AN ABSTRACT OF THE DISSERTATION OF

Younggi Choi for the degree of Doctor of Philosophy in Chemistry presented on February 4, 2003.

Title: TOTAL SYNTHESIS OF INDOLE ALKALOIDS: PART I. ASYMMETRIC SYNTHESIS OF (-)-IBOGAMINE. PART II. AN APPROACH TOWARD THE SYNTHESIS OF KOUMINE.

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Abstracted approved: _____

James D. White

PART I. The preparation of (–)-ibogamine (**1**) in fourteen steps from benzoquinone and in 10% overall yield is a powerful illustration of the value of the asymmetric Diels-Alder reaction as a starting point in a multistep synthesis. All four cycloadducts, **70**, **77**, **84** and **96**, obtained with the (*S*)-BINOL-$TiCl_2$ complex were found to have the same absolute configuration. Furthermore, they are in the same enantiomeric series that Mikami observed with 1,4-naphthoquinone using the same catalyst, lending confidence to future stereochemical predictions that may be made with this system.

PART II. Three different routes for the synthesis of the hexahydroisoquinoline **98** met obstacles which defeated our approach to

koumine. The Diels-Alder reaction of cyclic 1-azadienes **102** and **108** was abandoned due to the lack of reactivity of the dienes. An anionic oxy-Cope rearrangement of the azabicyclo[2.2.2]octane system caused mainly decomposition of the starting materials. Finally, an intramolecular [2+2] photocycloaddition generated "crossed", "straight" and hydroisoquinoline products in varing ratios, depending on the substituent pattern of the substrate, but this approach was not synthetically useful. The results from this last study may be valuable for predicting the regiochemical outcome of certain intramolecular photocycloadditions.

# TOTAL SYNTHESIS OF INDOLE ALKALOIDS:

# PART I. ASYMMETRIC SYNTHESIS OF (-)-IBOGAMINE.

# PART II. AN APPROACH TOWARD THE SYNTHESIS OF KOUMINE.

by

Younggi Choi

A DISSERTATION

submitted to

Oregon State University

in partial fulfillment of

the requirements for the

degree of

Doctor of Philosophy

Presented February 4, 2003

Commencement June 2003

Doctor of Philosophy dissertation of Younggi Choi presented on February 4, 2003

APPROVED:

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Major Professor, representing Chemistry

Redacted for privacy

Chair of the Department of Chemistry

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I understand that my dissertation will become part of the permanent collection of Oregon State University libraries. My signature below authorizes the release of my dissertation to any reader upon request.

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Younggi Choi, Author

# ACKNOWLEDGMENTS

I am very grateful for the help of many people who made the writing of this thesis possible. First and foremost, I would like to sincerely thank my major Professor James D. White for his patience, support and critical guidance. His help was invaluable and is greatly appreciated. I would also like to thank my committee members: Dr. Deinzer, Dr. Gable, Dr. Loeser, Dr. Dilles and Dr. Carter for their time and support.

I thank the past and present members of Dr. White group, Paul R. Blakemore, Cindy Browder, Rich G. Carter, Bobby Chow, Jorg Deerberg, Nicholas E. Drapela, Uwe Grether, Roger Hanselmann, Joshua D. Hansen, Carla Hassler, Bryan E. Hauser, Jian Hong, Peter Hrnciar, Scott J. Kemp, Linda E. Keown, Jungchul Kim, Sung-kee Kim, Eric A. Korf, Christian L. Kranman, Punlop Kuntiyong, Chang-Sun Lee, Nadine Lee, Tae-Hee Lee, Christopher M. Lincoln, Barton W. Phillips, Laura Quaranta, Sigrid Quay, Lonnie A. Robarge, Volker K. Schulze, Keith Schwartz, Sundaram M. Shanmugham, Helmars Smits, Kurt F. Sundermann, Michael Thutewohl, Guoqiang Wang, Shan Wang, Wolfgang Wenger, Qing Xu and Darrell Ziemski for their friendship and useful discussion.

I thank Alex Yokochi for X-ray crystallographic analysis and Rodger Kohnert for his advice and assistance on the NMR analysis.

Finally, I could not have come to where I am without the financial and spiritual support from my loving parents, Ilsup Choi and Younghee Jung.

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This dissertation is dedicated to my Mother and Father,

Younghee Jung and Ilsup Choi

in appreciation of their love.

# TOTAL SYNTHESIS OF INDOLE ALKALOIDS:

# PART I. ASYMMETRIC SYNTHESIS OF (-)-IBOGAMINE.

# PART II. AN APPROACH TOWARD THE SYNTHESIS OF KOUMINE.

## PART I. ASYMMETRIC SYNTHESIS OF (-)-IBOGAMINE.

# Chapter I. GENERAL INTRODUCTION

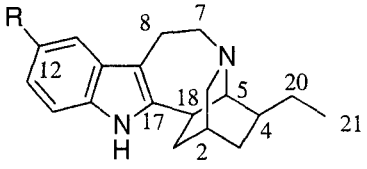
The term alkaloid refers to nitrogen-containing organic substances of natural origin with a greater or lesser degree of basic character. Organic chemists have long been interested in alkaloid chemistry because of the intriguing structures and interesting biological activities of these products of nature. Since alkaloids are often available in limited quantity from their natural source, the total synthesis of alkaloids is sometimes the only means for obtaining sufficient compound for further study. The synthesis of alkaloids has also been central to new drug discovery through the preparation of analogues based upon a parent structure.

The dissertation presented in the following pages describes synthetic efforts toward two indole alkaloids. The first part of the thesis describes an asymmetric synthesis of (-)-ibogamine, an alkaloid which was isolated from the west African shrub *Tabernanthe iboga*. An asymmetric Diels-Alder reaction of 1,4-benzoquinone in the presence of a chiral titanium derived catalyst is a key step in this synthesis. The second part of the thesis entails model studies for an eventual synthesis of (-)-koumine, an alkaloid isolated from the Chinese medicinal plant *Gelsemium elegans Bentham*. The key feature of this work is an examination of intramolecular [2+2] photocycloadditions of azabicyclo[2.2.2]octanes.

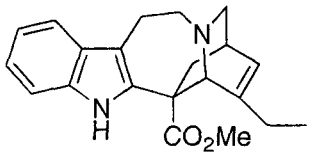
# Chapter II. ASYMMETRIC SYNTHESIS OF (-)-IBOGAMINE

## History and Background

(-)-Ibogamine (**1**) and its congener (-)-ibogaine (**2**) are indole alkaloids found in the west-African shrub *Tabernanthe iboga*.[1] Because of the remarkable CNS stimulating properties and hallucinogenic activities of these substances, African hunters used them to stay motionless for long periods without loss of concentration.




R = H, (-)-Ibogamine (**1**)
R = OMe, (-)-Ibogaine (**2**)



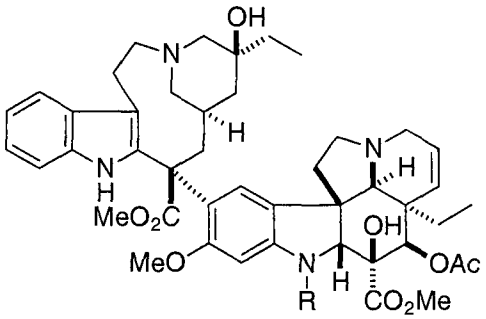

(+)-Catharanthine (**3**)

**Figure 1.1** Ibogane type alkaloids

The *iboga* alkaloids have attracted attention due to anecdotal evidence that they reduce addiction to heroin and cocaine.[2] Recently, preclinical studies have demonstrated that they attenuate both dependence and withdrawal symptoms associated with a variety of abused drugs including opiates, alcohols, nicotine, and psychostimulants.[3]

The structures of **1** and **2** were determined by Taylor in 1957 who employed both chemical degradation and X-ray crystallographic analysis;[4] the absolute configuration of (-)-ibogamine (**1**) was established by circular dichroism

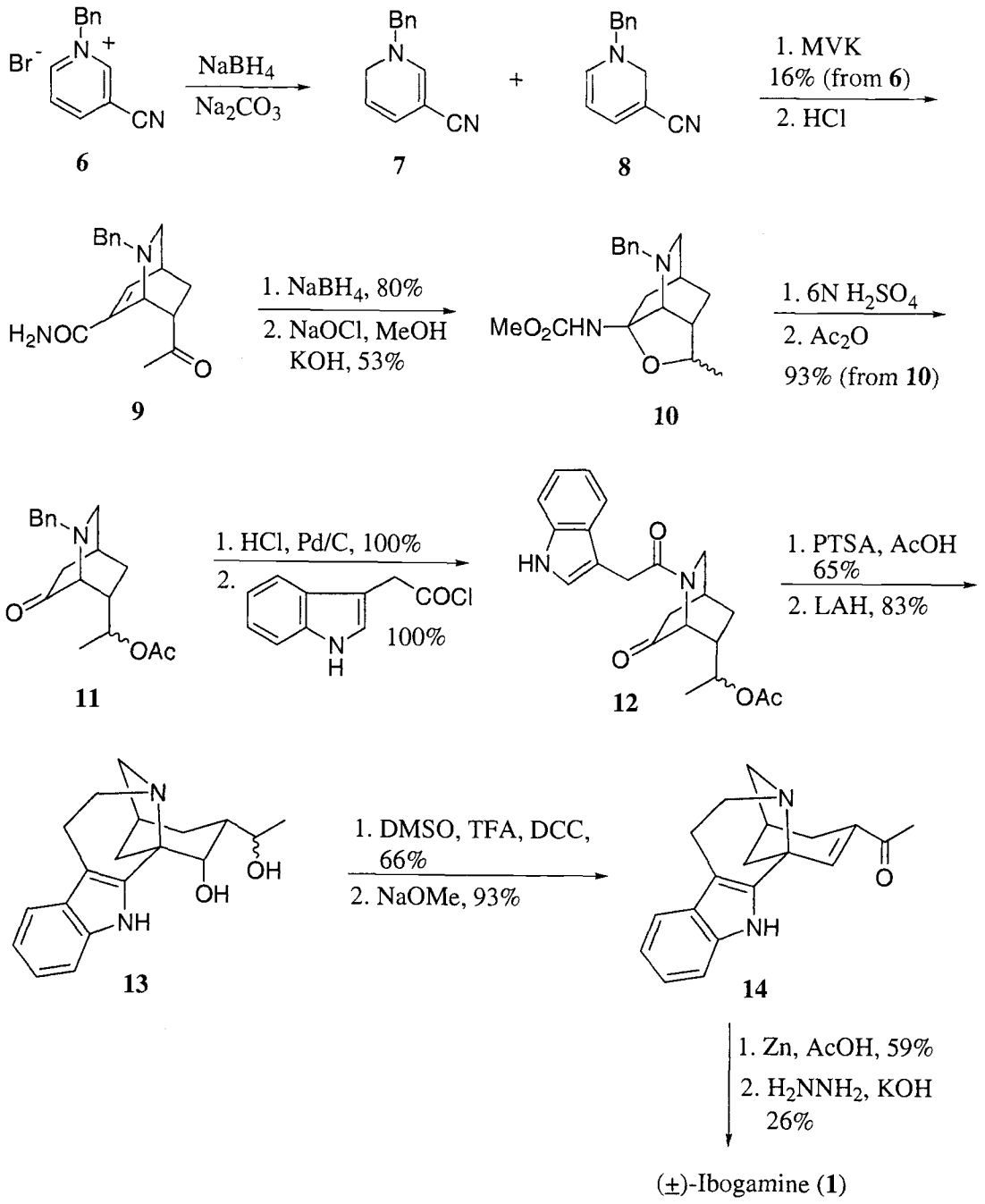
studies of ibogane-type alkaloids including (+)-catharanthine (**3**) (**Figure 1.1**).[5] Based on the observation of opposite absolute configuration, it has been postulated an intermediary stage in the biosynthesis of the ibogane-type alkaloids which could lead to both enantiomeric series.




R = Me, Vinblastine (**4**)
R = CHO, Vincristine (**5**)

(-)-Ibogamine (**1**) has been the target of synthetic investigations both for itself and as a prelude to the synthesis of the binary indole alkaloids, vinblastine (**4**) and vincristine (**5**), which have been used extensively as anticancer agents.[6]

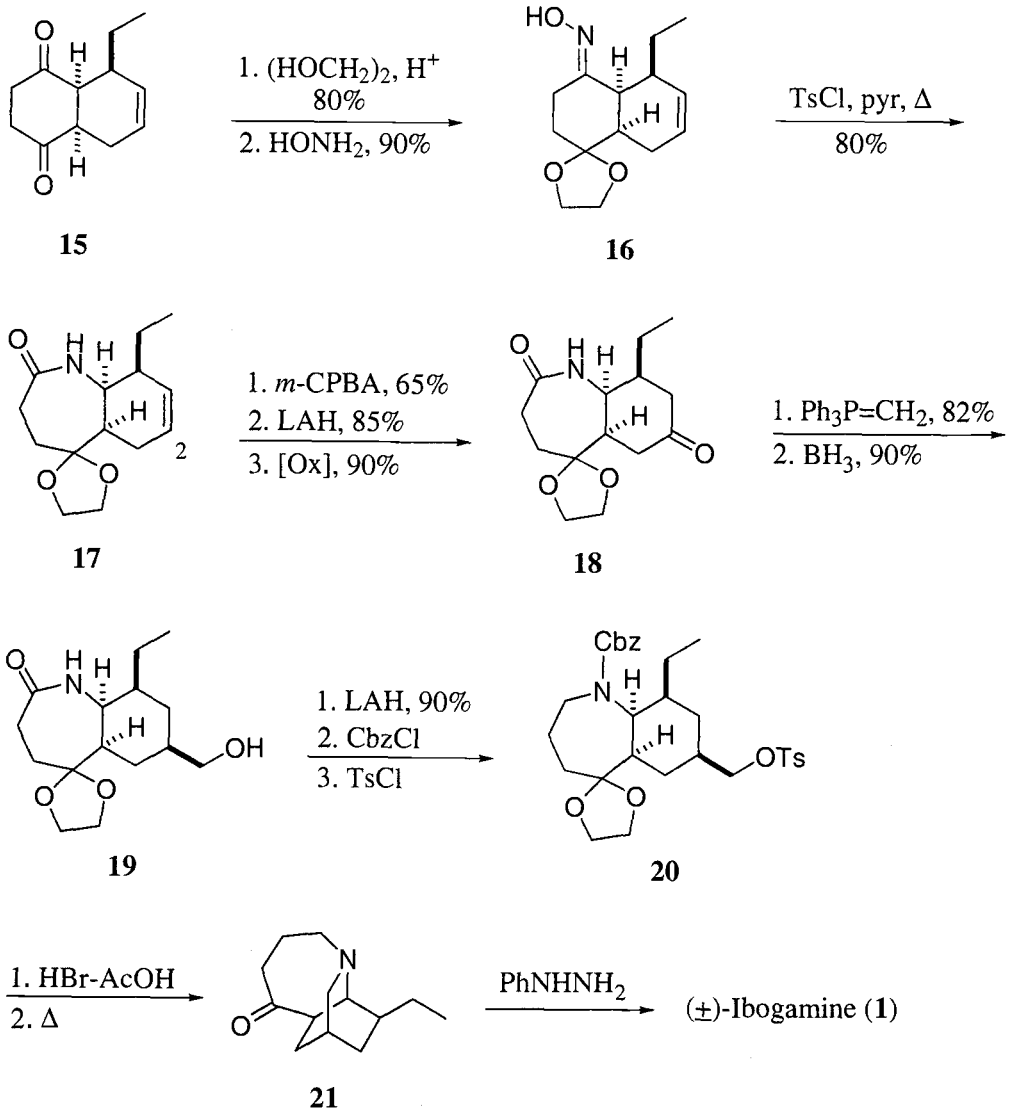
The first total synthesis of (±)-ibogamine (**1**) was reported by Büchi and coworkers in 1965 (**Scheme 1**).[7] Their synthesis started with sodium borohydride reduction of N-benzyl-3-cyanopyridinium bromide **6**. It is noteworthy that only the 1,6-dihydropyridine **7** in the mixture from reduction of **6** underwent a Diels-Alder reaction with methyl vinyl ketone to produce the isoquinuclidine **9**. Sodium borohydride reduction of **9** gave a mixture of epimeric alcohols which were subsequently oxidized with sodium hypochlorite to give the urethane **10** resulting from a Hofmann rearrangement.




**Scheme 1.** Büchi's synthesis of (±)-ibogamine

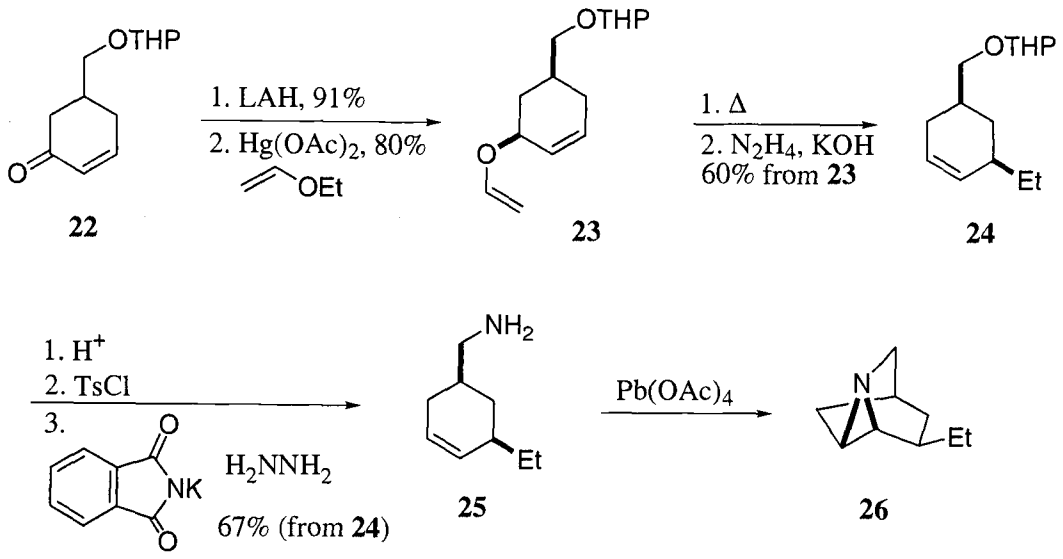
Hydrolysis of **10** followed by acetylation of the resulting pair of alcohols afforded **11** which was debenzylated and further condensed with β-indolylacetyl

chloride to yield **12**. When **12** was exposed to acidic conditions, an unexpected rearrangement of the bicyclo[2.2.2]octane skeleton to a bicyclo[3.2.1] framework occurred, and the product was identified as **13** after lithium aluminum hydride reduction. To generate ibogamine, the diol **13** was first oxidized and dehydrated to the enone **14**. Zinc reduction of **14** followed by Wolff-Kishner reduction then completed the synthesis of (±)-ibogamine (**1**).

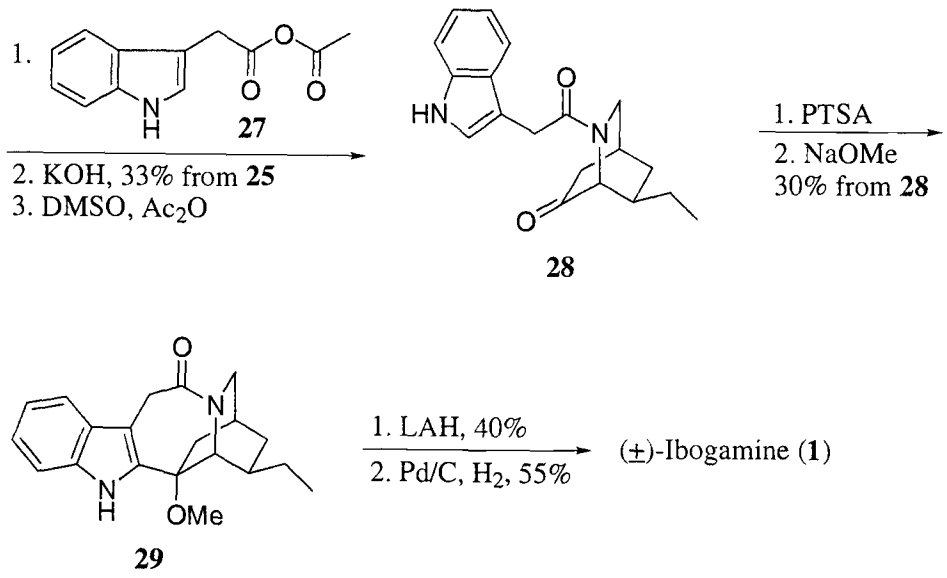



**Scheme 2.** Sallay's synthesis of (±)-ibogamine

Subsequent to Büchi's synthesis, numerous routes to racemic ibogamine were published.[8] Sallay's synthesis appeared in 1967 and began with the dione **15** which was readily available from a Diels-Alder reaction of benzoquinone with *trans* 1,3-hexadiene (**Scheme 2**).[8a] The less hindered ketone of **15** was protected as its ethylene ketal, and oxime formation at the remaining ketone provided **16**. The latter underwent a regioselective Beckmann rearrangement to give the ε-lactam **17**. In order to introduce the additional carbon at C-2 into the congested *endo* pocket of **17**, the double bond was epoxidized and the resulting epoxide was converted to the ketone **18**. A Wittig methylenation of **18** followed by hydroboration and oxidation furnished **19** which was advanced to **20** in three steps. When **20** was exposed to hydrogen bromide in acetic acid, cyclization occurred spontaneously to give the tricyclic amino ketone **21** which was successfully transformed to ibogamine by Fischer indolization.



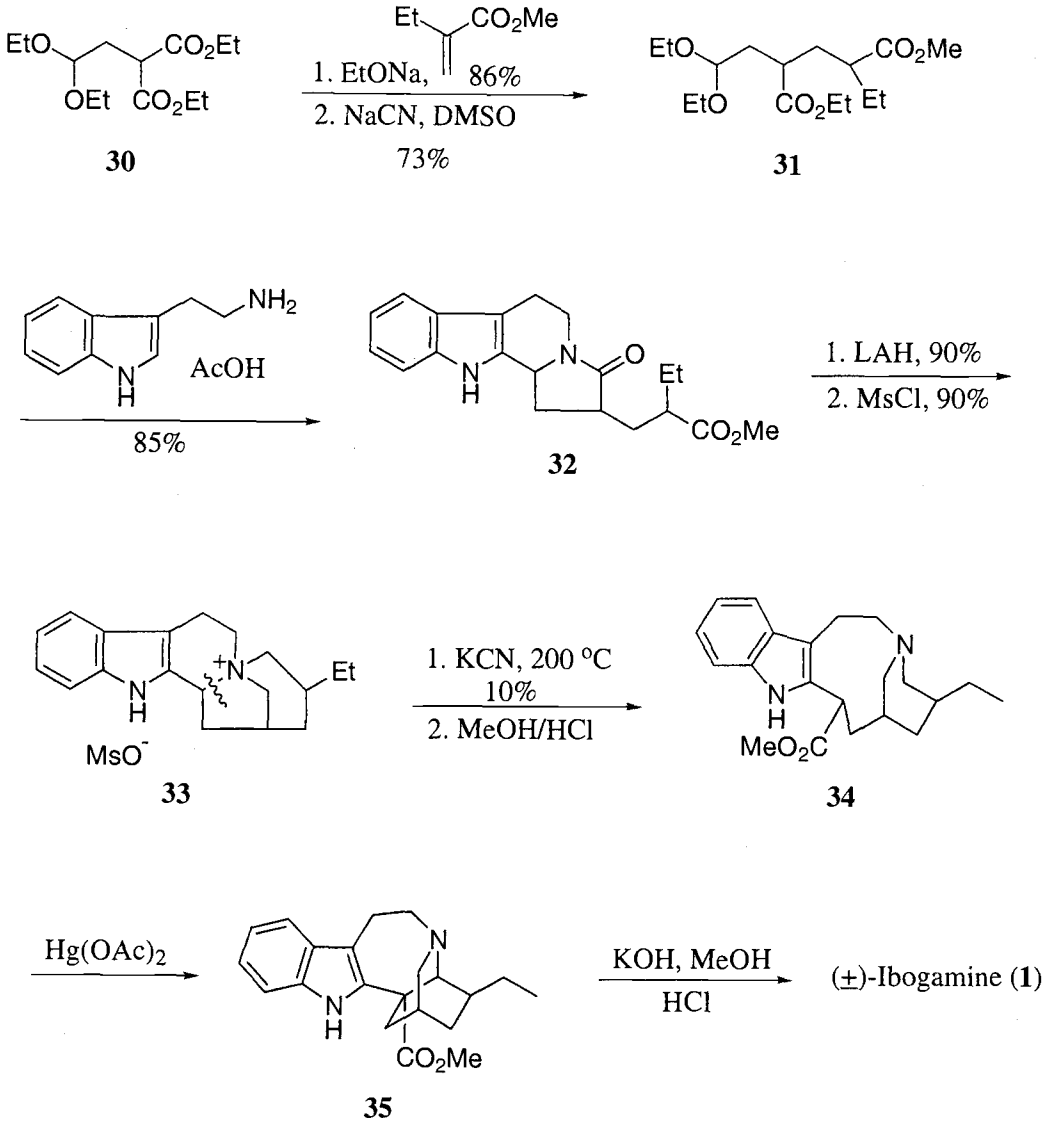

**Scheme 3.** Nagata's synthesis of (±)-ibogamine




**Scheme 3.** Nagata's synthesis of (±)-ibogamine

Nagata's synthesis of (±)-ibogamine employed a Claisen rearrangement at an early stage of the sequence to construct the *cis* disubstituted cyclohexene **25** (**Scheme 3**).[8b] The preparation of **25** was initiated by lithium aluminum hydride reduction of the enone **22** followed by vinylation to provide **23**. Claisen rearrangement of **23** and reduction of the resultant aldehyde led to **24**. Upon deprotection of **24**, the resulting alcohol was converted to its tosylate which was subjected to a Gabriel amine synthesis to afford **25**. Lead tetraacetate mediated oxidation of **25** generated the bridged aziridine **26** which was immediately acylated with the anhydride **27**, and the product was further oxidized to the ketone **28**. Cyclization of **28** was effected in the presence of *p*-toluenesulfonic acid, and subsequent methanolysis provided the lactam **29**. For completion of the synthesis, **29** was first reduced with lithium aluminum hydride to give a

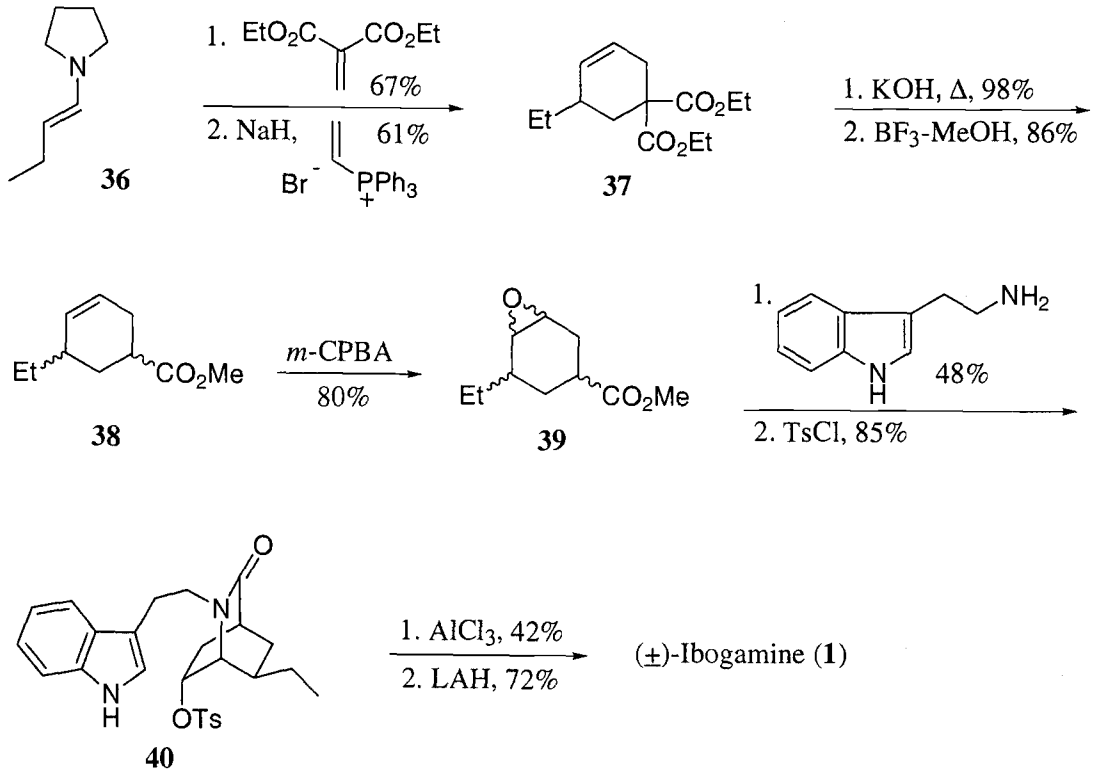
carbinolamine which was dehydrated and hydrogenated to furnish (±)-ibogamine (**1**).




**Scheme 4.** Atta-ur-Rahman's synthesis of (±)-ibogamine

The key reaction of Atta-ur-Rahman's approach involved cleavage of the pentacyclic quaternary salt **33** using activation by the indole nucleus (**Scheme 4**).[8e] En route to the synthesis of **33**, Michael addition of ethyl 2-carbethoxy-4,4-

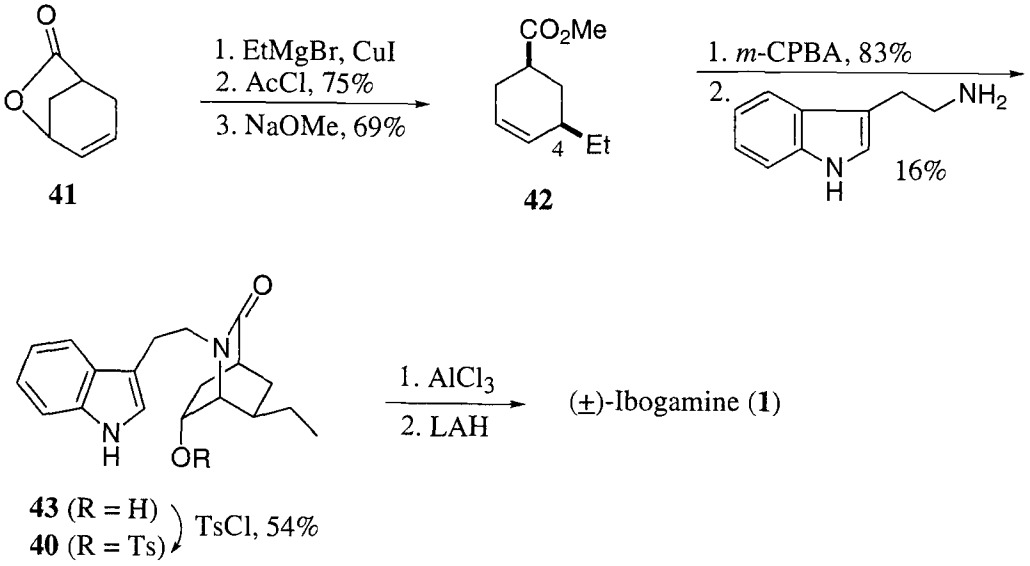
diethoxybutanoate **30** to methyl α-ethylacrylate followed by a Krapcho decarbethoxylation furnished **31**. Direct condensation of **31** with tryptamine produced **32** which was reduced and mesylated to yield the quaternary salt **33**. When **33** was heated with potassium cyanide at 200 °C, the desired C-N bond cleavage occurred, and subsequent methanolysis of the intermediate nitrile yielded **34**. Mercuric acetate mediated oxidation of **34** followed by decarbomethoxylation completed the synthesis of (±)-ibogamine (**1**).




**Scheme 5.** Kuehne's synthesis of (±)-ibogamine

Kuehne's synthesis began with alkylation of 1-pyrrolidinobutene **36** with diethyl methylenemalonate followed by cyclization with triphenylvinylphosphonium bromide (**Scheme 5**).[8g] The resulting dicarboxylate **37**

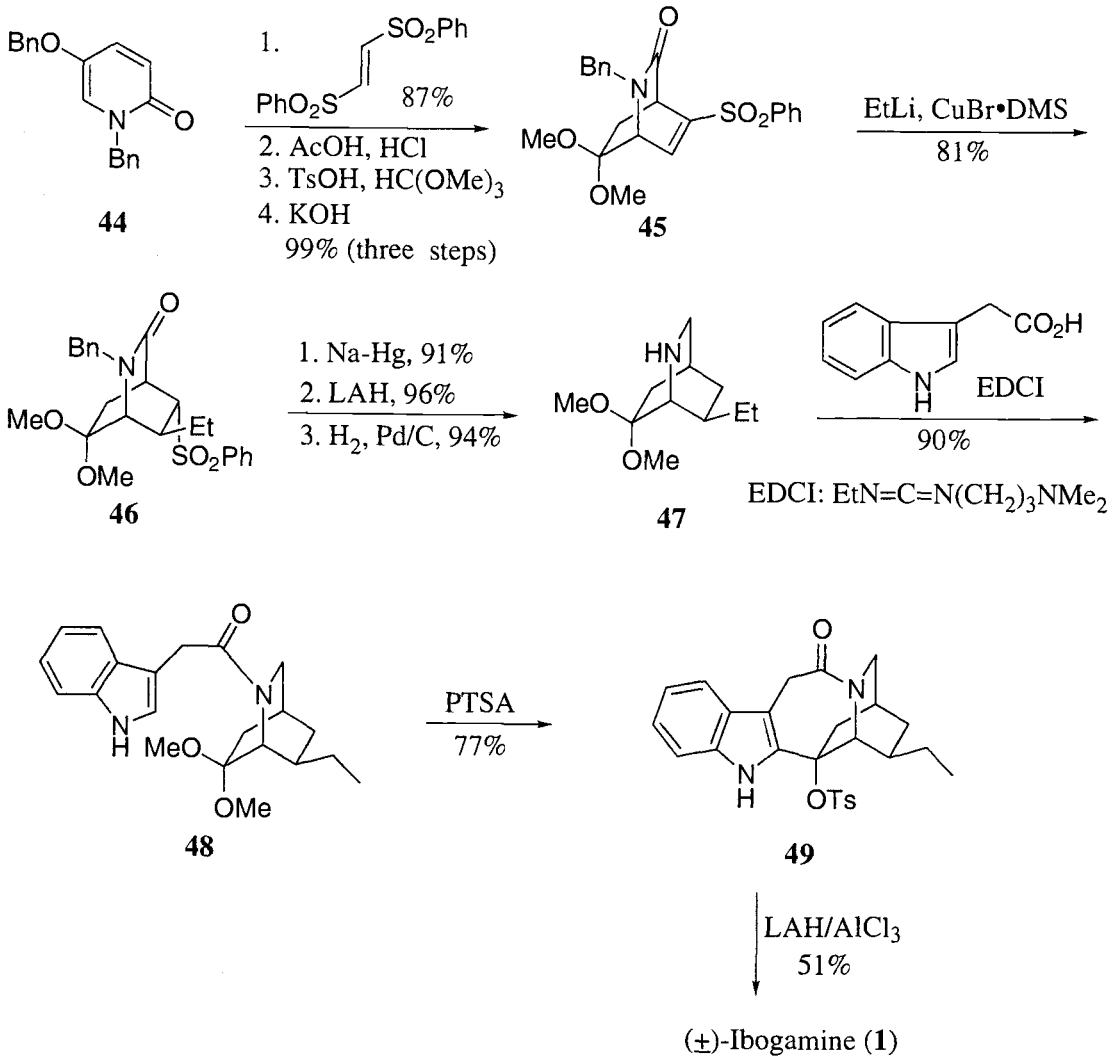
was hydrolyzed and then esterified to give a 1:1 mixture of *cis* and *trans* esters **38**. Epoxidation of **38** with *m*-chloroperbenzoic acid followed by condensation with tryptamine provided an alcohol which was converted to its tosylate **40**. The synthesis was completed by cyclization of **40** with aluminum chloride to provide 5-oxoibogamine which was reduced with lithium aluminum hydride to (±)-ibogamine (**1**).




**Scheme 6.** Huffman's formal synthesis of (±)-ibogamine

Shortly after Kuehne's synthesis was completed, Huffman and co-workers published their investigation which adopted a similar strategy to that of Kuehne in constructing a N-β-(indolylethyl)isoquinuclidine (**Scheme 6**).[8h] They found that addition of ethylmagnesium bromide in the presence of copper(I) iodide to bicyclic lactone **41** generated the $S_N2'$ product which was esterified and then equilibrated to give a 3:2 epimeric mixture at C-4 of **42**. Epoxidation of the mixture followed by condensation with tryptamine furnished the alcohol **43** which

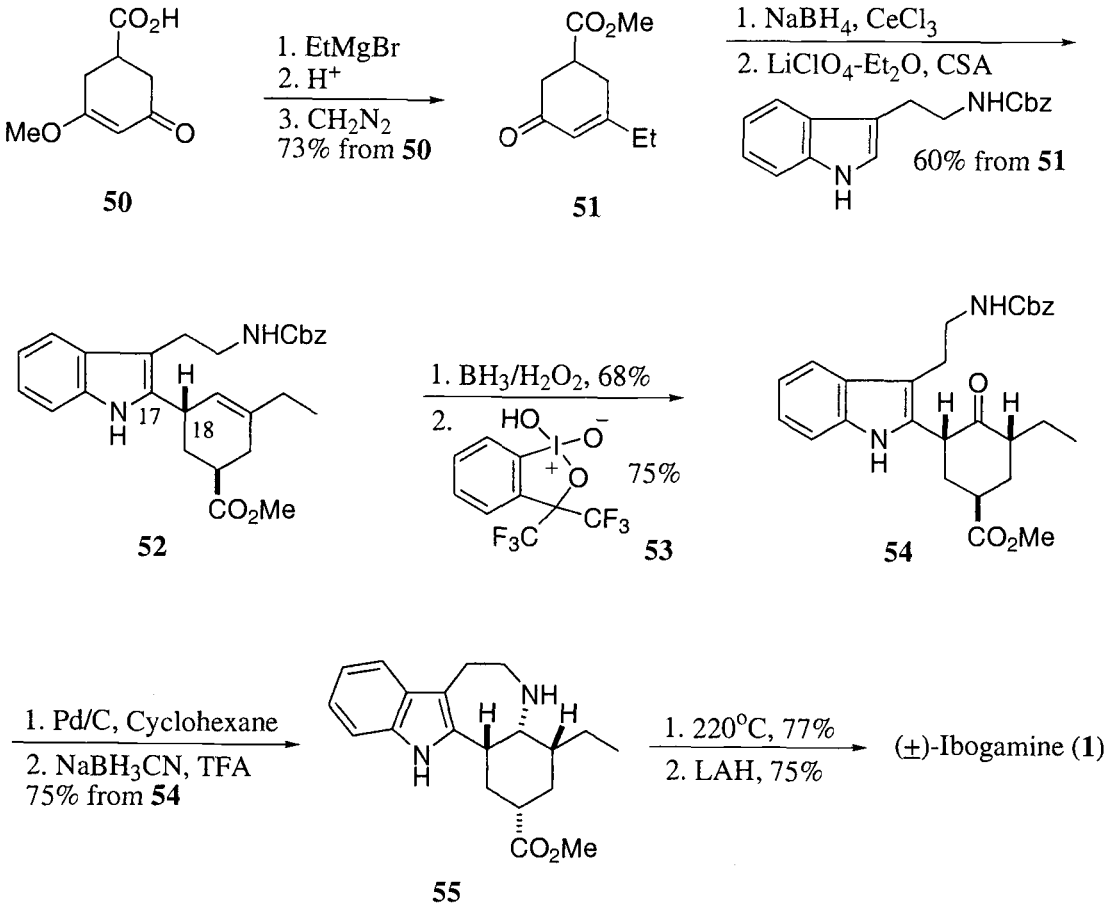
was converted to its tosylate **40**. Since the conversion of **40** to (±)-ibogamine (**1**) was already described by Kuehne,[8g] the preparation of **40** constituted a formal synthesis of the racemic natural product.




**Scheme 7.** Herdeis's synthesis of (±)-ibogamine

In a recent synthesis of (±)-ibogamine by Herdeis and coworkers, a Diels-Alder reaction of 1-benzyl-5-benzyloxy-2(1*H*)-pyridone **44** with (*E*)-1,2-bis-(phenylsulfonyl)ethene was used to construct the isoquinuclidine ring system of

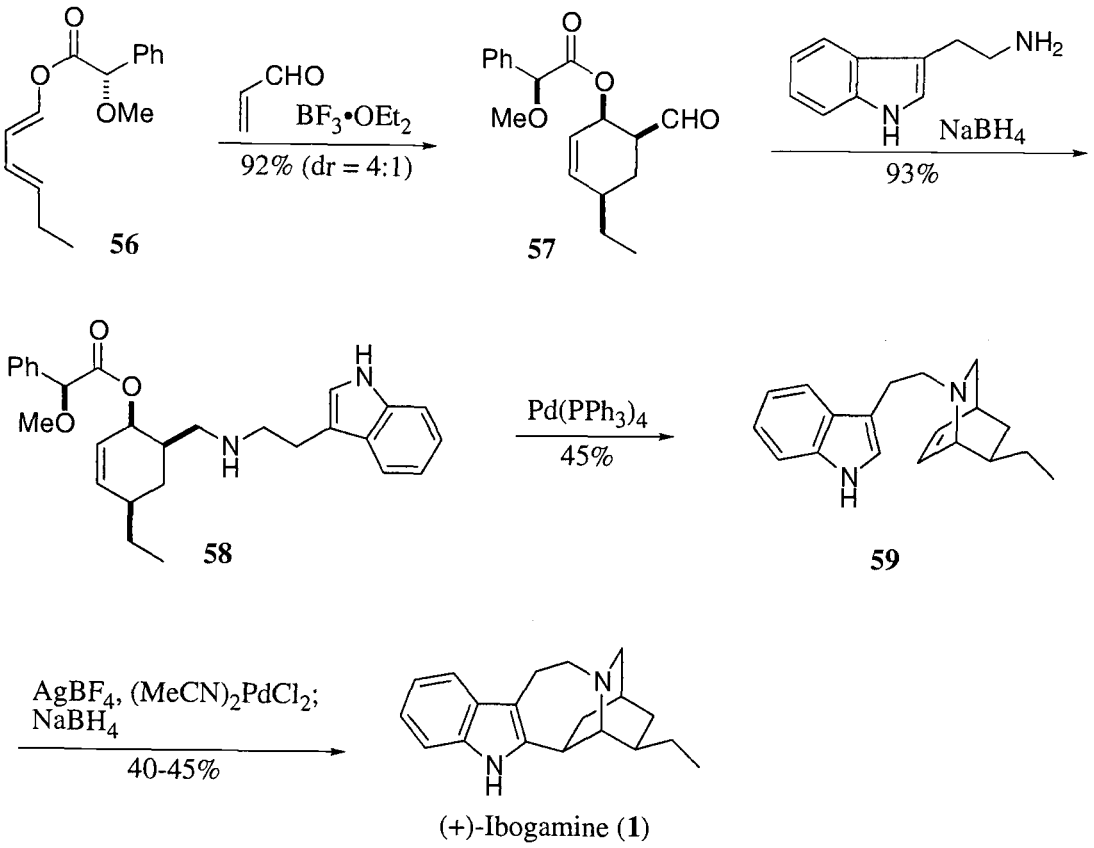
**45** (**Scheme 7**).[8i] A subsequent stereocontrolled cuprate addition gave the *trans* adduct **46** which was advanced to the bicyclic amine **47**. The condensation of **47** with 3-indolylacetic acid afforded **48** which spontaneously cyclized in the presence of *p*-toluenesulfonic acid to the ε-lactam **49**. The final step involved reduction with lithium aluminum hydride and aluminum chloride to furnish (±)-ibogamine (**1**).




**Scheme 8.** Grieco's synthesis of (±)-ibogamine

Grieco and coworkers have described a novel approach to ibogamine which featured formation of the $C_{17}$-$C_{18}$ bond at an early stage in order to direct

construction of a hydroazepine ring (**Scheme 8**).[8j] Thus, a Grignard reaction on the known vinylogous ester **50**, followed by an acidic workup and esterification, first gave the enone **51**. Luche reduction of **51** afforded a diastereomeric mixture of alcohols which was condensed with N-carbobenzyloxytryptamine to give **52**. Stereoselective hydroboration of **52** followed by oxidation with the hypervalent iodine complex **53** furnished the ketone **54**. Following removal of the amine protecting group from **54** using catalytic hydrogenation, intramolecular reductive amination provided the tetracyclic amine **55**. Final intramolecular cyclization of **55** and lithium aluminum hydride reduction of the resulting lactam completed the synthesis of (±)-ibogamine (**1**).




**Scheme 9.** Trost's synthesis of (+)-ibogamine

Only one asymmetric pathway to ibogamine has been reported and this concluded at a 80:20 mixture favoring the non-natural (+)-enantiomer (**Scheme 9**).[8k] Trost and coworkers used a catalyzed Diels-Alder reaction of the chiral diene **56** to construct the enantioenriched cyclohexene **57**. The latter underwent reductive amination with tryptamine to afford the amine **58** which cyclized in the presence of a palladium(0) catalyst to give the isoquinuclidine **59**. Completion of the synthesis was effected by a second palladium-mediated cyclization followed by a reductive workup. The synthesis of (+)-ibogamine in 17% overall yield and eight steps demonstrated that a concise approach to this structure was possible, albeit in enantiomerically impure form.

In summary, ibogamine (**1**) has been the target of numerous synthetic investigations, in large part due to its intriguing structure and interesting biological activities. The majority of the approaches to (±)-ibogamine have adopted a common strategy which constructs a N-β-(indolylethyl)isoquinuclidine and then effects subsequent cyclization to a hydroazepine ring . Our plan for the synthesis of (-)-ibogamine built upon the earlier work of Sallay,[8a] but foresaw the possibility of turning Sallay's route into one of greater economy by employing a more highly functionalized diene in the initial Diels-Alder reaction. More importantly, we postulated that the Diels-Alder reaction planned for our synthesis could be mediated by a chiral catalyst, thus leading to an asymmetric synthesis of natural (-)-ibogamine (**1**). This work will be described in detail in the following chapter.

## Results and Discussion

The asymmetric Diels-Alder reaction has become one of the most widely used constructs for the assembly of enantiomerically enriched chiral carbocycles.[9] In its catalyzed version, the reaction offers an especially powerful synthetic method which can lead to adducts from achiral materials in good yield and high enantiomeric excess at or below ambient temperature.[10] Catalyzed asymmetric cycloadditions have been particularly successful with dienophiles which can achieve a high level of organization in their coordination with Lewis acids.

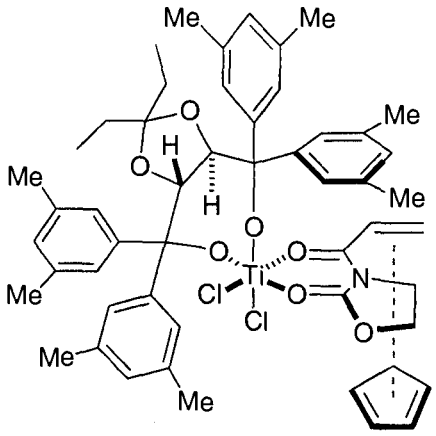
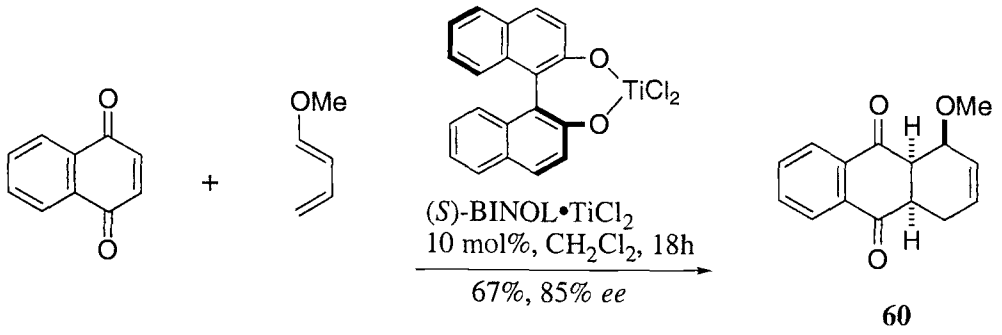



**Figure 1.2** Two-point ligation of β-dicarbonyl compounds

One class of dienophiles that meets this condition includes β-dicarbonyl compounds. These structures can form a relatively rigid, highly asymmetric, activated complex with a chiral catalyst by two-point ligation (**Figure 1.2**).[11,12] In

this complex, only one face of the dienophile is exposed for reaction with its diene partner resulting in high enantioselectivity.

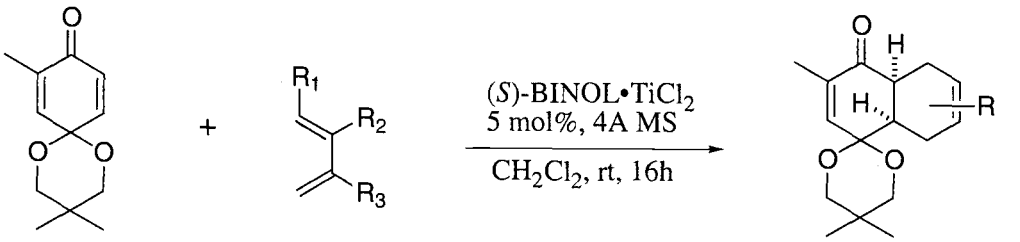



60

**Scheme 10**

The Diels-Alder reaction with a simple α,β-unsaturated ketone or a 1,4-quinone raises the question of whether stereocontrol can be exercised effectively by single-point ligation of a chiral catalyst with the lone pair of electrons of only one carbonyl group. This question was first answered in the affirmative by Mikami who showed that the reaction of 1,4-naphthoquinone with 1-methoxybuta-1,3-diene in the presence of a BINOL-Ti(IV) catalyst led to diketone **60** in high enantiomeric excess (**Scheme 10**).[13]

Subsequently, Corey and Breuning reported the participation of 1,4-benzoquinone monoketal **61** in asymmetric Diels-Alder reactions catalyzed by Mikami's BINOL-$TiCl_2$ system (**Scheme 11**).[14] In this paper, the authors announce that although the structure of Mikami's catalyst is unknown, it appears to be chloride free and to involve μ-oxo bridges between at least two Ti units.

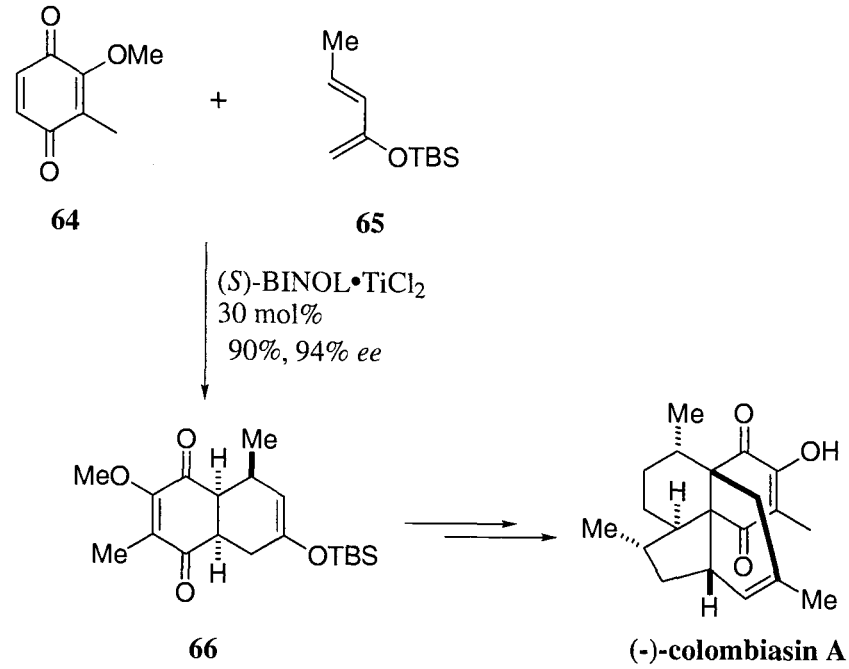



**61**

**62a**, $R_1$ = Me, $R_2$ = $R_3$ = H
**62b**, $R_1$ = OMe, $R_2$ = $R_3$ = H
**62c**, $R_1$ = $R_2$ = $R_3$ = H
**62d**, $R_1$ = H, $R_2$ = $R_3$ = Me
**62e**, $R_1$ = H, $R_2$ = Me, $R_3$ = H

**63a**, 90% (99% ee)
**63b**, 90% (99% ee)
**63c**, 95% (95% ee)
**63d**, 95% (90% ee)
**63e**, 91% (96% ee)

**Scheme 11**



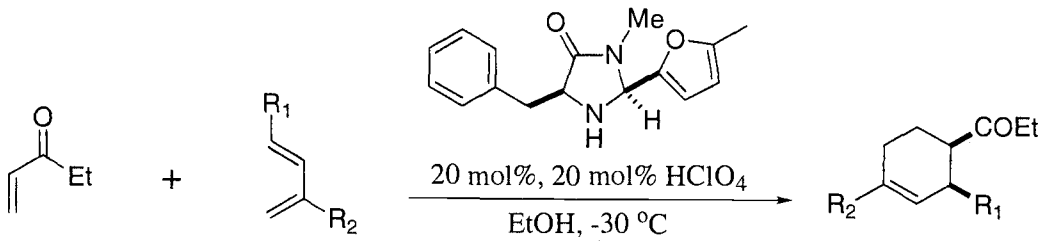

**64** **65**

**66** **(-)-colombiasin A**

**Scheme 12**

Nicolaou and coworkers employed a catalytic asymmetric Diels-Alder reaction in their total synthesis of (-)-colombiasin A with the addition of quinone **64** to diene **65** (**Scheme 12**).[15] This reaction produced the cycloadduct **66** in high

enantiomeric excess. However, the argument for single-point ligation is less clear in this case due to the possible bidentate coordination involving the methoxy group of **64** with the catalyst.




**67a**, $R_1$ = OMe, $R_2$ = H
**67b**, $R_1$ = NHCbz, $R_2$ = H
**67c**, $R_1$ = H, $R_2$ = Ph
**67d**, $R_1$ = Me, $R_2$ = Me
**67e**, $R_1$ = H, $R_2$ = Me

**68a**, 88% (96% ee)
**68b**, 91% (98% ee)
**68c**, 92% (90% ee)
**68d**, 90% (90% ee)
**68e**, 79% (85% ee)

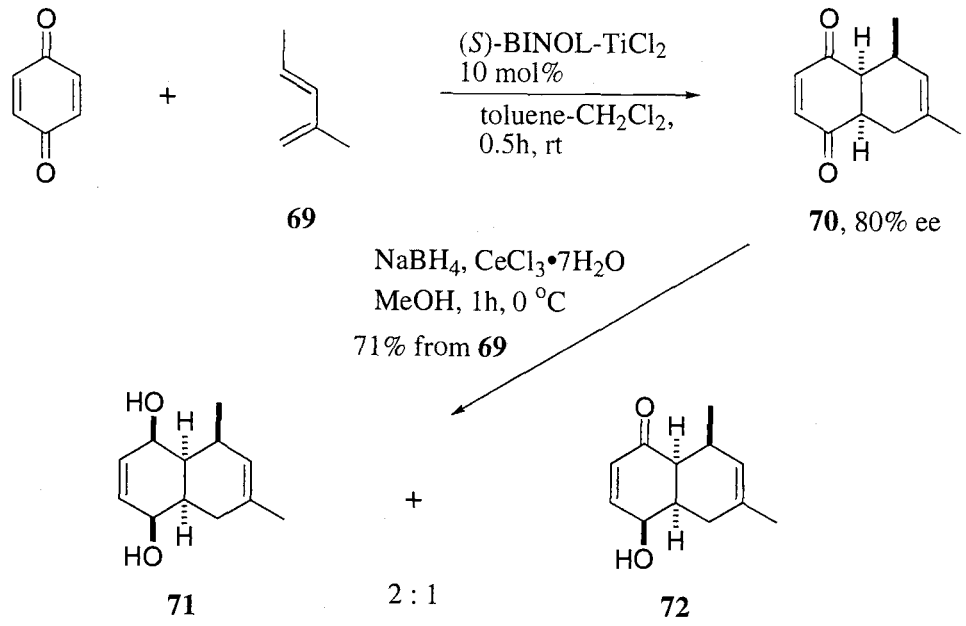
**Scheme 13**

Recently, MacMillan and Northrup showed that α,β-unsaturated ketones, for which single-point carbonyl ligation is obligatory, undergo Diels-Alder addition to various dienes in the presence of a chiral imidazolidinone to give cycloadducts in moderate to high enantiomeric excess. However, the generality of this process remains to be established (**Scheme 13**).[16]

In principle, any asymmetric catalyst attached to one of the carbonyl groups of 1,4-benzoquinone breaks the $D_{2d}$ symmetry of this dienophile and should therefore be capable of producing an asymmetric Diels-Alder adduct if (i) the 1,3-diene component is not symmetrical, and (ii) the rate of the catalyzed reaction substantially exceeds that of the uncatalyzed process. Despite the aforementioned examples which suggest that 1,4-benzoquinone could be employed successfully in an asymmetric Diels-Alder reaction with a chiral

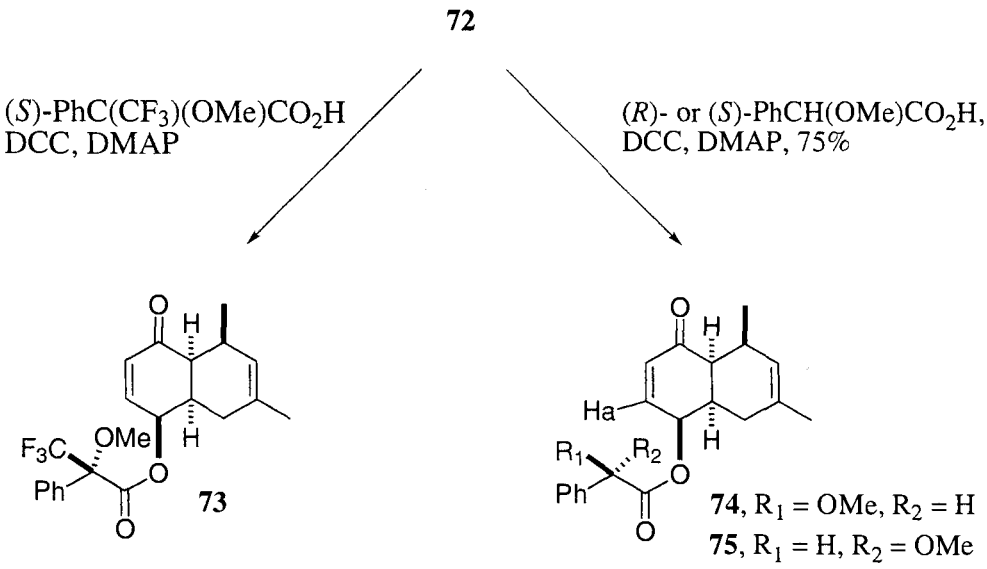
catalyst, a general strategy which could be used to prepare Diels-Alder adducts of quinones in high enantiomeric purity remained to be demonstrated. Thus, our initial goal was to investigate the asymmetric Diels-Alder reaction of 1,4-benzoquinone with several dienes in the presence of a chiral catalyst. If successful, we hoped to apply this process in an asymmetric synthesis of the indole alkaloid (-)-ibogamine (**1**).

Our first experiments with 1,4-benzoquinone, various dienes, and the TADDOL-$TiCl_2$ catalyst[17] at ambient temperature were not encouraging. The enantiomeric excess of Diels-Alder adducts was generally below 60%, and it became clear that this catalyst system was not sufficiently active to accelerate cycloaddition at lower temperatures where improved stereoselectivity might be observed. We therefore turned to the Mikami BINOL-$TiCl_2$ catalyst, a proven commodity in the context of asymmetric Diels-Alder addition to naphthoquinone,[13] and we were pleased to find that Diels-Alder adducts of 1,4-benzoquinone could be obtained in good yield and high enantiomeric excess with this catalyst.[18]

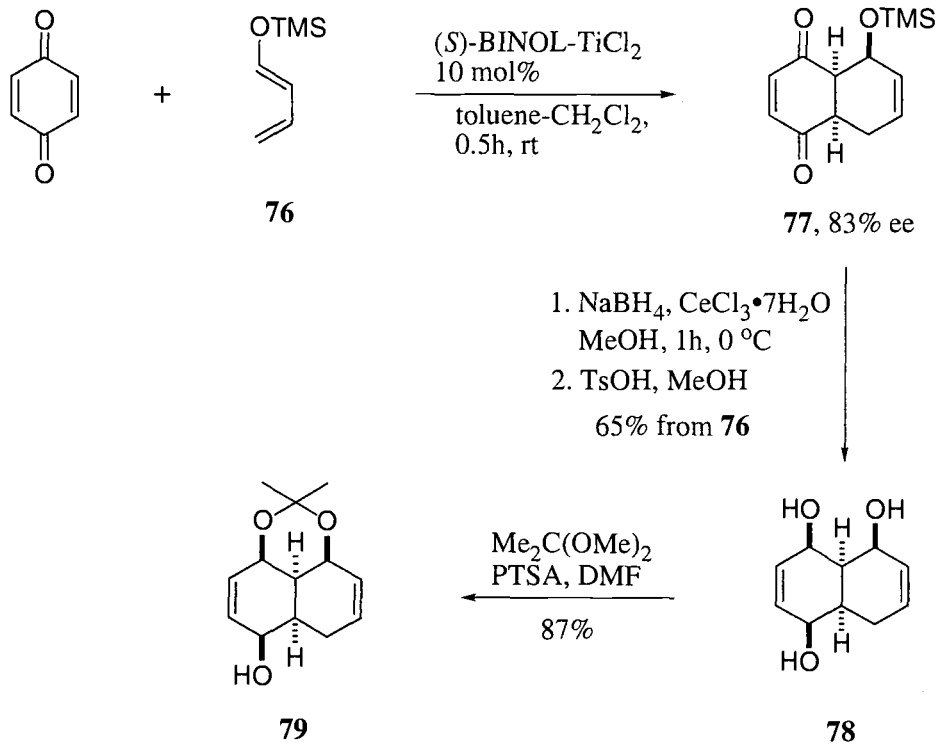



**Scheme 14**

Thus, addition of 2-methylpenta-1,3-diene to benzoquinone in the presence of 10 mol % of (*S*)-BINOL-$TiCl_2$ gave **70** in 80% ee (**Scheme 14**). Because the dione **70** was unstable to chromatography it was immediately subjected to Luche reduction[19] with sodium borohydride and cerium(III) chloride heptahydrate to afford a mixture of diol **71** and hydroxy ketone **72.** The latter was converted to its (*S*) Mosher ester **73**,[20] which permitted the determination of ee by NMR analysis of its $^{19}F$ spectrum; **72** was also esterified with (*R*)- and (*S*)-mandelic acids to produce mandelates **74** and **75** (**Scheme 15**). Shielding of $H_a$ by the phenyl ring of (*R*)-mandelate **74** relative to its (*S*) diastereomer **75** and applying Trost's model[21] enabled the absolute configuration of these esters and hence **70** to be determined as shown.

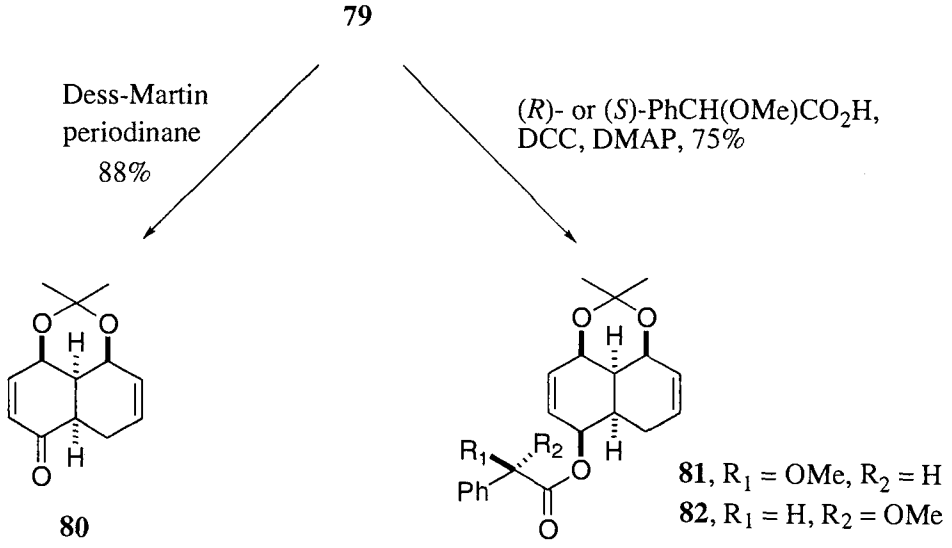



**Scheme 15**



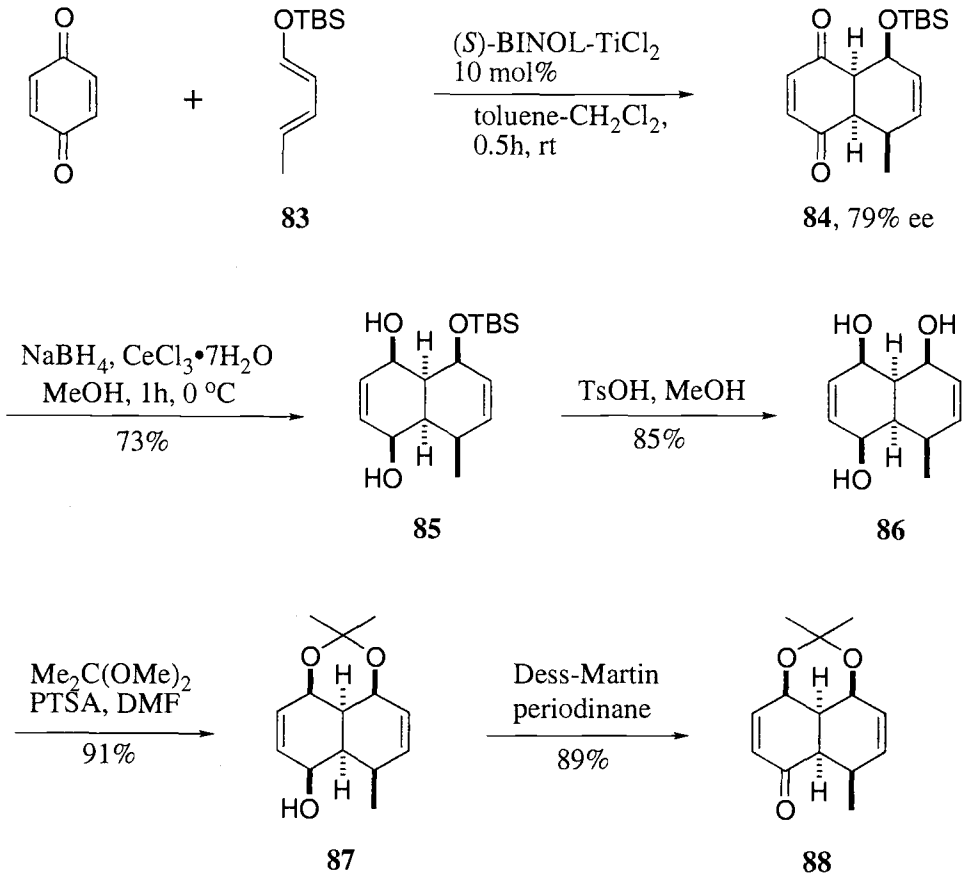

**Scheme 16**

We next examined the cycloaddition of silyloxydiene **76** with 1,4-benzoquinone in the presence of (*S*)-BINOL-$TiCl_2$ and again found that the reaction was greatly accelerated relative to the uncatalyzed process (**Scheme 16**). Luche reduction[19] of cycloadduct **77** and deprotection of the resultant diol provided the triol **78**. Ketal formation of **78** with 2,2-dimethoxypropane and *p*-toluenesulfonic acid gave the acetonide **79**.




**Scheme 17**

Dess-Martin oxidation of the protected allylic alcohol **79** led to α,β-unsaturated ketone **80** which allowed us to determine its ee (83%) by HPLC analysis using a chiral OD column (**Scheme 17**). Although none of the substances in the series originating from diene **76** could be crystallized, the (*R*)- and (*S*)-mandelates, **81** and **82**, prepared from **79** established that **77** possessed the absolute configuration shown.[21]




**Scheme 18**

Silyloxydiene **83** and benzoquinone were engaged in the asymmetric Diels-Alder reaction with (*S*)-BINOL-$TiCl_2$ to give the cycloadduct **84**, which was immediately reduced to diol **85** under Luche conditions (**Scheme 18**).[19] Cleavage of the silyl ether from **85** and acetonide formation afforded **87**. Alcohol **87** was oxidized to the α,β-unsaturated ketone **88** to determine its ee (79%) by HPLC analysis using a chiral OD column. Fortunately, diol **85** was conveniently crystalline which enabled its absolute configuration to be determined by X-ray crystallographic analysis (**Figure 1.3**).

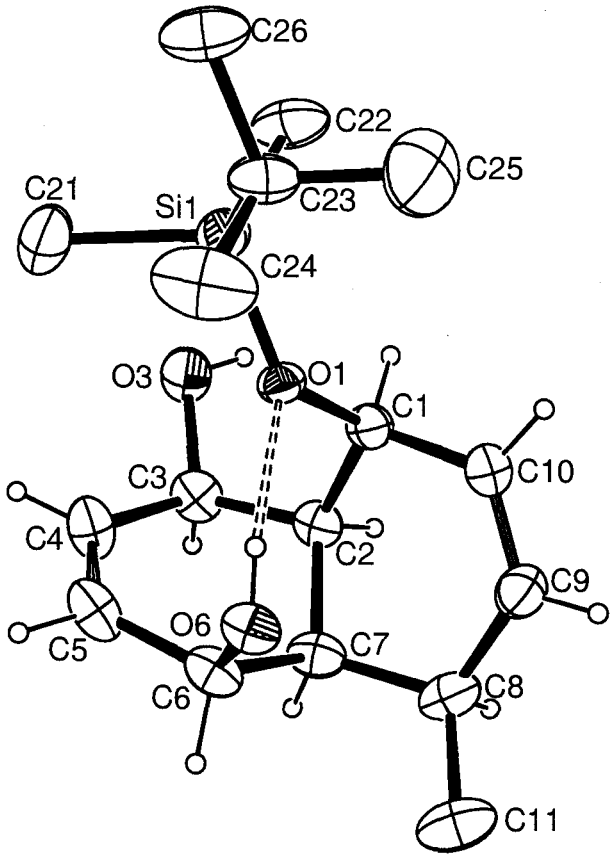
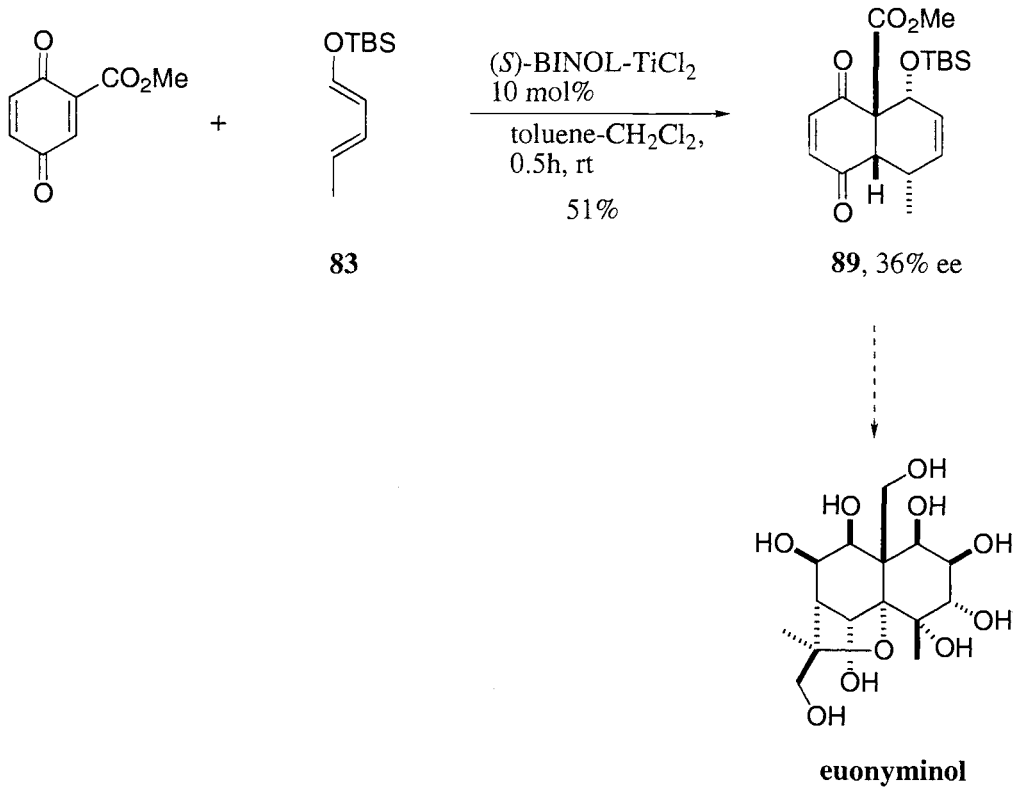



**Figure 1.3** ORTEP representation of X-ray structure of **85**

Thus, all three cycloadducts, **70**, **77**, and **84**, obtained with the (*S*)-BINOL-$TiCl_2$ complex are found to have the same absolute configuration. Furthermore, they are in the same enantiomeric series that Mikami observed with 1,4-naphthaquinone using the same catalyst, lending confidence to future stereochemical predictions that may be made with this system.

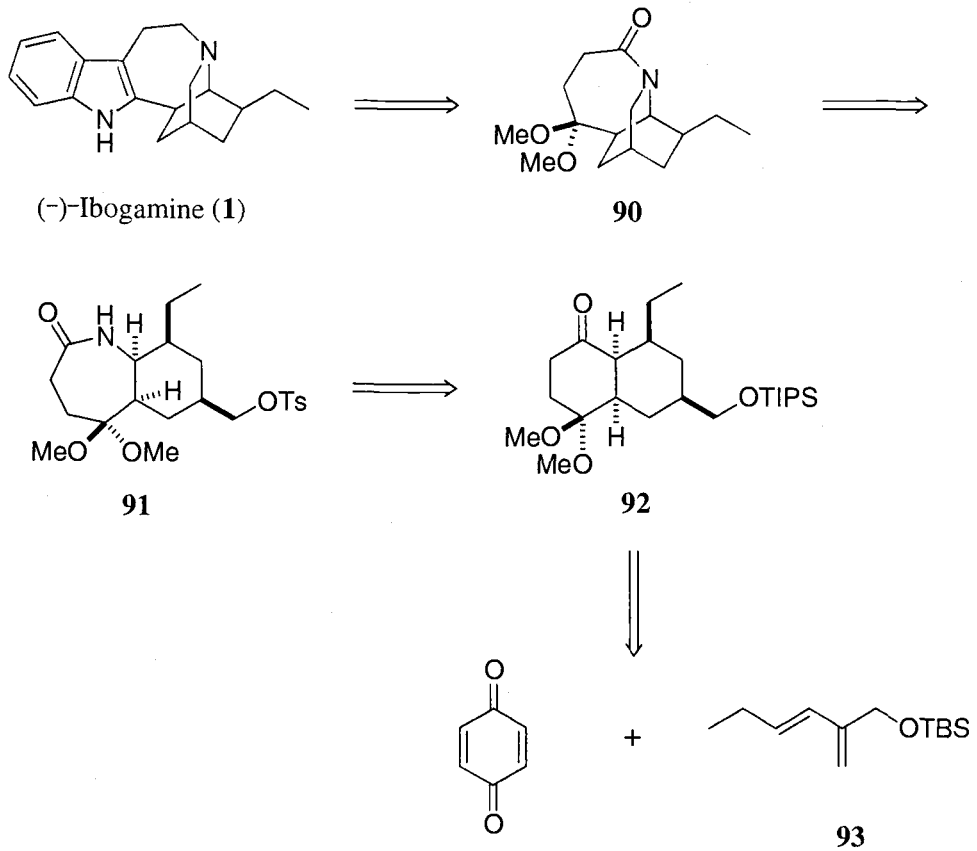



**83** **89**, 36% ee

**euonyminol**

**Scheme 19**

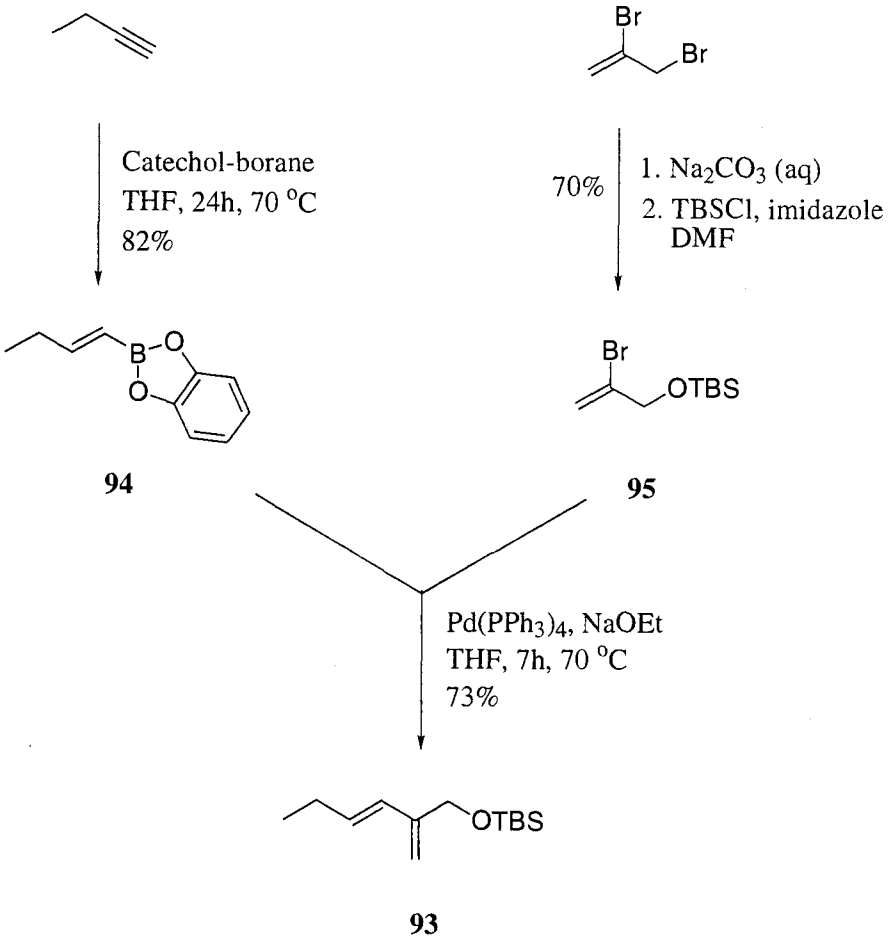
Unfortunately, an attempt to extend the BINOL-$TiCl_2$ catalyzed Diels-Alder reaction to methyl 1,4-benzoquinone-2-carboxylate was less successful (**Scheme 19**). The latter, prepared by oxidation of methyl 2,5-dihydroxbenzoate as reported by Kraus[22] and used in situ, was reacted with diene **83** to give cycloadduct **89** in only 36% ee. The racemic version of **89** has provided a convenient platform from which to launch syntheses of polyhydroxylated sesquiterpenoids of the agarofuran family, including (±)-euonyminol,[23] but an efficient asymmetric entry to the highly functionalized decalin core of this group remains elusive at this point.




**Scheme 20**

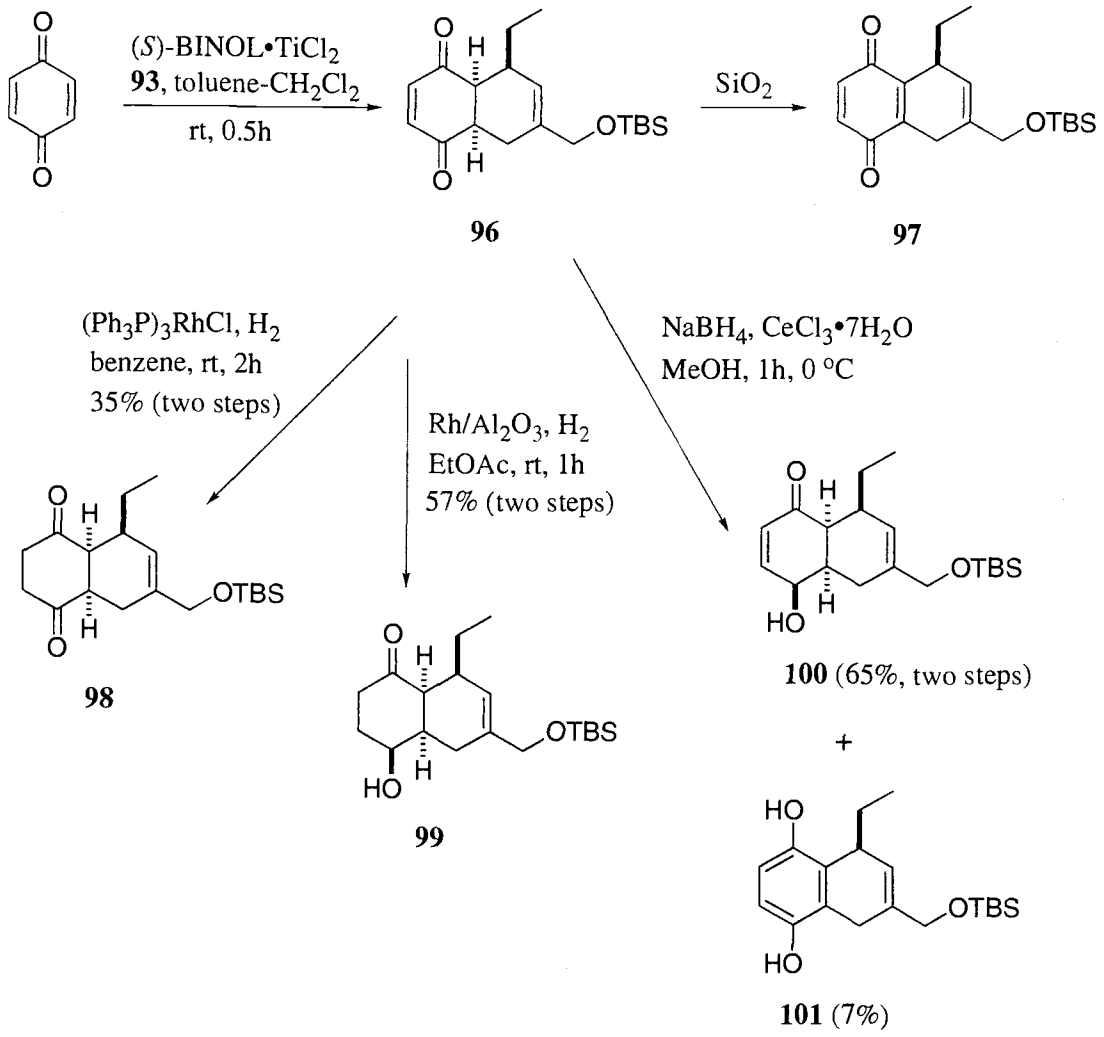
On the other hand, our effort to exploit the catalyzed asymmetric Diels-Alder reaction of 1,4-benzoquinone in a synthesis of the indole alkaloid (–)-ibogamine (**1**) was more rewarding. We envisaged the tricyclic lactam **90** with the absolute configuration shown as a plausible precursor of (-)-ibogamine (**1**) and conjectured that this intermediate could be accessed via an intramolecular alkylation of **91** (**Scheme 20**). A synthesis of the ε-lactam **91** would be possible by Beckmann rearrangement of the oxime of ketone **92**. The *cis*-decalin **92** could be conveniently derived from a Diels-Alder reaction of benzoquinone with the diene **93**. Our first focal point therefore became the preparation of a 1,3-

disubstituted butadiene **93** which carried appendages appropriate for constructing the non-indolic portion of **1** without the need to forge additional carbon-carbon bonds beyond the Diels-Alder step.




**Scheme 21**

The diene **93** was obtained by a Suzuki coupling of (*E*)-boronate **94**, prepared by the reaction of 1-butyne with catecholborane,[24] with the 2-bromoallyl silyl ether **95** (**Scheme 21**). The latter was acquired from 2-bromoallyl bromide by hydrolysis and protection of the resultant alcohol.[25]




**Scheme 22**

Although the reaction of **93** with benzoquinone was cleanly *endo* selective, completion of the uncatalyzed cycloaddition required two hours at 80 °C (**Scheme 22**). By contrast, the same Diels-Alder addition in the presence of Mikami's (*S*)-BINOL-$TiCl_2$ complex[13] (10 mol%) proceeded to completion in less than 30 minutes at room temperature and gave a single *endo* adduct **96** in high yield. The relative stereochemistry of **96** was deduced from the coupling

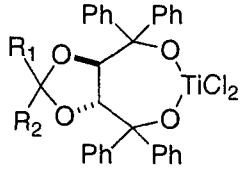
constant ($J$ = 5.6 Hz) between the ring junction protons. As with previous adducts, **96** was unstable towards chromatographic purification on silica, which resulted in its conversion to the quinone **97**, and it was not possible to determine either the enantiomeric purity or the absolute configuration of **96**. For this reason, the crude Diels-Alder adduct **96** was subjected to hydrogenation over either Wilkinson's catalyst or rhodium on alumina to give **98** in one case and **99** in the other. However, when **96** was exposed to Luche reduction[19] with sodium borohydride and cerium(III) chloride, the stable *endo* hydroxy ketone **100** resulting from reduction of the less hindered carbonyl could be purified for further assay. A small amount (7%) of the dihydronaphthalene **101** was also isolated from this reaction, presumably a consequence of tautomerization of the diketone **96**.

| Concentration of BINOL-$TiCl_2$ (mol %) | Yield of **100** (%) | ee of **100** (%) |
|---|---|---|
| 10 | 65 | 81 |
| 20 | 62 | 82 |
| 30 | 65 | 87 |

**Table 1.1** BINOL-$TiCl_2$ catalyzed Diels-Alder reaction of **93** with 1,4-benzoquinone

HPLC analysis of **100**, employing a chiral OD column and a hexane-isopropanol mixture as eluent, established that the enantiomeric excess of this substance, and hence **96**, was 81% (**Table 1.1**). An increase in the catalyst concentration from 10 mol% first to 20% and then to 30 mol% improved the ee of

**100**, but no enhancement beyond 87% ee occurred with increasing quantities of the catalyst. It is worth mentioning that Mikami's BINOL-$TiCl_2$ complex is only effective at room temperature; an attempt to catalyze the Diels-Alder reaction of **93** with benzoquinone below ambient temperature was not successful.



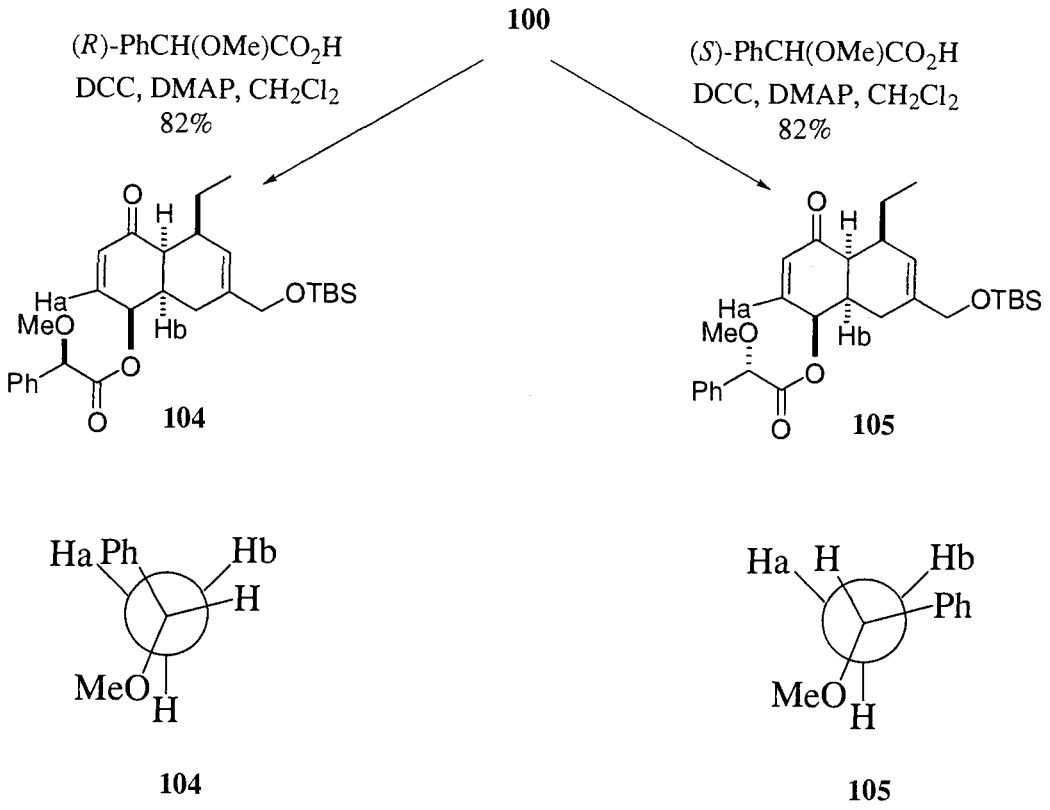

**102**, $R_1$=Ph, $R_2$=Me
**103**, $R_1$= $R_2$ =Et

| Catalyst (30 mol%) | Temperature (°C) | Yield of **100** (%) | ee of **100** (%) |
|---|---|---|---|
| **102** | 25 | 41 | 26 |
| **102** | 0 | 29 | 55 |
| **102** | -15 | 25 | 58 |
| **103** | 25 | 23 | 10 |

**Table 1.2** TADDOL-$TiCl_2$ catalyzed Diels-Alder reaction of **93** with 1,4-benzoquinone

For comparison, the same Diels-Alder reaction between 1,4-benzoquinone and **93** was run in the presence of the chiral titanium complexes **102** and **103** derived from α,α,α',α'-tetraaryl-1,3-dioxolane-4,5-dimethanol (TADDOLs)[17]. In these cases, the reaction was much slower than that with the Mikami catalyst and gave only a modest yield of adduct in low enantiomeric excess (**Table 1.2**).

The ee improved with catalyst **102** as the reaction temperature was decreased from ambient to 0 °C and then to –15 °C, but this was at the expense of chemical yield. A change of substituent groups $R_1$ and $R_2$, as in the TADDOL **103** did not improve either yield or ee. It is clear from the above results that BINOL is a much superior chiral ligand to TADDOL in catalyzing the addition of 1,4-benzoquinone to **93**. However, it is important to note that only the protocol specified by Mikami,[13] in which the catalyst is prepared *in situ* from BINOL and diisopropoxytitanium dichloride, was effective. An alternative catalyst preparation in which BINOL, titanium tetraisopropoxide, and silicon tetrachloride were used[26] resulted in both a lower yield and diminished ee of **100**.




**Scheme 23**

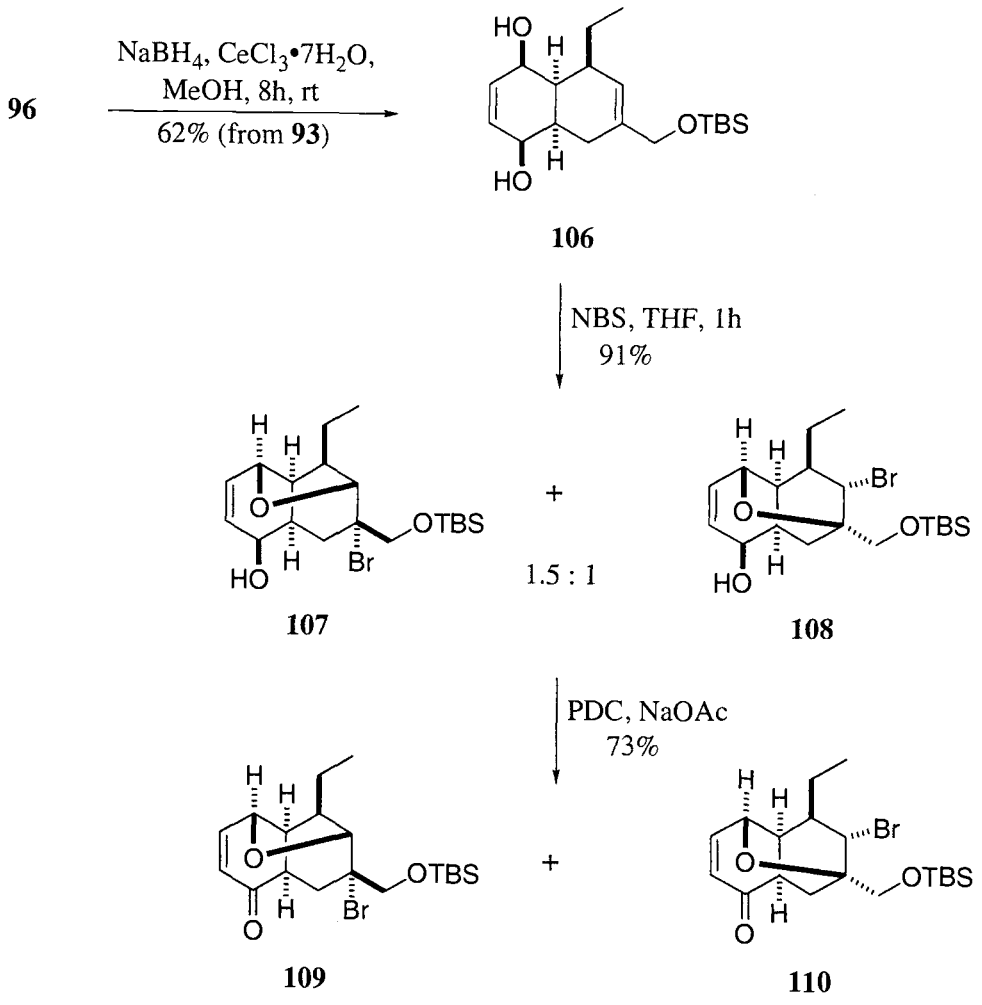
| | $\delta H_a$ (ppm) | $\delta H_b$ (ppm) |
|---|---|---|
| (*R*)-Mandelate, **104** | 6.24 | 2.89 |
| (*S*)-Mandelate, **105** | 6.45 | 2.75 |

**Table 1.3** $^1$H NMR shift of the R/S pairs of mandelates **104** and **105**

It was possible to ascertain the absolute configuration of **96** indirectly by employing the (*R*)- and (*S*)-mandelates, **104** and **105**, respectively, derived from hydroxy ketone **100** (**Scheme 23**). The $^1$H NMR spectra of both diastereomers showed the expected chemical shift patterns (**Table 1.3**) based on the projections proposed first by Mosher[20] and subsequently by Trost[21] as substituents in the vicinity of the *O*-methylmandelate aryl group are shielded. Thus, the upfield shift of $H_a$ in **104** relative to **105** ($\Delta\delta$ 0.2 ppm) agrees with the prediction for this enantiomer and gave assurance that we could proceed towards an asymmetric synthesis of (–)-ibogamine from this substance.

Subsequently, there developed a conclusive means for verifying that **96** was in the correct enantiomeric series when exhaustive Luche reduction of cycloadduct **96** was found to give *cis* diol **106** (**Scheme 24**). When **106** was treated with N-bromosuccinimide, it afforded a mixture of inseparable bromo ethers **107** and **108**, which upon oxidation with pyridinium dichromate yielded the bromo ketones **109** and **110**. These compounds were separated with relative ease by chromatography, and X-ray analysis of crystalline **109** using the anomalous dispersion technique established its absolute stereochemistry as shown in **Figure 1.4**. This result confirmed the absolute configuration of **96**, from

which **109** was derived, and illustrates the advantage of pursuing chemical transformations of reaction products of uncertain stereochemistry.




**Scheme 24**

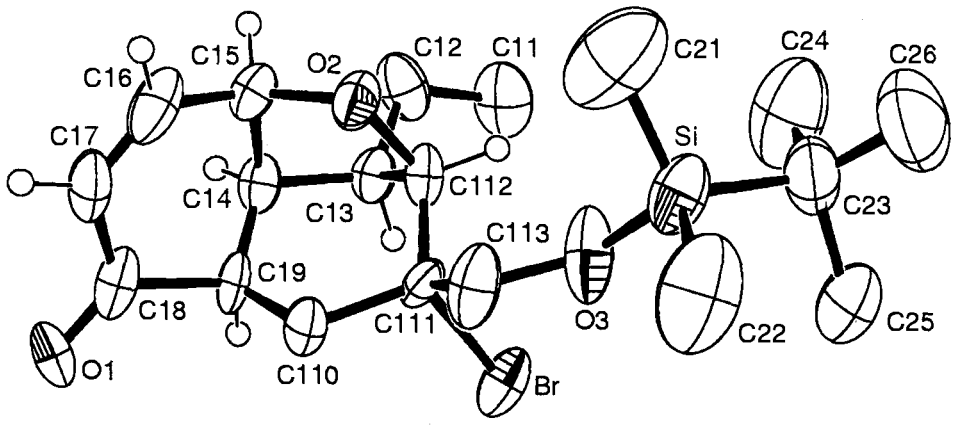
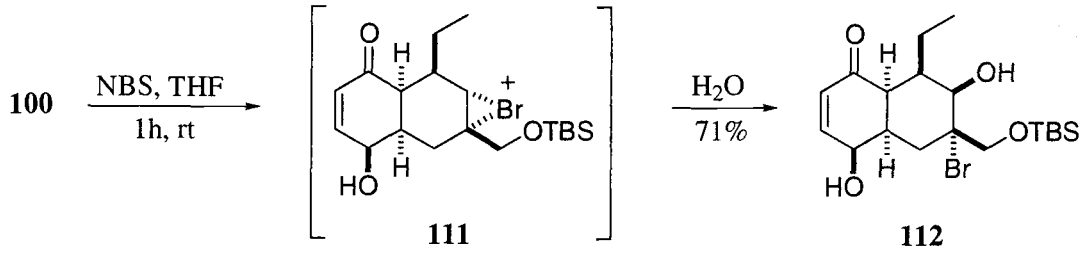



**Figure 1.4** ORTEP representation of X-ray structure of **109**




**Scheme 25**

In contrast to **106**, hydroxy ketone **100** did not produce a bromo ether upon exposure to N-bromosuccinimide but instead gave bromohydrin **112** resulting from external solvolytic attack on the intermediate bromonium ion **111** (**Scheme 25**).

A possible transition state for the enantioselective and regioselective *endo* Diels-Alder addition leading to **96** is shown in **Figure 1.5**. However, it must be remembered that the precise structure of the Mikami catalyst is unknown, and the formalism expressed as **Figure 1.5** is not in accord with speculations made by Corey.[14] This model postulates a $\pi$–$\pi$ interaction between the (*S*)-BINOL-$TiCl_2$

catalyst and benzoquinone which allows exposure of only one face of one of the two double bonds of the quinone to the diene.

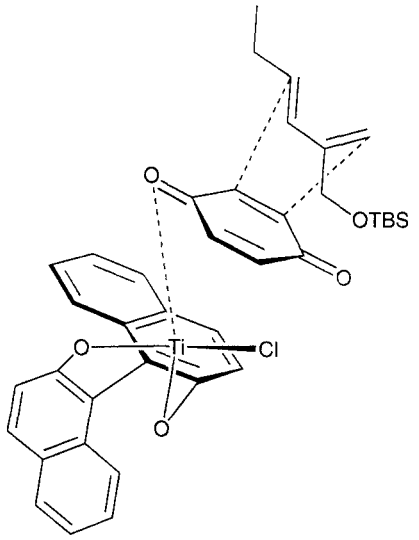
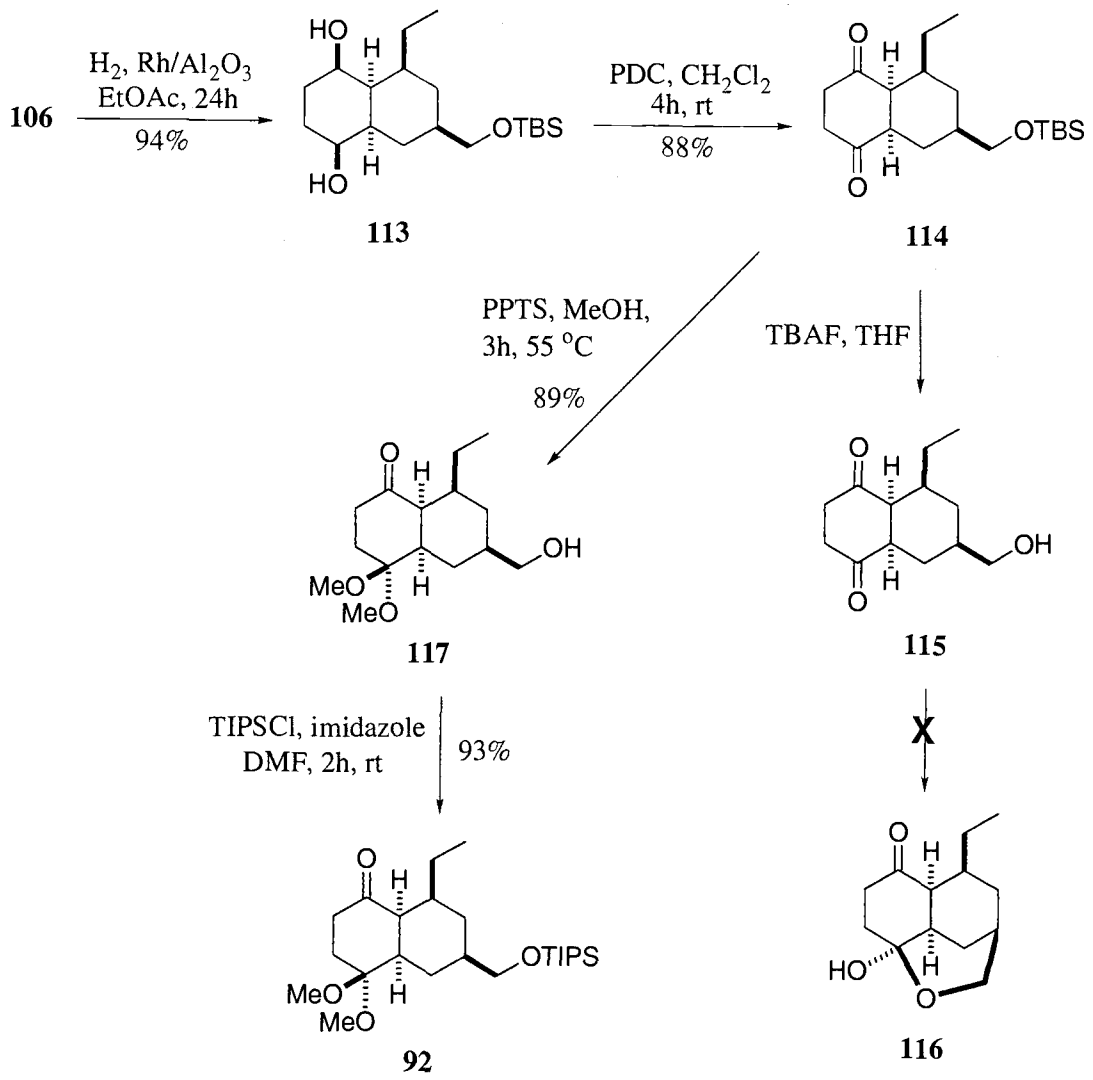



**Figure 1.5** Proposed (*S*)-BINOL-$TiCl_2$-benzoquinone complex

With diol **106** of known absolute configuration in hand, it was now necessary to modify the left-hand ring of this structure in a way that would lead to the tricyclic framework of the non-indolic portion of ibogamine (**1**). The first requirement toward this end was reduction of both olefinic bonds of **106**, a transformation that was accomplished in a single step by hydrogenation over rhodium on alumina (**Scheme 26**). The selection of this catalyst ensured that no hydrogenolysis of the three allylic oxygen functions would occur during saturation of **106**, but equally important was delivery of hydrogen to the trisubstituted olefin exclusively from the *exo* face. This would result in positioning the alkoxymethyl substituent on the concave interior of the *cis* decalin structure **113** for a subsequent cyclization that would create the azatricyclic core of ibogamine (**1**).

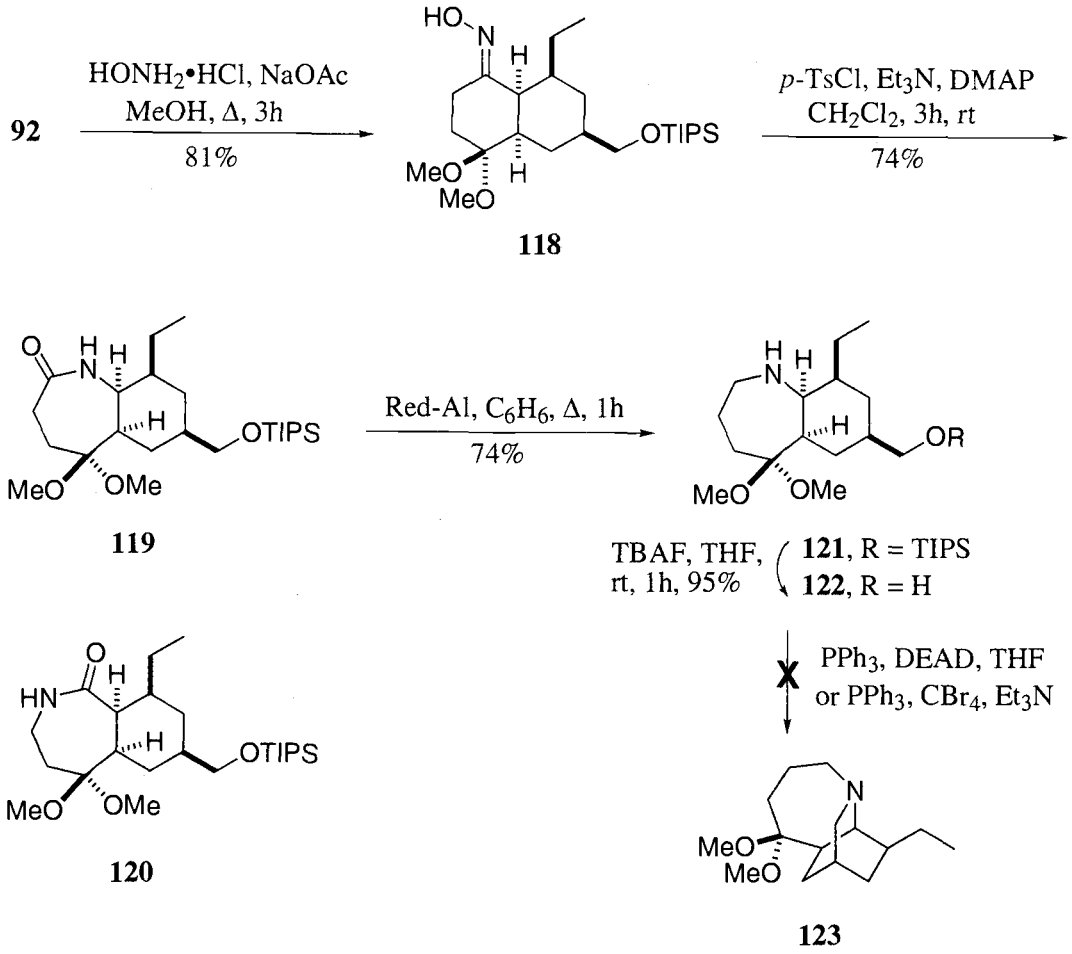



**Scheme 26**

Oxidation of diol **113** to diketone **114** with pyridinium dichromate was straightforward, but it now became necessary to distinguish between the two keto groups of **114** in order to proceed with chemistry on the ring that contained them. Our first attempt to discriminate between the keto groups of **114** involved cleavage of the silyl ether to give **115**, which, we had hoped, would close to the six-membered hemiketal **116** in acidic methanol. This would have provided a

means for blocking one ketone while synthetic operations were conducted on the other. Although the *endo* configuration of the hydroxymethyl substituent in **115** appeared to favor formation of **116**, no means could be found for effecting this conversion. A possible explanation for this failure is that the *cis* decalin **116** cannot attain a conformation in which both the hydroxymethyl and ethyl substituents occupy the axial orientation necessary for internal hemiketalization. In any case, this disappointing result forced us to consider other means for differentiating the keto groups of **114**, and it was quickly discovered that only the less hindered ketone formed a dimethyl ketal **117**. The process of ketalization led to simultaneous cleavage of the *tert*-butyldimethylsilyl ether of **114**, an observation which conveyed the message that more robust protection of the primary alcohol would be needed for the next transformation. Ketal **117** was therefore converted to its more durable triisopropylsilyl ether **92**.

The pivotal Beckmann rearrangement envisioned for enlargement of the ketone ring of **92** to an ε-lactam required the preparation of *anti* oxime **118**, a reaction which was accomplished in high yield with hydroxylamine hydrochloride and sodium acetate in methanol at reflux (**Scheme 27**). Although ketoximes are known to undergo Beckmann rearrangement under a wide variety of conditions,[27] previous experience had taught us that oxime tosylates are particularly good substrates for this transformation.[28] In the event, exposure of **118** to *p*-toluenesulfonyl chloride and triethylamine containing a small quantity of 4-(dimethylamino)pyridine led to its smooth conversions to lactam **119**. None of the isomeric lactam **120** resulting from migration of the less substituted carbon was detected in the reaction mixture.




