SYNTHESIS OF NITROGEN HETEROCYCLES VIA THE INTRAMOLECULAR [4+2] CYCLOADDITION OF IMINOACETONITRILES

By

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I have been fortunate to meet many wonderful people during my time in graduate school, and in particular I would to wish Bob Kennedy, Dana Buske, Kathy Franz, Tom "5 for 5" Gray, and Rob Dempski all the best in the future.

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 you.

And finally, I would like to thank my best friend and wife, Muria, for her friendship, her love, and her patience. Being married to a graduate student is not easy, but she has supported me throughout the process, encouraging me to do the best that I can. I couldn't have done it without you. I look forward to many years in Minnesota with you, especially the weekends!

To my wife Muria

and

my parents

Synthesis of Nitrogen Heterocycles via the Intramolecular [4+2] Cycloaddition of Iminoacetonitriles

by

David Thomas Amos

Submitted to the Department of Chemistry
on June 9, 2003 in partial fulfillment of the
requirements for the Degree of Doctor of Philosophy

ABSTRACT

Iminoacetonitriles have been shown to function as aza dienophiles in intramolecular Diels-Alder reactions, affording substituted quinolizidines and indolizidines. The cycloadducts are formed with a high preference for an *exo*-orientated cyano group due to the a-amino nitrile anomeric effect. The substrates for these [4+2] cycloadditions are prepared from readily available alcohols via a Mitsunobu reaction with the previously unknown *N*-cyanomethyltriflamide ($HN(Tf)CH_2CN$) followed by cesium carbonate promoted elimination of trifluoromethanesulfinate. The α-amino nitrile cycloadducts are versatile synthetic intermediates and can be elaborated via alkylation, reduction, and nucleophilic addition chemistry to provide a variety of substituted and functionalized nitrogen heterocycles. Initial investigations have been undertaken to explore the use of this methodology in the total synthesis of alkaloid natural products.

Thesis Supervisor: Rick L. Danheiser

Title: Professor of Chemistry

Table of Contents

Part I

Introduction and Background

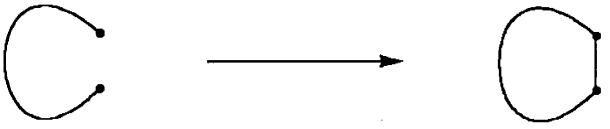
Chapter 1

Introduction

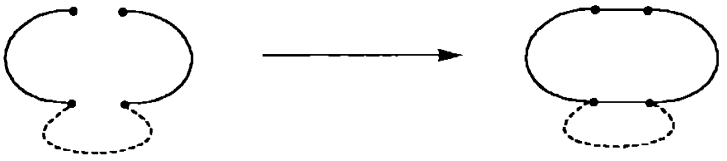
Cyclization and Annulation Strategies

The vast number of natural products and pharmaceutical agents that contain a cyclic core has motivated our research group's interest in developing practical and efficient methods for the preparation of cyclic and polycyclic molecules. There are two general strategies for the creation of such compounds, cyclization and annulation. The defining process in a cyclization strategy is the intramolecular formation of one new bond to form the cyclic structure. A more convergent and powerful strategy is the annulation approach, in which two components are brought together to form two new bonds producing the desired cyclic compound. As with any reaction where several bonds are formed, there exists the possibility of creating multiple stereocenters at the same time. Intramolecular versions of the annulation strategy are particularly powerful methods for the rapid assembly of polycyclic structures.

Cyclization Strategy



Annulation Strategy



Cycloadditions of Enynes

Annulation strategies can take many forms, ranging from a concerted reaction to a multi-step procedure. Recent efforts in the Danheiser laboratory have focused on developments in the concerted end of the spectrum. The Diels-Alder reaction, first reported in 1949 by Otto Diels and Kurt Alder,[1] has become one of the most powerful reactions in organic synthesis.[2,3] The [4+2] cycloaddition reaction of dienes and dienophiles, each of which can be substituted with a wide range of functionality, allows access to a diverse set of carbocyclic and heterocyclic molecules. Our interest has focused on the development of new [4+2] cycloaddition reactions, with inspiration coming from novel cycloaromatization reactions such as the Bergman reaction and the Moore cyclization. These reactions rely on highly unsaturated, conjugated molecules reacting to form new cyclic molecules. Recently our laboratory has explored the possibility of reacting an enyne with an enynophile, akin to the Diels-Alder cycloaddition, to form a new aromatic or dihydroaromatic system (Scheme 1).

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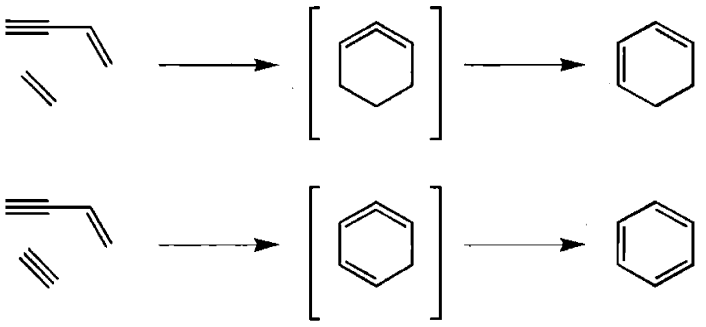
[1] Diels, O.; Alder, K. *Liebigs Ann. Chem.* **1928**, *460*, 98.

[2] 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.

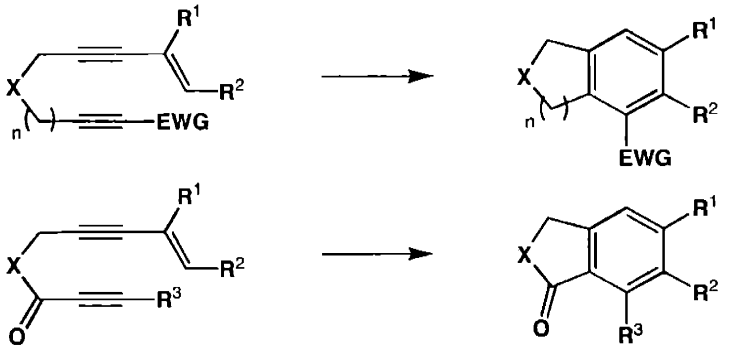
[3] For reviews of the intramolecular Diels-Alder reaction, see: (a) Rousch, W. R. In *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I., Eds.; Pergamon Press: Oxford, 1991, Vol. 5, pp 513-550. (b) Ciganek, E. In *Organic Reactions*; Dauben, W. G., Ed.; John Wiley & Sons: New York, 1984, Vol.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

Scheme 1



In 1994, our group was the first to report a systematic investigation of the scope of the intramolecular [4+2] cycloaddition of conjugated enynes.[4] Subsequent work in our group has demonstrated that this reaction can be conducted under thermal conditions as well as in the presence of Lewis acids with a variety of substituents on the enyne, enynophile, and connecting tether (Scheme 2).[5]

Scheme 2



Further studies have focused on utilizing this reaction to produce heterocyclic molecules. The first approach investigated involved replacing one of the carbon atoms in the connecting tether with a heteratom. A second approach involved replacing one of the

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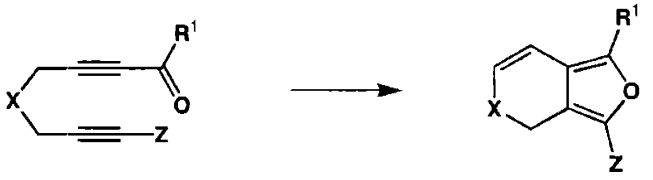
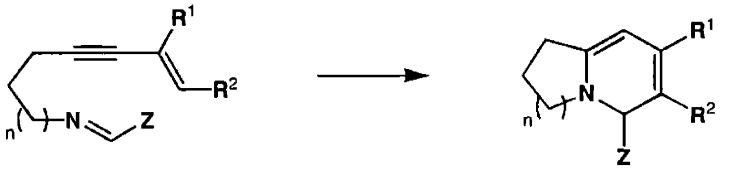
[4] Danheiser, R. L.; Gould, A. E.; Fernandez de la Pradilla, R.; Helgason, A. L. *J. Org. Chem.* **1994**, *59*, 5514.

[5] For a more in depth discussion of the enyne cycloaddition see: (a) Helgason, A. L. Ph. D. Thesis, Massachusetts Institute of Technology, May 1994. (b) Gould, A. E. Ph. D. Thesis, Massachusetts Institute of Technology, June 1996. (c) Palucki, B. L. Ph. D. Thesis, Massachusetts Institute of Technology, June 1997.

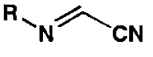
carbon atoms in the enyne with a heteroatom. Melanie Wills and Jason Diffendal demonstrated the feasibility of replacing one of the carbon atoms in the 4-π component with an oxygen atom. The [4+2] cycloaddition of conjugated alkynyl carbonyl compounds provides access to dihydroisobenzofurans with a variety of functionality. [6]



Recently, we turned our attention to exploring the replacement of one of the carbon atoms of the "enynophile" with a heteroatom. For example, the ability to use an imine as a reactive 2-π component would allow access to substituted nitrogen heterocycles and would be a powerful addition to the scope of the enyne cycloaddition.



Based on our studies in the carbocyclic series, we expected that an electron-deficient imine would be the most successful imine derivative for the proposed enyne cycloaddition. After considering a variety of alternative imine derivatives, we decided to focus our interest on cycloadditions of *iminoacetonitriles* (**1**).

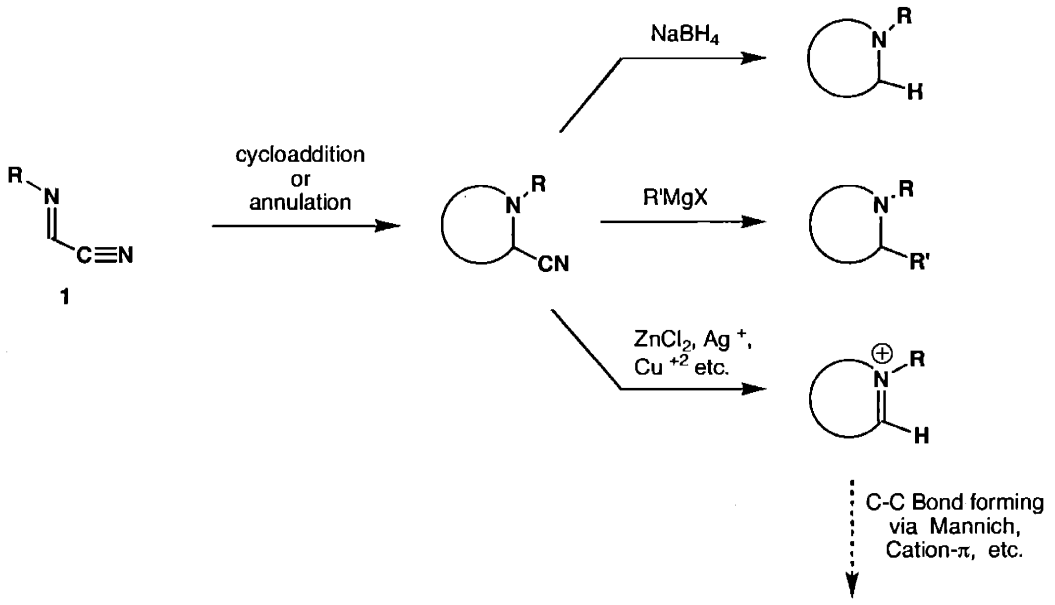


1

As discussed later, we believed these imines would be readily available, exceptionally reactive in the desired cycloaddition, and would provide access to cycloadducts with

[6] For a discussion regarding the scope and mechanism of this cycloaddition see: (a) Wills, M. S. B.; Danheiser, R. L. *J. Am. Chem. Soc.* **1998**, *120*, 9378. (b) Wills, M. S. B. Ph. D. Thesis, Massachusetts Institute of Technology, June 1998. (c) Diffendal, J. M. Ph. D. Thesis, Massachusetts Institute of Technology, September 2002.

regiochemical features different from that observed with conventional imines. As shown below, the resulting cycloadducts (α-amino nitriles) would be versatile synthetic intermediates amenable to further synthetic elaboration.



In fact, it appeared to us that this class of imines might serve as valuable components in a variety of different annulation and cycloaddition processes, including the hetero Diels-Alder reaction. To place our work in perspective, the next chapter provides an outline of prior work on the application of a variety of imines as aza-dienophiles in the Diels-Alder reaction.

Chapter 2

Diels-Alder Reactions of Imine Dienophiles

The development of methods employing imines as dienophiles in the hetero Diels-Alder reaction has increased the ease with which nitrogen heterocycles can be synthesized. This chapter provides background on the reaction of a variety of activated imino dienophiles in both the inter- and intramolecular aza Diels-Alder reaction. The chapter concludes with a discussion of the class of activated imines that are the subject of this thesis, iminonitriles.

Classes of Imino Dienophiles

The use of imines as dienophiles in the Diels-Alder reaction has received a great deal of attention.[7] This discussion will be emphasize the reactions of "activated" imines or imines with an attached electron-withdrawing group, since these imines tend to be the most reactive in hetero [4+2] cycloadditions. Simple unactivated imines can act as 2-π components in the aza Diels-Alder reaction but require higher temperatures, more reactive diene partners, or the presence of Lewis acids. Hetero Diels-Alder reactions of unactivated imines tend to be more limited in scope. However, Grieco and coworkers have found that *iminium ions* can function as relatively reactive aza dienophiles.[8]

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[7] For reviews of imino dienophiles, see: (a) Buonora, P.; Olsen, J.-C.; Oh, T. *Tetrahedron* **2001**, *57*, 6099. (b) Tietze, L. F.; Kettschau, G. *Top. Curr. Chem.* **1997**, *189*, 1. (c) Boger, D. L.; Weinreb, S. M. *Hetero Diels-Alder Methodology in Organic Synthesis*; Academic: San Diego, 1987; Chapter 2. (d) Weinreb, S. M. In *Comprehensive Organic Synthesis;* Trost, B. M.; Fleming, I., Eds.; Pergamon Press: Oxford, 1991, Vol. 5, pp 401-413. (e) Weinreb, S. M.; Levin, J. I. *Heterocycles* **1979**, *12*, 949. (f) Weinreb, S. M.; Staib, R. R. *Tetrahedron*, **1982**, *38*, 3087. (g) Weinreb, S. M. *Acc. Chem. Res.* **1985**, *18*, 16.

[8] Larsen, S. D.; Grieco, P. A. *J. Am. Chem. Soc.* **1985**, *107*, 1768.

Treatment of a variety of dienes, cyclic and acyclic, with an aqueous solution of formaldehyde and either benzylamine hydrochloride or ammonium chloride affords heterocyclic compounds in good to excellent yield (35-95%). Unfortunately, replacing formaldehyde with acetaldehyde or acetone leads to a reduction in rate and yield, as well as an increase in formation of byproducts. Recently, Wang and coworkers have reported that the scope of these hetero Diels-Alder reactions is expanded by the use of certain lanthanide triflates as catalysts.[9]

Broader in scope and most relevant to the work presented in this thesis are electron deficient imines. Activated imines can be subdivided into four categories: *N*-sulfonylimines, *N*-acylimines, *C*-acylimines, and oximino compounds. A comprehensive review of hetero Diels-Alder reactions involving *all* types of imines has recently been published by Oh et al.[7a]

Carbocyclic Diels-Alder reactions rely on low-lying LUMOs of electron poor alkenes interacting with HOMOs of electron-rich dienes. Most hetero Diels-Alder reactions involve the same interaction, so an electron deficient imine with a low lying LUMO is more reactive in [4+2] cycloadditions. As is the case with the carbocyclic Diels-Alder reaction, the $HOMO_{diene}$ and $LUMO_{dienophile}$ frontier molecular orbitals (FMOs) control the regiochemistry of aza Diels-Alder reactions.[10] Scheme 3 provides a graphical representation of the controlling forces described by FMO theory.[11] This powerful theory predicts that the strongest interactions involve the FMOs that have the

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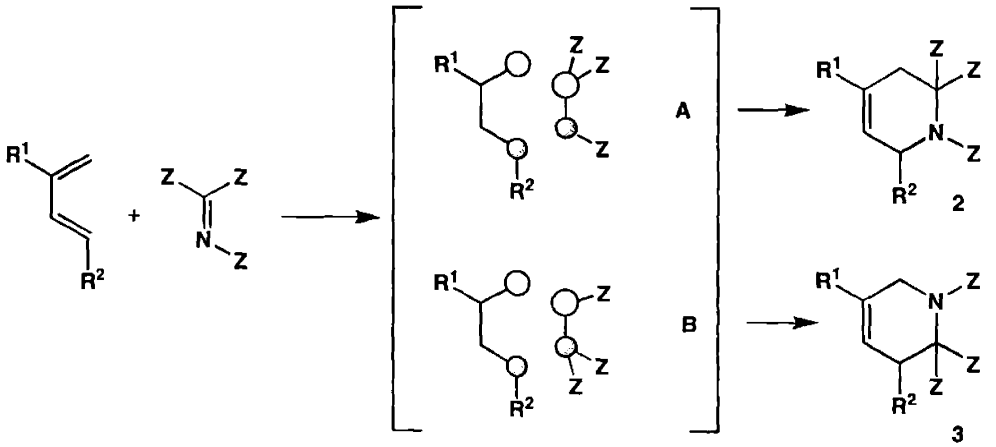
[9] Yu, L.; Chen, D.; Wang, P. G. *Tetrahedron Lett.* **1996**, *37*, 2169.

[10] (a) Fleming, I. *Frontier Orbitals and Organic Chemical Reactions*; John Wiley & Sons: New York, 1976. (b) Desimoni, G.; Barco, A.; Pollini, G. P. *Natural Products Synthesis Through Pericyclic Reactions*, ACS Monograph 180; American Chemical Society: Washington, D.C., 1983; pp 229-236. (c) Fukui, K. *Acc. Chem. Res.* **1971**, *4*, 57.

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

largest atomic coefficients. 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 **2**, while a larger coefficient on the nitrogen atom (**B**) favors regioisomeric product **3**. The great majority of imino dienophiles react to provide products with the substitution pattern of structure **2**.[12] Only in imines with two electron withdrawing groups on carbon does the alternate substitution pattern **3** emerge.



N-Sulfonylimines[13]

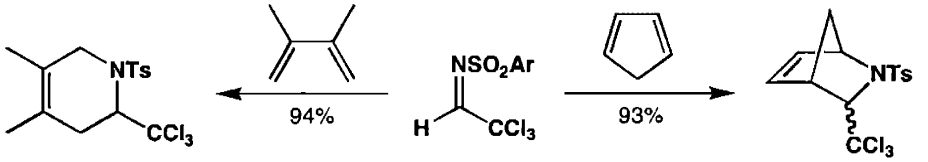
Albrecht and Kresze reported one of the earliest systematic studies of imino dienophiles in their investigation of the use of *N*-sulfonylimines as reactive 2-π components in the hetero Diels-Alder reaction.[14] This study focused on the reactions of trihalomethyl-substituted imines, which were prepared by the condensation of a trihaloacetaldehyde and toluenesulfonamide. As shown in eq 1, these *N*-sulfonylimines participate in cycloadditions with 2,3-dimethylbutadiene and cyclopentadiene to produce

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

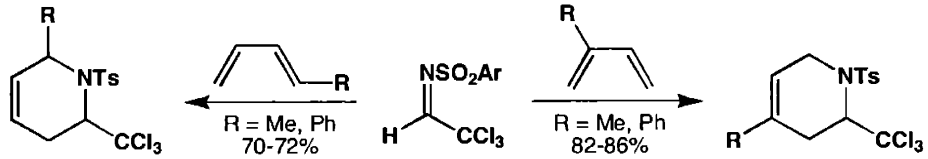
[13] For a review of *N*-sulfonylimines, see: Weinreb, S. M. *Top. Curr. Chem.* **1997**, *190*, 131.

[14] Albrecht, R.; Kresze, G. *Chem. Ber.* **1964**, *97*, 490.

the desired [4+2] cycloadducts. In a subsequent report,[15] the same authors disclosed the cycloaddition of these imines with a variety of mono-substituted dienes (eq 2). The products in eq 1 and 2 were all obtained by refluxing a mixture of the *N*-sulfonylimine and the indicated diene in benzene. Cycloaddition with cyclopentadiene produces a 78:22 mixture of endo and exo stereoisomers,[16] but no mention is made of the stereochemical outcome when 1-substituted dienes are employed.



(1)

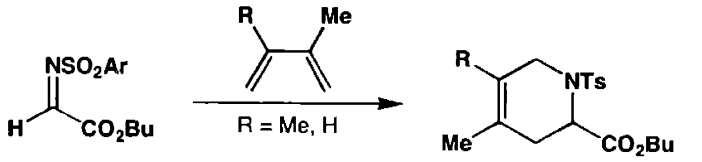


(2)

A drawback to this method is requirement for trihaloacetaldehyde-derived imines. In most cases, the trihalomethyl substituent in the product would probably have to be excised or incorporated into the final target molecule. Presumably the trihalomethyl group serves as an electron-withdrawing substituent on the dienophile and is required for success of the Diels-Alder cycloaddition. Albrecht and Kresze also explored the use of glyoxal-derived *N*-sulfonylimines in an effort to extend the scope of their methodology and avoid the use of the trihalomethyl group.[17] The cycloadditions of these activated imines proceed in refluxing benzene to provide cycloadducts in good yield and with good regiochemical control (eq 3). More recently, various groups have developed asymmetric

[15] Kresze, G.; Wagner. U. *Liebigs Ann. Chem.* **1972**, *762*, 106.
[16] Krow, G.; Rodebaugh, R.; Marakowski, J.; Ramey, K. C. *Tetrahedron Lett.* **1973**, 1899.
[17] Albrecht, R.; Kresze, G. *Chem. Ber.* **1965**, *98*, 1431.

variants of this hetero Diels-Alder strategy[18] by employing dienophiles derived from either chiral sulfonamides[19] or glyoxylates.[20]



(3)

There are several examples of the application of *N*-sulfonylimino Diels-Alder reactions in total synthesis.[21] Of particular note is Holmes' synthesis [21a] of racemic isoprosopinine B (Scheme 3). The key step in this synthesis involves the Diels-Alder reaction of methylgloxylate-derived imine **4** and diene **5**. This is a nice demonstration of using an annulation strategy to form multiple stereocenters in a single reaction, as discussed previously in Chapter 1. The cycloaddition sets all three of the stereocenters as they occur in the natural product, although one center is formed with only modest control (70:30 mixture of exo to endo isomers). The key cycloaddition proceeds at room temperature to afford, after silyl enol ether hydrolysis, **6** as a single regioisomer. The major product is then subjected to Baeyer-Villiger oxidation followed by reduction to afford triol **8**. At this point it is clear how employing the Diels-Alder reaction is an excellent strategy for controlling all three stereocenters. Compound **8** was then elaborated to the natural product through a series of protection, oxidation, Wittig olefination, and reduction steps.

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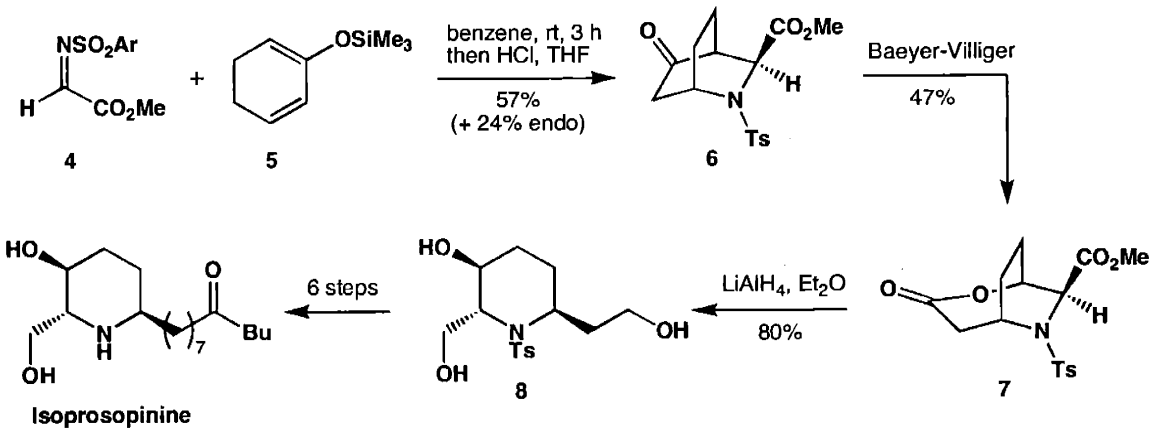
[18] For a review see: Rück-Braun, K.; Kunz, H. *Chiral Auxiliaries in Cycloadditions*; Wiley-VCH: New York, 1999; Chapter 4.

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

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

[21] (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.

Scheme 3



N-Acylimines and N-Acyliminium Ions

N-acylimines and *N*-acyliminium ions are the best known of the four classes of activated imines defined earlier.[22] *N*-Acyliminium ions are quite reactive, so they are usually generated *in situ*. Thus, iminium ion **11**, generated by treating biscarbamates (**9**) or α-alkoxy carbamates (**10**) with Lewis acids, reacts with a variety of dienes with excellent regioselectivity to provide cycloadducts with substitution patterns as depicted in **12** (Scheme 4).[23] The 4-π component in the reaction outlined in Scheme 4 must be fairly robust as the reaction is carried out in refluxing benzene in the presence of $BF_3 \bullet Et_2O$. This consideration, along with the modest yields of cycloaddition products, limits the synthetic utility of this methodology.

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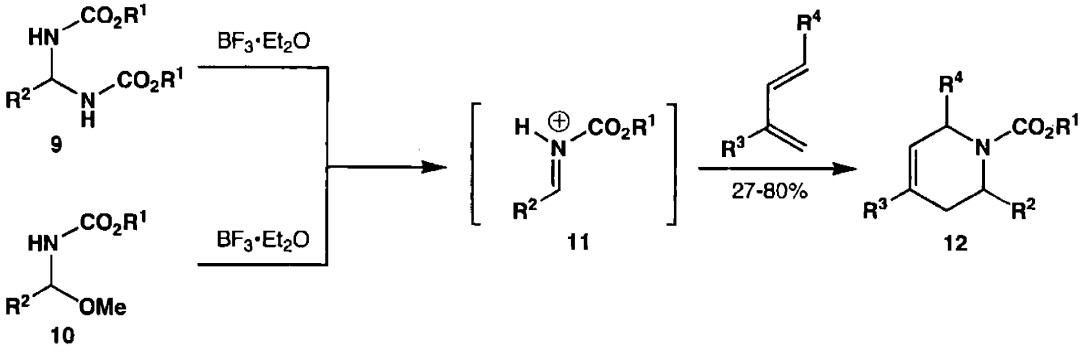
[22] Weinreb, S. M.; Scola, P. M. *Chem. Rev.* **1989**, *89*, 1525.

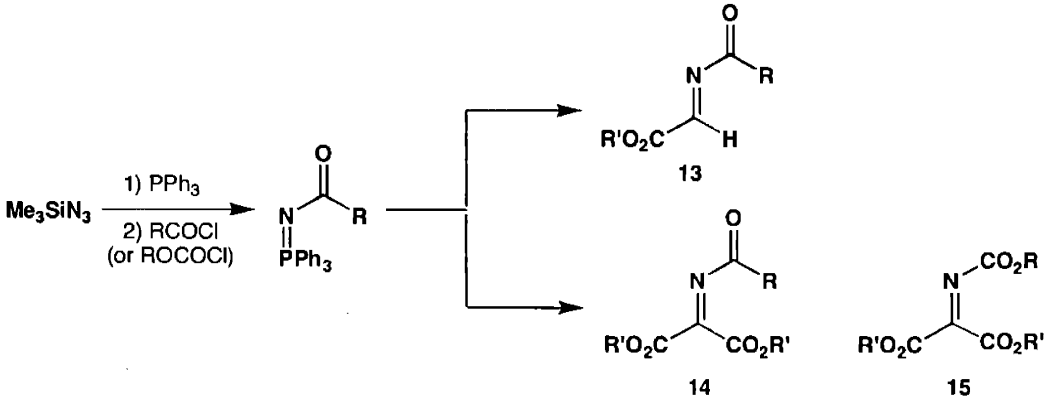
[23] (a) Merten, R.; Muller, G. *Angew. Chem.* **1962**, *74*, 866. (b) Merten, R.; Muller, G. *Chem. Ber.* **1964**, *97*, 682. (c) Baldwin, J. E.; Forrest, A. K.; Monaco, S.; Young, R. J. *J. Chem. Soc., Chem. Commun.* **1985**, 1586. (d) Fischer, G.; Frits, H.; Prinzbach, H. *Tetrahedron Lett.* **1986**,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

Scheme 4



N-acylimines also have been shown to participate in hetero Diels-Alder cycloadditions.[24] These imines are commonly prepared via aza- Wittig chemistry from the corresponding glyoxylates or oxomalonates, as outlined in Scheme 5.

Scheme 5

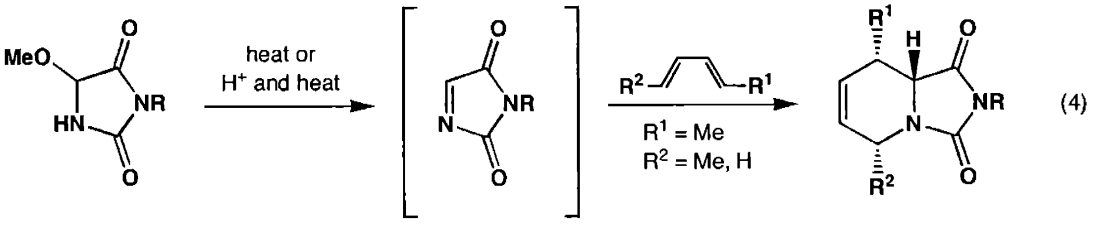


N-Acylimines are less reactive dienophiles relative to the *N*-acyliminium ions. *N*-Acylimines are less electron deficient than the corresponding iminium ions, and this explains the observed difference in reactivity. Note that dienophiles **13-15** all are substituted with additional electron-withdrawing groups at the imine carbon atom. Even so, imines of type **13** and **14** react only with electron-rich dienes such as Danishefsky's diene.[24a] In addition, cycloaddition of imine **14** with Danishefsky's diene leads to a

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

mixture of regioisomeric products, presumably due to the similarity of the atomic coefficients in the LUMO of the dienophile. Related carbamate **15** is also a poor dienophile in the Diels-Alder reaction, requiring high temperatures and pressures, with the exception of cycloaddition with cyclopentadiene which proceeds smoothly.[24b]

In addition to these acyclic *N*-acylimines, a variety of cyclic derivatives have been reported to participate in hetero Diels-Alder reactions. For example, dehydration of 4-methoxyhydantoin (**16**) generates imine **17**, which can be trapped by a variety of dienes as outlined in eq 4.[25] The dehydration can be achieved by simply heating **16** (toluene, 170 °C) or by treatment with acid in reluxing benzene. In general, cyclic *N*-acylimines are fairly reactive and demonstrate good regioselectivity in the Diels-Alder reaction. However, one drawback to this method is requirement of excess (4 equivalents) diene.



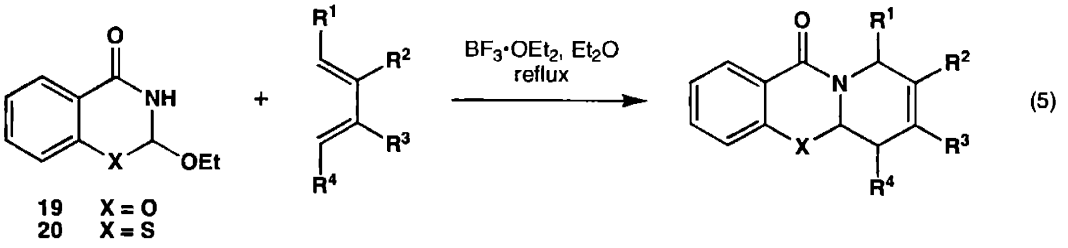
16 **17** **18** (4)

Several other related cyclic *N*-acylimines have been employed as aza dienophiles in the Diels-Alder reaction. Treatment of benzoxazinone **19** and benzothiazinone **20** with $BF_3 \bullet Et_2O$ in refluxing diethyl ether produces an imine that reacts with a variety of dienes as shown in eq 5.[26] The use of highly substituted dienes leads to products in good yield and excellent regioselectivity; however, less-substituted dienes like isoprene and 2,4-

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

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

pentadiene afford complex mixtures of products. The limited scope with regards to dienes that can be employed in this method reduces its utility for organic synthesis.



19 X = O
20 X = S

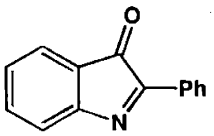
(5)

The methods developed for the Diels-Alder cycloadditions of cyclic *N*-acylimines suffer from a lack in the variety of heterocycles that can be prepared. While the *N*-sulfonyl and *N*-acylimines can be used to prepare a range of piperidine and related nitrogen heterocycles, the imines described in eq 4 and 5 provide access to very specific types of heterocyclic structure.

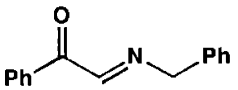
C-Acylimines

Relative few examples of Diels-Alder reactions of *C*-acylimines have been reported compared to the more extensive literature on *N*-sulfonylimines and *N*-acylimines. Indolone **21** has been reported to undergo a Diels-Alder reaction with cyclopentadiene at room temperature and with isoprene and 2,4-hexadiene in the presence of aluminum trichloride in refluxing benzene.[27] This dienophile, however, fails to react with butadiene or 1,3-cyclohexadiene. It is interesting to note that Proctor and McKay report that imines **22** and **23** do not react with dienes under thermal conditions or in the presence of Lewis acids.[28]

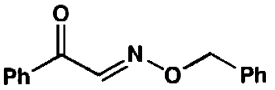
[27] Ch'ng, H. S.; Hooper, M. *Tetrahedron Lett.* **1969**, 1527.
[28] McKay, W. R.; Proctor, G. R. *J. Chem. Soc., Perkin Trans.1* **1981**, 2443.



21

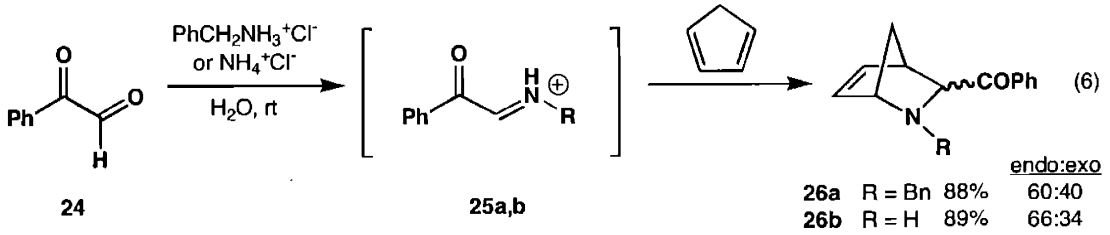


22



23

Grieco and co-workers have reported a related process based on *C*-acyliminium ions.[29] Phenylglyoxal and benzylamine hydrochloride can be mixed at ambient temperatures with cyclopentadiene to provide the desired bicyclic compound (**26a**) in good yield, but poor diastereoselectivity (eq 6). Grieco reports that treatment of **24** with ammonium chloride affords the corresponding cycloadduct with a secondary amino group (**26b**).



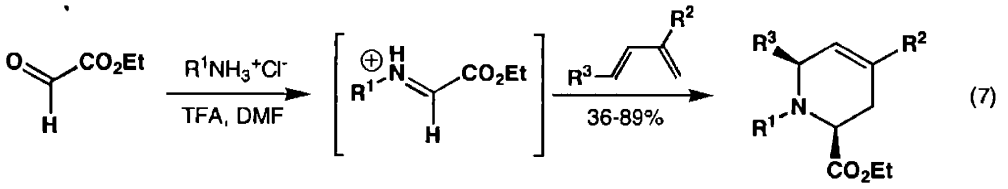
24 25a,b

In related studies, Bailey and coworkers have reported the reaction of ethyl glyoxylate with benzylamine hydrochloride in the presence of TFA and a trace of water to generate an iminium ion which reacts with a variety of dienes to afford cycloadducts in fair to good yield (eq 7).[30] Interestingly, the use of DMF is critical for the success of these reactions. Cyclic dienes provide a mixture of exo and endo products, favoring the exo cycloadduct, but acyclic dienes give almost exclusively the endo product. An asymmetric version of this reaction has been developed employing chiral amines. Cycloadditions of the chiral iminium ion with cyclic dienes provides products with good

[29] Grieco, P. A.; Larsen, S. D.; Fobare, W. F. *Tetrahedron Lett.* **1986**, *27*, 1975.

[30] (a) Bailey, P. D.; Wilson, R. D.; Brown, G. R. *Tetrahedron Lett.* **1989**, *30*, 6781. (b) Bailey, P. D.; Brown, G. R.; Korbec, F.; Reed, A.; Wilson, R. D. *Tetrahedron: Asymm.* **1991**, *2*, 1263.

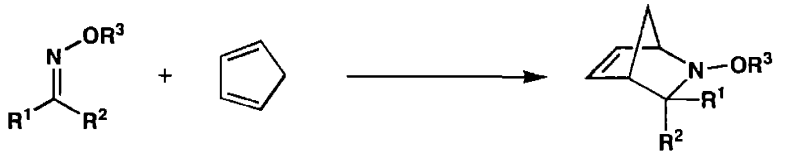
asymmetric induction (84-100% de), but reactions with acyclic dienes produce products with varying levels of selectivity (26-68% de).



(7)

Oximino Dienophiles

Compared to imines, oximes have received far less attention as dienophiles in the hetero Diels-Alder reaction. Fleury and his co-workers have reported a systematic study of a variety of oximino esters derived from 2-oxomalonates and related compounds.[31] As shown below, a variety of these electron-deficient oximes were found to react smoothly with cyclopentadiene in the Diels-Alder reaction.



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

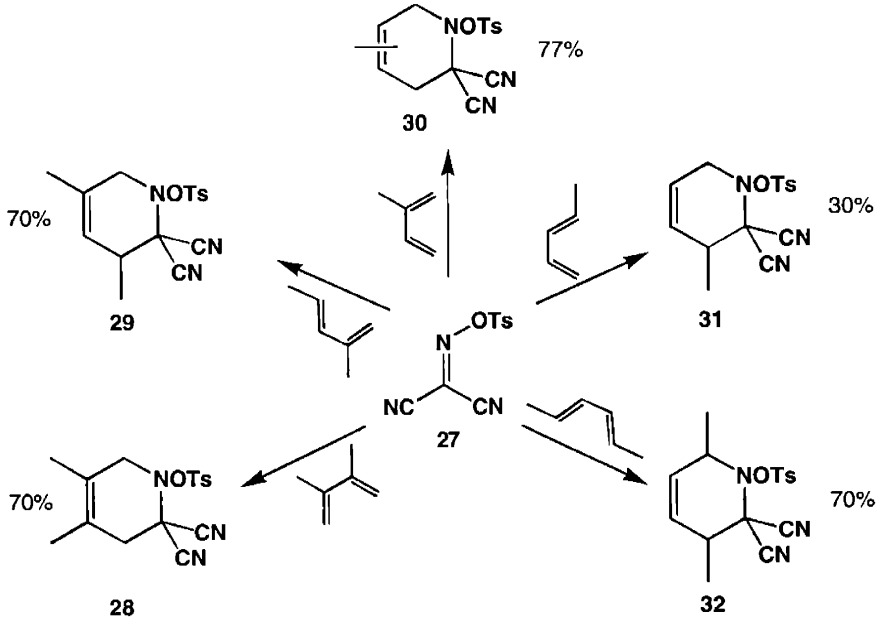
The most reactive dienophile examined by Fleury et al. proved to be the oximinosulfonate **27**. As shown in Scheme 6, this oximinosulfonate reacts with a variety of 1,3-dienes in refluxing benzene to provide the expected cycloadducts.[32] It is interesting to note that the cycloaddition of 1,3-pentadiene produces a product (**31**) with

[31] (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.

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

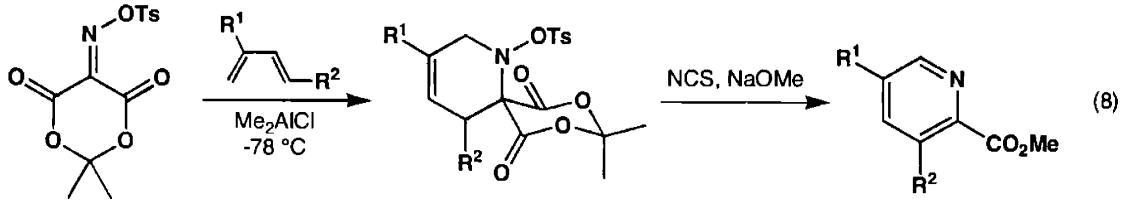
regiochemistry opposite from that seen with the imino dienophiles previously discussed in this chapter. This substitution pattern suggests that the larger atomic coefficient of the LUMO lies on nitrogen in oximino dienophile **27**. However, the reaction of **27** with isoprene provides a 58:42 mixture of the 5-methyl and 4-methyl regioisomers (**30**), so the regioselectivity of cycloaddition reactions with oximinosulfonate **27** is not always satisfactory. All of the reactions in Scheme 6 were carried out using 3 equivalents of diene, except for the reaction with isoprene (ca. 10 equiv of diene was used). Other dienes, such as butadiene and 2-methoxybutadiene, fail to react with **27**, which is also reported to be unstable above 90 °C, thereby limiting the range of conditions that could potentially be employed for less reactive dienes.

Scheme 6



Our group has employed the readily available oximinosulfonate **33**, derived from Meldrum's acid, for the synthesis of substituted pyridines via a [4+2] cycloaddition

strategy.[33] Treatment of a variety of dienes with **33** and Me_2AlCl at –78 °C provides cycloadducts of the type **34**, which are then treated with NCS and sodium methoxide to afford the desired pyridines **35** (eq 8). In most cases, the cycloaddition proceeds with excellent regioselectivity, but opposite of to that which is observed with conventional imino dienophiles. This switch in regioselectivity is due to the presence of the two electron-withdrawing groups on the carbon atom of the oxime. Furthermore, Adam Renslo demonstrated that this reaction proceeds smoothly in the presence of 1.5 equivalents of the diene and does not require a large excess of diene. Oximinosulfonate **33** also participates in thermal cycloadditions with highly reactve, electron-rich dienes.



33 **34** **35** (8)

A recent report from Weinreb and co-workers described the *intramolecular* cycloaddition of oximinomalonates of type **36**.[34] Heating a toluene solution of **36** or subjecting the same solution to high pressure (12 kbar) produces bicyclic compounds of type **37**. Treatment of compounds of type **37** with Cs_2CO_3 in DMF provides the desired substituted pyridines **38** (eq 9). While this method affords substituted pyridines, one of the substituents is required to be the carboxylic acid side chain. This, along with modest yields (50-70% for the cycloaddition) limits the type of synthetic targets that can be prepared with this methodology.

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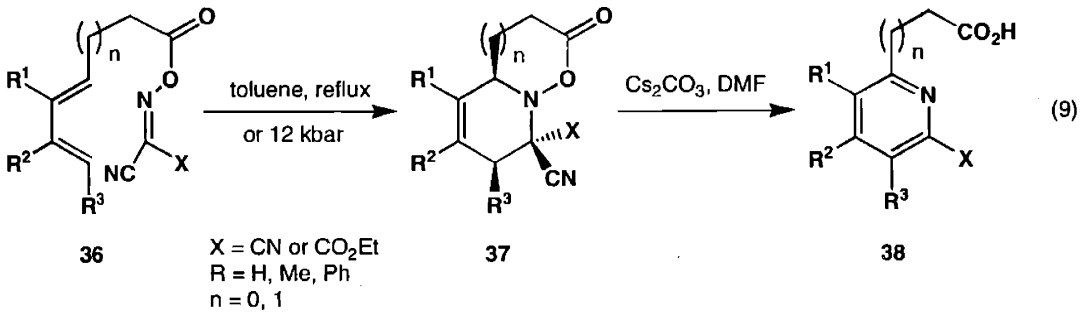
[33] (a) Renslo, A. R.; Danheiser, R. L. *J. Org. Chem.* **1998**, *63*, 7840. (b) Danheiser, R. L.; Renslo, A. R.; Amos, D. T.; Wright, G. T. *Org. Synth.* **2003**, *80*, 133.

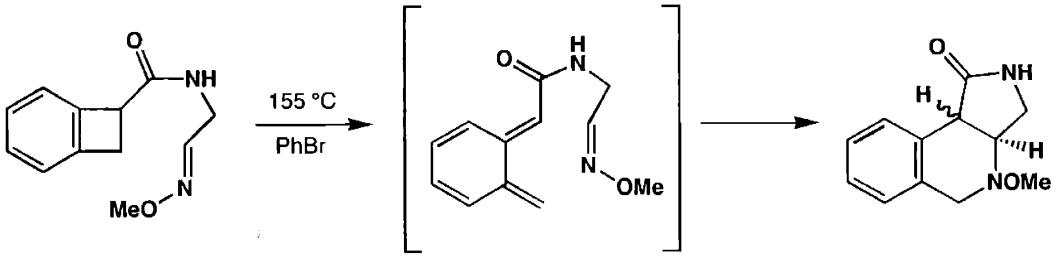
[34] Bland, D. C.; Raudenbush, B. C.; Weinreb, S. M. *Org. Lett.* **2000**, *2*, 4007.



36 37 38 (9)

Intramolecular Diels Alder Reactions of Imino Dienophiles

Oppolzer reported the first example of an intramolecular imino Diels-Alder reaction in 1972.[35] As shown below, heating a solution of benzocyclobutene **39** in bromobenzene generates a highly reactive *o*-quinodimethane intermediate (**40**), which undergoes an intramolecular Diels-Alder cycloaddition to provide **41** in 68% yield as a mixture of diastereomers.



39 40 41

Oppolzer has employed a variation of this strategy for the synthesis of racemic lysergic acid (Scheme 7).[36] The key step in this synthesis is a retro-Diels-Alder reaction of **42** to produce diene **43**, and subsequent cycloaddition to assemble the tetracyclic system of the target alkaloid in 67% yield. The cycloadduct **44** was readily converted in 3 steps to lysergic acid.

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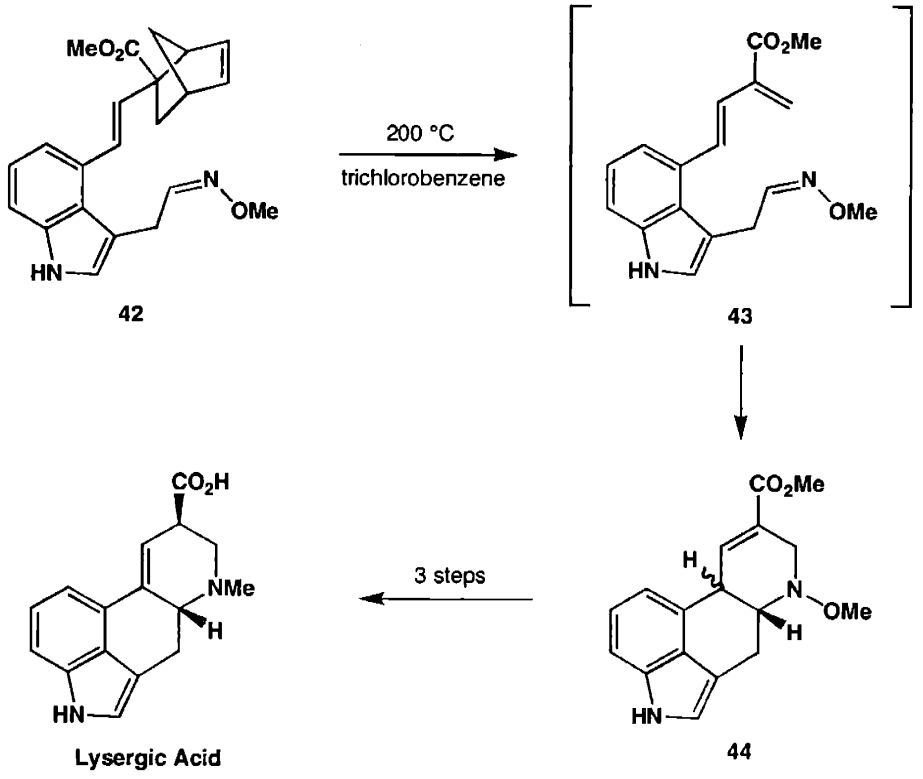
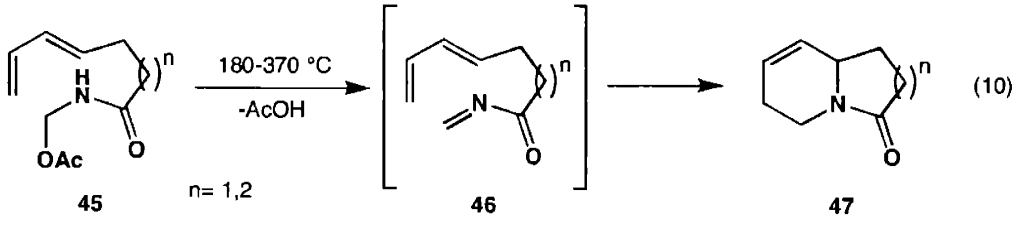
[35] Oppolzer, W. *Angew. Chem., Int. Ed. Engl.* **1972**, *11*, 1031.

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

Scheme 7

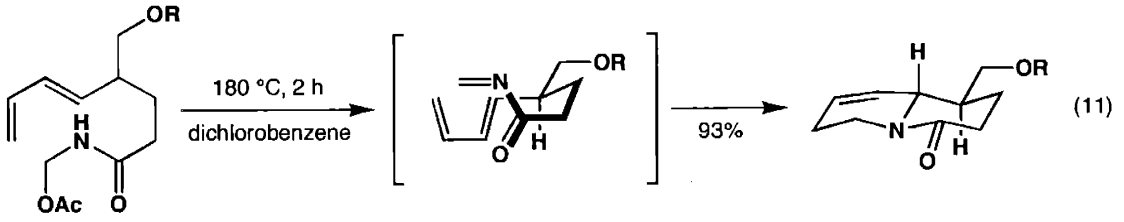


The laboratories of Weinreb and Grieco have carried out the most extensive investigations of the intramolecular imino Diels-Alder reaction. Weinreb's group has focused their studies on *N*-acylimines, while Grieco and coworkers have investigated cycloadditions of iminium ions. The Weinreb strategy[37] employs the thermolysis of *N*-actetoxymethyl amides **45** to generate *N*-acylimines **46** as the reactive dienophiles for the intramolecular [4+2] cycloaddition (eq 10).



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

Depending on the length of tether, this process can lead to either indolizidine (n = 1) or quinolizidine (n = 2) products. The products of the cycloaddition are usually obtained with excellent stereoselectivity, as seen in eq 11. Weinreb rationalizes this result by invoking the transition state shown in eq 11, where the carbonyl moiety adopts an endo orientation relative to the diene and the substituent on the connecting tether has a pseudoequatorial orientation.[38]



(11)

The Weinreb group has also reported intramolecular cycloadditions of imines acylated on carbon and nitrogen. These imines are conveniently prepared from carbamates of type **48**.[39] For example, thermolysis of **48** produces intermediate imine **49** that then undergoes a Diels-Alder reaction to produce the expected bicyclic carbamate (**50**) as a single diastereomer (eq 12). This cycloaddition requires relatively high temperatures, and the product is isolated in only modest yield. It is interesting to note that the product of this hetero Diels-Alder reaction has the carbomethoxy group in an "exo" position. This is in contrast to the related carbocycle-forming cycloaddition shown in eq 13.[40]

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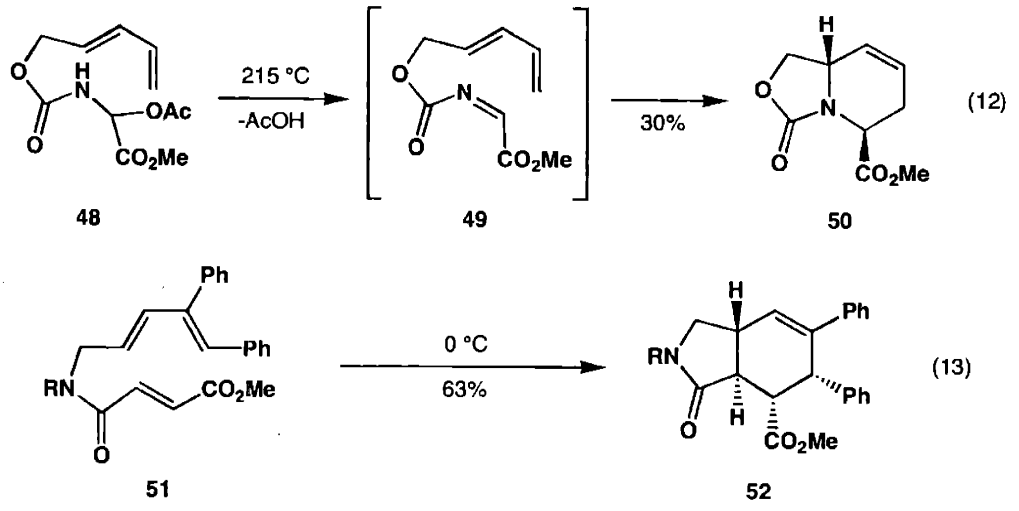
[38] (a) Bremmer, M. L.; Weinreb, S. M. *Tetrahedron Lett.* **1983**, *24*, 261. (b) Bremmer, M. L.; Khatri, N. A.; Weinreb, S. M. *J. Org. Chem.* **1983**, *48*, 3661.

[39] (a) Nader, B.; Franck, R. W.; Weinreb, S. M. *J. Am. Chem. Soc.* **1980**, *102*, 1153. (b) Nader, B.; Bailey, T. R.; Franck, R. W.; Weinreb, S. M. *J. Am. Chem. Soc.* **1981**, *103*, 7573.

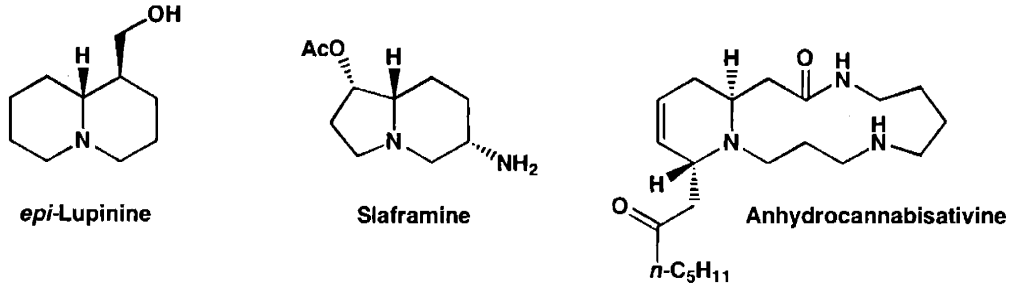
[40] Gschwend, H. W.; Lee, A. O.; Meier, H.-P. *J. Org. Chem.* **1973**, *38*, 2169.



48 49 50 (12)

51 52 (13)

The Weinreb group has applied their imino Diels-Alder methodology to the total synthesis of several natural products, including *epi*-lupinine,[38] slaframine,[41] and anhydrocannabisativene.[42]



epi-Lupinine Slaframine Anhydrocannabisativine

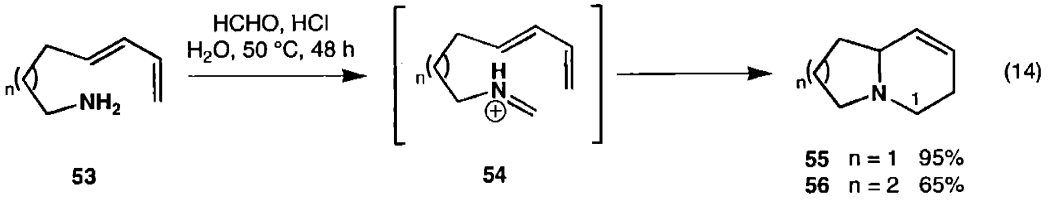
The intramolecular imino Diels-Alder reaction employed by the Grieco group also relies on the *in situ* generation of the reactive imino dienophile.[43] Treatment of amines of type **53** with aqueous HCl and formaldehyde generates iminium ions (**54**), which then undergo intramolecular cycloadditions to afford the expected indolizidine **55** or quinolizidine **56** cycloadduct (eq 14). It is important to note that only formaldehyde can be employed in this reaction, as Grieco reports that utilizing other aldehydes and ketones

[41] Gobao, R. A.; Bremmer, M. L.; Weinreb, S. M. *J. Am. Chem. Soc.* **1982**, *104*, 7065.

[42] Bailey, T. R.; Garigipati, R. S.; Morton, J. A.; Weinreb, S. M. *J. Am. Chem. Soc.* **1984**, *106*, 3240.

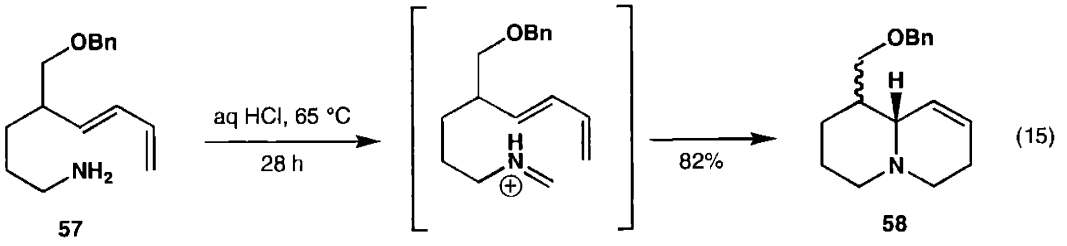
[43] (a) Larsen, S. D.; Grieco, P. A. *J. Am. Chem. Soc.* **1985**, *107*, 1768. (b) Grieco, P. A.; Larsen, S. D. *J. Org. Chem.* **1986**, *51*, 3553. (c) Grieco, P. A.; Parker, D. T. *J. Org. Chem.* **1988**, *53*, 3325.

leads to low yields and complex mixtures of products. Consequently, this method cannot be employed to prepare indolizidines and quinolizidines substituted at the C-1 position of the new heterocyclic ring. The use of lanthanide triflates to promote these *intramolecular* cycloadditions has not yet been reported.



53 **54** **55** n = 1 95% **56** n = 2 65% (14)

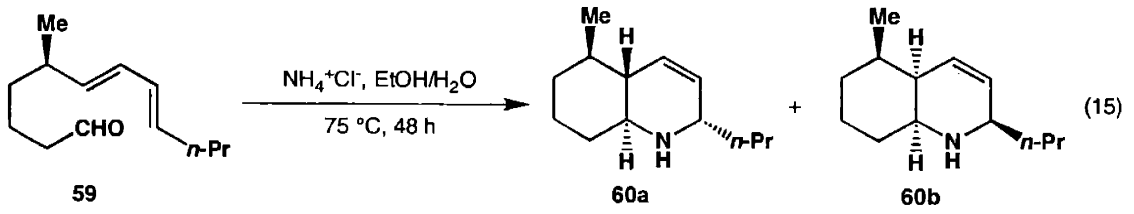
In contrast to the reactions studied by Weinreb, the intramolecular iminium ion Diels-Alder reaction developed by Grieco does not proceed with good stereocontrol. Subjecting amine **57** to the aforementioned reaction conditions delivers quinolizidine **58** as a 62:38 mixture of diastereomers in 82% yield (eq 15). Treatment of this mixture with H_2 and Pd/C provides racemic *epi*-lupinine and lupinine.



57 **58** (15)

Grieco has also extended his strategy to provide access to heterocycles in which the nitrogen atom is not located at the ring juncture of the new bicyclic system.[44] For example, treatment of dienyl aldehyde **59** with aqueous ammonium chloride provides cycloadducts **60a** and **60b** in 55% yield as a 69:31 mixture of diastereomers (eq 14). Hydrogenation over Pd/C converts the major diastereomer to (-)-8a-*epi*pumiliotoxin C.

[44] Grieco, P. A.; Parker, D. T. *J. Org. Chem.* **1988**, *53*, 3658.



Iminonitriles

As stated previously in Chapter 1, the overall goal of my project was to explore the use of iminoacetonitriles in the intramolecular enyne and Diels-Alder cycloaddition reactions. Surprisingly, there are few reports of the preparation of iminoacetonitriles in the literature, and no investigation of the reactivity of these species in cycloaddition reactions has been described. As outlined in Chapter 1, we felt iminoacetonitriles should be easily prepared, should be quite reactive in cycloaddition reactions, and the resulting cycloadducts (α-amino nitriles) should serve as versatile synthetic intermediates.[45] This method would be complimentary to Grieco's work because of the ease of accessing C-1 substituted heterocycles via α-amino nitrile chemistry. In contrast to iminoacetonitriles, there are a few more reports of iminonitriles in the literature, but these two classes of imines appear to be underutilized.

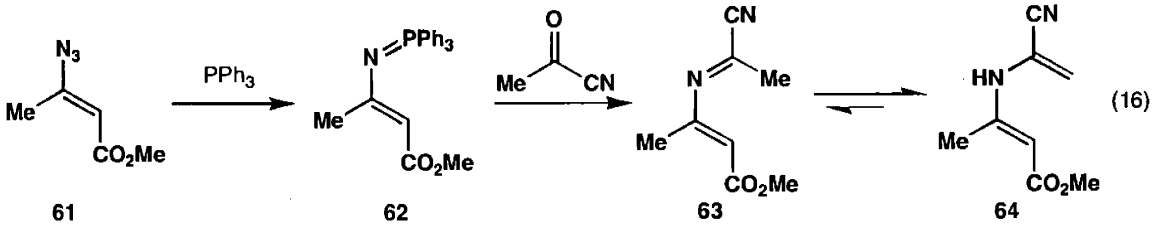
Iminonitriles

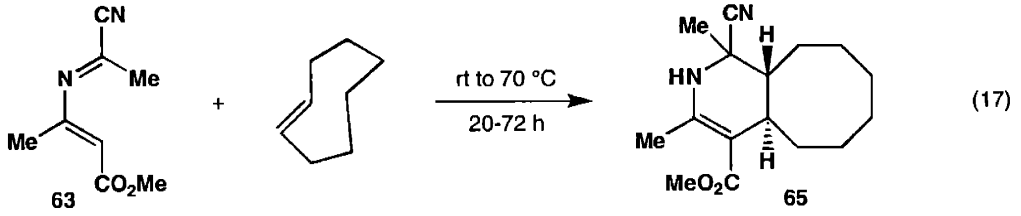
Several groups have reported the use of the aza-Wittig reaction to prepare iminonitriles. The first report of this approach came from the Palacios' group in Spain.[46] Treatment of vinyl azide **61** with triphenylphosphine affords phosphazene **62**, which

[45] (a) Enders, D.; Shilvock, J. P. *Chem. Soc. Rev.* **2000**, *29*, 359. (b) Husson, H.-P.; Royer, J. *Chem. Soc. Rev.* **1999**, *28*, 383.

[46] (a) Palacios, F.; Aparicio, D.; de los Santos, J. M. *Tetrahedron Lett.* **1993**, *34*, 3481. (b) Palacios, F.; de Heredia, I. P.; Rubiales, G. *J. Org. Chem.* **1995**, *60*, 2384.

reacts with acetylcyanide to yield the expected *N*-vinyl iminonitrile **63** (eq 16). This compound proved to be quite unstable, isomerizing to the corresponding enamine **64**. Imine **63** combines with *trans*-cyclooctene in an inverse electron demand Diels-Alder cycloaddition to provide bicyclic compound **65** (eq 17).

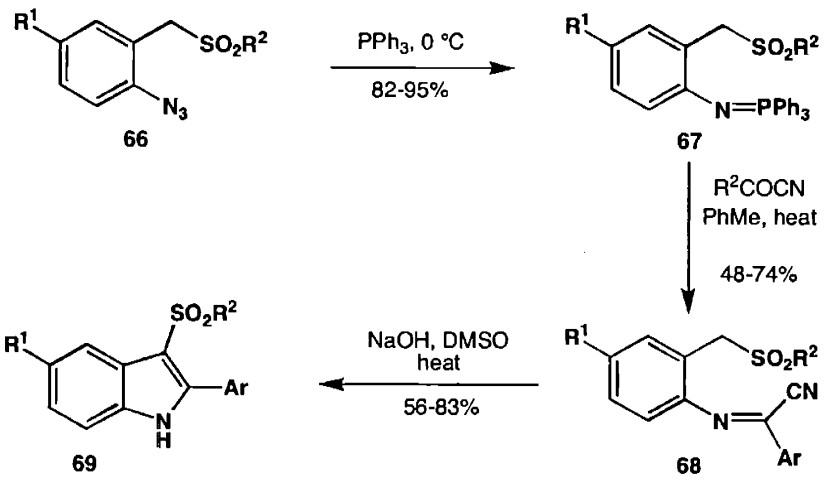




Takahashi and Suga have employed iminonitriles, prepared via the aza-Wittig reaction, as intermediates for the synthesis of substituted indoles.[47] Treatment of aryl azide of type **66** with triphenylphosphine provides iminophosphines **67**, which upon exposure to a variety of aroyl cyanides, produce the desired iminonitriles **68** in modest to good overall yield (39-70%). Base promoted cyclization at elevated temperatures affords the expected indole products **69**.

[47] Takahashi, M.; Suga, D. *Synthesis* **1998**, 986.

Scheme 8



The Fowler group has described both intramolecular[48] and intermolecular[49] hetero Diels-Alder cycloadditions involving 1-aza-2-cyanodienes and various dienophiles. In the intramolecular variant of these inverse electron-demand Diels-Alder reactions, an unsaturated amide **70** is treated with triflic anhydride, followed by lithium cyanide to prepare the desired iminonitriles **71** and **72**, albeit in modest yield. Heating these 1-azadienes for 24 h provides the expected indolizidine **73** and quinolizidine **74**. Each cycloadduct is obtained as a mixture of diastereomers, with the indolizidine series favoring a cis relationship between the bridgehead hydrogen and the methyl group, and the quinolizidine system favoring a trans relationship. The role of the methyl group in the cycloaddition is unclear. Fowler does not report substrates with an unadorned tether, and attempted cycloaddition of a substrate where the methyl group is replaced with a phenyl ring is successful only under FVP (flash vacuum pyrolysis) conditions.

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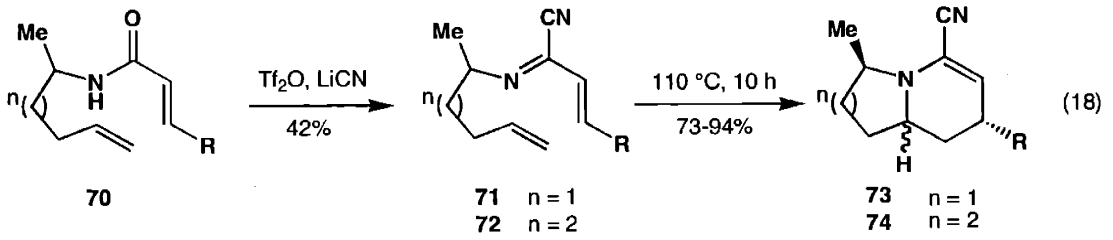
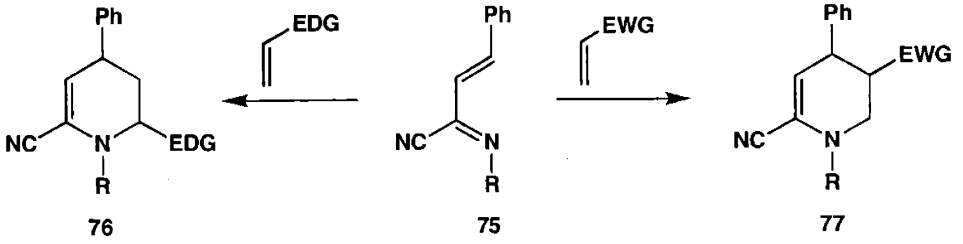
[48] (a) Sisti, N. J.; Zeller, E.; Grierson, D. S.; Fowler, F. W. *J. Org. Chem.* **1997**, *62*, 2093. (b) Motorina, I. A.; Fowler, F. W.; Grierson, D. S. *J. Org. Chem.* **1997**, *62*, 2098.

[49] (a) Teng, M.; Fowler, F. W. *Tetrahedron Lett.* **1989**, *30*, 2481. (b) Teng, M.; Fowler, F. W. *J. Org. Chem.* **1990**, *55*, 5646. (c) Trione, C.; Toledo, L. M.; Kuduk, S. D.; Fowler, F. W.; Grierson, D. S. *J. Org. Chem.* **1993**, *58*, 2075.



(18)

Fowler has also reported other methods for the preparation of 1-azadienes containing the iminonitrile functionality. These methdods include aza-Wittig strategies, treatment of a siloxyoxime with a chloroformate, and alkylation of a nitrile oxime. Cycloaddition reactions of **75** with a variety of dienophiles provide unsaturated piperidines with varying degrees of regio and stereoselectivity. Electron-rich olefins, such as ethyl vinyl ether, afford products with substitution patterns of type **76**, while electron-poor dienophiles give cycloadducts with the opposite regiochemistry (**77**).



The endo pathway is favored for this series of cycloadditions with selectivities ranging from 80:20 to 100:0. Another observation involves the effect of the substituent on nitrogen on the rate and yield of the cycloaddition. The use of carbamates (R = CO_2R) leads to rate and yield enhancements, while utilization of electron-donating substituents inhibit the desired cycloaddition and produce polymerized diene.

Summary

In summary, a variety of imine derivatives have previously been investigated as aza dienophiles for inter- and intramolecular hetero Diels-Alder reactions. Nonetheless,

we believed that iminoacetonitriles would have several advantages as 2-π components in [4+2] cycloadditions, and would provide access to substituted nitrogen heterocycles not easily obtained via previous methodology. Part II of this thesis will discuss preparation of iminoacetonitriles, and Part III will discuss their reactivity in the intramolecular Diels-Alder reaction.

Part II

Synthesis of Iminoacetonitriles

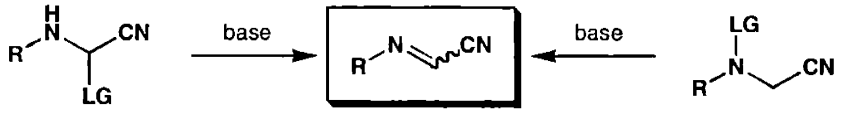
Chapter 1

Iminoacetonitriles: Introduction and Background

This chapter describes the alternative schemes we considered for the synthesis of the iminoacetonitriles required in our investigation, and also reviews the literature procedures that existed for the preparation of this class of imines prior to our work.

Retrosynthetic Analysis

Since there is a unit of unsaturation present in the imine of interest, we investigated utilizing an elimination reaction to install the double bond. This disconnection appeared promising and might be effected via a range of tactics. An elimination reaction requires the presence of a leaving group, and in the case of our imine, there were two separate locations for such a leaving group. One possibility was to place the leaving group on the carbon atom between the nitrogen and nitrile group (**78**), so that deprotonation of the nitrogen would provide the desired iminoacetonitrile (**79**). A second option was to place the leaving group directly on the nitrogen atom (**80**) and rely on the acidity of the protons on the methylene between the nitrogen and nitrile to control the regiochemistry of the elimination.

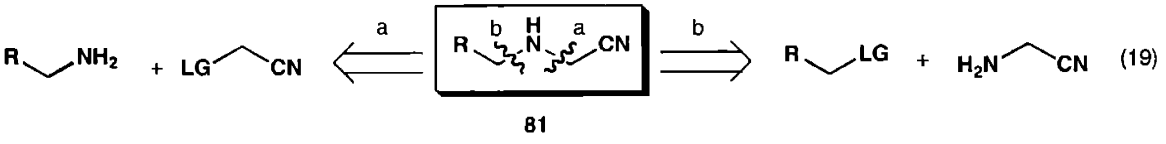


78 **79** **80**

Examining these two possibilities, it appeared that the second approach (via **80**) was more attractive. Synthesizing a substrate with a leaving group on the carbon atom would be feasible, but might not be as simple as installing the leaving group on nitrogen.

Another, and perhaps more serious, issue associated with substrate **78** is the possibility of competitive elimination of the cyano group rather than the intended leaving group. With the decision thus made to utilize a compound of type **80**, we next began examining strategies to gain access to this structural motif.

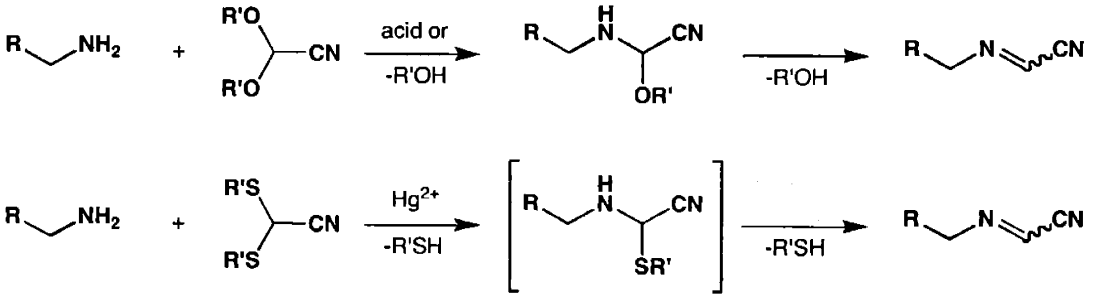
Since it seemed that the installation of a leaving group at the nitrogen of a secondary amine should be a facile process, we focused our attention on amine **81**. Once again, two potential disconnections were readily apparent, but in this case it was not immediately clear which would be more effective. Two different carbon-nitrogen bonds can be cleaved, in a retrosynthetic sense, and we have examined both possibilities. One approach involves alkylating a primary amine with a haloacetonitrile (disconnection a), while the alternative approach employs the alkylation of an aminoacetonitrile with an alkyl halide (disconnection b) (eq 19).



(19)

Although we have focused the majority of our attention and efforts on implementing the "alkylation" strategies outline above, we also considered an "acetal-exchange" protocol. One can imagine treating a free amine with either an acetal or a dithiane and under the appropriate conditions forming the desired iminoacetonitrile (Scheme 9).

Scheme 9

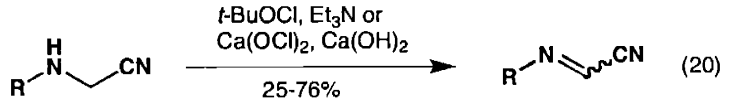


Acid catalysis could promote the exchange of an amine for an alkoxy group, and subsequent elimination of the remaining alkoxy group would provide an iminoacetonitrile. Once again, care would need to be exercised to avoid elimination of cyanide, leading to imidate formation. Addition of the free alcohol to the newly formed imine, and subsequent release of cyanide, could also produce an imidate. A second option would involve the use of a dithiane in place of an acetal. One can imagine that mercury(II) might promote an exchange reaction between one of the sulfur groups of a dithiane and an amine. With mercury's affinity for sulfur, selective elimination of the thiol might be a readily achievable goal. However, these speculative approaches appeared to us less attractive than the alkylation strategies, and we decided to focus our attention on the latter routes.

Previous Approaches to the Preparation of Iminoacetonitriles

As stated in the previous chapter, there are only a couple of examples of the preparation of iminoacetonitriles in the literature. In 1970, Boyer and Dabek reported the first synthesis of an iminoacetonitrile, employing an elimination reaction of an *N*-

chloroamine to produce the desired imine.[50] Treatment of *N-tert*-butylaminoacetonitrile with *tert*-butyl hypochlorite, followed by triethylamine provided the expected iminoacetonitrile in 46% yield (eq 20). A subsequent report examined the use of calcium hypochlorite and calcium hydroxide to effect the formation of the desired compounds.[51] Using this protocol, Boyer and Dabek were able to synthesize several *N*-alkyl substituted iminoacetonitriles in modest to good yield.



(20)

More recently, Selva and coworkers have reported a modification of Boyer's protocol, involving a one-pot procedure.[52] Treatment of several amino nitriles (e.g. R = *i*-Pr, *t*-Bu, c-Hex) with 1.5 equiv aqueous NaOCl at 10 °C afforded the expected iminoacetonitriles in good yield (67-90%) with a high preference for the *E* isomer.

The preparation of substituted iminonitriles (though not imino*aceto*nitriles) has also been reported. Kimpe and coworkers have employed Boyer and Dabek's conditions to prepare iminonitriles, utilizing *tert*-butyl hypochlorite in benzene and triethylamine or 1,4-diazobicyclo[2.2.2]octane (DABCO) to afford the desired imines in 61-73% yield.[53] Hisashi Yamamoto and coworkers described the synthesis of cyclic and acyclic iminonitriles via an organoaluminium-promoted Beckmann rearrangement of oximinosulfonates.[54] Treatment of oxime **82** with methanesulfonyl chloride, followed by

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

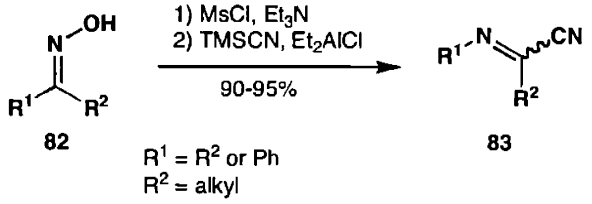
[51] Boyer, J. H.; Kooi, J. *J. Am. Chem. Soc.* **1976**, *98*, 1099.

[52] Perosa, A.; Selva, M.; Tundo, P. *Tetrahedron Lett.* **1999**, *40*, 7573.

[53] De Kimpe, N.; Verhé, R.; De Buyck, L.; Chys, J.; Schamp, N. *Synthesis*, **1978**, 895.

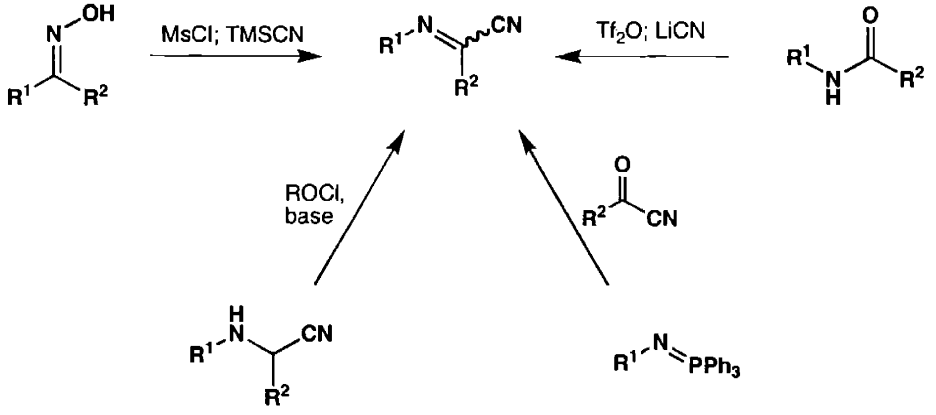
[54] Maruoka, K.; Miyazaki, T.; Ando, M.; Matsumura, Y.; Sakane, S.; Hattori, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1983**, *105*, 2831.

trimethylsilyl cyanide and diethylaluminum chloride, provided the expected iminonitriles (**83**) in 90-95% yield. The isolated yields for the preparation of cyclic iminonitriles appear to vary significantly (48-92%), although only two examples were reported.



Several other methods to prepare iminonitriles were discussed in Chapter 2 of Part I, and Scheme 10 provides an overview of the most common ways of preparing iminonitriles. In summary, however, the only prior report of the preparation of iminoacetonitriles (R^2 = H) was the method of Boyer involving chlorination of aminoacetonitriles

Scheme 10



Summary

Retrosynthetic analysis of the target iminoacetonitrile identified the "alkylation-elimination" approach as the most attractive strategy for the synthesis of the desired imines. The following chapter describes our initial efforts at the development and optimization of a practical and general synthetic route to iminoacetonitriles.

Chapter 2

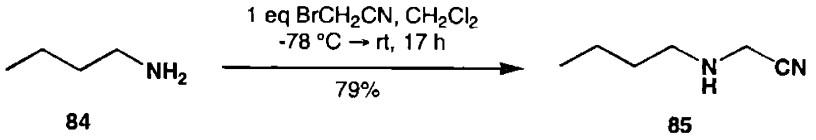
Alkylation Approach to Iminoacetonitriles

As described in the previous chapter, the first approach we examined for the preparation of iminoacetonitriles involved an alkylation-elimination strategy. Adam Renslo carried out the initial studies in this area and developed a protocol for alkylating a primary amine with $BrCH_2CN$ and then effecting the required dehydrogenation. My initial efforts were directed at optimizing this approach. This chapter describes these results and also discusses the assignment of stereochemistry to the imine products.

Feasibility of the Alkylation-Elimination Strategy

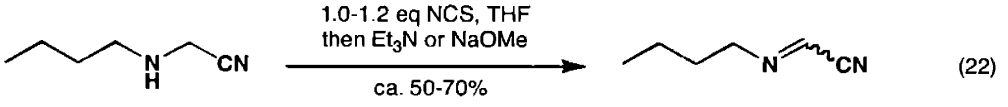
The first stage in the development of this route to iminoacetonitriles involved the identification of an optimal procedure for the preparation of aminoacetonitriles. Adam Renslo found that treatment of 3 equivalents of *n*-butylamine (**84**) with 1 equivalent of bromoacetonitrile affords secondary amine **85** in nearly quantitative yield. However, the use of excess amine is not ideal for the synthesis of intramolecular cycloaddition substrates, so efforts were focused on finding a procedure that would allow the use of only 1 equivalent of amine. Reaction of bromoacetonitrile with an equivalent amount of *n*-butylamine in the presence of 2.5 equivalents of triethylamine provided the alkylation product (**85**) in low yield (ca. 20%), along with recovered *n*-butylamine. Surprisingly, Renslo found that **85** could be obtained in 79% yield when equimolar amounts of *n*-butylamine and bromoacetonitrile were allowed to react in the absence of additional base (eq 21). Further discussion of this reaction, including previous literature procedures for

the synthesis of aminoacetonitriles, is presented later in connection with our optimization studies.



84 85 (21)

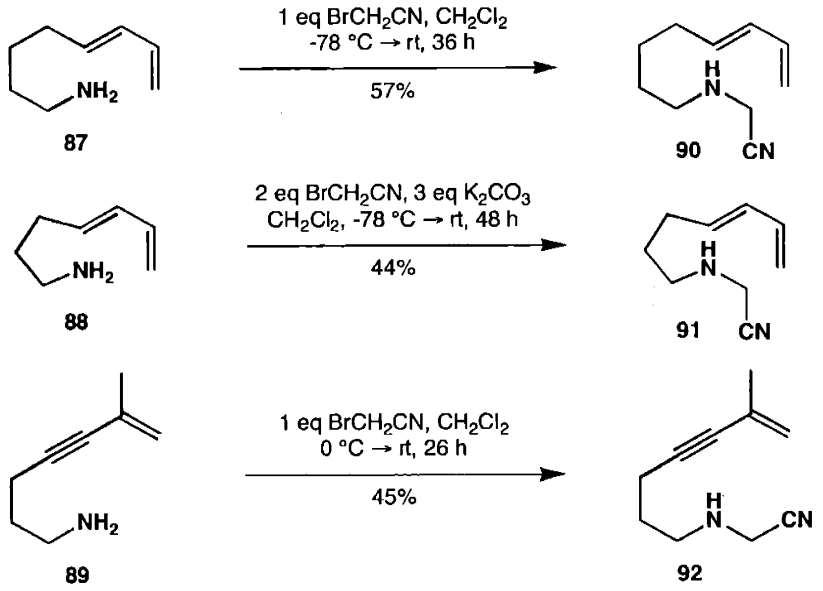
Generation of the desired iminoacetonitrile **86** formally requires a dehydrogenation of **85**. As previously discussed, this transformation can be accomplished by *N*-chlorination, using *tert*-butyl hypochlorite, followed by dehydrochlorination with base. Renslo found that the use of *N*-chlorosuccinimide (NCS) for the chlorination reaction and either sodium methoxide or triethylamine to effect the elimination step best provides the desired iminoacetonitrile in a simple "one-pot" operation (eq 22).



85 86 (22)

Although either base provided the desired imine (**86**) in acceptable yield (ca. 50-70%), reaction with sodium methoxide afforded material with higher purity. At this point, other bases were not examined, and the procedure described above for the alkylation of a secondary amine and subsequent elimination was applied to a series of three substrates. As shown in Scheme 11, the alkylation step proceeded uneventfully in each case in moderate yield to provide the desired amino nitrile

Scheme 11

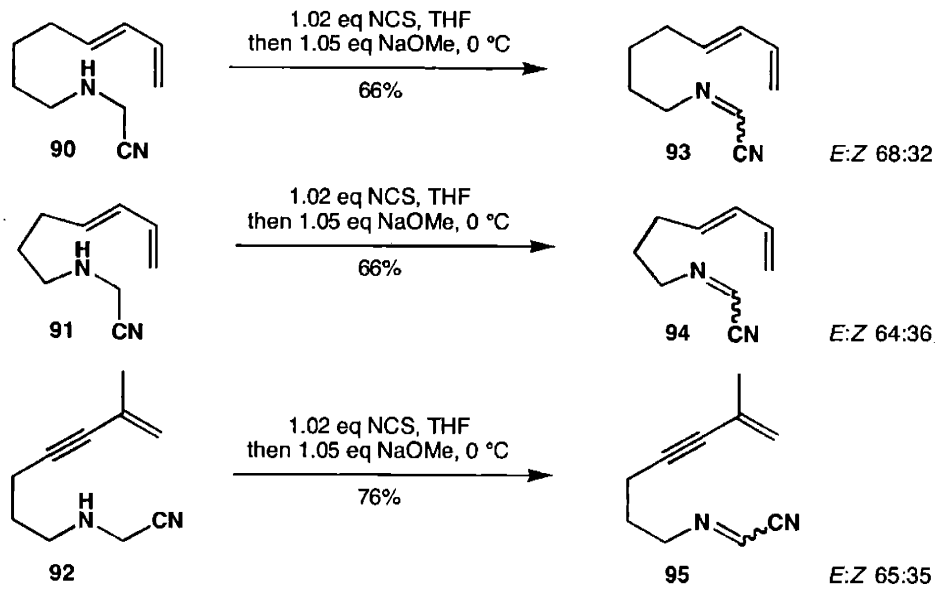


In all three cases the alkylation did not proceed to completion, presumably because of proton transfer from the secondary amine alkylation product to the more basic primary amine starting material. However, in the case of **88**, the use of excess base or alkylating agent did not improve the yield of **91**.

Applying the previously developed elimination protocol (NCS, NaOMe) to **90-92** provided the desired iminoacetonitriles **93**, **94**, and **95** in good yield after purification by column chromatography.[55] As shown in Scheme 12, the iminoacetonitriles are produced as a mixture of *E* and *Z* imine isomers, with modest selectivity for the *E* isomer.

[55] Iminoacetonitriles can be purified by careful column chromatography, provided that the silica gel is treated with 1% triethylamine and the column eluted with eluants containing 1% triethylamine.

Scheme 12



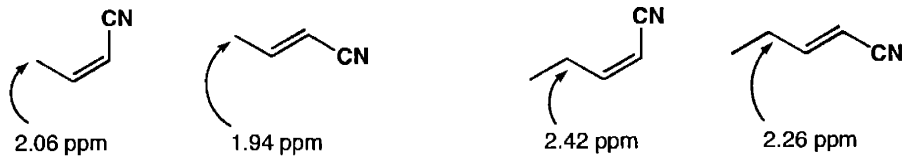
Stereochemical Assignment of Iminoacetonitriles

The resonances for the indicated α-methylene protons of the two imine isomers are well resolved in the ^{1}H NMR spectra of iminoacetonitriles, with the minor product having the more downfield shift. This imine was assigned as the *Z* isomer (**93Z**), since in this isomer these protons would be expected to be shifted downfield by the deshielding cone of the nitrile π bonds.

This proposal is consistent with the data reported by Selva,[56] where the protons α to *Z* iminoacetonitriles are shifted 0.14-0.52 ppm downfield relative to the *E* isomers.

[56] Perosa, A.; Selva, M.; Tundo, P. *Tetrahedron Lett* **1999**, *40*, 7573.

Additional evidence to support this hypothesis comes from data published on α,β-unsaturated nitriles.[57] As outlined below, the chemical shifts of the allylic protons are well resolved, with the resonances for the *Z* isomers appearing downfield relative to the *E* isomers.



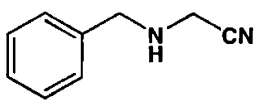
More conclusive evidence for these stereochemical assignments was obtained from the four-bond coupling observed between the imino hydrogen and the α-methylene hydrogen atoms. As shown below, coupling constants for *Z* and *E* aldimines have been reported,[58] and larger J values are observed for the *Z* isomers in which the imino proton and protons on the carbon attached to nitrogen have a trans relationship.

In the case of our iminoacetonitriles, the minor products were found to have the larger of the two coupling constants (2.1 Hz), suggesting a transoid relationship between the imino hydrogen and the methylene group. The major product, proposed to be the *E* isomer, has a smaller coupling constant (1.5 Hz), suggesting a cisoid relationship between the two groups. The chemical shift of the imino proton appears around 7.35-7.40 ppm in the ^{1}H NMR spectrum, and this class of imines also displays a characteristic

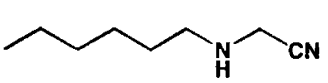
[57] (a) Boers, R. B.; Randulfe, Y. P.; van der Haas, H. N. S.; van Rossum-Baan, M.; Lugtenburg, *Eur. J. Org. Chem.* **2002**, 2094. (b) Gajewski, J. J.; Weber, R. J.; Braun, R.; Manion, M. L.; Hymen, B. *J. Am. Chem. Soc.* **1977**, *99*, 816.

[58] Yeh, H. J. C.; Ziffer, H.; Jerina, D. M.; Boyd, D. R. *J. Am. Chem. Soc.* **1973**, *95*, 2741.

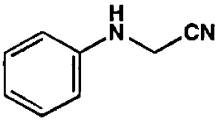
amino nitrile.[60] Overman and coworkers have reported the preparation of a variety of α-amino nitriles by either the Strecker reaction (**96**, **98**) or standard alkylation reactions (e.g., $ClCH_2CN$, *i*-Pr_2NEt) (**97**).[61]



96 (80%)



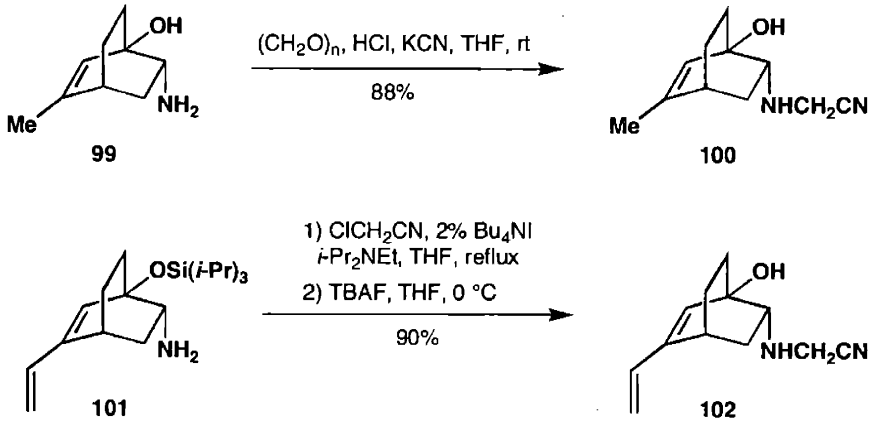
97 (75%)



98 (77%)

Overman has used both tactics in studies directed toward the total synthesis of gelsemine (Scheme 13).[62] The Strecker reaction of amine **99** proceeds smoothly to provide **100**, as does the alkylation of amine **101** to afford amino nitrile **102**. The alkylation of **101** is likely to be more straightforward than the alkylation of Renslo's amines (**87-89**), since amine **101** is fairly hindered and over-alkylation is not as serious a problem. Alkylation of primary amines with bromoacetonitrile usually occurs at or below room temperature, but alkylation of this amine required elevated temperatures, presumably due to steric hindrance.

Scheme 13

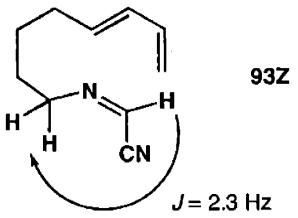


[60] Baker, W.; Ollis, W. D.; Poole, V. D. *J. Chem. Soc.* **1949**, 307.

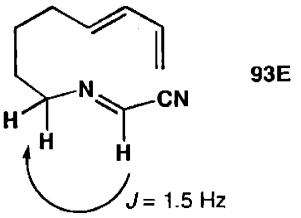
[61] Overman, L. E.; Burk, R. M. *Tetrahedron Lett.* **1984**, *25*, 1635.

[62] Earley, W. G.; Jacobsen, E. J.; Meier, G. P.; Oh, T.; Overman, L. E. *Tetrahedron Lett.* **1988**, *29*, 3781.

stretch (1620-1625 cm^{-1}) in their infrared spectra, consistent with the data reported by Boyer and Selva.



93Z



93E

Optimization Studies

Adam Renslo's initial studies provided access to the desired iminoacetonitriles, but we felt that there was room for improvement with regard to the efficiency of both steps in this approach. The first issue that required attention was the low yield obtained in the alkylation step. Mono-alkylation of primary amines is not necessarily a straightforward process, but can usually be accomplished in good yield by using appropriate tactics.[59] The other issue that needed to be examined was the yield in the elimination step. Since Dr. Renslo had only explored a limited number of bases, a systematic screening of bases was undertaken to identify superior conditions.

Optimization of the Alkylation Step

Several strategies have previously been employed to prepare α-amino nitriles. The retron for the Strecker reaction is an α-amino nitrile. By treating a primary amine with formaldehyde in the presence of potassium cyanide, one can obtain the desired α-

[59] For a recent review on various synthetic methods for the formation of secondary amines, see: Salvatore, R. N.; Yoon, C. H.; Jung, K. W. *Tetrahedron* **2001**, *57*, 7785.

Guillaument and coworkers have suggested the use of the cyanomethyl group as a protective agent for phenols, amines, and carbamates.[63] Although their report discusses only one example of the alkylation of a primary amine with bromoacetonitrile, the reaction does proceed in good yield (eq 23). Unfortunately, there are no experimental details provided in Guillaument's report.

(23)

Fukuyama and coworkers recently disclosed a series of alkylations of primary amines to form α-amino nitrile intermediates in a method for the synthesis of *N*-monoalkylhydroxylamines.[64] For unhindered primary amines, Fukuyama's optimal conditions involve reaction with 1.5 equivalents of chloroacetonitrile and 2.0 equivalents of potassium carbonate in acetonitrile at 60 °C for 24 h, with yields ranging from 93-96%. Fukuyama also reports that the same transformation can be accomplished in the case of more sterically demanding amines by employing slightly modified conditions.

We examined the application of Guillaument's conditions[65] to the synthesis of model α-amino nitrile **104**. Beginning with 2-phenylethylamine (**103**), the secondary amine **104** was isolated in reasonable and reproducible yield (eq 24), and no further attempts were made to optimize these conditions. Note that when Renslo's original protocol (see Scheme 11) was employed for the preparation of **104**, the desired product was isolated in only 38-44% yield.

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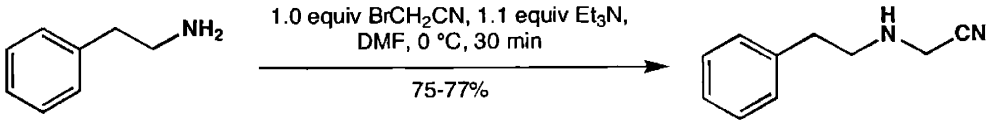
[63] Benrab, A.; Boye, S.; Savelon, L.; Guillaumet, G. *Tetrahedron Lett.* **1993**, *34*, 7567.

[64] Tokuyama, H.; Kuboyama, T.; Amano, A.; Yamashita, T.; Fukuyama, T. *Synthesis* **2000**, 1299.

[65] At the time these studies were carried out, Fukuyama's report had not yet appeared.



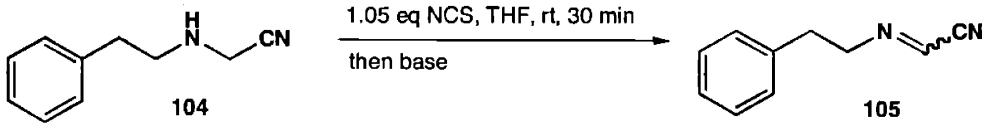
103 104 (24)

Optimization of the Elimination Step

With a reasonably efficient method for the preparation of model amino nitrile **104** in hand, we began to screen a range of conditions to identify the optimal procedure to effect the halogenation/elimination step. NCS was identified as the superior reagent for installation of a leaving group on nitrogen. *N*-bromosuccinimide was briefly examined but proved to be far less effective.

Table 1 summarizes the bases screened for the key elimination reaction. Although alkoxide bases were found to be quite effective, these reactions suffered from low yields and various minor side reactions. For example, nucleophilic addition of an alkoxide to imine **105** and subsequent release of cyanide led to the formation of the corresponding imidate in some cases. Sodium and potassium carbonate proved to be competent bases, especially when the reaction with potassium carbonate was carried out at elevated temperatures. The best success, however, was found with amine bases. Although triethylamine and Hünig's base were not effective, both DBU and DMAP were quite successful in effecting the desired elimination.

Table 1. Effectiveness of Bases in the Chlorination-Elimination Reaction



104 105

Base	Equivalents	Temp	Time	Yield[a]
NaOMe	1.0	0 °C	2 h	64%
KO*t*-Bu	1.02	0 °C	35 min	36%
KO*t*-Bu	1.02	-78 °C → rt	5 h	59%
Na_2CO_3	1.5	rt	22 h	58%
K_2CO_3	3.0	rt	21 h	52%
K_2CO_3	12	rt → 60 °C	5 h	69%
i-Pr_2NEt	1.0	0 °C→ rt	4 h	decomp
DBU	1.05	rt	30 min	71%
DBU	1.05	0 °C	45 min	74%
DMAP	1.05	0 °C→ rt	3 h	77%
DABCO	1.05	0 °C	1 h	68%

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

Conclusions

Adam Renslo's initial studies together with the optimization work described in this chapter provided us with an efficient protocol for the preparation of iminoacetonitriles. Screening a wide range of bases identified DMAP and DBU as optimal bases for the elimination reaction. Despite the success of this study, we were not satisfied with this approach. In particular, we noted that this approach begins with amines, and although amines are fairly simple to synthesize, all of the synthetic sequences we envisioned for the preparation of iminoacetonitrile cycloaddition substrates would involve the preparation of the amine from an alcohol derivative via substitution with azide or cyanide followed by reduction. It was clear that a more attractive and

expeditious route to iminoacetonitriles would be in hand if we could begin with an alcohol rather than an amine. The following chapter explores the development and implementation of such a "second generation" approach to iminoacetonitriles.

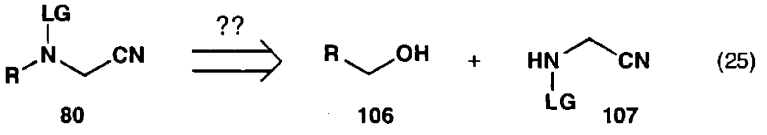
Chapter 3

Mitsunobu Approach to Iminoacetonitriles

Our initial attempts to synthesize iminoacetonitriles via the "alkylation-elimination" strategy proved fruitful, but we wanted to develop a more efficient and expeditious route to this class of imines. This chapter describes the development and implementation of a Mitsunobu reaction as the key step in a synthesis of iminoacetonitriles.

Retrosynthetic Analysis

As discussed earlier, our initial retrosynthetic analysis identified **80** as a key intermediate for the preparation of iminoacetonitriles. In order to utilize readily available alcohols (**106**) as precursors to **80**, we ideally required a reaction that would allow the installation of the nitrogen moiety, and possibly the leaving group as well, in a single transformation (eq 25).



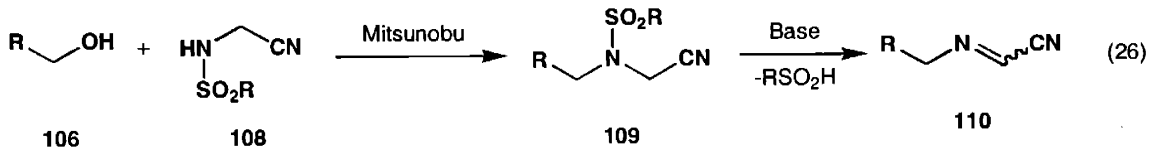
80 **106** **107** (25)

Mitsunobu Reaction

It is well known that various nitrogen nucleophiles can be used in the Mitsunobu reaction,[66] and it appeared that this reaction might provide an attractive solution for our

[66] For reviews of the Mitsunobu reaction, see: (a) Mitsunobu, O. *Synthesis* **1981**, 1. (b) Hughes, D. L. *Org. React.* **1992**, *42*, 335. (c) Hughes, D. L. *Org. Prep. Proced. Int.* **1996**, *28*, 127.

problem. For a nucleophile to react efficiently in the Mitsunobu reaction, the pKa of its conjugate acid must be less than 11-12. Nitrogen nucleophiles previously employed in the Mitsunobu reaction include imides, iminodicarbonates, sulfonamides, and azide. The ability to use a sulfonamide was particularly attractive to us, as one could imagine reacting an alcohol with a sulfonamide of type **108** to produce tertiary sulfonamide **109**, which might undergo elimination of the sulfinate group to directly provide the desired iminoacetonitrile **110** (eq 26).



106 **108** **109** **110** (26)

Nitrobenzenesulfoanamides,[67] *p*-toluenesulfonamides,[68] and trifluoromethanesulfonamides[69] were identified as potential candidates for our particular transformation, since all three have been shown to participate cleanly in the Mitsunobu reaction. Weinreb has reported the use of *N*-BOC tosylsulfonamide in the Mitsunobu reaction, and he also found that simple *N*-alkyl tosylsulfonamides participate in the reaction, albeit in slightly lower yields. Nonetheless, we were hopeful that employing a sulfonamide might expedite our synthesis of iminoacetonitriles.

To begin our investigations of the Mitsunobu strategy, we prepared a series of three sulfonamides utilizing the commercially available hydrochloride salt of aminoacetonitrile (**111**) as starting material (Scheme 14). The yields for the preparation of the two arylsulfonamides (**112** and **113**) were fairly good, but preparation of triflamide

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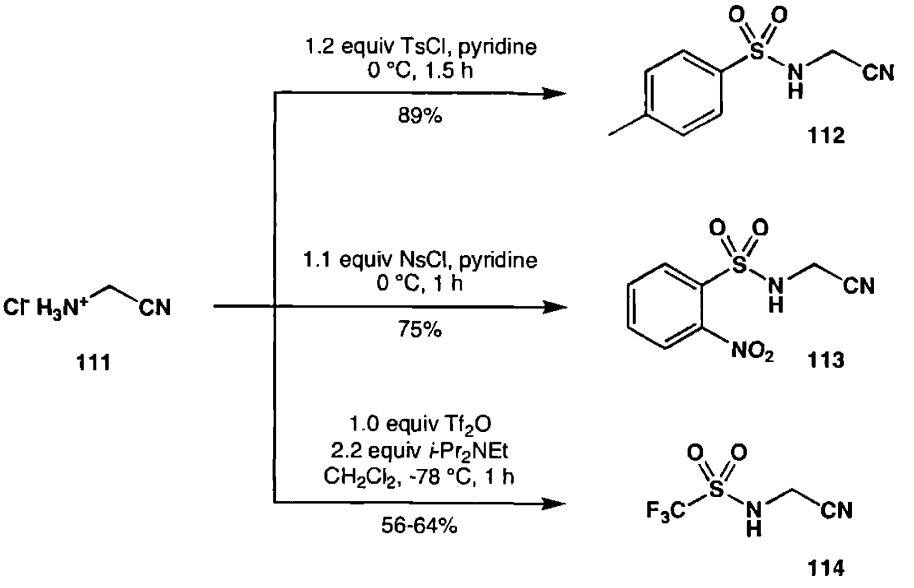
[67] (a) Fukuyama, T.; Jow, C.-K.; Cheung, M. *Tetrahedron Lett.* **1995**, *36*, 6373. (b) Fukuyama, T.; Cheung, M.; Jow, C.-K.; Hidai, Y.; Kan, T. *Tetrahedron Lett.* **1997**, *38*, 5831.

[68] Henry, J. R.; Marcin, L. R.; McIntosh, M. C.; Scola, P. M.; Harris Jr., G. D.; Weinreb, S. M. *Tetrahedron Lett.* **1989**, *30*, 5709.

[69] (a) Edwards, M. L.; Stemerick, D. M.; McCarthy, J. R. *Tetrahedron Lett.* **1990**, *31*, 3417. (b) Edwards, M. L.; Stemerick, D. M.; McCarthy, J. R. *Tetrahedron* **1994**, *50*, 5579.

114 required a fair amount of optimization. Optimization studies first identified Tf_2NCH_2CN as the major by-product of this reaction, so we then explored conditions to minimize its formation. This byproduct was presumably formed by the reaction of sulfonamide **114** and excess triflic anhydride, in an analogous fashion to the formation of *N*-phenyl triflimide from aniline and 2 equivalents of triflic anhydride.[70] Our optimization studies included screening a variety of amine bases and varying the amount of triflic anhydride that was employed. The best conditions that were identified from our survey are depicted in Scheme 14 and have been employed for the preparation of **114** on multigram scale. Compounds **112** and **113** are stable, white, crystalline solids. The previously unknown sulfonamide **114** is a low-melting solid and can be stored in solution at ca. 4 °C for a couple of months with no detectable decomposition.

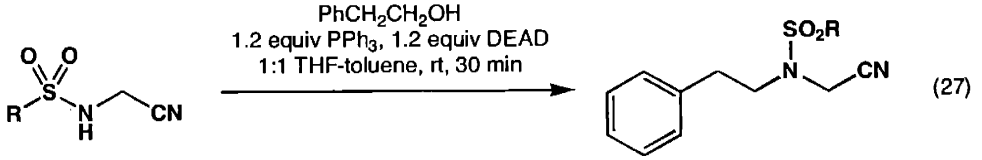
Scheme 14



With three different sulfonamides in hand, we next explored the reactivity of these compounds in the Mitsunobu reaction with 2-phenethyl alcohol. Employing the

[70] Hendrickson, J. B.; Bair, K. W.; Bergeron, R.; Giga, A.; Skipper, P. L.; Sternbach, D. D.; Wareing, J. A. *Org. Prep. Proced. Int.* **1977**, *9*, 173.

conditions described by Weinreb,[68] all three sulfonamides (**112-114**) delivered the expected product in excellent yield after purification by column chromatography (eq 27).



112 R = *p*-MeC_6H_4
113 R = *o*-$NO_2C_6H_4$
114 R = CF_3

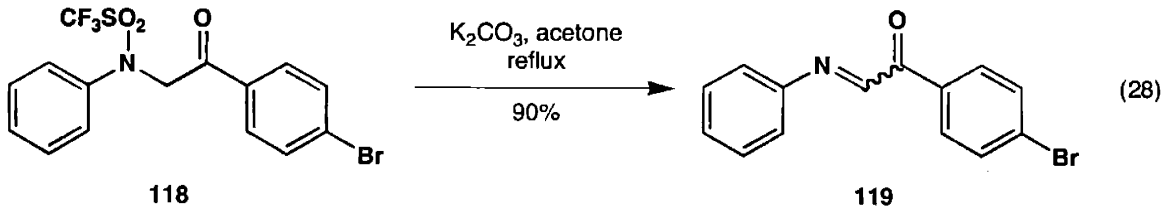
115 R = *p*-MeC_6H_4 100%
116 R = *o*-$NO_2C_6H_4$ 87%
117 R = CF_3 96%

Elimination of *N*-Sulfonylamino Nitriles

Efforts were next directed at identifying conditions to convert a *N*-cyanomethylsulfonamide into an iminoacetonitrile. Initial attempts focused on using lithium amide bases (LDA, LiTMP). With *p*-toluenesulfonamide **115**, little or no reaction occurred, and the starting material was recovered. Elimination reactions with sulfonamide **116** were plagued by what appeared to be electron transfer. Specifically, we observed that a colorless solution of **116** instantly became a brilliant purple color upon addition of the first drop of amide base. Attempts to isolate any products from these reactions afforded only recovered starting material and unidentifiable decomposition products. Attempts to use weaker bases, such as *t*-BuOK and various carbonate bases, also failed to deliver the desired imine.

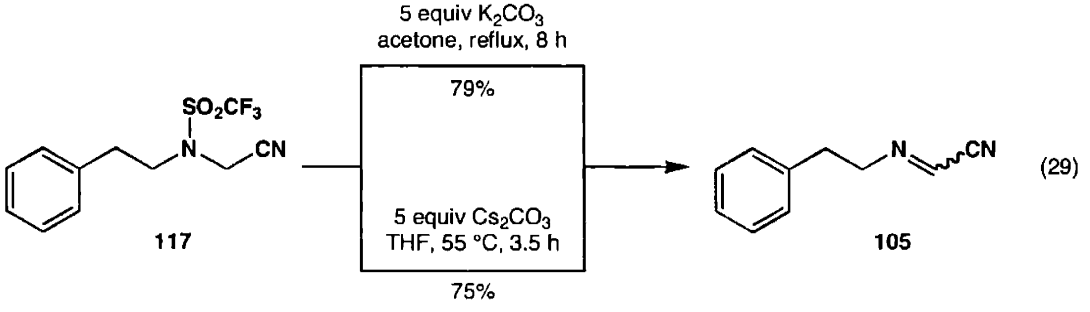
Hendrickson has previously described the elimination of trifluoromethanesulfinate from an α-amino ketone (eq 28)[71] in a process we viewed as analogous to our desired transformation.

[71] Hendrickson, J. B.; Bergeron, R.; Giga, A.; Sternbach, D. *J. Am. Chem. Soc.* **1973**, *95*, 3412.



118 119 (28)

To our delight, subjecting triflamide **117** to similar conditions afforded imine **105** in 79% yield as a 74:26 mixture of *E* and *Z* isomers (eq 29). We then set out to screen a variety of bases and conditions for this transformation. Elimination using cesium carbonate in warm THF was identified as the optimal conditions for the elimination (eq 29). Elimination of sulfinate from **117** does not require rigorously dried carbonate bases for success, and as will be seen later, we routinely employed ACS reagent grade cesium carbonate for the preparation of our iminoacetonitriles. The yields for elimination reactions carried out with potassium and cesium carbonate are comparable in this case, although the reaction time with cesium carbonate is shorter. As will be seen later, optimization studies on other substrates demonstrated the general superiority of cesium carbonate over potassium carbonate.

