Studies on the Stereo- and Regiochemistry of [4+2] Cycloaddition of Nitroso Compounds to Chiral Halobenzenediols. Total Synthesis of Lycoricidine.

by

Horacio F. Olivo

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

DOCTOR OF PHILOSOPHY
in
Chemistry

APPROVED:

Dr. Tomas Hudlicky, Chairman

Dr. David A. Becker

Dr. Neal Castagnoli

Dr. David G. I. Kingston

Dr. John G. Mason

Dr. James M. Tanko

Dr. Robert H. White

July 13, 1992
Blacksburg, Virginia

Abstract

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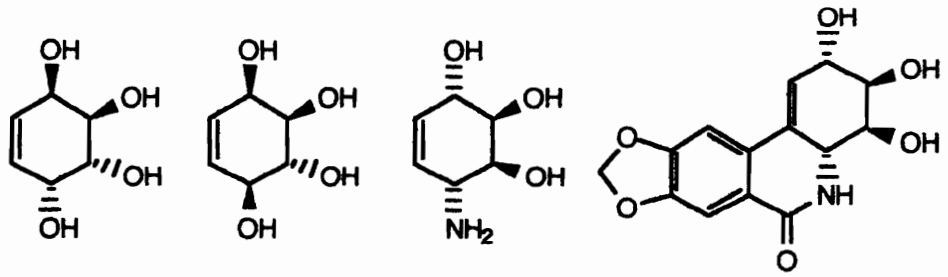
(Abstract)

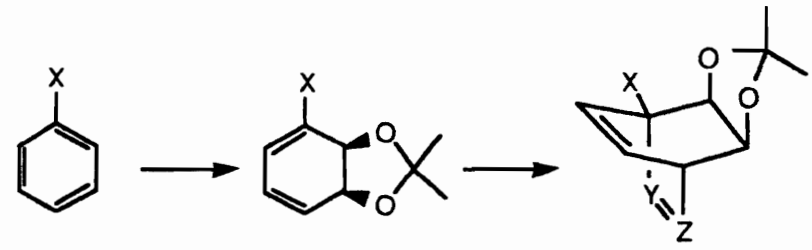
All four monosubstituted halobenzenes **5a-d** have been converted to the corresponding *cis*-arenediols by a microbial oxidation with the bacterium *Pseudomonas putida* strain 39-D. Enantiomerically pure *cis*-diols were obtained from chloro- and bromobenzene. The acetonides of these two diols have been utilized as useful synthons in the preparation of several natural products, like conduritols E **1** and F **2**, aminoconduritol A-1 **3** and lycoricidine **4**.



1 **2** **3** **4**

The optical purity of bromocyclohexadienediol, was determined by its conversion to three different natural products ((+)-conduritol E **1**, (-)-conduritol F **2**, and (+)-aminoconduritol A-1 **3**), and compared with their optical rotation.

Abstract



5a-d **6a-d** **7a-d** **8a-d** **9a-d**

a X= F
b X= Cl
c X= Br
d X= I

Y= CH Y= CCO_2Et Y= O
Z= CCO_2Et Z= CH Z= NCOOBn

Several dienophiles were added to the protected *cis*-arenediols to study the regio- and stereochemistry of the cycloaddition. The addition of dienophiles to the acetonide of the diols was anti in every case. When ethyl propiolate was used, two regioisomers **7** and **8** were obtained. In contrast, the addition of nitroso dienophiles, derived *in situ* from the oxidation of hydroxamic acids, to protected halocyclohexadienediols provided chiral bicyclic oxazines of type **9**, as single isomers. These compounds were converted by reductive cleavage to 1,4-hydroxy amides. The anti-addition to the acetonide and the stereospecific formation of the two new chiral centers adjacent to the acetonide was exploited in an approach to a more complex phenanthrene natural product lycoricidine **4**.

I lift up my eyes to the hills-
where does my help come from?
My help comes from the Lord,
the Maker of heaven and earth.

He will not let your foot slip-
he who watches over you will not slumber
indeed, he who watches over Israel
will neither slumber not sleep.

The Lord watches over you-
the Lord is your shade at your right hand;
the sun will not harm you by day,
nor the moon by night.

The Lord will keep you from all harm-
he will watch over your life;
the Lord will watch over your coming and going
both now and forevermore.

-Psalm 121

To my brother Oscar.

Acknowledgements

I would like to express my deepest appreciation of Professor Tomas Hudlicky's advice, guidance, and support during my career at Virginia Tech. Also, I would like to thank all of the members of my committee, Drs. David Becker, Neal Castagnoli, David Kingston, John Mason, James Tanko, and Robert White, for their patience and support.

A special mention goes to my good friend and colleague Dr. Hector Luna, for his valuable advice and continuous support inside and outside of the chemistry lab.

I would like to thank all of the former and the present members of Dr. Hudlicky's group that filled the atmosphere in the lab with their joy and motivation, and made every long day of work a very pleasent one.

I wish to express my gratitude to Tom Glass, Geno Ianaccone and Bill Babout in Analytical Services for their help in the NMR spectrometers and to Kim Harich for obtaining all the mass spectra.

I gratefully appreciate the advice of Drs. Martha Albores and Milos Hudlicky, who supported my desire to come to this country to further my studies in organic chemistry.

I also want to thank Ms. Veronica Cadorette, whose help and support during all of my stay in Blacksburg was invaluable to me. My most sincere appreciation to Michele Stabile and Dr. Christie Boros for helping me to proofread most of the entire manuscript of this dissertation.

Table of Contents

I. INTRODUCTION

Today, the production and the supply of both enantiomers of a natural product is a necessity. When a natural product has shown a promising biological activity, its synthesis in the laboratory is required, since isolation from natural sources is usually inconvenient. It is important to study the physiological activities of each enantiomer of a natural product separately, since they may have markedly different properties. In order to achieve this goal in the most effective fashion, the use of enzymatic reactions and other biotransformations have been steadily increasing in the synthesis area.[1]

Biotransformation technology is a very useful tool for synthetic organic chemists. This technology uses transformations of either pure enzymes or whole cells to functionalize non-activated positions in organic molecules or to achieve the preparation of enantiomerically pure compounds. Kinetic resolution or catalytic asymmetric induction are among the methods used to prepare optically pure substrates. The most effective manifestation of the use of enzymes is in the area of asymmetric synthesis or the production of an optically pure metabolite from an achiral substrate.

The first documented use of biotransformations may well be the fermentation of sugar to ethanol by yeast, a process that probably laid the foundation for microbiology as a science.[2] Many industrial processes use microorganisms to produce either a final product or an intermediate useful for the manufacture of other chemicals.

Microorganisms are also used to produce secondary metabolites like penicillins and cephalosporins (by *Penicillium* spp. and *Cephalosporium* spp., respectively).[3] Microbiological processes effectively compete with alternative or equivalent chemical processes a recent example is the hydrolysis of 6-aminopenicillanic acid by the bacterium *Escherichia coli*. Biological transformations are also displacing chemical processes, for example in the biopreparation of L-DOPA as compared to the asymmetric hydrogenation with rhodium catalysts.[4]

In the manufacture of steroids, for example, progesterone is oxidized to 11α-hydroxyprogesterone (*Rhizopus arrhizus*) and β-sitosterol is oxidized to androstenedione.[3] These biotransformations are carried out by microorganisms and do not yet have the

corresponding equivalents in chemical synthesis. In other cases, partially purified enzymes work as specific catalysts in selected processes. Enzymes like α-amylase and amyloglucosidase are used in the manufacture of sugar, and fructose is obtained from glucose isomerase, an enzyme from *Bacillus coagulans*.[4]

The development of processes such as those mentioned above has grown steadily for the past 100 years, and the research efforts in this area have greatly intensified during the last fifteen years. The stage is now set for the adjustment of known industrial processes to a more environmentally sound methodology. The use of enzymes or microorganisms constitutes a much cleaner way to manufacture chemicals and pharmaceuticals, since most transformations take place in aqueous media or other relatively innocuous solvents such as acetone or alcohols. The field of biocatalysis, or the combination of enzymatic processes with chemical synthesis, will gain further ground as the most effective way for preparation of required chemical substances.

This dissertation reviews the synthetic accomplishments in the area of biooxidation of aromatic compounds with a mutant strain of the soil bacterium *Pseudomonas putida* and describes to date the most efficient synthesis of lycoricidine, an alkaloid that belongs to a class of known antitumor compounds. It also reviews nitrosyl/diene cycloadditions, and describes model studies that provide further insight to such cycloadditions with polarized dienes. In this work, two areas of synthetic chemistry are combined to achieve a short enantiocontrolled synthesis of the natural product lycoricidine. An enantioselective biotransformation provides multi-gram quantities of a versatile chiral synthon for use in the early stages of the synthesis. Diels-Alder chemistry is used to achieve intermediates that are converted to important natural products like conduramines and lycoricidine.

II. HISTORICAL

1. Overview of Arene *cis*-Diols in Synthesis

Preparation. The focus on the study of the metabolism of aromatic hydrocarbons intensified with the concern of the toxic nature of these compounds and their wide spread use in the industry of pesticides, drugs, polymers and many other products. Microbial or higher organism degradation of aromatic compounds produces different oxygenated intermediates.[5-7] This overview is focused only on the bacterial products. References to monooxygenation of aromatics by higher organisms can be found in recent reviews.[8]

The precise manner in which the hydroxyl groups are introduced into the aromatic ring depends on the type of enzymes involved.[9] Oxidation of aromatic compounds in eukaryotic organisms (fungi, plants, and animals) proceeds via a monooxygenase-catalyzed reaction to arene oxides. Subsequent addition of water, catalyzed by the enzyme epoxide hydrase, leads to the formation of *trans*-dihydrodiols.[9-11] It was observed during labeling studies that only one atom of molecular oxygen is incorporated in the dihydrodiols in those metabolic pathways found to operate in mammals.[9]

On the contrary, in the case of dihydrodiol metabolites produced in prokaryotic organisms (bacteria), the two hydroxy groups are introduced stereospecifically yielding without exception diols with a *cis*-configuration. Experiments with labeled molecular oxygen indicated that both atoms of oxygen in the diols arise from the same molecule of molecular oxygen.[12] The *cis*-configuration has been demonstrated by different approaches.[13] The bacterial diols (with a *cis*-configuration) react easily with dimethoxypropane (DMP) in the presence of acid to form acetonides, whereas synthetic *trans*-diols only produce phenols under those conditions.

Cis-3,5-cyclohexadiene-1,2-diols, usually referred to as arene *cis*-diols, were identified by Gibson and co-workers during the studies of the metabolic pathway of the biodegradation of benzene and benzene derivatives with the bacterium *Pseudomonas putida*.[5] (+)-*cis*-2,3-Dihydroxy-1-methylcyclohexa-4,6-diene **1** was first isolated and reported by Gibson.[5,14]

Washed cells of *Pseudomonas putida* and cell extracts prepared from the same organism rapidly oxidize aromatic compounds. They also oxidize arene *cis*-diols further to catechols, which undergo either ortho or meta oxidative cleavage, as shown in Figure 1.[14]

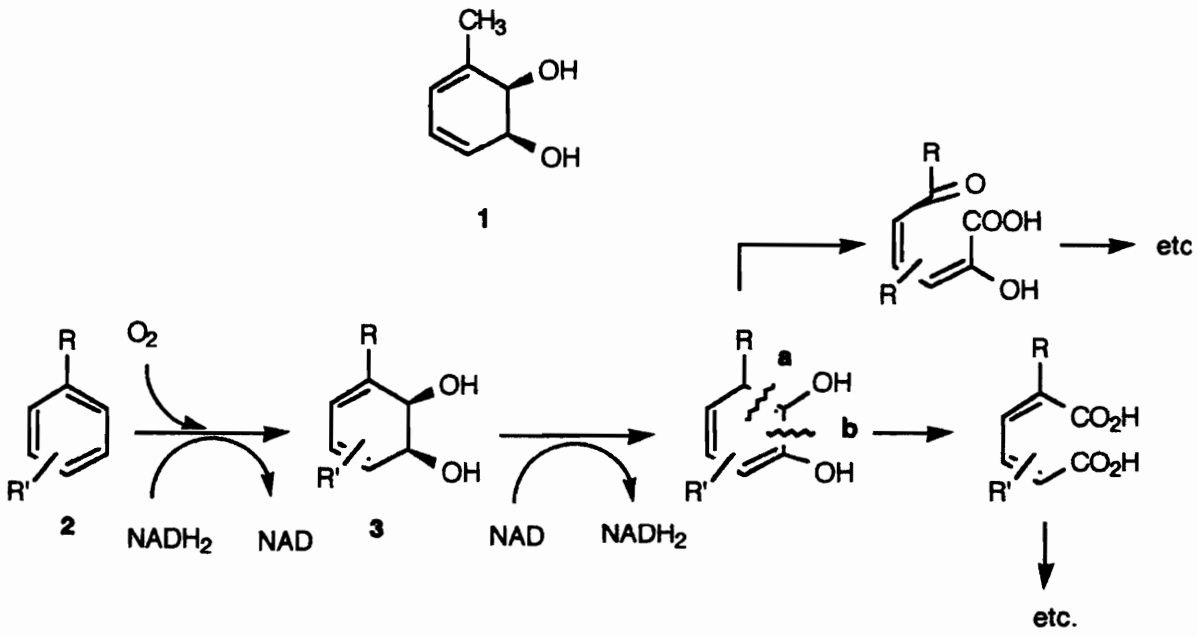


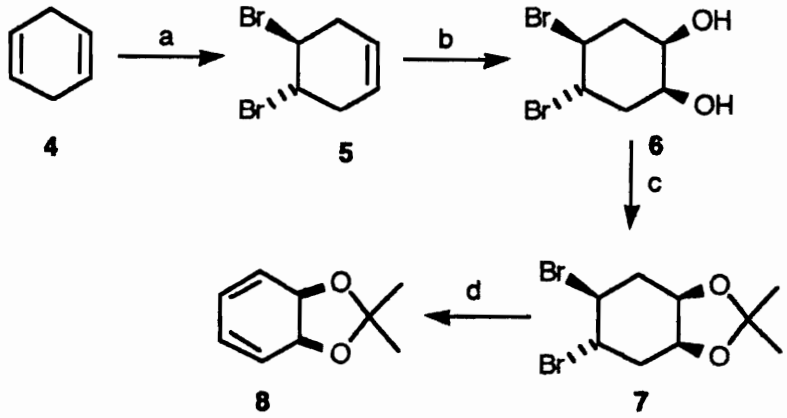
Figure 1. Biodegradation Pathway of Aromatic Compounds.

Mutants strains from *P. putida* were isolated and several of them were found to lead to the accumulation of (+)-*cis*-2,3-dihydroxy-1-methyl-cyclohexa-4,6-diene **1** in the culture medium. One of these strains was labeled *P. putida* 39/D and has been used extensively in the preparation of various substituted *cis*-diols. This strain was shown to incorporate oxygen to many aromatic compounds to yield *cis*-diols, without further oxidation of the aromatic ring, because it lacked the genes responsible for the expression of catechol dehydrogenase required for the next step. These enzymes have been overexpressed on *E. Coli* (JM 106) which is the most efficient system for toluene dioxygenase.[15] These studies provided the tools necessary to prepare different *cis*-diols, compounds which later proved to be useful chiral synthons for the preparation of many pharmaceutical products.[16-18]

The only arene *cis*-diol that has been synthesized by chemical means is benzene diol. *Cis*-benzene diol was synthesized from tetrachlorocyclohexene by oxidation with

potassium permanganate and dehydrochlorination with sodium hydroxide. The overall yield for these two steps was 40%.[19]

Protected benzene diol **8** has been synthesized in four steps from 1,4-cyclohexadiene **4**, as shown in Figure 2. Bromination of only one of the double bonds of 1,4-cyclohexadiene **4** followed by potassium permanganate oxidation yields *cis*-diol **6**. The resulting *cis*-diol was protected by ketal formation with 2,2-dimethoxypropane. Dehydrobromination with DBU (1,8-diazabicylo[5.4.0]undec-7-ene) provided acetonide **8** in 27.2% overall yield.[20,21]



Reagents. Br_2, 87%; b. $KMnO_4$, 49%; c. DMP, 98%
d. DBU, 65%

Figure 2. Synthesis of Protected Benzene Diol.

No other arene diols have been attained by chemical means. However many arene diols have been prepared by the microbial oxidation of the aromatic compound commonly using cultures of *P. putida* 39-D.[16] To date there have been about 130 arene *cis*-diols produced and some of them are now commercially available.[25] Some commonly used diols are listed in Table 1 (see also Figure 3).

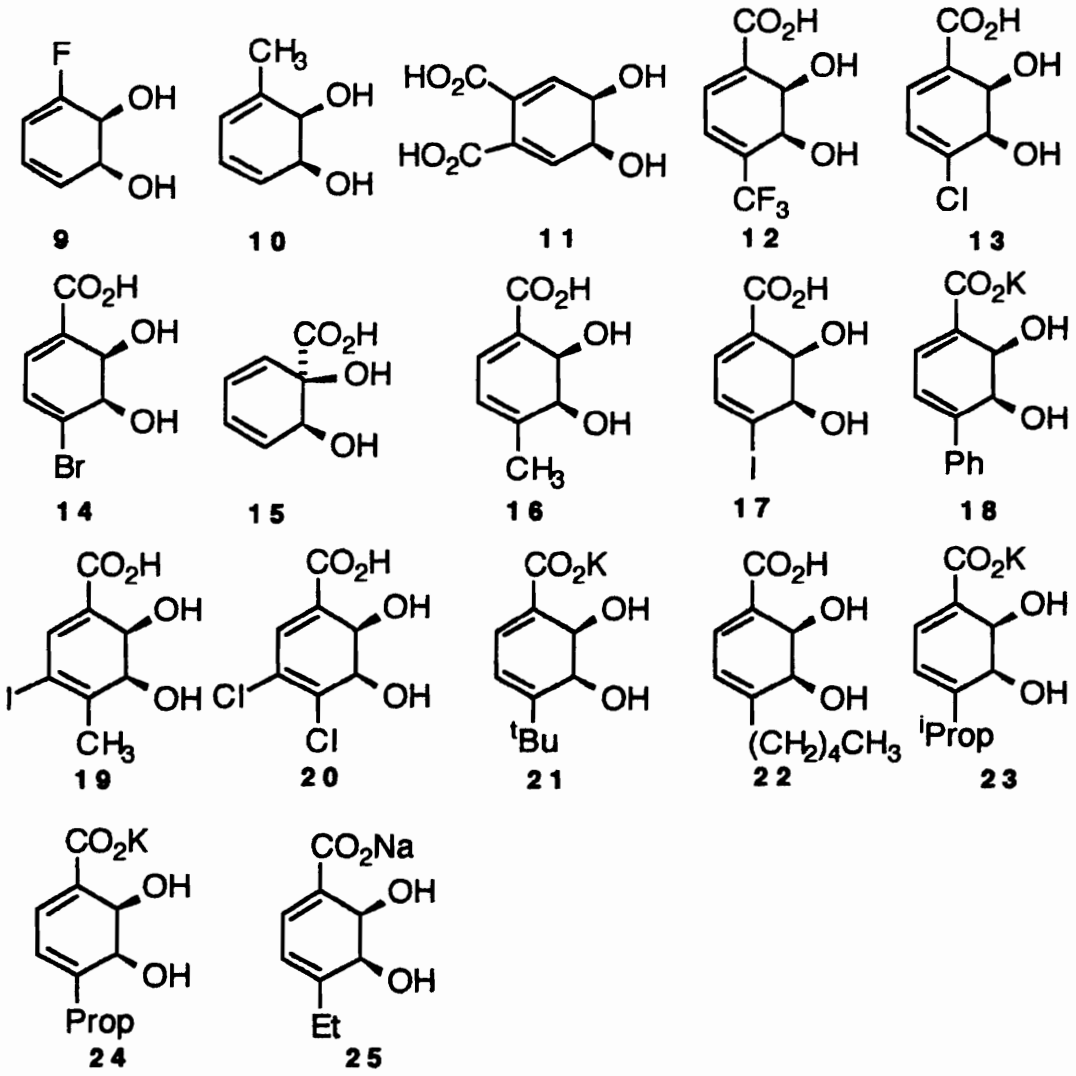


Figure 3. Commonly Used Diols Commercially Available.

Table 1. Commonly Used Diols Commercially Available.

9. *cis*-1,2-dihydro-3-fluorocatechol

10. *cis*-1,2-dihydro-3-methylcatechol

11. 1,2-dicarboxy-*cis*-4,5-dihydroxycyclohexa-2,6-diene

12. (2R,3S)-1-carboxy-4-trifluoromethyl-2,3-dihydroxy-cyclohexa-4,6-diene

13. (2R,3R)-1-carboxy-4-chloro-2,3-dihydroxy-cyclohexa-4,6-diene

14. (2R,3R)-4-bromo-1-carboxy-2,3-dihydroxy-cyclohexa-4,6-diene

15. (1R,2S)-1-carboxy-1,2-dihydrocyclohexa-3,5-diene

16. (2R,3R)-1-carboxy-2,3-dihydroxy-4-methylcyclohexa-3,5-diene

17. (2R,3R)-1-carboxy-4-iodo-2,3-dihydroxycyclohexa-4,6-diene
18. (2R,3S)-1-carboxy-4-phenyl-2,3-dihydroxycyclohexa-4,6-diene, K^+ salt
19. (2R,3S)-1-carboxy-5-iodo-4-methyl-2,3-dihydroxycyclohexa-4,6-diene
20. (2R,3R)-1-carboxy-4,5-dichloro-2,3-dihydroxycyclohexa-4,6-diene
21. (2R,3S)-1-carboxy-4-tert-butyl-2,3-dihydroxycyclohexa-4,6-diene, K^+ salt
22. (2R,3S)-1-carboxy-4-pentyl-2,3-dihydroxycyclohexa-4,6-diene
23. (2R,3S)-1-carboxy-4-isopropyl-2,3-dihydroxycyclohexa-4,6-diene, K^+ salt
24. (2R,3S)-1-carboxy-4-propyl-2,3-dihydroxycyclohexa-4,6-diene, K^+ salt
25. (2R,3S)-1-carboxy-4-ethyl-2,3-dihydroxycyclohexa-4,6-diene, Na^+ salt

On a laboratory scale, this biotransformation consists basically of two steps.[22] The first step is called induction. In this step the bacterium is grown in the presence of small amounts of an aromatic compound called the inducer. This stage is necessary for the cells to produce the required enzymes needed for the oxidation.

The second step is called production. In this step, the desired substrate is introduced in a controlled flow either in vapor phase along with a current of air, or in the case of solids, dissolved in a solvent. The process has been refined and developed for industrial application. It was found that by providing a reductant such as ethanol to regenerate $NADH_2$ consumed in the reaction, the cell system can be used in a catalytic mode with improved accumulations of the diol, Figure 4.[23]

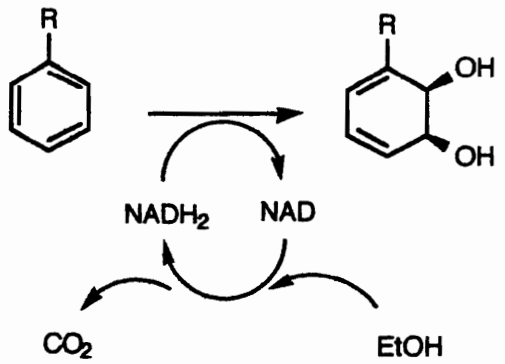


Figure 4. Regeneration of $NADH_2$ Consumed in the Oxidation.

After the diol accumulated in the fermentation broth, the cells are separated by centrifugation. The solution containing the diol is then saturated with sodium chloride and

extracted with a polar solvent such as ethyl acetate. Because of the importance of *cis*-diols as versatile synthons and the general interest of the synthetic community, this process has recently been scaled-up to produce dihydrodiols on a multikilogram scale.[24,25]

Other Pseudomonas species that have been used for the elaboration of *cis*-diols are:

Pseudomonas putida NCIB 12190
Pseudomonas putida NCIB 11680 mutant UV4
Pseudomonas desmolytica
Pseudomonas convexa
Pseudomonas testosteroni A3[26]

In most cases, the microbial transformation is regiospecific, providing the hydroxy groups *ortho* and *meta* to the substituent in the aromatic ring. In the case of *p*-halotoluenes, the oxidation also takes place only in the aromatic carbons.[10] When naphthalene is used as the substrate, it is oxidized only in the *alpha*- and *beta*-positions.[27] Exceptions are found in the oxidation of benzene derivatives substituted with carboxylates, such as benzoic and phthalic acids.[9] Two different products were identified as shown in Figure 5. 3,5-Cyclohexadiene-1,2-diol-1-carboxylic acids were isolated when the bacterium *Alcaligenes eutrophus* mutant strain B 9 was used.[9]

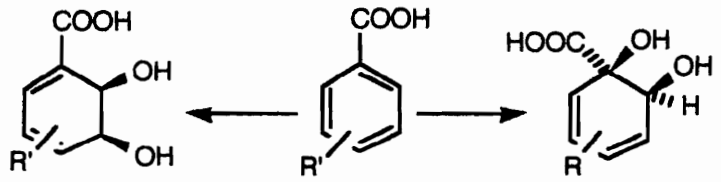


Figure 5. "Normal" and "Ipso" Oxidation of Benzoic Acid.

Products from normal dioxygenation, such as **26**, are obtained using *Pseudomonas putida* JT 107 and PL-pT-11/43 and *Pseudomonas testosteroni* (DSM 676). The products from *ipso* dioxygenation **27**, are obtained most notably when using *Alcaligenes eutrophus* 335 strain B9 (ATCC 17697), *Pseudomonas putida* strain JJ 103 and *Pseudomonas sp.* B13 (DSM 624). Mainly halo and alkyl substituted benzoic acids have been studied,[9] and the *cis*-diols products of both normal and *ipso* benzoic acid are available commercially.

In general the microbial oxidation appears consistent with regard to the regio- and stereochemistry of the resulting diols, and a variety of substituents on the aromatic ring are tolerated by the enzyme. In addition to the stereo- and regiospecificity of this reaction, high enantiomeric purity is found with most of the cases studied.[11] This factor alone contributes to the great importance of the arene-*cis*-diols as chiral synthons for enantioselective synthesis of pharmaceutical products. The range of derivatives that are available by fermentation coupled with the unusually rich and potentially extremely useful functional content of these diols finds expression in stereospecific organic synthesis.

The new field of biocatalysis combines the skills of microbiology and the art of synthesis to arrive at highly efficient preparation of optically pure compounds. The expression of diols as synthons has intensified in the last 4-5 years through the efforts of Ley, Hudlicky and others. The following discussion focuses on the review of synthetic potential of these metabolites.

Reactive Tendencies. Exposure of arene-*cis*-diols to acid produces the dehydration of these compounds to more thermodynamically stable aromatic phenols. This reaction has not been studied thoroughly from a point of view of chiral synthesis, since a compound with no optical activity is produced from a chiral starting material. However, this reaction is useful in synthesis of substituted phenols that may be difficult to prepare by other methods. It has recently been reported a biocatalytic route to catechol from D-glucose. Catechol is a molecule from which a variety of pharmaceuticals, pesticides, flavors, and polymerization inhibitors are industrially derived.[29]

The dehydration process proceeds through the most stable carbocation intermediate (Figures 6 and 8). Thus, the regiochemistry of the dehydrated product of the arene-*cis*-diols can be predicted. In the case of alkyl arene-diols, the major product is the 2-alkylphenol.[14,16,19,23,40] In the case of electron-withdrawing groups, like trifluoromethyl- the major product is the 3-trifluoromethylphenol,[23] Table 2.

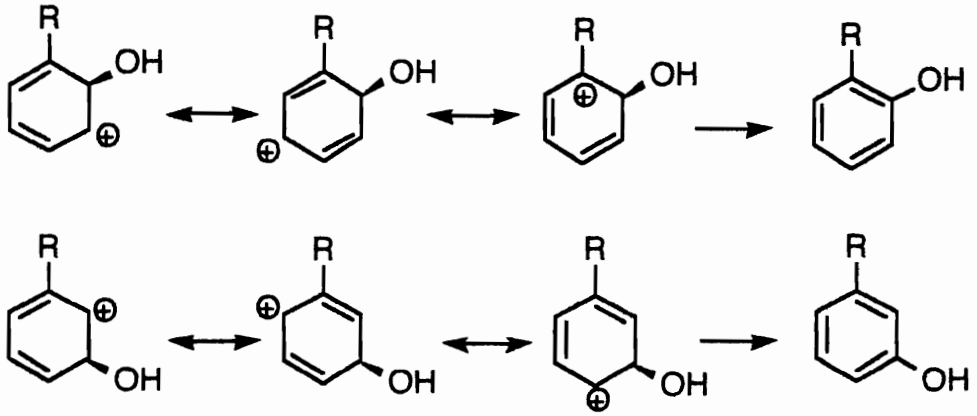
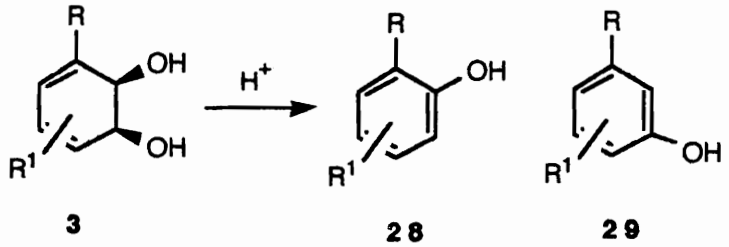


Figure 6. Acid Dehydration of 1-Substituted-arene-*cis*-diols.



3 28 29

Figure 7. Dehydration of Disubstituted Arene-*cis*-diols.

Table 2. Dehydration of Simple Monocyclic Arene-*cis*-Diols (Figure 6 and 7)

R	R1	Conditions	Product(s)	Ratio	Ref.
H	H	0.001M aq. HCl	Phenol		19
Me	H	1M aq. HCl	2-OH	Major	14
Et	H	3M aq. HCl	2-OH, 3-OH	40:1	16
Ph	H	Et_2O, cat. HCl	2-OH, 3-OH	2:1	33
F	H	Aq. HCl	2-OH, 3-OH	60:1	40
CF_3	H	2M aq. HCl	3-OH		40
Me	4-Cl	1M aq. HCl	2-OH	Major	40
			3-OH	Minor	34
Me	4-Me	Et_2O, cat. HCl	2-OH		41
Me	3-Me	spontaneous	2-OH		41
Cl	6-Cl	2M aq. HCl	2-OH, 3-OH	4:17	31
			3-OH, 5Cl	1	
COOH	4-CF_3	Heat, acid	3-OH		35

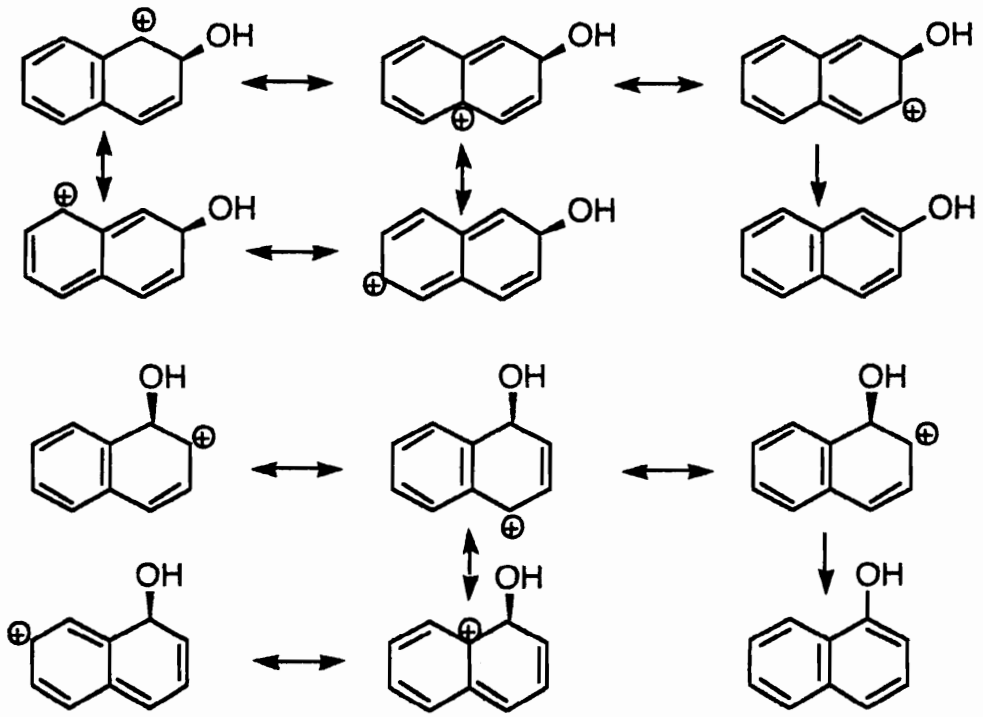


Figure 8. Dehydration of Naphthalene-*cis*-diols.

The dehydration of disubstituted arene-*cis*-diols **3** (R1≠ H), to give phenols **28** and **29**, has not been studied thoroughly, Figure 7. Only a few cases of this type have been reported.[31,34,35,40] The acid-catalyzed dehydration of *cis*-diols is 50 to 100 times faster than the corresponding *trans*-isomers, due to the antiperiplanar relationship of the hydrogens and hydroxyl groups. This elimination reaction is quantitative and usually only one regioisomer is formed, but there are reported instances where some rearrangement occurred to give a mixture of isomers,[31,42,40] Figure 9.

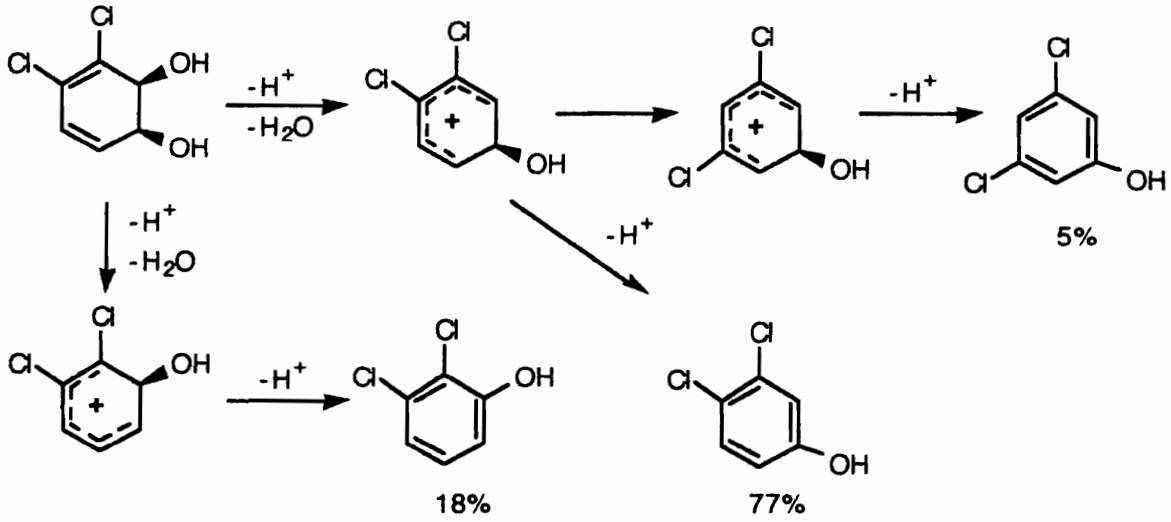


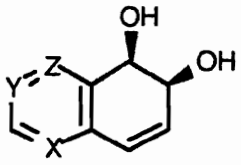
Figure 9. Dehydration of 3,4-Dichloro-1,2-Dihydroxy-3,5-Cyclohexadiene.

Dehydration of polycyclic arene-*cis*-diols occurs in a similar fashion to the monocyclic arene diols, Table 3. The results obtained for all polycyclic dihydro-diols are easily rationalized in terms of carbonium-ion stability. Figures 6 and 8 show the resonance structures of carbonium ion intermediates in the dehydration process. In the monocyclic diols, carbonium ions are more stable when the meta hydroxyl group is eliminated; in bicyclic systems carbonium ions are more stable when the β-hydroxyl is eliminated. Experiments with different 1,2-dihydroxy polycyclic compounds, showed that they rearrange to the stable α-hydroxypolycyclic compound.[27]

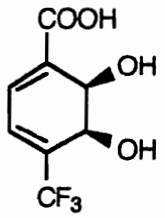
Table 3. Dehydration of Some Polycyclic Arene-*cis*-Diols

Arene-cis-Diol	Product(s)	Ratio	Ref.
Naphthalene	1-OH >95		27
8-Cl naphthalene	1-OH major		42
	2-OH minor		
Anthracene	1-OH, 2-OH	90:10	30
Phenanthrene (3,4)	2-OH > 98%		30
Benzofuran (1,2)	2-OH major		43
	1-OH minor		
Benzofuran (2,3)	1-OH, 2-OH	61:39	43

Heterocyclic *cis*-diols **31-35**, Figure 10, are more difficult to dehydrate. It is necessary to heat the dihydroquinolinediol **4** to 150 °C in order to cause its aromatization. This diol suffered no change after three weeks in a mixture of acetone/trifuoroacetic acid, at room temperature. The increased stability of these diols may be due to the presence of the fused heterocyclic rings (pyridine, pyrazine and pyrimidine).[29] Acid dehydration of diol **30**, gave only 4-trifluoromethyl-3-hydroxybenzoate, but the *trans*-diol of **30** gave a mixture of two phenols. The regiochemistry of the dehydration in *cis*-diol **30** was attributed to the influence of the strong electron-withdrawing properties of the 4-substituent in directing the course of the aromatization.[36]



31-35



30

	X	Y	Z
31	CH	CH	CH
32	N	CH	CH
33	CH	N	CH
34	N	N	CH
35	N	CH	N

Figure 10. Dehydration of Heterocyclic-*cis*-diols.

2-Hydroxy benzoic acids are formed by aromatization of *ipso*-benzoic acid-diols. Dehydration along with decarboxylation was observed for some *ipso*-benzoic acid-diols, and a mixture of substituted phenols and substituted salicylic acids was obtained.[38] Dehydration of the normal benzoic acid diols gives mainly the meta-hydroxy benzoic acid.[37] It is concluded that depending on the type of benzoic acid diol, ipso or normal, the regiochemistry of the phenol may be predicted to be ortho or meta.

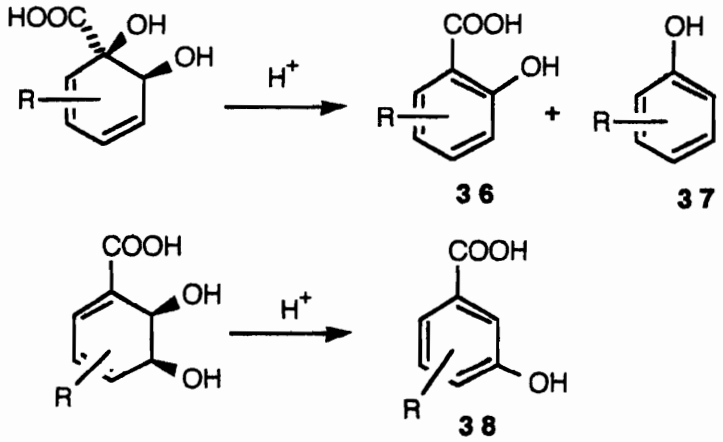


Figure 11. Dehydration of "ipso" Benzoic Acid-*cis*-diols.

Dehydration in alkaline medium has also been investigated. Heating the diols in the presence of aqueous or alcoholic bases will also accomplish the aromatization. Some changes in regioselectivity were observed in alkaline dehydration. Acid dehydration of flurobenzene-diol gives mainly ortho-fluorophenol, but under alkaline conditions a 2.4:1 mixture of ortho- and meta-fluorophenols is observed.

Catechols are formed by dehydrogenation of arene-diols. 3-Substituted arene-diols **39** can be dehydrogenated to 3-substituted catechols **40**. Although two chiral centers and the optical activity are lost during this transformation, this sacrifice might provide a worthwhile pathway to substituted catechols that could otherwise be very difficult to obtain by other means.[28]

This reaction can be accomplished either enzymatically or chemically. A partially purified preparation of diol dehydrogenase, obtained from the wild-type strain of *Pseudomonas putida*,[41] when incubated with *cis*-arene-diols **39**, under anaerobic conditions leads to the formation of the corresponding 3-substituted catechols **40**.[44] Catechol dioxygenase, isolated from *Alcaligenes eutrophus* B9,[45] not only oxidized halobenzenes to halocatechols, but converted the *ipso* diol **41** to the corresponding catechol **42**, when used in partially purified form, Figure 12.[45]

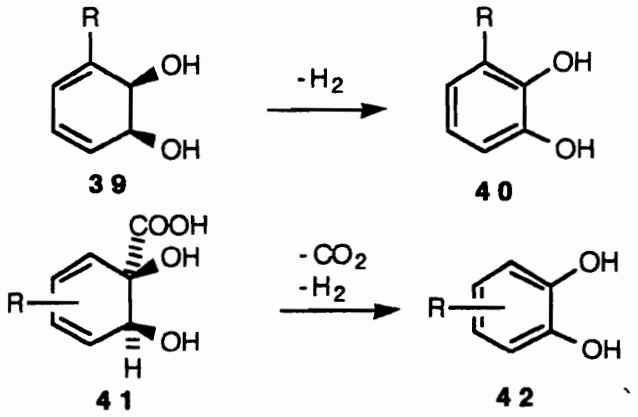


Figure 12. Oxidation of Arene-*cis*-diols to Catechols

Chemically, arene-*cis*-diols have been dehydrogenated by refluxing the diol in water in the presence of catalytic amounts of palladium on carbon.[46] A mixture of catechol and other dehydrogenated arene-diols is obtained by hydrogenation in the presence of palladium and barium sulphate, platinum or nickel, see Figure 13.[19]

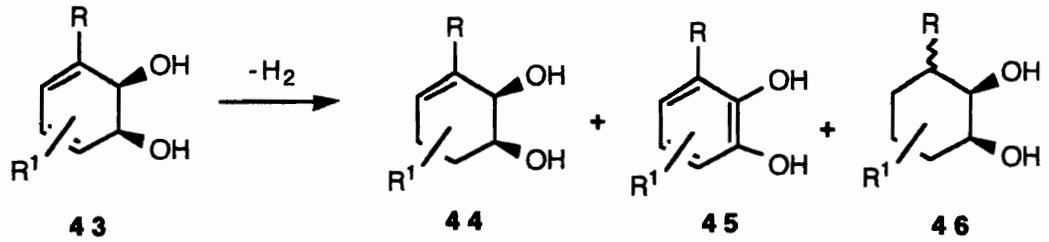


Figure 13. Dehydrogenation of Arene-*cis*-diols.

Much attention has been focused in trying to define the reactivity of different arene-*cis*-diols in Diels-Alder and other cycloaddition reactions.[21] Several specific applications resulting from these studies have been reported, and more applications will likely follow.[47,48]

The unsaturated system in arene-*cis*-diols typically behaves as the diene in Diels-Alder reactions, but there have been some cases where this system also behaves as the dienophile (see also Section II.2). Both free and protected diols have been studied thoroughly in this reaction. Different protecting groups (**47-52**) have been used with arene-*cis*-diols. The more popular acetonide **50** has been utilized in synthetic applications because of its relative

stability with respect to elimination reactions, and also because of the sterically hindered of the *beta-* face. Some examples are shown in Figure 14.

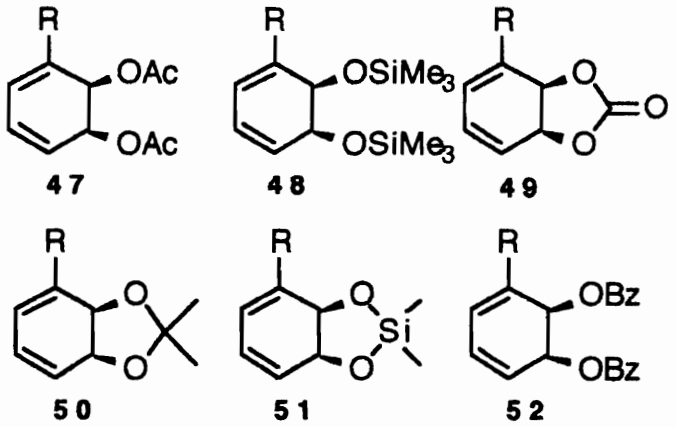


Figure 14. Some Examples of Protected Arene-*cis*-diols.

The addition of N-ethyl- and N-phenylmaleimide **54** to the diols has been studied thoroughly.[49,50] Unprotected benzenediol produced mainly the *syn* addition product; similar results were obtained when the diol was protected with linear groups (such as -Ac, -Bz, -SiMe3).[49] However, when the diols were protected with groups forming a rigid ring, such as the acetonide, the facial selectivity increased.

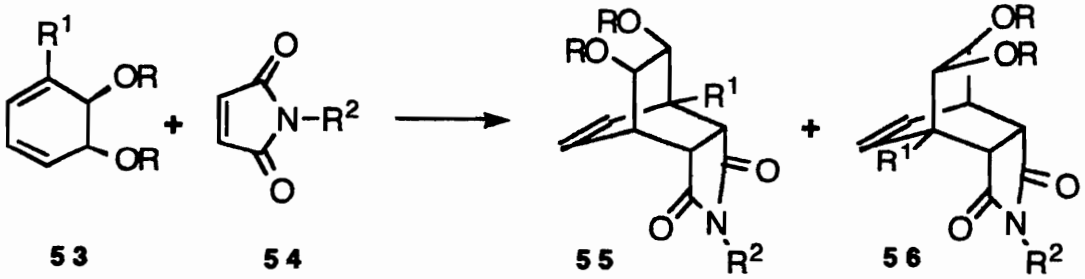


Figure 15. Reaction of Arene-*cis*-diol Derivatives with N-Substituted Maleimides.

Table 4. Reaction of Arene-*cis*-diol Derivatives with N-Substituted Maleimides

R	**R1**	**R2**	**Solvent**	**Yield**	**Syn-**	**Anti-**	**Ref.**
H	H	Ph	$CHCl_3$	High	94	6	49
Ac	H	Ph	$CHCl_3$	Good	88	12	49
$SiMe_3$	H	Ph	$CHCl_3$	Good	100	0	49
CMe_2	H	Ph	$CHCl_3$	-	60	40	49, 50

$SiMe_2$	H	Ph	$CHCl_3$	-	65	35	49
CMe_2	H	Ph	PhH	86	52	48	49,50,51
CMe_2	H	Ph	H_2O	95	33	67	49,50
CMe2	H	Ph	$(CH_2OH)_2$	95	27	73	50
CMe_2	H	Et	$CHCl_3$	99	50	50	49
CMe2	H	Et	PhH	96	39	61	50,51
CMe_2	H	Et	H_2O	79	18	82	50
CMe_2	H	Et	$(CH_2OH)_2$	73	12	88	50
CMe_2	CF_3	Et	PhH	88	43	57	50,51,52

Gibson reported the *anti* addition adduct from the cycloaddition of maleic anhydride and acetylated toluene-diol, and ethylbenzene,[14,16] but Burnell reported that careful analysis of the nmr spectra of these adducts and comparison with his results, proved that the compounds that Gibson obtained were the *syn*-adducts.[49] However *anti*-addition of 4-(p-bromophenyl-*0*-1,2,4-triazine-3,5-dione was established conclusively by X-ray analysis.[53] Ketenes have also been added to arene-*cis*-diols in an anti-fashion (Figure 19).[50] *Anti*-addition is observed when 4-aryl-1,2,4-triazoline-3,5-diones are aded to protected arene-*cis*-diols,[52,53] while *syn*-addition is observed with free diols.[13]

The stereochemistry of the addition, *syn* or *anti*-mode, depends on the nature of the arene-*cis*-diol protecting group, the nature of the substrate, and the reaction conditions. Precise definition allows the development of appropriate conditions to control the stereochemistry of the cycloaddition, Figure 16 and Table 5 show examples of the reaction of substituted arene-*cis*-diols and linear dienophiles. In all of these cases, the mode of the addition was found to be *anti*.

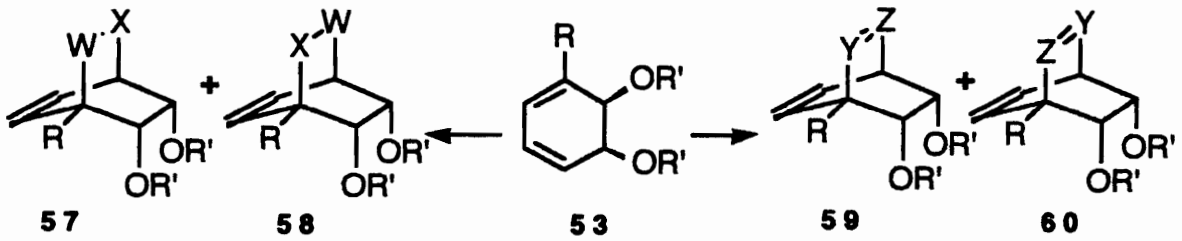


Figure 16. Diels-Alder Reactions of Arene-*cis*-diols with Linear Dienophiles.

