Low-Temperature Vinylcyclopropane Rearrangement in the Total Synthesis of (-) - Specionin

by

Michael George Natchus

Dissertation submitted to the Faculty of the
Virginia Polytechnic Institute and State University
in partial fulfillment of the requirements for the degree of

DOCTOR OF PHILOSOPHY

in

Chemistry

APPROVED:

Tomas Hudlicky, Chairman

James M. Tanko

David A. Becker

John G. Mason

Robert H. White

January, 1992
Blacksburg, Virginia

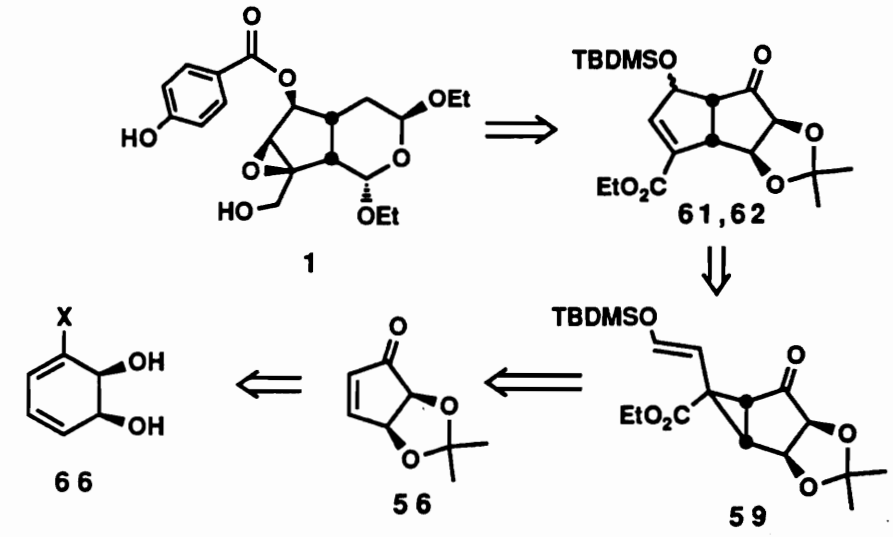
Low-Temperature Vinylcyclopropane Rearrangement in the Total Synthesis of (-) - Specionin

by

Michael George Natchus

(ABSTRACT)

The microbial oxidation of arenes to the corresponding *cis*-diols has been shown to be a convienient source of optically pure diols which can be used as synthons in asymmetric synthesis of complex, highly oxygenated molecules. The utility of such synthons has been demonstrated by the total synthesis of (-)-Specionin **1**. A key transformation in this sequence is a low-temperature rearrangement of vinylcyclopropane **59** to diquinanes **61** and **62**. Of additional merit is the development of an efficient preparation of enone **56** from *cis* arene diol **66**.



Acknowledgements

Foremost, I feel fortunate to have been associated for many years with an aggressive and diverse research operation which provided a unique training ground to test and elevate my scientific skills. Most importantly, I was lucky to have been surrounded for many years by extremely motivating , supportive and helpful coworkers who are far too numerous to properly acknowledge individually. Among those whose contributions to my development cannot go unmentioned are Drs. Gustavo Seoane, Larry Kwart, Lilian Radesca, James Frazier and Guru Sinai-Zingde. Thanks are also due to Dr. Alison Fleming and Dr. Nina Heard who did the initial investigations which led to this work. Advice from Dr. Hector Luna made it possible for me to become competent enough in the biolab to produce the diols which were necessary for this project. The help from Travis Dudding and Thomas Nugent in preparing starting materials is genuinely appreciated. Thanks Horacio for covering for me when necessary. Finally, I appreciate the stimulating and helpful blackboard sessions with Dr. John Price who contributed many helpful suggestions.

My gratitude is extended to Dr. Christe Boros for running and helping me to run some critical NMR experiments and to Tom Glass and the analytical services for providing me with 400 Mz spectra of many important intermediates. I am similarly indepted to Kim Harrich for determining the mass spectra.

A special word of appreciation is extended toward the faculty of the chemistry department and especially those who served on my graduate committee for their support and tolerance of my graduate efforts. Their

instruction and advice have provided an exciting program for the advancement of my education.

On a personal level, I am forever indepted to the financial and emotional support from my parents, George and Iris Natchus, without which I would never have maintained the personal character needed to persevere the rigors of formal education. Also, I am indebted to Penny and her family for their constant help and support toward growth in many personal areas of my life. The martial arts training I received from Dr. Ed Hampton cannot remain unmentioned since I am a better person for the strength of character it has imparted upon me and my career.

Finally, and most importantly, I offer my deepest heartfelt thanks and appreciation to my boss, research director, lead guitarist, dojo mate and friend Dr. Tomas Hudlicky for a very provocative and often turbulent relationship. His unique brand of professional motivation led to my discovery of talents and stamina that I had within myself that I was hitherto unaware resulting in a sense of self-confidence that may have otherwise have lain dormant. It is my hope that I will be able to repay such efforts by extending the same in some way to the next generation.

To a happy and successful life with Penny

Low Temperature Vinylcyclopropane Rearrangement in the Total Synthesis of (-) - Specionin

Table of Contents

A. Historical

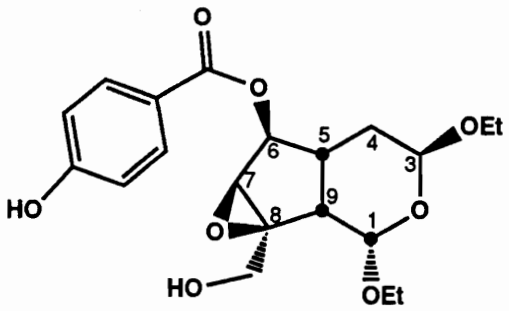
I. Introduction

It has been said that a journey of a thousand miles begins with a first step.[1] Perhaps the first step of a scientific journey begins with a thousand trials. Present scientific ideology dictates that no idea be considered of merit which does not gain general, time-tested acceptance. Despite the fact that such a statement may seem somewhat cynical, it carries a great deal of credibility. If an idea is to grow to fruition it must be developed through numerous examples and investigations which will come to pass only if an idea is presented in a form that is attractive and useful. A challenge in the Hudlicky group for the past decade has been to develop a clear understanding of the synthetic properties of vinylcyclopropanes and to exploit such knowledge for the formation of cyclopentene ring systems. Clearly, if such an idea is to receive the attention it deserves in practical synthetic organic laboratories, it must be tried and developed into a form that others in the discipline will appreciate.

The execution of this challenge to this point has resulted in the total synthesis of many linear and non-linear triquinanes[2] as well as pyrrolizidine alkaloids.[2,3] Pyrrolytic temperatures were classically required in order to effect the rearrangement of vinylcyclopropanes.[4] More recently, such rearrangements have been shown to be possible at -40°C to -78°C.[5] The last chapter of this saga will be written when the cyclopentene annulation occurs at room temperature and in an inexpensive, easily managed solvent such as ethanol which will not pollute the world around us. At this point one could feel

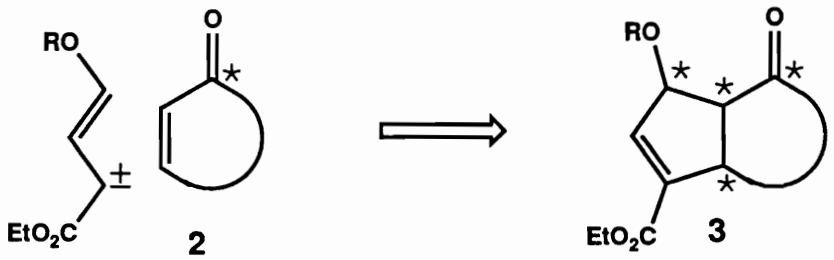
that the first step of the vinylcyclopropane-cyclopentene journey had been taken and that it is time for practical synthetic chemists to carry the next leg.

The current chapter of research is directed toward the total synthesis of (-)-specionin **1** which is an iridoid found in *Catalpa speciosa* and serves as a potent antifeedant against the spruce budworm which inflicts severe damage



1

each year to forests in the North American northwest and the lumber industry which thrives upon it. Approach to **1** will utilize state of the art [2+3] cyclopentene annulation technology. A synthon required for this strategy is enone **2** which contains chiral information capable of being transferred to other developing centers in cyclopentene products of type **3**. and a synthon, such as



4 **2** **3**

4 that is isoelectronic with a Diels - Alder type diene and which contains an oxygen functionality at the terminus to provide the oxo-substituent at C6 in

specionin.

Such investigations provided the first major stepping stone toward a practical form of the [2+3]-cyclopentene annulation. The presence of the oxo-functionality in **4** would not only provide the required C6 oxidation for specionin synthesis, but would ultimately provide a useful direct means of effecting low-temperature vinylcyclopropane rearrangements. Perhaps the final resolution to practical vinylcyclopropane technology will present itself under similar serendipitous conditions and allow a greater number of chemists to explore this useful transformation.

A. II. Review of [4+1] and [2+3] Annulation Methodology

Analysis of any synthetic design targeted toward ring closure reveals a disparity in charge distribution between even and odd membered ring synthons. Dissonant adjacent like charges will be encountered in the latter case.[6,7] This situation is exemplified in Figure 1 with five vs six membered ring synthons in Diels - Alder type cyclizations. The problem of conjuring the required charge distribution in the second case becomes immediately obvious when one attempts to create a system of functionalization which will realize the necessary

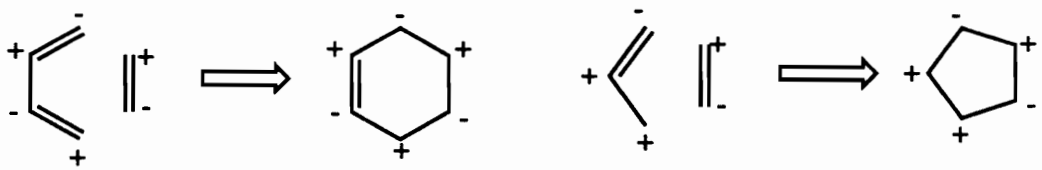


Figure 1

Charge Disparity of Six vs Five Membered Ring Synthons

dissonance. The challenge to circumvent such natural obstacles promoted a feverish effort in the field of five membered ring construction in the seventies and eighties which resulted in some ingenious resolutions to the problem. Some of the more commonly used methods are sketched in Figure 2. The [4+1] annulation technique was developed in recognition that it was possible to functionalize a carbon or heteroatom in such a way that it may serve both electrophilic and nucleophilic capacities and added sequentially across a diene unit as in the transformation of **5a** to **6**.[4,7] A similar solution represents a dienophile in the form of carbene **5b** as in the case when **A** is a carbon.

A second commonly used technique is the [2+3] annulation which is also

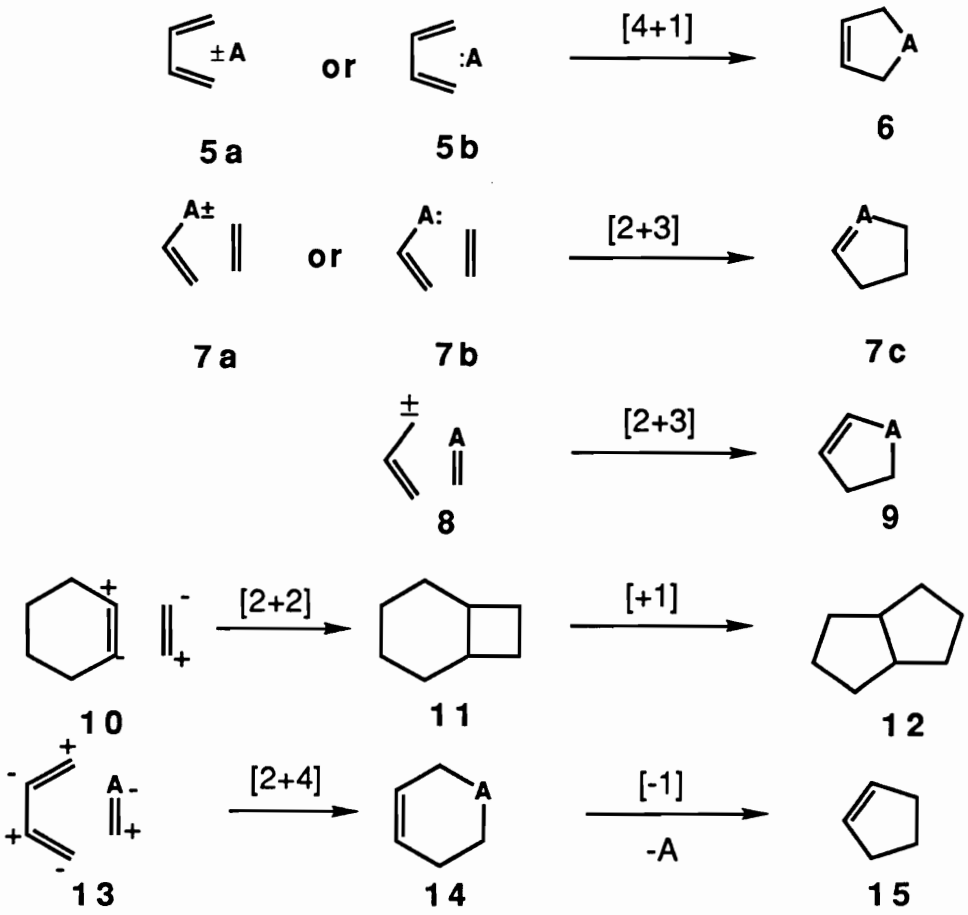


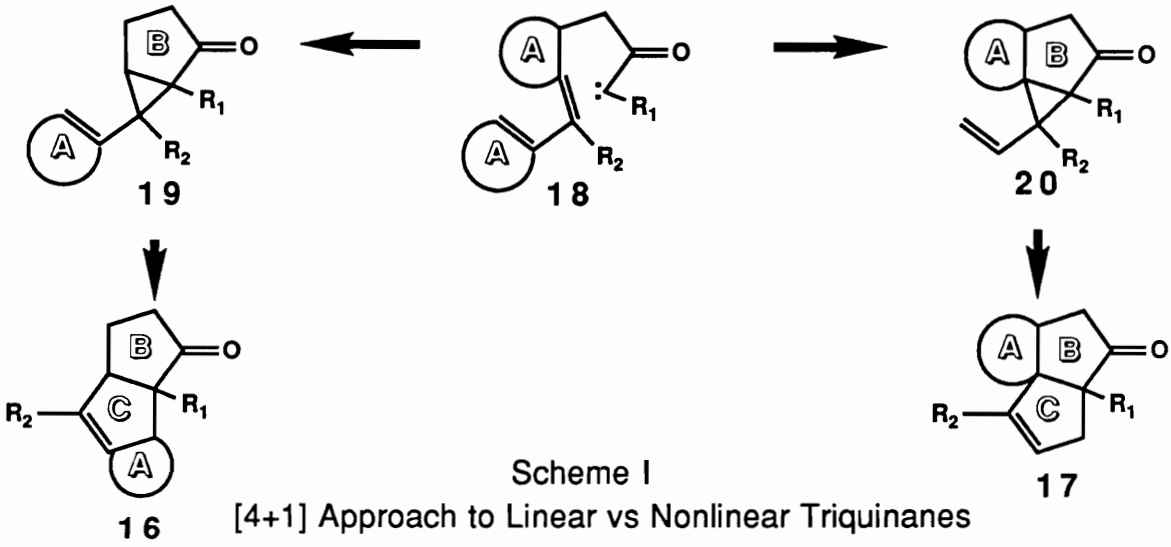
Figure 2

Cyclopentene Annulation Strategies

demonstrated in Figure 2 with two tethering systems.[7] The technique is similar to the [4+1] case in that either a synthon with a bifunctional atom such as **7a**, **8** or a carbene equivalent such as **7b** must be created. Here such functionality is generated on a pseudo-Diels-Alder diene equivalent which is added across a dienophile to give ring systems of type **7c** and **9**.

Methods also exist for five membered ring construction which allow one to exploit the charge consonance advantages of even membered ring systems.

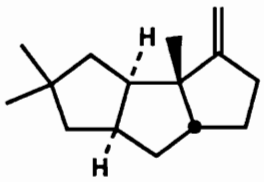
In the first example, [2+2] cyclization of precursors **10** provide 6,4 ring systems **11** which are then rearranged in an energetically downhill process to deliver desired 5,5 systems **12** for an overall [2+2+1] conversion.[8] A similar method utilizes a hetero Diels-Alder reaction of **13** to give six membered adducts of type **14** which are then later subjected to heteroatom elimination to arrive at desired five membered rings of type **15** in an overall [2+2-1] process.[9] Such examples are only a small sample of the clever ingenuity which was invested to approach the complicated task of five membered ring synthesis.



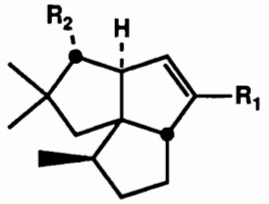
Scheme I
[4+1] Approach to Linear vs Nonlinear Triquinanes

The formation and rearrangement of vinylcyclopropanes has proven to be a well developed route for the synthesis of cyclopentenes and has been applied to the total synthesis of a rich variety of natural targets (see Table 1 at the end of this section for a comprehensive survey of those syntheses that featured vinylcyclopropane-cyclopentene rearrangement). Hudlicky has been a principal investigator in this field and the developments from his group are reviewed below.

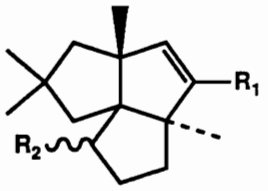
a. [4+1] Methodology. Cyclopentanoid annulation techniques have been under development in the Hudlicky group since the late seventies. The [4+1] approach was cleverly exploited in such a way as to allow entry into either linear **16** or non-linear **13** triquinane ring systems at will. The initial relative placement of ring 𝔸 in **18** allows one to strategically enter the ring system of choice and has led to system oriented approaches to many of the triquinanes through rearrangement of intermediate vinylcyclopropanes **19** and **20** (Scheme I).[2,10] Such research led to the total synthesis of the linear triquinane hirsutene **21**[11] and the non-linear or angular triquinanes epiisocomene **22**,[12,13] isocomenic acid **23** and epiisocomenic acid **24**,[14] and pentalenene **25** and pentalenic acid **26**.[15,16]



21

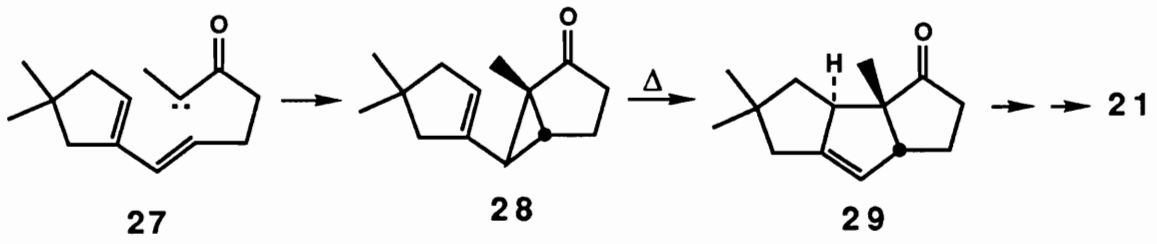


25 $R_1 = CH_3$, $R_2 = H$
26 $R_1 = CO_2H$, $R_2 = OH$



22 R = β-CH_3
23 R = α-CO_2H
24 R = β-CO_2H

Critical aspects of the divergent approach require carbene addition across one olefin of a diene to form a vinylcyclopropane, depending upon which ring system configuration is desired, followed by rearrangement to arrive at the desired cyclopentene. In the case of hirsutene, Hudlicky envisioned an intramolecular addition of a carbene **27**, generated from the corresponding diazo functionality, an across endocyclic diene moiety to deliver vinylcyclopropane **28** which rearranged to tricycle **29** under flash vacuum

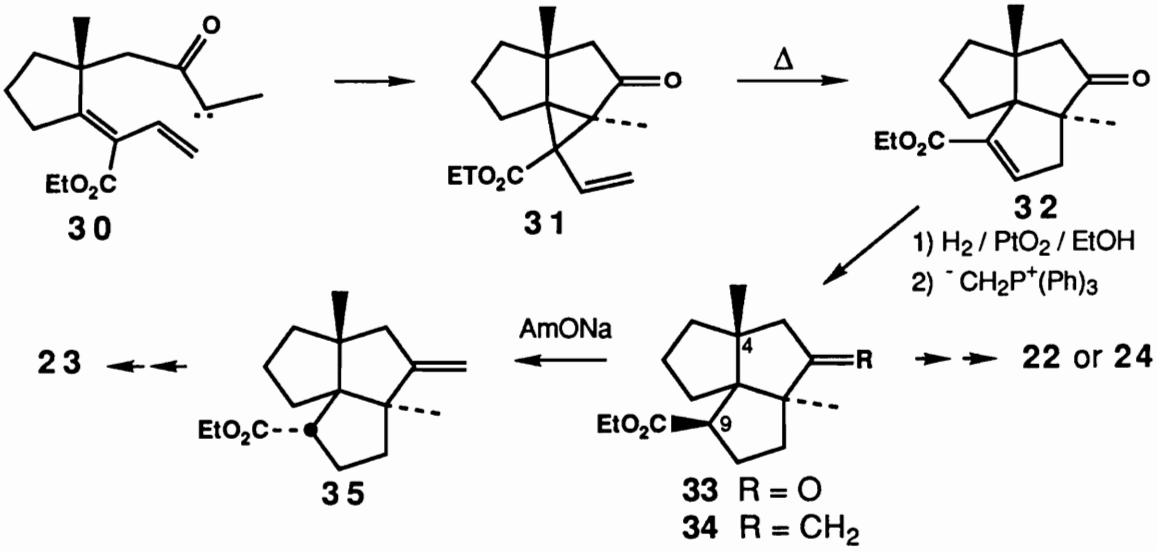


Scheme II

Hudlicky's Synthetic Plan for Hirsutene

pyrolytic conditions. The overall process delivered the linear hirsutene skeleton in two steps.

The next major developmental jump in vinylcyclopropane technology came about with Hudlicky's investigations of the isocommene-type analogs (Scheme III)[12-14] with the substitution on the diene system of an ethyl carboxylate unit as a critical functionality. The non-linear triquinane ring system was accessed through intramolecular addition of carbene **30** to an exocyclic diene unit to give cyclo- propane **31** which was rearranged under flash vacuum

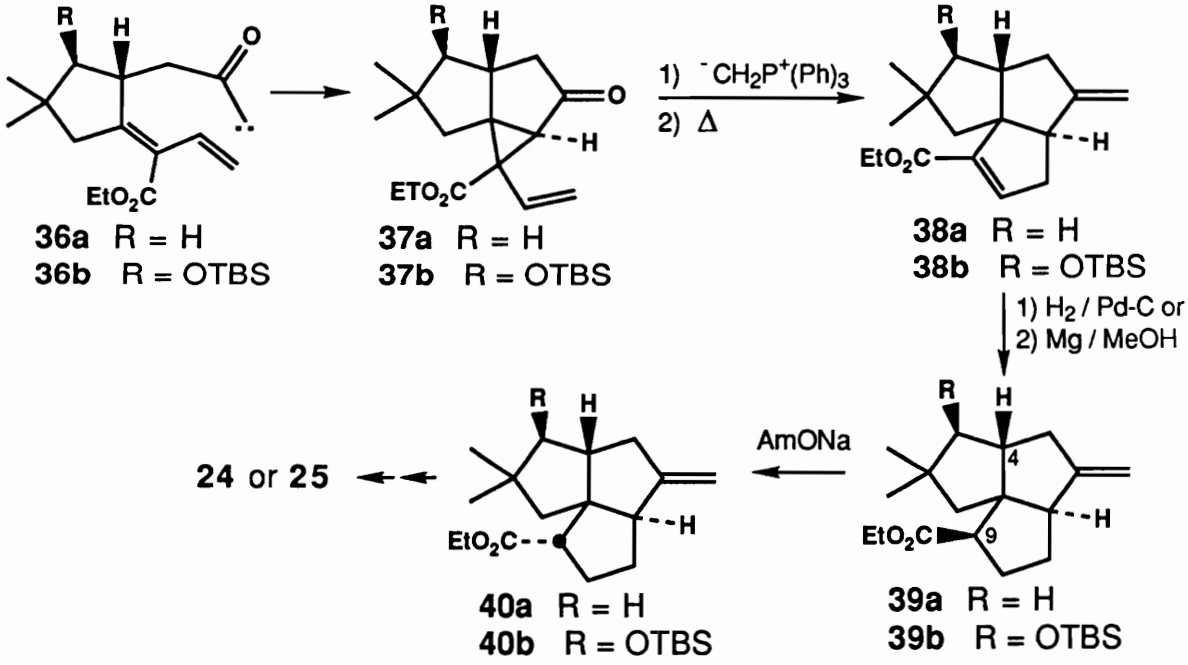


Scheme III

Hudlicky' Synthetic Plan for Isocomene Type Terpenes

pyrolytic conditions to yield the desired ring skeleton **32** in two synthetic operations. Hydrogenation of **32** occurred from the face which was unhindered by the C4 methyl group to give the least thermodynamically stable C9 epimer of **33** exclusively. After conversion to exomethylene **34**, the ethyl carboxylate function could be exploited to quantitatively equilibrate the C9 carbon to the more stable epimer **35** under basic conditions. The presence of the carboxylate unit therefor allows one to prepare isocommene type terpenes with either desired C9 configuration and any oxidation state of the C9 methyl group.

A similar investigation was conducted on pentalenene type terpenes to investigate the directing influence of the C4 substituent (Scheme IV).[15,16] Again, an intramolecular attack of carbene across an exocyclic diene **36ab**

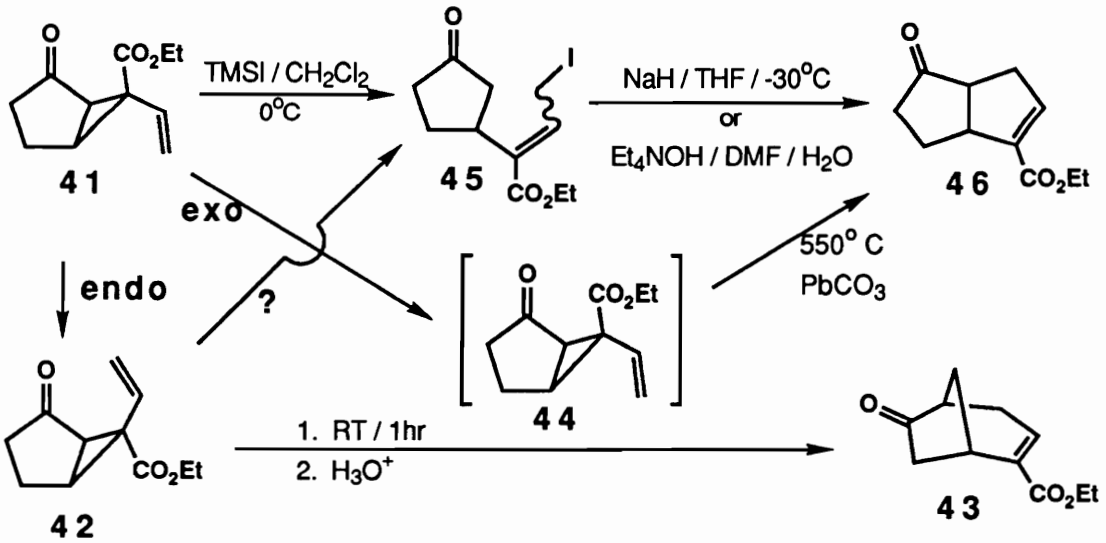


Scheme IV

Hudlicky' Synthetic Plan for Pentalenene Type Terpenes

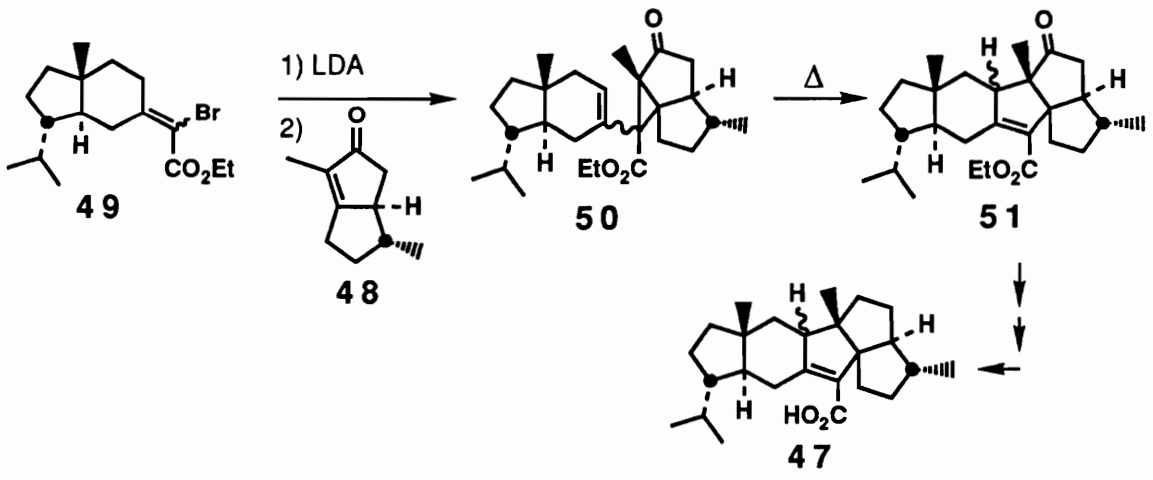
delivered a vinylcyclopropane of type **37ab** which, after conversion to exomethylene derivative via Dauben's Wittig conditions, was rearranged to the desired non- linear tricyclic skeleton **38ab**. The double bond reduction gave ratios of C9 epimers in the range of 80:20 to 95:5 for **39ab** which demonstrated that the C4 hydrogen was not as effective in directing the incoming hydrogen as the C4 methyl in the isocommene series. The effect was more dramatically demonstrated in the base catalyzed equilibration of **39ab** which gave a 60:40 mixture of **39a:40a** and a 70:30 mixture of **39b:40b** suggesting that the steric requirements imposed by the C4 hydrogen are not sufficiently demanding to completely control the C9 stereochemistry as were the C4 methyl group.

b. [2+3] methodology. Following the successful development of the [4+1] method of cyclopentene annulation, attention was turned to the [2+3] annulation technique. This was initially made possible upon realization that vinylcyclopropanes could be generated from the addition of lithium dienolate



Scheme V
TMSI-Mediated Rearrangement

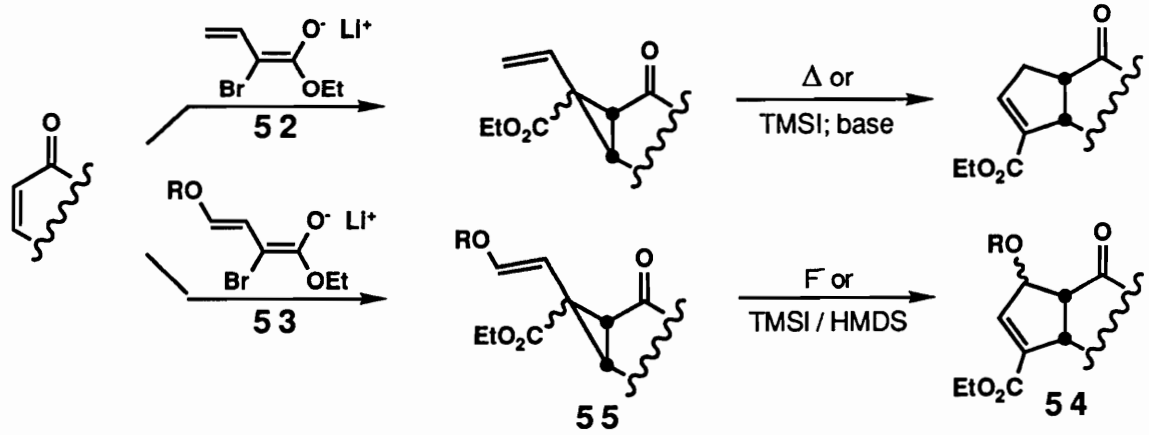
anions, formed from 2-bromocrotonates, to substituted enones.[17] Soon afterward this process was coupled with the application from the literature[18,19] describing the TMSI-promoted opening of α-ketocyclopropanes. It was shown that TMSI serves two functions: 1. I^- from TMSI opens vinylcyclopropanes of type **41** by nucleophillic attack at the terminal vinyl group and 2. TMS^+ serves as a Lewis acid to accelerate the process via complexation with the ketone oxygen.[20] Upon TMSI treatment, cyclopropanes with the olefin oriented in an *endo* fashion **42** gave, in addition to **45**, [3.2.1] bicyclic systems of type **43** via the Cope rearrangement of divinylcyclopropanes in which the second vinyl group, an enol ether, was generated by TMSI. Cyclopropanes with an *exo* oriented olefin **44** responded to TMSI by forming intermediate iodides **45** which required subsequent base treatment to effect ring closure to diquinanes of type **46**. Details of the product cross-section of these reactions have been published.[4]



Scheme VI
Hudlicky's Synthetic Plan for Retigeranic Acid

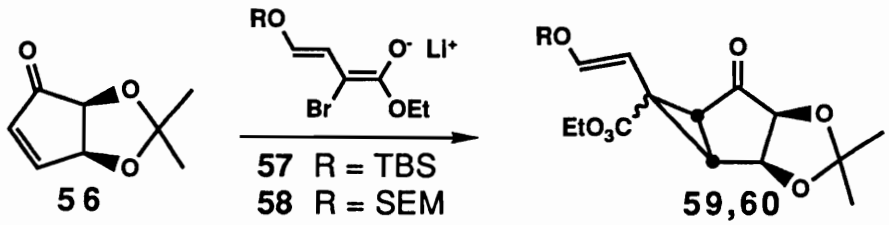
This information was further developed and tested in a later disclosure which describes the most efficient total synthesis of retigeranic acid **47** to date (Scheme VI).[21,4] This work featured the junction of two chiral synthons **48** and **49** containing the required enone functionality in the former case and 2-bromo crotonate unit in the later via the preconceived [2+3] annulation methodology to cleanly yield vinylcyclopropane **50**. This material yielded to pyrolytic rearrangement to deliver the requisite cyclopentene **51** which was then smoothly manipulated to deliver the target **47**.

c. Oxy [2+3] Methology. The exciting resolution to the pursuit of retigeranic acid synthesis stimulated further effort in the development of [2+3] annulation methodology. Specific aims at this point were to: 1) lower the required temperature necessary to promote the process; 2) extend the functional tolerance of 2-bromo-crotonate synthons **52**; 3) to examine the ability of chiral enones to transfer existing chiral information to developing chiral



Scheme VII
Oxy-Substituted [2+3] Annulations [23]

centers. Such goals were realized with the addition of a protected hydroxy substituent at the γ carbon of the crotonate **53** (Scheme VII).[5] This provided a method for the preparation of oxy-substituted cyclopentenes of type **54** which are present in many iridoids, prostaglandins, and sesquiterpenes[22] through vinylcyclopropanes of type **55**.



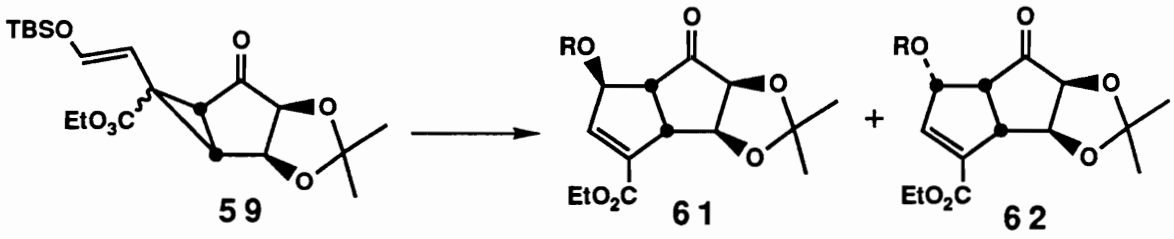
59 R = TBS	exo : endo = 66 : 34	Yield = 47%
60 R = SEM	exo : endo = 85 : 15	Yield = 53%

Scheme VIII

Cyclopropanation of Homochiral Enone **56**

Of particular interest was the [2+3] annulation of enone **56**[23] which could provide entry into many compounds in the iridoid class in an asymmetric fashion. The addition of 2-bromocrotonates **57** and **58** were reported to result in yields of oxyvinylcyclopropanes **59** and **60** ranging from 30% to 50% with the endo / exo ratio varying with different R protecting groups (Scheme VIII).[5] Fortunately, the endo / exo ratio turned out to be a trivial concern as the next rearrangement step proceeded smoothly in all cases regardless of the stereochemistry of the cyclopropane.

The reaction was investigated using a variety of conditions including classic flash vacuum pyrolysis which delivered a reasonable 75% yield of the desired cyclopentenes **61** and **62**. Application of conditions which promoted



VCP	CONDITIONS	PRODUCT RATIO	YIELD
EXO OR ENDO	A	R = TBS 1.0 : 4.0	75%
EXO OR ENDO	B	R = H 1.0 : 2.0	86%
EXO / ENDO	C	R = TBS 1.2 : 1.0	89%

CONDITIONS

A flash vacuum pyrolysis, 550 °C, (10^{-4} - 10^{-6} mm Hg)

B 2.0 eq TBAF, THF -40 °C, 10 min

C TMSI / HMDS, 3 : 1, CH_2Cl_2 / pentane, -78°C to -20 °C

Scheme IX
Oxy-Vinylcyclopropane Cylopentene Rearrangement

vinylogous cyclopropane ring opening and rearrangement at low temperatures were also realized. Treatment of **59** with TBAF as a source of F^- resulted in alkoxide formation from attack at silicon followed by a cascade of electrons to open the ring and set up intramolecular ring closure of the resulting aldehyde enolate. Treatment of **59** with TMSI promoted nucleophillic attack of I^- at the vinologous carbon and a similar chain of events as the TBAF case to smoothly deliver **61** and **62** at -78°C with complete transfer of chiral information.

The success of the oxy-substituted vinylcyclopropanes in undergoing low- temperature rearrangement in no way completes the saga of cyclopentene formation. Further goals include making the rearrangement amenable to room temperature conditions to draw interest to the reaction from the industrial sector

of the chemical community. Furthermore, the induction of chirality in the cyclopropanation of prochiral substrates from an outside chiral source remains as an unfulfilled goal.

The review presented above focussed on those methods connected with the discussion to follow. For a complete overview of cyclopentene annulations consult recent reviews**7** or monographs.**6**

Table 1
Summary of Vinylcyclopropane-Cyclopentene Rearrangements

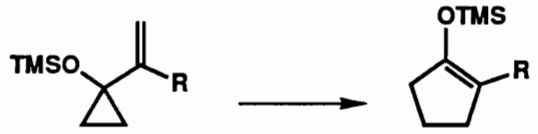
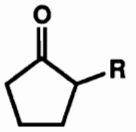
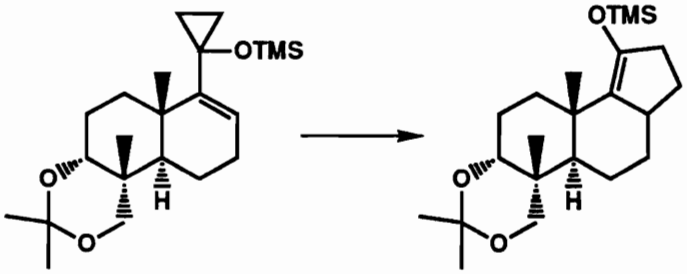
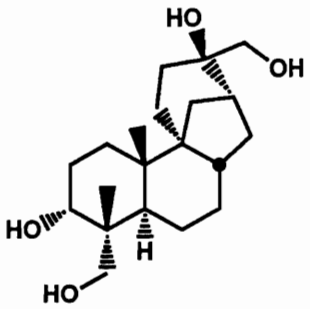
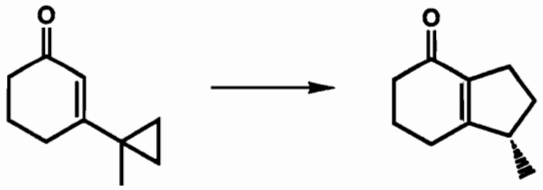
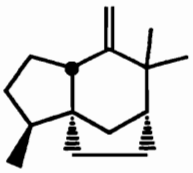
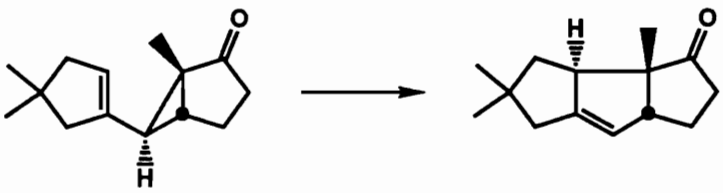
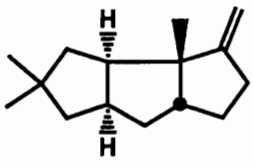
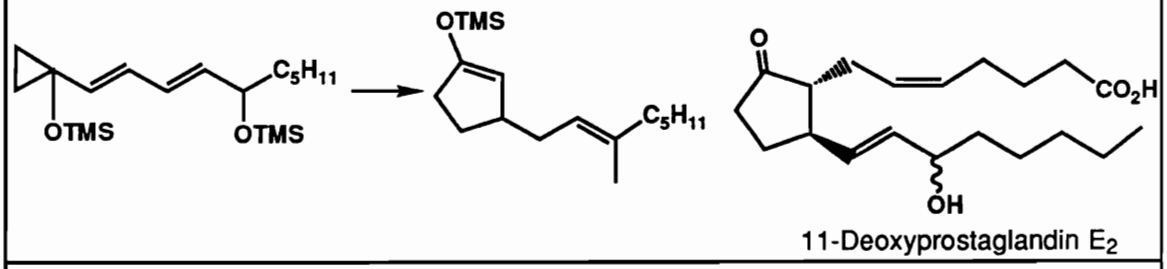
Author **Year** Ref Key transformation	Target
Trost **1974** 24  R = $(CH_2)_6CO_2t$-Bu	 Prostaglandin intermediate
Trost **1979** 25 	 Aphidicolon
Piers **1979** 26 	 Zizaene
Hudlicky **1980** 11 	 Hirsutene

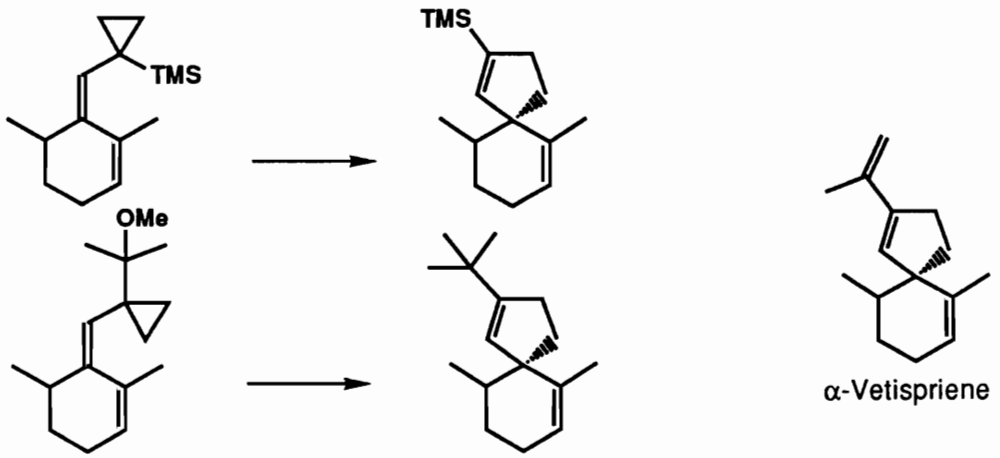
Table 1 (cont.)

Saluan **1981** 27



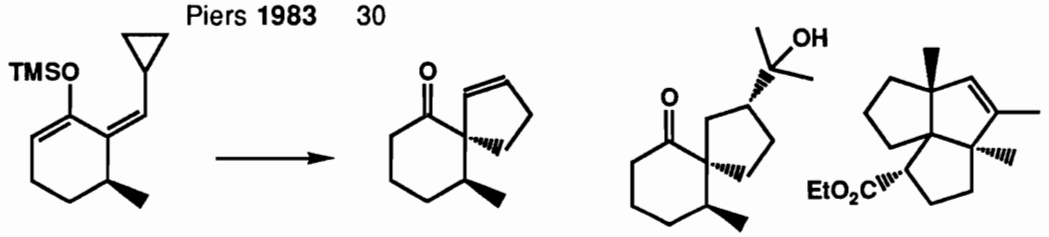
11-Deoxyprostaglandin E_2

Paquette **1982, 1984** 28,29



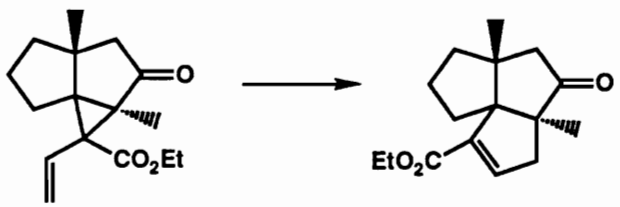
α-Vetispriene

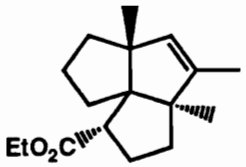
Piers **1983** 30



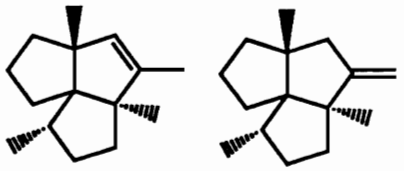
Hinesol Isocomenic Acid

Hudlicky **1984** 14,31





Isocomenic Acid **1983**



Isocomene β-Isocomene

Table 1 (cont.)

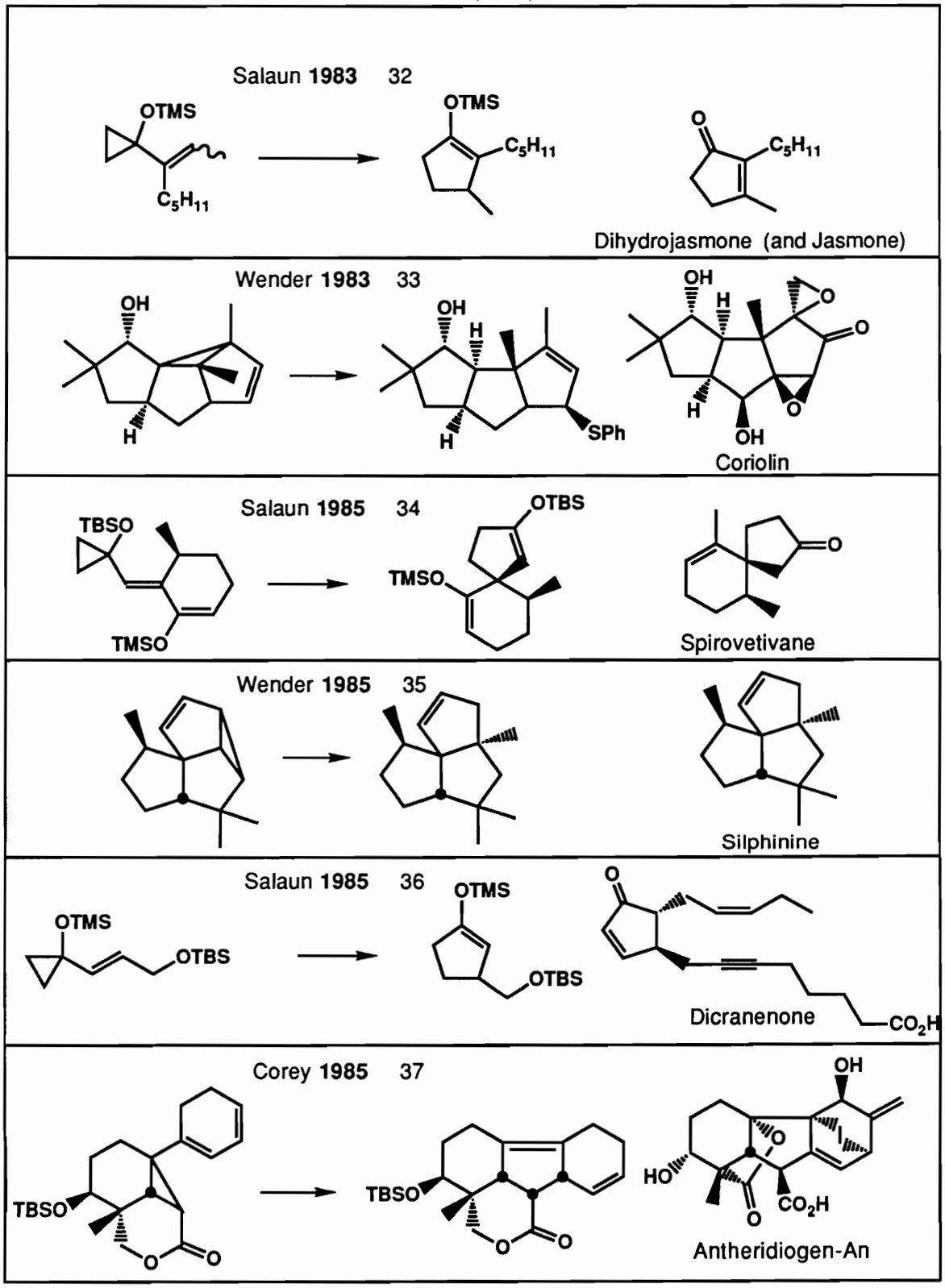
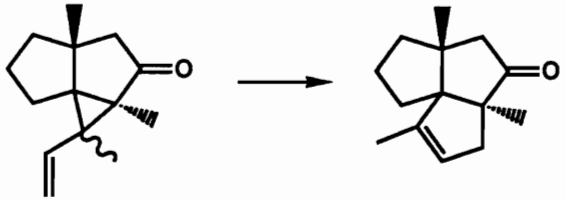
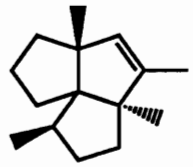

Salaun 1983 32
OTMS
C_5H_{11}
OTMS
C_5H_{11}
O
C_5H_{11}
Dihydrojasmone (and Jasmone)
Wender 1983 33
OH
H
OH
H
H
SPh
OH
H
O
O
H
O
OH
Coriolin
Salaun 1985 34
TBSO
TMSO
OTBS
TMSO
O
Spirovetivane
Wender 1985 35
Silphinine
Salaun 1985 36
OTMS
OTBS
OTMS
OTBS
O
Dicranenone
CO_2H
Corey 1985 37
TBSO
O
O
TBSO
O
O
OH
HO
O
O
CO_2H
Antheridiogen-An

Table 1 (cont.)

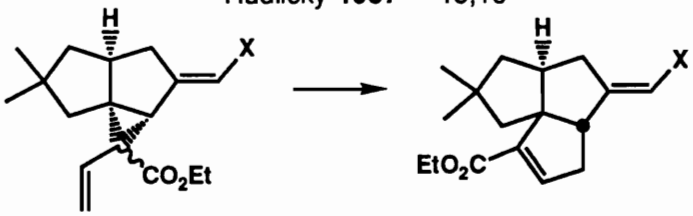
Hudlicky **1986** 12,13

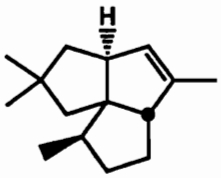




Epiisocomene

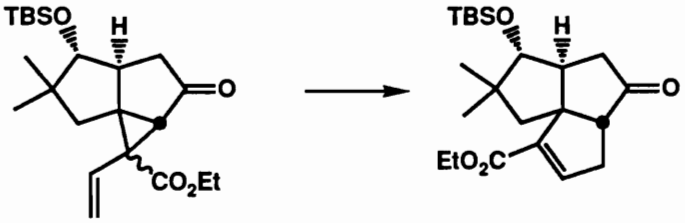
Hudlicky **1987** 15,16

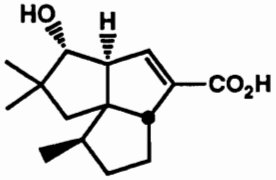




Pentalenene

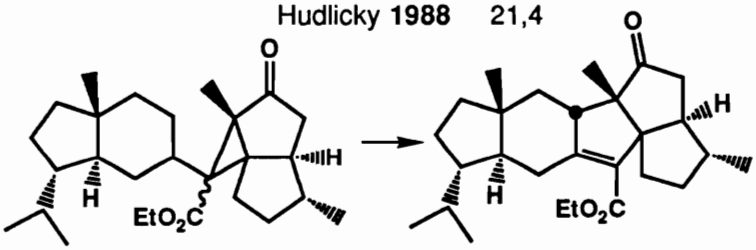
Hudlicky **1987** 16

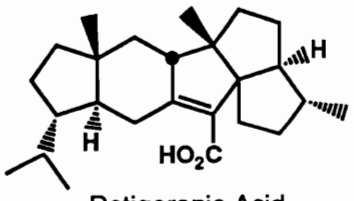




Pentalenic Acid

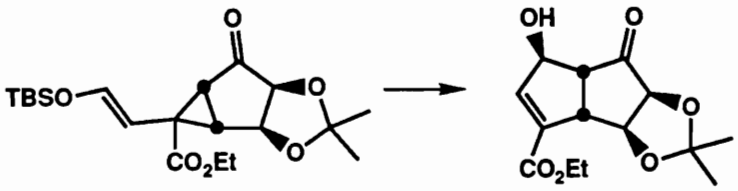
Hudlicky **1988** 21,4

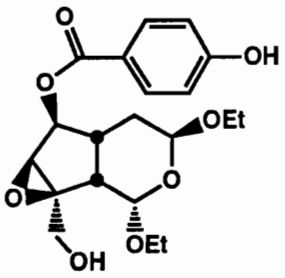




Retigeranic Acid

Hudlicky **1992** 4,5,38



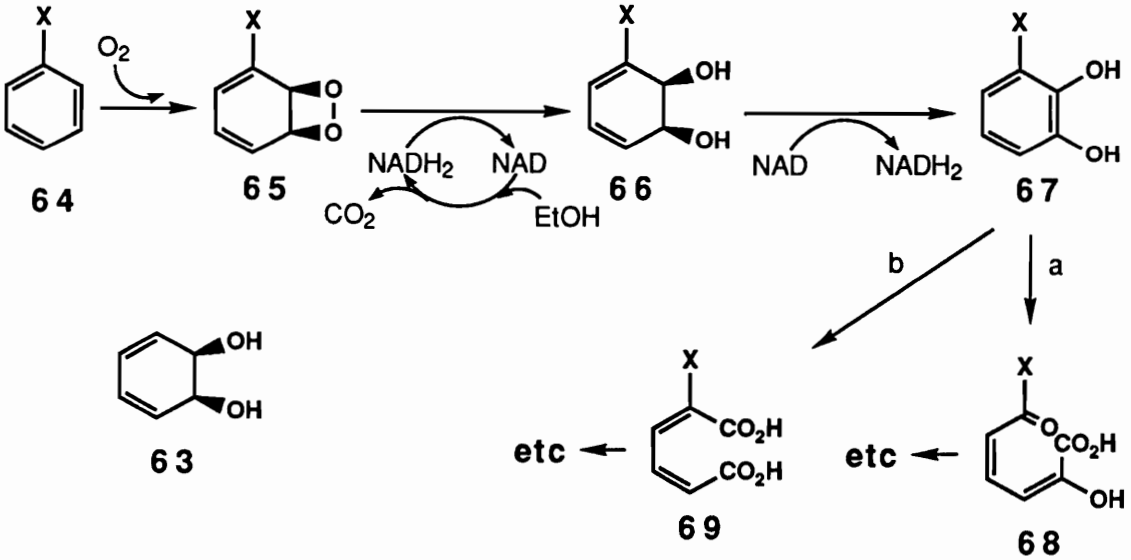


Specionin

A. III. Review of Arene-*cis*-Diols

Among the more humbling facts for organic chemists is that no laboratory procedure can efficiently create a homochiral center without an asymmetric template that is ultimately derived from natural sources. Since Mother Nature does not always provide the specific chiral building blocks that are required by synthetic chemists, a tremendous effort has been underway for the past two decades to "help" with the production of specific chiral pool synthons. Such efforts have stimulated a great deal of activity in the field of biocatalysis that has resulted in a close, symbiotic relationship between organic chemists and microbiologists.[39] A good example of such symbiosis is the development of arene-*cis*-diols as enantiomerically pure starting materials for synthesis.[40]

The first mention of arene-*cis*-diols was made by Gibson[41,42] who isolated and identified the parent arene diol **63** from the metabolic products of



Scheme X

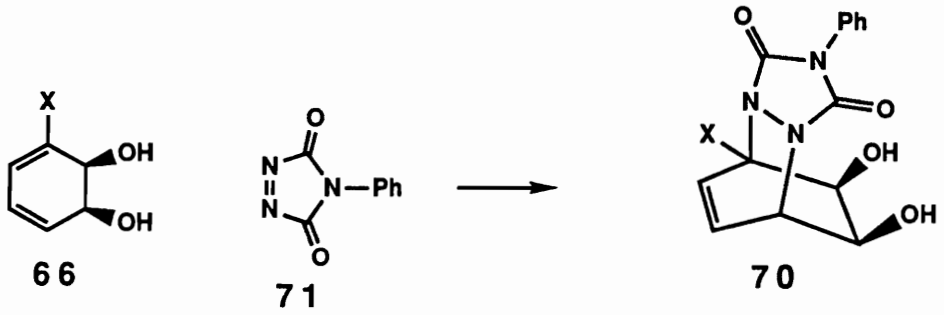
Pathway for Biodegredation of Arenes in *Pseudomonas Putida*

benzene from a mutant strain of *Pseudomonas putida*. Some of the enzymatic details of arene metabolism in this bacteria strain are known, especially regarding toluene[43,44] and polynuclear aromatic hydrocarbon[44,45] oxidation. The first step of the degradative process, shown in scheme X, is oxidative cycloaddition of oxygen to the substituted aromatic **64** which is normally directed to the ortho-meta position except in a few isolated cases.[46] The enzyme responsible for this transformation, toluene dioxygenase, has been purified and shown to be an iron-sulfur protein.[43] The cycloaddition of oxygen is responsible for the consistent stereospecific *cis* orientation of the diol unit except in the case of a single report of the formation of <2% of the *trans* isomer.[47] The resulting peroxide **65** is then reduced to the corresponding *cis* diol **66** by either a second enzyme, or possibly, a second cofactor enzyme. This process was improved by provision of a reductant such as ethanol to regenerate $NADH_2$ allowing the cell system to operate in a catalytic mode.[48,49,50] Such developments have made benzene-*cis*-diol **63** and a number of substituted derivatives commercially available.[51,52]

The following oxidation of *cis* diol **66** to its corresponding catechol **67** is easily effected by unmanipulated *Pseudomonas putida*, but genetically altered strains such as 39-D lack the coenzyme which is necessary to carry-out the conversion; thus, the diol accumulates in the medium until the cells die or until the fermentation is terminated. The natural organism will then continue to metabolize the catechol **67** to products such as **68** and **69**.