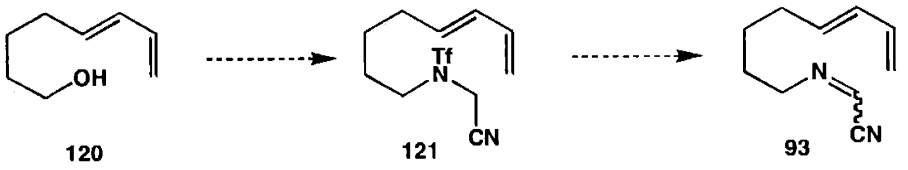


117 105 (29)

Application of the Mitsunobu Strategy

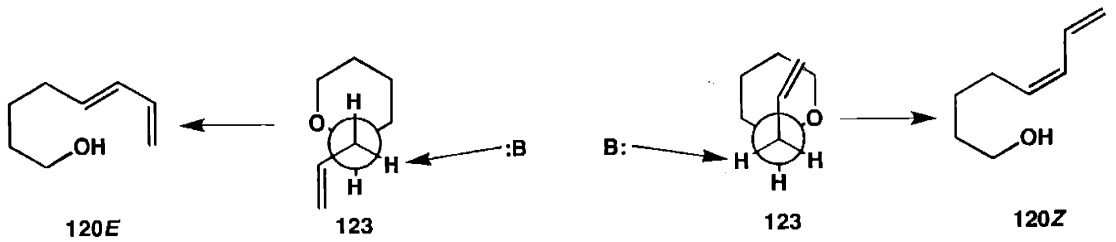
With the development of the "second-generation" synthesis of iminoacetonitriles described in the previous section, we turned our attention to applying this strategy to the

synthesis of imine **93**, previously prepared by Adam Renslo utilizing the "alkylation-elimination" approach. As seen below, the synthesis of **93** required dienyl alcohol **120**.



120 121 93

Previously, Schlosser has reported the preparation of this dienyl alcohol by a novel elimination that takes place on exposure of tetrahydropyran **123** to LDA in the presence of a catalytic amount of potassium *tert*-butoxide.[72] "Schlosser's base" (LDA-KO- *t*Bu) has the capacity to metalate alkenes at the allylic position and effect the elimination of an alkoxy group. Schlosser reports the preparation of alcohol **120** occurs with very high selectivity for the *E* isomer. Presumably the elimination proceeds through an anti-periplanar transition state, and the two possible conformations are shown below. The transition state on the right leads to the undesired *Z* diene isomer, but is higher in energy than the transition state on the left due to the gauche interactions of the vinyl group and the tetrahydropyran ring. The left-hand transition state is lower in energy and leads to the desired *E* diene.

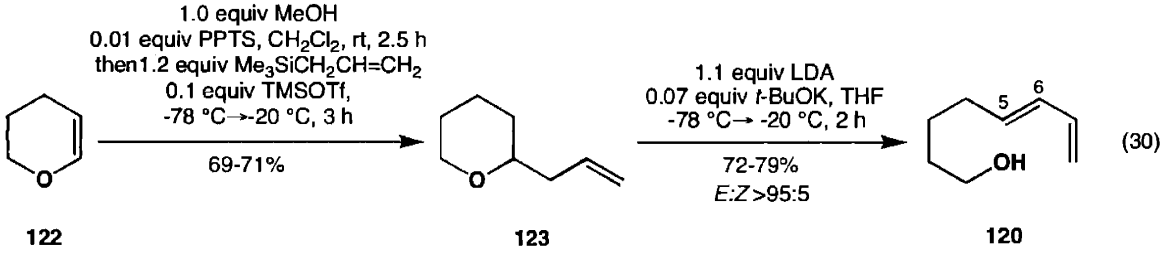


120*E* 123 123 120*Z*

Schlosser prepared tetrahydropyran **123** using the procedure of Gouin,[73] for the reaction of allylmagnesium chloride and 2-chlorotetrahydropyran. More recently, Noyori reported the preparation of **123**, employing a modified Sakurai reaction of 2-

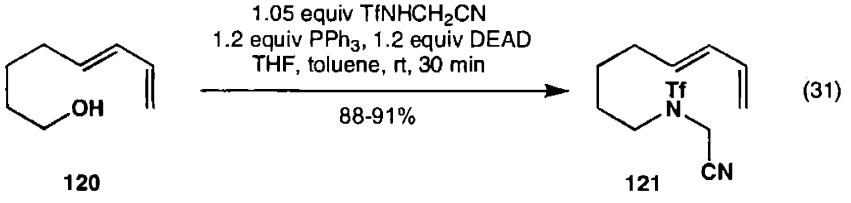
[72] Margot, C.; Rizzolio, M.; Schlosser, M. *Tetrahedron* **1990**, *46*, 2411.
[73] Riobé, O.; Gouin, L.; Chiron, R. *Bull. Soc. Chim. Fr.* **1963**, 2258.

methoxytetrahydropyran and allyltrimethylsilane.[74] We felt that allylation of dihydropyran (**122**) via *in situ* generation of 2-methoxytetrahydropyran would provide a more expeditious route to **123**. Thus, treatment of an excess (1.2 equivalents) of dihydropyran with 1 equivalent of methanol in the presence of catalytic PPTS (pyridinium *p*-toluenesulfonate) afforded a colorless solution which was then cooled to –78 °C and treated with allyltrimethylsilane and a catalytic amount of trimethylsilyl triflate. Isolation and purification afforded the desired tetrahydropyran **123** in good yield. Exposing **123** to Schlosser's base then provided dienyl alcohol **120** as a single stereoisomer (eq 30). The large coupling constant (17.5 Hz) observed between the protons on C-5 and C-6 indicated the presence of an *E*-olefin.



(30)

The Mitsunobu reaction of alcohol **120** with triflamide **114** afforded the desired dienyl triflamide **121** in excellent yield (eq 31). The preparation of triflamide **121** represented a significant advance in our methodology, because for the first time, we were able to transform an alcohol directly into an iminoacetonitrile precursor.

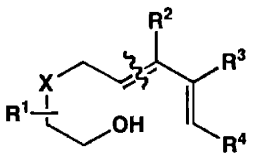


(31)

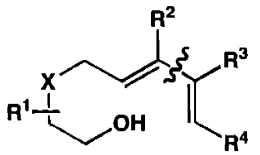
[74] Tsunoda, T.; Suzuki, M.; Noyori, R. *Tetrahedron Lett.* **1980**, *21*, 71.

Preparation of Alcohol Substrates

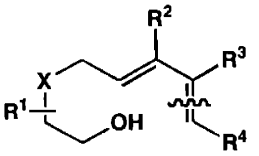
Having developed effective tactics for the synthesis of *N*-cyanomethyltriflamides, we next directed our efforts at preparing a variety of alcohol precursors to iminoacetonitrile cycloaddition substrates.



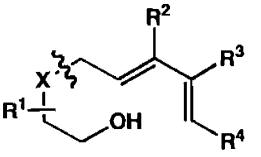
124



125



126



127

Several different strategies were employed to prepare the desired dienyl alcohols. As shown above, there are at least four straightforward disconnections for the construction of the type of molecule in which we were interested. Two well-studied disconnections are indicated in **124** and **126** involving Wittig olefination of an aldehyde or ketone and a phosphorous ylide.[75] Disconnection **125** represents another powerful and convergent strategy. With the developments in transition metal-mediated cross-coupling reactions,[76] the reaction of a vinyl stannane or organoboron compound with a vinyl halide should provide the desired diene moiety. If the target substrate contains a heteroatom in the tether, a third option is available (**127**), namely the alkylation of the heteroatom with a dienyl halide. For the following discussion, the various dienyl alcohol substrates are divided into three categories: (a) substrates bearing additional substituents on the diene moiety, (b) substrates with heteroatoms incorporated in the connecting chain, and (c) substrates with all-carbon tethers that bear additional substituents.

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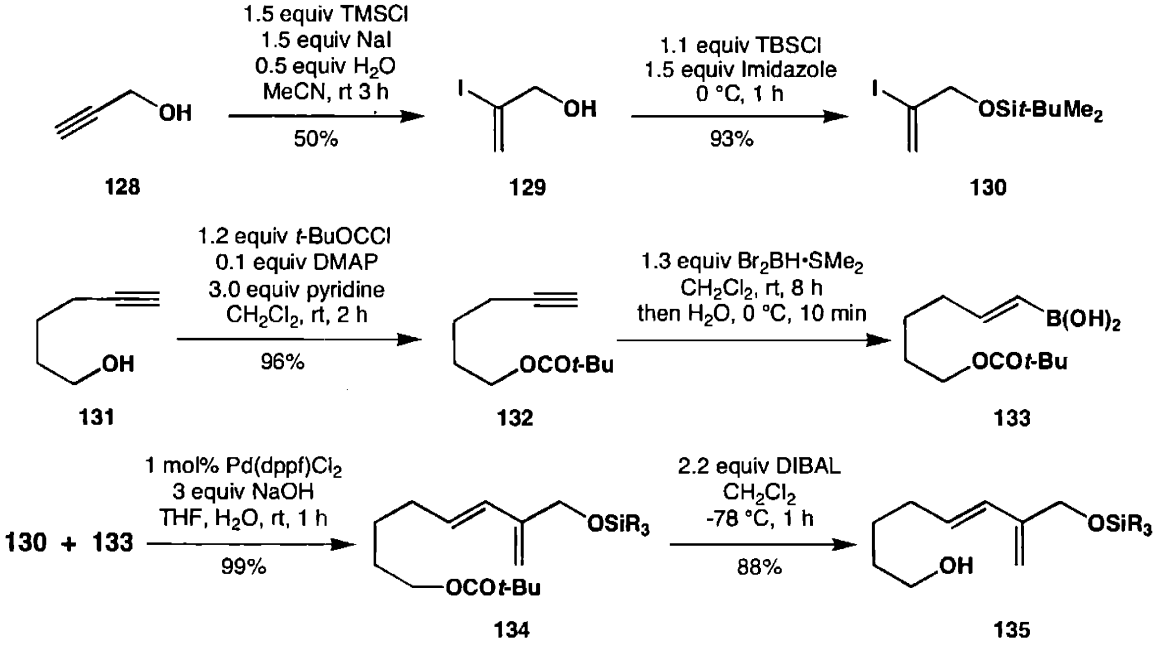
[75] (a) For reviews of the Wittig and related olefination reactions, see: Maryanoff, B. E.; Reitz, A. B. *Chem. Rev.* **1989**, *89*, 863. (b) Kelly, S. E. In *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I., Eds.; Pergamon Press: Oxford, 1991, Vol. 1, pp 755-782. (c) Kolodiazhnyi, O. I. *Phosphorus Ylides*; Wiley-VCH: Weinheim, 1999.

[76] *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F.; Stang, P. J., Eds; Wiley-VCH: New York, 1998.

Synthesis of Substrates with Substituted Dienes

The first system to be explored was a substrate with substitution at the 3-position of the diene. As shown below, this compound was prepared utilizing a Suzuki cross-coupling between a vinyl iodide (**130**) and a boronic acid (**133**). Silylation of known alcohol **129**[77] afforded the previously reported TBDMS ether **130**[78] in good yield. To prepare the requisite boronic acid **133**, commercially available 5-hexyn-1-ol (**131**) was protected as the corresponding pivalate ester and then subjected to H. C. Brown's conditions for the formation of boronic acids.[79]

Scheme 15



[77] For preparation of compound **129**, see: Irifune, S.; Kibayashi, T.; Ishii, Y.; Ogawa, M. *Synthesis* **1988**, 366.

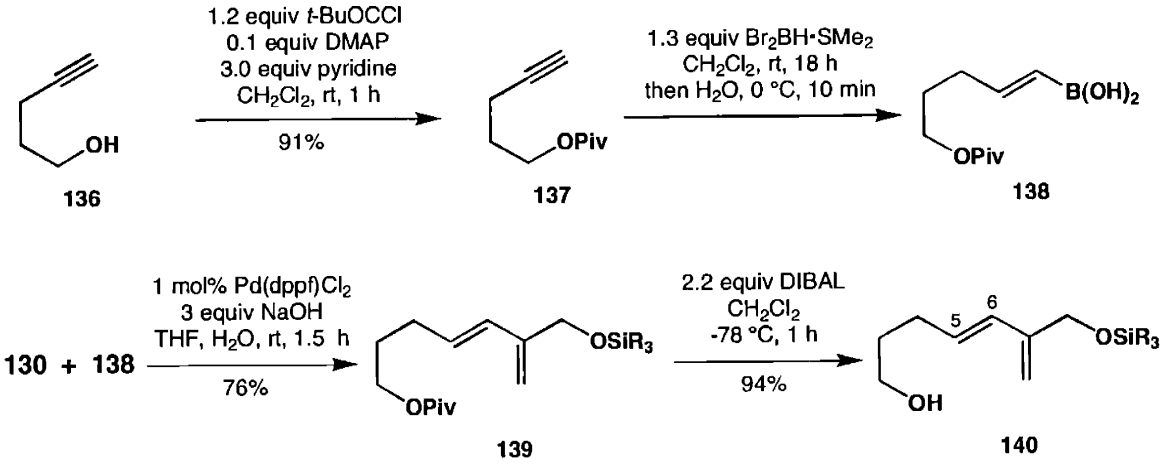
[78] Lai, M.; Li, D.; Oh, E.; Liu, H. *J. Am. Chem. Soc.* **1993**, *115*, 1619.

[79] (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.

Coupling vinyl iodide **130** and boronic acid **133** (used without further purification) under standard Suzuki cross-coupling[80] conditions afforded the desired diene **134** in nearly quantitative yield. DIBAL reduction then cleaved the pivalate group to provide alcohol **135** in good yield.

An analogous strategy provided efficient access to the related dienyl alcohol **140**, starting from 4-pentyn-1-ol (Scheme 16). The yields are comparable to those in the previous route, with exception of the Suzuki reaction.

Scheme 16



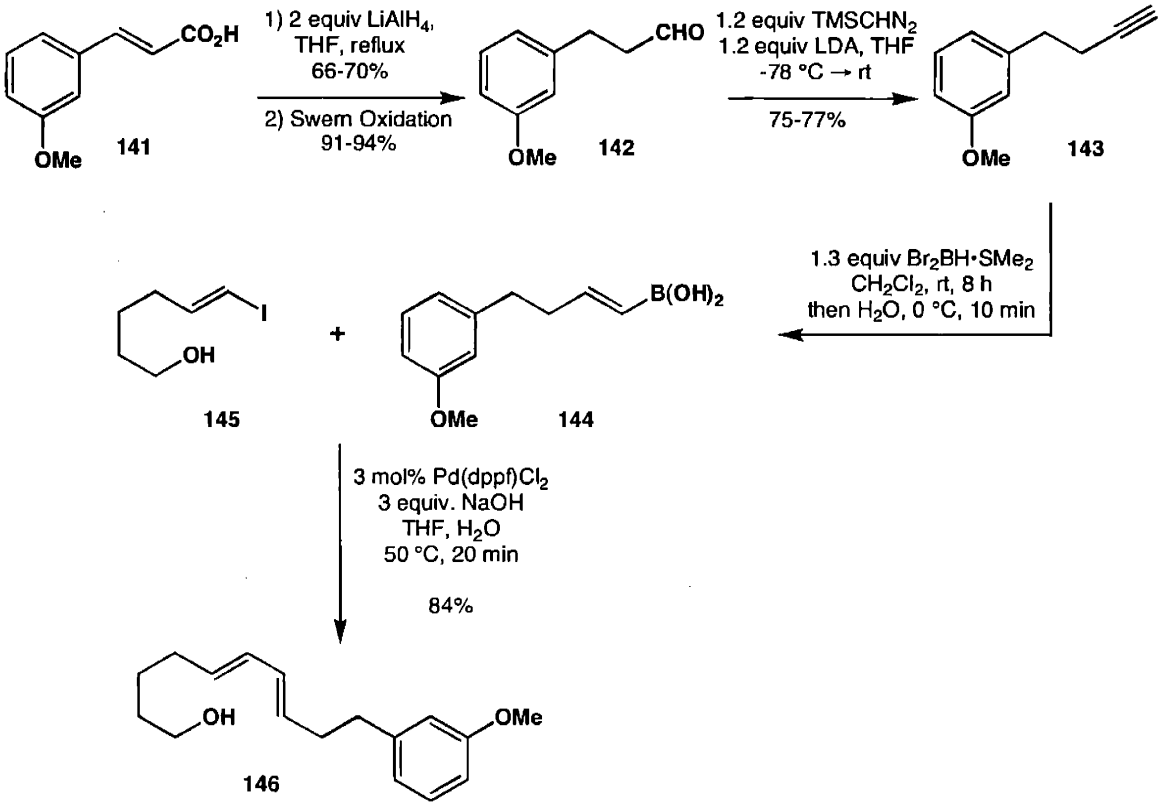
The *E*-stereochemistry assigned to dienes **135** and **140** follows from the well-established stereochemical course of hydroboration of alkynes. In addition, the ^{1}H NMR spectra of these dienes contain large coupling constants (16 Hz) for the spin-coupling of the protons on C-5 and C-6, consistent with a trans relationship.

Dienyl alcohol **146** served as a precursor to a cycloaddition substrate with a substituent at the terminal position of the diene. Our interest in this system derived from

[80] For a review of the Suzuki reaction, see: (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457. (b) Suzuki, A. *J. Organomet. Chem.* **1999**, *576*, 147.

the expectation that a suitable nucleophilic π-bond tethered to this position might be employed in later bond-forming reactions after cycloaddition (see Part IV).

Scheme 17



To access the desired diene, we again utilized a Suzuki cross-coupling reaction, in this case between the known vinyl iodide **145**[81] and boronic acid **144**. For the preparation of **144**, 3-methoxycinnamic acid (**141**) was reduced with $LiAlH_4$ to produce the expected saturated alcohol, which was oxidized to known aldehyde **142**.[82] Alkyne **143** was next obtained in good yield by employing the Colvin rearrangement which was effected by reaction of **142** with lithium(trimethylsilyl)diazomethane.[83] This alkene was then

[81] Previously prepared by treating 5-hexyn-1-ol with $Cp_2Zr(H)Cl$ followed by I_2. See: Lipshutz, B. H.; Keil, R.; Ellsworth, E. L. *Tetrahedron Lett.* **1990**, *31*, 7257.

[82] Manas, A. R. B.; Smith, R. A. J. *Tetrahedron* **1987**, *43*, 1847.

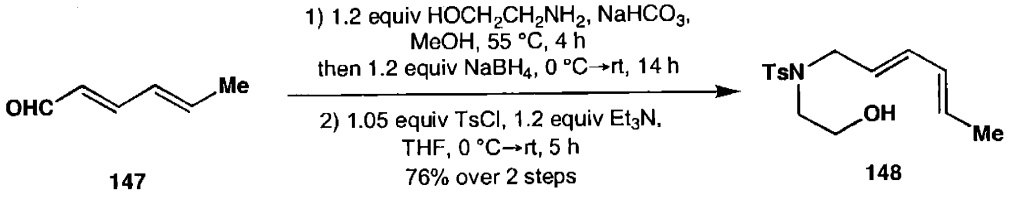
[83] (a) Colvin, E. W.; Hamill, B. J.; *J. Chem. Soc., Chem. Commun.* **1973**, 151. (b) Colvin, E. W.; Hamill, B. J. *J. Chem. Soc. Perkin I* **1977** 869. (c) Miwa, K.; Aoyama, T.; Shioiri, T. *Synlett* **1994**, 107.

converted to boronic acid **144** using Brown's protocol as in our previous system, and the crude boronic acid was coupled to vinyl iodide **145** using palladium catalysis to afford diene **146** (Scheme 17).

Another goal in our investigation of intramolecular iminoacetonitrile cycloadditions was to examine the effect of variations in the "tether" connecting the diene moiety to the iminoacetonitrile functional group. In particular, we were interested in studying substrates with heteroatoms and aromatic rings incorporated in the tether, and also chiral compounds with substituents on the connecting chain. We first turned our attention to substrates with heteroatoms incorporated in the tether.

Substrates with Substituted Tethers

Eq 32 outlines the synthesis of the alcohol precursor to a substrate with a nitrogen atom in the connecting chain. Reductive amination of sorbylaldehyde with 2-aminoethanol gave the desired secondary amine in good yield.[84] This is not a straightforward transformation, considering the possibilities for aminal formation[85] and conjugate (1,4 and 1,6) reduction of the dienyl imine.[86] Sulfonylation of the crude amino alcohol with tosyl chloride afforded the desired sulfonamide **148** in good overall yield from **147**.



(32)

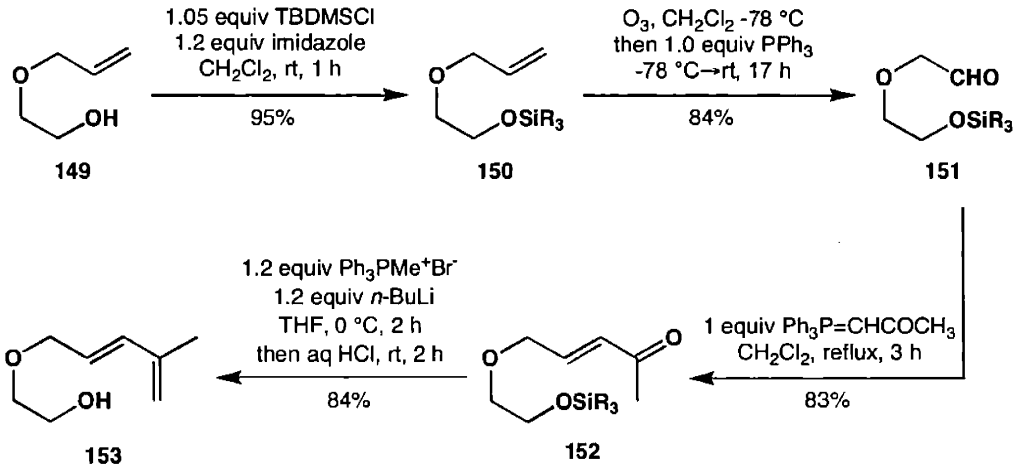
[84] For a related reaction, see: Stütz, A.; Petranyi, G. *J. Med. Chem.* **1984**, *27*, 1539.

[85] For an example of a reductive amination with 2-aminoethanol, see: Morie, T.; Kato, S.; Harada, H.; Yoshida, N.; Matsumoto, J. *Chem. Pharm. Bull.* **1994**, *42*, 877.

[86] For an example of a reduction of an α,β-unsaturated imine, see: De Kimpe, N.; Stanoeva, E.; Verhé, R.; Schamp, N. *Synthesis* **1988**, 587.

The preparation of a substrate with an ether connecting chain was accomplished in four steps as outlined in Scheme 18. Protection of commercially available 2-allyloxyethanol as a TBDMS ether (**150**), followed by ozonolysis of the double bond furnished aldehyde **151** in good yield. Wittig reaction of **151** with the indicated stabilized phosphorous ylide provided enone **152**, which was converted to diene **153** by a one-pot procedure involving a second Wittig reaction, followed by hydrolysis of the silyl ether with aqueous hydrochloric acid.

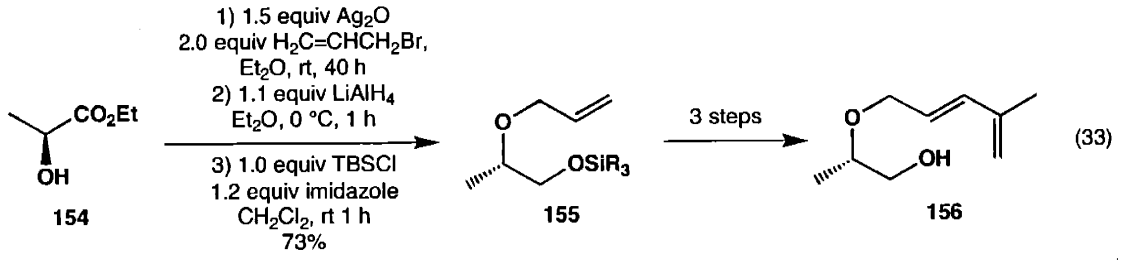
Scheme 18



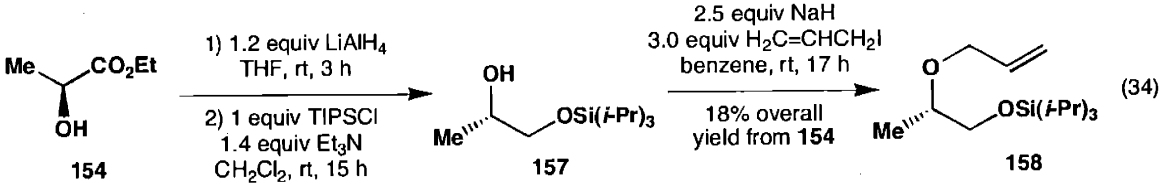
We employed a closely related strategy for the preparation of the dienyl alcohol **156** containing a stereogenic center in the connecting chain. Initially, (S)-ethyl lactate (**154**) was converted in three steps to allyl ether **155** by alkylation with allyl bromide[87] followed by reduction of the ester and protection of the resulting alcohol as a silyl ether (eq 33). Allyl ether **155** was then transformed to diene alcohol **156** in a fashion similar to the transformation of **150** to **153**. However, Mosher ester analysis of alcohol **156** prepared via this route indicated that an erosion of enantiomeric purity had occurred

[87] Schmidt, B.; Wildemann, H. *J. Org. Chem.* **2000**, *65*, 5817.

during the course of these reactions.[88] We found this puzzling, since Solladié-Cavallo and Bonne have reported the alkylation of ethyl lactate under the same conditions without any epimerization.[89]



An alternative, more lengthy route to **156** was therefore developed to circumvent the epimerization problem. In this second approach, the ester was reduced and protected prior to alkylation of the alcohol. Thus, reduction of (S)-ethyl lactate with $LiAlH_4$ gave 1,2-propandiol, which was mono-protected at the primary hydroxyl group with $(i\text{-Pr})_3SiCl$. Alkylation of the secondary alcohol (80% purity)[90] was carried out with great care to avoid silyl migration.[91] The desired silyl ether **158** was obtained in low overall yield (eq 34; not optimized).



As shown in Scheme 19, the conversion of allylic ether **158** to the desired diene **161** proceeded smoothly according to the route previously employed for substrate **153**.

---

[88] The de of the Mosher ester of **156** was only 88%, although enantiomerically pure ethyl lactate was used as starting material.

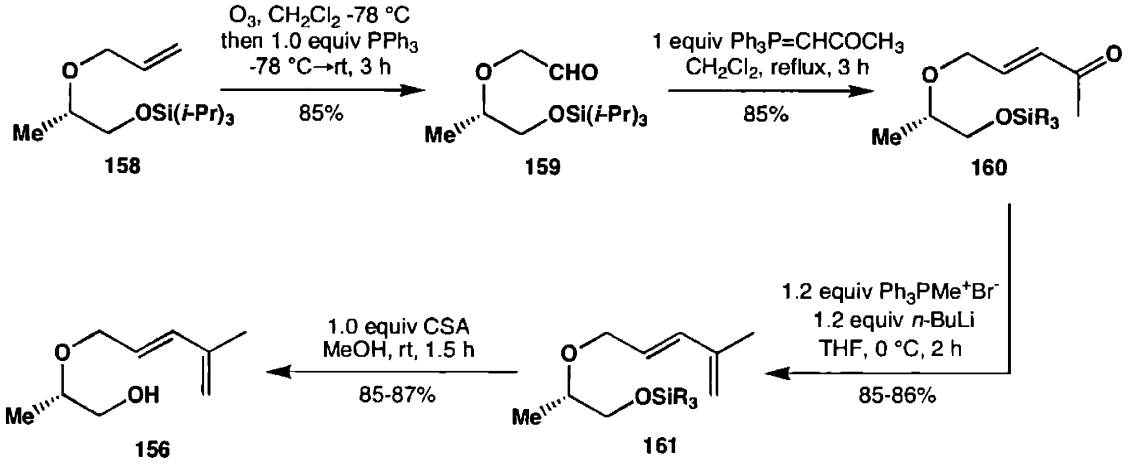
[89] Solladié-Cavallo, A.; Bonne, F. *Tetrahedron: Asymmetry* **1996**, *7*, 171.

[90] The desired product was deemed to be only ca. 80% pure by ^1H NMR analysis. The contaminant incorporated a silyl group, and all attempts to increase the purity of the desired compound were unsuccessful.

[91] Under all conditions explored for the alkylation step, the corresponding TBS silyl ether suffered extensive migration.

Exposure of silyl ether **161** to methanolic camphorsulfonic acid then provided the dienyl alcohol **156** in good yield after purification. Mosher ester analysis of alcohol **156** confirmed that this approach furnished material of >98% enatntiomeric purity.

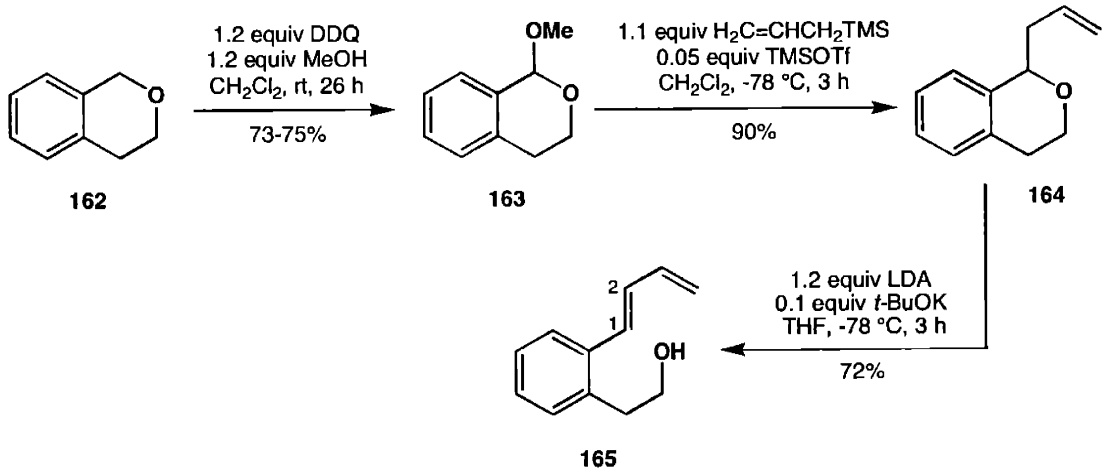
Scheme 19



We next turned our attention to synthesizing two systems containing an aryl group in the tether linking the diene and alcohol moieties. Both of these compounds were accessed using the Schlosser base-promoted elimination reaction employed in the synthesis of the simple dienyl alcohol **120**. We identified homoallyl ethers **164** and **168** as key substrates for the proposed Schlosser eliminations, and prepared each by a Noyori allylation of an appropriate methyl acetal. For the synthesis of **165**, the known acetal **163** was prepared by treatment of isochroman (**162**) with DDQ in methanol according to the literature procedure.[92] Exposure of **163** to allyltrimethylsilane and TMSOTf afforded the desired allyl-substituted product, and reaction with LDA and catalytic KO*t*-Bu then provided alcohol **165** as a single stereoisomer. The ^{1}H NMR spectrum of **165** displays a large (16 Hz) coupling constant for the interaction between the protons on C-1 and C-2 of the diene, consistent with the presence of an *E* olefin.

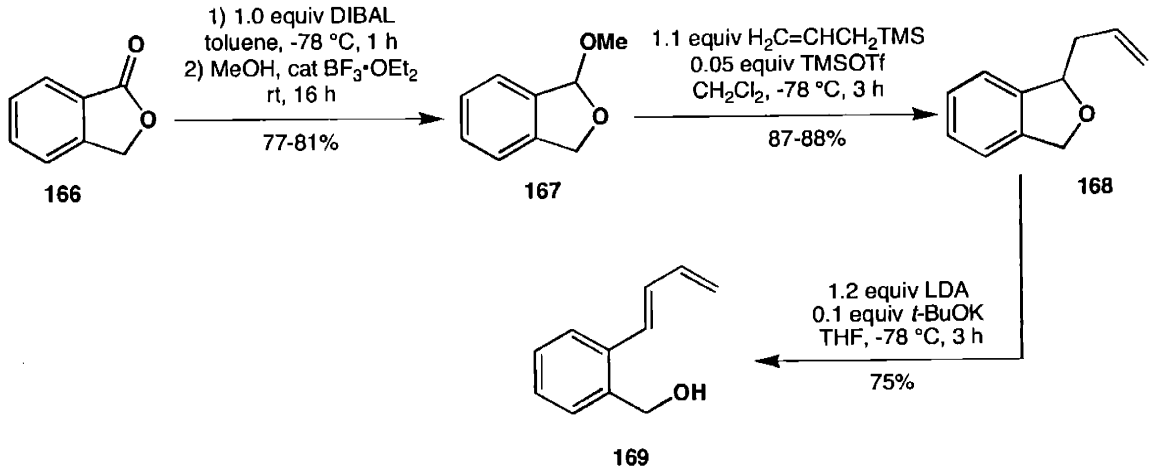
[92] Xu, Y.-C.; Lebeau, E.; Gillard, J. W.; Attardo, G. *Tetrahedron Lett.* **1993**, *34*, 3841.

Scheme 20



For the related aromatic substrate precursor **169**, our synthetic route commenced with the preparation of acetal **167** according to a modification of the procedure of Tidwell and co-workers (Scheme 21).[93] Thus, careful mono-reduction of phthalide (**166**) afforded the corresponding lactol, which was then immediately converted to the desired methyl acetal by the action of $BF_3 \cdot Et_2O$ and methanol. Addition of allyltrimethylsilane in the presence of TMSOTf provided the desired homoallyl ether (**168**). Finally, elimination with Schlosser's base delivered the desired dienyl alcohol **169** as a single olefin isomer.

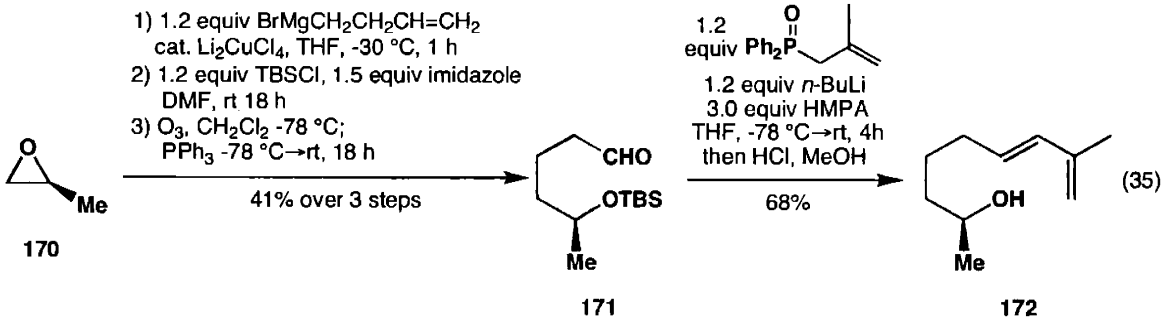
Scheme 21



[93] Rynard, C. M.; Thankachan, C.; Tidwell, T. T. *J. Am. Chem. Soc.* **1979**, *101*, 1196.

A number of projected applications of the iminoacetonitrile cycloaddition to the total synthesis of natural products would require chiral substrates with substituents attached along the connecting chain. The next set of cycloaddition substrates we investigated examined the stereochemical course of reactions involving these types of systems.

The preparation of the chiral secondary alcohol **172** was studied first. Mitsunobu displacement of this alcohol should proceed cleanly with inversion of configuration, and this would provide access to an iminoacetonitrile with a stereogenic center adjacent to the nitrogen atom. Eq 35 describes the synthesis of chiral alcohol **172**. Copper-catalayzed addition of the 3-butenyl Grignard reagent to propylene oxide (**170**) as described by Ley[94] gave the expected secondary alcohol, which without purification was protected as the corresponding TBDMS ether (eq 35). Ozonolysis of the double bond afforded aldehyde **171**, and a variation of the Horner-Wadsworths reaction[95] then gave the desired diene which was deprotected to afford the diene **172** as a single olefin isomer.



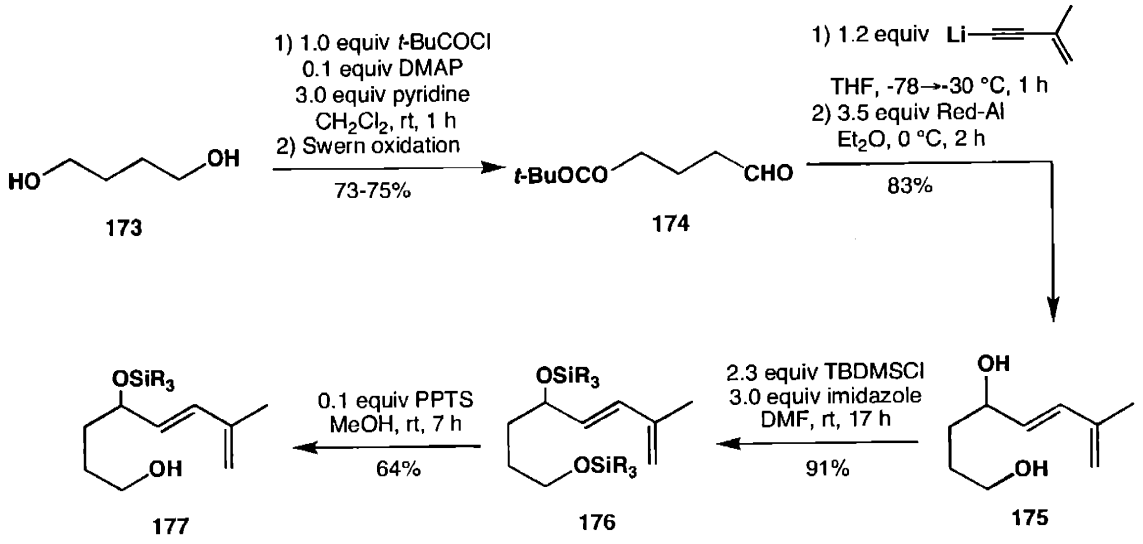
The synthesis of a second chiral dienyl alcohol, in this case containing a stereogenic center alpha to the diene, is outlined in Scheme 22. We chose this secondary

[94] Lainé, D.; Fujita, M.; Ley, S. V. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1639.

[95] (a) Ukai, J.; Ikeda, Y.; Ikeda, N.; Yamamoto, H. *Tetrahedron Lett.* **1983**, *24*, 4029. (b) Harmata, M.; Carter, K. W. *Synth. Commun.* **1997**, *27*, 3027. (c) Cramer, C. J.; Harmata, M.; Rashatasakhon, P. *J. Org. Chem.* **2001**, *66*, 5641.

alcohol (and protected derivatives) in order to simplify the synthesis of substrates, as one can imagine accessing such a compound via a nucleophilic addition of a metalated diene or diene precursor to the corresponding aldehyde (Scheme 22). Commercially available 1,4-butanediol (**173**) was mono-protected as the pivalate ester, and oxidation of the free alcohol using the Swern procedure afforded aldehyde **174**. Treatment of **174** with lithium isopropenylacetylide then provided a propargylic alcohol which was immediately reduced with Red-Al. This reagent effects the cleavage of the pivalate ester and simultaneously reduces the enyne triple bond to afford the desired diene alcohol **175**. With the backbone of the molecule in place, all that was left to do was to differentiate the two hydroxy groups. Global protection of the diol with TBDMSCl afforded the bis-TBDMS ether (**176**). Screening a variety of conditions identified treatment of **176** with catalytic PPTS in methanol as the optimal conditions to effect the monodeprotection of the bis-silyl ether. Using this procedure, the primary alcohol **177** was obtained in 64% yield along with 14% of diol **175**.

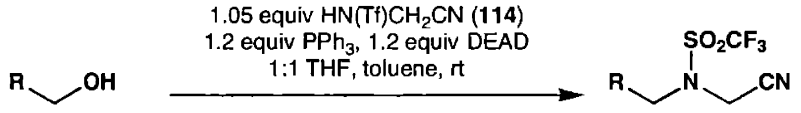
Scheme 22

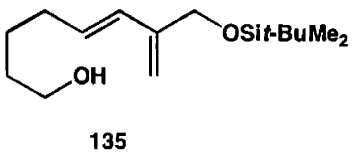
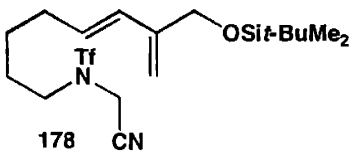
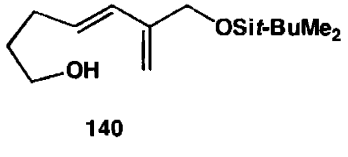
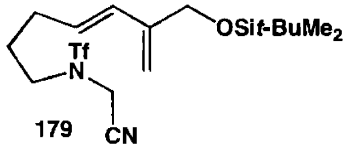
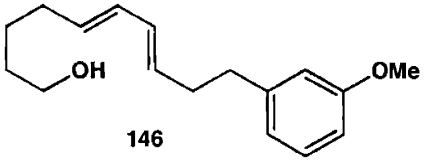
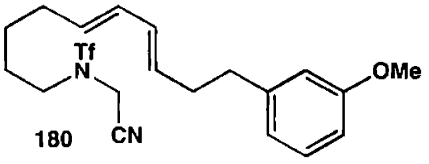


Scope of the Mitsunobu Reaction

With a variety of dienyl alcohols in hand, we turned our attention to exploring the scope of the Mitsunobu reaction for the preparation of the cyanomethyl triflamide precursors to our cycloaddition substrates. Table 2 presents our results for alcohols bearing substituted diene moieties. As expected, the Mitsunobu reaction of these substrates proceeded similarly to the reaction of the unadorned alcohol **120** (eq 31) and further optimization efforts were not undertaken. Thus, treatment of alcohols **135**, **140**, and **146** at room temperature with 1.05 equivalents of triflamide **114**, 1.2 equivalents of DEAD and 1.2 equivalents of triphenylphosphine in a 1:1 mixture of THF and toluene afforded the expected triflamides in good yield following purification by column chromatography. In general, the triflamides discussed in this thesis are isolated as oils and are stable to long term storage as solutions in dichloromethane.

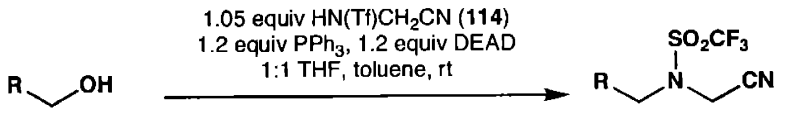
Table 2. Mitsunobu Reaction of Substrates Bearing a Substituted Diene

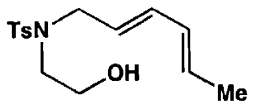
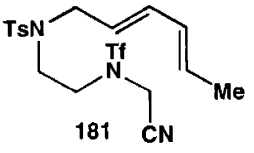
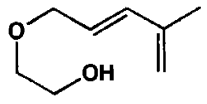
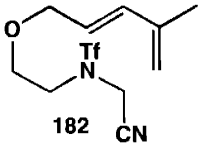
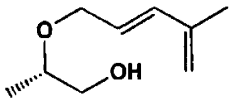
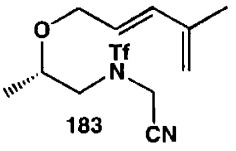


Alcohol	Time	Triflamide	Yield
 **135**	1 h	 **178**	81-94%
 **140**	1-2 h	 **179**	83-86%
 **146**	1 h	 **180**	83%

The Mitsunobu reaction of substrates with a heteroatom incorporated in the tether also proceeded in very good yield, but the time required varied from case to case. For example, alcohol **148** afforded the expected triflamide only after stirring at room temperature for 16-20 hours. We believe that the inductive effect of the electronegative sulfonamide nitrogen atom retards the rate of S_N2 reaction at the β-carbon in this compound. Interestingly, the presence of an electronegative oxygen in the tether did not impede the reaction of alcohol **153**. Neighboring group participation may help facilitate this reaction, although there is no experimental evidence to support this proposal. The tethering oxygen could act as an internal nucleophile to displace triphenylphosphine oxide, forming a three membered ring, which triflamide **114** could then open.

Table 3. Mitsunobu Reaction of Substrates Bearing Heteroatoms in the Tether

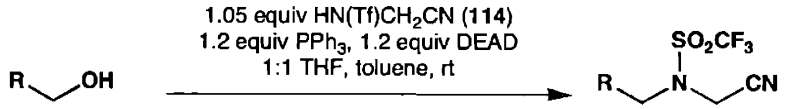


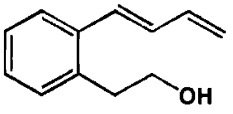
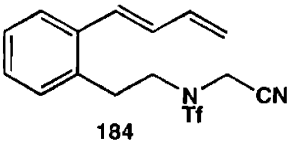
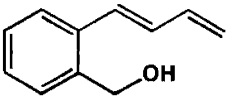
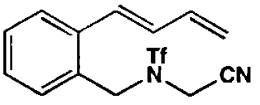
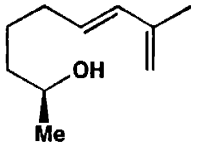
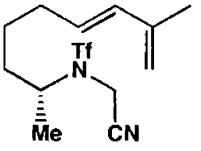
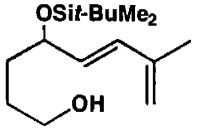
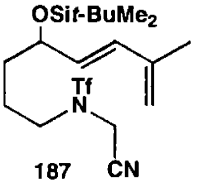
Alcohol	Time	Triflamide	Yield
 **148**	16-20 h	 **181**	93-94%
 **153**	2 h	 **182**	85%
 **156**	19-24 h	 **183**	81-82%

The Mitsunobu reaction with alcohol **156** produced triflamide **183** at a rate similar to that seen with **148**. Conceivably in this case, the branching at the α-carbon impedes nucleophilic displacement.

Similar variations in the rate of the Mitsunobu reaction were observed with the substrates with all-carbon tethers shown in Table 4.

Table 4. Mitsunobu Reaction of Substrates Bearing an All-Carbon Tether



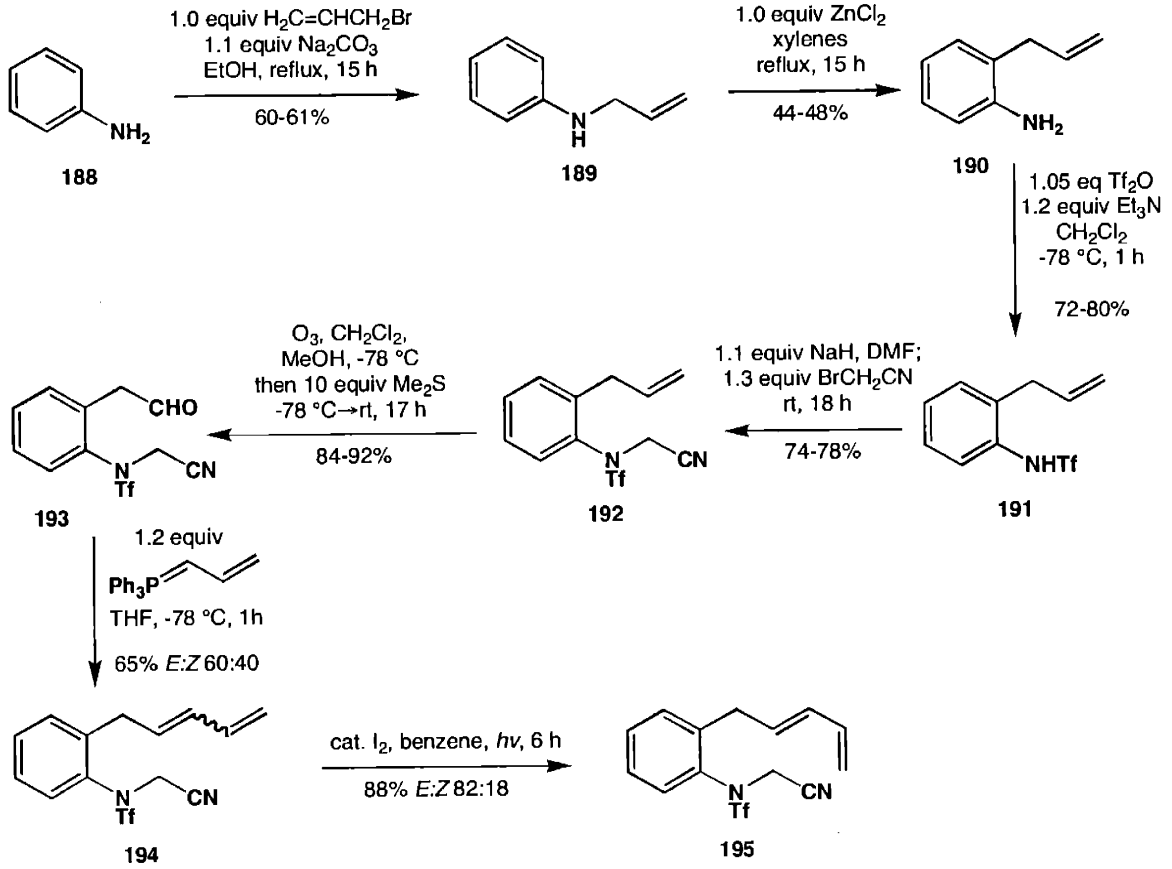
Alcohol	Time	Triflamide	Yield
 **165**	4-5 h	 **184**	81-91
 **169**	30 min	 **185**	87%
 **172**	17-30 h	 **186**	46-59%
 **177**	1 h	 **187**	87-92%

As expected, the benzylic alcohol **169** undergoes S_N2 reaction with particular facility, while the secondary alcohol **172** reacts sluggishly relative to the primary alcohols. The low yield in this case is due to incomplete conversion, and attempts to optimize this

reaction using the variants of the Mitsunobu reaction that have been developed to effect reaction of less reactive secondary alcohols.[66]

Finally, one additional substrate was prepared employing a different strategy. Aniline derivative **195** cannot be prepared via a Mitsunobu reaction, so we chose to employ an alkylation of the triflamide **191** to prepare the required cyanomethyl compound. The requisite starting material, 2-allylaniline (**190**), was prepared as previously reported[96] via the $ZnCl_2$-promoted aza- Claisen rearrangement shown in Scheme 23. Sulfonylation under standard conditions then afforded the triflamide **191**, which was deprotonated with sodium hydride and alkylated with bromoacetonitrile.

Scheme 23



[96] Smith, P. A. S.; Chou, S. P. *J. Org. Chem.* **1981**, *46*, 3970.

Ozonolytic cleavage of the allyl double bond furnished aldehyde **193** in excellent yield, and Wittig olefination then provided a 60:40 mixture of *E* and *Z* dienes **194** in good yield. Irradiation of this mixture in the presence of catalytic I_2 promoted partial isomerization of the *Z* olefin, and diene **195** was isolated as an 82:18 mixture of *E* and *Z* olefin isomers.

Several alternative strategies were also investigated for the preparation of sulfonamide **195**. One approach we envisioned would involve a Buchwald-Hartwig amination[97] of an appropriate aryl halide with H_2NCH_2CN. However, all attempts to achieve amination of 2-allylbromobenzene[98] with this amine were unsuccessful, although we found that the same aryl bromide reacted smoothly with *n*-hexylamine.

Hegedus has previously reported the preparation of 2-(2,4-pentadienyl)aniline via a route involving the Wittig reaction of allylidenephosphorane with (*o*-nitrophenyl) acetaldehyde.[99] Unfortunately, we were unable to repeat this reaction. Finally, several related routes were investigated involving alkylation of lithium reagents obtained by ortho-metalation of the *t*BOC derivative of aniline,[100] but these approaches were abandoned when we were unable to effect the alkylations in high yield.

Synthesis of Iminoacetonitrile Cycloaddition Substrates

Triflamide **121** served as the substrate for our studies on the optimization of the key elimination reaction to generate iminoacteonitrile cycloaddition substrates. As shown in eq 36, we found that cesium carbonate is more effective than potassium

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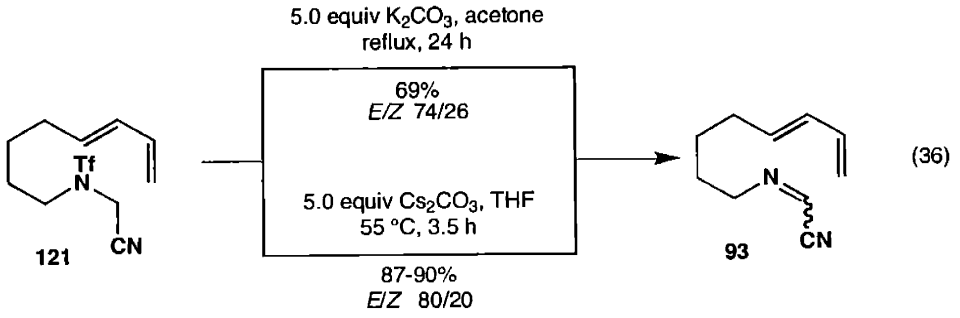
[97] For reviews, see: (a) Muci, A. R.; Buchwald, S. L. In *Topics in Current Chemistry*; Miyaura, N., Ed.; Springer-Verlag: Berlin, 2002; Vol. 219, p. 133. (b) Yang, B. H.; Buchwald, S. L. *J. Organomet. Chem.* **1999**, *576* (1-2), 125. (c) Hartwig, J. F. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 2046.

[98] Boymond, L.; Rottländer, M.; Cahiez, G.; Knochel, P. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 1701.

[99] Hegedus, L. S.; Winton, P. M.; Varaprath, S. *J. Org. Chem.* **1981**, *46*, 2215.

[100] Berger, J.; Kerly, D. L. *Heterocycles*, **1993**, *36*, 2051.

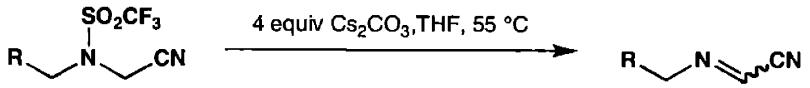
carbonate for this transformation. Using Cs_2CO_3, the reaction both proceeds faster and leads to fewer side products. Reaction at 55 °C proved optimal; at lower temperatures, the reaction proceeded significantly slower, and at higher temperatures an increase in byproducts is observed. In all cases 3 to 5 equivalents of cesium carbonate are employed, although we did not examine whether the reaction would proceed at a reasonable rate with less base.

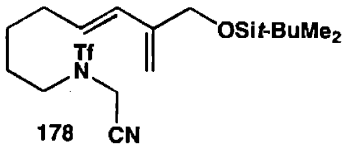
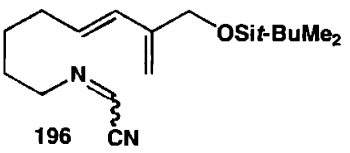
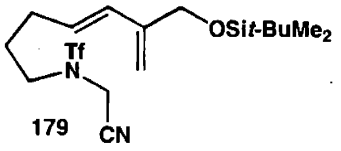
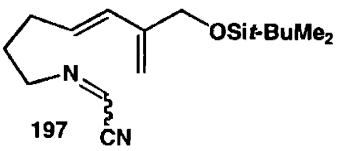
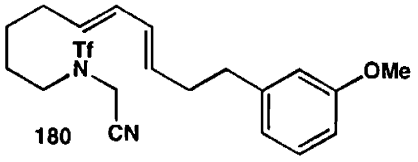
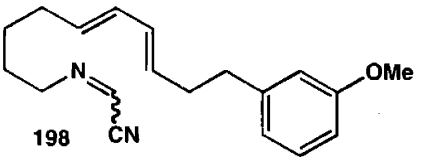


(36)

We next focused our attention on applying these conditions to the substrates shown in Table 5. In all three cases, the standard elimination conditions delivered the expected imines in good yield and as mixtures of *E* and *Z* imine isomers.

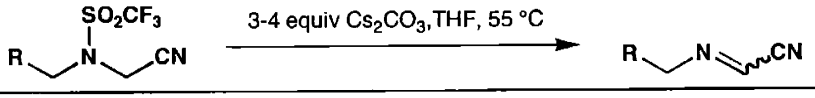
Table 5. Synthesis of Iminoacetonitriles Bearing Substituted Dienes



Triflamide	Time	Imine	Yield (*E*/*Z* ratio)
 **178**	1.5-3.5 h	 **196**	86-93% (77:23)
 **179**	2-3.5 h	 **197**	87-89% (76:24)
 **180**	2 h	 **198**	83-84% (78:22)

Application of our optimized protocol to triflamides **182** and **183** also provided the desired iminoacetonitriles in excellent yield (Table 6). Triflamide **181**, however, required a slight modification of our usual conditions since under those conditions the desired imine was obtained in low and irreproducible yields. Obtaining good yields of imine **199** required lowering the reaction temperature to 45 °C and decreasing the amount of cesium carbonate to 3 equivalents.

Table 6. Synthesis of Iminoacetonitriles Bearing Heteroatoms in the Tether



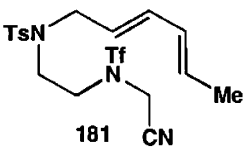
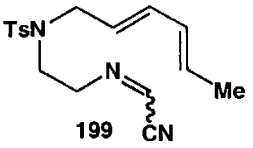
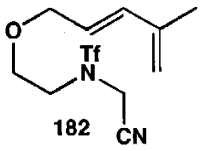
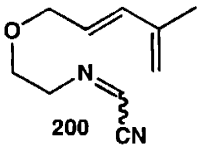
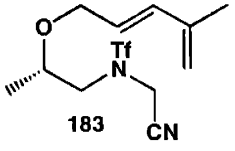
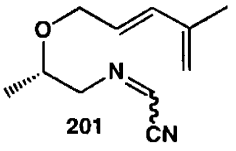
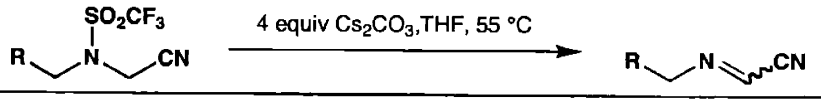
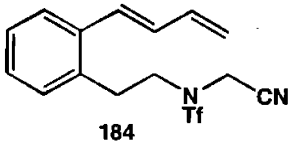
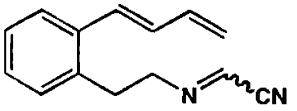
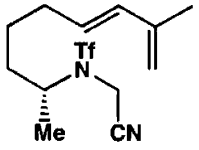
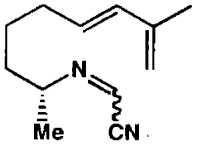
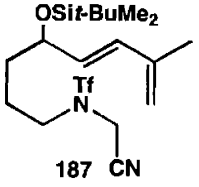
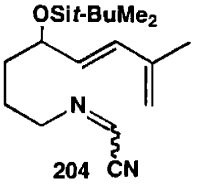
Triflamide	Time	Imine	Yield (*E*/*Z* ratio)
 **181**	2.0-3.5 h (@ 45 °C)	 **199**	71-80% (71:29)
 **182**	2.0-2.5 h	 **200**	87-88% (77:23)
 **183**	2.5-3.5 h	 **201**	88-90% (80:20)

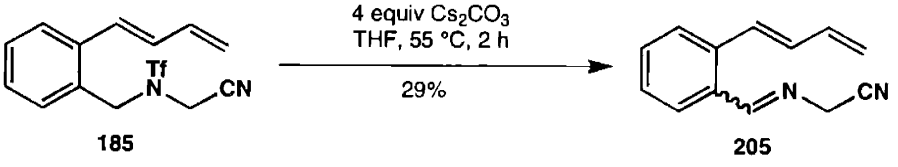
Table 7 depicts the results that were obtained upon exposure of the third series of substrates to cesium carbonate in warm THF. In all three cases, the reaction proceeds smoothly to afford the desired iminoacetonitriles as mixtures of *E* and *Z* imine isomers.

Table 7. Synthesis of Iminoacetonitriles Bearing an All-Carbon Tether



Triflamide	Time	Imine	Yield (*E*/*Z* ratio)
 **184**	2.5-3 h	 **202**	80-92% (77:23)
 **186**	2.5 h	 **203**	90% (87:13)
 **187**	2.5-3 h	 **204**	87-92% (74:26)

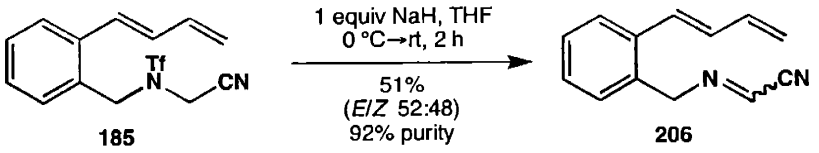
Unfortunately, when triflamide **185** was subjected to the standard elimination conditions, a low yield was obtained of a compound that was later identified as imine **205** (eq 37). The elimination reaction presumably produces the desired iminoacetonitrile, which then undergoes isomerization to the more stable, conjugated imine isomer.



185 **205** (37)

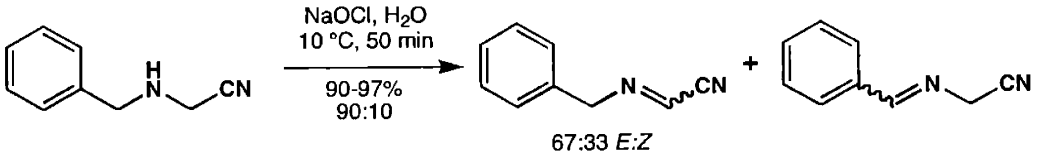
The use of sodium hydride in the elimination of **185** was examined in the hope that this base might permit elimination without subsequent isomerization of the imine double bond. In the event, reaction of **185** with 1 equiv of NaH in THF (0 °C to rt) delivered the crude iminoacetonitrile **206** as a 72:28 mixture of desired (**206**) and conjugated imine (**205**), and upon chromatographic purification on acetone-deactivated

silica gel, **206** was isolated in 51% yield as a 92:8 mixture of the desired imine and **205**. When the reaction product was purified (as in our other case) using triethylamine-deactivated silica gel, only the conjugated isomer was obtained.

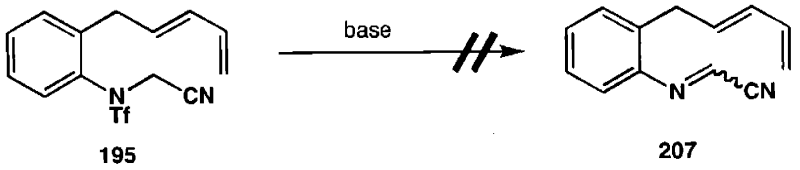


(38)

As shown below, in a related study Selva and coworkers obtained *N*-benzyliminoacetonitrile as a 90:10 mixture of isomers in very good yield upon treating *N*-(cyanomethyl)benzylamine with aqueous NaOCl.[101] It is possible that Seleva's protocol might provide efficient access to imine **206**, but the compatibility of the conjugated diene and aqueous bleach would need to be explored.



We next turned our attention to effecting the elimination of **195**, which would afford an *N*-aryliminoacetonitirle. Unfortunately, elimination of the sulfinate group from aryltriflamide **195** under our standard conditions afforded a very low yield of a complex mixture of products. Exploring a variety of different bases (NaH, *t*-BuOK, DBU, LDA, NaHMDS, LiHMDS) failed to identify conditions that led to the desired imine.

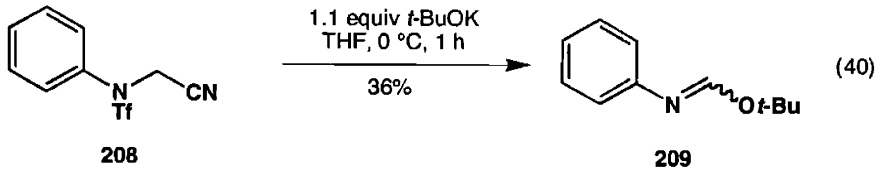


(39)

Interestingly, treatment of model triflamide **208** with *t*-BuOK leads to the formation of what appears to be *N*-phenyl-*O*-*tert*-butylimidate **209** in 36% yield. This

[101] Perosa, A.; Selva, M.; Tundo, P. *Tetrahedron Lett.* **1999**, *40*, 7573.

suggests that the desired elimination occurs, but addition of *tert*-butyl alcohol then takes place to generate **209** after elimination of cyanide. Apparently, *N*-aryliminoacetonitriles are particularly prone to nucleophilic attack. Additional experiments were not undertaken to address this problem, but further work may be warranted.



208 **209** (40)

Summary

This chapter described the development of our "second generation" approach to the synthesis of iminoacetonitriles. These substrates for the intramolecular aza Diels-Alder cycloaddition reaction are conveniently prepared from readily available alcohols in two steps. A Mitsunobu reaction with the previously unknown *N*-cyanomethyltriflamide **114** installs the *N*-cyanomethyl portion of the molecule, and subsequent elimination with cesium carbonate affords iminoacetonitriles in excellent yield. This methodology has been applied to the synthesis of several dienyl iminoacetonitriles, which, as discussed in Part III of this thesis, are employed in an intramolecular aza Diels-Alder reaction.

Part III

[4+2] Cycloadditions of Iminoacetonitriles

Chapter 1

Scope of the Iminoacetonitrile Cycloaddition

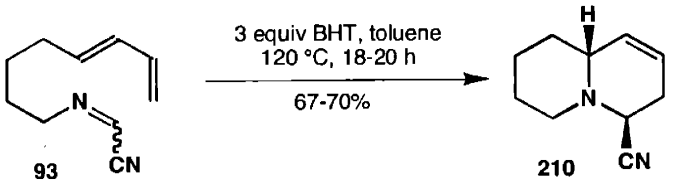
As described in Part II, our new methodology for the synthesis of iminoacetonitriles via a "Mitsunobu-elimination" strategy provided access to a variety of substrates for our proposed intramolecular aza Diels-Alder reaction. This chapter describes the identification of conditions to effect the desired cycloaddition, as well as the assignment of the stereochemistry of the resulting cycloadducts.

Feasibility of the Iminoacetonitrile Diels-Alder Reaction

With preparation of several dienyl iminoacetonitriles complete, our efforts were next directed at exploring the reactivity of iminoacetonitriles in the proposed intramolecular aza Diels-Alder cycloaddition. We were confident that iminoacetonitriles would prove to be reactive dienophiles in these cycloadditions, but it was unclear what effect the mixture of *E* and *Z* imine isomers would have on the stereoselectivity of the reaction.

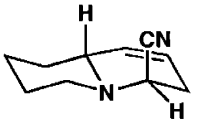
Our investigations began with the cycloaddition of imine **93**. Heating a toluene solution of **93** (75:25 mixture of *E* and *Z* imine isomers) in the presence of 3 equivalents of BHT in a sealed tube afforded, after purification by column chromatography, cycloadduct **210**, as a *single diastereomer* in 67-70% yield (eq 41). The diastereomeric

purity was confirmed by inspection of the ^{1}H and ^{13}C NMR spectra of quinolizidine **210**.[102]

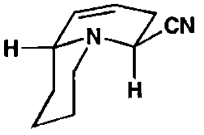


(41)

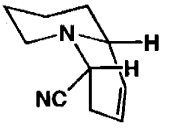
In order to assign the stereochemistry of **210** by analysis of its NMR spectrum, we first needed to determine the conformation of this azadecalin. Like decalin systems, quinolizidines such as **210** can potentially exist with either a trans or cis relationship between the nitrogen lone pair and the ring junction hydrogen, although quinolizidines generally prefer the trans conformation.[103] We calculated the energy of **210** for the cis and the trans conformations using MacroModel Version 6.5 (MM3 force field with Monte-Carlo conformation searching)[104] and, as shown below, we found that the trans conformation is 2.06-2.26 kcal/mole more stable then either cis conformation. Interestingly, there was only a 0.06 kcal/mole difference between the axial and equatorial nitrile isomers for the trans isomer.



210 trans
0.0 kcal/mole



210 cis1
2.02 kcal/mole



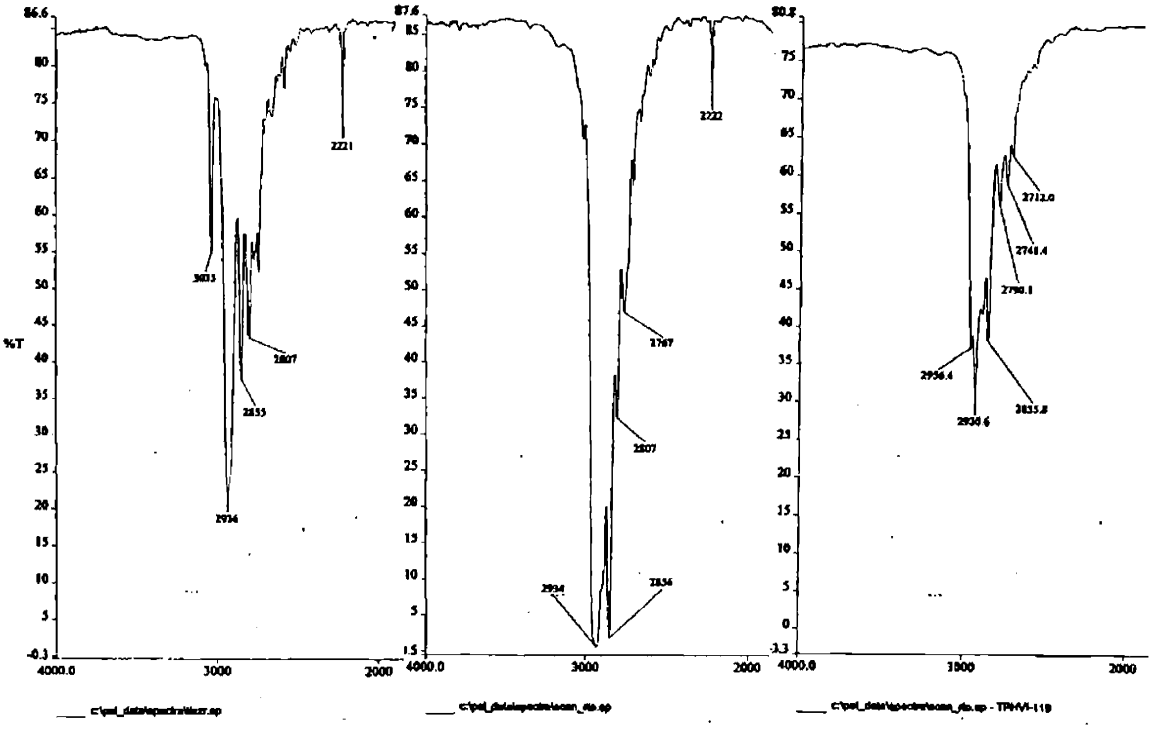
210 cis2
2.26 kcal/mole

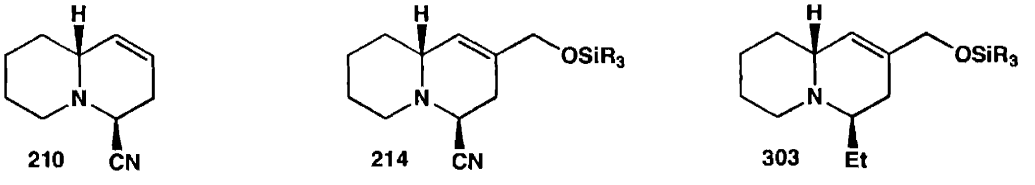
[102] Only 10 peaks were observed in the ^{13}C NMR spectra of the product. Analysis of the ^{1}H NMR spectrum was also consistent with the presence of a single diastereomer.

[103] (a) Johnson, C. D.; Jones, R. A. Y.; Katritzky, A. R.; Palmer, C. R.; Schofield, K.; Wells, R. J. *J. Chem. Soc.* **1965**, 6797. (b) Aaron, H. S.; Ferguson, C. P. *Tetrahedron Lett.* **1968**, 6191.

[104] MacroModel V6.5: Mohamadi, F.; Richards, N. G. J.; Guida, W. C.; Liskamp, R.; Lipton, M.; Caufield, C.; Chang, G.; Hendrickson, T.; Still, W. C. *J. Comput. Chem.* **1990**, *11*, 440.

Further evidence for the trans-azadecalin system is provided by the observation of Bohlmann bands[105] (2807 and 2855 cm $^{-1}$) in the IR spectrum of **210** (shown below). According to Bohlmann's theory, quinolizidines and indolizidines exhibit characteristic C-H stretches (2700-2850 cm^{-1}) in their IR spectra when two or more hydrogens α to a nitrogen have an antiperiplanar relationship with the nitrogen lone pair. This type of relationship can only exist in the case of **210 trans**. The presence of the cyano group in **210** does not effect the phenomenon of Bohlmann bands, as these characteristic stretches also appear in the IR spectrum of closely related quinolizidines we have prepared that do not contain the cyano group such as **303** (see Chapter 1 of Part IV).



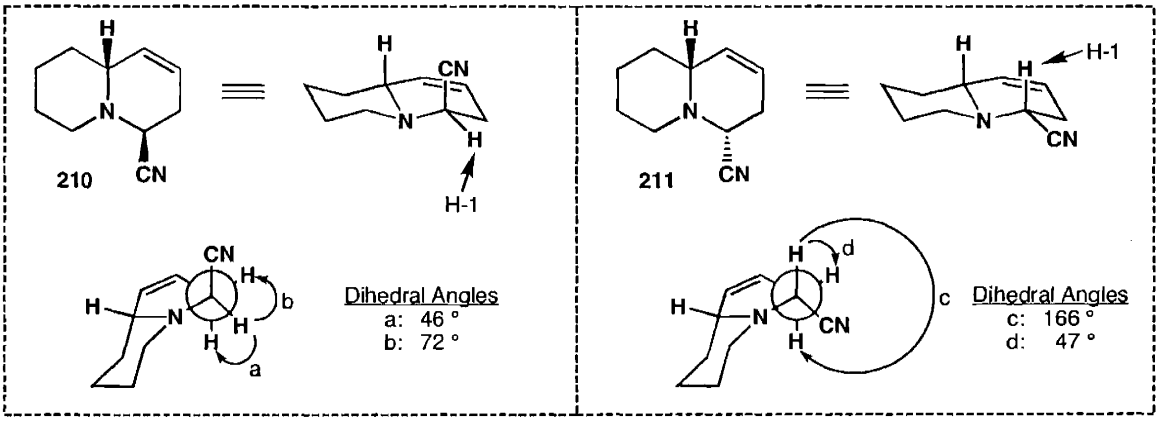


210 214 303

[105] Bohlman, F. *Chem. Ber.* **1958**, *91*, 2157.

To assign the stereochemistry of the cyano group, we first calculated the dihedral angles for **210** and **211** (shown in Scheme 24) using Chem3D (MM2).[106] Using the Karplus curve allowed us to predict coupling constants for the C-1 proton based on the calculated dihedral angles.[107] For **210**, coupling constant **a** would be expected to fall between 4 and 8 Hz while the coupling constant described as **b** should be quite small (0-2 Hz). In compound **211**, however, coupling constant **c** should be quite large (8-12 Hz) while that for **d** should still fall between 4 to 8 Hz. The signal for H-1 in **211** therefore should appear as a *doublet of doublets*. The observation of a doublet with a coupling constant around 6 Hz is therefore consistent only with structure **210**.

Scheme 24



The coupling constants reported for the previously reported[108] quinolizidine compounds **212** and **213**, shown below, provide corroborating evidence for the conclusions presented above. Specifically, the signal for H-1 in quinolizidine **212** is a doublet (J = 6.9 Hz) while that for quinolizidine **213** with endo aryl substitution appears as a doublet of doublets (J = 10.6, 3.9 Hz). Also, the axial C-1 proton in **213** is farther

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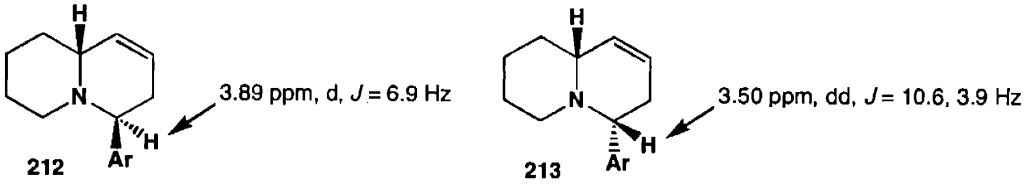
[106] *Chem3D*, version 5.0; CambridgeSoft: Cambridge, MA, 2000.

[107] Friebolin, H. *Basic One- and Two-Dimensional NMR Spectroscopy*, 2nd ed.; VCH: New York, 1993; pp 88-91; translated by J. K. Becconsall.

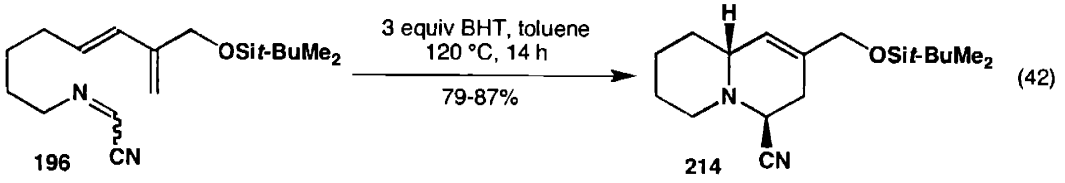
[108] Quick, J.; Khandelwal, Y.; Meltzer, P. C.; Weinberg, J. S. *J. Org. Chem.* **1983**, *48*, 5199.

upfield relative to the corresponding equatorial proton in **212**, as would be expected. It is known that equatorial protons tend to be shifted downfield relative to the corresponding axial proton by 0.1 to 0.7 ppm.[109]



The stereochemistry of **210** was thus assigned as shown in eq 41 by examining the ^{1}H NMR spectrum for **210** and in light of the above predictions. The resonance for H-1 in **210** appears at 3.79 ppm as a doublet with a coupling constant of 6.3 Hz. As explained in Scheme 24, of the two possible diastereomeric products **210** and **211**, only in **210** is H-1 predicted to appear as a simple doublet (Scheme 24).

Having successfully carried out an intramolecular [4+2] cycloaddition of dienyl imine **93**, we then directed our efforts at effecting the cycloaddition of iminoacetonitrile **196**. Intramolecular cycloaddition of **196** (63:37 mixture of *E* and *Z* imine isomers) afforded **214** in very good yield as a single diastereomer (eq 42). The C-1 proton in the ^{1}H NMR spectrum of **214** appeared as a doublet at 3.85 ppm with a coupling constant of 6.4 Hz, indicating an axially oriented cyano group. Once again, no trace of an isomeric cycloadduct could be detected in the crude reaction product.



(42)

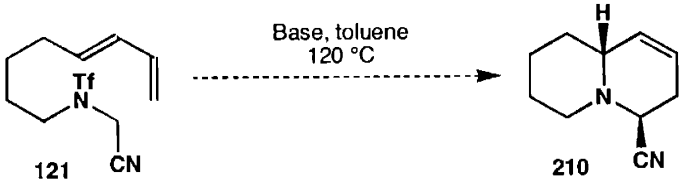
[109] Silverstein, R. M.; Webster, F. X. *Spectrometric Identification of Organic Compounds*, 6th ed.; John Wiley & Sons, Inc.: New York, 1998; pp 155-156.

Optimization of Conditions for the Cycloaddition

Having demonstrated that iminoacetonitriles are reactive as dienophiles in intramolecular aza Diels-Alder reactions, our efforts were next directed at optimizing conditions and exploring the scope of the cycloaddition.

One-Pot Procedure

Initial experiments explored the possibility of carrying out the elimination and cycloaddition reactions in one pot. Obviously, direct transformation of *N*-cyanomethyltriflamides to nitrogen heterocycles in a single step would be quite attractive. Thermolysis of triflamide **121** under basic conditions, as shown below, would hopefully effect the one pot transformation.



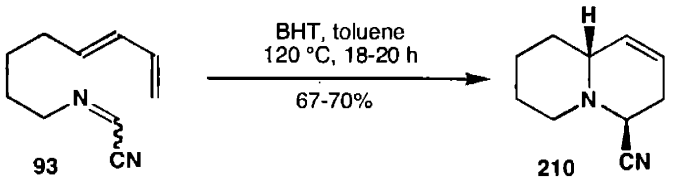
An examination of several amine and carbonate bases confirmed that cesium carbonate is the base of choice. For the one pot procedure, BHT was replaced with γ-terpinene due to a concern that iminoacetonitrile **93** could undergo base-catalyzed nucleophilic addition of BHT. Employing cesium carbonate as base, cycloadduct **210** was isolated in only 10-30% yield, with significant recovery of iminoacetonitrile **93**. Interestingly, subjecting crude imine **93**[110] (*without* prior purification) to our previous cycloaddition conditions (3 equiv BHT, toluene, 120 °C, 18-20 h) afforded cycloadduct **210** in only 29-34% yield along with recovered starting material in dramatic contrast to

[110] Prepared as described in Chapter 3 of Part II and then used without purification

the smooth reaction observed for purified imine (eq 41). The ^{1}H NMR spectra of the crude iminoacetonitrile and purified material appear very similar, but the two samples react at different rates. By removing traces of adventitious acid, basic residues from the elimination step may prevent the crude imine from undergoing the desired cycloaddition.

Optimization of [4+2] Cycloaddition with Regards to BHT

As depicted in eq 41, our initial cycloaddition conditions for imine **93** employed three equivalents of BHT, and although the BHT was easily removed by column chromatography, carrying out the reaction with less BHT was desirable. Unfortunately, when the cycloaddition of imine **93** was carried out in the presence of 1.0 or 0.1 equivalents of BHT, the desired quinolizidine product was obtained in only 31% yield (eq 43). Changing the number of equivalents of BHT present in the reaction mixture did not affect the rate of the reaction or increase the number of byproducts (by TLC and ^{1}H NMR analysis). We did not explore the possibility of increasing the concentration of the reaction (typically 0.05 M) while decreasing the number of equivalents of BHT, thereby maintaining the effective concentration of BHT. It is apparent that BHT is playing a significant role in the cycloaddition of our iminoacetonitrile substrates, but it is unclear if BHT is acting as a promoter for the cycloaddition or preventing radical mediated polymerization of starting material and product.

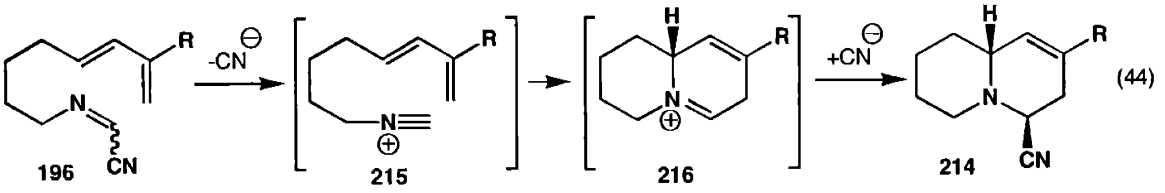


(43)

Equiv of BHT	Yield
3.0	67%
1.0	31%
0.1	31%

Solvent Effects in the [4+2] Cycloaddition

Having routinely carried out the cycloaddition of iminoacetonitriles at 0.05 M in toluene, we briefly explored the use of a polar solvent to facilitate the Diels-Alder reaction. This study was motivated by the hypothesis that under suitable conditions, ionization of an iminoacetonitrile might be induced to generate an iminium ion (**215**) which might undergo an unusually facile [4+2] cycloaddition[111] to eventually afford quinolizidine **214** (eq 44). Ionization of the cyano group could be promoted by carrying out the cycloaddition in a polar solvent or by treating the iminoacetonitrile with silver or copper salts.



R = CH_2OSi*t*-$BuMe_2$

We attempted to carry out the cycloaddition reaction of imine **196** in both acetonitrile and trifluoroethanol (TFE). Iminoacetonitrile **196** was unreactive, but stable, at room temperature in acetonitrile but slowly decomposed in TFE. When heated at reflux in TFE, imine **196** underwent complete decomposition within 90 minutes. In acetonitrile, **196** undergoes slow cycloaddition reaction with only 56% conversion observed after 18 h at 100 °C. From these preliminary results, we were not optimistic about the prospects for this strategy, so no further experiments were undertaken. It was later shown that the reactions of other cycloaddition substrates proceed at similar rates in toluene and acetonitrile. In addition, the yields for cycloadditions conducted in toluene

[111] For a review of polar cycloadditions, see: Schmidt, R. R. *Angew. Chem., Int. Ed. Engl.* **1973**, *12*, 212.

were better, due to partial decomposition in acetonitrile of both the imines and the cycloadducts.

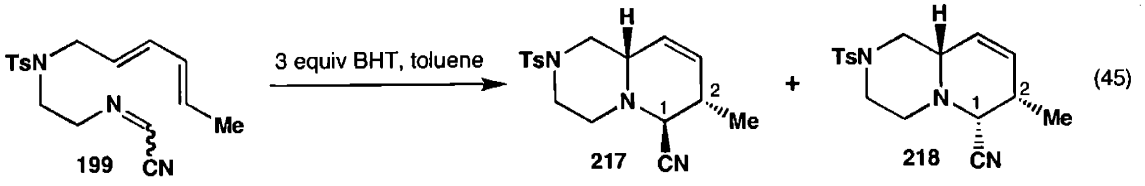
Lewis Acid Promoted Cycloadditions

Our efforts next focused on carrying out the Diels-Alder reaction of iminoacetonitriles in the presence of Lewis acids. We investigated the use of Lewis acids with a known affinity for cyano groups, such as copper, silver, and zinc salts, and the reactions were all conducted using dichloromethane as solvent. We were unable to effect the cycloaddition of imine **196** in the presence of Lewis acids when the reaction was carried out at 0°C, but upon warming the reaction mixture to room temperature, the cycloaddition did occur in the presence of copper(II) triflate or zinc(II) bromide. These reactions proved to be quite moisture sensitive, and if the Lewis acid was not dried sufficiently, hydrolysis of the imine to the corresponding formamide was a significant problem. Rigorous exclusion of moisture from the reaction vessel and all reagents avoids the problem of imine hydrolysis. With low catalyst loading (0.1 to 0.3 equivalents), the reaction proceeded to only ca. 25% conversion with significant recovery of imine **196**. At higher catalyst loading (0.5 equivalents), the number of by-products began to increase. Copper chloride is particularly effective at driving the reaction to completion but afforded the desired cycloadduct contaminated with several by-products. We believe the reason for low conversion is competitive binding of the Lewis acid to the product as well as to the starting imine. In addition, Lewis acids can promote reactions of α-amino nitriles, leading to decomposition of the cycloaddition product and decrease in yield.

Although more work is warranted, it is encouraging to see that certain metals could allow the cycloaddition reaction to be carried out at *room temperature*. The use of lithium salts, lithium perchloate in particular, was never examined but might be effective in catalyzing the cycloaddition, especially in light of Grieco's work with lithium ion promoted aza Diels-Alder cycloadditions.[112]

Cycloaddition of a Substrate Bearing a Heteroatom in the Tether

Efforts were next directed at investigating the Diels-Alder reaction of a dienyl iminoacetonitrile containing a heteroatom in the tether. Heating a toluene solution of imine **199** afforded the expected cycloadduct in excellent yield but as a mixture of cyano anomers (eq 45). Interestingly, this cycloaddition proceeds efficiently at temperatures below those required for the cycloaddition of imines **93** and **196**, and there is a slight change in the ratio of products observed when the reaction temperature is varied. The appearance of Bohlman bands in the IR spectra for **217** and **218** indicate that these compounds exist as trans azadecaline systems.



(45)

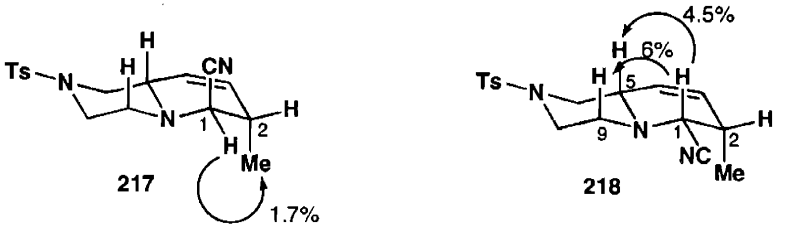
Temp	Yield	Ratio
85 °C	90%	37:63
110 °C	95%	39:61
120 °C	73%	44:56

The stereochemistry of the two cycloadducts was assigned based on ^{1}H-^{1}H COSY (COrrelated SpectroscopY) and difference-NOE (Nuclear Overhauser Effect) NMR

[112] Grieco, P. A.; Kaufman, M. D. *J. Org. Chem.* **1999**, *64*, 7586.

experiments.[113] The COSY NMR experiments provided spin-coupling relationships that allowed the assignment of all the resonances observed in the proton NMR spectra of **217** and **218**. The C-2 methyl group and the methine proton at the ring juncture exist in a trans relationship as a result of the superfacial [4+2] cycloaddition. With this information in hand, the stereochemistry of the hydrogen attached to the C-1 methine was elucidated using difference-NOE experiments (Scheme 25). Irradiating the proton attached at C-1 in compound **218** produced NOE enhancements in the axial C-5 and C-9 protons as shown in Scheme 25. The same irradiation sequence for C-1 in **217** produced only one small enhancement, occurring at the C-2 methyl group.

Scheme 25



In addition, the C-1 proton of **218** appears as a doublet at 3.57 ppm with a coupling constant of 4.0 Hz. This 4 Hz coupling is attributed to the interaction between the C-1 proton and the C-2 equatorial proton. The replacement of the C-2 axial hydrogen with a methyl group prevents the appearance of a large (10-12 Hz) axial-axial coupling constant. In the two previous cycloadducts **210** and **214**, a coupling of 6 Hz was observed for the C-1 proton and the axial proton on C-2. Replacement of the C-2 axial hydrogen with a methyl group results in the loss of the 6 Hz coupling. Thus, the C-1 methine proton for **217** appears as a singlet, consistent with an axial nitrile group. Based on this data, the structures of **217** and **218** were assigned as shown in eq 45.

[113] For a discussion of 2D NMR techniques, see ref 107, pp. 238-265.

The cycloaddition of imine **199** afforded the desired cycloadduct in very good yield but with fair stereochemical control. Interestingly, carrying out the reaction at 120 °C led to the formation of a 44:56 mixture of **217**:**218**. When **199** was allowed to stir at 120 °C for 6-7 days, the initial mixture of products was observed to slowly convert to **217**. From these observations, it appears that the stereochemistry of the cycloadducts is not controlled by the initial cycloaddition but is instead controlled by a subsequent isomerization to the more stable product. The isomerization of α-amino nitriles is a known phenomenon[114] and will be discussed in more detail in the following chapter.

Prolonged stirring of a toluene solution of imine **199** at 120 °C provided the cycloadduct **217** as the major cycloadduct along with a significant number of decomposition products. Since α-amino nitriles are known to isomerize through an iminium ion, we thought that employing a polar reaction solvent might facilitate the desired isomerization by stabilizing the intermediate cation. In fact, Husson and coworkers have described the epimerization of *N*-substituted *cis*-2,6-dicyanopiperidines to the corresponding *trans* derivative with by refluxing in ethanol.[115] We thus found that stirring a mixture of cycloadducts **217** and **218** in refluxing acetonitrile provided **217** as the major product with only minor decomposition (eq 46).[116] To expedite matters, cycloaddition of imine **199** was then carried out in refluxing acetonitrile to afford **217** directly (eq 47).

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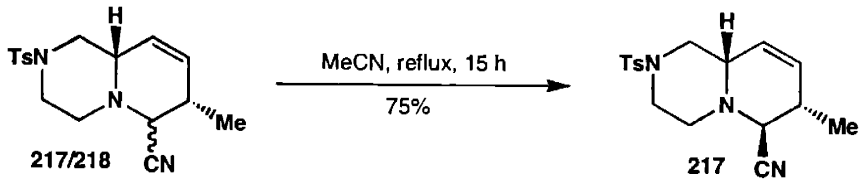
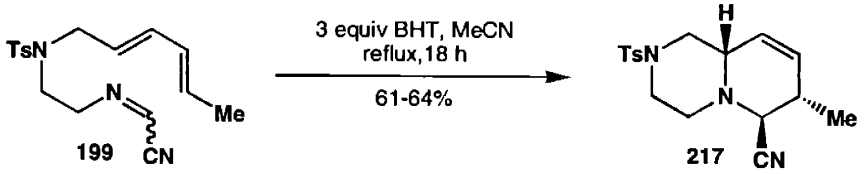
[114] (a) Bonin, M.; Romero, J. R.; Grierson, D. S.; Husson. H.-P. *J. Org. Chem.* **1984**, *49*, 2392. (b) Bonin, M.; Chiaroni, A.; Riche, C.; Beloeil, J.-C.; Grierson, D. S.; Husson. H.-P. *J. Org. Chem.* **1987**, *52*, 382.

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

[116] ^{1}H NMR analysis of the crude reaction mixture indicated a 94:6 mixture of **217** and **218**.



(46)



(47)

The cycloaddition reaction of **199** carried out in acetonitrile afforded the cycloadduct **217** in lower yield as compared to the reaction carried out in toluene, but after purification by column chromatography, cycloadduct **217** was isolated as a single diastereomer.[117]

Having developed optimal procedures for the intramolecular Diels-Alder cycloaddition of iminoacetonitriles, we next turned our attention to applying these conditions to cycloaddition reactions of the other dienyl imines prepared in the previous chapter of this thesis.

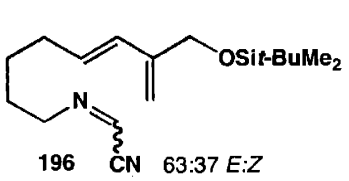
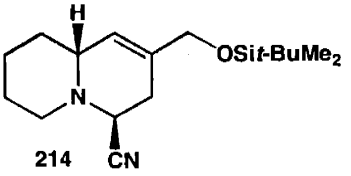
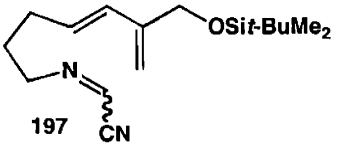
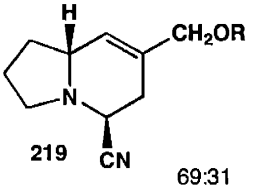
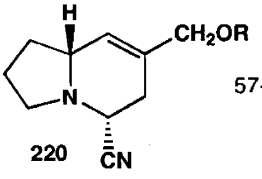
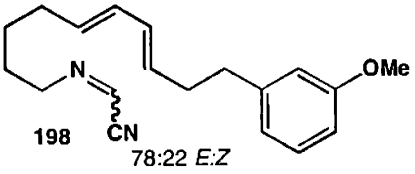
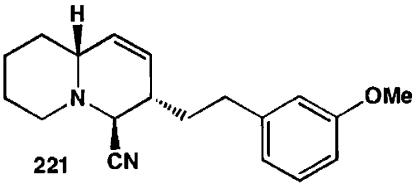
Effect of Diene Substitution on the Cycloaddition

Application of our optimized protocol to imines **196-198** provided the desired cycloadducts in good to excellent yield (Table 8). Imine **198** afforded 2-substituted quinolizidine **221** as a single diastereomer, and the C-1 methine proton of this cycloadduct appeared as a singlet in the ^{1}H NMR spectrum, indicating that the cyano group is axially oriented. As discussed for cycloadduct **217**, the C-1 proton appears as a

[117] ^{1}H NMR analysis of the crude reaction mixture showed 5-10% of **218**, but this isomer was easily removed by flash chromatography.

singlet because there is no axial proton at C-2 and the *J* value for the coupling to the equatorial C-2 proton is very small.

Table 8. Cycloadditions of Iminoacetonitriles Bearing Substituted Dienes[a]

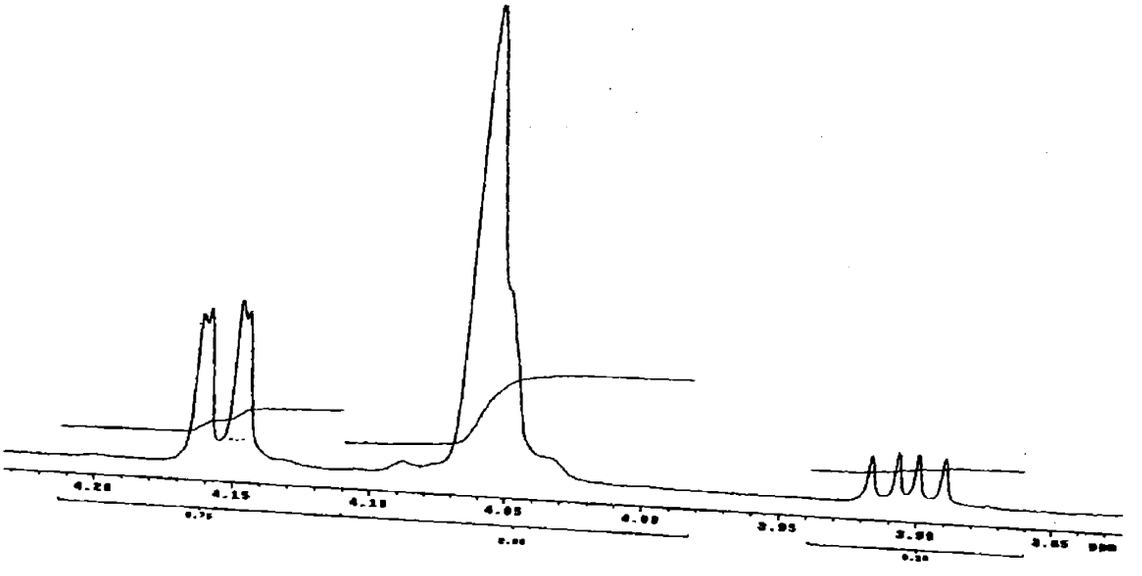
Imine	Time/Temp	Cycloadduct	Yield
 **196** 63:37 *E:Z*	14 h, 120 °C	 **214**	79-87%
 **197** 76:24 *E:Z*	24 h, 120 °C	 **219** 69:31  **220**	57-58%
 **198** 78:22 *E:Z*	18 h, 120 °C	 **221**	64%

[a] Cycloadditions were run in toluene (0.05 M) with 3 equiv of BHT in a resealable threaded Pyrex tube.

Cycloaddition of imine **197** afforded a mixture of indolizidine cycloadducts. Like quinolizidines, the trans conformation of indolizidines has been calculated to be more stable than the *cis* form.[103b] In addition, Bohlmann bands are observed in the IR spectrum of **219** and **220**, indicating a *trans* aza-hydrindane system. The ^{1}H NMR spectrum of the major product contains a doublet of doublets at 4.15 ppm with coupling constants of 7.0 and 1.5 Hz, and so this product was assigned as the β-cyano isomer **219** (Figure 1). The C-1 proton of the minor isomer (equatorial cyano group) appears as a doublet of doublets at 3.90 ppm with coupling constants of 8.5 and 4.9 Hz. The analysis and assignment of **219** and **220** is consistent with the argument presented in Scheme 24 for cycloadduct **210**. Heating the mixture of cycloadducts obtained from **197** in acetonitrile increased the ratio

of **219**:**220** from 69:31 to 81:19, but the increase in ratio of products was accompanied by minor decomposition. Further studies are required to explain why a mixture of products was observed upon cycloaddition of **197** but not with the reaction of **196**.

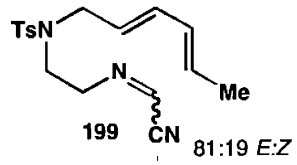
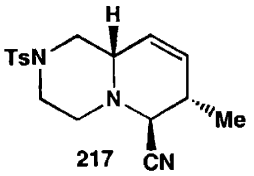
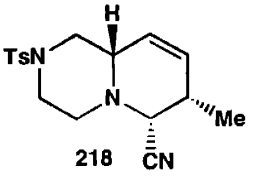
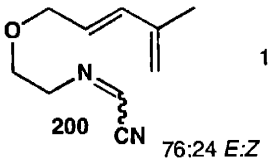
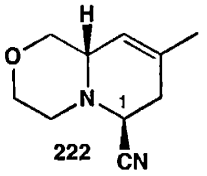
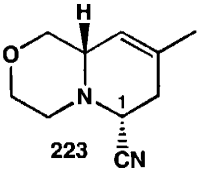
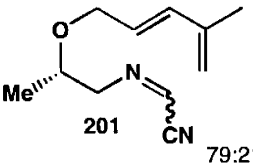
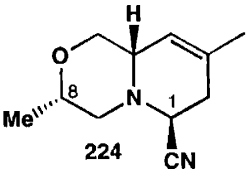
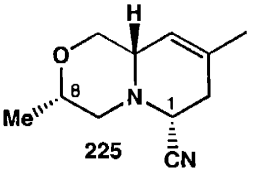
Figure 1. ^{1}H NMR Spectrum (500 MHz, $CDCl_3$) of 219 and 220.



Effect of Variations in the Tether on the [4+2] Cycloaddition

Our efforts were next directed at exploring the scope of the cycloaddition with regard to substrates with connecting chains containing a heteroatom. Both imines **200** and **201** delivered the expected cycloadducts in excellent yield, albeit as mixtures of stereoisomers (Table 9). As observed with the cycloaddition reaction of imines **199** and **201**, heating a toluene solution of imine **200** at reflux afforded cycloadduct **222** and **223**, but the cycloaddition requires 40 h for complete reaction and results in a slightly lower yield (90% yield of a 66:34 mixture of isomers) of cycloadducts as compared to reaction at 120 °C.

Table 9. Cycloadditions of Iminoacetonitriles Bearing Heteroatoms in the Tether[a]

Imine	Time/Temp	Cycloadducts	Yield (ratio)
 199 81:19 *E:Z*	17 h, reflux	 217  218	90-95% (37:63)
 200 76:24 *E:Z*	16 h, 120 °C	 222  223	96% (78:22)
 201 79:21 *E:Z*	16 h, reflux	 224  225	96% (44:56)

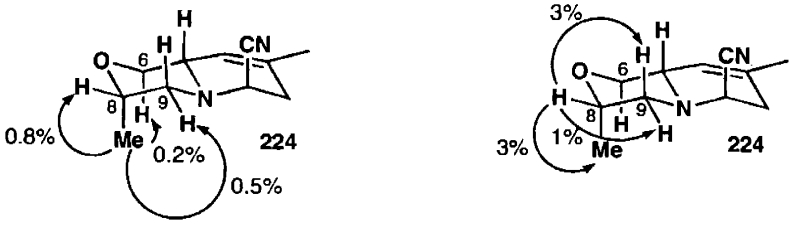
[a] Cycloadditions were run in toluene (0.05 M) with 3 equiv of BHT in a resealable threaded Pyrex tube.

The appearance of Bohlman bands in the IR spectra for all of the cycloadducts shown in Table 9 indicate that these heterocycles exist as trans aza-decalin like systems. The stereochemistry of the cyano group in cycloadducts **222** to **225** was assigned using the previously outlined arguments involving the coupling constants observed for the C-1 proton.[118] In addition to the stereochemistry of the cyano group at C-1, cycloadducts **224** and **225** contain a stereogenic carbon (C-8) substituted with a methyl group. Employing 2-D NMR techniques (COSY and difference NOE), resonances in the ^{1}H NMR spectra of **224** were assigned. Irradiating the C-8 methyl group in **224** produced enhancement at the C-8 proton, the axial C-6 proton, and the C-9 equatorial proton (Scheme 26). In addition,

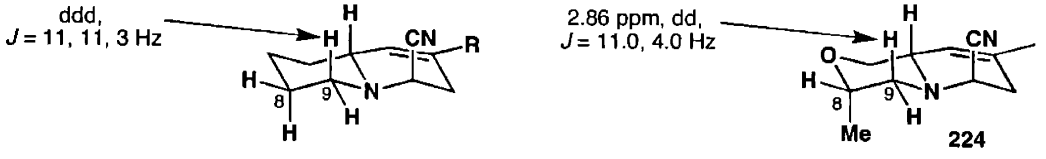
[118] The ^{1}H NMR spectrum of **222** displayed a doublet at 3.80 ppm with a coupling constant of 6.7 Hz. The ^{1}H NMR spectrum of **224** displayed a doublet at 3.74 ppm with a coupling constant of 5.8 Hz.

irradiation of the C-8 methine proton produced enhancement at the C-8 methyl group and both of the C-9 protons.

Scheme 26



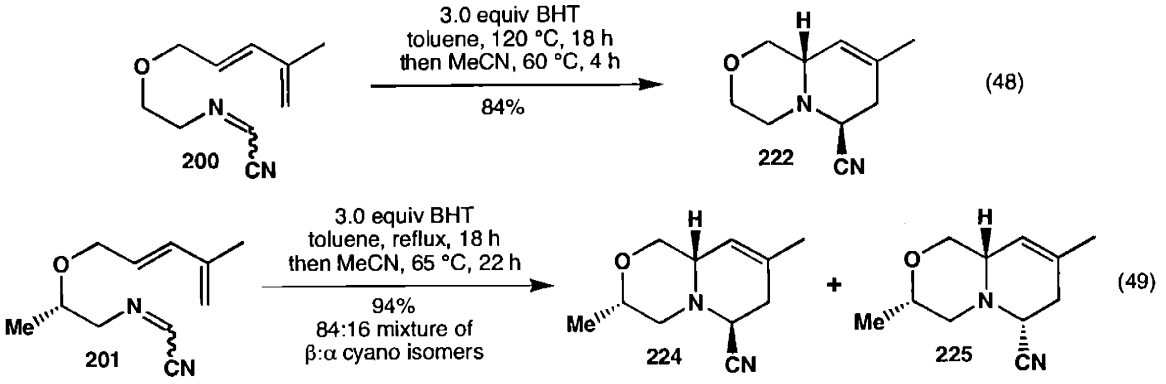
Coupling constants provided additional evidence for the assignment of the C-8 axial methyl group. As shown below, the axial C-9 proton of the other cycloadducts usually appeared as a doublet of doublet of doublets, with two large coupling constants (10-12 Hz) for the geminal coupling and the axial-axial coupling to the neighboring C-8 axial hydrogen and a smaller coupling constant (~3 Hz) for the coupling to the C-8 equatorial hydrogen.



In the case of **224**, the C-9 axial proton is a doublet of doublets with coupling constants of 11.0 and 4.0 Hz. This suggests that an axial proton at C-8 is no longer present. If the resonance for the C-9 axial proton had two large coupling constants, this would have been consistent with an equatorial methyl group at C-8. In summary, based on difference-NOE experiments and coupling constant analysis, the C-8 methyl group in **224** occupies an axial position. The selectivity for the methyl group is quite good, as the

cycloaddition of imine **201** provides less than 5% of the cycloadduct containing the methyl group in the equatorial position.[119]

Despite the good selectivity for the C-8 axial methyl group, the cycloaddition of imines **200** and **201** afforded a mixture of cyano isomers. When the cycloaddition reactions of imines **200** and **201** were carried out in acetonitrile, the desired cycloadducts were formed in low yield and poor purity. A superior procedure was to carry out the cycloaddition in toluene as shown in Table 9, remove the solvent upon completion of the reaction, and then heat a solution of crude product in acetonitrile to effect isomerization to the more stable axial cyano isomers (eq 48 and 49).



Implementing this protocol provided access to **222** in excellent yield and stereochemical purity after purification.[120] In the case of imine **201**, the cycloadduct is isolated in excellent yield, but heating in acetonitrile increased the ratio of nitrile isomers to only 84:16. Further heating of the mixture of products or increasing the reaction temperature to 83 °C did not afford a better ratio of products and led to increased decomposition of the cycloadduct.

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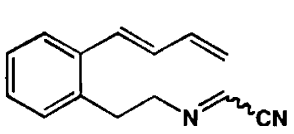
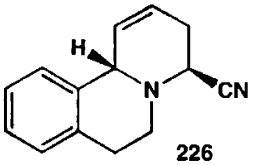
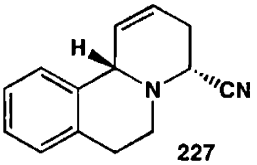
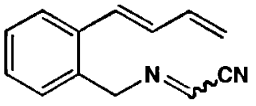
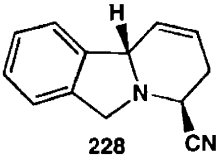
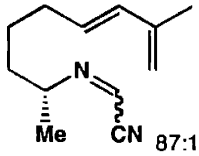
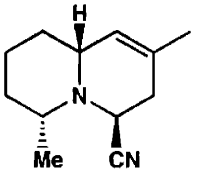
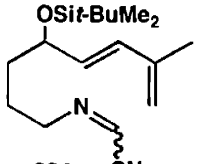
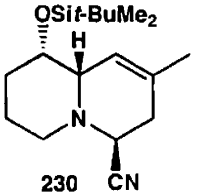
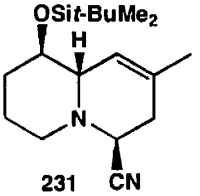
[119] The ^{1}H NMR spectrum of **224/225** shows only a trace of the other methyl isomer.

[120] ^{1}H NMR analysis of the crude reaction material indicates a 94:6 mixture of β:α cyano isomers. Following column chromatography **222** is isolated as a single isomer.

The cycloaddition reactions of substrates bearing all-carbon tethers are shown in Table 10. Imine **202** provided the desired cycloadduct **226** and **227** in moderate yield and with good stereocontrol. The rate of this cycloaddition is the slowest of all the successful cases examined. Attempts to employ the acetonitrile protocol led to decomposition of both the imine and the cycloadduct. At elevated temperatures, cycloadduct **226/227** suffered from instability, which may have contributed to the low yield observed in this case.

Table 10. Cycloadditions of Iminoacetonitriles Bearing an All-Carbon Tether[a]

Imine	Time/Temp	Cycloadduct	Yield
 **202** 75:25 *E:Z*	36 h, 120 °C	 **226**  **227**	45% (79:21)
 **206** 52:48 *E:Z*	120-140 °C	 **228**	-
 **203** 87:13 *E:Z*	120-130 °C	 **229**	0-5%
 **204** 80:20 *E:Z*	22 h, 120 °C	 **230**  **231**	73% (55:45)

[a] Cycloadditions were run in toluene (0.05 M) with 3 equiv of BHT in a resealable threaded Pyrex tube.

Coupling constants and difference-NOE experiments provided the data needed to assign the stereochemistry of the two isomers resulting from the cycloaddition of imine

202 (Scheme 27). Cycloadducts **226** and **227** exist as trans decalin systems, indicated by the appearance of Bohlman bands for both isomers. The ^{1}H NMR spectrum of the major isomer (**226**) displayed a doublet of doublets at 4.06 ppm with coupling constants of 6.1 and 0.6 Hz for the C-1 proton, consistent with an axial nitrile group (Figure 2). The resonance assigned to the C-1 proton in the minor isomer (**227**) appeared as a doublet of doublets at 4.12 ppm with coupling constants of 11.0 and 4.9 Hz, consistent with an equatorial nitrile group. Additional support for this assignment was obtained by irradiation of the C-1 proton of the minor isomer, which led to an NOE enhancement at the benzylic methine proton.