**Scheme 27**

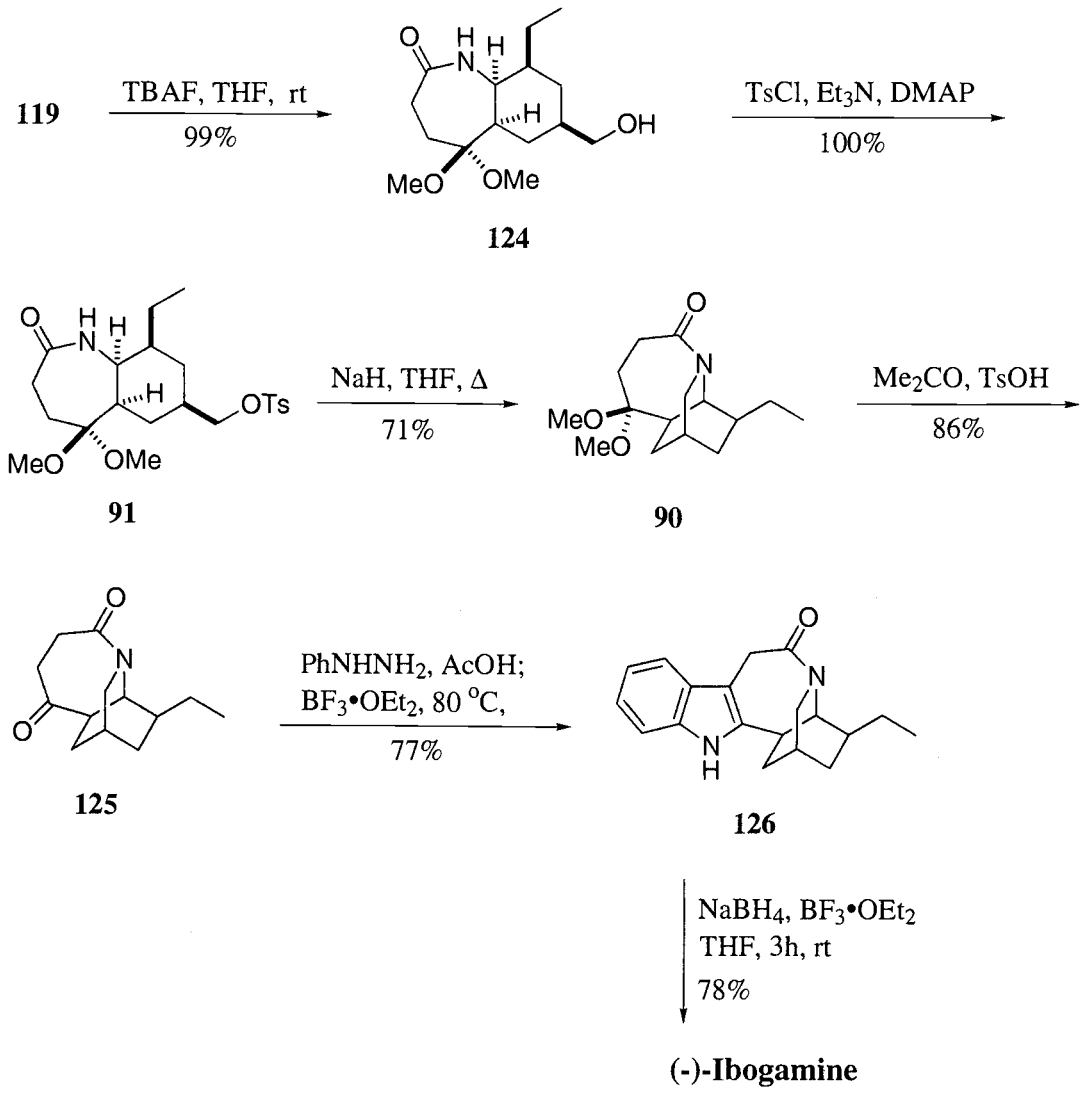
Our attention next turned to conversion of **119** into the azatricyclic core of ibogamine for which connection of the nitrogen atom to the carbon bearing the triisopropylsilyl ether group was the key step. A displacement across the *endo* face of the bicycle to forge this N-C bond required an active nitrogen nucleophile, and it was initially supposed that the secondary amine derived from reduction of lactam **119** would be best suited to this purpose. Lactam **119** was therefore reduced with sodium bis(2-methoxyethoxy)aluminum hydride (Red-Al), and the resulting amine **121** was treated with tetra-*n*-butylammonium fluoride to give

amino alcohol **122**. Surprisingly, all attempts to effect transannular cyclization of **122**, for example via a Mitsunobu reaction,[29] were unsuccessful. Subsequent examination of the transition state for this displacement not only provided an explanation for its failure but also suggested a remedy. Specifically, as the nitrogen atom of **122** is brought towards the methylene bearing the tosylate group for backside attack, a steric interaction develops between the *endo* hydrogen of the methylene adjacent to the nitrogen atom and the *endo* methoxy substituent in the azepine ring. This steric confrontation is evidently sufficient to block cyclization.

On the other hand, **119** with a $sp^2$ rather than a $sp^3$ carbon adjacent to nitrogen would suffer no such steric impediment, and closure of the lactam to the tricyclic core of ibogamine (**1**) should therefore be more facile (**Scheme 28**). On the basis of this hypothesis, **119** was advanced to alcohol **124** and then to its tosylate **91**. That our conjecture was indeed correct was confirmed by the fact that exposure of **91** to sodium hydride in tetrahydrofuran produced the tricyclic lactam **90** cleanly and in good yield. The displacement of tosylate **91** by the lactam nitrogen must be energetically quite favorable since the amide resonance of **91** is clearly lost in the course of its conversion to **90**.

The remaining transformation of **90** into (–)-ibogamine first required release of the keto function masked as its dimethyl ketal, a process that was most efficiently accomplished by transketalization with acetone in the presence of an acidic catalyst.[30] The resulting keto lactam **125** was next subjected to a Fischer indole synthesis[31] with phenylhydrazine in acetic acid, the initially formed hydrazone requiring extended treatment with hot boron trifluoride etherate to

complete the reaction. Only one indole can be formed from **125** since the keto group is situated next to a bridgehead carbon, and **126** was indeed produced in good yield by this process.




**Scheme 28**

The final stage, reduction of lactam **126**, proved to be more difficult than expected, conventional reagents such as lithium aluminum hydride being completely ineffective. Fortunately, a protocol due to Sundberg[32] using diborane

generated *in situ* from sodium borohydride and boron trifluoride etherate was successful and furnished crystalline (–)-ibogamine (**1**), identical with a sample of the natural alkaloid kindly provided by Professor Huffman of Clemson University.

The preparation of (–)-ibogamine (**1**) in fourteen steps from benzoquinone and in 10% overall yield is powerful illustration of the value of the asymmetric Diels-Alder reaction as a starting point in a multistep synthesis. Furthermore, the knowledge that catalyzed asymmetric Diels-Alder reactions can now be applied with efficiency to 1,4-benzoquinone, at least with Mikami's BINOL-$TiCl_2$ system, opens the way to more structurally varied chiral products than were attainable previously. It can be expected that much use will be made of this new paradigm of synthesis in the future.

## Experimental Section General

Starting materials and reagents were obtained from commercial sources and were used without further purification. Solvents were dried by distillation from the appropriate drying agents immediately prior to use. Tetrahydrofuran (THF), diethyl ether ($Et_2O$), and toluene were distilled from sodium benzophenone under an argon atmosphere. Diisopropylamine, triethylamine, benzene, acetonitrile and dichloromethane ($CH_2Cl_2$) were distilled from calcium hydride under argon. All solvents used for routine isolation of products and chromatography were reagent grade. Moisture and air sensitive reactions were carried out under an atmosphere of argon. Reaction flasks were flame dried under stream of argon gas, and glass syringes were oven dried at 120 °C and cooled in a desicator over anhydrous calcium sulfate prior to use. Unless otherwise stated, concentration under reduced pressure refers to a rotary evaporator at water aspirator pressure.

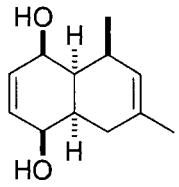
Analytical thin layer chromatography (TLC) was performed using precoated aluminum E. Merck TLC plates (0.2 mm layer thickness of silica gel 60 F-254). Compounds were visualized by ultraviolet light, and/or by heating the plate after dipping in a solution of 14% ammonium molybdate tetrahydrate and 1.4% cerium(IV) sulfate in 1.6 M sulfuric acid in water or 1% solution of vanillin in 0.1 M sulfuric acid in ethanol or 1% solution of potasium permanganate in 2% 1 N sodium hydroxide in water. Flash chromatography was carried out using E. Merck silica gel 60 (230-400 mesh ASTM). Radial chromatography was carried

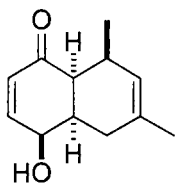
out on individual prepared rotors with layer thickness of 1, 2, or 4 mm using a Chromatotron manufactured by Harrison Research, Palo Alto, California.

Melting points were measured using a Büchi melting point apparatus, and are uncorrected. Infrared (IR) spectra were recorded with a Nicolet 5DXB FT-IR spectrometer using a thin film supported between NaCl plates or KBr discs. Specific optical rotations were measured at ambient temperature (23 °C) from $CHCl_3$ solutions on a Perkin-Elmer 243 polarimeter using a 1 mL cell with 1dm path length. Proton and carbon nuclear magnetic resonance (NMR) spectra obtained using either a Bruker AC-300 or a Bruker AM-400 spectrometer. All chemical shifts are reported in parts per million (ppm) downfield from tetramethylsilane using the $\delta$ scale. $^1$H NMR spectra data are reported in the order: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet and br = broad), coupling constant (*J*) in Hertz (Hz) and number of protons.

Chemical ionization (CI) high and low resolution mass spectroscopy (HRMS and MS) were obtained using a Kratos MS-50 spectrometer with a source temperature of 120 °C and methane gas as the ionizing source. Perfluorokerosene was used as a reference. Electron impact (EI) mass spectra (HRMS and MS) were obtained using a Varian MAT311 or a Finnegan 4000 spectrometer. X-ray crystallographic data were collected on a Siemens P4 instrument and these data were interpreted using the direct methods program contained in the SHELXTL (Silicon Graphics/Unix) software package.

## Experimental Section



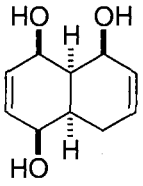

**(1S,4R,4aS,5S,8aR)-1,4,4a,5,8,8a-Hexahydro-5,7-dimethylnaphthalene-1,4-diol (71) and (4S,4aR,8S,8aS)-4a,5,8,8a-Tetrahydro-4-hydroxy-6,8-dimethylnaphthalen-1-(4H)-one (72).** To a solution of BINOL-$TiCl_2$ complex (1M solution in $CH_2Cl_2$, 0.1 mL) and 1,4-benzoquinone (108 mg, 1.0 mmol) in $CH_2Cl_2$ (5 mL) at room temperature was added a solution of *trans*-2-methyl-1,3-pentadiene (121 mg, 1.47 mmol) in toluene (2 mL), and the mixture was stirred for 30 min at room temperature. The resultant solution was diluted with MeOH (5 mL), cooled to 0 °C, and $NaBH_4$ (38 mg, 1 mmol) and $CeCl_3 \bullet 7H_2O$ (373 mg, 1 mmol) were added. The mixture was stirred for 1 h at 0 °C and was diluted with $Et_2O$ (30 mL). The solution was washed with $H_2O$ and saturated aqueous NaCl, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. Chromatography of the residue on silica gel (EtOAc-hexanes, 1:3) gave 138 mg (71% from benzoquinone) of a mixture of **71** and **72** as a colorless oil.

Data for **71**: $R_f$ 0.05 (EtOAc-hexanes, 1:3); $[\alpha]_D^{23}$ - 164.5 (c 1.0, $CHCl_3$); IR (neat) 3405, 2960, 2875, 1437, 1378, 1061, 998, 774 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ 1.23 (d, $J$ = 7.5 Hz, 3H), 1.69 (m, 3H), 1.77 (brs, 1H), 1.82-1.89 (m, 1H), 2.00-2.07 (m, 2H), 2.26-2.40 (m, 2H), 2.51-2.64 (m, 1H), 4.15-4.22 (m, 1H), 4.39-4.47 (m, 1H), 5.43-5.58 (m, 1H), 5.63-5.69 (m, 1H), 5.82 (ddd, $J$ = 2.3, 4.4, 10.2 Hz); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 17.4, 24.0, 27.7, 34.1, 37.6, 39.0, 64.9, 70.7,

128.9, 129.3, 130.7, 135.4; MS (CI) *m/z* 193 ($M^+$+H), 176, 159, 147, 143, 131, 119, 109, 98, 86; HRMS (CI) *m/z* 194.1306 (calcd for $C_{12}H_{18}O_2$: 194.1307).

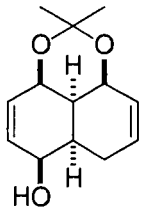
Data for **72**: $R_f$ 0.05 (EtOAc-hexanes, 1:3); $^1$H NMR (300 MHz, $CDCl_3$) δ 1.35 (d, *J* = 7.6 Hz, 3H), 1.58-1.62 (m, 3H), 1.93-2.06 (m, 3H), 2.25-2.62 (m, 2H), 2.67-2.78 (m, 1H), 4.84-4.89 (m, 1H), 5.27-5.31 (m, 1H), 5.77-5.85 (m, 1H), 6.56 (dt, *J* = 2.1, 10.3 Hz, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 19.2, 23.7, 26.9, 34.4, 44.5, 50.3, 70.9, 127.0, 130.1, 131.3, 147.9, 200.8.

(R)-O-Methylmandelate **74**: $^1$H NMR (400 MHz, $CDCl_3$) δ 6.24 ($H_a$). (S)-O-Methyl mandelate **75**: $^1$H NMR (400 MHz, $CDCl_3$) δ 6.42 ($H_a$).



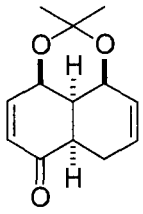

**(1S,4R,4aR,5S,8aR)-1,4,4a,5,8,8a-Hexahydronaphthalen-1,4,5-triol (78).** To a solution of BINOL-$TiCl_2$ complex (1M solution in $CH_2Cl_2$, 0.2 mL) and 1,4-benzoquinone (216 mg, 2.0 mmol) in $CH_2Cl_2$ (5 mL) at room temperature was added a solution of **76** (426 mg, 3.0 mmol) in toluene (2 mL), and the mixture was stirred for 30 min at room temperature. The solution was diluted with MeOH (5 mL), cooled to 0 °C, and $NaBH_4$ (114 mg, 3.0 mmol) and $CeCl_3$•$7H_2O$ (1.12 g, 3.0 mmol), were added. The mixture was stirred for 1 h at 0 °C and diluted with $Et_2O$ (50 mL). The solution was washed with $H_2O$ and saturated aqueous NaCl, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to give a crude diol. To a stirred solution of this diol (325 mg, 1.3 mmol) in MeOH (5 mL) at 0 °C was added *p*-toluenesulfonic acid (2 mg), and the mixture was

stirred for 1 h at 0 °C. The mixture was concentrated under reduced pressure, and the residue was chromatographed on silica gel (EtOAc-hexanes, 1:3, then MeOH-$CH_2Cl_2$, 1:15) to afford 237 mg (65% from benzoquinone) of **78** as a colorless oil. $R_f$ 0.05 (EtOAc-hexanes, 1:3); IR (neat) 3345, 3025, 2886, 1406, 1248, 1088, 1039, 1002 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ 2.13-2.23 (m, 2H), 2.29-2.34 (m, 1H), 2.34-2.41 (m, 1H), 3.93 (s, 3H), 3.96-3.99 (m, 1H), 4.43 (t, *J* = 4.4 Hz, 1H), 4.50 (d, *J* = 7.6 Hz, 1H), 5.76-5.84 (m, 3H), 5.91 (dt, *J* = 3.6, 10.0 Hz, 1H); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 28.1, 32.9, 39.3, 63.5, 67.3, 67.9, 127.9, 130.4, 130.8, 133.3; MS (CI) *m/z* 183 $(M+H)^+$, 165, 147, 130, 129, 119, 105, 91, 86; HRMS (CI) *m/z* 183.1021 (calcd for $C_{10}H_{15}O_3$: 183.1021).



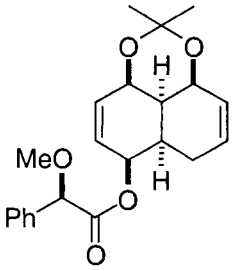

**(3aR,6S,6aR,9aS,9bR)-3a,6,6a,7,9a,9b-Hexahydro-2,2-dimethylnaphtho[1,8-de] [1,3]dioxin-6-ol (79).** To a stirred solution of **78** (132 mg, 0.73 mmol) in DMF (2 mL) at room temperature was added 2,2-dimethoxypropane (0.2 mL, 1.64 mmol) and *p*-toluenesulfonic acid (2 mg), and the mixture was stirred for 16 h. The mixture was diluted with saturated aqueous $NaHCO_3$ (1 mL) and was extracted with $Et_2O$ (25 mL). The extract was washed with saturated aqueous NaCl, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. Chromatography of the residue on silica gel (EtOAc-hexanes, 1:3) gave 140 mg (87%) of **79** as a colorless oil. $R_f$ 0.13 (EtOAc-hexanes, 1:3); $[\alpha]_D^{23}$ + 17.7 (*c* 1.39, $CHCl_3$); IR (neat) 3423, 3024, 2985, 2903, 1378, 1223, 1104, 1062 $cm^{-1}$; $^1H$

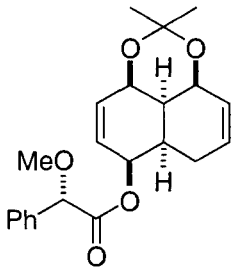
NMR (300 MHz, $CDCl_3$) δ 1.38 (s, 3H), 1.48 (s, 3H), 2.13-2.22 (m, 3H), 2.30-2.39 (m, 1H), 2.52-2.60 (m, 1H), 4.06-4.14 (m, 1H), 4.41-4.48 (m, 1H), 4.48-4.55 (m, 1H), 5.72-5.80 (m, 1H), 5.84 (ddd, *J* = 0.7, 3.5, 10.2 Hz, 1H), 5.94 (ddd, *J* = 1.6, 3.2, 10.2 Hz, 1H), 6.00-6.08 (m, 1H); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 24.4, 25.7, 29.7, 35.2, 64.3, 65.5, 102.2, 127.5, 129.6, 131.6, 133.0; MS (CI) *m/z* 223 $(M+H)^+$, 207, 165, 147, 129, 117, 91; HRMS (CI) *m/z* 223.1342 (calcd for $C_{13}H_{19}O_3$: 223.1334).



**(3aR,6aR,9aS,9bR)-6a,7,9a,9b-Tetrahydro-2,2-dimethylnaphtho[1,8-de] [1.3]dioxin-6-(3aH)-one (80).** To a stirred suspension of Dess-Martin periodinane (80 mg, 0.19 mmol) in $CH_2Cl_2$ (5 mL) at room temperature was added a solution of **79** (28 mg, 0.13 mmol) in $CH_2Cl_2$ (1 mL), and the mixture was stirred for 30 min at room temperature. The reaction was quenched by the simultaneous addition of saturated aqueous $NaHCO_3$ (3 mL) and 10% aqueous $Na_2S_2O_3$ (3 mL). This mixture was stirred for 30 min, the layers were separated, and the organic layer was washed with saturated aqueous NaCl, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. Chromatography of the residue on silica gel (EtOAc-hexanes, 1:3) gave 24 mg (88%) of **80** as a white solid: $R_f$ 0.3 (EtOAc-hexanes, 1:3); mp 80-81°C; The ee was measured by HPLC (*Diacel Chiralpak* OD, hexane/$^i$PrOH 99:1, flow rate 1.05 ml/min): $t_{minor}$ 21.8, $t_{major}$ 24.8; $[\alpha]_D^{23}$ + 110.2 (*c* 0.64, $CHCl_3$); IR (neat) 3033, 2987, 2891, 1681,

1379, 1226, 1084 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ 1.42 (s, 3H), 1.46 (s, 3H), 1.87 (dddd, *J* = 2.6, 5.2, 5.2, 16.8 Hz, 1H), 2.70 (ddd, *J* = 3.4, 5.1, 6.8 Hz, 1H), 2.85 (dddt, *J* = 0.9, 3.3, 6.0, 16.8 Hz, 1H), 3.16 (ddd, *J* = 7.6, 7.6, 7.6 Hz, 1H), 4.36-4.43 (m, 1H), 4.86 (dt, *J* = 2.7, 8.0 Hz, 1H), 5.67 (m, 1H), 5.99-6.05 (m, 1H), 6.06 (dd, *J* = 2.3, 10.4 Hz, 1H), 6.94 (ddd, *J* = 0.8, 3.1, 10.4 Hz, 1H); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 24.1, 25.1, 30.5, 40.3, 42.0, 62.1, 67.3, 102.4, 126.6, 129.8, 130.5, 150.0, 198.8; MS (CI) *m/z* 221 $(M+H)^+$, 205, 162, 149, 134, 133, 117, 105, 85; HRMS (CI) *m/z* 221.1179 (calcd for $C_{13}H_{17}O_3$: 221.1178).

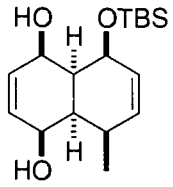



Data for (R)-O-Methylmandelate (**81**): $^1H$ NMR (400 MHz, $CDCl_3$) δ 1.39 (s, 3H), 1.48 (s, 3H), 1.88 (dt, *J* = 5.5, 17.1 Hz, 1H), 2.13 (dddd, *J* = 3.1, 4.9, 11.2, 17.1 Hz, 1H), 2.42 (ddt, *J* = 1.3, 5.0, 16.5 Hz, 1H), 2.49-2.56 (m, 1H), 3.47 (s, 3H), 4.22-4.27 (m, 1H), 4.63-4.68 (m, 1H), 4.84 (s, 1H), 5.32-5.36 (m, 1H), 5.51 (ddd, *J* = 1.6, 1.9, 10.3 Hz, 1H), 5.82 (ddd, *J* = 2.5, 3.4, 10.3 Hz, 1H), 5.84 (dt, *J* = 2.9, 10.3 Hz, 1H); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 21.7, 25.3, 30.0, 33.7, 34.8, 57.8, 60.9, 68.7, 73.1, 83.0, 101.7, 127.4, 128.7, 128.9, 129.1, 129.2, 129.7, 130.6, 136.5, 170.6.

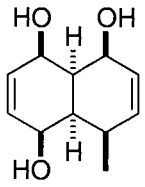
Data for (S)-O-Methylmandelate (**82**): $^1H$ NMR (400 MHz, $CDCl_3$) δ 1.24 (dt, *J* = 5.2, 17.2 Hz, 1H), 1.38 (s, 3H), 1.46 (s, 3H), 1.83-1.99 (m, 1H), 2.13-2.29 (m, 1H), 2.35-2.45 (m, 1H), 3.46 (s, 3H), 4.17-4.23 (m, 1H), 4.53-4.59 (m, 1H),

4.80 (s, 1H), 5.33-5.37 (m, 1H), 5.63-5.73 (m, 3H); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 21.1, 25.3, 29.9, 33.5, 34.7, 57.7, 60.9, 68.7, 72.9, 82.9, 101.6, 127.7, 128.8, 129.1, 129.3, 129.7, 130.3, 136.6, 170.5.

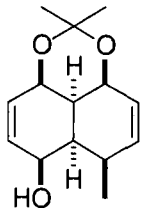



**(1S,4R,4aR,5S,8R,8aR)-5-{[(tert-Butyl)dimethylsilyl]oxy}-1,4,4a,5,8,8a-hexahydro-8-methylnaphthalene-1,4-diol (85).** To a solution of BINOL-$TiCl_2$ complex (1M solution in $CH_2Cl_2$, 0.1 mL) and 1,4-benzoquinone (107 mg, 1.0 mmol) in $CH_2Cl_2$ (5 mL) at room temperature was added a solution of **83** (754 mg, 3.81 mmol) in toluene (2 mL), and the mixture was stirred for 30 min at room temperature. The mixture was diluted with MeOH (5 mL), cooled to 0 °C, and $NaBH_4$ (68 mg, 1.79 mmol) and $CeCl_3 \bullet 7H_2O$ (671 mg, 1.80 mmol) were added. The mixture was stirred for 1 h at 0 °C and diluted with $Et_2O$ (50 mL). The solution was washed with $H_2O$ and saturated aqueous NaCl, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. Chromatography of the residue on silica gel (EtOAc-hexanes, 1:5) gave 203 mg (73%, from benzoquinone) of **85** as a white solid: $R_f$ 0.16 (EtOAc-hexanes, 1:5); mp 148-149 °C; $[\alpha]_D^{23}$ + 246.4 (*c* 1.26, $CHCl_3$); IR (KBr) 3412, 3325, 2957, 2929, 2854, 1469, 1248, 1086, 1025 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ 0.18 (s, 3H), 0.19 (s, 3H), 0.91 (s, 9H), 1.27 (d, *J* = 7.5 Hz, 3H), 1.95-2.00 (m, 1H), 2.07-2.17 (m, 1H), 2.38 (dt, *J* = 4.2, 7.5 Hz, 1H), 2.46-2.53 (m, 1H), 3.89-3.97 (m, 1H), 3.98-4.06 (m, 1H), 4.44-4.54 (m, 2H), 5.66 (ddd, *J* = 2.9, 4.8, 10.1 Hz, 1H), 5.71-

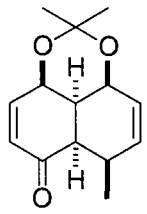
5.80 (m, 2H), 5.84 (ddd, $J$ = 2.4, 4.7, 10.1 Hz, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ -4.4, -3.1, 16.6, 18.3, 26.2, 34.0, 37.9, 41.6, 63.4, 64.6, 69.4, 125.6, 130.4, 133.1, 138.2; MS (CI) *m/z* 253 $(M\text{-}tBu)^+$, 235, 217, 199, 179, 161, 143, 128, 105, 86; HRMS (CI) *m/z* 311.2049 (calcd for $C_{17}H_{31}O_3Si$: 311.2043).




**(1S,4R,4aR,5S,8R,8aR)-1,4,4a,5,8,8a-Hexahydro-8-methylnaphthalene-1,4,5-triol (86).** To a stirred solution of **85** (105 mg, 0.34 mmol) in MeOH (5 mL) at room temperature was added *p*-toluenesulfonic acid (1 mg), and the mixture was stirred for 1 h at 50 °C. The mixture was concentrated under reduced pressure and the residue was chromatographed on silica gel (EtOAc-hexanes, 1:3, then MeOH-$CH_2Cl_2$, 1:15) to yield 56 mg (85%) of **86** as a colorless oil: $R_f$ 0.05 (EtOAc-hexanes, 1:3); $^1$H NMR (300 MHz, $CDCl_3$) δ 1.23 (d, $J$ = 7.6 Hz, 3H), 1.97 (dt, $J$ = 4.2, 6.4 Hz, 1H), 2.44 (dt, $J$ = 4.6, 7.9 Hz, 1H), 2.48-2.57 (m, 1H), 3.03 (d, $J$ = 8.7 Hz, 1H), 3.23 (d, $J$ = 7.0 Hz, 1H), 3.69 (d, $J$ = 7.4 Hz, 1H), 4.18 (dt, $J$ = 4.0, 6.6 Hz, 1H), 4.37-4.44 (m, 1H), 4.55 (t, $J$ = 7.6 Hz, 1H), 5.71-5.76 (m, 1H), 5.80 (ddd, $J$ = 2.7, 4.4, 10.1 Hz, 1H), 5.84-5.92 (m, 2H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 17.1, 33.6, 37.7, 40.8, 63.2, 63.4, 68.8, 127.6, 129.9, 134.5, 136.8.

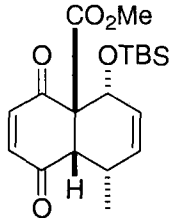


**(3aR,6S,6aR,7R,9aS,9bR)-3a,6,6a,7,9a,9b-Hexahydro-2,2,7-trimethyl-naphtho[1,8-de][1,3]dioxin-6-ol (87).** To a stirred solution of **86** (24 mg, 0.12 mmol) in DMF (1 mL) at room temperature was added 2,2-dimethoxypropane (0.1 mL, 0.82 mmol) and *p*-toluenesulfonic acid (1 mg), and the mixture was stirred for 16 h. The mixture was diluted with saturated aqueous $NaHCO_3$ (1 mL) and was extracted with $Et_2O$ (15 mL). The extract was washed with saturated aqueous NaCl, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. Chromatography of the residue on silica gel (EtOAc-hexanes, 1:5) gave 26 mg (91%) of **87** as a colorless oil: $R_f$ 0.23 (EtOAc-hexanes, 1:5); $[\alpha]_D^{23}$ + 150.7 (*c* 1.9, $CHCl_3$); IR (neat) 3474, 2984, 2936, 2903, 2878, 1373, 1221, 1068, 1031, 978 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ 1.23 (d, *J* = 7.5 Hz, 3H), 1.40 (s, 3H), 1.50 (s, 3H), 1.95 (ddd, *J* = 3.8, 6.1, 9.7 Hz, 1H), 2.34-2.46 (m, 1H), 2.69 (ddd, *J* = 6.0, 10.6, 11.9 Hz, 1H), 2.89 (d, *J* = 12.3 Hz, 1H), 4.08 (ddd, *J* = 3.6, 6.0, 12.2 Hz, 1H), 4.32-4.39 (m, 1H), 4.72 (ddt, *J* = 1.2, 3.5, 10.4 Hz, 1H), 5.62 (ddd, *J* = 3.1, 4.1, 10.0 Hz, 1H), 5.87-5.92 (m, 2H), 6.11 (ddd, *J* = 1.6, 6.0, 10.0 Hz, 1H); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 17.5, 26.3, 29.2, 32.5, 36.6, 38.2, 61.2, 62.9, 68.7, 103.0, 123.2, 132.3, 139.5; MS (CI) *m/z* 237 $(M+H)^+$, 221, 179, 161, 144, 143, 123, 117, 106, 91, 86; HRMS (CI) *m/z* 237.1491 (calcd for $C_{14}H_{21}O_3$: 237.1491).



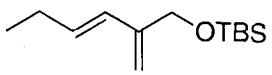
**(3aR,6aR,7R,9aS,9bR)-6a,7,9a,9b-Tetrahydro-2,2,7-trimethylnaphtho[1,8-de][1.3]dioxin-6-(3aH)-one (88).** To a stirred suspension of Dess-Martin periodinane (46 mg, 0.11 mmol) in $CH_2Cl_2$ (5 mL) at room temperature was added a solution of **87** (17 mg, 0.07 mmol) in $CH_2Cl_2$ (1 mL), and the mixture was stirred for 1 h at room temperature. The reaction was quenched by the simultaneous addition of saturated aqueous $NaHCO_3$ (2 mL) and 10% aqueous $Na_2S_2O_3$ (2 mL), and the mixture was stirred for 1 h. The layers were separated, and the organic layer was washed with saturated aqueous NaCl, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. Chromatography of the residue on silica gel (EtOAc-hexanes, 1:5) gave 15 mg (89%) of **88** as a white solid: $R_f$ 0.14 (EtOAc-hexanes, 1:5); mp 73-74 °C; The ee was measured by HPLC (*Diacel Chiralpak* OD, hexane/$^i$PrOH 97:3, flow rate 0.9 ml/min): $t_{minor}$ 13.3, $t_{major}$ 14.8; $[\alpha]_D^{23}$ + 52.6 (*c* 0.94, $CHCl_3$); IR (neat) 2988, 2936, 2876, 1686, 1375, 1225, 1087 cm$^{-1}$; $^1$H NMR (300 MHz, $CDCl_3$) δ 1.43 (d, *J* = 6.8 Hz, 3H), 1.44 (s, 3H), 1.48 (s, 3H), 2.22-2.30 (m, 1H), 2.72 (ddd, *J* = 0.8, 4.0, 6.5 Hz, 1H), 3.11 (ddd, *J* = 7.5, 7.5, 7.5 Hz, 1H), 4.43 (ddd, *J* = 2.6, 5.3, 7.8 Hz, 1H), 4.88 (dt, *J* = 2.7, 8.0 Hz, 1H), 5.63 (dt, *J* = 2.9, 10.1 Hz, 1H), 5.95 (ddt, *J* = 0.9, 2.5, 10.1 Hz, 1H), 6.03 (dd, *J* = 2.3, 10.3 Hz, 1H), 6.86 (ddd, *J* = 0.8, 3.2, 10.3 Hz, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 18.7, 25.1, 30.4, 32.9, 42.9, 47.5, 62.4, 67.6, 102.3,

125.7, 131.7, 136.7, 148.3, 199.8; MS (CI) *m/z* 235 $(M+H)^+$, 219. 177, 159, 148, 131, 121, 105, 94, 91; HRMS (CI) *m/z* 235.1333 (calcd for $C_{14}H_{19}O_3$: 235.1334).



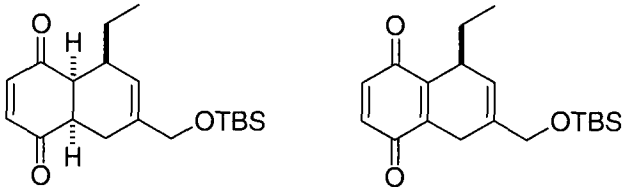

**Methyl (1R,4S,4aS,8aR)-4-{[(tert-Butyl)dimethylsilyl]oxy}-4,5,8,8a-tetrahydro -1-methyl-5,8-dioxonaphthalene-4a(1H)-carboxylate (89).** To a stirred solution of methyl gentisate (168 mg, 1.0 mmol) at 0 °C was added silver(I) oxide (464 mg, 2.0 mmol) in one portion. The mixture was warmed to room temperature and was stirred for 4 h. To a 0.1M solution of BINOL-$TiCl_2$ complex (1 mL in $CH_2Cl_2$, 0.1 mmol) in $CH_2Cl_2$ (5 mL) was added the solution obtained above, and the mixture was stirred for 5 min at room temperature. A solution of **83** (713 mg, 3.6 mmol) in toluene (1 mL) was added, and the mixture was stirred for 30 min at room temperature. The mixture was concentrated under reduced pressure and the residue was chromatographed on silica gel (EtOAc-hexanes, 1:10) to yield 186 mg (51%) of **89** as a colorless oil: $R_f$ 0.13 (EtOAc-hexanes, 1:10); The ee was measured by HPLC (*Diacel Chiralpak* OD, hexane/$^i$PrOH 98:2, flow rate 1.0 ml/min): $t_{major}$ 7.4, $t_{minor}$ 19.0; $[\alpha]_D^{23}$ - 67.7 (*c* 1.18, $CHCl_3$); IR (neat) 1749, 1710, 1686, 1253, 1227, 1089, 1058, 1037, 842 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ - 0.09 (s, 3H), 0.01 (s, 3H), 0.76 (s, 9H), 1.42 (d, *J* = 7.6 Hz, 3H), 2.13-2.22 (m, 1H), 3.66 (d, *J* = 4.8 Hz, 1H), 3.80 (s, 3H), 4.77-4.79 (m, 1H), 5.67-5.70 (m, 2H), 6.58 (d, *J* = 10.3 Hz, 1H), 6.77 (d, *J* = 10.3 Hz, 1H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ -

4.9, -4.8, 17.5, 18.2, 26.0, 30.1, 50.8, 53.4, 66.6, 67.5, 126.3, 133.1, 133.8, 144.7, 169.5, 196.4; MS (CI) *m/z* 365 $(M+H)^+$, 349, 307, 275, 267, 247, 225, 201, 195, 173, 141, 91; HRMS (CI) *m/z* 365.1782 (calcd for $C_{19}H_{29}O_5Si$: 365.1784).




**2-{{[(tert-Butyl)dimethylsilyl]oxy}methyl}hexa-1,3-diene (93).** Into a flame-dried pressure bottle cooled -78 °C was condensed 1-butyne (3.25 g, 60.1 mmol) under argon. A 1M solution of catecholborane-THF complex (60 mL in THF, 60 mmol) was injected into the stirred mixture, and the solution was heated at 70 °C for 24 h. After the solution had cooled to room temperature, it was distilled under reduced pressure to give 8.57 g (82%) of (*E*)-1-butenyl-1,3,2-benzodioxaborole **94** as a colorless oil: bp 77-78 °C (2.5 Torr); IR (neat) 3199, 2959, 1643, 1246, 742 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ 1.11 (t, *J* = 7.4 Hz, $CH_3$), 2.33 (ddq, *J* = 1.7, 7.5, 7.5 Hz, 2H), 5.83 (dt, *J* = 1.7, 18.0 Hz, 1H), 7.01-7.28 (m, 5H); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 12.2, 28.8, 106.1, 112.2, 122.5, 148.2, 159.2; MS (CI) *m/z* 174 $(M^+)$, 159, 146, 134, 120, 115, 101, 93, 69; HRMS (CI) *m/z* 174.0852 (calcd for $C_{10}H_{11}O_2{}^{11}B$: 174.0852). To a solution of $Pd(PPh_3)_4$ (1.04 g, 0.9 mmol) in THF (80 mL) was added a solution of **95** (7.53 g, 30.0 mmol) in THF (10 mL), and the mixture was stirred for 1 h at room temperature. To this mixture was added a solution of **94** (5.80 g, 33.3 mmol) in THF (10 mL) followed by NaOEt (66.6 mmol), and the resultant mixture was heated under reflux for 7 h. The mixture was allowed to cool to room temperature during 1 h and was treated with an aqueous solution of NaOH (3M, 1 mL) and $H_2O_2$ (30%, 1 mL) for 1 h at

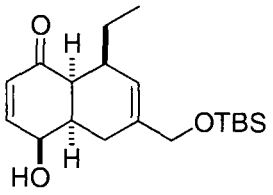
room temperature. The mixture was extracted with hexane (3 x 30 mL), and the extract was washed with saturated aqueous NaCl, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. Chromatography of the residue on silica gel (ether-pentane, 1:30) gave 4.96 g (73%) of **93** as a colorless oil: $R_f$ 0.4 (hexanes); IR (neat) 2957, 2883, 2359, 2337, 1253, 1110 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 0.09 (s, 6H), 0.92 (s, 9H), 1.02 (t, $J$ = 7.4 Hz, $CH_3$), 2.11 (m, 2H), 4.32 (m, 2H), 4.98 (s, 1H), 5.19 (m, 1H), 5.70 (dt, $J$ = 6.5, 16.1 Hz, 1H), 6.06 (d, $J$ = 16.1, Hz, 1H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ -5.4 (2C), 13.5, 18.3, 25.9 (3C), 26.1, 63.0, 112.1, 128.7, 131.4, 144.8; MS (CI) $m/z$ 227 ($M^+$+H), 211, 195, 193, 169, 139, 137, 95, 83, 75; HRMS (CI) $m/z$ 227.1815 (calcd for $C_{13}H_{27}OSi$: 227.1831).

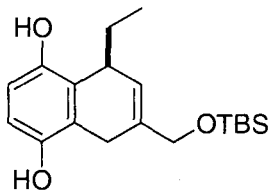



**(4aS,5S,8aR)-7-{{[(tert-Butyl)dimethylsilyl]oxy}methyl}-5-ethyl-4a,5,8,8a-tetrahydronaphthalene-1,4-dione (96).** To a solution of BINOL-$TiCl_2$ complex (1M solution in $CH_2Cl_2$, 1.7 mL) and 1,4-benzoquinone (603 mg, 5.58 mmol) in $CH_2Cl_2$ (3 mL) at room temperature was added a solution of **93** (1.47 g, 6.49 mmol) in toluene (2 mL), and the mixture was stirred for 30 min at room temperature. The mixture was concentrated under reduced pressure, and the crude **96** was used immediately for the next reaction due to its facile oxidation to **97**.

Data for **97**: IR (neat) 2951, 2926, 2847, 1664, 838 $cm^{-1}$; $^1H$ NMR (300

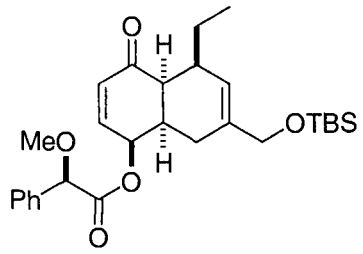
MHz, $CDCl_3$) δ 0.04 (s, 6H), 0.80 (t, *J* = 7.5 Hz, 3H), 0.93 (s, 9H), 1.51-1.72 (m, 2H), 2.85 (dd, *J* = 2.4, 6.3, 23.6 Hz, 1H), 3.13 (dd, *J* = 4.7, 23.6 Hz, 1H), 3.47-3.53 (m, 1H), 4.22 (brs, 1H), 5.77 (m, 1H), 6.71 (d, *J* = 1.6 Hz, 2H); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ -5.4 (2C), 9.9, 18.4, 25.0, 25.9 (3C), 28.2, 35.5, 66.1, 121.8, 134.9, 136.1, 136.6, 140.4, 143.2, 186.6, 186.9.



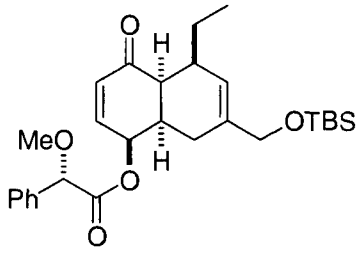

**(4S,4aR,8S,8aS)-6-{{[(tert-Butyl)dimethylsilyl]oxy}methyl}-8-ethyl-4a,5,8,8a-tetrahydro-4-hydroxynaphthalen-1(4H)-one (100) and (5S)-7-{{[(tert-Butyl)dimethylsilyl]oxy}methyl}-5-ethyl-5,8-dihydronaphthalene-1,4-diol (101).** To a solution of **96** obtained above in MeOH (5 mL) at 0 °C was added $NaBH_4$ (211 mg, 5.58 mmol) and $CeCl_3 \bullet 7H_2O$ (2.08 g, 5.58 mmol), and the mixture was stirred for 1 h at 0 °C. The mixture was diluted with $Et_2O$ (30 mL), and the solution was washed with $H_2O$ and saturated aqueous NaCl, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. Chromatography of the residue on silica gel (EtOAc-hexanes, 1:3) gave **100** (1.23 g, 65% from benzoquinone): $R_f$ 0.34 (EtOAc-hexanes, 1:3); $[\alpha]_D^{23}$ -35.3 (*c* 1.45, $CHCl_3$); IR (neat) 3370, 2953, 2926, 2853, 1685, 1673, 1254, 1073, 836, 777 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ 0.93 (t, *J* = 7.4 Hz, 3H), 1.80-2.27 (m, 5H), 2.73 (m, 2H), 3.98 (m, 2H), 4.92 (m, 1H), 5.62 (s, 1H), 5.83 (dd, *J* = 2.0, 7.0, 10.3 Hz), 6.57 (ddd, *J* = 2.0, 3.5, 10.3 Hz, 1H); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ -5.3, -5.2,

12.5, 18.4, 22.2, 25.6, 25.9 (3C), 41.3, 43.7, 48.2, 67.0, 70.7, 125.7, 129.6, 134.1, 147.4, 199.7 ; MS (CI) *m/z* 335 ($M^+$-H), 321, 279, 261, 205, 187, 159, 75; HRMS (CI) *m/z* 335.2047 (calcd for $C_{19}H_{31}O_3Si$: 335.2043). There was also obtained 130 mg (7%) of **101**: IR (neat) 3363, 2930, 2958, 2858, 1487, 1463, 1256, 1071, 836, 779 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ 0.09 (s, 6H), 0.79 (t, *J* = 7.4 Hz, 3H), 0.95 (s, 9H), 1.62-1.75 (m, 2H), 3.04 (dt, *J* = 3.1. 21.0 Hz, 1H), 3.28 (dd, *J* = 2.7, 21.0 Hz, 1H), 3.55-3.64 (m, 1H), 4.21-4.24 (m, 2H), 4.74-4.86 (m, 2H), 5.87-5.92 (m, 1H), 6.50-6.51 (m, 2H); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ -4.8, 10.5, 18.9, 25.6, 26.4, 29.0, 36.2, 67.3, 112.8, 113.4, 123.7, 123.8, 127.5, 135.1, 147.0; MS (CI) *m/z* 334 $(M)^+$, 319, 305, 277, 259, 247, 231, 189, 173, 145, 131, 115, 86; HRMS (CI) *m/z* 334.1968 (calcd for $C_{19}H_{30}O_3Si$: 334.1964).



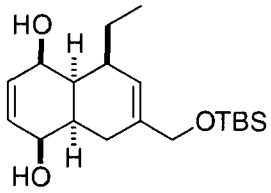

**(1S,4aS,5S,8aR)-7-{{[(tert-Butyl)dimethylsilyl]oxy}methyl}-5-ethyl-1,4,4a,5,8, 8a-hexahydro-4-oxonaphthalen-1-yl (R)-O-Methylmandelate (104).** To a solution of **100** (45 mg, 0.13 mmol), (*R*)-*O*-methylmandelic acid (24 mg, 0.15 mmol), and DCC (30 mg, 0.15 mmol) in $CH_2Cl_2$ (4 mL) at room temperature was added DMAP (8 mg, 0.07 mmol). After 30 min, the mixture was passed through a plug of cotton which was rinsed with hexanes. The eluant was diluted with saturated aqueous $NaHCO_3$ (1 mL), washed with saturated aqueous NaCl, dried over $MgSO_4$, filtered, and concentrated under reduced pressure.

Chromatography of the residue on silica gel (EtOAc-hexanes, 1:7) afforded 53 mg (82%) of **104** as a colorless oil: $R_f$ 0.25 (EtOAc-hexanes, 1:7), $[\alpha]_D^{23}$ -67.1 (*c* 1.2, $CHCl_3$). Integrations were performed in two regions of the crude $^1H$ NMR spectrum; they are labeled a and b in the following NMR data: IR (neat) 2950, 2920, 2852, 1751, 1689, 1252, 1168 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ 0.05 (s, 6 H), 0.91 (s, 9 H), 0.92 (t, *J* = 7.4 Hz, 3H), 1.72-2.09 (m, 4H), 2.15 (m, 1H), 2.79 (t, *J* = 3.9 Hz, 1H), 2.89 (m, 1H), 3.42 (s, 3H), 3.88-4.01[a] (m, 2H), 4.81 (s, 1H), 5.58 (m, 1H), 5.83 (dd, *J* = 2.5, 10.4 Hz, 1H), 5.93 (dt, *J* = 2.4, 5.3 Hz, 1H), 6.24[b] (ddd, *J* = 2.1, 4.0, 10.4 Hz, 1H), 7.31-7.52 (m, 5H); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ -5.3, -5.2, 12.4, 18.4, 22.8, 25.5, 25.9 (3C), 40.9, 41.0, 47.9, 57.4, 66.9, 73.3, 82.4, 125.5, 127.0 (2C), 128.9, 131.0, 133.9, 135.8, 142.4, 170.0, 198.7; MS (CI) *m/z* 483 ($M^+$-H), 469, 427, 353, 319, 261, 187, 121; MS (CI) *m/z* 483 ($M^+$-H), 469, 427, 353, 319, 261, 187, 121; HRMS (CI) *m/z* 483.2567 (calcd for $C_{28}H_{39}O_5Si$: 483.2559).



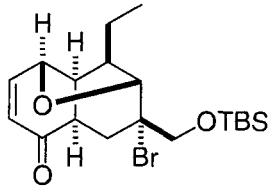

**(1S,4aS,5S,8aR)-7-{{[(tert-Butyl)dimethylsilyl]oxy}methyl}-5-ethyl-1,4,4a,5,8, 8a-hexahydro-4-oxonaphthalen-1-yl (S)-O-Methylmandelate (105).** To a solution of **100** (14 mg, 0.04 mmol), (*S*)-*O*-methylmandelic acid (11 mg, 0.06 mmol), and DCC (13 mg, 0.06 mmol) in $CH_2Cl_2$ (3 mL) at room temperature was added DMAP (3 mg, 0.02 mmol). After 30 min, the mixture was passed through a

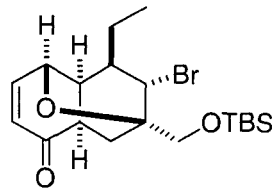
plug of cotton which was rinsed with hexanes. The mixture was diluted with saturated aqueous $NaHCO_3$ (1 mL), washed with saturated aqueous NaCl, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Chromatography of the residue on silica gel (EtOAc-hexanes, 1:5) gave 17 mg (82%) of **105** as a colorless oil: $R_f$ 0.22 (EtOAc-hexanes, 1:5); $[\alpha]_D^{23}$ -29.0 (*c* 1.53, $CHCl_3$); $^1H$ NMR (300 MHz, $CDCl_3$) δ 0.02 (s, 6 H), 0.89 (s, 9 H), 0.91 (t, *J* = 7.7 Hz, 3H), 1.36 (m, 1H), 1.71-1.97 (m, 3H), 2.09 (m, 1H), 2.64-2.78 (m, 2H), 3.42 (s, 3H), 3.70 (d, *J* = 12.9 Hz, 1H), 3.78 (d, *J* = 12.9 Hz, 1H), 4.81 (s, 1H), 5.52 (m, 1H), 5.87 (dd, *J* = 2.7, 10.3 Hz, 1H), 5.94 (dt, *J* = 2.5, 5.1 Hz, 1H), 6.45 (ddd, *J* = 1.7, 3.8, 10.3 Hz, 1H), 7.31-7.49 (m, 5H); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 5.3 (2C), 12.4, 18.3, 22.4, 25.5, 25.9 (3C), 40.7, 40.9, 47.9, 57.3, 66.4, 73.2, 82.3, 124.5, 127.2 (2C), 128.8 (2C), 129.0, 131.1, 133.7, 136.0, 142.5, 169.9, 198.6.




**(1S,4R,4aS,5S,8aR)-7-{{[(tert-Butyl)dimethylsilyl]oxy}methyl}-5-ethyl-1,4,4a,5,8,8a-hexahydronaphthalene-1,4-diol (106).** To a solution of **96**, obtained from **93** in MeOH (15 mL) at room temperature was added $NaBH_4$ (633 mg, 16.7 mmol) and $CeCl_3 \bullet 7H_2O$ (6.24 g, 16.7 mmol), and the mixture was stirred for 8 h at room temperature. Work-up as for **100** gave diol **106** (1.18 g, 62% from benzoquinone) as a white solid: $R_f$ 0.33 (EtOAc-hexanes, 1:3); mp 105-106 °C; $[\alpha]_D^{23}$ -129.7 (*c* 1.95, $CHCl_3$); IR (neat) 3387, 2956, 2928, 2881, 2858, 1254, 1005, 834, 776 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ 0.02 (s, 6H), 0.91 (s, 9H), 1.04 (t, *J*

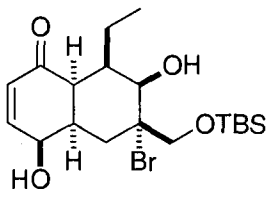
= 7.4 Hz, 3H), 1.69 (m, 2H), 1.89-2.11 (m, 4H), 2.14 (d, $J$ = 6.0 Hz, 1H), 2.23-2.35 (m, 2H), 4.01 (m, 2H), 4.15 (m, 1H), 4.44 (m, 1H), 5.65 (d, $J$ = 10.2 Hz, 1H), 5.76-5.83 (m, 2H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ -5.3 (2C) 12.4, 18.3, 23.1, 24.2, 25.9 (3C), 37.0, 37.3, 40.9, 64.4, 66.7, 70.3, 127.2, 128.4, 130.3, 137.5; MS (CI) *m/z* 337 ($M^+$-H), 321, 303, 262, 205, 189, 171, 161; HRMS (CI) *m/z* 337.2202 (calcd for $C_{19}H_{33}O_3Si$: 337.2199).



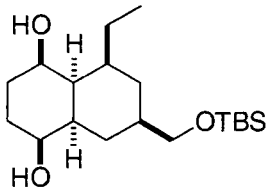

**(1R,2S,4R,8R,9S,10R)-2-Bromo-2-{{[(tert-butyl)dimethylsilyl]oxy}methyl}-10-ethyl-11-oxatricyclo[6.2.1.0$^{4,9}$]undec-6-en-5-one (109) and (1R, 3R,7R,8R,9R, 10S)-10-Bromo-1-{{[(tert-butyl)dimethylsilyl]oxy}methyl}-9-ethyl-11-oxatricyclo[5.3.1.0$^{3,8}$]undec-5-en-4-one (110).** To a solution of **106** (28 mg, 0.08 mmol) in THF (4 mL) was added N-bromosuccinimide (16 mg, 0.09 mmol), and the mixture was stirred for 1 h at room temperature. The mixture was passed through a short pad of silica gel, with EtOAc-hexanes (1:5) as an eluent, and the concentrated eluent was purified by column chromatography (EtOAc-hexanes, 1:5) to give 31 mg (91%) of a mixture of **107** and **108** as a colorless oil. The mixture was dissolved in $CH_2Cl_2$ (2 mL), and the solution was added dropwise to a suspension of PDC (68 mg, 0.18 mmol) and NaOAc (15 mg, 0.18 mmol) in $CH_2Cl_2$ (4 mL). The resulting mixture was stirred for 2 h at room temperature, then filtered through Florisil, and the filtrate was concentrated under reduced pressure. Chromatography (EtOAc:hexanes, 1:20 to 1:10) of the residue afforded

22 mg (73%) of a mixture of **109** and **110**. A pure sample of **109** was obtained as a white solid by repeated chromatography: $R_f$0.24 (EtOAc-hexanes, 1:5), mp 106-107 °C; $[\alpha]_D^{23}$ -29.2 (*c* 0.36, $CHCl_3$); IR (neat) 1689 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ 0.05 (s, 6H), 0.91 (s, 9H), 1.01 (t, *J* = 7.4 Hz, 3H), 1.33-1.62 (m, 2H), 1.99 (dd, *J* = 10.3, 16.1, 1H), 2.25 (dd, *J* = 8.1, 16.1 Hz, 1H), 2.50 (t, *J* = 3.8 Hz, 1H), 2.72 (t, *J* = 7.5 Hz, 1H), 2.85 (ddd, *J* = 3.8, 8.1, 11.0 Hz, 1H), 3.64 (d, *J* = 10.7 Hz, 1H), 3.75 (d, *J* = 10.7 Hz, 1H), 4.23 (s, 1H), 4.47 (t, *J* = 4.4 Hz, 1H), 5.96 (d, *J* = 9.9 Hz, 1H), 6.84 (dd, *J* = 5.0, 9.9 Hz, 1H); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ -5.4, 11.4, 18.3, 22.6, 25.8, 35.6, 43.1, 44.5, 46.5, 69.9, 70.8, 71.6, 82.9, 128.8, 141.5, 201.6; MS (CI) *m/z* 415 ($M^+$), 359, 335, 277, 259, 203, 175, 161, 105. HRMS (CI) *m/z* 413.1142 (calcd for $C_{19}H_{30}O_3SiBr$: 413.1148). The data for **110** was determined from the mixture of **109**: $R_f$0.22 (EtOAc-hexanes, 1:5); $^1H$ NMR (300 MHz, $CDCl_3$) δ 1.08 (t, *J* = 7.4 Hz, 3H), 1.61 (m, 1H), 1.70 (m, 1H), 1.76 (m, 1H), 2.13-2.21 (m, 2H), 2.37 (dd, *J* = 12.1, 14.5 Hz, 1H), 2.68 (m, 1H), 3.59 (s, 2H), 3.93 (m, 1H), 4.38 (m, 1H), 5.96 (d, *J* = 9.9 Hz, 1H), 7.01 (dd, *J* = 5.7, 9.9 Hz, 1H); $^{13}C$ NMR (75 MHz,$CDCl_3$) δ -5.3 (2C), 11.7, 23.7, 25.9 (3C), 36.1, 42.1, 49.5, 51.4, 63.5, 66.9, 106,0, 127.2, 147.0, 201.6.



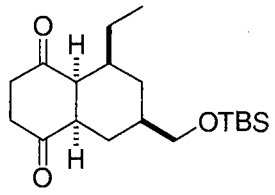

**(4S,4aR,6S,7R,8R,8aR)-6-Bromo-6-{{[(tert-butyl)dimethylsilyl]oxy}methyl}-8-ethyl-4a,5,6,7,8,8a-hexahydro-4,7-dihydroxynaphthalen-1-(4H)-one (112).** To a solution of **100** (28 mg, 0.08 mmol) in $CH_2Cl_2$ (3 mL) at room temperature was

added N-bromosuccinimide (16 mg, 0.09 mmol), and the mixture was stirred for 1 h. The mixture was passed through a short pad of silica gel, with EtOAc-hexanes (1:3) as eluent, and the concentrated eluent was purified by column chromatography (EtOAc-hexanes, 1:3) to give 25 mg of **112** (71%) as a colorless oil: $R_f$ 0.16 (EtOAc-hexanes, 1:3); IR (neat) 3445, 2953, 2853, 1663, 1248 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ 1.01 (t, $J$ = 7.4 Hz, 3H), 1.79-2.13 (m, 4H), 2.31 (m, 1H), 2.64 (dt, $J$ = 1.0, 4.4 Hz, 1H), 3.00 (m, 1H), 3.48 (d, $J$ = 3.3 Hz, 1H), 3.97 (d, $J$ = 10.9 Hz, 1H), 4.01 (d, $J$ = 10.9 Hz, 1H), 4.07 (brs, 1H), 4.91 (m, 1H), 5.94 (dd, $J$ = 2.6, 10.3 Hz, 1H), 6.70 (ddd, $J$ = 1.8, 3.2, 10.3 Hz, 1H); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ -5.4 (2C), 12.3, 18.3, 23.3, 25.8 (3C), 26.7, 42.4, 42.8, 46.5, 69.2, 70.7, 74.4, 75.2, 129.7, 149.4, 202.1; HRMS (CI) *m/z* 435.1391 (calcd for $C_{19}H_{34}O_4SiBr$: 435.1389).



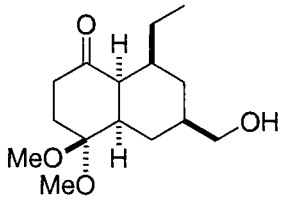

**(1S,4R,4aS,5S,7R,8aR)-7-{{[(tert-Butyl)dimethylsilyl]oxy}methyl}-5-ethyl-decahydronaphthalene-1,4-diol (113).** To a solution of **106** (913 mg, 2.70 mmol) in EtOAc (10 mL) was added 5% Rh on $Al_2O_3$ (1.40 g), and the mixture was placed under a balloon filled with $H_2$. After 24 h, the mixture was filtered through a pad of Celite, with EtOAc (10 mL) as an eluent, and the filtrate was concentrated under reduced pressure. Chromatography (EtOAc-hexanes, 1:3) of the residue on silica gel gave **113** (871 mg, 94%) as a colorless oil: $R_f$ 0.22 (EtOAc-hexanes, 1:3); mp 123-124 °C; $[\alpha]_D^{23}$ -3.4 (*c* 2.3, $CHCl_3$); IR (neat) 3439,

2952, 2928, 2856, 1500, 1462, 1254, 1104, 1079, 836 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ 0.04 (s, 6H), 0.89 (s, 9H), 0.93 (t, *J* = 7.1 Hz, 3H), 1.06 (br s, 1H), 1.23-1.91 (m, 15H), 3.44 (dd, *J* = 6.4, 9.9 Hz, 1H), 3.49 (dd, *J* = 4.5, 9.9 Hz, 1H), 3.74 (ddd, *J* = 4.5, 9.4, 11.5 Hz, 1H), 4.09 (br s, 1H); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ -5.3 (2C), 12.3, 18.4, 24.3, 24.7, 26.0 (3C), 26.5, 32.9, 33.3, 39.9, 41.3, 41.9, 43.1, 66.7, 69.0, 73.2.; MS (CI) *m/z* 343 ($M^+$+H), 325, 283, 267, 209, 193, 175; HRMS (CI) *m/z* 343.2674 (calcd for $C_{19}H_{39}O_3Si$: 343.2669).



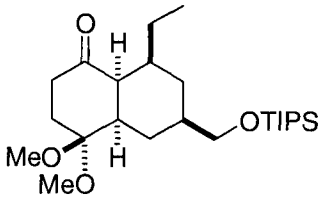

**(4aS,5S,7R,8aR)-7-{{[(tert-Butyl)dimethylsilyl]oxy}methyl}-5-ethyloctahydro-naphthalene-1,4-dione (114).** To a solution of pyridinium dichromate (1.20 g, 3.20 mmol) in $CH_2Cl_2$ (10 mL) was added a solution of **113** (730 mg, 2.13 mmol) in $CH_2Cl_2$ (3 mL), and the mixture was stirred for 4 h at room temperature. The mixture was diluted with $Et_2O$ (30 mL), and the solution was filtered through a Celite pad. The filtrate was concentrated, and the residue was chromatographed on silica gel (EtOAc-hexanes, 1:3) to yield 635 mg (88%) of **114** as a colorless oil: $R_f$ 0.16 (EtOAc-hexanes, 1:5); $[\alpha]_D^{23}$ +88.5 (*c* 1.42, $CHCl_3$); IR (neat) 2959, 2925, 2852, 1713, 1250, 1098, 837 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ 0.02 (s, 6H), 0.86 (s, 9H), 0.87 (overlapping m, 1H), 0.88 (t, *J* = 7.4 Hz, 3H), 1.21-1.35 (m, 2H), 1.53-1.76 (m, 4H), 2.00 (m, 1H), 2.35-2.49 (m, 1H), 2.59 (dt, *J* = 4.5, 13.6 Hz, 1H), 2.65-2.74 (m, 2H), 2.83 (m, 1H), 3.09 (m, 1H), 3.34 (dd, *J* = 6.4, 9.9 Hz, 1H), 3.43 (dd, *J* = 5.4, 9.9 Hz, 1H); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ -5.5 (2C),

12.3, 18.2, 25.8 (3C), 26.2, 29.6, 30.6, 37.0 (2C), 40.4, 40.6, 49.3, 51.8, 67.7, 208.9, 210.9; MS (CI) *m/z* 339 ($M^+$+H), 323, 281, 263, 207, 189, 147, 75; HRMS (CI) *m/z* 339.2352 (calcd for $C_{19}H_{35}O_3Si$: 339.2356).



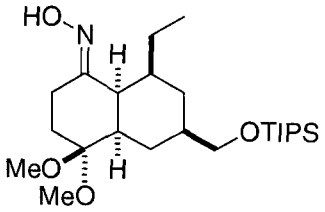

**(4aR,6R,8S,8aS)-8-Ethyl-3,4,4a,5,6,7,8,8a-octahydro-4,4-dimethoxy-6-(hydroxymethyl)naphthalen-1(2H)-one (117).** A solution of **114** (570 mg, 1.68 mmol) and pyridinium *p*-toluensulfonate (43 mg, 0.17 mmol) in MeOH (10 mL) was heated at 55 °C for 3 h, after which the mixture was allowed to cool to room temperature. The solution was diluted with saturated aqueous $NaHCO_3$ (3 mL) and was extracted with $Et_2O$ (20 mL). The extract was washed with saturated aqueous NaCl, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. Chromatography of the residue on silica gel (EtOAc-hexanes, 1:2) gave 404 mg (89%) of **117** as a colorless oil: $R_f$ 0.16 (EtOAc-hexanes, 1:2); $[\alpha]_D^{23}$ +15.7 (*c* 0.21, $CHCl_3$); IR (neat) 3419, 2923, 2867, 2831, 1712, 1461, 1123, 1097 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ 0.66 (ddd, *J* = 12.7, 12.7, 12.7 Hz, 1H), 0.84 (t, *J* = 7.5 Hz, 3H), 1.18 (m, 1H), 1.31 (ddd, *J* = 12.3, 12.3, 12.3 Hz, 1H), 1.49-1.67 (m, 4H), 1.76 (m, 1H), 1.79 (dt, *J* = 5.0, 14.3 Hz, 1H), 1.89 (br s, 1H, *OH*), 2.08 (ddd, *J* = 2.1, 5.0, 14.3 Hz, 1H), 2.13 (ddt, *J* = 2.5, 9.0, 14.3 Hz, 1H), 2.22 (ddt, *J* = 2.6, 4.6, 13.1 Hz, 1H), 2.41 (dt, 6.8, 14.3 Hz, 1H), 2.91 (m, 1H), 3.19 (s, 3H), 3.29 (s, 3H), 3.44 (dd, *J* = 6.0, 10.6 Hz, 1H), 3.46 (dd, *J* = 6.4, 10.6 Hz, 1H); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 12.4, 26.3, 28.1, 28.2, 30.1, 38.6, 40.5,

41.7, 45.7, 47.2, 47.9, 48.2, 68.1, 100.5, 211.6; MS (CI) *m/z* 270 ($M^+$), 253, 239, 221, 207, 189, 125, 101, 84; HRMS (CI) *m/z* 270.1830 (calcd for $C_{15}H_{26}O_4$: 270.1831).

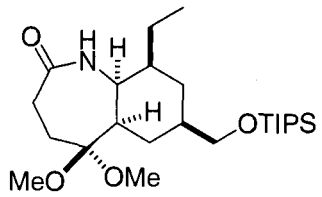



**(4aR,6R,8S,8aS)-8-Ethyl-3,4,4a,5,6,7,8,8a-octahydro-4,4-dimethoxy-6-{[(triisopropylsilyl)oxy]methyl}-naphthalen-1(2H)-one (92).** To a solution of TIPSCl (332 mg, 1.72 mmol) and imidazole (117 mg, 1.72 mmol) in DMF (5 mL) at room temperature was added a solution of **117** (310 mg, 1.15 mmol) in DMF (1 mL, 1.15 mmol), and the mixture was stirred for 2 h at room temperature. The mixture was diluted with pentane (20 mL), and the solution was washed with $H_2O$ (3 x 10 mL) and saturated NaCl, dried over $MgSO_4$, and concentrated under reduced pressure. Chromatography of the residue on silica (EtOAc-hexanes, 1:5) furnished 456 mg (93%) of **92** as a colorless oil: $R_f$ 0.23 (EtOAc-hexanes, 1:10); $[\alpha]_D^{23}$ + 6.6 (*c* 1.16, $CHCl_3$); IR (neat) 2956, 2942, 2864, 2361, 1719, 1116, 1097, 1055 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ 0.64 (ddd, *J* = 13.1, 13.1, 13.1 Hz, 1H), 0.85 (t, *J* = 7.5 Hz, 3H), 1.03-1.07 (m, 21H), 1.19 (m, 1H), 1.28 (ddd, *J* = 12.0, 12.0, 12.0 Hz, 1H), 1.49-1.69 (m, 4H), 1.73.1.87 (m, 2H), 2.08 (ddd, *J* = 2.1, 4.8, 11.3 Hz, 1H), 2.21 (ddt, *J* = 2.8, 5.3, 13.1 Hz, 1H), 2.40 (dt, *J* = 6.1, 13.5 Hz, 1H), 2.92 (m, 1H), 3.19 (s, 3H), 3.30 (s, 3H), 3.45 (dd, *J* = 6.8, 9.5 Hz, 1H), 3.53 (dd, *J* = 5.8, 9.5 Hz, 1H); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 11.9, 12.4, 17.9, 26.3, 28.0, 28.4, 30.3, 38.6, 41.0, 41.8, 45.9, 47.7, 47.8, 48.4, 68.5, 100.6, 211.5; MS (CI) *m/z* 426

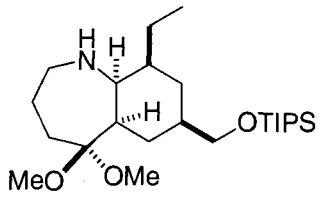
($M^+$), 409, 383, 351, 221, 184, 171, 147, 101; HRMS (CI) *m/z* 426.3162 (calcd for $C_{24}H_{46}O_4Si$: 426.3165).



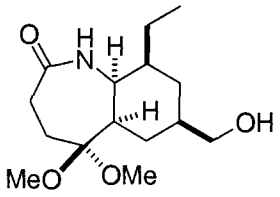

**(4aR,6R,8S,8aS)-8-Ethyl-3,4,4a,5,6,7,8,8a-octahydro-4,4-dimethoxy-6-{[(triisopropylsilyl)oxy]methyl}-naphthalen-1(2H)-one Oxime (118).** A suspension of **92** (312 mg, 0.73 mmol), hydroxylamine hydrochloride (508 mg, 2.31 mmol), and NaOAc (600 mg, 7.31 mmol) in MeOH (3 mL) was heated gently at reflux for 3 h. After cooling to room temperature, the mixture was concentrated under reduced pressure. Chromatography of the residue on silica gel (MeOH-$CH_2Cl_2$, 1:60) gave 261 mg (81%) of **118** as a colorless oil: $R_f$ 0.21 (EtOAc-hexanes, 1:5); $[\alpha]_D^{23}$ +20.1 (*c* 1.05, $CHCl_3$); IR (neat) 3404, 2956, 2941, 2864, 1462, 1120, 1099, 1056, 881 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 0.87 (t, *J* = 7.5 Hz, 3H), 0.88 (m, 1H), 1.07 (m, 21H), 1.3-1.7 (m, 9H), 1.93 (m, 1H), 2.02 (m, 1H), 2.77 (t, *J* = 3.4 Hz, 1H), 3.18 (s, 3H), 3.23 (s, 3H), 3.33 (m, 1H), 3.46-3.57 (m, 2H), 7.06 (brs, 1H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 11.9, 12.5, 17.9, 20.1, 26.6, 26.7, 26.8, 30.2, 41.4, 41.7, 43.1, 45.5, 47.3, 47.5, 68.7, 101.2, 158.2.



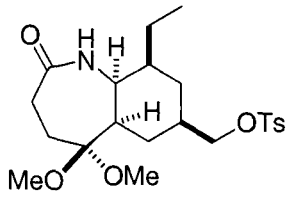

**(5aR, 7R, 9S, 9aS)-9-Ethyldecahydro-5,5-dimethoxy-7-{[(triisopropylsilyl) oxy]methyl}-2H-benz[b]azepin-2-one (119).** To a mixture of *p*-toluenesulfonyl chloride (203 mg, 1.07 mmol), triethylamine (0.15 mL, 1.07 mmol), and a catalytic amount of DMAP in $CH_2Cl_2$ (3 mL) was added a solution of **118** (186 mg, 0.43 mmol) in $CH_2Cl_2$ (5 mL), and the mixture was stirred for 3 h at room temperature. The mixture was diluted with $CH_2Cl_2$ (10 mL), and the solution was washed with $H_2O$ and saturated aqueous NaCl, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. Chromatography of the residue on silica gel (EtOAc-hexanes, 1:3, then MeOH-$CH_2Cl_2$, 1:15) afforded 138 mg (74%) of **119** as a colorless oil: $R_f$ 0.12 (EtOAc-hexanes, 1:3); $[\alpha]_D^{23}$ -8.4 (*c* 2.38, $CHCl_3$); IR (neat) 2956, 2941, 2864, 1663, 1461, 1106, 1055, 882 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 0.83 (ddd, $J$ = 12.8, 12.8, 12.8 Hz, 1H), 0.92 (t, $J$ = 7.4 Hz, 3H), 0.96-1.13 (m, 22H), 1.31 (dq, $J$ = 7.4, 7.4 Hz, 1H), 1.49-1.83 (m, 6H) 1H, 1.91 (ddt, $J$ = 1.7, 7.5, 13.6 Hz, 1H), 2.19-2.28 (m, 1H), 2.47 (dt, $J$ = 1.2, 13.1 Hz, 1H), 3.15 (s, 3H), 3.18 (s, 3H), 3.50 (brd, $J$ = 6.0, 2H), 3.79 (brs, 1H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 11.4, 11.8, 17.9, 23.3, 25.3, 25.8, 29.65, 29.70, 40.6, 42.8, 46.8, 47.2, 47.3, 49.6, 68.2, 102.0, 176.5; MS (CI) *m/z* 442 ($M^+$+H), 410, 398, 378, 366; HRMS (CI) *m/z* 442.3353 (calcd for $C_{24}H_{48}NO_4Si$: 442.3353).



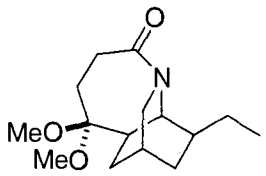

**(5aR,7R,9S,9aS)-9-Ethyldecahydro-5,5-dimthoxy-7-{[(triisopropylsilyl)oxy] methyl}-2H-benz[b]azepin (121).** To a solution of **119** (43 mg, 0.1 mmol) in benzene (3 mL) at room temperature was added a solution of Red-Al (3.4M solution in toluene, 0.3 mL), and the mixture was refluxed at 80 °C for 1 *h*. After the solution had cooled to room temperature, EtOAc (5 mL) was added. The mixture was concentrated, and the residue was chromatographed on silica gel (MeOH: $CH_2Cl_2$ = 1:30 to 1:15) to yield 39 mg (92%) of **121** as a colorless oil: $R_f$ 0.16 (MeOH-$CH_2Cl_2$, 1:15); IR (neat) 3441, 2941, 2892, 2863, 2827, 1469, 1462, 1455, 1260, 1108, 1065 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 0.83-0.91 (m, 1H), 0.90 (t, $J$ = 7.2 Hz, 3H), 1.04-1.10 (m, 21H), 1.23-1.41 (m, 4H), 1.54-1.68 (m, 6H), 1.75-1.82 (m, 3H), 2.81-2.93 (m, 2H), 3.01 (dt, $J$ = 7.2, 12.8 Hz, 1H), 3.13 (s, 3H), 3.21 (s, 3H), 3.52 (brd, 5.6 Hz, 2H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 11.8, 11.9, 18.0, 21.9, 24.7, 26.1, 27.5, 30.1, 40.6, 43.7, 46.8, 47.3, 47.7, 47.9, 55.5, 68.7, 104.1; HRMS (CI) *m/z* 427.3482 (calcd for $C_{24}H_{49}NO_3Si$: 427.3482).



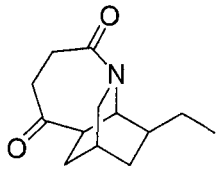

**(5aR,7R,9S,9aS)-9-Ethyldecahydro-7-(hydroxymethyl)-5,5-dimethoxy-2H-benz[b]azepin-2-one (124).** To a solution of **119** (125 mg, 0.28 mmol) in THF (3 mL) at room temperature under argon was added a 1M solution of TBAF (0.4 mL, 0.4 mmol), and the mixture was stirred for 1 h at room temperature. The mixture was diluted with $CH_2Cl_2$ (10 mL), and the solution was washed with saturated aqueous NaCl, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. Chromatography of the residue on silica gel (MeOH-$CH_2Cl_2$, 1:15) gave 79 mg (99%) of **124** as a colorless oil: $R_f$ 0.1 (MeOH-$CH_2Cl_2$, 1:15); $[\alpha]_D^{23}$ -31.7 (*c* 1.1, $CHCl_3$); IR (neat) 3385, 2956, 2929, 2872, 1655, 1452, 1104, 1054 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ 0.93 (ddd, *J* = 12.3, 12.3, 12.3 Hz, 1H), 0.94 (t, *J* = 7.3 Hz, 3H), 1.09 (ddd, *J* = 12.4, 12.4, 12.4 Hz, 1H), 1.33 (dq, *J* = 7.2, 7.2 Hz, 2H), 1.51-1.87 (m, 7H), 1.93 (ddt, *J* = 2.3, 7.6, 15.2 Hz, 1H), 2.26 (m, 1H), 2.48 (dt, *J* = 1.4, 13.7 Hz, 1H), 3.16 (s, 3H), 3.18 (s, 3H), 3.49 (m, 2H), 3.79 (m, 1H), 5.25 (br s, 1H); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 11.4, 23.2, 25.3, 25.7, 29.4, 29.7, 40.0, 42.8, 46.6, 47.3, 47.4, 49.6, 67.7, 101.9, 176.8; MS (CI) m/z ($M^+$) 286, 268, 254, 222, 204, 146, 114, 101; HRMS (CI) m/z 286.2013 (calcd for $C_{15}H_{28}NO_4$: 286.2019).



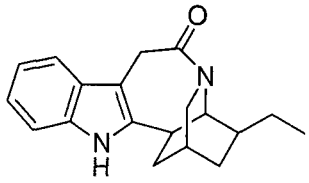

**(5aR,7R,9S,9aS)-9-Ethyldecahydro-5,5-dimethoxy-7-{{[(4-methylphenyl) sulfonyl]oxy}methyl}-2H-benz[b]-azepin-2-one** (**91**). To a mixture of *p*-toluenesulfonyl chloride (21 mg, 0.11 mmol), triethylamine (31 uL, 0.23 mmol), and a catalytic amount of DMAP in $CH_2Cl_2$ (3 mL) was added **124** (21 mg, 0.08 mmol), and the mixture was stirred for 3 h at room temperature. The mixture was diluted with $CH_2Cl_2$ (10 mL), and the solution was washed with $H_2O$ and saturated aqueous NaCl, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. Chromatography of the residue on silica gel (MeOH-$CH_2Cl_2$, 1:15) produced 33 mg (100%) of **91** as a colorless oil: $R_f$ 0.29 (MeOH-$CH_2Cl_2$, 1:15); $[\alpha]_D^{23}$ - 27.2 (*c* 1.2, $CHCl_3$); IR (neat) 2956, 1660, 1456, 1357, 1188, 1176, 1104, 1052 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 0.74 (ddd, $J$ = 12.8, 12.8, 12.8 Hz, 1H), 0.94 (t, $J$ = 7.3 Hz, 3H), 0.96 (ddd, $J$ = 12.7, 12.7, 12.7 Hz, 1H), 1.31 (dq, $J$ = 7.3, 7.3 Hz, 2H), 1.41-1.58 (m, 3H), 1.68 (dt, $J$ = 3.5, 13.6 Hz, 1H), 1.71-1.95 (m, 3H), 2.15-2.27 (m, 1H), 2.37-2.49 (m, 1H), 2.47 (s, 3H), 3.11 (s, 3H), 3.15 (s, 3H), 3.72-3.80 (m, 2H), 3.82 (dd, $J$ = 6.6, 9.6 Hz, 1H), 4.97 (br s, 1H); 7.36 (d, $J$ = 8.2 Hz, 2H), 7.76 (d, $J$ = 8.2 Hz, 2H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 11.4, 21.6, 22.9, 25.3, 25.6, 29.0, 29.7, 37.0, 42.5, 46.3, 47.36, 47.44, 49.1, 74.2, 101.7, 127.9, 129.9, 132.7, 144.9, 176.6; MS (CI) *m/z* ($M^+$-OMe) 408, 376, 285, 204, 173; HRMS (CI) *m/z* 439.2029 (calcd for $C_{22}H_{33}NO_6S$: 439.2028).




**(5aR,7R,9S,9aS)-9-Ethyl-4,5,5a,6,7,8,9,9a-octahydro-5,5-dimethoxy-1,7-methano-1H-benz[b]azepin-2(3H)-one (90).** To a solution of NaH (3 mg, 0.11 mmol) in THF (3 mL) at 0°C under argon was added a solution of **91** (16 mg, 0.04 mmol) in THF (1 mL), and the mixture was stirred for 30 min at room temperature and then refluxed for 1 h. The mixture was diluted with saturated aqueous $NH_4Cl$ (0.5 mL), and the solution was extracted with dichloromethane. The extract was washed with saturated aqueous NaCl, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. Chromatography of the residue on silica gel (MeOH-$CH_2Cl_2$, 1:15) yielded 6.6 mg (71%) of **90** as a colorless oil: $R_f$ 0.1 (MeOH-$CH_2Cl_2$, 1:15); $[\alpha]_D^{23}$ -21.2 (*c* 1.1, $CHCl_3$); IR (neat) 2930, 2358, 1658, 1634, 1454, 1404, 1102, 1064, 1051 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ 0.91 (t, *J* = 7.3 Hz, 3H), 1.12 (ddt, *J* = 2.4, 9.2, 13.6 Hz, 1H), 1.30-1.81 (m, 7H), 1.92-2.13 (m, 3H), 2.27 (ddd, *J* = 1.0, 7.4, 13.2 Hz, 1H), 2.72 (dt, *J* = 0.9, 13.3 Hz, 1H), 3.09 (m, 1H), 3.17 (s, 3H), 3.19 (s, 3H), 3.60 (brd, *J* = 2.8 Hz, 1H), 3.75 (ddd, *J* = 2.6, 4.3, 11.6 Hz, 1H); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 12.2, 25.8, 27.2, 27.4, 28.3, 30.0, 31.4, 40.5, 42.8, 47.7 (2C), 50.1, 50.7, 103.1, 179.2; MS (CI) *m/z* ($M^+$) 267, 252, 236, 220, 204, 138, 101; HRMS (CI) *m/z* 267.1835 (calcd for $C_{15}H_{25}NO_3$: 267.1834).

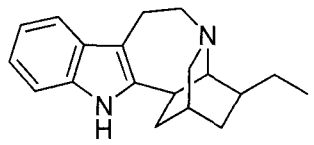


**(5aR,7R,9S,9aS)-9-Ethyl-3,4,5a,6,7,8,9,9a-octahydro-1,7-methano-1H-benz [b]azepin-2,5-dione (125).** To a solution of *p*-toluenesulfonic acid monohydrate (11 mg, 0.06 mmol) in acetone (3 mL) at 0 °C under argon was added a solution of **90** (15 mg, 0.06 mmol) in acetone (1 mL), and the mixture was stirred for 12 h at room temperature. The mixture was diluted with saturated aqueous $NaHCO_3$ (0.5 mL) and was extracted with $CHCl_3$. The extract was washed with saturated aqueous NaCl, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure to give 11 mg of **125** (86%) as a colorless oil: $^1$H NMR (300 MHz, $CDCl_3$) δ 0.97 (t, *J* = 7.3 Hz, 3H, $CH_3$), 1.33-1.60 (m, 4H), 1.69-1.87 (m, 2H), 1.89-2.06 (m, 2H), 2.54 (ddd, *J* = 4.9, 9.7, 13.8 Hz, 1H), 2.62-2.74 (m, 3H), 3.02 (ddd, *J* = 7.4, 10.1, 13.6 Hz, 1H) 3.17 (d, J = 11.8 Hz, 1H), 3.84-3.97 (m, 2H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 12.0, 26.0, 27.1, 28.6, 30.2, 31.5, 37.1, 38.4, 49.6, 49.9, 52.1, 175.8, 210.5.



**(+)-Ibogamine-7-one (126).** To a solution of **125** (7 mg, 0.03 mmol) in AcOH (1 mL) at room temperature was added a solution of phenylhydrazine (5 mg, 0.05 mmol) in AcOH (1 mL), and the mixture was stirred for 1 h at 50 °C. The mixture was allowed to cool to room temperature during 1h, after which boron trifluoride

etherate (9 mg, 0.06 mmol) was added. The resulting yellow solution was stirred for 12 h at 80 °C. After the mixture had cooled to room temperature, it was diluted with $CH_2Cl_2$, and the solution was washed with $H_2O$ and saturated aqueous NaCl, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. Chromatography of the residue on silica gel (MeOH-$CH_2Cl_2$, 1:30) gave 7 mg (77%) of **126** as a pale yellow solid: $R_f$ 0.23 (MeOH-$CH_2Cl_2$, 1:30); mp 230-232 °C; $[\alpha]_D^{23}$ + 27.9 (c 0.7, $CHCl_3$); IR (neat) 3429, 1631 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ 0.98 (t, $J$ = 7.4 Hz, 3H), 1.48-2.19 (m, 8H), 3.03 (m, 1H), 3.18 (d, $J$ = 11.8 Hz, 1H), 3.74 (d, $J$ = 15.7 Hz, 1H), 3.81 (m, 1H), 3.97 (dd , $J$ = 1.7, 15.7 Hz, 1H), 4.15 (s, 1H) 7.06-7.18 (m, 2H), 7.25 (m, 1H), 7.50 (m, 1H), 7.89 (br s, 1H) ; $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 12.1, 27.5, 28.6, 30.7, 32.1, 32.8, 35.9, 38.9, 49.3, 51.5, 102.6, 110.3, 118.2, 119.7, 121.7, 127.8, 135.0, 138.8, 175.8; MS (CI) *m/z* ($M^+$+H) 295, 279, 135, 122, 91, 73; HRMS (CI) *m/z* 294.1731 (calcd for $C_{19}H_{22}N_2O$: 294.1732).




**(–)-Ibogamine (1)**. To a solution of **126** (4.2 mg, 0.014 mmol) in dry THF (3 mL) was added $NaBH_4$ (28 mg, 0.74 mmol) in one portion. The mixture was cooled to 0 °C, and $BF_3$•$OEt_2$ (160 mg, 1.13 mmol) was syringed into the mixture dropwise. The resulting yellow suspension was stirred at room temperature for 3 h under argon. The solvent was evaporated, and MeOH (2 mL), $H_2O$ (0.4 mL), and 10% HCl (0.2 mL) were added. This solution was stirred at room temperature for 4h,

after which the MeOH was evaporated and the residue was taken up into $CH_2Cl_2$ (10 mL). The mixture was neutralized with saturated aqueous $NaHCO_3$, and the aqueous layer was extracted with $CH_2Cl_2$. The organic extract was dried over $MgSO_4$ and was concentrated to give a yellow solid. Column chromatography of this material (MeOH-$CH_2Cl_2$, 1:30) afforded 3.1 mg (78%) of **1** as a pale yellow crystalline solid; $R_f$ 0.23 (MeOH-$CH_2Cl_2$, 1:15); mp 156-157 °C; $[\alpha]_D^{23}$ -45.8 (*c* 0.2, EtOH); IR (neat) 3400 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 0.91 (t, $J$ = 7.1 Hz, 3H), 1.24 (m, 1H), 1.43-1.62 (m, 3H), 1.66 (ddd, $J$ = 3.4, 6.4, 13.2 Hz, 3H), 1.77-1.90 (m, 2H), 2.06 (m, 1H), 2.72 (m, 1H), 2.91 (s, 1H), 2.96 (ddd, $J$ = 1.6, 3.8, 11.7 Hz, 1H), 3.02-3.11 (m, 2H), 3.17 (m, 1H), 3.33 (ddd, $J$ = 4.4, 12.3, 16.6 Hz, 1H), 3.42 (m, 1H), 7.06-7.31 (m, 3H), 7.48 (d, $J$ = 7.1 Hz, 1H), 7.67 (brs, 1H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 11.9, 20.5, 26.3, 27.7, 31.9, 34.0, 41.1, 41.9, 49.9, 54.3, 57.7, 109.1, 110.1, 117.9, 119.2, 121.1, 129.6, 134.7, 141.5; MS (CI) *m/z* ($M^+$+H) 281, 195, 149, 136, 97, 69; HRMS (CI) *m/z* 280.1938 (calcd for $C_{19}H_{24}N_2$: 280.1940).

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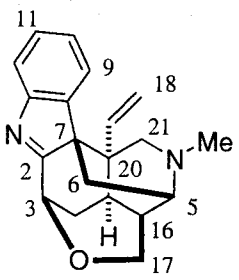
# PART II. AN APPROACH TOWARD THE SYNTHESIS OF KOUMINE.

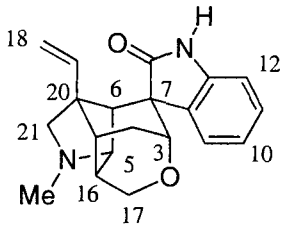
# Chapter III. AN APPROACH TOWARD THE SYNTHESIS OF KOUMINE

## History and Background

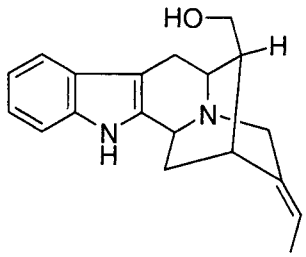
The plant genus *Gelsemium* (Loganiaceae) is a rich source of indole alkaloids with remarkably diverse and complex structures.[1] The *Gelsemium* alkaloids can be classified into five groups based on their skeletons, of which koumine (**1**), gelsemine (**2**), koumidine (**3**), gelsedine (**4**), and humanthenine (**5**) are representative members (**Figure 2.1**).



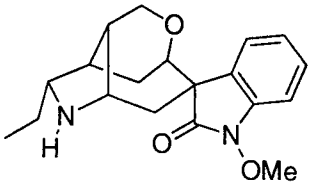

(-)-Koumine (**1**)



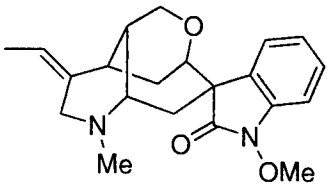

(+)-Gelsemine (**2**)




(-)-Koumidine (**3**)




(-)-Gelsedine (**4**)




(-)-Humanthenine (**5**)

**Figure 2.1** Some alkaloids from the plant genus *Gelsemium*.

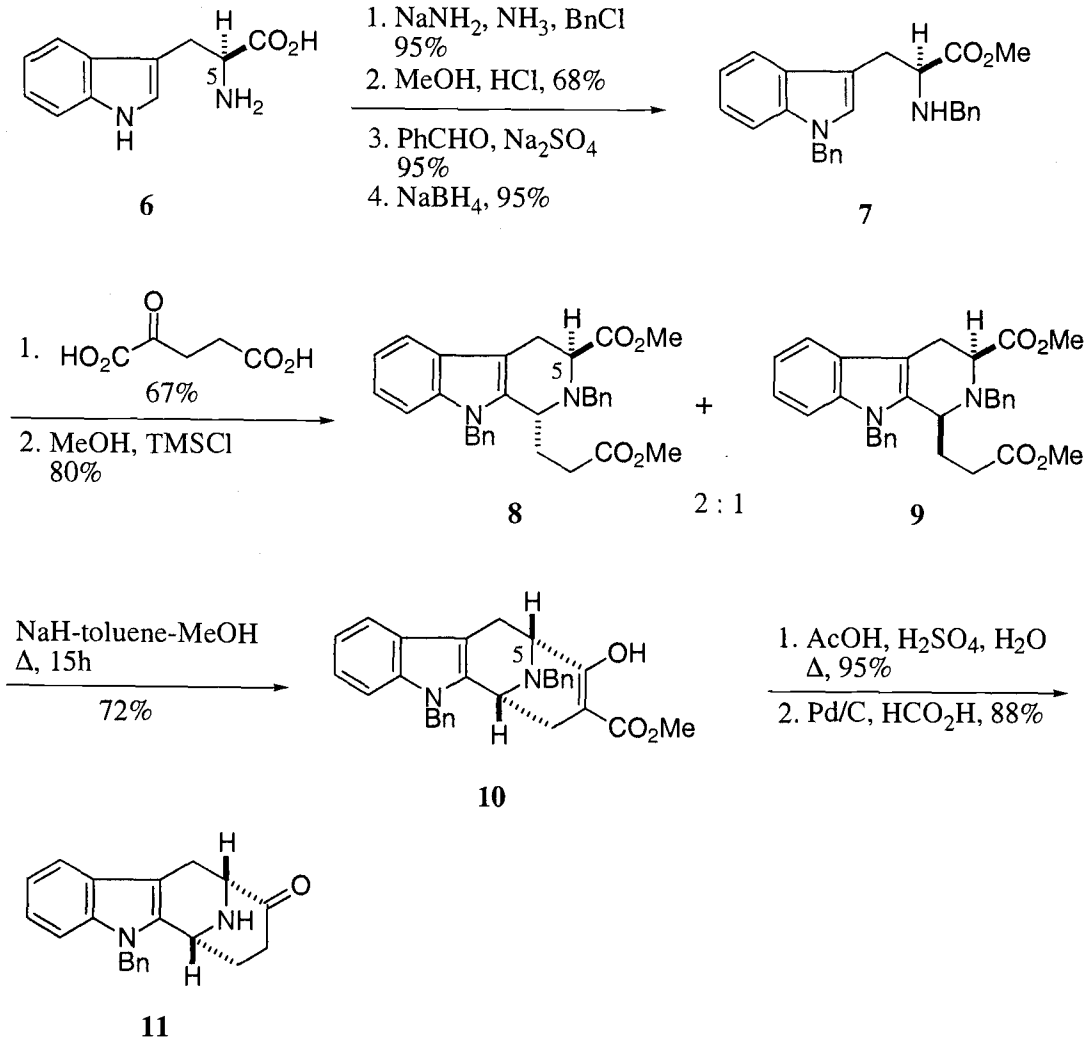
Koumine (**1**) is the principal alkaloid of the Chinese medicinal plant Kou-Wen, later identified as *Gelsemium elegans Bentham*. The constitution of

koumine (**1**) resisted elucidation by chemical degradation and spectroscopic analysis, and it was single crystal X-ray crystallography which eventually solved this structural problem.[2] The absolute configuration of natural (-)-koumine (**1**) was determined by its partial synthesis from the alkaloid vobasine.[3] While the plant *Gelsemium elegans* has been used in China for severe pain release, the pharmacological properties of koumine (**1**) have not been systematically investigated outside of China. However, recent clinical evaluation of koumine has shown promising results, especially for the treatment of malignant tumors.[4] Good analgesic activity has also been reported for this compound.[4]

(+)-Gelsemine (**2**), bearing some structural resemblance to (-)-koumine (**1**), was first isolated from *Gelsemium sempervirens* in 1870.[1] Like koumine, the exact constitution of (+)-gelsemine (**2**) remained elusive, until in 1959 independent reports of its structure appeared by Conroy and Wilson.[5,6] Gelsemine (**2**) has long been known for its strong central nervous system stimulant properties in western medicinal history. The alkaloid also shows analgesic as well as antihypertensive activities, and its pharmacological properties have been thoroughly investigated.[1]

Koumine (**1**) and gelsemine (**2**) have been the target of numerous synthetic investigations because of their intriguing structures and interesting biological activities. In 1990, Magnus and co-workers reported the first and so far only total synthesis of koumine leading to the unnatural (+)-enantiomer.[7] Their synthesis began with the natural amino acid (*S*)-(-)-tryptophan (**6**) which bears the same absolute configuration at C-5 as that found in natural (-)-koumine (**Scheme 1**). A four-step transformation of **6** provided the *N, N'*-

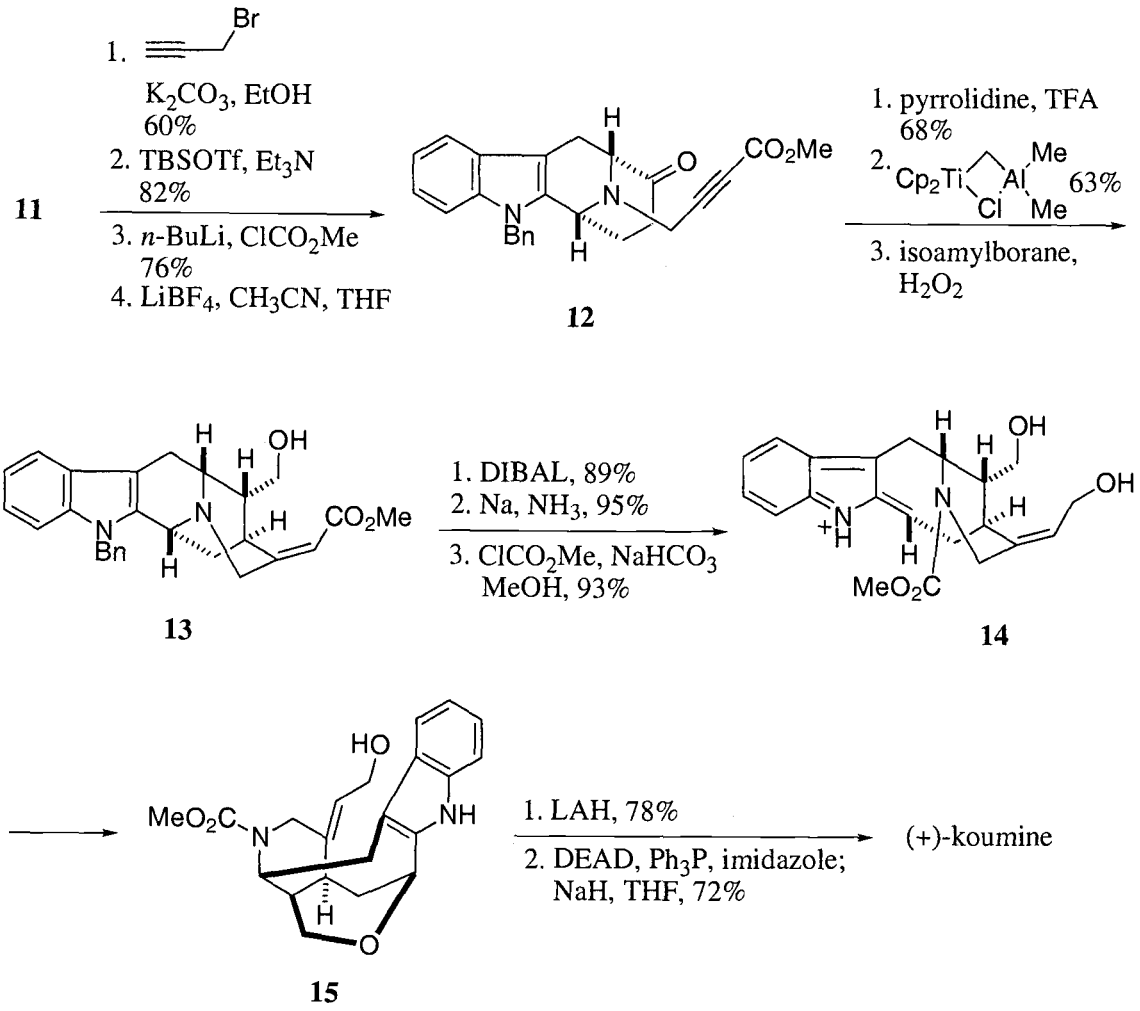
dibenzyltryptophan methyl ester **7** which underwent Pictet-Spengler condensation with 2-ketoglutaric acid to give a 2:1 mixture of diastereomeric esters **8** and **9** after methanolysis.




**Scheme 1.** Magnus' synthesis of (+)-koumine

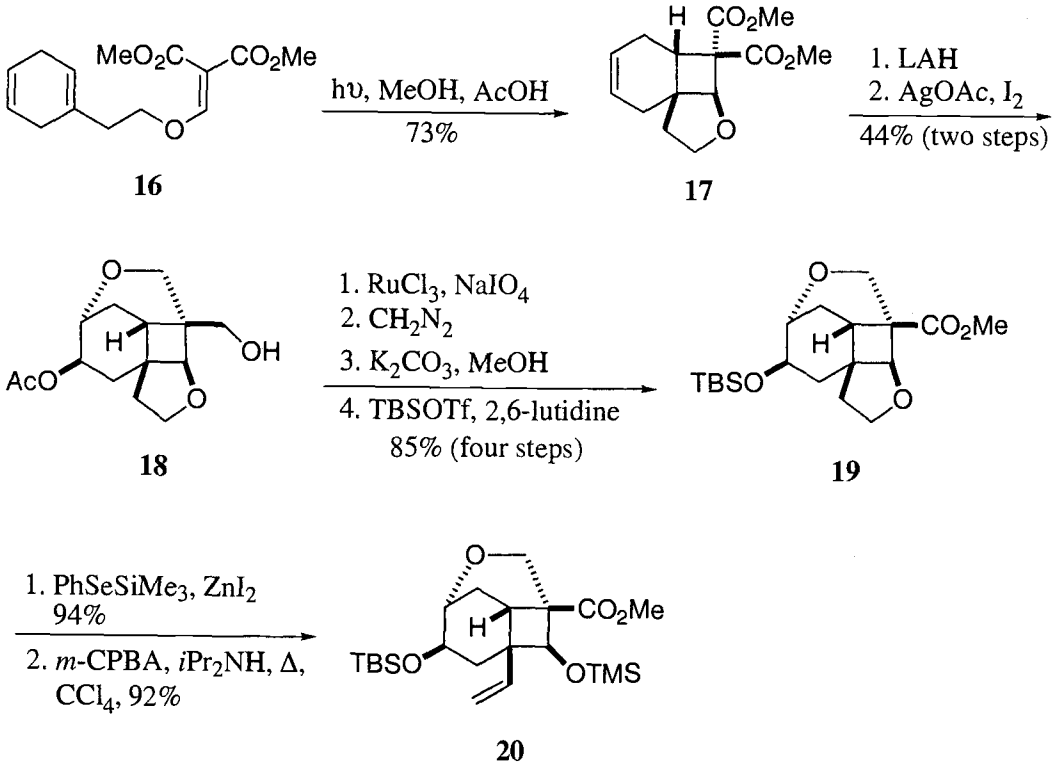
It was found that the C-5 stereocenter of **8** was epimerized in the course of its Dieckmann condensation, thus leading to nonnatural (+)-koumine (**1**). The tetracyclic intermediate **10**, arising from base treatment of **8**, was

decarbomethoxylated and subsequently debenzylated to yield the ketone **11**. The next phase of the synthesis was construction of the quinuclidine moiety using an intramolecular Michael addition of **12**, which was readily available from **11** in a straightforward manner (**Scheme 2**). In the event, intramolecular Michael reaction of **12** was effected with pyrrolidine and trifluoroacetic acid; this was followed by olefination with Tebbe's reagent and hydroboration to give the alcohol **13**.




**Scheme 2.** Magnus' synthesis of (+)-koumine

Reduction of **13** with diisobutylaluminum hydride followed by removal of the remaining benzyl group, afforded a diol which fragmented in the presence of methyl chloroformate, presumably *via* the extended iminium ion **14**, and then recyclized to form the pyran **15**. Lastly, reduction of carbamate **15** with lithium aluminum hydride to a N-methylamine followed by $S_N2$ cyclization in the presence of diethyl azodicarboxylate and triphenylphosphine completed the synthesis of (+)-koumine (**1**).

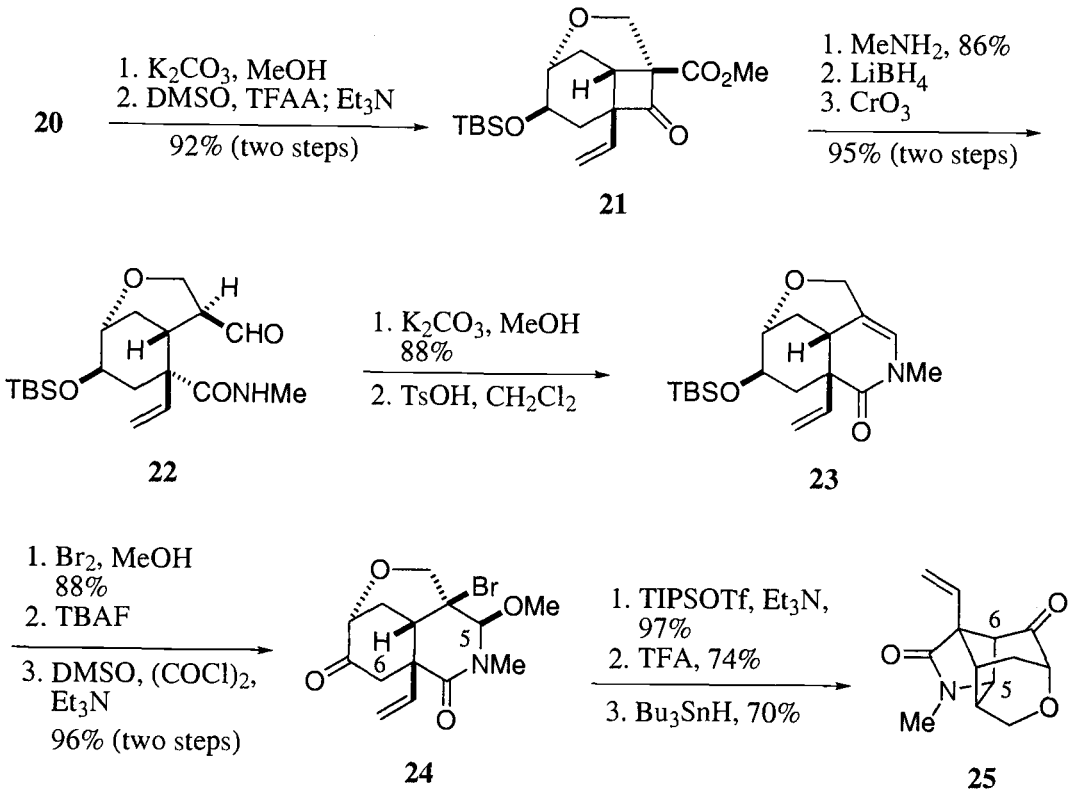



**Scheme 3.** Johnson's synthesis of (±)-gelsemine

In 1994, Johnson and coworkers described the first total synthesis of (±)-gelsemine, which commenced with an intramolecular [2+2] photocycloaddition of the triene **16** (**Scheme 3**).[8] Reduction of the photoadduct **17** and subsequent

pyran formation of the resultant diol with silver acetate and iodine afforded the acetoxy alcohol **18**. After a four-step transformation to **19**, cleavage of the tetrahydrofuran ring was accomplished with phenyltrimethylsilylselenide and zinc iodide; this was followed by oxidative deselenylation to provide the alkene **20**.

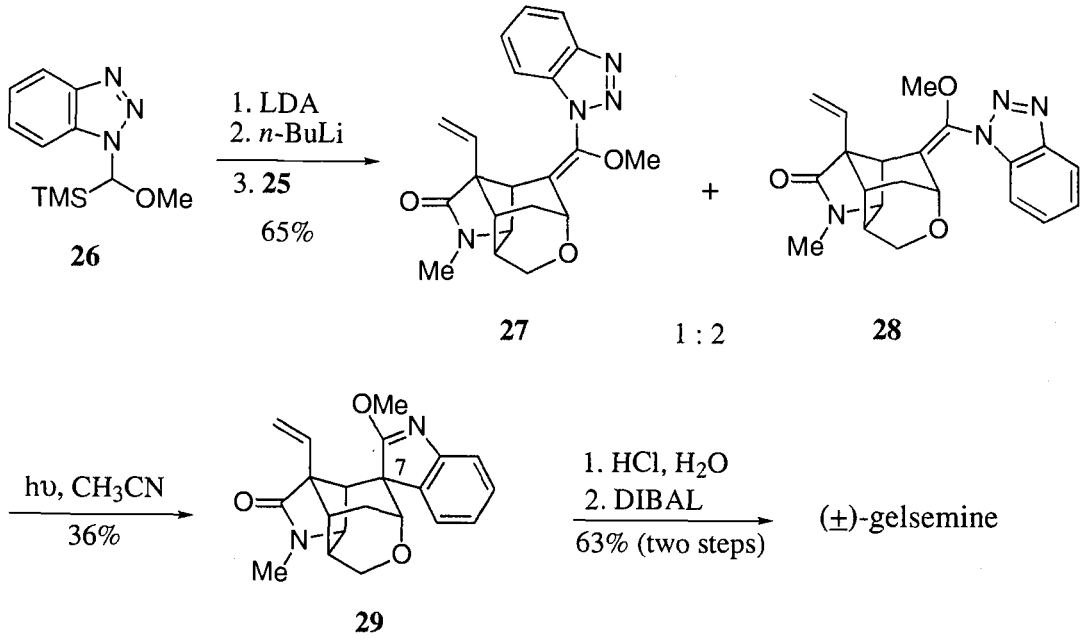
The next phase of Johnson's synthesis required opening of the cyclobutane ring to construct the δ-lactam moiety. In the event, desilylation of **20** gave an unstable cyclobutanol which was immediately oxidized to the β-ketoester **21** (**Scheme 4**).




**Scheme 4.** Johnson's synthesis of (±)-gelsemine

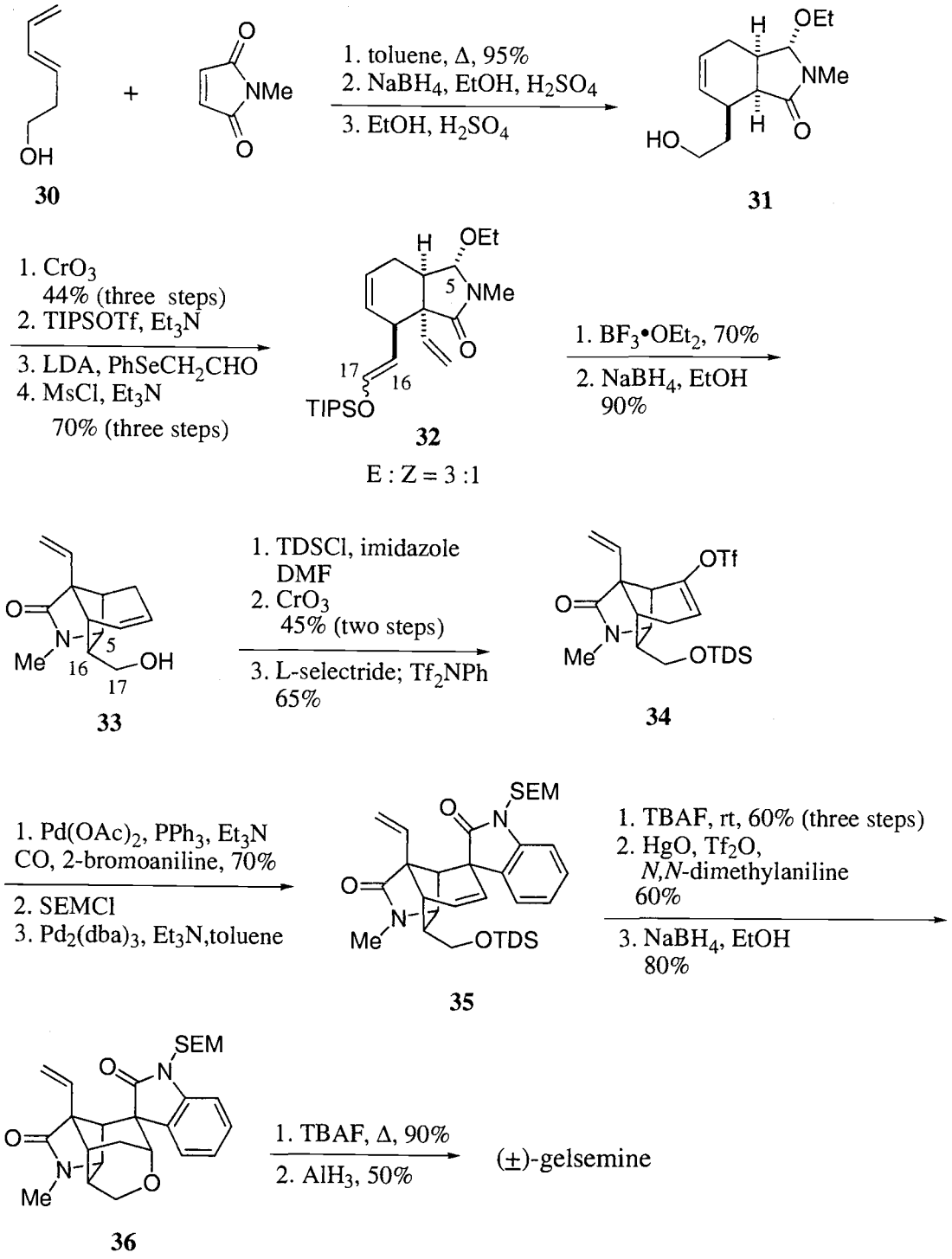
Cleavage of the cyclobutane ring of **21** was effected in a retro Claisen fashion by treatment with methylamine, and the resultant amido ester was

converted to the corresponding aldehyde **22** in a two-step process. Epimerization of **22** brought the two reacting sites, the carbonyl group of the aldehyde and the amide nitrogen, within bonding distance to allow cyclization to occur. This gave initially a hydroxy lactam which was then dehydrated to provide the enamide **23**. In order to construct the pivotal tetracyclic intermediate **25**, a prerequisite is functionalization of the enamide double bond. This was accomplished by exposure of **23** to methanolic bromine, and desilylation followed by oxidation of the resultant alcohol furnished the ketone **24**. Silyl enol ether formation then set the stage for the key intramolecular Mannich reaction. In practice, 5-*endo-trig* cyclization was effected in trifluoroacetic acid to construct the C5-C6 bond, and subsequent reductive debromination yielded the cage structure **25**.



