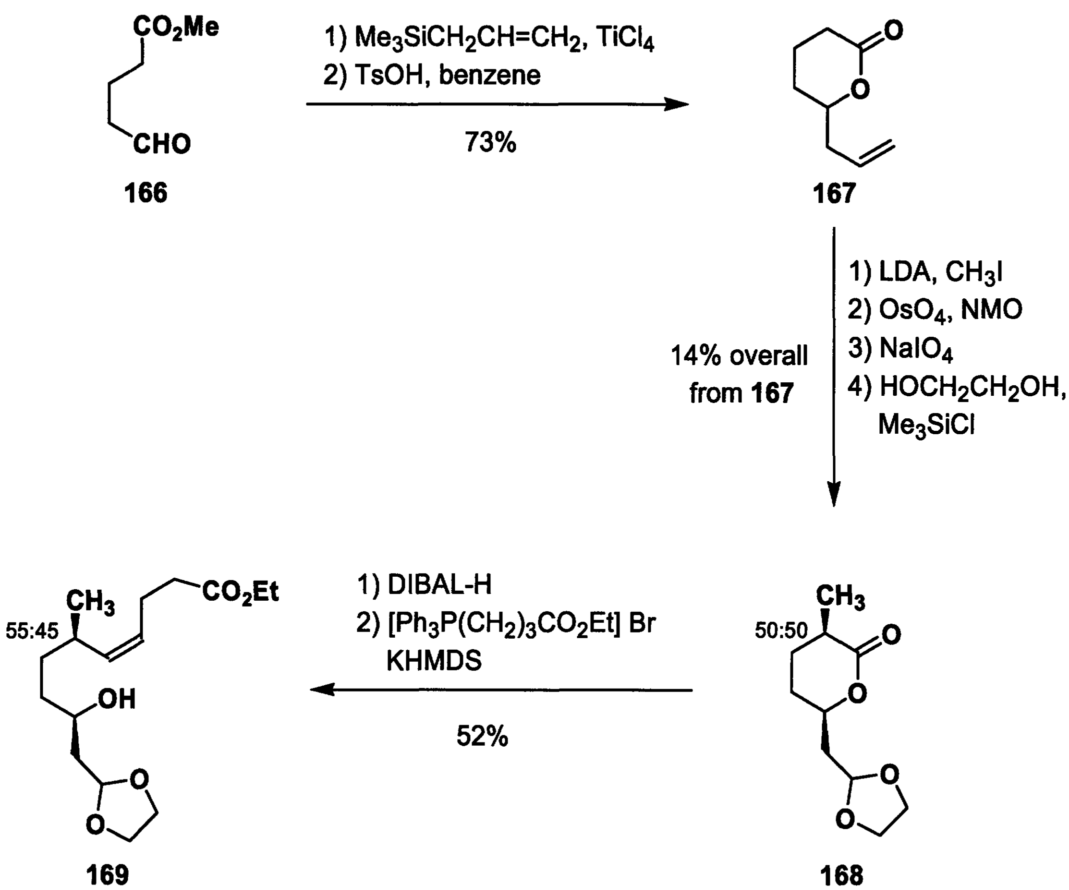
[104] Daly, J. W.; Kaneko, T.; Wilham, J.; Garraffo, H. M.; Spande, T. F.; Espinosa, A.; Donnelly, M. A. *PNAS* **2002**, *99*, 13996.
[105] Pearson, W. H.; Suga, H. *J. Org. Chem.* **1998**, *63*, 9910.
[106] Aldehyde **166** was prepared in 2 steps from commercially available valerolactone, see Huckstep, M.; Taylor, R. J. K. *Synthesis* **1982**, 130.

which were separated later in the synthesis. Reduction of lactone **168** and subsequent olefination afforded **169** in 52% yield.

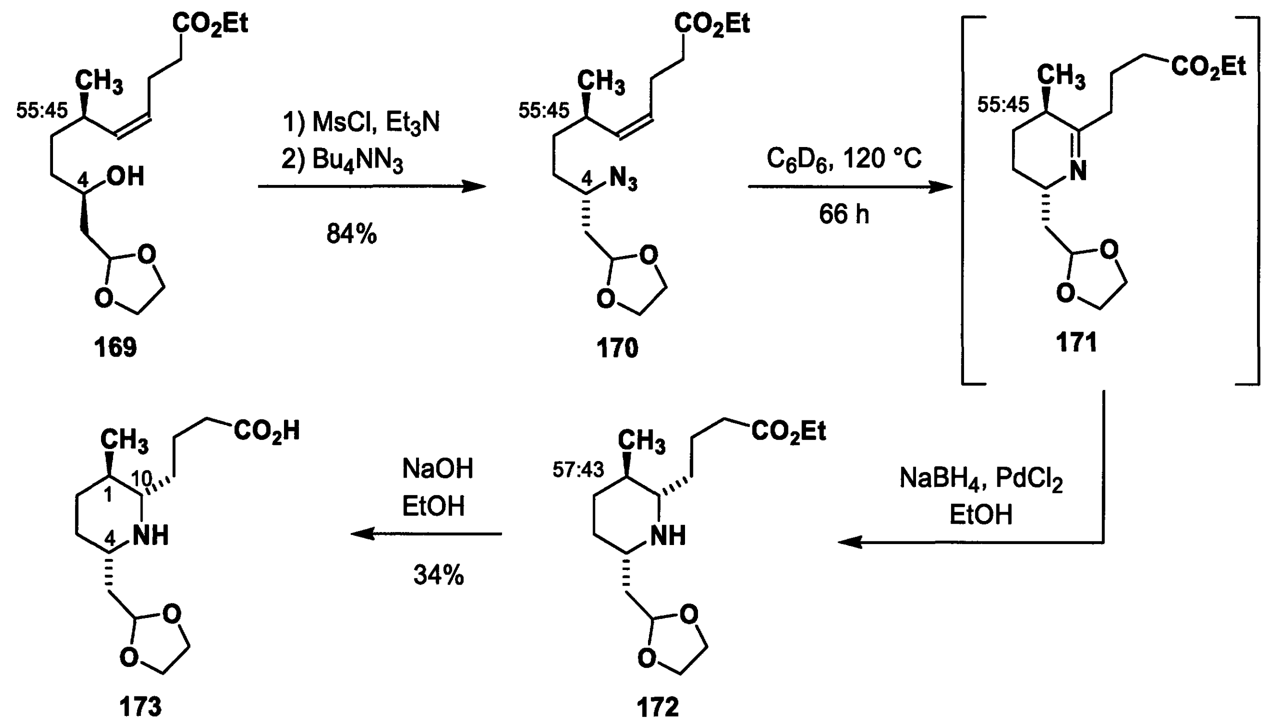
Scheme 37



The next stage of Pearson's synthesis utilized an azide cycloaddition and subsequent stereoselective imine reduction to form the trisubstituted piperidine subunit **173** (Scheme 38). Thus, installation of the azide group via standard displacement chemistry afforded **170** in 84% yield with inversion of the C-4 stereocenter. Next, dipolar cycloaddition of azide **170** afforded an intermediate triazoline which decomposed via elimination of N_2 to give imine **171**. Stereoselective reduction of imine **171** with $NaBH_4$ then produced piperidine **172** as a 57:43

mixture of epimers at C-1. Finally, saponification of **172** and separation of the diastereomers afforded **173** in 34% yield (overall from **170**).

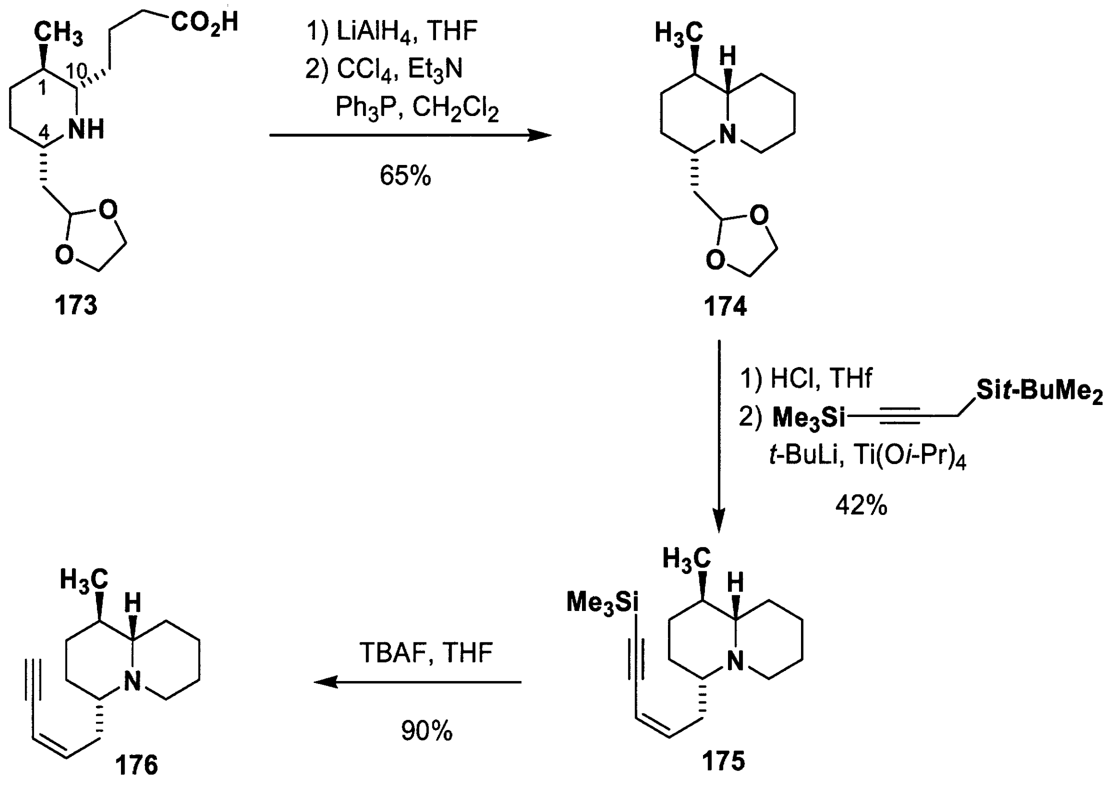
Scheme 38



With the stereocenters at C-4 and C-10 set, piperidine **173** was converted into alkaloid 217A in a straightforward fashion (Scheme 39). Reduction of the carboxylic acid and cyclization of the resulting alcohol afforded quinolizidine **174** in 65% yield. Liberation of the aldehyde and subsequent olefination using Yamamoto's method[107] provided the enyne **175** in 42% yield as a single isomer. Finally, desilylation of **175** afforded racemic quinolizidine 217A (**176**) in 90% yield. Although the synthesis provided racemic material and was fairly lengthy, it did confirm the relative stereochemistry proposed by Daly and coworkers.[102]

[107] Furuta, K.; Ishiguro, M.; Haruta, R.; Ikeda, N.; Yamamoto, H. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 2768.

Scheme 39



In 2003, Panek and coworkers reported the first enantioselective synthesis of quinolizidine (–)-217A via an approach requiring 20 steps.[108] The key step in Panek's route is an intramolecular imine crotylation using a chiral organosilane to give a highly enantioenriched tetrahydropyridine. As shown in Scheme 40, enantiopure vinylsilane **177**,[109] prepared via resolution, was converted into **178** via a DCC-mediated esterification. Silyl enol ether formation and subsequent heating afforded the Ireland ester Claisen rearrangement product **179** in 70% yield as a single diastereomer. Esterification of **179** followed by reduction of the azide provided amine **180** in 74% yield.

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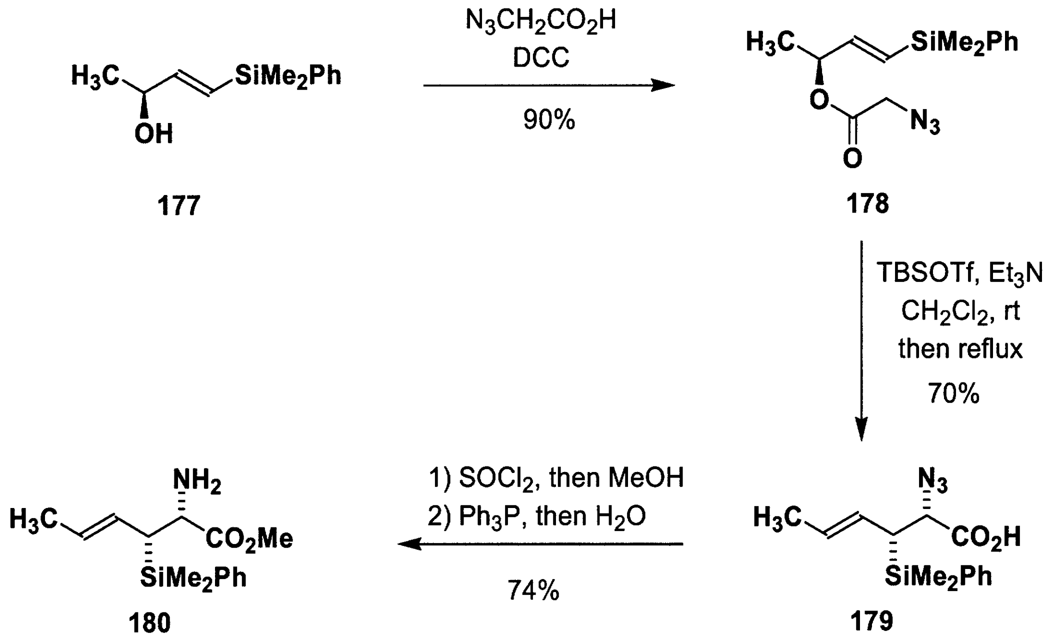
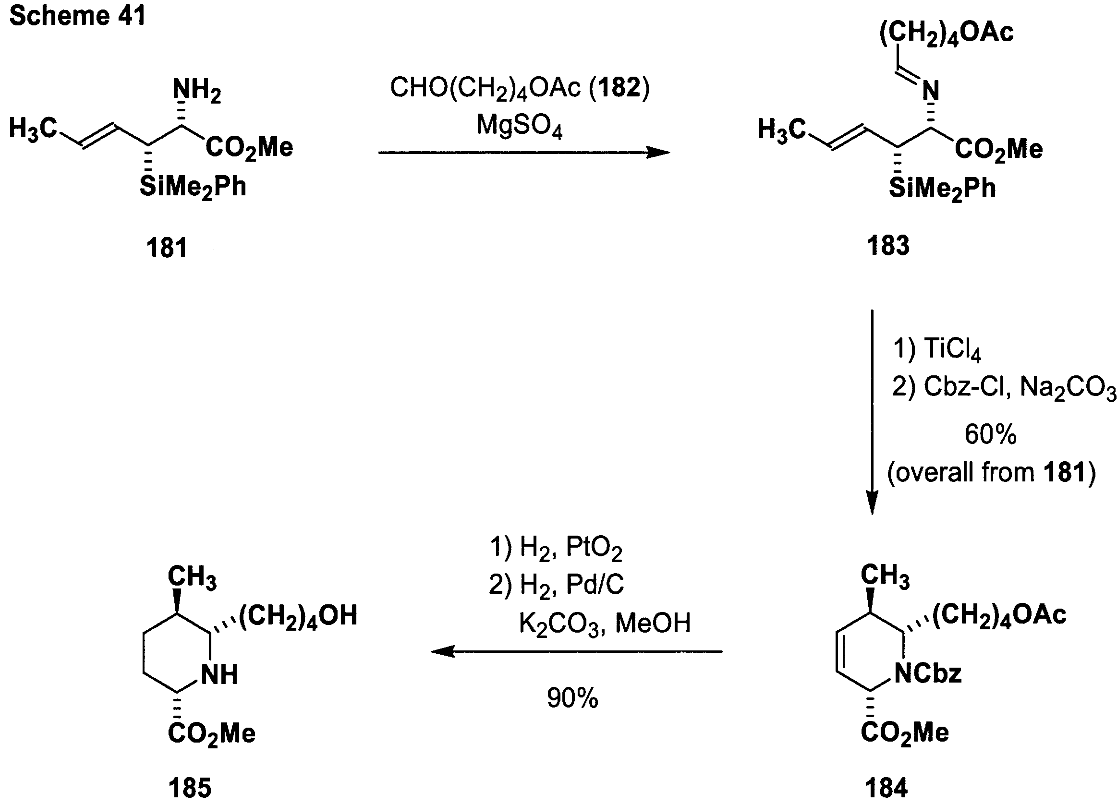
[108] Huang, H.; Spande, T. F.; Panek, J. S. *J. Am. Chem. Soc.* **2003**, *125*, 626.
[109] Vinylsilane **177** was prepared in 5 steps from *trans*-crotonaldehyde, see Panek, J. S.; Sparks, M. A. *Tetrahedron: Asymmetry* **1990**, *1*, 801.

Scheme 40



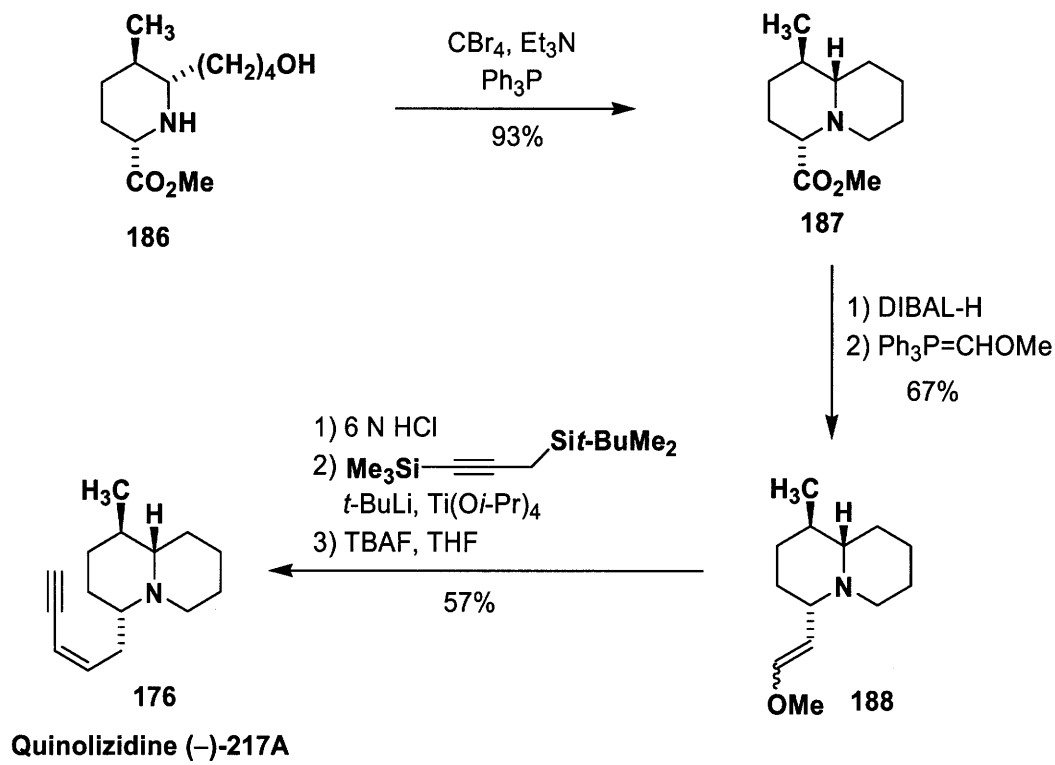
With the synthesis of chiral silane **180** complete, the stage was set for the key [4+2] tetrahydropyridine annulation (Scheme 41). In the event, condensation of amine **181** with aldehyde **182** afforded imine **183**. Subsequent cyclization via an intramolecular crotylsilane addition and Cbz-protection afforded tetrahydropyridine **184** in 60% yield as a single diastereomer. Hydrogenation and deacetylation of **184** provided piperidine **185** in 90% yield.

Scheme 41



As depicted in Scheme 42, cyclization of alcohol **186** afforded quinolizidine **187** in 93% yield. Homologation of the ester via reduction to the aldehyde and Wittig olefination provided enol ether **188** in 67% yield as an *E*/*Z* mixture of isomers. Hydrolysis of enol ether **188** and subsequent Yamamoto olefination installed the enyne side chain which upon desilylation afforded alkaloid (–)-217A (**176**) in 57% yield (overall from **188**).

Scheme 42



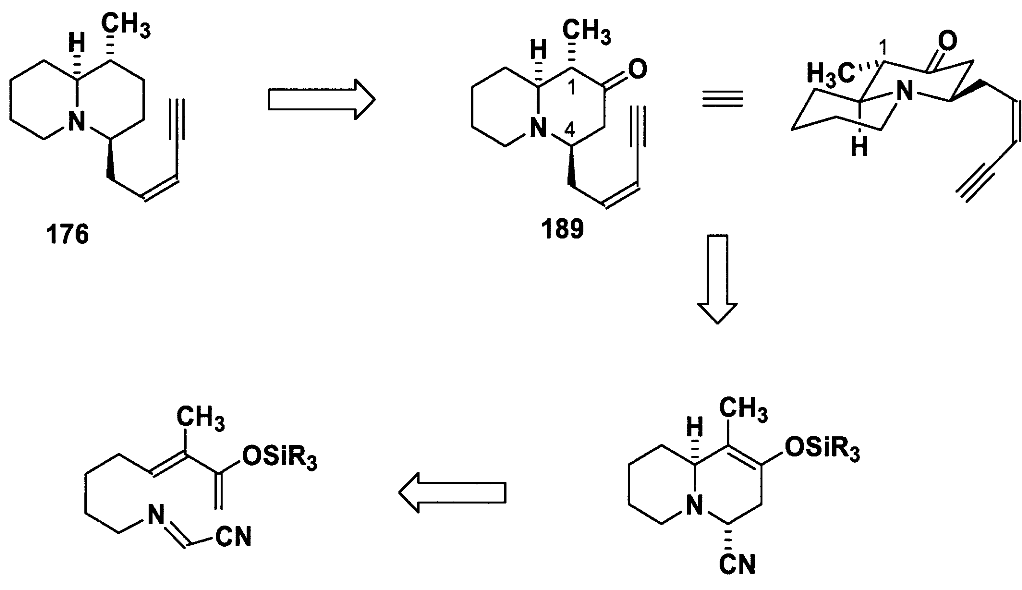
Total Synthesis of Quinolizidine (–)-217A

Retrosynthetic Analysis

Our goal was the development of an approach to the synthesis of quinolizidine 217A considerably more efficient than these earlier syntheses and capable of supporting the preparation of significant quantities of the target alkaloid. Scheme 43 outlines our retrosynthetic strategy, which features the intramolecular iminoacetonitrile cycloaddition **191**→**190** as a pivotal step. Alkylation of **190** would then be employed to install the enynylmethyl side chain, and stereoelectronic control in the subsequent reductive decyanation step was expected to deliver the desired stereochemistry at C-4. Control of the stereochemistry at C-1 would be established by epimerization of the ketone intermediate **189** derived from the silyl enol ether cycloadduct. In this first generation synthesis, we elected to employ resolution to provide access to the natural

(−)-isomer as well as the unnatural isomer, deferring for future study the possibility of employing chiral Brønsted acids to catalyze an asymmetric version of the cycloaddition.

Scheme 43



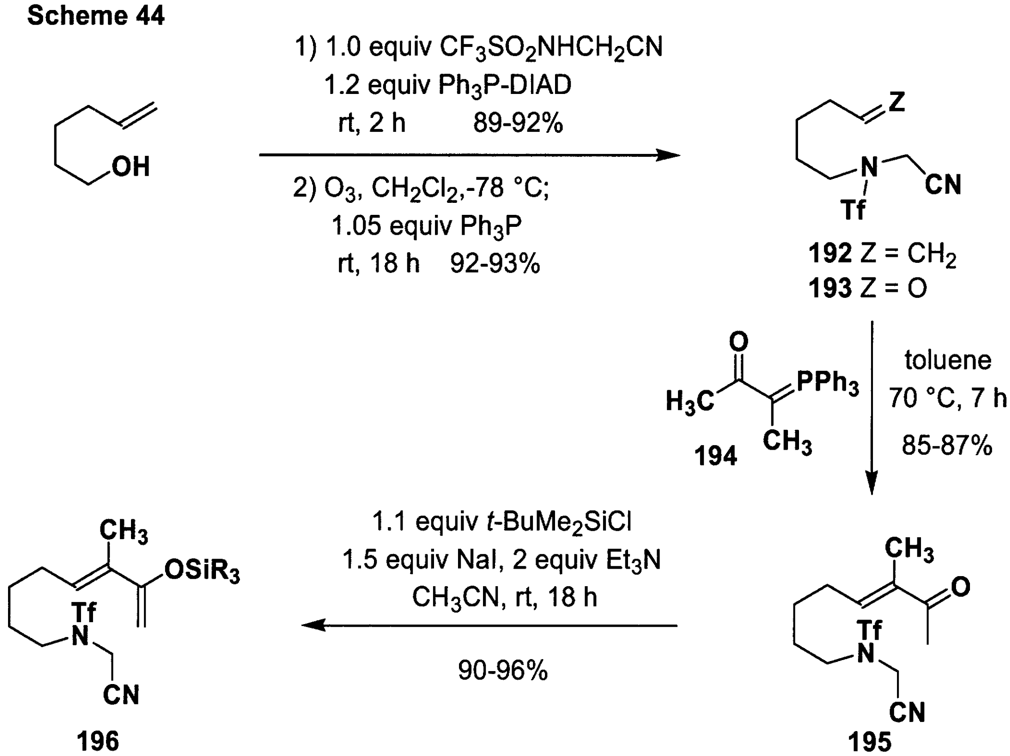
*Preparation of α-Amino Nitrile Cycloadduct **190***

Our first synthetic subgoal was the development of an efficient route to cycloaddition substrate **191**. Based on our previous studies, we anticipated that **191** would be available from sulfonamide **196** by elimination of trifluoromethanesulfinate on exposure to a weak base such as carbonate. Scheme 44 outlines our efficient four-step route to **196**. Mitsunobu coupling of commercially available 5-hexenol with $CF_3SO_2NHCH_2CN$ provided the expected sulfonamide, and ozonolysis then furnished aldehyde **193** in excellent yield. Wittig olefination of **193** using the acylphosphorane **194**[110] produced the desired (*E*)-α,β-unsaturated ketone **195** in 85-87%

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

yield after purification by column chromatography.[111] Finally, conversion to the desired enol ether was achieved using the general procedure of Dunogues et al.[112] to afford **196** in excellent yield after purification by column chromatography on acetone-deactivated silica gel. Attempts to use stronger bases, such as NaH and LDA, for formation of the silyl enol ether were unsuccessful due to decomposition of the base-sensitive triflamide moiety.

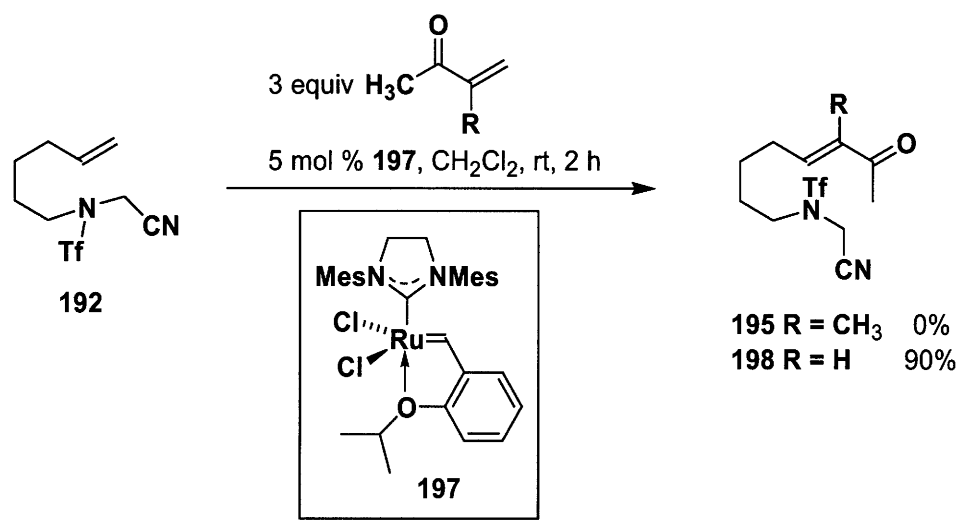
Scheme 44



Inspired by the recent advances made in olefin metathesis,[113] we envisioned a more direct route for the synthesis of **195** employing a cross-metathesis strategy (eq 28). However, all attempts to synthesize **195** via the cross-metathesis reaction of triflamide **192** and 3-methyl-3-

[111] The crude product of the Wittig reaction consisted of a 90:10 mixture of *E* and *Z* enones.
[112] Cazeau, P.; Duboudin, F.; Moulines, F.; Babot, O.; Dunogues, J. *Tetrahedron* **1987**, *43*, 2075.
[113] For reviews on cross metathesis, see: (a) reference 92 (b) Connon, S. J.; Blechert, S. *Angew. Chem., Int. Ed.* **2003**, *42*, 1900. (c) Chatterjee, A. K.; Choi, T.-L.; Sanders, D. P.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 11360.

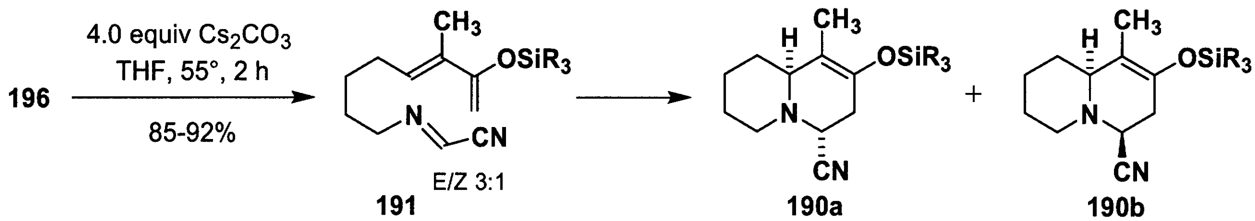
buten-2-one were frustrated by the homodimerization of **192**. Also, efforts to isolate and re-subject the homodimer of **192** to the cross-metathesis reaction were completely unsuccessful leading to the conclusion that the dimer is unreactive in secondary metathesis. Interestingly, the cross-metathesis reaction of triflamide **192** with methyl vinyl ketone afforded the expected enone **198** in 90% yield as a single isomer.



(28)

As shown in Scheme 45, exposure of **196** to the action of cesium carbonate led to the elimination of trifluoromethanesulfinate and formation of iminoacetonitrile **191** as the expected mixture of *E* and *Z* imine isomers. The stereochemistry of this intermediate is not crucial, since iminoacetonitrile isomers interconvert under the conditions of the [4+2] cycloaddition. Heating iminoacetonitrile **191** at 130 °C for 36 h then produced the desired α-amino nitrile cycloadduct **190a** in good yield. As discussed in Chapter 4, addition of BHT was found to be beneficial in suppressing decomposition of the desired product. As expected, the isomer with an *exo*-oriented (axial) cyano group was isolated as the exclusive product of the reaction as a consequence of the "α-amino nitrile anomeric effect."[45]

Scheme 45



SiR_3 = Si*t*-BuMe$_2$

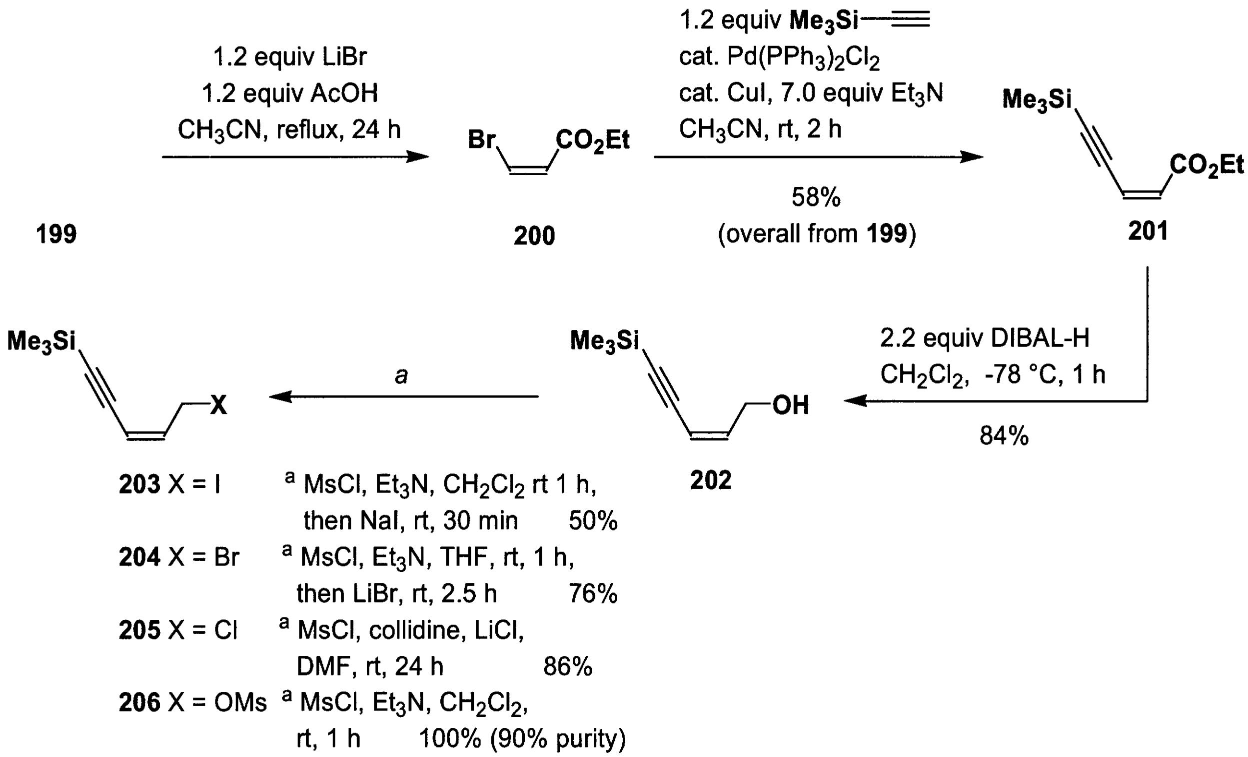
3.0 equiv BHT, toluene, 120 °C, 20 h	55-59%	100 : 0
1.0 equiv MsOH CH_2Cl_2, -78 °C, 1 h	68%	55 : 45
1.0 equiv MsOH CH_2Cl_2, -78 °C, 1 h; CH_3CN, 45 °C, 1.5 h	68%	100 : 0

Next, we explored the acid-promoted cycloaddition of iminoacetonitrile **196**. Initial attempts were frustrated by decomposition of **196** presumably via competing reaction of the silyl enol ether moiety with MsOH. However, conducting the reaction at -78 °C with dropwise addition of MsOH afforded cycloadducts **190a** and **190b** in 68% yield as a mixture of epimers at C-4. As previously discussed, simply heating the mixture in CH_3CN at 45 °C for 1.5 h delivers **190a** as a single diastereomer (axial nitrile). It should be emphasized that the α/β mixture of nitriles is inconsequential due to the fact that further transformations at the C-4 carbon are controlled by stereoelectronic principles independent of the C-4 cyano group stereochemistry (see Chapter 6).

*Alkylation/Reductive Decyanation of α-Amino Cycloadduct **190***

For the next stage of the synthesis, alkylation of α-amino nitrile **190**, we initially focused our attention on the enynylmethyl compounds **203-206**. As shown in Scheme 46, alcohol **202** was prepared from ethyl propiolate in good yield utilizing a previously published method.[114] Alkylating agents **203-206** were then prepared from alcohol **202** as previously described in good yield.[115]

Scheme 46

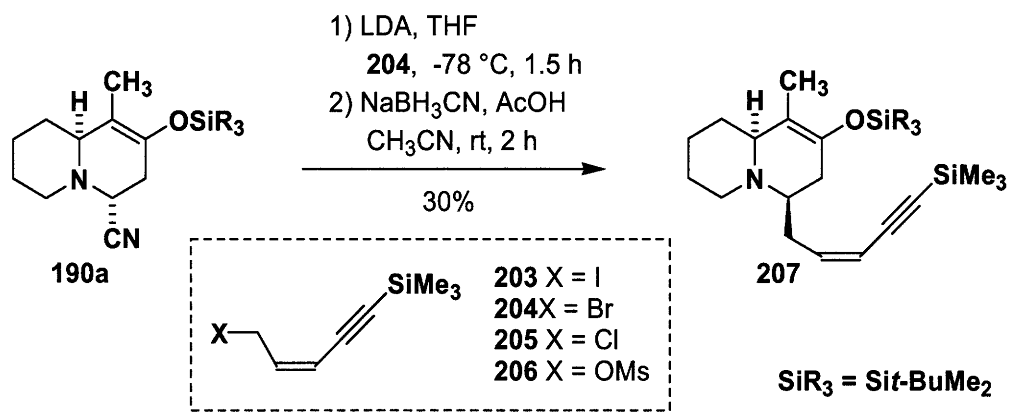


Surprisingly, the desired enyne **170** was obtained at best in only 30% overall yield after alkylation of **190a** with any of these enynes followed by reductive decyanation (Scheme 47). It is important to recall that purification of the intermediate alkylation product is best avoided due to decomposition of the tertiary α-amino nitrile on silica gel. Although alkylation with model alkylating agents such as allyl bromide proceeded smoothly (quantitative yield), complex

[114] Hartung, I. V.; Eggert, U.; Haustedt, L. O.; Niess, B.; Schafer, P. M.; Martin, H.; Hoffmann, R. *Synthesis* **2003**, 1844.
[115] For **203** and **206**, see: Feldman, K. S. *Tetrahedron Lett.* **1982**, *23*, 3031. For **204** and **205**, see Tsushima, K.; Murai, A. *Tetrahedron Lett.* **1992**, *33*, 4345.

mixtures resulted from the reaction of **190** with enynylmethyl derivatives **203-206**. Interestingly, the addition of additives known to improve alkylation reactions, such as DMPU, HMPA, DMSO, and LiCl, had no effect on the reaction.

Scheme 47

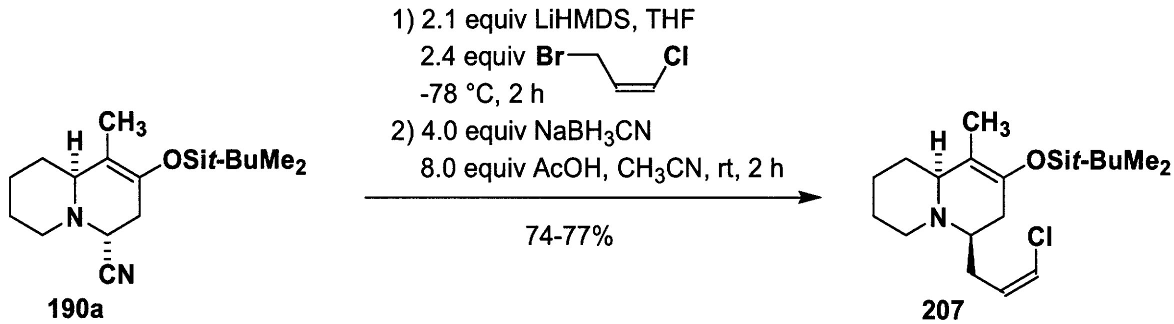


Although we have been unable to characterize any of the byproducts of this reaction, we speculate that electron transfer to the enynylmethyl halide from the metalated nitrile (thus generating a captodative stabilized amino nitrile radical) may be complicating this alkylation.[116] Other conceivable side reactions include the deprotonation of the enynylmethyl halide[117] and addition of the lithiated nitrile to the enyne moiety.[118] We therefore turned our attention to a less unsaturated allylic halide, (*Z*)-3-bromo-1-chloro-propene, with the idea of later elaborating the full enyne moiety via a Sonogashira coupling reaction.

In the event, we were pleased to find that alkylation of **190** with (*Z*)-3-bromo-1-chloro-propene proceeded cleanly, and reductive decyanation of the unpurified alkylation product with

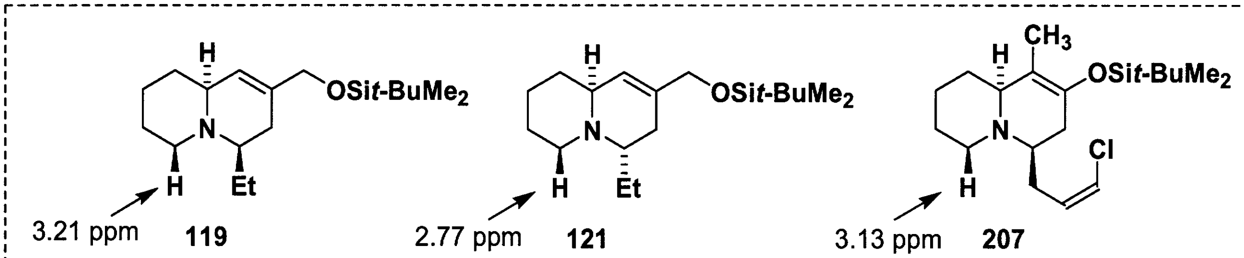
[116] For a review of the capto-dative effect, see Viehe, H. G.; Mernyi, R.; Stella, L.; Janousek, Z. *Angew. Chem. Int. Ed.* **1979**, *18*, 917.
[117] For examples of the metalation of allylic halides, see Julia, M.; Verpeaux, J.-N.; Zahneisen, T. *Synlett* **1990**, 769.
[118] For addition of organolithium compounds to conjugated enynes, see Brandsma, L. *Synthesis of Acetylenes, Allenes, and Cumulenes*; Elsevier: Oxford, 2004; p 74.

sodium cyanoborohydride then afforded the desired quinolizidine **207** in 74-77% overall yield (eq 29).



(29)

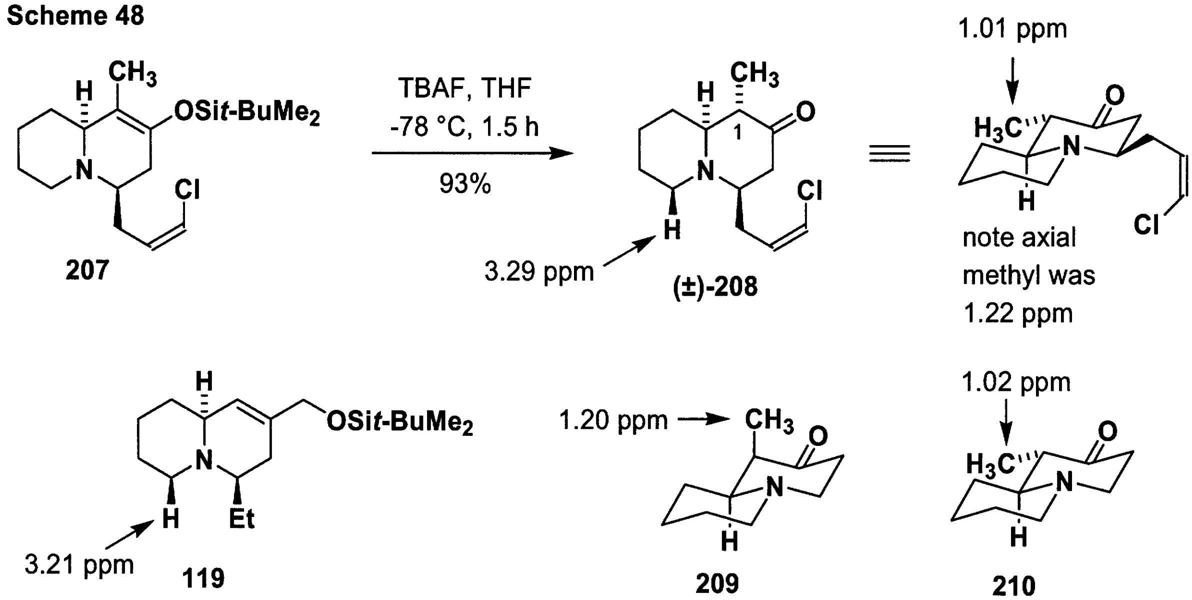
As discussed in chapter 6, axial delivery of hydride to the intermediate iminium ion leads to formation of the desired diastereomer as the exclusive product of the reaction. The allyl group of **207** was assigned as equatorial (*endo*) based on NMR analysis and comparison with the spectra previously reported by Amos[36] for the related compounds **119** and **121** as shown below.



*Preparation and Reductive Deoxygenation of Ketone **207***

With the synthesis of quinolizidine **207** complete, we were poised to unmask the C-2 carbonyl. Treatment of silyl enol ether **207** with 1.1 equiv of *n*-Bu_4NF in THF generated ketone **208** as a single diastereomer with the C-1 methyl group in the desired equatorial orientation (Scheme 48). The stereochemical assignment of the C-1 methyl group was based on the comparison of its chemical shift to that of an equatorial and axial oriented methyl group in the related compounds **209** and **210.**[119] Comparison of the C-6 equatorial proton of **208** to that of **119** confirmed the assignment of the C-4 stereocenter as shown below. As expected, reactions employing less than 1 equiv of *n*-Bu_4NF afforded a mixture of epimers at C-1 confirming that excess *n*-Bu_4NF was in fact equilibrating the C-1 methyl group to the thermodynamically favored equatorial orientation.

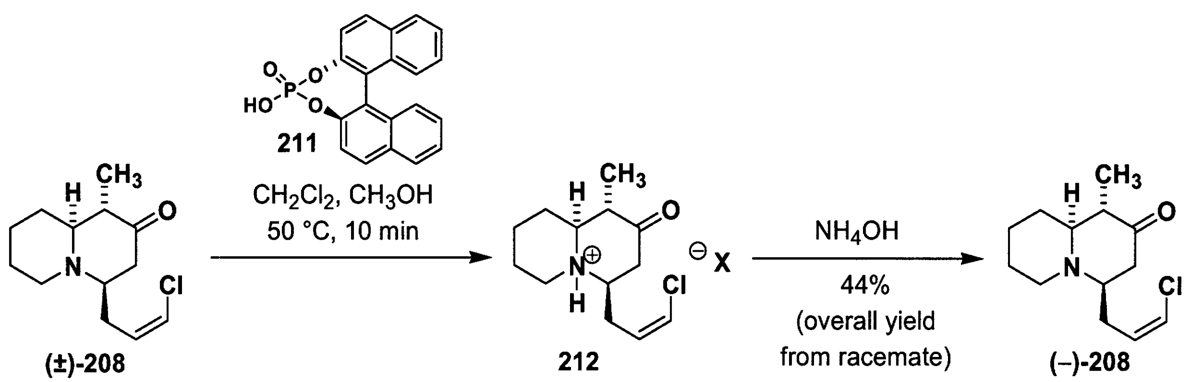
Scheme 48



At this stage of the synthesis, we decided to investigate the resolution of quinolizidine (±)-**208.** We chose (*R*)-(–)-1,1′-binaphthyl-2,2′-diylphosphoric acid (**211**)[120] as our resolving agent based on the fact that several examples exist in the literature of **211** being used to resolve related quinolizidines.[121] Thus, treatment of (±)-**208** with 1.0 equiv of **211** afforded a white solid which was recrystallized twice from MeOH and then treated with 10% ammonium hydroxide solution to give enantiomerically pure (–)-**208** in 44% overall yield from the racemate. The

[119] Quéguiner, G.; Ribereau, P.; Godard, A. *Tetrahedron* **1995**, *51*, 3247.
[120] Jacques, J.; Fouquey, C. *Tetrahedron Lett.* **1971**, *12*, 4617.
[121] For examples, see: (a) Imhof, R.; Kyburz, E.; Daly, J. J. *J. Med. Chem.* **1984**, *27*, 165. (b) Bøgesø, K. P.; Arnt, J.; Lundmark, M.; Sundell, S. *J. Med. Chem.* **1987**, *30*, 142.

enantiomeric purity of the product was determined by ^{1}H NMR analysis of the salt formed by reaction with (*R*)-(–)-1,1'-binaphthyl-2,2'-diylphosphoric acid:[122] the phosphoric acid (1.0 equiv) was added to a solution of **208** in ca. 0.7 mL of $CDCl_3$. The C-1 methyl group appeared as a doublet (J = 6.5 Hz) at 1.01 ppm; no doublet at 1.19 ppm could be detected. Similar analysis of racemic **208** showed two doublets (1:1 ratio) at 1.19 and 1.01 ppm.

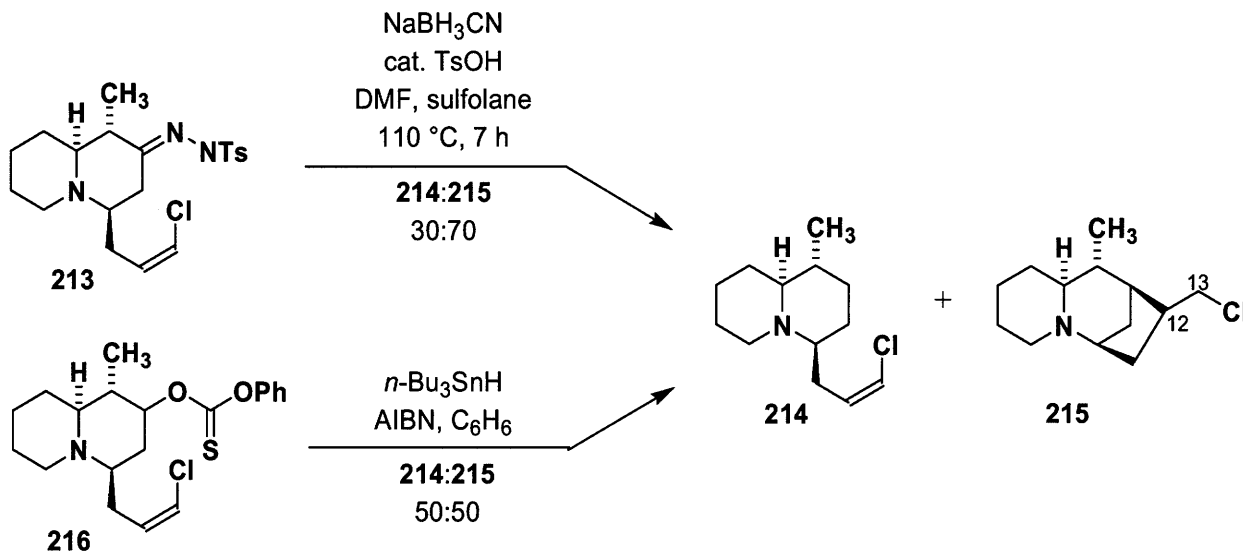


(30)

The next stage of the synthesis, involving reductive excision of the carbonyl group, proved unexpectedly difficult. Initial attempts to effect deoxygenation of ketone **208** (as well as derivatives of the corresponding alcohol) were complicated by the formation of a byproduct tentatively identified as the tricyclic amine **215**.[123] As shown in Scheme 49, treatment of tosylhydrazone **213** with $NaBH_3CN$ in acidic DMF/sulfolane[124] afforded a 30:70 mixture of the desired deoxygenated product **214** and tricyclic amine **215**. Similarly, Barton-McCombie reduction[125] of **216** with *n*-Bu_3SnH and AIBN delivered a 50:50 mixture of **214** and **215**.[126]

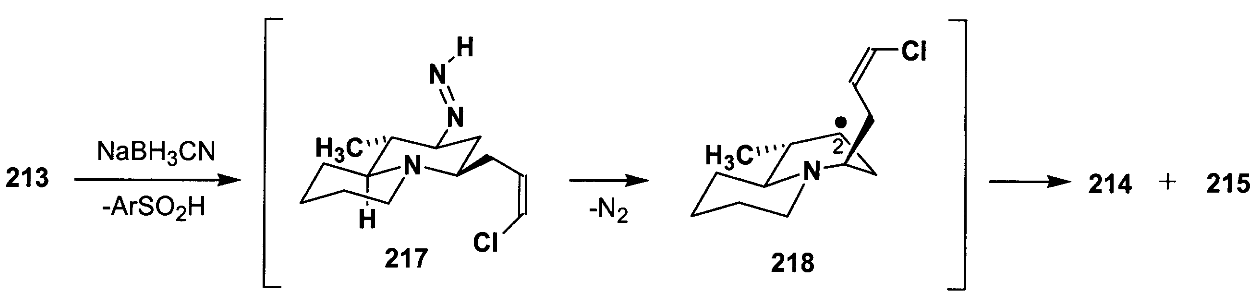
[122] Shapiro, M. J.; Archinal, A. E.; Jarema, M. A. *J. Org. Chem.* **1989**, 54, 5826.
[123] The structure of **215** was tentatively assigned based on its molecular formula, $C_{13}H_{22}NCl$ (MW = 227 found by mass spectrometry), and ^{1}H NMR spectrum. The absence of vinyl protons and the presence of a primary alkyl chloride with the C-13 methylene protons coupled to the C-12 methine proton suggest a tricyclic structure. In addition, the presence of Bohlmann bands in the FT-IR indicate a *trans*-fused quinolizidine.
[124] Hutchins, R. O.; Milewski, C. A.; Maryanoff, B. E. *J. Am. Chem. Soc.* **1973**, *95*, 3662.
[125] Barton, D. H. R.; McCombie, S. W. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1574.
[126] Ratio of products (**214**:**215**) determined by gas chromatography.

Scheme 49



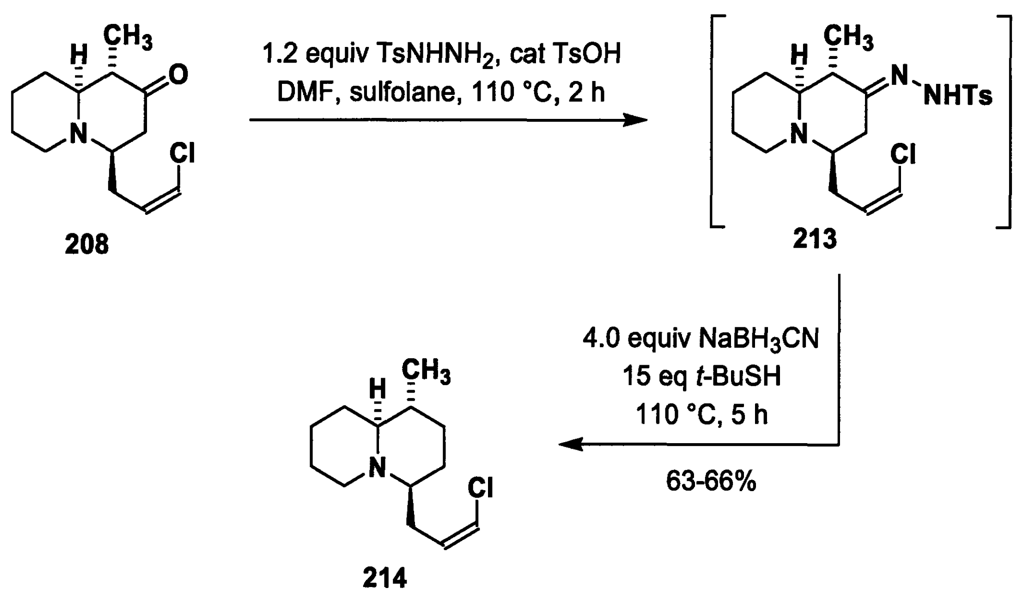
Although two seemingly unrelated methods afforded the same byproduct, this was not totally unexpected in view of the fact that both reactions proceed through radical intermediate **218** (Scheme 50). For example, hydride reduction of tosylhydrazone **213** is expected to afford the intermediate diazene **217** which then fragments to give radical intermediate **218**. Cyclization onto the vinyl chloride furnishes **215** whereas intermolecular hydrogen abstraction delivers **214**. Consistent with this mechanistic explanation, we found that the ratio of the two products was influenced by the concentration of the reaction mixture with lower concentrations favoring the cyclization product.

Scheme 50



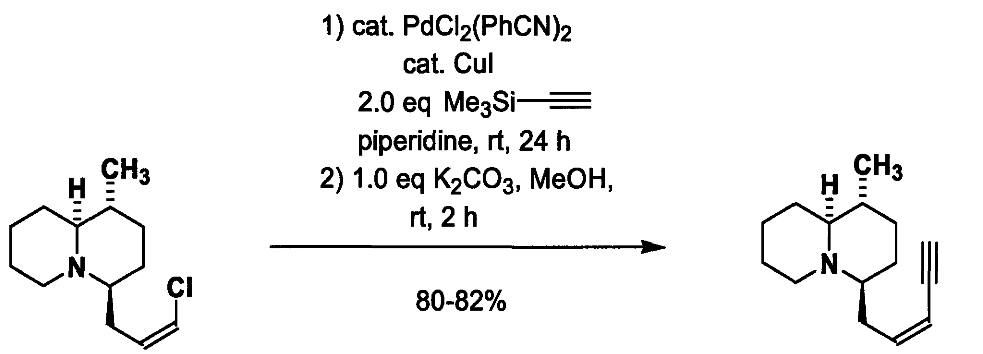
Since this byproduct appeared to arise from cyclization of a C-2 radical intermediate onto the vinyl chloride appendage, we focused our attention on strategies in which the reduction step could be carried out in the presence of efficient hydrogen atom transfer agents so as to more effectively intercept the intermediate radical prior to cyclization. Success was achieved by means of the one-pot protocol outlined in Scheme 51. Thus, reduction of the tosylhydrazone of (–)-**208** with $NaBH_3CN$ in the presence of *tert*-butyl mercaptan completely suppressed the undesired radical cyclization and furnished vinyl chloride **214** in 63-66% overall yield.

Scheme 51



Endgame

Having effectively removed the C-2 carbonyl group, we were poised to conquer the total synthesis of quinolizidine 217A. As shown in eq 31, Sonogashira coupling with trimethylsilylacetylene proceeded smoothly, provided that the acetylene was added slowly to suppress competing alkyne dimerization. Finally, desilylation with K_2CO_3 in methanol afforded quinolizidine (–)-217A ($[\alpha]^{22}_{D}$ -14 (c 0.8, $CHCl_3$), lit.[108] $[\alpha]^{20}_{D}$ -13.75 (c 0.4, $CHCl_3$)) with spectral characteristics identical with those reported for synthetic 217A by Pearson and Panek (Tables 6 and 7).[105,108] The only structural information that exists in the literature for natural 217A is the ^{1}H NMR of 217A•DCl.[104] Therefore, Pearson and coworkers converted their synthetic material to its DCl salt, and then compared their ^{1}H NMR spectrum with that of an authentic sample of the alkaloid. This experiment showed that their synthetic 217A had spectral characteristics identical with those reported for the natural product. Since the spectral data for our synthetic 217A matches that of Pearson's synthetic material, we are confident that our material is in fact the natural product 217A.



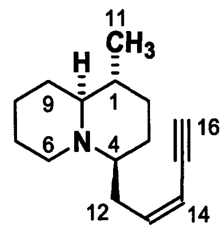
214

176

Quinolizidine (–)-217A

Summary

In conclusion, the intramolecular iminoacetonitrile [4+2] cycloaddition functions as a key step in an efficient assembly of the quinolizidine core of the amphibian alkaloid (–)-217A, enabling the total synthesis of this natural product in only 12 steps. The application of iminoacetonitrile cycloadditions in the synthesis of other bioactive alkaloids is currently under investigation.



Quinolizidine (–)-217A

Table 6. **^{1}H NMR ($CDCl_3$) Spectral Data for Quinolizidine 217A[68,71]**

		Pearson (400 MHz)		Panek (400 MHz)		Maloney (500 MHz)	
Atom #	*m*	**δ**	***J* (Hz)**	**δ**	***J* (Hz)**	**δ**	***J* (Hz)**
H(14)	dt (1H)	6.1	11	6.09	10.8, 7.25	6.1	10.9, 7.1
H(13)	ddt (1H)	5.52	1.9, 10.7, 1.6	5.49	10.8, 1.3	5.48	10.9, 2.0, 1.6
H(6)	br d (1H)	3.27	11	3.25	10.5	3.29	11.1
H(16)	d (1 H)	3.07	1.6	3.05	1.6	3.09	2
H(12,10)	m (2H)	2.50-2.65		2.47-2.62		2.53-2.63	
H(12)	m (1H)	2.07		2.03		2.05-2.10	
H(6)	m (1H)	1.91		1.89	11.9	1.93	11.9
H(1-4, 7-9)	m (12H)	0.94-1.80		0.94-1.75		1.02-1.79	
H(11)	d (3H)	0.85	6.6	0.83	6.6	0.87	6.5

Table 7. **^{13}C NMR ($CDCl_3$) Data for Quinolizidine 217A[68,71]**

Pearson (100 MHz)	Panek (75 MHz)	Maloney (75 MHz)
δ	δ	δ
143.5	143.4	143.9
109.5	109.2	109.6
81.8	81.5	82
80.8	81.5	81
69.8	69.5	69.9
63.2	63	63.4
51.9	51.7	52
36.4	36.3	36.7
35.1	34.9	35.3
34	33.8	34.2
31.9	31.7	32.1
30.3	30.1	30.5
26.3	26.2	26.6
24.8	24.6	25
19.4	19.2	19.6

Chapter 8 – Studies Directed Toward the Total Synthesis of Indolizidine (–)-235B′

As demonstrated in the previous chapters, intramolecular [4+2] cycloaddition of iminoacetonitriles provide access to α-amino nitrile cycloadducts, which have proved to be versatile synthetic intermediates for the synthesis of nitrogen heterocycles. This chapter discusses our efforts toward the total synthesis of indolizidine 235B′ utilizing an iminoacetonitrile cycloaddition as the key step.