Much work has been directed toward the establishment of the absolute configuration of the arene-*cis* diols which result from the fermentation of

substituted arenes with *Pseudomonas putida* and has been shown to be 1S, 2R (3-substituent). A variety of methods have been used; for example, the configuration of toluene diol has been proven by chemical degradation to the known 2-R-methyladipic acid[53,54] and by X-ray crystallography of a Diels Alder derivative.[55] The same absolute configuration has been established for the diols from ethyl-,[54,56] phenyl-,[54] and chloro-benzene[54,57] as well as for the diols derived from fermentation of naphthalene,[58] 2-methylnaphthalene,[59] and anthracene.[60]

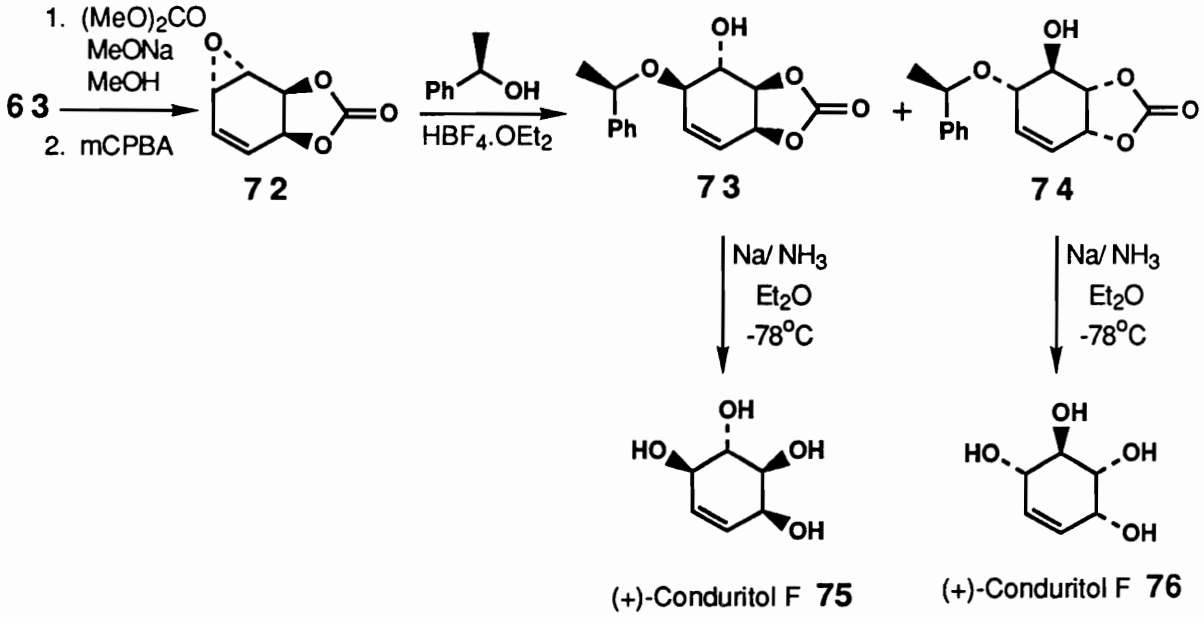


Scheme XI

Formation of Diels-Alder Adduct From Diols

Following establishment of reliable procedures for determination of absolute configuration, a general method for the measurement of optical purity was developed (Scheme XI).[61] The method relies upon the formation of a stable Diels-Alder adduct **70** between a diol **66** and 4-phenyl-1,2,4-triazoline-3,5-dione **71**. The optical purity is the determined by ^{1}H NMR of the Mosher ester of **70** and the absolute stereochemistry is determined by a correlation of the chemical shift of the lower field methoxy group of the diester.[62]

The highly functionalized nature of arene-*cis*-diols has promoted intensive investigation toward their potential in asymmetric synthesis. The

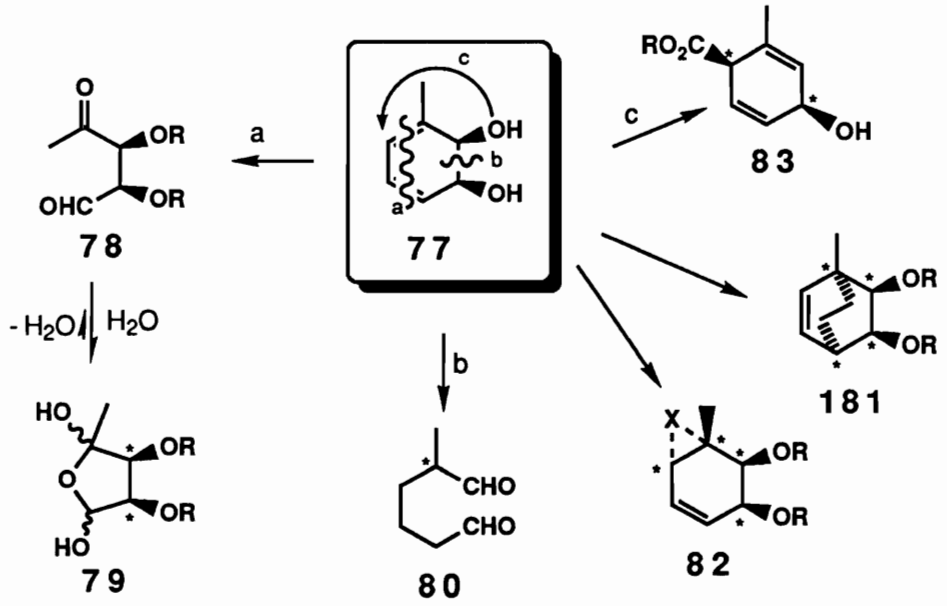


Scheme XII

Ley's Synthesis of (+) and (-)-Conduritol F

unique functionalization of these molecules allow a staggering variety of avenues for synthetic manipulation. One strategy developed by Ley[63,64] demonstrates that a single olefin of protected benzene diol can be epoxidized to furnish **72** (Scheme XII). Opening of the epoxide with a chiral nucleophile then allowed separation of diastereomers **73** and **74** and their final conversion to (+)-**75** and (-)-**76**-conduritol F.

In a report describing the synthesis of prostaglandin type synthons, Hudlicky offers a summary of some interesting strategies for exploitation of the rich functionalization found in toluene diol **77** (Scheme XIII)[65]. The diene moiety can be cleaved while retaining the diol units in **78**, which exists as **79**, or the diol function can be oxidatively cleaved after transfer of chirality as in **80**.



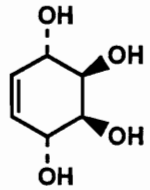
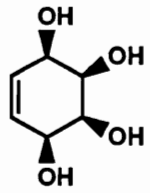
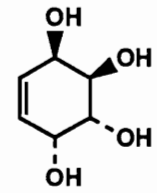
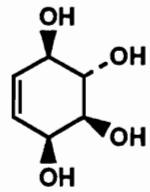
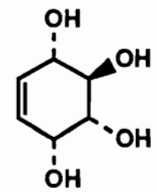
Scheme XIII

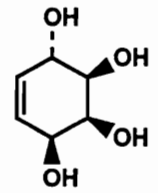
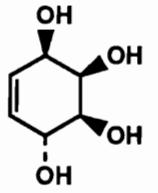
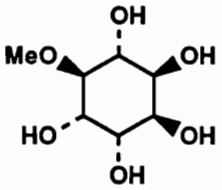
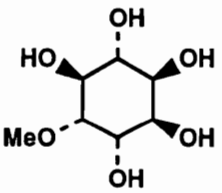
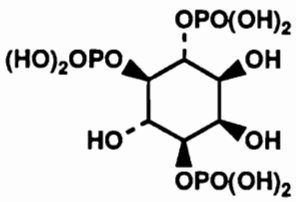
Synthetic Strategies with Toluene Diol

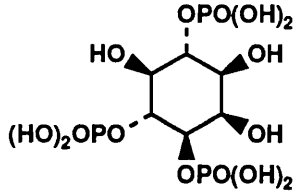
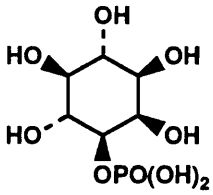
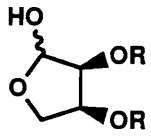
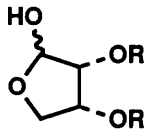
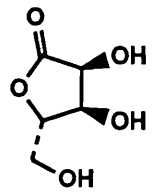
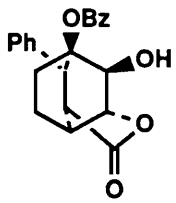
Other interesting strategies are offered including cycloaddition to **81**, epoxidation to **82**, and functional rearrangement to **83**.

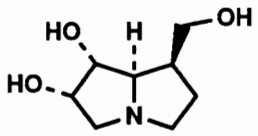
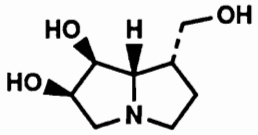
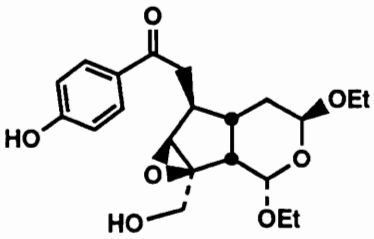
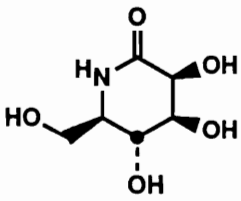
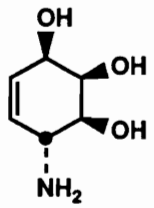
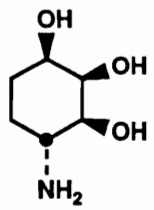
These and other strategies have since been developed for the diols derived from benzene-**(63)**, toluene-**(77)**, and many others. The scope of this discussion does not allow a complete elaboration of all such methods, but Table 2[66] summarizes all completed approaches to natural targets from arene-*cis*-diols up to the time of this writing with thorough references. Current progress in the field seems to insure further developments in the future.

Table 2 Tabular Survey of Natural Product Synthesis from Arene-*cis*-Diols

Stucture	Author	Date	Ref
 Conduritol A	Hudlicky, T. Carless, H. A. J. Balci, M	1991 1989 1988	67 68 69
 Conduritol D	Carless, H. A. J. Carless, H. A. J.	1991 1989	70 68
 (+)-Conduritol E	Hudlicky, T.	1991	81
 (+)-Conduritol F	Ley, S. V. Ley, S. V.	1991 1990	63 64
 (-)-Conduritol F	Ley, S. V. Hudlicky, T.	1990 1991	64 81

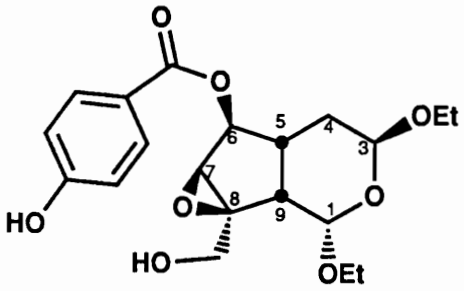
Stucture	Author	Date	Ref
 (+)-Conduritol C	Carless, H. A. J.	1991	70
 (-)-Conduritol C	Hudlicky, T. Hudlicky, T.	1991 1991	71a 67
 (+)-Pinitol	Ley, S. V. Ley, S. V. Hudlicky, T. Hudlicky, T.	1991 1989 1991 1990	63 72 67 73
 (-)-Pinitol	Ley, S. V. Ley, S. V. Hudlicky, T. Hudlicky, T.	1991 1989 1991 1990	63 72 67 73
(±)-Pinitol	Carless, H. A. J. Ley, S. V.	1989 1987	74 75
 (D)-(-)-1,4,5-IP_3	Ley, S. V. Ley, S. V.	1991 1990	63 76

Stucture	Author	Date	Ref
 (L)-(+)-1,4,5-IP_3	Ley, S. V.	1990	76
(±)-1,4,5-IP_3	Ley, S. V. Ley, S. V. Ley, S. V.	1990 1991 1988	76 63 77
 Inositol L-Phosphate	Ley, S. V. Ley, S. V.	1991 1990	63 76
 L-erythrose (acetonide)	Hudlicky, T. Hudlicky, T.	1990 1989	57 78
 D-erythrose (acetonide)	Hudlicky, T. Hudlicky, T.	1990 1989	57 78
 L-ribonic α-lactone	Hudlicky, T.	1990	79
 (-)-Zeylena	Hudlicky, T.	1989	80

Stucture	Author	Date	Ref
 (+)-trihydroxyheliotridane	Hudlicky, T.	1989	57
 (-)-trihydroxyheliotridane	Hudlicky, T.	1989	57
 (-)- Specionin	Hudlicky, T.	1992	38
 mannojirimycin	Hudlicky, T.	1992	71b
 Conduramine A	Hudlicky, T.	1991	71c
 Dihydroconduramine A	Hudlicky, T.	1991	71c

A. IV. Review of (-)-Specionin

a. Isolation and Structure Elucidation The Eastern spruce budworm inflicts serious damage to trees in the North American fir and spruce forests anually in May. This results in significant losses to the lumber industry each year. In response to the problem, Nakanishi et al[82] extracted the foliage from forty different trees which appeared to be immune to budworm infestation in an attempt to find an effective antifeedant against the pest. Such efforts led to the isolation of (-)-Specionin **1** from the leaves of *Catalpa speciosa* Warder (Bignoniaceae). It was purified from 9 g of crude EtOH extract to give 7 mg of



1

pure compound. Specionin **1** belongs to the group of Iridoids, a highly oxygenated class of compounds characterized by a cyclopentano [3,4 b] tetrahydropyran ring system. The class contains compounds which fall primarily into two groups: one has a ten carbon skeleton which contains a carbon bearing functionality at both C-4 and C-8 while the other has a nine carbon framework with functionality only at C-8.[83] Most of the naturally occurring iridoids contain a non-reducing β-link to a sugar, usually glucose and exhibit a wide range of activities. Some have also been shown to be intermediates in the

the biosynthesis of many important families of plant alkaloids.[83]

The structure of specionin was originally assigned on the basis of various spectral data. Initial evidence was obtained from an adsorption chemical ionization mass spectrum which exhibited a quasi-molecular peak at *m/z* 395 {[M - H]$^+$} and fragmentation peaks at *m/z* 349 {[M-45]$^+$} and *m/z* 303 {[M-45-46]$^+$} suggesting the presence of ethoxy moities. A mass peak at *m/z* 121 combined with a UV absorption at λ_{max} (MeOH) 254 nm (ε 1 140) to suggest the presence of a hydroxybenzoate moiety.

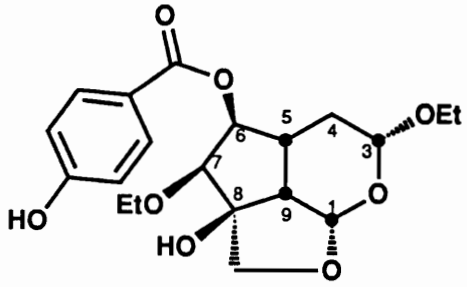
The ^{13}C NMR data showed the isolated iridoid to contain two methyl groups (δ 15.6 and 15.5), one methylene (30.4, C-4), two methines (34.2 and 41.2, C-5 and C-9), three hydroxymethylenes (61.2, 64.0, and 64.8, C-7 and CH_2O of the two ethoxy groups), two hydroxymethines (61.4 and 80.7, C-10 and C-6), two C-O (quaternary) (67.3, C-8), two hemiacetal methines (94.8 and 97.7, C-3 and C-1), four unsubstituted carbons (116.3, 116.3, 132.8, and 132.8, C-3', C-5', C-2', and C-6'), two substituted aromatic carbons (121.5, and 164.0, C-1'

Table 3

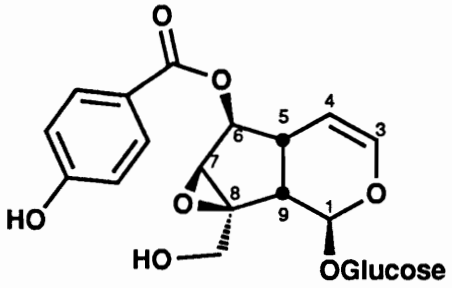
^1H NMR data for specionin **1**, 250 MHz, $CDCl_3$, δ and *J* Hz[82]

1-H	5.10, d, 4.1	3-OCHa	3.50, dq
3-H	4.90, dd, 2.8, 6.3	3-OCHb	3.85, dq
4-Ha	1.81, ddd, 6.3, 7.4, 13.6	7-OCHa	3.50, dq
4-Hb	1.94, ddd, 2.8, 5.2, 13.6	7-OCHb	3.85, dq
5-H	2.34, dddd, 5.2, 7.4. 8.1, 8.5	Me(OCH_2CH_3)	1.17, dd, 7.0, 7.0
6-H	5.32, dd, 1.1, 8.5		1.21, dd, 7.0, 7.0
7-H	3.60, d, 1.1	3'-H, 5'-H	6.83, d, 7.8
9-H	2.80, dd, 4.1, 8.1	2'-H, 6'-H	7.89, d, 7.8
10-Ha	3.55, d, 12.5		
10-Hb	4.05, d, 12.5		

and C-4'), and one carbonyl carbon (168.2 ppm) for a total of twenty carbon resonances. The NMR data in Table 3 is the result of extensive decoupling experiments and two dimensional spectroscopy.[84] To determine the relative stereochemistry around the periphery the molecule, a series of Nuclear Overhauser effect (NOE) difference spectra was determined. Irradiation of 6-H (d 5.32) caused a 16% NOE at the 7-H while no NOE was observed for 5-H.



84

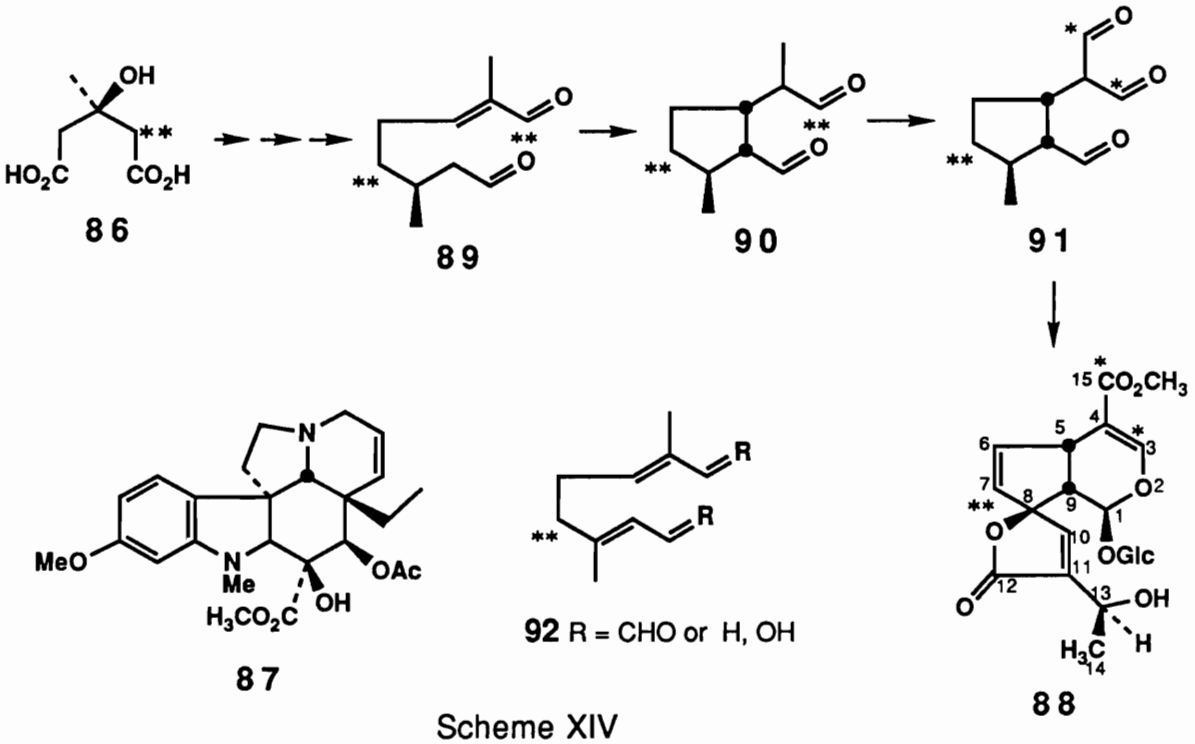


85

Irradiation of the 5-H peak (δ 2.34) exerted NOE's of 25% on 9-H, 6% on 1-H, and 14% on 4-H_a, but no effect on 6-H. Irradiation of 9-H gave 20% and 25% NOE for 5-H and 1-H, respectively, while irradiation of 1-H at δ 5.20 led to an 11% NOE for 9-H. Interpretation of all of the combined spectral data prompted Nakanishi to propose **84** as the absolute structure of Specionin. A close structural relationship of **84** to the well known iridoid glucoside catalposide **85**,[85] which has also been found in the ethanol extract of the Catalpa leaves, was noted. The incorrect assignment was finally solved by chemical synthesis[86,87] and the structure established as **1**.

b. Biosynthesis. The Iridoids represent a very diverse spectrum of compounds with markedly different structures.[88] The elucidation of a general biosynthetic pathway for the class has therefore been approached by many

different research groups and resulted in a wide array of mechanistic options for various compounds.[89] Suprisingly, the earliest attempts at elucidation were directed toward the biosynthetic origin of the non-tryptophan moiety of indole alkaloids which stimulated much controversy.[90-95] A turning point in the



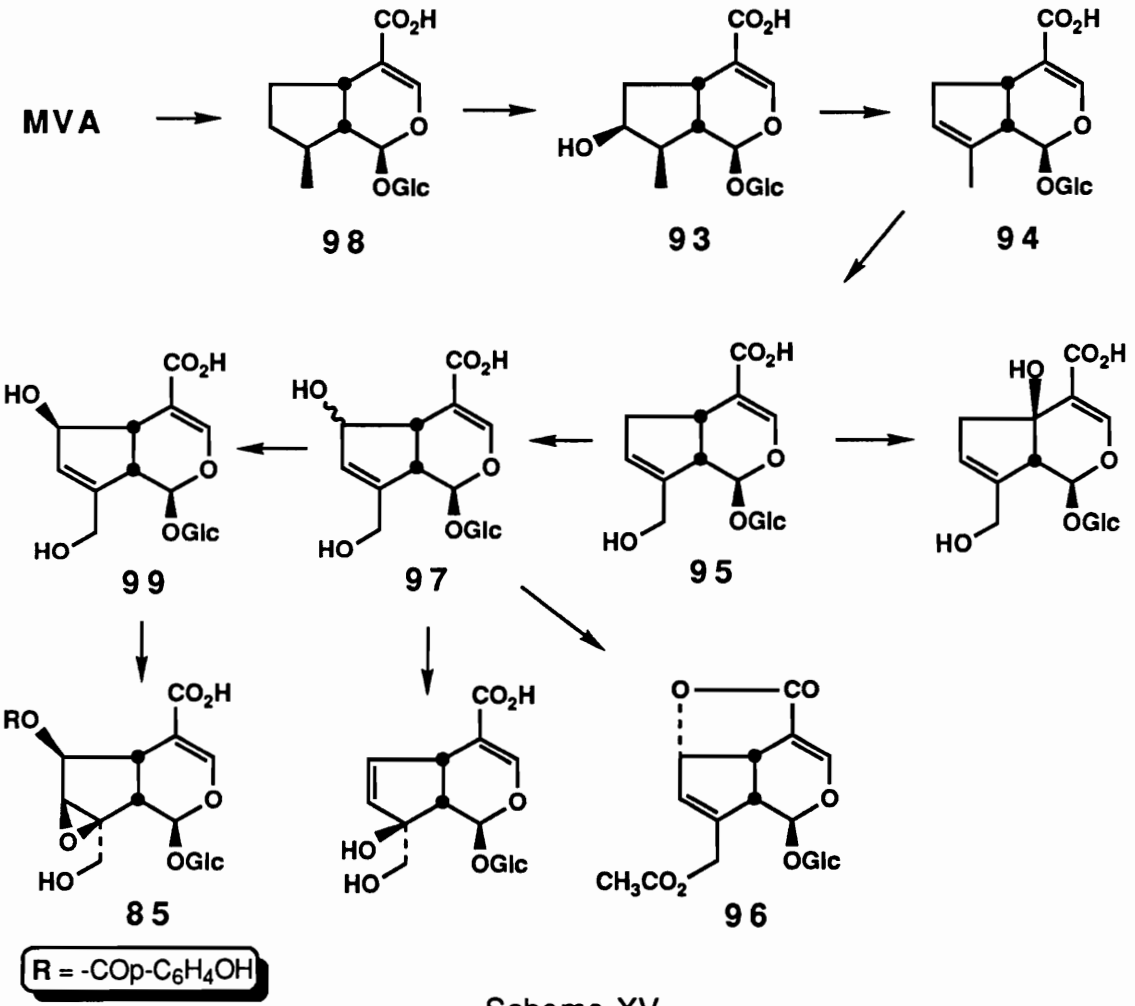
Scheme XIV

Suggested Mechanism of Plumeride **88** Biosynthesis

argument was encountered when Scott[96-98] and Arigony[99] demonstrated that mevalonic acid **86** is incorporated into vindoline **87**. Thus a precedent was established to implicate mevalonic acid as an ultimate precursor to the iridoid portion of vincamine type alkaloids and the iridoid class of compounds.

A second breakthrough was established when Schmidt[100] carried out tracer studies using Plumiera acutiflia with [2-^{14}C] MVA which demonstrated

^{14}C incorporation into C7, C3 and C15 of plumeride **88**. This led to the implication of a Michael type cyclization of 10-oxocitronellal **89** to iridoidal **90**. Further oxidation to iridotrial **91** allowed scrambling of C3 and C15. A general biosynthetic scheme could then be proposed to encompass the iridoid family which pivots around the cyclization of compounds of type **92** and follows a pathway similar to that shown in scheme XIV.

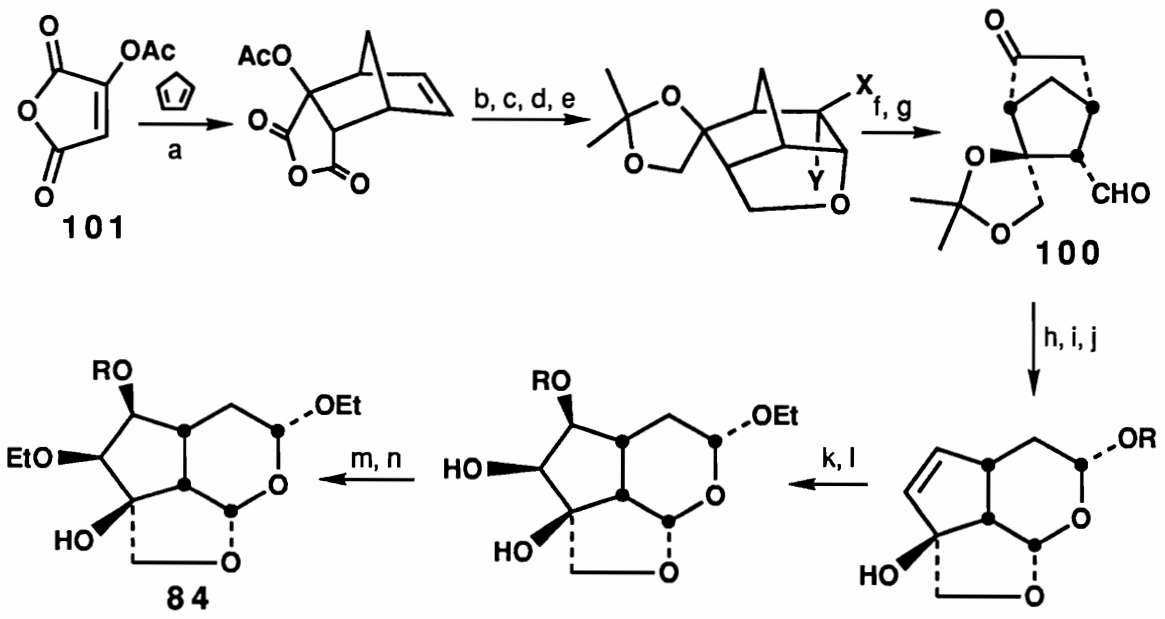


Scheme XV

Suggested Mechanism of Catalposide **85** Biosynthesis

There exists some data on the biosynthesis of iridoids beyond the closure of the cyclopentene ring which applies to the formation of catalposide **85** and therefore specionin **1**. Arigony[101] and Battersby[102] demonstrated that compounds of type **92** are incorporated into loganin **93** (scheme XV). Postulating that deoxygeniposidic acid **94** was an intermediate following loganin in the biosynthesis of iridoid glucosides, Inouye[103] fed [10-^{3}H] geniposide **95**, biosynthetically prepared from **94**, to *Daphniphyllum macropodum* and demonstrated incorporation into **96**. They also prepared [10-^{3}H] scandoside **97** biosynthetically from [10-^{3}H] deoxyloganic acid **98** and demonstrated incorporation into aucubin **99** which was subsequently incorporated into catalposide **85** of *Catalpa ovato*. Thus, a reasonable biosynthetic scheme for catalposide **85** can be proposed and assumed to apply to specionin **1** which has been accused of being an artifact of **85**.[104]

c. Total Synthesis. The structural assignment of Specionin was first tested synthetically in 1985 by Vandewalle[86] who published a total synthesis of **84** (scheme XVI). The synthesis features a straight forward construction of ketone **100** from an initial Diels-Alder reaction of **101**[87] with cyclopentadiene followed by a Norrish I type fragmentation. Subsequent functional group manipulation delivered the desired compound **84** whose ^{1}H NMR spectrum did not prove to be identical with a ^{1}H NMR spectrum of natural specionin. Since Vandewalle did not have any reason to believe that the compound which was synthesized was not **84**, he concluded that the structure of specionin was different than the one originally proposed. He further pointed out a similarity in the spectrum of specionin and some earlier reported 7,8-epoxy iridoids[88] and



R = $COC_6H_4OCH_2C_6H_5$

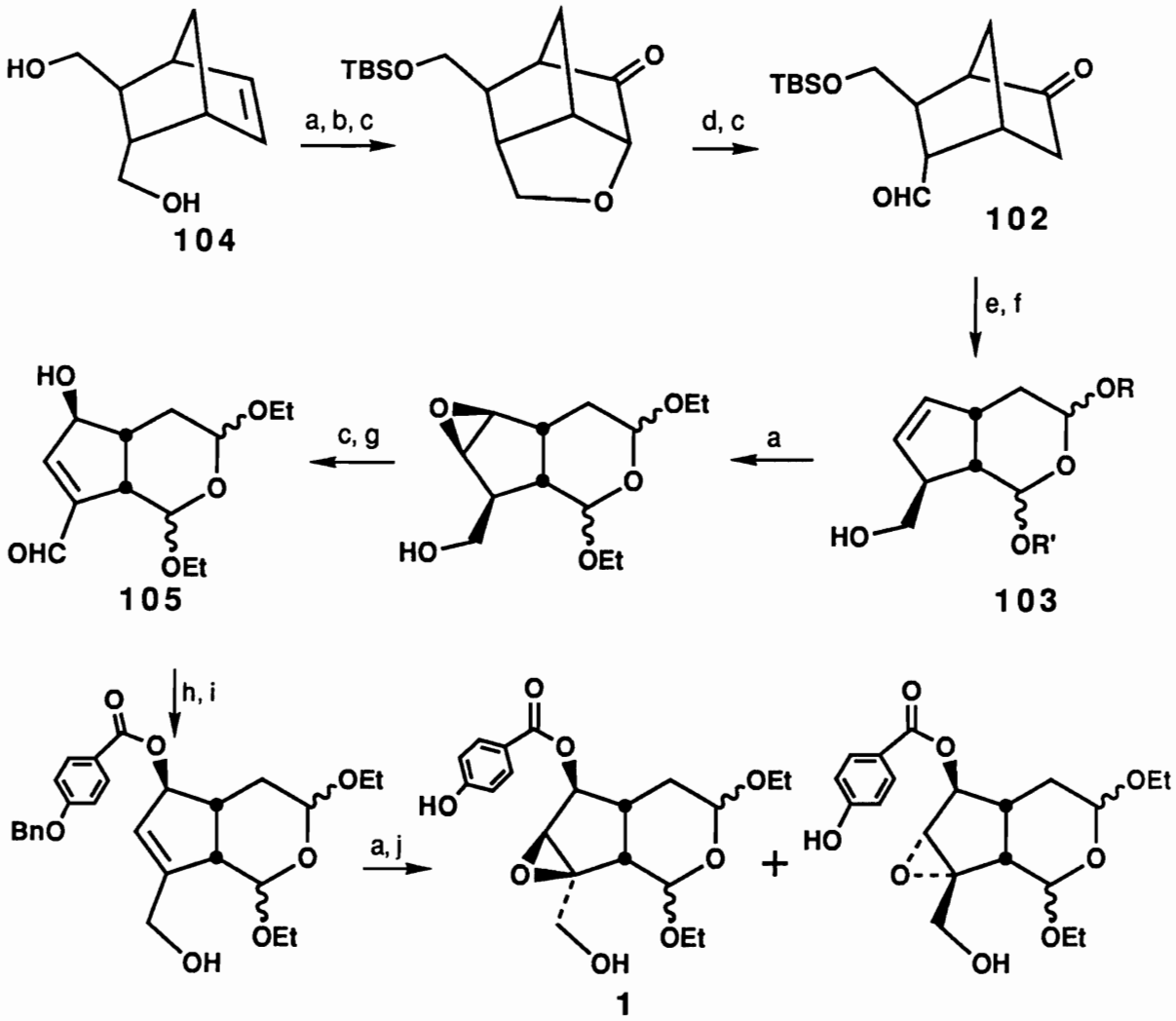
a) PhH / RT b) $LiAlH_4$ / THF c) Me_2CO / CH_2Cl_2 / p-TsOH / $CuSO_4$ anh d) mCPBA / CH_2Cl_2 e) $(COCl)_2$ / DMSO / Et_3N / CH_2Cl_2 f) Al-Hg / EtOH / THF g) $(COCl)_2$ / DMSO / Et_3N / CH_2Cl_2 h) H_2O / dowex 50 x 8 - 100 i) 254 nm / EtOH / $NaHCO_3$ j) EtOH / Dowex 50 x 8 - 100 k) OsO_4 / NMMO / H_2O / Me_2CO l) p-$BnOC_6H_4COCl$ / Et_3N / CH_2Cl_2 m) CH_3CHN_2 / $BF_3{\cdot}Et_2O$ / CH_2Cl_2 / Et_2O n) Pd-C / H_2 / EtOH

Scheme XVI

Vandewalle's Synthesis of Specionin Structural Isomer **84**

mentioned that such similarity strongly suggested a structure of type **1** for specionin.

With the new postulated structure for specionin, Vandewalle set out to complete a total synthesis of structure **1** which resulted in the first reported construction of the molecule (Scheme XVII).[86,87] His strategy was similar to one he used for the synthesis of iridoid **84** which featured a Norrish I type fragmentation of norbornanone **102** with ethyl acetal formation to form



a) mCPBA / CH_2Cl_2 b) TBDMSCl / DBU / CH_2Cl_2 c) $(COCl)_2$ / DMSO / Et_3N / CH_2Cl_2 / -60°C d) Al-Hg / EtOH / THF / RT e) hv at 254 nm / EtOH f) p-TsOH / EtOH / RT g) DBU / CH_2Cl_2 / RT h) p-$BnOC_6H_4COCl$ / Et_3N / CH_2Cl_2 / RT i) $NaBH_4$ / EtOH / THF / 0°C j) Pd-C / H_2 / EtOH

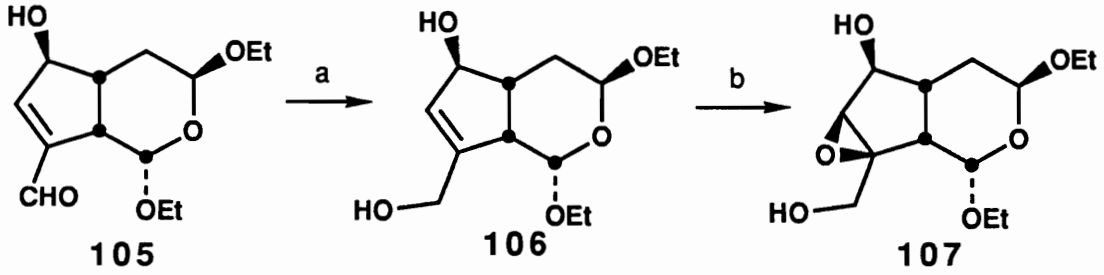
Scheme XVII

Vandewalle's Synthesis of Specionin

heterocycle **103** in the diastereomeric ratio of 1:4:1:4 (for C1,C3 as α,β: β,α: α,α: β,β). The resulting mixture allowed the ultimate assignment of the proper C-1 and C-2 stereochemistry which was hitherto not known. The starting

norbornene **104**[108] is available with either enantiomeric configuration, therefore the synthesis is enantiodivergent.

The left ring was functionalized in a straight forward fashion through stereoselective epoxidation and base promoted ring opening to give aldehyde **105** which was esterified with the desired para-substituted benzoic acid followed by epoxidation of the remaining double bond. Steric hindrance from the C-6 ester caused problems with diastereo control and delivered the epoxide



a) $NaBH_4$ / EtOH / 0°C b) mCPBA / CH_2Cl_2

Scheme XVIII

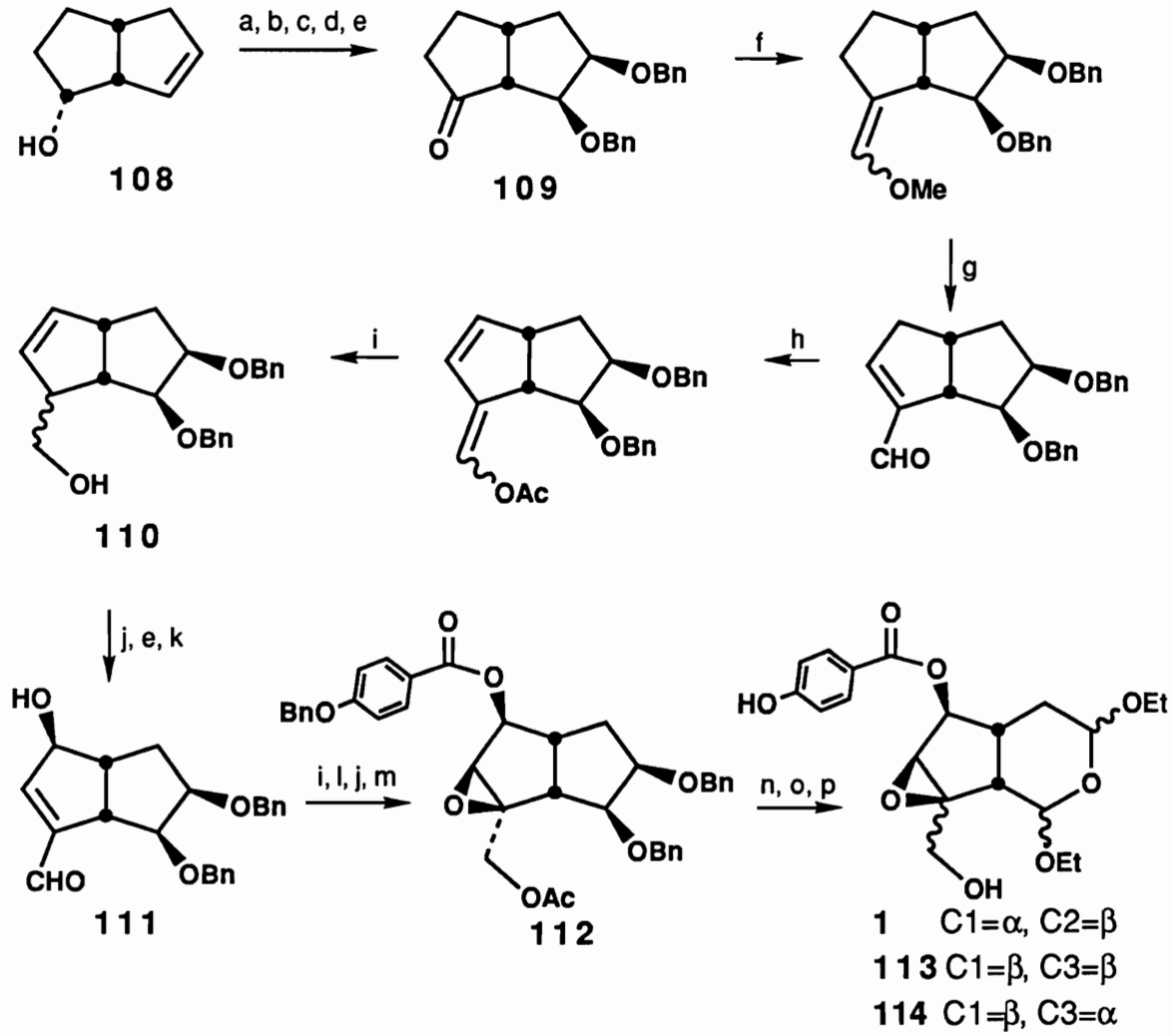
Vandewalle's Functionalization of the Left Ring of Specionin

to the α : β positions in a 1 : 1.2 respective ratio. The synthesis was therefore modified (scheme XVIII) so that diol **106** was subjected to epoxidation conditions which delivered a stereoselective formation of epoxide **107**. The primary alcohol had to be protected before the benzyl ester could be made adding two extra steps to the synthesis. Vandewalle's synthesis firmly established the actual structure and relative and absolute stereochemistry of specionin. Comparison of the synthetic product with an authenic sample confirmed the assignments.

A second synthesis of specionin **1** was reported by Leonard in 1987 (Scheme XIX).[104] His work began before the corrected structure elucidation of **1** was reported by Vandewalle, so the effort was initially targeted for **84**, but the route was easily adjusted when the proper target became known. The synthesis began with endo-cis-bicyclo [3.3.0]oct-7-en-2-ol **108**[109]. The initial strategy was to first cleave the cyclopentene ring to form the bis acetal followed by functionalization of the other ring; however, this strategy led to a complex mixture of diastereomers of the acetal, a problem similar to that which Vandewalle also encountered. The other ring was therefore functionalized first under the assumption that the previously set stereocenters would control the acetal stereochemistry as it was believed that specionin may have been an artifact resulting from the extraction process.

The first few steps of the synthesis involved the preparation of diol **109** from the olefin which was protected with benzyl groups as difficulties were experienced in removing acetonide protecting groups in early model studies.[104] The left hand ring was functionalized by using Wittig technology to add the last required skeletal carbon followed by functional group manipulation to arrive at alcohol **110**. The C-6 stereocenter of **111** was set using a stereoselective epoxidation followed by base promoted epoxide opening with the C-8 enolate. After subsequent reduction of the aldehyde functionality, an interesting monoacetalation of the primary alcohol was performed which was described as being successful, however, an unreported amount of starting material and diacetate was also recovered.

Upon arrival at **112** and protecting group removal, the critical bis-acetal



a) TBSCl / imidazole / DMF b) OsO_4 / NMO / tBuOOH / THF c) i. NaH / THF ii. $PhCH_2Br$ d) Bu_4NF / THF e) $(COCl)_2$ / DMSO / Et_3N / -78°C, 72% over 5 steps f) $NaN(TMS)_2$ / $MeOCH_2PPh_3Cl$ / THF / 0°C g) i. meso-tetraphenylporphine / hv / O_2 / PhH / pyr, ii. PPh_3, 51% over 2 steps h) i. tBuOK / THF / RT, ii. Ac_2O / 0°C i) $NaBH_4$ / $CeCl_3$ / MeOH, 56% over 2 steps j) tBuOOH / $VO(acac)_2$ / CH_2Cl_2 / reflux k) DBU / CH_2Cl_2 / RT, 50% over 3 steps l) $(AcO)_2O$ / Et_3N / CH_2Cl_2, 42% + SM + diacetate m) p-$BnOC_6H_4COCl$ / CH_2Cl_2, 77% over 2 steps n) H_2 / Pd-C o) $NaIO_4$ / EtOH p) EtOH / TsOH, 72% over 3 steps

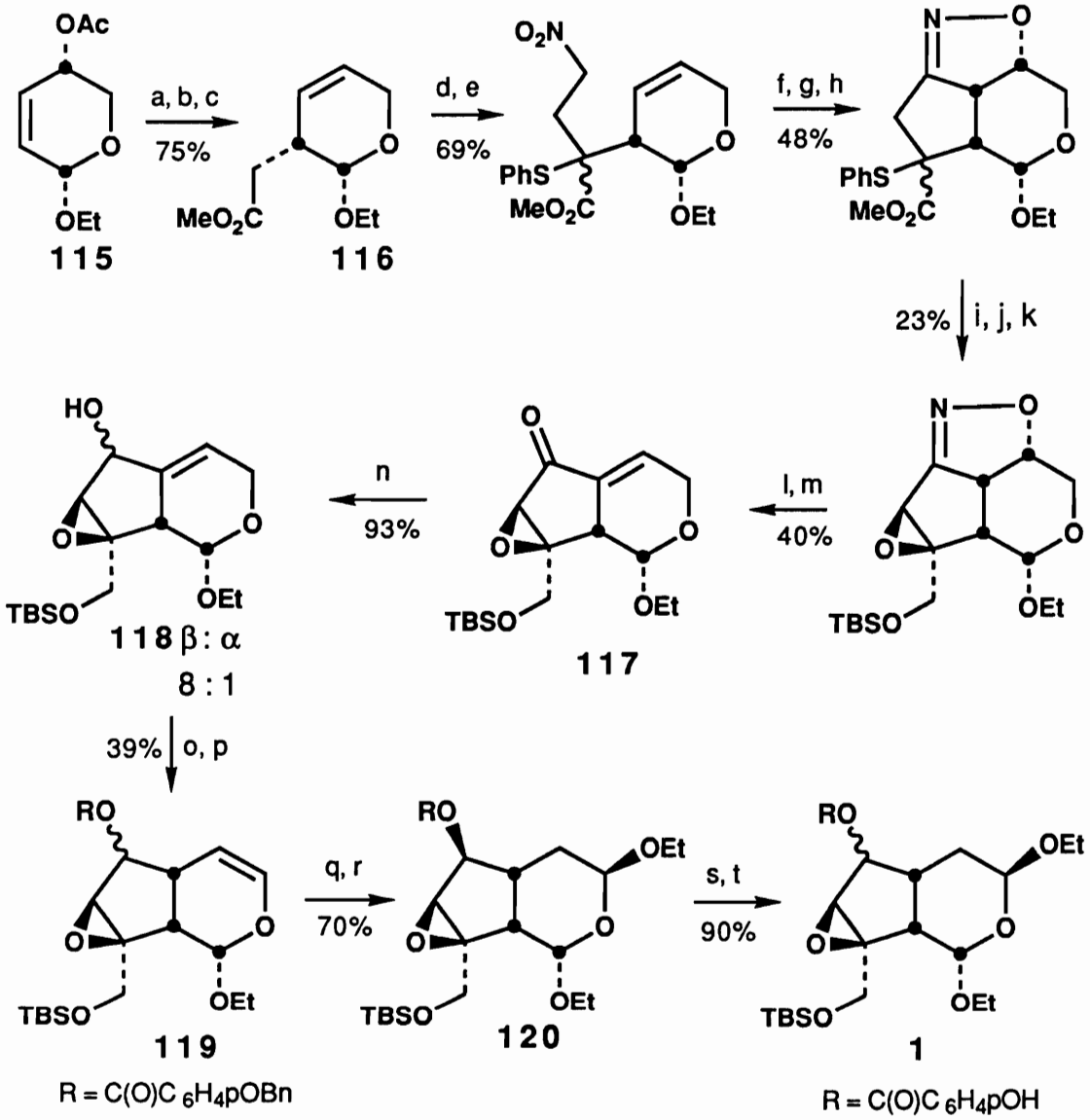
Scheme XIX

Leonard's Synthesis of Specionin

cyclization reaction was performed. Execution of such cyclization revealed an intriguing competition for kinetic versus thermodynamic control. Monitoring of the reaction at 10 hr revealed a 1:1:0.1 mixture of diastereomers **1**, **113** and **114**. However, when the mixture was allowed to stand overnight and examined at 300 MHz, the ^{1}H NMR spectrum revealed a respective 0:4:1 mixture which was interpreted as evidence that specionin is the most stable acetal anomer and arises either from biosynthesis from catalposide **85** by glycolysis followed by acetal formation, or more likely, as an extraction artifact of catalposide **85**.

Like Vandewalle, Curran published an approach to (-)-Specionin (Scheme XX) which was originally targeted toward the iridoid **84**.[110,83] His approach was also easily modified to the correct target. His starting material was **115**[111], of which either enantiomer is available from Ferrier rearrangement of D-xylal. The proper stereochemical disposition at C-1 and C-3 was unknown at the time, but Curran correctly assumed that one of the two trans configurations represents the most stable stereochemistry; however, since they each possess an axial and equitorial position in the chair like ring he could not be certain which was the most stable. Fortuitously, he initiated the synthesis with the correct isomer.

The synthesis began with an Ireland Claisen reaction of **115** to arrive at **116** followed by the addition of C-6 and C-7 in the form of nitroethane addition and many functional group manipulations including a stereospecific epoxidation and rearrangement to set up the important reduction of ketone **117**. Lithium aluminum hydride delivered alcohol **118** as a 3 : 1 mixture of



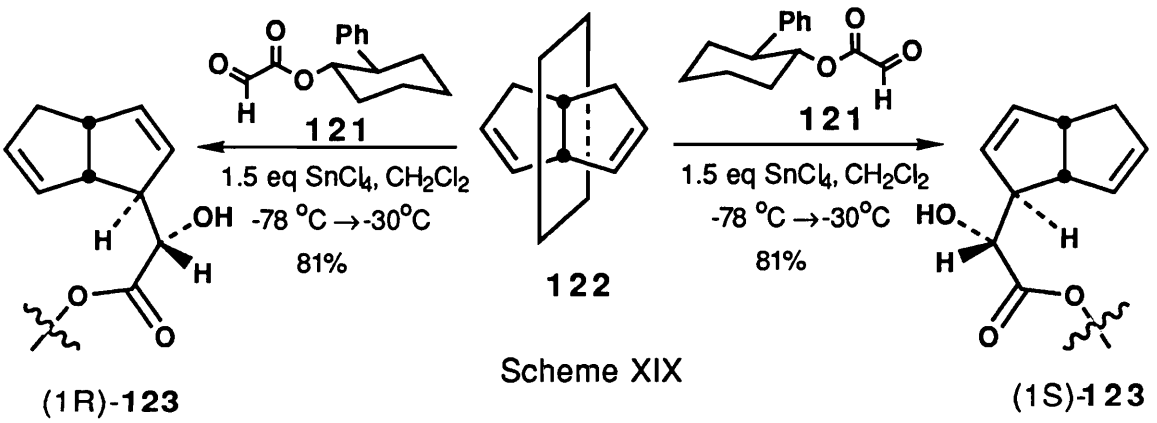
a) LDA / TBSCl / DMPU b) 110°C c) CH_3I / KF / K_2CO_3 d) LDA / PhSSPh e) LDA / CH_2=$CHNO_2$ f) p-ClC_6H_4NCO / Et_3N / 110°C g) mCPBA h) PhH / 80°C i) $(i\text{-}Bu)_2(n\text{-}Bu)AlHLi$ j) TBSCl / DMAP / Et_3N k) 3,5-DMPBA / Na_2HPO_4 / CH_2Cl_2 l) Rh-Al / H_2 / $B(OH)_3$ / MeOH / H_2O m) CH_3SO_2Cl / Et_3N n) $NaBH_4$ / $CeCl_3$ / THF / -78°C O) cat. $RuH_2(PPh_3)_4$ p) p-$BnOC_6H_4CO_2H$ / DCC / DMAP q) $Hg(OAc)_2$ / EtOH r) $NaBH_4$ / NaOH s) TBAF / THF t) H_2 / Pd-C

Scheme XX

Curran's Synthesis of Specionin

β : α isomers which was improved to 8 : 1 respectively with $NaBH_4$ reduction. Smooth ester formation and olefin migration set up the addition of the C-3 ethoxy group via oxymercuration of **119** and in situ reductive ethanolysis to yield **120** in a *stereospecific* fashion. Two deprotection steps gave (-)-Specionin in 20 overall steps and confirmed the stereochemical assignment which was made by Vandewall.

The most recent asymmetric total synthesis of (-)-Specionin to date was completed by Whitesell and reported in 1988.[112] The synthesis was built around the advantage of knowing the proper stereocemical disposition at each

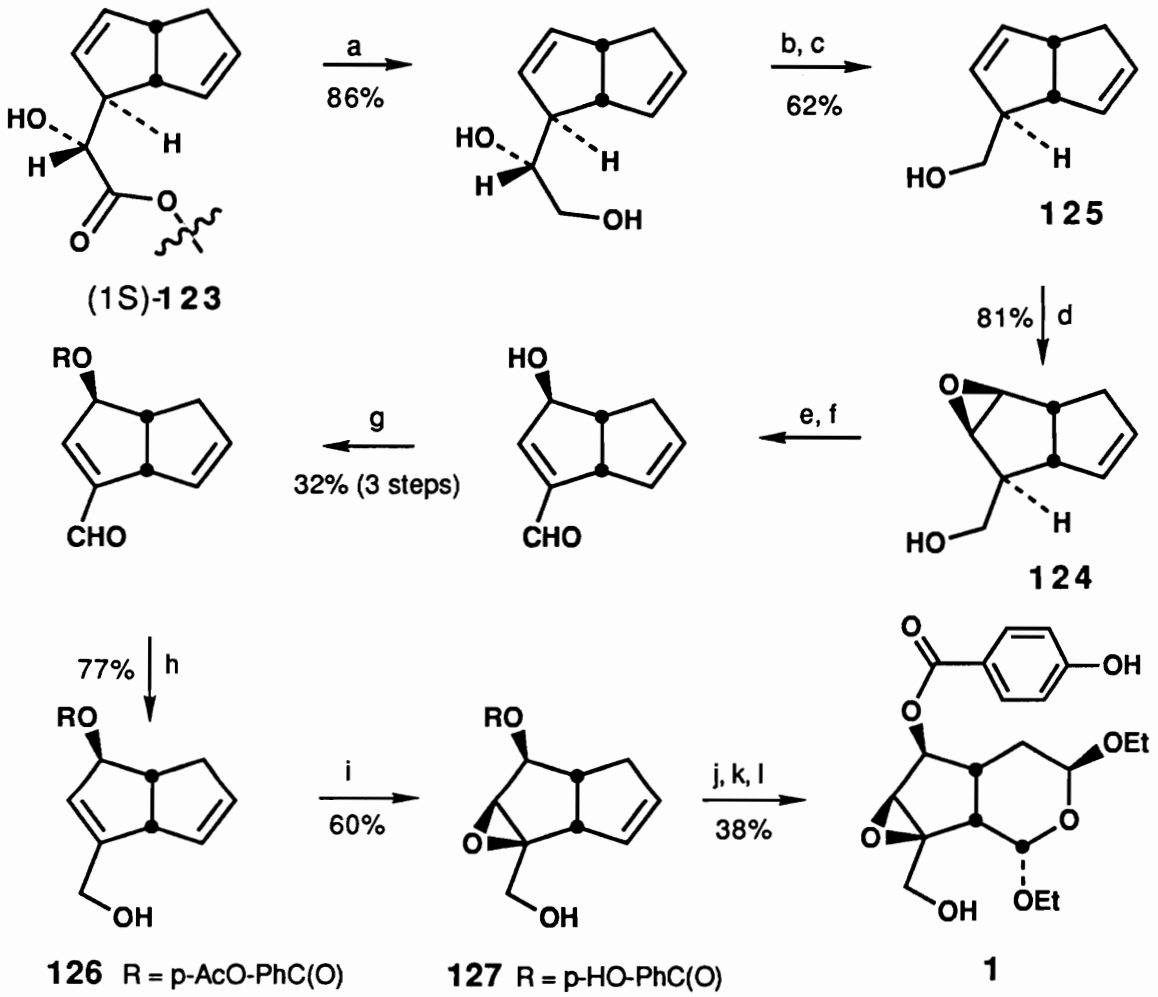


(1R)-**123** Scheme XIX (1S)-**123**

carbon. The synthetic plan called for completion of the left ring first and allow the preset stereochemical bias direct the ethanolysis and acetal formation. The acetal formation also demonstrated that the substituents at C-1 and C-3 positions in specionin enjoy a most thermodynamically stable configuration.

Whitesell introduced asymmetry into the first step of the synthesis via an enantiomerically pure glyoxylate reagent **121** which successfully participated in a homochiral ene reaction (Scheme XXI).[113] The enantiomeric success of this

reaction hinged on the ability of the glyoxylate to discriminate between two olefins which were related by a chiral plane within the substrate **122**. Both enantiomeric forms of **121** are available, thus rendering either ene product **123** accessible.



a) LAH / THF b) $NaIO_4$ / acetone-H_2O c) $NaBH_4$ / EtOH d) $VO(acac)_2$ / tBuOOH e) $(COCl)_2$ / DMSO / CH_2Cl_2 / -78°C f) Et_3N / -78°C → RT g) (p-AcO)-PhCOOH / DMAP / TsOH / CH_2Cl_2 h) $NaBH_4$ / EtOH i) $VO(acac)_2$ / tBuOOH / CH_2Cl_2 / acetone j) O_3 / EtOH k) H_2 / Pd-C l) p-TsOH / EtOH / pH ~3

Scheme XXII

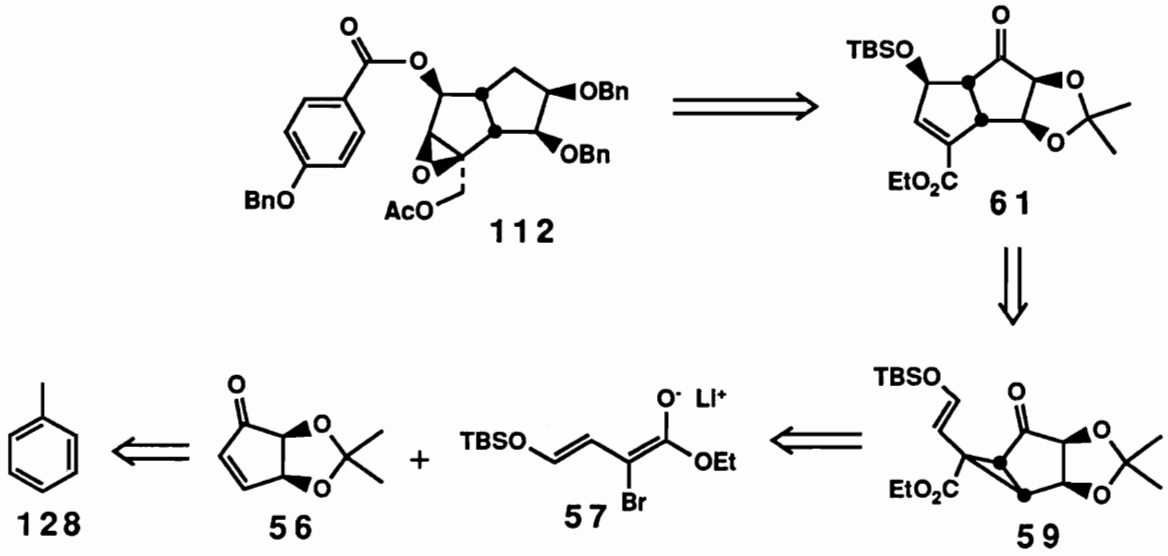
Whitsell's Synthesis of Specionin

The conversion of **123** to epoxide **124** involved cleavage of the excess carbons from the ene addition and a regioselective epoxidation of diene **125** in which the close proximity of the homoallylic alcohol to the C6-7 olefin was explioted (Scheme XXII). Further functional group manipulations then smoothly delivered allylic alcohol **126**. The alcohol functionality was then exploited to deliver the epoxide *specifically* from the exo face despite possible hinderance from the benzoic acid moiety which resulted in respectable 60% yield of **127**.

Thus, there have been four successful syntheses of specionin **1** to date: Vandewalle's fourteen step synthesis completed in 1.8% overall yield, Leonard's nineteen step synthesis accomplished in 2.4% overall yield, Curran's twenty step synthesis finished in 0.52% overall yield, and Whitsell's thirteen step synthesis which provided 2.4% overall yield.

A. V. Unpublished Efforts Toward (-)-Specionin

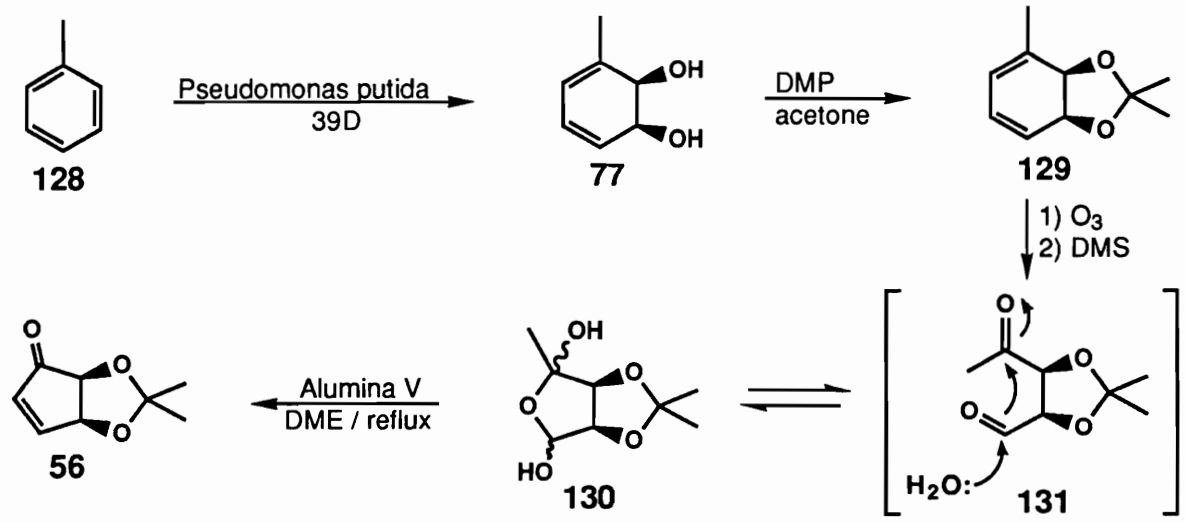
Following the appearance of the work of Whitesell,[112] an unfinished attempt toward the total synthesis of (-)-specionin appeared[23] which exploits the [2+3] oxycyclopentene rearrangement published by the Hudlicky group in the form of a model study.[5] A retrosynthetic plan of the work (Scheme XXIII) describes an approach to intercept diquinane intermediate **112** which was



Scheme XXIII

Hudlicky / Fleming Retrosynthetic Analysis of (-)-Specionin

encountered in Leonard's synthesis of specionin.[104] Cyclopentene **61** serves as a pivotal intermediate as routine functional group manipulation should allow entry to **112**. The desired tricycle **61** is available from the [2+3] annulation of chiral enone **56** and oxydienolate **57**. Microbial oxidation of toluene provided chiral intermediates which made chiral enone **56** accessible.