Table 5. Diels-Alder Reactions of Arene-*cis*-diols with Linear Dienophiles

R	W	X	Y	Z	Yield%	Ref.
H	CH_2	CHCOOMe	-	-	80	54
H	CHCN	CHCN	-	-	52	54
H	CHCOOMe	CHCOOMe	-	-	70	54
H	$C(CN)_2$	$C(CN)_2$	-	-	71	54
H	NCOOEt	NCOOEt	-	-	100	54
H	-	-	CH	CCOOMe	86	54
H	-	-	CCOOMe	CCOOMe	70	54
H	PhN	O	-	-	70	51,54
CF_3	PhN	O	-	-	90	51,52
CF_3	-	-	CH	CCOOMe	54	52
CF_3	-	-	CCOOMe	CCOOMe	83	51,52
H	NH	O	-	-	89	49
H	Ph_2CC	O	-	-	24	50
H	MePhCC	O	-	-	0	50
H	Ph_2CC	O	-	-	77	50

The more electron rich double bond of the protected trifluorotoluene-*cis*-diol **61** acts chemoselectively as a dienophile in the addition to cyclopentadiene **62**, Figure 17.[52] The reactive nature of the ketal **64** as diene and dienophile was reflected in the ready dimerization of the compound at low temperature to give a stable [4+2] adduct **65**, in an *anti*-mode addition.[52]

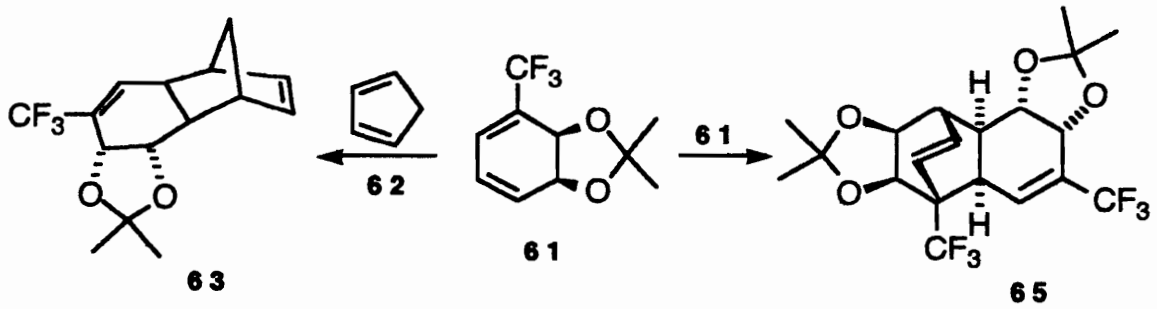
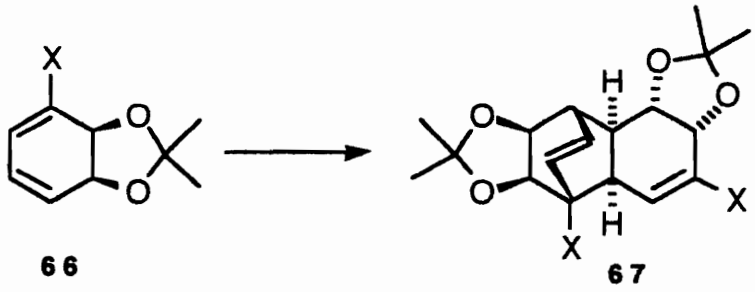


Figure 17. Arene-*cis*-diols as dienophiles.

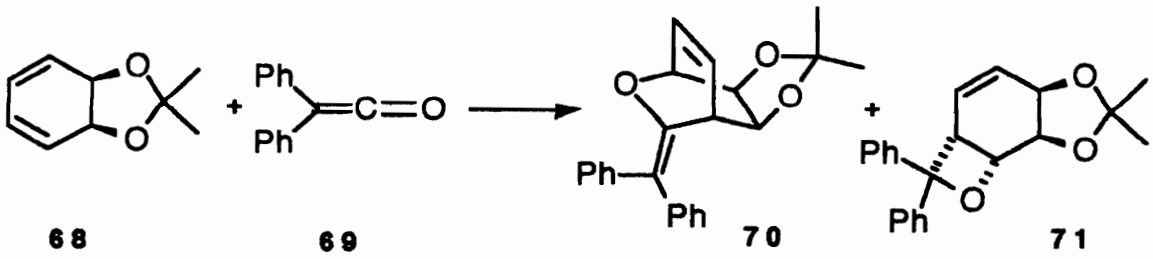
Halogenated arene-*cis*-diol acetonides **66** dimerize in a completely stereoselective fashion to highly stable crystalline dimers **67**, Figure 18.[55,56] Acetonide protected arene-*cis*-diols **66** have been reported to dimerize from temperatures as low as -30°C to temperatures as high as 110°C. Dimerization is retarded by storage of acetonides as dilute solutions in methylene chloride at -30°C.[56]



66 **67**

Figure 18. Dimerization of Haloarene-*cis*-diol Acetonides.

Diphenylketene **69** was added to the protected parent diol **68** and a mixture of [4+2] and [2+2] adducts was obtained (**70** and **71**, respectively), both of them *anti* to the protecting group.[51] It was shown that no interconversion between the two adducts **70** and **71** took place, and that the [4+2] cycloaddition appeared to proceed through a non-polar transition state, in contrast with previous report on [4+2] cycloaddition of ketenes to 1,3-dienes.[57]



68 **69** **70** **71**

Figure 19. Addition of Diphenylketene to Benzene-*cis*-diol Acetonide.

Ethyldiazoacetate and dichlorocarbene were added to the protected arene-diol **72** with only one type of regioisomeric cyclopropane observed (**74**).[50] These carbeneoids (**73**) added to the less hindered face of the cyclic dienes. When dichlorocarbene was added to the protected fluorobenzene-*cis*-diol, two products were observed (**74** and **75**). The

addition took place in a ratio of 2:1 at both olefinic sites, the fluoropropane **75** was the minor compound, both cycloadducts **74** and **75** contained *anti*-stereochemistry.[50]

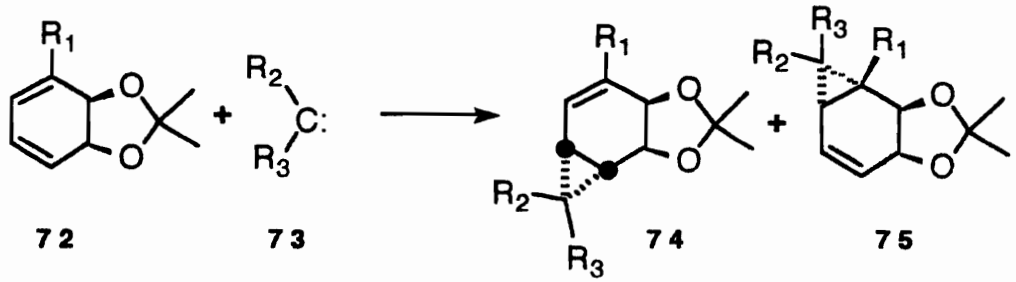


Figure 20. Addition of Carbenoids to Arene-*cis*-diol Acetonides.

R_1	R_2	R_3
H	Cl	Cl
H	H	CO_2Et
CF_3	Cl	Cl
F	Cl	Cl

The parent compound, benzene-*cis*-diol **76** was subjected to photosensitized dimerization, to yield a mixture of dimers from which tetraol **77** was isolated by recrystallization.[59] Tetrol **77** was deoxygenated to **78**, a compound with some interesting physical and chemical properties, Figure 21.[59]

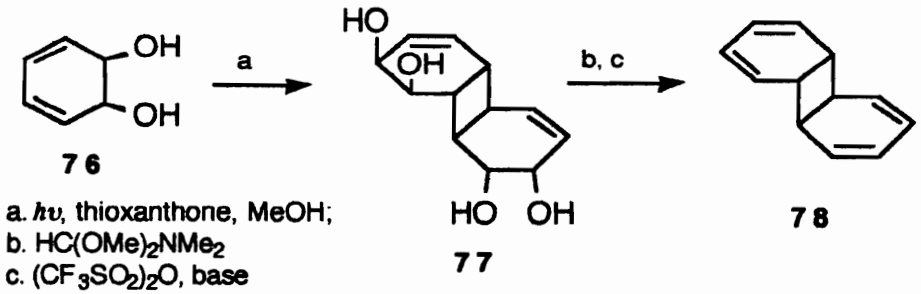
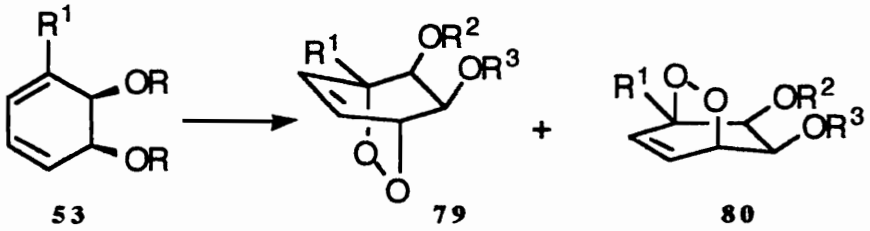


Figure 21. Dimerization of Benzene-*cis*-diol.

Synthetic utility. The unsaturated system of the arene-*cis*-diols offers advantage in further oxygenation to diverse oxygenated cyclohexane derivatives, such as carbohydrates, conduritols and cyclitols, including aminocyclitols and inositols.[59]

The incorporation of further oxygen into the cyclohexane derivatives can be accomplished with singlet oxygen, peroxy acids or osmium tetroxide. Singlet oxygen has been added to arene-*cis*-diols either by photooxygenation using light in the presence of a sensitizer, or chemically-generated using triphenylphosphite and ozone.[18,60-63] A mixture of *endo* and *exo* peroxides (**79** and **80**) is observed when oxygen is added to the free diols (benzene and toluene). Usually *anti* addition predominates (**79** > **80**), but when oxygen is added to the protected diol only the one stereoadduct is observed (**80**), Figure 22 and Table 6.



53 **79** **80**

Figure 22. Photooxygenation of Arene-*cis*-diols.

Table 6. Photooxygenation of Arene-*cis*-diols.

R^1	R	endo	exo	Yield	Ref.
H	CMe_2	100	-	95	60
H	H	75	25	-	61
H	$SiMe_2tBu$	100	-	32	62
CH_3	H	60	40	-	62
CH_3	CMe_2	100	-	84	18
Cl	CMe_2	100	-	93	63

These peroxides **81** can be reductively cleaved by thiourea in methanol or aluminium amalgam[18] to give 1,4-diols **82**, which are precursors of conduritol A-1.[60,61] Base-catalyzed opening of peroxides gives 4-hydroxy-unsaturated ketone **83**, which after deprotection gave dehydroconduritols. Formation of diepoxides was observed by addition of cobalt-meso-tetraphenylporphyrin.[60]

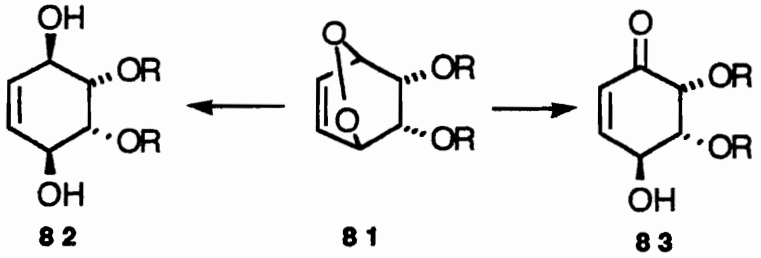


Figure 23. Opening of Bicyclic Peroxides.

Another method that has been used extensively to introduce oxygenated functionalities to the arene-*cis*-diols is epoxidation. This reaction is carried out in a chlorinated solvent, and *m*-chloroperoxybenzoic acid is usually the oxidizing agent, but other reagents have also been used.[64,65,72]

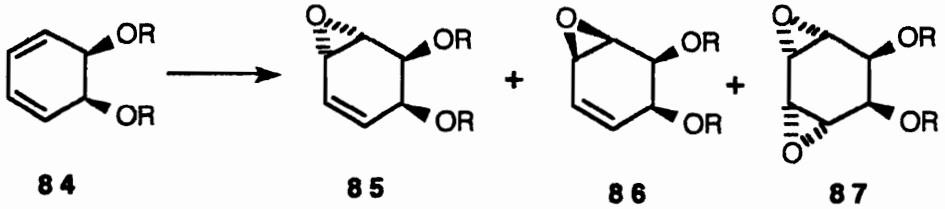


Figure 24. *alpha*- and *beta*-Epoxidation of Arene-*cis*-diols.

Epoxidation of protected benzene-*cis*-diol **84** produced a mixture of α- and β-epoxides **85** and **86**, respectively, as shown in Figure 24 and Table 7. When the diol is protected with diphenyl-t-butylchlorosilane, a good selectivity is observed, and the α-diepoxide **87** is also isolated. Selectivity is not as good with other protecting groups, Table 7.

Table 7. Ratios of Stereoisomers formed in the Epoxidation of the Protected Diol 1 (Scheme 17)

R	Yield	Ratio 85:86	Ref.
Ac	87	86:14	64
Bz	90	81:19	64
CO	57	82:18	65
$SitBuPh_2$	82	94:6	64

Cleavage of the weak oxygen-oxygen bond by photolysis of endoperoxide **81a** in benzene solution led to a 3:1:1 mixture of epoxyketones **88** and **89** and the diepoxide **87**.

The same diepoxide was the major product of the catalyzed rearrangement of endoperoxides **81a** and **81b** using cobalt(II) tetraphenylporphyrin (TPP).[62,64]

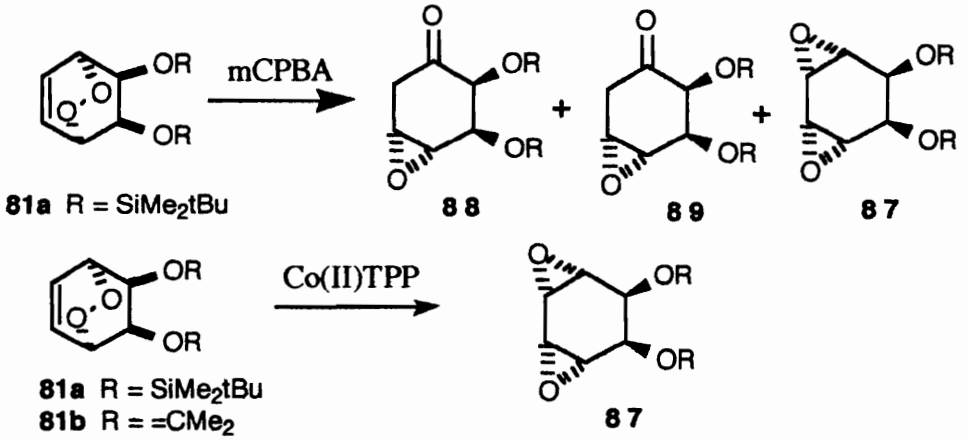


Figure 25. Preparation of Epoxides *via* Peroxides.

Epoxidation of the free benzene-*cis*-diol affords the expected β-monoepoxide by hydroxyl directed top face epoxidation.[67] Similar face selectivity is observed when isopropylidene-derivatives are epoxidized with perbenzimidic acid.[68]

Chemoselective epoxidation of 3-methyl arene-*cis*-diols leads to the oxidation of the more electron rich olefin, in this case the more substituted double bond. A mixture of α- and β-monoepoxides was obtained in the epoxidation of protected toluene-*cis*-diol. In the case of halo-benzene-diols, the oxidation also occurs at the more electron rich double bond, in this case, the less substituted double bond, see Figure 26 and Table 8. Complete regio- and stereoselectivity can be achieved when halo- and alkyl-benzene-*cis*-diols are protected as acetonides or carbonates.

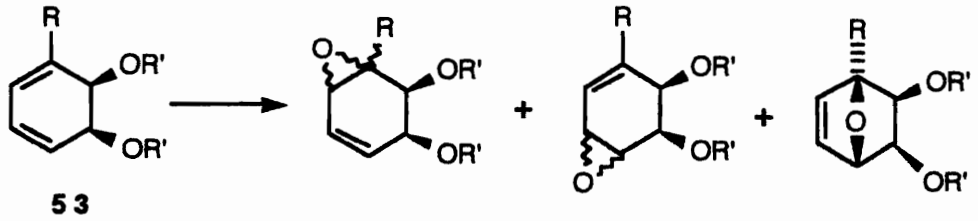


Figure 26.

Table 8. Regio- and Stereo-electivity in the Epoxidation of 3-Substituted Arene-*cis*-diols (Figure 26)

Product Ratios

R	R'	90a	90b	91a	91b	92	Yield	Ref.
CH_3	Ac	80	20					69
CH_3	-CMe_2-	100	0				40	69
F	H				66	34		67
F	-CMe_2-			100			51	40
F	-CO-			100			36	40
F	Bz			60	40		34	40
Cl	-CMe_2-			100			89	71
Br	-CMe_2-			100			82	70

Osmylation has been applied to halobenzene-diol acetonides **66** in the synthesis of Conduritol E[72] and (+)- and (-)-pinitol,[71] Figure 27. Osmylation occurs only on the *alpha*-face of the diene, opposite side of the acetonide group. Halobenzene diol acetonides **66** (X= Cl and Br) are selectively oxidized on the electron-rich olefin to give diol **93**, Figure 27.[72]

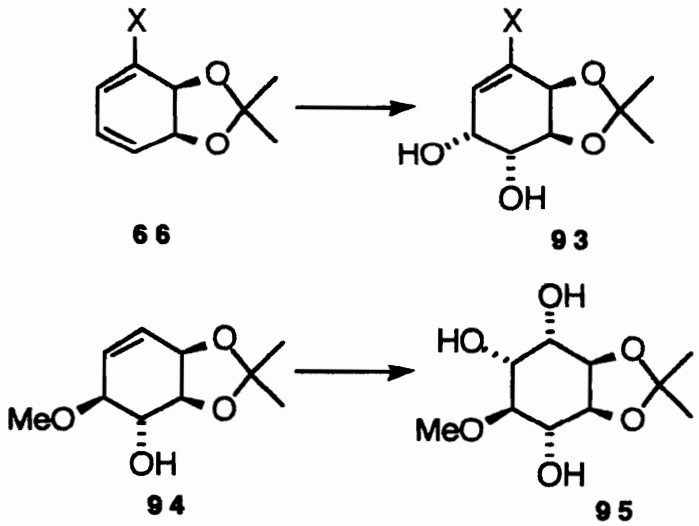


Figure 27. Osmylation of Halobenzene-*cis*-diol Acetonides.

A strategy to remove two carbons of the arene-diol and retain the diol moiety was employed for the preparation of cyclopentenone **98**, an important intermediate in the synthesis of prostaglandins, Figure 28.[18] This strategy employed ozonolysis in either dichloromethane or ethyl acetate at -78°C. Diacetate **47** was ozonized to a stable keto aldehyde **96**, and acetonide **50** was ozonized to hemiacetal **97** which was converted to synthon **98**. Another method to prepare synthon **98**, is by ozonolysis of chloroacetonide **99**, and further manipulation of **99**. This new method is superior in yield to the previous one.

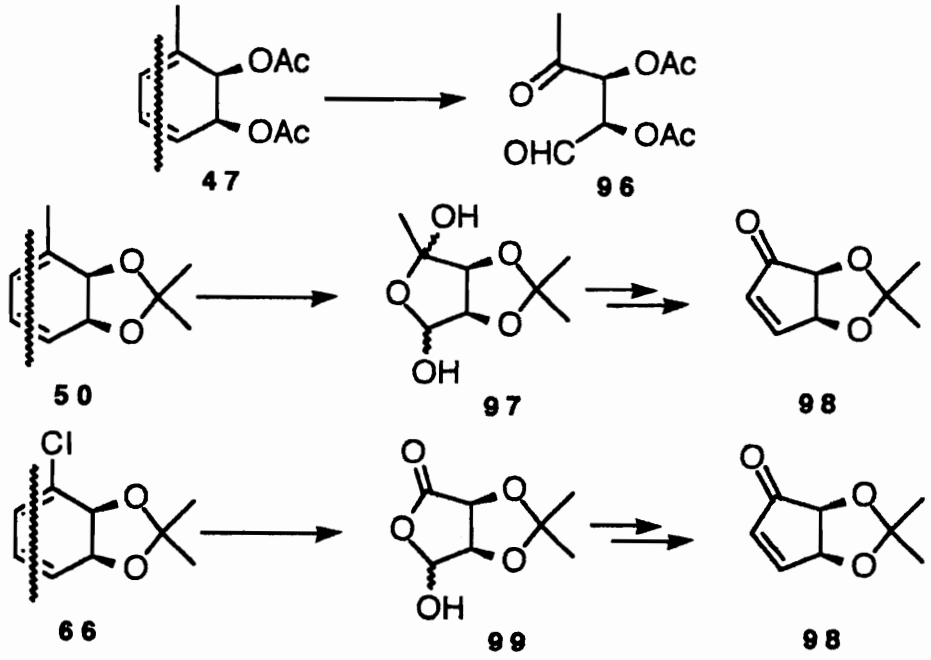
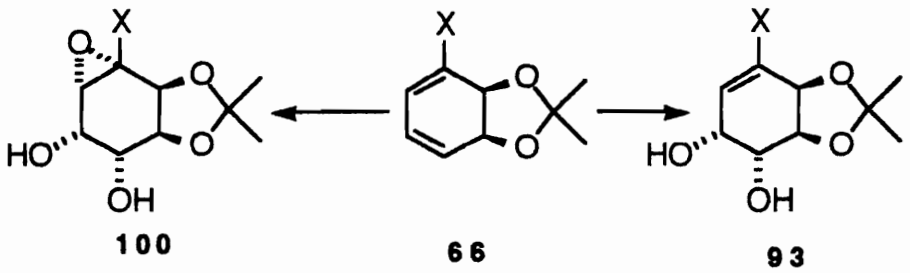


Figure 28. Ozonolysis of Arene-*cis*-diols.

Exposure of haloacetonide **66** to aqueous $KMnO_4$ at low temperature gives diol **100** as the major product, while diol **93** is the major product at higher temperatures, Figure 29.[74] The formation of the haloepoxide **100** is unusual. These haloepoxides are remarkably stable and have been transformed to a great variety of oxygenated compounds.



100 66 93

Figure 29. Oxidation of Haloarene-*cis*-diol Acetonides with Potassium Permanganate.

Synthetic Applications. In the last five years arene-*cis*-diols have been used as chiral synthons. Table 9 summarizes synthetic applications of arene-*cis*-diols directed towards the total synthesis of natural products. The structure of the synthetic target is given on the first column. Key steps of the synthesis are shown in the second column, and the principal author's name and reference are given in the last column.

Table 9. Application of Arene-*cis*-diols in the Synthesis of Natural Products.

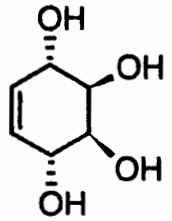
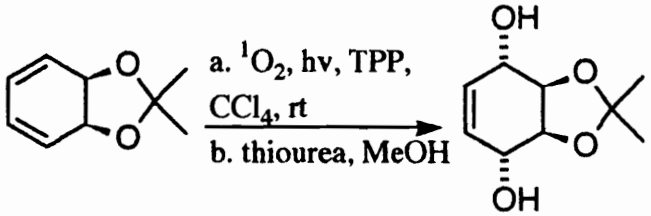
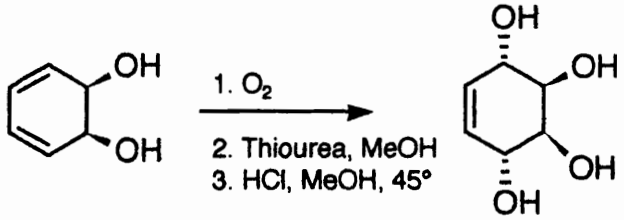
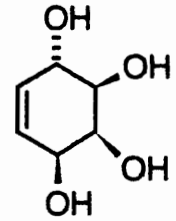
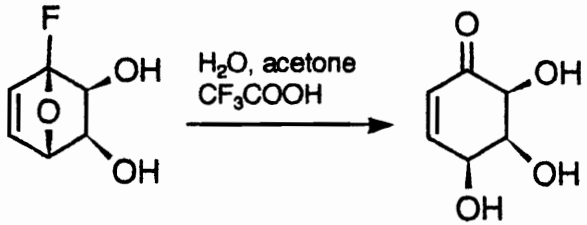
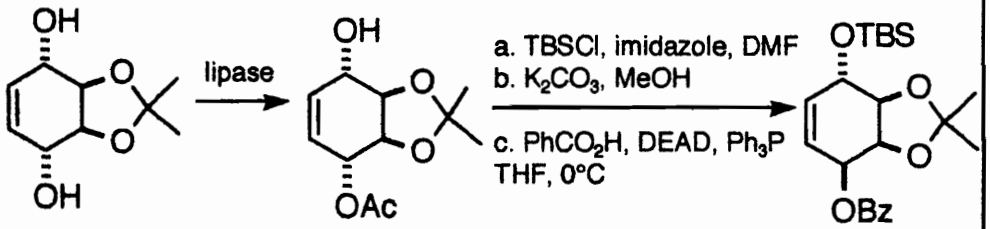
 Conduritol A	 a. $^1O_2$, hv, TPP, CCl_4, rt; b. thiourea, MeOH	Balci 20
	 1. O_2; 2. Thiourea, MeOH; 3. HCl, MeOH, 45°	Carless 61 Hudlicky 63,70
 (+)-Conduritol C	 H_2O, acetone CF_3COOH	Carless 67
	 lipase; a. TBSCl, imidazole, DMF b. K_2CO_3, MeOH; c. $PhCO_2H$, DEAD, Ph_3P THF, 0°C	Johnson 75

Table 9. Application of Arene-*cis*-diols in the Synthesis of Natural Products.

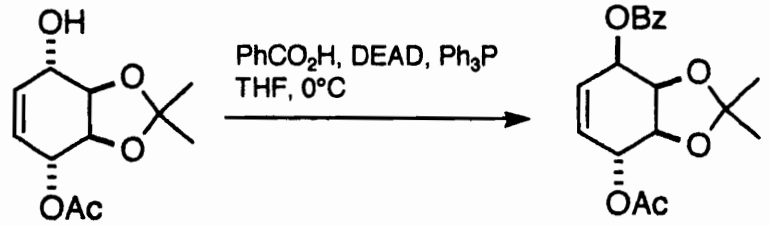
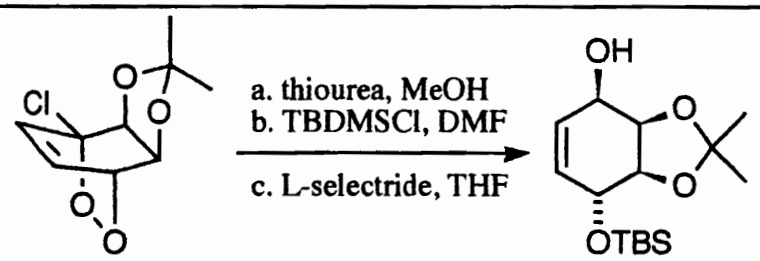
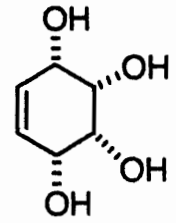
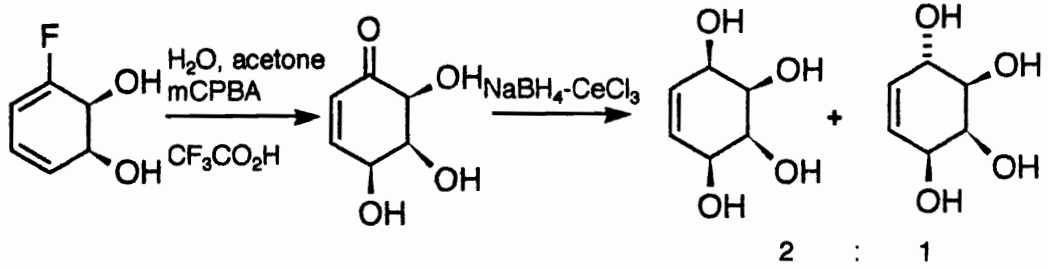
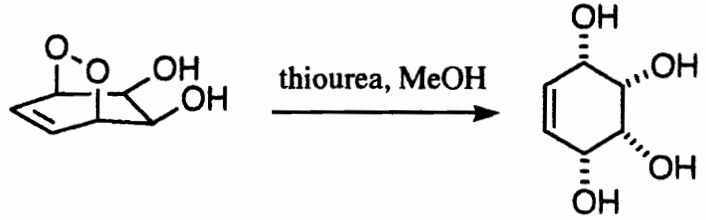
(-)-Conduritol C		Johnson 75
		Hudlicky 70
 Conduritol D		Carless 67
		Carless 67

Table 9. Application of Arene-*cis*-diols in the Synthesis of Natural Products.

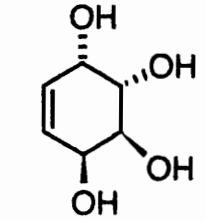
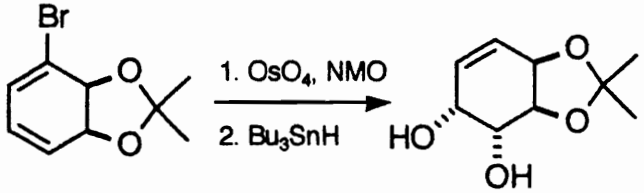
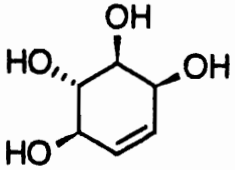
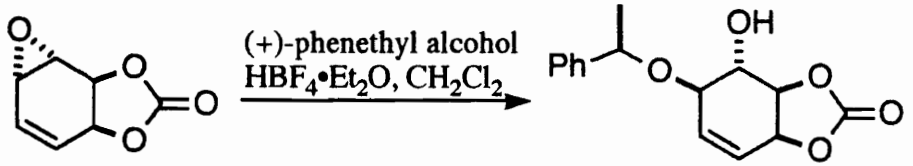
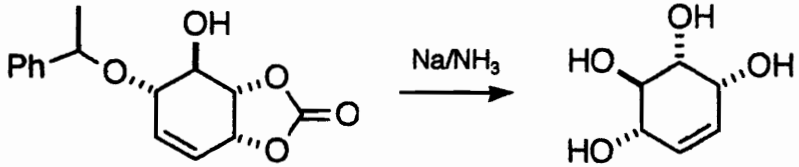
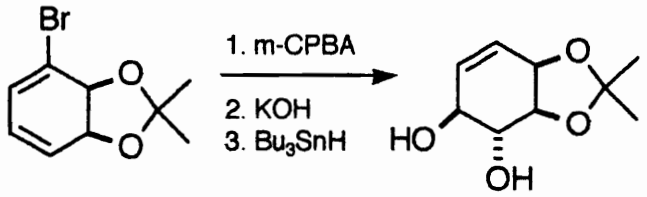
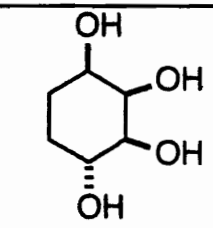
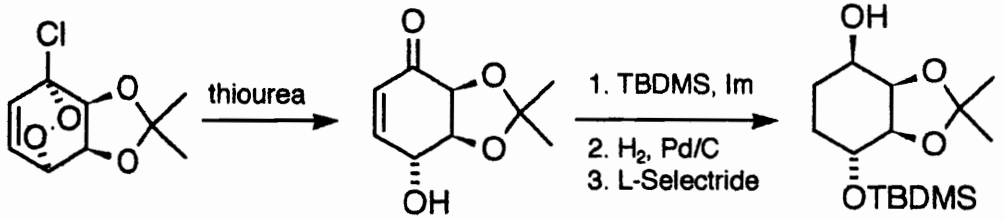
 Conduritol E	 1. OsO_4, NMO; 2. Bu_3SnH	Hudlicky 72
 (+)-Conduritol F	 (+)-phenethyl alcohol; $HBF_4 \cdot Et_2O$, CH_2Cl_2	Ley 76,77
	 Na/NH_3	Ley 76,77
	 1. m-CPBA; 2. KOH; 3. Bu_3SnH	Hudlicky 72
 (-)-Dihydro Cond C	 thiourea; 1. TBDMS, Im; 2. H_2, Pd/C; 3. L-Selectride	Hudlicky 78

Table 9. Application of Arene-*cis*-diols in the Synthesis of Natural Products.

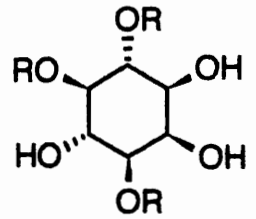
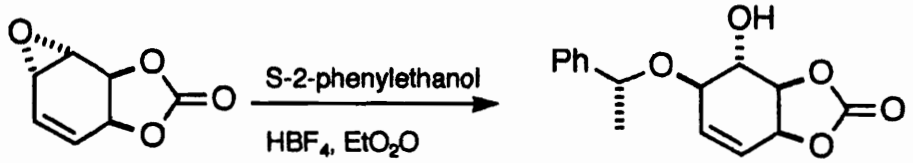
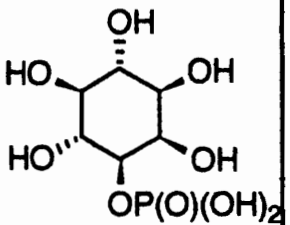
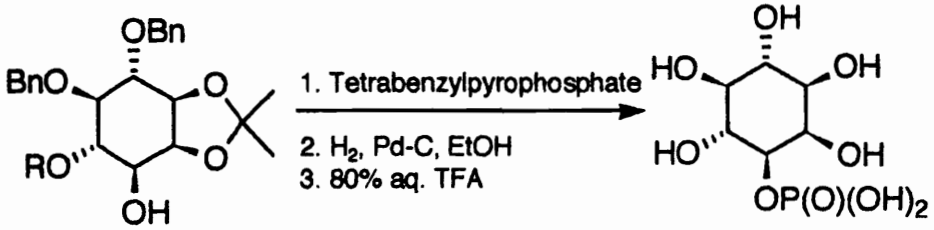
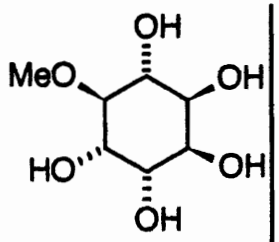
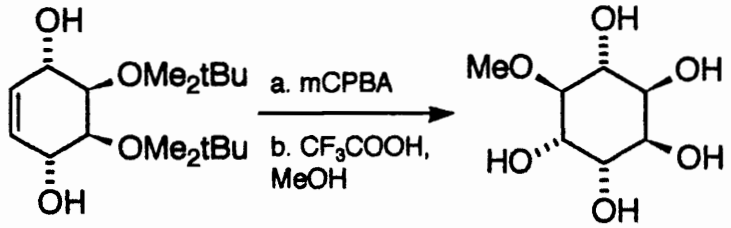
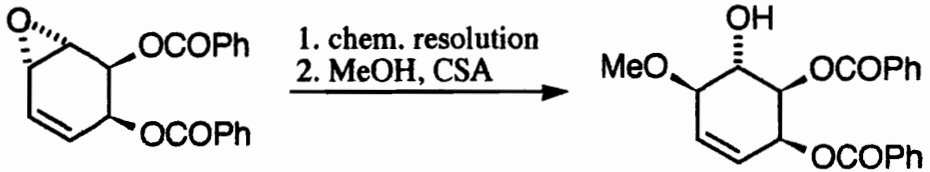
 R= $P(O)(OH)_2$ (D)-(-)-1,4,5- IP_3	 S-2-phenylethanol; HBF_4, EtO_2O (+ 3,4 diasteromer)	Ley 65,77 80,81
 inositol-1-phosphate	 1. Tetrabenzylpyrophosphate; 2. H_2, Pd-C, EtOH; 3. 80% aq. TFA	Ley 65,77 81
 (±)-Pinitol	 a. mCPBA; b. CF_3COOH, MeOH	Carless 82
	 1. chem. resolution; 2. MeOH, CSA	Ley 64,77 83

Table 9. Application of Arene-*cis*-diols in the Synthesis of Natural Products.

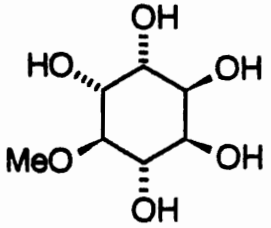
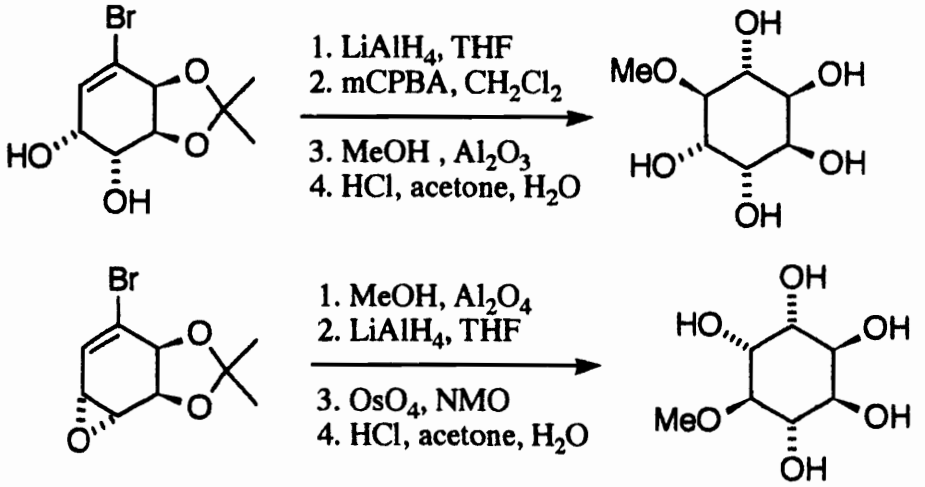
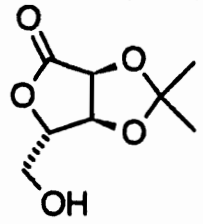
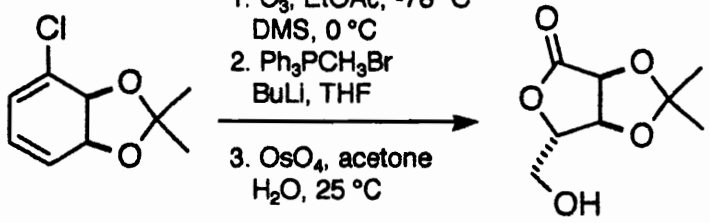
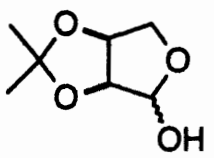
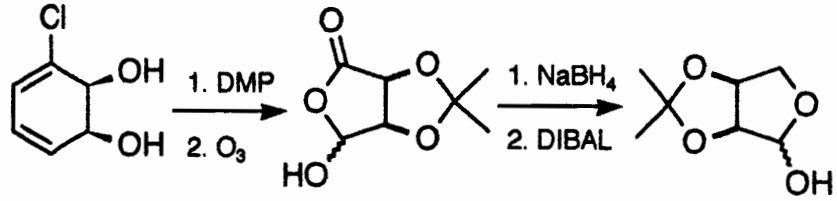
(+)-Pinitol  (-)-Pinitol		Hudlicky 63,71
 L-ribonic-γ-lactone (acetonide)		Hudlicky 84
 L-erythrose (acetonide)		Hudlicky 85

Table 9. Application of Arene-*cis*-diols in the Synthesis of Natural Products.

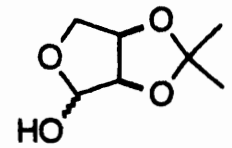
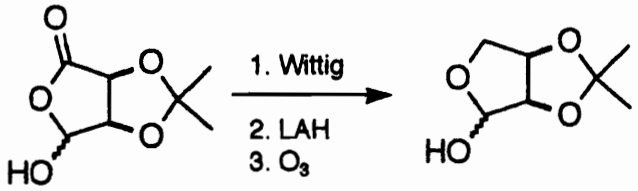
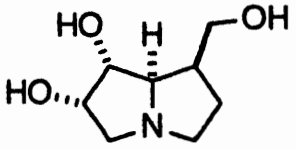
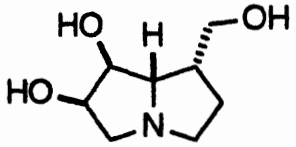
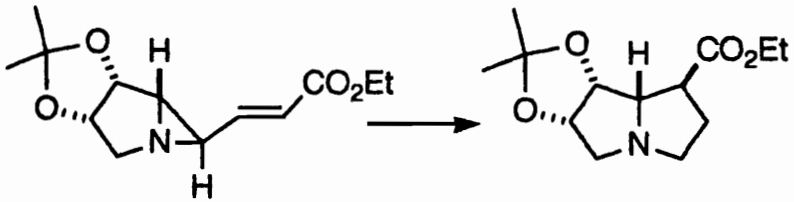
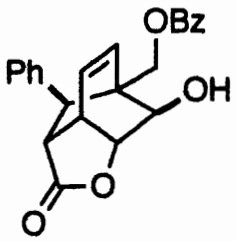
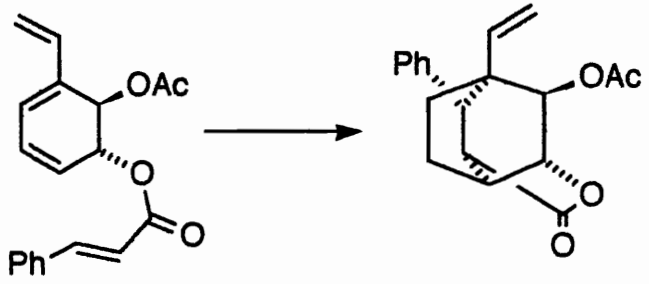
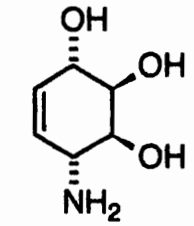
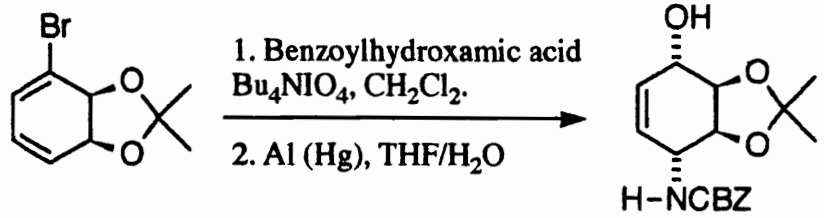
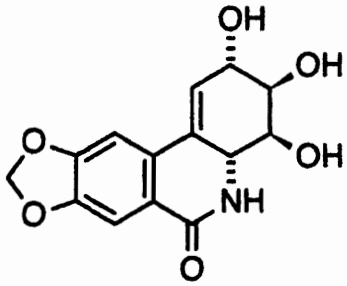
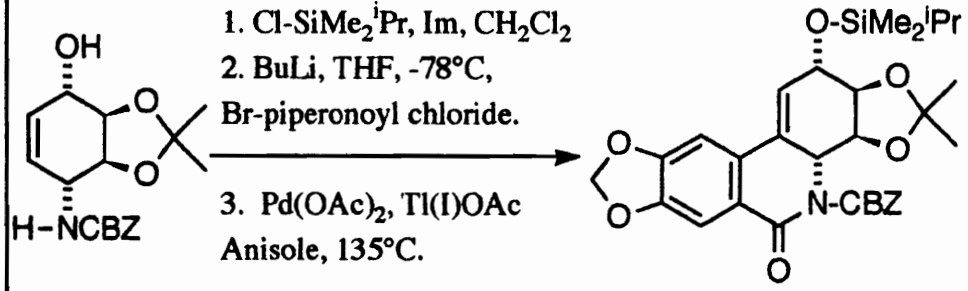
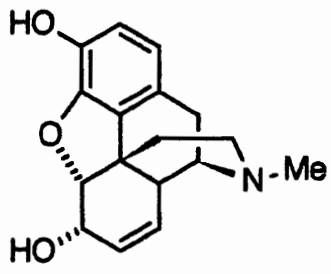
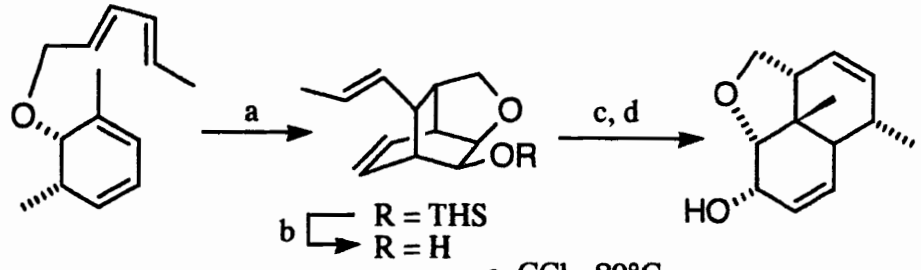
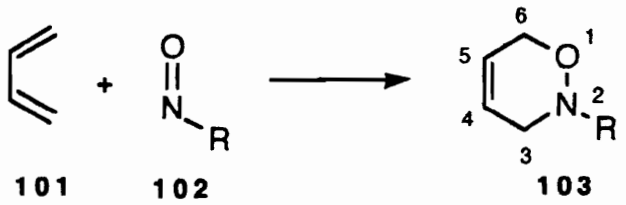
 D-erythrose (acetonide)		Hudlicky 85
 (+)-Trihydroxyheliotridane  (-)-Trihydroxyheliotridane		Hudlicky 86
 (-)-Zeylena		Hudlicky 87

Table 9. Application of Arene-*cis*-diols in the Synthesis of Natural Products.

 Conduramine A-1	 1. Benzoylhydroxamic acid Bu_4NIO_4, CH_2Cl_2. 2. Al (Hg), THF/H_2O	Hudlicky 47 Werbitzky 48
 Lycoricidine	 1. Cl-$SiMe_2{}^iPr$, Im, CH_2Cl_2 2. BuLi, THF, -78°C, Br-piperonoyl chloride. 3. $Pd(OAc)_2$, Tl(I)OAc Anisole, 135°C.	Hudlicky 88
 (-)-Morphine	 a. CCl_4, 80°C b. TBAF, THF, rt c. PCC, CH_2Cl_2 d. xylenes, 250°C	Hudlicky 89

II. HISTORICAL.

2. Diels-Alder Cycloadditions of the Nitrosyl Group.



101 102 103

Aryl-, α-chloroalkyl, C-acyl-, and O-acylnitroso and cyanonitroso compounds **102** react thermally with conjugated dienes **101** to afford 3,6-dihydro-1,2-oxazines **103**. N-nitroso compounds do not usually undergo [4+2] cycloadditions like C-nitroso compounds. These 3,6-dihydro-1,2-oxazines are potentially useful intermediates with functionality at four contiguous carbon atoms since the double bond can be functionalized and the N-O bond can be reductively cleaved. Oxazines of this type (**103**) have been used in recent total synthesis, such as Keck's heliotridine and retronecine,[94,95] Fuch's cephalotaxine,[96] Watanabe's gephyrotoxin 223AB,[97] Kresze's conduramine F-1 synthesis,[98] and Viehe's aminoconduritol preparations.[99] Reviews on the chemistry of these cycloadditions have appeared in the literature.[90,91,92] A brief review of the latest studies on the regiochemistry studies of these cycloadditions is presented here.

The mechanistic course of the nitroso Diels-Alder reaction is not clearly understood. A series of kinetic and regiochemical studies indicate that the mechanisms may vary from concerted perycyclic processes to those involving dipolar intermediates. Kinetic studies of the cycloaddition of 1,3-cyclohexadiene to a variety of substituted nitrosobenzenes showed that electron withdrawing substituents on the dienophile increase the reaction rate and electron donating substituents retard the reaction rate. Nitrosobenzene falls into the familiar class of electron-demanding dienophiles.[100]

Investigation of the dependence of reaction rates on solvents allows conclusions to be drawn about changes in the polarity when going from edduct to transition state; an increase in the reaction rate with increasing solvent polarity proves that the transition state is more polar than the ground state, Table 10.[93]

Table 10. Solvent influence on the [4+2] Cycloaddition of Nitrosobenzene with the 1,3-Cyclohexadiene.

Solvent	$10^2 * k_2$
EtOH	1.16
CH_2Cl_2	1.07
$CHCl_3$	1.11
C_6H_6	1.00
CCl_4	1.04

Cycloaddition reaction of N-carbonyl-1,2-dihydropyridines **104** with nitrosobenzene **105** afforded a mixture of 3-phenyl-2-oxa-3,6-diazabicyclo[2.2.2]oct-7-ene rotamers **106** and **107**.[102,103] Rotamers **106** and **107** which differ in configuration at the carbonyl to N (amide) bond, exhibit dual resonances for C(1)H, C(5)H and the N(6) acetyl (R_1= OCH_3) substituents. A ^{1}H-NMR temperature study indicated that **106** and **107** coalesce at about 100 °C. The regiospecificity of the cycloaddition was rationalized using approximate frontier orbital theory.

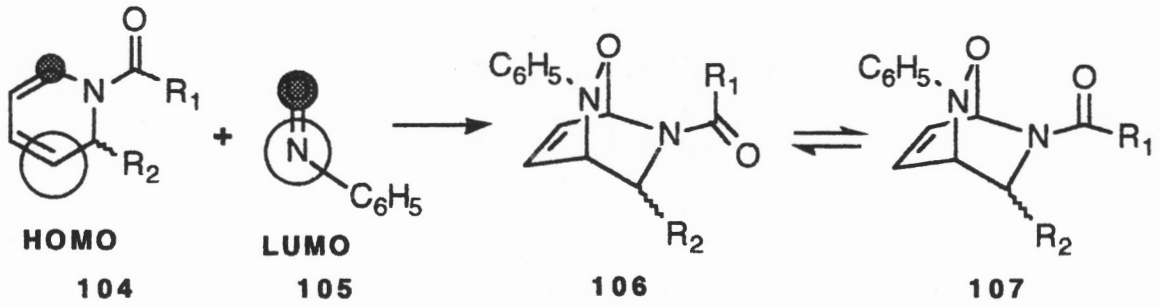
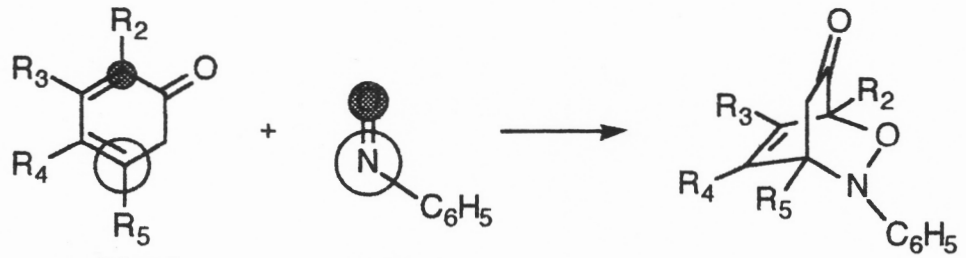


Figure 30. Cycloaddition of Dihydropyridines and Nitrosobenzene.

Coefficients are to be largest for these orbitals at C-3 of the N-substituted 1,2-dihydropyridine **104** and on the nitrogen of the nitroso group (**105**) leading to the formation of a C(3)N and C(6)O bond in the cycloaddition products, figure 30.

The orientation of nitrosobenzene cycloadducts **109** has been discussed at length. It has been observed that both steric and electronic factors can be involved, Table 10. The high regioselectivity in all cases where there are no steric problems can be rationalized using approximate frontier orbital theory.[101] The most important interactions are between

the HOMO of the dienone or dienal (such as **108**) and the LUMO of nitrosobenzene **105**. Coefficients are expected to be largest for these orbitals at C_5 of the dienone or dienol and on the N of the nitroso group, accounting for the formation of a C_5-N and C_2-O bond in the cycloaddition products, as shown in Figure 31.