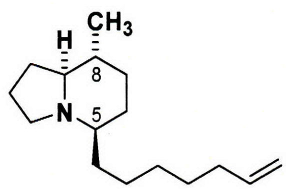
Introduction

The isolation, biological evaluation, and total synthesis of naturally occurring alkaloids isolated from the skin extracts of the Dendrobatidae family of neotropical arrow poison frogs has been an active area of research.[98] In particular, a small sub-group of 5,8-disubstituted indolizidines have been identified as inhibitors of nicotinic acetylcholine receptors.[127] These receptors act as key components in the physiological processes of reward, cognition, learning, and memory, and are widely expressed in the mammalian brain. Thus, nicotinic acetylcholine receptors are implicated in several neurological disorders such as Alzheimer's disease, schizophrenia, and bipolar disorder.

One 5,8-disubstituted indolizidine that has generated considerable interest in the past few years is alkaloid (–)-235B′. Indolizidine (–)-235B′ was isolated in minute quantities by Daly and coworkers in 1988 from skin extracts of the Panamanian poison frog *Dendrobates speciosus*.[128]

[127] Daly, J. W.; Nishizawa, Y.; Padgett, W. L.; Tokuyama, T.; Smith, A. L.; Holmes, A. B.; Kibayashi, C.; Aronstam, R. S. *Neurochem. Res.* **1991**, *16*, 1213.
[128] Daly, J. W.; Edwards, M. W.; Myers, C. W. *J. Nat. Prod.* **1988**, *51*, 1188.

Recently, Toyooka and coworkers discovered that alkaloid (–)-235B′ is a potent noncompetitive inhibitor of α2β2-neuronal acetylcholine receptors in a highly subtype-selective manner. These results suggest that alkaloid (–)-235B′ is a promising lead compound for the development of drugs to treat cholinergic disorders such as autosomal dominant nocturnal frontal lobe epilepsy.[129]



Indolzidine (–)-235B'

This chapter describes the application of the iminoacetonitrile cycloaddition as a key step in the total synthesis of indolizidine (–)-235B′. Our goal is the development of an efficient approach to the synthesis of this alkaloid capable of supporting the preparation of significant quantities of material.

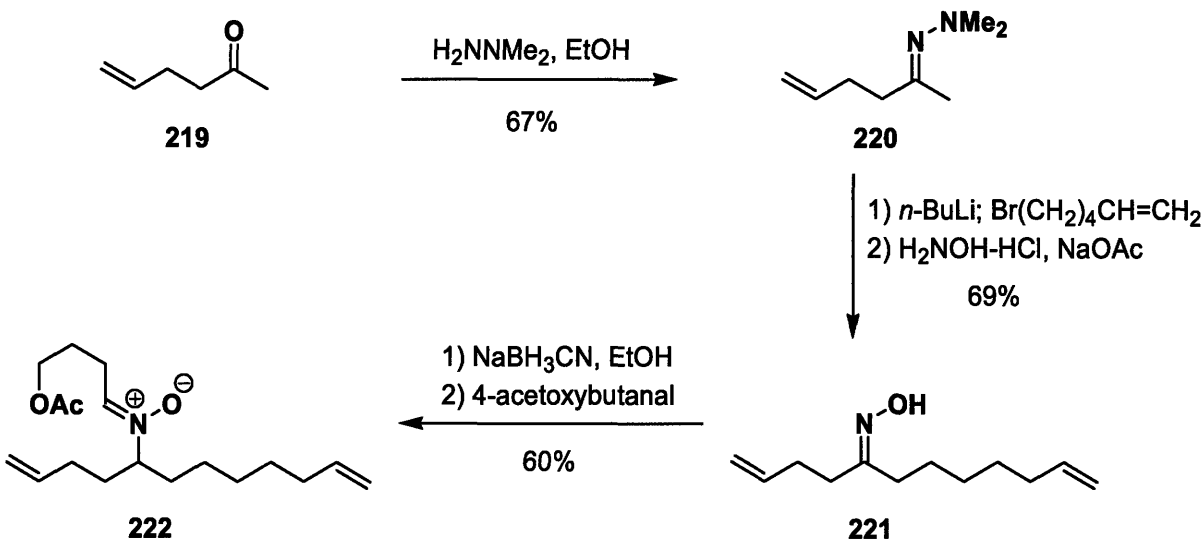
Previous Syntheses of 235B′

Holmes and coworkers published the first total synthesis of 235B′ in 1991, producing racemic 235B′ in 14 steps.[130] Their approach employed an intramolecular nitrone dipolar cycloaddition as a key step to control the relative stereochemistry of the substituents of the piperidine subunit. As shown in Scheme 52, the first stage of the synthesis involved the

[129] (a) Toyooka, N.; Tsuneki, H.; Kobayashi, S.; Dejun, Z.; Kawasaki, M.; Kimura, I.; Sasaoka, T.; Nemoto, H. *Curr. Chem. Biol.* **2007**, *1*, 97. (b) Tsuneki, H.; You, Y.; Toyooka, N.; Kagawa, S.; Kobayashi, S.; Sasaoka, T.; Nemoto, H.; Kimura, I.; Dani, J. A. *Mol. Pharmacol.* **2004**, *66*, 1061.
[130] Collins, I.; Fox, M. E.; Holmes, A. B.; Williams, S. F.; Baker, R.; Forbes, I. J.; Thompson, M. *J. Chem. Soc., Perkin Trans. 1* **1991**, 175.

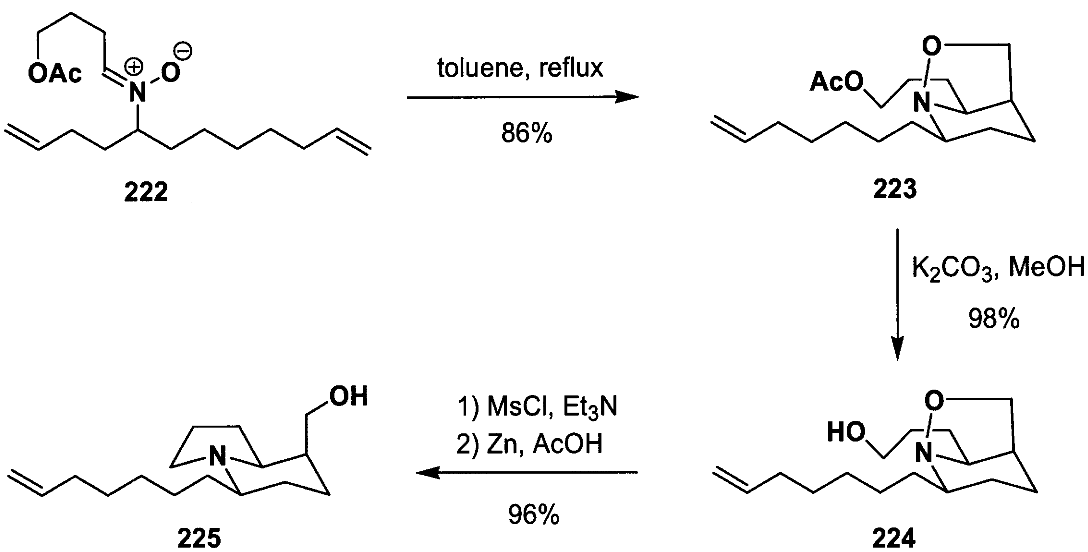
preparation of cycloaddition substrate **222**. The synthesis began with the formation of hydrazone **220** from commercially available hex-5-en-2-one in 67% yield. Regioselective alkylation of hydrazone **220** with 6-bromohexene followed by treatment with hydroxylamine hydrochloride delivered oxime **221** in 69% yield. Oxime **221** was then reduced with sodium cyanoborohydride and the resulting hydroxylamine was condensed with 4-acetoxybutanal to give nitrone **222** in 60% yield.

Scheme 52



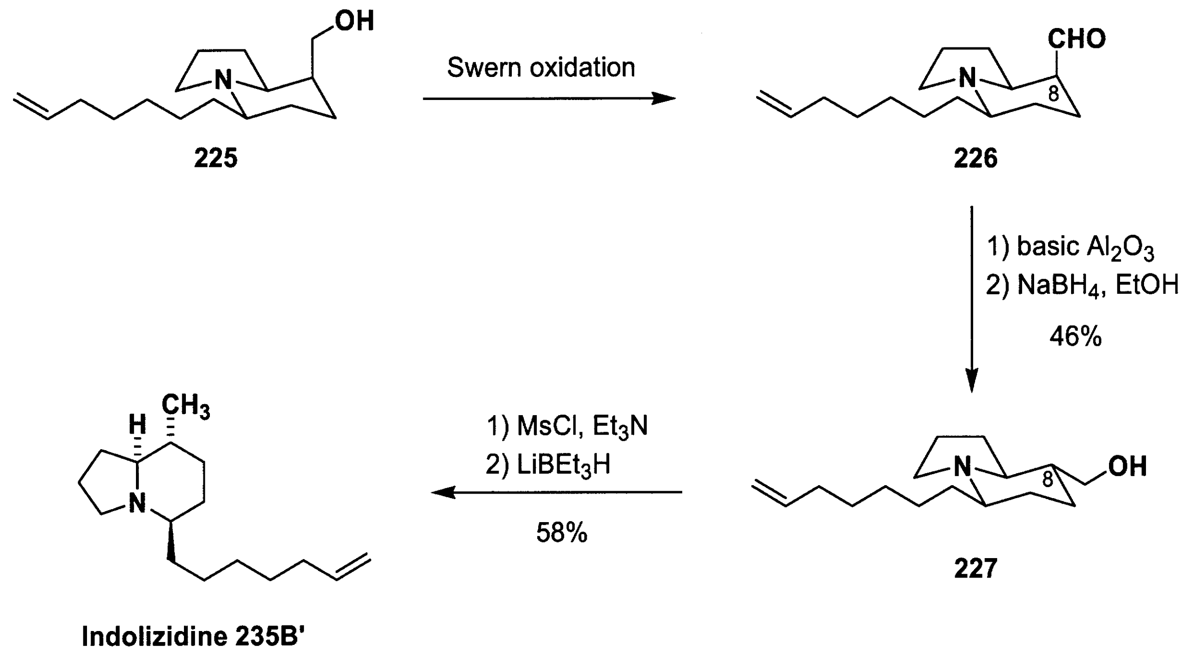
With the synthesis of nitrone **222** complete, the stage was set for the key intramolecular dipolar cycloaddition (Scheme 53). In the event, heating a toluene solution of **222** afforded cycloadduct **223** which upon hydrolysis delivered alcohol **224** in excellent yield as a single diastereomer. Mesylation of alcohol **224** led to spontaneous cyclization to give the quaternary ammonium salt, and subsequent reductive cleavage of the N-O bond with zinc in acetic acid furnished indolizidine **225** in excellent yield.

Scheme 53



As depicted in Scheme 54, indolizidine **225** was converted into the target alkaloid in a straightforward fashion. Inversion of the C-8 stereochemistry of **225** was achieved by Swern oxidation to give aldehyde **226**, followed by epimerization on basic alumina to give predominantly the equatorial isomer (ca. 13:1). Subsequent reduction and purification of the resulting equatorial alcohol afforded **227** in 46% yield. Lastly, mesylation of alcohol **227** and reduction with $LiBEt_3H$ gave racemic indolizidine 235B′ in 58% yield.

Scheme 54



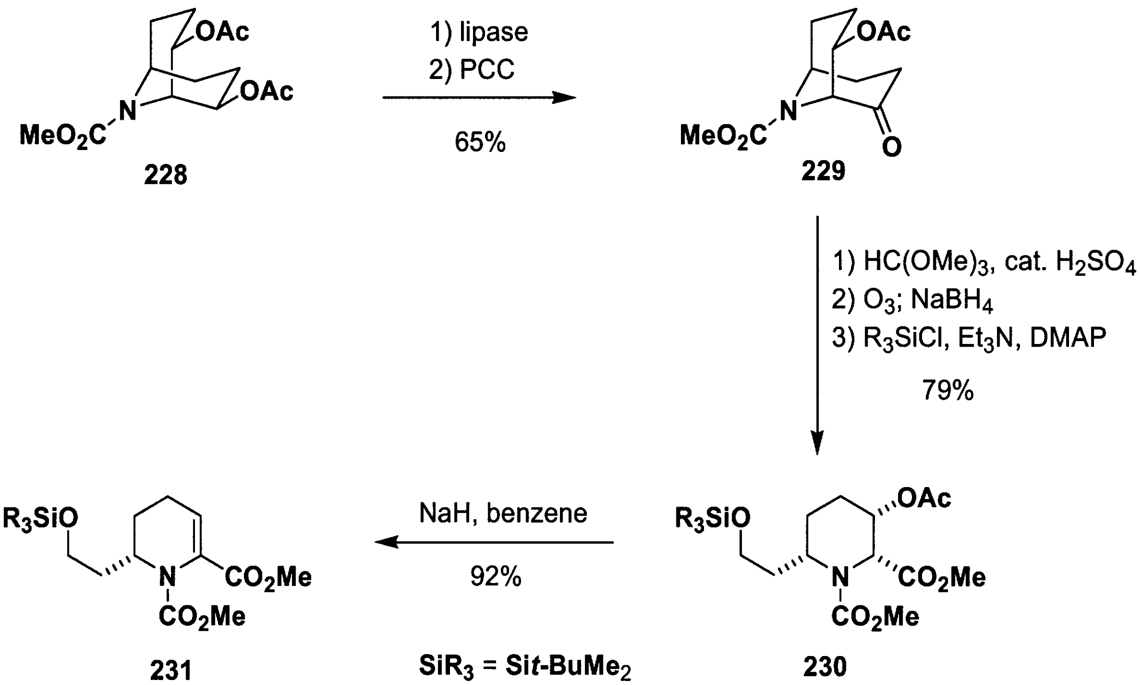
In 1997, Toyooka and coworkers reported the first enantioselective synthesis of indolizidine (–)-235B′ via a 29 step route.[131] Although the length of this synthesis precludes it from providing useful quantities of material, the synthesis does display a high level of selectivity in generating the three stereocenters. Toyooka controlled the stereochemistry at C-5 by employing a 9-azabicyclo[3.3.1]nonene derivative in a cyclic template strategy, cleaving an internal olefin to afford the piperidine subunit of 235B′ with the desired C-5 stereochemistry. A subsequent stereoselective cuprate addition afforded the piperidine subunit with all three stereocenters set.

As shown in Scheme 55, the synthesis commenced with meso diacetate **228**, prepared in 9 steps from 1,5-cyclooctadiene.[132] Lipase-catalyzed hydrolysis of diacetate **228** followed by oxidation afforded ketone **229** in 65% yield as a single enantiomer. Enol ether formation

[131] (a) Toyooka, N.; Tanaka, K.; Momose, T. *Tetrahedron* **1997**, *53*, 9553. (b) Momose, T.; Toyooka, N. *J. Org. Chem.* **1994**, *59*, 943. (c) Momose, T.; Toyooka, N.; Jin, M. *Tetrahedron Lett.* **1992**, *33*, 5389.
[132] Portman, R. E.; Ganter, C. *Helv. Chim. Acta.* **1973**, *56*, 1991.

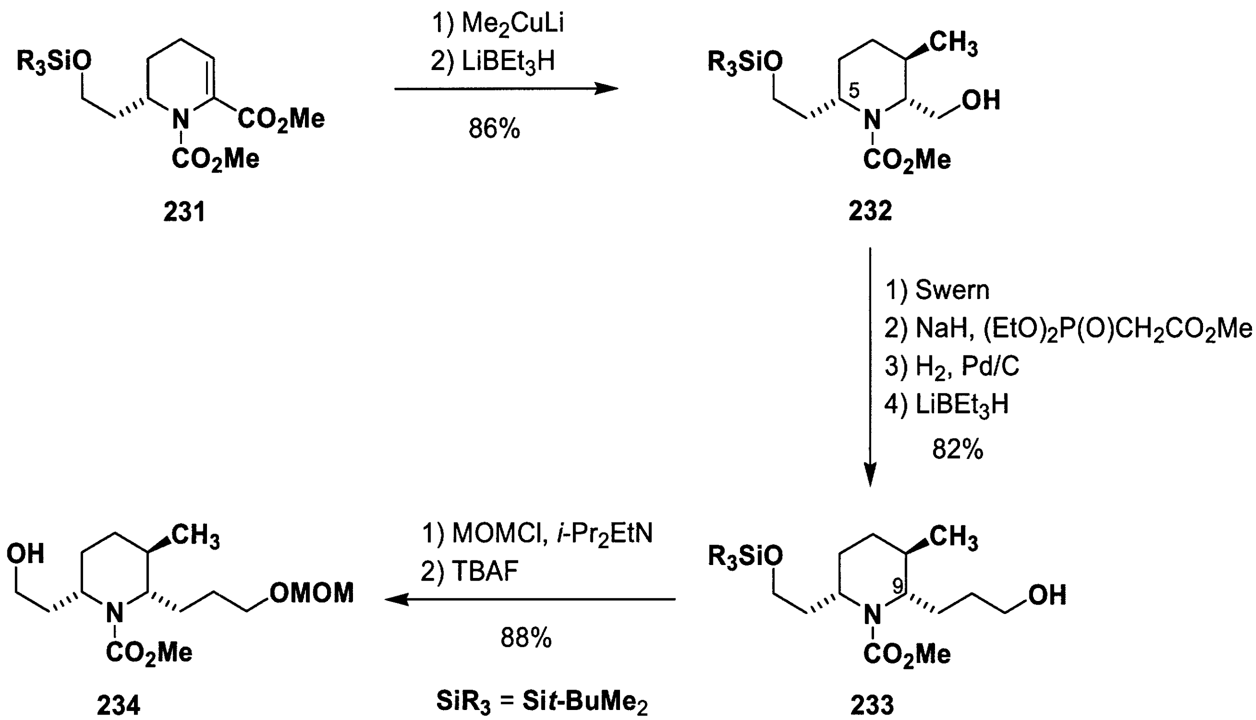
followed by ozonolysis, reduction, and silylation provided piperidine **230** in 79% yield as a single diastereomer. Sodium hydride elimination of acetic acid from **230** afforded the cuprate addition precursor **231** in 92% yield.

Scheme 55



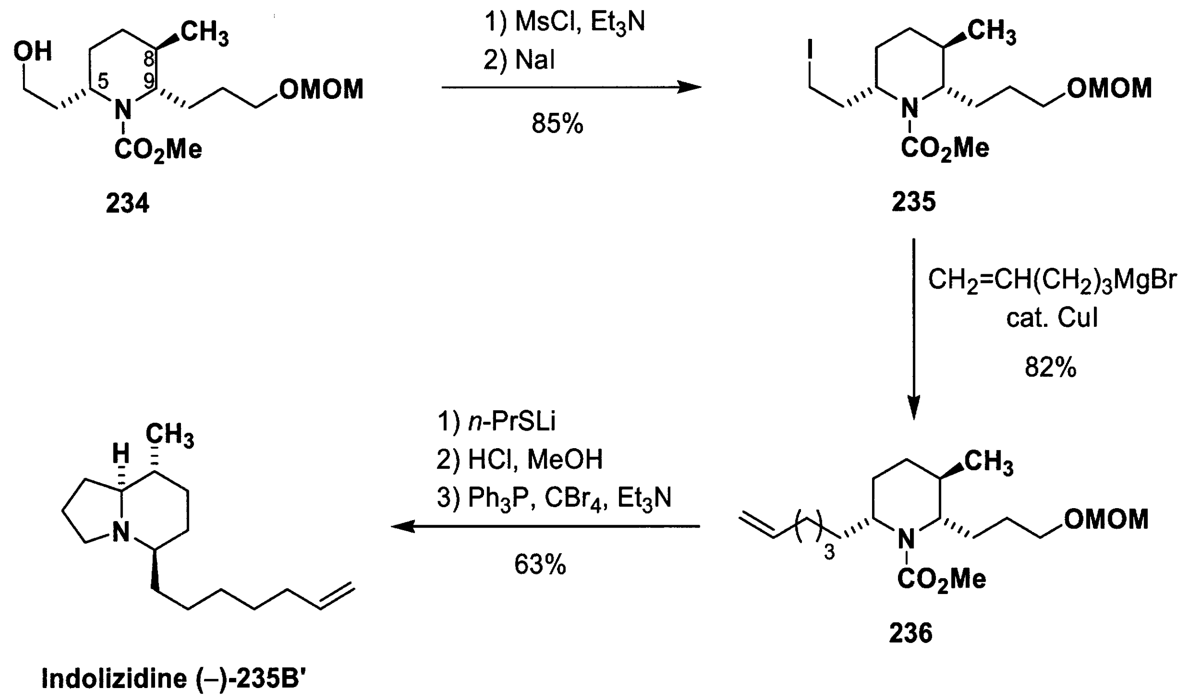
With the synthesis of **231** complete, the stage was set for the key stereoselective cuprate addition to set the final two stereocenters. As depicted in Scheme 56, addition of methyl cuprate to **231** followed by hydride reduction of the ester group afforded piperidine **232** in 86% yield as a single diastereomer. The stereochemistry of the methyl cuprate addition is a result of preferred axial attack of the cuprate reagent, leading to a chair-like intermediate where the C-5 side chain occupies a pseudo-axial orientation owing to $A^{1,3}$ strain. Subjecting **232** to a series of functional group manipulations afforded piperidine **233**. This series of steps elongated the C-9 side chain by two carbons. Protection of the free hydroxyl group of **233** and subsequent desilylation delivered alcohol **234** in 88% yield.

Scheme 56



With the C-5, C-8, and C-9 stereocenters set, alcohol **234** was converted into alkaloid 235B′ in a straightforward manner (Scheme 57). The carbon chain homologation of **234** at the C-5 position to give **236** was performed via a sequence involving mesylation of the hydroxyl group, substitution of the resulting mesylate group with NaI to give **235**, and subsequent cross coupling. Finally, cyclization of the amino alcohol resulting from liberation of the amino and hydroxyl groups delivered indolizidine (–)-235B′ in 65% yield.

Scheme 57



Efforts Toward the Total Synthesis of Indolizidine (–)-235B′

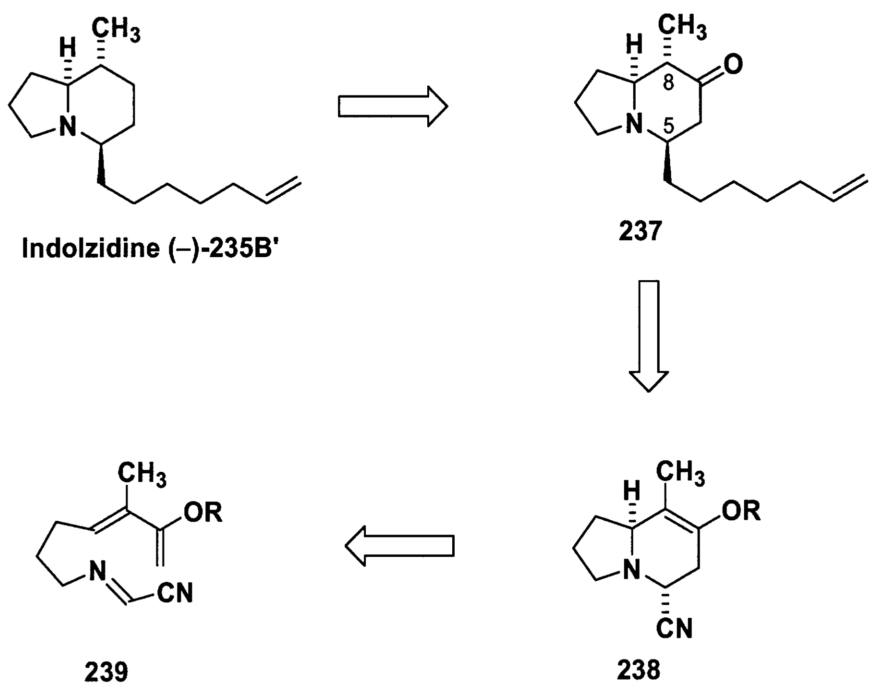
Retrosynthetic Analysis

Our goal was the development of an approach to the synthesis of indolizidine (–)-235B′ that would be considerably more efficient than these earlier syntheses and capable of supporting the preparation of significant quantities of the target alkaloid. Our retrosynthetic strategy closely resembles that of quinolizidine 217A with the only major difference being that it involves the synthesis and elaboration of an indolizidine cycloadduct instead of a quinolizidine cycloadduct.

Scheme 51 outlines our retrosynthetic strategy, which features the intramolecular iminoacetonitrile cycloaddition **239**→**238** as a pivotal step. Alkylation of **238** would then be employed to install the heptenyl side chain, and stereoelectronic control in the subsequent reductive decyanation step was expected to deliver the desired stereochemistry at C-5. Control of the stereochemistry at C-8 would be established by epimerization of the ketone intermediate

237 derived from the enol ether cycloadduct. In this first generation synthesis, we elected to employ resolution to provide access to the natural (–)-isomer as well as the unnatural isomer, deferring for future study the possibility of employing chiral Brønsted acids to catalyze an asymmetric version of the cycloaddition.

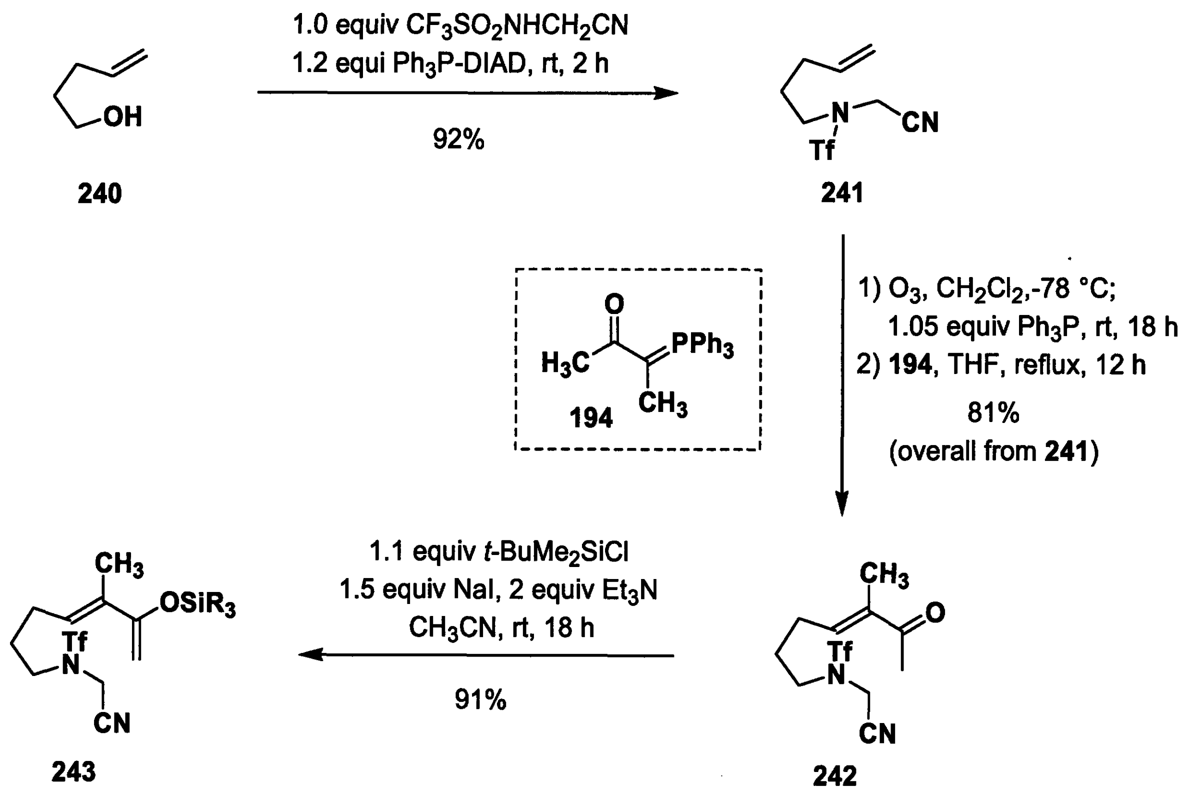
Scheme 58



Preparation of α-Amino Nitrile Cycloadduct

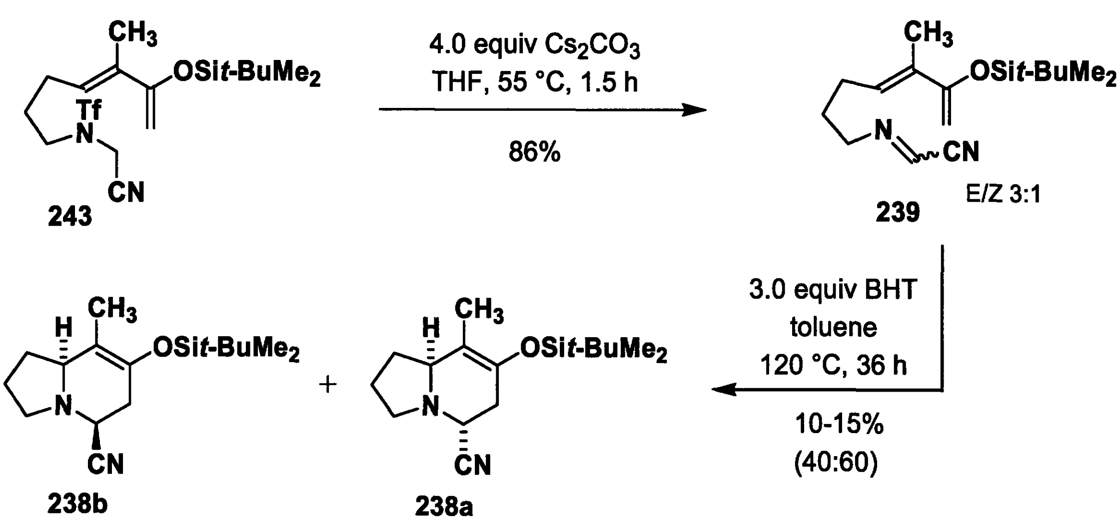
Our first synthetic subgoal was the development of an efficient route to cycloaddition substrate **239**. Based on our previous studies on the total synthesis of 217A, we anticipated that **239** would be available from sulfonamide **243**. Scheme 59 outlines our efficient four-step route to **243** which closely resembles the analogous sequence in our synthesis of 217A. Mitsunobu coupling of commercially available 4-pentenol (**240**) with $TfNHCH_2CN$ provided the expected sulfonamide **241** in 92% yield. Ozonolysis of triflamide **241** and subsequent Wittig olefination of the resulting aldehyde using the acylphosphorane **194**[110] produced the desired (*E*)-α,β-unsaturated ketone **242** in 81% overall yield after purification by column chromatography. Unexpectedly, the intermediate aldehyde was unstable to silica gel and therefore was used in the Wittig olefination without further purification. We also discovered that switching from toluene at 70 °C (conditions used in our 217A route) to refluxing THF led to consistently higher yields (ca. 10%) in the Wittig reaction. Finally, conversion to the desired silyl enol ether **243** was achieved using the general procedure of Dunogues et al.[112] to afford **243** in 91% yield after purification on acetone-deactivated silica gel.

Scheme 59



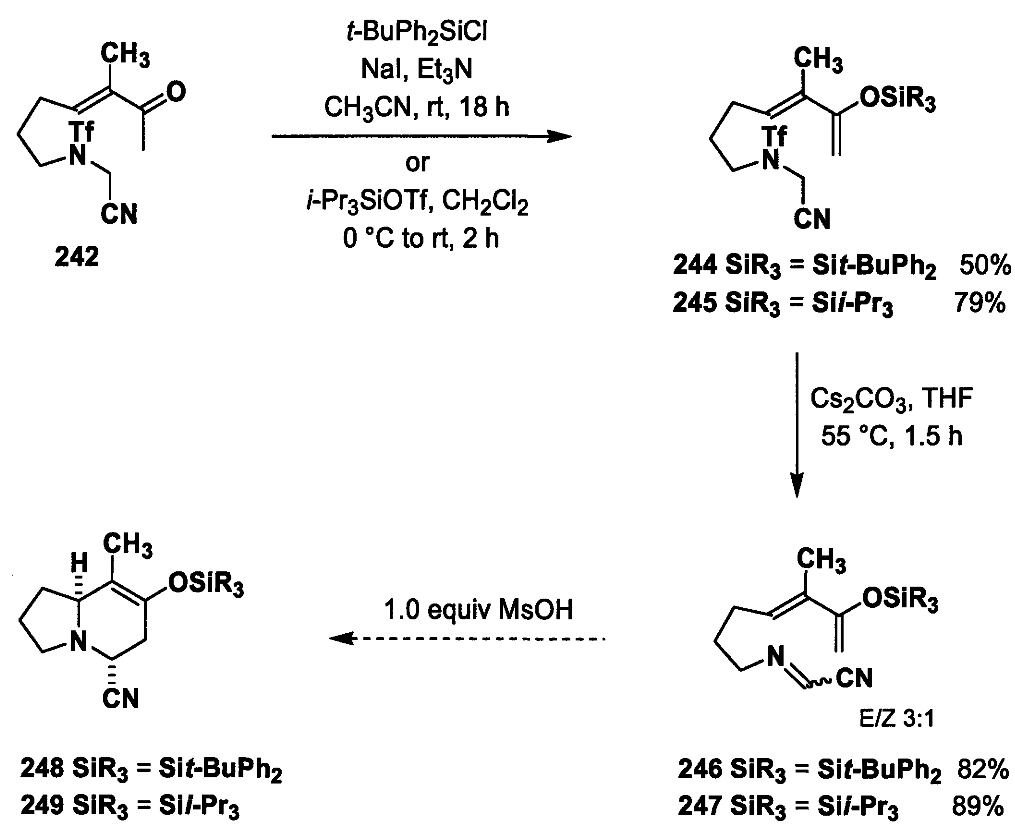
As shown in Scheme 60, exposure of **243** to the action of cesium carbonate led to the elimination of trifluoromethanesulfinate and formation of iminoacetonitrile **239** as the expected mixture of *E* and *Z* imine isomers. Heating iminoacetonitrile **239** at 120 °C for 36 h then produced the desired α-amino nitrile cycloadducts **238a** and **238b** in 10-15% yield as a 60:40 mixture of epimers (Scheme 60). Discouraged by this result, we shifted our focus to the acid-promoted cycloaddition of **239**. Unfortunately, cycloaddition of **239** at -78 °C failed to deliver cycloadduct **238** and led to recovered iminoacetonitrile. This was not unexpected as previous results have shown that cycloadditions affording indolizidines are extremely sluggish at -78 °C. However, efforts to conduct the cycloaddition at higher temperatures (-40 to 0 °C) were complicated by competing decomposition of the iminoacetonitrile presumably via reaction of the silyl enol ether with acid. We also explored the possibility of increasing the reaction rate of the cycloaddition by increasing the polarity of the solvent. However, switching the solvent from dichloromethane to propionitrile afforded a complex mixture of several products with no sign of the desired cycloadduct.

Scheme 60



Next, we explored the possibility of increasing the stability of iminoacetonitrile **239** by increasing the acid stability of the silyl enol ether portion. We felt that by switching from a *t*-butyldimethylsilyl group to a more acid stable group such as *t*-butyldiphenylsilyl or triisopropylsilyl would allow the reaction temperature to be increased to promote the cycloaddition while avoiding the competing decomposition pathway. As shown in Scheme 61, imines **246** and **247** were synthesized in excellent yield from enone **242**. Disappointingly, the acid-promoted cycloadditions of **246** and **247** were completely unsuccessful. At -78 °C with 1 equiv of MsOH in dichloromethane, both imines were completely unreactive. However, upon warming to -30 °C, cycloadducts **206** and **207** were obtained in ca. 5% yield with extensive decomposition of the iminoacetonitriles.

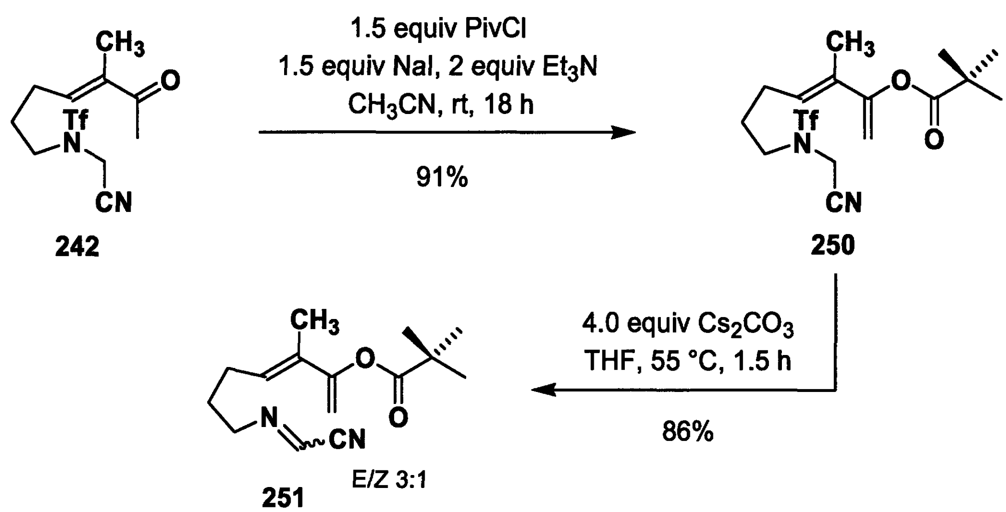
Scheme 61



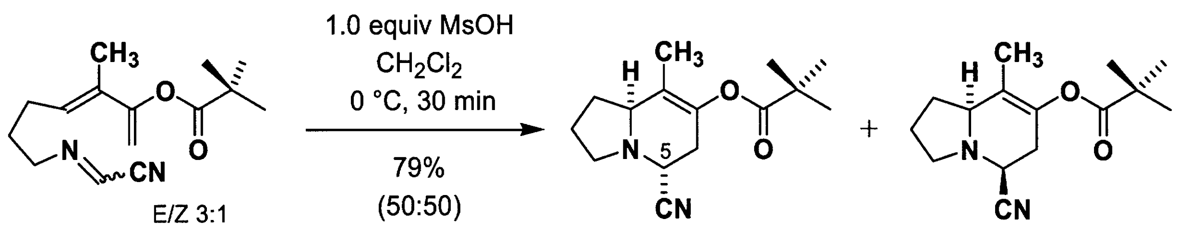
Discouraged by these results, we shifted our focus to enol acetate derivatives (e.g., **251**). We felt that the less electron-donating acetate group would reduce the susceptibility of the dienyl enol acetate towards protonation and subsequent decomposition in acid-promoted cycloadditions. Although an enol acetate should be fairly stable under acidic conditions, we were concerned about basic hydrolysis under our elimination conditions. Therefore, we decided to use an enol pivalate which would be expected to be stable under both acidic and basic conditions.

As shown in Scheme 62, iminoacetonitrile **251** was synthesized in two steps from enone **242**. Initially, the synthesis of enol pivalate **250** proved unexpectedly difficult. Attempts to install the enol pivalate using pivaloyl chloride or trimethylacetic anhydride with a variety of bases, such as pyridine and DMAP, were unsuccessful leading to recovered starting material. However, we found that activation of the pivaloyl chloride with NaI in the presence of triethylamine afforded **250** in 91% yield. Finally, elimination of trifluoromethanesulfinate furnished iminoacetonitrile **251** in 86% yield as a 75:25 mixture of *E* and *Z* isomers.

Scheme 62



With imine **251** in hand, the stage was set for the key iminoacetonitrile cycloaddition. In the event, the acid-promoted cycloaddition of iminoacetonitrile **251** afforded cycloadducts **252a** and **252b** in 79% yield as a 50:50 mixture of epimers at C-5 (eq 32). As predicted, the enol pivalate **251** was significantly more stable than the silyl enol ethers **246** and **247** under the acidic reaction conditions allowing the cycloaddition to occur smoothly at 0 °C without significant decomposition. It is important to emphasize that the mixture of epimers at C-5 is inconsequential due to the fact that further transformations at the C-5 carbon are controlled by stereoelectronic principles independent of the C-5 cyano group stereochemistry (see Chapter 6).



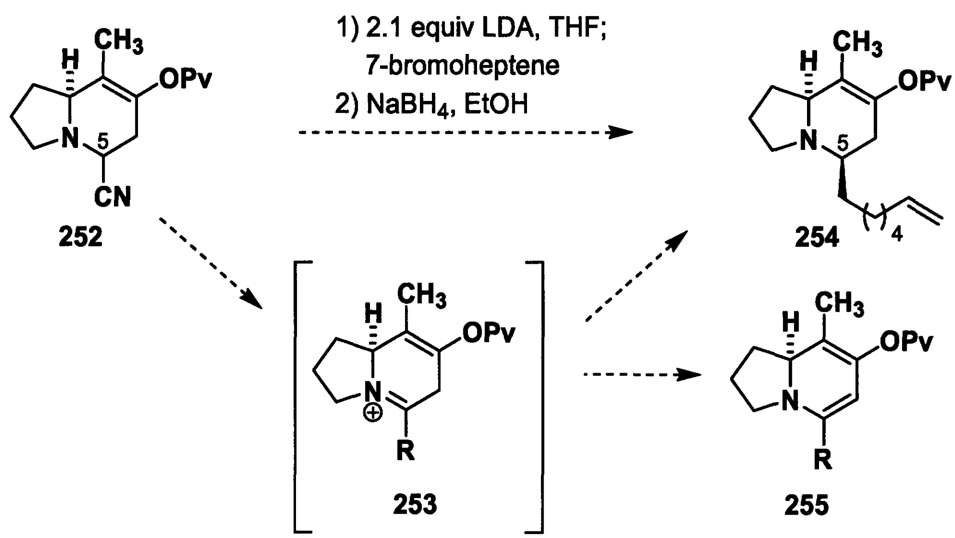
(32)

251 **252a** **252b**

Alkylation/Reductive Decyanation of α-Amino Cycloadduct 252

Having completed the synthesis of cycloadduct **252**, we focused our attention on installing the C-5 side chain of the target alkaloid. As depicted in Scheme 63, we were pleased to find that alkylation of **252** with 7-bromoheptene proceeded cleanly; however, reductive decyanation of the unpurified alkylation product with several hydride reagents ($NaBH_4$, $ZnBH_4$, $NaBH_3CN$) afforded a complex mixture of several products. Presumably, the intermediate iminium ion **253** is decomposing via dienamine **255**. It should be mentioned that similar problems were encountered in the attempted alkylation-reductive decyanation of cycloadduct **238** (silyl enol ether case). Interestingly, as seen in our 217A synthesis, the tandem alkylation-reductive decyanation of the related quinolizidine **190** works beautifully. One possible explanation is that the accelerated rate of formation of the dienamine byproduct (**255**) in the indolizidine case versus the quinolizidine case is a result of the increased angle strain in the intermediate iminium ion (**253**).

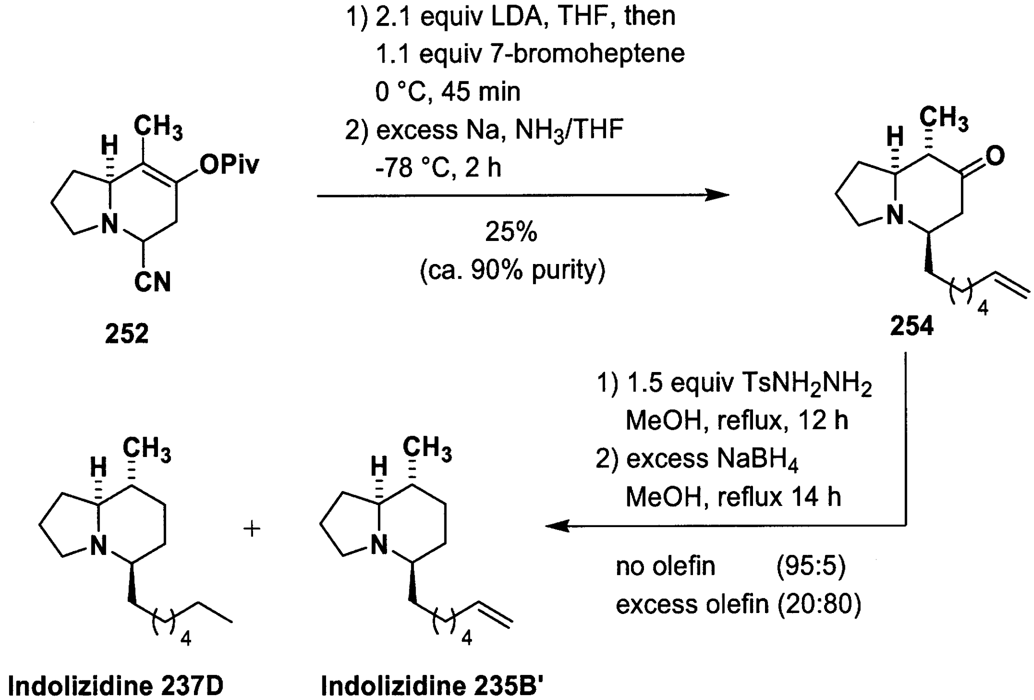
Scheme 63



We therefore next shifted our focus to a radical-based reductive decyanation procedure that would avoid the formation of an iminium ion. As shown in Scheme 64, alkylation of **252** with 7-bromoheptene followed by reductive decyanation with sodium in liquid ammonia afforded quinolizidine **254** in 25% yield (ca. 90% purity) as a single diastereomer.[133] As expected, sodium in liquid ammonia not only removed the cyano group but also cleaved the enol pivalate revealing the C-2 carbonyl. Unfortunately, the overall yield of the two-step reaction sequence was fairly low, and difficulties were encountered in purifying ketone **254**.

[133] NMR analysis and comparison to quinolizidine **208** (p 95) confirmed the stereochemistry at C-5 and C-8.

Scheme 64



However, with ketone **254** in hand we were poised to complete the total synthesis of alkaloid (–)-235B′. Unexpectedly, deoxygenation of **254** via the tosyl hydrazone derivative afforded a 95:5 mixture of indolizidine 237D and indolizidine 235B′. Based on the hypothesis that reduction of the alkene was presumably occurring via the in situ generation of diimide, we decided to employ a sacrificial olefin to inhibit the undesired reduction. Adding excess 1-hexene or cyclopentene to the reaction mixture afforded a much improved 20:80 mixture of indolizidine 237D and the desired indolizidine 235B′. Unfortunately, attempts to completely suppress the reduction through the addition of dicyclopentadiene and 1-hexyne, as well as the use of different reaction solvents (dioxane, THF, EtOH, AcOH, and DMF), were fruitless. Therefore, we decided to explore other deoxygenation methods.[134]

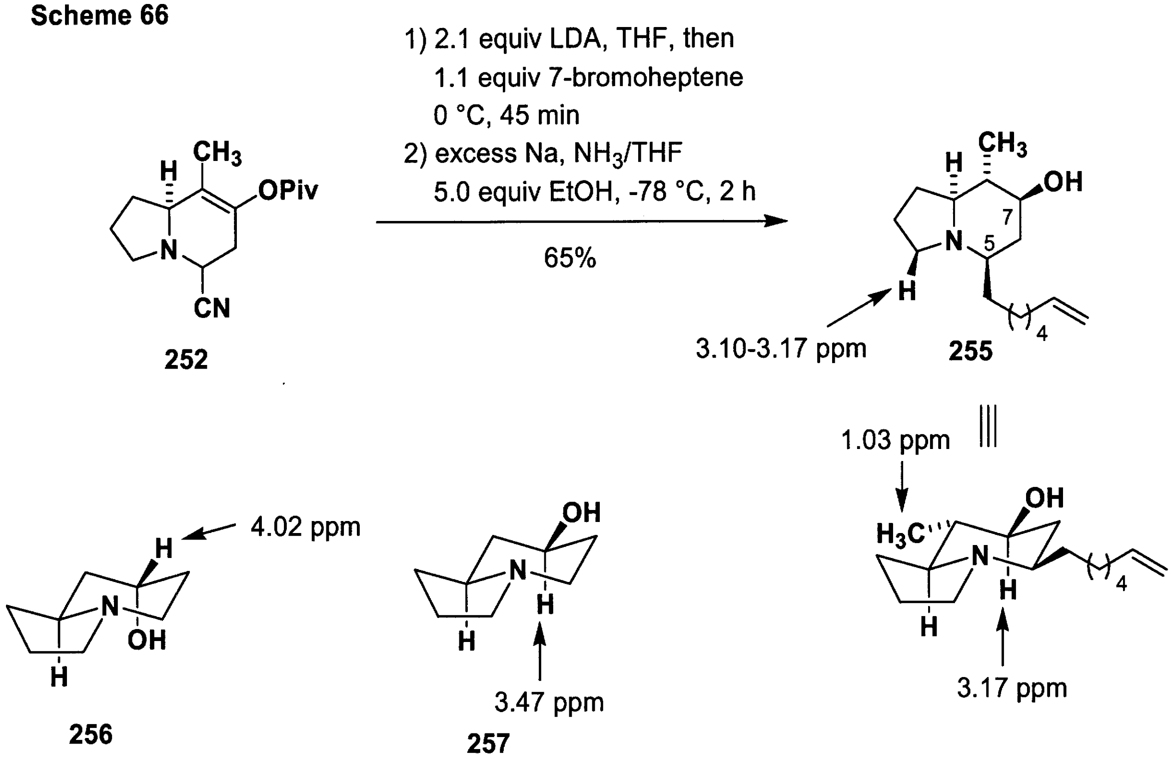
[134] For general reviews on the deoxygenation of alcohols, see: (a) McCombie, S. M. In *Comprehensive Organic Synthesis;* Trost, B. M.; Fleming, I., Eds.; Pergamon Press: Oxford, 1991, Vol. 8, pp 811-833. (b) Hartwig, W. *Tetrahedron* **1983**, *39*, 2609.

Interested in the possibility of using a Barton-McCombie deoxygenation reaction,[135] we shifted our focus to the synthesis of alcohol **255** (Scheme 66). Surprisingly, we found that simply adding ethanol to the sodium/liquid ammonia reduction flask delivered the desired alcohol **255** in 65% yield as a single diastereomer. As shown below, the assignment of the C-7 stereocenter of **255** was based on the chemical shift of the C-7 proton which is consistent with an axial orientation.[136] The C-5 side chain of **255** was assigned as equatorial based on NMR analysis and comparison with the spectra reported by Polniaszek[83] for related indolizidine compounds (see **126** and **127** on pp 66). Unfortunately, initial efforts using the classical Barton-McCombie deoxygenation to remove the C-7 hydroxyl group have been unsuccessful due to problems synthesizing the thiocarbonyl derivatives.

[135] (a) Barton, D. H. R.; McCombie, S. W. *J. Chem. Soc., Perkin Trans. 1* 1975, 1574. (b) Barton, D. H. R.; Blundell, P.; Dorchak, J.; Jang, D. O.; Jaszberenyi, J. C. *Tetrahedron* **1991**, *47*, 8969. (c) Barton, D. H. R.; Dorchak, J.; Jaszberenyi, J. C. *Tetrahedron* **1992**, *48*, 7435. (d) Lopez, R. M.; Hays, D. S.; Fu, G. C. *J. Am. Chem. Soc.* **1997**, *119*, 6949.

[136] For ^{1}H NMR data of **256** and **257**, see Rader, C. P.; Young, R. L.; Aaron, H. S. *J. Org. Chem.* **1965**, *30*, 1536.

Scheme 66



Summary

In conclusion, this chapter describes our efforts toward the total synthesis of indolizidine (–)-235B′ utilizing the intramolecular Diels-Alder cycloaddition of iminoacetonitriles as a key step. These studies are by no means complete, and further efforts are currently underway in the Danheiser laboratory to complete the total synthesis of indolizidine (–)-235B′.

Part IV

Experimental Procedures

General Procedures. All reactions were performed in flame-dried or oven-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 by syringe or cannula and introduced into reaction vessels through rubber septa. Reaction product solutions and chromatography fractions were concentrated by rotary evaporation at ca. 20 mmHg and then at ca. 0.1 mmHg (vacuum pump) unless otherwise indicated. Thin layer chromatography was performed on Merck precoated glass-backed silica gel 60 F-254 0.25 mm plates. Column chromatography was performed on EM Science silica gel 60 or Silicycle silica gel 60 (230-400 mesh).

Materials. Commercial grade reagents and solvents were used without further purification except as indicated below. Dichloromethane and tetrahydrofuran were purified by pressure filtration through activated alumnia. Toluene was purified by pressure filtration through activated alumina and Cu(II) oxide. *N,N*-Diisopropylamine, triethylamine, and diisopropylethylamine were distilled under argon from calcium hydride. Methanesulfonic acid and trifluoromethanesulfonic anhydride were distilled under argon from phosphorus pentoxide. NaI was dried under vacumm (0.1 mmHg) at 70 °C for 24 h. Copper(I) iodide was extracted with THF for 24 h in a Soxhlet extractor and then dried under vacuum (0.1 mmHg). Palladium(II) chloride (bis)triphenylphosphine was recrystallized from boiling chloroform. *n*-Butyllithium was titrated in tetrahydrofuran with diphenylacetic acid.[137]

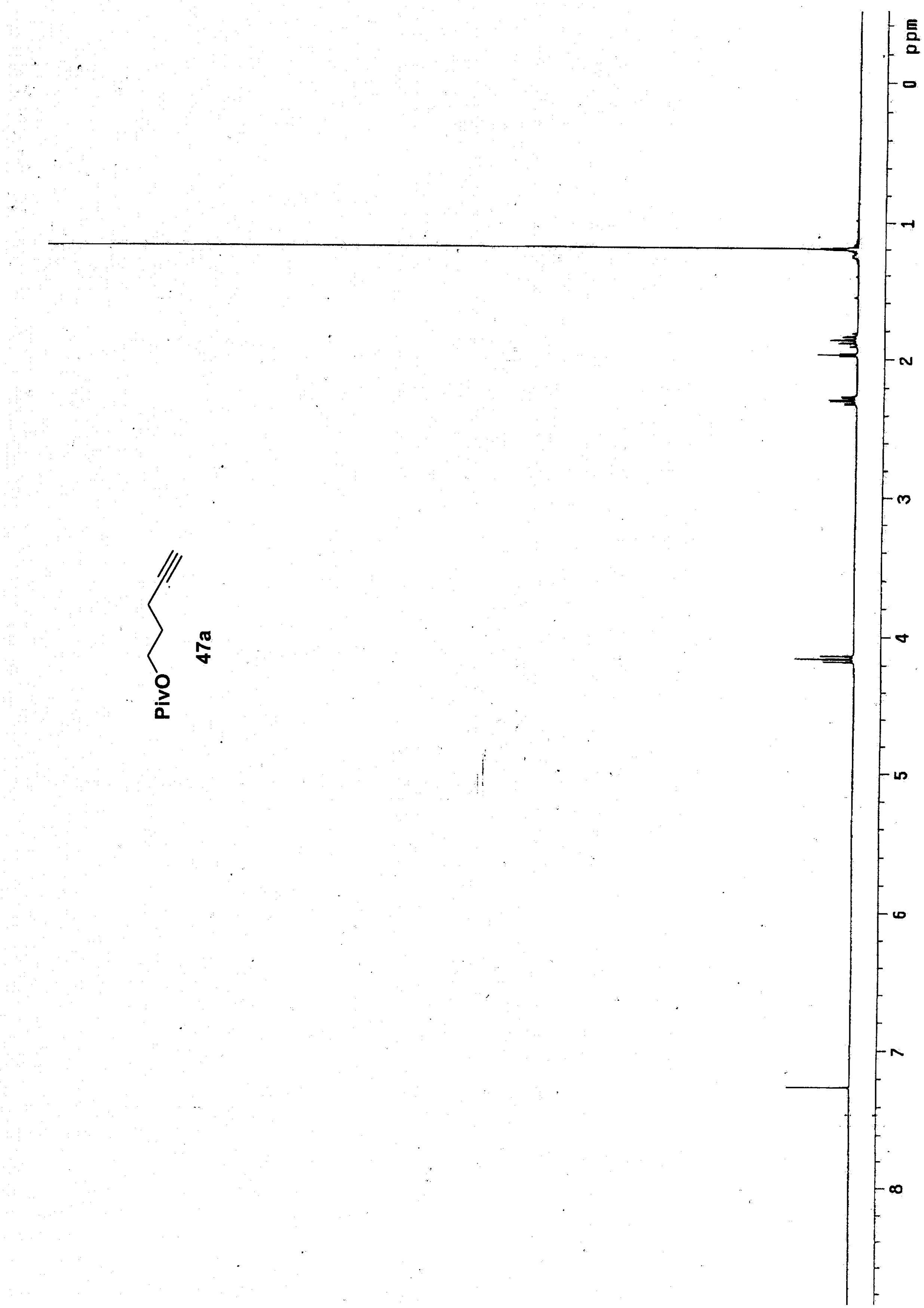
Instrumentation. Melting points were determined with a Fisher-Johns melting point apparatus and are uncorrected. Infrared spectra were obtained using a Perkin Elmer 2000 FT-IR

[137] Kofron, W. G.; Baclawski, L. M. *J. Org. Chem.* **1976**, *41*, 1879.

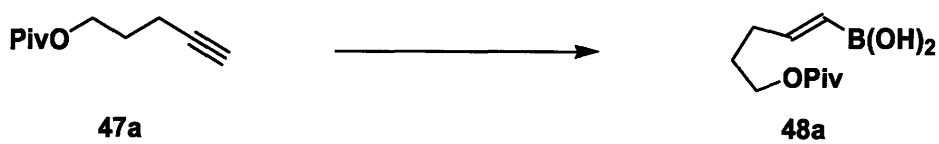
spectrophotometer. Ozonolysis was performed using a Welsbach Ozone machine with an ozone flow rate of ca. 2.75 mmol/3 min. ^{1}H NMR and ^{13}C NMR spectra were measured with an Inova 500, Inova 300, and Bruker 400 spectrometers. ^{1}H NMR chemical shifts are expressed in parts per million (δ) downfield from tetramethylsilane (with the $CHCl_3$ peak at 7.27 ppm used as a standard). ^{13}C NMR chemical shifts are expressed in parts per million (δ) downfield from tetramethylsilane (with the central peak of $CHCl_3$ at 77.23 ppm used as a standard). High resolution mass spectra (HRMS) were measured on a Bruker Daltonics APEXII 3 telsa Fourier transform mass spectrometer. Elemental analyses were performed by E&R Microanalytical Laboratory, Inc. of Parsippany, NJ.

Experimental Procedures for Synthesis of Alcohol Substrates

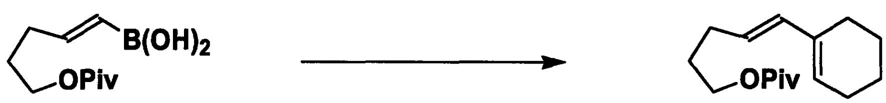
2,2-Dimethylpropionic acid 4-pentynyl ester (47a). A 25-mL, two-necked, round-bottomed flask equipped with a rubber septum and argon inlet adapter was charged with DMAP (0.066 g, 0.54 mmol) and 10 mL of CH_2Cl_2. 4-Pentyn-1-ol (0.50 mL, 0.45 g, 5.4 mmol) and pyridine (1.30 mL, 1.30 g, 16.1 mmol) were added via syringe. Pivaloyl chloride (0.79 mL, 0.78 g, 6.4 mmol) was then added dropwise over 2 min via syringe, and the resulting solution was stirred at room temperature for 1 h. The reaction mixture was diluted with 50 mL of ether and washed with two 20-mL portions of 1.0 N aq HCl solution and 20 mL of brine, dried over $MgSO_4$, filtered, and concentrated to give 0.938 g of colorless oil. Column chromatography on 20 g of silica gel (elution with 2% EtOAc-hexanes) provided 0.820 g (91%) of **47a** as a colorless oil: IR (film): 2974, 2874, 2121, 1730, 1482, 1463, 1399, 1366, 1285, 1230 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.16 (t, J = 6.3 Hz, 2 H), 2.30 (dt, J = 7.1, 2.6 Hz, 2 H), 1.97 (t, J = 2.6 Hz, 1 H), 1.87 (app quint, J = 6.7 Hz, 2 H), 1.20 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.4, 83.2, 69.1, 63.0, 39.0, 27.9, 27.4, 15.5; HRMS (m/z) $[M+Na]^+$ calcd for $C_{10}H_{16}O_2Na$, 191.1043; found, 191.1047.



