INFORMATION TO USERS

This manuscript has been reproduced from the microfilm master. UMI films the text directly from the original or copy submitted. Thus, some thesis and dissertation copies are in typewriter face, while others may be from any type of computer printer.

The quality of this reproduction is dependent upon the quality of the copy submitted. Broken or indistinct print, colored or poor quality illustrations and photographs, print bleedthrough, substandard margins, and improper alignment can adversely affect reproduction.

In the unlikely event that the author did not send UMI a complete manuscript and there are missing pages, these will be noted. Also, if unauthorized copyright material had to be removed, a note will indicate the deletion.

Oversize materials (e.g., maps, drawings, charts) are reproduced by sectioning the original, beginning at the upper left-hand corner and continuing from left to right in equal sections with small overlaps.

Photographs included in the original manuscript have been reproduced xerographically in this copy. Higher quality 6" x 9" black and white photographic prints are available for any photographs or illustrations appearing in this copy for an additional charge. Contact UMI directly to order.

Bell & Howell Information and Learning
300 North Zeeb Road, Ann Arbor, MI 48106-1346 USA
800-521-0600

UMI®

Université d'Ottawa • University of Ottawa

The Effect of DBU on the Tandem Oxy-Cope/Ene Reaction and Total Synthesis of (+)-Arteannuin M

by

Dan Deon

B.Sc. (Honours), Dalhousie University, 1999

A Thesis Submitted to the School of Graduate Studies and Research In Partial Fulfillment of the Requirements for the Degree of Master of Science

Ottawa-Carleton Chemistry Institute
Department of Chemistry
University of Ottawa
Ottawa, Ontario
Canada

Candidate	Supervisor
Daniel H. Deon	Dr. L. Barriault

The University of Ottawa

August 2001

National Library of Canada
Acquisitions and Bibliographic Services
395 Wellington Street
Ottawa ON K1A 0N4
Canada

Bibliothèque nationale du Canada
Acquisitions et services bibliographiques
395, rue Wellington
Ottawa ON K1A 0N4
Canada

Your file Votre référence

Our file Notre référence

0-612-67804-0

TABLE OF CONTENTS

LIST OF SCHEMES

LIST OF FIGURES

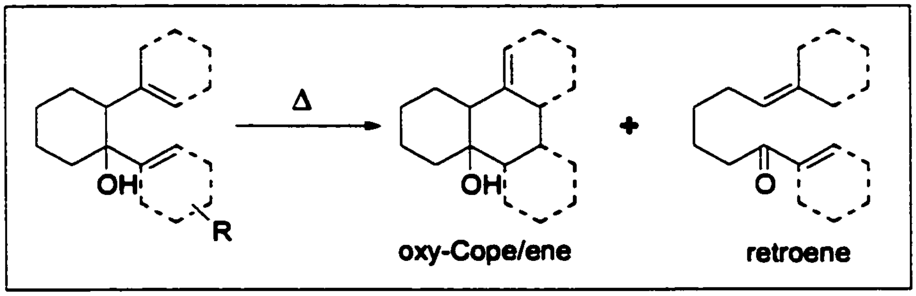
LIST OF ABBREVIATIONS

Bn	benzyl
*t*Bu	tertiary butyl
DBU	1,8-diazobicyclo[5.4.0]undec-7-ene
DCC	1,3-dicyclohexylcarbodiimide
DMAP	4-dimethylaminopyridine
DPS	tertiarybutyldiphenylsilyl
eq.	equivalents
Et	ethyl
Ether	diethyl ether
g	grams
HPLC	high pressure liquid chromatography
HRMS	high resolution mass spectrum
*i*Pr	isopropyl
IR	infrared
l	litres
LDA	lithium diisopropylamide
Me	methyl
ml	milliltres
mp	melting point
NMR	nuclear magnetic resonance
Ph	phenyl

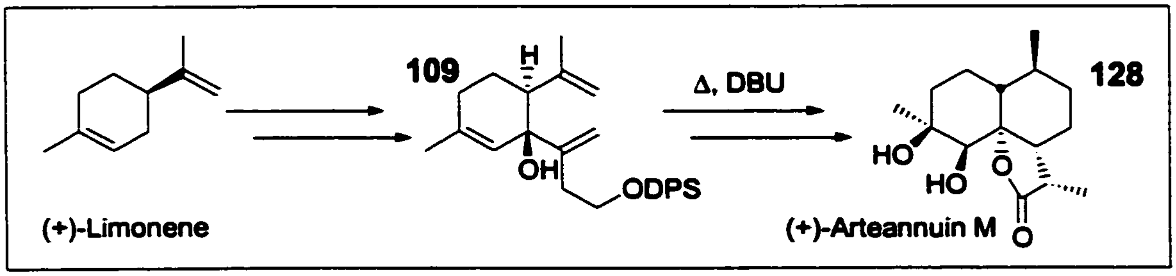
ppm	parts per million
Py	pyridine
TBAF	tetrabutylammonium fluoride
THF	tetrahydrofuran
TLC	thin layer chromatograpy
TMS	trimethylsilyl
μl	microlitres

ABSTRACT

Tandem reactions have been proven to be powerful methods for creating new types of carbon-carbon bonds in organic synthesis. One such type of reaction is the oxy-Cope/ene reaction of 1,2-divinylcyclohexanols. This reaction has been shown to be a highly diastereoselective method for creating polycyclic compounds with tertiary alcohols at a ring junction. Unfortunately, in many of the previously reported cases, undesired retroene products were also observed.



A new method has been developed that increases the ratio of oxy-Cope/ene with respect to retroene product that involves the use of DBU as a co-solvent in this reaction. This methodology was applied to intermediate **109** (readily obtainable from (+)-limonene) as a key step in the total synthesis of (+)-Arteannuin M (**128**), a potential drug for the treatment of malaria.



ACKNOWLEDGEMENTS

First and foremost I would like to thank my supervisor Dr. Louis Barriault for his guidance, patience and support throughout all phases of this project. I cannot imagine a better environment in which to have completed my Masters degree. Louis always gave me the freedom to investigate interesting aspects of the projects we worked on and in the process I learned a great deal. I will never forget his favourites: stereoelectronic effects, Diels-Alder processes and FMO theory. During my stay in Ottawa, Louis was not only a great supervisor but also a good friend.

Thanks to Dr. Tony Durst and Dr. Alex Fallis with whom I shared many interesting and helpful conversations over the past two years, not only about chemistry but also about life.

Although we had our share of ups and downs, I owe much gratitude to labmate Irina Denisova for our sometimes helpful discussions. Big thanks to my other labmates: 'the ol'' Jeff Warrington, Jermaine Thomas, Roxanne Clement, Valerie Charboneau, Ross Maclean and Danny Gauvreau. Long after the chemistry has been forgotten, I will remember you.

I also want to give a big shout out to everyone here in the department with whom I shared many a good time: Pat Bazinet, Romyr, Joe, Brad, Bingcan, Mary, Sam, Gan, Cindy, Marie, Tamara, Dr. Morin, Matt, Deyu and everyone else. Thanks for making my time here in Ottawa truly memorable.

Sandra Rifai has been a huge part of my life not only the past two years, but since Dr. Grundy's class back at Dalhousie. I could never repay her for all of the kindness she has shown me, such that I could dedicate this entire page to her. Thanks for the breakfast, lunch and supper; quantum, analytical and phys chem and everything else. I love you. "Sauce."

Thanks to both Dr. Glenn Facey (who made me laugh and cry on several occasions) and Raj Capoor for all of their help pertaining to NMR spectroscopy.

Keep on rockin' Dr. Grindley. Go 'G' Force!!

Thanks to Dr. Sean Barry for proofreading this thesis.

Finally thank you to my parents Hubert and Barbara for their emotional, spiritual and financial (Mom) support. Thank-you for having me, Marcia and Mark. I love you both very much and I fear that I will never be able to do enough to repay you.

Thanks to God; Giver of salvation, Creator of chemistry and Sustainer of life.

To my parents, Hubert and Barbara D'Eon.....

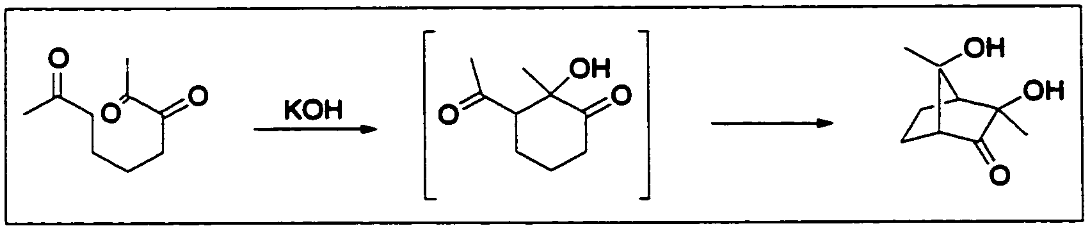
Chapter 1: Introduction

1.1 Tandem Reactions

Tandem reactions may be defined as those that occur in successive order.[1] Not only are they a good way to make new carbon-carbon bonds but they also provide a powerful method for creating advanced intermediates for the synthesis of natural products. Due to awareness in the chemical literature, many genuine tandem reactions are not defined as being tandem. To avoid confusion, a proper tandem reaction may be defined as one that involves a series of two or more reactions occurring in a distinct order and if sequential reagents are added, these reagents must be incorporated into the final product. For example, an aldol condensation followed by dehydration can be considered as a tandem reaction, but if a new reagent is employed in the dehydration step, each reaction will be considered as specific.

Tandem reactions are made up of commonplace reactions and thus, no particular expertise is needed to understand them. What makes tandem reactions unique is that the structural prerequisite that is not present in the starting material but is necessary for the secondary reaction to occur, is triggered by the initial reaction. In essence, the first reaction in a tandem process can be regarded as a deblocking of a certain functionality within the molecule, but achieves far more toward the synthetic goal.

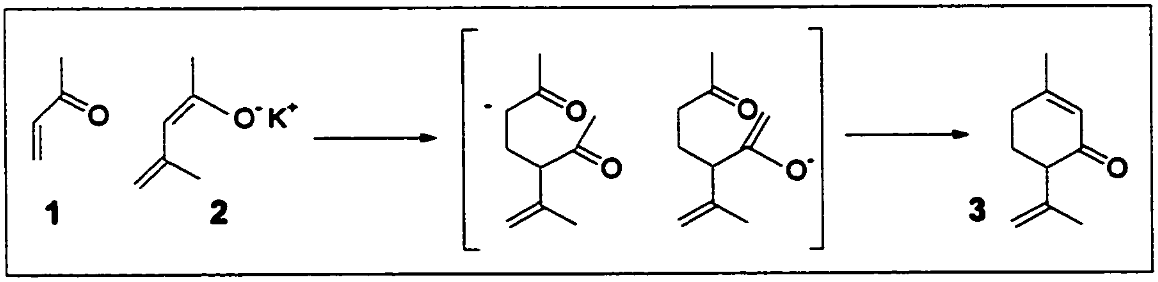
One particular type of tandem reaction involves multiple aldol condensations, which can occur when a molecule has the proper spacing of its carbonyl groups (Scheme 1).[2]



Scheme 1: Multiple Aldol Condensations

For the construction of six-membered cyclohexenones, Robinson annulation has served organic chemists well over the years. Robinson annulation can be defined as a Michael/Aldol tandem reaction that involves a base catalysed Michael reaction between an enolate and an α,β-unsaturated ketone, an intramolecular aldol reaction and finally dehydration.[3]

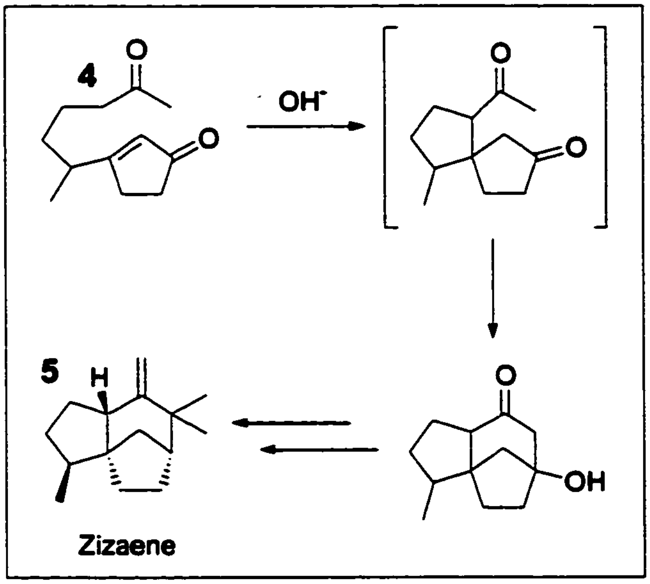
The annualtion of mesityl oxide (2) with methyl vinyl ketone (1) is a good method for making piperitenone (3) (Scheme 2).[4] To avoid the self condensation of mesityl oxide to form isoxylitone, the reaction may be done under heterogeneous conditions such as KOH in THF.



Scheme 2: Annulation of Mesityl Oxide

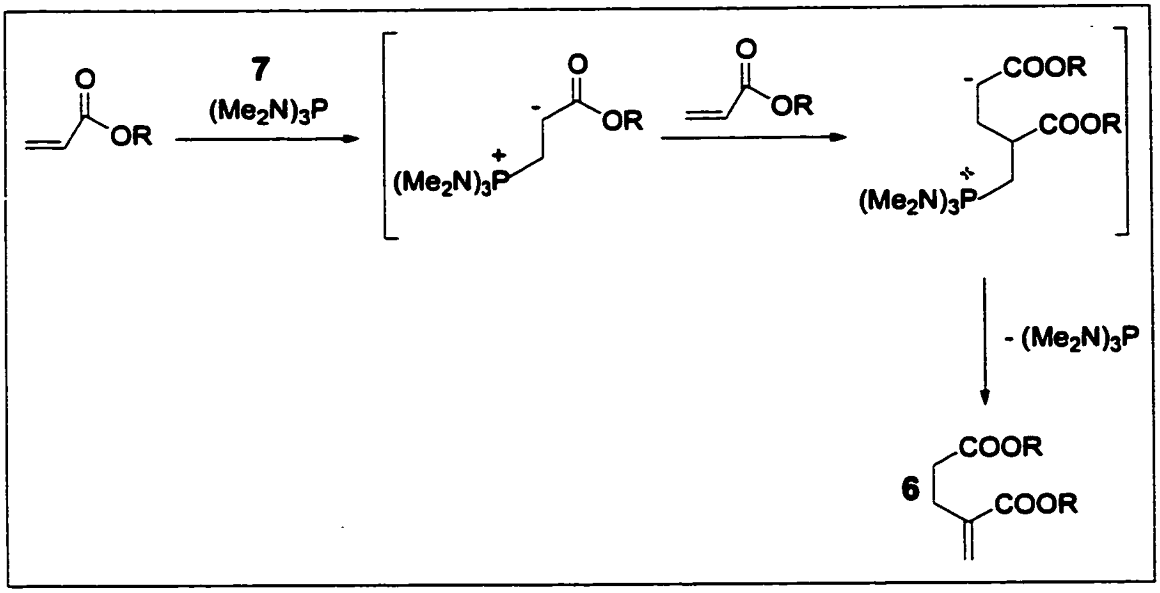
Many total syntheses have made use of the tandem Michael/aldol process as a key step for the construction of an internal ring.[5] The utility of the intramolecular

Michael/aldol reaction for the construction of a bridged ring system as imposed by the relative location of the two ketone groups in **4** is well illustrated in the synthesis of zizaene (**5**) (Scheme 3).[6]



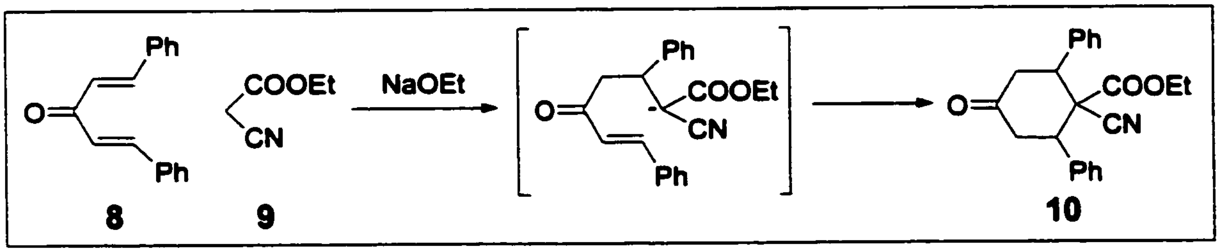
Scheme 3: Alexakis' Approach to Zizaene

Two bonds may be formed in one step by a double Michael tandem process. β-unsaturated acrylic esters for which enolization is not an option may be functionalized at the α-position by a double Michael reaction. Tertiary amines and phosphines catalyze the dimerization of acrylic esters by forming zwitterions which can add to a second molecule of the acrylic ester. Intramolecular or intermolecular proton transfer causes elimination to occur which then regenerates the catalyst. A series of 2-methyleneglutaric esters (**6**) were synthesized by Amri by using trisdimethylaminophosphine (**7**) as a catalyst (Scheme 4).[7]

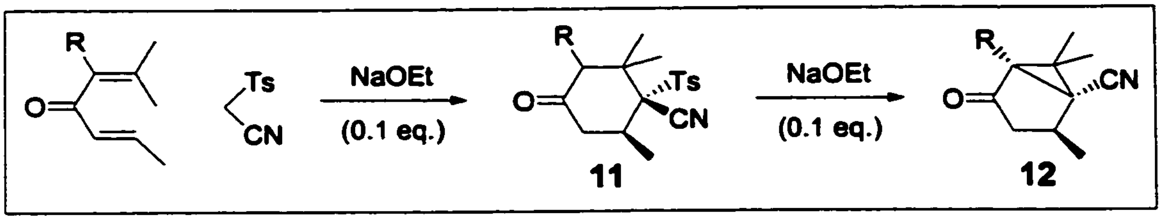


Scheme 4: Amri's Synthesis of 2-Methyleneglutaric Esters

The double Michael reaction is very useful when reactions are controlled to give the desired products. Cross-conjugated dieneones such as **8** can be transformed directly into six-membered ring compounds (**10**) by reaction with Michael donors containing an active XH_2 unit (**9**) (Scheme 5).[8] In the event that one of the activating groups is also a good leaving group, as is the case with **11**, 1,3-elimination of the cyclic ketones may be induced to generate species such as **12** (Scheme 6).[9]



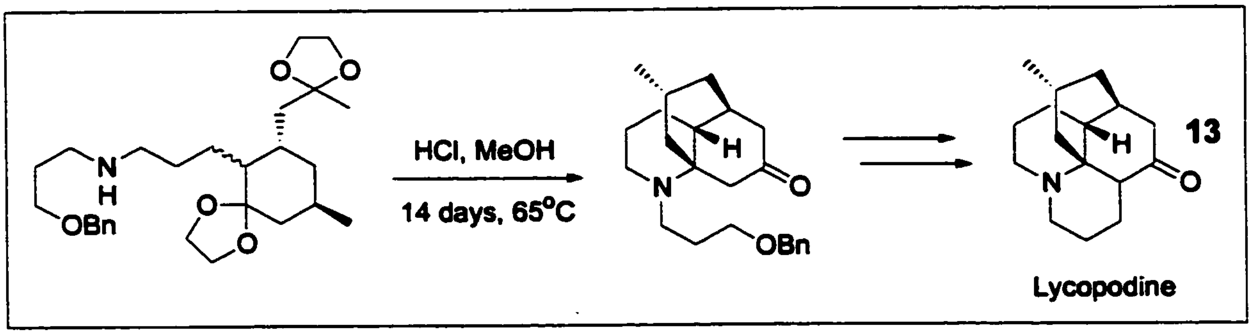
Scheme 5: Double Michael Reaction of Cross Conjugated Dieneones



Scheme 6: Double Michael Reaction of Cross Conjugated Dieneones

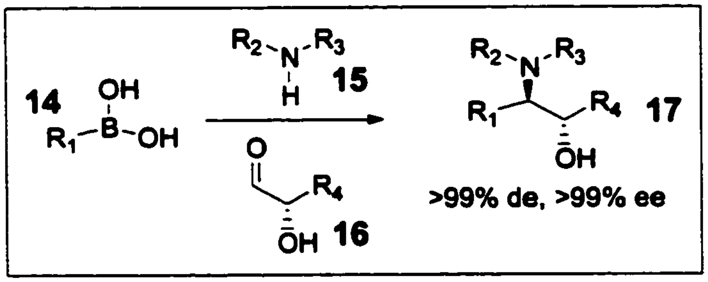
Three components are involved in the Mannich reaction. An amine (usually secondary) and a carbonyl undergo condensation to form an iminium species that is then intercepted by an enol (donor species). By this interpretation the Mannich reaction is an authentic tandem process.

Azabicyclic structures may be formed from self-condensation of aminodicarbonyl compounds. In order for these reactions to be useful, they must be well planned out to ensure that the first step is regioselective. This is illustrated in scheme 7, which shows an approach by Heathcock, toward the molecule lycopodine (13).[10] The formation of a six-membered ring is preferred over an eight-membered ring once the imine has been formed.



Scheme 7: Heathcock's aproach to Lycopodine

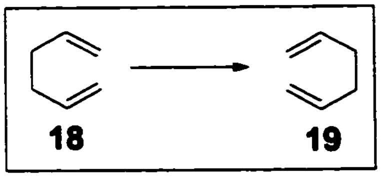
More recently, Petasis and Zavialov have reported a highly stereocontrolled one-step synthesis of *anti*-β-amino alcohols.[11] This one-step three-component reaction is illustrated in scheme 8, where an organoboronic acid **14**, an amine **15**, and an α-hydroxy aldehyde **16** directly give the corresponding β-amino alcohol **17**. The reaction proceeds with a very high degree of diastereocontrol, exclusively forming the *anti*-products in greater than 99% de. When optically pure α-hydroxy aldehydes are used, no racemization occurs, and the products are obtained as single enantiomers, with greater than 99% ee.



Scheme 8: *Petasis' One-Step Synthesis of Anti-β-Amino Alcohols*

1.2 The Cope Rearrangement

The Cope rearrangement, discovered by Arthur Cope in 1940, involves the transformation of a 1,5-hexadiene (**18**) system into an isomeric 1,5-hexadiene (**19**) by a [3,3]-sigmatropic mechanism (Scheme 9).[12] Cope rearrangements are generally reversible processes. Since there are no changes in the number of types of bonds present in the final product with respect to the initial substrate, the total bond energy remains unchanged. Because of this, the position of the final equilibrium will be governed by the substituents present on the 1,5-diene system that influence the relative stability of the starting material, and product.



***Scheme 9:** The Cope Rearrangement*

The Cope rearrangement is both stereospecific and stereoselective. It is stereospecific since the configuration at the terminal olefins, *Z* or *E*, is maintained throughout the transition state and governs the stereochemical outcome of the final product.[13] When the possibility of having either the *E* or *Z* stereoisomer for the final product arises, there will be stereoselectivity in favor of one. Cope rearrangements usually proceed via chairlike transition states and the stereochemical outcome will be consistent with that which has the larger substituent at C-3 (or C-4) in the equatorial-like conformation (Figure 1).

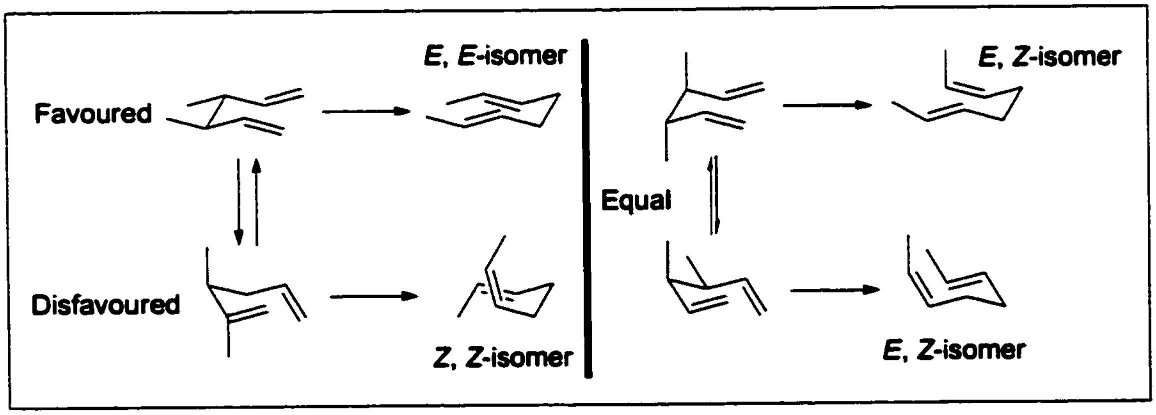


***Figure 1:** Stereospecificity and Stereoselectivity in the Cope Rearrangement*

This interesting stereochemical feature of the Cope rearrangement can be explained by frontier molecular orbital theory. Examination of the frontier orbitals of the chair and boatlike transition states reveals that there is an antibonding interaction between the lobes on C-2 and C-2^i (Figure 2). In the chairlike transition state, these orbitals are too far apart to interact, thus making it the preferred of the two transition states.

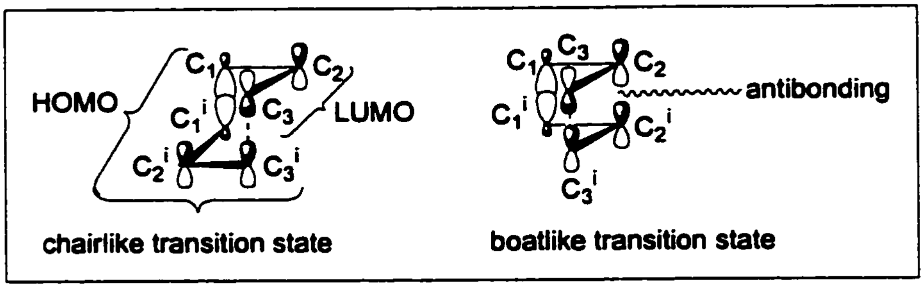
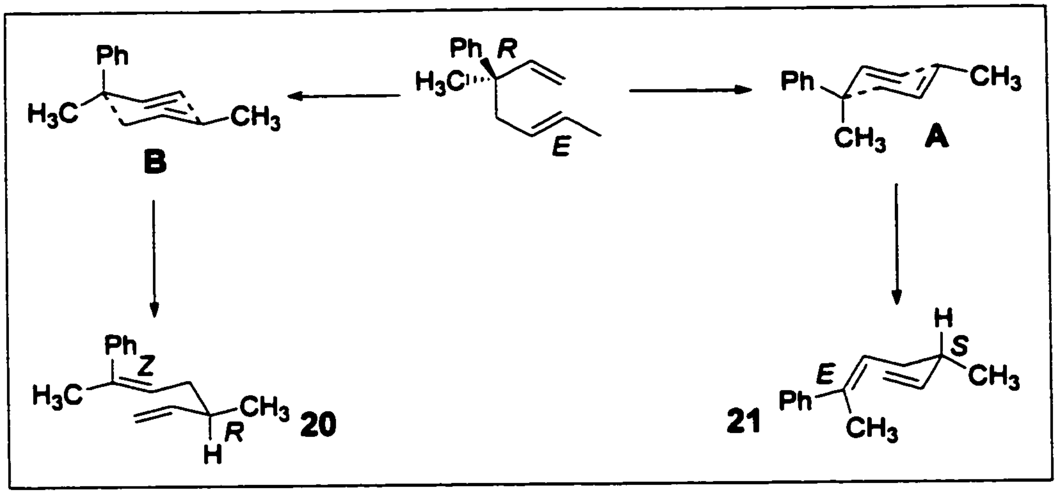


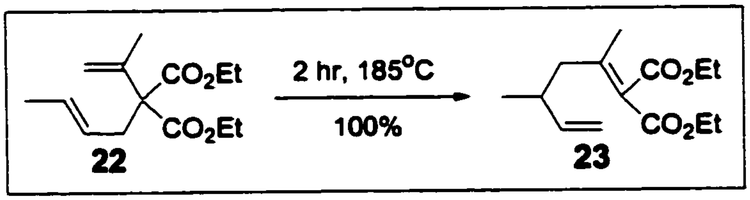
Figure 2: FMO View of the Cope Rearrangement

Since the mechanism is a concerted one, the chiral center at C-3 or C-4 will lead to the enantiospecific formation of the new chiral center at C-1 or C-6.[14] These associations are shown in scheme 10. The chairlike transition state dictates the configuration of both the new chiral center and the new double bond. Although there are two stereogenic centers from which 4 possible stereoisomers could be formed, only two are produced. The isomer that contains the *E*-olefin has the *S*-configuration at C-4 (**20**) whereas the *Z*-isomer has the *R*-configuration at C-4 (**21**). The two competing chair transition states will govern the stereochemistry of the new double bond. The relative amount of the products **20** and **21** is determined by the relative stability of the two transition states, which is based on the Curtin-Hammet principle.[15] Because of its axially oriented phenyl group, transition state **B** will be the less preferred making **20** the minor product of the reaction.



Scheme 10: Stereochemistry of the Cope Rearrangement

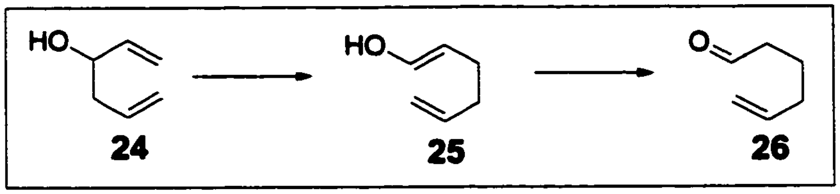
In his original publication, Cope constructed his 1,5-hexadiene systems such that the driving force of the reaction would be the ensuing double bond conjugation with cyano, carbethoxy or phenyl groups.[16] Good to excellent yields were recovered for the rearrangement of these systems at 150 to 200°C. An example is shown in scheme 11, where the malonic ester derivative **22** provides product **23** in quantitative yield after 2 hours at 185°C.



Scheme 11: Cope Rearrangement to Conjugated Products

1.3 The Oxy-Cope Rearrangement

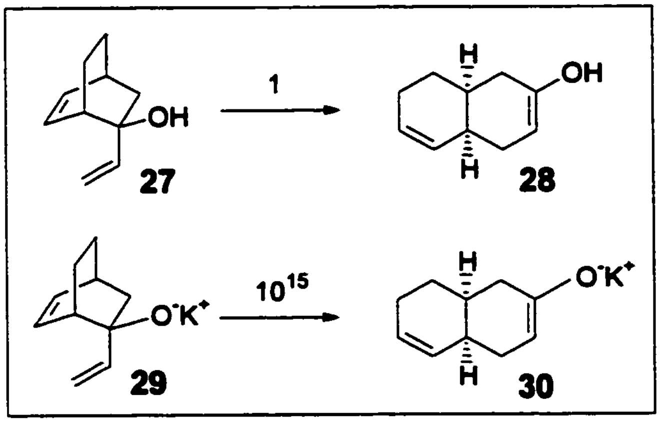
In 1964, Berson coined the term "oxy-Cope rearrangement" to describe Cope rearrangements of 1,5-hexadienes bearing a hydroxyl group at the C-3 position (**24**).[17] Attachment of a hydroxyl group at C-3 generates an enol (**25**) after rearrangement, which then undergoes ketonization to provide the δ,ε-unsaturated carbonyl compound **26**, which is the net driving force of the reaction (Scheme 12). This was demonstrated by heating **27** in the gas phase in an ammonia-washed tube at 320°C, which gave **28** as 90% of the isolated material (Scheme 13).



Scheme 12: *The Oxy-Cope Rearrangement*

1.4 The Anionic Oxy-Cope Rearrangement

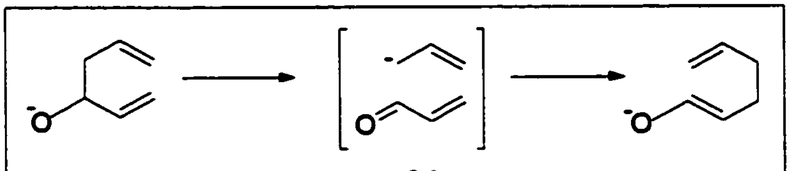
In 1975 Evans discovered that an increase in reaction rate (~10^{15}) was observed when the oxanion (**29**) of the oxy-Cope substrate was produced (Scheme 15).[18] This base catalysed reaction was dubbed the "anionic oxy-Cope rearrangement".



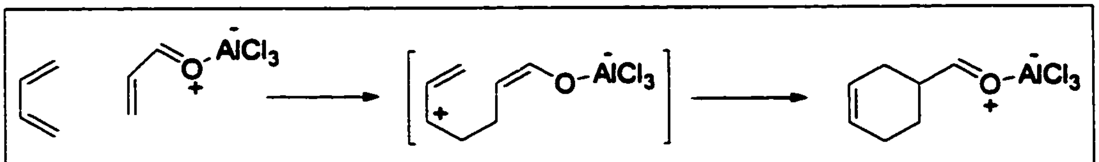
Scheme 13: *Oxy-Cope Rearrngement of 27 versus Anionic Oxy-Cope Rearrangement of 29*

In this case, the formation of an anion provides an electron "push" that aids in the breaking of carbon-carbon bonds.[19] Making the anion more basic and therefore less stable can increase the rates of anionic oxy-Cope rearrangements. Using more polar solvents or the addition of complexing agents such as crown ethers can accomplish this as well.[20] It is also known that sterically hindered alkoxides, derived from tertiary alcohols, usually react faster. With respect to cation coordination at the oxy anion, the trend in reactivity is $Cs^+ > K^+ > Na^+ > Li^+$.[21] This is based on the hardness of the cation and its ability to coordinate to the oxygen anion.

One can write a polarized transition state **31** for the anionic oxy-Cope rearrangement that resembles an anion-carbonyl complex (Scheme 14). This formalism can be compared to the Lewis acid catalysis (Scheme 15) of the Diels-Alder reaction where stabilization of the bond-making step **32** is important. Thermodynamic estimation indicates that bond weakening by an alkoxide susbtituent provides 13-17 kcal/mol for cleavage of the sigma bond.[22] Ab initio calculations also confirm the dramatic effect of the alkoxide substituent in weakening an adjacent bond.


31

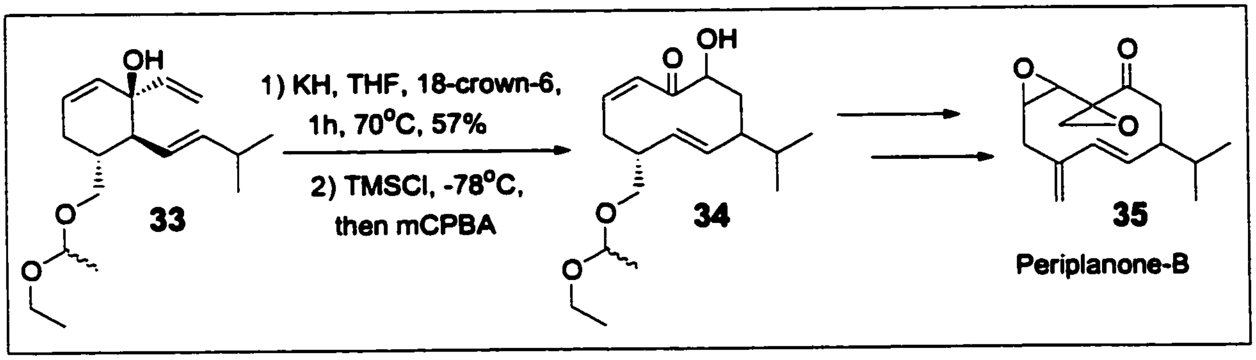
Scheme 14: Polarized Transition State for the Anionic Oxy-Cope Rearrangement


32

Scheme 15: Lewis Acid Catalysis of the Diels-Alder Reaction

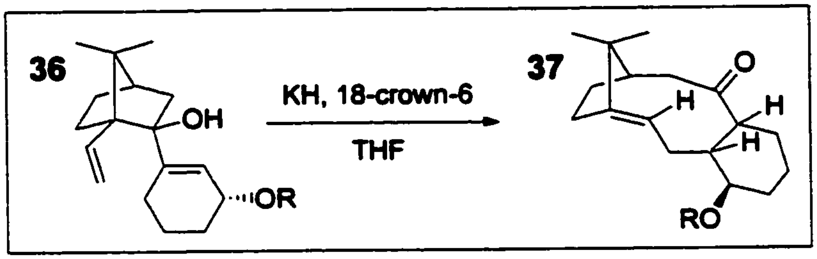
Oxy-Cope rearrangements and their anionic counterparts have played a key role in recent years in the synthesis of natural products. In the total synthesis of perplanone-

B (**35**) by Still, an anionic oxy-cope rearrangement of **33** was used to synthesize the key intermediate **34** shown in scheme 16.[23]



Scheme 16: Anionic Oxy-Cope Rearrangement in theTotal Synthesis of Periplanone-B

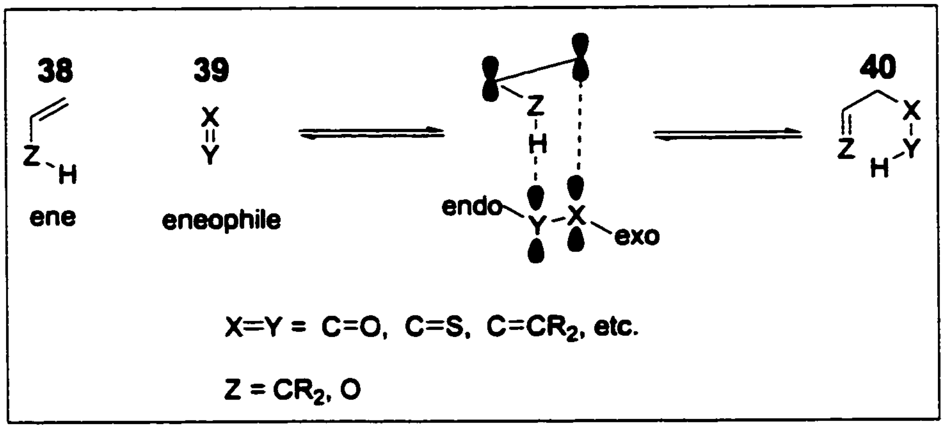
More recently, in the total synthesis of (+)-taxusin, Paquette and co-workers used a cleverly orchestrated anionic oxy-Cope rearrangement of **36** for the construction of the macrocyclic ring **37** (Scheme 17).[24]



Scheme 17: Anionic Oxy-Cope Rearrangement as a Key Step in the Total Synthesis of (+)-Taxusin

1.5 The Ene Reaction

The ene reaction, first discovered and investigated by Kurt Alder in 1943,[25] usually involves a reaction between an alkene containing an allylic hydrogen (ene donor: **38**) with an electron deficient double or triple bond (eneophile: **39**) to form **40** as shown in scheme 18. Orbital symmetry considerations[26] as well as experimental evidence[27] are consistent with a concerted pathway involving *supra-supra*facial *endo-* or *exo-*oriented interaction. It therefore resembles the Diels-Alder reaction[28] and [1,5] sigmatropic shifts, which are also considered to involve a 6 e transition state.[29]



X=Y = C=O, C=S, $C=CR_2$, etc.

Z = CR_2, O

Scheme 18: The Ene Reaction

Examples of the ene reaction have been reported as early as the 1930-s,[30] yet its great synthetic utility was not realized until the 1970-s when there was an increased interest in [4+2] and [3+2] cycloadditions. As with cycloadditions, the intramolecular ene reactions are done with preparatively useful stereo- and regioselectivity. This is demonstrated in the three possible types of thermally induced cyclizations, in which the eneophile is connected to the ene donor by the olefinic terminal (Type I), the central atom (Type II), or the allylic terminal (Type III) (Figure 3).

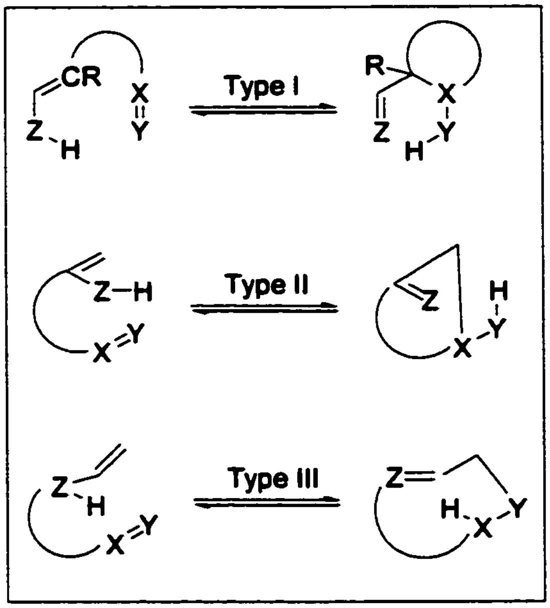
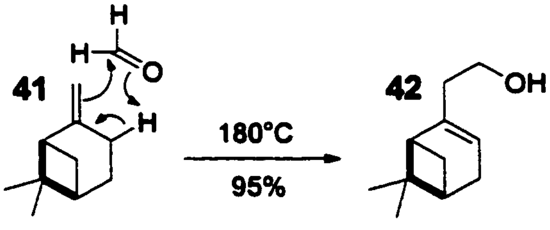


Figure 3: Types of Ene Reactions

The carbonyl ene reaction involves the use of a ketone or aldehyde as the eneophile. Formaldehyde undergoes thermal carbonyl ene reactions with 1,1-disubstituted and trisubstituted alkenes at 180-220°C. β-Pinene **41**, a particularly reactive ene component, reacts with formaldehyde at 180°C to give nopol **42** in 95% yield (Scheme 19).[31]

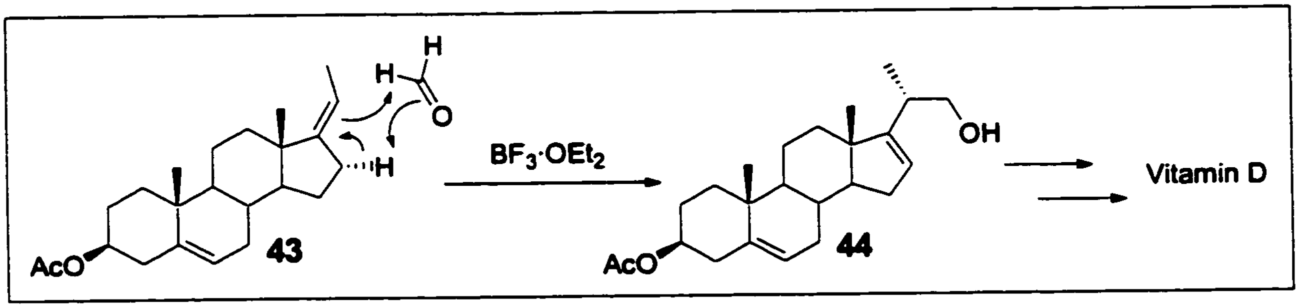
41



42

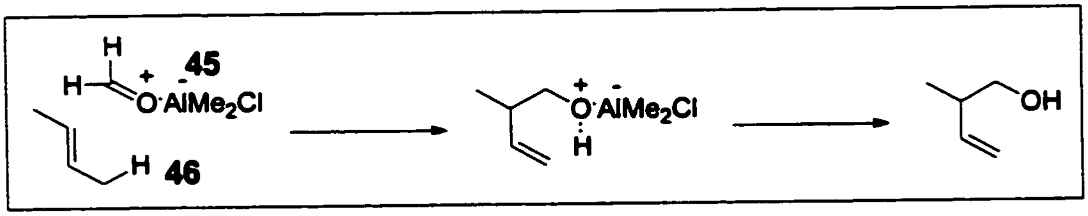
Scheme 19: Ene Reaction of β-Pinene with Formaldehyde

Several Lewis acid catalysed carbonyl ene reactions have been shown to have excellent yields. The $BF_3\cdot OEt_2$ as well as $SnCl_4$ catalysed addition of formaldehyde to olefins such as **43** have been used in the synthesis of the vitamin D side chain **44** (Scheme 20).[32]



Scheme 20: Lewis Acid Catalysed Carbonyl Ene Reaction in the Total Synthesis of Vitamin D

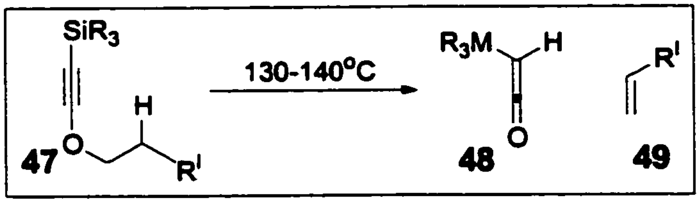
The role of the Lewis acid is to complex with the oxygen of the carbonyl group to form a salt **45** (Scheme 21), which is a more reactive and selective eneophile.[33] When the cationic nature is increased, the LUMO of the eneophile becomes lower in energy and therefore more reactive toward the ene donor **46**. The increase in reactivity is made manifested increases in rates as well as stereoselectivity.