HOMO **LUMO**

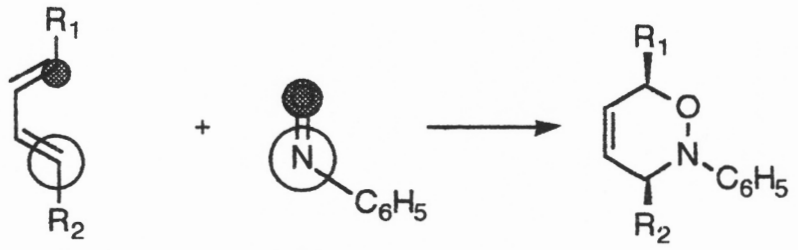
108 **105** **109**

Figure 31. Frontier Molecular Orbitals of Dienone and Nitrosobenzene.

Table 10. Cycloaddition of Several Dieneones to Nitrosobenzene.[100]

108, 109	**R2**	**R3**	**R4**	**R5**	**Yield**
a	H	H	H	H	traces
b	H	CH_3	CH_3	H	51%
c	CH_3	CH_3	CH_3	H	100%
d	CH_3	CH_3	CH_3	CH_3	100% (1:1)

Nitrosobenzene **105** reacted with pentadienal **110a** and hexadienal **110b** regiospecifically producing one regioadduct **111**.[105,106] This regiospecificity was in accordance with the predictions of the FMO theory, see Figure 32. Reaction of nitrosobenzene **105** with methoxybutadiene **110c** also formed the meta adduct. This proved that the higher coefficient of the HOMO/DIENE is always on C-4 either with electron withdrawing or electron donating groups on 1-substituted dienes, figure 32. Reaction of nitrosobenzene **105** with 2-phenylbutadiene produced the adduct via the more sterically hindered activated complex. This is an indication that the steric factor does not play a dominant role in condensations involving C-2 phenyl substituted butadienes.[104]

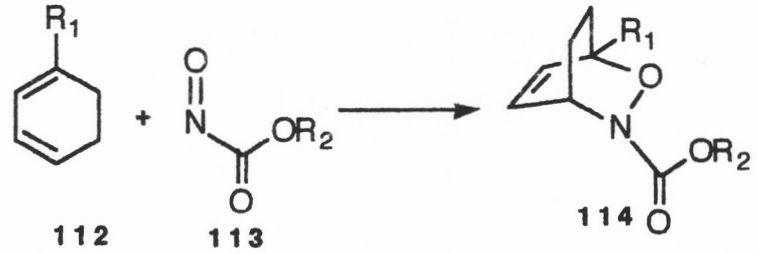


HOMO 110 LUMO 105 111

Diene	R_1	R_2	Oxazine	Ref.
10A	CHO	H	11A	105
10B	CHO	CH_3	11B	105
10C	OCH_3	H	11C	106

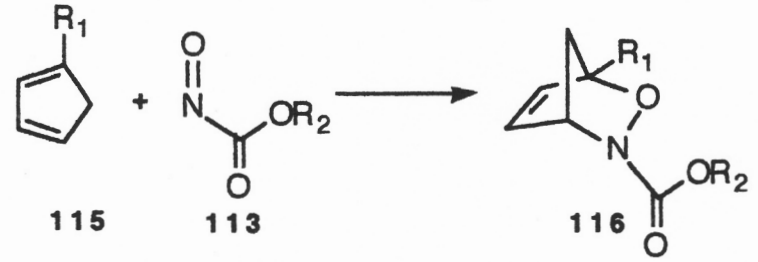
Figure 32. Cycloaddition of Nitrosobenzene to Dienals.

Acylnitroso compounds **113** are useful heterodienophiles and can best be generated by periodate oxidation of a hydroxamic acid. Acylnitroso compounds tend to undergo ene reactions that are sometimes competitive with the Diels-Alder. However, [4+2] cycloadditions are usually more rapid than the corresponding ene reaction.



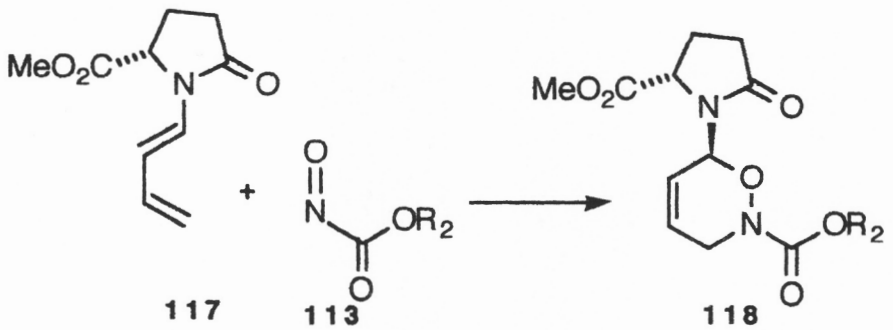
112 113 114

Diene	R_1	Acylnitroso	R_2	Oxazine	Ref.
112a	CO_2Et	**113a**	CH_2Ph	**114a**	110,112
112b	CN	**113a**	CH_2Ph	**114b**	111,112



115 113 116

Diene	R_1	Acylnitroso	R_2	Oxazine	Ref.
115a	$COCH_3$	**113a**	CH_2Ph	**116a**	109



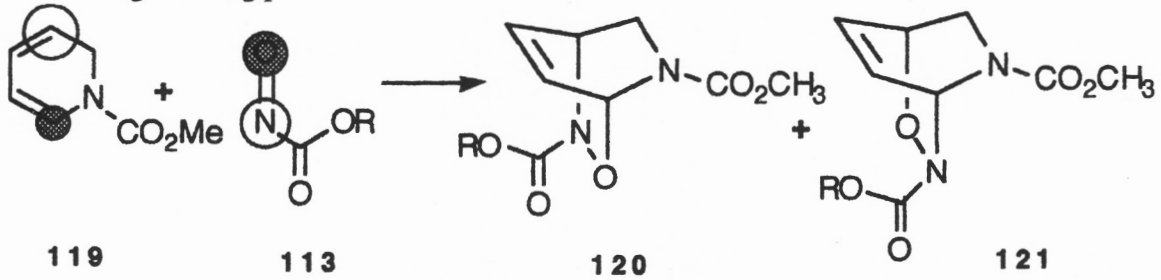
117 113 118

Acylnitroso	R_2	Oxazine	Ref.
113a	CH_2Ph	**118a**	107
113b	Me	**118b**	107
113c	$CH_2CH_2SiMe_3$	**118c**	107

Figure 33. Cycloaddition of O-Acylnitroso Compounds to 1-Substituted Dienes.

The reaction of O-acylnitrosocompounds with electron deficient dienes bearing an electron-withdrawing substituent at the 1-position have been studied and have found synthetic applicability. The addition affords exclusively the proximal (meta) adducts as illustrated in Figure 33. In the absence of a better rationalization, the formation of the proximal adducts has been attributed to steric factors.

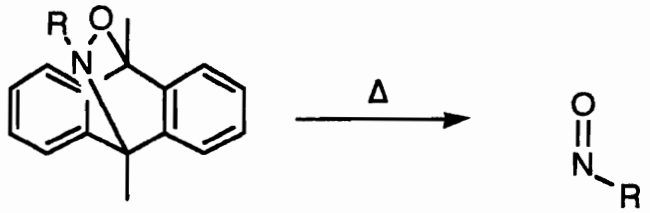
When O-acylnitroso compounds **113** were added to dihydropyridines **119** a mixture of two oxazines (**120** and **121**) was observed, figure 34. In the LUMO of O-acylnitroso dienophiles **113** (R= CH_3 and CH_2Ph) which lead to a mixture of both regioisomers the orbital coefficients at the N-atom and at the O-atom (of the NO group) are of similar magnitude; this being due to a reduced electron-withdrawing effect of the corresponding carbonyl moieties (urethane and urea derivatives). As a result, regiospecific cycloadditions are no longer taking place.



119 113 120 121

Figure 34. Cycloaddition of O-Acylnitroso compounds to Dihydropyridines.

An alternative method to prepare a variety of nitroso derivatives is by thermolysis of the nitroso anthracene **122**. These type of compounds are generated by periodate oxidation of a hydroxamic acid in the presence of 9,10-dimethylanthracene.[113] Complementary approaches to N-substituted oxazines have also been reported by Viehe.[114-116]



122 **102**

Figure 35. Thermolysis of Nitroso Anthracene.

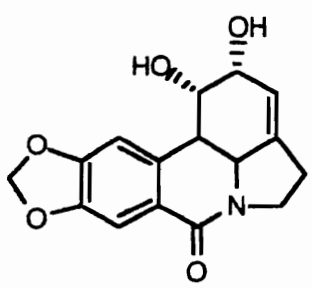
Regioselectivity is observed in most of the cases studied, except in cases where steric factors are not important. However, it is hard to draw a conclusion stating that these cycloadditions are directed purely by either steric effects, or stereoelectronic considerations. More studies should be expected about this topic.

In the next section, a review on lycoricidine alkaloids is presented. Isolation and structure elucidation, along with biogenesis and biological activity of lycoricidine is reviewed before the presentation of the methodology employed in this project for a short and efficient total synthesis of (+)-lycoricidine.

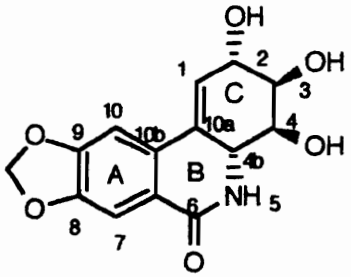
3. LYCORICIDINE ALKALOIDS

3.1. Isolation and Structure Determination

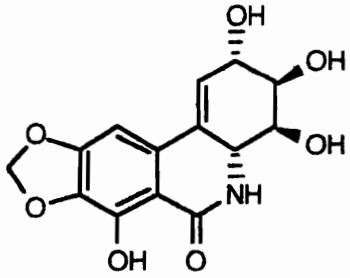
From very ancient times, man had used plant extracts as magic, medicinal, and poisonous potions. The medicinal properties associated with certain species of the plant kingdom later attracted scientists to the study of these natural products. The study of Amaryllidaceae alkaloids began with the isolation of the alkaloid lycorine **123** from *Narcissus pseudonarcissus* in 1877.[117] Since that time over 100 structurally different alkaloids have been isolated from Amarillidaceae species. Reviews of this topic have appeared on different occasions.[117-119]



123



124



125

Lycoricidine **124** and Lycoricidinol **125** (Narciclasine), are non-basic constituents of Amaryllidaceae plants. These two alkaloids were isolated and their structures were determined by Okamoto.[120] The extraction and purification method used to isolate these alkaloids from the methanolic extract of the bulbs of *Lycoris radiata* Herb. is outlined in Figure 36.

The methanol extract of the bulbs of *Lycoris radiata* Herb. had strong growth-inhibiting actions on Avena straight growth test and rice seedling test,[120] which prompted Okamoto and coworkers to isolate the active compounds. The extract was purified, and two plant growth inhibitors, lycoricidine **124** and lycoricidinol **125**, were isolated.

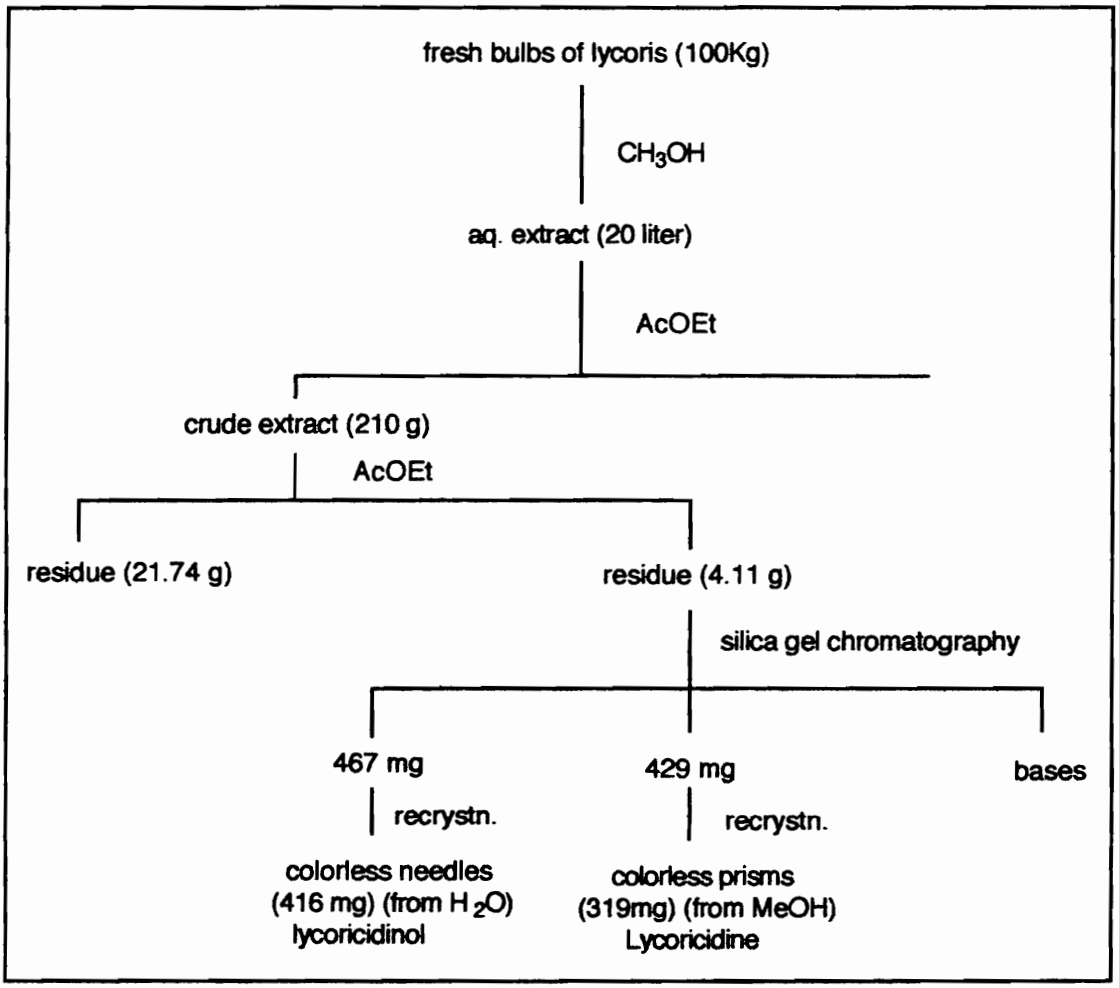
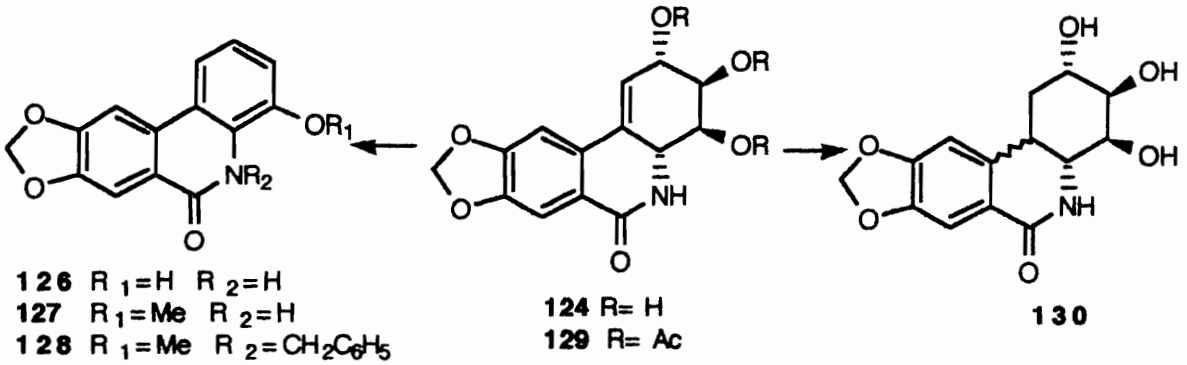


Fig 36. Extraction and Purification of Lycoricidine and Lycoricidinol (Narciclasine).

Lycoricidinol **125** was easily soluble in aqueous sodium hydroxide solution and gave a deep green-violet color with ferric chloride, indicating the presence of a phenolic hydroxyl group in **125**. Compound **124** did not show that property. In the infrared spectra both **124** and **125** showed the bands assignable to carbonyl and hydroxyl groups. In the NMR spectra the signals at 6.0 and 5.95 ppm were assigned to a methylenedioxy group. When **124** was treated with acetic anhydride in pyridine, the triacetate **129** was produced (mp 201-202 °C).[120]



126 R_1=H R_2=H
127 R_1=Me R_2=H
128 R_1=Me R_2=$CH_2C_6H_5$

124 R= H
129 R= Ac

130

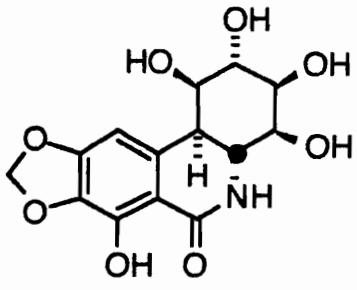
On catalytic hydrogenation lycoricidine took up one mole of hydrogen, giving the dihydrocompound **130**, mp 258-261 °C (decomp.).[120] The marked blue shift in the UV spectra of the dihydro compound **130** indicated that the double bond in **124** is conjugated with the aromatic ring. The dissappearance in **130** of the 6.1 ppm signal of **124**, indicated that the hydrogenated double bond was trisubstituted. When **124** was treated with methanolic hydrochloric acid or dehydrated on palladium-charcoal catalyst, arolycoricidine **126** was obtained, with the concomitant elimination of two molecules of water. Arolycoricidine **126** was converted to arolycoricidine methyl ether **127**, mp 292-300 °C (decomp.), and **127** was converted further to N-benzylated product **128**, mp 175-176 °C, with sodium hydride and benzyl chloride. This sample was identical to the one reported in the literature.[120] Okamoto realized that the isolated lycoricidinol **125** was identical to the compound narciclasine reported by Piozzi.[121]

Ohta[124,125] assumed the stereochemistry of lycoricidine to be as in **124**, since the NMR spectrum of lycoricidine triacetate **129** corresponded very well with that of lycoricidinol tetraacetate,[120] whose structure had already been determined by X-ray analysis.[123] In 1975, Mondon[123] proved that the compound isolated by Fuganti[121,122] and named margetine was identical to Okamoto's lycoricidine, **124**.

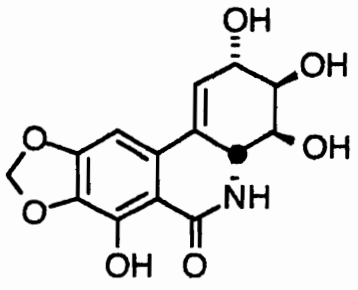
3.2. Biological Activity

Lycoricidine and narciclasin are compounds of biological interest because of their antimitotic activity. Both alkaloids show strong growth-inhibiting activity on *Avena*

coleoptile sections and rice seedling test, and exhibit anti-tumor activity against Ehrlich carcinoma.[120] They also show marked inhibitory action on cell division in tobacco tissue culture, and they have carcinostatic activity.[127] Recent *in vitro* testing of lycoricidine triacetate indicated antiviral activity.[128]



131
Pancratistatin



125
Narciclasin

From the same phytochemical source two other congeners have been isolated, pancratistatin **131** and narciclasin **125**.[129] Pancratistatin **131** showed promising activity in several anticancer test systems administered by the National Cancer Institute. In protocols where test (T) to control (C) survival ratios of 180 are taken to be indicative of promising activity, pancratistatin has registered T:C values as high as 206. In comparative evaluations, pancratistatin has exhibited significantly greater activity than either narciclasine or lycoricidine.[130]

3.3. Biogenesis

The biosynthesis of lycoricidine has not yet been studied, probably because of its poor natural abundance (~0.00032% in fresh bulbs of *Lycoris*);[120] however, the biosynthesis of its analog narciclasine, a lactam widespread among several Amaryllidaceae plants,[131] has been studied extensively by Fuganti.[132-134]

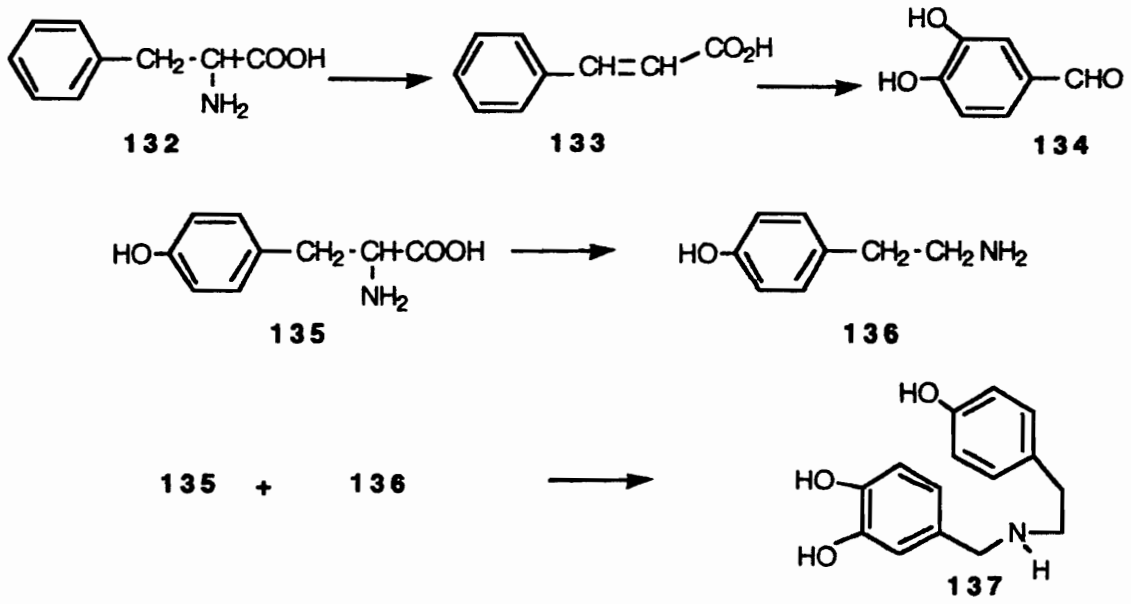


Figure 37. Biosynthesis of Norbelladine.

Amaryllidaceae alkaloids are derived biogenetically from norbelladine **137**, a key biosynthetic intermediate in these alkaloids.[136] Amaryllidaceae alkaloids can be classified into three main groups depending on the mode of the oxidative phenol coupling within a molecule of type **137**. The three modes of coupling are ortho-para, para-para and para-ortho coupling. Examination of **137** indicates an assembly from a C_6-C_1 and a C_6-C_2 unit which can be followed through to specific target alkaloids. From the results of radioactive feeding experiments, it has been established for representative alkaloids, that the C_6-C_2 unit arises from tyrosine **135** (a common source for such units) via tyramine **136** and that the C_6-C_1 unit arises from phenylalanine **132** (a common source of C_6-C_1 and C_6-C_3 units) by way of cinnamic acid **133**, its 3,4-dihydroxy derivative, and protocatechualdehyde **134**, as shown in figure 37.[136]

Hydroxy groups *ortho* and/or *para* to the sites of new bond formation between aromatic rings are essential for biogenesis to proceed. Studies on the incorporation of *O*-[methyl-^{14}C]methyl-norbelladine (as **138**) into haemanthamine demonstrated that a methylenedioxy group arises by oxidative ring closure of an *ortho*-methoxy phenol (as in **138**). The mechanism may be the one involving radicals or cationic species, figure 38.[136]

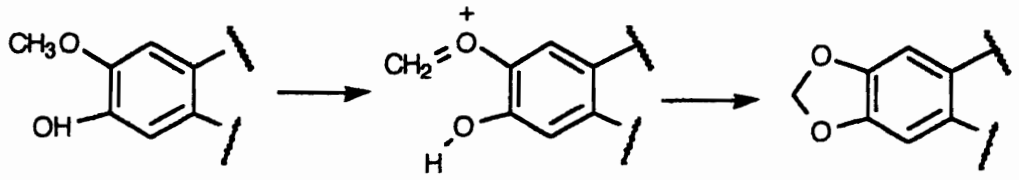


Figure 38. Formation of the Methylenedioxy Group.

Narciclasine is formed biogenetically, as shown in Figure 39, from *O*-methylnorbelladine **138** by para-para phenol-coupling,[132] and its biosynthesis was proven by conversion to oxocrinine **140**, reduction to vittatine **141**, and oxidative ring closure of the *ortho*-methoxy phenol to crinine **142**.[134]

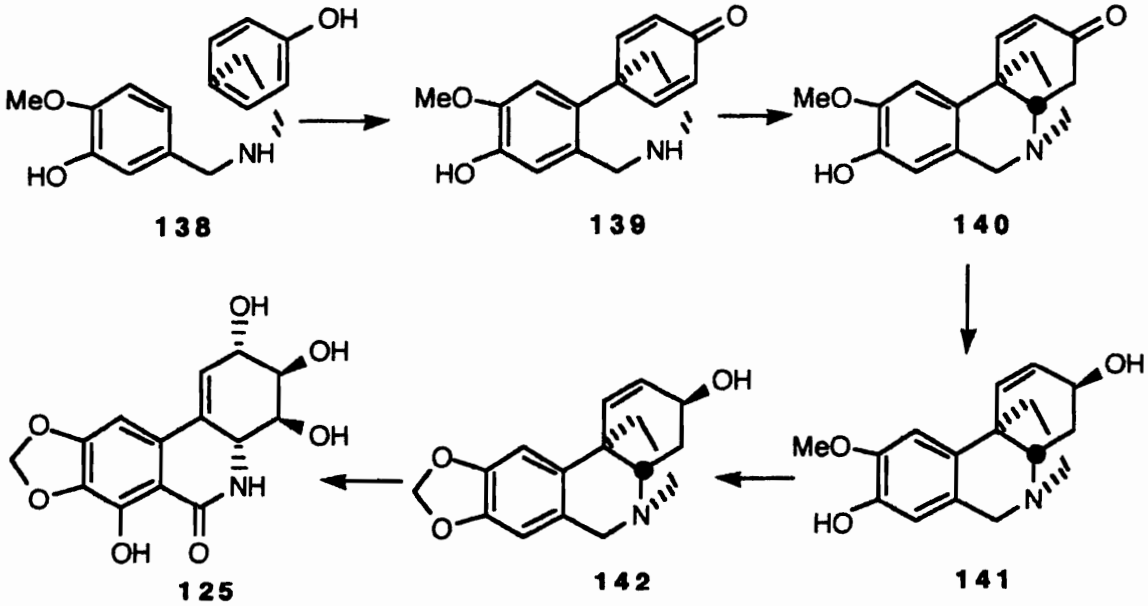
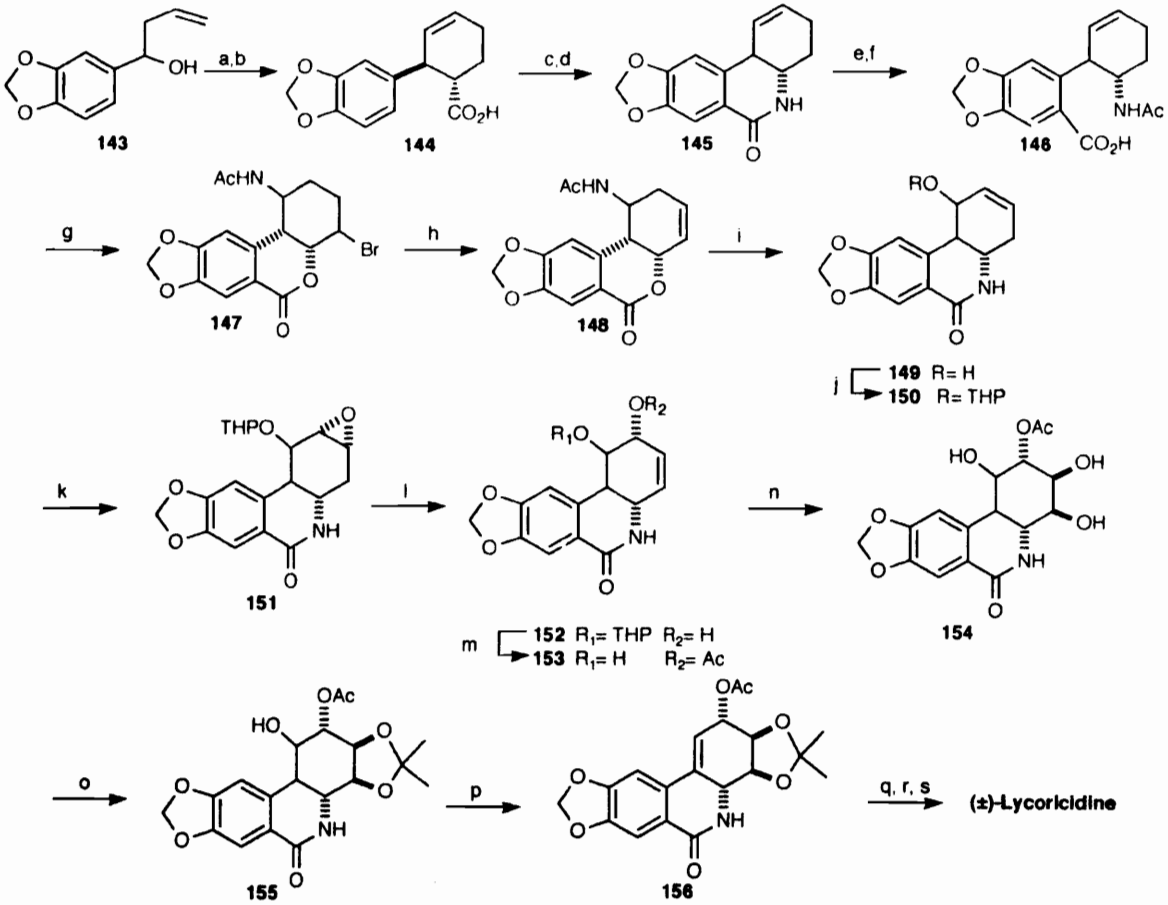


Figure 39. Biosynthesis of Narciclasine.

3.4. Total Syntheses and Synthetic Approaches

There have been two total syntheses of racemic lycoricidine. The first total synthesis was reported by Ohta,[124,125,137] and later, the last steps of his synthesis were improved by Schubert.[128] There have been two enantiocontrolled syntheses of the natural enantiomer of lycoricidine, these were reported by Paulsen,[138,139] and Chida.[140] These syntheses will be reviewed on the following pages.

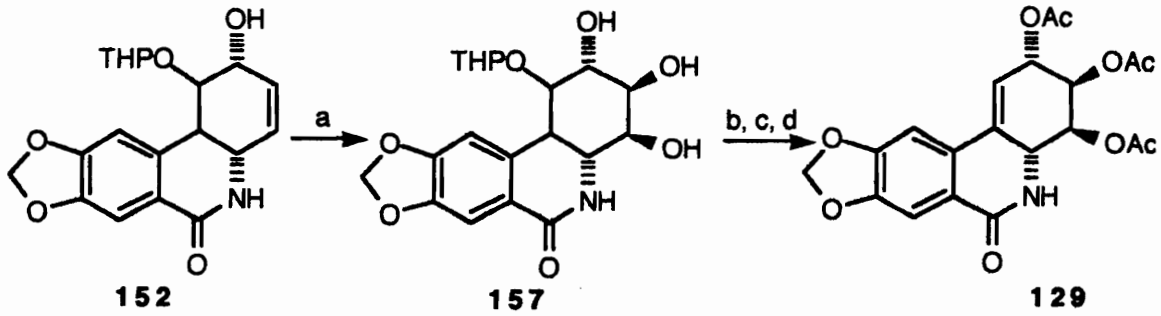
Total Syntheses. The first total synthesis of racemic lycoricidine **124** was reported by Ohta and Kimoto in 1975, Figure 40.[124,125,137] One of the key steps in this synthesis was the cyclization of the isocyanate generated by a modified Curtius reaction using boron trifluoride etherate to lactam **145**. The trans-acid **144** was obtained from the known 3,4-methylenedioxy allyl carbinol **143** in two steps. The lactam **145** was treated with acetic anhydride-pyridine and the product was hydrolyzed to carboxylic acid **146**. The bromolactone **147** was obtained by treating acid **146** with N-bromosuccinimide. The olefinic lactone resulted from heating bromolactone **147** in pyridine. Hydrolysis and cyclization of lactone **148** yielded lactam **149**, which was protected to the tetrahydropyranyl ether **150**, and epoxidized to **151**. Epoxide **151** was converted to the allylic alcohol **152**, and then hydrolyzed to the monoacetylated diol **153**. Oxidation of the olefinic monoacetate diol **153** yielded the *cis*-diol **154**, which was protected to acetonide **155** and dehydrated to the racemic lycoricidine derivative **156**. Hydrolysis and acetylation yielded lycoricidine triacetate. Lycoricidine triacetate was also hydrolyzed to obtain the natural product. This synthesis was accomplished in 19 steps, 1.5% overall yield starting from piperonal.



a. ethyl acrylate, 80° **b.** EtONa, EtOH **c.** Ethyl chloroformate, NaN_3 **d.** $BF_3{\cdot}Et_2O$, rt **e.** Ac_2O, Py **f.** KOH, MeOH/H_2O **g.** NBS, THF **h.** Pyridine, reflux **i.** aq. NaOH, 90° **j.** DHP, pTsOH **k.** $(PhSe)_2$, $NaBH_4$, H_2O_2 **l.** mCPBA, $CHCl_3$ **m.** Ac_2O, Py **n.** OsO_4, Py **o.** DMP, DMF, pTsOH **p.** $SOCl_2$/ Py **q.** pTsOH, H_2O, MeOH, $CHCl_3$ **r.** Ac_2O, Py **s.** NH_3/MeOH, rt.

Figure 40. Ohta's First Total Synthesis of (±)-Lycoricidine

In 1987 Schubert reported an improved synthesis of (±)-lycoricidine triacetate, Figure 41.[128] This improvement consisted in reducing the number of steps in Ohta's synthesis and using small amounts of the toxic reagent osmium tetroxide. Allylic alcohol **152** was prepared in 12 steps following Ohta's procedure, in less than 19.4% overall yield.[124] Direct hydroxylation of **152** by utilizing catalytic amounts of osmium tetroxide and N-methylmorpholine-N-oxide yielded trihydroxy compound **157.** After acetylation of the three hydroxy groups in **157**, the resulting O-tetrahydropyranyl derivative was hydrolyzed and dehydrated to yield lycoricidine triacetate **129.** Schubert took 5 steps to obtain (±)-lycoricidine starting from Ohta's intermediate **152**, in 37%yield This sequence constitutes a 19 step synthesis of lycoricidine starting from piperonal, with a 7.2% overall yield.

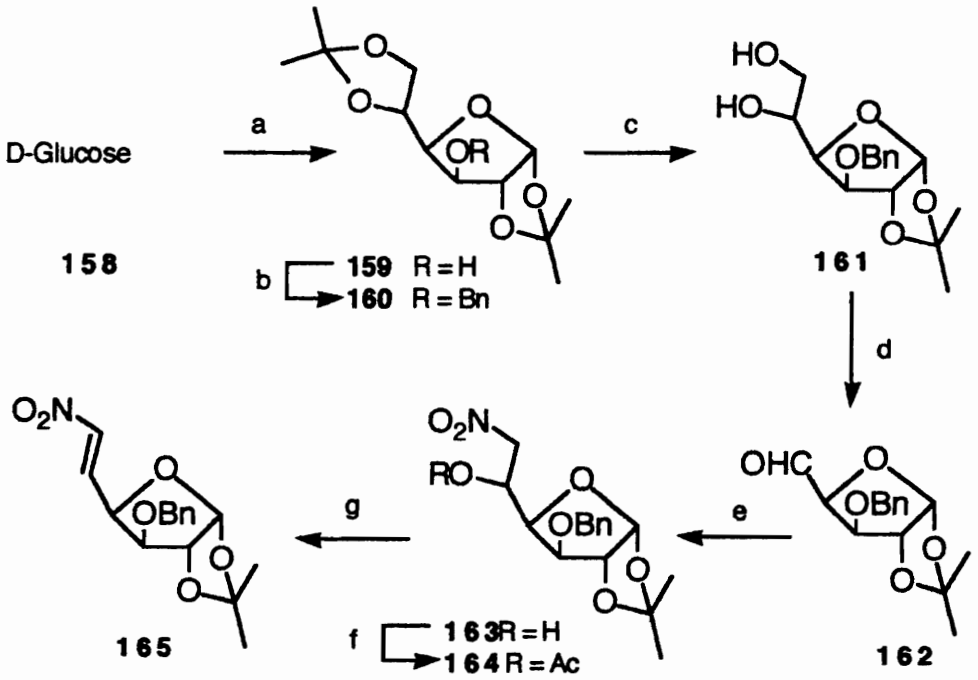


152 **157** **129**

a.t-C_4H_9OH/acetone/H_2O, NMO/OsO_4 (cat), rt, 48h **b**.Pyr/Ac_2O, rt, 1d
c.EtOH/TsOH refl, 2h, **d**. Pyr/$SOCl_2$/rt 1d

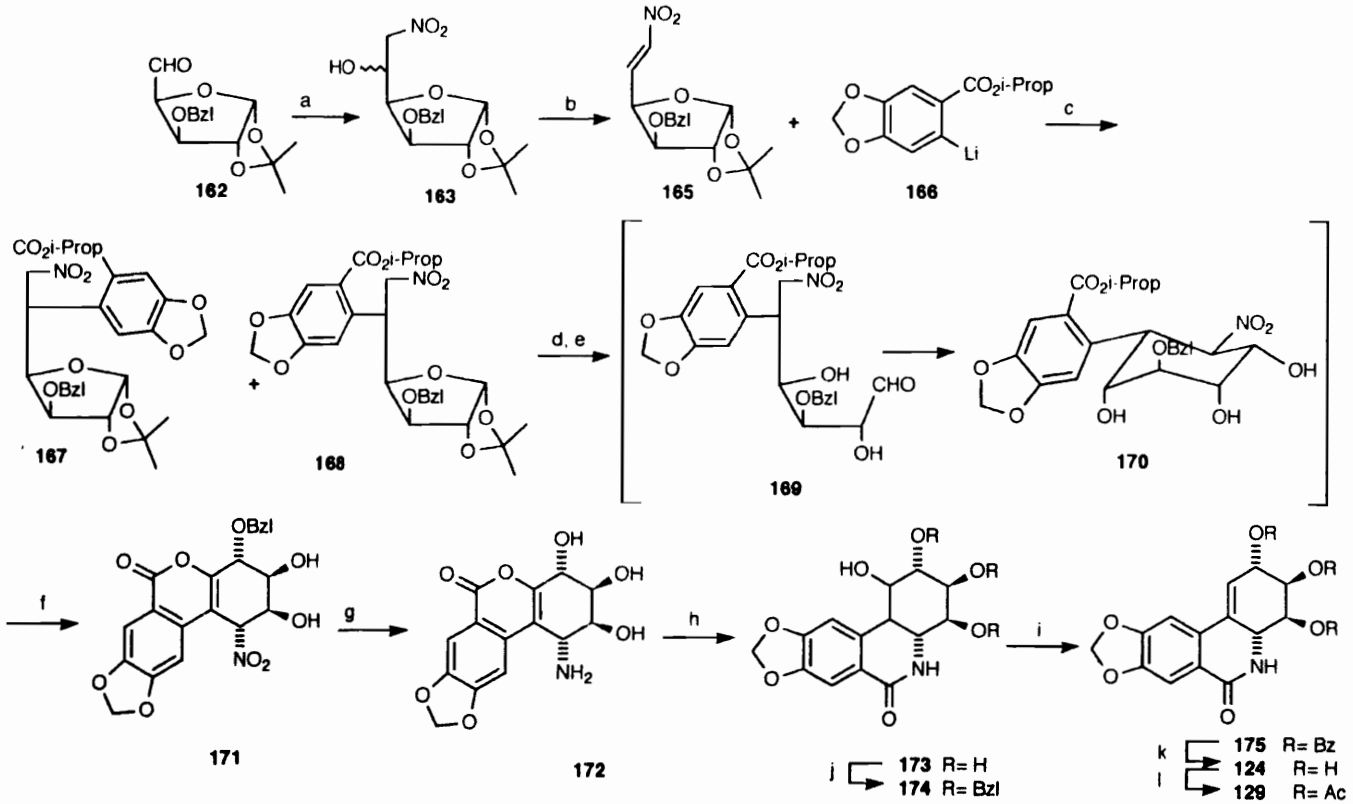
Figure 41. Schubert's Synthesis of (±)-Lycoricidine Triacetate.

The first enantioselective synthesis of (+)-Lycoricidine was reported by Paulsen in 1982.[138,139] This synthesis involved the use of nitroolefin **165**, prepared from D-glucose in seven steps (41.2% yield),[144-150] Figure 42. The key step in this synthesis is the Michael addition of the aromatic anion **166** to the nitroolefin **165**, which gave the branched-chain sugars **167** and **168**, see Figure 46. Liberation of the aldehyde functionality in **167** and intramolecular aldol addition, yielded lactone **171**, a branched-chain nitroinositol with *muco* configuration. Reduction of the nitro group gave amine **172** and rearrangement under basic conditions gave lactam **173.** Selective benzoylation to **174** followed by dehydration gave **175** which allowed deprotection to (+)-lycoricidine **124** and its triacetate **129.** This synthesis was acomplished in 16 steps from D-glucose in 3.9% overall yield.



Reagents: a. Acetone, H^+; b. Benzylbromide; c. H^+; d. $Pb(OAc)_4$, Benzene, reflux; e. CH_3NO_2, NaOH, EtOH; f. Ac_2O, p-TsOH; g. K_2CO_3, benzene.

Figure 42. Synthesis of Paulsen's Nitroolefin from D-Glucose.

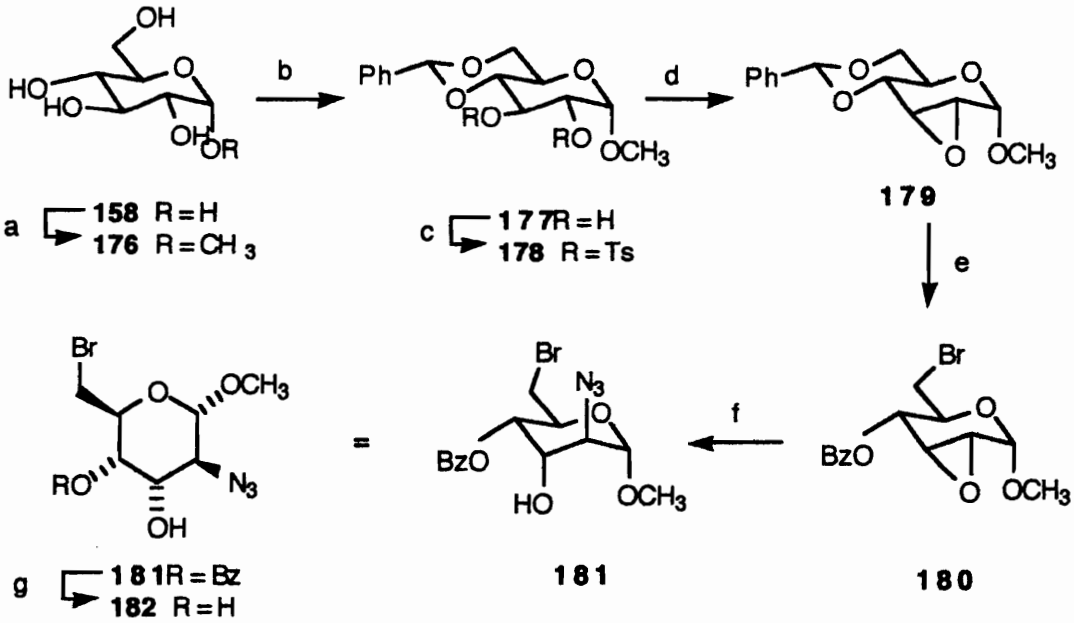


Reagents: a. CH_3NO_2 b. Ac_2O, p-TsOH, then K_2CO_3, Benzene; c. -110°C, THF d. AcOH, reflux e. K_2CO_3 f. Na_2CO_3, MeOH g. Pd/C; h. K_2CO_3 i, BzlBr j. $SOCl_2$, pyridine k. NH_3, MeOH l. Ac_2O, pyridine

Figure 43. Paulsen's Synthesis of (+)-Lycoricidine

A stereoselective synthesis of (+)-Lycoricidine was published very recently by Chida,[140] Figure 45. The staring material for this synthesis was the known diol **182**, prepared in seven steps from D-glucose.

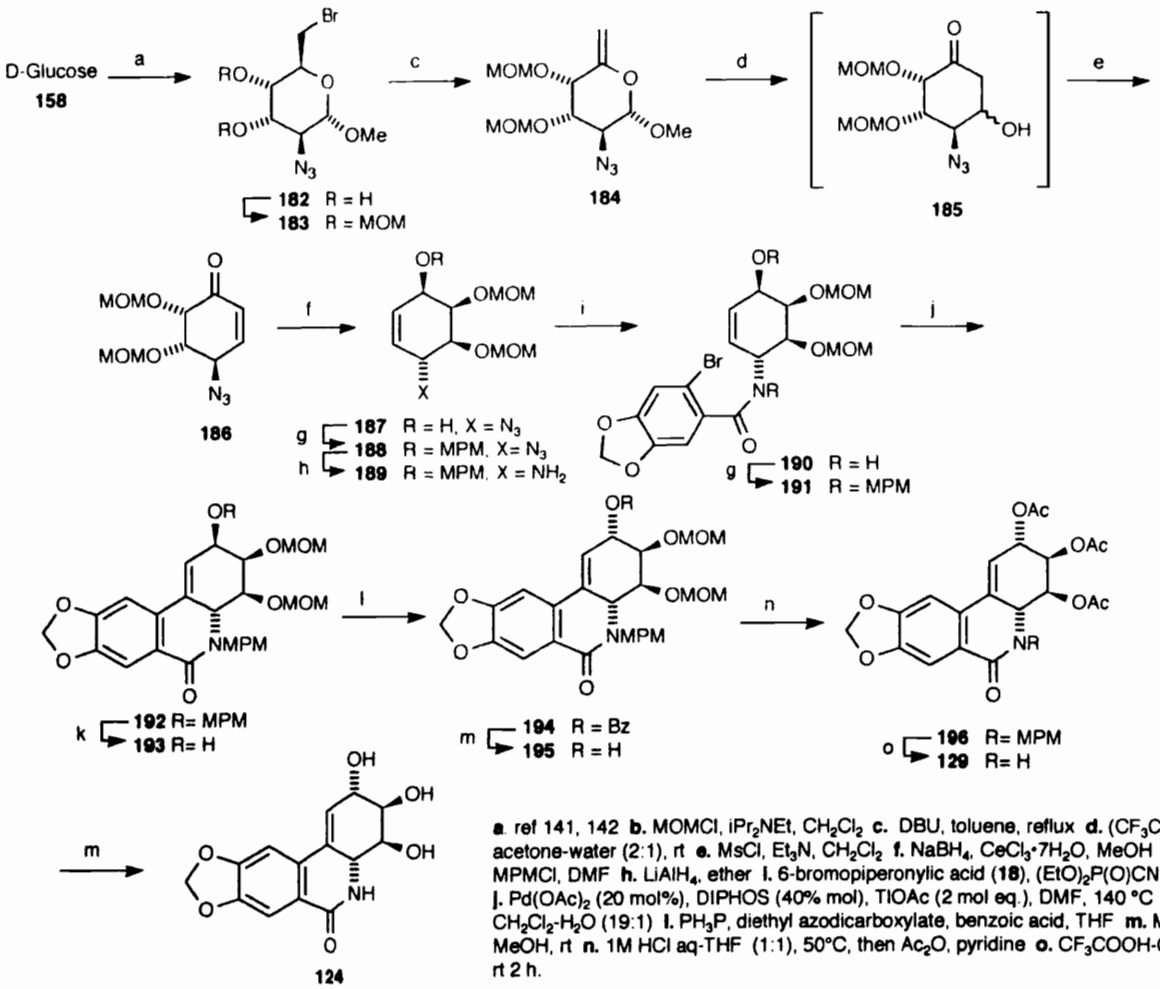
Hanessian reported the preparation of diol **182** from epoxide **179**, in three steps in an overall yield of 6.8%.[141,142] Epoxide **179** was prepared from D-glucose in four steps by Richtmeyer in 45% overall yield.[143] The overall yield for the preparation of diol **47** from D-glucose is less than 3%, Figure 44.



Reagents: a. MeOH, HCl; b. PhCHO, $ZnCl_2$,(70%); c. TsCl, Pyridine, 3-4 days, (70%); d. NaOMe, (90%); e. NBS, benzoyl peroxide, (53%); f. NaN_3, NH_4Cl, rt, 4 days, $MeOCH_2CH_2OH$, H_2O, (15%); g. Sodium methylate, Dowex-50 (85%).

Scheme 7a. Preparation of Chida's Diol **47**.