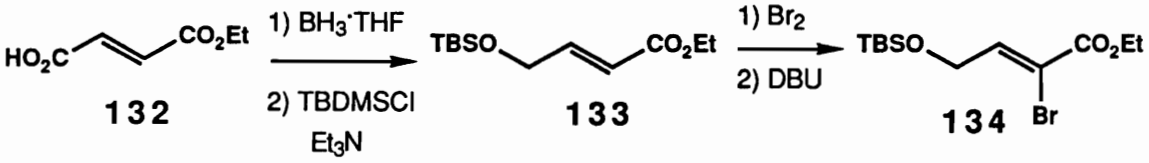
Scheme XXIV
Synthesis of Enone **56** from Toluene

The microbial oxidation of substituted arenes has been shown to produce diols of type **77**.[41] Such diols were seen as potential chiral synthons and as a possible starting point for the synthesis of desired enone **56**. A publication resulted in 1988[65] which describes the synthesis of enone **56** from toluene diol **77** in 45 % overall yield. Ozonolysis of the diene unit of acetonide protected **129** delivered a waxy solid which was assigned as hemiacetal **130**. The mechanism of the product formation is as yet undetermined although a hydration mechanism of type **131** is plausible. A question remains however as to what the source of water may be and whether or not the diene undergoes stepwise ozonation and fragmentation before the addition of dimethylsulfide as indicated by Griesbaum.[114]

It was noted that the following aldol cyclization would require dehydration of hemiacetal **130** and that such reactions usually demand in situ generation

of hemiacetal **130** and that such reactions usually demand in situ generation of the enolate anion of compounds of type **131**. Both functions were accommodated upon exposure of **130** to excess alumina in refluxing DME which promoted the desired cyclization in 65% yield.

With a respectable amount of chiral enone **56** in hand, the stage was set for the [2 + 3] cyclopentene sequence. A properly protected γ-hydroxy crotonate was needed and was readily prepared in multigram quantities according to the sequence in Scheme XXV.[115] Readily available fumaric acid monoethylester **132** was reduced to alcohol **133** followed by bromination tributyldiomethylsilyl-



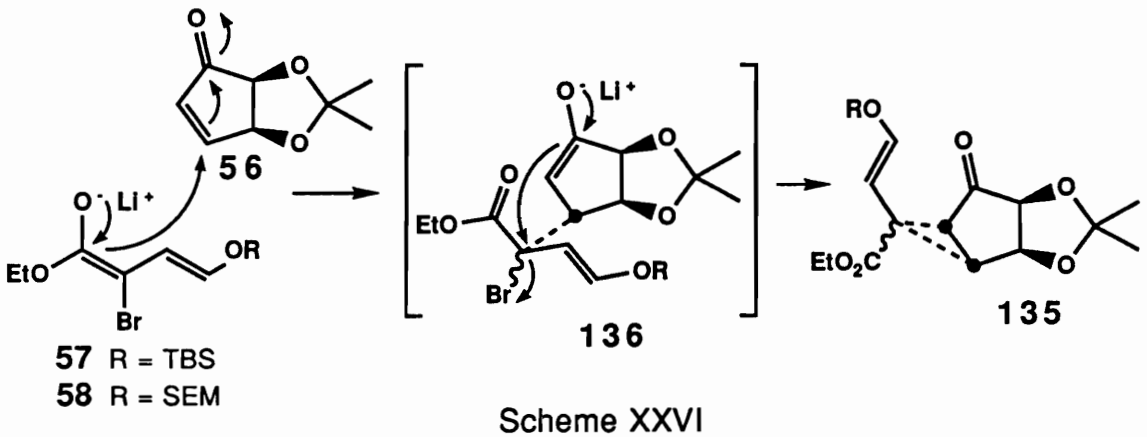
Scheme XXV
Synthesis of Ethyl γ-hydroxycrotonate

protection of the double bond and base promoted elimination of the β-bromine to provide γ-hydroxy-2-bromocrotonate **134** in a 12% overall yield. The ultimate choice of proper hydroxy protecting group depended on how the resulting properties manifested themselves during the cyclopropanation and later steps.

A detailed study of cyclopropanation conditions was carried out with a variety of protected γ-hydroxy-2-bromocrotonates and enones[5] which provided insight into proper reaction conditions. The presence of the oxygen atom in **134** hindered its conversion to **57** due to extensive dimerization and

decomposition of the lithium dienolates, a probable a reflection of the lower acidity of the γ-hydrogen. The problem was circumvented by forming the enolate in very dilute (.04 M) solution and at very low temperatures (-105 °C).[4,116]

It was thought that either the SEM or the TBS protecting group would provide useful crotonate derivatives. Their enolates **57** and **58** were generated with LDA and added to the enone **56** as depicted in scheme XXVI. The E/Z geometry of the dienolate **57** has been briefly investigated[117,118]. Trapping the dienolate **57** proved to be impossible, but ^{13}C NMR at -100°C indicated one set of resonances and ^{1}H NMR indicated a 15:85 mixture. The configuration of the predominate isomer could not be determined due to poor resolution of the spectra, but it is clear that one isomer predominates. The Michael reaction occurred exclusively from the α-carbon of the ambident crotonate nucleophile **57** and was stereospecifically directed to the α-face of enone **56** because of the steric crowding of the β-face by the acetonide group. This process provided in one step the intermediate **136** with all of the chiral information completely

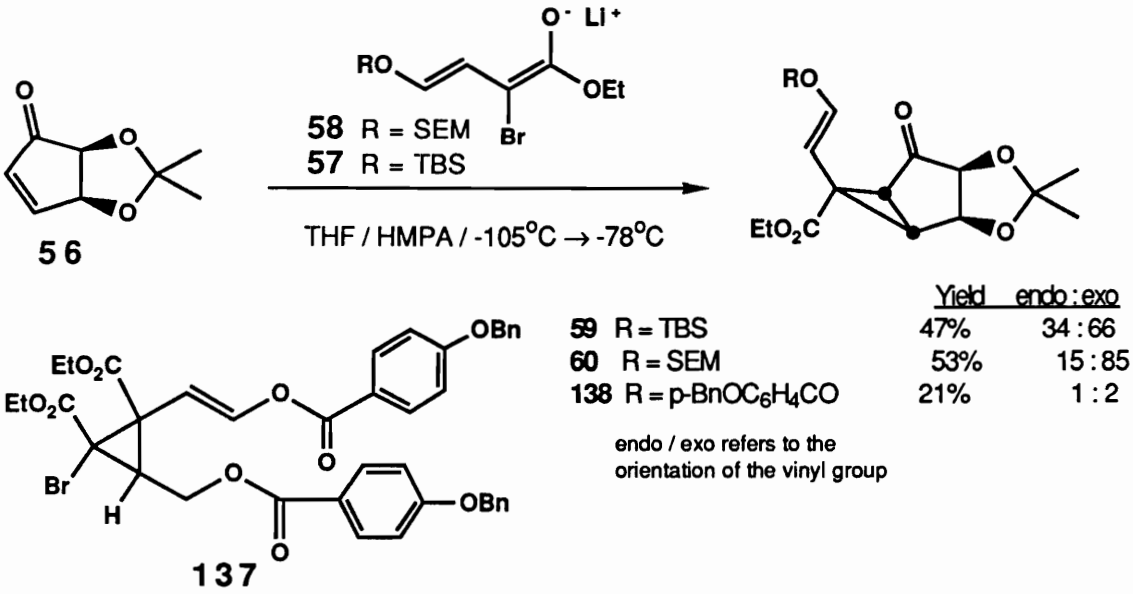


Scheme XXVI

Vinylcyclopropanation Mechanism

transferred from the masked diol carbons which closed in situ to the cyclopropane **135**.

Since the vinylcyclopropane methodology was ultimately to be used for (-)-Specionin synthesis, the alcohol from BH_3 reduction of **132** was protected as a p-benzylbenzoate ester which would be well suited to become the ester functionality found on the C6 center in the target molecule and would lead to significant shortening of the synthesis. The vinylcyclopropanation reaction however suffered from a very low yield due to extensive dimerization of the crotonate unit to form cyclopropane **137** as a major product and desired cyclopropane **138** as only a minor component in the reaction mixture (Scheme XXVII).[23] It then seemed that the crotonate might react more efficiently as a protected alcohol, so enone **56** was treated with the SEM **58** and TBS **57** protected dienolates to deliver far superior, albeit modest, yields of



	Yield	endo : exo
59 R = TBS	47%	34 : 66
60 R = SEM	53%	15 : 85
138 R = p-BnOC$_6$H$_4$CO	21%	1 : 2

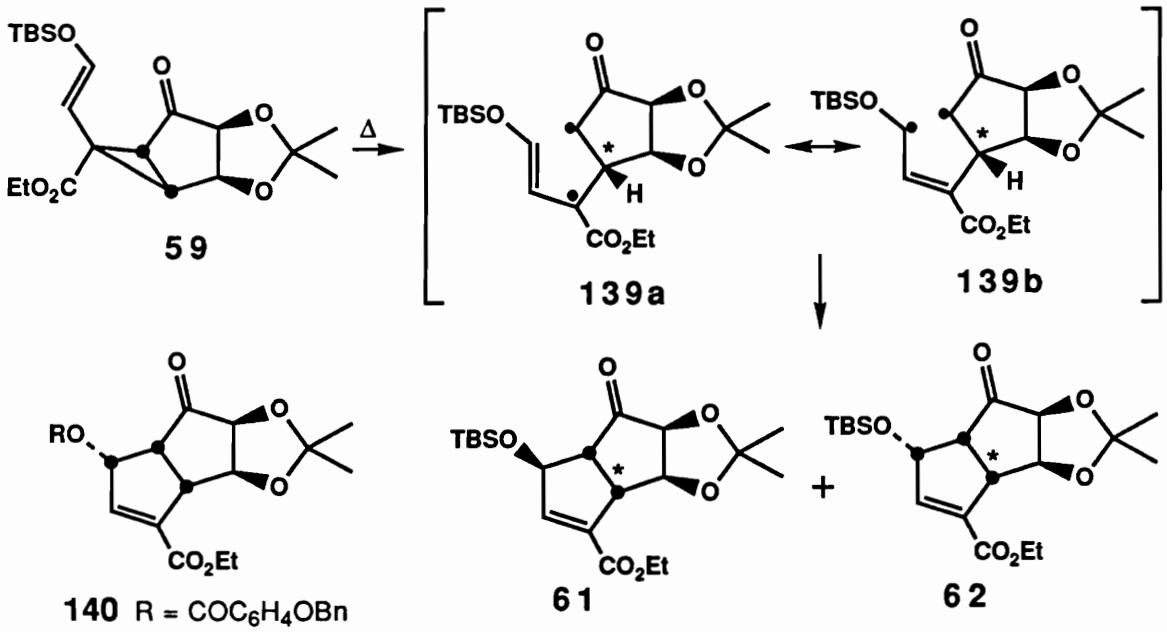
endo / exo refers to the orientation of the vinyl group

Scheme XXVII

Initial Vinylcyclopropanation Results

cyclopropanes **60** and **59** respectively. The endo / exo ratio of the three vinyl - cyclopropane derivatives differed widely, however this was not anticipated to be a problem since the low pKa values of the α-CO hydrogens disables enolate formation in these molecules and should preclude any chance of unwanted cope rearrangement[119] and render both isomers capable of successful cyclopentene rearrangement.

Various methods of cyclopentene rearrangement have been developed and applied to cyclopropane **59.**[5] The most well known is flash vacuum pyrolysis which proceeds via homolytic cleavage of the cyclopropane to form intermediates of type **139** which are stabilized in this case by the TBS enol ether (Scheme XXVIII)[15,16]. Rearrangement and reclosure of the diradical then forms the more thermodynamically stable cyclopentenes **61** and **62**. Chiral

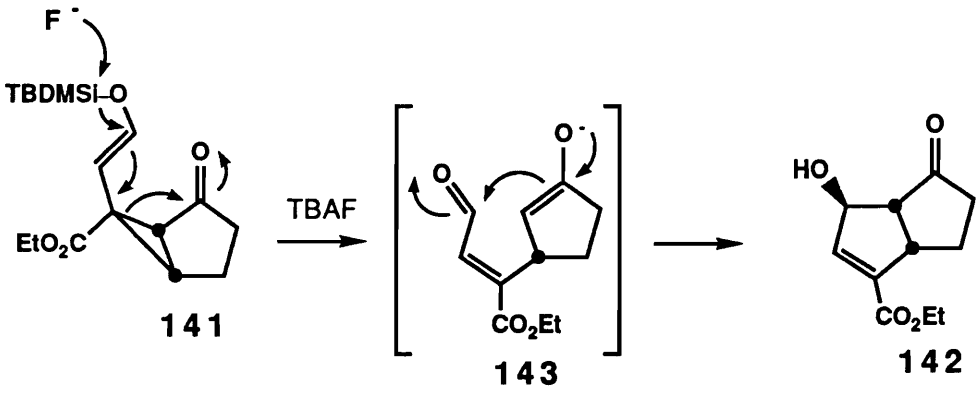


Scheme XXVIII

Mechanism of Vinylcyclopropane Pyrolysis

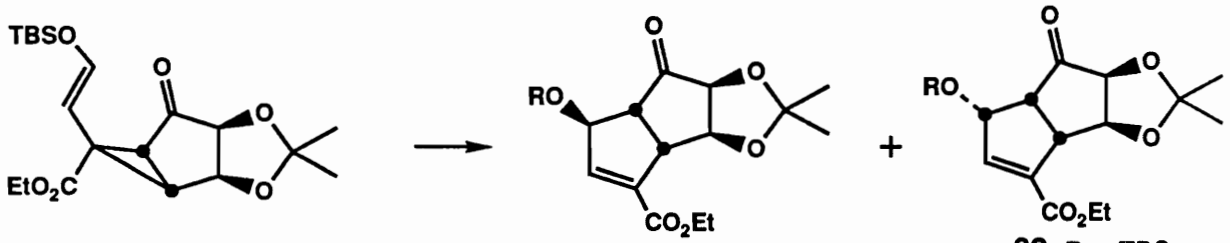
information is retained because one center (marked with *) remains intact and two cyclopentane rings can fuse only in a *cis* fashion. The yield for the case of **59** was a respectable 75%, but flash vacuum pyrolysis has serious limitations as seen in the case of benzyl protected cyclopropane **138** which was converted to cyclopentene **140** in 28% yield due to its extremely low volatility. A method was therefore sought to extend the [2 + 3] methodology to a greater more diverse group of compounds.

A useful method was inadvertently discovered from an attempt to deprotect a TBS protected vinylcyclopropane **141** which resulted in complete conversion to cyclopentene **142** (Scheme XXIX). Apparently, the enolate anion which resulted from the fluoride mediated silicon-oxygen bond cleavage promoted a retroaldol type reaction through enolate intermediate **143** to give **142** after subsequent aldol type ring closure. Initial ring opening is driven both by the relief of 27 kcal of ring strain and the formation of a stable Si-F bond as in a Sakurai type reactions.[120] The reaction was optimized and applied to the vilylcyclopropane **59** to deliver tricycles **144** and **145** in a very respectable



Scheme XXIX
Mechanism of Floride Rearrangement

86% yield (Scheme XXX). As in the pyrolysis reaction, the chiral information is transferred completely to the diquinane. The fluoride promoted rearrangement does not discriminate against compounds with high volatilities and is thermally milder by almost 600°C!



59

61 R = TBS
144 R = H

62 R = TBS
145 R = H

VCP	CONDITIONS		PRODUCT RATIO	YIELD
Exo or Endo	A	R = TBS	1.0 : 4.0	75%
Exo or Endo	B	R = H	1.0 : 2.0	86%
Exo / Endo	C	R = TBS	1.2 : 1.0	89%

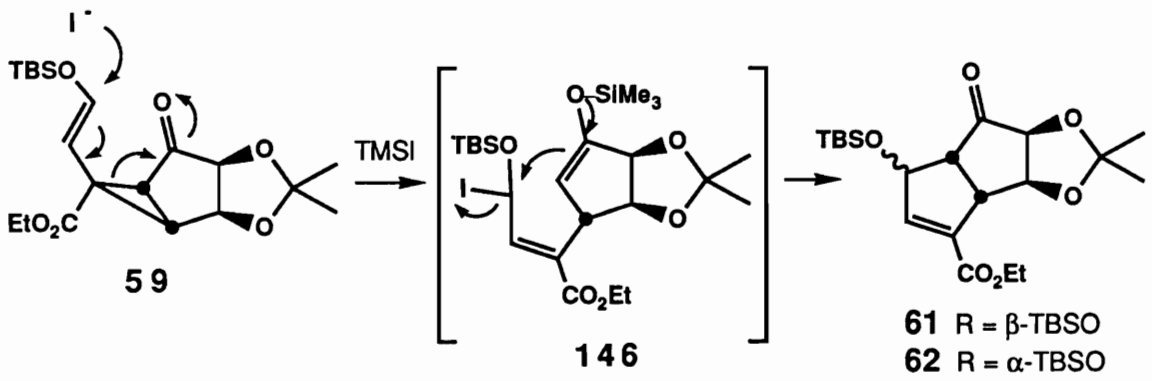
CONDITIONS

A flash vacuum pyrolysis, 550 °C, (10^{-4} - 10^{-6} mm Hg)
B 2.0 eq TBAF, THF -40 °C, 10 min
C TMSI / HMDS, 3 : 1, CH_2Cl_2 / pentane, -78°C to -20 °C

Scheme XXX

Cyclopropane - Cyclopentene Annulation

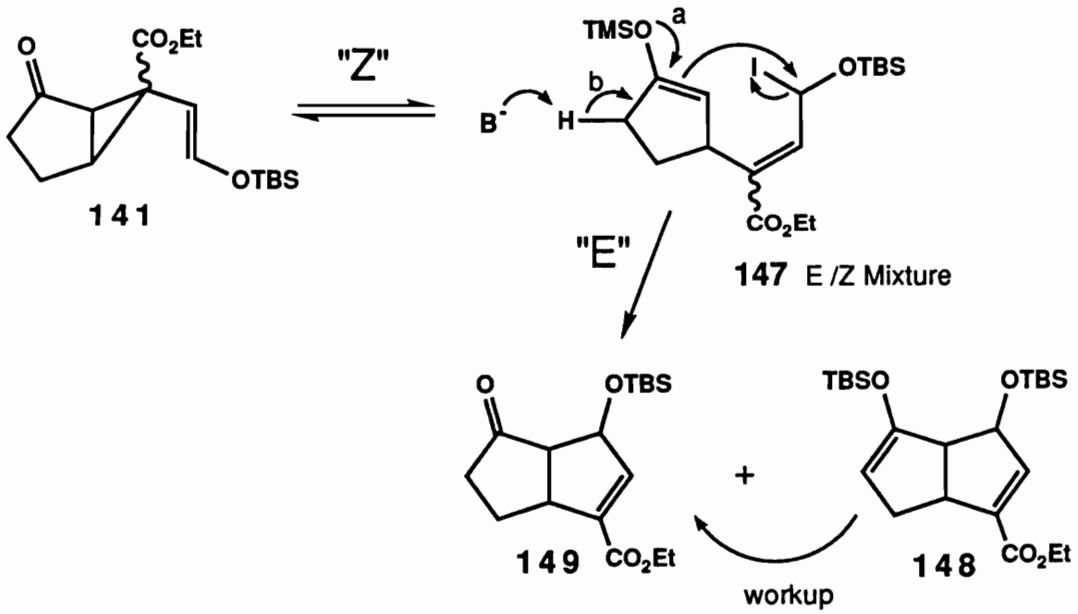
Another method of low temperature rearrangement is promoted by complexation of a hard acid (Me_3Si^+) with the carbonyl oxygen followed by attack of the vinyl group by a soft nucleophile (I^-)[121,122] resulting in cyclopropane ring opening (Scheme XXXI). The reactions of cyclopropyl ketones with TMSI are known to deliver iodo ketones via ring opening;[123,124] therefore, it seems reasonable to assume by analogy that a similar mechanism in this case could lead to ring opened intermediate **146** followed by iodide



Scheme XXXI

Mechanism of TMSI Ring Opening

displacement to deliver the diquinane diastereomers **61** and **62**. The C-6 stereochemistry was assigned on the basis of NOE ^{1}H NMR experiments and coupling constant evaluation.[125] Since the diastereomeric ratio of the two tricycles is nearly 1 : 1, synthetic planning must incorporate an inversion of the

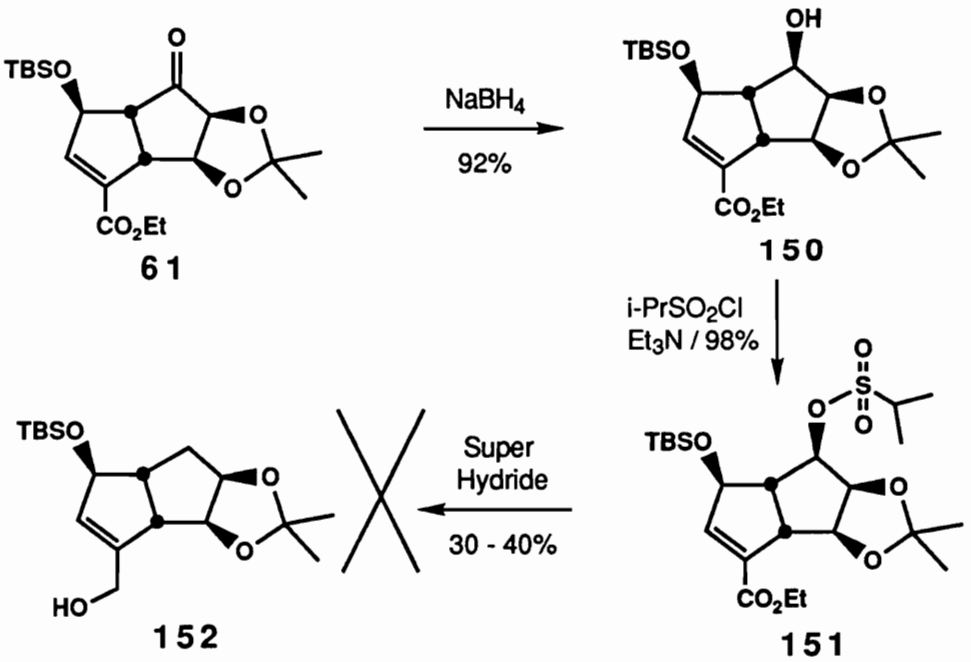


Scheme XXXII

Low Temperature ^{1}H NMR Study

C6 stereochemistry of **62** by a Mitsonobu inversion[126] so that all of the product mass can be converted to specionin. Such processes will be commented upon below.

A low temperature NMR study was conducted to elucidate the mechanism of the aforementioned TMSI promoted rearrangement using vinylcyclopropane **141** (Scheme XXXII).[127] ^{1}H, ^{13}C and ^{17}O NMR experiments were conducted at -40°C to -50°C. The presence of intermediate **147** was firmly established to be present as a mixture of E and Z isomers. The E isomer is properly arranged to allow ring closured either directly (a) or by aid of a base (b) to give **148** and **149** which goes exclusively to **149** upon workup. The Z isomer of intermediate **147** equilibrates with **141** until all of the material cycles to **149**.



Scheme XXXIII

Unsuccessful C4 Carbonyl Reduction

Completion of the [2+3] annulation studies left enough of tricycle **61** in hand to begin the final functional manipulation assault on (-)-specionin. The first order of business was to deoxygenate the C4 carbonyl functionality to a methylene. Since there are no reliable methods to effect such transformations in one step, **61** was first reduced with sodium borohydride which selectively delivered alcohol **150** (Scheme XXXIII) which was to be reduced further as its sulfonate ester. In view of a report by Hua[128] that hydride attack on hindered sulfonates can occur at sulfur to regenerate starting alcohols, a bulky isopropyl sulfonate ester **151** was prepared to preclude such an eventuality. Unfortunately, reduction of **151** with superhydride did not give the expected alcohol **152**, but rather an unknown product which was never identified; however, it was suggested that the unknown product may be a cyclic ether.

B. Discussion

I. Introduction:

Iridoid total synthesis has proven to be a challenging endeavor because of the high degree of oxygenation and the large number of closely spaced chiral centers of the targets in this class. Such difficulties were challenged in the previously mentioned syntheses of specionin. The first successful synthesis which was completed by Vandewalle[86,87] was a significant milestone as it provided synthetic evidence of the absolute configuration at the C1, C3, C6, and C8 centers. Unfortunately, serious problems of stereochemical control encountered during the synthesis resulted in a mixture of 8 specionin epimers with the natural epimer comprising only a small portion. Thus, although the actual proof of structure of specionin was provided by this synthesis, the overall effort was synthetically very unpractical.

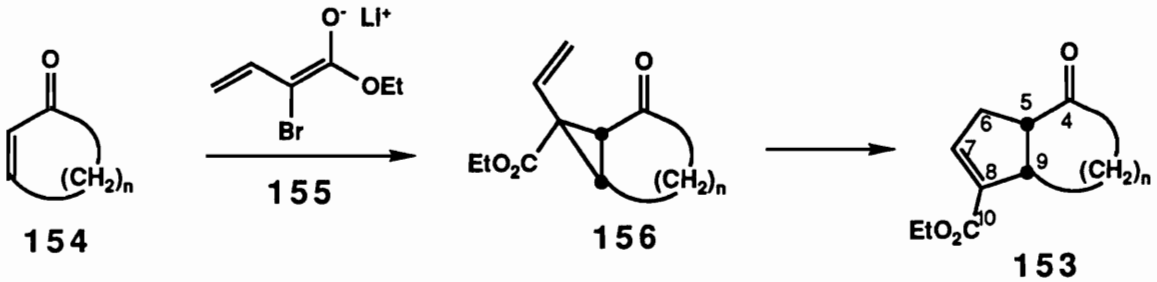
The synthesis completed by Leonard[104] in 1987 demonstrated superior synthetic design over the previous one. He achieved good regio- and stereocontrol in the construction of all stereocenters except for the C1 and C3 anomeric centers which were delivered in their natural ratio of 4:1, reflecting the thermodynamic equilibrium. Some of the weak points of his approach include the lack of incorporation of asymmetry and the lengthy (>20 steps) pursuit.

Curran's[110,83] approach to the title compound showed an overall improvement due to the implementation of planned asymmetric control. The choice of the starting acetal **115**[111] allowed for the synthesis of either enantiomer of specionin and the stereocontrol was good even for the C1 and

C3 anomeric centers; however, the overall result was still a lengthy process in excess of 20 steps.

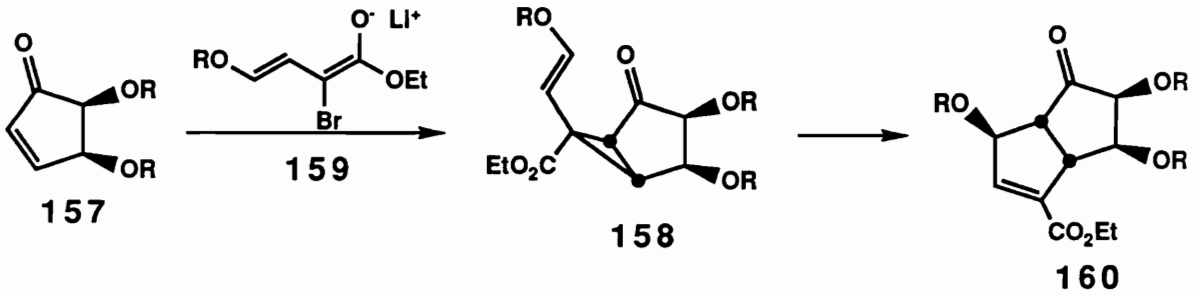
The most attractive synthesis to date was completed by Whitesell.[112] He employed a chiral ene process that proved capable of delivering gram quantities of starting material in either enantiomeric configuration. Regio- and stereocontrol in the construction of all chiral centers was very good and the brief (13 steps) outcome provided a formidable challenge for any future synthetic endeavors. In order to complete a total synthesis of specionin that would compare favorably with such elegant work, the following criteria would have to be met: the synthesis must be asymmetric, the skeleton must be constructed efficiently with a maximum number of chiral centers set in place, and the functional group manipulations must be kept to a minimum. Such were the guidelines at the time of conception of the current work.

The cyclopentanoid structure of specionin seemed to make the molecule well suited for the origonal [2 + 3] cyclopenteniod annulation approach which was developed in the Hudlicky group (Scheme XXXIV).[7] The first generation approach led to rapid construction of cyclopentanoid moieties **153**



Scheme XXXIV
General [2+3] Cyclopentene Annulation Scheme

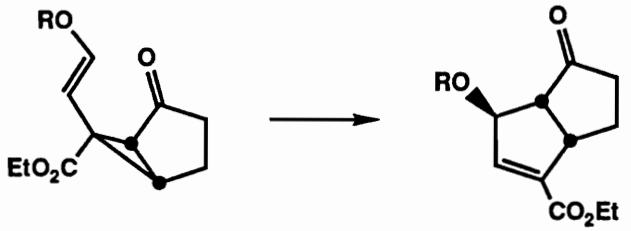
from α,β - unsaturated ketones **154** and 2 - bromocrotonate esters **155** via intermediate vinylcyclopropanes **156**. The methodology also provided a cyclopentene carboxylate substituent which proved to be easily converted to secondary functionalities found in many terpenoids. This functionality could conveniently serve to supply the required epoxy alcohol unit found in specionin. Adaptation of the methodology to specionin synthesis, however, required that three major issues be addressed: 1) incorporation of chirality into the sequence, 2) development of milder methods of vinylcyclopropane rearrangements, 3) additional oxygenation placement at C6 and therefore at the γ-position of dienolate **155**. It seemed that these requirements could ideally be met by using a protected form of diol **157** as the enone substrate. If the chiral information could be successfully transferred to the ring junction of cyclopropane **158**, then the hydroxylated cyclopentane ring would be set up for conversion to the required acetal moiety found in specionin by previously reported methods.[104] Of additional concern was the benzyl ester functionality at C6 which would require dienolate **159** to contain some form of oxygen functionality at the γ carbon. The protocol for the rearrangements of **158** → **160** for example has



Scheme XXXV

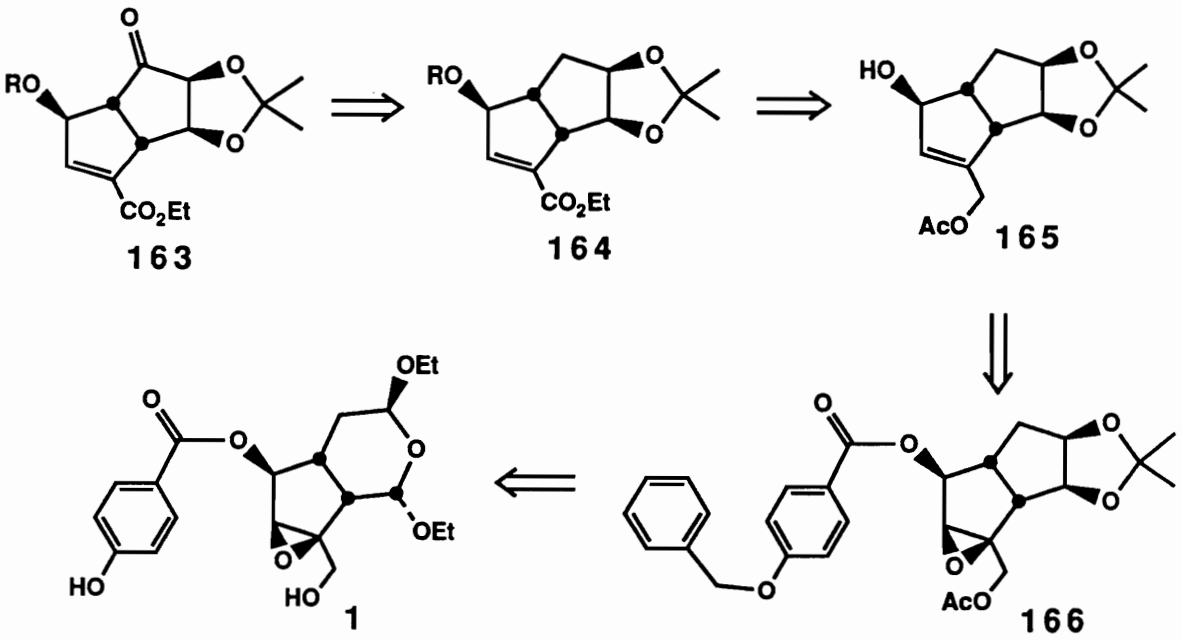
[2+3] Annulation Scheme for Specionin

been adequately solved during other studies in the Hudlicky group in which second and third generation schemes were provided for a mild rearrangement of systems such as **161** to oxycyclopentenes of type **162**.[5]



161 **162**

Thus, the requirements were in place to complete the design of specionin synthesis. Functional group manipulations would remain to be performed on tricycle **163** according to the retrosynthetic analysis shown in scheme XXXVI. The C4 carbon must first be deoxygenated by some reductive method to deliver



163 **164** **165** **1** **166**

Scheme XXXVI

Retrosynthetic Analysis of Specionin Synthesis

164 followed by selective 1,2 reduction and acetylation of the carboxylate group. Unmasking of the C6 hydroxyl group in alcohol **165** to the free hydroxyl group can then be used to stereoselectively direct epoxidation to give **166** after subsequent esterification. The remaining steps then involve only deprotection of the various hydroxyl groups and acetal formation to arrive at Specionin **1**.

With this plan then in hand the pursuit of synthesis was initiated. The foundation of the design appeared to rest on solid evidence. The effort known to lie ahead and posing potential problems was divided into three parts all of which required solution: 1) the synthesis of adequate amount of enone **56** (R = $C(CH_3)_2$) whose preparation in the Hudlicky group proved irreproducible, 2) rapid assembly of the specionin nucleus and reduction of C=O to furnish **164**, and 3) efficient final transformation. The synthesis will therefore be divided into three sections with the final section also comprising the second and vastly improved approach.

The evaluation of the present goals in terms of competition or comparison with Whitesell's synthesis will be addressed in the conclusion.

164 followed by selective 1,2 reduction and acetylation of the carboxylate group. Unmasking of the C6 hydroxyl group in alcohol **165** to the free hydroxyl group can then be used to stereoselectively direct epoxidation to give **166** after subsequent esterification. The remaining steps then involve only deprotection of the various hydroxyl groups and acetal formation to arrive at Specionin **1**.

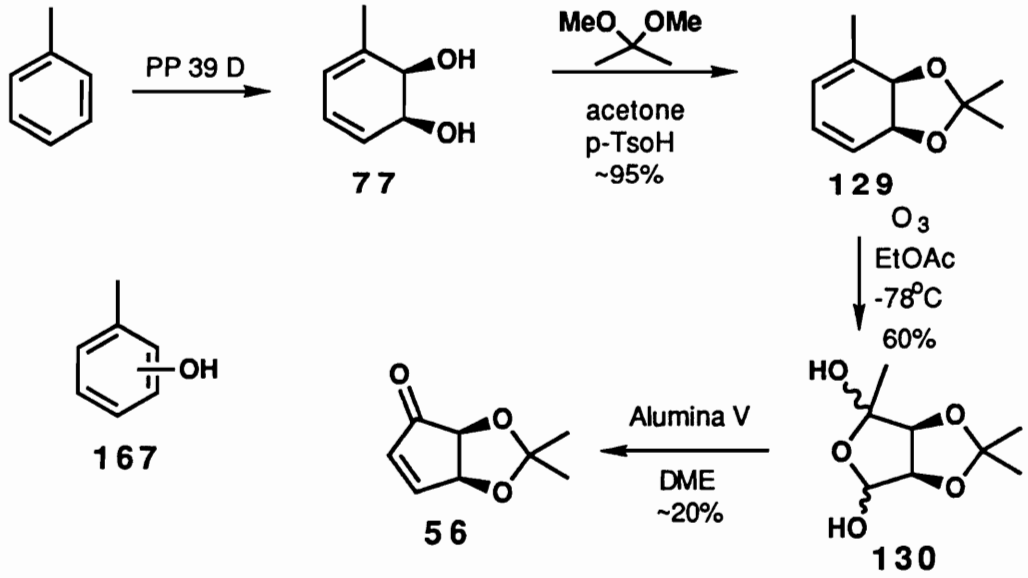
With this plan then in hand the pursuit of synthesis was initiated. The foundation of the design appeared to rest on solid evidence. The effort known to lie ahead and posing potential problems was divided into three parts all of which required solution: 1) the synthesis of adequate amount of enone **56** (R = $C(CH_3)_2$) whose preparation in the Hudlicky group proved irreproducible, 2) rapid assembly of the specionin nucleus and reduction of C=O to furnish **164**, and 3) efficient final transformation. The synthesis will therefore be divided into three sections with the final section also comprising the second and vastly improved approach.

The evaluation of the present goals in terms of competition or comparison with Whitesell's synthesis will be addressed in the conclusion.

B. II. Asymmetric Synthesis of Enone 56

The total synthesis of (-)-Specionin depends on an efficient and high yielding synthesis of a homochiral starting enone of type **56**. With the diol functionality protected as an acetonide, one face is sufficiently blocked to force nucleophilic attack exclusively from the least hindered face. The seemingly simple structure of this compound coupled with a respectable number of reported synthetic approaches[65,129-137] portended for a short research endeavor to produce an adequate supply to complete the remaining synthetic investigations.

The synthetic method that was most tested and readily available in the Hudlicky group was a three step route starting from toluene that involved biocatalysis as a method of chiral induction (Scheme XXXVII).[65] The method

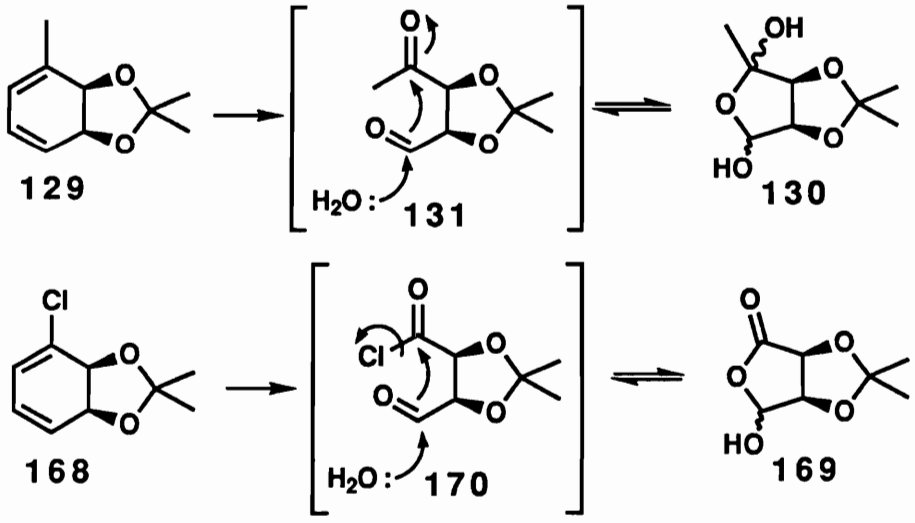


Scheme XXXVII

Synthesis of Enone **56** From Toluene

involved microbial oxidation of toluene to *cis* diol **77** with the 39 D strain of *Pseudomonas putida.* The fermentation process was at an early stage of development and could deliver about 2.2g of toluene diol **77** from three 0.5 liter batches of fermentation broth which limited the rate at which further research could progress. The diol could be easily protected with 2,2-dimethoxypropane to form acetonide **129** in 85% yield. The major impurity was the cresol **167** resulting from acid catalyzed dehydration of diol **77** during protection. This compound was inseparable from the desired product and had to be removed at a later stage.

Ozonolysis of **129** proceeded smoothly albeit in 60% yield which was slightly lower than that reported. Little work has been done on ozonolysis of conjugated dienes,[138,139] so it was difficult to understand what measures might be appropriate to optimize this transformation. The mechanism is poorly



Scheme XXXV

General Ozonolysis Mechanism

understood, but it is certain that addition of water is required as in **131** in order to arrive at the lactol **130** which was the major product (Scheme XXXVIII). The ozonolysis of protected chlorodiol **168** delivered a hydroxy lactone **169** which seems to have arrived via a similar mechanism via intermediate **170**.[140] A question whether the ozonide is completely reduced before rearrangement occurs still remains especially in view of the fact that it is highly unlikely that the closed ring system could accommodate two adjacent ozonide functionalities simultaneously unless a step-wise mechanism is considered.[141] The reaction delivers an optimum yield when ethyl acetate is used as a solvent and $NaHCO_3$ is added as an acid scavenger.

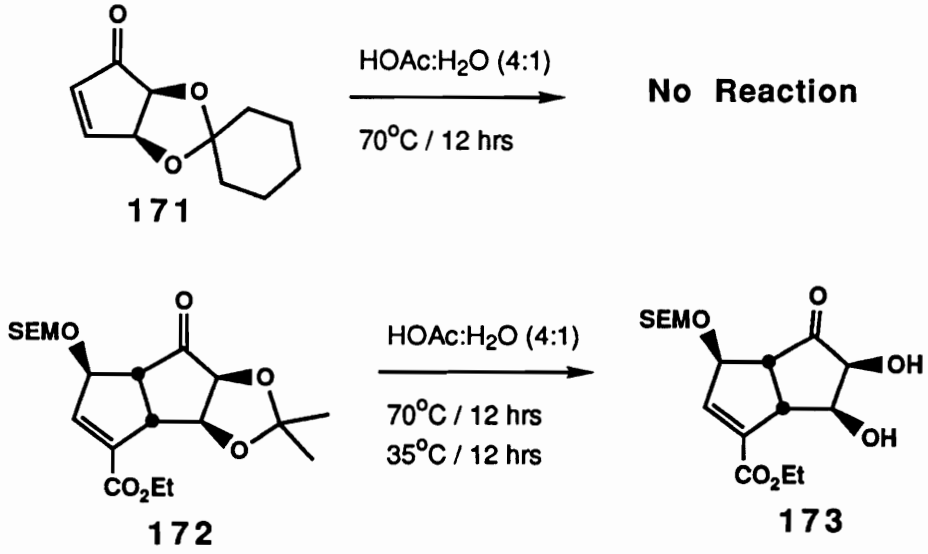
Dehydration and rearrangement of acetal **130** to arrive at the desired enone **56** resulted in a frustrating investigation that produced some interesting results. Reported optimized conditions gave a 70% yield for the transformation using alumina V^{A}[65,142] as a dehydrating agent in refluxing DME. Repetition of this work yielded only ~10% of the desired enone **56** in pure form. An unusually low 60% crude mass balance suggested that much of the product was being irreversibly adsorbed onto the alumina. Such frustrating results led to an exhaustive study of the catalyst preparation to ascertain if higher yields of **56** could be obtained by adjusting the activity of the alumina catalyst.[143] Eight samples of alumina were prepared which ranged in activity from 0% to 40% water and were used as catalyst for the dehydration of **130**. The yields for all reactions seemed to be around 10% for the catalysts in the 5% to 20% activity range and fell to minima with high and low water contents. In view of the fruitless investigation of catalyst activity, alternate solvents were investigated to

study the effect of reaction temperature. DME was compared to ether, methoxy ethoxyethane, and diethoxyethane and found that reaction in ether did not promote any transformation and conversion in the higher boiling solvents gave lower yields due to decomposition of materials.

Ultimately, a more efficient and higher yielding catalyst was prepared as a one to one mixture of activated alumina and $MgSO_4$[144]. The more active catalyst was used more sparingly and thus a smaller amount of material was irreversibly adsorbed onto the catalyst and 70% of the crude material could be recovered which appeared to be fairly clean enone **56** by NMR. Problems were again encountered with purification and the yield of pure material was ~20% which extrapolates to a 10% overall yield of **56** from diol **77**. The improved yield, coupled with a higher availability of diol **77** from the new 15 liter fermenter, provided a reasonable source of starting material.

As the preparation from toluene was being developed, a source of enone **56** was required which could support further research toward the total synthesis of (-)-specionin. A method was chosen from the literature[132] due to its high 42% overall yield and seemingly simple practical transformations. L-mannose was used as an enantiomerically pure starting material. The preparation was followed exactly as written; however, in our hands we obtained a 4% overall yield of pure cyclohexylidine protected enone **171**. To further complicate the problem, none of a myriad of reported acid catalyzed conditions successfully removed the cyclohexylidine protecting group.[145]

This was confirmed with a model study that was performed to ascertain which protecting group would be the easiest to remove. The cyclohexylidine

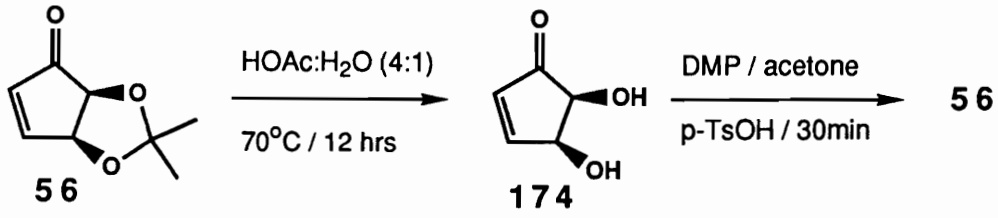


Scheme XIL

Diol Deprotection Studies

protecting group was compared to the acetonide group using the reactions shown in scheme XIL. Cyclopentene **171** and tricycle **172** were heated overnight at 70°C in a 4:1 mixture of acetic acid and water. TLC and ^{1}H NMR analysis clearly indicated that the cyclohexylidine protected diol **171** remained unchanged while the acetonide protected diol experienced a near quantitative dealkylation to diol **173**. It was later found that the acetonide group could also be removed using less thermally stressful conditions which would prove useful in later steps of the synthesis where more complex intermediates may have to be deprotected. Thus it became overwhelmingly obvious that acetonide would be the required protecting group.

As a precaution against unexpected future complications, a sample of the desired enone **56** was deprotected to diol **174** using the conditions which were developed in the above model study and then reprotected using standard



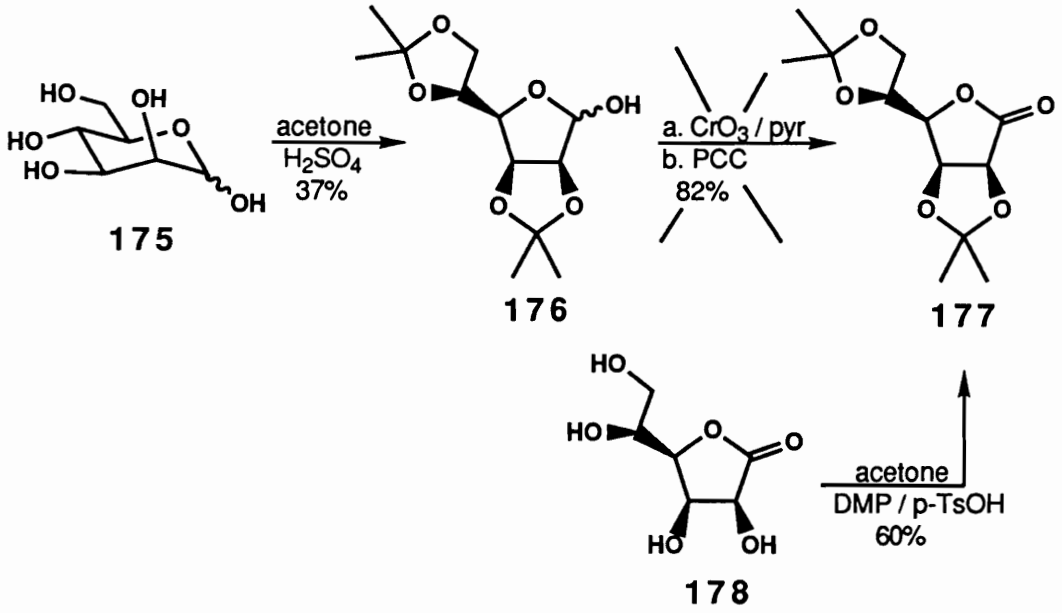
Scheme XL

Chiral Deprotection / Reprotection Study

conditions for acetonide formation (Scheme XL). The optical rotation of the starting enone **56** (α_D^{25} = +63.4°) was then compared to the product from the reprotection (α_D^{25} = +61.2°). The similar rotation values for each compound indicated that this and similar diols could be safely deprotected without fear of racemization.

It was necessary at this point to modify Borchardt's synthesis of the required enone **171** to accommodate an acetonide rather than cyclohexylidine protecting group. It was reasoned that such a goal could be realized by simply substituting the cyclohexylidine protecting group for an acetonide throughout the synthesis beginning with the protection of D-mannose **175** (Scheme XLI). The acid catalyzed conversion of D-mannose **175** to its diacetonide **176** in 88% yield was reported by Ohle and Berend[146] and later by Guthrie and Honeyman.[147] Repetition of this work resulted in a 37% yield of a compound which had a melting point of 124°C which seemed reasonable compared to the reported 120°C.[146]

Oxidation of diacetonide **176** with Collin's reagent in accord with Borchardt's protocol consistently gave impure mixtures of products which did

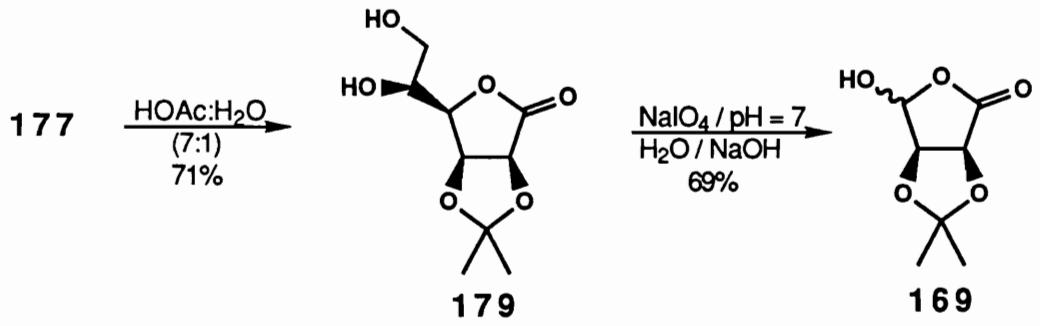


Scheme XLI

Synthesis of L-Gulonolactone Diacetonide

not recrystallize cleanly and could not be chromatographed practically on the required scale. The problem was alleviated by performing the oxidation with pyridinium chloroformate which resulted in an 82% yield of a pure compound which was tentatively assigned the structure represented by **177**. At this time experiments were initiated to selectively deprotect the side-chain acetonide when a preparation of lactone **177** from L-gulonic lactone **178** appeared in the literature[148] which reported the melting point of **177** to be 151°-153°C as opposed to 123°C which was observed. The work of Fleet was then repeated and found to give a 60% yield of **177** in a very pure state, so the route from D-Mannose **175** was abandoned without further investigation in favor of the later route.

Attention at this point was again turned to selective deprotection of the

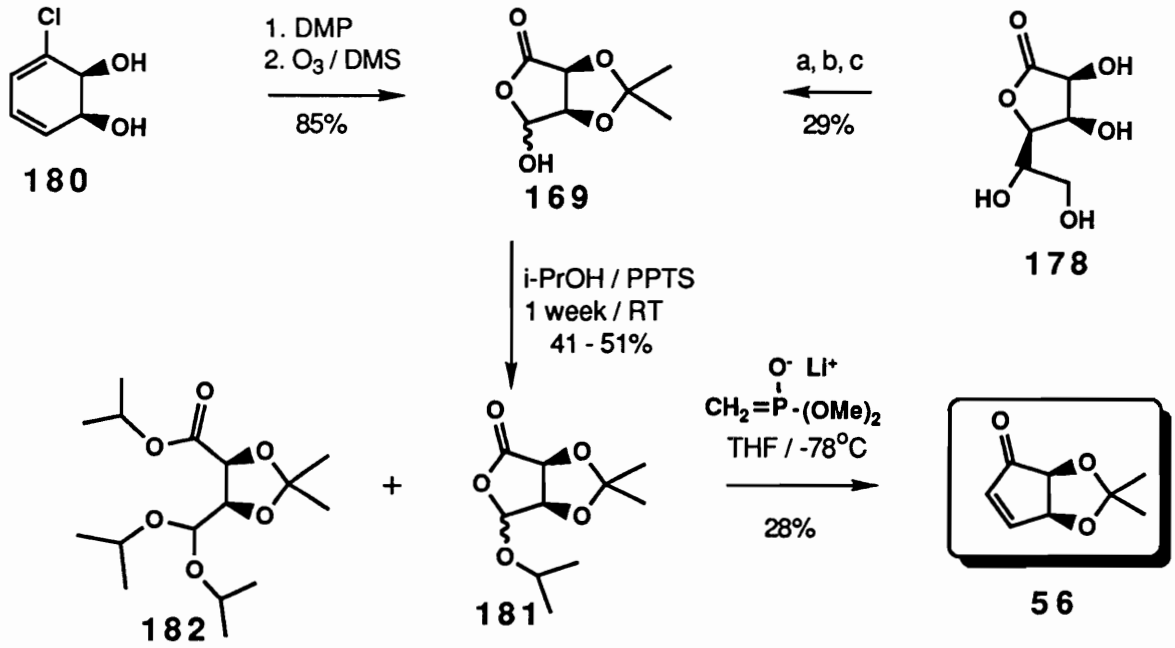


Scheme XLII

Conversion of Diacetonide **177** to Hydroxylactone **169**

side-chain acetonide of **177**. The method reported by Fleet et. al. was smoothly repeated and give a respectable 71% yield of the monoprotected lactone **179** (Scheme XLII). A number of other methods for selective deprotection were tried which included: 1. Dowex 50W H^+ / EtOH / H_2O,[132] 2. 1.3eq HCl / MeOH / H_2O,[149,150] and 3. H_2SO_4 / MeOH / H_2O.[151] None of the three conditions were selective and resulted in products which did not show evidence of the presence of an acetonide group in the ^1H NMR.

With the emergence of a reproducible route to the hydroxylactone intermediate **169** from a sugar precursor **178**, it became apparent that **169** could be intercepted by a route that was published by the Hudlicky group. The intermediate **169** was prepared and used in the total syntheses of (+) and (-) trihydroxyheliotridane,[57] (+) and (-) erythrose,[78] and ribonolactone.[79] The source of chirality in these papers was microbial oxidation of chlorobenzene to give enantiomerically pure diol **180** which could subsequently be protected with DMP and cleaved with ozone to deliver hydroxy lactone **169** in two steps from diol **180** in an 85% overall yield (Scheme XLIII). This compares favorably with the route from L-gulonic lactone **178** both in yield and hours of labor



a. acetone, 2,2-dimethoxypropane, p-TsOH b. HOAc: H_2O c. $NaIO_4$

Scheme XLIII

Synthesis of Enone **56** From Chlorobenze Diol **180**

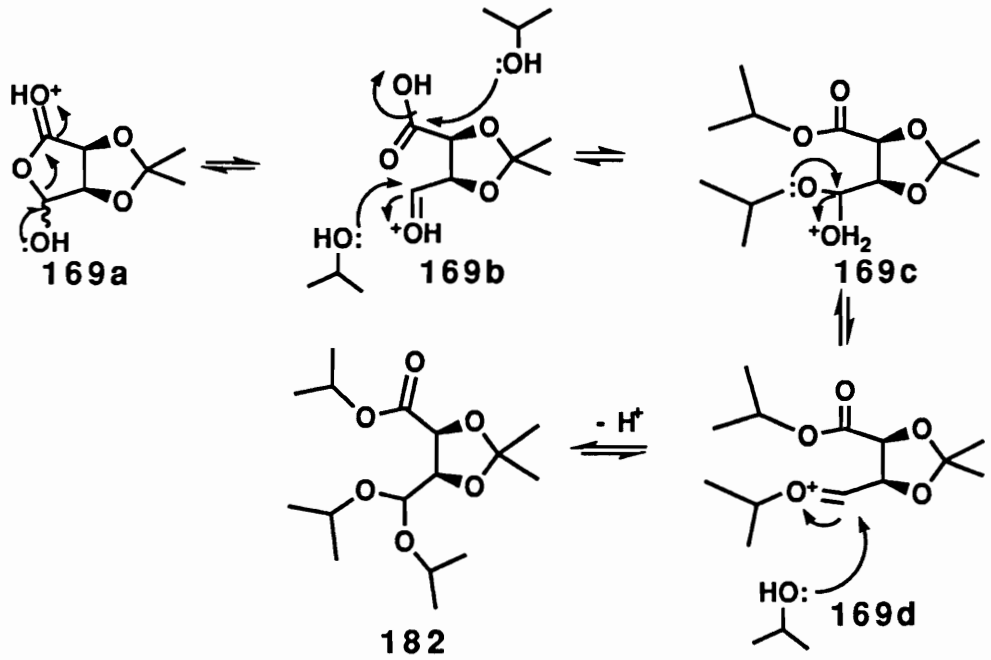
required.

Having arrived at an excellent preparation of hydroxy lactone **169**, it remained only to optimize the reaction conditions in the remaining two steps to achieve a plausible synthesis of the starting enone **56**. The protection of the hydroxy group proved to be problematic since acidic conditions at elevated temperatures removed the acetonide group and led to further decomposition of the starting material resulting in very low yields of **181**. This prompted a study of many reaction conditions for the acid-catalyzed protection of **169**, (Table 3) which culminated in two sets of acceptable methods. In most cases, a major impurity present in the reaction mixture was isopropyl ester **182** which resulted

Table 3 Formation of Hemiacetal **181**

CONDITIONS	% YIELD **181**	% YIELD **182**
CH_3CO_2H / i-PrOH / reflux / 1.5hr	17	8
p-TsOH / i-PrOH / reflux / 1.5hr	23	15
PPTS / i-PrOH / reflux / 1.5hr	21	12
PhH / p-TsOH / i-PrOH / reflux /1.5hr / mol.sieves	19	11
PPTS / i-PrOH / RT / 1 week	41 - 51	9
PPTS / iPrOH / 0°C / 1 month	0	0
$HClO_4$ / iPrOH:acetone (1:3) / 4°C / 24 hr	36	>5

from acid catalyzed opening of the lactone ring **169a** followed by esterification of the acid functionality in **169b** and acetal formation of the aldehyde (Scheme XLIV). Reaction temperature was a critical parameter and is clearly seen in the temperature profile for treatment of **169** with pyridinium paratoluene sulfonate (PPTS) in isopropanol. At reflux, a large amount of acetonide deprotection is



Scheme XLIV

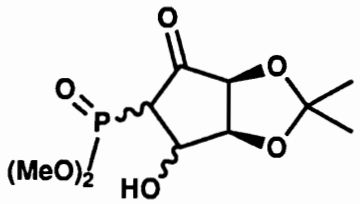
Mechanism of Formation of Ester **182**

accompanied by decomposition. Under these conditions a higher degree of ester formation is observed with less conversion to **181** via intramolecular acetal closure. The undesired intermolecular acetal formation becomes competitive as evidenced by the high ratio of **182** to **181** and the low overall yield. The situation improves at room temperature as evidenced by the improved yield and lower ratio of **182** to **181**. Unfortunately, the rate of the reaction is slowed to the extent that the reaction must stand a week at room temperature in order to reach completion. The extreme of this situation occurs at 0°C where there seems to be too little energy for initial ring opening, and thus, no reaction occurs.

The above observations were supported by adaptation of a literature precedent[134,152] where $HClO_4$ was used as a stronger acid to overcome the sluggish ring opening at cold temperatures and allow the reaction to go to completion in 24 hours at 0°C. In this case the ratio of **182** to **181** was extremely high in keeping with the trend of increasing competition of intramolecular acetal formation at lower temperatures. Furthermore a successful and improved transformation of **169** to **181** was developed which proceeded overnight under mild conditions with minimum formation of acetal **182**.

Following the development of an acceptable route to lactone **181**, it remained only to repeat the final Wittig transformation to the desired enone **56** which seemed simple in view of two reports of such reaction proceeding in 80% yield[132,143]. Unfortunately, this reported yield translated to a maximum of 28% in practical application! The situation worsened as the reaction was scaled up

as the yield decreased with increasing amounts of compound to ~10% in the 1.5g range. Once more an exhaustive study was undertaken to optimize a literature procedure which included a temperature profile, a study of counter ions, and a study of other Wittig conditions including Dauben's thermodynamic controlled conditions.[153,154] No improvement was observed. The only lead to an answer to the problem was an unknown compound which was isolated in ~50% yield from the aqueous layer after workup which is thought to be phosphonate **183**, but it has not been adequately purified to allow unambiguous identification. Repeated attempts to force the Wittig reaction to go to completion under basic conditions have been as yet fruitless. The overall maximum yield of enone from this preparation is 12% from chlorobenzene diol **180**.