Scheme 21: Lewis Acid Catalysed Carbonyl Ene Reaction

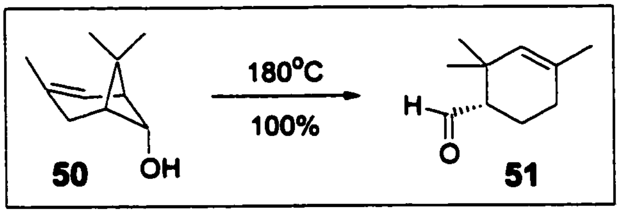
1.6 The Retroene Reaction

The retroene reaction, which is sometimes responsible for side products that are formed upon performing ene reactions, corresponds to the thermal decomposition of an olefin into its two alkene subunits (ene donor and eneophile) which could react to produce it via the ene pathway. This is illustrated in scheme 22, where **47** undergoes a retroene reaction to generate ketene **48** and the olefin **49**.[34]



Scheme 22: The Retroene Reaction of 47

In some cases, the retroene pathway is preferred due to unfavorable ring strain or steric effects. This is illustrated in scheme 23 where loss of cyclobutane ring strain in **50** facilitates the related cleavage to generate the γ,β-unsaturated aldehyde **51**.[35]

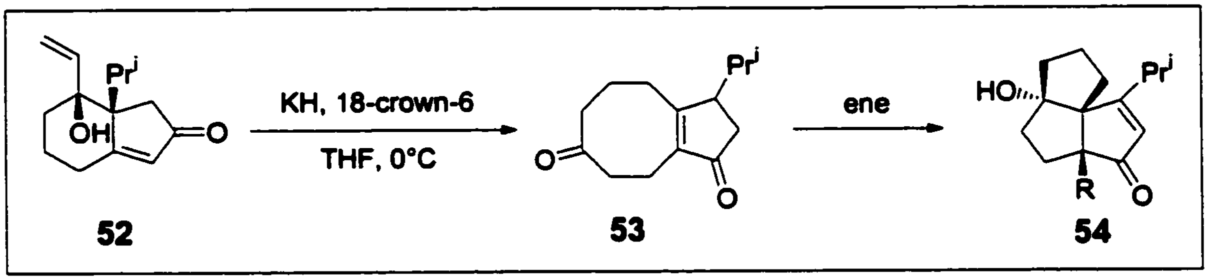


Scheme 23: Retroene Reaction of 49

Chapter 2: Studies of the Effect of DBU on the Tandem Oxy-Cope/Ene Reaction

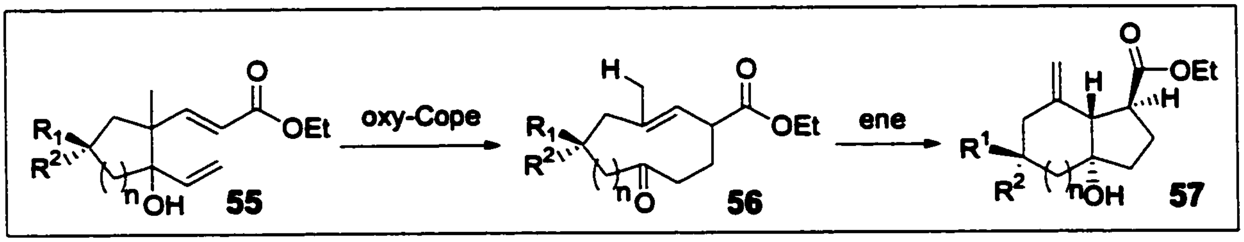
2.1 Introduction

The oxy-Cope followed by transannular ene reaction is a tandem process whose development is still in its infancy. Before any systematic investigations of the tandem oxy-Cope/ene reaction were performed, the process had previously been observed as a side reaction. The first of these by Sutherland *et al.*, showed **54** as an undesired side product from an anionic oxy-Cope rearrangement of **52** which generated **53** as the precursor to the transannular ene reaction (Scheme 24).[36]



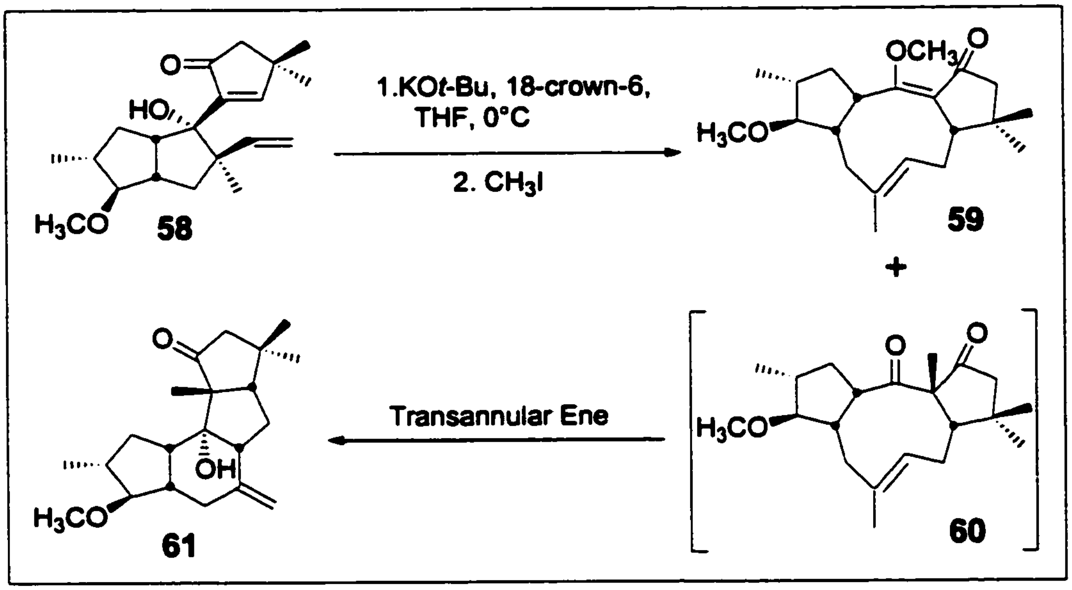
Scheme 24: Sutherland's Oxy-Cope/Ene Side Products

While developing methods for the synthesis of [4.3.0] and [4.4.0] systems, Rajagopalan and co-workers observed the side product **57** upon attempting oxy-Cope rearrangements with substrates such as **55** (Scheme 25)[37]. They reported the side product **57**, which was due to a transannular ene reaction of the macrocycle **56**.



Scheme 25: The Oxy-Cope/Ene Reaction of 55

While working towards the synthesis of jatrophatrione 1, Paquette and co-workers performed an anionic oxy-Cope reaction on the tricyclic compound **58**.[38] Besides isolating the desired compound **59**, they also obtained **61**, which was derived from a transannular ene reaction of the macrocyclic ketone **60** (Scheme 26).

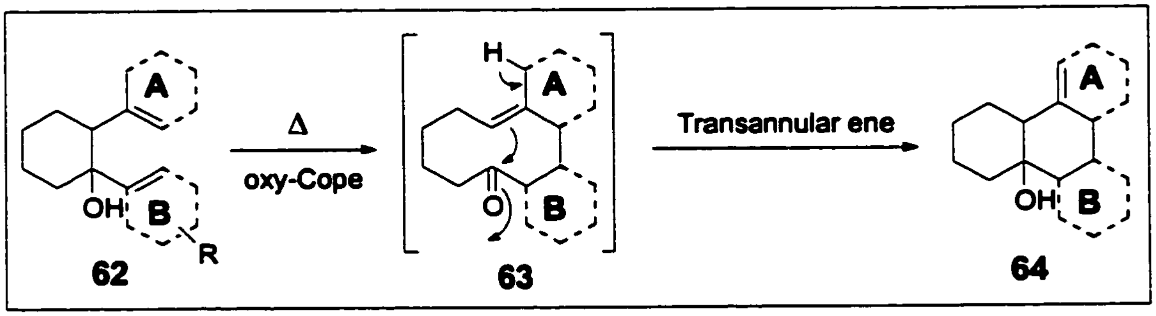


Scheme 26: Paquette's Oxy-Cope/Ene Side Product

There are several reasons for studying the tandem oxy-Cope/ene process. Not only does the reaction allow a simple and inexpensive scale-up due to the fact that only heat is needed to drive the reaction, but it also provides a rapid method for the construction of polycyclic compounds with a tertiary alcohol at the ring junction. The examples mentioned above clearly illustrate that the tandem oxy-Cope/ene reaction is a powerful tool for the creation polycyclic compounds with tertiary alcohols at the ring junction. In order to further demonstrate its utility, the Barriault group investigated this tandem method using 1,2-divinylcyclohexanols as initial substrates for the reaction.[39]

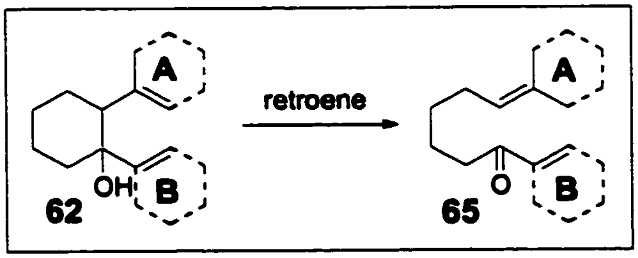
2.2 Initial Studies on the Tandem Oxy-Cope/Ene Process

The idea behind Barriault's investigation of the oxy-Cope/ene process with 1,2-divinylcyclohexanols is illustrated in scheme 27. When a 1,2-divinylcyclohexanol **62** is heated, it can undergo an oxy-Cope rearrangement to provide a macrocyclic ketone **63**. The macrocyclic ketone **63** can then proceed via a transannular ene reaction to furnish the desired bicyclic product **64**.



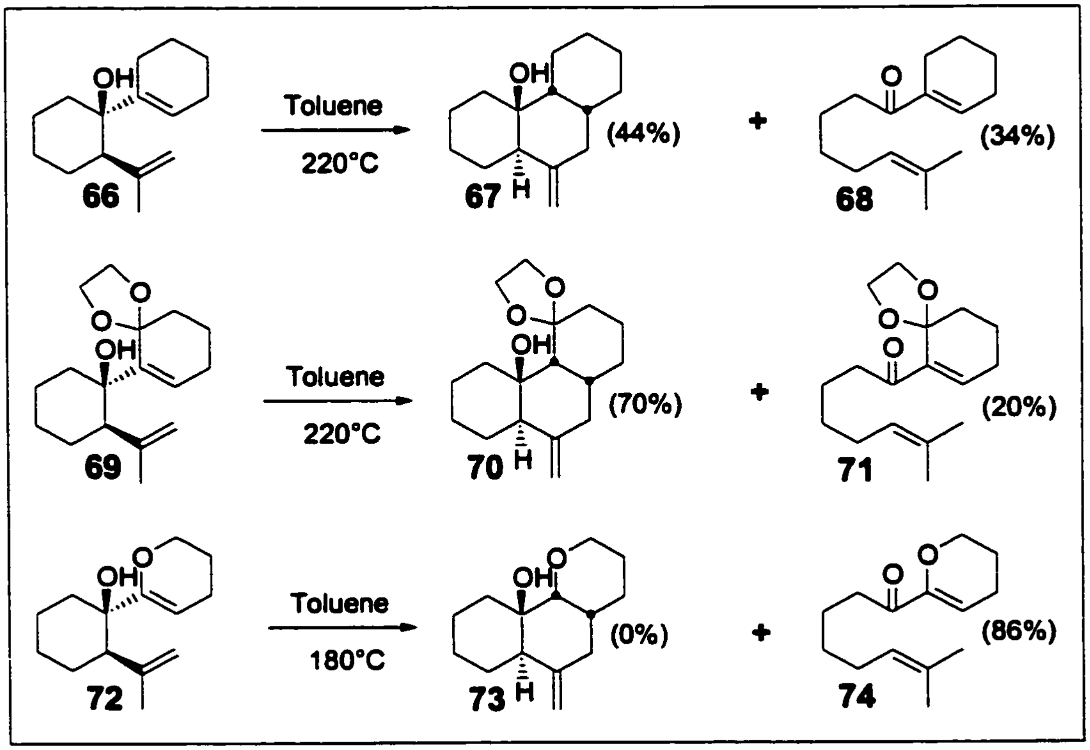
Scheme 27: Barriault's Tandem Oxy-Cope/Ene Strategy

It was reported that when **B** (**62**) is a six membered ring, considerable amounts of retroene products (**65**) can be formed (Scheme 28). When **A** (**62**) is a six membered ring, no retroene products are observed.[40]



Scheme 28: Retroene Reaction

When 1,2-divinylcyclohexanol **66** was heated in toluene in a sealed tube for 5 hours, it produced the corresponding tricyclic product **67** (44%) as well as the retroene product **68** (34%) (Scheme 29). Heating **69** in toluene gave similar results, producing the tricyclic product **70** in good yield (70%) as well as the retroene product **71** (20%). When **72** was treated in the same manner, it gave none of the desired oxy-Cope/ene product **73** but produced the retroene product **74** exclusively. It is important to note that in each case, the tricyclic products (**67** and **70**) were formed as single diastereomers with *trans-syn-cis* stereochemistry. The high diastereoselectivity was rationalized according to the most favourable transition state for the reaction.

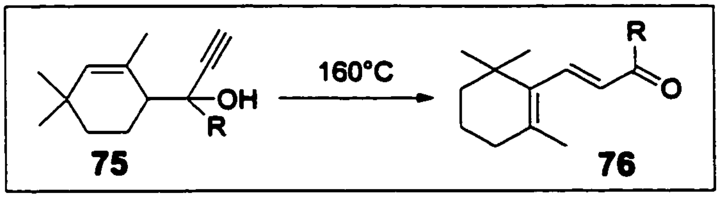


Scheme 29: Barriault's Oxy-Cope/Ene Reactions

Based on these results, the use of this protocol seemed feasible for performing the tandem oxy-Cope/ene reaction with 1,2-divinylcyclohexanols with high diastereoselectivity. However, the fact that the retroene product was often observed as a side product of the tandem oxy-Cope/ene reaction was distressing in the event that it would be applied within a total synthesis. The goal of our study was to eventually apply this methodology to the total synthesis of a natural product, and thus a method was needed to decrease the ratio of retroene product with respect to the oxy-Cope/ene product in some specific cases. This was done by a solvent assisted oxy-Cope rearrangement.

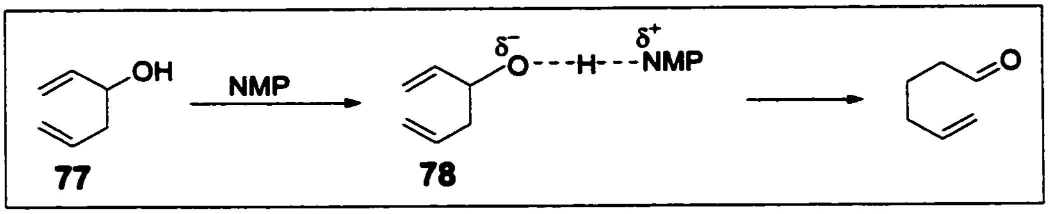
2.3 Solvent Assisted Oxy-Cope Rearrangements

Solvent assisted oxy-Cope rearrangements are scarce in the literature, and in each previously reported case, NMP was used as solvent.[41] One such example is shown in scheme 30, where Fujita *et al.* demonstrated that when **75** was heated in NMP at 160°C the oxy-Cope product **76** was formed in 58% yield as opposed to 0% when performed in *n*-decane (Scheme 30).



Scheme 30: *Fujita's Solvent Assisted Oxy-Cope Rearrangement*

Although the precise effect of NMP has not been elucidated, it has been postulated that NMP participates in hydrogen bonding with the hydroxyl at C-3 of the 1,5-hexadiene system (**77**). This hydrogen bonding serves to increase the negative character of the hydroxyl oxygen (**78**) and thus provides the needed 'electron push' that promotes carbon-carbon bond breaking mentioned earlier (Scheme 32).



Scheme 32: The Effect of NMP on the Oxy-Cope Rearrangement

Our use of a solvent assisted oxy-Cope rearrangement hinged on the hypothesis that when retroene products were observed, it was due to the high cost in energy upon effecting the oxy-Cope mechanism compared to the retroene one. This idea is illustrated in figure 4. When the 1,2-divinylcyclohexanol **A** undergoes a non-solvent assisted oxy-Cope rearrangement via transition state **B** it will produce the macrocyclic ketone **E**. Ketone **E** that can then proceed to the desired product **H** via the ene pathway **G**. When the retroene transition state **C** is preferred over **B**, it will form the retroene product **F**. When the solvent participates in facilitating the oxy-Cope rearrangement (**D**) the energy required for the oxy-Cope rearrangement will be lower thereby producing transition state **D**. This will thus favour the formation of the desired oxy-Cope/ene product **H**.

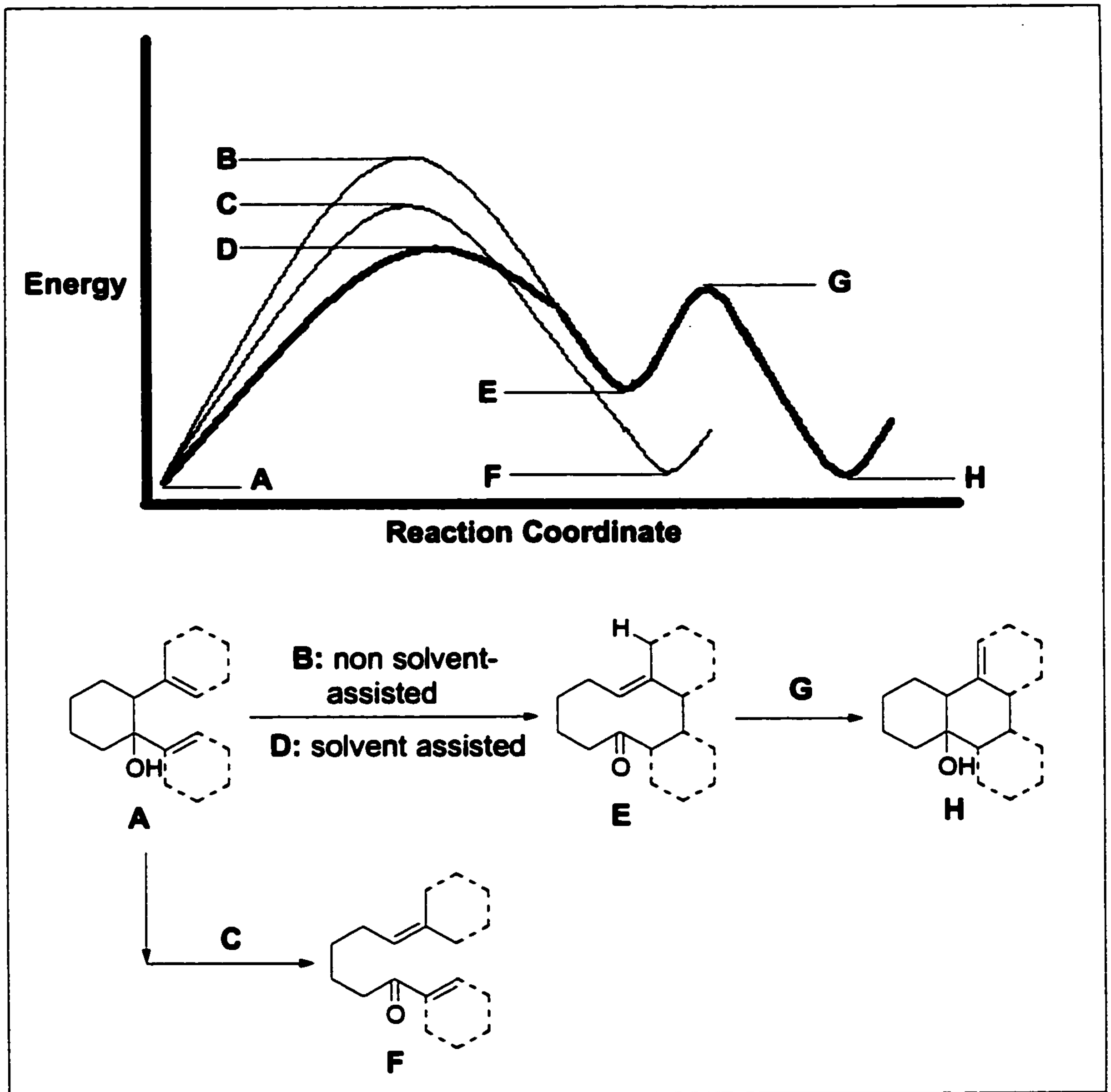


Figure 4: Solvent Assisted and Non-Solvent Assisted Oxy-Cope/Ene Pathways

2.4 Heating Methods

The results described herein involve the thermal oxy-Cope/ene tandem reaction. The first results were obtained using conventional heating methods and the second set was obtained using microwaves as a heating source. These two heating methods are described below.

2.5 Conventional Heating

The conventional heating method involves using a sealed pressure tube and a wax bath as a heat source (Figure 5). The substrate is first dissolved in the appropriate solvent and placed in the tube. The tube is then submerged in the wax bath heated on a hot plate. The temperature reported for these experiments is not measured from directly inside the reaction vessel but rather from the wax itself. Therefore, the temperature reported is only an approximation as to what the actual temperature of the solvent/substrate mixture may be. It is also important to note that this method actually serves to reflux the mixture and so the temperature is not uniform throughout the entire system. This non-uniformity can be mediated by placing a layer of glass wool encased in aluminum foil around the upper portion of the pressure tube that is not submerged in the wax bath.

Each reaction described below was performed in toluene at 220°C unless otherwise noted.

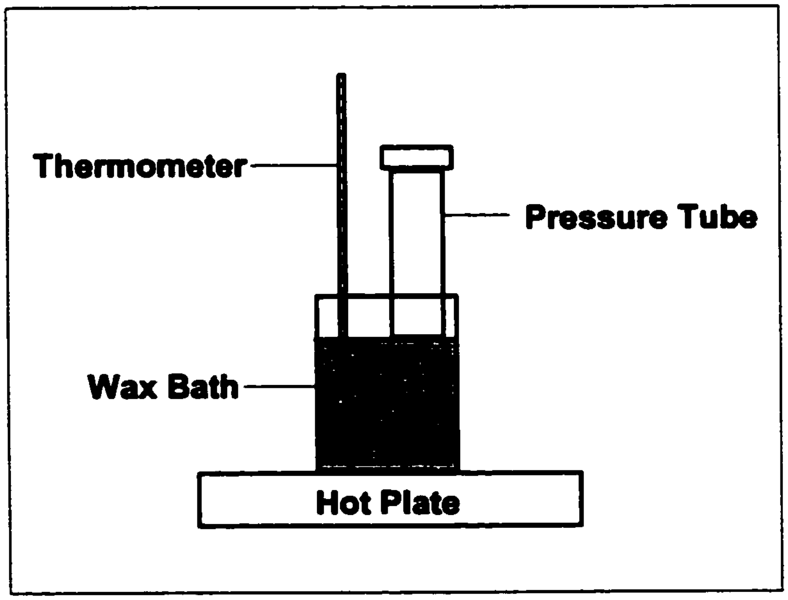
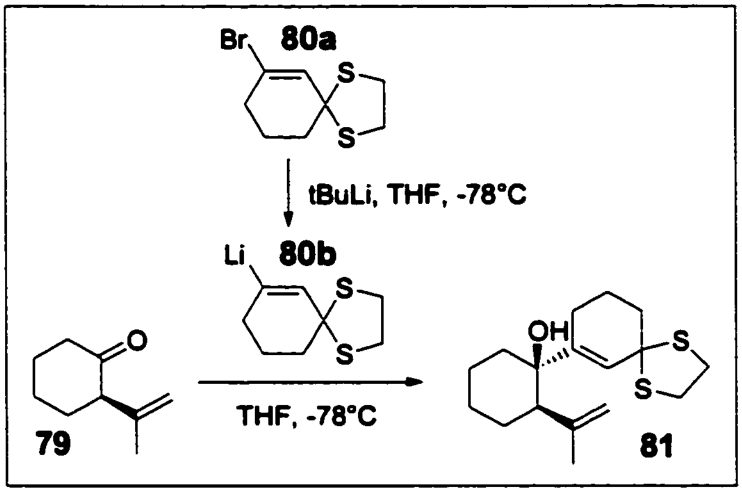


Figure 5: Pressure Tube Heating Apparatus

2.5.1 Results and Discussion: Conventional Heating

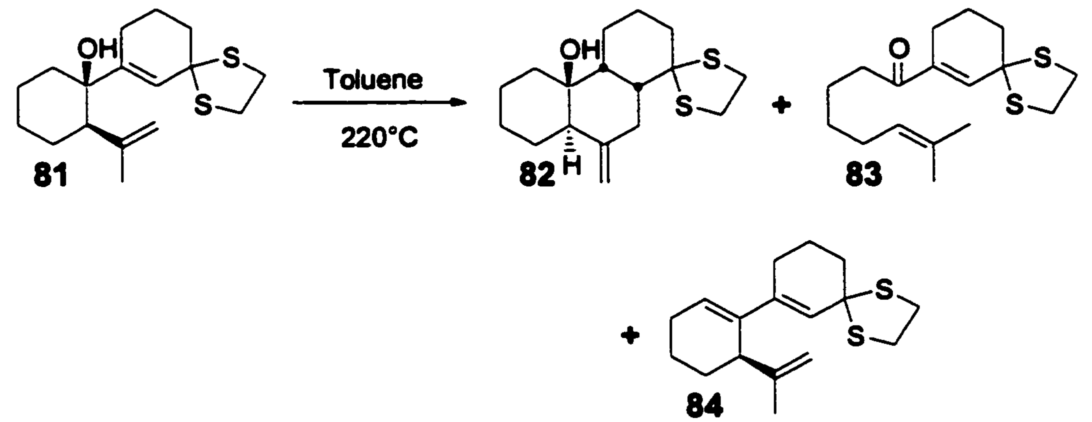
The investigation of solvent assisted tandem oxy-Cope/ene reactions began with **81**, which has a thioacetal on the cyclohexene moiety; it was produced in a 61% yield by treatment of **79**[42] with cyclohexenyllithium **80b**[43] in THF at –78°C (Scheme 33).



Scheme 33: Synthesis of 79

Using the original method developed in our lab,[44] **81** was heated in a pressure tube for 20 hours in toluene and it resulted in a mixture of both oxy-Cope/ene and retroene products **82** and **83** in a 75% yield collectively (Scheme 34). The ratio of **82** and **83** was 1 : 3 respectively. When **81** was heated for 8 hours using NMP as solvent, it gave a mixture of **82**, **83** and the dehydrated product **84**. The ratio of these three products was 1 : 1 : 2 respectively. Although the use of NMP as solvent did serve to increase the relative amount of **82** with respect to **83**, the facts that the collective yield is quite low (24%), and that **84** was also observed as a side product, demonstrates that in this particular case the use of NMP as solvent is ineffective in helping us achieve our goal.

When **81** was heated for 7 hours in toluene with 20 equivalents of DBU as co-solvent at a concentration of 0.68 M, it gave a mixture of **82** and **83** in a 1 : 1 ratio with a 56% overall yield. This demonstrated that DBU had a beneficial effect on the tandem oxy-Cope/ene process by increasing the relative amount of the oxy-Cope/ene product without any devastating degradation effects. The complete results are summarized in scheme 34.



	co-solvent	oxy-Cope/ ene (82)	retroene .(83)	dehydrated .(84)	% yield
	none	1	3	0	75
	NMP	1	2	1	24
[0.68 M]	DBU (20 eq.)	1	1	0	56

Scheme 34: Solvent Assisted Oxy-Cope/Ene Reactions of 81

In each case, **82** was formed as a single diastereomer with *trans-syn-cis* stereochemistry. The high diastereoselectivity of the reaction can be rationalized according to the transition state shown in figure 6.

When **81** undergoes thermal oxy-Cope rearrangement, it produces the enol **85**. The highly diastereoselective tautomerization that ensues produces the intermediate **86** which can react via a transannular ene pathway to give **82** as a single diastereomer. It has been shown in the literature by Terada and Yamamura,[45] that transannular ene reactions proceed via transition states which adopt chairlike conformations. An examination of transititon states **B** and **C** reveals a pseudo-1,3-diaxial methyl-methylene interaction in **B** and a boatlike conformation in transition state **C**. Conformation **A**, possesses neither of these unfavourable interactions and thus transition states **B** and **C** will be the less preferred. This readily explains the exclusive formation of **82** over **87**.

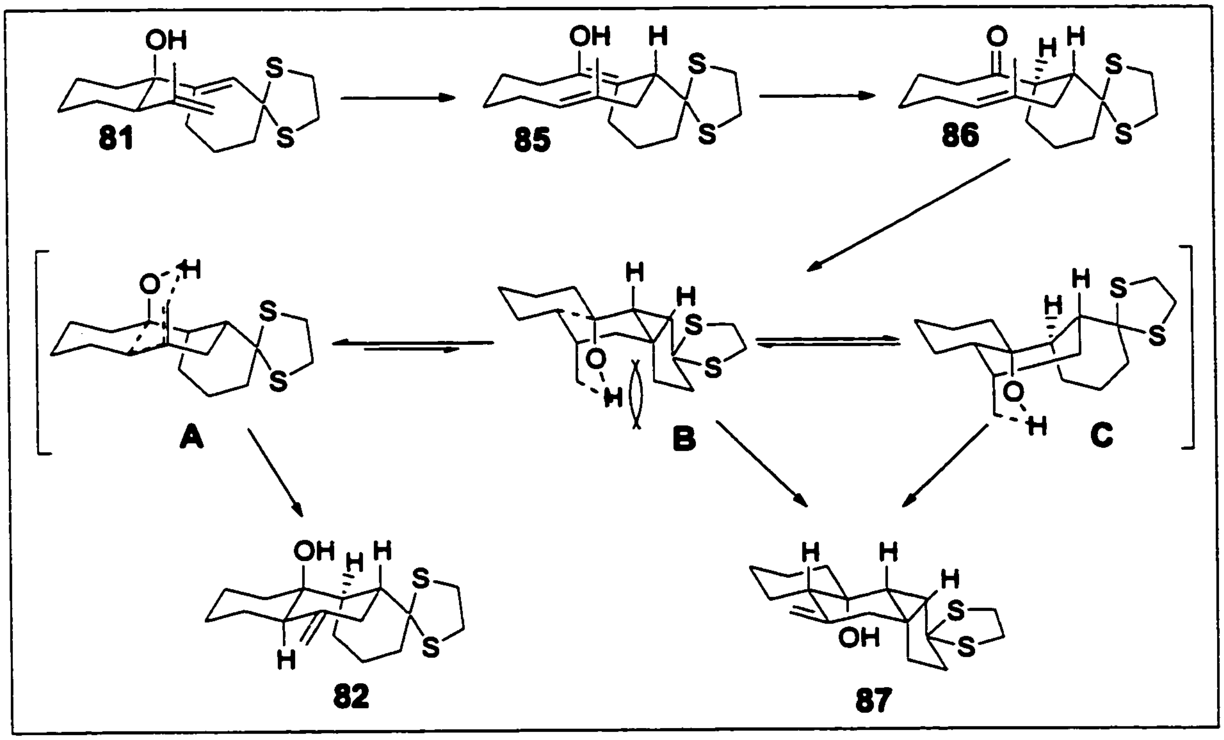
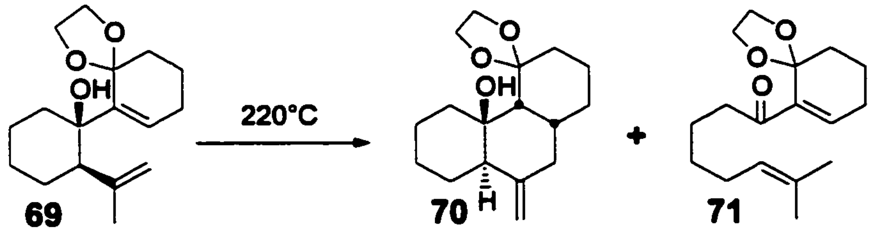


Figure 6: Transition State of the Oxy-Cope/Ene Reaction of 81

With these promising results in hand, the next step was to test the effect of DBU on several other substrates for which retroene products had been observed.

When **69** was heated in toluene for 5 hours it gave a 3.5 : 1 mixture of **70** to **71** respectively in a 90% overall yield (Scheme 31). When the same molecule was heated in NMP for 8 hours the mixture obtained was an 11 : 1 ratio of **70** : **71** but with a low yield overall of 18% (Scheme 35). As in the previous case using NMP as a solvent, although it did result in an increase in the relative amount of the desired product (**70**), the yield is too low to be useful in any synthetic applications.



co-solvent	oxy-Cope/ ene (70)	retroene .(71)	% yield
none	3.5	1	77
NMP	11	1	18
[0.54 M] DBU (20 eq.)	20	1	75

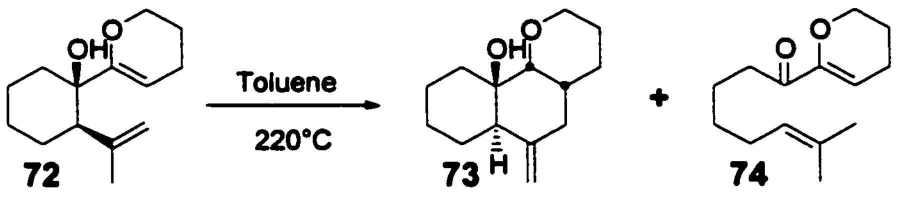
Scheme 35:** Solvent Assisted Oxy-Cope/Ene Reactions of **69

Heating **69** in toluene for 8 hours with 20 equivalents of DBU at a concentration of 0.54 M resulted in a 20 : 1 mixture of **70** : **71** with an overall yield of 75%. This was our most promising result to date: it demonstrated the great utility of DBU in increasing the relative amount of the desired oxy-Cope/ene product (**70**) with respect to the undesired retroene product (**71**) while maintaining a high yield.

In order to probe the effect of DBU on the tandem oxy-Cope/ene reaction of **72**, it was subjected to a series of experiments with varied amounts of DBU. The concentration was 0.10 M for each reaction.

As mentioned earlier, when **72** was heated in toluene at 220°C (scheme 31 and 36) with no co-solvents it gave exclusively the undesired retroene product **74** (86%). When **72** was heated in toluene with 0.5 equivalents of DBU, again at 220°C, some of the desired product **73** was formed as well as the retroene product **74** in a 1 : 7.9 ratio in 80%

yield overall. When the number of equivalents of DBU was increased to 20, there was an consequent increase in the amount of oxy-Cope/ene product **73** in a 1 : 2.75 ratio with **74** and a yield of 77% collectively. When the number of equivalents was increased to 105, more oxy-Cope/ene product (**73**) was produced than retroene (**74**), in a ratio of 1.38 : 1, although the yield was somewhat low in this case, being 46%. These results prove that even in the case of **72**, where heating alone in toluene cannot form the oxy-Cope/ene product, the formation of **73** is made possible by using DBU as a co-solvent. The complete results are summarized in scheme 36.



toluene	DBU	oxy-Cope/ ene(73)	retroene (74)	% yield
0	1	1	1.25	50
	105 eq.	1.38	1	46
	52.5 eq.	1	3	89
	20 eq.	1	2.75	77
	2 eq.	1	6.2	100
	0.5 eq.	1	7.9	80
1	0	0	1	86

***Scheme 36:** DBU Assisted Oxy-Cope/Ene Reactions of 72*

2.6 Microwave Heating

As early as 1975, there were reports of microwaves being used as heating sources in chemistry.[46] These early studies showed that microwave-promoted reactions often occur with a decrease in reaction time compared to conventional heating methods.[47]

Unlike the conventional heating method described above, the use of a sealed reaction vessel in a microwave allowed for direct measurement of temperature by use of a fibre optic probe that was submerged into the reaction mixture. A pressure probe can also measure the pressure.

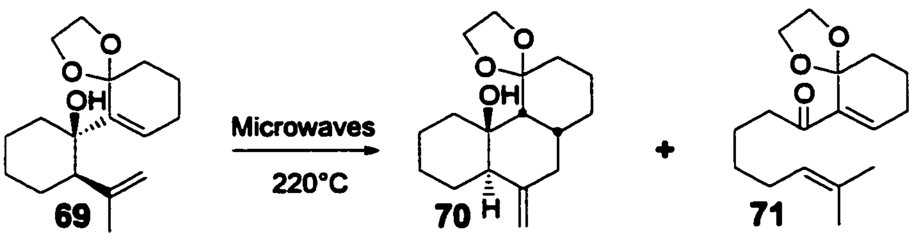
All reactions described herein were carried out using a CEM Model ESP-1500 PLUS oven equipped with a pressure monitoring device and an EST-300 Plus fibre optic temperature probe. The magnetron tube supplies 1200 watts. Effective power levels of 0-100% of this value are available as a train of timed pulses. The ESP-1500 unit is designed so that irradiation stops when a predetermined pressure is reached. All experiments were performed in sealed quartz tubes.

Since the solvent used, toluene, is non-polar and does not absorb microwaves, the use of a carboflon bar was employed. Carboflon readily absorbs microwave energy and gives off heat to the reaction mixture through conduction, which provides heat indirectly to the reaction.

All reactions were performed in toluene at 220°C unless otherwise stated.

2.6.1 Results and Discussion: Microwave Heating

The first results obtained using microwaves as a heating source involved examining the effect of various amounts of DBU on the tandem oxy-Cope/ene reaction of **69**. Each reaction was performed at a concentration of 6.95×10^{-3} M. When **69** was heated in toluene without DBU at 220°C in the microwave oven (Scheme 37) it gave a mixture of **70** and **71** in the same ratio as was obtained using the conventional heat source; 3.5 : 1 respectively.



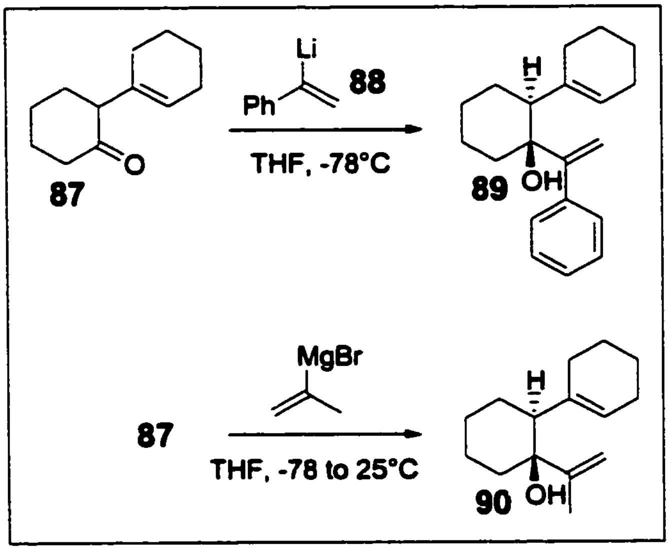
DBU	oxy-Cope/ ene(70)	retroene (71)	time (min.)	% yield
0	3.5	1	40	91
20	5.7	1	40	95
40	17	1	40	90
60	1	0	40	98

Scheme 37: *DBU/ Microwave Accelerated Oxy-Cope/Ene of* ***69***, *[ ] =* $6.95\times10^{-3}M$

What differentiated the two experiments was that when the microwave oven was used, the overall yield was slightly higher (91% versus 75% previously) and the reaction was complete in 40 minutes, as opposed to the previously reported 5 hours in the pressure tube. When **69** was heated at 220°C with 20 equivalents of DBU, again the reaction was complete in only 40 minutes which is a dramatic increase from 8 hours in the wax bath. Another difference was that the ratio of **70** and **71** produced was 5.7 : 1 unlike that obtained by conventional heating methods which was 20 : 1. This difference can be attributed to the difference in concentration between the two experiments. The trend observed as the number of equivalents and therefore concentration of DBU increases for the tandem oxy-Cope/ene process with **69** is similar to that observed with **72** (Scheme 36). As the amount of DBU within the reaction mixture increases, the relative amounts of oxy-Cope/ene products are increased and the amounts of retroene products are decreased. The complete results obtained for the treatment of **69** with microwaves and various concentrations of DBU are summarized in scheme 37.