47a



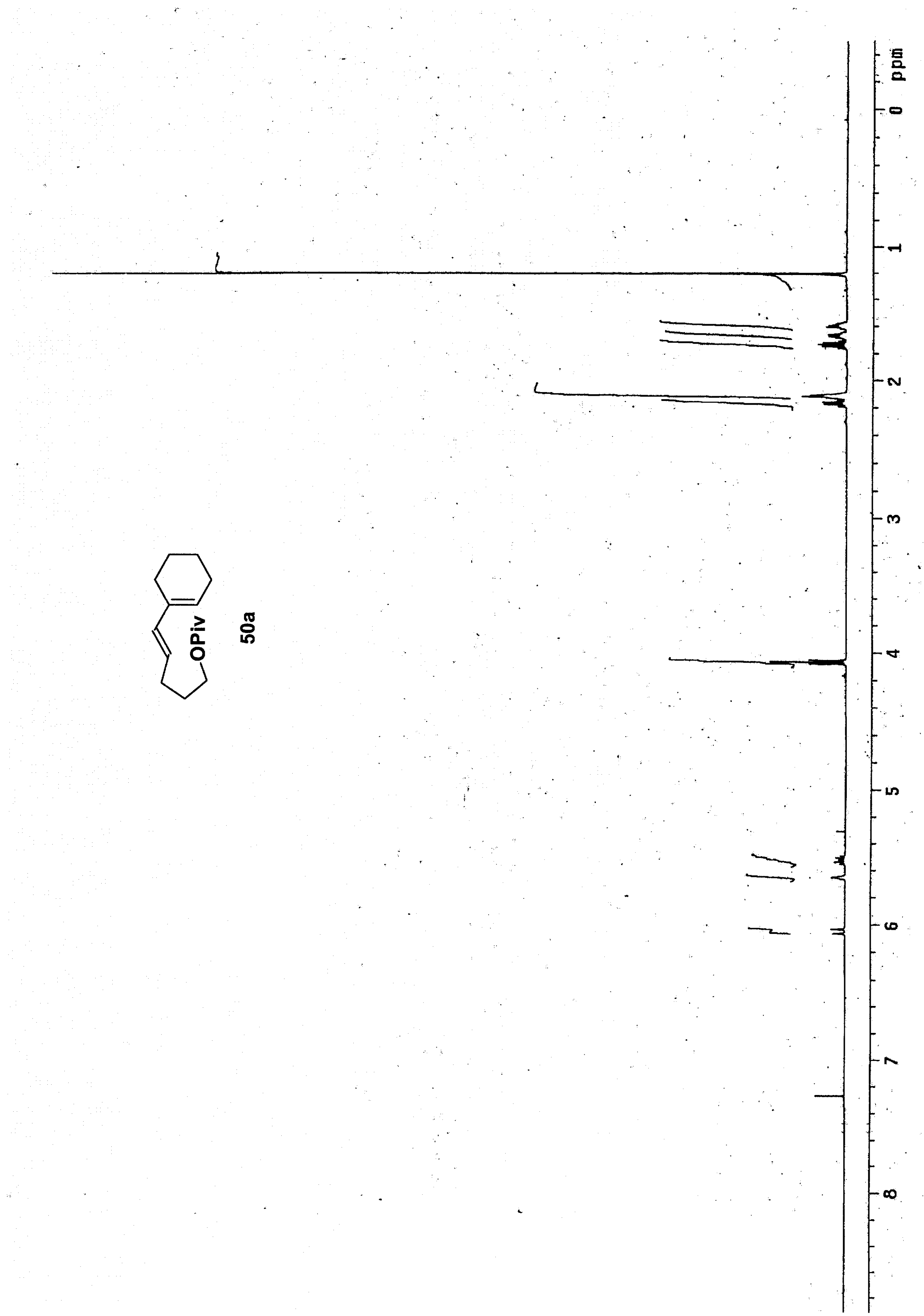
5-Trimethylacetoxy-(*E*)-1-pentenyl boronic acid (48a). A 25-mL, two-necked, pear-shaped flask equipped with a rubber septum and argon inlet adapter was charged with **47a** (0.334 g, 1.99 mmol) and 3 mL of CH_2Cl_2. Dibromoborane-dimethylsulfide solution (2.6 mL, 1.0 M in CH_2Cl_2, 2.6 mmol) was added dropwise via syringe over 3 min. The pale yellow solution was stirred at rt for 17 h, then cooled at 0 °C, and transferred via cannula to a 25-mL round-bottomed flask containing 6 mL of ether and 2 mL of water cooled at 0 °C. The resulting mixture was stirred at 0 °C for 10 min and was then diluted with 40 mL of ether. The organic layer was washed with two 25-mL portions of ice-cold water, and the combined aqueous layers were extracted with 20 ml of ether. The combined organic layers were washed with 25 mL of brine, dried over $MgSO_4$, filtered, and concentrated to give 0.420 g (99% crude yield) of **48a** as a pale yellow solid, which was used in the next step without further purification.



48a

50a

5-(1-Cyclohexenyl)-1-trimethylacetoxy-(*E*)-4-pentene (50a). A 100-mL, round-bottomed flask equipped with a rubber septum and argon inlet needle was charged with the crude boronic acid **48a** (1.863 g, 8.70 mmol), 40 mL of THF, 1-iodocyclohexene[37] (1.533 g, 7.37 mmol), and $PdCl_2dppf\bullet CH_2Cl_2$ (0.054 g, 0.07 mmol). Sodium hydroxide solution (3.0 M in water, 7.37 mL, 22.11 mmol) was then added, and the reaction mixture was stirred at rt for 1.5 h. The resulting orange solution was then diluted with 50 mL of water, and the aqueous layer was separated and extracted with three 40-mL portions of ether. The combined organic layers were washed with 50 mL of brine, dried over $MgSO_4$, filtered, and concentrated to give 2.011 g of an orange oil. Column chromatography on 20 g of silica gel (elution with 5% EtOAc-hexanes) provided 1.474 g (80%) of **50a** a colorless oil: IR (film): 3024, 2931, 2838, 1731, 1480, 1284 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.05 (d, J = 15.9 Hz, 1 H), 5.65 (br s, 1 H), 5.53 (dt, J = 15.6, 7.3 Hz, 1 H), 4.07 (t, J = 6.4 Hz, 2 H), 2.17 (q, J = 7.3 Hz, 2 H), 2.11 (m, 4 H), 1.73 (quint, J = 6.4 Hz, 2 H), 1.63-1.70 (m, 2 H), 1.56-1.62 (m, 2 H), 1.21 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.7, 135.6, 134.5, 127.9, 125.1, 64.1, 39.1, 30.0, 29.0, 27.6, 26.4, 25.0, 23.0, 22.9; HRMS (m/z) $[M+Na]^+$ calcd for $C_{16}H_{26}O_2Na$, 273.1825; found, 273.1816.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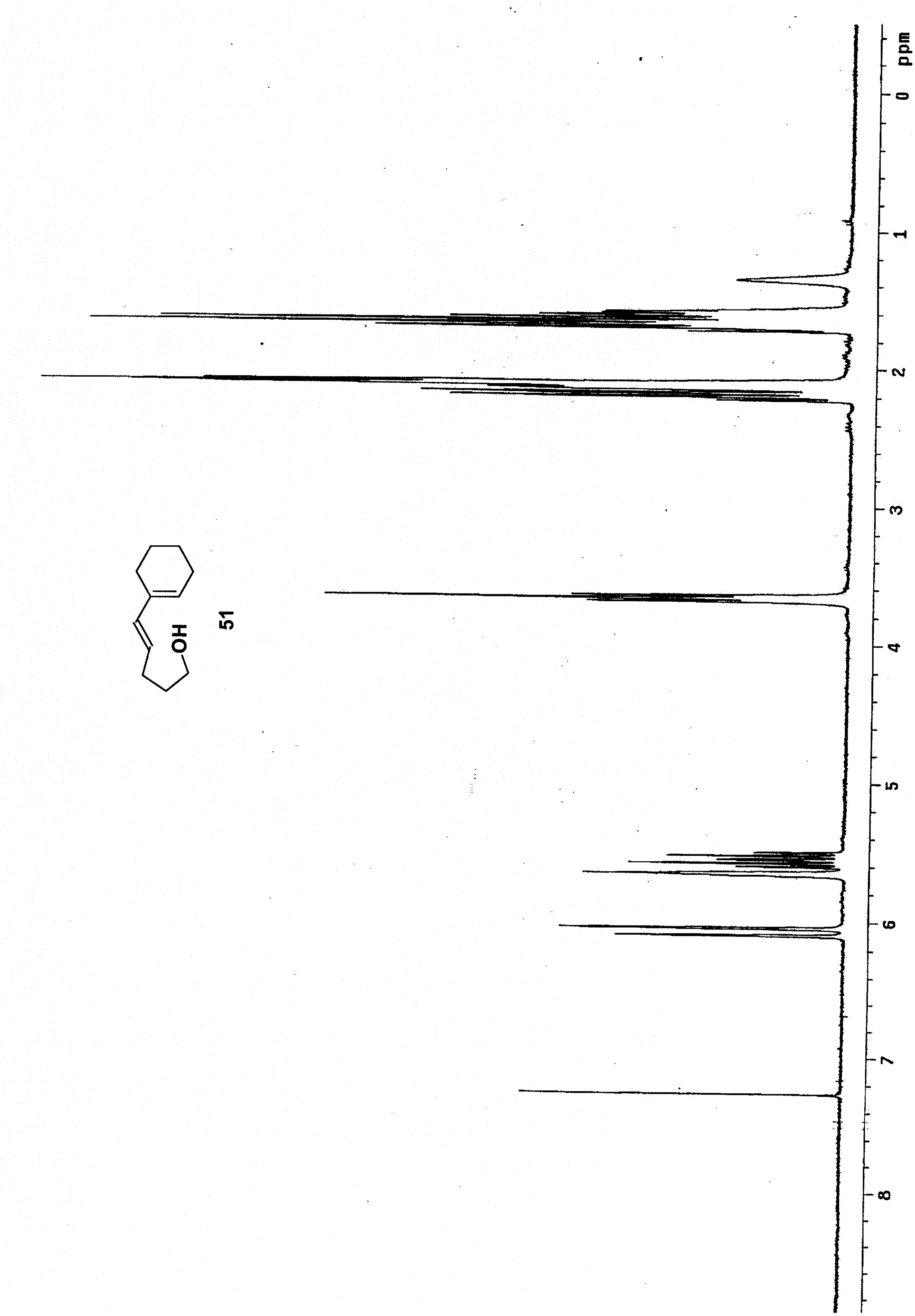
50a **51**

5-(1-Cyclohexenyl)-(*E*)-4-penten-1-ol (51). A 25-mL, two-necked, round-bottomed flask equipped with a rubber septum and argon inlet adapter was charged with pivalate ester **50a** (0.505 g, 1.91 mmol) and 5 mL of CH_2Cl_2. The flask was cooled at -78 °C while DIBAL solution (1.0 M in toluene, 2.4 mL, 2.42 mmol) was added dropwise over 3 min via syringe. The solution was stirred at -78 °C for 1 h and then diluted with 10 mL of 10% aq Rochelle salt solution. The cooling bath was removed, and the reaction mixture was stirred at rt for 2 h. The biphasic mixture was then diluted with 20 mL of water, the aqueous layer was separated and extracted with three 20-mL portions of CH_2Cl_2, and the combined organic layers were washed with 25 mL of brine, dried over $MgSO_4$, filtered, and concentrated to give 0.215 g of a colorless oil. Column chromatography on 10 g of silica gel (elution with 20% EtOAc-hexanes) afforded 0.142 g (85%) of **51** as a colorless oil: IR (film): 3328, 3022, 2985, 2928, 2858, 2836, 1651, 1625, 1447, 1436 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.07 (d, J = 15.6 Hz,1 H), 5.65 (br s, 1 H), 5.55 (dt, J = 15.6, 7.0 Hz, 1 H), 3.67 (t, J = 6.5 Hz, 1 H), 2.10-2.22 (m, 6 H), 1.56-1.73 (m, 6 H), 1.36 (br s, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.5, 134.1, 127.6, 125.7, 62.6, 32.8, 29.4, 26.0, 24.9, 22.9, 22.8; HRMS (m/*z*) $[M+Na]^+$ calcd for $C_{11}H_{18}ONa$, 189.1250; found, 189.1254.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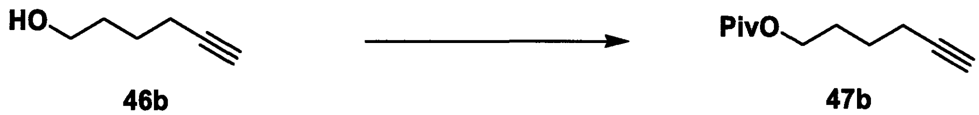
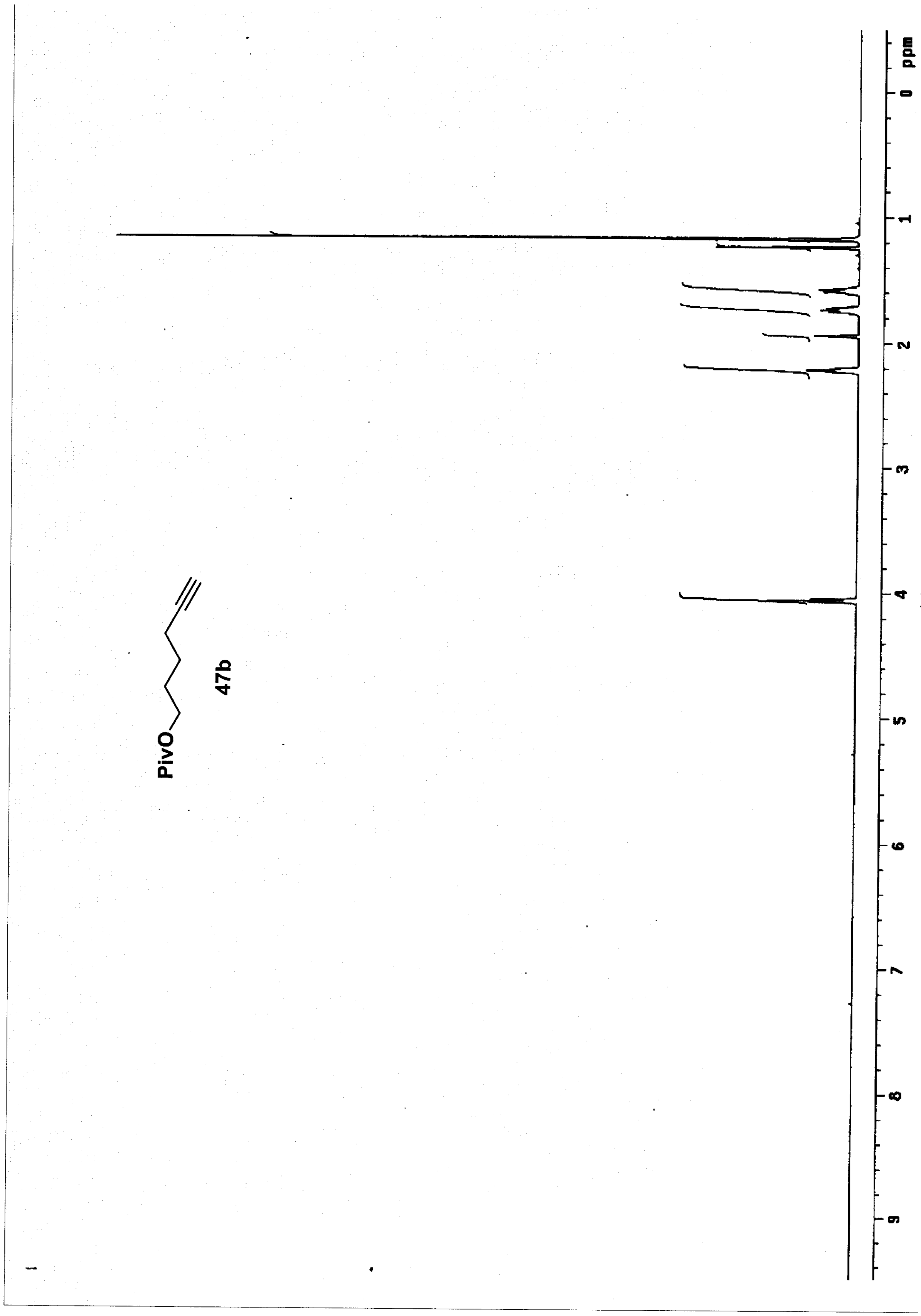


2,2-Dimethylpropionic acid 5-hexynyl ester (47b). A 250-mL, three-necked, round-bottomed flask equipped with a glass stopper, rubber septum, and argon inlet adapter was charged with DMAP (0.443 g, 3.63 mmol), 75 mL of CH_2Cl_2, 5-hexyn-1-ol (4.0 mL, 3.6 g, 36 mmol), and pyridine (8.8 mL, 8.6 g, 109 mmol). Pivaloyl chloride (5.4 mL, 5.3 g, 44 mmol) was then added dropwise over 5 min via syringe, and the resulting solution was stirred at rt for 2 h. The reaction mixture was diluted with 120 mL of ether and 60 mL of satd aq $NaHCO_3$ solution. The organic layer was separated and washed with two 50-mL portions of aq 1.0 M HCl solution, 60 mL of brine, dried over $MgSO_4$, filtered, and concentrated to give 6.62 g of colorless oil. Column chromatography on 80 g of silica gel (elution with 2% EtOAc-hexanes) provided 6.34 g (96%) of the **47b** as a colorless oil: IR (film): 2959, 2872, 2118, 1728, 1481, 1459, 1398, 1366, 1284 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.05 (t, J = 6.3 Hz, 2 H), 2.21 (dt, J = 7.0, 2.8 Hz, 2 H), 1.94 (t, J = 2.6 Hz, 1 H), 1.71-1.76 (m, 2 H), 1.54-1.61 (m, 2 H) 1.17 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.7, 84.0, 68.9, 63.9, 38.9, 27.8, 27.3, 25.1, 18.2; HRMS (m/z) $[M+Na]^+$ calcd for $C_{11}H_{18}O_2Na$, 205.1204; found, 205.1209.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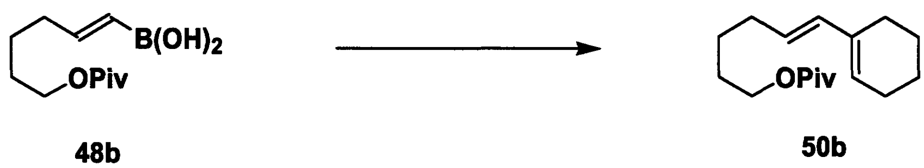
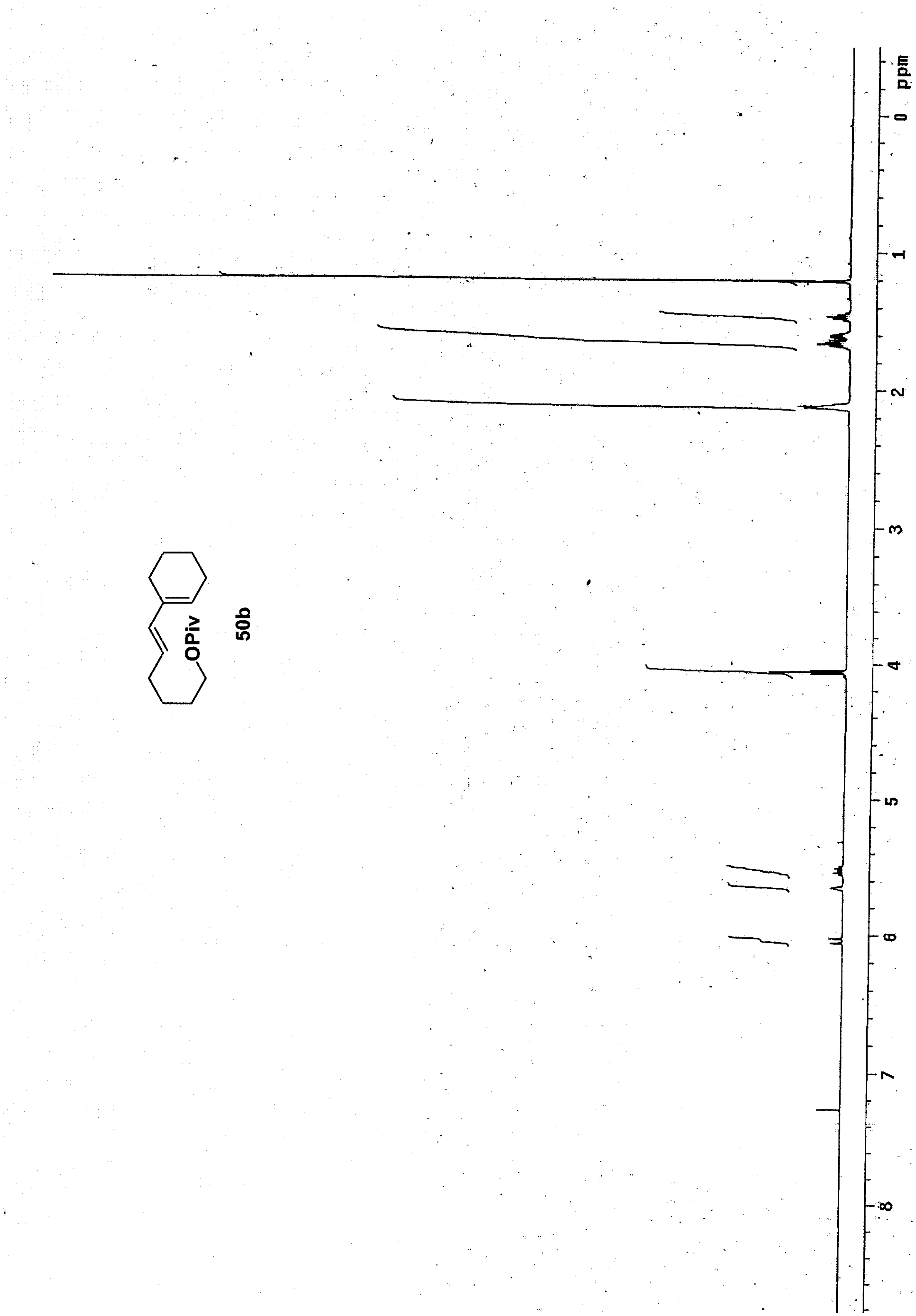
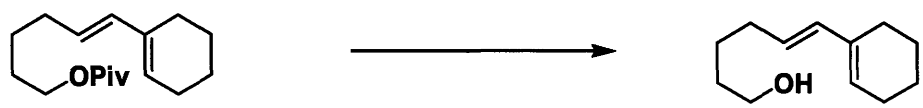
6-Trimethylacetoxy-(*E*)-1-hexenylboronic acid (48b). A 100-mL, two-necked, pear-shaped flask equipped with a rubber septum and a 60-mL pressure-equalizing addition funnel with a claisen head fitted with a rubber septum and argon inlet adapter was charged with **47b** (6.34 g, 34.8 mmol) and 18 mL of CH_2Cl_2. The addition funnel was charged with dibromoborane-dimethylsulfide solution (1.0 M in CH_2Cl_2, 45.2 mL, 45.2 mmol), which was added dropwise over 20 min. The pale yellow solution was stirred at rt for 8 h, was then cooled to 0 °C and transferred via cannula to a 250-mL round-bottomed flask containing 60 mL of ether and 20 mL of water cooled to 0 °C under argon. The biphasic mixture was stirred at 0 °C for 10 min and was then diluted with 120 mL of ether, and the organic layer was washed with two 50-mL portions of cold water. The combined aqueous layers were extracted with 30 mL of ether, and the combined organic layers were washed with 80 mL of brine, dried over $MgSO_4$, filtered, and concentrated to give 7.96 g (100 % crude yield) of **48b** as a tan solid, which was used in the next step without further purification.



6-(1-Cyclohexenyl)-1-trimethylacetoxy-(*E*)-5-hexene (50b). A 100-mL, round-bottomed flask equipped with a rubber septum and argon inlet needle was charged with crude boronic acid **48b** (0.843 g, 3.69 mmol), 25 mL of THF, 1-iodocyclohexene[37] (0.500 g, 2.40 mmol), and $PdCl_2dppf{\bullet}CH_2Cl_2$ (0.020 g, 0.02 mmol). Sodium hydroxide solution (3.0 M in water, 2.6 mL, 7.20 mmol) was then added in one portion, and the reaction mixture was stirred at rt for 1 h. The resulting orange solution was then diluted with 50 mL of water, and the aqueous layer was separated and extracted with three 40-mL portions of ether. The combined organic layers were washed with 50 mL of brine, dried over $MgSO_4$, filtered, and concentrated to give 1.017 g of an orange oil. Column chromatography on 25 g of silica gel (elution with 3% EtOAc-hexanes) provided 0.558 g (88%) of **50b** a colorless oil: IR (film): 3023, 2932, 2838, 1730, 1480, 1459, 1285, 1157 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.04 (d, J = 15.6 Hz, 1 H), 5.65 (br s, 1 H), 5.53 (dt, J = 15.6, 6.7 Hz, 1 H), 4.06 (t, J = 6.7 Hz, 2 H), 2.12 (m, 6 H), 1.58–1.69 (m, 6 H), 1.46 (q, J = 7.9 Hz, 2 H), 1.20 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.9, 135.8, 134.1, 127.7, 126.2, 64.5, 39.0, 32.6, 28.4, 27.5, 26.2, 26.0, 24.9, 22.9, 22.8; HRMS (m/*z*) $[M+Na]^+$ calcd for $C_{17}H_{28}O_2$, 287.1982; found, 287.1977.

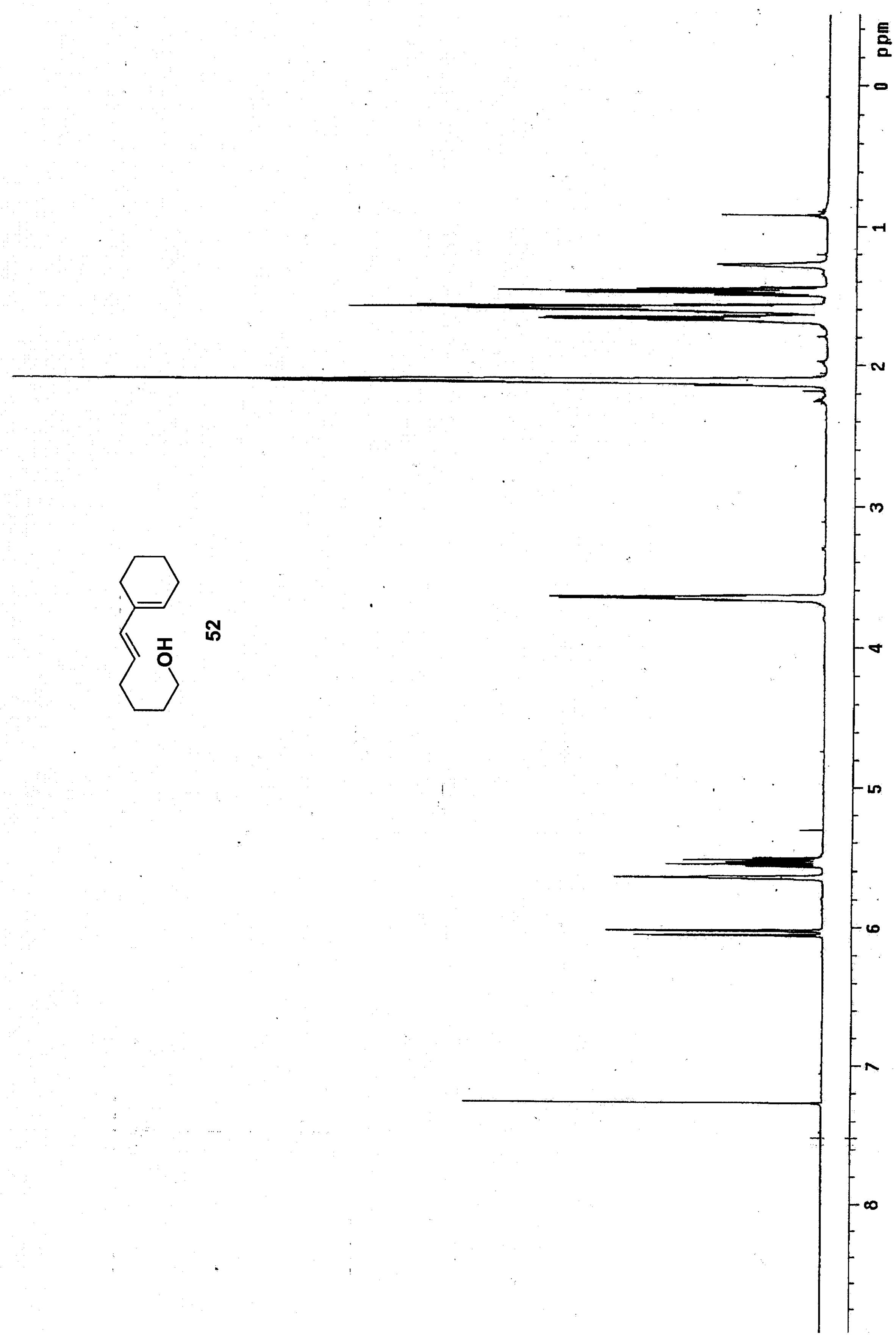


50b



50b **52**

6-(1-Cyclohexenyl)-(*E*)-5-hexen-1-ol (52). A 50-mL, two-necked, round-bottomed flask equipped with a rubber septum and argon inlet adapter was charged with pivalate ester **50b** (0.505 g, 1.91 mmol) and 10 mL of CH_2Cl_2. The flask was cooled at -78 °C while DIBAL solution (1.0 M in toluene, 4.2 mL, 4.20 mmol) was added dropwise over 6 min via syringe. The solution was stirred at -78 °C for 1 h and then diluted with 20 mL of 10% aq Rochelle salt solution. The cooling bath was removed, and the reaction mixture was stirred at rt for 2 h. The biphasic mixture was then diluted with 35 mL of water, the aqueous layer was separated and extracted with three 20-mL portions of CH_2Cl_2, and the combined organic layers were washed with 35 mL of brine, dried over $MgSO_4$, filtered, and concentrated to give 0.463 g of a colorless oil. Column chromatography on 20 g of silica gel (elution with 20% EtOAc-hexanes) afforded 0.303 g (88%) of **52** as a colorless oil: IR (film): 3335, 3022, 2927, 2858, 2837, 1650, 1625, 1448, 1436 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.04 (d, J = 15.6 Hz, 1 H), 5.64 (br s, 1 H), 5.54 (dt, J = 15.6, 6.7 z, 1 H), 3.66 (q, J = 6.4 Hz, 2 H), 2.13 (m, 6 H), 1.57-1.69 (m, 6 H), 1.47 (m, 2 H), 1.28 (s, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.8, 134.1, 127.6, 126.4, 63.2, 32.8, 32.5, 26.0, 25.9, 24.8, 22.9, 22.8; HRMS (m/z) $[M+Na]^+$ calcd for $C_{12}H_{20}ONa$, 203.1412; found, 203.1403.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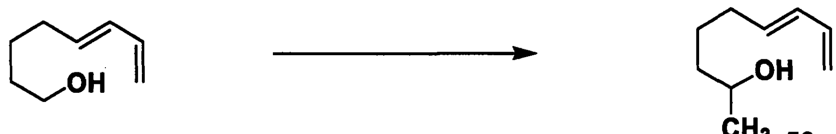
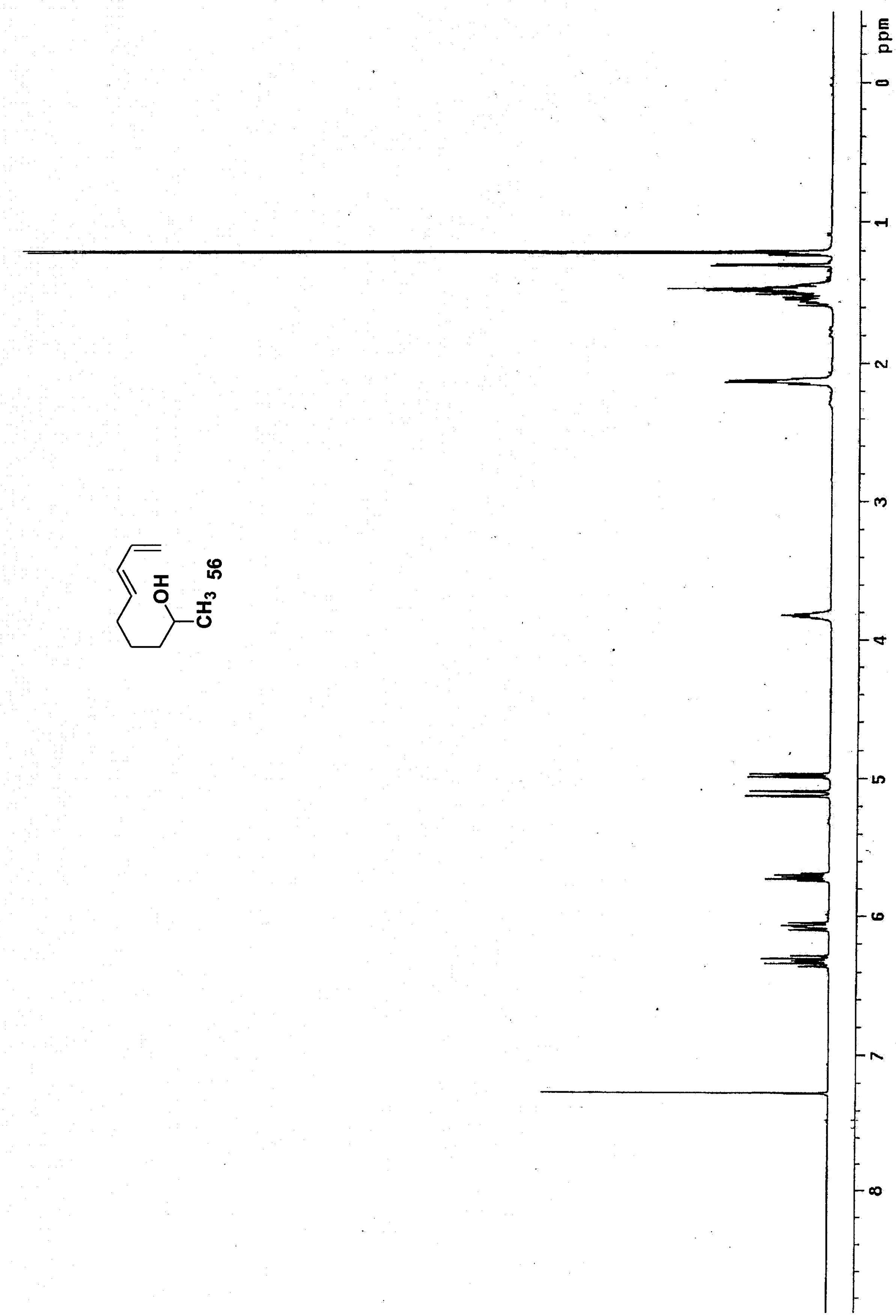


44 → 56

1-Methyl-(*E*)-5,7-octadien-1-ol (56). A 100-mL, three-necked, round-bottomed flask equipped with a rubber septum, glass stopper, and argon inlet adapter was charged with 8 mL of CH_2Cl_2 and oxayl chloride (0.138 mL, 0.205 g, 1.61 mmol). The solution was cooled at -78 °C while DMSO (0.249 mL, 0.252 g, 3.22 mmol) was added dropwise via syringe over 1 min. The solution was stirred at -78 °C for 10 min and then a solution of alcohol **44** (0.156 g, 1.24 mmol) in 4 mL of CH_2Cl_2 was added dropwise over 2 min. After the reaction mixture was stirred at -78 °C for 20 min, Et_3N (0.691 mL, 0.502 g, 4.96 mmol) was added over 2 min, and the solution was stirred at -78 °C for 10 min and rt for 45 min. The cloudy, yellow solution was diluted with 10 mL of CH_2Cl_2 and 10 mL of satd aq $NaHCO_3$ solution, and the aqueous layer was separated and extracted with three 15-mL of CH_2Cl_2. The combined organic layers were washed with 10 mL of brine, dried over $MgSO_4$, filtered, and concentrated to give 0.154 g of a yellow oil, which was used in the next step without further purification.

A 25-mL, two-necked, round-bottomed flask equipped with a septum and argon inlet adapter was charged with the crude aldehyde from the previous step (0.154 g, 1.24 mmol) and 8 mL of Et_2O. The reaction mixture was cooled at 0 °C while methylmagnesium bromide solution (3.0 M in ether, 0.496 mL, 1.49 mmol) was added via syringe over 1 min, and the reaction mixture was stirred at 0 °C for 2 h, and then diluted with 10 mL of satd aq NH_4Cl solution and 15 mL of Et_2O. The aqueous layer was separated and extracted with three 12-mL portions of ether, and the combined organic layers were washed with 10 mL of brine, dried over $MgSO_4$, filtered, and concentrated to give 0.235 g of a yellow oil. Purification by column chromatography on 20 g of silica gel (gradient elution with 20-35% EtOAc-hexanes) afforded

0.139 g (80%) of **56** as a colorless oil: IR (film): 3353, 3086, 298, 2932, 2860, 1652, 1603, 1458, 1415, 1374 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.33 (ddd, J = 17.0, 10.3, 10.3 Hz, 1H), 6.07 (dd, J = 15.2, 10.3 Hz, 1 H), 5.71 (dt, J = 15.2, 6.9 Hz, 1 H), 5.11 (d, J = 17.0 Hz, 1 H), 4.98 (d, J = 10.3 Hz, 1 H), 3.82 (m, 1 H), 2.13 (app q, J = 7.1 Hz, 2 H), 1.43-1.59 (m, 4 H), 1.30 (d, J = 4.8 Hz, 1 H), 1.21 (d, J = 6.3 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.4, 135.2, 131.5, 115.2, 68.2, 39.0, 32.7, 25.5, 23.8; HRMS (m/z) [M+H]$^{+}$ calcd for $C_9H_{17}O$, 141.1280; found, 141.1279.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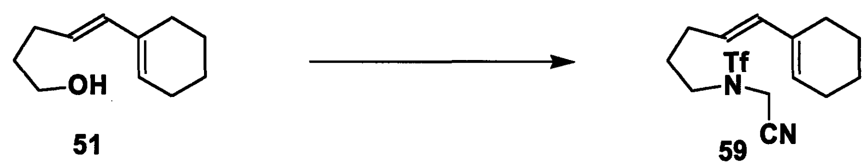
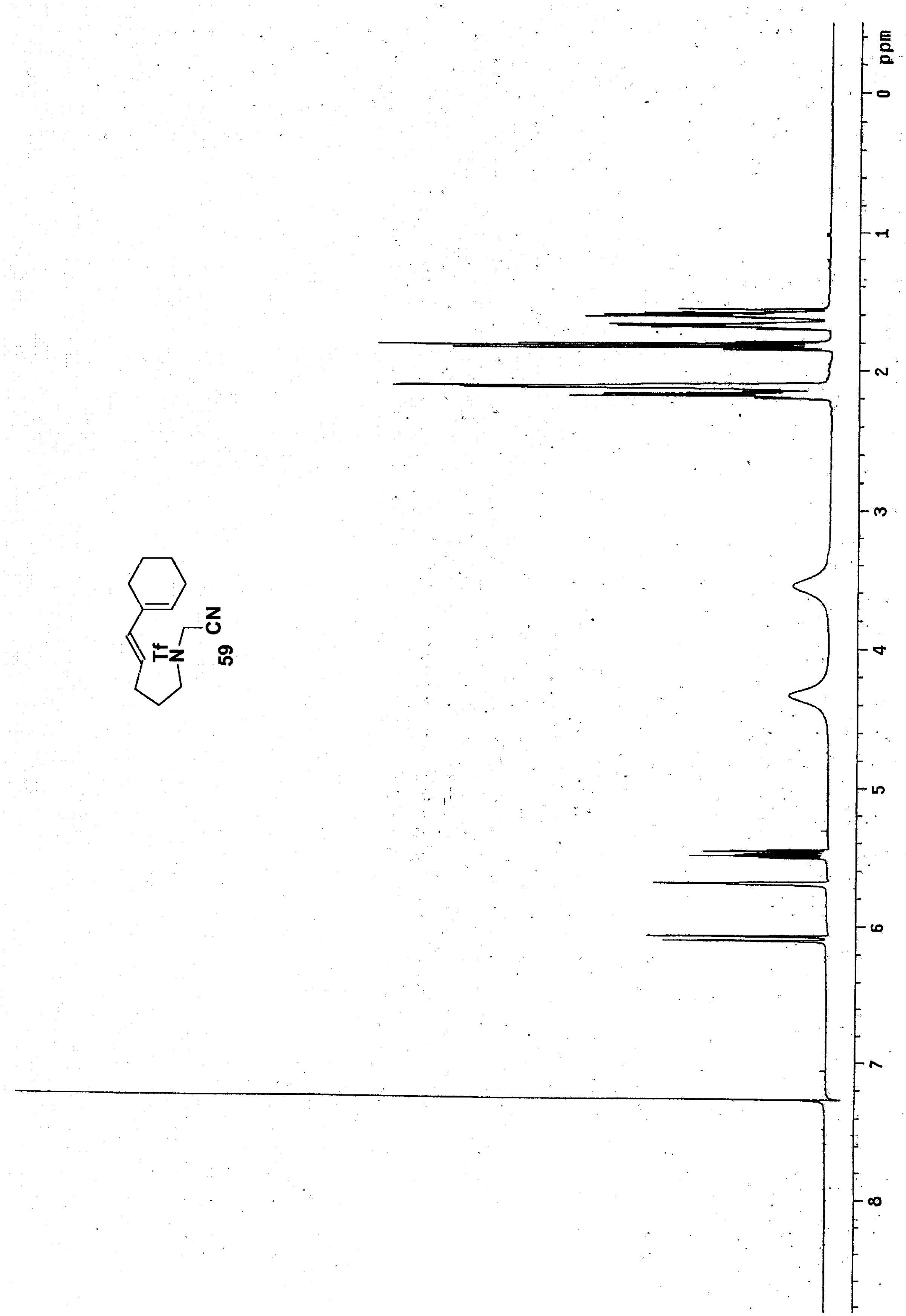
Experimental Procedures for Synthesis of Triflamides



N-(Cyanomethyl)-N-(5-(1-cyclohexenyl)-(E)-4-pentenyl)trifluoromethanesulfonamide (59). A 50-mL, two-necked, round-bottomed flask equipped with a rubber septum and argon inlet adapter was charged with triphenylphosphine (0.519 g, 1.98 mmol), a solution of HN(Tf)CH_2CN (0.341 g, 1.82 mmol) in 10 mL of THF, and a solution of alcohol **51** (0.275 g, 1.65 mmol) in 10 mL of toluene. DEAD (0.31 mL, 0.345 g, 1.98 mmol) was added dropwise via syringe over 2 min, and the resulting reaction mixture was stirred at rt for 2 h and then concentrated to give 1.243 g of a yellow semi-solid. A solution of this material in CH_2Cl_2 was concentrated onto 2.5 g of silica gel and transferred to the top of a column of 40 g of silica gel. Elution with 10% EtOAc-hexanes provided 0.498 g (90%) of **59** as a colorless oil: IR (film): 3025, 2989, 2932, 2860, 2839, 1651, 1625, 1398, 1230 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.09 (d, J = 15.6 Hz, 1 H), 5.69 (br s, 1 H), 5.48 (dt, J = 15.6, 6.7 Hz, 1 H), 4.33 (br s, 2 H), 3.55 (br s, 2 H), 2.18 (q, J = 6.7 Hz, 2 H), 2.10-2.12 (m, 4 H), 1.82 (quint, J = 7.3 Hz, 2 H), 1.58-1.70 (m, 4 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.7, 128.9, 128.6, 123.3, 119.0 (q, J = 322 Hz), 113.3, 49.2, 36.0, 29.5, 27.6, 26.0, 24.8, 22.8, 22.7; HRMS (m/z) $[M+Na]^+$ calcd for $C_{14}H_{19}F_3N_3O_3SNa$, 359.1012; found, 359.1017.



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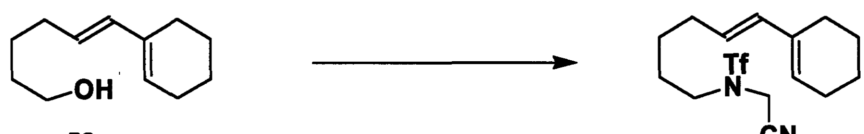
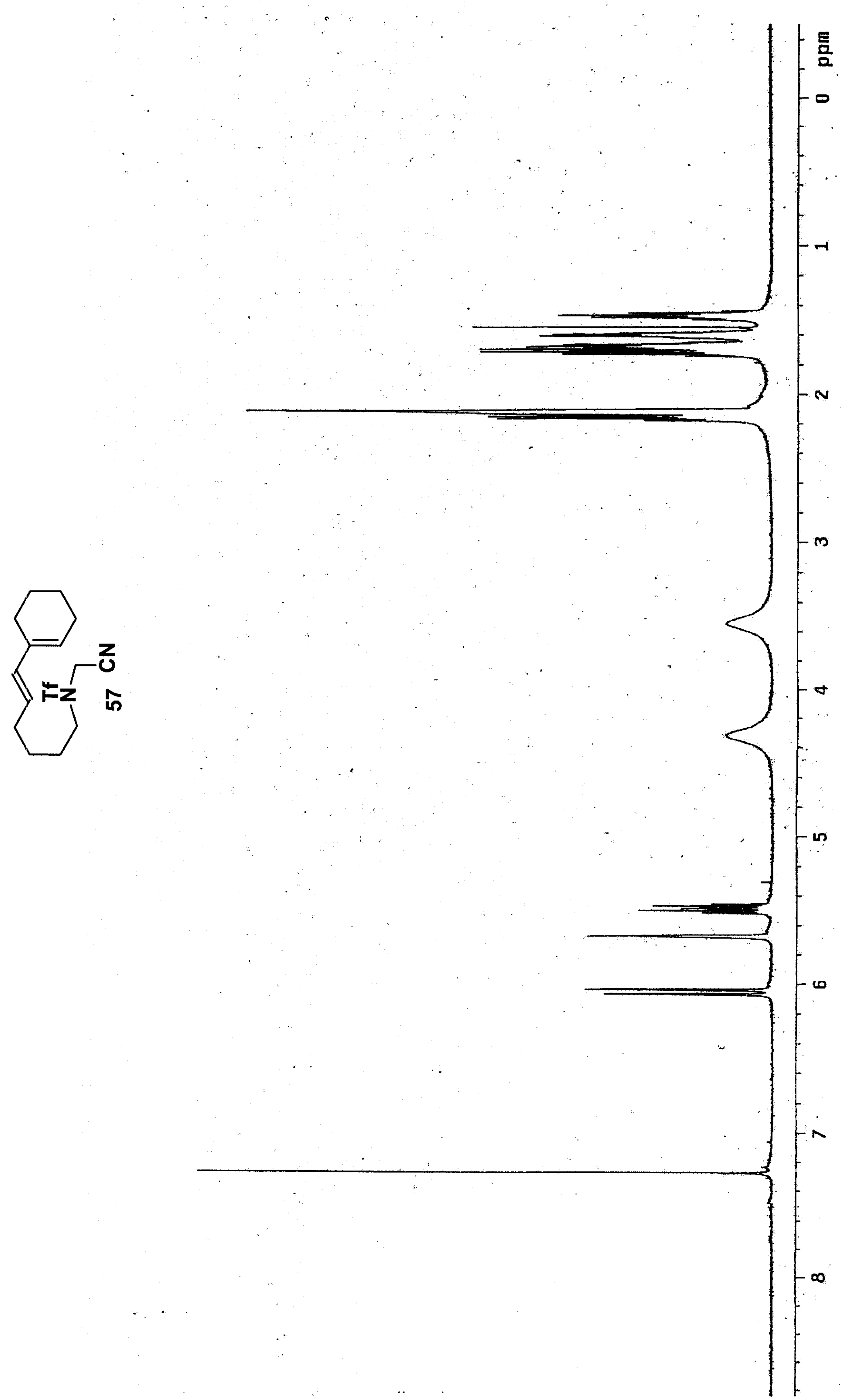


52 → 57

***N*-(Cyanomethyl)-*N*-(6-(1-cyclohexenyl)-(*E*)-5-hexenyl)trifluoromethanesulfonamide (57).** A 50-mL, two-necked, round-bottomed flask equipped with a rubber septum and argon inlet adapter was charged with triphenylphosphine (0.312 g, 1.19 mmol), a solution of HN(Tf)CH_2CN (0.224 g, 1.19 mmol) in 8 mL of THF, and a solution of alcohol **52** (0.178 g, 0.99 mmol) in 8 mL of toluene. DEAD (0.19 mL, 0.207 g, 1.19 mmol) was added dropwise via syringe over 2 min, and the resulting reaction mixture was stirred at rt for 2 h and then concentrated to give 1.213 g of a yellow semi-solid. A solution of this material in CH_2Cl_2 was concentrated onto 2.5 g of silica gel and transferred to the top of a column of 30 g of silica gel. Elution with 10% EtOAc-hexanes provided 0.293 g (85%) of **57** as a colorless oil: IR (film): 3024, 2988, 2932, 2860, 2838, 1651, 1625, 1398 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.06 (d, J = 15.7 Hz, 1 H), 5.67 (br s, 1 H), 5.49 (dt, J = 15.6, 6.9 Hz, 1 H), 4.32 (br s, 2 H), 3.55 (br s, 2 H), 2.12-2.18 (m, 6 H), 1.58-1.75 (m, 6 H), 1.47 (quint, J = 7.5 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.6, 134.9, 128.3, 125.0, 119.9 (q, J = 322 Hz), 113.3, 49.3, 35.8, 32.2, 26.9, 26.1, 26.0, 24.8, 22.8, 22.7; HRMS (m/z) $[M+H]^+$ calcd for $C_{15}H_{22}F_3N_2O_2S$, 351.1349; found, 351.1340.


Tf
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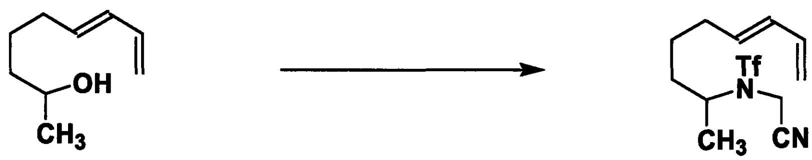
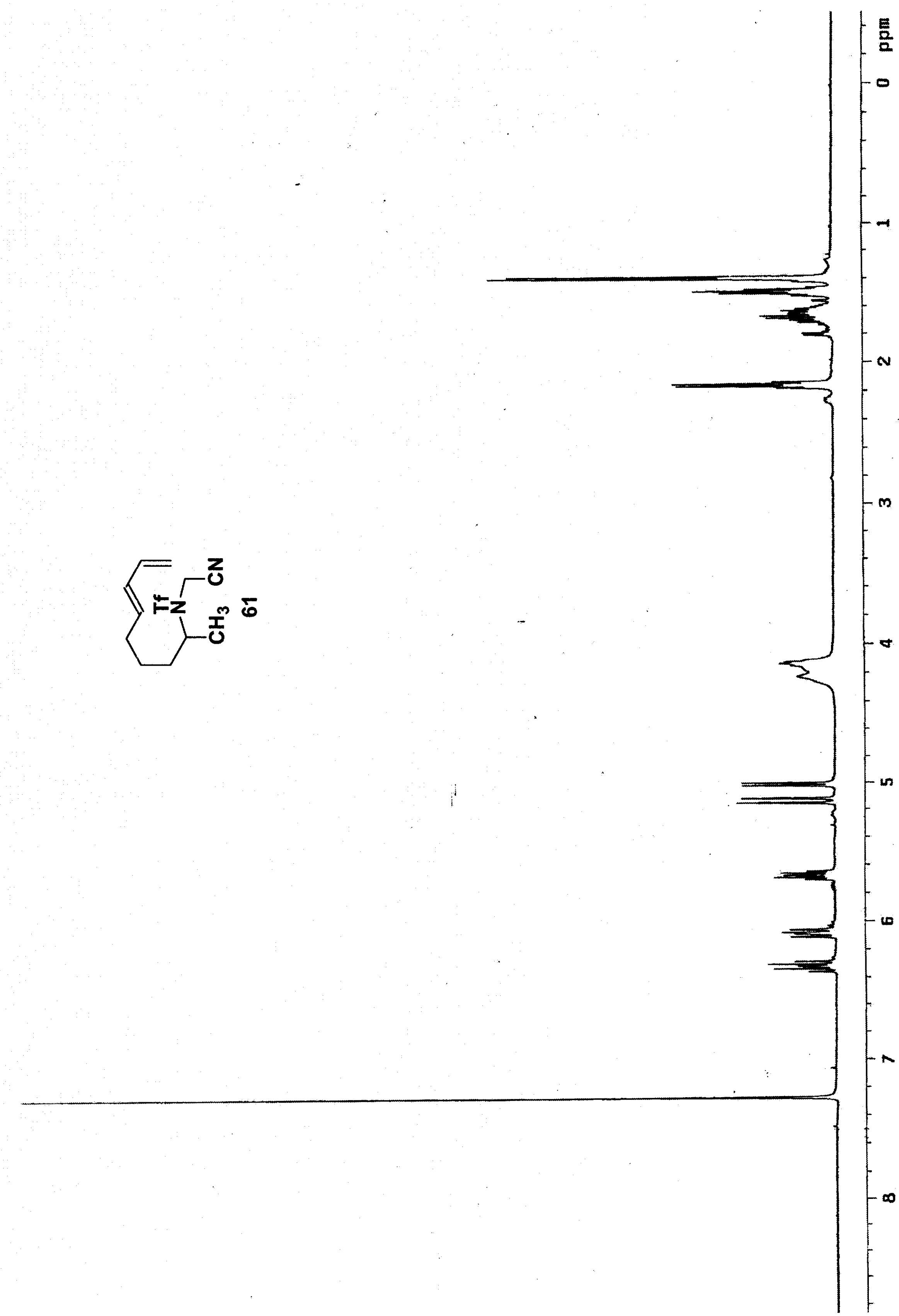


56 → **61**

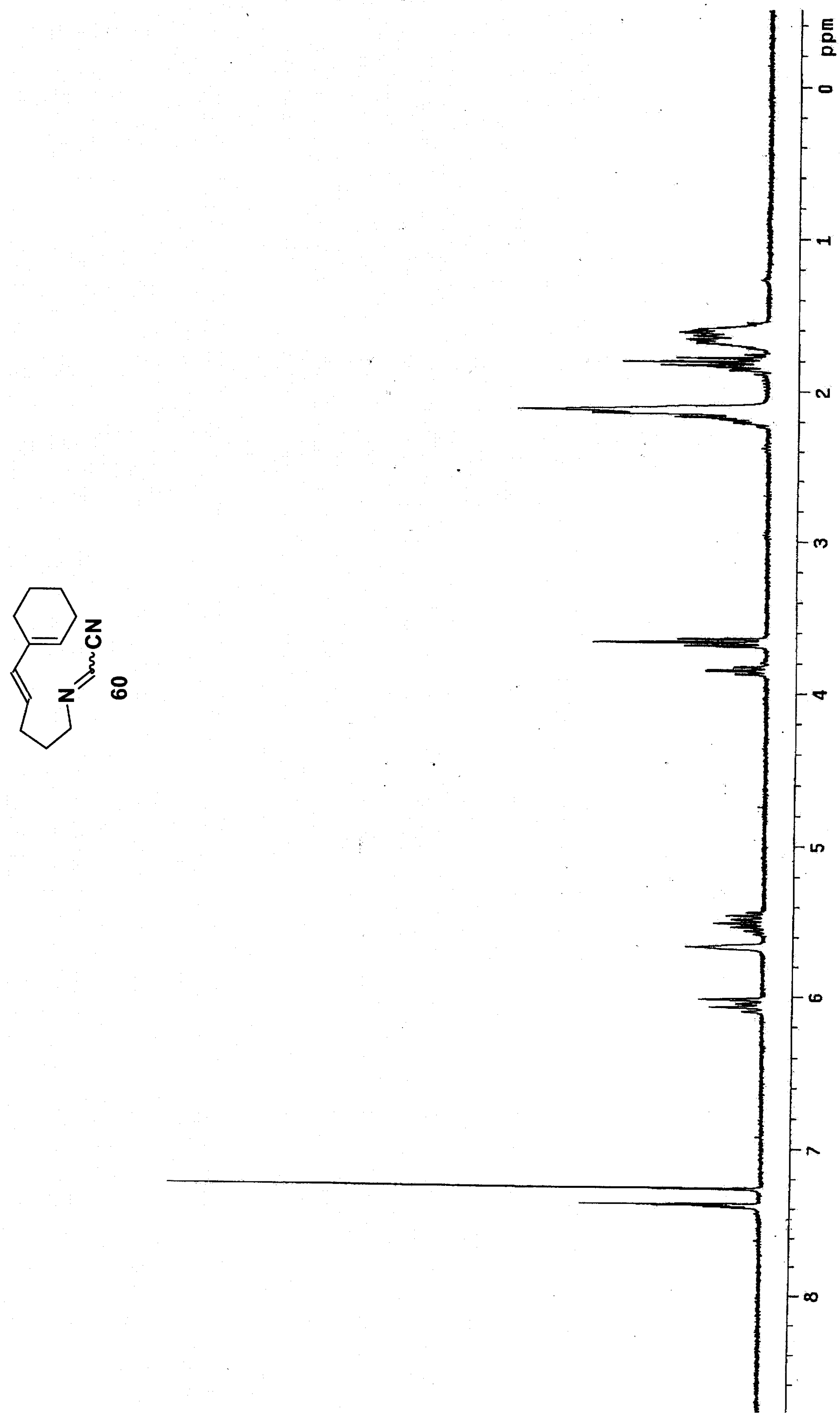
***N*-(Cyanomethyl)-*N*-(1-Methyl-(*E*)-5,7-octadienyl)trifluoromethanesulfonamide**

(61). A 50-mL, two-necked, round-bottomed flask equipped with a rubber septum and argon inlet adapter was charged with triphenylphosphine (1.18 g, 4.49 mmol), a solution of $HN(Tf)CH_2CN$ (0.774 g, 4.11 mmol) in 8 mL of benzene, and a solution of alcohol **56** (0.525 g, 3.74 mmol) in 7 mL of benzene. DIAD (0.868 mL, 0.908 g, 4.49 mmol) was added dropwise via syringe over 2 min, and the resulting mixture was stirred at rt for 12 h and then at 60 °C for 4 h. The reaction mixture was allowed to cool to rt and then concentrated to give 3.91 g of a red solid. This material was concentrated onto 8 g of silica gel and added to a column of 100 g of silica gel. Gradient elution with 10-35% EtOAc-hexanes provided 0.912 g (78%) of **61** as a colorless oil: IR (film): 3089, 3056, 2989, 2939, 2864, 1653, 1603, 1462, 1422, 1396, 1303, 1266 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.32 (ddd, J = 17.0, 10.4, 10.3 Hz, 1H), 6.08 (dd, J = 15.2, 10.6 Hz, 1 H), 5.67 (dt, J = 15.1, 7.1 Hz, 1 H), 5.14 (d, J = 17.1 Hz, 1 H), 5.01 (d, J = 10.3 Hz, 1 H), 4.12-4.23 (m, 3 H), 2.16 (app q, J = 7.1 Hz, 2 H), 1.62-1.72 (m, 2 H), 1.50 (app quint, J = 7.5 Hz, 2 H), 1.40 (d, J = 6.9 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.1, 133.8, 132.2, 117.6 (q, J = 322 Hz), 115.8, 115.0, 57.5, 34.1, 32.1, 30.8, 26.0, 24.6; HRMS $[M+H]^+$ Calcd. for $C_{12}H_{18}F_3N_2O_2S$: 311.1036. Found: 311.1046.