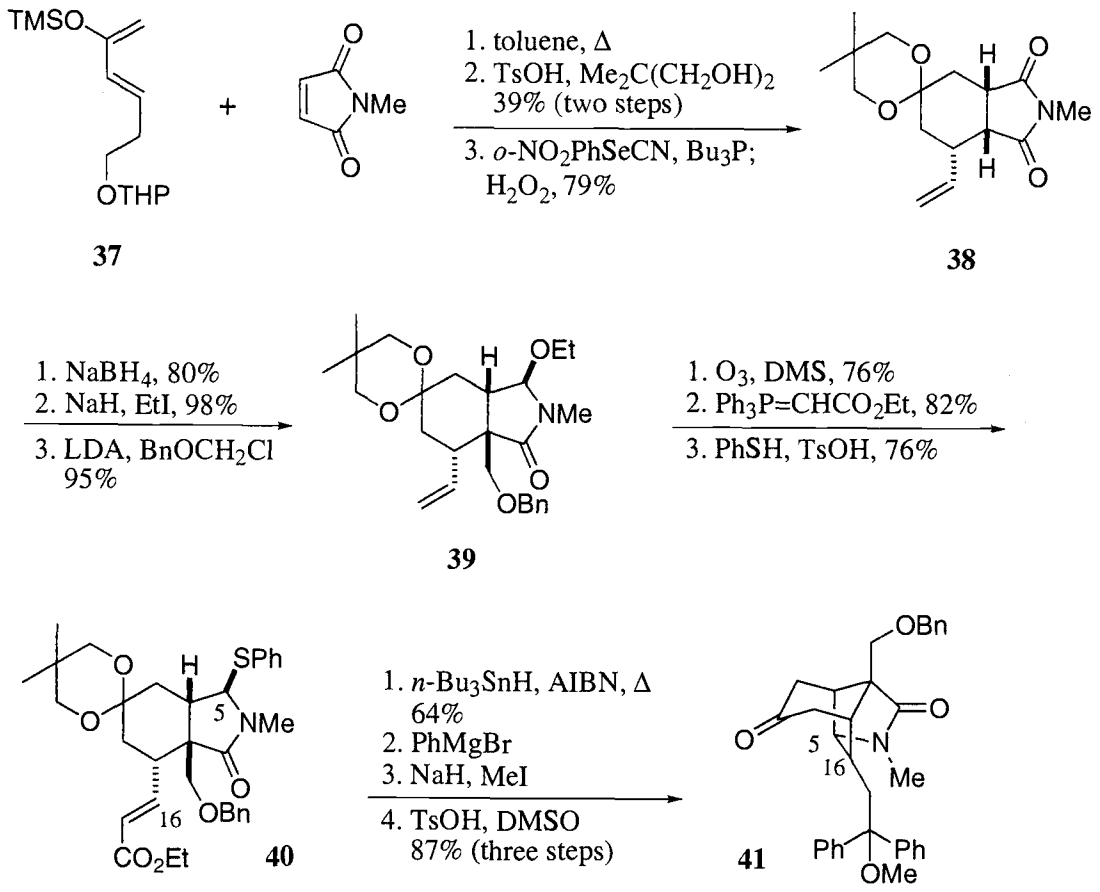

**Scheme 5.** Johnson's synthesis of (±)-gelsemine

With the tetracyclic intermediate **25** in hand, completion of the synthesis required only conversion of ketone **25** to a spiro-oxindole system. However, conventional methods to create the necessary quaternary center of gelsemine (**2**) proved unsuccessful. This led to the development of an interesting oxindole annelation based on Wender's indole synthesis (**Scheme 5**).[9] Thus, the metallated species derived from **26** was added to ketone **25** to provide a mixture of *Z* and *E* alkenes **27** and **28**. Photolysis of the mixture yielded the cyclized product **29** along with its diastereomer at C7. Finally, the minor isomer **29** was converted to (±)-gelsemine by a two-step sequence.




**Scheme 6.** Speckamp's synthesis of (±)-gelsemine

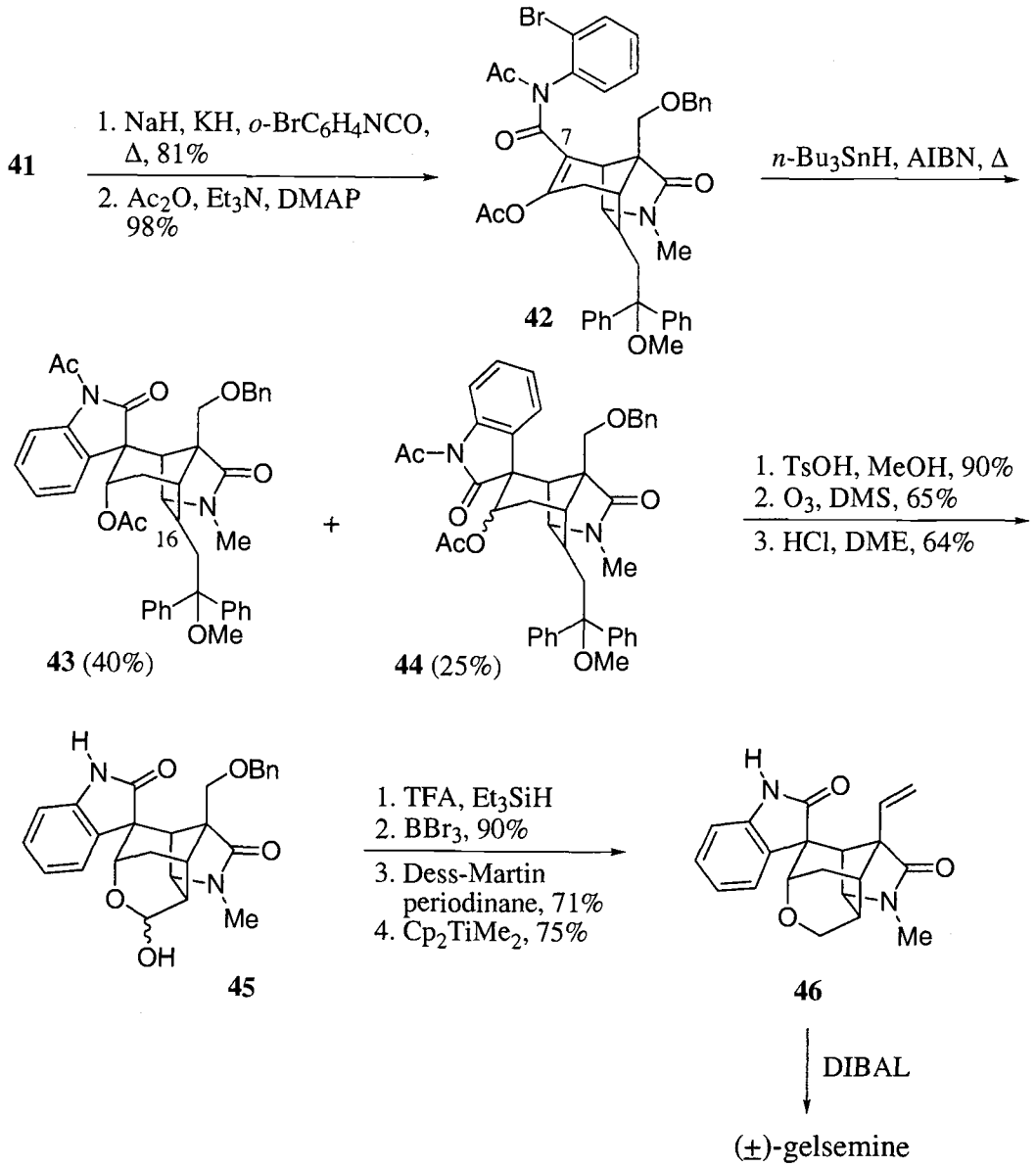
Speckamp and coworkers utilized a Diels-Alder reaction between (*E*)-hexa-3,5-diene-1-ol (**30**) and *N*-methylmaleimide as the entry point for their synthesis of (±)-gelsemine (**Scheme 6**).[10] Partial reduction of the resultant *endo* adduct with sodium borohydride, followed by ethanolysis furnished the ethoxy lactam **31**. Oxidation of **31** and silyl enol ether formation of the resultant aldehyde provided a 3:1 mixture of geometrical isomers which was converted to the α-vinyl γ-lactam **32**. Upon exposure of **32** to boron trifluoride diethyl etherate, a highly stereospecific *N*-acyliminium ion cyclization occurred to generate a tricyclic aldehyde which was reduced to the corresponding alcohol **33**. To construct the spiro-oxindole moiety present in gelsemine, **33** was protected as its thexyldimethylsilyl (TDS) ether and then oxidized with a complex derived from chromium trioxide and 3,5-dimethylpyrazole. The resulting enone was reduced in a 1,4-selective manner with L-Selectride to generate a lithium enolate which was trapped with Comins reagent to furnish the enol triflate **34**. Palladium catalyzed carbonylation of **34** with 2-bromoaniline, followed by protection of the resultant lactam as its trimethylsilylethoxymethyl (SEM) derivative set the stage for the pivotal Heck cyclization. The intramolecular Heck reaction was effected under Overman's conditions[11] to give the desired spiro-oxindole **35**. Desilylation of **35** and subsequent pyran formation was achieved by exposure of the generated free alcohol to a complex derived from mercury(II) triflate and *N,N*-dimethylaniline. Reductive demercuration with sodium borohydride afforded SEM-protected 21-oxogelsemine **36**. Finally, cleavage of the SEM group followed by selective lactam reduction completed the synthesis of (±)-gelsemine.




**Scheme 7.** Hart's synthesis of (±)-gelsemine

Hart and coworkers also employed a Diels-Alder reaction to construct a bicyclic compound as a starting point for their synthesis of gelsemine. (**Scheme 7**).[12] Ketalization of the Diels-Alder adduct from **37** and N-methylmaleimide, followed by dehydration using Grieco's protocol provided the alkene **38**. Stereoselective reduction of **38** with sodium borohydride gave a carbinol lactam which was advanced to **39** in a two-step sequence. Ozonolysis of **39** and homologation of the resultant aldehyde provided an α,β-unsaturated ester which underwent an ethoxy-thiophenoxy exchange to produce **40**. Intramolecular

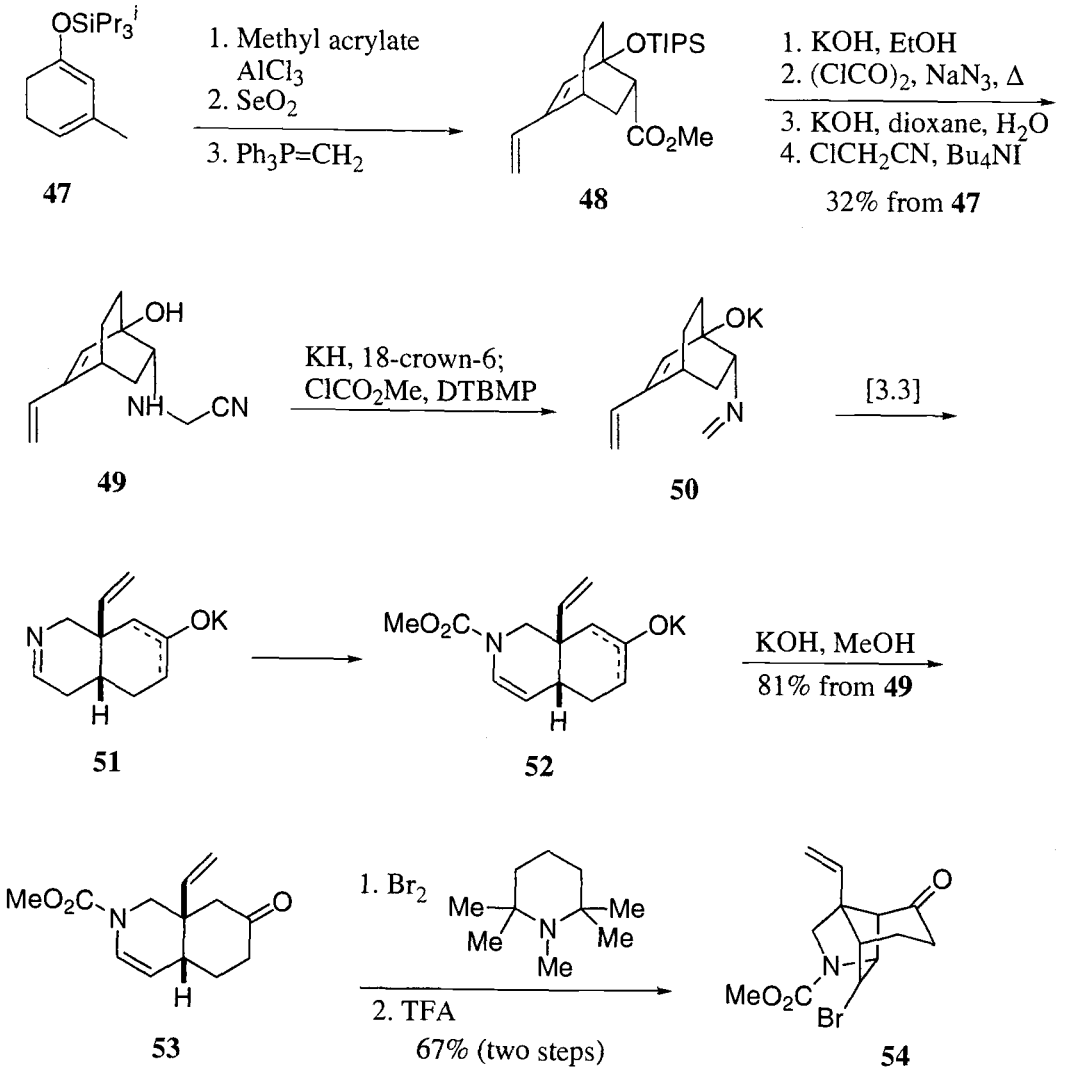
radical cyclization of **40** was effected under standard conditions with tri-*n*-butyltin hydride and 2,2'-azobisisobutyronitrile (AIBN) to give a tricyclic ketallactam which was treated with phenylmagnesium bromide. The resultant tertiary alcohol was methylated with iodomethane, and subsequent deblocking of the ketal using *p*-toluenesulfonic acid in acetone yielded **41**.




**Scheme 8.** Hart's synthesis of (±)-gelsemine

The next phase of Hart's synthesis involved construction of the quaternary center at C7 using a radical cyclization of **42**. The latter was prepared from ketone **41** in a straightforward manner (**Scheme 8**). Thus, exposure of **42** to tri-*n*-butyltin hydride under photochemical conditions provided the desired oxindole **43** in 40% yield, along with 25% of **44**. At this point, the configuration at C16 required inversion for the planned pyran formation, and this was accomplished by exposure of **43** to *p*-toluenesulfonic acid, followed by ozonolysis of the resultant alkene to give an aldehyde which was subsequently isomerized to afford a mixture of hemiacetals **45**. Reduction of this hemiacetal with triethylsilane and trifluoroacetic acid furnished a pyran which was advanced to 21-oxogelsemine **46** in a three-step sequence. Completion of the synthesis was achieved by reduction of **46** with diisobutylaluminum hydride to give the racemic alkaloid.

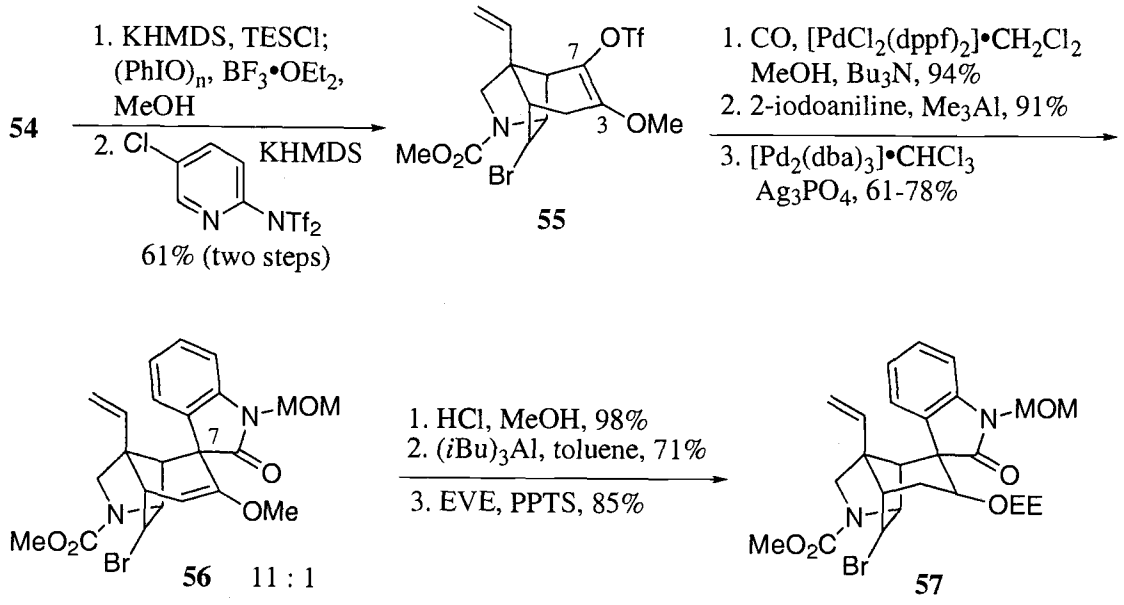
Overman and coworkers employed an aza-Cope rearrangement of the readily available bicyclo[2.2.2]octene precursor **49** to construct the *cis*-hexahydroisoquinolinone **53** (**Scheme 9**).[13] The preparation of **49** commenced with a Diels-Alder reaction between 1,3-cyclohexadiene **47** and methyl acrylate. The resulting *endo* adduct was oxidized and homologated to the diene **48** which was converted to **49** in four steps. Anionic aza-Cope rearrangement of **49** was effected *via* the alkoxide **50** to yield the imine enolate **51** which was quenched with methyl chloroformate and then hydrolyzed to afford **53**. Upon exposure of **53** to bromine, the resultant dibromide underwent an intramolecular Mannich reaction in trifluoroacetic acid to generate the azatricyclodecanone **54**.




**Scheme 9.** Overman's synthesis of (±)-gelsemine

The next stage of Overman's synthesis involved construction of the spirooxindole at C7 of **56** in such a way that C3 was substituted with an oxygen functionality which could be employed to form the pyran ring of gelsemine (**Scheme 10**). Thus, oxidation of the silyl enol ether derived from ketone **54** with iodosobenzene and $BF_3 \bullet OEt_2$ in the presence of methanol generated an α-methoxy ketone which was converted to the enol triflate **55** with Comins' reagent.

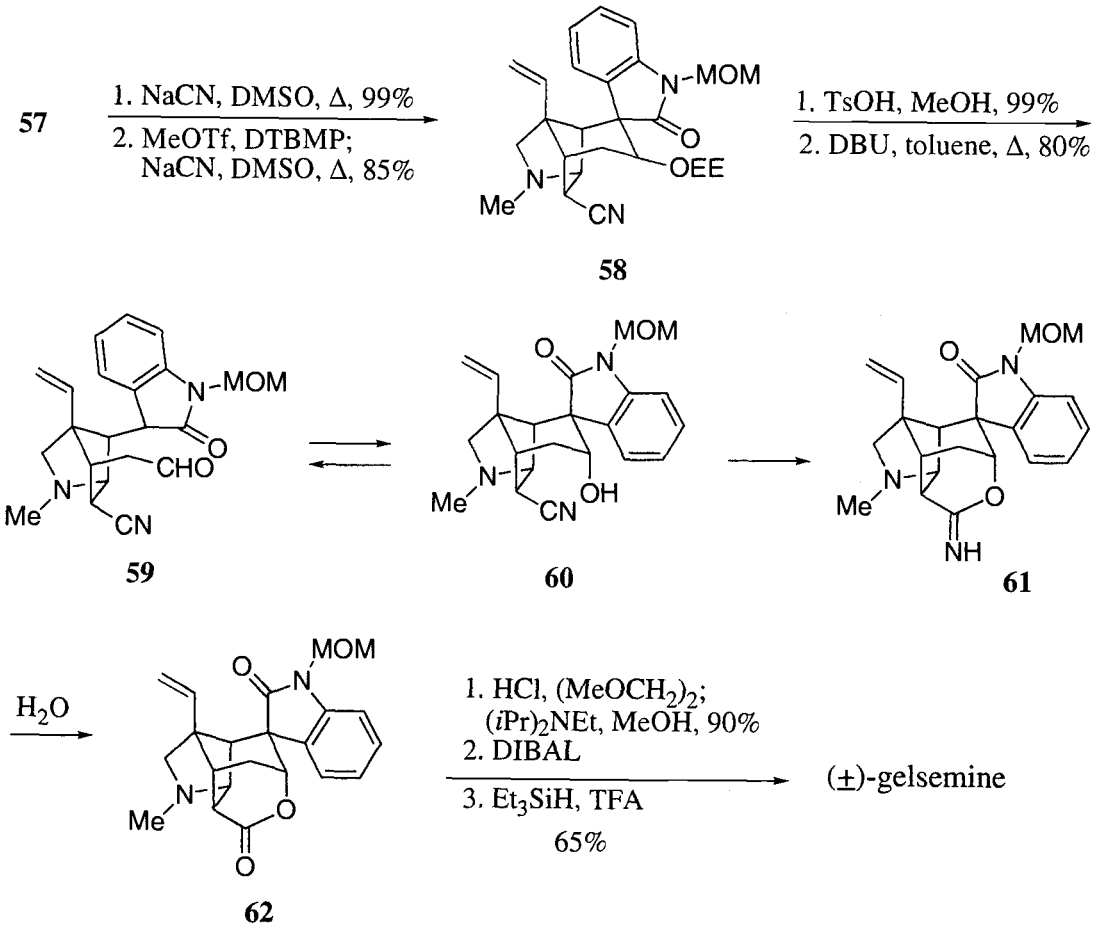
Palladium-catalyzed carbonylation of **55** in methanol yielded a methyl ester which was subsequently condensed with 2-iodoaniline. After protection of the resulting amide, the pivotal intramolecular Heck reaction was effected in the presence of silver phosphate to give a 11:1 mixture of spirooxindole diastereoisomers **56**. Unfortunately, the major product was found to have the opposite configuration at the spirooxindole to that required for gelsemine. After hydrolysis of enol ether **56**, the resulting ketone was reduced to the equatorial alcohol which was protected as its ethoxyethyl ether **57**.



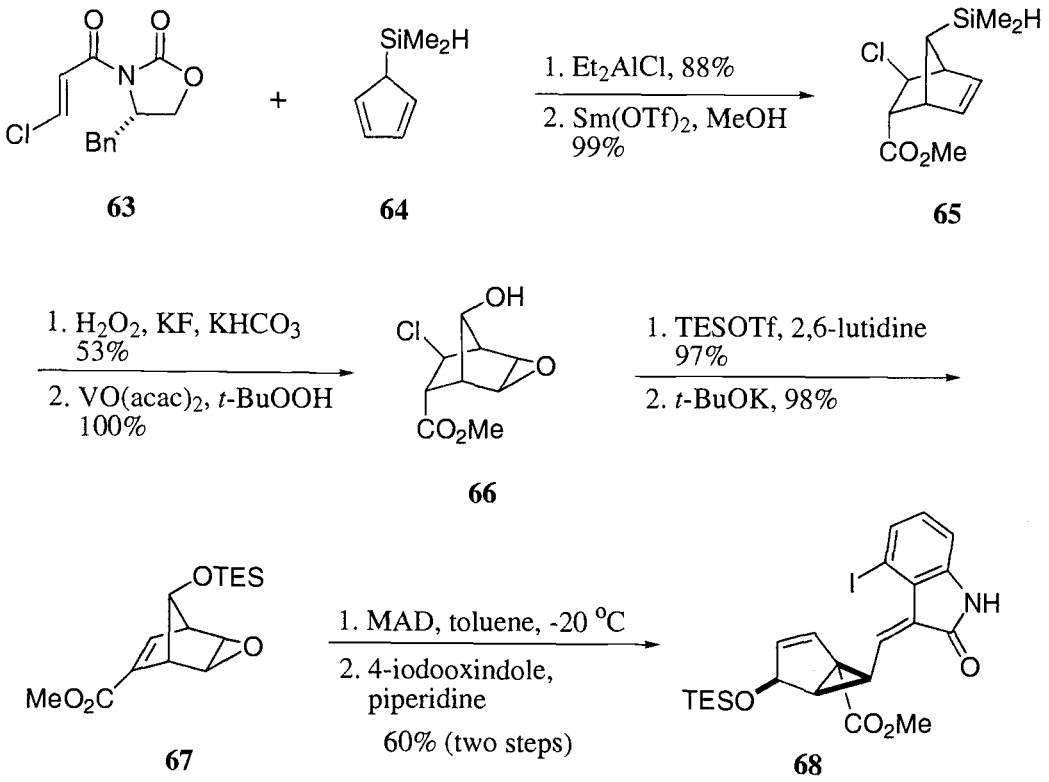

**Scheme 10.** Overman's synthesis of (±)-gelsemine

Treatment of **57** with sodium cyanide in dimethyl sulfoxide delivered an aziridine which was opened regioselectively to give the nitrile **58** (**Scheme 11**). Removal of the ethoxyethyl protecting group and treatment of the resultant alcohol with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) provided the hexacyclic

lactone **62**. This complex reorganization process was presumably initiated by a retro aldol cleavage to give an open intermediate **59** which underwent σ bond rotation, and reclosure to generate the axial alcohol **60**. Subsequent addition of the alcohol to the proximal nitrile generated hexacyclic imidate **61**, which was followed by hydrolysis to yield the lactone **62**. Completion of Overman's synthesis was accomplished by removal of the methoxymethyl protecting group, and a two-step reduction of the δ-lactone to the tetrahydropyran ring of gelsemine.



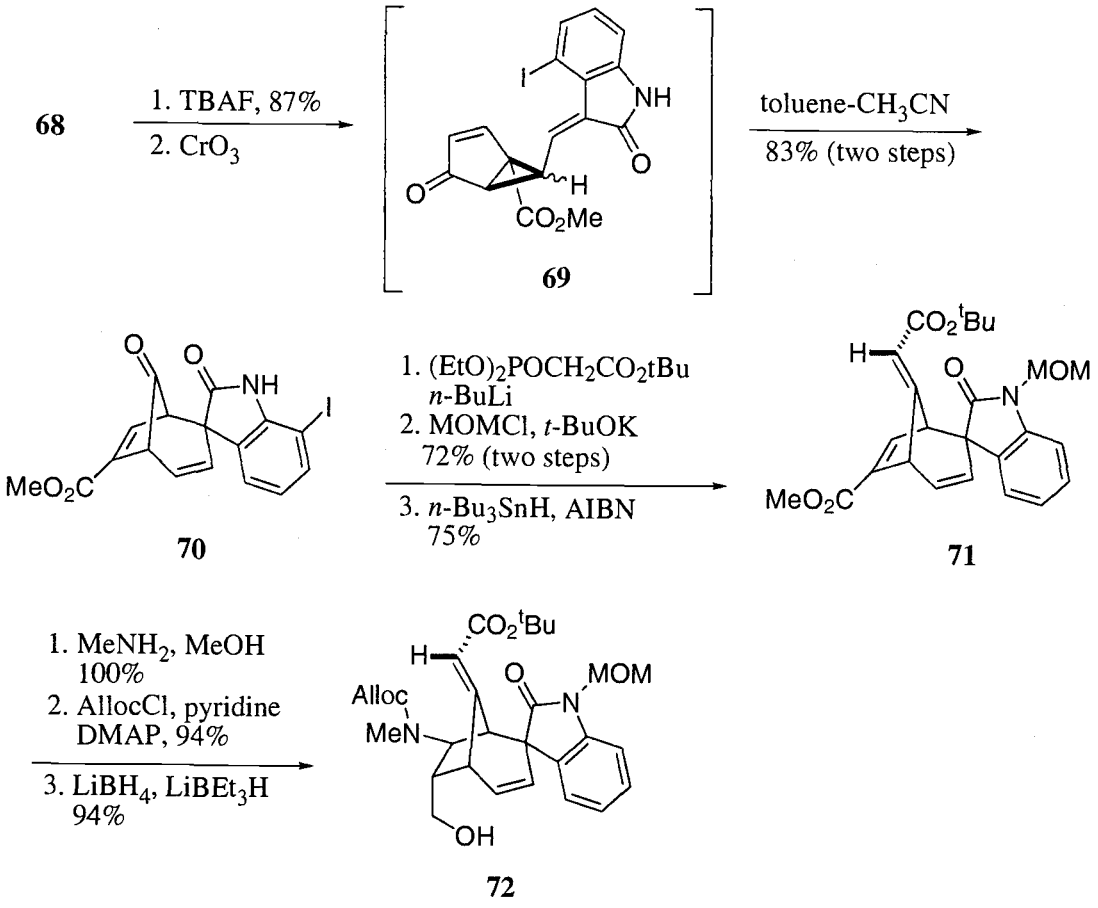

**Scheme 11.** Overman's synthesis of (±)-gelsemine




**Scheme 12.** Fukuyama's synthesis of (+)-gelsemine

Recently, Fukuyama and coworkers reported the first asymmetric synthesis of gelsemine leading to the (+)-enantiomer (**Scheme 12**).[14] Their synthesis commenced with a chiral auxiliary-controlled Diels-Alder reaction between dienophile **63** and 5-dimethylsilylcyclopentadiene **64** in the presence of diethylaluminum chloride to give a single isomer which was converted to its methyl ester **65**. Tamao-Fleming oxidation of **65**, followed by a directed epoxidation of the resultant homoallylic alcohol provided the epoxide **66**. After protection of the secondary alcohol, dehydrochlorination by potassium *t*-butoxide furnished the α,β-unsaturated ester **67**. Rearrangement of **67** in the presence of

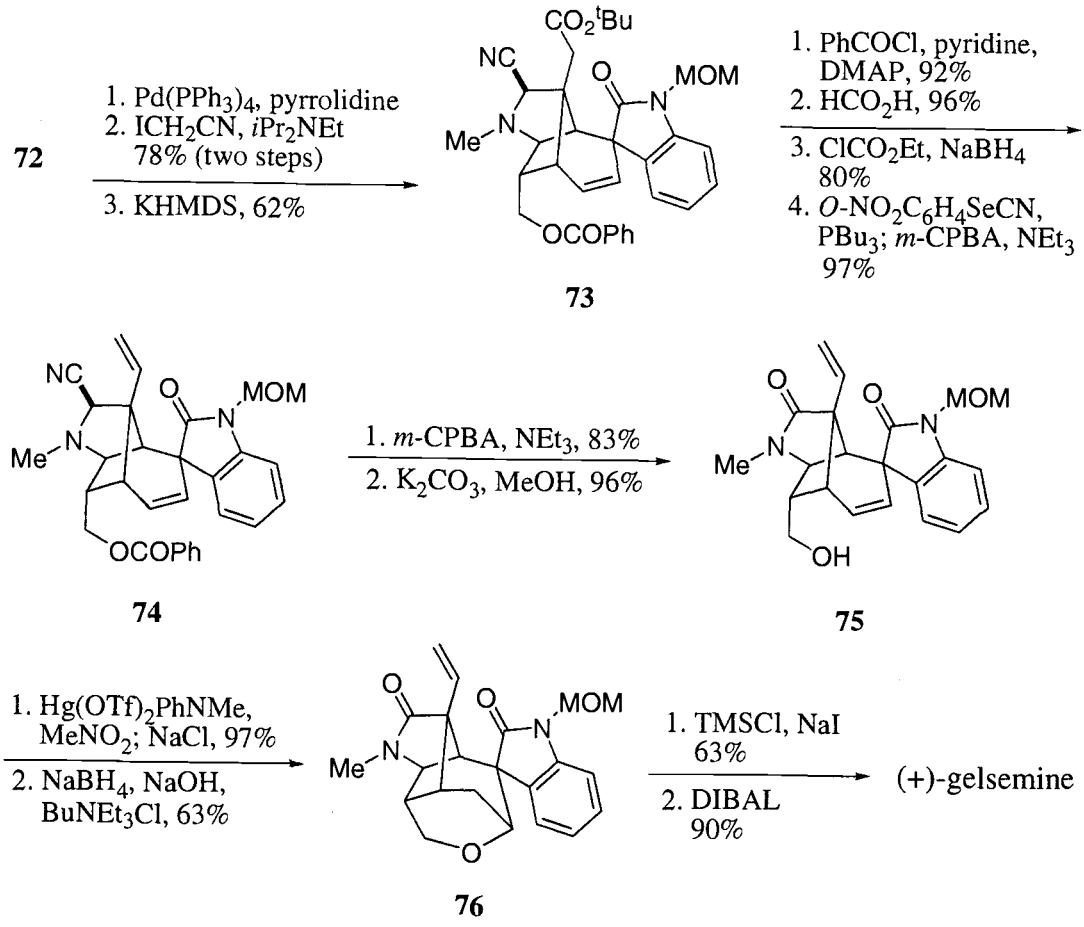
methylaluminum bis(2,6-di-*tert*-butyl-4-methylphenoxide), followed by condensation with 4-iodooxindole gave the (*Z*)-alkylidene **68**.




**Scheme 13.** Fukuyama's synthesis of (+)-gelsemine

After removal of the triethylsilyl group, the resultant alcohol was subjected to Jones' oxidation to give the enone **69** which spontaneously underwent divinylcyclopropane-cycloheptadiene rearrangement to provide the bicyclo[3.2.1]octadienone **70** (**Scheme 13**). With the bicyclic core of gelsemine established, Horner-Emmons reaction of **70**, protection of the indolinone nitrogen, and subsequent reductive deiodination produced α,β-unsaturated ester

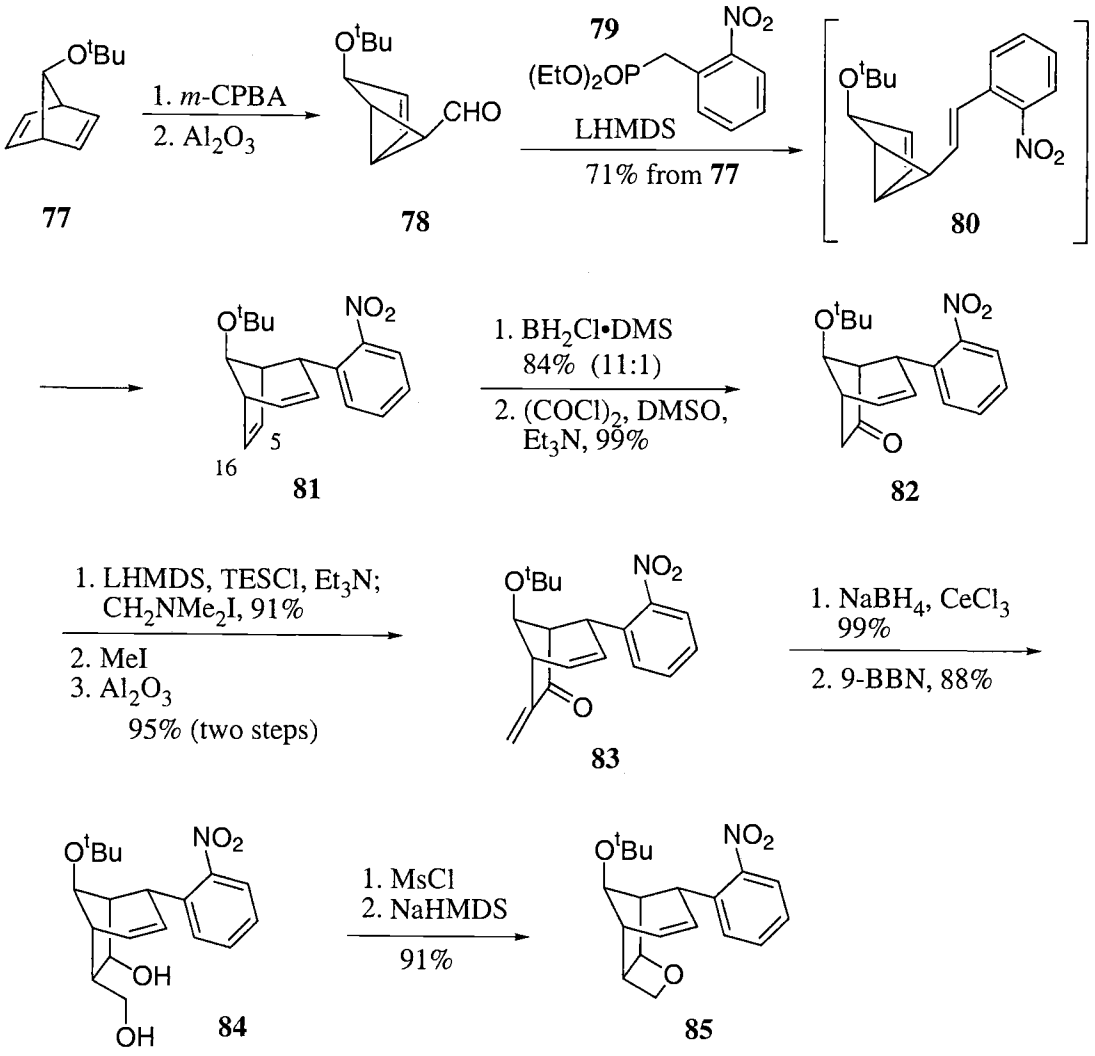
**71**. When **71** was exposed to methylamine, Michael addition took place from the less hindered *exo* face to give a *trans*-aminoester which was protected as its allyl carbamate. The ester moiety was then reduced to the corresponding alcohol **72**.




**Scheme 14.** Fukuyama's synthesis of (+)-gelsemine

At this stage, a cyanomethyl group was attached to the amine to perform the critical intramolecular Michael addition that would complete the pentacyclic skeleton (**Scheme 14**). Thus, removal of the Alloc group from **72** followed by cyanomethylation gave an aminonitrile which underwent intramolecular Michael addition with potassium bis(trimethylsilyl)amide to afford the pyrrolidine **73**. After

protection of the alcohol **73** as its benzoate, the vinyl side chain of **74** was installed in a three-step sequence. Oxidation of **74** with *m*-chloroperbenzoic acid followed by treatment with triethylamine converted the pyrrolidine ring of **74** to a γ-lactam, and the benzoate was subjected to methanolysis to yield the alcohol **75**. Intramolecular oxymercuration of **75**, followed by reductive demercuration gave the tetrahydropyran **76** which was successfully converted to (+)-gelsemine by a two-step process.

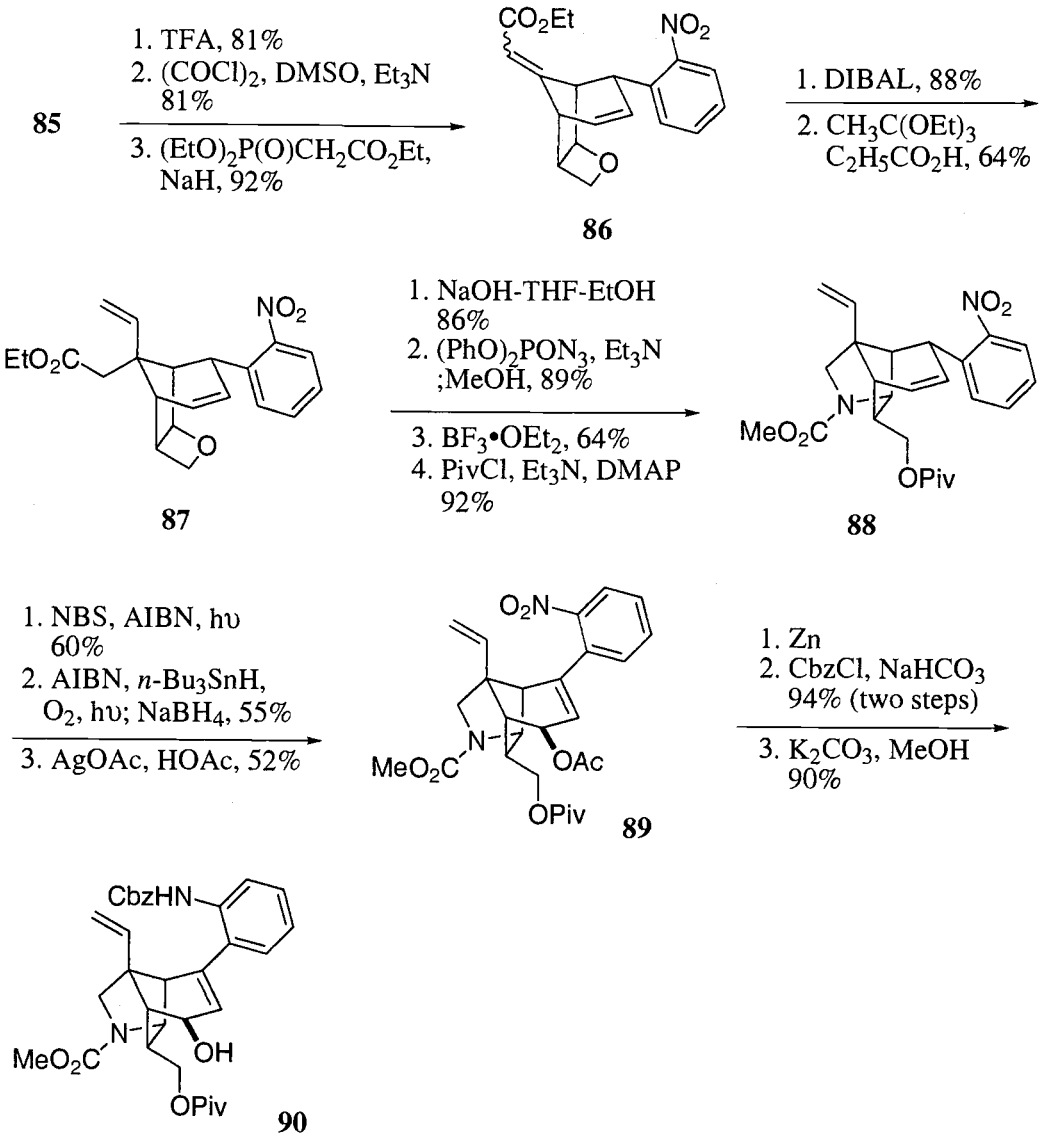



**Scheme 15.** Danishefsky's synthesis of (±)-gelsemine

Danishefsky's synthesis of racemic gelsemine commenced with epoxidation of 7-*tert*-butoxynorbornadiene (**77**), followed by an alumina-promoted rearrangement to give the aldehyde **78** (**Scheme 15**).[15] Wadsworth-Emmons *o*-nitrobenzylidenation of **78** using the phosphonate **79**, led to **81** presumably *via* rearrangement of divinylcyclopropane **80**. Hydroboration of **81** followed by oxidative workup afforded a 11:1 mixture of alcohols at C5 relative to its regioisomer at C16, and subsequent oxidation yielded the pure ketone **82**. α-Methylenation of **82** was accomplished by a three-step sequence leading to **83**, and Luche reduction of **83** followed by hydroboration from the less hindered convex face furnished the diol **84**. The latter was converted to the oxetane **85** in a straightforward manner.

With the crucial oxetane **85** in hand, the next phase of Danishefsky's synthesis searched for a viable route for construction of the pyrrolidine unit (**Scheme 16**). Thus, cleavage of *t*-butyl ether **85**, followed by oxidation provided a ketone which underwent a Horner-Emmons reaction to give a 3:2 mixture of (*E*) and (*Z*) α,β-unsaturated esters **86**. Upon reduction of **86**, the resulting mixture of isomeric allylic alcohols converged to a single γ,δ-unsaturated ester **87** *via* a Johnson-Claisen rearrangement. Hydrolysis of the ester **87** followed by Curtius rearrangement afforded a urethane, after which the oxetane ring was opened with the aid of boron trifluoride diethyl etherate to give a primary alcohol. The latter was protected as its pivalate ester **88**. Due to the highly hindered nature of the α-face of **88**, allylic bromination and subsequent debromination proceeded with retention of stereochemistry to give a β alcohol which was converted to its

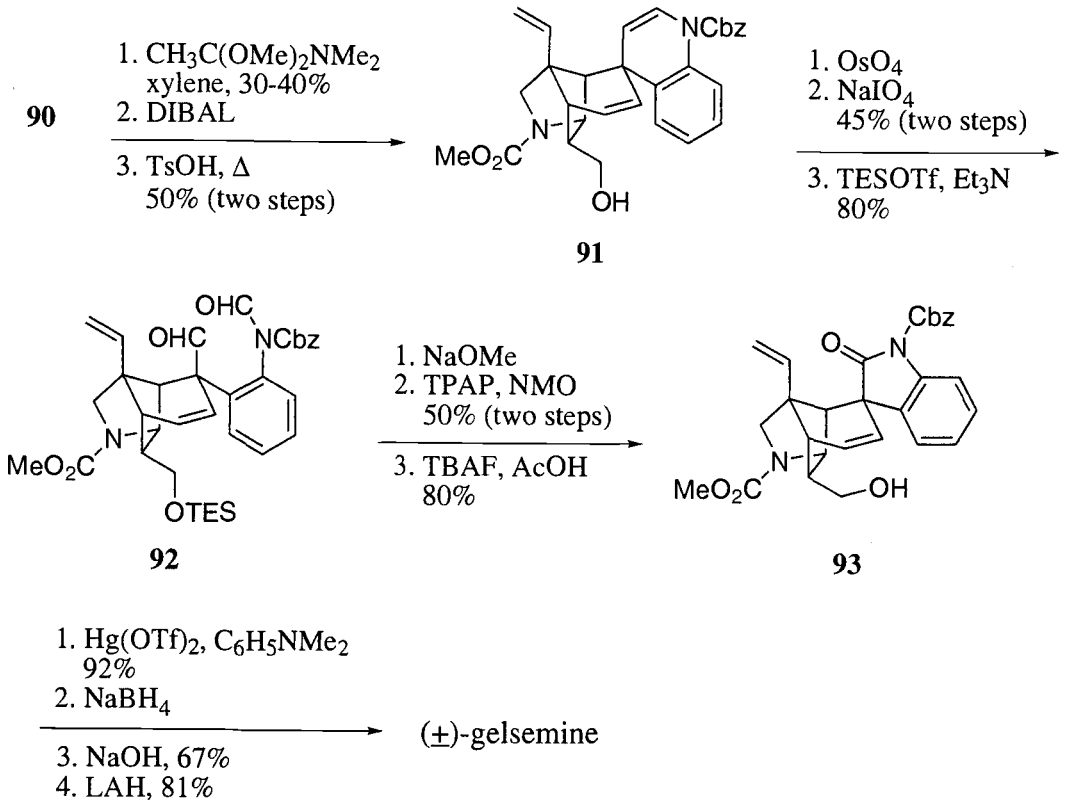
acetate **89**. Further transformation of **89** by a three-step sequence yielded the allylic alcohol **90**.



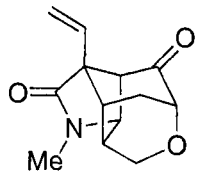

**Scheme 16.** Danishefsky's synthesis of (±)-gelsemine

In practice, it was found that Eschenmoser-Claisen rearrangement of **90** took place in the desired sense to provide a δ-lactam which was converted to the enamide **91** (**Scheme 17**). Unfortunately, the synthetic route became

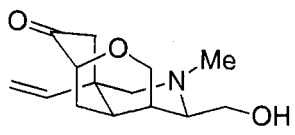
complicated at this point in that its continuation required excision of a carbon atom from **91** in order to complete the oxindole moiety. In the event, a ring contraction of **91** was initiated by oxidative cleavage of the dihydroquinoline nucleus to the dialdehyde **92**, which was subsequently cyclized to the spiroanilide **93**. Finally, oxymercuration and demercuration using Fukuyama's protocol[14] formed the tetrahydropyran of gelsemine and this substance which was successfully converted to the natural product.




**Scheme 17.** Danishefsky's synthesis of (±)-gelsemine




94

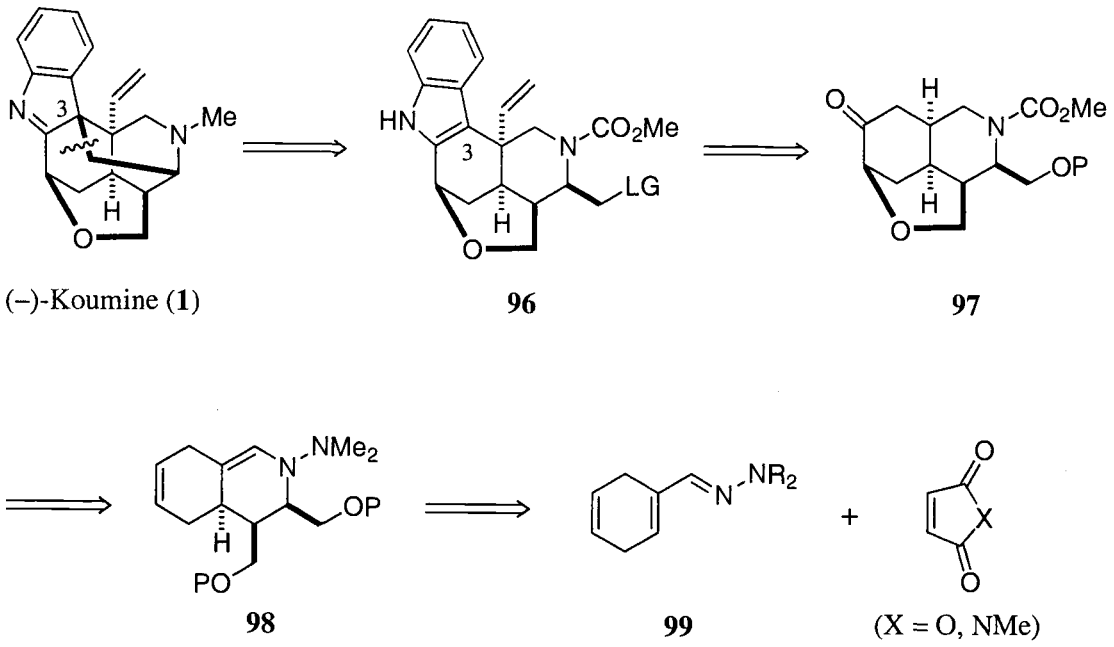



95

In summary, although several syntheses of gelsemine (**2**) have been published, Magnus has completed the only total synthesis of its close relative koumine (**1**) thus far. The most common strategy for the synthesis of gelsemine has been to first build the tetracyclic ketone **94** and then annulate the spirooxindole onto this platform; our goal became a novel entry to **95**, which is structurally related to **94**, as the focus of our approach to koumine (**1**). A detailed description of our synthetic efforts towards this goal is included in the chapter which follows.

## Results and Discussion

Our retrosynthetic analysis of koumine is outlined in **Scheme 18**. We envisaged that an intermediate **96** would be transformed to the natural substance utilizing an intramolecular alkylation at C-3 of the indole moiety. Fischer indolization of **97** would proceed in a regioselective manner to provide the pentacyclic **96**. Thus, the initial effort was focused on the construction of hydroisoquinoline **97** which contains the five chiral centers found in koumine. The first attempt to assemble **97** was made *via* **98** using a hetero Diels-Alder reaction of the 1-azadiene **99**.



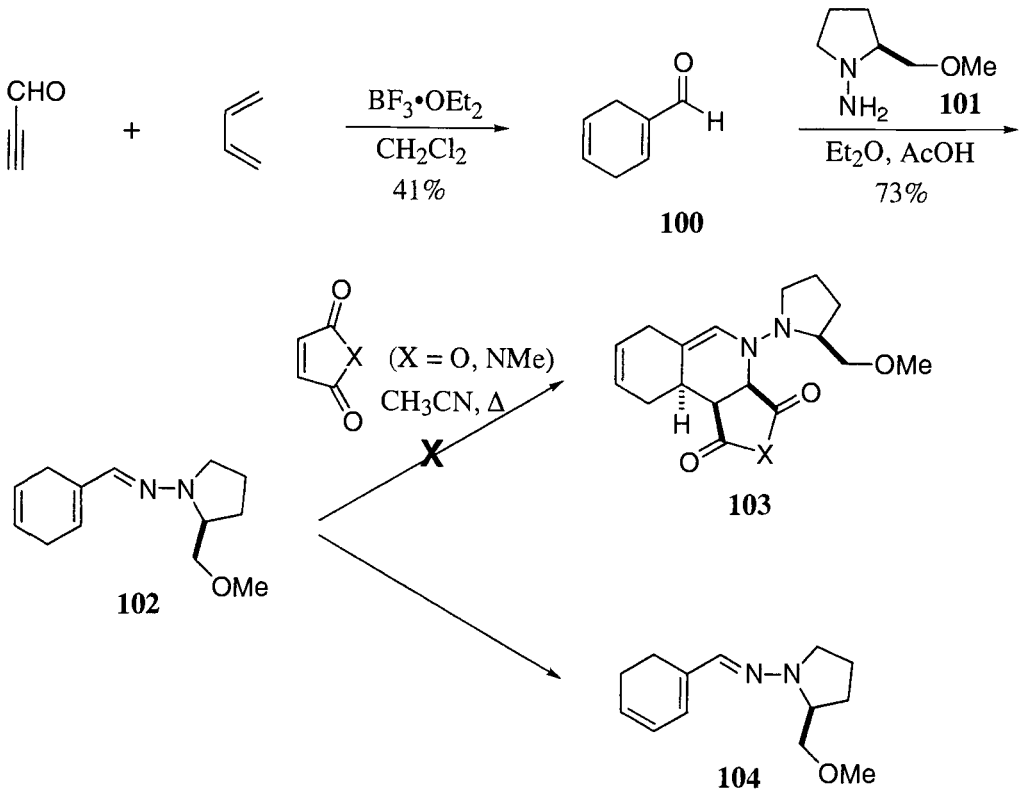

(–)-Koumine (**1**) **96** **97**

**98** **99** (X = O, NMe)

**Scheme 18**

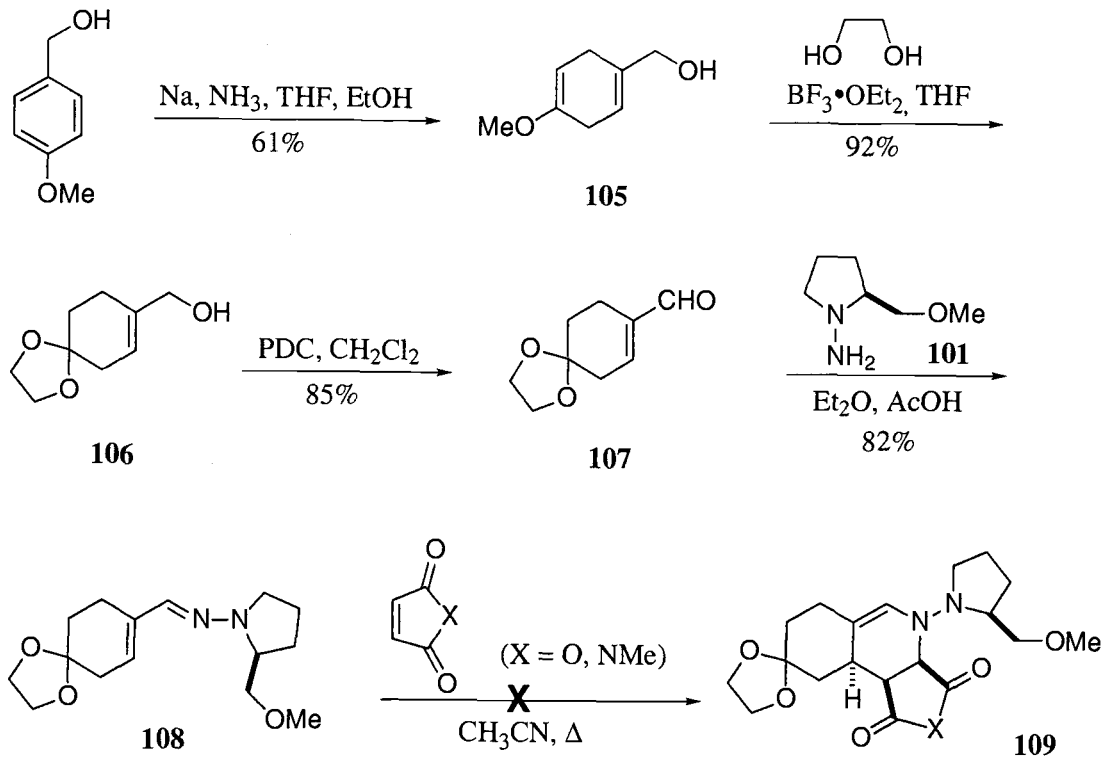
Ghosez reported the first example of a hetero Diels-Alder reaction of an α,β-unsaturated *N,N*-dimethylhydrazone in 1982, and this cycloaddition has been

successfully exploited in the building of numerous six-membered heterocycles.[16] Recently, Ghosez has extended the utility of this ring construction to asymmetric Diels-Alder reactions using α,β-unsaturated hydrazones derived from Ender's chiral hydrazines.[17] Ghosez's research demonstrates that 1-azadienes engage in a normal ($HOMO_{diene}$ controlled) Diels-Alder reaction with electron deficient dienophiles, confirming that the tertiary amino group increases the nucleophilic character of the azadiene system and overcomes the electron-withdrawing effect of the N-1 atom by interaction of the nitrogen lone pair with the π-system.[16]



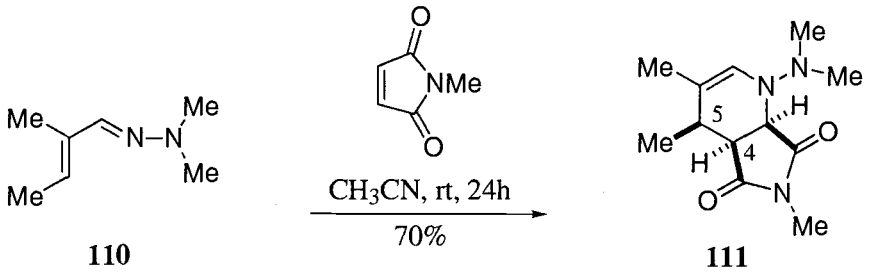

**Scheme 19**

We first decided to examine the cycloaddition of azadiene **102** which is readily available *via* condensation of 1-formyl-1,4-cyclohexadiene **100**[18] with Ender's hydrazine **101** (**Scheme 19**). Disappointingly, Diels-Alder reaction of **102** with maleic anhydride or *N*-methylmaleimide did not provide the desired cycloadduct **103**, and most of the starting diene and dienophile were recovered intact. The only new peaks observed in the crude $^1$H NMR spectrum of the mixture corresponded to the conjugated triene **104** arising from isomerization of a double bond into conjugation. The apparent lack of reactivity of the diene **102** was puzzling, but it was nevertheless decided to examine the reactivity of other 1-azadienes.




**Scheme 20**

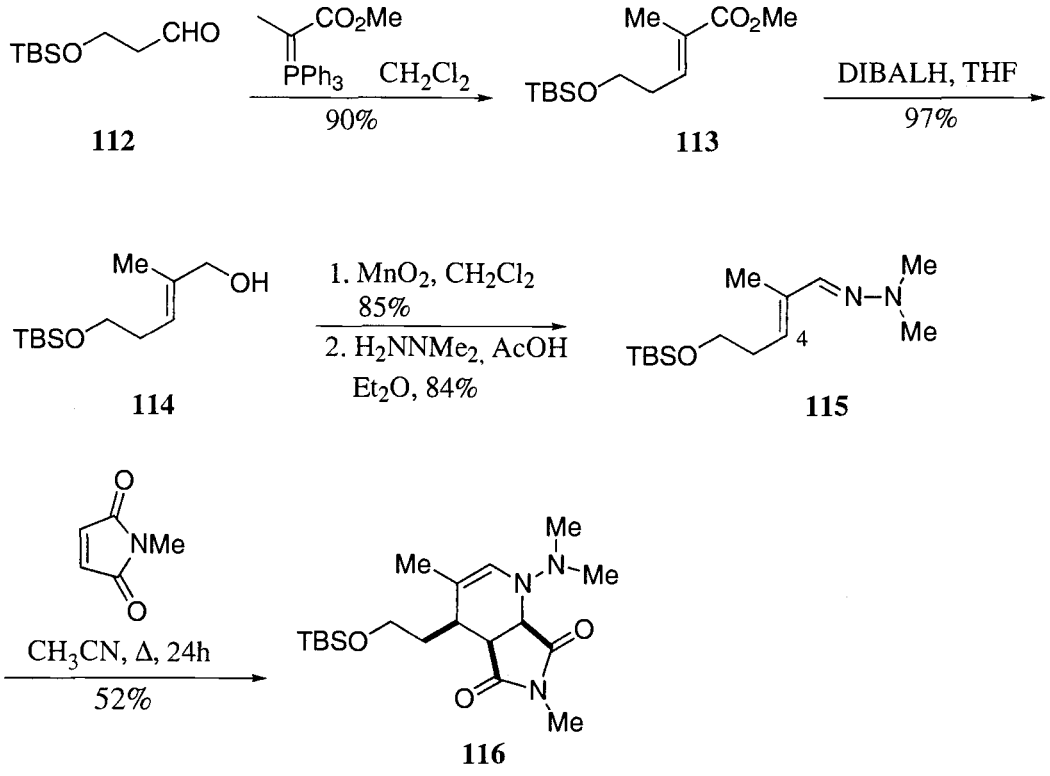
The chiral diene **108** was chosen in order to avoid the isomerization seen with **102** (**Scheme 20**). It was also hoped that asymmetric induction from the Enders hydrazone would provide a route to enantio enriched cycloadducts. The preparation of **108** began with Birch reduction of *p*-anisyl alcohol, followed by ketalization of the resulting enol ether **105** to provide the ethylene ketal **106**.[19] Pyridinium dichromate (PDC) oxidation of allylic alcohol **106** furnished the corresponding α,β-unsaturated aldehyde **107** which was condensed with (*S*)-(-)-1-amino-2-(methoxymethyl)pyrrolidine to give the hydrazone **108**. With the stage now set for a test of azadiene **108** as a Diels-Alder partner, this compound was exposed to maleic anhydride or *N*-methylmaleimide at a range of temperatures. Unfortunately, none of these reaction gave any trace of a cycloadduct. Lewis acid catalysis of the reaction with boron trifluoride diethyl etherate, indium(III) chloride and titanium dichloro diisopropoxide did not change the outcome.




**Scheme 21**

The significant difference in reactivity between our cyclic dienes such as **102** and **108** and the acyclic dienes used successfully by Ghosez was surprising and we therefore decided to verify Ghosez' results.[16] The dimethylhydrazone **110** was prepared in nearly quantitative yield from *trans*-2-methyl-2-butenal (**Scheme**

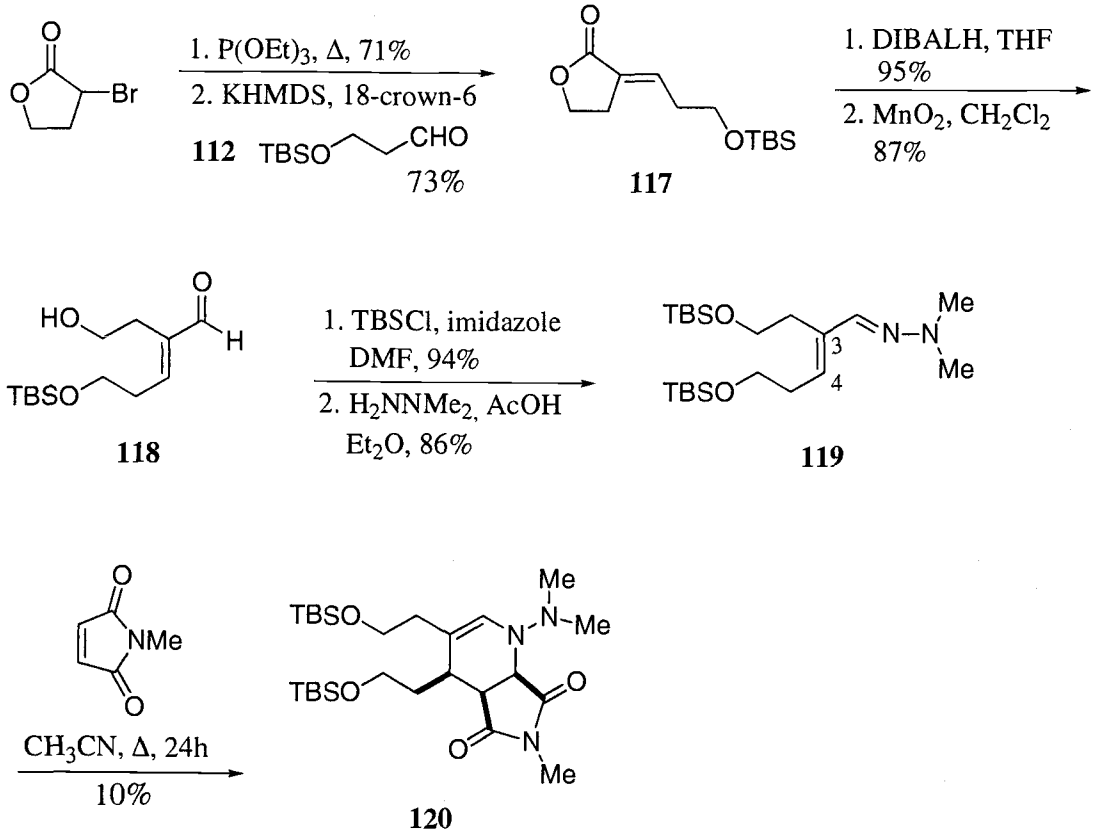
**21**), and its Diels-Alder reaction with N-methylmaleimide was carried out in acetonitrile at ambient temperature to afford cycloadduct **111** in 70% yield. The assignment of structure to **111** is in accord with related work by Ghosez where the cycloaddition is highly stereoselective.[17] The coupling constant ($J$ = 6.3 Hz) between the H-4 and H-5 protons of **111** indicates a *cis* relationship between these protons, thus establishing an *endo* transition state for the reaction.




**Scheme 22**

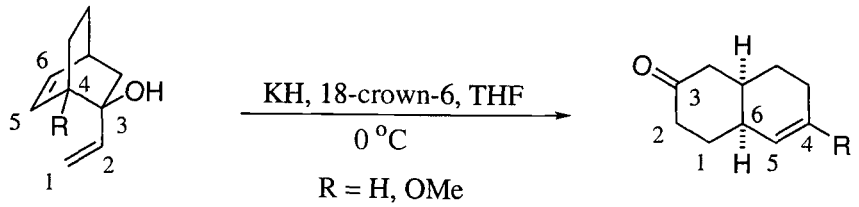
The azadiene **115** which has a longer carbon chain at C-4 was next examined to see whether there is a steric influence on the cycloaddition (**Scheme 22**). The preparation of **115** began with Wittig olefination of aldehyde **112** to give α,β-unsaturated ester **113**. After reduction of **113** with

diisobutylaluminum hydride (DIBALH), the resulting allylic alcohol **114**[20] was oxidized with manganese(IV) oxide to provide an aldehyde which was condensed with 1,1-dimethylhydrazine to give hydrazone **115**. Diels-Alder reaction of **115** with *N*-methylmaleimide was slower than with **110** and could only be effected at elevated temperature. Furthermore, cycloadduct **116** was obtained in only modest yield. This result indicates that an increase in bulkiness of the substituent at C-4 of the azadiene causes steric resistance to its cycloaddition with *N*-methylmaleimide.




**Scheme 23**

The more elaborate acyclic diene **119** was next prepared to determine whether a steric effect at C-3 as well as C-4 was responsible for the failed cycloaddition of **108** (**Scheme 23**). The synthesis of **119** commenced with an Arbuzov reaction[21] of α-bromo-γ-valerolactone to yield a phosphonate which underwent Horner-Emmons condensation with aldehyde **112**[22] resulting in *E*-alkylidene lactone **117**.[23] Reduction of **117** with diisobutylaluminum hydride (DIBALH), followed by oxidation with manganese(IV) oxide furnished the α,β-unsaturated aldehyde **118**. After protection of alcohol **118** as its *t*-butyldimethylsilyl ether (TBS), formation of hydrazone **119** was effected under standard conditions. When diene **119** was subjected to a Diels-Alder reaction with N-methylmaleimide, cycloadduct **120** was formed in only 10% yield. Thus, it appears from these results that the Diels-Alder reaction of 1-azadienes is highly dependent upon the steric bulk of substituents at both C-3 and C-4 of the diene. The absence of any cycloaddition product with the cyclic 1-azadienes **102** and **108** can be rationalized in this light and caused us to abandon this strategy.

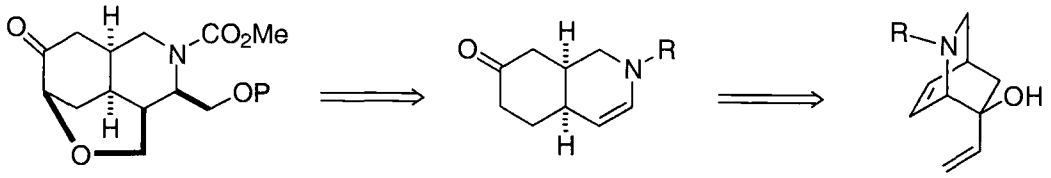



**121** **122**

**Scheme 24**

Our second approach to the *cis*-hydroisoquinoline **97** was based on an anionic oxy-Cope rearrangement of an azabicyclo[2.2.2]octene system, and was

patterned on the carbocyclic analogy originally investigated by Evans[24] and subsequently exploited in numerous synthetic applications.[25] The anionic oxy-Cope rearrangement of **121**, for example, shows great kinetic acceleration ($10^{10}$-$10^{17}$) which is believed to originate from alkoxide-induced weakening of the C3-C4 σ bond. Rearrangement takes place at 0 °C and results in *cis*-decalin **122** (**Scheme 24**).

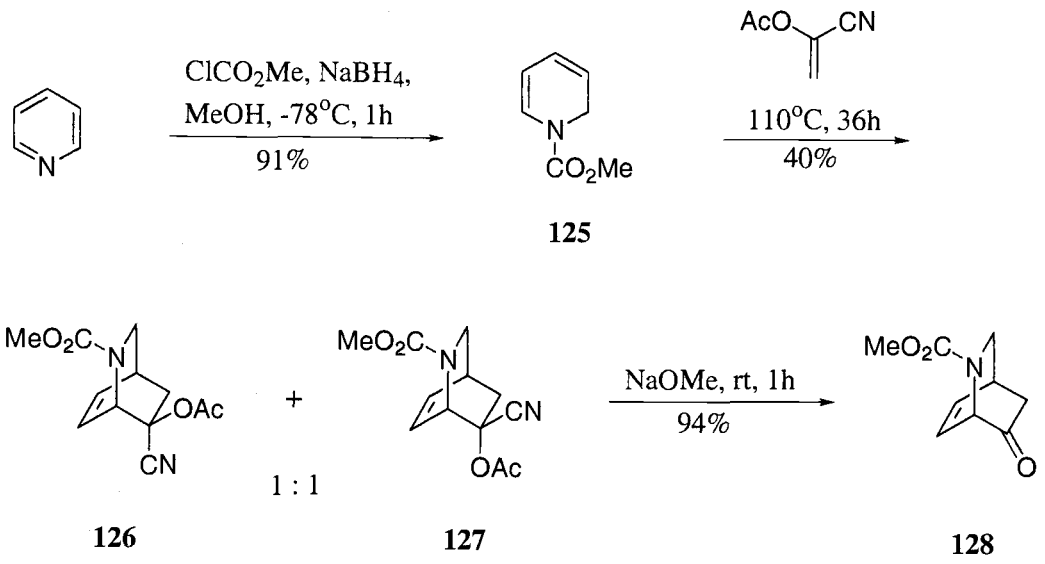



**97** **123** **124**

**Scheme 25**

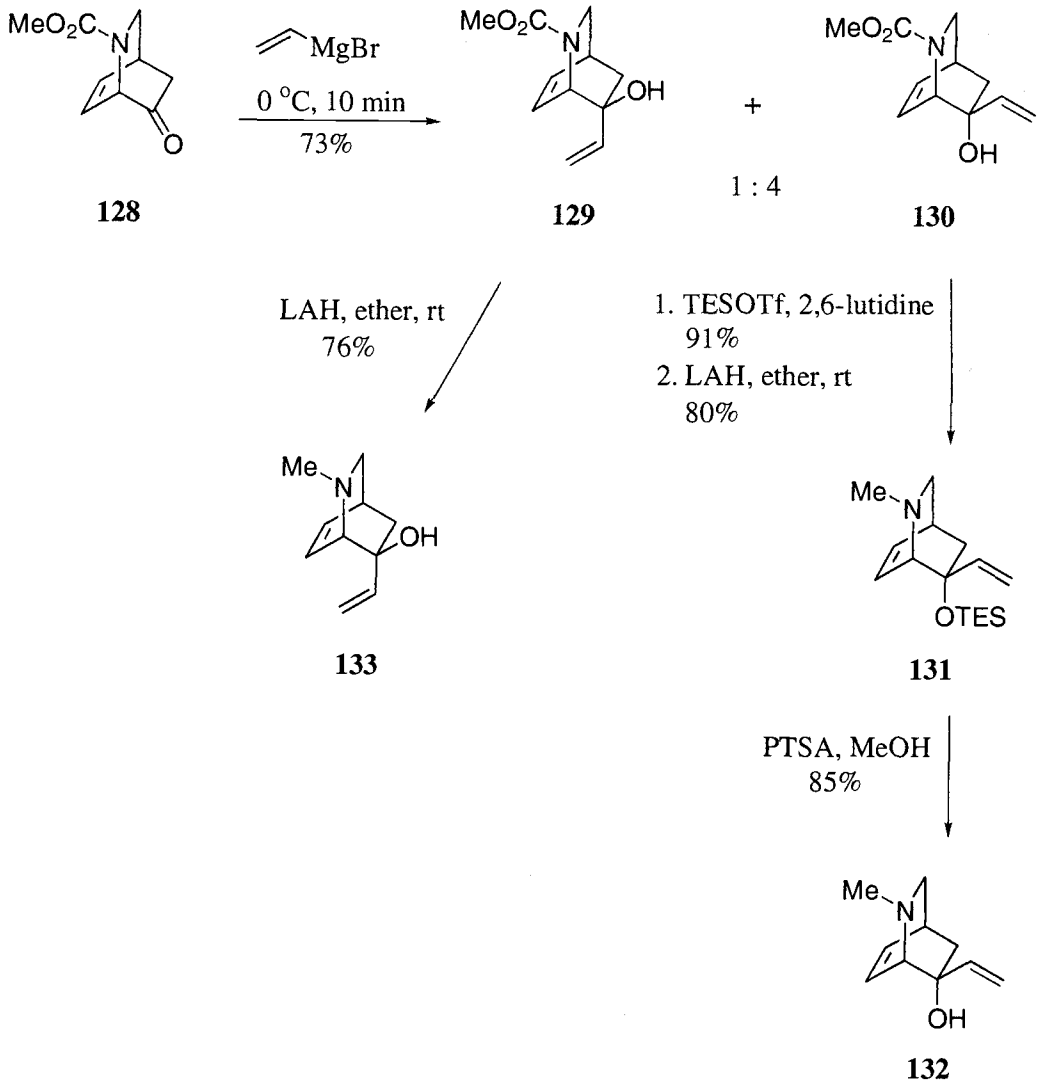
We believed that the allylic alcohol **124** should behave in a fashion similar to its carbocyclic analogue **121** in an anionic oxy-Cope rearrangement and should therefore provide the *cis*-hydroisoguinoline **123** (**Scheme 25**). This octahydroisoquinolone would afford an entry into the pivotal intermediate **97** needed for our route to koumine.

The preparation of several possible substrates for our proposed anionic oxy-Cope rearrangement began with a Fowler reduction of pyridine (**Scheme 26**).[26] The resultant *N*-(methoxycarbonyl)dihydropyridine **125** engaged in a Diels-Alder reaction with the ketene equivalent 1-cyanovinyl acetate to give a 1:1 mixture of stereoisomeric isoquinuclidines **126** and **127** which were transformed as the mixture to ketone **128** by treatment with sodium methoxide.[27]




**Scheme 26**

Addition of vinylmagnesium bromide to the bicyclic ketone **128** afforded a 1:4 mixture of *exo* **129** and *endo* **130** alcohols which were either separated by radial chromatography or utilized directly in the subsequent step (**Scheme 27**). Stereochemical assignment to the alcohols **129** and **130** was initially carried out by a $^1$H NMR analysis which shows the vinyl protons at the terminus of the allylic alcohol moiety of **129** at higher field (0.1-0.3 ppm) than the corresponding protons of **130** due to diamagnetic shielding by the endocyclic double bond.[28] More conclusive evidence for the stereochemistry came from a NOE experiment with the *N*-methylamine **132** which was obtained from **130** by a silylation, reduction and desilylation sequence. When H-1 was irradiated, the observed 1% signal enhancement of H-3 confirmed our assignment (**Figure 2.2**).




**Scheme 27**

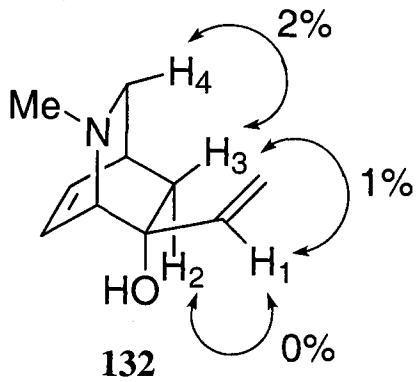
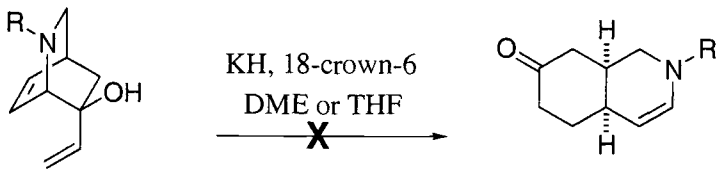



**Figure 2.2** NOE data for the *N*-methylamine **132**




**129**, R = $CO_2Me$
**133**, R = Me

**134**, R = $CO_2Me$
**135**, R = Me

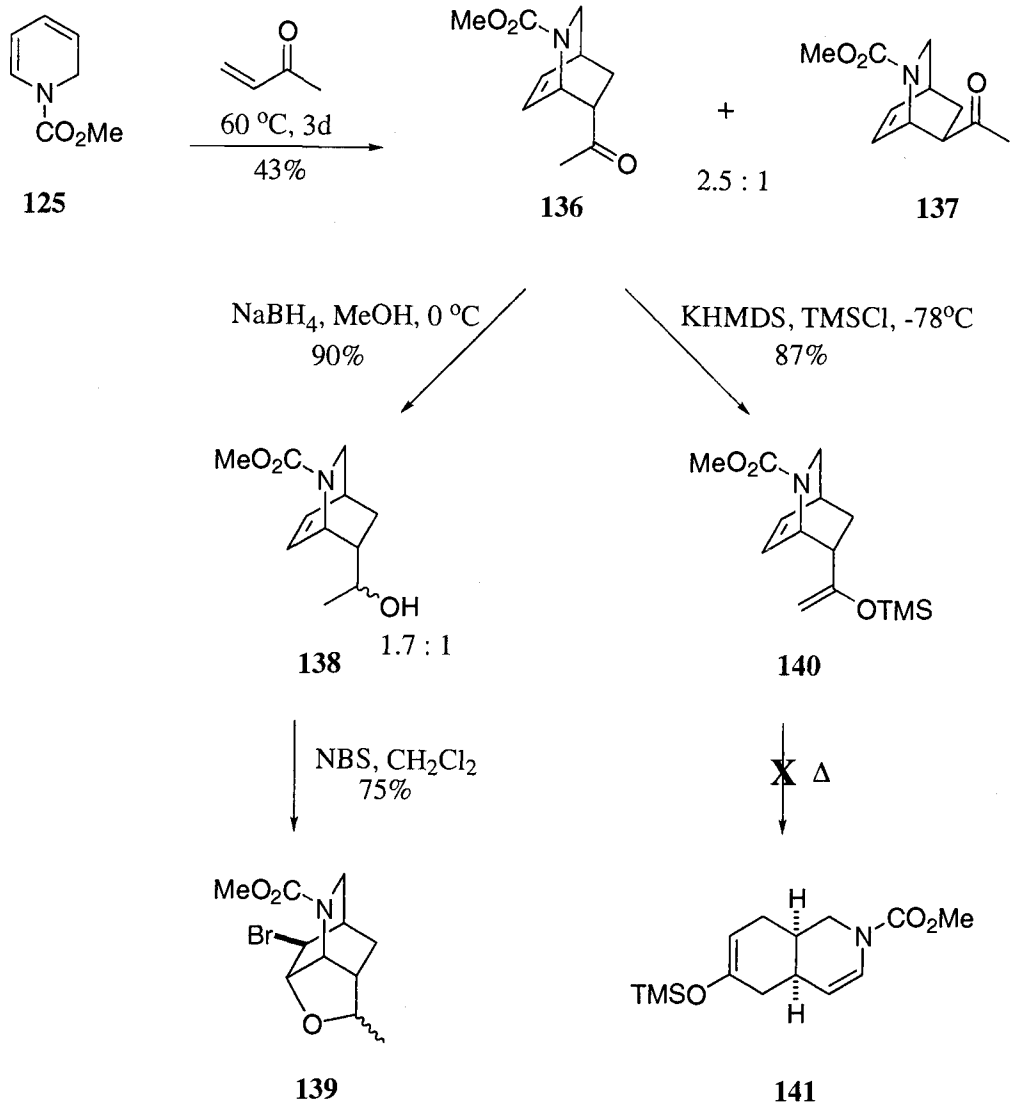
**Scheme 28**

When the *exo* alcohol **129** was subjected to potassium hydride and 18-crown-6, the expected anionic oxy-Cope rearrangement did not occur and only fragmentation of the starting material was observed (**Scheme 28**). The same behavior of this azabicyclo[2.2.2] system was also observed in case of the *N*-methylamine **133**, derived from **129** by lithium aluminum hydride reduction.

It has been shown that a heteroatom at either C-4 or C-6 of a substrate such as **129** or **133** affects not only the reaction rate of the oxy-Cope rearrangement but also changes the reaction mechanism.[29] It seems that a nitrogen atom at C-4 disfavors a concerted pathway for the rearrangement and that a competing fragmentation of the C-C bond adjacent to the alkoxide substituent dominates.

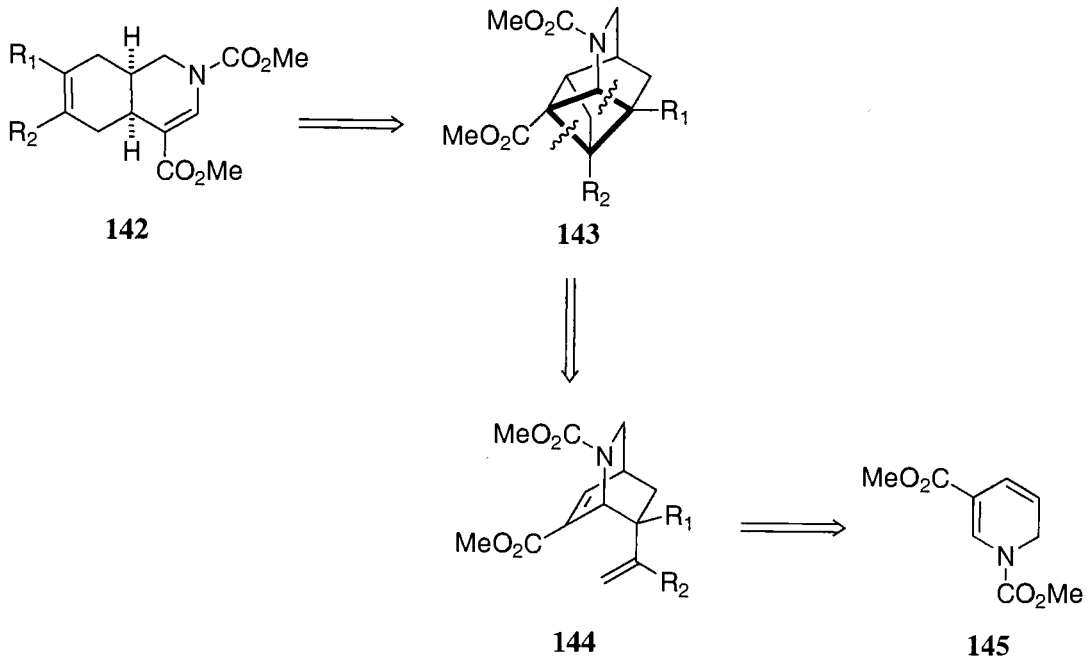
In conjunction with the approach using an anionic oxy-Cope rearrangement, the Cope rearrangement[30] of silyl enol ether **140** was also investigated (**Scheme 29**). A Diels-Alder reaction of *N*-(methoxycarbonyl)dihydropyridine **125**[26] with methyl vinyl ketone (MVK) gave 7-acetylisoquinuclidines, *endo* **136** and *exo* **137**, determined by $^1H$ NMR analysis to be a 2.5:1 mixture.[31] Reduction of *endo* ketone **136** with sodium borohydride

followed by treatment of the resulting mixture of diastereomeric alcohols **138** with *N*-bromosuccinimide (NBS) provided stereoisomeric bromoethers **139**, confirming the *endo* stereochemical assignment made to **136**. With the *endo* ketone **136** in hand, silyl enol ether **140** was prepared with lithium hexamethyldisilazide (LHMDS) and trimethylsilyl chloride at -78 °C.




**Scheme 29**

Disappointingly, a solution of **140** heated at 230 °C in solvents such as xylene and mesitylene did not provide the *cis*-hydroisoquinoline **141**. Only the intact starting material was recovered under these conditions.



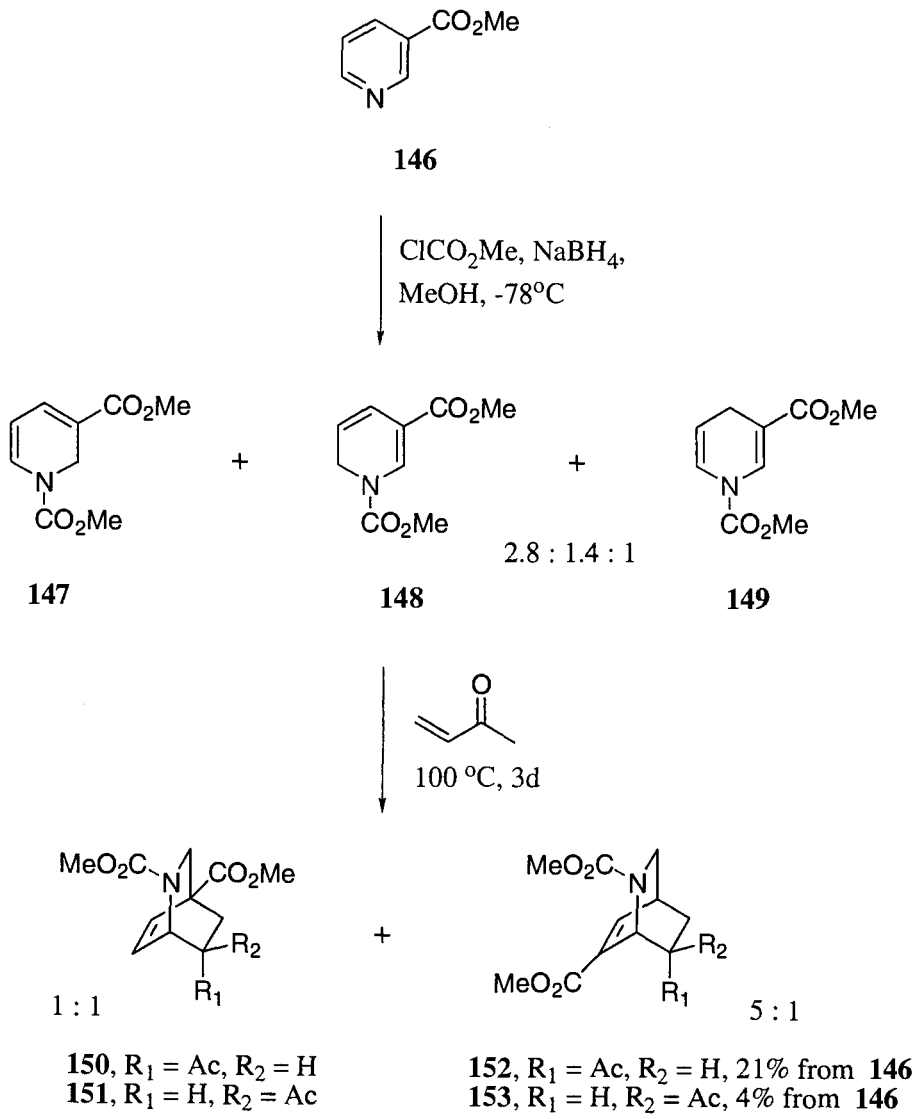

142 143 144 145

**Scheme 30**

As an alternative approach to the *cis*-hydroisoquinoline system, it was envisaged that the strained photoadduct **143** could be induced to fragment in the desired sense as shown to produce **142** (**Scheme 30**). The substrate **144** required for the intramolecular [2+2] photocycloaddition that would yield **143** would be available *via* a Diels-Alder route starting from the 1,6-dihydropyridine **145**.

Toward this end, reduction of methyl nicotinate **146** with sodium borohydride in the presence of methyl chloroformate resulted in a 2.8:1.4:1

mixture of dihydropyridines **147**, **148**, and **149** as determined by $^1$H NMR analysis (**Scheme 31**).[32] This mixture was subjected directly to a Diels-Alder reaction with methyl vinyl ketone.[33] The desired 1,6-*endo* cycloadduct **152** (*endo*:*exo* = 5:1) could be separated from the mixture of the 1,2-cycloadducts **150** and **151** *via* crystallization, and its relative configuration was unambiguously determined by X-ray analysis (**Figure 2.3**).




**Scheme 31**

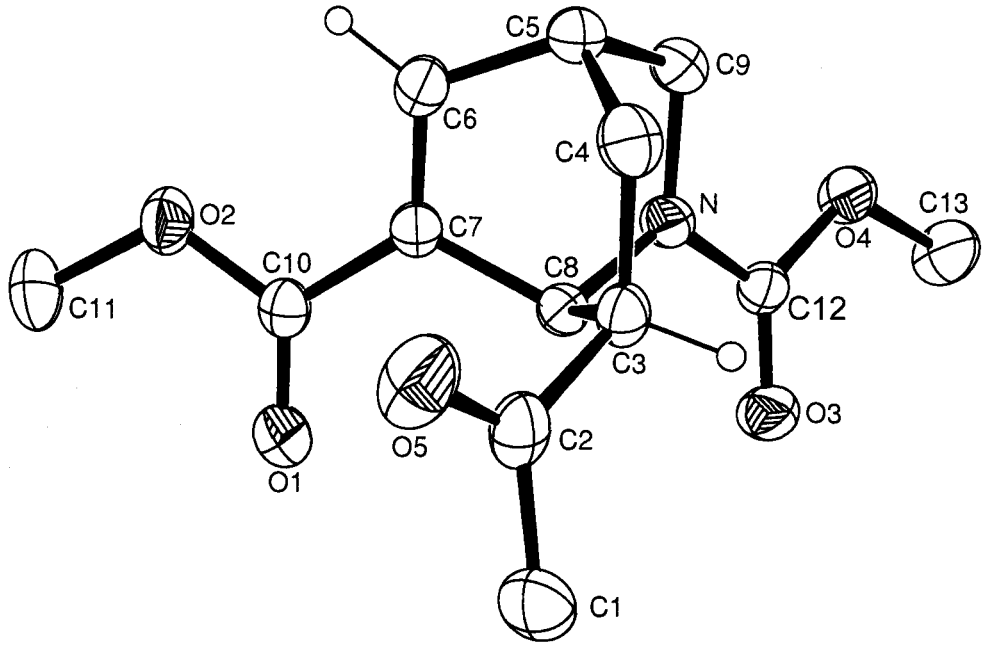
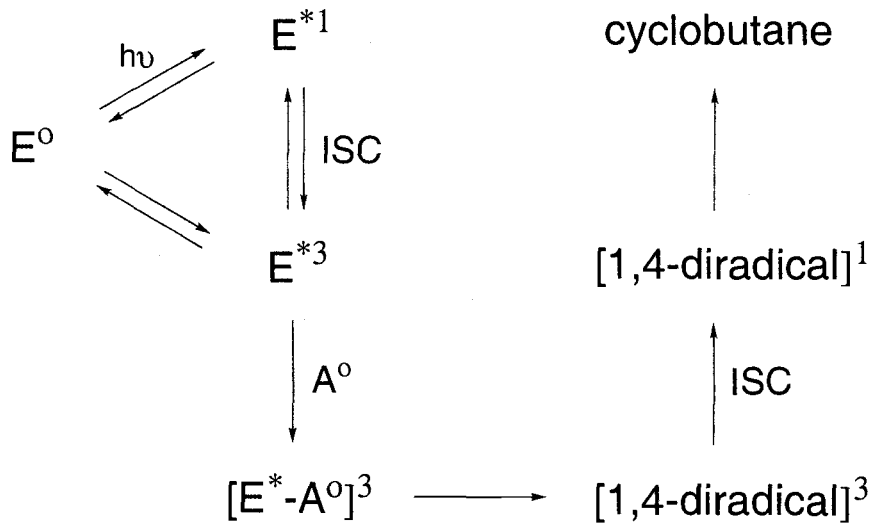



**Figure 2.3** ORTEP representation of X-ray structure of **152**

Intramolecular [2+2] enone-olefin photocycloaddition has been recognized as a powerful tool for the construction of cyclobutanes.[34] While a variety of mechanistic studies have been performed to shed light on the photocycloaddition process, the exact mechanistic details are still uncertain. The generally accepted pathway is shown in **Scheme 32**.[35] Absorption of a photon by the ground state enone $E^{\circ}$ normally produces the short-lived excited singlet $E^{*1}$ which can then decay back to the ground state or can undergo intersystem crossing (ISC) to a long-lived excited triplet state $E^{*3}$. The next step is usually considered to be complexation of the triplet state $E^{*3}$ with a ground state alkene to generate a short-lived triplet exciplex $(E^{*}\text{-}A^{\circ})^{3}$.

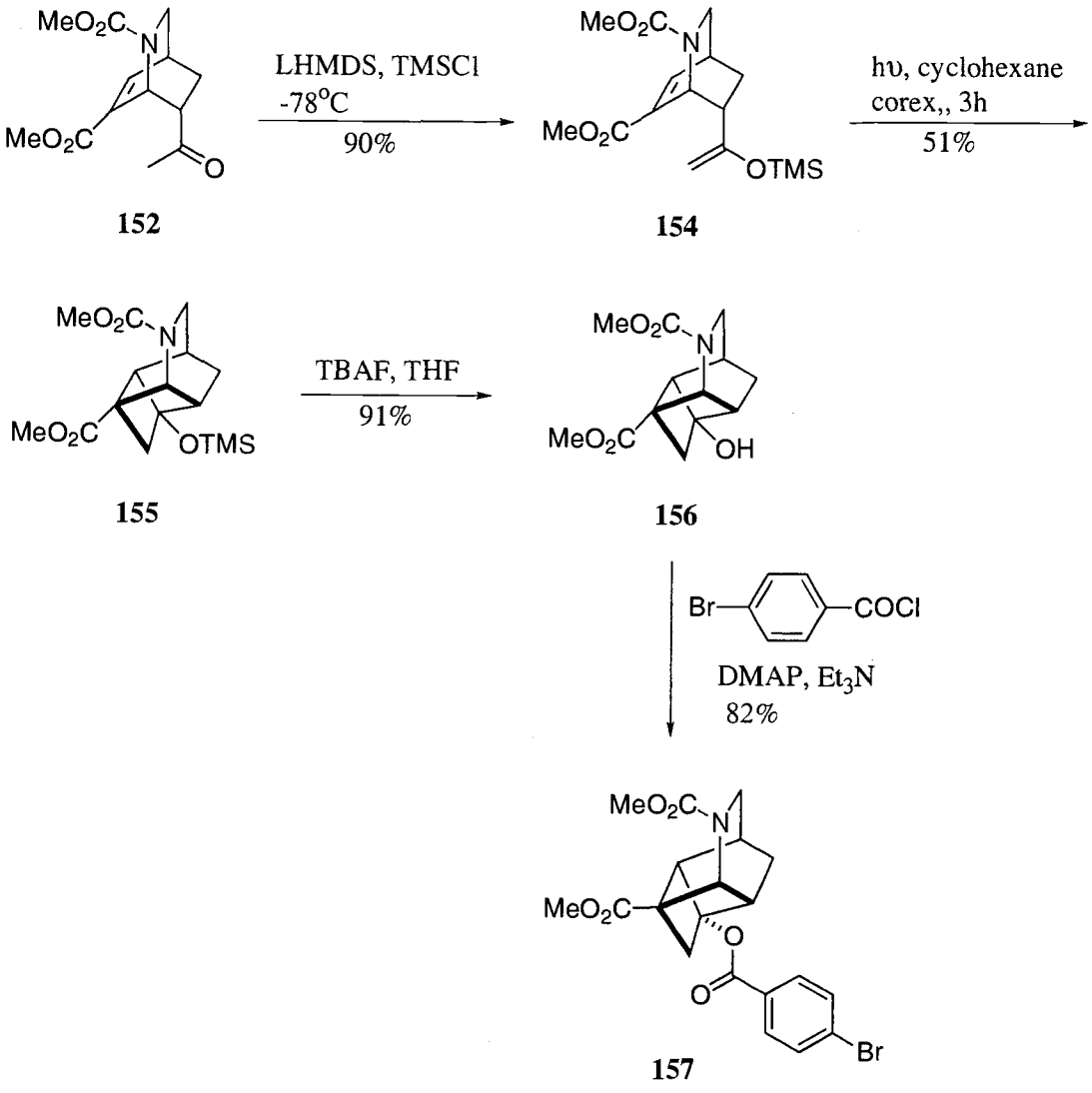



**Scheme 32.** The mechanism of [2+2] enone-olefin photocycloaddition

Although it has never been directly observed, this complex has been used to explain the regioselectivity of many intermolecular photocycloadditions and to rationalize the observation that the rates of photocycloaddition are much higher than those of normal radical additions to olefins. The exciplex leads to formation of a carbon-carbon bond and produces a triplet 1,4-biradical intermediate. This species must undergo spin inversion to the singlet biradical before ring closure to the cyclobutane can occur.

Our initial investigation of the intramolecular [2+2] photocycloaddition in the context of a route to **142** was performed with silyl enol ether **154** derived from the *endo* ketone **152** by reaction with lithium hexamethyldisilazide and chlorotrimethylsilane (**Scheme 33**). In the event, irradiation of **154** in cyclohexane through a Corex filter ($\lambda$> 250 nm) proceeded with complete regioselectivity resulting in the intramolecular photoadduct **155**. A conclusive structural determination of the photoadduct **155** was obtained by its conversion to

benzoate **157** by desilylation with tetrabutylammonium fluoride (TBAF) and subsequent benzoylation of the resultant alcohol **156** with *p*-bromobenzoyl chloride. X-ray analysis of the crystalline benzoate **157** established the structure of **155** and hence confirmed the regiochemical outcome in the photocycloaddition of **154** (**Figure 2.4**).




**Scheme 33**

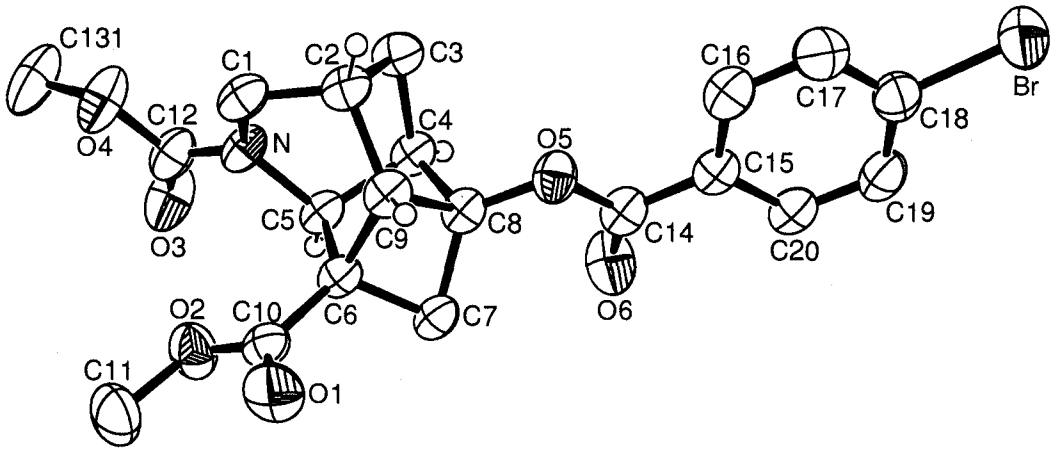
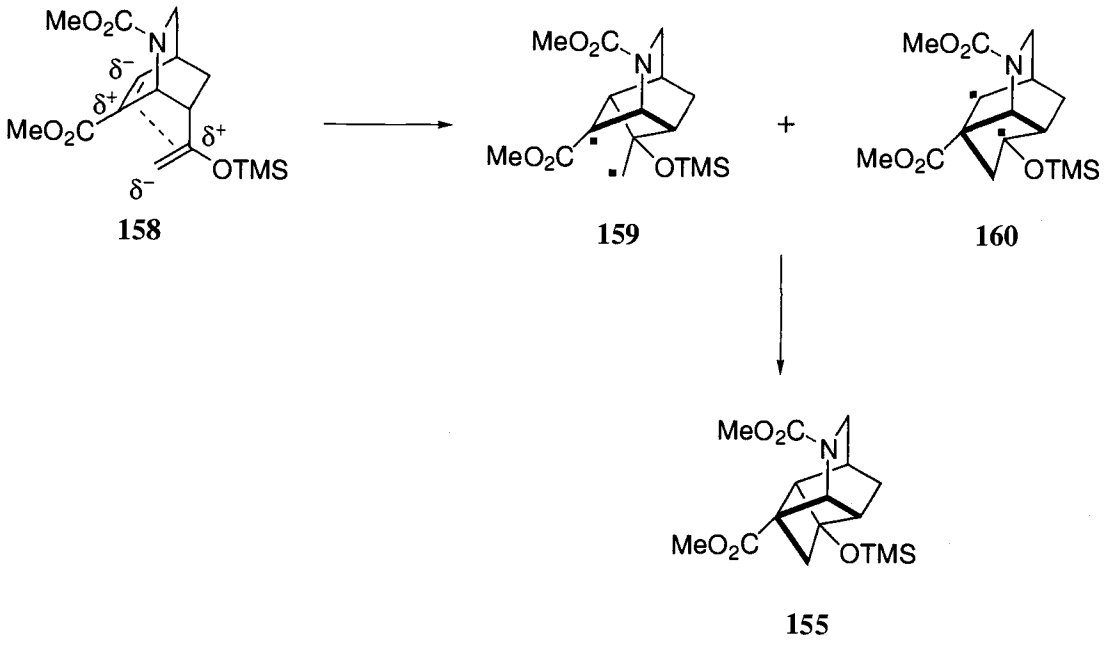
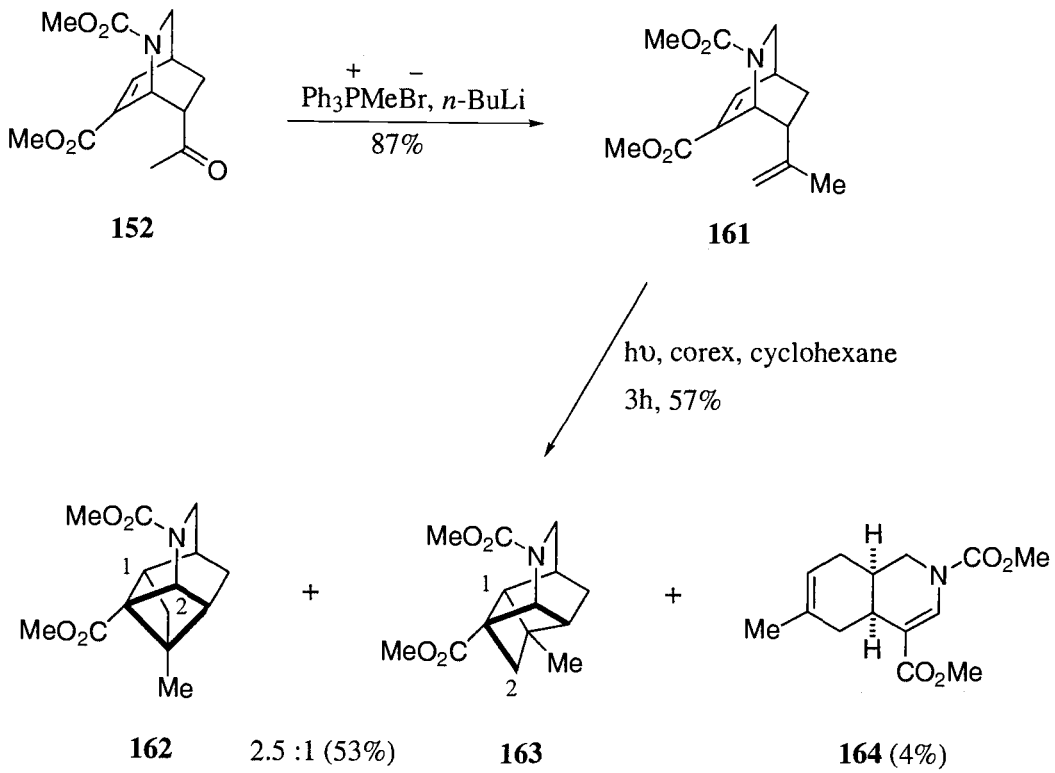



**Figure 2.4** ORTEP representation of X-ray structure of **157**




**Scheme 34**

The clean regioselectivity observed in the intramolecular photocycloaddiiton of **154** can be explained in terms of the Corey-de Mayo mechanism[36] which includes two types of intermediates: an exciplex **158** and alternative triplet 1,4-biradicals **159** and **160** (**Scheme 34**). The exciplex **158** is believed to be a complex in which the excited enone and ground-state alkene are oriented in such a fashion that destabilizing polar interactions are minimized. It has been hypothesized that the dipole moment of the excited triplet enone results in an electronic charge redistribution in which electron density is higher at Cβ than at Cα.[37] The orientation of this complex is then reflected in the regiochemistry of the cycloadduct **155**.



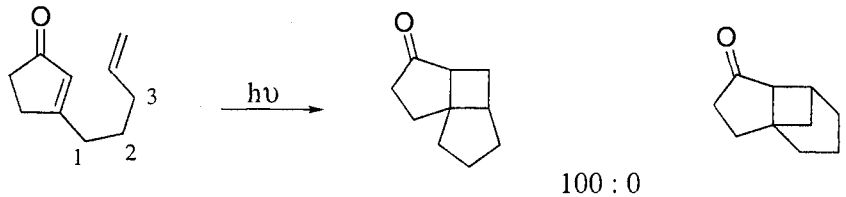

**152** **161**

**162** 2.5 :1 (53%) **163** **164** (4%)

**Scheme 35**

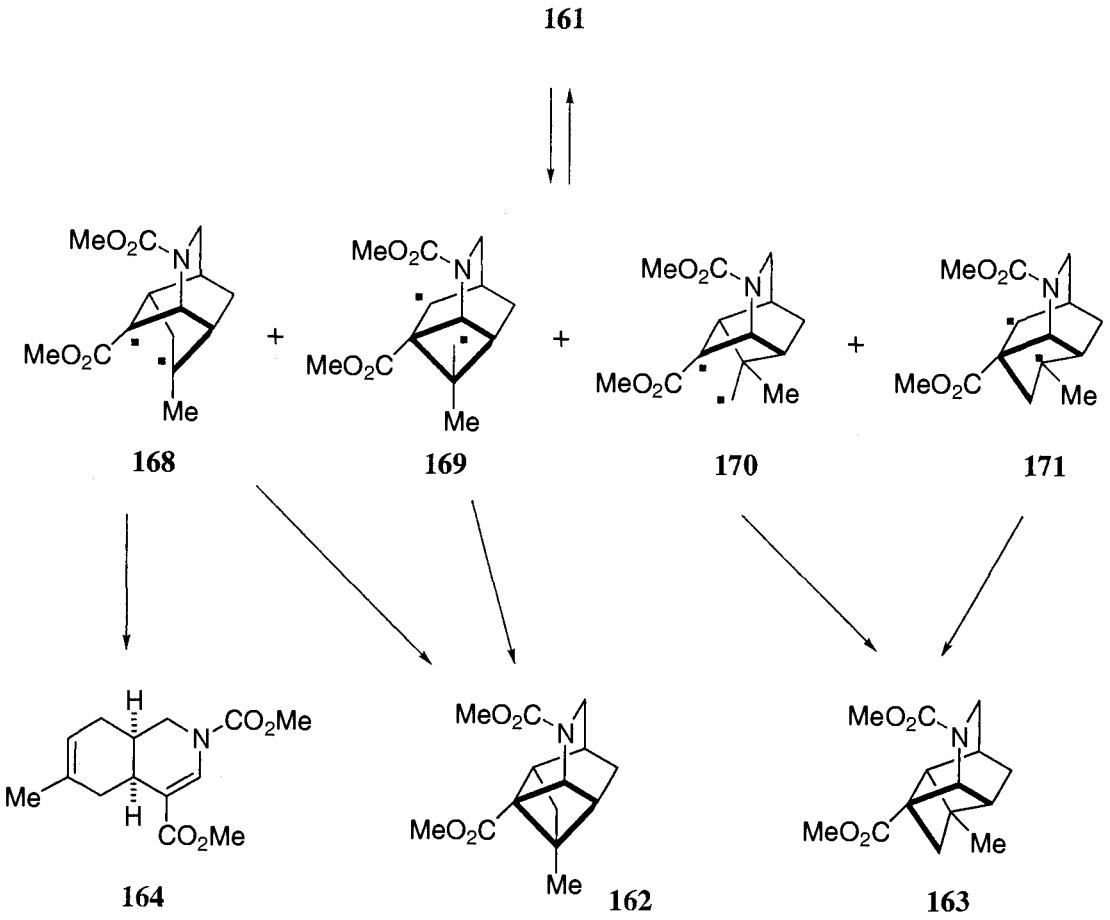
In an attempt to investigate the regioselectivity of this intramolecular photocycloaddition more broadly, the olefin **161** was prepared from *endo* ketone **152** by a Wittig reaction with methyltriphenylphosphonium bromide in the presence of *n*-butyllithium (**Scheme 35**). It was found that the intramolecular photocycloaddition process was markedly dependent on the substituent attached to the pendant alkene. Irradiation of photosubstrate **161** in cyclohexane (450-W Hanovia mercury lamp) through a Corex filter ($\lambda > 250$ nm) led to the formation of a mixture of three products **162**, **163**, and **164** in a 57% combined yield. The two major products, "crossed" adduct **162** and "straight" adduct **163**, could be distinguished by means of extensive 2D NMR experiments which identified the presence or absence of the proton-proton correlation between H-1 and H-2.