2.6.1.1 Studies with Cyclic Ene Donors

As mentioned previously, when the tandem oxy-Cope/ene reaction is performed with substrates that contain a cyclic ene donor, retroene products are not observed. The synthesis of 1,2-divinylcyclohexanols containing a cyclic ene donors was effected using the method shown in scheme 38. When 2-(1-cyclohexenyl)cyclohexanone **87**, was treated with vinyllithium derivative **88** in THF at –78°C it provided **89** (*trans* diastereomer) in 30%. Treatment of **83** with isopropenylmagnesium bromide in THF at –78°C while warming to room temperature generated the desired compound **90** (*trans* diastereomer) in 23% yield.



Scheme 38: Synthesis of 89 and 90

When **89** was heated in the microwave oven with no co-solvents, it produced **91** as a single diastereomer (Scheme 39) in 53% yield after 80 minutes. Although this experiment did generate the desired compound, the ^{1}H NMR spectrum of crude **91** contained several peaks present near the olefinic region (4.6-5.6 ppm) (Figure 7), which were derived from a side product of the reaction. Although the side product was not fully characterized, our hypothesis was that it was produced by a radically induced mechanism. Based on this, the same experiment was repeated with 0.38 equivalents of BHT to act as a radical inhibitor. When the experiment was performed with BHT in toluene, the ^1H NMR spectrum of the crude product possessed none of the aforementioned foreign peaks (Figure 7). It gave **91** in a much higher yield (91%) but the reaction time was longer, being 110 minutes.

When **89** was heated with microwaves in toluene ($[\ ] = 8.35\times10^{-3}$) at 220°C with 20 equivalents of DBU, it provided **91**, in 66% yield after 60 minutes. Again, in the ^1H NMR spectrum of crude **91** there were several peaks (4.6-5.6 ppm) that corresponded to those of the aforementioned side product (Figure 7). Because of this, the same reaction (20 equivalents DBU, $[\ ] = 8.35\times10^{-3}$) was attempted with 0.38 equivalents of BHT to act as a radical inhibitor. When **89** was heated at 220°C in the presence of 20 equivalents of DBU and 0.38 equivalents of BHT in toluene it again eliminated the undesired side product and gave **91** in a 92% yield in 60 minutes. These experiments demonstrate the ability of BHT to eliminate side products that may occur as well as the effect of DBU in increasing the rate of the reaction.

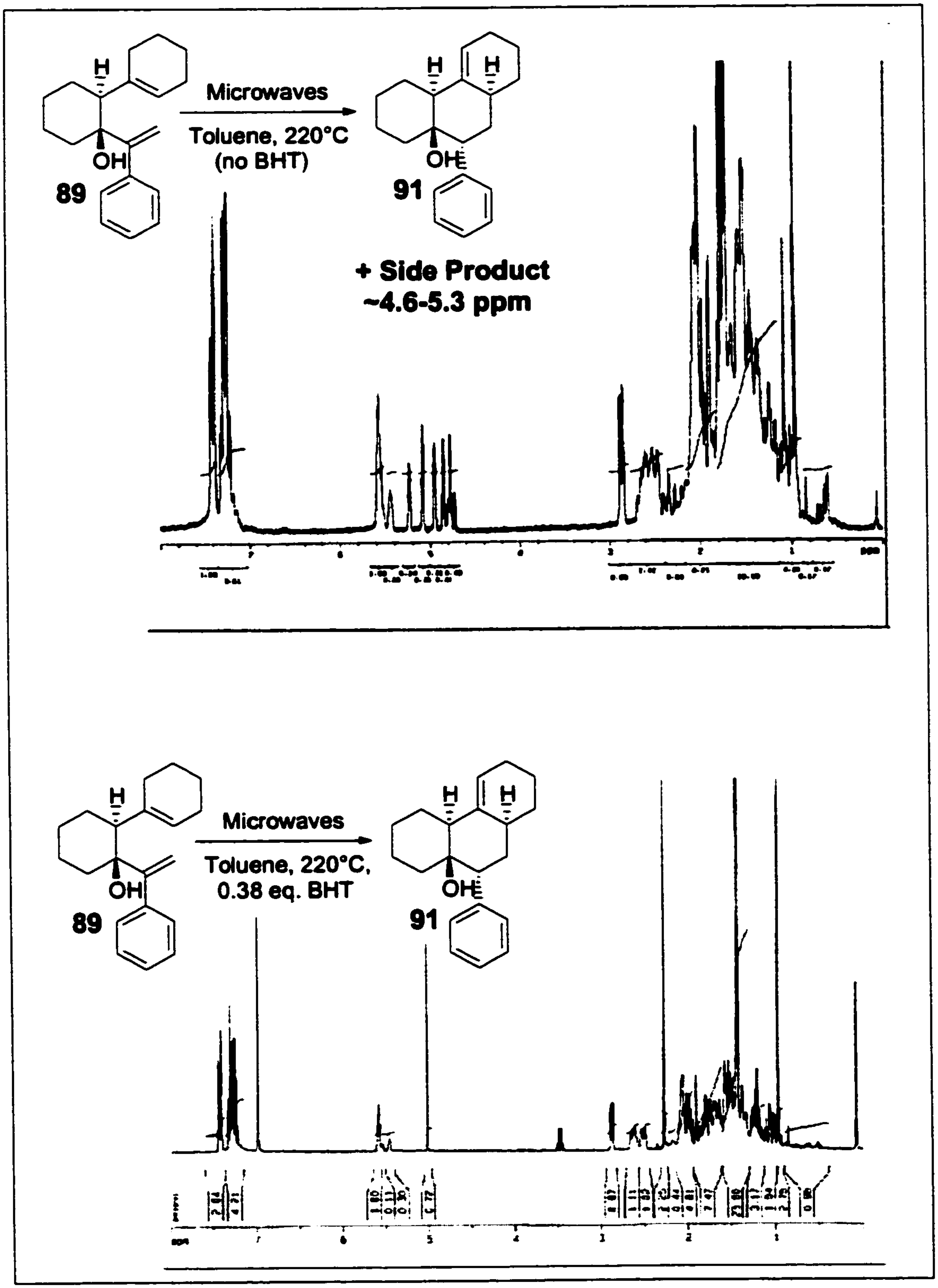
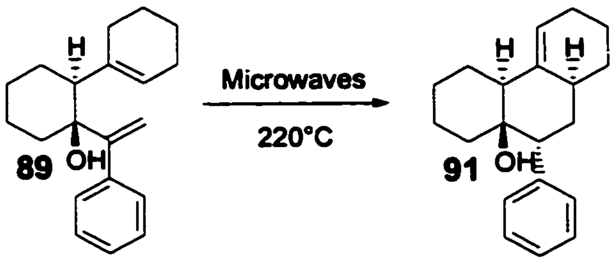


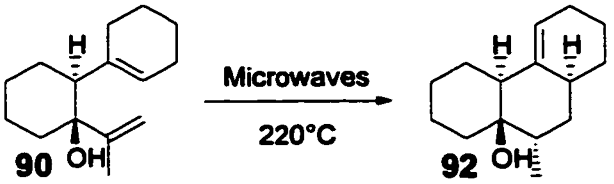
Figure 7: Microwave Reactions of ***89*** *with and without BHT, [ ] = 8.35×10^{-3} M*



DBU	BHT	time (min.)	% yield
20	0	60	66
20	0.38	60	92
0	0.38	110	91
0	0	80	53

Scheme 39: *DBU Assisted/ Microwave Accelerated Oxy-Cope/Ene Reactions of* ***89****, [ ] = 8.35×10^{-3}M*

When **90** was heated in toluene at 220°C with no co-solvents, it formed **92** as a single diastereomer in an 82% yield after 145 minutes (Scheme 40). The amount of time required to effect the same transformation was dramatically reduced to 60 minutes by heating **90** at 220°C with 20 equivalents of DBU at a concentration of 6.85×10^{-3}M. It produced **92** in an identical yield (82%). When **90** was submitted to the same conditions again but with 40 equivalents of DBU, it gave **92** in a 66% yield in 55 minutes. Surely these experiments demonstrate the ability of DBU to accelerate the tandem oxy-Cope/ene process.



DBU	time (min.)	% yield
0	145	82
20	60	82
40	55	66

Scheme 40: *DBU Assisted/ Microwave Accelerated Oxy-Cope/Ene Reactions of **90**, [ ] = 6.85×10^{-3}M*

The fact that both **91** and **92** were produced as single diastereomers can be explained according to the transition states shown in figure 8. When **89** or **90** undergoes the oxy-Cope rearrangement to produce **A**, it will tautomerize to form the macrocyclic ketone **B**. As mentioned previously transannular aldol ene reactions must proceed via chairlike transition states and **B** is the only possible conformation that will allow this thereby making **B** the preferred transition state for the ene reaction **C**.

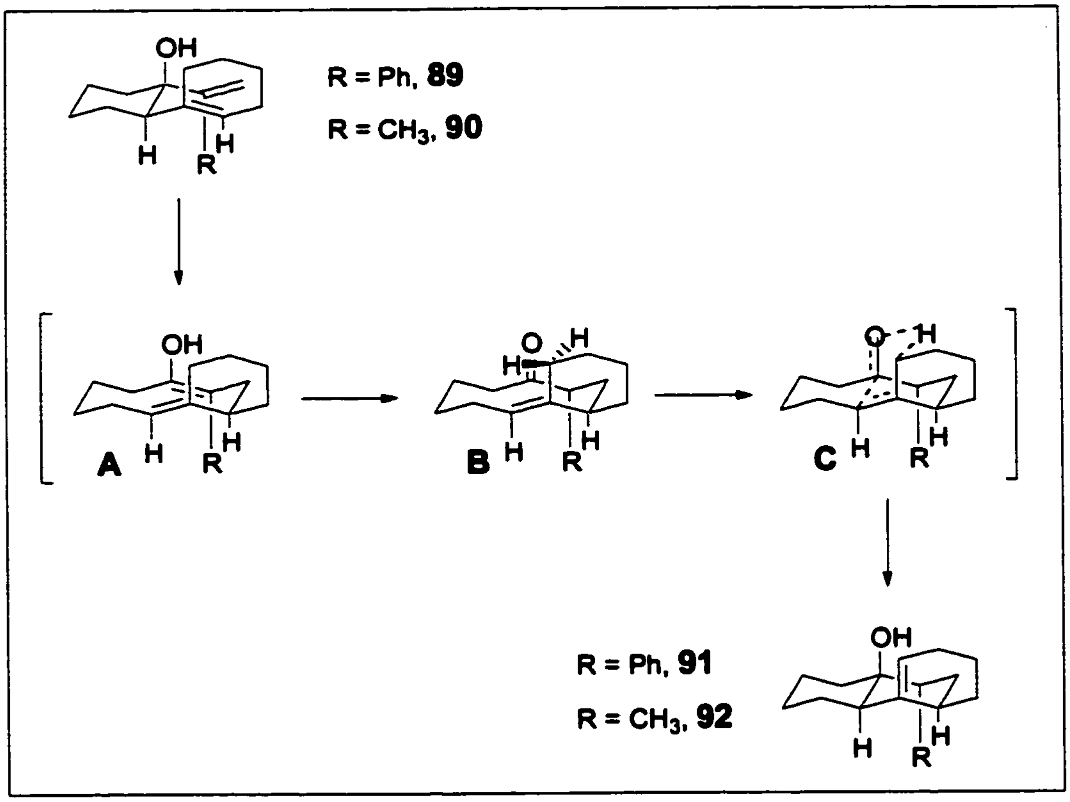
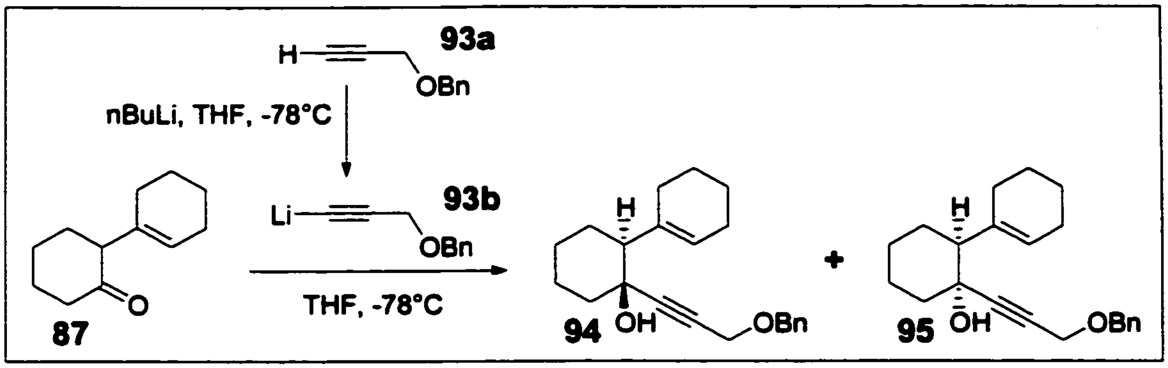


Figure 8: Transition State of Oxy-Cope/Ene Reaction with 85 and 86

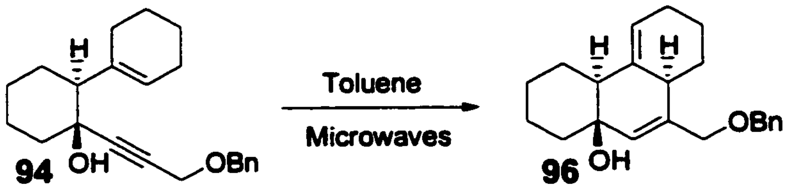
2.6.1.2 Studies with 1-(3-[1-(Benzyloxy)-propynyl])-2-(1-cyclohexenyl)-cyclohexan-1-ols

In order to test the effect of having triple bonds present during solvent assisted oxy-Cope/ene reactions, diastereomeric 1-alkyn-2-cyclohexenols were synthesized. The compound 2-(1-cyclohexenyl)cyclohexanone (**87**) was treated with the lithiated benzylated propargyl alcohol **93b** in THF at –78°C, to produce a mixture of *trans* and *cis* diastereomers **94** and **95** in 27% and 21% yields respectively (Scheme 41).



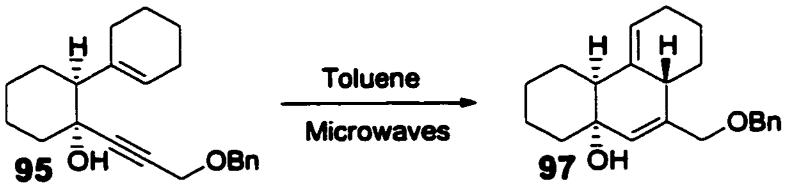
Scheme 41: Synthesis of 94 and 95

When the *trans* diastereomer **94**, was heated in toluene with 20 equivalents of DBU at a concentration of 4.24×10^{-3}M, it produced **96** in 90% yield after 90 minutes of heating as a single diastereomer with the *trans* ring (Scheme 42). When the *cis* diastereomer **95** was heated under the same conditions with DBU, after 360 minutes of heating the reaction was still not complete, but it had produced the tricyclic compound **97** in 50% yield, based on the mass of starting material (Scheme 43). These results demonstrate that although in these types of cases, the tandem process can be effected on both *cis* and *trans* diastereomers, those which involve a *cis*-molecule require more energy. These results are summarized in schemes 42 and 43.



DBU	time (min.)	% yield
20	90	90

Scheme 42: *DBU Assisted Oxy-Cope/Ene Reaction of* ***94***, *[ ] = $4.25\times10^{-3}M$*



DBU	time (min.)	% yield
20	360	50

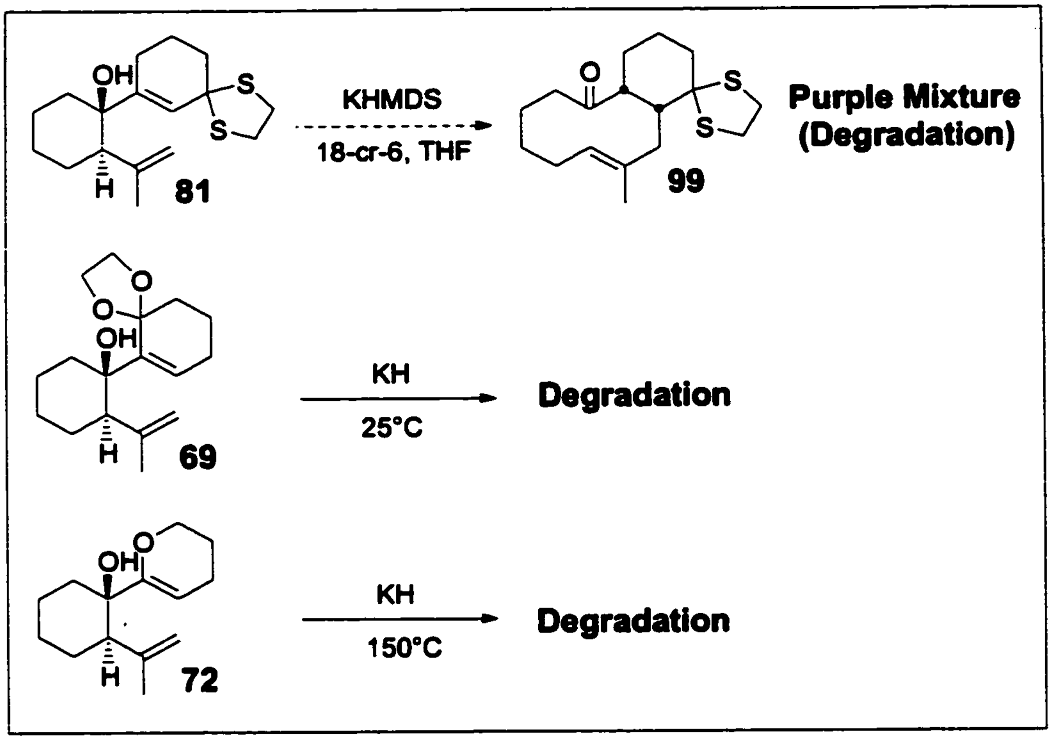
Scheme 43: *DBU Assisted Oxy-Cope/Ene Reaction of* ***95***, *[ ] = $4.25\times10^{-3}M$*

2.7 Thermal Oxy-Cope versus Anionic Oxy-Cope Rearrangments

These experiments clearly demonstrate the effect of DBU on the tandem oxy-Cope/ene reaction. In each specific case, DBU served to increase the relative amount of oxy-Cope/ene product with respect to the related retroene product. The effect was most dramatically observed with **72**, where no oxy-Cope/ene product can be produced in the absence of DBU. With **69**, there is a difference in the ratio of the two products formed when 20 equivalents of DBU is used in the microwave versus the sealed tube. This discrepancy can be attributed to of DBU the difference in concentration between the two reactions. When 20 equivalents is used at a concentration of 6.95×10^{-3}M, the ratio is 5.7 : 1, whereas when the concentration is increased to 0.54 M, the ratio of oxy-Cope/ene product increases to 20 : 1. These results are consistent with the fact that an increase in amount of DBU increases the relative amount of oxy-Cope/ene product observed.

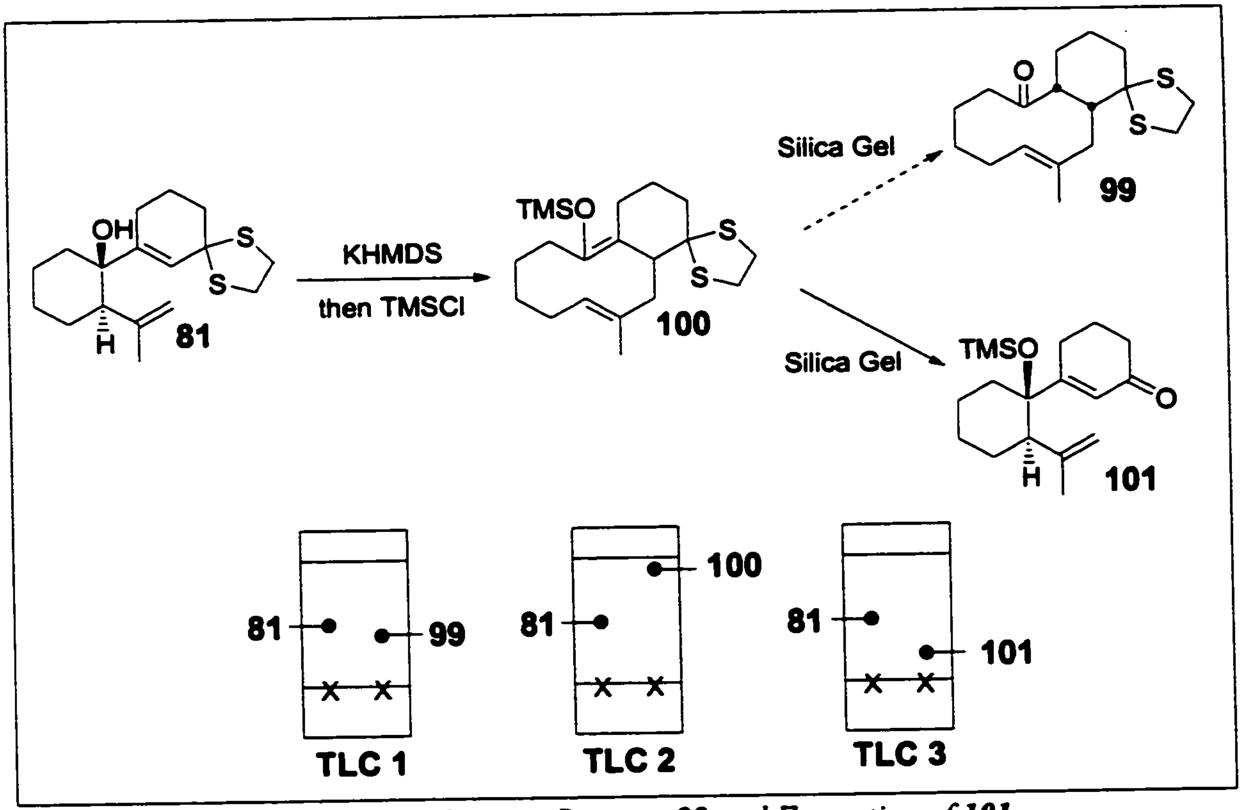
As mentioned earlier, it has been postulated that effect of NMP on oxy-Cope reactions involves a hydrogen bonding mechanism that increases the electron density of the hydroxyl oxygen, thus facilitating the oxy-Cope rearrangement (Scheme 31). Although the precise effect of DBU has not been elucidated, some observations were made in the lab that provided some insight with respect to the effect of DBU in the tandem oxy-Cope/ene process.

When an attempt was made to synthesize **99** by an anionic oxy-Cope rearrangement of **81**[48], it resulted in a purple mixture, which after appropriate work-up yielded what was determined to be a result of complete degradation of the starting material (Scheme 44). Similar results were obtained when anionic oxy-Cope reactions were performed with compounds **69**[49] and **72**[50] (Scheme 44).



Scheme 44: *Attempted Anionic Oxy-Cope Rearrangements of* ***81***, ***69*** *and* ***72***.

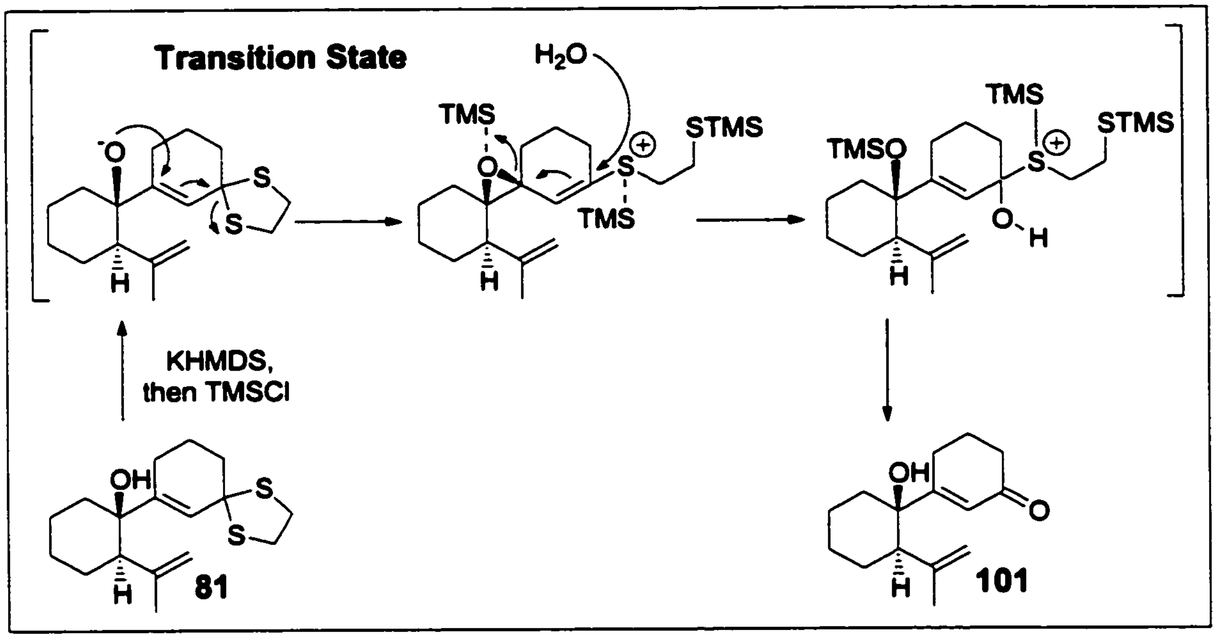
Based on these results, an alternate route to the desired compound (**99**) was designed which involved formation of the macrocyclic enol silyl ether **100** and subsequent hydrolysis on silica gel to generate the ketone **99**. The route and the appropriate TLC representations are illustrated in scheme 45.



*Scheme 45: Alternate Route to **99** and Formation of **101***

As shown by TLC 1, treatment of **81** with KHMDS provided a compound which was slightly more polar than **81**. This was believed to be the desired product **99** as a result of an aqueous quench in the capillary tube. After TMSCl was added (TLC 2), a product was formed which was much less polar than the starting material **81**. This seemed to be a very reasonable result based on the absence of polar functionalities on **100**. Finally, when **100** was treated with silica gel in methylene chloride, instead of generating a product with the same Rf as **81**, it produced an even more polar compound which after appropriate work-up and purification was determined to be **101** (18%).

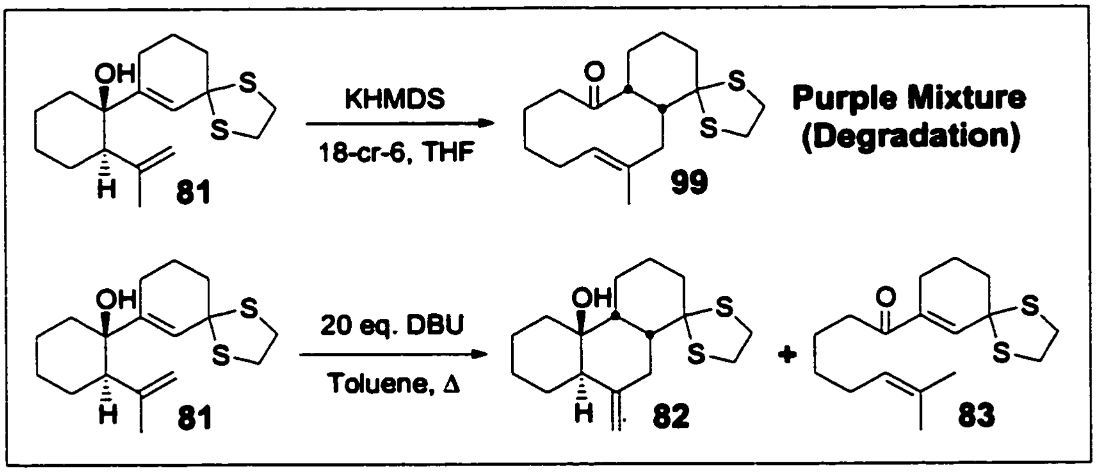
An attempt was made to rationalize the formation of this product, which is represented in scheme 46. After the oxanion of **81** has been formed, an S_N2 prime reaction can take place that can eject a thiolate from the thioacetal moiety of the molecule. Capping with TMS-groups and subsequent hydrolysis (Scheme 46) could then furnish the isolated product **101**. Although no intermediates of the reaction were isolated, we believe this to be a plausible explanation for the formation of **101**.



Scheme 46: Proposed Mechanism for the Formation of 101

As mentioned above, none of the macrocyclic ketones corresponding to **69**, **72** and **81** were isolated via anionic oxy-Cope rearrangements (Scheme 44). In practically all cases, these reactions resulted in degradation of the starting materials.

Although anionic oxy-Cope reactions with **69**, **72** and **81** cannot be effected, we have demonstrated that oxy-Cope (and subsequent ene) reactions are highly feasible with DBU such that they are more favourable that those oxy-Cope/ene reactions performed in the absence of DBU. One such example is shown in scheme 47. When **81** is heated in toluene with 20 equivalents of DBU at 220°C it provides the oxy-Cope/ene product **82** in a 1 to 1 ratio with the retroene product **83**. When anionic oxy-Cope reactions are attempted with the same molecule, the result is always degradation of the starting material. This proves that the mechanism for the oxy-Cope rearrangement of **81** with DBU cannot be an anionic one since there is no degradation of starting material.



Scheme 47:** Effect of Anionic versus Non-Anionic Oxy-Cope Reactions on **81

Based on these results, the effect of DBU (i.e. mechanism via hydrogen bonding) must be similar to that of NMP on oxy-Cope rearrangements (Scheme 32). The idea is illustrated in figure 9. It is believed that the DBU molecule **102** forms a hydrogen bond with the tertiary hydroxyl group of the substrate **103**, which in turn increases the negative charge on the oxygen atom. This effective increase in electron density on the oxygen is similar to that of the anionic oxy-Cope but not as strong. As explained above, the mechanism cannot be an anionic one as shown in figure 10. This shows the very subtle and useful effect of DBU to assist the oxy-Cope rearrangement. Once the oxy-Cope rearrangement has been effected to produce the enol **104**, subsequent tautomerization will then produce the ketone **105**.

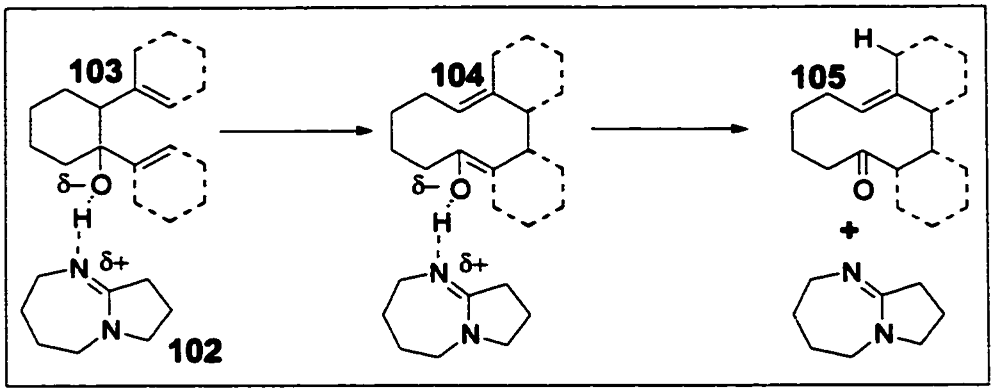


Figure 9: *The Effect of DBU on the Tandem Oxy-Cope/Ene Reaction*

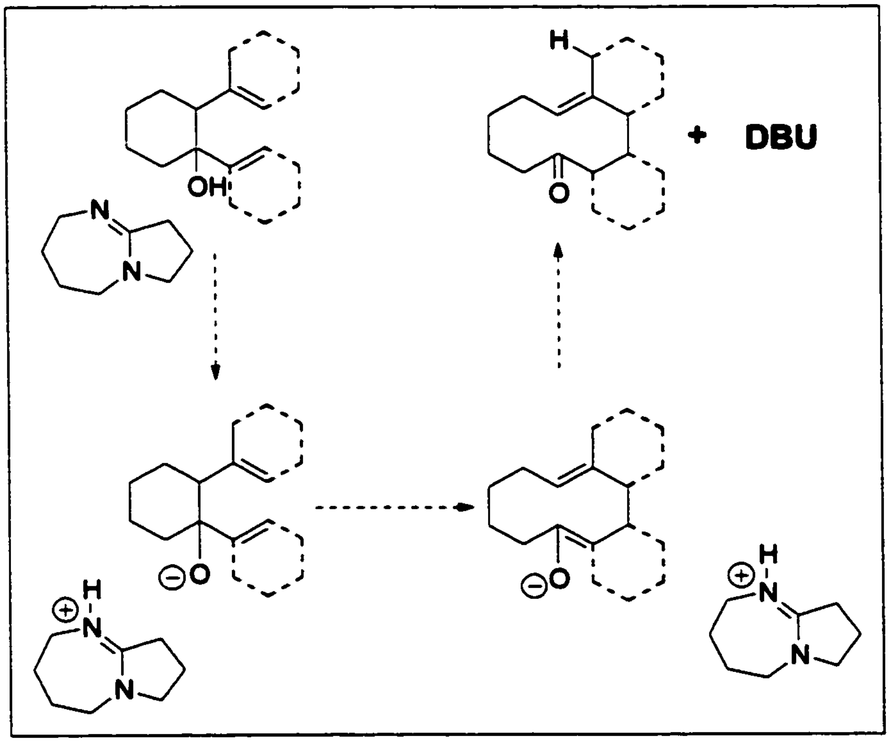


Figure 10: *The Non-Probable Effect of DBU on the Tandem Oxy-Cope/Ene Reaction*

2.8 Microwaves versus Conventional Heating Source

The main difference observed between reactions performed in the microwave and those performed using the wax bath is the amount of time required to complete the reaction. In all cases reported herein, reactions performed in the microwave were 7.5 to

12 times faster than those in the wax bath. This difference in reaction rate can most likely be attributed to a difference in temperature between the microwave and non-microwave driven reactions. A common rule in chemistry is that as temperature increases, so does reaction rate. This tenet is based on the Arrhenius equation.[51] Unlike the sealed tube system, the main source of heat that drives the reaction in the microwave comes from the carboflon bar via blackbody emission of the energy of the absorbed microwaves. This localization of heat provides a consistently very hot surface and therefore, provides much of energy to the system. The heat within the sealed tube is not as intense as it permits refluxing to occur. Since the temperature is not uniform throughout, the heat in the microwave is much more intense than that of the wax bath. This readily explains the observed increase in reaction rates.

Chapter 3: Total Synthesis of (+)-Arteannuin M

3.1 Introduction

Artemisia annua L., first isolated by Chinese scientists in 1972, is the source of the sesquiterpene endoperoxide artemisinin **106**, which has become one of the most important drugs for the treatment of malaria in South East Asia (Figure 11).[52] In 1998, Geoffrey Brown and co-workers isolated 26 new cadinane sesquiterpenes from this plant one of which was arteannuin M (**107**).[53] It is important to note that both the stereochemistry at C-4 and the absolute configuration of the molecule was unknown.

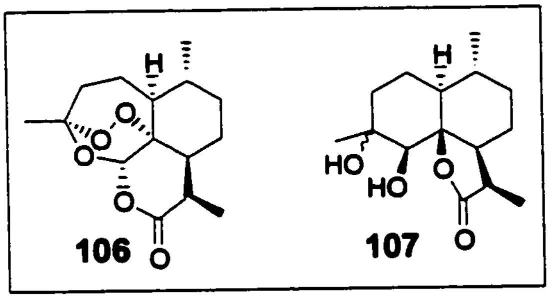
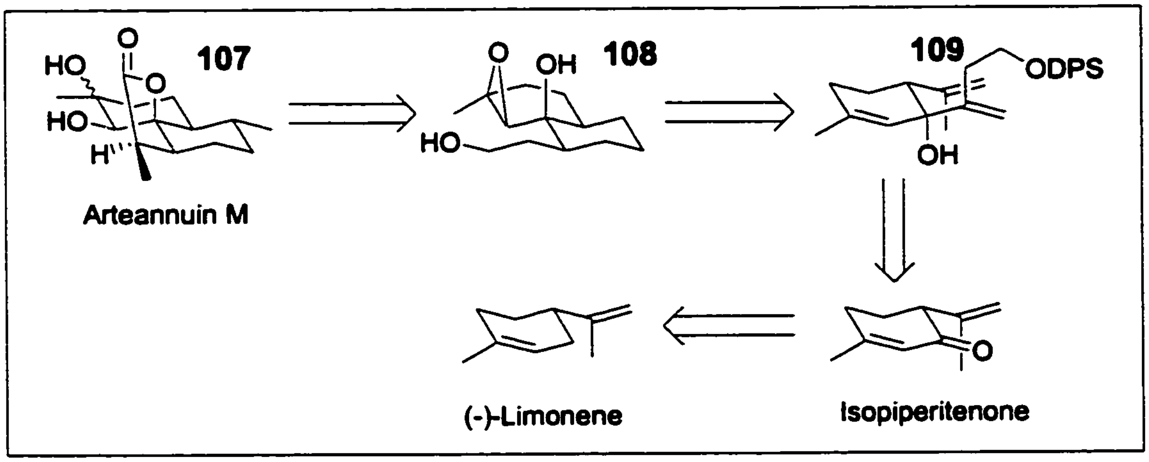


Figure 11: Endoperoxide Artemisin (106) and Arteannuin M (107)

No previous synthesis of the natural product had been reported. The solvent-assisted tandem oxy-Cope/transannular ene reaction (discussed in Chapter 1) has been proven to be an effective method for the synthesis of bi- and tricyclic compounds with a tertiary alcohol at the ring junction.

3.2 Retrosynthetic Analysis

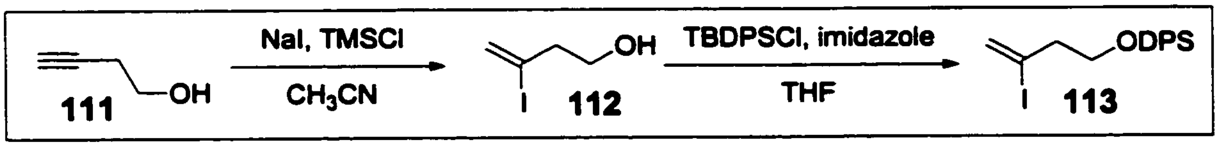
The retrosynthetic analysis began with construction of the 5-membered lactone from primary alcohol oxidation of **108** (Scheme 48). Bicyclic intermediate **109** can be produced from a tandem oxy-Cope/ene reaction of the 1,2-divinylcyclohexanol **110**, which is readily obtained by alkylation of isopiperitenone. Isopiperitenone can be synthesized according to the procedure of Dauben, which involves an allylic oxidation (-)-limonene.[54]



Scheme 48: Retrosynthetic Analysis of Arteannuin M

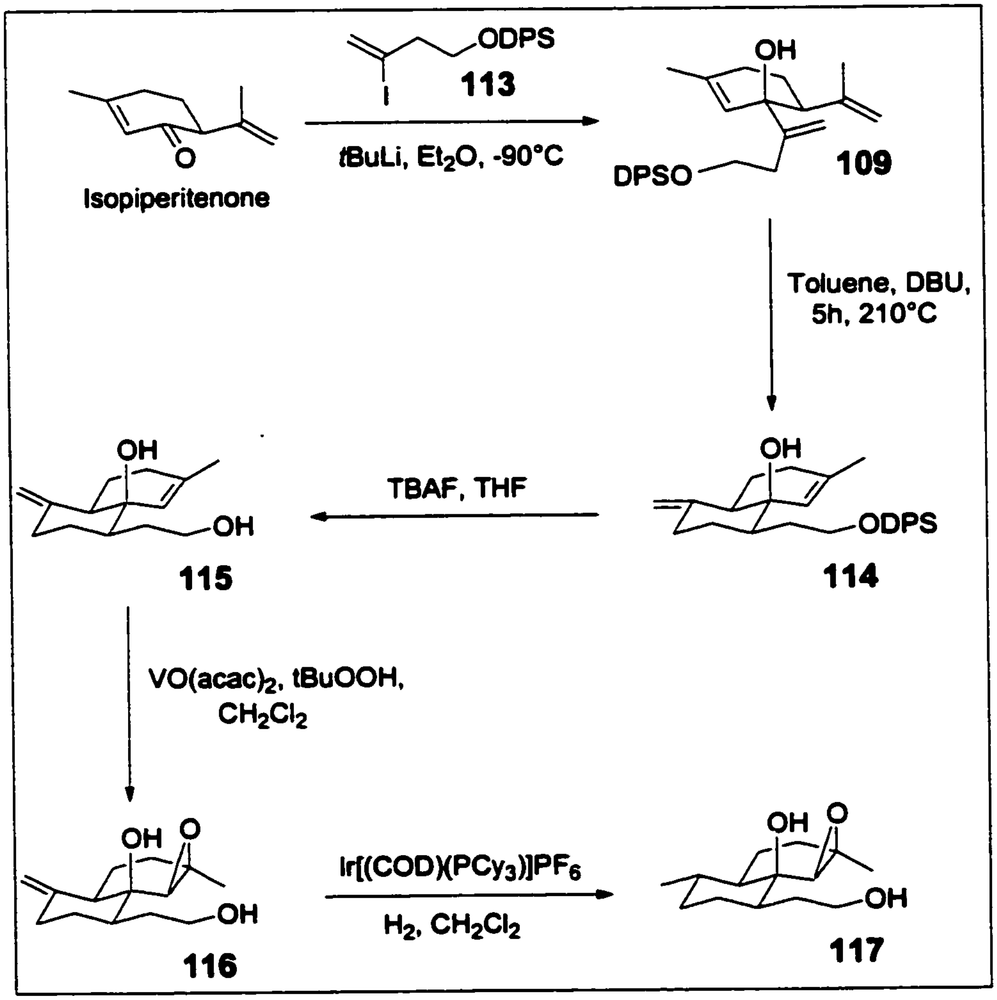
3.3 Synthesis of (+)-Arteannuin M

The synthesis began by making 3-iodo-3-butenol silyl ether **110**. 3-Butyn-1-ol (**99**) was treated with sodium iodide and trimethylsilyl chloride in acetonitrile to generate 3-iodo-3-buten-1-ol (**112**) in 9.5% yield (Scheme 49). The primary alcohol **112** was then protected with a *tert*-butyldiphenylsilyl protecting group by treatment with *tert*-butyldiphenylsilyl chloride and imidazole in THF to form the desired compound (**113**) in quantitative yield.