Scheme 27

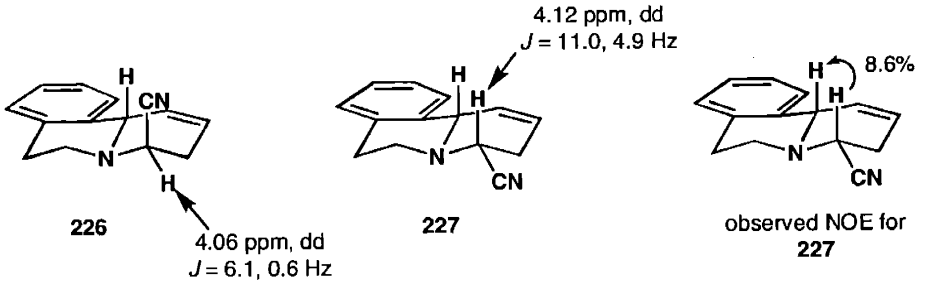
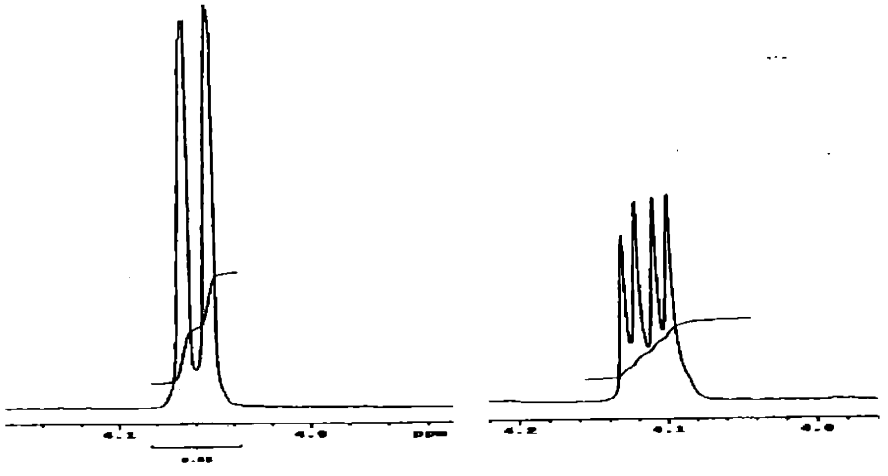
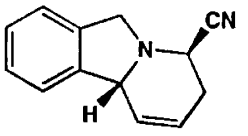


Figure 2. ^{1}H NMR spectrum (500 MHz, $CDCl_3$) of the C-1 proton in 226 and 267.

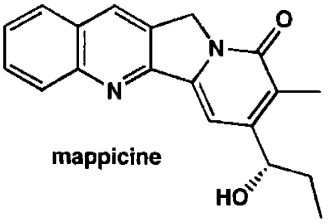


226 **227**

We were particularly interested in the Diels-Alder cycloaddition of imine **206**, which would afford tricyclic compound **228**. This compound contains the core structure of the antiviral agent mappicine.[121] A more fully adorned version of imine **206** would provide access to this biologically active natural product.

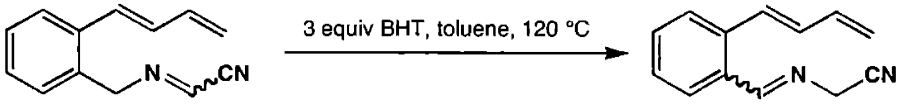


227



mappicine

Efforts to carry out the cycloaddition of imine **206** failed to yield the desired product, and even more worrisome, imine **206** isomerized to conjugated imine **205** under our standard cycloaddition conditions (eq 50). We next explored adding base to a toluene solution of **205** in hopes that we could produce small amounts of **206** *in situ*. Formed under equilibrium conditions in this fashion, iminoacetonitrile **206** could then undergo the desired cycloaddition thereby converting **205** into the desired cycloadduct **228**. Unfortunately, all attempts to employ this strategy failed to deliver cycloadduct **228**.



206 **205** (50)

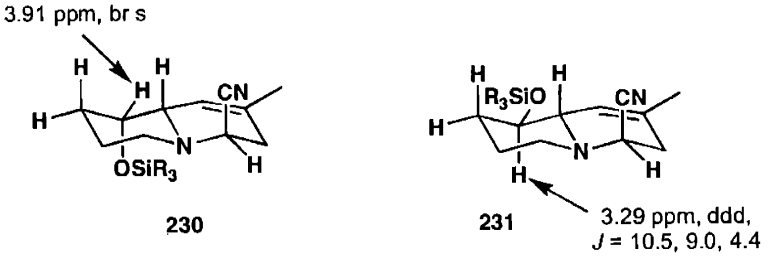
Surprisingly, imine **203** fails to react in the intramolecular Diels-Alder reaction. Only a trace of the desired product is observed in the crude ^{1}H NMR spectrum along with a significant amount of recovered starting material. The methyl group could be interfering with the adoptive of the necessary reactive conformation of the transition

[121] Govindachari, T. R.; Ravindranath, K. R.; Viswanathan, N. *J. Chem. Soc., Perkin Trans. 1* **1974**, 1215.

state,[122] or an isomerization to the presumably more stable isomeric imine could be occurring.

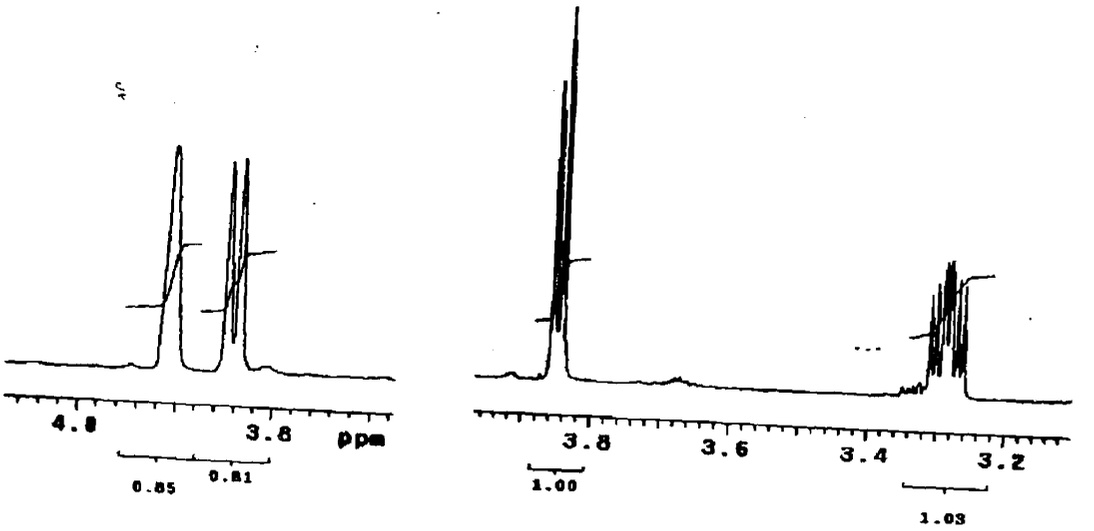
Cycloaddition of imine **204** afforded cycloadducts **230** and **231** in good yield and as single cyano isomers. However, the stereogenic center alpha to the diene exerts little directing effect on the resulting stereochemical relationship between the siloxy group and the adjacent methine hydrogen. The cycloadduct was isolated as 55:45 mixture of two diastereomers, with the major isomer containing an axial siloxy group. The presence of Bohlman bands indicated both isomers exist as trans aza-decalin systems. ^{1}H NMR analysis provided the chemical shifts and coupling constants used to assign the stereochemistry of the two cycloadducts (Scheme 28). The minor isomer (**231**) displayed a doublet of doublet of doublets with two large coupling constants (axial-axial couplings) and one smaller coupling (axial-equatorial coupling) for the C-6 proton. For the same proton in the major isomer, the ^{1}H NMR spectrum displayed a broad singlet, further downfield relative to that in **230**.[109]

Scheme 28



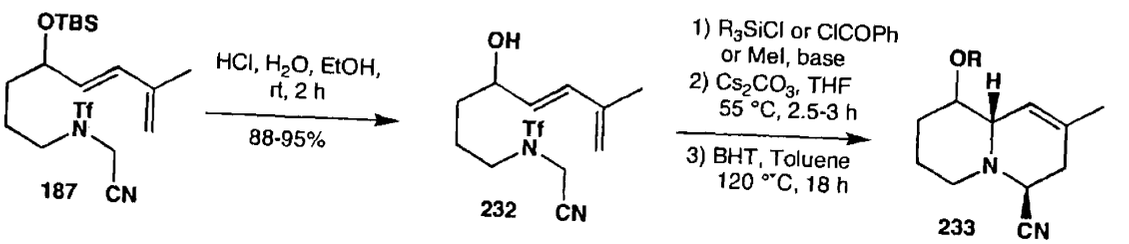
[122] Interestingly, imine **197** has the highest *E*:*Z* ratio (87:13) of all the imines prepared.

Figure 3. ^{1}H NMR spectrum (500 MHz, $CDCl_3$) of C-6 proton in 230 and 231.



Efforts to improve the ratio of isomers obtained in the cycloaddition of imine **204** were undertaken. Hydrolysis of the TBDMS ether in triflamide **187** with aqueous acid afforded alcohol **232**, which was then protected with three different groups and subjected to our standard elimination and cycloaddition conditions. As seen in Scheme 29, little effect was observed upon changing the group on oxygen.

Scheme 29



OR Group	Ratio of Axial/Equatorial	Yield
$OSiMe_2t$-Bu	55:45	73%
$OSi(i$-$Pr)_3$	54:46	60%
OCOPh	50:50	40%
OMe	61:39	38%

Summary

Dienyl iminoacetonitriles participate in intramolecular [4+2] cycloaddition reactions, affording indolizidine and quinolizidine ring systems. The reaction tolerates a range of substitution on the diene and, to a lesser degree, substitution on the connecting chain. In this chapter, several questions regarding the mechanism and stereochemical course of the reaction have been raised, and the following chapter will to address these questions.

Chapter 2

Mechanism and Stereochemical Course of the Iminoacetonitrile Cycloaddition

The previous chapter of this thesis described the results of our studies on the scope of the intramolecular [4+2] cycloaddition of iminoacetonitriles. Interestingly, we found that the cycloadducts have a strong preference for an axial cyano group. In addition, substrates containing a stereocenter along the connecting chain afforded products with varying degrees of stereochemical induction. This chapter outlines our rationale for the results described in the previous chapter.

The Amino Nitrile Anomeric Effect

As described in Chapter 1, the intramolecular cycloaddition of iminoacetonitriles produces cyclic α-amino nitriles with a high preference for the cyano group to occupy an axial position. Equilibration of cycloadducts containing a mixture of cyano isomers by heating in acetonitrile afforded the axial anomer as the major if not sole product. There are no obvious steric reasons why one isomer would be preferred over the other as hydrogen and cyanide have very similar A-values.[123] We believe that the reasons for this observed preference for the axial cyano group involve secondary orbital interactions (and other factors) and represents a variant of the "anomeric effect" well known from carbohydrate chemistry. As illustrated below for **210** and **211**, the axial orientation of the nitrile moiety allows for a favorable dipole-dipole interaction.

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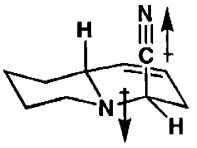
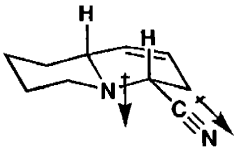
[123] Jensen, F. R.; Bushweller, C. H. *Adv. Alicyclic Chem.* **1971**, *3*, 140.



210



211

In terms of molecular orbitals, the anomeric effect has been attributed to an interaction between the lone pair of electrons on a heteroatom and the σ* orbital of the neighboring C-X bond (X = OR, SR, halogen, CN, etc.). A similar type of interaction in **210** would be expected to lower the energy of this axial cyano isomer.

Discussions of the anomeric effect usually appear in the context of the chemistry of carbohydrates and other oxygen-containing heterocycles, but secondary orbital interactions can play a role in other types of heterocyclic systems.[124] For oxygen heterocycles, numerous studies have been undertaken to determine the energetic value of the anomeric effect, and for most carbohydrates and related compounds the anomeric effect affords 0.9-2.3 kcal/mole of stabilization. However, this value increases as the electron-withdrawing ability of the substituent α to the heteroatom increases. For example, the energetic value of the anomeric effect in 2-nitropyranoses ranges from 2.4 to 3.4 kcal/mole, depending on the neighboring substituents.

Since the early 1980's, it has been known that certain cyclic amines exhibit anomeric effects analogous to those well known for oxygen heterocycles. In fact, Kirby states in his book on the anomeric effect "no doubt electronegative substituents at the 2-positions of *N*-alkylpiperidines would also favor the axial conformation." Husson and co-workers have carried out seminal studies examining the isomerization of α-amino

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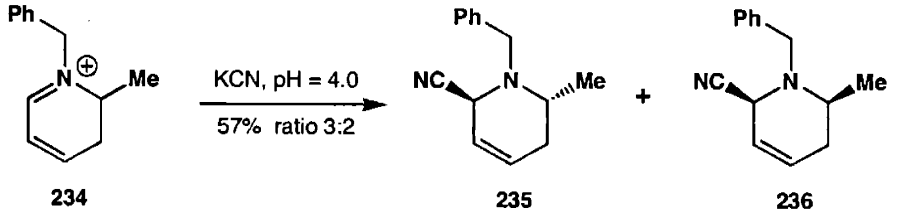
[124] (a) Kirby, A. J. *The Anomeric Effect and Related Stereoelectronic Effects at Oxygen*; Springer-Verlag: New York, 1983. (b) Juaristi, E.; Cuevas, G. *The Anomeric Effects* CRC Press: Ann Arbor, 1995.

nitriles,[125] and found that treatment of iminium ion **234** with potassium cyanide afforded a mixture of two isomeric α-amino nitriles (**235** and **236**) in a 60:40 ratio (eq 51).



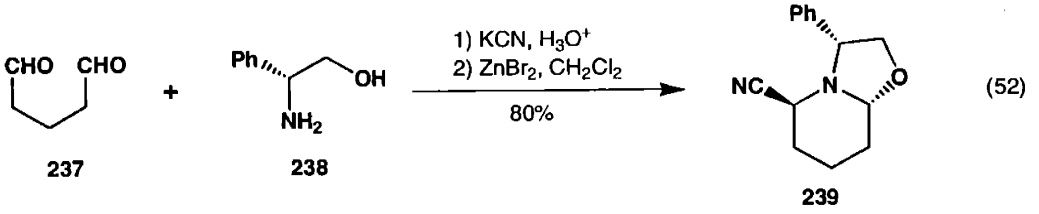
234 **235** **236** (51)

Spectroscopic analysis indicates that the nitrile group in **235** and **236** occupy an pseudoaxial orientation, which is surprising considering that this requires **236** to contain an pseudoaxial methyl group as well. Apparently, in **236** the stabilization energy afforded by the α-amino nitrile anomeric effect is large enough to prevent inversion to the conformation in which both groups occupy pseudoequatorial positions. In the discussion of this observation, Husson states that "this preferred orientation of the nitrile group in piperideine (and piperidine) amino nitriles appears to be a general phenomenon which we believe can be likened to the 'anomeric effect' observed in pyranose sugars."[125a]

In connection with their preparation of non-racemic nitrogen heterocycles, Husson and co-workers developed an elegant method for the asymmetric synthesis of piperidines (eq 52).[126] In one variant of their method, reaction of glutaraldehyde (**237**) and (*R*)-(—)-phenylglycinol (**238**) with potassium cyanide afforded **239**, which was

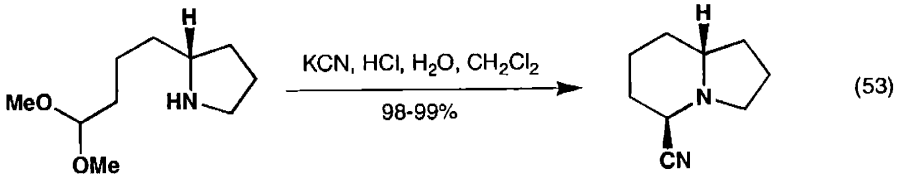
[125] (a) Bonin, M.; Romero, J. R.; Grierson, D. S.; Husson, H.-P. *J. Org. Chem.* **1984**, *49*, 2392. (b) Bonin, M.; Chiaroni, A.; Riche, C.; Beloeil, J.-C.; Grierson, D. S.; Husson, H.-P. *J. Org. Chem.* **1987**, *52*, 382.
[126] (a) Guerrier, L.; Royer, J.; Grierson, D. S.; Husson, H.-P. *J. Am. Chem. Soc.* **1983**, *105*, 7754. (b) Grierson, L.; Royer, J.; Guerrier, L.; Husson, H.-P. *J. Org. Chem.* **1986**, *51*, 4475. (c) Husson, H.-P.; Royer, J. *Chem. Soc. Rev.* **1999**, *28*, 383.

employed as a precursor to a variety of piperidines.[127] In this case it was found that the nitrile group exists exclusively in the axial position due to the anomeric effect.



237 238 239 (52)

In connection with their work on the total synthesis of naturally occurring indolizidine alkaloids, Polniaszek and Belmont disclosed another example of the α-amino nitrile anomeric effect.[128] Treatment of amino acetal **240** with potassium cyanide and aqueous acid afforded indolizidine **241** in nearly quantitative yield as a single stereoisomer (eq 53).



240 241 (53)

From the information presented above, along with the results discussed in the previous chapter, it appears reasonable that the α-amino nitrile anomeric effect exerts a controlling force over the stereochemistry of the products formed in our iminoacetonitrile cycloadditions. With a few exceptions, the dienyl imines examined in the previous chapter provide cycloadducts as a single cyano isomer. It does not seem likely that a stereoselective cycloaddition produces the observed products, but rather the cycloaddition generates a mixture of stereoisomeric products and subsequent isomerization equilibrates the amino nitrile cycloadduct, leading to the observed axial nitrile product.

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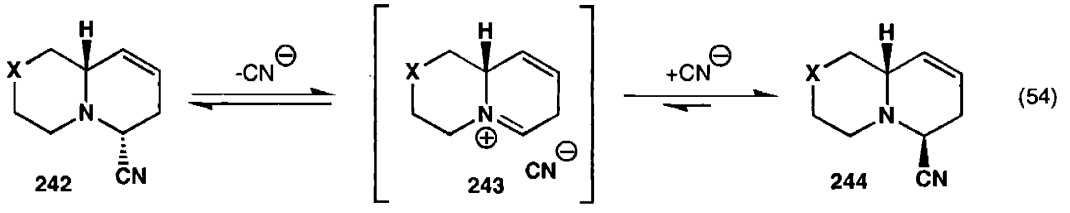
[127] Bonin, M.; Grierson, D. S.; Royer, J.; Husson, H.-P. *Org. Synth*, **1991**, *70*, 54.

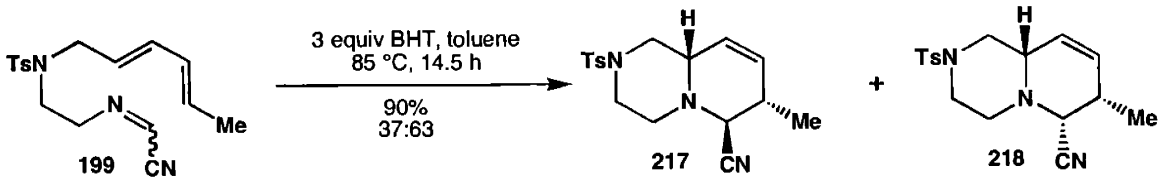
[128] (a) Polniaszek, R. P.; Belmont, S. E. *J. Org. Chem.* **1990**, *55*, 4688. (b) Polniaszek, R. P.; Belmont, S. E. *J. Org. Chem.* **1991**, *56*, 4868.

The exceptions to this observation are the three cases with heteroatoms in the tether and the aryl linked case, in which mixtures of amino nitrile isomers are produced when the reaction is carried out in toluene. Although the cycloaddition reactions of these substrates afford a mixture of products, we attribute this to an incomplete isomerization in these systems, not to a decrease in the preference for the axial anomer. Presumably, the isomerization of the amino nitrile proceeds through ionization to produce an iminium ion pair **243**, which collapses to form the favored axial isomer **244** (eq 54).



242 243 244 (54)

We suggest that systems incorporating a heteroatom in the connecting chain (e.g., **242** X = NTs or O) are slower to isomerize because the heteroatom inductively destabilizes the intermediate iminium ion **243**. A non-polar solvent like toluene does not stabilize the intermediate iminium ion to a great extent, but a more polar solvent, such as acetonitrile, can stabilize a charged intermediate, lowering the energetic barrier for the isomerization. The cycloaddition of imine **199** (*N*-tosyl linked substrate) in toluene at 85 °C affords what we believe is the kinetic ratio of products (37:63 β to α-nitrile). This was confirmed by heating solutions of the separate isomers in toluene at 85 °C for 45 h with 3 equivalents of BHT and observing that no isomerization of either compound occurs. When these same solutions were heated at reflux (110 °C), the equatorial nitrile isomer **218** slowly isomerized to the axial isomer (**217**).



For reasons discussed earlier, employing a polar solvent should facilitate the isomerization of **218** to **217**, and, in fact, refluxing **199** in acetonitrile affords mainly **217** (94:6 ratio). Similar results are observed with substrates containing an oxygen in the tether. In the case of the aryl linked tether, the sp^2 hybridized carbons of the aryl group inductively destabilize the intermediate iminium ion, leading to a mixture of cyano anomers for the same reasons as described for the heteroatom-tether systems.

Effect of Iminoacetonitrile Stereochemistry on the Cycloaddition

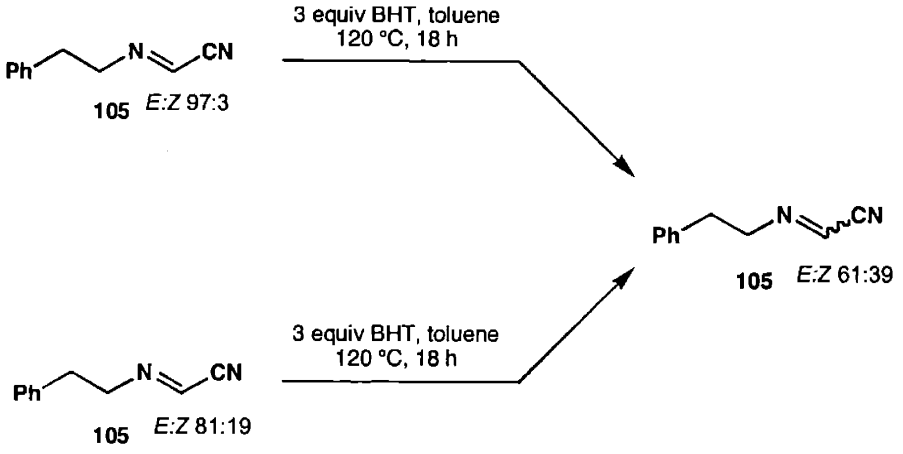
It will be recalled that the cycloadditions discussed in the previous chapter were carried out employing mixtures of *E* and *Z* imine isomers, containing between 70 to 80% of the *E* imine isomer. Adam Renslo observed that interrupting the cycloaddition of imine **93** before completion afforded iminoacetonitrile **93** with a 71:29 ratio of *E* and *Z* imine isomers (starting material in this case had a ratio of 72:28).[129] This would be expected if the *E* and *Z* isomers undergo cycloaddition at the same rate, but could also be explained if this ratio represents the equilibrium ratio of imine isomers. The following experiments were carried out to investigate this issue further.

Preparation of iminoacetonitrile **105,** as described in Part II, Chapter 3, and careful purification by column chromatography furnished samples of imine **105** enriched in the *E* isomer. Subjecting these samples to our standard cycloaddition conditions (3 equiv of BHT, toluene, 120 °C, 18 h) afforded in both cases a mixture of imine isomers

[129] Renslo, A. R. Ph.D. Thesis, Massachusetts Institute of Technology, June 1998, p 48.

with the identical ratio of *E* and *Z* isomers (Scheme 30). Iminoacetonitrile **105** also undergoes isomerization when the same experiment is carried out without BHT present.

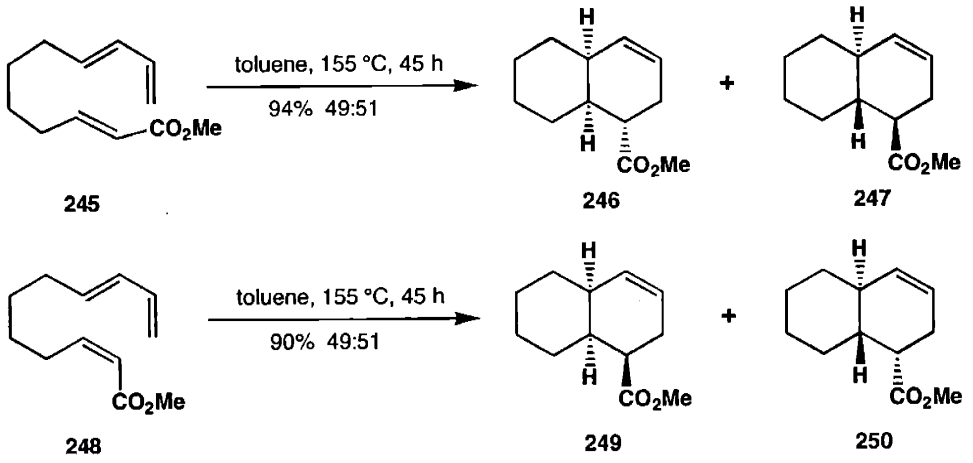
Scheme 30



These experiments suggest that the iminoacetonitriles undergo equilibration under the conditions employed for our cycloaddition reactions. The next question is whether both isomers undergo [4+2] cycloaddition at the same rate, or whether one isomer reacts preferentially. In this connection, the observations of Roush and coworkers concerning the intramolecular Diels-Alder reaction are informative. As shown in Scheme 31, Roush found that in some cases there is no difference in the rate of cycloaddition for isomeric dienophiles such as **245** and **248** and no preference for the endo Diels-Alder adduct.[130]

[130] Roush, W. R.; Hall, S. E. *J. Am. Chem. Soc.* **1981**, *103*, 5200.

Scheme 31

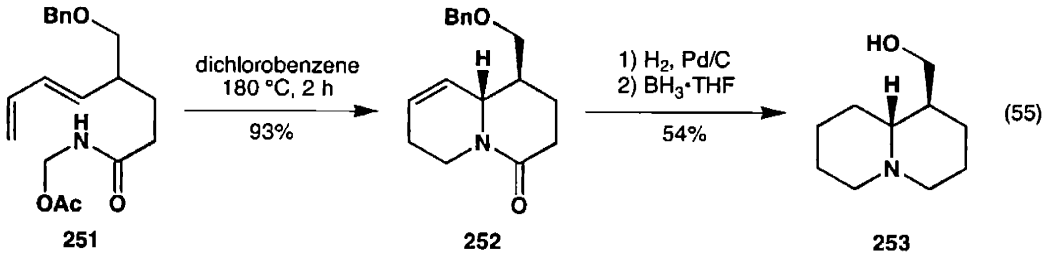


Although there are differences between the carbocyclic and heterocyclic intramolecular Diels-Alder reaction, Roush's result is at least suggestive that our two imine isomers might react at the same rate. With isomerizations occurring with both the imine starting material and the amino nitrile cycloadduct, the mechanistic basis of the stereochemical course of the intramolecular cycloaddition of iminoacetonitriles is likely quite convoluted. The next section discusses this complex subject.

Possible Transition States for the Iminoacetonitrile Cycloaddition

Before discussing the stereochemical course of our iminoacetonitrile cycloadditions, it is instructive to review the previous analyses of Weinreb and Grieco concerning the stereochemical course of the intramolecular aza Diels-Alder reactions investigated in their laboratories.

Weinreb's total synthesis of epi-lupinine (**253**) features the [4+2] cycloaddition of the *N*-acyl imine derived from amide **251**.[131] Thermolysis of **251** afforded **252** as a single diastereomer, which upon reduction provided **253**.

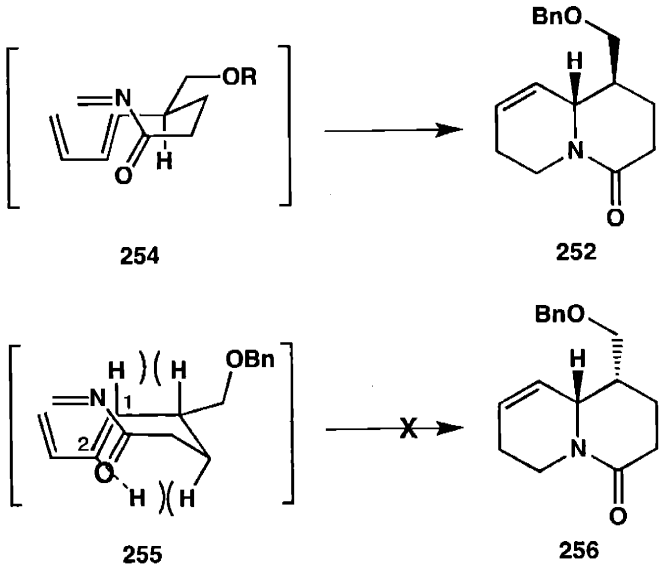


251 **252** **253** (55)

In his report, Weinreb proposes two possible transition states to account for the stereochemical course of his key intramolecular Diels-Alder reaction and suggests that transition state **254** is preferred over **255**. Weinreb assumes that the amide carbonyl group must be endo with respect to the 4-π diene component in the cycloaddition, and that the benzyloxymethyl substituent should prefer to be equatorial with respect to the connecting chain. He also assumes that the acylimine moiety is planar and possesses the *s-cis* conformation shown below. Note that in **254** the connecting chain has a boat-like conformation, while in **255** the conformation is chair-like.

[131] Bremmer, M. L.; Khatri, N. A.; Weinreb, S. M. *J. Org. Chem.* **1983**, *48*, 3661.

Scheme 32



The primary destabilizing interaction in **254** is the flagpole interaction between the nitrogen lone pair and a proton on the connecting chain. This interaction, however, is not as severe as the non-bonded interaction in **255** between C-2 proton of the diene and the indicated proton on the connecting chain. In addition, the formation of **256** is disfavored by an $A^{(1,2)}$ interaction between the C-1 proton of the diene and the adjacent methine proton.

Grieco has completed total syntheses of epi-lupinine and lupinine based on intramolecular iminium ion Diels-Alder reactions.[132] As shown in eq 56, treatment of amine **257** with aqueous formaldehyde and HCl afforded a mixture of two diastereomeric cycloadducts. Hydrogenation in the presence of palladium converted **258** to epi-lupinine, and upon similar treatment, quinolizidine **259** afforded lupinine. Thus, Grieco's synthesis allowed access to the target natural product, but the cycloaddition proceeded with significantly less stereocontrol than Weinreb's Diels-Alder reaction.

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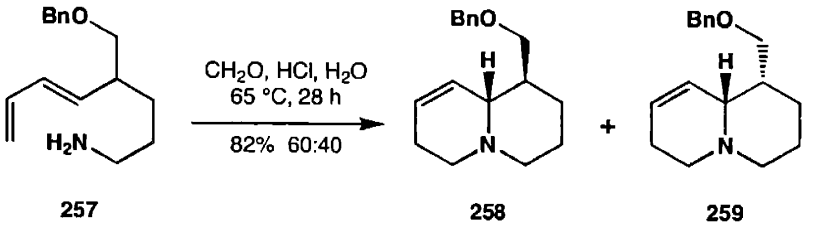
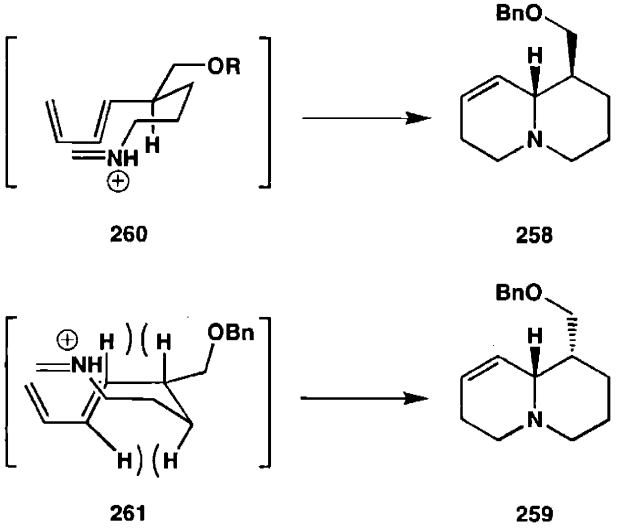
[132] Grieco, P. A.; Parker, D. T. *J. Org. Chem.* **1988**, *53*, 3325.



257 258 259 (56)

Grieco rationalizes the stereochemical course of this reaction by suggesting that the two chair-like transition states **260** and **261** give rise to **258** and **259**, respectively. In agreement with Weinreb, Grieco suggests that transition state **261** is destabilized by the two non-bonded interactions shown in Scheme 33. However, Grieco reports isolating a 60:40 mixture of **258** and **259**, indicating that transition state **261** is only ca. 0.3 kcal/mole higher in energy than **260**. The key difference between Grieco and Weinreb's systems is the presence of the carbonyl group in **254**. Because of the preference of this group to be endo, a chair-like transition state analogous to **260** is not available in Weinreb's cycloaddition.

Scheme 33

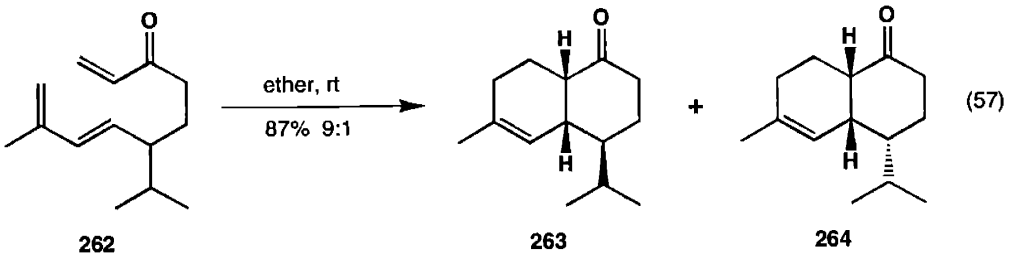


260 258

261 259

In a related carbocyclic example, Taber and coworkers employed an intramolecular Diels-Alder reaction to construct the bicyclic framework of the natural

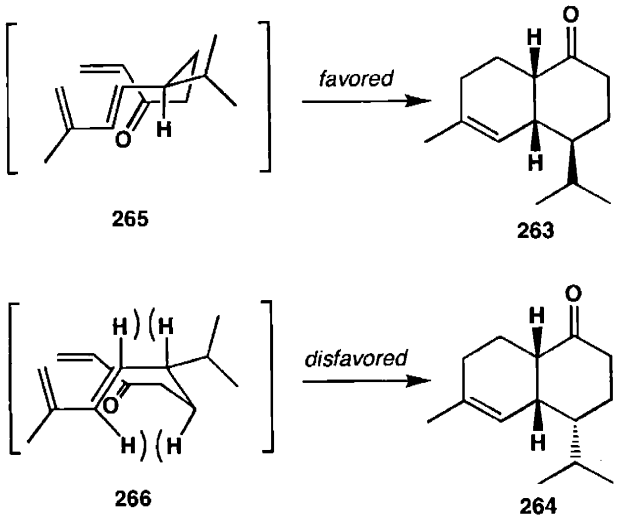
product torreyol (eq 57).[133] Enone **262** spontaneously undergoes an intramolecualr Diels-Alder reaction at room temperature to afford a 90:10 mixture of cycloadducts.



262 **263** **264**

Taber again suggests the carbonyl group must adopt an endo orientation with respect to the diene and that the bulky isopropyl group will prefer an equatorial orientation on the connecting chain. In this case, however, the observed 90:10 mixture of products suggests that the boat-like transition state **265** is more stable than the chair-like transition state **266** by ca. 1.5 kcal/mole.

Scheme 34



265 **263**

266 **264**

Weinreb has reported two additional examples that are relevant to our own iminoacetonitrile cycloaddition.[134] As shown in eq 9, intramolecular cycloaddition of oximinomalonates of type **36** afforded heterocycles of type **37** as single stereoisomers.

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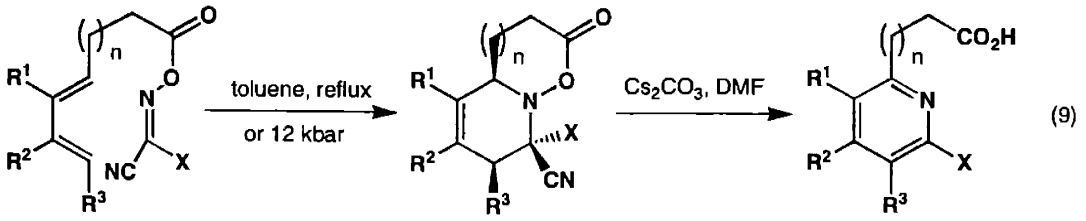
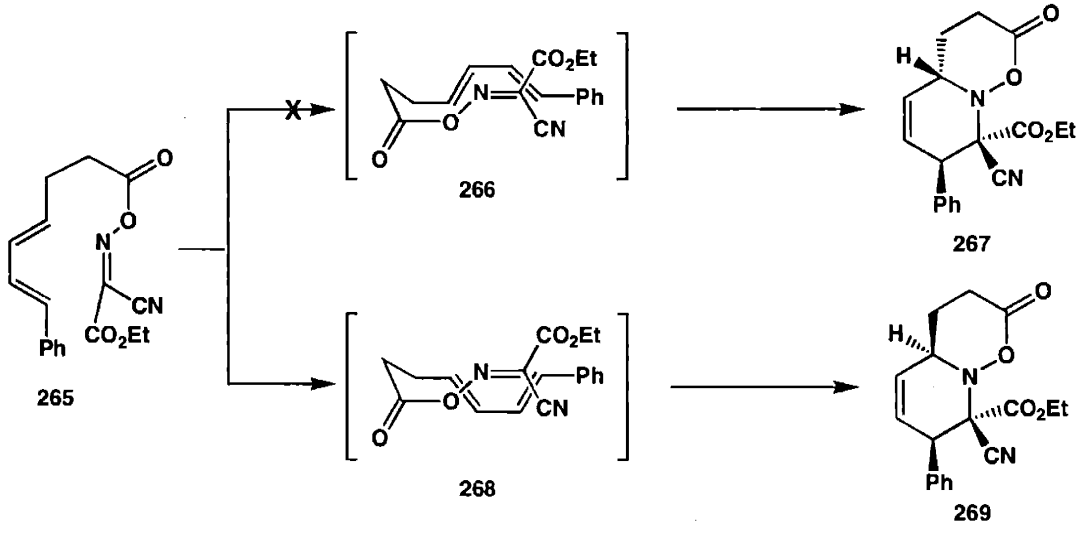
[133] Taber, D. F.; Gunn, B. P. *J. Am. Chem. Soc.* **1979**, *101*, 3992.



36 37 38 (9)

In order to produce the observed stereochemistry, the reaction must proceed through transition state **268** as shown in Scheme 35. Molecular mechanics calculations indicate that transition state **266**, leading to **267** (not observed to form), is 2.8 kcal/mole less stable then **268**. Chair-like transition states related to **266** and **268** are reported to be considerably higher in energy. Interestingly, Fleury notes that the *intermolecular* cycloaddition of related oximinosulfonates with cyclopentadiene afforded products having exclusively an *exo* cyano group (see page 28).

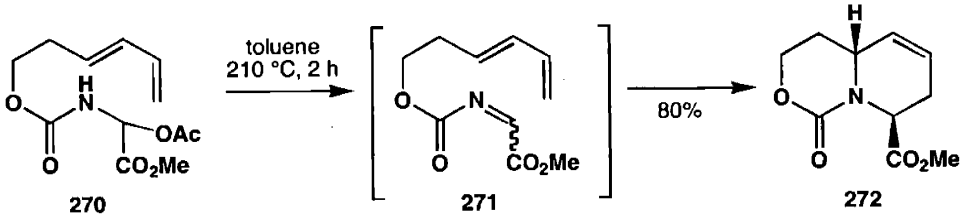
Scheme 35



265 266 267 268 269

[134] Bland, D. C.; Raudenbush, B. C.; Weinreb, S. M. *Org. Lett.* **2000**, *2*, 4007.

As discussed in the first section of this thesis, Weinreb has employed imines that are acylated on both carbon and nitrogen for intramolecular Diels-Alder reactions.[135] As shown in eq 58, thermolysis of **270** generates imine **271**, which undergoes an intramolecular cycloaddition to afford carbamate **272** in good yield.

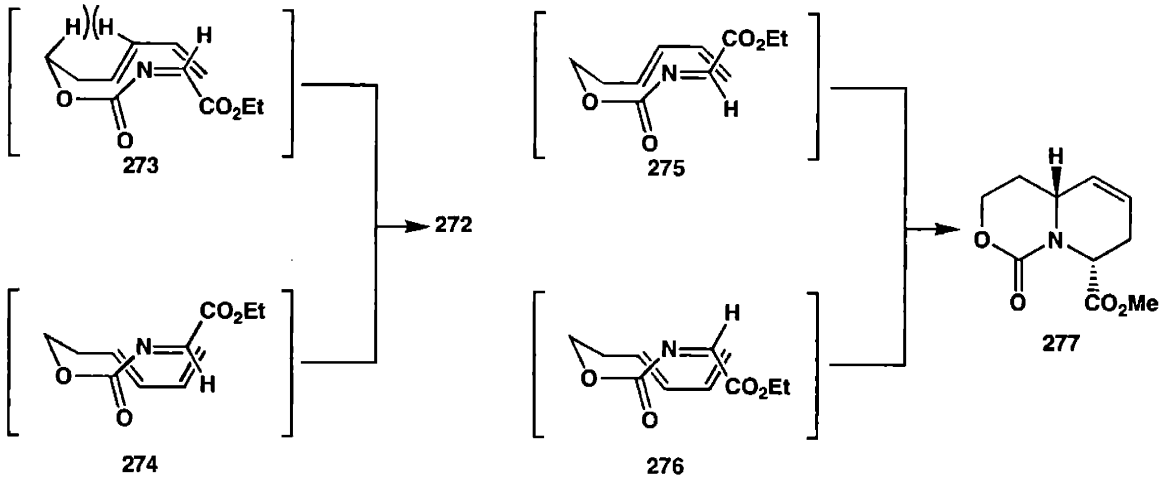


(58)

Because dienophile **271** is generated *in situ*, Weinreb did not determine the stereochemistry of the imine. There are four possible transition states, and the observed product is formed by either transition state **273** (*Z*-imine, both carbonyl moieties exo) or transition state **274** (*E*-imine, with the *N*-acyl group endo). Interestingly, transition state **276**, with both carbonyl groups endo, would provide the unobserved isomer **277**. Weinreb speculates that the cycloaddition is proceeding through transition state **274**, as having both carbonyl groups in an exo orientation (**273**) would be less energetically favorable relative.

[135] (a) Nader, B.; Franck, R. W.; Weinreb, S. M. *J. Am. Chem. Soc.* **1980**, *102*, 1153. (b) Nader, B.; Bailey, T. R.; Franck, R. W.; Weinreb, S. M. *J. Am. Chem. Soc.* **1981**, *103*, 7573. (c) Bailey, T. R.; Garigipati, R. S.; Morton, J. A.; Weinreb, S. M. *J. Am. Chem. Soc.* **1984**, *106*, 3240.

Scheme 36



When analyzing the transition states that are possible for the intramolecular cycloaddition of iminoacetonitriles, there are four different stereochemical control elements that deserve consideration: (1) the tendency of the cyano group to be endo or exo; (2) the preference for syn vs. anti transition states; (3) the conformation of the connecting chain; and (4) long-range non-bonded interactions.

As shown in Scheme 31, Roush has demonstrated that secondary orbital interactions (Alder endo rule) are not a significant factor in at least some intramolecular Diels-Alder cycloadditions.[136] In addition, the *intermolecular* cycloaddition of acrylonitrile with cyclopentadiene and 1,3-pentadiene affords cycloadducts with only a modest preference (55:45) for the endo isomer.[137] Thus it appears that the cyano moiety is not a tremendously effective *endo* director. Unfortunately, in our system the stereochemical analysis is complicated by the isomerization of the iminoacetonitrile

[136] (a) Rousch, W. R. In *Advances in Cycloaddition*; Curran, D. P., Ed.; JAI Press: London, 1990, Vol. 2, pp 91-146. (b) Rousch, W. R. In *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I., Eds.; Pergamon Press: Oxford, 1991, Vol. 5, pp 513-550.

[137] (a) Braun, R.; Schuster, F.; Sauer, J. *Tetrahedron Lett.* **1986**, *27*, 1285. (b) Güner, O. F.; Ottenbrite, R. M.; Shillady, D. D.; Alston, P. V. *J. Org. Chem.* **1988**, *53*, 5348.

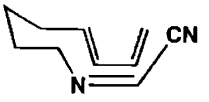
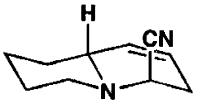
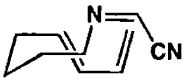
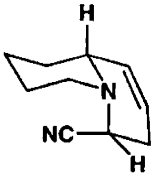
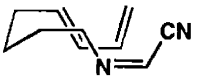
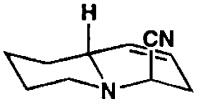
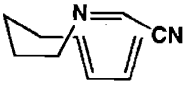
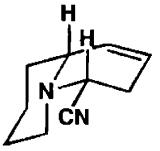
dienophile as well as the resulting α-amino nitrile cycloadducts, and the product structure therefore does not provide unequivocal information with regard to the stereochemical course of the cycloaddition reaction.

In the case of the *anti* transition state, in which the connecting chain bond to the azadienophile adopts an "endo" orientation, the resulting cycloadduct will be a trans-fused bicyclic system. The *syn* transition state ("exo" orientation of the connecting chain bond) affords a cis-fused structure. Once again, there is not a strong preference for either transition state in the carbocyclic series, unless a strong electron-withdrawing group is present or a Lewis acid is employed. Roush and others have put forth the idea of "twist asynchronicity", wherein one of the two new C-C bonds is forming in advance of the second bond in the transition state. With an internally activated dienophile, the external bond is more advanced in the transition state, favoring the cis-fused product. The trans-fused product is favored with externally activated dienophiles, which lead to greater formation of the internal C-C bond in the transition state. Analysis of our system is complicated by the fact that the nitrogen can undergo inversion, converting a cis-azadecalin system to a trans-azadecalin structure.

The conformation of the connecting chain must also be considered. Typically, boat-like conformations are disfavored due to additional torsional and non-bonded interactions not present in chair-like conformations. However, substituents or replacement of carbon atoms in the connecting chain with heteroatoms can alter this preference.

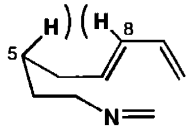
As discussed in the analysis of Weinreb, Grieco, and Tabers' transition states, long-range non-bonded interactions such as the interaction between C-5 and C-8 (see

Table 11. Transition States for Z-Imine 93

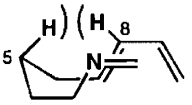
Entry	Connecting Chain	Cyano Group	Transition State	Product
Z-1	chair-anti	exo		
Z-2	chair-syn	endo		
Z-3	boat-anti	exo		
Z-4	boat-syn	endo		

Entries Z-1 and Z-3 both provide trans-azadecalin systems with the anomeric effect already in place. Z-3 requires a ring flip from the initial boat-like structure to the chair shown above. Entries Z-2 and Z-4 both provide cis-azadecalin systems with no anomeric effect. Transformation of these products to the observed cycloadduct requires both a nitrogen inversion and an isomerization of the nitrile group.

below), the so called "1,4-flagpole" interactions, can destabilize the chair-syn and boat-anti transition state. The above analysis focuses on non-bonded and torsional interactions in conformations available to ground state conformations of the starting material. However, if the transition state is late, it may be more productive to examine product structure and its relationship to the transition state.



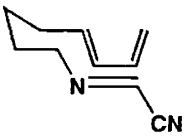
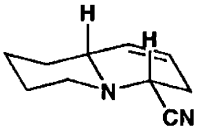
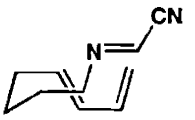
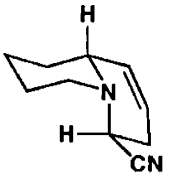
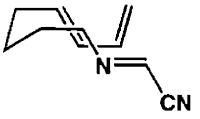
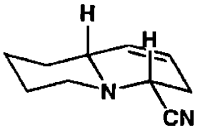
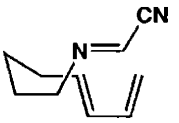
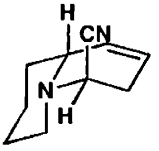
chair-syn



boat-anti

As shown in Table 11 and 12, each imine isomer can react via four diastereomeric transition states. The connecting chain can adopt either chair-like or boat-like conformations, and the cyano group can adopt either an *exo* or *endo* orientation with respect to the diene. The *exo* transition states all lead to the observed product with an axial nitrile, while the *endo* transitition states would provide a quinolizidine with an equatorial cyano group.

Table 12. Transition States for *E*-Imine 93

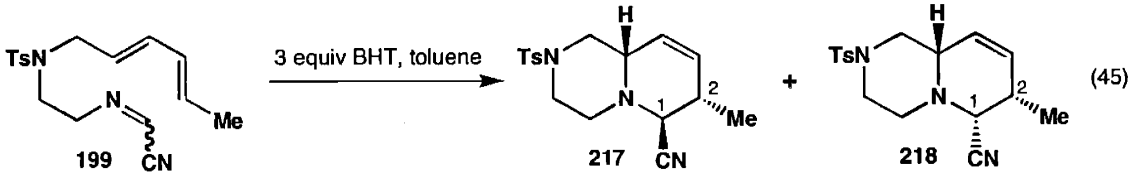
Entry	Connecting Chain	Cyano Group	Transition State	Product
E-1	chair-anti	endo		
E-2	chair-syn	exo		
E-3	boat-anti	endo		
E-4	boat-syn	exo		

All of the transition states shown in Table 12 afford cycloadducts that require an isomerization of the cyano group to afford the observed product. Entries E-1 and E-3 both provide a trans-azadecalin system, while E-2 and E-4 require an inversion at nitrogen to afford the observed products.

Theoretically all eight transition states can provide the observed cycloadduct **210**, but it appears as though Z-1 and E-1 are the favored transition states as they avoid unfavorable non-bonded interactions and provide the observed product without the need for a nitrogen inversion. If the Diels-Alder reaction of iminoacetonitriles proceeds through a late transition state, Z-1 would be expected to be favored as the anomeric effect is already present in the transition state. E-1 only requires an epimerization to provide the observed product. Transition states Z-4 and E-4 are also plausible, requiring a nitrogen inversion and an isomerization of the cyano group to provide the observed

product. These are both boat-type transition states, but are more favorable than Z-2, E-2, Z-3, and E-3, where the 1,4-flagpole non-bonded interactions should destabilize these four transition states.

By examining the cycloaddition of imine **199**, it appears that the initial cycloaddition is producing a mixture of products. The result seen in equation 45 can be explained by applying Occam's razor[138] to the above analysis.



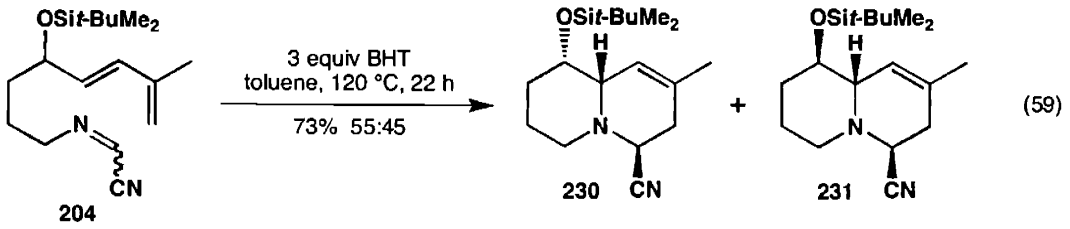
(45)

Temp	Yield	Ratio
85 °C	90%	37:63
110 °C	95%	39:61
120 °C	73%	44:56

When the cycloaddition is carried out at 85 °C, the kinetic ratio of products is obtained with E-1 providing **218**, and Z-1 affording the minor product **217**. The product distribution can be explained by the greater abundance of the *E*-imine isomer in **199** (81:19 *E*:*Z*). The isomerization of the imine isomers presumably prevents the product ratio from reflecting the ratio of imine isomers. The incorporation of a heteroatom in the connecting chain removes the 1,4-flagpole interactions which may allow Z-2, E-2, Z-3, and E-3 to be competitive transition states.

Cycloaddition of imine **204** produced a mixture of two quinolizidines in a nearly 1:1 ratio, with a slight preference for the product with an axial siloxy group (**230**).

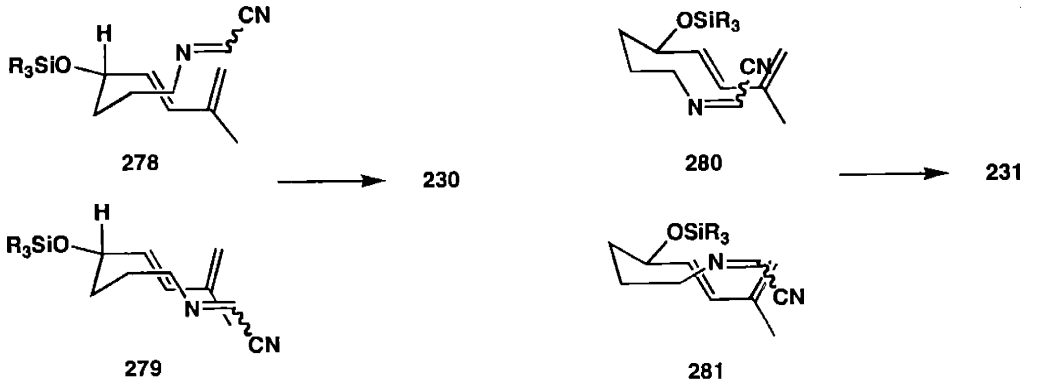
[138] Occam's razor suggests that the best explanation of an event is the one that is the simplest and requires the fewest assumptions.



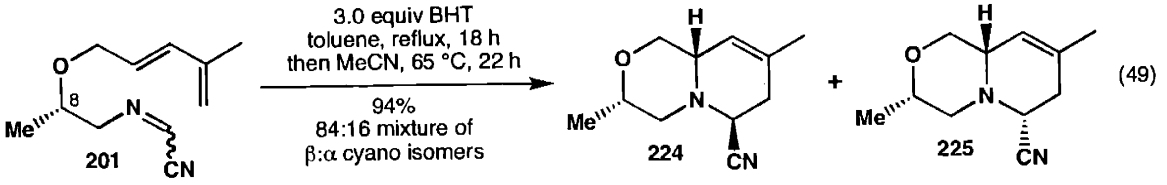
As shown in Scheme 38, cycloaddition of imine **204**, assuming the siloxy group is equatorial, through transition states Z-1 or E-1 (**280**) would provide the minor isomer **231**, as would Z-4 and E-4 (**281**). The major product **230** can only be accessed by transition states Z-2, E-2, (**278**), Z-3, and E-3 (**279**), assuming once again that the siloxy group is equatorial. As described above, the two transition states (**278** and **279**) that afford the major product are destabilized by both $A^{(1,2)}$ and 1,4-flagpole non-bonded interactions. Based on this analysis one would expect that **230** would be the minor product, however cycloaddition of imine **204** afforded **230** and **231** in nearly equal ratio. The other possibility is that the siloxy group adopts an axial orientation,[139] thereby allowing the presumed favored transition states Z-1 and E-1 (or Z-4 and E-4) to afford the major product, while the minor product is provided by Z-2, E-2, Z-3, and E-3. Because it is unclear if the siloxy group adopts an equatorial or axial orientation in the transition state, cycloaddition of imine **204** provides limited information with regards to the preferred transition state for the intramolecular Diels-Alder reaction of iminoacetonitriles. It does suggest that at least two pathways are comparable in energy, as the observed ratio of products indicates that the transition states leading to the **230** and **231** are quite similar (ca. 0.1 kcal difference) in energy.

[139] For examples of allylic alkoxy groups adopting axial positions in the IMDA reaction see: (a) ref 136b. (b) Roush, W. R. *J. Org. Chem.* **1979**, *44*, 4008. (c) Marshall, J. A.; Shearer, B. G.; Crooks, S. L. *J. Org. Chem.* **1987**, *52*, 1236.

Scheme 38



The cycloaddition reaction of imine **201** provided cycloadduct **224** and **225** as a mixture of cyano isomers but as virtually a single isomer[140] with regards to the C-8 methyl group (eq 49).

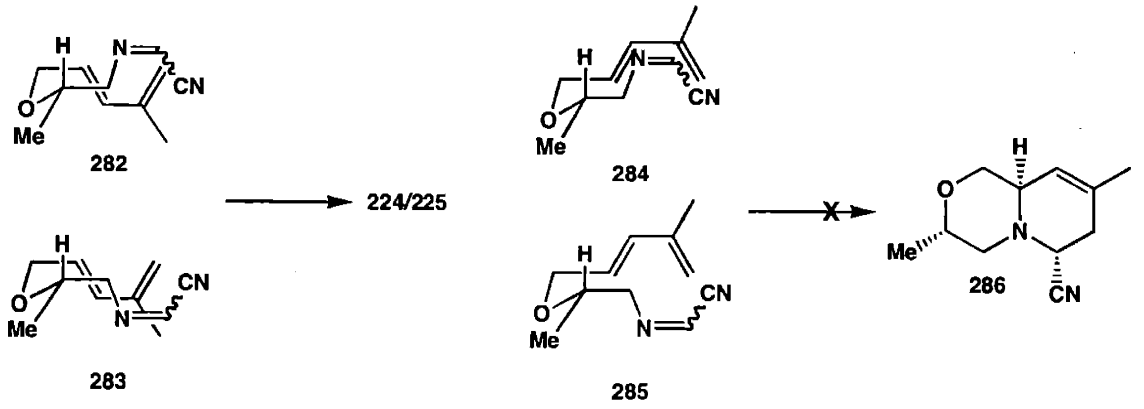


(49)

Analysis of the four transition states shown in Scheme 39 (ignoring transition states with the methyl group in an axial orientation and imine isomers) does not immediately indicate why formation of **224** and **225** is overwhelmingly favored. Transition states Z-1, E-1 (**284**) and Z-4, E-4 (**285**) lead to the unobserved methyl isomer **286**. Assuming the methyl group adopts an equatorial orientation in the transition state, chair-like transition state **282** (Z-2, E-2) and boat-like transition state **283** (Z-3, E-3) afford the observed products.

[140] Greater than 95:5 by ^{1}H NMR analysis.

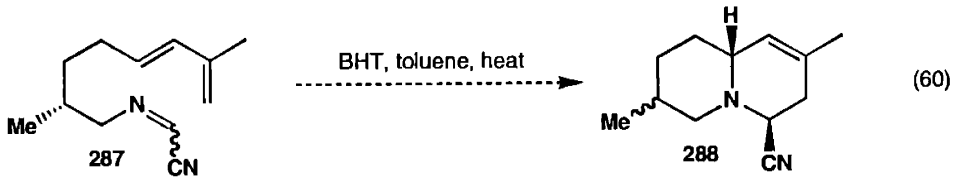
Scheme 39



Transition states Z-2, E-2, Z-3, and Z-4 (**282** and **283**) are predicted to be destabilized by a 1,4-flagpole-like non-bonded interaction, however, in transition states **282** and **283** this flagpole interaction is much less severe because the proton on the diene is interacting with only a lone pair of electrons on the oxygen and not a hydrogen atom. It would be expected that the boat-like transition states **282** and **283**, leading to **224/225**, would be lower in energy than the all carbon variant. In Grieco's report the transition states for the cycloaddition of the iminium ion derived from **257** (eq 56) appear to be energetically separated by only 0.3 kcal/mole. It is possible that the loss of the 1,4-flagpole interaction (Scheme 39) changes the energetics of the transition states enough to favor conformations **282** and **283**.

It would be interesting to prepare the all-carbon analog **287** and examine the selectivity observed in the subsequent Diels-Alder cycloaddition. As shown in eq 60, if imine **287** affords a mixture of cycloadducts **288**, this would implicate the 1,4-flagpole interaction as being a crucial component of stereocontrol in the intramolecular

cycloaddition of iminoacetonitriles. Unfortunately, without further experiments it is difficult to unambiguously know why the cycloaddition of imine **201** proceeds with such high selectivity.



(60)

Summary

The intramolecular cycloaddition reaction of iminoacetonitriles provides α-amino nitriles with a high preference for products with an axial nitrile group. Literature precedent and experimental results implicate the anomeric effect as the controlling factor. The cycloaddition reactions of iminoacetonitriles with a stereogenic center in the connecting chain can lead to a mixture of products or virtually a single product, depending on the location of the stereogenic center.

Part IV

Synthetic Utility of α-Amino Nitrile Cycloadducts

Chapter 1

Transformations of α-Amino Nitrile Cycloadducts

As discussed earlier, one of the primary reasons for our interest in iminoacetonitriles as 2-π components in aza Diels-Alder reactions was our expectation that the α-amino nitrile cycloadducts could serve as versatile synthetic intermediates amenable to further elaboration. This chapter discusses the chemistry of this synthetically useful moiety.

Introduction and Background

α-Amino nitriles are exceptionally versatile intermediates which can react by multiple pathways.[141] One important mode of reactivity involves functional group transformations of the nitrile group. Strecker, in 1850, discovered the ease with which amino acids can be synthesized using α-amino nitriles.[142] Simple hydrolysis of the nitrile group affords the desired amino acid. Nitriles participate in numerous other reactions, such as nucleophilic addition and reduction, but the focus of this chapter will be on the following two modes of reactivity.

Of particular interest to us is the ability of α-amino nitriles to function as stable precursors to iminium ions. The ease with which this ionization of cyanide occurs provides for a wide range of reaction possibilities, such as Mannich reactions, "cation-π"-

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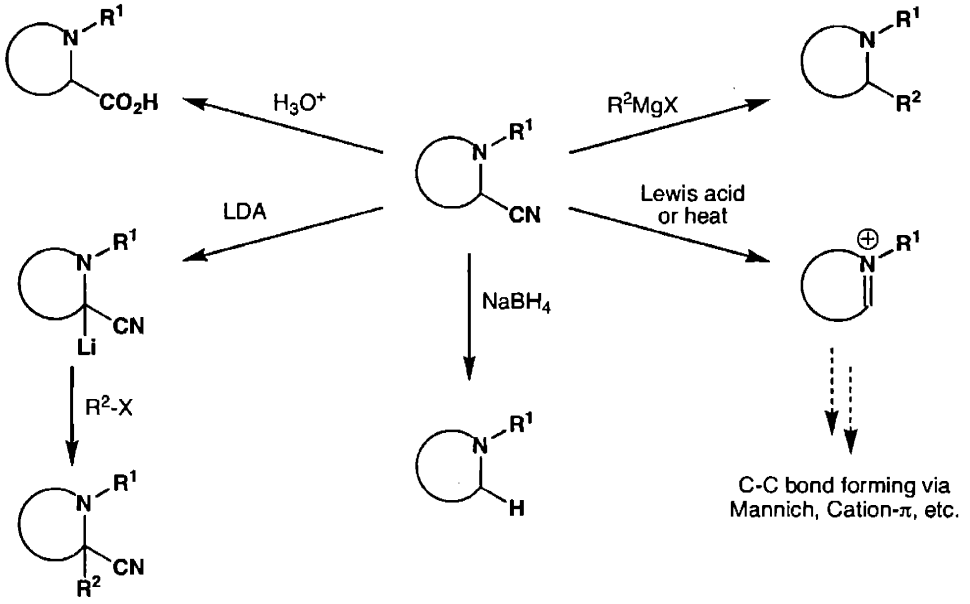
[141] For reviews, see: (a) Ender, D.; Shilvock, J. P. *Chem. Soc. Rev.* **2000**, *29*, 359. (b) Shafran, Y. M.; Bakulev, V. A.; Mokrushin, V. S. *Russ. Chem. Rev.* **1989**, *58*, 148. (c) Rubiralta, M.; Giralt, E.; Diez, A. In *Piperidine: Structure, Preparation, Reactivity, and Synthetic Applications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

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

type cyclizations, and reaction with organosilanes and Grignard reagents ("the Bruylants reaction"). Another mode of reactivity, complementary to the iminium ion chemistry, involves metallation to afford stabilized carbanions that can then undergo alkylation and other carbon-carbon bond forming reactions. As shown in Scheme 40, α-amino nitriles display umpolung character. Depending on the conditions employed, the carbon atom of the α-amino nitrile can be either nucleophilic or electrophilic.

Scheme 40

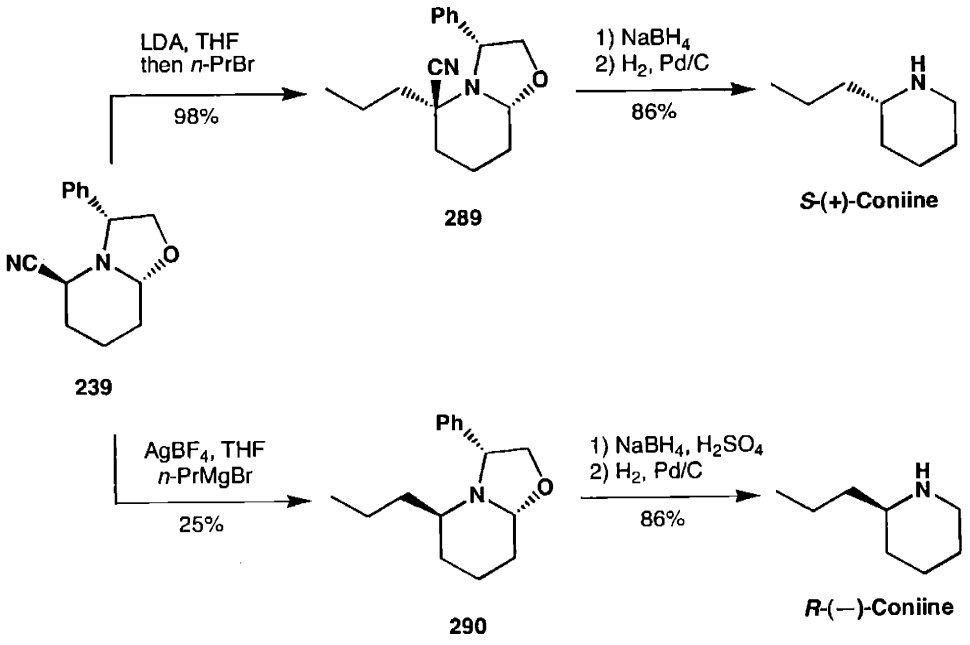


Some of the best illustrations of this last point come from the laboratories of Husson.[143] As mentioned in the previous chapter, Husson and coworkers have utilized non-racemic *N*-(cyanomethyl)oxazolidines (**239**) in the synthesis of nitrogen heterocycles and alkaloid natural products. As shown in Scheme 41, treatment of **239** with lithium diisopropylamide, followed by propyl bromide afforded the substituted amino nitrile **289**. Immediate reduction of this compound gave an intermediate amino alcohol, which upon removal of the chiral auxiliary by hydrogenolysis provided (*S*)-(+)-coniine in good yield

[143] For a review of Husson's CN(*R*,*S*) method, see: Husson, H.-P.; Royer, J. *Chem. Soc. Rev.* **1999**, *28*, 383.

and excellent entantiomeric purity (99% ee). To access (*R*)-(–)-coniine, α-amino nitrile **239** was treated with silver tetrafluoroborate and propylmagnesium bromide to afford axial substituted aminal **290**, albeit in low yield. Two step removal of the chiral alcohol provided (*R*)-(—)-coniine with excellent stereochemical purity. Scheme 41 demonstrates the power of combining a ring template strategy with the versatility of α-amino nitrile transformations.

Scheme 41



Polniaszek and Belmont have employed bicyclic α-amino nitriles in the total synthesis of indolizidine alkaloids.[144] As shown in Scheme 42, treatment of α-amino nitrile **291** with LDA, followed by an alkyl bromide afforded **292**, which upon reduction gave indolizidine **293**. Employing the Grignard reagent prepared from the same alkyl bromide afforded the stereocomplementary product **294**.

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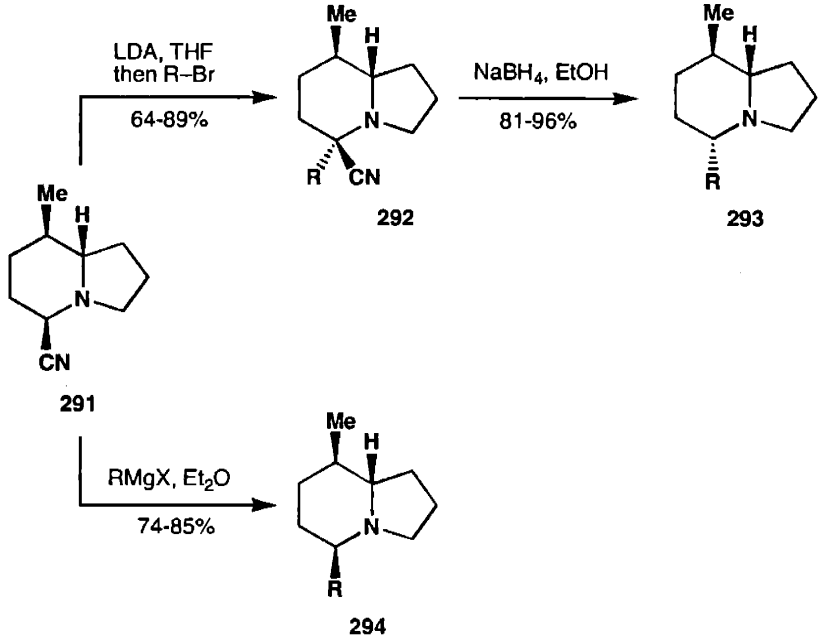
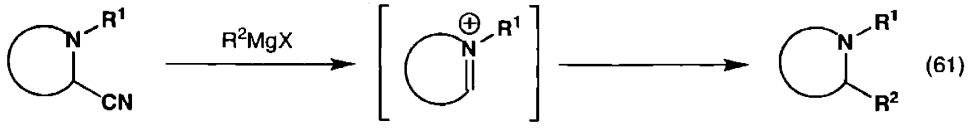
[144] (a) Polniaszek, R. P.; Belmont, S. E. *J. Org. Chem.* **1990**, *55*, 4688. (b) Polniaszek, R. P.; Belmont, S. E. *J. Org. Chem.* **1991**, *56*, 4868.

Scheme 42



The conversions of **239** to **290** and **291** to **294** deserve special attention due to the unique nature of these transformations. Typically, organometallic species add to a cyano group in an analogous fashion to the addition to carbonyl compounds. However, in the case of α-amino nitriles, the Lewis acidic nature of Grignard reagents promotes the ionization of the cyano group. First reported in 1924 by Bruylants[145] (the reaction now bears his name), treatment of an α-amino nitrile with an organomagnesium compound thus affords a *substitution* product rather than a "normal" *addition* product. As shown in eq 61, the Bruylants reaction commences with the ionization of the nitrile group, followed by nucleophilic addition of the organometallic reagent to the resulting iminium ion.



(61)

[145] Bruylants, P. *Bull. Soc. Chem. Belg.* **1924**, *33*, 467.

Although in a typical Bruylants reactio the α-amino nitrile is treated with a solution of a Grignard reagent to afford the substituted product, the reaction can also be carried out in the presence of a Lewis acid, which allows for low temperature reactions (-78 °C).[146] Recently Couty has reported a systematic study of the Bruylants reaction with various vinyl organometallic species.[147] Couty reports that this reaction proceeds most efficiently with vinylmagnesium reagents in the presence of stoichiometric silver tetrafluoroborate. Vinylmetal compounds that react less efficiently include aluminum, lithium, and silyl derivatives.

The latent electrophilic character of α-amino nitriles has been exploited in the synthesis of several polycyclic alkaloids. For example, Stork's approach to reserpine illustrates the versatility of α-amino nitriles in organic synthesis.[148] Heating an acetonitrile solution of α-amino nitrile **295** affords *iso*-reserpine. The observed stereochemistry is attributed to the iminium ion and cyanide ion forming a tight ion pair and directing nucleophilic attack of the aromatic ring to the β-face. To access the stereochemistry present in reserpine, α-amino nitrile **295** was treated with silver tetrafluoroborate to break up the tight ion pair and permit the nucleophilic π-bond to approach from the preferred axial direction (α-face).

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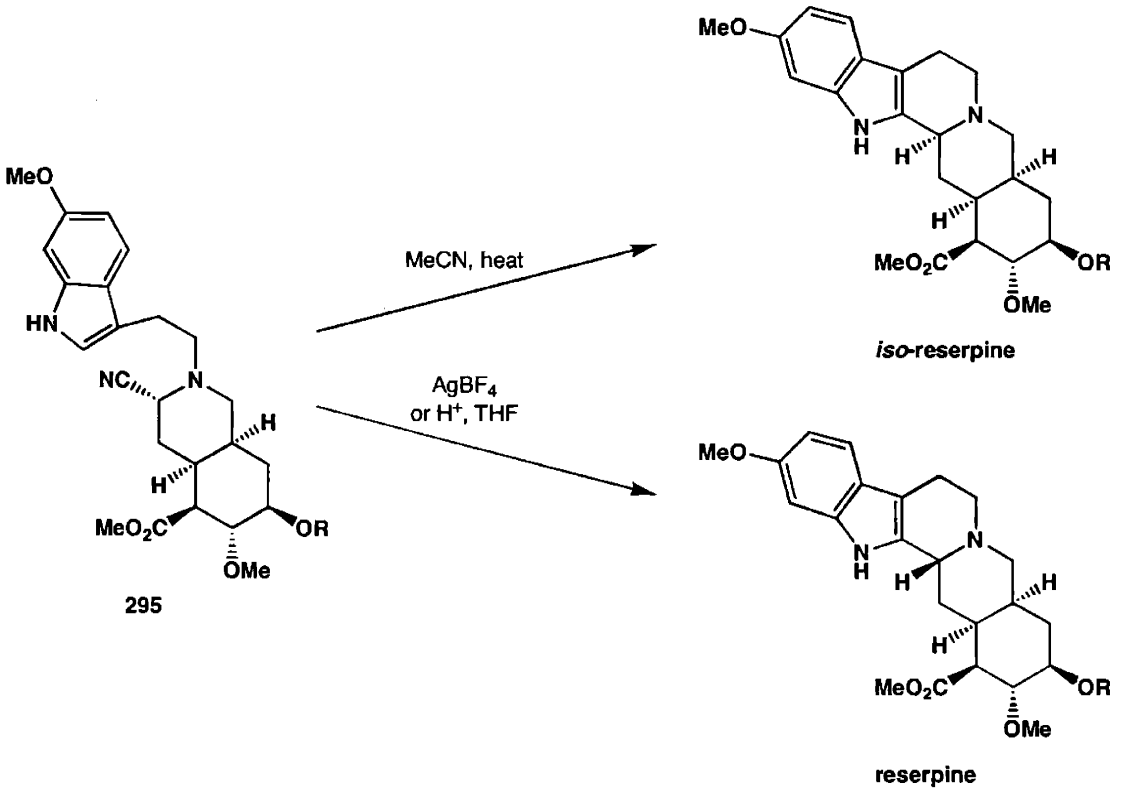
[146] Ahlbrecht, H.; Dollinger, H. *Synthesis*, **1985**, 743.

[147] Agami, C.; Couty, F.; Evano, G. *Org. Lett.* **2000**, *2*, 2085.

[148] Stork, G. *Pure Appl. Chem.* **1989**, *61*, 439.



Overman and co-workers have employed α-amino nitriles as latent iminium ions in their investigations of the aza Cope rearrangement.[149] Thus, treatment of α-amino nitrile **296** with a Lewis acids generates iminium ion **297**. This intermediate then undergoes a [3,3]-sigmatropic rearrangement, providing cyclic iminium ion **298**, which was trapped by an internal Mannich reaction to deliver the desired heterocycle **299**. In addition, Overman has developed the anion-accelerated version of the aza Cope reaction and utilized it in his synthesis of gelsimine.[150]

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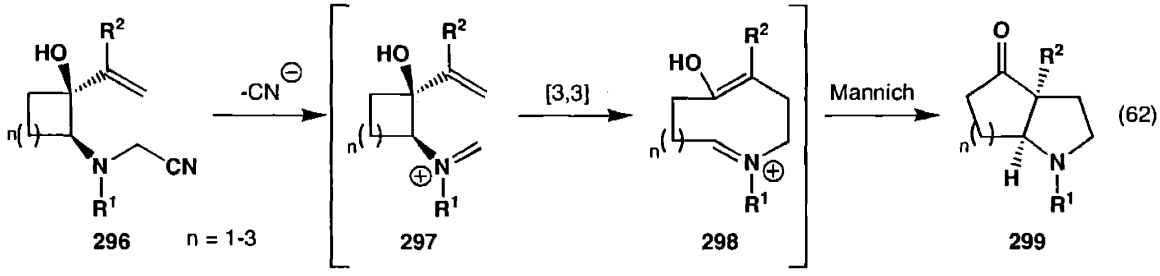
[149] Overman, L. E.; Kakimoto, M.; Okazaki, M. E.; Meier, G. P. *J. Am. Chem. Soc.* **1983**, *105*, 6622. (b) Overman, L. E.; Mendelson, L. T.; Jacobsen, E. J. *J. Am. Chem. Soc.* **1983**, *105*, 6629. (c) Doedens, R. J.; Meier, G. P.; Overman, L. E. *J. Org. Chem.* **1988**, *53*, 685.

[150] Madin, A.; O'Donnell, C. J.; Oh, T.; Old, D. W.; Overman, L. E.; Sharp, M. J. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 2934.



(62)

In summary, α-amino nitriles are extremely versatile synthetic intermediates, with a wide range of reactive possibilities. The ability to access cyclic α-amino nitriles was one of the factors motivating our investigation of the use of iminoacetonitriles in cycloaddition reactions.

Transformations of Cyanoquinolizidine Cycloadducts

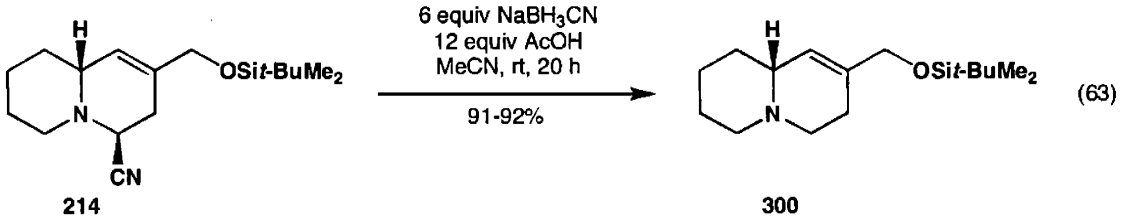
For our studies on the transformations of α-amino nitrile cycloadducts, we chose quinolizdine **214** as the system to employ for optimizing conditions. This cycloadduct was readily accessible on multigram scale, stable to long term storage, and easy to handle.

Reductive Decyanation

The first transformation examined was the reductive decyanation of **214** to provide quinolizidine **300**. This type of reduction of α-amino nitriles is usually carried out with $NaBH_4$ in ethanol and either heating the solution or using a large excess of reducing agent (10 equiv) to drive the reaction to completion.[151] Reduction of **214** with

[151] A variety of conditions have been reported for reductive decyanation. (a) $LiAlH_4$: Froelich, O.; Desos, P.; Bonin, M.; Quirion, J.-C.; Husson, H.-P. *J. Org. Chem.* **1996**, *61*, 6700. (b) BH_3: Ogura, K.; Shimamura, Y.; Fujita, M.; *J. Org. Chem.* **1991**, *56*, 2920. (c) $Zn(BH_4)_2$: Zhu, J.; Quiron, J.-C. Husson, H.-P. *Tetrahedron Lett.* **1989**, *30*, 5137. (d) $NaBH_3CN$: Mitch, C. H. *Tetrahedron Lett.* **1988**, *29*, 6831. (e) KBH_4: Kuehne, M. *J.*; Xu, F. *Org. Chem.* **1997**, *62*, 7950.

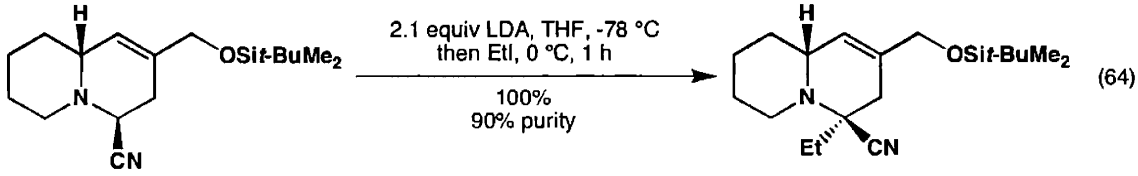
$NaBH_4$ in ethanol at rt or reflux afforded **300** in 83-85% yield. Despite this success, various combinations of borohydride reagents ($NaBH_4$ and $NaBH_3CN$) and protic acids (AcOH, TFA) were explored. In the optimal protocol, treatment of **214** with $NaBH_3CN$ and acetic acid in acetonitrile afforded **300** in excellent yield (eq 63). Efforts to reduce the amount of $NaBH_3CN$ utilized were not undertaken. The reduction can be carried out with $NaBH_4$ in place of $NaBH_3CN$, but the reaction was significantly slower (42 h at rt) and afforded the product in lower yield (82%).



214 300 (63)

Alkylation/Reduction

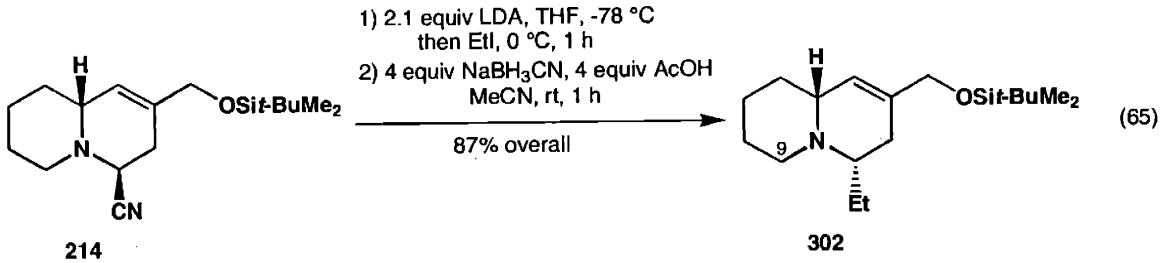
Efforts were then directed at effecting the alkylation of α-amino nitrile **214**. Treatment of **214** with 2.1 equivalents of LDA,[152] followed by quenching the metalated nitrile with ethyl iodide afforded the tertiary α-amino nitrile **301** in nearly quantitative yield but only 90% purity (this compound suffered a partial decomposition upon purification by silica gel chromatography). The ^1H NMR spectrum of **301** clearly showed the presence of only one diastereomer, but the stereochemistry of the product was not deduced until later (vide infra).



214 301 (64)

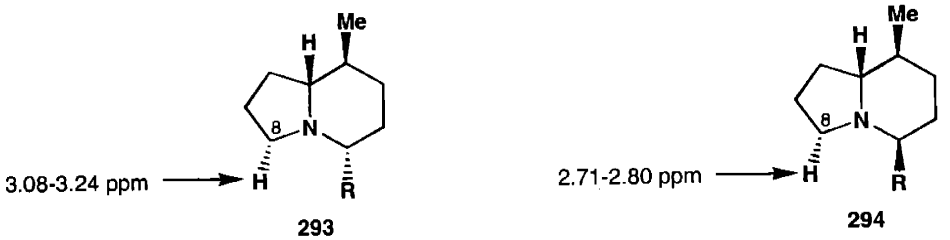
[152] Employing less LDA led to recovered starting material.

Under optimized conditions, the crude alkylated product was treated with $NaBH_3CN$ and acetic acid to afford **302** in very good overall yield from **214** (eq 65). The time required for the reduction of **214** (20 h) is significantly longer than the time required for the reduction of the more substituted α-amino nitrile **301** (1 h).



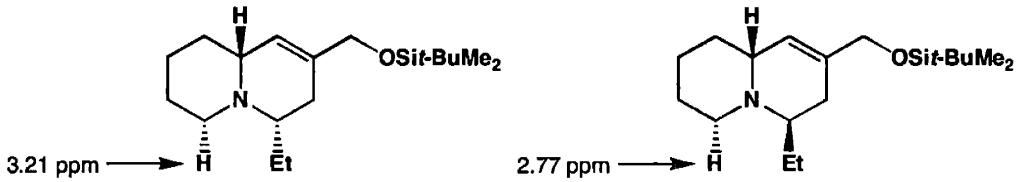
(65)

This suggests that ionization of the nitrile group in **301** is significantly easier than in **214**, which is not unexpected, considering that the reduction of **301** proceeds through a nitrogen-stabilized tertiary carbocation, and the reduction of **214** proceeds through a nitrogen-stabilized secondary carbocation. Quinolizidine **302** was isolated as a single diastereomer, and the ethyl group was assigned as equatorial (endo) based on NMR analysis and comparison with the spectra previously reported by Polniaszek and Belmont[144] for related compounds as shown below. Polniaszek and Belmont employed a series of NOE and other NMR experiments to determine the relative configuration of **293** and **294**.

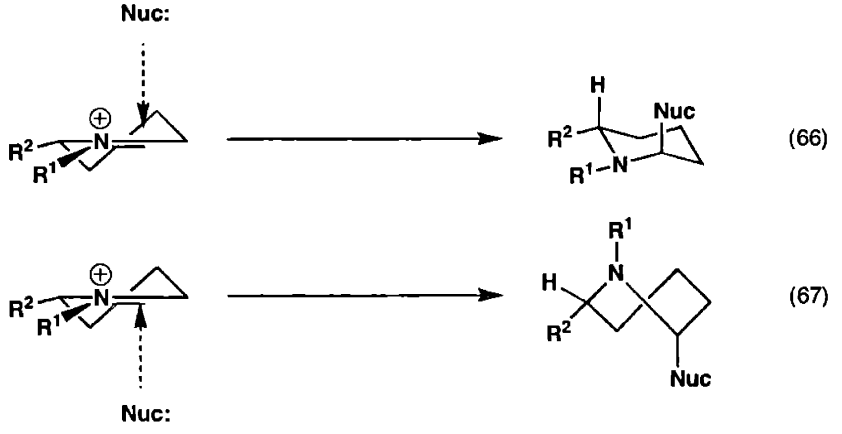


Quinolizidine **302** displays a resonance at 3.21 ppm in the ^1H NMR spectrum, assigned to the equatorial proton at C-9 of the quinolizidine. This assignment was further strengthened when the spectrum of **302** was compared to the ^1H NMR spectrum for the

diastereomeric compound with an axial ethyl group (**303**), which displays the C-9 equatorial proton at 2.77 ppm. As shown below the signals for the equatorial protons α to the nitrogen in **302** and **303** correlate well with the observations of Polniaszek and Belmont.

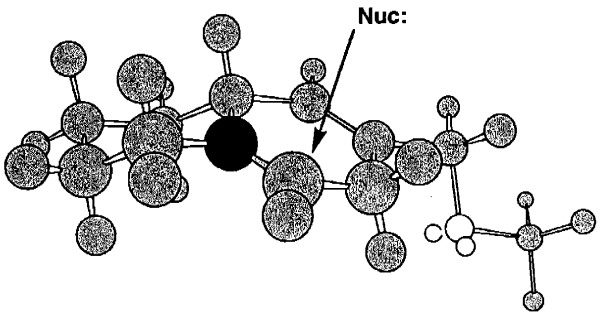


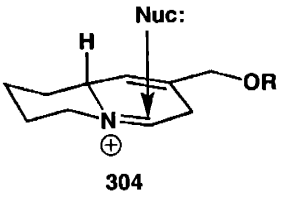
The equatorial ethyl group of **302** was also consistent with the predicted stereochemistry, based on axial delivery of hydride to the iminium ion. Stevens reported investigations of nucleophilic additions to tetrahydropyridinium salts.[153] During the course of several total syntheses of alkaloids, he noticed a strong preference for axial addition of nucleophiles to cyclic iminium ions via a chair-like transition state (eq 66). Axial addition to the bottom face of the iminium ion requires a boat-like transition state (eq 67).



[153] (a) Steven, R. V.; Lee, A. W. M. *J. Chem. Soc., Chem. Commun.* **1982**, 103. (b) Stevens, R. V. *Acc. Chem. Res.* **1984**, *17*, 289.

Our system is a bicyclic structure, and possibilities exist for several conformations of the intermediate iminium ion. Minimizing iminium ion **304** with Chem3D leads to the structure shown below with concave and convex faces. It was anticipated that the nucleophile would approach from the top (convex) face, affording the observed products.



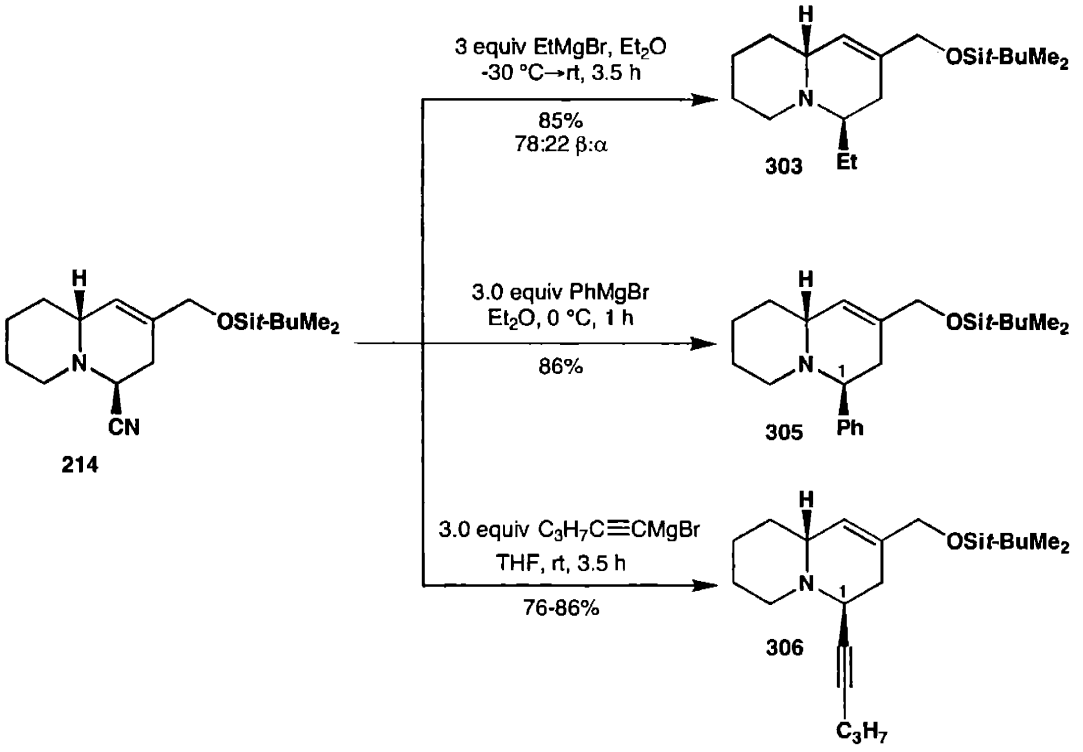


304

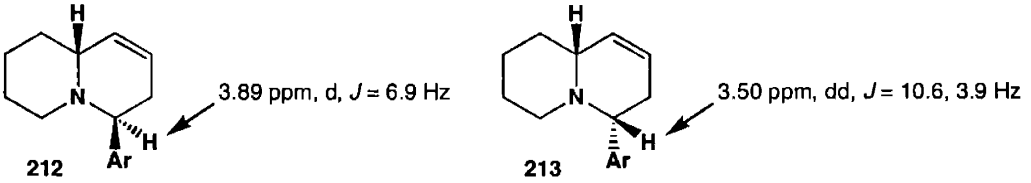
Bruylants Reaction

Efforts were next focused on converting cycloadduct **214** to the stereoisomeric quinolizidine **303**. This was accomplished by treatment of **214** with 3 equivalents of ethylmagnesium bromide in ether (Scheme 43). Quinolizidine **303** was isolated as a 78:12 mixture of β and α ethyl stereoisomers, with the minor isomer corresponding to **302**.

Scheme 43



Treatment of **214** with phenylmagnesium bromide afforded the expected phenyl substituted quinolizidine (**305**) as a single stereoisomer. Examination of the ^{1}H NMR spectrum of **305** indicates an axial orientation of the phenyl group as well. The C-1 proton appears in the ^{1}H NMR spectrum of **305** as a doublet with a coupling constant of 5.8 Hz, which is consistent with the reported coupling constants for **212** and **213**.[154]

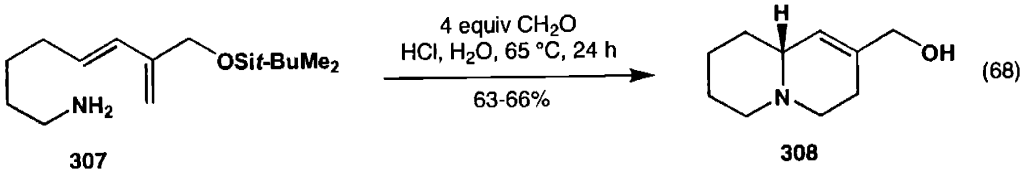


Reaction of quinolizidine **214** with 1-pentynlmagnesium bromide provided **306** as a single stereoisomer. The alkyne group is assigned as occupying an axially position based on the appearance of the C-1 proton in the ^{1}H NMR spectrum as a doublet with a

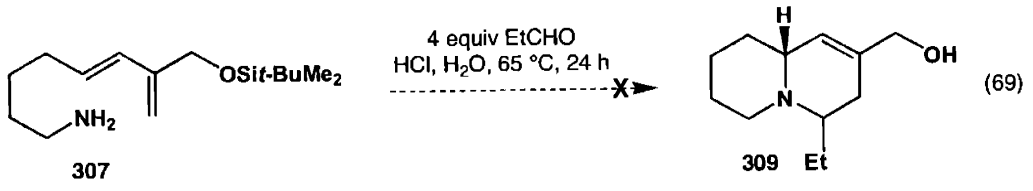
[154] Quick, J.; Khandelwal, Y.; Meltzer, P. C.; Weinberg, J. S. *J. Org. Chem.* **1983**, *48*, 5199.

coupling constant of 4.9 Hz. The ^{1}H NMR spectra for **305** and **306** are also similar in appearance to those obtained for cycloadducts containing an axial nitrile group.

The availability of substituted quinolizidines **302-306** 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. Grieco has reported that whereas iminium ions derived from formaldehyde undergo the desired cycloaddition, in the case of iminium ions derived from acetaldehyde "the reaction rate was substantially retarded. and the number of byproducts were significantly increased."[155] To obtain further data on the scope of the Grieco iminium ion Diels-Alder reaction, we investigated the reactions shown in eq 68 and 69. As expected, the formiminium ion derived from **307** afforded the expected cycloadduct in good yield. However, the analogous reaction of **307** and propionaldehyde failed to deliver the expected cycloadduct and instead resulted in a complex mixture of products (eq 69). In contrast, as discussed above, our iminoacetonitrile cycloaddition strategy not only provides access to substituted quinolizidines such as **309**, but also allows us to selectively generate either of the two stereoisomers.



307 **308** (68)



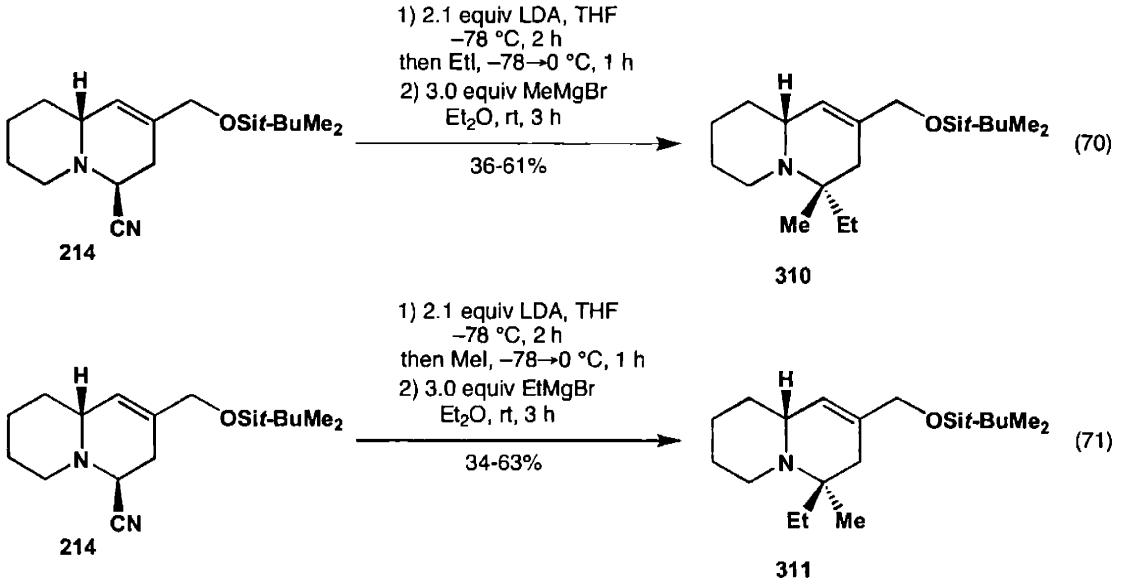
307 **309** (69)

[155] Larsen, S. D.; Grieco P. A. *J. Am. Chem. Soc.* **1985**, *107*, 1768.

It is important to note that George Wang and coworkers have demonstrated that benzaldehyde and several aliphatic aldehydes can be employed in *inter*molecular cycloadditions of iminium ions when the reaction is carried out in the presence of certain lanthanide triflates.[156] However, Wang does not report examining the *intra*molecular cycloaddition reaction of iminium ions.

Synthesis of Quinolizidines with Quaternary Centers

It was expected that by using a combination of alkylation chemistry and the Bruylants reaction, stereoisomeric quinolizidines with quaternary centers could be prepared with a high degree of stereocontrol. In the event, alkylation of **214** with ethyl iodide followed by treatment of the product with methylmagnesium bromide afforded quinolizidine **310** as a single stereoisomer (eq 70). As shown in eq 71, the diastereomer **311** was prepared by quenching the metallated nitrile with methyl iodide and subsequent reaction of the alkylated α-amino nitrile with ethylmagnesium bromide.



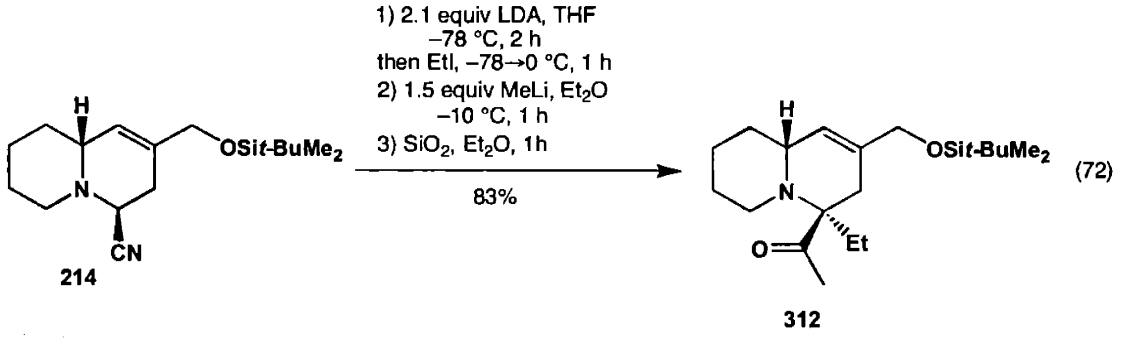
[156] Yu, L.; Chen, D.; Wang, P. G. *Tetrahedron Lett.* **1996**, *37*, 2169.

The range in yields shown in eq 70 and 71 resulted from of difficulties encountered in scaling up the reaction. When carried out on small scale (<100 mg), both reactions afforded the desired product in 61-63% overall yield. Carrying out the Bruylants reaction on larger scale (>150 mg) led to lower and more variable yields (35-45%), with recovery of more of the unreacted alkylated α-amino nitrile. Longer reaction times led to lower yields and decomposition of starting material. Exploration of several variables (temperature, addition of Lewis acids, and quantity of Grignard reagent employed) have thus far failed to provide a reproducible procedure for the large scale preparation of **310** and **311**.

The stereochemical assignments of the quaternary centers in **310** and **311** are based on the observed resonances for the methyl groups in the ^{1}H NMR spectrum. The protons of the methyl group in quinolizidine **311** are shifted downfield (1.10 ppm vs 0.88 ppm) relative to the protons in the methyl group of **310**. 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. Chapter 1 of Part III of this thesis discusses this concept with regards to axial and equatorial protons. This assignment is consistent with axial delivery of the Grignard nucleophile to the top face of the iminium ion as previously discussed.

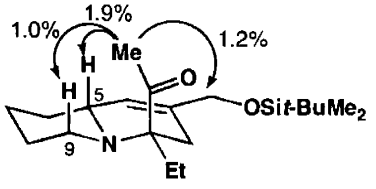
Quinolizidine **214** was transformed into α-amino ketone **312** by exploiting the nucleophilic character of a metalated amino nitrile and the reactivity of the nitrile group itself. Alkylation of **214** afforded **301**, which without purification was treated with methyllithium to provide the expected imine. Stirring an ether solution of the crude

imine and silica gel at rt effected the hydrolysis of the imine, affording **312** in good yield and as a single stereoisomer (eq 72).

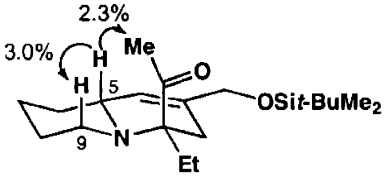


(72)

The cyano group of alkylated α-amino nitrile **301** (the intermediate in the synthesis of **312**) was anticipated to be axially disposed due to the anomeric effect, and thus ketone **312** should have the stereochemistry shown in eq 71. Employing difference NOE and NOESY experiments allowed for an unambiguous assignment of the stereochemistry of **312**. Irradiation of the acetyl methyl group produced NOE enhancements at the axial protons on C-5 and C-9, as well as the siloxymethyl group. In addition, irradiation of the C-5 hydrogen afforded enhancements at the acetyl group and the C-9 axial proton.



NOE enhancements for **312**



NOE enhancements for **312**

The preceding three reaction sequences take advantage of all three reactive characteristics of α-amino nitriles. The alkylation of **214** employs the nucleophilic character of metalated α-amino nitriles, while the Bruylants reaction exploits the latent iminium ion character present in this functional group, and the formation of ketone **312**

demonstrates the electrophilicty of the cyano group. Deploying the appropriate tactics in the correct sequence allows the incorporation of different functional groups with complementary stereochemistry.

Cation-π Cyclization

As discussed in the introductory section of this chapter, α-amino nitriles have been used as iminium ion precursors in cation-π cyclization reactions,[157] and we hoped to develop a tandem Diels-Alder cycloaddition/cation-π cyclization sequence to effect the rapid assembly of polycyclic molecules. Quinolizidine **221** contains an electron rich aryl group that can serve as a nucleophile in a cation-π type cyclization reaction, and this cycloadduct was prepared with the aim of using it to explore the possibility of effecting iminium ion cyclizations of the type outlined in Scheme 44. Examination of a variety of conditions, varying solvent, temperature, and Lewis acid, did not identify conditions to effect the desired transformation, and all attempts resulted in recovery or decomposition of starting material. Examination of models reveals a large amount of steric congestion in the transition state required for the cyclization.

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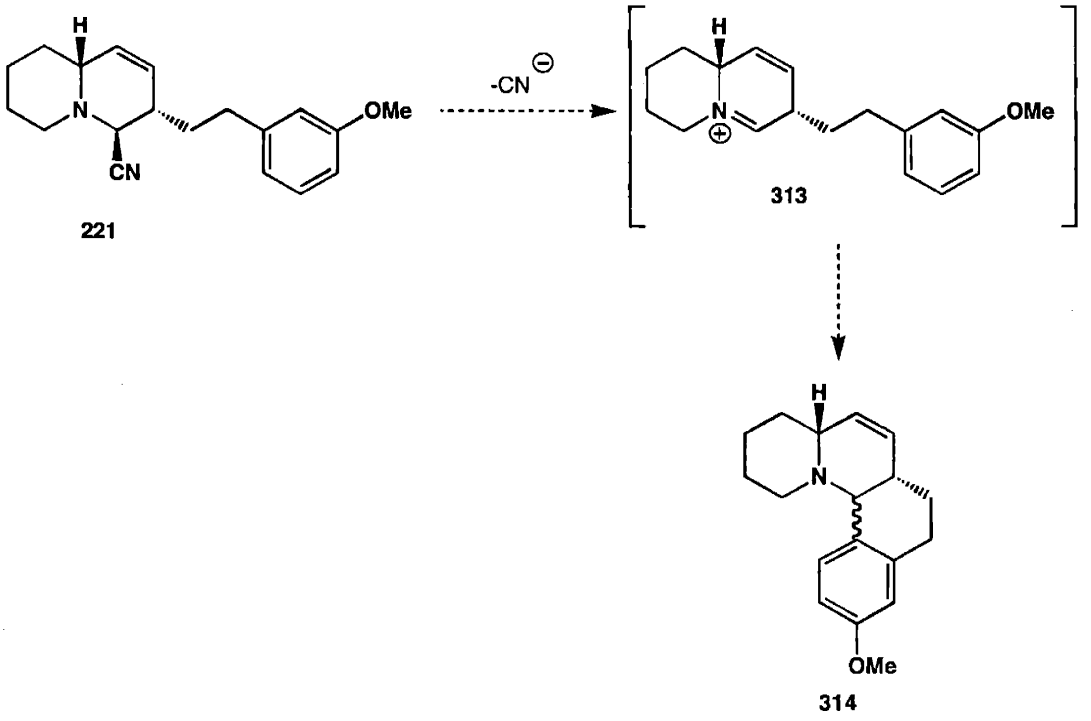
[157] (a) Fry, E. M.; Beisler, J. A. *J. Org. Chem.* **1970**, *35*, 2809. (b) Bonjoch, J.; Casamitjana, N.; Gracia, J.; Bosch, J. *Tetrahedron Lett.* **1989**, *30*, 5659. (c) Santamaria, J.; Kaddachi, M. T.; Ferroud, C. *Tetrahedron Lett.* **1992**, *33*, 781. (d) Lounasmaa, M.; Miettinen, J.; Hanhinen, P.; Jokala, R. *Tetrahedron Lett.* **1997**, *38*, 1455.

Scheme 44



Mannich Reactions

Iminium ions also serve as useful electrophilic partners in other carbon-carbon bond forming reactions, such as the Mannich reaction.[158] We were interested in exploring the intermolecular Mannich reaction between the iminium ion derived from **214** and a silyl enol ether.[159] Other research groups have reported examples of intermolecular 1,4-additions of silyl enol ethers to iminium ions derived from α-amino nitriles,[160] as well as intramolecular Mannich reactions of α-amino nitriles with ketones.[161] Our initial efforts

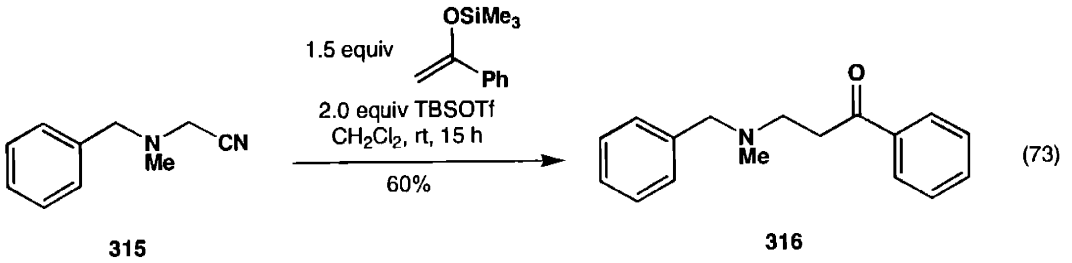
[158] For a review, see: Kleinman, E. F. In *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I., Eds.; Pergamon Press: Oxford, 1991, Vol. 2, pp 893-951.

[159] For examples, see: (a) Holy, N.; Fowler, R.; Burnett, E.; Lorenz, R. *Tetrahedron* **1979**, *35*, 613. (b) Danishefsky, S.; Prisbylla, M.; Lipisko, B. *Tetrahedron Lett.* **1980**, *21*, 805.

[160] (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.

[161] Bonjoch, J.; Casamitjana, N.; Gracia, J.; Bosch, J. *Tetrahedron Lett.* **1989**, *30*, 5655.

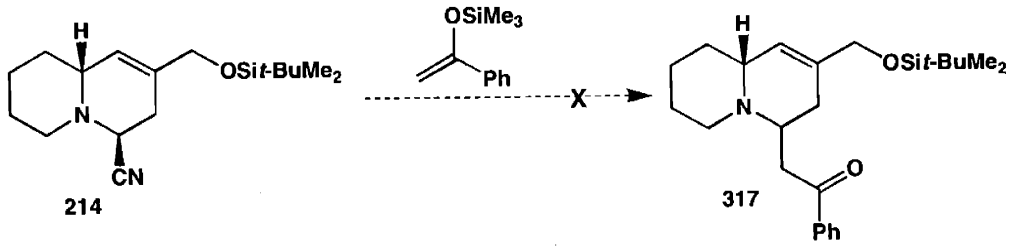
employed model studies with α-amino nitrile **315**, prepared by alkylating *N*-methylbenzylamine with bromoacetonitrile. Treatment of **315**with TBSOTf and the trimethylsilyl enol ether of acetophenone afforded **316** in an unoptimized yield of 60% (eq 73). Excess enol ether was employed, as the major side reaction is the desilylation of the nucleophilic enol ether.



(73)

315 **316**

Unfortunately, applying these conditions to the Mannich reaction of quinolizidine **214** afforded only recovered starting material and acetophenone (eq 74). Examining a range of reaction solvents and Lewis acids failed to identify conditions to effect the desired transformation.



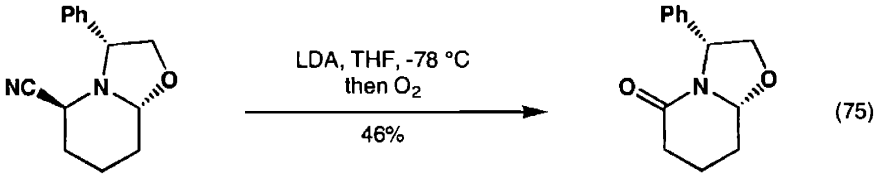
(74)

214 **317**

Relative to the iminium ion derived from **315**, the iminium ion derived from **214** suffers from either decreased electrophilic character or steric congestion, leading to a lack of reactivity in the Mannich reaction, as well as the cation-π cyclization reaction.

Oxidation of α-Amino Nitrile Cycloadducts

We next turned our attention to identifying conditions to effect the oxidation of α-amino nitrile **214** to the corresponding lactam. The oxidation of aliphatic nitriles to the corresponding ketones is a well-known reaction, and there are a number of examples of the oxidation of α-amino nitriles to amides.[162] Husson and Royer reported an example related to our proposed reaction in which they treated 2-cyano-6-oxazolopiperidine (**239**) with LDA and molecular oxygen,[163] isolating lactam **318** in 46% yield, along with recovered starting material (eq 75).