It has been shown that, as the electron-donating ability of the substituent on the alkene decreases, regiochemical control by that substituent through an exciplex intermediate is less dominant and hence regioselectivity is less predictable.[35] The regiochemical outcome from photocycloaddition of **161** must arise from a combination of several factors because the electron-donating effect of the methyl group on the alkene would be expected to favor the "straight" adduct **163**. For example, irradiation of the three-atom tethered photosubstrate **165** leads exclusively to formation of the "straight" adduct **166** with none of the "crossed" adduct **167** observed (**Scheme 36**).[38] Since five-membered ring formation is kinetically preferred over the formation of four- and six-membered rings, a "rule of five" has been postulated to explain the regioselectivity of the intramolecular photocycloaddition in general.[39]




**165** **166** **167**

**Scheme 36**




**Scheme 37**

However, the formation of "crossed" product **162** as the major product from irradiation of **161** constitutes a violation of the "rule of five", and hence an

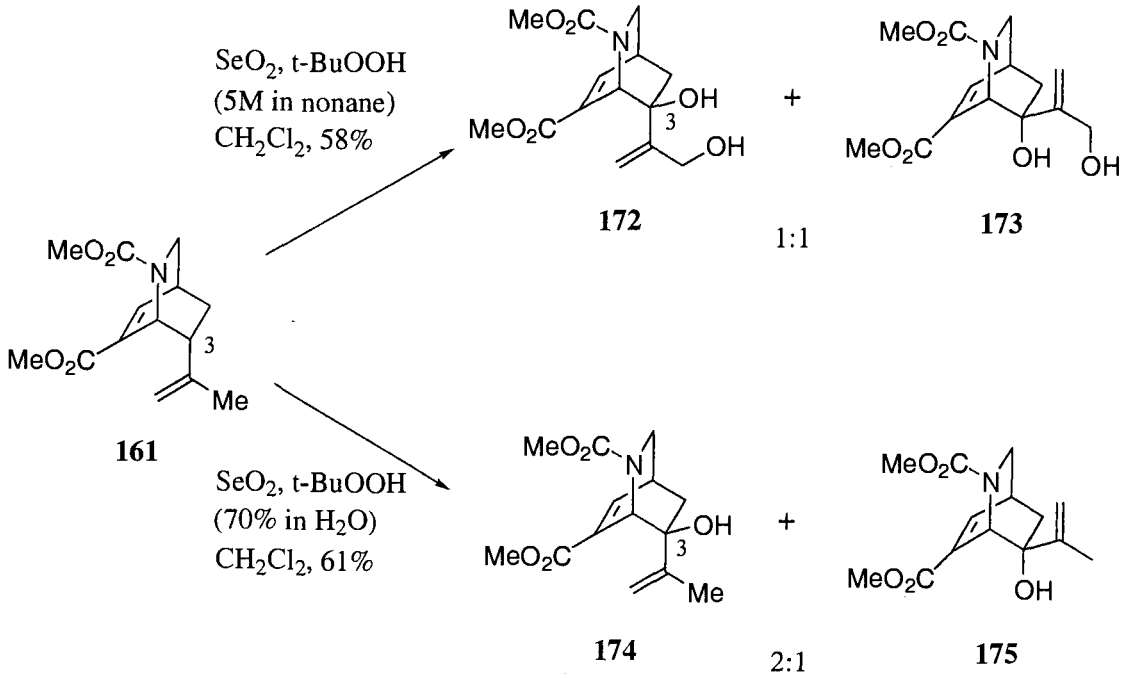
alternative explanation should be considered to rationalize this result. For this purpose, the relative efficiencies with which the isomeric biradicals **168-171** are converted to their cyclobutane products in competition with fragmentation to the ground state starting material must be taken into account (**Scheme 37**). It has been demonstrated that simple molecular mechanics calculations may be used to analyze the geometry of intermediate biradical species and inter-radical distances (IRD) shorter than 3Å are considered as the upper limit for effective orbital interaction leading to bond closure.[40] We used the semi-empirical AM1 model to calculate the relative stability and geometry of the four possible intermediate biradicals **168-171**, and the results are summarized in **Table 2.1**.

| Biradical | Relative energy (Kcal/mol) | Inter-radical distance (Å) |
|---|---|---|
| **168** | 7.3 | 2.7 |
| **169** | 49.4 | 3.0 |
| **170** | 60.5 | 2.9 |
| **171** | 0.0 | 3.2 |

**Table 2.1** Interatomic separation of radical centers (IRD) for the minimum energy conformation of biradicals **168-171**

Of the two biradicals **168** and **169** which lead to the "crossed" adduct **162**, **168** is lower in energy than **169**; however both would have inter-radical distances (IRD) sufficiently short for fast ring closure. In the case of biradicals **170** and **171** which lead to the "straight" adduct **163**, **171** turned out to be the most stable of the four whereas **170** was the least stable biradical. However, the calculated IRD

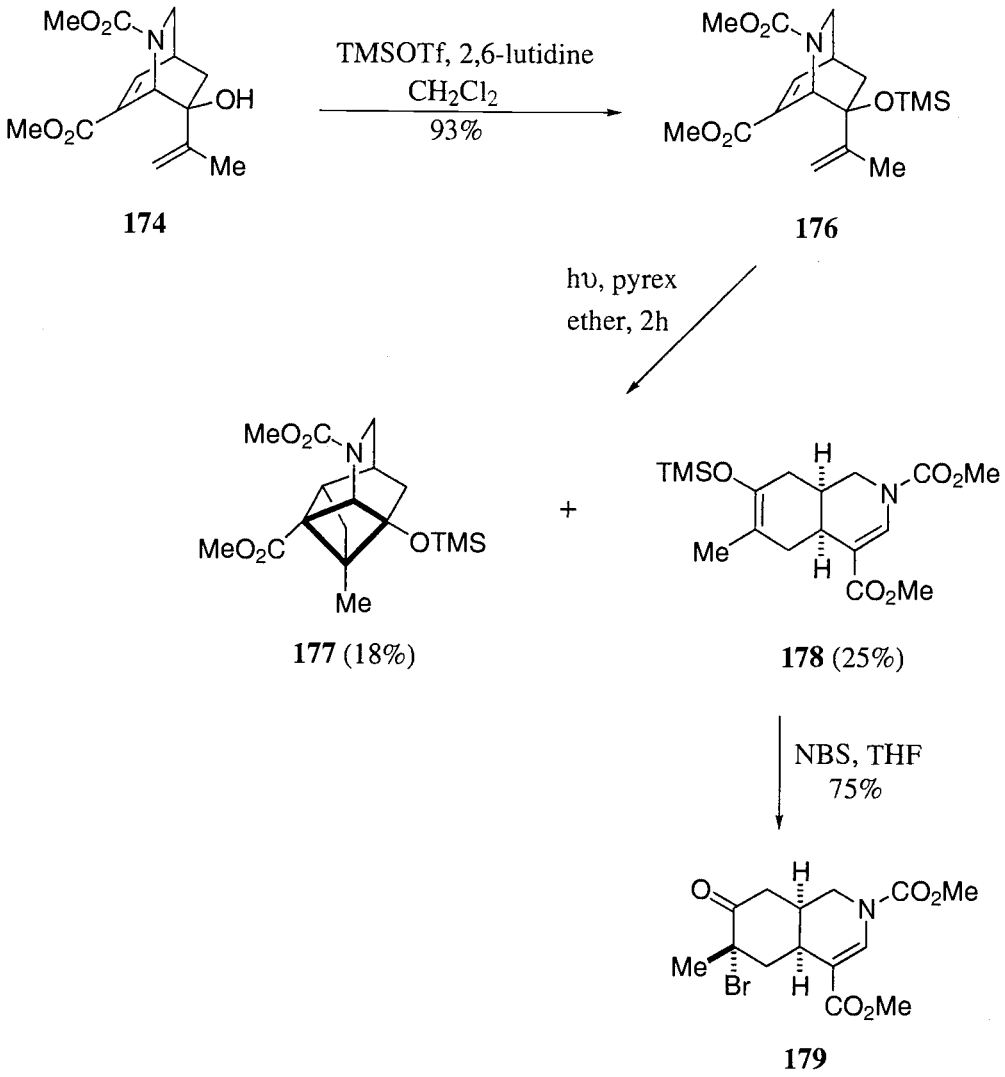
value of **171** is too large to allow collapse to a cyclobutane, and reversion to the ground state therefore occurs. Thus, the lower energy of **171** in relation to **168** is overridden by the shorter IRD of **168**, in agreement with the experimentally observed regioselectivity in favor of "crossed" adduct **162**. The generation of a small portion of **164** from **161** is believed to be due to disproportionation of the biradical **168**.




**Scheme 38**

The markedly different photochemical behavior of **154** and **161** prompted us to examine a case where there was a heteroatom substituent at C-3 in the photosubstrate. Toward that end, allylic oxidation of **161** using Sharpless conditions[41] with dichloromethane as solvent led to the formation of a 1:1 mixture of diols **172** and **173**, epimeric at C-3 (**Scheme 38**). On the other hand,

oxidation in a heterogeneous medium gave a 2:1 mixture of alcohols **174** and **175**, respectively.

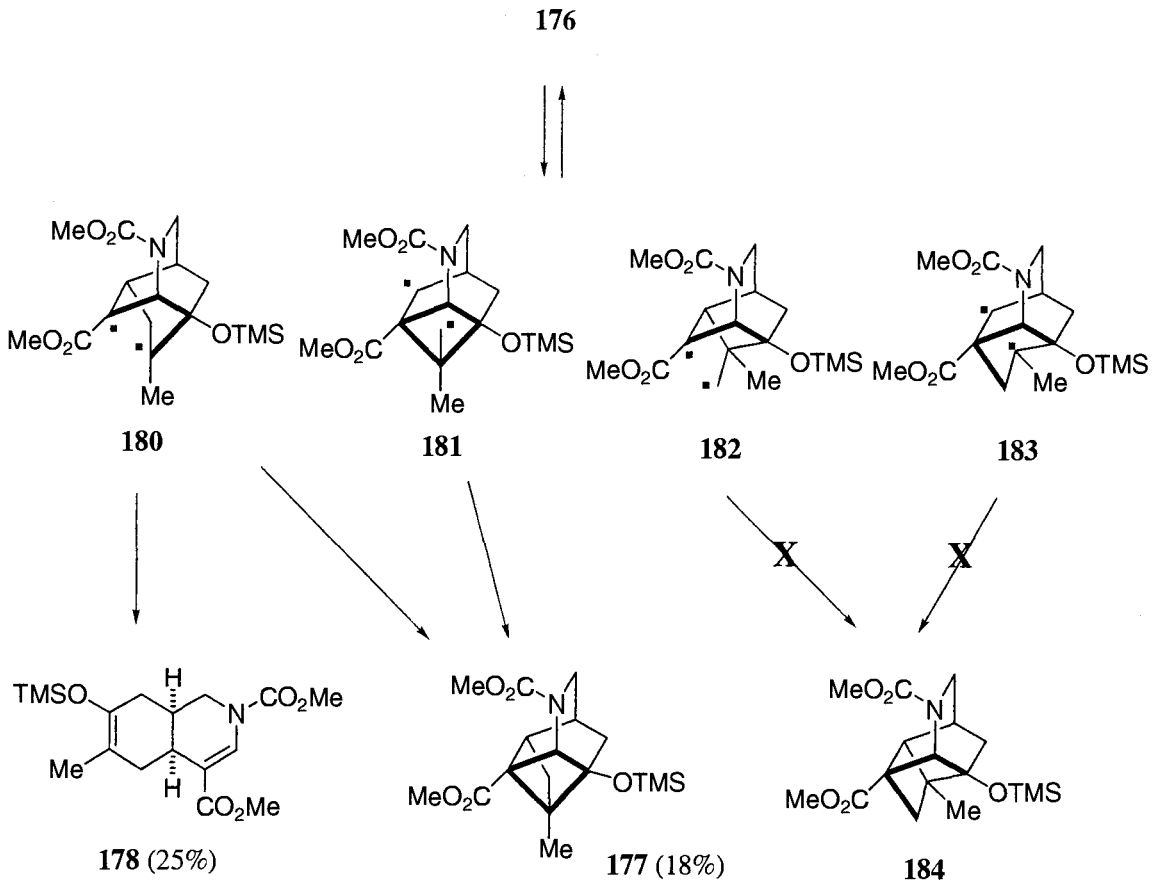



**174** **176** **177** (18%) **178** (25%) **179**

**Scheme 39**

After silylation of the alcohol **174** with trimethylsilyl trifluoromethanesulfonate (TMSOTf) and 2,6-lutidine, the resulting silyl ether **176** was subjected to irradiation to give a mixture of the "crossed" adduct **177** and the *cis*-octahydroisoquinoline **178** (**Scheme 39**). These compounds were readily separable by column chromatography. For the structure assignment, *cis*-

octahydroisoquinoline **178** was treated with *N*-bromosuccinimide (NBS) to furnish the α-bromoketone **179**, which produced a cleaner $^1$H NMR spectrum.




**Scheme 40**

It is noteworthy that the yield of *cis*-octahydroisoquinoline **178** increased significantly whereas generation of the "straight" adduct **184** was suppressed completely with incorporation of the TMS ether at C-3 of the photosubstrate **176** (**Scheme 40**). Once again, the relative efficiencies with which the isomeric biradicals **180-183** are converted to their cyclobutane products in competition with fragmentation to the ground state starting material could be estimated by

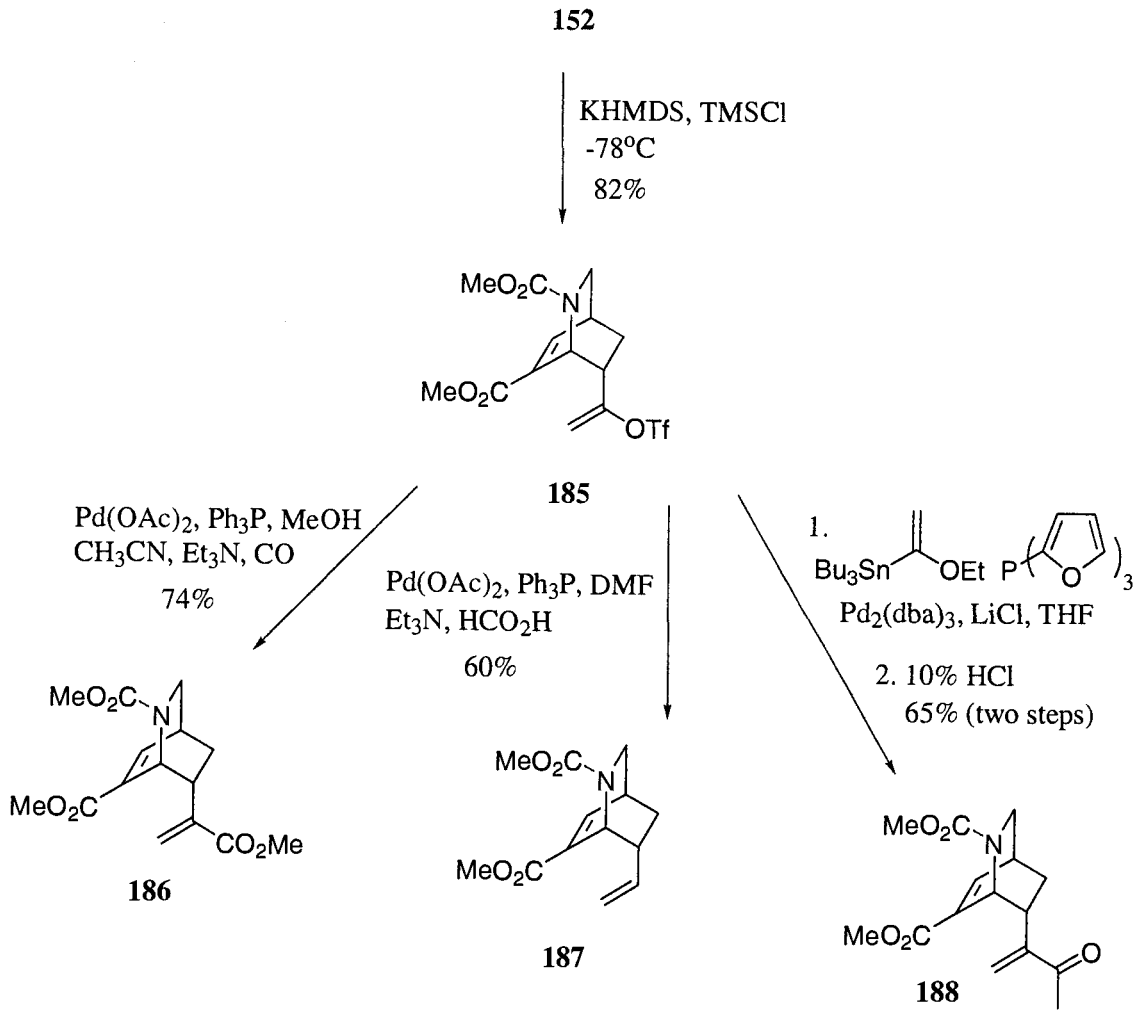
using simple molecular mechanics calculations (**Table 2.2**). The biradicals **180** and **183** are believed to be the predominant intermediates formed upon irradiation of **176**. The inter-radical distance (IRD) of the more stable biradical **183** is too large to generate the "straight" adduct **184**, and this species therefore reverts to the ground state of **176**. However, the enery difference between biradicals **180** and **183** is small enough for the photocycloaddition of **176** to proceed through **180** to **177** and **178**.

| Biradical | Relative energy (Kcal/mol) | Inter-radical distance (Å) |
|---|---|---|
| **180** | 4.1 | 2.7 |
| **181** | 47.1 | 3.0 |
| **182** | 52.1 | 2.9 |
| **183** | 0.0 | 3.2 |

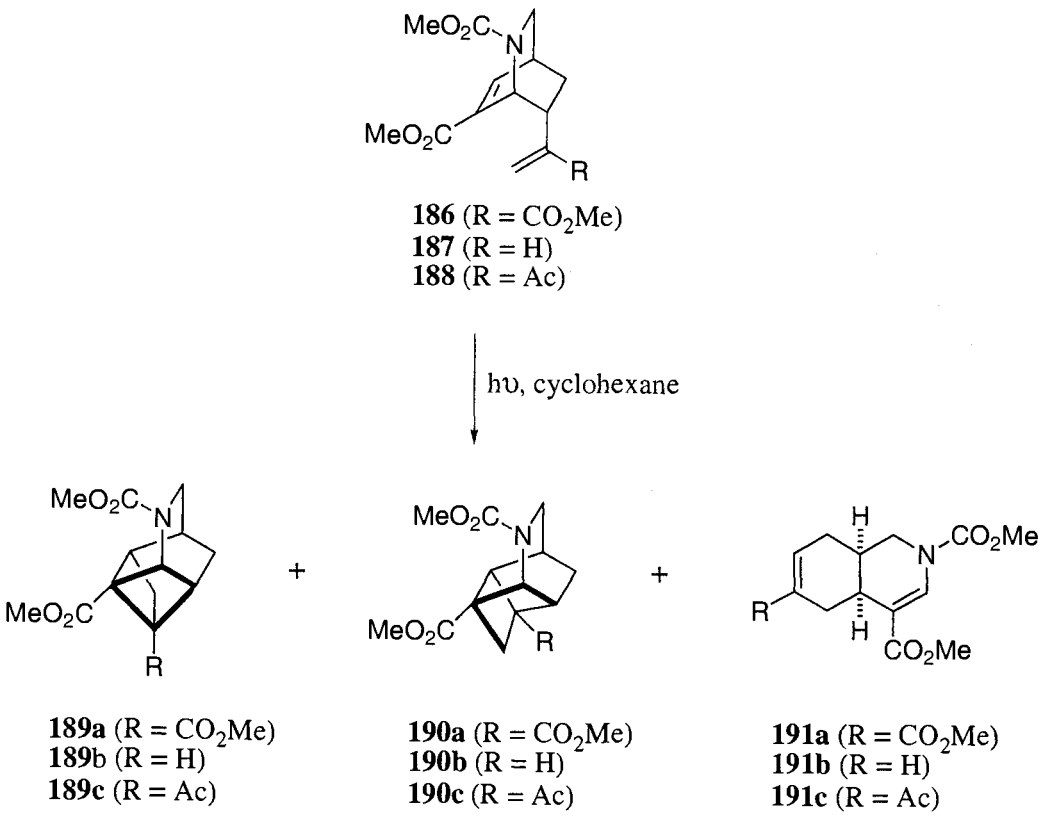
**Table 2.2** Interatomic separation of radical centers (IRD) for the minimum energy conformation of biradicals **180-183**

In a further extension of this intramolecular photoaddition, deprotonation of ketone **152** with potassium hexamethyldisilazide (KHMDS) followed by addition of *N*-phenyltrifluoromethanesulfonimide ($Tf_2NPh$) furnished the enol triflate **185** which proved to be a useful precursor for the preparation of several additional photosubstrates (**Scheme 41**).[42] Palladium-catalyzed alkoxy-carbonylation of **185** produced the α,β-unsaturated ester **186**.[43]

A combination of triethylamine and formic acid together with catalytic amounts of palladium acetate and triphenylphosphine were used to hydrogenate **185** which gave the alkene **187**.[44] Stille coupling of **185** with (α-ethoxyvinyl)tributylstannane[45] was effected in the presence of tris(dibenzylideneacetonyl)bispalladium(0) ($Pd_2dba_3$) and tris(2-furyl)phosphine and furnished the enone **188** after acidic hydrolysis.[46]




**Scheme 41**




**186** (R = $CO_2Me$)
**187** (R = H)
**188** (R = Ac)

**189a** (R = $CO_2Me$)
**189b** (R = H)
**189c** (R = Ac)

**190a** (R = $CO_2Me$)
**190b** (R = H)
**190c** (R = Ac)

**191a** (R = $CO_2Me$)
**191b** (R = H)
**191c** (R = Ac)

**Scheme 42**

| Run | Substrate | Filter | Time | Ratio of **189** and **190** | Yields of **189** and **190** | Yield of **191** |
|---|---|---|---|---|---|---|
| 1 | **186** | Corex | 5 h | 1.1:1 | 55% | 3% |
| 2 | **186** | Pyrex | 5 h | 1:1 | 57% | 2% |
| 3 | **187** | Corex | 20 h | 1:1.5 | 54% | 3% |
| 4 | **188** | Pyrex | 8 h | 1:8 | 47% | 0% |

**Table 2.3** Photocycloaddition of alkenes **186-188**

With these photosubstrates in hand, their photochemistry was studied in detail (**Scheme 42**). Irradiation of **186** in cyclohexane (450-W Hanovia mercury lamp) through a Corex filter ($\lambda$> 250 nm) gave a separable mixture of two photoadducts, **189a** and **190a**, in a 1.1:1 ratio, along with a trace amount of the *cis*-octahydroisoquinoline **191a** (run 1, **Table 2.3**). The regioselectivity of this photocycloaddition did not seem to be affected significantly by the irradiation conditions (run 2, **Table 2.3**).

Structural determination of the individual isomers was carried out using extensive 2D NMR experiments. In particular, a NOE experiment of the "crossed" adduct **189a** indicated the vicinal relationship of H-6 with H-7 and H-8 (**Figure 2.5**). In the same way, a NOE experiment with the "straight" adduct **190a** showed a 2% signal enhancement of H-6 when H-7 was irradiated; the same enhancement of H-2 occurred when H-8 was irradiated. This confirms the structure assignments made to **189a** and **190a**.

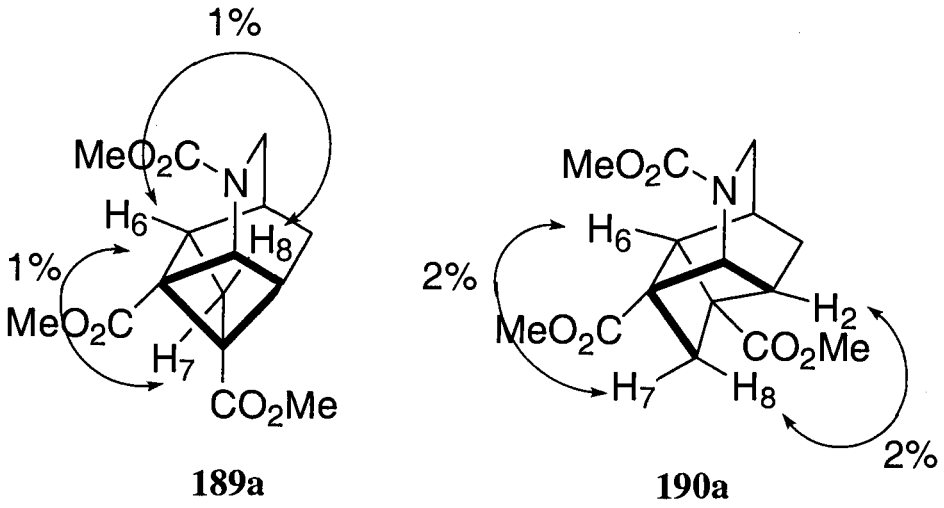
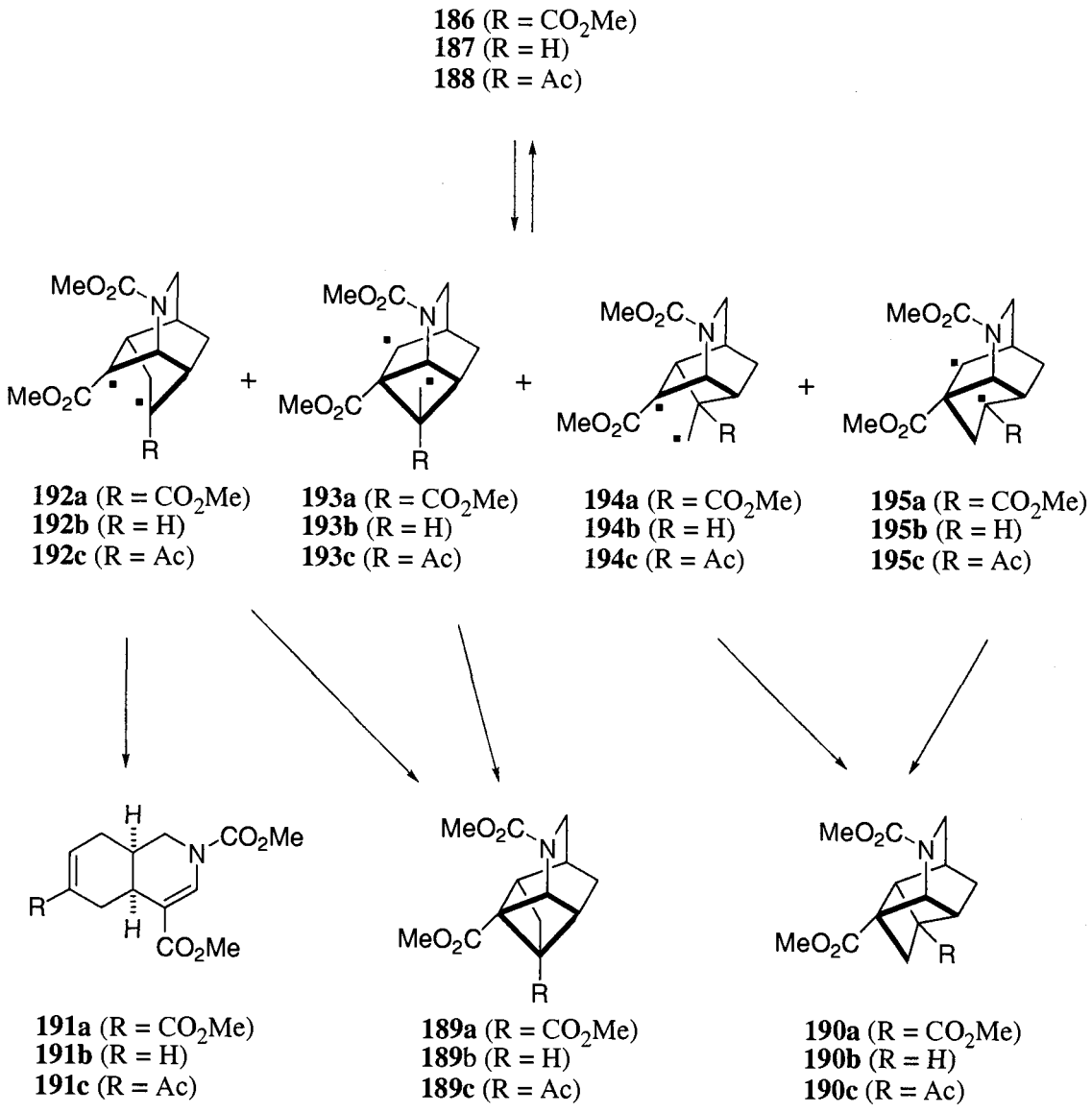



**Figure 2.5** NOE data for the photoadducts **189a** and **190a**

Recently, many examples have appeared in the literature in which intramolecular photocycloaddition is not regioselective or the regiochemistry is the reverse of that predicted by the Corey-de Mayo model. This is especially true when the alkenes are substituted by electron withdrawing group.[47]



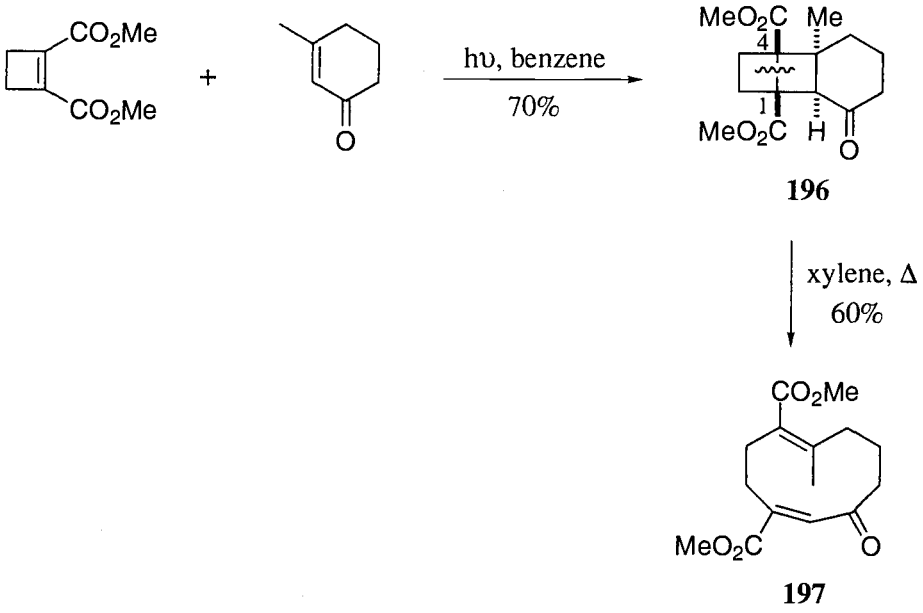

**Scheme 43**

| Biradical | Relative energy (Kcal/mol) | Inter-radical distance (Å) |
|---|---|---|
| **192a** | 9.1 | 2.7 |
| **193a** | 45.6 | 3.0 |
| **194a** | 58.5 | 2.9 |
| **195a** | 0.0 | 3.1 |
| **192b** | 8.0 | 2.7 |
| **193b** | 40.5 | 3.1 |
| **194b** | 43.7 | 2.9 |
| **195b** | 0.0 | 3.2 |
| **192c** | 10.2 | 2.7 |
| **193c** | 51.0 | 3.0 |
| **194c** | 60.8 | 2.9 |
| **195c** | 0.0 | 3.1 |

**Table 2.4** Interatomic separation of radical centers (IRD) for the minimum energy conformation of biradicals **192-195**

Again, molecular mechanics calculations indicate that the regiochemical outcome from irradiation of **186** appears to be affected by the relative energy and the inter-radical distance (IRD) of the biradicals **192a** and **195a** (**Scheme 43**, **Table 2.4**). The presence of a carbomethoxy group confers a little higher energy on the biradical **192a**, and the contribution of **192a** towards generating the "crossed" adduct **189a** should thus be diminished (**Table 2.3**). The photocycloaddition of **187** proceeded more slowly than **186** and afforded a 1:1.5 mixture of the photoadducts **189b** and **190b**, along with a small quantity of **191b** (run 3, **Table 2.3**). The reversed regiochemistry with **187** is explained by the

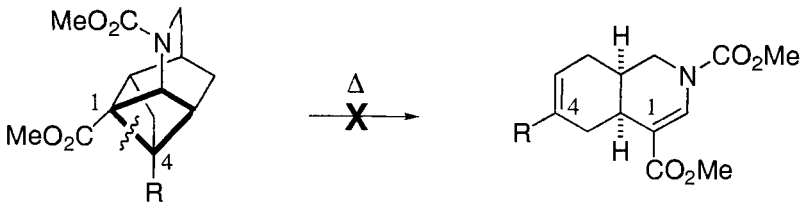
contribution of intermediate biradical **194b** in the photocycloaddition. In the case of the enone **188**, the photocycloaddition yielded the "straight" adduct **190c** as the major product (run 4, **Table 2.3**). This regiochemical outcome is unexpected here because the enone **188** should behave similarly to the corresponding α,β-unsaturated ester **186**. A possible explanation for this result is the higher energy of the biradical **192c**. Thus, although it has an appropriate inter-radical distance (IRD), the relatively high energy of **192c** makes it a less important contributor to the photocycloaddition of **186**.




**Scheme 44**

The concept of a [2+2] photocycloaddition-cycloreversion strategy has been recognized as a powerful tool for the synthesis of medium-ring structures.[48] For example, irradiation of dimethyl cyclobutene-1,2-dicarboxylate and 3-methyl-2-cyclohexenone resulted in the formation of the cycloadduct **196** which was

heated to produce the 1,5-cyclodecadiene **197** (**Scheme 44**).[49] Evidently, two fused cyclobutanes impart a sufficiently large degree of strain that fragmentation of the interior cyclobutane bond and subsequent cycloreversion become a relatively facile process.




**162** (R = Me)
**189a** (R = $CO_2Me$)

**164** (R = Me)
**191a** (R = $CO_2Me$)

**Scheme 45**

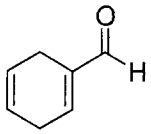
The strained photoadduct **162**, which also has a bicyclo[2.2.0]hexane moiety embedded in its framework, was subjected to thermolysis at temperature up to 250 °C (**Scheme 45**), but this substance turned out to be completely inert to these reaction conditions. Since it has been demonstrated that an electron-withdrawing substituent at C-1 or C-4 facilitates cycloreversion by stabilizing the diradical intermediate which is presumably formed under thermolytic condition,[50] the photoadduct **189a** was also subjected to thermolysis. Once again, there was no indication of a cycloreversion and the starting material was recovered intact.

The lack of thermal reactivity of **162** and **189a** is surprising, in part because a substructure search using the Cambridge Crystallographic Data Base shows that the average C1-C4 bond length of a bicyclo[2.2.0]hexane system is 1.59Å, making this undoubtedly a weak bond and therefore one which should be

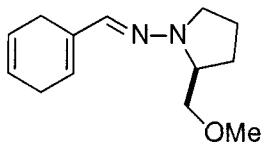
cleaved under thermal conditions. Unfortunately, no crystallographic data on any of our "crossed" photoadducts is available for a direct comparison of bond lengths with literature values.

In summary, three different routes for the synthesis of hexahydroisoquinoline **98** met obstacles which defeated our approach to koumine. The Diels-Alder reaction of cyclic 1-azadienes was abandoned due to the lack of reactivity of the dienes. An anionic oxy-Cope rearrangement of the azabicyclo[2.2.2]octane system caused mainly decomposition of the starting materials. Finally, although an intramolecular [2+2] photocycloaddition generated "crossed", "straight" and hydroisoquinoline products in varing ratios, depending on the substituent pattern of the substrate, this approach was not synthetically useful. The results from this last study may be valuable for predicting the regiochemical outcome of certain intramolecular photocycloadditions, but it appears that a new strategy must be developed if a viable route to (-)-koumine is to be found.

## Experimental Section

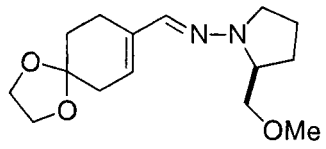



**Cyclohexa-1,4-dienecarbaldehyde (100).** To a solution of propiolaldehyde (101 mg, 1.87 mmol) in $CH_2Cl_2$ (5 mL) at 0 °C under argon was added a solution of boron trifluoride etherate (0.21 mL, 1.68 mmol), and the mixture was stirred for 10 min at 0 °C. A solution of 1,3-butadiene (360 mg, 6.66 mmol) in $CH_2Cl_2$ (1 mL) was added, and the mixture was stirred for 3 h at 0 °C. The mixture was diluted with saturated aqueous $NaHCO_3$ (1 mL), and was extracted with $CH_2Cl_2$. The extract was washed with saturated aqueous NaCl, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. Chromatography of the residue on silica (EtOAc-hexanes, 1:5) gave 89 mg (44 %) of **100** as a colorless: $R_f$ 0.15 (EtOAc-hexanes, 1:10); $^1$H NMR (300 MHz, $CDCl_3$) δ 2.81 (m, 2H), 2.97 (m, 2H), 5.66 (m, 1H), 5.80 (m, 1H), 6.78 (m, 1H), 9.48 (s, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 22.5, 27.4, 122.3, 124.0, 138.7, 147.5, 193.6.



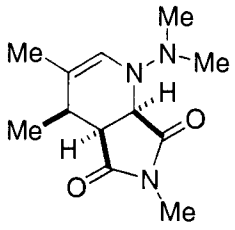

**Cyclohexa-1,4-dienylmethylene-(2-methoxymethyl-pyrrolidin-1-yl)-amine (102).** To a solution of (*S*)-(-)-1-amino-2-(methoxymethyl)pyrrolidine (SAMP) **101** (38 mg, 0.29 mmol) in acetic acid (0.5 mL) at room temperature was added a

solution of **100** (21 mg, 0.19 mmol) in $Et_2O$ (3 mL), and the mixture was heated at reflux for 30 min. The reaction mixture was concentrated under reduced pressure. Chromatography of the residue on silica (EtOAc-hexanes, 1:5) gave 31 mg (73%) of **102** as a yellow oil: $R_f$ 0.51 (EtOAc-hexanes, 1:5); $^1$H NMR (300 MHz, $CDCl_3$) δ 1.79-2.06 (m, 4H), 2.79-3.12 (m, 5H), 3.41 (s, 3H), 3.40-3.64 (m, 4H), 6.66-6.83 (m, 3H), 7.01 (s, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 22.1, 25.0, 26.7, 26.9 49.2, 59.2, 63.2, 74.6, 123.3, 124.8, 125.0, 134.0, 137.4.

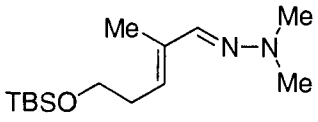



**(1,4-Dioxa-spiro[4.5]dec-7-en-8-ylmethylene)-(2-methoxymethyl-pyrrolidin-1-yl)-amine (108).** To a solution of (*S*)-(-)-1-amino-2-(methoxymethyl)pyrrolidine (SAMP) **101** (187 mg, 1.43 mmol) in acetic acid (0.5 mL) at room temperature was added a solution of **107** (185 mg, 1.10 mmol) in $Et_2O$ (3 mL), and the mixture was stirred at room temperature for 30 min. The reaction mixture was concentrated under reduced pressure. Chromatography of the residue on silica (EtOAc-hexanes, 1:3) gave 253 mg (82%) of **108** as a yellow oil: $R_f$ 0.24 (EtOAc-hexanes, 1:3); $[\alpha]_D^{23}$ -95.9 (c 3.0, $CHCl_3$); IR(neat) 2946, 2922, 2878, 1339, 1198, 1115, 1060 cm$^{-1}$; $^1$H NMR (300 MHz, $CDCl_3$) δ 1.81 (t, *J* = 6.6 Hz, 2H), 1.95-2.02 (m, 4H), 2.42 (m, 2H), 2.55 (m, 2H), 2.87 (m, 1H), 3.42 (s, 3H), 3.31-3.51 (m, 3H), 3.60 (dd, *J* = 3.2, 8.6 Hz, 1H), 3.98 (s, 4H), 5.65 (t, *J* = 4 Hz, 1H), 6.98 (s, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 22.5, 23.4, 27.1, 31.2, 36.5, 49.6, 59.6, 63.5, 64.8 (2C), 75.0, 108.8, 124.7, 136.7, 137.0; MS (CI) *m/z* 280 ($M^+$),

235, 168, 149, 119, 84, 69.

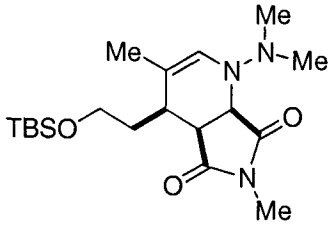


**1-Dimethylamino-3,4,6-trimethyl-1,4,4a,7a-tetrahydro-pyrrolo[3,4-*b*]pyridine-5,7-dione (111)**. To a solution of N-methylmaleimide (555 mg, 5 mmol) in $CH_3CN$ (10 mL) at room temperature under argon was added a solution of **100** (630 mg, 5 mmol) in $CH_3CN$ (1 mL), and the mixture was stirred for 24 h at room temperature. The reaction mixture was concentrated under reduced pressure. Chromatography of the residue on silica (EtOAc-hexanes, 1:1) gave 830 mg (70%) of **111** as a yellow solid: IR(neat) 2962, 1710, 1456, 1432, 1381, 1293, 1275 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 0.74 (d, $J$ = 7.1 Hz, 3H), 1.70 (s, 3H), 2.55 (m, 1H), 2.80 (s, 6H), 2.91(dd, $J$ = 6.3, 9 Hz, 1H), 3.01 (s, 6H); 4.05 (d, $J$ = 9 Hz, 1H), 5.99 (s, 1H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 13.6, 19.1, 24.3, 32.7, 42.2, 42.9 (2C), 57.0, 110.5, 124.4, 177.5, 177.7; MS (CI) *m/z* 237 ($M^+$), 220, 215, 201, 193, 179, 173, 161, 149, 135, 126, 111, 109; HRMS (CI) *m/z* 237.1480 (calcd for $C_{12}H_{19}N_3O_2$: 237.1477).



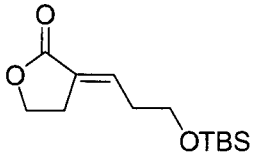
***N'*-[5-(*tert*-Butyl-dimethyl-silanyloxy)-2-methyl-pent-2-enylidene]-*N*-*N*-dimethyl-hydrazine (115).** To a solution of **114** (41 mg, 0.18 mmol) in $CH_2Cl_2$ (3

mL) at room temperature under argon was added manganese (IV) oxide (78 mg, 0.90 mmol), and the mixture was stirred for 4 h at room temperature. The mixture was filtered through a pad of Celite with $Et_2O$ (15 mL), and the filtrate was concentrated under reduced pressure. To a solution of obtained above was added a solution of N, N-dimethylhydrazine (16 mg, 0.26 mmol) in acetic acid (0.5 mL) at room temperature, and the mixture was stirred for 1 h at room temperature. The reaction mixture was concentrated under reduced pressure. Chromatography of the residue on silica (EtOAc-hexanes, 1:5) gave 35 mg (71%) of **115** as a yellow oil: IR(neat) 2954, 2929, 2857, 1472, 1256, 1103, 1024, 835 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 0.03 (s, 6H), 0.91 (s, 9H), 1.84 (s, 3H), 2.43 (dt, $J$ = 7.1, 7.2 Hz, 2H), 2.93 (s, 6H), 3.66 (t, $J$ = 7.0 Hz, 2H), 5.56 (t, $J$ = 7.3 Hz, 2H), 7.01 (m, 1H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ -4.9 (2C), 12.2, 18.8, 26.4 (3C), 32.5, 43.5 (2C), 63.1, 129.2, 136.3, 140.5; MS (CI) *m/z* 270 ($M^+$), 255, 213, 171, 168, 141, 137, 125, 102, 86, 84; HRMS (CI) *m/z* 270.2126 (calcd for $C_{14}H_{30}N_2OSi$: 270.2127).



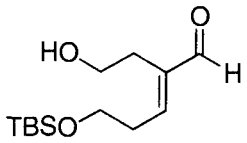

**4-[2-(*tert*-Butyl-dimethyl-silanyloxy)-ethyl]-1-dimethylamino-3,6-dimethyl-1,4,4a,7a-tetrahydro-pyrrolo[3.4-*b*]pyridine-5,7-dione (116).** To a solution of *N*-methylmaleimide (15 mg, 0.14 mmol) in $CH_3CN$ (3 mL) at room temperature under argon was added a solution of **115** (30 mg, 0.11 mmol) in $CH_3CN$ (1 mL),

and the mixture was heated at reflux for 24 h. The reaction mixture was concentrated under reduced pressure. Chromatography of the residue on silica (EtOAc-hexanes, 1:10 to 1:1) gave 22 mg (52%) of **116** as a yellow solid: IR(neat) 2930, 2856, 1716, 1684, 1457, 1436, 1100, 835 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 0.01 (s, 6H), 0.89 (s, 9H), 1.21-1.27 (m, 2H), 1.69 (s, 3H), 2.58 (s, 6H), 2.71 (m, 1H), 2.91 (dd, $J$ = 5.8, 9.1 Hz, 1H), 2.97 (s, 3H), 3.56 (m, 2H), 3.98 (d, $J$ = 9.1 Hz, 1H), 6.08 (s, 1H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ -5.0, -4.9, 18.6, 20.7, 24.5, 26.3, 31.9, 35.0, 43.0, 43.3, 58.6, 61.3, 110.6, 125.0, 177.3, 177.5; MS (CI) *m/z* 381 ($M^+$), 277, 270, 203, 177, 125, 88, 84; HRMS (CI) *m/z* 381.2449 (calcd for $C_{19}H_{35}N_3O_3Si$: 381.2448).



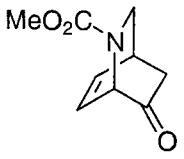

**3-[3-(*tert*-Butyl-dimethyl-silanyloxy)-propylidene]-dihydro-furan-2-one (117).** To a solution of $\alpha$-bromo-$\gamma$-butyrolactone (5.78 g, 35.0 mmol) at room temperature under argon was added triethyl phosphite (4.85 g, 29.2 mmol), and the mixture was heated at reflux for 4 h. The mixture was allowed to cool to room temperaure during for 30 min, and concentrated under reduced pressure. Distillation of the residue gave 4.79 g (71%) of $\alpha$-diethoxyphosphinyl-$\gamma$-butyrolactone as a colorless oil. B.p. 120-122 °/0.05 Torr. To a solution of the phosphonate (993 mg, 4.47 mmol), 18-crown-6 (6.2 g, 23.5 mmol) in THF (60 mL) at -78°C under argon was added a solution of potassium hexamethyldisilazide (0.5 M in toluene,10 mL, 5.0 mmol), and the mixture was

30 min at -78 °C. A soluiton of **112** (885 mg, 4.71 mmol) in THF (5 mL) was added dropwise, and the mixture was allowed to warm to room temperature during 1h. The mixture was diluted with saturated aqueous $NH_4Cl$ (10 mL) and was extracted with ether (30 mL). The extract was washed with saturated aqueous NaCl, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. Chromatography of the residue on silica (EtOAc-hexanes, 1:10) gave 835 mg (73%) of **117** as a colorless oil. IR(neat) 2929, 2955, 2857, 1756, 1256, 1185, 1096, 1028 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 0.05 (s, 6H), 0.91 (s, 9H), 2.85-2.99 (m, 4H), 3.71 (t, $J$ = 6.1 Hz, 2H), 4.32 (t, $J$ = 7.3 Hz, 2H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ -4.9, 18.7, 26.3, 29.5, 31.4, 62.5, 65.7, 125.0, 141.3, 170.5; MS (CI) *m/z* 212 ($M^+$), 197, 151, 139, 125, 111, 109, 87, 84; HRMS (CI) *m/z* 212.1529 (calcd for $C_{11}H_{20}N_2O_2$: 212.1525).



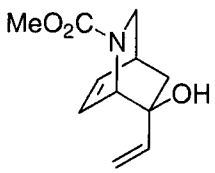

**5-(*tert*-Butyl-dimethyl-silanyloxy)-2-(2-hydroxy-ethyl)-pent-2-enal (118).** To a solution of **117** (80 mg, 0.31 mmol) in THF (5 mL) at 0 °C under argon was added a solution of diisobutylaluminium hydride (0.12 mL, 0.68 mmol), and the mixture was stirred for 30 min at 0 °C. The mixture was diluted with Rochelle's solution (5 mL) and was extracted with $Et_2O$ (20 mL). The extract was washed with saturated aqueous NaCl, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. Chromatography of the residue on silica (EtOAc-hexanes, 1:1) gave 77 mg (94%) of diol as a colorless oil: IR (neat) 3336, 2929,

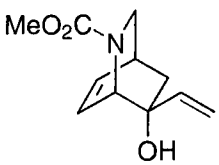
2857 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ 0.09 (s, 6H), 0.90 (s, 9H), 2.29-2.40 (m, 4H), 2.74-3.25 (m, 2H), 3.65 (t, *J* = 5.8 Hz, 2H), 3.72 (t, *J* = 5.7 Hz, 2H), 4.06 (s, 2H), 5.43 (t, *J* = 8.1 Hz, 2H); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ -5.1, 18.9, 26.4, 31.5, 41.1, 60.3, 62.6, 62.7, 128.7, 140.3; MS (CI) *m/z* 261 $(M+H)^+$, 243, 225, 197, 185, 155, 111, 93, 89, 75; HRMS (CI) *m/z* 261.1891 (calcd for $C_{13}H_{29}O_3Si$: 261.1886). To a solution of diol (17 mg, 0.06 mmol) in $CH_2Cl_2$ (3 mL) at room temperature under argon was added manganese (IV) oxide (56 mg, 0.64 mmol), and the mixture was stirred for 3 h at room temperature. The mixture was filtered through a pad of Celite with $Et_2O$ (15 mL), and the filtrate was concentrated under reduced pressure to give 14.3 mg (87%) of **118** as a colorless oil: $^1H$ NMR (300 MHz, $CDCl_3$) δ 0.09 (s, 6H), 0.90 (s, 9H), 2.52 (t, *J* = 6.7 Hz, 2H), 2.64 (dt, *J* = 6.4, 6.9 Hz, 2H), 3.62 (t, *J* = 6.7 Hz, 2H), 3.77 (t, *J* = 6.3 Hz, 2H).




**2-Methoxycarbonyl-2-azabicyclo[2.2.2]oct-5-ene-7-one (128).** To a solution of pyridine (1 mL, 12.6 mmol) and sodium borohydride (490 mg, 13.0 mmol) in MeOH (20 mL) at -78 °C under argon was added a solution of methyl chloroformate (1 mL, 12.6 mmol) in $Et_2O$ (3 mL), and the mixture was stirred for 1.5 h at -78 °C. The mixture was diluted with ice water and was extracted with $Et_2O$ (30 mL). The extract was washed with saturated aqueous NaCl, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure to give **125** as a yellow oil. To a solution of **125** at room temperature under argon was added a

solution of 1-cyanovinyl acetate (2.10 g, 18.9 mmol), and the mixture was heated at 110 °C for 36 h. Chromatography of the residue on silica (EtOAc-hexanes, 1:2 to 1:1) gave 937 mg (36%) of **126** and **127** as a 1:1 inseparable mixture. To a solution of **126** and **127** (937 mg, 3.75 mmol) at 0 °C under argon was added a 1M solution of NaOMe (7.5 mL, 7.5 mmol), and the mixture was stirred for 1h at room temperature. The mixture was diluted with ice water and was extracted with ether (30 mL). The extract was washed with saturated aqueous NaCl, dried over $MgSO_4$, and concentrated under reduced pressure. Chromatography of the residue on silica (EtOAc-hexanes, 1:1) gave 638 mg (94%) of **128** as a colorless oil: $R_f$ 0.28 (EtOAc-hexanes, 1:1); IR(neat) 2956, 1735, 1699, 1448, 1387, 1283, 1186, 1112, 713 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ 1.62-1.66 (m, 1H), 2.20-2.24 (m, 2H), 3.12-3.26 (m, 2H), 3.42-3.56 (m, 1H), 3.73 (s, 3H), 4.80-4.90 (m, 0.5H), 4.99-5.06 (m, 0.5H), 6.37-6.50 (m, 1H), 6.60-6.72 (m, 1H); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 32.5, 32.7, 36.9, 46.6, 46.9, 53.3, 57.8, 58.3, 128.3, 128.9, 139.6, 140.1, 155.7, 203.3; MS (CI) *m/z* 181 ($M^+$), 150, 139, 124, 108, 102, 94, 84, 80, 67; HRMS (CI) *m/z* 181.0740 (calcd for $C_9H_{11}NO_3$: 181.0739).



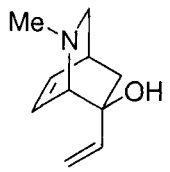

**2-Methoxycarbonyl-7-*endo*-vinyl-7-*exo*-hydroxy-2-azabicyclo[2.2.2]oct-5-ene (129), 2-Methoxycarbonyl-7-*endo*-hydroxy-7-*exo*-vinyl-2-azabicyclo [2.2.2]oct-5-ene (130).**

To a solution of **128** (395 mg, 2.18 mmol) in THF (10 mL) at 0 °C under argon was added a 1M solution of vinylmagnesium bromide in THF (2.3 mL, 2.3 mmol), and the mixture was stirred for 30 min at room temperature. The mixture was diluted with saturated aqueous $NH_4Cl$ (2 mL) and was extracted with ether (20 mL). The extract was washed with saturated aqueous NaCl, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. Chromatography of the residue on silica (EtOAc-hexanes, 1:3 to 1:2) gave 333 mg (73%) of **129** and **130** as a colorless oil.

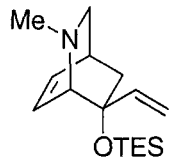
Data for **129**: $R_f$ 0.19 (EtOAc-hexanes, 1:1); IR(neat) 3421, 1684, 1457, 1397, 1340, 1279, 1121, 997 995 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ 1.54-1.84 (m, 2H), 2.27-2.42 (m, 1H), 2.75-2.85 (m, 1H), 2.97-3.13 (m, 1H), 3.43 (dd, *J* = 2.1, 10.2 Hz, 1H), 3.70 (s, 3H), 4.31-4.36 (m, 0.5H), 4.46-4.52 (m, 0.5H), 5.06 (d, *J* = 10.6 Hz, 1H), 5.27 (d, *J* = 17.6 Hz, 1H), 5.77 (dd, *J* = 10.7, 17.3 Hz, 1H), 6.33-6.45 (m, 2H); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 31.7, 31.7, 31.9, 39.0, 39.3, 46.9, 47.3, 53.0, 55.9, 56.7, 113.4, 113.7, 131.1, 131.5, 135.2, 142.9, 143.4, 157.2, 158.0; MS (CI) *m/z* 210 $(M+H)^+$, 192, 178, 139, 124, 105, 94, 81, 67; HRMS (CI) *m/z* 209.1052 (calcd for $C_{11}H_{15}NO_3$: 209.1052).

Data for **130**: $R_f$ 0.2 (EtOAc-hexanes, 1:1); IR(neat) 3446, 1699, 1684, 1653, 1456, 1395, 1338, 1296, 1119, 995 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ 1.47 (dt, *J* = 2.9, 3.5 Hz, 0.5H), 1.52 (dt, *J* = 2.9, 3.5 Hz, 0.5H), 1.84-1.89 (m, 1H), 1.89 (dd, *J* = 2.2, 6.8 Hz, 0.5H), 1.93 (dd, *J* = 2.2, 6.8 Hz, 0.5H), 2.80-2.99 (m, 2H), 3.14 (dd, *J* = 2.0, 6.9 Hz, 0.5H), 3.17 (dd, *J* = 2.0, 6.9 Hz, 0.5H), 3.62 (s, 3H), 4.45 (d, *J* = 5.8 Hz, 0.5H), 4.63 (d, *J* = 5.4 Hz, 0.5H), 5.12 (d, *J* = 10.8 Hz, 0.5H), 5.14 (d, *J* =, 10.8 Hz, 0.5H), 5.31 (d, *J* = 17.3 Hz, 0.5H), 5.37 (d, *J* = 17.4

Hz, 0.5H), 6.00 (dd, $J$ = 10.9, 17.3 Hz, 0.5H), 6.04 (dd, $J$ = 10.9, 17.4 Hz, 0.5H), 6.39-6.50 (m, 1H), 6.51-6.62 (m, 1H); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 31.7, 31.9, 41.0, 41.2, 46.5, 46.7, 52.9, 54.2, 54.9, 76.0, 113.6, 113.7, 131.1, 131.6, 135.8, 136.4, 142.4, 156.2, 156.7; MS (CI) *m/z* 210 $(M+H)^+$, 192, 178, 150, 139, 124, 105, 94, 84, 80, 67; HRMS (CI) *m/z* 210.1129 (calcd for $C_{11}H_{16}NO_3$: 210.1130).

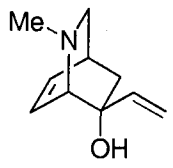



**2-Methyl-7-*endo*-vinyl-7-*exo*-hydroxy-2-azabicyclo[2.2.2]oct-5-ene (133).** To a solution of $LiAlH_4$ (16 mg, 0.41 mmol) in THF (5 mL) at 0°C under argon was added a soluiton of **129** (17 mg, 0.08 mmol) in THF (0.5 mL), and the mixture was stirred for 5 h at room temperature. The mixture was diluted with aqueous $Na_2SO_4$ (0.5 mL) and was extracted with $Et_2O$ (20 mL). The extract was dried over anhydrous $MgSO_4$, and concentrated under reduced pressure to give 10 mg (76%) of **133** as a yellow oil: $R_f$ 0.05 (MeOH-$CH_2Cl_2$, 1:10); $^1H$ NMR (300 MHz, $CDCl_3$) δ 1.46 (dd, $J$ = 2.7, 13.5 Hz, 1H), 1.57 (dt, $J$ = 2.7, 13.5 Hz, 1H), 1.77 (dd, $J$ = 2.4, 9.5 Hz, 1H), 2.24 (s, 3H), 2.54-2.63 (m, 1H), 2.97 (dt, $J$ = 1.3, 5.6 Hz, 1H), 3.21 (dd, $J$ = 2.4, 9.6 Hz, 1H), 5.01 (dd, $J$ = 1.8, 10.7 Hz, 1H), 5.27 (ddd, $J$ = 0.4, 1.8, 17.3 Hz, 1H), 5.73 (dd, $J$ = 10.7, 17.3 Hz, 1H), 6.15 (ddd, $J$ = 1.4, 5.6, 8.1 Hz, 1H), 6.41-6.48 (m, 1H).



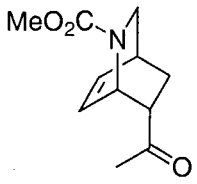

**2-Methyl-7-*endo*-triethylsilyloxy-7-*exo*-vinyl-2-azabicyclo[2.2.2]oct-5-ene (131).** To a solution of triethylsilyl trifluoromethanesulfonate (635 mg, 2.40 mmol) and 2,6-lutidine (0.37 mL, 3.23 mmol) in $CH_2Cl_2$ (10 mL) at 0 °C under argon was added a solution of **130** (335 mg, 1.60 mmol) in $CH_2Cl_2$ (1 mL), and the mixture was stirred for 30 min at room temperature. The mixture was diluted with saturated aqueous $NaHCO_3$ (2 mL) and was extracted with $CH_2Cl_2$ (20 mL). The extract was washed with $H_2O$, saturated aqueous NaCl, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. Chromatography of the residue on silica (EtOAc-hexanes, 1:3 to 1:1) gave 471 mg (91%) of silylether as a colorless oil: $R_f$ 0.4 (EtOAc-hexanes, 1:3); IR(neat) 2954, 2913, 2876, 1706, 1448, 1393, 1336, 1101, 1078, 1017, 741, 699 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ 0.52 (q, $J$ = 7.7 Hz, 6H), 0.89 (t, $J$ = 7.6 Hz, 4.5H), 0.90 (t, $J$ = 7.8 Hz, 4.5H), 1.52 (dt, $J$ = 3.0, 13.4 Hz, 0.5H), 1.54 (dt, $J$ = 3.0, 13.5 Hz, 0.5H), 2.01 (dd, $J$ = 2.5, 13.4 Hz, 1H), 2.80 (m, 1H), 2.86 (dt, $J$ = 2.5, 10.1 Hz, 0.5H), 2.91 (dt, $J$ = 2.5, 10.5 Hz, 0.5H), 3.07 (ddd, $J$ = 2.2, 10.3, 11.9 Hz, 1H), 3.65 (s, 1.5H), 3.66 (s, 1.5H), 4.37 (dd, $J$ = 1.4, 5.8 Hz, 0.5H), 4.58 (dd, $J$ = 3.5, 3.8 Hz, 0.5H), 5.08 (dd, $J$ = 0.7, 10.8 Hz, 0.5H), 5.11 (dd, $J$ = 0.8, 10.8 Hz, 0.5H), 5.22 (dd, $J$ = 0.7, 17.4 Hz, 0.5H), 5.24 (dd, $J$ = 0.7, 17.4 Hz, 0.5H), 5.94 (dd, $J$ = 10.8, 17.4 Hz, 0.5H), 6.02 (dd, $J$ = 10.8, 17.4 Hz, 0.5H), 6.31-6.45 (m, 2H); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 6.2, 6.8, 7.2, 7.3, 31.7, 31.9, 39.4, 39.5, 46.2, 46.4, 52.7, 54.7, 55.4, 78.4,

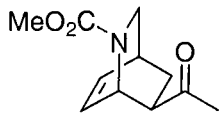
114.2, 132.0, 132.4, 133.4, 133.9, 144.0, 144.2, 156.2, 156.6; MS (CI) *m/z* 324 $(M+H)^+$, 294, 219, 185, 157, 139, 124, 103, 83, 69; HRMS (CI) *m/z* 324.1996 (calcd for $C_{17}H_{30}NO_3Si$: 324.1995). To a solution of $LiAlH_4$ (140 mg, 3.70 mmol) in ether (20 mL) at 0°C under argon was added a solution of silylether (240 mg, 0.74 mmol) in ether (1 mL), and the mixture was stirred for 10 h at room temperature. The mixture was diluted with aqueous $Na_2SO_4$ (1 mL) and was extracted with $Et_2O$ (20 mL). The extract was dried over anhydrous $MgSO_4$, and concentrated under reduced pressure to give 165 mg (80%) of **131** as a colorless oil: $R_f$ 0.25 (EtOAc-hexanes, 1:1); IR(neat) 2952, 2875, 2842, 1237, 1155, 1078, 1008, 738, 698 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ 0.52 (q, *J* = 7.9 Hz, 6H), 0.90 (t, *J* = 7.9 Hz, 9H), 1.41 (dt, *J* = 2.9, 13.2 Hz, 1H), 1.69 (dt, *J* = 2.5, 9.3 Hz, 1H), 1.84 (dd, *J* = 2.4, 13.1 Hz, 1H), 2.20 (s, 3H), 2.51 (m, 1H), 2.91 (dd, *J* = 2.2, 9.3 Hz, 1H), 3.12 (dd, *J* = 1.4, 5.2 Hz, 1H), 5.11 (dd, *J* = 1.4, 10.6 Hz, 1H), 5.30 (dd, *J* = 1.5, 17.3 Hz, 1H), 6.20 (dd, *J* = 10.6, 17.3 Hz, 1H), 6.23 (m, 1H), 6.39 (ddd, *J* = 1.3, 6.6, 8 Hz, 1H); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 7.1, 7.5, 32.5, 39.4, 45.1, 54.7, 65.8, 78.8, 112.7, 131.2, 132.8, 146.7; MS (CI) *m/z* 279 $(M^+)$, 250, 155, 127, 103, 95, 75; HRMS (CI) *m/z* 279.2014 (calcd for $C_{16}H_{29}NOSi$: 279.2018).




**2-Methyl-7-*endo*-hydroxy-7-*exo*-vinyl-2-azabicyclo[2.2.2]oct-5-ene (132).** To a solution of **131** (83 mg, 0.29 mmol) in MeOH (5 mL) was added *p*-

toluenesulfonic acid monohydrate (28 mg, 0.15 mmol) at room temperature, and the mixture was stirred for 10 h at room temperature. The reaction mixture was concentrated under reduced pressure. The mixture was diluted with $CHCl_3$ (5 mL) and was washed with saturated aqueous $K_2CO_3$, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. Chromatography of the residue on silica (MeOH-$CH_2Cl_2$, 1:10) gave 41 mg (85%) of **132** as a colorless oil: $R_f$ 0.05 (MeOH-$CH_2Cl_2$, 1:10); IR(neat) 3436, 2939, 2842, 2787, 1309, 1179, 1149, 968, 703 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 1.33 (dt, $J$ = 3.1, 13.6 Hz, 1H), 1.63 (brs, 1H), 1.71 (dt, $J$ = 2.4, 9.1 Hz, 1H), 1.79 (dd, $J$ = 2.2, 13.6 Hz, 1H), 2.21 (s, 3H), 2.60 (m, 1H), 3.01 (dd, $J$ = 2.4, 9.2 Hz, 1H), 3.16 (dd, $J$ = 1.4, 5.2 Hz, 1H), 5.12 (dd, $J$ = 1.6, 10.8 Hz, 1H), 5.37 (dd, $J$ = 1.6, 17.4 Hz, 1H), 6.29 (ddd, $J$ = 1.3, 5.2, 8 Hz, 1H), 6.38 (dd, $J$ = 10.8, 17.4 Hz, 1H), 6.61 (ddd, $J$ = 1.3, 6.7, 8.0 Hz, 1H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 32.4, 40.9, 45.0, 55.1, 65.1, 76.4, 112.0, 129.9, 136.2, 144.6; MS (CI) *m/z* 166 $(M+H)^+$, 165, 164, 150, 148, 139, 133, 123, 110, 105, 94, 91, 79, 69, 67; HRMS (CI) *m/z* 116.1154 (calcd for $C_{10}H_{15}NO$: 165.1154).



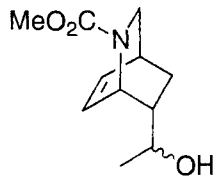




**7-*endo*-Acetyl-2-aza-bicyclo[2.2.2]oct-5-ene-2-carboxylic acid methyl ester (136) and 7-*exo*-Acetyl-2-aza-bicyclo[2.2.2]oct-5-ene-2-carboxylic acid methyl ester (137).** To a solution of **125** (2.01 g, 14.5 mmol) at room temperature under argon was added methyl vinyl ketone (3.37 g, 48.0 mmol),

and the mixture was heated at 60 °C for 72 h. Chromatography of the residue on silica (EtOAc-hexanes, 1:2 to 1:1) gave 1.30 g (43%) of **136** and **137** as a 2.5:1 mixture of colorless oil.

Data for **136**: $R_f$ 0.23 (EtOAc-hexanes, 1:1); IR(neat) 2955, 2878, 1699, 1449, 1393, 1345, 1302, 1280, 1116, 768 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ 1.65-1.92 (m, 2H), 2.11 (s, 1.5H), 2.15 (s, 1.5H), 2.77-2.86 (m, 1H), 2.91 (dt, *J* = 2.6, 10.1 Hz, 0.5H), 2.96 (dt, *J* = 2.6, 10.1 Hz, 0.5H), 3.02-3.14 (m, 1H), 3.22-3.29 (m, 1H), 3.67 (s, 1.8H), 3.70 (s, 1.2H), 4.92-4.98 (m, 0.5H), 5.10-5.17 (m, 0.5H), 6.26 (dd, *J* = 1.6, 6 Hz, 0.5H), 6.28 (dd, *J* = 1.6, 6 Hz, 0.5H), 6.36 (dd, *J* = 1.2, 6.7 Hz, 0.5H), 6.39 (dd, *J* = 1.2, 6.7 Hz, 0.5H); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 25.0, 25.6, 28.6, 28.8, 30.9, 31.2, 47.1, 47.2, 47.3, 47.6, 52.8, 53.2, 130.4, 130.5, 135.4, 135.5, 155.6, 156.2, 206.8, 207.1; MS (CI) *m/z* 209 ($M^+$), 151, 139, 124, 94, 84; HRMS (CI) *m/z* 209.1053 (calcd for $C_{11}H_{15}NO_3$: 209.1052).

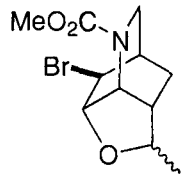
Data for **137**: $R_f$ 0.25 (EtOAc-hexanes, 1:1); IR(neat) 2956, 2878, 1699, 1449, 1393, 1339, 1302, 1193, 1115, 767 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ 1.23-1.39 (m, 1H), 2.09-2.16 (m, 1H), 2.18 (s, 1H), 2.24 (s, 2H), 2.60 (ddd, *J* = 2.1, 4.1, 10.7 Hz, 0.5H), 2.64 (ddd, *J* = 2.1, 4.1, 10.7 Hz, 0.5H), 2.67-2.77 (m, 1H), 2.85 (dt, *J* = 2.7, 10.0 Hz, 0.5H), 2.92 (dt, *J* = 2.7, 10.0 Hz, 0.5H), 3.22 (dd, *J* = 2.2, 10.0 Hz, 1H), 3.56 (s, 2H), 3.60 (s, 1H), 4.88-4.92 (m, 0.5H), 5.08 (dt, *J* = 1.8, 5.9 Hz, 0.5H), 6.37-6.49 (m, 2H); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 23.6, 28.9, 29.2, 30.4, 30.6, 47.5, 47.8, 48.0, 48.2, 52.7, 52.9, 131.9, 132.3, 135.9, 136.1, 155.7, 156.7, 207.2, 207.8; MS (CI) *m/z* 209 ($M^+$), 178, 168, 151, 139, 135, 124, 102, 94, 84, 79; HRMS (CI) *m/z* 209.1051 (calcd for $C_{11}H_{15}NO_3$: 209.1052).




**7-*endo*-[(1-Hydroxy)-1-ethyl]-2-azabicyclo[2.2.2]oct-5-ene-2-carboxylic acid methyl ester (138).** To a solution of **136** (222 mg, 1.06 mmol) in MeOH (10 mL) at 0°C under argon was added $NaBH_4$ (81 mg, 2.12 mmol), and the mixture was stirred for 30 min at room temperature. The mixture was diluted with ice water and was extracted with $Et_2O$ (30 mL). The extract was washed with saturated aqueous NaCl, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. Chromatography of the residue on silica (EtOAc-hexanes, 1:1) gave 201 mg (90%) of **138** as a 1.7:1 mixture of colorless oil.

Data for major diastereomer: $R_f$ 0.22 (EtOAc-hexanes, 1:1); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 0.78-0.89 (m, 1H), 1.09 (d, $J$ = 6.1 Hz, 1.5H), 1.10 (d, $J$ = 6 Hz, 1.5H), 1.70 (dd, $J$ = 2.7, 9.3 Hz, 0.5H), 1.75 (dd, $J$ = 2.7, 9.3 Hz, 0.5H), 1.92-2.06 (m, 1H), 2.27 (brs, 1H), 2.67-2.75 (m, 1H), 2.87-2.99 (m, 1H), 3.00-3.13 (m, 1H), 3.17-3.24 (m, 1H), 3.65 (s, 1.5H), 3.66 (s, 1.5H), 4.87-4.93 (m, 0.5H), 4.99-5.05 (m, 0.5H), 6.29-6.43 (m, 2H).

Data for minor diastereomer: $R_f$ 0.20 (EtOAc-hexanes, 1:1); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 1.18 (d, $J$ = 5.9 Hz, 1.5H), 1.19 (d, $J$ = 6.2 Hz, 1.5H), 1.32-1.45 (m, 1H), 1.57 (brs, 1H), 1.72-1.84 (m, 1H), 2.02-2.14 (m, 1H), 2.74-2.85 (m, 1H), 2.91 (dt, $J$ = 2.5, 10.1 Hz, 0.5H), 2.97 (dt, J = 2.5, 10.1 Hz, 0.5H), 3.17-3.26 (m, 1H), 3.27-3.39 (m, 1H), 3.66 (s, 1.5H), 3.69 (s, 1.5H), 4.49-4.55 (m, 0.5H), 4.66-4.72 (m, 0.5H), 6.27-6.36 (m, 1H), 6.39-6.48 (m, 1H).

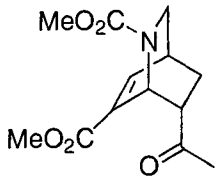


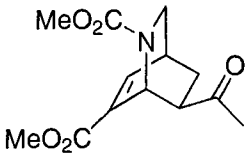

**2-Bromo-5-methyl-4-oxa-8-aza-tricyclo[4.3.1.0$^{3,7}$]decane-8-carboxylic acid methyl ester (139).** To a solution of N-bromosuccinimide (42 mg, 0.24 mmol) in $CH_2Cl_2$ (5 mL) at room temperature under argon was added a solution of **138** (33 mg, 0.16 mmol) in $CH_2Cl_2$ (1 mL), and the mixture was stirred for 1 h at room temperature. The mixture was diluted with $H_2O$ (3 mL) and was extracted with $Et_2O$ (15 mL). The extract was washed with saturated aqueous NaCl, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. Chromatography of the residue on silica (EtOAc-hexanes, 1:3) gave 39 mg (84%) of **139** as a colorless oil.

Data for major diastereomer: $R_f$ 0.25 (EtOAc-hexanes, 1:3); IR(neat) 2955, 1701, 1450, 1407, 1355, 1314, 1119, 1044, 1013, 766 cm$^{-1}$; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 1.18 (d, $J$ = 6.5 Hz, 3H), 1.56-1.66 (m, 1H), 2.12-2.28 (m, 3H), 3.09-3.18 (m, 1H), 3.74 (s, 3H), 3.79-3.89 (m, 2H), 4.00 (d, $J$ = 3.7 Hz, 1H), 4.34 (d, $J$ = 5.5 Hz, 0.5H) 4.37 (d, $J$ = 5.5 Hz, 0.5H), 4.43 (t, $J$ = 4.8 Hz, 0.5H), 4.63 (t, $J$ = 4.8 Hz, 0.5H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 22.1, 22.2, 31.1, 31.3, 33.6, 39.3, 39.5, 45.3, 49.5, 49.9, 53.2, 54.8, 55.2, 81.0, 81.2, 83.4, 83.5, 156.3, 156.9; MS (CI) *m/z* 290 ($M^+$), 274, 260, 258, 231, 228, 210, 178, 166, 150, 135, 126, 107, 91; HRMS (CI) *m/z* 290.0385 (calcd for $C_{11}H_{17}NO_3Br$: 290.0392).

Data for minor diastereomer: $R_f$ 0.24 (EtOAc-hexanes, 1:3); IR(neat) 2953, 2881, 1701, 1450, 1387, 1362, 1317, 1120, 1005 cm$^{-1}$; $^1$H NMR (300 MHz,

$CDCl_3$) δ 1.16 (d, *J* = 6.4 Hz, 3H), 1.82-1.89 (m, 2H), 2.10-2.22 (m, 1H), 2.23-2.36 (m, 1H), 3.13-3.20 (m, 1H), 3.73 (s, 1H), 3.74 (s, 2H), 3.83-3.93 (m, 2H), 4.00-4.10 (m, 1H), 4.28 (d, *J* = 6.1 Hz, 0.5H), 4.31 (d, *J* = 5.8 Hz, 0.5H) 4.44 (t, *J* = 4.9 Hz, 0.5H), 4.62 (t, *J* = 4.9 Hz, 0.5H); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 16.5, 16.6, 23.6, 30.2, 30.4, 37.6, 37.7, 45.7, 52.2, 52.8, 53.1, 53.2, 55.1, 55.4, 76.0, 80.7, 80.8, 156.1, 156.7; MS (CI) *m/z* 290 ($M^+$), 274, 258, 246, 231, 210, 178, 149, 135, 126, 107, 91; HRMS (CI) *m/z* 290.0383 (calcd for $C_{11}H_{17}NO_3Br$: 290.0392).



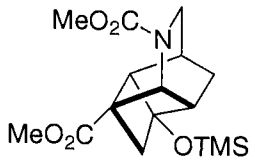




**7-*endo*-Acetyl-2-aza-bicyclo[2.2.2]oct-5-ene-2,6-dicarboxylic acid dimethyl ester (152) and 7-*exo*-Acetyl-2-aza-bicyclo[2.2.2]oct-5-ene-2,6-dicarboxylic acid dimethyl ester (153).** To a suspension of methyl nicotinate **146** (15.1 g, 0.11 mol) and sodium borohydride (4.2 g, 0.11 mol) in MeOH (250 mL) at -78 °C under argon was added a solution of methyl chloroformate (10.4 g, 0.11 mol) in $Et_2O$ (10 mL), and the mixture was stirred for 1.5 h at -78 °C. The mixture was poured into ice water (100 mL) and was extracted with $Et_2O$ (300 mL). The extract was washed with saturated aqueous NaCl, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure to give yellow oils. The $^1H$ NMR shows a 2.8:1.4:1 mixture of **147**, **148** and **149**. To a mixture of **147**, **148** and **149** at room temperature under argon was added a solution of methyl vinyl ketone (22 mL, 0.26 mol), and the mixture was heated at 100 °C for 72 h. Chromatography

of the residue on silica (EtOAc-hexanes, 1:3 to 1:1) followed by recrystallization gave 7.34 g (21%) of **152** and 1.47 g (4%) of **153** as a crystalline solid:

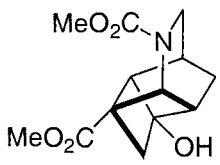
Data for **152**: $R_f$ 0.13 (EtOAc-hexanes, 1:1); mp 130-131°C; IR(neat) 1715, 1448, 1394, 1271, 1252, 1121, 1095 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ 1.54-1.75 (m, 1H), 1.76-1.92 (m, 1H), 2.14 (s, 1.5H), 2.16 (s, 1.5H), 2.82-3.01 (m, 2H), 3.10-3.19 (m, 1H), 3.22 (d, $J$ = 10.0 Hz, 0.5H), 3.23 (d, $J$ = 10.0 Hz, 0.5H), 3.60-3.68 (m, 3H), 5.48 (brs, 0.5H), 5.64 (brs, 0.5H), 7.26 (d, $J$ = 7.0 Hz, 0.5H), 7.27 (d, $J$ = 7.0 Hz, 0.5H); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 23.7, 24.1, 28.9, 31.6, 31.9, 46.3, 46.7, 47.2, 47.3, 52.2, 52.6, 52.9, 53.1, 134.3, 134.4, 145.0, 155.4, 155.9, 163.9, 164.1, 206.0; MS (CI) *m/z* 268 $(M+H)^+$, 252, 236, 226, 197, 182, 161, 141, 123, 99, 84, 71; HRMS (CI) *m/z* 267.1101 (calcd for $C_{13}H_{17}O_5N$: 267.1107).

Data for **153**: $R_f$ 0.14 (EtOAc-hexanes, 1:1); mp 137-138°C; IR(neat) 1716, 1448, 1392, 1242, 1120, 1093 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ 1.27-1.43 (m, 1H), 2.26-2.37 (m, 4H), 2.60-2.73 (m, 1H), 2.86-3.03 (m, 2H), 3.27-3.35 (m, 1H), 3.61 (s, 1.5H), 3.65 (s, 1.5H), 3.80 (s, 3H), 5.53 (brs, 0.5H), 5.71 (brs, 0.5H), 7.41 (d, $J$ = 7.0 Hz, 1H); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 23.5, 29.0, 29.3, 31.6, 31.8, 46.4, 46.9, 47.7, 48.0, 52.4, 52.6, 53.0, 136.7, 137.2, 145.9, 146.0, 155.6, 156.4, 163.9, 206.4, 207.1; MS (CI) *m/z* 268 $(M+H)^+$, 252, 236, 209, 197, 182, 161, 151, 138, 99, 88; HRMS (CI) *m/z* 267.1100 (calcd for $C_{13}H_{17}O_5N$: 267.1107).




**1,3-Dimethoxycarbonyl-8-trimethylsilyloxy-3-azatetracyclo[6.1.1.$0^{2,7}$.$0^{5,9}$] decane (155).** To a solution of **152** (942 mg, 3.53 mmol) in THF (20 mL) at -78 °C was added a solution of lithium bis(trimethylsilyl)amide (1 M in THF, 5.3 mL, 5.3 mmol), and the mixture was stirred for 1 h at -78 °C. A solution of chlorotrimethylsilane (770 mg, 7.06 mmol) was added, and the mixture was allowed to warm to room temperature during 1 h. Then triethylamine (1.07 g, 10.6 mmol) was added at 0 °C. The mixture was diluted with aqueous phosphate buffer (5 mL) and was extracted with ether. The extracted was washed with saturated aqueous NaCl, dried over $MgSO_4$, and concentrated under reduced pressure. Chromatography of the residue on silica (EtOAc-hexanes-$Et_3N$, 1:3:0.01) gave 1.08 g (90%) of **154** as a colorless oil. A solution of **154** (125 mg, 0.35 mmol) in cyclohexane (65 mL) in a photoreaction vessel was purged with argon for 1 h and was irradiated with a 450-W Hanovia medium pressure mercury lamp using a Corex filter for 3 h at room temperature. The solvent was evaporated under reduced pressure and chromatography of the residue on silica (EtOAc-hexanes, 1:3) gave 65 mg (51%) of **155** as a colorless oil. $R_f$ 0.23 (EtOAc-hexanes, 1:1); $^1$H NMR (300 MHz, $CDCl_3$) δ 0.1-0.2 (m, 9H), 1.50-1.56 (m, 1H), 2.03-2.10 (m, 2H), 2.13-2.31 (m, 2H), 2.34 (dt, $J$ = 1.8, 6.4 Hz, 0.5H), 2.37 (dt, $J$ = 1.8, 6.4 Hz, 0.5H), 2.72 (dt, $J$ = 2.0, 5.1 Hz, 0.5H), 2.76 (dt, $J$ = 2.0, 5.3 Hz, 0.5H), 2.98 (brd, $J$ = 11.2 Hz, 0.5H), 3.07 (brd, $J$ = 10.9 Hz, 0.5H), 3.46 (dd, $J$ = 3.9, 10.9 Hz, 0.5H), 3.54 (dd, $J$ = 3.9, 11.2 Hz, 0.5H), 3.66 (s, 3H), 3.69

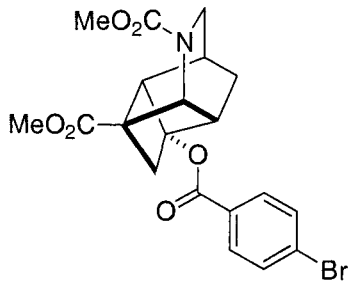
(s, 1.5H), 3.72 (s, 1.5H), 4.38 (dd, $J$ = 1.9, 6.5 Hz, 0.5H), 4.53 (dd, $J$ = 2.0, 6.6 Hz, 0.5H) ; $^{13}$C NMR (75 MHz, $CDCl_3$) δ 31.1, 31.2, 34.6, 34.8, 40.7, 40.9, 46.5, 46.7, 47.5, 47.8, 48.15, 48.22, 52.3, 52.4, 52.9, 55.1, 55.4, 56.9, 57.1, 82.3, 157.4, 157.5, 172.5, 172.6.




**1,3-Dimethoxycarbonyl-3-azatetracyclo[6.1.1.0$^{2,7}$.0$^{5,9}$]decane-8-ol (156).**

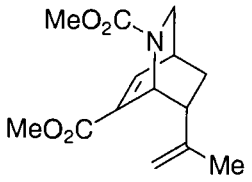
To a solution of **155** (22 mg, 0.06 mmol) in THF (3 mL) at room temperature under argon was added a 1M solution of TBAF in THF (0.09 mL, 0.09 mmmol), and the mixture was stirred for 30 min at room temperature. The mixture was diluted with $H_2O$ (0.5 mL) and was extracted with $Et_2O$ (10 mL). The extract was washed with saturated aqueous NaCl, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. Chromatography of the residue on silica (EtOAc-hexanes, 1:1) gave 16 mg (91%) of **156** as a colorless oil: $R_f$ 0.11 (EtOAc-hexanes, 1:1); IR(neat) 3395, 2956, 1733, 1702, 1675, 1456, 1402, 1340, 1285, 1252, 1196, 1112 cm$^{-1}$; $^1$H NMR (300 MHz, $CDCl_3$) δ 1.65 (m, 1H), 2.04-2.14 (m, 2H), 2.18-2.35 (m, 3H), 2.37-2.44 (m, 1H), 2.70 (dt, $J$ = 2.0, 5.5 Hz, 0.5H), 2.74 (dt, $J$ = 2.0, 5.5 Hz, 0.5H), 3.00 (brd, $J$ = 11.2 Hz, 0.5H), 3.08 (d, $J$ = 11.0 Hz, 0.5H), 3.48 (dd, $J$ = 3.9, 10.9 Hz, 0.5H), 3.56 (dd, $J$ = 4.0, 11.2 Hz, 0.5H), 3.67 (s, 3H), 3.70 (s, 1.5H), 3.72 (s, 1.5H), 4.45 (dd, $J$ = 1.9, 6.5 Hz, 0.5H), 4.59 (dd, $J$ = 2.0, 6.5 Hz, 0.5H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 31.0, 31.1, 34.8, 35.0, 40.4, 40.6, 46.5, 46.6, 46.9, 47.1, 47.8, 52.4, 52.5, 52.9, 55.6, 56.0, 57.2,

57.3, 81.9, 157.3, 157.4, 172.1, 172.2; MS (CI) *m/z* 267 ($M^+$), 252, 235, 219, 208, 197, 182, 169, 152, 138, 126, 116, 102, 91; HRMS (CI) *m/z* 267.1108 (calcd for $C_{13}H_{17}O_5N$: 267.1107).



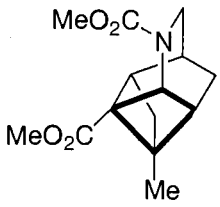

**1,3-Dimethoxycarbonyl-8-oxo-3-azatetracyclo[6.1.1.$0^{2,7}$.$0^{5,9}$]decanyl-*p*-bromobenzoate (157).** To a solution of *p*-bromobenzoyl chloride (10 mg, 0.05 mmol) in $CH_2Cl_2$ (3 mL) at room temperature under argon was added triethylamine (15 mg, 0.14 mmol), **156** (6 mg, 0.02 mmol) in $CH_2Cl_2$ (1 mL), and the mixture was stirred for 1 h at room temperature. The mixture was diluted with $H_2O$ (0.5 mL) and was extracted with $CH_2Cl_2$ (10 mL). The extract was washed with saturated aqueous NaCl, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. Chromatography of the residue on silica (EtOAc-hexanes, 1:1) gave 7 mg (82%) of **157** as a white crystalline. mp 115-117 °C; IR(neat) 1728, 1704, 1449, 1399, 1288, 1270, 1254, 1199, 1105, 1086 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ 1.58-1.66 (m, 1H), 2.01-2.12 (m, 1H), 2.30-2.55 (m, 3H), 2.89-2.96 (m, 1H), 3.06 (d, *J* = 11.4 Hz, 0.5H), 3.15 (d, *J* = 11.2 Hz, 0.5H), 3.23-3.29 (m, 1H), 3.52 (dd, *J* = 3.9, 10.9 Hz, 0.5H), 3.61 (dd, *J* = 3.8, 11.2 Hz, 0.5H), 3.70 (s, 3H), 3.72 (s, 1.5H), 3.74 (s, 1.5H), 4.62 (dd, *J* = 1.8, 6.4 Hz, 0.5H), 4.71 (dd, *J* = 2.0, 6.7 Hz, 0.5H), 7.58 (d, *J* = 8.4 Hz, 2H), 7.86 (d, *J* = 8.4 Hz, 2H);

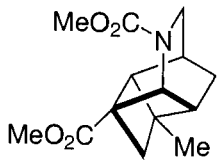
$^{13}C$ NMR (75 MHz, $CDCl_3$) δ 31.0, 31.1, 34.5, 34.7, 38.7, 39.0, 45.45, 45.52, 46.3, 46.4, 52.5, 52.6, 53.0, 55.1, 55.3, 55.5, 84.6, 128.9, 129.2, 131.6 (2C), 132.2 (2C), 157.3, 157.5, 165.2, 171.7; MS (CI) *m/z* 449 (M-H), 420, 392, 372, 340, 312, 266, 249, 206, 183, 157, 131, 105; HRMS (CI) *m/z* 449.0475 (calcd for $C_{20}H_{20}O_6NBr$: 449.0474).

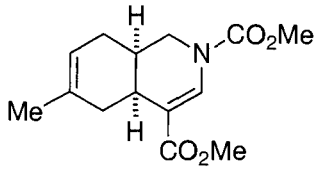



**7-*endo*-Isopropenyl-2-aza-bicyclo[2.2.2]oct-5-ene-2,6-dicarboxylic acid dimethyl ester (161).** To a suspension of dry (90 °C, 1 mm Hg, 18h) methyltriphenylphosphonium bromide (467 mg, 1.31 mmol) in THF (10 mL) at 0°C under argon was added *n*-BuLi (0.7 mL, 1.05 mmol, 1.5 M in hexane) dropwise, and the mixture was stirred for 1.5 h at 0 °C. The yellow solution was recooled to -78°C, treated with a solution of **152** (148 mg, 0.55 mmol) in THF (5 mL) at -78 °C for 0.5 h, and the mixture was allowed to warm to room temperature during 1 h. The mixture was diluted with $H_2O$ (5 mL) and was extracted with $Et_2O$ (30 mL). The extract was washed with saturated aqueous NaCl, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. Chromatography of the residue on silica (EtOAc-hexanes, 1:3) gave 127 mg (87%) of **161** as a white solid: $R_f$ 0.21 (EtOAc-hexanes, 1:3); mp 59-61°C; IR(neat) 1717, 1449, 1393, 1276, 1251, 1120, 1094 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ 1.33-1.44 (m, 1H), 1.69-1.75 (m, 3H), 1.78-1.94 (m, 1H), 2.71-2.84 (m, 1H), 2.89-3.03 (m, 2H), 3.23-3.34 (m, 1H), 3.67 (s, 1.5H), 3.71 (s, 1.5H), 3.74 (s,

3H), 4.47-4.51 (m, 1H), 4.69-4.72 (m, 1H), 5.24-5.29 (m, 0.5H), 5.40-5.45 (m, 0.5H), 7.35-7.41 (m, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 22.8, 22.9, 28.3, 32.1, 32.4, 45.4, 45.6, 46.1, 46.4, 48.6, 48.9, 52.2, 52.8, 53.1, 111.3, 135.4, 135.9, 144.1, 144.5, 145.6, 155.7, 155.9, 164.7; MS (CI) *m/z* 265 $(M)^+$, 234, 206, 197, 182, 166, 152, 138, 121, 119, 106, 86; HRMS (CI) *m/z* 265.1312 (calcd for $C_{14}H_{19}O_4N$: 265.1314).



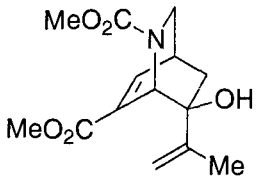

**2,10-Dimethoxycarbonyl-7-methyl-2-azatetracyclo[4.4.0.0$^{4,9}$.0$^{7,10}$]decane (162), 1,3-Dimethoxycarbonyl-8-methyl-3-azatetracyclo[6.1.1.0$^{2,7}$.0$^{5,9}$]decane (163) and 6-methyl-4a,5,8,8a-tetrahydro-1*H*-isoquinoline-2,4-dicarboxylic acid dimethyl ester(164).** A solution of **161** (186 mg, 0.72 mmol) in cyclohexane (65 mL) in a photoreaction vessel was purged with argon for 1 h and was irradiated with a 450-W Hanovia medium pressure mercury lamp using a Corex filter for 3 h at room temperature. The solvent was evaporated under reduced pressure and chromatography of the residue on silica (EtOAc-hexanes, 1:5 to 1:3) gave 7 mg (4%) of **164** and 96 mg (53%) of **162** and **163** in a 2.5:1 mixture as a colorless oil.

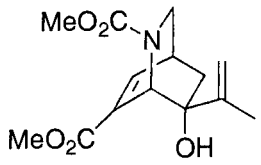
Data for **162**: $R_f$ 0.32 (EtOAc-hexanes, 1:1); IR(neat) 2952, 1702, 1449, 1401, 1341, 1289, 1235, 1110 cm$^{-1}$; $^1$H NMR (300 MHz, $CDCl_3$) δ 1.11 (s, 1.5H), 1.12 (s, 1.5H), 1.58-1.64 (m, 1H), 1.98 (brd, *J* = 10 Hz, 1H), 2.22 (brd, *J* = 7 Hz,

1H), 2.25 (brd, $J$ = 11 Hz, 1H), 2.28-2.37 (m, 1H), 2.43-2.52 (m, 1H), 2.57-2.63 (m, 1H), 3.06-3.14 (m, 1H), 3.60-3.65 (m, 1H), 3.68 (s, 1.5H), 3.69 (s, 1.5H), 3.71 (s, 3H), 4.68 (d, $J$ = 8 Hz, 0.5H), 4.84 (d, $J$ = 8 Hz, 0.5H) ; $^{13}$C NMR (75 MHz, $CDCl_3$) δ 20.1, 24.3, 24.4, 29.8, 33.7, 33.8, 35.9, 36.0, 42.7, 42.9, 44.5, 47.0, 47.2, 48.2, 52.0, 52.8, 56.0, 156.4, 171.7; MS (CI) *m/z* 265 $(M)^+$, 250, 234, 197, 183, 182, 169, 152, 138, 131, 106, 102, 91; HRMS (CI) *m/z* 265.1311 (calcd for $C_{14}H_{19}O_4N$: 265.1314).

Data for **163**: $R_f$ 0.32 (EtOAc-hexanes, 1:1); $^1$H NMR (400 MHz, $CDCl_3$) δ 1.11 (s, 3H), 1.51 (dd, $J$ = 1.7, 12 Hz, 0.5H), 1.53 (dd, $J$ = 1.5, 12 Hz, 0.5H), 1.70-1.75 (m, 2H), 1.86-1.93 (m, 1H), 2.11-2.21 (m, 1H), 2.23-2.32 (m, 1H), 2.50 (dt, $J$ = 2, 5 Hz, 0.5H), 2.53 (dt, $J$ = 2, 5 Hz, 0.5H), 3.00 (brd, $J$ = 11 Hz, 0.5H), 3.10 (brd, $J$ = 11 Hz, 0.5H), 3.44 (d, $J$ = 4, 11 Hz, 0.5H), 3.53 (d, $J$ = 4, 11 Hz, 0.5H), 3.67 (s, 3H), 3.72 (s, 1.5H), 3.73 (s, 1.5H), 4.49 (dd, $J$ = 2, 6 Hz, 0.5H), 4.64 (dd, $J$ = 2, 6 Hz, 0.5H) ; $^{13}$C NMR (75 MHz, $CDCl_3$) δ 17.5, 17.6, 31.3, 31.4, 34.9, 35.1, 38.2, 38.4, 46.9, 47.0, 47.8, 48.1, 51.2, 51.4, 52.2, 52.8, 53.9, 54.0, 55.0, 55.2, 57.0, 57.4, 156.4, 171.7.

Data for **164**: $R_f$ 0.51 (EtOAc-hexanes, 1:1); IR(neat) 1733, 1700, 1635, 1445, 1437, 1252, 1211 $cm^{-1}$; $^1$H NMR (300 MHz, $CDCl_3$) δ 1.57 (s, 3H), 1.65-1.75 (m, 1H), 1.82-2.01 (m, 2H), 2.25-2.32 (m, 1H), 2.39-2.51 (m, 1H), 2.75-2.86 (m, 1H), 3.13-3.25 (m, 1H), 3.71-3.75 (m, 1H), 3.75 (s, 3H), 3.85 (s, 3H), 5.31 (brs, 1H), 7.91-8.10 (m, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 23.7, 28.0, 28.6, 29.6, 33.3, 43.9, 51.7, 54.1, 118.0, 130.8, 134.7, 168.0; MS (CI) *m/z* 265 $(M)^+$, 234, 197, 182, 164, 152, 138, 101, 94; HRMS (CI) *m/z* 265.1316 (calcd for $C_{14}H_{19}O_4N$: 265.1314).

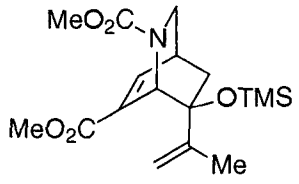



**7-*exo*-Hydroxy-7-*endo*-isopropenyl-2-azabicyclo[2.2.2]oct-5-ene-2,6-dicarboxylic acid dimethyl ester (174) and 7-*endo*-Hydroxy-7-*exo*-isopropenyl-2-azabicyclo[2.2.2]oct-5-ene-2,6-dicarboxylic acid dimethyl ester (175).** To a solution of selenium dioxide (64 mg, 0.57 mmol) in $CH_2Cl_2$ (5 mL) at 0 °C under argon was added a solution of *tert*-hydoperoxide (70%, 0.2 mL, 1.56 mmol), and the mixture was stirred for 30 min at 0 °C. A solution of **161** (152 mg, 0.57 mmol) in $CH_2Cl_2$ (1 mL) was added, and the mixture was stirred for 18 h at room temperature. The reaction mixture was concentrated under reduced pressure. Chromatography of the residue on silica (EtOAc-hexanes, 1:1 to MeOH-$CH_2Cl_2$, 1:15) gave 98 mg (61%) of **174** and **175** in a 2:1 mixture as a colorless oil.

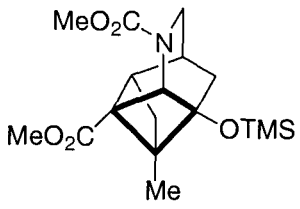
Data for **174**: $R_f$ 0.17 (EtOAc-hexanes, 1:1); IR (neat) 3434, 2955, 1717, 1455, 1397, 1251, 1236, 1128 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ 1.64 (dd, $J$ = 2.5, 13.9 Hz, 1H), 1.81 (s, 3H), 1.83-1.98 (m, 1H), 2.26-2.45 (m, 1H), 2.95-3.10 (m, 2H), 3.47 (dd, $J$ = 1.8, 10.2 Hz, 1H), 3.71(s, 3H), 3.75 (s, 3H), 4.76 (brs, 1H), 4.82 (brs, 1H), 5.21 (brs, 0.5H), 5.36 (brs, 0.5H), 7.32 (d, $J$ = 6.6 Hz, 1H); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 19.2, 32.0, 36.7, 45.7, 46.2, 52.3, 53.2, 54.0, 54.5, 78.5, 78.9, 113.2, 136.6, 144.6, 147.7, 157.0, 157.9, 164.3; MS (CI) *m/z* 282 $(M+H)^+$, 264, 250, 197, 181, 166, 152, 138, 105, 88; HRMS (CI) *m/z* 281.1261 (calcd for $C_{14}H_{19}O_5N$: 281.1263).

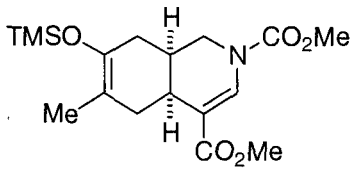
Data for **175**: $R_f$ 0.17 (EtOAc-hexanes, 1:1); IR (neat) 3450, 2951, 1717, 1451, 1394, 1274, 1253, 1126, 1091 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ 1.43-1.52 (m, 1H), 1.63-1.74 (m, 1H), 1.90 (s, 1.5H), 1.92 (s, 1.5H), 2.10 (dd, *J* = 2.1, 14 Hz, 0.5H), 2.19 (dd, *J* = 2.2, 14 Hz, 0.5H), 2.92 (dt, *J* = 2.4, 10.3 Hz, 0.5H), 2.95 (dt, *J* = 2.4, 10.6 Hz, 0.5H), 2.99-3.08 (m, 1H), 3.16 (dd, *J* = 2.1, 10.2 Hz, 0.5H), 3.20 (dd, *J* = 2.0, 10.5 Hz, 0.5H), 3.64 (s, 1.5H), 3.68 (s, 1.5H), 3.79 (s, 1.5H), 3.80 (s, 1.5H), 4.93-4.98 (m, 1H), 5.04 (s, 0.5H), 5.15 (s, 0.5H), 5.23 (d, *J* = 1.2 Hz, 0.5H), 5.42 (d, *J* = 1.2 Hz, 0.5H), 7.40-7.46 (m, 1H); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 19.4, 19.5, 32.1, 32.3, 37.8, 37.9, 45.5, 45.7, 52.1, 52.4, 52.6, 53.0, 77.8, 78.2, 112.5, 112.9, 135.9, 136.6, 143.4, 144.0, 146.7, 146.8, 156.0, 156.2, 165.0, 165.1; MS (CI) *m/z* 282 $(M+H)^+$, 280, 264, 250, 219, 197, 177, 149, 88; HRMS (CI) *m/z* 282.1346 (calcd for $C_{14}H_{20}O_5N$: 282.1342).




**7-*endo*-Isopropenyl-7-*exo*-trimethylsilyloxy-2-azabicyclo[2.2.2]oct-5-ene-2,6-dicarboxylic acid dimethyl ester (176).** To a solution of trimethylsilyl trifluoromethanesulfonate (46 mg, 0.21 mmol) and 2,6-lutidine (30 mg, 0.28 mmol) in $CH_2Cl_2$ (3 mL) at 0 °C under argon was added a solution of **174** (39 mg, 0.14 mmol) in $CH_2Cl_2$ (1 mL), and the mixture was stirred for 1 h at room temperature. The mixture was diluted with saturated aqueous $NaHCO_3$ (1 mL) and was extracted with $CH_2Cl_2$ (10 mL). The extract was washed with $H_2O$, saturated aqueous NaCl, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. Chromatography of the residue on silica (EtOAc-hexanes, 1:1)

gave 46 mg (93%) of **176** as a white solid: $R_f$ 0.55 (EtOAc-hexanes, 1:1); IR (neat) 2956, 1712, 1440, 1394, 1284, 1251, 1070, 845 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ 0.08 (s, 4.5H), 0.09 (s, 4.5H), 1.63 (t, $J$ = 3.2 Hz, 0.5H), 1.67 (t, $J$ = 3.1 Hz, 0.5H), 1.80-1.83 (m, 3H), 2.01 (dt, $J$ = 2.9, 13.6 Hz, 0.5H), 2.06 (dt, $J$ = 3, 13.7 Hz, 0.5H), 2.94-2.99 (m, 1H), 3.01 (t, $J$ = 2.6 Hz, 0.5H), 3.03 (t, $J$ = 2.5 Hz, 0.5H), 3.41 (dd, $J$ = 1.8, 10 Hz, 0.5H), 3.48 (dd, $J$ = 1.9, 10.3 Hz, 0.5H), 3.69 (m, 1.5 Hz), 3.72 (m, 1.5H), 3.74 (m, 3H), 4.65 (s, 0.5H), 4.71 (s, 0.5H), 4.82-4.85 (m, 1H), 5.20 (d, $J$ = 1.4 Hz, 0.5H), 5.39 (d, $J$ = 1.4 Hz, 0.5H), 7.25-7.28 (m, 1H); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 19.7, 32.5, 32.7, 36.2, 36.9, 45.7, 46.3, 52.2, 52.7, 52.8, 54.3, 54.8, 81.0, 113.9, 114.2, 136.1, 137.0, 144.0, 144.5, 147.9, 148.0, 156.8, 157.1, 164.3, 164.4; MS (CI) *m/z* 353 ($M^+$), 337, 322, 264, 198, 196, 157, 138, 105, 88; HRMS (CI) *m/z* 353.1665 (calcd for $C_{17}H_{27}O_5NSi$: 353.1659).



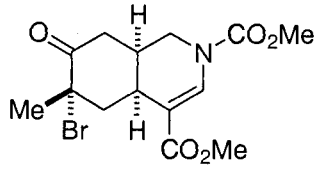

**2,10-Dimethoxycarbonyl-6-trimethylsilyloxy-7-methyl-2-azatetracyclo [4.4.0.0$^{4,9}$.0$^{7,10}$]decane (177) and 6-methyl-7-trimethylsilyloxy-4a,5,8,8a-tetrahydro-1*H*-isoquinoline-2,4-dicarboxylic acid dimethyl ester (178).**

A solution of **176** (29 mg, 0.08 mmol) in $Et_2O$ (65 mL) in a photoreaction vessel was purged with argon for 1 h and was irradiated with a 450-W Hanovia medium pressure mercury lamp using a Pyrex filter for 3 h at room temperature. The solvent was evaporated under reduced pressure and chromatography of the

residue on silica (EtOAc-hexanes, 1:7) gave 5.2 mg (18%) of **177** and 7.3 mg (25%) of **178** as a colorless oil.

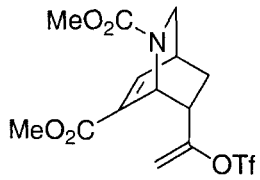
Data for **177**: $^1$H NMR (300 MHz, $CDCl_3$) δ 0.08 (9H), 1.06 (3H), 1.61-1.68 (m, 1H), 1.99-2.04 (m, 1H), 2.21-2.57 (m, 3H), 2.92-3.03 (m, 1H), 3.71-3.82 (m, 7H), 4.62 (s, 0.5H), 4.79 (s, 0.5H).

Data for **178**: $R_f$ 0.43 (EtOAc-hexanes, 1:3); IR (neat) 1733, 1700, 1445, 1370, 1252, 1209, 871, 844 cm$^{-1}$; $^1$H NMR (300 MHz, $CDCl_3$) δ 0.18 (s, 9H), 1.56 (s, 3H), 1.68-1.90 (m, 2H), 2.03-2.14 (m, 1H), 2.29-2.39 (m, 1H), 2.49-2.62 (m, 1H), 2.77-2.85 (m, 1H), 3.14-3.26 (m, 1H), 3.75-3.80 (m, 1H), 3.81 (s, 3H), 7.92-8,11 (m, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 1.1, 16.4, 29.6, 30.9, 32.7, 33.8, 43.9, 51.8, 54.1, 108.7, 134.7, 140.4, 167.9; MS (CI) *m/z* 353 $(M)^+$, 281, 250, 197, 152, 119, 91; HRMS (CI) *m/z* 353.1656 (calcd for $C_{17}H_{27}O_5SiN$: 353.1659).



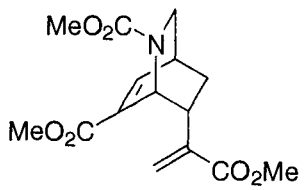

**6-Bromo-6-methyl-7-oxo-4a,5,6,7,8,8a-hexahydro-1*H*-isoquinoline-2,4-dicarboxylic acid dimethyl ester (179).** To a solution of **178** (4 mg, 0.011 mmol) in THF (2 mL) was added *N*-bromosuccinimide (3 mg, 0.017 mmol) at room temperature in one portion, and the mixture was stirred for 30 min at room temperature. The mixture was diluted with $Et_2O$ (15 mL) and was washed with saturated aqueous NaCl, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. Chromatography of the residue on silica gel (EtOAc-hexanes, 1:3) gave 3 mg (75%) of **179** as a colorless oil: IR (neat) 1716, 1635, 1444, 1257, 1208 cm$^{-1}$; $^1$H NMR (300 MHz, $CDCl_3$) δ 1.58 (d, $J$ = 11.9 Hz, 0.5H), 1.63

(d, $J$ = 11.9 Hz, 0.5H), 1.78 (s, 3H), 2.27-2.37 (m, 1H), 2.38-2.50 (m, 1H), 2.63 (dd, $J$ = 1.6, 4.1 Hz, 0.5H), 2.69 (dd, $J$ = 1.7, 4 Hz, 0.5H), 2.89-3.00 (m, 1H), 3.53-3.62 (m, 1H), 4.79 (s, 3H), 4.78-4.82 (m, 2H), 4.83 (s, 3H); MS (CI) *m/z* 361 $(M+H)^+$, 328, 300, 280, 264, 248, 220, 196, 182, 172, 152; HRMS (CI) *m/z* 359.0369 (calcd for $C_{14}H_{18}O_5NBr$: 359.0368).

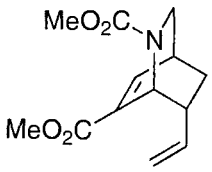



**7-*endo*-{(1-Trifluoromethanesulfonyloxy)-1-vinyl)-2-azabicyclo[2.2.2]oct-5-ene-2,6-dicarboxylic acid dimethyl ester (185).** To a solution of **152** (1.23 g, 4.61 mmol) in THF (20 mL) at -78 °C was added a solution of potassium bis(trimethylsilyl)amide (0.5 M in toluene, 10.2 mL, 5.10 mmol), and the mixture was stirred for 1 h at -78 °C. A solution of *N*-phenyltrifluoromethanesulfonimide (1.97 g, 5.53 mmol) in THF (5 mL) was added, and the mixture was stirred for 1 h at -78 °C. The mixture was diluted with saturated aqueous $NH_4Cl$ (3 mL) and was extracted with $Et_2O$ (20 mL). The extract was washed with saturated aqueous NaCl, dried over $MgSO_4$, and concentrated under reduced pressure. Chromatography of the residue on silica (EtOAc-hexanes, 1:2) gave 1.51 g (82%) of **185** as a colorless oil: IR(neat) 1720, 1450, 1417, 1395, 1250, 1212, 1131, 928 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 1.64-1.71 (m, 1H), 1.82-1.92 (m, 1H), 2.52-2.64 (m, 1H), 3.02-3.13 (m, 2H), 3.33-3.42 (m, 1H), 3.71 (s, 1.5H), 3.74 (s, 1.5H), 3.84 (s, 3H), 5.24 (d, $J$ = 4.1Hz, 0.5H), 5.26 (d, $J$ = 4.3 Hz, 0.5H), 5.32 (d, $J$ = 4.3 Hz, 0.5H), 5.43 (d, $J$ = 4.3 Hz, 0.5H), 5.43 (brs, 0.5H), 5.54 (brs,

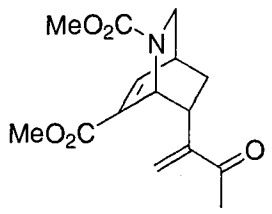
$^{13}C$ NMR (75 MHz, $CDCl_3$) δ 26.6, 31.5, 31.6, 43.5, 43.7, 47.5, 47.9, 52.5, 53.1, 105.3, 116.7, 120.9, 137.3, 138.0, 144.0, 144.3, 156.2, 156.7, 163.6; MS (CI) *m/z* 399 $(M)^+$, 368, 281, 266, 250, 218, 197, 182, 152, 138, 106, 86; HRMS (CI) *m/z* 400.0663 (calcd for $C_{14}H_{17}O_7NF_3S$: 400.0678).



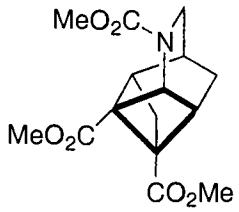

**7-*endo*-[(1-Methoxycarbonyl)-1-vinyl]-2-azabicyclo[2.2.2]oct-5-ene-2,6-dicarboxylic acid dimethyl ester (186).** To a solution of **185** (197 mg, 0.49 mmol) in $CH_3CN$ (5 mL) at room temperature was added palladium acetate (11 mg, 0.05 mmol), $Ph_3P$ (26 mg, 0.10 mmol), $Et_3N$ (100 mg, 0.99 mmol) and MeOH (1 mL), and the mixture was kept for 1 h at room temperature under CO balloon. The solvent was evaporated under reduced pressure and chromatography of the residue on silica (EtOAc-hexanes, 1:1) gave 113 mg (74%) of **186** as a colorless oil: IR(neat) 1716, 1630, 1449, 1394, 1352, 1276, 1192, 1093, 967, 767 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ 1.19-1.33 (m, 1H), 2.02-2.17 (m, 1H), 2.95-3.04 (m, 2H), 3.30-3.44 (m, 2H), 3.65-3.81 (m, 9H), 5.27-5.46 (m, 2H), 6.08-6.15 (m, 1H), 7.38-7.43 (m, 1H); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 29.4, 29.6, 32.0, 32.3, 39.6, 45.8, 46.3, 48.4, 48.9, 52.2, 52.4, 52.8, 53.1, 124.8, 125.1, 135.1, 135.7, 141.6, 141.8, 144.8, 144.9, 155.7, 164.5, 167.4; MS (CI) *m/z* 309 $(M)^+$, 277, 249, 246, 203, 197, 152, 138, 119, 86; HRMS (CI) *m/z* 309.1205 (calcd for $C_{15}H_{19}O_6N$: 309.1212).