Scheme 49: Synthesis of 113

A halogen-metal exchange of **113** using *tert*-butyllithium (1.7 M in pentane) followed by addition of (+)-isopiperitenone furnished the 1,2-divinylcyclohexanol **109** in 91% yield as the sole diastereomer (Scheme 50). This compound was then heated in toluene with 5 equivalents of DBU for 5 hours at 210°C to give **114** as the only detectable diastereomer in 55-60%.[55] Interestingly, DBU is essential for the tandem reaction to proceed in a good yield. Without DBU, the reaction yields a complex mixture of products, from which **114** was not isolated.



Scheme 50:* *Progress toward the Synthesis of Arteannuin M

The high diastereoselectivity of the tandem process can be rationalized according to the proposed mechanism and transition state shown in figure 12. Thermal rearrangement of **109** produces the enol **118**, which immediately undergoes a highly diastereoselective tautomerization to produce the ketone **119**. As mentioned in chapter 1, transannular aldol/ene reactions proceed via transition states that adopt chairlike conformations. Therefore, there are two competing reactive conformers **A** and **B** that can produce **120** and **114** respectively. Close examination of the two transition states reveals that the alkyl chain in transition state **A** is in a pseudoaxial position whereas the alkyl chain in transition state **B** is in a pseudoequatorial conformation. This readily explains the preferred formation of **114** over **120**.

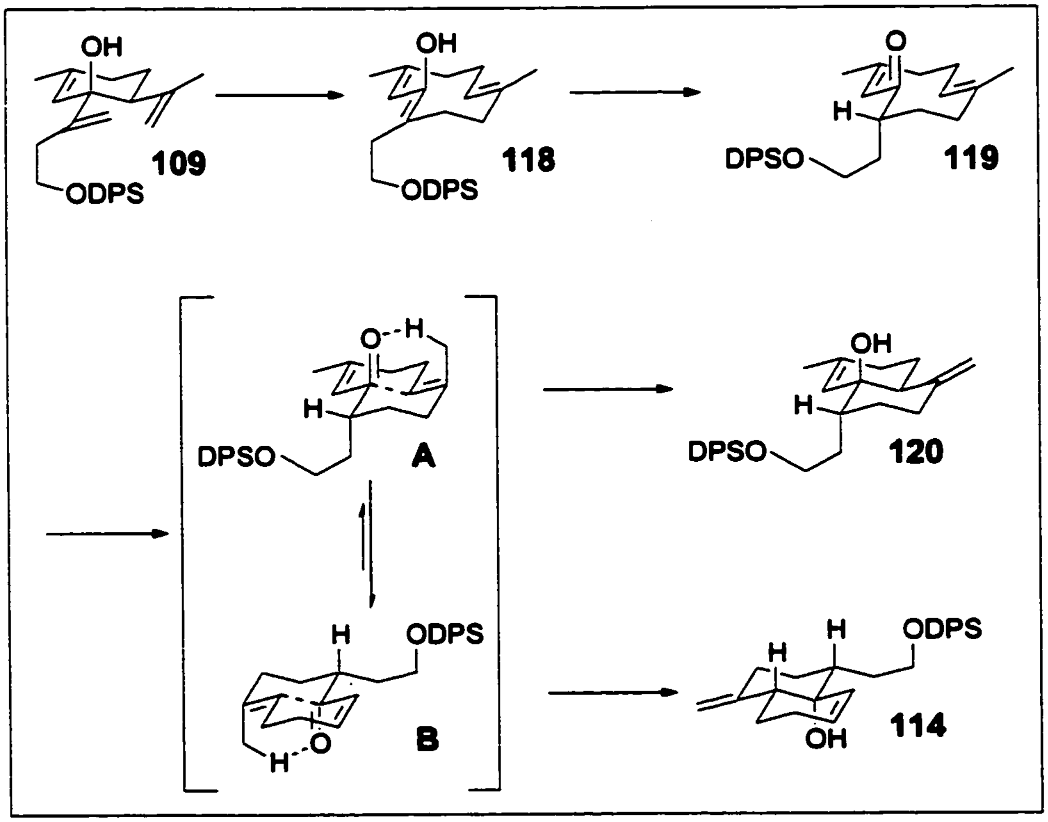
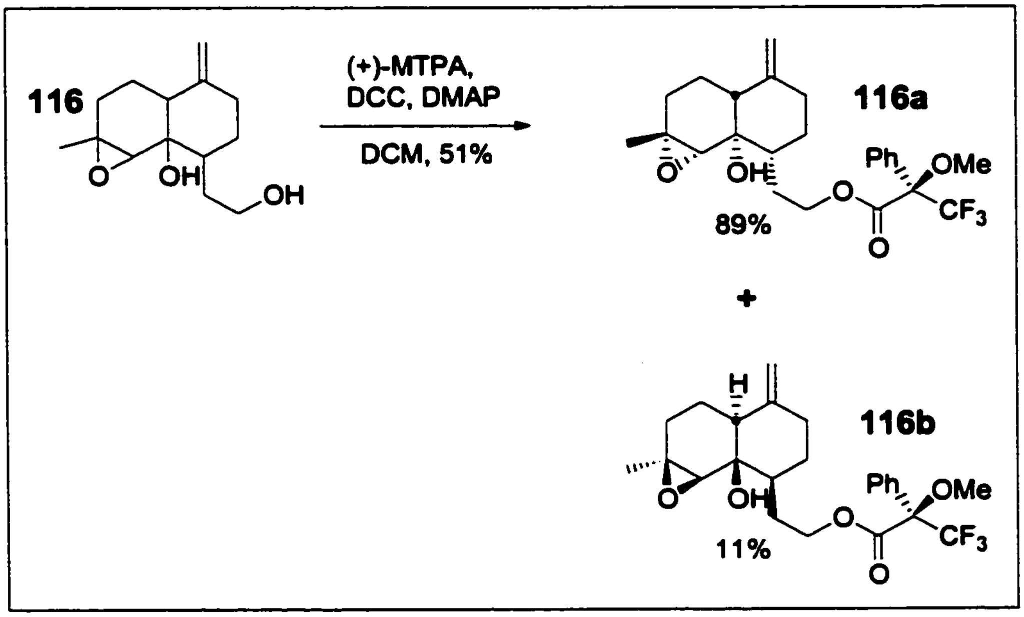


Figure 12: Transition State of the Oxy-Cope/Ene Reaction of 109

The transfer of chirality by the tandem process was evaluated by 500 MHz ^1H NMR analysis of the Mosher ester **116a** and **116b** (diastereomeric ratio of 89%) (Scheme 51). The high control of enantioselectivity observed throughout the oxy-Cope rearrangement can be explained on the basis of both the barrier of conversion of **118** into *ent*-**118** and by stereofacial protonation (Figure 13).



Scheme 51: Mosher Esters of 116

The macrocycle **118** possesses a conjugated dienol (*E,Z*) and another *E* double bond (ene donor), which together create a very strained and rigid macrocyclic ring.

Due to this strained arrangement, the conversion of **118** into *ent*-**118** requires that the enol moiety to rotate inside the ring, which is very energetically demanding. At the same time, stereofacial protonation of enol **118** can only occur from the β-face to yield ketone **119**. The preferred formation of **119** over *ent*-**119** is thus readily explained.

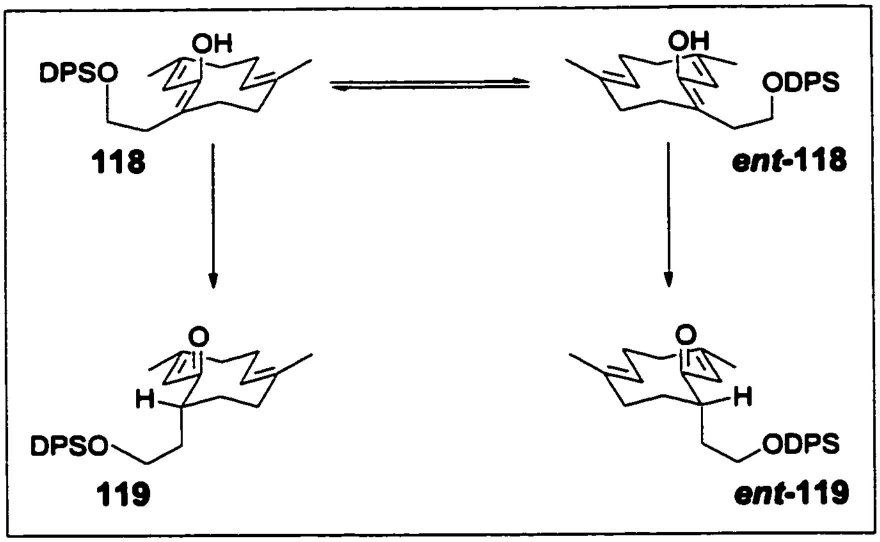


Figure 13: High Enantioselectivity of the Oxy-Cope/Ene Process

Treatment of **114** with TBAF served to deprotect the primary alcohol in quantitative yield (Scheme 50). At this stage, diastereoselective oxirane formation and exo-cyclic olefin reduction took advantage of the C-6 tertiary alcohol, which was used as a chelating source. Allylic epoxidation of **115** with $VO(acac)_2$ and TBHP in dichloromethane proceeded smoothly to generate the desired epoxide **116** in 95% yield.[56]

Single crystal structural analysis of **116** (Figure 14) enabled the undisputable stereochemical assignments for the molecule.

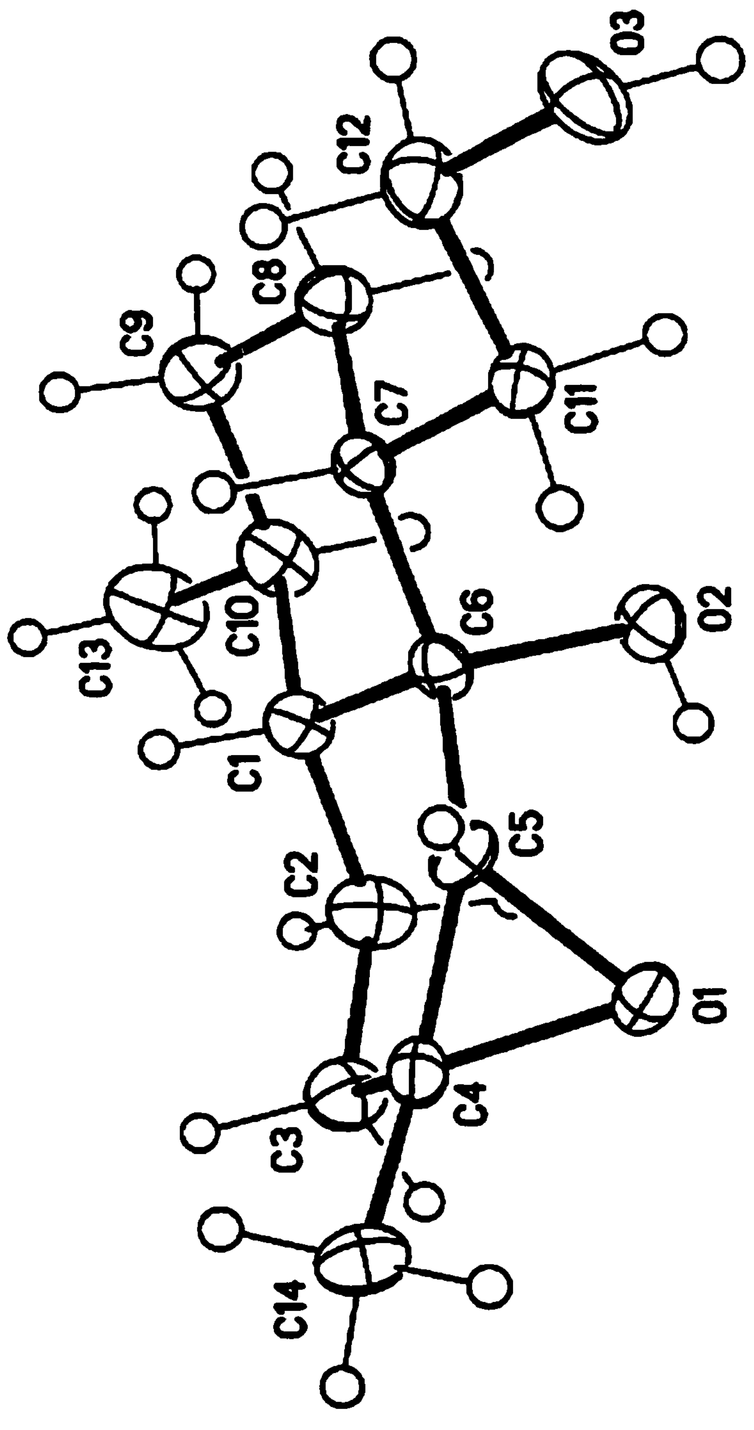
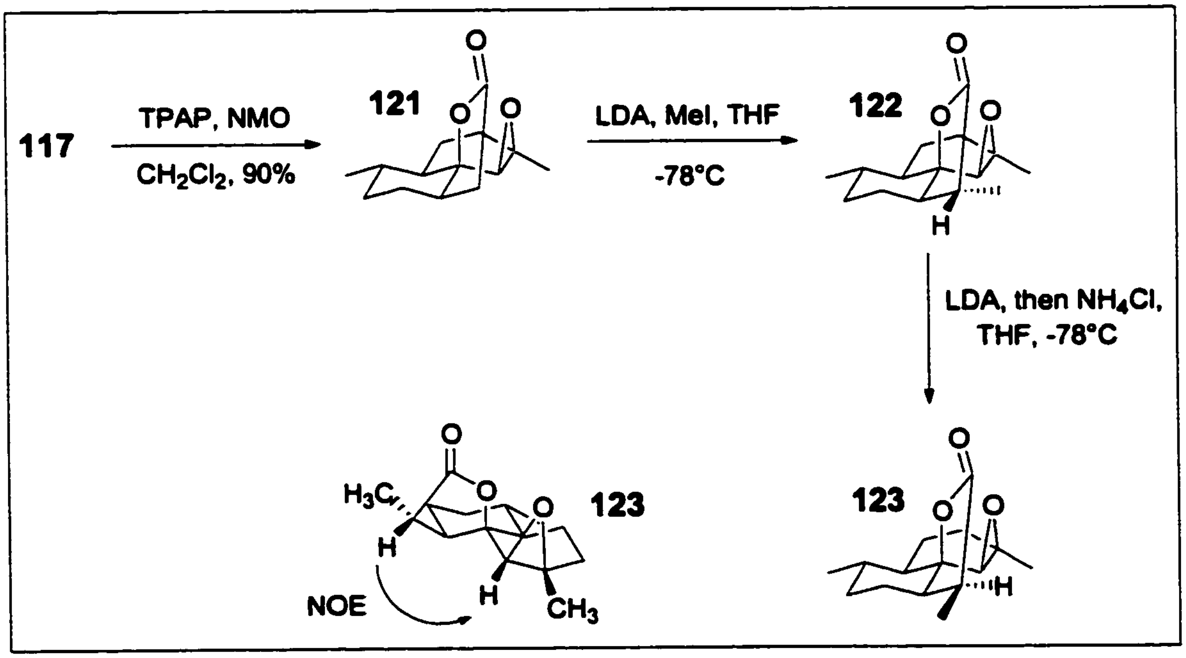


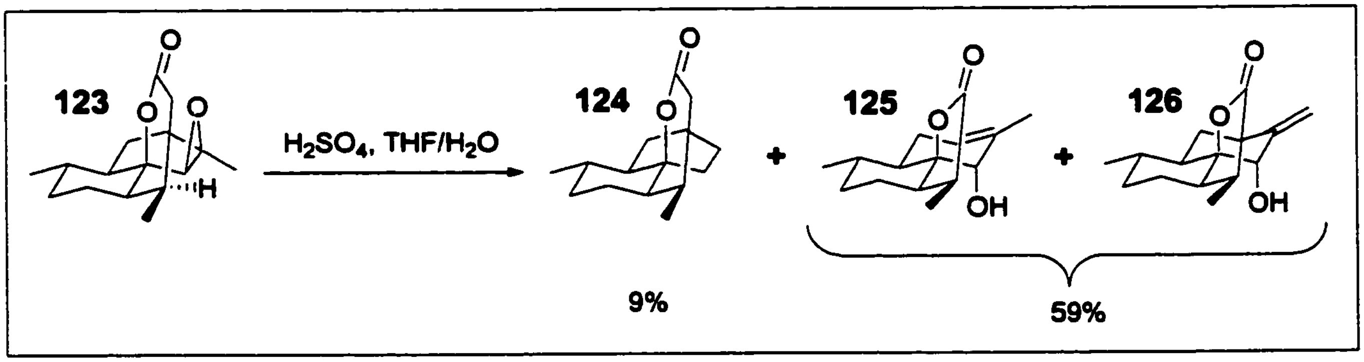
Figure 14: Single Crystal Structure of 116

A second hydroxy-directed reaction was performed using Crabtree's catalyst under an atmosphere of H_2 to reduce the olefin. Compound **117** was produced in 99% yield with the correct stereochemistry at the C-10 position (diastereomeric ration of 11:1 at C-10).[57] Sequential oxidation of **117** with TPAP and NMO in methylene chloride provided the five-membered lactone**121** in 90% yield (Scheme 52).[58] In order to install the methyl group at C-11 on compound **121**, the lithium enolate was formed (LDA, THF, -78°C) and then quenched with iodomethane at -78°C to give **122** in 72% yield. The methylation step proceeded with a high level of stereocontrol in that only the β-isomer **122** is formed (>98:2). Inversion of configuration at C-11 by formation of the lithium enolate and subsequent protonation with ammonium chloride afforded the desired α-isomer **123** in a quantitative yield. NOESY experiments confirmed that **123** possesses the 11*S* configuration (Scheme 52).



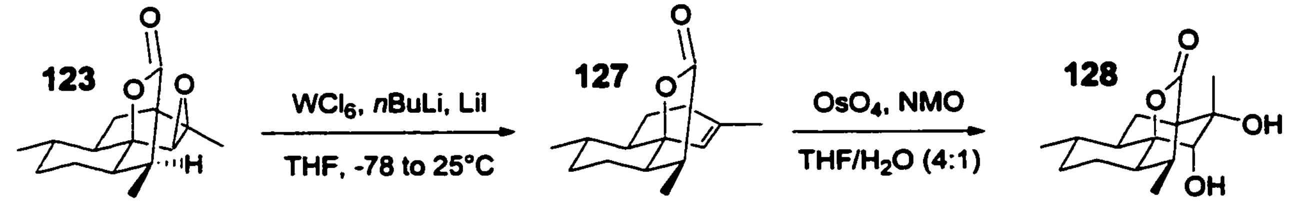
Scheme 52: α-Methylation of the Lactone

At this point all that was needed to synthesize an isomer of arteannuin M was to cleave the epoxide under acidic conditions to furnish a diol at C-4 and C-5. ^{1}H NMR experiments would then be able to determine whether or not the natural product was produced. When **123** was treated with sulfuric acid in THF/H_2O it gave a mixture of the *trans*-diol compound **124** in 9% yield with the two dehydrated products **125** and **126** in a 59% yield collectively (Scheme 53). The NMR data acquired for **124** were not identical to those of arteannuin M.



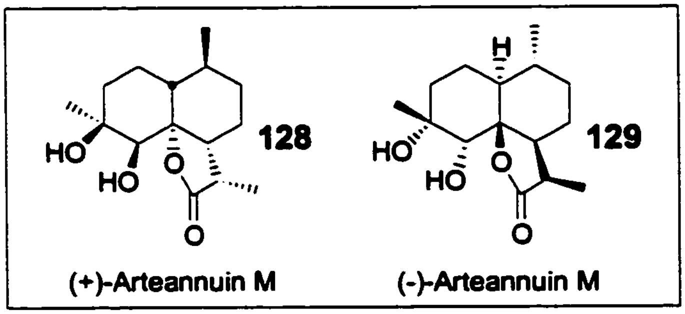
Scheme 53: Cleavage of Epoxide of 123

At this point in the synthesis the remaining unsettled question concerned the possible stereochemistry of the C4-C5 diol. During the course of the synthesis, Brown et al. revised their stereochemical assignments at C-4 and C-5. They confirmed the presence of a C4-C5 *cis* diol in **107**, but were unable to determine the relative configuration of C-4 and C-5.[59] To assign these stereogenic centers correctly, regeneration of the double bond in ring A was imperative. Deoxygenation was succesfully performed according to the Sharpless protocol to furnish **127** in 67% yield (Scheme 54).[60] A catalytic hydroxylation on **127** was then done with OsO_4 and NMO in THF/H_2O (4:1) that produced **128** having a *cis* diol *anti* to the lactone in 66% yield.



Scheme 54: Final Steps in the Total Synthesis of Arteannuin M

The 500 MHz ^{1}H and 125 MHz ^{13}C NMR spectra ($CDCl_3$) of **128** were identical to those of the natural product. This confirms without ambiguity the relative configuration of C-4 and corrects the stereochemistry at C-5. Furthermore, the positive optical rotation of **128** ($[\alpha]_D$=+34.1°, *c* 0.26 in CH_2Cl_2), which is opposite in sign to the natural product, established the absolute configuration as shown in **129** ($[\alpha]_D$=-31.1°, *c* 1.25 in $CHCl_3$) (Figure 15).



(+)-Arteannuin M (-)-Arteannuin M

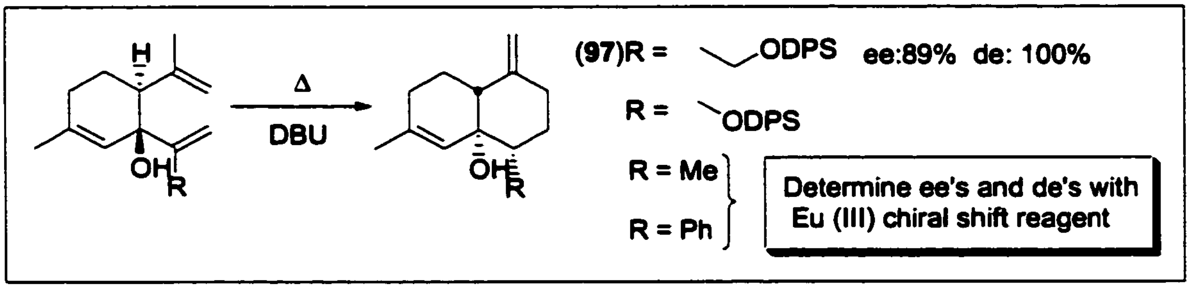
Figure 15: (+) and (-)-Arteannuin M

3.4 Conclusion

In summary, the total synthesis of (+)-arteannuin M (**128**) was accomplished in 10 steps starting from readily available (+)-isopiperitenone with an overall yield of 14.1%. Expeditious construction of the arteannuin M core with a high control of diastereoselectivity demonstrated the power and versatility of the tandem oxy-Cope/ene reaction of 1,2-divinylcyclohexanols. In addition, the absolute configuration and the correct relative stereochemistry of C-4 and C-5 has been established for (-)-arteannuin M (**129**) as shown in figure 14.

3.5 Future Work

The future plans for the research described above will involve evaluating the enantioselectivity of the oxy-Cope/ene reaction of substrates similar to **109**, but with different R-groups (Scheme 55). The enantiomeric excesses will be determined either by chiral HPLC or by ^{1}H NMR spectroscopy using a europium III chiral shift reagent.[61]



Scheme 55: Evaluation of Enantio- and Diastereoselectivity of the Tandem Oxy-Cope/Ene Reaction

From the total synthesis of (+)-arteannuin M it is known that the reaction proceeds with very high diastereoselectivity and an enantioselectivity of 89% for **109** (when R = CH_2CH_2ODPS). This high enantioselectivity is based on the transition state shown in chapter 2 (Figure 13) and below (Figure 16).

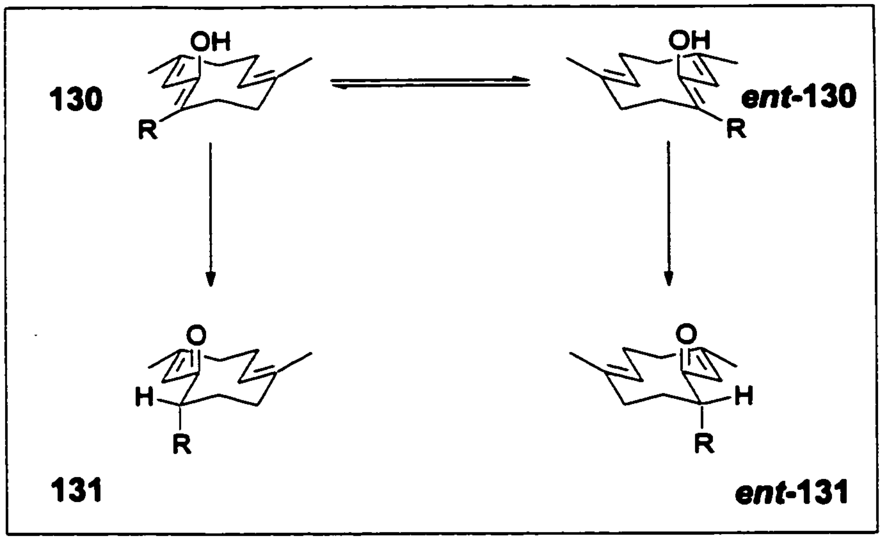
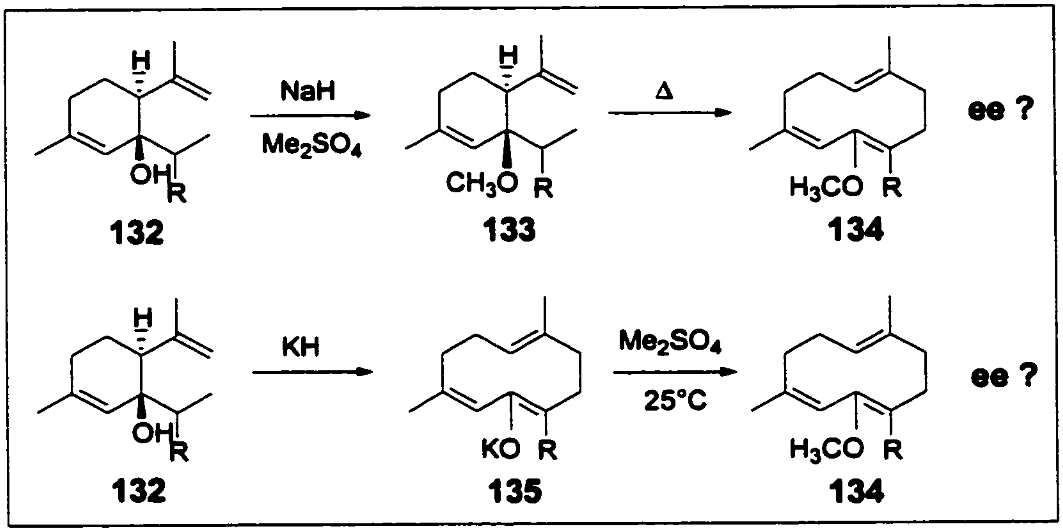


Figure 16: *High Enantioselectivity of the Oxy-Cope/Ene Process*

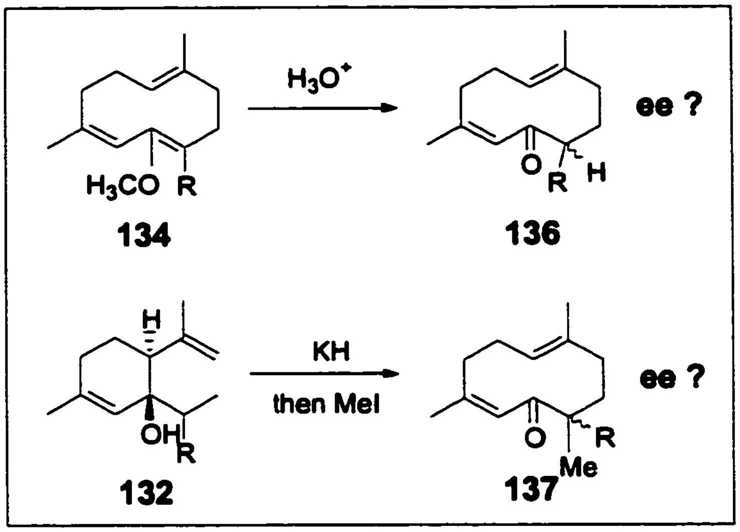
As mentioned in chapter 2, it was postulated that the high energy barrier for rotation of **130** into *ent*-**130** was responsible for the high enantioselectivity observed in the oxy-Cope/ene reaction. Part of this energy barrier is believed to come from the steric effects associated with the R-group on **130**, which must rotate inside the ring in order to be transformed into *ent*-**130**. The same oxy-Cope/ene reaction will be performed with different R-groups in order to determine their respective effect on the enantioselectivity of the reaction.

Further evaluation of the high enantioselectivity of the tandem oxy-Cope/ene process will be done via synthesis of the *O*-methylated product **134**. Two separate routes have been designed (Scheme 56), which will determine the effect of temperature on the oxy-Cope rearrangement of that produces **134**. Firstly, treatment of enantiopure **132** with NaH and then quenching with dimethylsulfate will furnish **133** that will then be heated to undergo oxy-Cope rearrangement and thus furnish the chiral enol ether **134**. The second route involves treatment of **132** with KH at room temperature to generate the enolate **135** via an oxy-Cope rearrangement and subsequent quenching with dimethylsulfate to produce **134**. These two experiments will serve to measure the enantioslectivity of the oxy-Cope rearrangement to produce **134** at both elevated and room temperatures.



Scheme 56: Two Routes to 134

Finally, the enantioselectivity of stereofacial protonation during the oxy-Cope/ene process (see above) will be determined by hydrolysis of the enol ether **134** and subsequent formation of the ketone **136** (Scheme 57). The effect of stereofacial *C*-alkylation will also be tested by treatment of **132** with KH and then iodomethane to furnish the ketone **137**. In all cases shown in schemes 56 and 57, chiral HPLC will be used to determine the enantiomeric excesses.



Scheme 57: Stereofacial Protonation and Alkylation

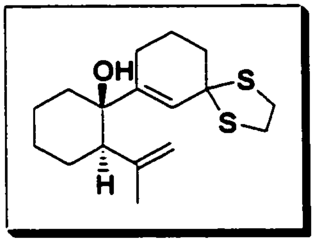
Experimental

General. Infrared (IR) spectra were obtained either as neat films, or as a thin film of a dichloromethane solution of the compound on sodium chloride plates. All IR spectra were recorded on a Bomem Michaelson 100 Fourier transform infrared spectrometer (FT-IR) and the data are recorded in reciprocal centimeters (cm^{-1}). Proton magnetic resonance (^1H NMR) were measured at 500 MHz with a Bruker AMX500, 300 MHz with a Bruker AMX300 or at 200 MHz with a Varian Gemini spectrometer in deuterated chloroform ($CDCl_3$) unless otherwise stated. Carbon magnetic resonance (^{13}C NMR) were measured at 125 MHz (Bruker), 75 MHz (Bruker) or 50 MHz (Varian) in $CDCl_3$ unless otherwise stated. Chemical shifts are reported in parts per million (ppm) downfield from trimethylsilane (δ scale). The multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, qu = quintet?), number of protons and coupling constants (reported in Hz) are indicated in parentheses. Optical rotations were recorded on a Perkin-Elemer 241 polarimeter operating at 589 nm. Mass spectra (MS) were determined on a V.G. micromass 7070 HS instrument using an ionization energy of 70 eV. The purity of all compounds was judged to be >90 % as determined by a combination of HRMS, ^1H NMR and ^{13}C NMR analyses.

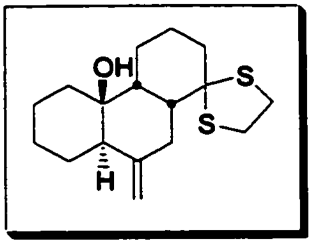
Unless otherwise stated, all non-aqueous reactions were performed under an atmosphere of dry nitrogen in flame-dried glassware equipped with a magnetic stir bar and a rubber septum. Standard inert atmosphere techniques were used in handling all air and moisture sensitive reagents and products. Reactions were monitored by thin layer chromatography (TLC) using commercial aluminum sheets pre-coated (0.2 mm layer thickness) with silica gel 60 F_{254} (E. Merck). The TLC spots were viewed under ultraviolet light and by heating the TLC plate after treatment, with either phosphomolybdic acid or a *p*-anisaldehyde staining solution (80ml 69% ethanol, 2.9 ml sulfuric acid, 0.86 ml acetic acid, 2.1 ml *p*-anisaldehyde). Products purification by conventional flash column chromatography was performed using E. Merck Silica Gel (230-400 mesh). Solutions in organic solvents were dried over $MgSO_4$ and stripped of solvents with a rotary evaporator connected to an air or water aspirator. Trace solvents were removed on a vacuum pump, much to the chagrin of Dr. Barriault. All compounds were stored at -15°C in vials flushed with nitrogen. Degassing was done by bubbling argon for 5 minutes prior to starting the reaction.

Petroleum ether refers to a mixture of hydrocarbons with a boiling range of 30-60°C. Anhydrous diethyl ether (ether), anhydrous tetrahydrofuran (THF) were freshly distilled from benzophenone/sodium. Dry benzene, toluene, dichloromethane (CH_2Cl_2), acetonitrile, triethylamine, diisopropylamine and hexanes were distilled from CaH. All commercial starting materials were purchased from Aldrich Chemical Company or Strem Chemicals unless otherwise stated.

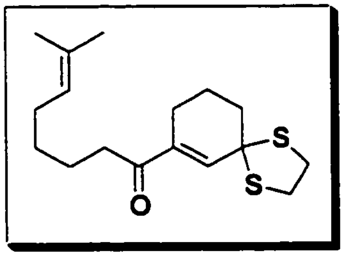
(1R*, 2R*)-1-(3-[1,4-Dithia-spiro]-1-cyclohexenyl)-2-isopropenyl-cyclohexan-1-ol (81): To a solution of **80a** (701.0 mg, 2.79 mmol) in THF (10 ml) at –78°C was added *t*BuLi (5.12 ml, 5.58 mmol). The solution was stirred for 30 minutes to form **80b** *in situ* and **79** was added via canula. The reaction mixture was allowed to stir for 15 minutes and then quenched with NH_4Cl (sat. aq.) at –78°C. It was extracted with ether, dried ($MgSO_4$) and concentrated down to dryness. Flash with 5% ether in petroleum ether gave **81** as a colourless oil (205.4 mg, 0.661 mmol, 36%). IR (neat, cm^{-1}) 3512, 2930, 2855, 1636, 1439; ^1H NMR (500 MHz, $CDCl_3$) δ 5.81 (s, 1H), 4.80 (t, J = 1.6 Hz, 1H), 4.66 (s, 1H), 3.35-3.18 (m, 4H), 2.21-2.10 (m, 2H), 2.06-1.87 (m, 3H), 1.79-1.52 (m, 7H), 1.66 (s, 3H), 1.50-1.37 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.9, 144.5, 124.8, 112.0, 74.5, 65.8, 50.2, 41.3, 39.9, 39.6, 36.7, 27.5, 26.0, 24.7, 24.2, 22.7, 21.1; HRMS (EI) *m/z* (M^+) calcd 310.1425 for $C_{17}H_{26}OS_2$, obsd 310.1416.



(1R*, 2R', 7R*, 10R*)-6-(1,4-Dithia-spiro)-tricyclo-*trans-cisoide-cis*-[8,4,0,0^{2,7}]-tetradeca-9'-en-1-ol (82): To a solution of **81** (42.4 mg, 0.136 mmol) in toluene (4 ml) was added DBU (0.407 ml, 2.72 mmol). This was heated in a pressure tube for 22 hours at 240°C. Flash with 15% ethyl acetate in hexanes afforded **82** as a light yellow oil (19.4 mg, 0.0625 mmol, 46%). IR (neat, cm^{-1}) 3452, 2923, 1602, 1433, 1134; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.93 (d, J = 1.6 Hz, 1H), 4.64 (d, J = 1.4, 1H), 3.28-3.21 (m, 4H), 2.48 (ddd, J = 1.2, 3.4, 12.4 Hz, 1H), 2.38 (dt, J = 3.53, 13.3 Hz, 1H), 2.26 (t, J = 12.9 Hz, 1H), 2.10-2.00 (m, 2H), 1.91-1.85 (m, 2H), 1.80-1.73 (m, 2H), 1.67-1.37 (m, 9H), 1.25-1.15 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.2, 109.6, 74.2, 73.3, 48.2, 47.8, 43.3, 38.5, 37.9, 37.1, 35.8, 35.3, 25.7, 25.2, 24.0, 21.2, 21.0; HRMS (EI) *m/z* (M^+) calcd 310.1425 for $C_{17}H_{26}OS_2$, obsd 310.1430.

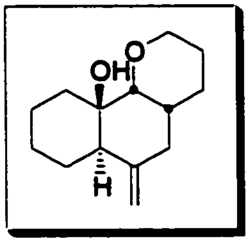


1-(1,4-Dithia-spiro[4.5]dec-6-en-7-yl)-7-methyl-oct-6-en-1-one (83): A solution of **81** (26.6 mg, 0.0856 mmol) and NMP (4.0 ml) in a pressure tube, was degassed with nitrogen for 6 minutes. It was then heated for 8 hours at 220°C. Flash with 20% ethyl acetate in hexanes gave **83** as a colourless oil (18.3 mg, 0.059 mmol, 69%). IR (neat, cm^{-1}) 2926, 2858, 1670, 1623, 1438; ^1H NMR (500 MHz, $CDCl_3$) δ 6.75 (s, 1H), 5.10-5.07 (t, J = 7.11 Hz, 1H), 3.43-3.34 (m, 4H), 2.65-2.62 (t, J = 7.5 Hz, 2H), 2.20-2.14 (m, 5H), 1.99-1.95 (q, J = 7.3 Hz, 2H), 1.80-1.75 (m, 2H), 1.62-1.54 (m, 4H), 1.58 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.5, 141.1, 136.7, 131.6, 124.3, 105.7, 64.4, 40.2, 37.3, 29.5, 27.8, 25.7, 24.2, 22.3, 22.2, 17.7; HRMS (EI) *m/z* (M^+) calcd 310.1425 for $C_{17}H_{26}OS_2$, obsd 310.1438.

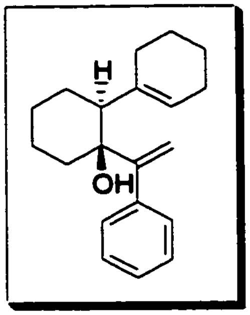


(1R*, 2R*, 7R*, 10R*)-3-Oxa-tricyclo-*trans-cisoide-cis*-[8,4,0,$0^{2,7}$]-tetradecan-9'-en-1-ol (73): To a solution of **72** (156.7 mg, 0.705 mmol) in toluene (2.5 ml) was added DBU (2.11 ml, 14.1 mmol). The solution was degassed with nitrogen for 5 minutes and heated in a pressure tube for 5 hours. Flash with 10% ethyl acetate in hexanes gave **73** as a colourless oil (28.0 mg, 0.126 mmol, 18%). IR (neat, cm^{-1}) 3472, 2927, 1644, 1441; ^1H

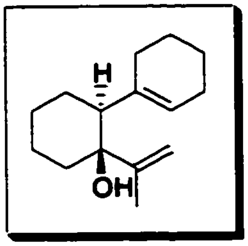
NMR (300 MHz, $CDCl_3$) δ 4.90 (d, *J* = 1.7 Hz, 1H), 4.64 (d, *J* = 1.3, 1H), 4.01 (dd, *J* = 4.5, 11.1 Hz, 1H), 3.41 (td, *J* = 2.2, 11.3 Hz, 1H), 3.03 (s, 1H), 2.54 (t, *J* = 11.2 Hz, 1H), 2.28 (dt, *J* = 1.7, 11.7 Hz, 1H), 1.99-1.21 (m, 15H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.6, 109.3, 82.8, 74.0, 69.5, 43.5, 35.8, 33.8, 33.6, 28.6, 25.9, 23.9, 21.5, 21.4; HRMS (EI) *m/z* (M^+) calcd 222.1620 for $C_{14}H_{22}O_2$, obsd 222.1610.



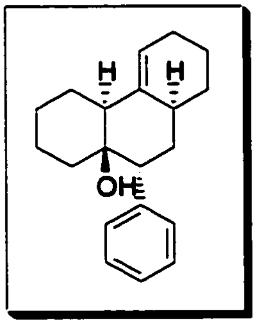
(2S*, 6R*)-2-(1-Cyclohexenyl)-1-(2-styrenyl)-cyclohexan-1-ol (89): α-Bromostyrene was placed in dry THF (40 ml) and cooled to –78°C and stirred for 45 minutes to form **88**. 2-(1-cyclohexenyl)cyclohexanone (300.1 ml, 1.68 mmol) was then added via canula and allowed to stir for 20 minutes. The reaction was then quenched with NH_4Cl (sat. aq.) and extracted with ether. Flash with 15% ether in hexanes afforded **89** as a clear oil (143.2 mg, 0.507 mmol, 30%). IR (neat, cm^{-1}) 3479, 2929, 2859, 1626, 1450, 1356; ^1H NMR (500 MHz, $CDCl_3$) δ 7.28-7.24 (m, 5H), 5.53 (s, 1H), 5.33 (d, *J* = 1.4 Hz, 1H), 5.03 (d, *J* = 1.4 Hz, 1H), 2.21 (dd, *J* = 3.5, 12.5 Hz, 1H), 2.04-1.97 (m, 4H), 1.80-1.46 (m, 11H), 1.26-1.22 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.3, 142.1, 140.1, 128.7 (2 C), 127.5 (2 C), 126.7, 123.7, 114.0, 76.0, 52.2, 40.3, 30.0, 28.2, 26.2, 25.4, 23.2, 22.4, 21.6; HRMS (EI) *m/z* (M^+) calcd 282.1984 for $C_{20}H_{26}O$, obsd 282.2003.