(75)

239 **318**

Applying Husson's conditions, treatment of **214** with LDA and molecular oxygen afforded only recovered starting material and a complex mixture of products. Employing other bases (NaH, *t*-BuOK, KHMDS) also failed to deliver the desired lactam. Treatment of the metallated nitrile (lithium and potassium) with Davis' oxazirdine[164] afforded a complex mixture of products, along with recovered starting material. Applying Fukuyama's protocol, *m*CPBA and potassium hydroxide, afforded only a complex mixture of products, none of which appeared to be the desired product or to contain an

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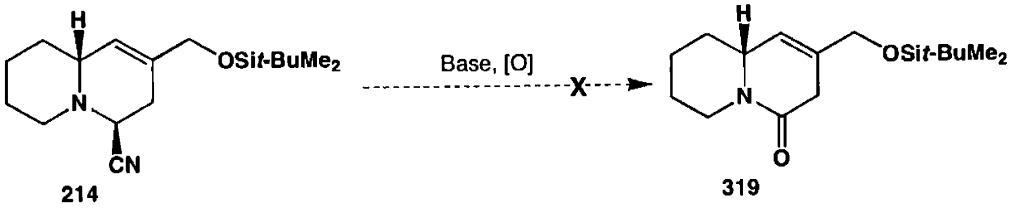
[162] For examples, see: (a) Thomas, O. P.; Zaparucha, A.; Husson, H.-P. *Eur. J. Org. Chem.* **2002**, 157. (b) Yokoshima, S.; Kubo, T.; Tokuyama, H.; Fukuyama, T. *Chem. Lett.* **2002**, 122. (c) Yuste, F.; Origel, A. E.; Brena, L. *Synthesis* **1993**, *36*, 1493. (d) Takahashi, H.; Iguchi, M.; Onda, M. *Chem. Pharm. Bull.* **1985**, *33*, 4775. (e) Ishii, H.; Chen, I.-S.; Ueki, S.; Akaike, M.; Ishikawa, T. *Chem. Pharm. Bull.* **1987**, *35*, 2717. (f) Ishikawa, T.; Takami, A.; Abe, M.; Chen, I.-S.; Harayama, T.; Ishii, H. *Chem. Pharm. Bull.* **1995**, *43*, 766.

[163] Royer, J.; Husson, H.-P. *Heterocycles* **1993**, *36*, 1493.

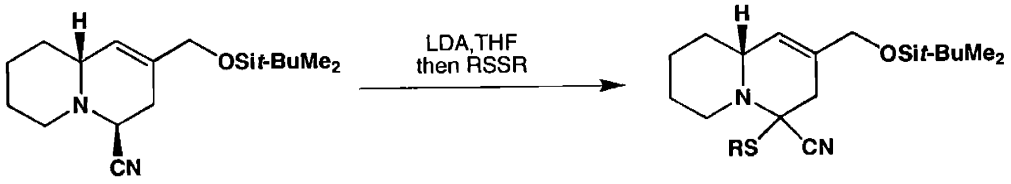
[164] (a) Davis, F. A.; Chattopadhyay, S.; Towson, J. C.; Lal, S.; Reddy, T. *J. Org. Chem.* **1988**, *53*, 2087. (b) Vishwakarma, L. C.; Stringer, O. D.; Davis, F. A. *Org. Synth.* **1988**, *66*, 203.

epoxide. It may still be worthwhile to examine these conditions using a substrate in which the alkene has first been removed by hydrogenation.



214 319 (76)

Our efforts then focused on a two-step oxidation procedure. Metallation of **214** and subsequent alkylation was quite successful, so we examined the installation of a heteroatom at the C-1 position. Based on the work with ketene equivalents in the Diels-Alder reaction,[165] we were interested in the use of α-thio and α-halo nitriles as precursors to the amide functionality. As shown in eq 77, we briefly explored the preparation of both the thiomethyl and thiophenyl derivatives. The α-amino, α-thio nitriles proved to be unstable and decomposed upon purification. Attempts to hydrolyze the crude compounds to the corresponding amide were unsuccessful.



214

320 R = Ph
321 R = Me

(77)

Summary

Employing iminoacetonitriles in cycloaddition reactions provides access to α-amino nitriles, and as is shown in this chapter, α-amino nitriles undergo a variety of useful synthetic transformations. These transformations take advantage of both the

[165] Aggarwal, V. K.; Ali, A.; Coogan, M. P. *Tetrahedron* **1999**, *55*, 293.

electrophilic and nucleophilic character of α-amino nitriles, along with the reactivity of the nitrile group. Our examination of the previously described transformations provided a better understanding of the reactivity of our α-amino nitrile cycloadducts, enabling us to begin applying this methodology to the total synthesis of naturally occurring alkaloids.

Chapter 2

Application of the Iminoacetonitrile Cycloaddition to the Total Synthesis of Natural Products

As shown in the previous chapter, cycloaddition reactions of iminoacetonitriles provide access to cyclic α-amino nitriles, which are versatile compounds that are amenable to further synthetic transformations. This chapter describes our initial efforts at applying the methodology described in this thesis to the total synthesis of alkaloids.

Lythraceae Alkaloids

The Lythraceae alkaloids are a class of alkaloid natural products, most of which contain a 1-arylquinolizidine substructure.[166] First isolated in 1978 by Fuji and co-workers,[167] these alkaloids have been the focus of significant synthetic work. The three compounds shown below are of particular interest to us because of the potential to prepare these compounds via intramolecular cycloaddition reaction of an iminoacetonitrile and subsequent elaboration of the resulting α-amino nitrile cycloadduct. Myrtine does not contain a 1-arylquinolizidine substructure, but instead posseses a methyl substituent at the C-1 position. Lasubine I and subcosine I both contain a 1-arylquinolizidine core and differ only at the C-3 position, with the conversion of lasubine I to subcosine I accomplished by acylation of the C-3 alcohol.

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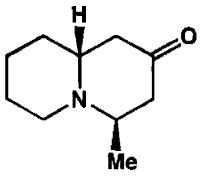
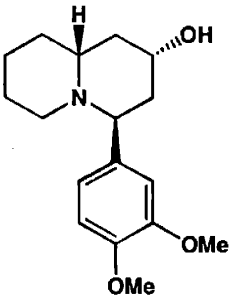
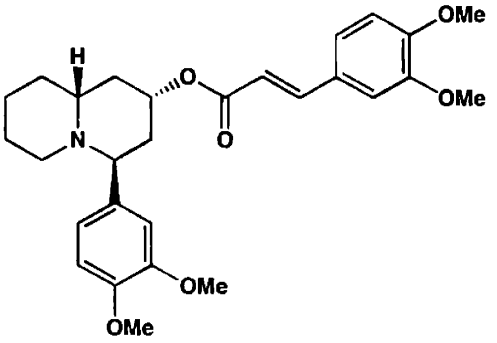
[166] Elbein, A. D.; Molyneus, R. J. In *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Eds.; Wiley: New York, 1987; Vol. 5, Chapter 1.
[167] Fuji, K.; Yamada, T.; Fujita, E.; Murata, H. *Chem. Pharm, Bull.* **1978**, *26*, 2515.



(+)-Myrtine



(–)-Lasubine I



(+)-Subcosine I

Previous Syntheses

Six previous total syntheses of myrtine have been reported,[168] only one of which provides enantiopure material.[169] Many of the synthetic approaches suffer from poor selectivity in creating the cis-relationship between the axial proton at the ring juncture and the C-1 methyl group. Of the reported syntheses, two deserve further examination. Pilli and coworkers have reported a short synthesis of myrtine, which also exhibits good stereocontrol.[168e] Commencing from lactam **322**, reduction of the amide carbonyl with $NaBH_4$ in ethanol provided ethoxy aminal **323**. Treatment of carbamate **323** with 2-trimethylsiloxy-1,3-pentadiene[170] and TMSOTf afforded, after basic workup, racemic myrtine and 4-*epi*myrtine in an 85:15 ratio (eq 78). Pilli's synthesis is the shortest reported synthesis of myrtine and also displays good selectivity for the β-methyl group.

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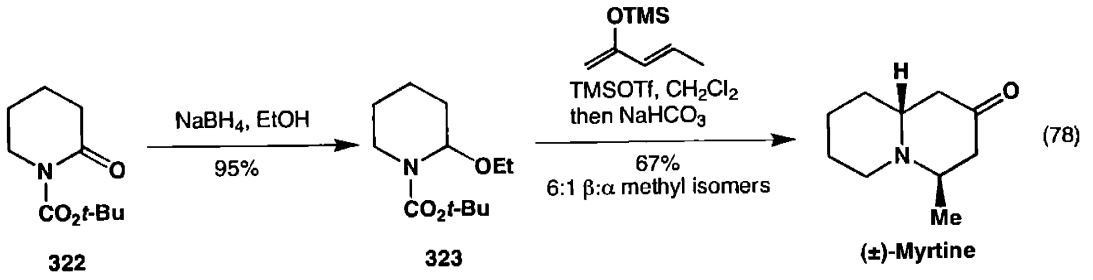
[168] (a) Slosse, P.; Hootelé, C. *Tetrahedron* **1981**, *37*, 4287. (b) King, F. D. *J. Chem. Soc., Perkin Trans. I* **1983**, *24*, 3281. (c) Comins, D. L.; LaMunyon, D. H. *Tetrahedron Lett.* **1989**, *30*, 5053. (d) Beckwith, A. L. J.; Joseph, S. P.; Mayadunne, R. T. A. *J. Org. Chem.* **1993**, *58*, 4198. (e) Pilli, R. A.; Dias L. C.; Maldaner, A. O. *J. Org. Chem.* **1995**, *60*, 717.

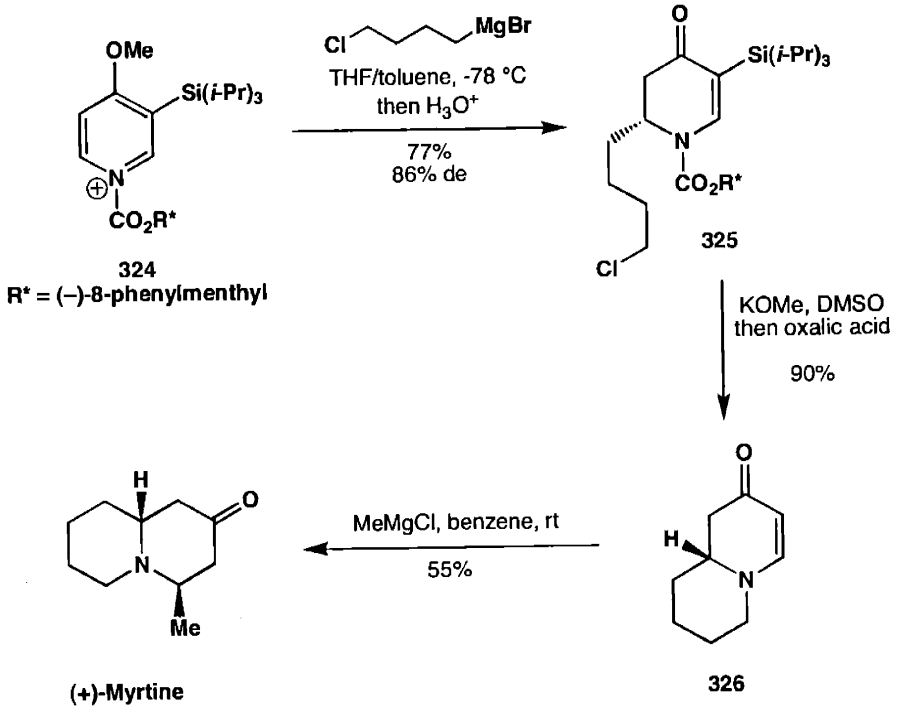
[169] Comins, D. L.; LaMunyon, D. H. *J. Org. Chem.* **1992**, *57*, 5807.

[170] Prepared *in situ* and used immediately in the annulation step.



Daniel Comins has reported two different syntheses of myrtine, one providing racemic alkaloid[168c] and the other leading to non-racemic product.[169] Both syntheses rely on a similar strategy, so only the enantiomeric variant is discussed here (Scheme 45). Treatment of 1-acylpyridinium salt **324**[171] with 4-chloro-1-magnesium bromide, followed by acidic hydrolysis, afforded diastereomerically pure carbamate **325** in good yield after removal of the minor diastereomer by column chromatography.

Scheme 45

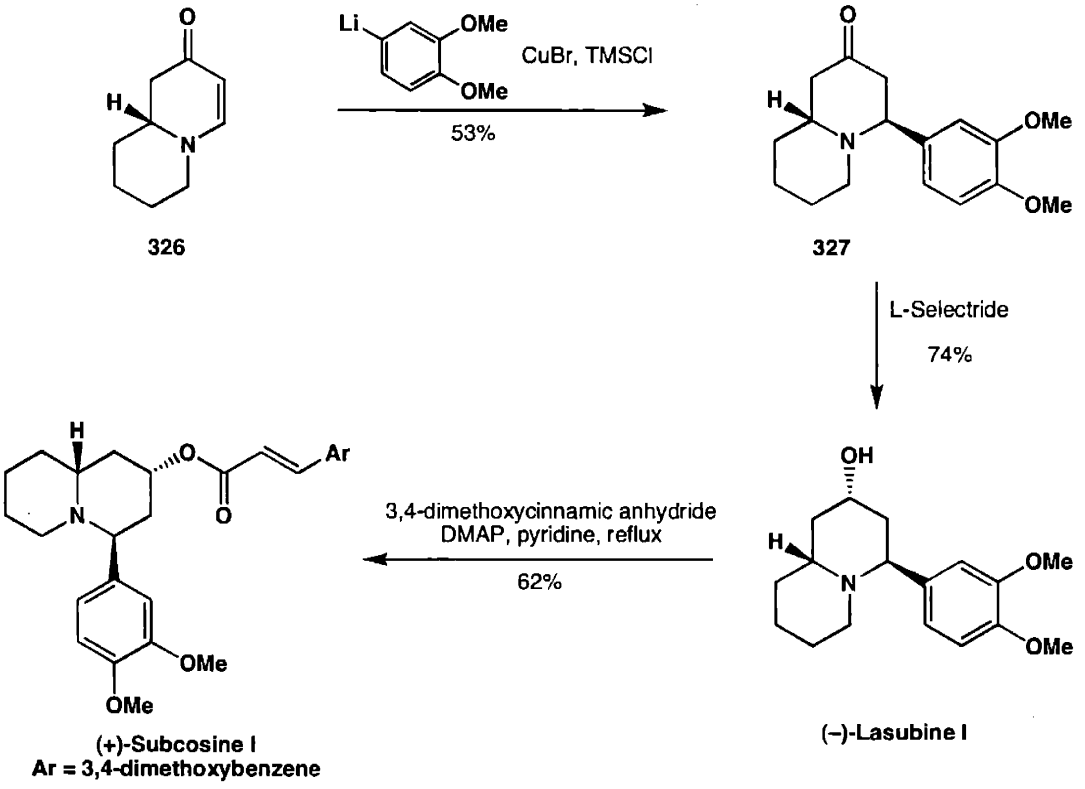


[171] Comins, D. L.; Goehring, R. R.; Joseph, S. P.; O'Connor, S. *J. Org. Chem.* **1990**, *55*, 2574.

Enantiopure **325** underwent loss of the carbamate group upon exposure to base, and a subsequent intramolecular alkylation afforded the cyclic core of myrtine. Proto-desilylation with oxalic acid provided vinylogous amide **326**, which afforded enantiopure myrtine upon treatment with methylmagnesium chloride. Comins' synthesis is the only enantioselective synthesis of myrtine and is also quite efficient (4-steps, including the preparation of **324**).

As shown in scheme 46, Comins has also employed intermediate **326** in his syntheses of (–)-lasubine I and (+)-subcosine I. Conjugate addition of an aryl cuprate reagent to **326** afforded a 90:10 mixture of stereoisomers, which upon purification provided **327** in 53% yield.

Scheme 46



Stereoselective reduction of ketone **327** with L-selectride supplied (–)-lasubine I, which upon acylation with 3,4-dimethoxycinnamic anhydride furnished enantiopure (+)-subcosine I.

Comins' strategy provides access to all three quinolizidine natural products with good stereocontrol and efficiency. There is only one other reported synthesis of subcosine I,[172] while there are several other syntheses of lasubine I,[173] of which two are enantioselective.[174] Some of the other approaches to the Lythraceae alkaloids are comparable in length to Comins' syntheses but suffer from lack of stereoselectivity, while others achieve good stereocontrol at the expensive of brevity. Comins' work excels in its efficiency *and* stereoselectivity.

Retrosynthetic Analysis

The three alkaloids presented above are attractive targets for the testing and further refinement of the methodology discussed in this thesis because all three natural products would be accessible from a common intermediate. As shown in Scheme 47, all three natural products contain the general structure of type **328**, accessed by treatment of **329** with a Grignard reagent (Bruylants reaction) and subsequent silyl enol ether hydrolysis. Quinolizidine **329** is the expected product of the intramolecular cycloaddition of iminoacetonitrile **330**, accessible by the elimination of sulfinate from triflamide **331**.

---

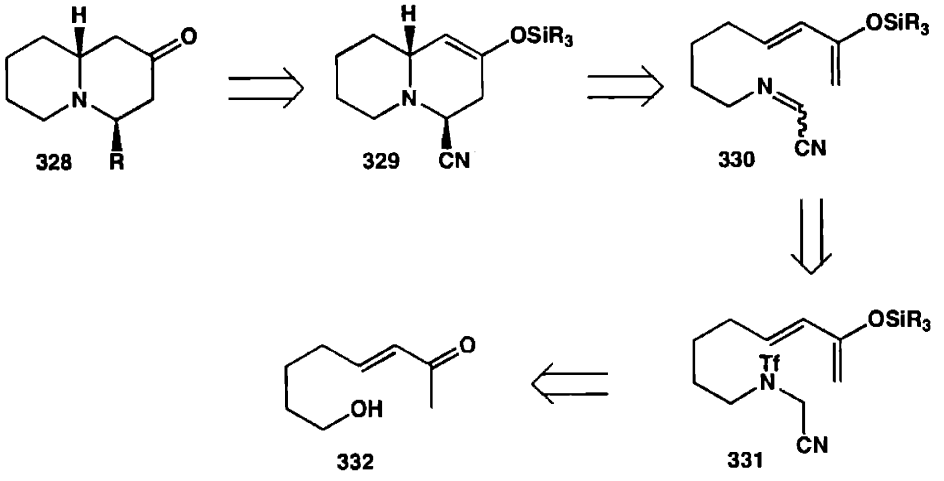
[172] Iida, H.; Tanaka, M.; Kibayashi, C. *J. Org. Chem.* **1984**, *49*, 1909.

[173] (a) Takano, S.; Shishido, K. *J. Chem. Soc., Chem. Commun.* **1981**, 940. (b) ref 172. (c) Ent, H.; de Koning, H.; Speckamp, W. N. *Heterocycles* **1988**, *27*, 237. (c) ref 168d. (d) Bardot, V.; Gardette, D.; Gelas-Mialhe, Y.; Gramain, J.-C.; Remuson, R. *Heterocycles* **1998**, *48*, 507.

[174] (a) Ratni, H.; Kündig, E. P. *Org. Lett.* **1999**, *1*, 1999. (b) Chalard, P.; Remuson, R.; Gelas-Mialhe, Y.; Gramain, J.-C. *Tetrahedron: Asymmetry* **1998**, *9*, 4361.

A Mitsunobu reaction between our triflamide reagent **114** and known enone **332**[175] should provide access to **331** upon subsequent silyl enol ether formation.

Scheme 47



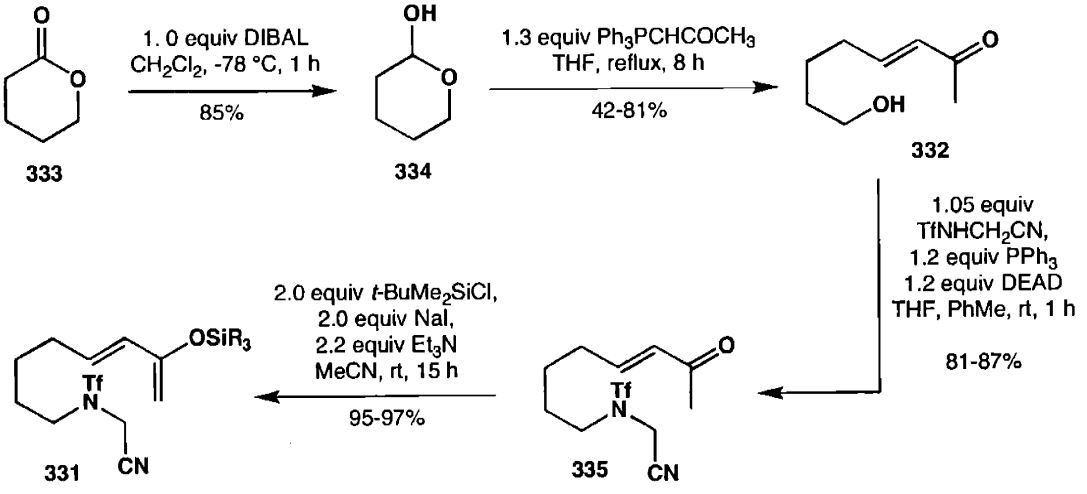
Preparation of α-Amino Nitrile Cycloadduct (329)

Mono-reduction of commercially available δ-valerolactone **333** with 1 equivalent of DIBAL afforded lactol **334**. Unfortunately, the literature report of the preparation of **332** provides few experimental details, so efforts were directed at optimizing the synthesis of **332**. Treatment of **334** with 1-triphenylphosphoranylidene-2-propanone, as shown in Scheme 48, provided the desired enone, although in somewhat variable yield. Addition of a catalytic amount of propionic acid[176] to the reaction mixture improved the yield of the reaction, but due to laborious purification large scale preparation of enone **332** proved tedious. Mitsunobu reaction of alcohol **332** afforded triflamide **335** in good yield after a non-trival purification. Separation of 1,2-dicarbethoxyhydrazine, the DEAD reduction product and triflamide **335** escalated in difficulty as the scale of the reaction

[175] Ihara, M.; Taniguchi, T.; Yamada, M.; Tokunaga, Y.; Fukumoto, K. *Tetrahedron Lett.* **1995**, *36*, 8071.
[176] Williams, D. R.; McGill, J. M. *J. Org. Chem.* **1990**, *55*, 3457.

increased. Despite purification difficulties encountered with the preparation of **335**, efforts were then directed at identifying conditions for the formation of silyl enol ether **331**. To avoid affecting the base-sensitive triflamide moiety, the mild conditions reported by Katz and co-workers[177] were employed, allowing the synthesis of silyl enol ether **331** to proceed in high yield. The four step sequence shown in Scheme 45 provided access to the desired dienyl triflamide but contained two steps that were viewed as potential bottlenecks for bringing up material: (1) Wittig olefination of lactol **334**, and (2) purification of the Mitsunobu reaction mixture. Employing a Horner-Wadsworth-Emmons reaction between **334** and an α-keto phosphonate may provide **332** more efficiently, but this olefination strategy was not explored due the difficulty encountered with the purification of **335**.

Scheme 48

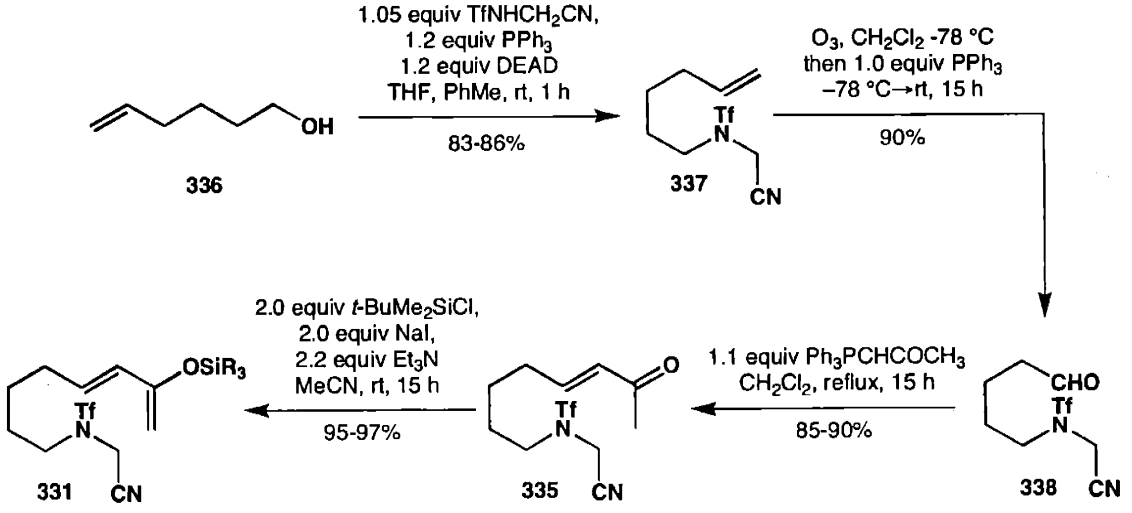


Because of difficulties encountered in the route depicted in Scheme 48, a second approach to dienyl triflamide **331** was developed. As shown in Scheme 49, commercially available 5-hexen-1-ol (**336**) reacted smoothly under standard Mitsunobu conditions to

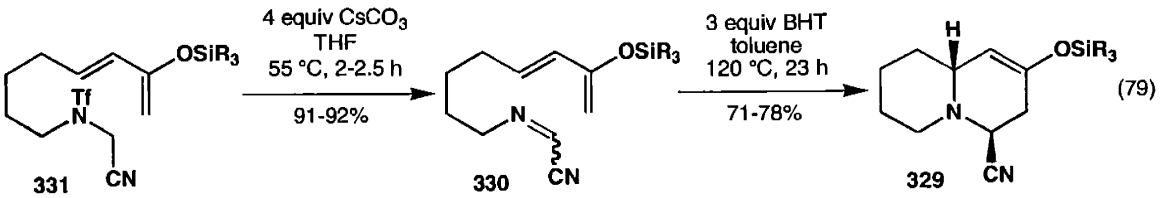
[177] Katz, T. J.; Liu, L.; Willmore, N. D.; Fox, J. M.; Rheingold, A. L.; Shi, S.; Nuckolls, C.; Rickman, B. H. *J. Am. Chem. Soc.* **1997**, *119*, 10054.

afford triflamide **337**. Cleavage of the double bond with ozone provided aldehyde **323**, which underwent Wittig olefination to afford *E*-enone **335** as the sole product. As previously discussed, silylation of intermediate **335** provided the substrate for the elimination reaction (**331**). The synthetic sequences in Schemes 48 and 49 both provided dienyl triflamide **331** in four steps, but the second approach proceeded with more reproducible yields as well as simplified purification.

Scheme 49



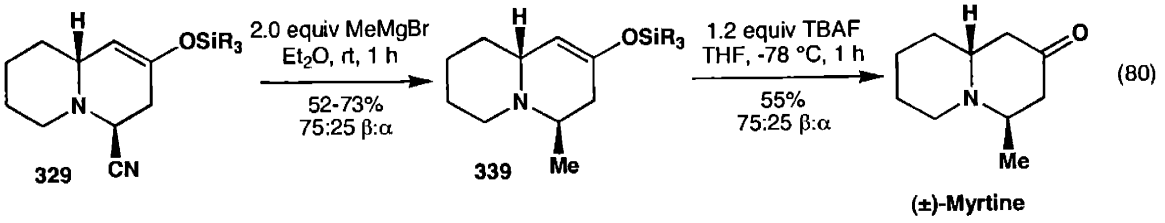
With the development of an efficient method for the preparation of **331**, efforts were then directed at converting triflamide **331** to cycloadduct **329** (eq 79). Elimination of trifluoromethansulfinate proceeded smoothly to afford iminoacetonitrile **330**, cycloaddition of this imine provided cycloadduct **329** in good yield and as a single stereoisomer. Based on its ^{1}H NMR spectrum, cycloadduct **329** contains an axially oriented nitrile group, as the C-1 proton appears as a doublet with a coupling constant of 5.5 Hz.



(79)

Endgame

With α-amino nitrile **329** in hand, efforts were initially directed at transforming cycloadduct **329** into myrtine. Bruylants reaction between **329** and methylmagnesium bromide afforded **339** in modest yield and as a mixture of isomers at C-1 (eq 80). In an effort to improve the ratio of isomers, the use of $MeTi(O\textit{i}\text{-}Pr)_3$ was examined but failed to deliver the desired product. Treatment of purified **339** with TBAF afforded a modest yield of racemic myrtine and *epi*-myrtine in a 75:25 ratio. In a subsequent run, reaction of **329** with 3.0 equiv of methylmagnesium bromide and then treatment of the crude product with 1.5 equiv of TBAF furnished (±)-myrtine in 33% overall yield after purification by column chromatography. It is known that myrtine can epimerize to form *epi*-myrtine where the methyl group occupies an equatorial position, however, this epimerization is very slow at rt and requires prolonged reflux in the presence of HCl or K_2CO_3.[168a] We observed no change in the ratio of isomers during the deprotection of **339**.

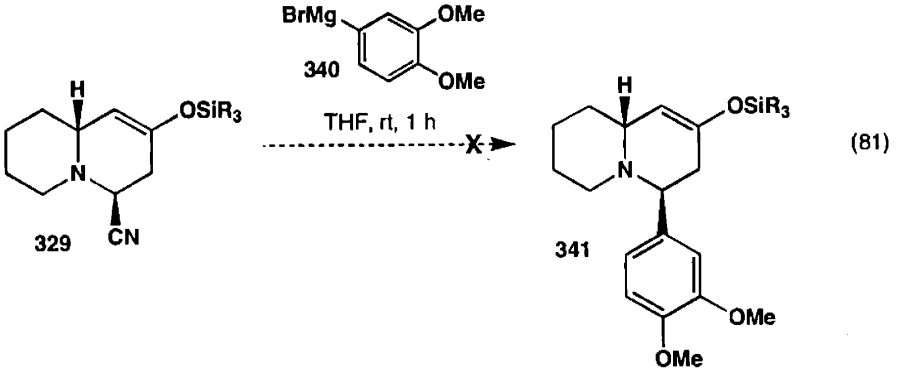


(80)

While the last two steps of this synthesis are disappointing and require further optimization, the [4+2] cycloaddition reaction of iminoacetonitrile **330** combined with α-

amino nitrile transformation chemistry provided access to the naturally occurring alkaloid myrtine.

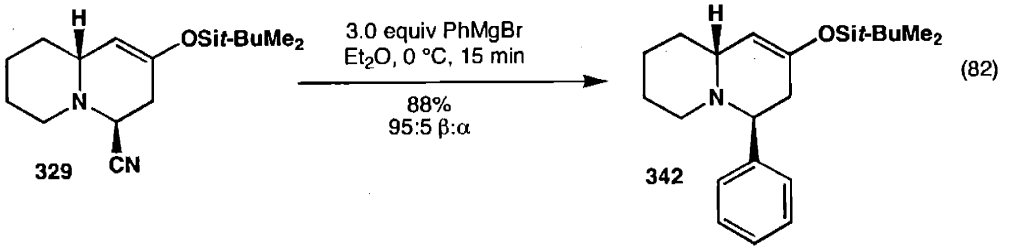
Efforts were then directed towards developing a synthesis of lasubine I and subcosine I. As discussed in the previous chapter, addition of ethylmagnesium bromide to α-amino nitrile **214** afforded a 78:22 mixture of products, not unlike the ratio observed with the reaction of methylmagnesium bromide and **329**. However, addition of phenylmagensium bromide to **214** provided the substituted product as a single diastereomer. We were hopeful that addition of an arylmagnesium compound to cycloadduct **314** would afford, with high diastereoselectivity, a precursor to lasubine I and subcosine I. Employing the Grignard reagent derived from 1-bromo-3,4-dimethoxybenzene, we hoped to expedite our synthesis of lasubine I and subcosine I by installing the fully adorned C-1 substituent in a single step. Commercially available Grignard reagent **340** is soluble in THF but not in diethyl ether, so the Bruylants reaction of **340** and **329** was carried out in THF. Unfortunately, the reaction did not afford the desired product, but instead returned starting material and a mixture of unidentifiable products (eq 81).



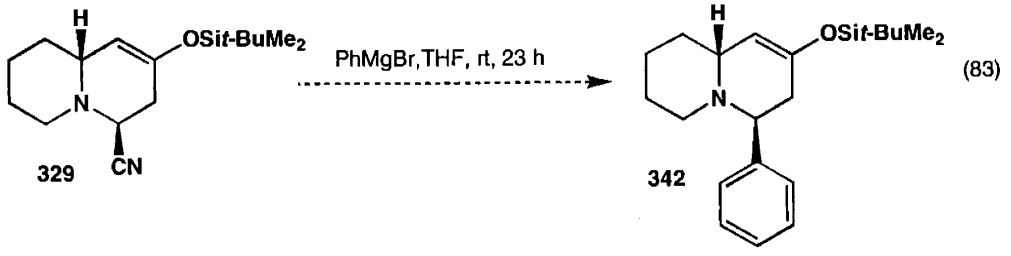
(81)

Varying the temperature and number of equivalents of nucleophile did not improve the reaction. Carrying out the reaction in the presence of Lewis acids led to a

complex mixture of products. In an effort to identify the problem, model studies with α-amino nitrile **329** were carried out with phenylmagnesium bromide. Treatment of **329**, as a solution in ether, with phenylmagnesium bromide afforded the expected product **342** in 88% yield and as a 95:5 mixture of diastereomers (eq 82). As shown in eq 83, when the same reaction was carried out employing THF as solvent, only half of the starting material was consumed after 23 h at room temperature. Not only was the reaction in THF significantly slower than the reaction in ether, but the reaction in THF also produced more byproducts.



(82)



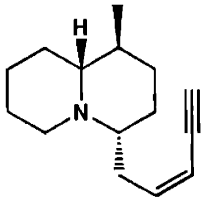
(83)

The results summarized in eq 82 and 83 suggest that utilizing THF as solvent in the reaction of **329** and **340** may be responsible for the observed lack of reactivity. The Lewis basicity of the oxygen atom in THF is greater than that of the oxygen atom in diethyl ether. A consequence of this may be tighter coordination of THF to the magnesium atom, decreasing the reactivity of the Grignard reagent and altering the reaction pathway. Unfortunately, employing other solvents, including dichloromethane, ether, and toluene, resulted in recovered starting material. A solution to this problem could involve employing a Grignard reagent that is soluble in ether, allowing the

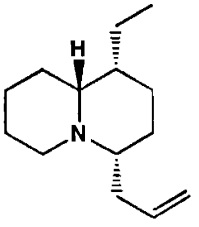
Bruylants reaction to be carried out in ether. Ideally the aryl group would be easily transformed with a minimal number of steps into the desired C-1 substituent. Further studies were not undertaken to explore this idea as efforts were turned towards the total synthesis of a second class of quinolizidine natural products.

1,4-Disubstituted Quinolizidine Natural Products

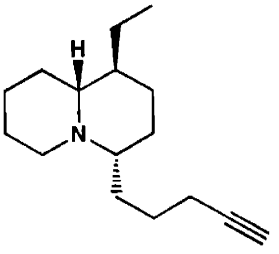
Natural product isolation efforts have identified a large number of biologically active alkaloids in the skin of poison frogs and toads,[178] and the great majority of these alkaloids consist of an azabicyclic structure, specifically pyrrolizidines, indolizidines, and quinolizidines. Several 1,4-disubstituted quinolizidines have been isolated recently from skin extracts of frogs and are believed to be dietary in origin. [179] This belief arises from the fact that many of "izidine" type alkaloids have also been detected in ants, which the Mantelline and Dendrobates frogs are known to eat.



217A



207I



233A

Successful application of our recently developed methodology to the synthesis of the above alkaloids could be of particular importance due to the lack of material isolated

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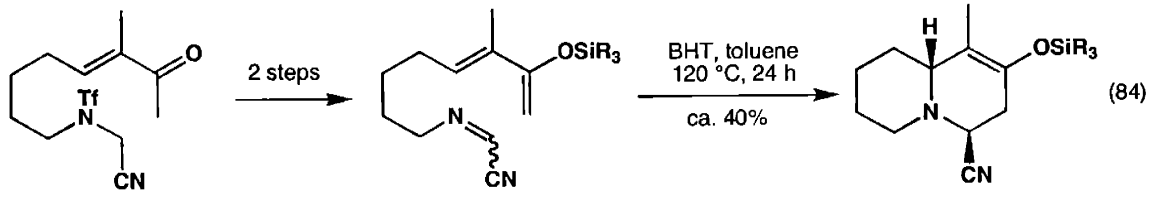
[178] (a) Daly, J. W.; Spande, T. F. In *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Wiley: New York, 1986; Vol. 4, pp 1-274. (b) Daly, J. W.; Garraffo, H. M.; Spande, T. F. In *The Alkaloids*; Cordell, G. A., Ed.; Academic Press: San Diego, 1993; Vol. 43, pp 185-288. (c) Daly, J. In *The Alkaloids*; Cordell, G. A., Ed.; Academic Press: New York, 1997; Vol. 50.

[179] (a) Garraffo, H. M.; Spande, T. F.; Daly, J. W.; Baldessari, A.; Gros, E. G. *J. Nat. Prod.* **1993**, *56*, 357. (b) Garraffo, H. M.; Caceres, J.; Daly, J. W.; Spande, T. F.; Andriamaharavo, N. R.; Andriantsiferana, M. *J. Nat. Prod.* **1993**, *56*, 1016. (c) Jain, P.; Garraffo, H. M.; Yeh, H. J. C.; Spande, T. F.; Daly, J. W.; Andriamaharavo, N. R.; Andriantsiferana, M. *J. Nat. Prod.* **1996**, *59*, 1174.

from natural sources. Originally based on data obtained from GC-HRMS and GC-IR experiments, the structures, and the stereochemistry, have recently been confirmed by total synthesis.[180,181] Unfortunately, the published total syntheses suffer from a lack of efficiency (20-30 steps) and are not practical enough to deliver significant quantities of material. The scarcity of material is one of the reasons the biological activity of these compounds has not been studied. By employing an intramolecular Diels-Alder cycloaddition of an iminoacetonitrile, we anticipate being able to access the bicyclic core of these 1,4-disubstituted quinolizidines in only 6-7 steps. With an α-amino nitrile functional handle, we can then elaborate the aforementioned cycloadducts into the fully adorned natural products. Thus, Kevin Maloney, a graduate student in our group, has synthesized the core of 217A (unoptimized at time of writing), employing the iminoacetonitrile cycloaddition shown in eq 84.



(84)

Previous Syntheses of 207I

Rassat and co-workers published the first total synthesis of 207I, producing racemic 207I in 21 steps.[181a] The length of this synthesis precludes it from providing useful quantities of material, but the synthesis displays good control of the relative stereochemistry. Rassat controls the stereochemistry by employing a 9-

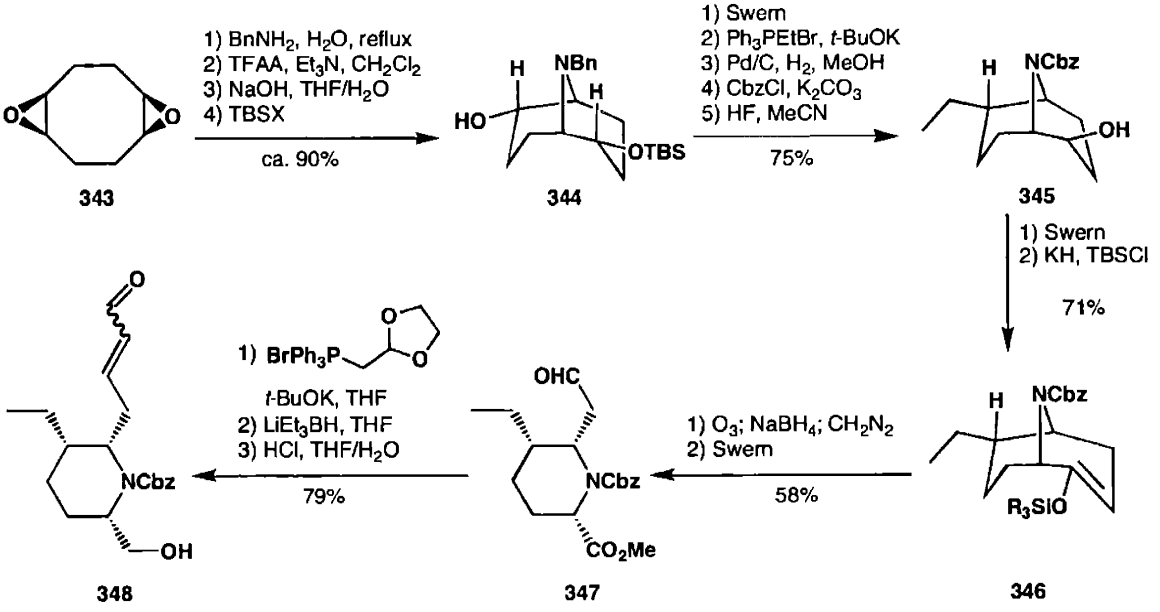
[180] For total syntheses of 217A, see: (a) Pearson, W. H.; Suga, H. *J. Org. Chem.* **1998**, *63*, 9910. (b) Huang, H.; Spande, T. F.; Panek, J. S. *J. Am. Chem. Soc.* **2003**, *125*, 626.

[181] For total syntheses of 207I, see: (a) Rassat, A.; Michel, P.; Daly, J. W.; Spande, T. F. *J. Org. Chem.* **2000**, *65*, 8908. (b) Nemoto, H.; Toyooka, N. *Tetrahedron Lett.* **2003**, *44*, 569.

azabicyclo[3.3.1]nonene derivative in a cyclic template strategy, cleaving an internal olefin to afford the right hand portion of 207I with all three stereocenters present. An intramolecular reductive amination reaction assembles the second ring, and then subsequent elaboration affords 207I.

As shown in Scheme 50, Rassat's synthesis commences with diepoxide **343**, which was converted to azabicyclo[3.3.1]nonane **344** as described in a previous publication.[182] Subjecting alcohol **344** to a series of functional group manipulations afforded carbamate **345**. This series of steps installed the C-1 ethyl group present in 207I, relying on the bicyclic structure to control the stereochemistry. Silyl enol ether **346** was prepared in 2 steps from **345** and then cleaved with ozone to afford, after functional group manipulations, piperidine **347**. Aldehyde **347** was converted to the reductive amination substrate **348** by homologation of the aldehyde, followed by reduction of the ester, and cleavage of the acetal.

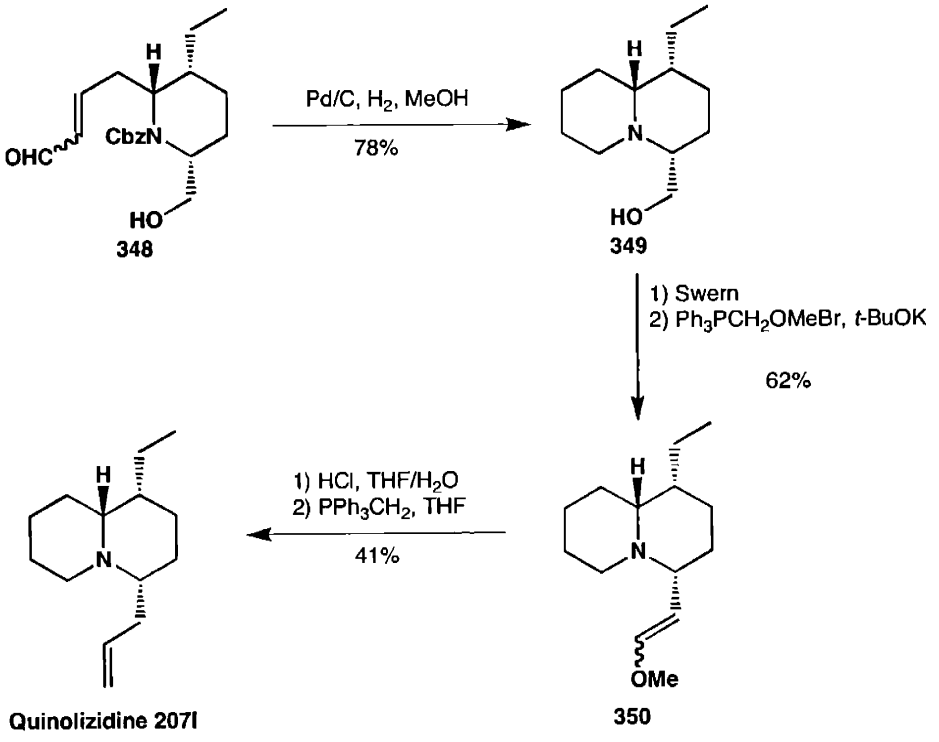
Scheme 50



[182] Michel, P.; Rassat, A. *J. Org. Chem.* **2000**, *65*, 2572.

Catalytic hydrogenation converted unsaturated aldehyde **348** to quinolizidine **349** in a cascade of reactions. The olefin and benzoyloxycarbonyl group were reduced by hydrogen, allowing the saturated aldehyde to react with the nitrogen of the piperidine ring. The newly formed cyclic iminium ion was then reduced *in situ*, providing alcohol **349**. Elaboration of the C-1 side chain provided the alkaloid natural product (Scheme 51). The route is fairly lengthy, especially considering the lack of complexity present in the molecule, but allowed the confirmation of the proposed structure.

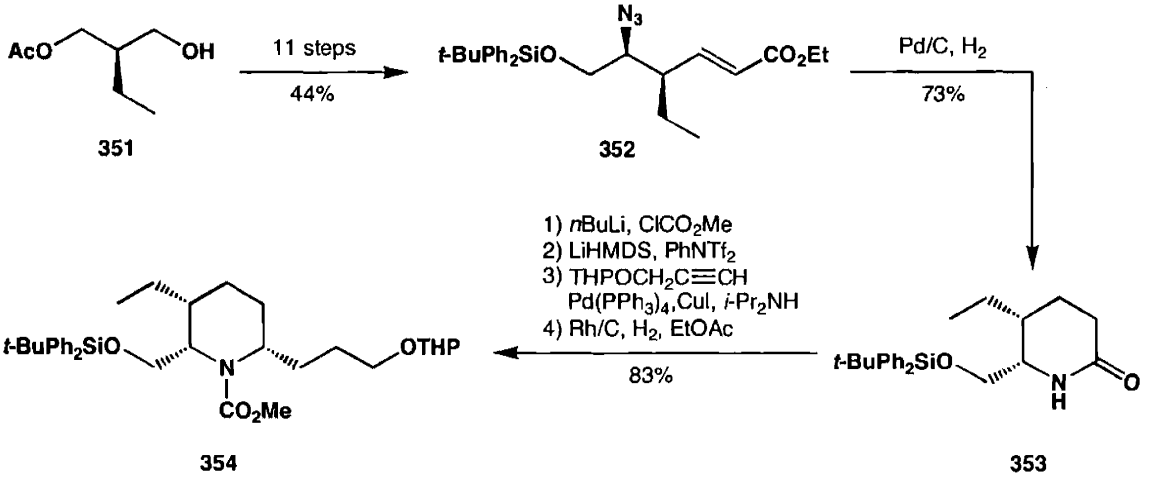
Scheme 51



Toyooka reported a total synthesis of 207I very recently,[180b] and although his route affords enantiopure material, it is even longer than Rassat's approach. Employing a similar strategy, Toyooka sets all three stereocenters on the right hand ring and then closes the second ring with an intramolecular alkylation.

As depicted in Scheme 52, enantiopure actetate **351**, prepared by enzymatic means,[183] was converted to azido ester **352** through a series of functional group manipulations and homologations.[184] Exposure to hydrogen and palladium on carbon reduced the azide and the olefin, with subsequent lactamization affording **353** in one step. The nitrogen of lactam **353** was protected and then triflation of the carbonyl group provided the intermediate vinyl triflate. Sonogashira cross-coupling of THP-protected propargyl alcohol afforded an enyne, which was reduced to piperidine **354**. The two stereocenters on the ring directed the hydrogenation to the top face of the olefin.

Scheme 52



With the three stereocenters set, the two side chains needed to be elaborated, one to an allyl group and the other to a precursor for the intramolecular alkylation. In the event, the siloxymethyl group was homologated by removal of the silyl group, oxidation, Wittig olefination, and catalytic hydrogenation to afford **355**. The right-hand side chain is converted into an allyl group (**356**) through a series of three reactions. Deprotection of

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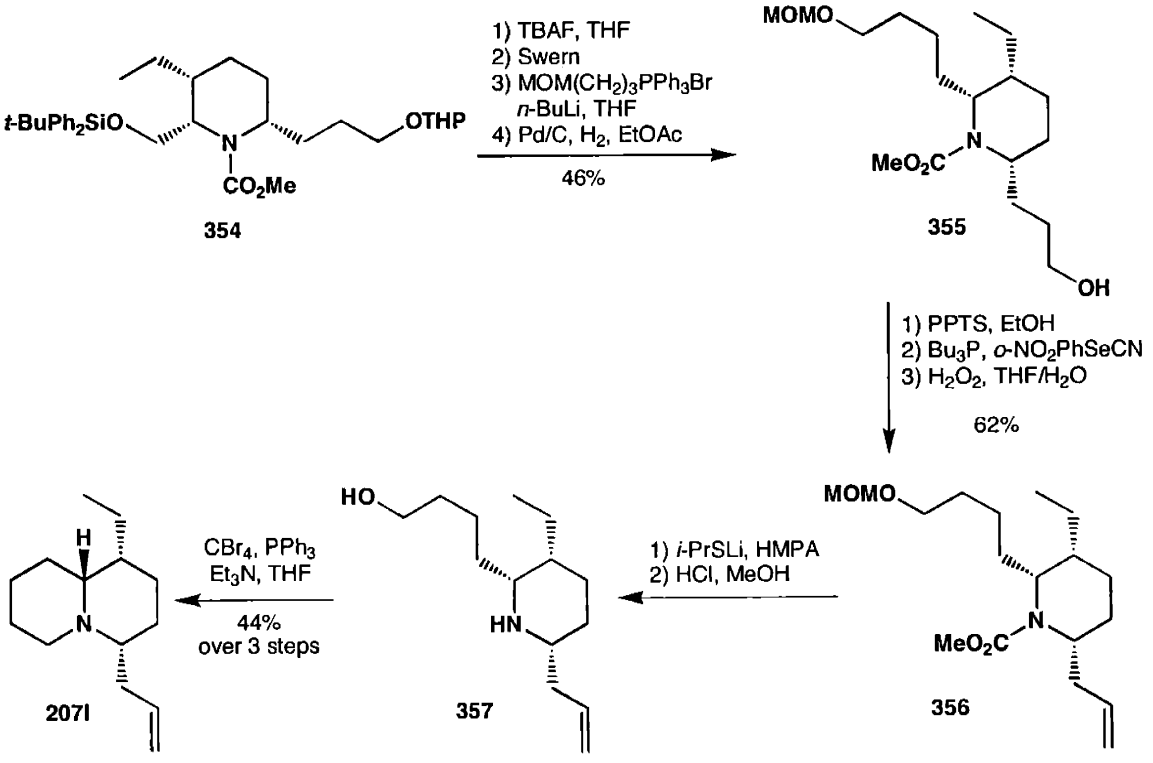
[183] Izquierdo, I.; Plaza, M. T.; Rodríguez, M.; Tamayo, J. *Tetrahedron: Asymmetry*, **1999**, *10*, 449.

[184] Toyooka, N.; Fukutome, A.; Nemoto, H.; Daly, J. W.; Spande, T. F.; Garraffo, H. M.; Kaneko, T. *Org. Lett.* **2002**, *4*, 1715.

the amine and alcohol affords amino alcohol **357**, which upon exposure to carbon tetrabromide and triethylamine provided 207I.

At 28 steps, this synthesis is quite lengthy and is not practical. The synthesis does deliver enantiomerically pure material and allows for the determination of the absolute stereochemistry, which is opposite of the material prepared by Toyooka. Unfortunately, neither this synthesis nor Rassat's is capable of providing useful quantities of 207I.

Scheme 53



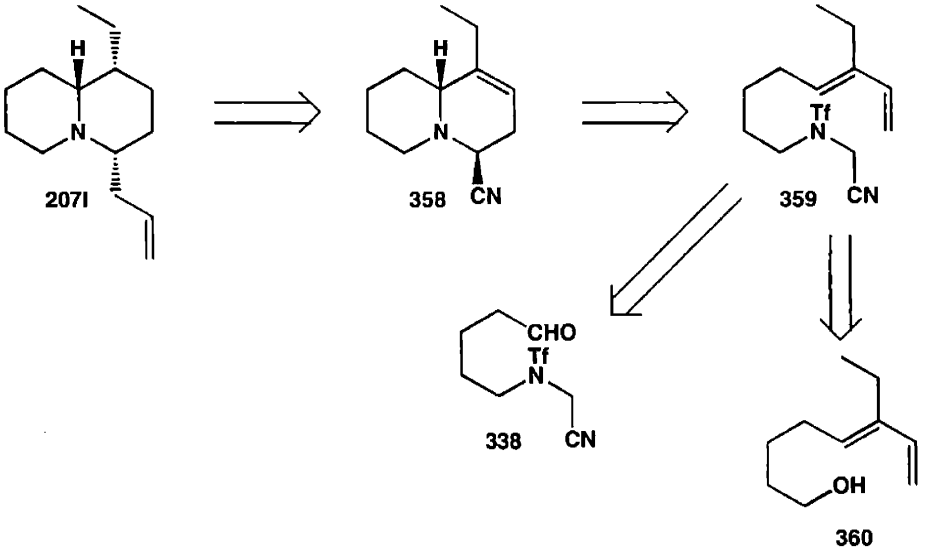
Retrosynthetic Analysis

The unmet need for useful quantities of 207I encouraged us to apply our iminoacetonitrile Diels-Alder chemistry to the synthesis of 207I. Our strategy is markedly different from the strategies employed by Toyooka and Rassat, as we propose

to assemble both rings of the quinolizidine core in a single step, as opposed to a stepwise process.

As shown in Scheme 54, we envisioned preparing quinolizidine 207I from α-amino nitrile **358**, employing hydrogenation of the top face of the olefin to set the stereochemistry of the ethyl group. Alkylation and then reduction of the α-amino nitrile moiety, as discussed in the previous chapter, would install the allyl group in an equatorial position. Cycloadduct **358** would be prepared from dienyl triflamide **359** using standard elimination and cycloaddition conditions. Triflamide **359**, in turn, can be prepared from either alcohol **360** or triflamide **338**, previously employed in our studies directed towards the total synthesis of the Lythraceae alkaloids.

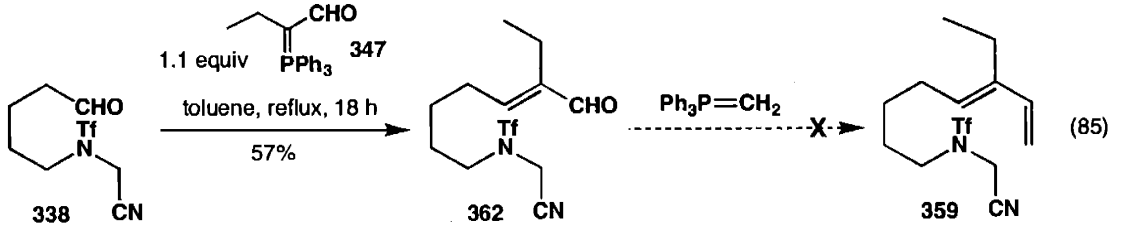
Scheme 54



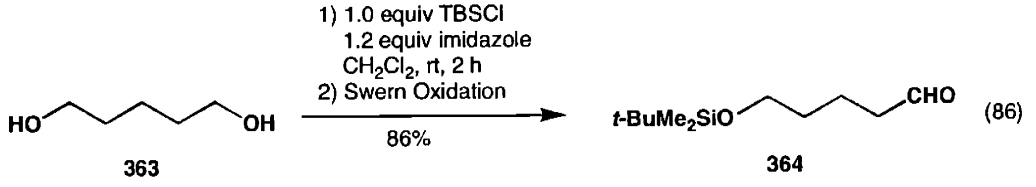
Efforts Directed Towards the Total Synthesis of 207I

Both potential routes have been investigated in an effort to identify the optimal approach. Treatment of aldehyde **338** with phosphorane **361** afforded unsaturated aldehyde **362** in good yield (eq 85). Unfortunately, attempts to olefinate this compound

with methylenetriphenylphosphorane failed, delivering a mixture of starting material, iminoacetonitrile, and other unidentifiable products. We only explored the use of the strongly basic Wittig ylide and did not investigate less basic conditions that might provide the desired dienyl triflamide **359**.

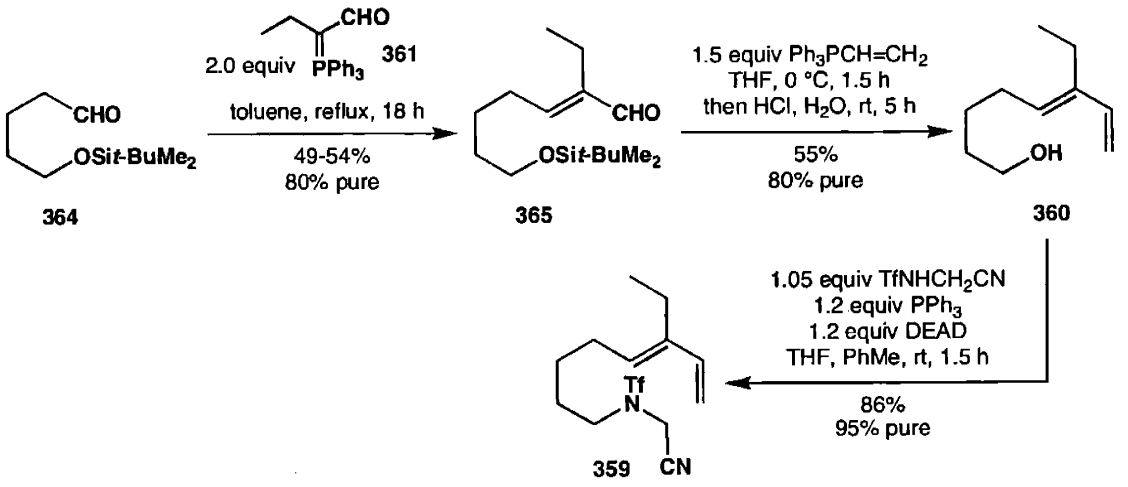


In addition to the above investigations, we undertook the preparation of alcohol **360** in an effort to identify the optimal route to cycloadduct **358**. Thus, mono-protection of 1,5-pentandiol as a TBDMS ether allowed the free alcohol to be oxidized, affording aldehyde **364** (eq 86).

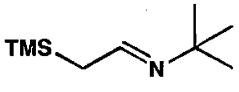


Wittig reaction between **364** and **361** did not proceed as smoothly as the reaction depicted in eq 85. Refluxing a toluene solution of the two components for 40 h afforded a 49% yield of an 85:15 mixture of desired **365** and starting material **364**. Attempts to separate the two components by column chromatography were unsuccessful, so the mixture was used in the next step. Wittig olefination of the mixture afforded, after acid hydrolysis, a mixture of 4-penten-1-ol and the desired dienyl alcohol **360**.

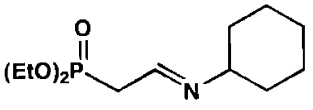
Scheme 55



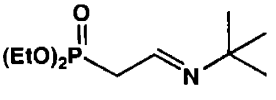
Subjecting this mixture to our standard Mitsunobu conditions provided triflamide **359** contaminated with less than 5% of triflamide **337**.[185] To address the problem of incomplete olefination, there are several other reagents that should be explored in the olefination step. Corey (**366**),[186] Nagata (**367**),[187] and Meyers (**368**)[188] have all developed reagents for a 2-carbon homologation reaction that afford an α,β-unsaturated aldehyde. Employing one of these reagents might improve the synthesis of **365**.



366



367



368

Summary

This chapter describes our initial efforts at applying the intramolecular Diels-Alder reaction of iminoacetonitriles and subsequent transformation of α-amino nitriles to

[185] Formed from the unreacted **364** by methylenation, desilylation, and Mitsunobu reaction.

[186] Corey, E. J.; Enders, D.; Bock, M. G. *Tetrahedron Lett.* **1976**, *17*, 7.

[187] Nagata, W.; Wakabayashi, T.; Hayase, Y. *Org. Syn.* **1973**, *53*, 44.

[188] Meyers, A. I.; Tomioka, K.; Fleming, M. P. *J. Org. Chem.* **1978**, *43*, 3788.

the synthesis of several naturally occurring alkaloids. These studies are by no means complete, and further development of efficient routes to the aforementioned natural products is ongoing.

Part V

Experimental Procedures

General Procedures.

All reactions were performed in flame-dried glassware under a positive pressure of argon. Reaction mixtures (with the exception of sealed-tube reactions) were stirred magnetically unless otherwise indicated. Air- and moisture-sensitive liquids and solutions were transferred by syringe or cannula and were introduced into reaction vessels through rubber septa. Reaction product solutions and chromatography fractions were concentrated by using a Büchi rotary evaporator at ca. 20 mmHg and then at ca. 0.1 mmHg (vacuum pump) unless otherwise indicated.

Materials

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

(a) Distilled under argon from calcium hydride:

acetonitrile, benzene, chlorotrimethylsilane, dichloromethane, *N,N*-diisopropylamine, *N,N*-diisopropylethylamine, toluene, triethylamine, trimethylsily triflate

(b) Distilled under argon from sodium benzophenone ketyl or dianion:

diethyl ether, tetrahydrofuran

(c) Distilled under argon or vacuum:

dihydropyran, methyl iodide, oxalyl chloride, pivaloyl chloride

(d) Purified by pressure filtration through activated alumina:

dichloromethane, diethyl ether, tetrahydrofuran, toluene

(e) Dried at 100 °C under ca. 0.1 mm Hg vacuum:

methytiphenylphosphonium bromide, sodium iodide

(e) Other:

Trifluoromethanesulfonic anhydride was distilled from phosphorus pentoxide.

Pyridine was dried over potassium hydroxide.

Alkyllithium reagents were titrated in tetrahydrofuran with menthol using 1,10-phenanthroline as the indicator.[189]

Chromatography

Analytical thin layer chromatography was performed on Merck precoated glass-backed silica gel 60 F-254 0.25 mm plates. Visualization was effected by one or more of the following techniques: (a) ultraviolet, (b) exposure to iodine vapor, (c) immersion of the plate in an ethanolic solution of 3% *p*-anisaldehyde containing 0.5% concentrated sulfuric acid followed by heating to ca. 200 °C, (d) immersion of the plate in an ethanolic solution of 3% *p*-vanillin containing 0.5% concentrated sulfuric acid followed by heating to ca. 200 °C, (e) immersion of the plate in a 10% solution of phosphomolybdic acid in ethanol followed by heating to ca. 200 °C, (f) immersion of the plate in an aqueous solution of 6% ammonium molybdate and 1% cerium(IV) sulfate containing 12% concentrated sulfuric acid followed by heating to ca. 200 °C.

Column chromatography was performed on Silicycle silica gel 60 (230-400 mesh).

Instrumentation.

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

---

[189] Watson, S. C.; Eastham, J. F. *J. Organomet. Chem,* **1967**, *9*, 165.

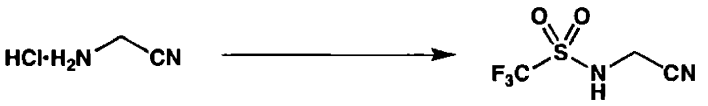
Infrared spectra were obtained using a Perkin Elmer 1320 grating spectrophotometer, a Perkin Elmer 1600 FT-IR spectrophotometer, and a Perkin Elmer 2000 FT-IR spectrophotometer.

^{1}H NMR spectra were measured with Varian XL-300 (300 MHz), Unity-300 (300 MHz), and Inova 500 (500 MHz) spectrometers. 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 spectra were measured with Varian XL-300 (75 MHz) and Inova 500 (125 MHz) spectrometers. ^{13}C NMR chemical shifts are expressed in parts per million (δ) downfield of tetramethylsilane (with the central peak of $CDCl_3$ at 77.23 ppm used as a standard).

High resolution mass spectra (HRMS) were measured on a Bruker Daltonics APEXII 3 tesla fourier transform mass spectrometer.

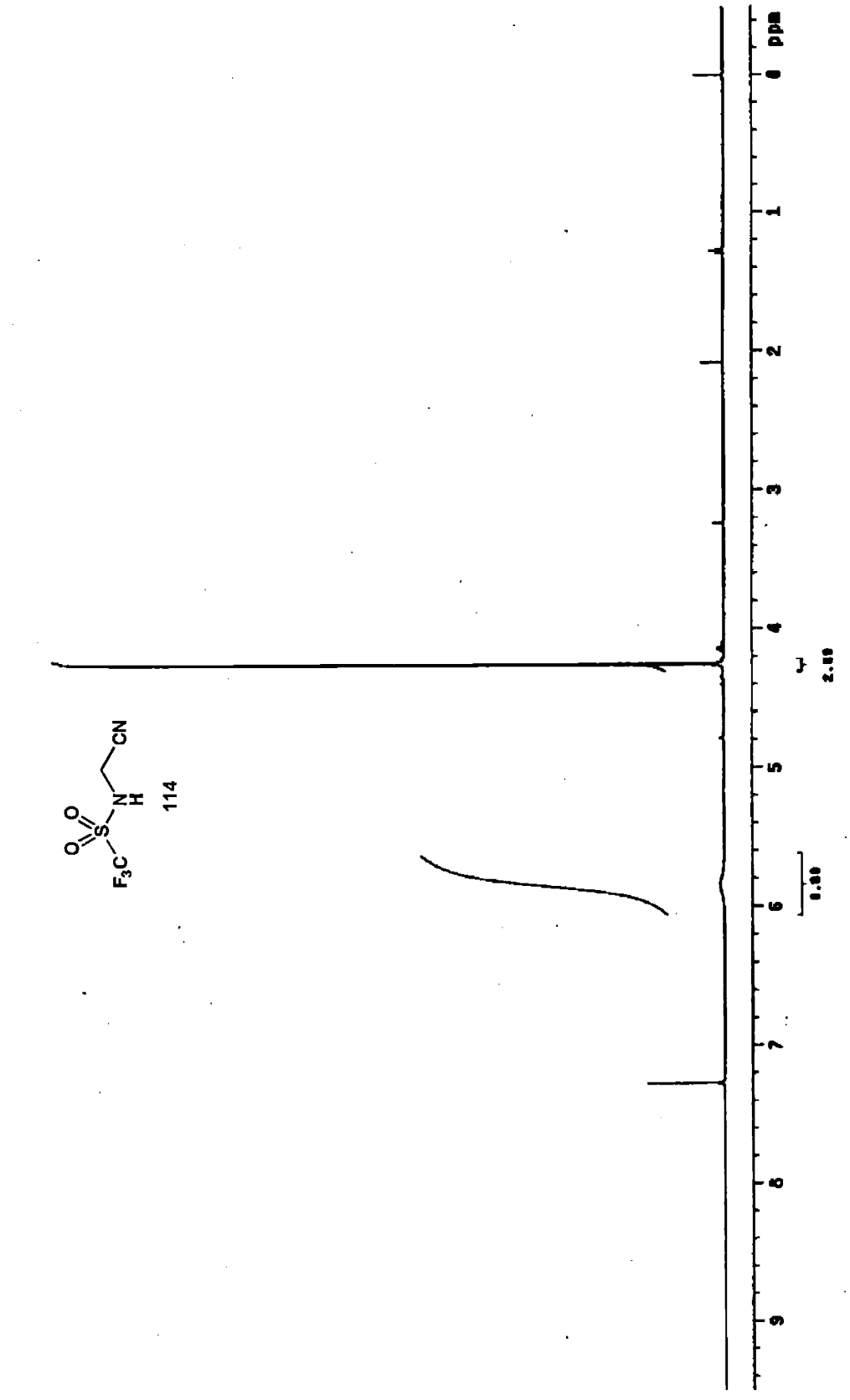
Elemental analyses were performed by E&R Microanalytical Laboratory, Inc and Complete Analysis Laboratories, Inc. of Parsippany, NJ.

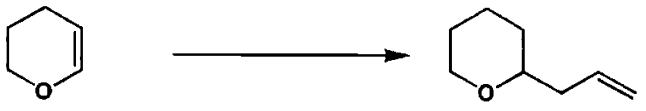


111 114

***N*-(Cyanomethyl)trifluoromethanesulfonamide (114).** A 100-mL, three-necked, round-bottomed flask equipped with a rubber septum, glass stopper, and argon inlet adapter was charged with $NCCH_2NH_3Cl$ (3.00 g, 32.4 mmol), 50 mL of CH_2Cl_2, and diisopropylethylamine (12.4 mL, 9.22 g, 71.3 mmol). The pale yellow solution was cooled at –78 °C while trifluoromethanesulfonic anhydride (5.7 mL, 9.6 g, 34 mmol) was added by syringe over six min. The resulting red-brown solution was stirred at –78 °C for 1 h. Aq 1N HCl solution (30 mL) was then added, and the reaction mixture was allowed to warm to room temperature. The aqueous layer was separated and extracted with three 30-mL portions of CH_2Cl_2, and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated to give 16.5 g of a brown solid. This material was deposited onto 16 g of silica gel and purified on 55 g of silica gel (elution with 25% EtOAc-hexanes) to afford 3.66 g (60%) of triflamide **114** as a pale, yellow oil.

IR (film):	3315, 3001, 2966, 2911, 2721, 2274, 1423, 1382, 1198, 1145, 1091, 996, 910, 841	
^1H NMR (500 MHz, $CDCl_3$):	5.86 (br s, 1 H), 4.25 (s, 2 H)	
^{13}C NMR (125 MHz, $CDCl_3$):	119.4 (q, J = 320 Hz), 114.5, 31.9	
HRMS $[M-H]^-$:	Calcd for $C_3H_2F_3N_2O_2S$:	186.9784
	Found:	186.9782


CN
N
H
O
O
S
F3C
114
ppm

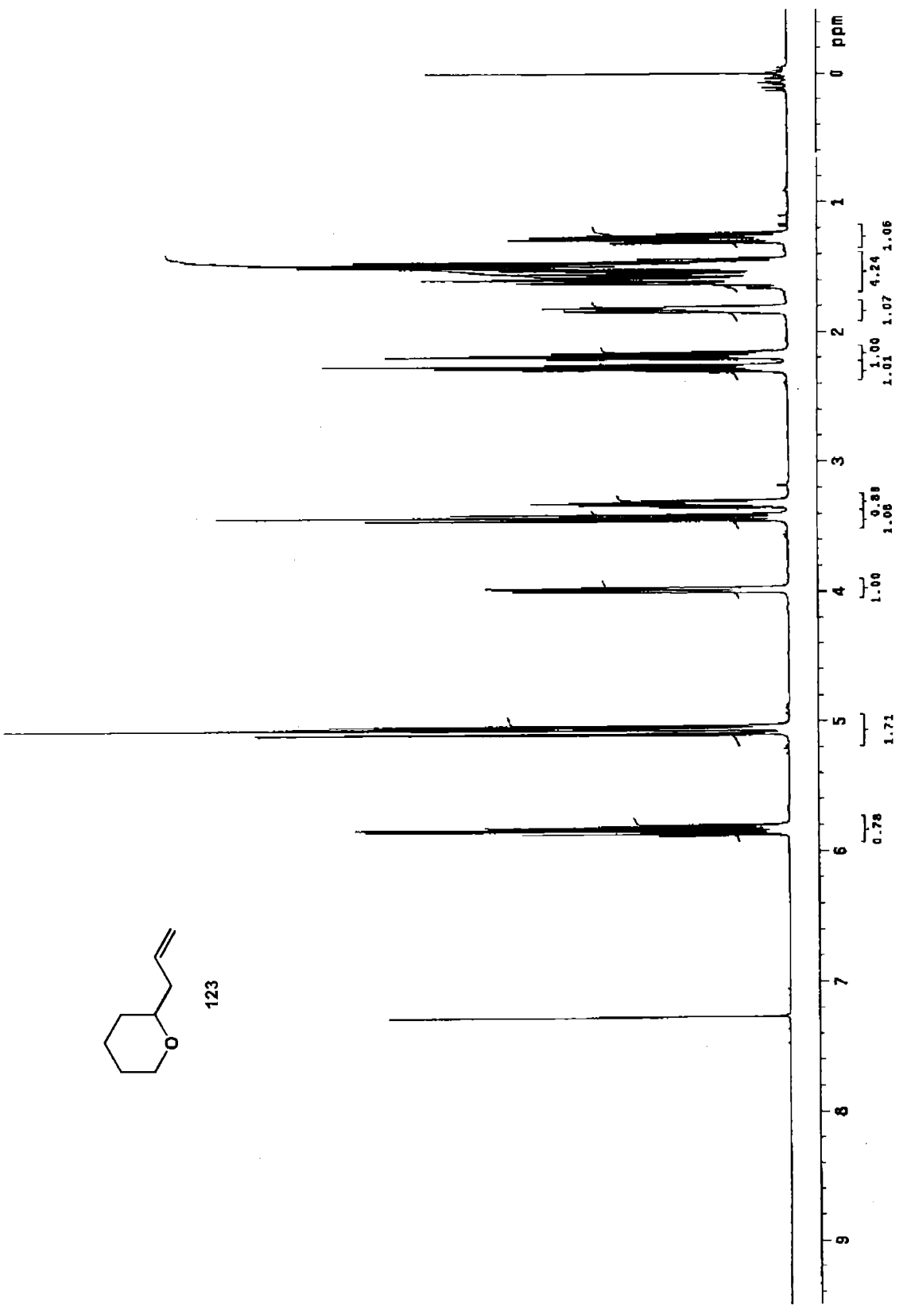


122 123

Tetrahydro-2-(2-propenyl)-2H-pyran (123).[190] A 100-mL, 3-necked, round-bottomed flask equipped with an argon inlet adapter, rubber septum, and glass stopper was charged with PPTS (0.075 g, 0.30 mmol), methanol (1.2 mL, 0.95 g, 30 mmol), and 40 mL of CH_2Cl_2. Dihydropyran (3.25 mL, 3.00 g, 35.7 mmol) was added dropwise over 5 min, and the reaction mixture was stirred at rt for 2.5 h. The solution was then cooled at –78 °C and allyltrimethylsilane (5.7 mL, 4.1 g, 36 mmol) was added in one portion, followed by TMSOTf (0.54 mL, 0.66 g, 3.0 mmol) which was added dropwise over 1 min. The reaction mixture was next allowed to slowly warm to rt over 22 h, and the resulting black mixture was diluted with 50 mL of satd aq $NaHCO_3$ solution. The aqueous layer was separated and extracted with two 20-mL portions of CH_2Cl_2, and the combined organic layers were washed with 60 mL of brine, dried over $MgSO_4$, filtered, and concentrated at 0 °C to give 7.27 g of a brown oil. Column chromatography on 70 g of silica gel (elution with 0-5% Et_2O-pentanes) afforded 2.65 g (71%) of **123** as a colorless oil.

IR (film):	3075, 2920, 2836, 2735, 1632, 1433, 1365, 1343, 1278, 1252, 1194, 1169, 1085, 1041, 988, 905
^{1}H NMR (500 MHz, $CDCl_3$):	5.83 (ddt, J = 17.1, 10.1, 7.1 Hz, 1 H), 5.08 (dd, J = 15.4, 1.8 Hz, 1 H), 5.04 (dd, J = 11.7, 1.8 Hz, 1 H), 3.98 (dt, J = 11.6, 2.1 Hz, 1 H), 3.42 (dt, J = 11.6, 2.1 Hz, 1 H), 3.31 (m, 1 H), 2.27 (m, 1 H), 2.15 (m, 1 H), 1.81 (dm, J = 10.4 Hz, 1 H), 1.59 (m, 2 H), 1.48 (m, 2 H), 1.26 (m, 1 H)
^{13}C NMR (125 MHz, $CDCl_3$):	135.3, 116.8, 77.5, 68.8, 41.3, 31.7, 26.2, 23.7

[190] Tsunoda, T.; Suzuki, M.; Noyori, R. *Tetrahedron Lett.* **1980**, *21*, 71.


123
O
9
8
7
6
5
4
3
2
1
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0.78
1.71
1.00
0.88
1.08
1.00
1.01
1.07
4.24
1.06

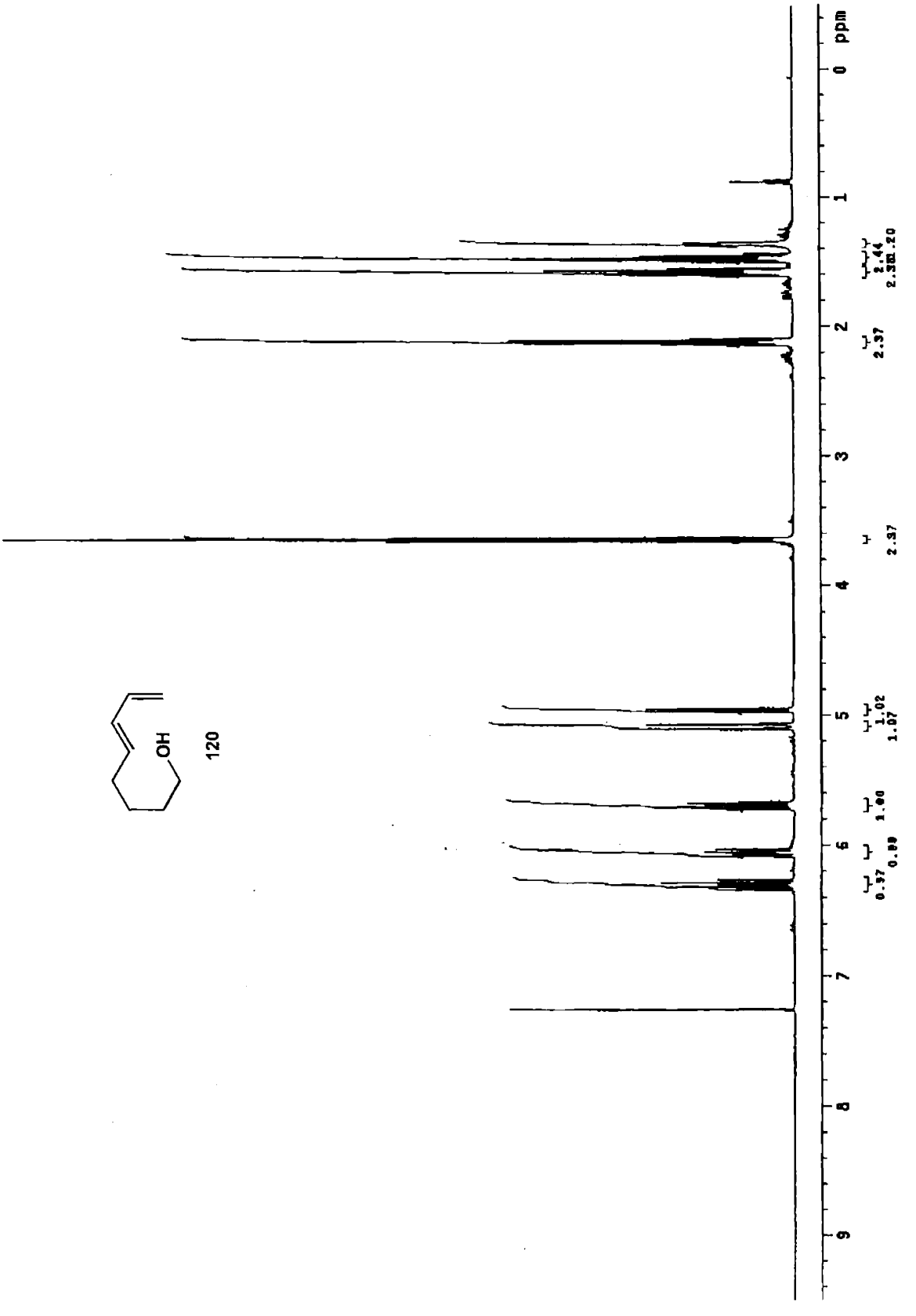
123 120

(*E*)-5,7-Octadien-1-ol (120).[191] A 3-necked, 100-mL, round-bottomed flask equipped with a septum, glass stopper, and argon inlet adapter was charged with tetrahydropyran **123** (2.02 g, 16.0 mmol) and 25 mL of THF. This solution was cooled at –78 °C while potassium *tert*-butoxide (0.125 g, 1.11 mmol) was added. A 25-mL, pear-shaped flask equipped with a rubber septum and argon inlet-needle was charged with 6.90 mL of *n*-BuLi solution (2.54 M in hexane, 17.6 mmol), and the solvent was removed at 1.0 mmHg. The resulting yellow residue was cooled at ca. –50 °C while 18 mL of THF was added, followed by diisopropylamine (2.50 mL, 1.78 g, 17.6 mmol). The resulting solution was stirred at 0 °C for 15 min, cooled to –78 °C, and then transferred via cannula over 20 min to the flask containing **123** and KO*t*-Bu. The reaction mixture was allowed to warm to –50 °C over 1 h and then stirred at –50 °C for 1 h. Satd aq NH_4Cl solution (20 mL) was then added, and the resulting mixture was allowed to warm to rt. The aqueous layer was separated and extracted with three 20-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 4.79 g of an orange oil. Column chromatography on 50 g of silica gel (elution with 25% EtOAc-hexanes) provided 1.16 g (79%) of **120** as a colorless oil with spectral data consistent with that previously reported for this compound.[191]

IR (film):	3348, 3075, 2995, 2922, 2875, 1643, 1595, 1437, 1368, 1242, 1050, 995, 942, 900, 740
^{1}H NMR (500 MHz, $CDCl_3$):	6.30 (ddd, J = 17.7, 10.4, 10.4 Hz, 1 H), 6.06 (dd, J = 15.3, 10.4 Hz, 1 H), 5.70 (dt, J = 15.3, 7.6 Hz, 1 H), 5.09 (d, J =

[191] Margot, C.; Rizzolio, M.; Schlosser, M. *Tetrahedron* **1990**, *46*, 2411.

	17.1 Hz, 1 H), 4.96 (dd, J = 10.0, 1.5 Hz, 1 H), 3.65 (t, J = 6.4 Hz, 2 H), 2.12 (app q, J = 7.0 Hz, 2 H), 1.58 (m, 2 H), 1.48 (m, 2 H), 1.36 (br s, 1 H)
^{13}C NMR (125 MHz, $CDCl_3$):	137.3, 135.1, 131.4, 115.0, 62.8, 32.4, 32.3, 25.4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9
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2.37
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1.00
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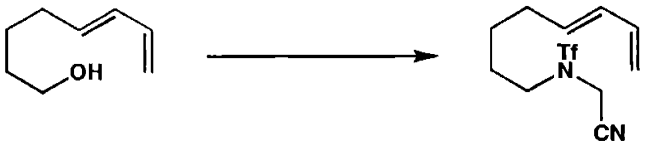
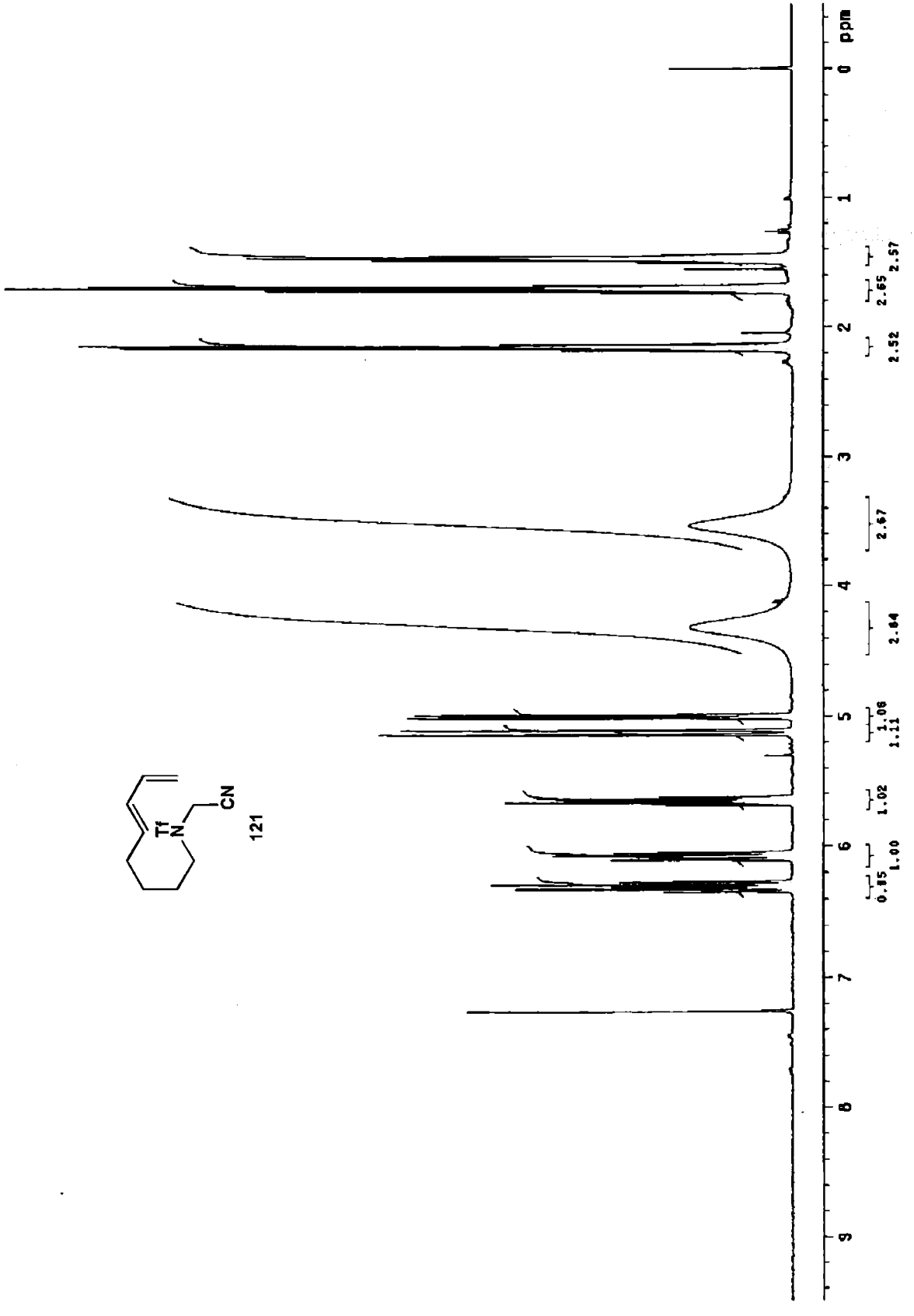


120 121

***N*-(Cyanomethyl)-*N*-((*E*)-5,7-octadienyl)trifluoromethanesulfonamide (121).** A 50-mL, two-necked, round-bottomed flask equipped with a rubber septum and argon inlet adapter was charged with triphenylphosphine (1.70 g, 6.48 mmol), a solution of $HN(Tf)CH_2CN$ (1.07 g, 5.67 mmol) in 10 mL of THF, and a solution of alcohol **120** (0.681 g, 5.40 mmol) in 10 mL of toluene. DEAD (1.02 mL, 1.13 g, 6.48 mmol) was added dropwise via syringe over 8 min, and the resulting mixture was stirred at rt for 1 h and then concentrated to give 6.18 g of a yellow solid. This material was concentrated onto 6.0 g of silica gel and added to a column of 110 g of silica gel. Gradient elution with 10-20% EtOAc-hexanes provided 1.39 g (87%) of **121** as a colorless oil:

IR (film):	3078, 2983, 2935, 2856, 1745, 1598, 1390, 1200, 1135, 1097, 1030, 1000, 947, 900	
^{1}H NMR (500 MHz, $CDCl_3$):	6.31 (ddd, J = 17.1, 10.4, 10.4 Hz, 1 H), 6.08 (dd, J = 15.3, 10.4 Hz, 1 H), 5.66 (dt, J = 15.0, 7.0 Hz, 1 H), 5.13 (d, J = 17.1 Hz, 1 H), 5.00 (d, J = 9.8 Hz, 1 H), 4.31 (br s, 2 H), 3.53 (br s, 2 H), 2.16 (app q, J = 7.0 Hz, 2 H), 1.71 (quint, J = 7.6 Hz, 2 H), 1.48 (quint, J = 7.4 Hz, 2 H)	
^{13}C NMR (125 MHz, $CDCl_3$):	137.0, 133.6, 132.3, 119.8 (q, J = 322 Hz), 115.8, 113.3, 49.3, 35.8, 31.8, 26.8, 25.6	
HRMS $[M+Na]^+$:	Calcd for $C_{11}H_{15}F_3N_2NaO_2S$:	319.0698
	Found:	319.0689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5
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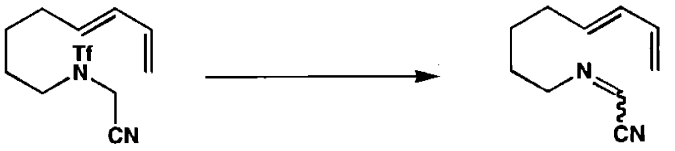
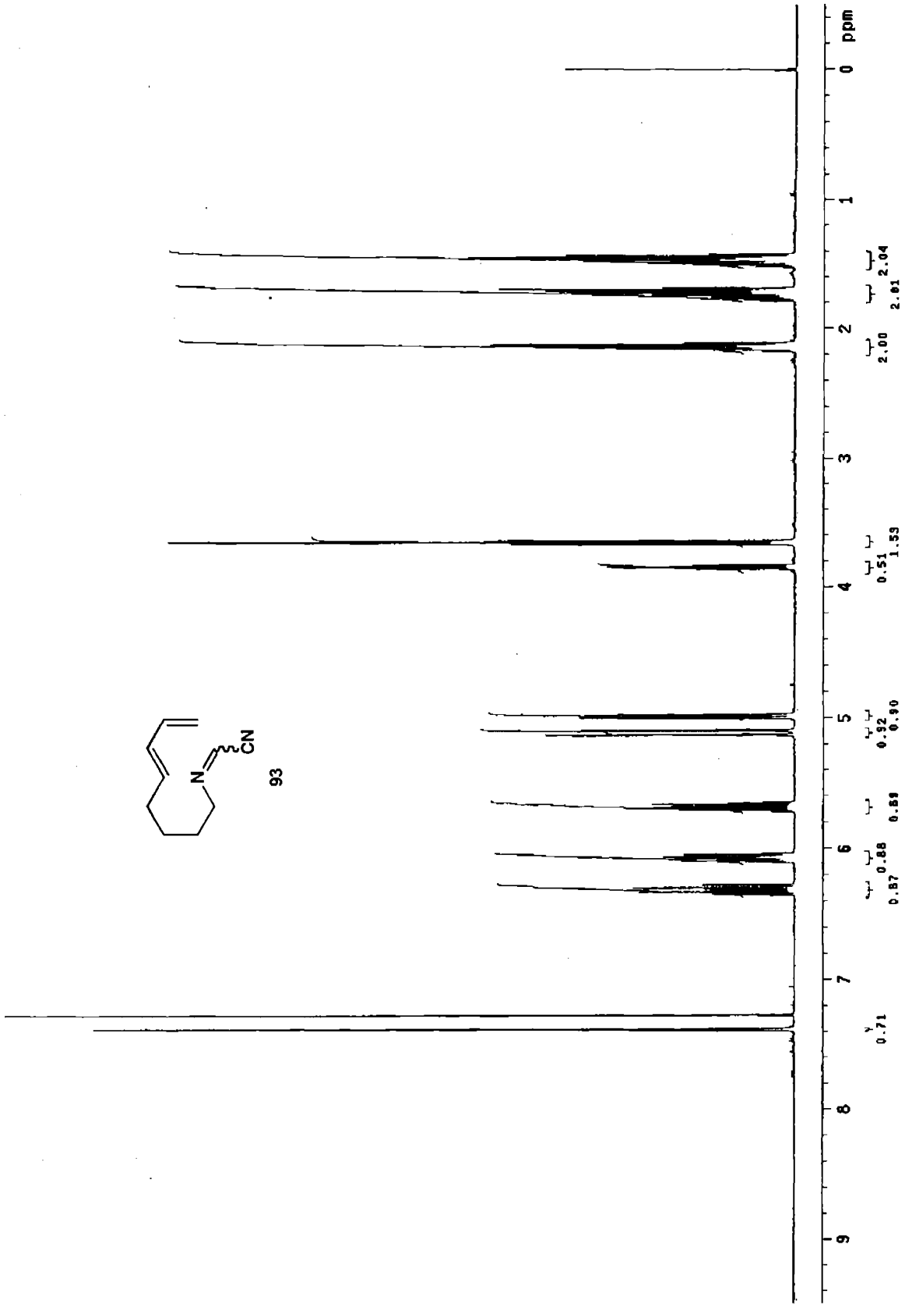


121 93

(*E*)-5,7-Octadienyliminoacetonitrile (93). A 50-mL, one-necked, round-bottomed flask equipped with a reflux condenser fitted with an argon inlet adapter was charged with Cs_2CO_3 (5.15 g, 15.8 mmol) and 14 mL of THF. A solution of triflamide **121** (1.17 g, 3.95 mmol) in 6 mL of THF was added, and the reaction mixture was heated at 55 °C for 3.5 h. The resulting mixture was allowed to cool to room temperature and then diluted with 30 mL of ether and 30 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 0.799 g of a yellow oil. Column chromatography on 21 g of Et_3N-deactivated silica gel (elution with 1% Et_3N-15% ether-pentanes) provided 0.602 g (90%) of **93** (as a 75:25 mixture of E and Z imine isomers by ^1H NMR analysis) as a yellow oil.

IR (film):	3086, 3037, 3008, 2937, 2859, 2235, 1803, 1651, 1623, 1603, 1455, 1440, 1331, 1190, 1158, 1005, 953, 900, 734
For E isomer:	
^1H NMR (500 MHz, $CDCl_3$):	7.38 (t, J = 1.5 Hz, 1 H), 6.31 (ddd, J = 17.4, 10.1, 10.1 Hz, 1 H), 6.04-6.10 (m, 1 H), 5.68 (dt, J = 15.3, 6.7 Hz, 1 H), 5.11 (d, J = 16.5 Hz, 1 H), 4.99 (d, J = 10.2 Hz, 1 H), 3.66 (dt, J = 6.9, 1.4 Hz, 2 H), 2.13 (q, J = 7.6 Hz, 2 H), 1.69-1.78 (m, 2 H), 1.42-1.52 (m, 2 H)
^{13}C NMR (125 MHz, $CDCl_3$):	136.9, 135.7, 134.2, 131.4, 115.1, 114.3, 62.7, 31.9, 29.2, 26.4
For Z isomer:	
^1H NMR (500 MHz, $CDCl_3$):	7.39 (t, J = 2.1 Hz, 1 H), 6.32 (ddd, J = 17.4, 10.1, 10.1 Hz, 1 H), 6.04-6.10 (m, 1 H), 5.69 (dt, J = 15.3, 6.7 Hz, 1 H), 5.11 (d, J = 16.5 Hz, 1 H), 4.99 (d, J = 10.2 Hz, 1 H), 3.85 (dt, J = 6.9, 2.1 Hz, 2 H), 2.15 (q, J = 7.6 Hz, 2 H), 1.69-

	1.78 (m, 2 H), 1.42-1.52 (m, 2 H)
^{13}C NMR (125 MHz, $CDCl_3$):	137.0, 134.3, 131.4, 131.3, 115.0, 109.2, 59.4, 31.9, 29.2, 26.4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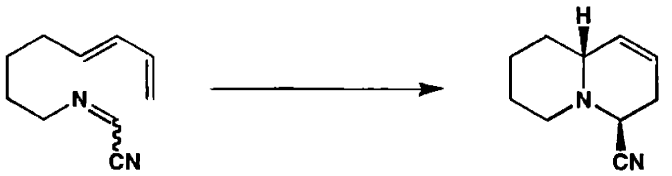
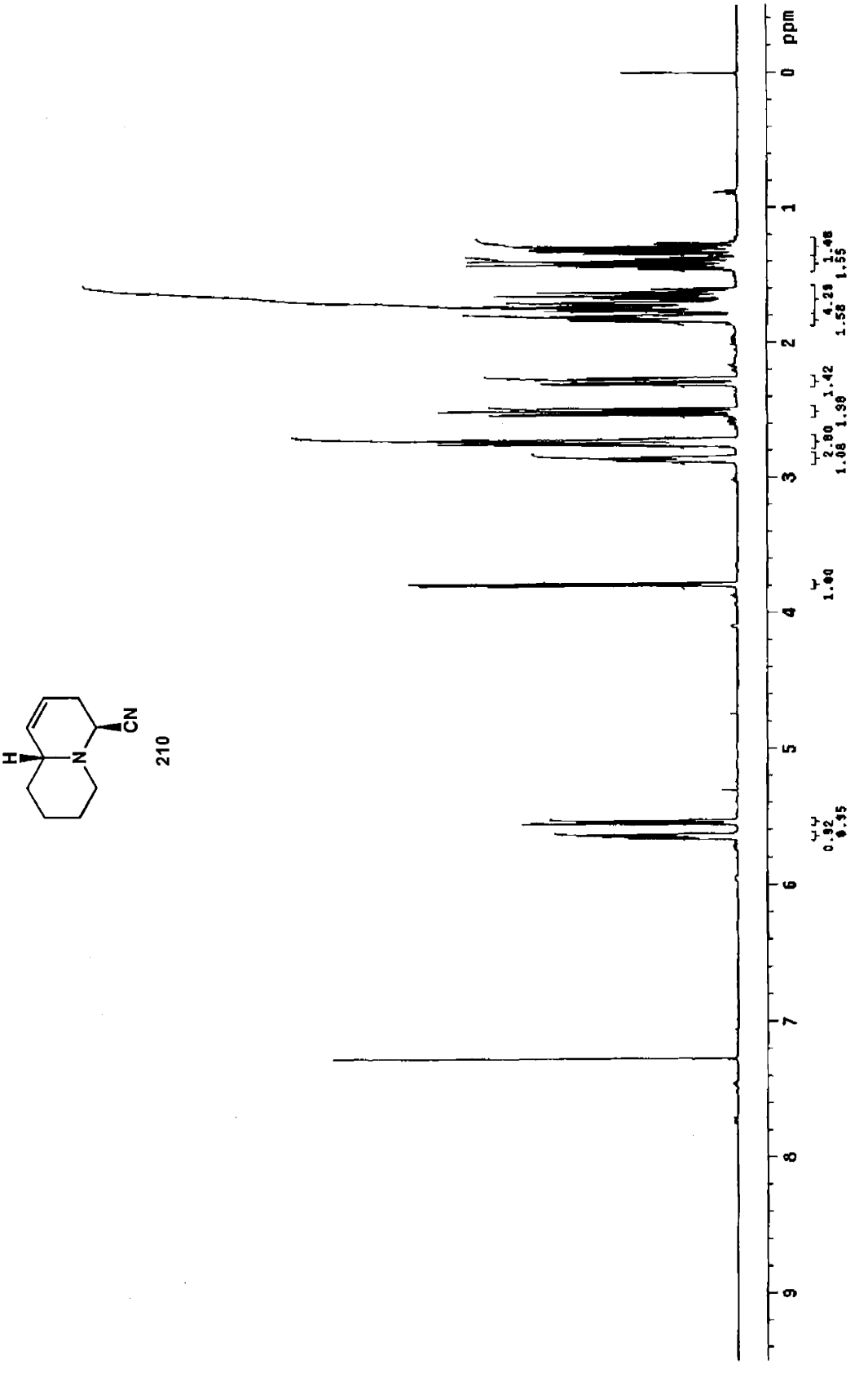
0.87
0.71



93 210

***cis*-1,2-Didehydro-4-cyanoquinolizidine (210).** A threaded Pyrex tube (ca. 100 mL capacity) equipped with a rubber septum and argon inlet needle was charged with imine **93** (0.567 g, 3.49 mmol), BHT (2.31 g, 10.5 mmol), and 60 mL of toluene. The solution was degassed by three freeze-pump-thaw cycles and then sealed with a threaded Teflon cap. The reaction mixture was heated in a 120 °C oil bath for 20 h and then allowed to cool to rt. Concentration gave 4.14 g of a brown oil which was purified by column chromatography on 38 g of silica gel (gradient elution with 1% Et_3N-20-25% EtOAc-hexanes) to yield 0.386 g (68%) of **210** as a yellow oil.

IR (film):	3035, 2936, 2855, 2807, 2221, 1442, 1396, 1332, 1287, 1237, 1205, 1181, 1128, 1106, 1082, 1021, 849, 796
^{1}H NMR (500 MHz, $CDCl_3$):	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, $CDCl_3$):	130.5, 120.4, 116.9, 56.7, 54.0, 51.9, 31.7, 29.5, 25.7, 24.5
Elemental Analysis:	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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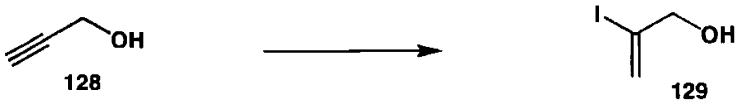
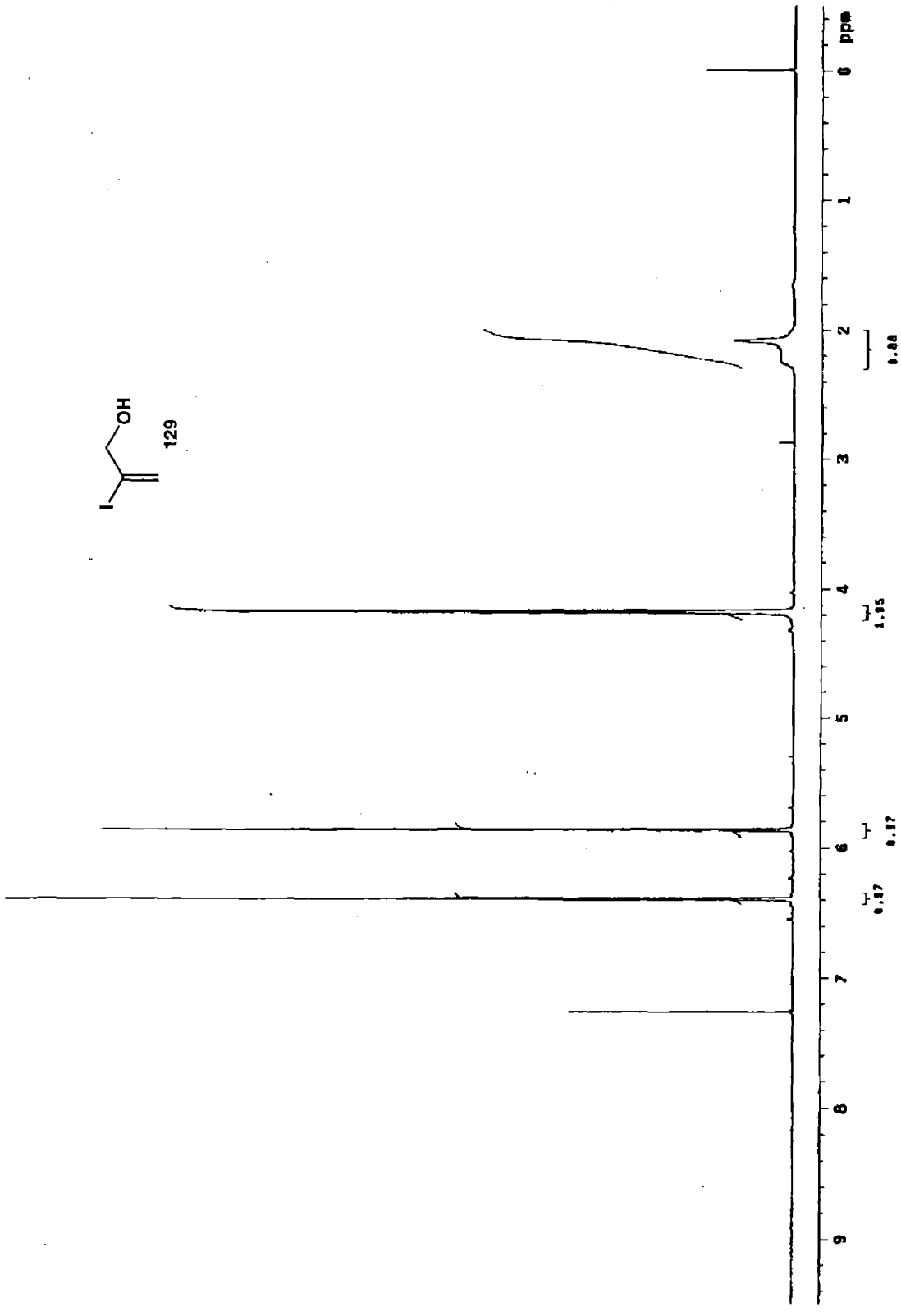


2-Iodo-2-propen-1-ol (129). A 250-ml, 3-necked, round-bottomed flask, equipped with a rubber septum, glass stopper, and argon inlet adapter, was charged with NaI (15.5 g, 103 mmol) and 100 mL of MeCN. Distilled TMSCl (13.1 mL, 11.2 g, 103 mmol) was added dropwise, and the solution was allowed to stir at rt for 5 min. The flask was then cooled at 0 °C while H_2O (0.62 mL, 0.62 g, 34 mmol) was added dropwise. The resulting solution was stirred at 0 °C for 10 min, propargyl alcohol (4.0 mL, 3.9 g, 69 mmol) was then added, and the resulting mixture was stirred at rt in the dark for 3 h. The resulting brown solution was diluted with 100 mL of ether and 80 mL of water. The aqueous layer was separated and extracted with three 60-mL portions of ether, and the combined organic layers were washed with 100 mL of saturated $Na_2S_2O_3$ solution, 100 mL of brine, dried over anhydrous $MgSO_4$, filtered, and concentrated to give 12.0 g of yellow oil. Column chromatography on 120 g of silica gel (gradient elution 10–25% EtOAc-hexanes) provided 6.32 g (50%) of iodide **129** as a pale yellow oil with spectral data consistent with that previously reported for this compound.[192]

IR (film):	3316, 2911, 2857, 1627, 1443, 1399, 1230, 1145, 1032, 974, 901
^{1}H NMR (500 MHz, $CDCl_3$):	6.39 (app q, J = 1.7 Hz, 1 H), 5.86 (app q, J = 1.4, Hz, 1 H), 4.17 (s, 2 H), 2.13 (s, 1 H)
^{13}C NMR (75 MHz, $CDCl_3$):	124.7, 110.6, 71.3

[192] Lai, M.; Li, D.; Oh, E.; Liu, H. *J. Am. Chem. Soc.* **1993**, *115*, 1619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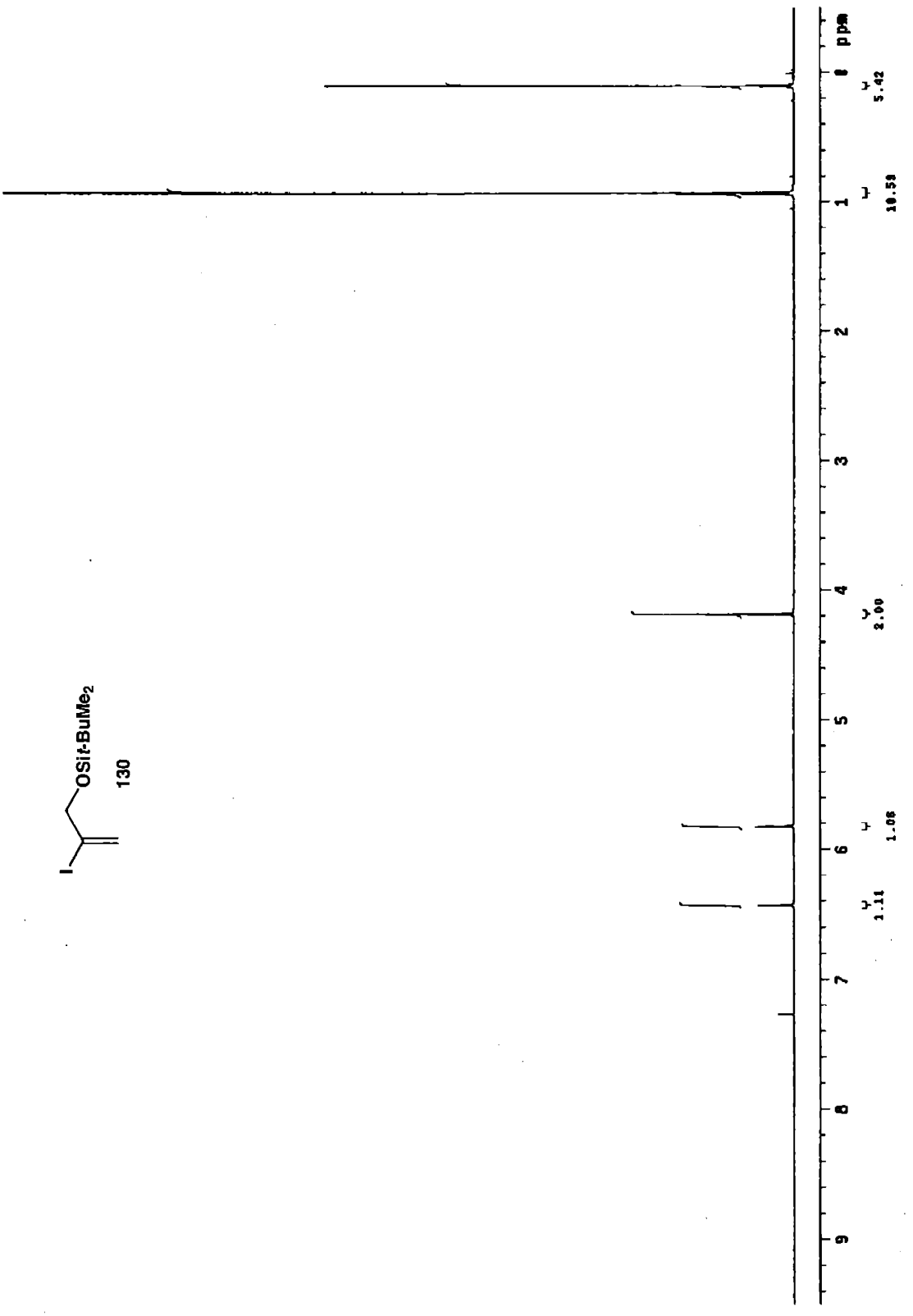
0.57
0.57
0.88

1-(*tert*-Butyldimethylsiloxy)-2-iodo-2-propene (130). A 250-ml, 3-necked, round-bottomed flask, equipped with a rubber septum, glass stopper, and argon inlet adapter was charged with imidazole (3.49 g, 51.3 mmol), 80 mL of CH_2Cl_2, and **129** (6.3 g, 34 mmol). The flask was cooled at 0 °C while *tert*-butyldimethylsilyl chloride (5.68 g, 37.7 mmol) was added in one portion. The cloudy solution was stirred at 0 °C for 1 h and was then diluted with 30 mL of CH_2Cl_2 and 60 mL of water. The aqueous layer was separated and extracted with 30 mL of CH_2Cl_2, and the combined organic layers were washed with 60 mL of brine, dried over anhydrous $MgSO_4$, filtered, and concentrated to give 10.4 g of colorless oil. Column chromatography on 80 g of silica gel (elution with 1% EtOAc-hexanes) provided 9.49 g (93%) of **130** as a colorless oil with spectral data consistent with that previously reported for this compound.[192]

IR (film):	2955, 2927, 2885, 2856, 1626, 1472, 1391, 1362, 1257, 1134, 1083, 1006, 898, 838, 778
^{1}H NMR (500 MHz, $CDCl_3$):	6.43 (app q, J = 1.8 Hz, 1 H), 5.82 (app q, J = 1.6, Hz, 1 H), 4.18 (t, J = 1.8 Hz, 2 H), 0.93 (s, 9 H), 0.10 (s, 6 H)
^{13}C NMR (75 MHz, $CDCl_3$):	123.2, 109.9, 71.3, 26.0, 18.6, -5.1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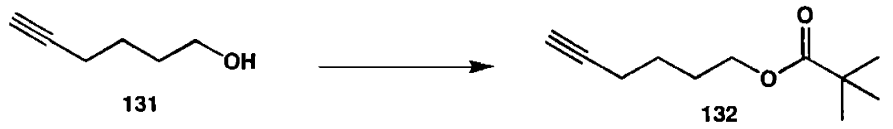
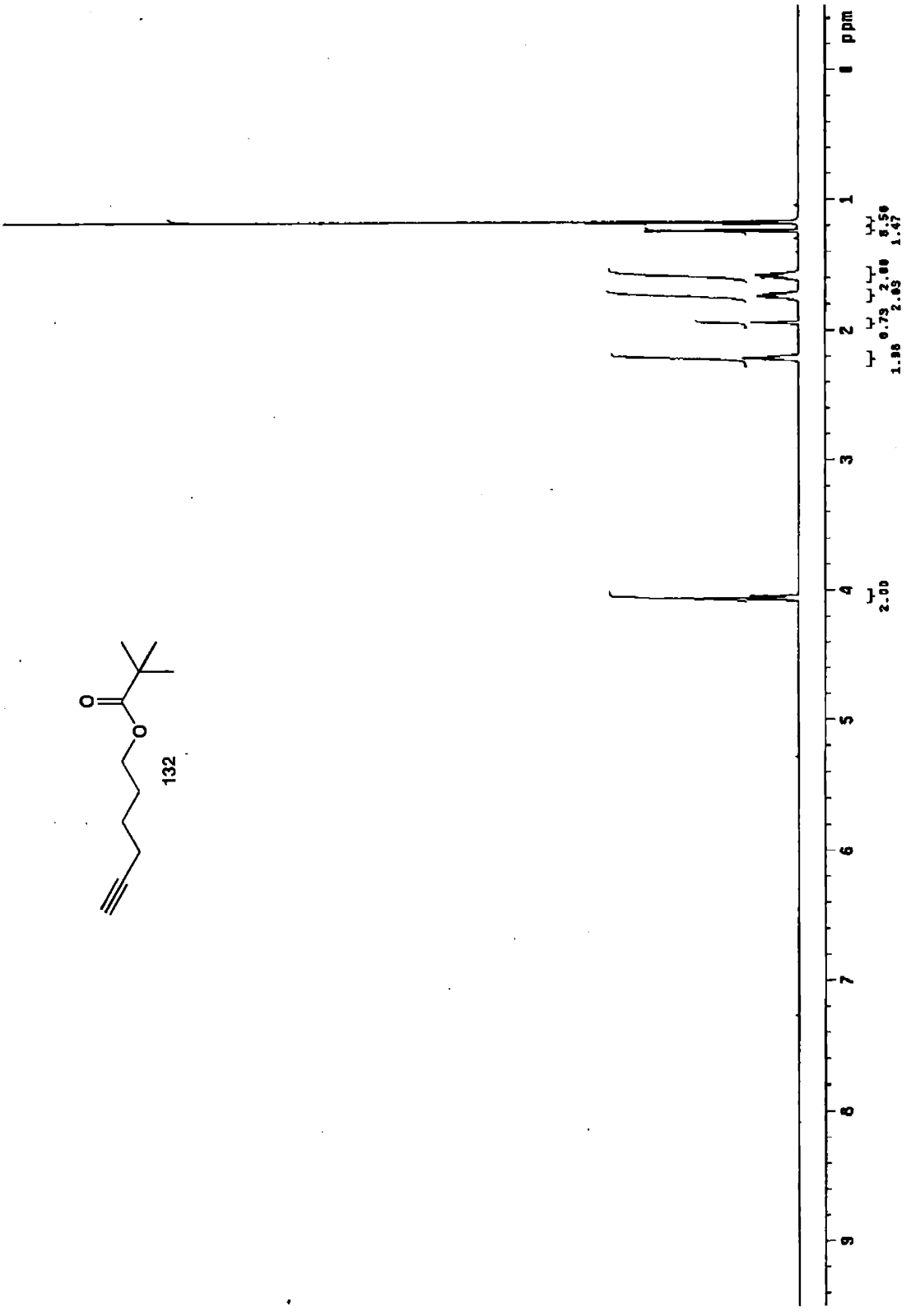


2,2-Dimethylpropionic acid 5-hexynyl ester (132). A 250-mL, 3-necked, round-bottomed flask equipped with a glass stopper, a rubber septum, and argon inlet adapter was charged with DMAP (0.443 g, 3.63 mmol), 75 mL of CH_2Cl_2, 5-hexyn-1-ol (**131**) (4.0 mL, 3.6 g, 36 mmol), and pyridine (8.8 mL, 8.6 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 room temperature 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 **132** as a colorless oil. ^{1}H NMR analysis indicates desired product with 6% pivalic acid present as an impurity.