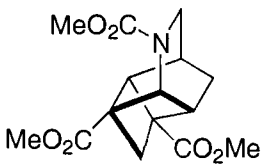


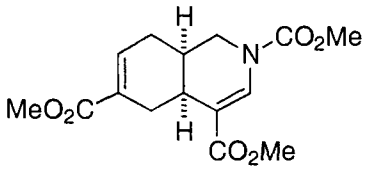

**7-*endo*-Vinyl-2-azabicyclo[2.2.2]oct-5-ene-2,6-dicarboxylic acid dimethyl ester (187).** To a solution of **185** (190 mg, 0.48 mmol) in DMF (2 mL) at room temperature was added palladium acetate (2.1 mg, 0.01 mmol), $Ph_3P$ (5 mg, 0.02 mmol), $Et_3N$ (144 mg, 1.43 mmol) at room temperature, and the mixture was stirred for 5 min. To the reaction mixture was added formic acid (0.05 mL, 0.10 mmol) dropwise, and the mixture was heated at 60 °C for 1 h. The mixture was diluted with 10% HCl (0.15 mL) and extracted with ether (20 mL). The extract was washed with saturated aqueous $NaHCO_3$ and saturated aqueous NaCl, dried over $MgSO_4$, and concentrated under reduced pressure. Chromatography of the residue on silica (EtOAc-hexanes, 1:2) gave 72 mg (60%) of **187** as a colorless oil: IR(neat) 2953, 1716, 1449, 1393, 1351, 1276, 1252, 1224, 1191, 1120, 1090, 767 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ 1.19 (ddd, *J* = 3, 4.5, 5.9 Hz, 0.5H), 1.22 (ddd, *J* = 3, 4.6, 5.9 Hz, 0.5H), 1.87-1.97 (m, 1H), 2.80-2.98 (m, 3H), 3.22-3.29 (m, 1H), 3.64-3.76 (m, 6H), 4.90 (d, *J* = 10.3 Hz, 1H), 4.96 (dd, *J* = 2.1, 17.3 Hz, 0.5H), 5.08 (brs, 0.5H), 5.24 (brs, 0.5H), 5.31 (ddd, *J* = 7, 10.3, 17.3 Hz, 0.5H), 5.36 (ddd, *J* = 6.6, 10.3, 17.3 Hz, 0.5H), 7.36 (d, *J* = 1.5 Hz, 0.5H), 7.38 (d, *J* = 1.5 Hz, 0.5H); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 29.08, 29.13, 31.9, 32.2, 42.7, 43.0, 46.1, 46.5, 49.6, 50.0, 52.2, 52.8, 52.9, 115.8, 115.9, 135.2, 135.8, 139.8, 144.6, 144.9, 155.6, 155.9, 164.5; MS (CI) *m/z* 251 $(M)^+$, 220, 197, 169, 152, 138, 119, 106, 86; HRMS (CI) *m/z* 251.1148 (calcd for $C_{13}H_{17}O_4N$: 251.1158).




**7-*endo*-[(1-Acetyl)-1-vinyl]-2-azabicyclo[2.2.2]oct-5-ene-2,6-dicarboxylic acid dimethyl ester (188).** To a solution of **185** (187 mg, 0.47 mmol) in dry degassed THF (10 mL) at room temperature under argon was added tri(2-furyl)phosphine (11 mg, 0.05 mmol), $Pd_2dba_3$ (22 mg, 0.02 mmol) and LiCl (99 mg, 2.35 mmol), and the mixture was stirred for 20 min at room temperature. A solution of ($\alpha$-ethoxyvinyl)tributyltin (185 mg, 0.51 mmol) in THF (2 mL) was added, and the mixture was heated at reflux for 3 h. After hydrolysis of the reaction mixture with 10% HCl, the mixture was extracted with $Et_2O$ (15 mL). The extract was washed with saturated aqueous NaCl, dried over $MgSO_4$, and concentrated under reduced pressure. Chromatography of the residue on silica (EtOAc-hexanes, 1:1) gave 89 mg (65%) of **188** as a colorless oil: IR(neat) 1715, 1449, 1394, 1276, 1251, 1120, 1092 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 1.09-1.28 (m, 1H), 2.10-2.18 (m, 1H), 2.30 (s, 3H), 2.91-3.03 (m, 2H), 3.29-3.37 (m, 1H), 3.43-3.53 (m, 1H), 3.65-3.75 (m, 6H), 5.13 (s, 0.5H), 5.32 (s, 0.5H), 5.51 (s, 0.5H), 5.57 (s, 0.5H), 5.94 (s, 0.5H), 5.96 (s, 0.5H), 7.40-7.44 (m, 1H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 26.5, 29.4, 30.0, 32.1, 32.4, 38.0, 38.3, 45.7, 46.3, 48.3, 48.9, 52.3, 52.9, 53.1, 124.7, 125.3, 135.3, 135.8, 145.0, 150.0, 150.4, 155.7, 164.7, 199.5; MS (CI) *m/z* 293 $(M)^+$, 261, 230, 218, 197, 182, 175, 152, 138, 106, 92; HRMS (CI) *m/z* 293.1262 (calcd for $C_{15}H_{19}O_5N$: 293.1263).



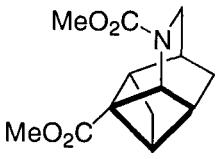

**2,7,10-Trimethoxycarbonyl-2-azatetracyclo[4.4.0.0$^{4,9}$.0$^{7,10}$]decane (189a), 1,3,8-Trimethoxycarbonyl-3-azatetracyclo[6.1.1.0$^{2,7}$.0$^{5,9}$]decane (190a) and 4a,5,8,8a-tetrahydro-1*H*-isoquinoline-2,4,6-tricarboxylic acid trimethyl ester(191a).** A solution of **186** (123 mg, 0.40 mmol) in cyclohexane (60 mL) in a photoreaction vessel was purged with argon for 1 h and was irradiated with a 450-W Hanovia medium pressure mercury lamp using a Corex filter for 5 h at room temperature. The solvent was evaporated under reduced pressure and chromatography of the residue on silica (EtOAc-hexanes, 1:2) gave 4 mg (3%) of **191a** and 68 mg (55%) of **189a** and **190a** in a 1.1:1 mixture as a colorless oil.

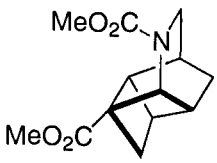
Data for **189a**: IR(neat) 1728, 1704, 1450, 1401, 1286, 1258, 1236, 1125 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) δ 1.74 (d, *J* = 4.1 Hz, 0.5H), 1.78 (d, *J* = 3.7 Hz, 0.5H), 2.10 (d, *J* = 3 Hz, 0.5H), 2.13 (d, *J* = 3.1 Hz, 0.5H), 2.30-2.37 (m, 1H), 2.38-2.48 (m, 1H), 2.57-2.64 (m, 1H), 2.82 (dd, *J* = 4.9, 7.1 Hz, 0.5H), 2.84 (dd, *J* = 5, 7.3 Hz, 0.5H), 3.11-3.22 (m, 2H), 3.67-3.79 (m, 10H), 4.91 (d, *J* = 7.6 Hz, 0.5H), 5.06 (d, *J* = 7.6 Hz, 0.5H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 24.1, 24.2, 28.6, 29.5, 36.3, 36.4, 40.1, 40.4, 47.0, 47.6, 48.4, 48.6, 52.4, 52.5, 52.9, 58.4, 156.3, 156.5, 170.7, 172.2; MS (CI) *m/z* 309 $(M)^+$, 277, 250, 218, 198, 197, 182, 152, 138, 119, 103, 86; HRMS (CI) *m/z* 309.1216 (calcd for $C_{15}H_{19}O_6N$: 309.1212).

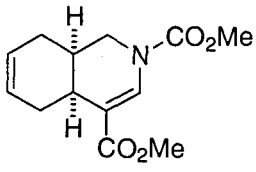
Data for **190a**: IR(neat) 1731, 1704, 1450, 1399, 1256, 1203 cm$^{-1}$; $^1$H NMR (300 MHz, $CDCl_3$) δ 1.59 (d, *J* = 6.9 Hz, 0.5H), 1.62 (d, *J* = 6.8 Hz, 0.5H), 1.96 (d,

*J* = 7.9 Hz, 0.5H), 2.00 (d, *J* = 7.9 Hz, 0.5H), 2.02 (ddd, *J* = 1.7, 3.4, 7.1 Hz, 0.5H), 2.05 (ddd, *J* = 1.6, 3.4, 7.1 Hz, 0.5H), 2.19 (d, *J* = 2.7 Hz, 0.5H), 2.21 (d, *J* = 2.9 Hz, 0.5H), 2.28-2.38 (m, 1H), 2.87 (ddd, *J* = 1.6, 3.4, 6.1 Hz, 0.5H), 2.90 (ddd, *J* = 1.6, 3.4, 6.1 Hz, 0.5H), 2.90 (ddd, *J* = 1.6, 3.4, 6.2 Hz, 0.5H), 3.06 (d, 11.3 Hz, 0.5H), 3.16 (d, 11.3 Hz, 0.5H), 3.16-3.18 (m, 0.5H), 3.20 (ddd, *J* = 1.9, 3.7, 5.3 Hz, 0.5H), 3.51 (dd, *J* = 3.9, 10.9 Hz, 0.5H), 3.60 (dd, *J* = 4.0, 10.3 Hz, 0.5H), 3.64-3.94 (m, 9H), 4.59 (dd, *J* = 1.9, 6.3 Hz, 0.5H), 4.74 (dd, *J* = 1.9, 6.3 Hz, 0.5H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 31.37, 31.43, 35.5, 35.7, 35.9, 36.1, 46.4, 46.5, 52.25, 52.33, 52.4, 53.0, 53.55, 53.63, 55.6, 55.8, 56.06, 56.17, 56.24, 56.4, 157.4, 157.7, 171.8, 172.0, 172.2; MS (CI) *m/z* 310 $(M+H)^+$, 309, 278, 277, 250, 234, 218, 196, 190, 169, 152, 131, 126, 103, 86; HRMS (CI) *m/z* 309.1219 (calcd for $C_{15}H_{19}O_6N$: 309.1212).

Data for **191a**: $^1$H NMR (300 MHz, $CDCl_3$) δ 1.81-1.91 (m, 1H), 2.12-2.30 (m, 2H), 2.64-2.73 (m, 1H), 2.81-2.93 (m, 2H), 3.05-3.18 (m, 1H), 3.65-3.91 (m, 10H), 6.96 (m, 1H), 8.01-8.17 (m, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 27.3, 28.3, 28.6, 29.1, 43.7, 51.9, 52.1, 54.2, 113.4, 127.4, 130.0, 135.0, 136.6, 158.7, 167.6.



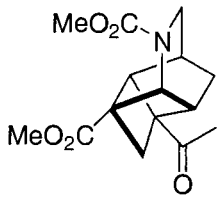

**2,10-Dimethoxycarbonyl-2-azatetracyclo[4.4.0.0$^{4,9}$.0$^{7,10}$]decane (189b), 1,3-Dimethoxycarbonyl-3-azatetracyclo[6.1.1.0$^{2,7}$.0$^{5,9}$]decane (190b) and 4a,5,8,8a-tetrahydro-1*H*-isoquinoline-2,4-dicarboxylic acid dimethyl**

**ester(191b).** A solution of **187** (120 mg, 0.48 mmol) in cyclohexane (60 mL) in a photoreaction vessel was purged with argon for 1 h and was irradiated with a 450-W Hanovia medium pressure mercury lamp using a Corex filter for 20 h at room temperature. The solvent was evaporated under reduced pressure and chromatography of the residue on silica (EtOAc-hexanes, 1:3) gave 3.6 mg (3%) of **191b** and 65 mg (54%) of **189b** and **190b** in a 1:1.5 mixture as a colorless oil.

Data for **189b**: $^{1}$H NMR (300 MHz, $CDCl_3$) δ 1.55-1.70 (m, 3H), 1.91 (d, *J* = 10.5 Hz, 1H), 2.22-2.30 (m, 1H), 2.49-2.74 (m, 2H), 2.85-2.92 (m, 1H), 3.07-3.15 (m, 1H), 3.59 (d, *J* = 4.3 Hz, 0.5H), 3.62 (d, *J* = 4.3 Hz, 0.5H), 4.64 (d, *J* = 7.6 Hz, 0.5H), 4.79 (d, *J* = 7.7 Hz, 0.5H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 23.7, 23.8, 27.6, 27.7, 30.4, 36.2, 36.4, 36.5, 37.9, 38.7, 47.7, 48.5, 48.7, 52.8, 55.1, 157.6, 157.8, 172.6.

Data for **190b**: $^{1}$H NMR (300 MHz, $CDCl_3$) δ 1.55-1.66 (m, 3H), 1.85-1.93 (m, 1H), 2.09-2.21 (m, 1H), 2.34-2.42 (m, 1H), 2.60-2.69 (m, 1H), 2.84-2.92 (m, 1H), 3.02 (brd, *J* = 11.2 Hz, 0.5H), 3.12 (brd, *J* = 10.8 Hz, 0.5H), 3.43 (dd, *J* = 3.9, 10.8 Hz, 0.5H), 3.52 (dd, *J* = 3.9, 11.2 Hz, 0.5H), 3.66-3.77 (m, 6H), 4.46 (dd, *J* = 1.9, 6.3 Hz, 0.5H), 4.60 (dd, *J* = 2.0, 6.4 Hz, 0.5H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 31.46, 31.52, 33.0, 33.2, 37.6, 37.8, 43.5, 43.7, 44.9, 45.0, 46.7, 46.9, 52.1, 52.2, 52.4, 52.8, 52.9, 55.4, 55.7, 56.8, 56.9, 157.6, 157.8, 172.8, 173.2.

Data for **191b**: $^{1}$H NMR (300 MHz, $CDCl_3$) δ 1.79-2.04 (m, 1H), 2.39-2.55 (m, 2H), 2.79-2.85 (m, 1H), 3.14-3.30 (m, 1H), 3.54-3.80 (m, 7H), 4.87-5.05 (m, 1H), 5.52-5.65 (m, 2H), 7.89-8.10 (m, 1H).




**8-Acetyl-1,3-dimethoxycarbonyl-3-azatetracyclo[6.1.1.$0^{2,7}$.$0^{5,9}$]decane (190c).** A solution of **188** (40 mg, 0.14 mmol) in cyclohexane (60 mL) in a photoreaction vessel was purged with argon for 1 h and was irradiated with a 450-W Hanovia medium pressure mercury lamp using a Pyrex filter for 8 h at room temperature. The solvent was evaporated under reduced pressure and chromatography of the residue on silica (EtOAc-hexanes, 1:3 to 1:2) gave 19 mg (47%) of **190c** as a colorless oil.

Data for **190c**: IR(neat) 1731, 1699, 1449, 1399, 1253, 1197, 1124 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ 1.50-1.57 (m, 1H), 1.73-1.82 (m, 1H), 1.97-2.06 (m, 1H), 2.09-2.16 (m, 1H), 2.13 (s, 3H), 2.23-2.35 (m, 1H), 2.82-2.89 (m, 1H), 3.01-3.16 (m, 2H), 3.48 (dd, *J* = 4, 11 Hz, 0.5H), 3.57 (dd, *J* = 4, 11.3 Hz, 0.5H), 3.77-3.85 (m, 6H), 4.60 (dd, *J* = 2, 6.3 Hz, 0.5H), 4.75 (dd, *J* = 2, 6.3 Hz, 0.5H); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 27.3, 27.4, 31.3, 35.6, 35.7, 36.0, 36.2, 46.2, 46.3, 46.4, 46.6, 52.4, 52.5, 53.0, 53.2, 54.3, 54.4, 56.3, 56.7, 63.36, 63.43; MS (CI) *m/z* 293 $(M)^+$, 263, 261, 234, 218, 206, 190, 182, 158, 152, 138, 117, 103, 91; HRMS (CI) *m/z* 293.1258 (calcd for $C_{15}H_{19}O_5N$: 293.1263).

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# Chapter IV. GENERAL CONCLUSION

The research described in this dissertation presents results on the synthesis of two biologically active indole alkaloids, (-)-ibogamine and koumine.

The synthesis of (-)-ibogamine has accomplished in fourteen steps from 1,4-benzoquinone and in a 10% overall yield. The two titanium derived catalysts, TADDOL-Ti and BINOL-Ti, were employed for the pivotal asymmetric Diels-Alder reaction of 1,4-benzoquinone with various dienes, and the latter turned out to be a superior catalyst for the high enantiomeric excess. A transition state which would provide a glimpse of the reaction mechanism was proposed based on the absolute configuration of the Diels-Alder adducts.

Three different routes have been investigated as an entry for the synthesis of koumine. The Diels-Alder reaction of cyclic 1-azadienes and an anionic oxy-Cope rearrangement of the azabicyclo[2.2.2]octane system did not provide any desired product. An intramolecular [2+2] photocycloaddition generated the unique "crossed", "straight", and hydroisoquinoline products in varing ratio, depending on the substituent pattern of the substrate. Although this approach was not synthetically useful, the knowledge from this last study may be useful for predicting the regiochemical outcome of the intramolecular photocycloaddition.

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# Appendices

# APPENDIX A

## SUPPLEMENTARY CRYSTALLOGRAPHIC INFORMATION ON DIOL 85

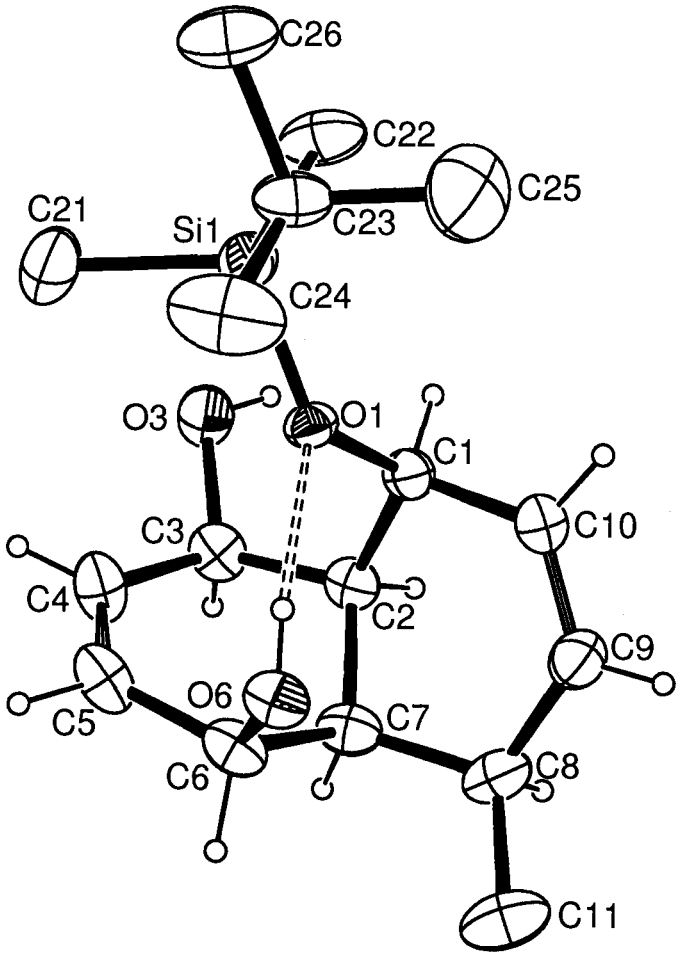


**Table A.1 Crystal data and structure refinement for 85**

| | | |
|---|---|---|
| Empirical formula | $C_{17}H_{30}O_3Si$ | |
| Formula weight | 310.50 | |
| Temperature | 290(2) K | |
| Wavelength | 1.54178 Å | |
| Crystal system | Orthorhombic | |
| Space group | $P2_12_12_1$ (#19) | |
| Unit cell dimensions | a = 10.7230(10) Å | $\alpha$= 90°. |
| | b = 12.579(2) Å | $\beta$= 90°. |
| | c = 13.737(2) Å | $\gamma$ = 90°. |
| Volume | 1852.9(4) $Å^3$ | |
| Z | 4 | |
| Density (calculated) | 1.113 $Mg/m^3$ | |
| Absorption coefficient | 1.172 $mm^{-1}$ | |
| F(000) | 680 | |
| Crystal size | 0.20 x 0.20 x 0.10 $mm^3$ | |
| Theta range for data collection | 4.77 to 67.49°. | |
| Index ranges | -6<=h<=6, -15<=k<=13, -16<=l<=16 | |
| Reflections collected | 2289 | |
| Independent reflections | 1965 [R(int) = 0.0220] | |
| Completeness to theta = 67.49° | 64.1 % | |
| Max. and min. transmission | 0.8918 and 0.7994 | |
| Refinement method | Full-matrix least-squares on $F^2$ | |
| Data / restraints / parameters | 1965 / 0 / 192 | |
| Goodness-of-fit on $F^2$ | 1.081 | |
| Final R indices [I>2sigma(I)] | R1 = 0.0439, wR2 = 0.1031 | |
| R indices (all data) | R1 = 0.0646, wR2 = 0.1233 | |
| Absolute structure parameter | -0.05(6) | |
| Largest diff. peak and hole | 0.147 and -0.166 $e.Å^{-3}$ | |

**Table A.2 Atomic coordinates ( x $10^4$) and equivalent isotropic displacement parameters ($Å^2$x $10^3$) for 85.**

U(eq) is defined as one third of the trace of the orthogonalized $U^{ij}$ tensor.

| | x | y | z | U(eq) |
|---|---|---|---|---|
| Si(1) | 7766(2) | 8640(1) | 6765(1) | 76(1) |
| O(1) | 6483(3) | 8635(2) | 7440(2) | 58(1) |
| O(3) | 5158(4) | 7142(2) | 5903(2) | 83(1) |
| O(6) | 4891(3) | 10125(2) | 8187(2) | 70(1) |
| C(1) | 5815(6) | 7753(3) | 7866(3) | 61(2) |
| C(2) | 4481(6) | 7677(3) | 7544(3) | 63(2) |
| C(3) | 4254(6) | 7718(4) | 6451(3) | 75(2) |
| C(4) | 4213(6) | 8828(4) | 6081(4) | 86(2) |
| C(5) | 3990(5) | 9670(4) | 6642(4) | 86(2) |
| C(6) | 3858(6) | 9615(4) | 7711(4) | 75(2) |
| C(7) | 3624(5) | 8469(3) | 8063(3) | 70(2) |
| C(8) | 3674(7) | 8295(4) | 9170(4) | 83(2) |
| C(9) | 4973(8) | 8103(4) | 9506(4) | 80(2) |
| C(10) | 5924(6) | 7844(4) | 8953(4) | 75(2) |
| C(11) | 3000(6) | 9164(4) | 9754(4) | 114(2) |
| C(21) | 7394(7) | 9276(6) | 5575(4) | 132(3) |
| C(22) | 8371(6) | 7283(4) | 6553(5) | 116(2) |
| C(23) | 8944(6) | 9468(5) | 7413(5) | 89(2) |
| C(24) | 8414(7) | 10587(5) | 7602(6) | 151(3) |
| C(25) | 9259(7) | 8943(7) | 8402(5) | 166(4) |
| C(26) | 10149(7) | 9560(6) | 6811(6) | 130(3) |

**Table A.3 Bond lengths [Å] and angles [°] for 85.**

| | | | |
|---|---|---|---|
| Si(1)-O(1) | 1.659(3) | C(1)-O(1)-Si(1) | 129.8(3) |
| Si(1)-C(22) | 1.850(5) | O(1)-C(1)-C(2) | 113.7(4) |
| Si(1)-C(21) | 1.863(5) | O(1)-C(1)-C(10) | 107.7(4) |
| Si(1)-C(23) | 1.863(6) | C(2)-C(1)-C(10) | 111.8(4) |
| O(1)-C(1) | 1.444(5) | C(1)-C(2)-C(3) | 116.2(4) |
| O(3)-C(3) | 1.425(6) | C(1)-C(2)-C(7) | 113.2(4) |
| O(6)-C(6) | 1.437(6) | C(3)-C(2)-C(7) | 109.9(4) |
| C(1)-C(2) | 1.500(7) | O(3)-C(3)-C(4) | 108.6(4) |
| C(1)-C(10) | 1.503(6) | O(3)-C(3)-C(2) | 113.3(4) |
| C(2)-C(3) | 1.522(6) | C(4)-C(3)-C(2) | 111.9(4) |
| C(2)-C(7) | 1.532(6) | C(5)-C(4)-C(3) | 123.7(5) |
| C(3)-C(4) | 1.487(6) | C(4)-C(5)-C(6) | 123.8(5) |
| C(4)-C(5) | 1.331(7) | O(6)-C(6)-C(5) | 110.9(5) |
| C(5)-C(6) | 1.477(7) | O(6)-C(6)-C(7) | 113.6(4) |
| C(6)-C(7) | 1.540(6) | C(5)-C(6)-C(7) | 111.8(4) |
| C(7)-C(8) | 1.537(7) | C(2)-C(7)-C(8) | 110.3(4) |
| C(8)-C(9) | 1.487(8) | C(2)-C(7)-C(6) | 111.4(4) |
| C(8)-C(11) | 1.537(7) | C(8)-C(7)-C(6) | 115.9(4) |
| C(9)-C(10) | 1.312(7) | C(9)-C(8)-C(11) | 113.2(5) |
| C(23)-C(26) | 1.538(8) | C(9)-C(8)-C(7) | 111.3(5) |
| C(23)-C(24) | 1.540(8) | C(11)-C(8)-C(7) | 113.5(5) |
| C(23)-C(25) | 1.548(8) | C(10)-C(9)-C(8) | 126.1(5) |
| | | C(9)-C(10)-C(1) | 122.3(6) |
| O(1)-Si(1)-C(22) | 112.0(2) | C(26)-C(23)-C(24) | 109.4(6) |
| O(1)-Si(1)-C(21) | 108.3(3) | C(26)-C(23)-C(25) | 108.7(6) |
| C(22)-Si(1)-C(21) | 109.5(3) | C(24)-C(23)-C(25) | 108.8(6) |
| O(1)-Si(1)-C(23) | 107.3(2) | C(26)-C(23)-Si(1) | 110.8(4) |
| C(22)-Si(1)-C(23) | 110.7(3) | C(24)-C(23)-Si(1) | 109.9(5) |
| C(21)-Si(1)-C(23) | 108.9(3) | C(25)-C(23)-Si(1) | 109.2(4) |

Symmetry transformations used to generate equivalent atoms:

**Table A.4 Anisotropic displacement parameters ($Å^2 x\ 10^3$) for 85.**

The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

| | $U^{11}$ | $U^{22}$ | $U^{33}$ | $U^{23}$ | $U^{13}$ | $U^{12}$ |
|---|---|---|---|---|---|---|
| Si(1) | 75(1) | 76(1) | 77(1) | 1(1) | 9(1) | 0(1) |
| O(1) | 48(3) | 60(2) | 66(2) | 5(1) | 13(2) | 0(2) |
| O(3) | 111(3) | 64(2) | 74(2) | -8(2) | 2(2) | 6(2) |
| O(6) | 62(3) | 55(2) | 92(2) | -9(2) | -4(2) | -2(2) |
| C(1) | 64(6) | 47(2) | 72(3) | 6(2) | 9(3) | 3(3) |
| C(2) | 62(5) | 50(2) | 77(3) | -2(2) | 0(3) | -4(3) |
| C(3) | 80(5) | 63(3) | 81(3) | -9(2) | -8(3) | -3(3) |
| C(4) | 111(5) | 69(3) | 78(3) | 7(3) | -22(3) | 3(3) |
| C(5) | 93(6) | 62(3) | 102(4) | 3(3) | -33(4) | 8(3) |
| C(6) | 65(5) | 61(3) | 99(4) | -6(3) | -10(3) | 6(3) |
| C(7) | 50(4) | 61(3) | 99(3) | -11(3) | 2(3) | -7(3) |
| C(8) | 84(7) | 75(3) | 91(4) | -12(3) | 33(4) | -7(4) |
| C(9) | 88(7) | 82(3) | 72(3) | 8(2) | 14(4) | 2(4) |
| C(10) | 75(6) | 77(3) | 71(3) | 13(3) | -1(3) | 8(3) |
| C(11) | 104(6) | 111(4) | 125(5) | -48(4) | 40(4) | -9(4) |
| C(21) | 129(7) | 184(6) | 83(3) | 42(4) | 10(4) | 3(6) |
| C(22) | 100(6) | 101(4) | 148(5) | -34(4) | 45(5) | 12(4) |
| C(23) | 47(6) | 106(4) | 114(4) | -13(4) | 6(4) | -6(3) |
| C(24) | 106(7) | 102(5) | 246(9) | -56(5) | 2(7) | -13(5) |
| C(25) | 120(8) | 253(10) | 124(6) | 13(6) | -43(5) | -45(6) |
| C(26) | 65(7) | 154(6) | 172(6) | -18(5) | 33(6) | -20(5) |

**Table A.5 Hydrogen coordinates ( x $10^4$) and isotropic displacement parameters ($Å^2$x $10^3$) for 85.**

| | x | y | z | U(eq) |
|---|---|---|---|---|
| HO3 | 5243 | 6546 | 6137 | 125 |
| HO6 | 5545 | 9852 | 8004 | 104 |
| H(1) | 6238 | 7096 | 7667 | 73 |
| H(2) | 4198 | 6972 | 7751 | 75 |
| H(3) | 3439 | 7394 | 6325 | 90 |
| H(4) | 4350 | 8941 | 5421 | 103 |
| H(5) | 3913 | 10330 | 6344 | 103 |
| H(6) | 3112 | 10026 | 7879 | 90 |
| H(7) | 2772 | 8290 | 7862 | 84 |
| H(8) | 3217 | 7635 | 9295 | 100 |
| H(9) | 5126 | 8173 | 10169 | 96 |
| H(10) | 6691 | 7713 | 9245 | 89 |
| H(11A) | 2166 | 9246 | 9512 | 170 |
| H(11B) | 3441 | 9824 | 9687 | 170 |
| H(11C) | 2973 | 8965 | 10429 | 170 |
| H(21A) | 7084 | 9982 | 5684 | 198 |
| H(21B) | 6771 | 8864 | 5243 | 198 |
| H(21C) | 8134 | 9309 | 5183 | 198 |
| H(22A) | 8565 | 6956 | 7166 | 174 |
| H(22B) | 9110 | 7319 | 6160 | 174 |
| H(22C) | 7750 | 6868 | 6222 | 174 |
| H(24A) | 8227 | 10924 | 6992 | 227 |
| H(24B) | 9018 | 11004 | 7948 | 227 |
| H(24C) | 7666 | 10531 | 7982 | 227 |
| H(25A) | 9622 | 8256 | 8291 | 248 |
| H(25B) | 8511 | 8866 | 8778 | 248 |
| H(25C) | 9841 | 9382 | 8749 | 248 |
| H(26A) | 9970 | 9908 | 6205 | 196 |
| H(26B) | 10474 | 8862 | 6686 | 196 |
| H(26C) | 10753 | 9967 | 7167 | 196 |

**Table A.6 Torsion angles [°] for 85.**

| | | | |
|---|---|---|---|
| C(22)-Si(1)-O(1)-C(1) | 0.3(5) | C(6)-C(7)-C(2) | 43.7(6) |
| C(21)-Si(1)-O(1)-C(1) | 121.1(4) | O(6)-C(6)-C(7)-C(8) | 44.4(7) |
| C(23)-Si(1)-O(1)-C(1) | -121.4(4) | C(5)-C(6)-C(7)-C(8) | 170.9(5) |
| Si(1)-O(1)-C(1)-C(2) | -121.6(4) | C(2)-C(7)-C(8)-C(9) | 42.0(5) |
| Si(1)-O(1)-C(1)-C(10) | 113.9(4) | C(6)-C(7)-C(8)-C(9) | -85.7(6) |
| O(1)-C(1)-C(2)-C(3) | 50.5(5) | C(2)-C(7)-C(8)-C(11) | 171.1(5) |
| C(10)-C(1)-C(2)-C(3) | 172.8(4) | C(6)-C(7)-C(8)-C(11) | 43.3(8) |
| O(1)-C(1)-C(2)-C(7) | -78.2(4) | C(11)-C(8)-C(9)-C(10) | -145.5(5) |
| C(10)-C(1)-C(2)-C(7) | 44.1(6) | C(7)-C(8)-C(9)-C(10) | -16.3(7) |
| C(1)-C(2)-C(3)-O(3) | 39.6(6) | C(8)-C(9)-C(10)-C(1) | 2.7(8) |
| C(7)-C(2)-C(3)-O(3) | 169.8(4) | O(1)-C(1)-C(10)-C(9) | 109.3(6) |
| C(1)-C(2)-C(3)-C(4) | -83.5(6) | C(2)-C(1)-C(10)-C(9) | -16.4(7) |
| C(7)-C(2)-C(3)-C(4) | 46.7(6) | O(1)-Si(1)-C(23)-C(26) | -177.3(4) |
| O(3)-C(3)-C(4)-C(5) | -146.2(6) | C(22)-Si(1)-C(23)-C(26) | 60.2(5) |
| C(2)-C(3)-C(4)-C(5) | -20.5(8) | C(21)-Si(1)-C(23)-C(26) | -60.2(5) |
| C(3)-C(4)-C(5)-C(6) | 5.1(9) | O(1)-Si(1)-C(23)-C(24) | -56.3(5) |
| C(4)-C(5)-C(6)-O(6) | 111.2(6) | C(22)-Si(1)-C(23)-C(24) | -178.8(5) |
| C(4)-C(5)-C(6)-C(7) | -16.7(8) | C(21)-Si(1)-C(23)-C(24) | 60.8(6) |
| C(1)-C(2)-C(7)-C(8) | -58.3(5) | O(1)-Si(1)-C(23)-C(25) | 63.0(5) |
| C(3)-C(2)-C(7)-C(8) | 169.9(5) | C(22)-Si(1)-C(23)-C(25) | -59.5(6) |
| C(1)-C(2)-C(7)-C(6) | 71.9(5) | C(21)-Si(1)-C(23)-C(25) | -179.9(5) |
| C(3)-C(2)-C(7)-C(6) | -59.9(6) | | |
| O(6)-C(6)-C(7)-C(2)-82.8(5)C(5)- | | | |

Symmetry transformations used to generate equivalent atoms:

# APPENDIX B

## SUPPLEMENTARY CRYSTALLOGRAPHIC INFORMATION ON BROMOKETONE 109

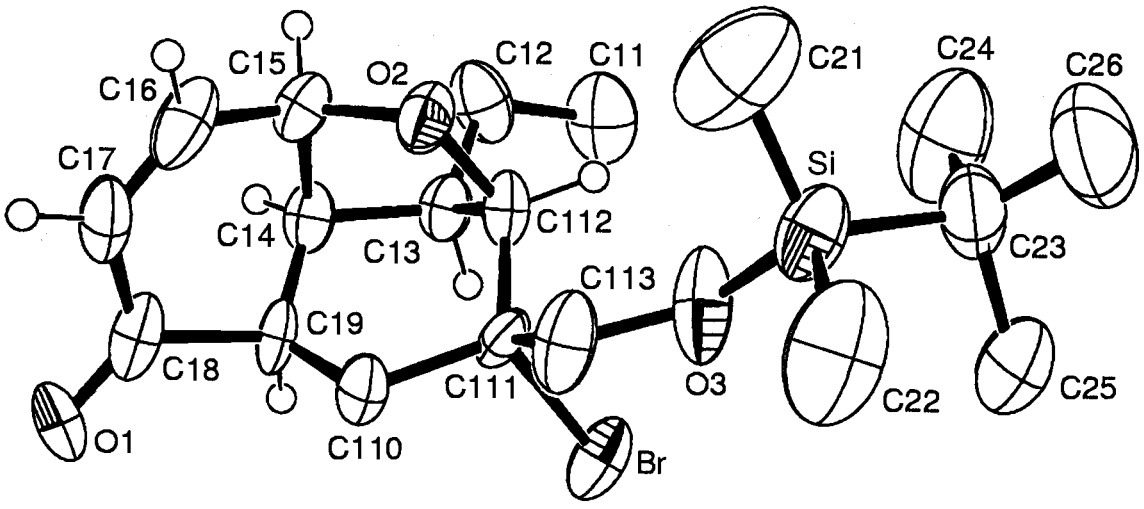


**Table B.1 Crystal data and structure refinement for bromoketone 109**

| | | |
|---|---|---|
| Identification code | STR 32 | |
| Empirical formula | $C_{19}$ $H_{31}$ Br $O_3$ Si | |
| Formula weight | 415.44 | |
| Temperature | 298(2) K | |
| Wavelength | 1.54178 Å | |
| Crystal system | Monoclinic | |
| Space group | $P2_1$ (#4) | |
| Unit cell dimensions | a = 12.019(3) Å | $\alpha$= 90°. |
| | b = 6.524(5) Å | $\beta$= 105.64(2)°. |
| | c = 14.017(5) Å | $\gamma$ = 90°. |
| Volume | 1058.4(9) $Å^3$ | |
| Z | 2 | |
| Density (calculated) | 1.304 $Mg/m^3$ | |
| Absorption coefficient | 3.290 $mm^{-1}$ | |
| F(000) | 436 | |
| Crystal size | 0.30 x 0.30 x 0.30 $mm^3$ | |
| Theta range for data collection | 3.27 to 57.74°. | |
| Index ranges | -13<=h<=13, -7<=k<=6, -15<=l<=15 | |
| Reflections collected | 3185 | |
| Independent reflections | 2747 [R(int) = 0.0779] | |
| Completeness to theta = 57.74° | 97.2 % | |
| Max. and min. transmission | 0.4386 and 0.4386 | |
| Refinement method | Full-matrix least-squares on $F^2$ | |
| Data / restraints / parameters | 2747 / 1 / 219 | |
| Goodness-of-fit on $F^2$ | 2.565 | |
| Final R indices [I>2sigma(I)] | R1 = 0.0876, wR2 = 0.2660 | |
| R indices (all data) | R1 = 0.0894, wR2 = 0.2694 | |
| Absolute structure parameter | 0.05(5) | |
| Extinction coefficient | 0.0030(17) | |
| Largest diff. peak and hole | 1.183 and -1.632 $e.Å^{-3}$ | |

**Table B.2 Atomic coordinates ( x $10^4$) and equivalent isotropic displacement parameters ($Å^2$x $10^3$) for bromoketone 109.**

U(eq) is defined as one third of the trace of the orthogonalized $U^{ij}$ tensor.

| | x | y | z | U(eq) |
|---|---|---|---|---|
| Br | 1796(1) | 2110(1) | 3558(1) | 67(1) |
| O(1) | 5032(7) | 1144(11) | 1287(5) | 68(2) |
| O(2) | 2691(4) | 6952(11) | 2011(4) | 48(1) |
| O(3) | 55(5) | 4969(16) | 2279(4) | 74(2) |
| C(11) | 3640(9) | 7520(20) | 5022(7) | 76(3) |
| C(12) | 4152(7) | 7396(19) | 4173(7) | 61(2) |
| C(13) | 3740(6) | 5554(14) | 3535(5) | 41(2) |
| C(14) | 4360(6) | 5009(14) | 2745(5) | 43(2) |
| C(15) | 3909(6) | 6751(14) | 2005(6) | 46(2) |
| C(16) | 3993(8) | 6170(20) | 969(7) | 65(3) |
| C(17) | 4356(8) | 4497(18) | 742(6) | 56(2) |
| C(18) | 4540(7) | 2724(17) | 1413(6) | 57(2) |
| C(19) | 4040(7) | 3069(15) | 2308(5) | 46(2) |
| C(110) | 2715(6) | 2628(14) | 1896(6) | 46(2) |
| C(111) | 1968(7) | 3816(13) | 2448(5) | 41(2) |
| C(112) | 2522(6) | 5779(16) | 2853(5) | 44(2) |
| C(113) | 786(7) | 4060(20) | 1756(6) | 64(3) |
| Si | -1104(2) | 6356(5) | 1854(2) | 63(1) |
| C(21) | -694(19) | 8480(40) | 1238(12) | 130(7) |
| C(22) | -2180(10) | 4810(40) | 936(9) | 113(6) |
| C(23) | -1609(8) | 7080(20) | 2947(10) | 84(4) |
| C(24) | -656(14) | 8180(40) | 3758(10) | 124(7) |
| C(25) | -1885(14) | 4940(30) | 3408(15) | 115(5) |
| C(26) | -2709(13) | 8360(40) | 2671(19) | 143(8) |

**Table B.3 Bond lengths [Å] and angles [°] for bromoketone 109.**

| | | | |
|---|---|---|---|
| Br-C(111) | 1.968(8) | C(19)-C(14)-C(15) | 111.4(6) |
| O(1)-C(18) | 1.224(13) | C(13)-C(14)-C(15) | 99.5(6) |
| O(2)-C(112) | 1.466(10) | O(2)-C(15)-C(16) | 110.3(6) |
| O(2)-C(15) | 1.472(9) | O(2)-C(15)-C(14) | 103.4(6) |
| O(3)-C(113) | 1.417(12) | C(16)-C(15)-C(14) | 111.0(8) |
| O(3)-Si | 1.633(7) | C(17)-C(16)-C(15) | 125.0(9) |
| C(11)-C(12) | 1.482(15) | C(16)-C(17)-C(18) | 121.9(8) |
| C(12)-C(13) | 1.500(13) | O(1)-C(18)-C(17) | 124.5(8) |
| C(13)-C(112) | 1.525(10) | O(1)-C(18)-C(19) | 123.2(9) |
| C(13)-C(14) | 1.534(11) | C(17)-C(18)-C(19) | 112.3(8) |
| C(14)-C(19) | 1.413(14) | C(14)-C(19)-C(18) | 111.2(7) |
| C(14)-C(15) | 1.536(12) | C(14)-C(19)-C(110) | 117.1(7) |
| C(15)-C(16) | 1.529(13) | C(18)-C(19)-C(110) | 104.7(6) |
| C(16)-C(17) | 1.251(17) | C(111)-C(110)-C(19) | 113.2(6) |
| C(17)-C(18) | 1.469(16) | C(112)-C(111)-C(113) | 114.0(8) |
| C(18)-C(19) | 1.547(10) | C(112)-C(111)-C(110) | 111.3(6) |
| C(19)-C(110) | 1.567(10) | C(113)-C(111)-C(110) | 107.9(6) |
| C(110)-C(111) | 1.543(11) | C(112)-C(111)-Br | 108.5(5) |
| C(111)-C(112) | 1.484(13) | C(113)-C(111)-Br | 106.8(6) |
| C(111)-C(113) | 1.497(12) | C(110)-C(111)-Br | 108.2(6) |
| Si-C(21) | 1.77(2) | O(2)-C(112)-C(111) | 106.8(6) |
| Si-C(23) | 1.856(12) | O(2)-C(112)-C(13) | 103.7(6) |
| Si-C(22) | 1.859(16) | C(111)-C(112)-C(13) | 114.4(8) |
| C(23)-C(26) | 1.52(2) | O(3)-C(113)-C(111) | 108.7(6) |
| C(23)-C(24) | 1.55(2) | O(3)-Si-C(21) | 106.8(9) |
| C(23)-C(25) | 1.61(2) | O(3)-Si-C(23) | 106.1(5) |
| | | C(21)-Si-C(23) | 113.5(9) |
| C(112)-O(2)-C(15) | 108.2(6) | O(3)-Si-C(22) | 108.5(8) |
| C(113)-O(3)-Si | 129.1(5) | C(21)-Si-C(22) | 108.7(8) |
| C(11)-C(12)-C(13) | 112.3(9) | C(23)-Si-C(22) | 112.9(6) |
| C(12)-C(13)-C(112) | 113.8(7) | C(26)-C(23)-C(24) | 110.8(15) |
| C(12)-C(13)-C(14) | 118.0(7) | C(26)-C(23)-C(25) | 108.4(12) |
| C(112)-C(13)-C(14) | 98.1(6) | C(24)-C(23)-C(25) | 107.2(16) |
| C(19)-C(14)-C(13) | 113.1(7) | C(26)-C(23)-Si | 112.7(13) |

| | | | |
|---|---|---|---|
| C(24)-C(23)-Si | 112.4(8) | C(25)-C(23)-Si | 104.9(9) |

Symmetry transformations used to generate equivalent atoms:

**Table B.4 Anisotropic displacement parameters ($Å^2 x\ 10^3$) for bromoketone 109.**

The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

| | $U^{11}$ | $U^{22}$ | $U^{33}$ | $U^{23}$ | $U^{13}$ | $U^{12}$ |
|---|---|---|---|---|---|---|
| Br | 65(1) | 88(1) | 61(1) | 13(1) | 36(1) | -12(1) |
| O(1) | 82(4) | 61(4) | 77(4) | -18(3) | 52(4) | 12(4) |
| O(2) | 37(2) | 58(3) | 52(3) | 12(3) | 19(2) | 3(3) |
| O(3) | 41(3) | 136(7) | 49(3) | 11(4) | 17(2) | 25(4) |
| C(11) | 67(5) | 105(9) | 52(4) | -28(6) | 9(4) | -7(6) |
| C(12) | 50(4) | 78(7) | 53(4) | -24(5) | 7(3) | 6(5) |
| C(13) | 33(3) | 54(4) | 37(3) | 1(3) | 10(3) | 0(3) |
| C(14) | 30(3) | 60(5) | 39(4) | 1(4) | 12(3) | 1(4) |
| C(15) | 34(3) | 58(5) | 48(4) | 3(4) | 16(3) | -7(3) |
| C(16) | 51(5) | 99(8) | 49(4) | 31(5) | 21(4) | 2(5) |
| C(17) | 51(4) | 81(7) | 45(5) | -13(5) | 28(4) | -6(5) |
| C(18) | 44(4) | 89(7) | 44(4) | 3(4) | 24(3) | -5(5) |
| C(19) | 43(4) | 69(5) | 35(3) | 2(4) | 28(3) | -1(4) |
| C(110) | 46(4) | 56(5) | 43(4) | 0(3) | 24(3) | -1(4) |
| C(111) | 48(4) | 46(4) | 38(4) | -16(3) | 26(3) | -27(3) |
| C(112) | 37(3) | 65(5) | 36(3) | -3(4) | 19(3) | 3(4) |
| C(113) | 38(4) | 111(8) | 42(4) | -4(5) | 11(3) | -6(5) |
| Si | 38(1) | 93(2) | 55(1) | 6(1) | 9(1) | -9(1) |
| C(21) | 149(15) | 156(16) | 89(9) | -20(11) | 39(9) | -70(14) |
| C(22) | 51(6) | 190(17) | 83(8) | 6(11) | -6(6) | -8(9) |
| C(23) | 58(5) | 85(7) | 119(9) | -51(8) | 43(6) | -19(6) |
| C(24) | 108(10) | 200(20) | 72(7) | -25(11) | 36(7) | -29(13) |
| C(25) | 120(11) | 100(10) | 161(14) | 22(10) | 100(11) | -3(9) |
| C(26) | 79(9) | 131(15) | 230(20) | -45(16) | 61(13) | 9(10) |

**Table B.5 Hydrogen coordinates ( x $10^4$) and isotropic displacement parameters ($Å^2$x $10^3$) for bromoketone 109.**

| | x | y | z | U(eq) |
|---|---|---|---|---|
| H(11A) | 2813 | 7475 | 4783 | 113 |
| H(11B) | 3873 | 8773 | 5375 | 113 |
| H(11C) | 3903 | 6377 | 5458 | 113 |
| H(12A) | 4987 | 7342 | 4421 | 74 |
| H(12B) | 3953 | 8625 | 3774 | 74 |
| H(13) | 3760 | 4360 | 3964 | 49 |
| H(14) | 5200 | 5102 | 3016 | 51 |
| H(15) | 4331 | 8024 | 2229 | 55 |
| H(16) | 3756 | 7146 | 470 | 78 |
| H(17) | 4513 | 4367 | 131 | 67 |
| H(19) | 4367 | 2020 | 2805 | 55 |
| H(11D) | 2474 | 2993 | 1200 | 55 |
| H(11E) | 2582 | 1171 | 1947 | 55 |
| H(112) | 2030 | 6538 | 3185 | 53 |
| H(11F) | 822 | 4916 | 1201 | 76 |
| H(11G) | 483 | 2729 | 1502 | 76 |
| H(21A) | -31 | 9129 | 1668 | 195 |
| H(21B) | -1321 | 9437 | 1062 | 195 |
| H(21C) | -508 | 8013 | 649 | 195 |
| H(22A) | -1837 | 4309 | 436 | 169 |
| H(22B) | -2837 | 5643 | 633 | 169 |
| H(22C) | -2422 | 3667 | 1264 | 169 |
| H(24A) | -435 | 9424 | 3495 | 186 |
| H(24B) | 5 | 7294 | 3965 | 186 |
| H(24C) | -947 | 8486 | 4315 | 186 |
| H(25A) | -1942 | 5163 | 4070 | 172 |
| H(25B) | -1274 | 3984 | 3422 | 172 |
| H(25C) | -2602 | 4401 | 3008 | 172 |
| H(26A) | -2968 | 8600 | 3252 | 214 |
| H(26B) | -3296 | 7631 | 2189 | 214 |

| | | | | |
|---|---|---|---|---|
| H(26C) | -2558 | 9644 | 2398 | 214 |

# APPENDIX C

## SUPPLEMENTARY CRYSTALLOGRAPHIC INFORMATION ON KETONE 152

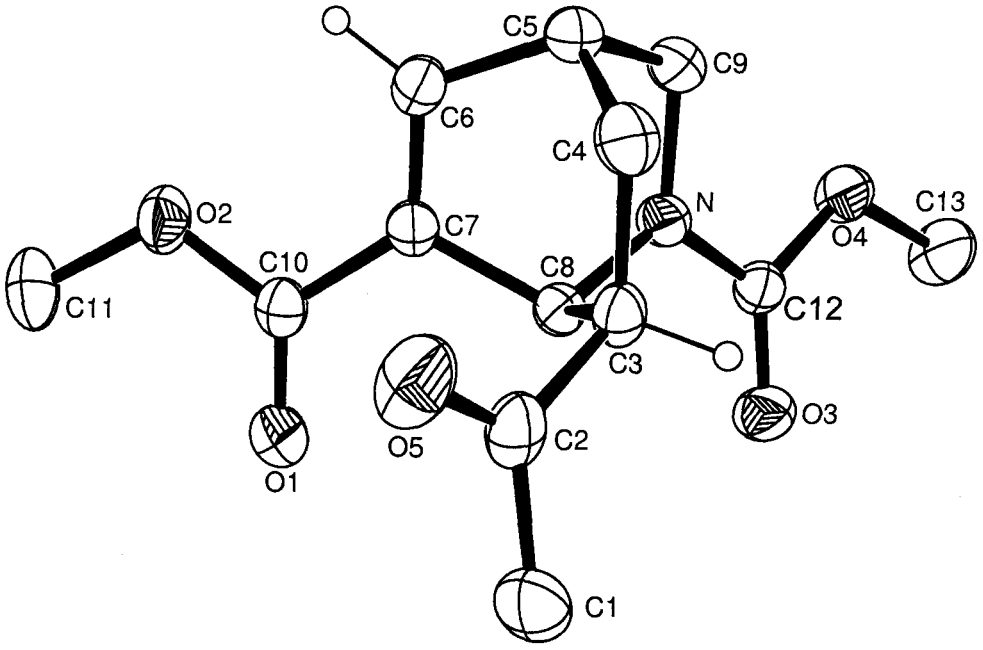


**Table C.1 Crystal data and structure refinement for 152.**

| | | |
|---|---|---|
| Empirical formula | $C_{13}H_{17}NO_5$ | |
| Formula weight | 267.28 | |
| Temperature | 290(2) K | |
| Wavelength | 1.54178 Å | |
| Crystal system | Monoclinic | |
| Space group | $P2_1/c$ | |
| Unit cell dimensions | a = 10.236(1) Å | $\alpha = 90°$. |
| | b = 6.463(1) Å | $\beta = 93.19(1)°$. |
| | c = 19.977(2) Å | $\gamma = 90°$. |
| Volume | 1319.5(3) $Å^3$ | |
| Z | 4 | |
| Density (calculated) | 1.345 $Mg/m^3$ | |
| Absorption coefficient | 0.871 $mm^{-1}$ | |
| F(000) | 568 | |
| Crystal size | 0.3 x 0.3 x 0.2 $mm^3$ | |
| Theta range for data collection | 4.33 to 67.21°. | |
| Index ranges | -12<=h<=0, -7<=k<=1, -23<=l<=23 | |
| Reflections collected | 2637 | |
| Independent reflections | 2180 [R(int) = 0.0372] | |
| Completeness to theta = 67.21° | 91.9 % | |
| Absorption correction | Empirical | |
| Max. and min. transmission | 0.8152 and 0.4417 | |
| Refinement method | Full-matrix least-squares on $F^2$ | |
| Data / restraints / parameters | 2180 / 0 / 177 | |
| Goodness-of-fit on $F^2$ | 1.075 | |
| Final R indices [I>2sigma(I)] | R1 = 0.0409, wR2 = 0.1100 | |
| R indices (all data) | R1 = 0.0507, wR2 = 0.1223 | |
| Extinction coefficient | 0 | |
| Largest diff. peak and hole | 0.150 and -0.144 $e.Å^{-3}$ | |

**Table C.2 Atomic coordinates ( x $10^4$) and equivalent isotropic displacement parameters ($Å^2$x $10^3$) for 152.**

U(eq) is defined as one third of the trace of the orthogonalized $U^{ij}$ tensor.

| | x | y | z | U(eq) |
|---|---|---|---|---|
| O(1) | 1196(2) | 3598(2) | 947(1) | 66(1) |
| O(2) | -367(1) | 1235(2) | 741(1) | 57(1) |
| O(3) | 3265(2) | 3495(2) | 3097(1) | 62(1) |
| O(4) | 2423(1) | 1161(2) | 3795(1) | 59(1) |
| O(5) | 3749(2) | -1029(3) | 643(1) | 87(1) |
| N | 2198(2) | 624(2) | 2699(1) | 46(1) |
| C(1) | 4755(2) | 2041(4) | 1039(1) | 73(1) |
| C(2) | 4019(2) | 88(4) | 1117(1) | 56(1) |
| C(3) | 3589(2) | -420(3) | 1814(1) | 47(1) |
| C(4) | 3100(2) | -2649(3) | 1905(1) | 56(1) |
| C(5) | 1701(2) | -2632(3) | 2156(1) | 49(1) |
| C(6) | 866(2) | -1450(3) | 1653(1) | 47(1) |
| C(7) | 1261(2) | 492(3) | 1565(1) | 40(1) |
| C(8) | 2465(2) | 1061(3) | 1995(1) | 41(1) |
| C(9) | 1718(2) | -1469(3) | 2823(1) | 52(1) |
| C(10) | 716(2) | 1953(3) | 1063(1) | 44(1) |
| C(11) | -958(2) | 2562(4) | 228(1) | 69(1) |
| C(12) | 2684(2) | 1894(3) | 3185(1) | 45(1) |
| C(13) | 2922(3) | | | |

**Table C.3 Bond lengths [Å] and angles [°] for 152.**

| | |
|---|---|
| O(1)-C(10) | 1.199(2) |
| O(2)-C(10) | 1.334(2) |
| O(2)-C(11) | 1.444(2) |
| O(3)-C(12) | 1.211(2) |
| O(4)-C(12) | 1.349(2) |
| O(4)-C(13) | 1.436(2) |
| O(5)-C(2) | 1.210(2) |
| N-C(12) | 1.345(2) |
| N-C(9) | 1.464(2) |
| N-C(8) | 1.474(2) |
| C(1)-C(2) | 1.482(3) |
| C(2)-C(3) | 1.520(2) |
| C(3)-C(4) | 1.538(3) |
| C(3)-C(8) | 1.555(2) |
| C(4)-C(5) | 1.544(3) |
| C(5)-C(6) | 1.492(3) |
| C(5)-C(9) | 1.529(3) |
| C(6)-C(7) | 1.333(3) |
| C(7)-C(10) | 1.464(2) |
| C(7)-C(8) | 1.508(2) |
| | |
| C(10)-O(2)-C(11) | 116.13(16) |
| C(12)-O(4)-C(13) | 115.62(16) |
| C(12)-N-C(9) | 123.80(14) |
| C(12)-N-C(8) | 119.33(14) |
| C(9)-N-C(8) | 114.80(14) |
| O(5)-C(2)-C(1) | 121.4(2) |
| C(9)-C(5)-C(4) | 108.71(16) |
| C(7)-C(6)-C(5) | 113.88(16) |
| C(6)-C(7)-C(10) | 126.24(16) |
| C(6)-C(7)-C(8) | 113.44(15) |
| C(10)-C(7)-C(8) | 120.06(15) |
| O(5)-C(2)-C(3) | 121.5(2) |
| C(1)-C(2)-C(3) | 117.06(18) |

| | |
|---|---|
| C(2)-C(3)-C(4) | 115.00(17) |
| C(2)-C(3)-C(8) | 109.66(15) |
| C(4)-C(3)-C(8) | 107.43(14) |
| C(3)-C(4)-C(5) | 110.20(15) |
| C(6)-C(5)-C(9) | 108.22(16) |
| C(6)-C(5)-C(4) | 106.95(15) |
| N-C(8)-C(7) | 107.96(13) |
| N-C(8)-C(3) | 106.43(14) |
| C(7)-C(8)-C(3) | 107.97(14) |
| N-C(9)-C(5) | 107.16(14) |
| O(1)-C(10)-O(2) | 123.56(17) |
| O(1)-C(10)-C(7) | 124.07(16) |
| O(2)-C(10)-C(7) | 112.36(16) |
| O(3)-C(12)-N | 125.60(16) |
| O(3)-C(12)-O(4) | 123.70(16) |
| N-C(12)-O(4) | 110.69(16) |

Symmetry transformations used to generate equivalent atoms:

**Table C.4 Anisotropic displacement parameters ($Å^2 x\ 10^3$) for 152.**

The anisotropicdisplacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

| | $U^{11}$ | $U^{22}$ | $U^{33}$ | $U^{23}$ | $U^{13}$ | $U^{12}$ |
|---|---|---|---|---|---|---|
| O(1) | 72(1) | 62(1) | 63(1) | 16(1) | -13(1) | -7(1) |
| O(2) | 52(1) | 63(1) | 55(1) | 2(1) | -13(1) | 5(1) |
| O(3) | 72(1) | 66(1) | 49(1) | -2(1) | 2(1) | -22(1) |
| O(4) | 65(1) | 78(1) | 35(1) | -2(1) | 3(1) | -21(1) |
| O(5) | 69(1) | 137(2) | 54(1) | -24(1) | 13(1) | -19(1) |
| N | 53(1) | 50(1) | 34(1) | 1(1) | 4(1) | -9(1) |
| C(1) | 65(1) | 92(2) | 64(1) | 15(1) | 16(1) | -3(1) |
| C(2) | 35(1) | 86(2) | 48(1) | -1(1) | 4(1) | 6(1) |
| C(3) | 37(1) | 61(1) | 42(1) | 2(1) | -1(1) | 3(1) |
| C(4) | 54(1) | 54(1) | 59(1) | 1(1) | 1(1) | 13(1) |
| C(5) | 55(1) | 43(1) | 48(1) | 3(1) | -2(1) | -6(1) |
| C(6) | 42(1) | 55(1) | 43(1) | -3(1) | -1(1) | -3(1) |
| C(7) | 36(1) | 47(1) | 37(1) | 1(1) | 4(1) | 1(1) |
| C(8) | 42(1) | 47(1) | 34(1) | 2(1) | 3(1) | -4(1) |
| C(9) | 58(1) | 55(1) | 43(1) | 7(1) | 3(1) | -9(1) |
| C(10) | 42(1) | 52(1) | 38(1) | -4(1) | 3(1) | 4(1) |
| C(11) | 74(1) | 76(2) | 55(1) | 0(1) | -19(1) | 21(1) |
| C(12) | 39(1) | 56(1) | 39(1) | 1(1) | 4(1) | -4(1) |
| C(13) | 89(2) | 109(2) | 39(1) | -13(1) | 4(1) | -34(2) |

**Table C.5 Hydrogen coordinates ( x $10^4$) and isotropic displacement parameters ($Å^2$x $10^3$) for 152.**

| | x | y | z | U(eq) |
|---|---|---|---|---|
| H(1A) | 5200 | 1999 | 629 | 121(4) |
| H(1B) | 5383 | 2201 | 1410 | 121(4) |
| H(1C) | 4158 | 3187 | 1028 | 121(4) |
| H(3) | 4333 | -189 | 2135 | 63(2) |
| H(4A) | 3683 | -3370 | 2225 | 63(2) |
| H(4B) | 3103 | -3378 | 1480 | 63(2) |
| H(5) | 1371 | -4044 | 2206 | 63(2) |
| H(6) | 136 | -2015 | 1423 | 63(2) |
| H(8) | 2706 | 2513 | 1933 | 63(2) |
| H(9A) | 845 | -1413 | 2987 | 63(2) |
| H(9B) | 2290 | -2162 | 3155 | 63(2) |
| H(11A) | -1156 | 3880 | 419 | 121(4) |
| H(11B) | -1750 | 1937 | 44 | 121(4) |
| H(11C) | -362 | 2752 | -121 | 121(4) |
| H(13A) | 3859 | 2281 | 4390 | 121(4) |
| H(13B) | 2574 | 1857 | 4759 | 121(4) |
| H(13C) | 2665 | 3791 | 4290 | 121(4) |

# APPENDIX D

## SUPPLEMENTARY CRYSTALLOGRAPHIC INFORMATION ON BENZOATE 157

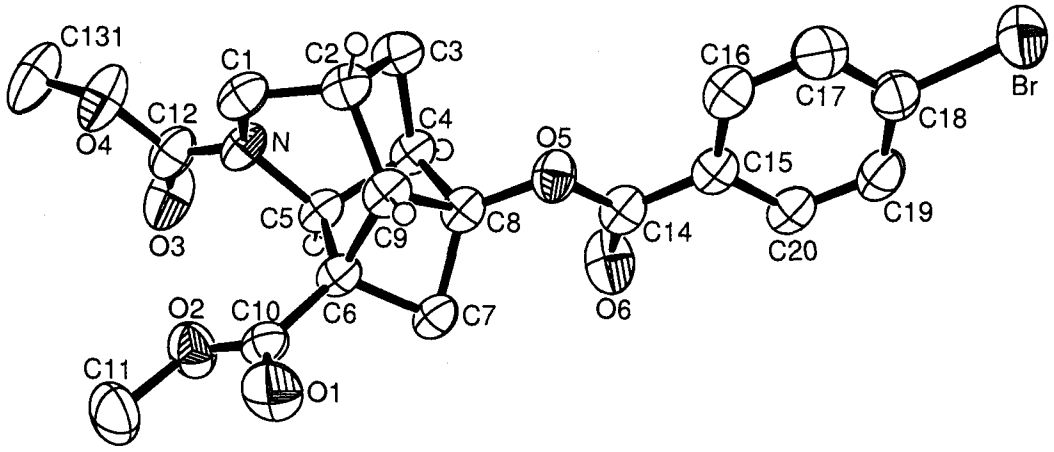


**Table D.1 Crystal data and structure refinement for 157.**

| | | |
|---|---|---|
| Empirical formula | $C_{20}H_{20}BrNO_6$ | |
| Formula weight | 450.28 | |
| Temperature | 290(2) K | |
| Wavelength | 1.54178 Å | |
| Crystal system | Monoclinic | |
| Space group | I2/a (#15) | |
| Unit cell dimensions | a = 13.358(1) Å | $\alpha$= 90°. |
| | b = 9.281(1) Å | $\beta$= 91.95(1)°. |
| | c = 31.128(2) Å | $\gamma$ = 90°. |
| Volume | 3856.9(6) $Å^3$ | |
| Z | 8 | |
| Density (calculated) | 1.443 $Mg/m^3$ | |
| Absorption coefficient | 3.012 $mm^{-1}$ | |
| F(000) | 1840 | |
| Crystal size | 0.20 x 0.20 x 0.10 $mm^3$ | |
| Theta range for data collection | 2.84 to 67.23°. | |
| Index ranges | -14<=h<=12, -11<=k<=1, -37<=l<=15 | |
| Reflections collected | 3848 | |
| Independent reflections | 3234 [R(int) = 0.0435] | |
| Completeness to theta = 67.23° | 87.1 % | |
| Absorption correction | Empirical | |
| Max. and min. transmission | 0.3880 and 0.0227 | |
| Refinement method | Full-matrix least-squares on $F^2$ | |
| Data / restraints / parameters | 3234 / 8 / 282 | |
| Goodness-of-fit on $F^2$ | 1.066 | |
| Final R indices [I>2sigma(I)] | R1 = 0.0409, wR2 = 0.1079 | |
| R indices (all data) | R1 = 0.0439, wR2 = 0.1109 | |
| Largest diff. peak and hole | 0.298 and -0.505 $e.Å^{-3}$ | |

**Table D.2 Atomic coordinates ( x $10^4$) and equivalent isotropic displacement parameters ($Å^2$x $10^3$) for 157.**

U(eq) is defined as one third of the trace of the orthogonalized $U^{ij}$ tensor.

| | x | y | z | U(eq) |
|---|---|---|---|---|
| C(1) | -338(2) | 10519(2) | 6284(1) | 46(1) |
| C(2) | -50(2) | 10571(2) | 6763(1) | 43(1) |
| C(3) | 36(2) | 8989(2) | 6922(1) | 47(1) |
| C(4) | -1057(2) | 8711(2) | 7020(1) | 40(1) |
| C(5) | -1722(2) | 9259(2) | 6624(1) | 38(1) |
| C(6) | -1992(2) | 10750(2) | 6802(1) | 38(1) |
| C(7) | -2359(2) | 10389(2) | 7258(1) | 43(1) |
| C(8) | -1274(2) | 9959(2) | 7330(1) | 40(1) |
| C(9) | -940(2) | 11139(2) | 7017(1) | 41(1) |
| C(10) | -2554(2) | 11851(2) | 6537(1) | 43(1) |
| C(11) | -3439(2) | 12338(3) | 5885(1) | 73(1) |
| C(12) | -1454(2) | 8896(3) | 5859(1) | 51(1) |
| C(131) | -962(17) | 8580(20) | 5139(4) | 86(5) |
| C(132) | -1310(30) | 9100(40) | 5109(3) | 103(6) |
| C(14) | -1185(2) | 9198(2) | 8059(1) | 43(1) |
| C(15) | -582(2) | 9322(2) | 8467(1) | 41(1) |
| C(16) | 372(2) | 9901(3) | 8487(1) | 50(1) |
| C(17) | 917(2) | 9936(3) | 8872(1) | 57(1) |
| C(18) | 498(2) | 9385(3) | 9233(1) | 54(1) |
| C(19) | -460(2) | 8822(3) | 9224(1) | 54(1) |
| C(20) | -996(2) | 8778(2) | 8838(1) | 46(1) |
| Br | 1272(1) | 9340(1) | 9757(1) | 90(1) |
| N | -1130(1) | 9431(2) | 6239(1) | 43(1) |
| O(1) | -2678(2) | 13072(2) | 6654(1) | 68(1) |
| O(2) | -2910(1) | 11327(2) | 6166(1) | 60(1) |
| O(3) | -2153(2) | 8082(2) | 5800(1) | 71(1) |
| O(4) | -873(2) | 9363(2) | 5540(1) | 70(1) |
| O(5) | -762(1) | 9945(2) | 7739(1) | 48(1) |
| O(6) | -1936(1) | 8509(2) | 8009(1) | 64(1) |

**Table D.3 Bond lengths [Å] and angles [°] for 157.**

| | | | |
|---|---|---|---|
| C(1)-N | 1.523(3) | N-C(1)-C(2) | 106.67(17) |
| C(1)-C(2) | 1.534(3) | C(1)-C(2)-C(3) | 107.12(18) |
| C(2)-C(3) | 1.552(3) | C(1)-C(2)-C(9) | 107.2(2) |
| C(2)-C(9) | 1.614(3) | C(3)-C(2)-C(9) | 102.13(17) |
| C(3)-C(4) | 1.630(3) | C(2)-C(3)-C(4) | 98.18(18) |
| C(4)-C(8) | 1.546(3) | C(8)-C(4)-C(5) | 96.46(16) |
| C(4)-C(5) | 1.615(3) | C(8)-C(4)-C(3) | 102.37(17) |
| C(5)-N | 1.503(3) | C(5)-C(4)-C(3) | 110.77(17) |
| C(5)-C(6) | 1.545(3) | N-C(5)-C(6) | 110.32(15) |
| C(6)-C(10) | 1.527(3) | N-C(5)-C(4) | 107.88(18) |
| C(6)-C(7) | 1.566(3) | C(6)-C(5)-C(4) | 99.08(16) |
| C(6)-C(9) | 1.670(3) | C(10)-C(6)-C(5) | 122.68(19) |
| C(7)-C(8) | 1.615(4) | C(10)-C(6)-C(7) | 116.42(18) |
| C(8)-O(5) | 1.450(3) | C(5)-C(6)-C(7) | 103.27(15) |
| C(8)-C(9) | 1.551(3) | C(10)-C(6)-C(9) | 121.71(17) |
| C(10)-O(1) | 1.204(3) | C(5)-C(6)-C(9) | 95.91(17) |
| C(10)-O(2) | 1.339(3) | C(7)-C(6)-C(9) | 90.63(17) |
| C(11)-O(2) | 1.476(3) | C(6)-C(7)-C(8) | 79.92(16) |
| C(12)-O(3) | 1.264(3) | O(5)-C(8)-C(4) | 115.74(18) |
| C(12)-N | 1.351(3) | O(5)-C(8)-C(9) | 113.51(17) |
| C(12)-O(4) | 1.389(3) | C(4)-C(8)-C(9) | 93.76(16) |
| C(131)-O(4) | 1.446(7) | O(5)-C(8)-C(7) | 125.50(18) |
| C(132)-O(4) | 1.479(13) | C(4)-C(8)-C(7) | 108.26(18) |
| C(14)-O(6) | 1.258(3) | C(9)-C(8)-C(7) | 93.26(16) |
| C(14)-O(5) | 1.372(3) | C(8)-C(9)-C(2) | 110.06(17) |
| C(14)-C(15) | 1.517(3) | C(8)-C(9)-C(6) | 78.66(15) |
| C(15)-C(20) | 1.409(3) | C(2)-C(9)-C(6) | 116.95(17) |
| C(15)-C(16) | 1.471(4) | O(1)-C(10)-O(2) | 123.0(2) |
| C(16)-C(17) | 1.407(4) | O(1)-C(10)-C(6) | 123.3(2) |
| C(17)-C(18) | 1.393(4) | O(2)-C(10)-C(6) | 113.74(18) |
| C(18)-C(19) | 1.471(4) | O(3)-C(12)-N | 126.5(2) |
| C(18)-Br | 1.942(3) | O(3)-C(12)-O(4) | 125.2(2) |
| C(19)-C(20) | 1.405(4) | N-C(12)-O(4) | 108.2(2) |
| | | O(6)-C(14)-O(5) | 124.4(2) |

| | | | |
|---|---|---|---|
| O(6)-C(14)-C(15) | 127.2(2) | C(20)-C(19)-C(18) | 120.8(2) |
| O(5)-C(14)-C(15) | 108.36(19) | C(19)-C(20)-C(15) | 117.2(2) |
| C(20)-C(15)-C(16) | 120.9(2) | C(12)-N-C(5) | 118.2(2) |
| C(20)-C(15)-C(14) | 114.5(2) | C(12)-N-C(1) | 124.04(19) |
| C(16)-C(15)-C(14) | 124.6(2) | C(5)-N-C(1) | 115.87(17) |
| C(17)-C(16)-C(15) | 122.3(2) | C(10)-O(2)-C(11) | 117.0(2) |
| C(18)-C(17)-C(16) | 115.8(3) | C(12)-O(4)-C(131) | 114.9(5) |
| C(17)-C(18)-C(19) | 123.0(2) | C(12)-O(4)-C(132) | 110.5(10) |
| C(17)-C(18)-Br | 115.8(2) | C(131)-O(4)-C(132) | 27.4(11) |
| C(19)-C(18)-Br | 121.16(19) | C(14)-O(5)-C(8) | 114.76(18) |

Symmetry transformations used to generate equivalent atoms:

**Table D.4 Anisotropic displacement parameters ($Å^2 x\ 10^3$) for 157.**

The anisotropicdisplacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + ...\ + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

| | $U^{11}$ | $U^{22}$ | $U^{33}$ | $U^{23}$ | $U^{13}$ | $U^{12}$ |
|---|---|---|---|---|---|---|
| C(1) | 49(2) | 35(1) | 54(1) | 2(1) | 19(1) | -8(1) |
| C(2) | 42(2) | 34(1) | 54(1) | 3(1) | 10(1) | -7(1) |
| C(3) | 46(2) | 33(1) | 61(1) | 5(1) | 12(1) | 3(1) |
| C(4) | 50(1) | 24(1) | 48(1) | 4(1) | 13(1) | -2(1) |
| C(5) | 45(1) | 26(1) | 44(1) | -1(1) | 14(1) | -6(1) |
| C(6) | 45(1) | 26(1) | 44(1) | 1(1) | 12(1) | 1(1) |
| C(7) | 50(2) | 36(1) | 44(1) | -1(1) | 14(1) | 1(1) |
| C(8) | 47(1) | 31(1) | 42(1) | 0(1) | 7(1) | -4(1) |
| C(9) | 51(2) | 23(1) | 49(1) | -1(1) | 8(1) | -4(1) |
| C(10) | 45(1) | 36(1) | 50(1) | 5(1) | 13(1) | 1(1) |
| C(11) | 90(2) | 65(2) | 63(2) | 20(1) | -4(2) | 10(2) |
| C(12) | 68(2) | 39(1) | 47(1) | -2(1) | 18(1) | -8(1) |
| C(131) | 103(9) | 111(9) | 46(3) | -23(4) | 28(4) | -40(7) |
| C(132) | 147(16) | 112(13) | 52(5) | -6(6) | 28(7) | -37(10) |
| C(14) | 56(2) | 26(1) | 48(1) | 3(1) | 9(1) | -4(1) |
| C(15) | 53(2) | 25(1) | 45(1) | 0(1) | 9(1) | 1(1) |
| C(16) | 59(2) | 40(1) | 51(1) | 2(1) | 11(1) | -6(1) |
| C(17) | 54(2) | 55(2) | 63(2) | -9(1) | 2(1) | -3(1) |
| C(18) | 64(2) | 49(1) | 47(1) | -8(1) | 0(1) | 18(1) |
| C(19) | 72(2) | 46(1) | 45(1) | 3(1) | 15(1) | 11(1) |
| C(20) | 56(2) | 32(1) | 50(1) | 2(1) | 13(1) | 2(1) |
| Br | 89(1) | 125(1) | 54(1) | -14(1) | -12(1) | 30(1) |
| N | 53(1) | 32(1) | 45(1) | -2(1) | 18(1) | -8(1) |
| O(1) | 93(2) | 35(1) | 77(1) | -3(1) | 0(1) | 19(1) |
| O(2) | 79(1) | 46(1) | 55(1) | 5(1) | -4(1) | 10(1) |
| O(3) | 95(2) | 65(1) | 53(1) | -11(1) | 17(1) | -37(1) |
| O(4) | 94(2) | 70(1) | 47(1) | -6(1) | 25(1) | -28(1) |
| O(5) | 55(1) | 47(1) | 43(1) | 5(1) | 6(1) | -11(1) |
| O(6) | 78(1) | 54(1) | 60(1) | 14(1) | -6(1) | -32(1) |

**Table D.5 Hydrogen coordinates ( x $10^4$) and isotropic displacement parameters ($Å^2$x $10^3$) for 157.**

| | x | y | z | U(eq) |
|---|---|---|---|---|
| H(1A) | -553(5) | 11500(20) | 6182(2) | 58(2) |
| H(1B) | 205(11) | 10209(6) | 6109(4) | 58(2) |
| H(2) | 523(18) | 11150(18) | 6824(2) | 58(2) |
| H(3A) | 436(9) | 8904(3) | 7179(5) | 58(2) |
| H(3B) | 258(5) | 8348(14) | 6699(5) | 58(2) |
| H(4) | -1198(5) | 7760(30) | 7126(3) | 58(2) |
| H(5) | -2284(17) | 8610(20) | 6567(2) | 58(2) |
| H(7A) | -2803(10) | 9576(17) | 7268(1) | 58(2) |
| H(7B) | -2565(5) | 11228(17) | 7426(4) | 58(2) |
| H(9) | -875(3) | 12120(30) | 7143(4) | 58(2) |
| H(11A) | -3613(17) | 11861(14) | 5615(7) | 120(7) |
| H(11B) | -3055(11) | 13180(20) | 5827(7) | 120(7) |
| H(11C) | -4001(16) | 12640(20) | 6027(5) | 120(7) |
| H(13A) | -360(40) | 8590(50) | 4994(10) | 120(7) |
| H(13B) | -1450(30) | 9030(40) | 4952(11) | 120(7) |
| H(13C) | -1140(40) | 7570(70) | 5199(6) | 120(7) |
| H(13D) | -820(40) | 9200(80) | 4882(16) | 120(7) |
| H(13E) | -1830(60) | 9820(90) | 5051(11) | 120(7) |
| H(13F) | -1570(60) | 8080(80) | 5098(8) | 120(7) |
| H(16) | 629(8) | 10263(12) | 8233(8) | 58(2) |
| H(17) | 1590(20) | 10348(13) | 8885(1) | 58(2) |
| H(19) | -719(9) | 8485(11) | 9481(8) | 58(2) |
| H(20) | -1680(20) | 8356(13) | 8826(1) | 58(2) |

**Table D.6 Torsion angles [°] for 157.**

| | |
|---|---|
| N-C(1)-C(2)-C(3) | 46.5(2) |
| N-C(1)-C(2)-C(9) | -62.5(2) |
| C(1)-C(2)-C(3)-C(4) | -84.4(2) |
| C(9)-C(2)-C(3)-C(4) | 28.1(2) |
| C(2)-C(3)-C(4)-C(8) | -54.8(2) |
| C(2)-C(3)-C(4)-C(5) | 47.1(2) |
| C(8)-C(4)-C(5)-N | 123.02(16) |
| C(3)-C(4)-C(5)-N | 17.1(2) |
| C(8)-C(4)-C(5)-C(6) | 8.12(18) |
| C(3)-C(4)-C(5)-C(6) | -97.76(19) |
| N-C(5)-C(6)-C(10) | 60.6(3) |
| C(4)-C(5)-C(6)-C(10) | 173.61(19) |
| N-C(5)-C(6)-C(7) | -165.40(19) |
| C(4)-C(5)-C(6)-C(7) | -52.4(2) |
| N-C(5)-C(6)-C(9) | -73.4(2) |
| C(4)-C(5)-C(6)-C(9) | 39.65(17) |
| C(10)-C(6)-C(7)-C(8) | -156.18(19) |
| C(5)-C(6)-C(7)-C(8) | 66.37(18) |
| C(9)-C(6)-C(7)-C(8) | -29.85(13) |
| C(5)-C(4)-C(8)-O(5) | -176.73(17) |
| C(3)-C(4)-C(8)-O(5) | -63.8(2) |
| C(5)-C(4)-C(8)-C(9) | -58.33(17) |
| C(3)-C(4)-C(8)-C(9) | 54.64(19) |
| C(5)-C(4)-C(8)-C(7) | 36.36(19) |
| C(3)-C(4)-C(8)-C(7) | 149.32(17) |
| C(6)-C(7)-C(8)-O(5) | 154.57(19) |
| C(6)-C(7)-C(8)-C(4) | -62.58(17) |
| C(6)-C(7)-C(8)-C(9) | 32.46(15) |
| O(5)-C(8)-C(9)-C(2) | 83.6(2) |
| C(4)-C(8)-C(9)-C(2) | -36.6(2) |
| C(7)-C(8)-C(9)-C(2) | -145.12(18) |
| O(5)-C(8)-C(9)-C(6) | -161.59(18) |
| C(4)-C(8)-C(9)-C(6) | 78.19(15) |
| C(7)-C(8)-C(9)-C(6) | -30.36(14) |

| | |
|---|---|
| C(1)-C(2)-C(9)-C(8) | 116.95(19) |
| C(3)-C(2)-C(9)-C(8) | 4.5(2) |
| C(1)-C(2)-C(9)-C(6) | 29.8(2) |
| C(3)-C(2)-C(9)-C(6) | -82.7(2) |
| C(10)-C(6)-C(9)-C(8) | 153.4(2) |
| C(5)-C(6)-C(9)-C(8) | -72.05(15) |
| C(7)-C(6)-C(9)-C(8) | 31.36(14) |
| C(10)-C(6)-C(9)-C(2) | -99.8(2) |
| C(5)-C(6)-C(9)-C(2) | 34.8(2) |
| C(7)-C(6)-C(9)-C(2) | 138.25(17) |
| C(5)-C(6)-C(10)-O(1) | -171.3(2) |
| C(7)-C(6)-C(10)-O(1) | 60.2(3) |
| C(9)-C(6)-C(10)-O(1) | -48.6(3) |
| C(5)-C(6)-C(10)-O(2) | 9.8(3) |
| C(7)-C(6)-C(10)-O(2) | -118.8(2) |
| C(9)-C(6)-C(10)-O(2) | 132.5(2) |
| O(6)-C(14)-C(15)-C(20) | -10.1(3) |
| O(5)-C(14)-C(15)-C(20) | 171.43(18) |
| O(6)-C(14)-C(15)-C(16) | 167.5(2) |
| O(5)-C(14)-C(15)-C(16) | -10.9(3) |
| C(20)-C(15)-C(16)-C(17) | 0.3(3) |
| C(14)-C(15)-C(16)-C(17) | -177.2(2) |
| C(15)-C(16)-C(17)-C(18) | 0.1(4) |
| C(16)-C(17)-C(18)-C(19) | -1.1(4) |
| C(16)-C(17)-C(18)-Br | 176.90(18) |
| C(17)-C(18)-C(19)-C(20) | 1.8(4) |
| Br-C(18)-C(19)-C(20) | -176.09(17) |
| C(18)-C(19)-C(20)-C(15) | -1.3(3) |
| C(16)-C(15)-C(20)-C(19) | 0.3(3) |
| C(14)-C(15)-C(20)-C(19) | 178.07(19) |
| O(3)-C(12)-N-C(5) | -10.4(4) |
| O(4)-C(12)-N-C(5) | 171.0(2) |
| O(3)-C(12)-N-C(1) | -174.1(3) |
| O(4)-C(12)-N-C(1) | 7.4(3) |
| C(6)-C(5)-N-C(12) | -118.7(2) |
| C(4)-C(5)-N-C(12) | 134.1(2) |

| | |
|---|---|
| C(6)-C(5)-N-C(1) | 46.3(3) |
| C(4)-C(5)-N-C(1) | -60.9(2) |
| C(2)-C(1)-N-C(12) | -167.5(2) |
| C(2)-C(1)-N-C(5) | 28.5(3) |
| O(1)-C(10)-O(2)-C(11) | 2.8(4) |
| C(6)-C(10)-O(2)-C(11) | -178.2(2) |
| O(3)-C(12)-O(4)-C(131) | -15.0(15) |
| N-C(12)-O(4)-C(131) | 163.5(14) |
| O(3)-C(12)-O(4)-C(132) | 14(2) |
| N-C(12)-O(4)-C(132) | -167.1(19) |
| O(6)-C(14)-O(5)-C(8) | 3.2(3) |
| C(15)-C(14)-O(5)-C(8) | 178.28(17) |
| C(4)-C(8)-O(5)-C(14) | -89.7(2) |
| C(9)-C(8)-O(5)-C(14) | 163.53(18) |
| C(7)-C(8)-O(5)-C(14) | 50.8(3) |

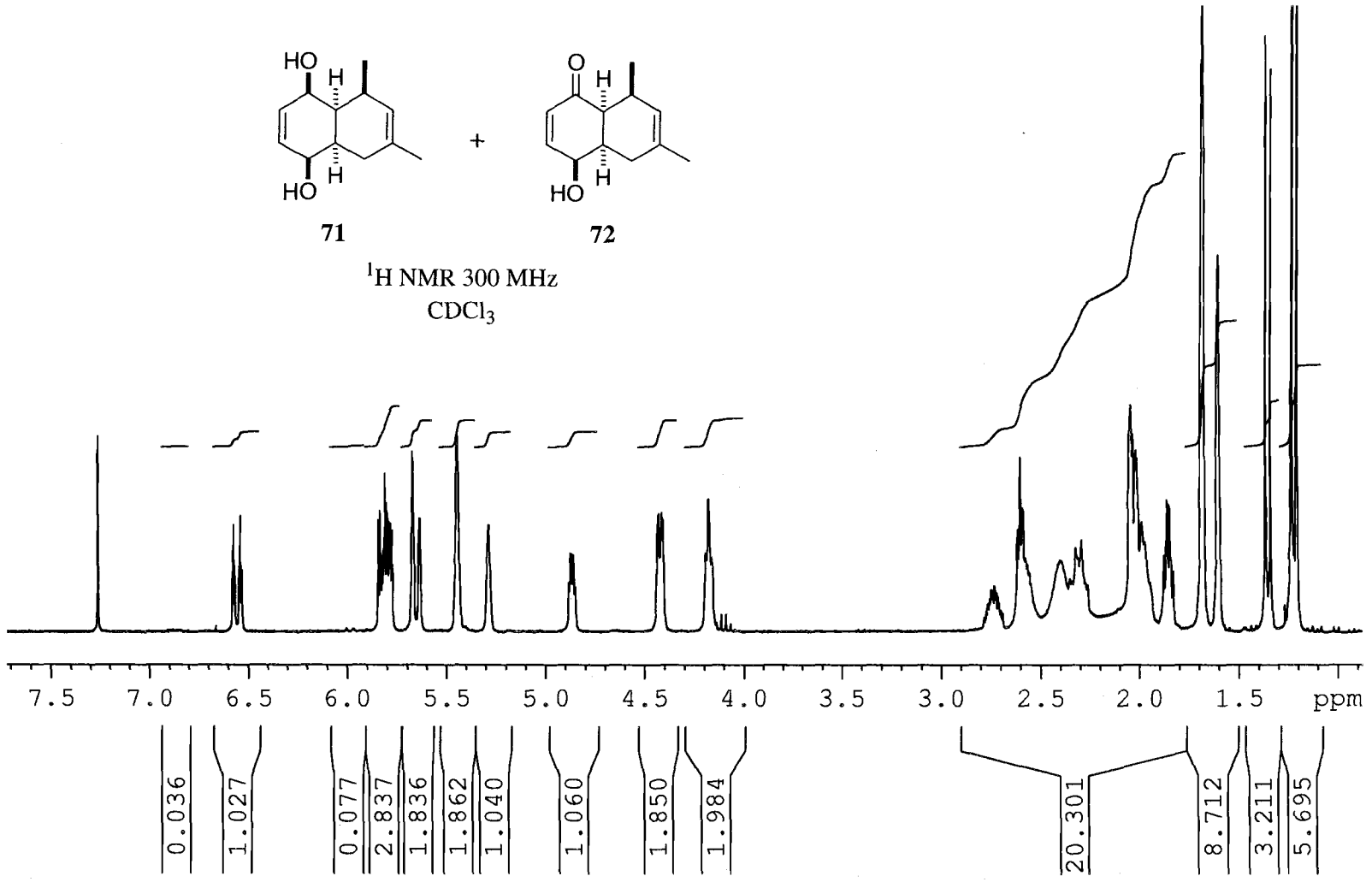
---

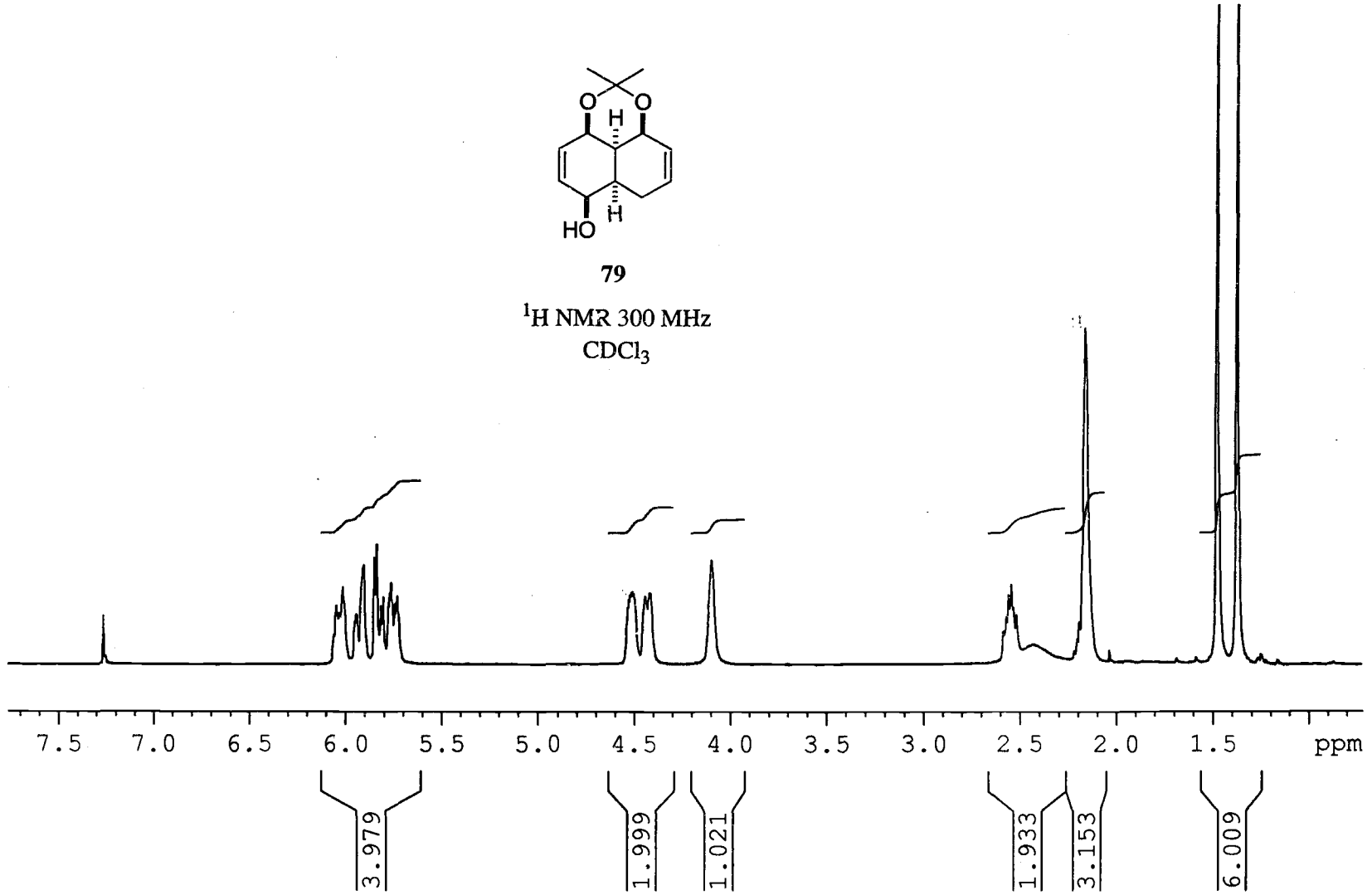
Symmetry transformations used to generate equivalent atoms:

**Table D.7 Hydrogen bonds for 157 [Å and °].**

| D-H...A | d(D-H) | d(H...A) | d(D...A) | <(DHA) |
|---|---|---|---|---|
| O(6)-HO6...O(1) | 0.82 | 1.99 | 2.735(4) | 150.9 |
| O(3)-HO3...O(6)#1 | 0.82 | 2.02 | 2.829(4) | 168.7 |

Symmetry transformations used to generate equivalent atoms:
#1 -x+1,y-1/2,-z+3/2

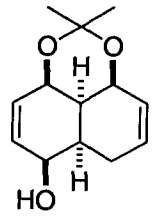

HO
H
H
HO
+
O
H
H
HO
71
72
$^1$H NMR 300 MHz
$CDCl_3$
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
ppm
0.036
1.027
0.077
2.837
1.836
1.862
1.040
1.060
1.850
1.984
20.301
8.712
3.211
5.695




**79**

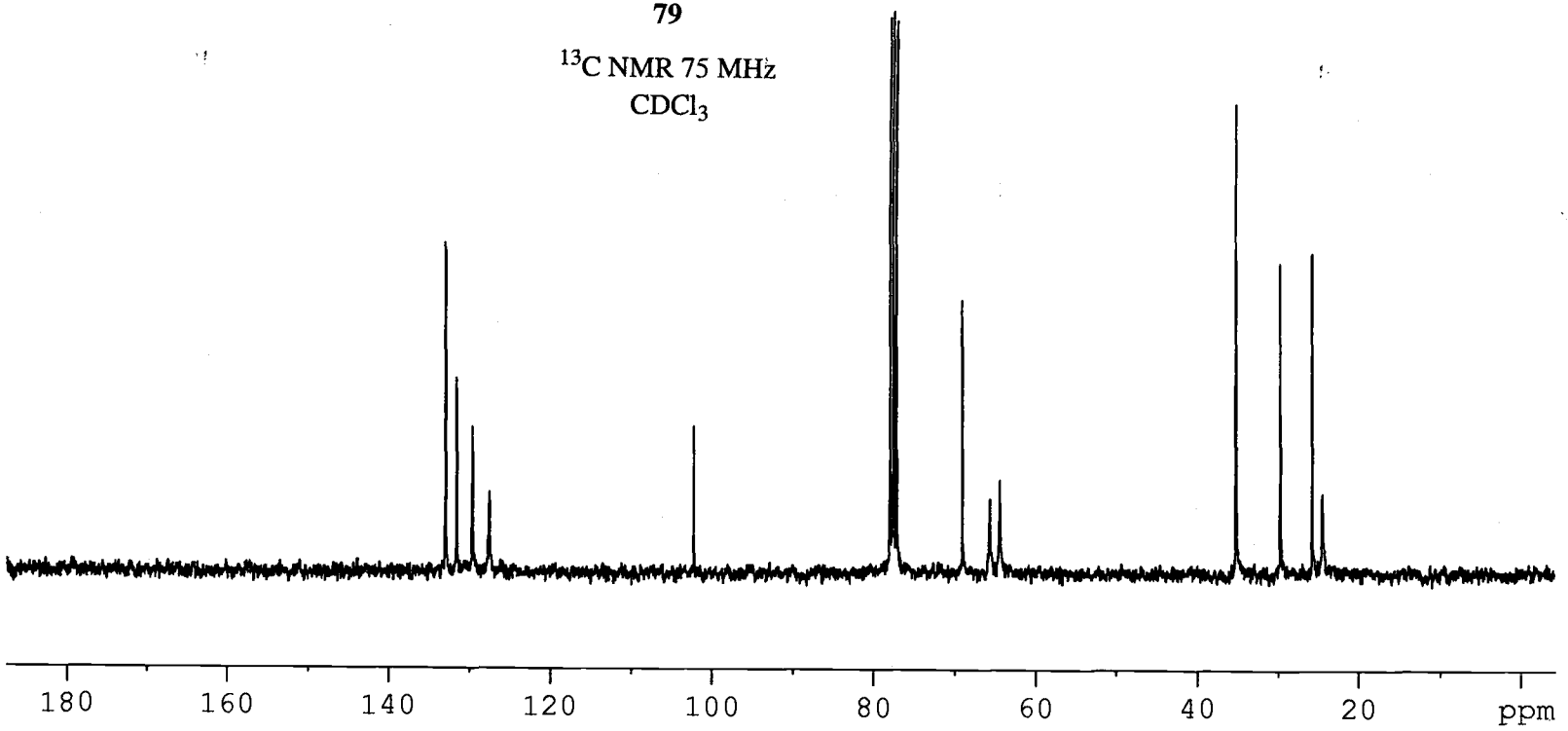
$^1$H NMR 300 MHz

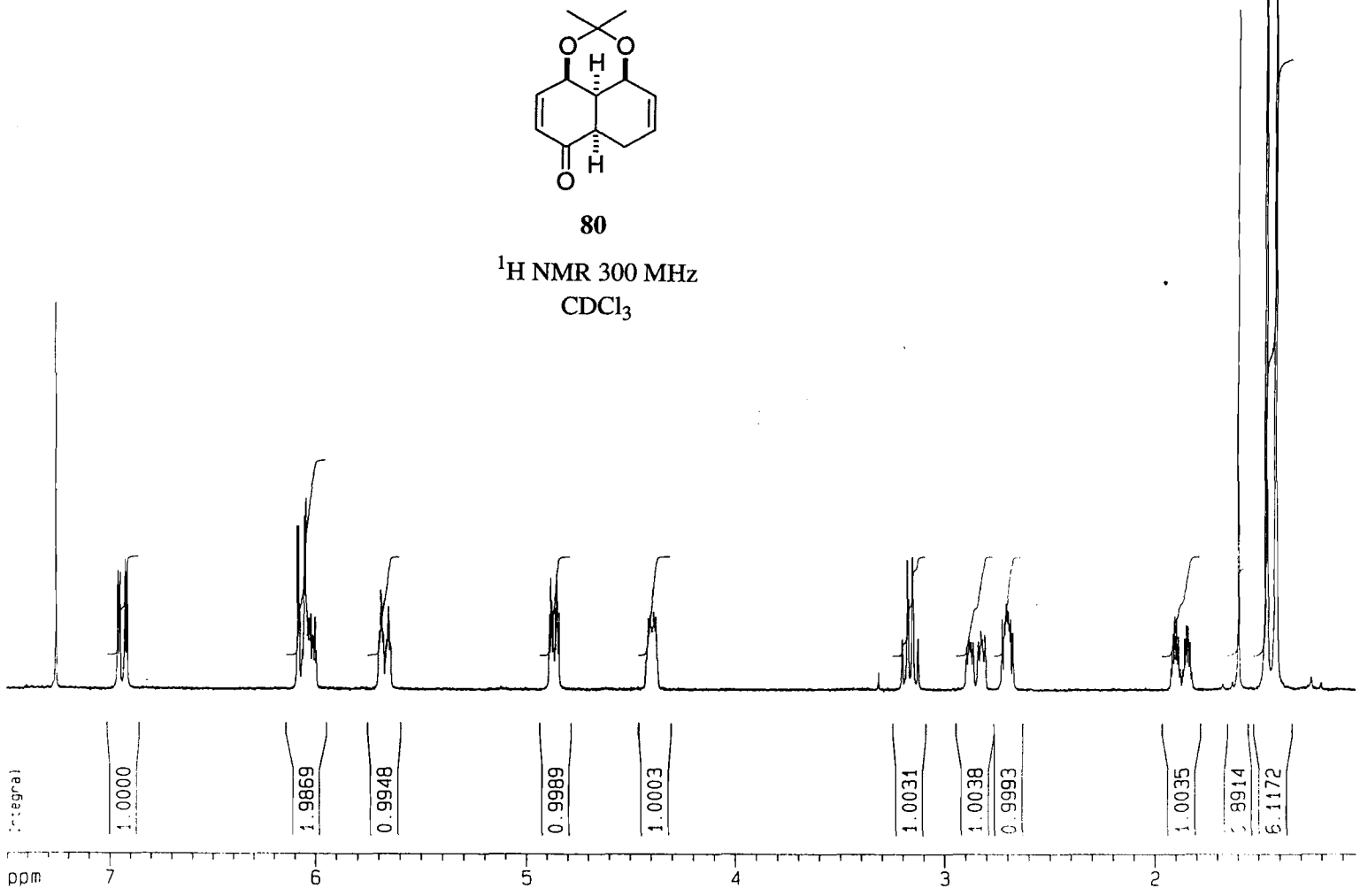
$CDCl_3$




**79**

$^{13}C$ NMR 75 MHz
$CDCl_3$

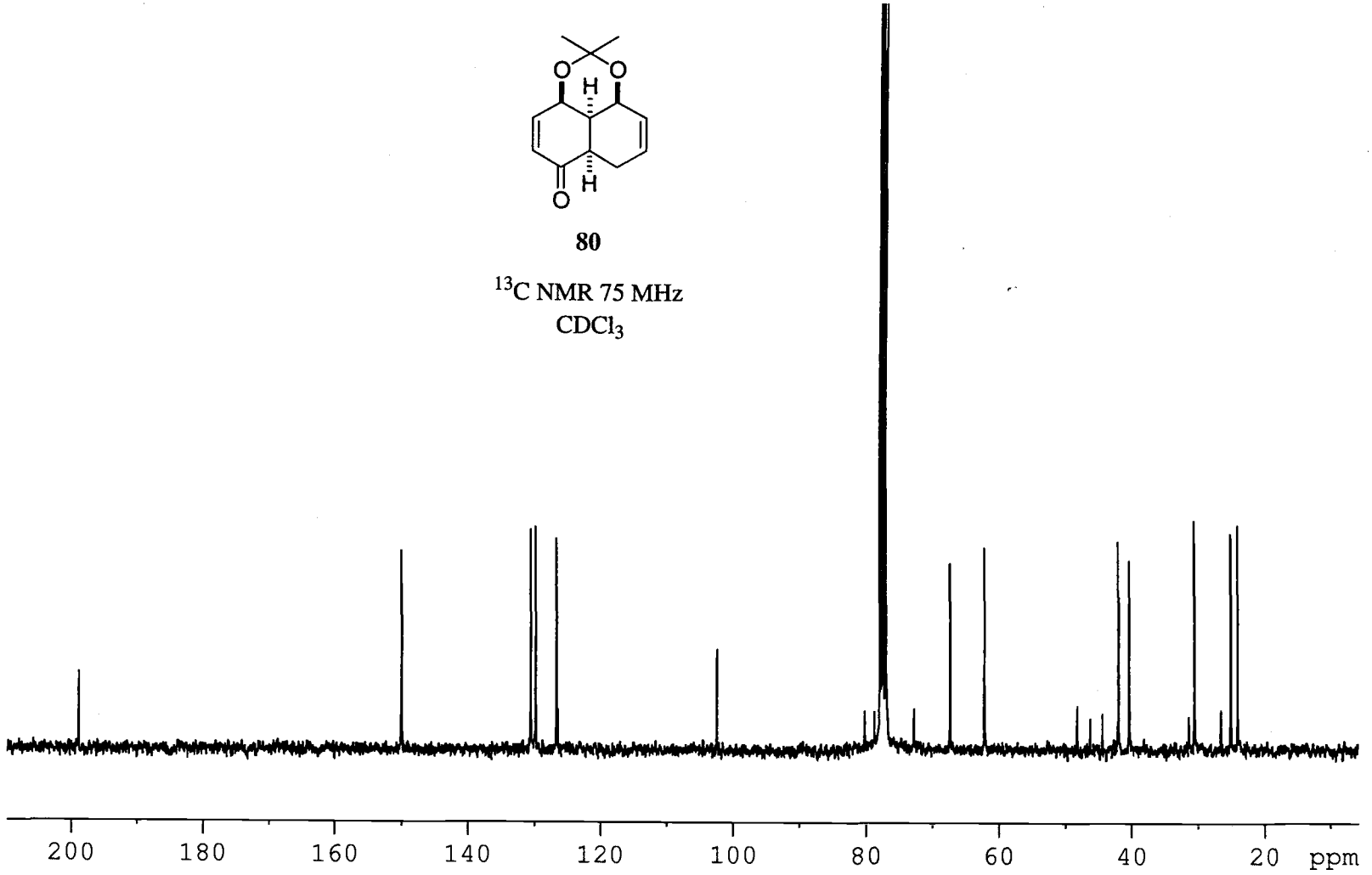





**80**

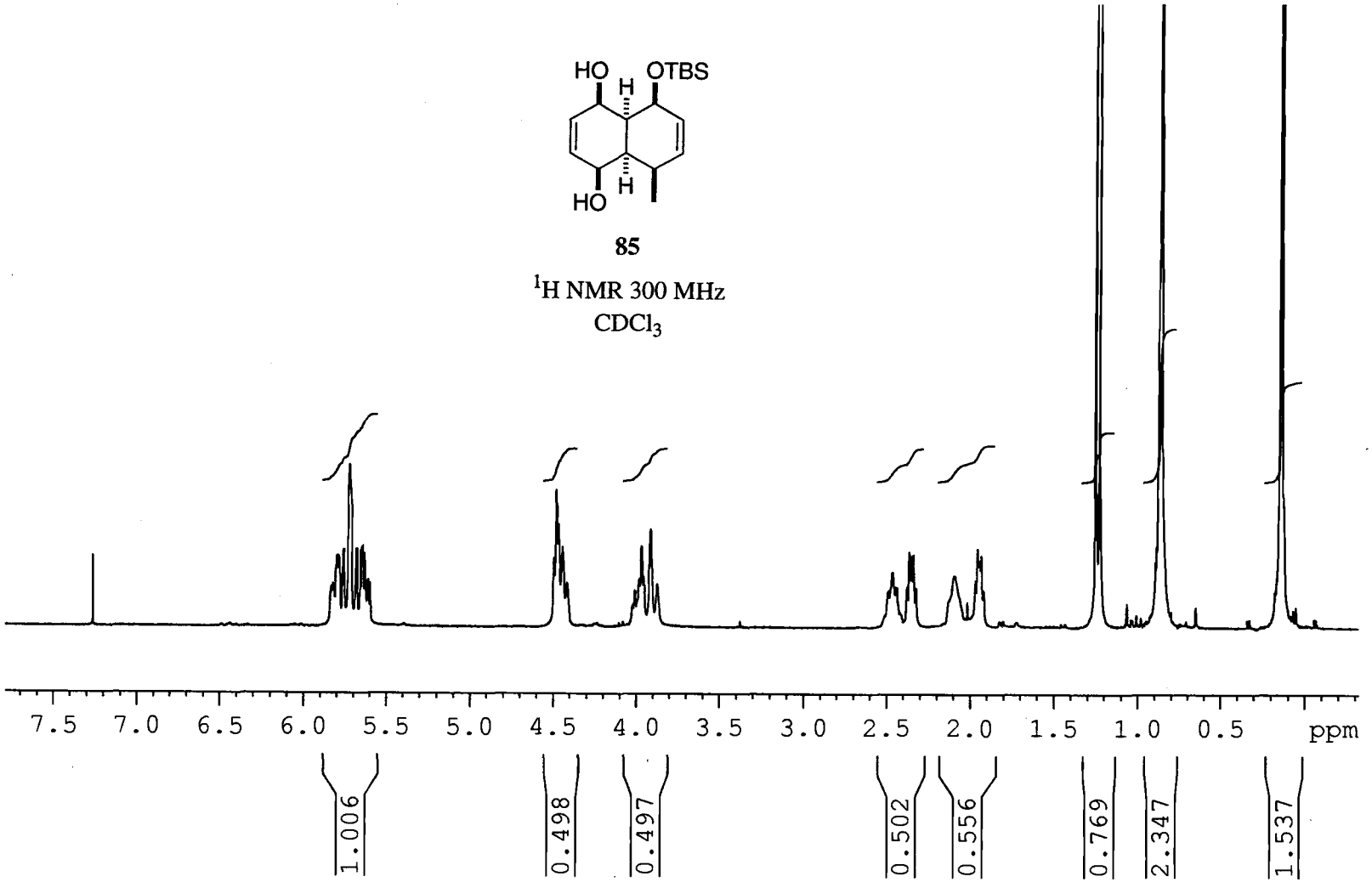
$^1$H NMR 300 MHz

$CDCl_3$




**80**

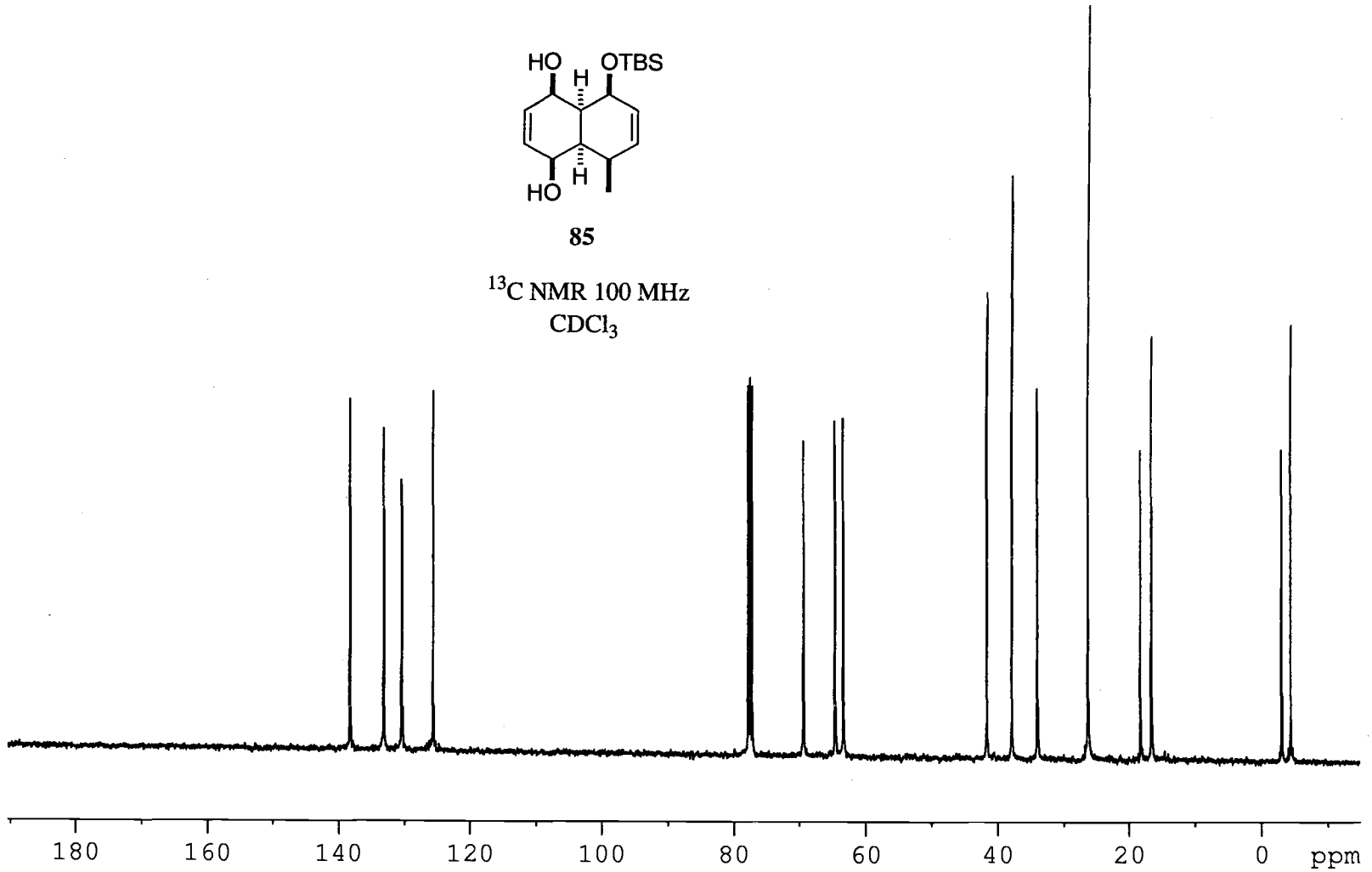
$^{13}C$ NMR 75 MHz
$CDCl_3$

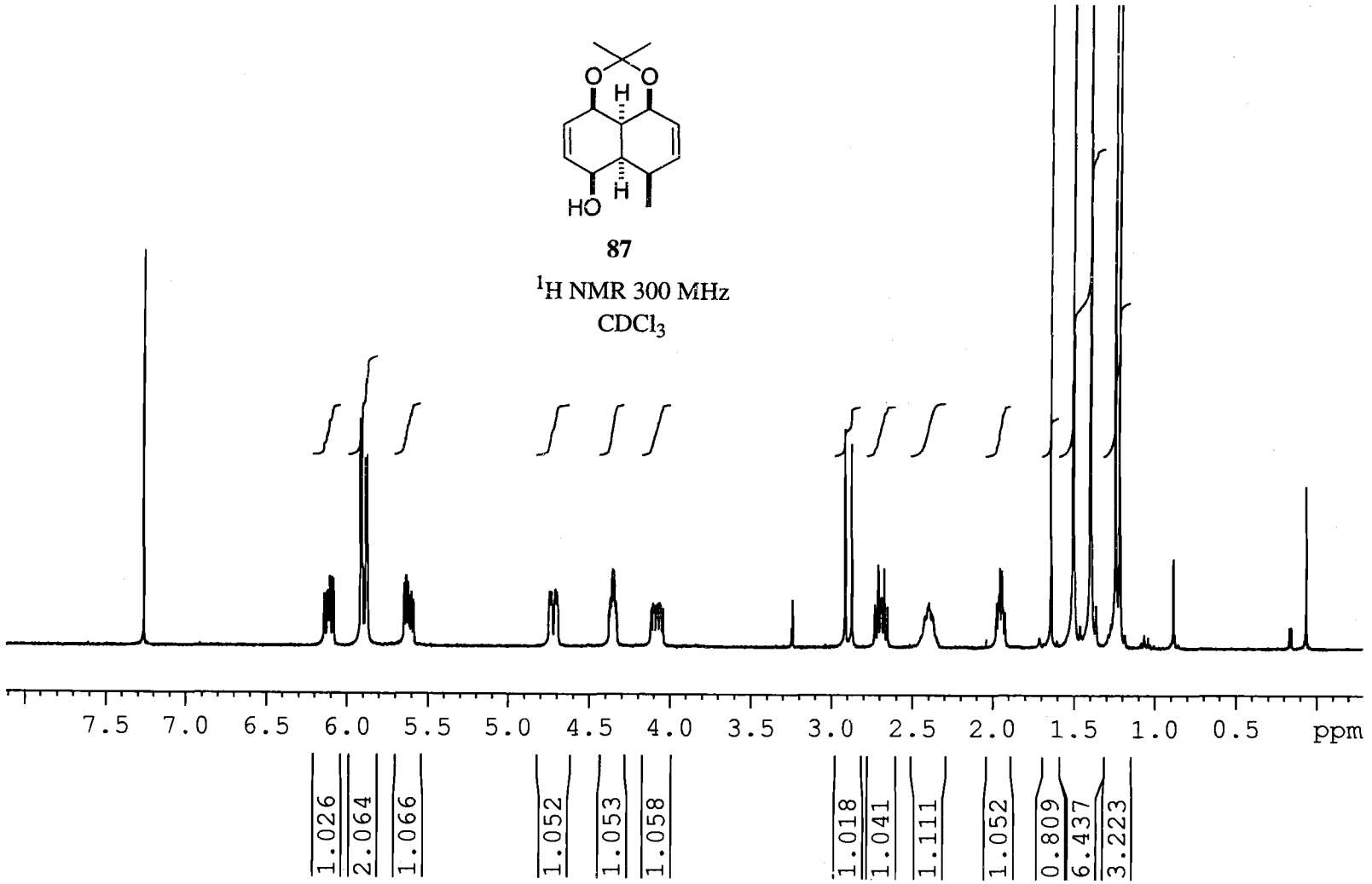



**85**

$^1$H NMR 300 MHz

$CDCl_3$

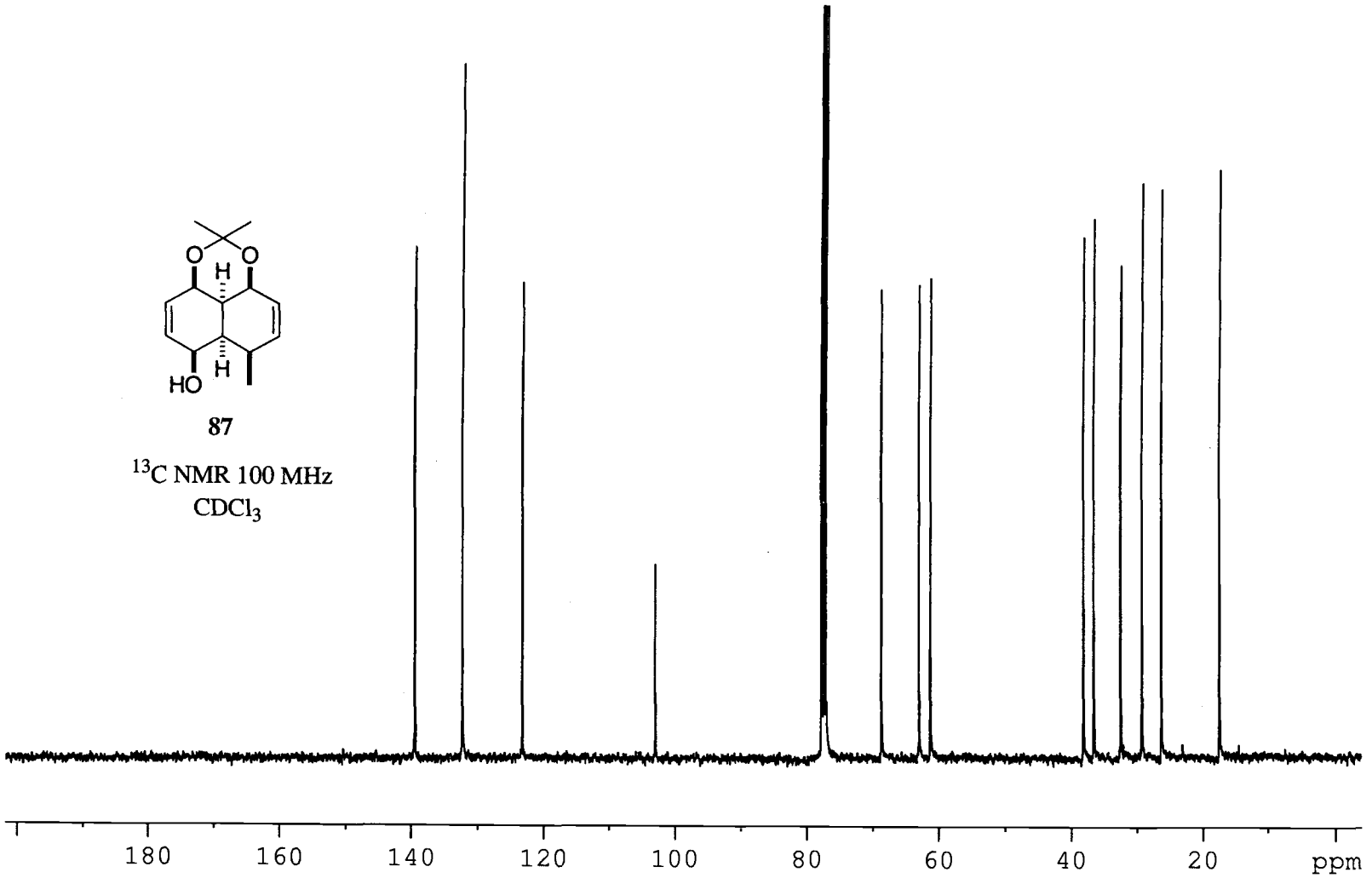

HO
OTBS
H
H
HO
85
$^{13}$C NMR 100 MHz
$CDCl_3$
180
160
140
120
100
80
60
40
20
0
ppm