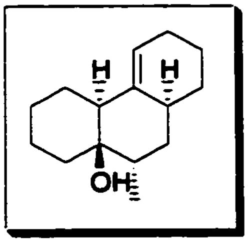
(2S*, 6R*)-2-(1-Cyclohexenyl)-isopropenyl-cyclohexan-1-ol (90): To a solution of 2-(1-cyclohexenyl)cyclohexanone (**87**) (501.0 μl, 2.80 mmol) in THF (40 ml) at –78°C was added isopropenylmagnesium bromide (16.8 ml, 8.40 mmol). The reaction mixture was stirred while warming to room temperature. The reaction was then quenched with NH_4Cl (sat. aq.) and extracted with ethyl acetate. Flash with 10% ether in hexanes afforded **90** as a clear oil (144.9 mg, 0.66 mmol, 23.4%). IR (neat, cm^{-1}) 3548, 2931, 2856, 1450, 1357; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.43 (s, 1H), 4.92 (s, 1H), 4.72 (s, 1H), 2.08 (dd, *J* = 3.6, 12.5 Hz, 1H), 1.98-1.83 (m, 4H), 1.82 (d, J = 1.6 Hz, 1H), 1.77-1.57 (m, 4H), 1.74 (s, 3H), 1.52-1.37 (m, 7H), 1.25-1.17 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.3, 140.4, 122.4, 109.2, 49.9, 36.4, 30.3, 27.3, 26.3, 25.3, 23.1, 22.4, 21.3, 20.2; HRMS (EI) *m/z* (M^+) calcd 220.1827 for $C_{15}H_{24}O$, obsd 220.1831.



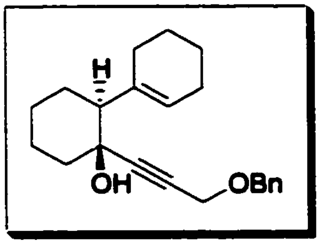
(1R*, 2S*, 4S*, 10S*)-2-Phenyl-tricyclo-[8,4,0,0^{4,9}]-tetradecan-8-en-1-ol (91): **89** (41.1 mg, 0.146 mmol) was placed in toluene (17.5 ml). DBU (435.6 υl, 2.91 mmol) and BHT (16.4 mg, 0.074 mmol) were added and the mixture was degassed with argon for 5 minutes. The mixture was heated with microwaves at 220°C for 60 minutes. Flash with 40% ether in hexanes afforded **91** as a colourless oil (38.0 mg, 0.135 mmol, 92%). IR (neat, cm^{-1}) 3423, 2925, 1600, 1363; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42-7.39 (m, 2H), 7.31-7.19 (m, 3H), 5.56 (quintet, *J* = 1.9 Hz, 1H), 2.86 (d, *J* = 5.2 Hz, 1H), 2.63-2.57 (m, 1H), 2.49 (m, 1H), 2.08-0.94 (m, 17H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 144.6, 140.4, 129.3 (2 C), 128.2 (2 C), 126.2, 122.3, 74.3, 53.7, 44.3, 36.8, 36.3, 33.4, 31.2, 25.9, 25.6, 24.2, 21.3, 20.8; HRMS (EI) *m/z* (M^+) calcd 282.1984 for $C_{20}H_{26}O$, obsd 282.1970.



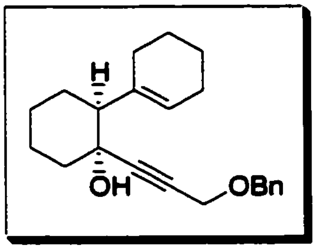
(1R*, 2S*, 4S*, 10S*)-2-Methyl-tricyclo-[8,4,0,$0^{4,9}$]-tetradecan-8-en-1-ol (92): To a solution of **90** (31.9 mg, 0.145 mmol) in toluene (21.2 ml) was added DBU (866.0 υl, 5.79 mmol). The mixture was degassed with argon for 5 minutes and then heated with microwaves for 55 minutes. Flash with 20% ether in hexanes afforded the desired product as a colourless oil (20.9 mg, 0.095 mmol, 66%). IR (neat, cm^{-1}) 3479, 2925, 1598, 1447, 1381, 1097; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.43 (s, 1H), 2.18 (m, 1H), 2.12 (m, 1H), 1.99 (m, 2H), 1.82-1.68 (m, 4H), 1.65-1.51 (m, 5H), 1.51-1.38 (m, 5H), 1.26-1.15 (m, 2H), 1.08 (d, *J* = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 141.6, 121.2, 74.8, 43.0, 40.2, 38.6, 35.4, 32.0, 31.1, 26.2, 26.1, 24.1, 21.6, 21.1, 16.4; HRMS (EI) *m/z* (M^+) calcd 220.1827 for $C_{15}H_{24}O$, obsd 220.1807.



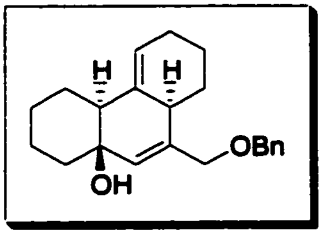
(1R*, 2S*)-1-(3-[1-(Benzyloxy)-propynyl])-2-(1-cyclohexenyl)-cyclohexan-1-ol (94): To a solution of **93a** in THF at –78°C was added *n*BuLi (1.34 ml, 3.36 mmol). After stirring for 20 minutes, 2-(1-cyclohexenyl)cyclohexanone (501.0 μl, 2.80 mmol) was added. The reaction was stirred at –78°C for 40 minutes and quenched with an aqueous solution of NH_4Cl and extracted with ether. Flash with 20% ether in hexanes afforded **94** as a colourless oil (246.6 mg, 0.760 mmol, 27%). IR (neat, cm^{-1}) 3455, 2931, 1621, 1447; ^1H NMR (500 MHz, $CDCl_3$) δ 7.33-7.27 (m, 5H), 5.57 (s, 1H), 4.56 (s, 2H), 4.17 (s, 2H), 2.49-2.44 (m, 1H), 2.20 (d, *J* = 1.7 Hz, 1H), 2.12 (dd, *J* = 1.6, 13.2 Hz, 1H), 2.07-1.99 (m, 4H), 1.72-1.40 (m, 9H), 1.28-1.18 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 140.4, 137.6, 128.3, 127.9 (2 C), 127.7, 123.4 (2 C), 91.7, 78.8, 71.3, 67.5, 57.4, 53.0, 39.7, 31.6, 26.4, 25.9, 25.3, 23.1, 22.4, 20.6; HRMS (EI) *m/z* (M^+) calcd 324.2089 for $C_{22}H_{28}O_2$, obsd 324.2070.



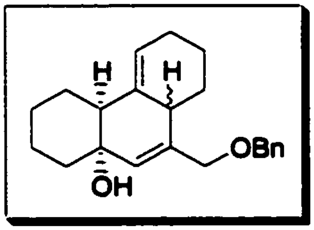
(1S*, 2S*)-1-(3-[1-(Benzyloxy)-propynyl])-2-(1-cyclohexenyl)-cyclohexan-1-ol (95): Flash with 20% ether in hexanes also afforded **95** as a colourless oil (189.6 mg, 0.584 mmol, 21%). IR (neat, cm^{-1}) 3448, 2931, 1619, 1448; ^1H NMR (500 MHz, $CDCl_3$) δ 7.34-7.27 (m, 5H), 5.65 (s, 1H), 4.60 (s, 2H), 4.22 (s, 2H), 2.77 (s, 1H), 2.42-2.36 (m, 1H), 2.11-1.94 (m, 5H), 1.74-1.44 (m, 10H), 1.27-1.22 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.9, 137.8, 128.8 (2 C), 128.4 (2 C), 128.2, 127.2, 89.4, 82.2, 71.8, 70.4, 57.9, 57.4, 40.9, 28.5, 26.7, 26.2, 25.8, 24.4, 23.4, 22.8; HRMS (EI) *m/z* (M^+) calcd 324.2089 for $C_{22}H_{28}O_2$, obsd 324.2094.



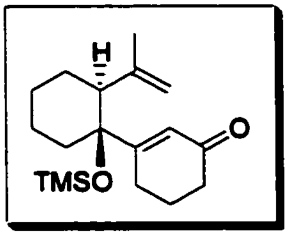
(1R*, 4R*, 10S*)-3-Benzyloxymethyl-tricyclo-[8,4,0,$0^{4,9}$]-tetradecan-8-en-1-ol (96): To a solution of DHD-394(1) (27.6 mg, 0.085 mmol) in toluene (20 ml) was added DBU (254 μl, 1.70 mmol). The solution was degassed with argon for 5 minutes. It was then heated with microwaves at 220°C for 90 minutes. Flash with 30% ether in hexanes to give DHD-402 as a colourless oil (24.8 mg, 0.076 mmol, 90%). IR (neat, cm^{-1}) 3370, 2924, 1653, 1456; ^1H NMR (300 MHz, $CDCl_3$) δ 7.37-7.25 (m, 5H), 5.67 (s, 1H), 5.47 (d, J =2.3 Hz, 1H), 4.48 (quar, J = 9.0 Hz, 2H), 4.12 (d, J = 12.1 Hz, 1H), 3.83 (d, J = 12.1 Hz, 1H), 2.85-2.82 (m, 1H), 2.16-1.99 (m, 4H), 1.84-1.78 (m, 3H), 1.69-1.02 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) 139.9, 138.6, 138.4, 133.0, 128.8, 128.2, 128.0, 121.8, 72.6, 71.9, 69.3, 47.7, 39.0, 37.4, 28.2, 26.4, 25.6, 23.5, 22.6, 21.4; HRMS (EI) *m/z* (M^+ - H_2O) calcd 306.1983 for $C_{22}H_{26}O$, obsd 306.1951.



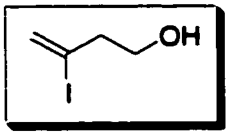
(1S*, 4R*, 10S*)-3-Benzyloxymethyl-tricyclo-[8,4,0,0^{4,9}]-tetradecan-8-en-1-ol (97): To a solution of **95** (26.9 mg, 0.083 mmol) in toluene (19.5 ml) was added DBU (248 μl, 1.66 mmol). The solution was degassed with argon for 5 minutes. It was then heated with microwaves at 220°C for 360 minutes. Flash with 30% ether in hexanes gave **97** as a colourless oil (13.4 mg, 0.041 mmol, 50%). IR (neat, cm^{-1}) 3370, 2924, 1653, 1456; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33-7.30 (m, 2H), 7.29-7.04 (m, 3H), 5.64 (s, 1H), 5.55 (d, *J* =2.6 Hz, 1H), 4.35 (dd, *J* = 12.1, 14.0 Hz, 2H), 4.02 (d, *J* = 12.2 Hz, 1H), 3.72 (d, *J* = 12.2 Hz, 1H), 2.86-2.81 (m, 1H), 2.15-1.96 (m, 3H), 1.86-1.78 (m, 2H), 1.68-1.05 (m, 10H) 0.93-0.80 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.6, 139.1, 138.9, 131.0, 128.7 (2 C), 127.9 (2 C), 127.5, 124.4, 72.2, 72.0, 70.3, 53.7, 38.8, 35.1, 29.6, 27.6, 25.9, 25.4, 24.0, 23.0; HRMS (EI) *m/z* (M^+ - H_2O) calcd 306.1983 for $C_{22}H_{26}O$, obsd 306.1963.



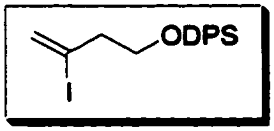
(1R*, 2S*)-1-(3-[2-Cyclohexen-1-one])-2-isopropenyl-cyclohexan-1-trimethylsilyl-ether (101): To a solution of **81** (61.1 mg, 0.197 mmol) in THF (2 ml) was added KHMDS (1.97 ml, 0.985 mmol). The reaction mixture was heated to reflux until all of the starting material was consumed. The mixture was then cooled to room temperature and TMSCl was added (30.0 μl, 0.236 mmol). After stirring for 1 minute the reaction mixture was quenched with a saturated aqueous solution of $NaHCO_3$ and then extracted with ethyl acetate and concentrated down to dryness. The resultant purple oil was then dissolved in methylene chloride (5 ml) and then stirred with silica gel (~ 1 g). This was allowed to stir for 3 hours and then the silica was filtered off. The filtrate was then dried ($MgSO_4$), filtered and concentrated. Flash with 15% ethyl acetate in hexanes gave **101** as a colourless oil (11.0 mg, 0.036 mmol, 18%). IR (neat, cm^{-1}) 3628, 3070, 2949, 2863, 1670, 838; ^1H NMR (500 MHz, $CDCl_3$) δ 6.05 (s, 1H), 4.60 (s, 1H), 4.50 (s, 1H), 2.36-2.24 (m, 4H), 2.11-1.23 (m, 14H), 0.18 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.0, 170.2, 147.3, 124.7, 112.6, 82.2, 54.2, 37.4, 35.4, 27.2, 27.1, 25.9, 22.7, 21.3, 20.7, 2.7 (3 C); HRMS (EI) *m/z* (M^+) calcd 306.2015 for $C_{18}H_{30}O_2Si$, obsd 306.2007.



3-Iodo-but-3-en-1-ol (112): To a solution of flame dried NaI (7.70g, 51.4 mmol) in dry acetonitrile (80ml), TMSCl (6.53ml, 51.4mmol) was added. After stirring for 10 minutes, a white precipitate was formed. Butynol (**111**) (3.24ml, 42.8mmol) was added dropwise and this was stirred for only 10 minutes in order to avoid degradation by HI. The reaction was quenched with water and solid $NaHCO_3$ was added slowly until all bubbles had subsided. This was extracted with 50% hexanes in ether (3x 60ml). The combined organic phases were washed with an aqueous solution of sodium sulfite. The organic phase was then dried ($MgSO_4$), filtered and concentrated down to dryness. Flash with 40% ethyl acetate in hexanes afforded **112** as a cloudy oil (1.21g, 6.11mmol, 14.3%); IR (neat, cm^{-1}) 3347, 1617; ^1H NMR (500 MHz, $CDCl_3$) δ 6.15 (s, 1H), 5.82 (s, 1H), 3.73 (t, J = 5.8 Hz, 2H), 2.61 (t, J = 5.9 Hz, 2H), 1.58 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 128.4, 107.3, 60.8, 48.0; HRMS (EI) *m/z* (M^+) calcd 197.9501 for C_4H_7OI, obsd 197.9527.

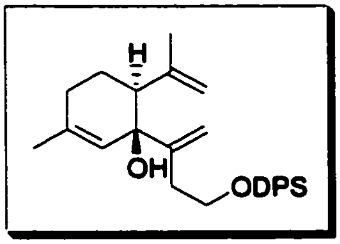


***tert*-Butyl-(3-iodo-but-3-enyloxy)-diphenyl-silane (113):** To a solution of imidazole (1.24g, 18.3mmol) in THF (15ml) was added 3-Iodo-but-3-en-1-ol (**112**) (1.21g, 6.11mmol). After 2 minutes of stirring, TBDPSCl (1.75ml, 6.72mmol) was added dropwise and this was allowed to stir for 20 minutes. The reaction mixture was then quenched with NH_4Cl (sat. aq.) and extracted with ethyl acetate (3x 20ml). The organic phase was then dried ($MgSO_4$), filtered and concentrated. Flash with 50% ethyl acetate in hexanes afforded the cloudy oil (**113**) (2.66g, 6.11mmol, 100%); IR (neat, cm^{-1}) 2958, 1427, 1135; ^1H NMR (500 MHz, $CDCl_3$) δ 7.67-7.65 (m, 4H), 7.41-7.36 (m, 6H), 6.09 (s, 1H), 5.77 (s, 1H), 3.76 (t, $J = 6.2$ Hz, 2H), 2.60 (t, $J = 6.2$ Hz, 2H), 1.03 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) 135.6 (4 C), 133.6 (2 C), 129.6 (2 C), 127.6 (4 C), 127.4, 62.2, 48.1, 26.8 (3 C), 19.4; HRMS (EI) *m/z* (M^+ - C_4H_9) calcd 378.9975 for $C_{16}H_{16}OSiI$, obsd 378.9871.

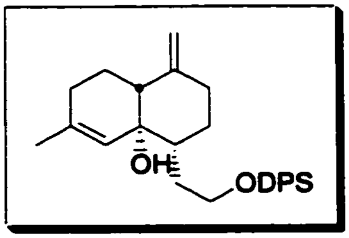


1S-{-[2-(*tert*-Butyl-diphenyl-silanyloxy)-ethyl]-vinyl}-6-isopropenyl-3-methyl-cyclohex-2-enol (109):__To a solution of vinyl iodide (**113**) (184.6mg, 0.423mmol) in ether (4ml) at –90°C *t*-BuLi (0.56ml, 0.423mmol) was added and this was allowed to stir for 10 minutes. During this time, a cloudy white precipitate was formed inside the flask. The ketone (42.3mg, 0.282mol), which was also in ether (5ml) at –90°C was transferred into the solution of the metallated compound. The solution was allowed to stir while warming to –40°C at which time it was quenched with a saturated aqueous solution of ammonium chloride. It was then extracted with ethyl acetate (3x 15ml), dried ($MgSO_4$), filtered and concentrated. A flash with 10% ethyl acetate in hexanes gave a colourless oil (115.3mg, 0.25 mmol, 89%). IR (neat, cm^{-1}) 3526, 1434, 1102; ^1H NMR (500 MHz, $CDCl_3$) δ 7.67-7.65 (m, 4H), 7.42-7.35 (m, 6H), 5.15 (d, $J = 6.6$ Hz, 2H), 4.90 (s, 1H), 4.84 (s 1H), 4.73 (s, 1H), 3.81-3.78 (m, 2H), 2.37-2.23 (m, 3H), 2.11 (s, 1H), 1.99-1.97 (m, 2H), 1.94-1.86 (m, 1H), 1.71 (s, 3H), 1.65 (s, 3H), 1.56 (s, 1H), 1.04 (s, 9H); ^{13}C

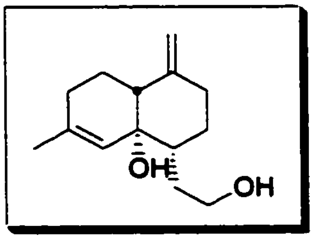
NMR (125 MHz, $CDCl_3$) 151.2, 147.2, 138.3, 135.5 (2 C), 135.5, 133.8, 129.5 (4 C), 127.6 (4 C), 126.5, 112.9, 110.0, 73.9, 63.8, 48.0, 35.0, 30.8, 26.8 (3 C), 24.6, 24.5, 23.4, 19.1; HRMS (EI) *m/z* (M^+ - $C_4H_{11}O$) calcd 385.1988 for $C_{26}H_{29}OSi$, obsd 385.1989, $[\alpha]_D$= +10.5°, c=3.82 in CH_2Cl_2.



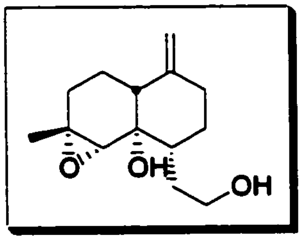
(1R, 6S, 7R)-7[(2-tert-butyldiphenylsiloxy) ethyl]-10-methylene-4-methylbicyclo [4.4.0^{1,6}] deca-4-en-6-ol (114): To a solution of **109** (93.5mg, 0.203mmol) in toluene (3ml) in a pressure tube was added DBU (0.152ml, 1.01mmol). The pressure tube was then flushed with nitrogen, sealed and heated for 4 hours at 220°C. It was then concentrated in order to remove all toluene and then flashed with 10% ethyl acetate in hexanes to afford an oil (55.2mg, 0.120mol, 60%). IR (neat, cm^{-1}) 2930, 1111, 702; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68-7.65 (m, 4H), 7.42-7.35 (m, 6H), 5.69 (s, 1H), 4.87 (s, 1H), 4.63 (s 1H), 3.79-3.75 (m, 1H), 3.69-3.66 (m, 1H), 2.34 (s, 1H, OH), 2.28 (dq, *J* = 2.1, 13.1 Hz 1H), 2.06-1.97 (m, 5H), 1.73-1.65 (m, 6H), 1.53-1.52 (m, 1H), 1.40-1.24 (m, 3H), 1.05 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.5, 138.8, 135.6 (4 C), 134.0 (2 C), 129.5, 127.6 (4 C), 124.5, 124.4, 107.5, 71.6, 62.6, 48.2, 41.7, 35.8, 32.2, 30.6, 30.0, 26.9 (3 C), 23.7, 20.5, 19.2; HRMS (EI) *m/z* (M^+ - H_2O) calcd 442.2692 for $C_{26}H_{29}OSi$, obsd 442.2529 $[\alpha]_D$= -66.3°, c=2.79 in CH_2Cl_2.



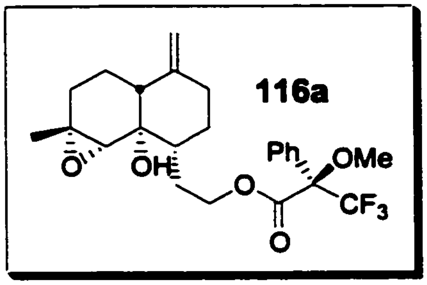
(1R, 6S, 7R)-7-[(2-Hydroxy) ethyl]-10-methylene-4-methylbicyclo [4.4.0^{1,6}] deca-4-en-6-ol (115): To a solution of **114** (107.6mg, 0.234mmol) in THF (7ml) TBAF (0.257ml, 0.257mmol) was added dropwise. The reaction mixture was allowed to stir for 1.5 hours at which time it was deemed complete by TLC. It was concentrated and flashed with 25% hexanes in ethyl acetate to remove all impurities. This afforded a colourless oil (52.0mg, 0234mmol, 100%) that was used immediately for the next reaction.



(1R, 4R, 5R, 6S, 7R)-4,5-Epoxy-7-[(2-hydroxy) ethyl]-10-methylene-4-methylbicyclo [4.4.0^{1,6}] decan-6-ol (116): To a solution of **115** (12.2mg, 0.055mmol) in DCM (1.5ml) was added VO(acac)$_2$ (65.9ul, 0.01M solution in DCM). The reaction mixture turned from faintly green to deep purple immediately upon addition of *tert*-butyl hydroperoxide (8.3ul, 0.060mmol). After stirring for 1 hour the mixture had turned light yellow and was deemed complete (TLC). It was washed with an aqueous saturated solution of $Na_2S_2O_3$ (3x 5ml), dried ($MgSO_4$), filtered and concentrated down to dryness. Flash with 20% hexanes in ethyl acetate gave an oil (12.4mg, 0.052mmol, 95%). IR (neat, cm^{-1}) 2935, 1059; ^1H NMR (500 MHz, $CDCl_3$) δ 4.80 (s, 1H), 4.51 (s 1H), 3.78-3.73 (qt, $J = 5.6$ Hz, 1H), 3.65-3.60 (m, 1H), 3.11 (s, 1H), 2.50 (br.s, 1H), 2.33 (dq, $J = 2.1$, 13.1 Hz, 1H), 2.12-1.91 (m, 4H), 1.85-1.80 (m, 1H), 1.76-1.54 (m, 5H), 1.44-1.33 (m, 2H), 1.32 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.9, 107.3, 70.6, 63.7, 61.2, 60.4, 48.5, 40.9, 35.6, 32.4, 30.1, 29.4, 23.3, 17.3; HRMS (EI) *m/z* (M^+) calcd 238.1569 for $C_{14}H_{22}O_3$, obsd 238.1555, $[\alpha]_D = -66.2°$, c=1.56 in CH_2Cl_2.

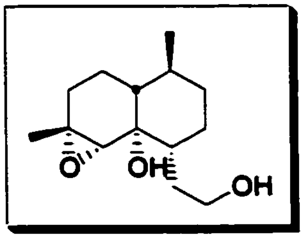


116a: To a solution of 116 (33.7 mg, 0.141 mmol) in dichloromethane (3.4 ml), was added (R.)-(+)-methoxy(trifluoromethyl) phenylacetic acid (36.3 mg, 0.155 mmol) and DCC (32.0 mg, 0.155 mmol). This was stired for 30 seconds and DMAP (1.71 mg, 0.014 mmol) was added by canula and 1 ml of dichloromethane. The mixture was allowed to stir for 75 minutes. It was then quenched with a saturated aqueous solution of NH_4Cl and extracted with ethyl acetate. Flash with 60% hexanes in ethyl acetate afforded the desired product as a viscous clear oil (38.0 mg, 0.084 mmol, 64%).

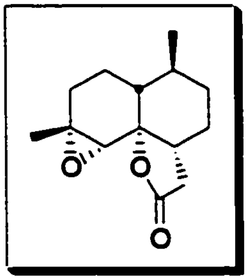


116a

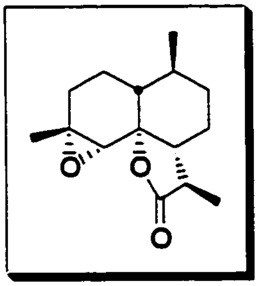
(1R, 4R, 5R, 6S, 7R, 10S)-4,5-Epoxy-7-[(2-hydroxy) ethyl]-4,10-methylbicyclo $[4.4.0^{1,6}]$ decan-6-ol (117): To a solution of **116** (12.0mg, 0.050mmol) in DCM (1.5ml) a balloon of H_2 with a stopcock was attached. The flask was evacuated and replenished with hydrogen 3 times. Crabtree's catalyst was then added (252ul, 0.005M solution in DCM). After stirring for 2 hours the reaction was complete (TLC). It was then filtered through celite with ethyl acetate and concentrated down to dryness to yield a white solid (12.1mg, 0.050mmol, 100%). IR (neat, cm^{-1}) 2926, 1056; ^1H NMR (500 MHz, $CDCl_3$) δ 3.78-3.74 (qt, *J* = 5.6 Hz, 1H), 3.65-3.60 (m, 1H), 3.05 (s, 1H), 2.55 (br.s, 1H), 2.05 (dd, *J* = 4.3, 15.2 Hz, 2H), 1.96-1.90 (m, 1H), 1.69-1.42 (m, 8H), 1.30 (s, 3H), 1.08-0.94 (m, 2H), 0.80-0.79 (d, *J*= 6.6 Hz, 3H), 0.61-0.56 (t, *J* = 11.6 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 68.8, 64.1, 61.7, 60.5, 50.5, 41.0, 35.3, 32.6, 30.6, 29.7, 27.5, 23.4, 19.7, 17.1; HRMS (EI) *m/z* (M^+) calcd 240.1725 for $C_{14}H_{24}O_3$, obsd 240.1678, mp:79-81°C, $[\alpha]_D$= -1.25°, c=2.27 in CH_2Cl_2.



(1R, 4R, 5R, 6S, 7R, 10S)-4,5-Epoxy-6,7-[7, 11-(2*H*)-furan-12-one]-4,10-dimethylbicyclo [4.4.0^{1,6}] decane (121): To a solution of 117 (9.5mg, 0.040mmol) in DCM (1.4ml), TPAP (1mg, 0.002mmol), NMO (7mg, 0.060mmol) and molecular sieves (20.0mg, 4Å) were all added at the same time. The reaction was followed by TLC. After 1.5 hours of stirring, the reaction was judged to be complete. It was then concentrated to near dryness and placed directly on a column and flashed with 30% hexanes in ethyl acetate. It gave an white solid (8.5mg, 0.036mmol, 90%). IR (neat, cm^{-1}) 1768, 1175; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.93 (dd, *J* = 6.7, 17.2 Hz, 1H), 2.78 (s, 1H), 2.25 (dd, *J* = 6.7, 8.2 Hz, 1H), 2.18 (d, *J* = 17.2 Hz, 1H), 2.15-2.12 (m, 1H), 1.90-1.84 (m, 1H), 1.67-1.60 (m, 2H), 1.54-1.47 (m, 2H), 1.38 (td, *J* = 4.62, 12.3 Hz, 1H), 1.32 (s, 1H), 1.11-1.04 (m, 1H), 0.88 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.1, 83.6, 62.4, 58.2, 46.8, 38.8, 36.6, 31.1, 31.0, 27.8, 27.7, 25.4, 22.8, 19.5, 17.8; HRMS (EI) *m/z* (M^+) calcd 236.1412 for $C_{14}H_{20}O_3$, obsd 236.1404, mp:64-66°C $[\alpha]_D$= -15.6°, c=1.85 in CH_2Cl_2.

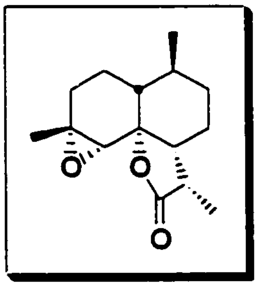


(1R, 4R, 5R, 6S, 7R, 10S, 11R)-4,5-Epoxy-6,7-[7, 11-(2*H*)-furan-12-one]-4,10,11-trimethylbicyclo [4.4.0^{1,6}] decane (122): To a solution of 121 (53.7mg, 0.227mmol) in THF (3ml) at –78°C was added LDA (272ul, 1.0M solution). After stirring for 25 minutes CH_3I (141ul, 2.27mmol) was added and this was stirred for 5 minutes. The reaction was then quenched with NH_4Cl (saturated aqueous solution) and extracted with ethyl acetate (3x 7ml). After drying ($MgSO_4$), filtering and concentrating the product was flashed with 50% hexanes in ethyl acetate. It gave a white solid (40.9mg, 0.163mmol, 72%), IR (neat, cm^{-1}) 2926, 1771; ^1H NMR (500 MHz, $CDCl_3$) δ 2.85 (s, 1H), 2.44-2.40 (q, $J = 7.9$ Hz, 1H), 2.16-2.14 (m, 1H), 2.12-2.07 (m, 1H), 1.86-1.79 (m, 1H), 1.65-1.50 (m, 3H), 1.47-1.45 (d, $J = 7.9$ Hz, 3H), 1.44-1.36 (m, 2H), 1.33-1.28 (m, 4H), 1.16-1.12 (m, 1H), 0.90-0.89 (d, $J = 6.7$ Hz, 3H), 0.88-0.85 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 179.9, 83.4, 64.3, 58.5, 45.5, 44.0, 43.7, 30.9, 26.3, 26.1, 25.9, 22.7, 20.3, 18.9, 18.0; HRMS (EI) *m/z* (M^+) calcd 250.1569 for $C_{15}H_{22}O_3$, obsd 250.1552, mp: 63-64°C, $[\alpha]_D = -16.3°$, c=0.97 in CH_2Cl_2.



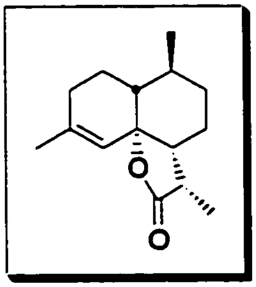
(1R, 4R, 5R, 6S, 7R, 10S, 11S)-4,5-Epoxy-6,7-[7, 11-(2*H*)-furan-12-one]-4,10,11-trimethylbicyclo [4.4.0^{1,6}] decane (123): To a solution of **122** (11.3mg, 0.045mmol) in THF (2.0ml) at –78°C was added LDA (0.45ml, 1.0M solution). This was allowed to stir for 25 minutes. It was then quenched with a saturated aqueous solution of ammonium chloride. It was extracted with ethyl acetate (3x, 5ml), dried ($MgSO_4$), filtered and concentrated. It was flashed with 40% hexanes in ethyl acetate to remove any impurities. It gave a white solid (11.0mg, 0.044mmol, 97%), IR (neat, cm^{-1}) 2926, 1768; ^1H NMR

(500 MHz, $CDCl_3$) δ 3.09-3.06 (q, *J* = 6.8 Hz, 1H), 2.83 (s, 1H), 2.20-2.10 (m, 2H), 1.73-1.58 (m, 3H), 1.50-1.43 (m, 3H), 1.30 (s, 3H), 1.28-1.20 (m, 1H), 1.15-1.13 (d, *J* = 7.1 Hz, 3H), 1.06-1.01 (m, 1H), 0.87-0.86 (d, *J* = 6.6 Hz, 3H), 0.83-0.82 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.4, 81.3, 62.2, 57.9, 47.1, 42.9, 38.7, 31.5, 30.8, 28.2, 22.9, 22.7, 19.4, 17.6, 9.3; HRMS (EI) *m/z* (M^+) calcd 250.1569 for $C_{15}H_{22}O_3$, obsd 250.1565, mp: 74-75°C, $[\alpha]_D$= -13.6°, c=2.46 in CH_2Cl_2.

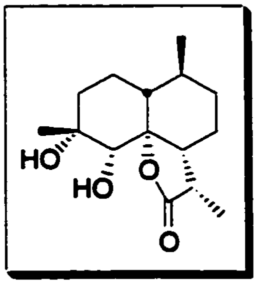


(1R, 6S, 7S, 10S, 11S)-6,7 [7, 11-(2*H*)-Furan-12-one]4,10,11-triethylbicyclo [4.4.0^{1,6}] decan-4-ene (127): To THF (1.4ml) at –78°C was added WCl_6 (82.9mg, 0.22mmol) all at once. Five minutes later *n*BuLi (0.33ml, 0.628mmol) was added dropwise over 5 minutes. After stirring for 10 minutes at –78°C the mixture was slowly warmed over 1 hour to room temperature. After several colour changes (greenish brown, light yellow, dark brown), LiI (0.80mg, 0.006mmol) was added and 5 minutes later **123** (19.4mg, 0.078mmol) was added (via canula and 1.0ml THF). The mixture was stirred for 2.5 hours and then poured into a cold aqueous solution of $NaHCO_3$ and then extracted with ethyl acetate (2x 10ml). After drying ($MgSO_4$), filtering and concentrating it was flashed with 25% ethyl acetate in hexanes to afford some starting material (2.0mg, 0.008mmol) and an oil which was **127** (11.0mg, 0.047mmol, 67%), IR (neat, cm^{-1}) 2930, 1764; ^1H

NMR (500 MHz, $CDCl_3$) δ 5.61 (s, 1H), 3.14-3.09 (q, *J* = 6.3 Hz, 1H), 2.11-1.96 (m, 3H), 1.89-1.84 (m, 1H), 1.72-1.61 (m, 6H), 1.54-1.49 (m, 1H), 1.44-1.38 (m, 1H), 1.22-1.14 (m, 1H), 1.13-1.12 (d, *J* = 7.2 Hz, 3H), 1.06-0.98 (m, 1H), 0.92-0.91 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 179.2, 142.1, 121.7, 83.1, 46.5, 42.7, 39.6, 32.4, 30.8, 29.6, 23.7, 23.4, 20.9, 19.5, 9.4; HRMS (EI) *m/z* (M^+) calcd 234.1620 for $C_{15}H_{22}O_2$, obsd 234.1600. $[\alpha]_D$= -42.2°, c=0.35 in CH_2Cl_2.



(+)-Arteannuin M (128): To a solution of **127** (6.8mg, 0.029mmol) in THF (1.0ml) was added NMO (4.0mg, 0.033mmol) as well as a 4% by weight solution of OsO_4 in H_2O (18.5ul, 0.003mmol). This was allowed to stir for 40 hours. It was then quenched with brine and extracted with ethyl acetate (2x 5ml). Flash with 30% hexanes in ethyl acetate gave an oil (5.1mg, 0.019mmol, 66%) that was **128**. IR (neat, cm^{-1}) 3347, 1766; ^1H NMR (500 MHz, $CDCl_3$) δ 3.43 (s, 1H), 3.06 (dq, *J* = 6.9, 6.9 Hz, 1H), 2.65-2.60 (m, 1H), 1.77-1.67 (m, 3H), 1.62-1.56 (m, 2H), 1.53-1.47 (m, 2H), 1.37-1.29 (m, 1H), 1.36 (s, 3H), 1.23 (br.s 1H), 1.11 (d, *J* = 6.9 Hz, 3H), 1.08-1.03 (m, 1H), 0.90 (d, *J* = 6.7 Hz, 3H) ; ^{13}C NMR (125 MHz, $CDCl_3$) δ 179.1, 86.2, 74.2, 72.6, 41.7, 39.1, 38.8, 34.3, 32.3, 29.9, 26.6, 23.9, 22.1, 20.1, 9.3; HRMS (EI) *m/z* (M^+-H_2O) calcd 250.1569 for $C_{15}H_{22}O_3$, obsd 250.1569 $[\alpha]_D$= -34.3°, c=0.26 in CH_2Cl_2.


HO
HO
O
O

CLAIMS TO ORIGINAL RESEARCH

1. The use of DBU as a co-solvent for the assistance of the tandem oxy-Cope/ene reaction.
2. The total synthesis of (+)-Arteannuin M (**128**), which employed the DBU assisted tandem oxy-Cope/ene reaction as a key step in the synthesis.
3. Publication: L. Barriault; D. H. Deon; *Org. Lett.* **2001**, *3*, 1925.
4. Oral Presentations: (a)'Progress Toward the Total Synthesis of Artreannuin M' D. Deon and L. Barriault, November 11, 2000, York University, Toronto Ontario, Canada. (b) 'Highly Diastereoselective Synthesis of Tricyclic Compounds Using the Tandem Oxy-Cope/Ene Reaction. The First Total Synthesis of (+)-Arteannuin M' D. Deon and L. Barriault (i) March 26, 2001, Bristol-Myers Squibb, Candiac Quebec, Canada (ii) March 30, 2001, Astra-Zeneca, Montreal Quebec, Canada (iii) April 5, 2001, Pfizer Global Research and Development, Ann-Arbor Michigan, U.S.A. (iv) April 11, 2001, Merck-Frosst Canada, Montreal Quebec, Canada.
5. Poster Presentations: 'Highly Diastereoselective Synthesis of Tricyclic Compounds Using the Tandem Oxy-Cope/Ene Reaction. The First Total Synthesis of (+)-Arteannuin M' D. Deon and L. Barriault (a) Ottawa-Carleton Chemistry Institute Day, May 8, 2001 (1st prize) (b) Canadian Society for Chemistry, May 27, 2001, Montreal Quebec, Canada.
6. Conference Contributions: (a) The 83rd Canadian Society for Chemistry (CSC) Conference and Exhibition, May 2000, Calgary Alberta. (b) The 84th Canadian Society for Chemistry (CSC) Conference and Exhibition, May 2001 Montreal Quebec. (c) Pacifichem International Congress/Honolulu December 2000, Honolulu Hawaii (d) 41st IUPAC General Assembly, June/July 2001, Brisbane Australia.

REFERENCES

1 . Ho, T.-L. *Tandem Organic Reactions* ; John Wiley and Sons, Inc., **1992**; p.1

2 . Snider, B.B.; Kirk, T.C.; *J. Am. Chem. Soc.* **1983**, *105*, 2364.

3. Gawley, R.E.; *Synthesis* **1976**, 777.

4. Beereboom, J.J.; *J. Org. Chem.* **1966**, *31*, 2026.

5. Ho, T.-L.; Carbocycle Construction in Terpene Synthesis; VCH: New York, 1988.

6. Alexakis, A.; Chapdelaine, M.J.; Posner, G.H.; *Tetrahedron Lett.* **1978**, 4209.

7. Amri, H.; Rambaud, M.; Villieras, J. ; *Tetrahedron Lett.* **1989**, *30*, 7381.

8. Marvel, C.S. ; Moore, A.C. ; *J. Am. Chem. Soc.* **1949**, *71*, 28.

9. Britten-Kelly, M.R.; Willis, B.J.; Barton, D.H.R.; *J. Org. Chem.* **1981**, *46*, 5027.

10. Heathcock, C.H.; Kleinman, E.F.; Binkley, E.S.; *J. Am. Chem. Soc.* **1982**, *104*, 1054.

11. Petasis, N.A. ; Zavialov, I.A. ; *J. Am. Chem. Soc.* **1998**, *120*, 11798.

12. Cope, A.C.; Hardy, E.M.; *J. Am. Chem. Soc.* **1940**, *62*, 441.

13. Doering, W. von E.; Roth, W.R.; *Tetrahedron* **1962**, *18*, 67.

14. (a) Hill, R.K.; Gilman, N.W.; *J. Chem. Soc., Chem. Commun.* **1967**, 619 (b) Hill, R.K. Asymmetric Synthesis, Vol. 3, Morrison, J.D. (ed.); Academic Press, 1984; pp. 503-572.

15. (a) Curtin, D.Y.; *Rec. Chem. Prog.* **1954**, *15*, 111. (b) Eliel, E.L.; *Stereochemistry of Carbon Compounds*, McGraw-Hill, **1962**; p.151-152, 237-238.

16. see 12.

17. Berson, J.A.; Jones, M. Jr., *J. Am. Chem. Soc.* **1964**, *86*, 5017.

18. Evans, D.A.; Golob, A.M.; *J. Am. Chem Soc.* **1975**, *97*, 4765.

19. Gajewski, J.J.; *Acc. Chem. Res.* **1980**, *13*, 142.

20. (a) Georges, M.; Tam, T.-F.; Frasier-Reid, B.; *J. Org. Chem.* **1985**, *50*, 5747. (b) Seebach, D.; Geiss, K.-H.; Pohmakotr, M.; *Angew. Chem. Int. Ed. Engl.* **1976**, *15*, 437.

21. Partington, S.M.; Watt, C.I.F.; *J. Chem. Soc., Perkin. Trans.* **1988**, *2*, 983.

22. (a) Evans, D.A.; Baillargeon, D.J.; *Tetrahedron Lett.* **1978**, 3315. (b) Evans, D.A.; Baillargeon, D.J.; *Tetrahedron Lett.* **1978**, 3319.

23. Still, W.C.; *J. Am. Chem. Soc.* **1979**, *101*, 2493.

24. Paquette, L.A.; Zhao, M.; *J. Am. Chem. Soc.* **1998**, *120*, 5203.

25. Alder, K.; Pascher, F.; Schmitz, A.; *Ber. Dtsch. Chem. Ges.* **1943**, *76*, 27.

26. Inagaki, S.; Fujimoto, H.; Fukui, K.; *J. Am. Chem. Soc.* **1976**, *98*, 4693.

27. (a) Stephenson, L.M.; Mattern, D.L.; *J. Org. Chem.* **1976**, *41*, 3614. (b) Benn, F.R.; Dwyer, J.; Chappell, I.; *J. Chem. Perkin. Trans.* **1977**, *2*, 533.