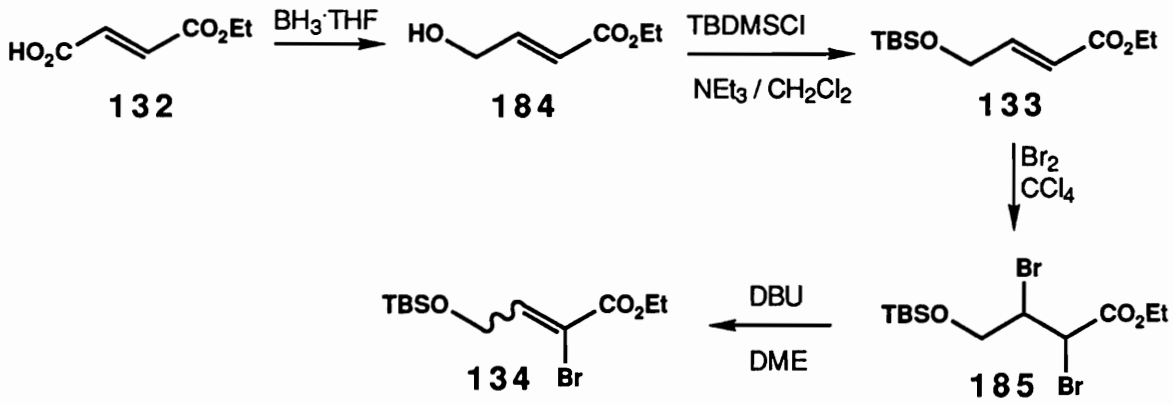


183

At the time of this writing, it has become routine preparative practice to convert 10g of diol **180** to 3-4g of protected hydroxy lactone **181** with $HClO_4$ as acid catalyst for the protection step over 4 days at a time expense of about 10 man hours. After Wittig reaction, this leads to 0.43-0.37g of enone **56** at an overall yield of 5.2-4.5%. The yield can be increased to as high as 12% if the scale of the Wittig is lowered. But this becomes prohibitive if large amounts of enone **56** are required. The relative small time investment for the process has allowed for the production of workable amounts of enone **56**.

B. III. First Generation Total Synthesis of (-)-Specionin

As with all total synthetic efforts, it was foreseen that successful completion of specionin would demand a constant supply of reagents for the [2+3] annulation sequence. Having investigated the preparation of chiral enone **56**, it remained to prepare an adequate quantity of the required γ-oxybromocrotonate **134**. The sequence developed by Alison Fleming[23,115] was repeated on a preparative scale from fumaric acid **132** and was completed in 10% overall yield. The observed E:Z ratio for **134** was 80:20 as determined

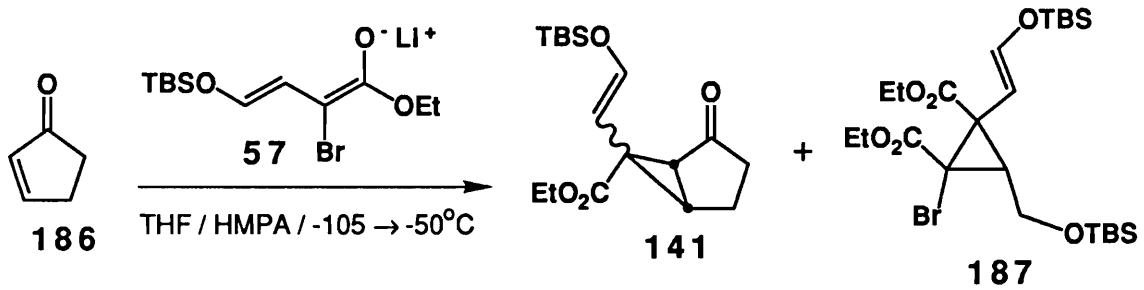


Scheme XLV
Synthesis of Ethyl 4-t-Bulyldimethylsilyloxy2-bromocrotonate

by ^{1}H NMR analysis. The oxycrotonate **184** was carried forward without purification and the t-butyl-dimethylsilyl derivative **133** was merely filtered through silica gel so accurate yields for these steps are unavailable. Likewise, dibromide **185** was subjected to elimination conditions in a crude state so only an overall yield for the entire process can be evaluated. It was carried out on a scale large enough to deliver 30g of **134** which would have been enough

material to finish the project; unfortunately however, it was discovered that the material decomposed over a three month period at -4°C. A second batch was prepared in 15% overall yield and was stored at -78°C for 18 months without sign of decomposition.

Repetition of the [2+3] annulation sequence was not a trivial exercise. The cyclopropanation reaction must be carried out under meticulously controlled conditions which require the development of specific anhydrous and extreme cold techniques. The scarce supply of enone **56** precluded the opportunity for repeated trial reactions to develop such techniques, so a closely related model reaction was run with cyclopentenone **186** on a moderate (6.2 mmol) and small (1.0 mmol) scale, to learn the practical requirements of the reaction. Respective yields of 22.8% and 26.3% were obtained for vinylcyclopropane **141**. The *endo* : *exo* ratio was 2 : 1 with respect to the vinyl group as determined in both cases by ^{1}H NMR intigration of the olefin protons in the crude spectra and by isolated yields. As previously reported[23,5] dimerization of the dienolate **57**, derived from bromocrotonate **134**, proved to



186 **141** **187**

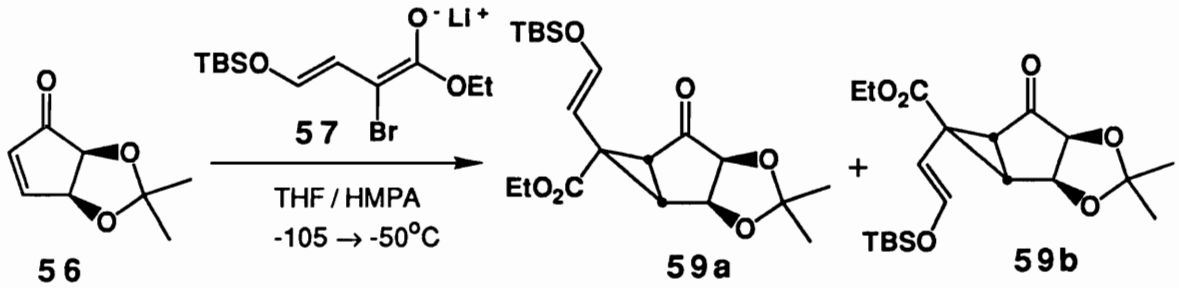
Dimer:Endo:Exo = 1:1:2

Scheme XLVI

Cyclopropanation of Cyclopentenone **186**

be a problem even at -105°C and although the situation could not be improved, it could be compensated for by using 1.3 equivalents of bromocrotonate **134** per equivalent of enone **186**. Surprisingly, TLC of the crude reaction mixture revealed only the two product spots, the dimer spot, and and an origin spot. ^1H NMR of the origin spot revealed polymeric material. The low yield must therefore be attributed to polymerization during the reaction.

Experience gained from the cyclopropanation of **186** was applied to a similar conversion with enone **56**. Again the problem of low yields of the expected vinylcyclopropane **141** was encountered. Although dimerization of dienolate **57** was encountered, it was not sufficient to completely account for the loss of material. Furthermore, the fact that none of the starting enone **186** was recovered tends to suggest that some form of polymerization of the reactants was taking place. The reaction consistently furnished yields in the range of 24-32%. Ratios of *endo* : *exo* isomers were determined from the integration of crude spectra.

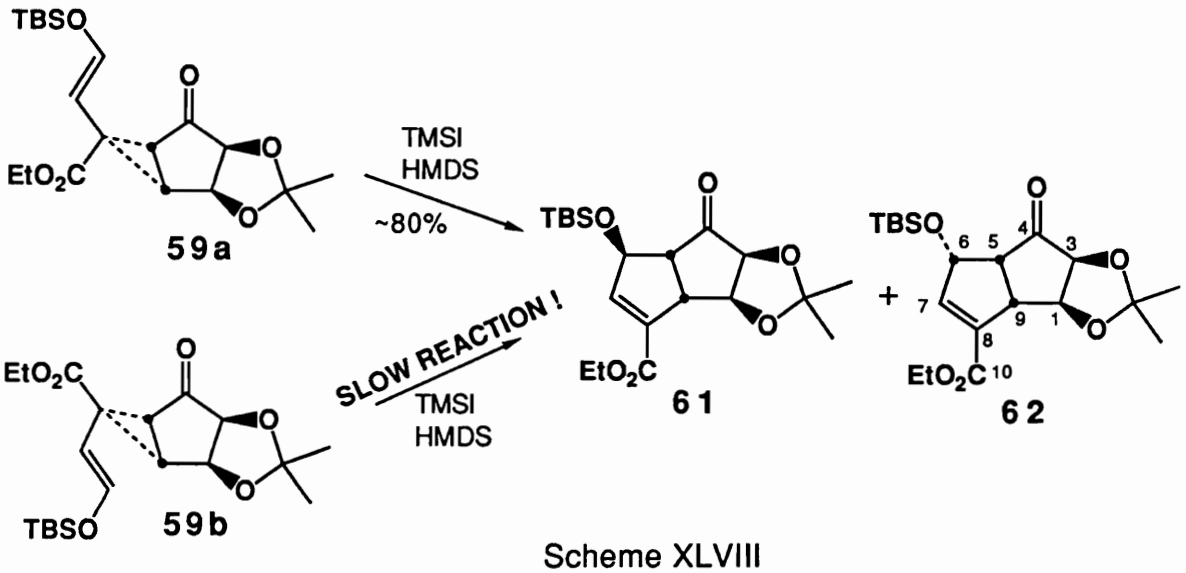


exo:endo = 85:15

Scheme XLVII

Cyclopropanation of Cyclopentenone **56**

Cyclopentene rearrangement was approached with the expectation that the resulting cyclopentene would be required to have the C6 hydroxy protecting group intact. The method of choice therefore seemed to be the TMSI promoted rearrangement which has been shown to occur at -78°C for a number of vinylcyclopropanes.[5] However, when the established reaction conditions were applied to a mixture of vinylcyclopropanes **59a** and **59b**, only the *exo* isomer **59a** reacted (Scheme XLVIII). The yield for this isomer was quite good (~80%) and gave a 1:1 mixture of cyclopentenes **61** and **62**.



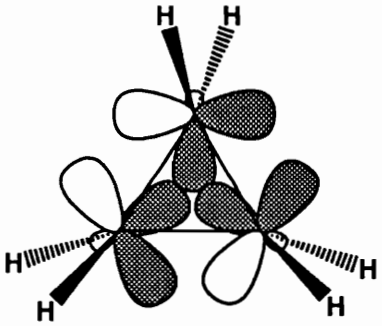
Scheme XLVIII

TMSI Promoted Vinylcyclopropane Rearrangement

Initial C6 stereochemistry was assigned on the basis of coupling constants. Tricycle **62** had a distinct 9.0 Hz coupling constant between the C5 and C6 hydrogens while tricycle **61** showed no coupling between the two atoms (For the purpose of discussion, the corresponding numbering for specionin, as shown on p.28, is used for diquinane **62**. In the experimental

section the correct IUPAC numbering system is used). Molecular models clearly indicate that the two hydrogens in question are nearly perpendicular in **62** and nearly orthogonal in **61**. Arguments based on the Karplus equation strongly suggest that the structural assignment in scheme XLVIII is valid.

The *endo* vinylcyclopropane isomer **59b** proved to rearrange at a much slower rate at -78°C. A sample was then subjected to trimethylsilyl iodide and hexamethyldisilizane at -78°C and the reaction allowed to warm slowly. Disappearance of starting material ocurred close to room temperature to give a complex mixture of products by TLC analysis which appeared to contain ~10% starting material and ~15% of a mixture of cyclopentenes **61** and **62**. The striking difference in reactivity between the exo and endo vinylcyclopropanes can be rationalized by considering a stereoelectronic evaluation of the orbital system in terms of the Walsh (Sugden) model[155] of cyclopropane[156] (Figure 3).



(HOMO)

Figure 3 Walsh (Sugden) model for cyclopropane

Here, a cyclopropyl ring is envisioned as being built from three sp^2-hybridized methylenes with three sp^2 hybrid orbitals oriented radially toward the center of the ring and three p-orbitals oriented coplanar to the ring.[157] Assuming this model to be valid, the π-orbitals of a vicinal olefin must be in a perpendicular

orientation to the plane of a cyclopropane in order for conjugation to occur.

In the case of *endo* vinylcyclopropane **59b**, the vinyl group must assume either conformation **C** or **D** (Figure 4) in order for conjugation to occur with the cyclopropyl π-orbitals and this is necessary to polarize the double bond and make it kinetically active toward nucleophillic attack. Unfortunately, serious steric interaction occurs between the vinyl H_3 and the ring junction H_1 and H_2 in conformation **C**. The situation is even worse with regard to H_4 in conformation

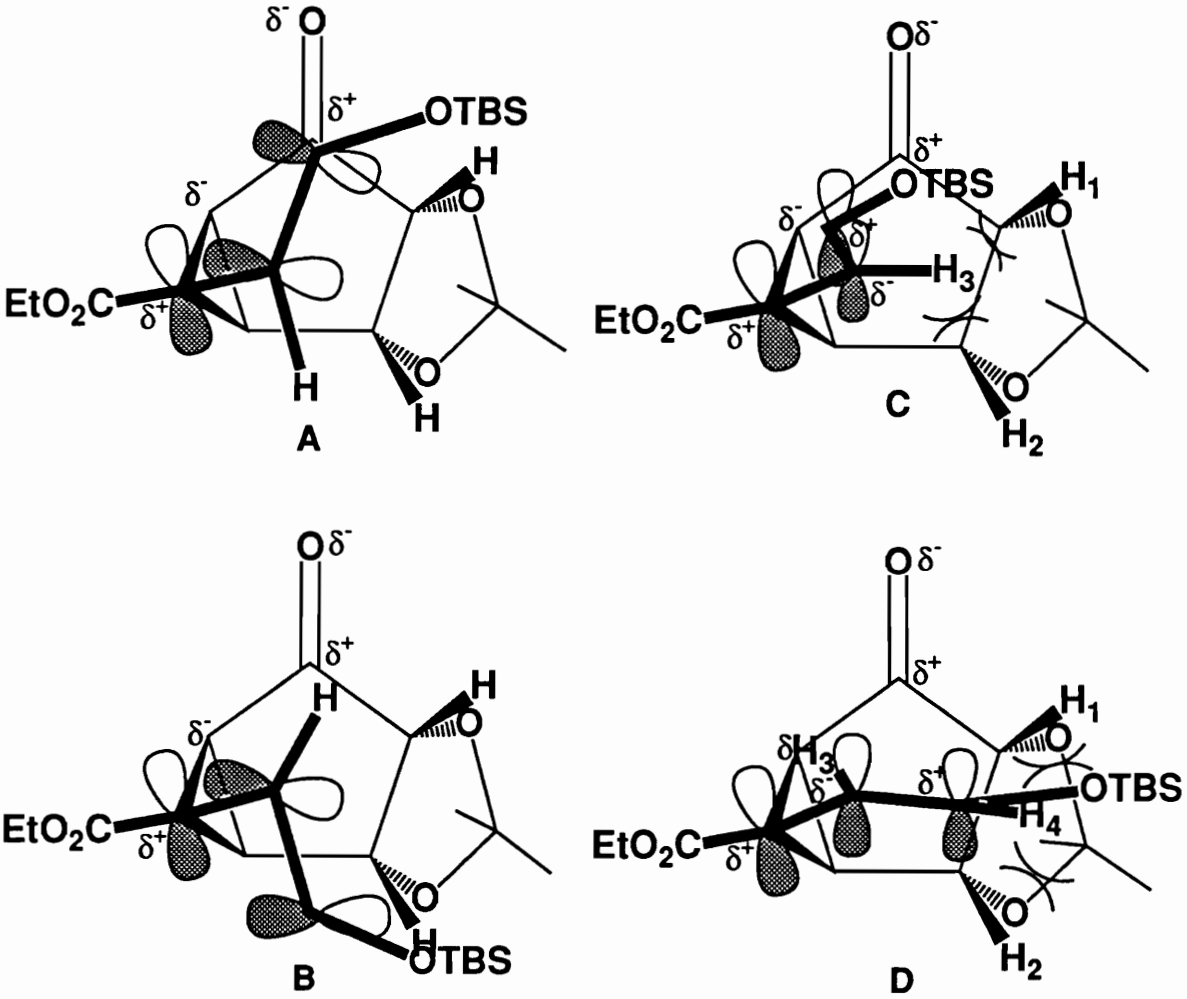
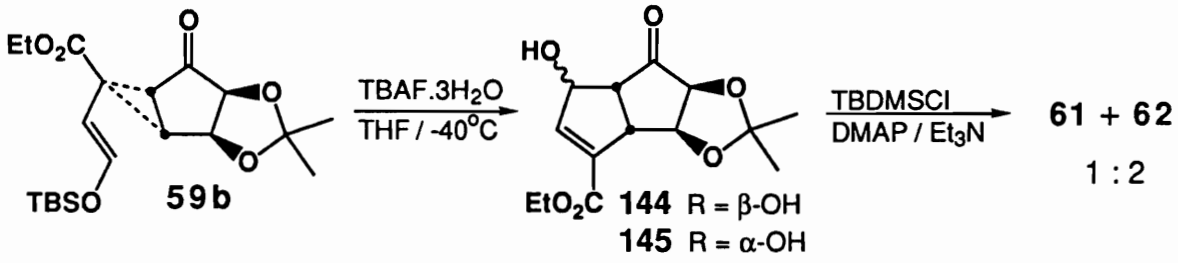


Figure 4 Four Possible Conformations of *Endo* Cyclopropane **56b**

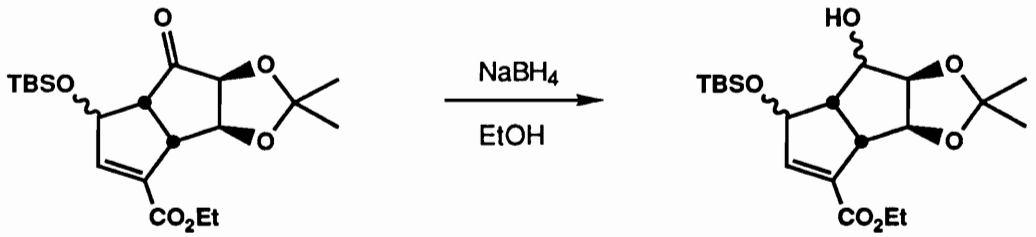
D. The molecule is therefore forced to adopt either conformation **A** or **B** and place the olefinic π-orbitals in an orthogonal configuration with respect to the cyclopropane π-orbitals. The π character of the olefin is thus insulated from the polar integrity of the carbonyl from which it should derive kinetic, electrophilic reactivity. A similar effect was encountered by Tanko[158] who found that an unprecedented hydrogen atom abstraction ocurred instead of an expected cyclopropyl ring opening when 9-cyclopropylanthracene was exposed atomic bromine. He explained the phenomenon by pointing out that steric factors force the cyclopropyl group to adopt a perpendicular geometry thus freezing the π-orbitals orthogonal to the anthracene π-system and insulating them from orbital communication.



Scheme IL
TBAF Salvage Operation

In order to salvage the integrity of the TMSI promoted cyclization, *endo* vinylcyclopropane **59b** was converted to cyclopentene **144** and **145** with tetrabutylammonium fluoride·$3H_2O$ (complete details of TBAF promoted rearrangement are contained in section **B.IV.**) and subsequently reprotected with t-butyl-dimethylsilyl chloride for a 68% overall yield (Scheme IL).

Upon successful completion of the [2 + 3] cyclization, attention was



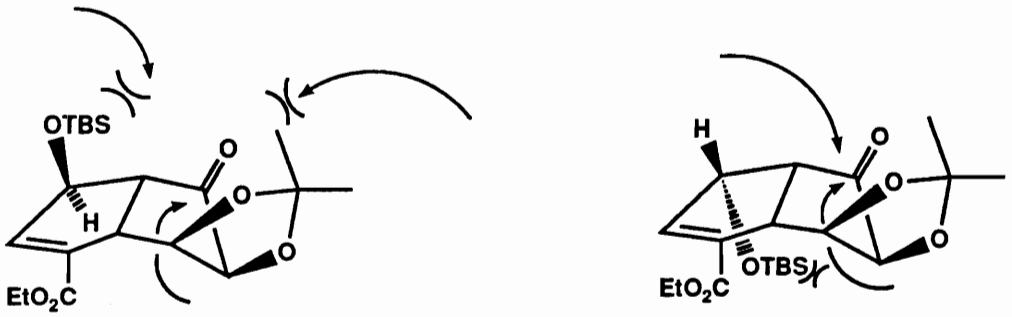
61 R = β-TBSO
62 R = α-TBSO

188 R = α-TBSO, α-OH
189 R = α-TBSO, β-OH
150 R = β-TBSO, β-OH

Scheme L

Reduction of Tricycles **61** and **62**

turned to deoxygenation of the ketone functionality. Since there are yet no mild one pot methods to directly reduce a hindered ketone to an alkane, the mixture of tricycles, **61** and **62**, were first reduced with $NaBH_4$ to give a 1 : 1 : 2 mixture of alcohols **188**, **189** and **150** respectively (Scheme L). The assignment of the stereochemistry of the hydroxyl functionality for **188** and **189** was unknown until synthetic evidence discussed below was obtained. It was not surprising that ketone **61** reduced 100% from the concave α-face since the β-face is also concave with added steric hindrance from the acetonide methyl group and the α-OTBS group as seen in figure 5. Ketone **62**, on the other hand, has steric

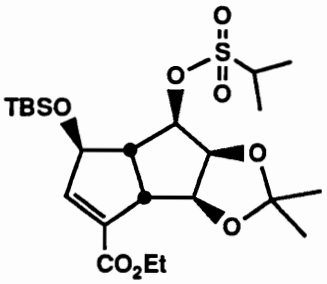


61 **62**

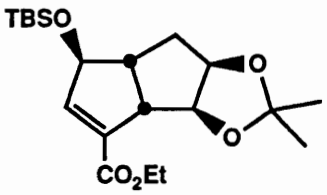
Figure 5 Hydride Approach Vectors

hindrance from the OTBS group in the α-face which balances steric effects on either face and provides an equal distribution of hydride delivery.

The hindered position of the hydroxyl groups in alcohols **188**, **189** and **150** lead to some problems in their removal. Initial studies were carried out with alcohol **150** and directed toward sulfonation of the alcohol with isopropyl sulfonyl chloride instead of methane sulfonyl chloride since Hua found that with hindered sulfonates, hydride attack can occur at sulfur to regenerate the starting

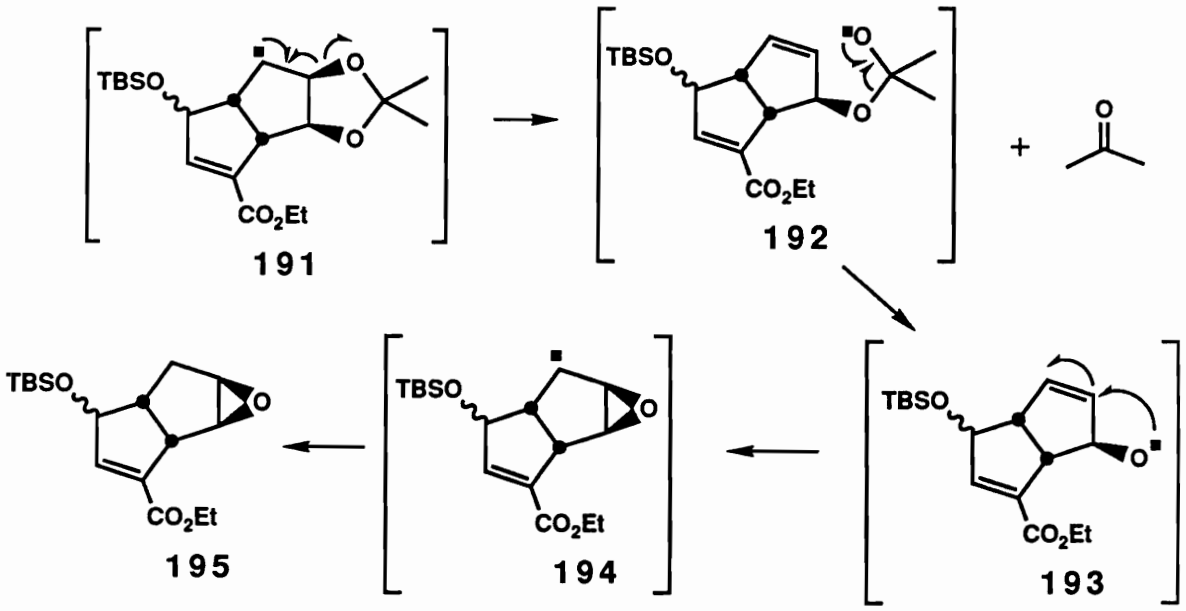


151



190

alcohol.[128] Despite this precaution, superhydride reduction of sulfonate **151** yielded an unknown compound which was neither the starting alcohol **150** nor the desired hydrocarbon **190**. A different strategy was therefore called for to effect the reduction. Barton has developed a method of converting alcohols to dithiocarbonate esters rendering the carbon - oxygen bond vulnerable to homolytic cleavage with tributyltin hydride.[159] There was some concern however that radical formation on the C4 methylene of intermediate **191** would provoke homolytic β–elimination of the C3 acetonide oxygen to give an oxyradical of type **192** or **193** which should close to form epoxyradical **194** and then epoxide **195**. (Scheme LI). The approach, however, seemed to merit investigation.

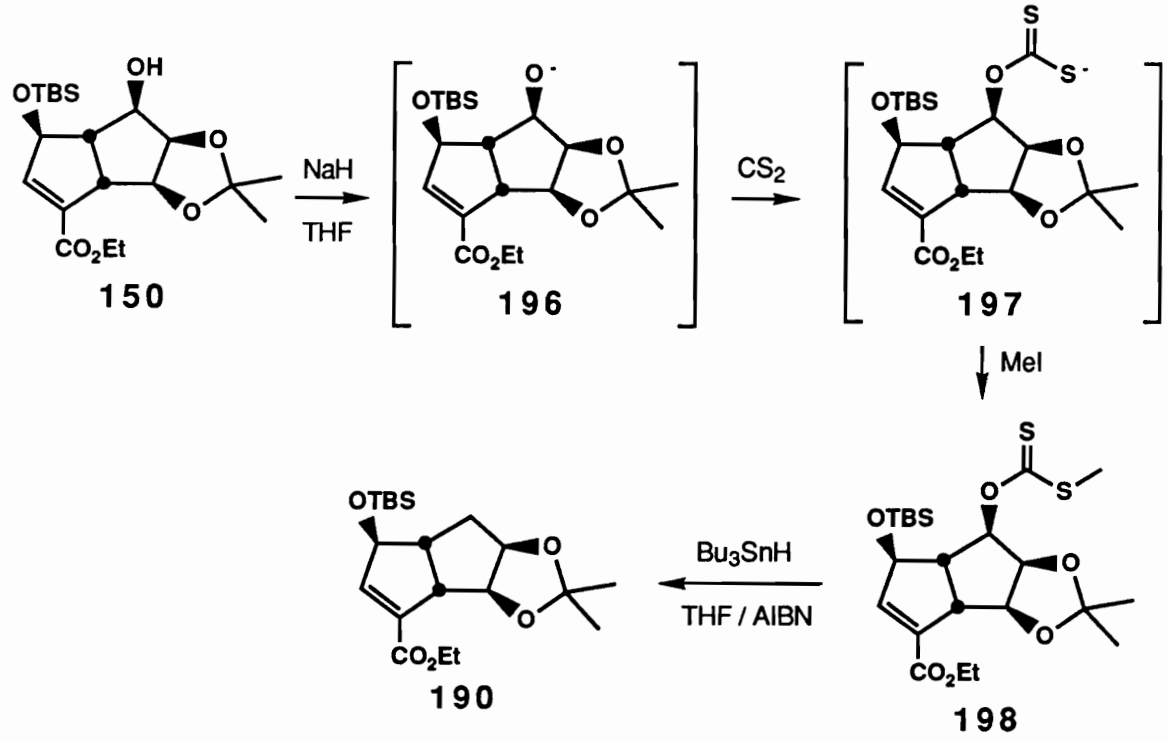


Scheme LI

β-Elimination Process

Alcohol **150** was available in the greatest quantity and was therefore used to test Barton's method. Alkoxide **196** was generated with NaH at room temperature from alcohol **150** which was then added to CS_2 in a nucleophillic fashion in the same pot (Scheme LII). The resulting dithiocarbonic acid salt **197** was quenched with MeI to deliver xanthate **198** in 72% yield. The xanthate was then treated with tin butylhydride in refluxing toluene affording desired tricycle **190** in 76% yield without any evidence of β-elimination.

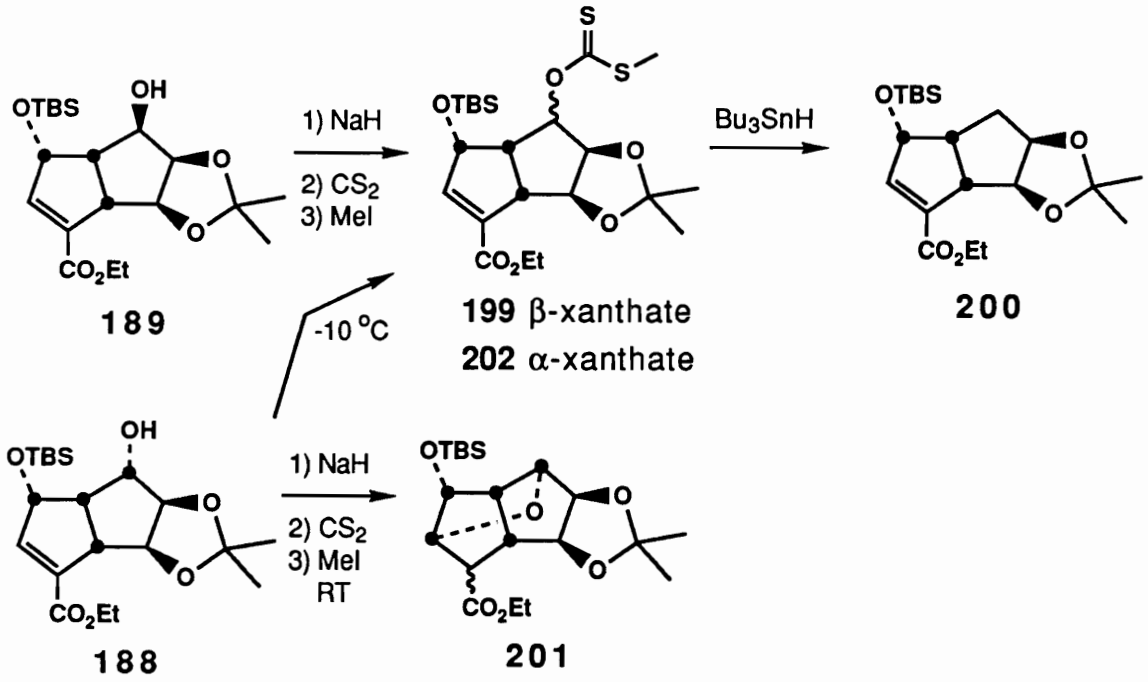
Following successful deoxygenation of alcohol **150** similar reaction conditions were employed for the reduction of alcohols **188** and **189**. Alcohol **189** was smoothly converted to xanthate **199** in 70% yield



Scheme LII

Deoxygenation of Alcohol **150**

which, in turn, provided a 84.5% yield of tricycle **200** upon treatment with Bu_3SnH (Scheme LIII). Deoxygenation of alcohol **188** proved to be surprisingly problematic. Inspection of the crude ^1H NMR spectrum after the xanthate formation sequence revealed that the product had no methylthioester group and that the α,β-unsaturated olefin was no longer present. It is probable that the alkoxide from NaH treatment participated in an intramolecular, nucleophillic attack in a Michael fashion to the olefinic ester to give the cyclic ether **201**. Inspection of molecular models indicated that the alkoxide is in close enough proximity for such a nucleophillic reaction to take place. Although the ether was an undesired product, its formation provided strong evidence for of the C4 stereochemistry which was hitherto uncertain. Fortunately, the problem was



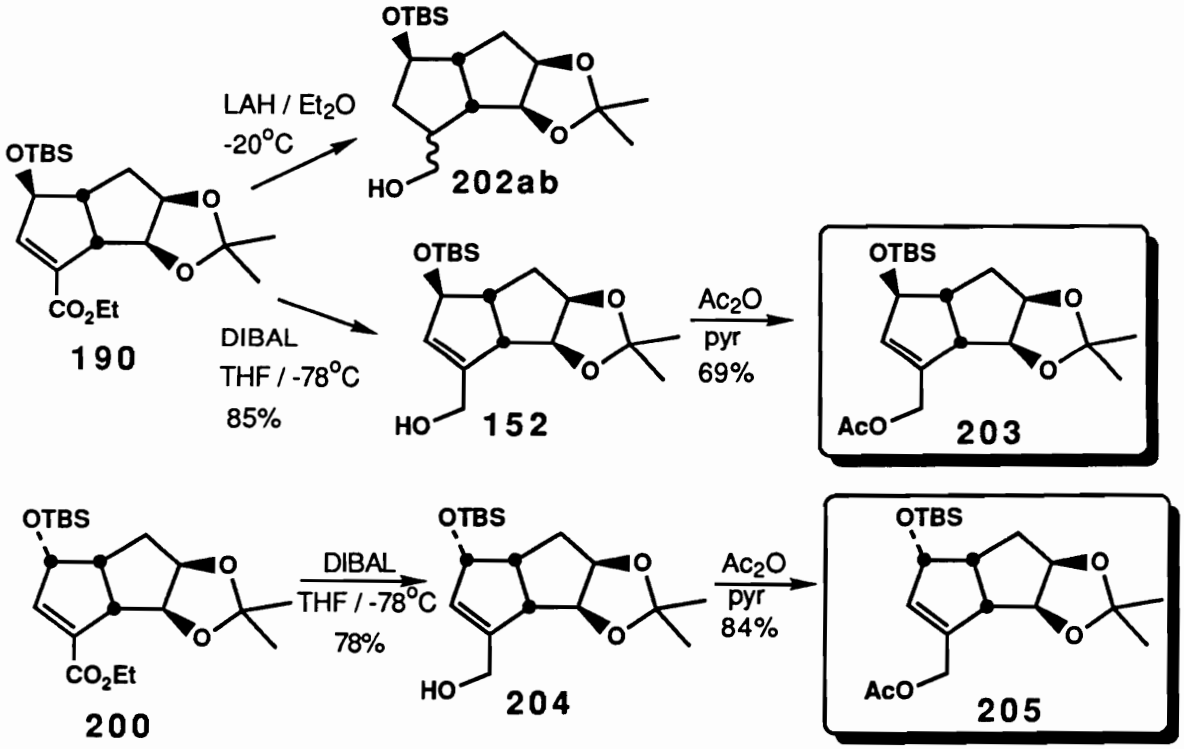
Scheme LIII

Deoxygenation of alcohols **188** and **189**

resolved rather easily by performing the NaH promoted proton extraction at -10°C and warming the reaction mixture to room temperature only after addition of CS_2 providing a modest 52% yield of xanthate **202**. The decrease in thermal energy was apparently sufficient to prohibit cyclization of the alkoxide as evidenced by the absence of ether **201** from the reaction mixture.

Successful deoxygenation allowed attention to be turned to further functional group manipulation with initial interest in selective 1,2 reduction of the α,β-usaturated ester moiety. Care had to be taken when reducing such esters in order to avoid unwanted 1,4 reduction which commonly occurs when lithium aluminum hydride is used as a reductant.[160] This case was observed in a single experiment where ~5 mg of tricycle **190** was reduced with $LiAlH_4$ in

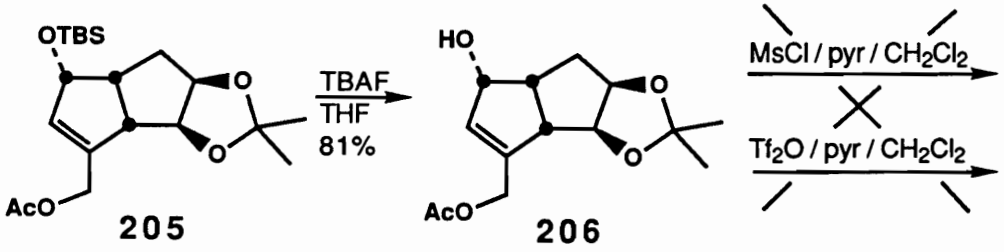
Et_2O at -9°C. TLC analysis suggested the presence of two major products and the ^1H NMR showed that the olefinic proton had almost completely dissappeared. It therefore seems that the 1,4 mode of reduction had indeed dominated the transformation and left esters **202ab** as primary products. It therefore seemed more advantageous to employ diisobutlyaluminum hydride (DIBAL-H) as it has been shown that this reagent provides for predominant 1,2 reduction.[161] Indeed DIBAL-H reduction of **190** resulted in clean 1,2 reduction of the ester function to give alcohol **152** which was acetylated cleanly with acetic anhydride and pyridine to provide acetate **203** in 59% overall yield. The endo tricycle **200** followed suit to give alcohol **204** and acetate **205** in 66% overall yield.



Scheme LIV

Reduction and Acetylation of Esters

Arrival at the allylic acetate stage of the synthesis allowed for convergence of the synthesis to a single isomer. The desired configuration about the C6 carbon for specionin synthesis is correctly established in acetate **203**. The C6 stereochemistry in **205** therefore had to be inverted. The Mitsunobu inversion offered one possible method of inversion, however, a report appeared which determined that electron donating *para* substituents on benzoic acid derivatives tend to inhibit their reaction under Mitsonobu conditions causing low yields whereas electron withdrawing substituents tend to accelerate the reaction.[162] Attention was therefore turned to S_N2 displacement of a sulfonate derivative of the corresponding alcohol (Scheme

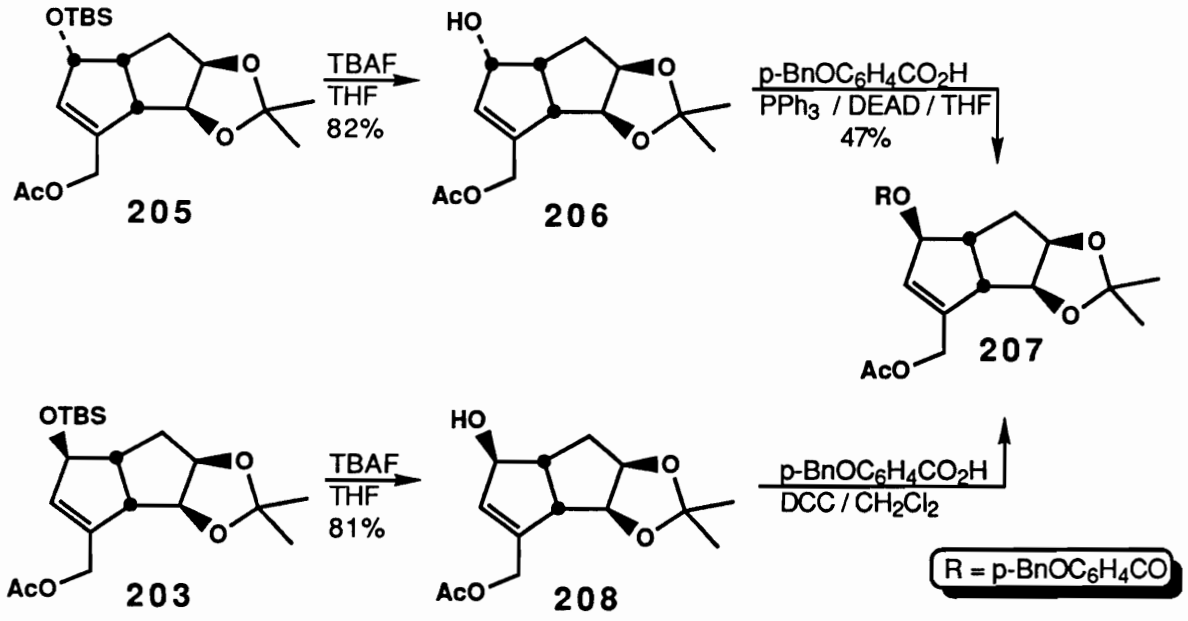


Scheme LV

Sulfonation Attempts

LV). Removal of the TBDMS protecting group with tetrabutylammonium fluoride·$3H_2O$ proceeded cleanly to provide the free alcohol **206**. Sulfonation with mesityl chloride was unsuccessful and yielded only recovered starting material. A second attempt was made with trifloromethanesulfonic anhydride[163] which led to complete consumption of starting material with multiple products. A serious lack of material prompted abandonment of this route without further exploration.

Efforts were focused on Mitsunobu conditions, despite the negative



Scheme LVI

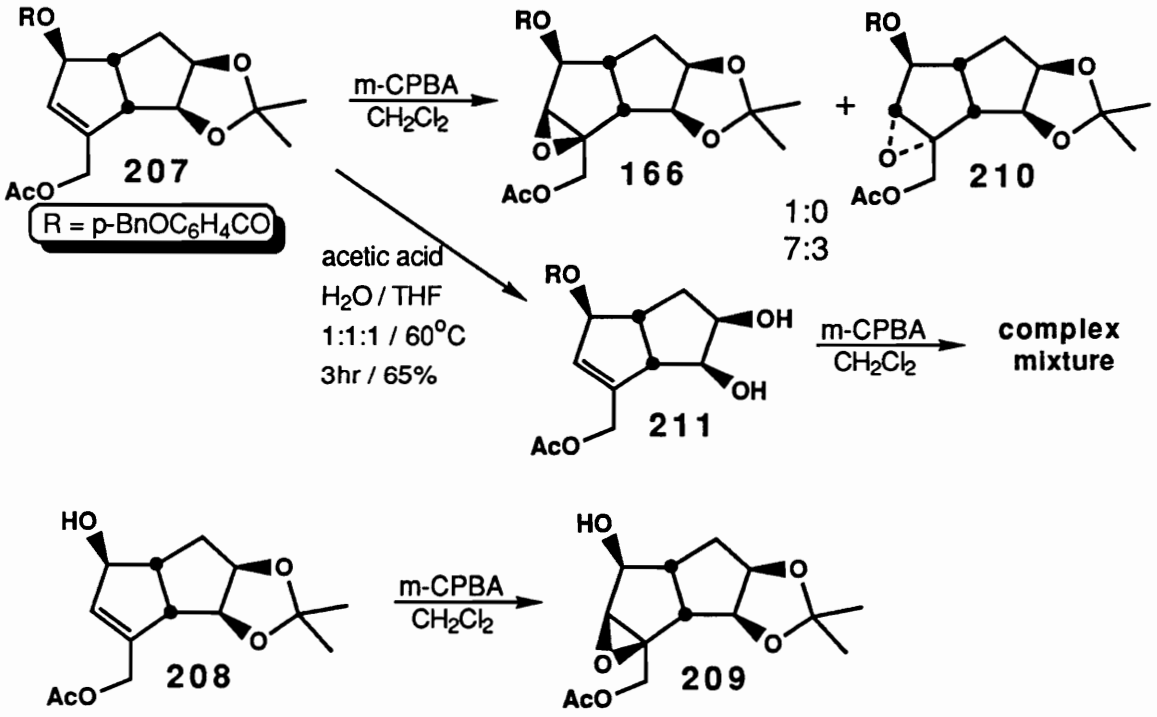
Conversion of Acetate Isomers

portend regarding e- donating substituents[162] as shown in scheme LVI. Surprisingly, all of the starting alcohol **206** was consumed with the appearance of only one product spot which proved to be the desired benzoate ester **207**. The moderate 47% yield reflects a difficult purification due to an unfortunate chromatographic overlap of the product and a derivative of diethylazodicarboxylate. In practice, the product can be carried forward semipure without suffering the loss of yield encountered with extensive chromatography.

Similarly, the TBDMS group on acetate **203** was removed with TBAF·$3H_2O$ for an excellent 81% yield of alcohol **208**. A small sample (3mg) of **208** was esterified via dicyclohexylcarbodiimide coupling to provide **207** and the proof of the convergence of acetate isomers **203** and **205**. The remainder

of available alcohol **208** was used for epoxidation experiments.

Epoxidation of the C7-C8 olefin was unexpectedly problematic. The steric constraints of **208** (Scheme LVII) dictated oxygen delivery by *meta*-chloroperoxybenzoic acid to the convex β-face which could be clearly seen with molecular models. Treatment of **208** however gave two spots on TLC. The lower spot proved to be 35% of desired epoxide **209** slightly contaminated with *m*-chlorobenzoic or m-chloroperbenzoic acid and the upper one was a complex mixture without resemblance to **208** or **209**. Tragically, an attempt to remove *m*-chlorobenzoic acid from **209** with dilute NaOH resulted in epoxide opening and diol formation.



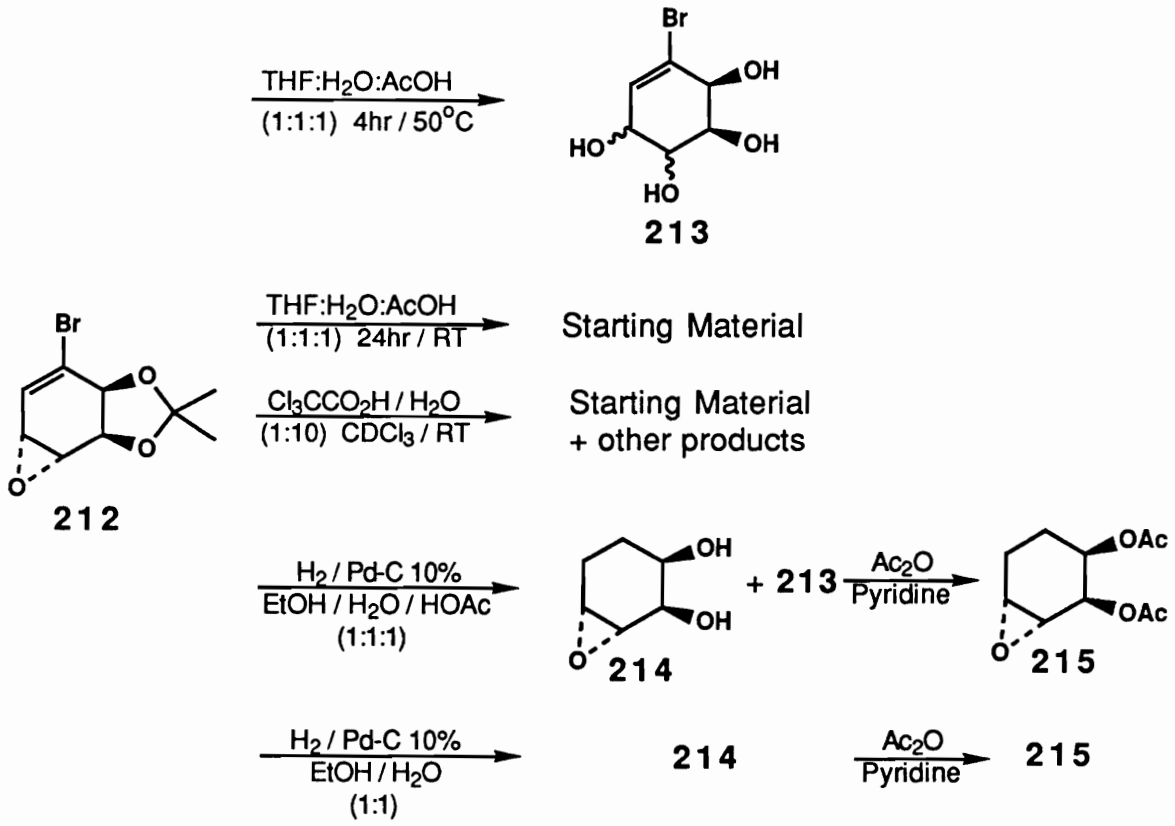
Scheme LVII

Epoxidation Experiments

The epoxidation stereochemistry of **207** was less certain due to additional steric hindrance of the β-face by the benzoate ester. Whitesell established a precedent with a similar olefinic ester **126** (Scheme XX) which epoxidized stereospecifically from the β-face.[112] Oddly, conflicting results were obtained. Treatment of **207** with *m*-CPBA gave a single diastereomer in 56% yield. The compound was determined to be the epoxide **166** from the disappearance of the olefin peak in the ^{1}H NMR and the appearance of a singlet at 3.7 ppm. The sample also contained ~20% m-chlorobenzoic acid. A second experiment which was run similarly gave a 70:30 ratio of two diastereomeric epoxides **166** and **210**. The configuration of the epoxides had to be assumed at this point until proof could be obtained by conversion to a known compound.

It was feared that acid catalyzed removal of the acetonide group might result in epoxide opening, so the acetonide **207** was deprotected and the resulting clean diol **211** treated with m-CPBA. This effort was met with a complex mixture of products and thus abandoned.

The severe lack of material at this point (>2mg) prompted the study of a model system compound **212** which approximated the system which was under investigation (Scheme LVIII). A method was required which could selectively deprotect an acetonide functionality while retaining the unopened epoxide. Three acid catalyzed systems were investigated. A mixture of **212** and THF:H_2O:AcOH (1:1:1) was warmed to 55°C in order to consume all starting material, but the result was a compound which showed no acetonide or epoxide by ^{1}H NMR and was assumed to be tetrol **213**. Identical conditions caused no



Scheme LVIII

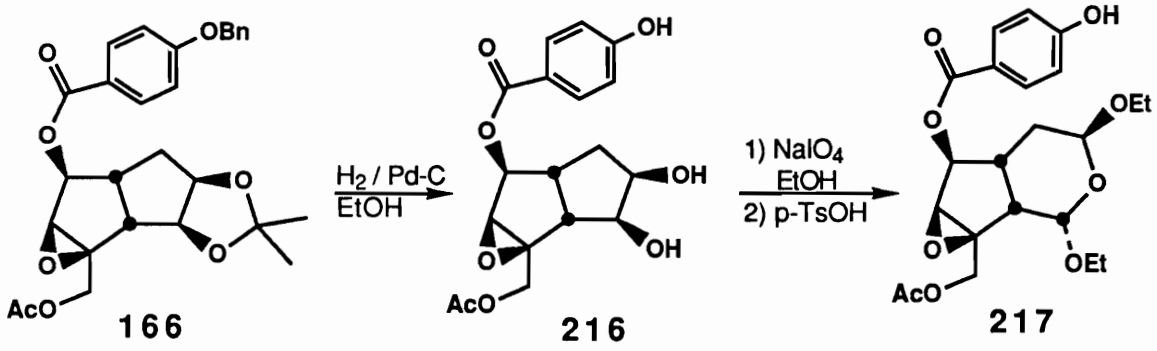
Acetonide Deprotection Model Study

change to **212** after 24 hr at room temperature. Trichloroacetic acid was also explored as an acid catalyst since its conjugate base is less nucleophillic than that of acetic acid. Unfortunately its use led only to a mixture of products which contained mostly starting material and was therefore judged to be an unacceptable alternative. Following an observation that acetonides can be hydrogenated to give diols in some cases,[164] **212** was hydrogenated at 40psi over Pd-C in the presence of acetic acid and gave two products neither of which showed the presence of an acetonide and the major one, assigned as **214**,

clearly posessed an epoxide. This result was confirmed by treating the mixture with acetic anhydride and pyridine to give a product with two major acetate peaks thought to be **215**. The hydrogenation was repeated without the presence of acetic acid and gave a product identified as **214**. Treatment with acetic anhydride and pyridine gave a clean product thought to be exclusively diacetate **215**.

Evidence from hydrogenation of **212** was sufficient to prompt its application to a mixture of 3.5 mg of impure epoxides **166** and **210** (The epoxides were in a ratio of ~85:15. m-Chlorobenzoic acid was a major impurity. The configuration of epoxides were unknown at the time.) Hydrogenation yielded a product which was much polar than the starting mixture on TLC, and this material was isolated by filtration through a plug of 10% deactivated silica gel to give 0.7 mg of impure material that clearly had no benzyl group and seemed to be lacking an acetonide group. The material was assumed to be diol **216**. This material was treated with sodium periodate in ethanol according to the procedure of Leonard.[104] After 16 hrs, a small crystal of *para* toluenesulfonic acid was added and the mixture allowed to equilibrate for 24 hrs. The crude mixture was analyzed by 400 Mz ^{1}H NMR. The mixture had a multitude of extraneous peaks, but the majority of peaks from an authenic sample of specionin acetate **217**, kindly supplied by Leonard, were identifiable (See p. xx-xx) for spectral comparison with authenic material).

The extremely small amount of actual sample (~10-20μg) precluded an analysis of the ratio of C1 and C3 isomers, but it is clear that natural specionin acetate predominated by at least 5 fold.

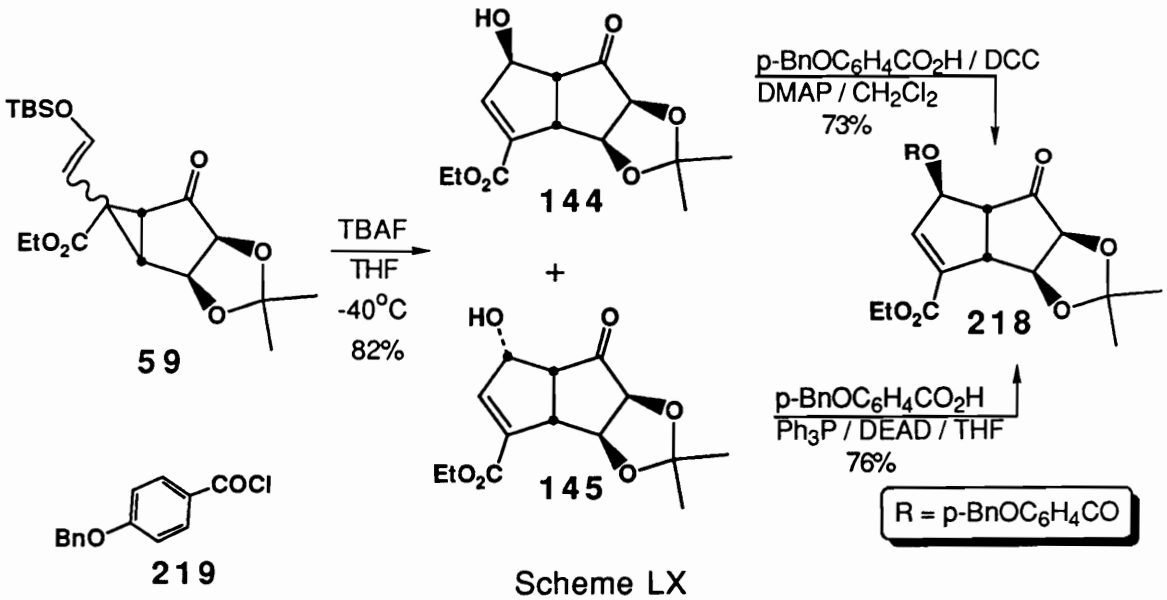


Scheme LIX

Final Run to Specionin Acetate **217**

B. IV. Second Generation Synthesis of (-)-Specionin

A serious drawback of the first generation synthesis is the cumbersome handling of two separate diastereomers through long synthetic sequences before convergence to a single compound can take place. A second synthetic endeavor was undertaken to converge the intermediates at an earlier stage of the process. The anticipated scheme is outlined in scheme LX and hinges on tetrabutylammonium fluoride promoted rearrangement of *endo* and *exo* vinyl-cyclopropane **59**. A lack of reactivity with the *endo* isomer was not observed as in the TMSI promoted case and the reaction gave a mixture of alcohols **144** and **145** in 82% yield. This supports the argument presented in section **B. III.** since this system does not depend on orbital communication with the carbonyl to establish a nucleophillic site on the silicon atom. The kinetics of this reaction are therefore not affected by the conformation of the *endo* isomer.



Scheme LX

Second Generation Conversion

The inversion of alcohol **145** under Mitsunobu conditions[162] cleanly provided benzoate ester **218** in 76% yield. Interestingly, two subsequent inversion trials under the same conditions failed to give any reaction and resulted only in recovery of starting material. The reaction was again successful when a new bottle of diethylazodicarboxylate was used which suggests that DEAD has a tendency to "go bad" over time.

Esterification of alcohol **144** with DCC yielded a 73% yield of **218** which provided proof that the synthesis could be converged at an early stage and thus dramatically decrease the required amount of work and increase the efficiency if the rest of the sequence proves successful. A problem with the DCC coupling reaction was encountered upon purification when a DCC derivative proved to be inseparable from ester **218**. An alternate method of esterification was investigated. Alcohol **144** was treated with acyl chloride **219** which was generated with oxalyl chloride and the corresponding acid. The yield of ester **218** in this case was only 38% and difficulty with separation of **219** from the product was encountered. This esterification method therefore did not seem to provide any advantage over the DCC promoted method.

With the convergence to **218** established, a major hurdle was anticipated. Success of this route depended upon selective reduction of the ethyl ester in the presence of the benzoate ester. This seemed possible due to the presence of an electron donating substituent on the *para* position of the benzoate ester. The system exists as resonance forms **220** and **221** which tend to indicate that carbon A should be much more electron rich than carbon B and thus less electrophillic and subject to hydride reduction.