IR (film):	2959, 2872, 2118, 1728, 1481, 1459, 1398, 1366, 1284, 1157, 1042, 1007
^{1}H NMR (500 MHz, $CDCl_3$):	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, $CDCl_3$):	178.7, 84.0, 68.9, 63.9, 38.9, 27.8, 27.3, 25.1, 18.2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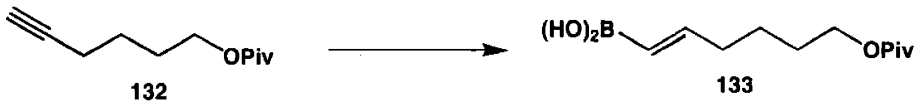
2.00



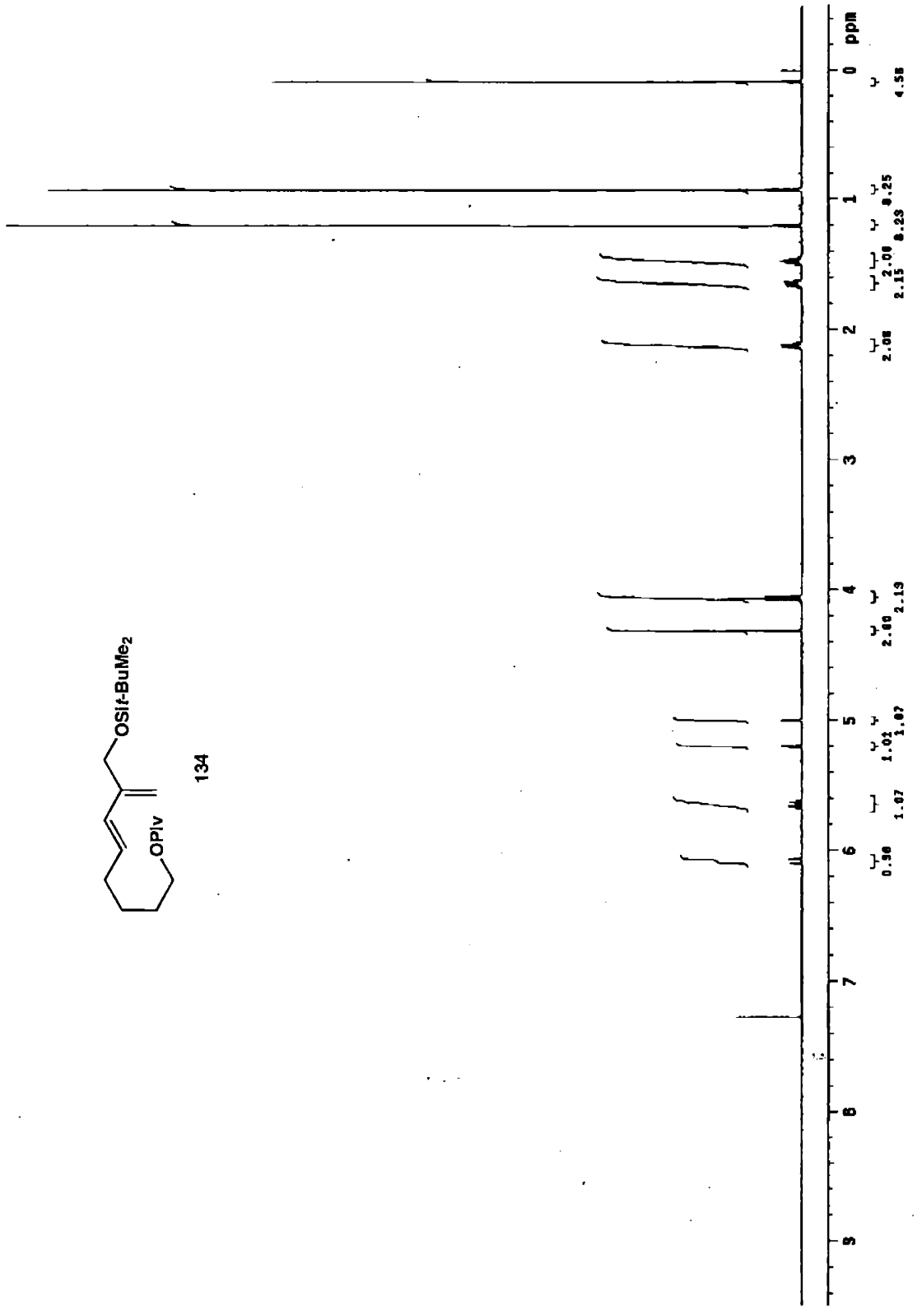
132 133

6-Trimethylacetoxy-(*E*)-1-hexenylboronic acid (133). A 100-ml, 2-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 **132** (6.34 g, 34.8 mmol) and 18 mL of CH_2Cl_2. The addition funnel was charged with 45.2 ml of dibromoborane-dimethylsulfide solution (1.0 M in CH_2Cl_2, 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 **133** as a tan solid, which was used in the next step without further purification.

133 134

7-(*tert*-Butyldimethylsiloxymethyl)-1-trimethylacetoxy-(*E*)-5,7-octadiene (134). A 100-mL, one-necked, round-bottomed flask containing the crude boronic acid **133** (7.93 g, 34.8 mmol) was equipped with a rubber septum and argon-inlet needle. The flask was charged with vinyl iodide **130** (8.64 g, 29.0 mmol), 50 ml of THF, and $PdCl_2dppf{\bullet}CH_2Cl_2$ (0.237 g, 0.29 mmol). 29 mL of a sodium hydroxide solution (3.0 M in water, 87 mmol) was then added, and the reaction was stirred at rt for 1 h. The resulting orange solution was then diluted with 80 mL water, and the aqueous later was separated and extracted with three 100-mL portions of ether. The combined organic layers were washed with 100 mL of brine, dried over $MgSO_4$, filtered, and concentrated to give 11.68 g of orange oil. Column chromatography on 80 g of silica gel (gradient elution with 2-4% EtOAc-hexanes) provided 10.16 g (99% based on vinyl iodide **130**) of **134** as a yellow oil.

IR (film):	2957, 2857, 1731, 1651, 1611, 1472, 1462, 1398, 1362, 1284, 1253, 1157, 1113, 1035, 1007, 965, 939, 894, 836, 776
^{1}H NMR (500 MHz, $CDCl_3$):	6.08 (d, *J* = 15.9 Hz, 1 H), 5.64 (dt, J = 16.2, 6.9 Hz, 1 H), 5.20 (d, *J* = 1.5 Hz, 1 H), 5.00 (s, 1 H), 4.31 (s, 2 H), 4.06 (t, *J* = 6.6 Hz, 2 H), 2.12 (app q, *J* = 7.0 Hz, 2 H), 1.62-1.67 (m, 2 H), 1.44-1.50 (m, 2 H), 1.20 (s, 9 H), 0.93 (s, 9 H), 0.09 (s, 6 H)
^{13}C NMR (125 MHz, $CDCl_3$):	178.8, 144.9, 130.4, 129.5, 112.8, 64.4, 63.2, 38.9, 32.8, 28.3, 27.4, 26.1, 25.8, 18.6, -5.2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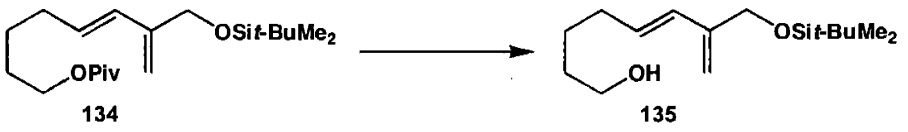
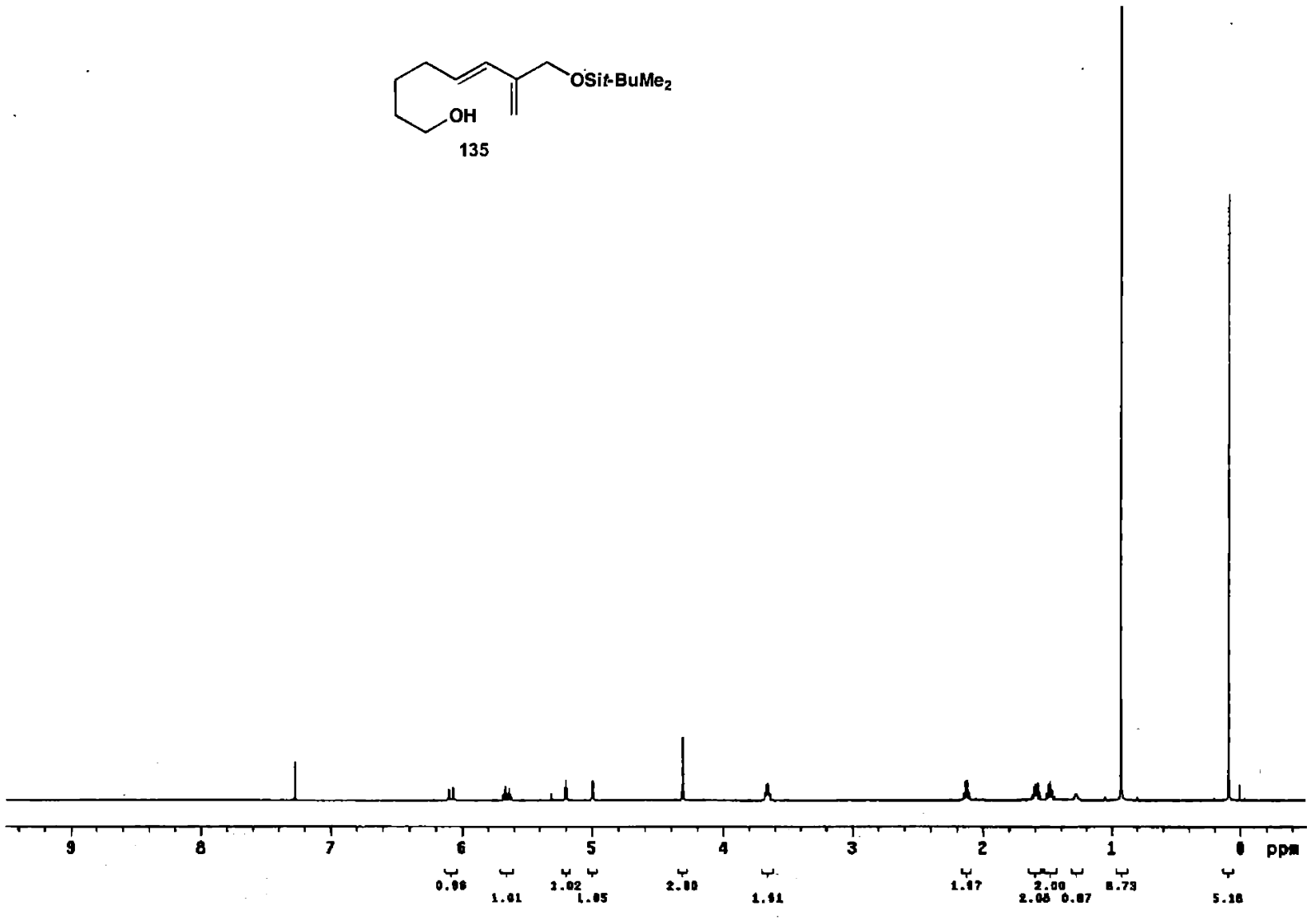


134 135

7-(*tert*-Butyldimethylsilyoxymethyl)-(*E*)-5,7-octadien-1-ol (135). A 100-mL, two-necked, round-bottomed flask with a rubber septum and argon inlet adapter was charged with pivalate ester **134** (4.00 g, 11.3 mmol) and 35 mL of CH_2Cl_2. The flask was cooled at –78 °C while 16.5 mL of a DIBAL solution (1.5 M in toluene, 24.8 mmol) was added dropwise over 10 min via syringe. The solution was stirred at –78 °C for 1 h and then diluted with 30 mL of 10% aq Rochelle salt solution. The cooling bath was removed, and the mixture was stirred at rt for 2 h. The biphasic mixture was then diluted with 50 mL of water, the aqueous layer was separated and extracted with three 30-mL portions of CH_2Cl_2, and the combined organic layers were washed with 50 mL of brine, dried over $MgSO_4$, filtered, and concentrated to give 2.95 g of pale yellow oil. Column chromatography on 60 g of silica gel (gradient elution with 10-20% EtOAc-hexanes) afforded 2.62 g (86%) of **135** as a colorless oil.

IR (film):	3340, 2951, 2921, 2855, 1601, 1453, 1382, 1356, 1243, 1105, 1003, 957, 887, 830, 769
^{1}H NMR (500 MHz, $CDCl_3$):	6.08 (d, *J* = 16.2 Hz, 1 H), 5.65 (dt, J = 16.1, 7.0 Hz, 1 H), 5.20 (d, *J* = 1.8 Hz, 1 H), 4.99 (s, 1 H), 4.31 (t, *J* = 1.4 Hz, 2 H), 3.66 (dt, *J* = 6.4, 4.8 Hz, 2 H), 2.13 (app dq, *J* = 7.0, 1.2 Hz, 2 H), 1.57-1.62 (m, 2 H), 1.45-1.51 (m, 2 H), 1.28 (br, 1 H), 0.93 (s, 9 H), 0.09 (s, 6 H)
^{13}C NMR (125 MHz, $CDCl_3$):	144.8, 130.2, 129.7, 112.7, 63.2, 63.0, 33.0, 32.4, 26.1, 25.6, 18.6, -5.2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2.00
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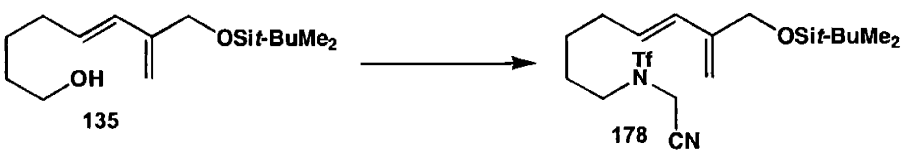
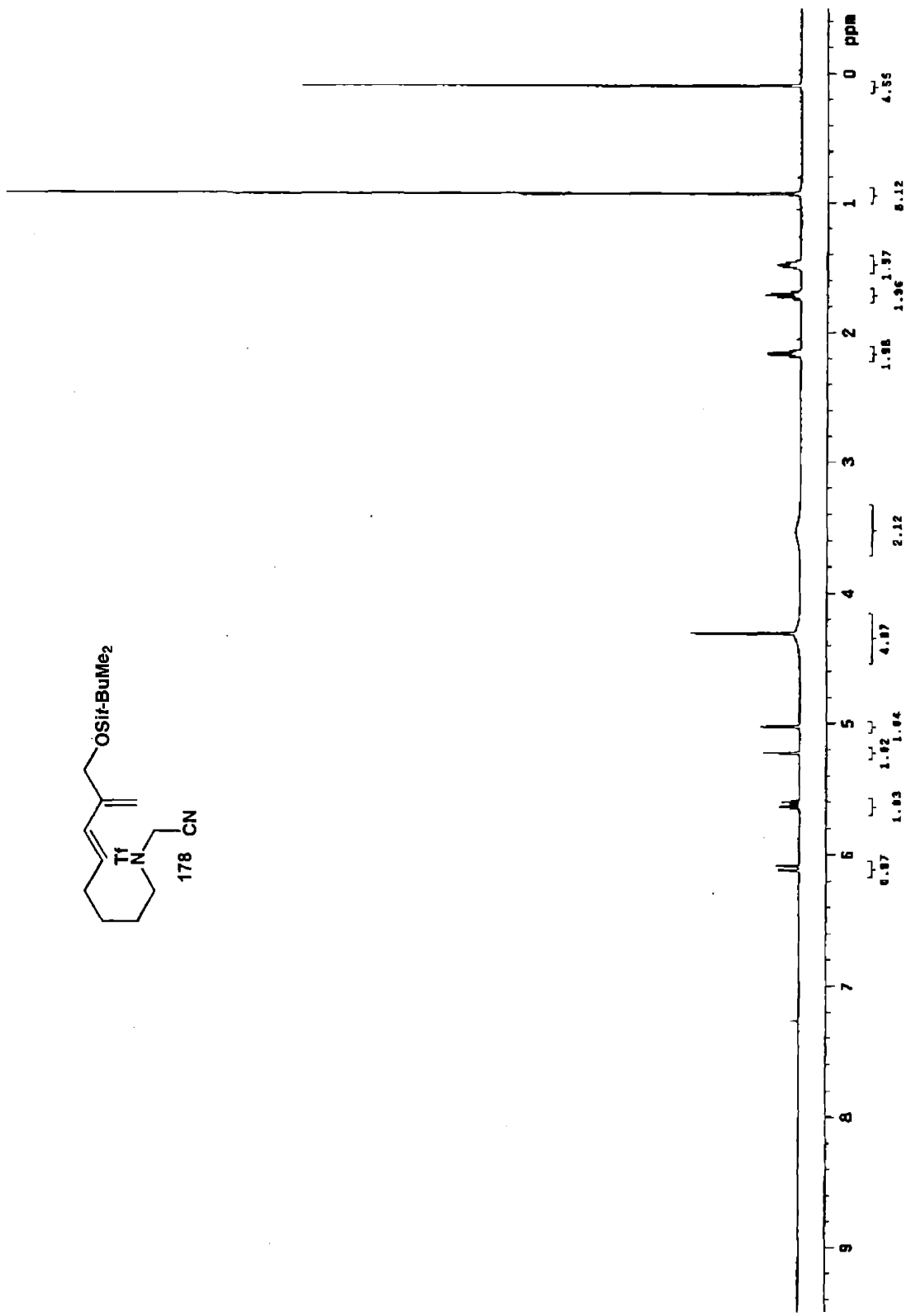


***N*-(Cyanomethyl)-*N*-(7-(*tert*-butyldimethylsiloxymethyl)-(*E*)-5,7-octadienyl)trifluoromethanesulfonamide (178).** A 50-mL, two-necked, round-bottomed flask equipped with a rubber septum and an argon inlet adapter was charged with triphenylphosphine (1.05 g, 4.02 mmol), a solution of $HN(Tf)CH_2CN$ (0.662 g, 3.52 mmol) in 10 mL of THF, and a solution of alcohol **135** (0.906 g, 3.35 mmol) in 10 mL of toluene. DEAD (0.63 mL, 0.70 g, 4.0 mmol) was added dropwise via syringe over 5 min, and the resulting mixture was stirred at rt for 2 h and then concentrated to give 4.44 g of a white solid. This material was concentrated onto 9.0 g of silica gel and applied to a column of 60 g of silica gel. Gradient elution with 5-20% EtOAc-hexanes provided 1.40 g (94%) of **178** as a colorless oil.

IR (film):	2940, 2910, 2880, 2840, 1725, 1600, 1445, 1385, 1245, 1225, 1220, 1035, 1005, 960, 893, 835, 765
^1H NMR (500 MHz, $CDCl_3$):	6.10 (d, J = 15.9 Hz, 1 H), 5.62 (dt, J = 15.9, 7.2 Hz, 1 H), 5.22 (d, J = 1.2 Hz, 1 H), 5.02 (br s, 1 H), 4.35 (br s, 2 H), 4.31 (s, 2 H), 3.54 (br m, 2 H), 2.16 (app q, J = 7.1 Hz, 2 H), 1.71 (quint, J = 7.6 Hz, 2 H), 1.48 (quint, J = 7.4 Hz, 2 H), 0.93 (s, 9 H), 0.09 (s, 6 H)
^{13}C NMR (125 MHz, $CDCl_3$):	144.6, 131.1, 128.4, 119.8 (q, J = 322 Hz), 113.4, 113.3, 63.2, 49.3, 35.8, 32.4, 26.8, 26.1, 25.7, 18.6, -5.2
HRMS $[M+H]^+$:	Calcd for $C_{18}H_{32}F_3N_2O_3SSi$: 441.1850 Found: 441.1862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CN
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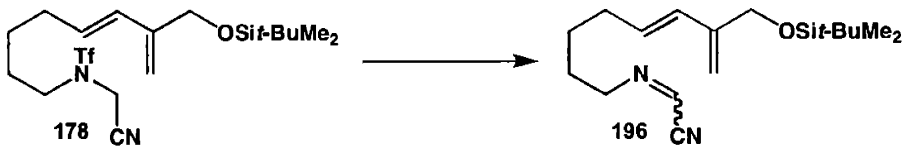
ppm



7-(*tert*-Butyldimethylsiloxymethyl)-(*E*)-5,7-octadienyliminoacetonitrile (196). A 50-mL, one-necked, round-bottomed flask equipped with a reflux condenser fitted with an argon inlet adapter was charged with Cs_2CO_3 (8.16 g, 25.1 mmol) and 15 mL of THF. A solution of triflamide **178** (2.76 g, 6.26 mmol) in 10 mL of THF was added, and the reaction mixture was heated at 55 °C for 90 min. The resulting mixture was allowed to cool to room temperature and then diluted with 40 mL of ether and 50 mL of water. The aqueous layer was separated and extracted with two 40-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 1.97 g of a yellow oil. Column chromatography on 35 g of Et_3N-deactivated silica gel (elution with 1% Et_3N-10% EtOAc-hexanes) provided 1.81 g (94%) of **196** (as an 63:37 mixture of E and Z imine isomers by ^1H NMR analysis) as a pale yellow oil.

IR (film): 3020, 2950, 2930, 2890, 2850, 1625, 1470, 1398, 1370, 1340, 1262, 1110, 1015, 975

For E isomer:

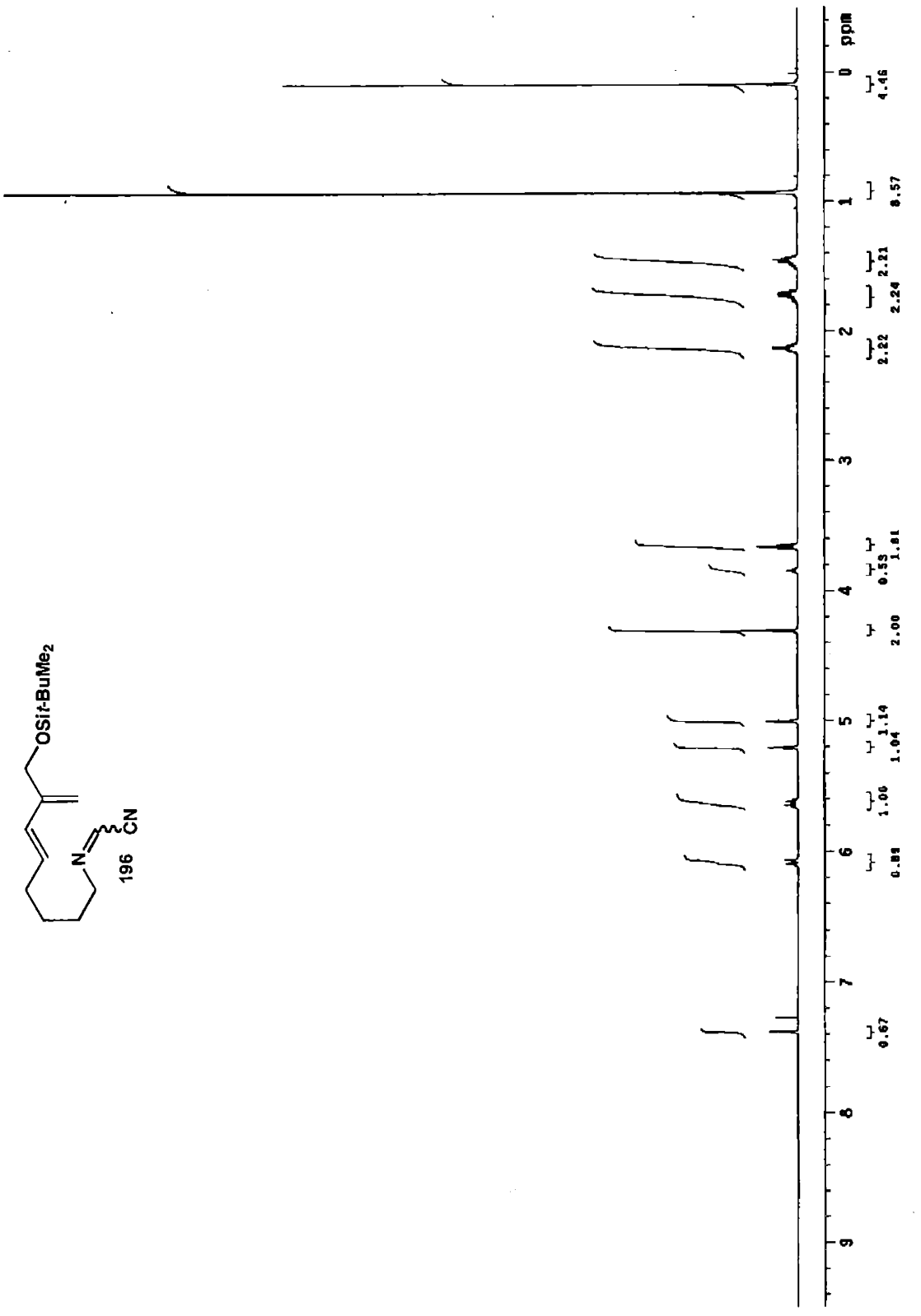
^1H NMR (500 MHz, $CDCl_3$): 7.38 (t, J = 1.5 Hz, 1 H), 6.08 (d, J = 15.9 Hz, 1 H), 5.60-5.67 (m, 1 H), 5.20 (d, J = 1.8 Hz, 1 H), 5.00 (s, 1 H), 4.31 (s, 2 H), 3.66 (dt, J = 6.9, 1.5 Hz, 2 H), 2.13 (q, J = 7.3 Hz, 2 H), 1.68-1.78 (m, 2 H), 1.42-1.50 (m, 2 H), 0.93 (s, 9 H), 0.09 (s, 6 H)

^{13}C NMR (125 MHz, $CDCl_3$): 144.7, 135.9, 130.5, 129.1, 114.6, 112.8, 63.1, 63.0, 32.7, 29.5, 26.8, 26.0 18.5, -5.2

For Z isomer:

^1H NMR (500 MHz, $CDCl_3$): 7.39 (t, J = 2.1 Hz, 1 H), 6.10 (d, J = 15.9 Hz, 1 H), 5.60-5.67 (m, 1 H), 5.20 (d, J = 1.8 Hz, 1 H), 5.00 (s, 1 H), 4.31 (s, 2 H), 3.84 (dt, J = 6.9, 2.1 Hz, 2 H), 2.13 (q, J = 7.3 Hz, 2 H), 1.68-1.78 (m, 2 H), 1.42-1.50 (m, 2 H), 0.93 (s, 9 H), 0.09 (s, 6 H)

^{13}C NMR (125 MHz, $CDCl_3$): 144.7, 131.5, 130.4, 129.1, 112.9, 109.5, 63.1, 59.7, 32.8, 29.5, 26.9, 26.0 18.5, -5.2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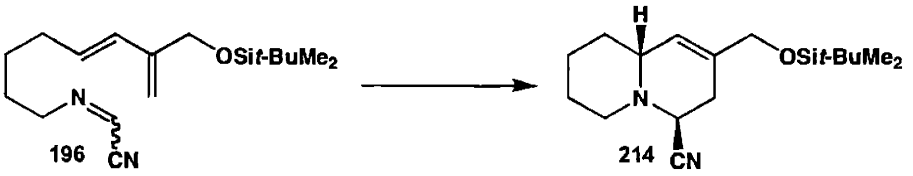
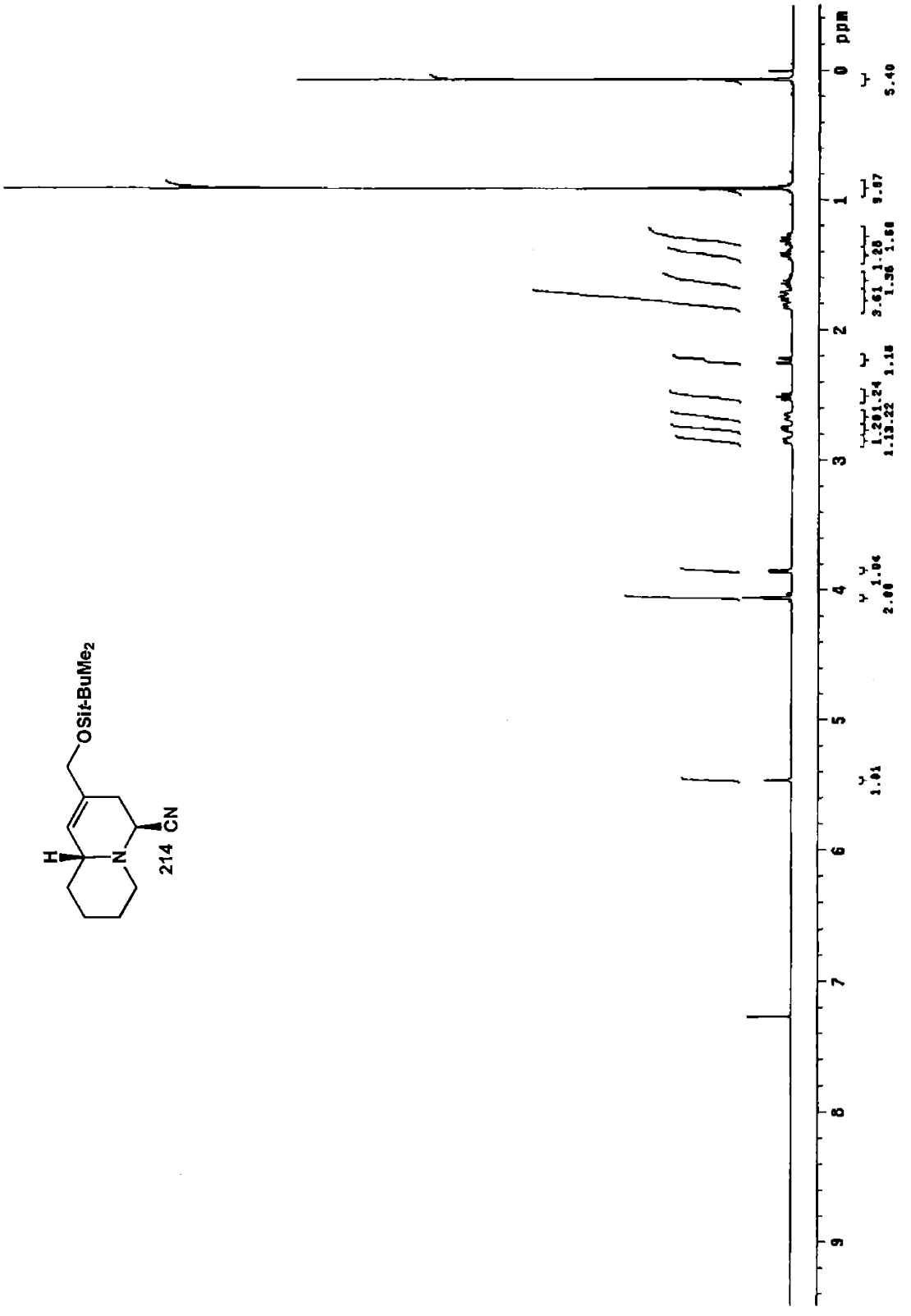


2-(*tert*-Butyldimethylsiloxymethyl)-*cis*-1,2-didehydro-4-cyanoquinolizidine (214). A threaded Pyrex tube (ca. 250 mL capacity) equipped with a rubber septum and argon inlet needle was charged with imine **196** (1.81 g, 5.90 mmol), BHT (3.90 g, 17.7 mmol), and 118 mL of toluene. The solution was degassed by three freeze-pump-thaw cycles and then sealed with a threaded Teflon cap. The reaction mixture was heated in a 120 °C oil bath for 14 h and then allowed to cool to rt. Concentration gave 6.23 g of a brown oil which was concentrated onto 12 g of silica gel and applied to a column of 55 g of silica gel. Gradient elution with 1% Et_3N-5-10% EtOAc-hexanes yielded 1.59 g (88%) of **214** as a pale yellow oil.

IR (film):	2934, 2856, 2807, 2767, 2222, 1471, 1462, 1388, 1360, 1326, 1289, 1256, 1229, 1194, 1156, 1129, 1067, 1026, 1006, 939, 838, 777, 738, 667	
^{1}H NMR (500 MHz, $CDCl_3$):	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, $CDCl_3$):	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	
Elemental Analysis:	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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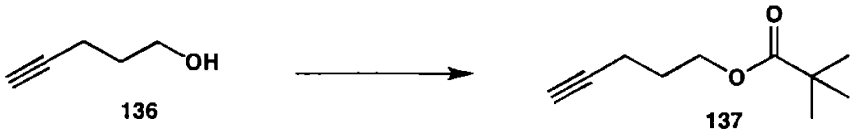
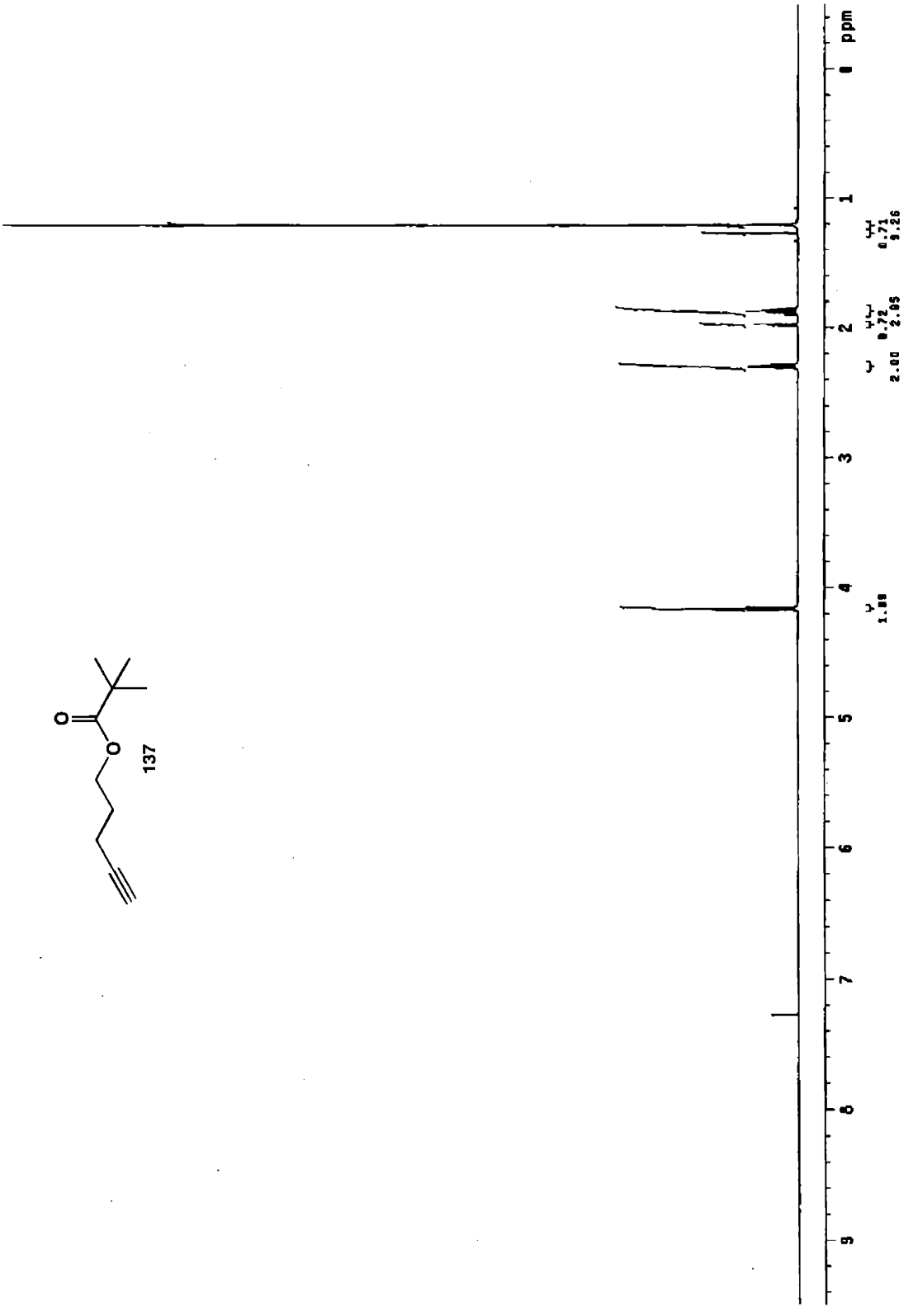


136 137

2,2-Dimethylpropionic acid 4-pentynyl ester (137). A 25-mL, 2-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 the **137** as a colorless oil. ^{1}H NMR analysis indicates desired product with 5% pivalic acid present as an impurity.

IR (film):	2974, 2874, 2121, 1730, 1482, 1463, 1399, 1366, 1285, 1230, 1158, 1089, 1040, 1008, 941, 887
^{1}H NMR (500 MHz, $CDCl_3$):	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, $CDCl_3$):	178.4, 83.2, 69.1, 63.0, 39.0, 27.9, 27.4, 15.5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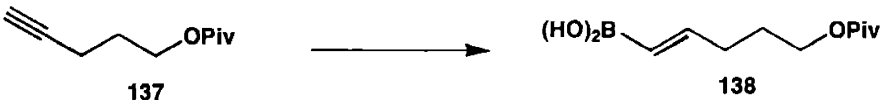
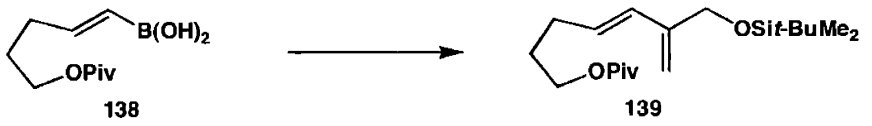


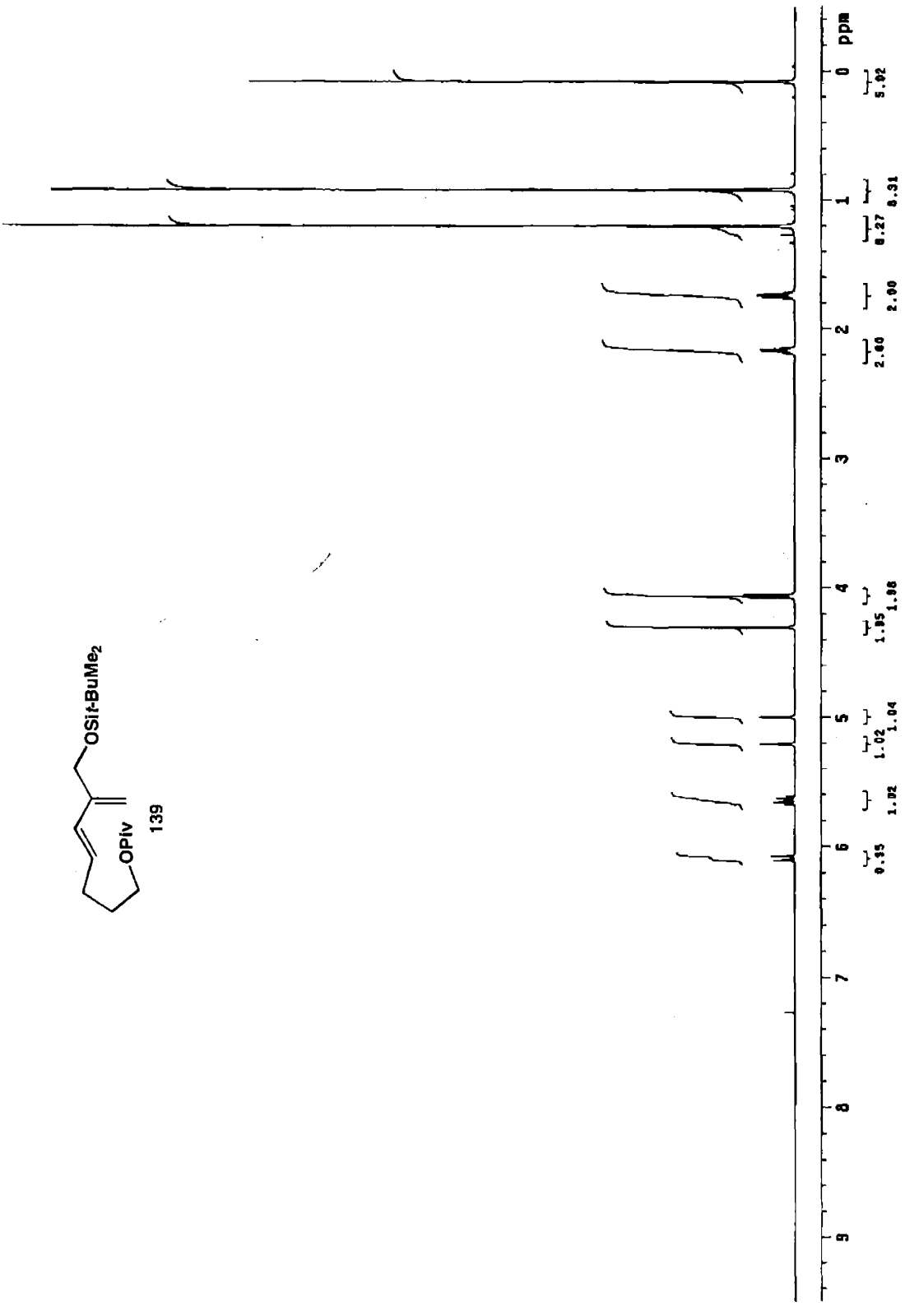
5-Trimethylacetoxy-(*E*)-1-pentenyl boronic acid (138). A 25-ml, 2-necked, pear-shaped flask equipped with a rubber septum and argon inlet adapter was charged with **137** (0.334 g, 1.99 mmol) and 3 mL of CH_2Cl_2. Dibromoborane-dimethylsulfide solution (2.6 mL, 1.0 M in CH_2Cl_2, 2.6 mmol) was added 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 **138** as a pale yellow solid, which was used in the next step without further purification.



138 139

6-(*tert*-Butyldimethylsiloxymethyl)-1-trimethylacetoxy-4,6-heptadiene (139). A 25-mL, one-necked, round-bottomed flask containing the crude boronic acid **138** (0.410 g, 1.92 mmol) was equipped with a rubber septum and argon-inlet needle and charged with vinyl iodide **130** (0.476 g, 1.60 mmol), 7 ml of THF, and $PdCl_2dppf{\bullet}CH_2Cl_2$ (0.013 g, 0.16 mmol). Sodium hydroxide solution (1.6 mL, 3.0 M in water, 4.8 mmol) was then added, and the reaction was stirred at room temperature for 90 min. The resulting orange solution was diluted with 25 mL of water, and 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 give 0.601 g of orange oil. Column chromatography on 20 g of silica gel (gradient elution with 0-3% EtOAc-hexanes) provided 0.413 g (76% based on vinyl iodide **130**) of **139** as a yellow oil.

IR (film):	2957, 2931, 2857, 1733, 1473, 1458, 1284, 1254, 1155, 1119, 1037, 1007, 965, 894, 837, 776, 668
^{1}H NMR (500 MHz, $CDCl_3$):	6.09 (d, J = 15.9 Hz, 1 H), 5.64 (dt, J = 16.2, 7.0 Hz, 1 H), 5.20 (d, J = 1.8 Hz, 1 H), 5.00 (s, 1 H), 4.30 (s, 2 H), 4.06 (t, J = 6.6 Hz, 2 H), 2.16 (q, J = 7.0 Hz, 2 H), 1.74 (quint, J = 6.7 Hz, 2 H), 1.20 (s, 9 H), 0.92 (s, 9 H), 0.08 (s, 6 H)
^{13}C NMR (125 MHz, $CDCl_3$):	178.8, 144.7, 130.8, 128.5, 113.1, 64.0, 63.2, 39.0, 29.7, 28.5, 27.4, 26.1, 18.6, -5.2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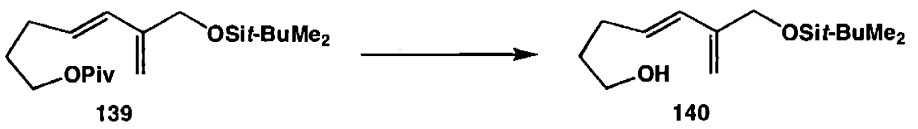
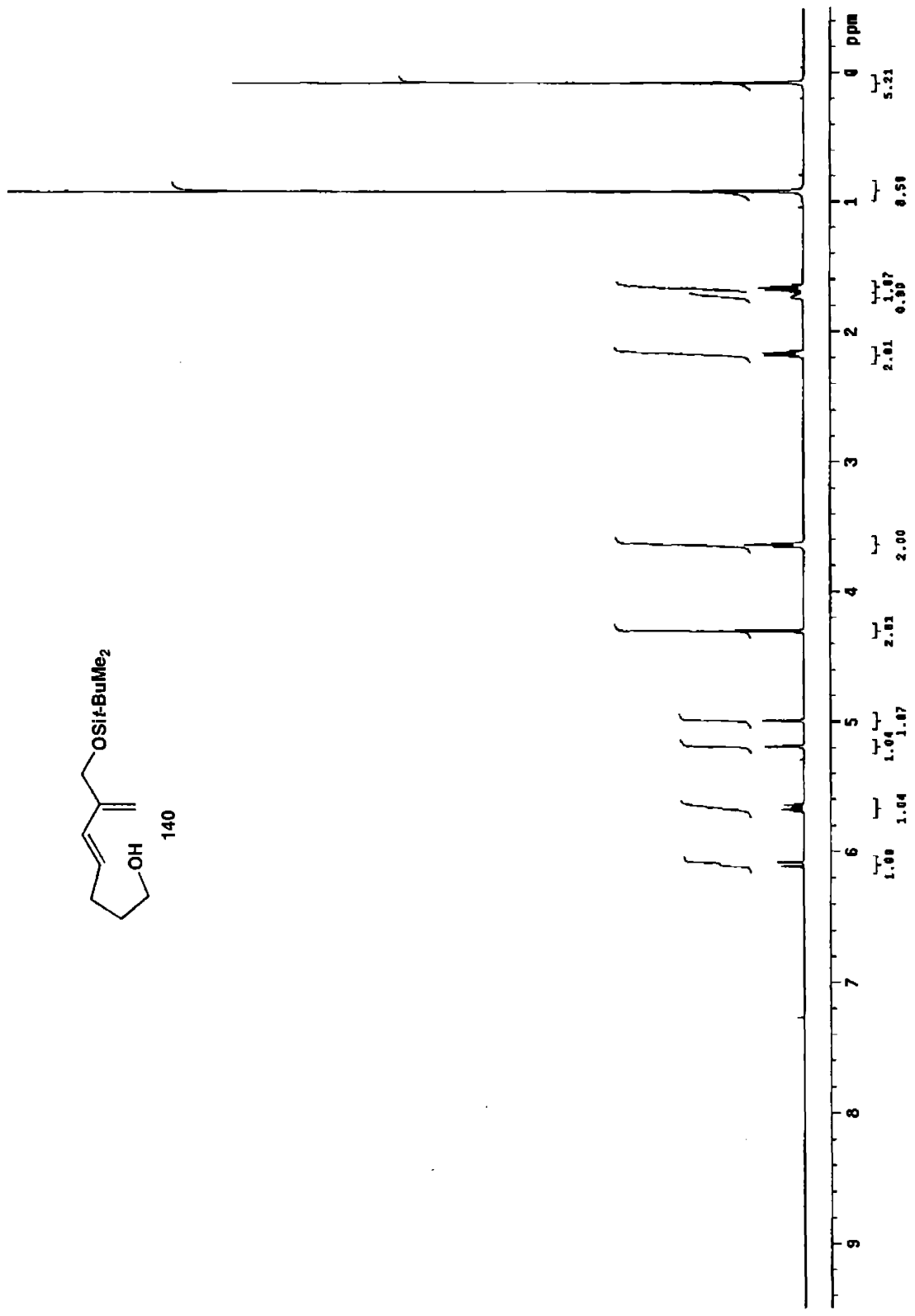
0.95



139 140

6-(*tert*-Butyldimethylsilyoxymethyl)-4,6-heptadien-1-ol (140). A 50-mL, two-necked, round-bottomed flask equipped with a rubber septum and argon inlet adapter was charged with pivalate ester **139** (0.420 g, 1.23 mmol) and 6 mL of CH_2Cl_2. The flask was cooled at –78 °C while 2.7 mL of DIBAL solution (1.0 M in hexane, 2.7 mmol) was added dropwise over 3 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 mixture was stirred at rt for 1 h. The biphasic mixture was then diluted with 20 mL of water, and the aqueous layer was separated and extracted with two 25-mL portions of CH_2Cl_2. The combined organic layers were washed with 25 mL of brine, dried over $MgSO_4$, filtered, and concentrated to give 0.336 g of pale yellow oil. Column chromatography on 15 g of silica gel (elution with 20% EtOAc-hexanes) afforded 0.298 g (94%) of **140** as a colorless oil.

IR (film):	3341, 2930, 2885, 2857, 1652, 1612, 1472, 1463, 1254, 1117, 964, 894, 836, 776
^{1}H NMR (500 MHz, $CDCl_3$):	6.10 (d, J = 16.2 Hz, 1 H), 5.66 (dt, J = 16.2, 7.0 Hz, 1 H), 5.19 (d, J = 1.2 Hz, 1 H), 4.99 (s, 1 H), 4.30 (s, 2 H), 3.64 (t, J = 6.6 Hz, 2 H), 2.17 (q, J = 7.3 Hz, 2 H), 1.73 (br, 1 H), 1.67 (quint, J = 6.7 Hz, 2 H), 0.92 (s, 9 H), 0.08 (s, 6 H)
^{13}C NMR (75 MHz, $CDCl_3$):	144.6, 130.3, 129.1, 112.8, 63.2, 62.5, 32.4, 29.7, 26.2, 18.7, -5.0


OSit-BuMe2
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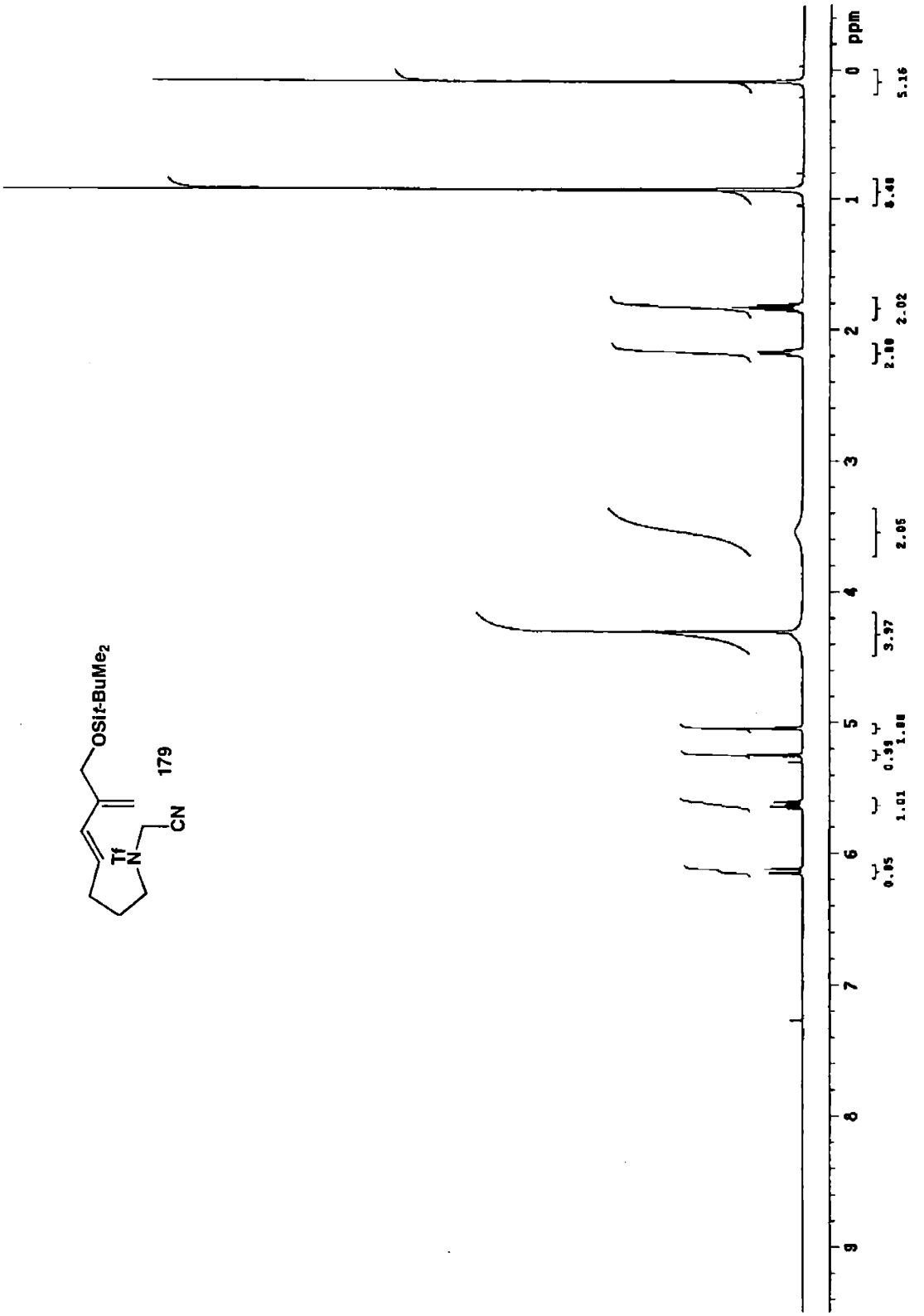
140
ppm
0
1
2
3
4
5
6
7
8
9
5.21
8.58
1.87
0.89
2.01
2.00
2.03
1.04
1.07
1.04
1.08

7-(*tert*-Butyldimethylsiloxymethyl)-5,7-octadienyl-(N-trifluoromethanesulfonyl) glycine nitrile (179). A 25-mL, two-necked, round-bottomed flask equipped with a rubber septum and an argon inlet adapter was charged with triphenylphosphine (0.292 g, 1.11 mmol), a solution of $HN(Tf)CH_2CN$ (0.183 g, 0.97 mmol) in 4 mL of THF, and a solution of alcohol **140** (0.238 g, 0.93 mmol) in 4 mL of toluene. DEAD (0.18 mL, 0.19 g, 1.1 mmol) was added dropwise via syringe over 2 min, and the resulting mixture was stirred at rt for 2 h and then concentrated to give 1.05 g of a pale yellow solid. This material was concentrated onto 2.0 g of silica gel and applied to a column of 25 g of silica gel. Gradient elution with 5-20% EtOAc-hexanes provided 0.339 g (86%) of **179** as a colorless oil.

IR (film):	2956, 2932, 2887, 2858, 1612, 1472, 1464, 1399, 1231, 1198, 1146, 1115, 967, 901, 838, 779
^1H NMR (500 MHz, $CDCl_3$):	6.14 (d, *J* = 16.2 Hz, 1 H), 5.63 (dt, J = 16.0, 6.9 Hz, 1 H), 5.25 (d, *J* = 1.5 Hz, 1 H), 5.04 (s, 1 H), 4.30 (br s, 4 H), 3.40-3.65 (br m, 2 H), 2.17 (q, *J* = 7.1 Hz, 2 H), 1.83 (quint, *J* = 7.5 Hz, 2 H), 0.93 (s, 9 H), 0.09 (s, 6 H)
^{13}C NMR (125 MHz, $CDCl_3$):	144.4, 131.7, 126.8, 119.8 (q, *J* = 322 Hz), 113.9, 113.3, 63.1, 49.2, 36.0, 29.7, 27.2, 26.1, 18.5, -5.2
HRMS $[M+Na]^+$:	Calcd for $C_{17}H_{29}F_3N_2NaO_3SSi$: 449.1512 Found: 449.1524


OSi-t-BuMe2
179
Tf
N
CN
ppm
0
1
2
3
4
5
6
7
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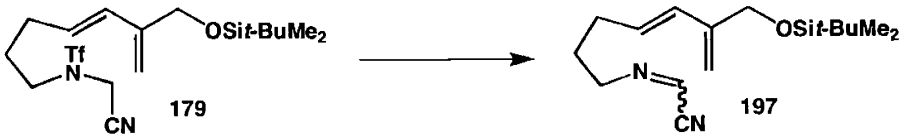
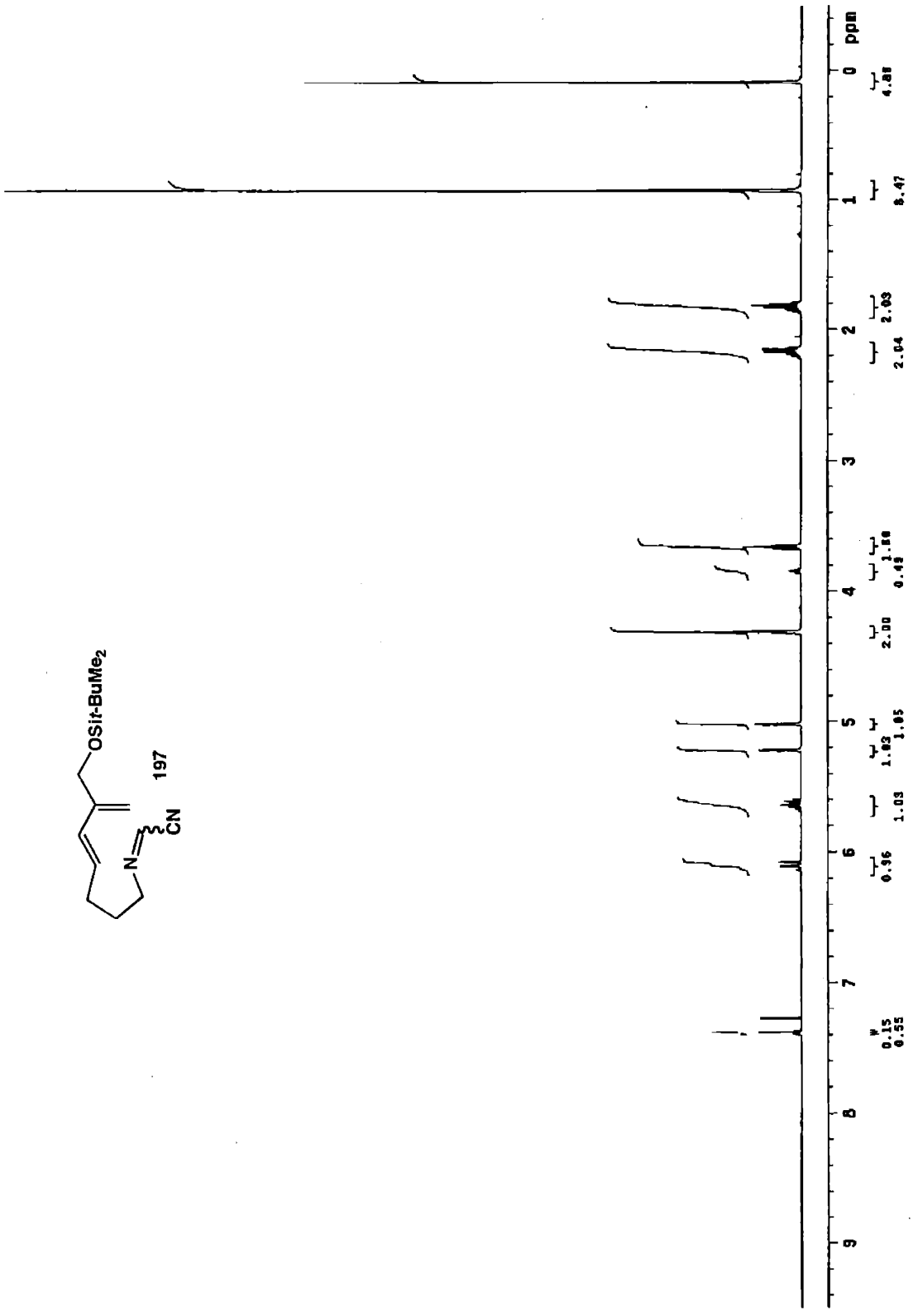
8.48
2.02
2.00
2.05
3.97
0.98
1.88
1.01
0.85



6-(*tert*-Butyldimethylsiloxymethyl)-4,6-heptadienyliminoacetonitrile (197). 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 (1.07 g, 3.28 mmol) and 3 mL of THF. A solution of triflamide **179** (0.350 g, 0.82 mmol) in 5 mL of THF was added, and the reaction mixture was heated at 55 °C for 3.5 h. The resulting mixture was allowed to cool to room temperature and then diluted with 25 mL of ether and 30 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 25 mL of brine, dried over $MgSO_4$, filtered, and concentrated to give 0.242 g of a yellow oil. Column chromatography on 8 g of Et_3N-deactivated silica gel (elution with 1% Et_3N-10% EtOAc-hexanes) provided 0.212 g (88%) of **197** (as an 76:24 mixture of E and Z imine isomers by ^1H NMR analysis) as a pale yellow oil.

IR (film):	2954, 2930, 2886, 2857, 1624, 1612, 1472, 1463, 1389, 1361, 1253, 1112, 1008, 966, 896, 837, 777
For E isomer:	
^1H NMR (500 MHz, $CDCl_3$):	7.38 (t, J = 1.5 Hz, 1 H), 6.09 (d, J = 15.9 Hz, 1 H), 5.63 (dt, J = 16.2, 7.0 Hz, 1 H), 5.22 (d, 1 H), 5.02 (s, 1 H), 4.31 (s, 2 H), 3.66 (dt, J = 6.9, 1.5 Hz, 2 H), 2.16 (q, J = 7.3 Hz, 2 H), 1.81 (quint, J = 7.0 Hz, 2 H), 0.93 (s, 9 H), 0.09 (s, 6 H)
^{13}C NMR (75 MHz, $CDCl_3$):	144.4, 136.0, 130.9, 128.1, 114.5, 113.3, 63.1, 62.4, 30.6, 29.5, 26.2, 18.6, -5.0
For Z isomer:	
^1H NMR (500 MHz, $CDCl_3$):	7.39 (t, J = 2.2 Hz, 1 H), 6.12 (d, J = 15.9 Hz, 1 H), 5.66 (dt, J = 16.2, 7.0 Hz, 2 H), 5.22 (s, 1 H), 5.02 (s, 1 H), 4.32 (s, 2 H), 3.84 (dt, J = 6.9, 2.2 Hz, 2 H), 2.19 (q, J = 7.3 Hz,

	2 H), 1.84 (quint, J = 7.0 Hz, 2 H), 0.93 (s, 9 H), 0.09 (s, 6 H)
^{13}C NMR (75 MHz, $CDCl_3$):	144.5, 131.6, 130.9, 128.1, 113.1, 110.4, 63.1, 59.2, 30.8, 29.7, 26.2, 18.6, -5.0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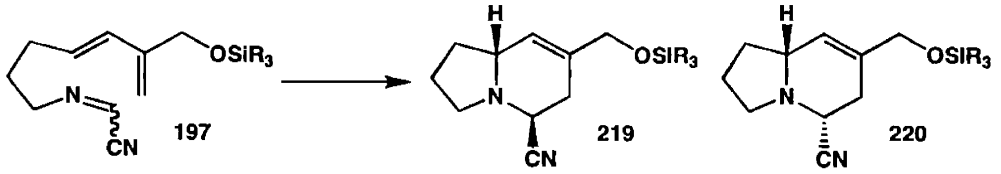
CN
N
ppm



2-(*tert*-Butyldimethylsiloxymethyl)-*cis*-1,2-didehydro-4-cyanoquinolizidine (219) and **2-(*tert*-Butyldimethylsiloxymethyl)-*trans*-1,2-didehydro-4-cyanoquinolizidine (220).** A threaded Pyrex tube (ca. 40 mL capacity) equipped with a rubber septum and argon inlet needle was charged with imine **197** (0.208 g, 0.71 mmol), BHT (0.470 g, 2.13 mmol), and 14 mL of toluene. The solution was degassed by three freeze-pump-thaw cycles and then sealed with a threaded Teflon cap. The reaction mixture was heated in a 120 °C oil bath for 24 h and then allowed to cool to rt. Concentration gave 0.810 g of a brown oil, and column chromatography on 15 g of silica gel (gradient elution with 1% Et_3N-10-15% EtOAc-hexanes) afforded 0.121 g (58%) of **219** and **220** (73:27 mixture by ^1H NMR analysis) as a pale yellow oil.

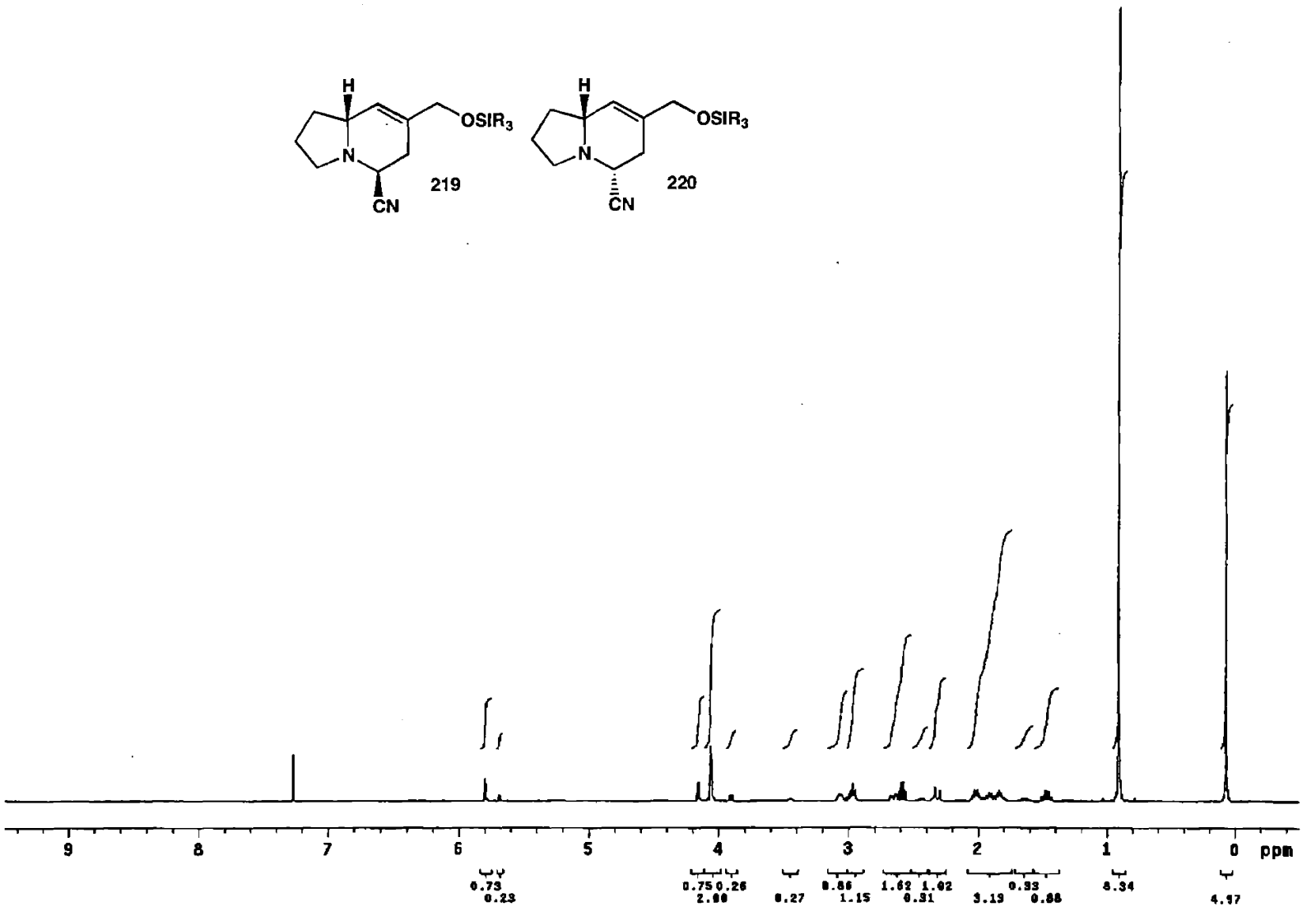
IR (film):	2956, 2930, 2857, 1472, 1463, 1361, 1253, 1179, 1165, 1084, 1066, 1006, 838, 777	
HRMS $[M]^+$:	Calcd for $C_{16}H_{28}N_2OSi$:	292.1965
	Found:	292.1954

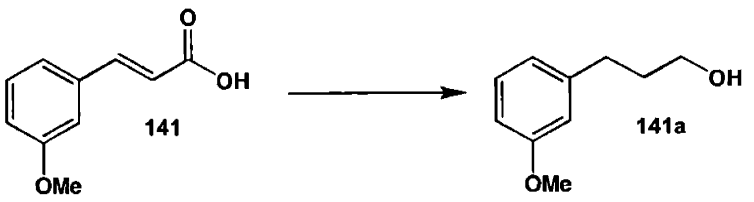
For (**219**):

^1H NMR (500 MHz, $CDCl_3$):	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, $CDCl_3$):	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 (**220**):

^{1}H NMR (500 MHz, $CDCl_3$):	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, $CDCl_3$):	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

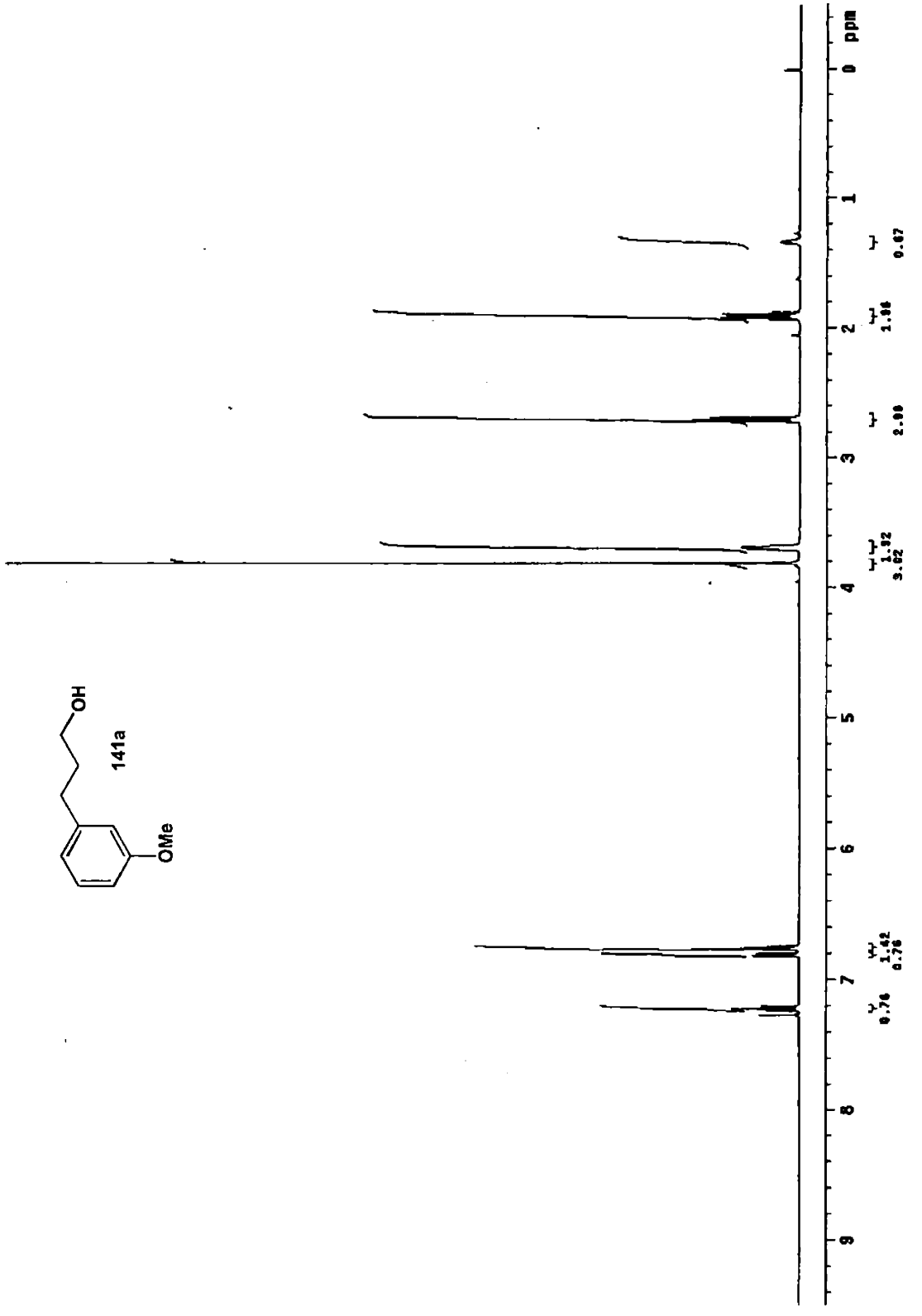

H
OSIR3
N
CN
219
H
OSIR3
N
CN
220
9
8
7
6
5
4
3
2
1
0
ppm
0.73
0.23
0.75
0.26
2.00
0.27
0.86
1.15
1.62
1.02
0.31
0.93
3.13
0.88
0.34
4.97



3-(3-Methoxyphenyl)-1-propanol (141a). A 250-mL, round-bottomed flask equipped with a reflux condenser fitted with an argon inlet adapter was charged with cinammic acid **141** (3.00 g, 16.8 mmol) and 75 mL of THF. $LiAlH_4$ (1.28 g, 33.7 mmol) was then added in three equal portions over 10 min. The resulting mixture was heated at reflux for 16 h, and then allowed to cool to rt. The excess hydride was destroyed by careful addition of 10 mL of 1 N aq HCl solution, followed by dilution with 100 mL of sat aq Rochelle salt solution. After stirring at rt for 30 min, the aqueous layer was separated and extracted with three 50-mL portions of ether. The combined organic layers were washed with two 50-mL portions of 1 M aq NaOH solution and 60 mL of brine, dried over $MgSO_4$, filtered, concentrated to give 2.84 g of a yellow oil. Column chromatography on 70 g of silica gel (gradient elution 25-40% EtOAc-hexanes) afforded 1.84 g (66%) of **141a** as a colorless oil with spectral data consistent with that previously reported for this compound.[193]

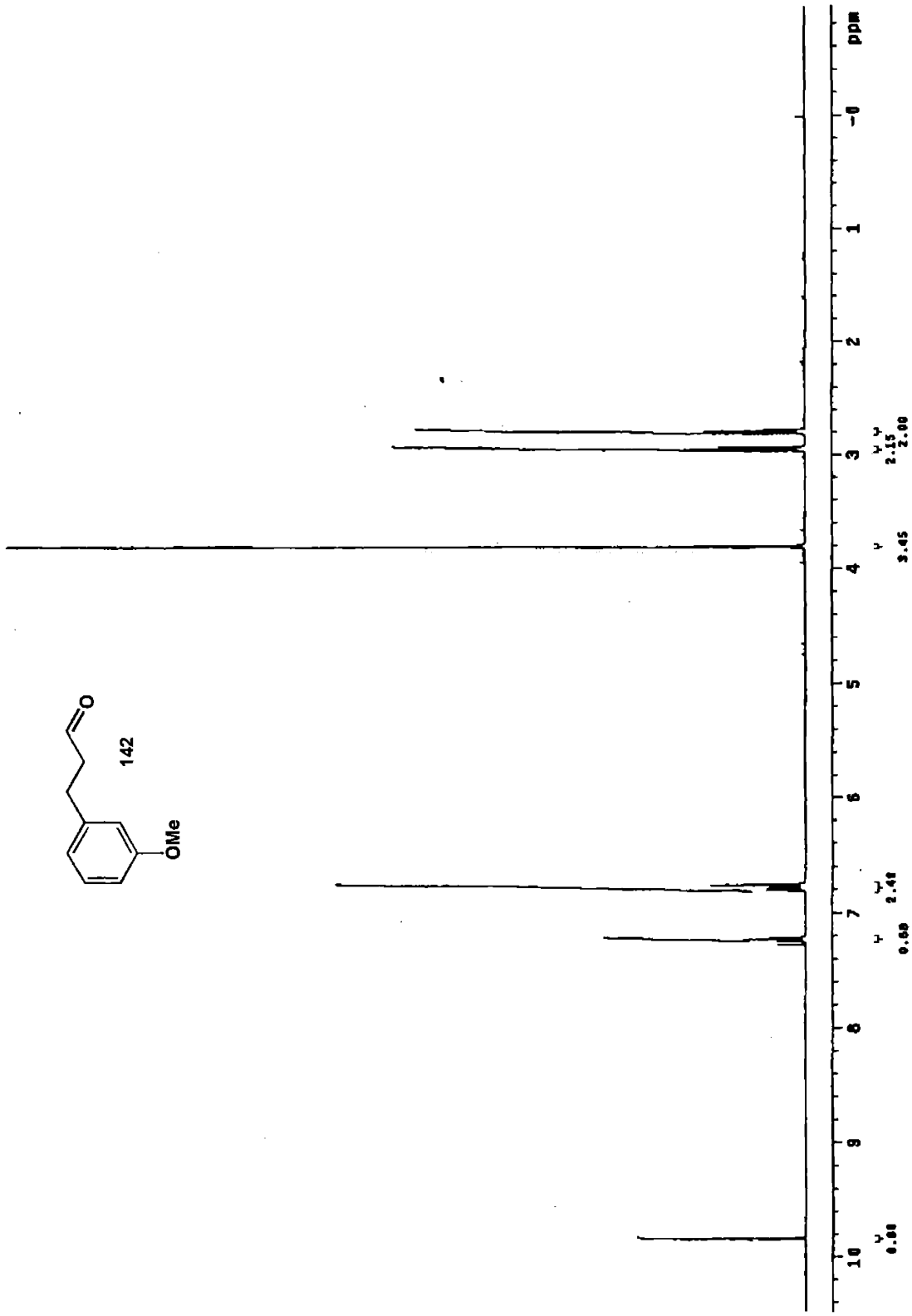
IR (film):	3353, 3000, 2941, 2836, 1602, 1489, 1455, 1437, 1315, 1260, 1152, 1039, 996, 932, 911, 874
^{1}H NMR (500 MHz, $CDCl_3$):	7.22 (dd, J = 7.6, 7.6 Hz, 1 H), 6.81 (d, J = 7.6 Hz, 1 H), 6.74-6.77 (m, 2 H), 3.82 (s, 3 H), 3.69 (br m, 2 H) 2.70 (t, J = 7.6 Hz, 2 H), 1.88-1.94 (m, 2 H), 1.34 (br, 1 H)
^{13}C NMR (125 MHz, $CDCl_3$):	159.7, 143.7, 129.5, 121.0, 114.3, 111.2, 62.3, 55.3, 34.2, 32.3

[193] Manas, A. R. B.; Smith, R. A. J. *Tetrahedron* **1987**, *43*, 1847.


OH
141a
OMe
ppm

3-(3-Methoxyphenyl)-1-propanal (142). A 100-mL, round-bottomed flask equipped with a rubber septum and argon inlet needle was charged with 30 mL of CH_2Cl_2 and oxalyl chloride (1.20 mL, 1.75 g, 13.8 mmol). The solution was cooled at –78 °C while DMSO (1.95 mL, 2.15 g, 27.5 mmol) was added dropwise via syringe over 4 min. The solution was stirred at –78 °C for 10 min and then alcohol **141a** (1.76 g, 10.6 mmol) in 15 mL of CH_2Cl_2 was added dropwise over 10 min. After stirring at –78 °C for 20 min, Et_3N (5.9 mL, 4.3 g, 42 mmol) was added over 2 min and the solution was stirred at –78 °C for 10 min and then rt for 1 h. The cloudy, yellow solution was diluted with 10 ml of CH_2Cl_2 and 40 mL of water. The aqueous layer was separated and extracted with two 20-mL portions of CH_2Cl_2. The combined organic layers were washed with 30 mL of brine, dried over $MgSO_4$, filtered, and concentrated to give 2.12 g of an oily, yellow solid. This material was concentrated onto 4 g of silica gel and applied to a column of 45 g of silica gel. Elution with 25% EtOAc-hexanes afforded 1.58 g (91%) of **142** as a yellow oil with spectral data consistent with that previously reported for this compound.[193]

IR (film):	2980, 2920, 2818, 2710, 1715, 1595, 1578, 1483, 1450, 1430, 1258, 1150, 1034
^{1}H NMR (500 MHz, $CDCl_3$):	9.83 (t, J = 1.4 Hz, 1 H), 7.23 (dd, J = 7.8, 7.8 Hz, 1 H), 6.79 (d, J = 7.3 Hz, 1 H), 6.75-6.78 (m, 2 H), 3.81 (s, 3 H), 2.95 (t, J = 7.5 Hz, 2 H) 2.79 (dt, J = 7.5, 1.4 Hz, 2 H)
^{13}C NMR (125 MHz, $CDCl_3$):	201.8, 159.9, 142.1, 129.8, 120.8, 114.3, 111.7, 55.4, 45.4, 28.3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OMe
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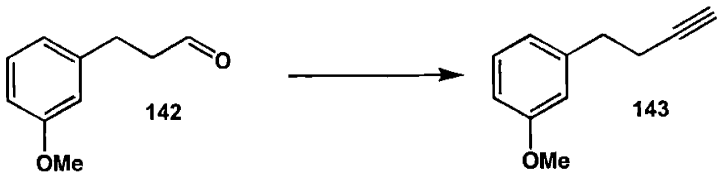
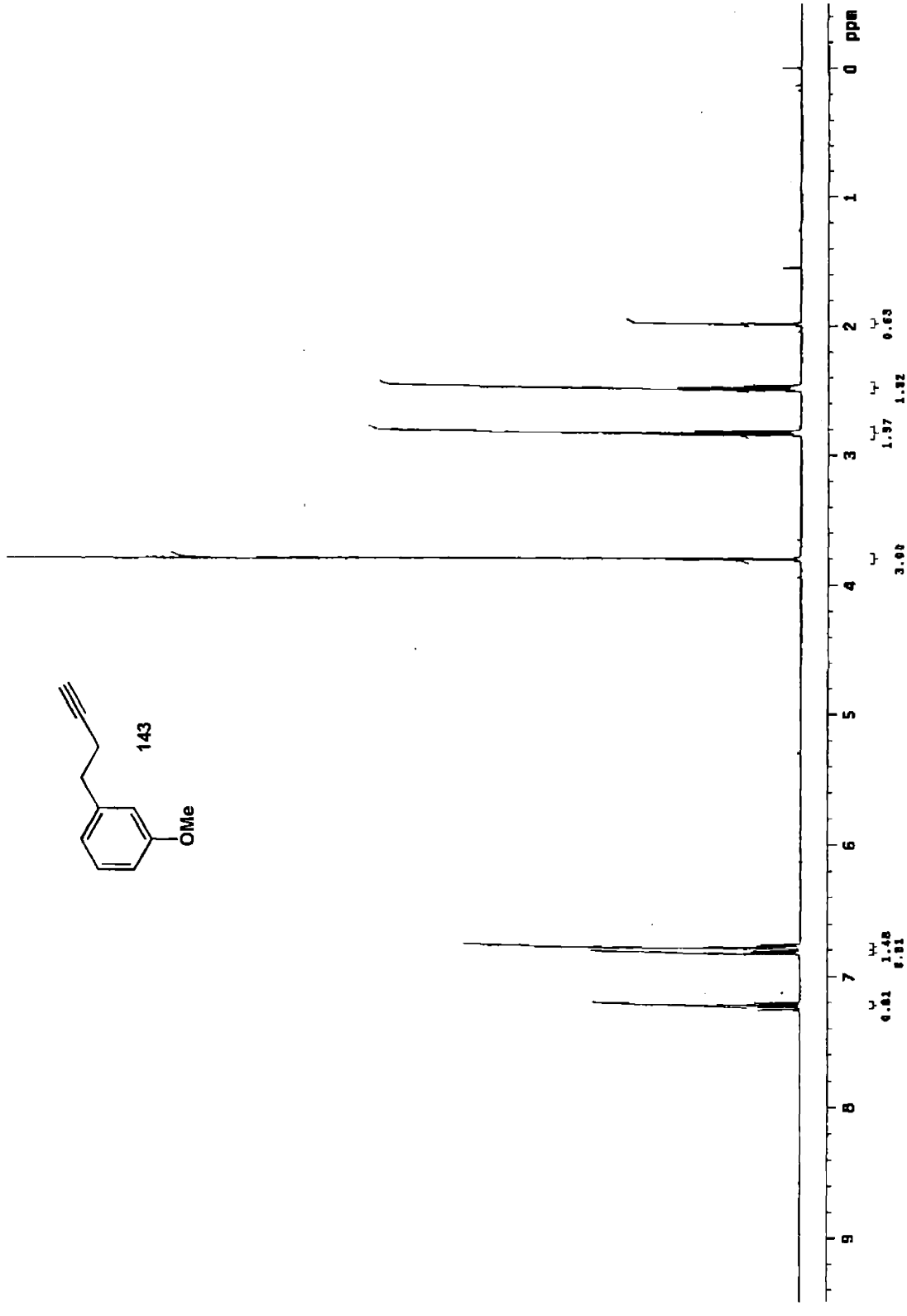
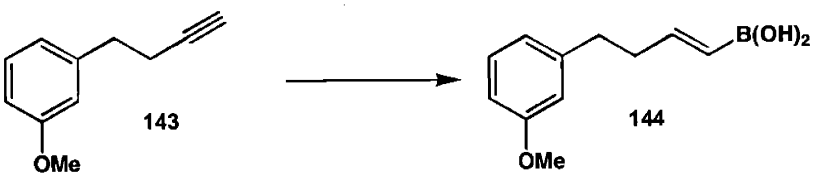
0.88
0.88



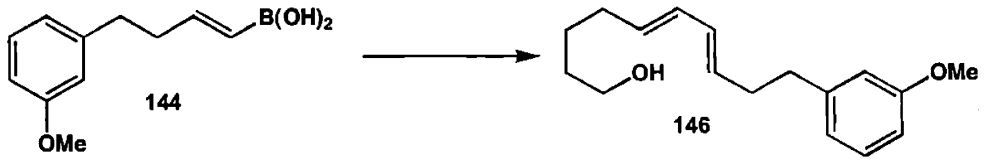
3-(3-Butynyl)-1-methoxybenzene (143). A 25-mL, two-necked, round-bottomed flask equipped with a rubber septum and argon inlet adapter was charged with diisopropylamine (0.56 mL, 0.40 g, 4.0 mmol) and 8 mL of THF. The solution was cooled at 0 °C while 1.60 mL of *n*-BuLi solution (2.49 M in hexane, 3.98 mmol) was added dropwise via syringe over 3 min. This solution was allowed to stir at 0 °C for 10 min and then cooled at –78 °C while aldehyde **142** in 8 mL of THF was added dropwise over 10 min. The resulting solution was stirred at –78 °C for 5 h and rt for 2 h. The solution was diluted with 5 mL of satd aq NH_4Cl solution, 20 mL of water, and 20 mL of ether. The aqueous layer was separated and extracted with three 15-mL portions of ether, and the combined organic layers were washed with 30 mL of brine, dried over $MgSO_4$, filtered, and concentrated to provide 0.695 g of yellow oil. Column chromatography on 20 g of silica gel (elution with 2% EtOAc-hexanes) afforded 0.398 g (75%) of **143** as a colorless oil.

IR (film):	3293, 3030, 3002, 2938, 2863, 2836, 2118, 1603, 1585, 1490, 1466, 1455, 1437, 1261, 1153, 1092, 1084, 1053, 995, 875, 779, 740, 696, 635
^{1}H NMR (500 MHz, $CDCl_3$):	7.22 (dd, J = 7.6, 7.6 Hz, 1 H), 6.82 (d, J = 7.6 Hz, 1 H), 6.76-6.78 (m, 2 H), 3.80 (s, 3 H), 2.83 (t, J = 7.6 Hz, 2 H) 2.48 (dt, J = 7.5, 2.6 Hz, 2 H), 1.99 (t, J = 2.6 Hz, 1 H)
^{13}C NMR (125 MHz, $CDCl_3$):	159.7, 142.1, 129.5, 120.9, 114.3, 111.7, 83.9, 69.1, 55.2, 35.0, 20.6


143
OMe
ppm



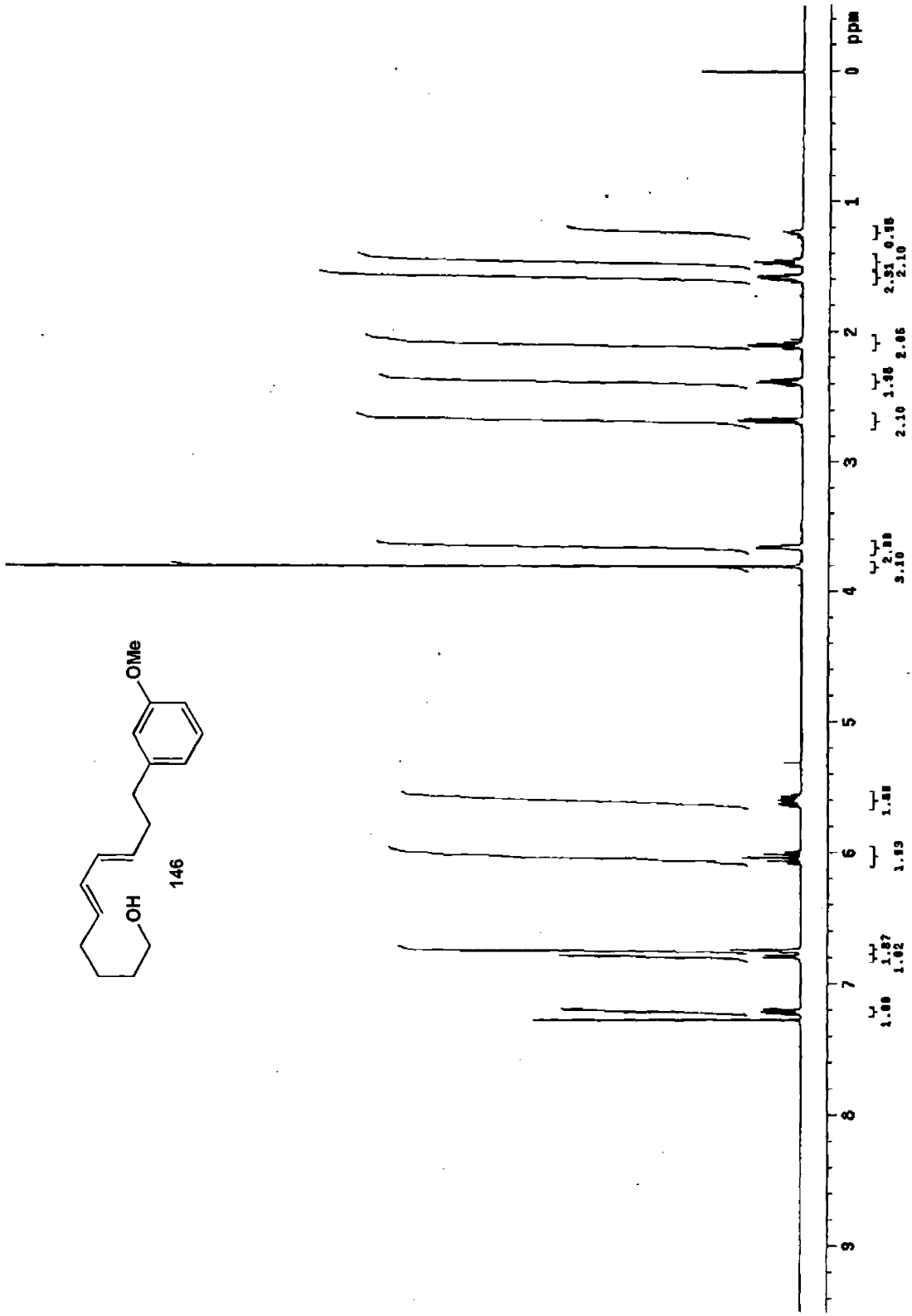
4-(3-Methoxyphenyl)-(*E*)-1-butenylboronic acid (144). A 25-ml, two-necked, pear-shaped flask equipped with a rubber septum and an argon inlet adapter was charged with alkyne **143** (0.283 g, 1.77 mmol) and 3 mL of CH_2Cl_2. Dibromoborane-dimethylsulfide solution (2.8 mL, 1.0 M in CH_2Cl_2, 2.8 mmol) was added dropwise over 4 min via syringe. The resulting solution was stirred at rt for 8 h, and then was cooled at 0 °C and transferred via cannula to a 25-mL, round-bottomed flask containing 8 mL of ether and 2 mL of water cooled at 0 °C under argon. The biphasic mixture was stirred at 0 °C for 10 min and then diluted with 40 mL of ether. The organic layer was separated and washed with two 20-mL portions of cold water. The combined aqueous layers were extracted with 20 ml of ether, and the combined organic layers were washed with 80 mL of brine, dried over $MgSO_4$, filtered, and concentrated to give 0.348 g (96% crude yield) of **144** as a pale yellow solid, which was used in the next step without further purification.



10-(3-Methoxyphenyl)-(*E*),(*E*)-5,7-decadien-1-ol (146). A 25-mL, one-necked, round-bottomed flask equipped with a reflux condenser fitted with an argon inlet adapter was charged with crude boronic acid **144** (0.311 g, 1.51 mmol) and (*E*)-6-iodo-5-hexen-1-ol[194] **145** (0.310 g, 1.37 mmol), 6 ml of THF, and $PdCl_2dppf{\bullet}CH_2Cl_2$ (0.0.34 g, 0.041 mmol). Sodium hydroxide solution (1.4 mL, 3.0 M in water, 4.1 mmol) was then added, and the reaction mixture was stirred at 50 °C for 25 min. The resulting orange solution was allowed to cool to rt and diluted with 20 mL water 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 25 mL of brine, dried over anhydrous $MgSO_4$, filtered, and concentrated to give 0.396 g of orange oil. Column chromatography on 15 g of silica gel (elution with 20% EtOAc-hexanes) provided 0.299 g (84% based on vinyl iodide **145**) of **146** as a yellow oil.

IR (film):	3354, 3014, 2934, 2857, 2836, 1601, 1584, 1488, 1454, 1436, 1314, 1260, 1190, 1164, 1152, 1048, 989, 910, 873, 778, 735, 695
^{1}H NMR (500 MHz, $CDCl_3$):	7.21 (dd, J = 8.9, 7.6 Hz, 1 H), 6.79 (d, J = 7.9 Hz, 1 H), 6.74-6.76 (m, 2 H), 5.99-6.08 (m, 2 H), 5.55-5.65 (m, 2 H) 3.81 (s, 3 H), 3.66 (app q, J = 4.9 Hz, 2 H), 2.68 (t, J = 8.2 Hz, 2 H) 2.38 (app q, J = 7.3 Hz, 2 H), 2.10 (app q, J = 7.3 Hz, 2 H), 1.56-1.62 (m, 2 H), 1.45-1.50 (m, 2 H), 1.23 (br, 1 H)
^{13}C NMR (125 MHz, $CDCl_3$):	159.7, 143.7, 132.5, 131.5, 131.0, 130.7, 129.4, 121.0, 114.3, 111.2, 62.9, 55.3, 36.0, 34.5, 32.4, 32.4, 25.6

[194] Prepared as reported according to: Lipshutz, B. H.; Keil, R.; Ellsworth, E. L. *Tetrahedron Lett.* **1990**, *31*, 7257.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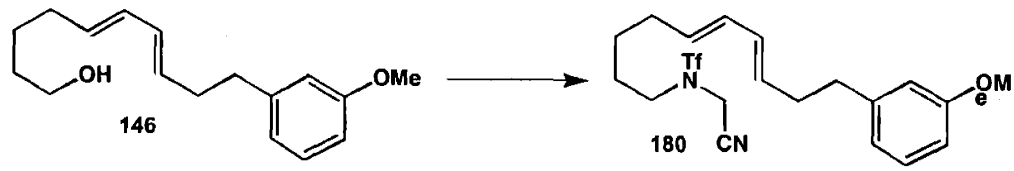
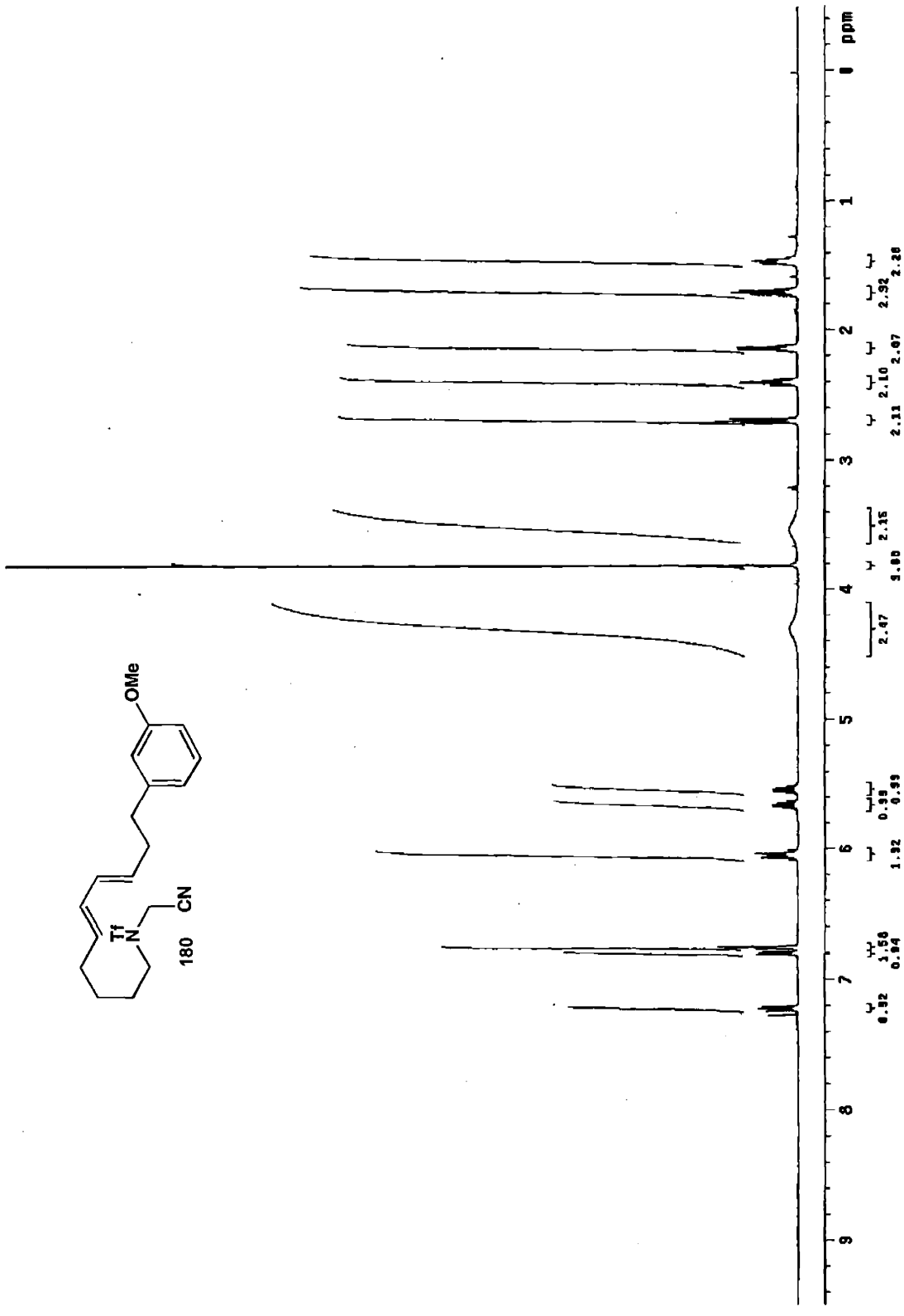
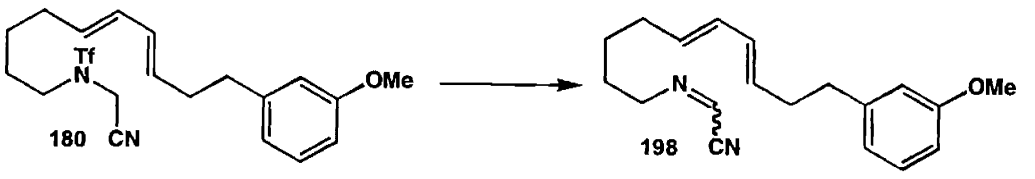
146
0 ppm



***N*-(Cyanomethyl)-*N*-(10-(3-methoxyphenyl)-(*E*),(*E*)-5,7-decadienyl)trifluoromethanesulfonamide (180).** A 25-mL, two-necked, round-bottomed flask equipped with a rubber septum and an argon inlet adapter was charged with triphenylphosphine (0.415 g, 1.58 mmol), a solution of $HN(Tf)CH_2CN$ (0.260 g, 1.38 mmol) in 6 mL of THF, and a solution of alcohol **146** (0.343 g, 1.32 mmol) in 6 mL of toluene. DEAD (0.25 mL, 0.28 g, 1.6 mmol) was added dropwise via syringe over 2 min, and the resulting mixture was stirred at rt for 1 h and then concentrated to give 1.5 g of a yellow solid. This material was concentrated onto 3.0 g of silica gel and applied to a column of 45 g of silica gel. Gradient elution with 10-20% EtOAc-hexanes provided 0.468 g (83%) of **180** as a colorless oil.

IR (film):	3015, 2939, 2859, 2838, 1733, 1601, 1584, 1488, 1454, 1437, 1397, 1352, 1261, 1230, 1196, 1144, 1044, 991, 900, 782, 738, 696
^{1}H NMR (500 MHz, $CDCl_3$):	7.22 (dd, J = 8.8, 7.6 Hz, 1 H), 6.80 (d, J = 7.6 Hz, 1 H), 6.75-6.76 (m, 2 H), 6.03-6.07 (m, 2 H), 5.65 (dt, J = 13.9, 6.9 Hz, 1 H), 5.54 (dt, J = 14.0, 7.0 Hz, 1 H), 4.15-4.45 (br, 2 H), 3.81 (s, 3 H), 3.41-3.68 (br, 2 H), 2.70 (t, J = 7.6 Hz, 2 H) 2.40 (dt, J = 8.2, 7.0 Hz, 2 H), 2.14 (app q, J = 7.1 Hz, 2 H), 1.71 (quint, J = 7.6 Hz, 2 H), 1.46 (quint, J = 7.3 Hz, 2 H)
^{13}C NMR (125 MHz, $CDCl_3$):	159.8, 143.6, 132.3, 131.6, 131.0, 130.6, 129.5, 121.0, 119.8 (q, J = 322 Hz), 114.4, 113.3, 111.2, 55.3, 49.2, 36.0, 35.7, 34.5, 31.9, 26.7, 25.8
HRMS $[M+Na]^+$:	Calcd for $C_{20}H_{25}F_3N_2NaO_3S$: 453.1430 Found: 453.1446


OMe
Tf
N
CN
180
ppm



(10-(3-Methoxyphenyl)-(*E*),(*E*)-5,7-decadienyl)iminoacetonitrile (198). 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 (1.14 g, 3.49 mmol). A solution of triflamide **180** (0.376 g, 0.87 mmol) in 5 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 30 mL of water. The aqueous layer was separated and extracted with three 15-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 0.251 g of a yellow oil. Column chromatography on 10 g of Et_3N-deactivated silica gel (elution with 1% Et_3N-10% EtOAc-hexanes) provided 0.214 g (83%) of **198** (as an 78:22 mixture of E and Z imine isomers by ^1H NMR analysis) as a pale yellow oil.