The C ring of lycoricidine was prepared from 5-enopyranoside **182**, using Ferrier rearrangement.[151,152] The key step in the synthesis is the Heck cyclization to construct the phenanthridone skeleton by a palladium-catalyzed cyclization of bromoolefin **191**.[153] This synthesis proceeded in 24 steps from D-glucose, in 0.042% overall yield

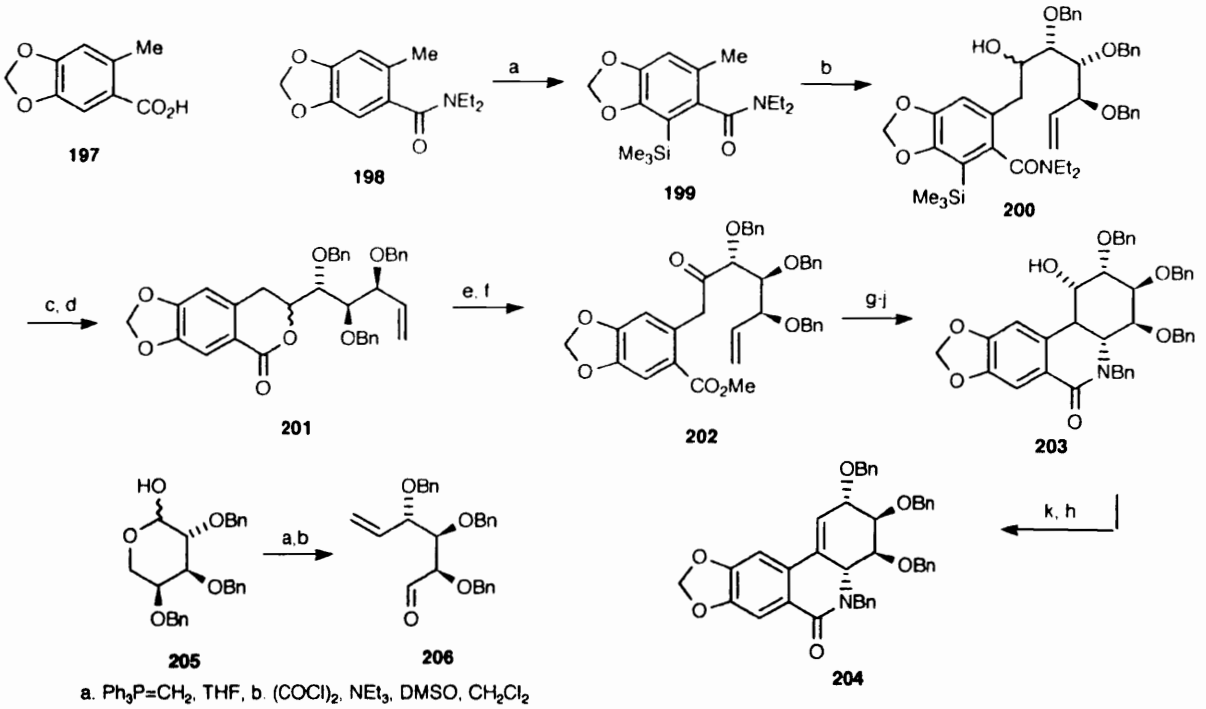


a. ref 141, 142 **b.** MOMCl, iPr_2NEt, CH_2Cl_2 **c.** DBU, toluene, reflux **d.** $(CF_3CO_2)_2Hg$ (1mol%), acetone-water (2:1), rt **e.** MsCl, Et_3N, CH_2Cl_2 **f.** $NaBH_4$, $CeCl_3 \cdot 7H_2O$, MeOH **g.** NaH, MPMCl, DMF **h.** $LiAlH_4$, ether **i.** 6-bromopiperonylic acid (**18**), $(EtO)_2P(O)CN$, Et_3N, DMF **j.** $Pd(OAc)_2$ (20 mol%), DIPHOS (40% mol), TlOAc (2 mol eq.), DMF, 140 °C **k.** DDQ, CH_2Cl_2-H_2O (19:1) **l.** PH_3P, diethyl azodicarboxylate, benzoic acid, THF **m.** MeONa, MeOH, rt **n.** 1M HCl aq-THF (1:1), 50°C, then Ac_2O, pyridine **o.** CF_3COOH-$CHCl_3$ (1:1) rt 2 h.

Figure 45. Chida's Synthesis of (+)-Lycoricidine

Synthetic Approaches. The antitumor activity of dihydronarciclasines attracted the attention to synthesize different analogues of lycoricidine.[156] Several approaches to the lycoricidine skeleton have been reported in the liteature by Kallmerten,[154] Keck,[155,156] Seeback[160] and Tsuda.[157]

Kallmerten reported a convergent synthesis of (+)-tetrabenzyllycoricidine and an approach to pancratistatin, Figure 46.[154] His approach consists in the sequential addition of a nucleophilic aryl subunit **199** to the respective termini of a carbohydrate-derived dialdehyde synthon **206**. Oxidation of a homobenzylic alcohol provides the necessary ketoaldehyde to undergo an intermolecular aldocyclization in order to form the A ring of the phenanthridone. Addition of benzylamine immediately provides the B ring forming hydroxylactam **203**, which was dehydrated to benzyllycoricidine **204**. This protected lycoricidine was not debenzylated, and therefore is not considered a total synthesis of the natural product. This synthesis takes 12 steps from amide **198**.



a. s-BuLi, Me_3SiCl, THF, TMEDA, -78°; s-BuLi, THF, TMEDA, MeI **b.** s-BuLi, THF, -78° , 7 **c.** Bu_4NF, THF, 0-25° **d.** CSA, PhH, 90° **e.** LiOH, THF-MeOH, then CH_2N_2, Et_2O **f.** $(COCl)_2$, DMSO, NEt_3, CH_2Cl_2 **g.** O_3, MeOH, -78°, then Me_2S **h.** DBU, THF i. $PhCH_2NH_2$, PPTs **j.** $NaCNBH_3$, MeOH-10% aqueous HCl **k.** $MeP(OPh_3)I$, HMPA, 100°

Figure 46. Kallmerten's Synthesis of (+)-Tetrabenzyllycoricidine

Keck has approached the synthesis of lycoricidine analogues. His initial approach[155] was based on creating the C ring of lycoricidine with the three alcoholic groups and the amine group with the symmetry required in the lycoricidine skeleton. He obtained compound **75** in three steps, starting with cyclohexadiene **112c** and 3,4-methylenedioxybenzhydroxamic acid **207** Figure 47. *In situ* oxidation of **207** with Pr_4NIO_4 in DMF afforded the nitroso dienophile which was trapped with diene **112c**. Reductive cleavage of the oxazine formed yielded the 1,4-hydroxyamine. Oxidation of the olefin with osmium tetroxide and N-methyl-morpholine-N-oxide produced the triol **208**. Keck confirmed the stereochemistry of the chiral centers by making the isomeric compound with the cis-diol syn to the 1,4-hydroxyamine by a different methodology.

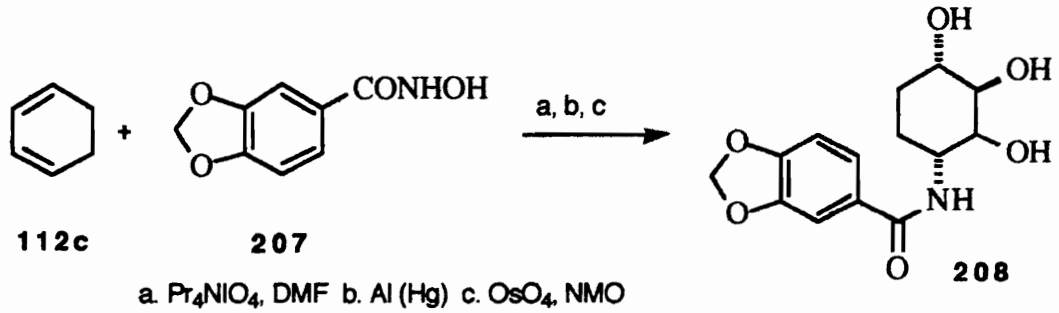


Figure 47. Keck's Approach to Dihydrolycoricidine

The antitumor activity of dihydronarciclasines, and the absence of biological essays of lycoricidine and its dihydro derivatives led Keck to synthesize dihydrolycoricidine by a different approach, Figure 48.[156]

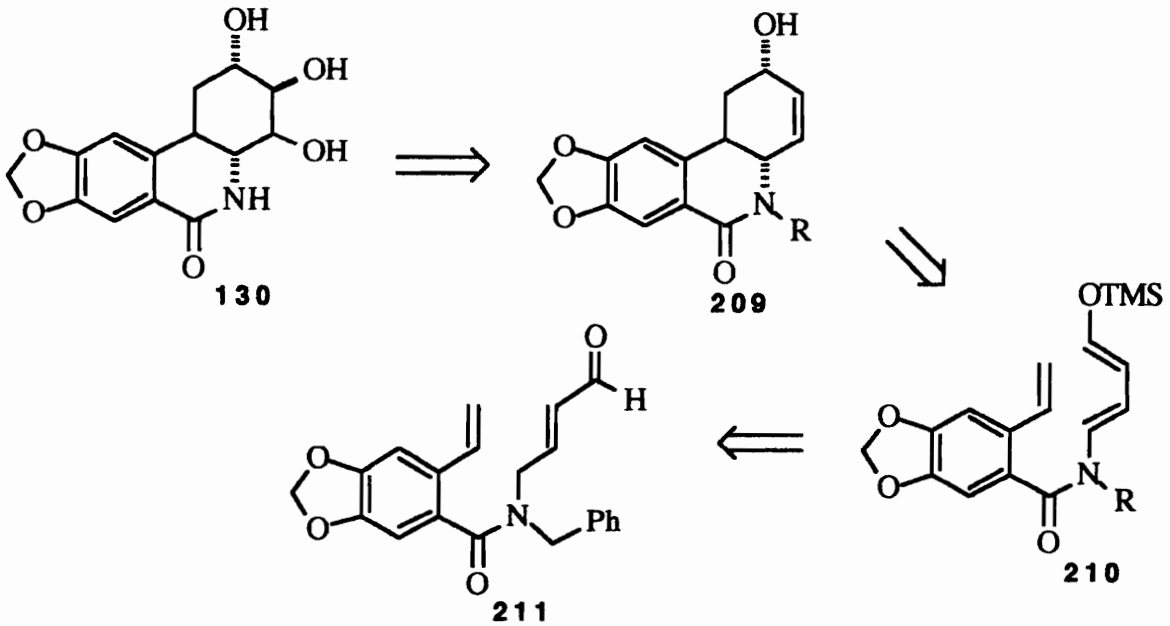
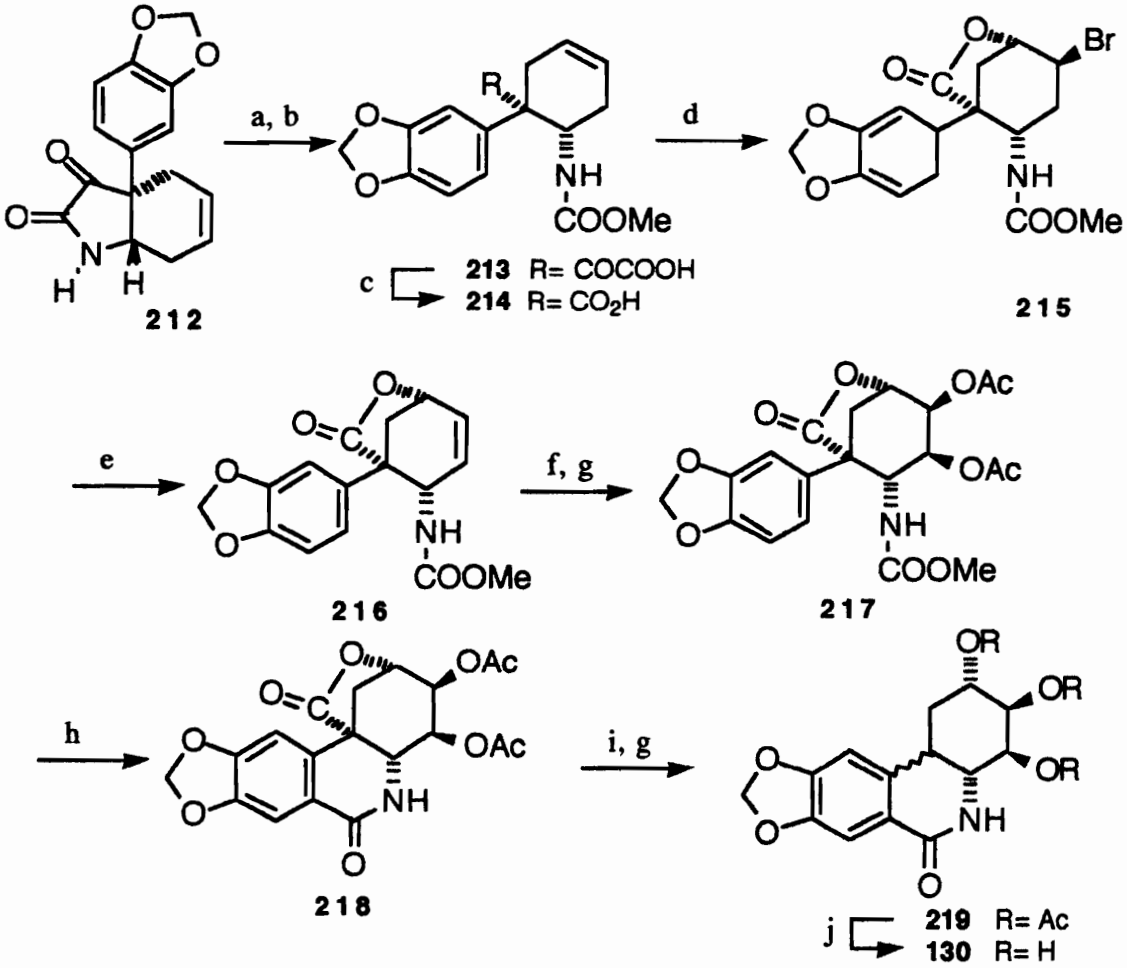


Figure 48. Keck's approach to Dihydrolycoricidine

The key aldehyde **211**, was prepared in six steps starting from bromopiperonal. Formation of the sylil ether **210** produced the Diels-Alder adduct, and exposure to acidic medium yielded alcohol **209**. Acetylation of alcohol **209** and catalytic osmium tetroxide oxidation with further acetylation and hydrogenation gave dihydrolycoricidine triacetate.

Tsuda[157] reported the synthesis of (±)-dihydrolycoricidines starting from compound **212**,[158] Figure 49. Protection of the amide nitrogen and hydrolysis of the lactam afforded **213**. Oxidation of the α-ketoacid yielded acid **214**. On treatment with NBS **214** was converted to bromo lactone **215** which was debrominated to **216**. Oxidation followed by acetylation of the resulting glycol afforded diacetate **217**. Modified Bischler-Napieralski cyclization[159] afforded lactam-acetate **218**. Decarboxylation was carried out by irradiation in alkaline medium to afford a mixture of epimers **219**.

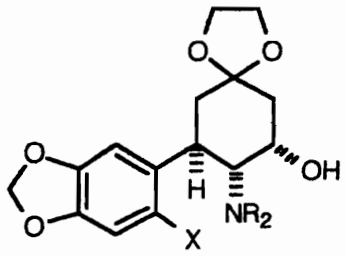


Reagents: **a.** methyl chloroformate, KOH, CH_3CN, r.t. **b.** 10% KOH in MeOH **c.** H_2O_2-NaOH **d.** NBS, CH_2Cl_2 **e.** DBU, Toluene, 100 °C **f.** OsO4 **g.** Ac_2O, Pyridine **h.** Bischler-Napieralski **i.** 0.1N NaOH irradiation **j.** MeOH-NH_3

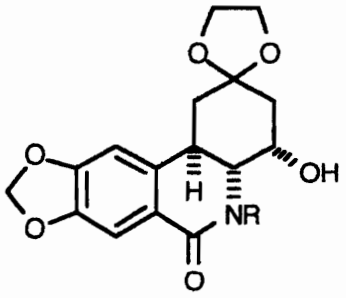
Figure 49. Tsuda's approach.

Seebach was able to construct the lycoricidine skeleton by carbonylation of an aromatic bromide and an imine, Figure 50.[160] Compound **219** was obtained by Michael addition of doubly deprotonated acetyl acetaldehyde to 1-methylenedioxyphenyl-2-nitro-ethene, and protection of the carbonyl group. Reduction of the nitro group in **219** lead to amine **220**. Bromination in acidic medium of **220** yielded compound **221**, and alkylation of the primary amine with benzaldehyde yielded the hydroxy-imine **222**. Cyclization of **222** in the presence of $Pd(OAc)_2$ in a CO-atmosphere produced the B-ring of the lycoricidine skeleton in poor yield. A similar approach was used for the synthesis of the lycorine

skeleton.



219 X= H, R= O
220 X= R = H
221 X= Br, R= H
222 X= Br, R= CHC_6H_5



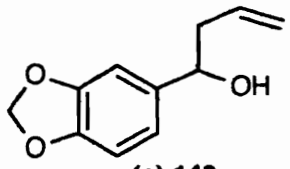
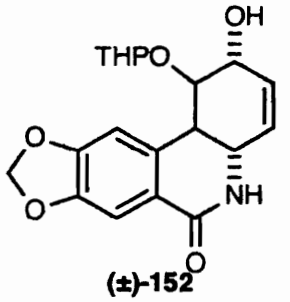
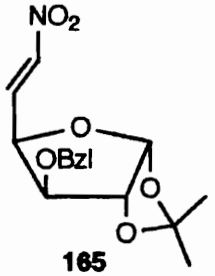
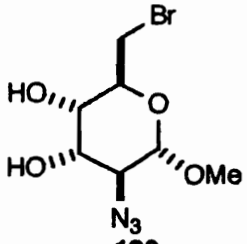
223

Figure 50. Seebach's Approach to Lycoricidine.

In summary, two total syntheses of (±)-Lycoricidine have been reported in the literature. The first total synthesis by Ohta, and the second one, a shorter synthesis, using methodology identical to that of Ohta, reported by Schubert. Also, two enantiocontrolled syntheses of (+)-Lycoricidine have been reported, the first one by Paulsen, and the second one by Chida.

Table 11 presents the starting materials comercially available and the starting materials the authors used in their synthesis with the number of steps to prepare them and the overall yield. It also shows the number of steps in their synthesis and the overall yields from their starting materials.

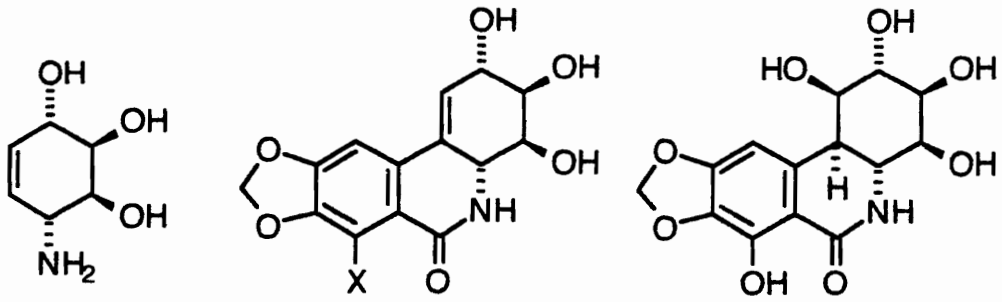
Table 11. Total Synthesis of Lycoricidine

Starting Material	Starting Intermediate	Number of Steps	Yield [Overall yield]	Reference
piperonal	 **(±)-143** (1 step, XX%)	**19**	**1.5%** from **143**	Ohta, 1975 (ref. 124)
piperonal	 **(±)-152** (13 steps, 19.4%)	**17**	**37%** from **152** [7.2%]	Schubert, 1987 (ref. 128)
D-glucose	 **165** (6 steps, 41.2%)	**13**	**9.5%** from **165** [3.9%]	Paulsen, 1982 (ref. 138)
D-glucose	 **182** (7 steps, 3%)	**24**	**1.4%** from **182** [0.042%]	Chida, 1991 (ref. 140)

III. Discussion.

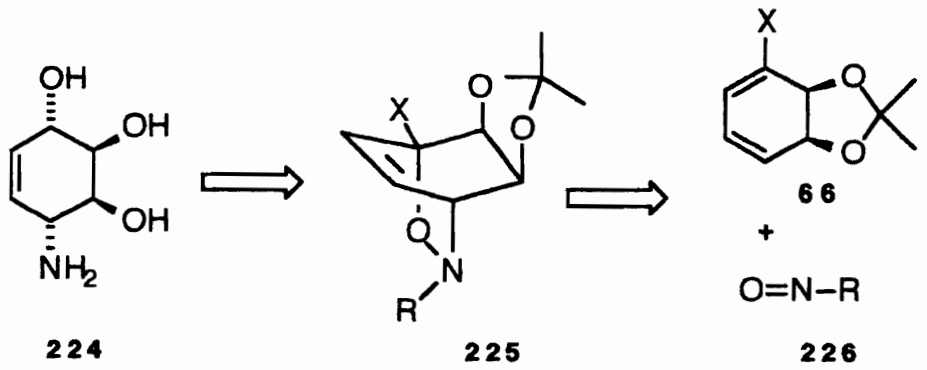
1. Introduction.

There are several natural products that contain the 1,4-*cis*-hydroxyamine functionality *trans* to a 2,3-*cis*-diol functionality on a cyclohexane ring (such as **224**). Examples are conduramine A-1 **224**, lycoricidine **124**, narciclasin **125**, and pancratistatin **131**.



Aminocyclitols like conduramine A-1 **224** have shown interesting inhibitory activity of some glycosidases and are important intermediates in the synthesis of aminoinositols.[127] Narcissus alkaloids such as lycoricidine **124** and pancratistatin **131** have shown inhibition of protein synthesis and potent antitumor activity against larynx and cervix carcinoma (See the historical review of lycoricidine in Section II.3.).[128] A new synthetic methodology was desired which would lead to a variety of narcissus alkaloids (such as **124**, **125** and **131**) in a short and enantiocontrolled fashion.

It was envisioned that the ring functionality in **224** could be constructed by the cycloaddition of a nitroso dienophile **226** to a halobenzene-*cis*-diol acetonide **66** followed by reductive cleavage of the N-O oxazine bond of cycloadduct **225**.



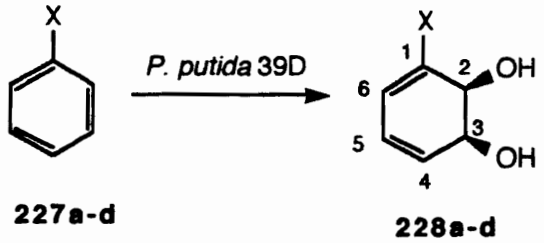
224 225 226

It is therefore the objective of this work to determine the enantiomeric excess and absolute configuration of all halobenzenediols, products of the enantioselective bioxidation of halobenzenes by the bacterium *P. putida* 39-D. The cycloaddition of alkyl dienophiles and nitroso compounds was studied, and new short synthetic routes were designed to synthesize amino-polyhydroxy compounds (such as **224** and **124**).

2. Determination of Optical Purity of Four halobenezenediols.

There is a large number (>120) of arene-*cis*-diols reported in the literature resulting from the biooxidation of arenes (see Section II.1). However, only a small number of them (<10%) are of known optical purity or absolute stereochemistry. A number of methods have been used to determine the enantiomeric excess and absolute stereochemistry of these diols, including stereochemical correlation, circular dichroism spectroscopy and use of a chiral lanthanide shift reagent.[161,162]

The four halobenzenes **227a-d** were subjected to the microbial oxidation using the bacterium *Pseudomonas putida* 39-D. The methods employed have become a routine in Hudlicky's group and have been described in Section II.1.[22] In all four cases, only one product **228a-d** was isolated from the organic extract. These compounds were stored in a freezer at -78 °C.



227a-d **228a-d**

Figure 51. Microbial Oxidation of Halobenzenes.

In order to be able to work confidently with the halobenzene-*cis*-diols it was necessary to determine their enantiomeric excess and absolute configuration. In principle, enantiomeric purity is determined by measuring the optical rotation, but this method is applicable only when the rotation of the pure enantiomer is known. A commonly used method to determine enantiomeric excess is to prepare diasteromeric mixtures from the enantiomers.

When a derivative of a chiral compound is prepared in which a new chiral center is introduced, the two diasteromers will show different physical properties, including optical rotations. A chiral derivitizing agent widely used in the NMR is the Mosher's reagent, α-methoxy-α-(trifluoromethyl)phenylacetic acid.[163-165] This compound is useful because its aromatic ring usually induces markedly different chemical shifts in the two diasteromeric products that are formed, and its methoxy-signal is easily identified in the ^{1}H-NMR spectra (poorly resolved quartet at ~3.4 ppm), and the trifluoromethyl signal in the ^{19}F-NMR spectra. Integration ratio of these signals provides information about the enantiomeric purity. This method was applied to bromo- and iodobenzene-*cis*-diols **228c** and **228d**.

Fluorobenzene-*cis*-diol. We observed immediate decomposition of **228a** upon exposure of the diol to acid vapors. Careful handling allowed us to determine its physical properties. Boyd reported the enantiomeric excess of this diol to be ca. 60%.[13] Boyd's fluorodiol was obtained using the bacterium *Pseudomonas putida* UV4; the apparent difference in strain (UV4 *versus* 39-D) and the enantioselective synthesis of Carless[67] using fluorobenzene diol to prepare enantiomerically pure (+)-Conduritol C prompted us to determine the optical rotation of our fuorobenzenediol (from strain 39-D). We obtained exactly the same optical value as Boyd ($[\alpha]_D$= -33°), indicating that **228a** from strain 39-D was not enantiomerically pure.

Chlorobenzene-*cis*-diol. Chlorobenzene-*cis*-diol **228b** was recently used as the starting chiral block for the preparation of both L- and D- enantiomers of erythrose acetonide[85] **229** along with both trihydroxyheliotridane enantiomers **230** by Hudlicky's group.[86] Independently, both erythroses were synthesized from L- and D- arabinose to prove the enantiomeric integrity of the erythroses synthesized from the chlorodiol **228b** (Figure 52). These results proved the absolute stereochemistry of the diol **228b** as shown in Figure 52.

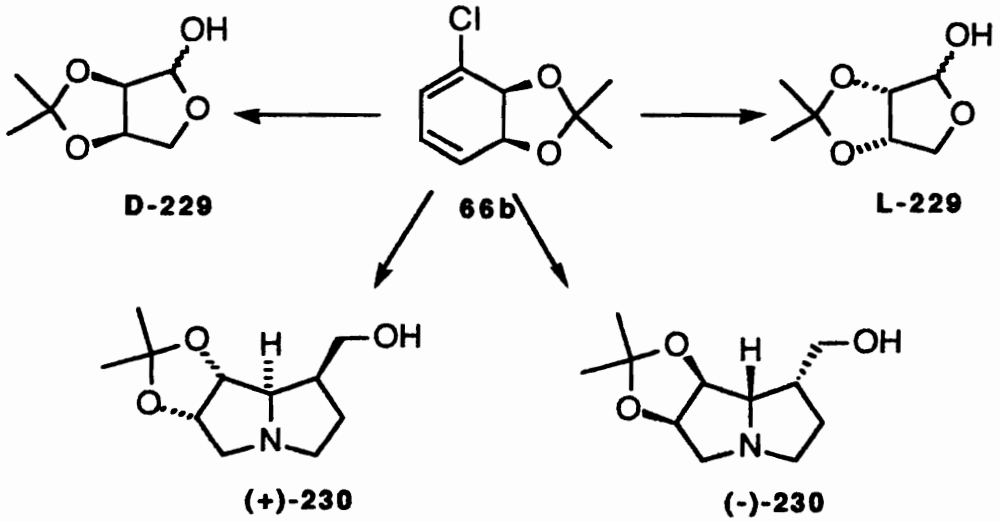
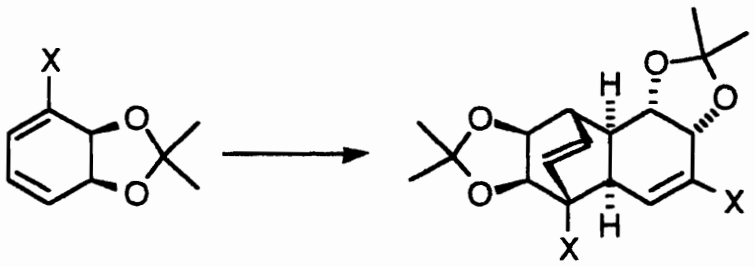


Figure 52. Synthesis of Erythrose Acetonides and Trihydroxyheliotridanes from Chlorobenzene-*cis*-diol Acetonide.

It was observed that halogenated arene-*cis*-diol acetonides dimerize in a completely stereoselective fashion to highly stable crystalline dimers **67** (Figure 53).[56] A convenient method of dimerization consists of refluxing the acetonides in benzene under argon.[56] A similar dimerization of trifluorotoluenediol acetonide **61** was described by Roberts,[52] and the dimerization of bromobenzenediol acetonide **66b** was also described recently by Ley.[55]

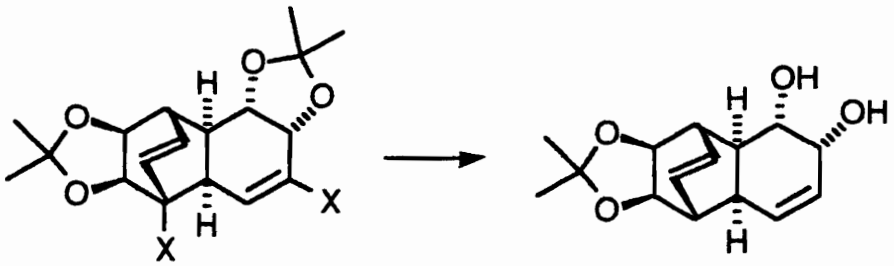


66b X=Cl
66c X=Br
61 X=CF_3

67b X=Cl
67c X=Br
65 X=CF_3

Figure 53. Dimerization of Some Arene-*cis*-diol Acetonides.

The absolute stereochemistry of bromodimer **67c** was established by X-ray crystallography which confirmed indirectly the absolute configuration of the *P. putida* 39-D metabolite **228c** of bromobenzene.[56] The absolute configuration of chlorodimer **67b** was established by chemical correlation to the dehalogenated and partially deprotected dimer **233**.



67b $X_1=X_2=Cl$
67c $X_1=X_2=Br$
231 $X_1=H$ $X_2=Cl$

232 R,R = ^iPr
233 R=H

Bromodimer **67c** was smoothly reduced to **232** with Bu_3SnH and AIBN in refluxing toluene. Similar treatment of chlorodimer **67b** removed only the bridgehead chlorine atom, and the resulting vinylic chloride **231** was obtained in almost quantitative yield. Conversely, exposing chlorodimer **67b** to sodium metal either in liquid ammonia or refluxing ethanol accomplished the desired conversion to **232**. Optical rotations of **232** were too small to provide accurate comparison of optical activity. For this reason, **232** was converted to **233** by treatment with acetic acid. Optical rotations of **233** from both the bromo and chlorodimers were virtually equivalent ($[\alpha]_D$= -78°).[56]

The facial selectivity observed in the dimerizations is best explained by steric effects. Assuming a concerted mechanism, the transition state leading to **67b** and **67c** provides for a minimum of steric interactions (*anti* addition). The regioselectivity in the reaction appears to be consistent with inverse electron demand since the double bond bearing the electron withdrawing group (the halogen atom) does not serve as the dienophile in these instances (Figure 54).

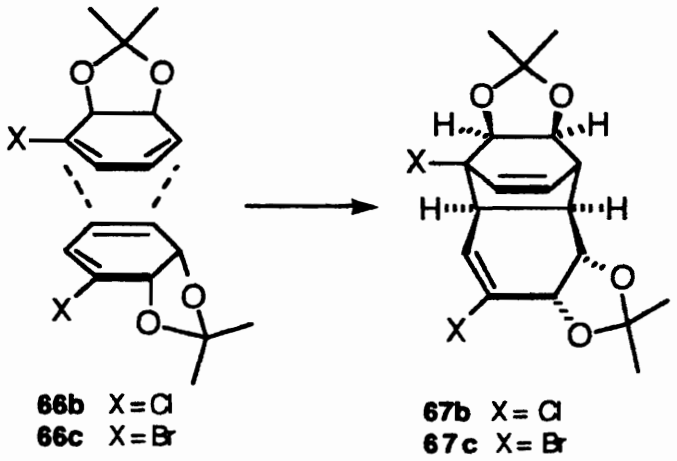
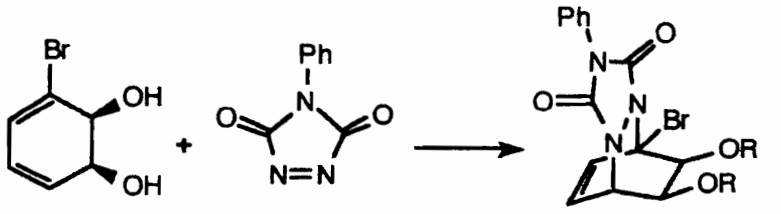


Figure 54. Dimerization of Haloarene-*cis*-diol Acetonides.

Bromobenzene-*cis*-diol. Bromodiol **228c** has been used by Hudlicky in his elegant synthesis of both (+)- and (-)- enantiomers of pinitol.[63,71] Although this bromodiol (**228c**) has already been reported in the literature, its optical rotation, enantiomeric excess and absolute stereochemistry have not yet been reported at the time of this synthesis. The method to determine enantiomeric excess and absolute stereochemistry reported by Boyd[13] for the fluoro- and chlorobenzene-*cis*-diols **228a** and **228b** was applied to bromobenzene-*cis*-diol **228c**.

4-Phenyl-1,2,4-triazoline-3,5-dione **234** was added to a methylene chloride solution of bromodiol **228c**. The cycloadduct obtained was identified as **235**. This compound was soluble in THF ($[\alpha]_D$= +10°) and DMSO (^{1}H- and ^{13}C-NMR) but not in chloroform. R- and S-α-methoxy-α-(trifluoromethyl)phenylacetic acid chlorides were prepared from the appropriate Mosher acid (note that R acid chloride is prepared from S acid) using thionyl chloride in refluxing pyridine in the presence of dimethyl aminopyridine (DMAP).[163-165]



228c **234**

235 R = H
236 R = MTPA

The ^{1}H-NMR spectra of diesters **236** show two different singlet signals corresponding to the methoxy protons of the Mosher acid moiety. These signals are well resolved in both cases and the downfield methoxy proton signals appear at different chemical shifts.

Boyd determined that when a 3-substituted arene-*cis*-diol with 1S,2S configuration is treated with triazoline **234** and subsequently esterified with both enantiomeric forms of Mosher acid, the downfield methoxy proton chemical shift of the diester group should appear at those values shown in Table 12.[13]

Table 12. Correlation of Chemical Shift Methoxy Protons of Diesters.[13]

Mosher Ester	**Downfield Methoxy Proton Signal**
R-MTPA	3.61 - 3.65 ppm
S-MTPA	3.21-3.55 ppm

When (S)-MTPA-Cl was used to esterify cycloadduct **235**, the ^{1}H-NMR methoxy proton downfield signal of the R-MTPA diester **236-R** appeared at 3.60 ppm. And when (R)-MTPA-Cl was used to esterify cycloadduct **235**, the ^{1}H-NMR methoxy proton downfield signal of the S-MTPA diester **236-S** appeared at 3.35 ppm. These results were in agreement with the values determined by Boyd; thus, the absolute stereochemistry of bromodiol was assigned as shown for **228c**, in agreement with the result obtained from X-ray crystallographic studies of the bromodimer **67c**. Only two methoxy signals were observed on the ^{1}H-NMR spectra of each diester (and no four signals), this observation proves the enantiomeric purity of the bromobenzene diol **228c**.

Iodobenzene-*cis*-diol. Boyd has recently studied the enantiomeric excess and absolute stereochemistry of this diol **228d** by chemical correlation *via* formation of the 4-phenyl-

1,2,4-triazoline-3,5-dione cycloadduct and subsequent diesterification using both (+)- and (-)- MTPA.[166] Iodobenzene **227d** was metabolized to iodobenzene-*cis*-diol **228d** by growing cultures of *P. putida* UV4 ($[\alpha]_D$= +41, in MeOH). He found that diol **228d** was essentially enantiopure (>98% e.e.) and of 1S,2S absolute configuration.

3. Determination of Stereo- and Regioselectivity of the [4+2] Cycloaddition of Halobenzenes and Several Dienophiles.

The cycloadditions of several dienophiles to both free and protected benzene-*cis*-diols (**228** and **66**, respectively), have been reported and reviewed in Section II.1. However, the cycloadditions of such dienophiles to halobenzene-*cis*-diols have not received any attention. It was our interest to study the regiochemistry of addition of dienophiles to halobenzene-*cis*-diols. Ethyl propiolate **237** was chosen as the model dienophile in cycloadditions to halobenzenediols because of its simplicity and because the adducts obtained would provide background in order to study the stereo- and regiochemistry of the cycloadditions of other dienophiles. Ultimately, the information gathered during this study would be applied to total synthesis (see Section III.4 and III.5).

Each of the four halobenzenes **227a-d** was oxidized by *Pseudomonas putida* strain 39-D and the corresponding halobenzene-*cis*-diols **228a-d** were isolated and stored at -80 °C.[22] Those diols that were protected as acetonides (2,2-dimethoxypropane, acetone and p-toluensulphonic acid) were used immediately to avoid dimerization.

Ethyl propiolate **237** was added to each of the four halobenzene-*cis*-diol acetonides **66a-d** in a solution of benzene under reflux. The yields of this reaction were good (from 40 to 80%). In each case two products, **238** and **239**, were observed (Figure 55). The less polar cycloadduct **238** had polarity similar to that of the acetonide and was initially confused with the starting material. These cycloadducts were easily separated and purified by flash column chromatography.

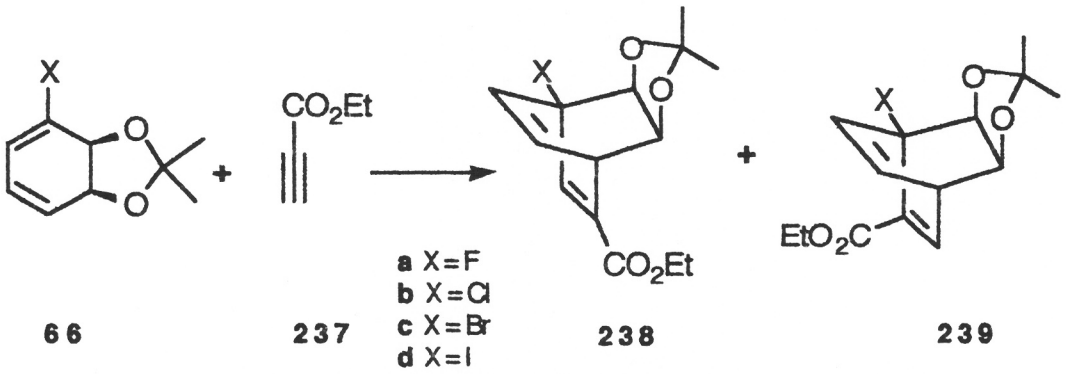


Figure 55. Cycloaddition of Ethyl Propiolate to Halobenzenediols.

The regioselectivity of Diels-Alder cycloadditions can be predicted by the frontier molecular orbital theory.[101] It is necessary to estimate the energies of the HOMO and the LUMO of both components (diene and dienophile) and identify which HOMO/LUMO pair is closer in energy. Normal electron demand occurs when the difference in energy is less in the case of HOMO$_{DIENE}$ and LUMO$_{DIENOPHILE}$. The opposite case is called inverse electron demand (more rare) and this occurs when the difference in energy is less in the case of HOMO$_{DIENOPHILE}$ and LUMO$_{DIENE}$. Using the HOMO/LUMO pair with less energy difference, one can estimate the relative magnitudes of the coefficients of the atomic orbitals on the atoms at which bonding is to take place, and match up the larger coefficient on one component with the larger on the other, as indicated in Figure 56.

It has been established that any C-, Z- (Z= electron withdrawing group), or X- (X= electron donating group) substituted olefin with a 1-C- or 1-Z- substituted diene will give the "ortho" adduct in greater amount. In the case of electron rich dienophiles it is observed that the major product is the "meta" adduct.[101]

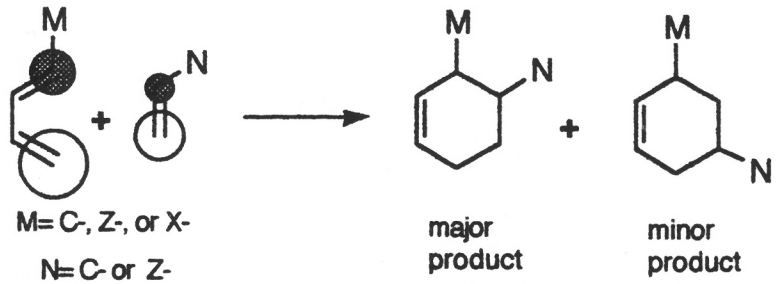


Figure 56. Regioselectivity in Diels-Alder Reactions Predicted by Frontier Molecular Orbitals.

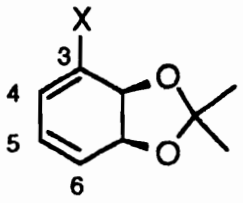
The identification of each regioisomer adduct **238a-d** and **239a-d** was possible by ^{1}H-NMR spectroscopy. The most deshielded proton in the spectra of these cycloadducts is the proton on the unsaturated carbon β to the ethoxycarbonyl group. In the case of adduct **238** this proton appears at even lower fields (7.4-7.1 ppm) than the proton of adduct **239** (7.0-6.8 ppm); this is due to some deshielding effect of the halogen atom. This proton appears as a singlet in adducts **238a-d** and as a doublet (J= 7 Hz) in adducts **239a-d**. There was only a slight preference in the regioselectivity of the cycloaddition, and in most cases the favored product was the "meta" adduct **239** (Table 13).

Table 13. Ratio of Ethyl Propiolate Cycloadducts.

X	**Yield**	**238**	**239**
F	78	40	60
Cl	40	55	45
Br	61	35	65
I	54	38	62

To rationalize the observed regioselectivities, HOMO coefficients of all halobenzene-*cis*-diol acetonides were obtained. AM1 calculations were performed and provided by Professor J. Tanko (AM1 approximation was developed by Dewar et al.[167] and implemented through MOPAC, version 5.0 (QCPE 1989, No. 455)) see Table 14. Comparing the HOMO coefficients on carbons C-3 and C-6, it is observed that coefficients on C-3 are slightly higher than on C-6, exception is fluorobenzenediol acetonide **66a**, where the coefficient on C-6 is slightly higher than on C-3. These results prompted us to investigate the regiochemistry of the Diels-Alder cycloaddition of more polarized dienophiles to halobenzene derivatives.

Table 14. HOMO Coefficients for Halobenzene-*cis*-diol Acetonides.

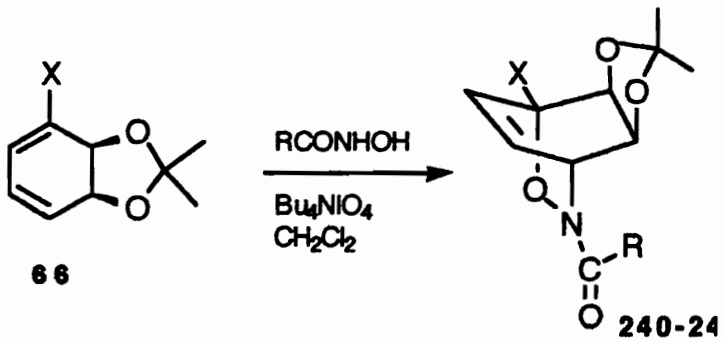


66

		C_3	C_4	C_5	C_6
66a	X = F	0.502	0.465	-0.359	-0.516
66b	X = Cl	0.504	0.441	-0.354	-0.498
66c	X = Br	0.498	0.417	-0.348	-0.473
66d	X = I	-0.493	-0.396	0.350	0.465

In order to study the addition of nitrosyl compounds, the use of an acyl nitroso compound protected with the benzyloxycarbonyl group was envisioned as the most useful for future synthetic work. Nitrosyl derivatives are obtained from their respective hydroxamic acid; therefore, benzylhydroxamic acid was prepared easily from benzylchloroformate. Benzoyl- and acetylhydroxamic acids were therefore prepared using benzoyl chloride and acetyl chloride, respectively.[168]

Hydroxamic acids are oxidized with tetraalkyl ammonium periodate and without isolation the nitrosyl dienophile is trapped by the arenediol.[168] The commercially available oxidizing agent tetrabutylammonium periodate was used in this step. The hydroxamic acid was slowly added to a solution of the halobenzenediol acetonide **66** and the oxidizing agent. Only one cycloadduct (**240-242**) was observed in every reaction, Table 15.



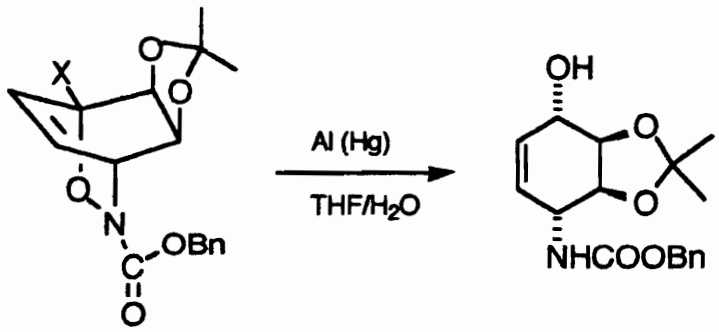
66 **240-24**

Table 15. Diels-Alder Cycloaddition of Nitrosyl Derivatives.

Acetonide	X	Oxazine	X	R
66a	F	**240a**	F	OBn
66b	Cl	**240b**	Cl	OBn
66c	Br	**240c**	Br	OBn
66b	Cl	**241b**	Cl	Ph
66c	Br	**241c**	Br	Ph
66b	Cl	**242b**	Cl	CH_3
66c	Br	**242c**	Br	CH_3

According to the HOMO coefficient calculations, fluorooxazines and bromooxazines derived from fluoro- and bromodiols should possess different regiochemistry. In order to verify these results, each oxazine was converted to a common compound.

There are several methods to cleave the N-O bond of oxazines. Usually these methods require acidic conditions, but recently a milder method utilizing an excess of aluminium amalgam was reported.[169]



240a X = F
240c X = Br

243

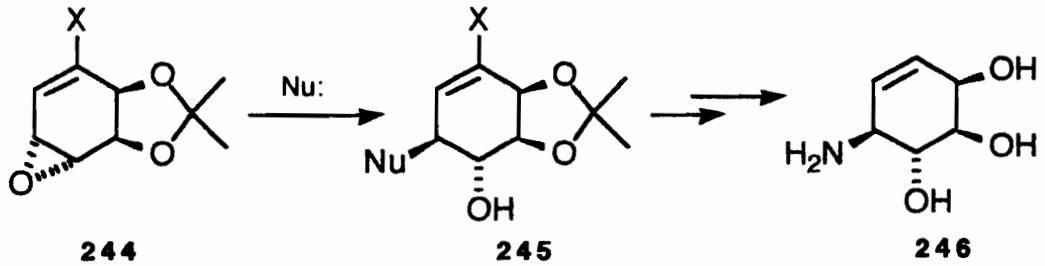
Oxazines **240a** and **240c** were reduced to an α,β-unsaturated hydroxyamide **243**. The optical rotations of these products were determined and shown to be of equal sign and magnitude. These results refuted the idea of different regiochemistry of addition for fluoro- and bromodiene diols as predicted by the calculations, and proved that with both halodiols the cycloaddition proceeds with the same regiochemistry.

According to the calculation of HOMO coefficients of halo-benzene-diol acetonides (**66a-d**), different regiochemical isomers were expected in the cycloaddition of nitrosyl derivatives to fluoro- and bromo-acetonides **66a** and **66c**, respectively. However, similar ^{1}H-NMR chemical shifts of the bridgehead proton of the cycloadducts **240** (δ= 5.05 ppm) presumed a similar regiochemistry, thus, these results were confirmed by reducing these oxazines (**240a** and **240c**) to the same hydroxycompound **243**. The absolute stereochemistry in the aminoalcohol **243** and the relative regiochemistry of oxazines **240-242** remained undetermined. It was thought that by converting this hydroxyamide to an aminoconduritol, the regiochemistry of the cycloaddition could be determined. The next section describes the total synthesis of conduramines and shows how the stereochemistry of adducts was determined.

4. Synthesis of Aminoconduritols.

Aminoconduritols or conduramines are cyclohexenes containing one amino and three hydroxy functionalities. They are important components in a great number of aminoglycoside antibiotics[170] and are found in families like fortimicins[171] and sporaricins.[172] Aminoconduritols also show interesting inhibitory activity for some glycosidases, and they serve as important intermediates in the synthesis of aminoinositols.[176-179] The synthesis of some aminoconduritols has been reviewed.[173,174]

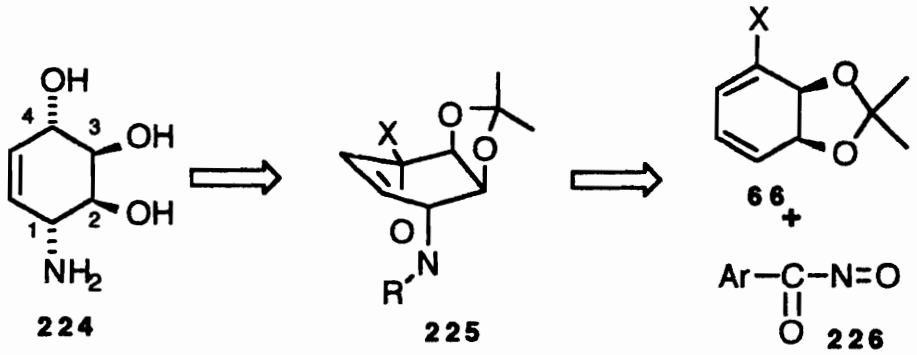
Initially, a methodology for the synthesis of aminoconduritols from arene-*cis*-diols was approached in Hudlicky's group.[22] This methodology consists of the opening of epoxides of type **244** by nitrogen nucleophiles to give *trans*-amino-hydroxy cyclohexanes **245** which possess the appropriate stereochemistry of conduramine F-4 (**246**). Nucleophilic attack by other groups and further elaboration would lead to other conduramines.



244 245 246

Figure 57. Nucleophilic Opening of Epoxides.

In order to define the relative and absolute stereochemistry of the cycloaddition of nitrosyl dienophiles to arene-*cis*-diols (Section III.3) and to investigate this reaction as a new method for the preparation of aminoconduritols, the synthesis of conduramine A-1 (**224**) was undertaken. Conduramine A-1 **224** is named after conduritol A, since they possess identical stereochemistry. The number refers to the carbon where the amino group is located in the cyclohexene ring, see Figure 58.



224 225 226

Figure 58. Synthetic Approach to the Synthesis of Conduramine A-1.

In this conduramine (**224**) two adjacent hydroxy groups have a *cis*-configuration, and the amino and third hydroxyl groups have a *trans*-configuration with respect to the *cis*-diol. It was envisioned that the *cis*-configuration of the 1,4-hydroxy-amino functionalities of conduramine A-1 could be achieved by cleavage of the N-O bond of an oxazine such as **225**. This oxazine could be the product of a [4+2] *anti*-cycloaddition of a nitrosyl derivative **226** and the acetonide of an arene-*cis*-diol (**66**).