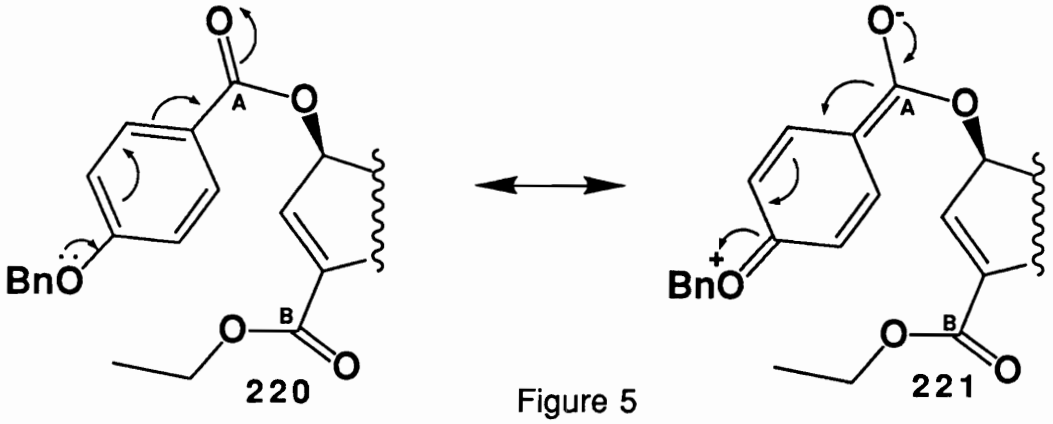
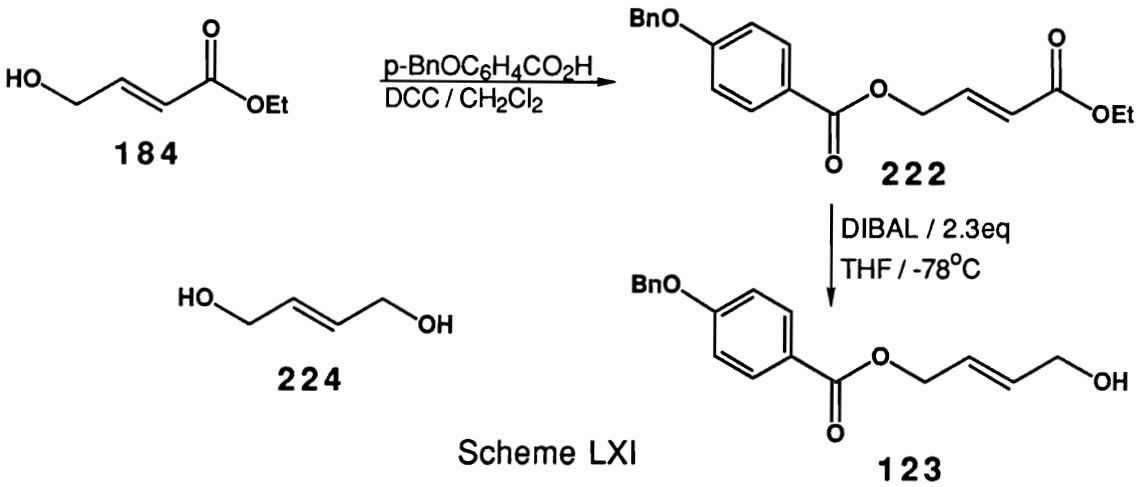


Figure 5

Comparison of Electrophillicity of Two Esters

In order to test the selectivity potential between the two esters, a model compound **222** was prepared. It was easily obtained from DCC promoted esterification of alcohol **184** which was in turn produced by borane reduction of fumaric acid monoethyl ester. The critical reduction was carried out by dropwise addition of 2.3 eq of diisobutylaluminum hydride at -78°C. TLC analysis clearly indicated that a single more polar product had formed and that there was still starting material present after 20 min. The reaction was quenched after 1 hr. ^{1}H NMR of the crude product indicated the presence of

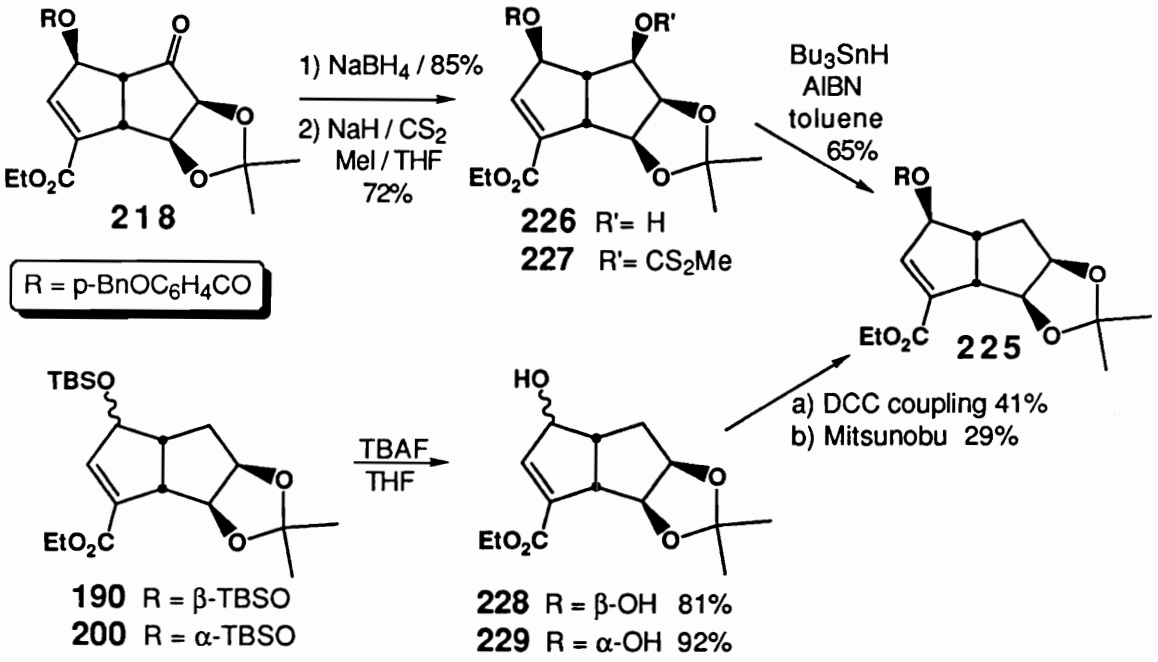


Scheme LXI

Selective Reduction Model Study

~20% starting material and another product which retained the characteristic peak pattern of the starting benzoate ester and a major signal at 5.3 ppm which is characteristic of an unconjugated olefin such as **223**. There was no olefinic singlet to indicate the presence of the over-reduced product **224**. This reaction seemed to suggest that selective reduction of an α,β-unsaturated ethyl ester could be accomplished in the presence of a p-substituted benzoate ester and that the second generation route should be pursued.

The synthesis had to be carried forward to the diester **225** to set up the critical reduction study. The C4 ketone was reduced according to Barton's method[159] which had been developed in the first generation. Sodium borohydride reduction of ketone **218** gave one diastereomer of alcohol **226**



Scheme LXII

Preparation of Diester **225**

which was subsequently converted to the corresponding xanthate **227**. Neither compound was meticulously purified until confirmation was obtained that the route would work. Tributyltin hydride reduction then furnished the desired diester **225**. The diester **225** was also accessible from tricycles **190** and **200** by first converting them to their corresponding alcohols **228** and **229**. Subsequent respective dicyclohexylazodicarboxylate ester coupling and Mitsunobu inversion converged the two alcohols to diester **225**. The small reaction scale promoted low yields in these two cases.

The selective reduction study had to be carried out on a scale of 5 mg of **225**. The reaction was carried out as with model compound **22**. Unfortunately, the result was revealed to be a mixture of polar compounds by TLC analysis. ^{1}H NMR analysis suggested that the mixture contained ~10% starting material, a compound with an unconjugated olefin, a compound with a conjugated olefin which was not the starting material, and some olefinic impurities. Clearly this attempt to accomplish a selective reduction was unsuccessful, possibly due to the extremely small scale. The second generation route was therefore abandoned until the selective reduction could be tested on a larger scale.

It is interresting to compare this second generation approach with the first generation sequence. The first generation synthesis converged all diastereomeric intermediates to acetate **207** in 18 working steps in an overall yield of 2.1% from enone **56**. Successful reduction could lead to an 8 step synthesis for the same transformation if subsequent reactions proved successful. This vast difference in workload should motivate research to resolve the selective reduction problem in the future.

C. Conclusion

The first objective undertaken was to devise an efficient and reproducible preparation of enone **56**. Inspection of the 5% overall production yield for a 4 step sequence may suggest failure in this respect, especially in comparison to higher yielding preparations reported in the literature.[65,129-137] However in view of the many unsuccessful attempts to reproduce much of the published work, one must appreciate the fact that a synthetic method is now available which provides a dependable yield of product. Of additional merit is the relatively small amount of work required to carry out the sequence to completion.

Regarding the low temperature cyclopentene annulation sequence, a hitherto unknown problem with trimethylsilyl iodide promoted rearrangement of endo vinyl-cyclopropane **59b** was revealed and a reasonable resolution was developed. The tetrabutylammonium fluoride promoted rearrangement proved to be successful as reported[5] and was explioted in an ill-fated second generation approach to specionin total synthesis.

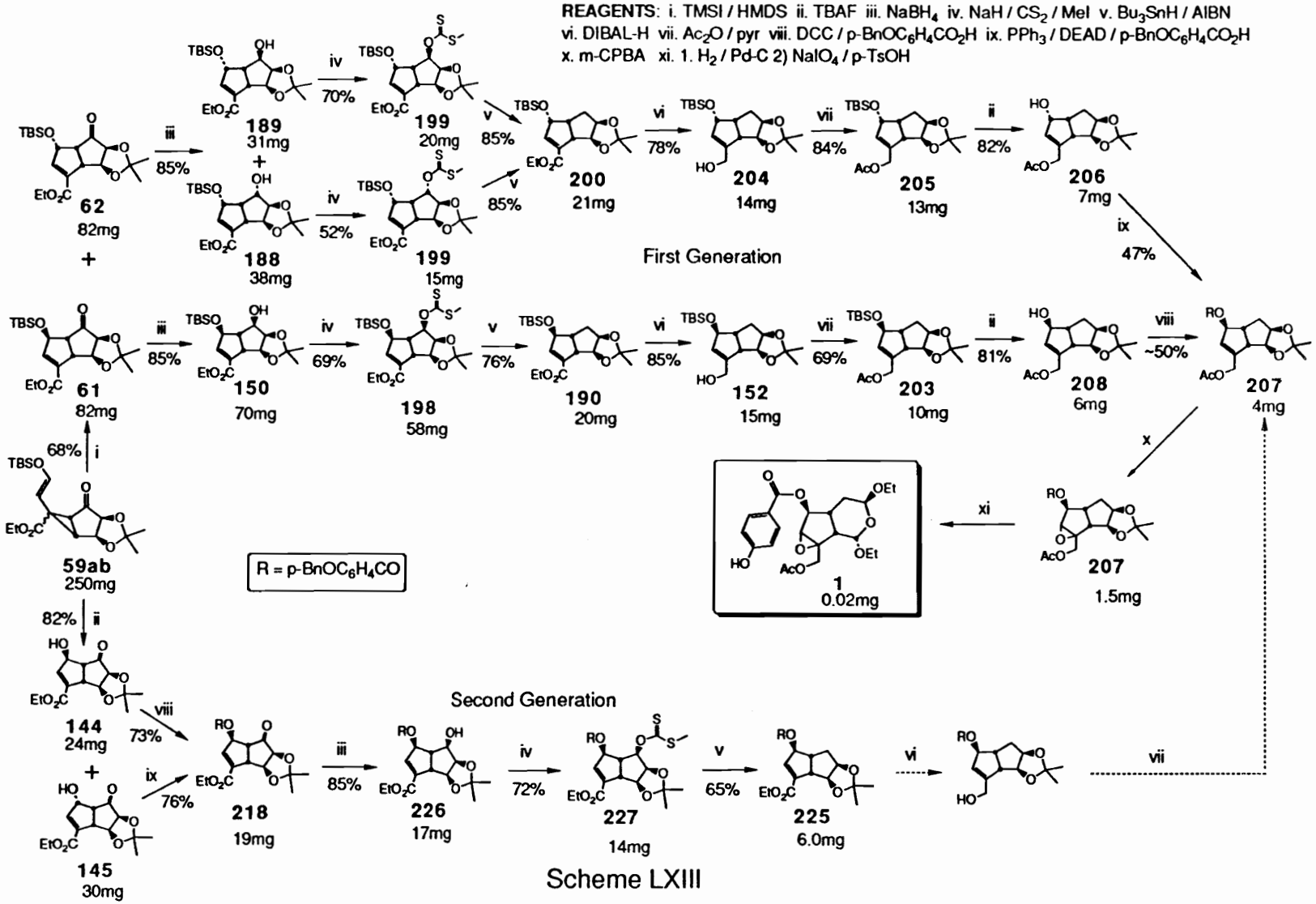
Functional manipulation of the diquinane skeleton to prepare (-)-specionin was met with many complications which inherently arise when very little material is available for research. The Barton deoxygenation was fortunately successful, but scarce availability of material slowed spectral analyses of the intermediates until ultimately, the last few steps had to be carried out with impure materials to provide a synthetic sample of specionin for comparison with a natural sample. Furthermore, a shortage of material was probably responsible for preventing

successful realization of a second generation approach which would have eliminated more than half of the working steps required to complete the synthesis.

On the positive side, this work demonstrated the powerful potential for oxy-vinylcyclopropanes as synthetic intermediates. It also demonstrated the tremendous amount of information that can be gathered with minute quantities of material when stringent situations demand such necessities. In view of current limited funding and environmental concerns, it may soon become routine practice to complete total synthesis investigations on similar scales and chemists will have to develop skills to accommodate such demands.

This work compares reasonably well with that of Whitesell[112] with respect to overall yield (1.4% here and 2.4% in Whitesell's case) and this synthesis is completed in the same (13) number of steps. However, the fact that two diastereomers must be carried independently through seven steps distracts from its impact. Successful completion of the second generation approach, however, could provide an eleven step synthesis without the problem of diastereomeric convergence. The two approaches are summarized in Scheme LXIII. The yields and amounts of material for each step depicted in Scheme LXIII represent average quantities, not the highest yields obtained.

In conclusion, what remains to be done to improve this project is the completion of the second generation synthesis and optimization of all the steps using larger scale of experimentation. This will leave the asymmetric induction for the cyclopropanation of achiral enones as the only unfulfilled task for the development of this particular methodology.



Scheme LXIII

Summary of (-)-Specionin Total Synthesis

D. Experimental

All nonhydrolytic reactions were carried out in an argon atmosphere with standard techniques for the exclusion of air and moisture. Glassware used for moisture sensitive reactions was flame dried under vacuum. THF, DME, and toluene were distilled from benzophenone ketyl. Dichloromethane, diisopropyl amine, and HMPA were distilled from calcium hydride. Thin layer chromatography was performed on Kiselgel 60F-254 plates (analytical 0.25mm thickness, preparative, 0.5mm; EM Reagents). Flash chromatography was performed on Kieselgel 60 (EM Reagents, 230-400 mesh). Mass spectra were recorded on a Varian MAT-112 instrument (low resolution) or on a double focusing VG 7070 E-HF instrument (exact mass). Infrared were recorded on a Perkin Elmer 283B or 710B instruments. Proton and Carbon NMR spectra were obtained on Bruker WP-270, Bruker WP-200, or Varian NR-400 instruments. Proton chemical shifts are reported in parts per million (ppm) relative to TMS as an internal reference (0.00). Carbon chemical shifts are reported in ppm relative to the center line of the $CHCl_3$ triplet (77.0 ppm) and the multiplicity is indicated by CH_3, CH_2, CH, C (DEPT experiments). Rotations were recorded on a Perkin Elmer 241 digital polarimeter.

2,3-(isopropylidinedioxy)-4-cyclopentenone 56. Dimethyl methyl phosphonate (672 mL, 6.20 mmol) was added via syringe to 10 mL of dry THF under argon and cooled to -78 ^{o}C followed by slow addition of n-butyl lithium (2.58 mL, 2.4 M in hexanes, 6.20 mmol) via syringe. The solution became noticeably cloudy. This mixture was stirred at -78 ^{o}C for 15 min. whereupon isopropoxy lactone **181** (1.03 g, 4.77 mmol) was added via cannula in 4 mL of dry

THF. The resulting mixture was stirred for 20 min. at -78 °C and then allowed to warm to room temperature over 1 h at which time the reaction was quenched with NH_4Cl (sat.) and partitioned between water (10 mL) and ether (100 mL). The layers were separated and the organic layer extracted 1x with water and brine. The organic layer was then dried over $MgSO_4$, filtered and evaparated to give 640 mg of crude oil. The residue was chromatographed over 10% deactivated silica gel with hexane : ethyl acetate (3 : 1, 2 : 1) as eluant to give 205 mg (1.34 mmol, 28%) of pure enone **56** as white crystals; **mp** 41 - 42 °C (lit.[3] mp 42 °C); $[\alpha]_D^{25}$ +63.4° (*c* 1.12, $CDCl_3$) (lit.[65] $[\alpha]_D^{25}$ +62.8° (c 0.7, $CDCl_3$), **IR** (KBr pellet) 3000, 2940, 1730, 1380 cm^{-1}; **^{1}H NMR** ($CDCl_3$) δ 7.65 (dd, J=5.9, 2.2 Hz, 1H), 6.22 (d, J = 5.9 Hz, 1H), 5.27 (dd, J=5.5, 2.2 Hz, 1H), 4.46 (d, J = 5.5 Hz, 1H), 1.42 (s, 6H).

(7S,8R)-2-carbethoxy-4-hydroxy-7,8-isopropylidine-dioxy-bicyclo[3.3.0]oct-2-en-6-one 144,145. To a solution of vinylcyclopropane **59** (341.8 mg, 0.86 mmol) in 15 mL of THF at -40°C was added TBAF·$3H_2O$ (0.543 g, 1.73 mmol). The cooling bath was removed, stirring was continued for 10 min, and the reaction was quenched with saturated aqueous NH_4Cl solution. The aqueous layer was extracted three times with ethyl acetate. The organic extracts were combined, washed with brine, and dried (MgSO4). Flash chromatography (silica gel, 3:1, 2:1, 1:1 hexane / ethyl acetate) gave 73.6 mg of the exo alcohol **144** and 134.7 mg of the endo alcohol **145** (86%).

The endo isomer was retreated with TBAF·$3H_2O$ (0.5 equiv., 75 mg) at room temperature for 6 hr. Following the same procedure for workup and chromatography gave 37.9 mg of the exo alcohol and 37.7 mg of the endo. The

overall yield was 111.5 mg (44%) of the exo alcohol **144** and 37.7 mg (15%) of the endo **145**.

144-exo: R_f = 0.34 (hexane:EtOAc, 1:1); $[\alpha]_D^{25}$ = -122.4; **IR** (neat) 3465 (broad), 2980, 2935, 1755, 1720, 1628, 1375, 1260 cm^{-1}; **^{1}H NMR** ($CDCl_3$) δ 6.76 (dd, J=2.38, 2.38 Hz, 1H), 4.98 (d, J=5.04, 1H), 4.92 (br s,1H), 4.30 (m, 2H), 4.18 (d, J=4.76, 2H), 4.03 (br d, J=7.48, 1H), 3.22 (ddd, J=7.17, 1.14, 1.14 Hz, 1H), 2.70 (br s, 1H), 1.44 (s, 3H), 1.37 (s, 3H), 1.34 (t, J=7.01 Hz, 3H); **^{13}C NMR** ($CDCl_3$) δ 214.07 (C), 163.63 (C), 143.77 (CH), 138.86 (C), 112.40 (C), 78.86 (CH), 78.36 (CH), 77.90 (CH), 61.21 (CH_2), 57.53 (CH), 49.02 (CH), 27.00 (CH_3), 25.01 (CH_3), 14.19 (CH_3); **MS** (CI, m/e (rel. int.)) 283 (40), 282 (10, M^+), 267 (10), 253 (15), 237 (18), 225 (100), 209 (30), 207 (28), 195 (15), 179 (45), 155 (15), 123 (12), 91 (25), 85 (50); **HRMS**, calcd for $C_{14}H_{19}O_6$: 283.1181. Found: 283.1102

145-endo: R_f = 0.29 (hexane:EtOAc, 1:1); $[\alpha]_D^{25}$ = -210.2; **IR** (neat) 3460 (broad), 2990, 1755, 1720, 1635, 1383, 1250 cm^{-1}; **^{1}H NMR** ($CDCl_3$) δ 6.76 (dd, J=2.01, 2.01 Hz, 1H), 5.19 (d, J=9.22 Hz, 1H), 4.85 (d, J=5.13 Hz, 1H), 4.33 (m, 1H), 4.30 (q, J=7.16 Hz, 2H), 3.76 (br d, J=8.32 Hz, 1H), 3.37 (ddd, J=8.60, 8.60, 1.11 Hz, 1H), 2.98 (br s, 1H), 1.43 (s, 3H), 1.36 (s, 3H), 1.34 (t, J=7.04 Hz, 3H); **^{13}C NMR** ($CDCl_3$) δ 215.02 (C), 163.70 (C), 144.65 (CH), 136.33 (C), 112.51 (C), 80.52 (CH), 77.90 (CH), 76.16 (CH), 61.12 (CH_2), 51.48 (CH), 48.71 (CH), 27.06 (CH_3), 25.30 (CH_3), 14.19 (CH_3); **MS** (CI, m/e (rel. int.)) 283 (23), 282 (43, M^+), 267 (50), 237 (30), 225 (75), 224 (75), 207 (45), 182 (85), 179 (100), 167 (25), 151 (38), 123 (45), 100 (100), 85 (35); **HRMS**, calcd for $C_{14}H_{18}O_6$: 282.1103. Found: 282.1131.

(7S,8R) - 4 - [(*tert*-Butyldimethylsilyl) oxy] - 2 - carbethoxy - 7,8 - isopropylidenedioxy-bicyco[3.3.0]oct-2-en-6-ol 150, 188, 189. A solution of ketones **61, 62** (165 mg, 0.42 mmol, 1:1 mixture) in ethanol (4 mL) was cooled to 0 °C, and $NaBH_4$ (24 mg, 0.63 mmol) was added. After 30 min, TLC indicated complete consumption of starting material, so the reaction was quenched with NH_4Cl sat. (2 mL) and warmed to room temperature. The aqueous layer was extracted three times with ethyl acetate; the extracts combined, washed with brine, and dried over $MgSO_4$. Flash chromatography (10% deac. silica gel,4:1, 2:1 hexane / ether) gave 38.6 mg (23.4%) 4-endo, 6 endo **188**, 31.3 mg (18.9%) of 4-endo, 6-exo **189**, 70.4 mg (42.7%) of 4 exo, 6 endo **150**. All diastereomers were clear oils except **150** which was a waxy solid.

4-endo, 6-endo 188: R_f = 0.45 (hexane:Et_2O, 2:1); $[\alpha]_D^{25}$ = -14.1; **IR** (neat) 3500 br, 2930, 2850, 1715, 1630, 1465, 1370, 1255, 1205, 1050, 855, 835, 775, 745, cm^{-1}: **^{1}H NMR** ($CDCl_3$) δ 6.51 (dd, J= 2.2, 2.2 Hz, 1H), 5.14 (ddd, J=7.8, 2.2, 2.2 Hz, 1H), 4.99 (dd, J=5.0, 1.5 Hz, 1H), 4.50 (d, J=5.1 Hz, 1H), 4.46 (d, J=4.5 Hz, 1H), 4.26 (m, 2H), 3.49 (s, 1H), 3.32 (ddd, J=8.0, 8.0, 4.6 Hz, 1H), 3.22 (m, 1H), 1.48 (s, 3H), 1.33 (t, 3H, J=7.1 Hz, 3H), 1.33 (s, 3H), 0.94 (s, 9H), 0.19 (s, 3H), 0.17 (S, 3H); **^{13}C NMR** ($CDCl_3$) δ 164.19 (C), 144.17 (CH), 137.55 (C), 110.74 (C), 85.74 (CH), 84.44 (CH), 77.03 (CH), 76.77 (CH), 60.68 (CH_2), 56.74 (CH), 50.20 (CH), 27.30 (CH_3), 25.61 (CH_3, triple intensity), 25.07 (CH_3), 18.00 (C), 14.27 (CH_3), -4.97 (CH_3), -5.21 (CH_3); **MS** (70 eV, m/e (rel int.)) 397 (15), 383 (9), 355 (17), 341 (30), 325 (65), 299 (30), 283 (100), 267 (100), 249 (100), 237 (70), 225 (85), 209 (95), 193 (45), 179 (35), 163 (50), 133 (100), 115 (35).

4-endo, 6-exo 189: R_f = 0.34 (hexane:Et_2O, 2:1); $[\alpha]_D^{25}$ = -39.7; **IR** (neat) 3460 br, 2920, 2850, 1720, 1630, 1465, 1370, 1255, 1055, 835, 770 cm^{-1}; **1H NMR** (400 MHz, $CDCl_3$). δ 6.51 (dd, J=2.1, 2.1 Hz, 1H), 5.02 (ddd, J=7.3, 2.1, 2.1 Hz, 1H), 4.66 (dd, J=5.2, 2.1 Hz, 1H), 4.55 (dd, J=4.9, 4.9 Hz,1H), 4.24 (m, 3H), 3.19 (m, 1H), 3.08 (ddd, J=7.6, 7.6, 7.6 Hz, 1H), 2.41 (d, J=4.4 Hz, 1H), 1.53 (s, 3H), 1.34 (s, 3H), 1.31 (t, J=7.1 Hz, 3H), 0.92 (s, 9H), 0.14 (s, 6H); **^{13}C NMR** ($CDCl_3$) δ 164.31 (C), 144.94 (CH), 136.25 (C), 111.41 (C), 81.75 (CH), 81.64 (CH), 76.45 (CH), 73.25 (CH), 60.76 (CH_2), 53.50 (CH), 51.81 (CH), 26.87 (CH_3), 25.83 (CH_3, triple intensity), 24.82 (CH_3), 18.13 (C), 14.27 (CH_3), -4.79 (CH_3), -4.99 (CH_3); **MS** (70eV m/e (rel. int.)) 397 (1, M^+-1), 383 (2), 341 (10), 307 (4), 283 (7), 265 (35), 249 (20), 237 (15), 209 (20), 191 (15), 163 (30), 135 (25).

4-exo, 6-exo 150: **mp** 87.5 - 89.5 °C: R_f = 0.21 (hexane:Et_2O, 2:1); $[\alpha]_D^{25}$ = -52.7; **IR** (neat) 3500, 2940, 1715, 1617, 1260, 1055, 840 cm^{-1}; **^{1}H NMR** ($CDCl_3$) δ 6.54 (br s, 1H), 4.75 (br s, 1H), 4.67 (d, J=5.3 Hz 1H), 4.44 (dd, J=5.0, 5.0 Hz, 1H), 4.23 (q, J=7.1 Hz, 2H), 3.57 (ddd, J=9.0, 9.0, 4.7 Hz, 1H), 3.52 (br d, J=8.0 Hz, 1H), 2.57 (dd, J= 7.6, 7.6, 1H), 2.30 (d, J=9.9 Hz, 1H), 1.51 (s, 3H), 1.31 (s, 3H), 1.29 (t, J=7.1 Hz, 1H), 0.87 (s, 9H), 0.10 (s, 3H),0.09 (s, 3H); **^{13}C NMR** ($CDCl_3$) δ 164.47 (C), 142.99 (CH), 138.78 (C), 111.17 (C), 81.20 (CH, double intensity), 79.00 (CH), 75.85 (CH), 60.74 (CH_2), 57.47 (CH), 53.67 (CH), 26.71 (CH_3), 25.86 (CH_3, triple intensity), 24.82 (CH_3), 18.26 (C), 14.26 (CH_3), -4.61 (CH3), -4.62 (CH_3); **MS** (70 eV m/e (rel. int.)) 398 (1, M^+), 383 (9), 354 (4), 341 (40), 313 (10), 255 (10), 237 (17), 224 (20), 209 (25), 86 (100), 75 (100); **HRMS**, calcd for $C_{20}H_{34}O_6Si$: 398.2125. Found: 398.2101.

(7S, 8R)-2-hydroxymethyl-4-[(tert)-butyldimethylsilyl)oxy]-7,8-isopropylidinedioxy-bicyclo[3.3.0]oct-2-ene 152, 204. Ester **190** (20.1 mg, 0.053 mmol) was dissolved in THF (3 mL) and cooled to -78°C and diisobutylaluminum hydride (789 μL, 1M in THF, 0.79 mmol) is added dropwise via syringe. TLC indicated complete reaction after 20 min. The reaction was quenched at -78°C with 1 mL of saturated NH_4Cl, diluted with 2 mL of H_2O, and extracted 3X with 5 mL of Et_2O. The combined organic layers were dried over MgSO4 at which time the solution thickened to a white, geletinous mass. This mixture was separated by centrifugation and the liquid filtered and evaparated to give 19.4 mg of crude oil which was purified over 10% deactivated silica gel with hexane:EtOAc (4:1 → 1:1) to give 15.2 mg (85%) of clear alcohol **152**. The endo isomer **200** (21 mg, 0.055 mmol) was reduced similarly to give 14.6 mg (78%) of clear alcohol **204**.

Exo-152: $\mathbf{R_f}$ = 0.21 (hexane:EtOAc, 2:1) **^{1}H NMR** ($CDCl_3$) δ 5.56 (s, 1H), 4.61 (dd, J=5.01, 5.01 Hz, 1H), 4.49 (d, J=5.11, 1H), 4.42 (s, 1H), 4.31 (s, 2H), 3.35 (d, J=7.27 Hz, 1H), 2.85 (ddd, J=9.34, 7.88, 7.88 Hz, 1H), 2.22 (dd, J=14.37, 7.95 Hz, 1H), 1.69 (s, 1H), 1.48 (s, 3H), 1.39 (m, 1H), 1.30 (s, 3H), 0.89 (s, 9H), 0.09 (s, 3H), 0.08 (s, 3H).

Endo-204: $\mathbf{R_f}$ = 0.21 (hexane:EtOAc, 2:1) **^{1}H NMR** ($CDCl_3$) δ 5.50 (dd, J=1.8, 1.8 Hz, 1H), 4.83 (ddd, 7.12, 1.77, 1.77, 1H), 4.63 (ddd, J=4.94, 4.94, 1.62 Hz), 4.57 (dd, J=5.37, 1.08 Hz, 1H), 4.28 (m, 2H), 3.18 (dddd, J=8.80, 7.53, 7.53, 7.53 Hz, 1H), 2.99 (br d, J=7.23 Hz, 1H), 2.02 - 1.83 (m, 2H), 1.60 (dd, J=5.77, 5.77 Hz, 1H), 1.47 (s, 3H), 1.29 (s, 3H), 0.89 (s, 9H), 0.07 (s, 6H).

(7S,8R)-2-Acetoxymethyl-2,3-epoxy-7,8-isopropylidinedioxybicyclo [3.3.0] oct-2-en-*exo*-4-yl p-benzyloxybenzoate 166. Olefinic acetate **207** (4.1 mg, xxx mmol) was dissolved in CH2Cl2 at room temperature. Meta-chloroperoxybenzoic acid (4 mg, xxx mmol) was added and the mixture was allowed to stir 18 hrs. TLC indicated complete consumption of starting material so the mixture was evaparated under vacuum and purified over 10% deactivated silica gel with hexane:ether (4:1 → 1:1) to give 3.8 mg (xx%) of epoxide **166** which contained ~15% of m-CPBA derivatives as contaminants. ^{1}H NMR indicated the epoxide to be a 4:1 mixture of *exo* :*endo* isomers, but on a subsequent run gave the *exo* isomer exclusively as deterrmined by integration of the epoxide singlets. **Rf** = 0.19 hexane:EtOAc (4:1); ^{1}H NMR ($CDCl_3$) δ 7.97 (br d, 9.0 Hz, 2H), 7.45-7.30 (m, 5H), 7.00 (br d, 9.0 Hz, 2H), 5.14 (s, 1H), 5.12 (s, 1H), 4.82 (d, J=5.0 Hz, 1H), 4.73 (dd, J=4.9 Hz, 1H), 4.63 (d, J=14.8 Hz, 2H), 4.25 (d, J=8.0 Hz, 2H), 3.65 (s, 1H), 3.10 (ddd, J=7.8, 7.8, 7.8 Hz, 1H), 2.82 (d, J=8.0 Hz, 1H), 2.22 (m, 1H), 2.12 (s, 3H), 1.78 (m, 1H), 1.47 (s, 3H), 1.32 (s, 3H).

2,3-(Isopropylidenedioxy)-4,4-dihydroxybutanic Acid Lactone (169). Chlorobenzene diol **180** (10.0 g, 6.83 mmol) was dissolved in 10 ml of acetone and 3 ml. of 2,2-dimethoxypropane and stirred with 50 mg of para-toluenesulfonic acid at room temperature for 1 h whereupon it was neutralized with 1 mL of $NaHCO_3$ (sat) and evaparated to dryness. The crude oil was taken in 100 mL of ether and washed with water and then brine, dried over $MgSO_4$, filtered and evaparated to give 1.22 (6.58 mmol, 96 %) of clear oil. The crude mixture was taken in 100 mL of ethyl acetate.and cooled to -78 °C. Oxygen was bubbled through the mixture for 5 min. followed by ozone enriched oxygen for about 20 min. until the solution turned deep blue, and then oxygen again for 5 min. until

the mixture was again clear. Dimethyl sulfide (15 mL) was added to the solution and the entire reaction vessel was stored overnight at -20 °C. The mixture was then evaparated to dryness, taken in ether (100 mL) and washed with water and brine. The organic layers were dried over $MgSO_4$, filtered, and evaparated to give 1.02 g of crude hydroxylactone **169** which was sufficiently clean for the next step. Purification over 10 % deactivated silica gel with hexane:ethyl acetate (2:1) delivered a white solid, **mp** = 102 - 104 °C (lit. = 103 - 104 °C)[165] which matched those previously reported in the literature

2,3-(Isopropylidinedioxy)-4-hydroxy-4-(2-propyloxy)-butanoic acid (181) Method 1. Hydroxylactone **169** (1.01 g, 5.80 mmol) was dissolved in 2-propanol (100 mL) and stirred at room temprature with 100 mg of pyridinium p-toluenesulfonate for 1 week whereupon the mixture was neutralized with 1 mL of $NaHCO_3$ sat and solvent removed under vacuum. The residue was taken in ether (100 mL) and washed with water and then brine. The organic layers were dried over $MgSO_4$, filtred and evaparated to give 1.3 g of crude oil which was purified over 10% deactivated silica gel to give 0.514 g (2.38 mmol, 41%) of pure **181** whose spectral properties matched those previously published. (IR, NMR).[132] $[a]_D^{25}$ = -34.6°. **mp** = 36 °C. **Method 2.** Hydroxylactone **169** (1.03 mg, 5.92 mmol) was dissolved in 75 mL of acetone and 25 mL of 2-propanol and chilled in the refrigerator to 4 °C whereupon $HClO_4$ (70 %, 100 ml) was added and the mixture placed back in the refrigerator for 24 hours. The solution was then neutralized with 1 ml of $NaHCO_3$ sat. and worked up as in method 1 to deliver 0.460 g (2.13 mmol, 36%) of pure **181**. In both methods, the crude oil contained ~10% of acetal **182** (see table 3 for exact amounts) which appeared as a slightly less polar spot on TLC than **181**.

(7S,8R) - 4 - [(*tert*-Butyldimethylsilyl) oxy] - 2 - carbethoxy - 7,8 - (isopropylidenedioxy) bicyco [3.3.0] oct - 2 - en 190, 200. Xanthate **199** (13 mg, .0267 mmol) was dissolved in 1.5 mL of dry toluene in a 10 mL round bottom flask equipped with a condenser under argon. Tributyltin hydride (28.7 μL, 0.107 mmol) was added via syringe and the mixture brought to reflux. AIBN was added against a flow of argon and the mixture was cooled to room temperature at which time TLC indicated complete consumption of starting material. The mixture was condensed under vacuum and chromatographed over 10% deactivated silica gel with hexane : EtOAc (4 : 1) as eluant to give 8.6 mg (84.5%) of pure **200**. Xanthate **198** (57.0 mg, 0.12 mmol) was similarly converted to exo isomer **190** (33.9 mg, 76%). The two isomers were also prepared simultaneously as a mixture and then separated via chromatography with a slightly lower yield due to a difficult separation.

4-exo-190: R_f = 0.34, hexane : EtOAc (4 : 1); $[\alpha]_D^{25}$ = -82.6; **IR** (neat) 2920, 2845, 1715, 1625, 1465, 1370, 1260, 1050, 830, 775, 660 cm^{-1}; **^{1}H NMR** ($CDCl_3$) δ 6.52 (t, J=2.36 Hz, 1H), 4.63 (d, J=5.24 Hz, 1H), 4.58 (dd, J=4.82, 4.82 Hz, 1H), 4.48 (br s, 1H), 4.26 (q, J=7.12 Hz, 2H), 3.58 (br d, J=6.56 Hz, 1H), 2.86 (ddd, J=9.82, 7.73, 7.73 Hz, 1H), 2.20 (dd, J=14.31, 8.07, 1H), 1.49 (s, 3H), 1.35 (ddd, J=14.51, 10.16, 4.71 Hz, 1H), 1.32 (t, J=7.05 Hz, 3H), 1.30 (s, 3H), 0.89 (s, 9H), 0.10 (s, 3H), 0.08 (s, 3H); **^{13}C NMR** ($CDCl_3$) δ 164.87 (C), 142.21 (CH), 138.86 (C), 109.98 (C), 82.97 (CH), 81.60 (CH), 80.66 (CH), 60.66 (CH_2), 56.75 (CH), 49.99 (CH), 35.08 (CH_2), 27.12 (CH_3), 25.87 (CH_3, triple intensity), 24.79 (CH_3), 18.32 (C), 14.30 (CH_3), -4.63 (CH_3), -4.69 (CH_3); **MS** (70 eV m/e (rel. int.)) 398 (1, M^+), 383 (9), 341 (40), 313 (10), 255 (10), 237 (17), 224 (20), 209

(25), 86 (100), 75 (100); **HRMS,** calcd for $C_{20}H_{34}O_6Si$: 398.2125. Found: 398.2101.

4-endo 200: R_f = 0.41, hexane : EtOAc (4 : 1); $[\alpha]_D^{25}$ = -8.87; **IR** (neat) 2945, 2842, 1715, 1625, 1457, 1365, 1350, 1190, 1115, 1045, 852, 835, 770, 665 cm^{-1}; **^{1}H NMR** ($CDCl_3$) δ 6.49 (dd, J=1.85, 1.85 Hz, 1H), 4.90 (ddd, J=6.67, 2.91, 1.90 Hz, 1H), 4.73 (d, J=5.35 Hz, 1H), 4.58 (ddd, J=5.55, 2.77, 2.77 Hz, 1H), 4.24 (qd, J=7.22, 1.07 Hz, 2H), 3.28 - 3.17 (m, 2H), 1.92 - 1.89 (m, 2H), 1.50 (s, 3H), 1.31 (t, J=7.11, 3H) 1.29 (s, 3H), 0.89 (s, 9H), 0.09 (s, 3H), 0.08 (s, 3H); **^{13}C NMR** ($CDCl_3$) δ 164.79 (C), 145.91 (CH), 134.70 (C), 109.78 (C), 84.58 (CH), 81.70 (CH), 76.23 (CH), 60.56 (CH_2), 56.12 (CH), 45.97 (CH), 31.67 (CH_2), 27.03 (CH_3), 25.74 (CH_3, triple intensity), 24.64 (CH_3), 18.14 (C), 14.29 (CH_3), -4.95 (CH_3), -4.98 (CH_3); **MS** (70 eV m/e (rel. int.)) 383 (4), 382 (4, M^+), 367 (13), 337 (5), 335 (22), 307 (10), 267 (40), 233 (10), 193 (70), 147 (30), 129 (25); **HRMS**, calcd for $C_{20}H_{35}O_6Si_1$: 383.2254. Found: 383.2181.

(7S,8R) -4- [(*tert*-Butyldimethylsilyl) oxy] -2- carbethoxy -6-oxymethyldithiocarbonate -7,8- (isopropylidenedioxy) bicyco[3.3.0] oct -2 -en 190, 199, 202. A flame dried 10 mL round-bottom flask was charged with a stirring bar and NaH (11 mg, 0.30 mmol., 60% disp. in mineral oil) under an argon atmosphere. The NaH was rinsed once with dry THF (1 mL) and again covered with THF (0.5 mL) and cooled to 0 °C. The starting alcohol **150** (65 mg, 0.048 mmol.) was dried in a separate 10 mL round-bottom flask and added to the NaH suspension via cannula in dry THF (1.5 mL). The mixture was allowed to stir for 30 min. at which time dry CS_2 (0.5 mL) was added. The mixture was allowed to warm to room temperature and stir for 30 min. followed by addition of

MeI (1.0ml). TLC after 10 min. indicated complete consumption of starting material so the reaction was quenched with NH_4Cl sat. (2mL). The aqueous layer was extracted twice with ether and the combined organic layers dried over $MgSO_4$, filtered, and evaparated to give 22 mg. of crude oil which was chromatographed over 10% deactivated silica with 4 : 1 hexane / ether to give pure xanthate **190** (58 mg, 72%). Alcohol **189** (6.2 mg, 0.013 mmol) was converted similarly to xanthate **199** (5.2 mg. 70%). Alcohol **188** (10.2 mg, 0.021 mmol) gave cyclic ether **201** (9.0 mg, 88%) under these reaction conditions; however, xanthate **202** (21 mg, 52%) was obtained cleanly when alcohol **188** (33 mg, 0.083) was treated at -10 to -15°C.

4-endo, 6-endo, 202: R_f = 0.35 (hexane:Et_2O, 4:1); **^{1}H NMR** ($CDCl_3$) δ 6.68 (dd, J=216 Hz, 1H), 6,08 (dd, J=5.65, 2.01 Hz, 1H0, 4.95 (ddd, J=7.25, 1.99, 1.99 Hz, 1H), 4.85 (dd, J=5.56, 1.47 Hz, 1H), 4.63 (m, 1H), 4.27 (q, J=7.12 Hz, 2H), 3,49 (ddd, J=7.29, 7.29, 5.73 Hz, 1H), 3.33 (br d, J=7.48 Hz, 1H),2.45 (s, 3H), 1.51 (s, 3H), 1.32 (t, J=7.01 Hz, 3H), 1.30 (s, 3H), 0.87 (s, 9H), 0.10 (s, 3H), 0.09 (s, 3H).

4-endo, 6-exo, 199: R_f = 0.35 (hexane:Et_2O, 4:1); **^{1}H NMR** ($CDCl_3$) δ 6.51 (dd, J=2.0, 2.0 Hz, 1H), 5.85 (dd, J=7.2, 5.1 Hz, 1H), 4.99 (ddd, J=7.4, 1.9, 1.9 Hz, 1H), 4.85 (dd, J=5.1, 5.1 Hz, 1H), 4.63 (dd, J_1=5.1, 1.4 Hz, 1H), 0.06 (s, 3H), 4.23 (q, J=7.1 Hz, 2H), 3.45 (ddd, 1H, J_1=7.6, 7.6, 7.6 Hz, 1H), 3.33 (br d, J=7.4 Hz, 1H), 2.54 (s, 3H), 1.49 (s, 3H), 1.30 (t, J=7.0 Hz, 3H), 1.27 (s, 3H), 0.85 (s, 9H), 0.09 (s, 3H),.

4-exo, 6-endo, 198: R_f = 0.33 (hexane;Et_2O, 4:1); **^{1}H NMR** ($CDCl_3$), δ 6.53 (t, J=2.3 Hz, 1H), 5.41 (dd, J=9.0, 4.4 Hz, 1H), 4.76 (dd, J=4.7, 4.7 Hz, 1H),

4.69 (m, 2H), 4.24 (q, J=7.2 Hz, 2H), 3.61 (br d, J=8.1 Hz, 1H), 3.10 (dd, J=8.3, 8.3 Hz, 1H), 2.58 (s, 3H), 1.52 (s, 3H), 1.30 (t, J=7.1 Hz, 3H), 1.28 (s, 3H), 0.87 (s, 9H), 0.09 (s, 3H), 0.07 (s, 3H); **MS** (CI, m/e (rel int)) 469 (1), 443 (1), 429 (3), 413 (1), 399 (2), 391 (3), 383 (3), 371 (15), 357 (20), 325 (35), 323 (35), 251 (20), 233 (15), 207 (15), 193 (100), 133 (55), 85 (85).

201: R_f = 0.27 (hexane:Et_2O, 4:1); **IR** (neat) 2930, 2890, 2850, 1730, 1450, 1375, 1260, 1245, 1225, 1205, 1175, 1155, 1130, 1050, 1030, 905, 865, 830, 775 cm^{-1}; **^{1}H NMR** ($CDCl_3$) δ 4.66 (d, J=5.10 Hz, 1H), 4.61 (d, J=5.15 Hz, 1H), 4.41 (dd, J=1.10, 1.10 HZ, 1H), 4.19-4.07 (m, 3H), 2.76 (br d, J=7.01 Hz, 1H), 2.31 (dd, J=2.74, 1.53 Hz, 1H), 1.44 (s, 3H), 1.30 (s, 3H), 1.25 (t, J=7.13 Hz, 1H), 0.90 (s, 9H), 0.10 (s, 6H).

(7S,8R)-2-acetoxymethyl-4-[(*tert*)-butyldimethylsilyl)oxy]-7,8-isopropylidenedioxy-bicyco[3.3.0]oct-2-en 203, 205. Alcohol **152** (14 mg, 0.041 mmol) was dissolved in 0.3 mL of acetic anhydride and 0.3 mL of pyridine at RT and allowed to stand for 2 hours. The mixture was then diluted with 5 mL of ether and washed 2X with 1 mL of $CuSO_4$ (sat) solution to remove pyridine. The organic layer was dried over MgSO4, filtered and evaparated to give 14 mg of crude oil which was chromatographed over 10%deactivated flash silica gel (Hexane : Et_2O, 8 : 1 → 2 : 1) to give 10.9 mg (69%) of pure acetate **203**. The endo isomer (14 mg, 0.041 mmol) **204** was converted similarly to acetate **205** (13.4 mg, 84%).

Exo 203; R_f = 0.44 (Hexane:Et_2O, 4:1); $[\alpha]_D^{25}$ = -31.3; **IR** (neat) 2957, 2923, 2857, 1745, 1657, 1472, 1462, 1370, 1248, 1159, 1058, 835, 776, 668 cm^{-1}; **^{1}NMR** ($CDCl_3$) δ 5.55 (br s, 1H), 4.75 (d, J=14.31 Hz, 1H), 4.66 (d, J=14.36

Hz, 1H), 4.60 (dd, J=5.04, 5.04 Hz, 1H), 4.50 (d, J=5.16 Hz, 1H), 4.40 (br s, 1H), 3.34 (br d, J=6.87 Hz, 1H), 2.84 (ddd, J=8.20, 8.20, 8.20 Hz, 1H), 2.20 (dd, J=14.31, 8.07 Hz, 1H), 2.10 (s, 3H), 1.48 (s, 3H), 1.38 (ddd, J=14.54, 9.78, 4.86 Hz, 1H), 1.30 (s, 3H), 0.89 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H); **^{13}C NMR** ($CDCl_3$) δ 170.63 (C), 142.19 (C), 129.31 (CH), 110.14 (C), 82.07 (CH), 81.92 (CH), 81.35 (CH), 61.65 (CH_2), 57.62 (CH), 50.93 (CH), 35.32 (CH_2), 27.18 (CH_3), 25.96 (CH_3, triple intensity), 24.86 (CH_3), 20.88 (CH_3), 18.37 (C), -4.55 (C), -4.56 (C); **MS** (CI, m/e (rel. int.)) 383 (4), 382 (1, M^+), 323, (65), 265 (40), 251 (50), 209 (15), 193 (100), 159 (20), 151 (75), 133 (40), 117 (50); NRMS, calcd for $C_{20}H_{35}O_5Si$: 383.2254. Found: 383.2286.

Endo 205; R_f = 0.46 (Hexane:Et_2O; 4:1); **$[\alpha]_D^{25}$** = -2.3; **IR** (neat) 2952, 2932, 2856, 1745, 1472. 1463, 1370, 1248, 1216, 1164, 1090, 1057, 869, 837, 776, 670 cm^{-1}; **^{1}NMR** ($CDCl_3$) δ 5.52 (dd, J=1.57, 1.57 Hz, 1H), 4.83 (ddd, J=7.11, 1.62, 1.62 Hz, 1H), 4.73 (dd, J=13.88, 1.06 Hz, 1H), 4.64 (dd, J=13.83, 1.12 Hz, 1H), 4.62 (m, 1H), 4.56 (dd, J=5.35, 0.99 Hz, 1H), 3.18 (dddd, J=8.77, 7.52, 7.52, 7.52 Hz, 1H), 2.99 (br d, J=7.14 Hz, 1H), 2.09 (s, 3H), 2.01-1.82 (m, 2H), 1.47 (s, 3H), 1.30 (s, 3H), 0.89 (s, 9H), 0.07 (s, 6H); **^{13}NMR** ($CDCl_3$) δ 170.65 (C), 138.30 (C), 132.83 (CH), 109.95 (C), 83.11 (CH), 82.33 (CH), 76.30 (CH), 61.38 (CH_2), 57.10 (CH), 46.37 (CH), 31.83 (CH_2), 27.11 (CH_3), 25.81 (CH_3, triple intensity), 24.68 (CH_3), 20.90 (CH_3), 18.18 (C), -4.85 (CH_3), -4.91 (CH_3); **MS** (CI, m/e (rel, int.)) 383 (25), 382 (10), 381 (32), 367 (12), 341 (10), 331 (32), 323 (95), 283 (10), 267 (50), 209 (15), 193 (100), 151 (12), 133 (40), 117 (40); **HRMS,** calcd for $C_{20}H_{35}O_5Si$: 383.2254. Found: 383.2256.

(7S,8R)-2-acetoxymethyl-7,8-isopropylidenedioxy-bicyco[3.3.0]oct-2-en-4-ol 206, 208 *Exo* TBDMS protected alcohol **203** (10.6 mg, 0.0312 mmol) was dissolved in 1 mL of dry THF under argon at room temprrature and the mixture charged with TBAF·$3H_2O$ (19.7 mg, 0.062 mmol) and the mixture stirred for 1 hr at which time TLC indicated complete consumption of starting material. The reaction was quenched with 0.5 mL of NH_4Cl sat. and diluted with 0.5 mL of water. The aqueous layer was extracted 4X with 4 mL of Et_2O. The combined organic layers were dried over MgSO4, filtered and evaparated to give 12.4 mg of crude oil which was chromatographed over 10% deactivated silica gel with hexane: EtOAC (4:1 → 1:2) to give 6.0 mg (81%) of pure alcohol **208**. The *endo* TBDMS protected alcohol **205** (13.2 mg, 0.035 mmol) was deprotected similarly to give 7.6 mg (82%) of alcohol **206**.

Endo 206: $\mathbf{R_f}$ = 0.32 (hexane:EtOAc, 2:1); **^{1}H NMR** ($CDCl_3$) δ 5.61 (dd, J=1.8, 1.8 Hz, 1H), 4.90 (br d, J=7.05 Hz, 1H), 4.75 (ddd, J=14.1, 1.2, 1.2 Hz, 1H), 4.70-4.61 (m, 2H), 4.59 (dd, 5.4, 1.3 Hz, 1H), 3.25 (dddd, J=9.26, 7.45, 7.45, 7.45 Hz, 1H), 3.04 (br d, J=7.2 Hz, 1H), 2.10 (s, 3H), 2.03-1.82 (m, 2H), 1.67 (br s, 1H), 1.47 (s, 3H), 1.30 (s, 3H).

6-Exo 208: $\mathbf{R_f}$ = 0.28 (hexane:EtOAc, 2:1); **^{1}H NMR** ($CDCl_3$) δ 5.69 (br s, 1H), 4.78 (dd, J=14.5, 0.8 Hz, 1H), 4.68 (dd, J=14.5, 0.9 Hz, 1H), 4.62 (dd, J=4.9, 4.9 Hz, 1H), 4.52 (d, J=5.2 Hz, 1H), 4.41 (br s, 1H), 3.34 (br d, J=6.43 Hz, 1H), 2.93 (ddd, J=9.79, 7.42, 7.42 Hz, 1H), 2.25 (dd, J=7.95, 14.37 Hz, 1H), 2.12 (s, 3H), 1.62 (br s, 1H), 1.47 (s, 3H), 1.37 (ddd, 14.6, 10.0, 4.8), 1.30 (s, 3H).

(7S,8R)-2-acetoxymethyl-7,8-isopropylidenedioxybicyco-[3.3.0]oct-2-en0-*exo*-4-yl p-benzyloxybenzoate 207. Alcohol **206** (7.6 mg, 0.028 mmol)

was dissolved in dry THF under argon. To the mixture was added triphenylphosphene (14.9 mg, 0.058 mmol) and 4-benzyloxy benzoic acid (12.9 mg, 0.058 mmol) against a flow of argon followed by diethylazodicarboxylate (8.97 μL, 0.058 mmol) via syringe. The deep yellow color from DEAD dissappeared after a few seconds and TLC analysis indicated that the reaction was complete after 5 min. The mixture was evaparated to dryness under vacuum and the residue chromatographed over 10% deactivated flash silica with hexane : Et_2O (8:1 → 1:1) to obtain 6.4 mg (54.6%) of clear oil which was rechromatographed similarly to remove a slight contaminant from the DEAD reagent to give 6.4 mg (47.2%) of clear benzoate ester **207**. $\mathbf{R_f}$ = 0.15, hexane : EtOAc (4 : 1); $[\alpha]_D^{25}$ = -45.69; **IR** (neat) 3064, 3033, 2983, 2932, 1744, 1707, 1605, 1455, 1371, 1248, 1167, 1095, 1057, 951, 848, 771, 738, 698 cm^{-1}; **^{1}H NMR** ($CDCl_3$) δ 7.97 (ddd,J=9.01, 2.64, 2.09 Hz, 2H), 7.44 - 7.32 (m, 5H), 6.98 (ddd, J=9.01, 2.66, 2.14 Hz, 2H), 5.78 (br s, 1H), 5.47 (s, 1H), 5.12 (s, 2H), 4.82 (ddd, J=14.8, 1.0, 1.0 Hz, 1H), 4.71 (ddd, J=14.9, 1.0, 1.0 Hz, 1H), 4.66 (dd, 4.68, 4.68. Hz, 1H), 4.55 (d, J=5.09, 1H), 3.38 (br d, J=6.88 Hz, 1H), 3.13 (ddd, 9.54, 7.74, 7.74 Hz, 1H), 2.37 (dd, J=14.78, 8.09 Hz, 1H), 2.12 (s, 3H), 1.55 (ddd, J=14.85, 9.86, 4.84 Hz, 1H), 1.47 (s, 3H), 1.31 (s, 3H); **^{13}C NMR** ($CDCl_3$) δ 170.52 (C), 166.13 (C), 162.49 (C), 146.30 (C), 136.20 (C), 131.66 (CH, double intensity), 128.66 (CH, double intensity), 128.19 (CH), 127.46 (CH, double intensity), 125.01 (CH), 129.91 (C), 114.42 (CH, double intensity), 110.28 (C), 82.81 (CH), 82.08 (CH), 81.70 (CH), 70.07 (CH_2), 61.39 (CH_2), 58.06 (CH), 47.51 (CH), 35.06 (CH_2), 27.13 (CH_3), 24.76 (CH_3), 20.83 (CH_3); **MS** (CI, m/e, (rel. int.)) 479 (1, M^+), 463 (2), 419 (7), 361 (3), 251 (80), 229 (50), 211 (40), 193

(100), 151 (30), 133 (40), 121 (20), 105 (10), 91 (90); **HRMS**, calad for $C_{20}H_{34}O_6Si$: 479.2070. Found: 479.2063.

(7S,8R)-2-acetoxymethyl-7,8-dihydroxybicyco-[3.3.0]oct-2-en-*exo*-4-yl p-benzyloxybenzoate 211. Acetonide **207** (6.2 mg, 0.013 mmol), was dissolved in 0.5 mL of solvent containing THF, acetic acid, and water (1:1:1). and the mixture heated to 55-60 °C for 3 hrs whereupon TLC indicated complete consumption of starting material. The material was then evaparated to dryness and then triturated 2X with toluene to remove residual solvents. The crude mixture was then filtered through a short column (0.4 cm X 1.5 cm) of 10% deactivated silica gel eluting first with hexane:EtOAc (4:1) to remove less polar impurities and then EtOAc to give 3.3 mg (58%) of pure diol **211** as a white solid. R_f = 0.21 (hexane:EtOAc, 1:4), **^{1}H NMR** ($CDCl_3$) d 7.98 (ddd,8.96 2.40, 2.40 Hz, 2H), 7.45-7.30 (m, 5H), 6.98 (ddd, J=8.97, 2.38, 2.38, Hz, 2H), 5.77 (s, 1H), 5.54 (s, 1H), 5.12 (s, 2H), 4.86 (d, J=14.24 Hz, 1H), 4.70 (d, J=14.21 Hz, 1H), 4.17 (s, 1H), 3.91 (s, 1H), 3.21 (br s, 1H), 3.06 (ddd, J=8.58, 6.92, 6.92 Hz, 1H), 2.78 (s, 1H), 2.29 (br s, 1H), 2.23 (dd, J=8.62, 5.04 Hz, 1H), 2.13 (s, 3H), 1.81 (ddd, J=13.63, 5.63, 5.63 Hz, 1H).

Specionin Acetate 217. A small sample of epoxide 166 (2.5 mg, xxx mmol) which was contaminated with 60% m-chlorobenzoic acid and m-chloroperoxybenzoic acid was dissolved in 1 mL of absolute ethanol and 5 drops of distilled water and the mixture charged with ~1mg of 10% palladium on carbon and the mixture hydrogenated under 40 psi of H_2 for ~15 hrs. The mixture was then filtered through celite and evaparated to give a crude product which was filtered through a small (4 x 10 cm) column of 10% deactivated silica gel with

hexane:EtOAc (1:1 then 0:1) to obtain 0.7 mg of an impure compound with an Rf (~0.05 with hexane:EtOAc (1:1)) which clearly was much lower than the starting material. ^{1}H NMR clearly indicates loss of the benzyl methylene peak at 5.12 ppm and the aromatic benzyl protons at 7.45 - 7.30 ppm suggesting successful removal of the benzyl group. More interrestingly, the acetonide singlets at 1.47 and 1.32 ppm were also missing suggesting acetonide removal to give triol **216**.

The triol 216 was dissolved in 0.5 mL of absolute EtOH at RT and stirred in the presence of ~2 mg of $NaIO_4$ for 16 hrs. A small crystal of p-TsOH was then added and the mixture stirred an additional 24 hrs. The reaction was quenched with 2 drops of $NaHCO_3$ sat., diluted with 0.25 mL of distilled water, and the aqueous phase extracted 3x with EtOAc. The combined organic layers were dried over MgSO4, filtered and evaparated to give ~150 mg of crude material which was very impure, but gave a 400 Mz ^{1}H NMR spectrum which contained peaks matching some from an authentic sample of specionin acetate.

(7S,8R)-2-carbethoxy-7,8-isopropylidinedioxy-6-oxobicyclo-[3.3.0]-oct-2-en-*exo*-4-yl p-benzyloxybenzoate 218. Method 1. Alcohol **228** (17 mg, 0.060 mmol) was dissolved in 2 mL of dry CH_2Cl_2 under argon and the flask charged with p-benzyloxybenzoic acid (34 mg, 0.15 mmol), 1,3-dicyclohexylcarbodiimide (31 mg, 0.0446 mmol), and DMAP (1 crystal), and the mixture stirred at room temperature for 6 hours at which time TLC indicated incomplete reaction. The solvent was then removed under vacuum and the residue chromatographed over 10% deactivated silica gel with Hexane : EtOAc (5:1 $\rightarrow$ 1:1) as eluent to obtain 21.7 mg (73%) of ester which is slightly contaminated with a DCC derivative.. **Method 2**. Alcohol **145** (7.0 mg, 0.025

mmol) was dissolved in THF (0.5 mL) and the flask charced with p-benzyloxybenzoic acid (11.3 mg, 0.050 mmol), triphenylphosphene (13.0 mg, 0.050 mmol), and diethylazodicarboxylate (7.8 μL, 0.050 mmol) at RT and TCL indicated complete reaction after 1 hr at RT. The mixture was evaparated under vacuum and chromatrographed over 10% deactivated silica gel (hexane:EtOAc, 8:1 → 2:1) to obtain 9.4 mg (29%) of clear oil. $\mathbf{R_f}$ = 0.30 (hexane:Et_2O, 4:1); **^{1}H NMR** ($CDCl_3$) δ 7.95 (ddd, J=8.98, 2.33, 2.33 Hz, 2H), 7.45-7.32 (m, 5H), 6.98 (ddd, 8.97, 2.35, 2.35 Hz, 2H), 6.90 (dd, J=2.42, 2.42 Hz, 1H), 5.89 (br s, 1H), 5.12 (s, 2H), 5.06 (d, J=5.10 Hz, 1H) 4.29 (qd, 7.17, 1.48 Hz, 2H), 4.24, (d, J=5.12, 1H), 4.12-4.06 (m, 1H) 3.46 (d, J=7.1 Hz, 1H), 1.45 (s, 3H), 1.38 (s, 2H), 1.34 (t, J=7.14 Hz, 3H).

(7S,8R)-2-carbethoxy-7,8-isopropylidenedioxy-bicyco[3.3.0] oct-2-en-*exo*-4-yl p-benzyloxybenzoate 225. Method 1. Alcohol **228** (6.0 mg, 0.022 mmol) was dissolved in 1 mL of dry CH_2Cl_2 under argon and the flask charged with p-benzyloxybenzoic acid (7.7 mg, 0.0336 mmol), 1,3-dicyclohexylcarbodiimide (9.1 mg, 0.0446 mmol), DMAP (1 crystal), and p-TsOH (1 crystal) and the mixture stirred at room temperature for 24 hours at which time TLC indicated incomplete reaction. Extra DCC (4.5 mg) was added and TLC indicated complete reaction after 24 hours. The solvent was then removed under vacuum and the residue chromatographed on a prep silica plate with Hexane : EtOAc (5:1) as eluent to obtain 4.4 mg (41%) of pure ester. **Method 2**. Alcohol **229** (4.6 mg, 0.017 mmol) was dissolved in THF (0.5 mL) and the flask charced with p-benzyloxybenzoic acid (7.8 mg, 0.034 mmol), triphenylphosphene (9.0 mg, 0.034 mmol), and diethylazodicarboxylate (6.0 mg, 0.034 mmol) at RT and TCL indicated complete reaction after 1 hr at RT. The mixture was evaparated under

vacuum and chromatrographed over 10% deactivated silica gel (hexane:ether, 8:1 → 2:1) to obtain 2.4 mg (29%) of clear oil. **Method 3**. Xanthate **227** (12 mg, 0.021 mmol) was dissolved in toluene under argon and brought to reflux. A crystal of AIBN was added and the reaction was shown to be complete after 10 min. by TLC. The mixture was evaparated under vacuum and separated over 10% deactivated silica gel (hexane:ether, 8:1 → 2:1) to obtain 6.5 mg (65%) of clear oil. $\mathbf{R_f}$ = 0.37 (hexane:ether, 4:1); **^{1}H NMR** ($CDCl_3$) δ 7.98 (ddd, J=8.99, 2.09, 2.09 Hz, 2H), 7.45 - 7.30 (m, 5H), 6.98 (ddd, J=8.89, 2.01, 2.01 Hz, 2H), 6.72 (dd, J=2.33, 2.33 Hz, 1H), 5.58 (dd, J=2.1, 2.1 Hz, 1H), 5.12 (s, 2H), 4.72 (d, J=5.14 Hz, 1H), 4.63 (dd, J=4.86 Hz, 1H), 4.28 (qd, J=7.18, 1.22 Hz, 2H), 3.62 (br d, J=6.80 Hz, 1H), 3.15 (ddd, J=9.96, 7.50, 7.50 Hz, 1H), 2.38 (dd, J=14.51, 8.12 Hz, 1H), 1.49 (s, 3H), 1.33 (t, J=7.23 Hz, 3H), 1.31 (s, 3H).