28. For reviews, see: (a) Woodward, R.B.; Hoffman, R.; *Angew. Chem.* **1976**, *81*, 797. (b) *Angew. Chem. Int. Ed. Engl.* **1969**, *8*, 781. (c) Houk, K.N.; *Acc. Chem. Res.* **1975**, *8*, 361.

29. (a) see 27 (b) Bingham, R.C.; Dewar, M.J.S.; *J. Am. Chem. Soc.* **1972**, *94*, 9107.

30. (a) Treibs, W.; Schmidt, H.; *Ber. Dtsch. Chem. Ges.* **1927**, *60*, 2335. (b) Grignard, V.; Doeuvre, J.; *C. R. Acad. Sci.* **1930**, *190*, 1164. (c) Ikeda, T.; Wakatusi, K.; *J. Chem. Soc. Jpn.* **1936**, *57*, 425. (d) *Chem. Abstr.* **1936**, *30*, 5937.

31. Bain, J.P.; *J. Am. Chem. Soc.* **1946**, 68, 638.

32. Batcho, A.D.; Berger, D.E.; Davoust, S.G.; Wovkulich, P.M.; Uskokovich, M.R.; *Helv. Chim. Acta.* **1981**, *64*, 1682.

33. (a) Alston, P.V.; Ottenbrite, R.M.; *J. Org. Chem.* **1975**, *40*, 1111. (b) Houk, K.N.; Strozier, R.W.; *J. Am. Chem. Soc.* **1973**, *95*, 4094. (c) Anh, N.T.; Seyden-Penne, J. *Tetrahedron*, **1973**, *29*, 3259.

34. Weiberg, N.; Preiner, G. ; Scheida, O. ; *Chem. Ber.* **1981**, *114*, 3518.

35. (a) Joulain, D.; Rouesasac, J. ; *J. Chem. Soc. Chem. Commun.* 1972, 314. (b) Ohloff, G. ; *Angew. Chem.* **1970**, *82*, 777; *Angew. Chem. Int. Ed. Engl.* **1970**, *9*, 743.

36. Chorlton, A.P.; Gareth, A.M.; Sutherland, J.K.; *J. Chem. Soc. Perkin. Trans.* **1991**, *1*, 1205.

37 . Balakumar, A.; Janardhanam, S.; Rajagopalan, K.; *J. Org. Chem.* **1993**, *58*, 5482.

38. Paquette, L.A.; Nakatani, S.; Zydowsky, T.M. ; Edmonsun, S.D. ; Sun, L.-Q.; Skerlj, R.; *J. Org. Chem.* **1999**, *64*, 3244.

39. Warrington, J.M.; Yap, G.P.A.; Barriault, L.; *Org. Lett.* **2000**, *2*, 663.

40. See reference 41.

41. (a) Fujita, Y. ; Onishi, T.; Nishida, T.; *SJ. Chem Soc. CC* **1978**, 651. (b) Fujita, Y. ; Onishi, T.; Nishida, T.; *Synthesis* **1978**, 934. (c) Utagawa, A.; Hirota, H.; Ohno, S.; Takahashi, T.; *Bull. Chem. Soc. Jpn.* **1988**, *61*, 1207.

42. Readily obtainable from cyclohexene oxide, see reference 41.

43. Shih, C.; Swenton, J. S.; *J. Org. Chem.* **1982**, *15*, 47.

44. See reference 41.

45. Terada, Y.; Yamamura, S. ; *Tetrahedron Lett.* **1979**, *20*, 1623.

46. Samra, A.A.; Morris, J.S.; Koirtyohann, S.R.; *Anal. Chem.* **1975**, *47*, 1475.

47. Majetich, G.; Hicks, R.; *Journal of Microwave Power and Electromagnetic Energy*; **1995**, *30*, 27.

48 . Anionic oxy-Cope rearrangements were attempted using (1) KH, 18-cr-6, THF, -78 to 25°C, (2) KO*t*Bu, 18-crown-6, -78°C to 25°C (3) KHMDS, THF both at 25°C and reflux.

49. Anionic oxy-Cope rearrangments were attempted using (1) KH, both with and without 18-cr-6, THF, -78°C to 25°C and at reflux (2) KO*t*Bu, 18-crown-6, -78°C (3) Both NaH and KHMDS, 18-cr-6, THF, -78 to 25°C

50. An anionic oxy-Cope rearrangement was attempted using KH, 18-cr-6, THF at –78 to 25°C

51. Temperature affects reaction rate through mean speed c, which is proportional to $T^{1/2}$.

52. Liu, J.-M.; Ni, M.-Y. ; Fan, Y.-F. ; Tu, Y.-Y. ; Wu, Z.-H. ; Wu, Y.-L. ; Zhou, W.S. *Acta Chim. Sin.* **1979**, *37*, 129.

53. Brown, G.D. ; Sy, L.-K.; Haynes, R. *Tetrahedron* **1998**, *54*, 4345.

54. Dauben, W.B.; Lorber, M.; Fullerton, D.S. *J. Org. Chem.* **1969**, *34*, 3587.

55. No other diastereomer was detected by 500 MHz ^{1}H NMR.

56. Sharpless, K.B.; Michaelson, R.C. *J. Am. Chem. Soc.* **1973,** *95*, 6136.

57. Crabtree, R.H.; Davis, M.W. *J. Org. Chem.* **1986,** *51*, 2655.

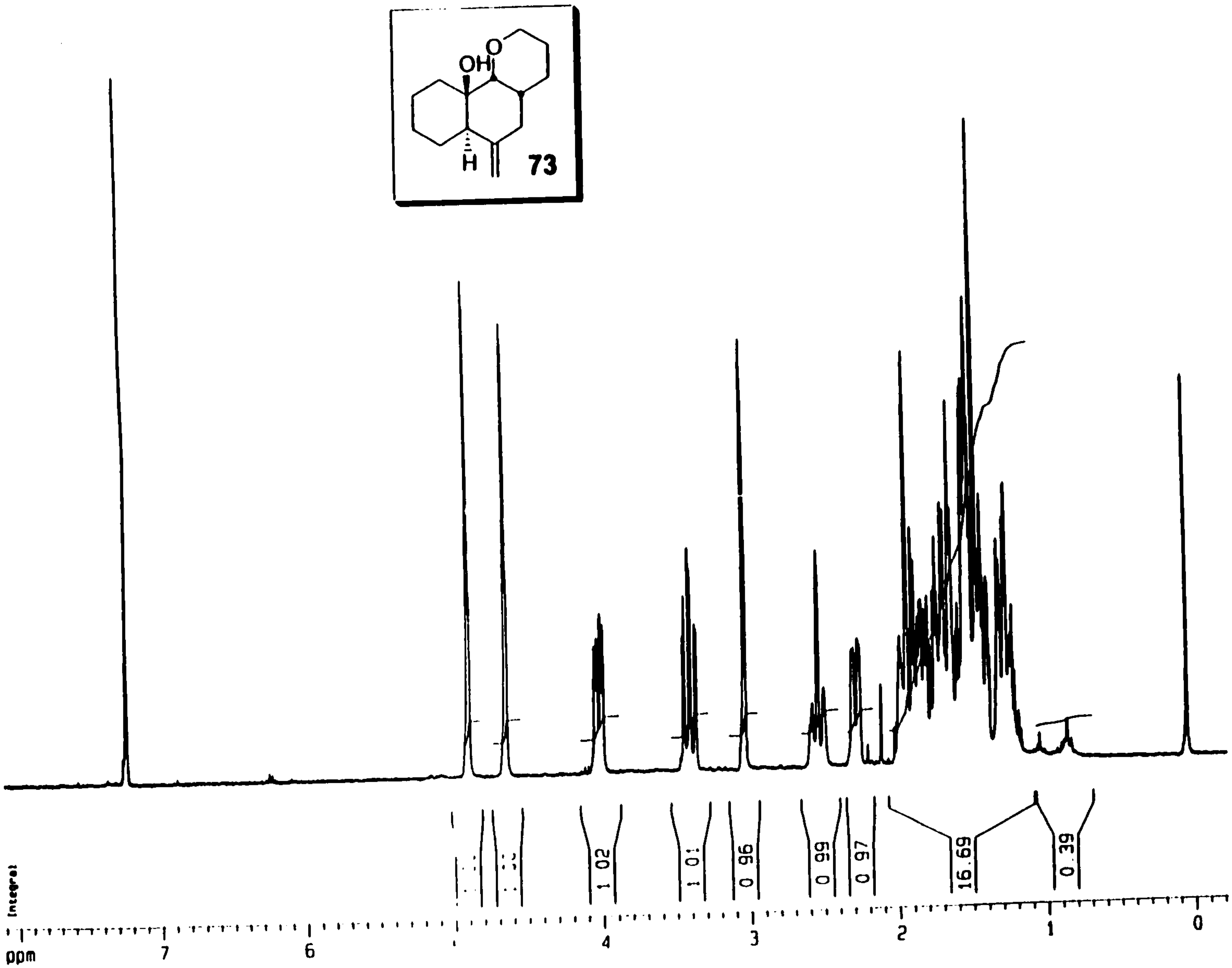
58. Ley, S.V.; Norman, J.; Griffith, W.P. *Synthesis* **1994,** 639.

59 . Brown, G.D.; private communication.

60. (a) Deslongchamps, P. et al. *Can J. Chem.* **1990,** *68*, 153. (b) Sharpless, K.B.; Umbreit, M.A.; Nieh, M.T.; Flood, T.C. *J. Am. Chem. Soc.* **1972,** *94*, 6538.

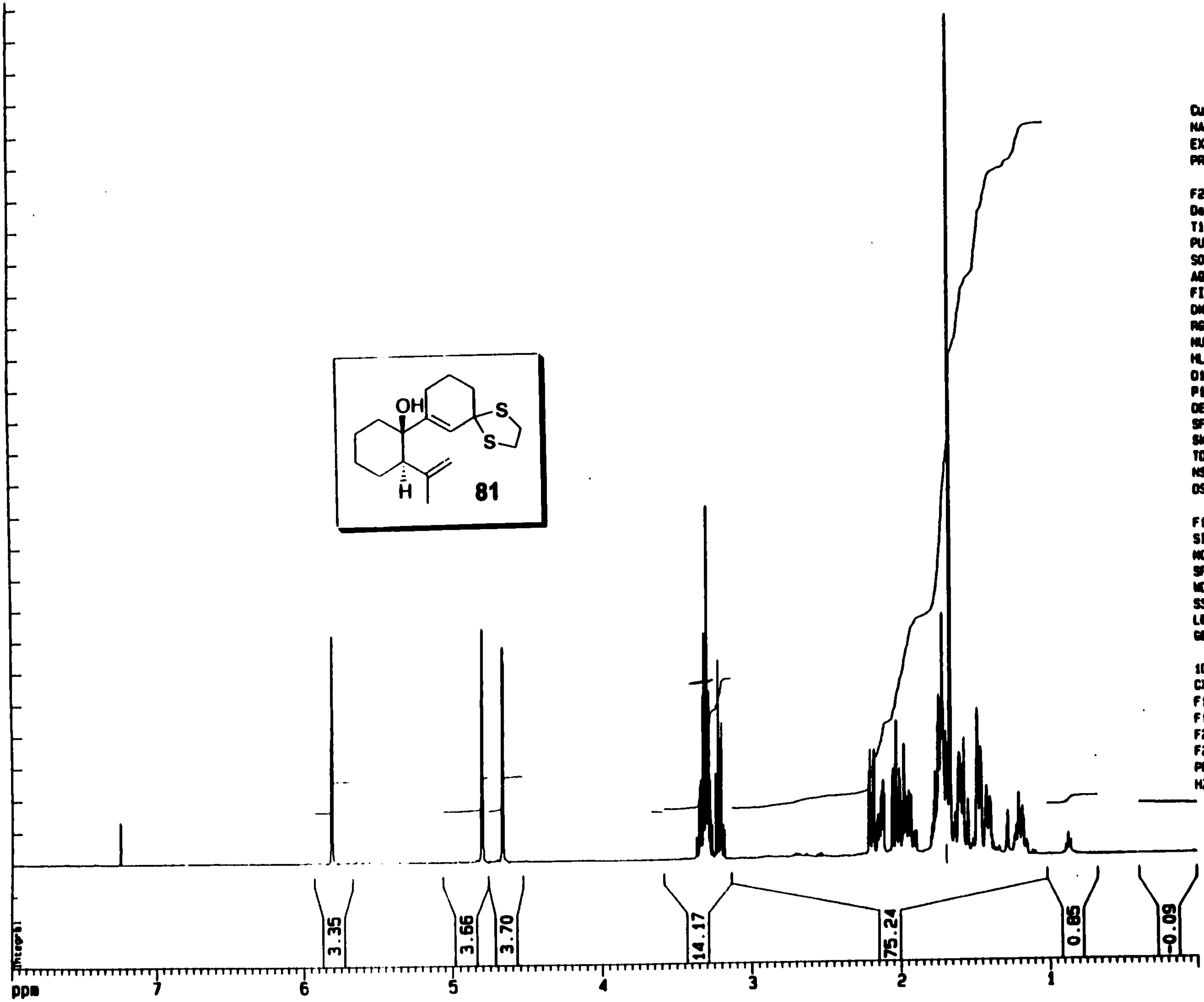
61. The chiral shift reagent to be used is: Tris[3-(heptafluoropropyl-hydroxymethylene)-(+)-camphorato], europium (III).

APPENDIX



73

```
Current Data Parameters
NAME            dhd_365
EXPNO                 1
PROCNO                1

F2 - Acquisition Parameters
Date_          20010302
Time              14.05
INSTRUM           av300
PROBHD    5 mm QNP 1H/1
PULPROG            zg30
TD                30720
SOLVENT           CDCl3
NS                   16
DS                    0
SWH          5081.301 Hz
FIDRES       0.165407 Hz
AQ          3.0228980 sec
RG                406.4
DW            98.400 usec
DE              6.00 usec
TE               300.0 K
D1         1.00000000 sec

============ CHANNEL f1 ============
NUC1                 1H
P1              9.50 usec
PL1             -3.00 dB
SFO1      300.1319477 MHz

F2 - Processing parameters
SI                65536
SF        300.1300000 MHz
WDW                  EM
SSB                   0
LB              0.10 Hz
GB                    0
PC                 1.00

1D NMR plot parameters
CX             20.00 cm
CY             10.00 cm
F1P           8.119 ppm
F1          2436.69 Hz
F2P          -0.221 ppm
F2           -66.34 Hz
PPMCM     0.41699 ppm/cm
HZCM     125.15182 Hz/cm
```



Current Data Parameters

NAME	dan
EXPNO	1
PROCNO	1

F2 - Acquisition Parameters

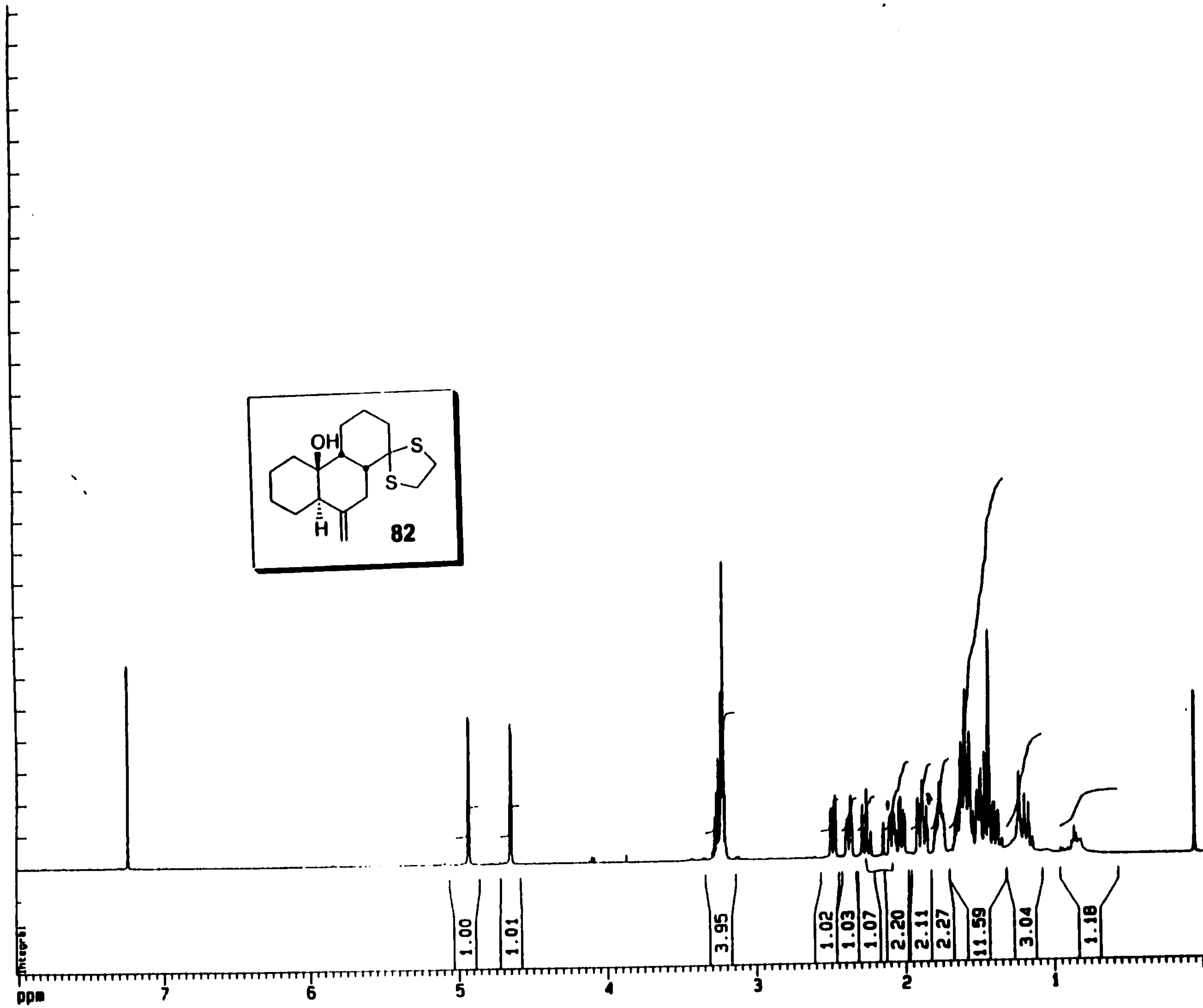
Date	20000502
Time	4.09
PULPROG	zg
SOLVENT	CDCl3
AQ	4.6530805 sec
FIDRES	0.107456 Hz
DW	71.0 usec
RG	512
NUCLEUS	1H
HL1	0 dB
D1	0.0100000 sec
P1	3.0 usec
DE	60.0 usec
SFO1	500.1381707 MHz
SWH	7042.25 Hz
TD	65536
NS	16
DS	0

F1 - Processing parameters

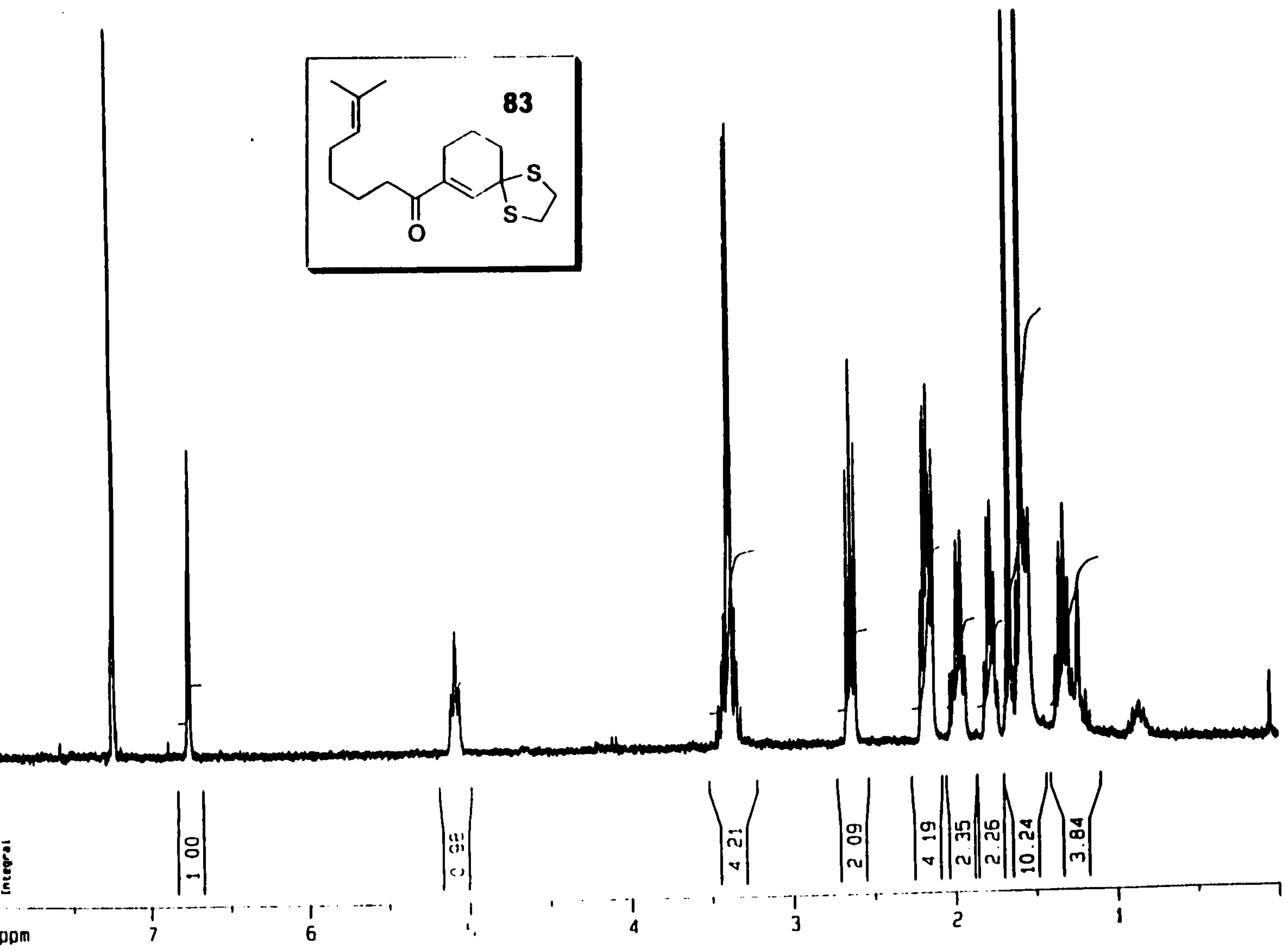
SI	32768
MC2	QF
SF	500.1354311 MHz
WDW	EM
SSB	0
LB	0.00 Hz
GB	0

1D NMR plot parameters

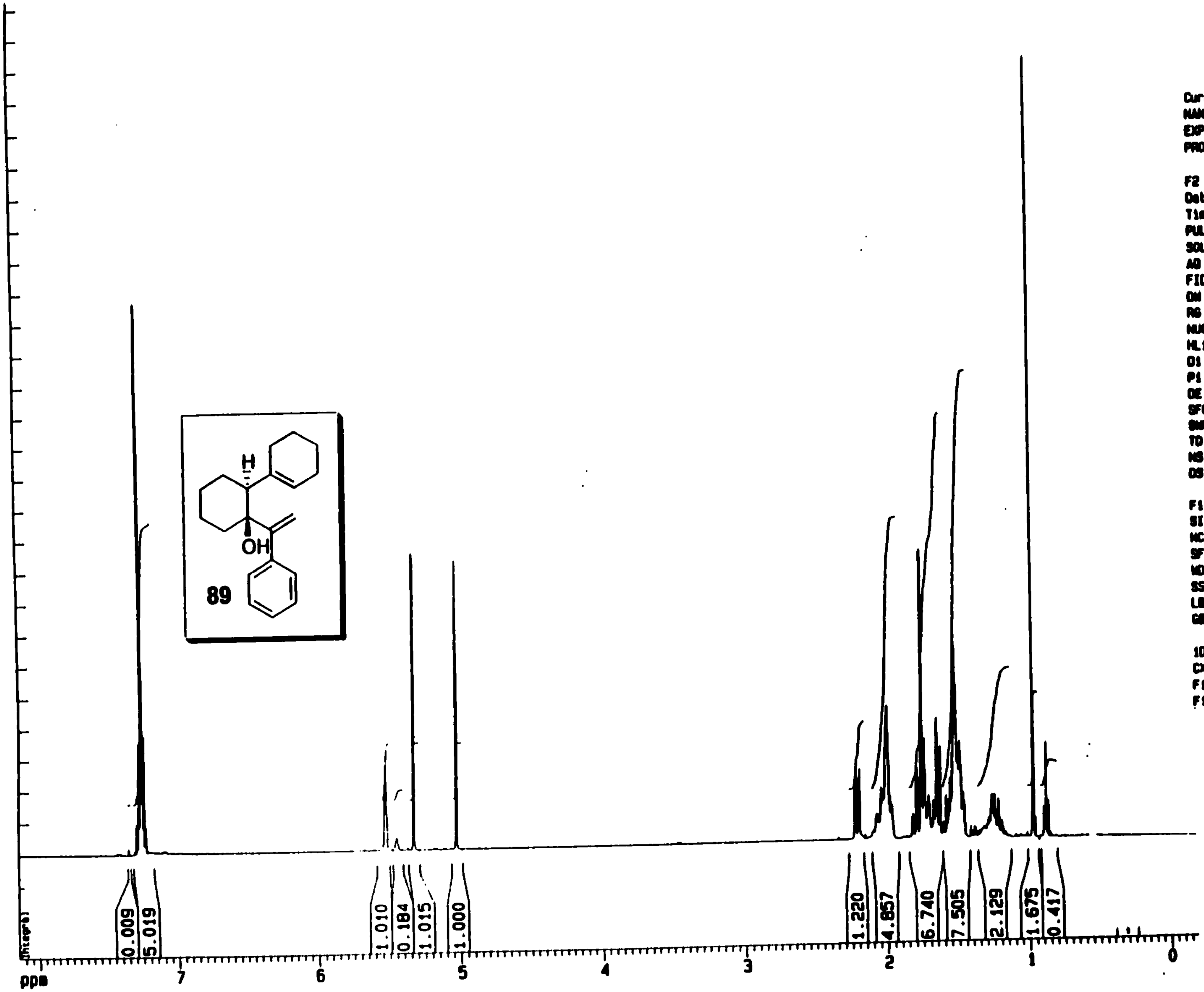
CX	22.00 cm
F1P	8.000 ppm
F1	4001.08 Hz
F2P	0.000 ppm
F2	0.00 Hz
PPMCM	0.36364 ppm/
HZCM	181.86743 Hz/(



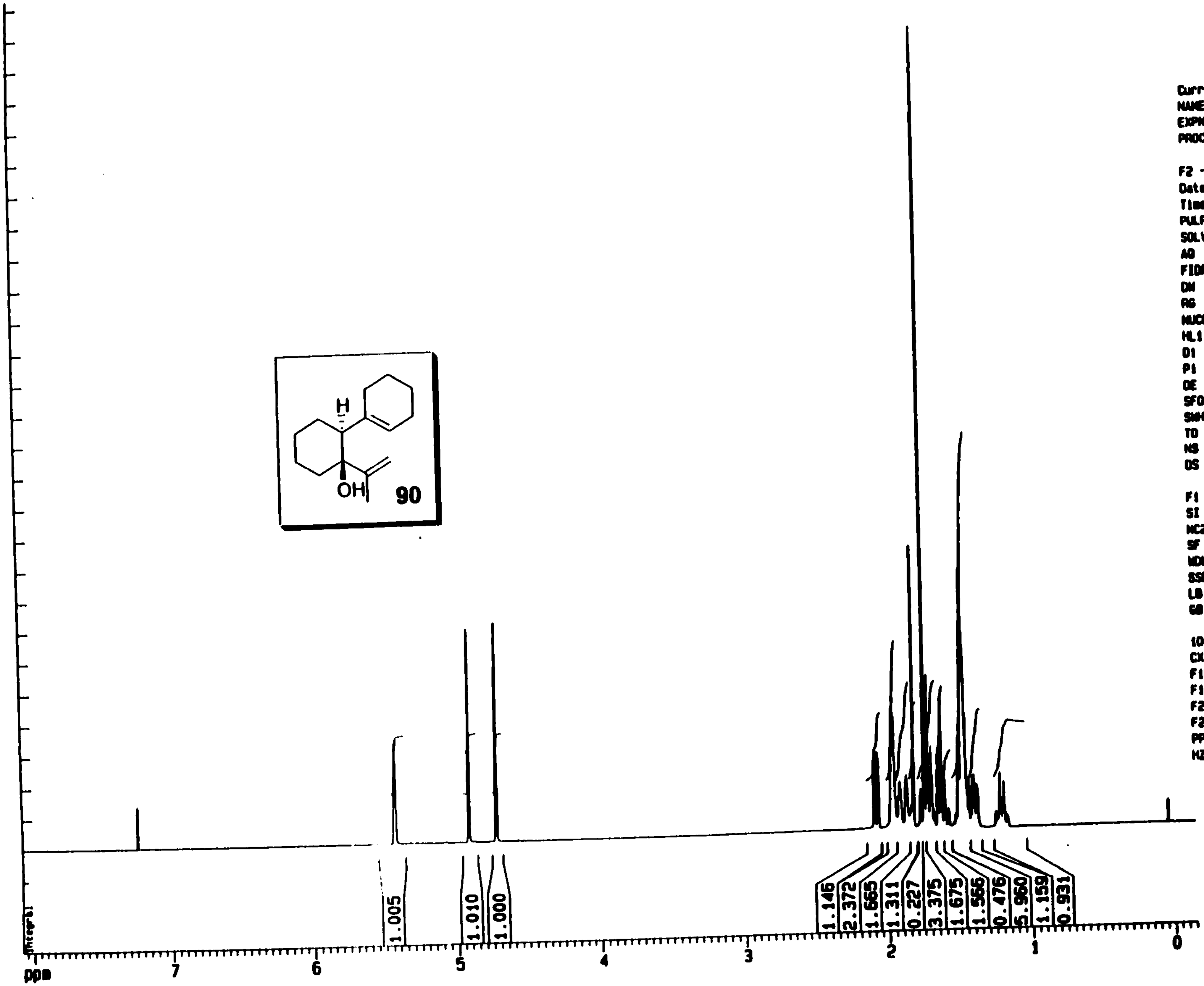
```
Current Data Parameters
NAME              dhd_gne2
EXPNO                    1
PROCNO                   1

F2 - Acquisition Parameters
Date              20010224
Time                  7.03
PULPROG                 zg
SOLVENT              CDCl3
AQ            4.6530805 sec
FIDRES         0.107456 Hz
DW                71.0 usec
RG                    1024
NUCLEUS                 1H
HL1                   0 dB
D1           0.0100000 sec
P1                 3.3 usec
DE                88.8 usec
SFO1       500.1381707 MHz
SWH            7042.25 Hz
TD                   65536
NS                      16
DS                       0

F1 - Processing parameters
SI                   32768
MC2                     QF
SF         500.1354311 MHz
WDW                     EM
SSB                      0
LB                 0.30 Hz
GB                       0

1D NMR plot parameters
CX                22.00 cm
F1P              8.015 ppm
F1              4008.58 Hz
F2P             -0.084 ppm
F2               -41.98 Hz
PPMCM          0.36813 ppm/
HZCM         184.11603 Hz/
```



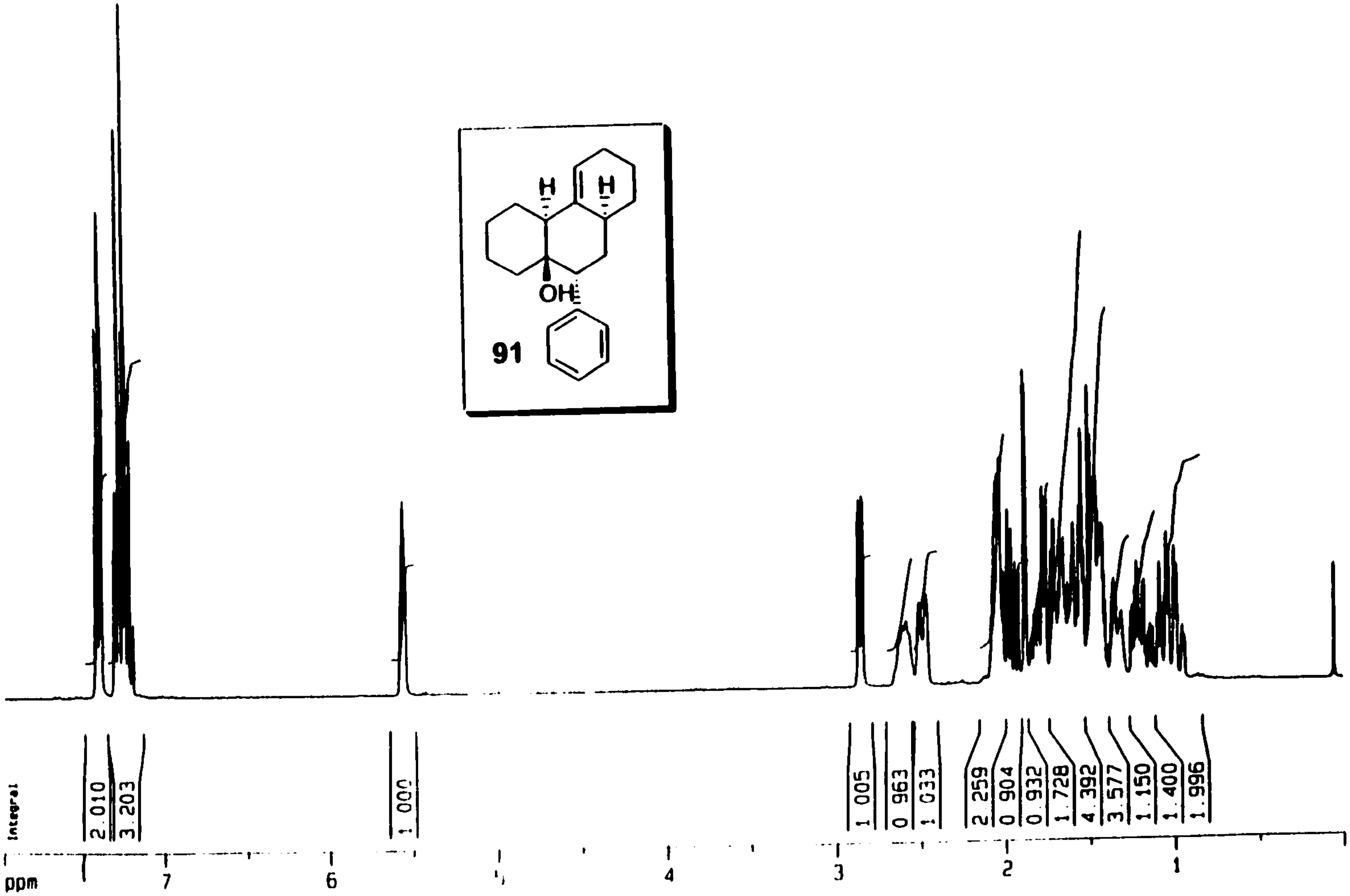
```
Current Data Parameters
NAME              dhdretro
EXPNO                    1
PROCNO                   1

F2 - Acquisition Parameters
Date_             20010530
Time                 14.31
INSTRUM              av300
PROBHD   5 mm QNP  1H/1
PULPROG               zg30
TD                   30720
SOLVENT              CDCl3
NS                      16
DS                       0
SWH             5081.301 Hz
FIDRES          0.165407 Hz
AQ             3.0228980 sec
RG                  1149.4
DW                 98.400 usec
DE                   6.00 usec
TE                  300.0 K
D1            1.00000000 sec

============ CHANNEL f1 =============
NUC1                    1H
P1                   9.50 usec
PL1                 -3.00 dB
SFO1        300.1319477 MHz

F2 - Processing parameters
SI                   65536
SF          300.1300000 MHz
WDW                     EM
SSB                      0
LB                    0.10 Hz
GB                       0
PC                    1.00

1D NMR plot parameters
CX                  20.00 cm
CY                  40.00 cm
F1P                 8.000 ppm
F1                2401.04 Hz
F2P                 0.000 ppm
F2                   0.00 Hz
PPMCM             0.40000 ppm/cm
HZCM            120.05200 Hz/cm
```



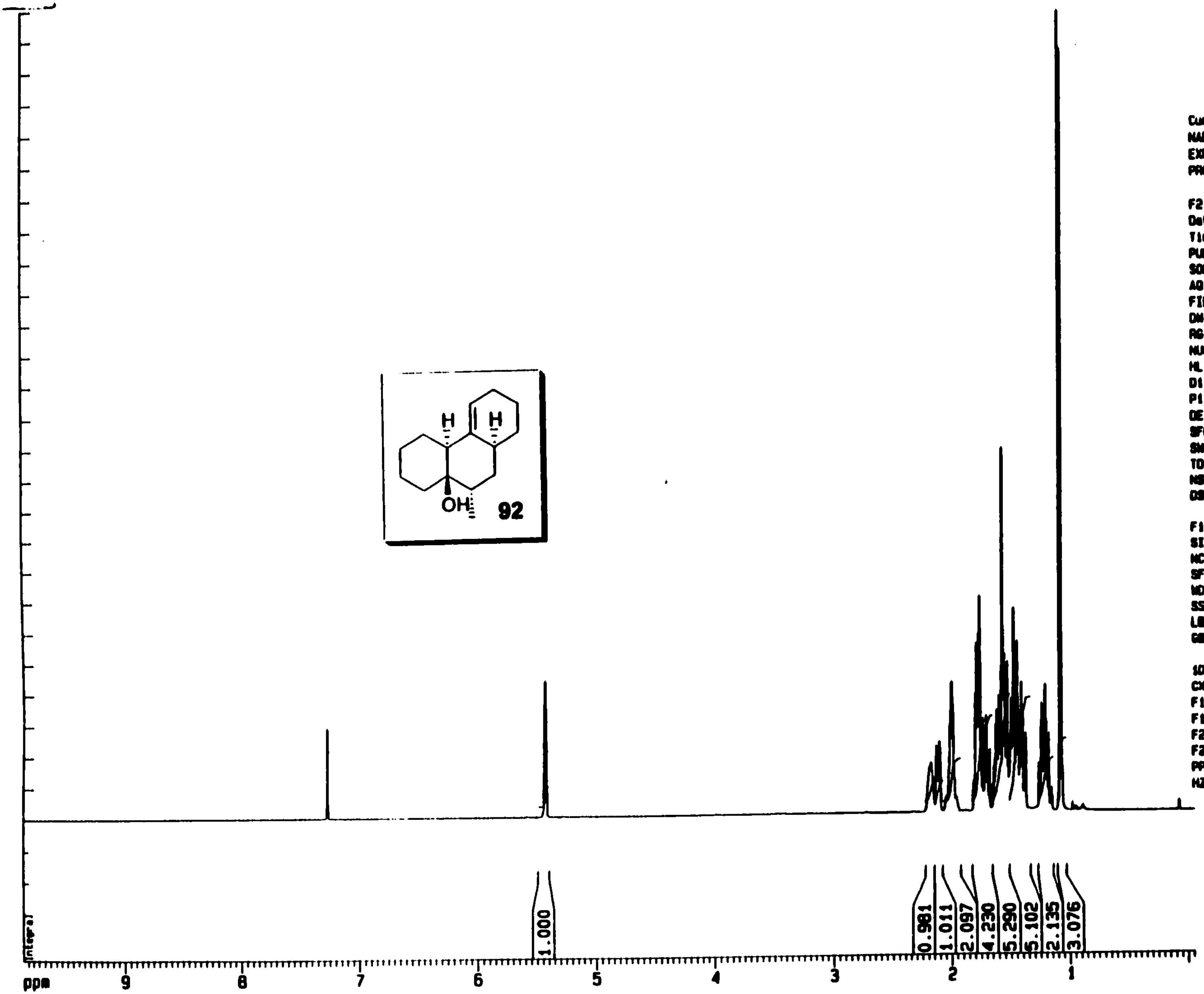
```
Current Data Parameters
NAME              dhd_386
EXPNO                   1
PROCNO                  1

F2 - Acquisition Parameters
Date_            20010416
Time                 4.58
PULPROG                zg
SOLVENT             CDCl3
AQ           4.6530868 sec
FIDRES        0.107456 Hz
DW               71.0 usec
RG                     64
NUCLEUS                1H
PL1                  0 dB
D1          0.0100000 sec
P1                3.0 usec
DE               60.0 usec
SFO1      500.1381707 MHz
SWH            7042.25 Hz
TD                  65536
NS                     16
DS                      0

F1 - Processing parameters
SI                  32768
MC2                    QF
SF        500.1354311 MHz
WDW                    EM
SSB                     0
LB                0.00 Hz
GB                      0

1D NMR plot parameters
CX               22.00 cm
F1P              8.149 ppm
F1             4075.81 Hz
                -0.185 ppm
                -92.40 Hz
   CM          0.37882 ppm/
   M         189.46378 Hz/
```