There are four different possible pathways in which nitroso compounds could add to 3-substituted arene-*cis*-diols. Each of these oxazines could be converted to three different conduramines as shown in Figure 59. Identifying the particular conduramine obtained would provide conclusive evidence as to which stereoisomer of the oxazine was formed in the cycloaddition and thus would define the transition state of the reaction.

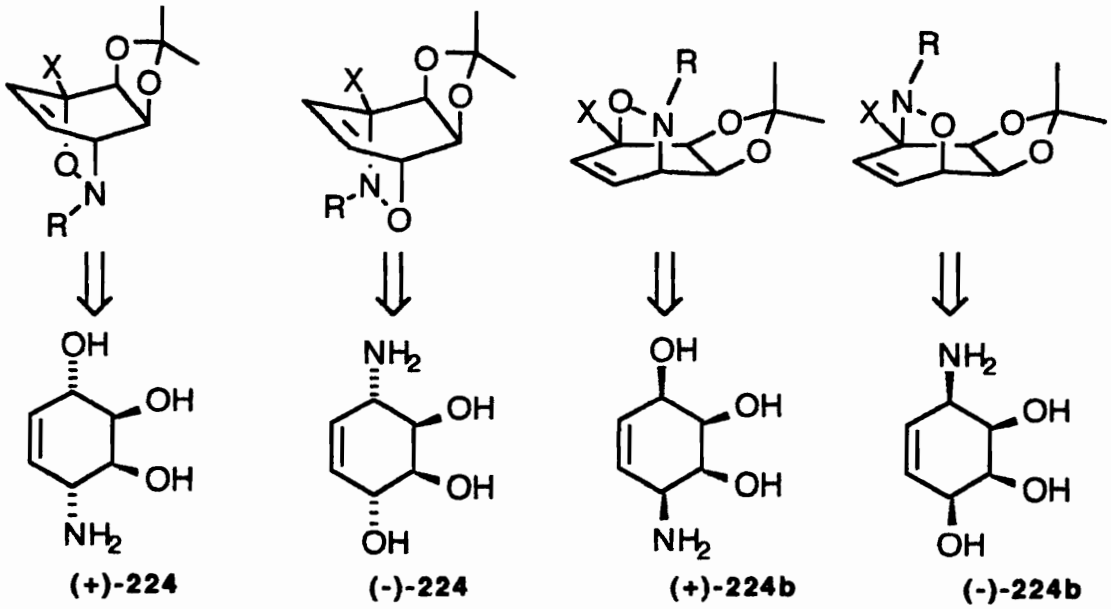
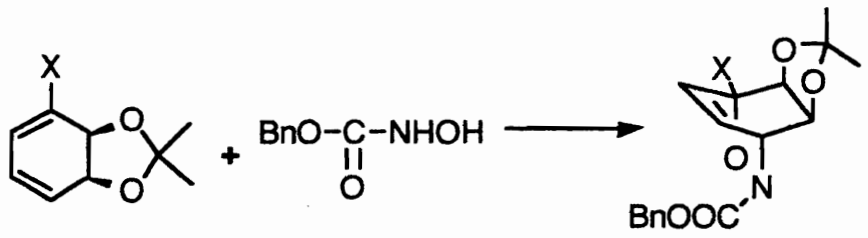


Figure 59. Possible Stereo- and Regiocycloadducts from Nitroso Cycloaddition.

The nitrosyl derivative used in this case was derived from benzylhydroxamic acid **247** which was prepared from benzylchloroformate using hydroxylamine.[168] Benzylhydroxamic acid **247** was added to a solution of the halobenzene acetonide **66a-c** containing an equivalent amount of tetrabutylammonium periodate to oxidize the hydroxamic acid to its nitrosyl derivative which was trapped *in situ* by the addition to the diene. Only one regioisomer **248a-c** was obtained with each halobenzenediol acetonide (Figure 60).



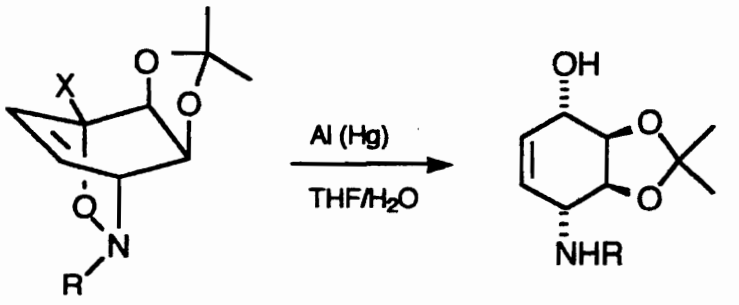
66a X=F
66b X=Cl
66c X=Br

247

248a X=F 20%
248bX=Cl 54%
248cX=Br 74%

Figure 60. Cycloaddition of Nitroso Derivatives to Halobenzenediol Acetonides.

The next step was the cleavage of the nitrogen-oxygen bond. In order to convert the oxazine to a conduramine the nitrogen-oxygen bond of oxazines has been cleaved using Zn and hydrochloric acid or acetic acid in methanol, but a milder method consists of treating the oxazine with freshly prepared aluminium amalgam in a mixture of THF and water.[169] Since the oxazine **248** possesses an acetonide group which is acid labile, the milder method was chosen. Only one isomer was obtained in the reduction in excellent yields (>90%), Figure 61.

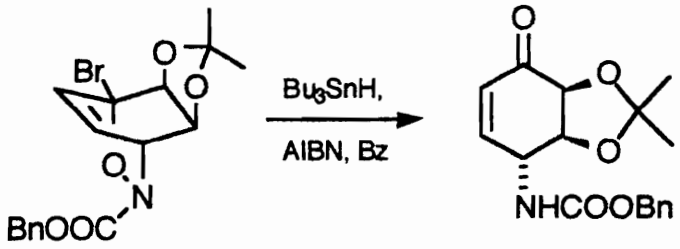


248b X=Cl R=COOBn
248c X=Br R=COOBn
249c X=Br R=Ac

243 R=COOBn
250 R=Ac

Figure 61. Reduction of Oxazines.

When tributyltin hydride was added to oxazine **248c** in the presence of AIBN and refluxing benzene, the α,β-unsaturated ketone **251** shown in Figure 62 was formed. Cleavage of the weak N-O bond occurs before the reduction of the bromine on the bridgehead of the bicyclic oxazine, and no further reduction of the ketone is achieved.

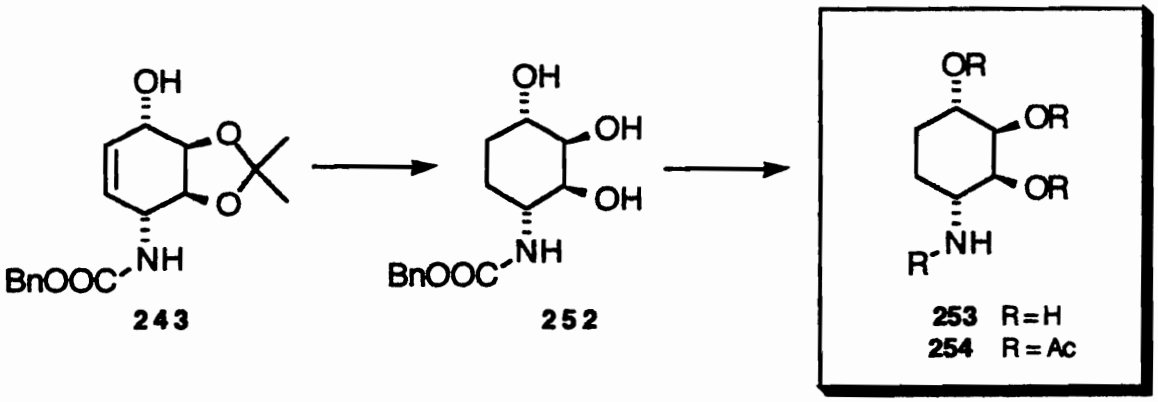


248c **251**

Figure 62. Cleavage of Oxazine with Tributyltin hydride.

Ketone **251** could be an important intermediate for the synthesis of conduramines A-1 and C-1. Ketone **251** could be reduced to a hydroxyurethane that could lead to these conduramines (see Carless' synthesis of conduritol D).[67]

Synthesis of Dihydroconduramine A-1. Carbamate **243** was treated with a mixture of acetic acid, THF, and H_2O in order to remove the acetonide group. Triol **252** was obtained in 99% yield. When this carbamate was subjected to hydrogenolysis in methanol in the presence of palladium on charcoal in a Parr hydrogenator, dihydroconduramine A-1 **253** was obtained in 99% yield. This conduramine was fully acetylated in a mixture of acetic anhydride and pyridine to afford tetraacetyldihydroconduramine A-1 (97%) **254**. This acetylated conduramine showed $[\alpha]_D$, ^1H- and ^{13}C-NMR data identical with literature values.[48]



243 **252**

Figure 63. Synthesis of Dihydroconduramine A-1.

Synthesis of Conduramine A-1. Hydroxy-amide **255** was deprotected under acidic conditions (AcOH, THF, H_2O), and the triol **256** was obtained in 99% yield. The triol **256** was fully protected in acetic anhydride and pyridine to afford tetra-acetylconduramine A-1 **257** in 63% yield. This compound showed physical and spectroscopic data ($[\alpha]_D$, ^1H- and ^{13}C-NMR) identical to those in the literature.[48]

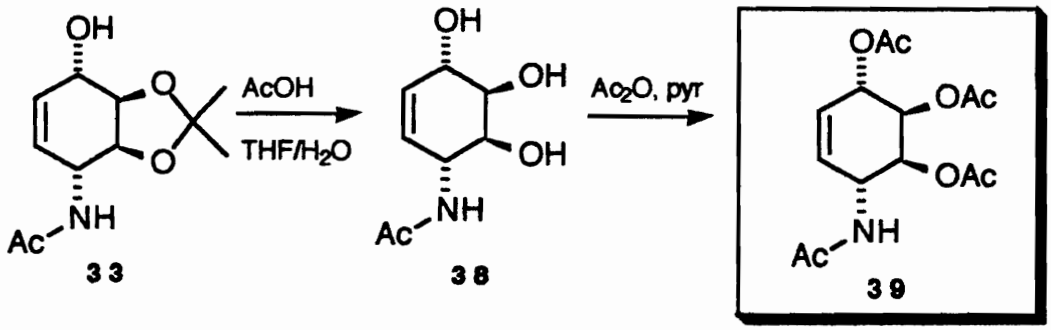


Figure 64. Synthesis of Conduramine A-1.

These two syntheses proved the absolute and relative stereochemistry of oxazines **248** and **249**. These accomplishments also provided a sound background for the approach to the total synthesis of lycoricidine discussed in the next section.

5. Synthesis of Lycoricidine.

The historical background of the natural product lycoricidine has been reviewed in Section II.3. The synthesis of this alkaloid was approached with a short enantio- and stereoselective design in mind. Lycoricidine (**2**) possesses four contiguous chiral centers on a cyclohexene ring which has the same stereochemistry as conduramine A-1. It was envisioned that this compound could be synthesized from a substituted amide such as **258** by formation of a C-C bond from ring A to ring C of the lycoricidine skeleton. Amide **258** could be derived in a convergent manner from a Diels-Alder adduct of an arene-*cis*-diol and an appropriate nitrosyl derivative as shown in Figure 65.

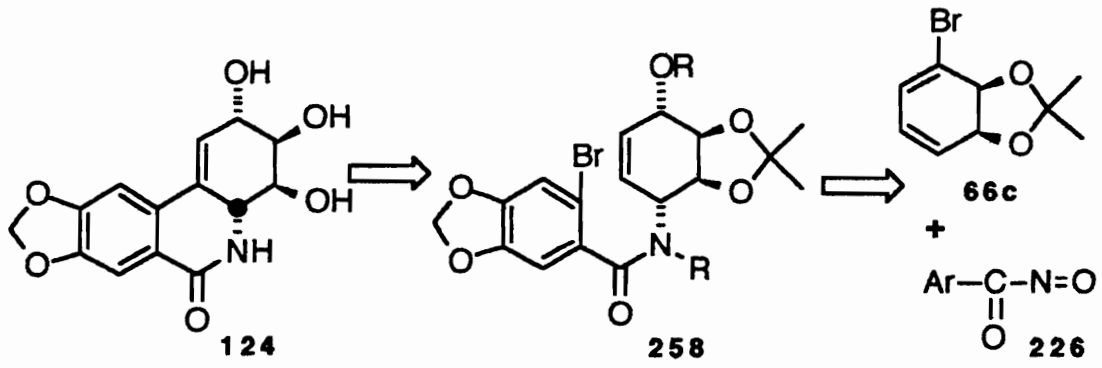


Figure 65. Retrosynthetic Analysis of Lycoricidine.

It was thought that amide **258** could be derived from an oxazine obtained by the addition of bromobenzene-diol acetonide **66c** and *ortho*-bromopiperonoyl hydroxamic acid **263**. The first step was to prepare **263**. This was done by regioselectively brominating piperonal **259** in carbon tetrachloride. Only the *ortho*-bromopiperonal **260** was obtained in the reaction.[180] Bromopiperonal **260** was oxidized using either potassium permanganate or silver oxide prepared *in situ* from silver nitrite and sodium hydroxide.[181] Bromopiperonylic acid **261** was treated either with thionyl chloride or oxalyl chloride to provide bromopiperonoyl chloride **262**.[180]

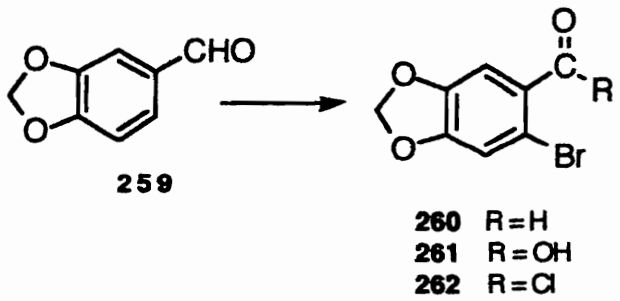


Figure 66. Preparation of Bromopiperonoyl chloride.

In order to obtain the respective hydroxamic acid **263** freshly prepared bromopiperonoyl chloride **262** was treated with hydroxylamine hydrochloride and sodium hydroxide.[168] Hydroxamic acid **263** was added to a mixture of bromobenzene-*cis*-diol acetonide **66c** and tetrabutylammonium periodate to obtain the nitrosyl dienophile which was trapped *in situ* with the diene **66c**, providing only cycloadduct **264** in 80% yield.

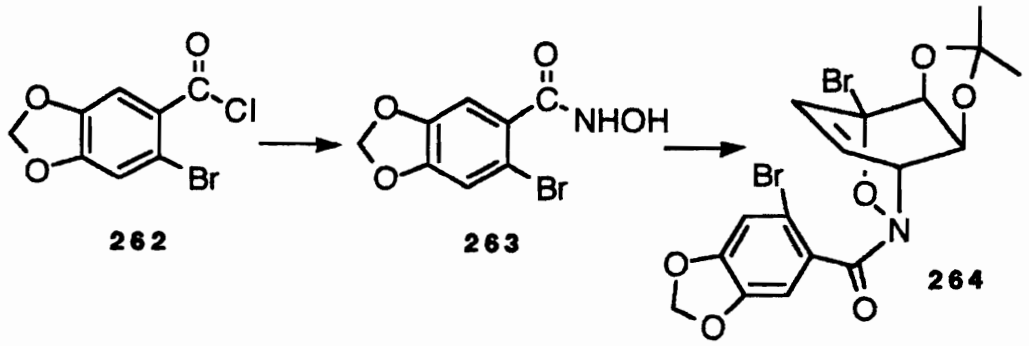


Figure 67. Preparation of Bromopiperonoyloxazine.

When the Diels-Alder cycloadduct **264** was subjected to the mild aluminium amalgam reduction conditions,[169] a mixture of products which was difficult to separate (same Rf on silica gel TLC) was obtained. Analytical HPLC on reversed phase silica (C_{18}) showed a mixture of two major products in about equal amounts and a 1:1 mixture of two other minor products.

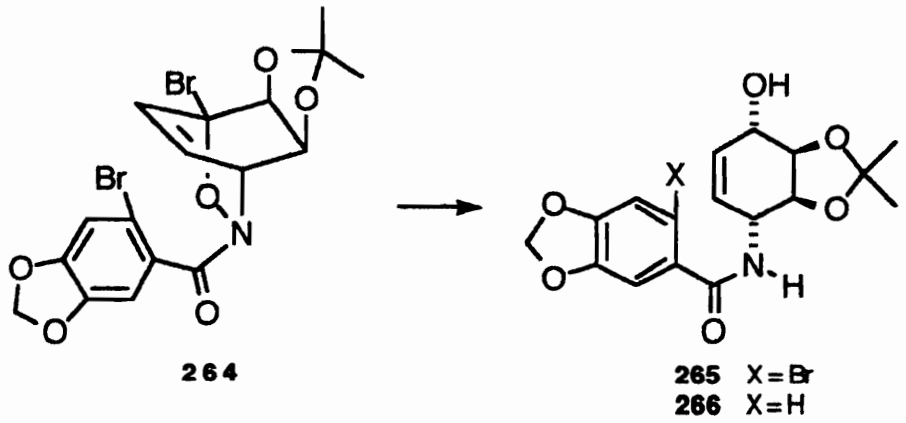


Figure 68. Reduction of Bromopiperonoyloxazine.

After several attempts to isolate these compounds, the two major products were purified and identified as the hydroxy-amides **265** and **266**. Some of the aromatic bromine was reduced by the excess aluminium in the reaction. Unfortunately, excess aluminium is required to drive the reaction to completion. Equimolar quantities of aluminium and oxazine would not furnish enough aluminium amalgam to obtain good yields in this reduction.

Thus, a different approach (Figure 69) was investigated to obtain a hydroxy-amide of type **258.** Hydroxamide **243** was protected with isopropyldimethylchlorosilane and imidazole in CH_2Cl_2. Amide **244** in THF was metallated at -78 °C with butyl lithium and freshly prepared bromopiperonoyl chloride **262** in THF was added.[182] The acylated carbamate **258** was obtained in good yield.

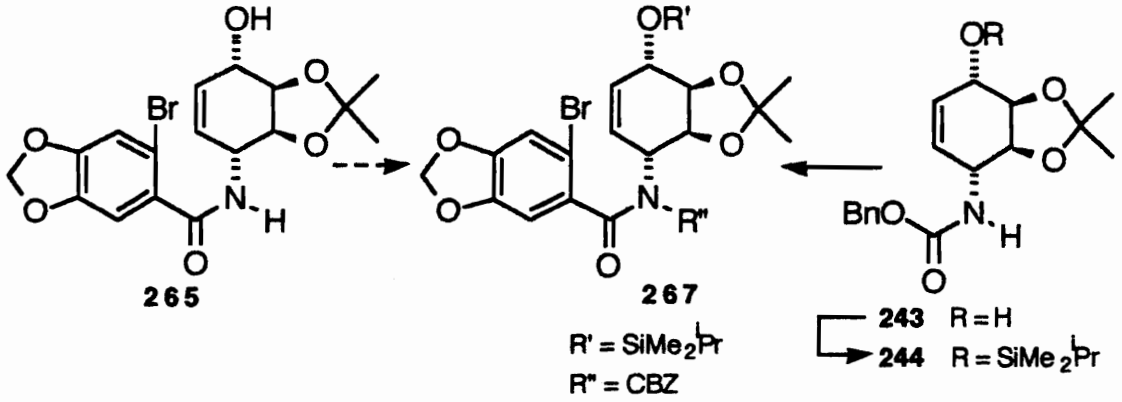
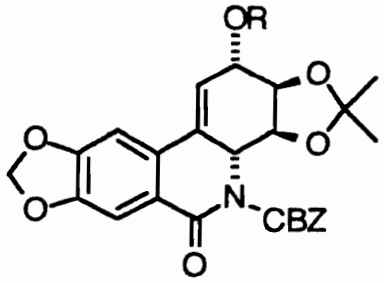


Figure 69. Acylation of Carbamate.

The first approach that was undertaken to form the B ring of the lycoricidine skeleton was an atom transfer cyclization.[183] Carbamate **258** was diluted in benzene and 0.1 equivalents of Bu_3SnH and a catalytic amount of AIBN were added. No reaction was observed after several trials at different concentrations, and this approach was abandoned.

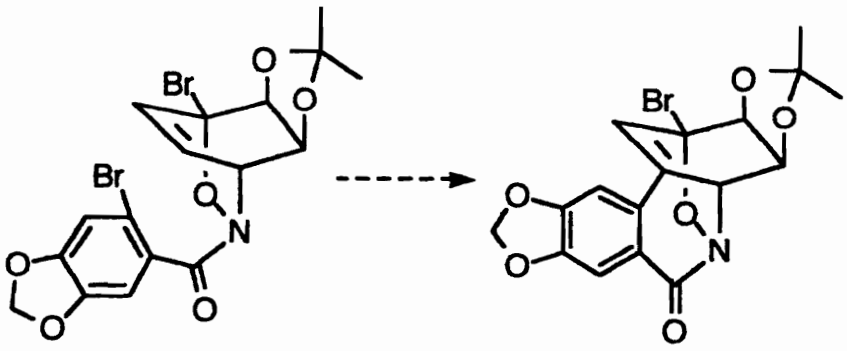
The second approach was the Heck cyclization which appeared in a publication during the pursuit of this work.[140] Chida's modified conditions using $Pd(OAc)_2$, Tl(I)OAc and DIPHOS in DMF were employed without success despite the provision of detailed experimentals by the authors.[140,184] However, when THF was used as the solvent a trace of cyclized compound was isolated and identified by mass spectrometry. It was thought that a higher boiling ether would produce better yields, and anisole was tried as the solvent. Reasonable amounts (30% yield) of cyclized compound **268** were obtained using anisole at a temperature slightly lower than its boiling point (135 °C). Two other cyclized products with higher polarity were also isolated from this reaction and identified as acetate **269** and alcohol **270.**



268 R = $SiMe_2{}^tBu$
269 R = Ac
270 R = H

These two side products (**269** and **270**) could also be converted to lycoricidine **2**. Alcohol **270** could be combined with the cyclized compound **268** and deprotected in two steps to lycoricidine **124**. Acetate **269** can be carried out together with compound **268** and **270** to a mixture of lycoricidine **124** and lycoricidine monoacetate, and then fully acetylate the mixture to lycoricidine triacetate **129**.

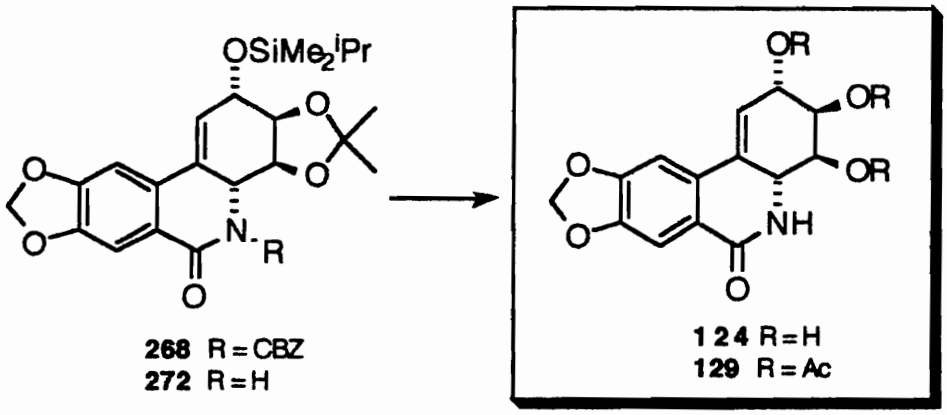
Further improvements in this procedure could be achieved by combining deprotecting steps and by attempting the cyclization on the oxazine. Bicyclic oxazine **264** was subjected to the modified Heck cyclization conditions in order to obtain tricyclic oxazine **271**, however, no reaction was observed using anisole as the solvent.[184]



264 **271**

The cyclized compound **268**, possessing the phenanthridone skeleton with the appropriate stereochemical centers of lycoricidine, was deprotected in two steps. N-Benzyloxycarbonyl groups are usually removed by catalytic hydrogenation.[185] In this case the conjugated unsaturation needed to be preserved for the final product, so direct

hydrogenation was not attempted, but rather the alternative method of transfer hydrogenation was tried.[186] Transfer hydrogenation is a simple and convenient method for removal of all protecting groups that are normally removed by catalytic hydrogenation. A hydrogen transfer reaction using palladium on carbon in a mixture of boiling cyclohexene-methanol removed the N-benzyloxycarbonyl group to yield **272** in quantitative yield.



268 R = CBZ
272 R = H

124 R = H
129 R = Ac

Low temperature hydrolysis in trifluoroacetic acid removed the both the silyloxy and the acetonide groups without elimination products to give the natural product (+)-lycoricidine **124**. The physical data was shown to be identical to the literature values, and the ^{1}H-NMR spectrum was superimposable on the spectrum provided by Professor Chida. Protection of the hydroxy functionalities with acetic anhydride in pyridine provided lycoricidine triacetate **129**, the ^{1}H-NMR spectrum of which was also superimposable on one provided by Professor Chida.

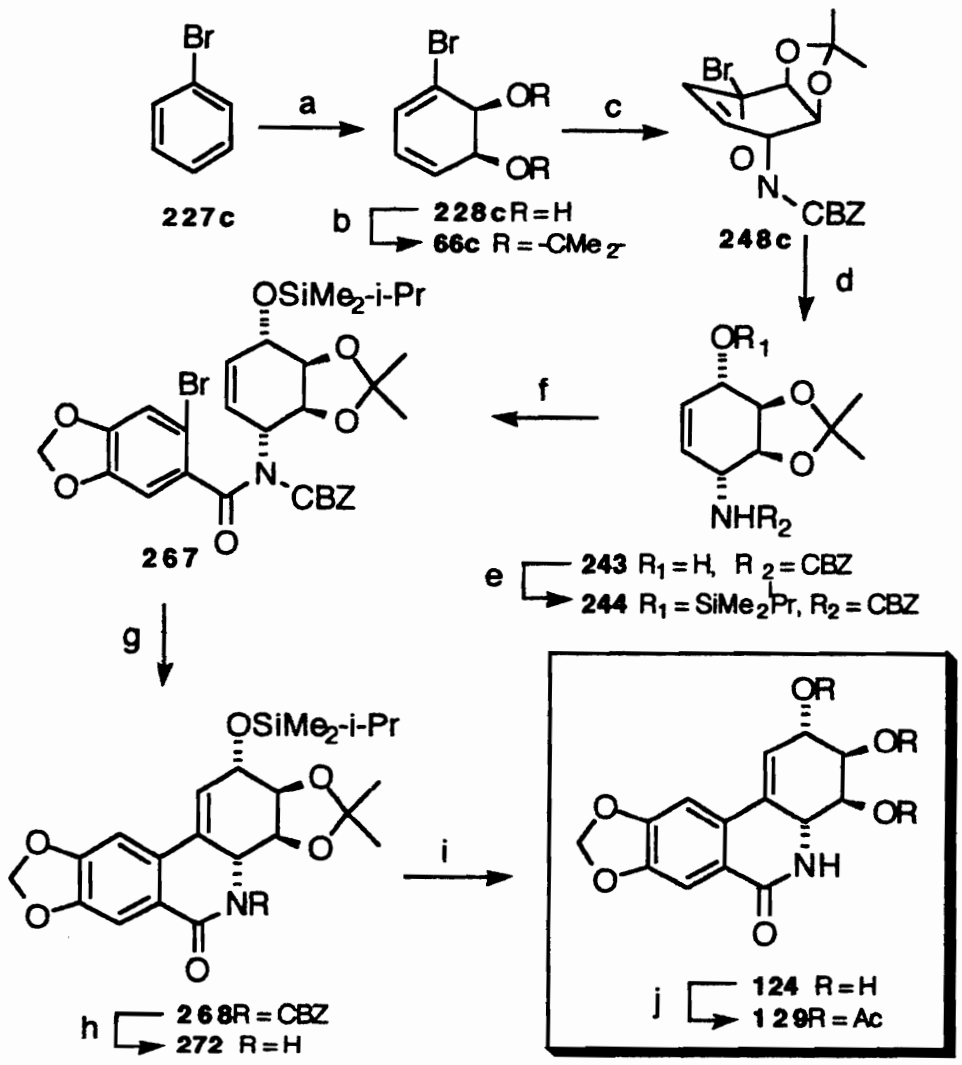
Lycoricidine **124** and lycoricidine triacetate **129** were thus synthesized in a short enantiocontrolled and convergent manner from bromobenzene and piperonal in only 9 steps with an overall yield of 11.4% as shown in Figure 70. This is the shortest synthesis of lycoricidine and lycoricidine triacetate reported with the best overall yield and using the simplest starting materials.

6. Conclusions.

This dissertation describes the necessary sequence of events that led to the highly efficient synthesis of lycoricidine. In the first part of the studt, four halobenzenes were oxidized by the bacterium *P. putida* strain 39-D, to yield the respective halobenzene-*cis*-diols. This strain produced halobenzenediols with the same enantiomeric excess and stereochemistry features as the strain UV4 which is used by other research groups.

Next, ethyl propiolate was added to all four halobenzene-*cis*-diol acetonides, and the ratios of regioisomeric products were determined. These results were rationalized in terms of frontier molecular orbitals. Interesting results were obtained when alkyl and acyl nitrosyl compounds were added to the haloacetonides. Only one regioisomer was produced. One of the cycloadducts were converted to conduramine A-1 and another one to dihydroconduramine A-1 in order to confirm the stereochemistry of the heterocycloadditions.

Finally, oxazine cycloadducts obtained by addition of nitrosyl compounds to haloacetonides were reduced to 1,4-hydroxyamides. Acylation of any of these products with the appropriate aryl moiety yielded an intermediate which was cyclized to construct the lycoricidine skeleton with the correct stereochemical centers. Deprotection in two steps yielded lycoricidine, as summarized in Figure 70.



Reagents: .**a** *P. putida* 39-D; **b.** DMP, acetone, p-TsOH; **c.** benzylhydroxamic acid , Bu_4NIO_4, CH_2Cl_2; **d.** Al (Hg), THF/H_2O; **e.** $ClSiMe_2{}^tPr$, Im, CH_2Cl_2; **f.** BuLi, THF, bromopiperonoylacid chloride; **g.** $Pd(OAc)_2$, Tl(OAc), DIPHOS, anisole; **h.** Pd(C), cyclohexene, MeOH; **i.** CF_3CO_2H; **j.** Ac_2O, pyridine.

Figure 70. Enantioselective Synthesis of (+)-Lycoricidine.

This new methodology is superior to the ones employed in the previous total syntheses of (+)-lycoricidine. In the two previous enantiocontrolled syntheses, Paulsen and Ogawa used D-glucose, a compound with five chiral centers, as the starting material. They both sacrificed one chiral center and prepared lycoricidine, a natural product with four chiral

carbons. In our synthesis, we started from bromobenzene, an achiral compound. Two of the chiral centers are created by the microbial oxidation using *P. putida* 39-D. The acetonide group on these two centers directs the *anti* cycloaddition of the nitroso dienophile to create the other two chiral centers. A brief comparison of efficiency of all total syntheses is shown in Table 16.

Table 16. Total Syntheses of Lycoricidine.

Author	**No. Steps**	**Overall Yield**
Ohta	19	1.5%
Schubert	17	7.2%
Paulsen	13	3.9%
Chida	24	0.042%
Hudlicky	9	11.4%

Further research may provide access to other narcissus alkaloids such as narciclasine and pancratistatine. Acylation of carbamate **243** with a modified bromopiperonylacid chloride could provide carbamate **273**, (Figure 71). Epoxidation of carbamate **273** could lead to **274**, and opening of epoxide **274** via metallation of the aromatic bromine may provide the pancratistatin skeleton **275** which after deprotection would lead to the natural product **131**. A different approach could also test the chemical oxidation of lycoricidine followed by enzymatic hydroxylation of the aromatic ring. The results presented in this dissertation provide solid foundation for further generations of efficient syntheses of this class of alkaloids.

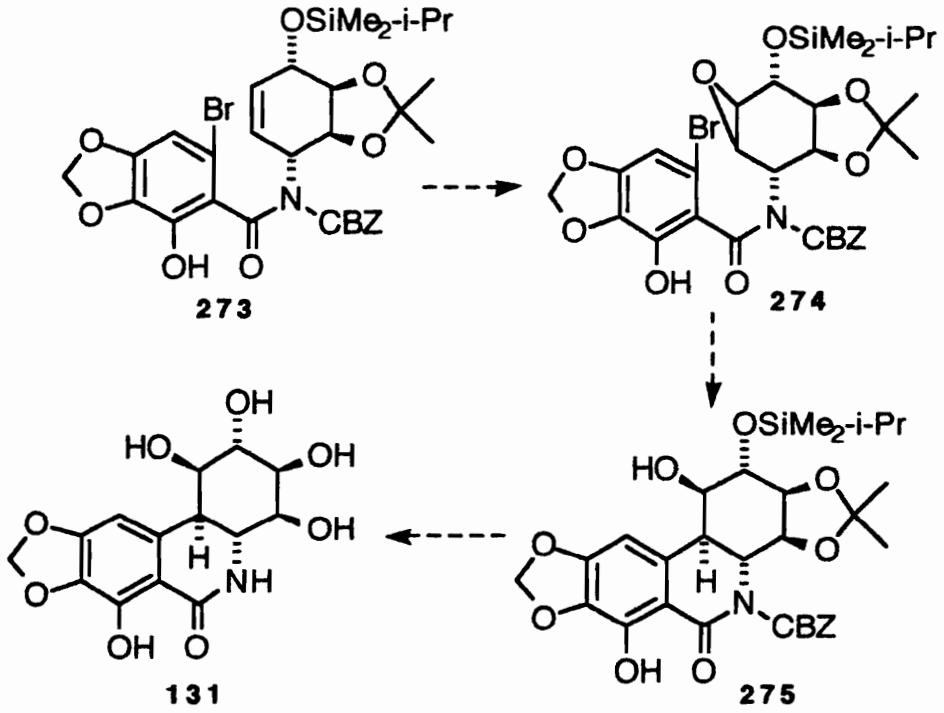


Figure 71. Approach to Pancratistatin.

IV. EXPERIMENTAL:

1. (1R,2S,5S,6S,7R,8S,9S,10S)-1,4-Dichloro-5,6:9,10-bis-(isopropiledenedioxy)tricyclo[6.2.2.0]dodeca-3,11-diene (67b)
2. (1R,2S,5S,6S,7S,8S,9S,10R)-4-Chloro-5,6:9,10-bis(iso-propylildenedioxy)tricyclo[6.2.2.0]dodeca-3,11-diene (231)
3. (1S,2S,3S,4R,7S,8R,9R,10S)-3,4:9,10-Bis(iso-propylildenedioxy)tricyclo[6.2.2.0]dodeca-5,11-diene (232)

4. (1S,2R,3S,6R)-6-Benzyloxycarbonylamino-1,2-O-isopropylidenecyclohex-4-ene-1,2,3-triol (243)
5. (1S,2R,3S,6R)-6-Acetamido-1,2-O-isopropyledenecyclohex-4-ene-1,2,3-triol (250)
6. (1S,2R,3S,6R)-6-Benzyloxycarbonylaminocyclohex-4-ene-1,2,3-triol (252)
7. (1S,2R,3S,6R)-6-Acetamidocyclohex-4-ene-1,2,3-triol (256)
8. (1S,2R,3S,4R)-4-Aminocyclohexane-1,2,3-triol: Dihydroconduramine A-1 (253)
9. (1S,2R,3S,4R)-4-Acetamidocyclohexane-1,2,3-triol triacetate: Dihydroconduramine A-1 Tetraacetate (254)
10. (1S,2R,3S,6R)-6-Acetamidocyclohex-4-ene-1,2,3-triol triaacetate: Conduramine A-1 Tetraacetate (257)

11. 3-Benzyloxycarbonyl-1-fluoro-5,6-O-isopropylidene-2-oxa-3-azabicyclo[2.2.2]oct-7-ene-5,6-diol (240a)
12. 3-Benzyloxycarbonyl-1-chloro-5,6-O-isopropylidene-2-oxa-3-azabicyclo[2.2.2]oct-7-ene-5,6-diol (240b)
13. 3-Benzyloxycarbonyl-1-bromo-5,6-O-isopropylidene-2-oxa-3-azabicyclo[2.2.2]oct-7-ene-5,6-diol (240c)
14. 3-Benzoyl-1-chloro-5,6-isopropylidene-2-oxa-3-azabicyclo[2.2.2]oct-7-ene (241b)
15. 3-Benzoyl-1-bromo-5,6-isopropylidene-2-oxa-3-azabicyclo[2.2.2]oct-7-ene (241c)
16. 3-Acetyl-1-chloro-5,6-O-isopropylidene-2-oxa-3-azabicyclo[2.2.2]oct-7-ene-5,6-diol (242b)

17. 3-Acetyl-1-bromo-5,6-O-isopropylidene-2-oxa-3-azabicyclo[2.2.2]oct-7-ene-5,6-diol (242c)

18. (1S,2S,3S,4R)-5-Ethoxycarbonyl-1-fluor-2,3-isopropylidene bicyclo[2.2.2]octa-5,7-diene (238a)
19. (1S,2S,3S,4R)-1-Chloro-5-ethoxycarbonyl-2,3-isopropylidene bicyclo[2.2.2]octa-5,7-diene (238b)
20. (1S,2S,3S,4R)-1-Bromo-5-ethoxycarbonyl-2,3-isopropylidene bicyclo[2.2.2]octa-5,7-diene (238c)
21. (1S,2S,3S,4R)-5-Ethoxycarbonyl-1-iodo-2,3-isopropylidene bicyclo[2.2.2]octa-5,7-diene (238d)
22. (1S,2S,3S,4R)-6-Ethoxycarbonyl-1-fluor-2,3-isopropylidene bicyclo[2.2.2]octa-5,7-diene (239a)
23. (1S,2S,3S,4R)-1-Chloro-6-ethoxycarbonyl-2,3-isopropylidene bicyclo[2.2.2]octa-5,7-diene (239b)
24. (1S,2S,3S,4R)-1-Bromo-6-ethoxycarbonyl-2,3-isopropylidene bicyclo[2.2.2]octa-5,7-diene (239c)
25. (1S,2S,3S,4R)-6-ethoxycarbonyl-1-iodo-2,3-isopropylidene bicyclo[2.2.2]octa-5,7-diene (239d)

26. (1S,2R,3S,6R)-6-Benzyloxycarbonylamino-1,2-O-isopropylidene-3-isopropyldimethylsilyloxycyclohex-4-ene-1,2,3-triol (244)
27. (1S,2R,3S,6R)-6-N-Benzyloxycarbonyl-6-N-(o-bromopiperonoyl)-1,2-O-isopropylidene-3-(isopropyldimethylsilyloxy)-cyclohex-4-ene-1,2,3-triol (267)
28 (2S,3R,4S,4aR)-5-Benzyloxycarbonyl-2-isopropyldimethylsyliloxy-3,4-O-isopropylidene-8,9-methylenedioxy-2,3,4,4a-tetrahydro-6-phenanthridone (268)
29. (2S,3R,4S,4aR)-2-isopropyldimethylsyliloxy-3,4-O-isopropylidene-8,9-methylenedioxy-2,3,4,4a,-tetrahydro-6-phenanthridone (272)
30. (2S,3R,4S,4aR)-8,9-methylenedioxy-2,3,4-trihydroxy-2,3,4,4a,-tetrahydro-6-phenanthridone. (+)-Lycoricidine (124)

EXPERIMENTAL SECTION:

Analytical TLC was performed on silica gel 60F-254 plates. Flash chromatography was performed on Kieselgel 60 (EM Reagents, 230-400 mesh). Mass spectra were recorded on a Varian MAT-112 instrument (low resolution). Infrared spectra were recorded on an FTIR Perkin-Elmer 1600 instrument. Proton NMR spectra were obtained on a Bruker WP-270 instrument. Proton chemical shifts are reported in parts per millio (ppm) relative to tetramethylsylane (TMS). Carbon NMR spectra were recorded on a Bruker WP-270 or NR-80 instruments. Carbon chemical shifts are reported in ppm relative to the center line of the $CHCl_3$ triplet (77.0 ppm) and the multiplicity is indicated by CH_3, CH_2, CH, C (INEPT experiments). Rotations were recordedon a Perkin Elmer 241 digital polarimeter. Elemental Analysis were performed by Atlantic Microlab, Inc. P.O. Box 2288, Norcross, Georgia 30091.

(1R,2S,5S,6S,7R,8S,9S,10S)-1,4-Dichloro-5,6:9,10-bis-(isopropiledenedioxy)tricyclo[6.2.2.0]dodeca-3,11-diene (67b).

3-Chloro-1,2-isopropylidenedioxycyclohexa-3,5-diene **66b** (30 mg) in 1 mL of $CDCl_3$ was poured in an NMR tube. The tube was flushed with argon and sealed. The tube was immersed in an oil bath and temperature was kept at 65°. The reaction was followed by NMR.

R_f= .41 (Hexane/Ethyl Acetate, 7:3); **mp**= 148-149°C; **$[\alpha]_D^{23}$**= +84 (c 0.35, $CHCl_3$); **IR** (KBr) υ 2981, 1660, 1378, 1217, 1087 cm^{-1};

^{1}H-NMR ($CDCl_3$) δ 6.16 (d, J= 3.9, 1H), 5.97 (m), 4.39 (dd, J= 7.2, 1H), 4.28 (d, J= 7.2, 1H), 4.21 (d, J= 3.9, 1H), 4.14 (d, J= 4.7, 1H), 2.88 (m), 2.71 (ddd, J= 8.9, 3.9, 1.6, 1H), 2.41 (d, J= 9.0, 1H), 1.38 (s, 3H), 1.35 (s, 6H), 1.30 (s,, 3H);

^{13}C-NMR ($CDCl_3$) δ 135.4 (CH), 133.3 (C), 128.1 (CH), 124.3 (CH), 110.1 (C), 108.9 (C), 82.9 (CH), 79.0 (CH), 78.9 (CH), 72.4 (CH), 42.7 (CH), 39.1 (CH), 35.1 (CH), 27.7 (CH_3), 26.6 (CH_3), 25.4 (CH_3), 25.1 (CH_3);

MS (EI, 70 eV) *m/z* (rel. intensity) 372 (M^+, 2), 357 (14), 221 (48), 129 (100);

Anal. calcd for $C_{18}H_{22}O_4Cl_2$: C, 57.92; H, 5.94; **Found**: C, 57.98; H, 5.98.

(1R,2S,5S,6S,7S,8S,9S,10R)-4-Chloro-5,6:9,10-bis(iso-propylildenedioxy)tricyclo[6.2.2.0]dodeca-3,11-diene (231).

Bu_3SnH (225 mg, 0.775 mmol) was added to a mixture of AIBN (cat. quant.) and the dichlorodimer **67b** (72.3 mg, 0.194 mmol). The reaction mixture was refluxed for 3 hrs. under argon. The solvent was evaporated and the residue was purified by column chromatography (silica gel, hexane-ethyl acetate, 4:1) to afford 65.5 mg (0.1945 mmol, 100% yield) of pure monochlorodimer.

R_f= 0.36 (hexane/ethyl acetate, 7:3); **mp**= 148-150 °C ; **$[\alpha]_D^{25}$**= +114° (c 0.6, $CHCl_3$);

IR (KBr) υ 2981, 1664, 1371, 1208, 1062 cm^{-1};

^{1}H-NMR ($CDCl_3$) δ 6.03 (m, 2H), 5.71 (d, J= 4.2 Hz, 1H), 4.25 (m, 3H), 4.14 (d, J= 4.7 Hz, 1H), 2.86 (m, 2H), 2.53 (m, 1H), 2.23 (d, J= 9.0 Hz, 1H), 1.37 (s, 3H), 1.34 (s, 3H), 1.29 (s, 3H), 1.25 (s, 3H);

^{13}C-NMR ($CDCl_3$) δ 132.5 (CH), 131.3 (C), 128.8 (CH), 127.9 (CH), 108.9 (C), 108.5 (C), 79.5 (CH), 78.6 (CH), 77.9 (CH), 72.7 (CH), 41.2 (CH), 40.4 (CH), 35.7 (CH), 34.3 (CH), 27.8 (CH_3), 26.6 (CH_3), 25.4 (CH_3), 25.0 (CH_3);

MS (EI, 70 eV) *m/z* (rel. intensity) 338 (M^+, 1.5), 323 (14), 222 (60), 169 (46), 129 (66), 95 (100);

Anal. Calcd for $C_{18}H_{23}O_4Cl$: C, 63.81; H, 6.84; **Found**: C, 63.84; H, 6.89.

(1S,2S,3S,4R,7S,8R,9R,10S)-3,4:9,10-Bis(iso-propylildenedioxy)tricyclo[6.2.2.0]dodeca-5,11-diene (232).

Dichlorodimer **67b** (100 mg, 0.268 mmol) was added (in THF, 2 mL) via syringe to a blue solution of sodium (25 mg, 1.1 mmol) in liquid ammonia (~ 5 mL). After 1 hr., ammonia was let evaporate. THF and methanol were added. Solution was washed with Na_2CO_3 solution and then brine. Na_2SO_4 was added to the organic extract, and then filtered. Solvent was evaporated and dimer was chromatographed (silica gel, hexane/ethyl acetate, 4:1) to afford 9.1 mg (0.1 mmol, 37% yield) of the dihalogenated dimer **232**.

mp = 150-151 °C;

^{1}H-NMR ($CDCl_3$) δ 5.96 (2H, m), 5.58 (1H, ddd, J= 10.2, 3.6, 1.4), 5.48 (1H, ddd, J= 10.2, 3.0, 1.5), 4.30 (1H, dd, J= 7.3, 3.1), 4.25 (1H, dd, J= 7.3, 3.0), 4.18 (1H, ddd, J= 4.9, 3.6, 1.4), 4.13 (1H, br d, J= 4.9), 2.85 (2H, m), 2.34 (1H, m), 2.20 (1H, br d, J= 9.0), 1.33 (3H, s), 1.31 (3H, s), 1.29 (3H, s), 1.26 (3H, s);

^{13}C-NMR ($CDCl_3$) δ 132.4 (CH), 129.3 (CH), 128.8 (CH), 126.6 (CH), 108.6 (C), 107.6 (C), 78.6 (CH), 77.6 (CH), 70.9 (CH), 41.0 (CH), 40.7 (CH), 34.3 (CH), 33.1 (CH), 28.3 (CH3), 26.8 (CH3), 25.4 (CH3), 25.0 (CH3).

Anal. calcd for $C_{18}H_{24}O_4$: C, 71.03; H, 7.95; **Found**: C, 70.89; H, 8.02.

(1S,2R,3S,6R)-6-Benzyloxycarbonylamino-1,2-O-isopropylidenecyclohex-4-ene-1,2,3-triol (243).

To a stirred solution of the Diels-Alder adduct 240c (221 mg,0.056 mmol) in aqueous tetrahydrofuran (THF:H_2O, 10:1, 11mL) cooled to 0°C was added aluminum amalgam (from 105 mg, 3.9 mmoL, 7 eq. of Reynolds heavy-duty aluminum foil), and stirring was continued at 0 °C. After 6 hrs, reaction was completed. The reaction mixture was diluted with 30 mL of THF, stirred for 10 min, then filtered through celite. The filtrate was diluted with toluene and concentrated under reduced pressure to afford the hydroxy carbamate **243** (161 mg, 0.51 mmol, 91%). An analytical sample was obtained by column chromatography (silica gel, Hexane/Ethyl Acetate, 1:1), and recrystallized from CH_2Cl_2/Hexane.

Rf=0.32 (Hexane/Ethyl Acetate, 1:1); **mp**= 113-114°C; $[\alpha]_D^{20}$=-41° (c .8, $CHCl_3$);
IR (KBr) u 3338, 2989, 1702, 1522, 1217, 1064 cm^{-1};
^{1}H-NMR ($CDCl_3$) δ 7.37 (m, 5H), 5.96 (m, 1H), 5.83 (dd, J=9.8, 2.2 Hz, 1H), 5.31 (bs, 1H), 5.13 (d, J=2.8 Hz, 1H), 4.23 (m, 4H), 4.18 (m, 1H), 2.64 (bs, 1H), 1.47 (s, 3H), 1.36 (s, 3H);
^{13}C-NMR ($CDCl_3$) δ 155.9 (CO), 136.3 (C), 131.1 (CH), 129.8 (CH), 128.5 (2CH), 128.2 (2CH), 109.2 (C), 79.2 (C), 77.0 (CH), 69.1 (CH), 67.0 (CH_2), 51.3 (CH), 27.0 (CH_3), 24.7 (CH_3);
MS (CI, 70 eV) *m/z* (relative intensity) 320 (M^++1, 20), 262 (30), 212 (100), 91 (50);
Anal. Calcd for $C_{17}H_{21}NO_5$: C, 63.94; H, 6.63. **Found:** C, 63.99; H, 6.64.

(1S,2R,3S,6R)-6-Acetamido-1,2-O-isopropylidenecyclohex-4-ene-1,2,3-triol (250).

A solution of the Diels-Alder adduct 242c (265 mg, 0.87 mmol) in aqueous tetrahydrofuran (THF:H_2O, 10:1, 11mL) was cooled to 0°C, aluminum amalgam (from 165 mg, 6.1 mmoL, 7 eq. of Reynolds heavy-duty aluminum foil) was added, and stirring was continued at 0 °C. After 6 hrs, reaction was complete. The reaction mixture was diluted with 30 mL of THF, stirred for 10 min, then filtered through celite. The filtrate was diluted with toluene and concentrated in vacuo to afford 152 mg (0.67 mmol, 77% yield) of hydroxy carbamate **250** as a white solid. An analytical sample was obtained by flash chromatography (silica gel, Hexane/Ethyl Acetate, 1:1), and recrystallized from CH_2Cl_2/Hexane.