(7S,8R)-2-carbethoxy-*exo*-6-hydroxy-7,8-isopropylidene-dioxybicyco[3.3.0]oct2-en-*exo*-4-yl p-benzyloxybenzoate 226. Ketone **218** (19 mg, 0.039) was dissolved in EtOH (1mL) under argon and cooled to -30°C. Sodium borohydride (6 mg) was added against a flow of argon and TLC indicated that the reaction was complete after 1 hr. The reaction was quenched with 1 mL of NH_4Cl (sat), diluted with 2 mL of water, and extracted 4X with Et_2O. The combined organic layers were dried over MgSO4, filtered, and evaparated. The crude mixture was chromatographed over 10% deactivated silica gel (hexane:EtOAc, 2:1 → 1:1) to give 18 mg (93%) of clear oil **226** which still contains a slight amount of DCC derivative. $\mathbf{R_f}$ = 0.15 (hexane:EtOAc, 4:1); **^{1}H NMR** ($CDCl_3$) d 7.97 (ddd, J=8.87, 2.04, 2.04 Hz, 2H), 7.45-2.80 (m, 5H), 6.99 (ddd, J=9.02, 2.11, 2.11 Hz, 2H), 6.77 (dd, J=2.51, 2.51 Hz, 1H), 5.81 (br s, 1H), 5.12 (s, 2H), 4.74 (d, J=5.21 Hz, 1H), 4.56 (dd, J=4.95 Hz, 1H), 4.27 (qd, J=7.14,

1.12 Hz, 2H), 3.85 (dd, J=8.10, 4.51 Hz, 1H), 3.62 (br d, J=7.4 Hz, 1H), 2.96 (d, J=7.68 Hz, 1H), 1.54 (s, 3H), 1.35 (s, 3H), 1.33 (t, J=7.15, 3H).

(7S,8R)-2-carbethoxy-*exo*-6-oxymethyldithiocarbonate-7,8-(isopropylidenedioxy)bicyco [3.3.0] oct-2-en-*exo*-4-yl p-benzyloxy-benzoate 227. A flame dried 10 mL round-bottom flask was charged with a stirring bar and NaH (5 mg, 60% disp. in mineral oil) under an argon atmosphere. The NaH was rinsed once with dry THF (1 mL) and again covered with THF (0.5 mL) and cooled to 0 ^{o}C. The starting alcohol **226** (11.8 mg, 0.024 mmol.) was dried in a separate 10 mL round-bottom flask and added to the NaH suspension via cannula in dry THF (1.5 mL). The mixture was allowed to stir for 30 min. at which time dry CS_2 (0.3 mL) was added. The mixture was allowed to warm to room temperature and stir for 30 min. followed by addition of MeI (0.5 ml). TLC after 10 min. indicated complete consumption of starting material so the reaction was quenched with NH_4Cl sat. (2mL). The aqueous layer was extracted twice with ether and the combined organic layers dried over $MgSO_4$, filtered, and evaparated to give 14.2 mg. of crude oil **227** (72%) which was carried forward without purification. $\mathbf{R_f}$ = 0.61 (hexane:EtOAC, 4:1), **^{1}H NMR** ($CDCl_3$) δ 7.97 (ddd, J=8.84, 1.93, 1.93 Hz, 2H), 7.50-7.30 (m, 5H), 6.99 (ddd, J=8.89, 2.05, 2.05 Hz, 2H), 6.80 (dd, J=2.53, 2.53 Hz, 1H), 5.77 (br s, 1H), 5.59 (dd, J=8.82, 4.43 Hz, 1H), 5.13 (s, 2H), 4.87 (dd, J=4.73, 4.73 Hz, 1H), 4.80 (d, J=4.91 Hz, 1H), 4.28 (q, J=7.14 Hz, 2H), 3.70 (br d, J=6.82 Hz, 1H), 3.45 (dd, J=7.32, 7.32 Hz, 1H), 2.62 (s, 2H), 1.55 (s, 3H), 1.33 (t, J=7.12 Hz, 3H), 1.32 (s, 3H).

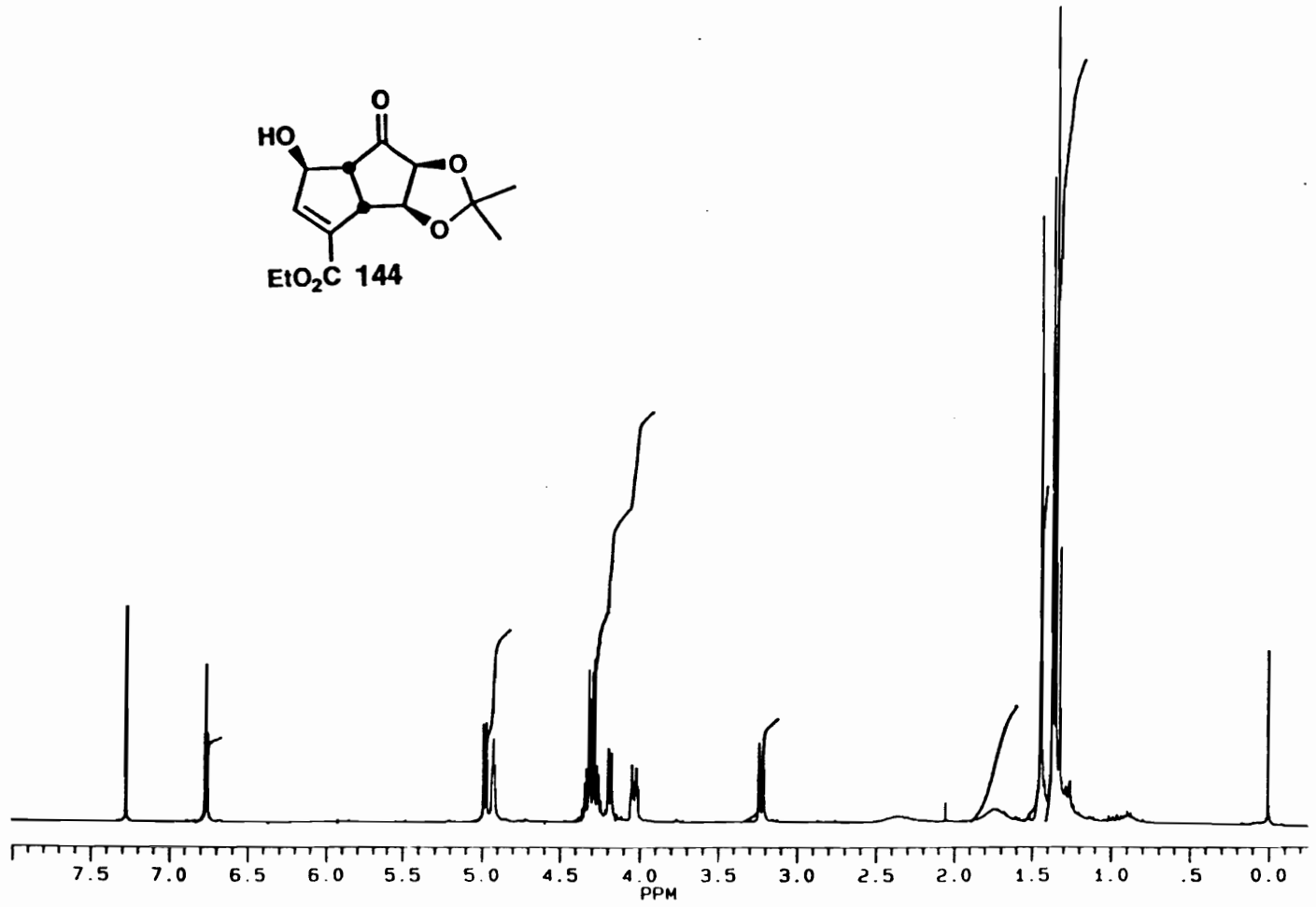
(7S,8R)-2-carbethoxy-7,8-isopropylidenedioxy-bicyco[3.3.0] oct-2-en-4-ol 228, 229. Protected alcohol **190** (11 mg, 0.029 mmol) was dissolved in THF,

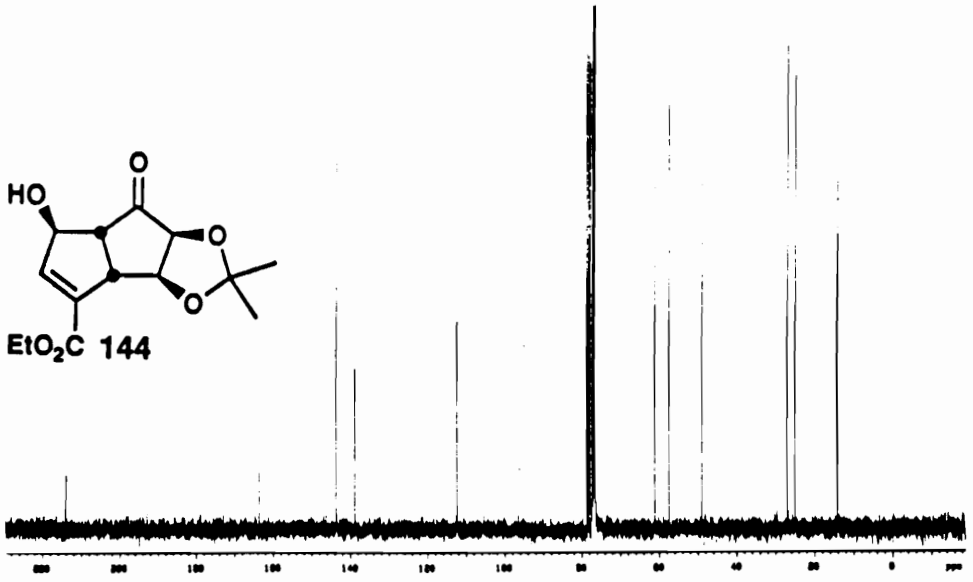
cooled to -40°C, and treated with TBAF. $3H_2O$. The mixture was stirred for 10 min slowly warmed to RT, and then stirred 1 hr. The mixture was quenched with NH_4Cl aq, diluted with 1 mL of water, and extracted 3X with EtOAc. The organic layer was dried over $MgSO_4$, filtered and evaparated to yield 10.5 mg of crude oil which was chromatographed over 10% deactivated silica gel with hexane/EtOAc (2/1) to give 6.5 mg (85.1%) of pure exo alcohol **228**. The endo protected alcohol **229** (7.0 mg, 0.018 mmol) was deprotected similarly to endo alcohol **229** (4.6 mg, 92%).

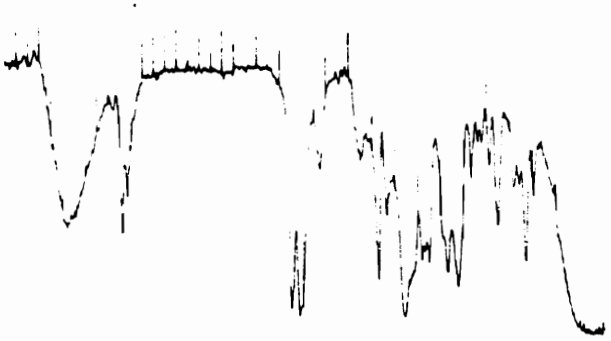
exo-228: $\mathbf{R_f}$ = 0.28 (Hexane:EtOAc, 2:1); **^{1}H NMR** ($CDCl_3$) δ 6.64 (dd, J=2.44, 2.44 Hz, 1H), 4.66 (d, J=5.16 Hz, 1H), 4.58 (dd, J=4.88, 4.88 Hz, 1H), 4.53 (br s, 1H), 4.27 (qd, J=7.1, 1.4 Hz, 2H), 3.57 (br d, J=6.92 Hz, 1H), 2.96 (ddd, J=10.20, 7.37, 7.37 Hz, 1H), 2.25 (dd, J=14.4, 7.95 Hz, 1H), 1.48 (s, 3H), 1.36 (ddd, J=14.9, 10.2, 4.7 Hz, 1H), 1.33 (t, J=7.1, 3H), 1.30 (s, 3H); **MS** (CI, m/e, (rel. int.)) 269 (10, M^++1), 253 (45), 251 (35), 233 (10), 211 (100), 193 (70), 177 (12), 165 (90), 147 (35), 137 (15), 121 (30), 119 (25), 108 (20), 91 (55), 79 (35).

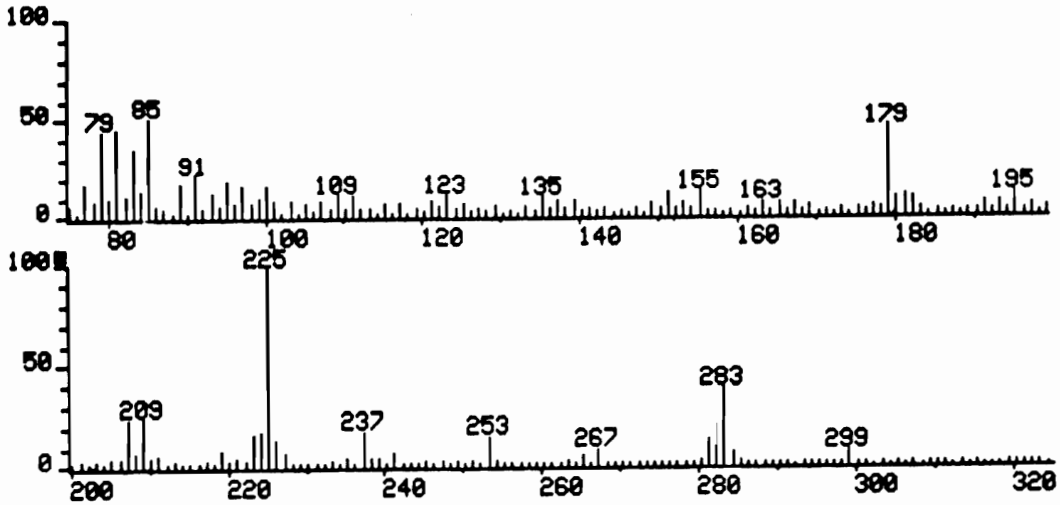
endo-229: $\mathbf{R_f}$ = 0.35 (Hexane:EtOAc, 2:1) **^{1}H NMR** ($CDCl_3$) δ 6.57 (dd, J=2.07 Hz, 1H), 5.00 (br s, 1H), 4.77(d, J=5.21 Hz, 1H), 4.63 (dd, J=4.84, 4.84 Hz, 1H), 4.25 (q, J=7.05, 2H), 3.36 - 3.23 (m, 2H), 1.99 (dd, J=14.41, 6.82 Hz, 1H), 1.87 - 1.76 (m, 2H), 1.48 (s, 3H), 1.31 (t, J=7.12 Hz, 3H), 1.30 (s, 3H).

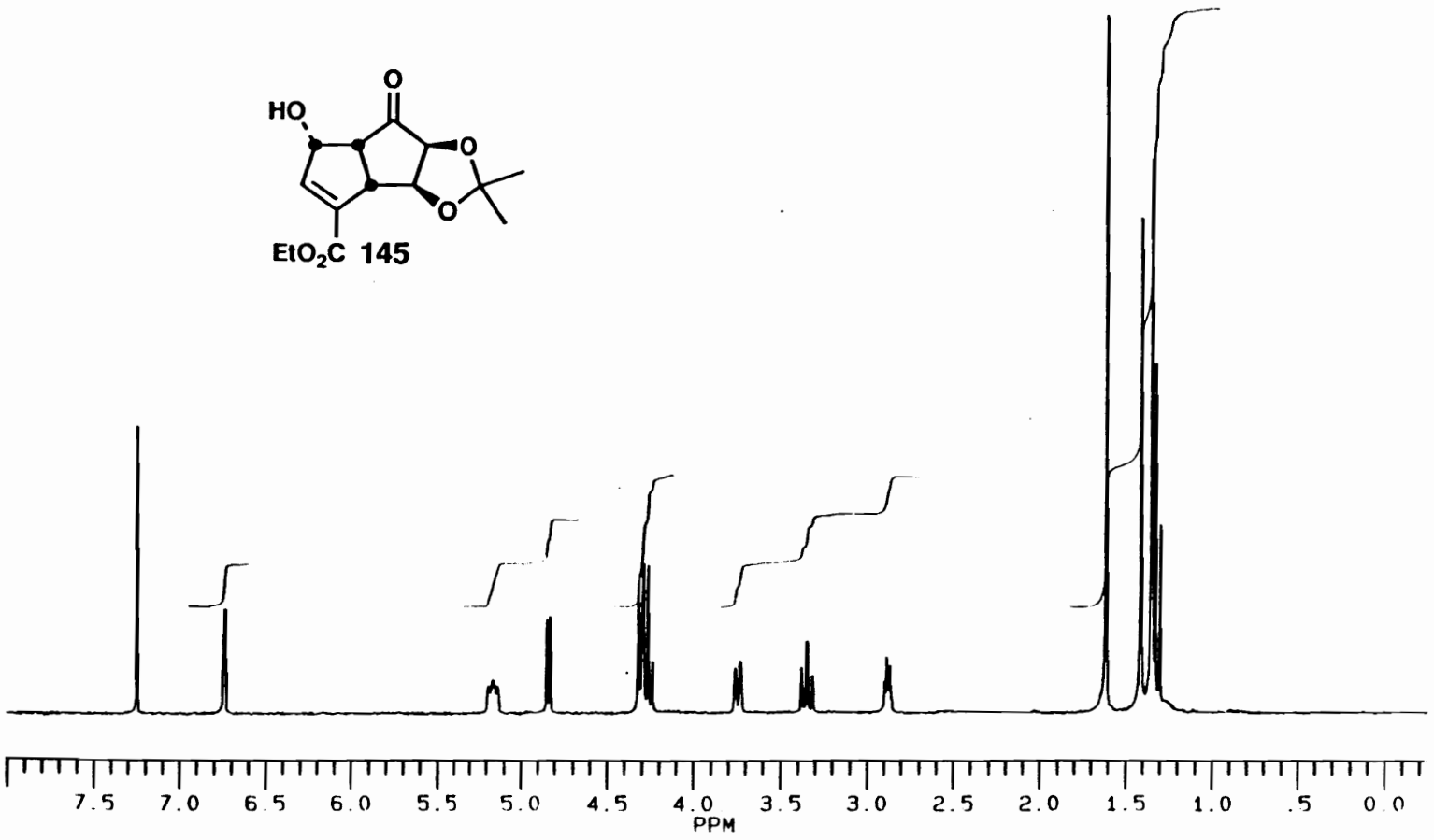
E. Spectra

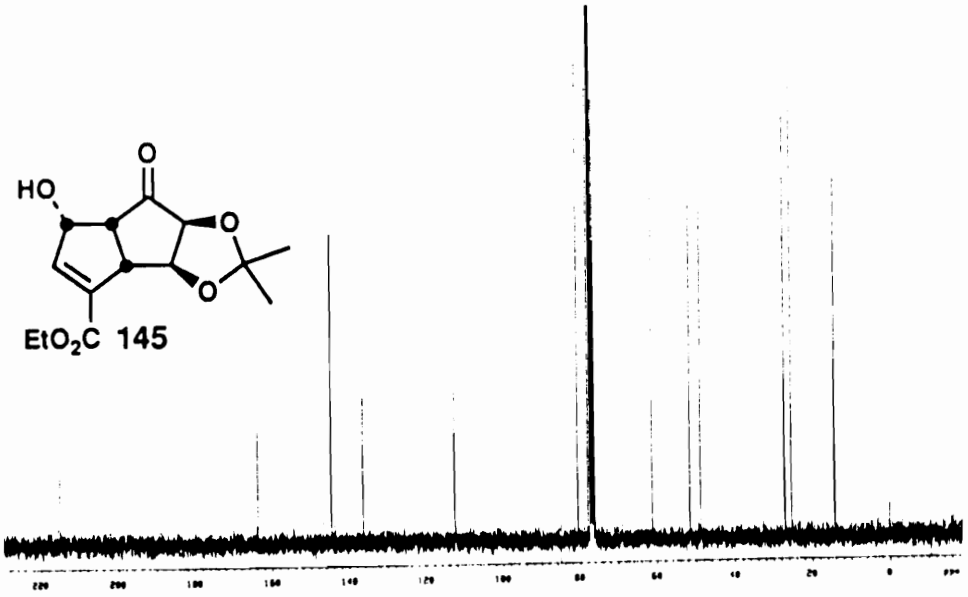

HO
O
O
O
EtO2C 144
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
.5
0.0
PPM

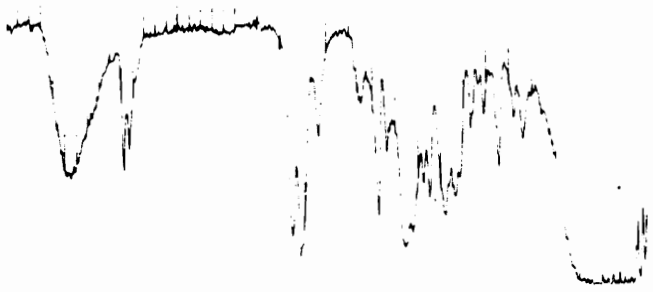

HO
O
O
O
EtO2C 144

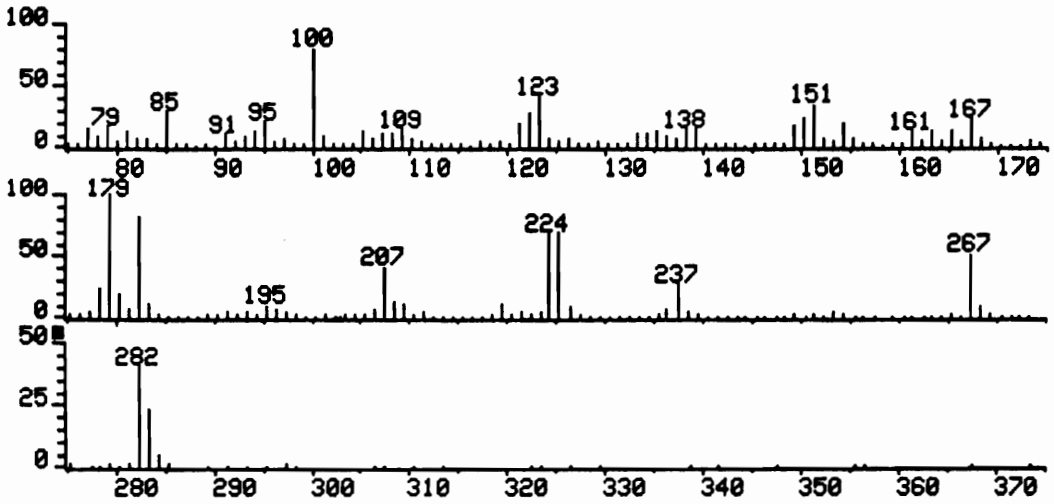


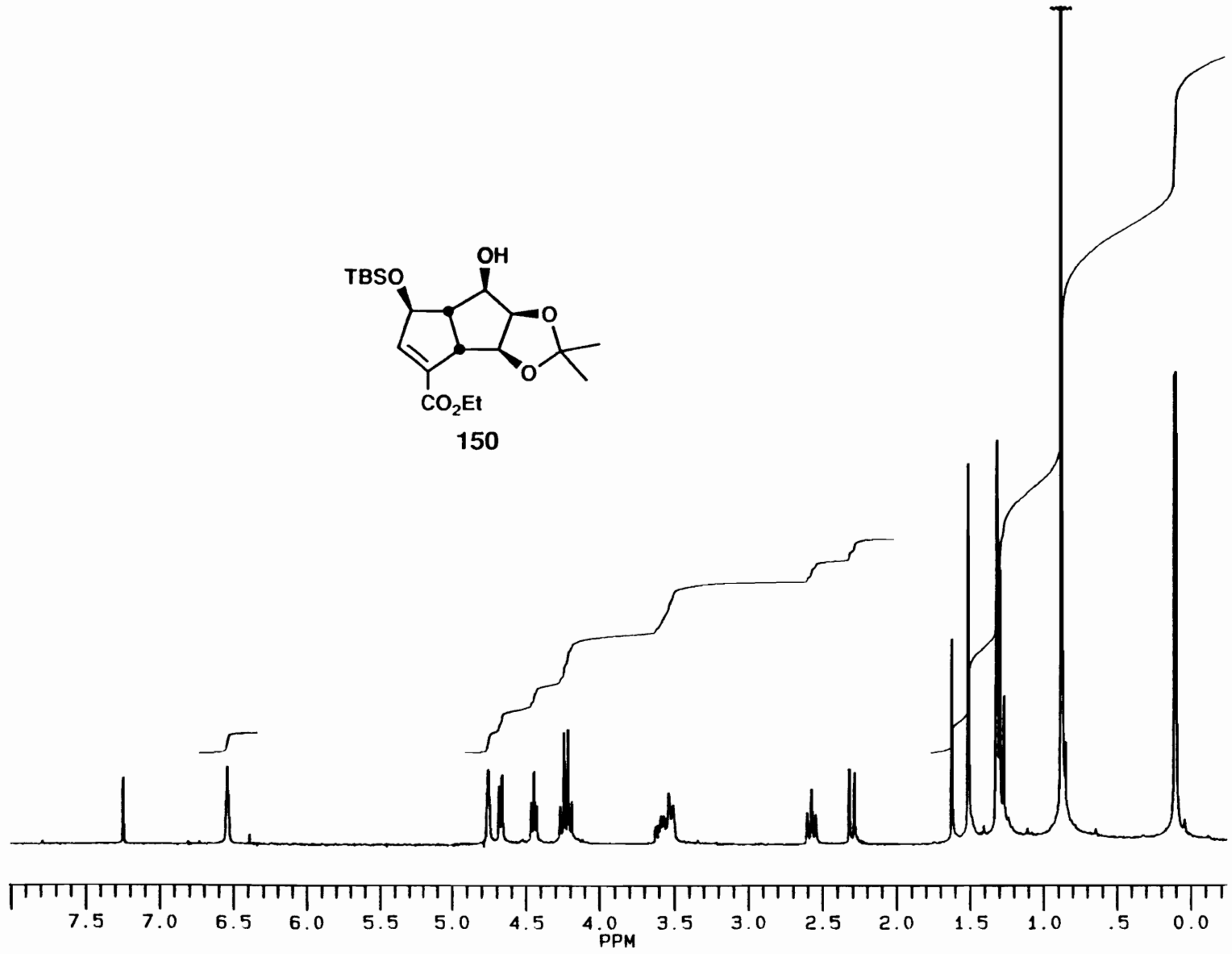

100
50
0
79
85
91
109
123
135
155
163
179
195
80
100
120
140
160
180
225
209
237
253
267
283
299
200
220
240
260
280
300
320

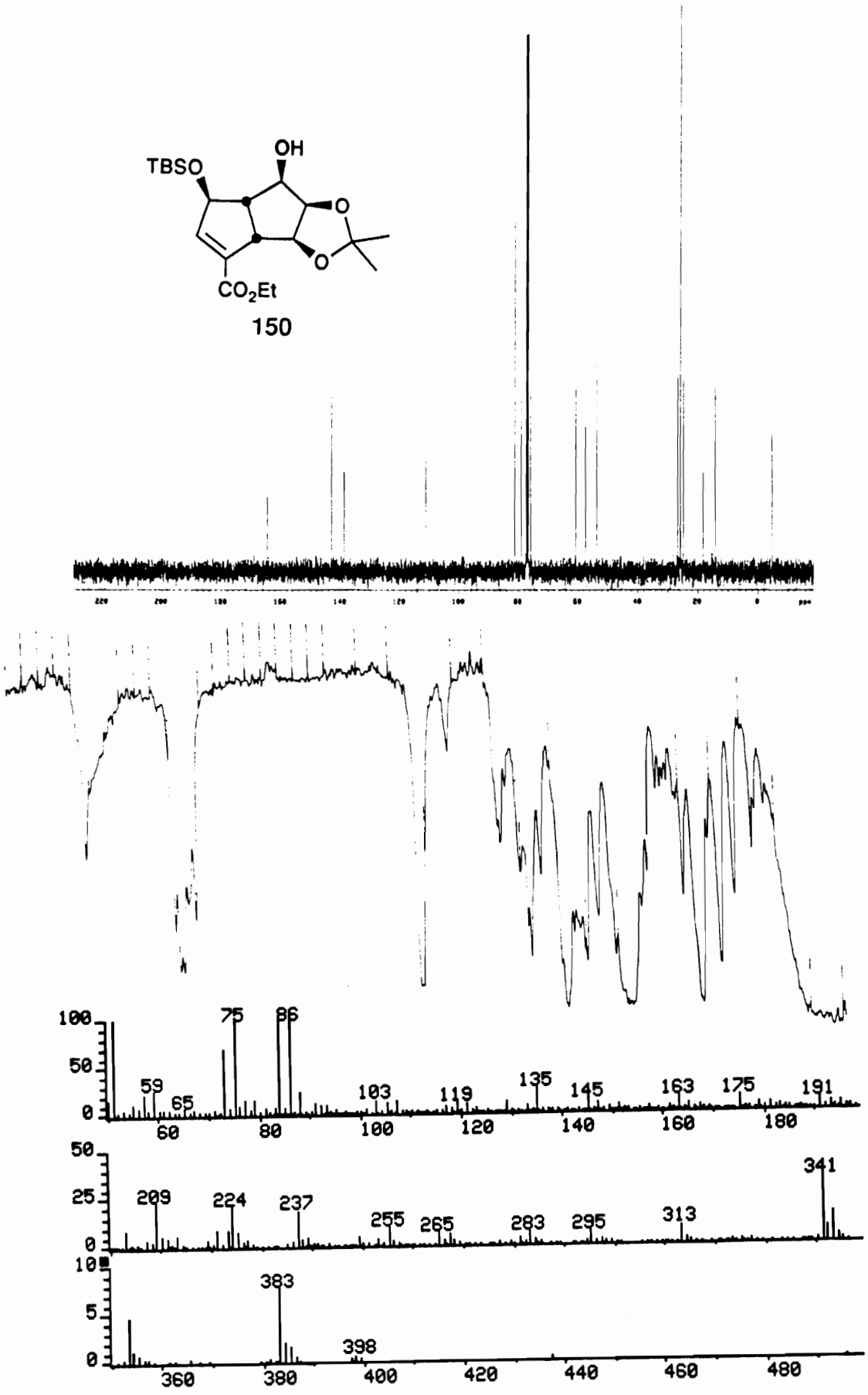

HO
O
O
O
EtO2C 145
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
.5
0.0
PPM

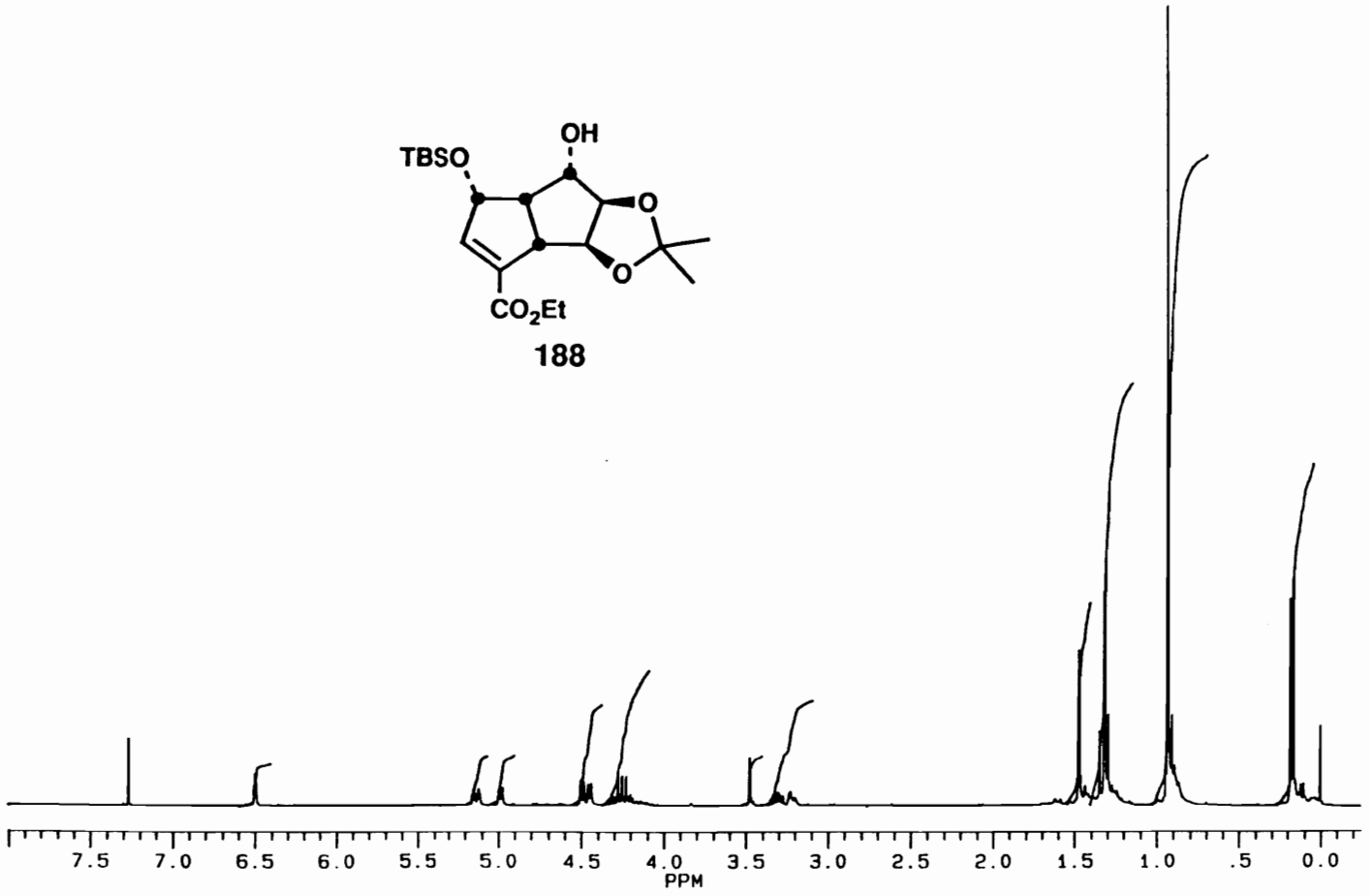

HO
O
O
O
EtO2C 145

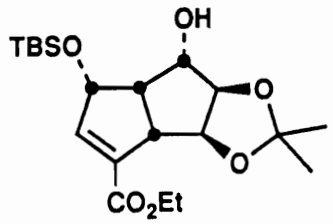



100
50
0
79
85
91
95
100
109
123
138
151
161
167
80
90
100
110
120
130
140
150
160
170
100
50
0
179
195
207
224
237
267
50
25
0
282
280
290
300
310
320
330
340
350
360
370

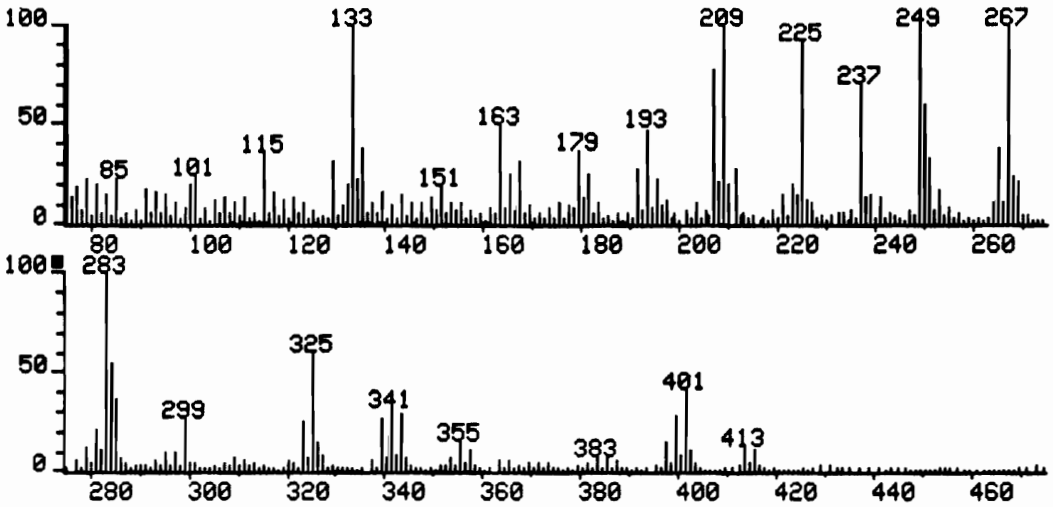

TBSO
OH
O
O
CO2Et
150
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
.5
0.0
PPM

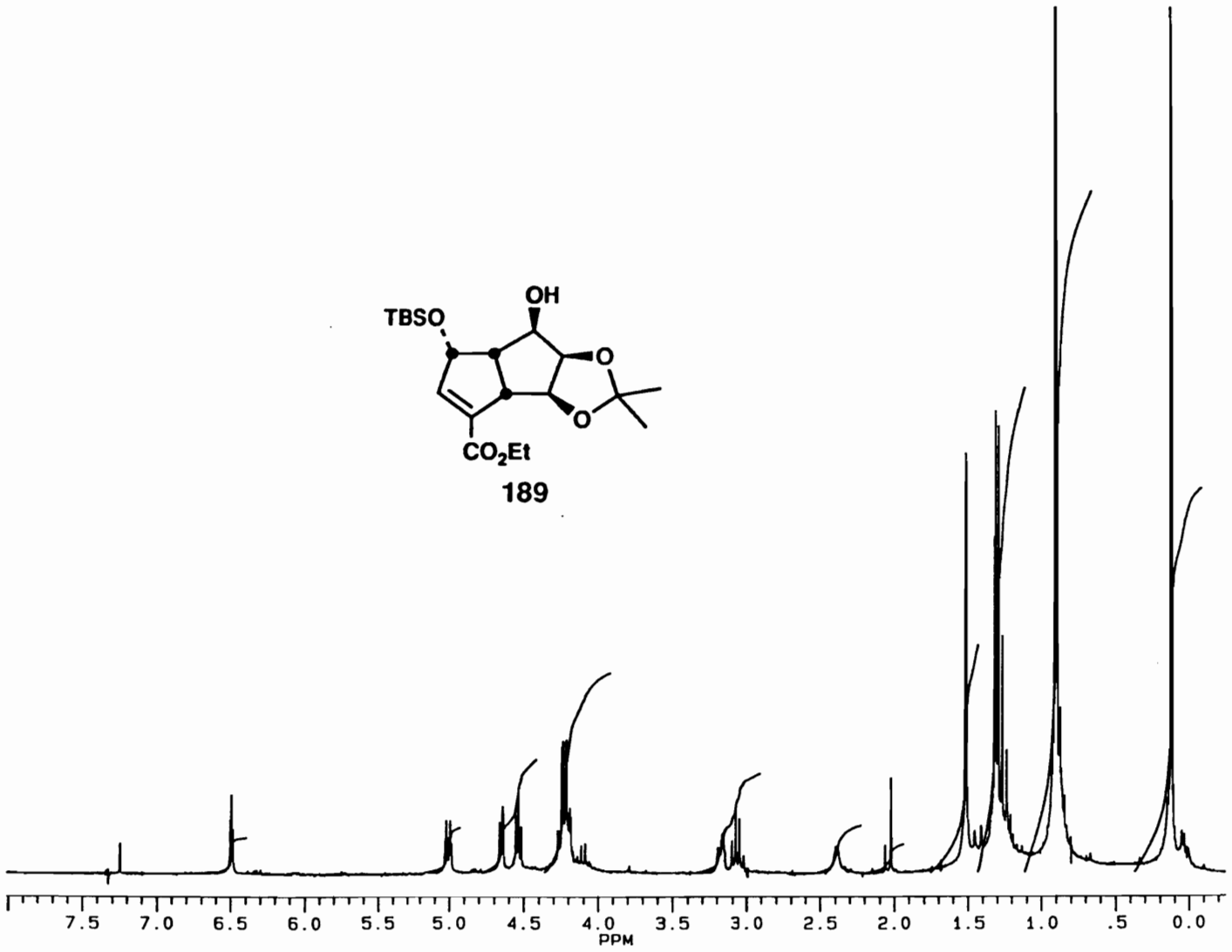

TBSO
OH
O
O
CO_2Et
150
100
50
0
59
65
75
86
103
119
135
145
163
175
191
60
80
100
120
140
160
180
50
25
0
209
224
237
255
265
283
295
313
341
10
5
0
383
398
360
380
400
420
440
460
480

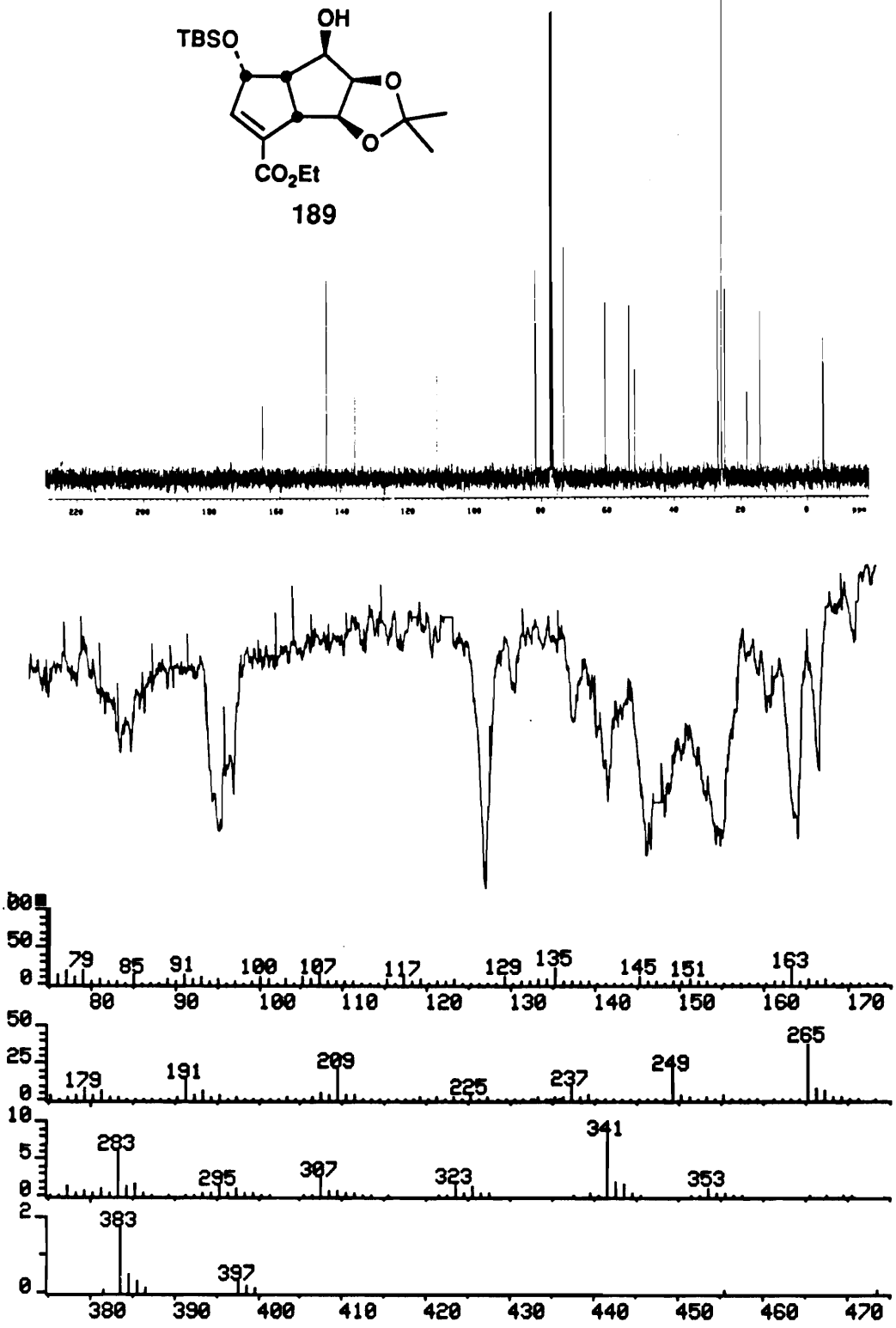

TBSO
OH
O
O
CO2Et
188
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
.5
0.0
PPM

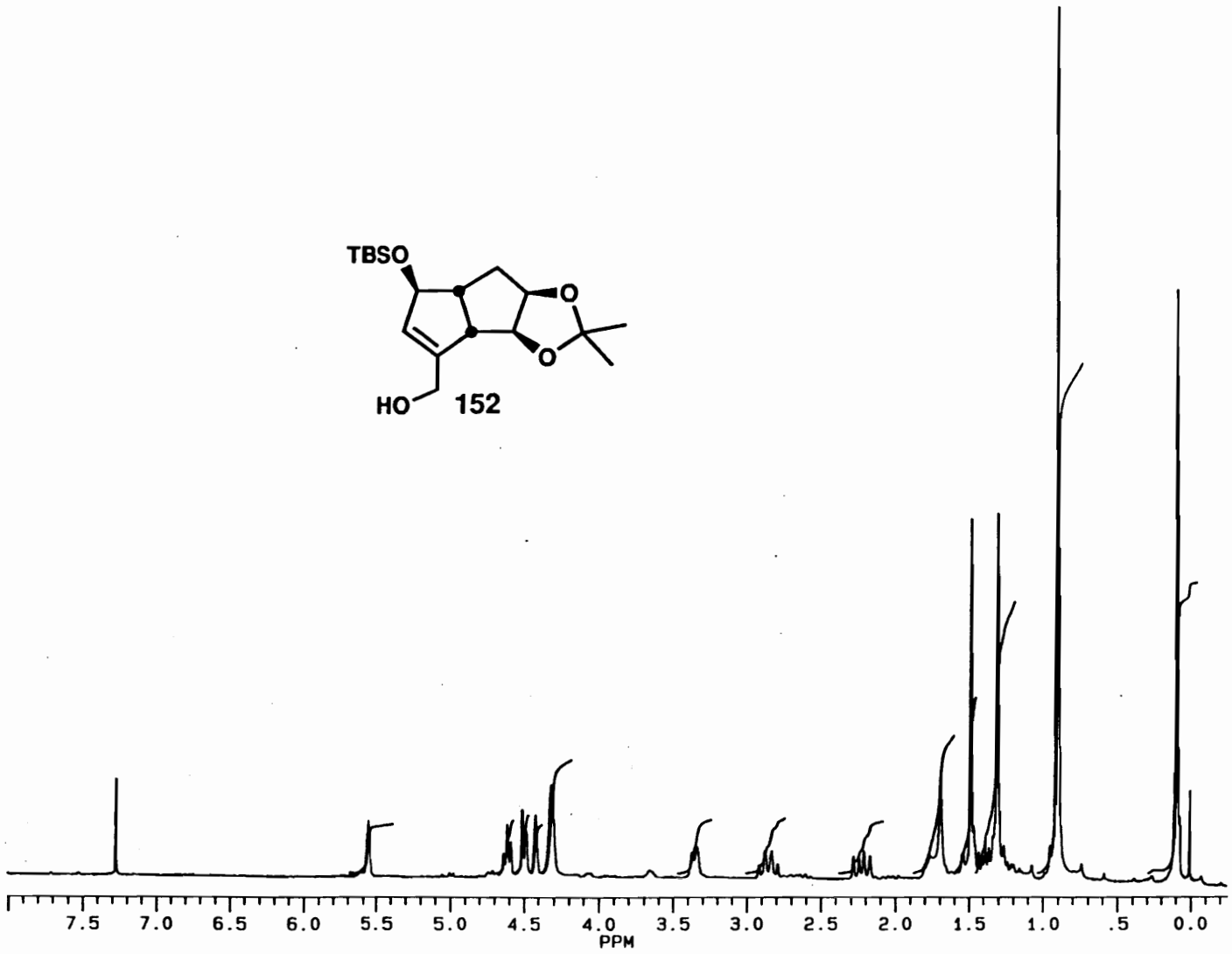

TBSO
OH
O
O
CO_2Et

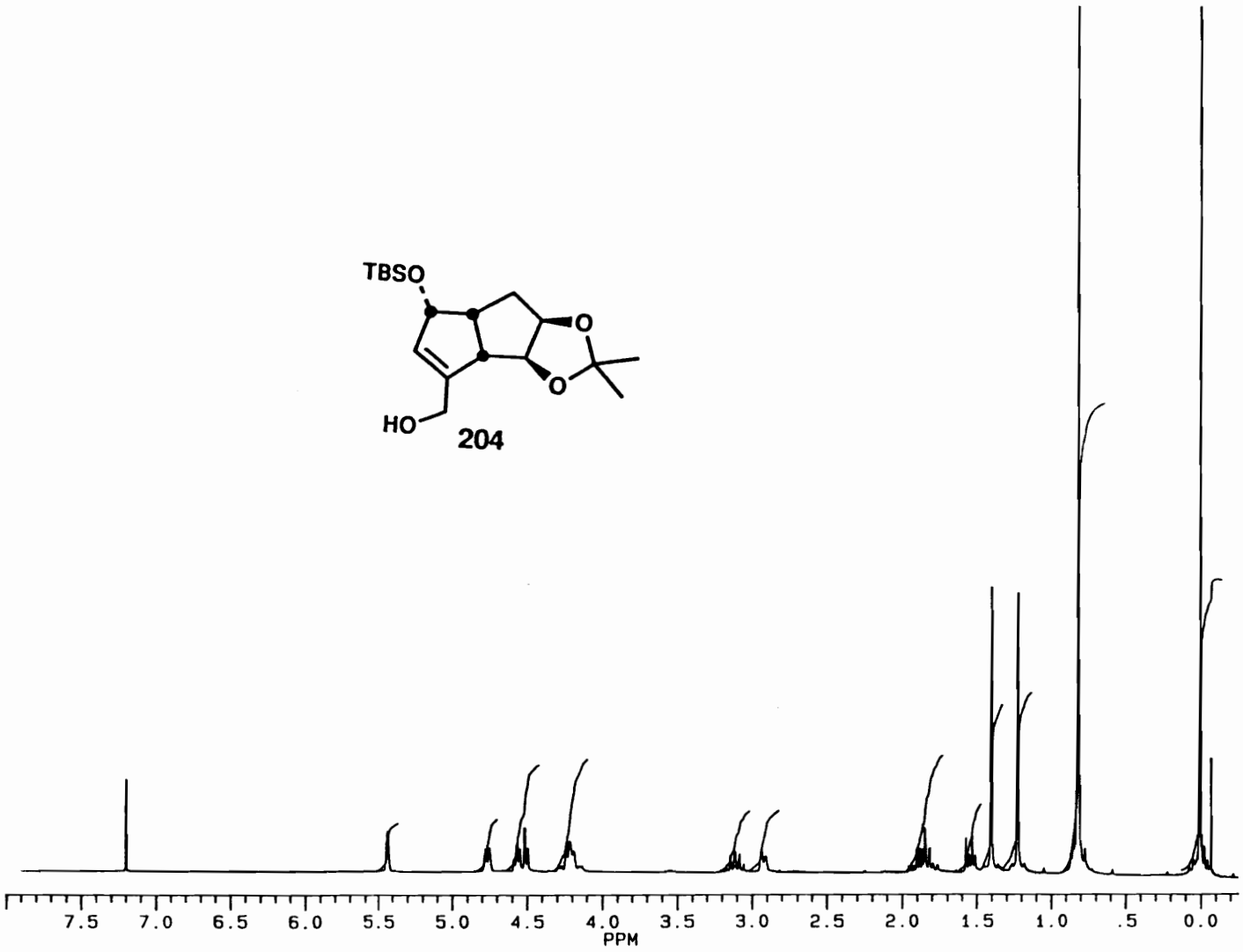
188

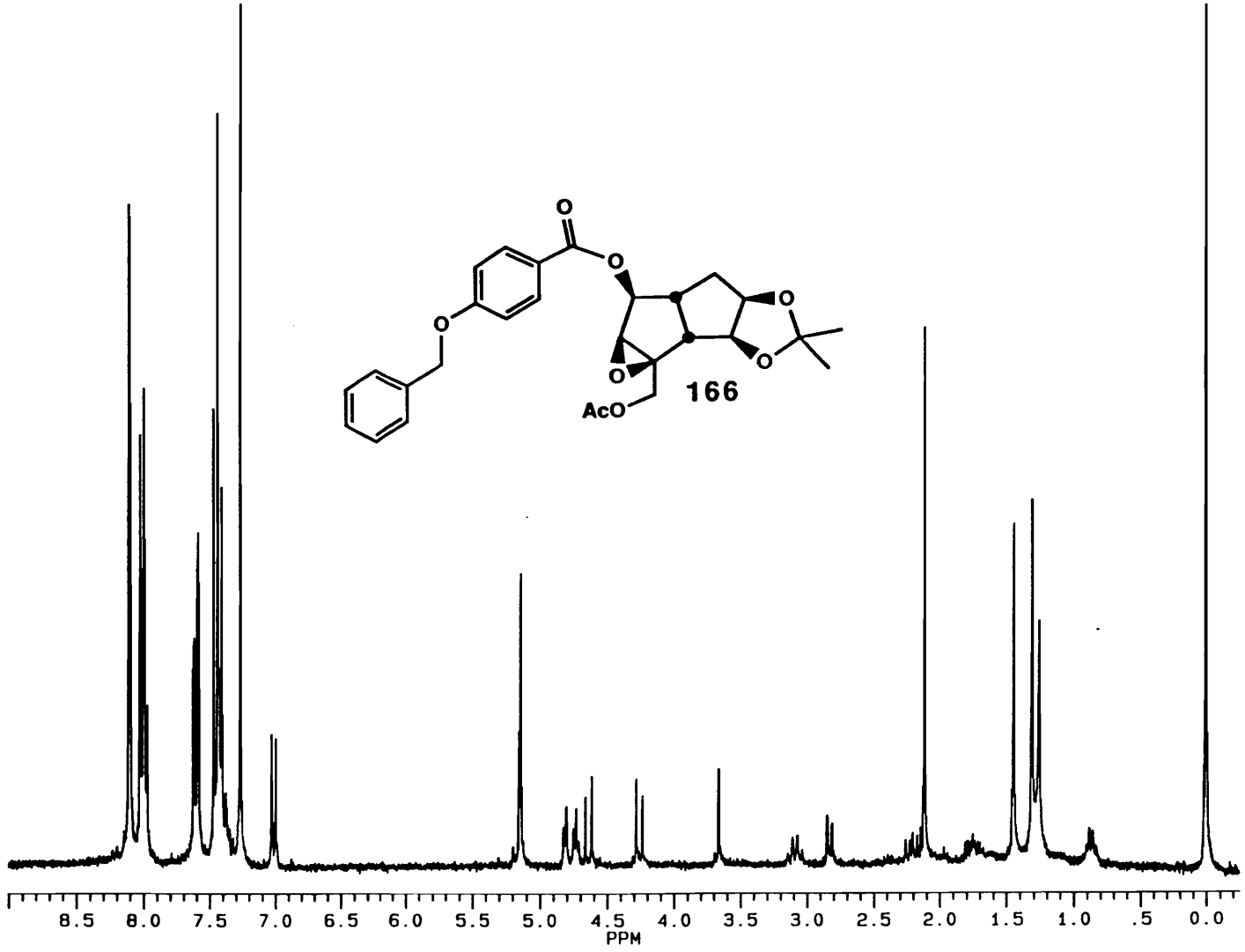

100
50
0
80
100
120
140
160
180
200
220
240
260
85
101
115
133
151
163
179
193
209
225
237
249
267
100
50
0
280
300
320
340
360
380
400
420
440
460
283
299
325
341
355
383
401
413

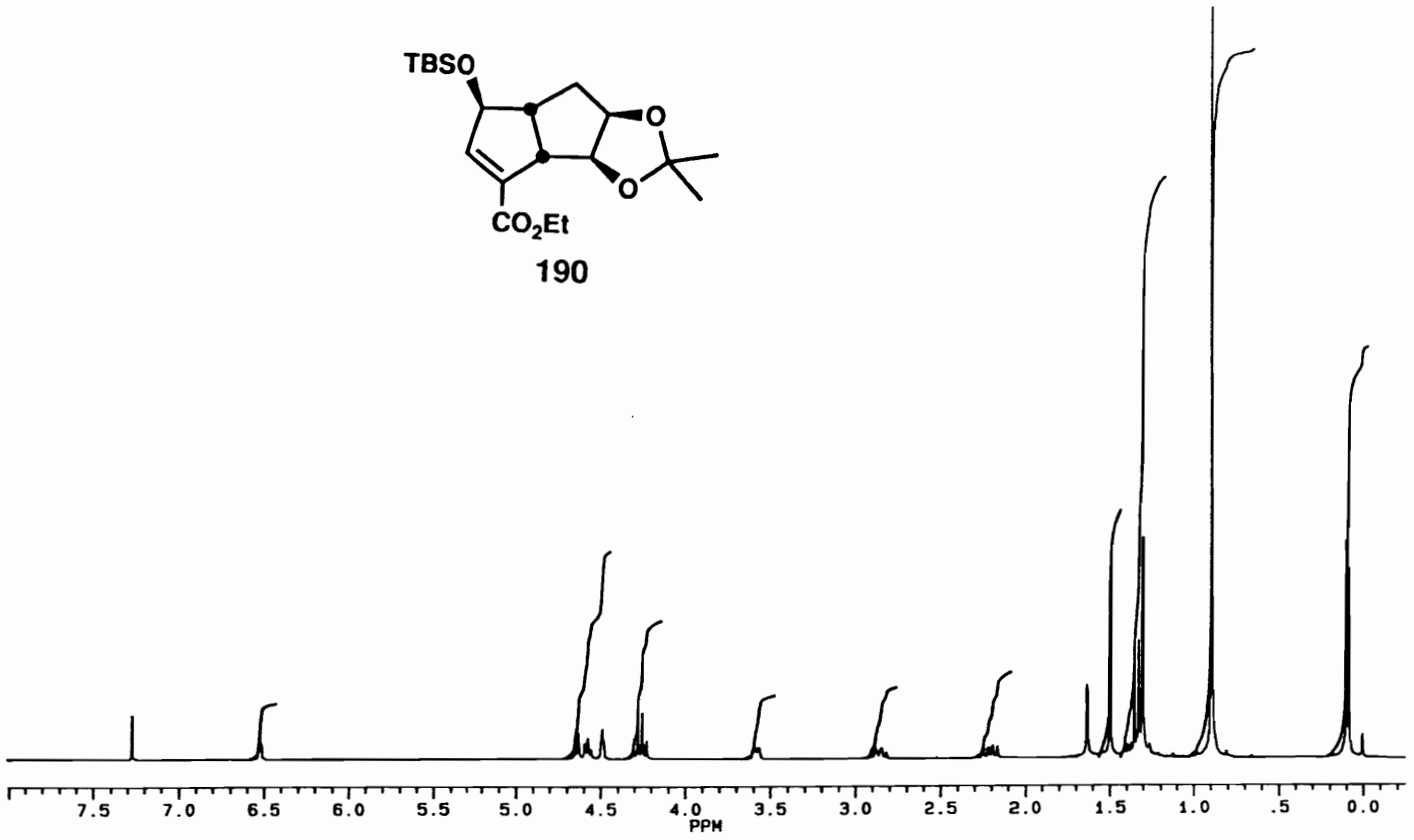

TBSO
OH
O
O
CO_2Et
189
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
.5
0.0
PPM

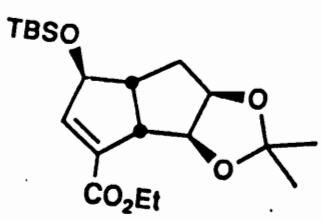

TBSO
OH
O
O
CO_2Et
189
79 85 91 100 107 117 129 135 145 151 163
179 191 209 225 237 249 265
283 295 307 323 341 353
383 397