IR (film): 3015, 2936, 2856, 1601, 1582, 1488, 1454, 1260, 1152, 1045, 990, 874, 780, 737, 696

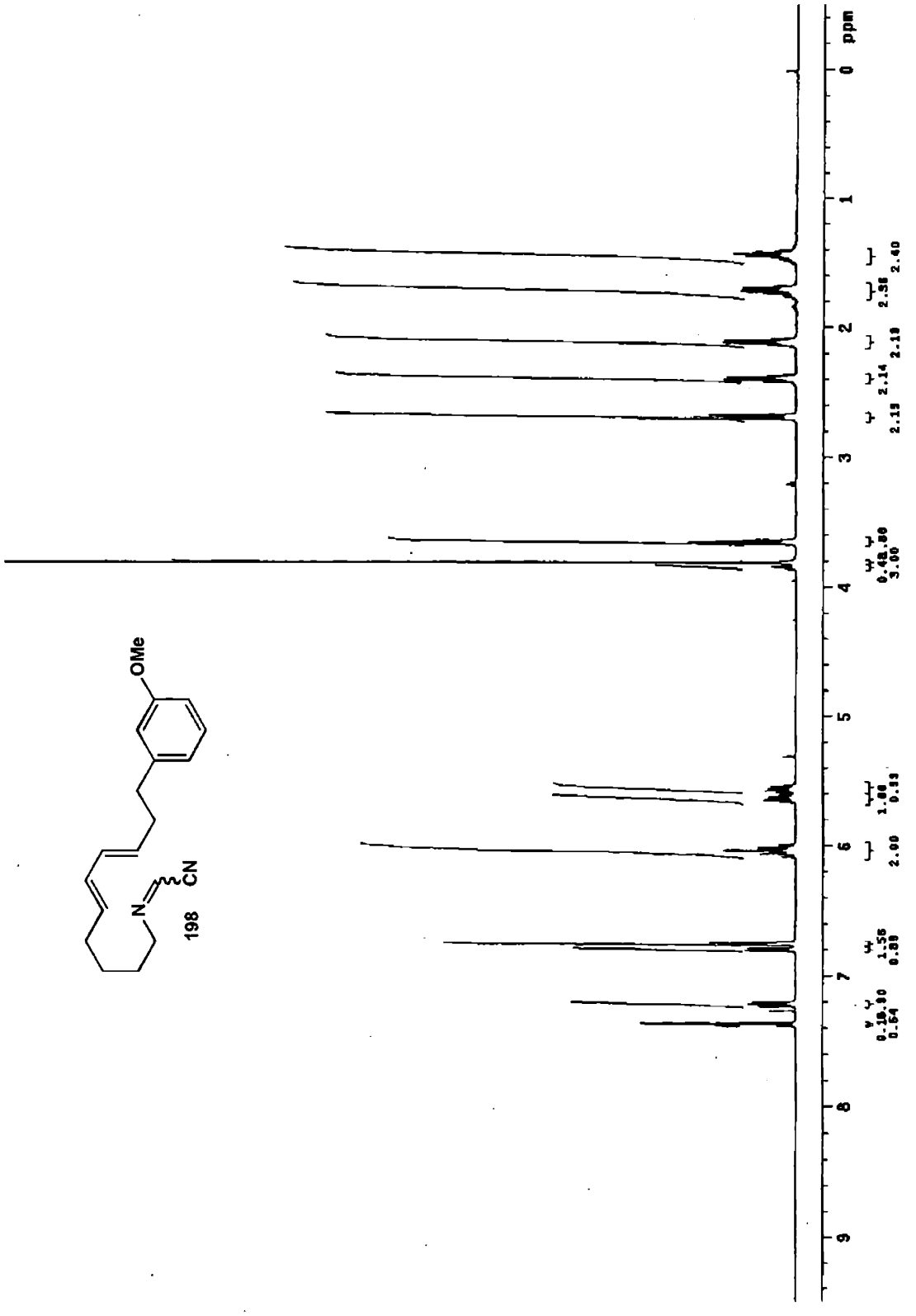
For E isomer:

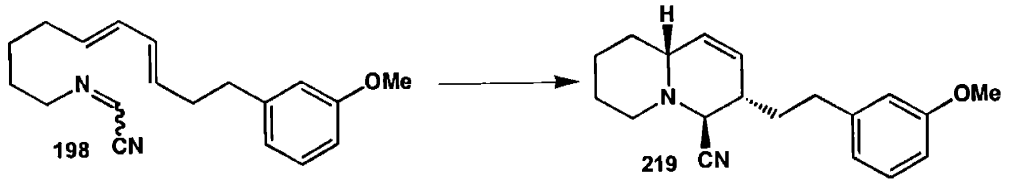
^1H NMR (500 MHz, $CDCl_3$): 7.36 (t, J = 1.4 Hz, 1 H), 7.21 (dd, J = 8.9, 7.3 Hz, 1 H), 6.79 (d, J = 7.6 Hz, 1 H), 6.75-6.76 (m, 2 H), 5.99-6.08 (m, 2 H), 5.60-5.66 (m, 1 H), 5.53-5.59 (m, 1 H), 3.81 (s, 3 H), 3.65 (dt, J = 6.9, 1.4 Hz, 1 H), 2.69 (t, J = 7.6 Hz, 2 H) 2.39 (app q, J = 7.5 Hz, 2 H), 2.09-2.15 (m, 2 H), 1.68-1.77 (m, 2 H), 1.40-1.50 (m, 2 H)

^{13}C NMR (125 MHz, $CDCl_3$): 159.7, 143.7, 135.9, 131.9, 131.8, 131.1, 130.8, 129.4, 121.0, 114.6, 114.4, 111.2, 63.1, 55.3, 36.0, 34.5, 32.3, 29.5, 26.9

For Z isomer:

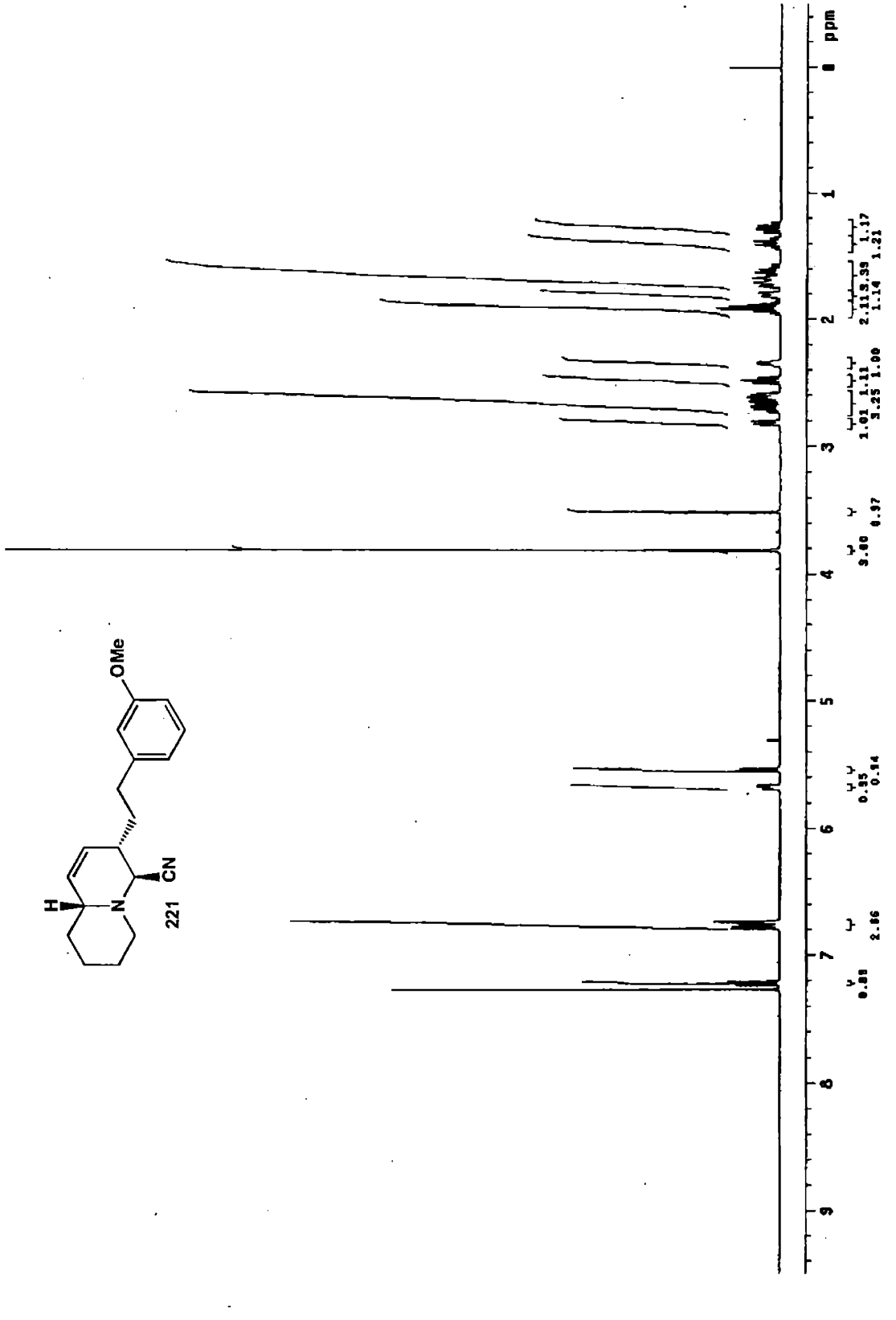
^{1}H NMR (500 MHz, $CDCl_3$):	7.38 (t, J = 2.1 Hz, 1 H), 7.21 (dd, J = 8.9, 7.3 Hz, 1 H), 6.79 (d, J = 7.6 Hz, 1 H), 6.75-6.76 (m, 2 H), 5.99-6.08 (m, 2 H), 5.60-5.66 (m, 1 H), 5.53-5.59 (m, 1 H), 3.84 (dt, J = 6.9, 2.0 Hz, 1 H), 3.81 (s, 3 H), 2.69 (t, J = 7.6 Hz, 2 H) 2.39 (app q, J = 7.5 Hz, 2 H), 2.09-2.15 (m, 2 H), 1.68-1.77 (m, 2 H), 1.40-1.50 (m, 2 H)
^{13}C NMR (125 MHz, $CDCl_3$):	159.7, 143.7, 132.0, 131.7, 131.5, 131.0, 130.9, 129.4, 121.0, 114.4, 114.3, 111.2, 59.8, 55.3, 36.0, 34.5, 32.3, 29.5, 27.0


OMe
N
CN
198
ppm



3-[2-(3-Methoxyphenyl)ethyl]-*cis*-1,2-didehydro-4-cyanoquinolizidine (219). A threaded Pyrex tube (ca. 60 mL capacity) equipped with a rubber septum and argon inlet needle was charged with imine **198** (0.205 g, 0.69 mmol), BHT (0.457 g, 2.07 mmol), and 14 mL of toluene. The solution was degassed by three freeze-pump-thaw cycles and then sealed with a threaded Teflon cap. The reaction mixture was heated in a 120 °C oil bath for 18 h and then allowed to cool to rt. Concentration gave 0.735 g of a brown oil which was concentrated onto 2 g of silica gel and applied to a column of 25 g of silica gel. Gradient elution with 1% Et_3N-0-5% EtOAc-hexanes afforded 0.132 g (64%) of **219** as a pale yellow oil.

IR (film):	3030, 2936, 2856, 2806, 2221, 1601, 1584, 1489, 1453, 1319, 1261, 1152, 1129, 1107, 1045, 907, 877, 849, 778, 749, 696
^{1}H NMR (500 MHz, $CDCl_3$):	7.22 (dd, J = 7.8, 7.8 Hz, 1 H), 6.78 (d, J = 7.6 Hz, 1 H), 6.74-6.78 (m, 2 H), 5.68 (ddd, J = 10.0, 5.1, 2.4 Hz, 1 H), 5.54 (d, J = 10.1 Hz, 1 H), 3.81 (s, 3 H), 3.51 (s, 1 H), 2.81 (dt, J = 11.4, 2.1 Hz, 1 H), 2.59-2.73 (m, 3 H) 2.48 (ddd, J = 11.6, 11.0, 3.1 Hz, 2 H), 2.32-2.37 (m, 1 H), 1.88-1.95 (m, 2 H), 1.79-1.82 (m, 1 H), 1.59-1.74 (m, 3 H), 1.39 1.96 (app tq, J = 12.9, 4.0 Hz, 1 H), 1.27 (app dq, J = 12.2, 3.7 Hz, 1 H)
^{13}C NMR (125 MHz, $CDCl_3$):	159.9, 143.4, 130.5, 129.7, 125.0, 120.9, 117.2, 114.4, 111.3, 57.5, 56.4, 55.4, 54.3, 39.7, 36.0, 33.6, 32.0, 26.0, 24.9
Elemental Analysis:	Calcd for $C_{19}H_{24}N_2O$: C, 76.74; H, 8.24; N, 9.42 Found: C, 76.99; H, 8.16; N, 9.45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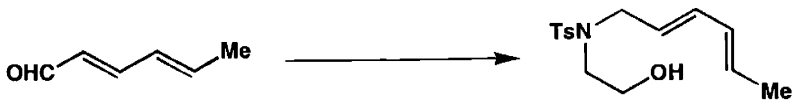
H
N
CN
221
ppm

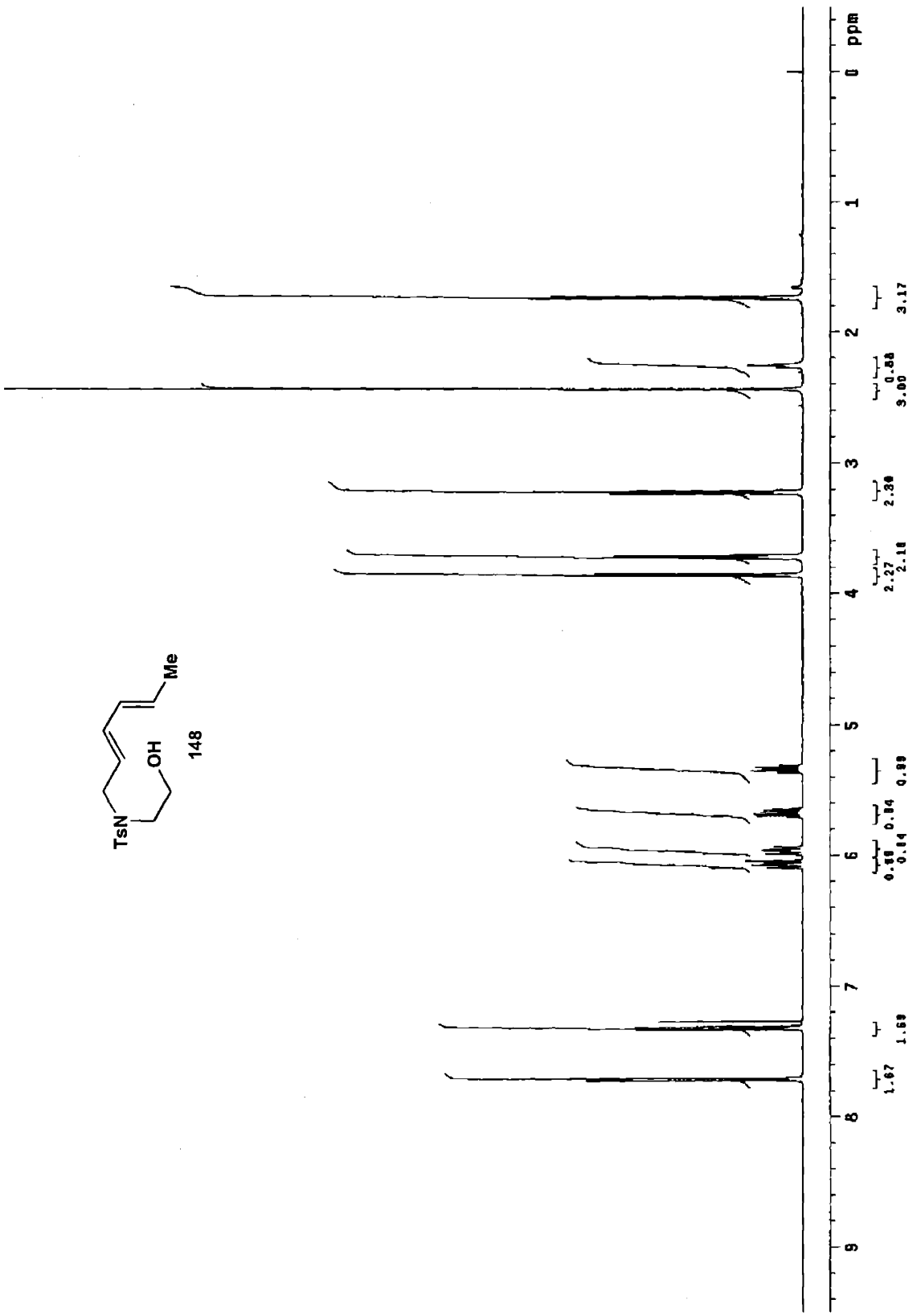


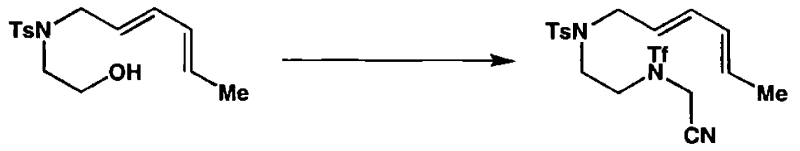
147 148

***N*-([(4-Methylphenyl)sulfonyl][(*E*),(*E*)-2,4-hexadienyl])aminoethanol (148).** A 25-mL, round-bottomed flask equipped with a reflux condenser fitted with an argon inlet adapter was charged with $NaHCO_3$ (0.570 g, 6.78 mmol), 12 mL of MeOH, sorbylaldehyde (**147**) (0.50 mL, 0.44 g, 4.5 mmol), and ethanolamine (0.33 mL, 0.59 g, 5.4 mmol). The reaction mixture was heated at 55 °C for 4 h, and then cooled at 0 °C while $NaBH_4$ (0.206 g, 5.4 mmol) was added in one portion. This mixture was allowed to slowly warming to rt and stirred for 17 h, after which the MeOH was removed by rotary evaporation. The residue was dissolved in 40 mL of EtOAc and washed with 40 mL of a half saturated K_2CO_3 solution. The aqueous layer was separated and extracted with six 15-mL portions of EtOAc, and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated to give 0.598 g of orange oil that was used in the next step without further purification.

A 25-mL, two-necked, round-bottomed flask equipped with a rubber septum and argon inlet adapter was charged with a solution of the crude amino alcohol from the previous step in 12 mL of THF. Triethylamine (0.70 mL, 0.51 g, 5.0 mmol) was added, and the solution was cooled at 0 °C while tosyl chloride (0.840 g, 4.40 mmol) was added in one portion. The reaction mixture was stirred for 4 h at rt and then diluted with 20 mL of 1 M aq HCl solution. The resulting solution was extracted with three 25-mL portions of EtOAc, and the combined organic layers were washed with 30 mL of brine, dried over $MgSO_4$, filtered, and concentrated to give 1.24 g of yellow oil. Column chromatography on 40 g of silica gel (gradient elution with 10-40% EtOAc-hexanes) provided 0.896 g (67%) of **148** as a pale, yellow oil.

IR (film):	3540, 3005, 2922, 1593, 1422, 1327, 1147, 1083, 980
^{1}H NMR (500 MHz, $CDCl_3$):	7.71 (d, J = 8.2 Hz, 2 H), 7.32 (d, J = 7.9 Hz, 2 H), 6.38 (dd, J = 15.2, 10.5 Hz, 1 H), 5.96 (ddd, J = 15.0, 10.4, 1.0 Hz, 1 H), 5.67 (dq, J = 15.0, 7.0 Hz, 1 H), 5.33 (dt, J = 15.0, 7.0 Hz, 1 H), 3.85 (d, J = 7.0 Hz, 2 H), 3.72 (t, J = 5.4 Hz, 2 H), 3.22 (t, J = 5.4 Hz, 2 H), 2.44 (s, 3 H), 2.34 (br, 1 H), 1.73 (d, J = 6.7 Hz, 3 H)
^{13}C NMR (125 MHz, $CDCl_3$):	143.7, 136.4, 135.1, 131.2, 130.3, 130.0, 127.5, 124.4, 61.3, 51.6, 49.7, 21.7, 18.3

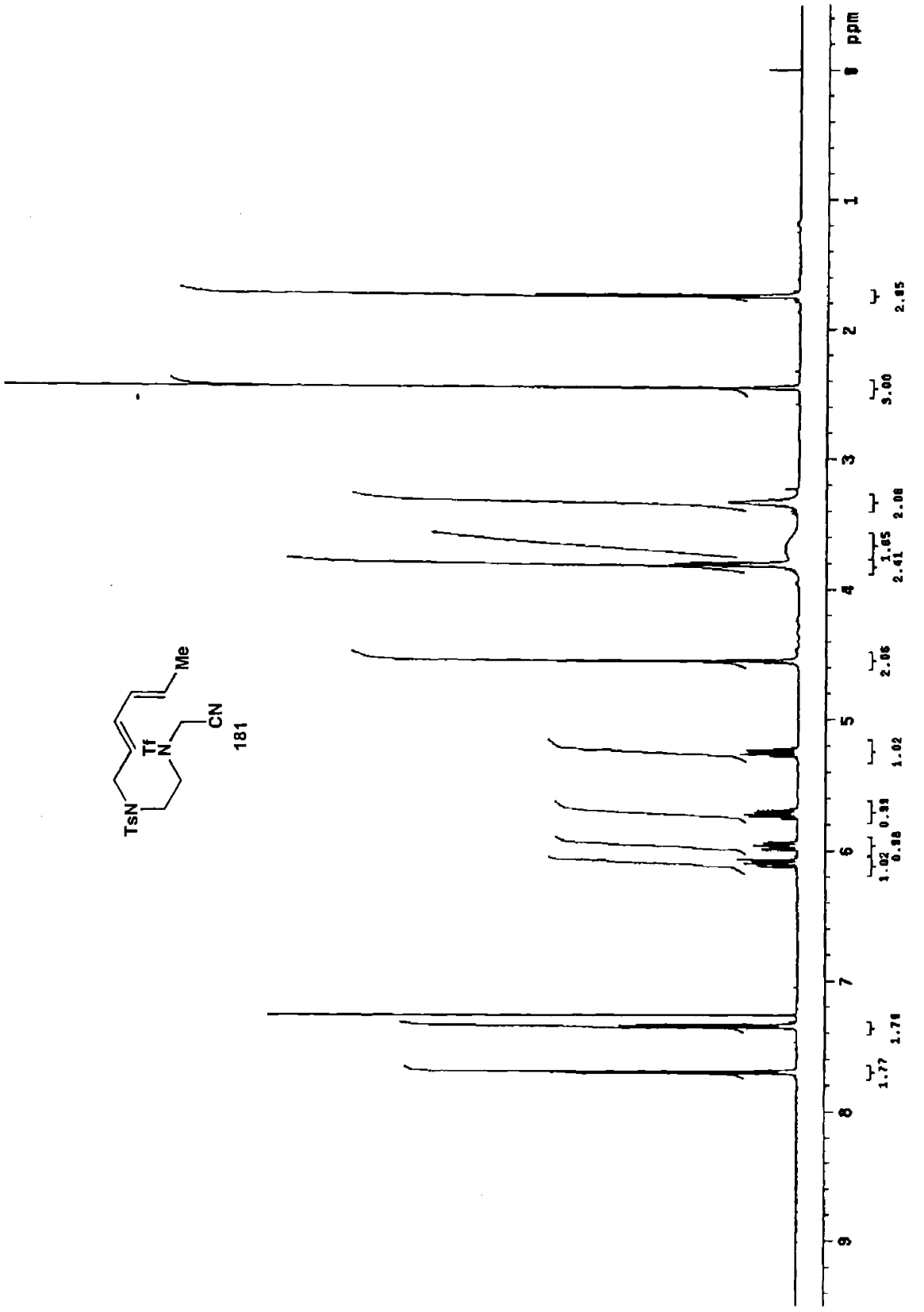

Me
OH
TsN
148
ppm



148 181

***N*-(Cyanomethyl)-*N*-(2-[[(4-methylphenyl)sulfonyl][(*E*),(*E*)-2,4-hexadienyl]amino]ethyl)trifluoromethanesulfonamide (181).** A 25-mL, two-necked, round-bottomed flask equipped with a rubber septum and argon inlet adapter was charged with triphenylphosphine (0.431 g, 1.64 mmol), a solution of $HN(Tf)CH_2CN$ (0.270 g, 1.44 mmol) in 5 mL of THF, and a solution of alcohol **148** (0.404 g, 1.37 mmol) in 5 mL of toluene. DEAD (0.26 mL, 0.29 g, 1.6 mmol) was added dropwise via syringe, and the resulting mixture was stirred at rt for 16 h and then concentrated to give 1.73 g of a yellow oil. This material was concentrated onto 3.5 g of silica gel and added to a column of 35 g of silica gel. Gradient elution with 10-25% EtOAc-hexanes provided 0.601 g (94%) of **181** as a colorless oil.

IR (film):	3010, 2960, 2912, 2838, 1646, 1580, 1485, 1433, 1390, 1335, 1220, 1190, 1148, 1082, 1038, 985, 918
^{1}H NMR (500 MHz, $CDCl_3$):	7.70 (d, J = 8.2 Hz, 2 H), 7.35 (d, J = 8.2 Hz, 2 H), 6.10 (dd, J = 15.0, 10.4 Hz, 1 H), 5.96 (ddd, J = 15.0, 10.4, 1.5 Hz, 1 H), 5.71 (dq, J = 15.0, 6.7 Hz, 1 H), 5.25 (dt, J = 15.0, 7.3 Hz, 1 H), 4.55 (br s, 2 H), 3.81 (d, J = 7.3 Hz, 2 H), 3.67 (br, 2 H), 3.33 (br s, 2 H), 2.45 (s, 3 H), 1.74 (d, J = 6.7 Hz, 3 H)
^{13}C NMR (125 MHz, $CDCl_3$):	144.3, 136.6, 135.4, 132.2, 130.2, 130.0, 127.5, 122.7, 119.8 (q, J = 322 Hz), 113.6, 51.5, 48.0, 45.1, 37.1, 21.7, 18.3
HRMS $[M+Na]^+$:	Calcd for $C_{18}H_{22}F_3N_3NaO_4S_2$: 488.0896 Found: 488.0903

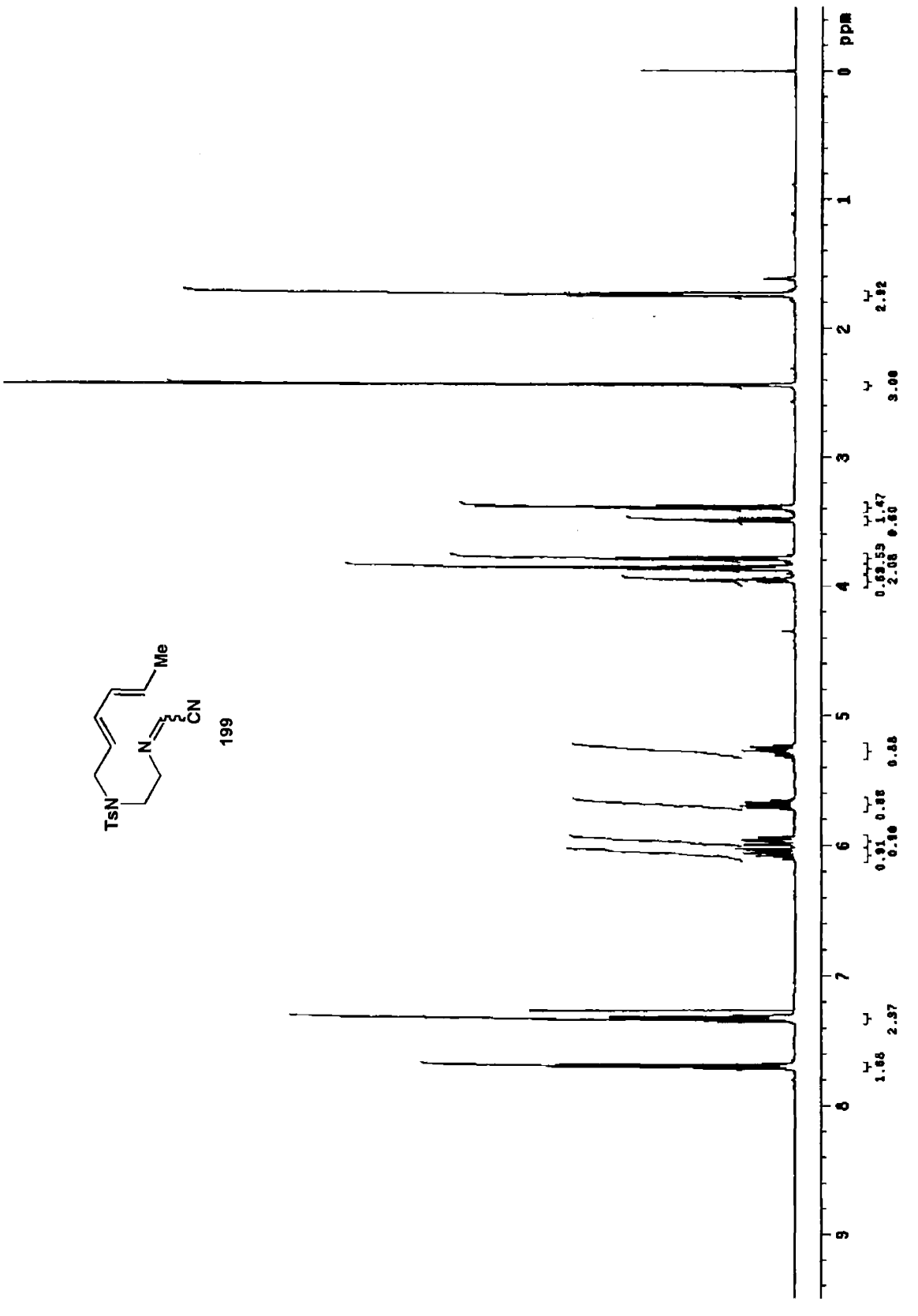

Me
CN
Tf
N
TsN
181
ppm
0
1
2
3
4
5
6
7
8
9
2.85
3.00
2.08
1.65
2.41
2.06
1.02
1.02
0.33
0.88
1.78
1.77

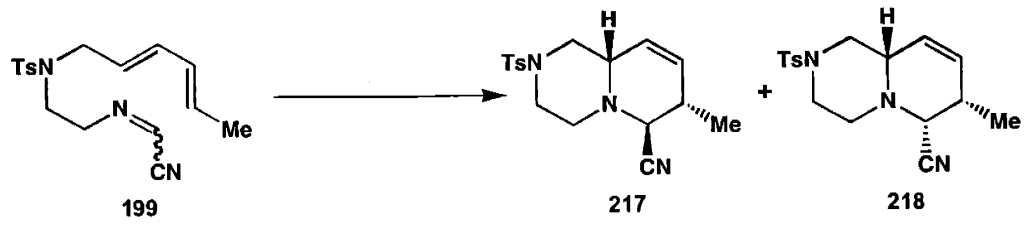
181 199

(2-[[(4-methylphenyl)sulfonyl][(*E*),(*E*)-2,4-hexadienyl]amino]ethyl)iminoacetonitrile (199). 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 (0.699 g, 2.15 mmol). A solution of triflamide **181** (0.333 g, 0.72 mmol) in 10 mL of THF was added, and the reaction mixture was heated at 45 °C for 2 h. The resulting mixture was allowed to cool to room temperature and then diluted with 25 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 25 mL brine, dried over $MgSO_4$, filtered, and concentrated to give 0.222 g of a yellow oil. Column chromatography on 12 g of Et_3N-deactivated silica gel (elution with 1% Et_3N-25% EtOAc-hexanes) provided 0.195 g (74%) of **199** (as an 81:19 mixture of E and Z imine isomers by ^1H NMR analysis) as a pale, yellow oil.

IR (film):	3020, 2980, 2920, 2860, 1650, 1610, 1590, 1485, 1435, 1330, 1148, 1080
For E isomer:	
^1H NMR (500 MHz, $CDCl_3$):	7.69 (d, J = 8.2 Hz, 2 H), 7.34 (t, J = 1.8 Hz, 1 H), 7.33 (d, J = 8.5 Hz, 2 H), 6.04 (dd, J = 15.3, 10.7 Hz, 1 H), 5.94-6.00 (m, 1 H), 5.64-5.73 (m, 1 H), 5.26 (dt, J = 15.0, 7.0 Hz, 1 H), 3.86 (dt, J = 6.4, 1.5 Hz, 2 H), 3.79 (d, J = 7.0 Hz, 2 H), 3.39 (t, J = 6.2 Hz, 2 H), 2.44 (s, 3 H), 1.74 (d, J = 6.7 Hz, 3 H)
^{13}C NMR (125 MHz, $CDCl_3$):	143.9, 138.0, 135.4, 133.1, 131.5, 130.3, 130.0, 127.4, 124.1, 114.4, 62.6, 51.9, 46.9, 21.7, 18.3
For Z isomer:	

^{1}H NMR (500 MHz, $CDCl_3$):	7.71 (d, J = 8.2 Hz, 2 H), 7.35 (t, J = 2.4 Hz, 1 H), 7.32 (d, J = 8.5 Hz, 2 H), 6.06 (dd, J = 15.3, 10.7 Hz, 1 H), 5.94-6.00 (m, 1 H), 5.64-5.73 (m, 1 H), 5.29 (dt, J = 15.0, 7.0 Hz, 1 H), 3.95 (dt, J = 6.4, 2.4 Hz, 2 H), 3.79 (d, J = 7.0 Hz, 2 H), 3.49 (t, J = 6.4 Hz, 2 H), 2.44 (s, 3 H), 1.74 (d, J = 6.7 H, 3 H)
^{13}C NMR (125 MHz, $CDCl_3$):	143.7, 136.4, 135.4, 132.5, 131.3, 130.3, 130.0, 127.4, 124.1, 109.4, 58.5, 51.0, 46.4, 21.7, 18.3

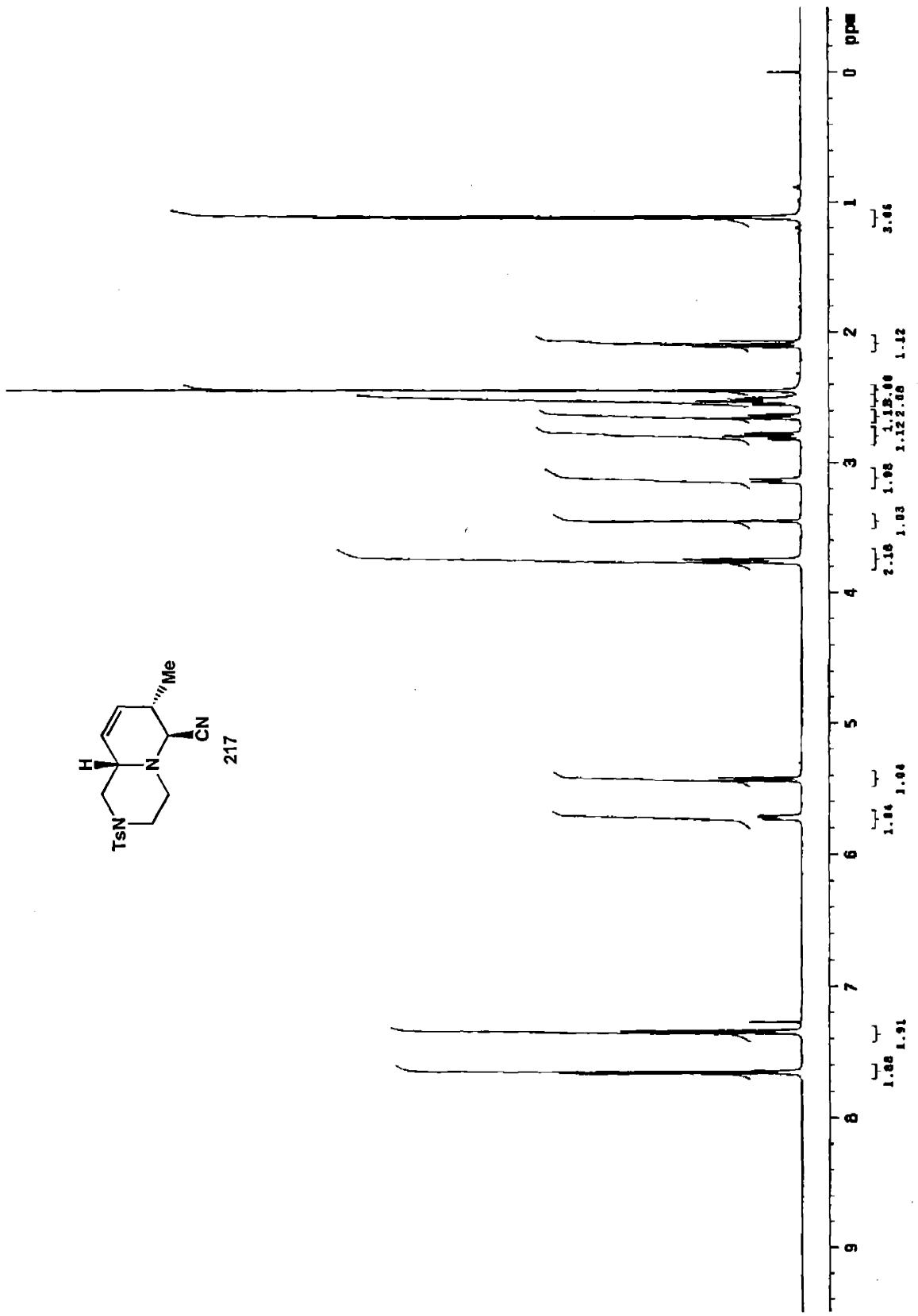

Me
CN
N
TsN
199
ppm



***cis*-7-Methyl-2(toluene-4-sulfonyl)-1,3,4,6,7,9*a*-hexahydro-6-cyano-*2H*-pyrido[1,2-*a*]pyrazine (217)** and ***trans*-7-Methyl-2(toluene-4-sulfonyl)-1,3,4,6,7,9*a*-hexahydro-6-cyano-*2H*-pyrido[1,2-*a*]pyrazine (218).** A 25-mL, one-necked, round-bottomed flask equipped with a reflux condenser fitted with an argon inlet adapter was charged with imine **199** (0.172 g, 0.52 mmol), BHT (0.343 g, 1.56 mmol), and 12 mL of toluene. The reaction mixture was heated at reflux for 17 h and then allowed to cool to rt. Concentration gave 0.591 g of a brown oil which was concentrated onto 1.2 g of silica gel and applied to a column of 15 g of silica gel. Gradient elution with 20-25% EtOAc-hexanes provided 0.163 g (95%) of **217** and **218** (39:61 mixture by ^{1}H NMR analysis) as a white foam: mp = 49-50 °C. Further purification allowed isolation of both individual diastereomers for analytical purposes.

For (**217**):	mp = 152-153 °C
IR (CH_2Cl_2):	3054, 2986, 2305, 1598, 1451, 1422, 1345, 1273, 1257, 1168, 1132, 1025, 896, 765
^{1}H NMR (500 MHz, $CDCl_3$):	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, $CDCl_3$):	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
Elemental Analysis:	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

For (**218**):	mp = 44 °C
IR (CH_2Cl_2):	3054, 2985, 2828, 1598, 1451, 1422, 1342, 1259, 1167, 1092, 896
^1H NMR (500 MHz, $CDCl_3$):	7.64 (d, J = 8.2 Hz, 2 H), 7.35 (d, J = 8.5 Hz, 2 H), 5.75 (ddd, J = 10.0, 5.0, 2.5 Hz, 1 H), 5.36 (d, J = 10.0 Hz, 1 H), 3.76 (dt, J = 7.9, 2.1 Hz, 1 H), 3.66 (dt, J = 11.0, 2.4 Hz, 1 H), 3.57 (d, J = 4.0 Hz, 1 H), 3.31-3.33 (m, 1 H), 2.96 (dt, J = 10.8, 2.2 Hz, 1 H), 2.54 (ddd, J = 8.2, 6.0, 1.7 Hz, 2 H), 2.46-2.50 (m, 1 H) 2.44 (s, 3 H), 2.09 (t, J = 10.8 Hz, 1 H), 1.19 (d, J = 7.0 Hz, 3 H)
^{13}C NMR (125 MHz, $CDCl_3$):	144.1, 132.5, 131.0, 130.0, 127.9, 124.1, 117.6, 59.9, 55.6, 51.2, 50.2, 45.9, 33.4, 21.7, 17.1
Elemental Analysis:	Calcd for $C_{17}H_{21}N_3O_2S$: C, 61.61; H, 6.39; N, 12.68 Found: C, 61.39; H, 6.68; N, 12.73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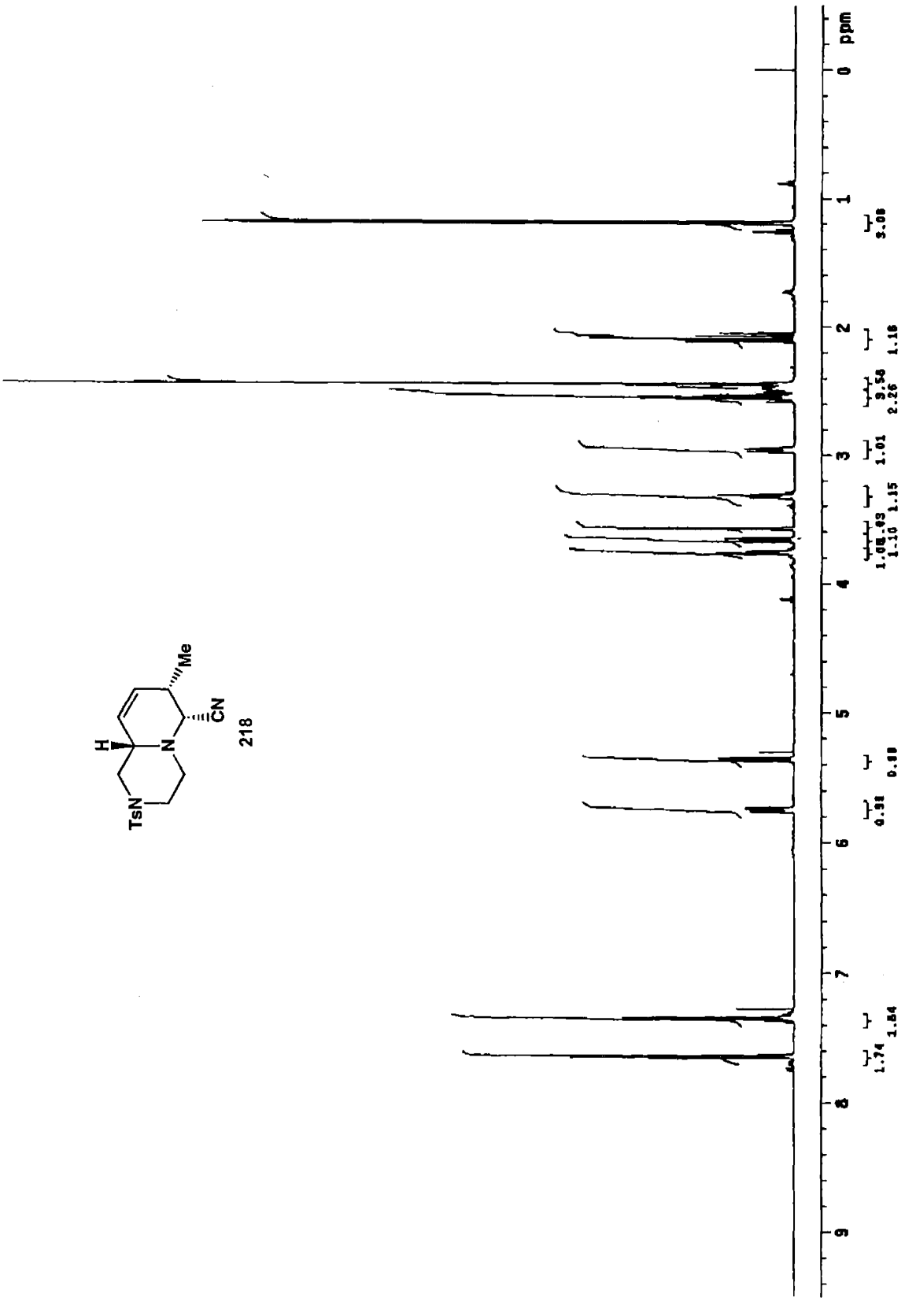
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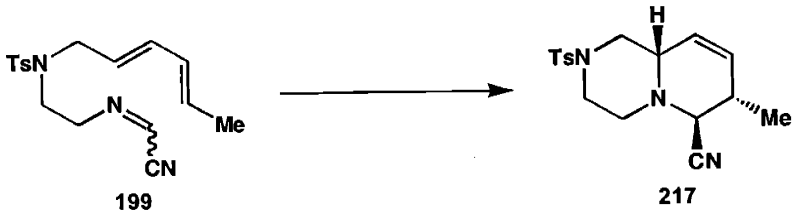
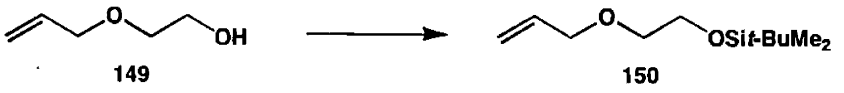


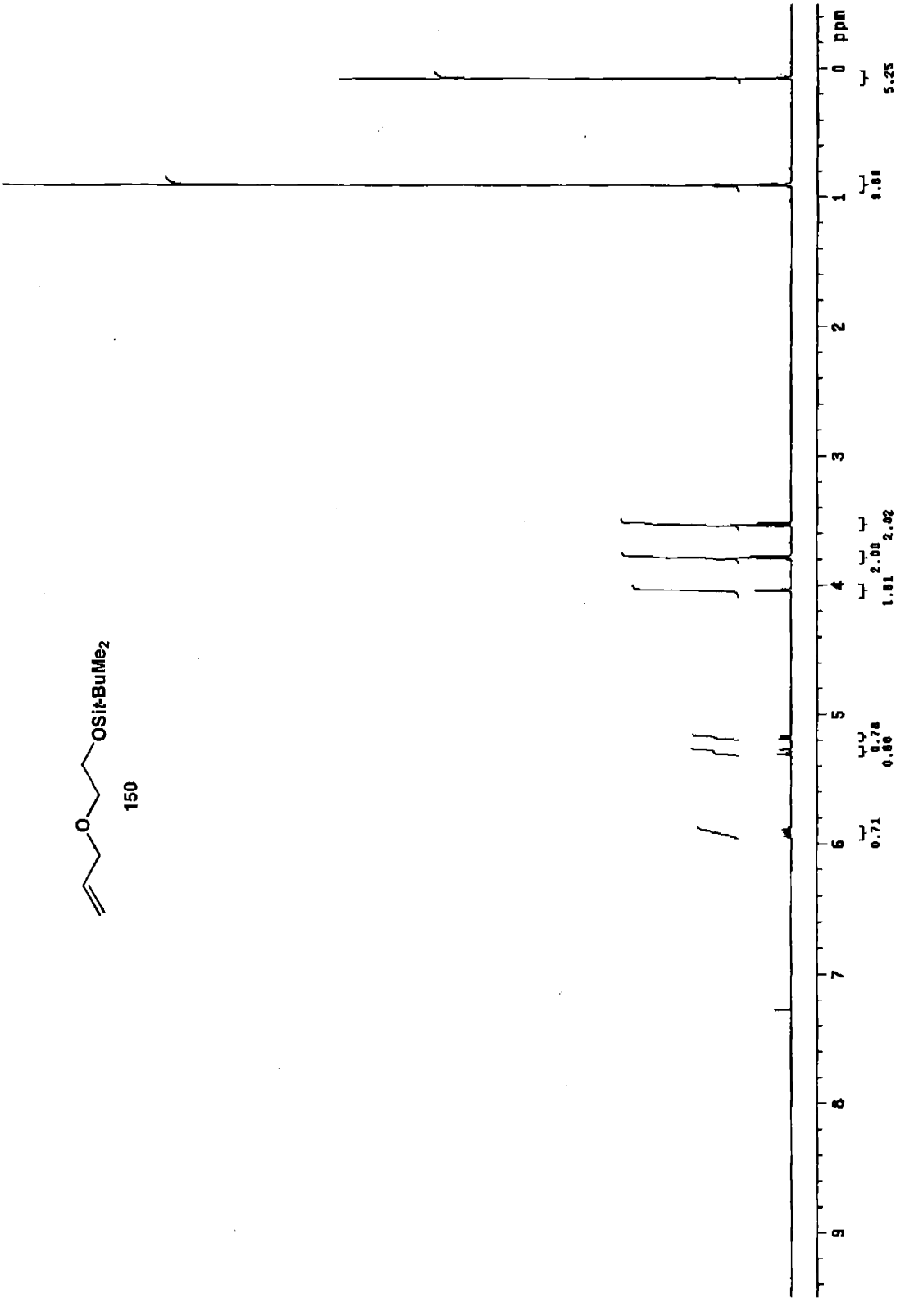
***cis*-7-Methyl-2(toluene-4-sulfonyl)-1,3,4,6,7,9*a*-hexahydro-6-cyano-2*H*-pyrido[1,2-*a*]pyrazine (217).** A 25-mL, one-necked, round-bottomed flask equipped with a reflux condenser fitted with an argon inlet adapter was charged with imine **199** (0.172 g, 0.52 mmol), BHT (0.343 g, 1.56 mmol), and 10 mL of acetonitrile. The reaction mixture was heated at reflux for 24 h and then allowed to cool to rt. Concentration gave 0.536 g of a brown oil which was concentrated onto 1 g of silica gel and added to a column of 20 g of silica gel. Gradient elution with 20-25% EtOAc-hexanes provided 0.105 g (61%) of **217** as a white solid with spectral characteristics identical with that reported on the preceding page.



149 150

***tert*-Butyldimethyl[2-(2-propenyloxy)ethoxy]silane (150).** A 100-ml, three-necked, round-bottomed flask, equipped with a rubber septum, glass stopper, and argon inlet adapter was charged with imidazole (1.14 g, 16.8 mmol), 40 mL of CH_2Cl_2, and alcohol **149** (1.50 mL, 1.43 g, 14.0 mmol). *tert*-Butyldimethylsilyl chloride (2.22 g, 14.7 mmol) was added in one portion, and the resulting solution was stirred at rt for 1 h and then diluted with 40 mL of water. The aqueous layer was separated and extracted with two 20-mL portions of CH_2Cl_2, and the combined organic layers were washed with 30 mL of brine, dried over anhydrous $MgSO_4$, filtered, and concentrated to give 4.11 g of colorless oil. Column chromatography on 30 g of silica gel (elution with 5% EtOAc-hexanes) provided 2.90 g (93%) of **150** as a colorless oil.

IR (film):	3082, 2956, 2930, 2858, 1648, 1473, 1463, 1361, 1293, 1255, 1106, 1006, 939, 924, 836, 777
^{1}H NMR (500 MHz, $CDCl_3$):	5.92 (ddt, J = 17.4, 10.4, 5.5 Hz, 1 H), 5.28 (app qd, J = 17.4, 1.5 Hz, 1 H), 5.18 (app qd, J = 10.4, 1.5 Hz, 1 H), 4.03 (dt, J = 5.5, 1.4 Hz, 2 H), 3.78 (t, J = 5.5 Hz, 2 H), 3.53 (t, J = 5.5 Hz, 2 H), 0.90 (s, 9 H), 0.08 (s, 6 H)
^{13}C NMR (75 MHz, $CDCl_3$):	135.1, 116.9, 72.4, 71.8, 63.0, 26.2, 18.6, -5.0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2
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5
6
7
8
9
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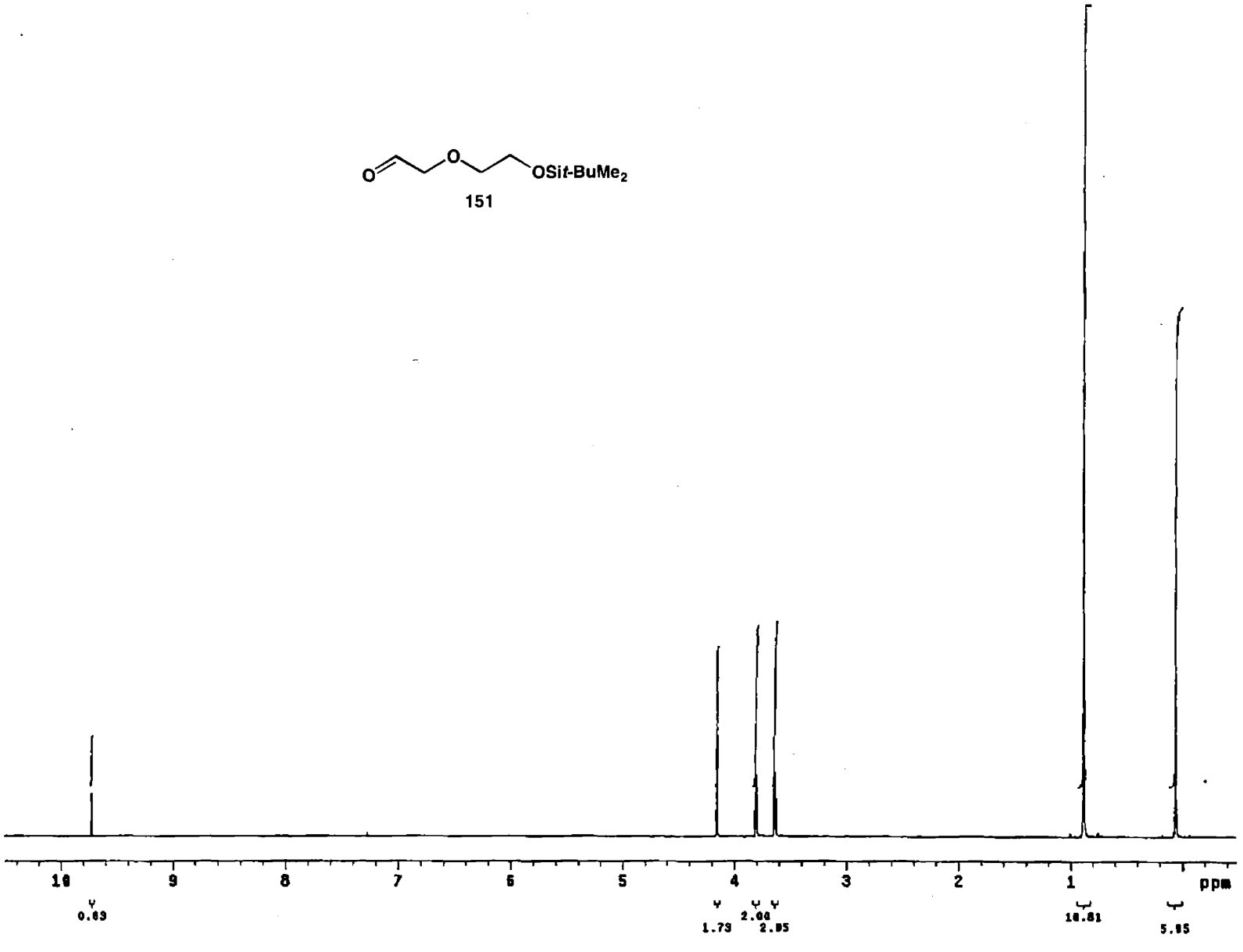
2.00
1.81
0.78
0.80
0.71

2-(2-*tert*-Butyldimethylsiloxyethyl)-ethenol (151). A 50-mL, recovery flask containing alkene **150** (2.90 g, 13.4 mmol) was fitted with a rubber septum and argon inlet needle and purged with argon. CH_2Cl_2 (30 mL) was added, and the flask was cooled at –78 °C while ozone was bubbled through the solution for 22 min. The resulting blue solution was degassed with a stream of argon for 10 min. Triphenylphosphine (3.69 g, 14.1 mmol) was added, and the solution was allowed to slowly warm to rt over 17 h. Concentration by rotary evaporation provided 9.78 g of a white solid which was triturated with EtOAc, filtered to remove triphenylphosphine oxide, and concentrated onto 8 g of silica gel and applied to a column of 60 g of silica gel. Gradient elution with 10-25% EtOAc-hexanes afforded after a second purification on 20 g of silica gel (gradient elution 5-25% EtOAc-hexanes) 2.55 g (87%) of **151** as a colorless oil.

IR (film):	2955, 2930, 2858, 1739, 1473, 1362, 1256, 1107, 1007, 950, 835, 778, 721
^{1}H NMR (500 MHz, $CDCl_3$):	9.72 (t, J = 0.9 Hz, 1 H), 4.15 (d, J = 0.9 Hz, 2 H), 3.80 (t, J = 4.7 Hz, 2 H), 3.63 (t, J = 5.1 Hz, 2 H), 0.88 (s, 9 H), 0.06 (s, 6 H)
^{13}C NMR (125 MHz, $CDCl_3$):	201.4, 77.2, 73.6, 63.1, 26.1, 18.5, -5.2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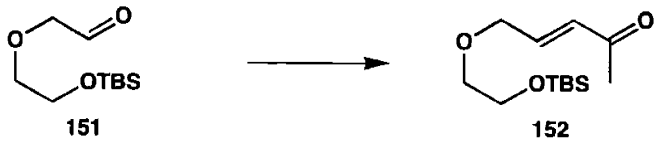
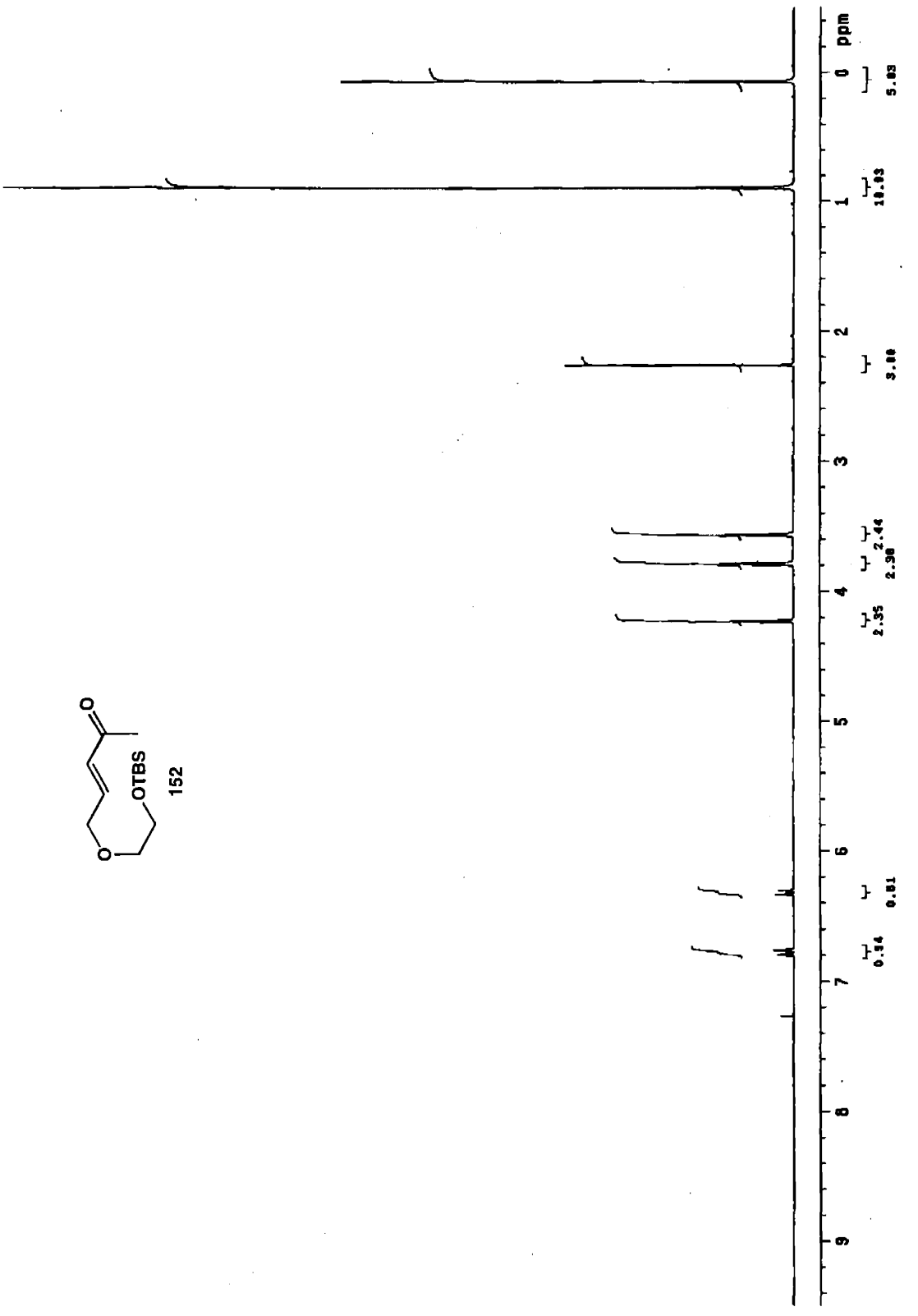
5.85



151 152

5-(2-*tert*-Butyldimethylsiloxyethyl)-(*E*)-3-penten-2-one (152). A 100-mL, round-bottomed flask equipped with a reflux condenser fitted with an argon inlet adapter was charged with aldehyde **151** (2.55 g, 11.7 mmol) and 40 mL of CH_2Cl_2. (Acetylmethylene)triphenylphosphorane (3.90 g, 12.3 mmol) was then added, and the reaction mixture was heated at reflux for 3 h. Concentration by rotary evaporation afforded 6.95 g of a yellow oil. This material was concentrated onto 13 g of silica gel and applied to a column of 80 g of silica gel. Gradient elution with 5-25% EtOAc-hexanes provided 2.16 g of **152** as a colorless oil, along with 0.750 g of **152** as a 70/30 mixture of *E*/*Z* olefin isomers. Column chromatography of the latter mixture on 20 g of silica gel (gradient elution 5-20% EtOAc-hexanes) afforded an additional 0.424 g of **152** for a total yield of 2.58 g (85%).

IR (film):	2955, 2930, 2886, 2858, 1680, 1636, 1472, 1464, 1360, 1297, 1254, 1147, 1107, 1007, 973, 940, 836, 778, 720
^{1}H NMR (500 MHz, $CDCl_3$):	6.78 (dt, J = 16.0, 4.3 Hz, 1 H), 6.33 (dt, J = 16.2, 1.8 Hz, 1 H), 4.24 (dd, J = 4.3, 1.8 Hz, 2 H), 3.79 (t, J = 4.9 Hz, 2 H), 3.58 (t, J = 5.5 Hz, 2 H), 0.91 (s, 9 H), 0.08 (s, 6 H)
^{13}C NMR (75 MHz, $CDCl_3$):	198.4, 143.5, 130.2, 72.7, 70.2, 63.0, 27.6, 26.1, 18.6, -5.1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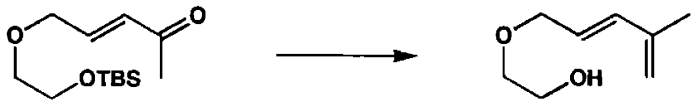
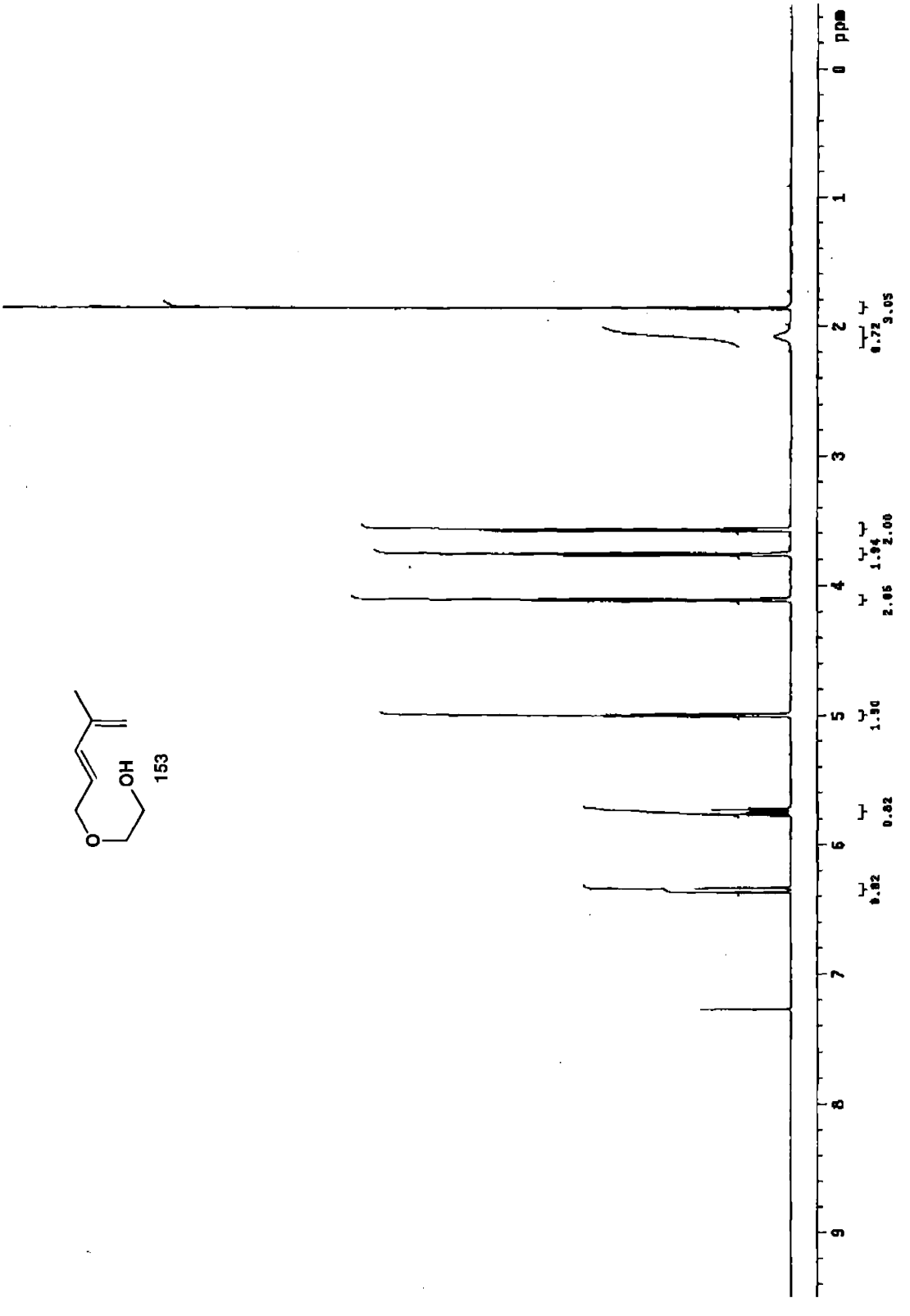


152 153

2-[(2*E*)-4-Methyl-2,4-pentadienyloxy]-ethanol (153). A 25-ml, two-necked, round-bottomed flask equipped with a rubber septum and argon inlet adapter was charged with methyltriphenylphosphonium bromide (0.501 g, 1.40 mmol) and 6 mL of THF. The solution was cooled at 0 °C while 0.58 mL of *n*-BuLi solution (2.41 M in hexanes, 1.4 mmol) was added dropwise via syringe over 1 min. The resulting solution was stirred at 0 °C for 50 min and then a solution of aldehyde **152** (0.302 g, 1.17 mmol) in 4 mL of THF was added dropwise over 5 min. The reaction mixture was stirred at 0 °C for 2 h and then diluted with 4 mL of 1 M aq HCl solution and stirred at rt for 1.75 h. The resulting solution was diluted with 25 mL of water, and the aqueous layer was separated and extracted with three 20-mL portions of ether. The combined organic layers were washed with 25 mL brine, dried over $MgSO_4$, filtered, and concentrated to afford 0.577 g of an oily, white solid. Column chromatography on 8 g of silica gel provided 0.140 g (84%) of **153** as a colorless oil.

IR (film):	3412, 2922, 2860, 1611, 1455, 1353, 1116, 1063, 969, 889
^{1}H NMR (500 MHz, $CDCl_3$):	6.35 (d, J = 15.6 Hz, 1 H), 5.75 (dt, J = 15.6, 6.3 Hz, 1 H), 5.01 (s, 1 H), 5.00 (s, 1 H), 4.11 (dd, J = 6.1, 1.2 Hz, 2 H), 3.76 (t, J = 4.6 Hz, 2 H), 3.57 (t, J = 4.7 Hz, 2 H), 2.08 (br s, 1 H), 1.86 (s, 3 H)
^{13}C NMR (75 MHz, $CDCl_3$):	141.3, 135.8, 125.7, 117.2, 71.9, 71.5, 62.1, 18.1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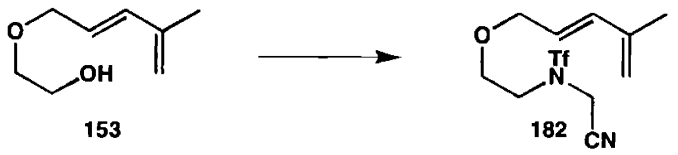
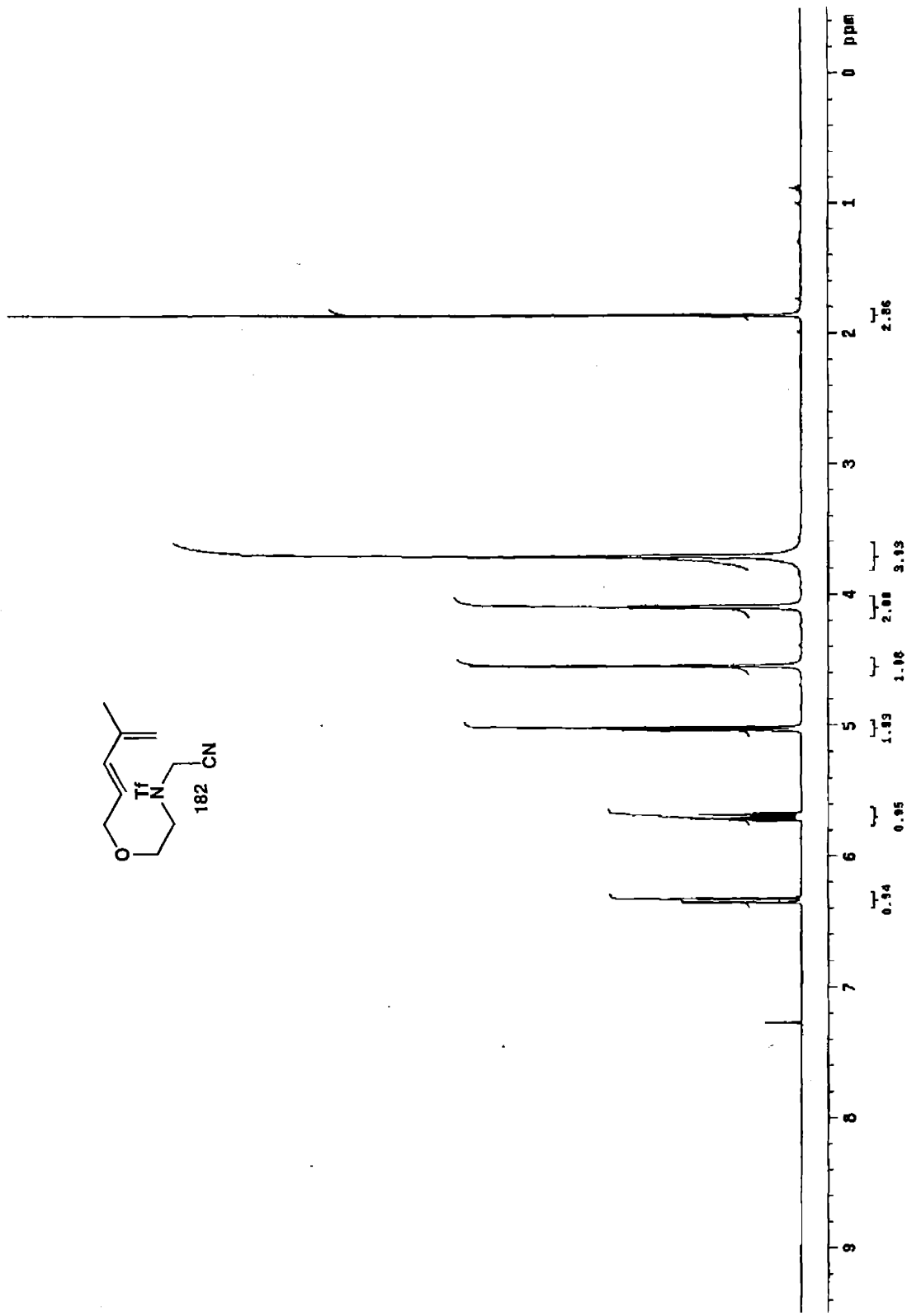


***N*-(Cyanomethyl)-*N*-(2-[(2*E*)-4-methyl-2,4-pentadienyloxy]ethyl)trifluoromethanesulfonamide (182).** A 25-mL, two-necked, round-bottomed flask equipped with a rubber septum and an argon inlet adapter was charged with triphenylphosphine (0.401 g, 1.53 mmol), a solution of $HN(Tf)CH_2CN$ (0.251 g, 1.34 mmol) in 5 mL of THF, and a solution of alcohol **153** (0.181 g, 1.27 mmol) in 5 mL of toluene. DEAD (0.24 mL, 0.27 g, 1.5 mmol) was added dropwise via syringe over 2 min, and the resulting mixture was stirred at rt for 2.5 h and then concentrated to give 1.71 g of a yellow solid. This material was concentrated onto 3.4 g of silica gel and applied to a column of 25 g of silica gel. Gradient elution with 10-20% EtOAc-hexanes provided 0.340 g (85%) of **182** as a colorless oil.

IR (film):	3085, 2996, 2950, 2867, 1611, 1442, 1396, 1359, 1286, 1230, 1196, 1149, 1116, 1048, 971, 900, 772, 731
^{1}H NMR (500 MHz, $CDCl_3$):	6.34 (d, J = 15.6 Hz, 1 H), 5.70 (dt, J = 15.6, 6.3 Hz, 1 H), 5.04 (s, 1 H), 5.02 (s, 1 H), 4.54 (br s, 2 H), 4.09 (d, J = 6.1 Hz, 2 H), 3.71 (br m, 4 H), 1.86 (s, 3 H)
^{13}C NMR (125 MHz, $CDCl_3$):	141.2, 136.6, 124.7, 119.7 (q, J = 322 Hz), 117.8, 114.0, 72.1, 69.5, 49.2, 38.3, 18.6
HRMS $[M+Na]^+$:	Calcd for $C_{11}H_{15}F_3N_2NaO_3S$: 335.0648 Found: 335.0649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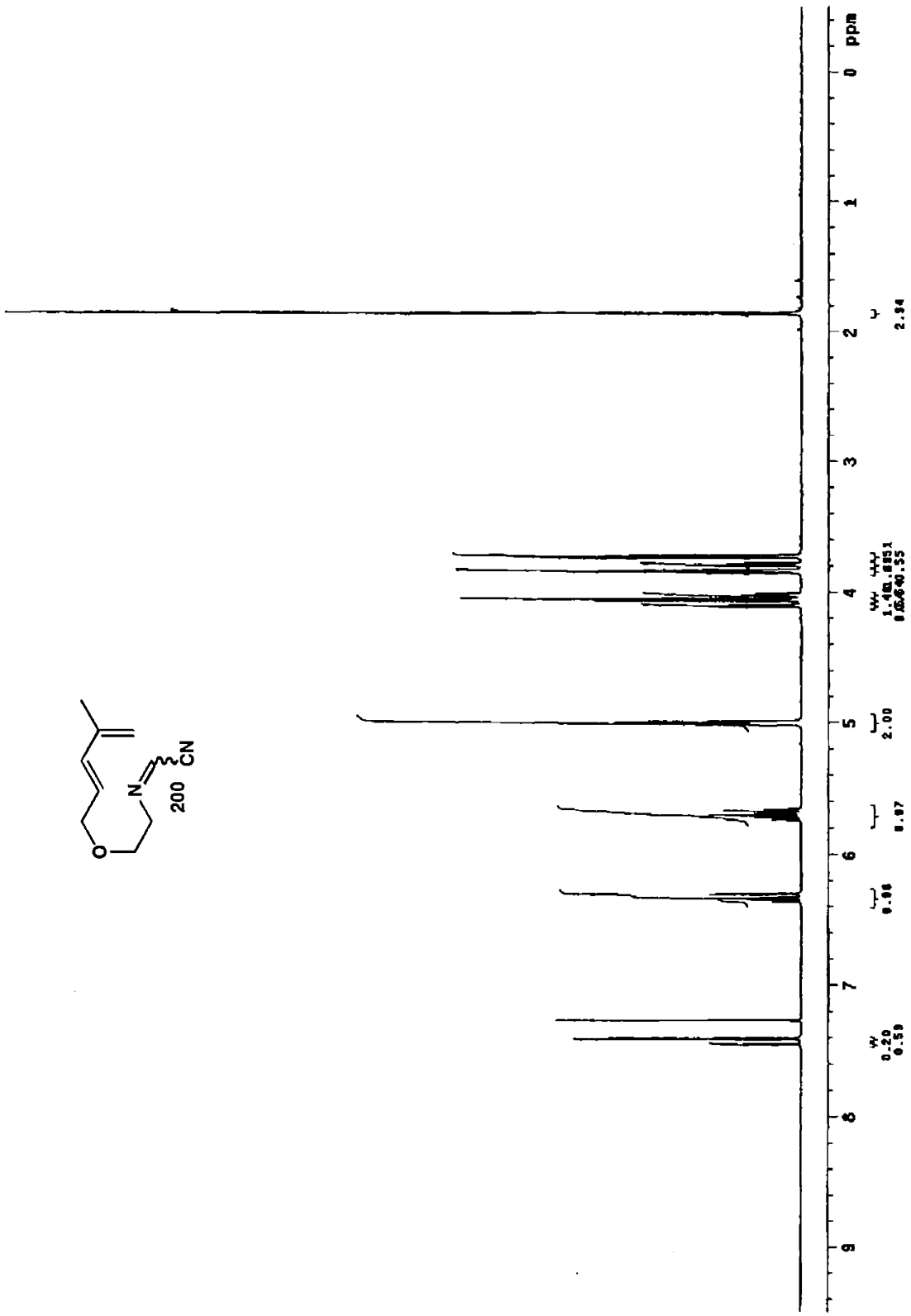
1.03
0.95
0.94

2-[(2*E*)-4-Methyl-2,4-pentadienyloxy]ethyliminoacetonitrile (200). 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 (1.46 g, 4.48 mmol). A solution of triflamide **182** (0.350 g, 1.12 mmol) in 8 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 20 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 25 mL of brine, dried over $MgSO_4$, filtered, and concentrated to give 0.196 g of a yellow oil. Column chromatography on 8 g of Et_3N-deactivated silica gel (gradient elution with 1% Et_3N-10-20% EtOAc-hexanes) provided 0.173 g (87%) of **200** (as an 76:24 mixture of E and Z imine isomers by ^1H NMR analysis) as a colorless oil.

IR (film):	3083, 3031, 2992, 2972, 2919, 2860, 2735, 1625, 1611, 1453, 1355, 1282, 1259, 1232, 1114, 971, 893
For E isomer:	
^1H NMR (500 MHz, $CDCl_3$):	7.41 (t, J = 1.5 Hz, 1 H), 6.32 (d, J = 15.6 Hz, 1 H), 5.69 (dt, J = 15.9, 6.1 Hz, 1 H), 5.01 (s, 1 H), 5.00 (s, 1 H), 4.06 (dd, J = 6.1, 1.9 Hz, 2 H), 3.84 (dt, J = 5.2, 1.5 Hz, 2 H) 3.73 (t, J = 5.2 Hz, 2 H), 1.86 (s, 3 H)
^{13}C NMR (125 MHz, $CDCl_3$):	141.3, 137.8, 135.9, 125.4, 117.3, 114.5, 71.8, 67.8, 62.3, 18.6
For Z isomer:	
^1H NMR (500 MHz, $CDCl_3$):	7.45 (t, J = 2.3 Hz, 1 H), 6.35 (d, J = 15.6 Hz, 1 H), 5.72 (dt, J = 15.9, 6.1 Hz, 1 H), 5.01 (s, 1 H), 5.00 (s, 1 H), 4.11 (dd, J = 6.1, 1.9 Hz, 2 H), 4.02 (dt, J = 5.2, 2.2 Hz, 2 H) 3.79 (t, J = 5.2 Hz, 2 H), 1.86 (s, 3 H)

^{13}C NMR (125 MHz, $CDCl_3$):	141.4, 135.7, 133.2, 125.6, 117.2, 109.5, 71.7, 68.3, 59.3 18.6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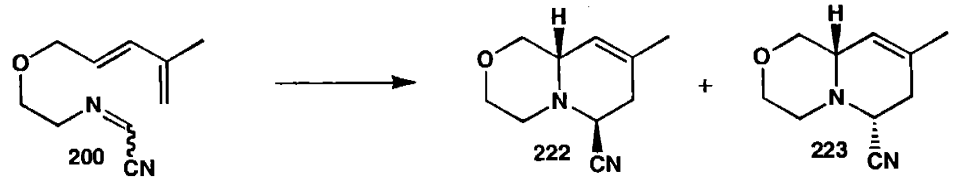


***cis*-8-Methyl-1,3,4,6,7,9*a*-hexahydro-6-cyano-pyrido[2,1-c][1,4]oxazine (222)** and ***trans*-8-Methyl-1,3,4,6,7,9*a*-hexahydro-6-cyano-pyrido[2,1-c][1,4]oxazine (223).** A threaded Pyrex tube (ca. 50 mL capacity) equipped with a rubber septum and argon inlet needle was charged with imine **200** (0.134 g, 0.75 mmol), BHT (0.497 g, 2.26 mmol), and 15 mL of toluene. The solution was degassed by three freeze-pump-thaw cycles and then sealed with a threaded Teflon cap. The reaction mixture was heated in a 120 °C oil bath for 16 h and then allowed to cool to rt. Concentration gave 0.653 g of a yellow oil. Column chromatography on 20 g of silica gel (gradient elution with 1% Et_3N-10-20% EtOAc-hexanes) afforded 0.101 g (75%) of **22** and 0.028 g (21%) of **223** as colorless oils, total yield 0.129 g (96%).

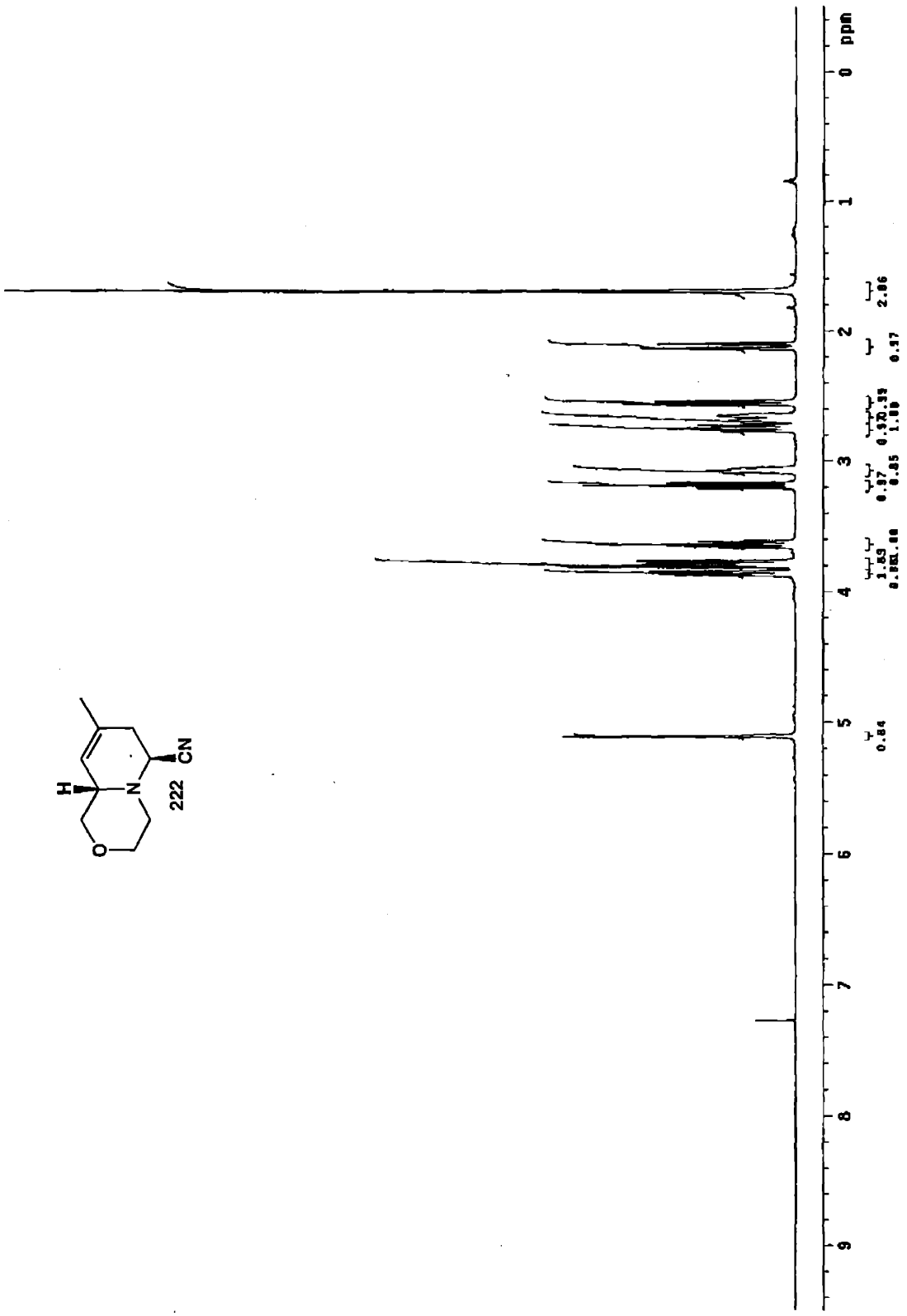
For (**222**):

IR (film):	3022, 2966, 2914, 2855, 2823, 2779, 2733, 2663, 2224, 1449, 1381, 1344, 1289, 1217, 1147, 1114, 1069, 992, 832
^{1}H NMR (500 MHz, $CDCl_3$):	5.11 (s, 1 H), 3.85 (d, J = 11.0 Hz, 1 H), 3.80 (d, J = 6.7 Hz, 1 H), 3.77 (d, J = 10.7 Hz, 1 H), 3.64 (app tt, J = 11.3, 2.3 Hz, 1 H) 3.18 (app dt, J = 10.6, 1.8 Hz, 1 H), 3.03-3.10 (m, 1 H), 2.74 (app tt, J = 11.3, 2.7 Hz, 1 H), 2.63-2.70 (m, 1 H), 2.55 (d, J = 11.0 Hz, 1 H), 2.12 (d, J = 17.4 Hz, 1 H), 1.69 (s, 3 H)
^{13}C NMR (75 MHz, $CDCl_3$):	131.1, 118.3, 116.5, 70.7, 66.8, 55.8, 52.1, 51.3, 33.8, 22.9
Elemental Analysis:	Calcd for $C_{10}H_{14}N_2O$: C, 67.39; H, 7.92; N, 15.72 Found: C, 67.61; H, 7.73; N, 15.88

For (**223**): mp = 80-81 °C

IR (CH_2Cl_2):	3055, 2971, 2917, 2859, 2819, 2247, 1449, 1381, 1347, 1307, 1266, 1150, 1115, 1069, 994, 900, 830, 739

^{1}H NMR (500 MHz, $CDCl_3$):	5.06 (s, 1 H), 3.90 (d, J = 11.6 Hz, 1 H), 3.67-3.74 (m, 2 H), 3.42 (dt, J = 6.4, 4.4 Hz, 1 H), 3.19-3.26 (m, 2 H), 2.84 (br s, 1 H), 2.59-2.68 (m, 1 H), 2.44-2.51 (m, 1 H), 2.28 (d, J = 17.1 Hz, 1 H), 1.69 (s, 3 H)	
^{13}C NMR (75 MHz, $CDCl_3$):	132.2, 118.6, 118.3, 70.7, 67.1, 60.1, 51.9, 51.3, 35.0, 22.6	
Elemental Analysis:	Calcd for $C_{10}H_{14}N_2O$:	C, 67.39; H, 7.92; N, 15.72
	Found:	C, 67.64; H, 7.76; N, 15.80


222
CN
H
N
O
ppm
0
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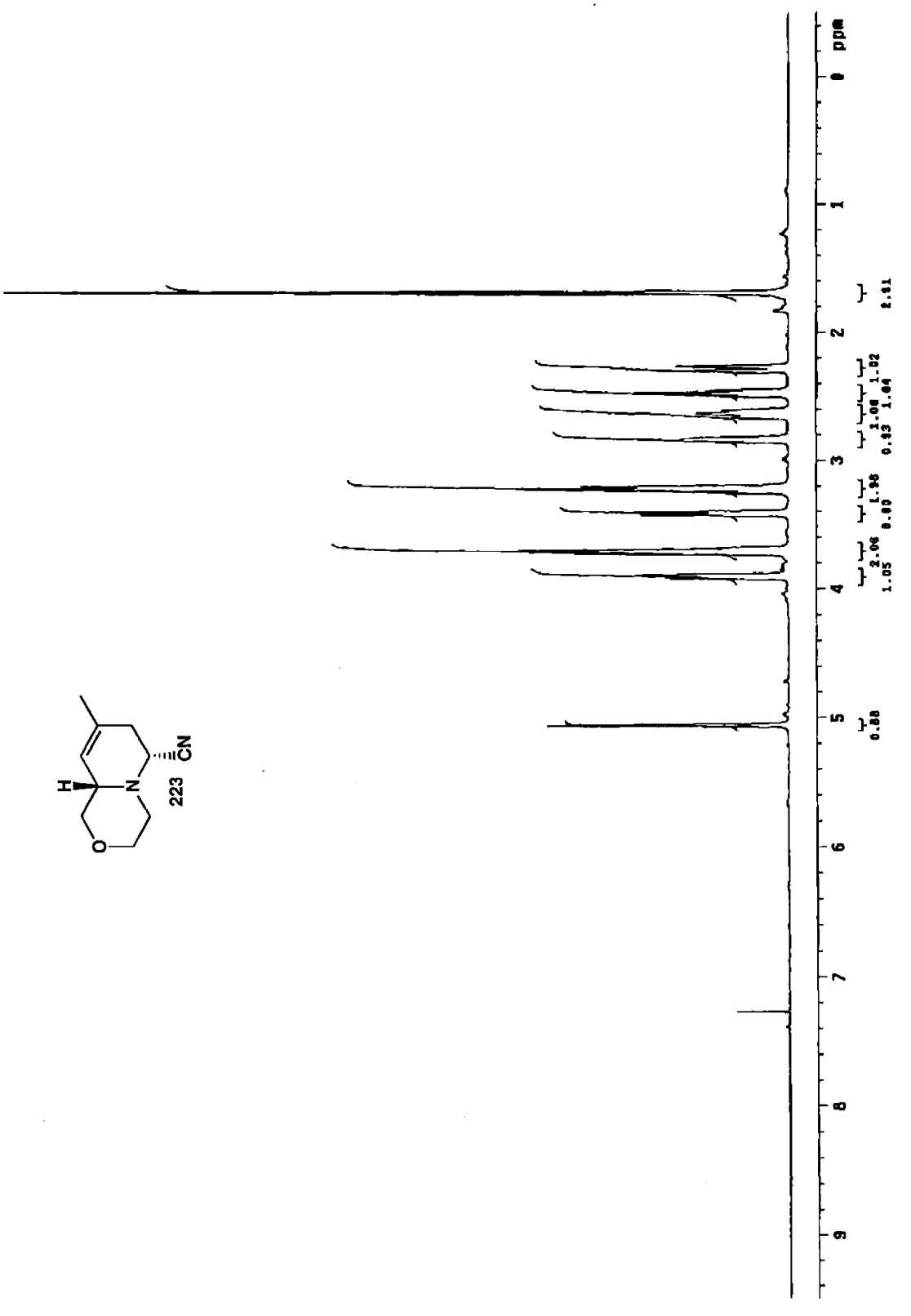
2
3
4
5
6
7
8
9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H
N
O
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3
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8
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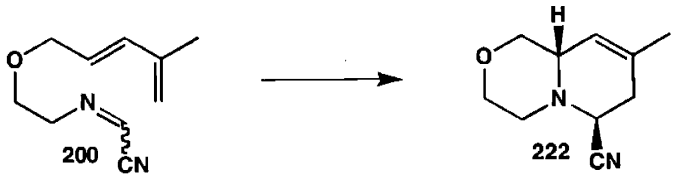
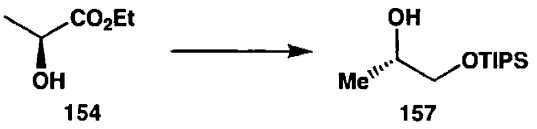
1.96
0.80
1.08
0.93
1.02
1.04
2.41



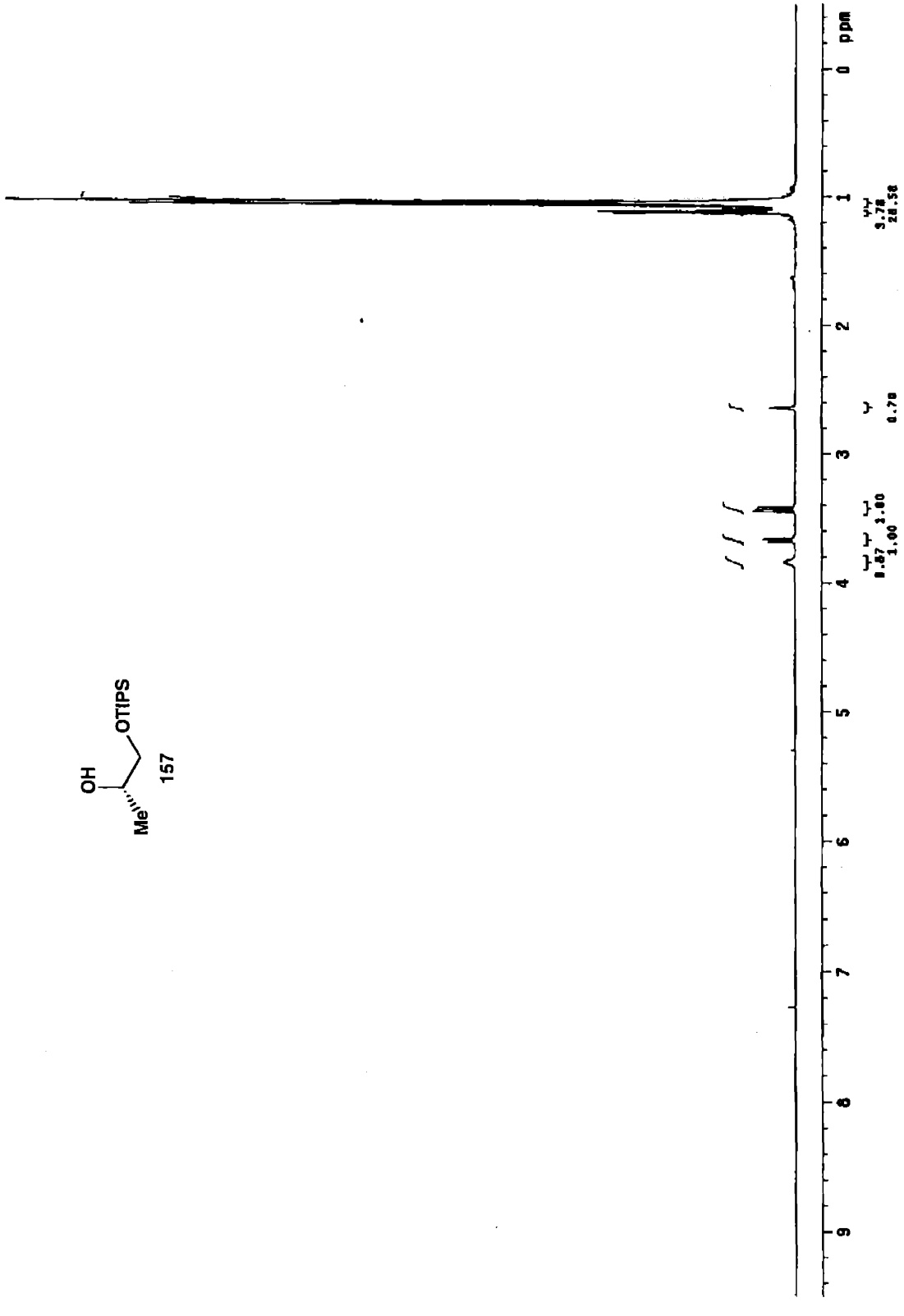
***cis*-8-Methyl-1,3,4,6,7,9*a*-hexahydro-6-cyano-pyrido[2,1-c][1,4]oxazine (222).** A threaded Pyrex tube (ca. 50 mL capacity) equipped with a rubber septum and argon inlet needle was charged with imine **200** (0.173 g, 0.97 mmol), BHT (0.642 g, 2.91 mmol), and 19 mL of toluene. The solution was degassed by three freeze-pump-thaw cycles and then sealed with a threaded Teflon cap. The reaction mixture was heated in a 120 °C oil bath for 18 h and then allowed to cool to rt. Concentration gave 0.857 g of a yellow oil that was then dissolved in 10 ml of dry acetonitrile and heated at 60 °C for 4 h. The resulting solution was allowed to cool to rt and concentrated to afford 0.819 g of brown oil. Column chromatography on 20 g of silica gel (gradient elution with 1% Et_3N-10-25% EtOAc-hexanes) afforded 0.146 g (84%) of **222** as a colorless oil with spectral properties consistent with that reported on the preceding pages

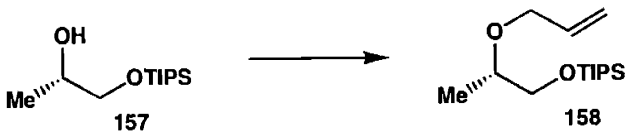


(*S*)-1-(Triisopropylsiloxy)-2-propanol (157). A 100-mL, three-necked, round-bottomed flask equipped with a rubber septum, argon inlet adapter, and 25-mL pressure equalizing addition funnel fitted with a rubber septum was charged with $LiAlH_4$ (0.603 g, 15.9 mmol) and 30 mL of THF. The flask was cooled at 0 °C while (-)-ethyl lactate (1.50 mL, 1.56 g, 13.2 mmol) in 6 mL of THF was added dropwise via the addition funnel over 8 min, followed by a 2 mL THF rinse. The ice bath was removed, and the grey suspension was allowed to stir at rt for 3 h and then quenched by careful addition of 15 g of solid $Na_2SO_4•(H_2O)_{10}$. The resulting mixture was stirred at rt for 3.5 h, filtered with the aid of 40 mL of ether, dried over K_2CO_3, filtered, and concentrated to afford 0.836 (83% crude yield) of the expected diol as a yellow oil used in the next step without further purification.

A 50-mL, two-necked, round-bottomed flask fitted with a rubber septum and argon inlet adapter was charged with DMAP (0.134 g, 1.10 mmol), 20 mL of CH_2Cl_2, and the crude diol (0.836 g, 11.0 mmol) from the previous step. Triethylamine (2.15 mL, 1.56 g, 15.4 mmol) was then added, followed by TIPS-Cl (2.20 mL, 2.00 g, 10.4 mmol). The resulting solution was stirred at rt for 15 h and then diluted with 50 mL of water and 50 mL of ether. The aqueous layer was separated and extracted with two 20-mL portions of ether, and the combined organic layers were washed with 30 mL of brine, dried over $MgSO_4$, filtered, and concentrated to afford 2.33 g of yellow oil. Column chromatography on 25 g of silica gel (gradient elution with 0-5% EtOAc-hexanes) provided 1.93 g (63% overall from **154**; 80% purity by ^1H NMR analysis) of **157** as a colorless oil.

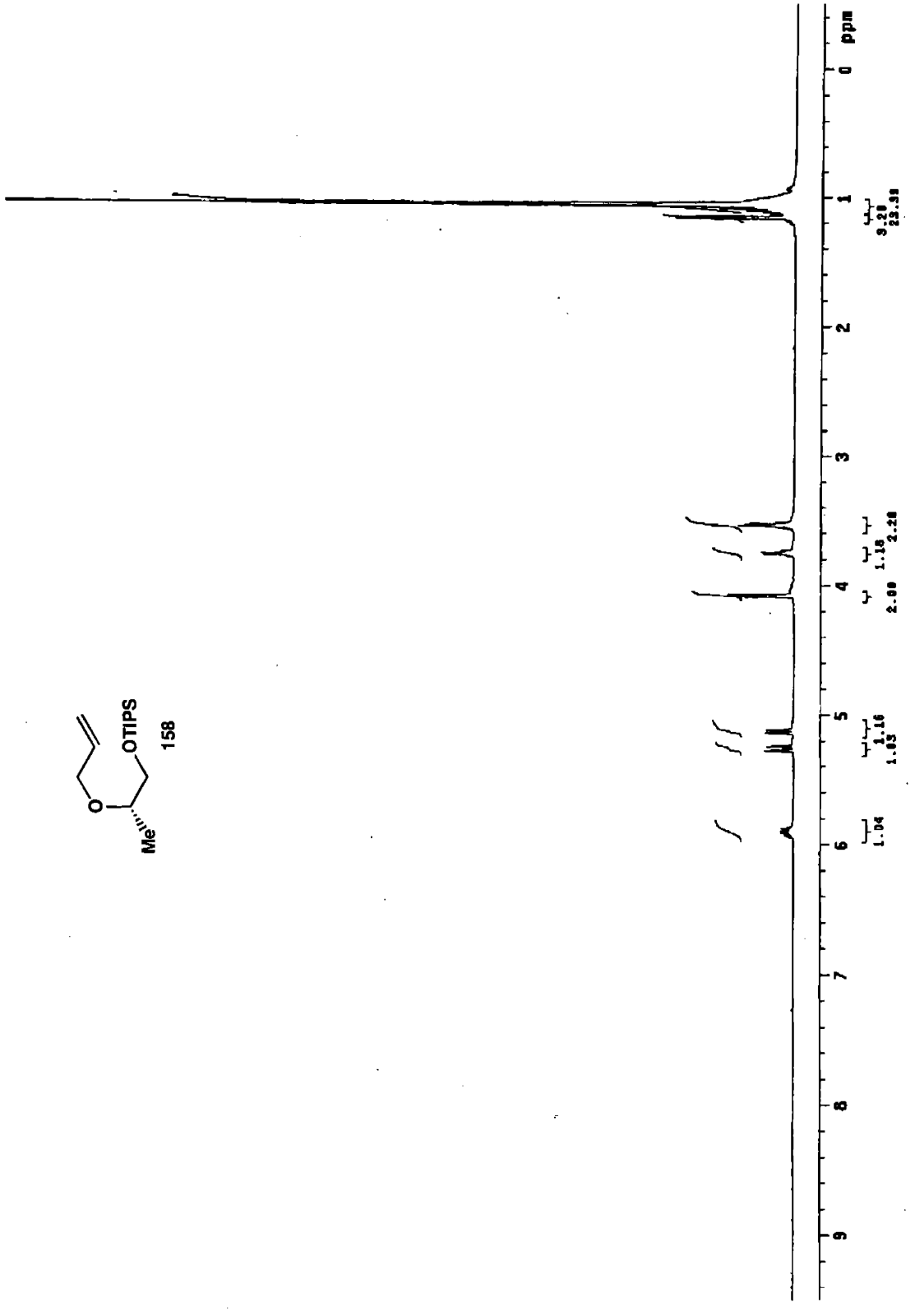
IR (film):	3391, 2944, 2893, 2867, 1464, 1383, 1251, 1102, 1069, 1014, 996, 883, 843, 793, 681
^{1}H NMR (500 MHz, $CDCl_3$):	3.82-3.86 (m, 1 H), 3.67 (dd, J = 9.8, 3.4 Hz, 1 H), 3.43 (dd, J = 9.6, 7.8 Hz, 1 H), 2.64 (br, 1 H), 1.12 (d, J = 6.4 Hz, 3 H), 1.03-1.08 (m, 21 H)
^{13}C NMR (125 MHz, $CDCl_3$):	69.0, 68.3, 18.1, 17.9, 12.1

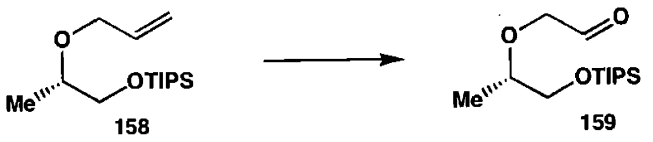

OH
OTIPS
Me
157
ppm



[(*S*)-2-(2-propenyloxy)propoxy]tris(1-methylethyl)silane (158). A 25-mL, two-necked, round-bottomed flask equipped with a rubber septum and argon inlet adapter was charged with NaH (60% wt in mineral oil, 0.452 g, 11.3 mmol) and 10 mL of benzene and cooled to 0 °C. A solution of alcohol **157** (1.05 g, 4.52 mmol) in 5 mL of benzene was then added, followed by allyl iodide (1.24 mL, 2.28 g, 13.6 mmol) in one portion. The ice bath was removed and the solution was allowed to stir at rt in the dark for 17 h. The reaction mixture was carefully diluted with 40 mL of water, and the aqueous layer was separated and extracted with three 30-mL portions of ether. The combined organic layers were washed with 40 mL of brine, dried over $MgSO_4$, filtered, and concentrated to afford 1.31 g of yellow oil. Column chromatography on 25 g of silica gel (elution with 2% EtOAc-hexanes) provided 0.355 g (29%) of **158** as a pale yellow oil.

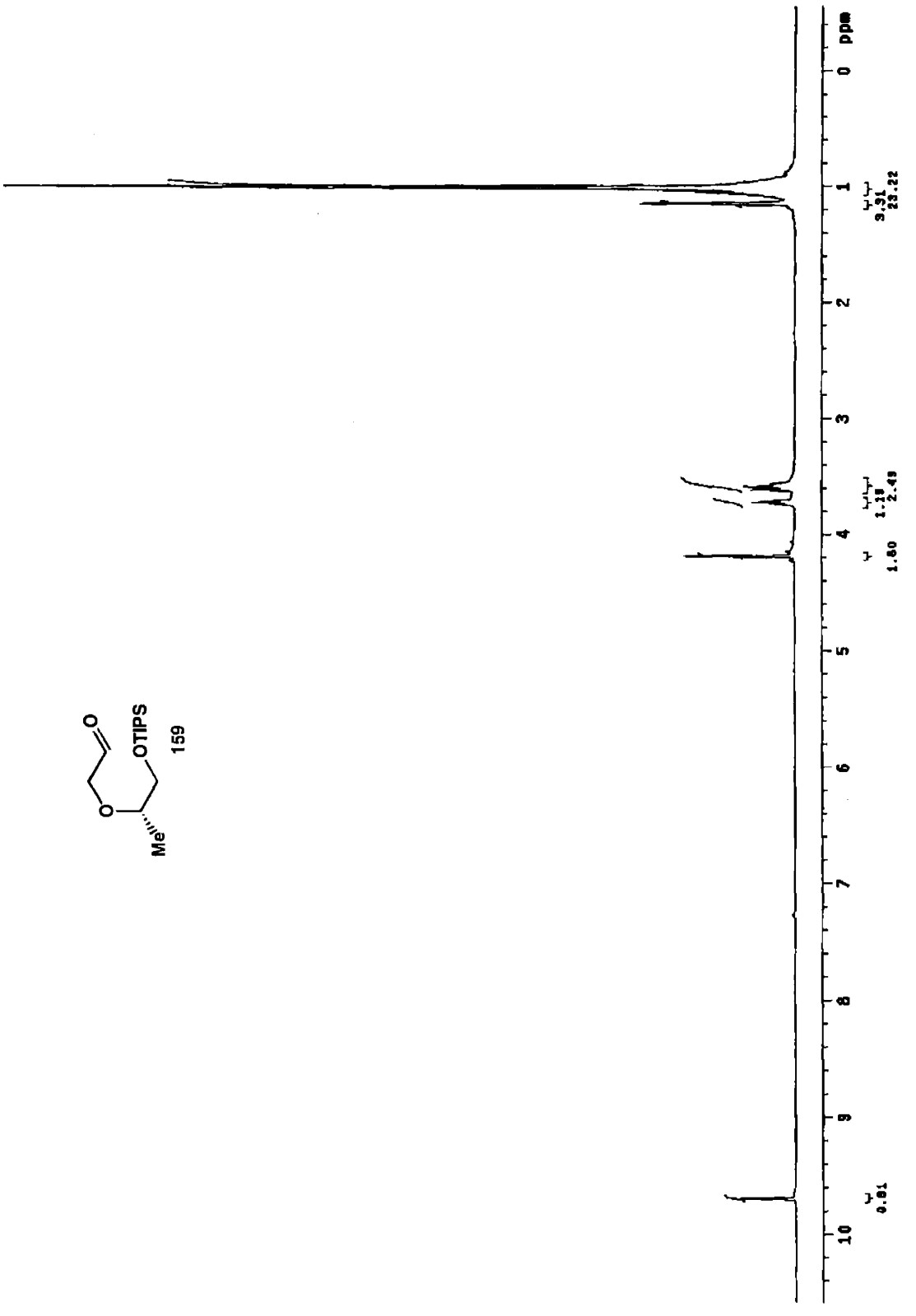
IR (film):	3081, 2943, 2867, 2756, 2726 1648, 1464, 1384, 1371, 1343, 1249, 1110, 1014, 996, 920, 883, 797, 682
^{1}H NMR (500 MHz, $CDCl_3$):	5.91 (ddt, J = 17.2, 10.3, 6.8 Hz, 1 H), 5.26 (d, J = 17.2 Hz, 1 H), 5.13 (d, J = 10.4 Hz, 1 H), 4.08 (d, J = 5.5 Hz, 2 H), 3.73-3.77 (m, 1 H), 3.51-3.56 (m, 2 H), 1.15 (d, J = 5.8 Hz, 3 H), 1.04-1.10 (m, 21 H)
^{13}C NMR (125 MHz, $CDCl_3$):	135.7, 116.5, 76.0, 70.6, 67.6, 18.1,17.4, 12.1

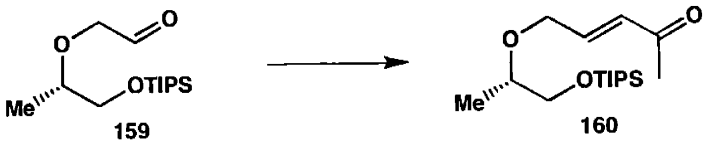

OTIPS
158
Me
O
ppm
0
1
2
3
4
5
6
7
8
9
9.29
23.31
1.18
2.28
2.00
1.16
1.03
1.04



(*S*)-2-(2-Triisopropylsiloxy-1-methylethoxy)-ethenol (159). A 25-mL, recovery flask containing alkene **158** (0.417 g, 1.53 mmol) was fitted with a rubber septum and argon inlet needle and purged with argon. CH_2Cl_2 (6 mL) was added, and the flask was cooled at –78 °C while ozone was bubbled through the solution for 4 min. The resulting blue solution was degassed with a stream of argon for 10 min. Triphenylphosphine (0.401 g, 1.53 mmol) was added, and the solution was allowed to slowly warm to rt over 3 h. Concentration by rotary evaporation afforded 0.930 g of a white solid, which was concentrated onto 2 g of silica gel and applied to a column of 20 g of silica gel. Gradient elution with 5-20% EtOAc-hexanes afforded 0.357g (85%) of **159** as a colorless oil.