Rf=0.3 ($CHCl_3$/MeOH, 9:1); **mp**= 113-114°C; $[\alpha]_D^{20}$= -38° (c 8.7, $CHCl_3$);
IR (KBr) υ 3300, 1640, 1360, 1050 cm^{-1};
^{1}H-NMR ($CDCl_3$) δ 6.45 (1H, bs), 5.75 (1H, ddd, J= 9.9, 2.8, 2.5 Hz), 5.51 (1H, ddd, J= 9.9, 2.8, 2.5 Hz), 4.34 (1H, m), 3.6 (1H, bs), 4.23 (3H, m), 1.97 (3H, s), 1.39 (3H, s), 1.30 (3H, s);
^{13}C-NMR ($CDCl_3$) δ 170.1 (C), 131.3 (CH), 129.7 (CH), 109.0 (C), 79.1 (C), 76.6 (CH), 68.3 (CH), 49.3 (CH), 26.9 (CH_3), 24.7 (CH_3), 23.4 (CH_3);
MS (EI, 70 eV) *m/z* (relative intensity) 212 (M^+-15, 25), 168 (35), 140 (50), 127 (90), 98 (75), 81 (100).

(1S,2R,3S,6R)-6-Benzyloxycarbonylaminocyclohex-4-ene-1,2,3-triol (252).

To a solution of acetonide **243** (29 mg, 0.09 mmol), in 5 mL of a 1:1 mixture of acetone/H_2O, was added conc. aq. HCl (1 drop). The solution was stirred for 12 hrs and concentrated to afford 25 mg (0.089 mmol, 99% yield) of carbamate triol **252.**
Rf= 0.44 (CH_3Cl/MeOH, 4:1); **mp** 122-124°C
^{1}H-NMR (CD_3OD) δ 7.25 (5H, m), 5.62 (1H, br d, J= 10.0 Hz), 5.49 (1H, br d, J= 10.0 Hz), 4.13 (1H, m), 4.03 (1H, m), 3.70 (1H, dd, J= 6.0, 2.2 Hz), 3.63 (1H, m).

(1R,2S,3R,6R)-6-Acetamidocyclohex-4-ene-1,2,3-triol (256).

Acetonide **250** (160 mg, 0.7 mmol) was dissolved in a mixture of AcOH/THF/H_2O (2:1:1, 8 mL). The solution was stirred at 60°C for 4 hrs. The sovent was evaporated and 130 mg (0.69 mmol, 99% yield) of triol **256** was obtained.
^{1}H-NMR (CD_3OD) δ 5.53 (1H, ddd, J= 10.0, 3.2, 1.9 Hz), 5.32 (1H, ddd, J= 10.0, 3.1, 1.0 Hz), 4.25 (1H, m), 3.94 (1H, m), 3.56 (1H, dd, J= 5.5, 2.3 Hz), 3.49 (1H, dd, J= 5.5, 2.3 Hz), 1.75 (3H, s);
^{13}C-NMR (CD_3OD) δ 173.1 (C), 130.7 (CH), 128.2 (CH), 73.9 (CH), 71.8 (CH), 69.9 (CH), 51.4 (CH), 22.4 (CH_3).

(1S,2R,3S,4R)-4-Aminocyclohexane-1,2,3-triol: Dihrydroconduramine A-1 (253).

Carbamate **252** (25 mg, 0.09 mmol), was dissolved in 5 mL of MeOH. Paladium over charcoal (15 mg) was added, and the mixture aws shaken in a Parr hydrogenator for 4 hrs.

at 30 psi of H_2. The mixture was then filtered through celite and the solvent evaporated to afford 13 mg (0.089 mmol, 99% yield) of Dihydroconduramine A-1 **253**.
^{1}H-NMR (CD_3OD) δ 3.77 (1H, m), 3.71 (1H, t, J= 3.3 Hz), 3.49 (1H, dd, J= 10.0, 3.1 Hz), 2.90 (1H, td, J= 10.0, 4.5 Hz), 1.8-1.4 (4H, m);
^{13}C-NMR (CD_3OD) δ 74.0 (CH), 73.2 (CH), 71.1 (CH), 51.9 (CH), 26.9 (CH_2), 26.2 (CH_2).

(1S,2R,3S,4R)-1-Acetamidocyclohexane-1,2,3-triol triacetate: Dihydroconduramine A-1 Tetraacetate (254).
Dihydroconduramine A-1 **253** (17 mg, 0.116 mmol) was stirred in a mixture of Ac_2O/Pyridine (1:1, 2 mL), for 3 hrs. The solution was washed with 10% HCl and extracted with ethyl acetate. Na_2SO_4 was added to the organic layer, filtered and the solvent evaporated to afford 35 mg (0.112 mmol, 97% yield) of the tetracetate **254**.
Rf= 0.35 (Hexane/Ethyl Acetate, 1:1); **$[\alpha]_D^{20}$**= +42° (c 0.9, $CHCl_3$);
^{1}H-NMR ($CDCl_3$) δ 5.68 (1H, d, J= 8.5 Hz), 5.22 (1H, t, J= 3.8 Hz), 5.06 (1H, dd, J= 10.4, 3.3 Hz), 4.98 (1H, m), 4.4-4.2 (1H, m), 2.10 (3H, s), 2.08 (3H, s), 1.98 (3H, s), 1.93 (3H, s);
^{13}C-NMR ($CDCl_3$) δ 171.4 (C), 169.7 (C), 169.4 (C), 169.2 (C), 71.0 (CH), 69.4 (CH), 69.3 (CH), 47.9 (CH), 25.9 (CH_2), 24.1 (CH_2), 23.3 (CH_3), 20.9 ($2CH_3$), 20.8 (CH_3);
MS (EI, 70 eV) *m/z* (relative intensity) 315 (M^+, 5), 195 (30), 153 (70), 94 (100).

(1S,2R,3S,6R)-6-Acetamidocyclohe-4-ene-1,2,3-triol triacetate: Conduramine A-1 Tetraacetate (257).
Triol **256** (72.6 mg, 0.388 mmol) was stirred in a mixture of Ac_2O/Pyridine (1:1, 2 mL), for 3 hrs. The solution was washed with 10% HCl and extracted with ethyl acetate. Na_2SO_4 was added to the organic layer, filtered and the solvent evaporated to afford 76 mg (0.243 mmol, 63% yield) of the tetracetate **257**.
Rf= 0.38 ($CHCl_3$/MeOH, 95:5); **$[\alpha]_D^{20}$**= +33° (c 0.36, $CHCl_3$);
^{1}H-NMR ($CDCl_3$) δ 5.78 (2H, m), 5.75 (1H, d, J= 9.0), 5.28-5.15 (3H, m), 4.80 (1H, dd, J= 8.3, 7.5), 2.06 (3H, s), 2.05 (3H, s), 2.04 (3H, s), 1.96 (3H, s);
^{13}C-NMR ($CDCl_3$) δ 170.6 (C), 169.8 (C), 169.6 (C), 131.1 (CH), 125.0 (CH), 69.6 (CH), 68.3 (CH), 47.8 (CH), 23.2 (CH_3), 20.8 (CH_3);
MS (EI, 70 eV) *m/z* (relative intensity) 254 (M^+-59, 80), 151 (100), 109 (95).

3-Benzyloxycarbonyl-1-chloro-5,6-O-isopropylidene-2-oxa-3-azabicyclo[2.2.2]oct-7-ene-5,6-diol (240b).

N-Hydroxybenzyl urethane (1.720g) was added slowly to a solution of protected chlorodiol **66b** (.915g) and Bu_4NIO_4 (2.403g) in CH_2Cl_2 (10mL) in an ice bath. After 1 h, the solution was washed with 20% sodium thiosulphate solution (10 mL), saturated Na_2CO_3 solution (10 mL), and brine (10 mL). The organic layer was dried over Na_2SO_4, filtered and evaporated. The Diels Alder adduct was purified by column chromatography (silica gel; 7.5:2.5, Hexane/Ethyl Acetate). 813 mg (52% yield) was obtained.

Rf=0.24 (Hexane/Ethyl Acetate, 8:2); $[\alpha]_D^{20}$=+21.4 (c 2.7, $CHCl_3$);

IR (KBr) υ 3067, 3034, 2991, 2937, 1755, 1610, 1384, 1269, 1220 cm^{-1};

^{1}H-NMR ($CDCl_3$) δ 7.40 (s, 5H), 6.45 (dd, J=8.0, 5 Hz, 1H), 6.37 (dd, J=8.6 Hz, 1H), 5.23 (d, J=12.3 Hz, 1H), 5.17 (d, J=12.3 Hz, 1H), 5.07 (m, 1H), 4.65 (dd, J= 7, 4 Hz, 1H), 4.51 (d, J= 7, 1H), 1.36 (s, 3H), 1.33 (s, 3H);

^{13}C-NMR ($CDCl_3$) δ 157.8 (CO), 135.4 (C), 132.9 (2CH), 131.7 (CH), 128.6 (2CH), 128.4 (CH), 128.0 (CH), 111.8 (C), 95.0 (C), 80.5 (CH), 74.3 (CH), 68.6 (CH_2), 53.7 (CH), 25.6 (CH_3), 25.4 (CH_3);

MS (CI, 70 eV) *m/z* (relative intensity) 352 (M^+, 5), 308 (25), 91 (100);

Anal. Calcd for $C_{17}H_{18}NO_5Cl$: C, 58.04; H, 5.16. **Found:** C, 58.14; H, 5.18.

3-Benzyloxycarbonyl-1-bromo-5,6-O-isopropylidene-2-oxa-3-azabicyclo[2.2.2]oct-7-ene-5,6-diol (240c).

N-Hydroxybenzyl urethane (1.720g, 10.3 mmol) was added slowly to a solution of protected bromodiol **66c** (.915g, 4.0 mmol) and Bu_4NIO_4 (2.403g, 5.5 mmol) in CH_2Cl_2 (10 mL) in an ice bath. After 1 h, the solution was washed with 20% sodium thiosulphate solution (10 mL), saturated Na_2CO_3 solution (10 mL), and brine (10 mL). The organic layer was dried over Na_2SO_4, filtered and evaporated. The Diels Alder adduct was purified by column chromatography (silica gel; 7.5:2.5, Hexane/Ethyl Acetate). 813 mg (52% yield) was obtained.

Rf=0.48 (Hexane/Ethyl Acetate, 7:3); $[\alpha]_D^{20}$=+16.1 (c 9.5, $CHCl_3$);

IR (KBr) υ 3067, 2992, 1755, 1714, 1607, 1269, 1212 cm^{-1};

^{1}H NMR ($CDCl_3$) δ 7.33 (s, 5H), 6.49 (dd, J=8.5,1.4 Hz, 1H), 6.36 (dd, J=8.6,5.6 Hz, 1H), 5.22 (d, J=12.3 Hz, 1H), 5.15 (d, J=12.3 Hz, 1H), 5.05 (m, 1H), 4.61 (m, 2H), 1.34 (s, 3H), 1.31 (s, 3H);

^{13}C NMR ($CDCl_3$) δ 157.8 (CO), 135.4 (C), 134.1 (2CH), 131.5 (CH), 128.5 (2CH), 128.4 (CH), 128.0 (CH), 111.5 (C), 87.5 (C), 81.4 (CH), 74.3 (CH), 74.3 (CH), 68.5 (CH_2), 53.3 (CH), 25.7 (CH_3), 25.4 (CH_3);
MS (EI, 70 eV) *m/z* (relative intensity) 395 (M^+, 1), 100 (10), 91 (100);
Anal. Calcd for $C_{17}H_{18}NO_5Br$: C, 51.53; H, 4.58. **Found:** C, 51.40; H, 4.58.

3-Benzoyl-1-bromo-5,6-isopropylidene-2-oxa-3-azabicyclo[2.2.2]oct-7-ene (241c).

Benzohydroxamic Acid (421 mg, 3.074 mmol) was added slowly to a solution of protected bromodiol # (355 mg, 1.537 mmol) and Bu_4NIO_4 (533 mg, 0.8 eq.) in CH_2Cl_2 (5 mL) in an ice bath. After 2 h, the solution was washed with 20% sodium thiosulphate solution (10 mL), saturated Na_2CO_3 solution (10 mL), and brine (10 mL). The organic layer was dried over Na_2SO_4, filtered and evaporated. The Diels Alder adduct was purified by column chromatography (silica gel; 9:1, Hexane/Ethyl Acetate). 350 mg (1.066 mmol, 70% yield) was obtained.
Rf=0.41 (Hexane/Ethyl Acetate, 7:3); **mp** = 150-155 °C; $[\alpha]_D^{20}$=+ 52° (c 1.0, $CHCl_3$);
IR (KBr) υ 3344, 3074, 2984, 1660, 1605, 1271 cm^{-1};
^{1}H-NMR ($CDCl_3$) δ 7.73 (2H, m), 7.45 (3H, m), 6.49 (2H, m), 5.44 (1H, m), 4.72 (2H, m), 1.38 (3H, s), 1.36 (3H, s);
^{13}C-NMR ($CDCl_3$) δ 172.2 (C), 133.9 (CH), 132.7 (CH), 132.4 (C), 131.9 (CH), 129.3 (2CH), 128.1 (2CH), 111.5 (C), 88.1 (C), 81.5 (CH), 74.1 (CH), 51.2 (CH), 25.6 (CH_3), 25.3 (CH_3);
MS (EI, 70 eV) *m/z* (relative intensity) 366 (M^+, 6), 228 (11), 105 (98), 77 (100);
Anal. Calcd for $C_{16}H_{16}NO_4Br$: C, 52.48; H, 4.40. **Found:** C, 52.53; H, 4.44.

3-Acetyl-1-bromo-5,6-O-isopropylidene-2-oxa-3-azabicyclo[2.2.2]oct-7-ene-5,6-diol (242c).

N-Acetohydroxamic acid (170.4 mg, 2.273 mmol) was added slowly to a solution of protected bromodiol **66c** (525 mg, 2.273 mmol) and Bu_4NIO_4 (492mg, 1.136 mmol) in CH_2Cl_2 (10mL) in an ice bath. After 1 h, the solution was washed with 20% sodium thiosulphate solution (10 mL), saturated Na_2CO_3 solution (10 mL), and brine (10 mL). The organic layer was dried over Na_2SO_4, filtered and evaporated. The Diels Alder adduct was purified by column chromatography (silica gel; 7.5:2.5, Hexane/Ethyl Acetate) 350.7 mg (1.153 mmol, 51% yield) was obtained.

Rf=0.34 (Hexane/Ethyl Acetate, 4:1); **mp** 99-102 °C; $[\alpha]_D^{20}$= -13.7° (c 4.3, $CHCl_3$);
IR (KBr) υ 3076, 1657, 1606, 1384 cm^{-1};
^{1}H-NMR ($CDCl_3$) δ 6.43 (1H, m), 5.41 (1H, m), 4.60 (1H, dd, J= 7.0, 0.6 Hz), 4.53 (1H, ddd, J= 7.0, 4.0, 0.7 Hz), 2.04 (3H, s), 1.34 (1H, s), 1.31 (3H, s);
^{13}C-NMR ($CDCl_3$) δ 174.2 (C), 133.8 (C), 132.5 (2CH), 111.5 (C), 88.2 (C), 81.4 (CH), 74.1 (CH), 49.8 (CH), 25.6 (CH_3), 25.3 (CH_3), 21.7 (CH_3);
MS (EI, 70 eV) *m/z* (relative intensity) 304 (M^+, 10), 288 (65), 156 (95), 124 (100), 94 (85).

(1S,2S,3S,4R)-5-Ethoxycarbonyl-1-Fluor-2,3-isopropylidene bicyclo[2.2.2]octa-5,7-diene (238a)

Fluorobenzene diol acetonide **66a** (237.5 mg, 1.397 mmoL) was diluted in benzene (5 mL). Ethyl propiolate **237** (0.283 mL, 2.79 mmoL)was added. Solution was heated to reflux under argon for 48 h. Solvent was evaporated and mixture was chromatographed in silica gel (Hexane/Ethyl Acetate, 9:1). Two cycloadducts were obtained, 119.6 mg (0.45 mmoL, 32%) of the less polar Diels Alder adduct **238a** was obtained as an oil.
Rf= 0.41 (Hexane/EtOAc, 4:1);
IR (KBr) υ 3020, 2983, 1712, 1374, 1216, 1051 cm^{-1};
^{1}H-NMR ($CDCl_3$) δ 7.2 (1H, d, J= 11 Hz), 6.43 (1H, dd, J= 9, 9 Hz), 6.30 (1H, m), 4.43 (1H, m), 4.35 (2H, m), 4.20 (2H, q, J= 7 Hz), 1.37 (3H, s), 1.29 (3H, s), 1.29 (3H, t, J= 7 Hz);
^{13}C-NMR ($CDCl_3$) δ 163.5 (CO), 143.9 (CH), 135.5 (C), 132.0 (CH), 115.0 (C), 80.0 (CH), 78.2 (CH), 61.1 (CH_2), 41.5 (CH), 25.8 (CH_3), 25.6 (CH_3), 14.2 (CH_3)
MS (CI, 70 eV) *m/z* (rel. intensity) 269 (M+, 60), 211 (20), 169 (95), 100 (100);
Anal. calcd for $C_{14}H_{17}O_4F$: C, 62.68; H, 6.39; **Found**: C, 62.75; H, 6.41.

(1S,2S,3S,4R)-1-Chloro-5-ethoxycarbonyl-2,3-isopropylidene bicyclo[2.2.2]octa-5,7-diene (238b)

Chlorobenzenediol acetonide **66b** (580 mg, 3.126 mmoL) was diluted in benzene (5 mL). Ethyl propiolate **237** (0.613 mL, 6.25 mmoL)was added. Solution was heated to reflux under argon for 48 h. Solvent was evaporated and mixture was chromatographed in silica gel (Hexane/Ethyl Acetate, 9:1). Two cycloadducts were obtained, 195 mg (0.685 mmoL, 22%) of the less polar Diels Alder adduct **238b** was obtained as an oil.
Rf= 0.42 (Hexane/EtOAc, 4:1); $[\alpha]_D^{20}$= +49.6° (c 1.4, $CHCl_3$);

IR (KBr) υ 3019, 2983, 1713, 1630, 1591, 1374, 1246, 1064 cm^{-1};
^{1}H-NMR ($CDCl_3$) δ 7.12 (1H, s), 6.37 (1H, m), 6.29 (1H, d, J= 7.5 Hz), 4.35 (3H, m), 4.19 (2H, q, J= 5.6 Hz), 1.37 (3H, s), 1.30 (3H, t, J= 5.6 Hz), 1.29 (3H, s);
^{13}C-NMR ($CDCl_3$) δ 163.2 (CO), 146.8 (CH), 137.0 (C), 135.0 (CH), 131.5 (CH), 114.3 (C), 83.9 (CH), 79.1 (CH), 69.8 (C), 61.0 (CH2), 41.1 (CH), 25.7(CH_3), 25.5 (CH_3), 14.1 (CH_3);
MS (CI, 70 eV) *m/z* (rel. intensity) 285 (M+1, 25), 227 (23), 185 (100), 151(30), 100 (95);
Anal. calcd for $C_{14}H_{17}O_4Cl$: C, 59.05; H, 6.02; **Found**: C, 59.00; H, 6.00.

(1S,2S,3S,4R)-1-Bromo-5-ethoxycarbonyl-2,3-isopropylidene bicyclo[2.2.2]octa-5,7-diene (238c).
Bromobenzenediol acetonide **66c** (1048 mg, 4.537 mmoL) was diluted in benzene (10 mL). Ethyl propynoate **273** (0.92 mL, 9 mmoL)was added. Solution was heated to reflux under argon for 24 h. Solvent was evaporated and mixture was chromatographed in silica gel (Hexane/Ethyl Acetate, 9:1). 318 mg (0.97 mmoL, 21%) of the Diels Alder adduct **238c** was obtained.
Rf= 0.41 (Hexane/EtOAc, 4:1); **$[\alpha]_D^{20}$**= + 46.7 ° (c 1.0, $CHCl_3$);
IR (KBr) u 3078, 2981, 1716, 1372, 1243, 1063 cm^{-1};
^{1}H-NMR ($CDCl_3$) δ 7.23 (1H, d, J= 1 Hz), 6.38 (1H, d, J= 7, 5 Hz), 6.32 (1H, m), 4.35 (3H, m), 4.22 (2H, q, J= 7 Hz), 1.39 (3H, s), 1.30 (3H, s), 1.29 (3H, t, J= 7 Hz);
^{13}C-NMR (CD_3OD) δ 163.3 (CO), 147.6 (CH), 137.6 (C), 136.1 (CH), 131.9 (CH), 114.2 (C), 84.7 (CH), 79.4 (CH), 61.1 (CH_2), 60.4 (C), 40.9 (CH), 25.8 (CH_3), 25.6 (CH_3), 14.1 (CH_3);
MS (CI, 70 eV) *m/z* (rel. intensity) 329 (M^+, 28), 151 (95), 100 (100);
Anal. calcd for $C_{14}H_{12}O_4Br$: C, 51.08; H, 5.20; **Found**: C, 50.99; H, 5.16.

(1S,2S,3S,4R)-5-Ethoxycarbonyl-1-iodo-2,3-isopropylidene bicyclo[2.2.2]octa-5,7-diene (238d).
Iodobenzenediol acetonide **66d** (263 mg, 0.946 mmoL) was diluted in benzene (10 mL). Ethyl propynoate **273** (0.92 mL, 9 mmoL)was added. Solution was heated to reflux under argon for 24 h. Solvent was evaporated and mixture was chromatographed in silica gel (Hexane/Ethyl Acetate, 9:1). 73.2 mg (0.195 mmoL, 21%) of the Diels Alder adduct **238d** was obtained.

R_f= 0.47 (Hexane/EtOAc, 4:1); **$[\alpha]_D^{20}$**= +45.5° (c 1.3 $CHCl_3$);
IR (KBr) υ 3073, 2981, 1716, 1623, 1584, 1372, 1243, 1061 cm^{-1};
^{1}H-NMR ($CDCl_3$) δ 7.36 (1H, d, J= 1.6 Hz), 6.47 (1H, dt, J= 7.4, 1.3 Hz), 6.18 (1H, td, J= 6, 1.3 Hz), 4.43 (1H, dd, J= 6.7, 1 Hz), 4.30 (2H, m), 4.21 (2H, q, J= 7 Hz), 1.38 (3H, s), 1.30 (3H, s), 1.30 (3H, t, J= 7 Hz);
^{13}C-NMR ($CDCl_3$) δ 163.1 (CO), 150.2 (CH), 138.7 (CH), 138.1 (C), 132.4 (CH), 113.6 (C), 86.3 (CH), 79.0 (CH), 61.1 (CH_2), 40.1 (CH), 36.0 (C), 25.8 (CH_3), 25.5 (CH_3), 14.1 (CH_3);
MS (CI, 70 eV) *m/z* (rel. intensity) 377 (M+1, 10), 277 (50), 100 (100);
Anal. calcd for $C_{14}H_{17}O_4I$: C, 44.70; H, 4.55; **Found**: C, 44.80; H, 4.56.

(1S,2S,3S,4R)-6-Ethoxycarbonyl-1-fluor-2,3-isopropylidene bicyclo[2.2.2]octa-5,7-diene (239a).
Fluorobenzenediol acetonide **66a** (237.5 mg, 1.397 mmoL) was diluted in benzene (5 mL). Ethyl propiolate **237** (0.283 mL, 2.79 mmoL)was added. Solution was heated to reflux under argon for 48 h. Solvent was evaporated and mixture was chromatographed in silica gel (Hexane/Ethyl Acetate, 9:1). Two cycloadducts were obtained, 174.6 mg (0.65 mmoL, 46.6%) of the more polar Diels Alder adduct **239a** was obtained.
R_f= 0.25 (Hexane/EtOAc, 4:1); **mp**= 64-65.5 °C ;
IR (KBr) υ 3077, 2985, 1724, 1370, 1245, 1104 cm^{-1};
^{1}H-NMR ($CDCl_3$) δ 6.94 (1H, dd, J= 6.2, 6.2 Hz), 6.50 (1H, m), 6.24 (1H, m), 4.51 (1H, ddd, J= 7, 7, 1.5 Hz), 4.35 (1H, m), 4.23 (2H, q, J= 7.2 Hz), 3.91 (1H, dddd, J= 3.5, 3.5, 3.5, 1.6 Hz), 1.37 (3H, s), 1.30 (3H, s), 1.30 (3H, t, J= 7.2 Hz);
^{13}C-NMR ($CDCl_3$) δ 162.8 (CO), 140.1 (CH), 139.5 (C, d, J= 21 Hz), 133.3 (CH, d, J= 21 Hz), 128.7 (CH, J= 12.6 Hz), 115.1 (C), 80.4 (CH, d, J= 17 Hz), 78.2 (CH), 60.8 (CH_2), 42.2 (CH), 25.8 (CH_3), 25.7 (CH_3), 14.2 (CH_3);
MS (CI, 70 eV) *m/z* (rel. intensity) 269 (M+, 100), 211 (15), 191 (20), 169 (60);
Anal. calcd for $C_{14}H_{17}O_4F$: C, 62.68; H, 6.39; **Found**: C, 62.68; H, 6.34.

(1S,2S,3S,4R)-1-Chloro-6-ethoxycarbonyl-2,3-isopropylidene bicyclo[2.2.2]octa-5,7-diene (239b).
Chlorobenzenediol acetonide **66b** (580 mg, 3.126 mmoL) was diluted in benzene (5 mL). Ethyl propiolate **273** (0.613 mL, 6.25 mmoL)was added. Solution was heated to reflux under argon for 48 h. Solvent was evaporated and mixture was chromatographed in silica

gel (Hexane/Ethyl Acetate, 9:1). Two cycloadducts were obtained, 156 mg (0.548 mmoL, 17.5%) of the more polar Diels Alder adduct **239b** was obtained.

Rf= 0.24 (Hexane/EtOAc, 4:1); **mp**= 78-79 °C ; $[\alpha]_D^{20}$= +42.4 ° (c 0.8, $CHCl_3$);

IR (KBr) υ 3019, 2984, 2936, 1722, 1630, 1588, 1374, 1215, 1093 cm^{-1};

^{1}H-NMR ($CDCl_3$) δ 6.91 (1H, d, J= 6.5 Hz), 6.36 (1H, m), 6.30 (1H, d, J= 7.5 Hz), 4.40 (2H, m), 4.23 (2H, q, J= 7 Hz), 3.92 (1H, m), 1.39 (3H, s), 1.31 (3H, t, J= 7 Hz), 1.31 (3H, s);

^{13}C-NMR ($CDCl_3$) δ 163.8 (CO), 140.2 (C), 139.3 (CH), 136.7 (CH), 130.5 (CH), 114.3 (C), 83.9 (CH), 78.9 (CH), 68.4 (C), 60.9 (CH_2), 41.6 (CH), 25.7(CH_3), 25.5 (CH_3), 14.0 (CH_3);

MS (CI, 70 eV) *m/z* (rel. intensity) 285 (m+1, 95), 227 (20), 185 (95), 100 (100);

Anal. calcd for $C_{14}H_{17}O_4Cl$: C, 59.05; H, 6.02; **Found**: C, 58.95; H, 6.01.

(1S,2S,3S,4R)-1-Bromo-6-ethoxycarbonyl-2,3-isopropylidene bicyclo[2.2.2]octa-5,7-diene (239c).

Bromobenzenediol acetonide **66c** (1048 mg, 4.537 mmoL) was diluted in benzene (10 mL). Ethyl propiolate **273** (0.92 mL, 9 mmoL)was added. Solution was heated to reflux under argon for 24 h. Solvent was evaporated and mixture was chromatographed in silica gel (Hexane/Ethyl Acetate, 9:1). 591 mg (1.8 mmoL, 40%) of the Diels Alder adduct **239c** was obtained.

Rf= 0.32 (Hexane/EtOAc, 4:1); **mp**= 87 °C ; $[\alpha]_D^{20}$= + 102 ° (c 1.4, $CHCl_3$);

IR (KBr) υ 3072, 2983, 1717, 1238, 1094 cm^{-1};

^{1}H-NMR ($CDCl_3$) δ 6.83 (1H, d, J= 7 Hz), 6.44 (1H, dt, J= 7, 1 Hz), 6.22 (1H, td, J= 7, 1 Hz), 4.43 (1H, dd, J= 7, 1 Hz), 4.32 (1H, ddd, J= 7, 3.5, 1 Hz), 4.22 (2H, q, J= 7 Hz), 3.88 (1H, m), 1.37 (3H, s), 1.29 ($2CH_3$, st , J= 7 Hz);

^{13}C-NMR ($CDCl_3$) δ 164.4 (CO), 140.4 (C), 138.8 (CH), 137.8 (CH), 131.0 (CH), 114.1 (C), 84.5 (CH), 79.0 (CH), 61.1 (CH_2), 58.9 (C), 41.5 (CH), 25.8 (CH_3), 25.5 (CH_3), 14.1 (CH_3);

MS (EI, 70 eV) *m/z* (rel. intensity) 313 (M^+-16, 1.5), 100 (100), 85 (95);

Anal. calcd for $C_{14}H_{12}O_4Br$: C, 51.08; H, 5.20; **Found**: C, 51.20; H, 5.24.

(1S,2S,3S,4R)-6-Ethoxycarbonyl-1-iodo-2,3-isopropylidene bicyclo[2.2.2]octa-5,7-diene (239d).

Iodobenzenediol acetonide **66d** (263 mg, 0.946 mmoL) was diluted in benzene (5 mL). Ethyl propiolate **273** (0.92 mL, 9 mmoL)was added. Solution was heated to reflux under argon for 48 h. Solvent was evaporated and mixture was chromatographed in silica gel (Hexane/Ethyl Acetate, 9:1). Two cycloadducts were obtained, 120 mg (0.32 mmoL, 34%) of the more polar Diels Alder adduct **239d** was obtained.

Rf= 0.27 (Hexane/EtOAc, 4:1); $[\alpha]_D^{20}$= +115 ° (c 1.1, $CHCl_3$); **mp**= 74-76 °C

IR (KBr) υ 3054, 2984, 1716, 1623, 1378, 1304, 1235, 1089 cm^{-1};

^{1}H-NMR ($CDCl_3$) δ 6.84 (1H, d, J= 6.5 Hz), 6.64 (1H, d, J= 7.5 Hz), 6.09 (1H, dd J= 7.6, 6.0 Hz), 4.45 (1H, d, J= 7.0 Hz), 4.30 (1H, dd, J= 7.0, 5.4 Hz), 4.21 (2H, q, J= 7.1 Hz), 3.90 (1H, m), 1.40 (3H, s), 1.32 (3H, t, J= 7.1 Hz), 1.31 (3H, s);

^{13}C-NMR ($CDCl_3$) δ 164.9 (CO), 141.3 (CH), 141.1 (C), 138.5 (CH), 131.6 (CH), 113.6 (C), 86.1 (CH), 78.9 (CH), 61.2 (CH_2), 41.2 (CH), 35.2 (CH), 25.9 (CH_3), 25.6 (CH_3), 14.2 (CH_3);

MS (CI, 70 eV) *m/z* (rel. intensity) 377 (M+1, 30), 277 (22), 191 (40), 151 (10), 100 (100);

Anal. calcd for $C_{14}H_{17}O_4I$: C, 44.70; H, 4.55; **Found**: C, 44.97; H, 4.58.

(1S,2R,3S,6R)-6-Benzyloxycarbonylamino-1,2-O-isopropylidene-3-isopropyldimethylsilyloxycyclohex-4-ene-1,2,3-triol (244).

Imidazole (293 mg, 4.305 mmole) was added to a solution of alcohol **243** (625 mg, 1.957 mmol) in 20 mL of dry CH_2Cl_2. The solution was cooled to 0°C. Isopropyldimethylsilane chloride was added (335 mg, 2.153 mmoL). After 10 hrs, the reaction was completed. Solution was filtered and washed with water (15 mL), brine (15 mL) and dried with sodium sulphate. Solvent was removed after filtration and 803 mg (1.914 mmoL, 98%) of solid **244** was obtained. An analytical sample was purified by column chromatography (silica gel, Hexane/Ethyl Acetate, 4:1).

Rf= 0.34 (Hexane/Ethyl Acetate, 4:1); **mp**= 71-72 °C; $[\alpha]_D^{20}$=-14 ° (c 1.0, $CHCl_3$);

IR (KBr) υ 3332, 3052, 2941, 1692, 1539, 1260, 1112, 1060 cm^{-1};

^{1}H-NMR ($CDCl_3$) δ 7.34 (m, 5H), 5.99 (m, 2H), 5.11 (m, 2H), 5.51 (bs, 1H), 4.25 (m 3H), 4.20 (m, 1H), 4.18 (m, 1H), 1.39 (s, 3H), 1.31 (s, 3H), 0.95 (m, 6H), 0.85 (m, 1H), 0.11 (s, 3H), 0.10 (s, 3H);

^{13}C-NMR ($CDCl_3$) δ 155.8 (CO), 136.7 (C), 132.5 (CH), 130.2 (CH), 128.4 (2CH), 127.9 (2CH), 108.5 (C), 79.0 (CH), 77.4 (CH), 77.2 (CH), 67.8 (CH), 66.7 (CH_2), 49.1 (CH), 26.6 (CH_3), 24.6 (CH_3), 16.8 (CH_3), 14.6 (CH_3), -3.9 ($2CH_3$);

MS (CI, 70 eV) *m/z* (relative intensity) 420 (M^++1, 40), 302 (100), 91 (70);
Anal. Calcd for $C_{22}H_{33}NSiO_5$: C, 62.98; H, 7.93, N; 3.34. **Found:** C, 62.79; H, 7.96; N: 3.29.

(1S,2R,3S,6R)-6-N-Benzyloxycarbonyl-6-N-(o-bromopiperonoyl)-1,2-O-isopropylidene-3-(isopropyldimethylsilyloxy)-cyclohex-4-ene-1,2,3-triol (267).

A 25 mL-two neck-flask containing a small stir bar was flame dried using a flow of argon. The same procedure was done with a pear flask. The previously weight carbamate **244** (200 mg, 0.476 mmoL) was introduced into the 2-neck flask. Freshlly distilled THF (4 mL) was added to the carbamate. Solution was cooled in an acetone-dry ice bath. n-BuLi (0.281 mL, 2.54M) was added. Acid chloride (266.4 mg, 0.953 mmoL) was introduced into the pear flask. THF (2X2 mL) was added to acid chloride. Solution was cannuled to reaction flask. Solution was warmed up to 0°C and stirred for 1 h. $KHCO_3$ solution was added and stirred for 1 h. Organic layer was separated, Aqueous solution was extracted with ethyl acetate. Combined organic layers were washed with brine and dried with Na_2SO_4. Evaporation of the solvent and column chromatography (silica gel, Hexane/ethyl acetate, 8:2) yielded 237.3 mg (0.367 mmoL, 77% yield) of **267**.
Rf= 0.33 (Hexane/Ethyl Acetate, 4:1); $[\alpha]_D^{20}$= -28.9° (c 0.9 $CHCl_3$);
IR (neat) ν 2953, 1740, 1679, 1620, 1481, 1244, 1111 cm^{-1}.
^{1}H-NMR ($CDCl_3$) δ 7.3 (3H, m), 7.12 (2H, m), 6.78 (1H, s), 6.75 (1H, s), 5.94 (2H, s), 5.69 (2H, s), 5.20 (1H, dd), 5.07 (1H, d, J= 12Hz), 5.02 (1H, d, J= 12Hz), 4.63 (1H, dd, J= 7.0 Hz), 4.20 (1H, dd, J= 5.5, 2.2 Hz), 4.10 (1H, dd, J= 7.1, 5.5 Hz), 1.47 (3H, s), 1.33 (3H, s), 0.95 (7H, m), 0.2 (6H, m) ;
C^{13}-NMR δ 169.6 (CO), 153.5 (CH), 149.2 (C), 147.2 (C), 134.1 (C), 132.4 (C), 131.3 (2CH), 128.8 (CH), 128.6 (2CH), 128.3 (2CH), 126.5 (CH), 112.8 (CH), 110.2 (CH), 108.4 (C), 102.0 (CH_2), 88.7 (CH), 80.2 (CH), 75.1 (CH), 71.3 (CH), 69.3 (CH_2), 57.0 (CH), 27.5 (CH_3), 25.5 (CH_3), 16.9 (CH_3), 14.7 (CH_3), -3.6 (CH_3), -3.9 (CH_3) ppm.
MS (CI, 70 eV) *m/z* (rel. intensity) 648 (M^+1, 2), 590 (10), 530 (100);
Anal. calcd for $C_{30}H_{36}O_8NSiBr$: C, 55.73; H, 5.61; N: 2.17; **Found**: C, 55.48; H, 5.60; N: 2.13.

(2S,3R,4S,4aR)-5-Benzyloxycarbonyl-2-isopropyldimethylsyliloxy-3,4-O-isopropylidene-8,9-methylenedioxy-2,3,4,4a-tetrahydro-6-phenanthridone (268). A mixture of bromo-olefin **267** (180 mg, 0.278 mg), $Pd(OAc)_2$ (12.5 mg, 0.055 mmol), 1,2-bis(diphenylphosphino)ethane (44.4 mg, 0.11 mmol), and Tl(OAc) (146.6 mg, 0.556 mmol), in anisole (6 mL) was heated at 135 °C for seven hours. The reaction mixture was diluted with EtOAc and the insoluble material was removed by filtration. The filtrate and washings (EtOAc) were combined, and concentrated to give a residue, which was chromatographed on a column of silica gel (Hexane/Ethyl acetate, 4:1).to give 42.6 mg (0.075 mmol, 27%) of cyclized compound **268**.

Rf= 0.22 (Hexane/Ethyl Acetate, 4:1); $[\alpha]_D^{20}$= + 20 ° (c 0.9 $CHCl_3$);

IR (neat) ν 3066, 2940, 1758, 1670, 1479, 1251, 1216 cm^{-1}.

^{1}H-NMR ($CDCl_3$) δ 7.61 (1H, s), 7.48 (2H, m), 7.38 (3H, m), 7.01 (1H, s), 6.24 (1H, t, J= 3 Hz), 6.04 (2H, s), 5.47 (1H, d, J= 12 Hz), 5.25 (1H, d, J= 12 Hz), 4.89 (1H, dd, J= 8, 3 Hz), 4.40 (1H, m), 4.18 (2H, m), 1.40 (3H, s), 1.26 (3H, s), 1.01 (7H, t, m), 0.14 (6H, t, s);

C^{13}-NMR ($CDCl_3$) δ 161.0 (CO), 155.0 (CH), 152.5 (C), 148.8 (C), 128.5 (C), 128.2 (3CH), 127.6 (2CH), 127.2 (CH), 111.7 (CH), 108.2 (2CH), 102.0 (CH_2), 101.0 (CH), 80.1 (CH), 79.9 (CH), 73.5 (CH), 69.4 (CH_2), 58.7 (CH), 26.9 (CH_3), 25.0 (CH_3), 16.9 (CH_3), 14.7 (CH_3), -3.6 (CH), -4.0 ($2CH_3$) ppm.

MS (CI, 70 eV) *m/z* (rel. intensity) 566 (M^+1, 30), 522 (50), 432 (70), 256 (70), 91(100);

Anal. calcd for $C_{30}H_{35}O_8NSi$: C, 63.70; H, 6.24; N: 2.48; **Found**: C, 63.56; H, 6.29; N: 2.44.

(2S,3R,4S,4aR)-2-isopropyldimethylsyliloxy-3,4-O-isopropylidene-8,9-methylenedioxy-2,3,4,4a,-tetrahydro-6-phenanthridone (272).

Carbamate **268** (61 mg, 0.108 mmol) was diluted in a mixture of ethanol (2 mL) and cyclohexadiene (4 mL). Palladium over carbon (50 mg) was added and mixture was refluxed for two hours. Mixture was filtered and 46 mg (0.106 mmoL, 99%) of compound **272** was obtained.

Rf= 0.37 (Hexane/Ethyl Acetate, 1:1); $[\alpha]_D^{20}$= +30.3° (c 1.1 $CHCl_3$);

IR (neat) ν 3381, 2936, 1678, 1477, 1256, 1062, 1031 cm^{-1}.

^{1}H-NMR ($CDCl_3$) δ 7.60 (1H, s), 7.03 (1H, s), 6.28 (1H, br s), 6.19 (1H, t, J= 3 Hz), 6.04 (1H, d, J= 2 Hz), 6.03 (1H, d, J= 2 Hz), 4.31 (1H, m), 4.08 (3H, m), 1.51 (3H, s), 1.36 (3H, s), 1.02 (7H, m), 0.17 (6H, s);
C^{13}-NMR ($CDCl_3$) δ 162.27 (CO), 151.67 (C), 148.51 (C), 128.5 (C), 127.1 (C), 127.06 (CH), 121.1 (C), 110.84 (C), 107.68 (CH), 101.79 (CH_2), 101.36 (CH), 79.53 (CH), 79.11 (CH), 73.33 (CH), 55.68 (CH), 27.18 (CH_3), 24.88 (CH_3), 16.83 (CH_3), 14.61 (CH_3), -4.03 (CH_3).
MS (CI, 70 eV) *m/z* (rel. intensity) 432 (M^+1, 50), 331 (25), 266 (30), 119 (100);
Anal. calcd for $C_{22}H_{29}O_6N$: C, 61.23; H, 6.77; N: 3.25; **Found**: C, 61.27; H, 6.77; N: 3.28.

(2S,3R,4S,4aR)-8,9-methylenedioxy-2,3,4-trihydroxy-2,3,4,4a,-tetrahydro-6-phenanthridone: (+)-Lycoricidine (124).
Trifluoroacetic acid (2 mL) was added to acetonide **272** (25 mg, 0.057 mmol) in an ice-cooled bath. Solution was stirred for 20 min and 14 mg (0.049 mmol, 85%) of triol **124** was obtained after solvent was removed.
Rf= 0.4 (CH_3Cl/MeOH, 4:1); $[\alpha]_D^{20}$= +17.0° (c 1, CH_3OH);
IR (neat) ν 3392, 2924, 1681, 1477, 1207, 1154 cm^{-1}.
^{1}H-NMR (CD_3OD) δ 7.31 (1H, s), 7.06 (1H, s), 6.07 (br t, J= Hz), 5.96 (2H, d, J= 6 Hz), 4.30 (br d, J= Hz), 4.16 (br d, J= Hz), 3.83 (2H, m);
C^{13}-NMR (CD_3OD) δ 166.58 (CO), 153.38 (C), 150.14 (C) 132.53 (C), 123.49 (CH), 123.49 (C), 107.81 (CH), 104.40 (CH), 103.53 (CH_2), 74.41 (CH), 71.06 (CH), 54.02 (CH);

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VI. SELECTED SPECTRA:

1. (1S,2R,3S,6R)-6-Benzyloxycarbonylamino-1,2-O-isopropylidenecyclohex-4-ene-1,2,3-triol (243)
2. (1S,2R,3S,6R)-6-Acetamido-1,2-O-isopropyledenecyclohex-4-ene-1,2,3-triol (250)

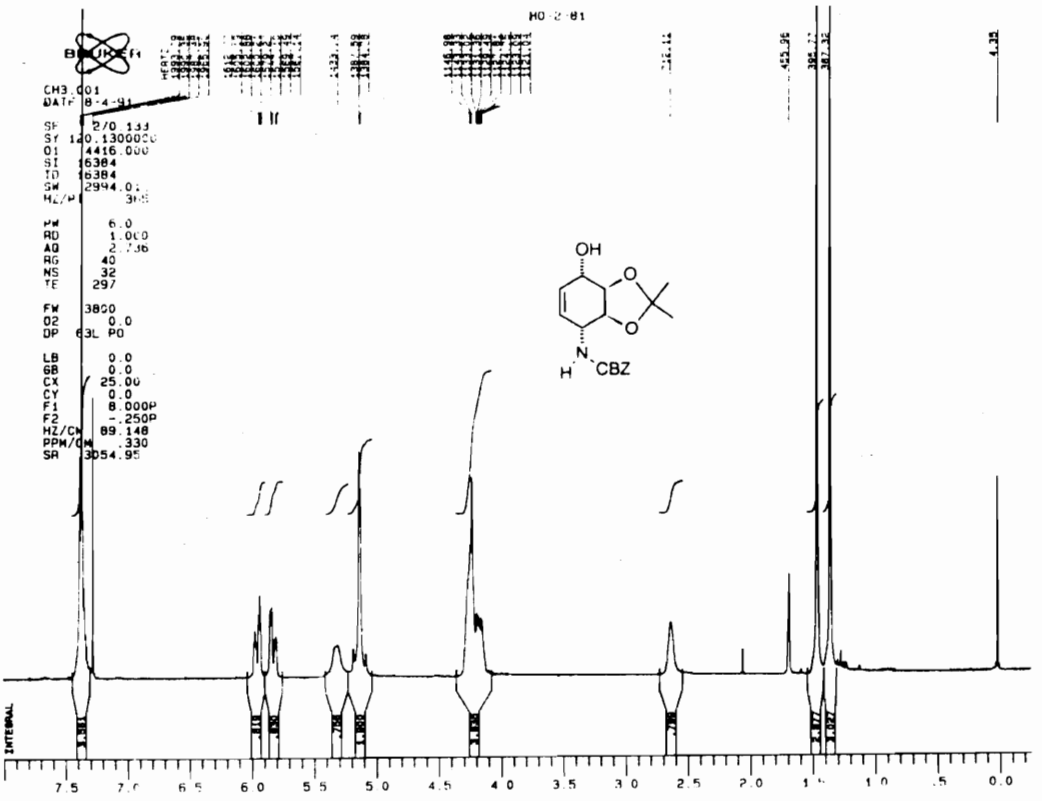
3. 3-Benzyloxycarbonyl-1-fluoro-5,6-O-isopropylidene-2-oxa-3-azabicyclo[2.2.2]oct-7-ene-5,6-diol (240a)
4. 3-Benzyloxycarbonyl-1-chloro-5,6-O-isopropylidene-2-oxa-3-azabicyclo[2.2.2]oct-7-ene-5,6-diol (240b)
5. 3-Benzyloxycarbonyl-1-bromo-5,6-O-isopropylidene-2-oxa-3-azabicyclo[2.2.2]oct-7-ene-5,6-diol (240c)
6. 3-Benzoyl-1-chloro-5,6-isopropylidene-2-oxa-3-azabicyclo[2.2.2]oct-7-ene (241b)
7. 3-Benzoyl-1-bromo-5,6-isopropylidene-2-oxa-3-azabicyclo[2.2.2]oct-7-ene (241c)
8. 3-Acetyl-1-chloro-5,6-O-isopropylidene-2-oxa-3-azabicyclo[2.2.2]oct-7-ene-5,6-diol (242b)
9. 3-Acetyl-1-bromo-5,6-O-isopropylidene-2-oxa-3-azabicyclo[2.2.2]oct-7-ene-5,6-diol (242c)

10. (1S,2S,3S,4R)-5-Ethoxycarbonyl-1-Fluor-2,3-isopropylidene bicyclo[2.2.2]octa-5,7-diene (238a)
11. (1S,2S,3S,4R)-1-Chloro-5-ethoxycarbonyl-2,3-isopropylidene bicyclo[2.2.2]octa-5,7-diene (238b)
12. (1S,2S,3S,4R)-1-Bromo-5-ethoxycarbonyl-2,3-isopropylidene bicyclo[2.2.2]octa-5,7-diene (238c)
13. (1S,2S,3S,4R)-5-Ethoxycarbonyl-1-iodo-2,3-isopropylidene bicyclo[2.2.2]octa-5,7-diene (238d)
14. (1S,2S,3S,4R)-6-Ethoxycarbonyl-1-fluor-2,3-isopropylidene bicyclo[2.2.2]octa-5,7-diene (239a)
15. (1S,2S,3S,4R)-1-Chloro-6-ethoxycarbonyl-2,3-isopropylidene bicyclo[2.2.2]octa-5,7-diene (239b)

16. (1S,2S,3S,4R)-1-Bromo-6-ethoxycarbonyl-2,3-isopropylidene bicyclo[2.2.2]octa-5,7-diene (239c)
17. (1S,2S,3S,4R)-6-ethoxycarbonyl-1-iodo-2,3-isopropylidene bicyclo[2.2.2]octa-5,7-diene (239d)

18. (1S,2R,3S,6R)-6-Acetamidocyclohex-4-ene-1,2,3-triol (256)
19. (1S,2R,3S,6R)-6-Acetamidocyclohex-4-ene-1,2,3-triol triaacetate: Conduramine A-1 Tetraacetate (257)
20. (1S,2R,3S,6R)-6-Benzyloxycarbonylaminocyclohex-4-ene-1,2,3-triol (252)
21. (1S,2R,3S,4R)-4-Aminocyclohexane-1,2,3-triol: Dihydroconduramine A-1 (253)
22. (1S,2R,3S,4R)-4-Acetamidocyclohexane-1,2,3-triol triacetate: Dihydroconduramine A-1 Tetraacetate (254)