TBSO
O
O
HO
152
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
.5
0.0
PPM

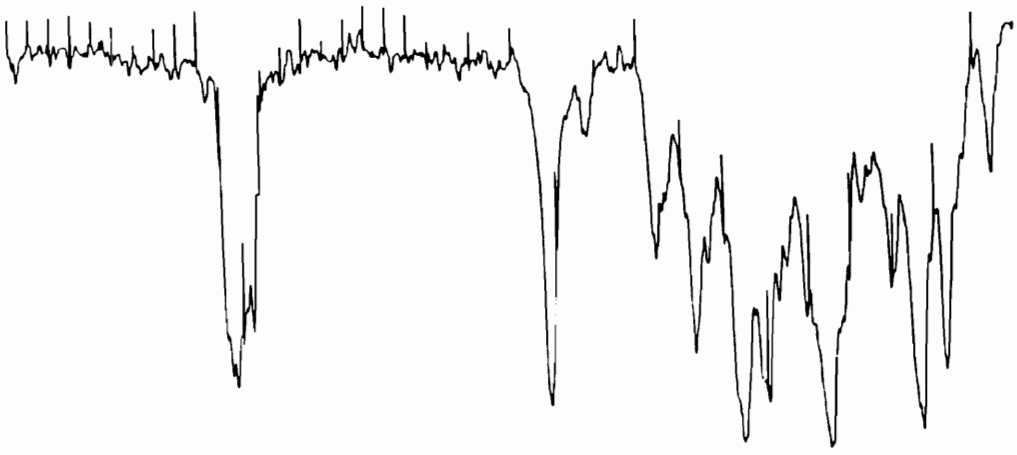

TBSO
O
O
HO
204
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
.5
0.0
PPM

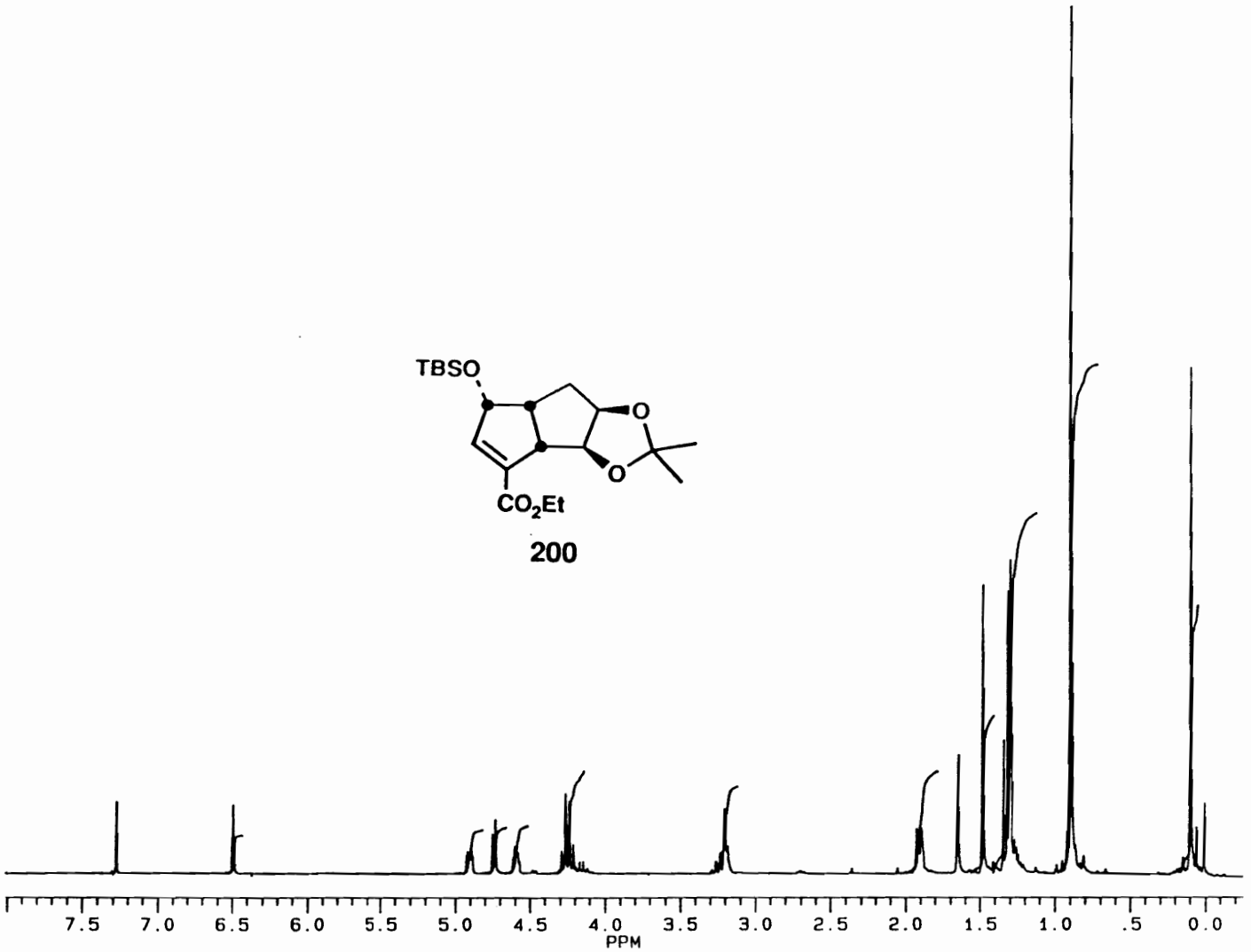

O
O
O
O
O
O
O
AcO
166
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
.5
0.0
PPM

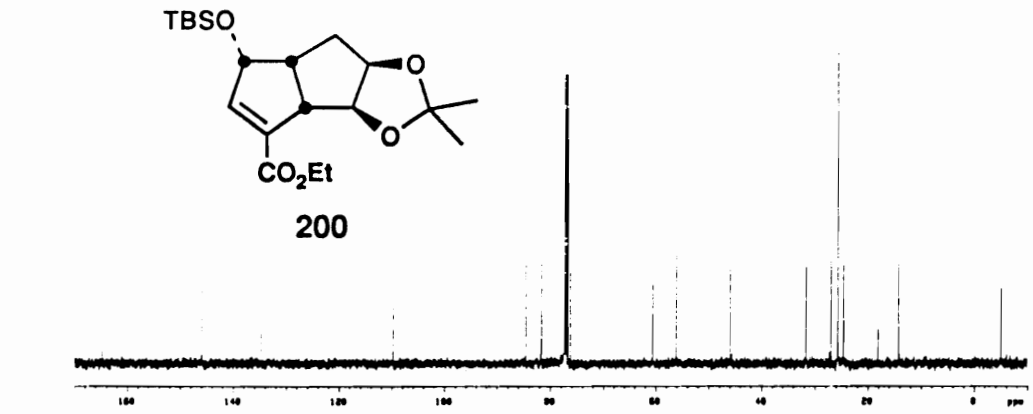

TBSO
O
O
CO2Et
190
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
.5
0.0
PPM



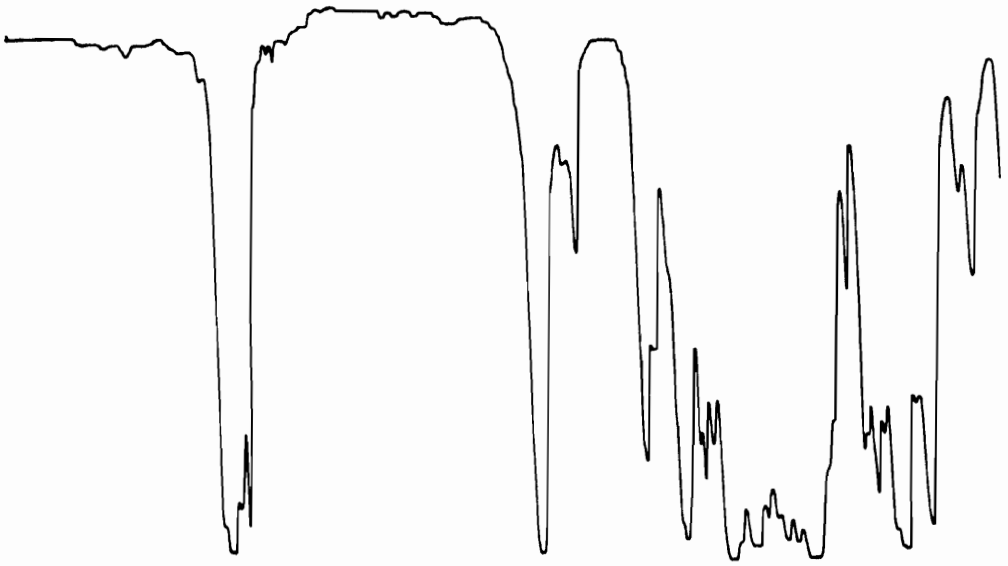
190

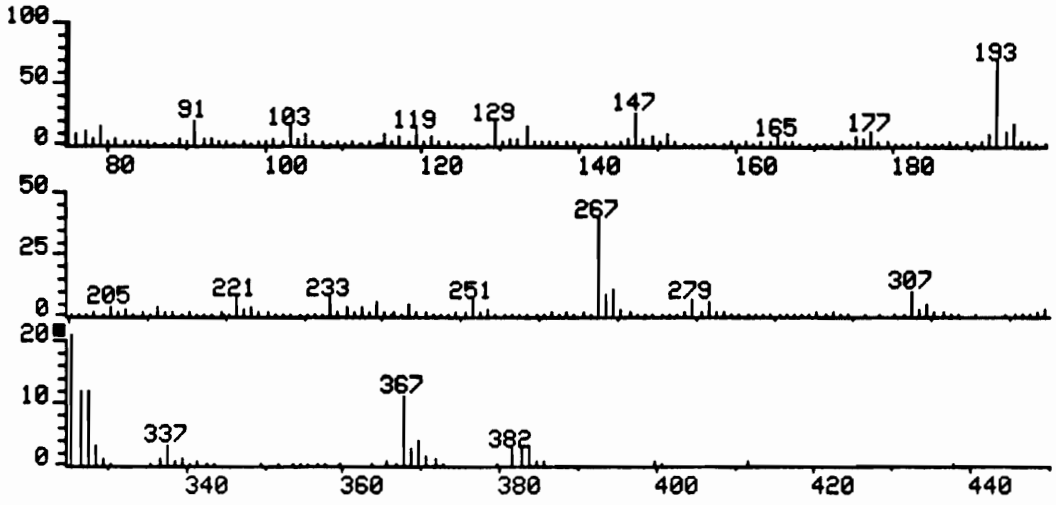


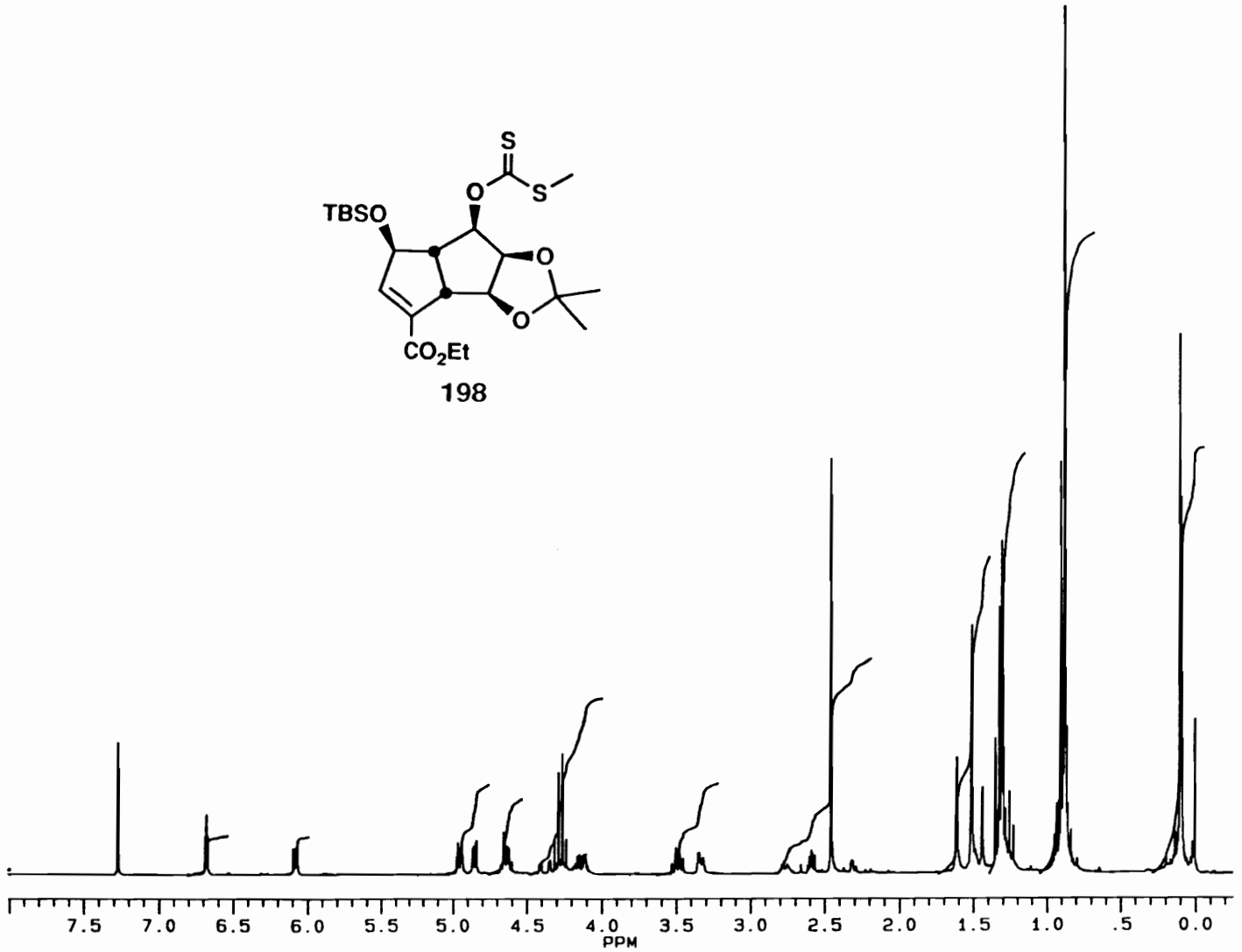

TBSO
O
O
CO2Et
200
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
.5
0.0
PPM

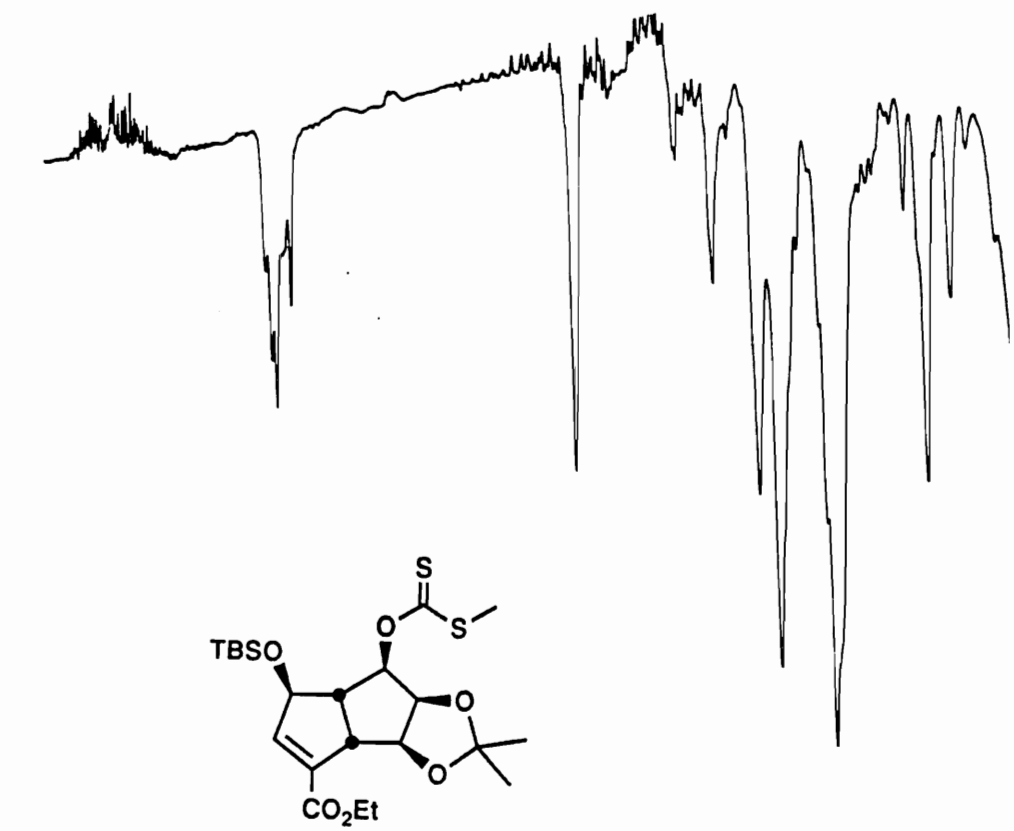

TBSO
O
O
CO_2Et

200

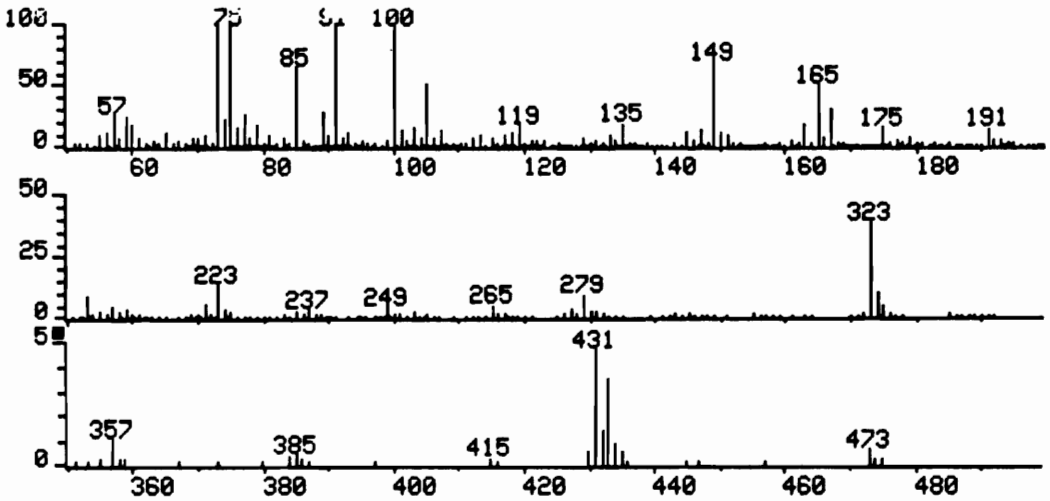



100
50
0
91
103
119
129
147
165
177
193
80
100
120
140
160
180
50
25
0
205
221
233
251
267
279
307
20
10
0
337
367
382
340
360
380
400
420
440

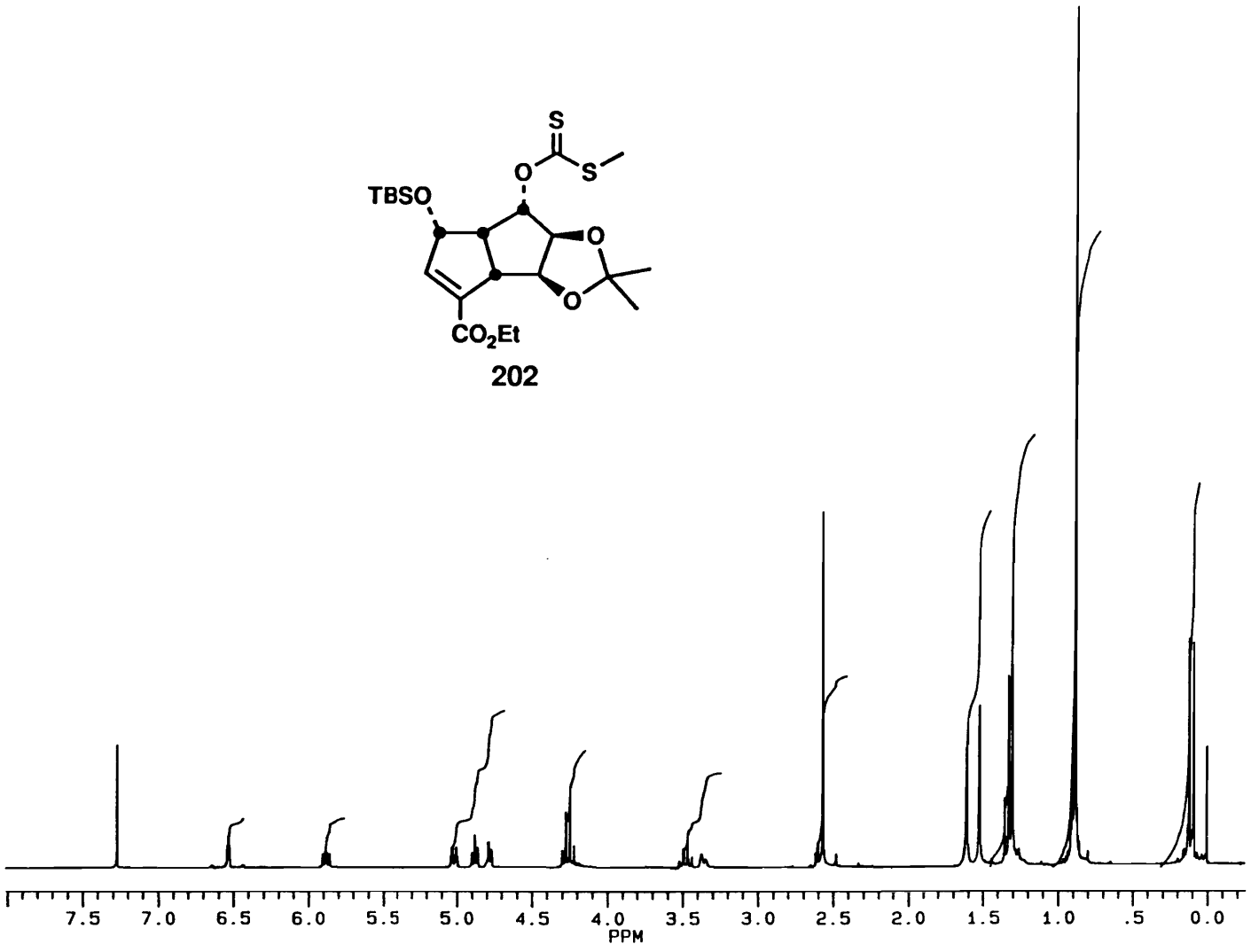

S
O
S
TBSO
O
O
CO2Et
198
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
.5
0.0
PPM


S
O
S
TBSO
O
O
CO2Et

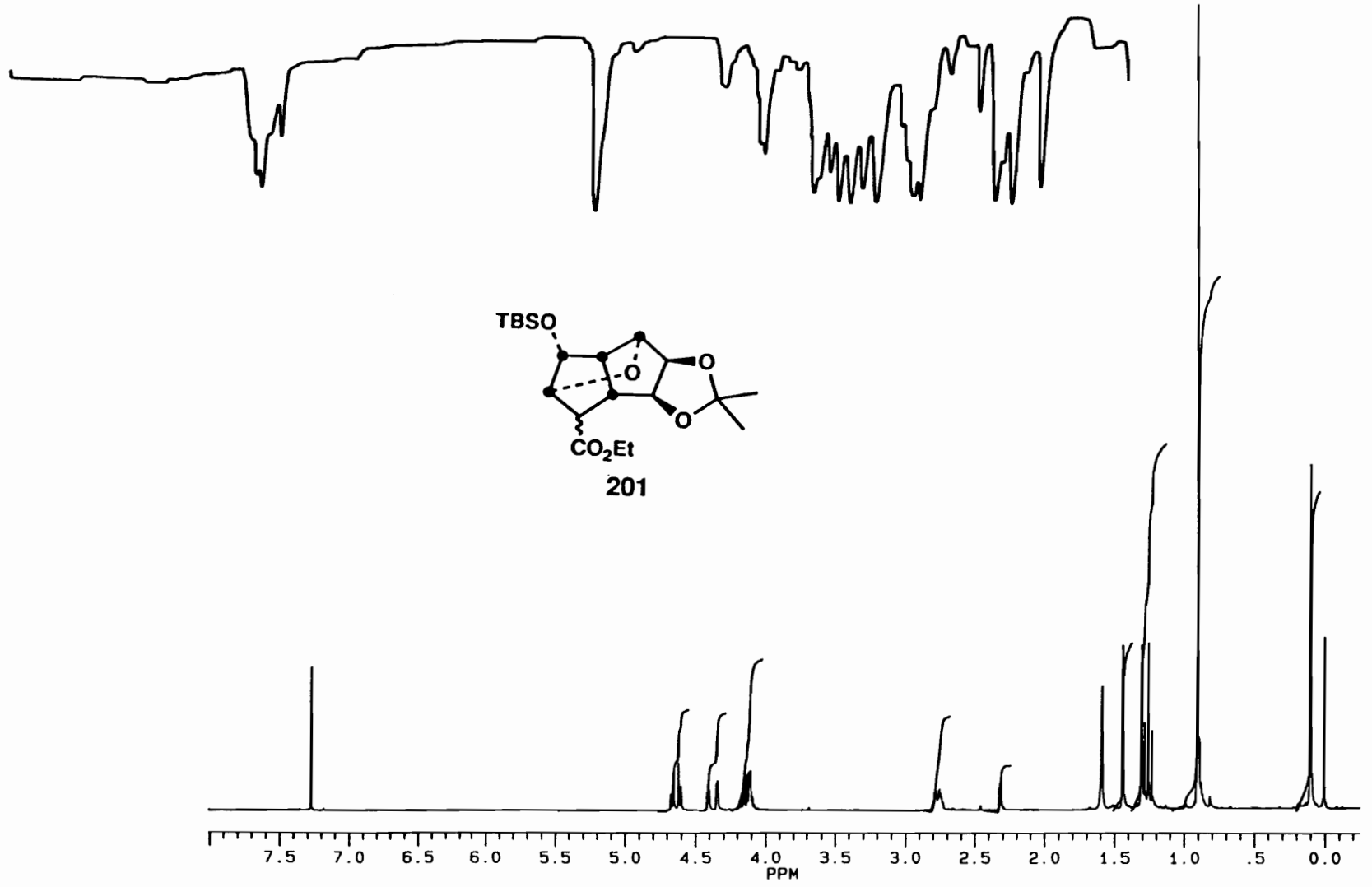
198


100
50
0
57
85
100
119
135
149
165
175
191
60
80
100
120
140
160
180
50
25
0
223
237
249
265
279
323
5
0
357
385
415
431
473
360
380
400
420
440
460
480

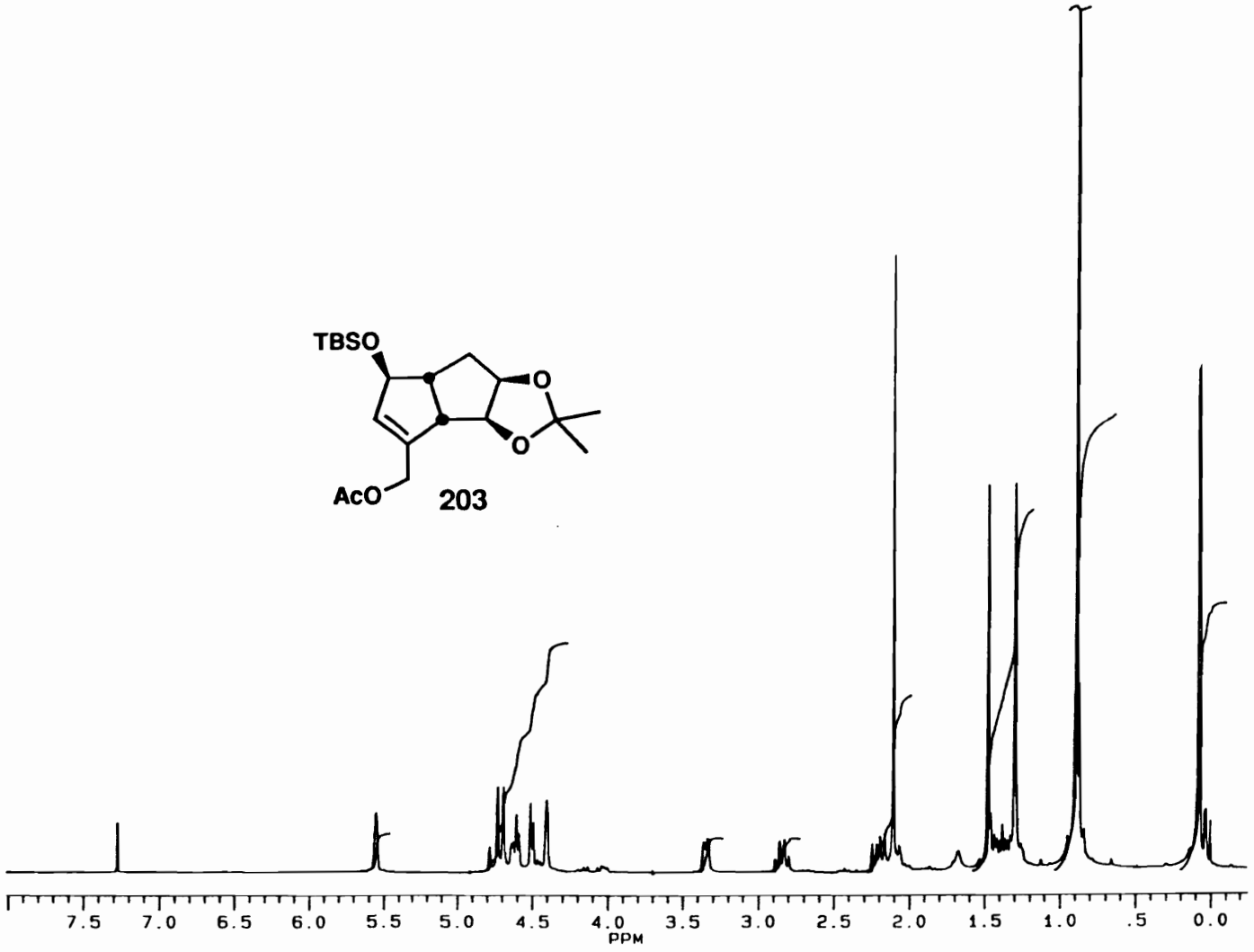
S
O
S
O
O
TBSO
CO2Et
199
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
.5
0.0
PPM

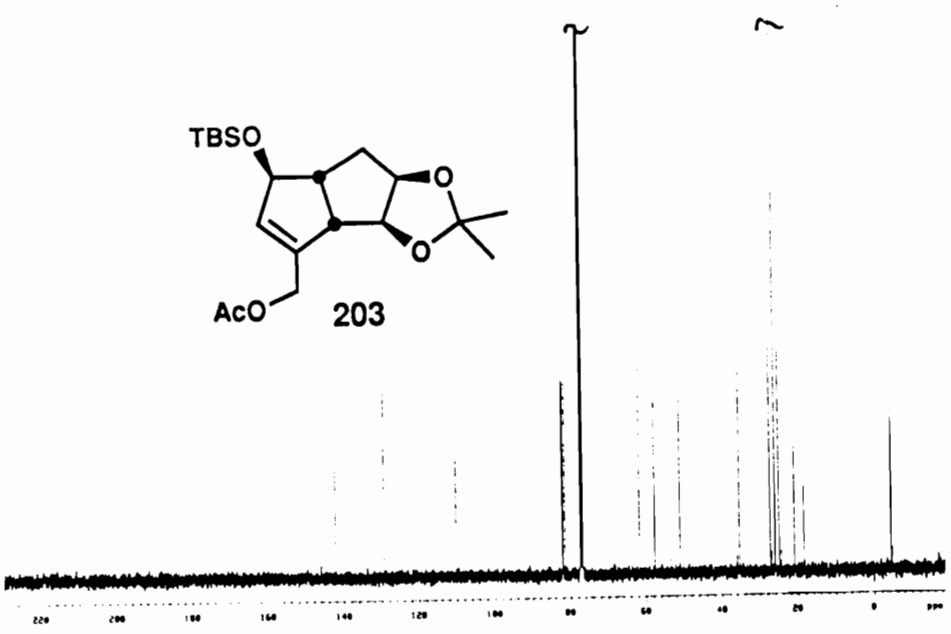


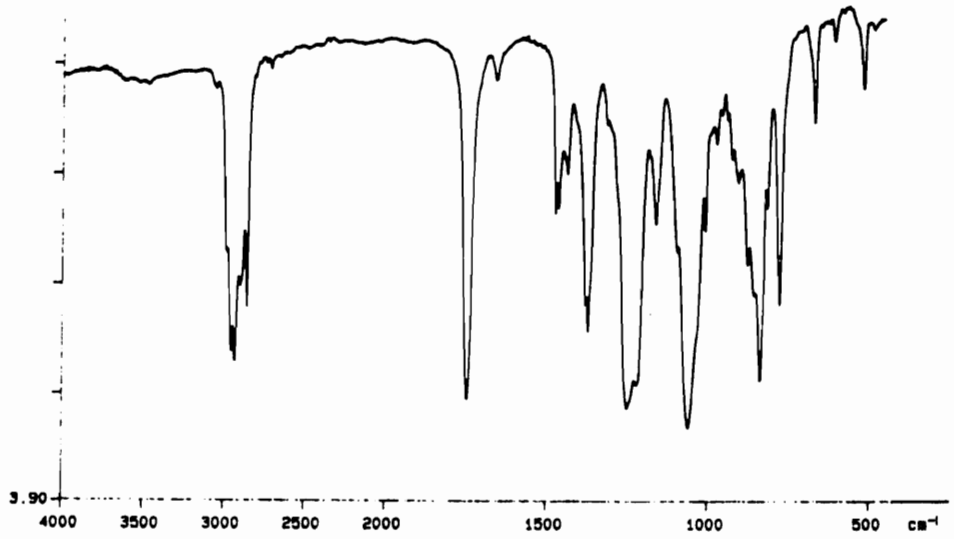
202

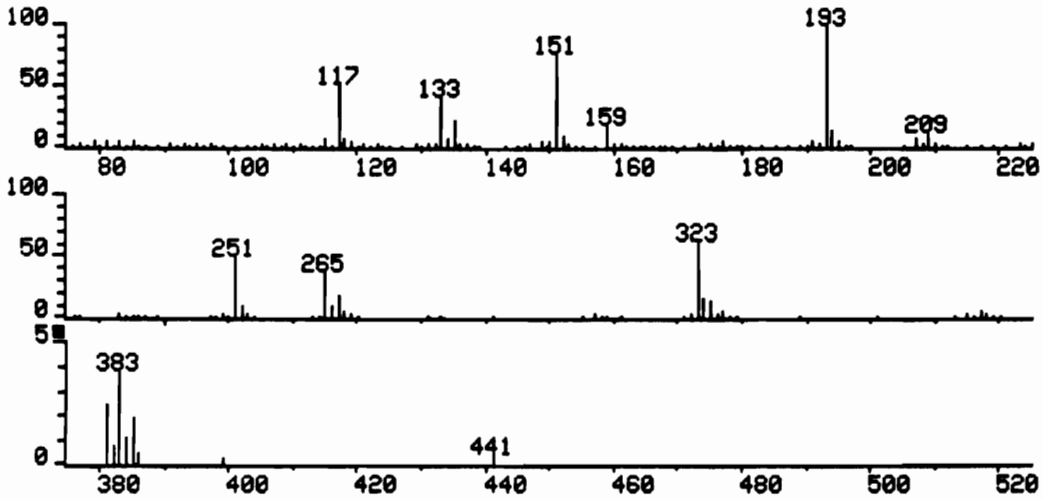


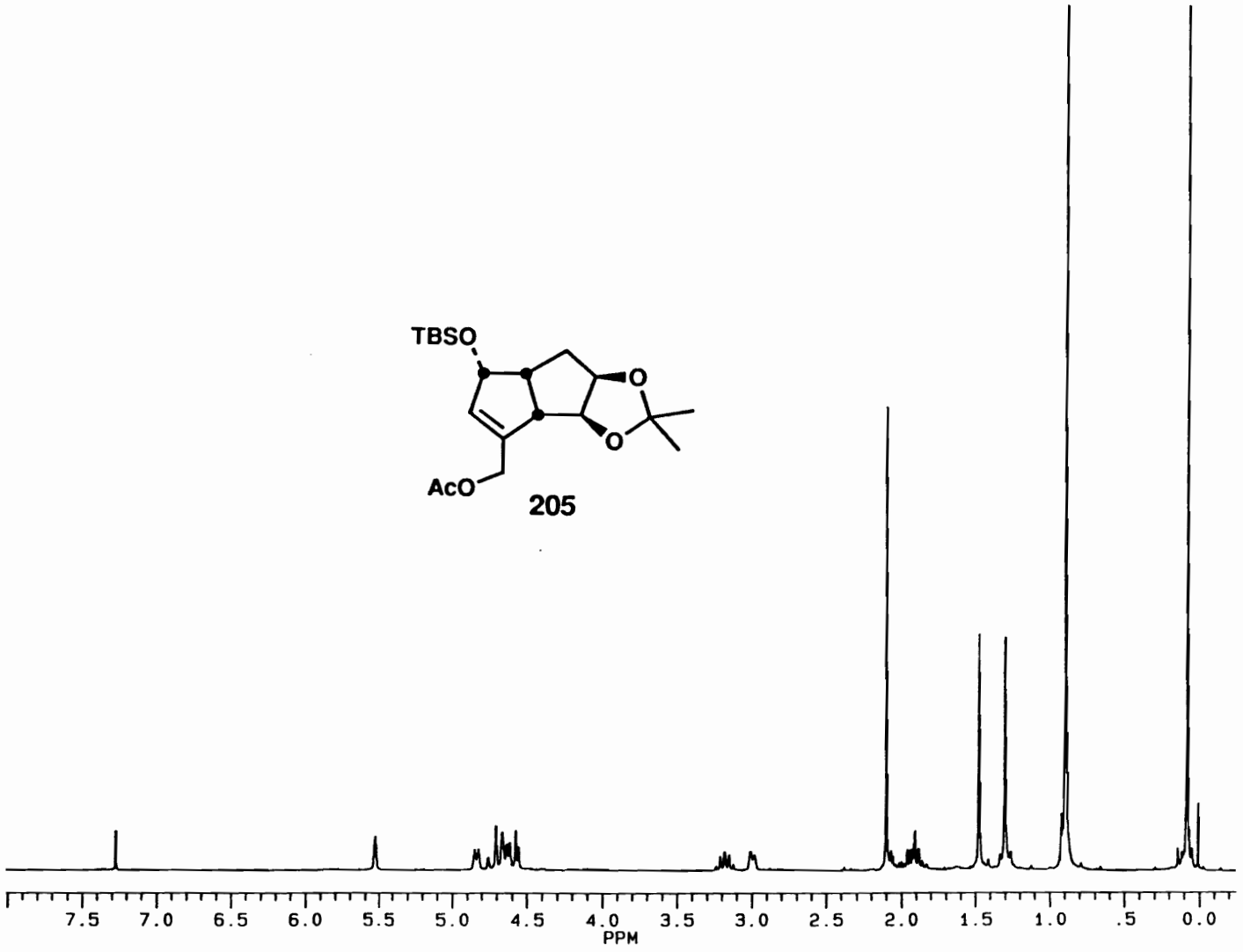
201

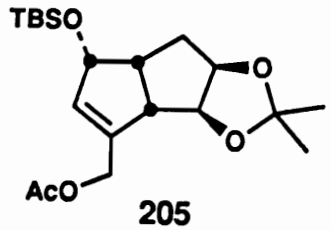

TBSO
O
O
AcO
203
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
.5
0.0
PPM


TBSO
O
O
AcO
203

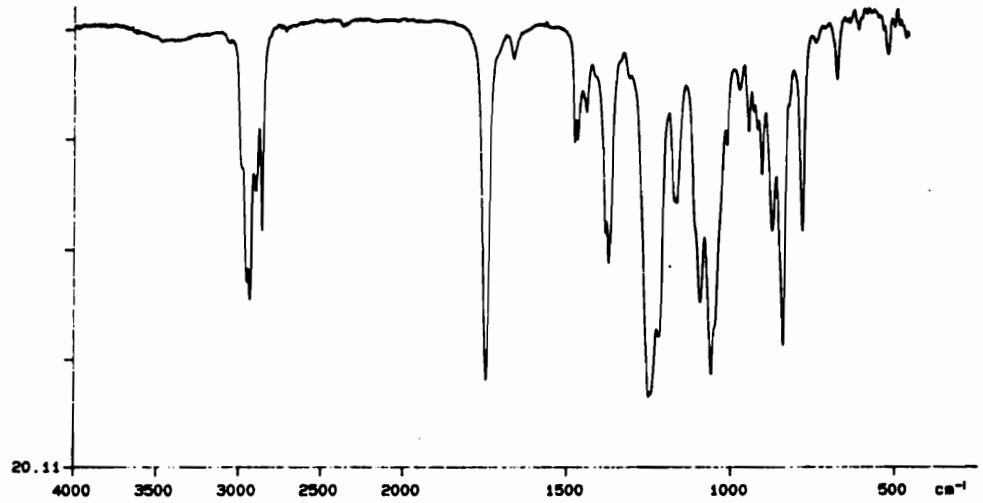

3.90
4000
3500
3000
2500
2000
1500
1000
500
cm⁻¹

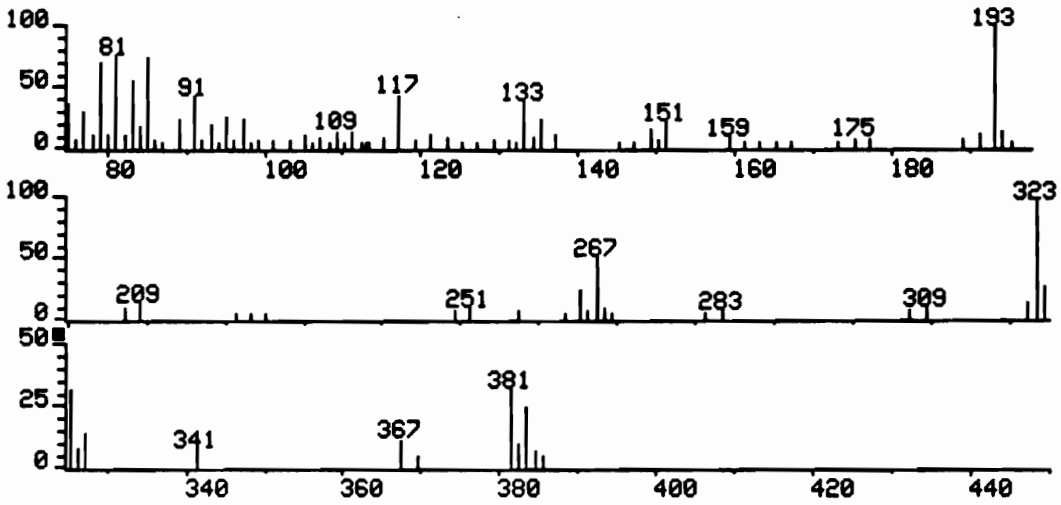

100
50
0
117
133
151
159
193
209
80
100
120
140
160
180
200
220
100
50
0
251
265
323
5
0
383
441
380
400
420
440
460
480
500
520

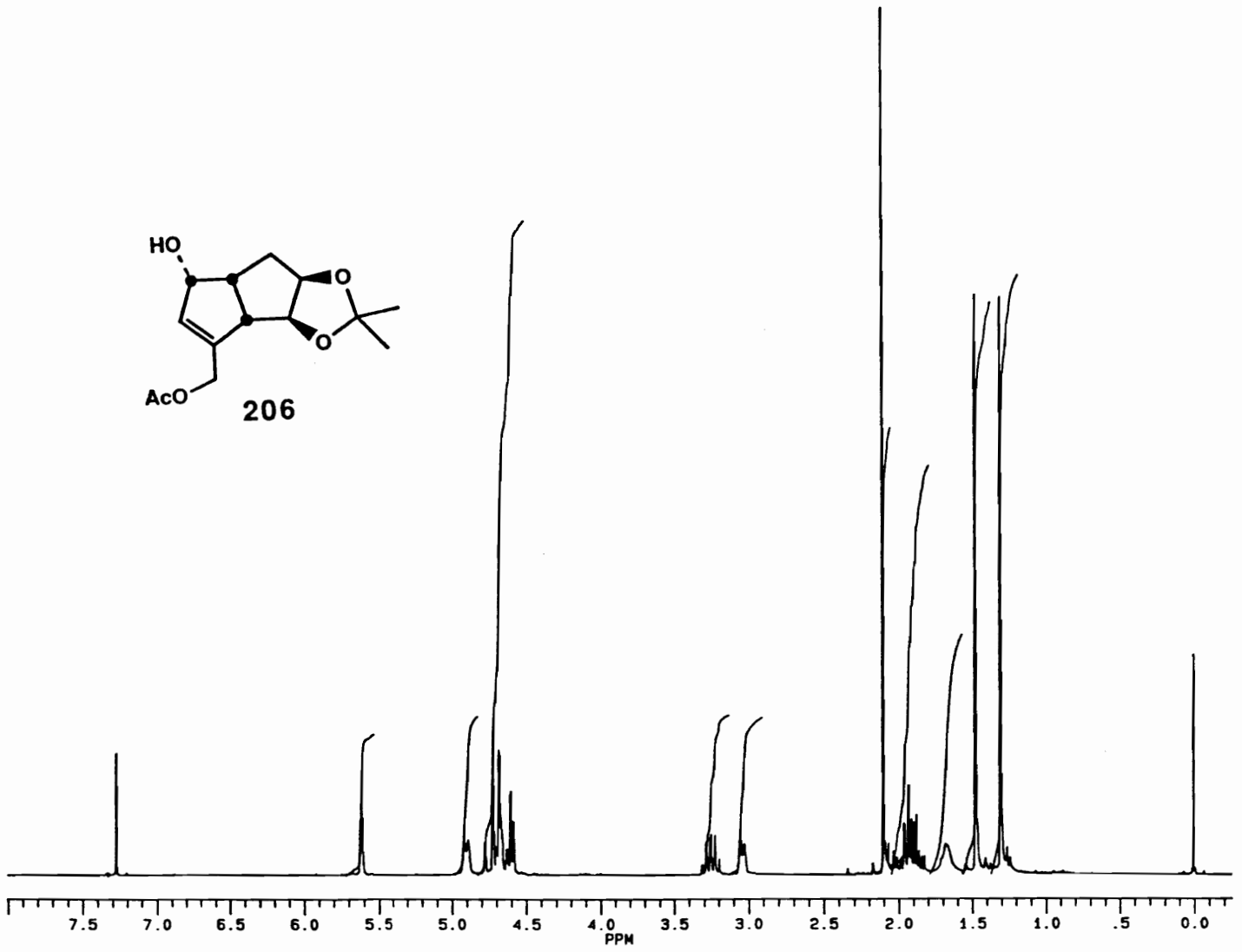

TBSO
O
O
AcO
205
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
.5
0.0
PPM

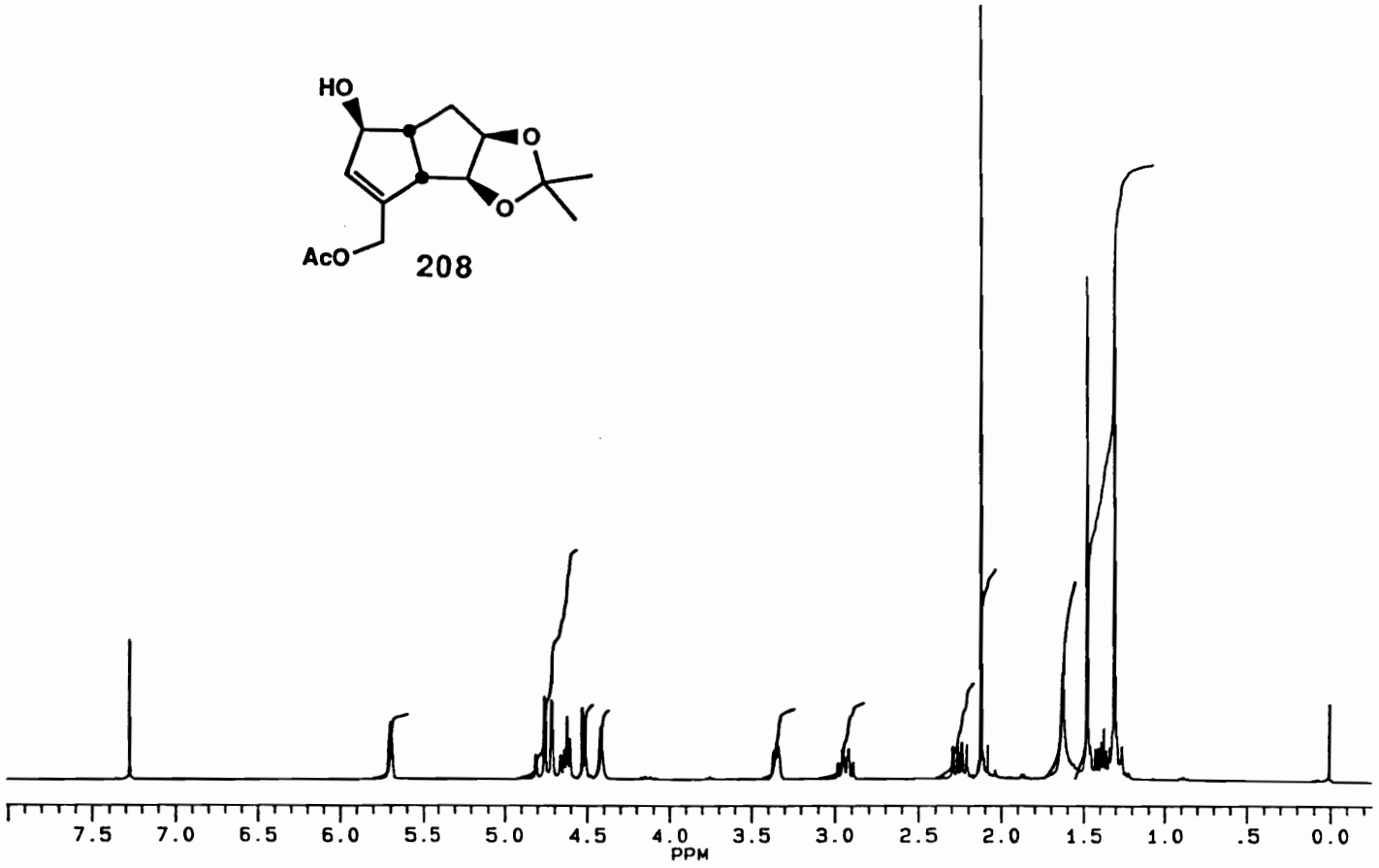

TBSO
O
O
AcO

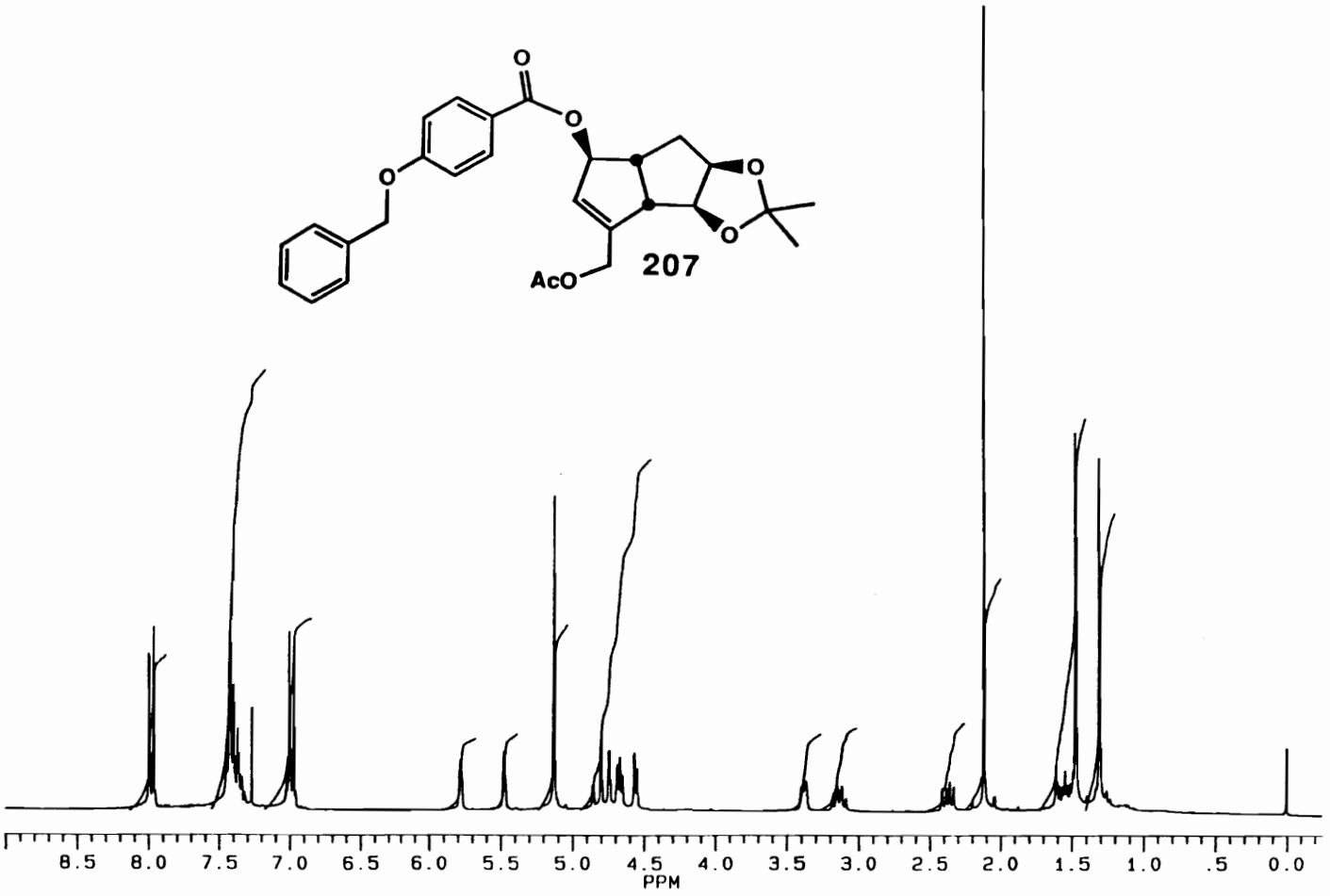
205

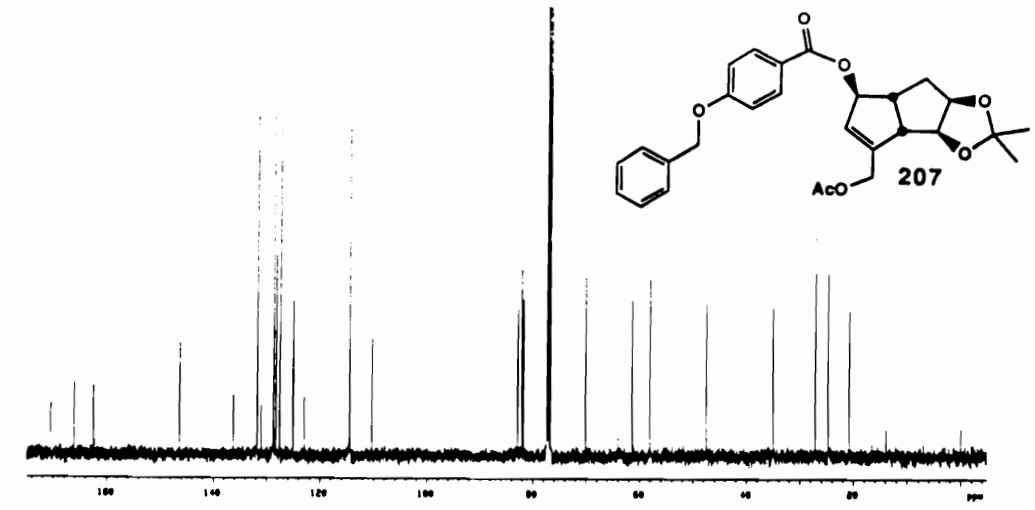

20.11
4000
3500
3000
2500
2000
1500
1000
500
cm⁻¹

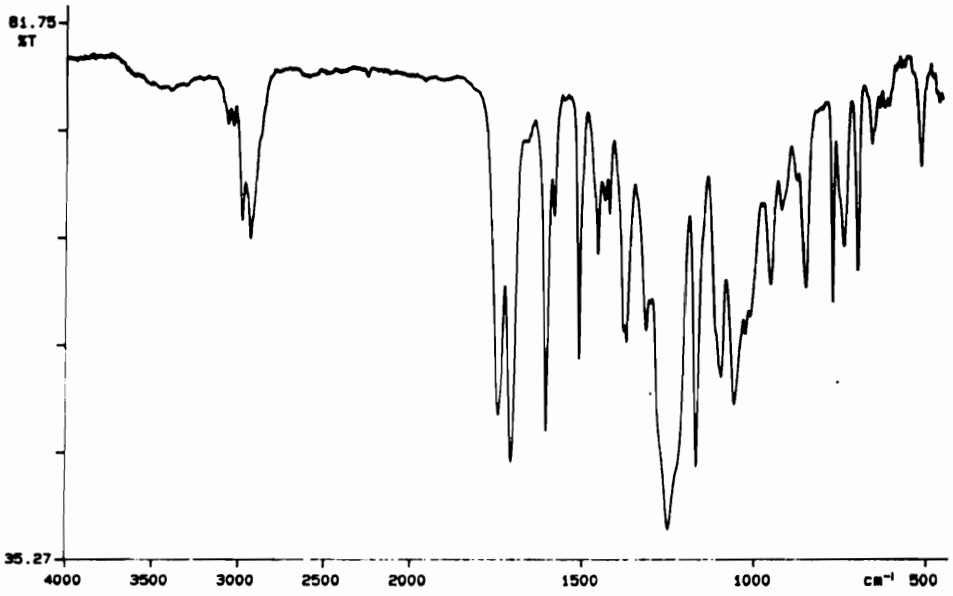

100
50
0
81
91
109
117
133
151
159
175
193
80
100
120
140
160
180
323
267
209
251
283
309
50
25
0
381
341
367
340
360
380
400
420
440

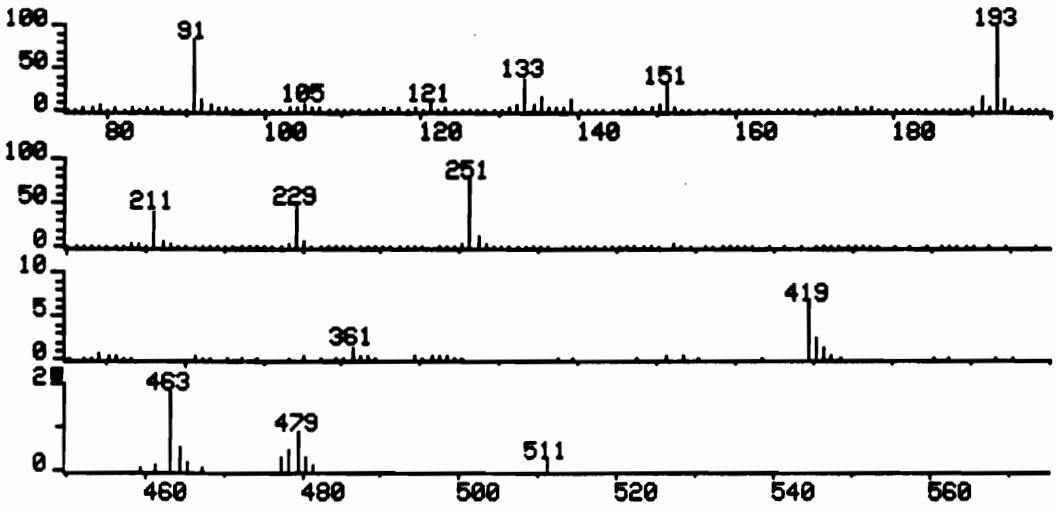

HO
O
O
AcO
206
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
PPM
3.5
3.0
2.5
2.0
1.5
1.0
.5
0.0