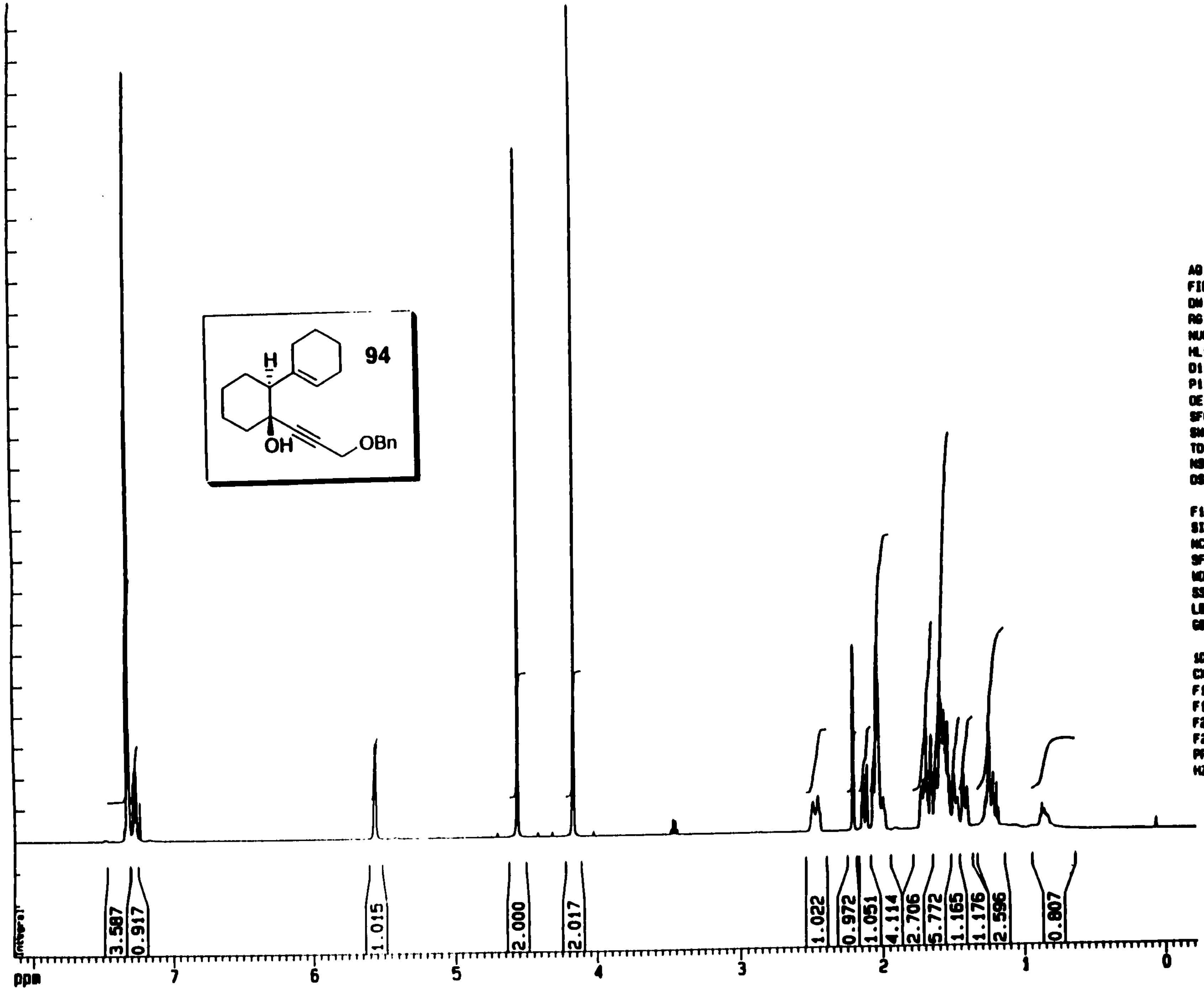
```
Current Data Parameters
NAME                dnd_309
EXPNO                     1
PROCNO                    1

F2 - Acquisition Parameters
Date_              20010408
Time                   8.50
PULPROG                  zg
SOLVENT               CDCl3
AQ             4.6530805 sec
FIDRES          0.107456 Hz
DW                  71.0 usec
RG                       64
NUCLEUS                  1H
HL1                       0 dB
D1             0.0100000 sec
P1                   3.0 usec
DE                  88.0 usec
SFO1         500.1381707 MHz
SWH              7042.25 Hz
TD                    65536
NS                       16
DS                        0

F1 - Processing parameters
SI                    32768
MC2                      QF
SF           500.1354311 MHz
WDW                      EM
SSB                       0
LB                   0.00 Hz
GB                        0

1D NMR plot parameters
CX                  22.00 cm
F1P                 8.082 ppm
F1                4042.19 Hz
F2P                -0.151 ppm
F2                 -75.59 Hz
PPMCM             0.37424 ppm/
HZCM            187.17186 Hz/c
```



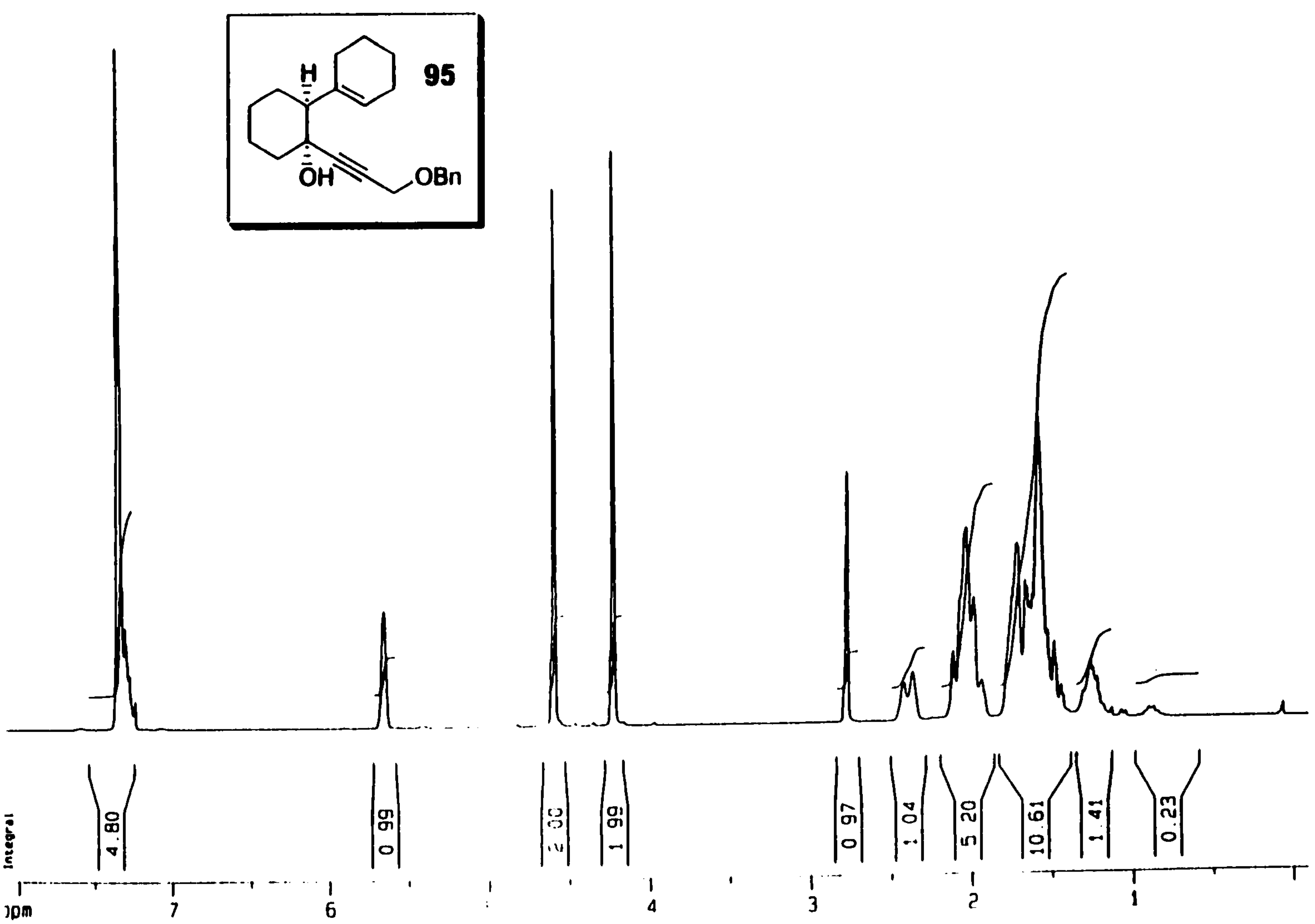
```
Current Data Parameters
NAME              dhd_398
EXPNO                   1
PROCNO                  1

F2 - Acquisition Parameters
Date_            20010423
Time                 9.42
INSTRUM             av300
PROBHD   5 mm QNP  1H/1
PULPROG              zg30
TD                  30720
SOLVENT             CDCl3
NS                     16
DS                      0
SWH             5081.301 Hz
FIDRES          0.165407 Hz
AQ             3.0228980 sec
RG                  203.2
DW                 98.400 usec
DE                   6.00 usec
TE                  300.0 K
D1            1.00000000 sec

============ CHANNEL f1 ============
NUC1                   1H
P1                   9.50 usec
PL1                 -3.00 dB
SFO1         300.1319477 MHz

F2 - Processing parameters
SI                  65536
SF           300.1300000 MHz
WDW                    EM
SSB                     0
LB                   0.10 Hz
GB                      0
PC                   1.00

1D NMR plot parameters
CX                  20.00 cm
CY                  10.00 cm
F1P                 8.000 ppm
F1                2401.04 Hz
F2P                 0.000 ppm
F2                   0.00 Hz
PPMCM             0.40000 ppm/cm
HZCM            120.05200 Hz/cm
```



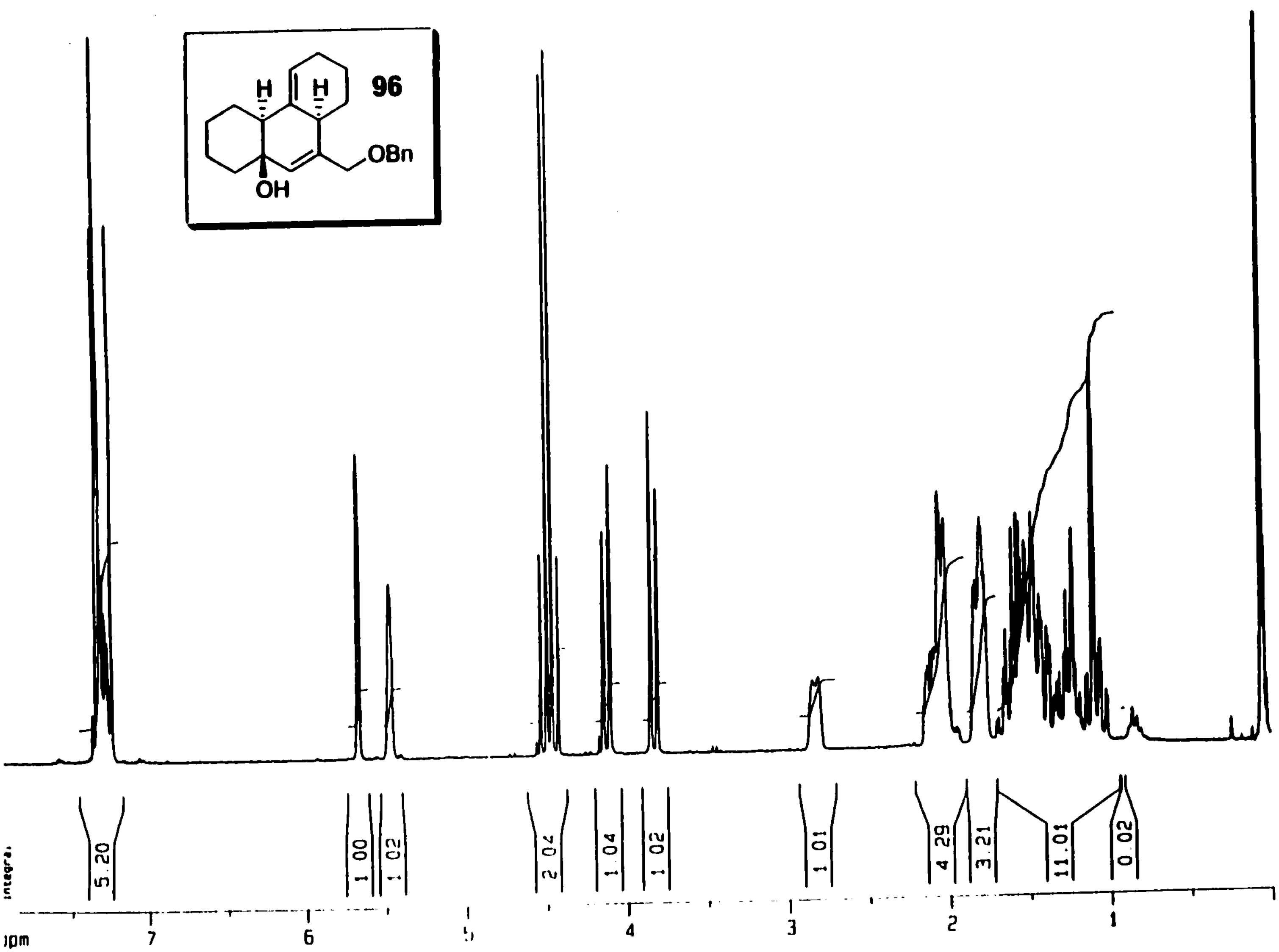
Current Data Parameters	
NAME	dan_383
EXPNO	1
PROCNO	1
F2 - Acquisition Parameters	
Date	20010416
Time	5.51
PULPROG	zg
SOLVENT	CDCl3
AQ	4.6530805 sec
FIDRES	0.107456 Hz
DW	71.0 usec
RG	128
NUCLEUS	1H
HL1	0 dB
D1	0.0100000 sec
P1	3.0 usec
DE	60.0 usec
SFO1	500.1381707 MHz
SWH	7042.25 Hz
TD	65536
NS	16
DS	0
F1 - Processing parameters	
SI	32768
MC2	QF
SF	500.1364159 MHz
WDW	EM
SSB	0
LB	0.00 Hz
GB	0
1D NMR plot parameters	
CX	22.00 cm
F1P	9.894 ppm
F1	4948.20 Hz
F2P	-0.053 ppm
F2	-26.76 Hz
PPMCM	0.45215 ppm/
HZCM	226.13419 Hz/(



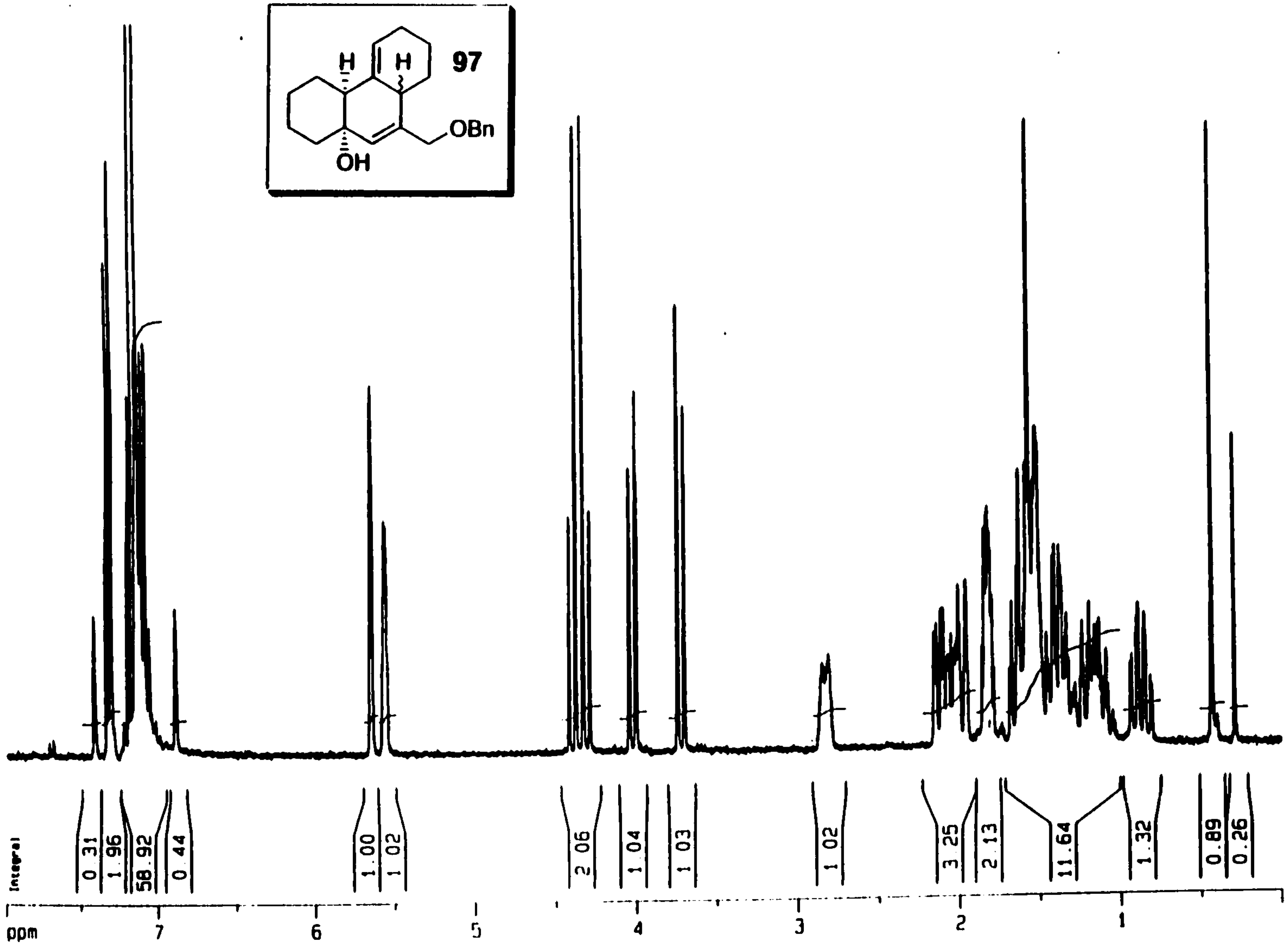
```
                 s Parameters
                     ahd_3841
                            1
                            1

               tion Parameters
                     20010414
                         3.04
                           zg
                        CDCl3
AQ                 4.6530805 sec
FIDRES              0.107456 Hz
DW                      71.0 usec
RG                       128
NUCLEUS                   1H
HL1                        0 dB
D1                 0.0100000 sec
P1                       3.0 usec
DE                      60.0 usec
SFO1             500.1381707 MHz
SWH                  7042.25 Hz
TD                     65536
NS                        16
DS                         0

F1 - Processing parameters
SI                     32768
MC2                       QF
SF               500.1354311 MHz
WDW                       EM
SSB                        0
LB                      0.00 Hz
GB                         0

1D NMR plot parameters
CX                     22.00 cm
F1P                    8.149 ppm
F1                   4075.61 Hz
F2P                   -0.218 ppm
F2                   -109.21 Hz
PPMCM                0.38035 ppm/
HZCM               190.22777 Hz/c
```



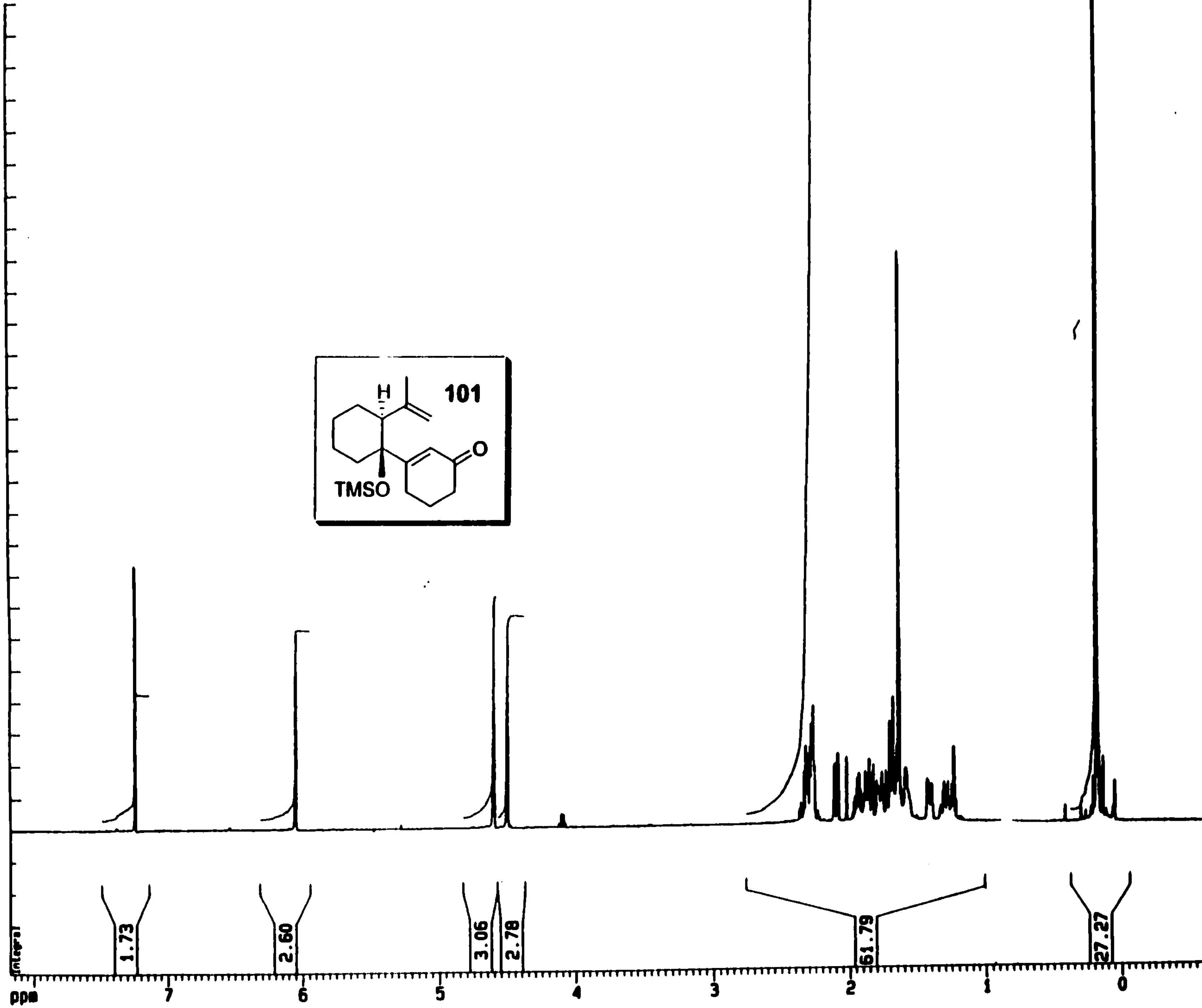
```
Current Data Parameters
NAME            dhd_3942
EXPNO                  1
PROCNO                 1

F2 - Acquisition Parameters
Date_           20010418
Time               11.34
INSTRUM            av300
PROBHD   5 mm QNP  1H/1
PULPROG             zg30
TD                 30720
SOLVENT            CDCl3
NS                    16
DS                     0
SWH             5081.301 Hz
FIDRES          0.165407 Hz
AQ             3.0228980 sec
RG                  45.3
DW                98.400 usec
DE                  6.00 usec
TE                 300.0 K
D1            1.00000000 sec

============ CHANNEL f1 ============
NUC1                  1H
P1                  9.50 usec
PL1                -3.00 dB
SFO1        300.1319477 MHz

F2 - Processing parameters
SI                 65536
SF          300.1300000 MHz
WDW                   EM
SSB                    0
LB                  0.10 Hz
GB                     0
PC                  1.00

1D NMR plot parameters
CX                 20.00 cm
CY                 10.00 cm
F1P                8.131 ppm
F1               2440.36 Hz
F2P               -0.100 ppm
F2                -29.91 Hz
PPMCM            0.41153 ppm/cm
HZCM           123.51362 Hz/cm
```



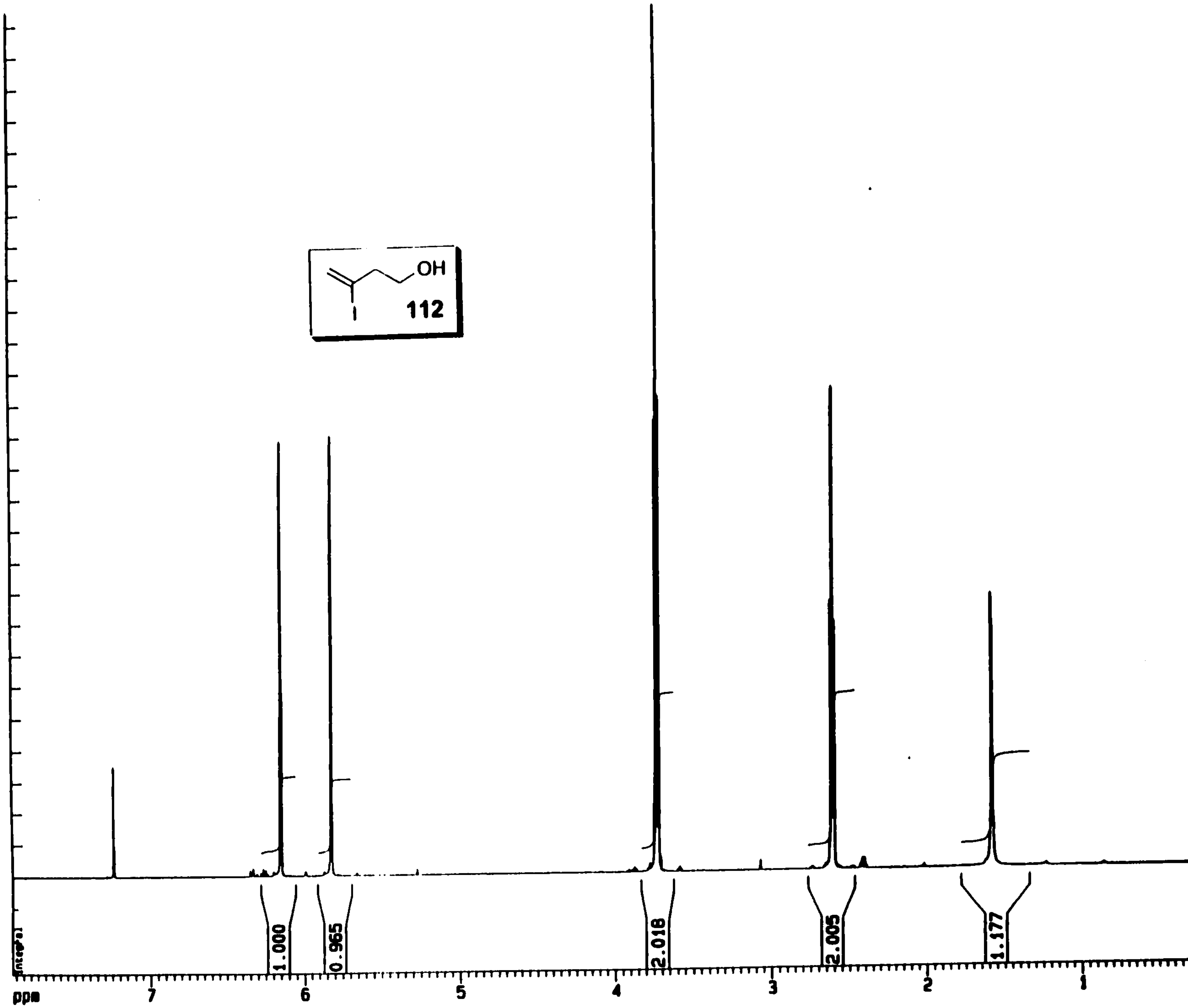
```
F2 - Acquisition Parameters
Date_          20010427
Time              12.16
INSTRUM           av300
PROBHD   5 mm QNP  1H/1
PULPROG            zg30
TD                30720
SOLVENT           CDCl3
NS                   16
DS                    0
SWH          5081.301 Hz
FIDRES       0.165407 Hz
AQ          3.0228980 sec
RG                  256
DW             98.400 usec
DE               6.00 usec
TE              300.0 K
D1         1.00000000 sec

============ CHANNEL f1 ============
NUC1                 1H
P1               9.50 usec
PL1             -3.00 dB
SFO1      300.1319477 MHz

F2 - Processing parameters
SI                65536
SF        300.1300000 MHz
WDW                  EM
SSB                   0
LB               0.10 Hz
GB                    0
PC                 1.00

1D NMR plot parameters
CX              20.00 cm
CY              90.00 cm
F1P             8.000 ppm
F1            2401.04 Hz
F2P             0.000 ppm
F2               0.00 Hz
PPMCM         0.40000 ppm/cm
HZCM        120.05200 Hz/cm
```



```
Current Data Parameters
NAME              dhd_403
EXPNO                   1
PROCNO                  1

F2 - Acquisition Parameters
Date_            20010502
Time                15.23
INSTRUM             av300
PROBHD     5 mm QNP  1H/1
PULPROG              zg30
TD                  30720
SOLVENT             CDCl3
NS                     16
DS                      0
SWH            5081.301 Hz
FIDRES         0.165407 Hz
AQ            3.0228980 sec
RG                  322.5
DW               98.400 usec
DE                 6.00 usec
TE                300.0 K
D1           1.00000000 sec

============ CHANNEL f1 ============
NUC1                   1H
P1                9.50 usec
PL1               -3.00 dB
SFO1        300.1319477 MHz

F2 - Processing parameters
SI                  65536
SF          300.1300000 MHz
WDW                    EM
SSB                     0
LB                0.10 Hz
GB                      0
PC                   1.00

1D NMR plot parameters
CX                20.00 cm
CY               380.00 cm
F1P               8.000 ppm
F1              2401.04 Hz
F2P               0.000 ppm
F2                 0.00 Hz
PPMCM           0.40000 ppm/cm
HZCM          120.05200 Hz/cm
```



```
Current Data Parameters
NAME                den
EXPNO                 1
PROCNO                1

F2 - Acquisition Parameters
Date           20000412
Time              13.40
PULPROG              zg
SOLVENT           CDCl3
AQ         4.6530806 sec
FIDRES      0.107458 Hz
DW             71.0 usec
RG                 2048
NUCLEUS              1H
NL1                0 dB
D1         0.0100000 sec
P1              3.0 usec
DE             88.0 usec
SFO1     500.1381707 MHz
SWH          7042.25 Hz
TD                65536
NS                   16
DS                    0

F1 - Processing parameters
SI                32768
MC2                  QF
SF       500.1364311 MHz
WDW                  EM
SSB                   0
LB              0.00 Hz
GB                    0

1D NMR plot parameters
CX             22.00 cm
F1P           8.183 ppm
F1           4092.61 Hz
F2P          -0.655 ppm
F2           -327.70 Hz
PPMCM       0.40174 ppm/
HZCM     200.92328 Hz/(
```



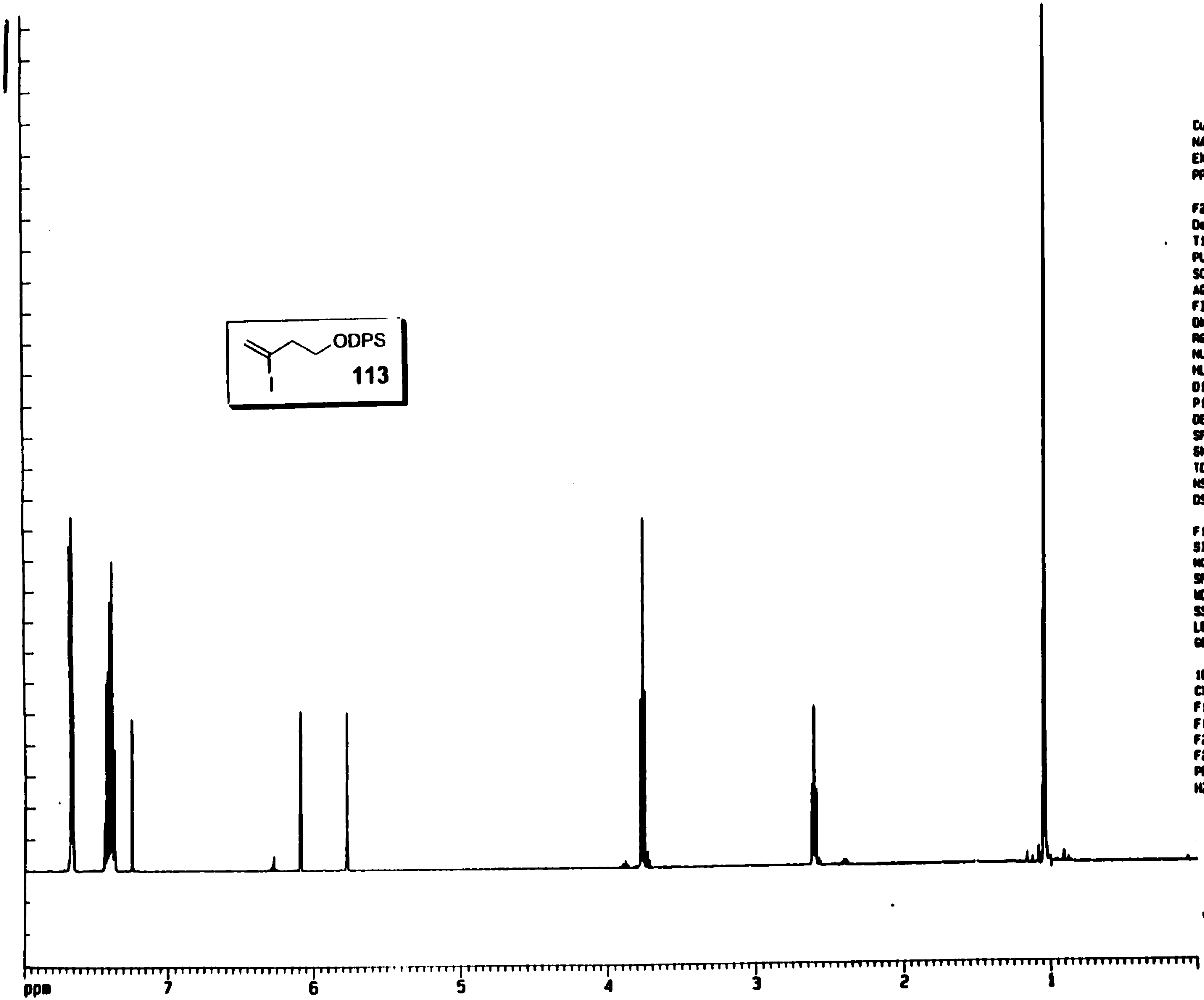
112

Current Data Parameters	
NAME	dhd_265
EXPNO	1
PROCNO	1

F2 - Acquisition Parameters	
Date	20000924
Time	20.18
PULPROG	zg
SOLVENT	CDCl3
AQ	4.6530806 sec
FIDRES	0.107456 Hz
DW	71.0 usec
RG	2048
NUCLEUS	1H
HL1	0 dB
D1	0.0100000 sec
P1	3.3 usec
DE	80.0 usec
SFO1	500.1381707 MHz
SWH	7042.25 Hz
TD	65536
NS	16
DS	1

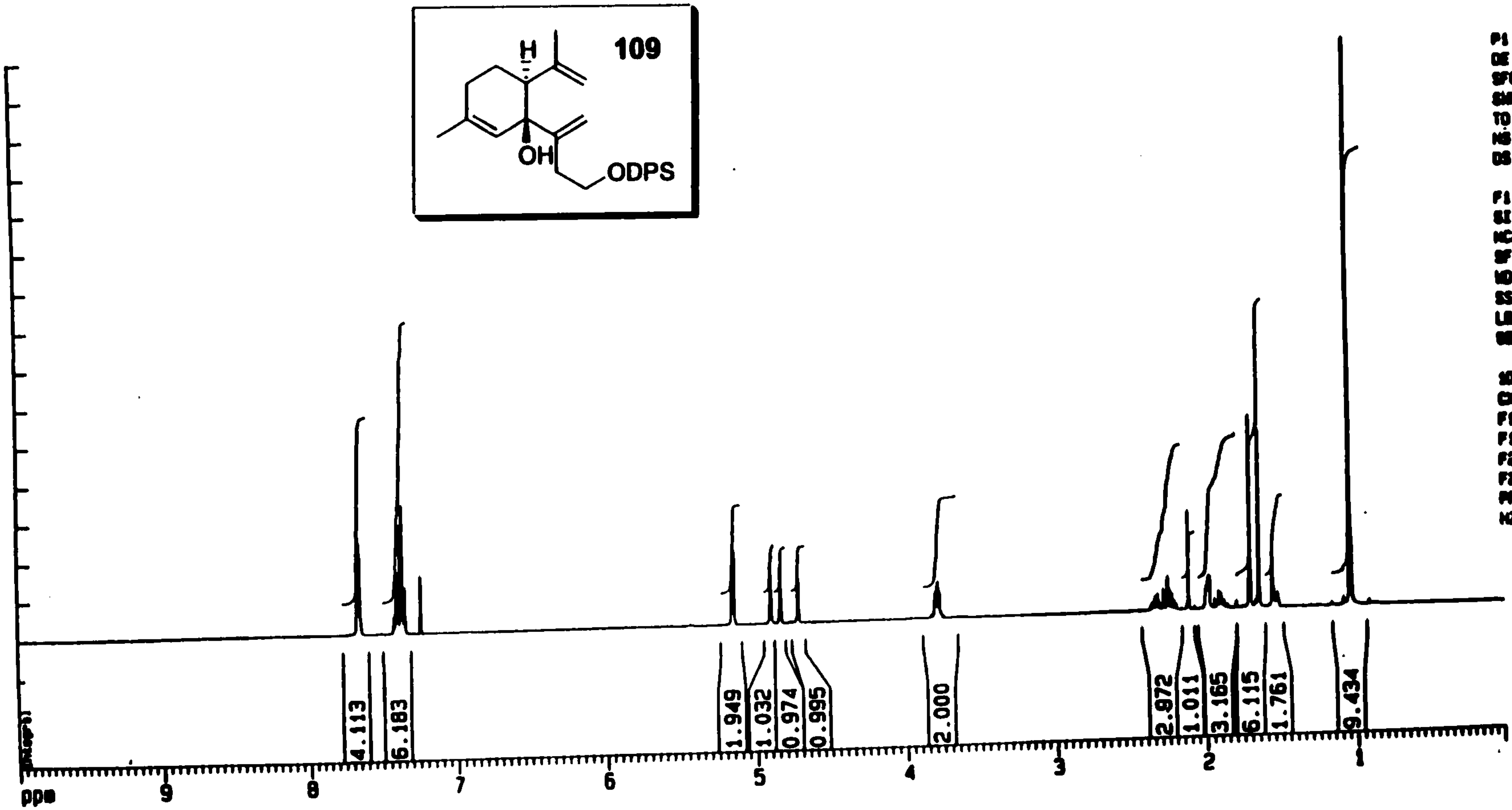
F1 - Processing parameters	
SI	32768
MC2	QF
SF	500.1354311 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0

1D NMR plot parameters	
CX	22.00 cm
F1P	7.924 ppm
F1	3962.08 Hz
F2P	0.263 ppm
F2	131.30 Hz
PPMCM	0.34823 ppm/
HZCM	174.16301 Hz/



113

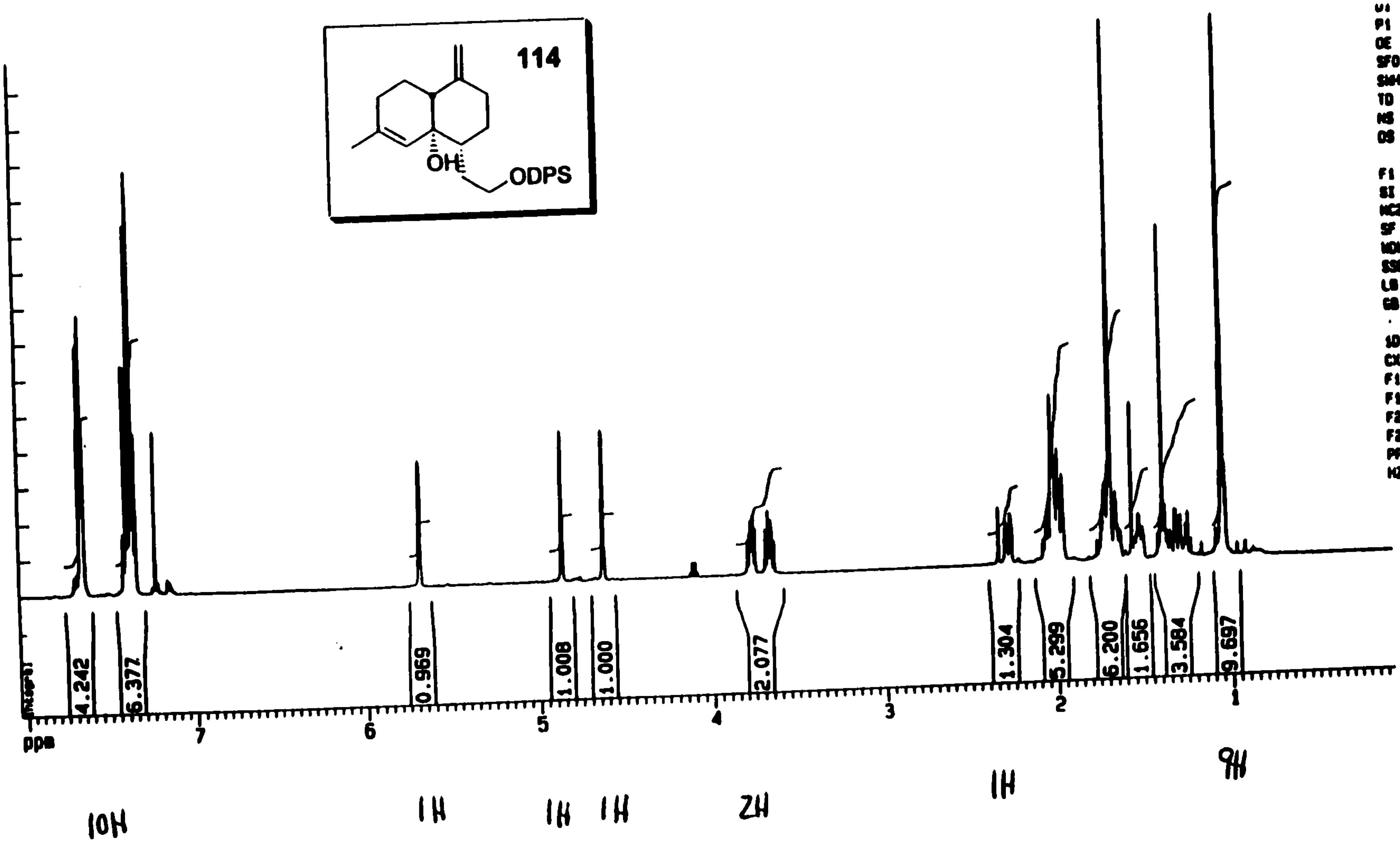
```
Current Data Parameters
NAME              dhd-111
EXPNO                   1
PROCNO                  1

F2 - Acquisition Parameters
Date             20010128
Time                13.48
PULPROG                zg
SOLVENT             CDCl3
AQ           4.6530806 sec
FIDRES        0.107456 Hz
DW                71.0 usec
RG                    512
NUCLEUS                1H
HL1                   0 dB
D1           0.0100000 sec
P1                 3.0 usec
DE                80.8 usec
SFO1       500.1381707 MHz
SWH            7042.25 Hz
TD                  65536
NS                      1
DS                      0

F1 - Processing parameters
SI                  32768
MC2                    QF
SF         500.1354311 MHz
WDW                    EM
SSB                     0
LB                0.00 Hz
GB                      0

1D NMR plot parameters
CX               22.00 cm
F1P              8.000 ppm
F1             4001.08 Hz
F2P              0.000 ppm
F2                0.00 Hz
PPMCM          0.36364 ppm/
HZCM         181.86743 Hz/
```