**87**

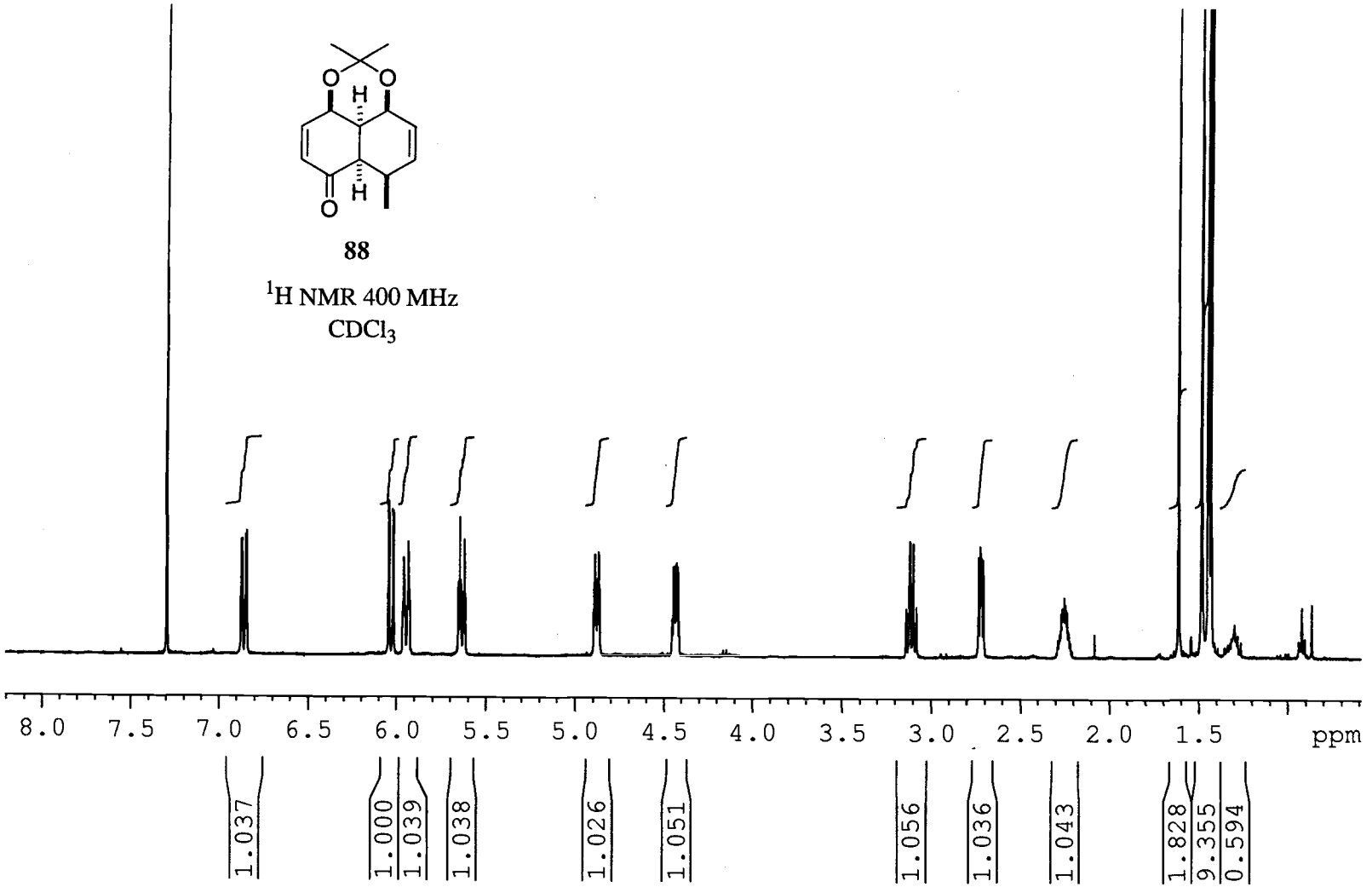
$^1$H NMR 300 MHz

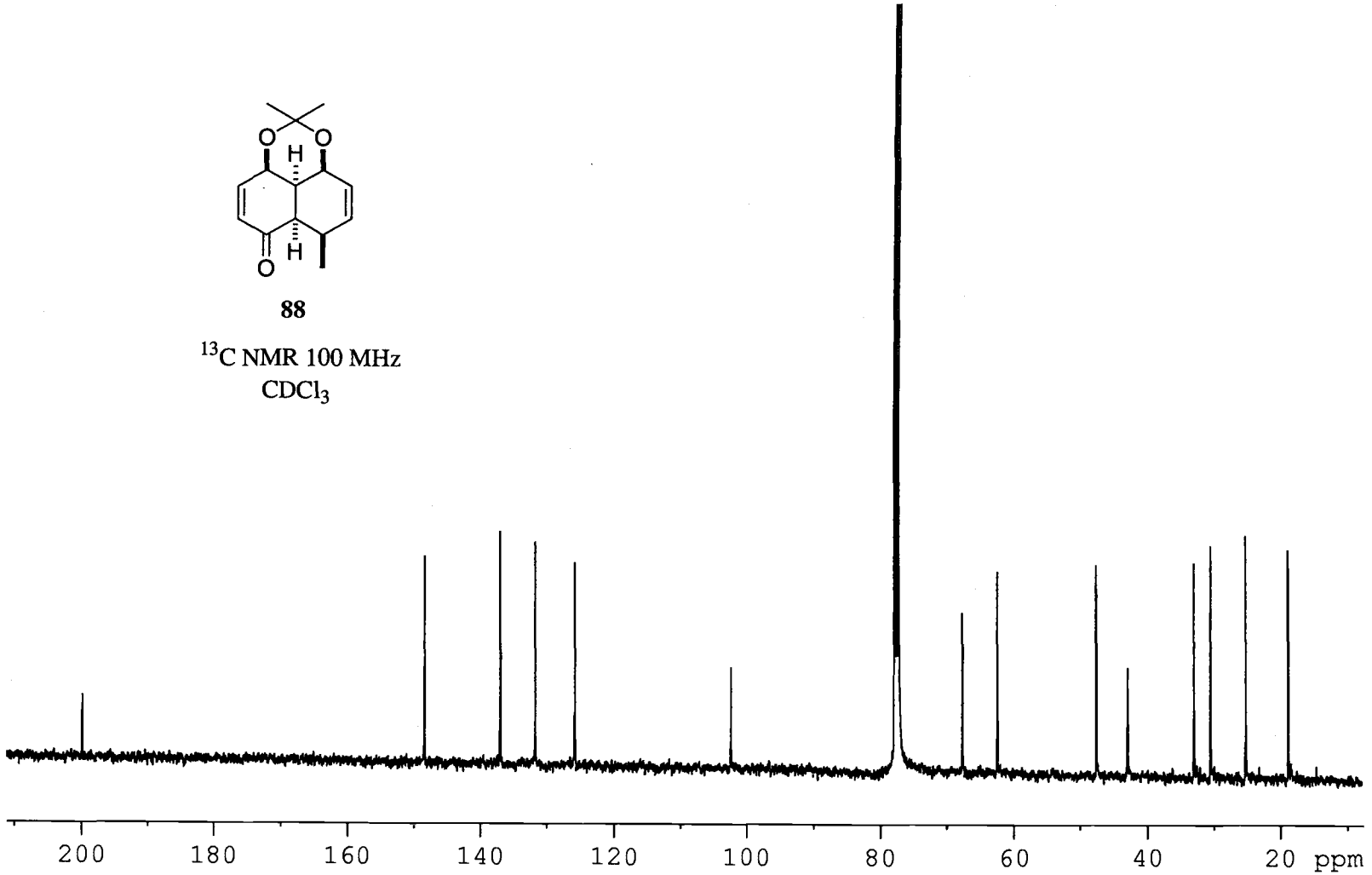
$CDCl_3$




**87**

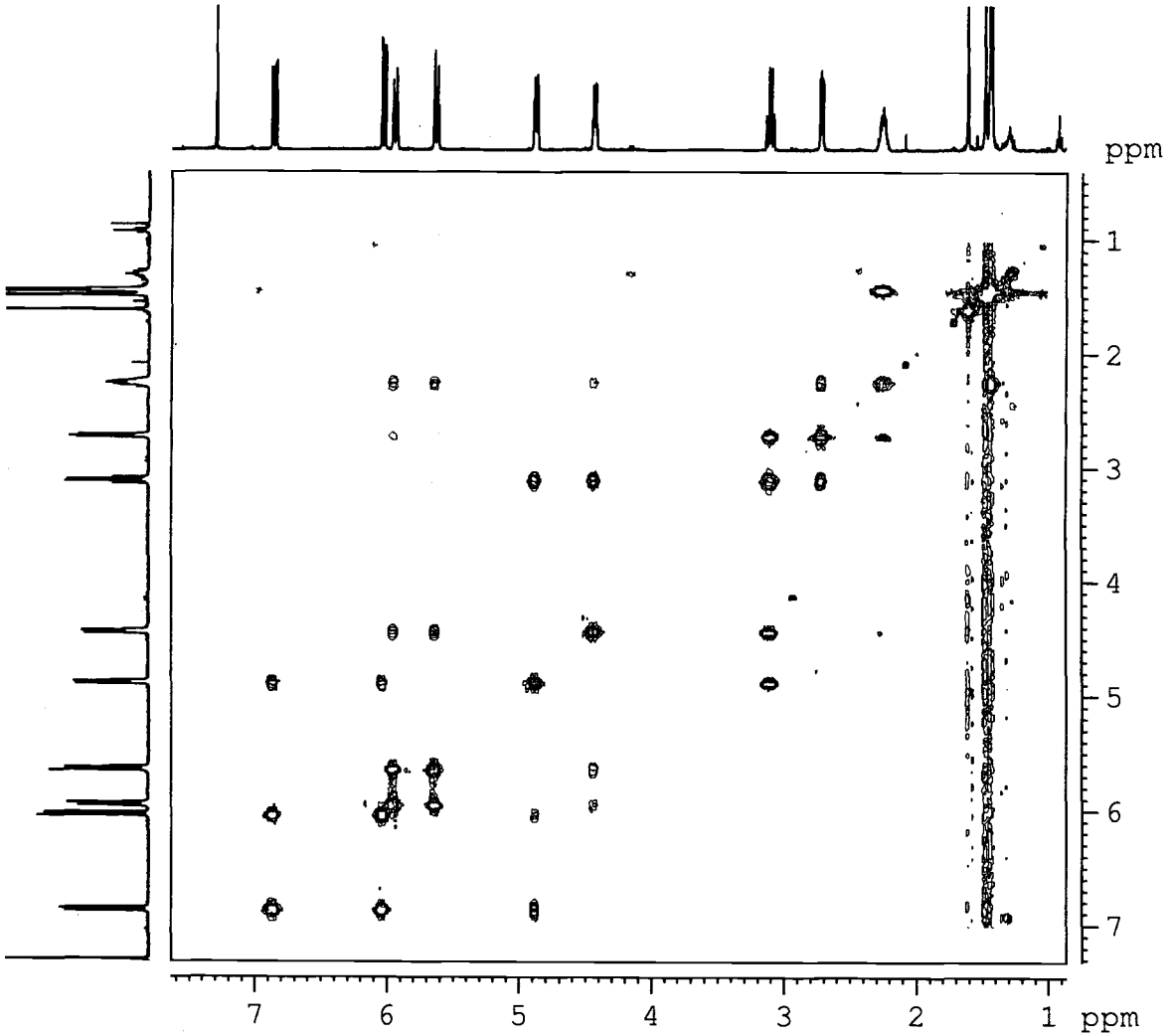
$^{13}C$ NMR 100 MHz
$CDCl_3$

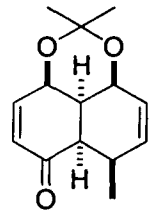

88
1H NMR 400 MHz
CDCl3
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
ppm
1.037
1.000
1.039
1.038
1.026
1.051
1.056
1.036
1.043
1.828
9.355
0.594




**88**

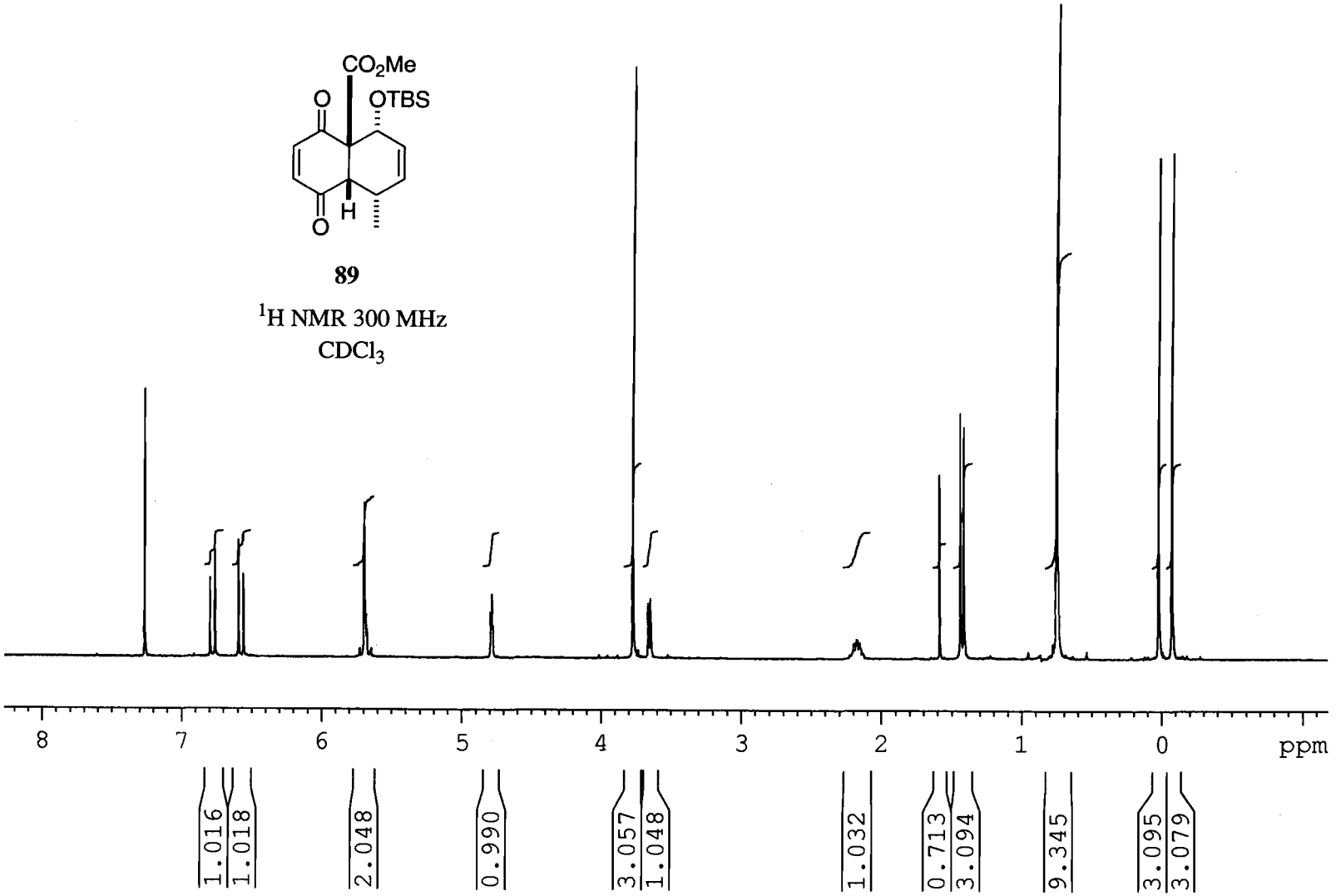
$^{13}C$ NMR 100 MHz
$CDCl_3$

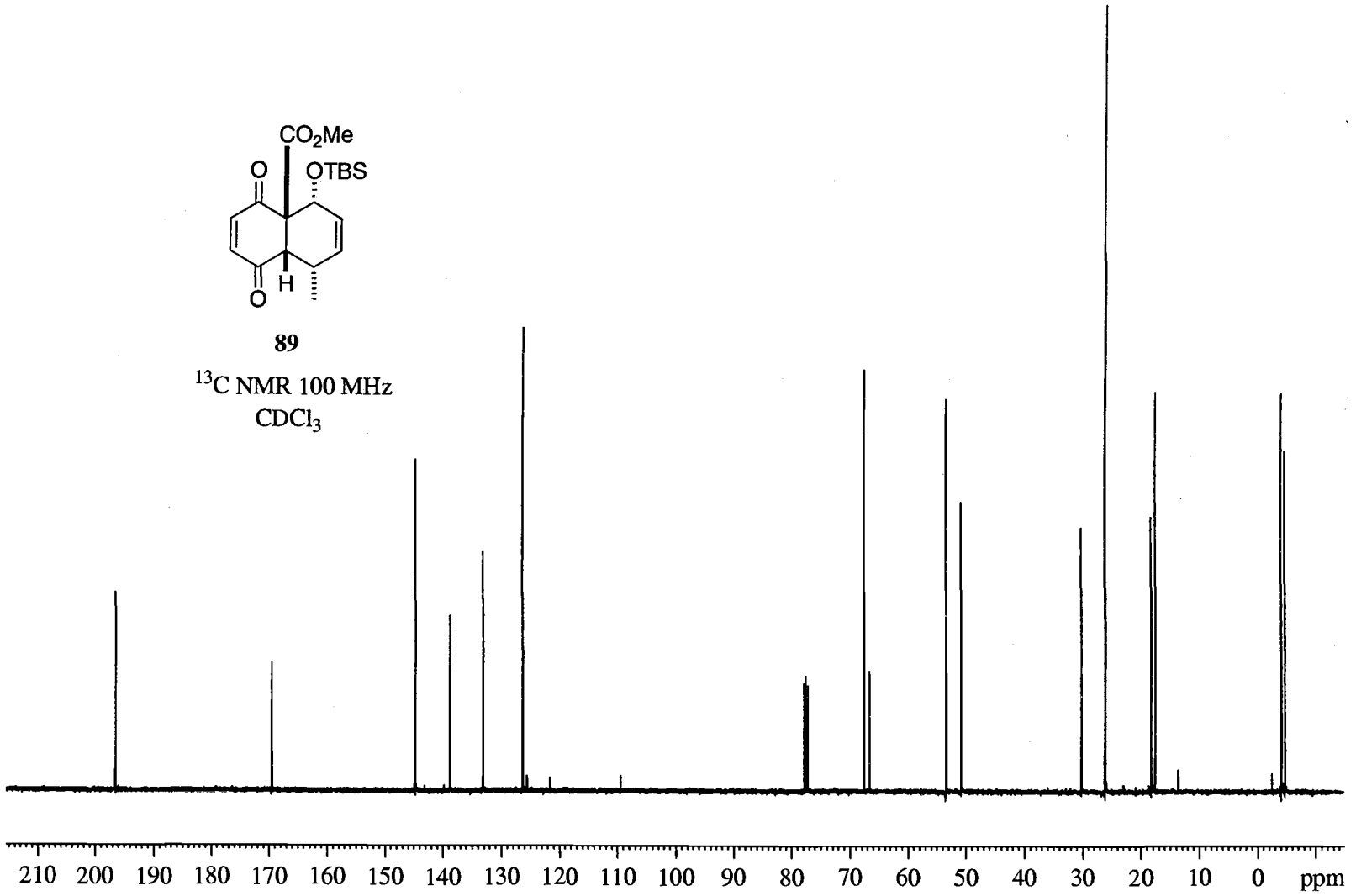


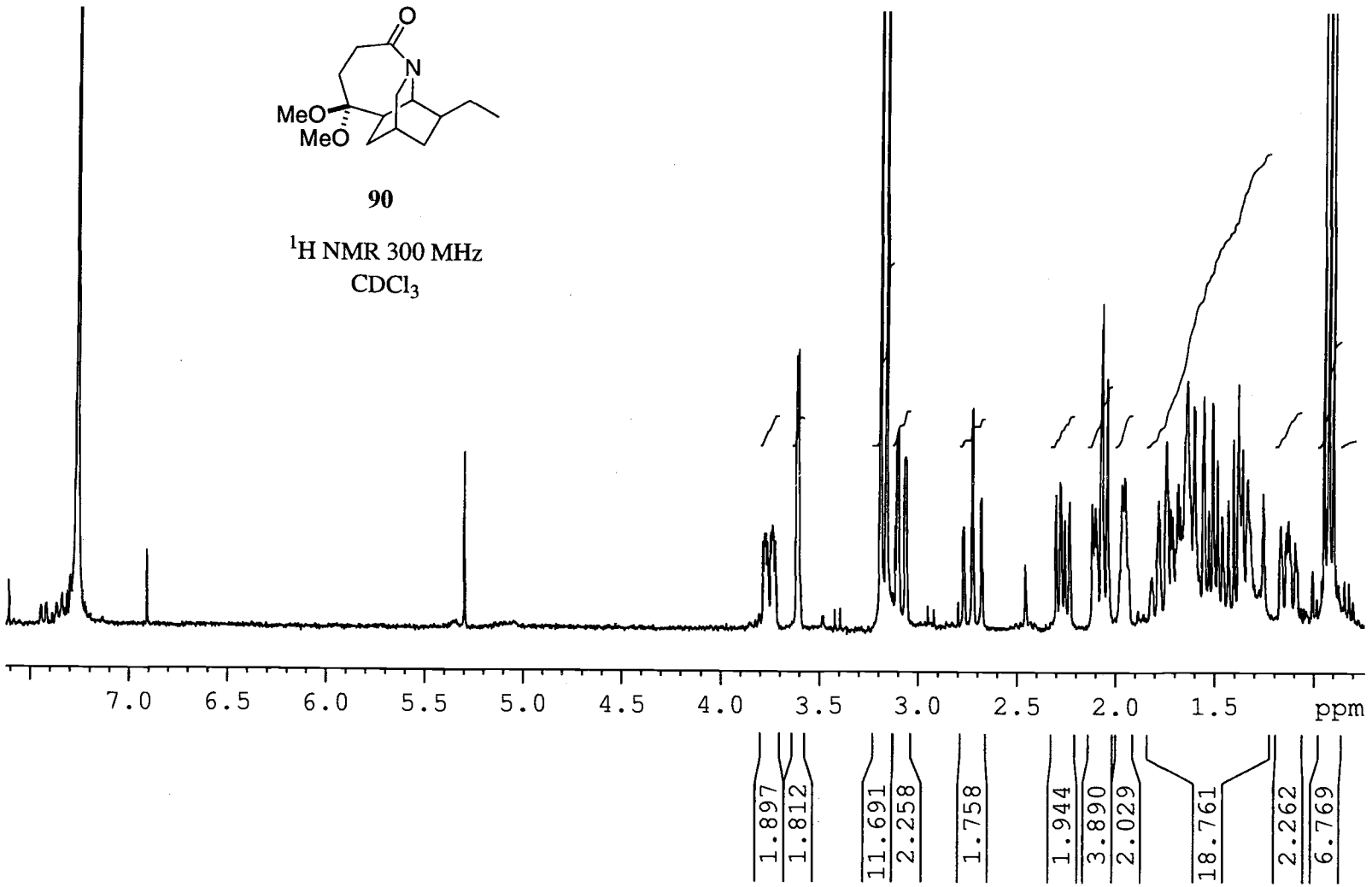



**88**

$^{1}H$-$^{1}H$ 2D NMR 300 MHz
$CDCl_3$

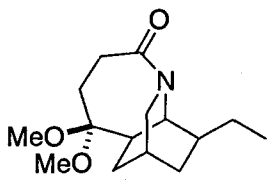

CO2Me
O
OTBS
H
O
89
1H NMR 300 MHz
CDCl3
8
7
6
5
4
3
2
1
0
ppm
1.016
1.018
2.048
0.990
3.057
1.048
1.032
0.713
3.094
9.345
3.095
3.079


CO2Me
O
OTBS
H
O
89
13C NMR 100 MHz
CDCl3
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm



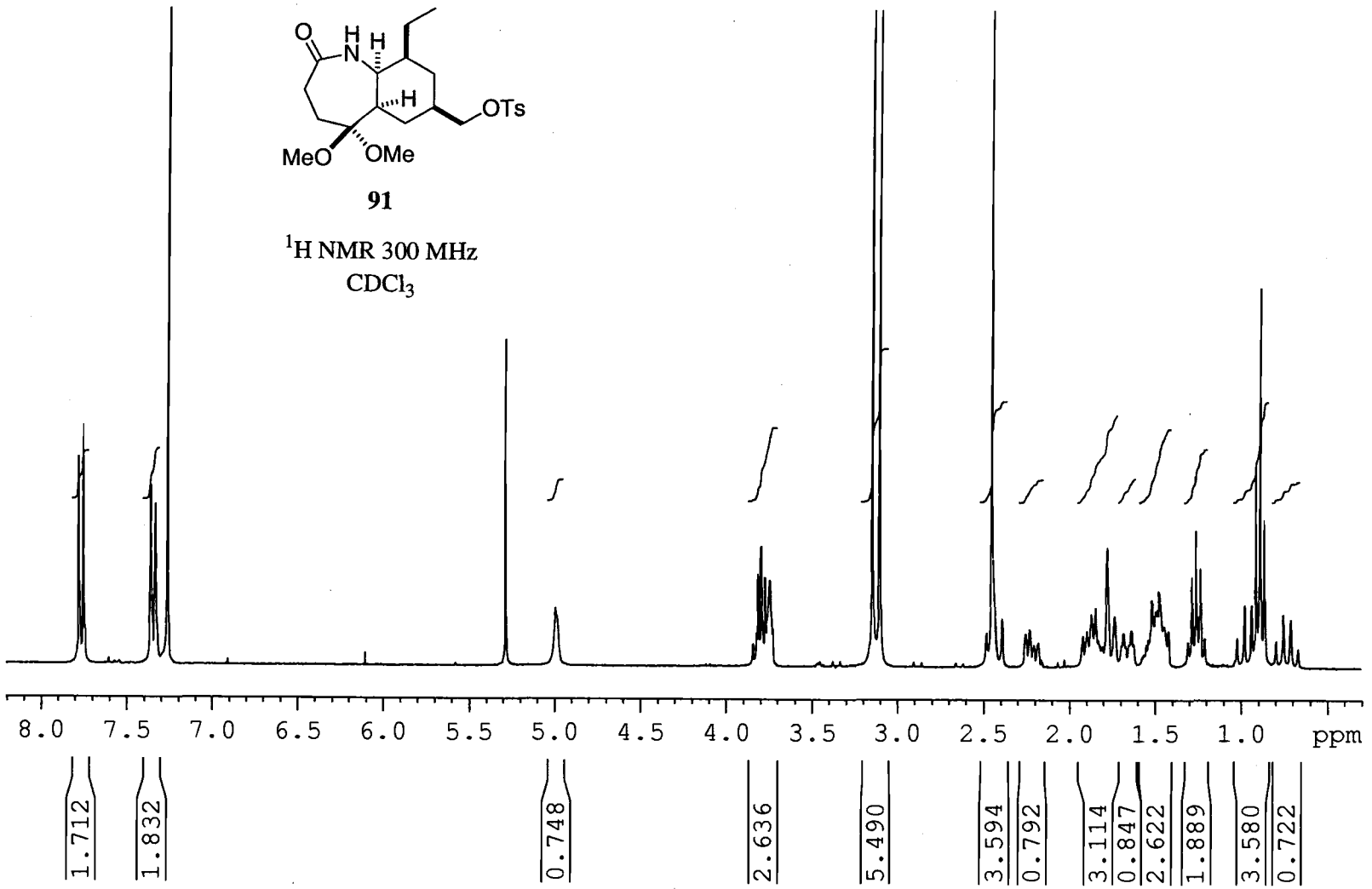

**90**

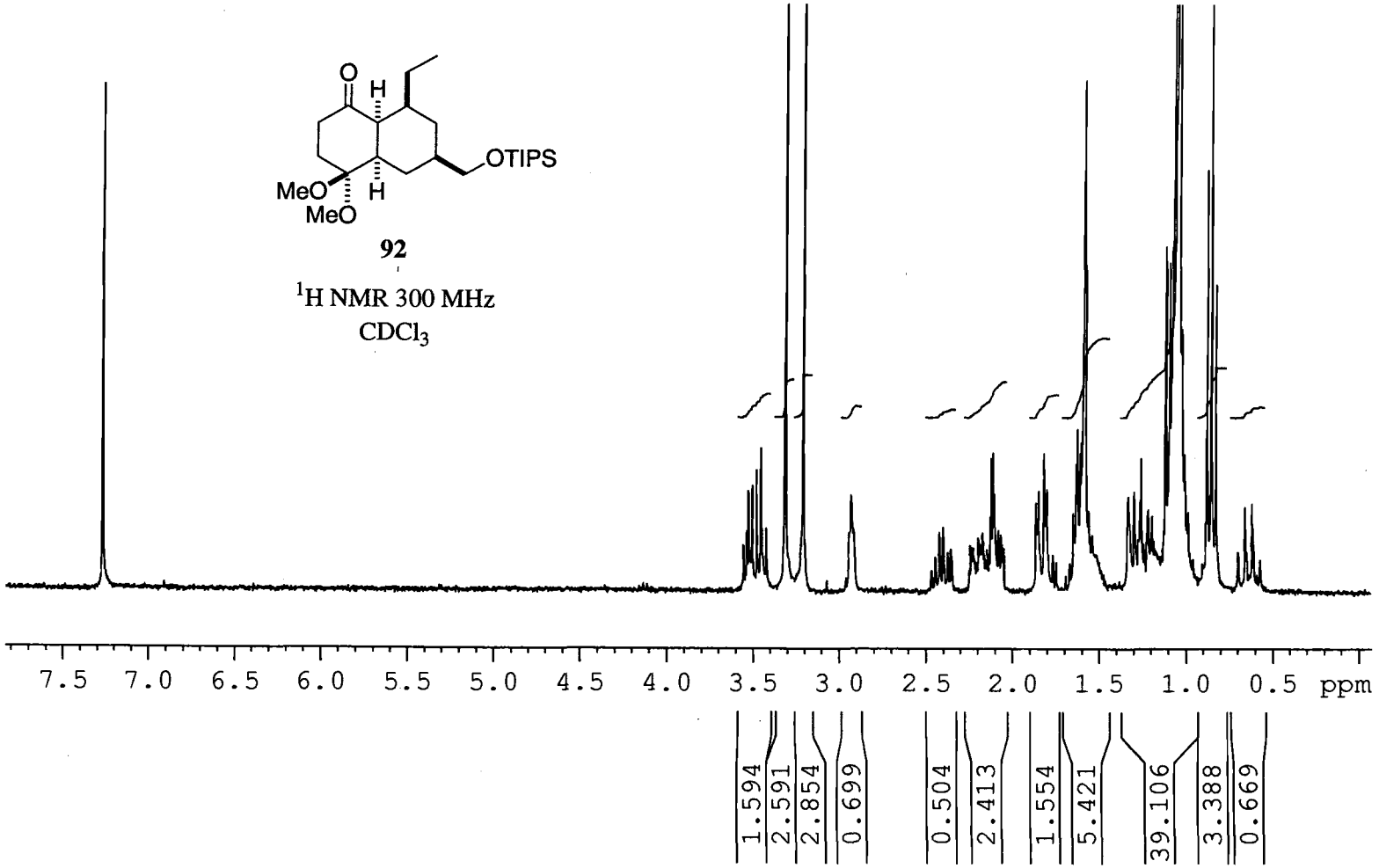
$^{1}$H NMR 300 MHz
$CDCl_3$

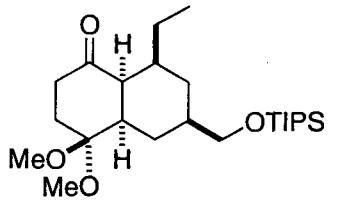



**90**

$^{13}C$ NMR 75 MHz
$CDCl_3$

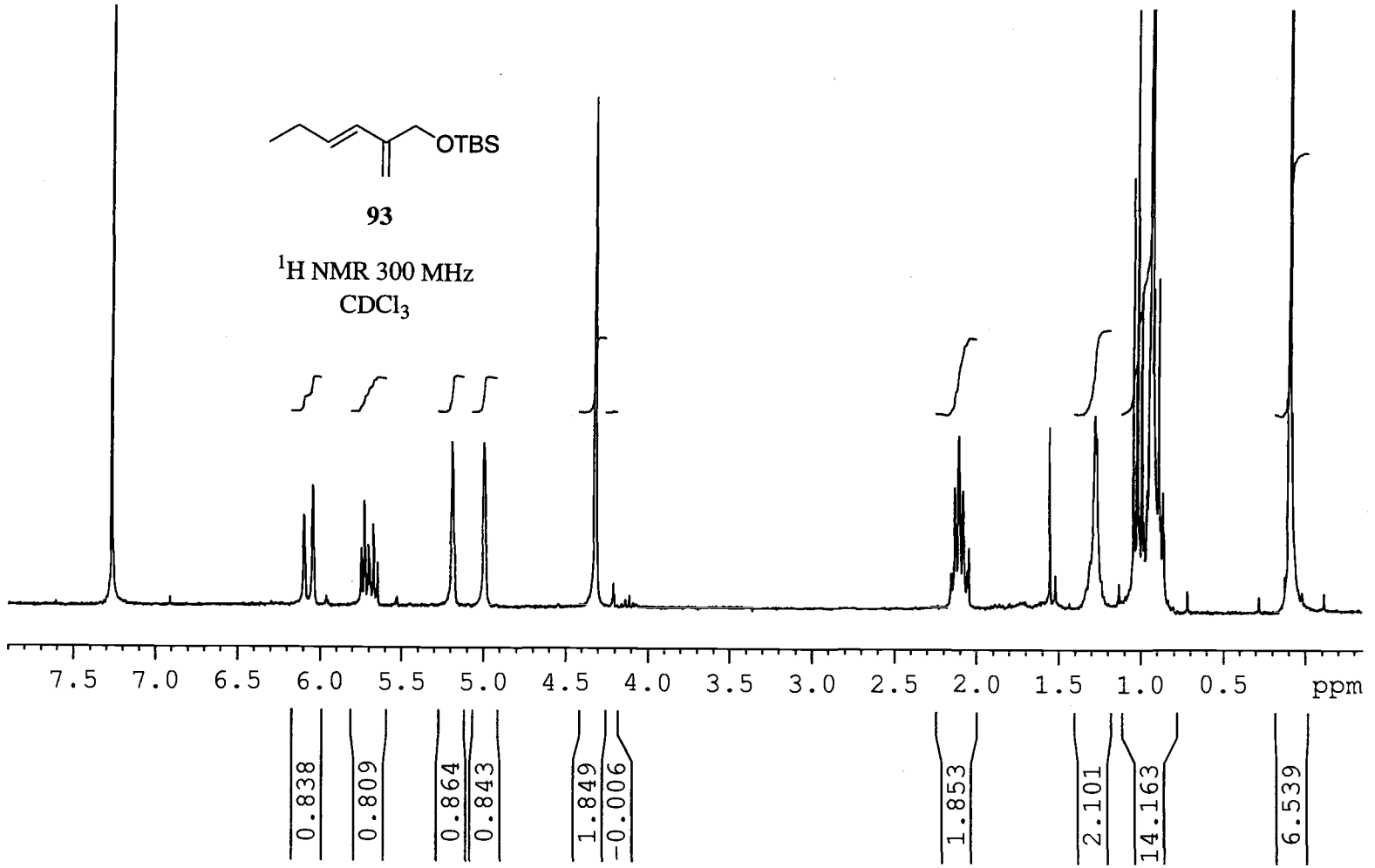

O
H
N
H
H
OTs
MeO
OMe
91
1H NMR 300 MHz
CDCl3
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm
1.712
1.832
0.748
2.636
5.490
3.594
0.792
3.114
0.847
2.622
1.889
3.580
0.722

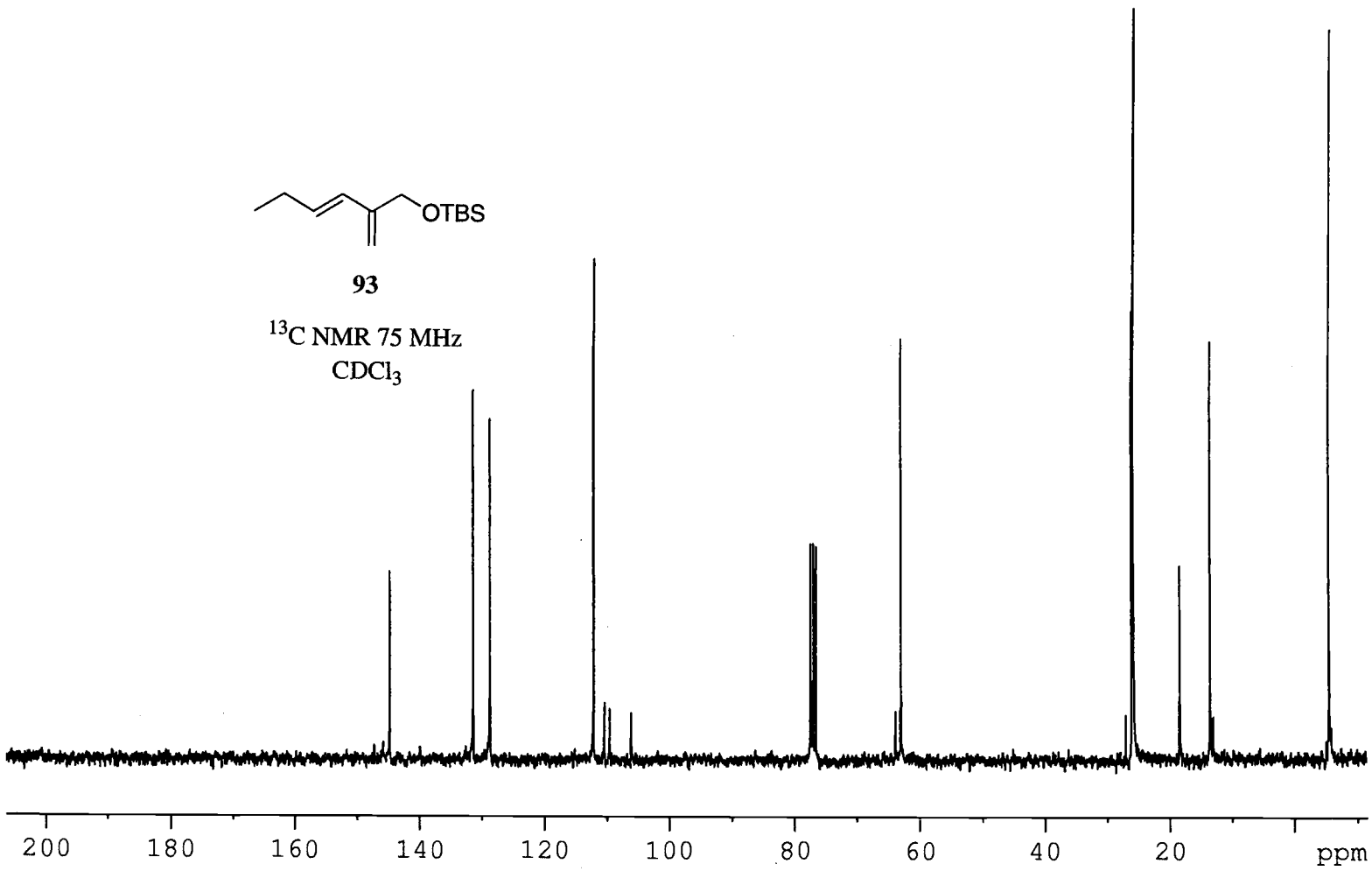

O
H
OTIPS
MeO
MeO
H
92
1H NMR 300 MHz
CDCl3
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
1.594
2.591
2.854
0.699
0.504
2.413
1.554
5.421
39.106
3.388
0.669

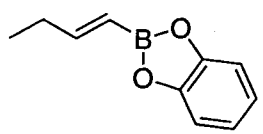



**92**

$^{13}C$ NMR 75 MHz
$CDCl_3$

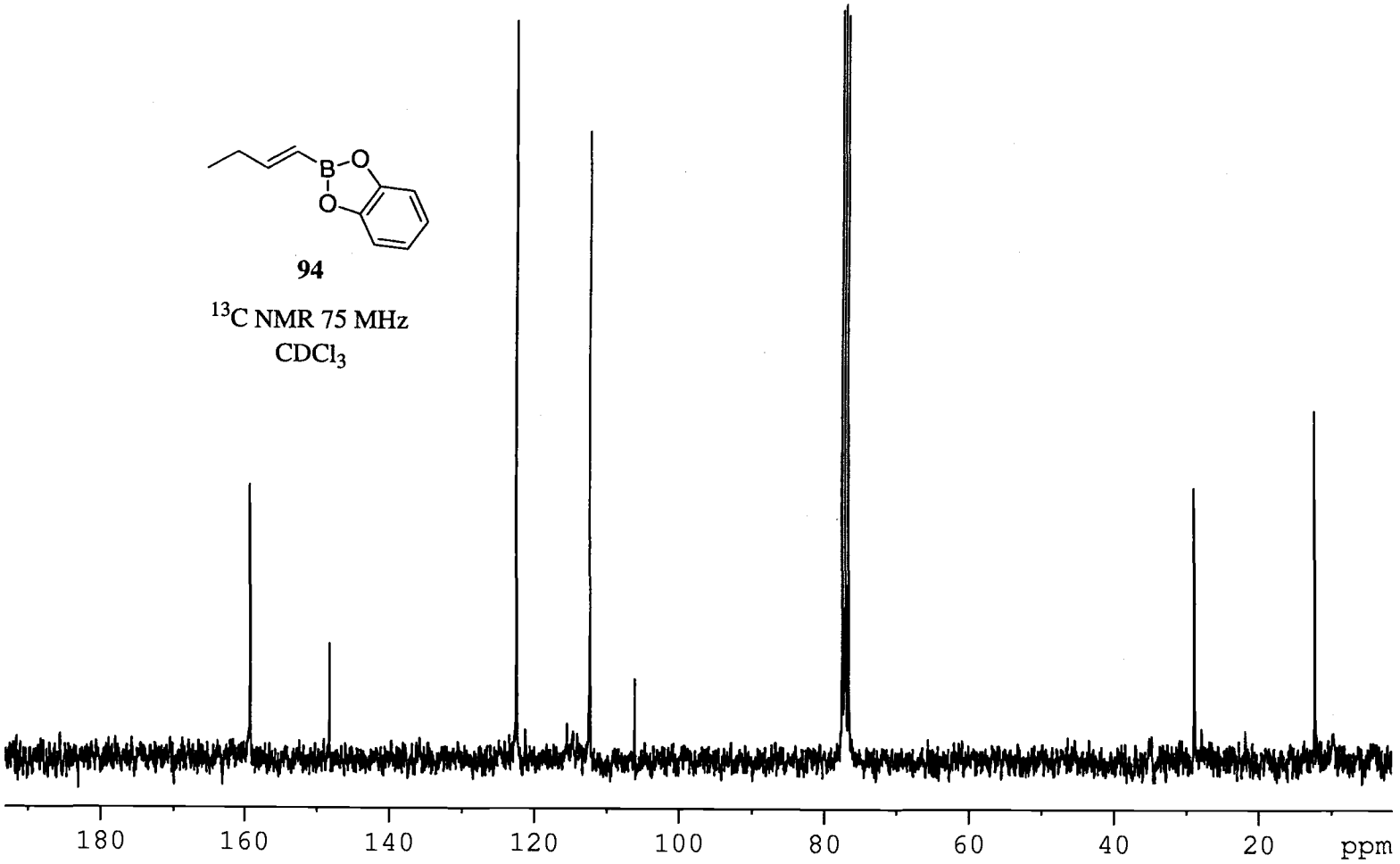

OTBS
93
1H NMR 300 MHz
CDCl3
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
0.838
0.809
0.864
0.843
1.849
-0.006
1.853
2.101
14.163
6.539


OTBS
93
$^{13}$C NMR 75 MHz
$CDCl_3$
200
180
160
140
120
100
80
60
40
20
ppm



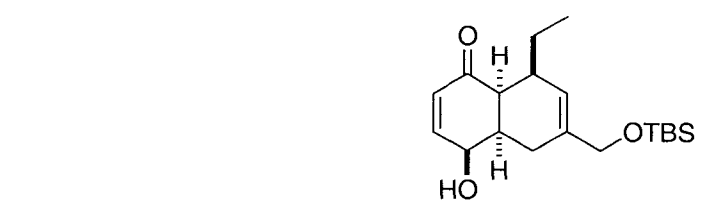
**94**

$^1$H NMR 300 MHz
$CDCl_3$




**94**

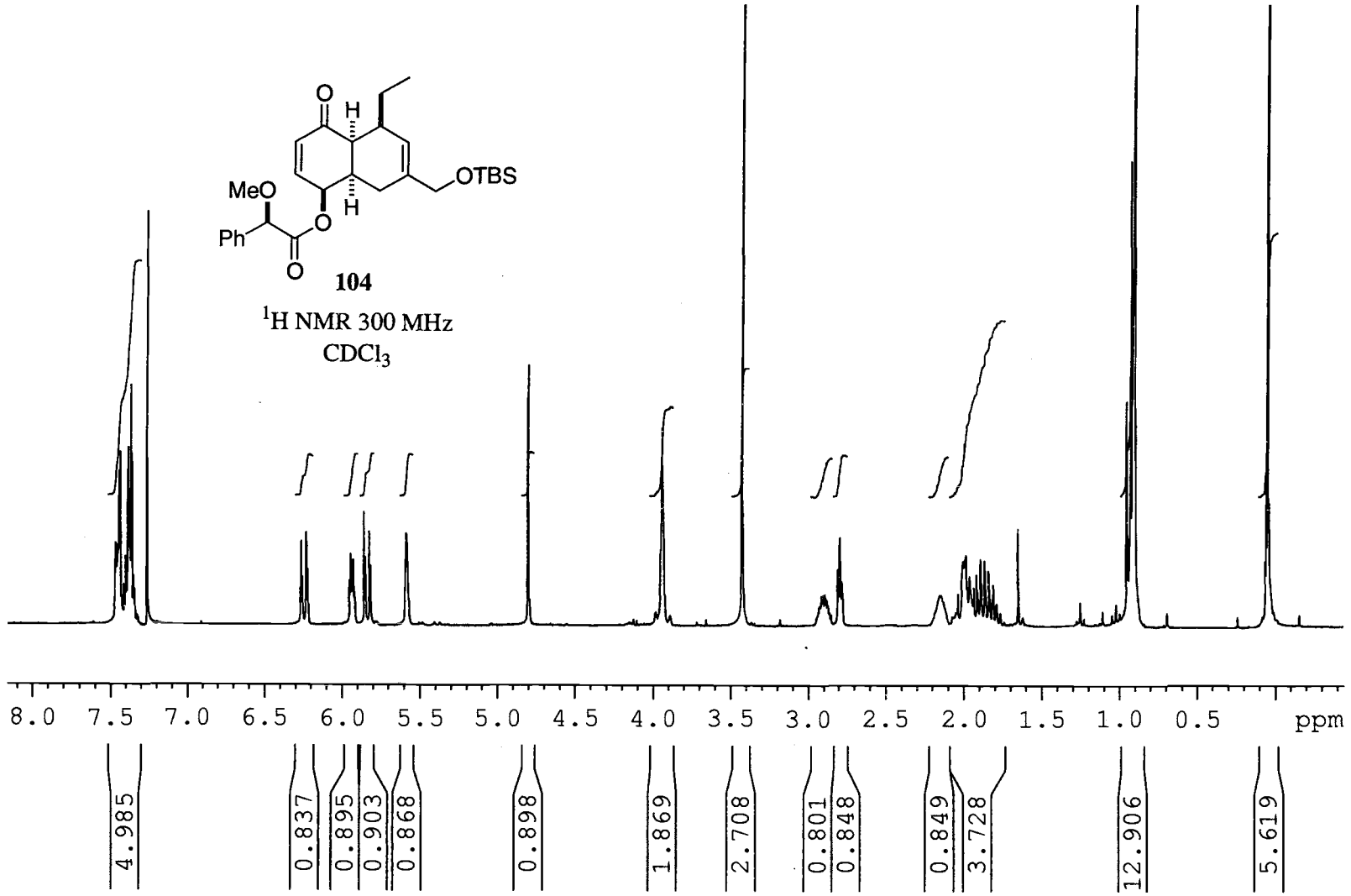
$^{13}C$ NMR 75 MHz
$CDCl_3$

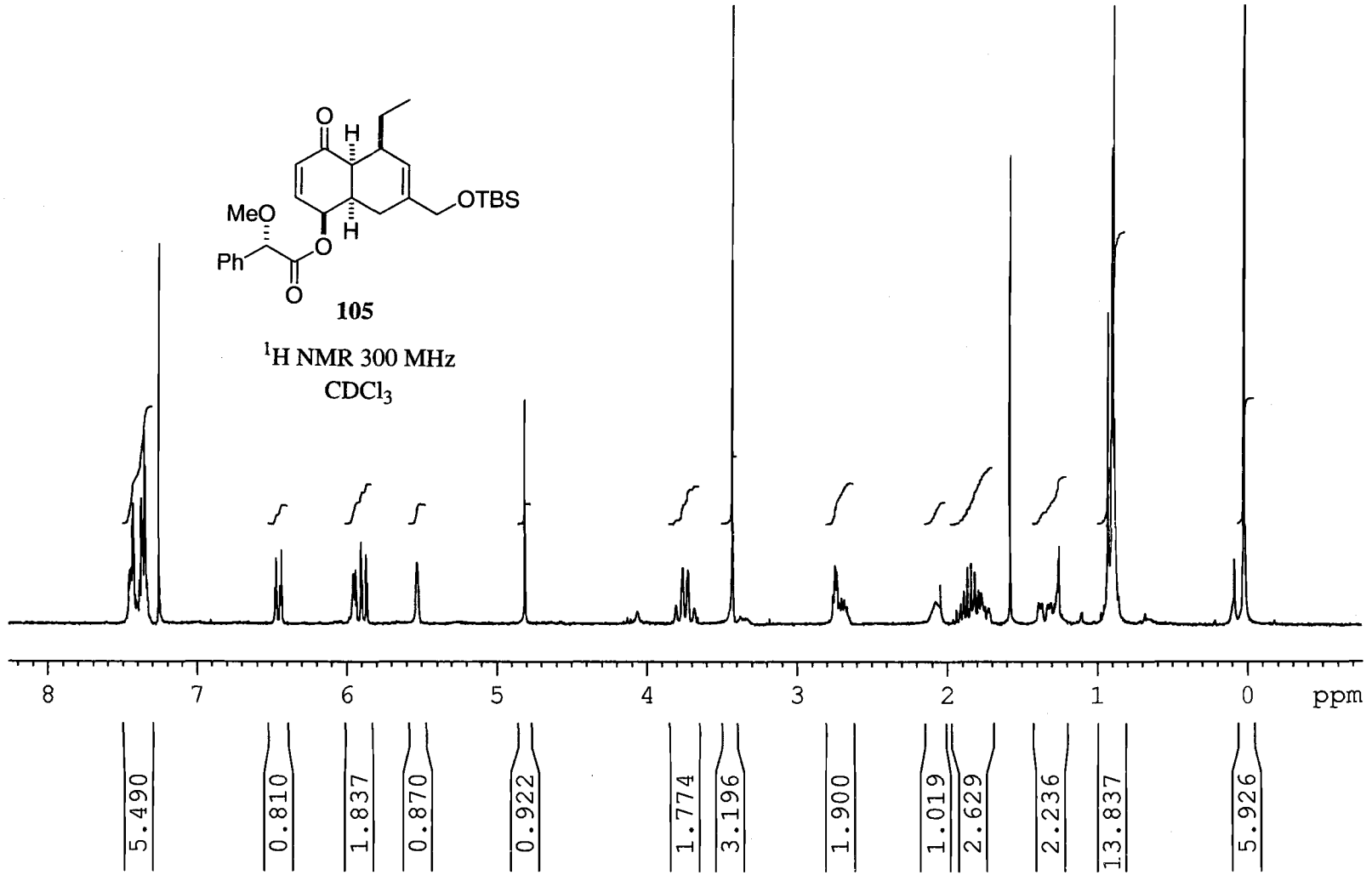


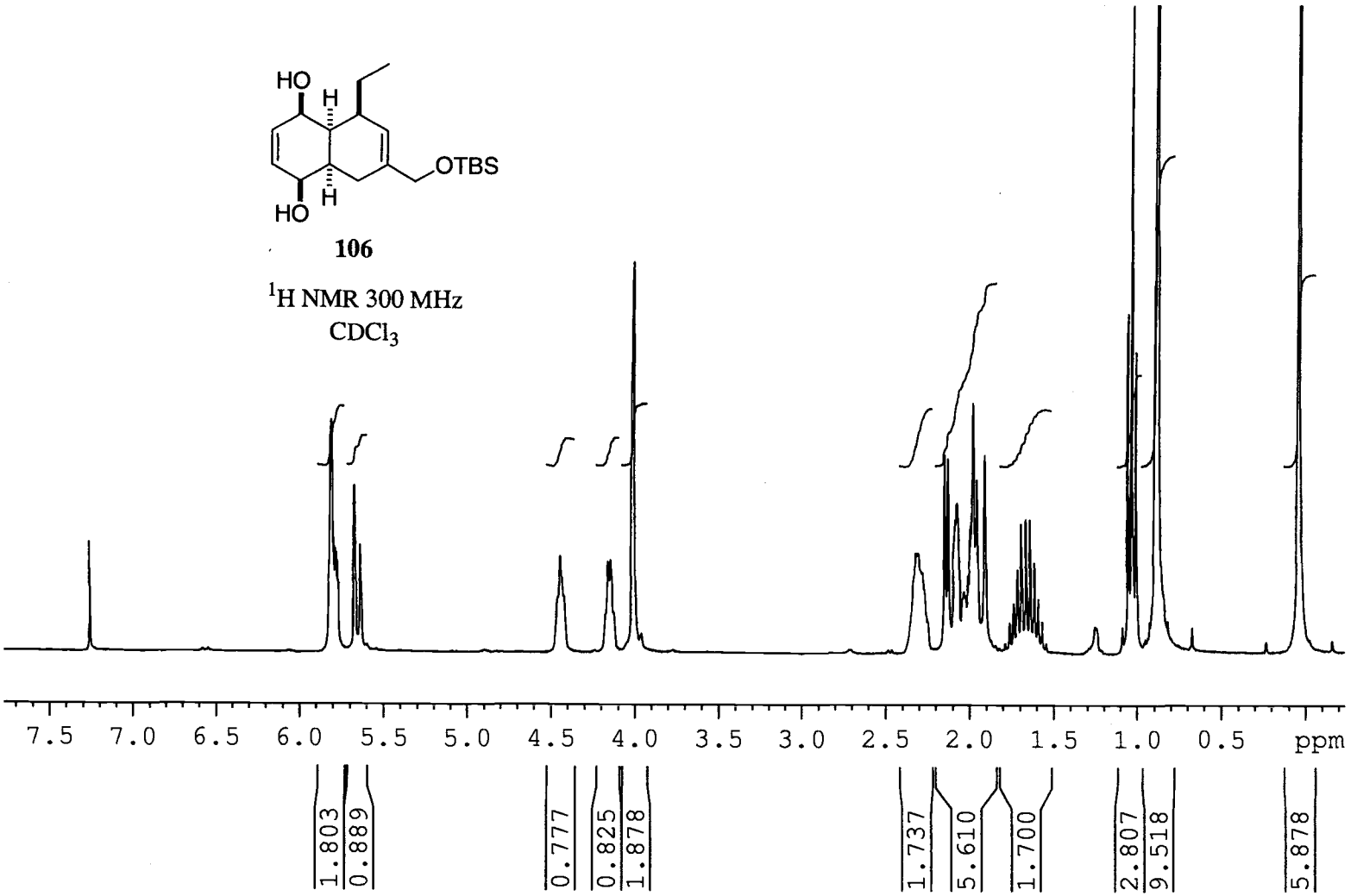

**100**

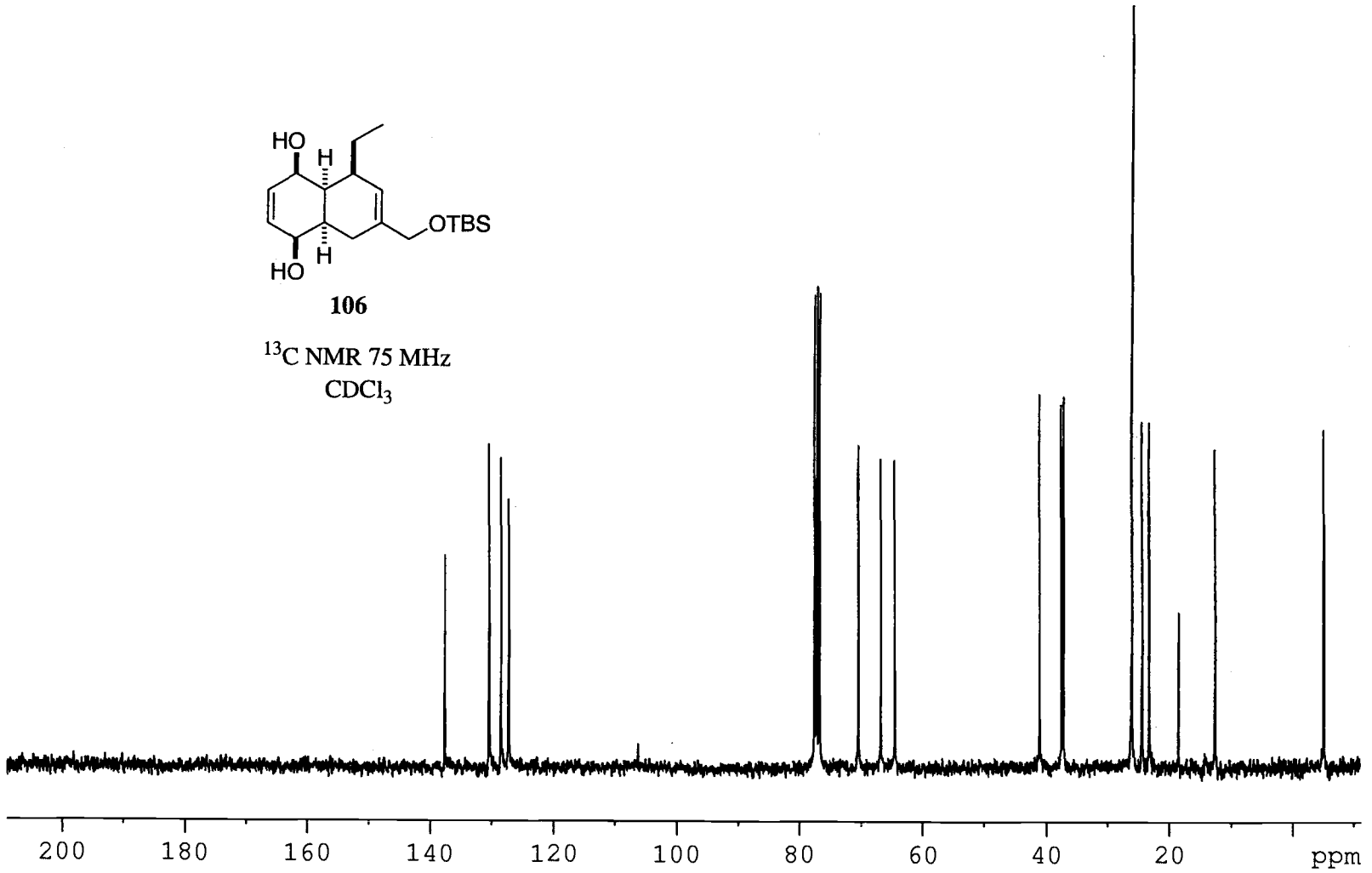
$^1$H NMR 300 MHz

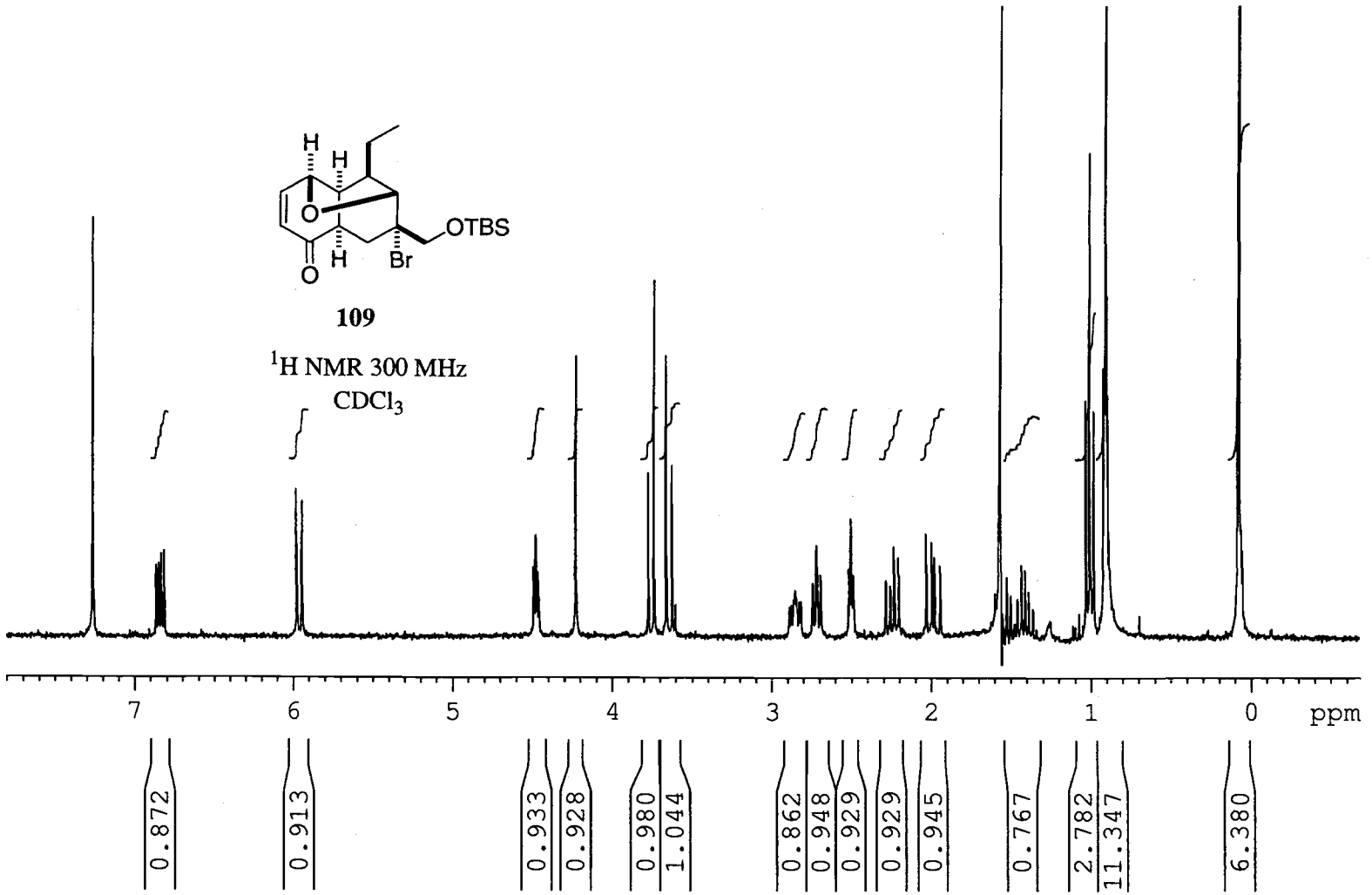
$CDCl_3$

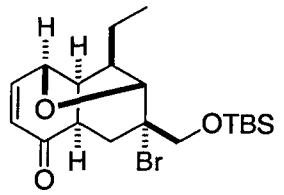

O
H
MeO
Ph
O
O
H
OTBS
O
104
$^1$H NMR 300 MHz
$CDCl_3$
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
4.985
0.837
0.895
0.903
0.868
0.898
1.869
2.708
0.801
0.848
0.849
3.728
12.906
5.619


O
H
MeO
OTBS
H
Ph
O
O
105
$^1$H NMR 300 MHz
$CDCl_3$
8
7
6
5
4
3
2
1
0
ppm
5.490
0.810
1.837
0.870
0.922
1.774
3.196
1.900
1.019
2.629
2.236
13.837
5.926


HO
H
OTBS
H
HO
106
1H NMR 300 MHz
CDCl3
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
1.803
0.889
0.777
0.825
1.878
1.737
5.610
1.700
2.807
9.518
5.878

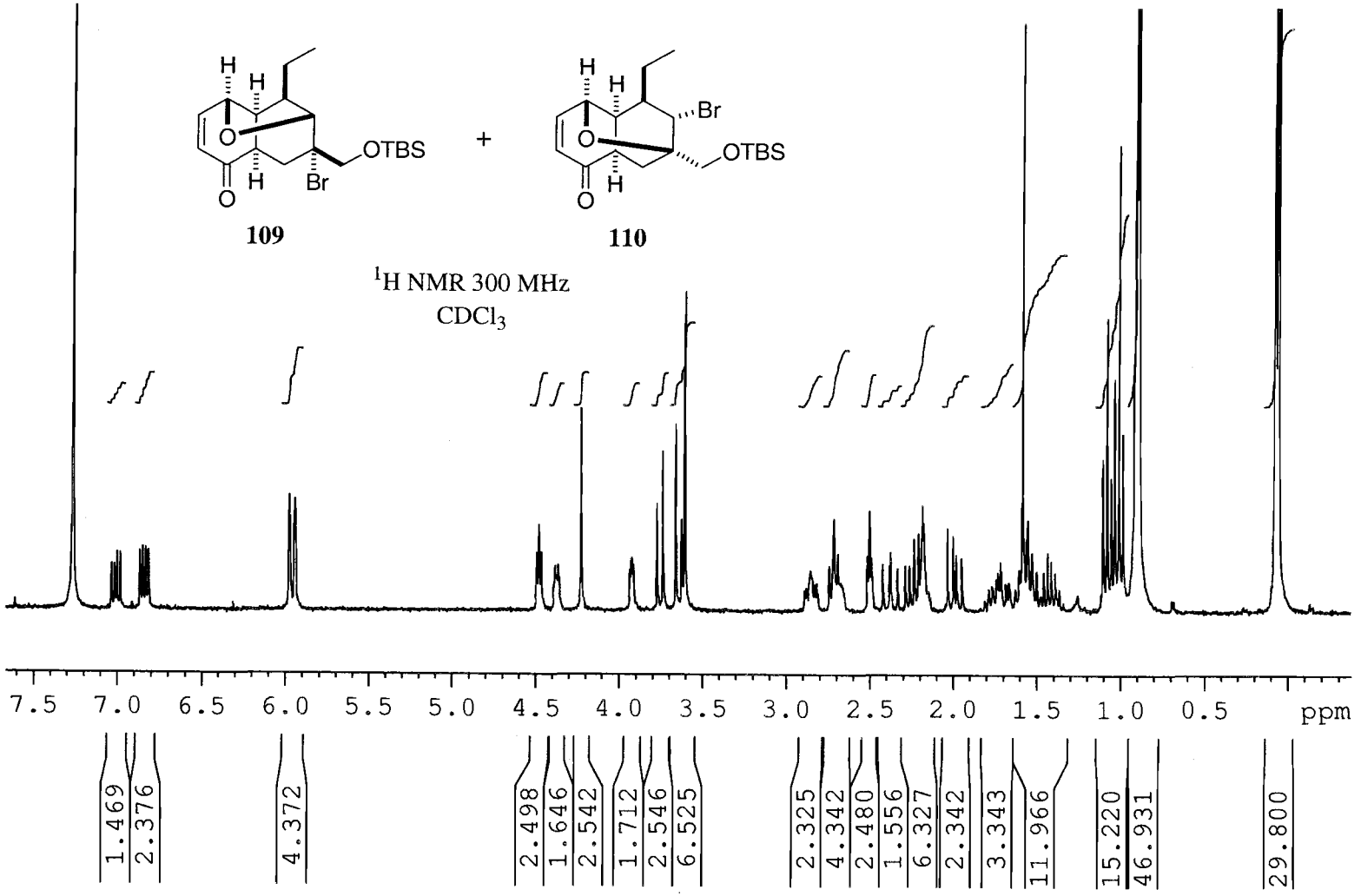

HO
H
OTBS
H
HO
106
$^{13}$C NMR 75 MHz
$CDCl_3$
200
180
160
140
120
100
80
60
40
20
ppm

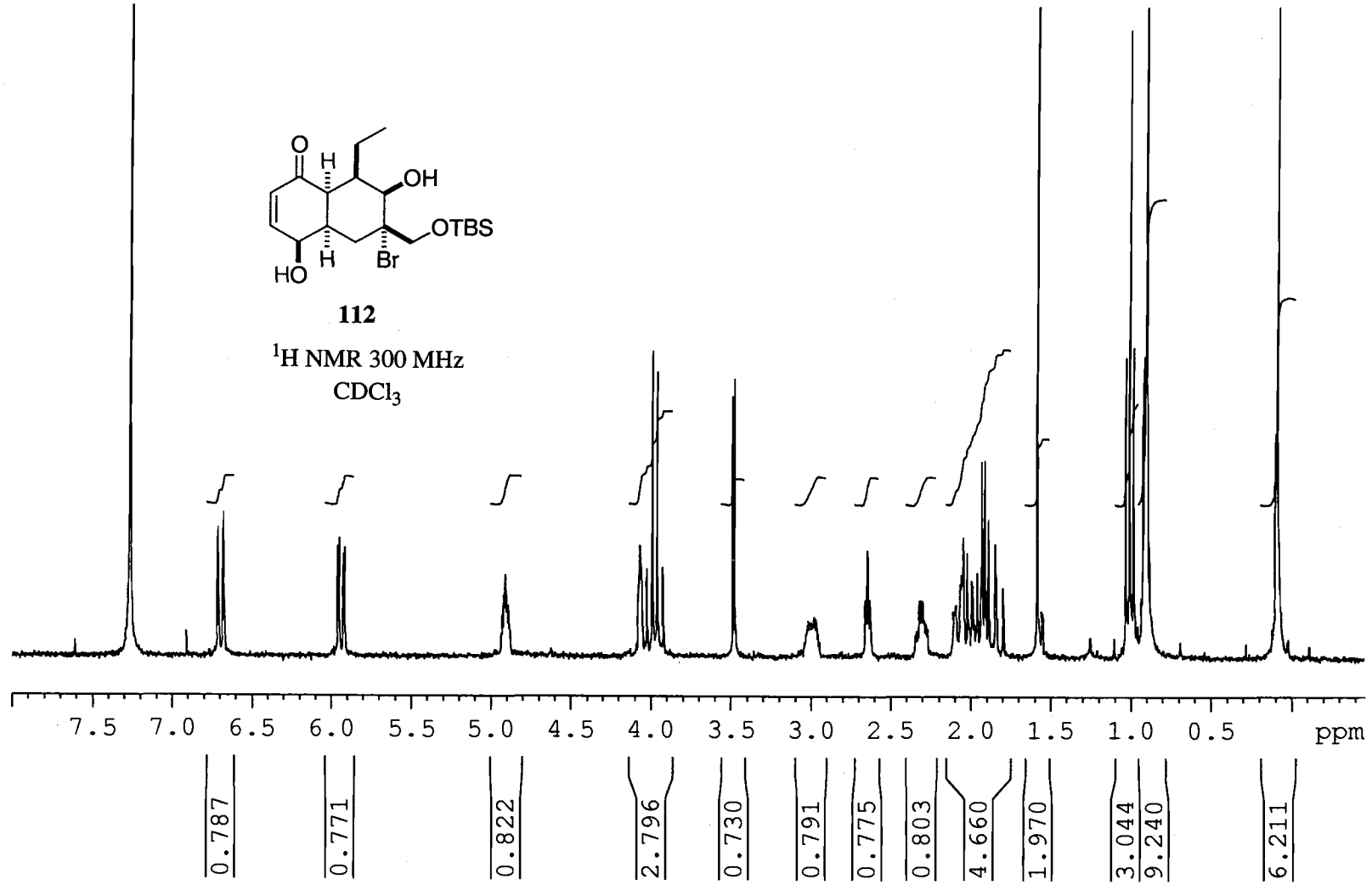

H
H
O
OTBS
H
Br
O
109
$^1$H NMR 300 MHz
$CDCl_3$
7
6
5
4
3
2
1
0
ppm
0.872
0.913
0.933
0.928
0.980
1.044
0.862
0.948
0.929
0.929
0.945
0.767
2.782
11.347
6.380

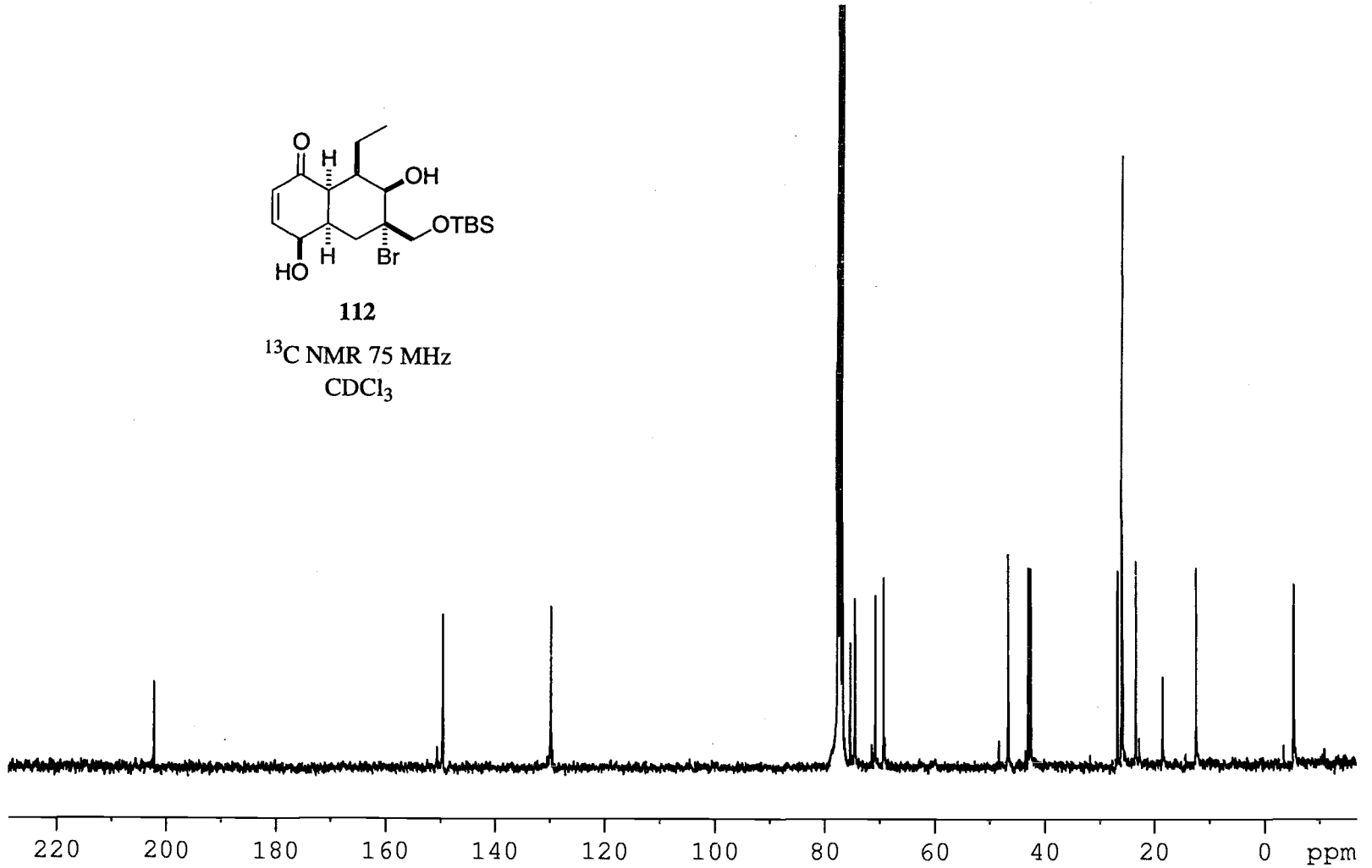



**109**

$^{13}C$ NMR 75 MHz
$CDCl_3$


OTBS
Br
109
+
Br
OTBS
110
$^1$H NMR 300 MHz
$CDCl_3$
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
1.469
2.376
4.372
2.498
1.646
2.542
1.712
2.546
6.525
2.325
4.342
2.480
1.556
6.327
2.342
3.343
11.966
15.220
46.931
29.800

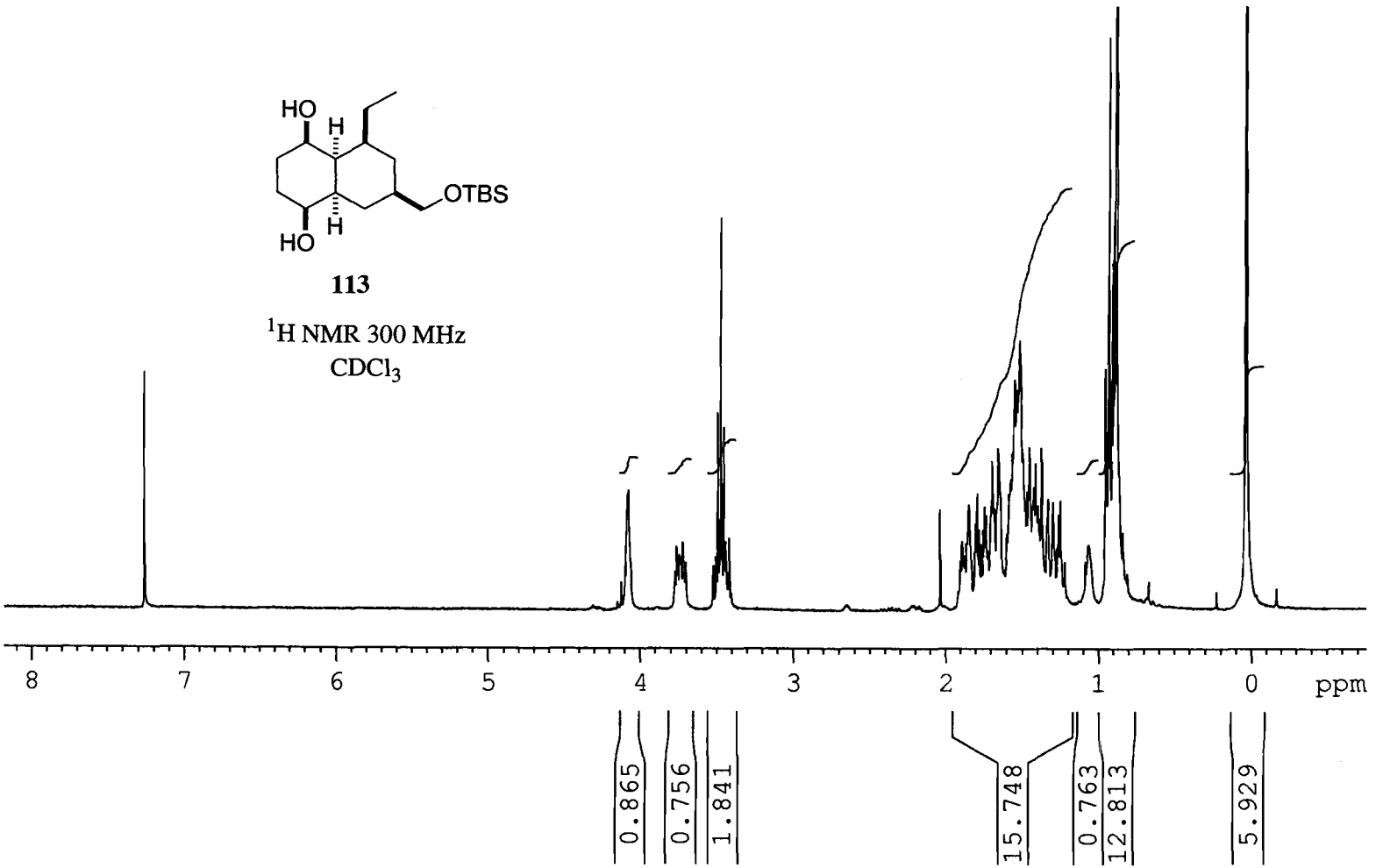

O
H
OH
OTBS
HO
H
Br
112
1H NMR 300 MHz
CDCl3
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
0.787
0.771
0.822
2.796
0.730
0.791
0.775
0.803
4.660
1.970
3.044
9.240
6.211

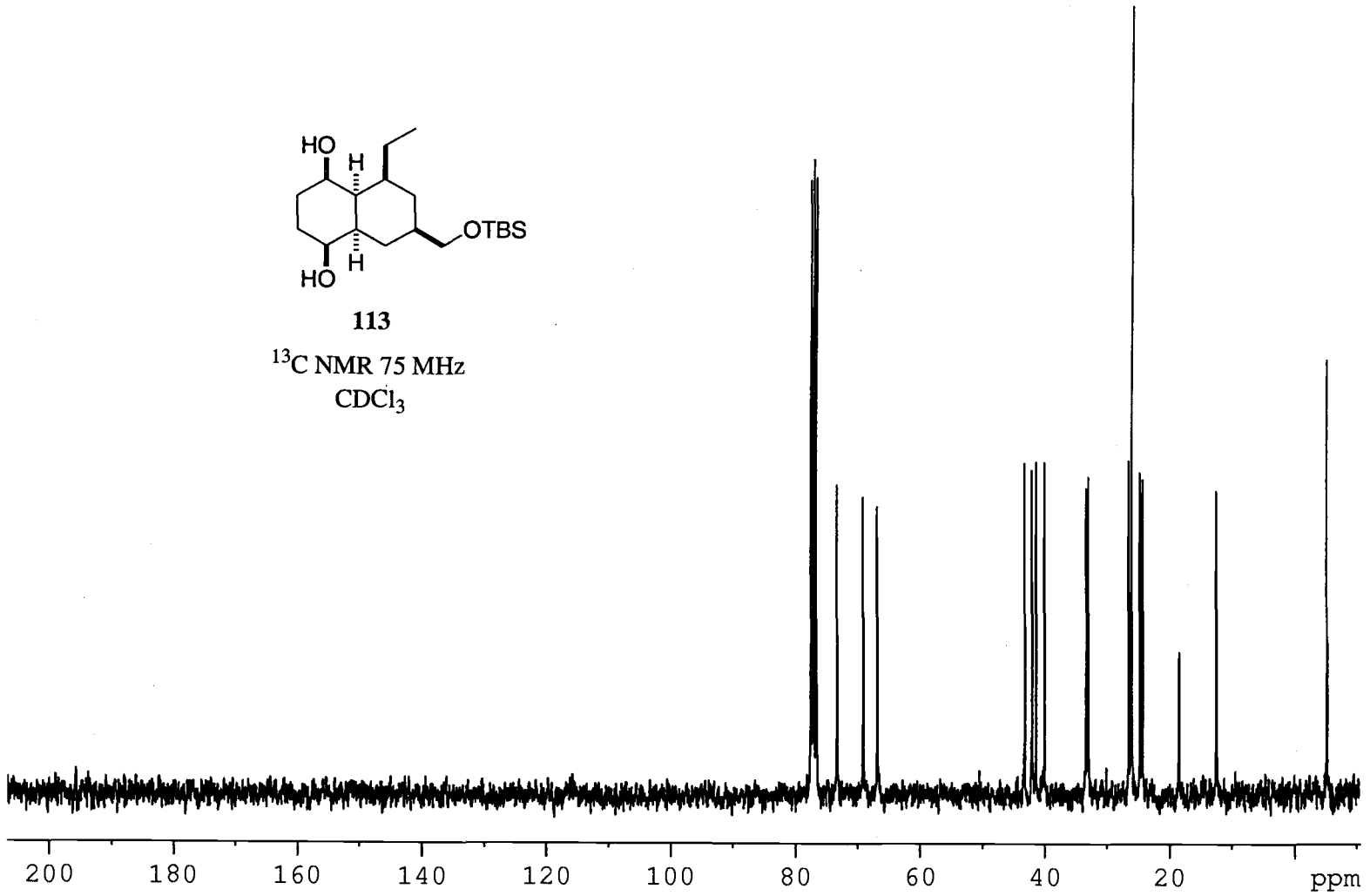



**112**

$^{13}C$ NMR 75 MHz

$CDCl_3$

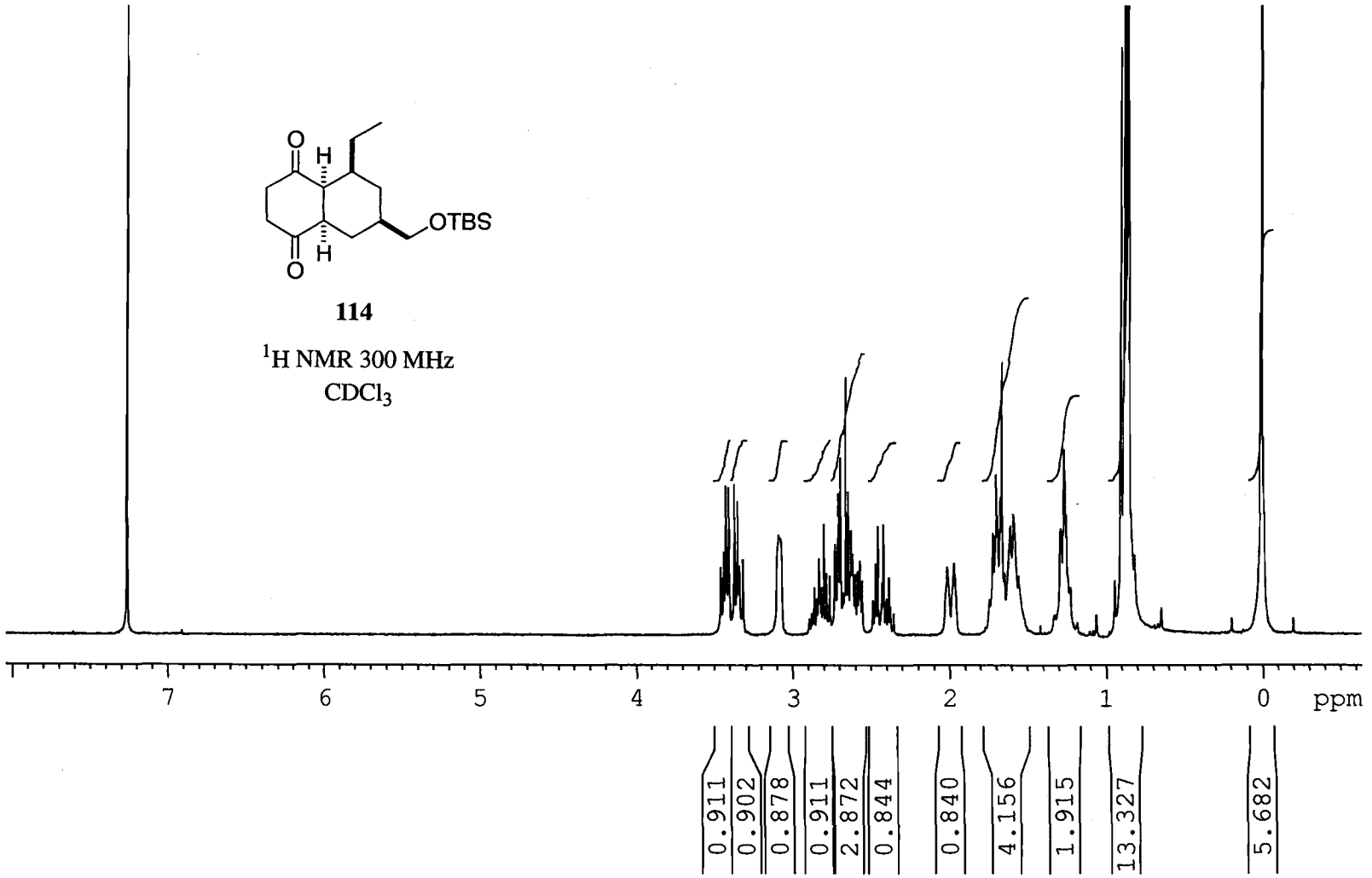

HO
H
OTBS
H
HO
113
$^1$H NMR 300 MHz
$CDCl_3$
8
7
6
5
4
3
2
1
0
ppm
0.865
0.756
1.841
15.748
0.763
12.813
5.929




**113**

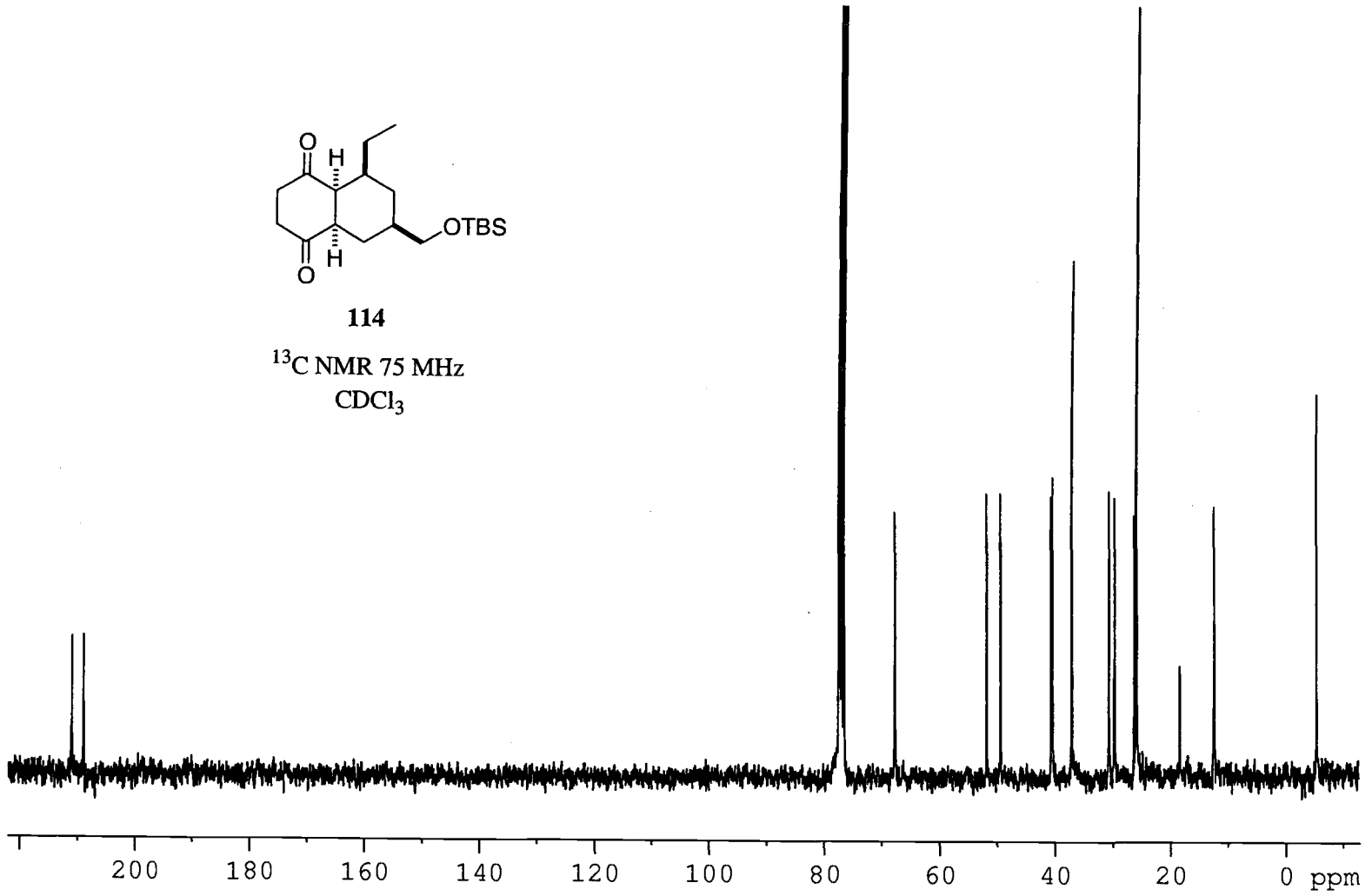
$^{13}C$ NMR 75 MHz

$CDCl_3$




**114**

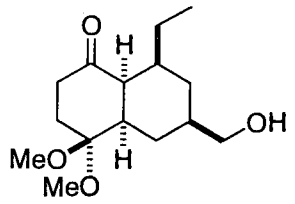
$^1$H NMR 300 MHz
$CDCl_3$




**114**

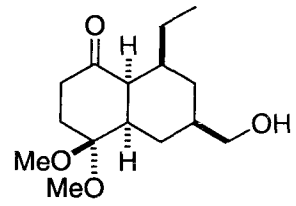
$^{13}C$ NMR 75 MHz

$CDCl_3$



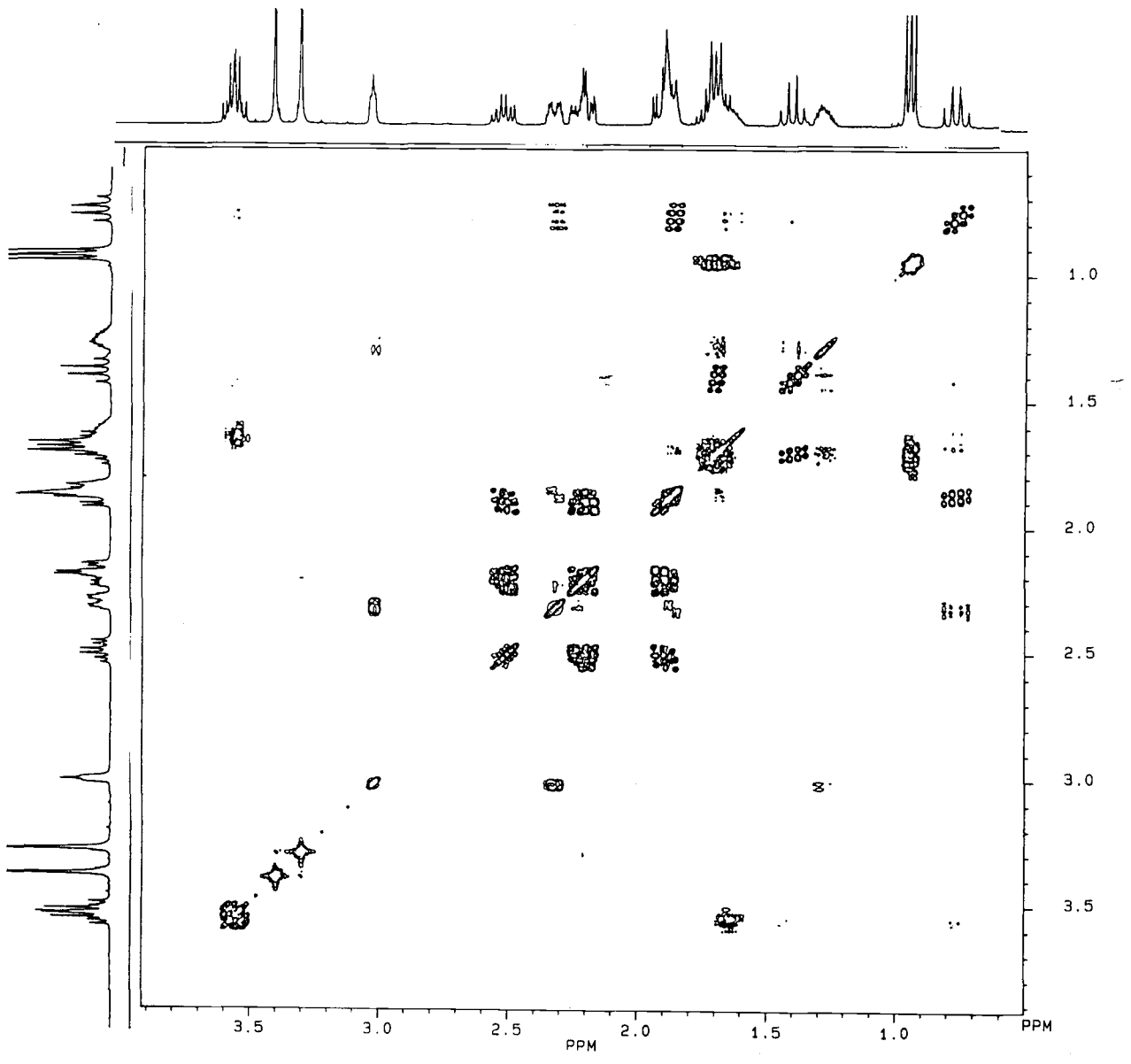

**117**

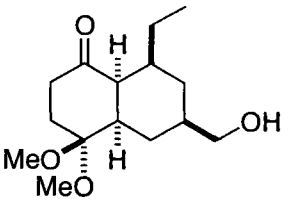
$^1$H NMR 300 MHz
$CDCl_3$




**117**

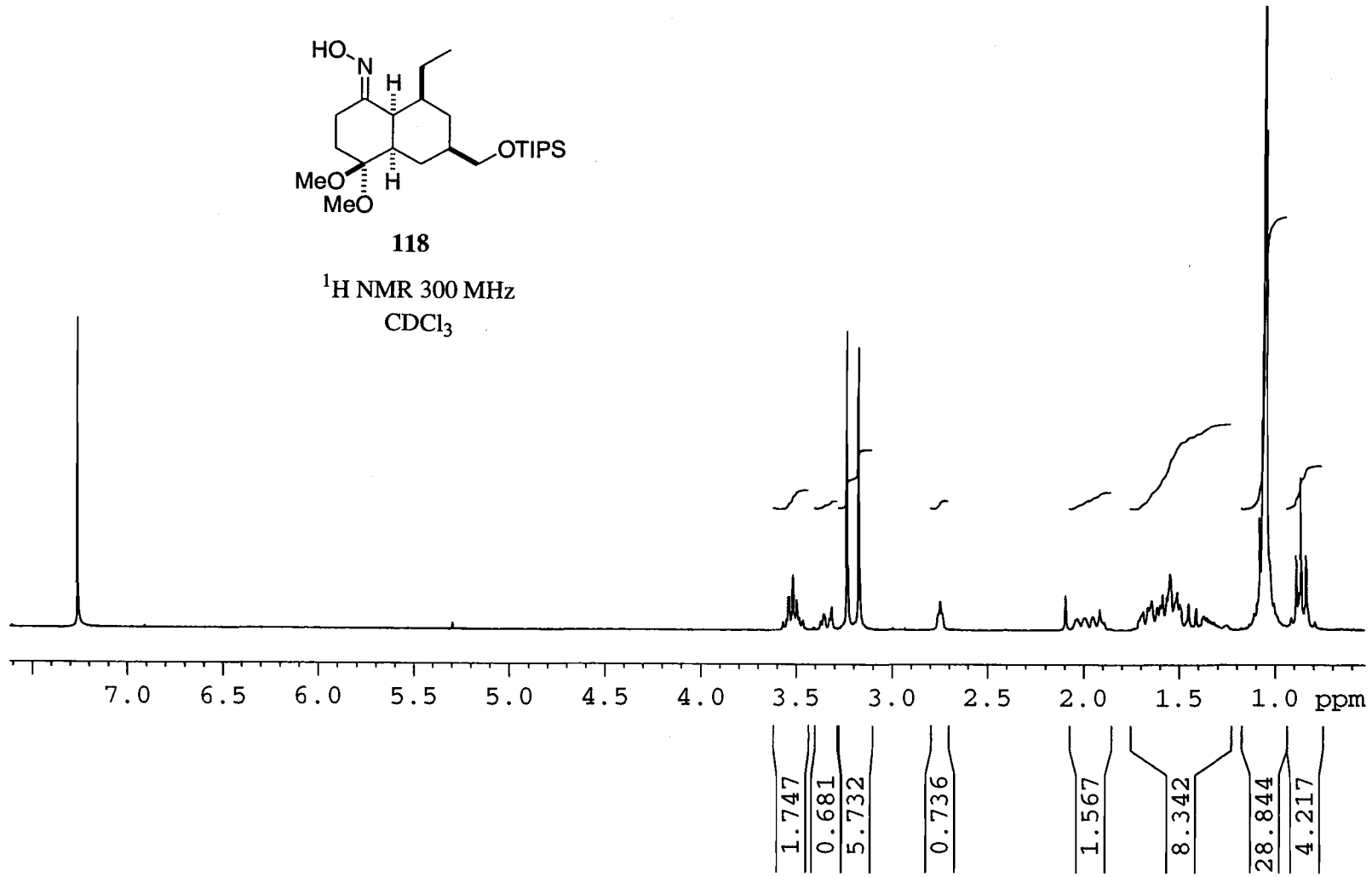
$^{13}C$ NMR 75 MHz
$CDCl_3$




**117**

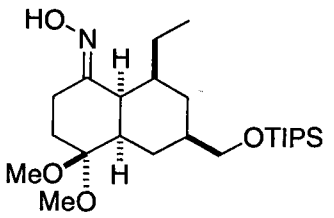
$^{1}H$-$^{1}H$ 2D NMR 300 MHz
$CDCl_3$




**118**

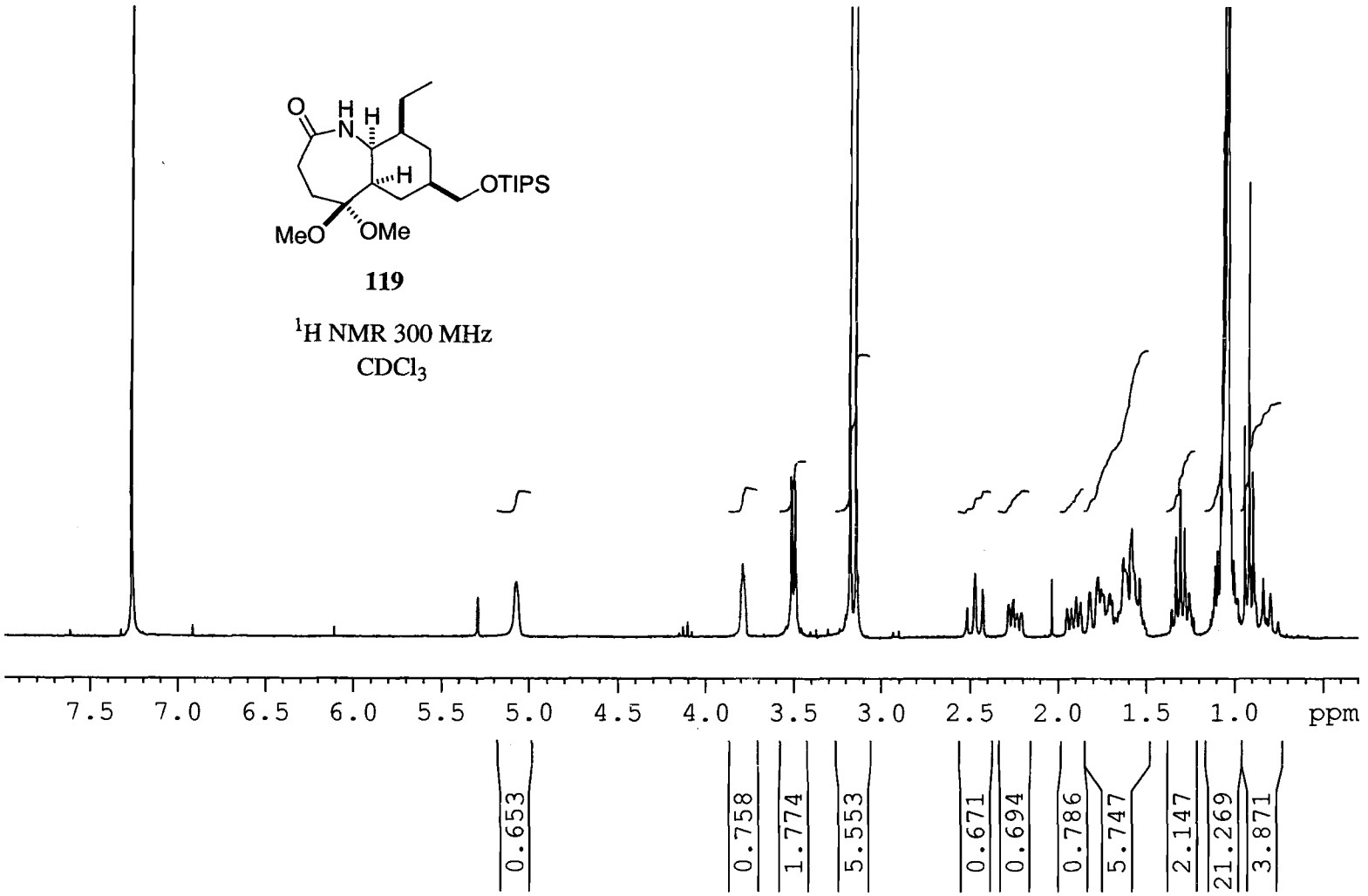
$^1$H NMR 300 MHz

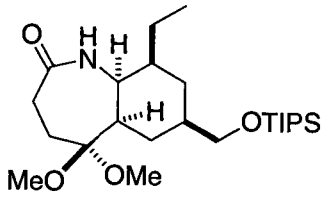
$CDCl_3$




**118**

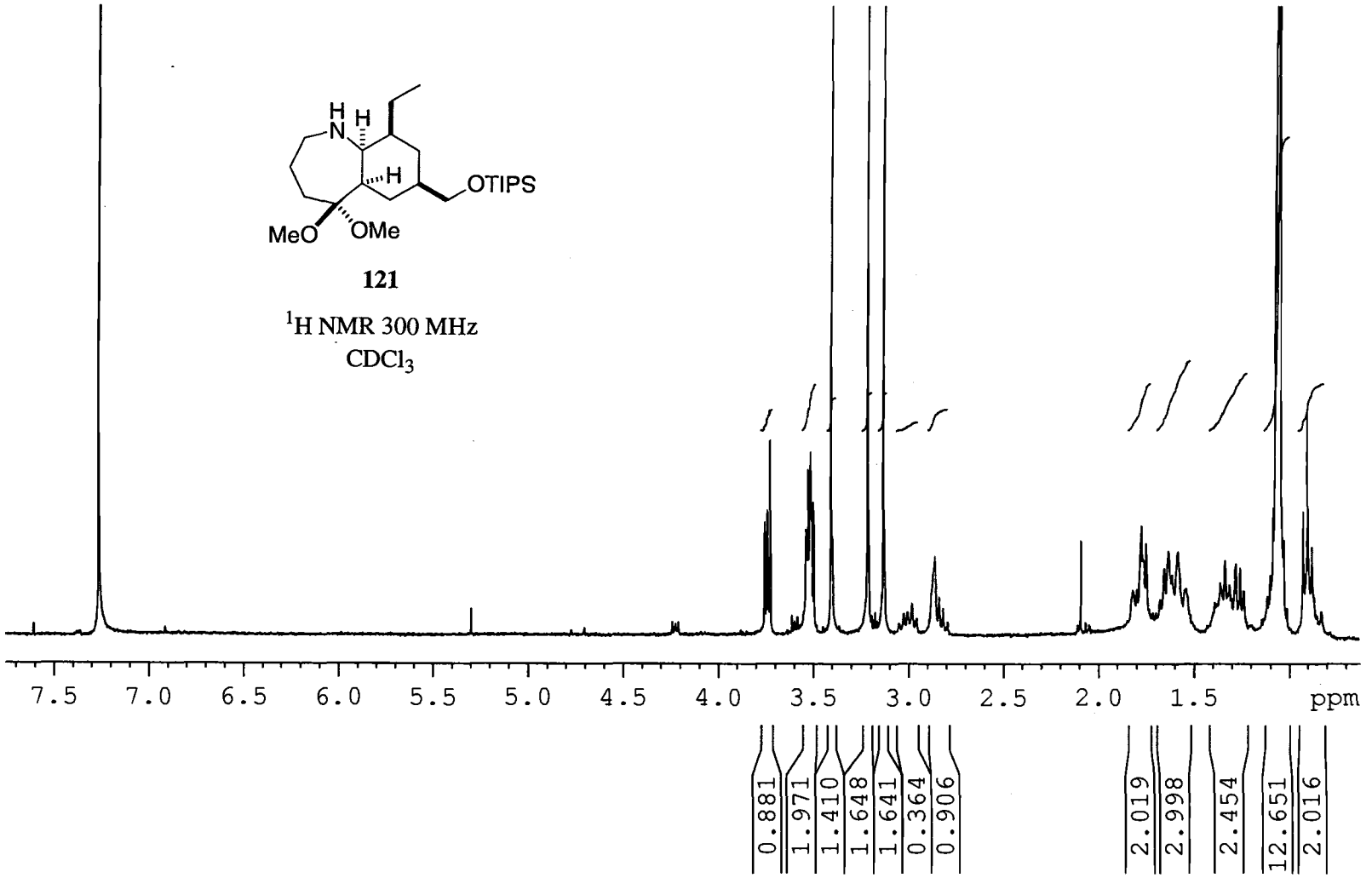
$^{13}C$ NMR 75 MHz
$CDCl_3$

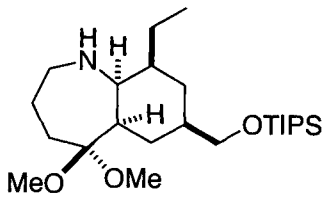

O
H
N
H
H
OTIPS
MeO
OMe
119
1H NMR 300 MHz
CDCl3
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm
0.653
0.758
1.774
5.553
0.671
0.694
0.786
5.747
2.147
21.269
3.871