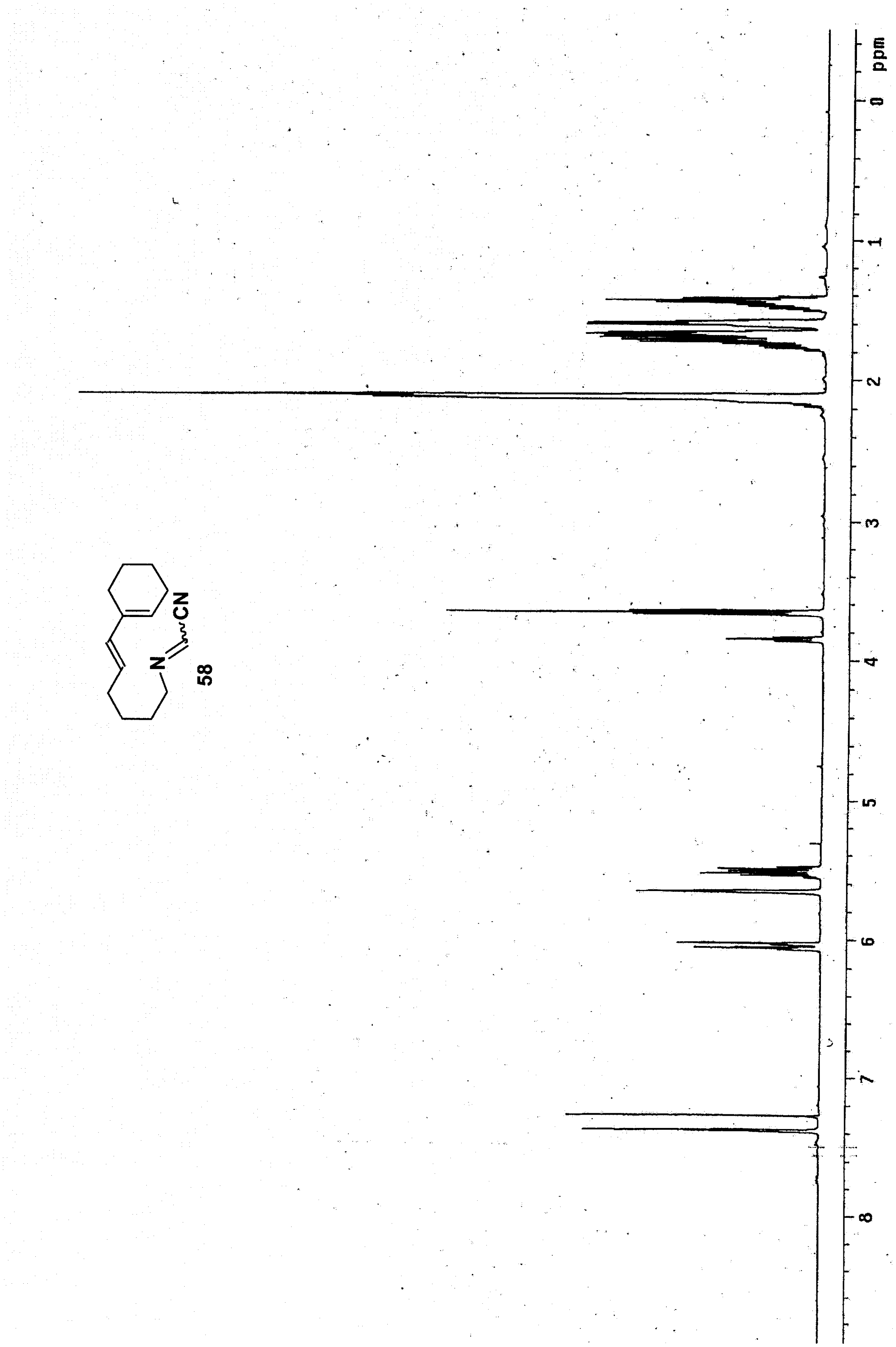

Tf
N
CN
CH3
61
ppm
0 1 2 3 4 5 6 7 8

Experimental Procedures for Synthesis of Iminoacetonitriles

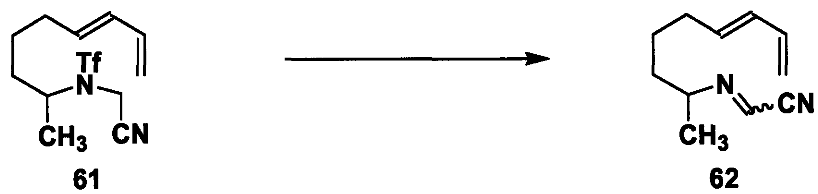
5-(1-Cyclohexenyl)-(*E*)-4-pentenyliminoacetonitrile (60). A 25-mL, one-necked, round-bottomed flask equipped with a reflux condenser fitted with an argon inlet adapter was charged with Cs_2CO_3 (2.131 g, 6.54 mmol) and 4 mL of THF. A solution of triflamide **59** (0.550 g, 1.64 mmol) in 6 mL of THF was added, and the reaction mixture was heated at 55 °C for 2.5 h. The resulting mixture was allowed to cool to rt and then diluted with 20 mL of ether and 40 mL of water. The aqueous layer was separated and extracted with two 25-mL portions of ether, and the combined organic layers were washed with 40 mL of brine, dried over $MgSO_4$, filtered, and concentrated to give 0.371 g of a yellow oil. Column chromatography on 15 g of Et_3N-deactivated silica gel (elution with 10% EtOAc-hexanes containing 1% Et_3N) provided 0.245 g (74%) of **60** (80:20 mixture of *E* and *Z* imine isomers by ^1H NMR analysis) as a pale yellow oil: IR (film): 2928, 2858, 1624, 1436, 1349 cm^{-1}; For *E* isomer: ^1H NMR (500 MHz, $CDCl_3$) δ 7.38 (app td, $J = 1.5, 0.3$ Hz, 1 H), 6.04 (d, $J = 15.7$ Hz, 1 H), 5.67 (s, 1 H), 5.44-5.58 (m, 1 H), 3.66 (td, $J = 6.8, 1.4$ Hz, 2 H), 2.12-2.21 (m, 6 H), 1.80-1.86 (m, 2 H), 1.58-1.78 (m, 4 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.1, 135.6, 135.0, 128.3, 124.7, 114.7, 62.6, 30.3, 29.8, 26.0, 24.8, 22.8, 22.7: For *Z* isomer: ^1H NMR (500 MHz, $CDCl_3$) δ 7.39 (t, $J = 2.3$ Hz, 1 H), 6.07 (d, $J = 15.5$ Hz, 1 H), 5.67 (s, 1 H), 5.44-5.58 (m, 1 H), 3.85 (td, $J = 6.8, 2.3$ Hz, 2 H), 2.12-2.21 (m, 6 H), 1.80-1.86 (m, 2 H), 1.58-1.78 (m, 4 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.7, 134.9, 131.6, 128.2, 124.8, 114.7, 59.4, 30.5, 30.1, 26.0, 24.8, 22.8, 22.7.


N
CN
60
ppm
0
1
2
3
4
5
6
7
8

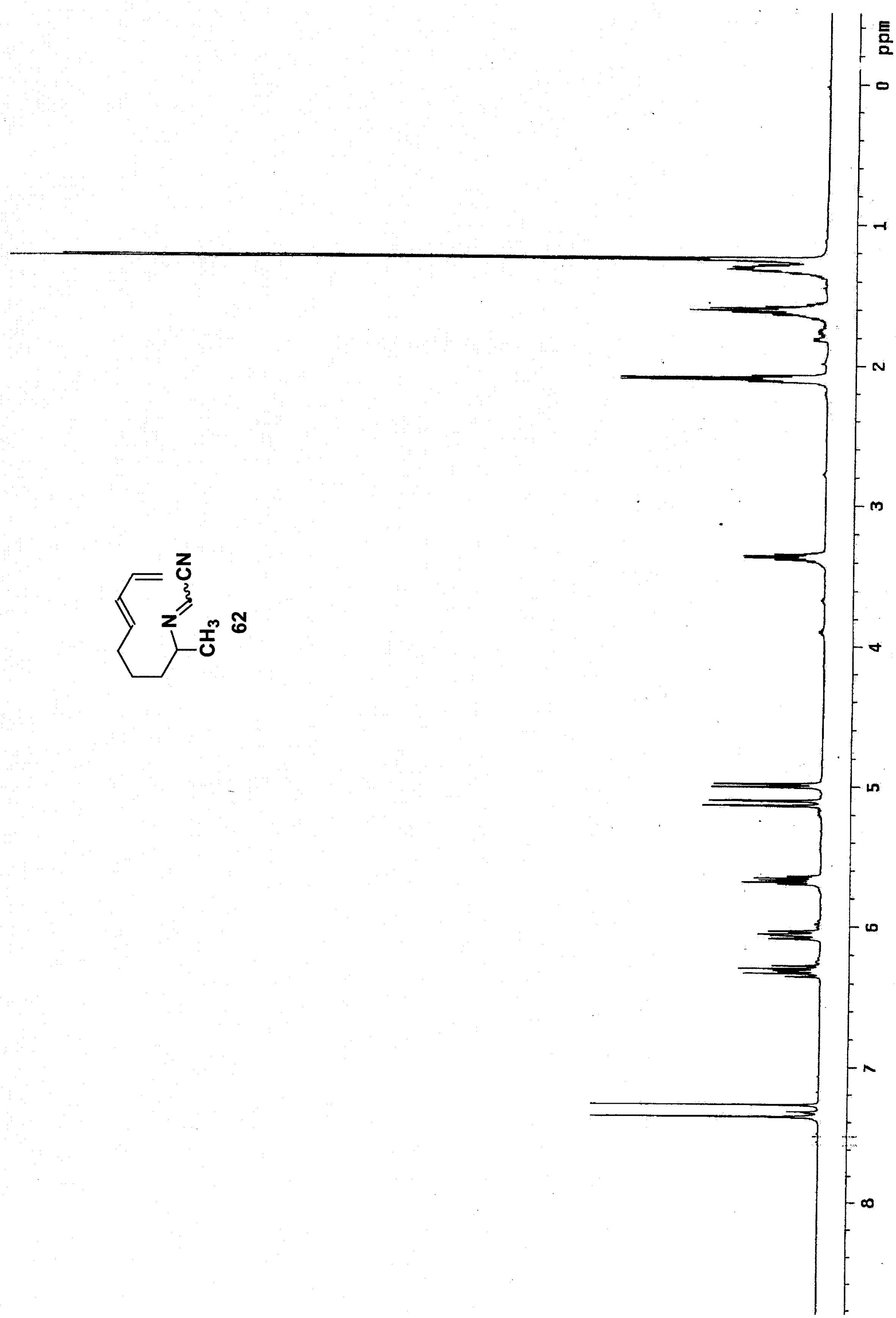
6-(1-Cyclohexenyl)-(*E*)-5-hexenyliminoacetonitrile (58). A 25-mL, one-necked, round-bottomed flask equipped with a reflux condenser fitted with an argon inlet adapter was charged with Cs_2CO_3 (1.490 g, 4.57 mmol) and 5 mL of THF. A solution of triflamide **57** (0.380 g, 1.08 mmol) in 3 mL of THF was added in one portion, and the reaction mixture was heated at 55 °C for 2.5 h. The resulting mixture was allowed to cool to rt and then diluted with 20 mL of ether and 20 mL of water. The aqueous layer was separated and extracted with two 20-mL portions of ether, and the combined organic layers were washed with 40 mL of brine, dried over $MgSO_4$, filtered, and concentrated to give 0.244 g of a yellow oil. Column chromatography on 20 g of Et_3N-deactivated silica gel (elution with 10% EtOAc-hexanes containing 1% Et_3N) provided 0.174 g (74%) of **58** (77:23 mixture of *E* and *Z* imine isomers by ^{1}H NMR analysis) as a pale yellow oil: IR (film): 3022, 2928, 2857, 2837, 1623, 1448, 1436, 1349, 1334, 1268 cm^{-1}; For *E* isomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 (m, 1 H), 6.04 (dt, J = 15.6, 5.8 Hz, 1 H), 5.66 (br s, 1 H), 5.51 (dt, J = 15.6, 7.0 Hz, 1 H), 3.66 (t, J = 7.0 Hz, 1 H), 2.11-2.19 (m, 6 H), 1.57-1.77 (m, 6 H), 1.40-1.52 (m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.9, 134.5, 128.0, 126.0, 114.9, 63.4, 32.7, 29.7, 27.4, 26.2, 25.0, 23.0, 22.9: For *Z* isomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 (m, 1 H), 6.05 (dt, J = 15.6, 5.8 Hz, 1 H), 5.66 (br s, 1 H), 5.51 (dt, J = 15.6, 7.0 Hz, 1 H), 3.84 (td, J = 6.7, 2.1 Hz, 1 H), 2.11-2.19 (m, 6 H), 1.57-1.77 (m, 6 H), 1.40-1.52 (m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.9, 134.5, 131.7, 128.0, 110.0, 60.1, 32.8, 29.8, 27.5, 26.2, 25.0, 23.0, 22.9.



N
CN
58
ppm
0
1
2
3
4
5
6
7
8



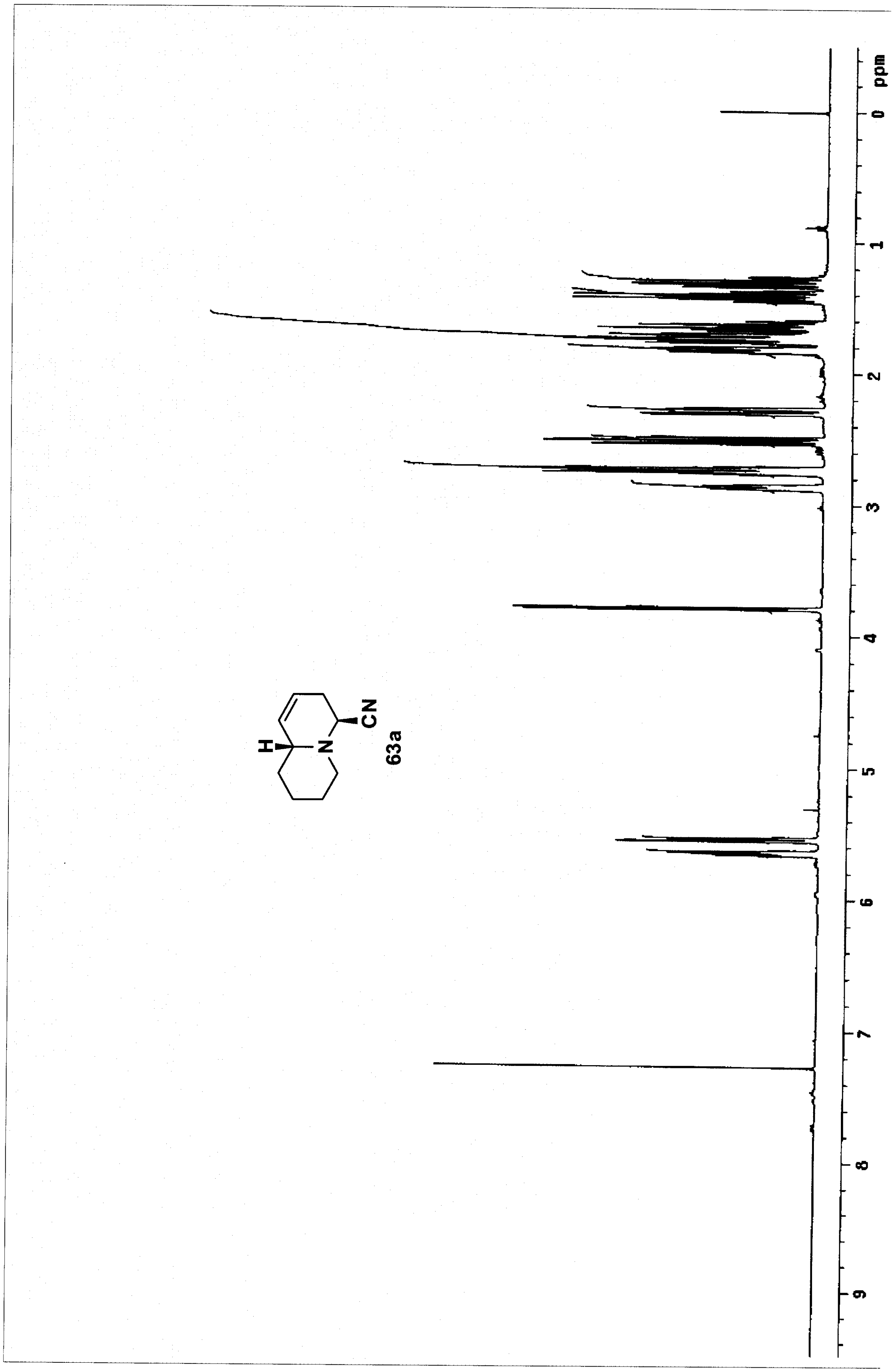
1-Methyl-(*E*)-5,7-octadienyliminoacetonitrile (62). A 100-mL, one-necked, round-bottomed flask equipped with a reflux condenser fitted with an argon inlet adapter was charged with Cs_2CO_3 (2.66 g, 8.16 mmol) and 14 mL of THF. A solution of triflamide **61** (0.634 g, 2.04 mmol) in 6 mL of THF was added, and the reaction mixture was heated at 55 °C for 2 h. The resulting mixture was allowed to cool to room temperature and then diluted with 30 mL of ether and 25 mL of water. The aqueous layer was separated and extracted with two 20-mL portions of ether, and the combined organic layers were washed with 40 mL of brine, dried over $MgSO_4$, filtered, and concentrated to give 0.449 g of a yellow oil. Column chromatography on 20 g of Et_3N-deactivated silica gel (elution with 10% EtOAc-hexanes containing 1% Et_3N) provided 0.331 g (90%) of **62** (as a 92:8 mixture of *E* and *Z* imine isomers by ^1H NMR analysis) as a pale yellow oil: IR (film): 3086, 2973, 2935, 2861, 2361, 1652, 1619, 1603, 1457, 1377, 1319 cm^{-1}; For *E* isomer: ^1H NMR (500 MHz, $CDCl_3$) δ 7.37 (s, 1H), 6.31 (ddd, J = 17.0, 10.3, 10.3 Hz, 1 H), 6.06 (dd, J = 15.2, 10.3 Hz, 1 H), 5.70 (dt, J = 15.2, 6.9 Hz, 1 H), 5.12 (d, J = 17.2 Hz, 1 H), 4.99 (d, J = 10.1 Hz, 1 H), 3.36 (m, 1 H), 2.09 (app q, J = 7.1 Hz, 2H), 1.56-1.67 (m, 2 H), 1.26-1.36 (m, 2 H), 1.25 (d, J = 6.6 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.3, 134.6, 134.7, 131.7, 115.5, 114.7, 68.7, 36.6, 32.4, 26.0, 21.9: For *Z* isomer: ^1H NMR (500 MHz, $CDCl_3$) δ 7.33 (s, 1H), 6.31 (ddd, J = 17.0, 10.3, 10.3 Hz, 1 H), 6.06 (dd, J = 15.2, 10.3 Hz, 1 H), 5.70 (dt, J = 15.2, 6.9 Hz, 1 H), 5.12 (d, J = 17.2 Hz, 1 H), 4.99 (d, J = 10.1 Hz, 1 H), 3.93 (m, 1 H), 2.09 (app q, J = 7.1 Hz, 2H), 1.81 (d, J = 7.3 Hz, 3 H), 1.56-1.67 (m, 2 H), 1.26-1.36 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.3, 134.7, 134.1, 131.7, 115.4, 114.7, 67.7, 36.7, 32.4, 26.0, 21.8.


N
CN
CH3
62
ppm
0
1
2
3
4
5
6
7
8

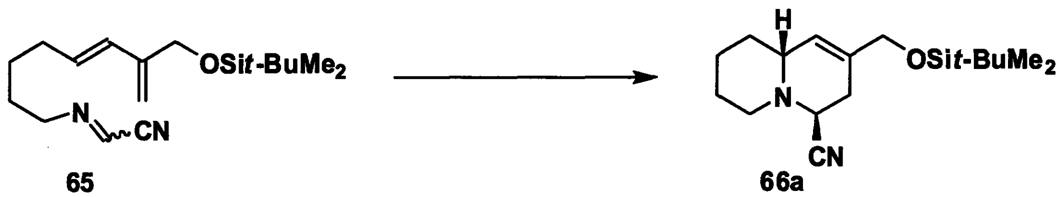
Experimental Procedures for Intramolecular Cycloadditions of Iminoacetonitriles

38 → 63a

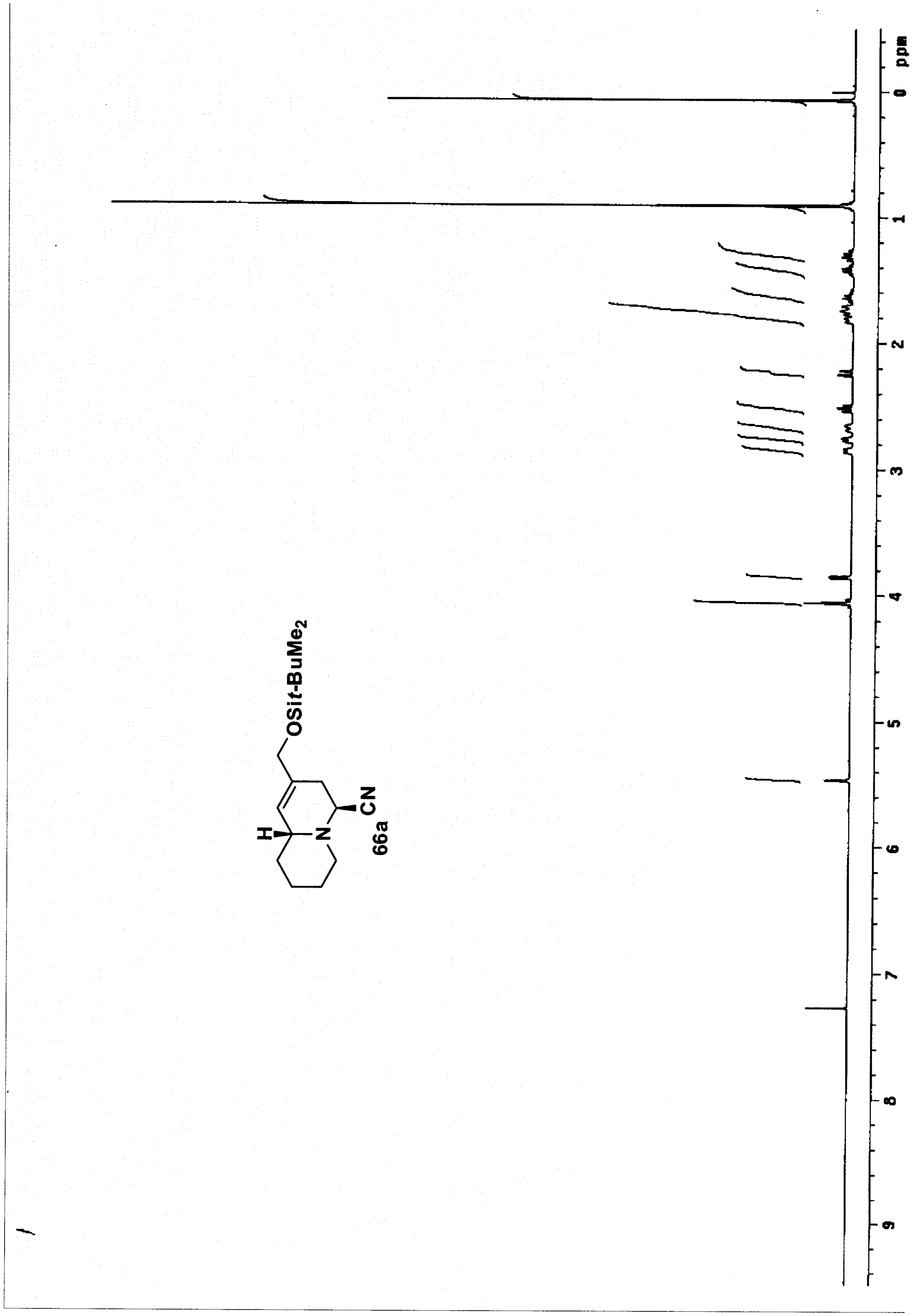
***cis*-1,2-Didehydro-4-cyanoquinolizidine (63a) (Acid-Promoted Cycloaddition).** A 50-mL, two-necked, round-bottomed flask equipped with a rubber septum and argon inlet adapter was charged with imine **38** (0.150 g, 0.92 mmol), 4Å molecular sieves (ca. 0.050 g), and 9 mL of CH_2Cl_2. Methanesulfonic acid (0.060 mL, 0.089 g, 0.92 mmol) was added dropwise via syringe over 1 min and the reaction mixture was stirred at rt for 30 min. The reaction mixture was diluted with 15 mL of satd aq $NaHCO_3$ and 10 mL of CH_2Cl_2, and the aq layer was separated and extracted with three 15-mL portions of CH_2Cl_2. The combined organic layers were washed with 15 mL of brine, dried over $MgSO_4$, filtered, and concentrated to give 0.181 g of an orange oil. A solution of this material in 10 mL of CH_3CN in a 25-mL round-bottomed flask was stirred at 45 °C under argon for 1.5 h, and then allowed to cool to rt and concentrated to give 0.181 g of an orange oil. Purification by column chromatography on 10 g of silica gel (elution with 10% EtOAc-hexanes containing 1% Et_3N) afforded 0.120 g (80%) of **63a** as a yellow oil: IR (film): 3035, 2936, 2855, 2807, 2221, 1442, 1396, 1332, 1287, 1237, 1205 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.63-5.67 (m, 1 H), 5.54 (d, J = 10.1 Hz, 1 H), 3.79 (d, J = 6.1 Hz, 1 H), 2.86 (br d, J = 11.6 Hz, 1 H), 2.70-2.77 (m, 2 H), 2.51 (dt, J = 3.1, 11.4 Hz, 1 H), 2.29 (m, 1 H), 1.79-1.85 (m, 1 H), 1.59-1.77 (m, 3 H), 1.26-1.46 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 130.5, 120.4, 116.9, 56.7, 54.0, 51.9, 31.7, 29.5, 25.7, 24.5; Anal. Calcd for $C_{10}H_{14}N_2$: C, 74.03; H, 8.70; N, 17.27. Found: C, 74.12; H, 8.74; N, 17.29.



63a
ppm
0
1
2
3
4
5
6
7
8
9



2-(*tert*-Butyldimethylsiloxymethyl)-*cis*-1,2-didehydro-4-cyanoquinolizidine (66a) (Acid-Promoted Cycloaddition). A 100-mL, two-necked, round-bottomed flask equipped with a rubber septum and argon inlet adapter was charged with imine **65** (0.615 g, 2.01 mmol), 4Å molecular sieves (ca. 100 mg), and 20 mL of CH_2Cl_2. Methanesulfonic acid (0.193 mL, 0.130 g, 2.01 mmol) was added dropwise via syringe over 1 min and the reaction mixture was stirred at rt for 15 min. The reaction mixture was diluted with 35 mL of satd aq $NaHCO_3$ and 30 mL of CH_2Cl_2. The aq layer was separated and extracted with three 25-mL portions of CH_2Cl_2. The combined organic layers were washed with 20 mL of brine, dried over $MgSO_4$, filtered, and concentrated to give 0.738 g of an orange oil. A solution of this material in 10 mL of CH_3CN in a 25-mL round-bottomed flask was stirred at 45 °C under argon for 1.5 h, and then allowed to cool ot rt and concentrated to give 0.738 g of an orange oil. Purification by column chromatography on 25 g of silica gel (elution with 10% EtOAc-hexanes 1% Et_3N) afforded 0.550 g (89%) of **66a** as a pale yellow oil: IR (film): 2934, 2856, 2807, 2767, 2222, 1471, 1462, 1388, 1360, 1326, 1289, 1256, 1229 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.47 (s, 1 H), 4.06 (s, 2 H), 3.85 (d, J = 6.4 Hz, 1 H), 2.84 (dd, J = 11.6, 1.6 Hz, 1 H), 2.76 (dd, J = 11.0, 2.0 Hz, 1 H), 2.64-2.70 (m, 1 H), 2.51 (dt, J = 3.1, 11.6 Hz, 1 H), 2.24 (d, J = 17.1 Hz, 1 H), 1.70-1.84 (m, 3 H), 1.63 (app tq, J = 4.1, 12.2 Hz, 1 H), 1.42 (app tq, J = 4.0, 12.8 Hz, 1 H), 1.30 (app dq, J = 3.4, 11.6 Hz, 1 H), 0.93 (s, 9 H), 0.09 (s, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 131.9, 124.2, 117.0, 65.9, 56.6, 54.0, 52.3, 32.0, 29.8, 26.0, 25.9, 24.7, 18.5, -5.1; Anal. Calcd for $C_{17}H_{30}N_2OSi$: C, 66.61; H, 9.87; N, 9.14. Found: C, 66.43; H, 10.05; N, 9.28.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H
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CN
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ppm
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3
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7
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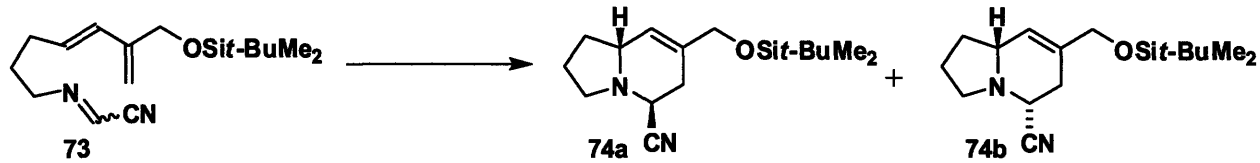
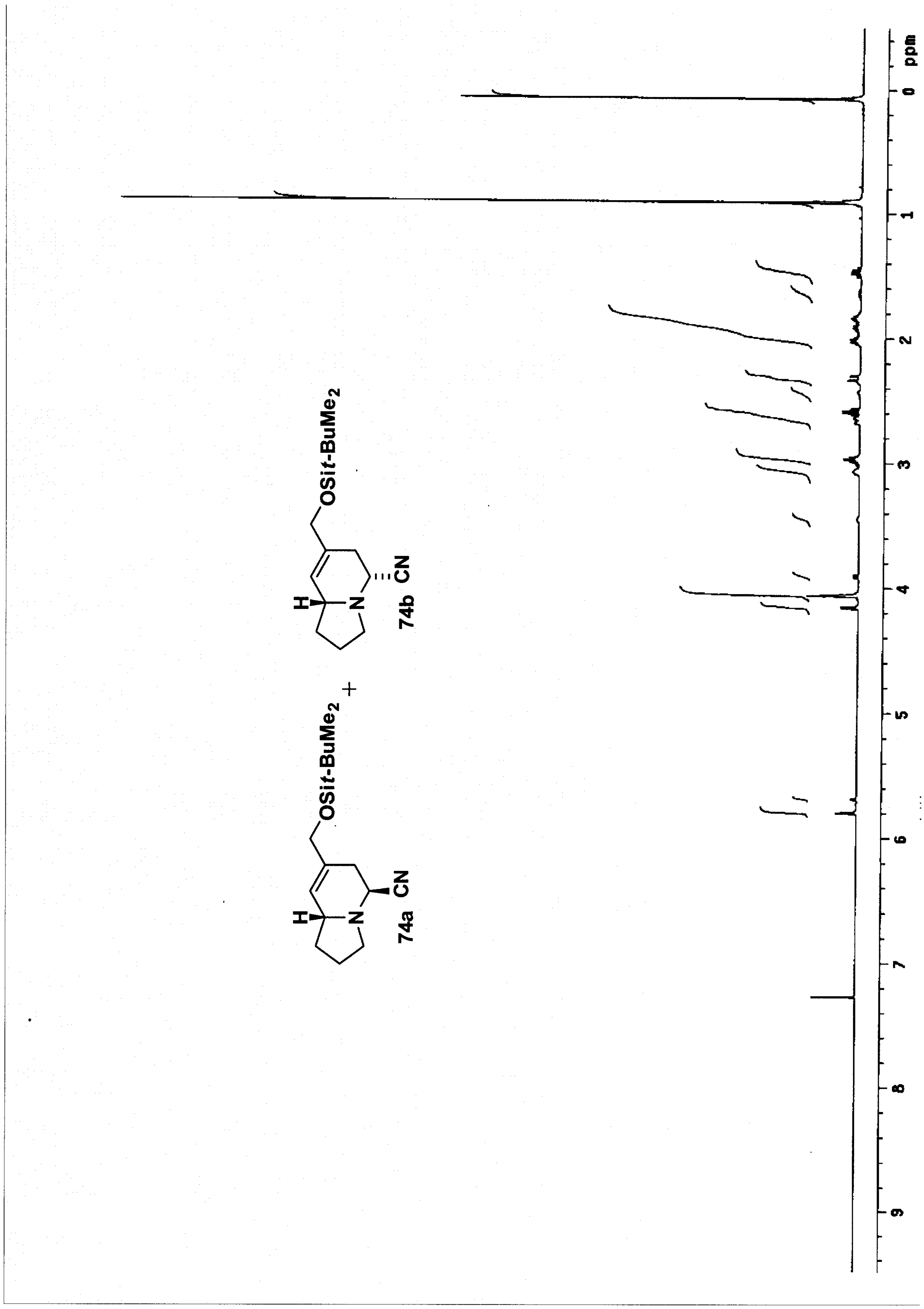
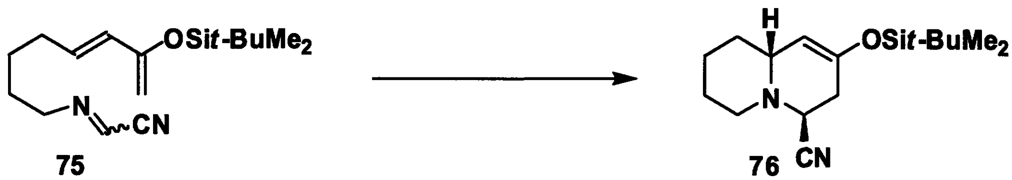
9



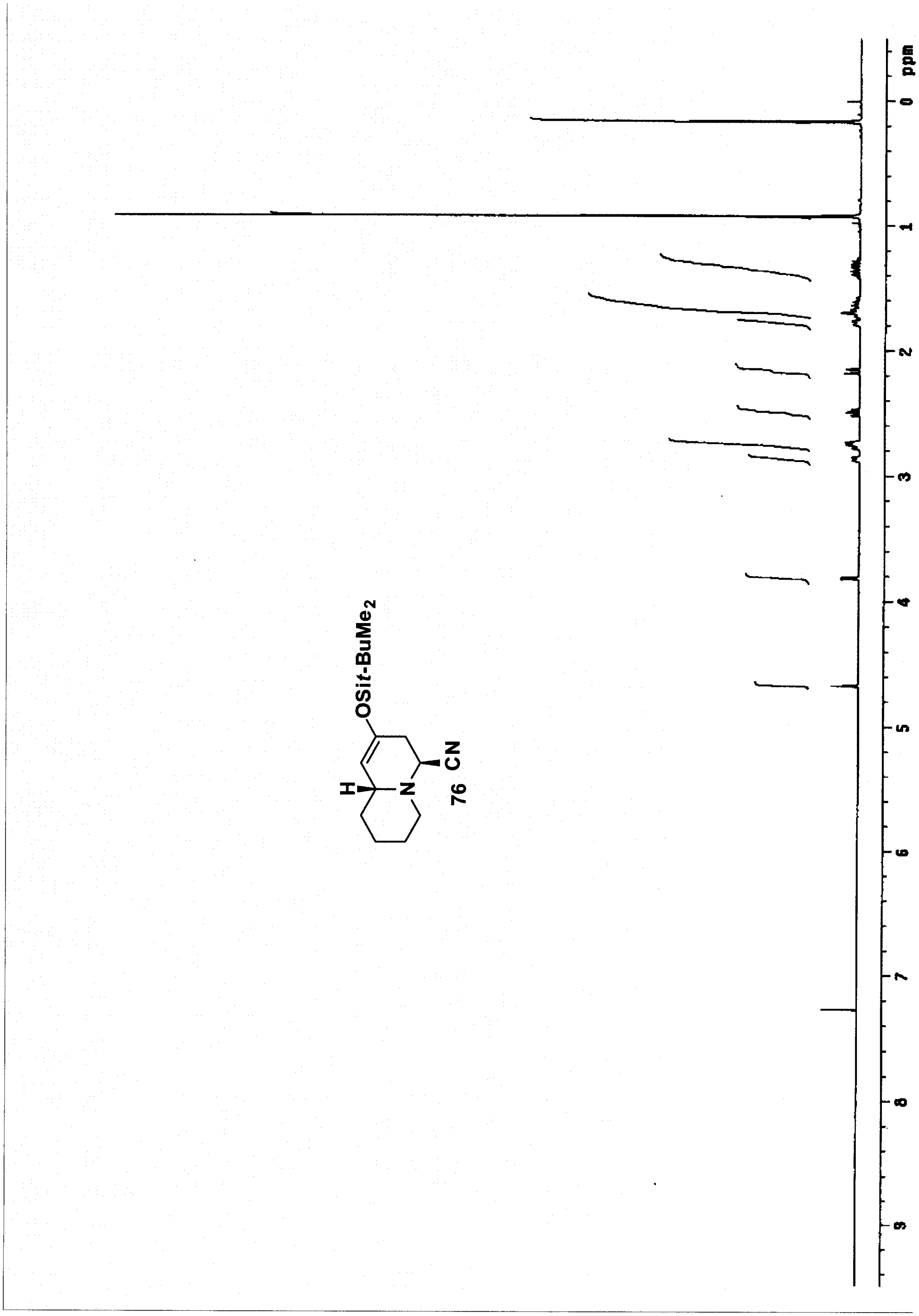
2-(*tert*-Butyldimethylsiloxymethyl)-*cis*-1,2-didehydro-4-cyanoquinolizidine (74a) and **2-(*tert*-Butyldimethylsiloxymethyl)-*trans*-1,2-didehydro-4-cyanoquinolizidine (74b) (Acid-Promoted Cycloaddition).** A 100-mL, two-necked, round-bottomed flask equipped with a rubber septum and argon inlet adapter was charged with imine **73** (0.592 g, 2.02 mmol), 4Å molecular sieves (ca. 100 mg), and 20 mL of CH_2Cl_2. Methanesulfonic acid (0.131 mL, 0.194 g, 2.02 mmol) was added dropwise via syringe over 1 min and the reaction mixture was stirred at rt for 30 min. The reaction mixture was diluted with 20 mL of satd aq $NaHCO_3$ and 20 mL of CH_2Cl_2, and the aq layer was separated and extracted with three 15-mL portions of CH_2Cl_2. The combined organic layers were washed with 15 mL of brine, dried over $MgSO_4$, filtered, and concentrated to give 0.729 g of an orange oil. A solution of this material in 15 mL of CH_3CN in a 25-mL round-bottomed flask was stirred at 45 °C under argon for 1.5 h, and then allowed to cool to rt and concentrated to give 0.181 g of an orange oil. Purification by column chromatography on 20 g of silica gel (gradient elution with 10-25% EtOAc-hexanes containing 1% Et_3N) afforded 0.491 g (83%) of **74a** and **74b** (81:19 mixture by ^{1}H NMR analysis) as a pale yellow oil: IR (film): 2956, 2930, 2857, 1472, 1463, 1361, 1253 cm^{-1}; For **74a**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.80 (s, 1 H), 4.15 (dd, J = 7.0, 1.5 Hz, 1 H), 4.06 (s, 2 H), 3.01-3.09 (m, 1 H), 2.96 (dt, J = 8.5, 3.4 Hz, 1 H), 2.62-2.68 (m, 1 H), 2.58 (app q, J = 8.5 Hz, 1 H), 2.32 (d, J = 17.4 Hz, 1 H), 1.79-2.05 (m, 3 H), 1.43-1.51 (m, 1 H), 0.91 (s, 9 H), 0.07 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 132.9, 122.1, 117.1, 66.2, 56.7, 49.9, 48.0, 29.7, 28.9, 26.2, 21.8, 18.7, -4.9: For **74b**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.69 (d, J = 1.5 Hz, 1 H), 4.06 (s, 2 H), 3.90 (dd, J =

8.5, 4.9 Hz, 1 H), 3.43-3.46 (m, 1 H), 2.96 (dt, *J* = 8.5, 3.4 Hz, 1 H), 2.62-2.68 (m, 1 H), 2.58 (app q, *J* = 8.5 Hz, 1 H), 2.44 (dd, *J* = 16.8, 8.5 Hz, 1 H), 1.79-2.05 (m, 3 H), 1.60-1.68 (m, 1 H), 0.91 (s, 9 H), 0.07 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 133.0, 123.4, 120.0, 66.1, 59.2, 49.3, 48.0, 30.3, 27.2, 26.2, 23.1, 18.6, -4.9; HRMS (m/*z*) $[M]^+$ calcd for $C_{16}H_{28}N_2OSi$, 292.1965; found, 292.1954.


74a
74b
OSit-BuMe2
OSit-BuMe2
CN
CN
ppm



2-(*tert*-Butyldimethylsiloxy)-*cis*-1,2-didehydro-4-cyanoquinolizidine (76) (Acid-Promoted Cycloaddition). A 25-mL, two-necked, round-bottomed flask equipped with a rubber septum and argon inlet adapter was charged with imine **75** (0.178 g, 0.61 mmol), 4Å molecular sieves (ca. 50 mg), and 6 mL of CH_2Cl_2. The reaction mixture was cooled at -78 °C while methanesulfonic acid (0.039 mL, 0.058 g, 0.61 mmol) was added dropwise via syringe over 1 min. The solution was stirred at -78 °C for 1 h, and then diluted with 10 mL of satd aq $NaHCO_3$ and 10 mL of CH_2Cl_2. The aq layer was separated and extracted with three 12-mL portions of CH_2Cl_2. The combined organic layers were washed with 10 mL of brine, dried over $MgSO_4$, filtered, and concentrated to give 0.191 g of an orange oil. A solution of this material in 5 mL of CH_3CN in a 25-mL round-bottomed flask was stirred at 45 °C under argon for 1.5 h, and then allowed to cool to rt and concentrated to give 0.191 g of an orange oil. Purification by column chromatography on 10 g of silica gel (gradient elution with 5-10% EtOAc-hexanes containing 1% Et_3N) afforded 0.092 g (52%) of **76** as a white solid: mp 61-62 °C; IR (CH_2Cl_2): 2933, 2857, 1678, 1472, 1372, 1287, 1256 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.67 (app t, J = 1.8 Hz, 1 H), 3.81 (d, J = 5.5 Hz, 1 H), 2.86 (br d, J = 10.2 Hz, 1 H), 2.73-2.79 (m, 2 H), 2.49 (dt, J = 11.5, 3.1 Hz, 1 H), 2.16 (dt, J = 17.0, 1.8 Hz, 1 H), 1.76-1.79 (m, 1 H), 1.61-1.73 (m, 3 H), 1.38 (tq, J = 12.8, 3.8 Hz, 1 H) 1.25-1.34 (m, 1 H), 0.92 (s, 9 H), 0.17 (s, 3 H), 0.16 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.4, 116.8, 107.1, 56.1, 53.7, 53.1, 33.9, 33.0, 25.9, 25.8, 24.3, 18.2, -4.2, -4.4; Anal. Calcd for $C_{16}H_{28}N_2OSi$: C, 65.70; H, 9.65; N, 9.58. Found: C, 65.56; H, 9.63; N, 9.44.



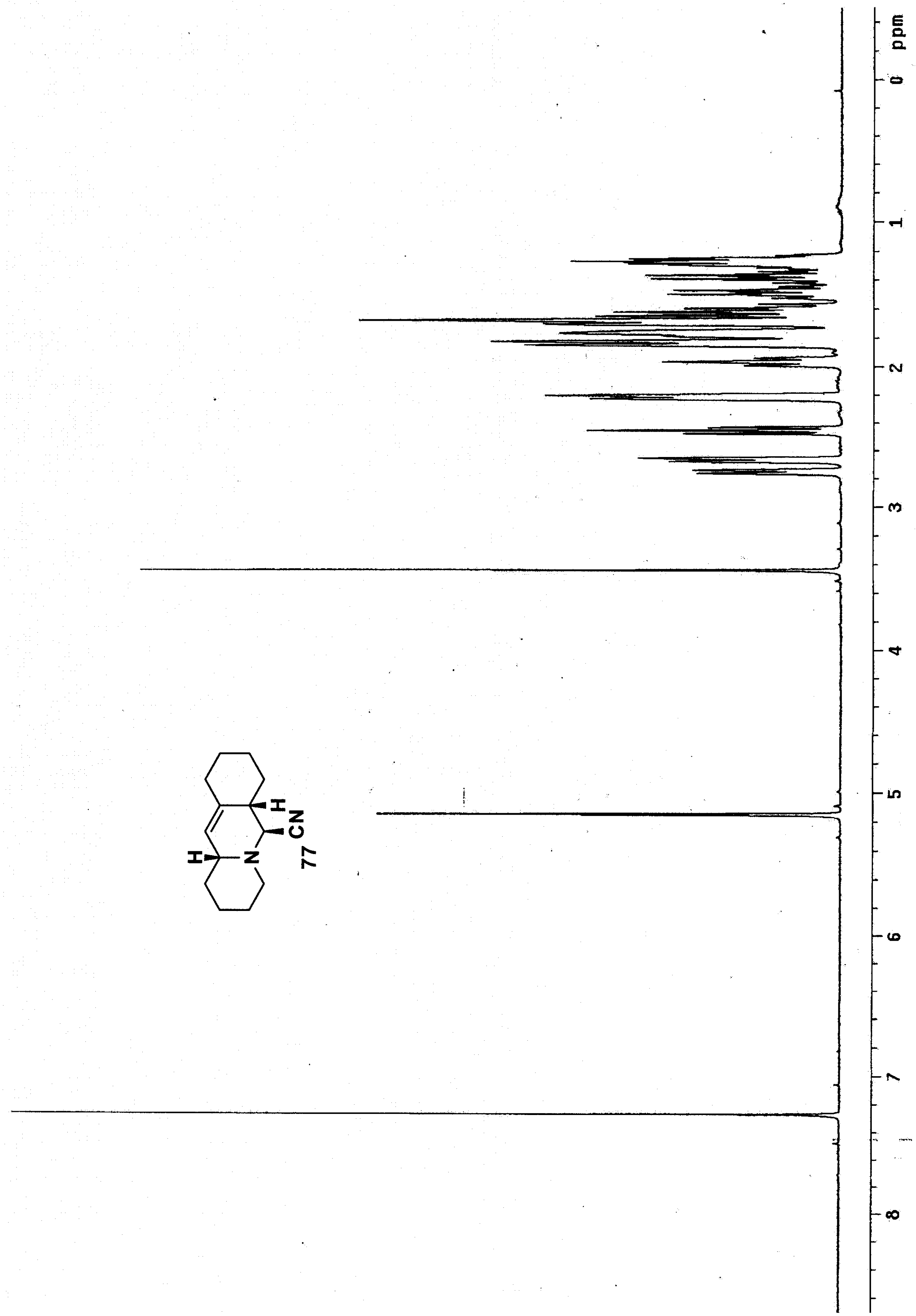
OSit-BuMe2
H
N
CN
76
ppm
0
1
2
3
4
5
6
7
8
9

58 → 77

6β-Cyano-1,3,4,6,6aβ,7,8,9,10,11aβ-decahydro-2H-benzo[b]quinolizine (77) Acid-Promoted Cycloaddition). A 25-mL, two-necked, round-bottomed flask equipped with a rubber septum and argon inlet adapter was charged with imine **58** (0.121 g, 0.56 mmol), 4Å molecular sieves (ca. 50 mg), and 5 mL of CH_2Cl_2. Methanesulfonic acid (0.040 mL, 0.059 g, 0.62 mmol) was added dropwise via syringe over 1 min and the reaction mixture was stirred at rt for 1 h. The reaction mixture was then diluted with 15 mL of saturated $NaHCO_3$ solution and 10 mL of CH_2Cl_2, and the aqueous layer was separated and extracted with three 8-mL portions of CH_2Cl_2. The combined organic layers were washed with 10 mL of brine, dried over $MgSO_4$, filtered, and concentrated to give 0.125 g of yellow oil. A solution of this material in 4 mL of CH_3CN in a 25-mL round-bottomed flask was stirred at 45 °C under argon for 1.5 h, and then allowed to cool to rt. Concentration gave 0.124 g of a yellow oil which was purified by column chromatography on 10 g of silica gel (elution with 10% EtOAc-hexanes containing 1% Et_3N) to give 0.102 g (84%) of **77** as a pale yellow oil: IR (film): 2933, 2856, 2807, 2763, 2222, 1683, 1443 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.15 (s, 1 H), 3.44 (s, 1 H), 2.75 (br d, J = 11.3 Hz, 1 H), 2.67 (dt, J = 11.0, 2.1 Hz, 1 H), 2.45 (td, J = 11.3, 3.1 Hz, 1 H), 2.19 – 2.23 (m, 2 H), 1.96 (m, 1 H), 1.73 – 1.86 (m, 4 H), 1.56 – 1.71 (m, 4 H), 1.22 – 1.53 (m, 4 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.8, 121.1, 117.5, 58.4, 56.3, 54.0, 43.5, 35.4, 34.1, 32.7, 28.8, 26.6, 26.0, 24.6; HRMS $[M+H]^+$ Calcd for $C_{14}H_{20}N_2$: 217.1699. Found: 217.1691.

(Thermal Cycloaddition). A threaded Pyrex tube (ca. 50-mL capacity) equipped with a rubber septum and argon inlet needle was charged with imine **58** (0.174 g, 0.80 mmol), BHT

(0.532 g, 2.41 mmol), and 16 mL of toluene. The solution was degassed by four freeze-pump-thaw cycles and then sealed with a threaded Teflon cap. The reaction mixture was heated in a 120 °C oil bath for 13 h, and then allowed to cool to rt and concentrated to afford 0.708 g of a brown oil. A solution of this material in CH_2Cl_2 was concentrated onto 1.5 g of silica gel and transferred to the top of a column of 40 g of silica gel. Gradient elution with 5-10% EtOAc-hexanes containing 1% Et_3N yielded 0.121 g (70%) of **77** as a colorless oil.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N
H
CN
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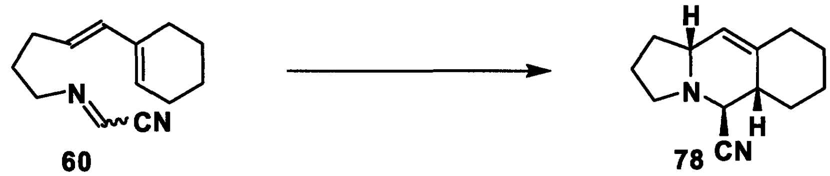
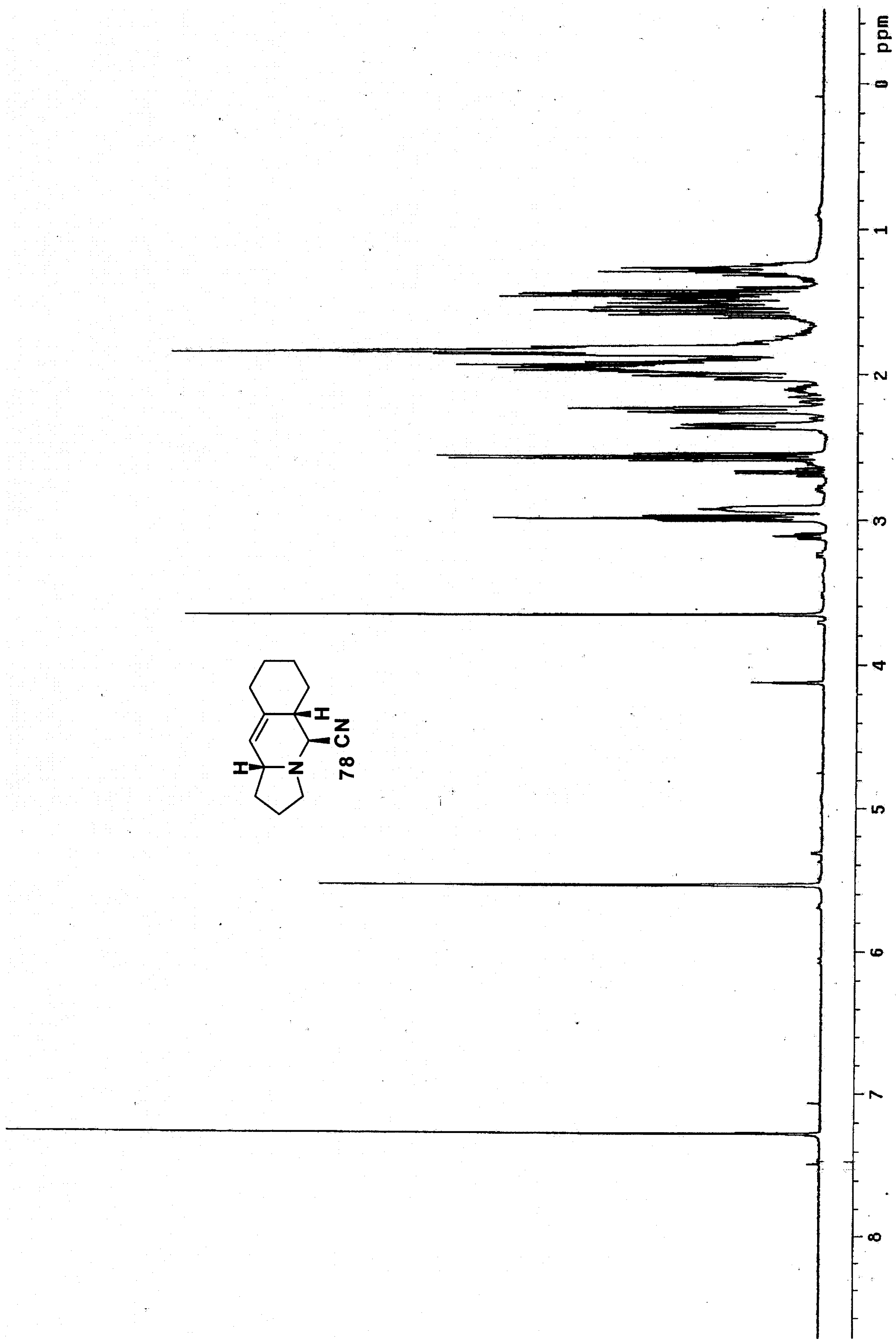
4
5
6
7
8



5β-Cyano-1,2,3,5,5aβ,6,7,8,9,10aβ-decahydro-benzo[b]indolizine (78) (Acid-Promoted Cycloaddition). A 25-mL, two-necked, round-bottomed flask equipped with a rubber septum and argon inlet adapter was charged with imine **34** (0.145 g, 0.72 mmol), 4Å molecular sieves (ca. 50 mg), and 7 mL of CH_2Cl_2. Methanesulfonic acid (0.051 mL, 0.076 g, 0.79 mmol) was added dropwise via syringe over 1 min and the reaction mixture was stirred at rt for 1.5 h. The reaction mixture was then diluted with 15 mL of saturated $NaHCO_3$ solution and 10 mL of CH_2Cl_2, and the aqueous layer was separated and extracted with three 8-mL portions of CH_2Cl_2. The combined organic layers were washed with 10 mL of brine, dried over $MgSO_4$, filtered, and concentrated to give 0.187 g of yellow oil. A solution of this material in 4 mL of CH_3CN in a 25-mL round-bottomed flask was stirred at 45 °C under argon for 1.5 h, and then allowed to cool to rt. Concentration gave 0.187 g of a yellow oil which was purified by column chromatography on 8 g of silica gel (elution with 10% EtOAc-hexanes containing 1% Et_3N) to give 0.101 g (70%) of **78** as a yellow oil (83:17 mixture of *trans-* and *cis*-fused indolizidines by ^{1}H NMR analysis): IR (film): 3049, 2932, 2856, 2769, 2221, 1670, 1459, 1446, 1370, 1320, 1258 cm^{-1}; for *trans*-fused indolizidine: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.54 (s, 1 H), 3.66 (d, J = 1.4 Hz, 1 H), 2.98 (dt, J = 8.8, 2.7 Hz, 1 H), 2.92 (m, 1 H), 2.56 (app q, J = 9.1 Hz, 1 H), 2.35 (br d, J = 13.1 Hz, 1 H), 2.24 (br d, J = 13.1 Hz, 1 H), 1.97-2.03 (m, 1 H), 1.87-1.97 (m, 2 H), 1.77-1.84 (m, 2 H), 1.39-1.60 (m, 4 H), 1.23-1.32 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.8, 119.5, 117.4, 57.2, 54.8, 50.5, 43.6, 35.4, 34.4, 29.3, 28.2, 26.5, 21.7; for *cis*-fused indolizidine: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.54 (s, 1 H), 4.12 (br s, 1 H), 3.11 (dt, J = 8.5, 3.2

Hz, 1 H), 2.92 (m, 1 H), 2.66 (app q, J = 8.8 Hz, 1 H), 2.24 (br d, J = 13.1 Hz, 1 H), 2.17 (br d, J = 13.1 Hz, 1 H), 2.07-2.12 (m, 1 H), 1.87-1.97 (m, 2 H), 1.77-1.84 (m, 2 H), 1.39-1.60 (m, 4 H), 1.23-1.32 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.8, 120.1, 117.4, 55.7, 54.8, 52.5, 40.0, 34.7, 30.7, 30.2, 27.3, 25.9, 21.5; HRMS [M+Na] Calcd. for $C_{13}H_{18}N_2Na$: 217.1699. Found: 217.1691.