P1 3.3 usec
DE 60.0 usec
SFO1 500.1381787 MHz
SWH 7042.25 Hz
TD 65536
NS 16
DS 0

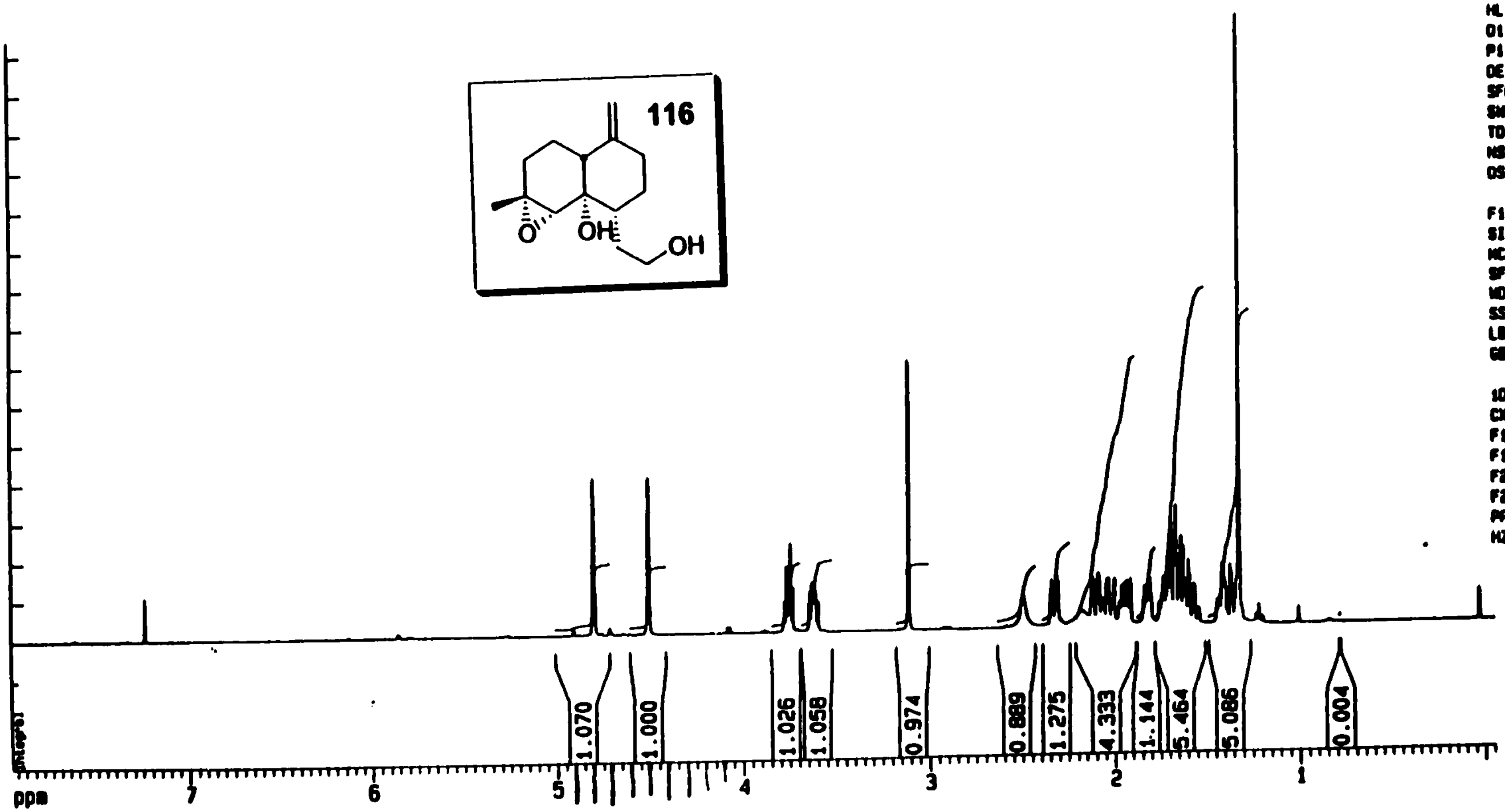
F1 - Processing parameters
SI 32768
MC2 QF
SF 500.1354311 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0

1D NMR plot parameters
CX 22.00 cm
F1P 10.000 ppm
F1 5001.35 Hz
F2P 0.000 ppm
F2 0.00 Hz
PPMCM 0.45455 ppm/
HZCM 227.33429 Hz/c



```
P1                 3.3 usec
DE                60.0 usec
SFO1      500.1381707 MHz
SWH           7042.25 Hz
TD              65536
NS                 16
DS                  0

F1 - Processing parameters
SI              32768
MC2                QF
SF        500.1364311 MHz
WDW                EM
SSB                 0
LB               0.30 Hz
GB                  0

1D NMR plot parameters
CX              22.00 cm
F1P             8.043 ppm
F1            4022.57 Hz
F2P             0.072 ppm
F2              35.81 Hz
PPMCM         0.36233 ppm/
HZCM        181.21636 Hz/
```

ABH



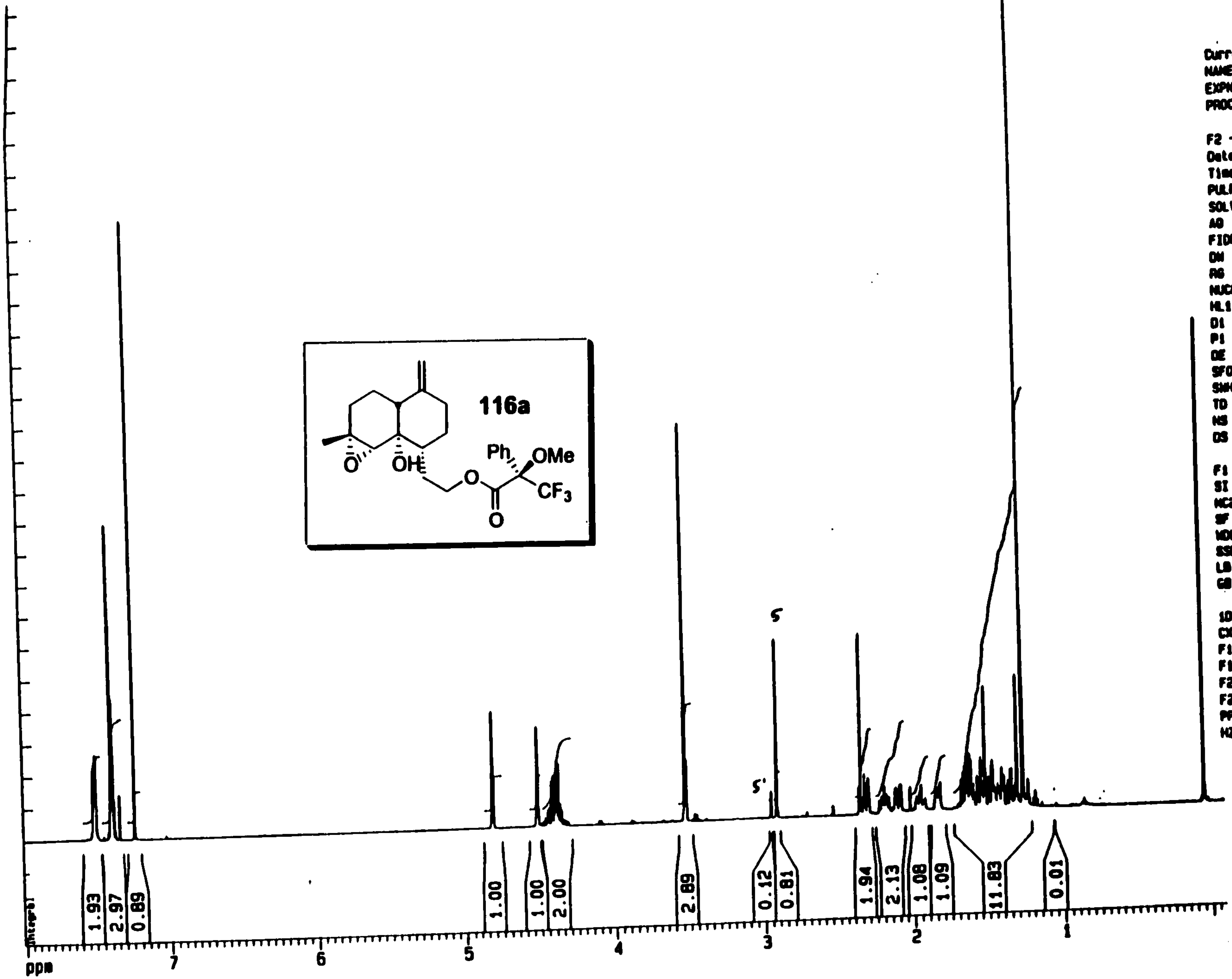
HL1	0 dB
D1	0.0100000 sec
P1	3.3 usec
DE	60.0 usec
SFO1	500.1381707 MHz
SWH	7042.25 Hz
TD	65536
NS	16
DS	1

F1 - Processing parameters

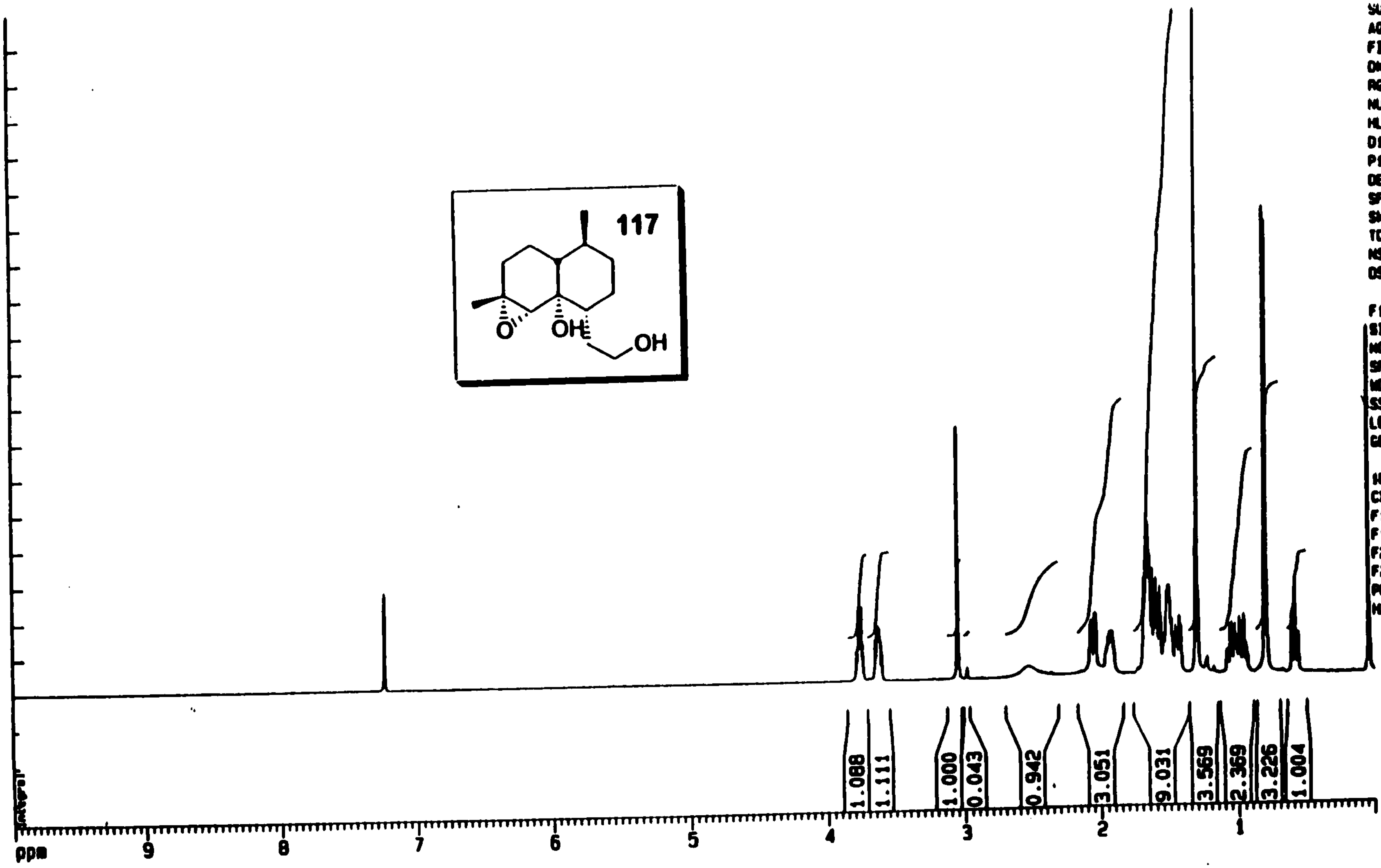
SI	32768
MC2	QF
SF	500.1384311 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0

1D NMR plot parameters

CX	22.00 cm
F1P	7.981 ppm
F1	3991.77 Hz
F2P	-0.050 ppm
F2	-25.17 Hz
PPMCM	0.36500 ppm/
HZCM	182.58818 Hz/c

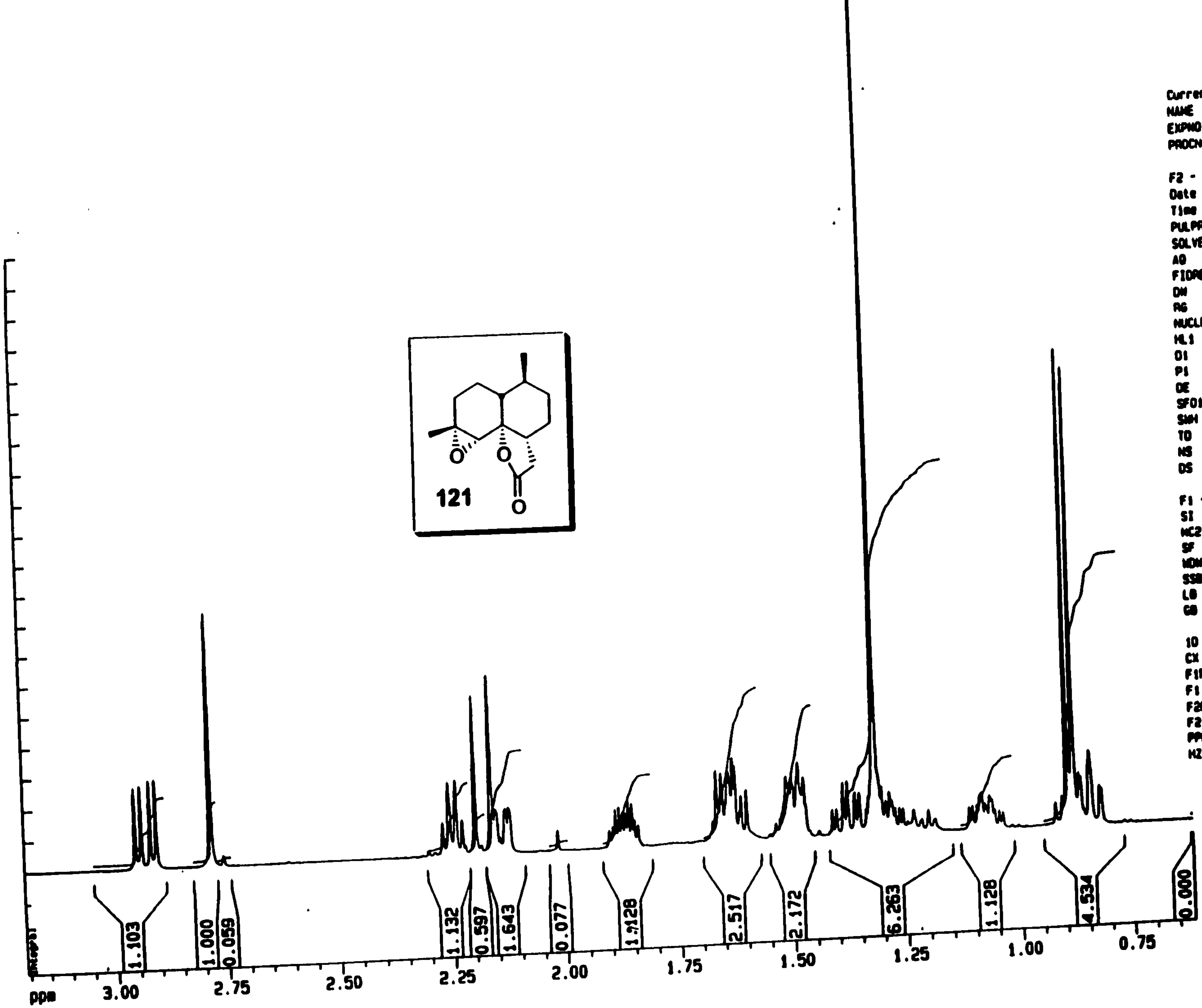


```
Current Data Parameters
NAME               dhd_329
EXPNO                    1
PROCNO                   1

F2 - Acquisition Parameters
Date_             20010116
Time                  4.25
PULPROG .               zg
SOLVENT              CDCl3
AQ            4.6530805 sec
FIDRES         0.107456 Hz
DW                71.0 usec
RG                     512
NUCLEUS                 1H
PL1                   0 dB
D1           0.0100000 sec
P1                 3.0 usec
DE                88.8 usec
SFO1        500.1301707 MHz
SWH             7042.25 Hz
TD                   65536
NS                      16
DS                       0

F1 - Processing parameters
SI                   32768
MC2                     QF
SF          500.1354311 MHz
WDW                     EM
SSB                      0
LB                 0.00 Hz
GB                       0

1D NMR plot parameters
CX                22.00 cm
F1P              8.015 ppm
F1              4008.59 Hz
F2P             -0.084 ppm
F2               -42.01 Hz
PPMCM         0.36814 ppm/
HZCM       184.11804 Hz/(
```



117

```
SOLVENT               CDCl3
AQ                4.6530805 sec
FIDRES             0.107456 Hz
DW                     71.0 usec
RG                     2048
NUCLEUS                  1H
NL1                       0 dB
D1                0.0100000 sec
P1                      3.0 usec
DE                     80.0 usec
SFO1            500.1381707 MHz
SWH                 7042.25 Hz
TD                    65536
NS                       16
DS                        0

F1 - Processing parameters
SI                    32768
MC2                      QF
SF              500.1354311 MHz
WDW                      EM
SSB                       0
LB                     0.00 Hz
GB                        0

1D NMR plot parameters
CX                    22.00 cm
F1P                   3.874 ppm
F1                  1937.46 Hz
F2P                   2.911 ppm
F2                  1455.87 Hz
PPMCM               0.04379 ppm/
HZCM               21.90038 Hz/(
```



121

Current Data Parameters

NAME	dnd_325
EXPNO	1
PROCNO	1

F2 - Acquisition Parameters

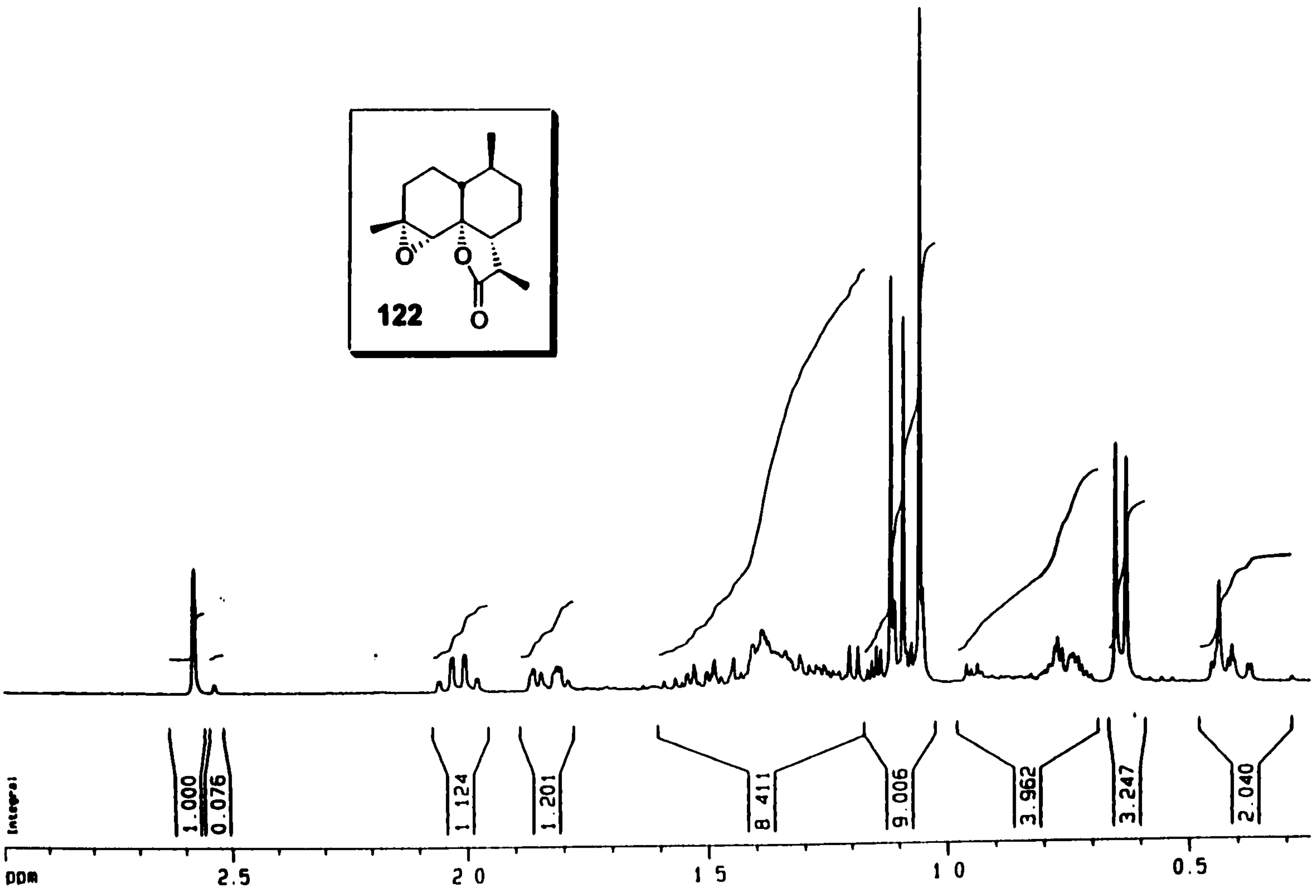
Date	20010112
Time	3.44
PULPROG	zg
SOLVENT	CDCl3
AQ	4.6530805 sec
FIDRES	0.107456 Hz
DW	71.0 usec
RG	4096
NUCLEUS	1H
HL1	0 dB
D1	0.0100000 sec
P1	3.0 usec
DE	80.0 usec
SFO1	500.1381707 MHz
SWH	7042.25 Hz
TD	65536
NS	16
DS	0

F1 - Processing parameters

SI	32768
MC2	QF
SF	500.1384311 MHz
WDW	EM
SSB	0
LB	0.00 Hz
GB	0

1D NMR plot parameters

CX	22.00 cm
F1P	3.207 ppm
F1	1603.97 Hz
F2P	0.617 ppm
F2	308.57 Hz
PPMCM	0.11773 ppm/
HZCM	58.88197 Hz/



SOLVENT	CDCl3
NS	16
DS	0
SWH	5081.301 Hz
FIDRES	0.165407 Hz
AQ	3.0228980 sec
RG	128
DW	98.400 usec
DE	6.00 usec
TE	300.0 K
D1	1.00000000 sec

============ CHANNEL f1 =============

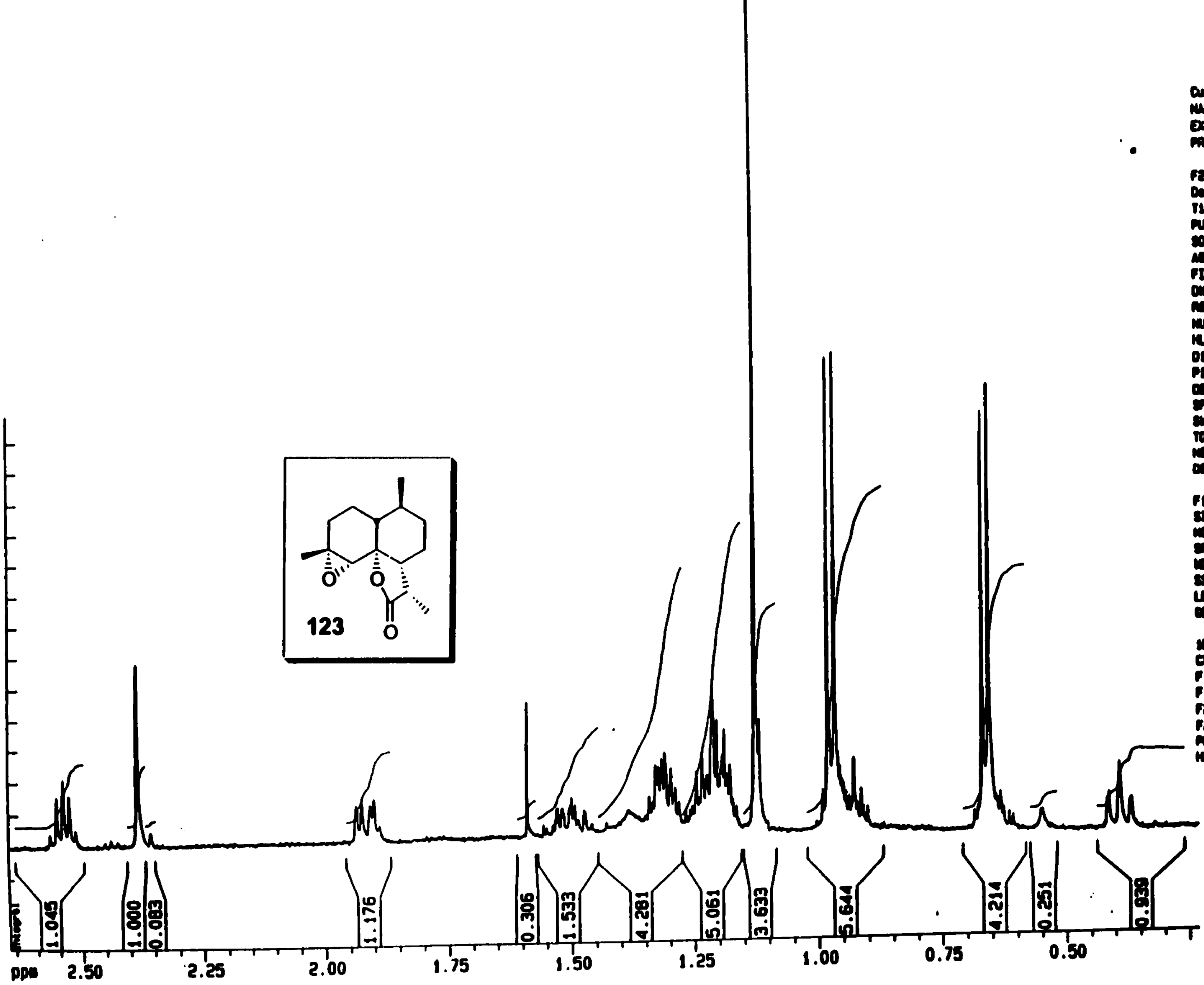
NUC1	1H
P1	9.50 usec
PL1	-3.00 dB
SFO1	300.1319477 MHz

F2 - Processing parameters

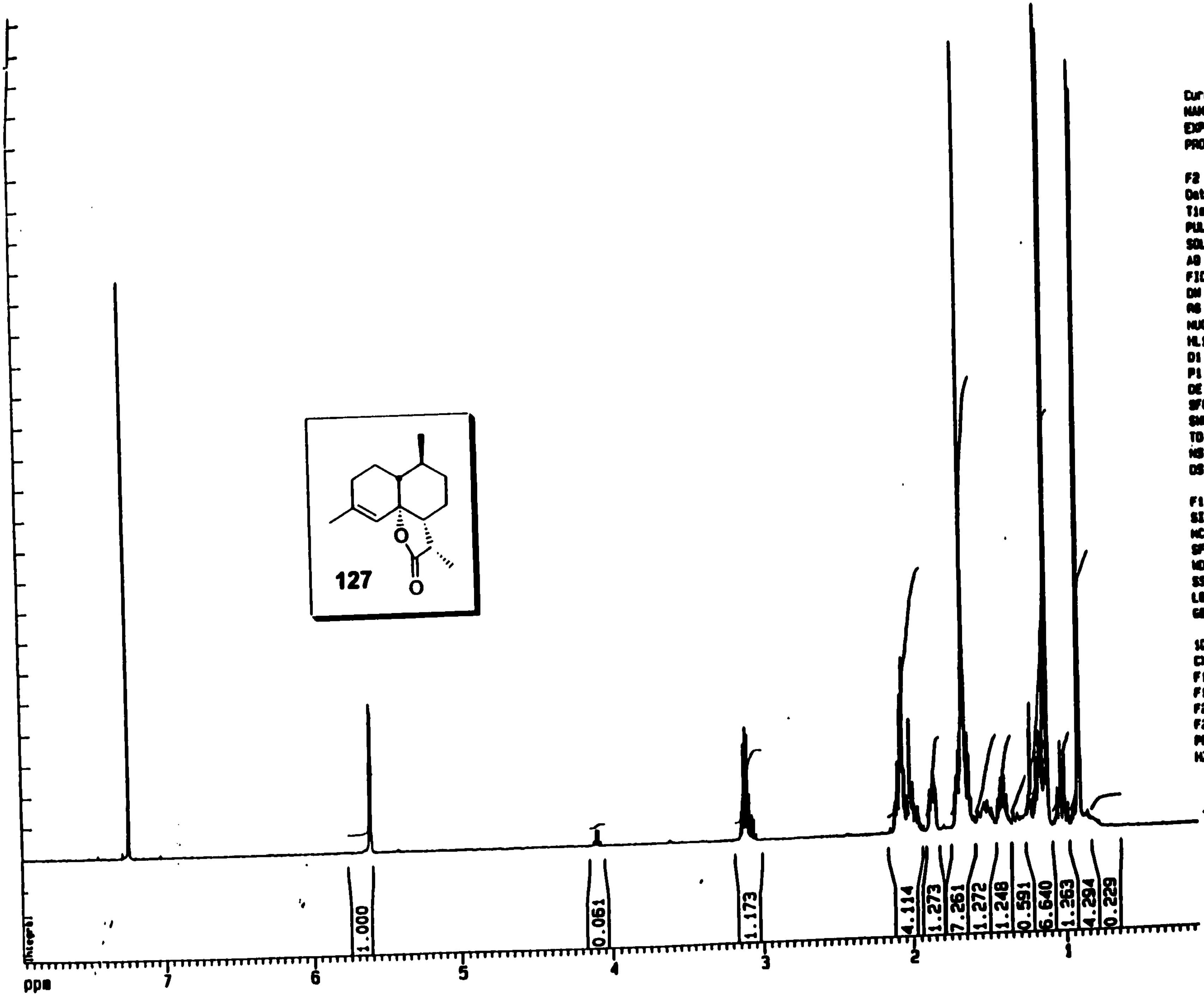
SI	65536
SF	300.1300000 MHz
WDW	EM
SSB	0
LB	0.10 Hz
GB	0
PC	1.00

1D NMR plot parameters

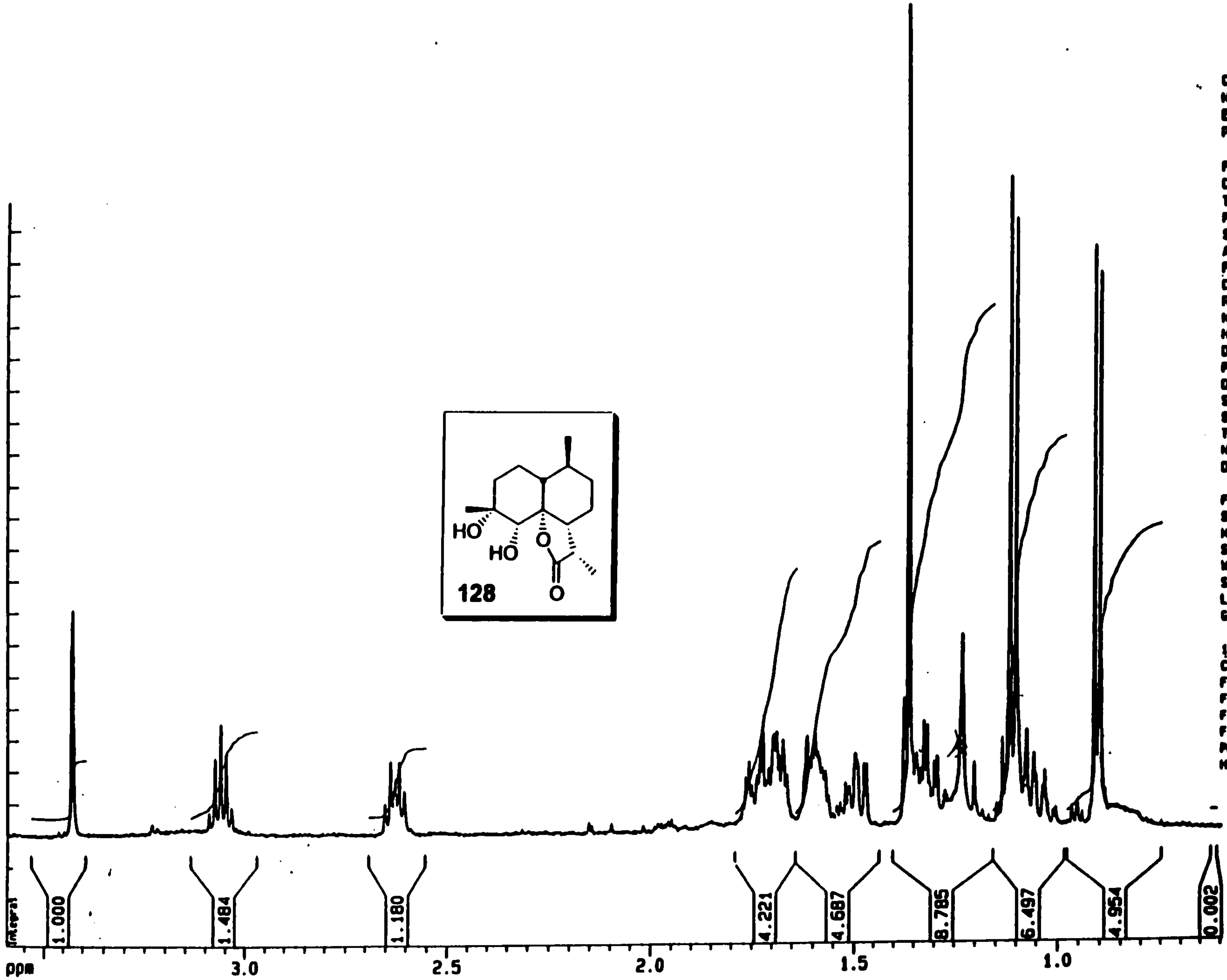
CX	20.00 cm
CY	10.00 cm
F1P	3.000 ppm
F1	900.39 Hz
F2P	0.250 ppm
F2	75.03 Hz
PPMCM	0.13750 ppm/cm
HZCM	41.26788 Hz/cm



```
Current Data Parameters
NAME              dhd_331
EXPNO                   1
PROCNO                  1

F2 - Acquisition Parameters
Date             20010120
Time                 8.04
PULPROG                zg
SOLVENT             CDCl3
AQ              4.6530808 sec
FIDRES           0.107456 Hz
DW                   71.0 usec
RG                   2048
NUCLEUS                1H
NL1                     0 dB
D1             0.0100000 sec
P1                    3.0 usec
DE                   60.0 usec
SFO1          500.1301707 MHz
SWH               7042.25 Hz
TD                  65536
NS                     16
DS                      0

F1 - Processing parameters
SI                  32768
MC2                    QF
SF            500.1300311 MHz
WDW                    EM
SSB                     0
LB                   0.00 Hz
GB                      0

1D NMR plot parameters
CX                  22.00 cm
F1P                 2.663 ppm
F1                1331.74 Hz
F2P                 0.232 ppm
F2                 115.84 Hz
PPMCM             0.11051 ppm/
HZCM             55.26646 Hz/(
```



```
Current Data Parameters
NAME            gnd_309
EXPNO                 1
PROCNO                1

F2 - Acquisition Parameters
Date           20001208
Time               6.05
PULPROG              zg
SOLVENT           CDCl3
AQ         4.6530805 sec
FIDRES      0.107456 Hz
DW             71.0 usec
RG             16384
NUCLEUS              1H
NL1                0 dB
D1        0.0100000 sec
P1              3.3 usec
DE             60.0 usec
SFO1     500.1381707 MHz
SWH          7042.25 Hz
TD             65536
NS                16
DS                 0

F1 - Processing parameters
SI             32768
MC2               QF
SF       500.1354311 MHz
WDW               EM
SSB                0
LB              0.30 Hz
GB                 0

1D NMR plot parameters
CX             22.00 cm
F1P            7.971 ppm
F1           3986.78 Hz
F2P            0.119 ppm
F2             59.60 Hz
PPMCM        0.35691 ppm/
HZCM       178.50352 Hz/c
```



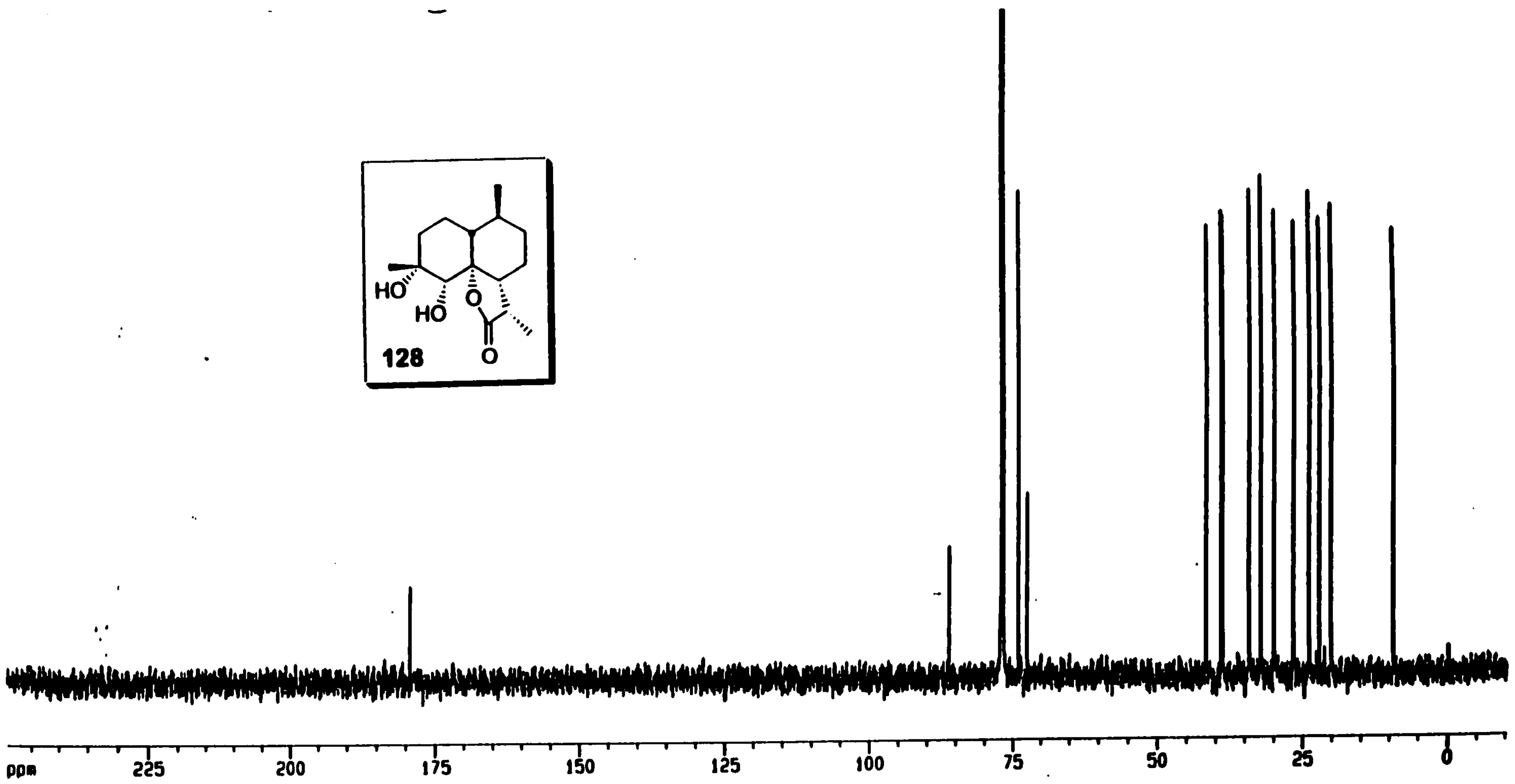
128

Current Data Parameters
NAME and_3033
EXPNO 1
PROCNO 1

F2 - Acquisition Parameters
Date 20010114
Time 3.40
PULPROG zg
SOLVENT CDCl3
AQ 4.6530805 sec
FIDRES 0.107456 Hz
DW 71.0 usec
RG 16384
NUCLEUS 1H
PL1 0 dB
D1 0.0100000 sec
P1 3.0 usec
DE 60.0 usec
SFO1 500.1381707 MHz
SWH 7042.25 Hz
TD 65536
NS 64
DS 0

F1 - Processing parameters
SI 32768
MC2 QF
SF 500.1354311 MHz
WDW EM
SSB 0
LB 0.00 Hz
GB 0

1D NMR plot parameters
CX 22.00 cm
F1P 3.579 ppm
F1 1790.20 Hz
F2P 0.580 ppm
F2 290.30 Hz
PPMCM 0.13632 ppm/
HZCM 68.17721 Hz/c


HO
HO
O
O
128
ppm
225
200
175
150
125
100
75
50
25
0