23. (1S,2R,3S,6R)-6-Benzyloxycarbonylamino-1,2-O-isopropylidene-3-isopropyldimethylsilyloxycyclohex-4-ene-1,2,3-triol (244)
19. (1S,2R,3S,6R)-6-N-Benzyloxycarbonyl-6-N-(o-bromopiperonoyl)-1,2-O-isopropylidene-3-(isopropyldimethylsilyloxy)-cyclohex-4-ene-1,2,3-triol (267)
20. (2S,3R,4S,4aR)-5-Benzyloxycarbonyl-2-isopropyldimethylsyliloxy-3,4-O-isopropylidene-8,9-methylenedioxy-2,3,4,4a-tetrahydro-6-phenanthridone (268)
21. (2S,3R,4S,4aR)-2-isopropyldimethylsyliloxy-3,4-O-isopropylidene-8,9-methylenedioxy-2,3,4,4a,-tetrahydro-6-phenanthridone (272)
22. (2S,3R,4S,4aR)-8,9-methylenedioxy-2,3,4-trihydroxy-2,3,4,4a,-tetrahydro-6-phenanthridone. (+)-Lycoricidine (124)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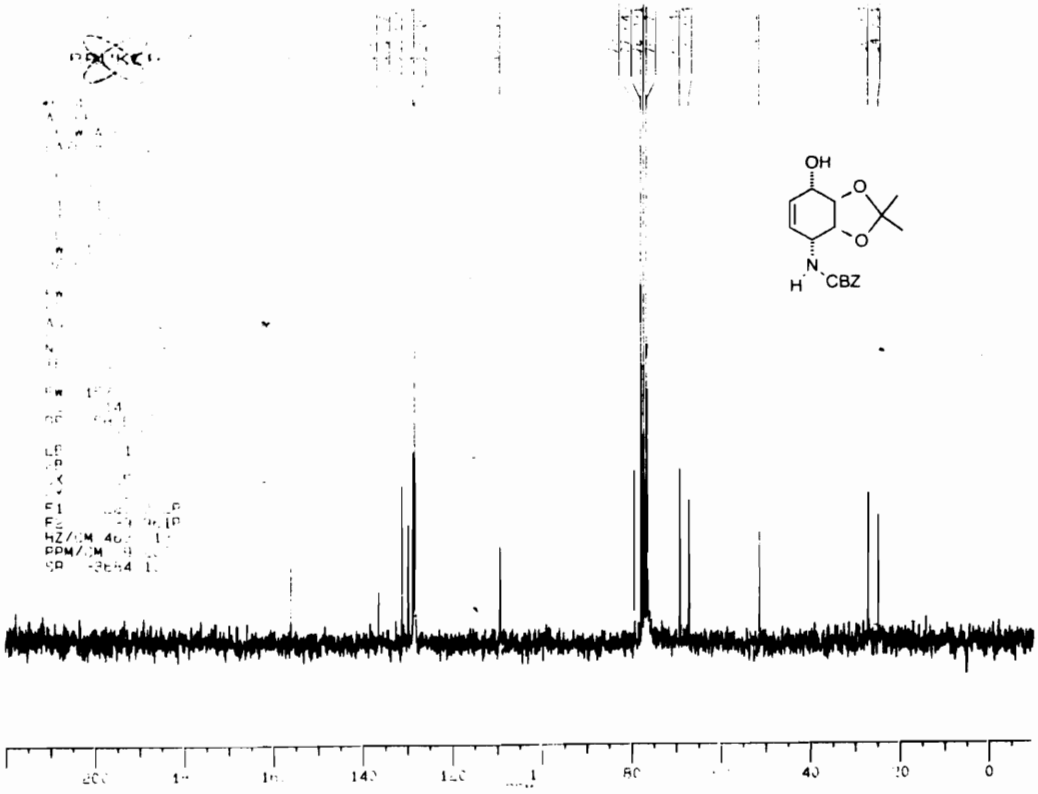
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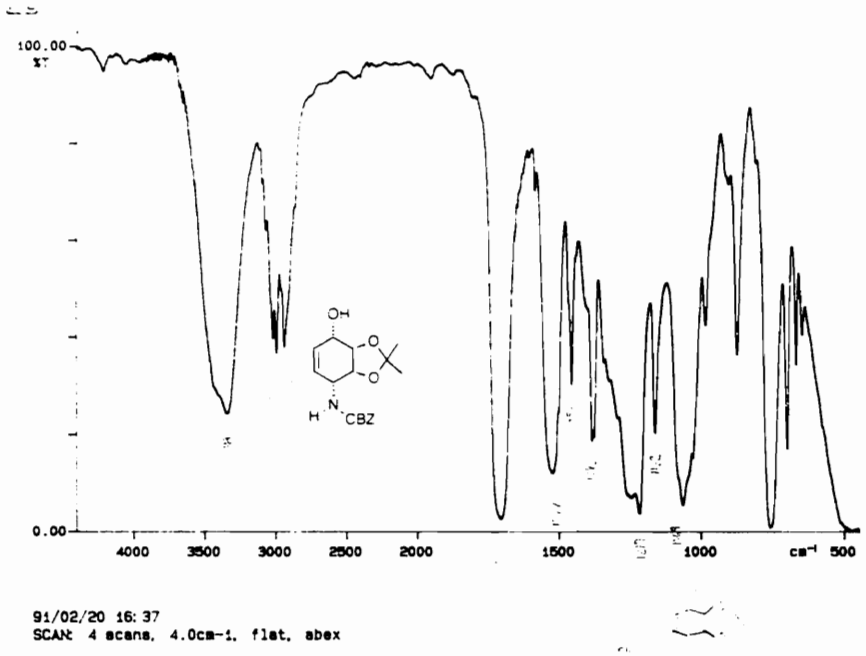
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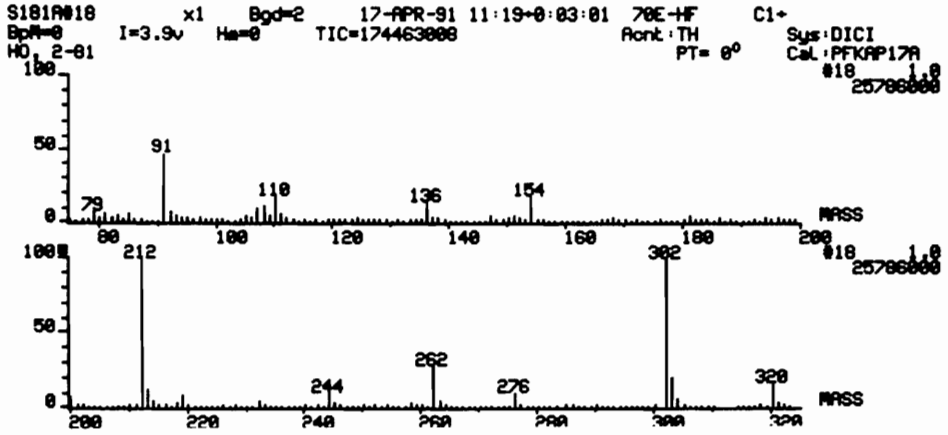
SCAN: 4 scans, 4.0cm-1, flat, abex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HD, 2-81 PT= 0° Cal:PFKAP17A
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0
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79
110
136
154
MASS
80
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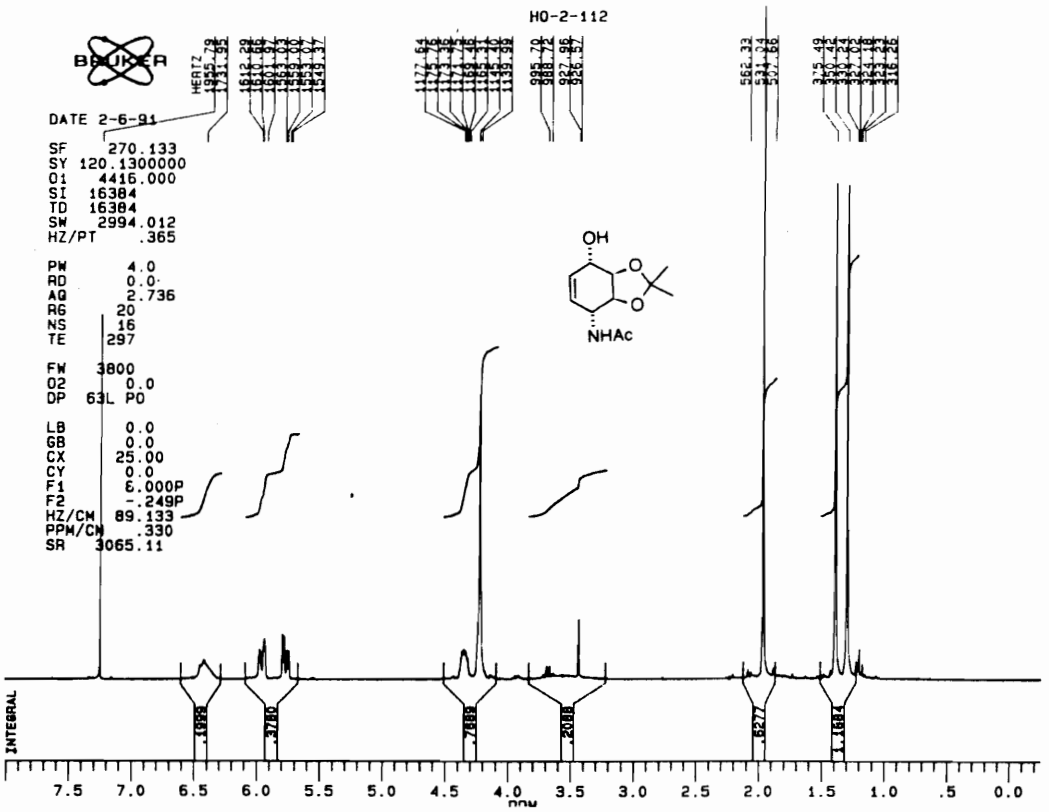
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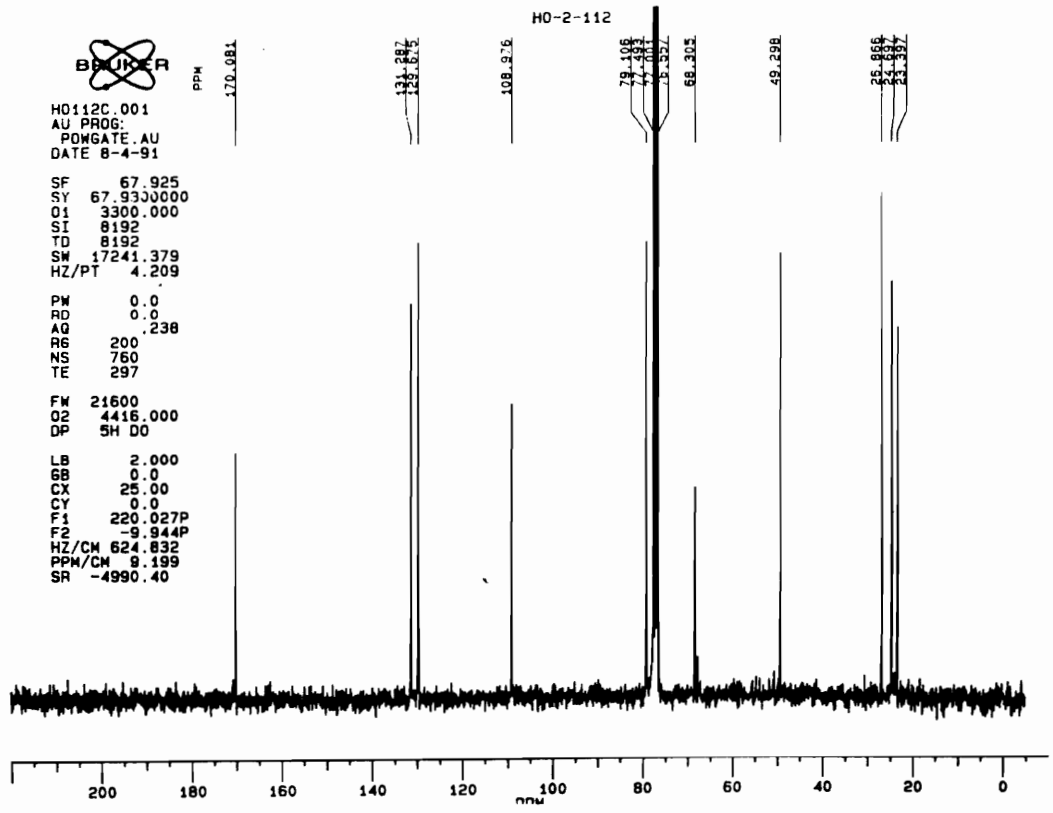
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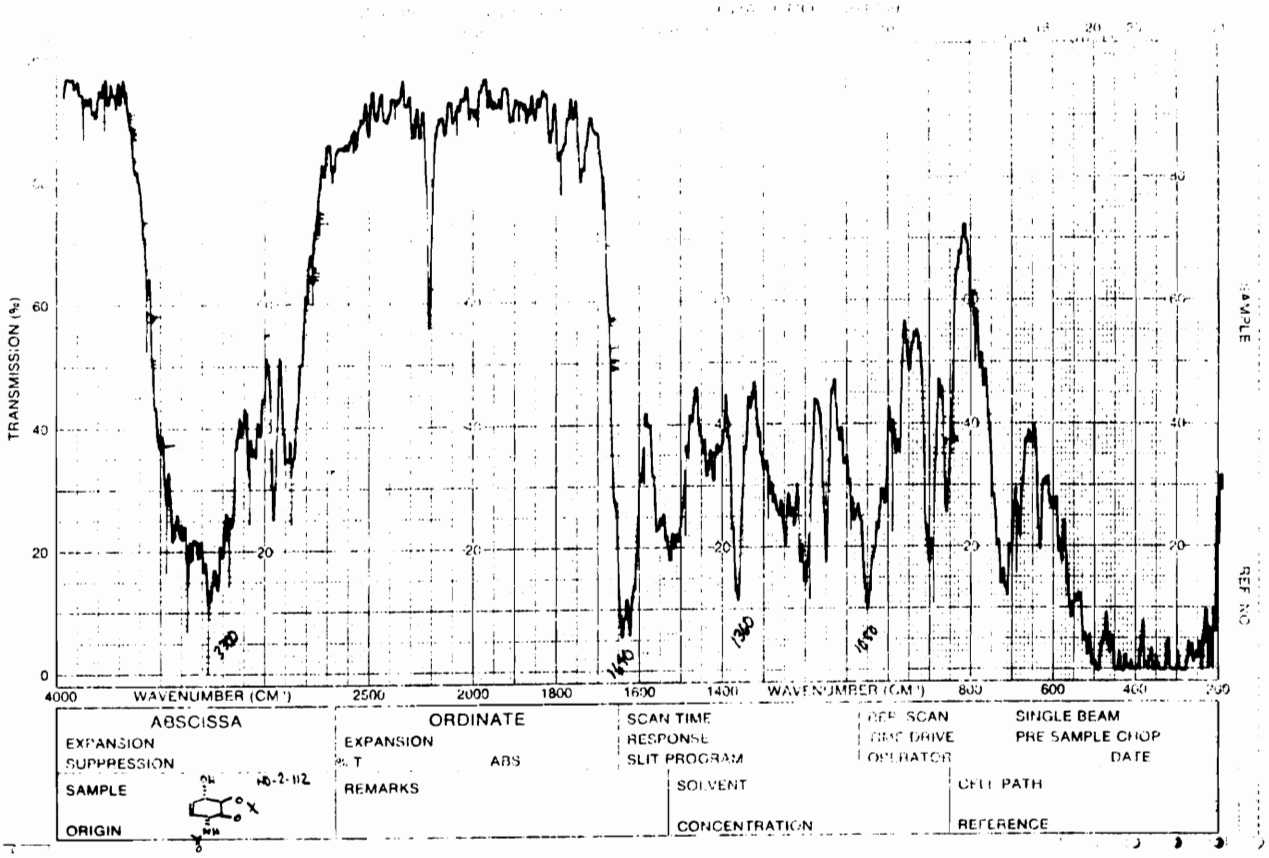
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40
60
ABSCISSA
EXPANSION
SUPPRESSION
SAMPLE
ORIGIN
ORDINATE
EXPANSION
%T
ABS
REMARKS
SCAN TIME
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SLIT PROGRAM
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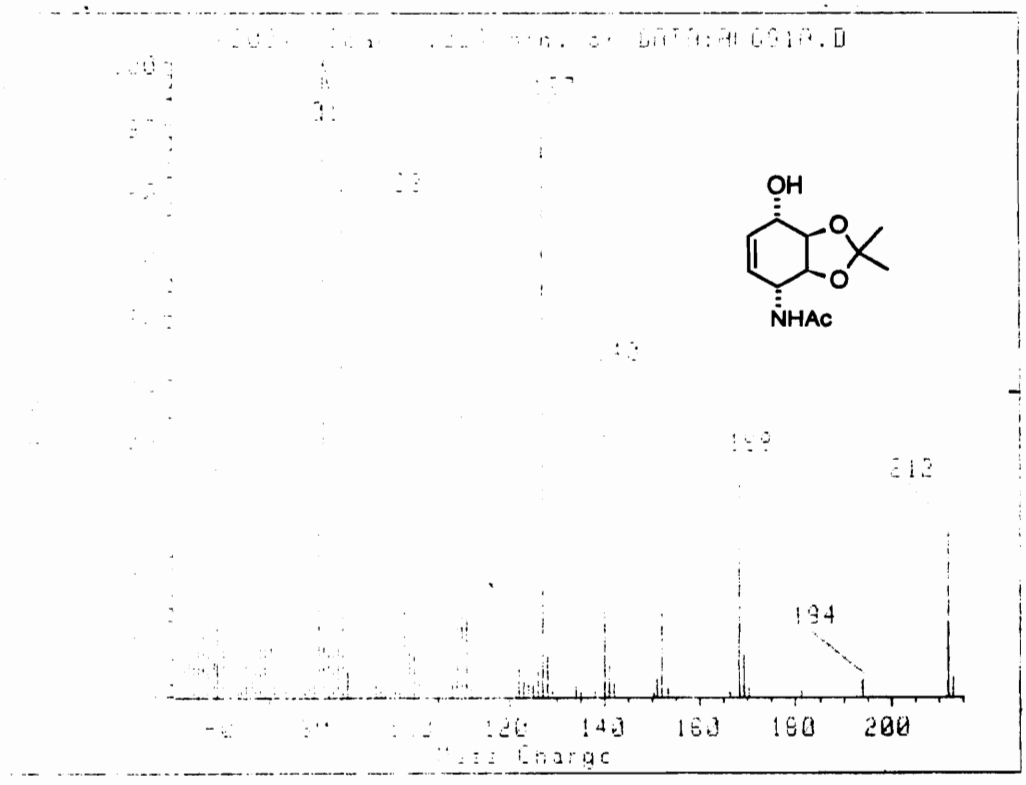
DATE
CELL PATH
REFERENCE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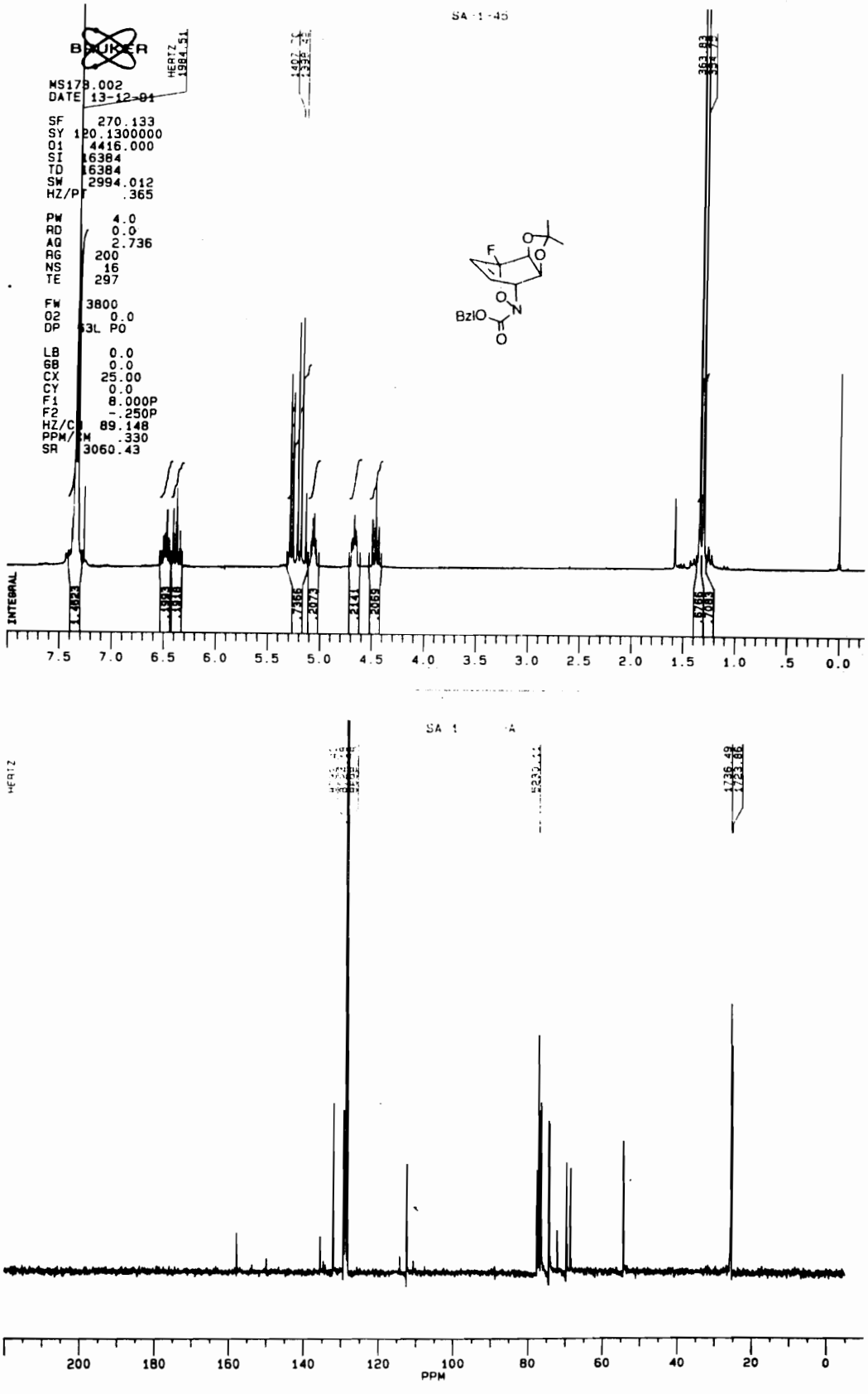
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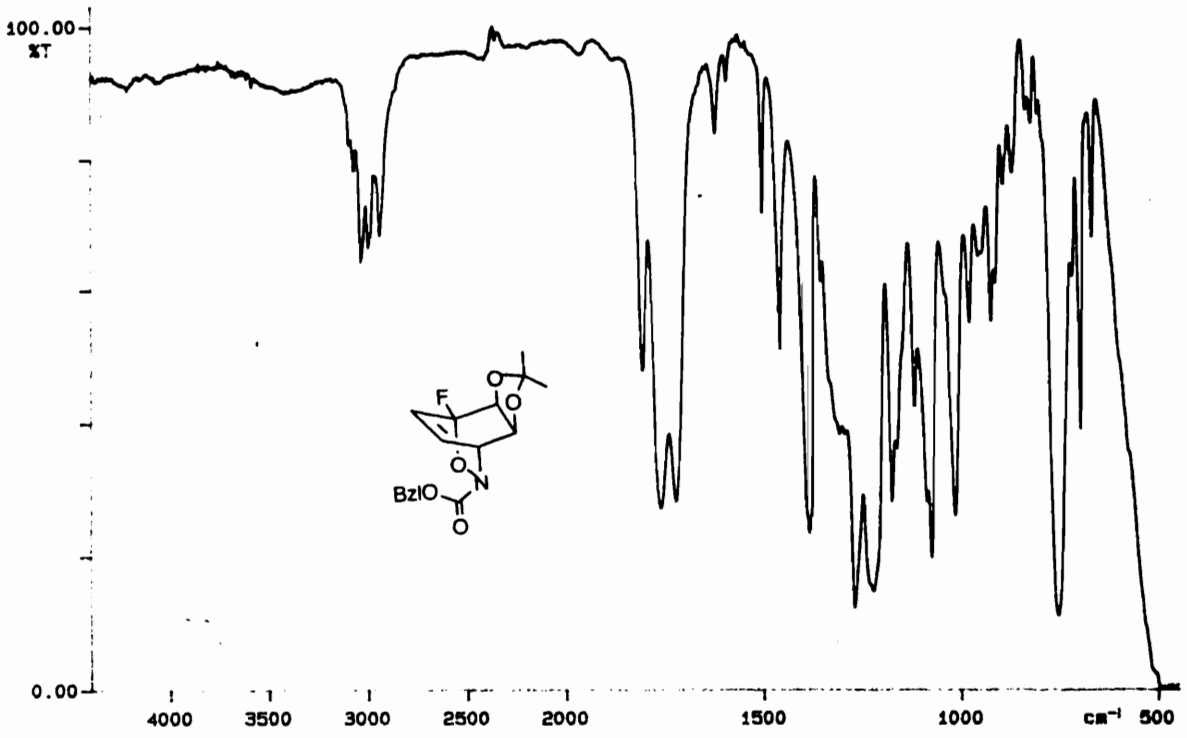

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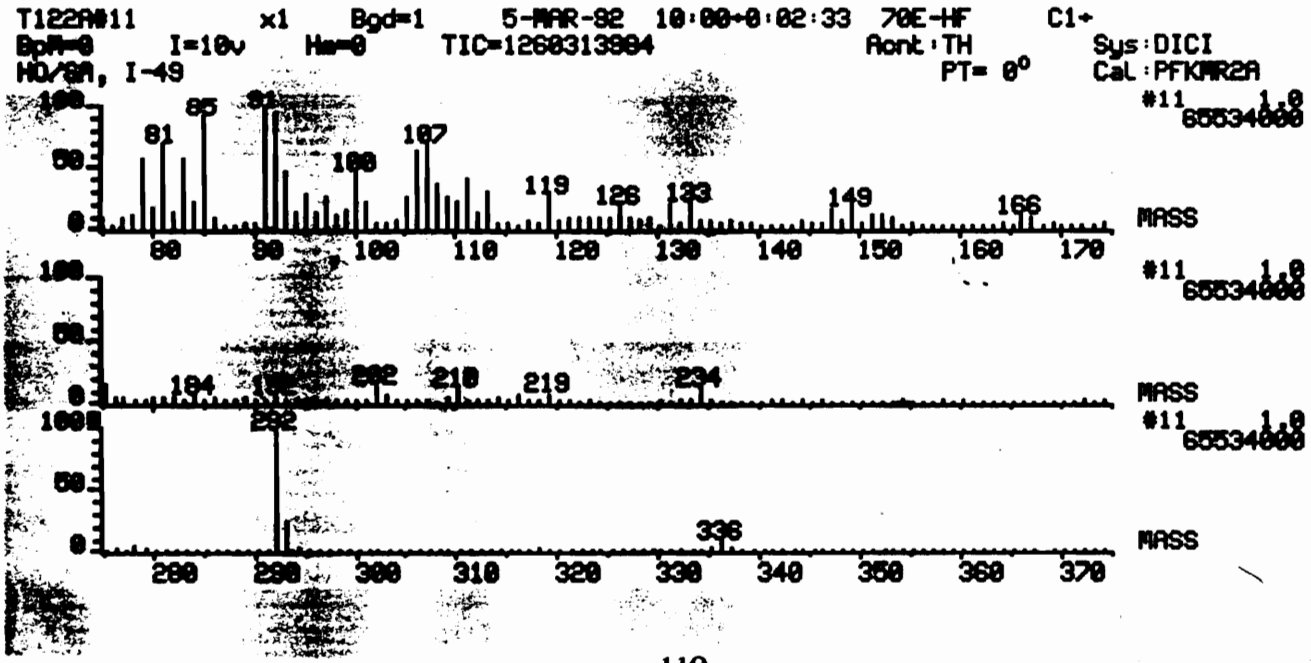

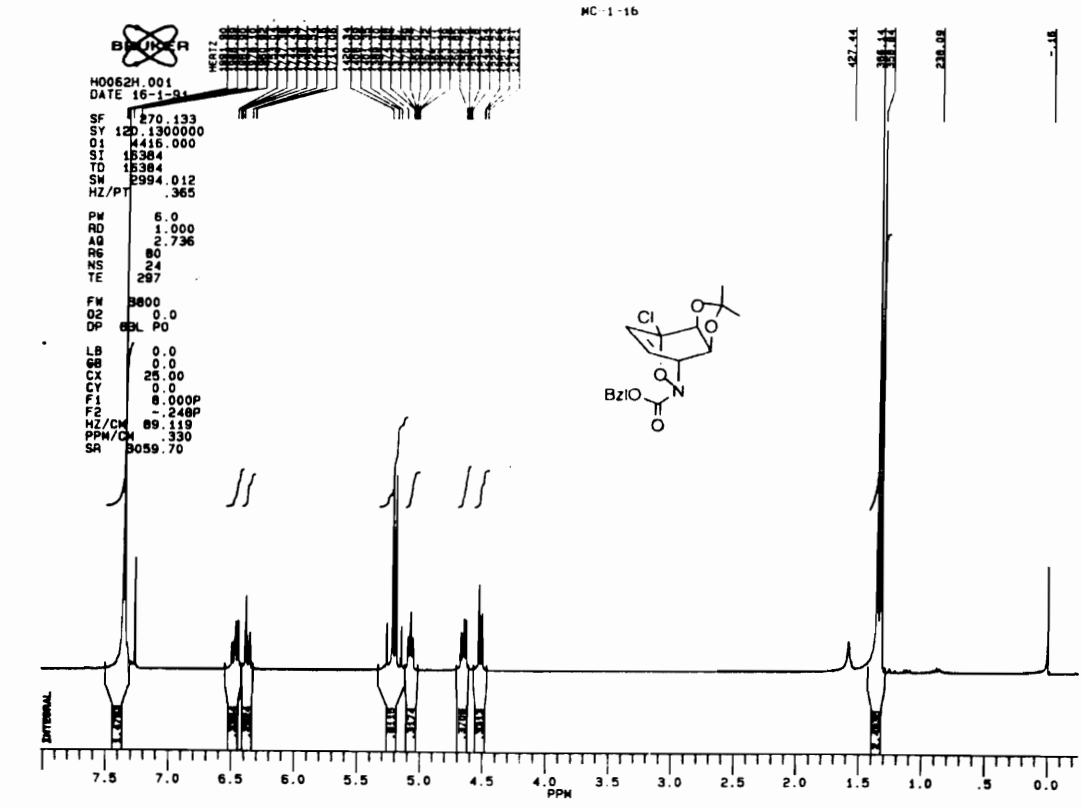
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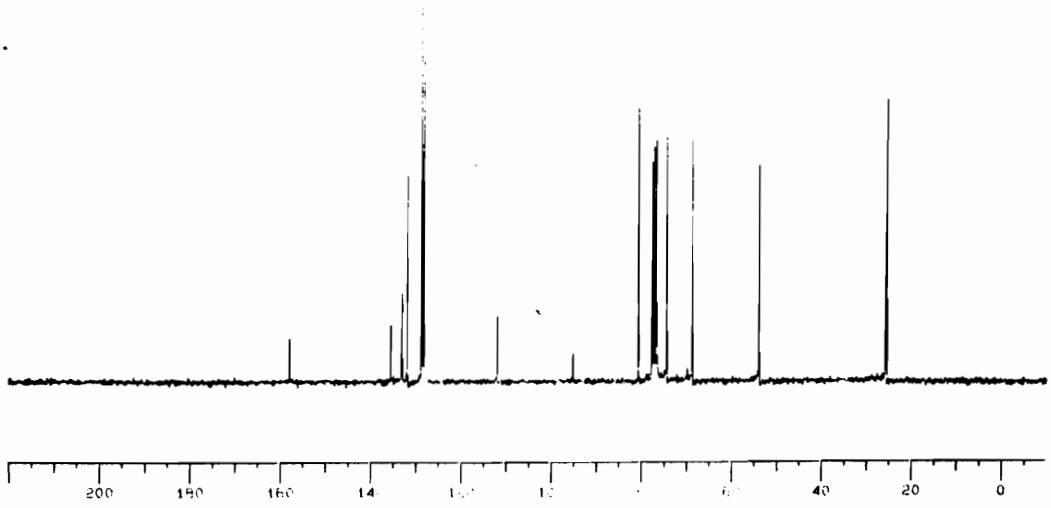

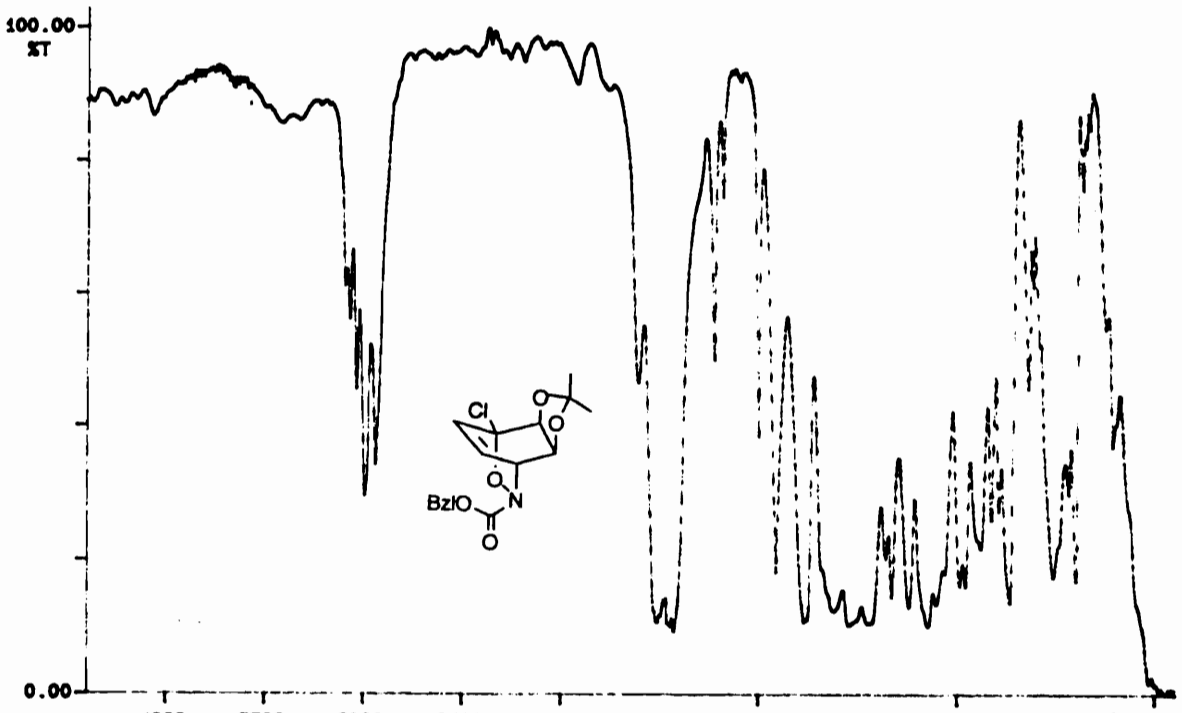

AA-2-32

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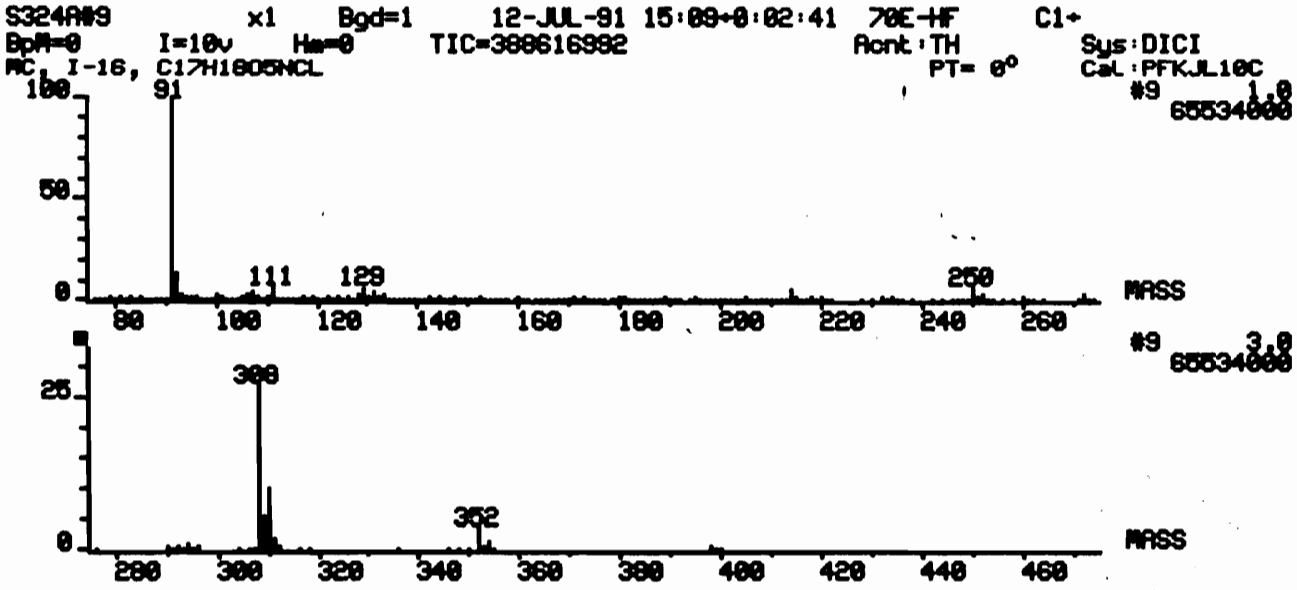

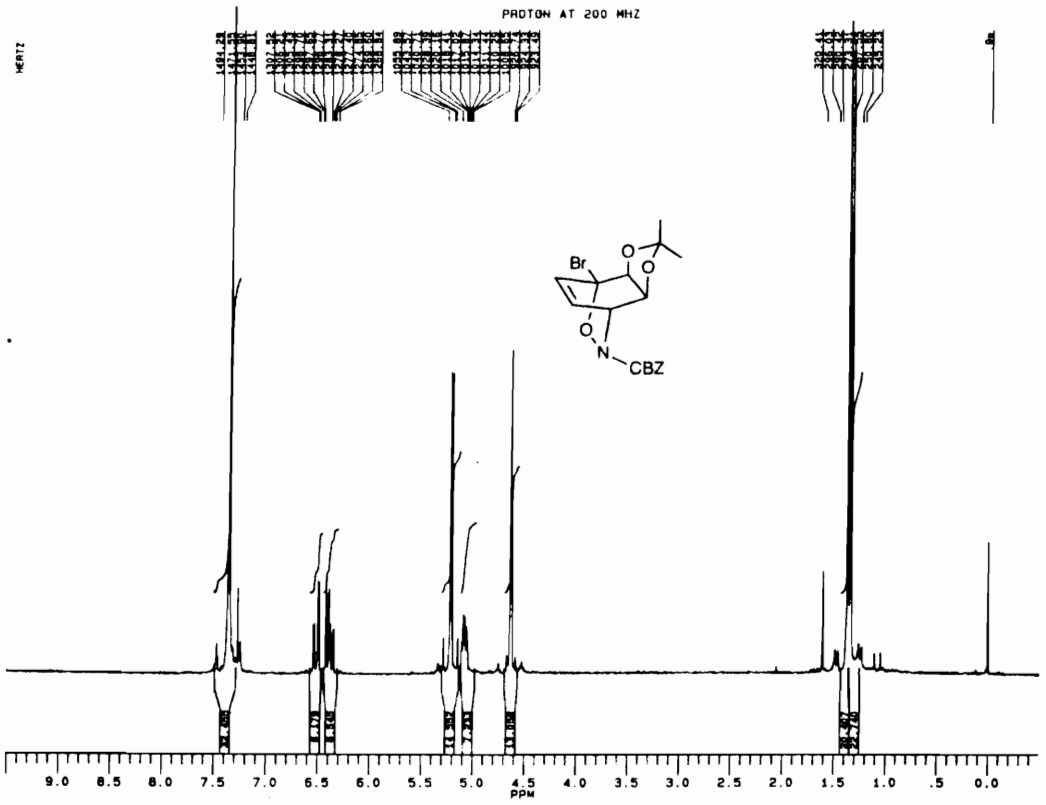
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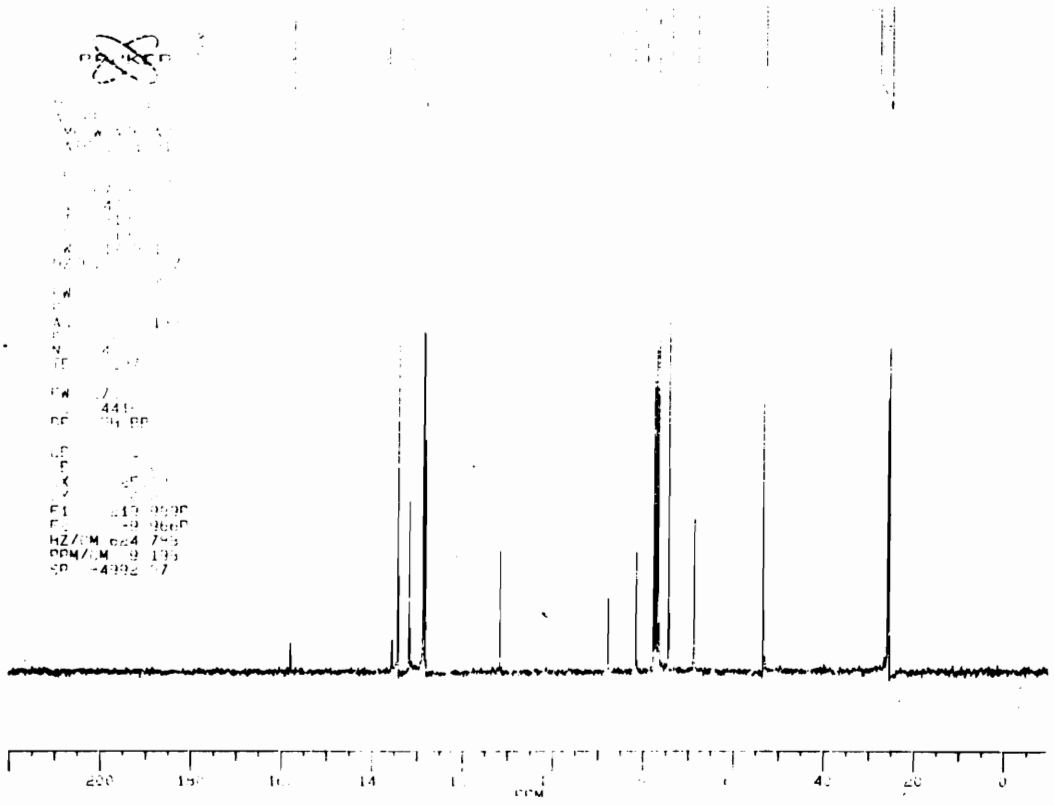
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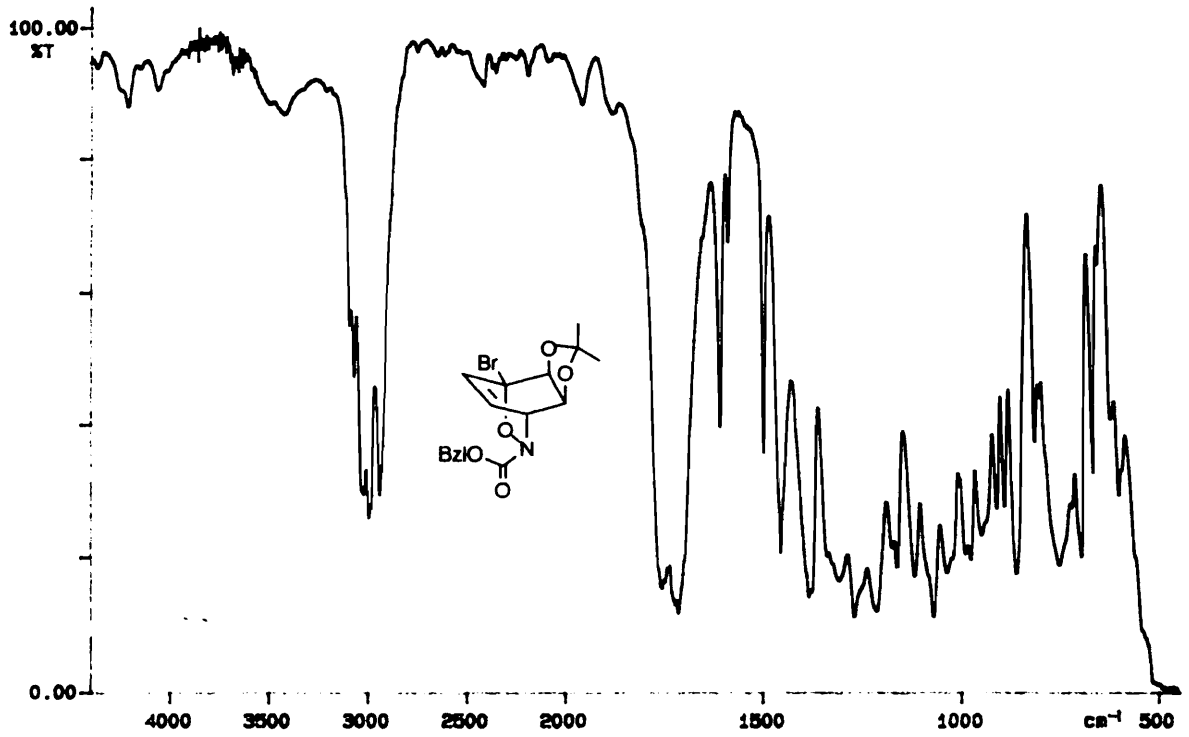

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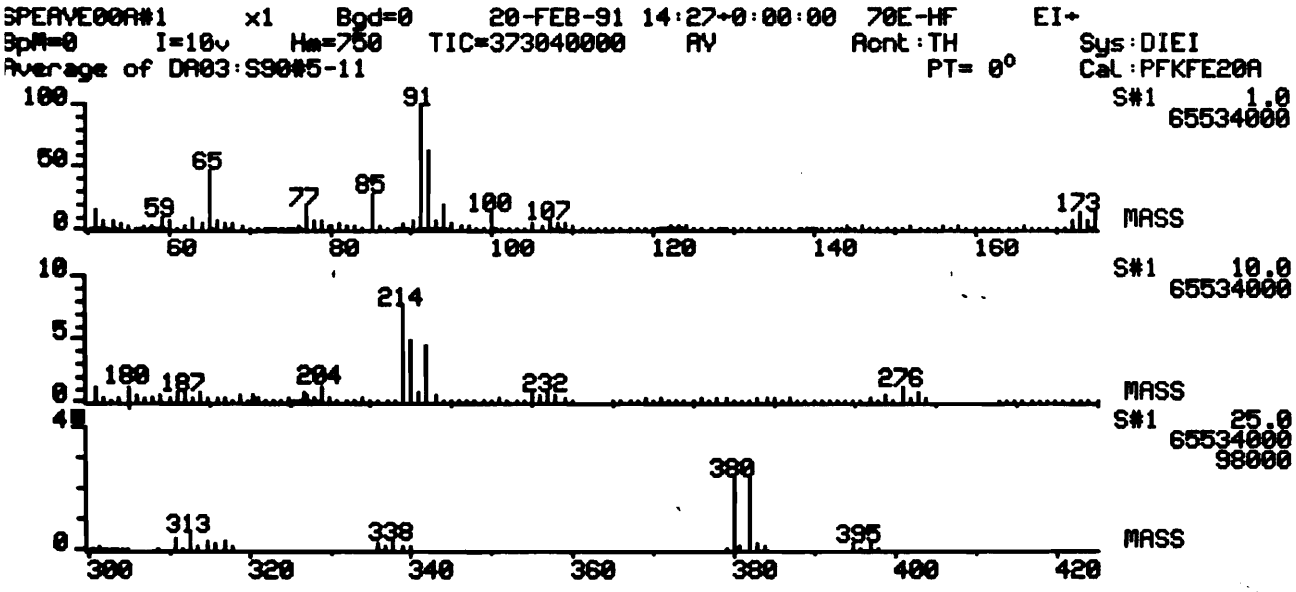