(Thermal Cycloaddition). A threaded Pyrex tube (ca. 100-mL capacity) equipped with a rubber septum and argon inlet needle was charged with imine **60** (0.214 g, 1.06 mmol), BHT (0.701 g, 3.18 mmol), and 21 mL of toluene. The solution was degassed by four freeze-pump-thaw cycles and then sealed with a threaded Teflon cap. The reaction mixture was heated in a 120 °C oil bath for 36 h, and then allowed to cool to rt and concentrated to afford 0.921 g of a white solid. A solution of this material in CH_2Cl_2 was concentrated onto 2 g of silica gel and transferred to the top of a column of 30 g of silica gel. Elution with 7% EtOAc-hexanes containing 1% Et_3N yielded 0.094 g (44%) of **78** as a yellow oil (83:17 mixture of *trans*- and *cis*-fused indolizidines by ^{1}H NMR analysis).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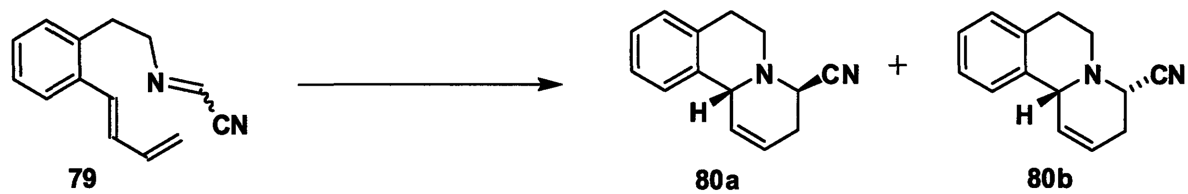
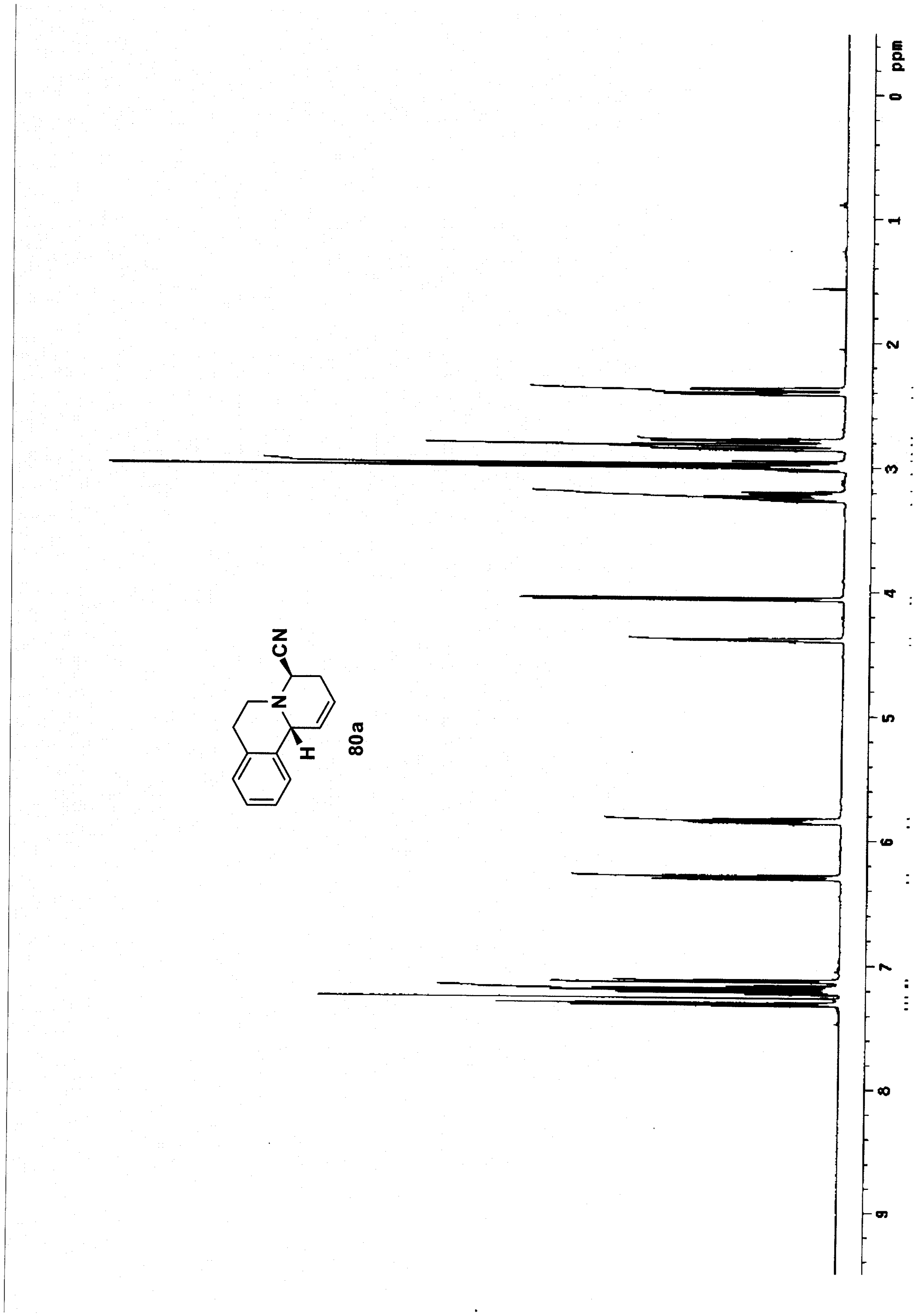


cis-3,6,7,11b-Tetrahydro-4-cyano-*4H*-pyrido[2,1-*a*]isoquinoline (80a) and *trans*-3,6,7,11b-Tetrahydro-4-cyano-*4H*-pyrido[2,1-*a*]isoquinoline (80b) (Acid-Promoted Cycloaddition). A 25-mL, two-necked, round-bottomed flask equipped with a rubber septum and argon inlet adapter was charged with imine **79** (0.173 g, 0.82 mmol), 4Å molecular sieves (ca. 50 mg), and 8 mL of CH_2Cl_2. Methanesulfonic acid (0.053 mL, 0.079 g, 0.82 mmol) was added dropwise via syringe over 1 min and the reaction mixture was stirred at rt for 30 min. The reaction mixture was then diluted with 15 mL of satd aq $NaHCO_3$ and 10 mL of CH_2Cl_2, and the aq layer was separated and extracted with three 15-mL portions of CH_2Cl_2. The combined organic layers were washed with 15 mL of brine, dried over $MgSO_4$, filtered, and concentrated to give 0.181 g of an orange oil. A solution of this material in 10 mL of CH_3CN in a 25-mL round-bottomed flask was stirred at 45 °C under argon for 1.5 h, and then allowed to cool to rt and concentrated to give 0.181 g of an orange oil. Purification by column chromatography on 10 g of silica gel (elution with 25% EtOAc-hexanes containing 1% Et_3N) afforded 0.104 g (60%) of **80a** and **80b** (79:21 mixture by ^{1}H NMR analysis) as a white solid: For **80a**: IR (CH_2Cl_2): 3054, 2934, 2826, 2736, 1494, 1432, 1332 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 (d, J = 7.6 Hz, 1 H), 7.16-7.23 (m, 2 H), 7.12 (dd, J = 7.0, 0.9 Hz, 1 H), 6.30 (d, J = 10.4 Hz, 1 H), 5.82-5.86 (m, 1 H), 4.39 (s, 1 H), 4.06 (dd, J = 6.1, 0.6 Hz, 1 H), 3.18-3.27 (m, 1 H), 2.97-3.02 (m, 2 H), 2.76-2.86 (m, 2 H), 2.36-2.42 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.5, 133.9, 129.4, 127.9, 126.7, 126.2, 124.7, 122.3, 117.0, 56.4, 52.4, 51.0, 29.5, 29.4; Anal. Calcd for $C_{14}H_{14}N_2$: C, 79.97; H, 6.71; N, 13.32. Found: C, 80.00; H, 7.02; N, 13.52. For **80b**: IR (CH_2Cl_2): 3053, 2985, 2933, 2849, 1637, 1496, 1422, 1273 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.12-7.26 (m, 4 H), 7.12 (dd, J = 7.0, 0.9 Hz, 1 H), 5.93 (dt, J = 8.2, 2.0 Hz, 1 H), 5.77-5.82 (m, 1 H), 4.54 (br s, 1 H), 4.12 (dd, J = 11.0, 4.9 Hz, 1 H), 3.18-3.27 (m, 1 H), 2.92-3.05 (m, 4 H), 2.56-2.66 (m, 1 H), 2.30-2.38 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.9, 134.5, 129.8, 129.1, 126.9, 126.4, 126.2, 122.7, 119.2, 58.7, 51.1, 43.4, 29.3, 25.7; Anal. Calcd for $C_{14}H_{14}N_2$: C, 79.97; H, 6.71; N, 13.32. Found: C, 79.62; H, 6.55; N, 13.10.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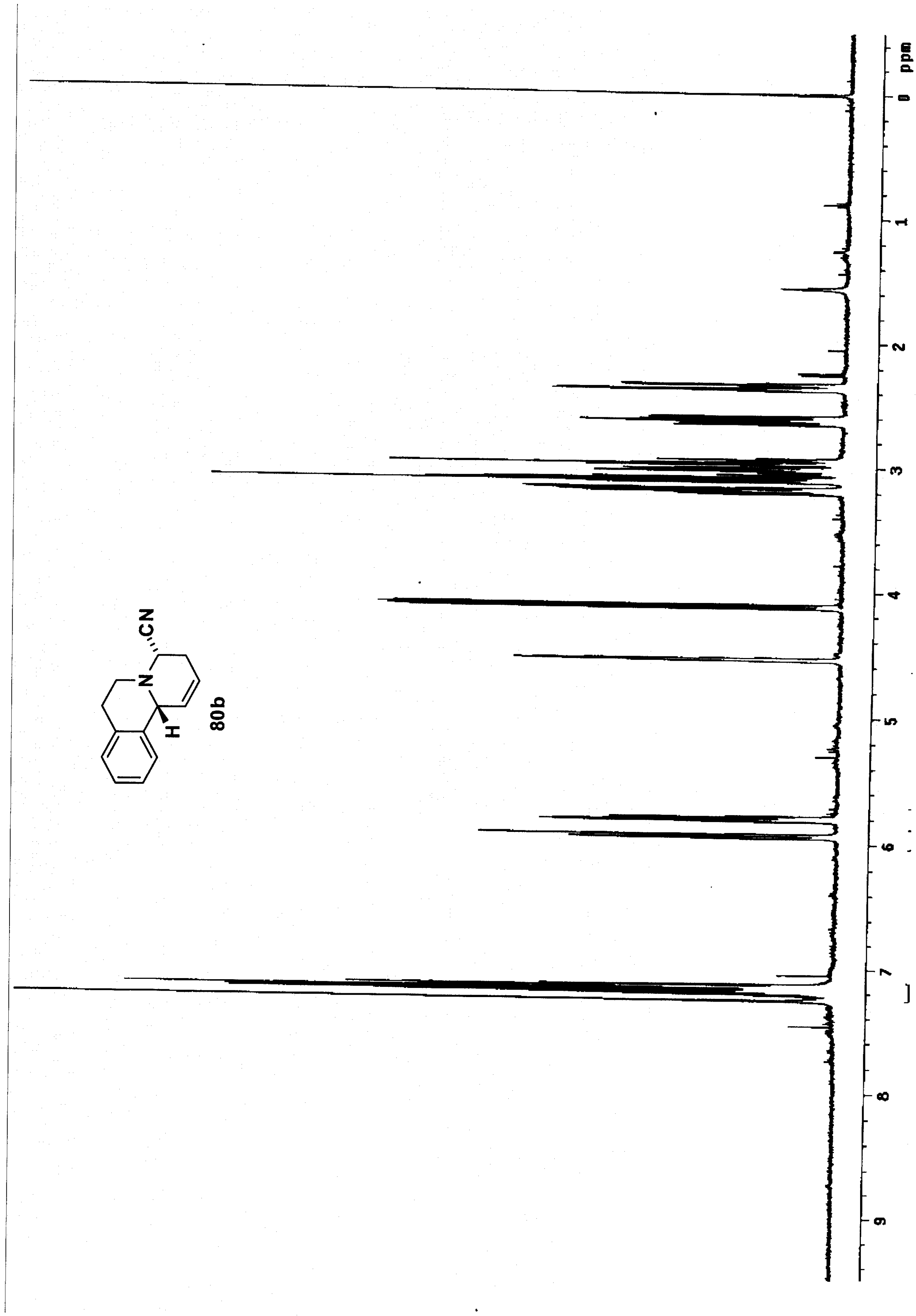
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N
H
80b
ppm
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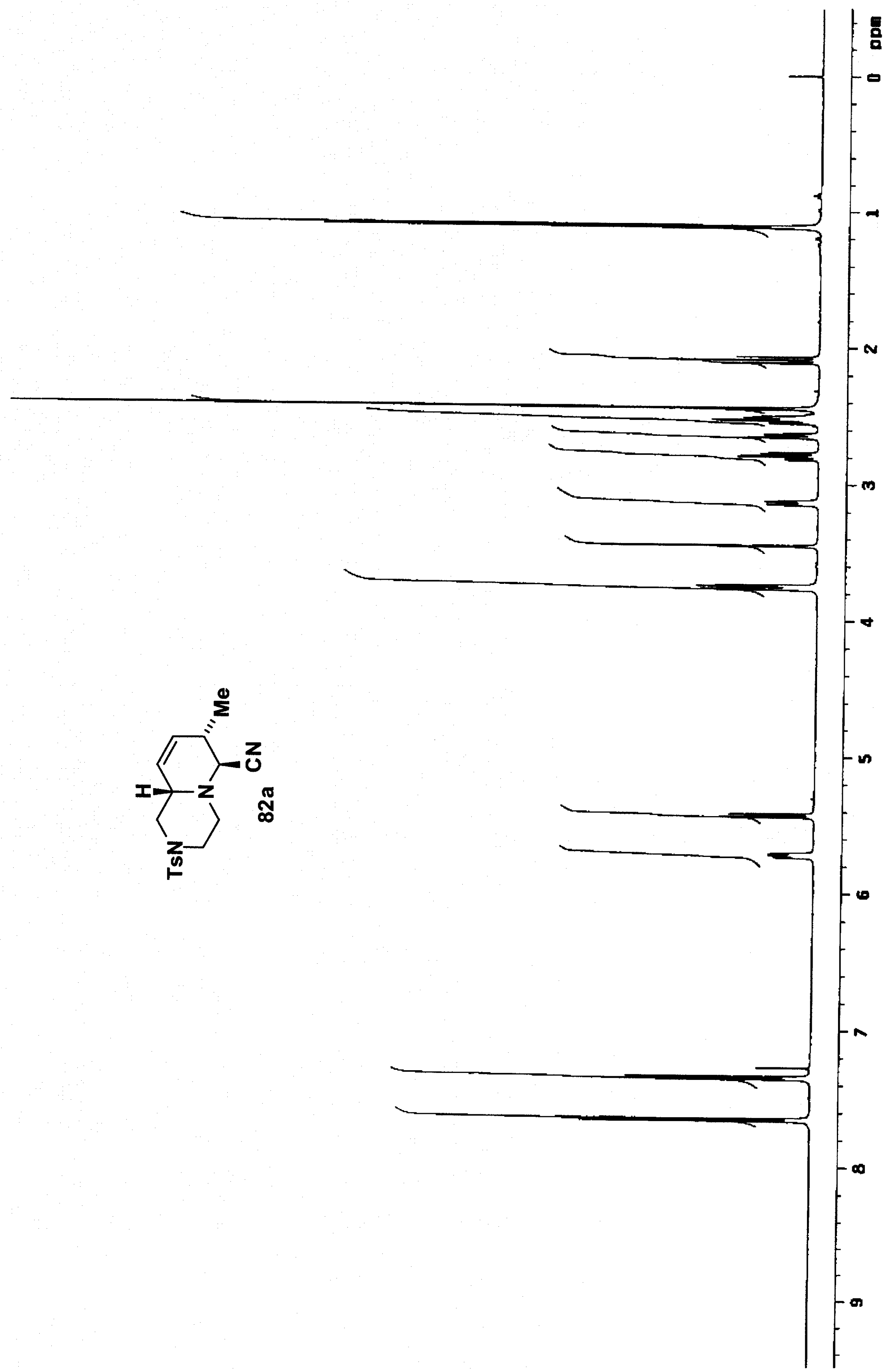
6
7
8
9

cis-7-Methyl-2(toluene-4-sulfonyl)-1,3,4,6,7,9*a*-hexahydro-6-cyano-2*H*-pyrido[1,2-*a*]pyrazine (82a) A 25-mL, two-necked, round-bottomed flask equipped with a rubber septum and argon inlet adapter was charged with imine **81** (0.151 g, 0.46 mmol), 4Å molecular sieves (ca. 50 mg), and 9 mL of CH_2Cl_2. Methanesulfonic acid (0.030 mL, 0.044 g, 0.46 mmol) was added dropwise via syringe over 1 min and the reaction mixture was stirred at rt for 15 min. The reaction mixture was then diluted with 15 mL of satd aq $NaHCO_3$ and 10 mL of CH_2Cl_2, and the aq layer was separated and extracted with three 15-mL portions of CH_2Cl_2. The combined organic layers were washed with 15 mL of brine, dried over $MgSO_4$, filtered, and concentrated to give 0.185 g of an orange oil. A solution of this material in 15 mL of CH_3CN in a 25-mL round-bottomed flask was stirred at reflux under argon for 18 h, and then allowed to cool to rt and concentrated to give 0.180 g of an orange oil. Purification by column chromatography on 20 g of silica gel (elution with 25% EtOAc-hexanes) provided 0.107 g (71%) of **82a** as a white solid: mp = 152-153 °C; IR (CH_2Cl_2): 3054, 2986, 2305, 1598, 1451, 1422, 1345, 1273, 1257 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.66 (d, J = 8.2 Hz, 2 H), 7.34 (d, J = 8.5 Hz, 2 H), 5.72 (ddd, J = 10.0, 5.0, 2.5 Hz, 1 H), 5.43 (d, J = 10.1 Hz, 1 H), 3.74-3.78 (m, 2 H), 3.44 (s, 1 H), 3.14 (dt, J = 11.0, 2.1 Hz, 1 H), 2.80 (dt, J = 11.3, 3.1 Hz, 1 H), 2.63 (dt, J = 11.1, 2.5 Hz, 1 H), 2.53 (dt, J = 11.5, 3.2 Hz, 2 H), 2.44 (s, 3 H), 2.09 (t, J = 11.0 Hz, 1 H), 1.11 (d, J = 6.7 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.1, 133.0, 130.0, 129.7, 127.9, 124.3, 116.2, 56.5, 55.5, 51.7, 50.2, 45.8, 35.1, 21.7, 19.9; Anal. Calcd for $C_{17}H_{21}N_3O_2S$: C, 61.61; H, 6.39; N, 12.68. Found: C, 61.57; H, 6.35; N, 12.47.



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82a
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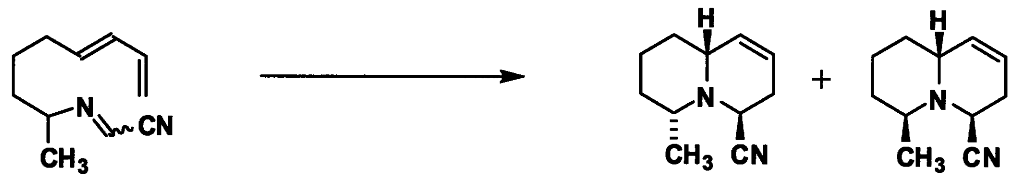
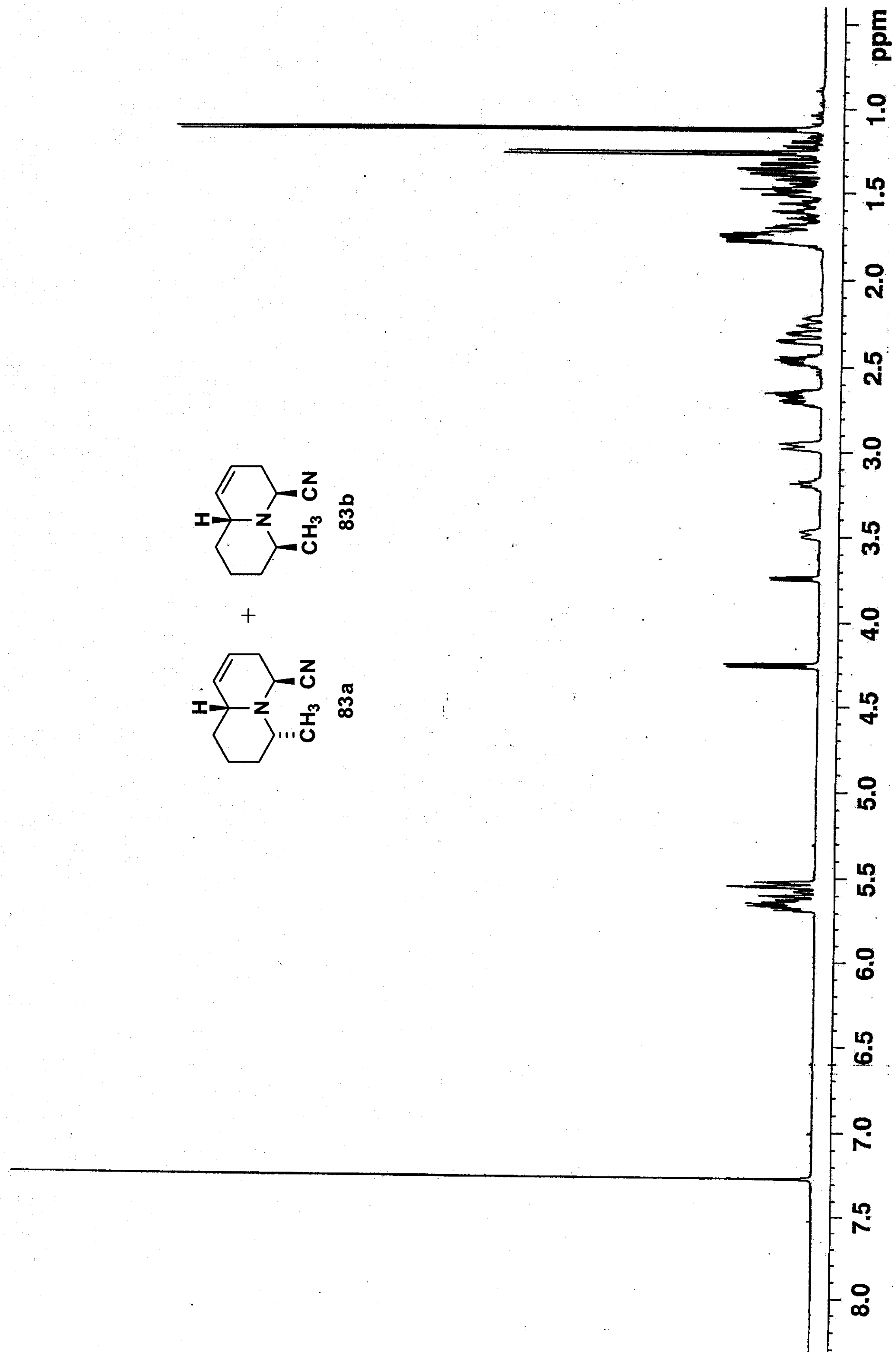


62 **83a** **83b**

***cis*-6-Methyl-*cis*-1,2-didehydro-4-cyanoquinolizidine (83a)** and ***cis*-6-Methyl-*cis*-1,2-didehydro-4-cyanoquinolizidine (83b) (Acid-Promoted Cycloaddition).** A 25-mL, two-necked, round-bottomed flask equipped with a rubber septum and argon inlet adapter was charged with imine **62** (0.141 g, 0.78 mmol), 4Å molecular sieves (ca. 50 mg), and 8 mL of CH_3CN. The reaction mixture was cooled at -35 °C while methanesulfonic acid (0.051 mL, 0.075 g, 0.78 mmol) was added dropwise via syringe over 1 min. The solution was stirred at -35 °C for 1 h, 0 °C for 2 h, and then allowed to warm to rt over 1 h. The reaction mixture was then diluted with 15 mL of satd aq $NaHCO_3$ and 10 mL of CH_2Cl_2, and the aq layer was separated and extracted with three 15-mL portions of CH_2Cl_2. The combined organic layers were washed with 15 mL of brine, dried over $MgSO_4$, filtered, and concentrated to give 0.150 g of an orange oil. A solution of this material in 10 mL of CH_3CN in a 25-mL round-bottomed flask was stirred at 45 °C under argon for 1.5 h, and then allowed to cool to rt and concentrated to give 0.150 g of an orange oil. Purification by column chromatography on 10 g of silica gel (gradient elution with 5-10% EtOAc-hexanes containing 1% Et_3N) afforded 0.098 g (70%) of **83a** and **83b** (67:33 mixture by ^{1}H NMR analysis) as a yellow oil: IR (film): 3035, 2969, 2933, 2856, 2797, 2221, 1456, 1439, 1378, 1266 cm^{-1}; For **83a**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.64-5.69 (m, 1 H), 5.54 (app dt, J = 10.1, 1.3 Hz, 1 H), 4.26 (d, J = 5.6 Hz, 1 H), 2.98 (br d, J = 9.3 Hz, 1 H), 2.63-2.73 (m, 1 H), 2.43-2.50 (m, 1 H), 2.33 (dm, J = 17.7 Hz, 1 H), 1.68-1.81 (m, 3 H), 1.20-1.65 (m, 3 H), 1.13 (d, J = 6.2 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 131.1, 120.6, 117.0, 56.0, 49.9, 45.9, 35.1, 32.5, 30.0, 24.6, 19.3; For **83b**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.64-5.69 (m, 1 H), 5.59 (app dt, J = 10.4, 1.8 Hz, 1 H), 3.74 (d, J = 5.8 Hz, 1 H), 3.49 (dm, J = 12.2 Hz, 1 H), 3.20 (m, 1 H), 2.63-2.73 (m, 1 H), 2.44 (dm, J = 17.0 Hz, 1 H), 1.68-1.81 (m, 3 H), 1.20-1.65 (m, 3 H), 1.27 (d, J = 6.8 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 132.1, 120.5, 117.0, 57.3, 49.3, 45.9, 33.0, 32.8, 31.6, 20.0, 11.6; HRMS $[M+H]^+$ Calcd. for $C_{11}H_{17}N_2$: 177.1386. Found: 177.1389.


83a
+
83b
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H
N
ppm
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1.5
2.0
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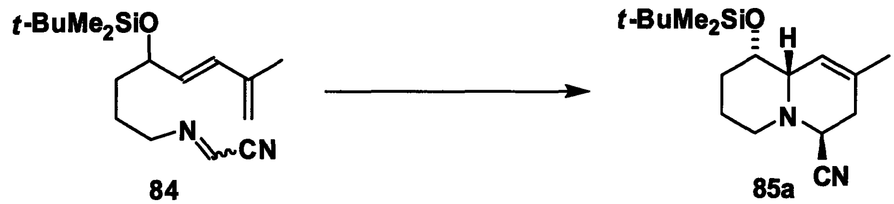
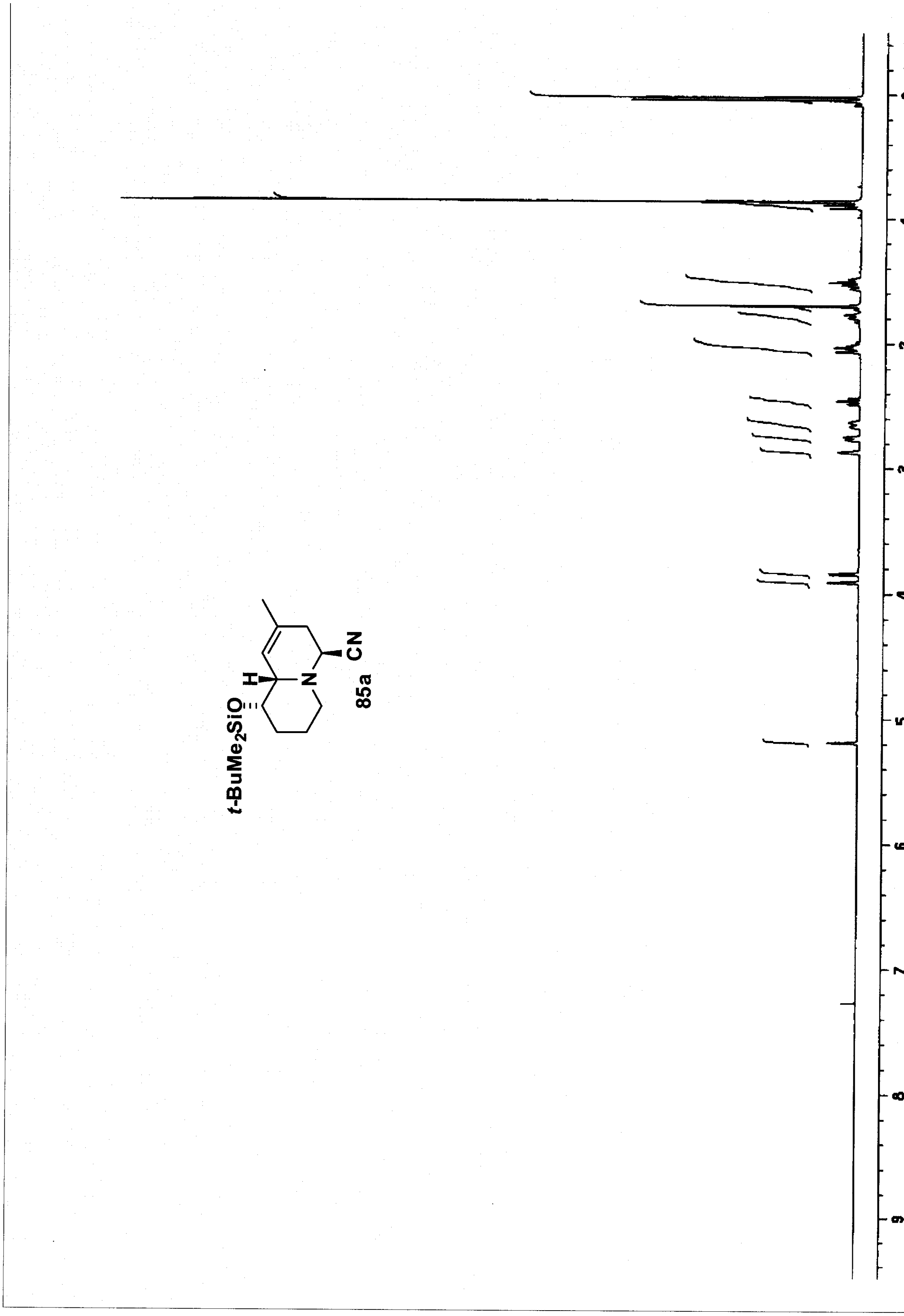
8.0



***cis*-9-(*tert*-Butyldimethylsiloxy)-2-methyl-*cis*-1,2-didehydro-4-cyanoquinolizidine (85a) (Acid-Promoted Cycloaddition).** A 25-mL, two-necked, round-bottomed flask equipped with a rubber septum and argon inlet adapter was charged with imine **84** (0.150 g, 0.49 mmol), 4Å molecular sieves (ca. 50 mg), and 6 mL of CH_2Cl_2. The reaction mixture was cooled at -78 °C while methanesulfonic acid (0.032 mL, 0.047 g, 0.49 mmol) was added dropwise via syringe over 1 min. The solution was stirred at -78 °C for 2 h, and then diluted with 15 mL of satd aq $NaHCO_3$ and 10 mL of CH_2Cl_2, and the aq layer was separated and extracted with three 12-mL portions of CH_2Cl_2. The combined organic layers were washed with 10 mL of brine, dried over $MgSO_4$, filtered, and concentrated to give 0.205 g of an orange oil. A solution of this material in 5 mL of CH_3CN in a 25-mL round-bottomed flask was stirred at 45 °C under argon for 1.5 h, and then allowed to cool to rt and concentrated to give 0.205 g of an orange oil. Purification by column chromatography on 10 g of silica gel (gradient elution with 2-5% EtOAc-hexanes containing 1% Et_3N) afforded 0.122 g (81%) of **85a** as a pale yellow oil: IR (film): 2929, 2856, 2804, 2759, 2222, 1472, 1462, 1388, 1368, 1252 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.19 (s, 1 H), 3.91 (s, 1 H), 3.84 (d, J = 6.1 Hz, 1 H), 2.87 (br s, 1 H), 2.75 (br d, J = 10.7 Hz, 1 H), 2.61-2.68 (m, 1 H), 2.43-2.49 (m, 1 H), 1.98-2.08 (m, 1 H), 2.05 (d, J = 16.5 Hz, 1 H), 1.75-1.83 (m, 1 H), 1.70 (s, 3 H), 1.47-1.58 (m, 2 H), 0.86 (s, 9 H), 0.05 (s, 3 H), 0.03 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 129.4, 123.4, 117.2, 69.2, 61.2, 53.6, 52.7, 33.7, 32.4, 26.0, 22.7, 20.5, 18.4, -4.2, -4.5; HRMS $[M+H]^+$ Calcd for $C_{17}H_{31}N_2OSi$: 307.2200. Found: 307.2198.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N
CN
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ppm
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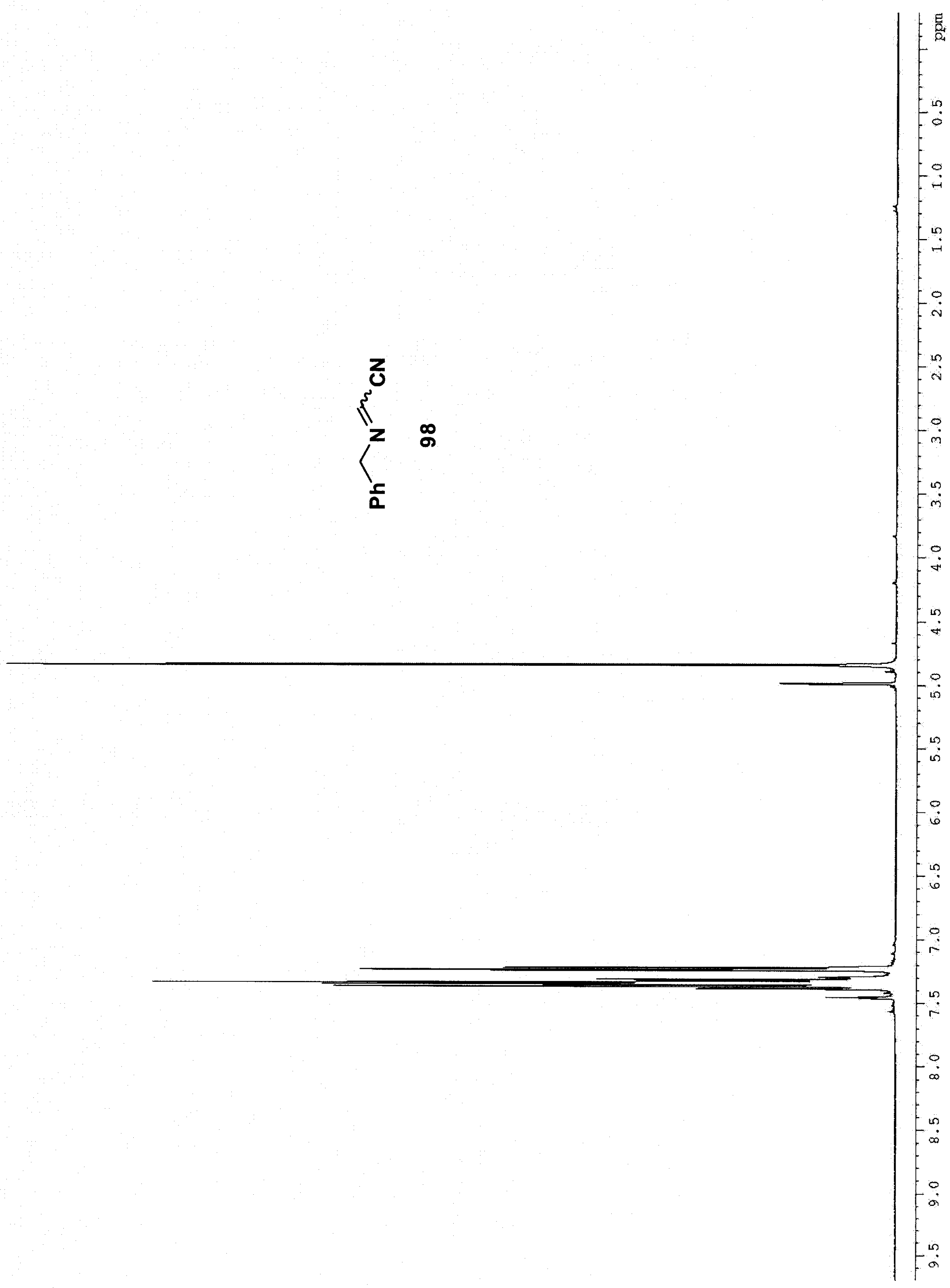
1
2
3
4
5
6
7
8
9

Experimental Procedures for Intermolecular Cycloadditions of Iminoacetonitriles

Benzyliminoacetonitrile (98). A 50-mL, two-necked, round-bottomed flask equipped with a rubber septum and argon inlet adapter was charged with NCS (0.311 g, 2.33 mmol) and 8 mL of THF. A solution of amine **97** (0.340 g, 2.33 mmol) in 4 mL of THF was added in one portion, and the reaction mixture was stirred at rt for 40 min. The resulting mixture was cooled at 0 °C while KOEt (1.41 M in ethanol, 1.65 mL, 2.33 mmol) was added dropwise via syringe over 3 min. The reaction mixture was stirred at 0 °C for 2 h, and then diluted with 15 mL of ether and 15 mL of water. The aqueous layer was separated and extracted with two 12-mL portions of ether, and the combined organic layers were washed with 15 mL of brine, dried over $MgSO_4$, filtered, and concentrated to give 0.395 g of an orange oil. Purification by column chromatography on 10 g of acetone-deactivated silica gel (elution with 5% EtOAc-hexanes) provided 0.240 g (72%) of **98** (88:12 mixture of *E* and *Z* imine isomers by ^{1}H NMR analysis) as a yellow oil: IR (film): 3226, 3065, 3033, 2906, 1622, 1496, 1454, 1361 cm^{-1}; For *E* isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (t, J = 1.6 Hz, 1 H), 7.29-7.35 (m, 3 H), 7.23 (d, J = 6.8 Hz, 2 H), 4.84 (d, J = 1.6 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.9, 129.2, 128.7, 128.3, 114.7, 66.1: For *Z* isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (t, J = 2.2 Hz, 1 H), 7.29-7.35 (m, 3 H), 7.23 (d, J = 6.8 Hz, 2 H), 4.99 (d, J = 2.2 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.6, 132.1, 129.1, 128.1, 114.7, 63.6.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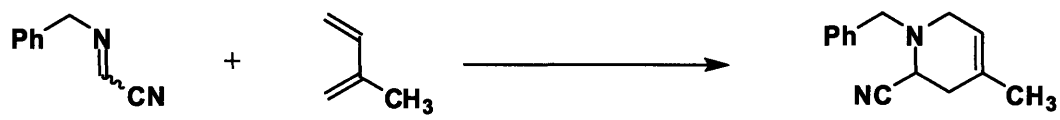
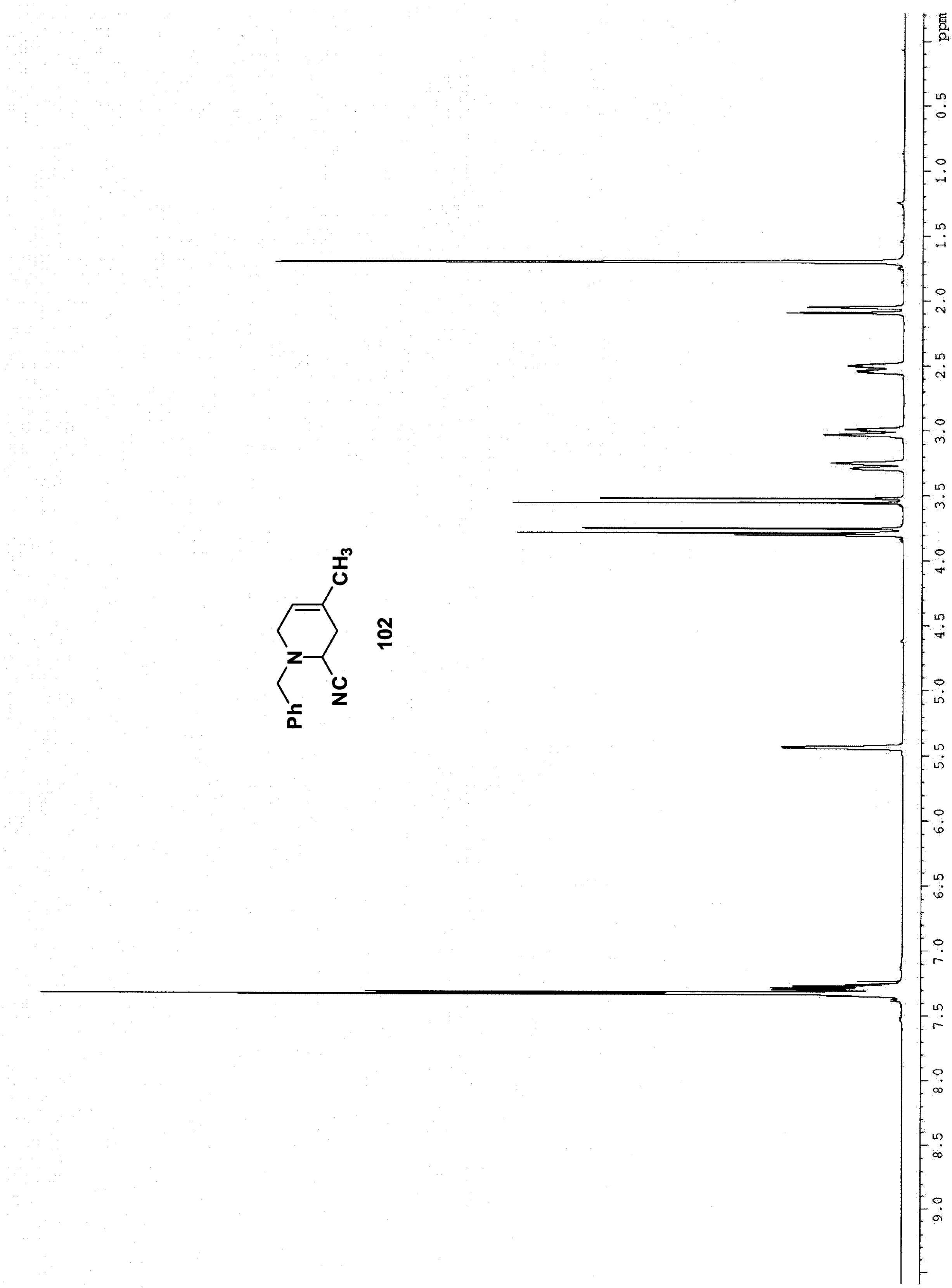
9.5



98 101 102

1-Benzyl-2-cyano-4-methyl-1,2,3,6-tetrahydopyridine (102). A 25-mL, two-necked, round-bottomed flask equipped with a rubber septum and argon inlet adapter was charged with imine **98** (0.120 g, 0.83 mmol), 4Å molecular sieves (ca. 0.040 g), isoprene (0.125 mL, 0.085 g, 1.25 mmol), and 5 mL of CH_2Cl_2. The solution was cooled at -78 °C while methanesulfonic acid (0.054 mL, 0.080 g, 0.83 mmol) was added via syringe. The reaction mixture was stirred at -78 °C for 1 h and then diluted with 12 mL of satd aq $NaHCO_3$, and the aqueous layer was separated and extracted with three 12-mL portions of CH_2Cl_2. The combined organic layers were washed with 10 mL of brine, dried over $MgSO_4$, filtered, and concentrated to give 0.170 g of an orange oil. Purification by column chromatography on 10 g of silica gel (gradient elution with 1-10% EtOAc-hexanes containing 1% Et_3N) afforded 0.152 g (91%) of **102** as a colorless oil: IR (CH_2Cl_2): 3027, 2932, 1603, 1496, 1453, 1383 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.25-7.35 (m, 5 H), 5.43 (d, J = 2.3 Hz, 1 H), 3.78 (dd, J = 6.5, 1.4 Hz, 1 H), 3.77 (d, J = 13.2 Hz, 1 H), 3.53 (d, J = 13.1 Hz, 1 H), 3.27 (dm, J = 16.5 Hz, 1 H), 3.01 (dm, J = 16.5 Hz, 1 H), 2.52 (dm, J = 17.2 Hz, 1 H), 2.07 (d, J = 17.2 Hz, 1 H), 1.70 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.8, 129.3, 129.2, 128.8, 128.0, 119.6, 116.8, 60.1, 49.3, 48.8, 34.0, 22.9; HRMS (m/z) $[M+H]^+$ calcd for $C_{14}H_{16}N_2$: 213.1386. Found: 213.1389.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6.0
6.5
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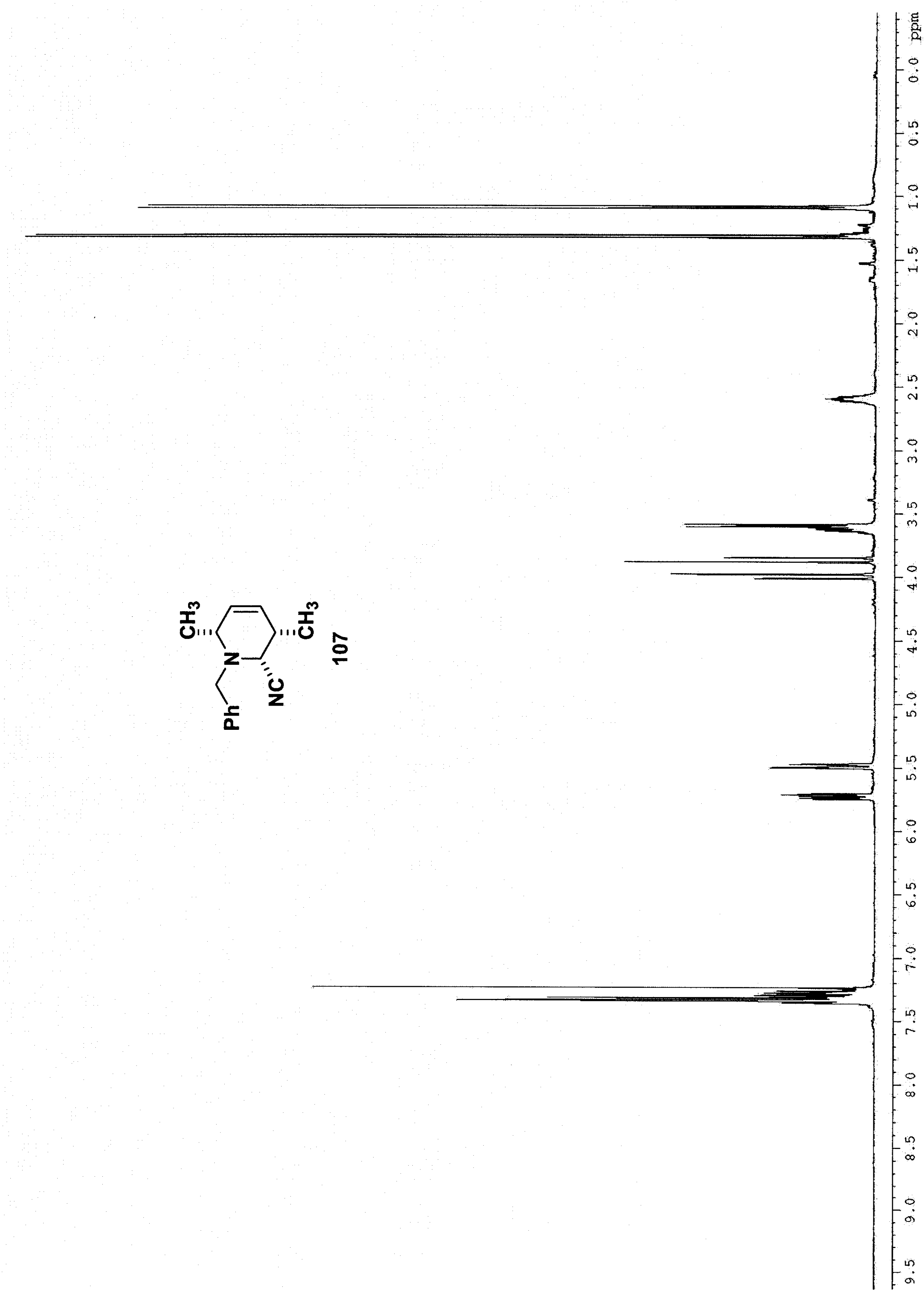
7.5
8.0
8.5
9.0

98 106 107

1-Benzyl-2-cyano-3,6-dimethyl-1,2,3,6-tetrahydopyridine (107). A 25-mL, two-necked, round-bottomed flask equipped with a rubber septum and argon inlet adapter was charged with imine **98** (0.090 g, 0.62 mmol), 4Å molecular sieves (ca. 0.030 g), 2,4-hexadiene (0.106 mL, 0.076 g, 0.93 mmol), and 3 mL of CH_2Cl_2. The solution was cooled at -78 °C while methanesulfonic acid (0.041 mL, 0.060 g, 0.62 mmol) was added via syringe. The reaction mixture was stirred at -78 °C for 1 h and then diluted with 12 mL of satd aq $NaHCO_3$, and the aqueous layer was separated and extracted with three 10-mL portions of CH_2Cl_2. The combined organic layers were washed with 10 mL of brine, dried over $MgSO_4$, filtered, and concentrated to give 0.170 g of an orange oil. Purification by column chromatography on 10 g of silica gel (elution with 10% EtOAc-hexanes containing 1% Et_3N) afforded 0.111 g (79%) of **107** as a yellow oil: IR (CH_2Cl_2): 3030, 2968, 2877, 1722, 1495, 1454, 1379, 1326 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.24-7.36 (m, 5 H), 5.73 (dt, J = 10.2, 3.2 Hz, 1 H), 5.48 (dt, J = 10.2, 1.8 Hz, 1 H), 3.99 (d, J = 13.7 Hz, 1 H), 3.86 (d, J = 13.7 Hz, 1 H), 3.56-3.65 (m, 1 H), 3.59 (d, J = 5.9 Hz, 1 H), 2.58-2.62 (m, 1 H), 1.32 (d, J = 7.0 Hz, 3 H), 1.09 (d, J = 7.4 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.7, 131.4, 128.9, 128.8, 127.8, 126.9, 119.5, 56.3, 53.0, 50.8, 32.4, 17.5, 14.9; HRMS (m/z) $[M+H]^+$ calcd for $C_{15}H_{18}N_2$: 227.1543. Found: 227.1550.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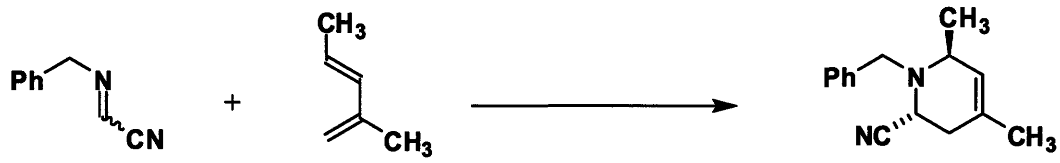
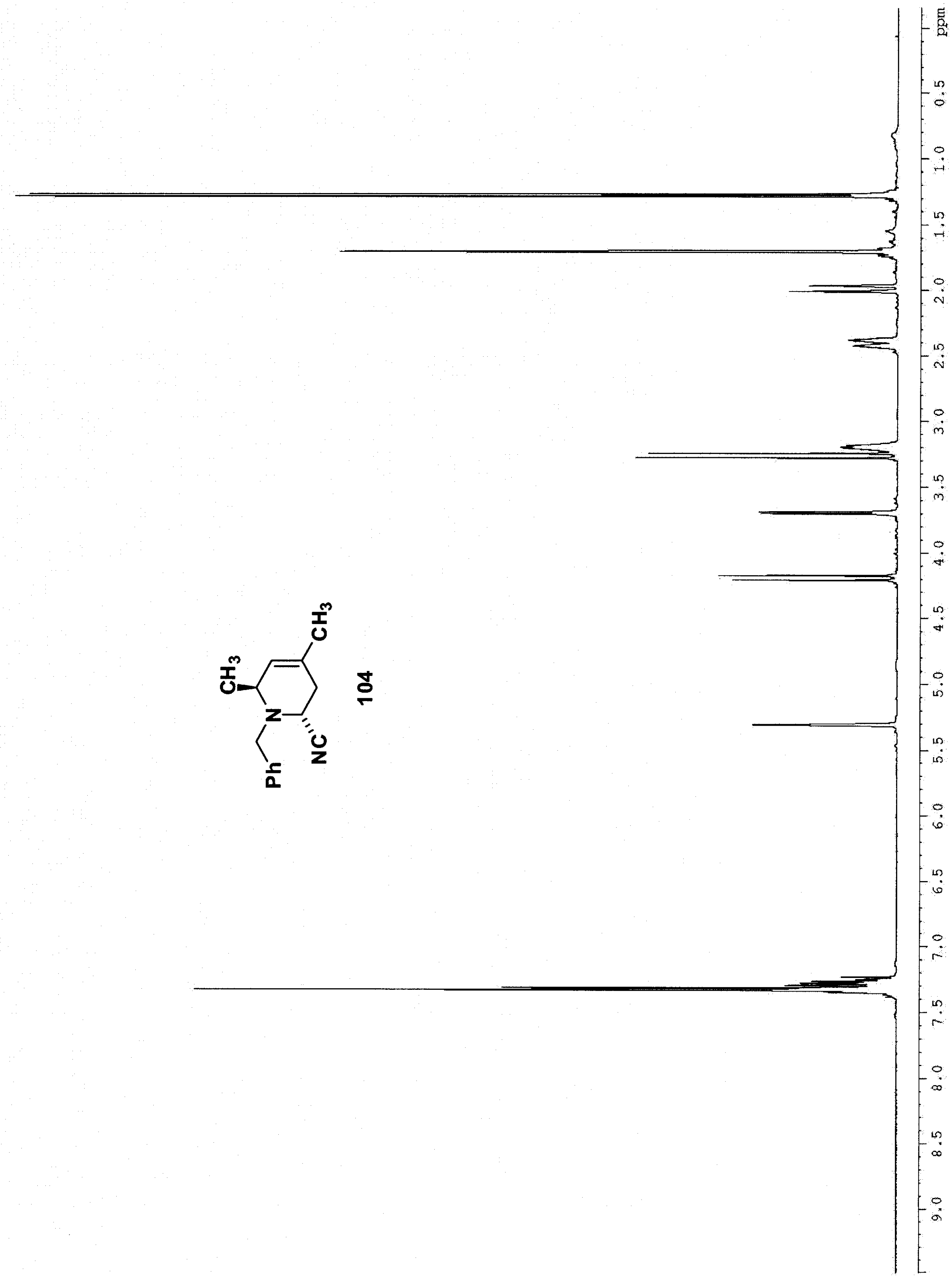
NC
CH3
CH3

107



98 103 104

1-Benzyl-2-cyano-4,6-dimethyl-1,2,3,6-tetrahydopyridine (104). A 25-mL, two-necked, round-bottomed flask equipped with a rubber septum and argon inlet adapter was charged with imine **98** (0.110 g, 0.76 mmol), 4Å molecular sieves (ca. 0.030 g), 2-methyl-1,3-pentadiene (0.130 mL, 0.094 g, 1.14 mmol), and 4 mL of CH_2Cl_2. The solution was cooled at -78 °C while methanesulfonic acid (0.049 mL, 0.073 g, 0.76 mmol) was added via syringe. The reaction mixture was stirred at -78 °C for 1 h and then diluted with 12 mL of satd aq $NaHCO_3$, and the aqueous layer was separated and extracted with three 10-mL portions of CH_2Cl_2. The combined organic layers were washed with 10 mL of brine, dried over $MgSO_4$, filtered, and concentrated to give 0.184 g of an orange oil. Purification by column chromatography on 10 g of silica gel (elution with 5% EtOAc-hexanes containing 1% Et_3N) afforded 0.150 g (87%) of **104** as a yellow oil: IR (CH_2Cl_2): 3064, 3029, 2972, 2917, 1495, 1454, 1382, 1345, 1330 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24-7.35 (m, 5 H), 5.31 (d, J = 1.5 Hz, 1 H), 4.19 (d, J = 13.7 Hz, 1 H), 3.69 (dd, J = 5.7, 1.7 Hz, 1 H), 3.26 (d, J = 13.7 Hz, 1 H), 3.18-3.22 (m, 1 H), 2.40 (dm, J = 17.0 Hz, 1 H), 1.99 (d, J = 17.0 Hz, 1 H), 1.70 (s, 3 H), 1.28 (d, J = 6.5 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.8, 129.1, 128.8, 128.6, 127.8, 126.3, 117.6, 55.9, 53.0, 48.3, 33.7, 22.9, 20.6; HRMS (m/z) $[M]^+$ calcd for $C_{15}H_{18}N_2$: 227.1543. Found: 227.1545.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Ph
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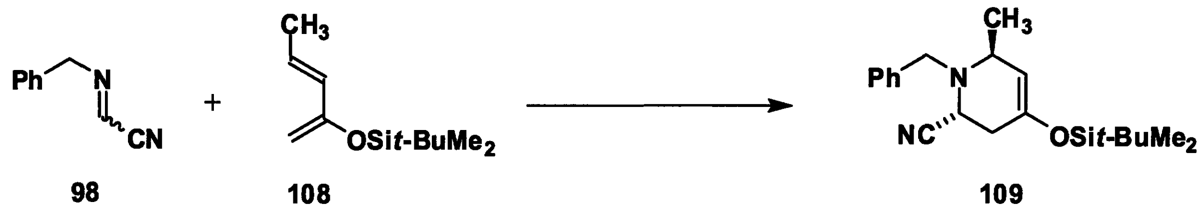
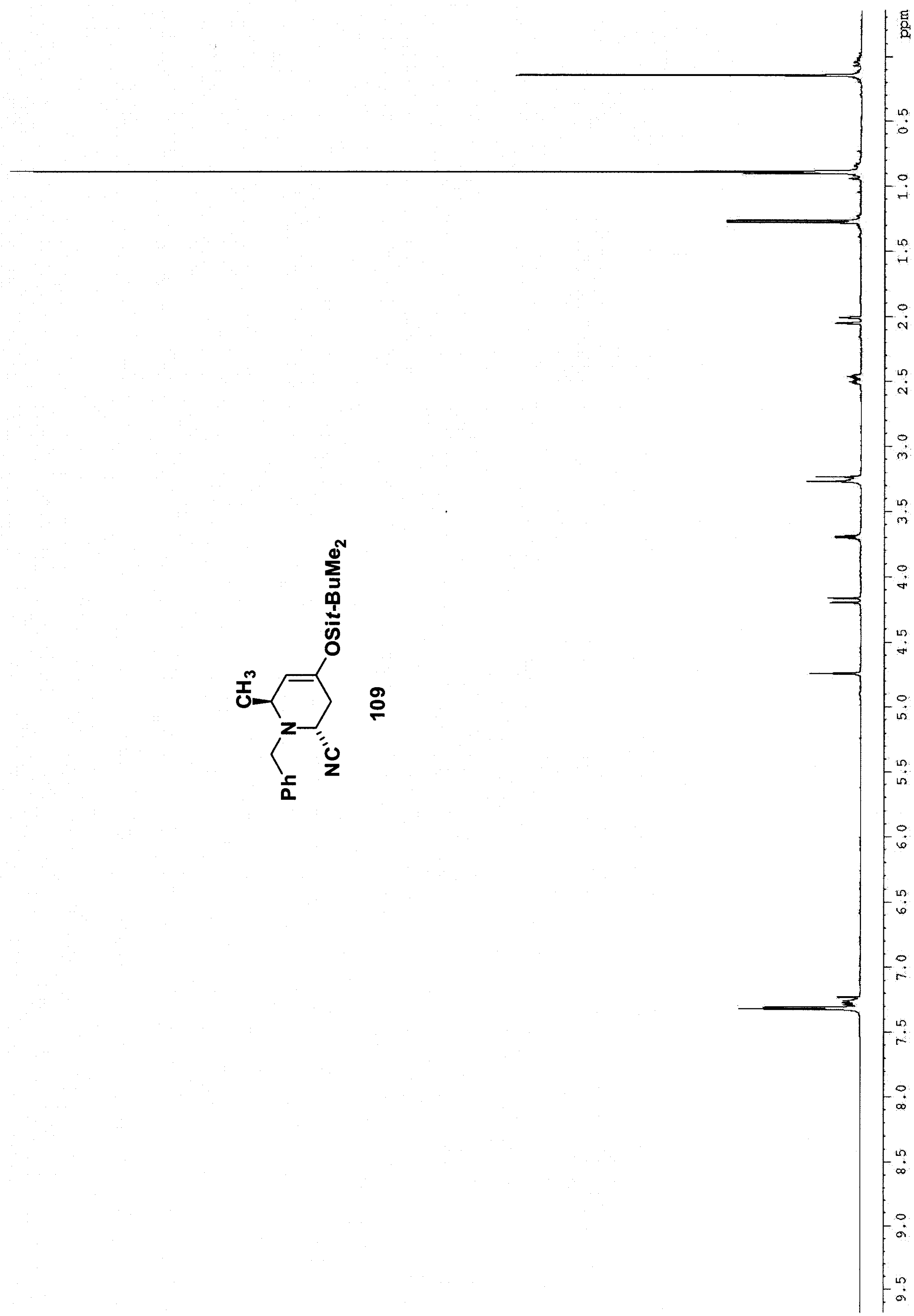
CH_3
CH_3
NC
104

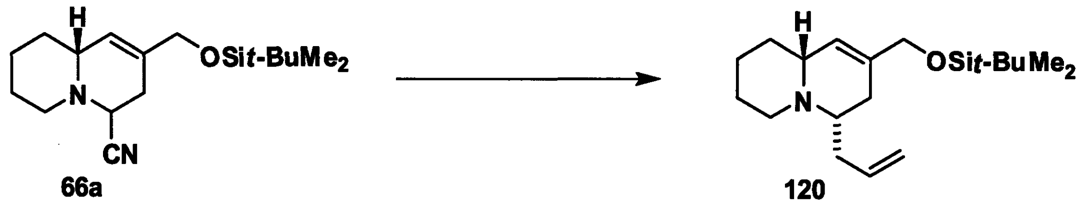


1-Benzyl-4-(*tert*-butyldimethylsiloxy)-2-cyano-6-methyl-1,2,3,6-tetrahydopyridine (109). A 25-mL, two-necked, round-bottomed flask equipped with a rubber septum and argon inlet adapter was charged with imine **98** (0.250 g, 1.73 mmol), 4Å molecular sieves (ca. 0.100 g), 2-(*tert*-butyldimethylsiloxy)-1,3-pentadiene (0.515 g, 2.60 mmol), and 18 mL of CH_2Cl_2. The solution was cooled at -78 °C while methanesulfonic acid (0.112 mL, 0.166 g, 1.73 mmol) was added via syringe. The reaction mixture was stirred at -78 °C for 1 h and then diluted with 20 mL of satd aq $NaHCO_3$, and the aqueous layer was separated and extracted with three 20-mL portions of CH_2Cl_2. The combined organic layers were washed with 15 mL of brine, dried over $MgSO_4$, filtered, and concentrated to give 0.184 g of an orange oil. A solution of this material in 10 mL of CH_3CN in a 25-mL round-bottomed flask was stirred at 45 °C under argon for 1.5 h, and then allowed to cool to rt and concentrated to give 0.195 g of an orange oil. Purification by column chromatography on 25 g of silica gel (elution with 2% EtOAc-hexanes containing 1% Et_3N) afforded 0.302 g (51%) of **109** as a yellow oil: IR (CH_2Cl_2): 3065, 3032, 2931, 2858, 1682, 1496, 1463, 1373, 1256 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.25-7.32 (m, 5 H), 4.74 (t, J = 2.1 Hz, 1 H), 4.18 (d, J = 13.7 Hz, 1 H), 3.70 (dd, J = 5.7, 1.8 Hz, 1 H), 3.25 (d, J = 13.7 Hz, 1 H), 3.24-3.30 (m, 1 H), 2.48 (dm, J = 16.7 Hz, 1 H), 2.03 (dt, J = 16.7, 1.8 Hz, 1 H), 1.27 (d, J = 6.3 Hz, 3 H), 0.89 (s, 9 H), 0.15 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.7, 137.8, 129.0, 128.8, 127.9, 117.2, 108.6, 55.5, 52.3, 48.7, 33.7, 25.8, 21.4, 18.2, -4.2; HRMS (m/z) $[M]^+$ calcd for $C_{20}H_{30}N_2OSi$: 343.2200. Found: 343.2205.



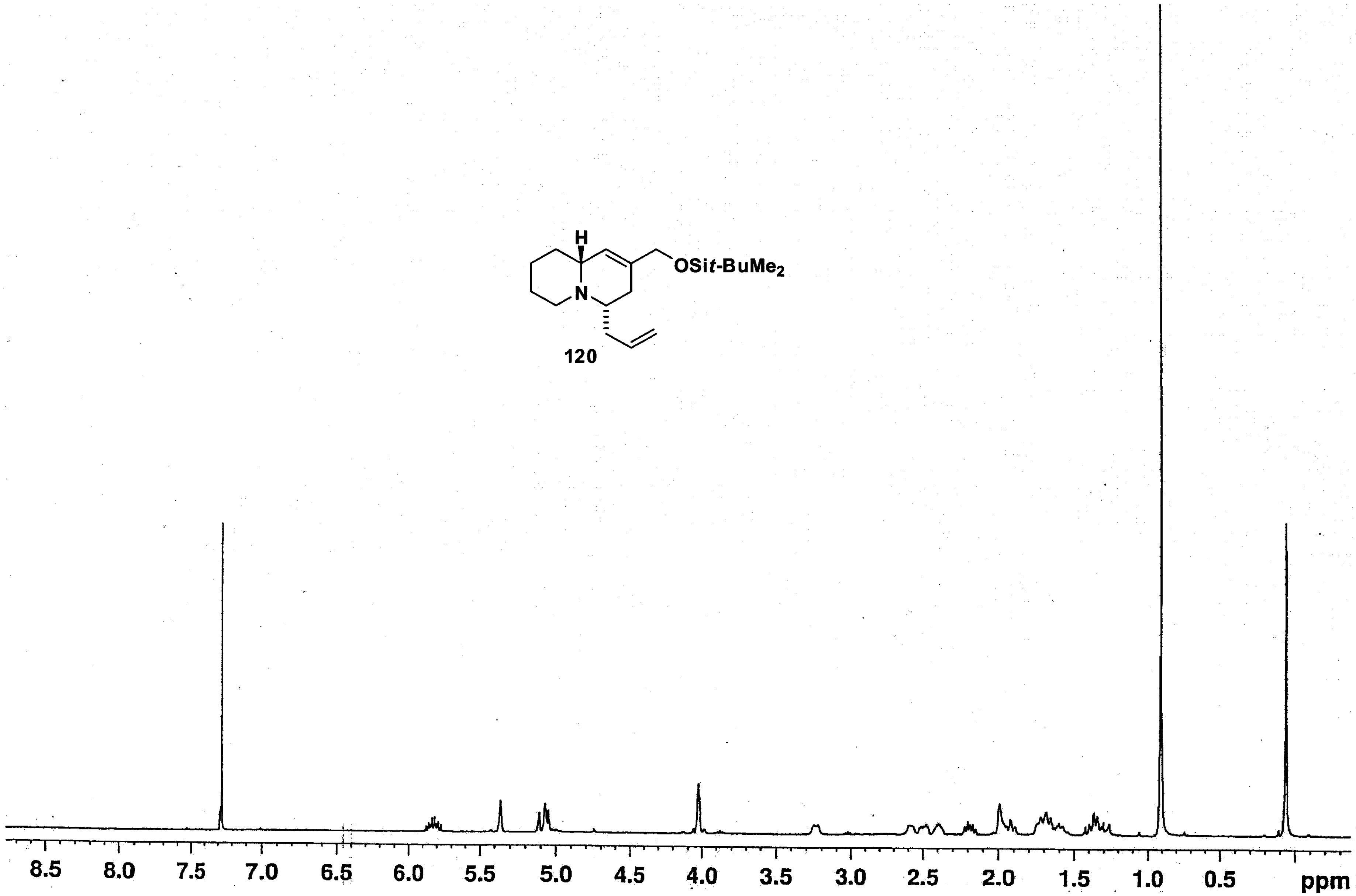
109

Experimental Procedures for Transformations of α-Amino Nitriles



2-(*tert*-Butyldimethylsiloxymethyl)*trans*-1,2-didehydro-4-(2-propene)quinolizidine (120). A 25-mL, two-necked, round-bottomed flask equipped with a rubber septum and argon inlet adapter was charged with diisopropylamine (0.144 mL, 0.104 g, 1.03 mmol) and 3 mL of THF. The solution was cooled at 0 °C while *n*-BuLi (2.54 M in hexanes, 0.406 mL, 1.03 mmol) was added dropwise via syringe over 1 min. The resulting solution was stirred at 0 °C for 10 min and then cooled at -78 °C while a precooled (-78 °C) solution of amino nitrile **66a** (0.15 g, 0.49 mmol) in 2 mL of THF was added dropwise via cannula over 1 min. The resulting solution was stirred at -78 °C for 1.5 h, and then allyl bromide (0.089 mL, 0.125 g, 1.03 mmol) was added rapidly dropwise. The reaction mixture was stirred at 0 °C for 1 h and then diluted with 15 mL of water and 15 mL of ether. The aqueous layer was separated and extracted with three 10-mL portions of ether, and the combined organic layers were washed with 10 mL of brine, dried over K_2CO_3, filtered, and concentrated to give 0.201 g of an orange oil that was used immediately in the next step without further purification.