**119**

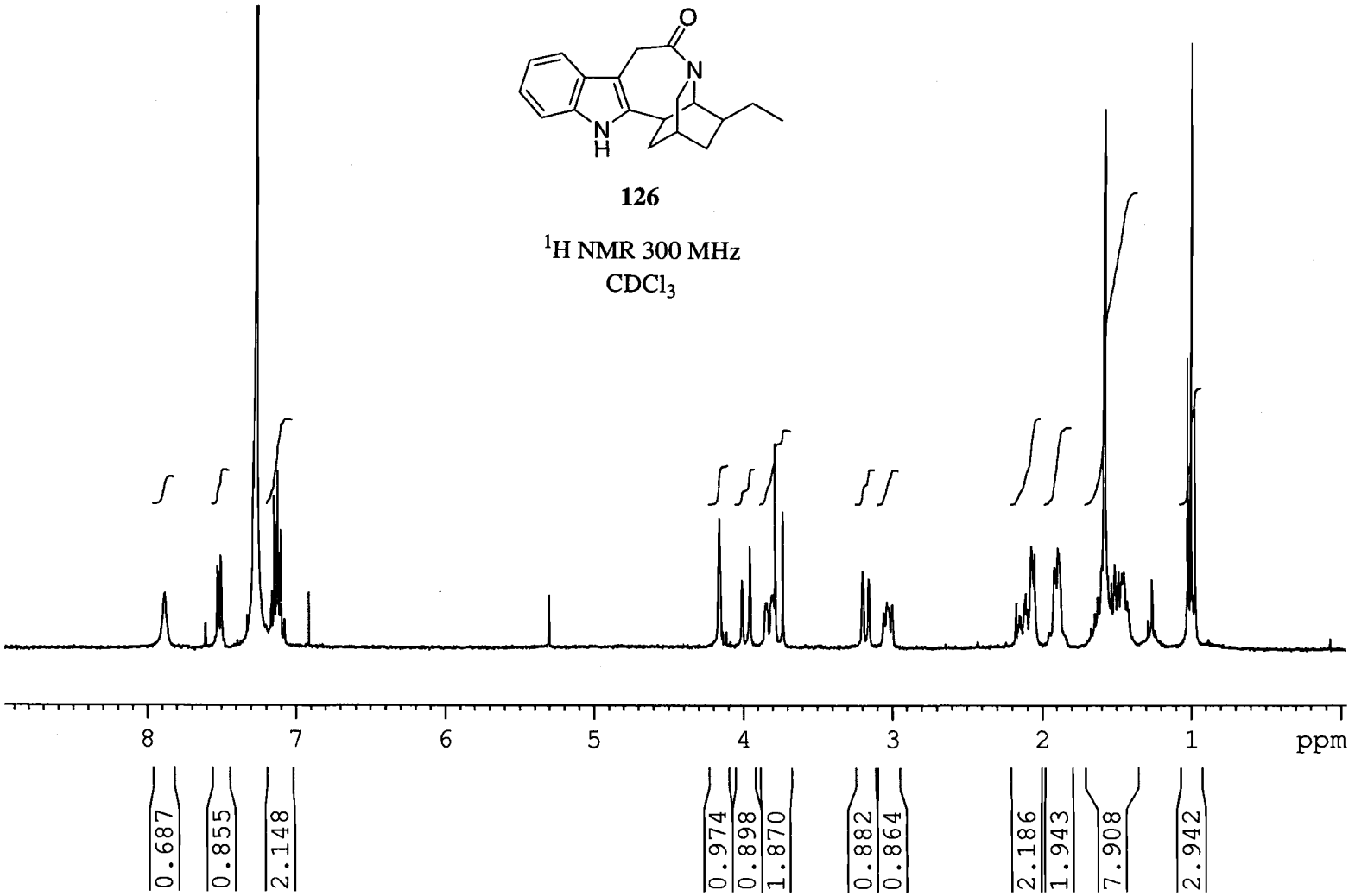
$^{13}C$ NMR 75 MHz
$CDCl_3$


H
H
N
H
OTIPS
MeO
OMe
121
1H NMR 300 MHz
CDCl3
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
ppm
0.881
1.971
1.410
1.648
1.641
0.364
0.906
2.019
2.998
2.454
12.651
2.016



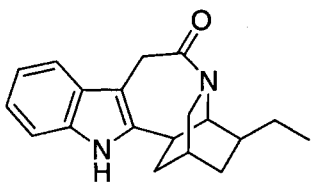

**121**

$^{13}C$ NMR 75 MHz
$CDCl_3$



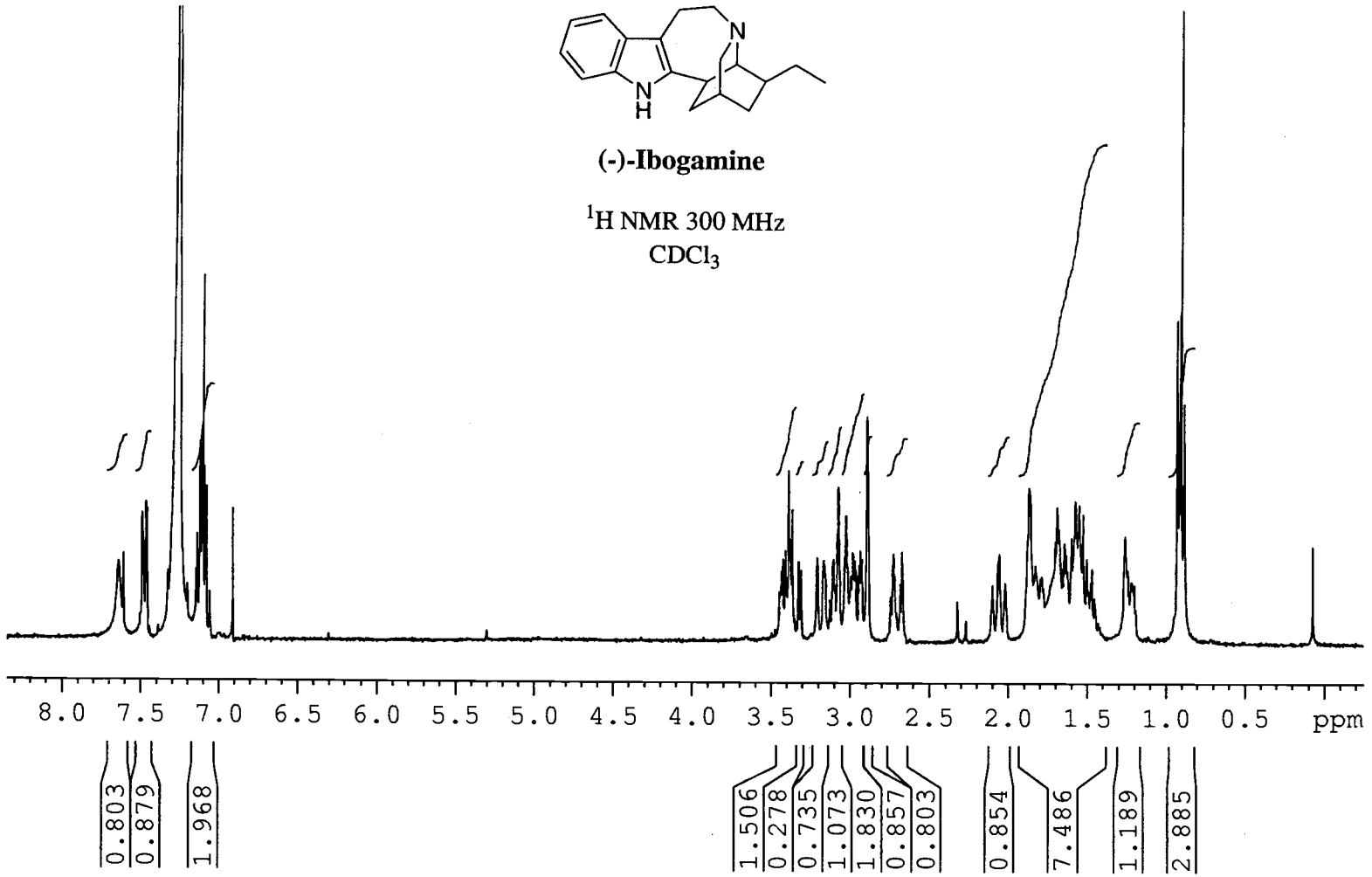

**126**

$^1$H NMR 300 MHz
$CDCl_3$



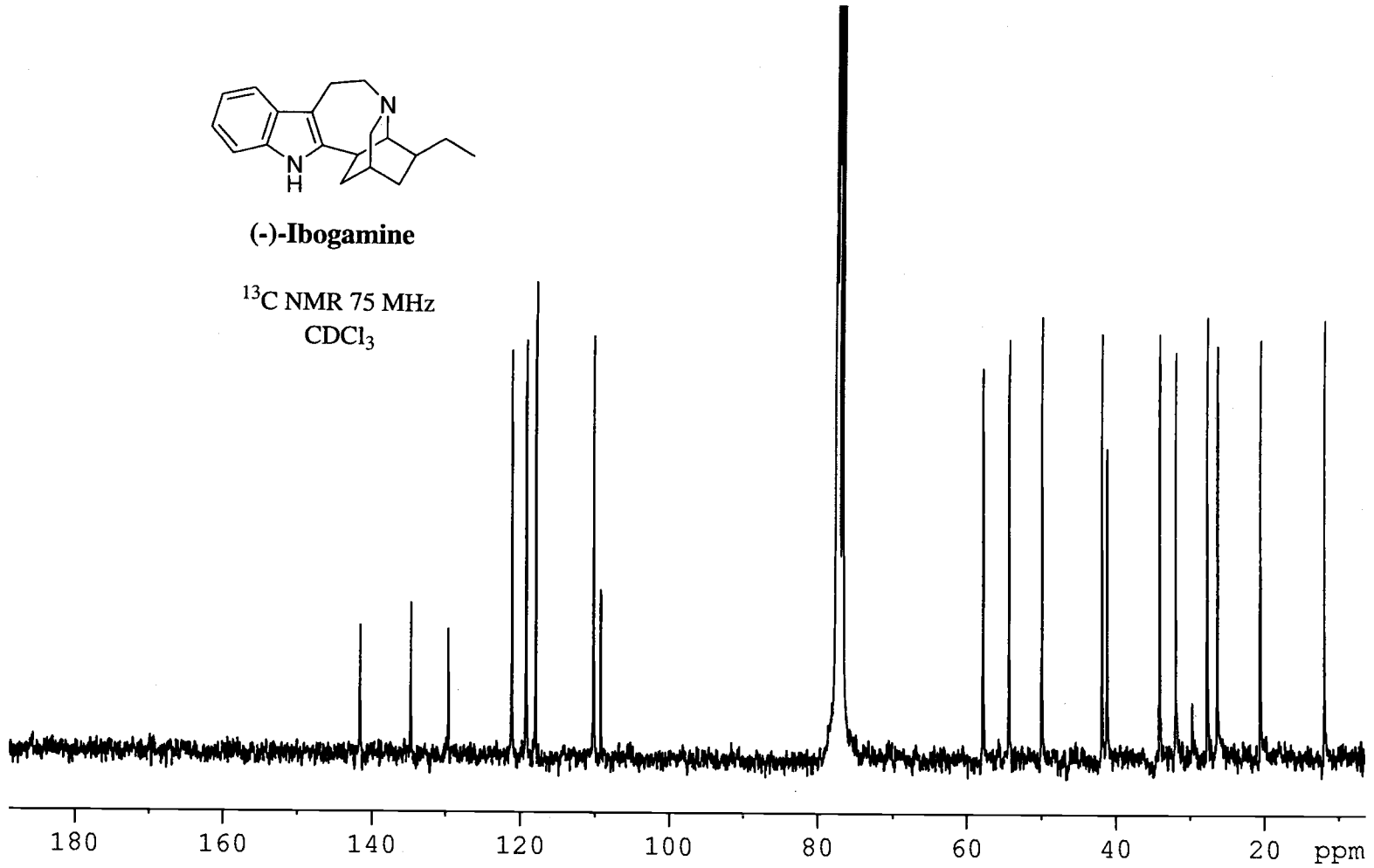

**126**

$^{13}C$ NMR 75 MHz
$CDCl_3$



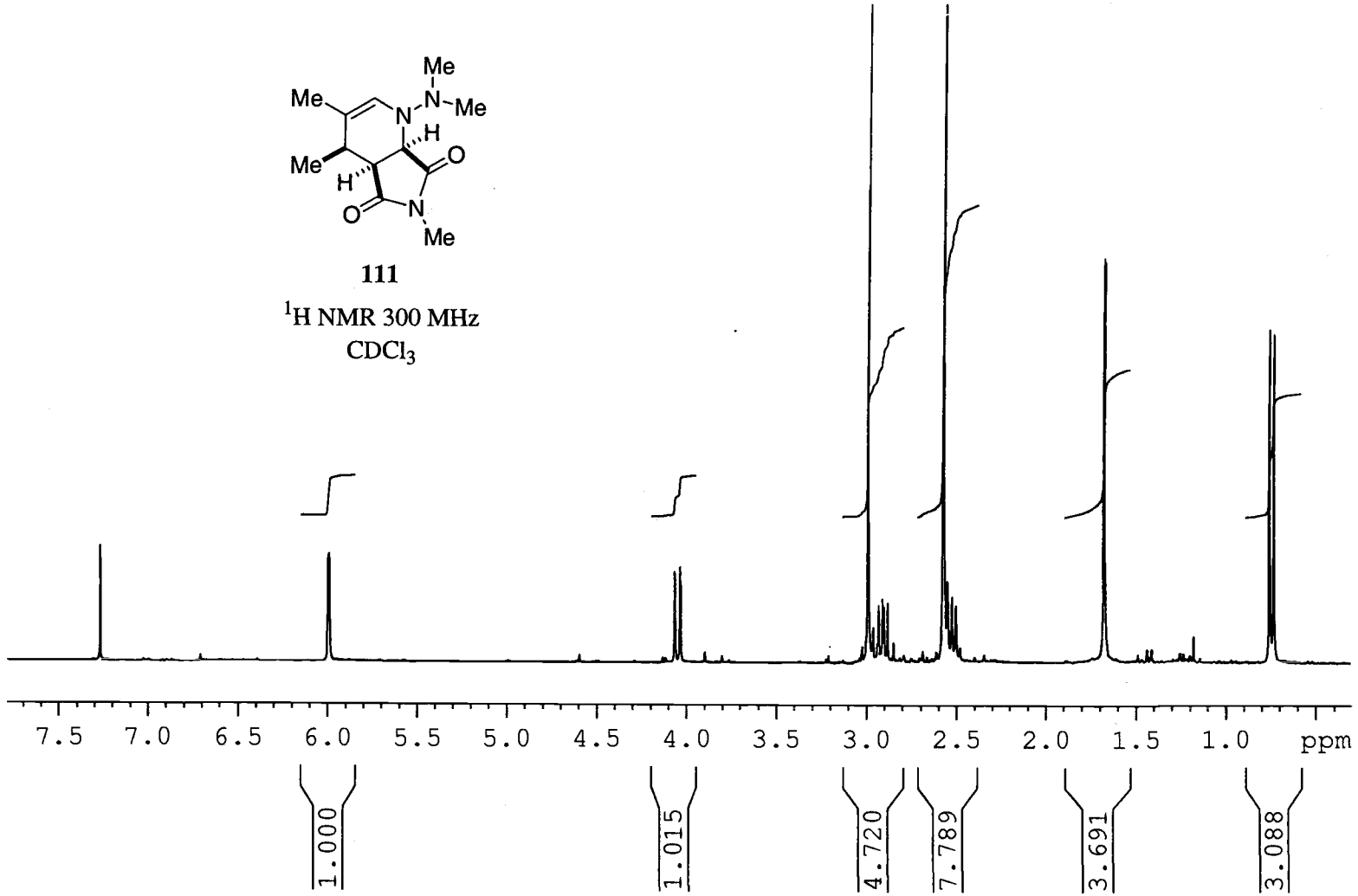

**(-)-Ibogamine**

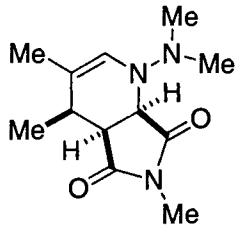
$^1$H NMR 300 MHz
$CDCl_3$




**(-)-Ibogamine**

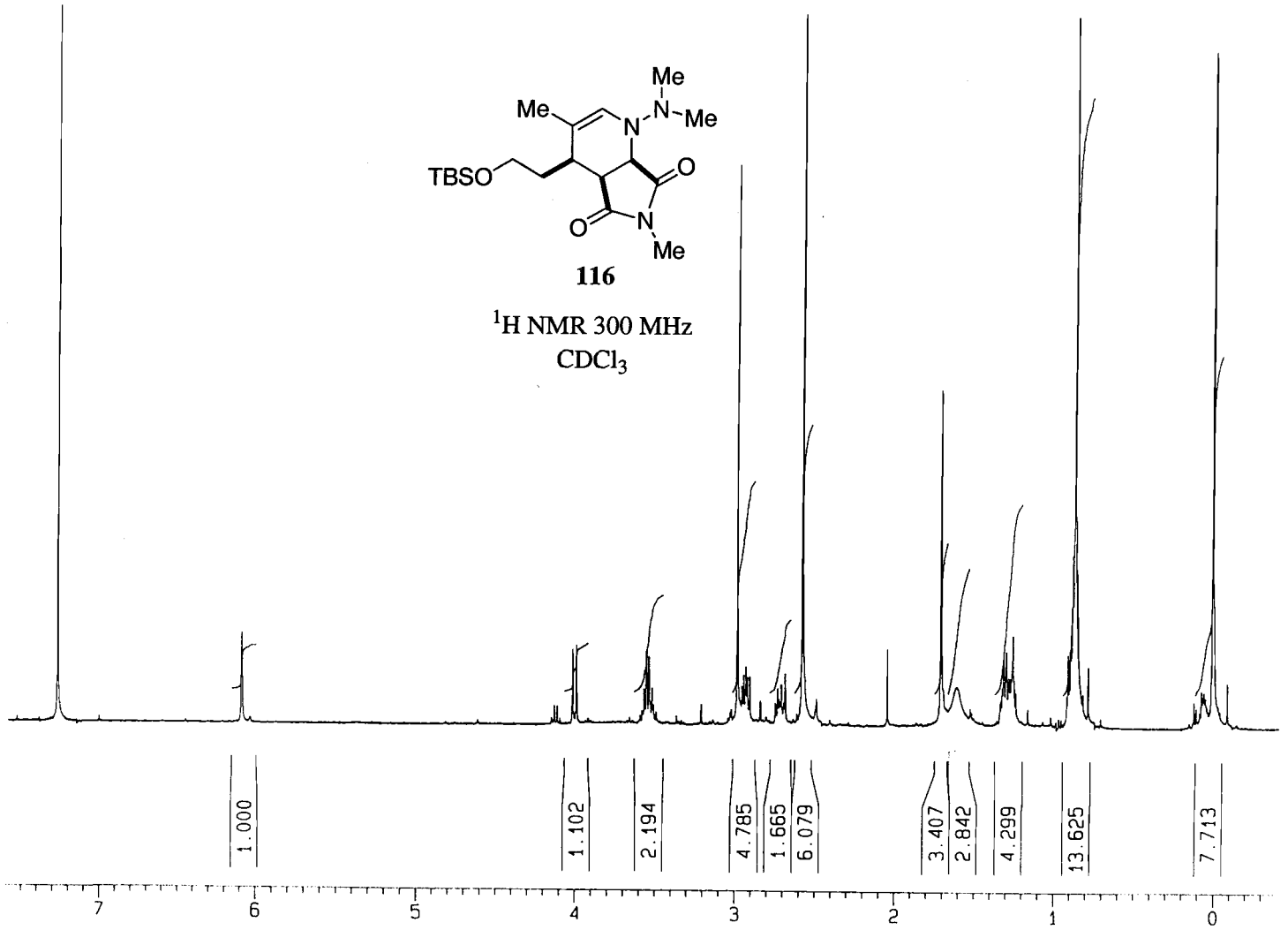
$^{13}C$ NMR 75 MHz
$CDCl_3$

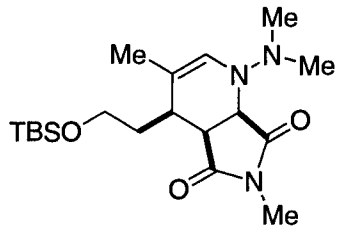

Me
N
Me
Me
N
H
Me
H
O
O
N
Me
111
1H NMR 300 MHz
CDCl3
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm
1.000
1.015
4.720
7.789
3.691
3.088




**111**

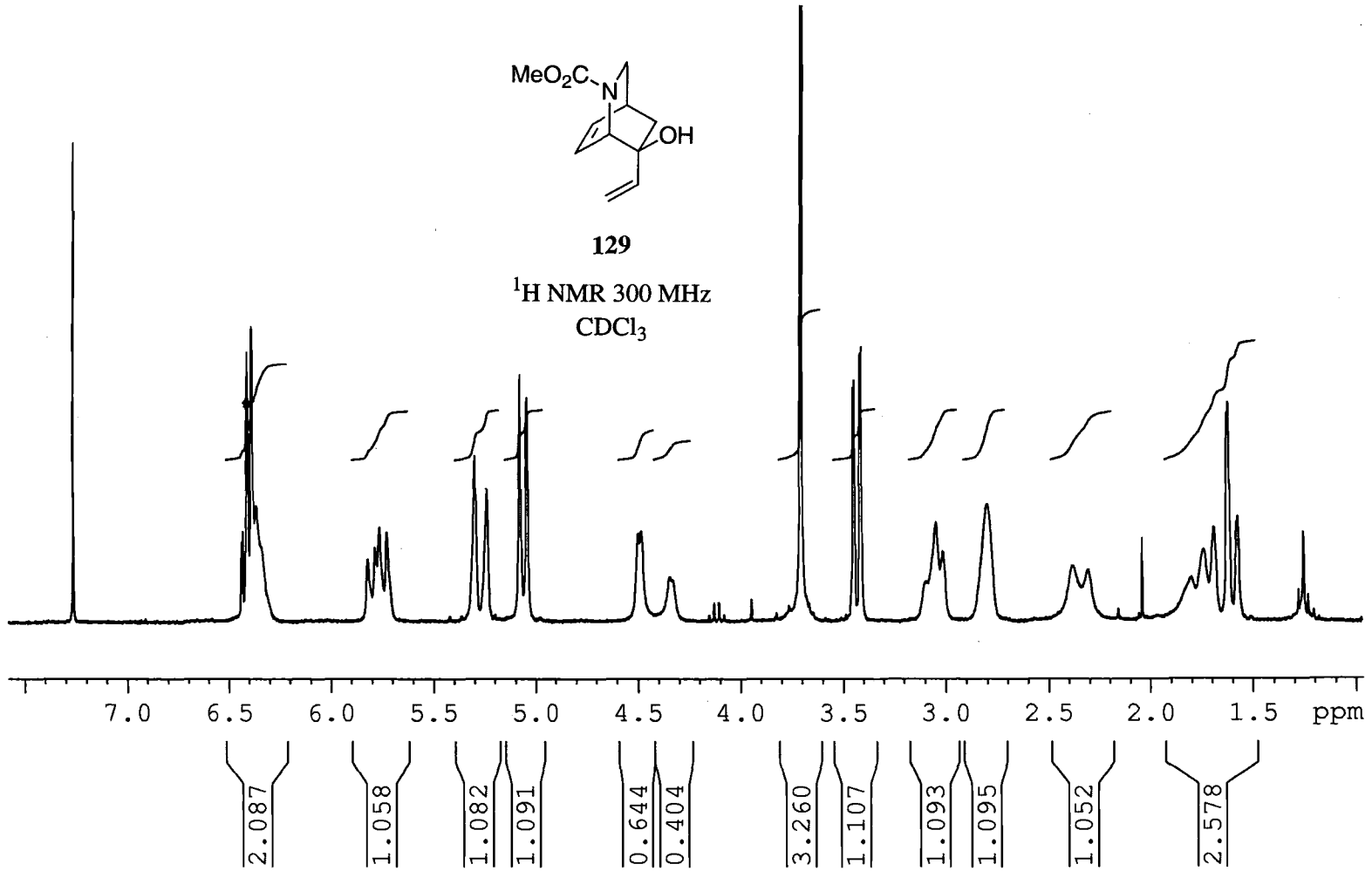
$^{13}C$ NMR 75 MHz
$CDCl_3$

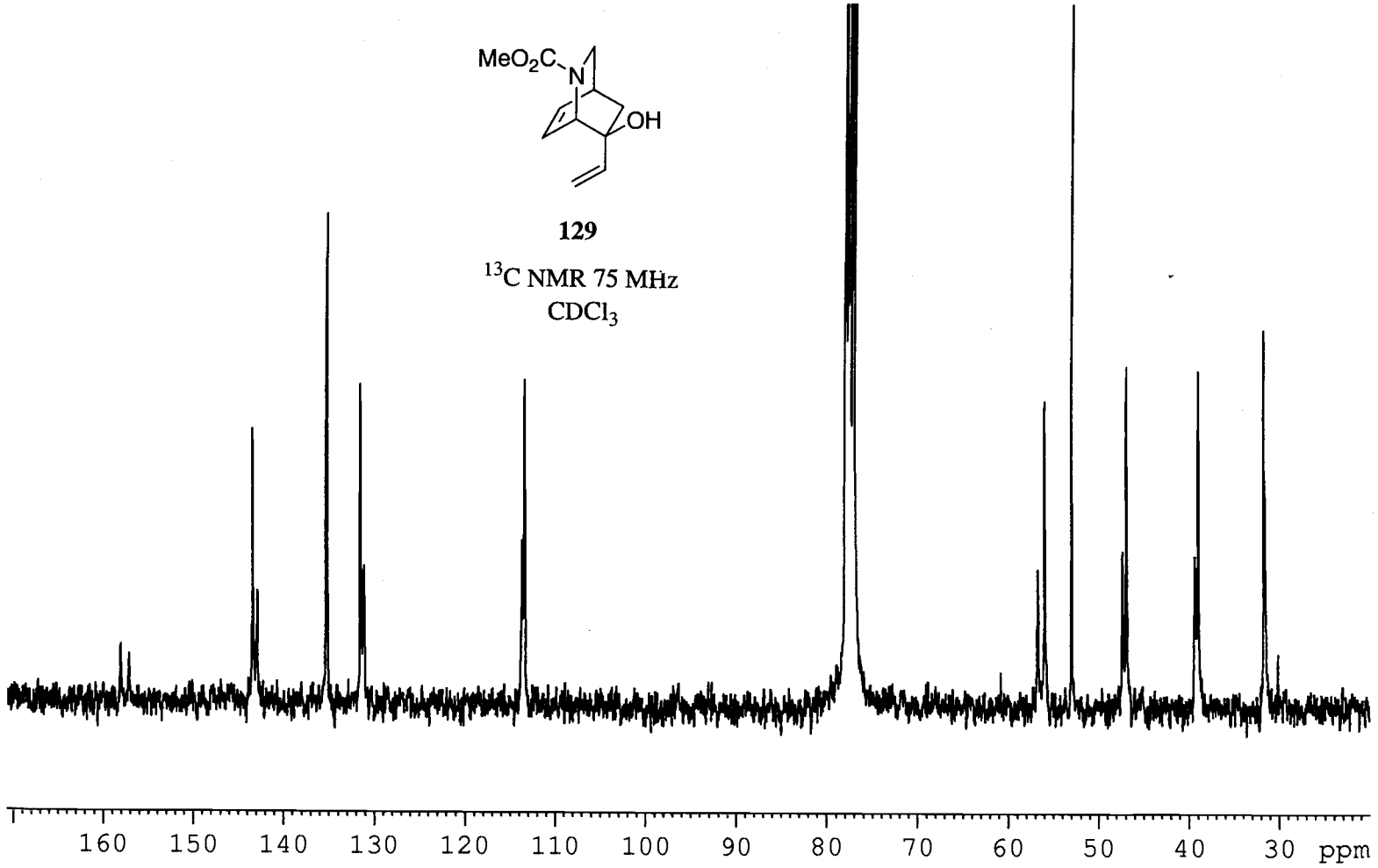

Me
Me
N
N
Me
TBSO
O
O
N
Me
116
1H NMR 300 MHz
CDCl3
1.000
1.102
2.194
4.785
1.665
6.079
3.407
2.842
4.299
13.625
7.713
7
6
5
4
3
2
1
0




**116**

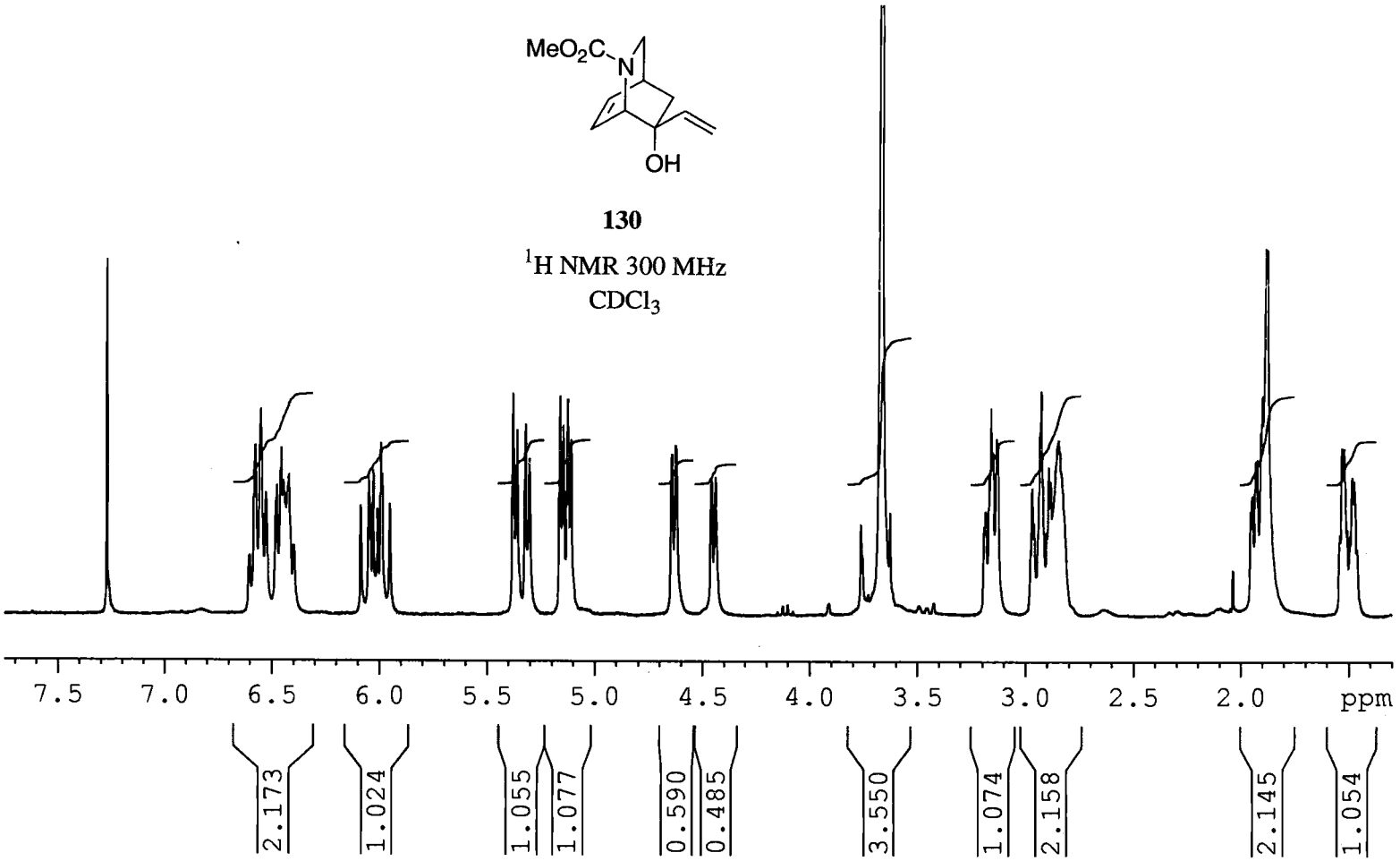
$^{13}C$ NMR 75 MHz
$CDCl_3$

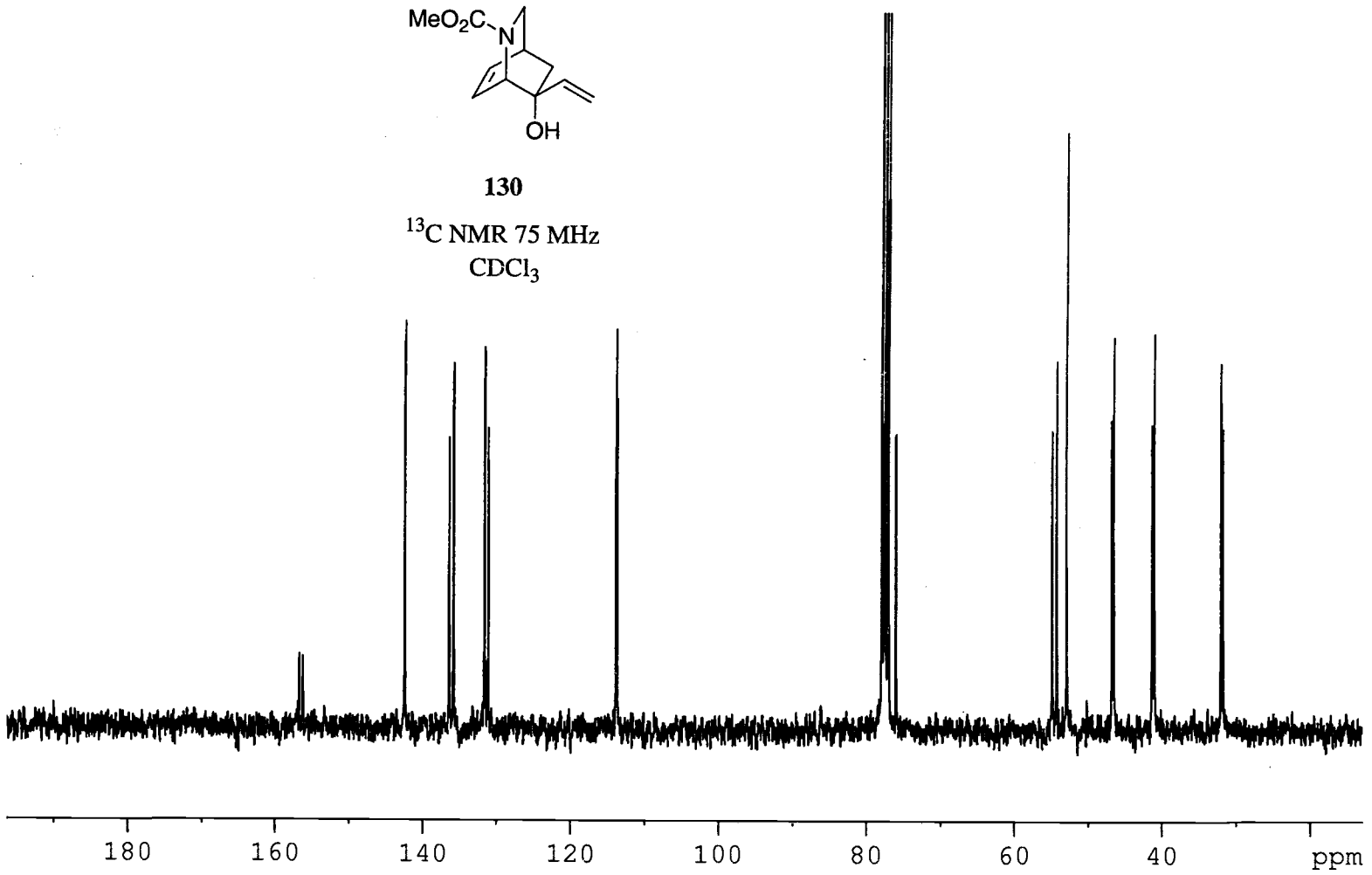

MeO2C
N
OH
129
1H NMR 300 MHz
CDCl3
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
ppm
2.087
1.058
1.082
1.091
0.644
0.404
3.260
1.107
1.093
1.095
1.052
2.578

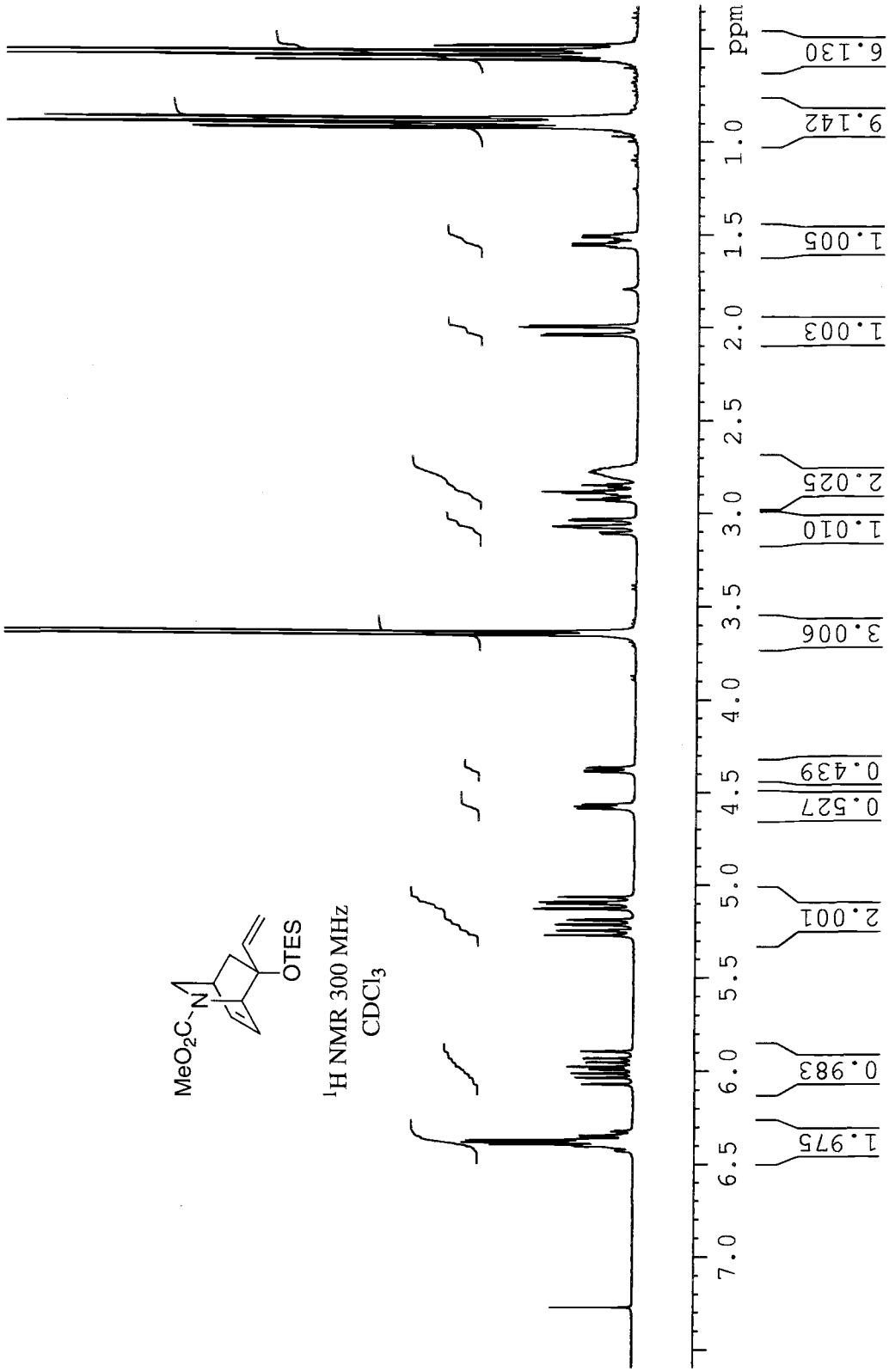


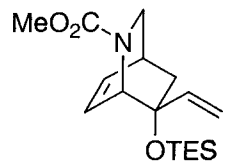

**129**

$^{13}C$ NMR 75 MHz
$CDCl_3$

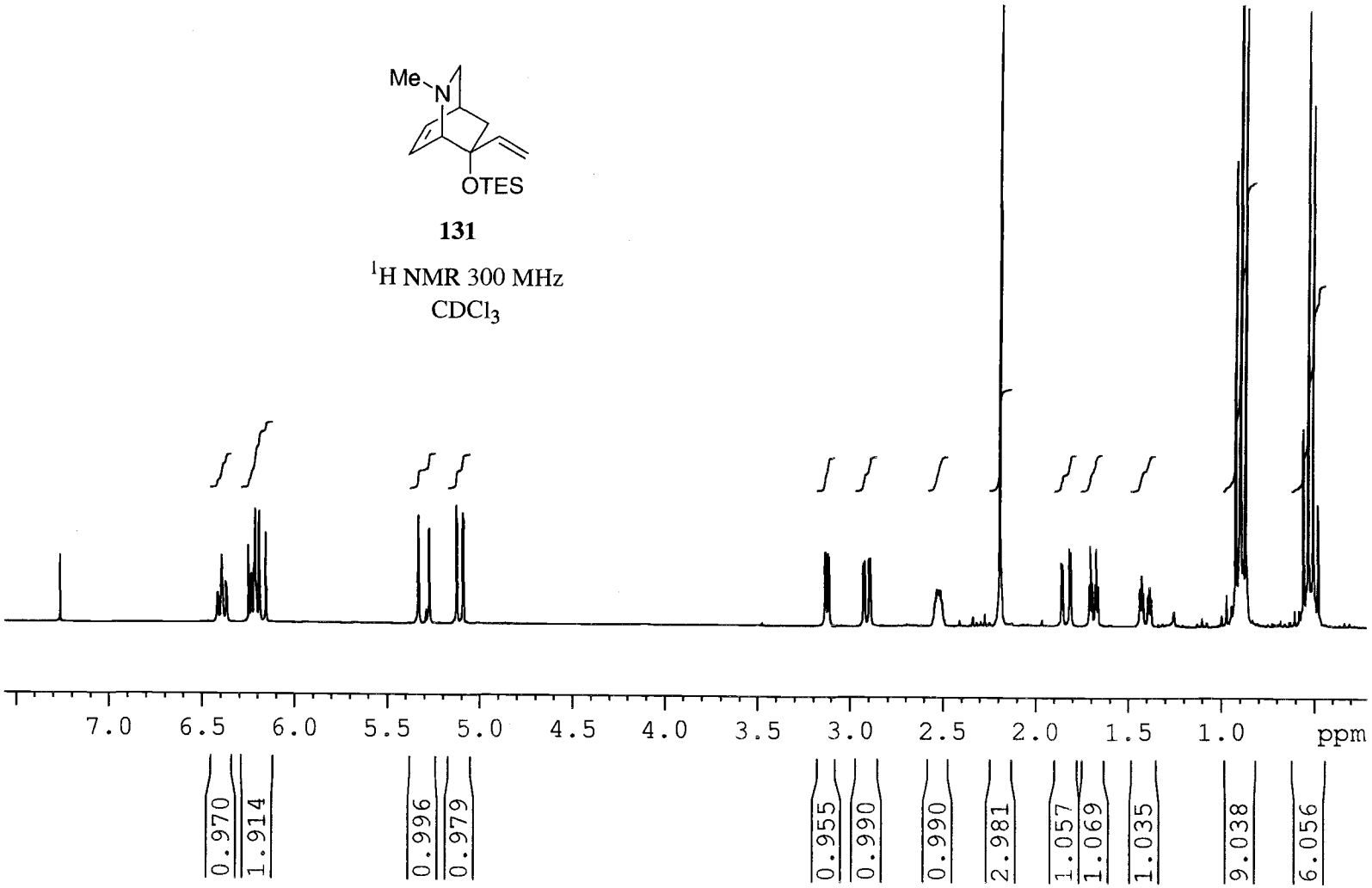

MeO2C
N
OH
130
1H NMR 300 MHz
CDCl3
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
ppm
2.173
1.024
1.055
1.077
0.590
0.485
3.550
1.074
2.158
2.145
1.054


MeO2C
N
OH
130
13C NMR 75 MHz
CDCl3
180
160
140
120
100
80
60
40
ppm


MeO2C
N
OTES
1H NMR 300 MHz
CDCl3
ppm
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
1.975
0.983
2.001
0.527
0.439
3.006
1.010
2.025
1.003
1.005
9.142
6.130

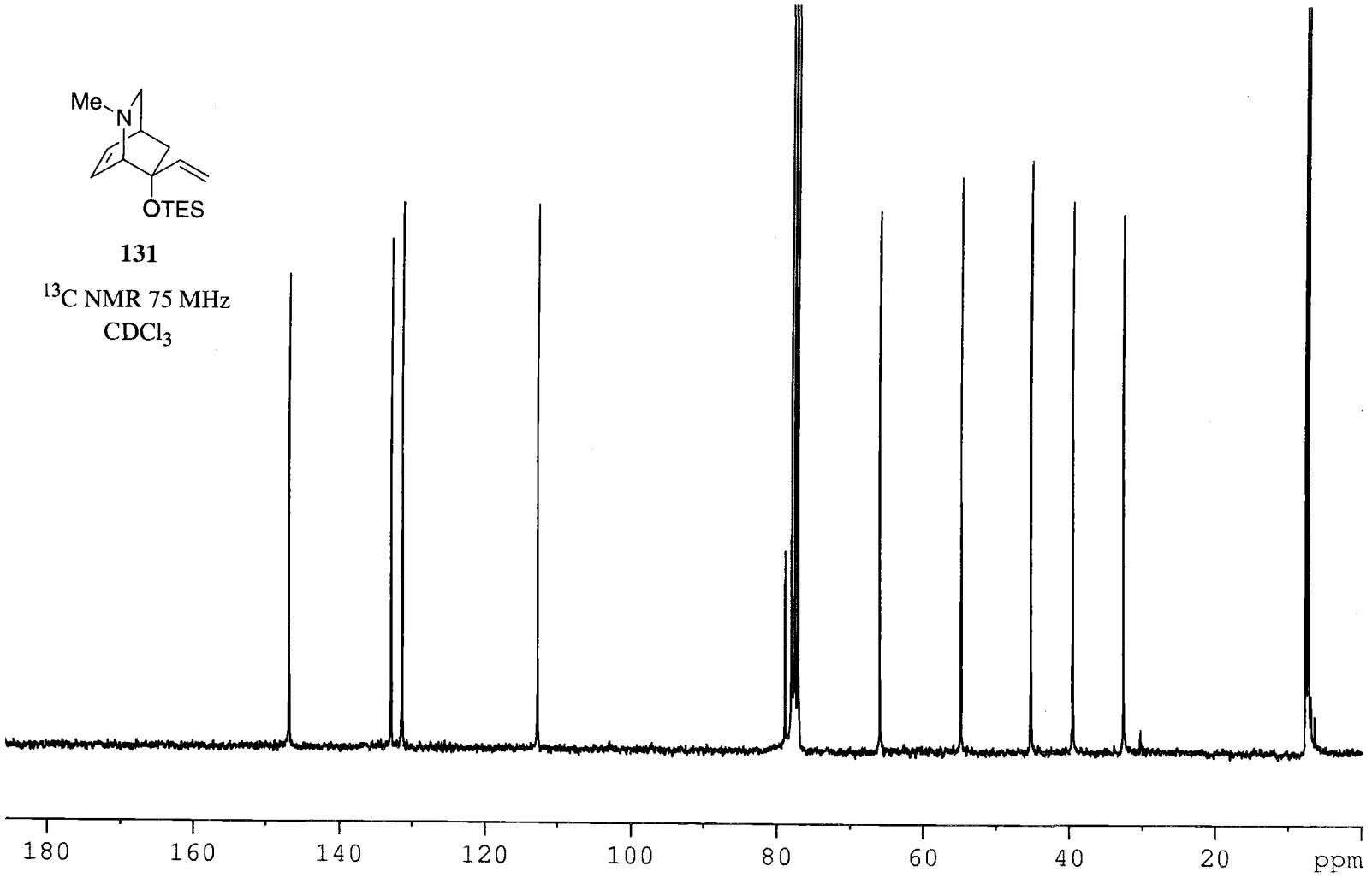


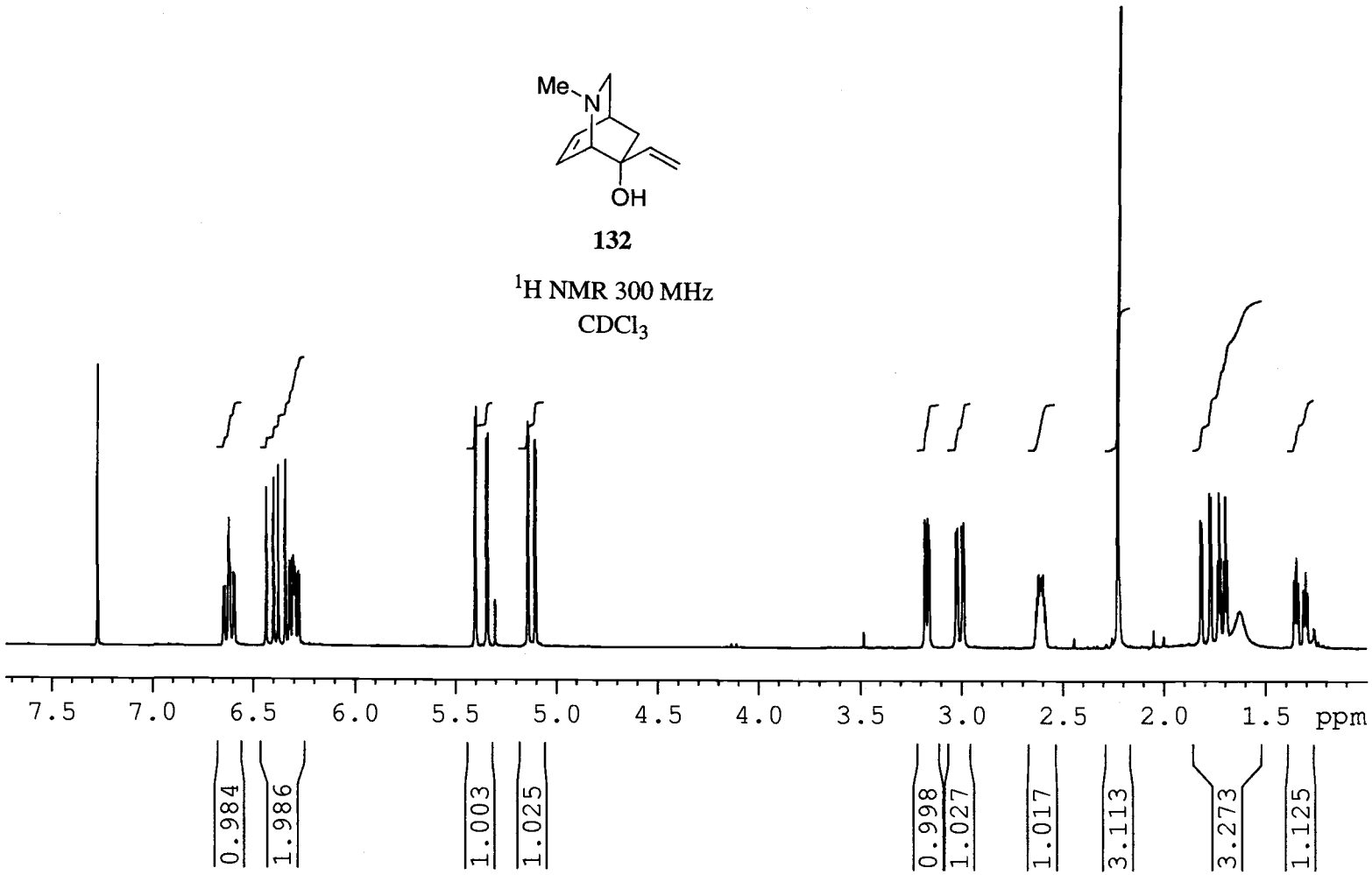

$^{13}C$ NMR 75 MHz
$CDCl_3$




**131**

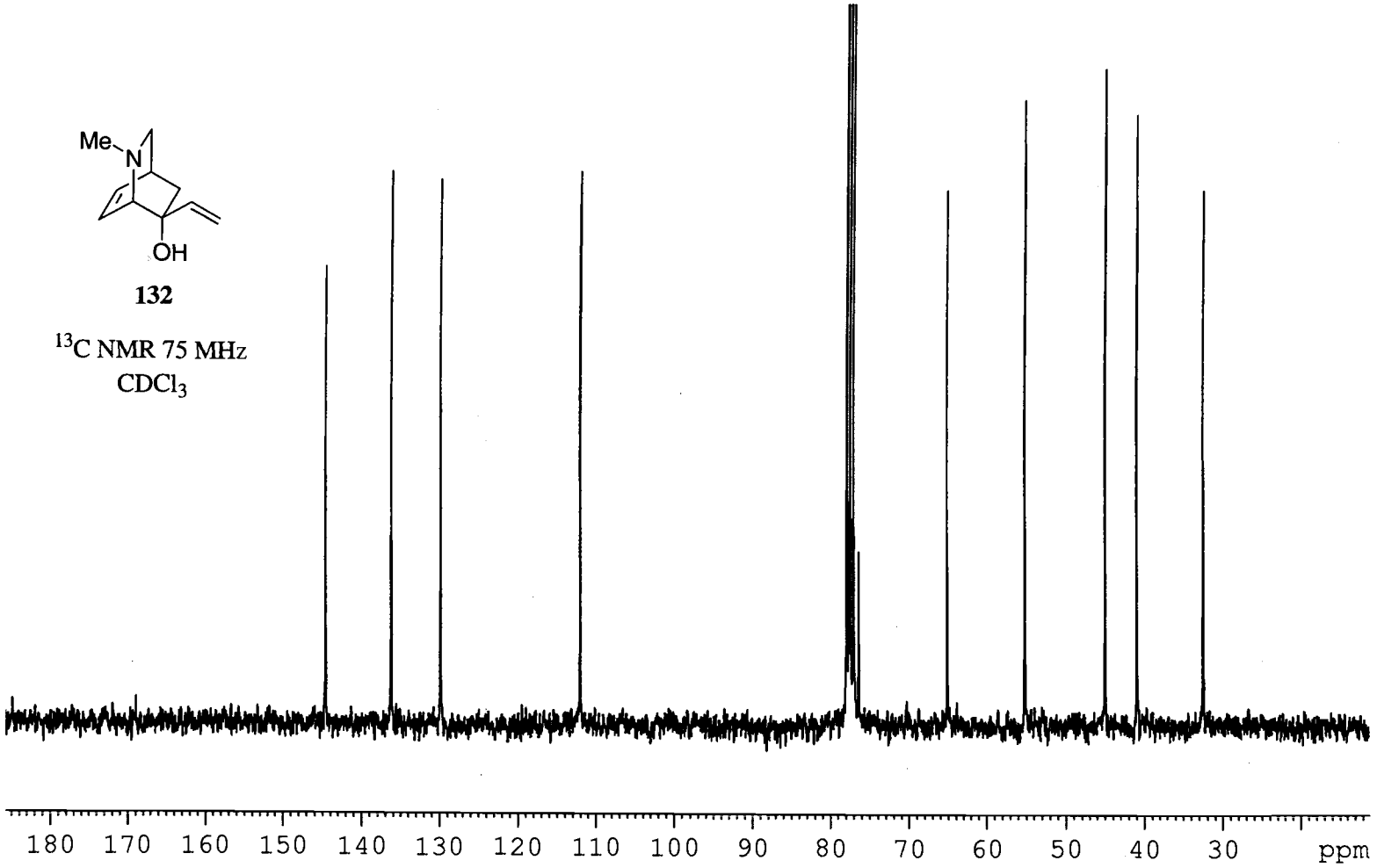
$^{1}$H NMR 300 MHz
$CDCl_3$


Me
N
OTES
131
$^{13}$C NMR 75 MHz
$CDCl_3$
180
160
140
120
100
80
60
40
20
ppm



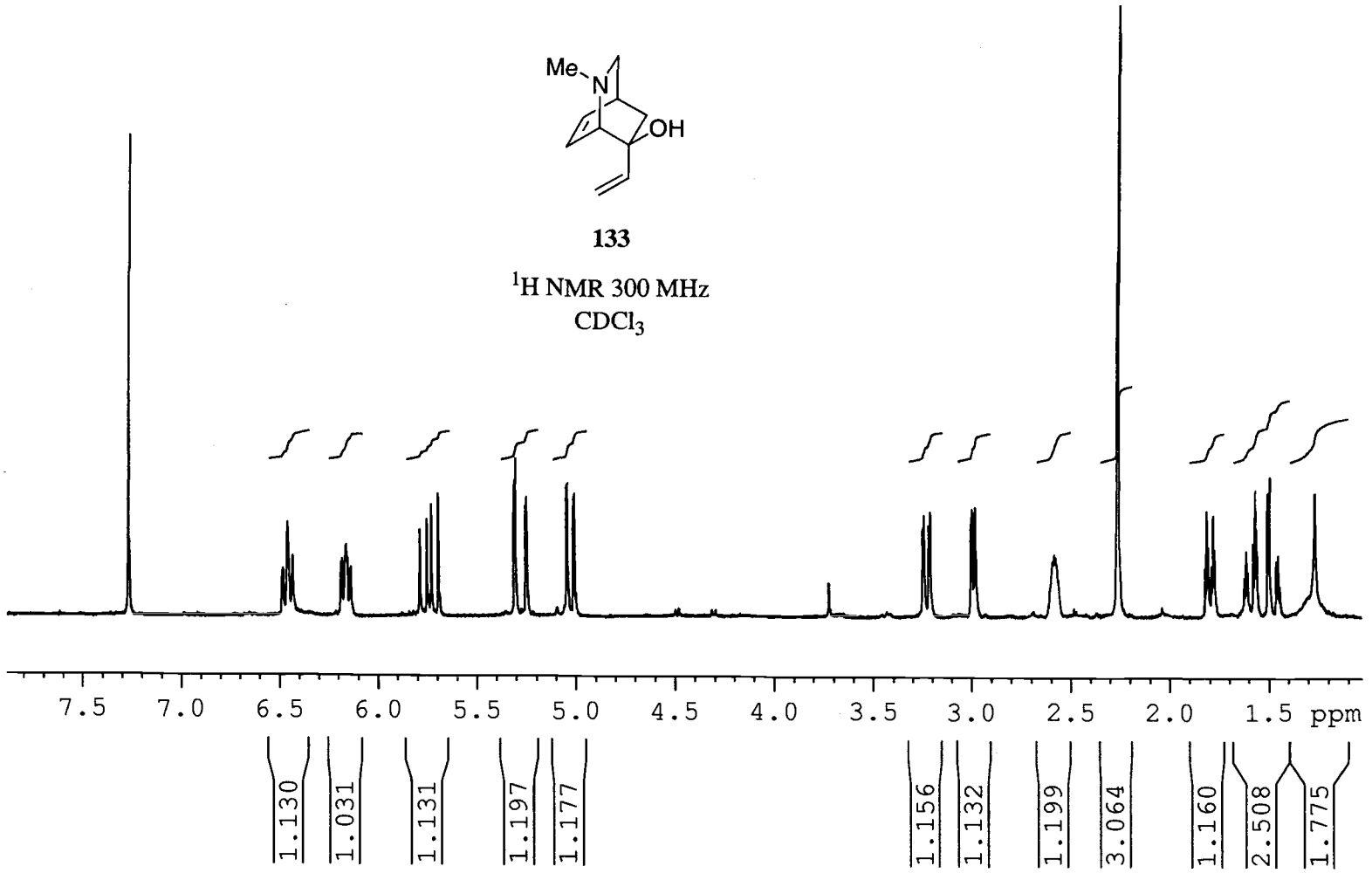

**132**

$^1$H NMR 300 MHz
$CDCl_3$



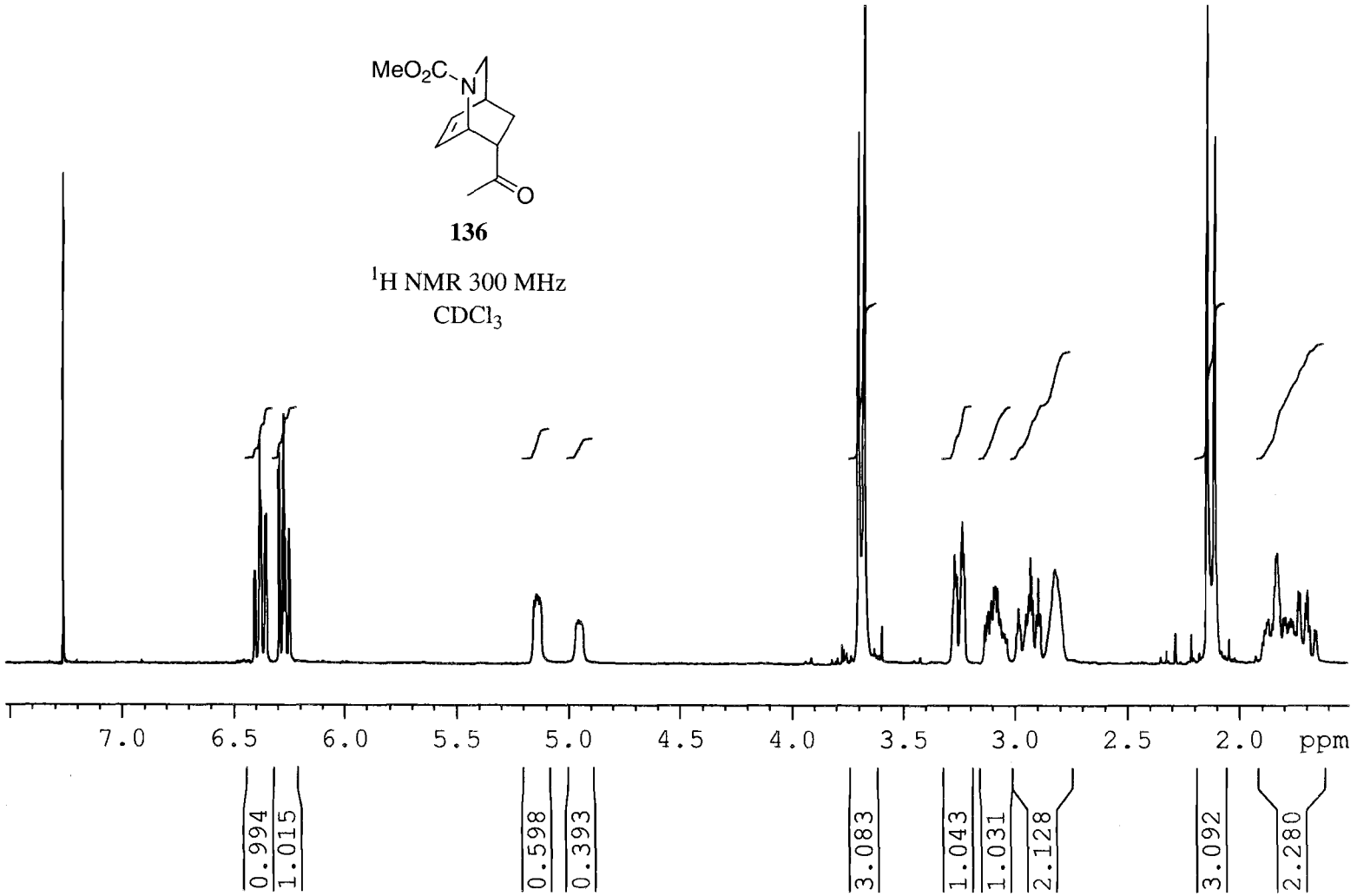

**132**

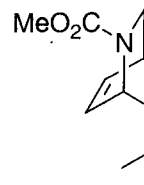
$^{13}C$ NMR 75 MHz
$CDCl_3$




**133**

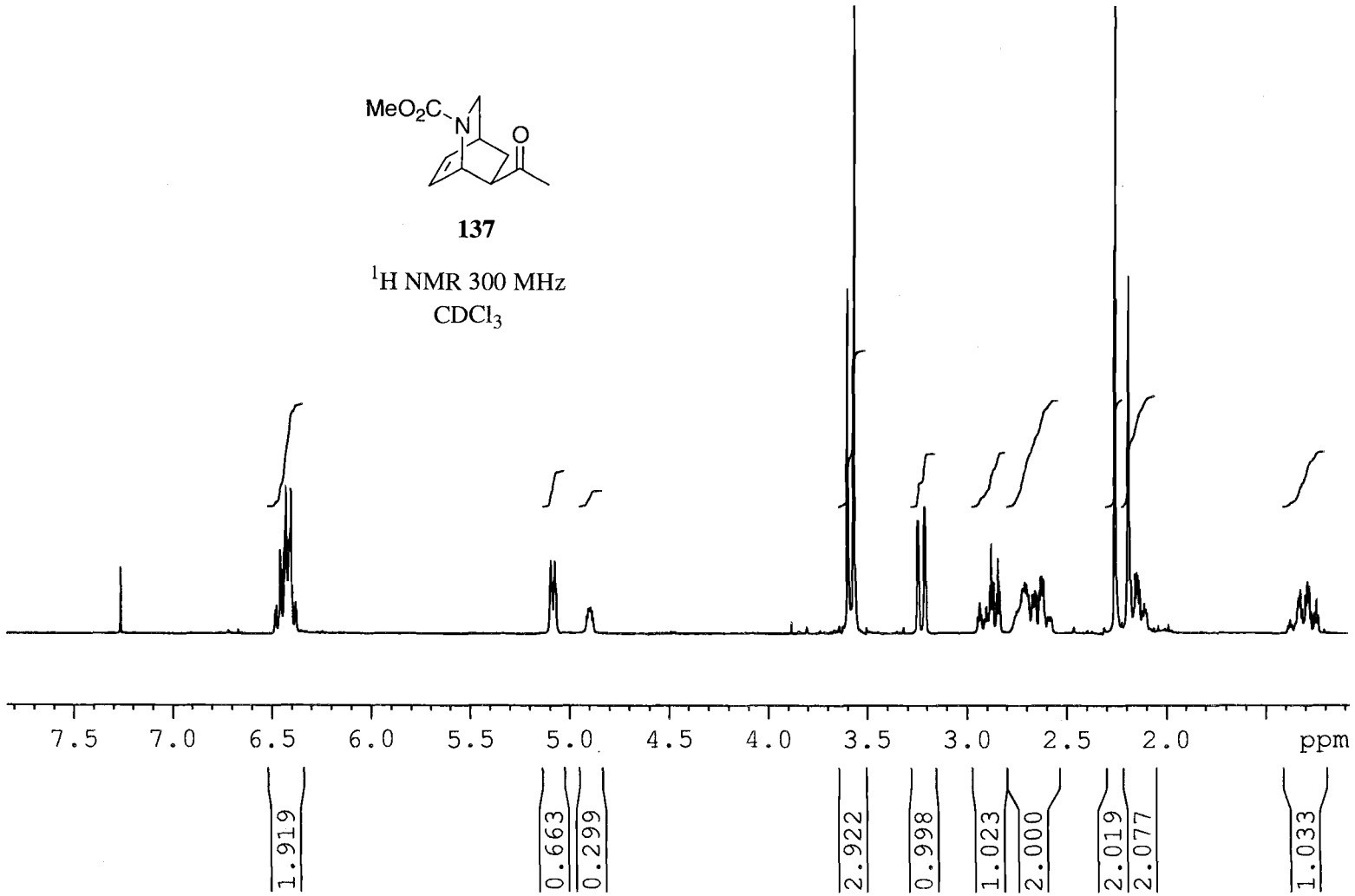
$^1$H NMR 300 MHz
$CDCl_3$

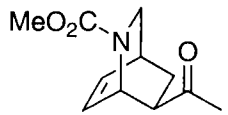

MeO2C
N
O
136
1H NMR 300 MHz
CDCl3
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
ppm
0.994
1.015
0.598
0.393
3.083
1.043
1.031
2.128
3.092
2.280




**136**

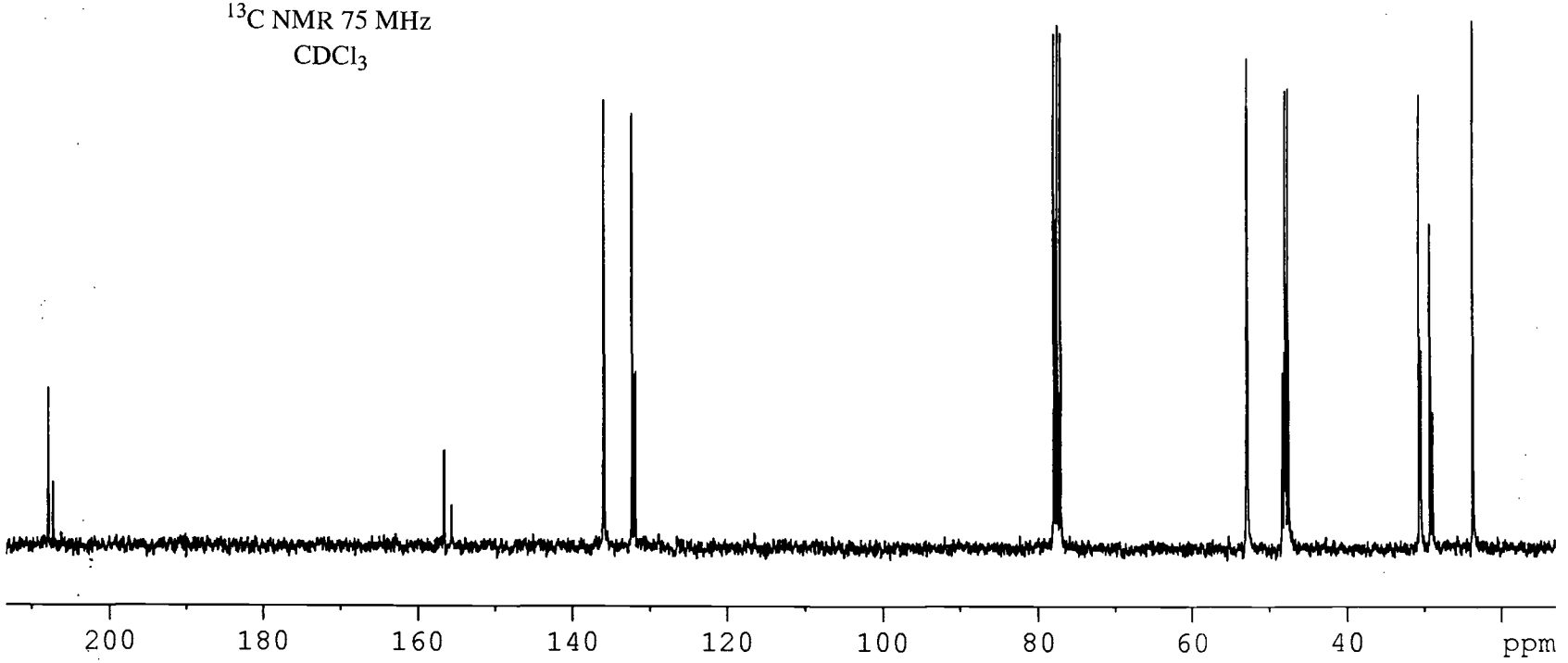
$^{13}C$ NMR 75 MHz
$CDCl_3$

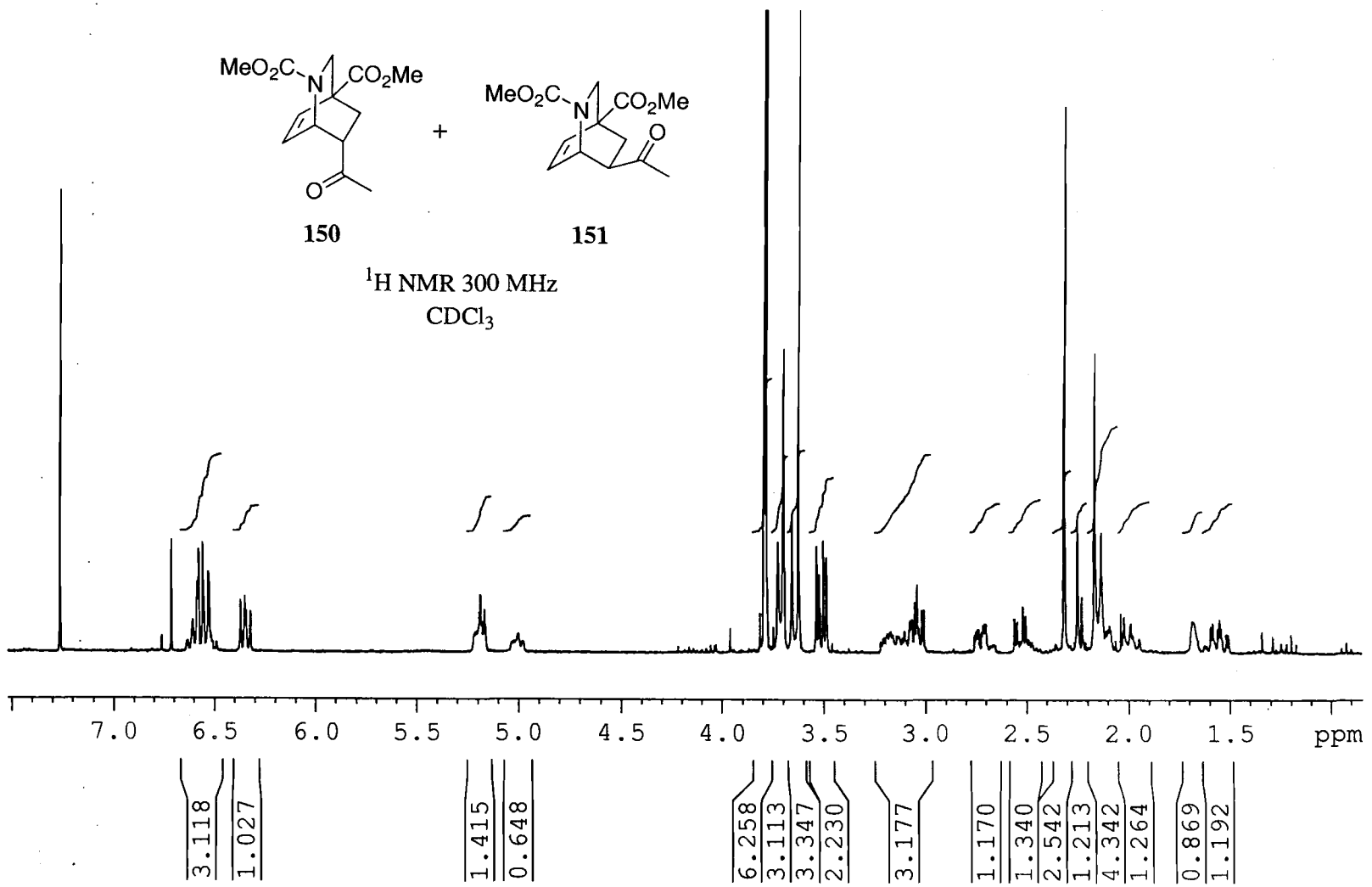

MeO2C
N
O
137
1H NMR 300 MHz
CDCl3
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
ppm
1.919
0.663
0.299
2.922
0.998
1.023
2.000
2.019
2.077
1.033

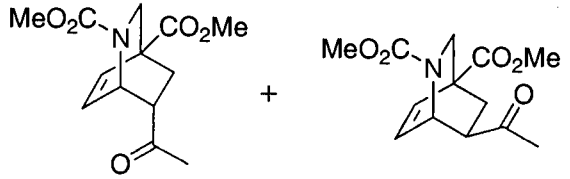



**137**

$^{13}C$ NMR 75 MHz
$CDCl_3$




MeO2C
N
CO2Me
O
+
MeO2C
N
CO2Me
O
150
151
1H NMR 300 MHz
CDCl3
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
ppm
3.118
1.027
1.415
0.648
6.258
3.113
3.347
2.230
3.177
1.170
1.340
2.542
1.213
4.342
1.264
0.869
1.192

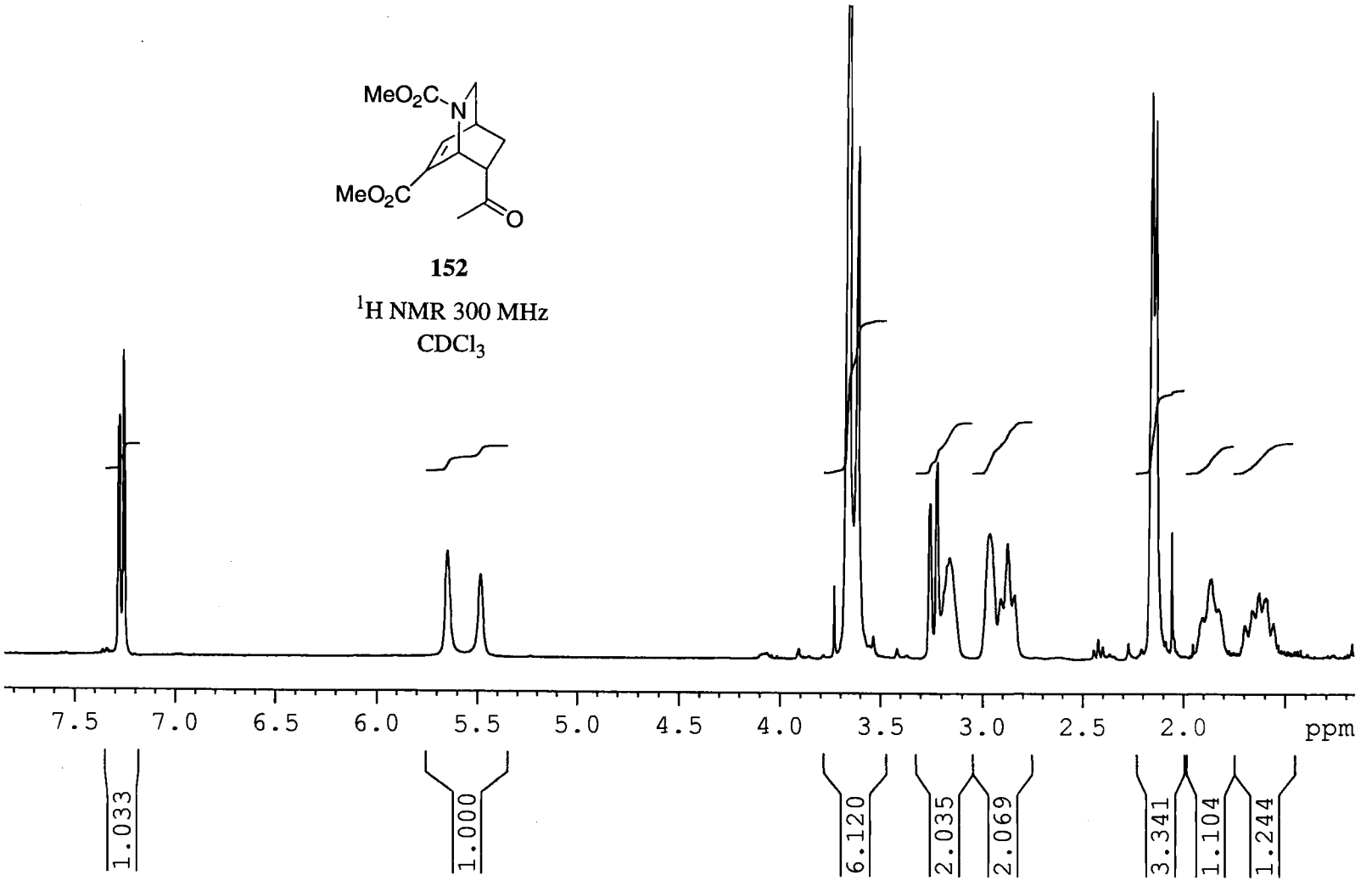


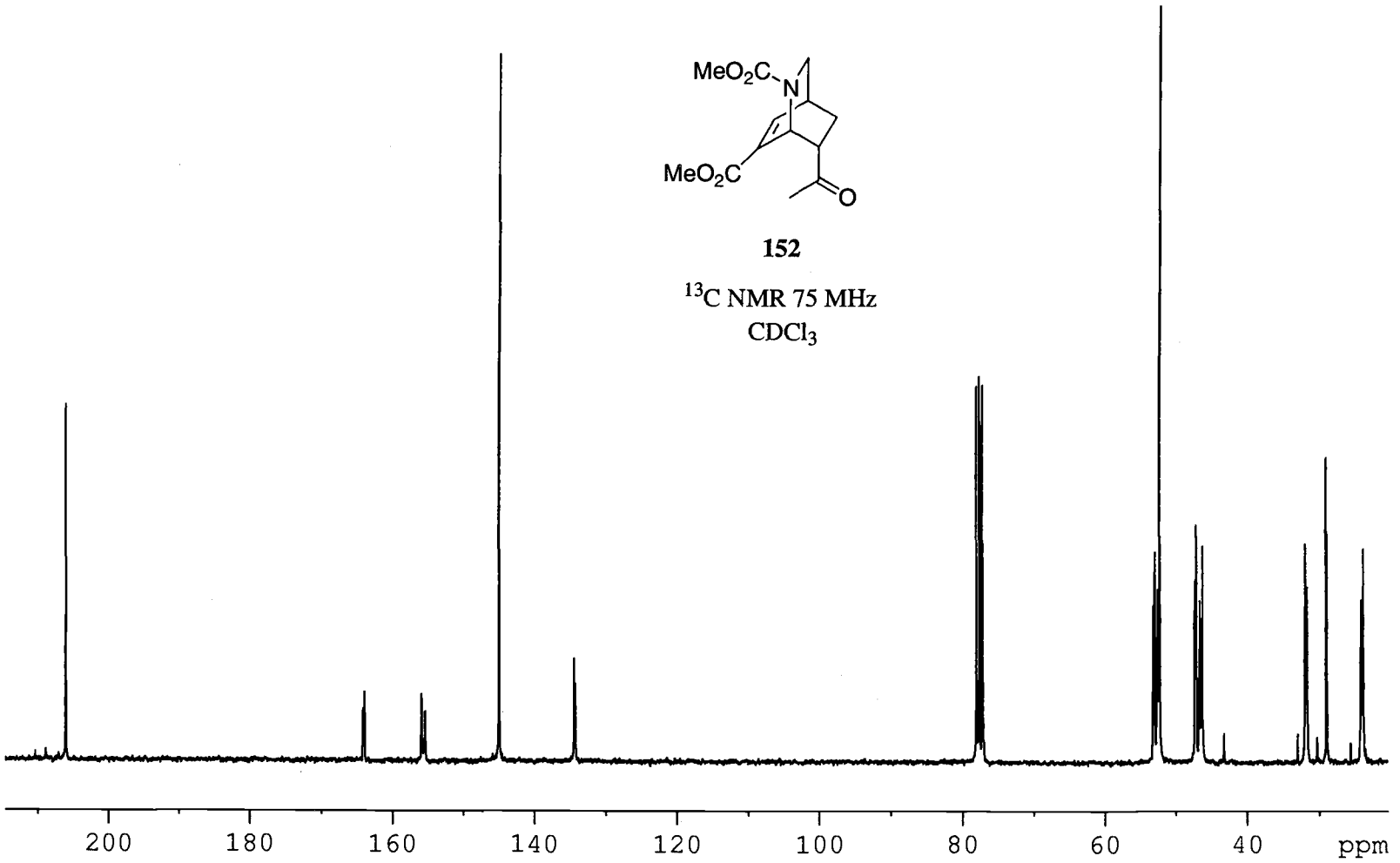

+

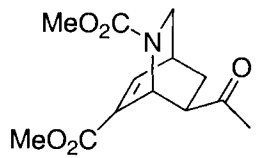



**150** **151**

$^{13}$C NMR 75 MHz
$CDCl_3$

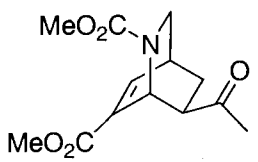

MeO2C
N
MeO2C
O
152
1H NMR 300 MHz
CDCl3
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
ppm
1.033
1.000
6.120
2.035
2.069
3.341
1.104
1.244


MeO2C
N
MeO2C
O
152
13C NMR 75 MHz
CDCl3
200
180
160
140
120
100
80
60
40
ppm



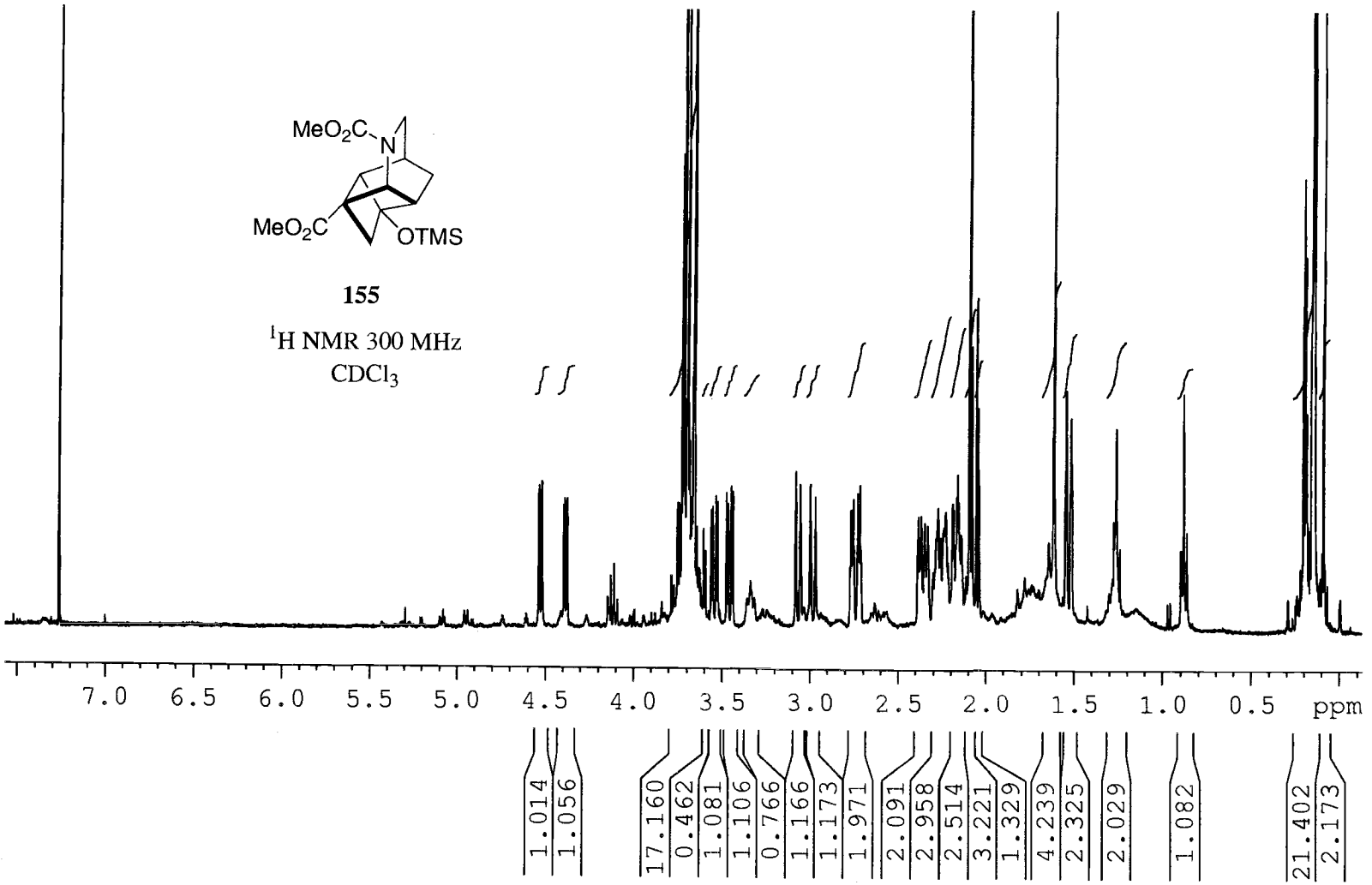

**153**

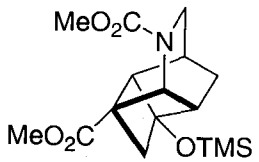
$^1$H NMR 300 MHz
$CDCl_3$




**153**

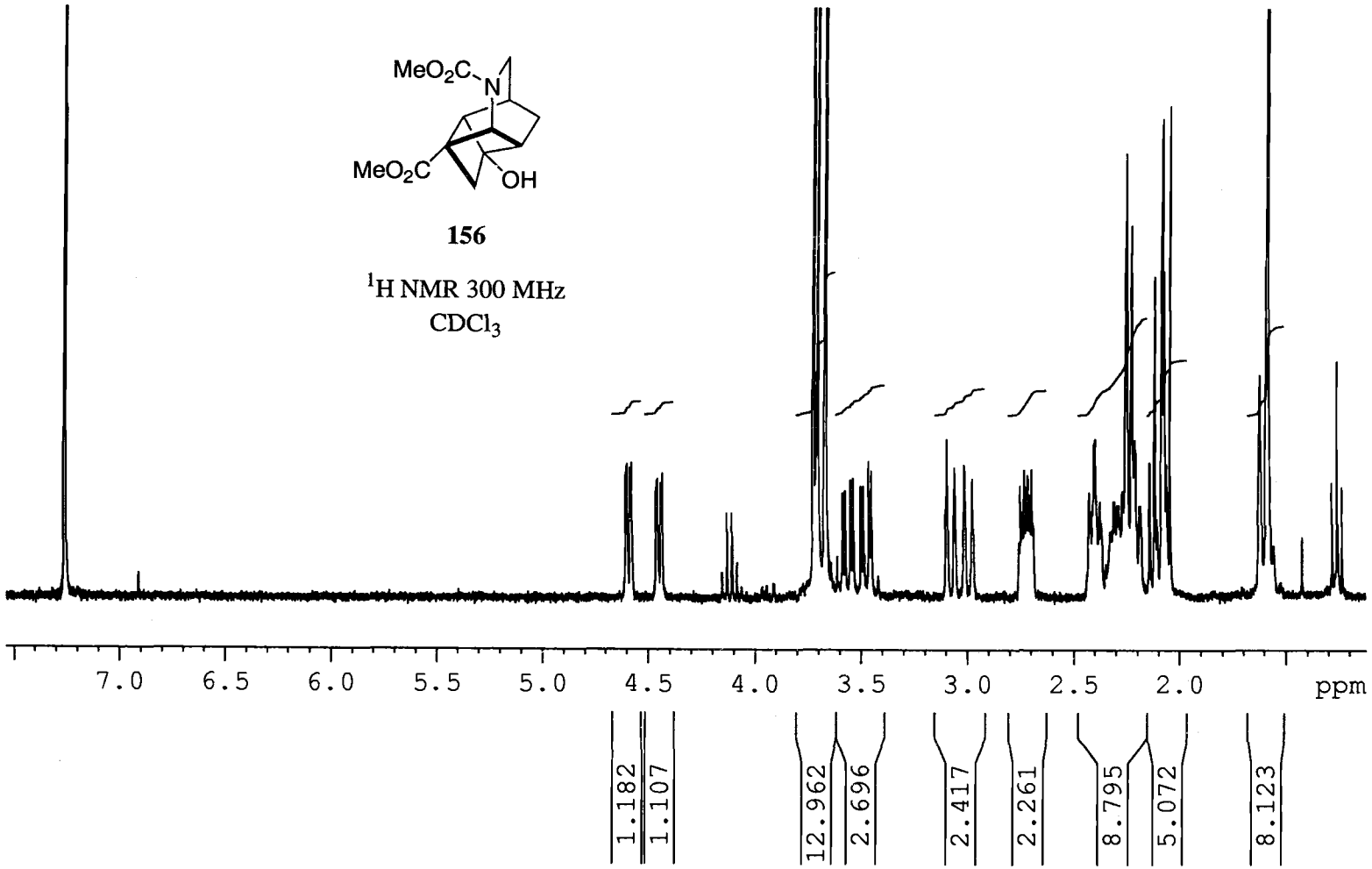
$^{13}C$ NMR 75 MHz
$CDCl_3$

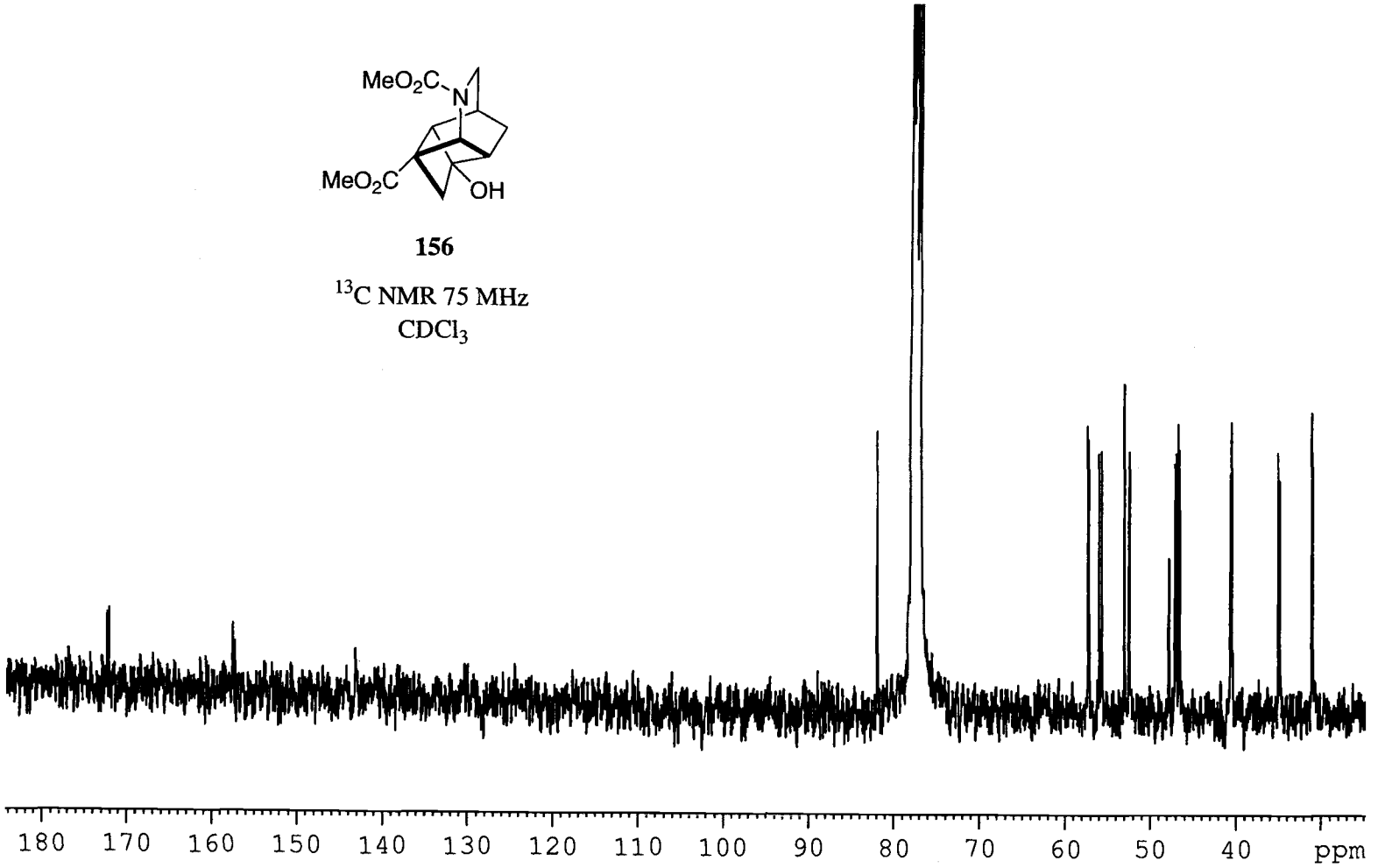

MeO2C
N
MeO2C
OTMS
155
1H NMR 300 MHz
CDCl3
7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
1.014
1.056
17.160
0.462
1.081
1.106
0.766
1.166
1.173
1.971
2.091
2.958
2.514
3.221
1.329
4.239
2.325
2.029
1.082
21.402
2.173

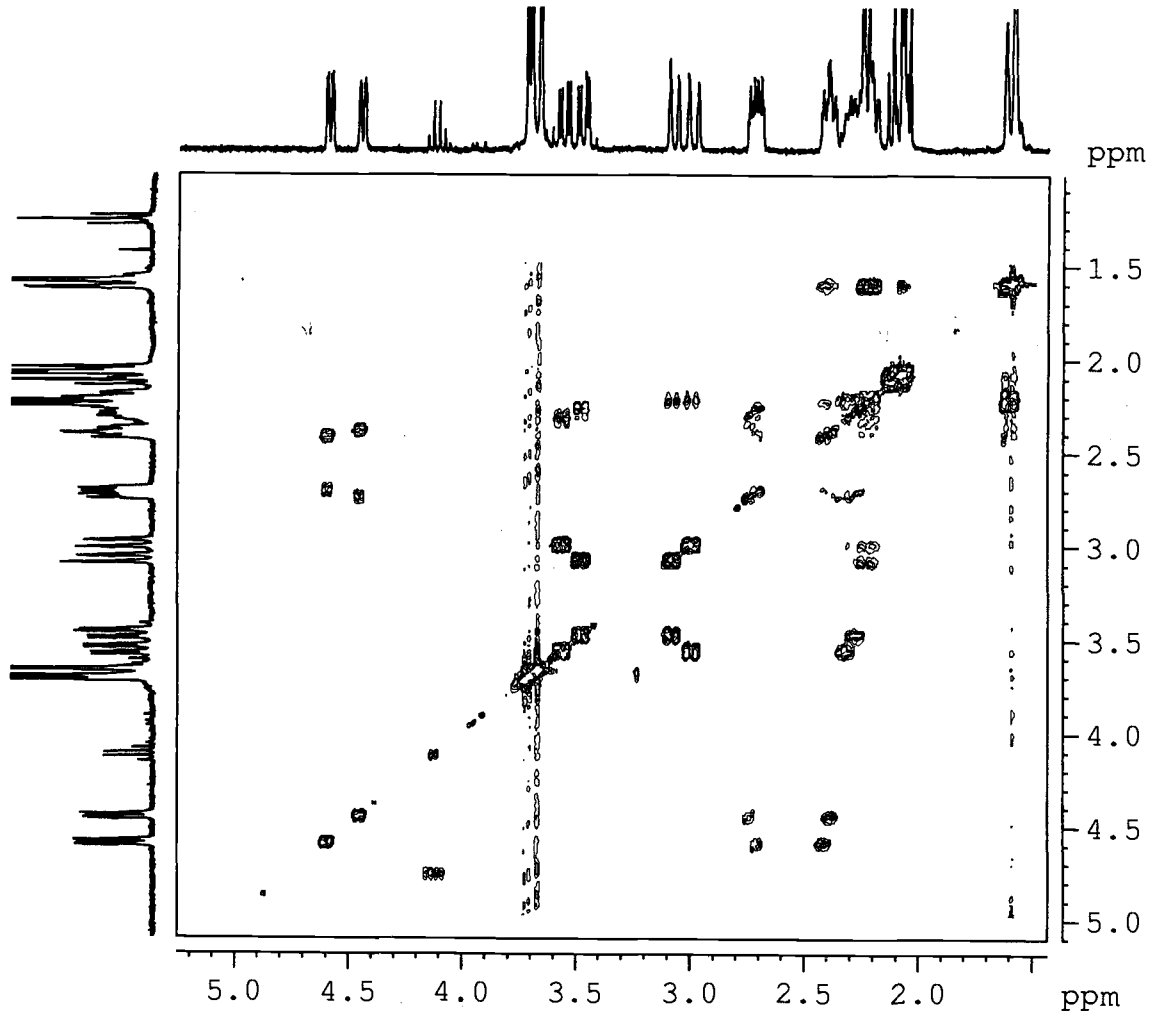


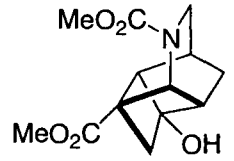

**155**

$^{13}C$ NMR 75 MHz
$CDCl_3$


MeO2C
N
MeO2C
OH
156
1H NMR 300 MHz
CDCl3
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
ppm
1.182
1.107
12.962
2.696
2.417
2.261
8.795
5.072
8.123

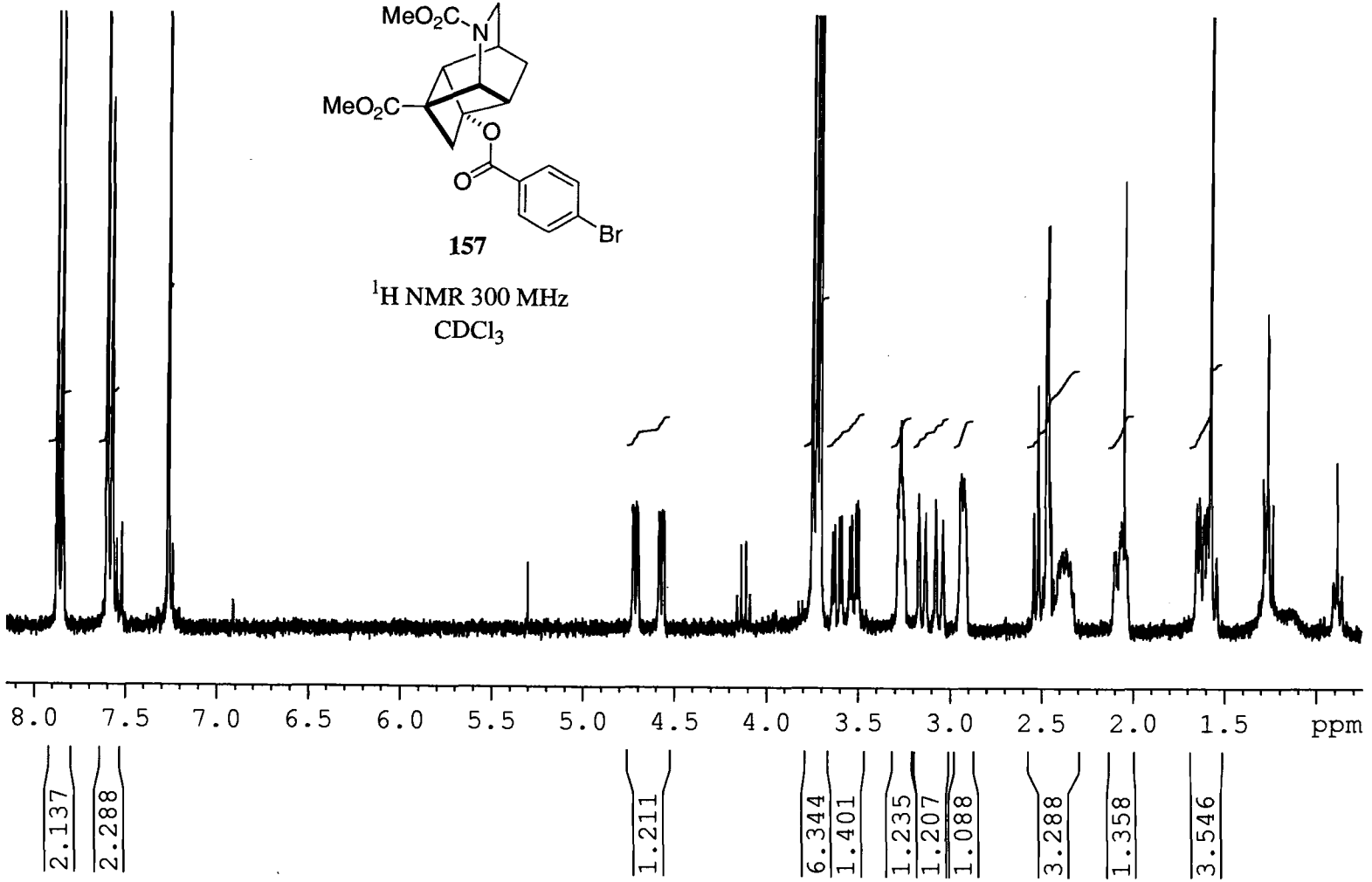

MeO2C
N
MeO2C
OH
156
13C NMR 75 MHz
CDCl3
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 ppm