IR (film):	2944, 2867, 2716, 1739, 1464, 1383, 1250, 1161, 1118, 1070, 1015, 919, 883, 794, 683, 660
^{1}H NMR (500 MHz, $CDCl_3$):	9.75 (t, *J* = 1.0 Hz, 1 H), 4.24 (d, *J* = 1.0 Hz, 2 H), 3.75-3.81 (m, 1 H), 3.59-3.67 (m, 2 H), 1.20 (d, *J* = 6.2 Hz, 3 H), 1.05-1.15 (m, 21 H)
^{13}C NMR (125 MHz, $CDCl_3$):	201.9, 78.2, 75.7, 68.1, 18.0, 17.0, 12.0

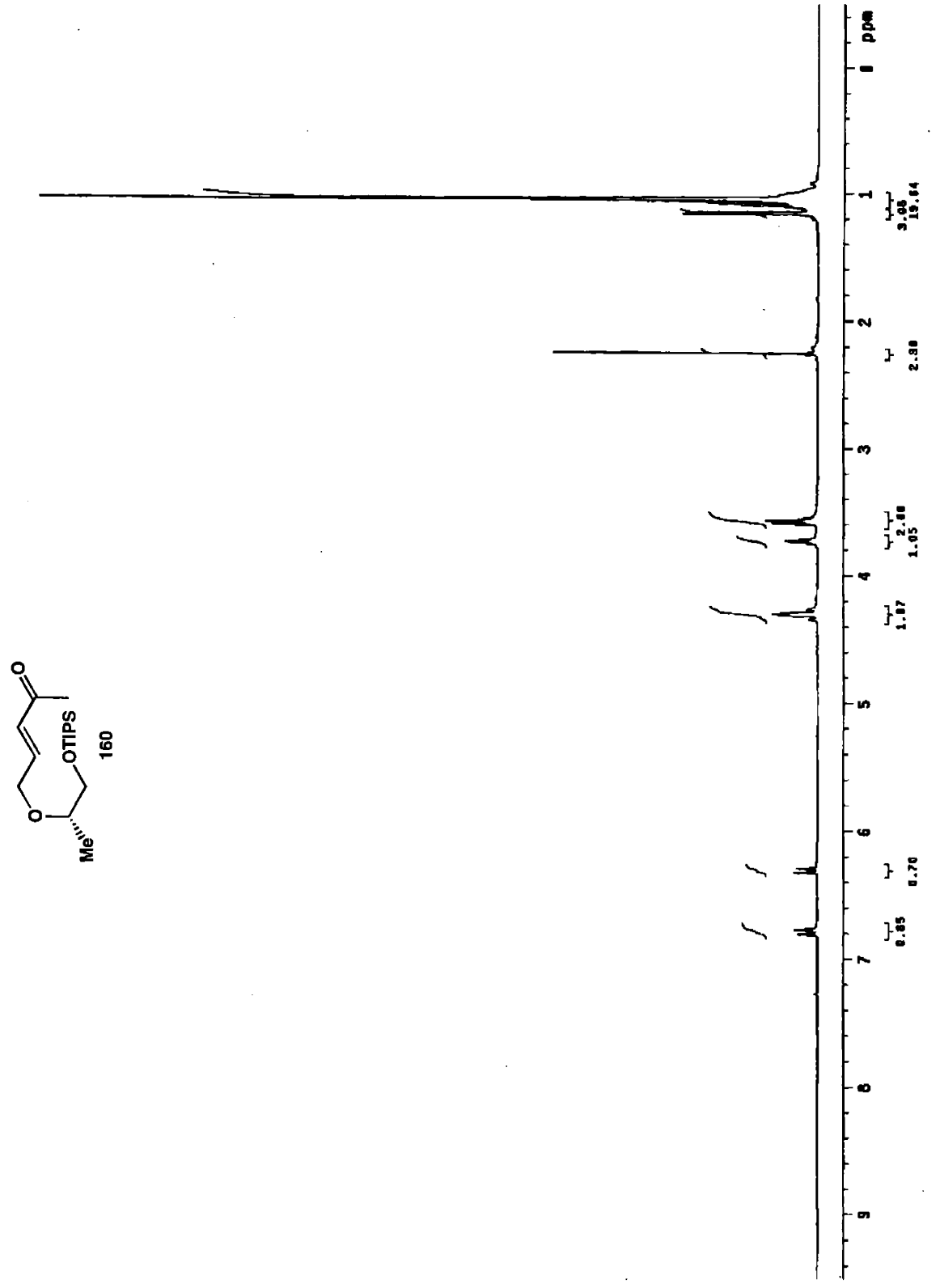

O
OTIPS
O
Me
159
ppm
0
1
2
3
4
5
6
7
8
9
10
9.31
23.22
1.19
2.49
1.80
0.81



159 160

(*S*)-5-(2-Triispropylsiloxy-1-methyl-ethoxy)-(*E*)-3-penten-2-one (160). A 25-mL, round-bottomed flask equipped with a reflux condenser fitted with an argon inlet adapter was charged with aldehyde **159** (0.333 g, 1.21 mmol) and 5 mL of CH_2Cl_2. (Acetylmethylene)triphenylphosphorane (0.425 g, 1.33 mmol) was then added, and the reaction mixture was heated at reflux for 3 h. Concentration by rotary evaporation afforded 0.745 g of a white solid. This material was concentrated onto 1.5 g of silica gel and applied to a column of 20 g of silica gel. Gradient elution with 5-10% EtOAc-hexanes provided 0.324 g (85%) of **160** as a colorless oil.

IR (film):	2944, 2867, 1701, 1682, 1636, 1463, 1361, 1253, 1111, 1070, 1014, 997, 975, 883, 794
^{1}H NMR (500 MHz, $CDCl_3$):	6.79 (dt, J = 16.1, 4.4 Hz, 1 H), 6.31 (dt, J = 16.2, 1.5 Hz, 1 H), 4.25-4.35 (m, 2 H), 3.71-3.75 (m, 1 H), 3.55-3.60 (m, 2 H), 2.25 (s, 3 H), 1.15 (d, J = 4.9 Hz, 3 H), 1.05-1.11 (m, 21 H)
^{13}C NMR (125 MHz, $CDCl_3$):	198.5, 144.3, 130.1, 77.1, 68.5, 67.9, 27.4, 18.1, 17.2, 12.0


O
OTIPS
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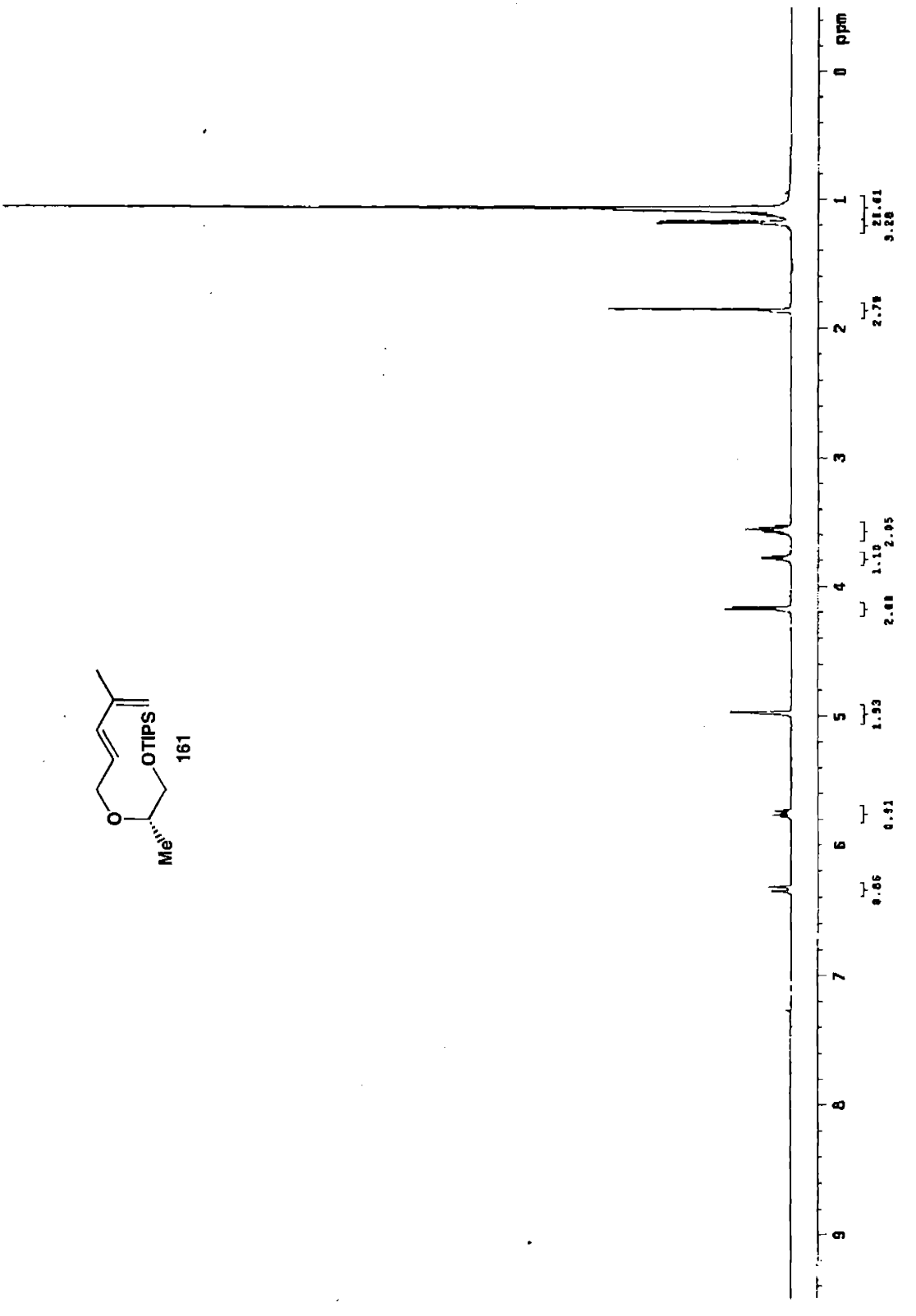
Me
160
ppm
1
2
3
4
5
6
7
8
9
3.00
19.84
2.38
2.00
1.05
1.87
0.85
0.70

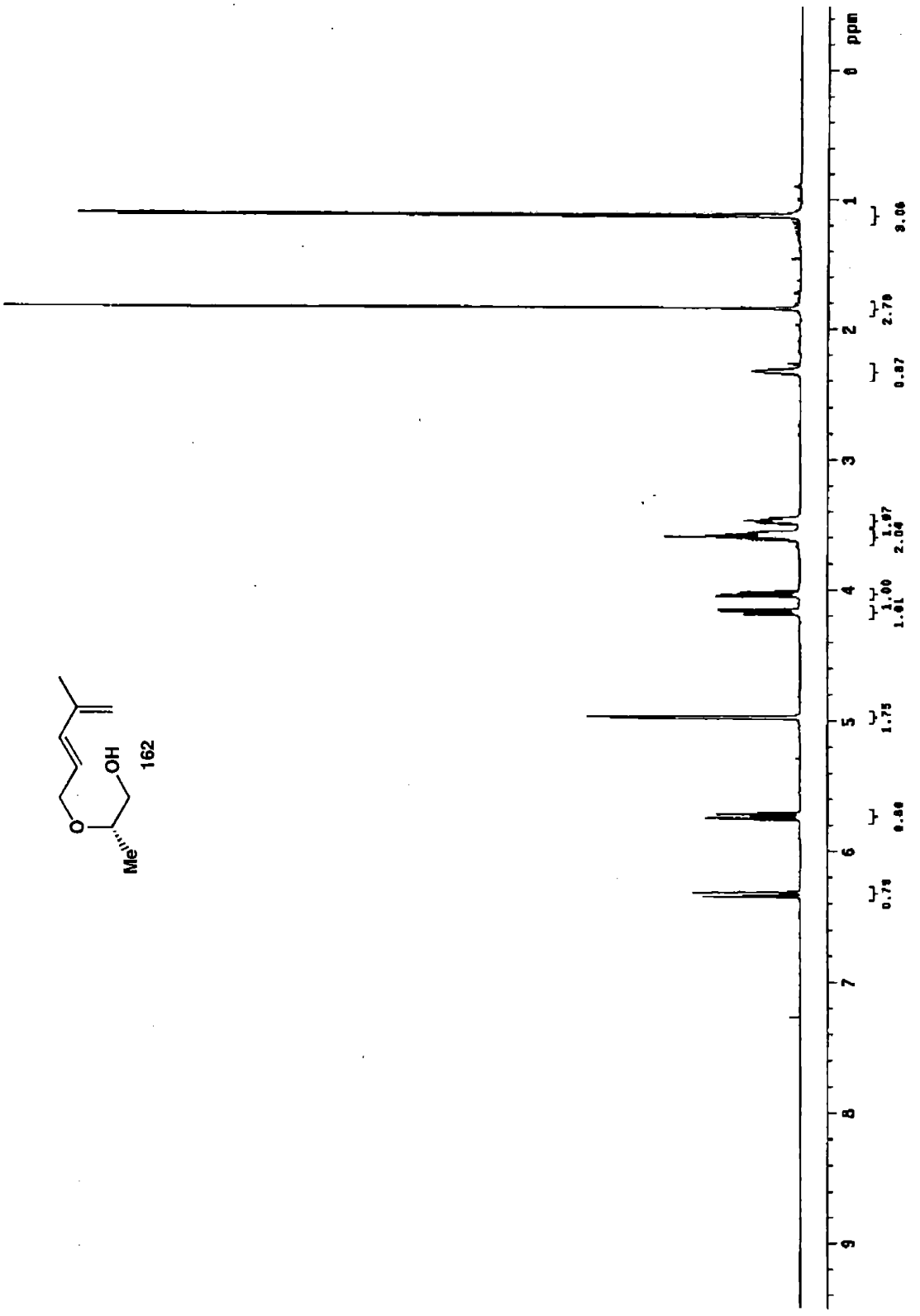
1-Triisopropylsiloxy-2-[(2*E*)-4-methyl-2,4-pentadienyloxy]propane (161). A 25-ml, two-necked, round-bottomed flask equipped with a rubber septum and argon inlet adapter was charged with methyltriphenylphosphonium bromide (0.442 g, 1.24 mmol) and 4 mL of THF. The solution was cooled at 0 °C while 0.49 mL of *n*-BuLi solution (2.50 M in hexanes, 1.24 mmol) was added dropwise via syringe over 1 min. The resulting solution was stirred at 0 °C for 30 min and then a solution of aldehyde **160** (0.324 g, 1.03 mmol) in 3 mL of THF was added dropwise over 3 min. The reaction mixture was stirred at 0 °C for 3.5 h and then diluted with 35 mL of water. The aqueous layer was separated and extracted with three 25-mL portions of ether, and the combined organic layers were washed with 30 mL brine, dried over $MgSO_4$, filtered, and concentrated to afford 0.645 g of a yellow solid. This material was concentrated onto 1.5 g of silica gel and applied to a column of 15 g of silica gel. Gradient elution with 0-1% EtOAc-hexanes provided 0.274 g (85%) of **161** as a colorless oil.

IR (film):	3083, 2944, 2867, 1611, 1463, 1382, 1342, 1249, 1159, 1111, 1071, 1014, 968, 883, 794
^{1}H NMR (500 MHz, $CDCl_3$):	6.34 (d, J = 15.7 Hz, 1 H), 5.75 (dt, J = 15.7, 6.1 Hz, 1 H), 4.97 (s, 2 H), 4.17 (dd, J = 6.1, 0.6 Hz, 2 H), 3.75-3.79 (m, 1 H), 3.53-3.59 (m, 2 H), 1.86 (s, 3 H), 1.18 (d, J = 6.0 Hz, 3 H), 1.05-1.12 (m, 21 H)
^{13}C NMR (125 MHz, $CDCl_3$):	141.7, 135.1, 126.9, 116.7, 76.1, 70.2, 67.7, 18.7, 18.2, 17.5, 12.1


OTIPS
Me
O
161
ppm

(*S*)-2-[(2*E*)-4-Methyl-2,4-pentadienyloxy]propanol (162). A 25-mL round-bottomed flask with argon inlet adapter was charged with silyl ether **161** (0.325 g, 1.04 mmol) and 5 mL of methanol. CSA (0.242 g, 1.04 mmol) was added and the resulting solution was stirred at rt for 90 min. Methanol was removed by rotary evaporation and the residue was dissolved in 25 mL of CH_2Cl_2 and washed with 25 ml of satd aq $NaHCO_3$ solution. The aqueous layer was separated and extracted with two 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 afford 0.299 g of colorless oil. Column chromatography on 8 g of silica gel (elution with 20% EtOAc-hexanes) provided 0.138 g (85%) of **162** as a colorless oil.

IR (film):	3427, 3082, 3031, 2972, 2931, 2872, 1611, 1454, 1375, 1340, 1228, 1146, 1118, 1059, 1015, 970, 890
^{1}H NMR (500 MHz, $CDCl_3$):	6.33 (d, J = 15.6 Hz, 1 H), 5.73 (dt, J = 15.7, 6.2 Hz, 1 H), 4.98 (s, 1 H), 4.97 (s, 1 H), 4.16 (dd, J = 12.5, 6.0 Hz, 1 H), 4.03 (dd, J = 12.5, 6.0 Hz, 1 H), 3.55-3.63 (m , 2 H), 3.44-3.49 (m, 1 H), 2.29 (br s, 1 H), 1.84 (s, 3 H), 1.12 (d, J = 6.1 Hz, 3 H)
^{13}C NMR (125 MHz, $CDCl_3$):	141.5, 135.5, 126.2, 117.1, 75.6, 69.5, 66.4, 18.7, 16.1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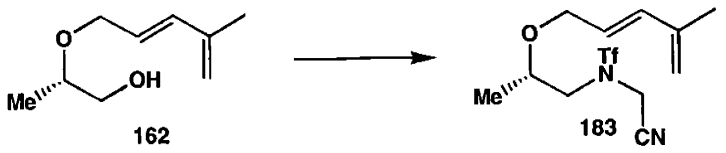
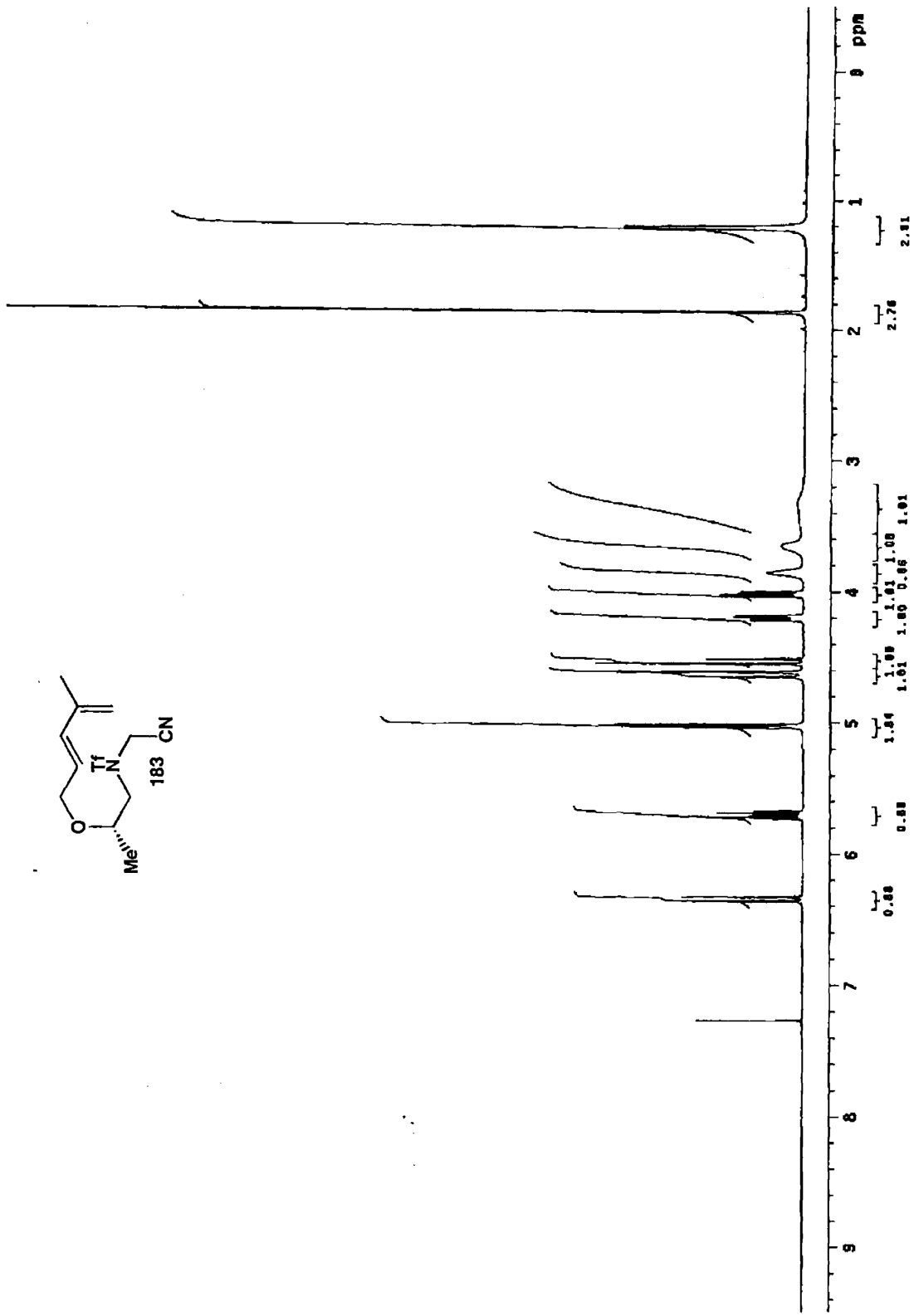
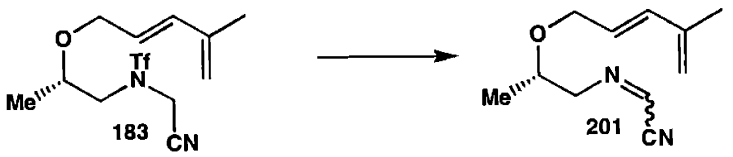
ppm



(*S*)-*N*-(Cyanomethyl)-*N*-(2-[(2*E*)-4-methyl-2,4-pentadienyloxy]propyl)trifluoromethanesulfonamide (183). A 50-mL, two-necked, round-bottomed flask equipped with a rubber septum and an argon inlet adapter was charged with triphenylphosphine (1.27 g, 4.83 mmol), a solution of $HN(Tf)CH_2CN$ (0.795 g, 4.23 mmol) in 15 mL of THF, and a solution of alcohol **162** (0.629 g, 4.03 mmol) in 15 mL of toluene. DEAD (0.76 mL, 0.84 g, 4.8 mmol) was added dropwise via syringe over 5 min, and the resulting mixture was stirred at rt for 24 h and then concentrated to give 4.62 g of a yellow solid. This material was concentrated onto 9 g of silica gel and applied to a column of 75 g of silica gel. Gradient elution with 5-20% EtOAc-hexanes provided 1.08 g (82%) of **183** as a colorless oil.

IR (film):	3085, 2978, 2940, 2866, 1612, 1455, 1440, 1398, 1353, 1272, 1230, 1198, 1149, 1122, 1055, 971, 940, 904, 893, 784, 749
^{1}H NMR (500 MHz, $CDCl_3$):	6.35 (d, J = 15.9 Hz, 1 H), 5.70 (dt, J = 15.9, 6.3 Hz, 1 H), 5.03 (s, 1 H), 5.02 (s, 1 H), 4.63 (d, J = 18.0 Hz, 1 H), 4.53 (d, J = 18.0 Hz, 1 H), 4.20 (dd, J = 12.7, 5.7 Hz, 1 H), 4.01 (ddd, J = 12.3, 6.5, 1.0 Hz, 1 H), 3.82-3.89 (br m, 1 H), 3.61-3.71 (br m, 1 H), 3.25-3.55 (br m, 1 H), 1.87 (s, 3 H), 1.21 (d, J = 5.8 Hz, 1 H)
^{13}C NMR (125 MHz, $CDCl_3$):	141.8, 136.0, 126.0, 120.6 (q, J = 323 Hz), 117.8, 114.4, 74.6, 69.4, 54.4, 38.2, 18.9, 16.5
HRMS $[M+Na]^+$:	Calcd for $C_{12}H_{17}F_3N_2NaO_3S$: 349.0804 Found: 349.0816

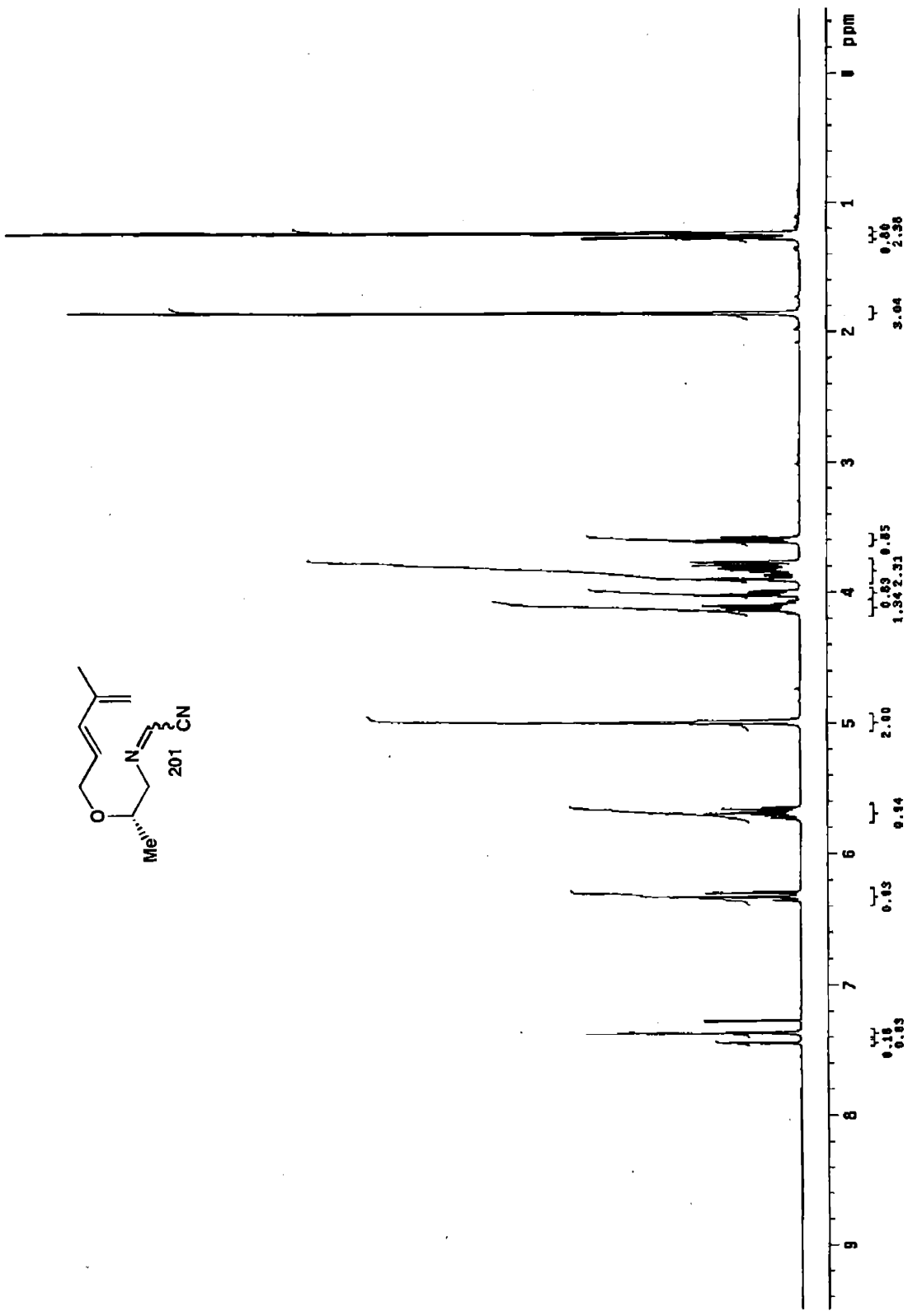

Tf
N
CN
O
Me
183
ppm



(*S*)-2-[(2*E*)-4-Methyl-2,4-pentadienyloxy]propyliminoacetonitrile (201). 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 (1.19 g, 3.64 mmol). A solution of triflamide **183** (0.297 g, 0.91 mmol) in 7 mL of THF was added, and the reaction mixture was heated at 55 °C for 3 h. The resulting mixture was allowed to cool to room temperature and then diluted with 20 mL of ether and 30 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 25 mL of brine, dried over $MgSO_4$, filtered, and concentrated to give 0.183 g of a pale yellow oil. Column chromatography on 8 g of Et_3N-deactivated silica gel (elution with 1% Et_3N-10% EtOAc-hexanes) provided 0.158 g (90%) of **201** (as an 79:21 mixture of E and Z imine isomers by ^1H NMR analysis) as a colorless oil.

IR (film):	3083, 3031, 2975, 2933, 2898, 2857, 2243, 1626, 1611, 1454, 1378, 1339, 1228, 1121, 1053, 1015, 971, 893, 734
For E isomer: ^1H NMR (500 MHz, $CDCl_3$):	7.36 (t, *J* = 1.2 Hz, 1 H), 6.31 (d, *J* = 15.9 Hz, 1 H), 5.67 (dt, *J* = 15.6, 6.1 Hz, 1 H), 4.99 (br s, 2 H), 4.11 (dd, *J* = 12.5, 6.1 Hz, 1 H), 4.01 (dd, *J* = 12.5, 6.1 Hz, 1 H), 3.76-3.91 (m, 2 H), 3.60 (ddd, *J* = 11.6, 6.7, 0.9 Hz, 1 H), 1.85 (s, 3 H), 1.23 (d, *J* = 6.4 Hz, 3 H)
^{13}C NMR (75 MHz, $CDCl_3$):	141.3, 137.4, 135.5, 125.8, 117.2, 114.5, 73.2, 69.9, 68.2, 18.8, 18.5
For Z isomer: ^1H NMR (500 MHz, $CDCl_3$):	7.44 (t, *J* = 2.1 Hz, 1 H), 6.34 (d, *J* = 15.9 Hz, 1 H), 5.71 (dt, *J* = 15.6, 6.1 Hz, 1 H), 4.99 (br s, 2 H), 4.14 (dd, *J* = 12.5, 6.1 Hz, 1 H), 4.09 (dd, *J* = 12.5, 6.1 Hz, 1 H), 3.76-

	3.91 (m, 3 H), 1.85 (s, 3 H), 1.23 (d, J = 6.4 Hz, 3 H)
^{13}C NMR (125 MHz, $CDCl_3$):	141.4, 135.2, 132.8, 126.0, 117.0, 110.2, 73.7, 69.8, 64.6, 18.8, 18.5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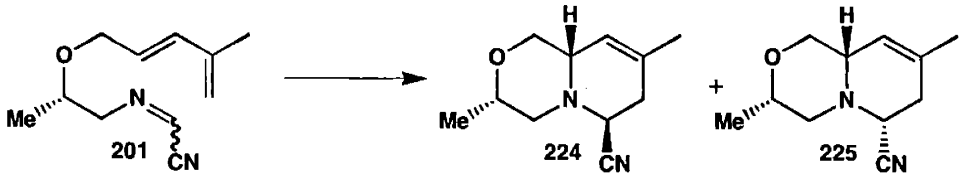


***cis*-3-(*S*)-Methyl-8-methyl-1,3,4,6,7,9*a*-hexahydro-6-cyano-pyrido[2,1-c][1,4]oxazine (224)** and ***trans*-3-(*S*)-Methyl-8-methyl-1,3,4,6,7,9*a*-hexahydro-6-cyano-pyrido[2,1-c][1,4]oxazine (225).** A 25-mL round-bottomed flask equipped with a reflux condenser fitted with an argon inlet adapter was charged with imine **201** (0.158 g, 0.82 mmol), BHT (0.543 g, 2.47 mmol), and 16 mL of toluene. The reaction mixture was heated at reflux for 16 h and then allowed to cool to rt. Concentration afforded 0.785 g of a yellow oil. Column chromatography on 18 g of silica gel (gradient elution with 1% Et_3N-10-15% EtOAc-hexanes) afforded 0.152 g (96%) of **224** and **225** (as a 44:56 mixture of diastereomers by ^1H NMR analysis) as a colorless oil.

For both isomers:

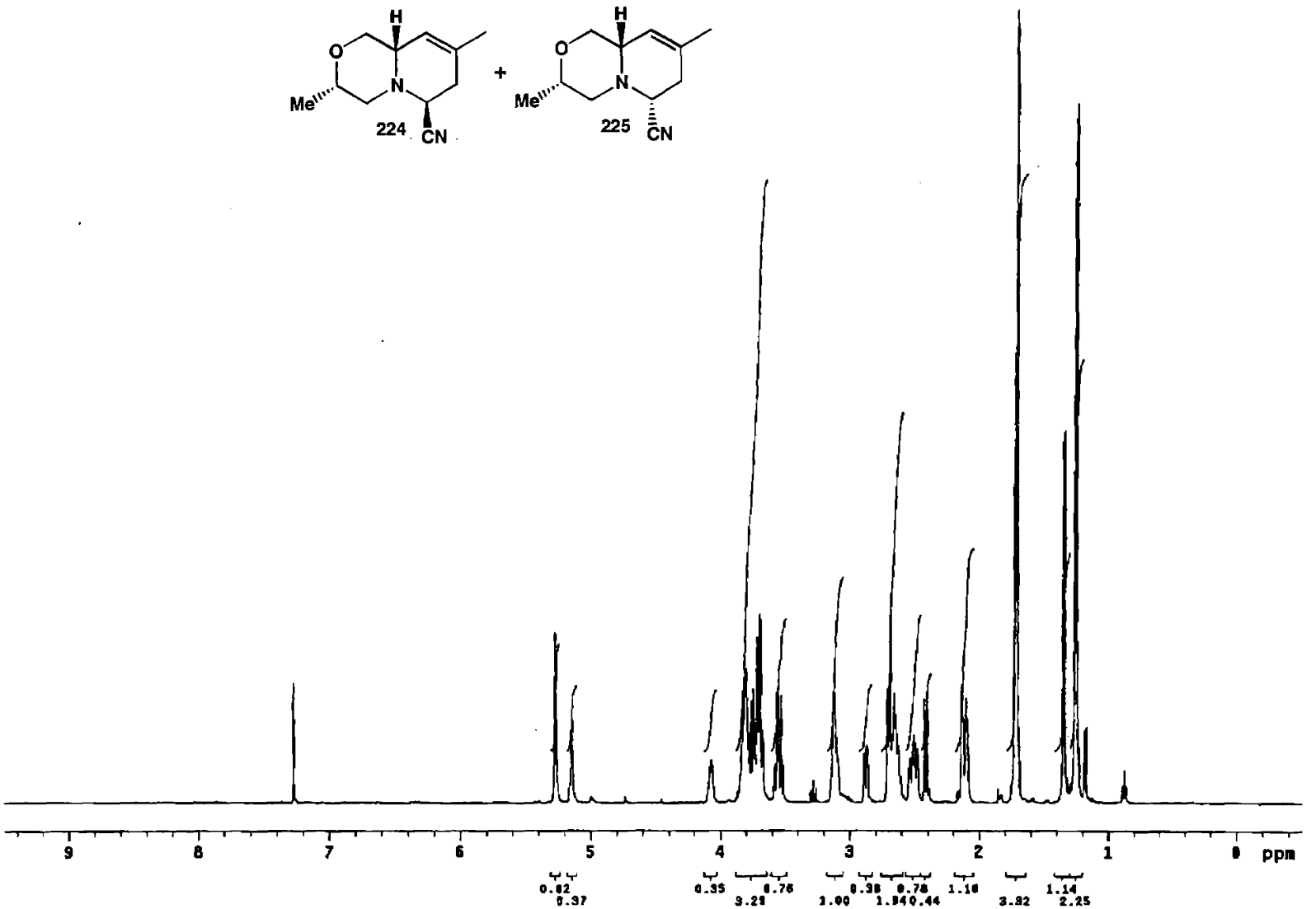
IR (film):	2972, 2913, 2861, 1448, 1381, 1343, 1328, 1260, 1212, 1178, 1158, 1137, 1107, 1040, 911, 873, 829
HRMS $[M+H]^+$:	Calcd for $C_{11}H_{17}N_2O$: 193.1335 Found: 193.1341

For (**224**):

^1H NMR (500 MHz, $CDCl_3$):	5.13 (s, 1 H), 4.03-4.08 (m, 1 H), 3.74 (d, J = 5.8 Hz, 1 H), 3.52-3.58 (m, 2 H), 3.06-3.11 (m, 1 H), 2.86 (dd, J = 11.0, 4.0 Hz, 1 H), 2.67 (br d, J = 17.4 Hz, 1 H), 2.40 (dd, J = 11.0, 1.2 Hz, 1 H), 2.11 (d, J = 17.4 Hz, 1 H), 1.71 (s, 3 H), 1.33 (d, J = 6.7 Hz, 1 H)
^{13}C NMR (75 MHz, $CDCl_3$):	131.0, 118.8, 116.8, 68.7, 64.5, 56.0, 55.8, 51.6, 33.5, 23.0, 16.9

For (**225**):

^{1}H NMR (500 MHz, $CDCl_3$):	5.27 (s, 1 H), 3.78-3.84 (m, 2 H), 3.70 (dd, J = 10.7, 4.6 Hz, 1 H), 3.66-3.73 (m, 1 H), 3.08-3.14 (br, 1 H), 2.70 (dd, J = 10.7, 2.7 Hz, 1 H), 2.61-2.71 (m, 1 H), 2.51 (app br t, J = 14.4, 1 H), 2.12 (d, J = 17.4, 1 H), 1.70 (s, 3 H), 1.25 (d, J = 6.4 Hz, 3 H)
^{13}C NMR (75 MHz, $CDCl_3$):	132.3, 120.7, 118.6, 71.2, 68.2, 56.4, 55.3, 51.2, 33.5, 22.9, 18.4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CN
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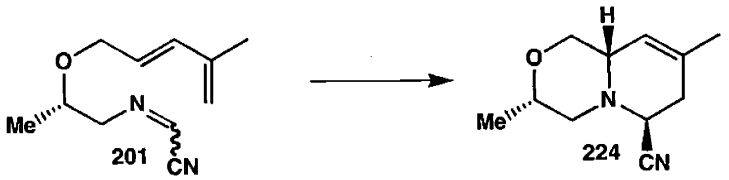
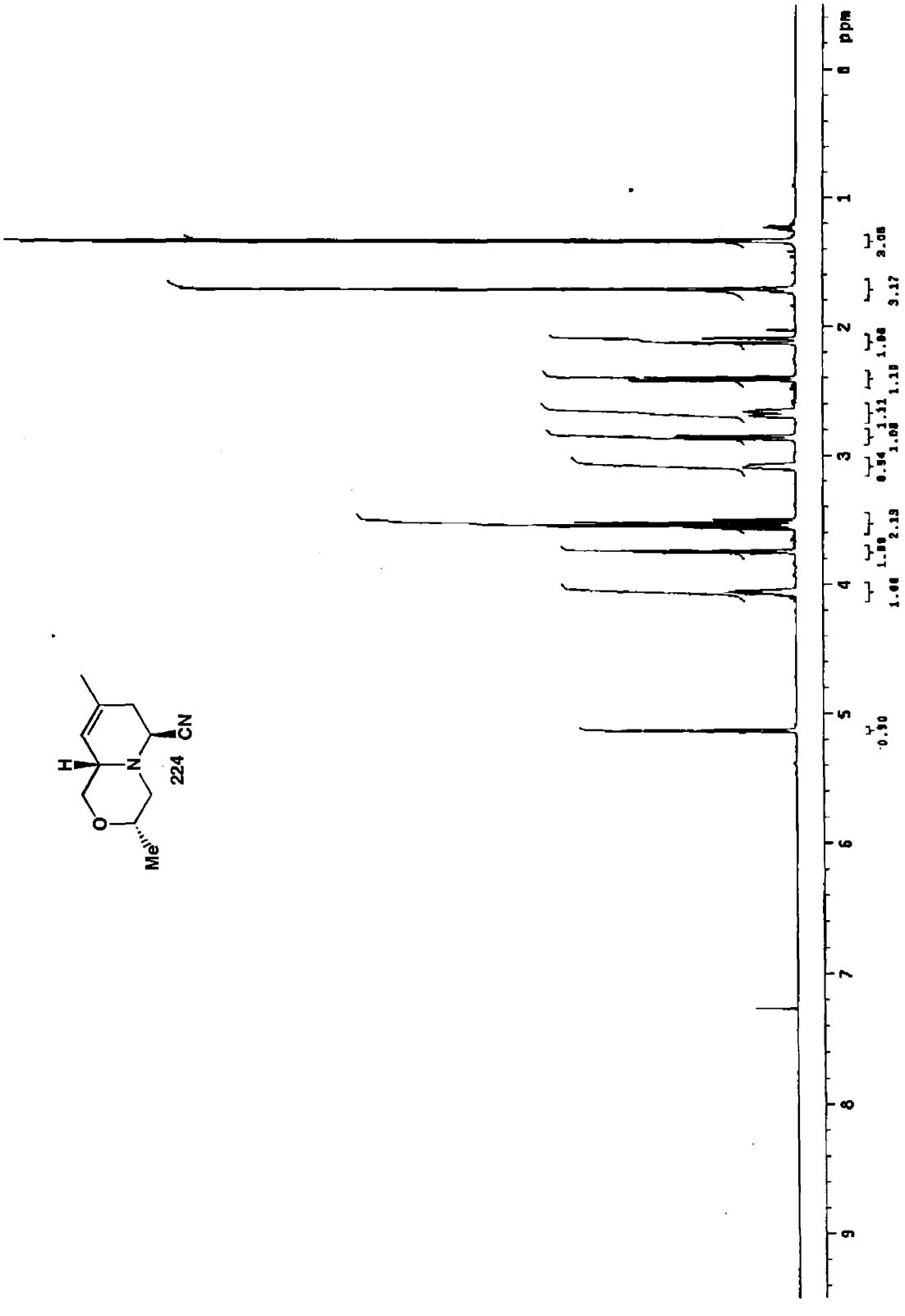


***cis*-3-(*S*)-Methyl-8-methyl-1,3,4,6,7,9*a*-hexahydro-6-cyano-pyrido[2,1-c][1,4]oxazine (224).** A 25-mL, round-bottomed flask equipped with a reflux condenser fitted with an argon inlet adapter was charged with imine **201** (0.147 g, 0.76 mmol), BHT (0.505 g, 2.29 mmol), and 15 mL of toluene. The solution was heated at reflux for 15 h and then allowed to cool to rt. Concentration provided a green oil that was then dissolved in 10 ml of acetonitrile and heated at 65 °C for 22 h. The reaction solution was allowed to cool to rt and concentration afforded 0.662 g of brown oil. Column chromatography on 18 g of silica gel (gradient elution with 1% Et_3N-10-15% EtOAc-hexanes) afforded 0.063 g (43%) of **224** as a white solid (mp 61-62 °C) and 0.075 g (51%) of **224** and **225** (as a 71:29 mixture of diastereomers by ^1H NMR analysis) as a colorless oil with spectral properties identical to those reported in the previous procedure for **224** and **225**. Total yield, 0.138 g (94%) of an 84:16 mixture of **224** and **225**.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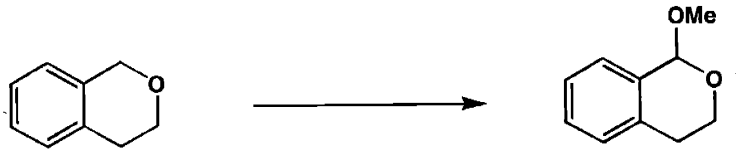


162 163

3,4-Dihydro-1-methoxy-1H-2-benzopyran (163). A three-necked, round-bottomed flask equipped with a rubber septum, glass stopper, and argon inlet adapter was charged with MeOH (0.23 mL, 0.18 g, 5.7 mmol), isochroman **162** (0.60 mL, 0.64 g, 4.8 mmol), and 20 mL of CH_2Cl_2. DDQ (1.30 g, 5.73 mmol) was added, and the red solution was stirred at rt for 28 h. The resulting solution was then diluted with 50 mL of satd aq $NaCHO_3$ solution, and the resulting biphasic mixture was stirred for 15 min. The aqueous layer was separated and extracted with three 25-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 0.793 g of yellow oil. Column chromatography on 16 g of silica gel (elution with 10% EtOAc/hexanes) provided 0.572 g (73%) of the **163** as colorless oil (5% isochroman present) with spectral data consistent with that previously reported for this compound.[195]

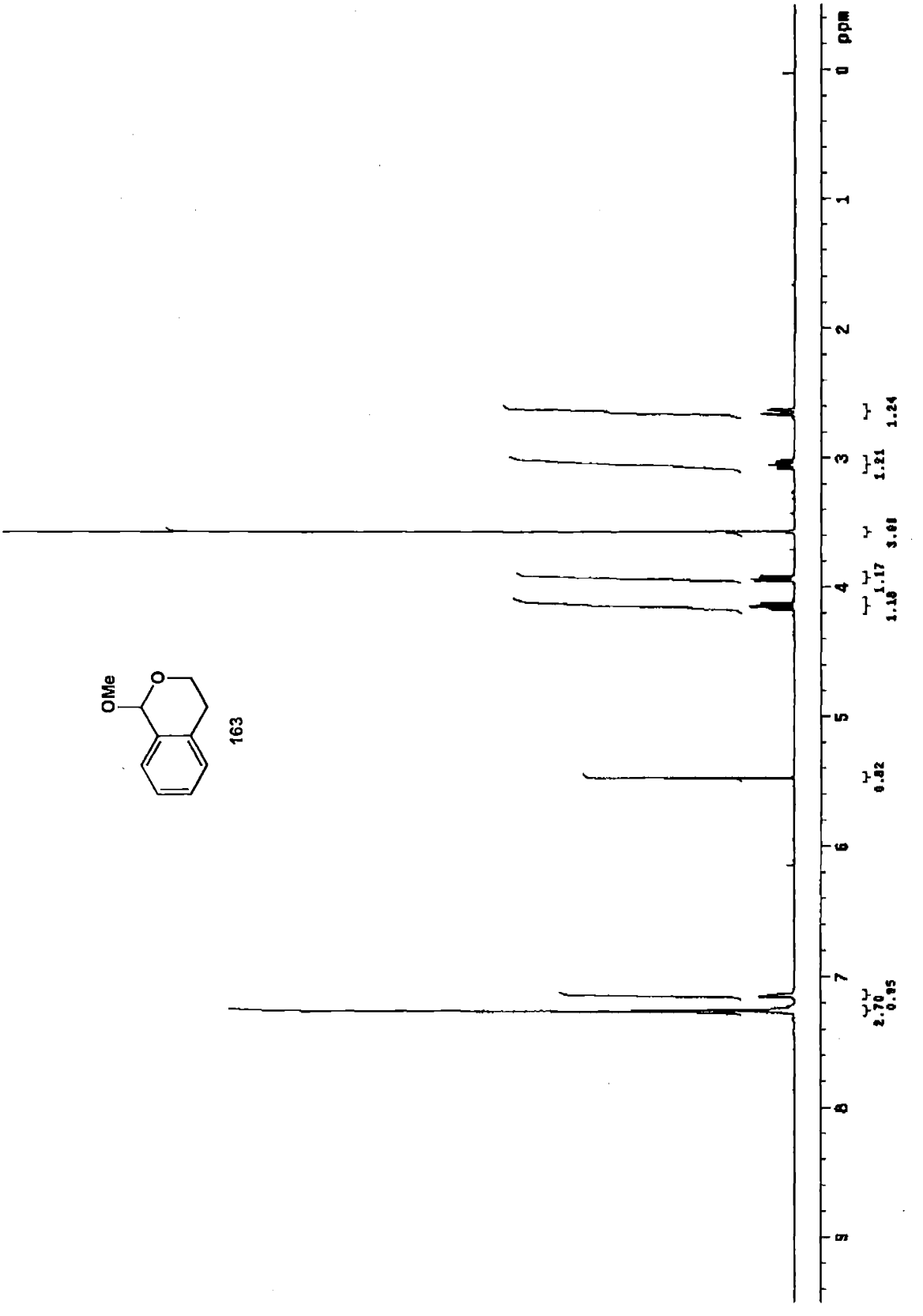
IR (film):	3020, 2925, 2875, 2818, 1480, 1450, 1410, 1372, 1340, 1262, 1190, 1175, 1082, 1060, 1038, 980, 942
^{1}H NMR (500 MHz, $CDCl_3$):	7.22-7.31 (m, 3 H), 7.14 (d, J = 6.7 Hz, 1 H), 5.47, (s, 3 H), 4.15 (dt, J = 11.3, 3.4 Hz, 1 H), 3.93 (ddd, J = 11.3, 6.1, 1.3 Hz, 1 H), 3.57 (s, 3 H), 3.05 (ddd, J = 16.5, 11.9, 6.1 Hz, 1 H), 2.64 (app dq, J = 16.5, 1.5 Hz, 1 H)
^{13}C NMR (125 MHz, $CDCl_3$):	134.3, 134.2, 128.6, 128.3, 127.6, 126.5, 97.9, 57.9, 55.5, 28.1

[195] Harling, J. D.; Orlek, B. S. *Tetrahedron*, **1998**, *54*, 14905.

163 164

3,4-Dihydro-1-(2-propenyl)-1H-2-benzopyran (164). A 50-mL, three-necked, round-bottomed flask equipped with an argon inlet adapter, rubber septum, and glass stopper was charged with acetal **163** (0.744 g, 4.54 mmol) and 20 mL of CH_2Cl_2. The solution was cooled at –78 °C while allyltrimethylsilane (0.79 mL, 0.57 g, 5.0 mmol) was added in one portion, followed by TMSOTf (0.04 mL, 0.05 g, 0.2 mmol) which was added dropwise over 20 sec. The reaction mixture was then stirred at –78 °C for 5 h and then diluted with 50 mL of satd aq $NaHCO_3$ solution. The aqueous layer was separated and extracted with three 15-mL portions of CH_2Cl_2, and the combined organic layers were washed with 30 mL of brine, dried over $MgSO_4$, filtered, and concentrated to give 0.807 g of colorless oil. Column chromatography on 20 g of silica gel (elution with 10% EtOAc-hexanes) afforded 0.712 g (71%) of **164** as a colorless oil.

IR (film):	3079, 3005, 2946, 2909, 2835, 1630, 1480, 1443, 1420, 1366, 1340, 1270, 1240, 996
^{1}H NMR (500 MHz, $CDCl_3$):	7.06-7.13 (m, 2 H), 7.00-7.03 (m, 2 H), 5.83 (dddt, *J* = 13.7, 13.6, 6.8, 1.2 Hz, 1 H), 5.05-5.10 (m, 1 H), 5.00-5.02 (m, 1 H) 4.75 (dd, *J* = 8.1, 3.5 Hz, 1 H), 4.08 (ddd, *J* = 11.3, 5.3, 3.5 Hz, 1 H), 3.69 (dt, *J* = 9.8, 3.7 Hz, 1 H), 2.91 (ddd, *J* = 16.2, 9.8, 5.5 Hz, 1 H), 2.59-2.66 (m, 1 H), 2.57 (t, *J* = 3.7 Hz, 1 H), 2.47-2.54 (m, 1 H)
^{13}C NMR (125 MHz, $CDCl_3$):	137.8, 135.2, 134.2, 129.0, 126.4, 126.2, 125.0, 117.1, 75.6, 63.5, 40.5, 29.2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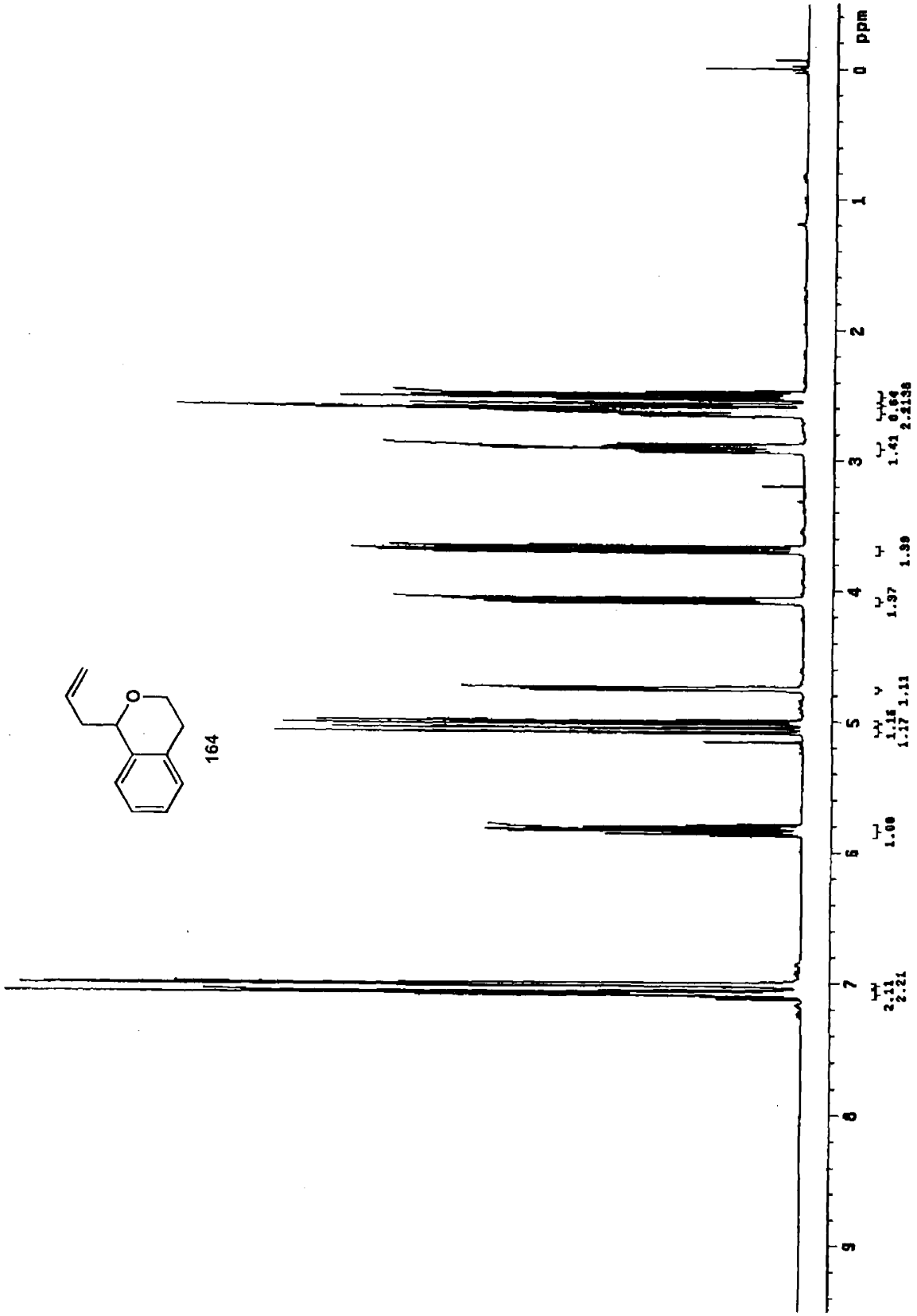
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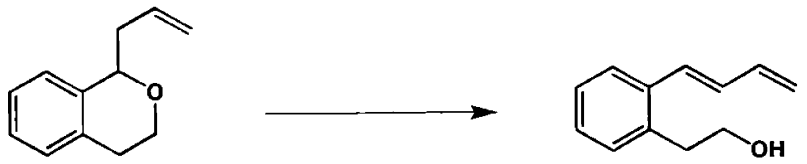
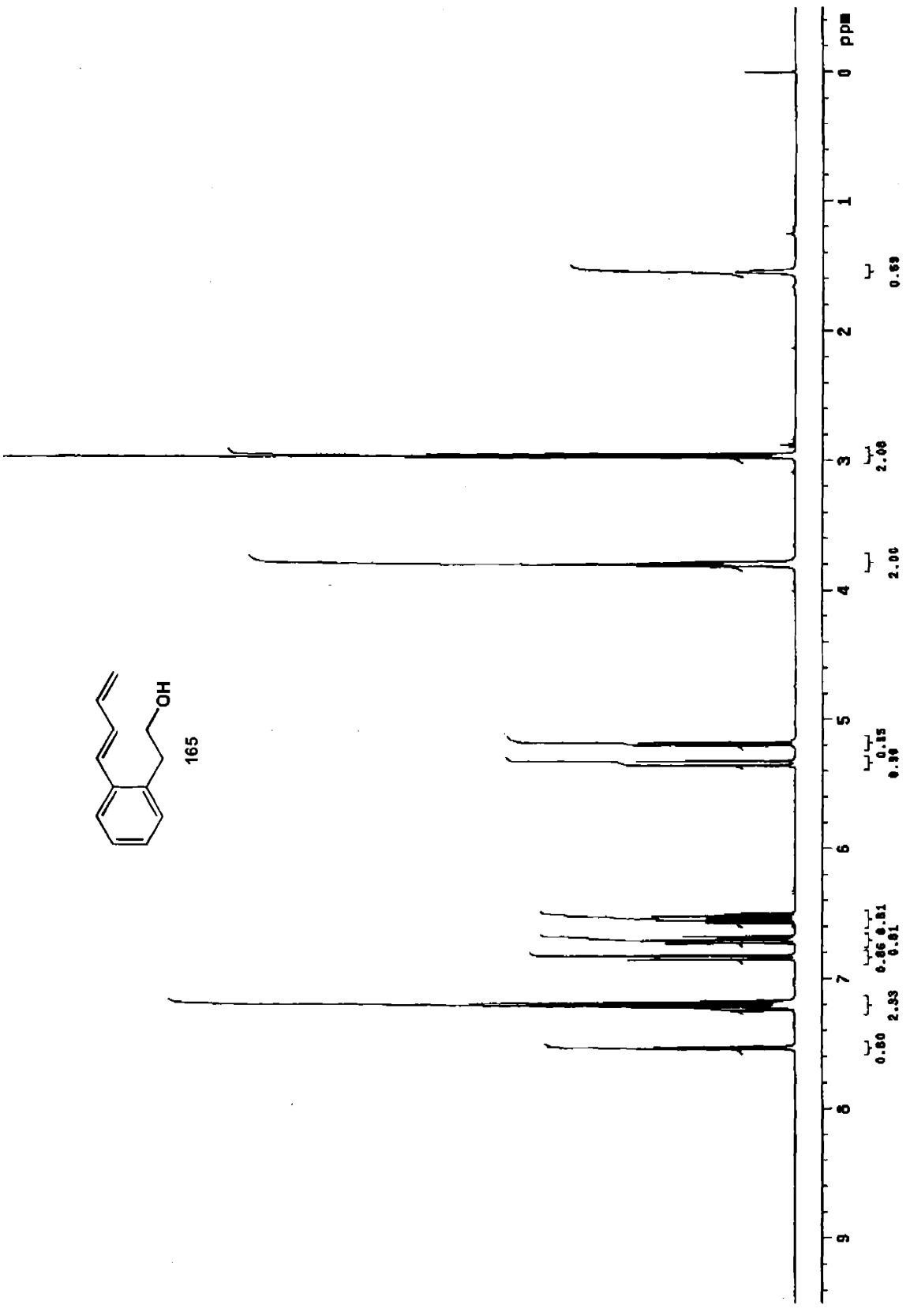


164 165

2-[2-((*E*)-1,3-Butadienyl)phenyl]ethanol (165). A two-necked, 25-mL, round-bottomed flask equipped with a rubber septum and argon inlet adapter was charged with tetrahydropyran **164** (0.243 g, 1.39 mmol) and 6 mL of THF. This solution was cooled at –78 °C while potassium *tert*-butoxide (0.017 g, 0.15 mmol) was added. A 10-mL, pear-shaped flask equipped with a rubber septum and argon inlet-needle was charged with diisopropylamine (0.23 mL, 0.169 g, 1.67 mmol) and 2 mL of THF. The solution was cooled at 0 °C while 0.70 mL of *n*-BuLi solution (2.38 M in hexane, 1.67 mmol) was added dropwise via syringe over 1 min. After stirring at 0 °C for 10 min, the solvent was removed at 1.0 mmHg. The resulting white residue was dissolved in 4 mL of THF, cooled to –78 °C, and then transferred via cannula over 3 min to the flask containing the solution of **164** and KO*t*-Bu. The reaction mixture was allowed to stir at –78 °C for 3 h, satd aq NH_4Cl solution (15 mL) was then added, and the resulting mixture was allowed to warm to rt. The aqueous layer was separated and extracted with three 15-mL portions of ether, and the combined organic layers were washed with 30 mL of brine, dried over $MgSO_4$, filtered, and concentrated to give 0.322 g of a yellow oil. Column chromatography on 50 g of silica gel (elution with 25% EtOAc-hexanes) provided 0.174 g (72%) of **165** as a colorless oil

IR (film):	3310, 3060, 3040, 3007, 2918, 2855, 1790, 1618, 1585, 1467, 1438, 1400, 1150, 1086
^{1}H NMR (500 MHz, $CDCl_3$):	7.53-7.54 (m, 1 H), 7.17-7.24 (m, 3 H), 6.84 (d, J = 15.3, Hz, 1 H), 6.70 (dd, J = 15.3, 10.4 Hz, 1 H), 6.54 (ddd, J = 16.8, 10.2, 10.2 Hz, 1 H), 5.34 (d, J = 16.8, Hz, 1 H), 5.19 (d, J = 9.8, Hz, 1 H), 3.80 (t, J = 6.9, Hz, 2 H), 2.96 (t, J = 7.0, Hz, 2 H), 1.55 (br, 1 H)

^{13}C NMR (125 MHz, $CDCl_3$): 137.5, 136.4, 136.0, 131.7, 130.7, 130.0, 127.9, 127.1, 126.0, 118.1, 63.4, 36.6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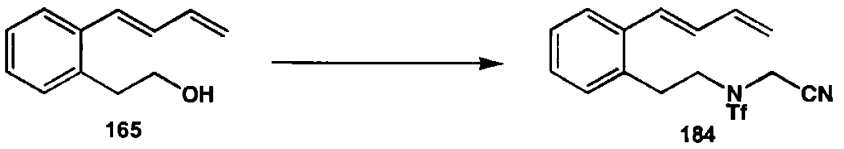
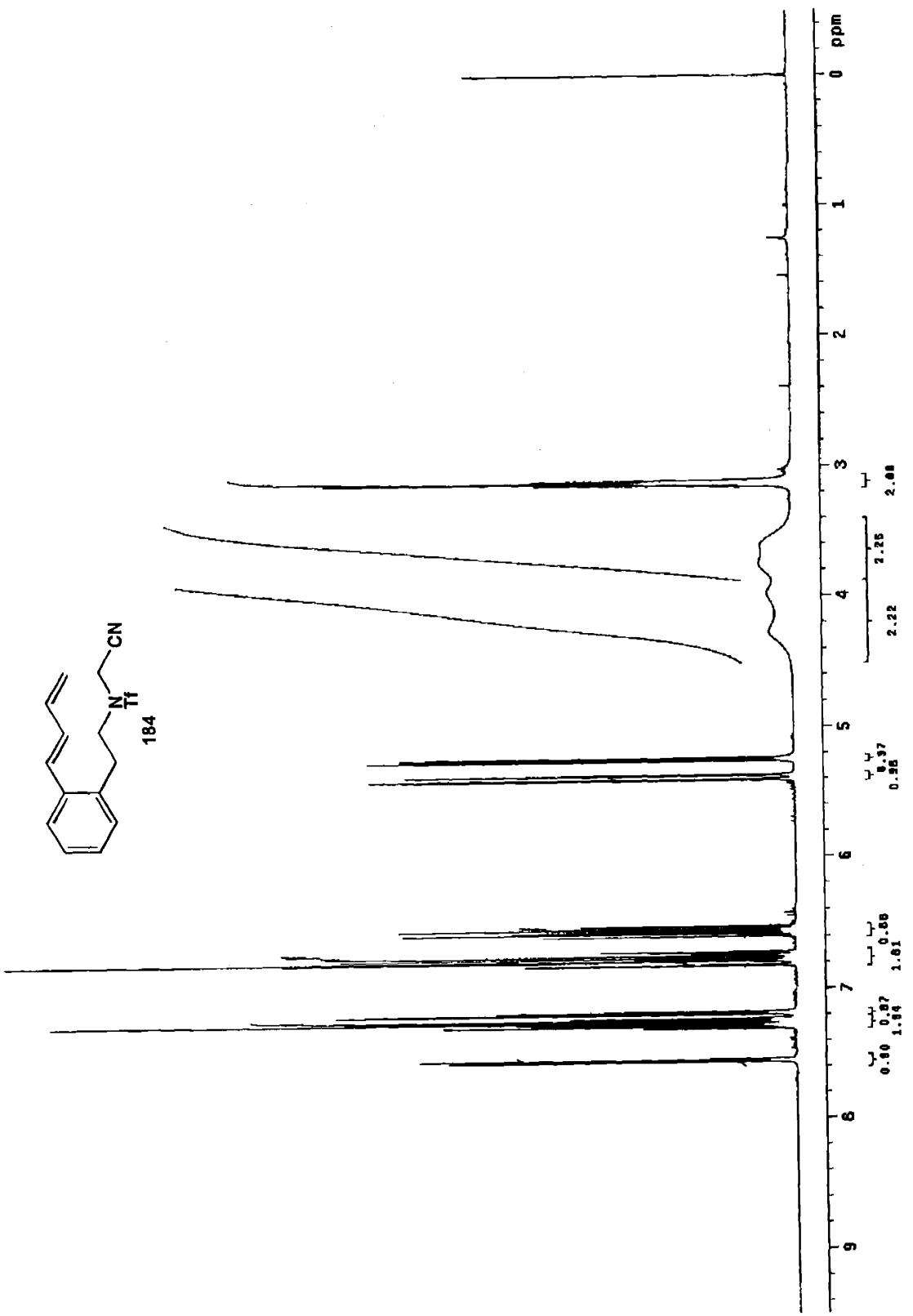


165 184

***N*-(Cyanomethyl)-*N*-[2-[2-((*E*)-1,3-butadienyl)phenyl]ethyl]trifluoromethanesulfonamide (184).** A 25-mL, two-necked, round-bottomed flask equipped with a rubber septum and argon inlet adapter was charged with triphenylphosphine (0.302 g, 1.15 mmol), a solution of $HN(Tf)CH_2CN$ (0.198 g, 1.05 mmol) in 3 mL of THF, and a solution of alcohol **165** (0.167 g, 0.96 mmol) in 3 mL of toluene. DEAD (0.18 mL, 0.20 g, 1.2 mmol) was added dropwise via syringe, and the resulting mixture was stirred at rt for 4 h and then concentrated to give 1.02 g of a yellow solid. This material was concentrated onto 1 g of silica gel and added to a column of 25 g of silica gel. Elution with 10% EtOAc-hexanes provided 0.302 g (91%) of **184** as a white solid, mp = 85.5-86 °C.

IR (CH_2Cl_2):	3054, 2987, 1600, 1422, 1398, 1231, 1200, 1142, 1104, 1067, 1005, 896
^1H NMR (500 MHz, $CDCl_3$):	7.55 (dd, J = 7.6, 1.2 Hz, 1 H), 7.29 (ddd, J = 7.6, 7.6, 1.5 Hz, 1 H), 7.24 (ddd, J = 7.3, 7.3, 1.5 Hz, 1 H), 7.19 (dd, J = 7.5, 1.4 Hz, 1 H), 6.80 (d, J = 15.6 Hz, 1 H), 6.74 (dd, J = 15.6, 9.8 Hz, 1 H), 6.56 (ddd, J = 16.8, 9.9, 9.9 Hz, 1 H), 5.39 (d, J = 16.8 Hz, 1 H), 5.24 (d, J = 10.1 Hz, 1 H) 3.4-4.4 (br m, 4 H), 3.13 (t, J = 7.7 Hz, 2 H)
^{13}C NMR (125 MHz, $CDCl_3$):	137.1, 136.5, 133.7, 133.2, 130.5, 128.7, 128.4, 128.2, 126.5, 119.8 (q, J = 323 Hz), 119.1, 113.4, 50.2, 36.9, 33.0
HRMS $[M+Na]^+$:	Calcd for $C_{15}H_{15}F_3N_2NaO_2S$: 367.0699 Found: 367.0689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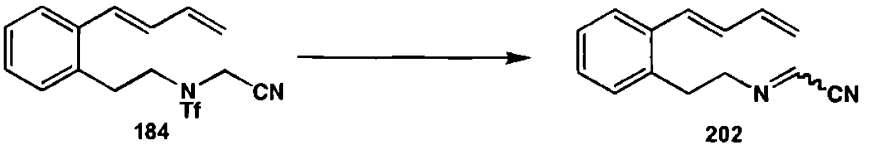


(2-[2-((*E*)-1,3-butadienyl)phenyl]ethyl)iminoacetonitrile (202). A 50-mL, one-necked, round-bottomed flask equipped with a reflux condenser fitted with an argon inlet adapter was charged with triflamide **184** (0.450 g, 1.31 mmol) and 15 mL of THF. Cs_2CO_3 (1.70 g, 5.23 mmol) was then added, and the reaction mixture was heated at 50 °C for 5 h. The resulting mixture was allowed to cool to room temperature and then diluted with 20 mL of ether and 20 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 30 mL of brine, dried over $MgSO_4$, filtered, and concentrated to give 0.286 g of a yellow oil. Column chromatography on 16 g of Et_3N-deactivated silica gel (elution with 1% Et_3N-15% EtOAc-hexanes) provided 0.239 g (87%) of **202** (as an 75:25 mixture of E and Z imine isomers by ^1H NMR analysis) as a yellow oil.

IR (film): 3078, 3058, 3020, 2955, 2855, 1620, 1595, 1477, 1445, 1355, 1330, 1160, 1095, 1060, 995

For E isomer:

^1H NMR (500 MHz, $CDCl_3$): 7.52 (dd, J = 7.5, 1.4 Hz, 1 H), 7.15-7.25 (m, 2 H), 7.12 (t, J = 1.5 Hz, 1 H), 7.09 (dd, J = 7.5, 1.7 Hz, 1 H), 6.69-6.86 (m, 2 H), 6.54 (ddd, J = 16.8, 10.0, 10.0 Hz, 1 H), 5.36 (dd, J = 16.8, 1.2 Hz, 1 H), 5.21 (dd, J = 10.1, 1.5 Hz, 1 H), 3.84 (dt, J = 7.2, 1.2 Hz, 2 H), 3.09 (t, J = 7.2 Hz, 2 H)

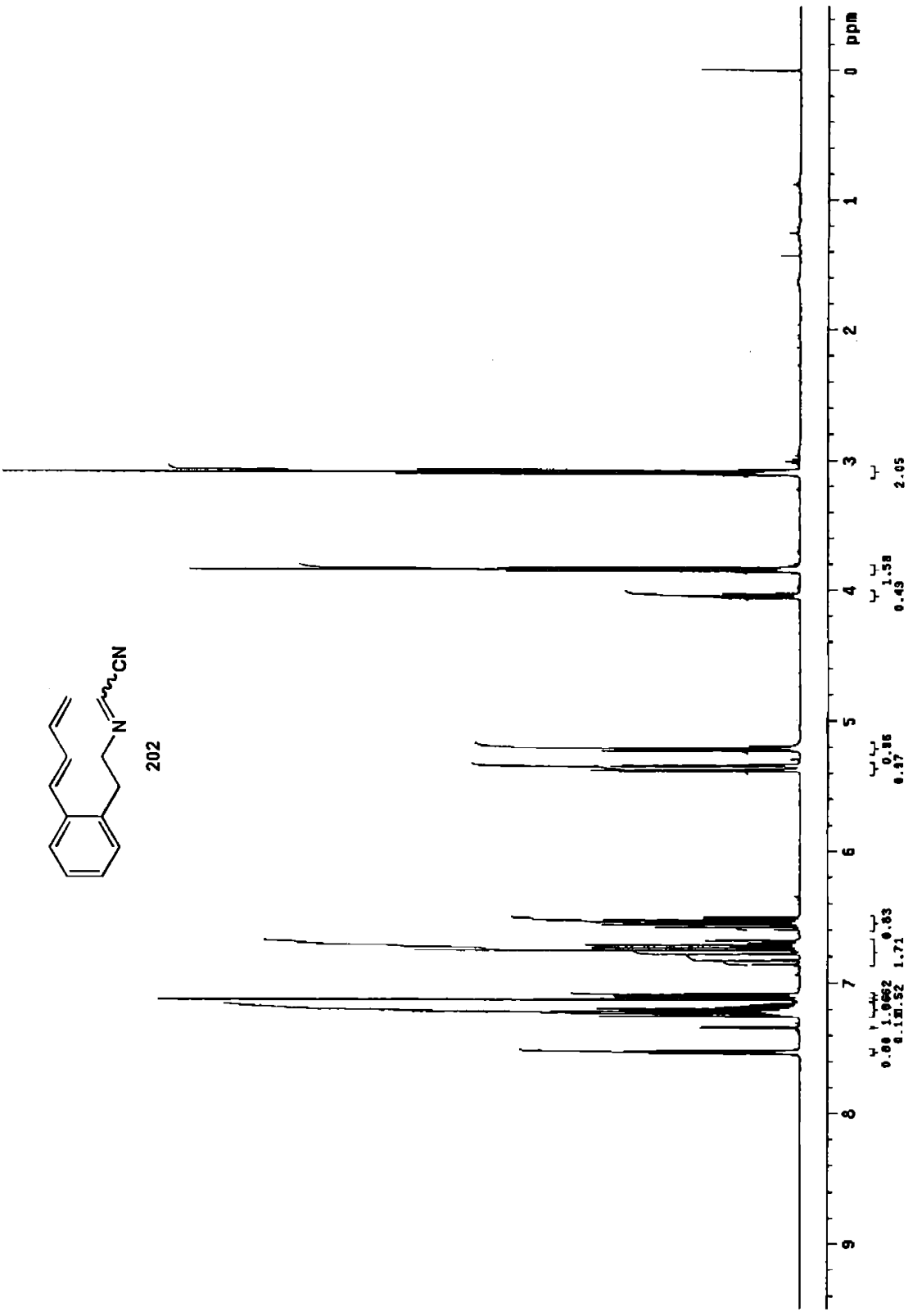
^{13}C NMR (125 MHz, $CDCl_3$): 137.8, 137.1, 136.7, 136.2, 132.6, 131.1, 130.1, 128.5, 128.0, 126.7, 119.0, 115.0, 64.3, 34.2

For Z isomer:

^1H NMR (500 MHz, $CDCl_3$): 7.53 (dd, J = 7.5, 1.4 Hz, 1 H), 7.34 (t, J = 2.0 Hz, 1 H), 7.15-7.25 (m, 2 H), 7.09 (dd, J = 7.5, 1.7 Hz, 1 H), 6.69-6.86 (m, 2 H), 6.56 (ddd, J = 16.8, 10.0, 10.0 Hz, 1 H), 5.35 (dd, J = 16.8, 1.2 Hz, 1 H), 5.20 (dd, J = 10.1, 1.5 Hz, 1 H),

4.04 (dt, J = 7.3, 2.1 Hz, 2 H), 3.09 (t, J = 7.2 Hz, 2 H)

^{13}C NMR (125 MHz, $CDCl_3$): 138.0, 136.9, 136.3, 132.7, 132.6, 131.1, 130.2, 128.5, 127.9, 126.7, 118.8, 100.1, 61.0, 34.2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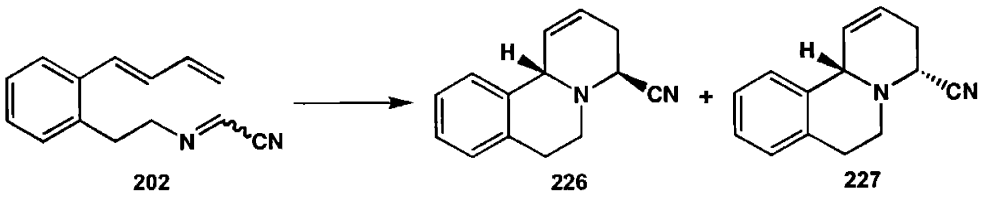


202 226 227

***cis*-3,6,7,11b-Tetrahydro-4-cyano-*4H*-pyrido[2,1-*a*]isoquinoline (226)** and ***trans*-3,6,7,11b-Tetrahydro-4-cyano-*4H*-pyrido[2,1-*a*]isoquinoline (227).** A threaded Pyrex tube (ca. 30 mL capacity) equipped with a rubber septum and argon inlet needle was charged with imine **202** (0.239 g, 1.14 mmol), BHT (0.751 g, 3.41 mmol), and 12 mL of toluene. The solution was degassed by three 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. Concentration gave 1.24 g of a brown oil which was concentrated onto 1.2 g of silica gel and added to a column of 20 g of silica gel. Gradient elution with 1% Et_3N-10-20% EtOAc-hexanes provided 0.085 g (36%) of **226**, mp = 130-131 °C, and 0.022 g (9%) of **227**, mp = 90-91 °C (total yield: 45%) as white solids.

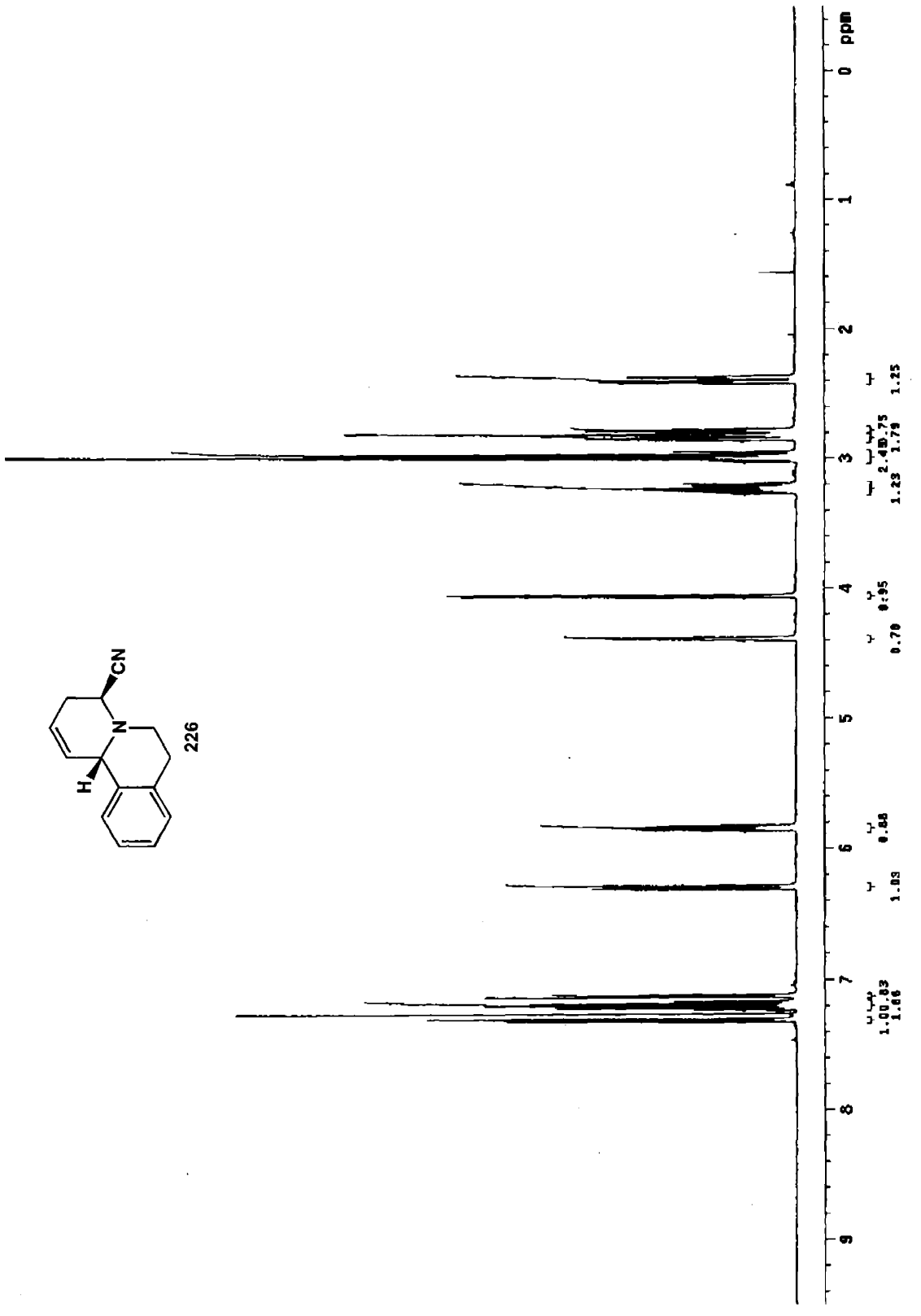
For **226**:

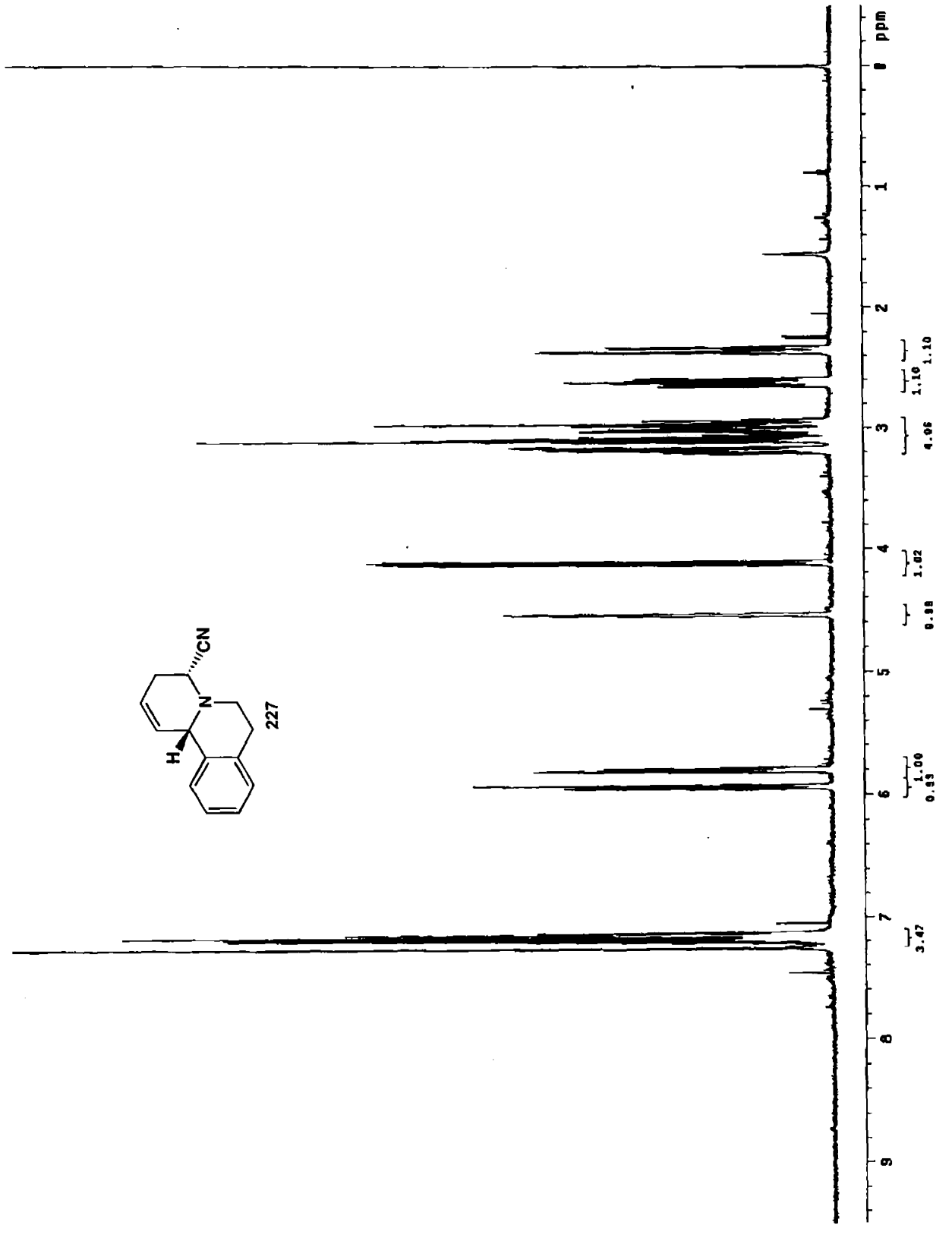
IR (CH_2Cl_2):	3054, 2934, 2826, 2736, 1494, 1432, 1332, 1274, 1129
^1H NMR (500 MHz, $CDCl_3$):	7.31 (d, J = 7.6 Hz, 1 H), 7.16-7.23 (m, 2 H), 7.12 (dd, J = 7.0, 0.9 Hz, 1 H), 6.30 (d, J = 10.4 Hz, 1 H), 5.82-5.86 (m, 1 H), 4.39 (s, 1 H), 4.06 (dd, J = 6.1, 0.6 Hz, 1 H), 3.18-3.27 (m, 1 H), 2.97-3.02 (m, 2 H), 2.76-2.86 (m, 2 H), 2.36-2.42 (m, 1 H);
^{13}C NMR (75 MHz, $CDCl_3$):	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
Elemental Analysis:	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 **227**:

IR (CH_2Cl_2):	3053, 2985, 2933, 2849, 1637, 1496, 1422, 1273, 1094, 896

^{1}H NMR (500 MHz, $CDCl_3$):	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, $CDCl_3$):	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
Elemental Analysis:	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


CN
N
H
226
0 ppm


CN
N
H
227
ppm
1
2
3
4
5
6
7
8
9
1.10
1.10
4.06
1.02
0.88
1.00
0.93
3.47

173 174

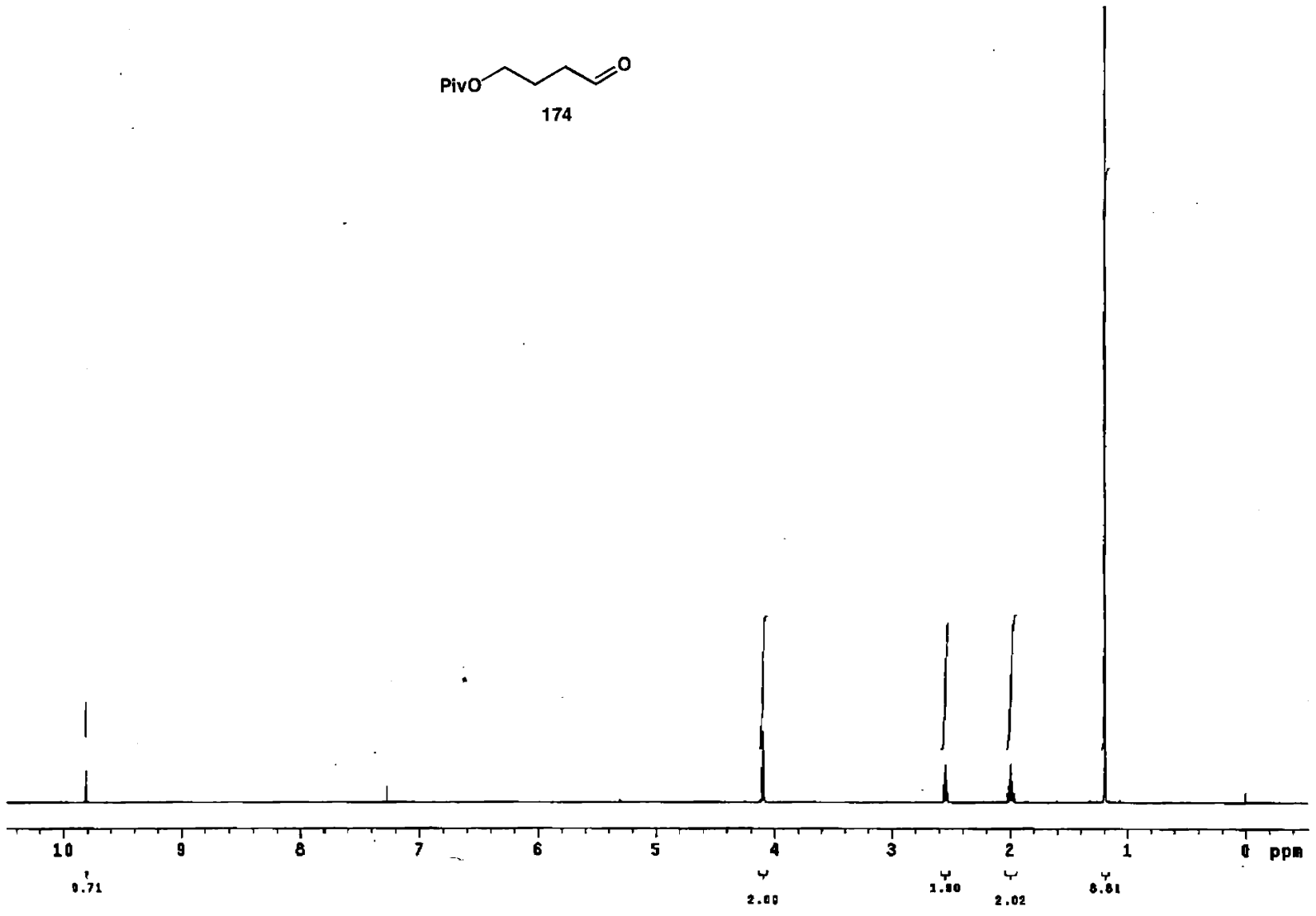
4-(Oxobutyl)dimethyl propanoate (174). A 250-mL, three-necked, round-bottomed flask equipped with a rubber septum, glass stopper, and argon inlet adapter was charged with DMAP (0.165 g, 1.35 mmol), pyridine (3.30 mL, 3.20 g, 40.5 mmol), 1,4-butanediol (3.00 mL, 3.05 g, 33.9 mmol) and 80 mL of CH_2Cl_2. Pivaloyl chloride (1.70 mL, 1.63 g, 13.5 mmol) was added dropwise via syringe over 3 min. The resulting solution was stirred at rt for 1 h and then diluted with 120 mL of ether. The resulting mixture was washed with 50 mL of satd aq $NaHCO_3$ solution, two 50-mL portions of 1 M aq HCl solution, 50 mL of brine, dried over $MgSO_4$, filtered, and concentrated to give 2.19 g of a colorless oil (crude yield 93%) that was immediately used in the next step.

A 100-mL, three-necked, round-bottomed flask with a rubber septum, glass stopper, and argon inlet adapter was charged with 25 mL of CH_2Cl_2 and oxayl chloride (1.40 mL, 2.07 g, 16.3 mmol). The solution was cooled at –78 °C while DMSO (2.50 mL, 2.56 g, 32.8 mmol) was added dropwise via syringe over 5 min. The solution was stirred at –78 °C for 10 min and then the crude alcohol from the previous step (2.19 g, 12.6 mmol) in 15 mL of CH_2Cl_2 was added dropwise over 10 min. After the reaction mixture was stirred at –78 °C for 20 min, Et_3N (7.0 mL, 5.1 g, 50 mmol) was added over 3 min, and the solution was stirred at –78 °C for 10 min and rt for 45 min. The cloudy, yellow solution was diluted with 20 ml of CH_2Cl_2 and 40 mL of satd aq $NaHCO_3$ solution, and the aqueous layer was separated and extracted with 25 mL of CH_2Cl_2. The combined organic layers were washed with 40 mL of brine, dried over $MgSO_4$, filtered, and concentrated to give 2.26 g of a yellow oil. Column chromatography on 40 g of

silica gel (elution with 10% EtOAc-hexanes) afforded 1.74 g (75% over 2 steps) of **174** as a pale yellow oil with spectral data consistent with that previously reported for this compound.[196]

IR (film):	2973, 2874, 2828, 2726, 1726, 1482, 1462, 1398, 1367, 1285, 1157, 1037, 972, 771
^{1}H NMR (500 MHz, $CDCl_3$):	9.81 (t, J = 1.4 Hz, 1 H), 4.10 (d, J = 6.3 Hz, 2 H), 2.55 (dt, J = 7.3, 1.4 Hz, 2 H), 1.99 (app quint, J = 6.4 Hz, 2 H), 1.20 (s, 9 H)
^{13}C NMR (125 MHz, $CDCl_3$):	201.4, 178.4, 63.4, 40.5, 38.8, 27.2, 21.4

[196] Bratz, M.; Bullock, W. H.; Overman, L. E.; Takemoto, T. *J, Am, Chem. Soc.* **1995**, *117*, 5958.


PivO
O
174
10
9
8
7
6
5
4
3
2
1
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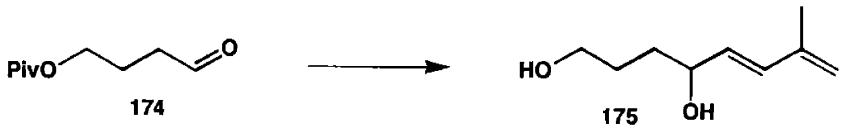
ppm
0.71
2.00
1.80
2.02
8.81

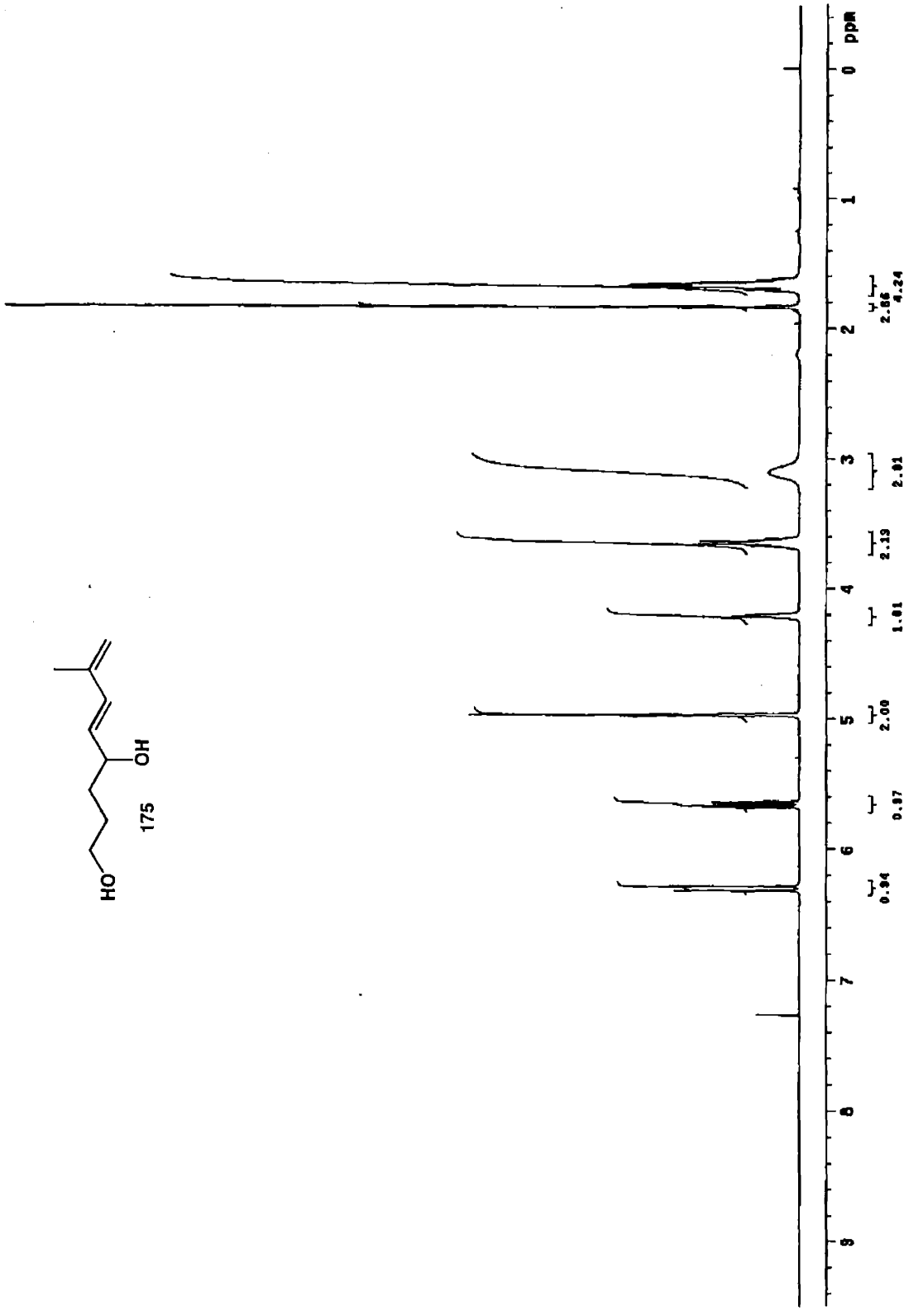


7-Methyl-(*E*)-5,7-octadien-1,4-diol (175). A 25-mL, two-necked, round-bottomed flask equipped with a rubber septum and argon inlet adapter was charged with isopropenylacetylene (0.46 mL, 0.32 g, 4.9 mmol) and 10 mL of THF. The solution was cooled at –78 °C while 2.0 mL of *n*-BuLi solution (2.40 M in hexane, 4.9 mmol) was added dropwise via syringe over 3 min. The resulting solution was stirred at –78 °C for 18 min, and then a solution aldehyde **174** (0.696 g, 4.04 mmol) in 8 mL of THF was added dropwise over 6 min. The resulting solution was allowed to slowly warm to –30 °C over 90 min and then was diluted with 5 mL of satd aq NH_4Cl solution and allowed to warm to rt. The resulting solution was further diluted with 30 mL of water, and the aqueous layer was separated and extracted with three 30-mL portions of ether. The combined organic layers were washed with 30 mL of brine, dried over $MgSO_4$, filtered, and concentrated to give 0.940 g of the crude enyne as a yellow oil that was used 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 the crude enyne from the previous step (0.940 g, ca. 3.90 mmol) and 15 mL of ether. The solution was cooled at 0 °C while 3.80 mL of Red-Al solution (3.6 M in toluene, 13.7 mmol) was added dropwise via syringe over 6 min. The resulting solution was stirred at 0 °C for 90 min, and then diluted by careful addition of 10 mL of 1 M aq HCl solution. The reaction mixture was stirred at rt for 25 min, then diluted with 40 mL of water. The aqueous layer was separated and extracted with three 30-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

0.894 g of a yellow oil. Column chromatography on 18 g of silica gel (elution with 50% EtOAc-hexanes) afforded 0.526 g of **175** as a colorless oil.

IR (film):	3331, 3081, 3018, 2943, 2870, 1610, 1436, 1374, 1336, 1171, 1118, 1056, 1007, 967, 887, 845
^{1}H NMR (500 MHz, $CDCl_3$):	6.33 (d, J = 15.9 Hz, 1 H), 5.69 (dd, J = 15.7, 6.9 Hz, 1 H), 4.99 (s, 2 H), 4.23-4.27 (m, 1 H), 3.66-3.73 (m, 2 H), 3.18 (br s, 2 H), 1.86 (s, 3 H), 1.65-1.75 (m, 4 H)
^{13}C NMR (125 MHz, $CDCl_3$):	141.4, 133.3, 132.2, 117.0, 72.9, 63.1, 34.7, 29.2, 18.9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175
ppm
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1
2
3
4
5
6
7
8
9
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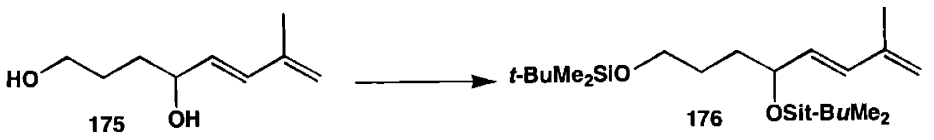
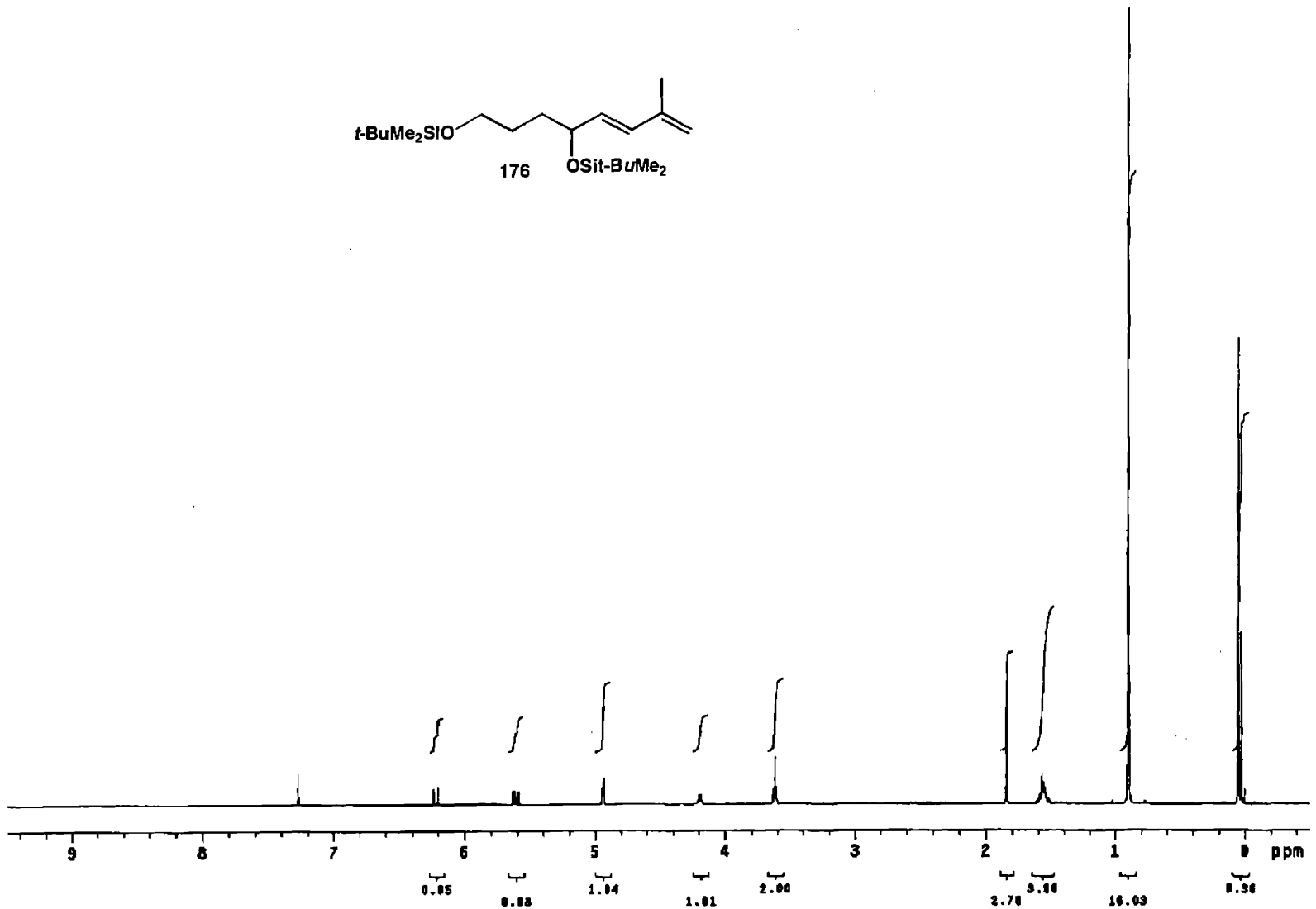
4.24
2.01
2.13
1.81
2.00
0.87
0.94



1,4-Di(*tert*-butyldimethylsiloxy)-7-methyl-(*E*)-5,7-octadiene (176). A 50-ml, two-necked, round-bottomed flask, equipped with a rubber septum and argon inlet adapter was charged with imidazole (0.992 g, 14.6 mmol), 12 mL of DMF, and alcohol **175** (0.759 g, 4.86 mmol). *tert*-Butyldimethylsilyl chloride (1.68 g, 11.2 mmol) was added in one portion. The cloudy solution was stirred at rt for 17 h and then diluted with 75 mL of ether and washed with two 30-mL portions of water. The combined aqueous layers were extracted with 20 mL of ether, and the combined organic layers were washed with 40 mL of brine, dried over anhydrous $MgSO_4$, filtered, and concentrated to give 1.94 g of pale yellow oil. Column chromatography on 40 g of silica gel (gradient elution with 1-3% EtOAc-hexanes) provided 1.70 g (91%) of **176** as a colorless oil.

IR (film):	2955, 2929, 2887, 2857, 1610, 1472, 1463, 1388, 1361, 1255, 1097, 1005, 966, 938, 886, 835, 774
^{1}H NMR (500 MHz, $CDCl_3$):	6.22 (d, J = 15.6 Hz, 1 H), 5.61 (dd, J = 15.7, 6.6 Hz, 1 H), 4.94 (s, 1 H), 4.93 (s, 1 H) 4.18 (app q, J = 5.6 Hz, 1 H), 3.62 (t, J = 6.3 Hz, 2 H), 1.84 (s, 3 H), 1.50-1.61 (m, 4 H), 0.91 (s, 9 H), 0.90 (s, 9 H), 0.06 (s, 3 H), 0.05 (s, 6 H), 0.03 (s, 3 H)
^{13}C NMR (125 MHz, $CDCl_3$):	141.7, 133.4, 132.1, 115.9, 73.6, 63.5, 35.1, 29.0, 26.3, 26.2, 19.0, 18.7, 18.6, -3.9, -4.4, -4.9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OSit-BuMe2
9
8
7
6
5
4
3
2
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0
ppm
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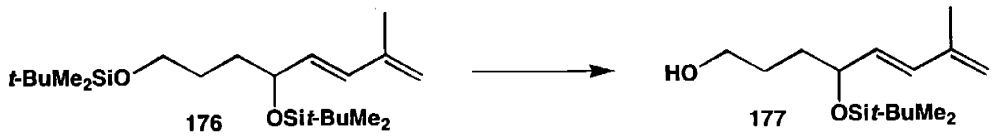
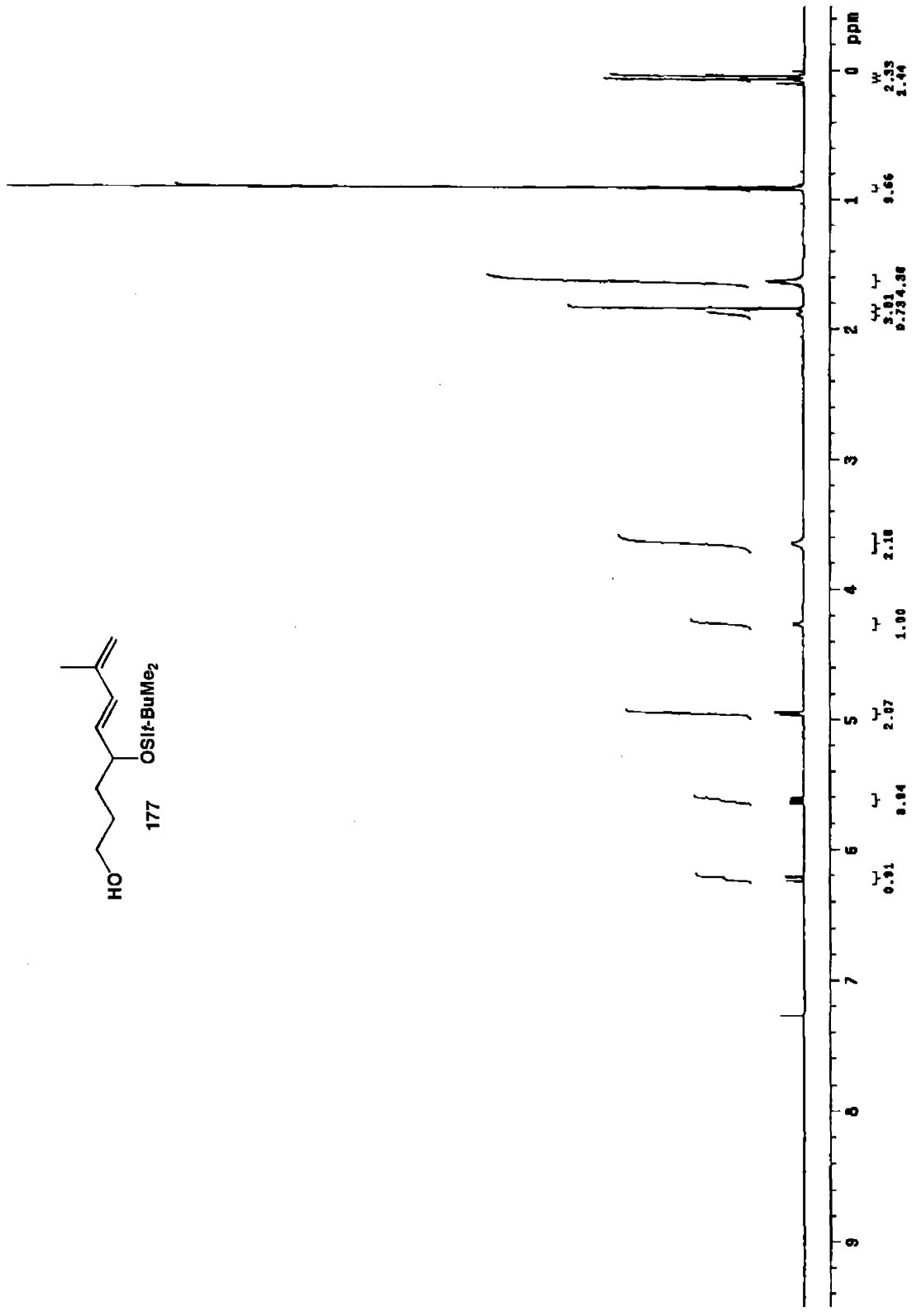
1.04
1.01
2.00
2.76
3.86
16.09
8.56



4-(*tert*-Butyldimethylsiloxy)-7-methyl-(*E*)-5,7-octadien-1-ol (177). A 50-mL round-bottomed flask equipped with a rubber septum and argon inlet needle was charged with **176** (1.03 g, 2.67 mmol) and 27 mL of EtOH. PPTS (0.067 g, 0.27 mmol) was added in one portion, and the resulting solution was stirred at rt for 7 h. The mixture was then diluted with 50 mL of CH_2Cl_2 and 20 mL of satd aq $NaHCO_3$ solution, and the aqueous layer was separated and extracted with two 20-mL portions of CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated to provide 0.838 g of colorless oil. Column chromatography on 20 g of silica gel (gradient elution with 10-75% EtOAc-hexanes) provided 0.464 g (64%) of **177** as a colorless oil and 0.058 g (14%) of diol **175** as a colorless oil.