A 25-mL, two-necked, round-bottomed flask equipped with a rubber septum and argon inlet adaptor was charged with $NaBH_3CN$ (0.123 g, 1.96 mmol) and 3 mL of CH_3CN. Acetic acid (0.225 mL, 0.235 g, 3.92 mmol) was added dropwise via syringe over 1 min. The resulting solution was stirred at rt for 30 min, and then a solution of the crude nitrile (0.170 g, 0.49 mmol) prepared in the previous step in 2 mL of CH_3CN was added over 1 min by cannula. The reaction mixture was stirred at rt for 2 h and then diluted with 15 mL of water and 12 mL of CH_2Cl_2. The aqueous layer was separated and extracted with three 10-mL portions of CH_2Cl_2, and the combined organic layers were washed with 10 mL of brine, dried over $MgSO_4$, filtered, and concentrated to give 0.201 g of an orange oil. Column chromatography on 10 g of silica gel (elution with 10% EtOAc-hexanes containing 1% Et_3N) afforded 0.136 g (86%) of the quinolizidine **120** as a pale yellow oil: IR (film): 3076, 2930, 2856, 2784, 2739, 1641, 1462, 1442, 1361, 1255 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.82 (ddt, J = 17.5, 10.3, 6.9 Hz, 1 H), 5.36 (s, 1 H), 5.05-5.11 (m, 2 H), 4.03 (s, 2 H), 3.24 (br d, J = 11.4 Hz, 1 H), 2.59 (br s, 1 H), 2.46-2.53 (m, 1 H), 2.37-2.41 (m, 1 H), 2.17-2.20 (m, 1 H), 1.89-1.99 (m, 3 H), 1.58-1.74 (m, 4 H), 1.26-1.42 (m, 2 H), 0.90 (s, 9 H), 0.07 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.8, 135.5, 124.5, 117.4, 66.5, 62.4, 59.0, 38.0, 33.2, 32.5, 26.7, 26.7, 26.4, 24.8, 18.8, -4.8; HRMS (m/z) $[M+H]^+$ calcd for $C_{19}H_{36}NOSi$, 322.2566; found, 322.2566.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2.0
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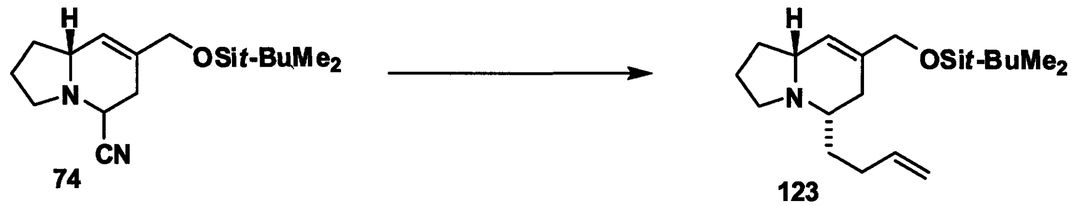
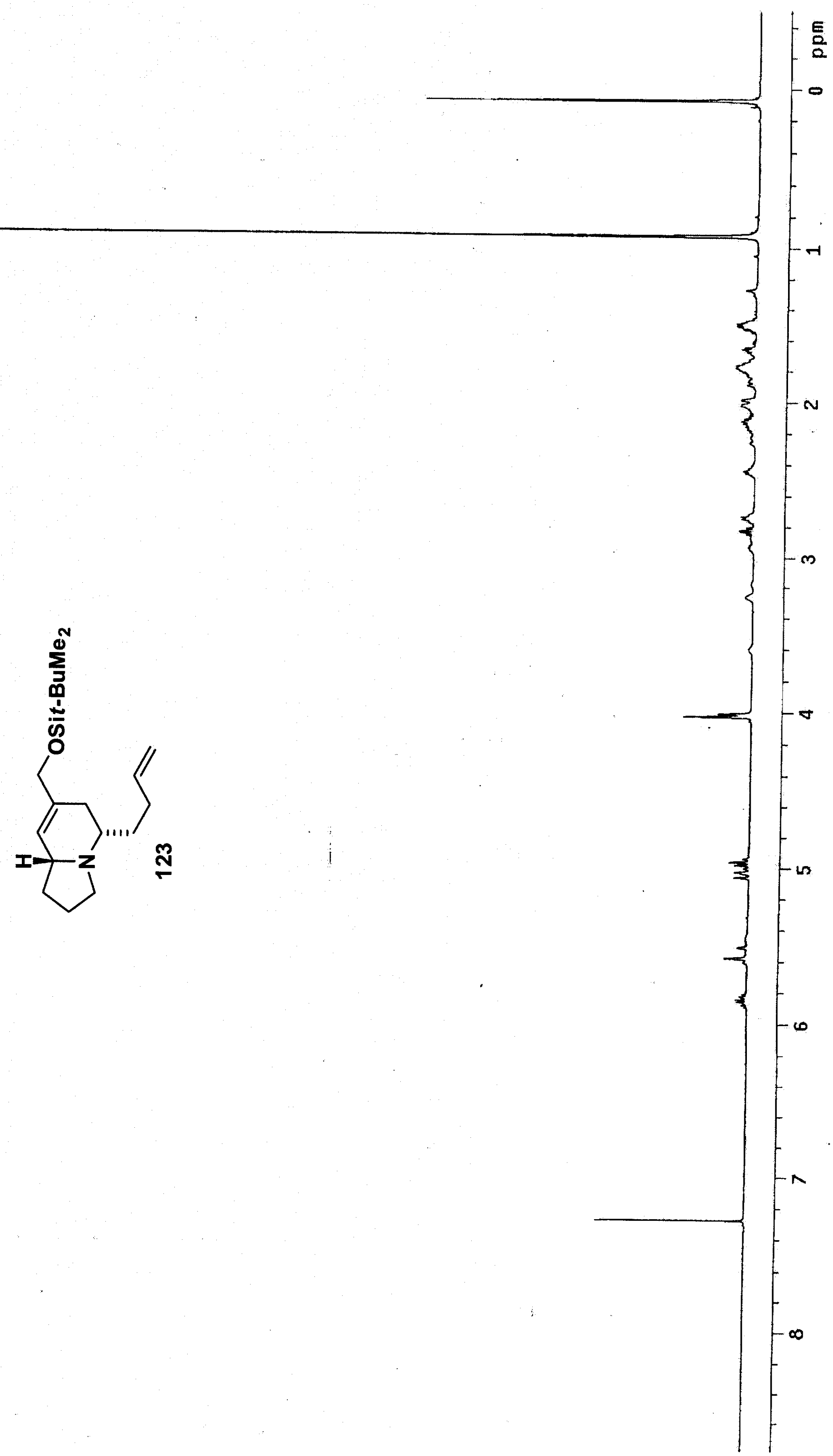
ppm



2-(*tert*-Butyldimethylsiloxymethyl)*trans*-1,2-didehydro-4-(3-butene)indolizidine (123). A 25-mL, two-necked, round-bottomed flask equipped with a rubber septum and argon inlet adapter was charged with diisopropylamine (0.200 mL, 0.145 g, 1.43 mmol) and 3 mL of THF. The solution was cooled at 0 °C while *n*-BuLi (2.41 M in hexanes, 0.593 mL, 1.43 mmol) was added dropwise via syringe over 1 min. The resulting solution was stirred at 0 °C for 10 min and then cooled at -78 °C while a precooled (-78 °C) solution of amino nitrile **74** (0.20 g, 0.68 mmol) in 2 mL of THF was added dropwise via cannula over 1 min. The resulting solution was stirred at -78 °C for 1.5 h, and then 4-bromobutene (0.076 mL, 0.101 g, 0.75 mmol) was added rapidly dropwise. The reaction mixture was stirred at 0 °C for 1 h and then diluted with 12 mL of water and 10 mL of ether. The aqueous layer was separated and extracted with three 10-mL portions of ether, and the combined organic layers were washed with 10 mL of brine, dried over K_2CO_3, filtered, and concentrated to give 0.236 g of an orange oil that was used immediately in the next step without further purification.

A 25-mL, two-necked, round-bottomed flask equipped with a rubber septum and argon inlet adaptor was charged with $NaBH_3CN$ (0.171 g, 2.72 mmol) and 3 mL of CH_3CN. Acetic acid (0.313 mL, 0.327 g, 5.44 mmol) was added dropwise via syringe over 1 min. The resulting solution was stirred at rt for 30 min, and then a solution of the crude nitrile (0.236 g, 0.68 mmol) prepared in the previous step in 2 mL of CH_3CN was added over 1 min by cannula. The reaction mixture was stirred at rt for 2 h and then diluted with 15 mL of water and 12 mL of CH_2Cl_2. The aqueous layer was separated and extracted with three 10-mL portions of CH_2Cl_2, and the combined organic layers were washed with 10 mL of brine, dried over $MgSO_4$, filtered, and concentrated to give 0.241 g of an orange oil. Column chromatography on 10 g of silica gel (elution with 5% EtOAc-hexanes containing 1% Et_3N) afforded 0.107 g (49%) of the indolizidine **123** (63:37 mixture of *trans*- and *cis*-fused indolizidines by ^1H NMR analysis) as a yellow oil: IR (film): 3077, 2956, 2929, 2856, 1641, 1471, 1361 cm^{-1}; For *trans*-fused indolizidine: ^1H NMR (500 MHz, $CDCl_3$) δ 5.85 (ddt, J = 17.0, 10.4, 6.6 Hz, 1 H), 5.58 (s, 1 H), 5.05 (dd, J = 17.1, 1.6 Hz, 1 H), 4.97 (d, J = 10.3 Hz, 1H), 4.02 (s, 2 H), 3.26 (br s, 1 H), 2.82 (dt, J = 5.9, 2.7 Hz,1 H), 2.74 (app q, J = 8.8 Hz, 1 H), 2.44 (app q, J = 5.9 Hz, 1 H), 1.95-2.26 (m, 4 H), 1.61-1.89 (m, 4 H), 1.46-1.55 (m, 2 H), 0.92 (s, 9 H), 0.08 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.9, 135.7, 123.7, 114.8, 66.7, 61.1, 56.1, 45.7, 34.5, 30.6, 29.5, 28.3, 26.2, 22.1, 18.7, -5.0: For *cis*-fused indolizidine: ^1H NMR (500 MHz, $CDCl_3$) δ 5.85 (ddt, J = 17.0, 10.4, 6.6 Hz, 1 H), 5.51 (s, 1 H), 5.02 (dd, J = 17.2, 1.6 Hz, 1 H), 4.95 (d, J = 10.3 Hz, 1H), 4.00 (s, 2 H), 3.60 (br s, 1 H), 2.86-2.95 (m, 1 H), 2.74 (app q, J = 8.8 Hz, 1 H), 2.44 (app q, J = 5.9 Hz, 1 H), 1.95-2.26 (m, 4 H), 1.61-1.89 (m, 4 H), 1.46-1.55 (m, 2 H), 0.92 (s, 9 H), 0.08 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.1, 133.2, 123.7, 114.6, 67.0, 54.3, 53.2, 50.3, 32.5, 31.3, 30.4, 26.2, 24.2, 22.8, 18.7, -5.0; HRMS (m/z) $[M+H]^+$ calcd for $C_{19}H_{36}NOSi$, 322.2566; found, 322.2561.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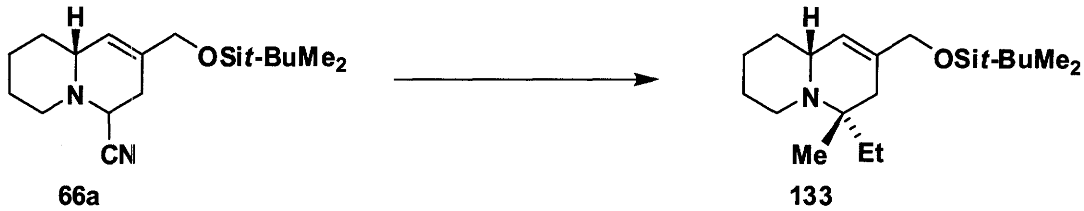
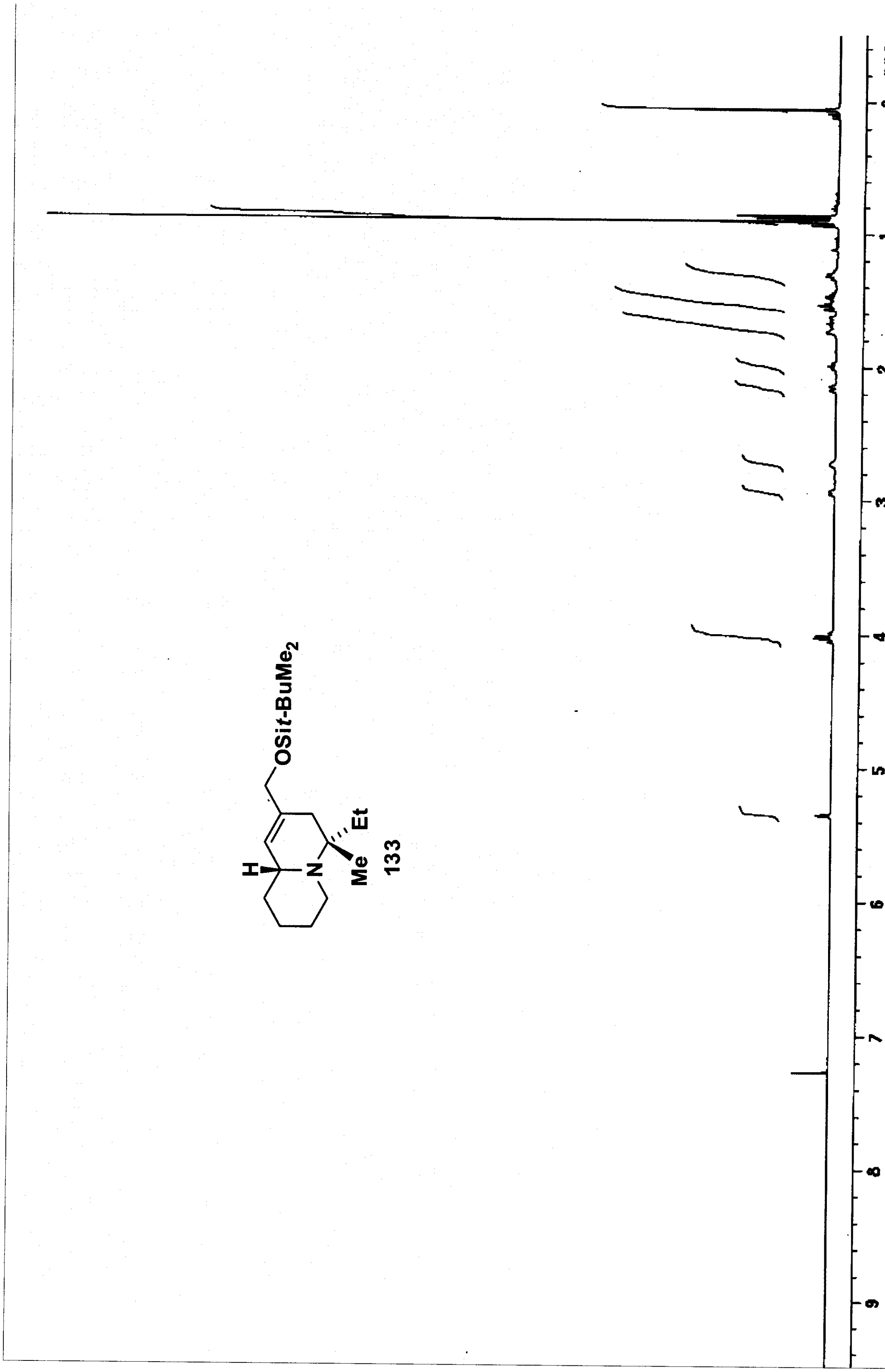


2-(*tert*-Butyldimethylsiloxymethyl)-1,2-didehydro-*cis*-4-methyl-4-ethylquinolizidine (133). A 50-mL, two-necked, round-bottomed flask equipped with a rubber septum and argon inlet adapter was charged with 7 mL of THF and diisopropylamine (0.259 mL, 0.187 g, 1.85 mmol). The solution was cooled at 0 °C while *n*-BuLi (2.32 M in hexanes, 0.797 mL, 1.85 mmol) was added dropwise via syringe over 1 min. The resulting solution was stirred at 0 °C for 10 min and then cooled at -78 °C while a precooled (-78 °C) solution of amino nitrile **66a** (0.270 g, 0.88 mmol) in 3 ml of THF was added dropwise over 2 min. The resulting solution was stirred at -78 °C for 2 h, and then ethyl iodide (0.211 mL, 0.412 g, 2.64 mmol) was added rapidly dropwise. The reaction mixture was stirred at 0 °C for 1 h and then diluted with 20 ml of water and extracted with three 30-mL portions of ether. The combined organic layers were washed with 25 mL of brine, dried over K_2CO_3, filtered, and concentrated to give 0.281 g of orange oil that was used immediately in the next step without further purification.

A 50-mL, round-bottomed flask equipped with a rubber septum and argon inlet needle was charged with the crude nitrile from the preceding step (0.281 g, 0.88 mmol) and 4 mL of ether. The solution was cooled at -78 °C while methylmagnesium bromide solution (3.0 M in ether, 0.88 mL, 2.64 mmol) cooled at 0 °C was added dropwise via cannula over 2 min. The resulting solution was allowed to slowly warm to rt over 4.5 h and then was diluted with 15 ml of satd aq NH_4Cl solution and 15 mL of ether. The aqueous layer was separated and extracted with three 20-mL portions of ether. The combined organic layers were washed with 20 mL of brine, dried over $MgSO_4$, filtered, and concentrated to afford 0.270 g of red oil. Column chromatography on 10 g of silica gel (gradient elution with 5-20% EtOAchexanes containing 1% Et_3N) provided 0.176 g (63%) of **133** as a yellow oil: IR (film): 2930, 2856, 2787, 2741, 1472, 1463, 1380, 1361 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.35 (s, 1 H), 4.03 (d, J = 13.1 Hz, 1 H), 3.99 (d, J = 13.1, 1 H), 2.94 (br d, J = 11.3 Hz, 1 H), 2.72 (br d, J = 8.2 Hz, 1 H), 2.15 (d, J = 16.5 Hz, 1 H), 1.99 (app dt, J = 11.5, 2.3 Hz, 1 H), 1.61-1.78 (m, 3 H), 1.42-1.58 (m, 4 H), 1.27-1.35 (m, 2 H), 0.90 (s, 9 H), 0.88 (t, J = 7.5 Hz, 3 H), 0.86 (s, 3 H), 0.06 (s, 3 H), 0.06 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 133.9, 123.5, 66.6, 56.9, 54.5, 45.2, 36.5, 33.5, 33.3, 26.9, 26.1, 25.3, 18.6, 14.6, 8.0, -5.0, -5.1; HRMS (m/z) $[M]^+$ calcd for $C_{18}H_{35}NOSi$, 323.2639; found, 323.2647.



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Me
Et
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ppm
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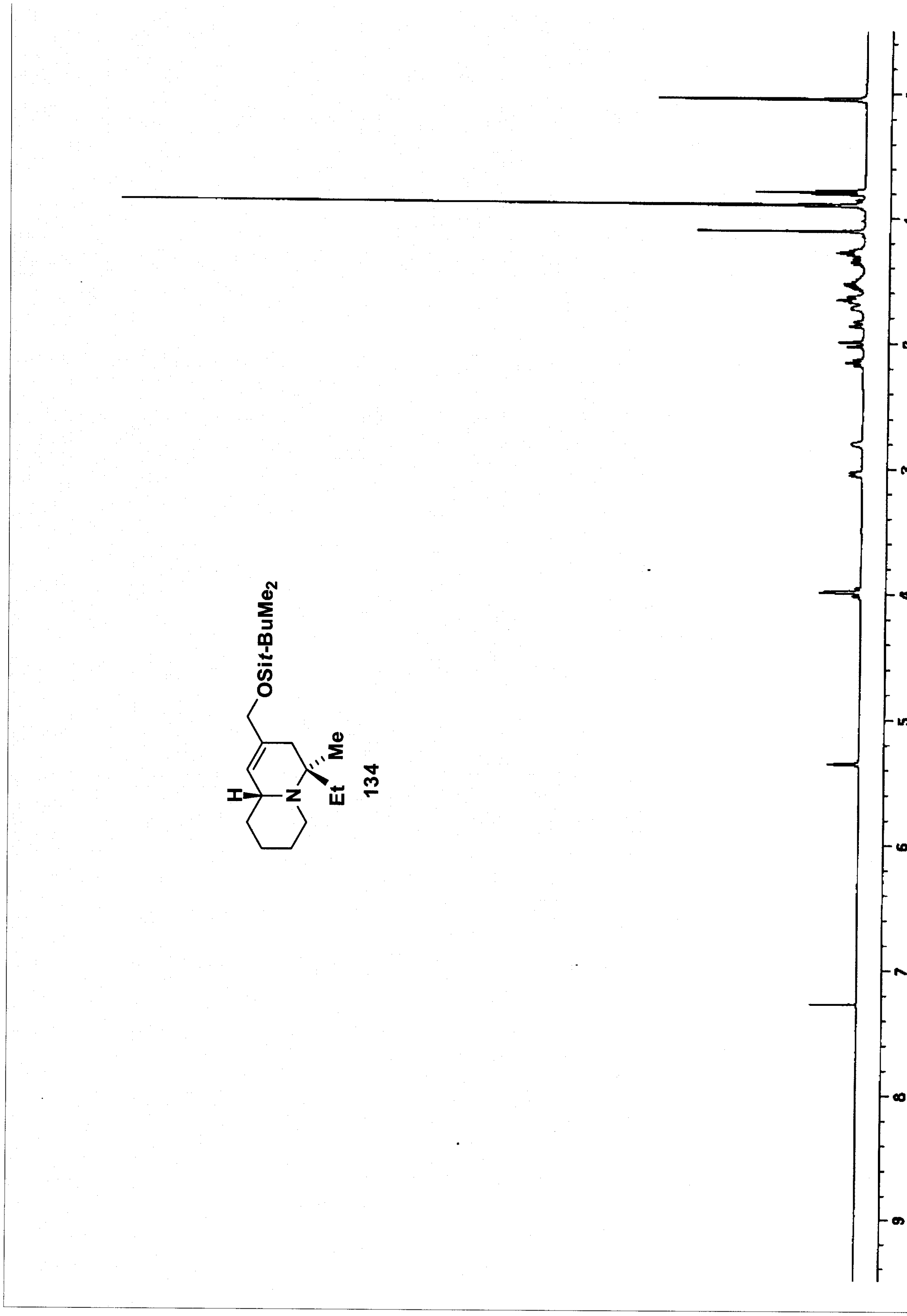
3
4
5
6
7
8
9

66a 134

2-(*tert*-Butyldimethylsiloxymethyl)-1,2-didehydro-4-methyl-*cis*-4-ethylquinolizidine (134). A 25-mL, two-necked, round-bottomed flask equipped with a rubber septum and argon inlet adapter was charged with 4 mL of THF and diisopropylamine (0.202 mL, 0.146 g, 1.44 mmol). The solution was cooled at 0 °C while *n*-BuLi (2.20 M in hexanes, 0.654 mL, 1.44 mmol) was added dropwise via syringe over 1 min. The resulting solution was stirred at 0 °C for 10 min and then cooled at -78 °C while a precooled (-78 °C) solution of amino nitrile **66a** (0.210 g, 0.69 mmol) in 2 ml of THF was added dropwise over 1 min. The resulting solution was stirred at -78 °C for 2 h, and then methyl iodide (0.106 mL, 0.242 g, 1.71 mmol) was added rapidly dropwise. The reaction mixture was stirred at 0 °C for 1 h and then diluted with 20 ml of water and extracted with three 20-mL portions of ether. The combined organic layers were washed with 25 mL of brine, dried over K_2CO_3, filtered, and concentrated to give 0.226 g of orange oil that was used immediately in the next step without further purification.

A 25-mL, round-bottomed flask equipped with a rubber septum and argon inlet needle was charged with crude nitrile from preceding step (0.226 g, 0.69 mmol) and 4 mL of ether. The solution was cooled at –78 °C while ethylmagnesium bromide solution (3.0 M in ether, 0.69 mL, 2.01 mmol) cooled at 0 °C was added dropwise via cannula over 1 min. The resulting solution was allowed to slowly warm to rt over 4.5 h and then was diluted with 15 ml of satd aq NH_4Cl solution and 15 mL of ether. The aqueous layer was separated and extracted with three 15-mL portions of ether. The combined organic layers were washed with 20 mL of brine, dried over $MgSO_4$, filtered, and concentrated to afford 0.238 g of red oil. Column chromatography on 10 g of silica gel (elution 5% EtOAc-hexanes containing 1% Et_3N) provided 0.144 g (64%) of **134** as a yellow oil: IR (film): 2930, 2856, 2785, 1462, 1379, 1360, 1333 1252 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.35 (s, 1 H), 4.00 (d, J = 13.1 Hz, 1 H), 3.97 (d, J = 13.1, 1 H), 3.04 (d, J = 11.0 Hz, 1 H), 2.80 (br d, J = 6.1 Hz, 1 H), 2.15 (dt, J = 11.3, 2.1 Hz, 1 H), 2.01 (d, J = 17.1 Hz, 1 H), 1.85 (d, J = 17.1 Hz, 1 H), 1.62-1.75 (m, 3 H), 1.46-1.58 (m, 2 H), 1.25-1.38 (m, 3 H), 1.10 (s, 3 H), 0.89 (s, 9 H), 0.79 (t, J = 7.5 Hz, 3 H), 0.05 (s, 3 H), 0.04 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 134.1, 124.2, 66.5, 56.4, 55.1, 45.1, 35.6, 33.3, 27.0, 26.2, 26.1, 25.2, 20.1, 18.6, 9.6, -5.0, -5.1; HRMS (m/z) $[M]^+$ calcd for $C_{18}H_{35}NOSi$, 323.2639; found $[M-CH_3]^+$; 308.2405.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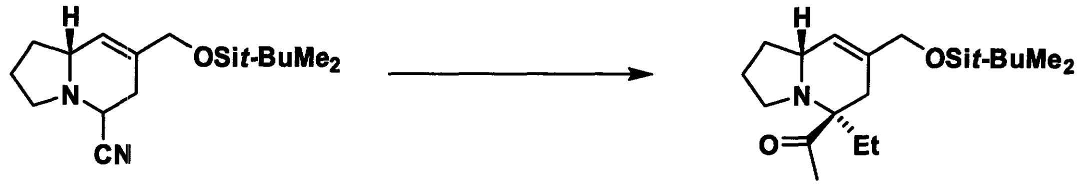
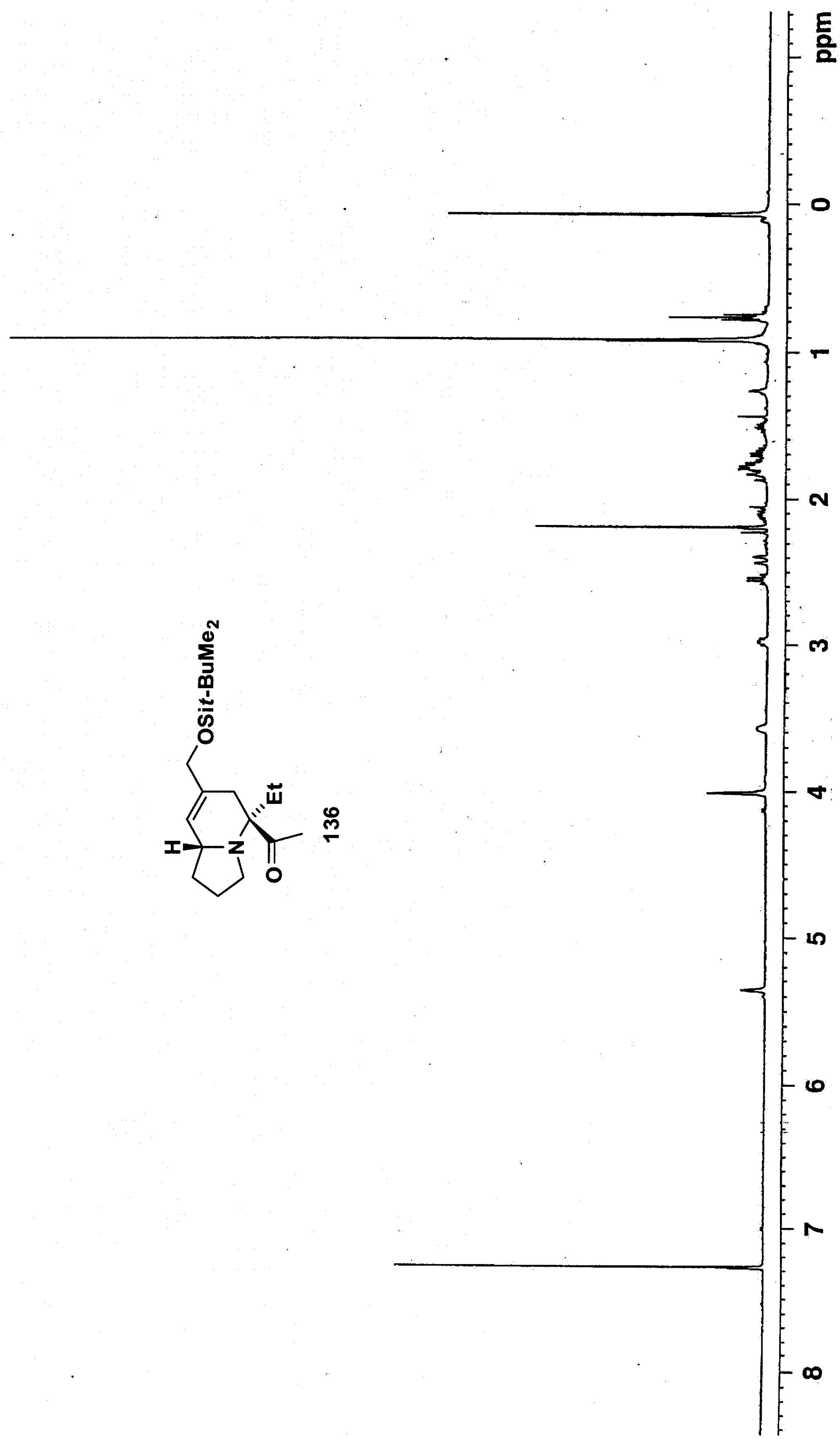


74 136

1-[2-(*tert*-Butyldimethylsiloxymethyl)-1,2-didehydro-4-ethylindolizidinyl)]ethanone (136). A 25-mL, two-necked, round-bottomed flask equipped with a rubber septum and argon inlet adapter was charged with 3 mL of THF and diisopropylamine (0.150 mL, 0.108 g, 1.07 mmol). The solution was cooled at 0 °C while *n*-BuLi (2.54 M in hexanes, 0.421 mL, 1.07 mmol) was added dropwise via syringe over 1 min. The resulting solution was stirred at 0 °C for 10 min and then cooled at -78 °C while a precooled (-78 °C) solution of amino nitrile **74** (0.150 g, 0.51 mmol) in 2 mL of THF was added dropwise over 1 min. The resulting solution was stirred at -78 °C for 2 h, and then ethyl iodide (0.102 mL, 0.199 g, 1.28 mmol) was added rapidly dropwise. The reaction mixture was stirred at 0 °C for 1 h and then diluted with 20 mL of water and extracted with three 10-mL portions of ether. The combined organic layers were washed with 8 mL of brine, dried over K_2CO_3, filtered, and concentrated to give 0.153 g of orange oil that was used immediately in the next step without further purification.

A 25-mL, round-bottomed flask containing the crude amino nitrile (0.153 g, 0.51 mmol) from the preceding step was fitted with a rubber septum and argon inlet needle, purged with argon, and charged with 3 mL of ether. The solution was cooled at -10 °C while MeLi solution (1.52 M in ether, 0.503 mL, 0.76 mmol) was added dropwise via syringe over 1 min. The resulting solution was stirred for 90 min while it slowly warmed to 0 °C and then was diluted with 10 mL of water. The aqueous layer was extracted with three 10-mL portions of ether, and the combined organic layers were washed with 10 mL of brine, dried over $MgSO_4$, filtered, and concentrated to a volume of ca. 5 mL. The flask was then fitted with an argon inlet adapter and purged with argon. Silica gel (1.5 g) was added and the resulting slurry was stirred at rt for 12 h. The mixture was then filtered, with the aid of 10 ml of ether, and concentrated to afford 0.247 g of yellow oil. Column chromatography on 8 g of silica gel (elution with 5% EtOAc-hexanes containing 1% Et_3N) provided 0.116 g (67%) of **136** as a yellow oil: IR (film): 2957, 2856, 1714, 1463, 1422, 1388, 1348 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.36 (s, 1 H), 4.01 (s, 2 H), 3.58 (br s, 1 H), 2.98 (s, 1 H), 2.55 (q, J = 8.2 Hz, 1 H), 2.41 (d, J = 16.8, 1 H), 2.19 (s, 3 H), 2.06-2.13 (m, 1 H), 1.66-1.88 (m, 5 H), 1.48-1.55 (m, 1 H), 0.91 (s, 9 h), 0.77 (t, J = 7.6 Hz, 3 H), 0.07 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 211.3, 134.0, 123.8, 69.8, 66.7, 56.3, 45.4, 31.1, 30.7, 26.1, 25.0, 24.5, 22.4, 18.7, 8.5, -5.0; HRMS (m/z) $[M+H]^+$ calcd for $C_{19}H_{36}NO_2Si$, 338.2510; found, 338.2493.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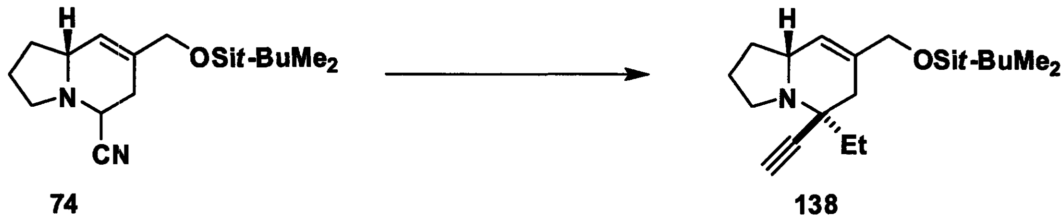
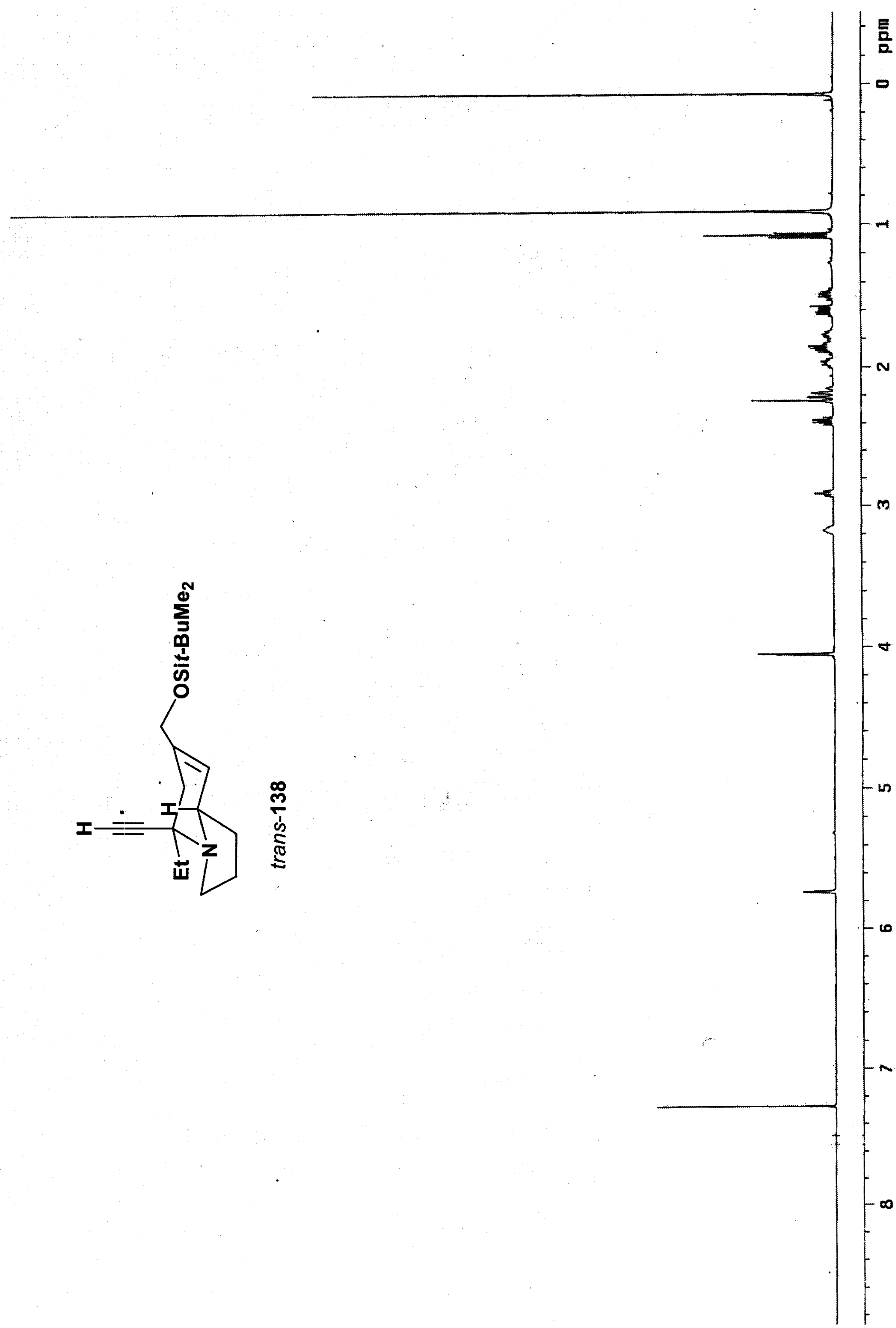


2-(*tert*-Butyldimethylsiloxymethyl)-1,2-didehydro-*cis*-4-ethynyl-4-ethylindolizidine (138). A 25-mL, two-necked, round-bottomed flask equipped with a rubber septum and argon inlet adapter was charged with 3 mL of THF and diisopropylamine (0.181 mL, 0.131 g, 1.29 mmol). The solution was cooled at 0 °C while *n*-BuLi (2.41 M in hexanes, 0.535 mL, 1.29 mmol) was added dropwise via syringe over 1 min. The resulting solution was stirred at 0 °C for 10 min and then cooled at -78 °C while a precooled (-78 °C) solution of amino nitrile **74** (0.18 g, 0.62 mmol) in 2 ml of THF was added dropwise over 1 min. The resulting solution was stirred at -78 °C for 2 h, and then ethyl iodide (0.123 mL, 0.240 g, 1.54 mmol) was added rapidly dropwise. The reaction mixture was stirred at 0 °C for 1 h and then diluted with 15 ml of water and extracted with three 15-mL portions of ether. The combined organic layers were washed with 15 mL of brine, dried over K_2CO_3, filtered, and concentrated to give 0.197 g of orange oil that was used immediately in the next step without further purification.

A 25-mL, round-bottomed flask equipped with a rubber septum and argon inlet needle was charged with the crude nitrile from the preceding step (0.197 g, 0.62 mmol) and 6 mL of ether. The solution was cooled at -78 °C while ethynylmagnesium bromide solution (0.5 M in THF, 3.69 mL, 1.85 mmol) cooled at 0 °C was added dropwise via cannula over 1 min. The resulting solution was allowed to slowly warm to rt over 15 h and then was diluted with 10 mL of satd aq NH_4Cl solution and 10 mL of ether. The aqueous layer was separated and extracted with three 12-mL portions of ether. The combined organic layers were washed with 15 mL of brine, dried over $MgSO_4$, filtered, and concentrated to afford 0.191 g of red oil. Column chromatography on 10 g of silica gel (gradient elution with 10-20% EtOAc-hexanes) provided 0.143 g (73%) of **138** (65:35 mixture of *trans*- and *cis*-fused indolizidines by ^{1}H NMR analysis) as an orange oil. Further purification by column chromatography provided analytical samples of each pure isomer: For *trans*-fused conformer: IR (film): 3308, 2957, 2883, 2857, 2709, 1680, 1473, 1464, 1360, 1302, 1257 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.73 (s, 1 H), 4.05 (s, 2 H), 3.17 (br s, 1 H), 2.91 (td, J = 8.7, 3.4 Hz, 1 H), 2.39 (app q, J = 8.7 Hz, 1H), 2.24 (s, 1 H), 2.23 (d, J = 17.0 Hz, 1 H), 2.17 (d, J = 17.0 Hz, 1 H), 1.94-2.00 (m, 1 H), 1.75-1.91 (m, 3 H), 1.56-1.65 (m, 1 H), 1.45-1.53 (m, 1 H), 1.08 (t, J = 7.5 Hz, 3 H), 0.91 (s, 9 H), 0.07 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 134.4, 121.9, 83.6, 72.2, 66.6, 58.1, 56.6, 45.1, 36.9, 34.0, 28.7, 26.2, 21.4, 18.6, 8.8, -5.0; HRMS (m/z) [M+H]$^+$ calcd for $C_{19}H_{33}NOSi$, 320.2404; found, 320.2408. For *cis*-fused conformer: IR (film): 3312, 2957, 2857, 1653, 1473, 1464, 1374, 1361 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.49 (s, 1 H), 4.00 (s, 2 H), 3.62 (br s, 1 H), 3.14 (m, 1 H), 2.82 (app q, J = 8.8 Hz, 1 H), 2.40 (d, J = 16.8 Hz, 1 H), 2.28 (s, 1 H), 2.02-2.09 (m, 1 H), 1.97 (d, J = 17.3 Hz, 1 H), 1.74-1.81 (m, 3 H), 1.56-1.67 (m, 2 H), 1.05 (t, J = 7.4 Hz, 3 H), 0.92 (s, 9 H), 0.08 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 133.1, 123.5, 83.5, 71.4, 66.8, 55.6, 55.1, 48.0, 31.0, 30.5, 30.3, 26.3, 22.8, 18.8, 9.5, -5.0; HRMS (m/z) [M+H]$^+$ calcd for $C_{19}H_{34}NOSi$, 320.2404; found, 320.2408.



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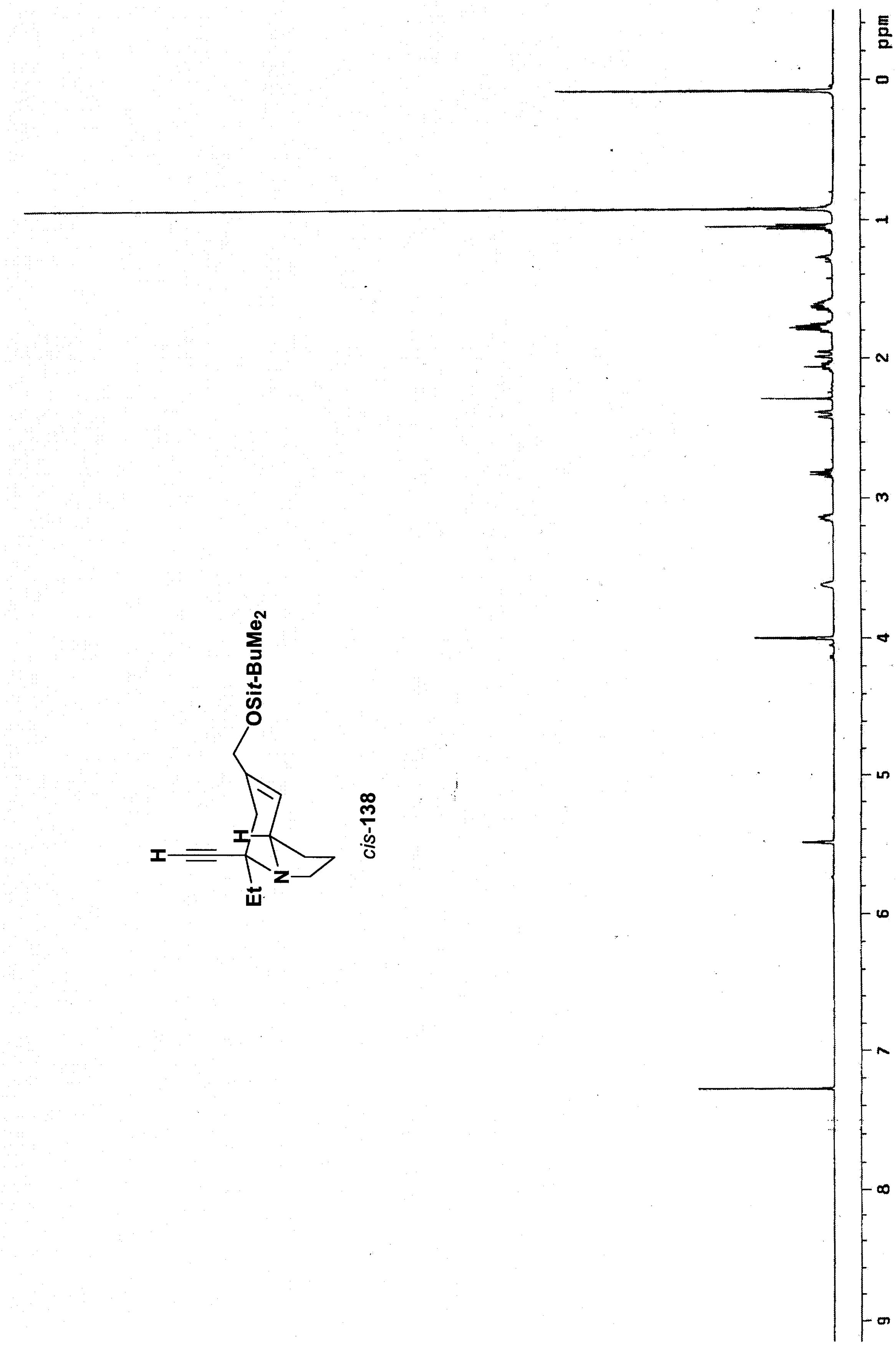
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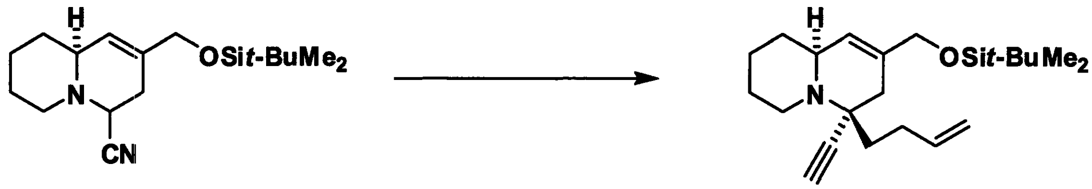
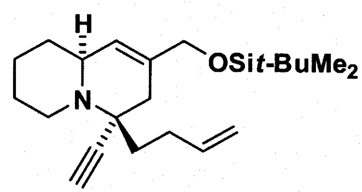


66a

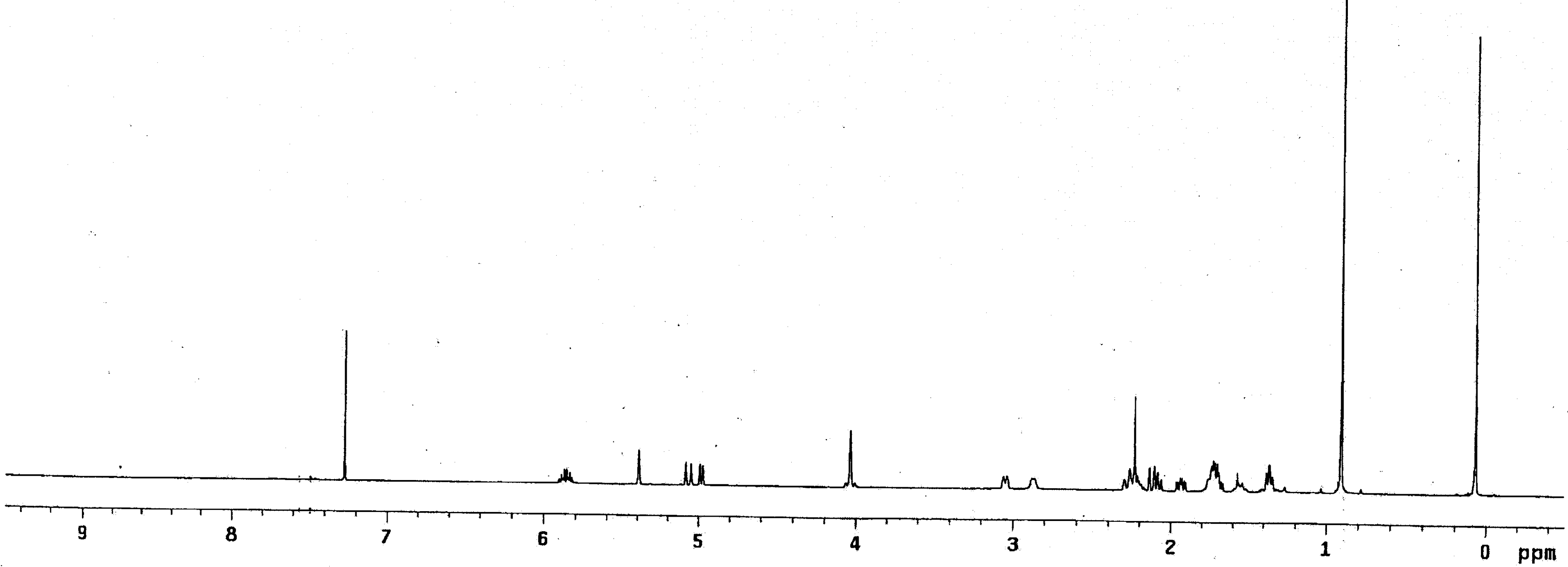
146

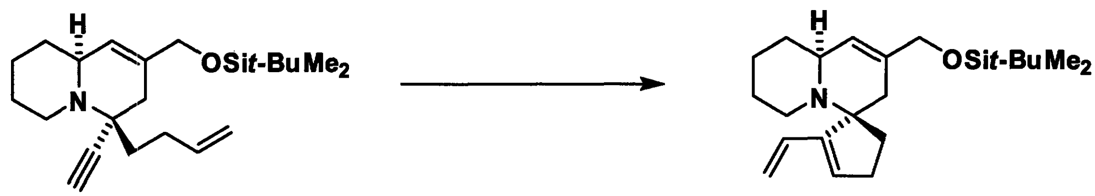
2-(*tert*-Butyldimethylsiloxymethyl)-1,2-didehydro-*cis*-4-ethynyl-4-(3-butene)quinolizidine (146). A 25-mL, two-necked, round-bottomed flask equipped with a rubber septum and argon inlet adapter was charged with 3 mL of THF and diisopropylamine (0.150 mL, 0.108 g, 1.07 mmol). The solution was cooled at 0 °C while *n*-BuLi (2.54 M in hexanes, 0.421 mL, 1.07 mmol) was added dropwise via syringe over 1 min. The resulting solution was stirred at 0 °C for 10 min and then cooled at -78 °C while a precooled (-78 °C) solution of amino nitrile **66a** (0.156 g, 0.51 mmol) in 2 ml of THF was added dropwise over 1 min. The resulting solution was stirred at -78 °C for 2 h, and then 4-bromobutene (0.057 mL, 0.076 g, 0.56 mmol) was added rapidly dropwise. The reaction mixture was stirred at 0 °C for 1 h and then diluted with 15 ml of water and extracted with three 15-mL portions of ether. The combined organic layers were washed with 15 mL of brine, dried over K_2CO_3, filtered, and concentrated to give 0.186 g of orange oil that was used immediately in the next step without further purification.

A 50-mL, round-bottomed flask equipped with a rubber septum and argon inlet needle was charged with the crude nitrile from the preceding step (0.186 g, 0.51 mmol) and 6 mL of ether. The solution was cooled at –78 °C while ethynylmagnesium bromide solution (0.5 M in THF, 3.06 mL, 1.53 mmol) cooled at 0 °C was added dropwise via cannula over 1 min. The resulting solution was allowed to slowly warm to rt over 15 h and then was diluted with 10 ml of satd aq NH_4Cl solution and 10 mL of ether. The aqueous layer was separated and extracted with three 12-mL portions of ether, and the combined organic layers were washed with 15 mL of brine, dried over $MgSO_4$, filtered, and concentrated to afford 0.191 g of red oil. Column chromatography on 10 g of silica gel (gradient elution with 5% EtOAc-hexanes) provided 0.120 g (65%) of **146** as an orange oil: IR (film): 2930, 2856, 1641, 1472, 1462, 1360, 1257 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.86 (ddt, J = 17.0, 10.3, 6.6 Hz, 1 H), 5.39 (s, 1 H), 5.06 (d, J = 17.0 Hz, 1 H), 4.98 (d, J = 10.3 Hz, 1 H), 4.04 (s, 2 H), 3.05 (br d, J = 10.9 Hz, 1 H), 2.87 (br d, J = 7.4 Hz, 1 H), 2.24 (s, 1 H), 2.19-2.30 (m, 3 H), 2.06-2.14 (m, 2 H), 1.94 (td, J = 13.4, 5.3 Hz, 1 H), 1.67-1.75 (m, 4 H), 1.53-1.58 (m, 1 H), 1.37 (app t, J = 9.5 Hz, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.7, 132.7, 124.3, 114.8, 83.8, 71.9, 66.4, 58.1, 56.1, 46.7, 39.2, 37.5, 33.0, 28.3, 26.6, 26.2, 25.0, 18.7, -5.0; HRMS (m/*z*) $[M+H]^+$ calcd for $C_{23}H_{42}NOSi$, 360.2723; found, 360.2714.



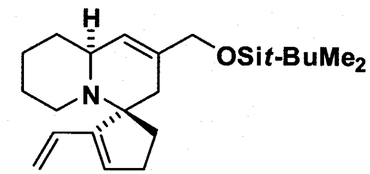
146



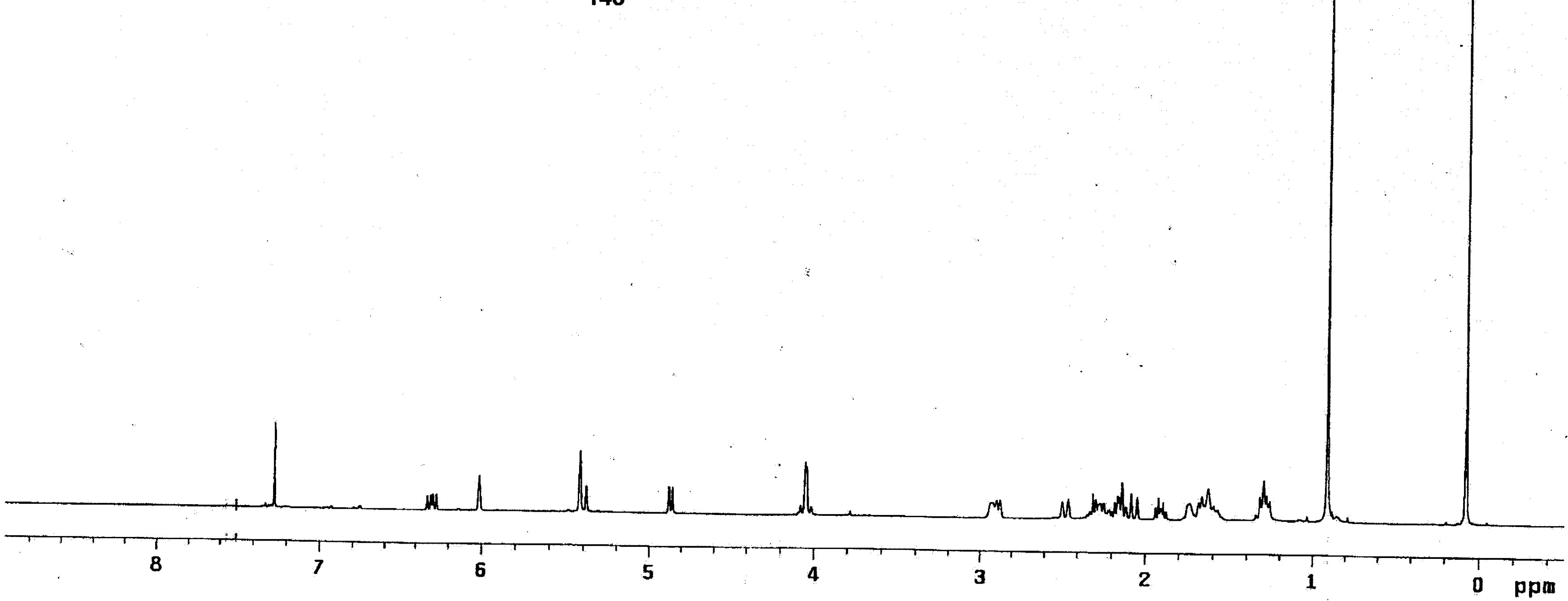


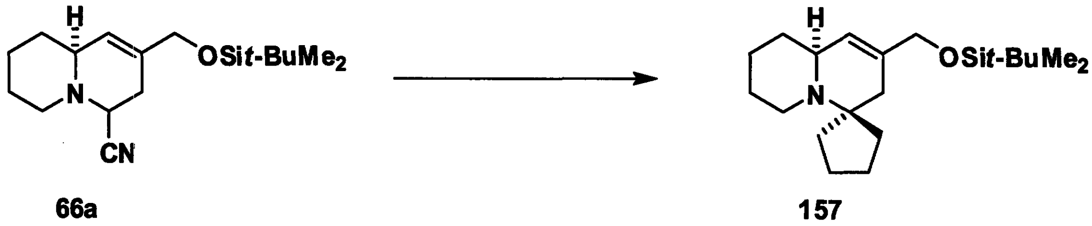
146 148

2′-(*tert*-Butyldimethylsiloxymethyl)-1′,2′-didehydrospiro[2-vinyl-2-cyclopentene-1,4′(3′H)-quinolizidine] (148). A 50-mL, round-bottomed flask equipped with a rubber septum and argon inlet needle was charged with Grubbs 2nd catalyst (0.014 g, 0.017 mmol) and 10 mL of toluene. A solution of quinolizidine **146** (0.120 g, 0.33 mmol) in 4 mL of toluene was added via cannula and the reaction mixture was heated at 85°C for 2 h. The reaction mixture was allowed to cool to rt and then concentrated to give 0.140 g of a black oil. Purification by column chromatography on 15 g of silica gel (gradient elution with 20-35% EtOAc-hexanes) afforded 0.097 g (81%) of the spiroquinolizidine **148** as a yellow oil: IR (film): 3081, 3035, 2929, 2855, 2795, 1680, 1610, 1462, 1360,1321 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.30 (dd, J = 17.3, 10.7 Hz, 1 H), 6.01 (s, 1 H), 5.42 (s, 1 H), 5.40 (d, J = 17.3 Hz, 1 H), 4.87 (d, J = 10.9 Hz, 1 H), 4.05 (s, 2 H), 2.93 (br s, 1 H), 2.87 (br d, J = 11.5 Hz, 1 H), 2.47 (d, J = 17.6 Hz, 1 H), 2.05-2.33 (m, 5 H), 1.91 (dt, J = 14.1, 9.0 Hz, 1 H), 1.57-1.74 (m, 4 H), 1.30 (app t, J = 11.2 Hz, 2 H), 0.91 (s, 9 H), 0.07 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.4, 135.0, 134.1, 128.5, 125.1, 114.0, 69.0, 66.4, 58.0, 47.0, 40.5, 39.4, 33.9, 31.3, 27.0, 26.4, 25.4, 18.9, -4.9; HRMS (m/z) $[M+H]^+$ calcd for $C_{22}H_{38}NOSi$, 360.2717; found, 360.2713.