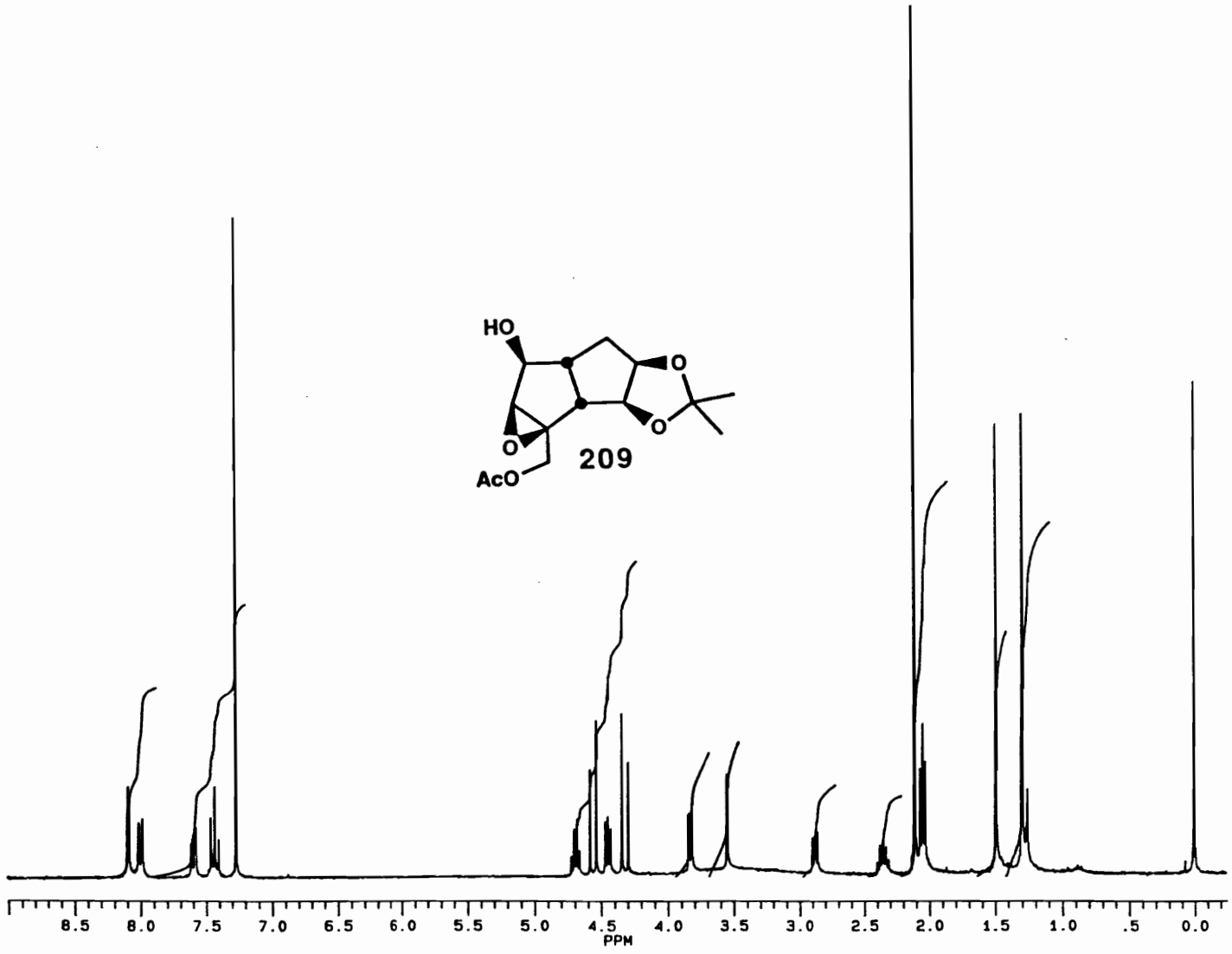

HO
O
O
AcO
208
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
.5
0.0
PPM

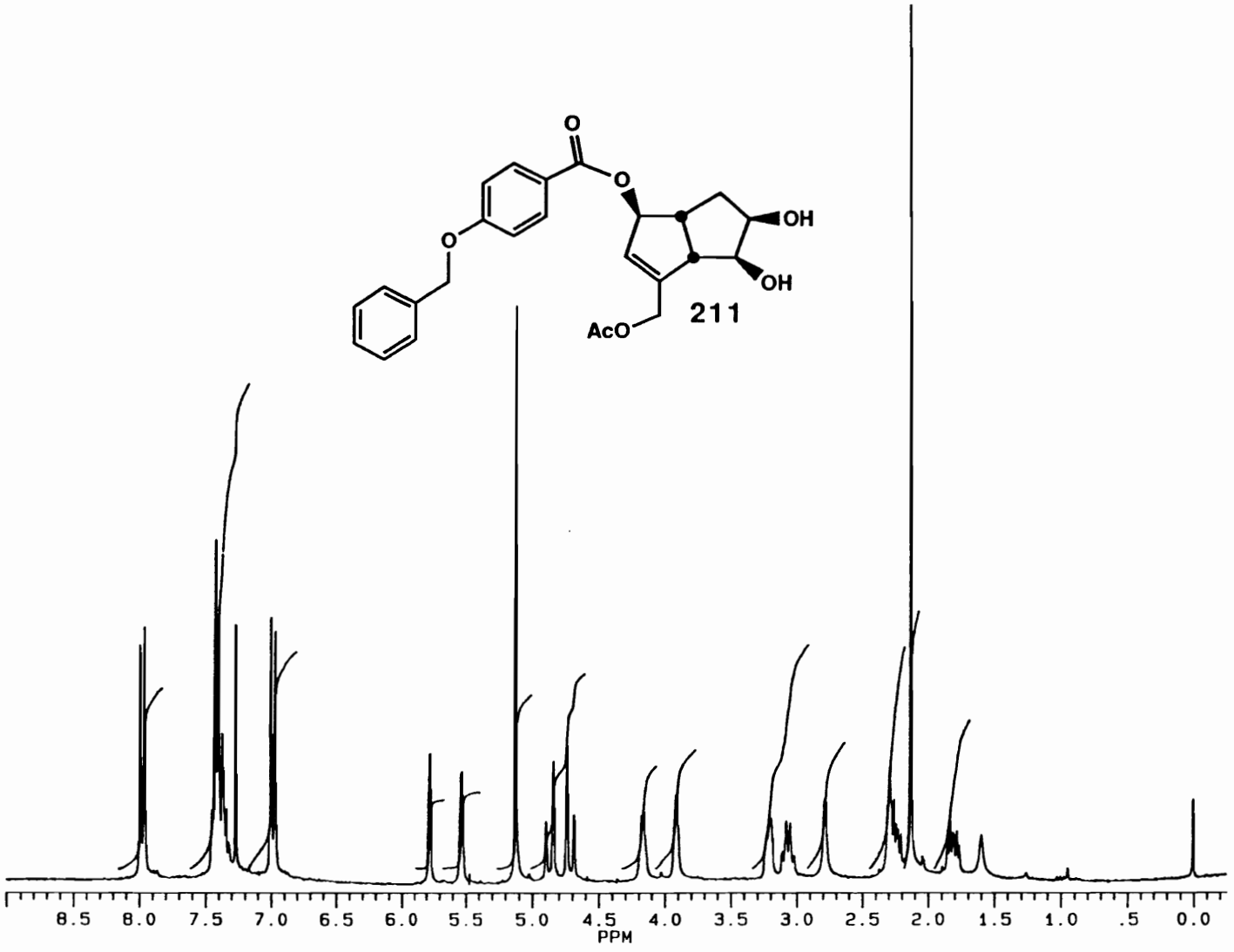

O
O
O
O
O
AcO
207
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
.5
0.0
PPM


AcO
207

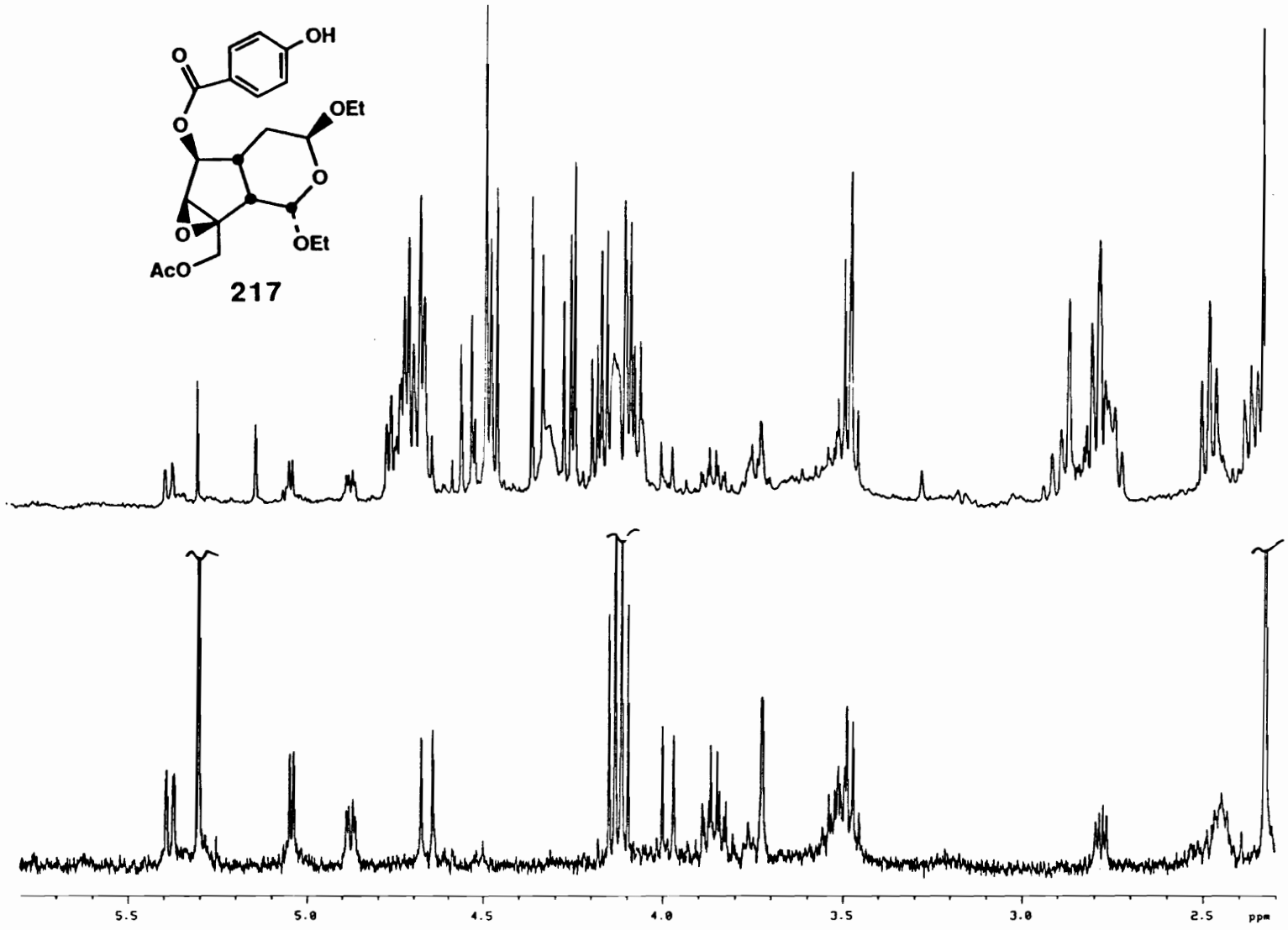

81.75
ST
35.27
4000
3500
3000
2500
2000
1500
1000
cm⁻¹
500

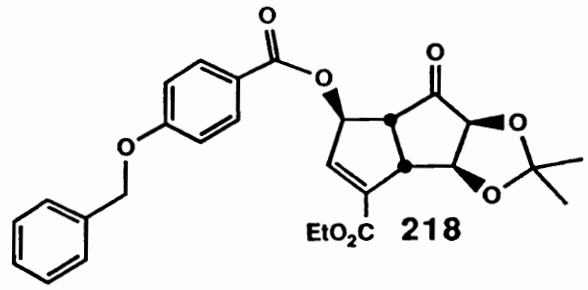

91
105
121
133
151
193
211
229
251
361
419
463
479
511


HO
O
O
O
AcO
209
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
PPM
4.0
3.5
3.0
2.5
2.0
1.5
1.0
.5
0.0

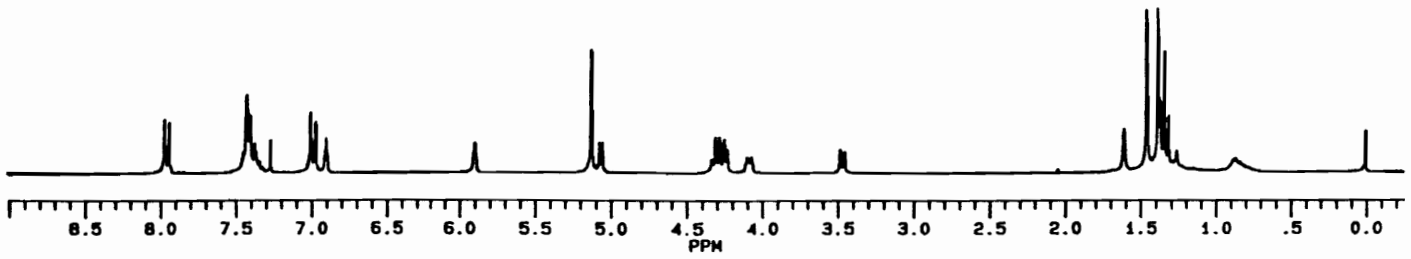

O
O
O
OH
OH
AcO
211
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
.5
0.0
PPM

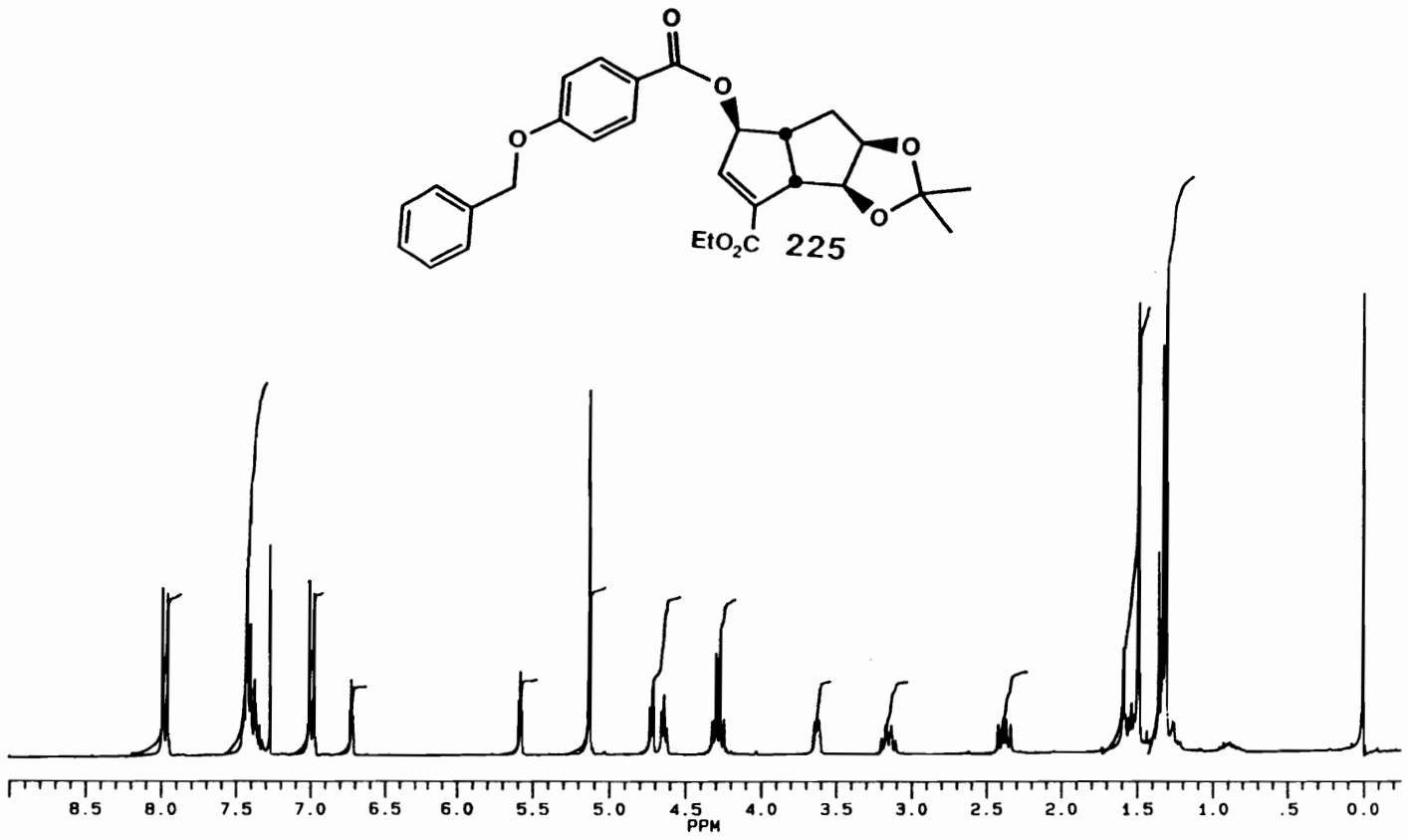
OH
OEt
OEt
O
O
O
O
AcO
217
ppm
1
2
3
4
5
6
7
8

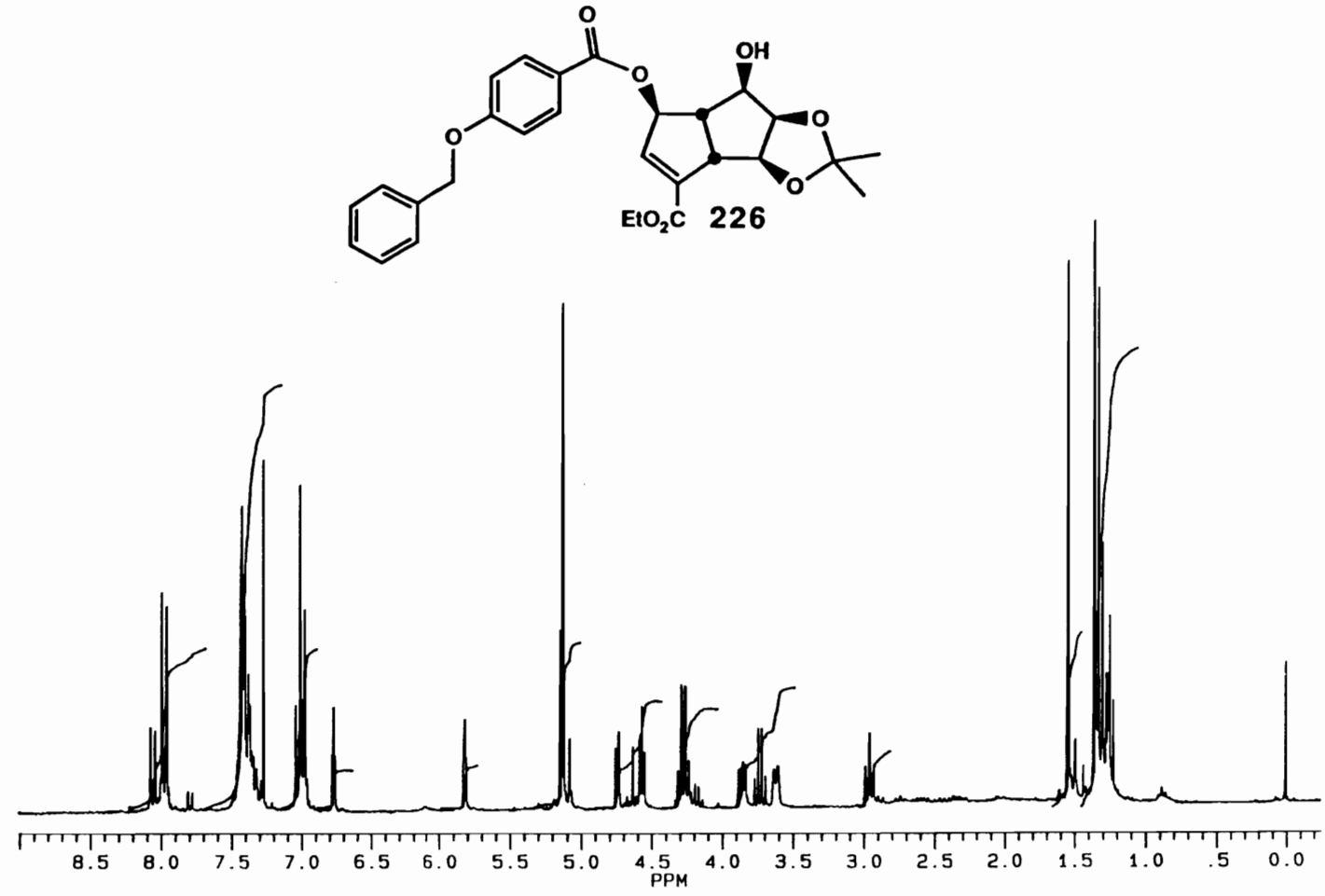

OH
O
O
OEt
O
O
O
OEt
AcO
217
5.5
5.0
4.5
4.0
3.5
3.0
2.5
ppm

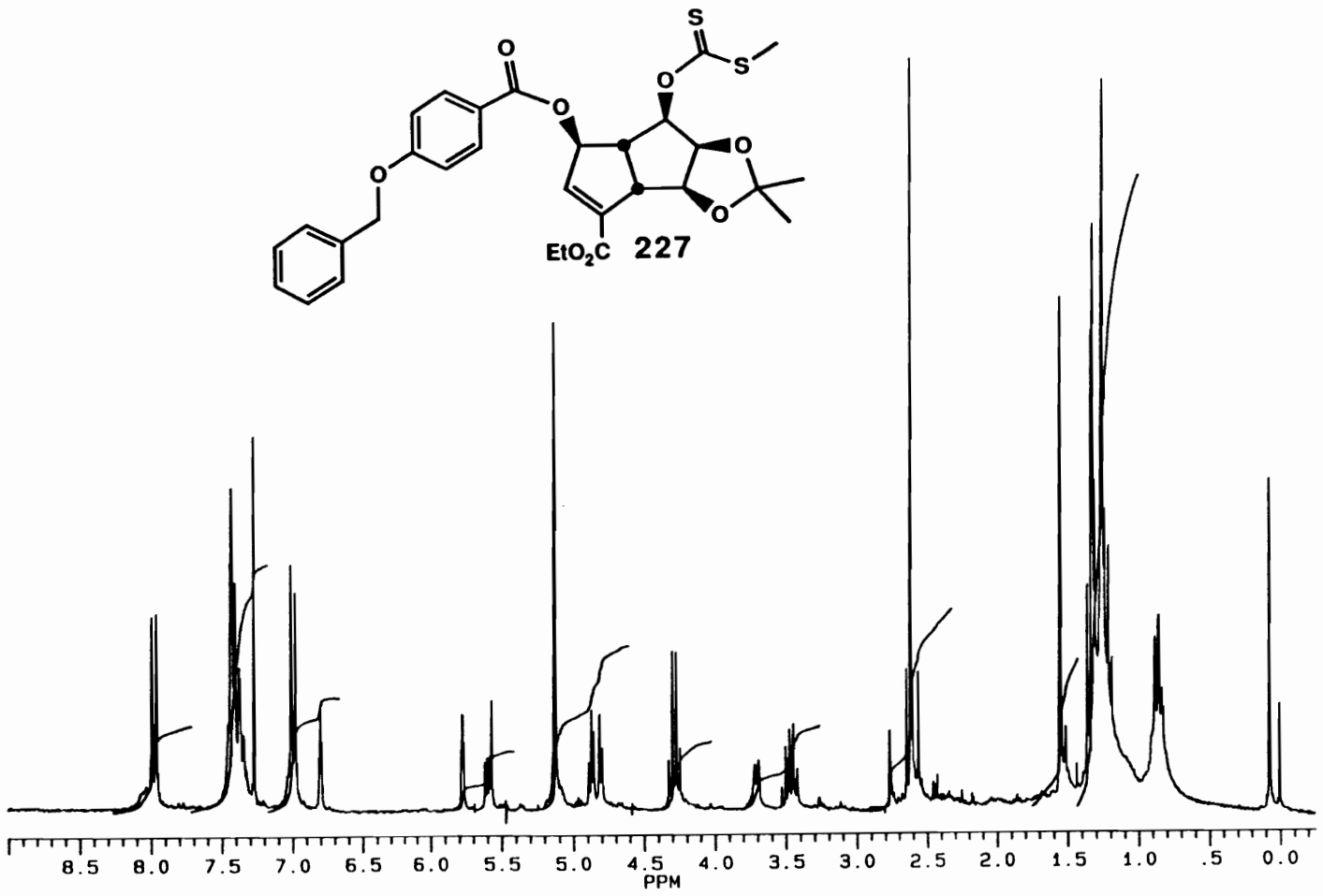


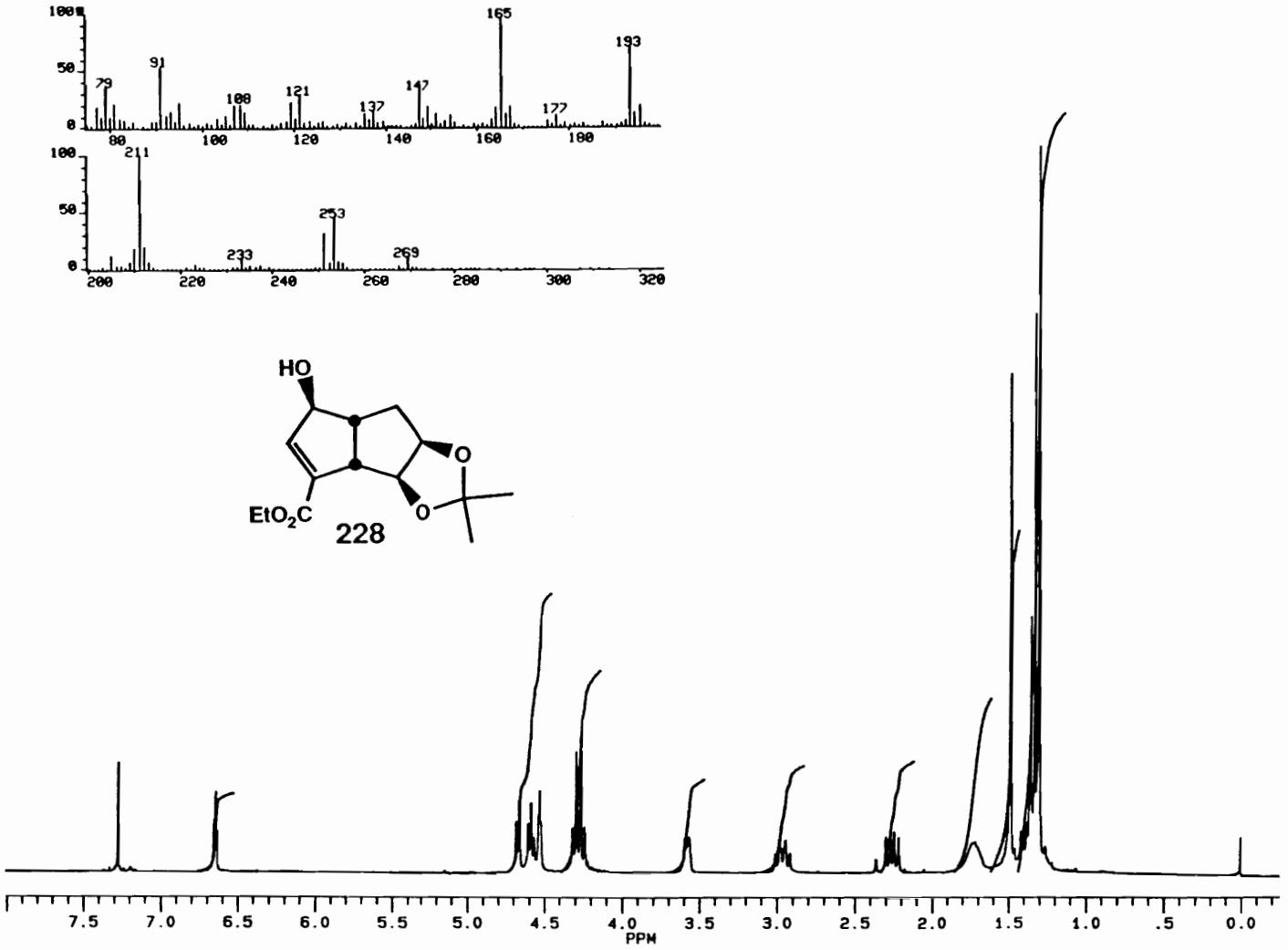
218

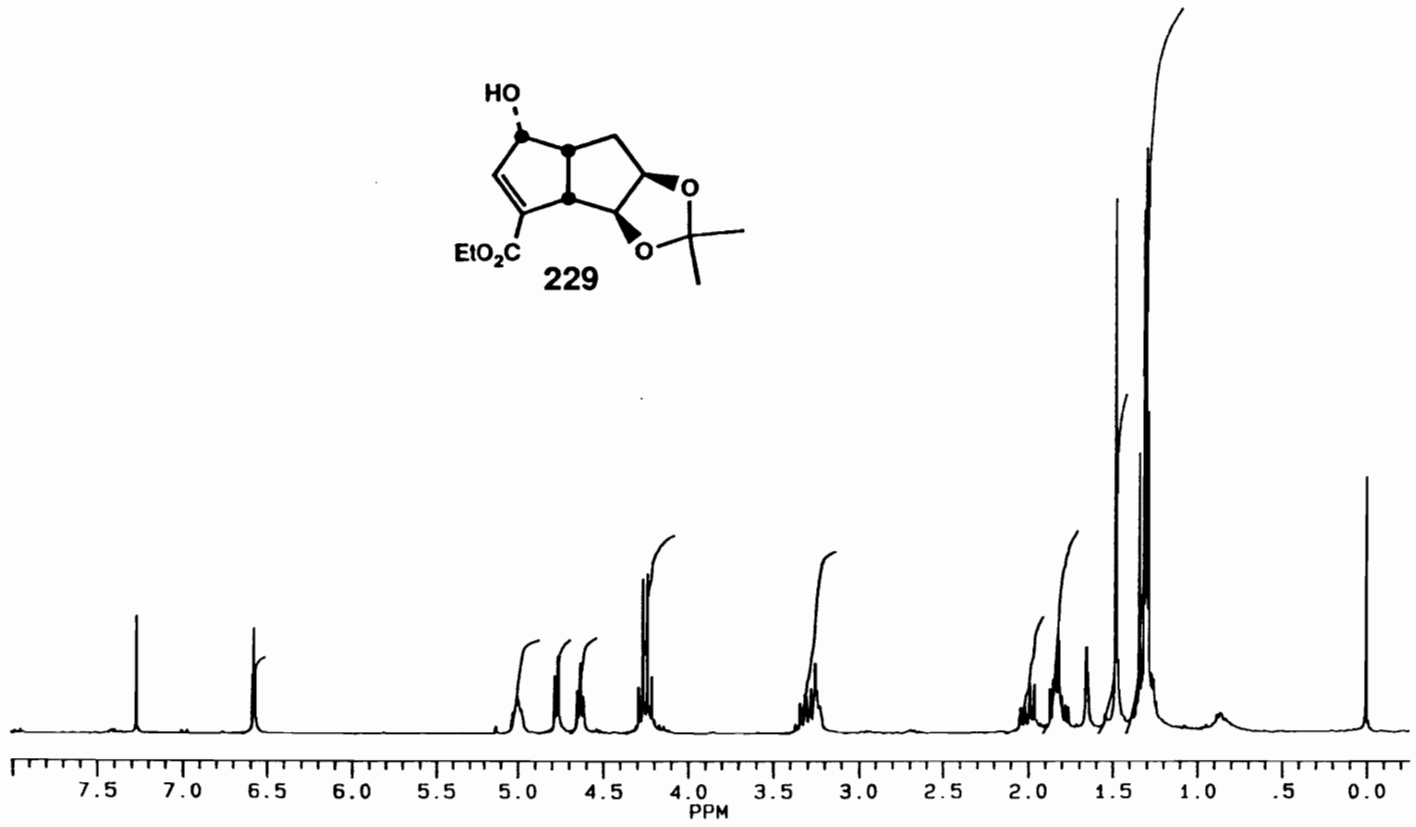



O
O
O
O
O
EtO_2C
225
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
.5
0.0
PPM


O
O
OH
O
O
O
EtO2C
226
8.5
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
.5
0.0
PPM


S
O
O
S
O
O
O
O
O
EtO2C
227
8.5
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
.5
0.0
PPM


100
50
0
79
91
108
121
137
147
165
177
193
80
100
120
140
160
180
100
50
0
211
233
253
269
200
220
240
260
280
300
320
HO
O
O
EtO2C
228
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
PPM
3.5
3.0
2.5
2.0
1.5
1.0
.5
0.0


HO
O
O
EtO2C
229
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
.5
0.0
PPM

F. References

(1) *The Funk and Wagnell New Comprehensive International Dictionary of the English Language: Encyclopedic Ed.*; J. G. Ferguson Pub. Co., New York; **1978**, 1572.

(2) Hudlicky, T.; Fan, R.; Lovelace, T. C.; Reed, J. W. "Synthesis of Natural Products Containing Five-Membered Rings. An Evolution of General Methodology." In *Studies in Natural Products Chemistry*; Atta-ur-Rahman, Ed.; Elsevier: New York, New York, **1989**; Vol. 3. Chapter 1. pp. 3-72.

(3) Hudlicky, T.; Seoane, G.; Price, J.; Gadmasetti, K. G. *Synlett*, **1990**, 433.

(4) Hudlicky, T.; Fleming, A.; Radesca, L. *J. Am. Chem. Soc.* **1989**, *111*, 6691, and references therein.

(5) Hudlicky, T.; Heard, N. E.; Fleming, A. *J. Org. Chem.* **1990**, *55*, 2270.

(6) For review of triquinane synthesis via vinylcyclopropane rearrangement see:

a) Wong, H. N. C.; Hon, M.-Y.; Tse, C.-W.; Yip, Y.-C.; Tanko, J.; Hudlicky, T. *Chem. Rev.* **1989**, *89*, 165.

b) Hudlicky, T.; Price, J. D. *Chem. Rev.*, **1989**, *89*, 1467.

c) Hudlicky, T.; Reed, J. W. "Rearrangements of Vinylcyclopropanes and Related Systems." In Comprehensive Organic Synthesis; Barry Trost, Ed.; Pergamon Press: New York, New York, **1991**,.Vol. 5, pp. 899-970.

d) Paquette, L. A. "Recent Synthetic Developments in Polyquinane Chemistry." In *Topics in Organic Chemistry* F. L. Boschke Ed.; Springer-Verlag: New York, New York, **1984**, Vol 119.

(7) Evans, D. Unpublished, private communication.

(8) Pirrung, M. C. *J. Am. Chem. Soc.*, **1979**, *101*, 7130; *Ibid*, **1981**, *103*, 82.

(9) Larsen, S. D. *J. Am. Chem. Soc.*, **1988**, *110*, 5932.

(10) Natchus, M. G. MS Thesis; Virginia Polytechnic Institute and State University, June, **1987**.

(11) a) Hudlicky, T.; Kutchan, T. M.; Wilson, S. R.; Mao, D. T. *J. Am. Chem. Soc.* **1980**, *102*, 6351.

b) Hudlicky, T.; Koszyk, F. J.; Kutchan, T. M.; Sheth, J. P. *J. Org. Chem.* **1980**, *45*, 5020.

(12) Kwart, L. D.; Tiedje, M.; Frazier, J. O.; Hudlicky, T. *Syn. Commun.* **1986**, *16*, 393.

(13) Hudlicky, T.; Kwart, L. D.; Tiedje, M. H.; Ranu, B. C.; Short, R. P.; Frazier J. O.; Rigby, L. *Synthesis* **1986**, 717.

(14) Short, R. P.; Revol, J-M.; Ranu, B. C.; Hudlicky, T. *J. Org. Chem.* **1983**, *48*, 4453.

(15) Hudlicky, T.; Natchus, M. G.; Sinai-Zingde G. *J. Org. Chem.* **1987**, *52*, 4641.

(16) Hudlicky, T.; Sinai-Zingde, G.; Natchus, M. G.; Ranu, B. C.; Papadopoulos, P. *Tetrahedron* **1987**, **43**, 5685.

(17) Hudlicky, T.; Radesca, L.; Luna, H. C.; Anderson, F. E., III *J. Org. Chem.* **1986**, *51*, 4647.

(18) Olah, G. A.; Narang, S. C. *Tetrahedron,* **1982**, *38*, 2225.

(19) Miller, R. D.; McKean D. R. *J. Org. Chem.* **1981**, *46*, 2412.

(20) Fleming, A.; Sinai-Zingde, G.; Natchus, M.; Hudlicky, T. *Tetrahedron Lett.* **1987**, *28*, 167.

(21) Hudlicky, T.; Radesca-Kwart, L.; Li, Q.; Bryant, T. *Tetrahedron Lett.* **1988**, *29*, 3283.

(22) *Handbook of Naturally Occuring Compounds;* Devon, T. K.; Scott, A. I., Eds.; Academic: New York, **1972**; Vol. 2.

(23) Fleming, A.; PhD Thesis; Virginia Polytechnic Institute and State University, October, **1989**. Also, see reference 5.

(24) Trost, B. M.; Kurozumi, S. Tetrahedron Lett. **1974**, 1929.

(25) Trost, B. M.; Nishimura, K.; Yamamoto, K.; McElvain, S. S. *J. Am. Chem. Soc.* **1979**, *101*, 1328.

(26) Piers, E.; Banville, J. *J. Chem. Soc., Chem. Commun.* **1979**, 1138.

(27) Salaun, J,; Olliver, *J. Nouv. J. Chim.* **1981**, *5*, 587.

(28) Yan, T. H.; Paquette, L. A. Tetrahedron Lett. **1982**, *23*, 3227.

(29) Wells, G. J.; Yan, T. H.; Paquette, L. A. *J. Org. Chem.* **1984**, *49*, 3604, 3610.

(30) Piers, E.; Law, C. K.; Nagakura, I. *Can. J. Chem.* **1983**, *61*, 288.

(31) Ranu, B. C.; Kavka, M.; Higgs, L. A.; Hudlicky, T. *Tetrahedron Lett.* **1984**, *25*, 2447.

(32) Salaun, J.; Almirantis, Y. *Tetrahedron* **1983**, *39*, 2421.

(33) Wender, P. A.; Hoegert, J. J. *Tetrahedron Lett.* **1983**, *24*, 5325.

(34) Barnier, J. -P.; Salaun, J. *Tetrahedron Lett.* **1984**, *25*, 1273.

(35) Wender, P. A.; Ternansky, R. J.; *Tetrahedron Lett.* **1985**, *26*, 2625.

(36) Ollivier, J.; Salaun, J. *J. Chem. Soc., Chem. Commun.* **1985**, 1269.

(37) Corey, E. J.; Meyers, A. G. *J. Am. Chem. Soc.* **1985**, *107*, 5574.

(38) Hudlicky, T.; Natchus, M. G. J. Org. Chem. **1992**, 57, (in preparation)

(39) For review of common biocatalytic methods see:

a) Empie, M. N.; Gross, A. *Annual Reports in Medical Chem.* **1988**, *23,* 305;

b) Klibanov, A. M. *ChemTech* **1986**, 354;

c) Butt, S.; Roberts, S. M. *Nat. Prod. Reports* **1986**, 489; *Chem. Brit.* **1987**, 127;

d) Whitesides, G. M. et al. *Chem. Brit.* **1987**, 645.

e) Turner, N. J. *Nat. Prod. Rep.* **1989**, 625.

f) Widdowson, D. A.; Ribbons, D. W.; *Janssen Chimica Acta* **1990**, *8*, 3.

g) Drueckhammer, D. G.; Hennen, W. J.; Pederson, R. L.; Barbas, C. F. III.; Gautheron, C. M.; Krach, T. K.; Wong, C.-H. *Synthesis* **1991**, 499.

(40) For review of Arene-cis Diols in synthesis see: Brown, S. M. In *Organic Synthesis: Theory and Applications;* Hudlicky, T., Ed.; JAI Press: Greenwich, Conneticut, **1992**, Vol. 2; in press.

(41) Gibson, D. T.; Koch, J. R.; Lallio, R. E. *Biochemistry* **1968**, *7*, 2653.

(42) Gibson, D. T.; Hensley, M.; Yoshioka, H.; Mabry, J. J. *Biochemistry* **1970**, *9*, 1626.

(43) Review: Gibson, D. T. *Crit. Rev. Microbiol.* **1971**, *1*, 199.

(44) a) Subramanian, V.; Liu, T. N.; Yeh, W. K.; Gibson, D. T. *Biochem. Biophys. Res. Commun.* **1979**, *91*, 1131;

b) Finetle, B.; Venkateswaran, S.; Gibson, D. T. *J. Bacter.* **1984**, *160*, 1003.

(45) Review: Hou, C. T. In *Microbial Transformation of Bioactive Compounds*; Rosazza, J. P., Ed.; CRC Press: Boca Raton, Fl, **1982**; Vol. 1.

(46) Boyd, D. R.; McMordie, R. A. S.; Porter, H. P.; Dalton, H.; Jenkins, R. O.; Howarth, O. W. J. C. S., *Chem. Commun.* **1987**, 1722.

(47) Jeffrey, A. M.; Yeh, H. J. C.; Jerina, D. M.; Patel, T. R.; Davey, J. F.; Gibson, D. T. *Biochemistry* **1975**, *14*, 575.

(48) Taylor, S. C. In *Enzymes in Organic Synthesis*, Ciba Foundation Symposium III. Pitman, London, **1985**, p. 71.

(49) ICI Plc, Eur. Pat. 76 606, **1983**, Biochemical Process.

(50) Brown, S. M.; Taylor, S. C. *Performance Chemicals* **1986**, Nov., 18.

(51) M. A. Jones, ICI Colours and Fine Chemicals, Blakeley, Manchester, England.

(52) Chlorodiol **180** as well as the bromo-derivative are commercially available from Genencor, Int., Rochester, NY and ICI Fine Chemicals, Manchester, UK.

(53) Ziffer, H.; Jerina, D. M.; Gibson, D. T.; Kobal, V. M. J. *Am. Chem. Soc.* **1973**, *95*, 4048.

(54) Ziffer, H.; Kabuto, K.; Gibson, D. T.; Kobal, V. M.; Jerina, D. M. *Tetrahedron* **1977**, *33*, 2491.

(55) Kobal, V. M.; Gibson, D. T.; Davis, R. E.;.Garza, A. *J. Am. Chem. Soc.* **1973**, *95*, 4420.

(56) Gibson, D. T.; Gschwendt, B.; Yeh, W. K.; Kobal, V. M. *Biochemistry* **1973**, *12*, 1520.

(57) Hudlicky, T.; Luna, H.; Price, J. D.; Rulin, F. *J. Org. Chem.* **1990**, *55*, 4683.

(58) Jeffrey, A. M.; Yeh, H. J. C.; Jerina, D. M.; Patel, T. R.; Davey, J. F.; Gibson, D. T. *Biochemistry* **1975**, *14*, 575.

(59) Deluca, M. E.; Hudlicky, T. *Tetrahedron Lett.* **1990**, *31*, 13.

(60) Akhtar, M. N.; Boyd, D. R.; Thompson, N. J.; Koreeda, M.; Gibson, D. T.; Mahadevan, V.; Jerina, D. M. *J. Chem. Soc.* **1975**, 2506.

(61) Boyd, D. R.; Dorrity, M. R. J. L.; Hand, M. V.; Malone, J. F.; Sharma, N. D.; Dalton, H.; Gray, D. J.; Sheldrake, G. N. *J. Am. Chem. Soc.* **1991**, *113*, 666.

(62) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543.

(63) Ley, S. V.; Redgrave, A. J.; Yeung, L. L. in *ACS Symposium Series, 'Myo-inositol phosphates: Synthesis and Theraputic Properties* (in press).

(64) Ley, S. V.; Redgrave, A. J. *Synlett* **1990**, 393.

(65) Hudlicky, T.; Luna, H.; Barbieri, G.; Kwart, L. D. *J. Am. Chem. Soc.* **1988**, *110*, 4735.

(66) Exerpted from reference 41.

(67) Hudlicky, T.; Rulin, F.; Tsunoda, T.; Luna, H.; Andersen, C.; Price, J. D. *Israel J.Chem.* **1992**, in Press.

(68) Carless, H. A. J.; Oak, O. Z. *Tetrahedron Lett.* **1989**, *30*, 1719.

(69) Sutbeyaz, Y.; Secen, H.; Balci, M. *J. C. S. Chem. Commun.* **1988**, 1330.

(70) Carless, H. A. J.; Oak, O. Z. *J. C. S. Chem. Commun.* **1991**, 61.

(71) a) Hudlicky, T.; Olivo, H.; Nugent, T.; Price, J. D.; Luna, H.; Anderson, C. M. *JCS, Perkin 1* **1991**, 2907.

b) Hudlicky, T.; Luna, H. *J. Am. Chem. Soc.* submitted.

c) Hudlicky, T.; Olivo, H. *Tetrahedron Lett.* **1991**, *32*, 6077.

(72) Ley, S. V.; Sternfeld, F. *Tetrahedron* **1989**, *45*, 3463.

(73) Hudlicky, T.; Price, J. D.; Rulin, F.; Tsunoda, T. *J. Am. Chem. Soc.* **1990**, *112*, 9439.

(74) Carless, H. A. J.; Billinge, J. R.; Oak, O. Z. *Tetrahedron Lett.* **1989**, *30*, 3113.

(75) Ley, S. V.; Sternfeld, F.; Taylor, S. *Tetrahedron Lett.* **1987**, *28*, 225.

(76) Ley, S. V.; Parra, M.; Redgrave, A. J.; Sternfeld, F. *Tetrahedron* **1990**, *46*, 4995.

(77) Ley, S. V.; Sternfeld, F. *Tetrahedron Lett.* **1988**, *29*, 5305.

(78) Hudlicky, T.; Luna, H.; Price, J. D.; Rulin, F. *Tetrahedron Lett.* **1989**, *30*, 4053.

(79) Hudlicky, T.; Price, J. D. *Synlett* **1990**, 159.

(80) Hudlicky, T.; Seoane, G. *J. Org. Chem.* **1989**, *54*, 4239.

(81) Hudlicky, T.; Price, J. D.; Olivo, H. O. *Synlett* **1991**, 645.

(82) Chang, C. C.; Nakanishi, K. *J. Chem. Soc.. Chem. Comm.*, **1983**, 605.

(83) Kim, B. H.; Jacobs, P. B.; Elliot, R. L.; Curran, D. P. *Tetrahedron*, **1988**, *44*, 3079.

(84) a) Aue, W. P.; Karhan, J.; Ernst, R. R. *J. Chem. Phys.* **1976**, *64*, 4226.

b) Wuthrich, K; Nagayama, K.; Ernst, R. R. *Trends Biochem. Sci.*, **1980**, *178.*

c) Hall, L. D.; Sanders, J. K. M. *J. Am. Chem. Soc.* **1980**, *102*, 5703.

(85) a) Classen, E. *Am. Chem. J.* **1888**, *10*, 328.

b) Clin, H.; Tanret, G.; Chollet, M. M. *C. R. Acad. Sci.*, **1943**, *216*, 677.

c) Chollet, M. M. *Bull. Soc. Chim. Biol.* **1946**, *28*, 668.

(86) Van der Eycken, E.; Van der Eycken, J.; Vandewalle, M. *J. Chem. Soc., Chem. Commun.* **1985**, 1719.

(87) Van der Eycken, E.; De Bruin, A.; Van Der Eycken, J.; Callant, P.; Vandewalle, M. *Tetrahedron*, **1986**, *42*, 5385.

(88) For a current compilation of compounds in the Iridoid family see:

a) Boros, C. A.; Stermitz, F. R. *J. Nat. Prod.* **1991**, *54*, 1173.

b) Ibid. **1990**, *53*, 1055.

c) El-Nagger, L. J.; Beal, J. L. J. *Nat. Prod.* **1980**, *43*, 649.

d) Devon, T. K.; Scott, A. I. *Handbook of Naturaly Occuring Compounds*; Academic Press:New York and London, **1972**, Vol. 2.

(89) For a comprehensive review of the biosynthesis of iridoids and secoiridoids see: Inouye, H.; Uesato, S. *Prog. Chem. Org. Nat. Prod.* **1986**, *50*, 169.

(90) Barger, G.; Scholtz, C. H*elv. Chem. Acta.* **1933**, *16*, 1343.

(91) Haha, G.; Werner, H. *Liebig's, Ann. Chem.* **1935, *520***, 123.

(92) Wenkert, E.; Bringi, N. V. *J. Am. Chem. Soc.* **1959**, *81*, 1474.

(93) Wenkert, E. *Experienta* **1959**, *15*, 165.

(94) Thomas, R. *Tetrahedron Lett.* **1961**, 544.

(95) Wenkert, E. *J. Am. Chem. Soc.* **1962**, *84*, 98.

(96) Money, T.; Wright, I. G.; McCapra, F.; Scott, A. I. *Proc. Natl. Acad. Sci. U.S.* **1965**, *53*, 901.

(97) McCapra, F.; Money, T.; Scott, A. I.; Wright, I. G. *Chem. Commun.* **1965**, 537.

(98) Money, T.; Wright, I. G.; McCapra, F.; Hall, E. S.; Scott, A. I. *J. Am. Chem. Soc.* **1968**, *90*, 4144.

(99) Geoggel, H.; Arigony, D. *Chem. Commun.* **1965**, 538.

(100) Yeowell, D. A.; Schmidt, H. *Experienta* **1964**, *20*, 250.

(101) Escher, S.; Loew, P.; Arigony, D. *Chem. Commun.* **1970**, 823.

(102) Battersby, A. R.; Brown, S. H.; Payne, T. G. *Chem. Commun.* **1970**, 827.

(103) Inouye, H.; Ueda, S.; Takeda, Y. C*hem. Pharm. Bull. (Japan)* **1972**, *20*, 1305.

(104) Hussain, N.; Leonard, J.*Tetrahedron Lett.*, **1987**, *28*, 4871.

(105) Van der Eycken, E.; Callant, P.; Vandewalle, M. *Tetrahedron Lett.*, **1985**, *26*, 367.

(106) Wohl, A.; Oesterlin, C. *Berichte*, **1901**, *34*, 1139.

(107) Chaudhuri, R. K.; Sticher, O. *Helv. Chim. Acta*, **1981**, *64*, 3.

(108) Alder, K.; Roth, W. *Chem. Ber.* **1954**, *87*, 161.

(109) Crandall, J. K.; Chang, L-H *J. Org. Chem.* **1967**, *32*, 532.

(110) Curran, D. P.; Jacobs, P. B.; Elliott, R. L.; Kim, B. H. *J. Am. Chem. Soc.*, **1987**, *109*, 5280.

(111) Fraiser-Reid, B.; McLean, A.; Usherwood, E. W.; Yunker, M. *Can. J. Chem.*, **1970**, *48*, 2877.

(112) Whitesell, J. K.; Allen, D. E. *J. Am. Chem. Soc.*, **1988**, *110*, 3585.

(113) For insight to the development of this method see the discussions and references cited in:

a) Whitesell; J. K.; Lawrence; R. M. *J. Org. Chem.* **1986**, *51*, 4779.

b) Whitesell; J. K.; Liu, C.-L.; Buchanan, C. B.; Chen, H.-H.; Minton, M. A. *J. Org. Chem.* **1986**, *51*, 551.

c) Whitesell, J. K.; Chen, H.-H.; Lawrence, R. M. *J. Org. Chem.* **1985**, *50*, 4663;

(d) Whitesell, J. K.; Allen, D. E. *J. Org. Chem.* **1985**, *50*, 3025.

(114) Griesbaum, K.; Jung, I. C.; Martens, H. *J. Org. Chem.* **1990**, *55*, 6024.

(115) Kende, A. S.; Fludzinski, P. *Org. Syn.* **1985**, *64*, 104.

(116) Hudlicky, T.; Fleming, A.; Lovelace, T. C.; *Tetrahedron*, **1989**, *45*, 3021.

(117) Barbieri-Arhancet, G. I., PhD Thesis; Virginia Polytechnic Institute and State University, December 1990.

(118) Hudlicky, T.; Barbieri, G. I. *J. Org. Chem.* **1992**, (in preparation)

(119) Hudlicky, T.; Nguyen, P. V *J. Org. Chem.* **1992**, *57*, xxxx.

(120) For leading references and review of allyl silane type cyclizations see: Majetich, G. In Organic Synthesis: *Theory and Applications* ; Hudlicky, T., Ed.; Jai Press Inc. Greenwich, Ct. **1989**, Vol 1, pp 173 - 240.

(121) Halides are commonly considered to be soft nucleophiles: March, J. *Advanced Organic Chemistry*, 3rd Ed.; John Wiley and Sons: New York, **1985**, p. 228, and references within.

(122) With enones, soft nucleophiles are known to prefer attack at the β–carbon rather than the carbonyl carbon: Carey, F. A.; Sundberg, R. J. *Advanced Organic Chemistry*, Part B.; 2nd Ed.; Plenum: New York, **1983**; pp 30 - 32.

(123) Miller, R, D.; McKean, D. R. *J. Org. Chem.* **1981**, *46*, 2412.

(124) Dieter, R. K.; Pounds, S. *J. Org. Chem.* **1982,** *47*, 3174.

(125) Fleming, A. Unpublished results.

(126) Mitsunobu, O. *Synthesis* **1981**, 1.

(127) Wild, C.; Heard, N.; Hudlicky, T. Unpublished Results

(128) Hua, D. H.; Venkataramen, S.; Ostrander, R. H; Sinai-Zingde, G.;McCann, P. J. *J. Org. Chem.* **1988**, *53*, 507.

(129) a) Johnson, C. R.; Penning, T. D. *J. Am. Chem. Soc.* **1986**, 108, 5655. b) ibid, **1988**, *110*, 4726.

(130) Deardorff, D. R.; Shambayati, S.; David C. M.; Heerding, D. *J. Org. Chem.* **1988**, *53*, 3614.

(131) Borchardt, R. T.; Wolfe, M. S.; Anderson, B. L.; Borcherding, D. R.; *J. Org. Chem.* **1990**, *55*, 4712.

(132) Borchardt, R. T.; Borcherding, D. R.; Scholtz, S. A. *J. Org. Chem.*, **1987**, *52*, 5457.

(133) Bestmann, H. J.; Roth, D. *Synlett* **1990**, 751; *Angew. Chem.* **1990**, *102*, 99.

(134) Ali, S. M.; Ramesh, K.; Borchardt, R. T. *Tetrahedron Lett.* **1990**, 31, 1509.

(135) Berlanger, P.; Prasit, P. *Tetrahedron Lett.* **1988**, *29*, 5521.

(136) Flann, J. C.; Mash, E. A. *Synth. Comm.* **1988**, *18*, 391.

(137) Hudlicky, T.; Natchus, M.; Nugent, T. *Synthetic Comm.* 1992, 21, xxx.

(138) Griesbaum, K.; Zwick, G.; Agarwal, S.; Keul, H.; Pfeffer, B.; Murray, R. W. *J. Org. Chem.* **1985**, *50*, 4194.

(139) Griesbaum, K.; Zwick, G. *Chem. Ber.* **1986**, *119*, 229.

(140) Bailey, P. *Ozonation in Organic Chemistry*, Acad. Press: New York, **1978**, Vol. 1: **1982**, Vol. 2.

(141) Griesbaum, K.; Martens, H.; Jung, I. C. *Can. J. Chem.* **1990**, *68*, 1369.

(142) For review see: Posner, G. H.; Runquist, A. W.; Chapdelaine, M. J.; Babiak, K. A.; Gurria, G. M.; Ellis, J.; Ponton, J.; Oda, M.; Miura, K.; Okada, S. S.; Rogers, D. Z.; Rose, R. K. *ACS Symposium on Imobilized Homogeneous Catalysts* **1982**, 661.

(143) a) Hudlicky, T.; Srnak, T. *Tetrahedron Lett.* **1981**, *22*, 3351.

b) Muzart, J. *Synthesis* **1982**, 60.

c) Posner, G. H. *Angew. Chem.* **1978**, *90*, 527; *Angew. Chem., Ed. Engl.* **1978**, *17*, 487.

(144) Private communication with Phuoc Nguyen

(145) Private communication with Nina Heard

(146) Ohle, H.; Berend, G. *Ber.* **1925**, *58*, 2590; see also:*ibid.* **1924**, *57*, 1571.

(147) Guthrie, R. D.; Honeyman, J. *J. Chem. Soc.* **1959**, 853.

(148) Fleet, G. W. J.; Ramsden, N. G.; Witty, D. R. *Tetrahedron* **1989**, *45*, 319.

(149) Quinkert, G.; Fernholz, E.; Eckes, P.; Neumann, D.; Durner, G. *Helv. Chim. Acta.* **1989**, *72*, 1753.

(150) Brimacoube, J. S.; Kabir, A. K. M. S. *Carbohydrate Res.* **1986**, *150*, 35.

(151) Ho, P-T. *Can. J. Chem.* **1979**, 381.

(152) Leonard, N. J.; Carraway, K. L. *J. Heterocycl. Chem.* **1966**, *3*, 485.

(153) Conia, J. M.; Limasset, J. C. *Bull. Soc. Chim. Fr.* **1967**, *6*, 1636.

(154) Dauben, W. G.; Walker, D. M. *J. Org. Chem.* **1981**, *46*, 1103.

(155) a. Walsh, A. D. *Nature (London)* **1947**, *159*, 167, 712.

b. Sugden, T. M. Nature (London) **1947**, *160*, 367.

(156) For review of cyclopropyl group chemistry see:

a. Rappoport, Z., Ed. *The Chemistry of the Group, Parts 1 and 2*; Wiley: New York, **1987**.

b. Greenberg, A.; Liebman, J. F. *Strained Organic Molecules*; Academic Press: New York, **1978**.

(157) Drumright, R. E.; Mas, R. H.; Merola, J. S.; Tanko, J. M. *J. Org. Chem.* **1990**, *55*, 4099.

(158) Tanko, J. M.; Mas, R. H.; Suleman, N. K. *J. Am. Chem. Soc.* **1990**, *112*, 5557.

(159) For review see:

a) Barton, D. H. R.; Motherwell, W. B. *Pure. Appl. Chem.* **1981**, *53*, 15.

(160) Hudlicky, M. *Reductions in Organic Chemistry*, Ellis Harwood Limited: Chichester, England, **1984**, pp 156 - 158, and references within.

(161) Miller, A. E. G.; Biss, J. W.; Schwarzman, L. H. *J. Org. Chem.* **1959**, *24*, 627.

(162) Martin, S. F.; Dodge, J. A. *Tetrahedron Lett.* **1991**, *32*, 3017.

(163) For review see: Howells, R. D.; McCrown, J. D. *Chem. Rev.* **1977**. *77*. 69.

(164) Luna, H. Unpublished results

(165) Beer, D.; Meuwly, R.; Vasella, A. *Helv. Chim. Acta* **1982**, *65*, 2570.

G. Vitae

Michael George Natchus was born in Richmond Virginia on November 27, 1962 to George and Iris Natchus. He recieved his Bachelors, Masters and PhD degrees from Virginia Polytechnic Institute and State University. During his stay there, he was married to his beloved wife Penny Papadopoulos in 1987. Before pursuing his PhD, he worked for TDC research as a technician preparing pharmaceuticals on a contract basis. After finishing his PhD work, he took a postdoctoral position at Stanford University under the direction of Dr. Paul Wender.

While working on his education, Michael actively suported himself as a musician in the local area and took positions as a drummer, bassist and freelance sound technician. He was fortunate enough to enlist the support of other chemists with exeptional musical talents who included Dr. Tomas Hudlicky, Dr. David Becker and Penny Papadopoulos. Their band, Dr. Work-Me-Not, performed at many local events and night clubs and were engaged to play at the 23rd Annual Gordon Conference in New Hampton, New Hamshire in 1992. Among his other collegues at that time were River Pheonix, "Queen of the Blues" Koko Taylor, The Noise Boys, Saphire and The Richard Jesse Project.

In the interrest of his health and well-being, Michael earned the level of green belt in 1991 in karate under the capable guidance of Dr. Ed Hampton.

G. Vitae

Michael George Natchus was born in Richmond Virginia on November 27, 1962 to George and Iris Natchus. He recieved his Bachelors, Masters and PhD degrees from Virginia Polytechnic Institute and State University. During his stay there, he was married to his beloved wife Penny Papadopoulos in 1987. Before pursuing his PhD, he worked for TDC research as a technician preparing pharmaceuticals on a contract basis. After finishing his PhD work, he took a postdoctoral position at Stanford University under the direction of Dr. Paul Wender.

While working on his education, Michael actively suported himself as a musician in the local area and took positions as a drummer, bassist and freelance sound technician. He was fortunate enough to enlist the support of other chemists with exeptional musical talents who included Dr. Tomas Hudlicky, Dr. David Becker and Penny Papadopoulos. Their band, Dr. Work-Me-Not, performed at many local events and night clubs and were engaged to play at the 23rd Annual Gordon Conference in New Hampton, New Hamshire in 1992. Among his other collegues at that time were River Pheonix, "Queen of the Blues" Koko Taylor, The Noise Boys, Saphire and The Richard Jesse Project.

In the interrest of his health and well-being, Michael earned the level of green belt in 1991 in karate under the capable guidance of Dr. Ed Hampton.