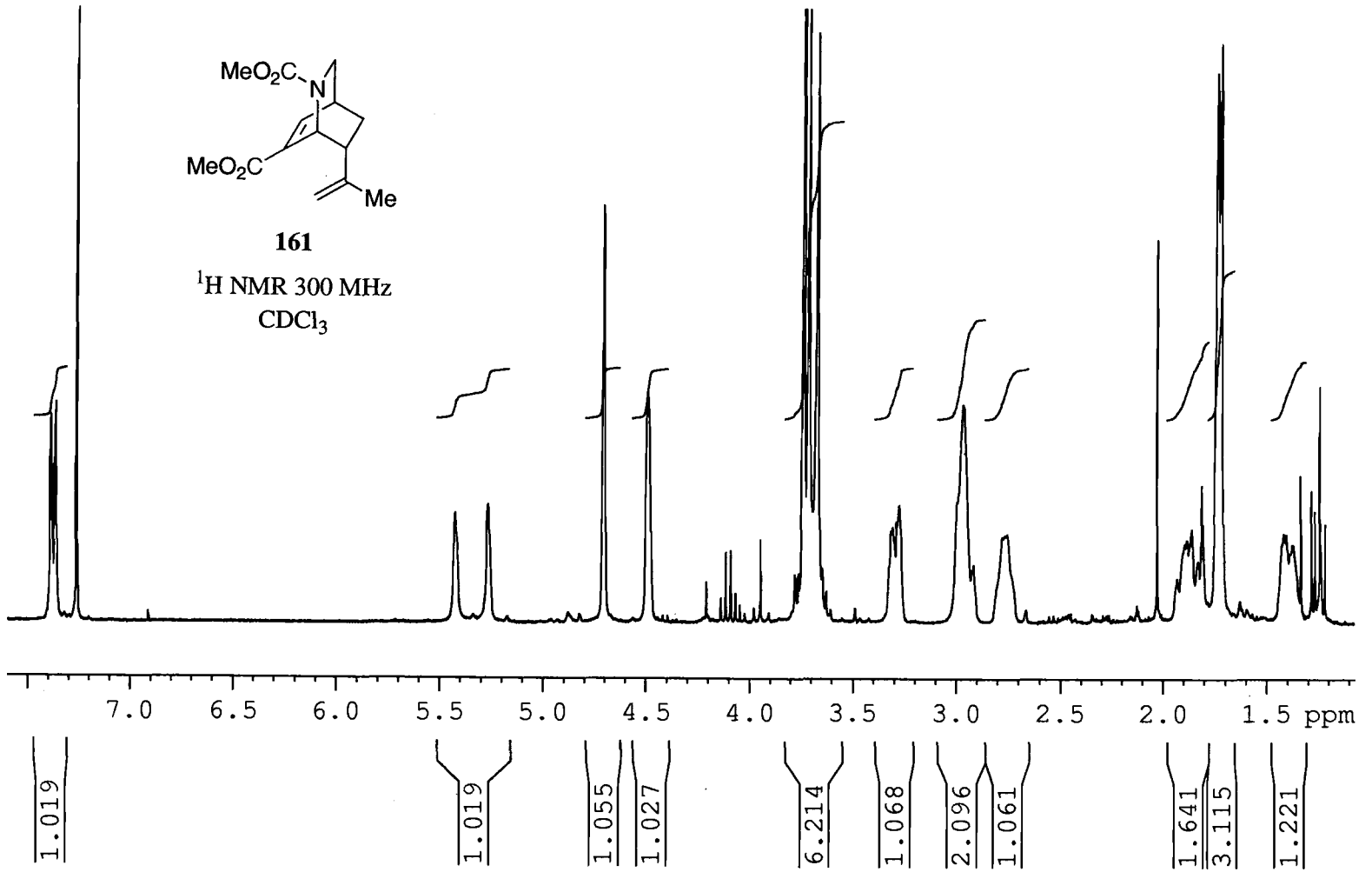


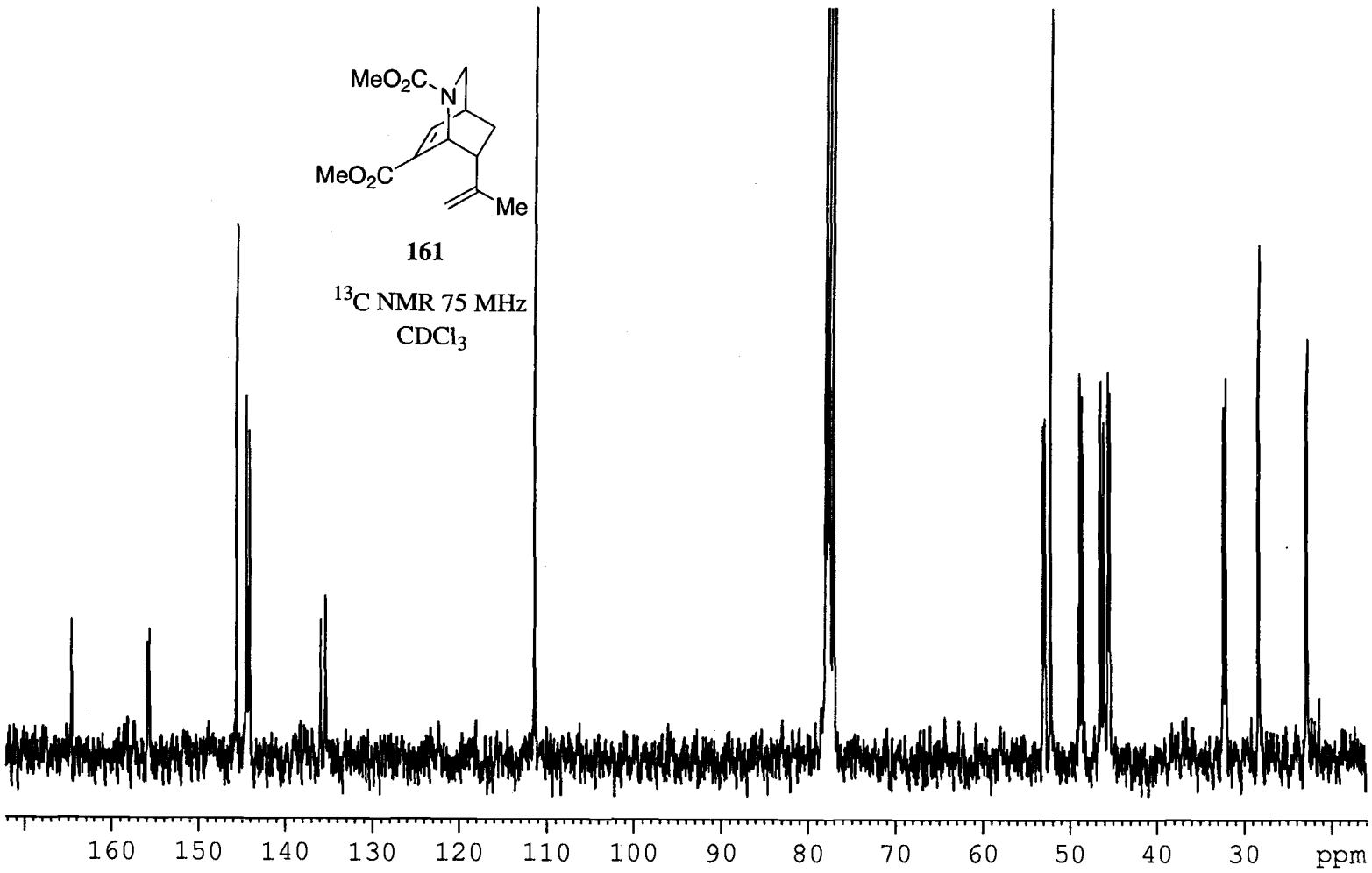



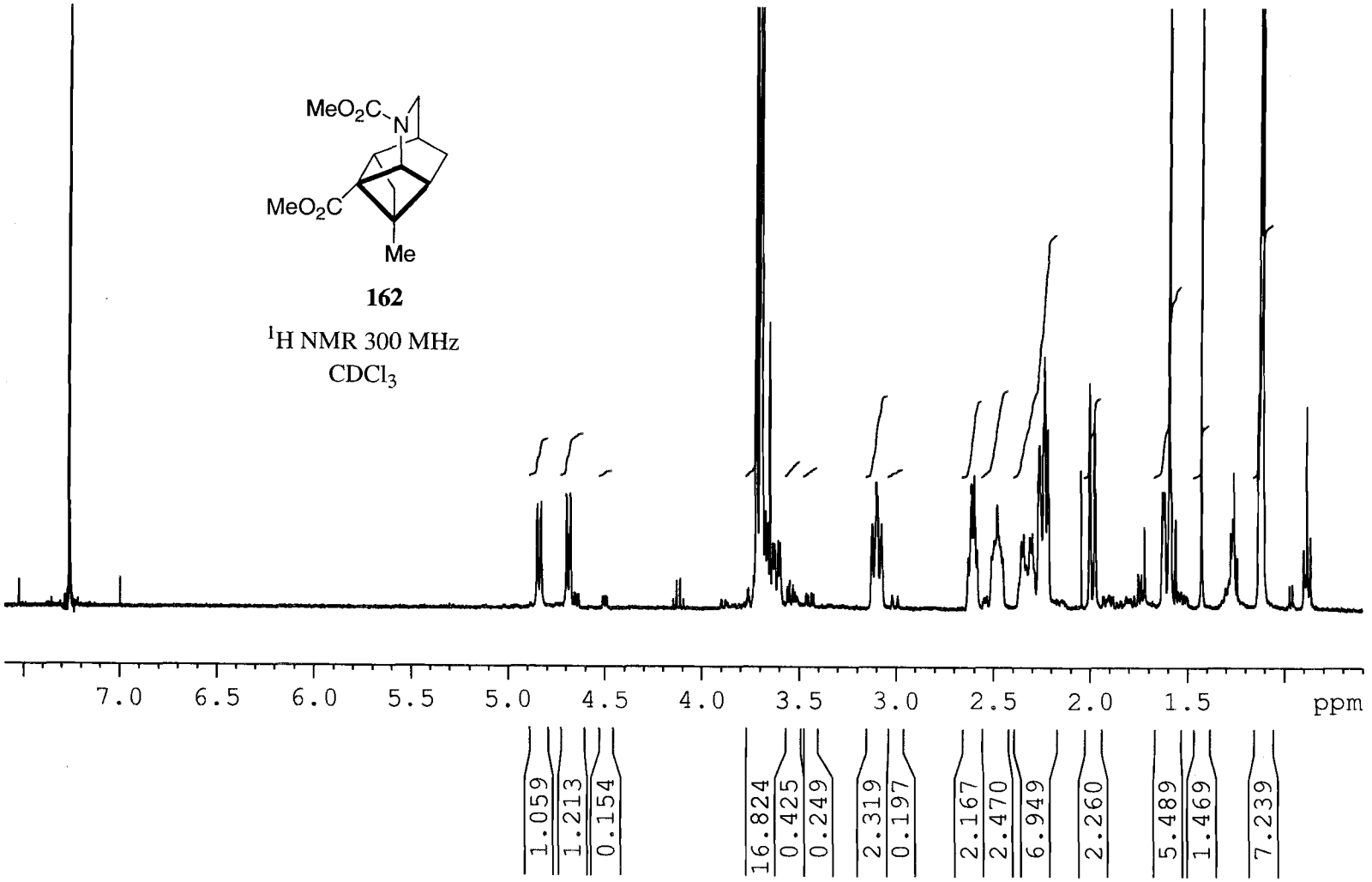

**156**

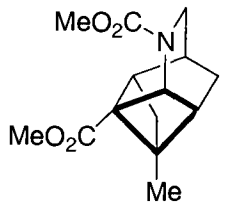
$^{1}H$-$^{1}H$ 2D NMR 300 MHz
$CDCl_3$


MeO2C
N
MeO2C
O
O
Br
157
1H NMR 300 MHz
CDCl3
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
ppm
2.137
2.288
1.211
6.344
1.401
1.235
1.207
1.088
3.288
1.358
3.546


MeO2C
N
MeO2C
Me
161
1H NMR 300 MHz
CDCl3
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5 ppm
1.019
1.019
1.055
1.027
6.214
1.068
2.096
1.061
1.641
3.115
1.221

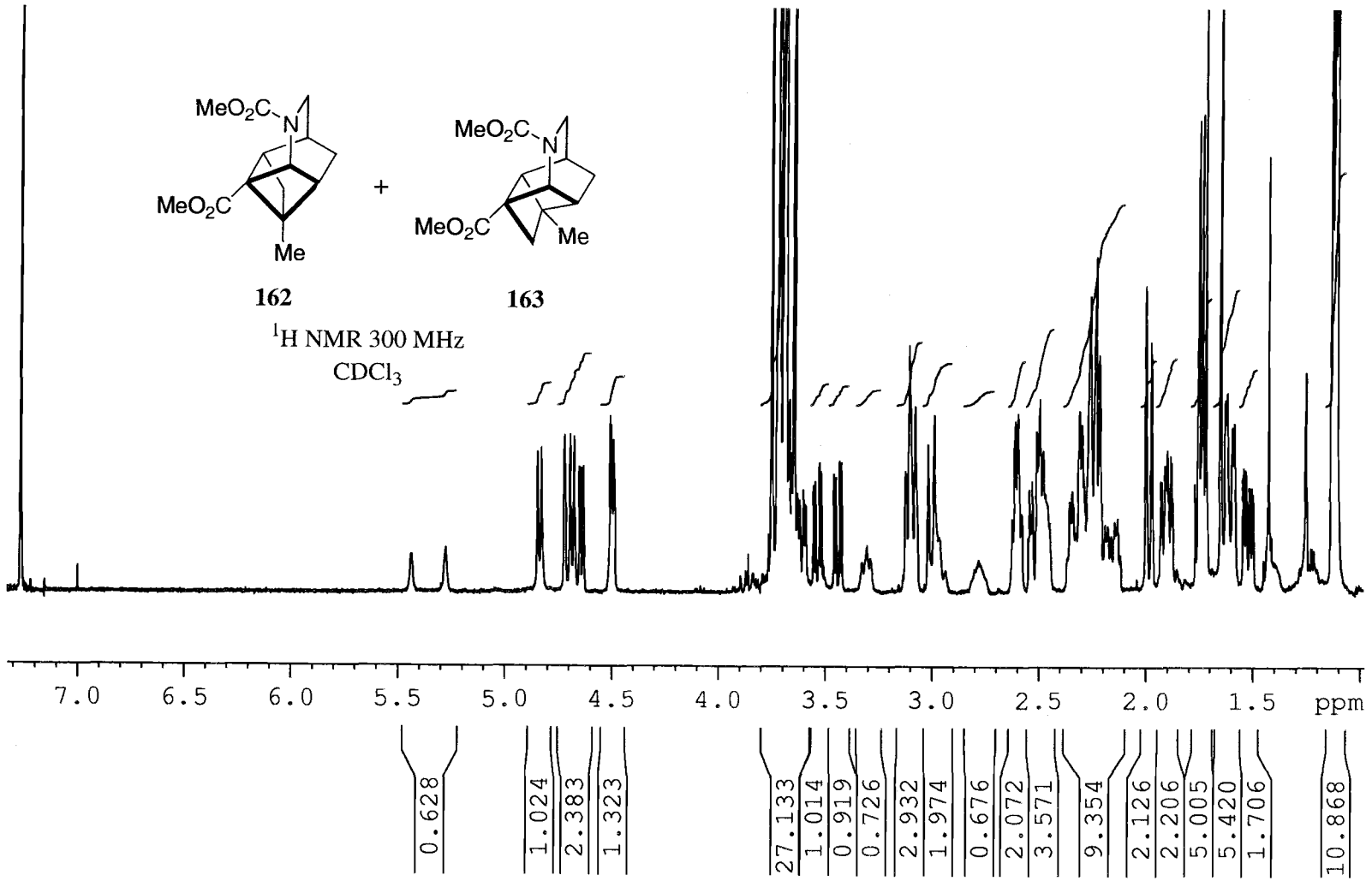

MeO2C
N
MeO2C
Me
161
13C NMR 75 MHz
CDCl3
160
150
140
130
120
110
100
90
80
70
60
50
40
30
ppm

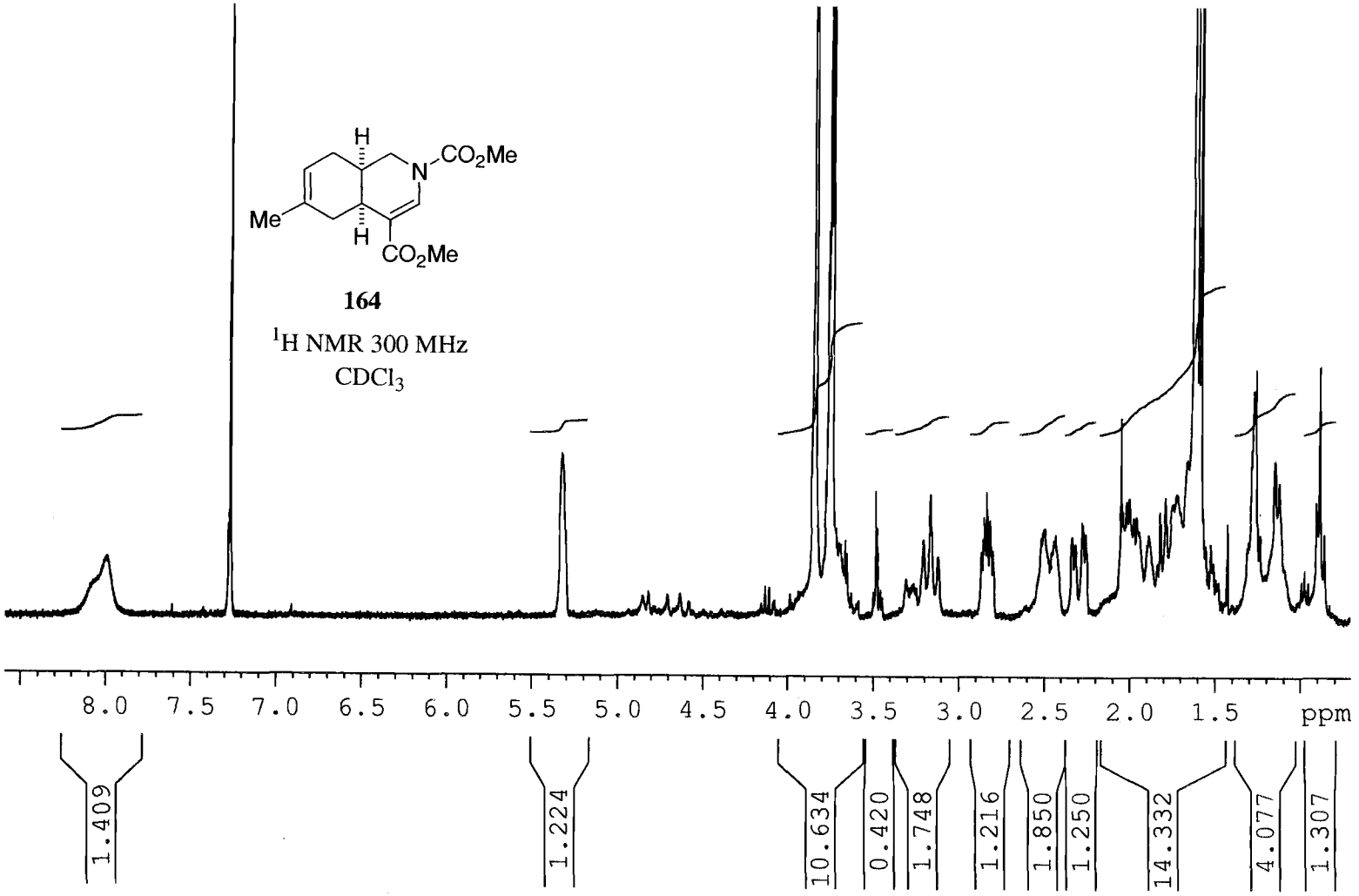

MeO2C
N
MeO2C
Me
162
1H NMR 300 MHz
CDCl3
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
ppm
1.059
1.213
0.154
16.824
0.425
0.249
2.319
0.197
2.167
2.470
6.949
2.260
5.489
1.469
7.239




**162**

$^{13}C$ NMR 75 MHz
$CDCl_3$

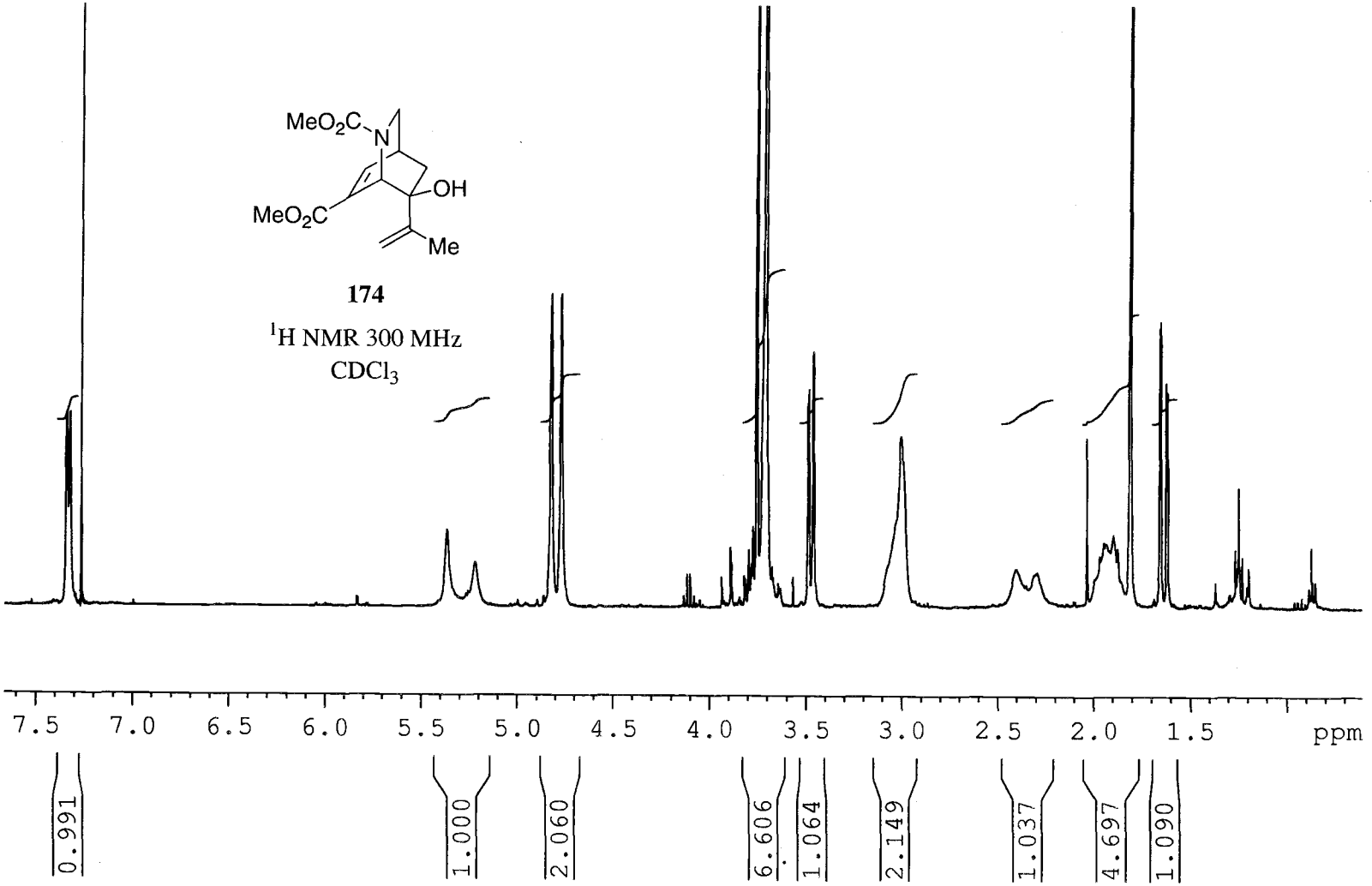

MeO2C
N
MeO2C
Me
+
MeO2C
N
MeO2C
Me
162
163
1H NMR 300 MHz
CDCl3
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
ppm
0.628
1.024
2.383
1.323
27.133
1.014
0.919
0.726
2.932
1.974
0.676
2.072
3.571
9.354
2.126
2.206
5.005
5.420
1.706
10.868

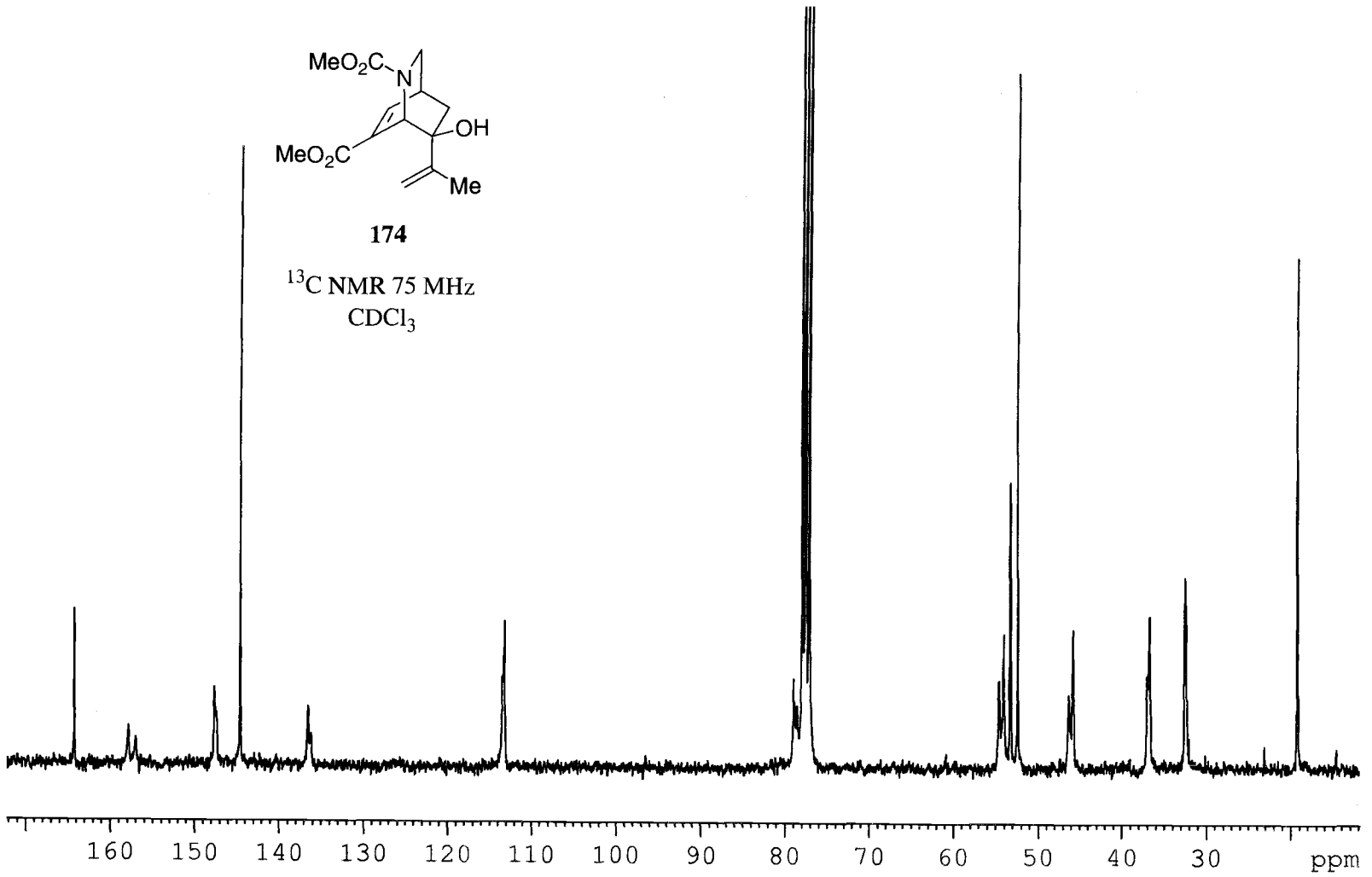



**164**

$^1$H NMR 300 MHz

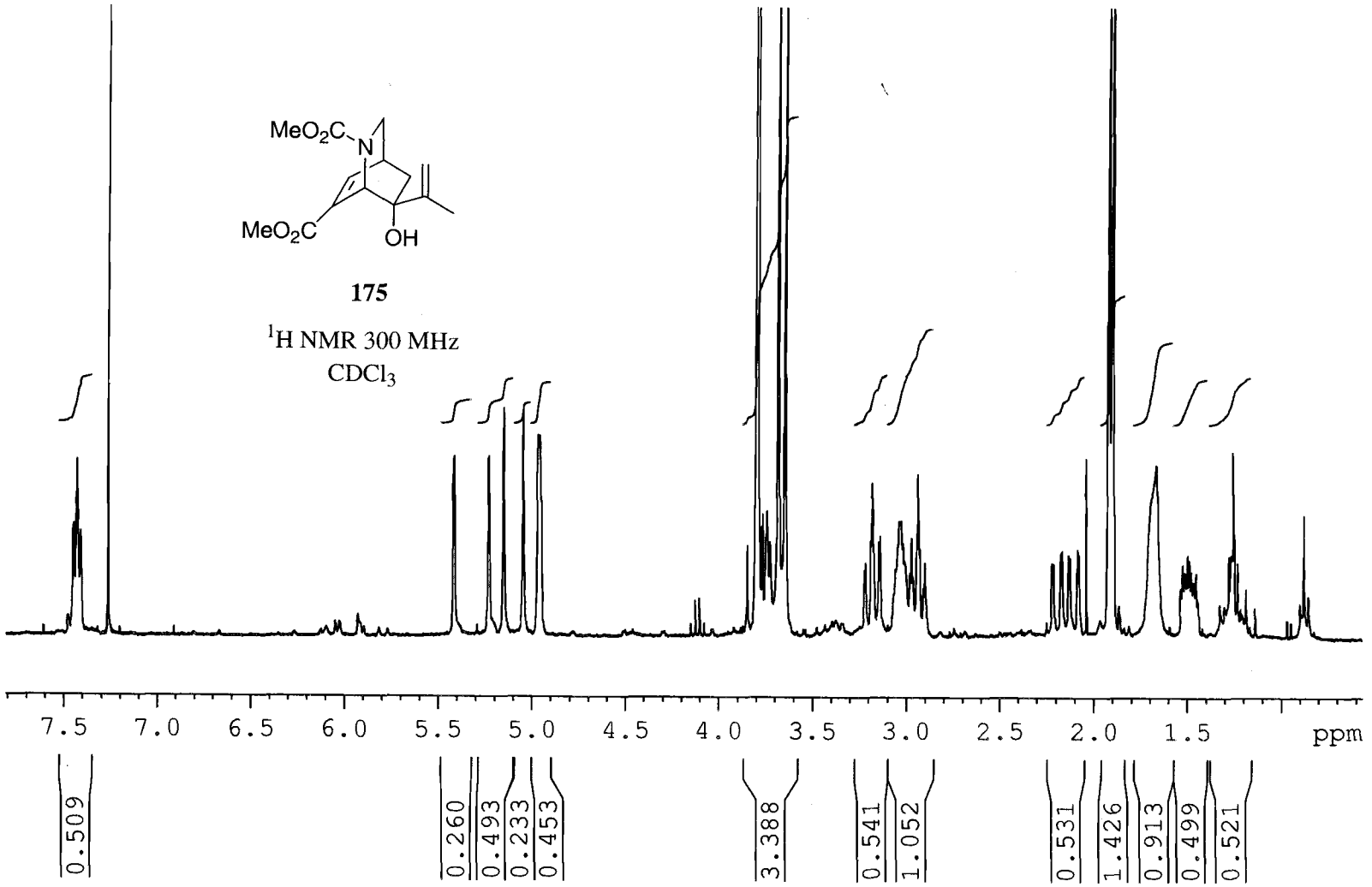
$CDCl_3$

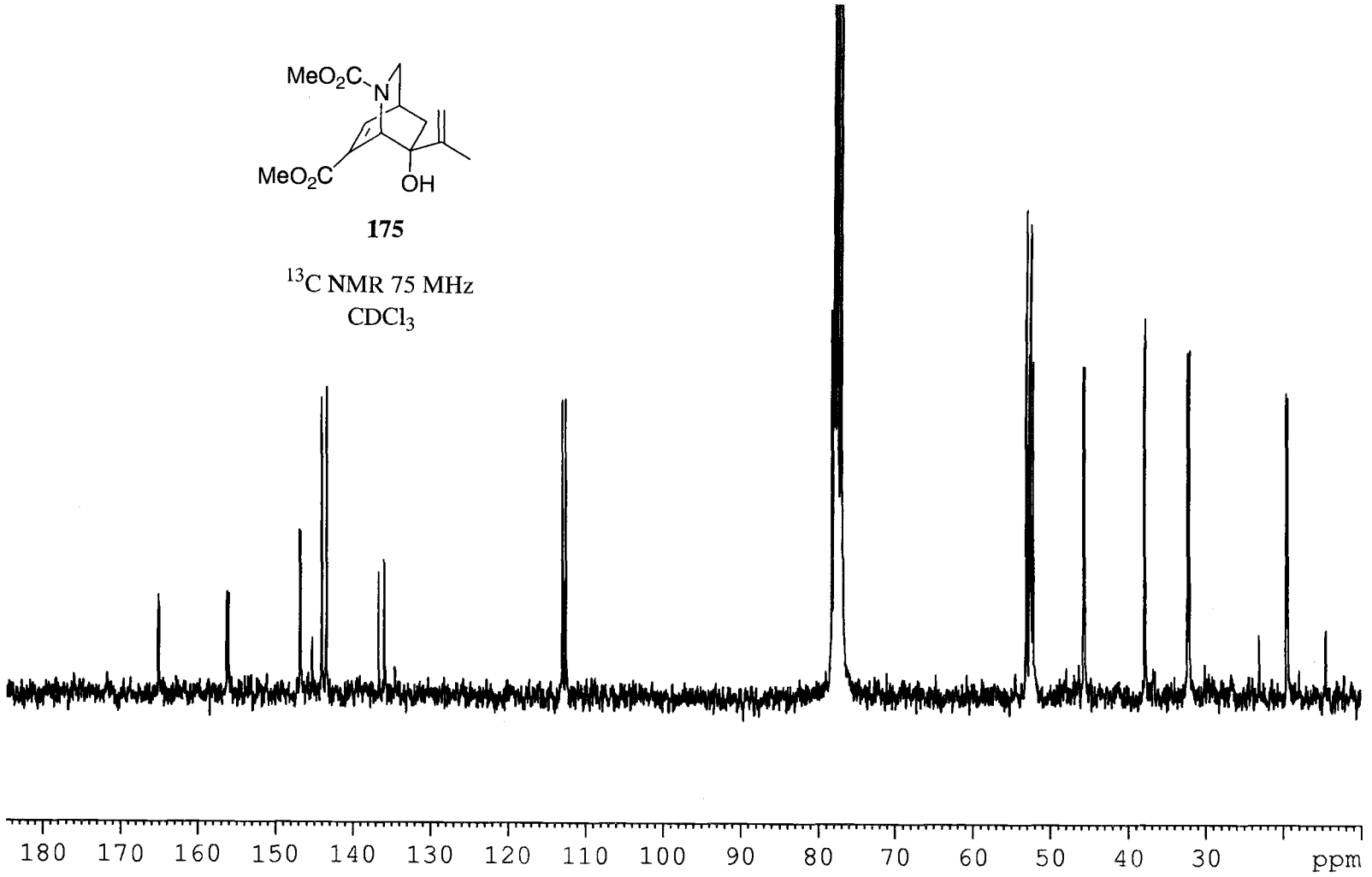

MeO2C
N
OH
MeO2C
Me
174
1H NMR 300 MHz
CDCl3
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
ppm
0.991
1.000
2.060
6.606
1.064
2.149
1.037
4.697
1.090

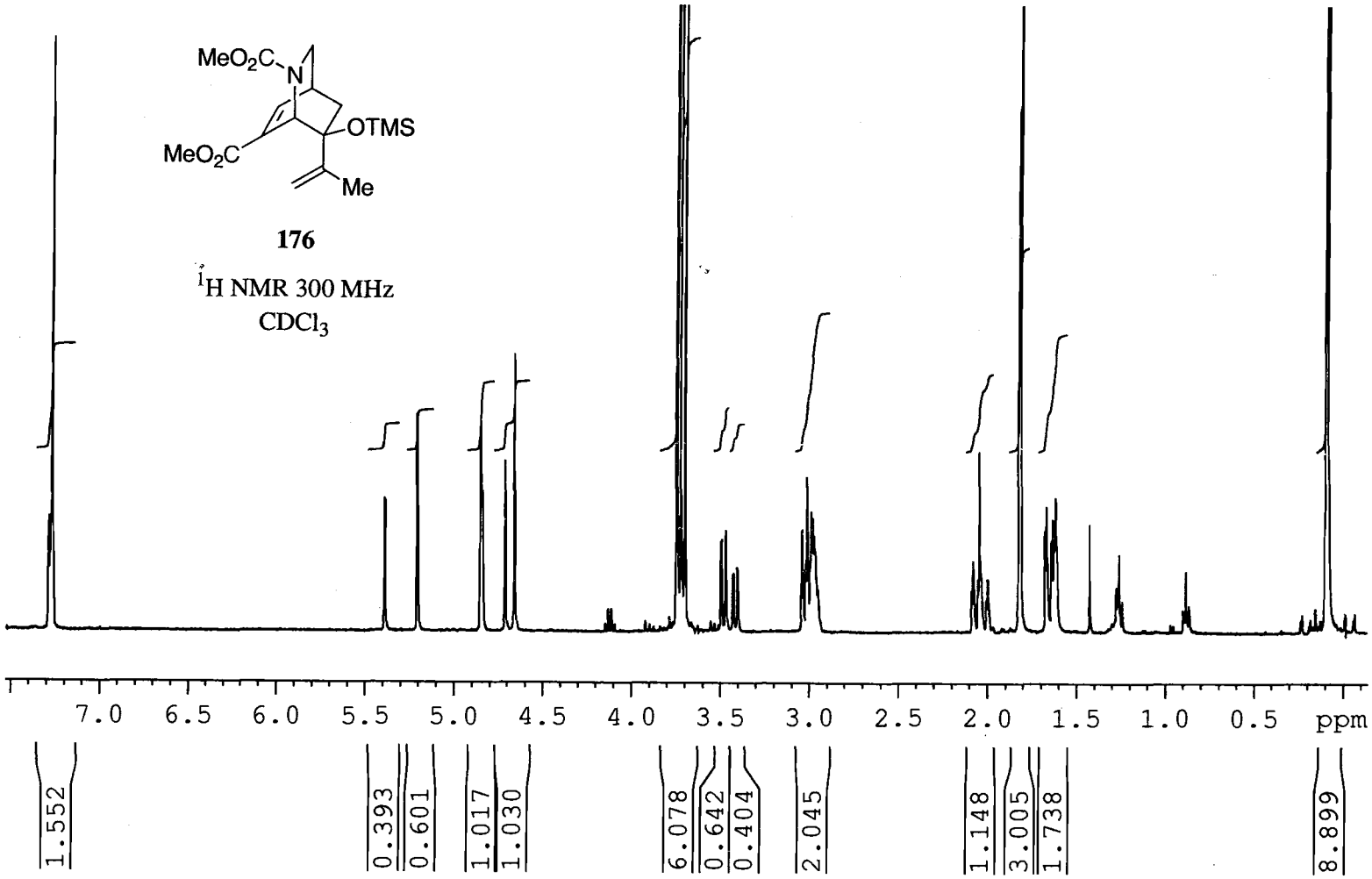


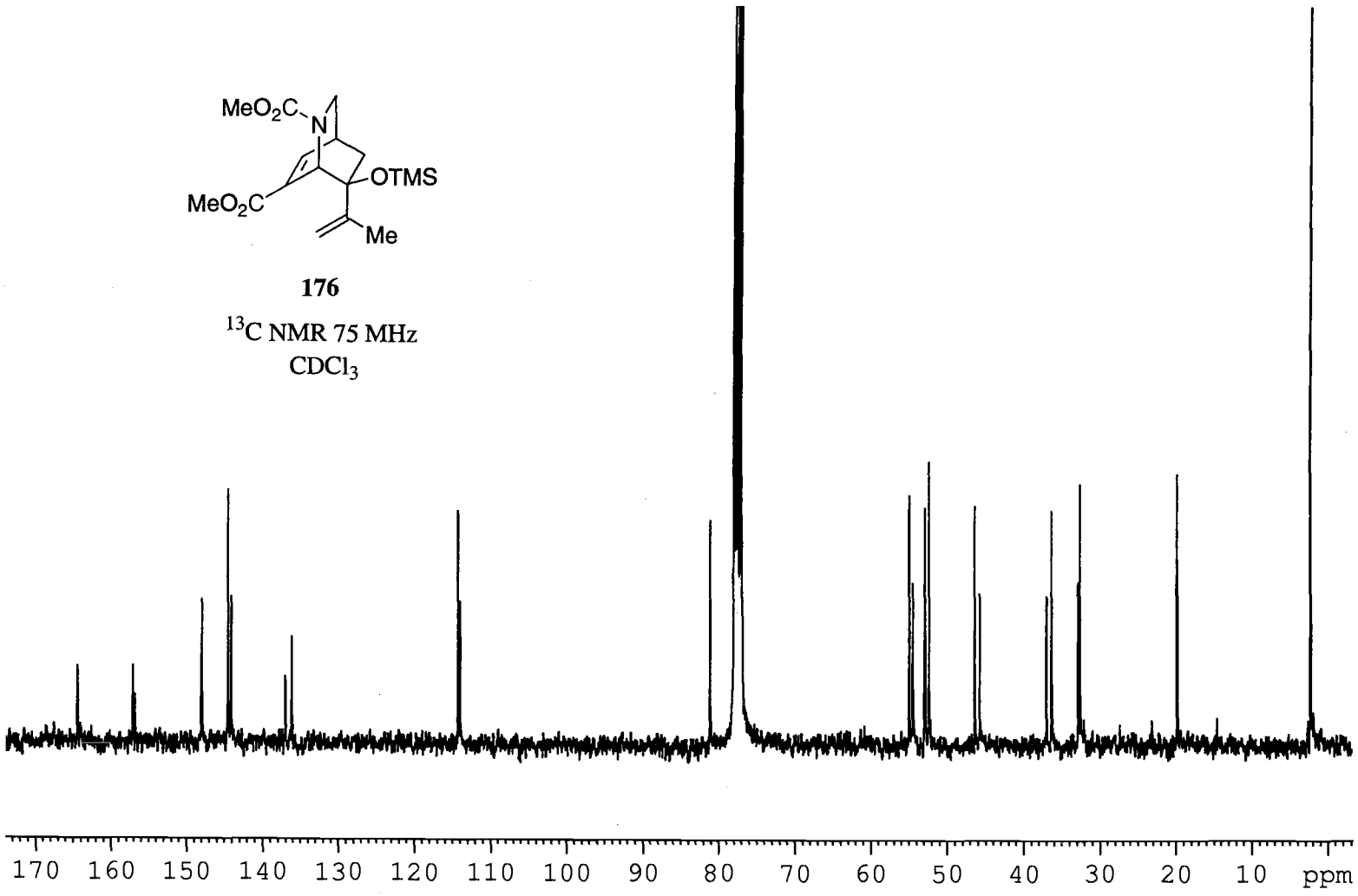

**174**

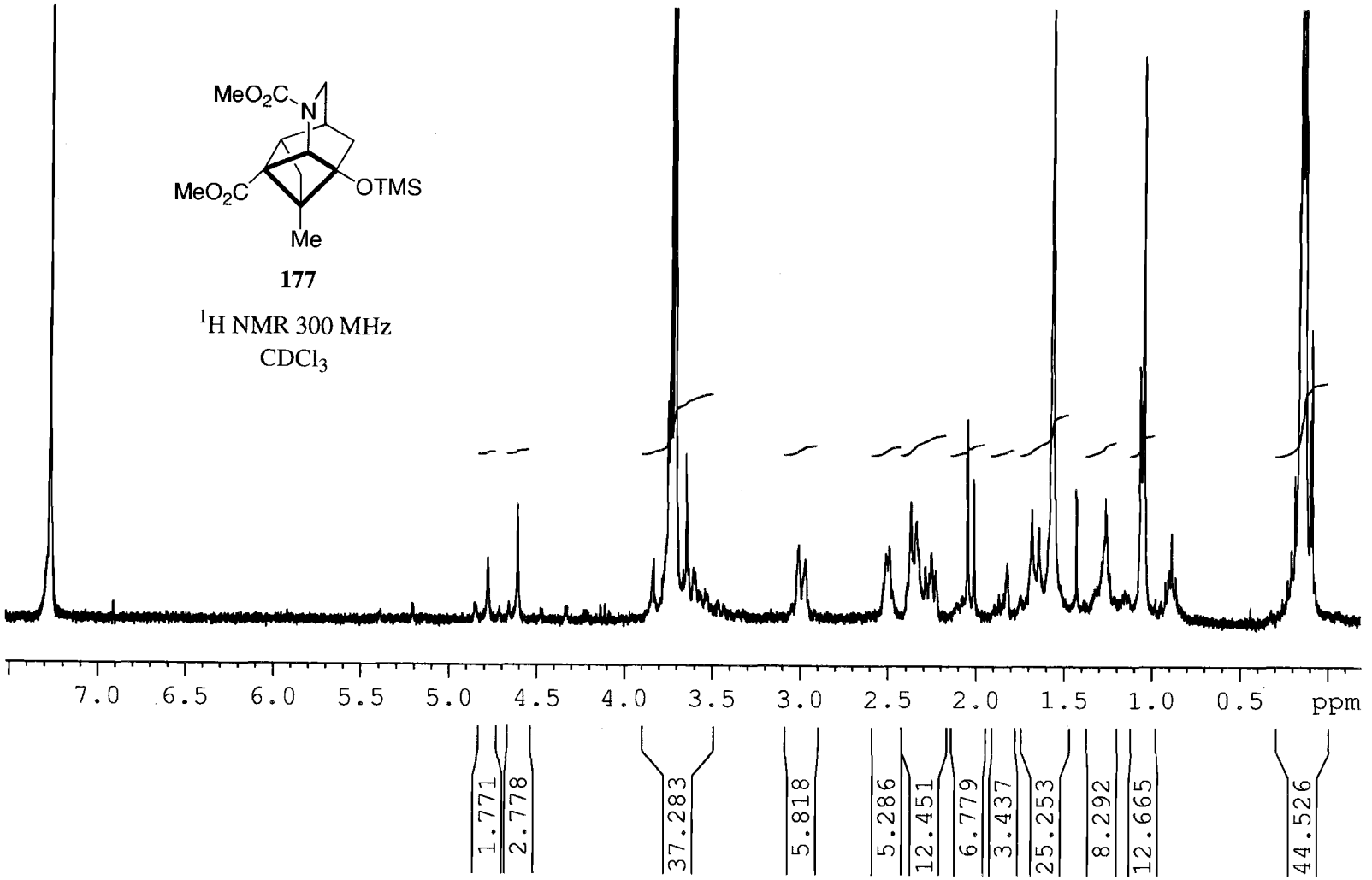
$^{13}C$ NMR 75 MHz
$CDCl_3$

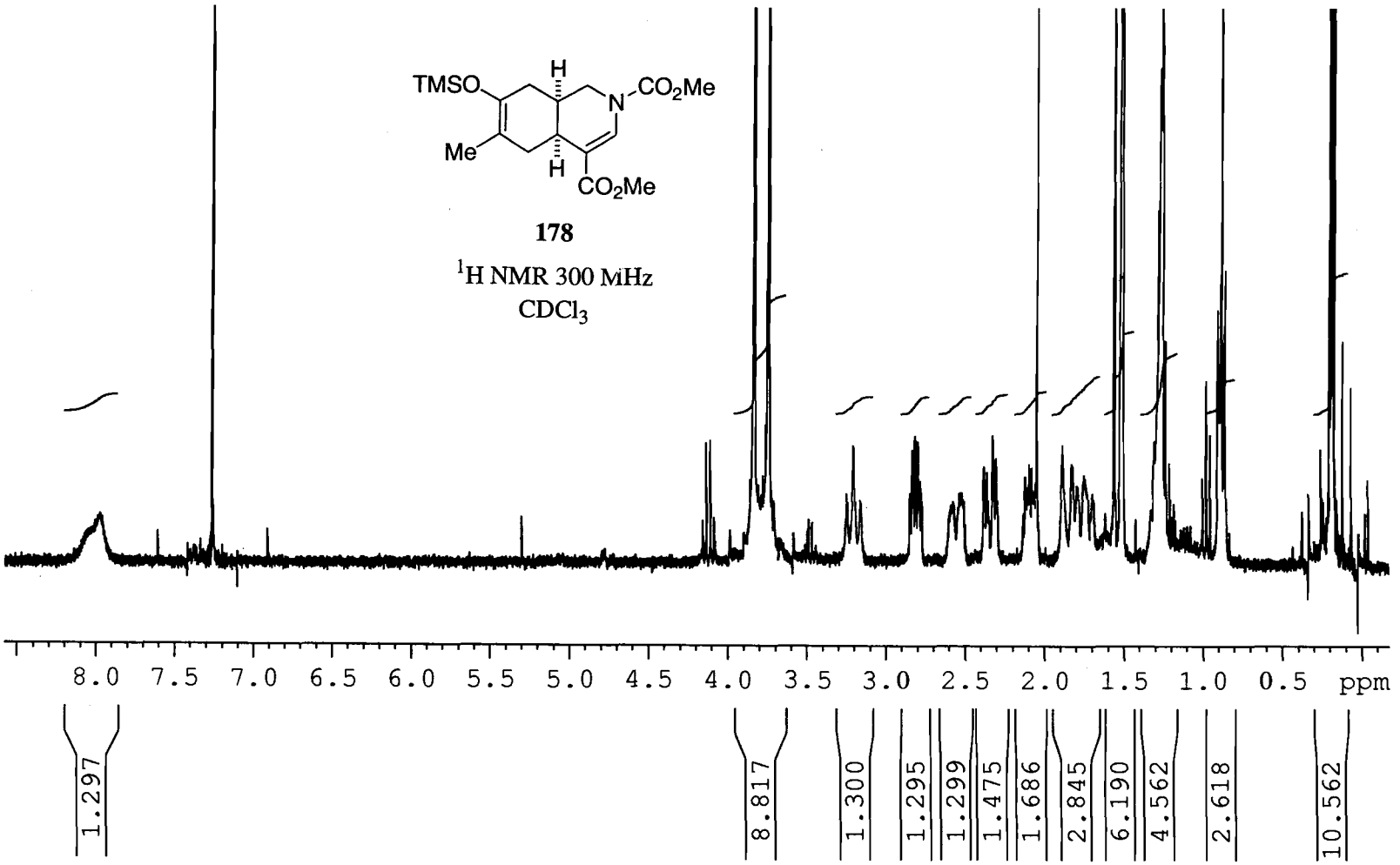

MeO2C
N
MeO2C
OH
175
1H NMR 300 MHz
CDCl3
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
ppm
0.509
0.260
0.493
0.233
0.453
3.388
0.541
1.052
0.531
1.426
0.913
0.499
0.521

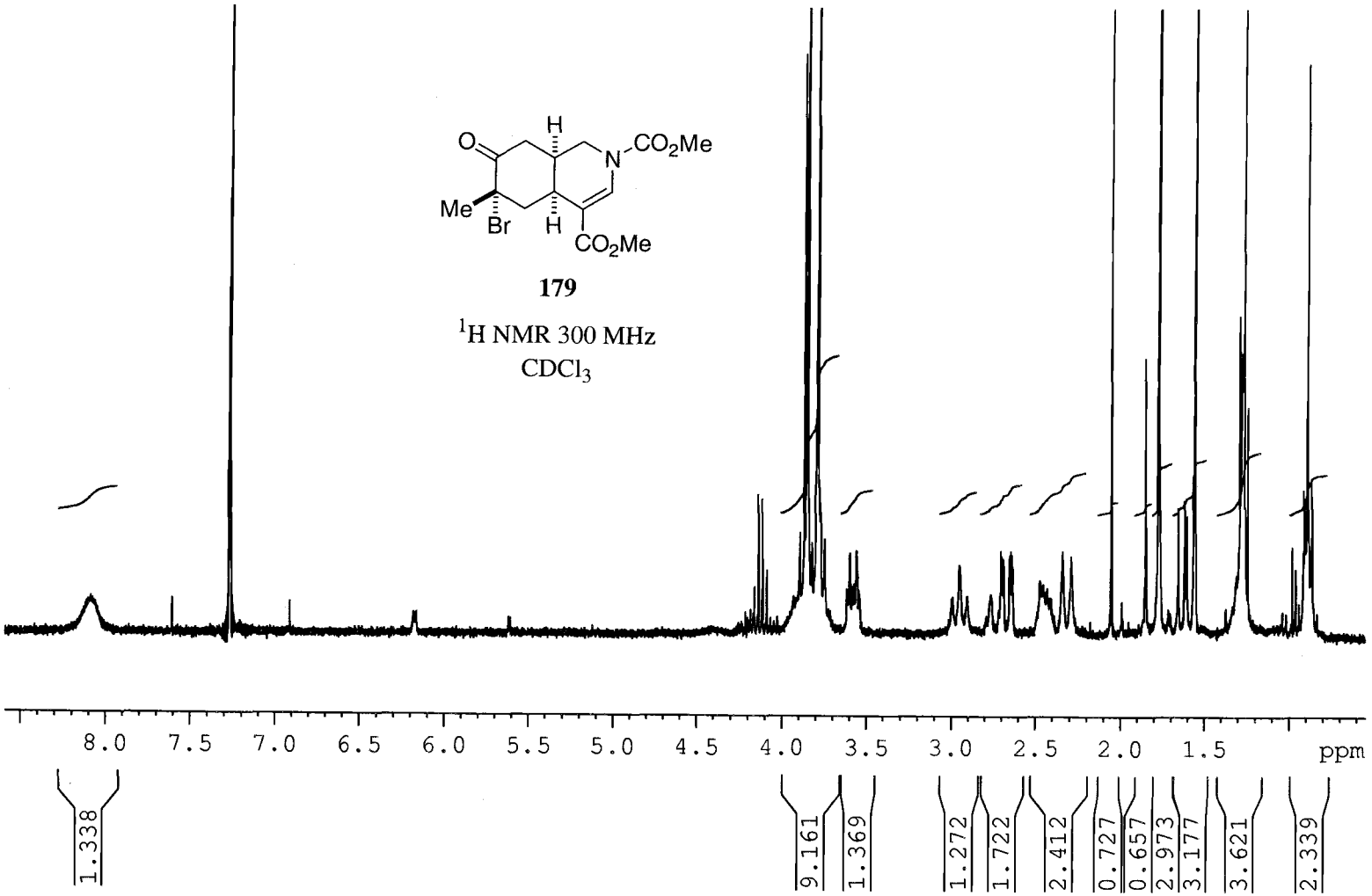

MeO2C
N
MeO2C
OH
175
13C NMR 75 MHz
CDCl3
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30
ppm


MeO2C
N
OTMS
MeO2C
Me
176
1H NMR 300 MHz
CDCl3
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
1.552
0.393
0.601
1.017
1.030
6.078
0.642
0.404
2.045
1.148
3.005
1.738
8.899


MeO2C
N
OTMS
MeO2C
Me
176
13C NMR 75 MHz
CDCl3
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

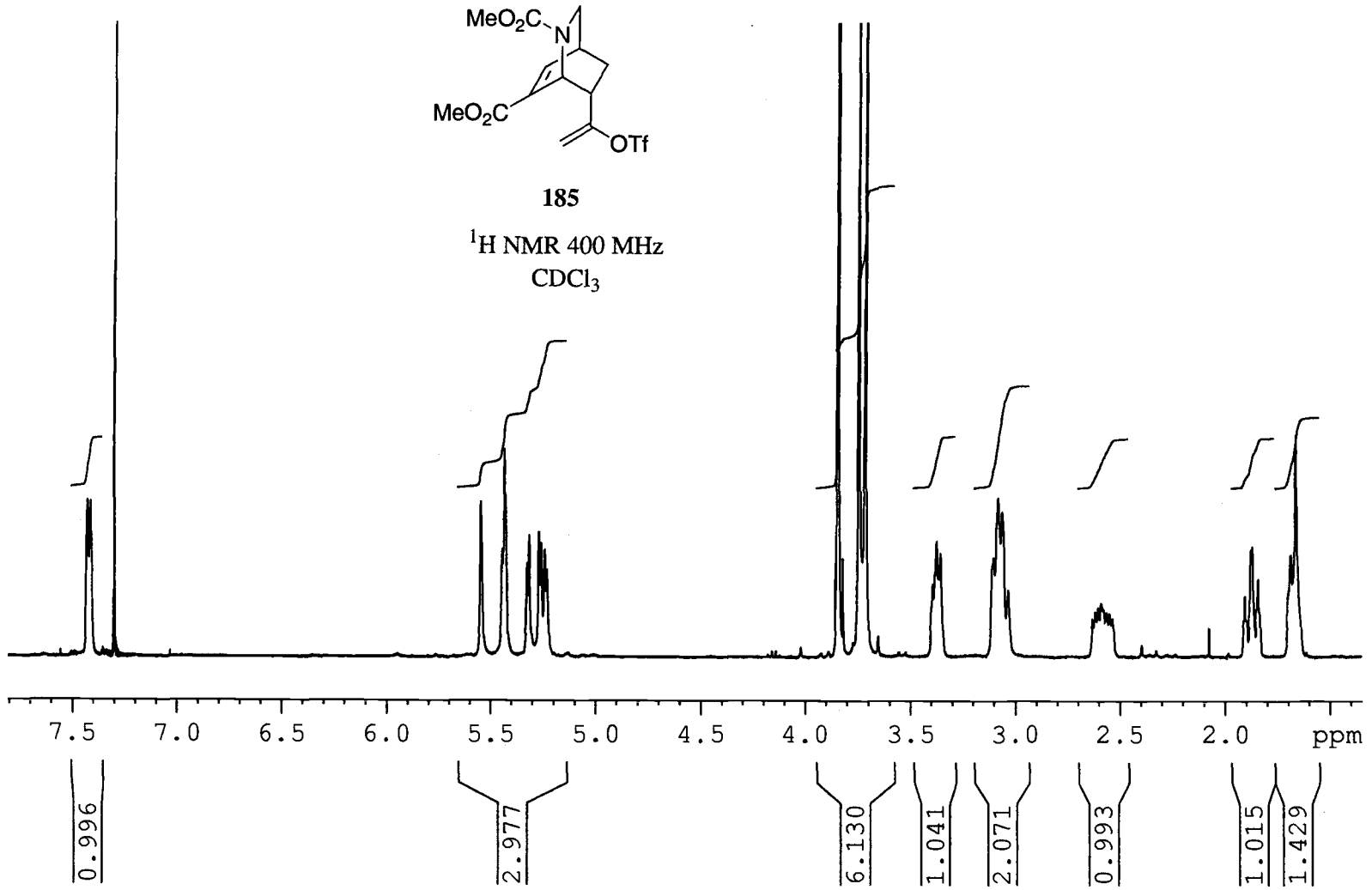

MeO2C
N
MeO2C
OTMS
Me
177
1H NMR 300 MHz
CDCl3
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
1.771
2.778
37.283
5.818
5.286
12.451
6.779
3.437
25.253
8.292
12.665
44.526

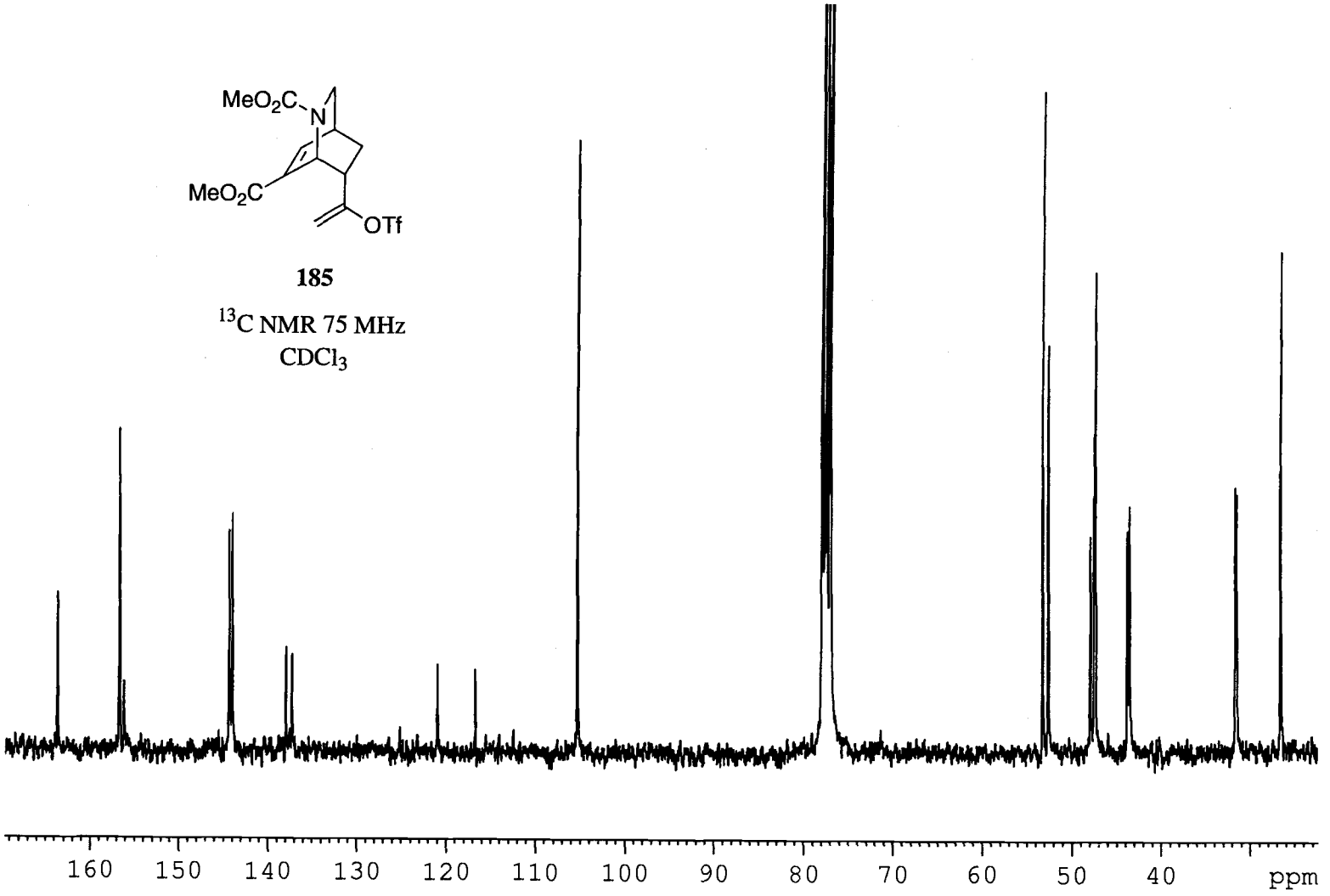

TMSO
H
N
CO2Me
Me
H
CO2Me
178
1H NMR 300 MHz
CDCl3
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
1.297
8.817
1.300
1.295
1.299
1.475
1.686
2.845
6.190
4.562
2.618
10.562




**179**

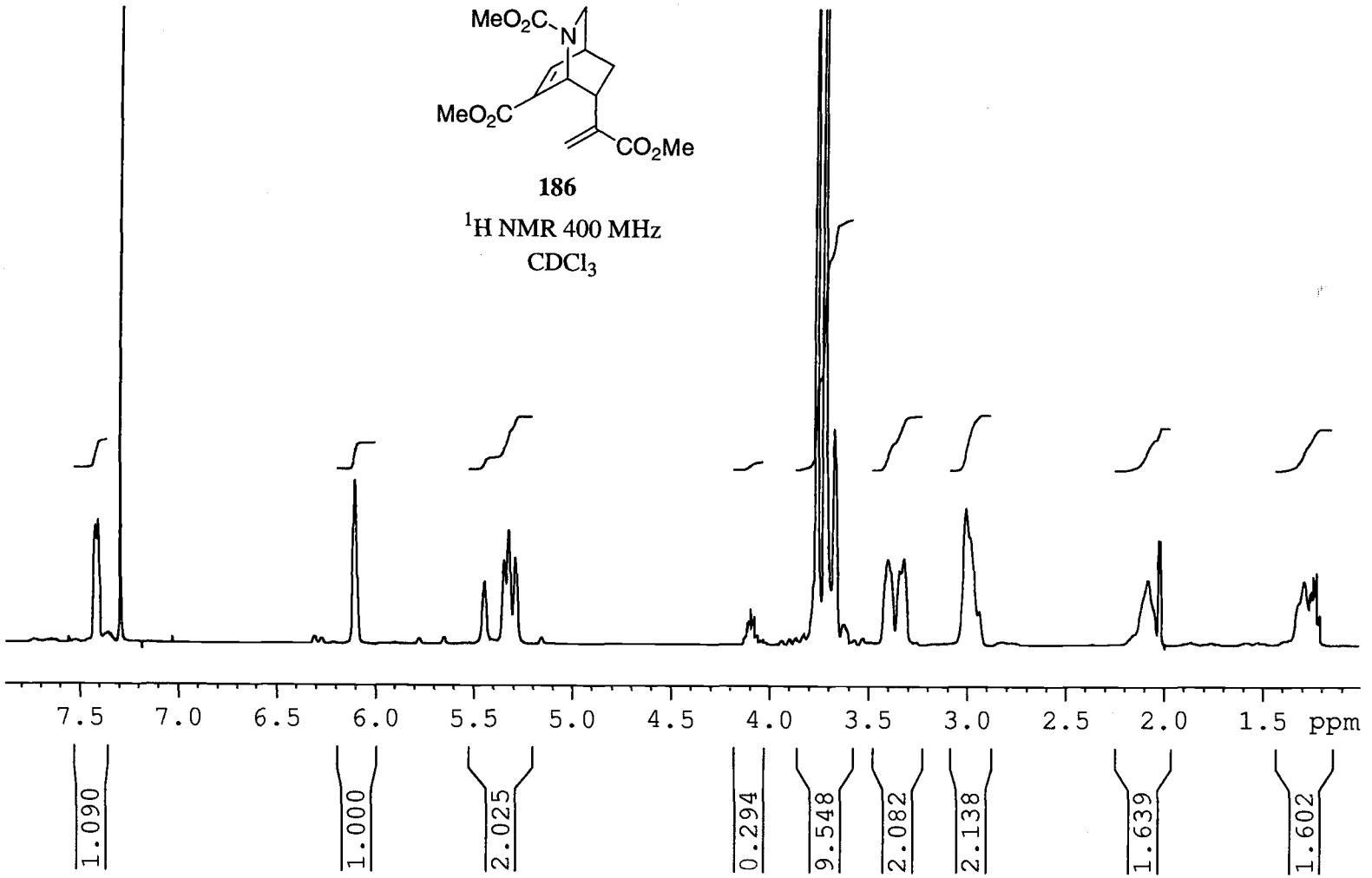
$^1$H NMR 300 MHz
$CDCl_3$


MeO2C
N
MeO2C
OTf
185
1H NMR 400 MHz
CDCl3
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
ppm
0.996
2.977
6.130
1.041
2.071
0.993
1.015
1.429




**185**

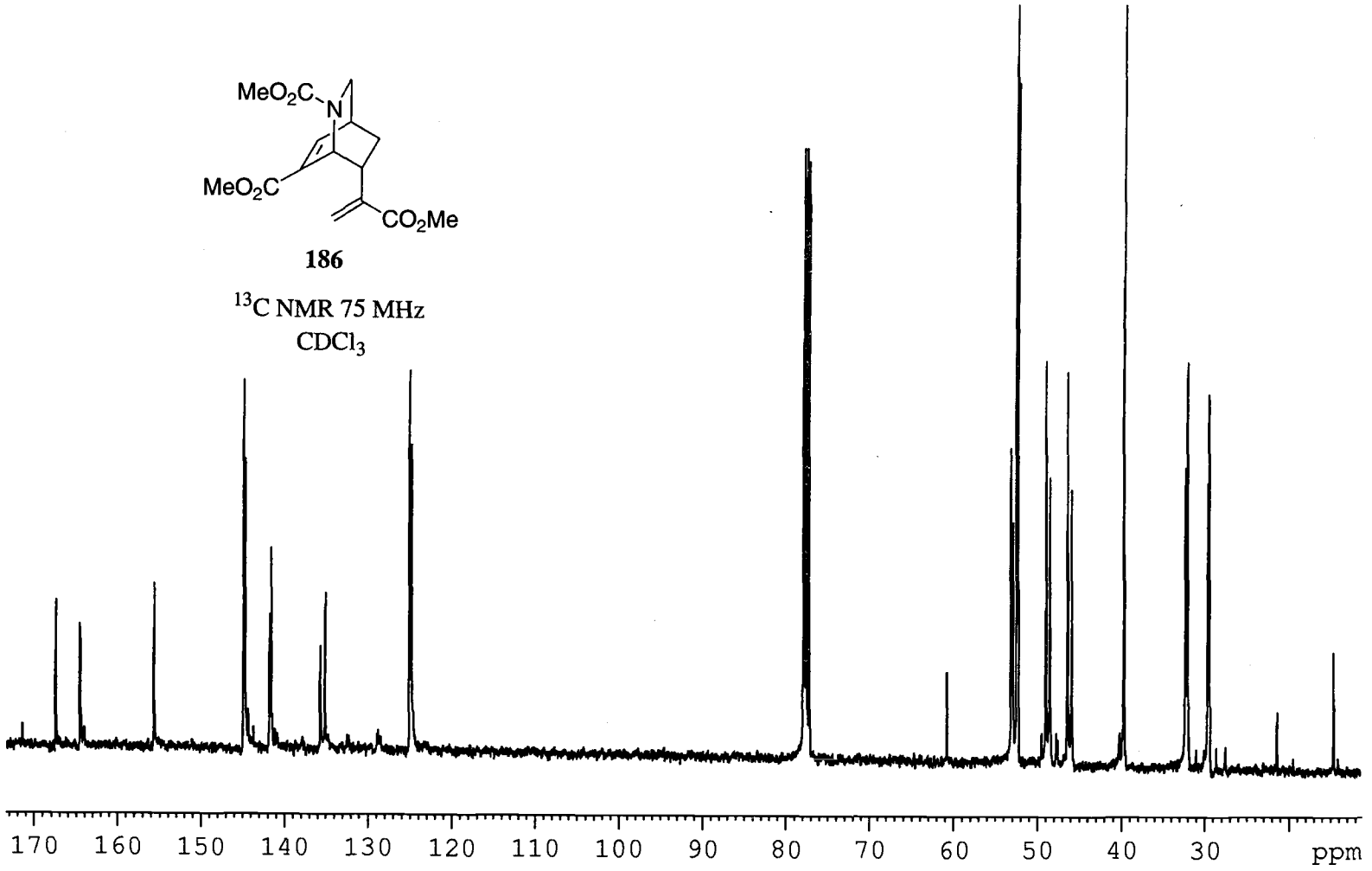
$^{13}C$ NMR 75 MHz
$CDCl_3$

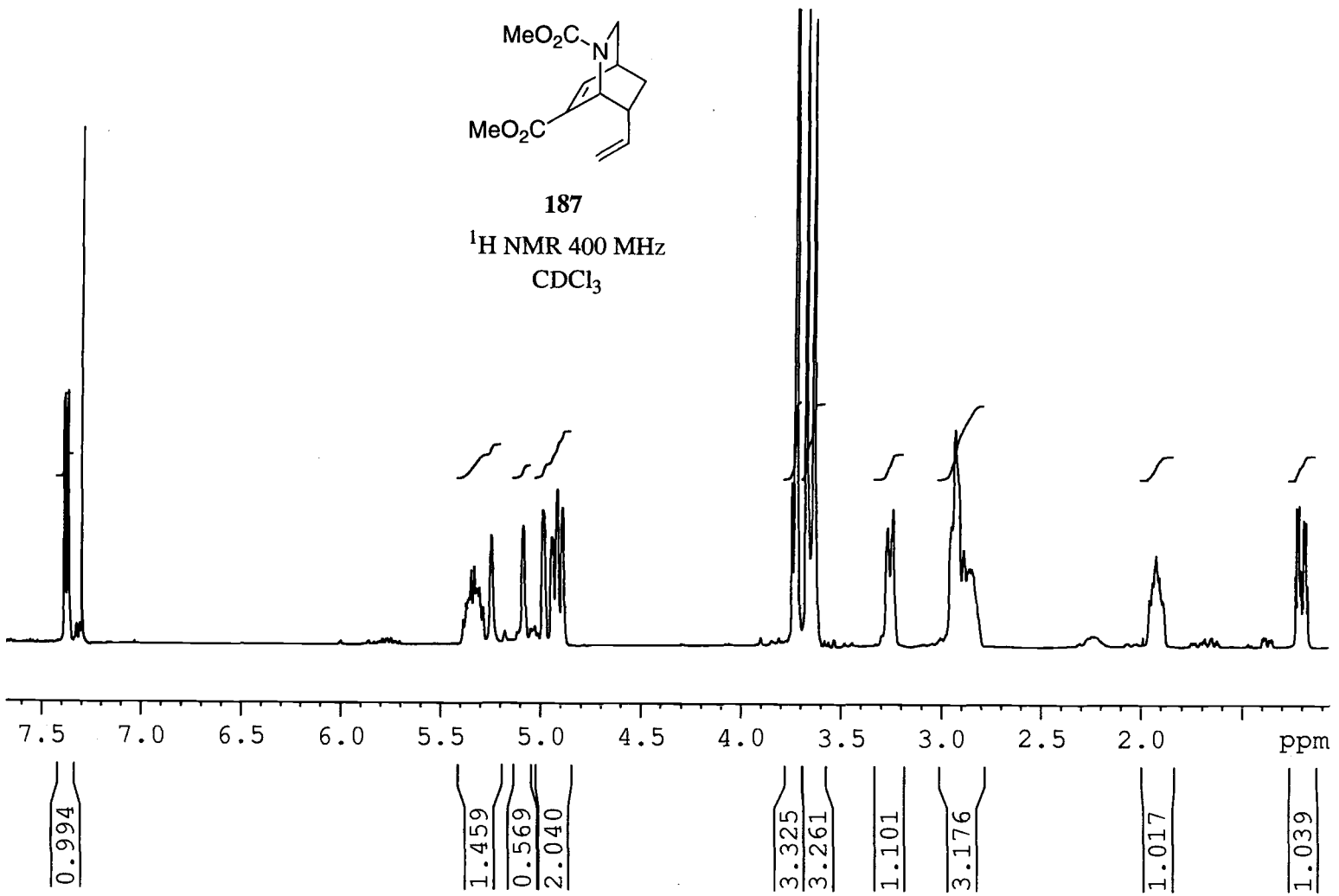


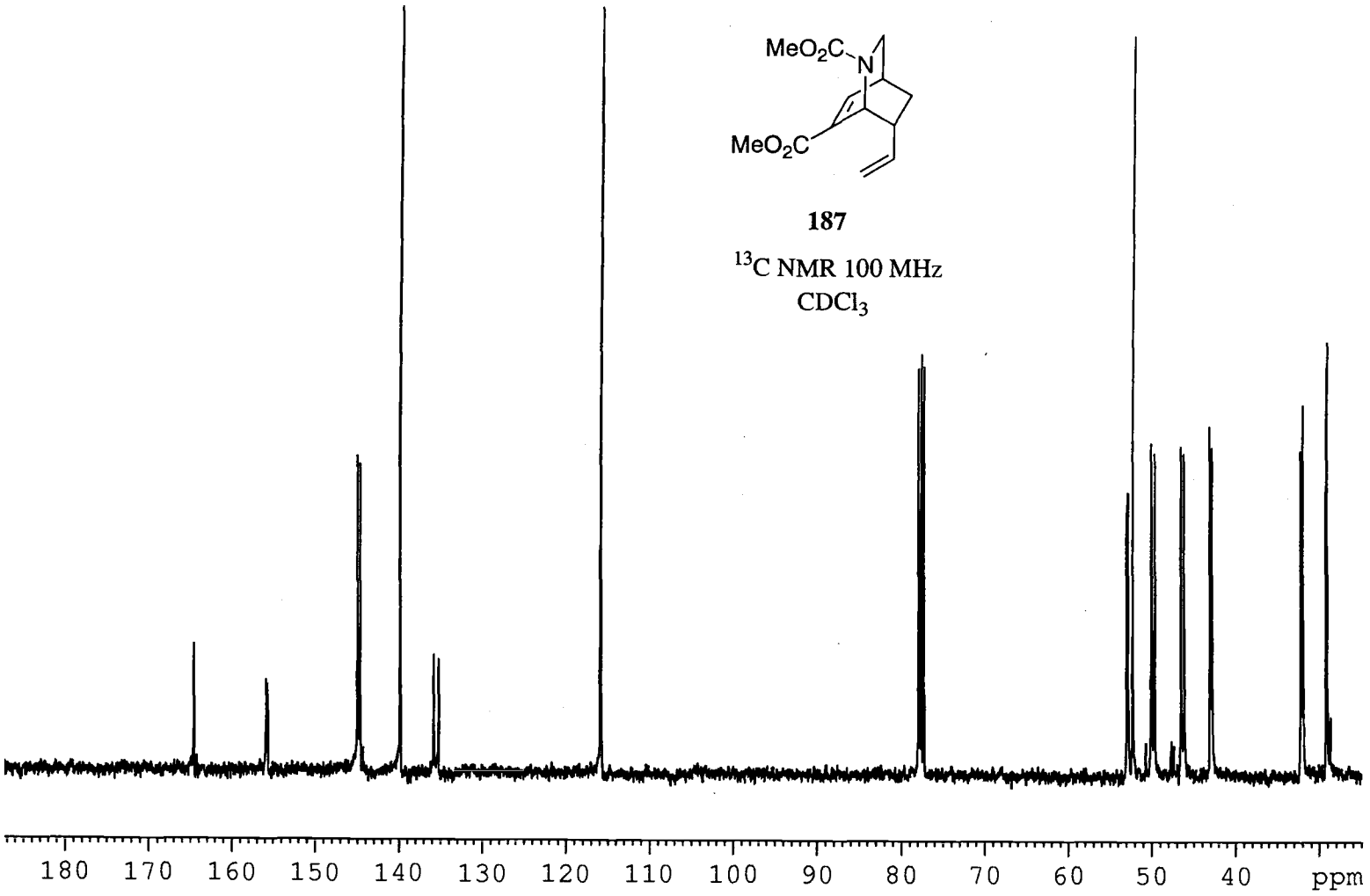

**186**

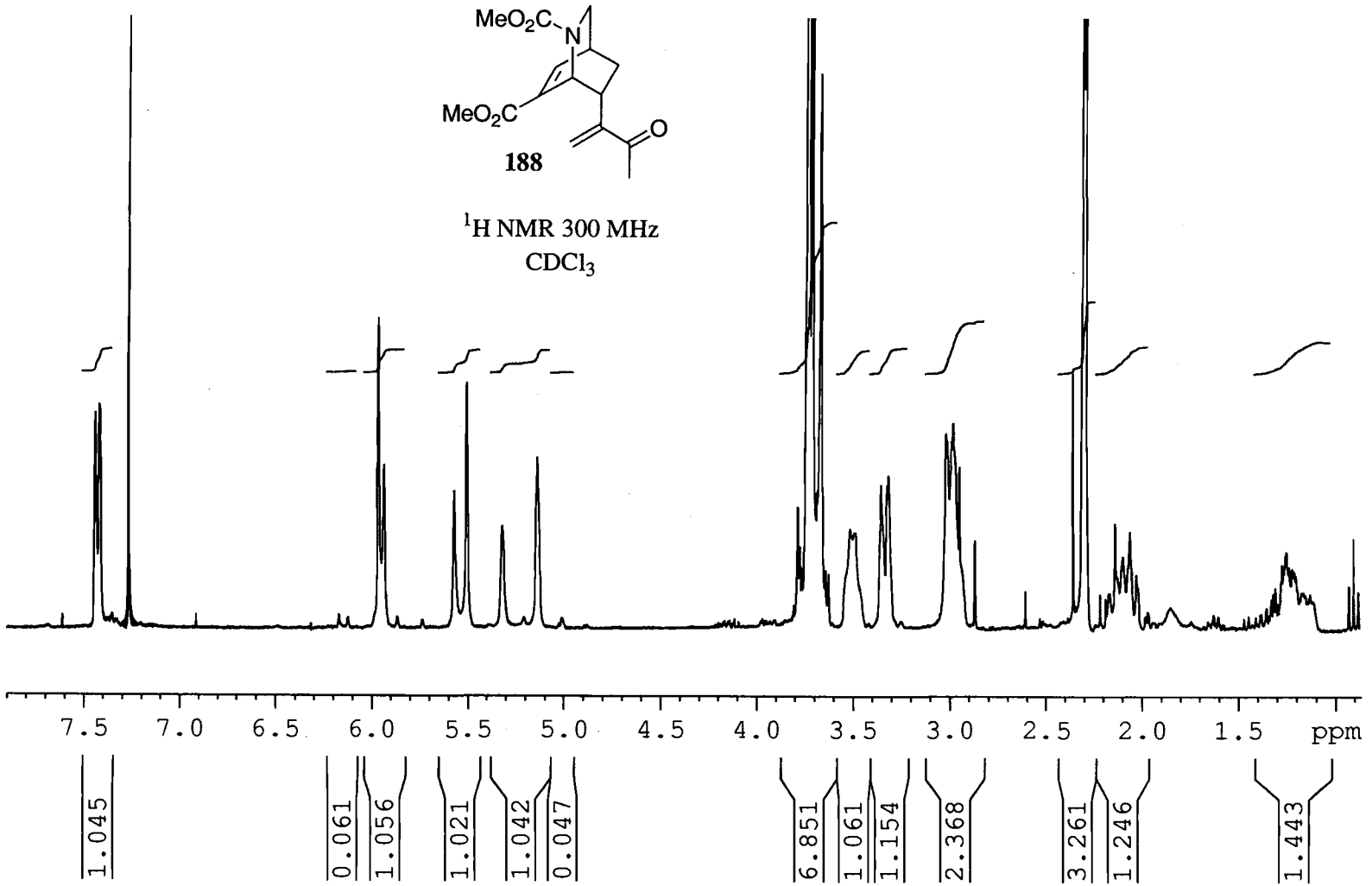
$^1$H NMR 400 MHz

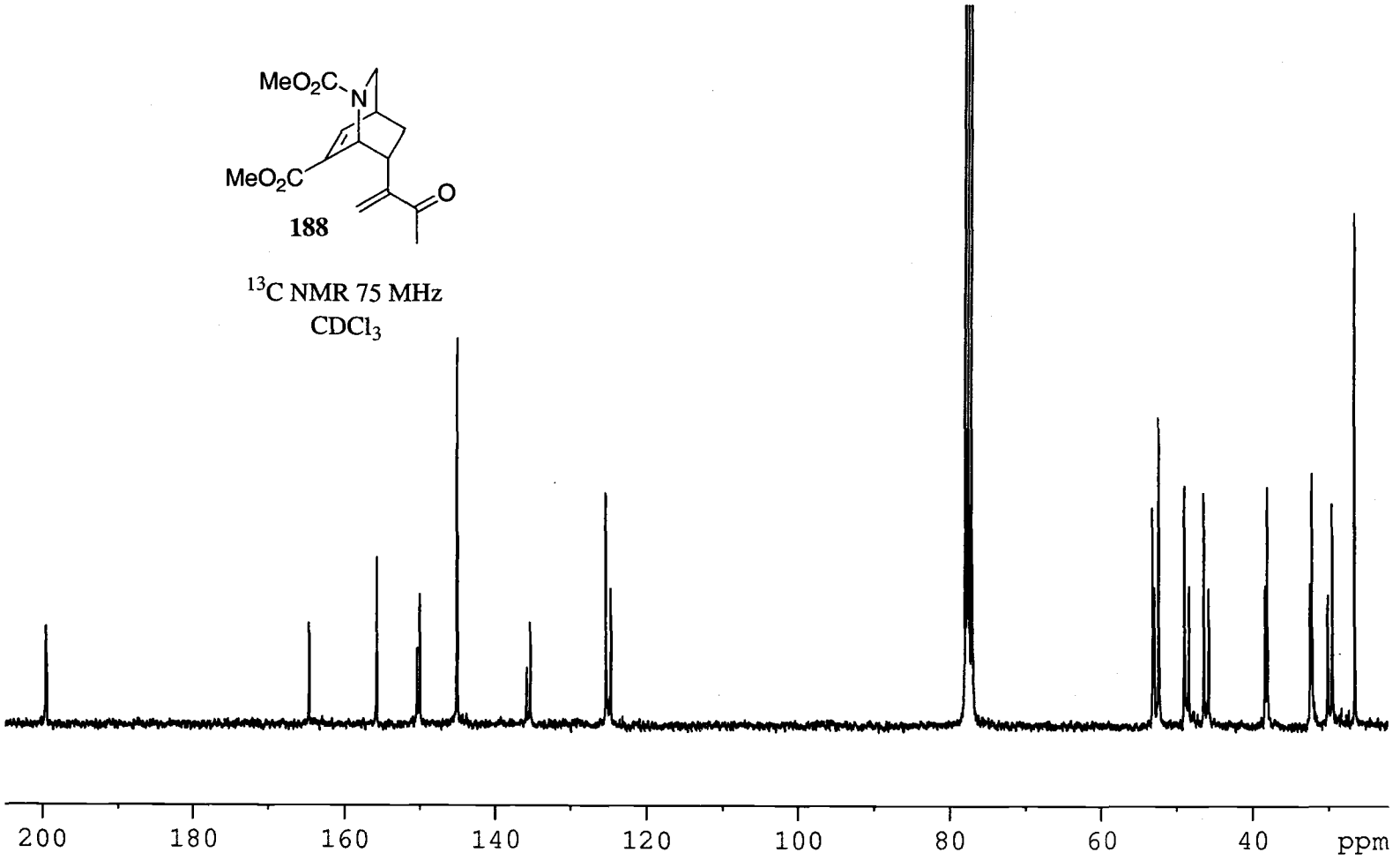
$CDCl_3$

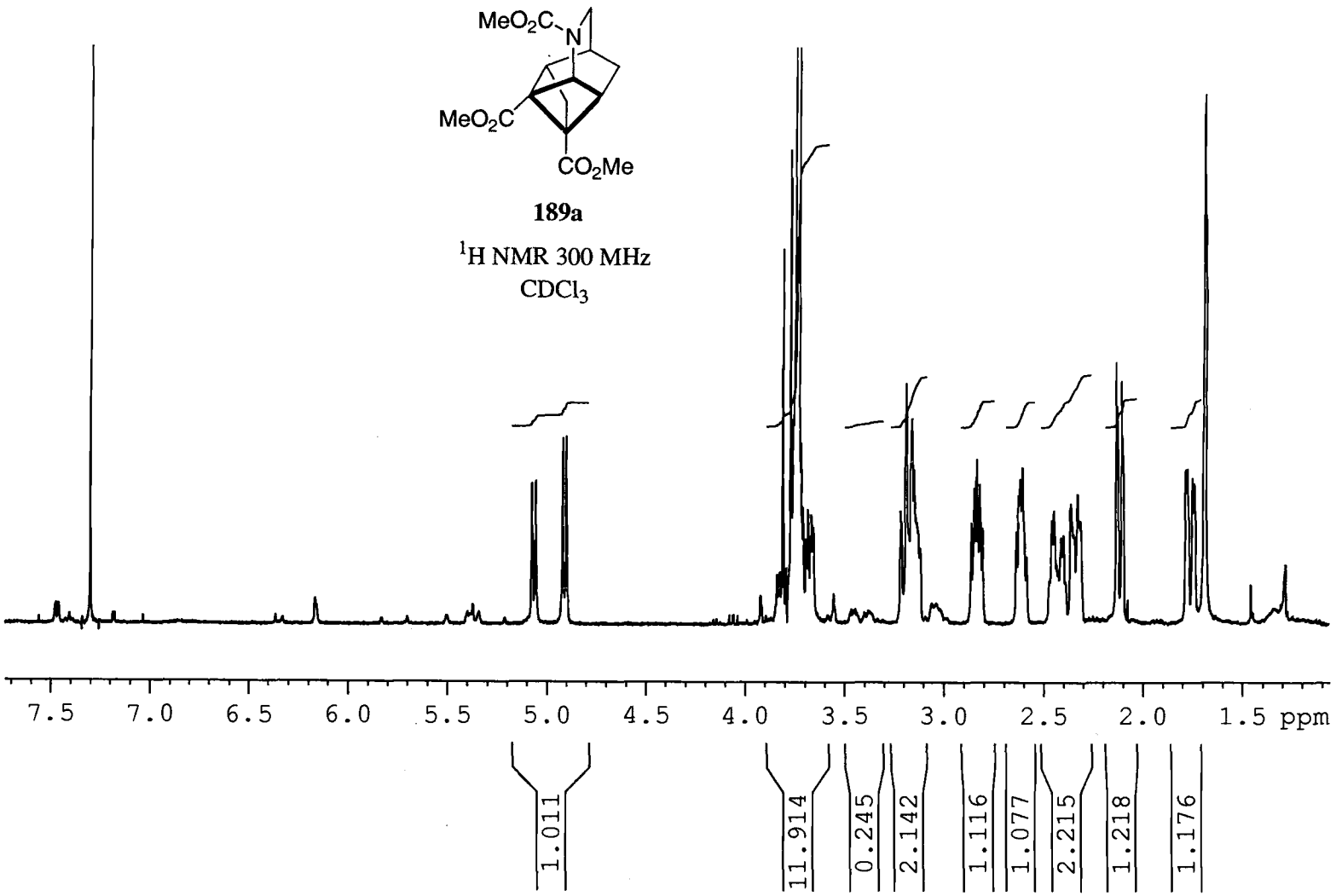

MeO2C
N
MeO2C
CO2Me
186
13C NMR 75 MHz
CDCl3
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 ppm

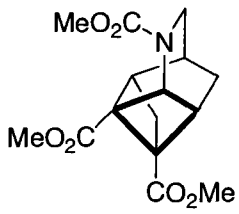

MeO2C
N
MeO2C
187
1H NMR 400 MHz
CDCl3
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
ppm
0.994
1.459
0.569
2.040
3.325
3.261
1.101
3.176
1.017
1.039


MeO2C
N
MeO2C
187
13C NMR 100 MHz
CDCl3
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 ppm


MeO2C
N
MeO2C
O
188
1H NMR 300 MHz
CDCl3
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
ppm
1.045
0.061
1.056
1.021
1.042
0.047
6.851
1.061
1.154
2.368
3.261
1.246
1.443

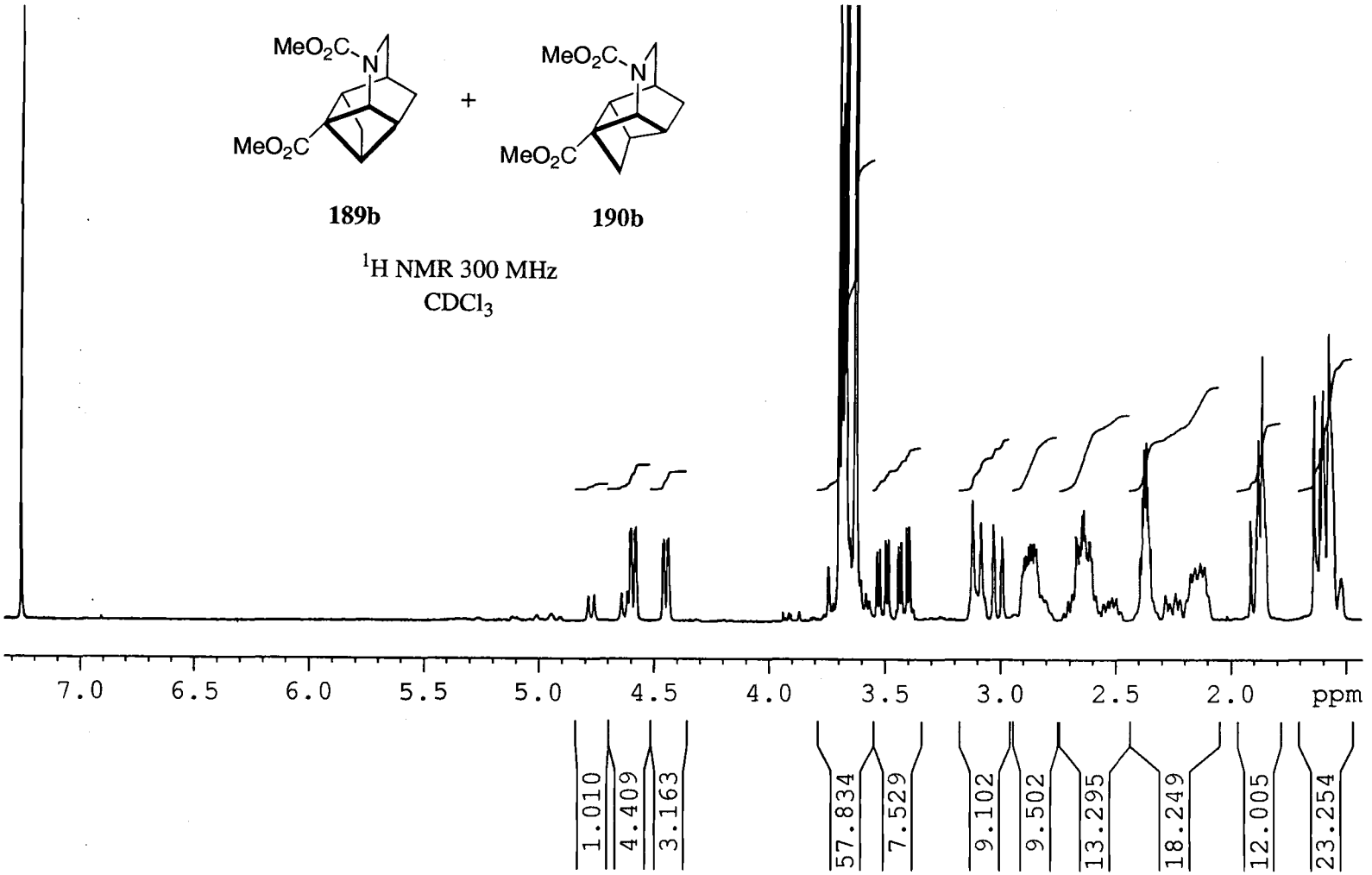

MeO2C
N
MeO2C
O
188
13C NMR 75 MHz
CDCl3
200
180
160
140
120
100
80
60
40
ppm

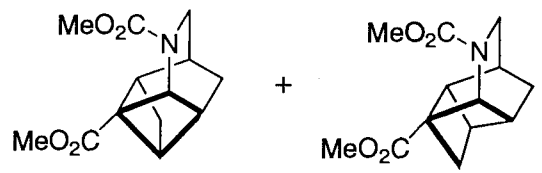

MeO2C
N
MeO2C
CO2Me
189a
1H NMR 300 MHz
CDCl3
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5 ppm
1.011
11.914
0.245
2.142
1.116
1.077
2.215
1.218
1.176




**189a**

$^{13}C$ NMR 75 MHz
$CDCl_3$


MeO2C
N
MeO2C
+
MeO2C
N
MeO2C
189b
190b
1H NMR 300 MHz
CDCl3
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
ppm
1.010
4.409
3.163
57.834
7.529
9.102
9.502
13.295
18.249
12.005
23.254

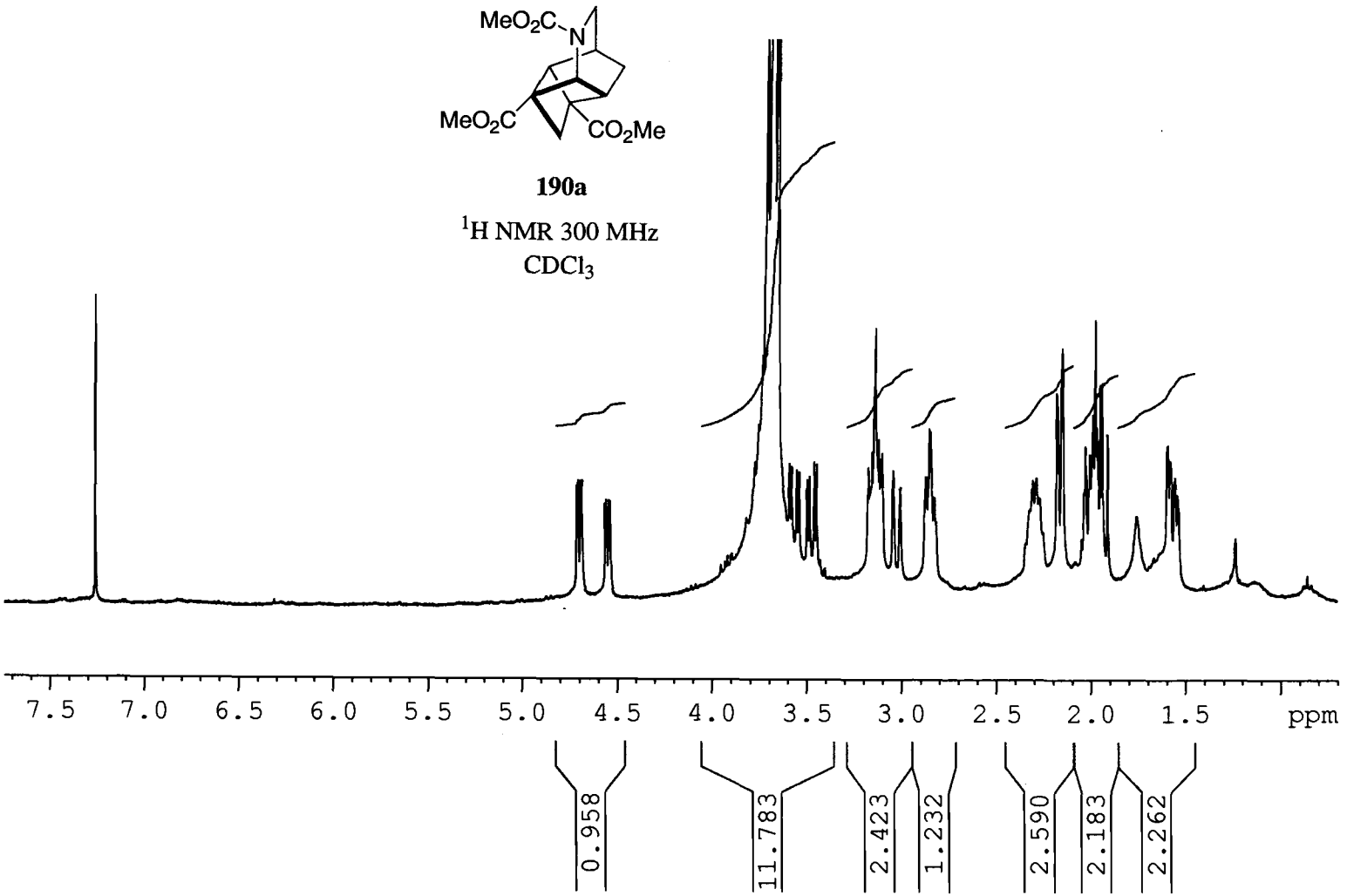


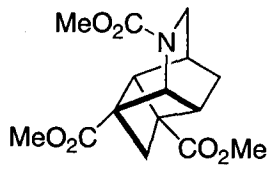

+




**189b** **190b**

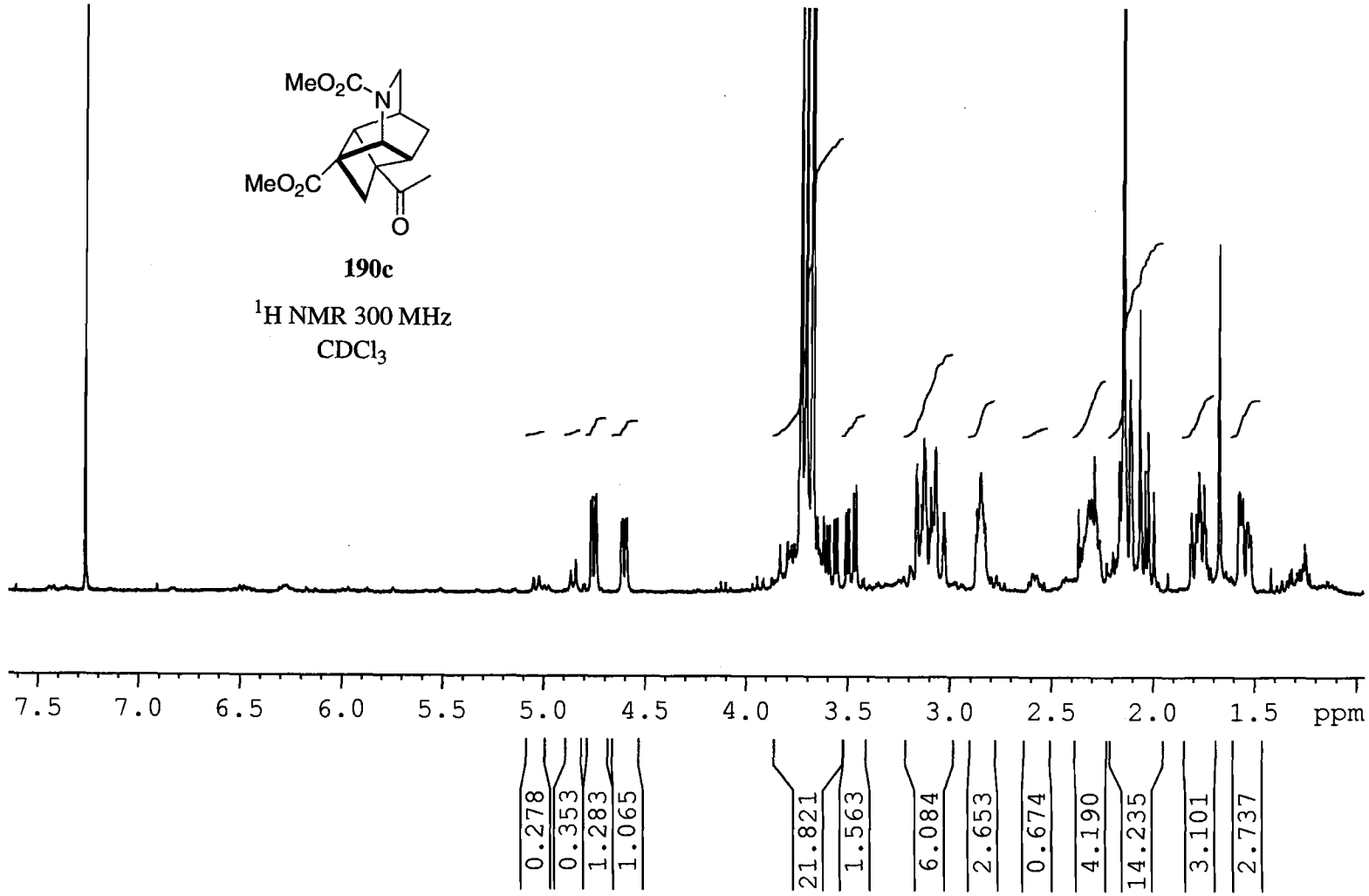
$^{13}C$ NMR 75 MHz
$CDCl_3$

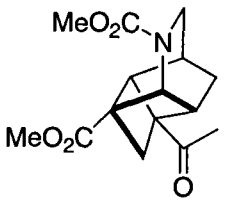

MeO2C
N
MeO2C
CO2Me
190a
1H NMR 300 MHz
CDCl3
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
ppm
0.958
11.783
2.423
1.232
2.590
2.183
2.262




**190a**

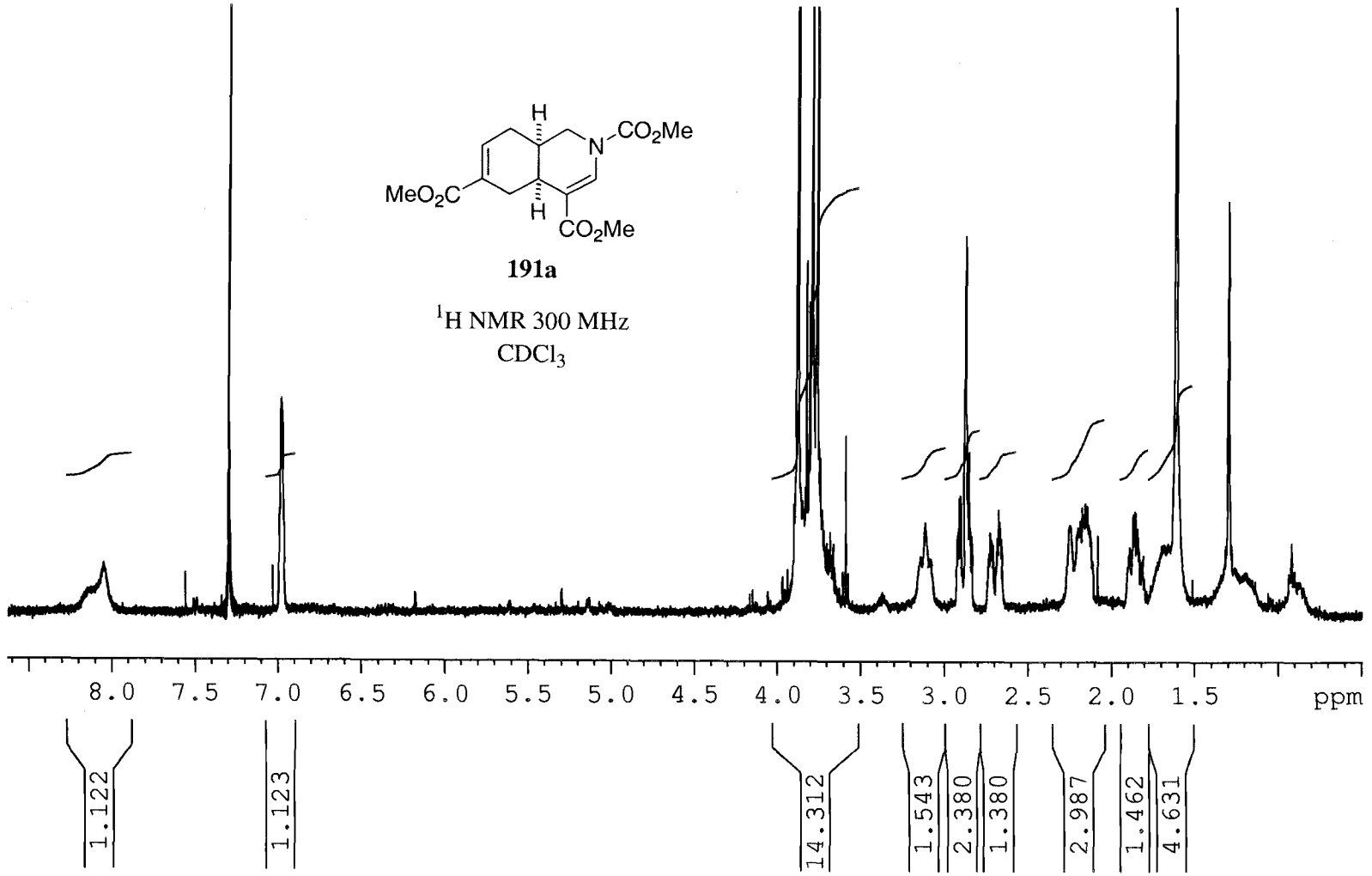
$^{13}C$ NMR 75 MHz
$CDCl_3$


MeO2C
N
MeO2C
O
190c
1H NMR 300 MHz
CDCl3
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
ppm
0.278
0.353
1.283
1.065
21.821
1.563
6.084
2.653
0.674
4.190
14.235
3.101
2.737



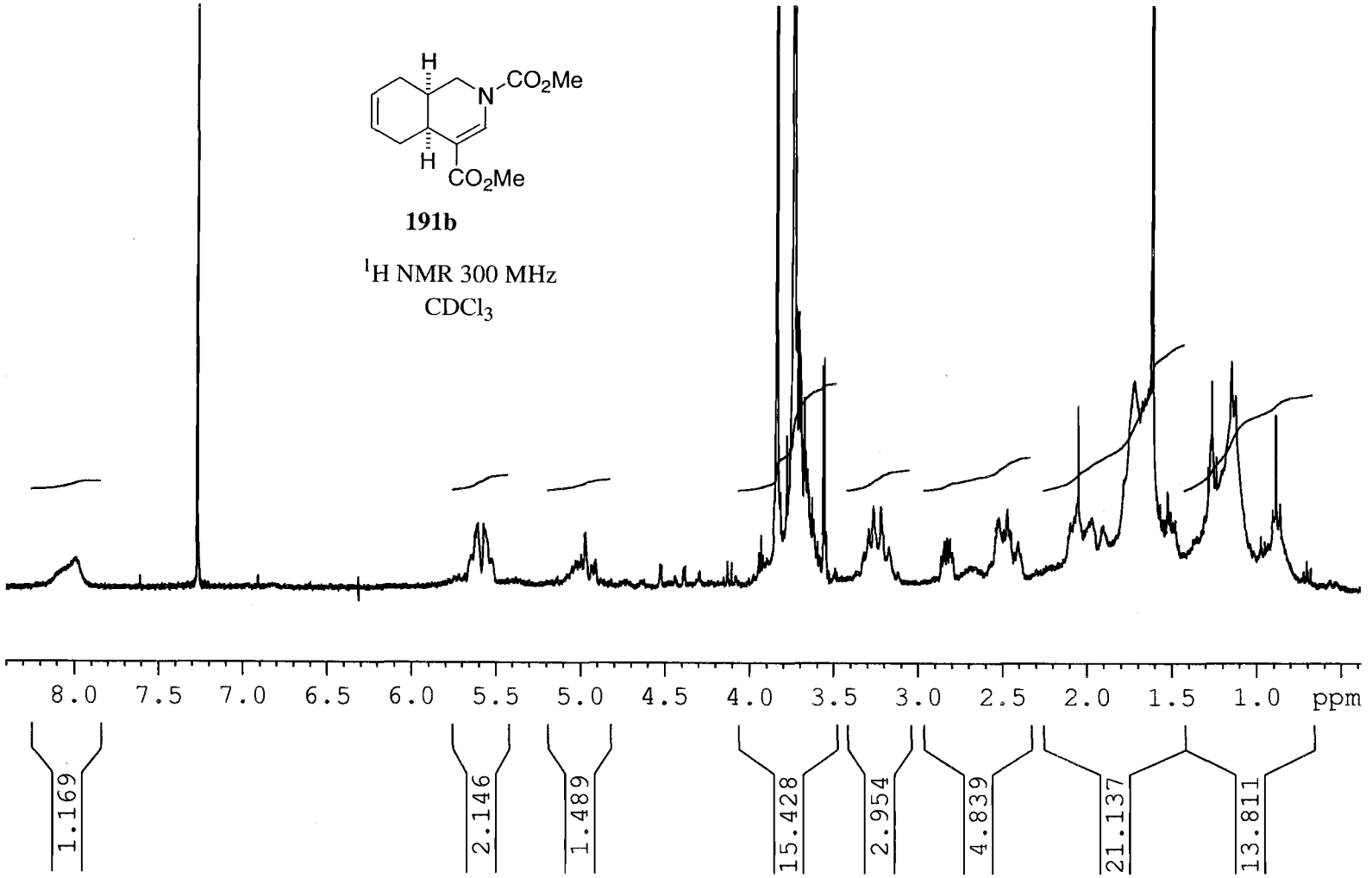

**190c**

$^{13}C$ NMR 75 MHz
$CDCl_3$




**191a**

$^{1}$H NMR 300 MHz
$CDCl_3$




**191b**

$^{1}$H NMR 300 MHz
$CDCl_3$