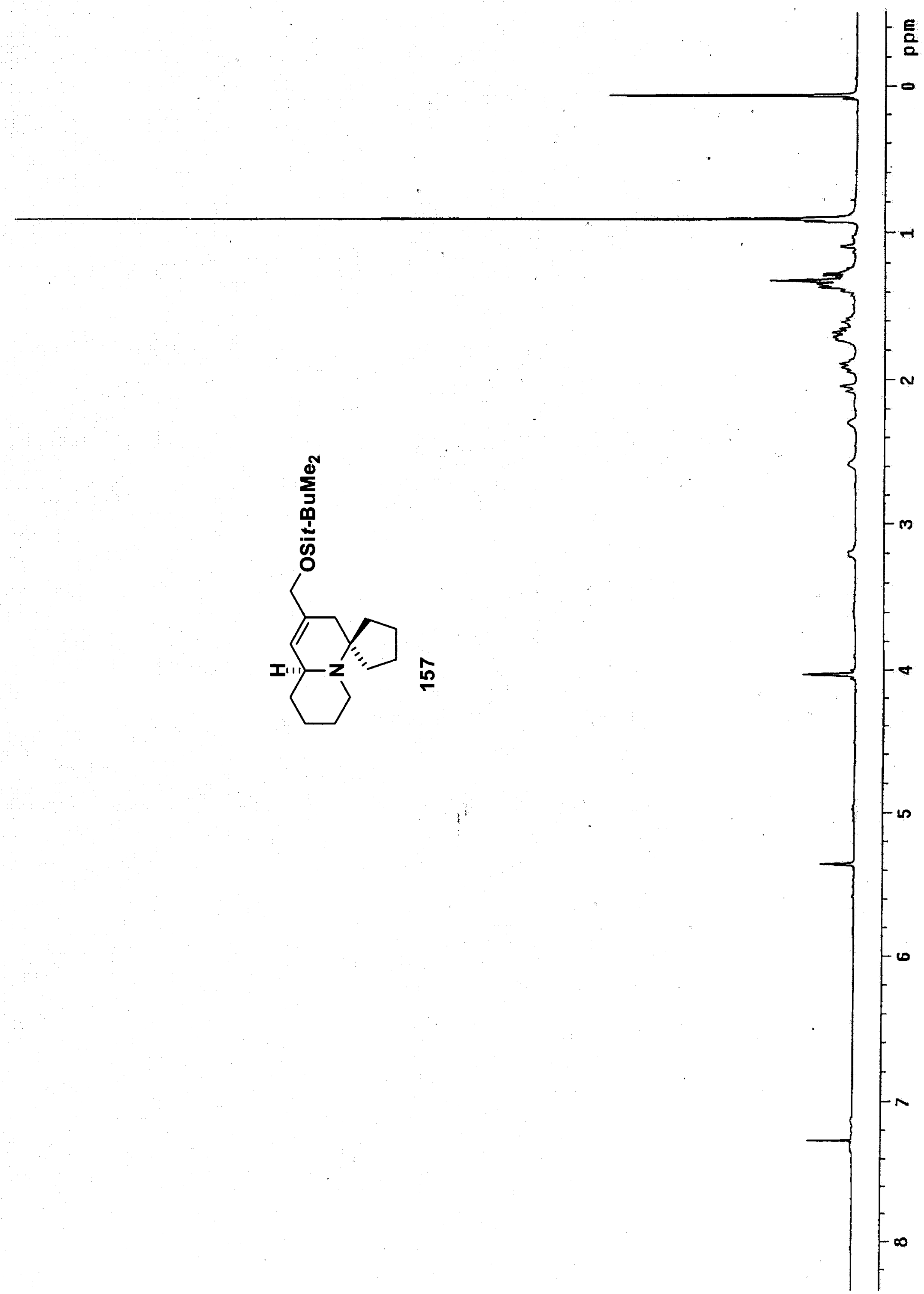
148





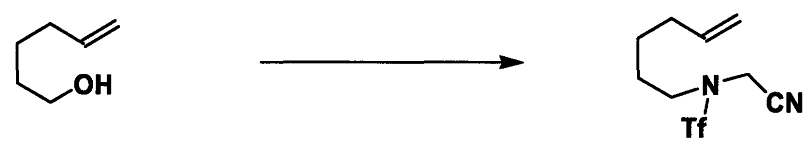
2′-(*tert*-Butyldimethylsiloxymethyl)-1′,2′-didehydrospiro[cyclopentane-1,4′(3′H)-quinolizidine] (157). A 25-mL, two-necked, round-bottomed flask equipped with a rubber septum and argon inlet adapter was charged with 5 mL of THF and diisopropylamine (0.184 mL, 0.133 g, 1.31 mmol). The solution was cooled at 0 °C while *n*-BuLi (2.54 M in hexanes, 0.516 mL, 1.31 mmol) was added dropwise via syringe over 1 min. The resulting solution was stirred at 0 °C for 10 min and then cooled at -78 °C while a precooled (-78 °C) solution of amino nitrile **66a** (0.192 g, 0.63 mmol) in 2 ml of THF was added dropwise over 1 min. The resulting solution was stirred at -78 °C for 2 h, and then 1-chloro-4-iodobutane (0.084 mL, 0.15 g, 0.69 mmol) was added rapidly dropwise. The reaction mixture was stirred at 0 °C for 1 h and then diluted with 15 ml of water and extracted with three 12-mL portions of ether. The combined organic layers were washed with 10 mL of brine, dried over K_2CO_3, filtered, and concentrated to give 0.249 g of **156** as an orange oil that was used immediately in the next step without further purification.

A 50-mL, two-necked, round-bottomed flask equipped with a rubber septum and argon inlet adapter was charged with LiDBB (0.4 M in THF, 9.45 mL, 3.78 mmol). The solution was cooled at -78 °C while the crude nitrile from preceding step (0.249 g, 0.63 mmol) was added dropwise via cannula. The reaction mixture was stirred at -78 °C for 1 h, and then diluted with 2 mL of MeOH and allowed to warm to rt. The reaction mixture was diluted with 10 mL of satd aq NH_4Cl solution and 20 mL of ether. The aqueous layer was separated and extracted with three 15-mL portions of ether. The combined organic layers were washed with 12 mL of brine, dried over $MgSO_4$, filtered, and concentrated to give 1.211 g of a white solid. A solution of this material in CH_2Cl_2 was concentrated onto 2 g of silica gel and transferred to the top of a column of 20 g of silica gel. Gradient elution with 10-35% EtOAc-hexanes yielded 0.107 g (51%) of **157** as a yellow oil: IR (film): 2928, 2787, 2738, 1463, 1361, 1256 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.36 (s, 1 H), 4.03 (s, 2 H), 3.20 (br s, 1 H), 2.59 (br s, 1 H), 2.29 (br s, 1 H), 2.06 (br d, J = 17.2 Hz, 1 H), 1.90 (m, 2 H), 1.58-1.73 (m, 5 H), 1.24-1.39 (m, 8 H), 0.91 (s, 9 H), 0.07 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.4, 124.5, 66.4, 62.2, 59.4, 49.7, 33.0, 32.8, 31.6, 28.0, 26.5, 26.2, 24.6, 23.4, 18.7, 14.3, -5.0; HRMS (m/z) $[M+H]^+$ calcd for $C_{20}H_{38}NOSi$, 336.2717; found, 336.2728.



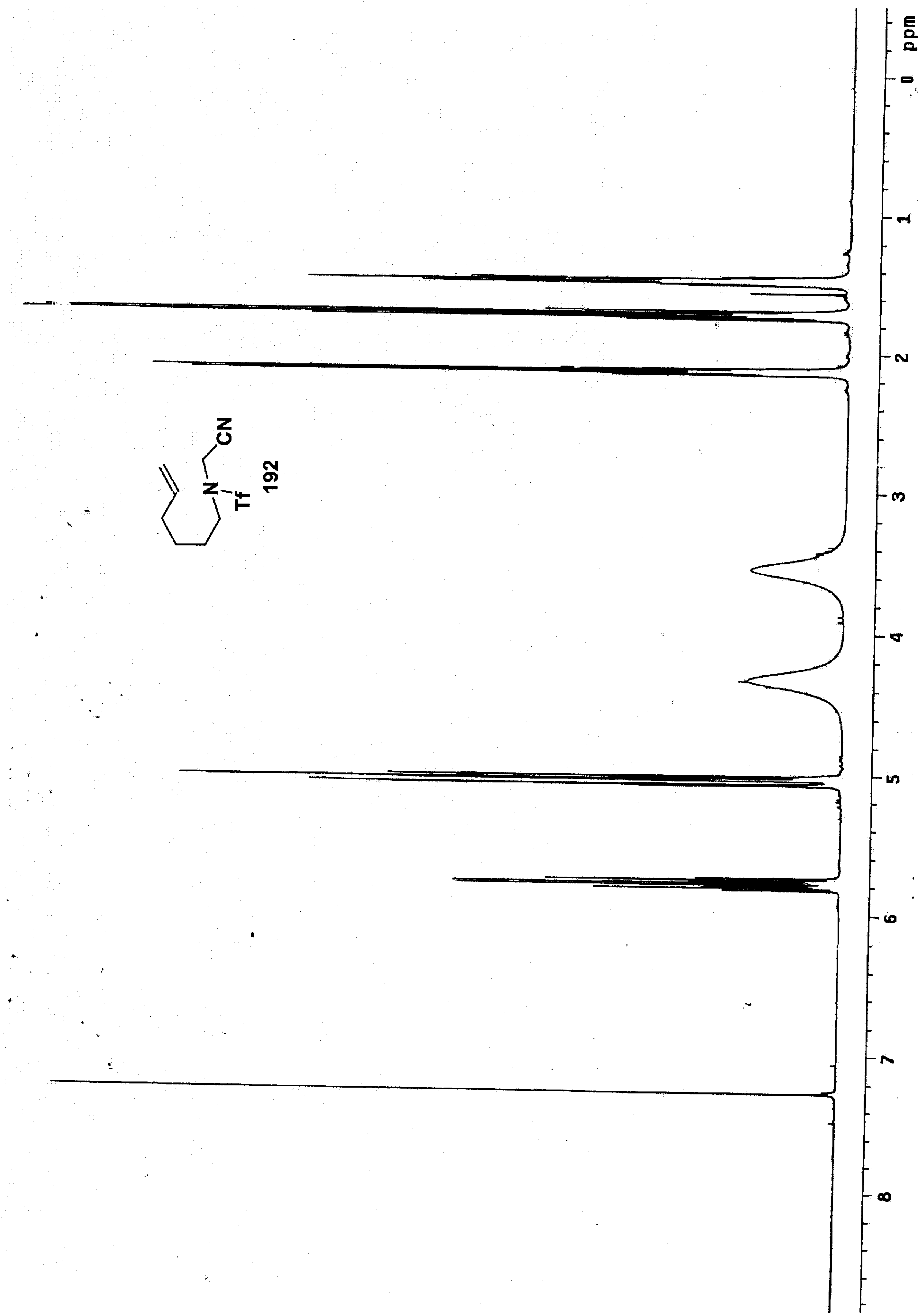
157

Experimental Procedures for Synthesis of Quinolizidine (–)-217A

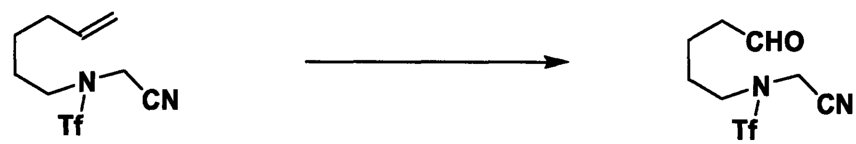


191 **192**

***N*-(Cyanomethyl)-*N*-(5-hexenyl)trifluoromethanesulfonamide (192).** A 500-mL, three-necked, round-bottomed flask equipped with a rubber septum, argon inlet adapter, and glass stopper was charged with triphenylphosphine (15.711 g, 59.9 mmol), 80 mL of THF, and $TfNHCH_2CN$ (10.330 g, 54.91 mmol). 5-Hexen-1-ol (6.00 mL, 5.00 g, 49.9 mmol) was then added in one portion, and then DIAD (11.60 mL, 12.11 g, 59.9 mmol) was added dropwise by syringe over 20 min. The resulting mixture was stirred at rt for 2 h and then concentrated to give 43.11 g of a yellow solid. A solution of this material in CH_2Cl_2 was concentrated onto 30 g of silica gel and transferred to the top of a column of 100 g of silica gel. Gradient elution with 10-20% EtOAc-hexanes yielded 12.357 g (92%) of **192** as a colorless oil: IR (film): 3081, 2997, 2942, 2866, 1642, 1393, 1355, 1296, 1271, 1231, 1143 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.78 (ddt, J = 17.1, 10.1, 6.7 Hz, 1 H), 5.01-5.08 (m, 2H), 4.35 (br s, 2 H), 3.55 (br s, 2 H), 2.13 (app q, J = 7.0 Hz, 2 H), 1.72 (quint, J = 7.6 Hz, 2 H), 1.47 (quint, J = 7.6 Hz, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.1, 119.8 (q, J = 322 Hz), 115.8, 113.4, 49.3, 35.8, 33.0, 26.7, 25.3; Anal. Calcd for $C_9H_{13}F_3N_2O_2S$: C, 40.00; H, 4.85; N, 10.36. Found: C, 39.62; H, 4.81; N, 10.22.

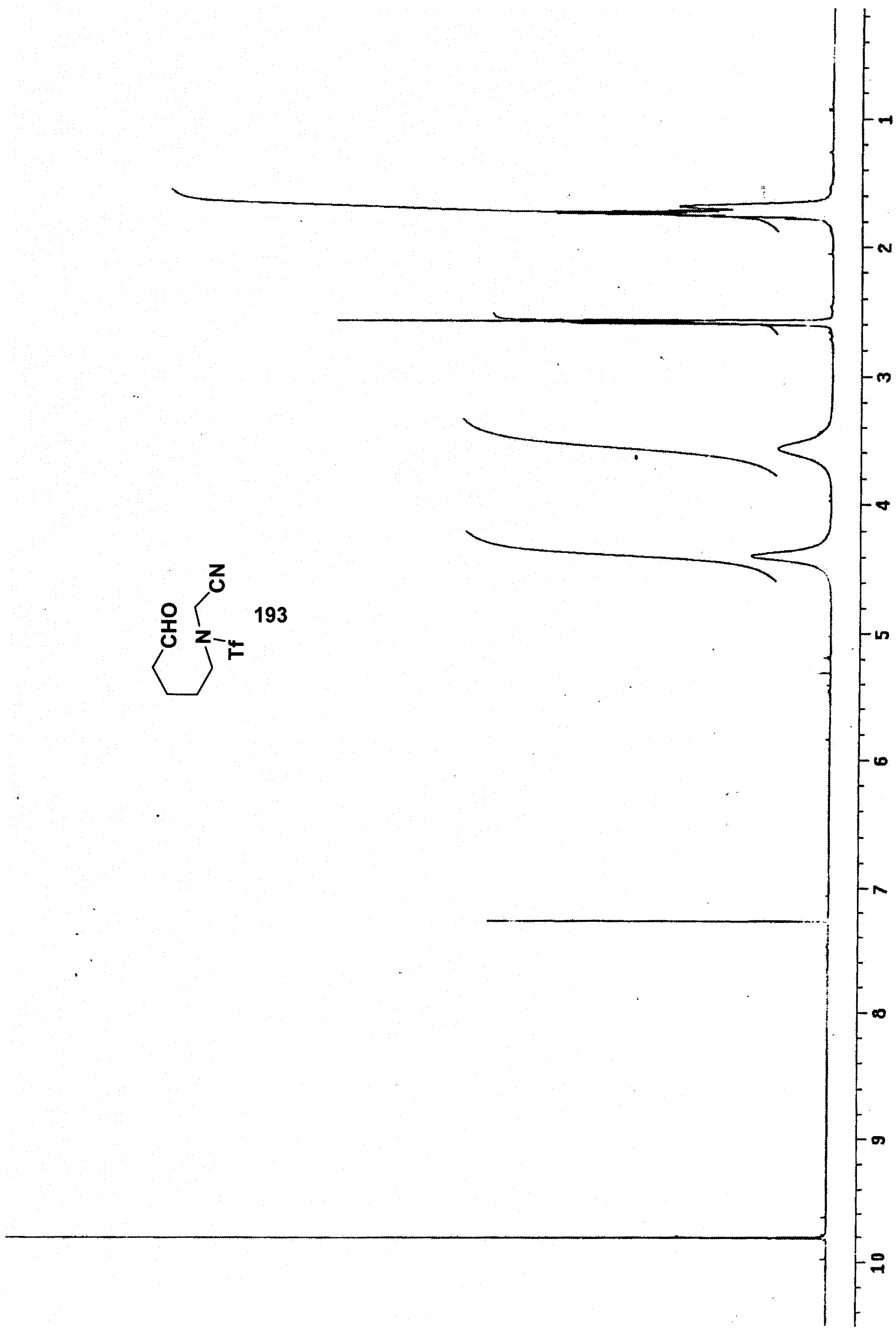


N
Tf
CN
192
ppm



192 → **193**

***N*-(Cyanomethyl)-*N*-(5-hexanal)trifluoromethanesulfonamide (193).** A 200-mL, recovery flask containing triflamide **192** (5.808 g, 21.49 mmol) was fitted with a rubber septum and argon-inlet needle and purged with argon. CH_2Cl_2 (80 mL) was added, and the flask was cooled at –78 °C while ozone was bubbled through the solution for 25 min. The resulting blue solution was degassed with a stream of argon for 10 min. Triphenylphosphine (5.918 g, 22.56 mmol) was added, and the solution was allowed to slowly warm to rt over 16 h. Concentration by rotary evaporation afforded 12.09 g of a cloudy, white oil. A solution of this material in CH_2Cl_2 was concentrated onto 24 g of silica gel and transferred to the top of a column of 110 g of silica gel. Elution with 25% EtOAc-hexanes provided 5.359 g (92%) of **193** as a colorless oil: IR (film): 2997, 2954, 2877, 2838, 2735, 1723, 1467, 1394, 1360, 1294, 1269, 1229, 1145 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.80 (t, J = 1.0 Hz, 1 H), 4.39 (br s, 2 H), 3.57 (br s, 2 H), 2.59 (t, J = 6.4 Hz, 2 H), 1.69-1.78 (m, 4 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.7, 119.7 (q, J = 322 Hz), 113.5, 49.1, 42.8, 35.7, 26.4, 18.2; Anal. Calcd for $C_8H_{11}F_3N_2O_3S$: C, 35.29; H, 4.07; N, 10.29. Found: C, 35.42; H, 4.02; N, 10.30.



CHO
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Tf
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193
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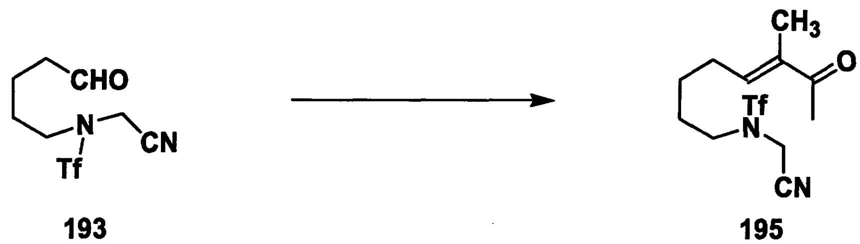
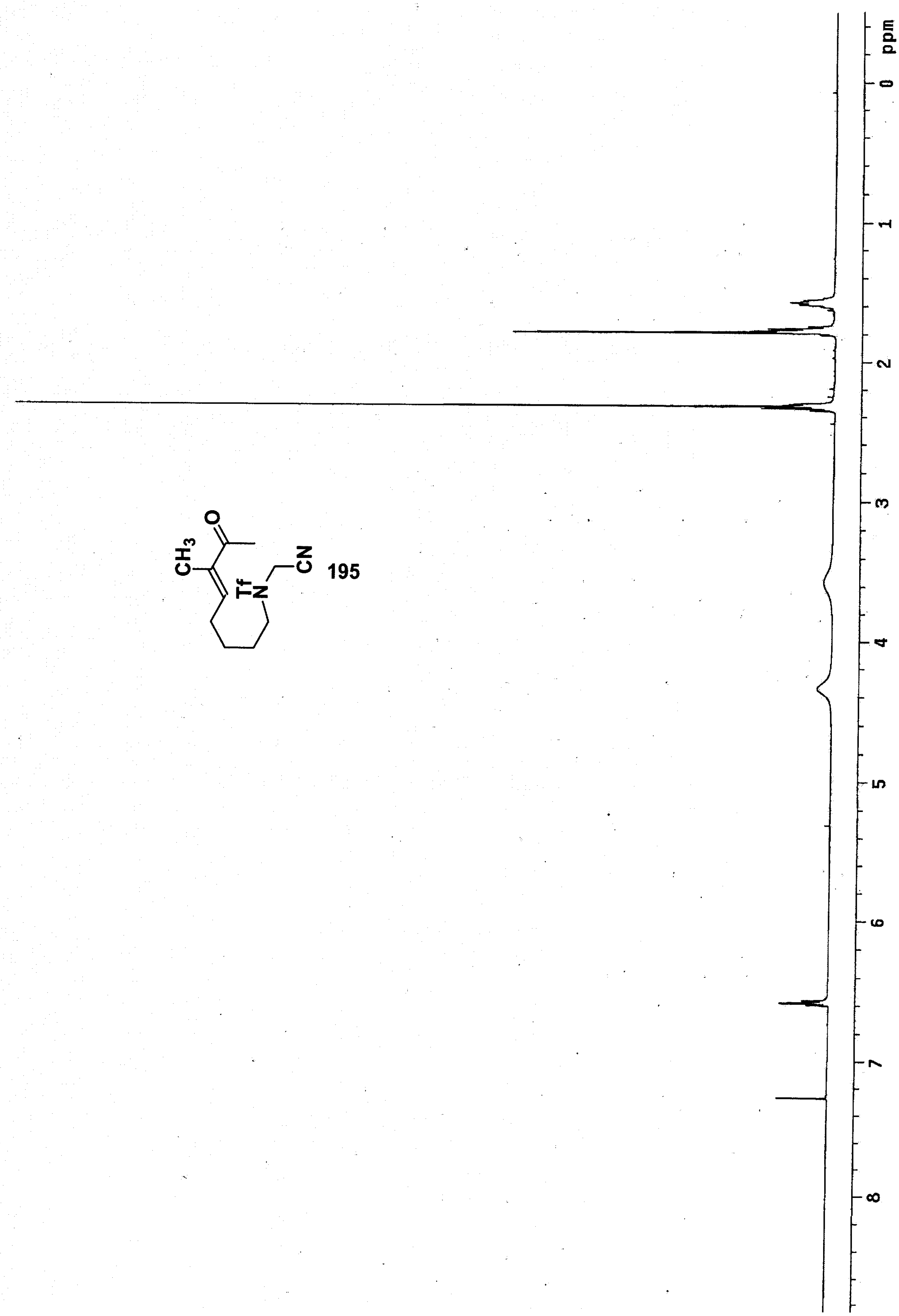
10



N-(Cyanomethyl)-N-(6-methyl-(E)-5-octen-7-one)trifluoromethanesulfonamide (195). A 300-mL, round-bottomed flask equipped with a rubber septum and argon inlet needle was charged with aldehyde **193** (7.394 g, 27.16 mmol) and 54 mL of toluene. 3-(Triphenylphosphoranylidene)butan-2-one **194** (10.010 g, 30.12 mmol) was then added in one portion, and the rubber septum was replaced with a reflux condenser equipped with an argon inlet adapter. The reaction mixture was heated at 70 °C for 7 h. Concentration by rotary evaporation afforded 17.92 g of a brown oil. A solution of this material in CH_2Cl_2 was concentrated onto 30 g of silica gel and transferred to the top of a column of 150 g of silica gel. Gradient elution with 20-30% EtOAc-hexanes provided 7.686 g (87%) of **195** as a yellow oil: IR (neat): 2994, 2945, 2869, 1735, 1666, 1396, 1230 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.58 (td, J = 7.3, 1.2 Hz, 1 H), 4.38 (br s, 2 H), 3.58 (br s, 2 H), 2.33 (m, 5 H), 1.78 (m, 5 H), 1.57 (app quint, J = 7.6 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.7, 141.6, 138.6, 113.9, 49.5, 36.2, 28.7, 27.5, 26.0, 25.5, 11.8; Anal. Calcd for $C_{12}H_{17}F_3N_2O_3S$: C, 44.17; H, 5.25; N, 8.58. Found: C, 43.95; H, 5.27; N, 8.84.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CN
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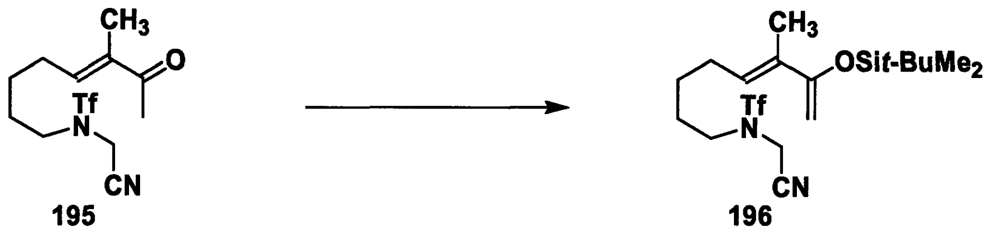
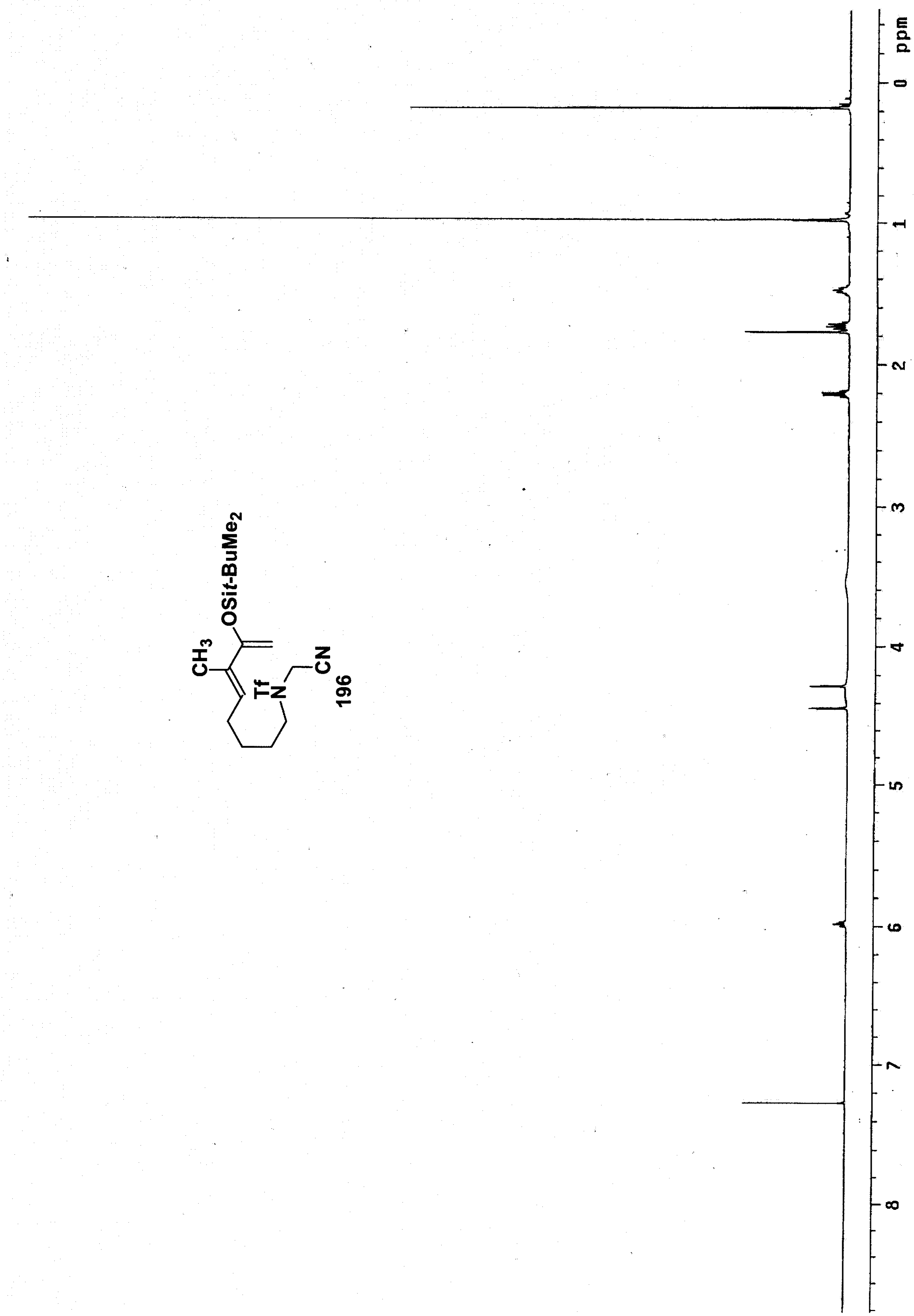
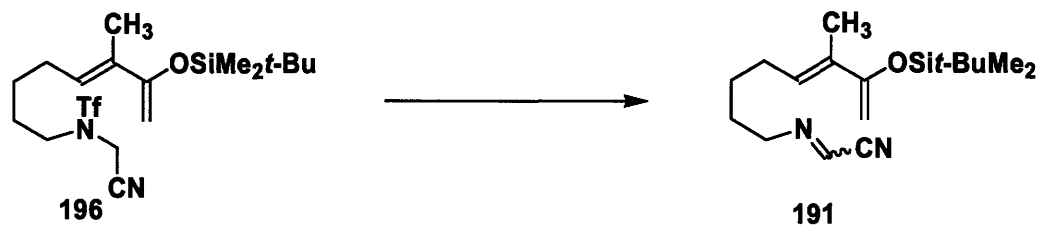


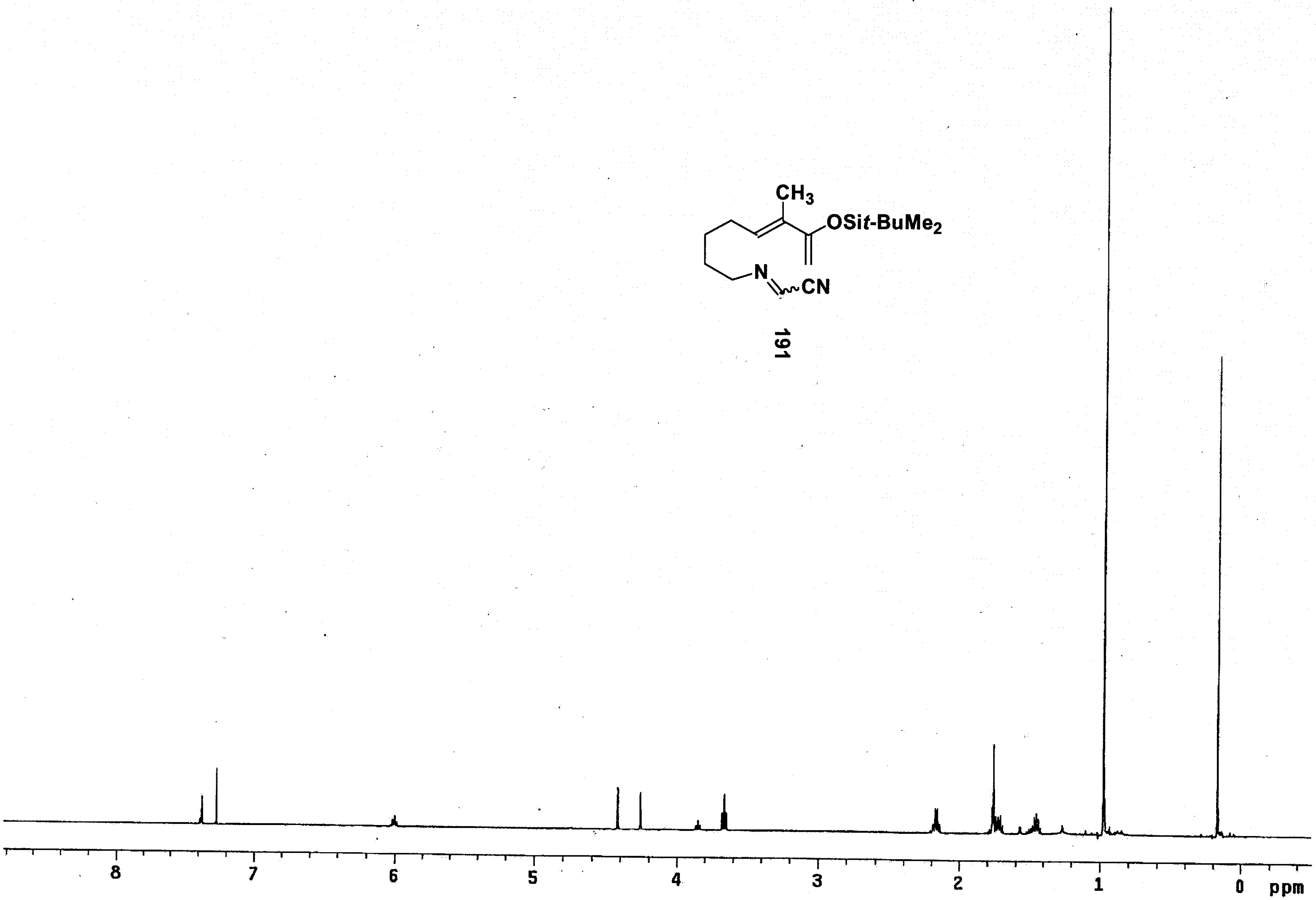
N-(Cyanomethyl)-N-(7-(*tert*-butyldimethylsiloxy)-6-methyl-(E)-5,7-octadienyl)trifluoromethanesulfonamide (196). A 250-mL, two-necked, round-bottomed flask equipped with a rubber septum and argon inlet adapter was charged with NaI (6.254 g, 41.72 mmol), a solution of enone **195** (9.076 g, 27.81 mmol) in 60 mL of CH_3CN, and Et_3N (5.86 mL, 4.22 g, 41.7 mmol). *tert*-Butyldimethylsilyl chloride (4.611 g, 30.59 mmol) was added in one portion, and the resulting mixture was stirred at rt in the dark for 18 h. The reaction mixture was then diluted with 50 mL of satd aq $NaHCO_3$ solution, and the aqueous layer was separated and extracted with three 40-mL portions of ether. The combined organic layers were washed with 30 mL of 1M NaOH solution, 30 mL of brine, dried over $MgSO_4$, filtered, and concentrated to afford 12.37 g of a yellow oil. Column chromatography on 150 of acetone-deactivated silica gel (elution with 10% EtOAc-hexanes containing 1% Et_3N) provided 11.814 g (96%) of **196** as a yellow oil: IR (film): 3127, 2933, 2860, 1645, 1596, 1464, 1398, 1231, 1197 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.98 (t, J = 7.3 Hz, 1 H), 4.43 (s, 1 H), 4.28-4.44 (br s, 2 H), 4.24 (s, 1 H), 3.55 (br s, 2 H), 2.20 (app q, J = 7.3 Hz, 2 H), 1.77 (s, 3 H), 1.73 (app quint, J = 7.3 Hz, 2 H), 1.47 (app quint, J = 7.6 Hz, 2 H), 0.98 (s, 9 H), 0.18 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.2, 132.2, 127.0, 119.8 (q, J = 322 Hz), 113.3, 91.7, 49.4, 35.8, 27.6, 27.2, 26.1, 25.9, 18.5, 13.5, -4.4; Anal. Calcd for $C_{18}H_{31}F_3N_2O_3SSi$: C, 49.07; H, 7.09; N, 6.36. Found: C, 48.82; H, 6.99; N, 6.55.



196



7-(*tert*-Butyldimethylsiloxy)-6-methyl-(*E*)-5,7-octadienyliminoacetonitrile (191). A 250-mL, round-bottomed flask equipped with a reflux condenser fitted with an argon inlet adapter was charged with Cs_2CO_3 (19.65 g, 60.3 mmol) and 60 mL of THF. A solution of triflamide **196** (6.643 g, 15.08 mmol) in 15 mL of THF was then added in one portion, and the reaction mixture was heated at 55 °C for 1.5 h. The resulting mixture was allowed to cool to rt and then diluted with 100 mL of water. The aqueous layer was separated and extracted with three 55-mL portions of ether, and the combined organic layers were washed with 50 mL of brine, dried over $MgSO_4$, filtered, and concentrated to give 5.88 g of a yellow oil. Column chromatography on 25 g of acetone-deactivated silica gel (elution with 10% EtOAc-hexanes containing 1% Et_3N) afforded 4.160 g (90%) of **191** (84:16 mixture of *E* and *Z* imine isomers by ^{1}H NMR analysis) as a colorless oil: IR (film): 2931, 2859, 1644, 1595, 1472, 1463, 1362, 1255 cm^{-1}; For Z isomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 (t, J= 2.1 Hz, 1 H), 6.00 (app t, J = 7.6 Hz, 1 H), 4.42 (s, 1 H), 4.26 (s, 1 H), 3.85 (td, J = 7.0, 2.1 Hz, 2 H), 2.16 (app q, J = 7.6 Hz, 2 H), 1.69-1.76 (m, 5 H), 1.41-1.57 (m, 2 H), 0.97 (m, 9 H), 0.17 (m, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.4, 131.7, 131.5, 127.9, 114.7, 91.5, 59.9, 29.9, 27.9, 27.2, 26.1, 18.6, 13.5, -4.4; For E isomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 (t, J = 1.5 Hz, 1 H), 6.00 (app t, J = 7.6 Hz, 1 H), 4.42 (s, 1 H), 4.26 (s, 1 H), 3.66 (td, J = 6.7, 1.5 Hz, 2 H), 2.16 (app q, J = 7.6 Hz, 2 H), 1.69-1.76 (m, 5 H), 1.41-1.57 (m, 2 H), 0.97 (m, 9 H), 0.17 (m, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.4, 135.9, 131.7, 127.8, 114.7, 91.5, 63.2, 29.8, 28.0, 27.3, 26.1, 18.6, 13.5, -4.4; Anal. Calcd for $C_{17}H_{30}N_2OSi$: C, 66.61; H, 9.87; N, 9.14. Found: C, 66.43; H, 9.96; N, 9.11.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CN
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6
5
4
3
2
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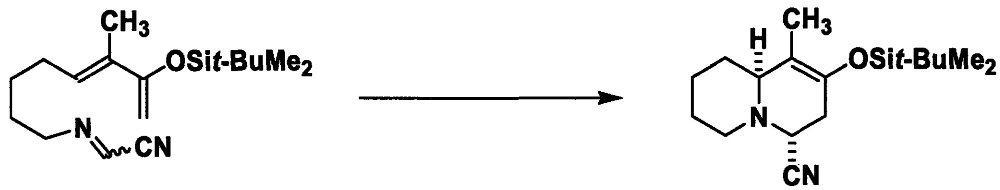
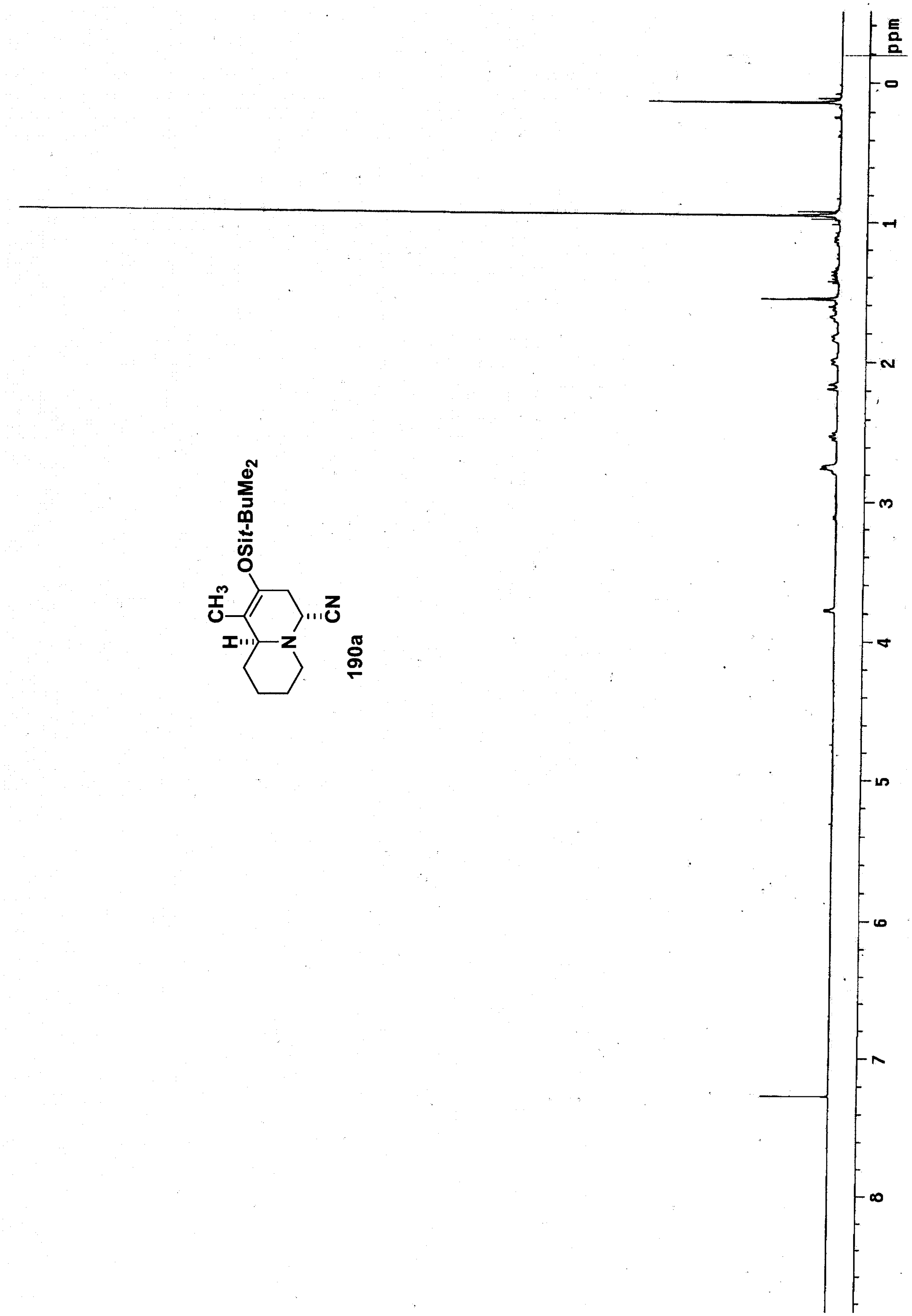
0
ppm



191 190a

2-(*tert*-Butyldimethylsiloxy)-1-methyl-*cis*-1,2-didehydro-4-cyanoquinolizidine (190a) (Thermal Cycloaddition). A threaded Pyrex tube (ca. 350-mL capacity) equipped with a rubber septum and argon inlet needle was charged with BHT (9.30 g, 42.2 mmol), imine **191** (4.312 g, 14.07 mmol), and 175 mL of toluene. The solution was degassed by four freeze-pump-thaw cycles and then sealed with a threaded Teflon cap. The reaction mixture was heated in a 130 °C oil bath for 36 h and then allowed to cool to rt. Concentration by rotary evaporation afforded 13.71 g of a yellow oil. A solution of this material in CH_2Cl_2 was concentrated onto 25 g of acetone-deactivated silica gel and transferred to the top of a column of 180 g of acetone-deactivated silica gel. Elution with 7% EtOAc-hexanes containing 1% Et_3N provided 2.415 g (56%) of **190a** as a white solid: mp 74-77 °C; IR (CH_2Cl_2): 2938, 2857, 2760, 1686, 1462, 1382, 1359, 1295, 1253, 1195, 1176 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.78 (dd, J = 5.5, 1.2 Hz, 1 H), 2.73-2.79 (m, 3 H), 2.52 (td, J = 11.9, 3.1 Hz, 1 H), 2.17 (dd, J = 15.6, 1.2 Hz, 1 H), 1.98-2.01 (m, 1 H), 1.82-1.85 (m, 1 H), 1.57-1.71 (m, 2 H), 1.56 (s, 3 H), 1.33-1.42 (m, 1 H), 1.08-1.17 (m, 1 H), 0.95 (s, 9 H), 0.14 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.0, 117.2, 113.7, 60.5, 54.6, 53.3, 34.2, 30.4, 26.1, 25.9, 24.9,18.5, 2.4, -3.5; Anal. Calcd for $C_{17}H_{30}N_2OSi$: C, 66.61; H, 9.87; N, 9.14. Found: C, 66.74; H, 9.80; N, 9.08.

(Acid-Promoted Cycloaddition). A 25-mL, two-necked, round-bottomed flask equipped with a rubber septum and argon inlet adapter was charged with imine **191** (0.210 g, 0.69 mmol), 4Å molecular sieves (ca. 50 mg), and 7 mL of CH_2Cl_2. The reaction mixture was cooled at -78 °C while methanesulfonic acid (0.044 mL, 0.066 g, 0.69 mmol) was added dropwise via syringe over 1 min. The solution was stirred at -78 °C for 1 h, and then diluted with 15 mL of satd aq $NaHCO_3$ and 10 mL of CH_2Cl_2. The aq layer was separated and extracted with three 15-mL portions of CH_2Cl_2. The combined organic layers were washed with 10 mL of brine, dried over $MgSO_4$, filtered, and concentrated to give 0.225 g of an orange oil. This material was diluted with 5 mL of CH_3CN and stirred at 45 °C for 2 h, and then concentrated to give 0.225 g of an orange oil. Purification by column chromatography on 10 g of silica gel (elution with 10% EtOAc-hexanes containing 1% Et_3N) afforded 0.142 g (68%) of **190a** as a white solid.



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H
N
CN
190a
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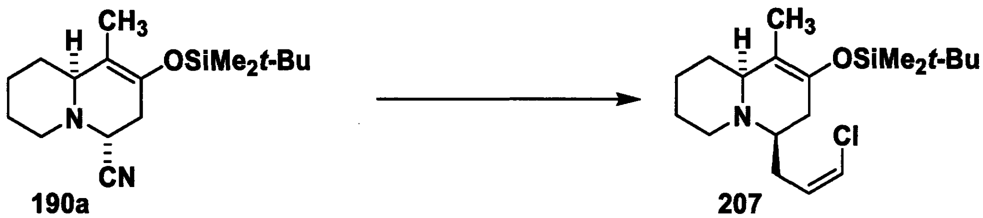
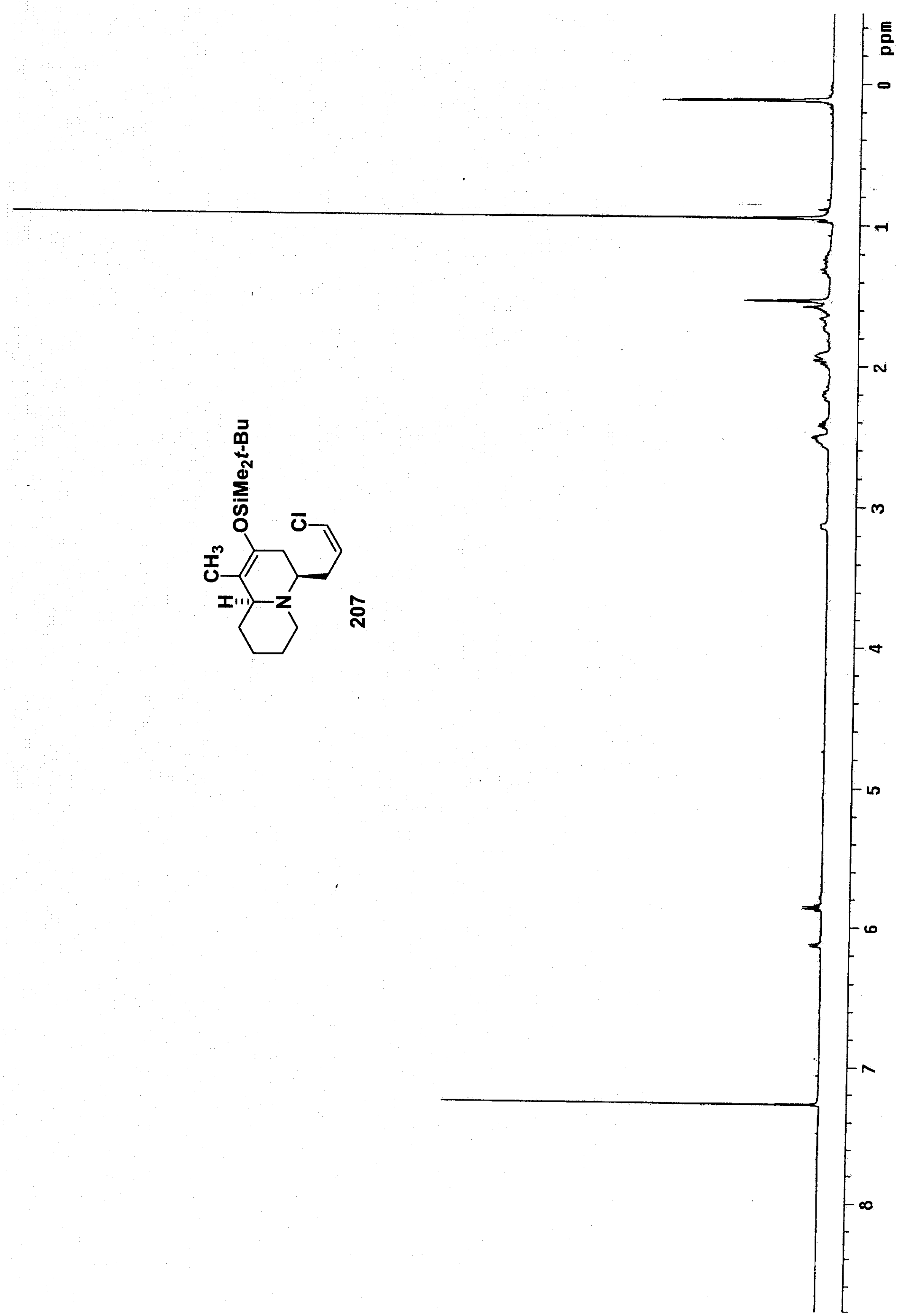


2-(*tert*-Butyldimethylsiloxy)-1-methyl-*trans*-1,2-didehydro-4-(3-chloro-(*Z*)-2-propene)quinolizidine (207). A 50-mL, two-necked, round-bottomed flask equipped with a rubber septum and argon inlet adapter was charged with HMDS (1.68 mL, 1.28 g, 7.9 mmol) and 10 mL of THF. The solution was cooled at 0 °C while 3.38 mL of *n*-BuLi solution (2.35 M in hexane, 7.9 mmol) was added dropwise via syringe over 1 min. The resulting solution was stirred at 0 °C for 10 min and then cooled at -78 °C while a precooled (-78 °C) solution of amino nitrile **190a** (1.015 g, 3.31 mmol) in 5 mL of THF was added dropwise via cannula over 5 min. The resulting solution was stirred at -78 °C for 3.5 h, and then a precooled (-78 °C) solution of 3-bromo-1-chloropropene (1.234 g, 7.94 mmol) in 5 mL of THF was added dropwise via cannula over 1 min. The reaction mixture was stirred at -78 °C for 1 h and then allowed to warm to 0 °C and stirred for an additional hour. The reaction mixture was diluted with 80 mL of ether and 30 mL of water. The aqueous layer was extracted with three 25-mL portions of ether, and the combined organic layers were washed with 30 mL of brine, dried over K_2CO_3, filtered, and concentrated to give 1.917 g of an orange oil that was used immediately in the next step without further purification.

A 50-mL, two-necked, round-bottomed flask equipped with a rubber septum and argon inlet adaptor was charged with $NaBH_3CN$ (0.832 g, 13.24 mmol) and 10 mL of CH_3CN. Acetic acid (1.52 mL, 1.59 g, 26.5 mmol) was added dropwise via syringe over 4 min. The resulting solution was stirred at rt for 30 min, and then a solution of the α-amino nitrile (1.917 g) prepared in the previous step in 8 mL of CH_3CN was added over 3 min by cannula. The reaction mixture was stirred at rt for 2 h and then diluted with 35 mL of water and 35 mL of dichloromethane. The aqueous layer was separated and extracted with three 25-mL portions of dichloromethane, and the combined organic layers were washed with 30 mL of bine, dried over $MgSO_4$, filtered, and concentrated onto 3.5 g of silica gel. The free-flowing powder was placed at the top of a column of 60 g of silica gel and eluted with 15% EtOAc-hexanes containing 1% Et_3N to provide 0.902 g (77%) of the quinolizidine **207** as a yellow oil: IR (neat): 2931, 2857, 2791, 2741, 1698, 1629, 1472, 1362, 1257, 1195 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.13 (app d, J = 6.60 Hz, 1 H), 5.86 (app q, J = 7.05 Hz, 1 H), 3.13 (app d, J = 11.21 Hz, 1 H), 2.40-2.54 (m, 4 H), 2.16-2.23 (m, 1 H), 1.90-2.01 (m, 3 H), 1.53-1.71 (m, 6 H), 1.20-1.34 (m, 2 H), 0.95 (s, 9 H), 0.12 (s, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.5, 129.2, 120.6, 113.2, 65.8, 58.6, 36.7, 31.0, 30.6, 26.4, 26.2, 24.8, 18.5, 12.4, -3.5, -3.9; Anal. Calcd for $C_{19}H_{34}ClNOSi$: C, 64.10; H, 9.63; N, 3.93. Found: C, 64.25; H, 10.62; N, 4.03.



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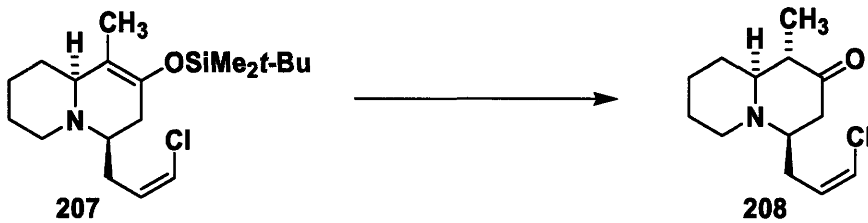
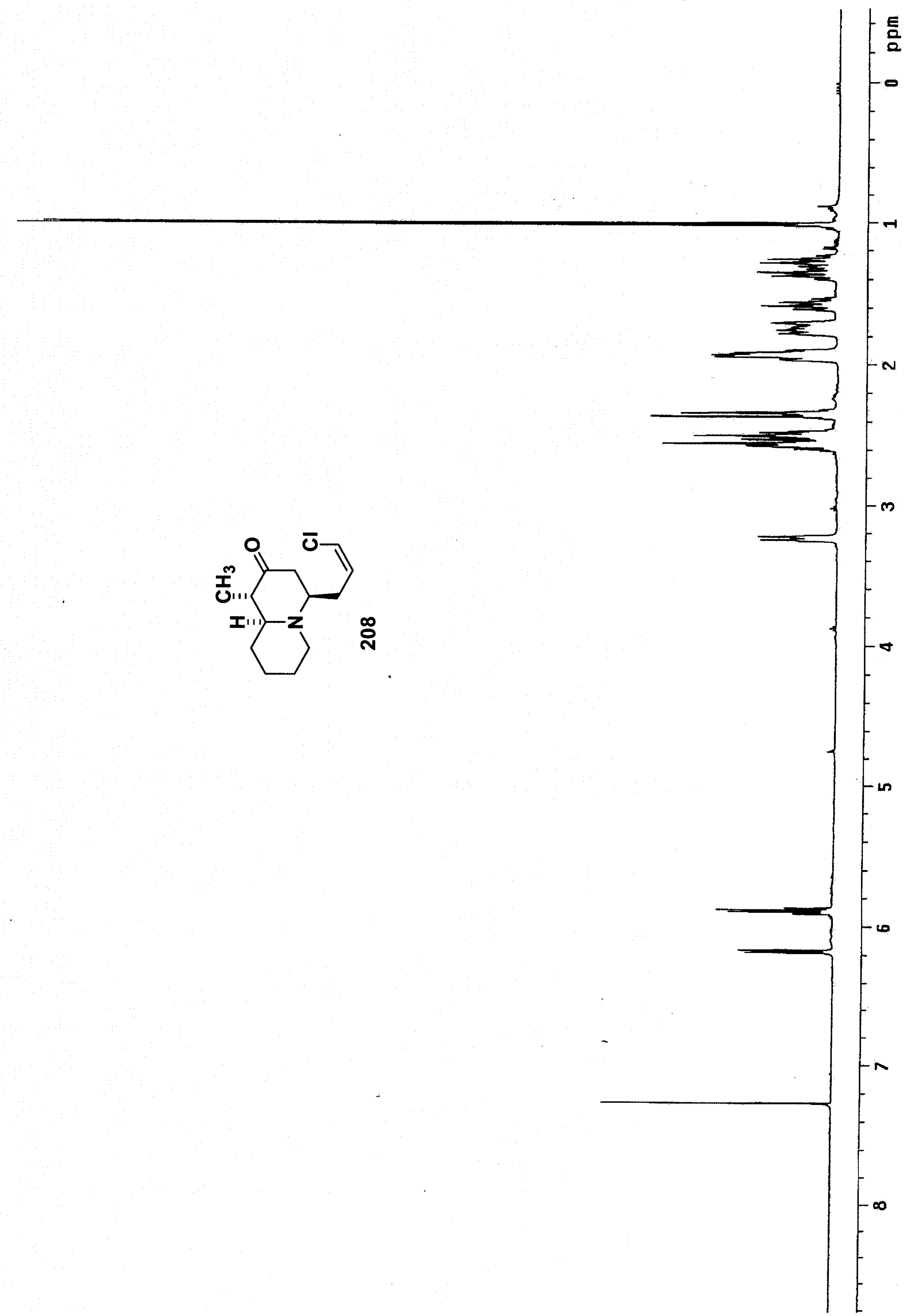


(1β, 4α, 10β)-4-(3-Chloro-(*Z*)-2-propene)-1-methyl-quinolizidin-2-one (208). A 50-mL, two-necked, round-bottomed flask equipped with a rubber septum and argon inlet adapter was charged with silyl enol ether **207** (1.60 g, 4.5 mmol) and 20 mL of THF. The reaction mixture was cooled at -78 °C while 4.94 mL of TBAF solution (1.0 M in THF, 4.9 mmol) was added dropwise via syringe over 2 min. The resulting solution was stirred at -78 °C for 1.5 h and then the reaction mixture was diluted with 35 mL of ether and 15 mL of water. The aqueous layer was separated and extracted with three 20-mL portions of ether, and the combined organic layers were washed with 25 mL of brine, dried over $MgSO_4$, filtered, and concentrated onto 3 g of silica gel. The free-flowing powder was placed at the top of a column of 25 g of silica gel and eluted with 15% EtOAc-hexanes containing 1% Et_3N to provide 0.951 g (88%) of the ketone **208** as a yellow oil: IR (neat): 2934, 2859, 2794, 1718, 1629, 1443, 1337, 1237, 1112 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.17 (d, J = 7.3 Hz, 1 H), 5.87 (app q, J = 7.0 Hz, 1 H), 3.24 (app d, J = 11.3 Hz, 1 H), 2.46-2.59 (m, 4 H), 2.33-2.38 (m, 2 H), 1.89-1.97 (m, 3 H), 1.70-1.78 (m, 2 H), 1.57 (qt, J = 12.8, 3.7 Hz, 1 H), 1.24-1.40 (m, 2 H), 1.01 (d, J = 6.7 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 210.3, 127.1, 120.7, 68.5, 62.8, 50.6, 49.4, 46.4, 31.7, 31.4, 26.0, 24.0, 10.4; Anal. Calcd for $C_{13}H_{20}ClNO$: C, 64.59; H, 8.34; N, 5.79. Found: C, 64.79; H, 8.13; N, 6.14.