IR (film):	3348, 2929, 2857, 1610, 1472, 1463, 1361, 1255, 1058, 966, 909, 887, 835, 775, 734, 667
^{1}H NMR (500 MHz, $CDCl_3$):	6.22 (d, J = 15.6 Hz, 1 H), 5.62 (dd, J = 15.7, 6.6 Hz, 1 H), 4.96 (s, 1 H), 4.94 (s, 1 H) 4.24-4.28 (m, 1 H), 3.62-3.68 (m, 2 H), 1.88 (br s, 1 H), 1.84 (s, 3 H), 1.59-1.68 (m, 4 H), 0.91 (s, 9 H), 0.07 (s, 3 H), 0.05 (s, 3 H)
^{13}C NMR (125 MHz, $CDCl_3$):	141.5, 132.8, 132.3, 116.2, 73.5, 63.1, 35.2, 28.6, 26.2, 19.0, 18.5, -4.0, -4.5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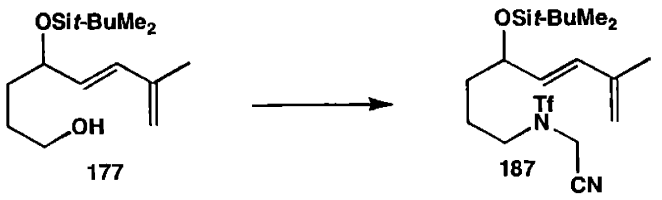
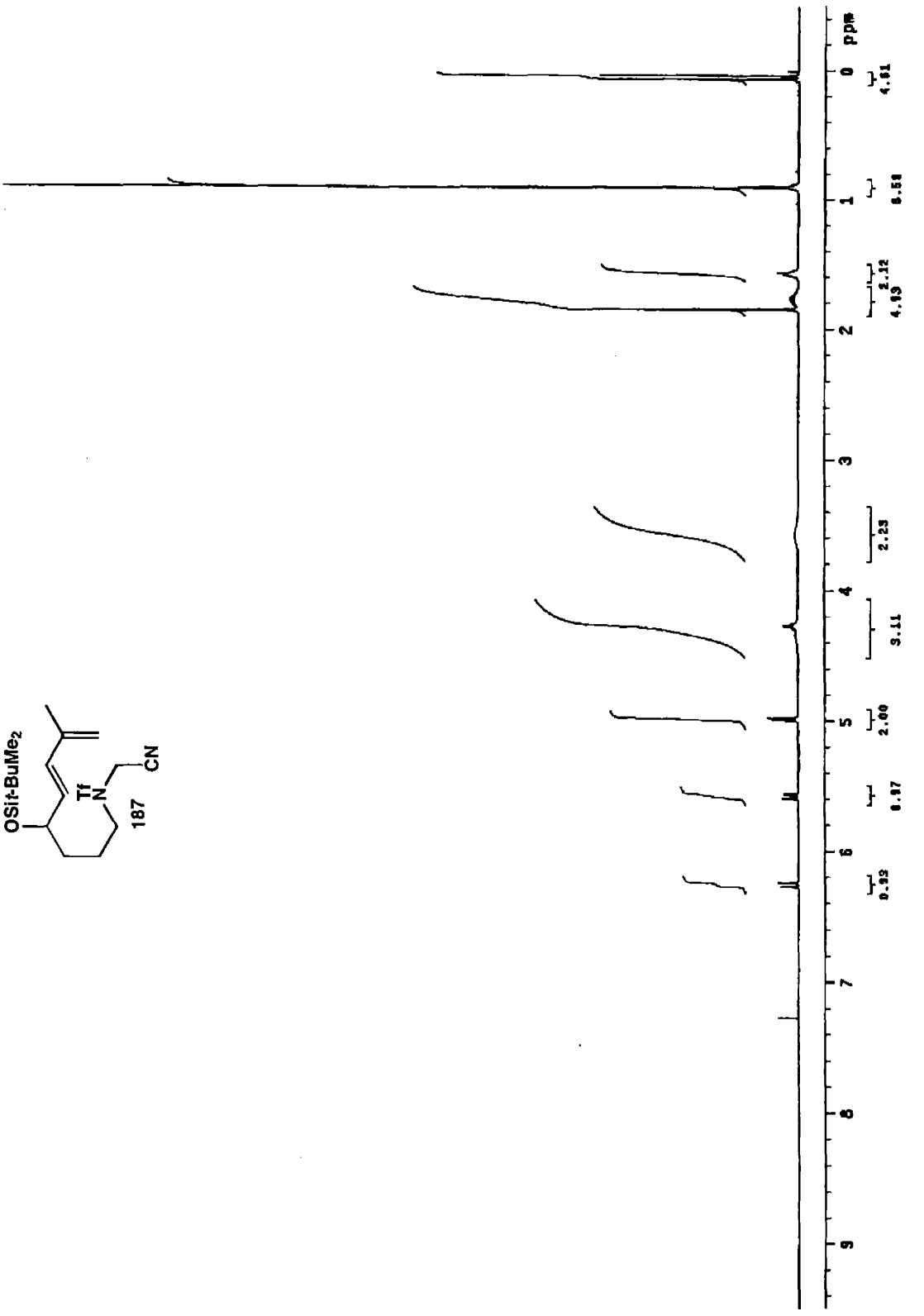
OSit-BuMe2
177
ppm



***N*-(Cyanomethyl)-*N*-(4-(*tert*-butyldimethylsiloxy)-7-methyl-(*E*)-5,7-octadienyl)trifluoromethanesulfonamide (187).** A 25-mL, two-necked, round-bottomed flask equipped with a rubber septum and an argon inlet adapter was charged with triphenylphosphine (0.526 g, 2.00 mmol), a solution of $HN(Tf)CH_2CN$ (0.330 g, 1.75 mmol) in 5 mL of THF, and a solution of alcohol **177** (0.452 g, 1.67 mmol) in 5 mL of toluene. DEAD (0.32 mL, 0.35 g, 2.0 mmol) was added dropwise via syringe over 2 min, and the resulting mixture was stirred at rt for 1 h and then concentrated to give 1.95 g of a white solid. This material was concentrated onto 4.0 g of silica gel and applied to a column of 35 g of silica gel. Gradient elution with 5-10% EtOAc-hexanes provided 0.640 g (87%) of **187** as a colorless oil.

IR (film):	3084, 2955, 2858, 2711, 1611, 1464, 1398, 1361, 1230, 1196, 1146, 969, 899, 837, 777, 737, 671
^{1}H NMR (500 MHz, $CDCl_3$):	6.26 (d, J = 15.6 Hz, 1 H), 5.58 (dd, J = 15.6, 6.6 Hz, 1 H), 4.99 (s, 1 H), 4.98 (s, 1 H), 4.17-4.45 (m, 2 H), 4.27 (q, J = 5.8 Hz, 1 H), 3.41-3.72 (br, 2 H), 1.85 (s, 3 H), 1.71-1.83 (m, 2 H), 1.55-1.61 (m, 2 H), 0.91 (s, 9 H), 0.07 (s, 3 H), 0.04 (s, 3 H)
^{13}C NMR (75 MHz, $CDCl_3$):	141.3, 132.9, 132.1, 119.7 (q, J = 322 Hz), 116.8, 113.2, 72.6, 49.4, 35.7, 34.7, 26.1, 23.0, 18.9, 18.5, -3.9, -4.5
HRMS $[M+Na]^+$:	Calcd for $C_{18}H_{31}F_3N_2NaO_3SSi$: 463.1669 Found: 463.1665


OSit-BuMe2
Tf
N
CN
187
ppm
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1
2
3
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2.23
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2.00
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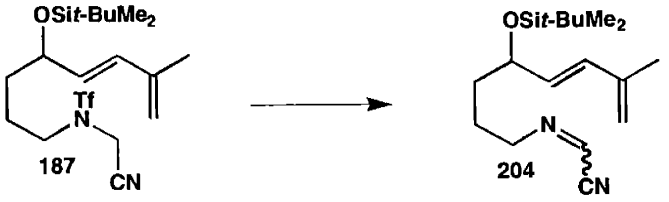
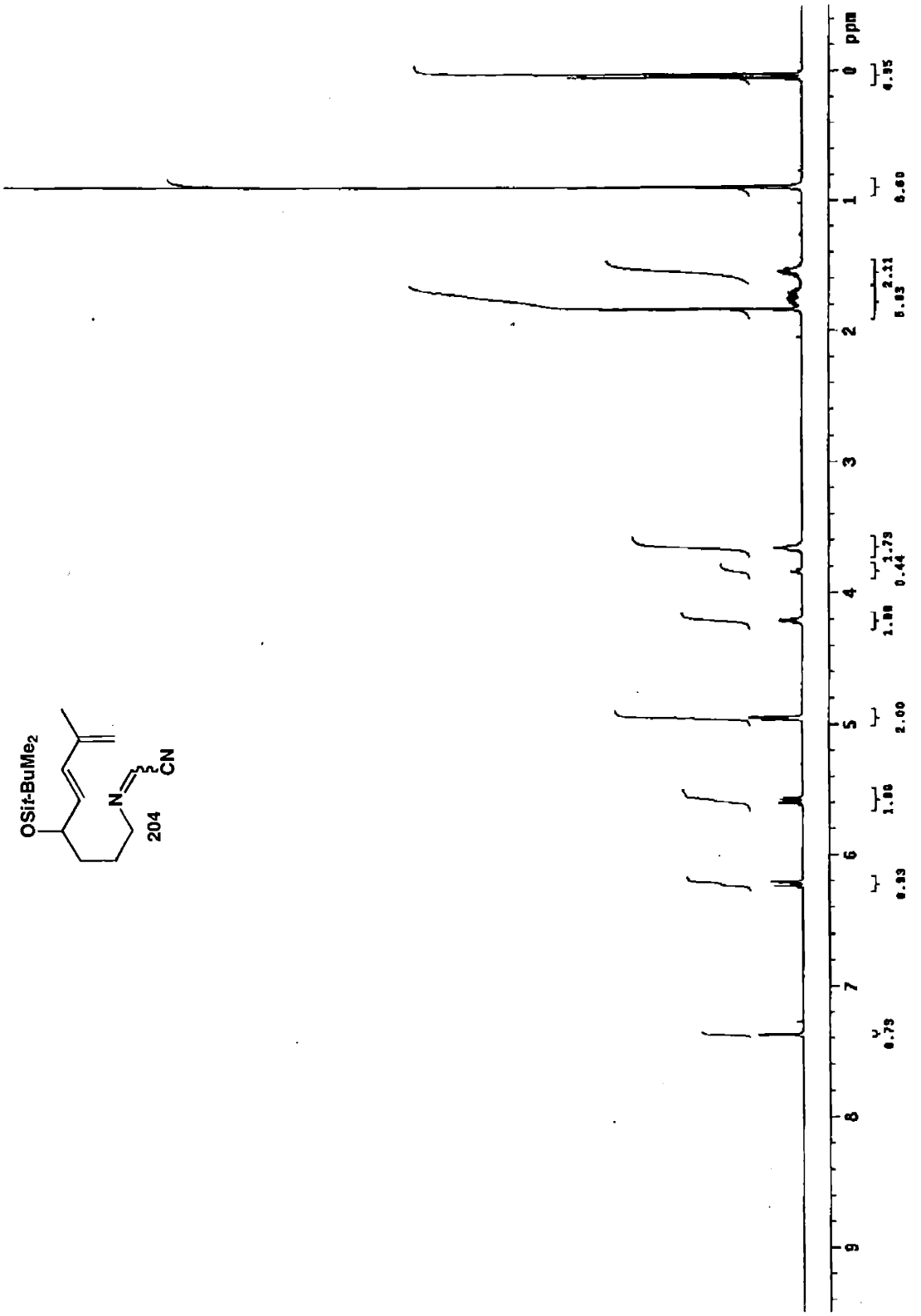


(4-(*tert*-Butyldimethylsiloxy)-7-methyl-(*E*)-5,7-octadienyl)iminoacetonitrile (204). A 25-mL, one-necked, round-bottomed flask equipped with a reflux condenser fitted with an argon inlet adapter was charged with Cs_2CO_3 (1.27 g, 3.90 mmol). A solution of triflamide **187** (0.430 g, 0.98 mmol) in 10 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 room temperature 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 25 mL of brine, dried over $MgSO_4$, filtered, and concentrated to give 0.394 g of a yellow oil. Column chromatography on 10 g of Et_3N-deactivated silica gel (elution with 1% Et_3N-5% EtOAc-hexanes) provided 0.277 g (92%) of **204** (80:20 mixture of E and Z imine isomers by ^1H NMR analysis) as a pale yellow oil.

IR (film):	3082, 2955, 2930, 2857, 1624, 1611, 1472, 1463, 1361, 1256, 1084, 968, 888, 836, 776, 671
For E isomer: ^1H NMR (500 MHz, $CDCl_3$):	7.37 (br s, 1 H), 6.23 (d, J = 15.7 Hz, 1 H), 5.58 (dd, J = 15.9, 6.7 Hz, 1 H), 4.96 (s, 1 H), 4.95 (s, 1 H) 4.21 (q, J = 6.3 Hz, 1 H), 3.62-3.69 (m, 2 H), 1.83 (s, 3 H), 1.67-1.82 (m, 2 H), 1.50-1.62 (m, 2 H), 0.91 (s, 9 H), 0.05 (s, 3 H), 0.03 (s, 3 H)
^{13}C NMR (125 MHz, $CDCl_3$):	141.6, 135.9, 132.9, 132.6, 116.5, 114.6, 73.2, 63.3, 35.9, 26.1, 25.9, 18.8, 18.4, -4.0, -4.6
For Z isomer: ^1H NMR (500 MHz, $CDCl_3$):	7.38 (t, J = 2.1 Hz, 1 H), 6.24 (d, J = 15.7 Hz, 1 H), 5.60

(dd, J = 15.9, 6.7 Hz, 1 H), 4.96 (s, 1 H), 4.95 (s, 1 H) 4.21 (q, J = 6.3 Hz, 1 H), 3.84 (dt, J = 6.9, 2.0 Hz, 2 H), 1.83 (s, 3 H), 1.67-1.82 (m, 2 H), 1.50-1.62 (m, 2 H), 0.91 (s, 9 H), 0.05 (s, 3 H), 0.03 (s, 3 H)

^{13}C NMR (125 MHz, $CDCl_3$): 141.6, 133.0, 132.6, 131.5, 116.4, 109.5, 73.2, 59.9, 36.0, 26.1, 25.9, 18.8, 18.4, -4.0, -4.6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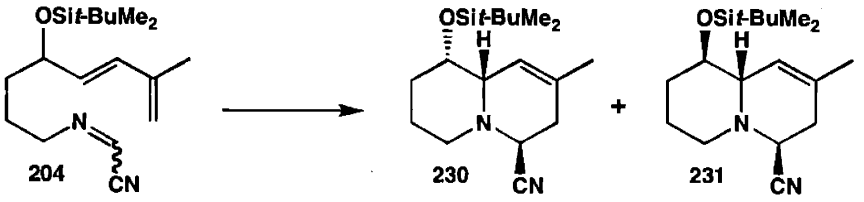
ppm



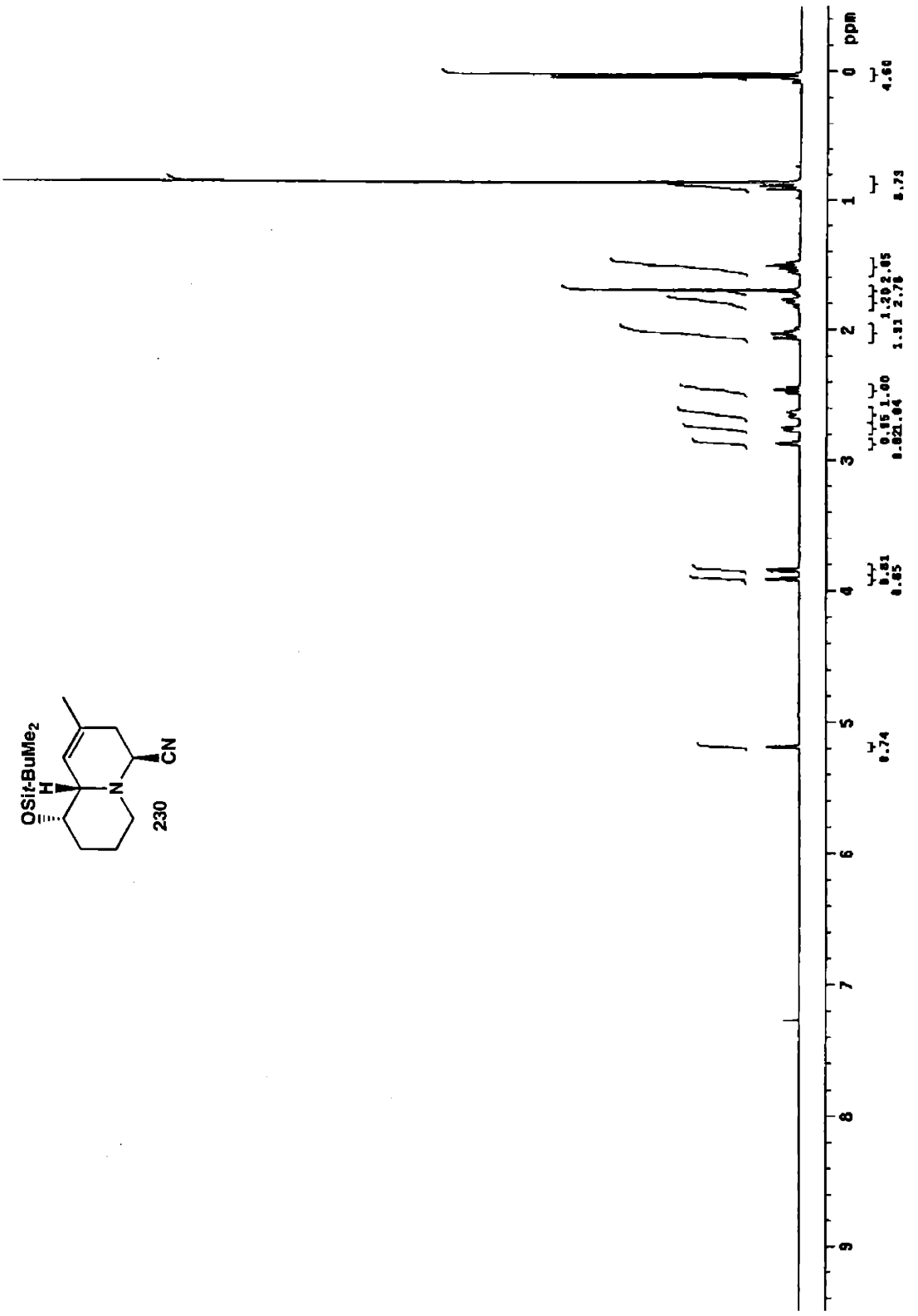
8-(*tert*-Butyldimethylsiloxy)-2-methyl-*cis*-1,2-didehydro-4-cyanoquinolizidine (230) and (231). A threaded Pyrex tube (ca. 50 mL capacity) equipped with a rubber septum and argon inlet needle was charged with imine **204** (0.277 g, 0.90 mmol), BHT (0.597 g, 2.71 mmol), and 18 mL of toluene. The solution was degassed by three freeze-pump-thaw cycles and then sealed with a threaded Teflon cap. The reaction mixture was heated in a 120 °C oil bath for 22 h and then allowed to cool to rt. Concentration gave 1.034 g of a brown oil which was concentrated onto 2 g of silica gel and applied to a column of 25 g of silica gel. Gradient elution with 1% Et_3N-2-5% EtOAc-hexanes afforded 0.202 g (73%) of **230** and **231** (55:45 mixture by ^1H NMR analysis) as a pale yellow oil. Further purification by column chromatography provided analytical samples of each pure isomer.

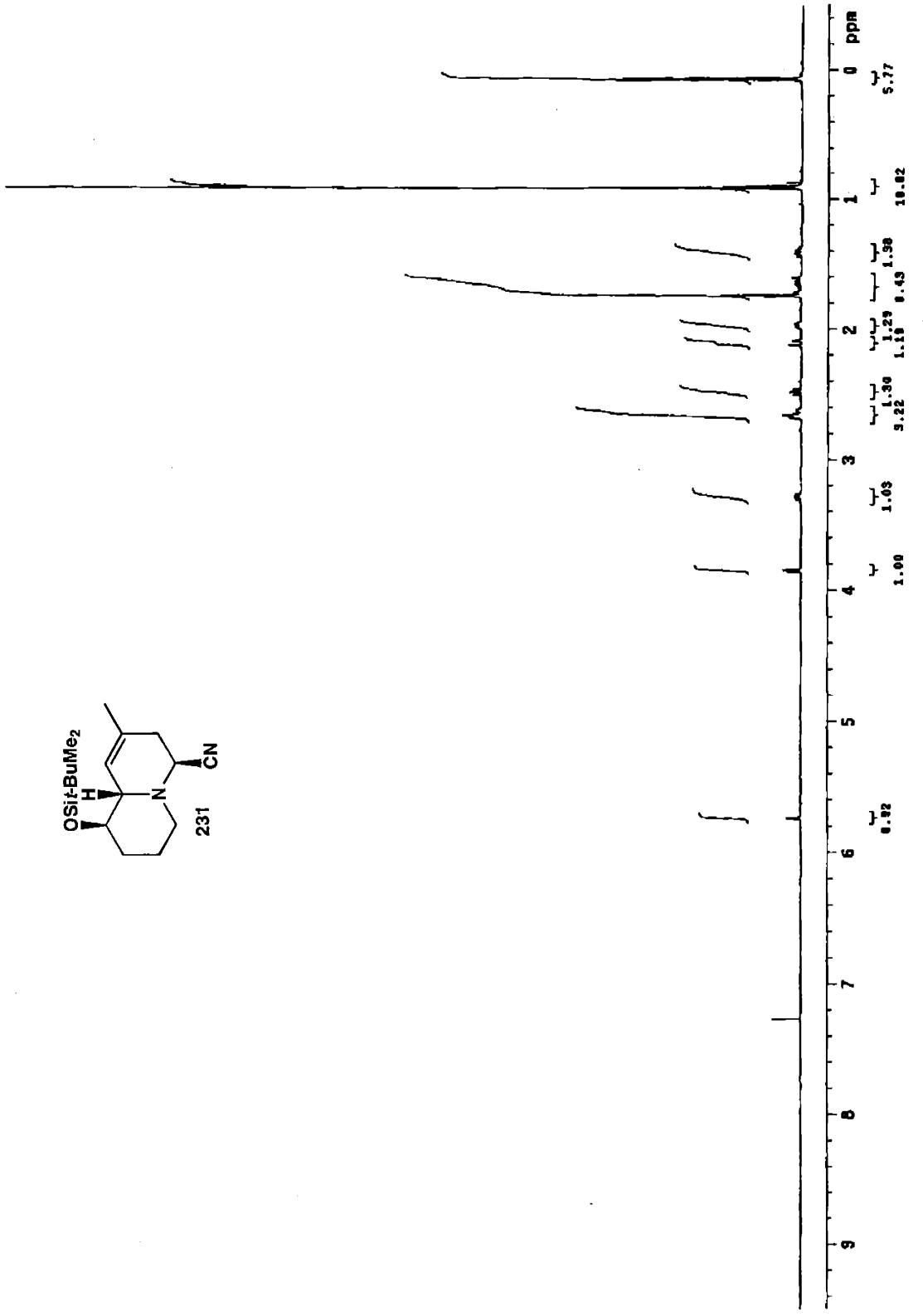
For **230**:

IR (film):	2929, 2856, 2804, 2759, 2222, 1472, 1462, 1388, 1368, 1252, 1211, 1137, 1081, 1050, 959, 912, 876, 836, 774
^1H NMR (500 MHz, $CDCl_3$):	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, $CDCl_3$):	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

For (**231**):

IR (film):	2930, 2858, 2811, 2775, 2223, 1472, 1463, 1441, 1383, 1362, 1329, 1258, 1137, 1120, 1097, 1077, 1009, 909, 896, 862, 836, 775
^{1}H NMR (500 MHz, $CDCl_3$):	5.74 (br s, 1 H), 3.85 (dd, J = 6.4, 1.5 Hz, 1 H), 3.29 (ddd, J = 10.5, 9.0, 4.4 Hz, 1 H), 2.60-2.64 (m, 3 H), 2.48 (ddd, J = 11.9, 11.0, 3.1 Hz, 1 H), 2.10 (d J = 16.2 Hz, 1 H), 1.94-2.00 (m, 1 H), 1.74 (s, 3 H), 1.71-1.75 (m, 1 H), 1.60-1.68 (m, 1 H), 1.37-1.45 (m, 1 H), 0.91 (s, 9 H), 0.08 (s, 3 H), 0.06 (s, 3 H)
^{13}C NMR (125 MHz, $CDCl_3$):	128.7, 121.5, 117.1, 72.3, 62.9, 53.3, 52.2, 34.7, 33.9, 26.0, 23.7, 23.0, 18.2, -3.9, -4.6
HRMS $[M+H]^+$:	Calcd for $C_{17}H_{31}N_2OSi$: 307.2200 Found: 307.2203


OSi-t-BuMe2
H
N
CN
230
ppm


OSi-t-BuMe2
H
N
CN
231
ppm
0
1
2
3
4
5
6
7
8
9
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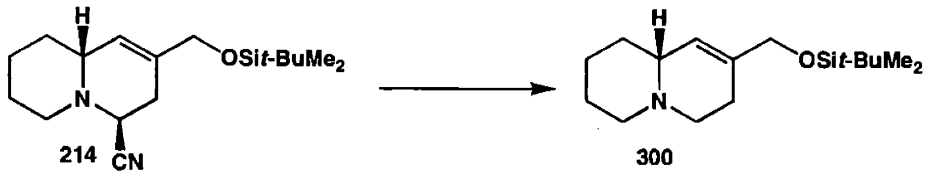
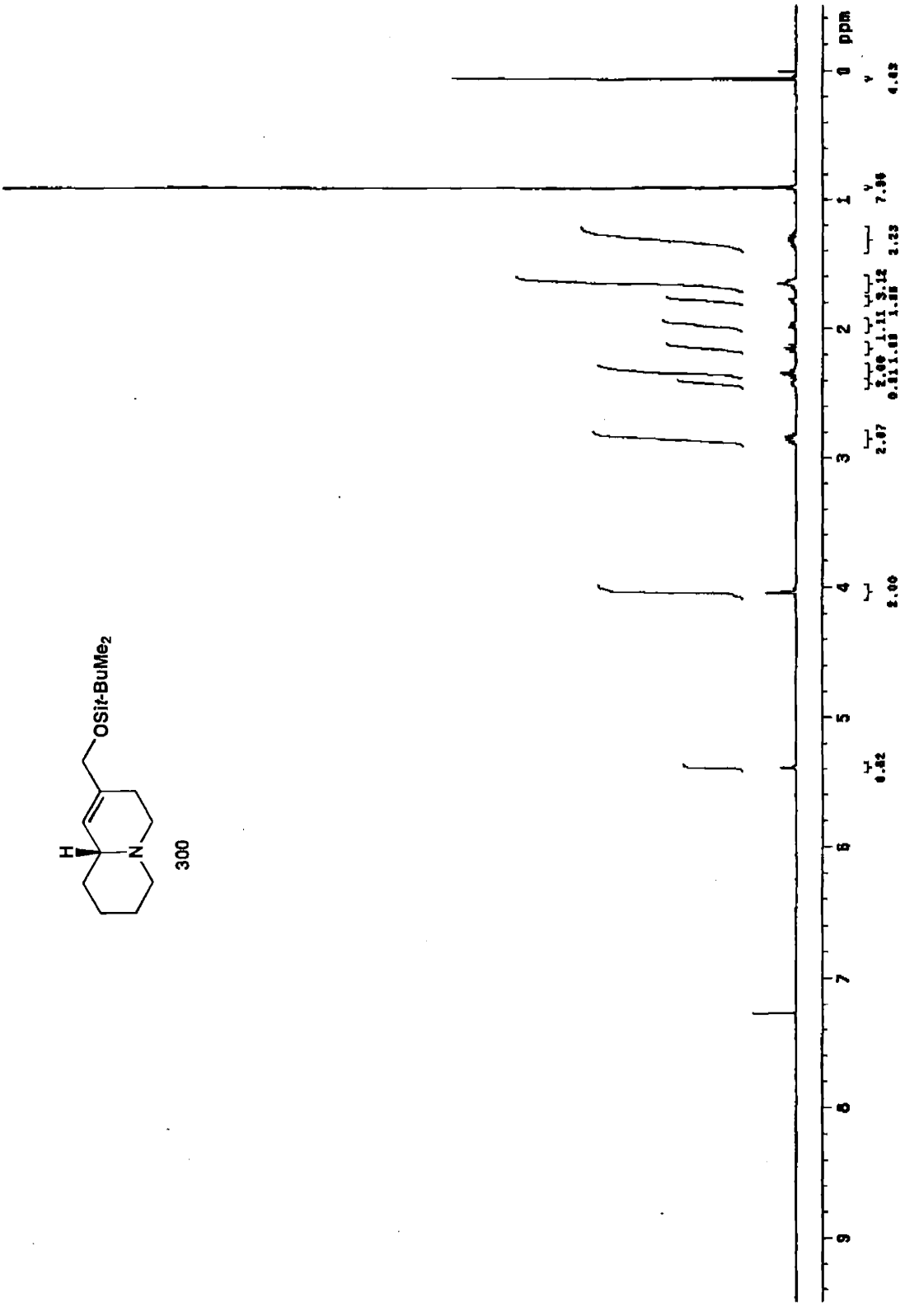
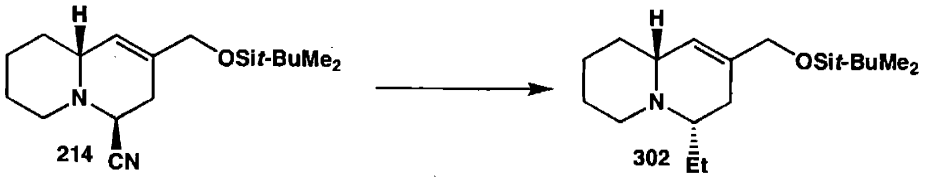
10.82
1.38
0.43
1.29
1.18
1.30
3.22
1.03
1.00
0.92



2-(*tert*-Butyldimethylsiloxymethyl)-1,2-didehydroquinolizidine (300). A 25-mL, two-necked, round-bottomed flask equipped with a rubber septum and argon inlet adapter was charged with $NaBH_3CN$ (0.187 g, 2.98 mmol) and 6 mL of acetonitrile. Acetic acid (0.34 mL, 0.36 g, 6.0 mmol) was added dropwise via syringe over 2 min. The resulting solution was stirred at rt for 30 min, and then a solution of nitrile **214** (0.152 g, 0.50 mmol) in 4 mL of acetonitrile was added over 2 min. The reaction mixture was stirred at rt for 20 h and then diluted with 30 mL of 1 M aq NaOH solution and 30 mL of CH_2Cl_2. The aqueous layer was separated and extracted with three 15-mL portions of CH_2Cl_2, and the combined organic layers were washed with 30 mL of brine, dried over $MgSO_4$, filtered, and concentrated to provide 0.140 g of colorless oil. Column chromatography on 8 g of silica gel (elution with 1% Et_3N-10% EtOAc-hexanes) provided 0.129 g (91%) of **300** as a colorless oil.

IR (film):	2930, 2855, 2797, 2740, 2709, 1463, 1441, 1390, 1360, 1294, 1252, 1216, 1187, 1153, 1132, 1116, 1066, 1007, 940, 836, 775, 733, 665	
^{1}H NMR (500 MHz, $CDCl_3$):	5.39 (br s, 1 H), 4.04 (br s, 2 H), 2.81-2.89 (m, 2 H), 2.42 (br d, J = 11.0 Hz, 1 H), 2.28-2.38 (m, 2 H), 2.15 (ddd, J = 11.1, 11.1, 4.0 Hz, 1 H), 1.94-2.01 (m, 1 H), 1.76-1.81 (m, 1 H), 1.59-1.69 (m, 3 H), 1.25-1.40 (m, 2 H), 0.91 (s, 9 H), 0.07 (s, 3 H), 0.06 (s, 3 H)	
^{13}C NMR (125 MHz, $CDCl_3$):	135.5, 124.4, 66.5, 61.5, 56.2, 52.5, 32.4, 26.3, 26.1, 26.0, 25.1, 18.6, -5.1, -5.2;	
HRMS $[M+H]^+$:	Calcd for $C_{16}H_{32}NOSi$:	282.2248
	Found:	282.2253


OSit-BuMe2
H
N
300
ppm

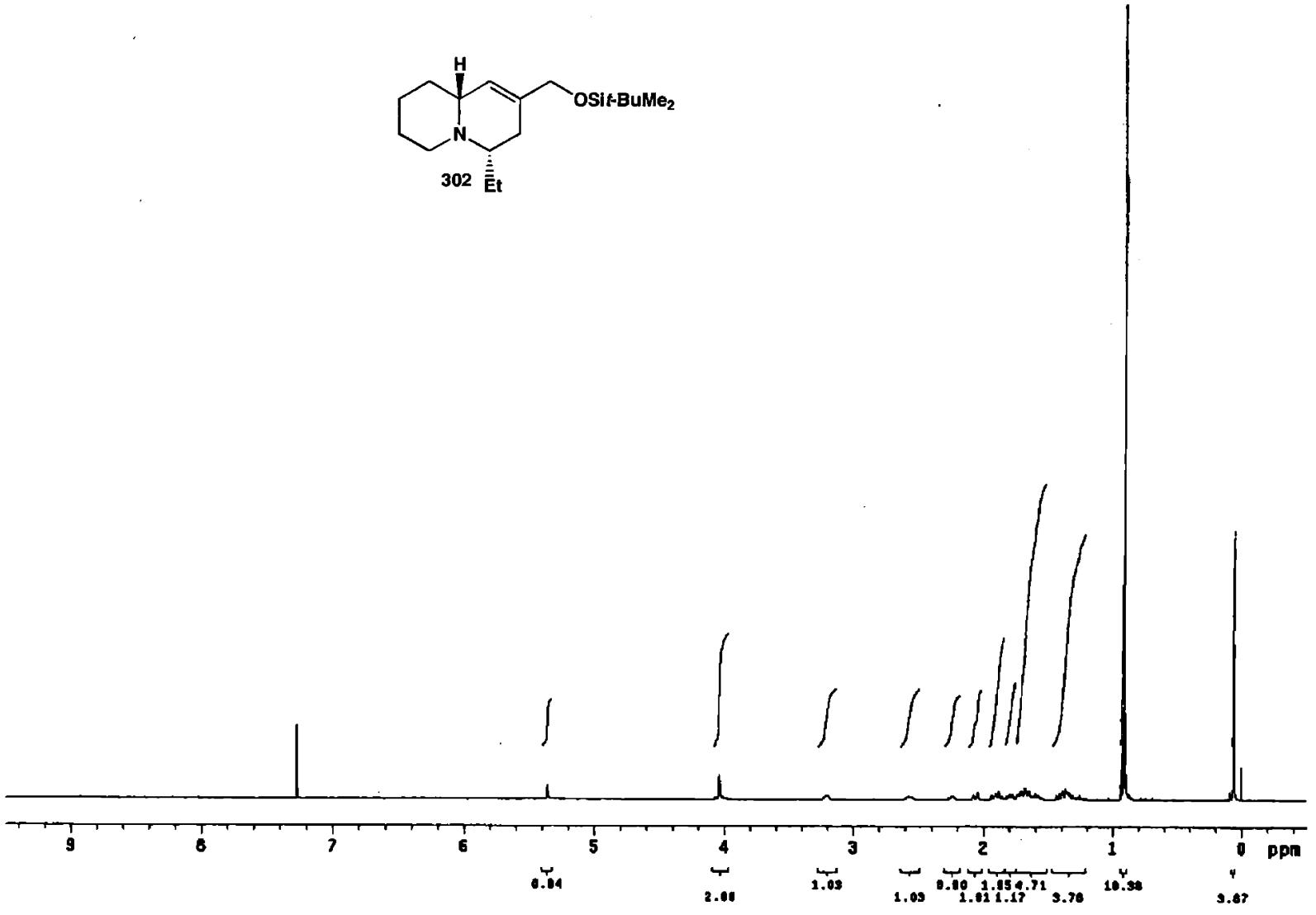


2-(*tert*-Butyldimethylsiloxymethyl)*trans*-1,2-didehydro-4-ethylquinolizidine (302). A 25-mL, round-bottomed flask equipped with a rubber septum and argon inlet needle was charged with 5 mL of THF and diisopropylamine (0.17 mL, 0.12 g, 1.2 mmol). The solution was cooled at 0 °C while 0.49 mL of *n*-BuLi solution (2.49 M in hexanes, 1.2 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 **214** (0.178 g, 0.58 mmol) in 5 ml of THF, was added dropwise via cannula over 3 min. The resulting solution was stirred at –78 °C for 2 h, and then ethyl iodide (0.19 mL, 0.36 g, 2.3 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 20 ml of ether. The aqueous layer was extracted with three 15-mL portions of ether, and the combined organic layers were washed with 25 mL of brine, dried over K_2CO_3, filtered, and concentrated to give 0.194 g of 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 adapter was charged with $NaBH_3CN$ (0.146 g, 2.32 mmol) and 5 mL of acetonitrile. Acetic acid (0.27 mL, 0.28 g, 4.6 mmol) was added dropwise via syringe over 2 min. The resulting solution was stirred at rt for 30 min, and then a solution of the crude nitrile (0.194 g, 0.50 mmol) from the previous step in 3 mL of acetonitrile was added over 2 min. The reaction mixture was stirred at rt for 90 min and then diluted with 20 mL of water and 20 mL of CH_2Cl_2. The aqueous layer was separated and extracted with three 15-mL portions of CH_2Cl_2, and the combined organic layers were washed with 30 mL of brine, dried over K_2CO_3, filtered, and concentrated to

provide 0.189 g of brown oil. Column chromatography on 8 g of silica gel (elution with 1% Et_3N-5% EtOAc-hexanes) provided 0.157 g (87%) of **302** as a colorless oil.

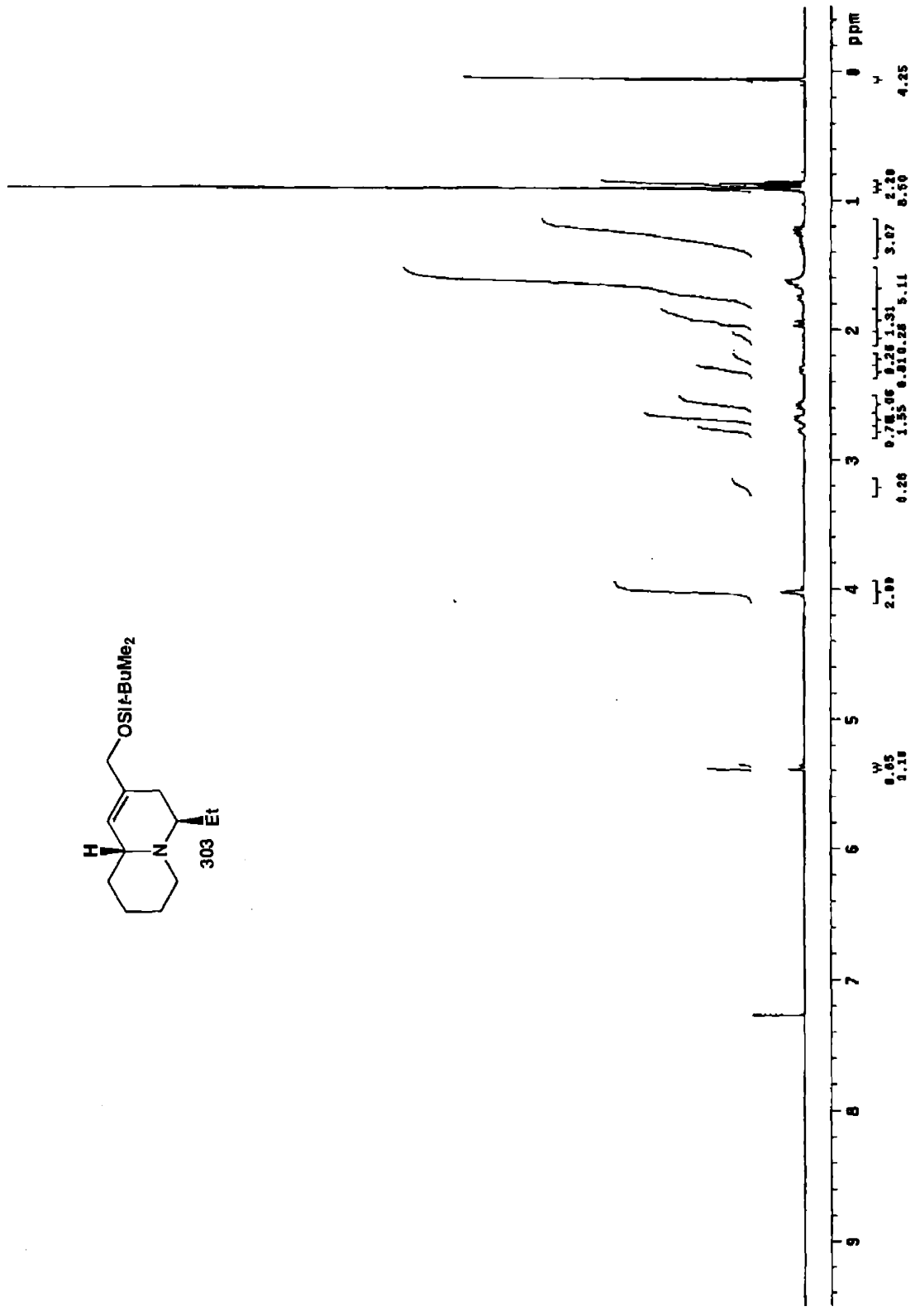
IR (film):	2930, 2856, 2785, 2738, 2681, 1471, 1462, 1387, 1360, 1253, 1193, 1146, 1099, 1070, 836, 776, 733	
^1H NMR (500 MHz, $CDCl_3$):	5.36 (s, 1 H), 4.04 (s, 2 H), 3.21 (d, J = 10.1 Hz, 1 H), 2.57 (br s, 1 H), 2.22-2.26 (m, 1 H), 2.06 (dt, J = 17.1, 3.1 Hz, 1 H), 1.84-1.94 (m, 2 H), 1.74-1.83 (m, 1 H), 1.54-1.74 (m, 4 H), 1.28-1.44 (m, 3 H), 0.92 (t, J = 7.6 Hz, 3 H), 0.91 (s, 9 H), 0.07 (s, 3 H), 0.06 (s, 3 H)	
^{13}C NMR (125 MHz, $CDCl_3$):	135.3, 124.5, 66.4, 62.2, 60.4, 49.7, 33.0, 31.4, 26.5, 26.1, 25.5, 24.7, 18.6, 10.0, -5.0, -5.1	
HRMS $[M+H]^+$:	Calcd for $C_{18}H_{35}NOSi$:	310.2561
	Found:	310.2564

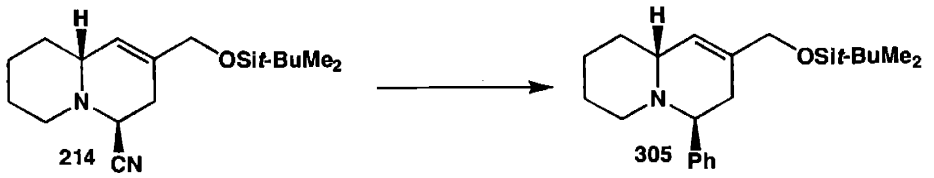

H
OSit-BuMe2
N
302
Et
9
8
7
6
5
4
3
2
1
0
ppm
0.84
2.00
1.03
1.03
0.80
1.01
1.85
1.17
4.71
3.78
10.38
3.07

2-(*tert*-Butyldimethylsiloxymethyl)*cis*-1,2-didehydro-4-ethylquinolizidine (303). A 25-mL, round-bottomed flask equipped with a rubber septum and argon inlet needle was charged with **214** (0.157 g, 0.51 mmol) and 6 ml of ether. The flask was cooled at –30 °C while 0.51 mL of ethylmagnesium bromide solution (3.0 M in ether, 1.5 mmol) was added dropwise via syringe over 2 min. The resulting solution was allowed slowly warm to rt over 3.5 h. The reaction mixture was diluted with 10 mL of water and 15 mL of ether, and the aqueous layer was separated and extracted with three 15-ml portions of ether. The combined organic layers were washed with 30 mL of brine, dried over K_2CO_3, filtered, and concentrated to afford 0.153 g of pale yellow oil. Column chromatography on 7 g of silica gel (elution 1% Et_3N-10% EtOAc-hexanes) provided 0.135 g (85%) of **303** and **302** (78:22 mixture of β and α ethyl diastereomers by ^1H NMR analysis) as a pale yellow oil.

For **303**:

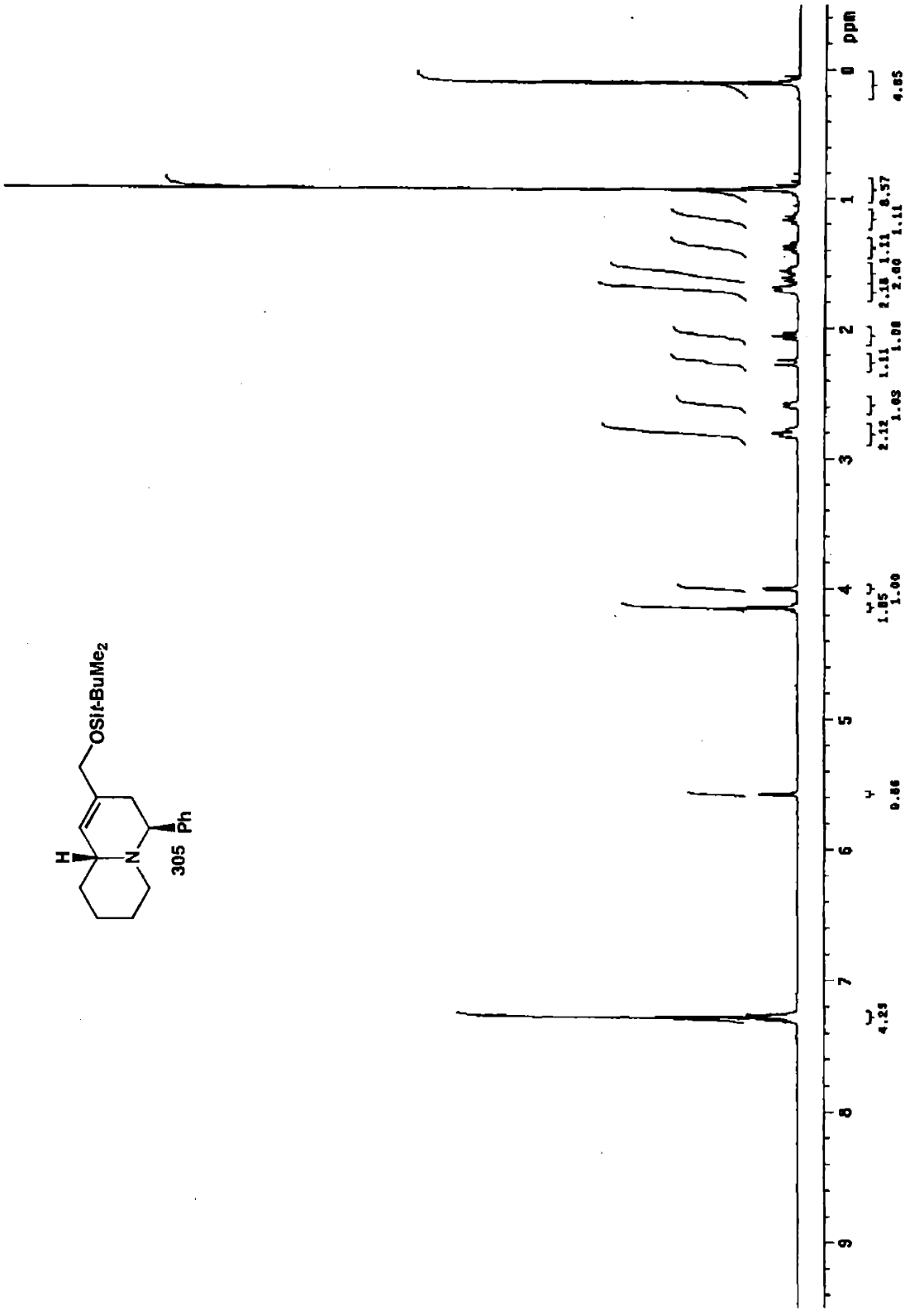
IR (film):	2956, 2931, 2856, 2790, 2741, 2712, 1462, 1362, 1332, 1254, 1193, 1154, 1064, 837, 775	
^1H NMR (500 MHz, $CDCl_3$):	5.39 (s, 1 H), 4.03 (d, J = 12.8 Hz, 1 H), 4.01 (d, J = 12.8 Hz, 1 H), 2.77 (br d, J = 10.4 Hz, 1 H), 2.65-2.72 (m, 2 H), 2.55-2.60 (m, 1 H), 2.31 (dm, J = 17.1 Hz, 1 H), 1.95 (d, J = 17.1 Hz, 1 H), 1.56-1.78 (m, 5 H), 1.18-1.40 (m, 3 H), 0.90 (s, 9 H), 0.87 (t, J = 7.5 Hz, 3 H), 0.06 (s, 3 H), 0.06 (s, 3 H)	
^{13}C NMR (125 MHz, $CDCl_3$):	133.7, 123.9, 66.8, 60.6, 54.8, 52.2, 32.7, 28.7, 26.3, 26.1, 25.2, 18.6, 16.5, 12.2, -5.0, -5.1	
HRMS $[M+H]^+$:	Calcd for $C_{18}H_{35}NOSi$:	310.2561
	Found:	310.2550

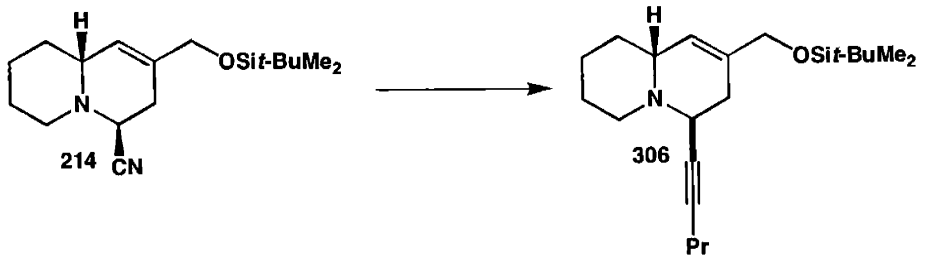

OSi-t-BuMe2
H
N
Et
303



2-(*tert*-Butyldimethylsiloxymethyl)*cis*-1,2-didehydro-4-phenylquinolizidine (305). A 25-mL, round-bottomed flask equipped with a rubber septum and argon inlet needle was charged with **214** (0.114 g, 0.37 mmol) and 4 ml of ether. The flask was cooled at 0 °C while phenylmagnesium bromide solution (3.0 M in ether, 0.37 mL, 1.1 mmol) was added dropwise via syringe over 4 min. The resulting solution was stirred at 0 °C for 1 h and then diluted with 5 mL of satd aq NH_4Cl solution, 25 mL of water, and 25 mL of ether. The aqueous layer was separated and extracted with two 25-ml portions of ether. The combined organic layers were washed with 30 mL of brine, dried over $MgSO_4$, filtered, and concentrated to afford 0.137 g of yellow oil. Column chromatography on 8 g of silica gel (elution 1% Et_3N-5% EtOAc-hexanes) provided 0.114 g (86%) of **305** as a yellow oil.

IR (film):	3084, 3062, 3026, 2930, 2856, 2748, 1602, 1493, 1472, 1462, 1453, 1361, 1324, 1257, 1193, 1152, 1066, 909, 837,
^{1}H NMR (500 MHz, $CDCl_3$):	7.24-7.32 (m, 5 H), 5.58 (s, 1 H), 4.14 (s, 2 H), 4.00 (d, J = 5.8 Hz, 1 H), 2.75-2.83 (m, 2 H), 2.58 (br d, J = 11.3 Hz, 1 H), 2.25 (d, J = 17.4 Hz, 1 H), 2.05 (app dt, J = 11.8, 3.1 Hz, 1 H), 1.67-1.73 (m, 2 H), 1.62 (app tq, J = 12.5, 4.0 Hz, 1 H), 1.52-1.57 (m, 1 H), 1.37 (app dq, J = 12.8, 4.0 Hz, 1 H), 1.15 (app dt, J = 13.1, 4.0 Hz, 1 H), 0.93 (s, 9 H), 0.11 (s, 3 H), 0.10 (s, 3 H)
^{13}C NMR (125 MHz, $CDCl_3$):	139.3, 134.7, 128.9, 128.0, 127.2, 125.0, 66.5, 61.8, 54.1, 52.7, 32.4, 31.7, 26.1, 25.9, 24.8, 18.6, -5.1, -5.1
HRMS $[M+H]^+$:	Calcd for $C_{22}H_{36}NOSi$: 358.2561 Found: 358.2556

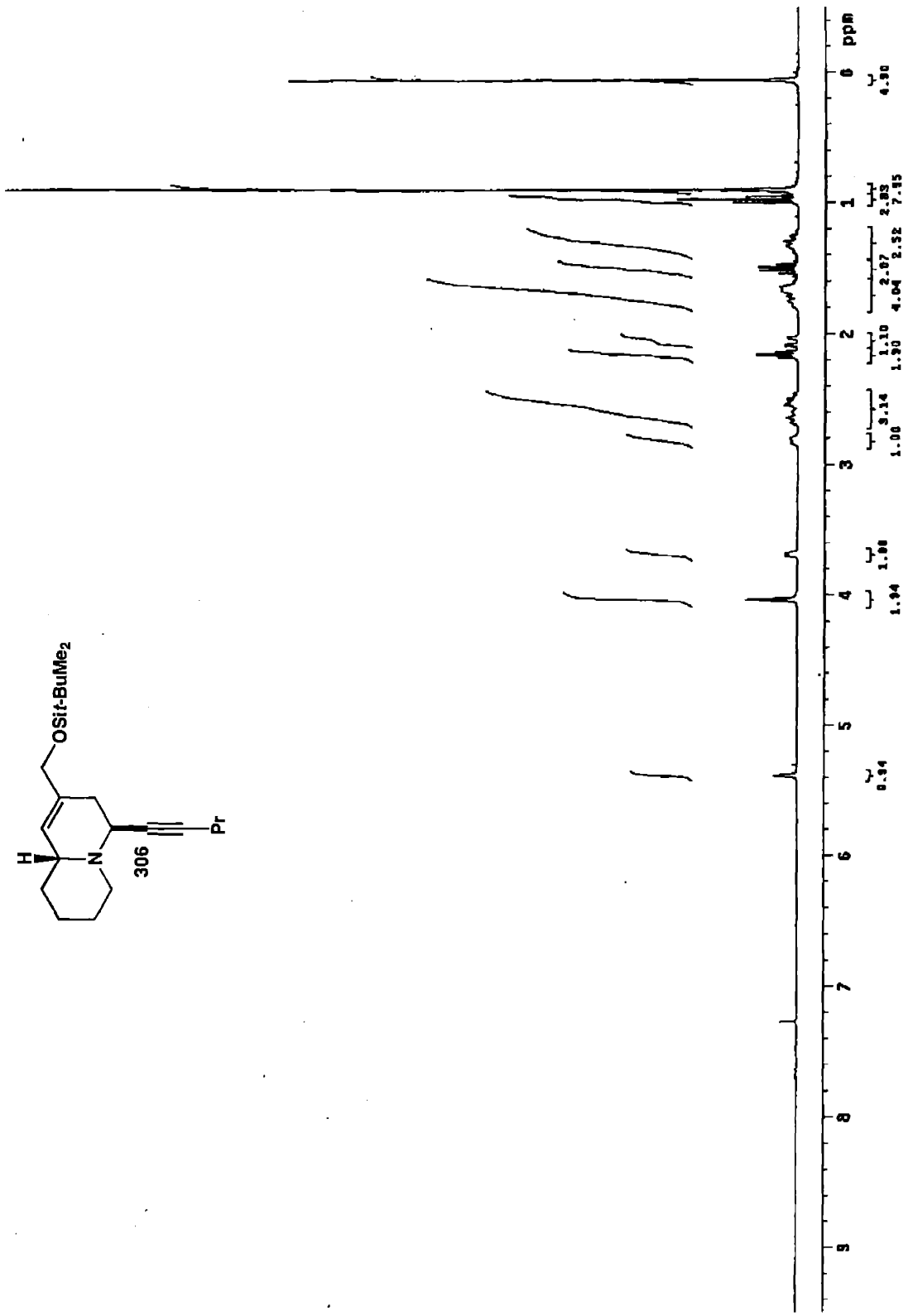

OSit-BuMe2
H
N
305 Ph
ppm

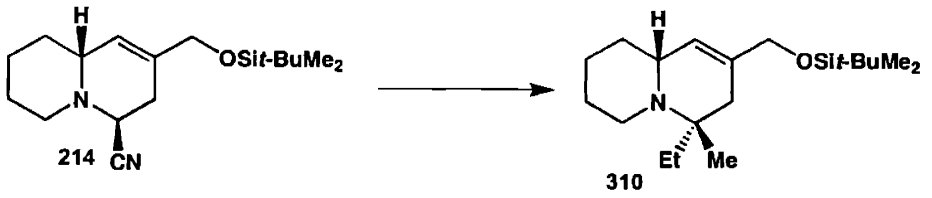


2-(*tert*-Butyldimethylsiloxymethyl)*cis*-1,2-didehydro-4-(1-pentynyl)quinolizidine (306). A 25-mL, round-bottomed flask equipped with a rubber septum and argon inlet needle was charged with nitrile **214** (0.132 g, 0.43 mmol) and 2 mL of THF. A 10-mL, pear-shaped flask equipped with a rubber septum and argon inlet needle was charged with 1-pentyne (0.13 mL, 0.088 g, 1.3 mmol) and 4 mL of THF. Ethylmagnesium bromide solution (0.43 mL, 3.0 M in ether, 1.3 mmol) was then added via syringe over 1 min, and the reaction mixture was stirred at rt for 1 h. The resulting solution was then transferred via cannula to the solution of the nitrile over 2 min. The reaction mixture was stirred at rt for 3.5 h and then diluted with 5 mL of satd aq NH_4Cl solution, 15 mL of water, and 15 mL of ether. The aqueous layer was separated and extracted with three 15-mL portions of ether, and the combined organic layers were washed with 25 mL of brine dried over K_2CO_3, filtered, and concentrated to provide 0.149 g of yellow oil. Column chromatography on 8 g of silica gel (gradient elution with 5-10% EtOAc-hexanes) provided 0.114 g (76%) of **306** as a colorless oil.

IR (film):	2931, 2855, 1462, 1360, 1325, 1292, 1255, 1225, 1193, 1153, 1072, 1005, 836, 776
^{1}H NMR (500 MHz, $CDCl_3$):	5.39 (br s, 1 H), 4.04 (br s, 2 H), 3.69 (d, J = 4.9 Hz, 1 H), 2.82 (br d, J = 10.1 Hz, 1 H), 2.66 (br d, J = 11.3 Hz, 1 H), 2.48-2.60 (m, 2 H), 2.16 (dt, J = 7.0, 2.1 Hz, 2 H), 2.07 (d, J = 14.3 Hz, 1 H), 1.61-1.79 (m, 4 H), 1.51 (sextet, J = 7.3 Hz, 2 H), 1.21-1.38 (m, 2 H), 0.98 (t, J = 7.3 Hz, 3 H), 0.91 (s, 9 H), 0.06 (s, 6 H)

^{13}C NMR (125 MHz, $CDCl_3$):	132.9, 124.0, 85.0, 77.5, 66.6, 55.5, 53.6, 51.4, 32.6, 32.3, 26.2, 26.1, 25.1, 22.7, 20.9, 18.6, 13.7 -5.0, -5.1	
HRMS $[M+H]^+$:	Calcd for $C_{21}H_{37}NOSi$:	348.2717
	Found:	348.2708


OSit-BuMe2
H
N
Pr
306
ppm

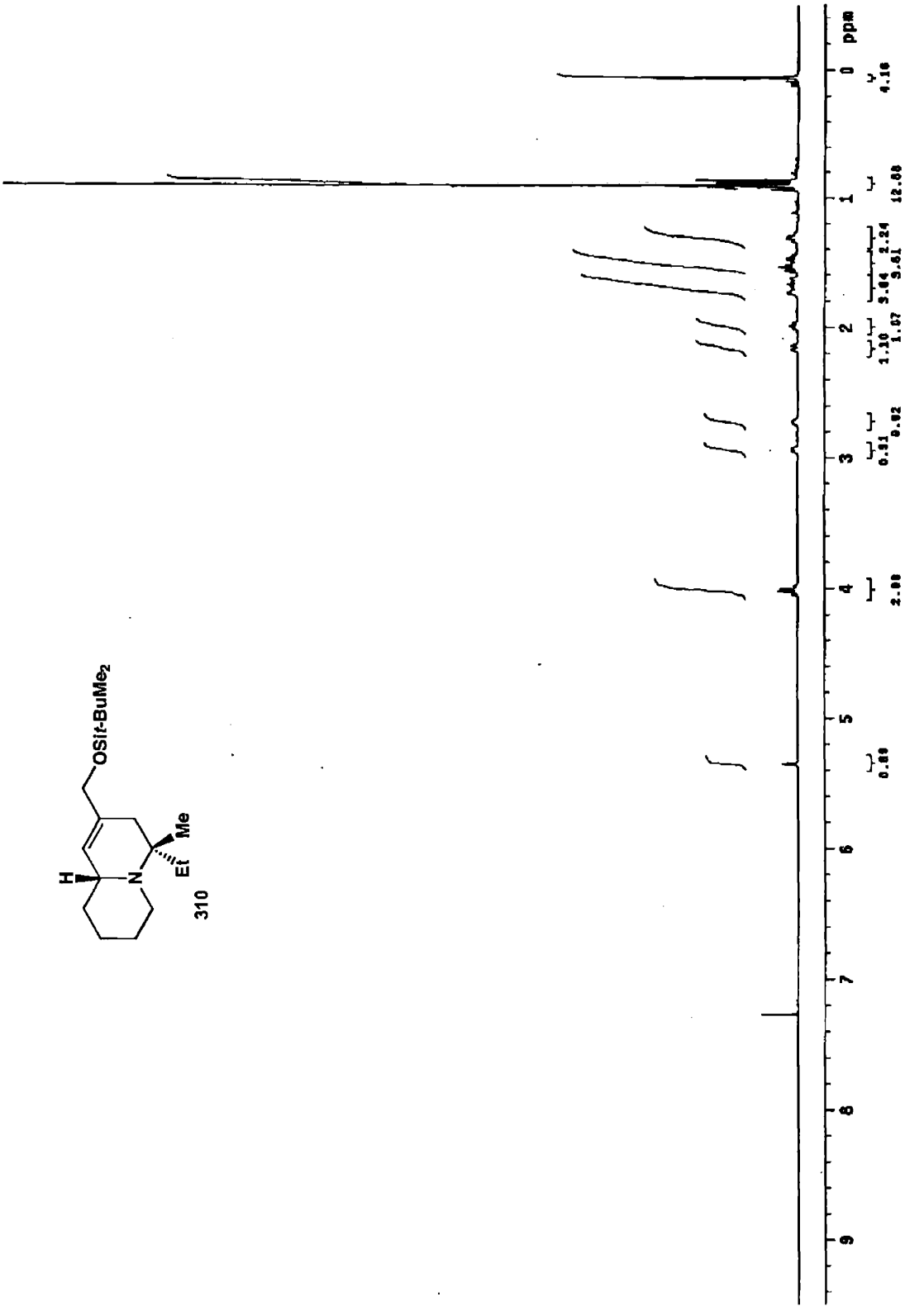


2-(*tert*-Butyldimethylsiloxymethyl)-1,2-didehydro-*cis*-4-methyl-4-ethylquinolizidine (310). A 25-mL, two-necked, round-bottomed flask equipped with a rubber septum and argon inlet adapter was charged with 3 mL of THF and diisopropylamine (0.07 mL, 0.054 g, 0.53 mmol). The solution was cooled at 0 °C while 0.24 mL of *n*-BuLi solution (2.21 M in hexanes, 0.53 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 **214** (0.078 g, 0.25 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 (0.08 mL, 0.16 g, 1.0 mmol) was added rapidly dropwise. The reaction mixture was stirred at 0 °C for 1 h, diluted with 20 ml of water, and the aqueous layer was extracted with three 20-mL portions of ether. The combined organic layers were washed with 25 mL of brine, dried over $MgSO_4$, filtered, and concentrated to give 0.083 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 the preceding reaction (0.083 g, 0.25 mmol) and 3 mL of ether. Methylmagnesium bromide solution (0.24 mL, 3.1 M in ether, 0.74 mmol) was added dropwise via syringe over 1 min. The resulting solution was stirred at rt for 2 h and then was diluted with 15 ml of satd aq NH_4Cl solution and 5 mL of water. The aqueous layer was separated and extracted with three 20-ml portions of ether. The combined organic layers were washed with 25 mL of brine, dried over $MgSO_4$, filtered, and concentrated to afford 0.074 g of

orange oil. Column chromatography on 8 g of silica gel (gradient elution 0-1% Et_3N-5% EtOAc-hexanes) provided 0.050 g (61%) of **310** as a yellow oil.

IR (film):	2930, 2856, 2787, 2741, 1472, 1463, 1380, 1361, 1253, 1152, 1135, 1066, 837, 776
^1H NMR (500 MHz, $CDCl_3$):	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, $CDCl_3$):	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 $[M]^+$:	Calcd for $C_{18}H_{35}NOSi$: 323.2639 Found : 323.2647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Et
H
N
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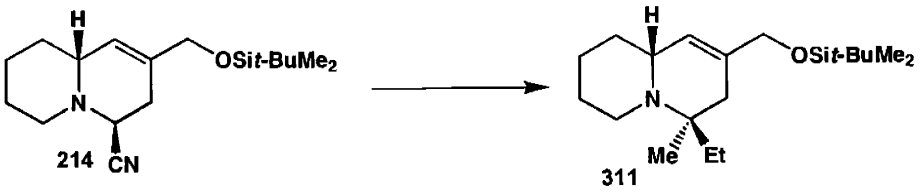
ppm

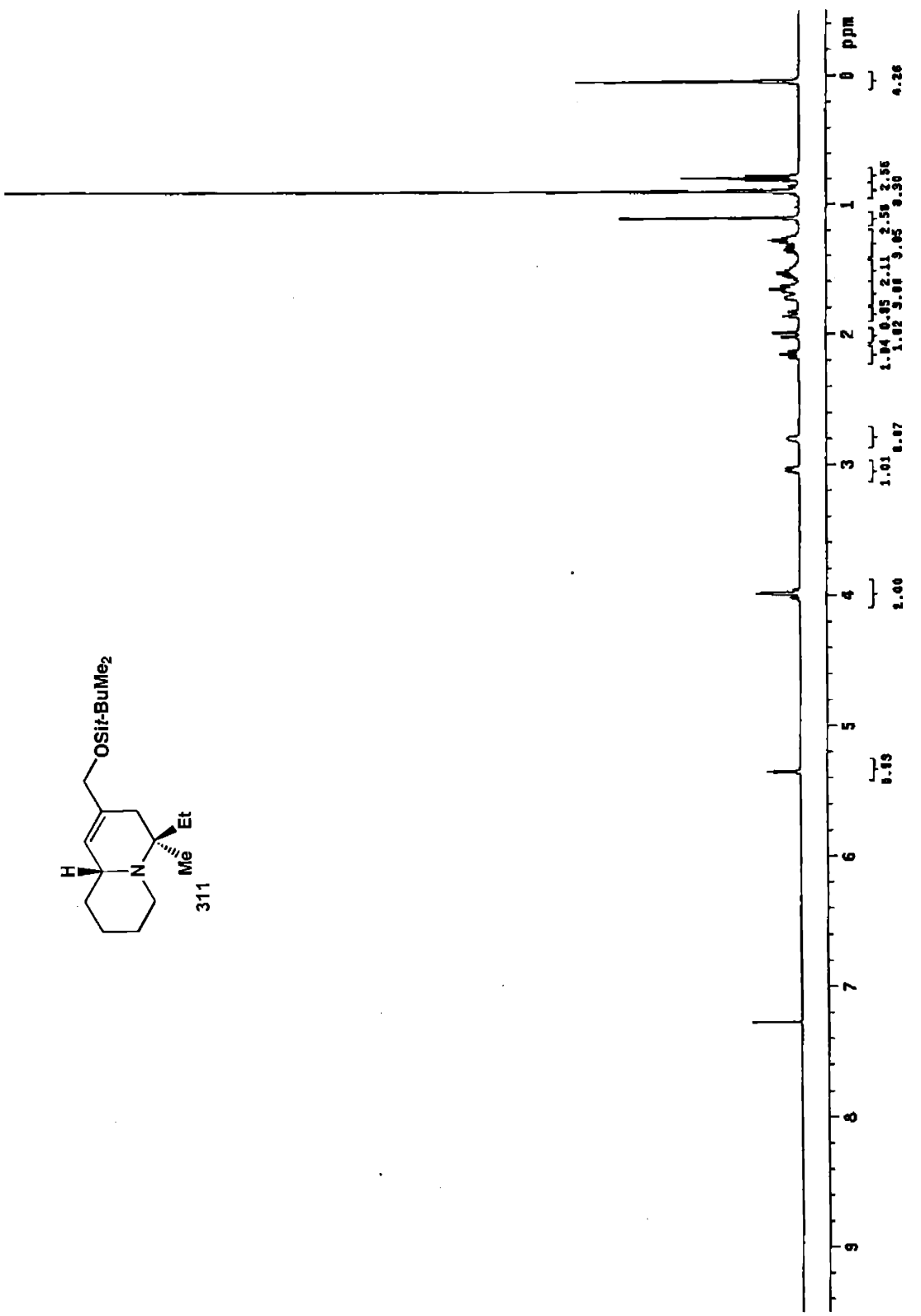


2-(*tert*-Butyldimethylsiloxymethyl)-1,2-didehydro-4-methyl-*cis*-4-ethylquinolizidine (311). A 25-mL, two-necked, round-bottomed flask equipped with a rubber septum and argon inlet adapter was charged with 2 mL of THF and diisopropylamine (0.05 mL, 0.035 g, 0.34 mmol). The solution was cooled at 0 °C while 0.14 mL of *n*-BuLi solution (2.40 M in hexanes, 0.34 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 **214** (0.050 g, 0.16 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 methyl iodide (0.03 mL, 0.093 g, 0.65 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 $MgSO_4$, filtered, and concentrated to give 0.057 g of orange oil that was used immediately in the next step without further purification.

A 10-mL, round-bottomed flask equipped with a rubber septum and argon inlet needle was charged with crude nitrile from preceding step (0.057 g, 0.18 mmol) and 3 mL of ether. The solution was cooled at –10 °C while 0.18 mL of ethylmagnesium bromide solution (3.0 M in ether, 0.53 mmol) was added dropwise via syringe over 1 min. The resulting solution was allowed to slowly warm to rt over 4.5 h and then was diluted with 10 ml of satd aq NH_4Cl solution and 10 mL of water. 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

K_2CO_3, filtered, and concentrated to afford 0.050 g of red oil. Column chromatography on 6 g of silica gel (elution 1% Et_3N-1% EtOAc-hexanes) provided 0.033 g (63%) of **311** as a yellow oil.

IR (film):	2930, 2856, 2785, 1462, 1379, 1360, 1333 1252, 1211, 1154, 1135, 1100, 1065, 1005, 837, 775	
^{1}H NMR (500 MHz, $CDCl_3$):	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, $CDCl_3$):	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 $[M]^+$:	Calcd for $C_{18}H_{35}NOSi$:	323.2639
	Found $[M\text{-}CH_3]^+$:	308.2405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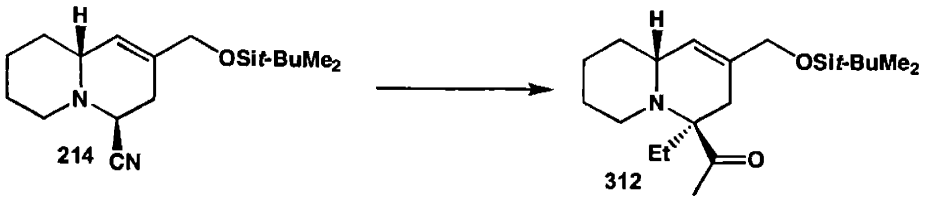
N
Me
Et
311
ppm

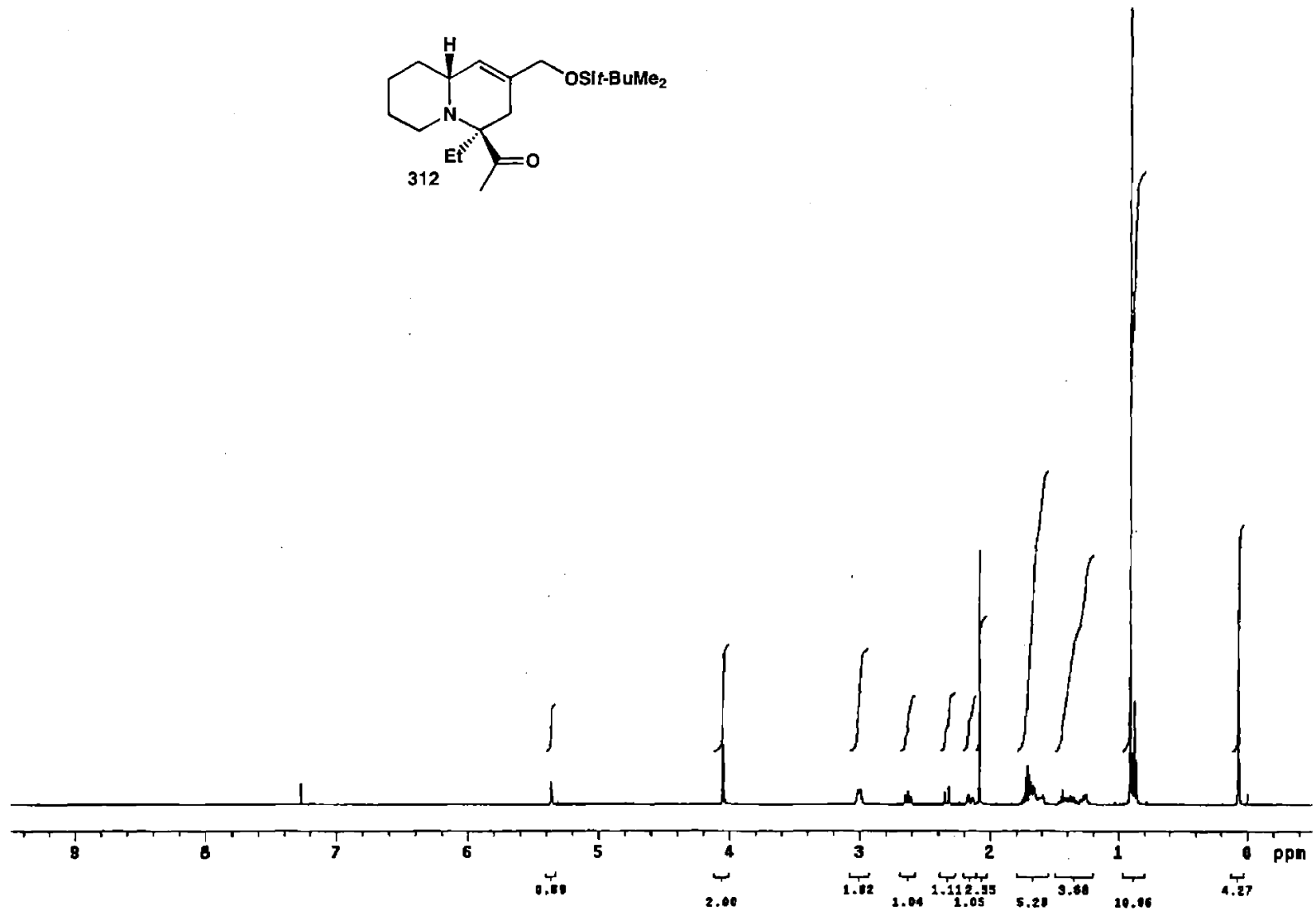


1-[2-(*tert*-Butyldimethylsiloxymethyl)-1,2-didehydro-4-ethylquinolizidinyl)]ethanone (312). A 25-mL, two-necked round-bottomed flask was equipped with a rubber septum and argon inlet adapter was charged with 5 mL of THF and diisopropylamine (0.17 mL, 0.13 g, 1.2 mmol). The solution was cooled at 0 °C while 0.56 mL of *n*-BuLi solution (2.21 M in hexanes, 1.2 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 **214** (0.180 g, 0.59 mmol) in 5 mL of THF was added dropwise over 3 min. The resulting solution was stirred at –78 °C for 2 h, and then ethyl iodide (0.19 mL, 0.37 g, 2.4 mmol) was added rapidly dropwise. The reaction mixture was stirred at 0 °C for 1 h and then diluted with 25 mL of water and extracted with three 25-mL portions of ether. The combined organic layers were washed with 25 mL of brine, dried over $MgSO_4$, filtered, and concentrated to give 0.200 g (102% crude yield) 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 (0.200 g, 0.60 mmol) from the preceding step was fitted with a rubber septum and argon inlet needle, purged with argon, and charged with 6 mL of ether. The solution was cooled at -10 °C while 0.56 mL of MeLi solution (1.6 M in ether, 0.90 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 20 mL of water. The aqueous layer was extracted with three 20-mL portions of ether, and the combined organic layers were washed with 25 mL of brine, dried over K_2CO_3, filtered, and concentrated to a volume of ca. 10 mL. The flask was then fitted with an argon inlet adapter and

purged with argon. Silica gel (3.0 g) was added and the resulting slurry was stirred at rt for 3 h. The mixture was then filtered, with the aid of 10 ml of ether, and concentrated to afford 0.186 g of yellow oil. Column chromatography on 8 g of silica gel (elution with 1% Et_3N-5% EtOAc-hexanes) provided 0.171 g (83%) of **312** as a yellow oil.

IR (film):	2930, 2856, 1705, 1472, 1463, 1380, 1351, 1252, 1164, 1112, 1067, 1006, 940, 917, 838, 777, 734, 667
^{1}H NMR (500 MHz, $CDCl_3$):	5.36 (br s, 1 H), 4.05 (s, 2 H), 3.00 (app d, J = 10.4 Hz, 2 H), 2.63 (dt, J = 11.0, 2.4 Hz, 1 H), 2.33 (dd, J = 17.1, 2.1 Hz, 1 H), 2.15 (br d, J = 16.5 Hz, 1 H), 2.08 (s, 3 H), 1.70 (q, J = 7.6 Hz, 2 H), 1.59-1.68 (m, 3 H), 1.25-1.44 (m, 3 H), 0.91 (s, 9 H), 0.87 (t, J = 7.5 Hz, 3 H), 0.07 (s, 3 H), 0.06 (s, 3 H)
^{13}C NMR (75 MHz, $CDCl_3$):	212.7, 133.8, 124.9, 68.5, 66.4, 57.1, 46.0, 33.6, 31.5, 28.6, 28.2, 27.3, 26.2, 24.6, 18.7, 8.1, -4.9, -5.0
HRMS $[M+H]^+$:	Calcd for $C_{20}H_{38}NO_2Si$: 352.2666 Found: 352.2663


H
OSit-BuMe2
N
Et
O
312
8
6
7
6
5
4
3
2
1
0
ppm
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1.02
1.04
1.11
2.35
1.05
5.28
3.68
10.86
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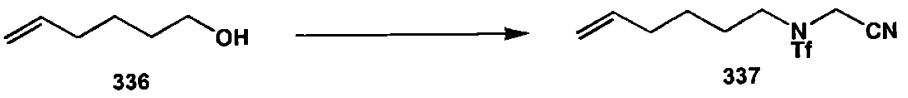
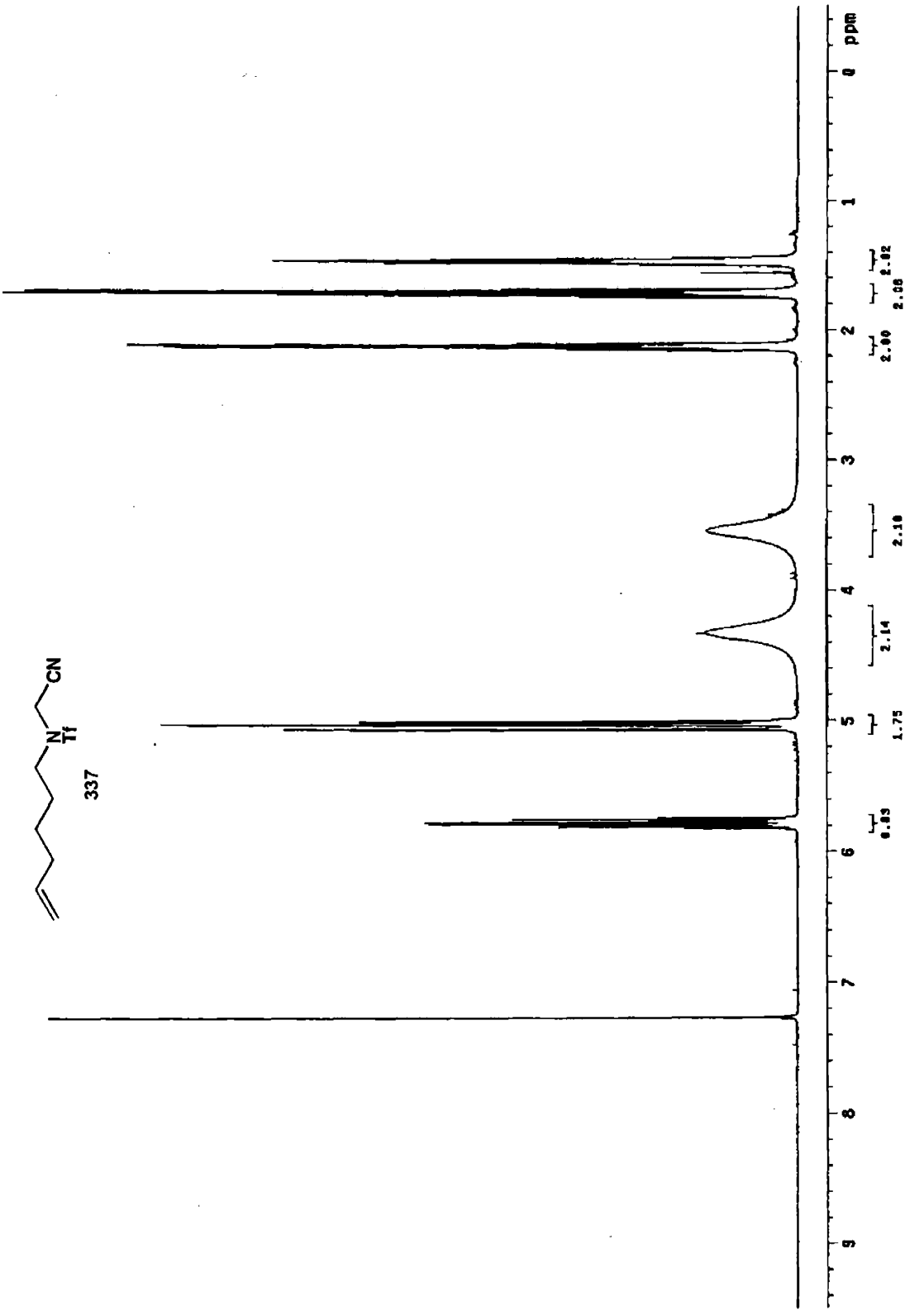


336 337

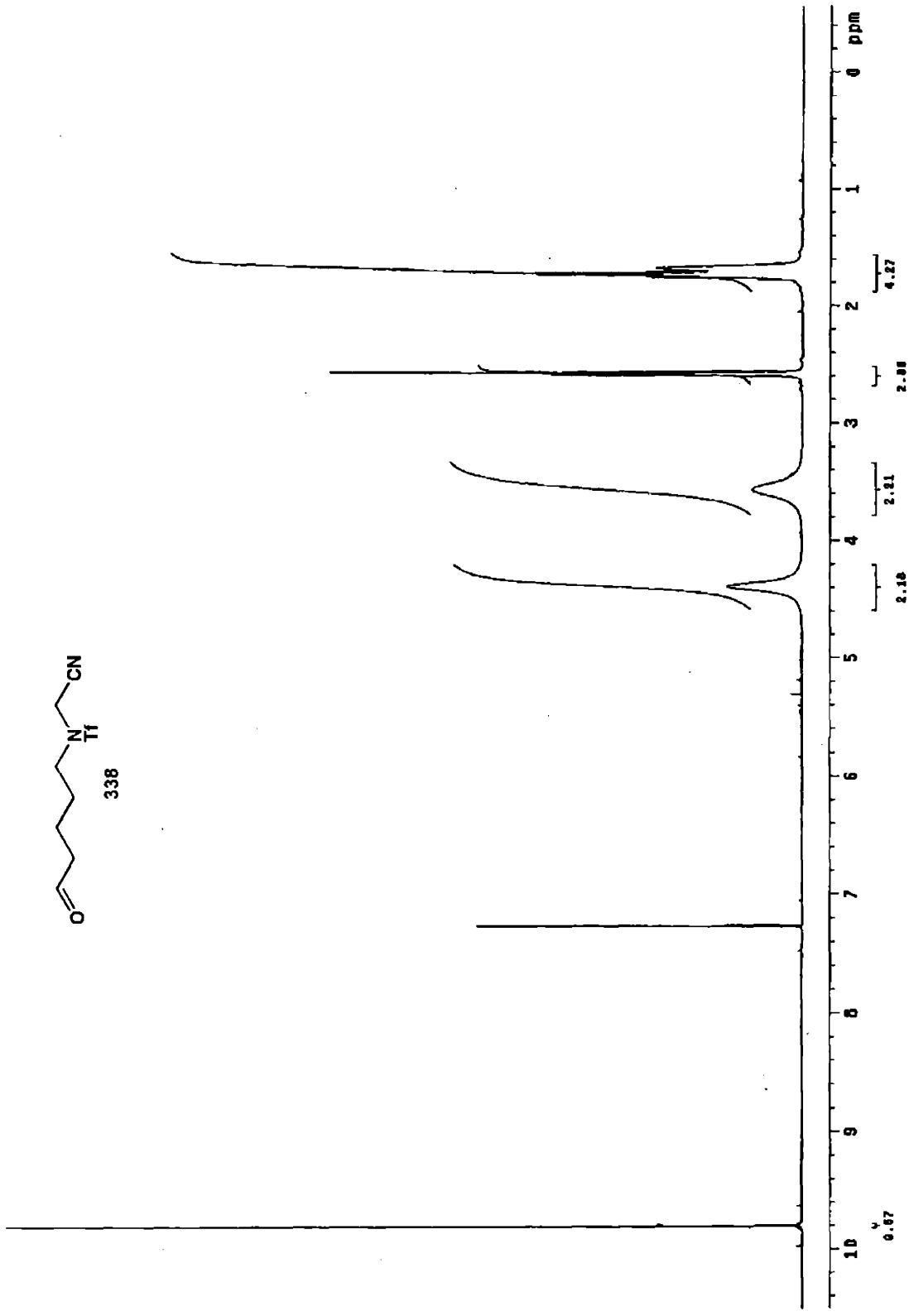
***N*-(Cyanomethyl)-*N*-(5-hexenyl)trifluoromethanesulfonamide (337).** A 50-mL, two-necked, round-bottomed flask equipped with a rubber septum and argon inlet adapter was charged with triphenylphosphine (1.31 g, 5.00 mmol), 15 mL of THF, 15 mL of toluene, and $HN(Tf)CH_2CN$ (0.822 g, 4.37 mmol). 4-Penten-1-ol (0.50 mL, 0.42 g, 4.2 mmol) was then added in one portion followed by dropwise addition of DEAD (0.79 mL, 0.87 g, 5.0 mmol) over 2 min. The resulting mixture was stirred at rt for 1 h and then concentrated to give 5.17 g of a yellow solid. This material was concentrated onto 10 g of silica gel and added to a column of 50 g of silica gel. Elution with 10% EtOAc-hexanes provided 0.924 g (83%) of **337** as a colorless oil.

IR (film):	3081, 2997, 2942, 2866, 1642, 1393, 1355, 1296, 1271, 1231, 1143, 1039, 996, 917, 781, 749, 730
^1H NMR (500 MHz, $CDCl_3$):	5.78 (ddt, J = 17.1, 10.1, 6.7 Hz, 1 H), 5.01-5.08 (m, 2 H), 4.35 (br, 2 H), 3.55 (br, 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, $CDCl_3$):	137.1, 119.8 (q, J = 322 Hz), 115.8, 113.4, 49.3, 35.8, 33.0, 26.7, 25.3


CN
N
Tf
337
ppm
0
1
2
3
4
5
6
7
8
9
2.00
2.02
2.08
2.10
2.14
1.75
0.83

***N*-(Cyanomethyl)-*N*-(5-hexanal)trifluoromethanesulfonamide (338).** A 50-mL, recovery flask containing alkene **337** (0.924 g, 3.42 mmol) was fitted with a rubber septum and argon inlet needle and purged with argon. CH_2Cl_2 (15 mL) was added, and the flask was cooled at –78 °C while ozone was bubbled through the solution for 9 min. The resulting blue solution was degassed with a stream of argon for 10 min. Triphenylphosphine (0.942 g, 3.59 mmol) was added, and the solution was allowed to slowly warm to rt over 16 h. Concentration by rotary evaporation afforded 2.18 g of a colorless oil, which was concentrated onto 4 g of silica gel and added to a column of 40 g of silica gel. Elution with 25% EtOAc-hexanes provided 0.838 g (90%) of **338** as a colorless oil.

IR (film):	2997, 2954, 2877, 2838, 2735, 1723, 1467, 1394, 1360, 1294, 1269, 1229, 1145, 1117, 1049, 970, 923, 904, 785, 733
^{1}H NMR (500 MHz, $CDCl_3$):	9.80 (t, J = 1.0 Hz, 1 H), 4.39 (br, 2 H), 3.57 (br, 2 H), 2.59 (t, J = 6.4 Hz, 2 H), 1.69-1.78 (m, 4 H)
^{13}C NMR (125 MHz, $CDCl_3$):	201.7, 119.7 (q, J = 322 Hz), 113.5, 49.1, 42.8, 35.7, 26.4, 18.2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Tf
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ppm
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2.21
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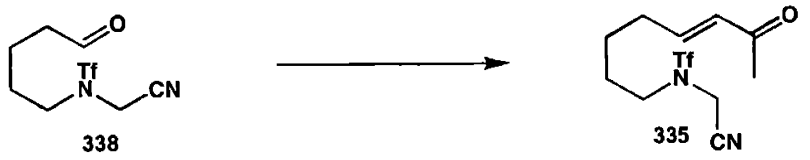
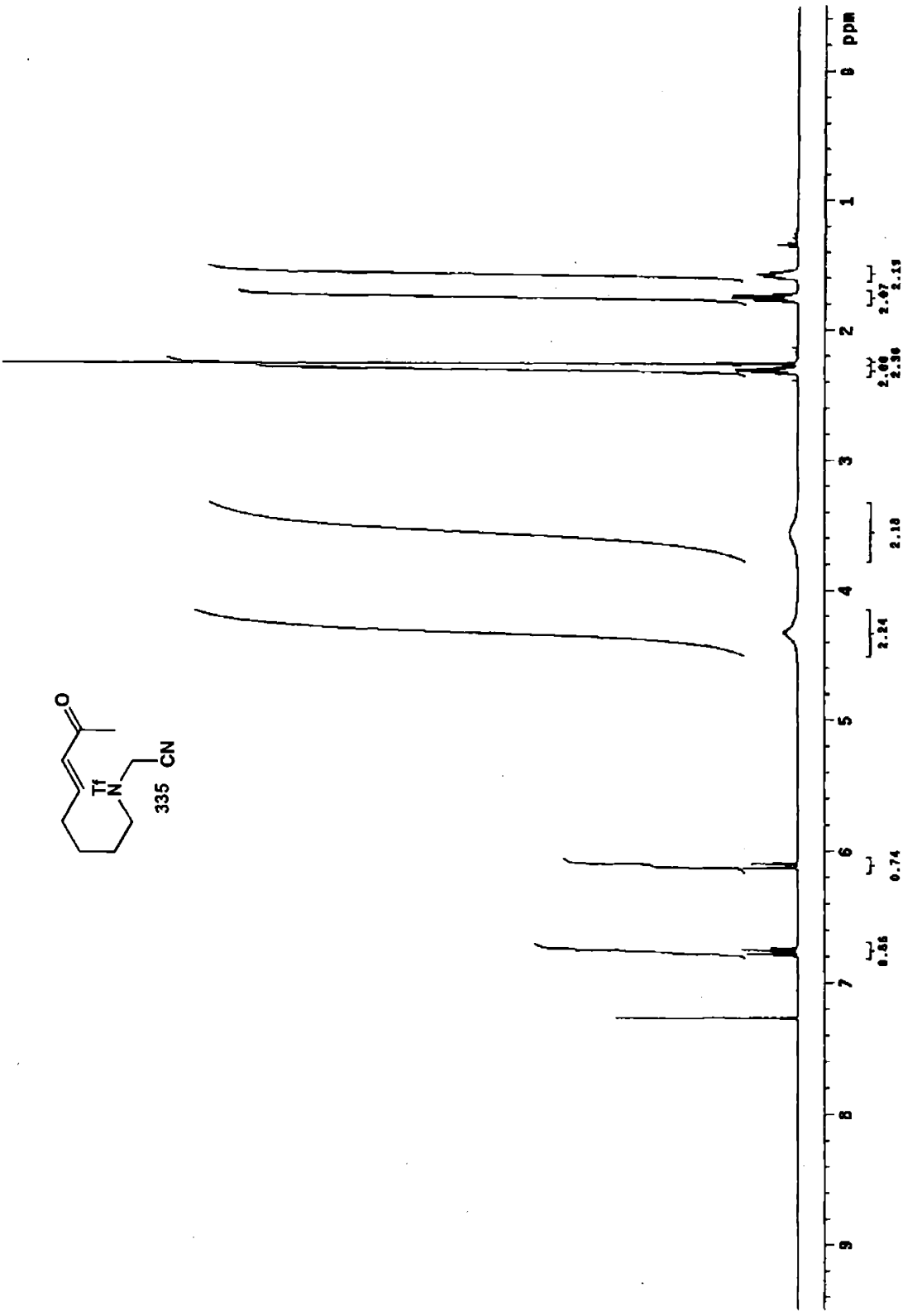


***N*-(Cyanomethyl)-*N*-((*E*)-5-octen-7-one)trifluoromethanesulfonamide (335).** A 50-mL, round-bottomed flask equipped with a reflux condenser fitted with an argon inlet adapter was charged with aldehyde **338** (0.706 g, 2.59 mmol) and 16 mL of CH_2Cl_2. (Acetylmethylene)triphenylphosphorane (0.908 g, 2.85 mmol) was then added, and the reaction mixture was heated at reflux for 14 h. Concentration by rotary evaporation afforded 1.76 g of a pink oil. This material was concentrated onto 3.5 g of silica gel and added to a column of 25 g of silica gel. Gradient elution with 25-50% EtOAc-hexanes provided 0.724 g (89%) of **335** as a colorless oil.

IR (film):	2995, 2947, 2869, 1674, 1628, 1396, 1364, 1258, 1230, 1196, 1145, 1038, 981, 918, 903, 784, 737
^{1}H NMR (500 MHz, $CDCl_3$):	6.76 (dt, J = 16.0, 6.9 Hz, 1 H), 6.11 (dt, J = 16.0, 1.5 Hz, 1 H), 4.32 (br, 2 H), 3.56 (br, 2 H), 2.31 (app dq, J = 7.0, 1.1 Hz, 2 H), 2.26 (s, 3 H), 1.75 (quint, J = 7.6 Hz, 2 H), 1.57 (quint, J = 7.3 Hz, 2 H)
^{13}C NMR (125 MHz, $CDCl_3$):	198.7, 146.6, 132.1, 119.7 (q, J = 322 Hz), 113.4, 49.3, 35.9, 31.7, 27.2, 26.9, 24.6


O
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ppm
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2.30
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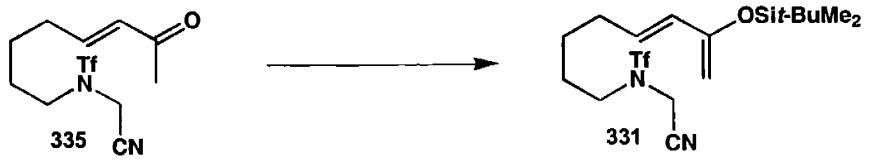
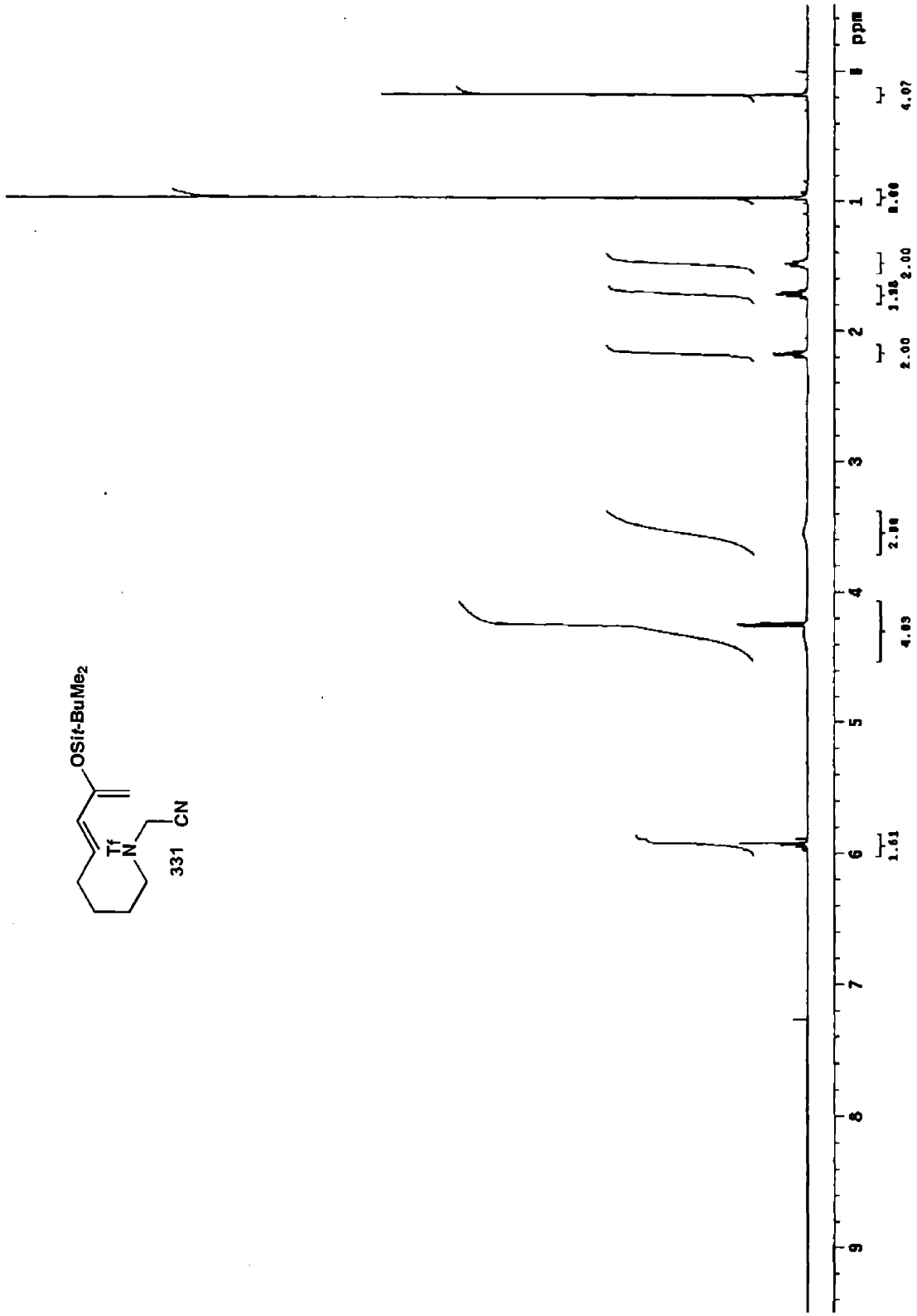
2.24
0.74
0.85



***N*-(Cyanomethyl)-*N*-(7-(*tert*-butyldimethylsiloxy)-(*E*)-5,7-octadienyl)trifluoromethanesulfonamide (331).** A 25-mL, two-necked, round-bottomed flask with a rubber septum and argon inlet adapter was charged with NaI (0.391 g, 2.61 mmol), a solution enone **335** (0.407 g, 1.30 mmol) in 10 ml of MeCN, and Et_3N (0.40 mL, 0.29 g, 2.9 mmol). *tert*-Butyldimethylsilyl chloride (0.393 g, 2.61 mmol) was added, and the resulting mixture was stirred at rt in the dark for 17 h. The reaction mixture was then diluted with 20 mL of satd aq $NaHCO_3$ solution, and the aqueous layer was separated and extracted with three 20-mL portions of ether. The combined organic layers were washed with 25 mL of 1 M NaOH solution, 25 mL of brine, dried over $MgSO_4$, filtered, and concentrated to afford 0.678 g of a yellow oil. Column chromatography on 15 g of acetone-deactivated silica gel (elution with 1% Et_3N-5% EtOAc-hexanes) provided 0.526 g (95%) of **331** as a white solid: mp 63.5-64.5 °C.

IR (CH_2Cl_2):	3040, 2980, 2850, 1585, 1412, 1390, 1250, 1220, 1192, 1138, 1014	
^1H NMR (500 MHz, $CDCl_3$):	5.89-5.98 (m, 2 H), 4.32 (br, 2 H), 4.25 (s, 1 H), 4.24 (s, 1 H), 3.55 (br, 2 H), 2.18 (app q, J = 6.8 Hz, 2 H), 1.72 (quint, J = 7.6 Hz, 2 H), 1.49 (quint, J = 7.5 Hz, 2 H), 0.98 (s, 9 H), 0.18 (s, 6 H)	
^{13}C NMR (125 MHz, $CDCl_3$):	154.9, 130.0, 129.3, 119.8 (q, J = 322 Hz), 113.2, 94.8, 49.2, 35.8, 31.4, 26.9, 26.0, 25.7, 18.5, -4.4	
HRMS $[M+H]^+$:	Calcd for $C_{17}H_{30}F_3N_2O_3SSi$:	427.1693
	Found:	427.1694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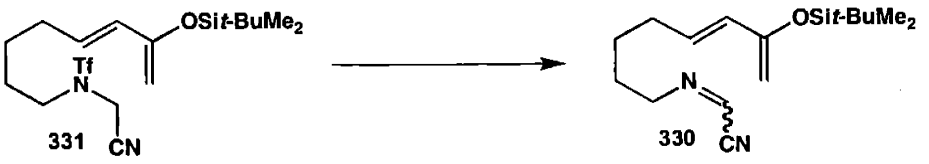
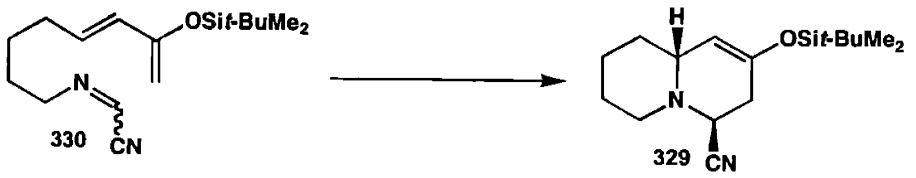


7-(*tert*-Butyldimethylsiloxy)-(*E*)-5,7-octadienyliminoacetonitrile (330). A 25-mL, one-necked, round-bottomed flask equipped with a reflux condenser fitted with an argon inlet adapter was charged with Cs_2CO_3 (1.58 g, 4.84 mmol). A solution of triflamide **331** in 8 mL of THF was added, and the reaction mixture was heated at 55 °C for 2 h. The resulting mixture was allowed to cool to room temperature and then diluted with 25 mL of water. The mixture was then 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 to give 0.352 g of a yellow oil. Column chromatography on 8 g of acetone-deactivated silica gel (elution with 1% Et_3N-10% EtOAc-hexanes) provided 0.326 g (92%) of **330** (83:17 mixture of E and Z imine isomers by ^1H NMR analysis) as a colorless oil.

IR (film):	2935, 2895, 2855, 1650, 1620, 1590, 1462, 1365, 1325, 1260, 1028, 970, 835
For E isomer:	
^1H NMR (500 MHz, $CDCl_3$):	7.37 (t, J = 1.5 Hz, 1 H), 5.94-5.99 (m, 1 H), 5.88 (d, J = 15.3 Hz, 1 H), 4.23 (s, 1 H), 4.21 (s, 1 H), 3.65 (dt, J = 6.9, 1.4 Hz, 2 H), 2.11-2.18 (m, 2 H), 1.68-1.76 (m, 2 H), 1.42-1.51 (m, 2 H), 0.97 (s, 9 H), 0.17 (s, 6 H)
^{13}C NMR (125 MHz, $CDCl_3$):	155.0, 135.9, 130.8, 128.7, 114.6, 94.4, 63.0, 31.7, 29.5, 26.7, 26.6, 18.4, -4.5
For Z isomer:	
^1H NMR (500 MHz, $CDCl_3$):	7.38 (t, J = 2.1 Hz, 1 H), 5.94-5.99 (m, 1 H), 5.89 (d, J = 15.2 Hz, 1 H), 4.23 (s, 1 H), 4.21 (s, 1 H), 3.84 (dt, J = 6.9, 2.1 Hz, 2 H), 2.11-2.18 (m, 2 H), 1.68-1.76 (m, 2 H), 1.42-1.51 (m, 2 H), 0.97 (s, 9 H), 0.17 (s, 6 H)

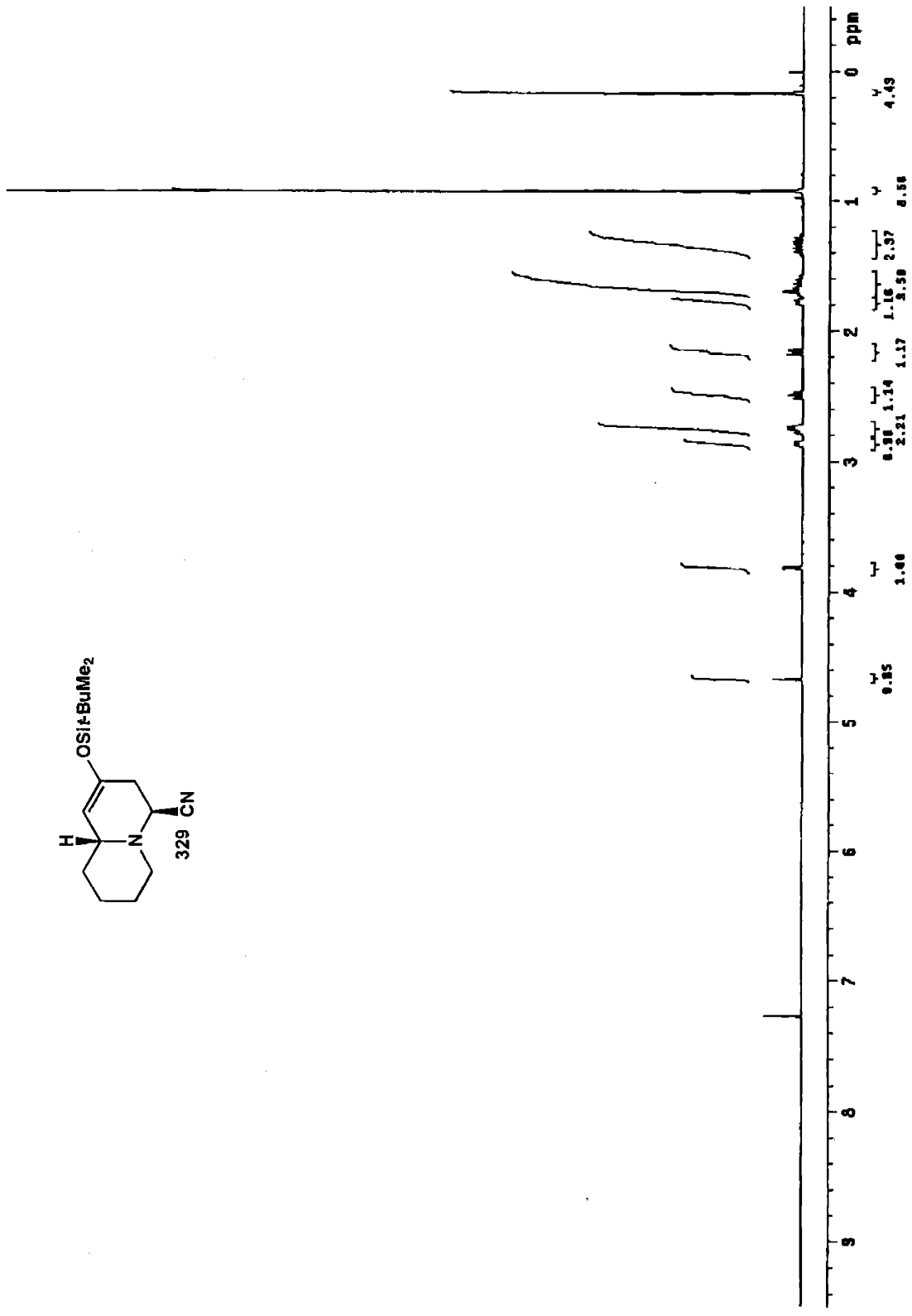
^{13}C NMR (125 MHz, $CDCl_3$): 155.1, 131.5, 130.9, 128.6, 109.5, 94.3, 59.7, 31.7, 29.6, 26.8, 26.0, 18.4, -4.5


OSit-BuMe2
CN
330
N
ppm



2-(*tert*-Butyldimethylsiloxy)-*cis*-1,2-didehydro-4-cyanoquinolizidine (329). A threaded Pyrex tube (ca. 50 mL capacity) equipped with a rubber septum and argon inlet needle was charged with imine **330** (0.321 g, 1.10 mmol), BHT (0.725 g, 3.29 mmol), and 22 mL of toluene. The solution was degassed by three freeze-pump-thaw cycles and then sealed with a threaded Teflon cap. The reaction mixture was heated in a 120 °C oil bath for 25 h and then allowed to cool to rt. Concentration gave 1.25 g of a pale yellow oil, and column chromatography on 30 g of silica gel (gradient elution with 1% Et_3N-0-5% EtOAc-hexanes) afforded 0.252 g (79%) of **329** as a white solid: mp 61-62 C°.

IR (CH_2Cl_2):	2933, 2857, 1678, 1472, 1372, 1287, 1256, 1212, 1171, 1127, 898, 835, 780, 689
^1H NMR (500 MHz, $CDCl_3$):	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, $CDCl_3$):	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
Elemental Analysis:	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
329
0 ppm
1
2
3
4
5
6
7
8
9
4.49
6.56
2.37
3.58
1.16
1.17
1.14
2.21
1.00
0.85

DAVID T. AMOS

Education

2003 — Ph.D., Organic Chemistry, Massachusetts Institute of Technology
Thesis Title: "Synthesis of Nitrogen Heterocycles via the Intramolecular [4+2] Cycloaddition of Iminoacetonitriles"
Advisor: Professor Rick L. Danheiser

1998 — B.A, Chemistry (magna cum laude) Hamline University, St. Paul, MN
Thesis title: "[2+2] Annulations for the Formation of CpCo-Cyclobutadienes"
Advisor: Professor Ronald G. Brisbois

Professional Experience

1998-Present — **Graduate Research Assistant, Massachusetts Institute of Technology**
- Developed [4+2] Diels-Alder cycloadditions of iminoacetonitriles
- Optimized formation of iminoacetonitriles, a novel azadienophile
- Designed multi-step synthesis of cycloaddition substrates
- Applied NMR techniques to stereochemical determination

1997-1998 — **Research Assistant, Hamline University**
Advisor: Ronald G. Brisbois
- Synthesis of functionalized cyclopentadienyl cobalt-cyclobutadienes

Summer 1997 — **NSF REU Research Fellow, The Pennsylvania State University**
Advisor: Raymond L. Funk
- Synthesis of menthol derivatives for asymmetric synthesis
- Applied system to asymmetric Diels-Alder and epoxidation reactions

Honors and Awards

- MIT Wyeth-Ayerst Scholar (April 2002)
- MIT Chemistry Department Outstanding Teaching Award (September 1999)

Presentations And Publications

Amos, D. T.; Renslo, A. R.; and Danheiser, R. L. *J. Am. Chem. Soc.* **2003**, *125*, 4970.

Danheiser, R. L.; Renslo, A. R.; Amos, D. T.; and Wright, G. T. *Org. Synth.* **2003**, *80*, 133.