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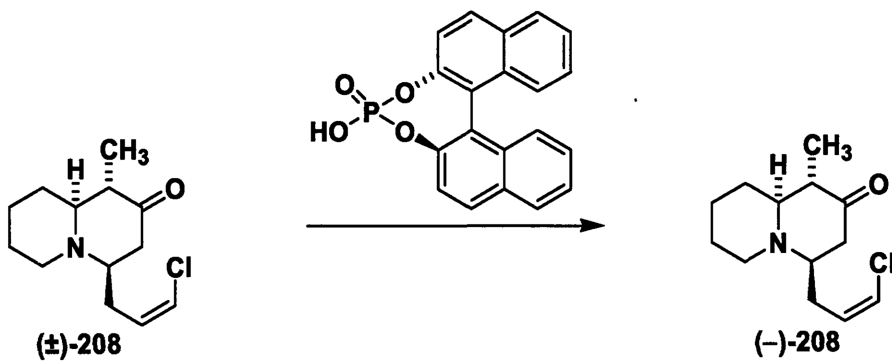
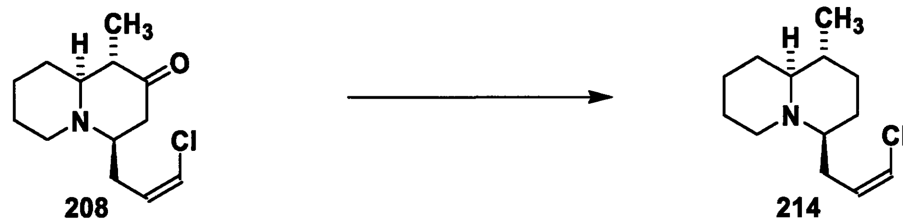
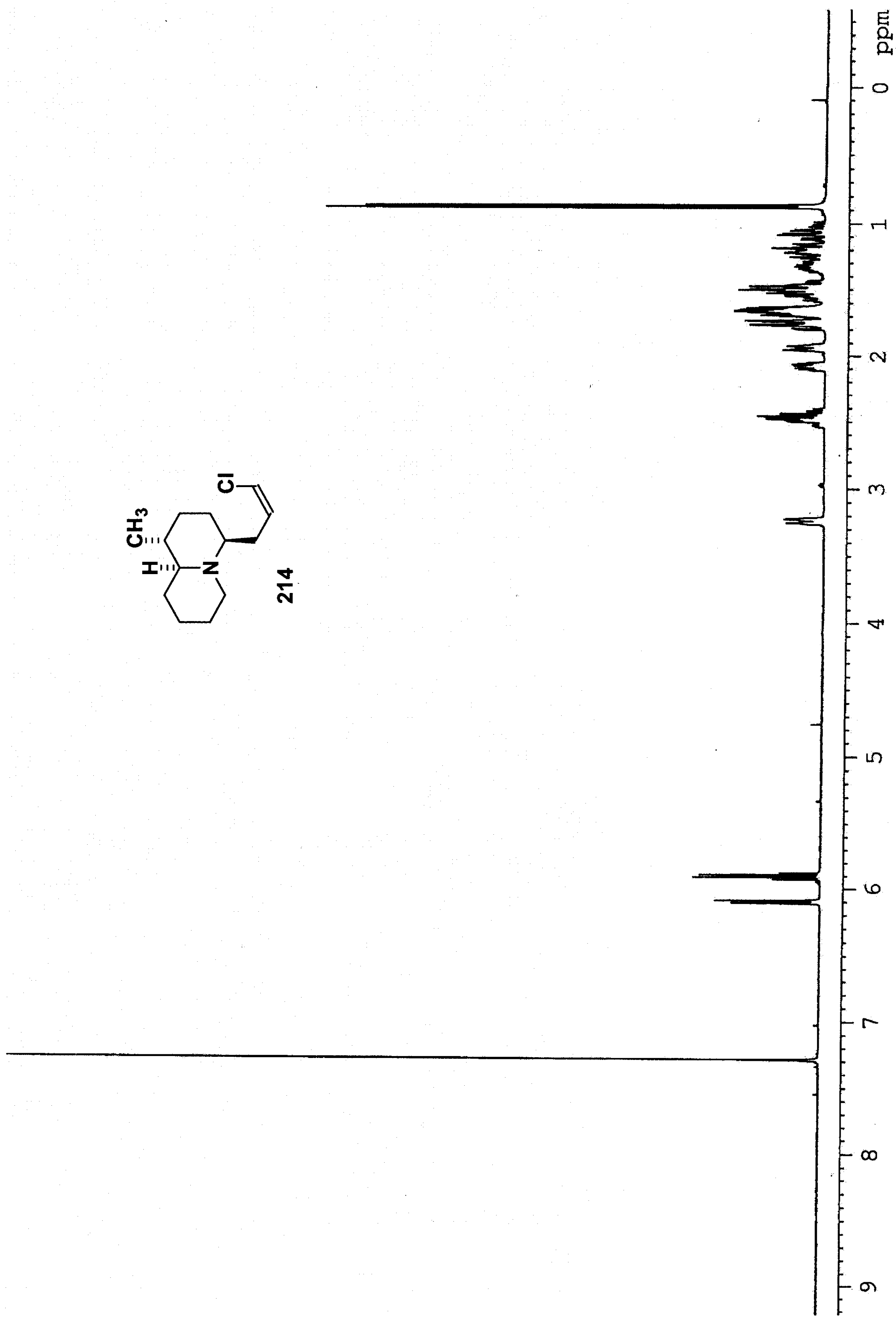
CH3
H
N
Cl
208



(1*R*, 4*S*, 10*S*)-4-(3-Chloro-(*Z*)-2-propene)-1-methyl-quinolizidin-2-one (208). A 100-mL, one-necked, pear-shaped flask was charged with the ketone (±)-**208** (0.430 g, 1.78 mmol), (*R*)-(–)-1,1'-binaphthyl-2,2'-diylphosphoric acid (0.681 g, 1.96 mmol), 10 mL of CH_2Cl_2, and 25 mL of methanol. The reaction mixture was heated at 50 °C for 30 min and then allowed to cool to rt. The reaction mixture was concentrated to a volume of ca. 10 mL and then placed in a freezer at -18 °C for 15 h. The resulting crystals were collected on a sintered funnel and air-dried to yield 0.364 g of white solid. Recrystallization of the solid obtained from the mother liquor from 25 mL of methanol afforded 0.132 g of a white solid. The two crops of crystals were combined and treated with 30 mL of EtOAc and 15 mL of 10% ammonium hydroxide solution. The aqueous layer was separated and extracted with three 20-mL of portions EtOAc, and the combined organic layers were washed with 25 mL of brine, dried over $MgSO_4$, filtered, and concentrated to give 0.189 g (44% from (±)-**208**; i.e., 88% of theoretical) of ketone (–)-**208** as a yellow oil: $[\alpha]_D^{22}$ -42° (c 2.76, $CHCl_3$).



(1*R*, 4*S*, 10*S*)-4-(3-Chloro-(*Z*)-2-propene)-1-methyl-quinolizidine (214). A 50-mL, one-necked, round-bottomed flask equipped with a reflux condenser fitted with an argon inlet adapter was charged with ketone **208** (0.184 g, 0.76 mmol), TsOH (0.045 g, 0.26 mmol), 1.5 mL of DMF, and 1.5 mL of sulfolane. The reaction mixture was heated at 110 °C for 2 h. $NaBH_3CN$ (0.191 g, 3.04 mmol), *t*-BuSH (1.29 mL, 1.03 g, 11.4 mmol), and 3 mL of cyclohexane were added in one portion and the resulting mixture was heated at 110 °C for 5 h. The reaction mixture was allowed to cool to rt and then diluted with 15 mL of ether and 40 mL of water. The aqueous layer was separated and extracted with three 10-mL portions of ether, and the combined organic layers were washed with 10 mL of water, 10 mL of satd $NaHCO_3$, 25 mL of brine, dried over $MgSO_4$, filtered, and concentrated to give 0.29 g of a yellow oil. Purification by column chromatography on 20 g of silica gel (elution with 0-20% EtOAc-hexanes containing 1% Et_3N) afforded 0.144 g (66%) of the quinolizidine **214** as a pale, yellow oil: $[\alpha]_D^{22}$ -60° (c 2.4, $CHCl_3$); IR (film): 2928, 2852, 2787, 2754, 1628, 1442, 1376, 1331, 1305, 1264 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.08 (dt, J = 7.1 Hz, 1.7 Hz, 1 H), 5.88 (q, J = 7.0 Hz, 1 H), 3.24 (app d, J = 11.0 Hz, 1 H), 2.42-2.49 (m, 2 H), 2.04-2.08 (m, 1 H), 1.90-1.94 (m, 1 H), 1.60-1.78 (m, 5 H), 1.45-1.53 (m, 3 H), 1.03-1.33 (m, 4 H), 0.86 (d, J = 6.5 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 129.4, 119.4, 69.8, 62.9, 52.1, 36.7, 34.2, 32.2, 32.1, 30.6, 26.6, 25.0, 19.6; Anal. Calcd for $C_{13}H_{22}ClN$: C, 68.55; H, 9.74; N, 6.15. Found: C, 68.49; H, 9.72; N, 6.12.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H
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Cl
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ppm
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3
4
5
6
7
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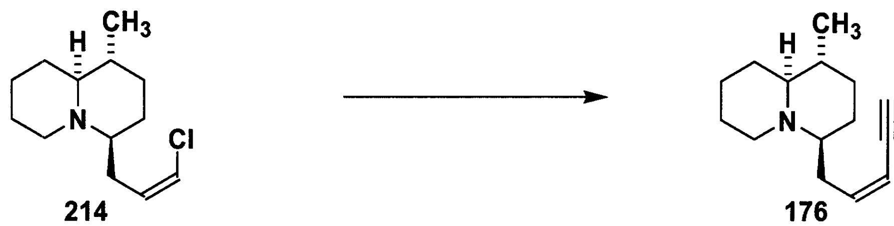
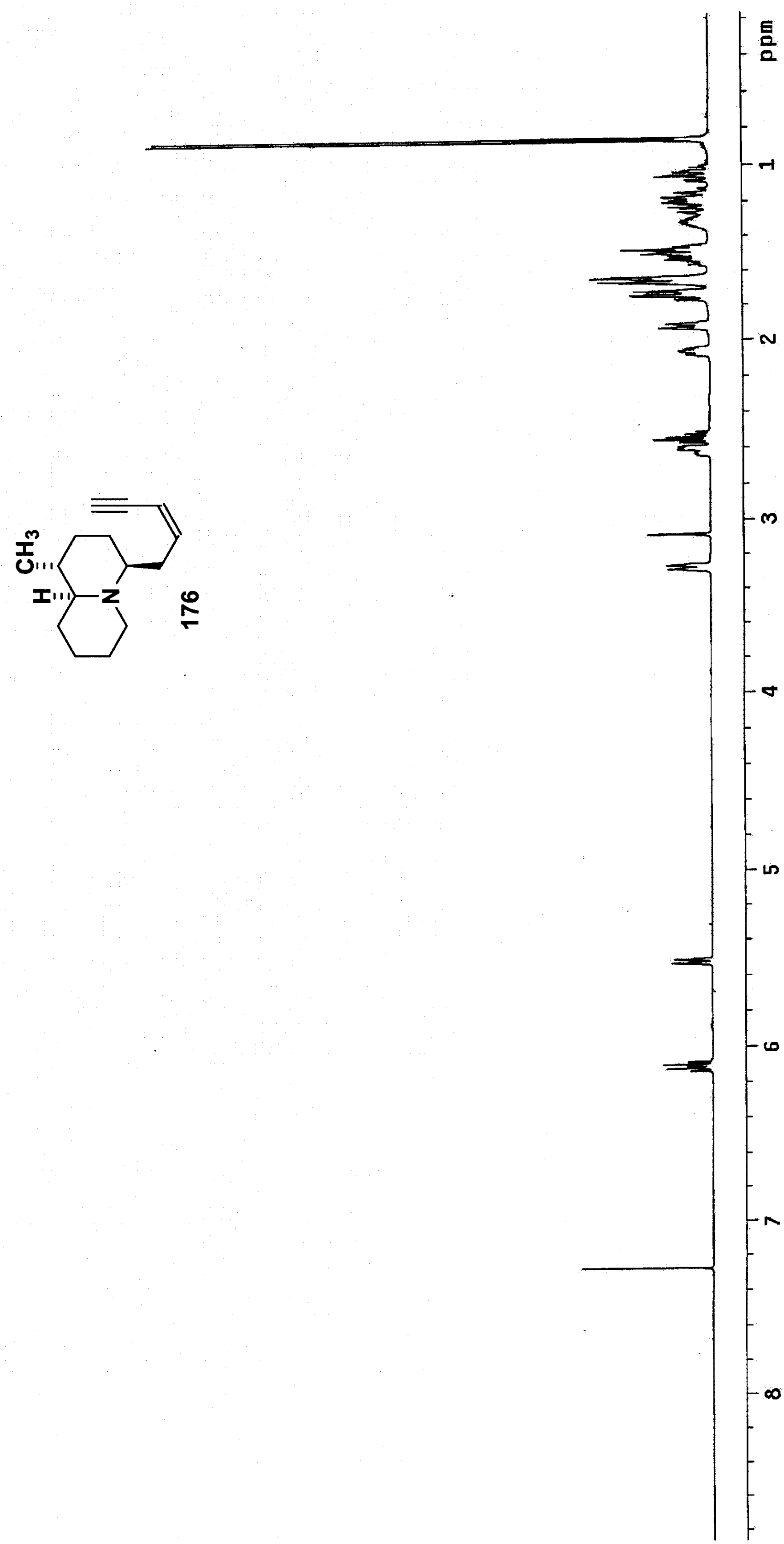


(1*R*, 4*S*, 10*S*)-4-(*Z*)-(Pent-2-en-4-ynyl)-1-methyl-quinolizidine 217A (176). A 25-mL, two-necked, round-bottomed flask equipped with a rubber septum and argon inlet adapter was charged with quinolizidine **214** (0.065 g, 0.29 mmol), $PdCl_2(PhCN)_2$ (0.011 g, 0.03 mmol), CuI (0.011 g, 0.06 mmol), and 1 mL of piperidine. A solution of trimethylsilylacetylene (0.081 mL, 0.056 g, 0.57 mmol) in 1 mL of piperidine was added dropwise via cannula over 1 h and then the reaction mixture was stirred at rt for 1 h. The reaction mixture was diluted with 15 mL of ether and 10 mL of 10% ammonium hydroxide solution. The aqueous layer was extracted with three 10-mL portions of ether, and the combined organic layers were washed with 10 mL of brine, dried over $MgSO_4$, filtered, and concentrated to give 0.150 g of a black oil. This material was dissolved in 2 mL of CH_2Cl_2 and stirred with charcoal (0.150 g) and 3-mercaptopropyl-functionalized silica gel (0.150 g) at rt for 18 h. Filtration through a 1-in plug of Celite in a disposable pipette gave 0.104 g of an orange oil which was used immediately in the next step without further purification.

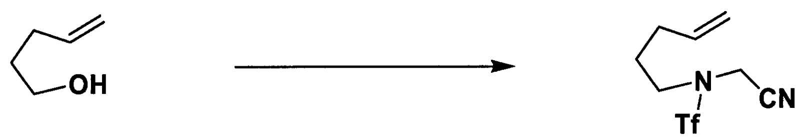
A 25-mL, one-necked, round-bottomed flask equipped with a rubber septum and argon inlet needle was charged with K_2CO_3 (0.040 g, 0.29 mmol), 1.5 mL of MeOH, and the quinolizidine (0.104 g) prepared in the previous step. The reaction mixture was stirred at rt for 2 h and then diluted with 15 mL of water and 15 mL of diethyl ether. The aqueous layer was separated and extracted with three 10-mL portions of diethyl ether, and the combined organic layers were washed with 10 mL of brine, dried over $MgSO_4$, filtered, and concentrated onto 0.5 g of silica gel. The free-flowing powder was placed at the top of a column of 8 g of silica gel and eluted with 0-25% EtOAc-hexanes containing 1% Et_3N to provide 0.051 g (82%) of quinolizidine (–)-217A **176** as a yellow oil: $[\alpha]_D^{22}$ -14° (c 0.8, $CHCl_3$) [lit:[2] $[\alpha]^{20}_D$ –13.75° (c 0.4, $CHCl_3$)]; IR (film): 3312, 2973, 2852, 2784, 2097, 1615, 1452, 1376 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.10 (dt, J = 10.9, 7.1 Hz, 1 H), 5.48 (ddt, J = 10.9, 2.0, 1.6 Hz, 1 H), 3.29 (br d, J = 11.1 Hz, 1 H), 3.09 (d, J = 2.0 Hz, 1 H), 2.53-2.63 (m, 2 H), 2.05-2.10 (m, 1 H), 1.93 (br d, J = 11.9 Hz, 3 H), 1.02-1.79 (m, 12 H), 0.87 (d, J = 6.5 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.9, 109.6, 82.0, 81.0, 69.9, 63.4, 52.0, 36.7, 35.3, 34.2, 32.1, 30.5, 26.6, 25.0, 19.6; Anal. Calcd for $C_{15}H_{23}N$: C, 82.89; H, 10.67; N, 6.44. Found: C, 82.83; H, 10.62; N, 6.42.

The enantiomeric purity of the product was determined by ^1H NMR analysis of the salt formed by reaction with (*R*)-(–)-1,1'-binaphthyl-2,2'-diylphosphoric acid: the phosphoric acid (0.018 g, 0.051 mmol, 1.1 equiv) was added to a solution of **176** (0.010 g, 0.046 mmol) in ca. 0.7 mL of $CDCl_3$. The C-1 methyl group appeared as a doublet (J = 6.5 Hz) at 0.69 ppm; no doublet at 0.77 ppm could be detected. Similar analysis of racemic quinolizidine 217A showed two doublets (1:1 ratio) at 0.77 and 0.69 ppm.



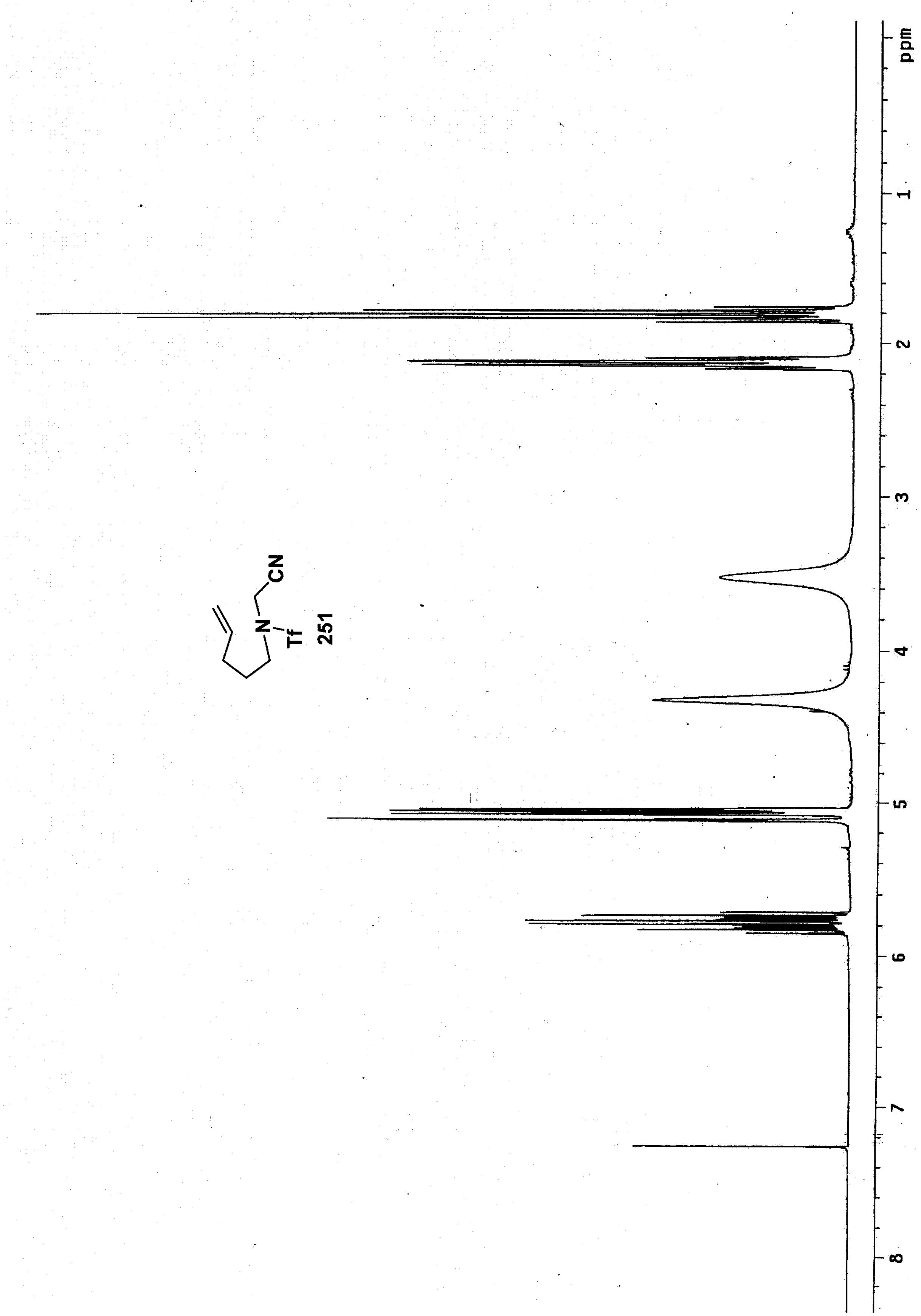
176

Experimental Procedures for Synthesis of Indolizidine (–)-235B′



240 **241**

***N*-(Cyanomethyl)-*N*-(4-pentenyl)trifluoromethanesulfonamide (241).** A 200-mL, three-necked, round-bottomed flask equipped with a rubber septum, argon inlet adapter, and glass stopper was charged with triphenylphosphine (5.59 g, 21.3 mmol), 50 mL of THF, and $TfNHCH_2CN$ (3.64 g, 19.4 mmol). 5-Hexen-1-ol (1.99 mL, 1.67 g, 19.4 mmol) was then added in one portion, and then DIAD (4.13 mL, 4.31 g, 21.3 mmol) was added dropwise by syringe over 20 min. The resulting mixture was stirred at rt for 1.5 h and then concentrated to give 16.11 g of a yellow solid. A solution of this material in 30 mL of CH_2Cl_2 was concentrated onto 30 g of silica gel and transferred to the top of a column of 150 g of silica gel. Gradient elution with 10-20% EtOAc-hexanes yielded 4.56 g (92%) of **251** as a colorless oil: IR (film): 3083, 2995, 2946, 1643, 1397, 1286, 1231 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.79 (ddt, J = 17.0, 10.2, 6.6 Hz, 1 H), 5.05-5.13 (m, 2H), 4.35 (br s, 2 H), 3.58 (br s, 2 H), 2.14 (app q, J = 7.0 Hz, 2 H), 1.82 (quint, J = 7.5 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.3, 119.8 (q, J = 322 Hz), 116.7, 113.5, 49.2, 36.0, 30.3, 26.7; Anal. Calcd for $C_8H_{11}F_3N_2O_2S$: C, 37.50; H, 4.33; N, 10.93. Found: C, 37.37; H, 4.27; N, 11.03.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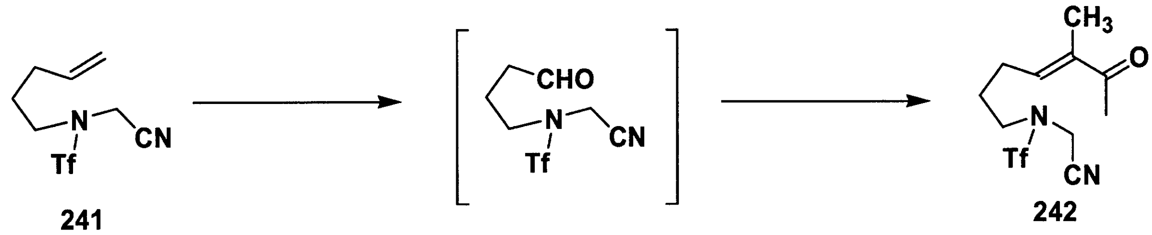
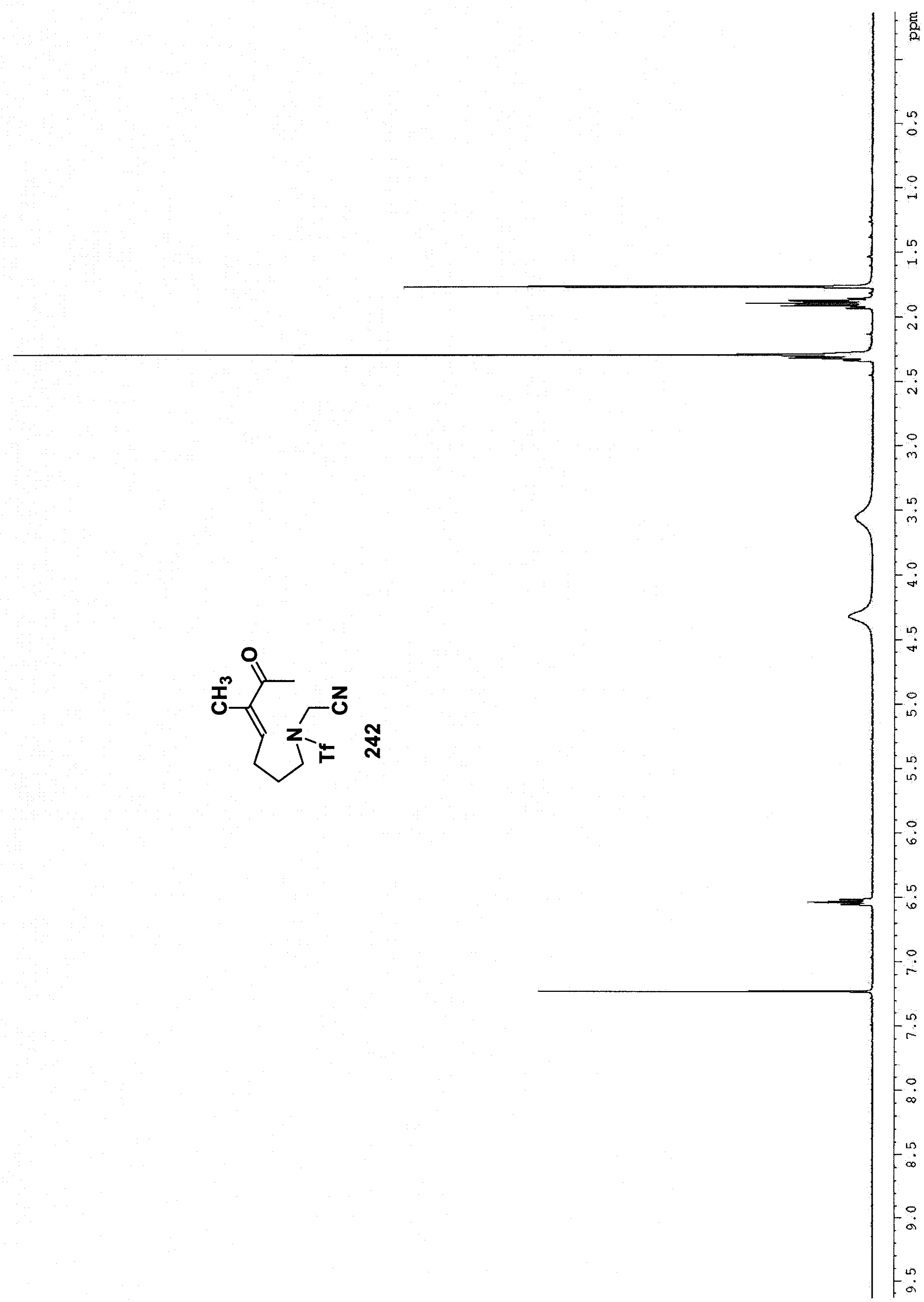


***N*-(Cyanomethyl)-*N*-(6-methyl-(*E*)-4-hepten-6-one)trifluoromethanesulfonamide (242).** A 200-mL, recovery flask containing triflamide **241** (2.34 g, 9.13 mmol) was fitted with a rubber septum and argon-inlet needle and purged with argon. CH_2Cl_2 (50 mL) was added, and the flask was cooled at –78 °C while ozone was bubbled through the solution for 30 min. The resulting blue solution was degassed with a stream of argon for 15 min. Triphenylphosphine (2.40 g, 9.13 mmol) was added, and the solution was allowed to slowly warm to rt over 16 h. Concentration by rotary evaporation afforded 4.81 g of a cloudy, white oil that was used immediately in the next step without further purification.

A 100-mL, round-bottomed flask equipped with a rubber septum and argon inlet needle was charged with a solution of the aldehyde (4.81 g) prepared in the previous step in 50 mL of THF. 3-(Triphenylphosphoranylidene)butan-2-one **194** (3.19 g, 9.59 mmol) was then added in one portion, and the rubber septum was replaced with a reflux condenser equipped with an argon inlet adapter. The reaction mixture was heated at reflux for 12 h, and then allowed to cool to rt and concentrated by rotary evaporation to give 8.11 g of an orange solid. A solution of this material in 30 mL of CH_2Cl_2 was concentrated onto 15 g of silica gel and transferred to the top of a column of 150 g of silica gel. Gradient elution with 20-35% EtOAc-hexanes provided 2.30 g (81%) of **242** as a yellow oil: IR (neat): 2995, 2953, 2869, 1667, 1396, 1275, 1230 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.53 (t, J = 7.3 Hz, 1 H), 4.32 (br s, 2 H), 3.56 (br s, 2 H), 2.28-2.33 (m, 2 H), 2.29 (s, 3 H), 1.89 (app quint, J = 7.5 Hz, 2 H), 1.76 (s, 3 H); ^{13}C NMR (100 MHz,

$CDCl_3$) δ 199.7, 139.9, 139.4, 119.8, 113.3, 49.2, 36.1, 26.7, 25.8, 25.7, 11.6; Anal. Calcd for $C_{11}H_{15}F_3N_2O_3S$: C, 42.30; H, 4.84; N, 8.97. Found: C, 42.35; H, 4.91; N, 8.91.



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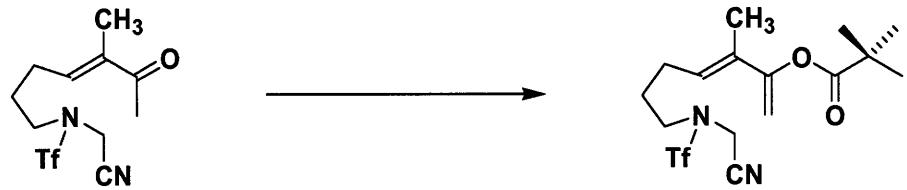
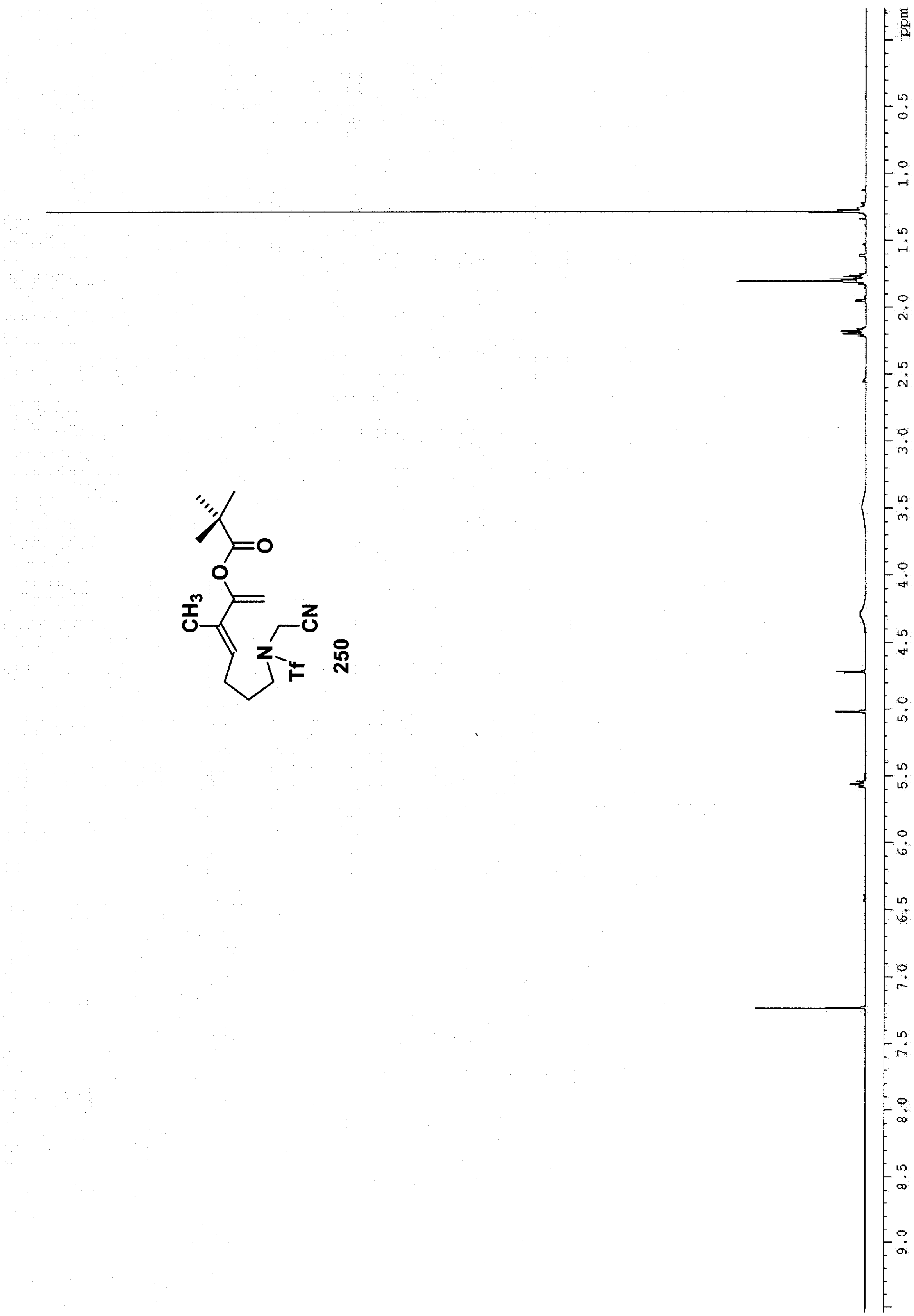
242



242 **250**

***N*-(Cyanomethyl)-*N*-(6-trimethyacetoxy)-5-methyl-(*E*)-4,6-heptadienyl)trifluoromethanesulfonamide (250).** A 250-mL, three-necked, round-bottomed flask equipped with a rubber septum, argon inlet adapter, and glass stopper was charged with NaI (4.25 g, 28.3 mmol), a solution of enone **242** (5.90 g, 18.9 mmol) in 100 mL of CH_3CN, and trimethylacetyl chloride (3.49 mL, 3.42 g, 28.3 mmol). Et_3N (5.31 mL, 3.82 g, 37.8 mmol) was added dropwise via syringe over 5 min, and the resulting mixture was stirred at rt in the dark for 18 h. The reaction mixture was then diluted with 50 mL of satd aq $NaHCO_3$ solution, and the aqueous layer was separated and extracted with three 40-mL portions of ether. The combined organic layers were washed 30 mL of brine, dried over $MgSO_4$, filtered, and concentrated to afford 11.72 g of a yellow oil. Column chromatography on 100 of silica gel (elution with 20% EtOAc-hexanes) provided 6.80 g (91%) of **250** as a yellow oil: IR (film): 2978, 2876, 1745, 1646, 1616, 1481, 1462, 1397, 1267 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.56 (t, J = 7.5 Hz, 1 H), 5.01 (s, 1 H), 4.72 (s, 2 H), 4.28 (br s, 1 H), 3.48 (br s, 2 H), 2.18 (app q, J = 7.3 Hz, 2 H), 1.75-182 (m, 2 H), 1.80 (s, 3 H), 1.27 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.9, 154.4, 130.5, 125.6, 119.8 (q, J = 322 Hz), 113.6,101.8, 49.4, 39.2, 36.2, 27.4, 27.2, 24.8, 13.5; Anal. Calcd for $C_{16}H_{23}F_3N_2O_4S$: C, 48.48; H, 5.85; N, 7.07. Found: C, 48.55; H, 5.81; N, 7.06.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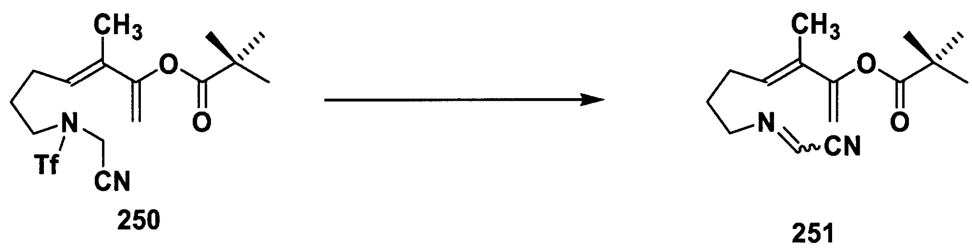
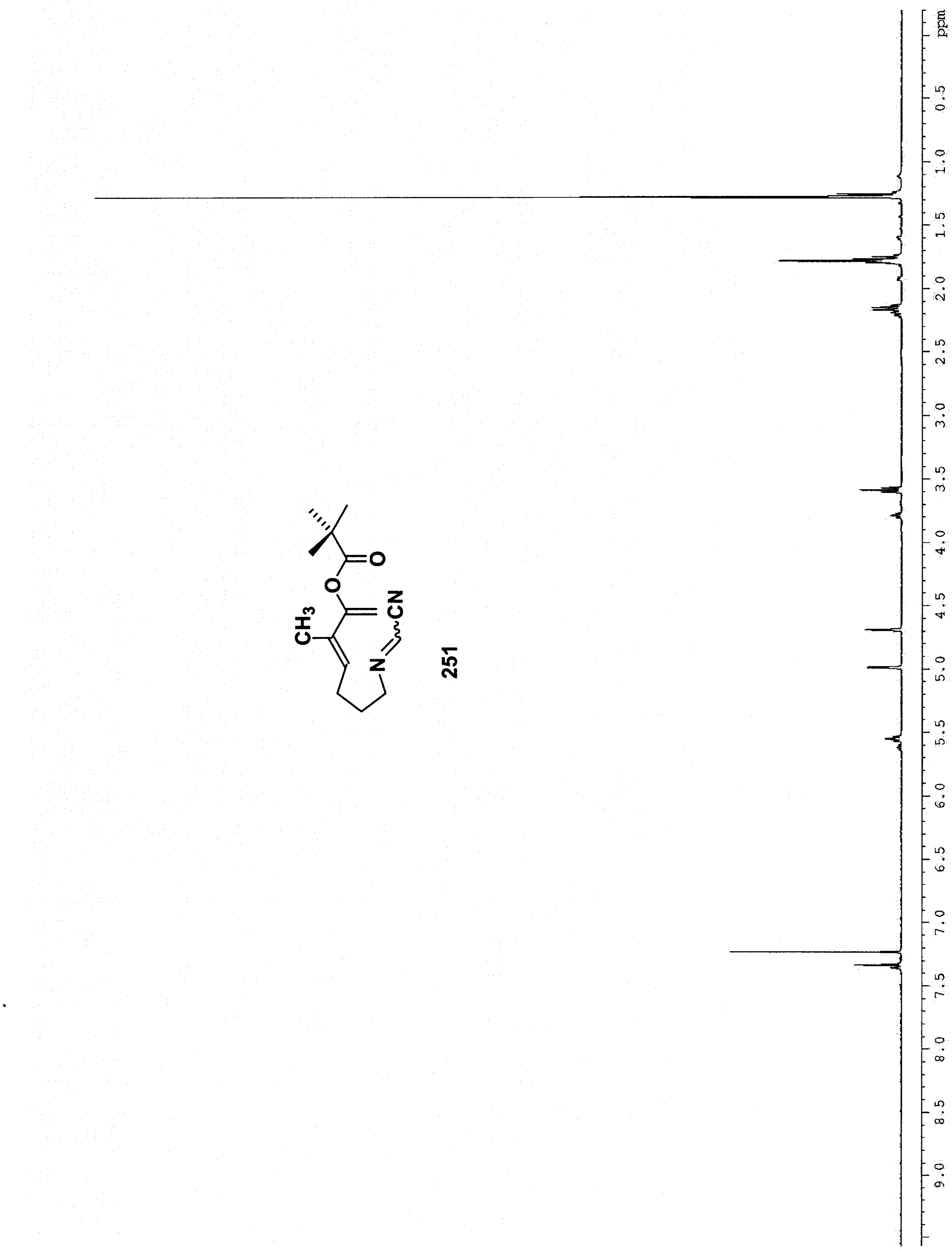


5-Methyl-6-trimethyacetoxy-(*E*)-4,6-heptadienyliminoacetonitrile (251). A 250-mL, round-bottomed flask equipped with a reflux condenser fitted with an argon inlet adapter was charged with Cs_2CO_3 (18.08 g, 55.5 mmol) and 60 mL of THF. A solution of triflamide **250** (5.50 g, 13.9 mmol) in 20 mL of THF was then added in one portion, and the reaction mixture was heated at 55 °C for 1.5 h. The resulting mixture was allowed to cool to rt and then diluted with 50 mL of water. The aqueous layer was separated and extracted with three 35-mL portions of ether, and the combined organic layers were washed with 25 mL of brine, dried over $MgSO_4$, filtered, and concentrated to give 5.91 g of a yellow oil. Column chromatography on 25 g of silica gel (elution with 20% EtOAc-hexanes containing 1% Et_3N) afforded 3.13 g (86%) of **251** (75:25 mixture of *E* and *Z* imine isomers by ^{1}H NMR analysis) as a yellow oil: IR (film): 2975, 2873, 1747, 1645, 1618, 1480, 1416, 1368, 1263 cm^{-1}; For *Z* isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (t, J = 2.2 Hz, 1 H), 5.62 (app t, J = 6.9 Hz, 1 H), 4.99 (s, 1 H), 4.69 (s, 1 H), 3.79 (td, J = 6.8, 2.2 Hz, 2 H), 2.13-2.26 (m, 2 H), 1.73-1.80 (m, 2 H), 1.78 (s, 3 H), 1.25 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.9, 154.6, 136.4, 131.8, 127.0, 114.6, 101.5, 59.3, 39.3, 29.7, 27.2, 25.9, 13.5; For *E* isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (t, J = 1.4 Hz, 1 H), 5.55 (app t, J = 7.3 Hz, 1 H), 4.99 (s, 1 H), 4.69 (s, 1 H), 3.59 (td, J = 6.8, 1.4 Hz, 2 H), 2.13-2.26 (m, 2 H), 1.73-1.80 (m, 2 H), 1.78 (s, 3 H), 1.26 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.9, 154.6, 136.4, 129.9, 126.8, 114.6, 101.5, 62.2, 39.3, 29.5, 27.4, 25.5, 13.5; Anal. Calcd for $C_{15}H_{22}N_2O_2$: C, 68.67; H, 8.45; N, 10.68. Found: C, 68.49; H, 8.49; N, 10.70.



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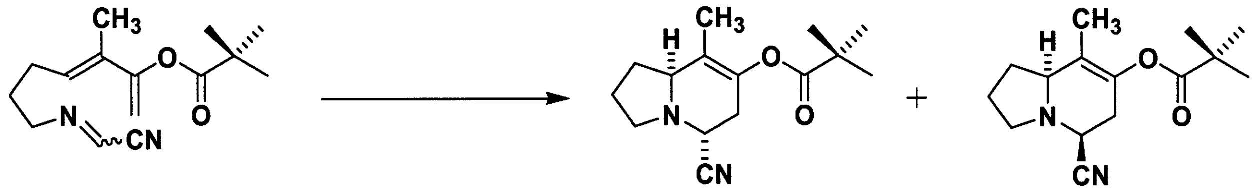
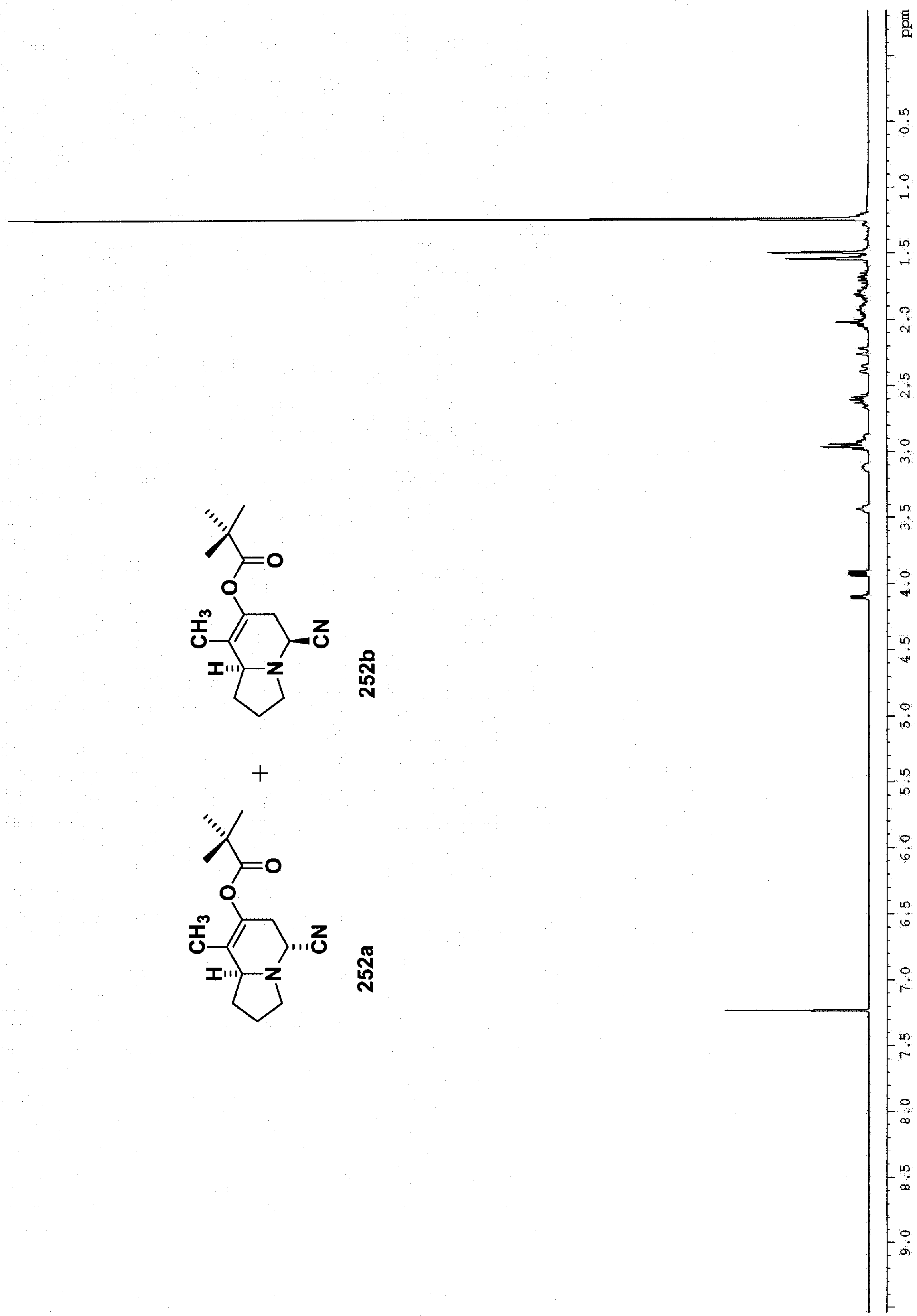


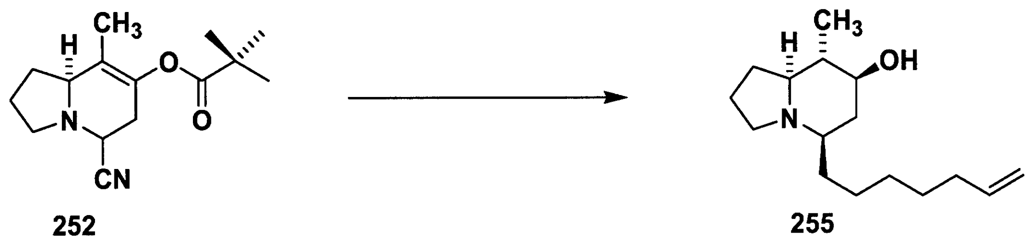
251 252a 252b

8-Methyl-*cis*-7,8-didehydro-7-trimethyacetoxy-5-cyanoindolizidine (252a) and **8-Methyl-*trans*-7,8-didehydro-7-trimethyacetoxy-5-cyanoindolizidine (252b).** A 250-mL, two-necked, round-bottomed flask equipped with a rubber septum and argon inlet adapter was charged with imine **251** (2.73 g, 10.4 mmol), 4Å molecular sieves (ca. 0.300 g), and 100 mL of CH_2Cl_2. The solution was cooled at 0 °C while methanesulfonic acid (0.676 mL, 1.00 g, 10.4 mmol) was added dropwise via syringe over 3 min. The reaction mixture was stirred at 0 °C for 30 min and then diluted with 60 mL of satd aq $NaHCO_3$, and the aqueous layer was separated and extracted with three 25-mL portions of CH_2Cl_2. The combined organic layers were washed with 20 mL of brine, dried over $MgSO_4$, filtered, and concentrated to give 2.91 g of an orange oil. A solution of his material 20 mL of CH_3CN in a 25-mL round-bottomed flask was stirred at 45 °C for 1.5 h, and then allowed to cool to rt and concentrated to give 2.91 g of an orange oil. Purification by column chromatography on 80 g of silica gel (elution with 1% Et_3N-25% EtOAc-hexanes) afforded 2.155 g (79%) of **252a** and **252b** (50:50 mixture by ^{1}H NMR analysis) as an orange oil: IR (CH_2Cl_2): 2974, 2874, 2817, 1743, 1703, 1481, 1462, 1397, 1368, 1328, 1277 cm^{-1}; For **252a**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.10 (d, J = 5.7 Hz, 1 H), 3.13 (br s, 1 H), 2.87-2.98 (m, 2 H), 2.57-2.67 (m, 1 H), 2.37 (dm, J = 16.1 Hz, 1 H), 1.98-2.08 (m, 1 H), 1.88-1.97 (m, 1 H), 1.76-1.83 (m, 1 H), 1.63-1.72 (m, 1 H), 1.24 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.4, 137.1, 122.0, 116.8, 60.0, 50.0, 47.7, 39.1, 30.6, 28.5, 27.3, 21.9, 12.1: For **252b**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.02 (dd, J = 9.2, 4.6 Hz, 1 H), 3.44 (t, J = 7.1 Hz, 1 H), 2.87-2.98 (m, 2 H), 2.57-2.67 (m, 1 H), 2.24 (d, J = 16.0 Hz, 1 H), 1.98-2.08 (m, 1 H), 1.88-1.97 (m, 1 H), 1.76-1.83 (m, 1 H), 1.63-1.72 (m, 1 H), 1.24 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.6, 137.1, 122.5, 119.3, 62.3, 49.1, 47.7, 39.1, 29.3, 28.5, 27.3, 23.1, 12.2; Anal. Calcd for $C_{15}H_{22}N_2O_2$: C, 68.67; H, 8.45; N, 10.68. Found: C, 68.49; H, 8.49; N, 10.70.



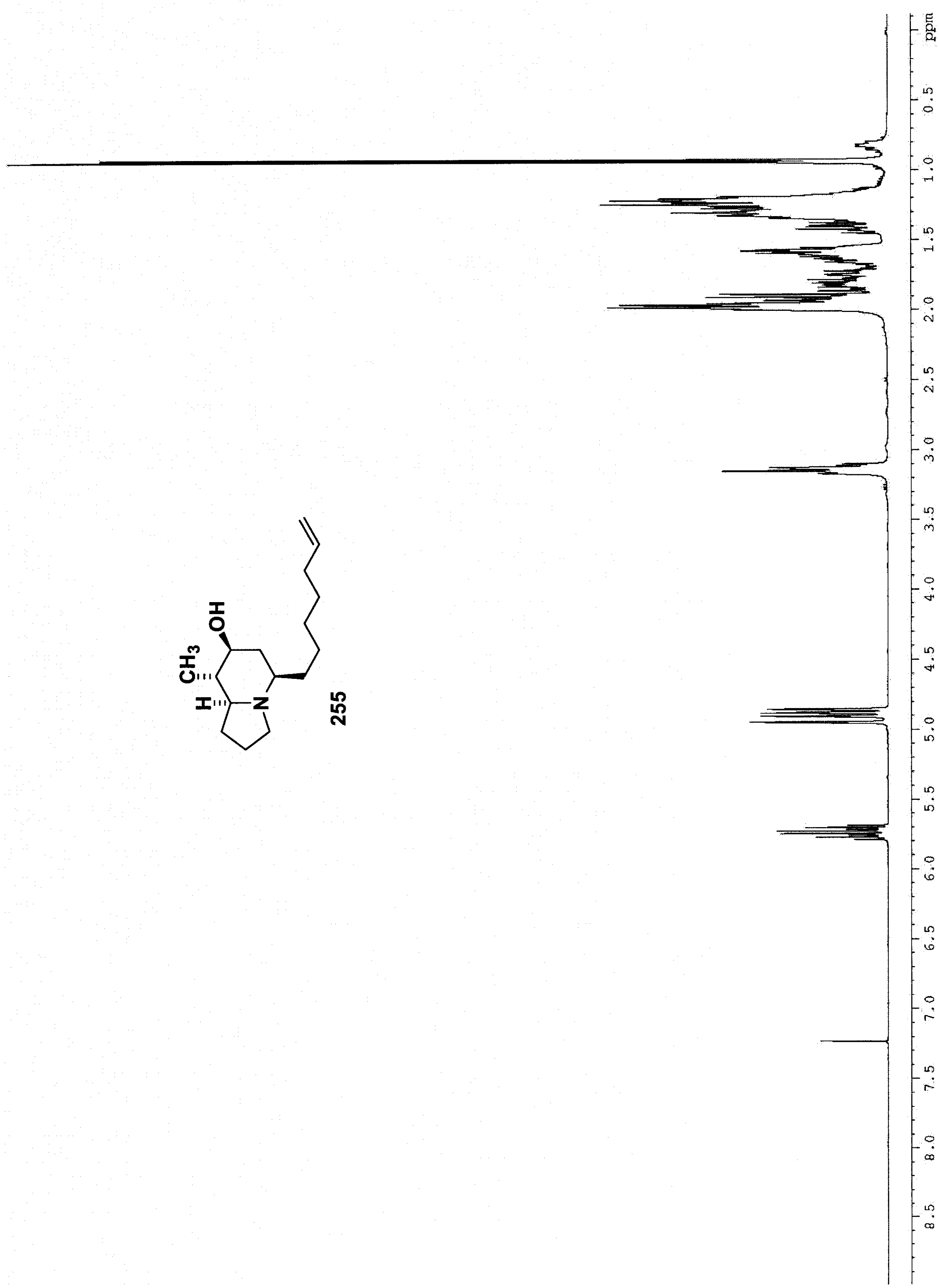
252a

252b



(5α,8β,9β)-5-(6-heptene)-8-methyl-7-indolizidinol (255). A 50-mL, two-necked, round-bottomed flask equipped with a rubber septum and argon inlet adapter was charged with HMDS (0.323 mL, 0.247 g, 1.53 mmol) and 5 mL of THF. The solution was cooled at 0 °C while 0.571 mL of *n*-BuLi solution (2.68 M in hexane, 1.53 mmol) was added dropwise via syringe over 1 min. The resulting solution was stirred at 0 °C for 10 min and then cooled at -78 °C while a precooled (-78 °C) solution of amino nitrile **252** (0.160 g, 0.61 mmol) in 3 mL of THF was added dropwise via cannula over 5 min. The resulting solution was stirred at -78 °C for 3.5 h, and then a precooled (-78 °C) solution of 7-bromoheptene (0.102 mL, 0.119 g, 0.67 mmol) was added rapidly via syringe. The reaction mixture was stirred at 0 °C for 1 h, and then diluted with 80 mL of ether and 30 mL of water. The aqueous layer was extracted with three 25-mL portions of ether, and the combined organic layers were washed with 30 mL of brine, dried over K_2CO_3, filtered, and concentrated to give 0.631 g of an orange oil that was used immediately in the next step without further purification.

A 50-mL, three-necked, round-bottomed flask equipped with a rubber septum, argon inlet adaptor, and cold-finger condenser was charged Na (0.351g, 15.3 mmol) and 25 mL of NH_3 at -78 °C. The resulting blue solution was stirred at -78 °C for 30 min, and then a solution of the α-amino nitrile (0.631 g) prepared in the previous step in 8 mL of THF was added over 2 min via cannula. The reaction mixture was stirred at -78 °C for 1 h, and then EtOH (0.178 mL, 0.141g, 3.05 mmol) was added via syringe and the resulting reaction mixture was stirred at -78 °C for 30 min. NH_4Cl (0.815 g, 15.3 mmol) was added in one portion and the colorless reaction mixture was allowed to warm to rt over 30 min. The reaction mixture was then diluted with 15 mL of satd aq $NaHCO_3$ solution, and the aqueous layer was separated and extracted with three 15-mL portions of CH_2Cl_2. The combined organic layers were washed with 15 mL of brine, dried over $MgSO_4$, filtered, and concentrated to afford 0.158 g of an orange oil. Purification by column chromatography on 5 g of Al_2O_3 (elution with 50% EtOAc-hexanes) afforded 0.099 g (65%) of **255** as a yellow semi-solid: IR (neat): 3355, 2930, 2789, 2694, 1641, 1460, 1375 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.74 (ddt, J = 17.0, 10.2, 6.7 Hz, 1 H), 4.93 (dm, J = 17.1 Hz, 1 H), 4.87 (dm, J = 10.2 Hz, 1 H), 3.10-3.17 (m, 2 H), 1.55-2.00 (m, 10 H), 1.19-1.45 (m, 11 H), 0.93 (t, J = 6.5 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.2, 114.4, 75.2, 69.4, 61.0, 51.4, 44.5, 40.5, 34.4, 33.9, 29.6, 29.0, 28.9, 25.6, 21.3, 14.6.



255
ppm

Kevin M. Maloney

Education

Ph.D. Organic Chemistry, ***Massachusetts Institute of Technology*** *May 2007*
Advisor: Professor Rick L. Danheiser
Thesis Title: "[4+2] Cycloadditions of Iminoacetonitriles: A General Strategy for the Synthesis of Quinolizidines, Indolizidines, and Piperidines"

B.S. Chemistry and B.S. Biochemistry, ***Stetson University,*** *Summa cum laude* *May 2002*
- Cumulative GPA: 4.0/4.0

Research Experience

Graduate Research, ***Massachusetts Institute of Technology*** *January 2003 - Present*
Advisor: Professor Rick L. Danheiser
- Developed an efficient total synthesis of the biologically active quinolizidine alkaloid (–)-217A
- Studies directed toward the total synthesis of indolizidine alkaloid (–)-235B′ and quinolizidine alkaloid (–)-207I
- Synthetic and mechanistic studies on [4+2] cycloadditions of iminoacetonitriles
- Supervised and mentored research projects for two undergraduate students

Undergraduate Research, ***Stetson University***
Advisor: Professor Dwaine D. Jackson *September 2000 – May 2001*
- Studied transcription in *E. coli* using molecular biology techniques

Advisor: Professor Ramee Indralingam *September 2001 – May 2002*
- Developed a bio-analytical teaching experiment involving the isolation and determination of the amount of iron found in chicken eggs

Howard Hughes Summer Fellow, ***Georgia Institute of Technology*** *May 2001 – September 2001*
Advisor: Professor Loren D. Williams
- Determined the thermodynamic properties and structural features of pseudouridine 55 synthase

Teaching and Service

Chemistry R.E.F.S., ***Massachusetts Institute of Technology*** *January 2004 - Present*
(Resource for Easing Friction & Stress)
- Serve as a resource for fellow graduate students to help manage adjustments, conflicts, and stress
- Massachusetts State Certified in mediation

Chemistry Outreach Coordinator, ***Massachusetts Institute of Technology*** *January 2002 – Present*
- Coordinate program in which MIT graduate students perform chemistry presentations at 35 local high schools each year

Teaching Assistant, ***Massachusetts Institute of Technology*** *September 2002 – May 2003*
- Led recitation sections and review sessions for organic chemistry

Publications and Presentations

Maloney, K. M.; Danheiser, R. L. "Total Synthesis of Quinolizidine Alkaloid (–)-217A. Application of Iminoacetonitrile Cycloadditions in Organic Synthesis", *Org. Lett.* **2005**, *7*, 3115.

Maloney, K. M.; Amos, D. T.; Danheiser, R. L. "Intramolecular [4+2] Cycloadditions of Iminoacetonitriles. A General Strategy for the Synthesis of Substituted Quinolizidines and Indolizidines." *J. Am. Chem. Soc.* Manuscript in preparation.

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Maloney, K. M.; Burnett, R.; Williams, L. D. "The Physical Characterization of Pseudouridine 55 Synthase" Howard Hughes Summer Research Presentation, Atlanta, GA, August 19-20, 2001. (Poster)

Honors and Awards

NIH Cancer Training Fellowship, 2003

SYNLETT Star Award – Promising Young Organic Chemists, 2003

Excellence in Teaching Award – Massachusetts Institute of Technology, 2003

Chemistry Student of the Year – Stetson University, 2002

Howard Hughes Summer Fellowship – Georgia Institute of Technology, 2001

Student-Athlete of the Year – Stetson University Athletic Department, 2000

Faculty Merit Scholarship – Stetson University, 1998

ACS Polymer Award in Organic Chemistry – American Chemical Society, 1998

Affiliations

American Chemical Society, Organic Division Member