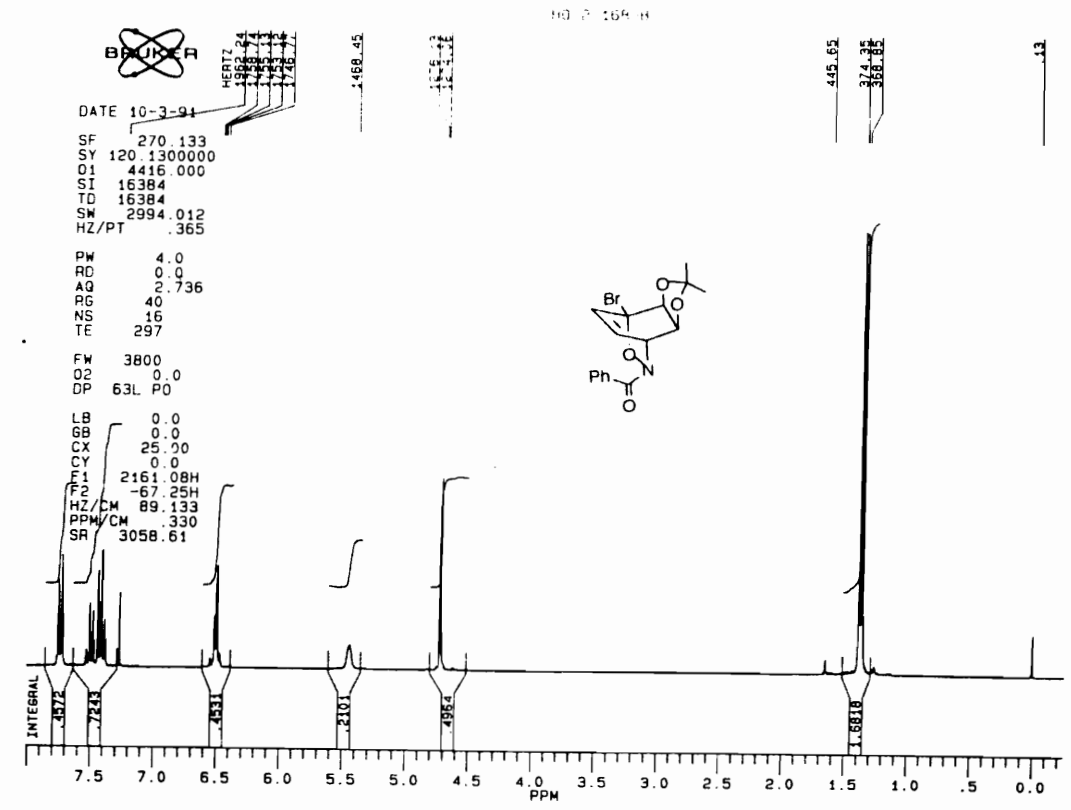
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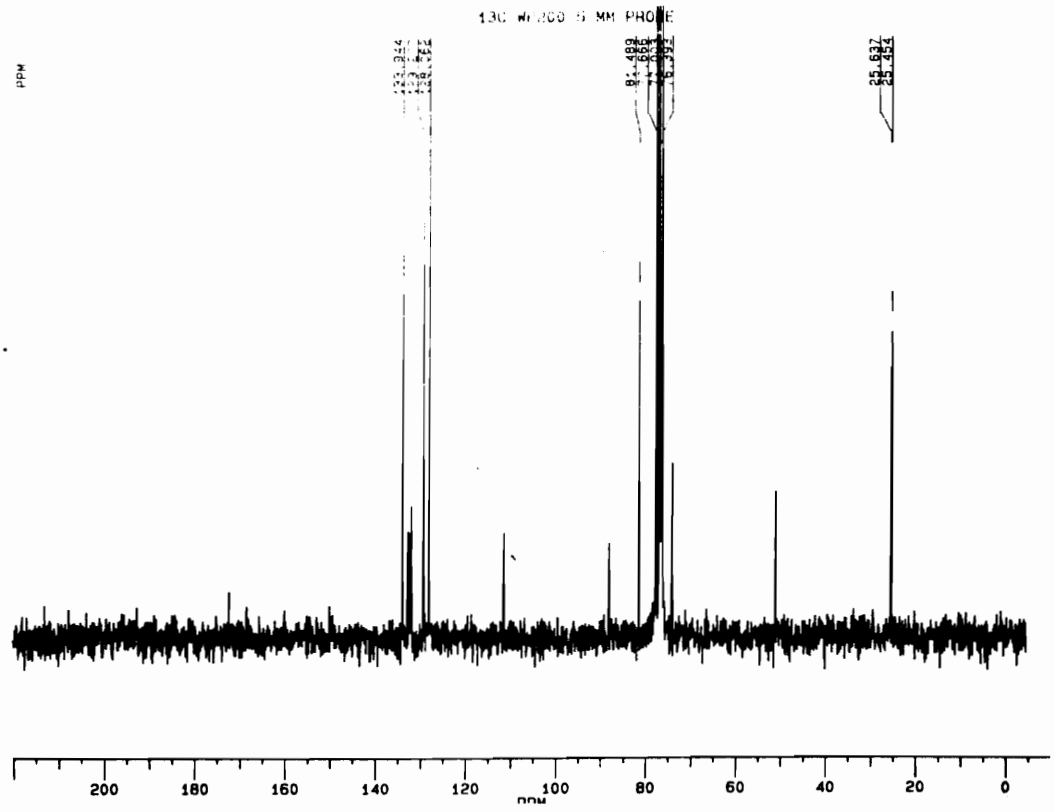
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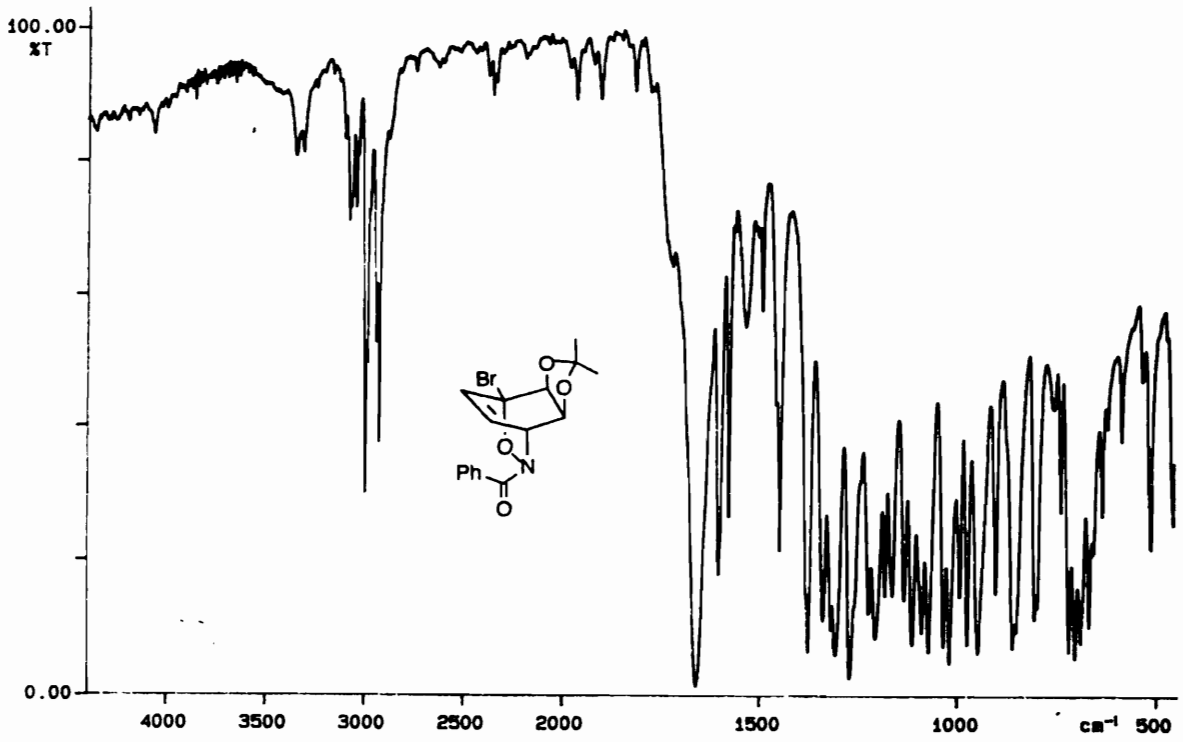

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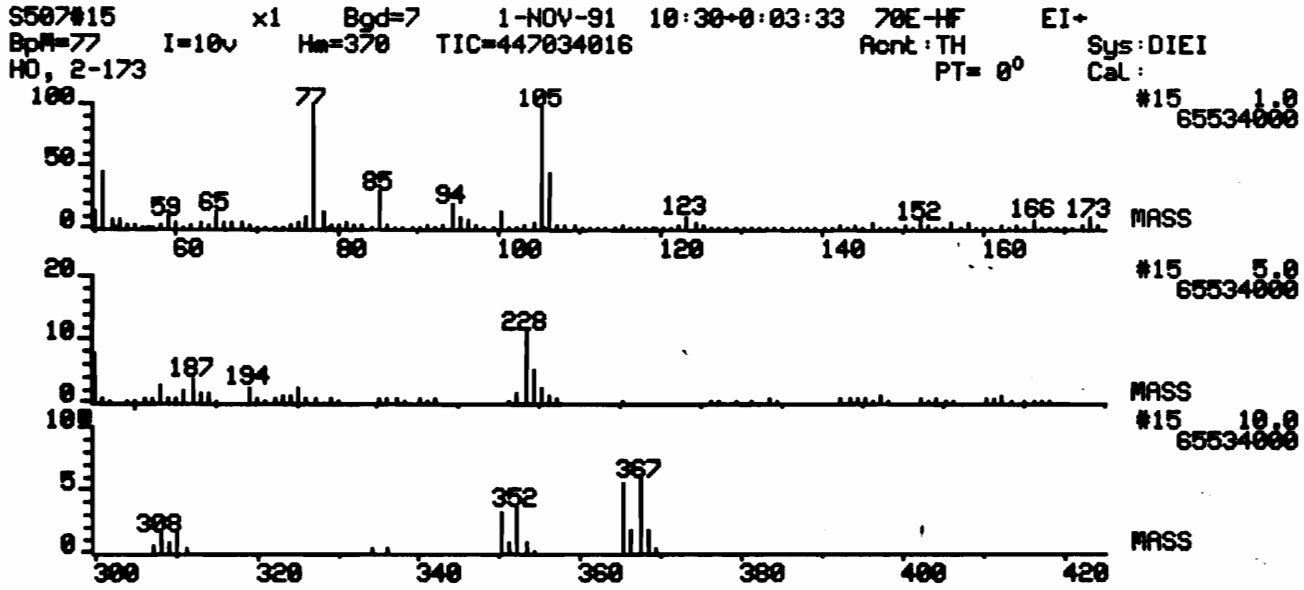

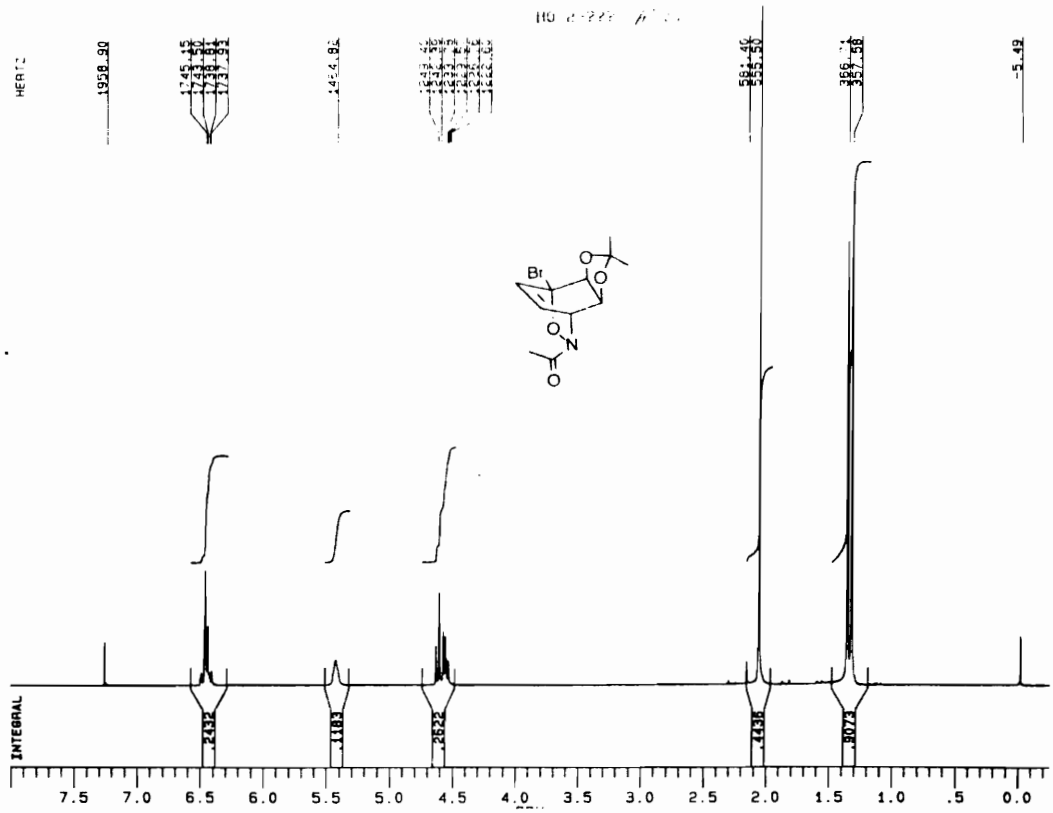
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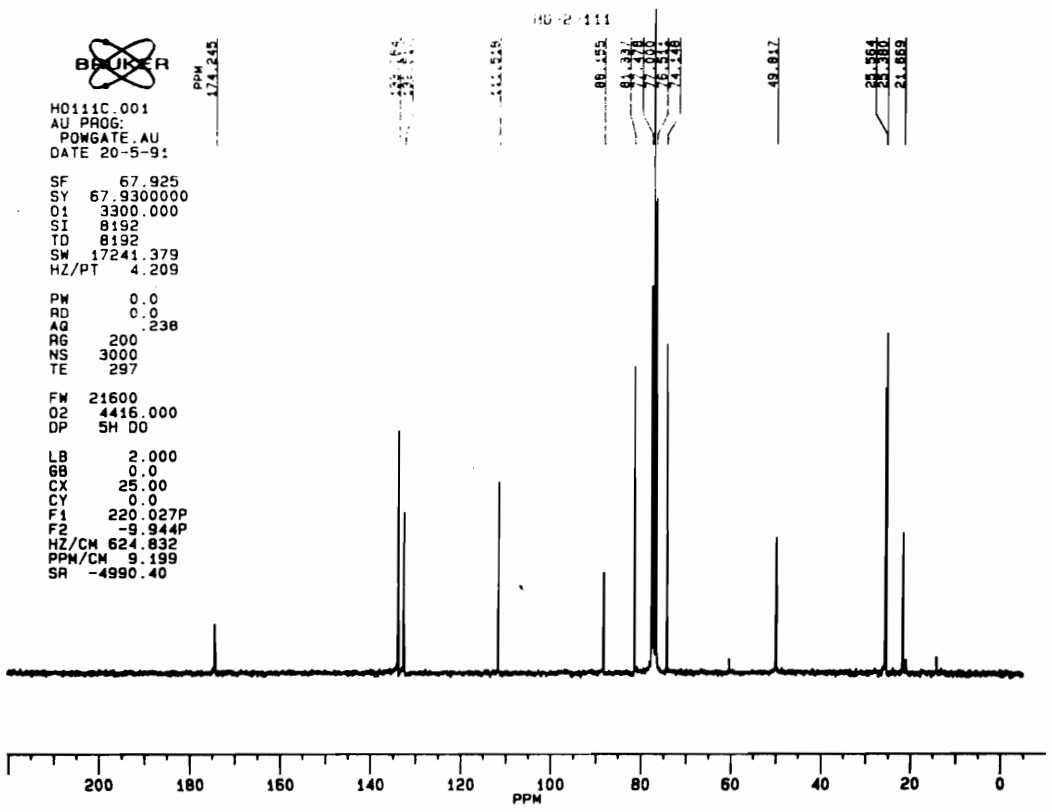
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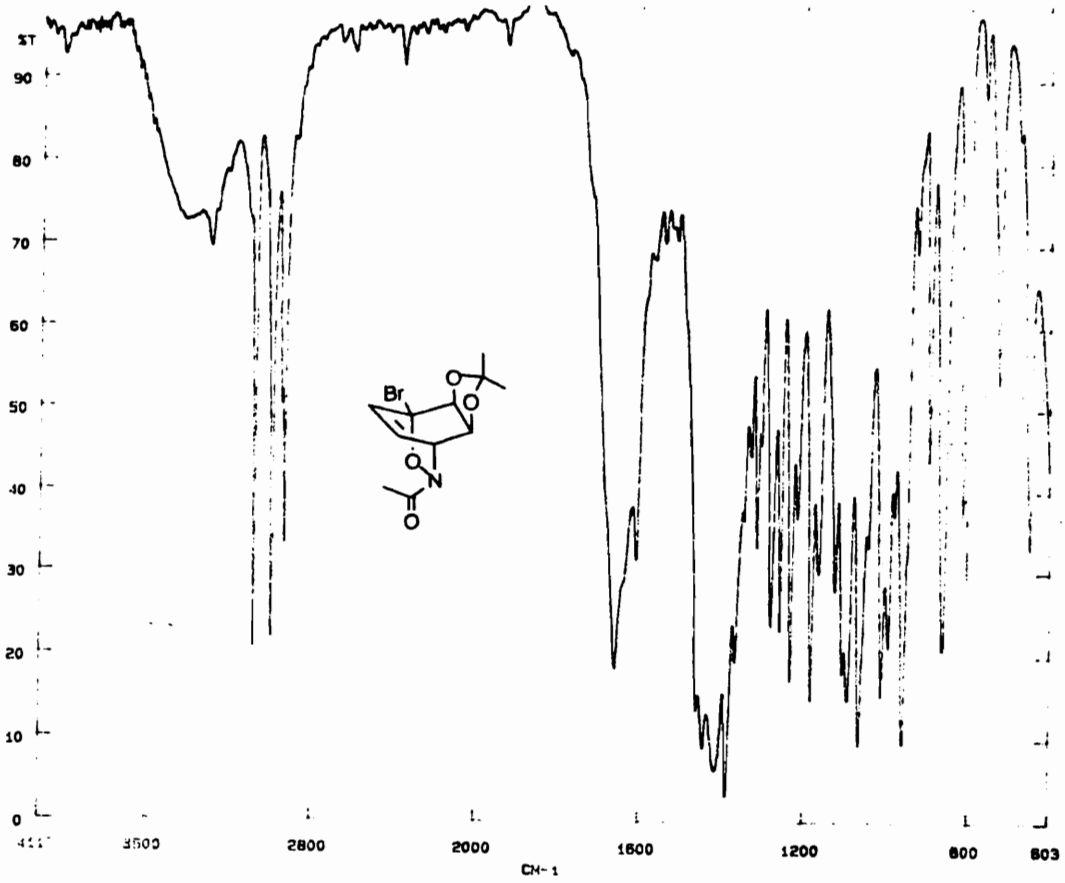
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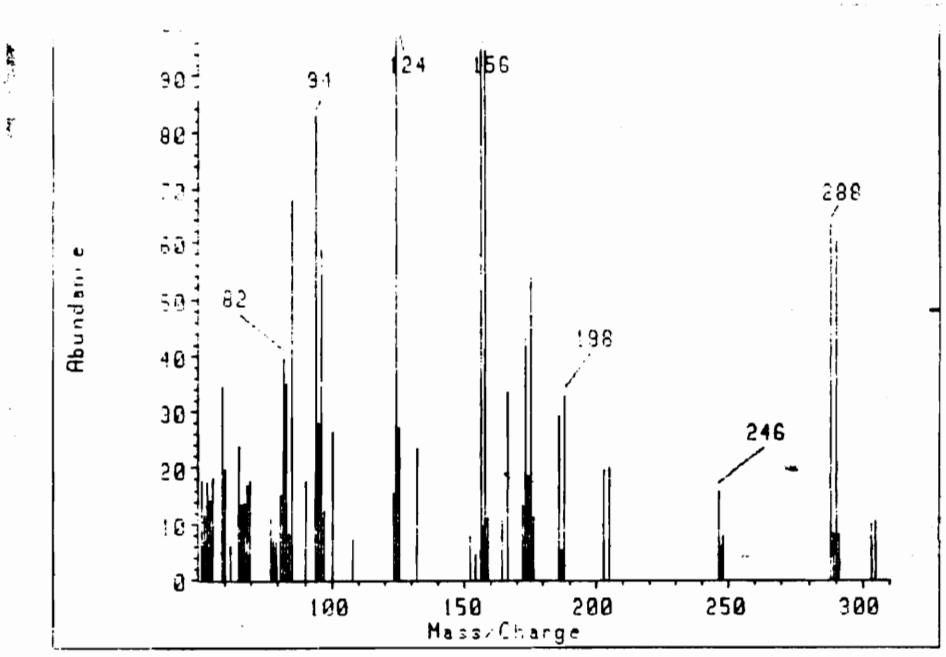
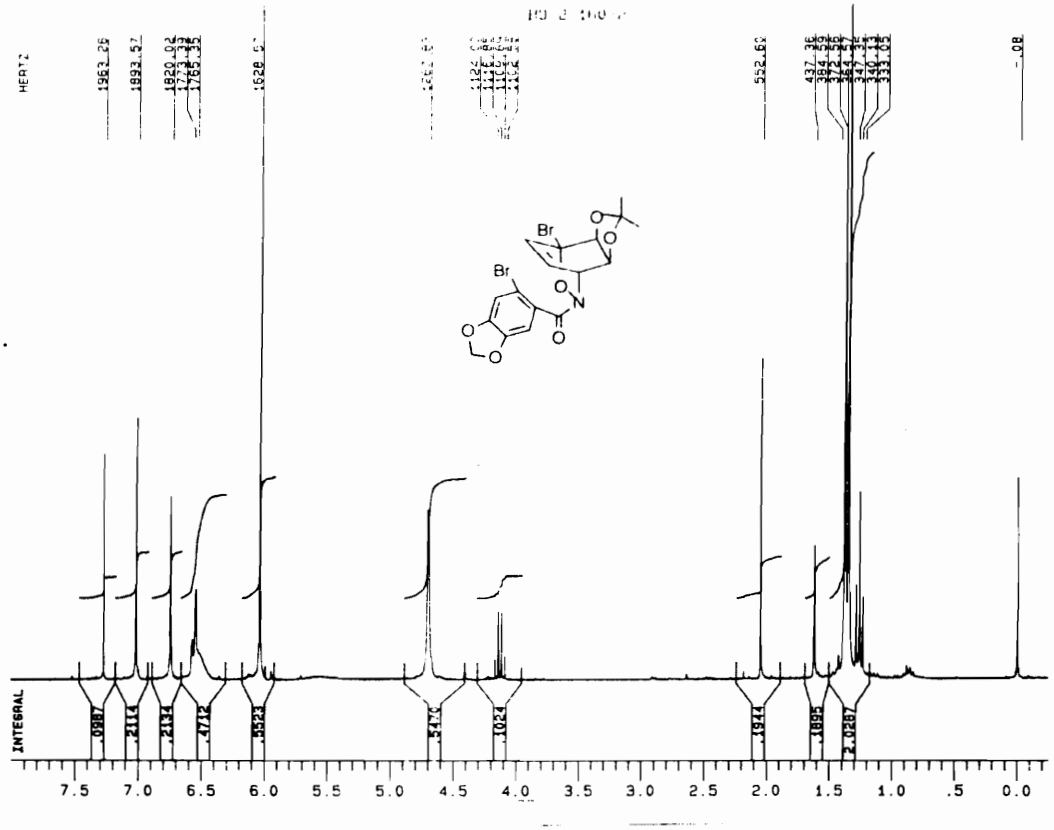
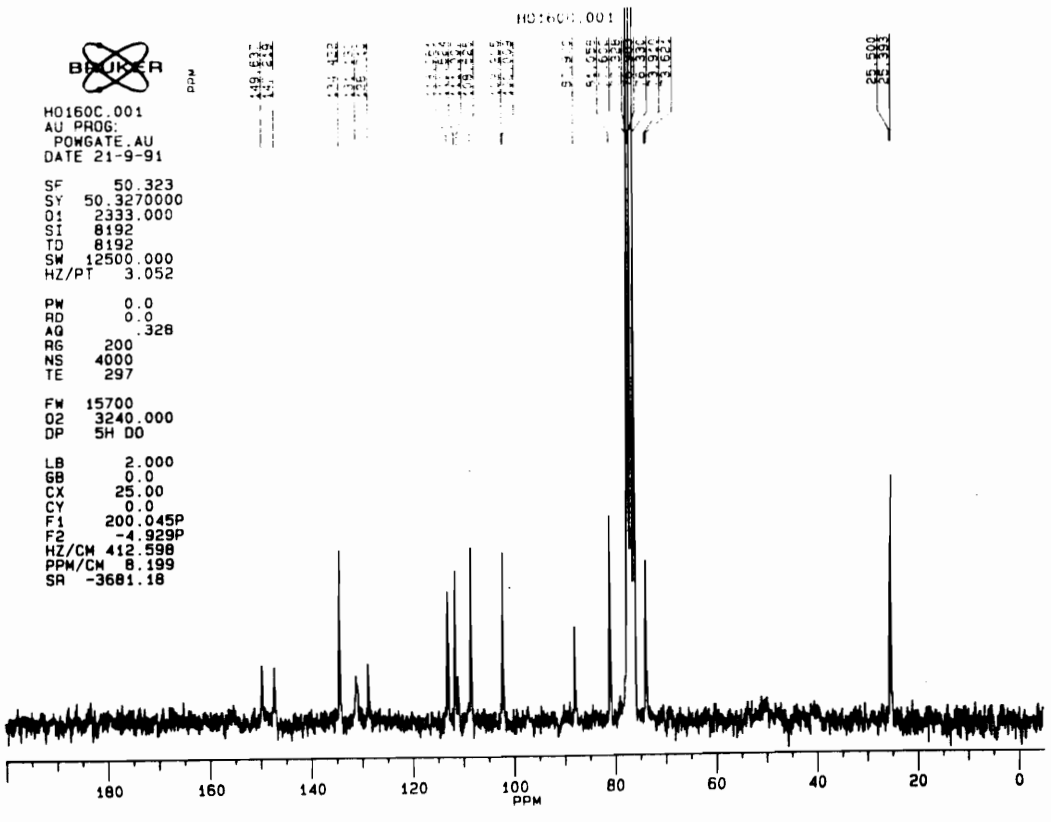
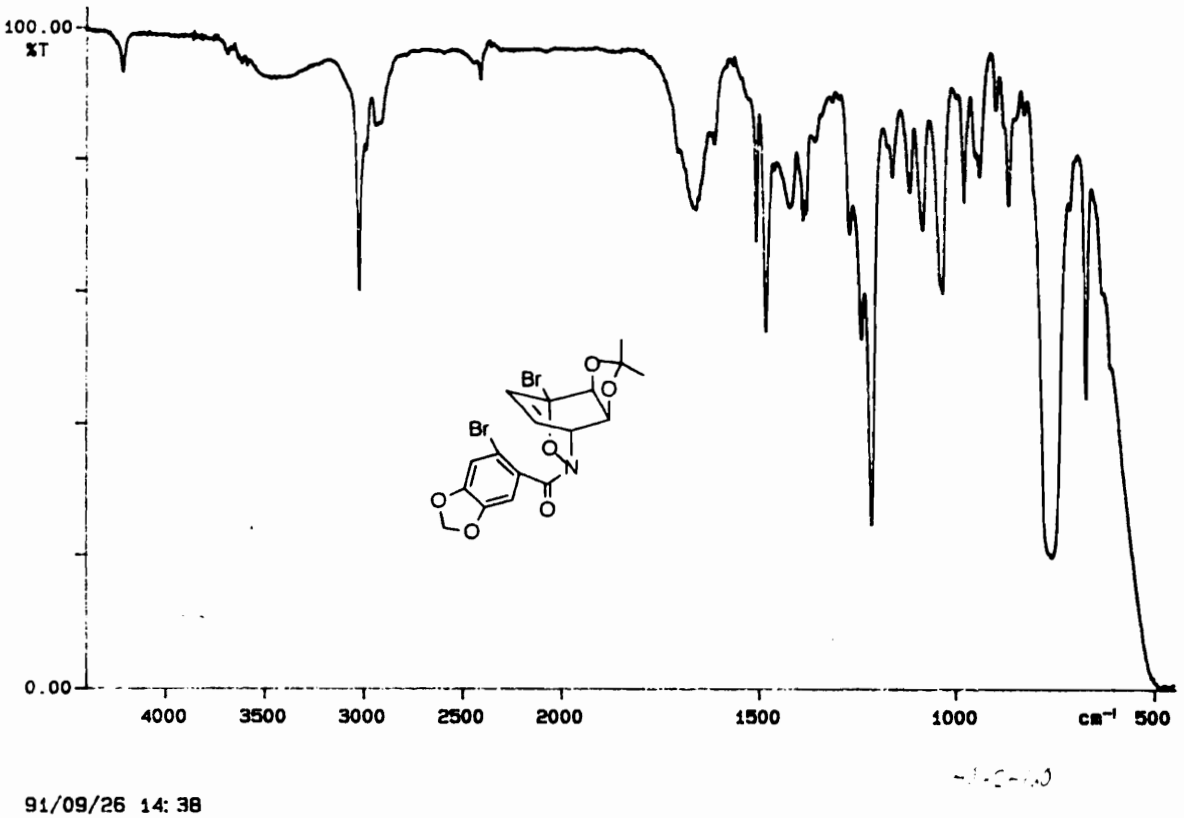
N
O

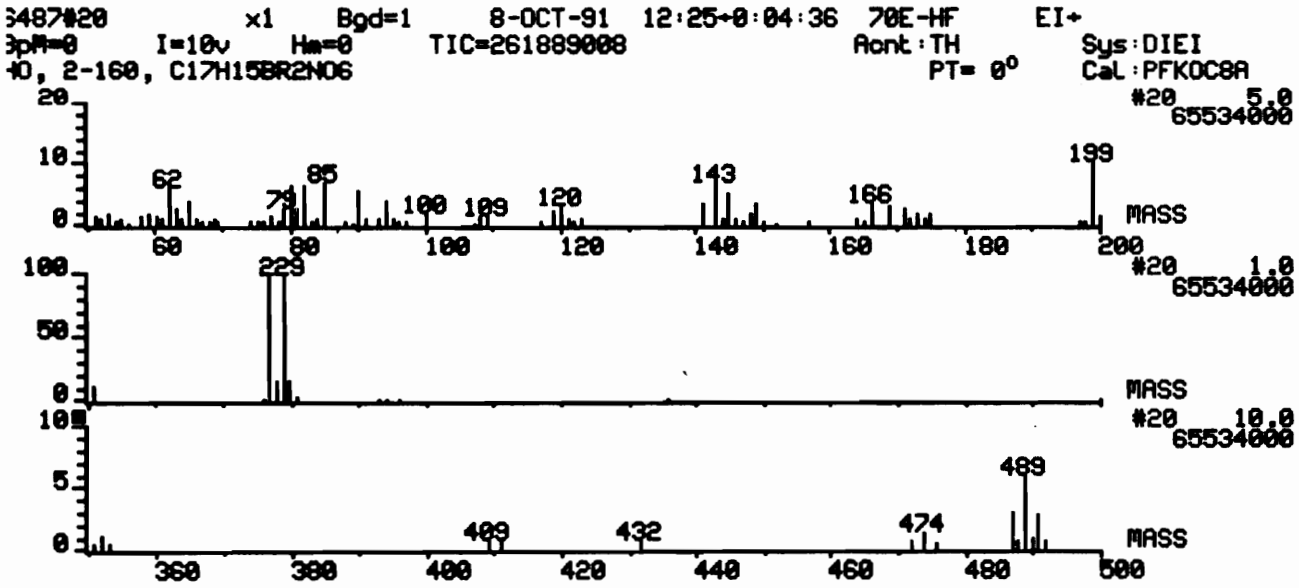

Abundance
90
80
60
50
40
30
20
10
0
82
91
124
156
198
246
288
100
150
200
250
300
Mass/Charge

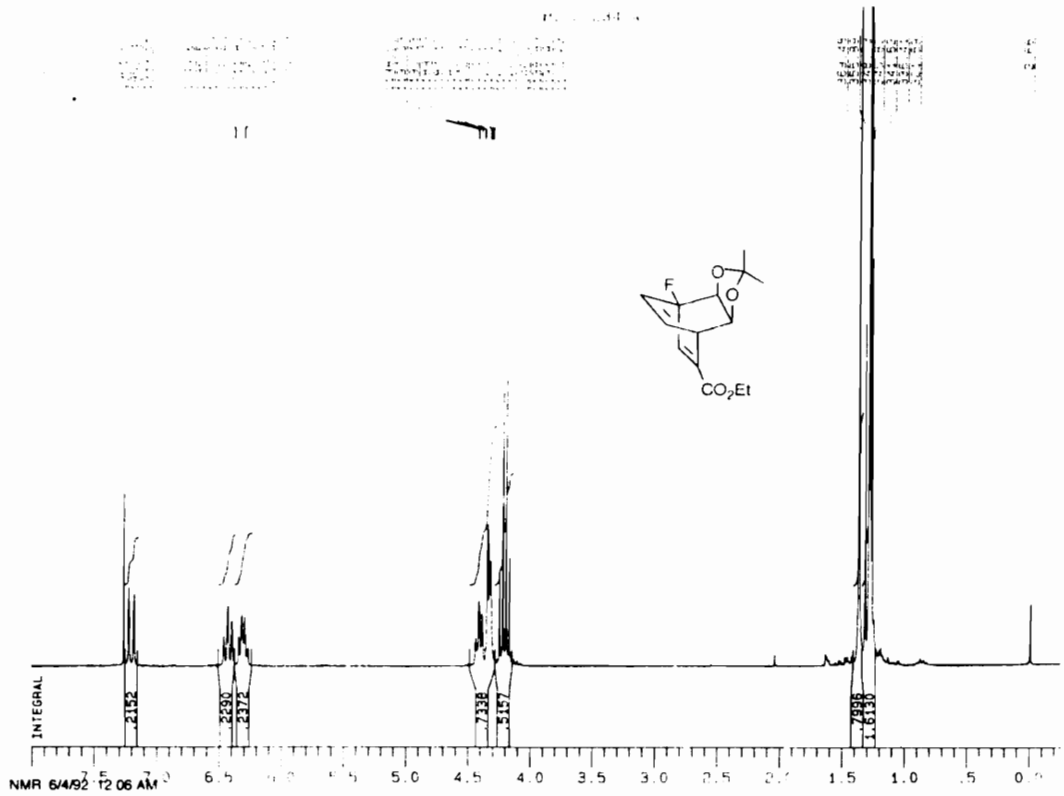

HERTZ
INTEGRAL
Br
Br
O
N
O
O
O
O
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
.5
0.0

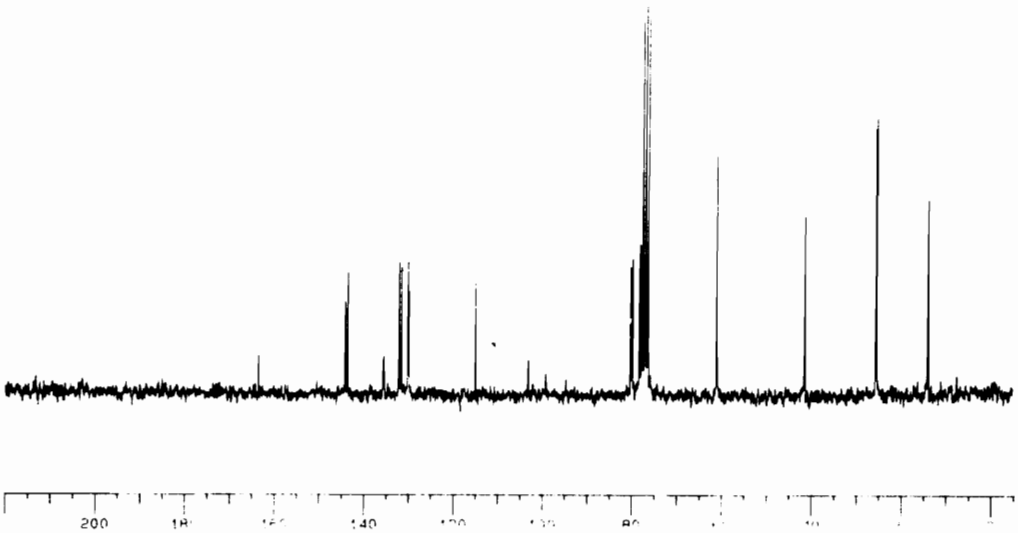

BRUKER
PPM
HO160C.001
AU PROG:
POWGATE.AU
DATE 21-9-91
SF 50.323
SY 50.3270000
O1 2333.000
SI 8192
TD 8192
SW 12500.000
HZ/PT 3.052
PW 0.0
RD 0.0
AQ .328
RG 200
NS 4000
TE 297
FW 15700
O2 3240.000
DP 5H DO
LB 2.000
GB 0.0
CX 25.00
CY 0.0
F1 200.045P
F2 -4.929P
HZ/CM 412.598
PPM/CM 8.199
SR -3681.18
180
160
140
120
100
80
60
40
20
0
PPM

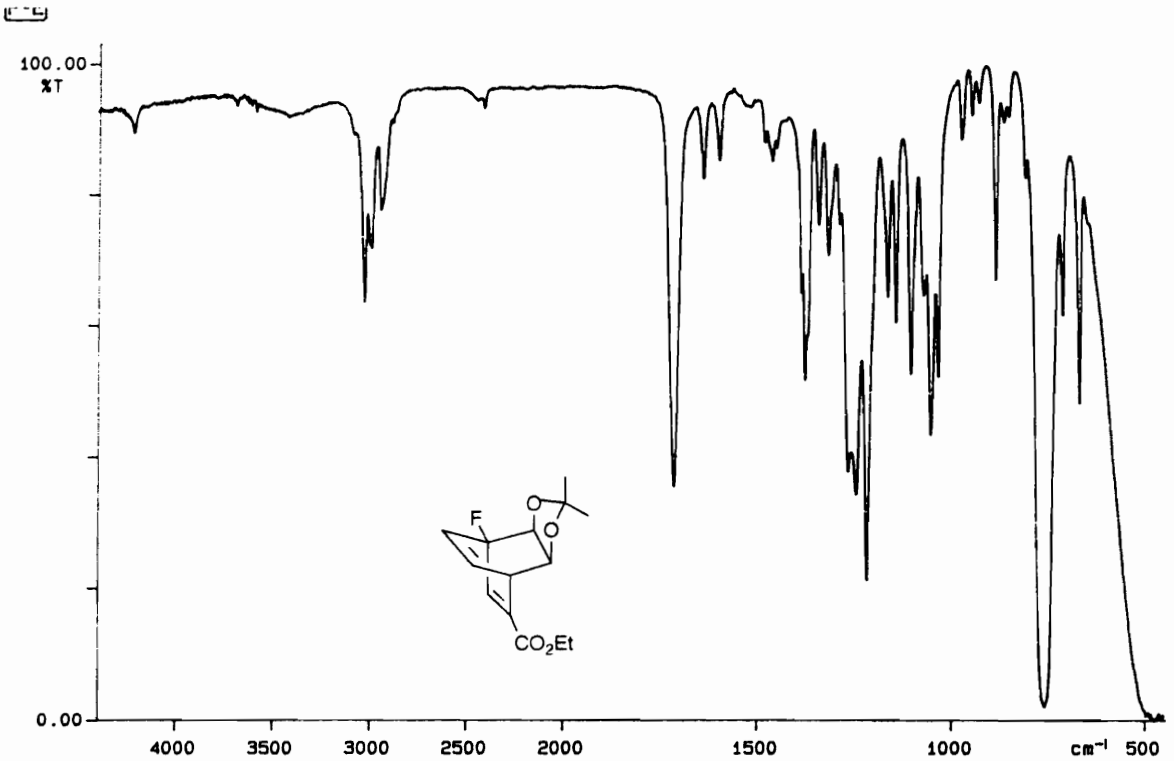


91/09/26 14:38
SCAN: 4 scans, 4.0cm-1, flat, abex



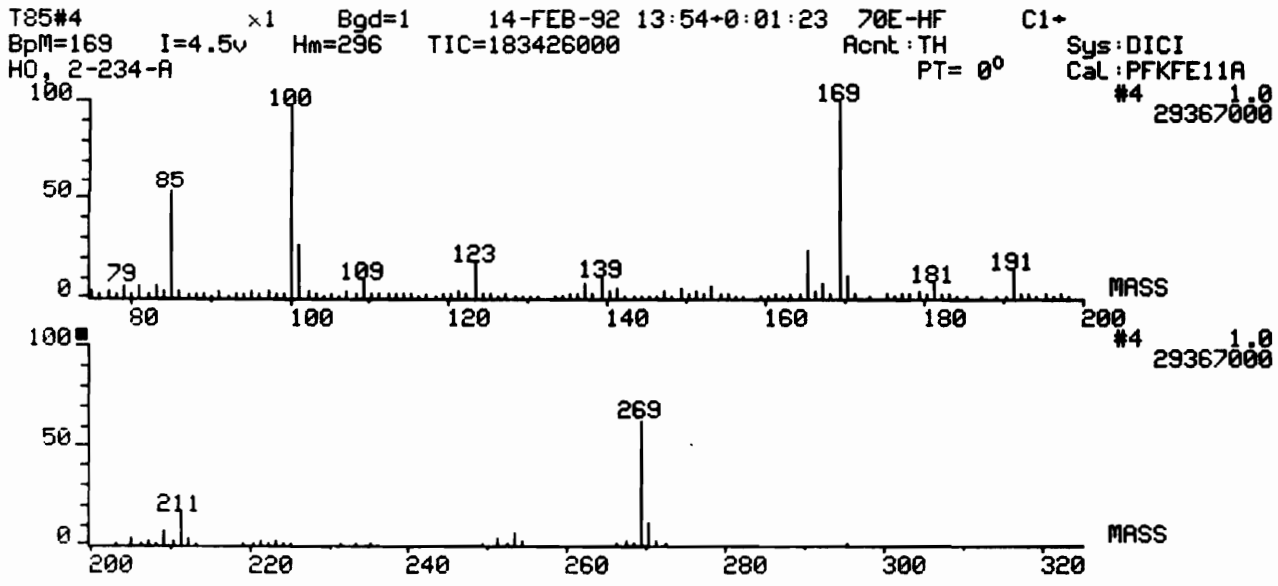

F
O
O
CO2Et
INTEGRAL
2.152
2.590
2.372
7.338
5.157
7.988
1.618
NMR 6/4/92 12:06 AM
7.5
7.0
6.5
5.0
4.5
4.0
3.5
3.0
1.5
1.0
.5

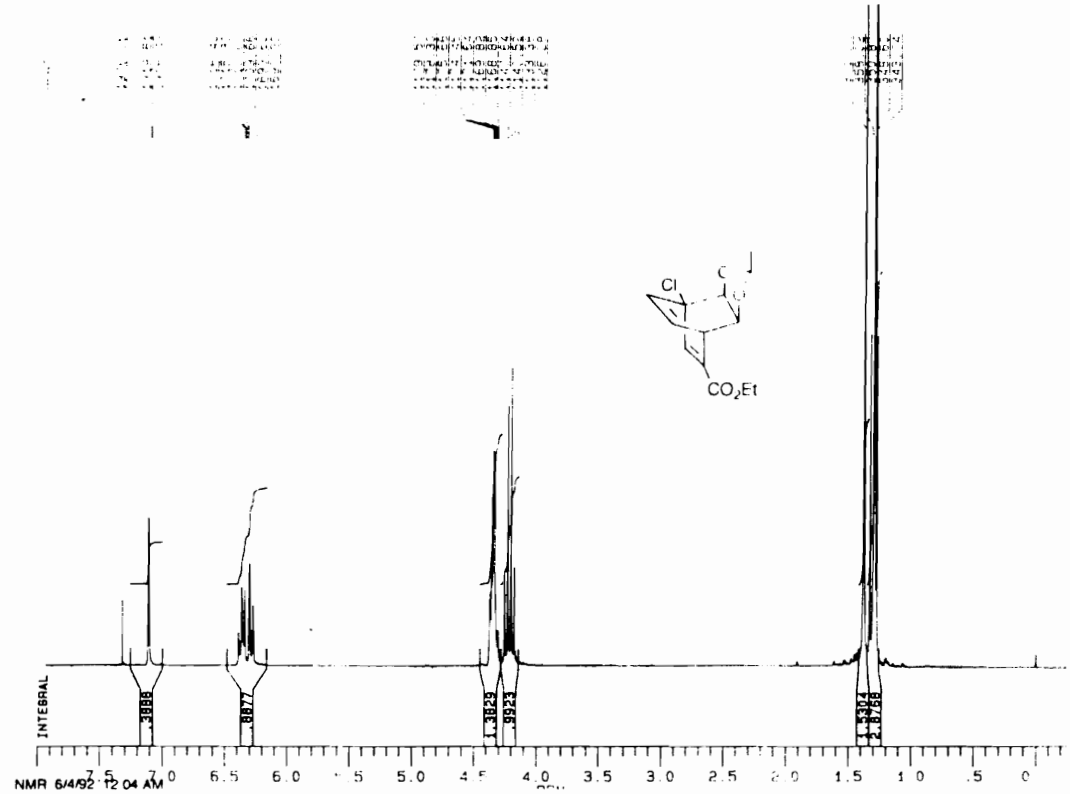

200
140

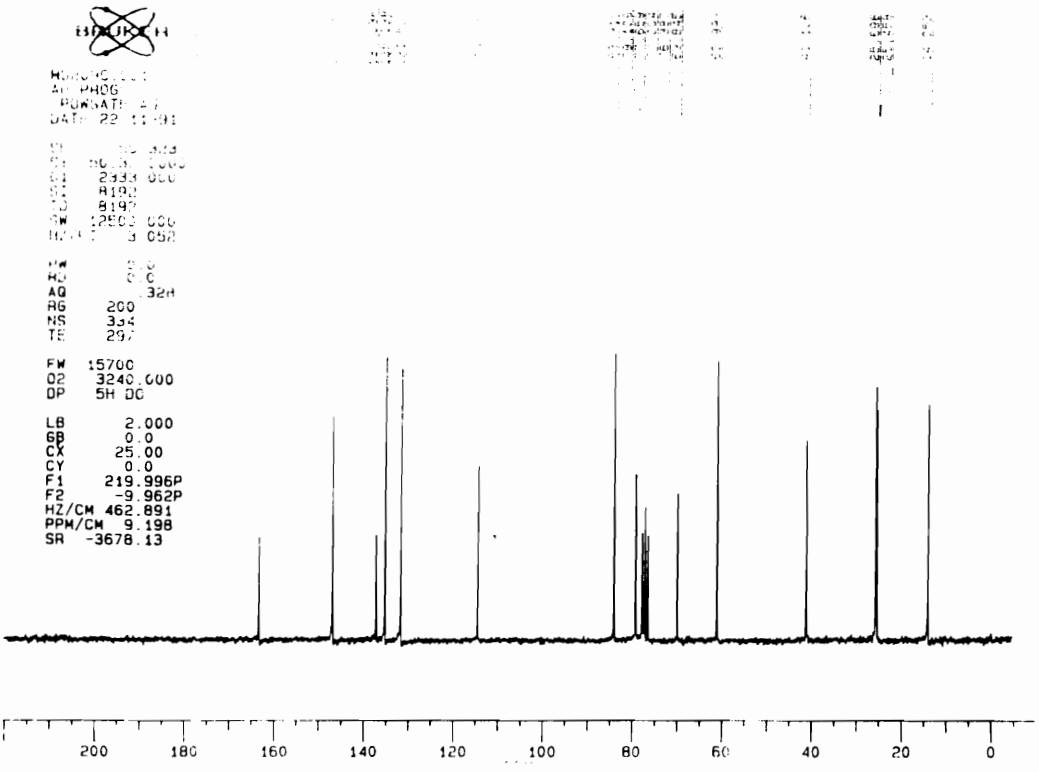


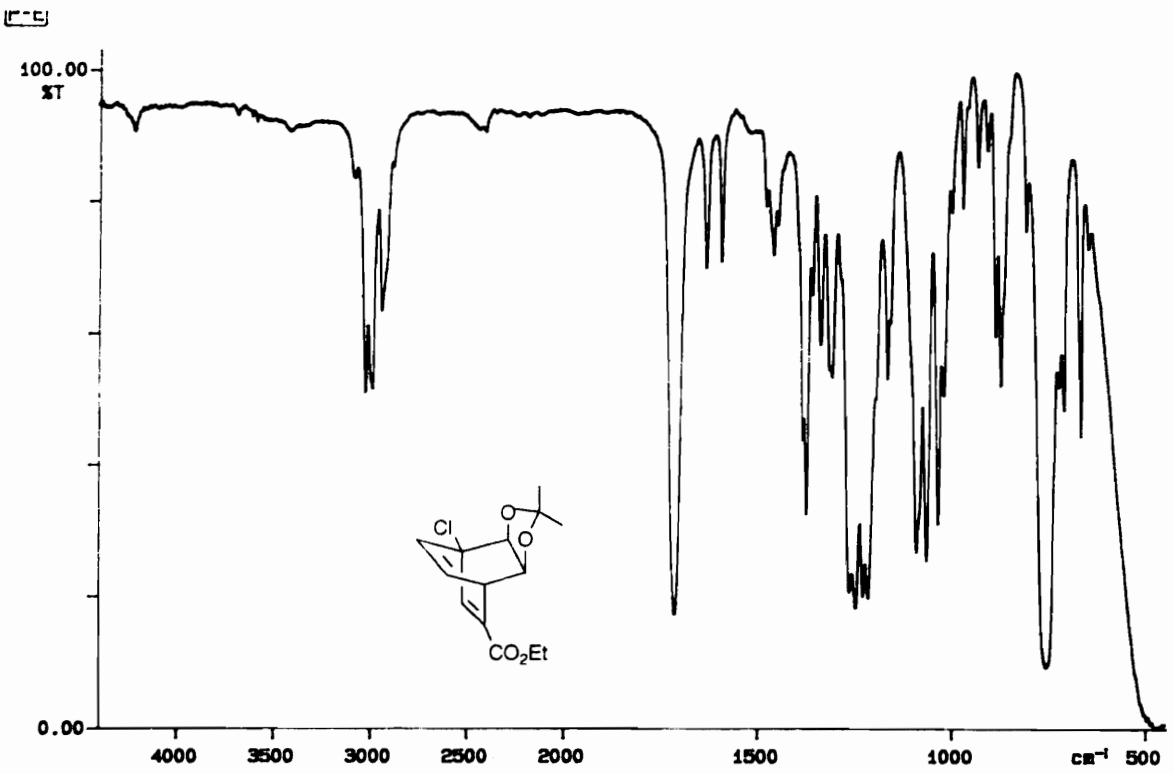
92/02/12 00:51
X: 4 scans, 4.0cm-1, flat, abex

IR FRAME 6/25/92 10:41 AM



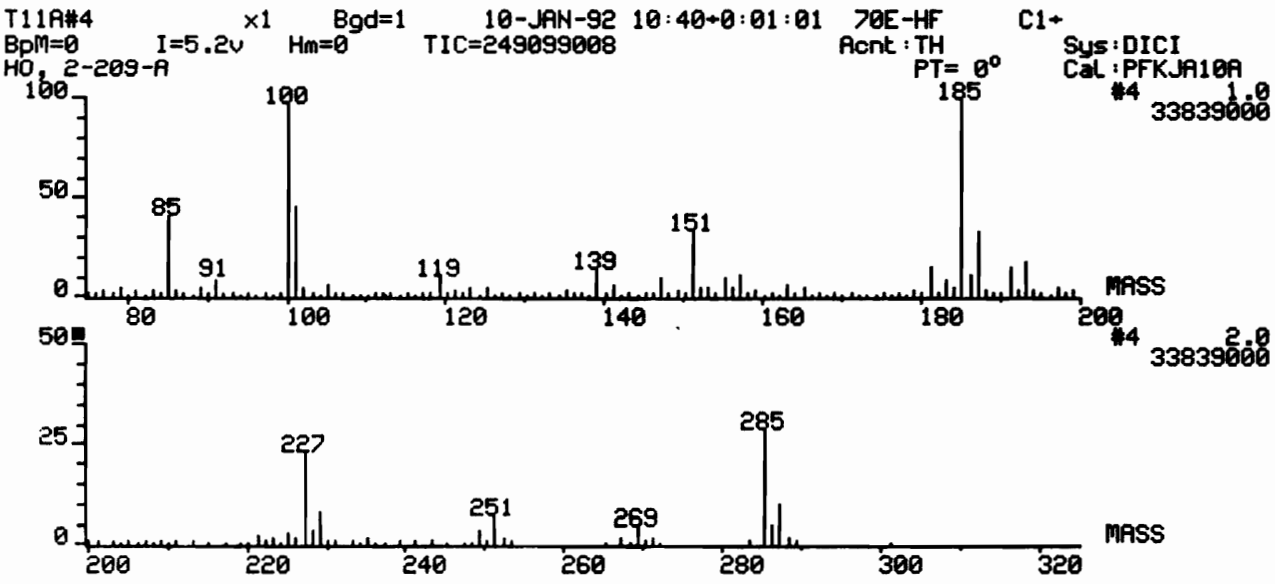

Cl
CO_2Et
INTEGRAL
3888
8877
3829
9923
NMR 6/4/92 12 04 AM
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
.5
0

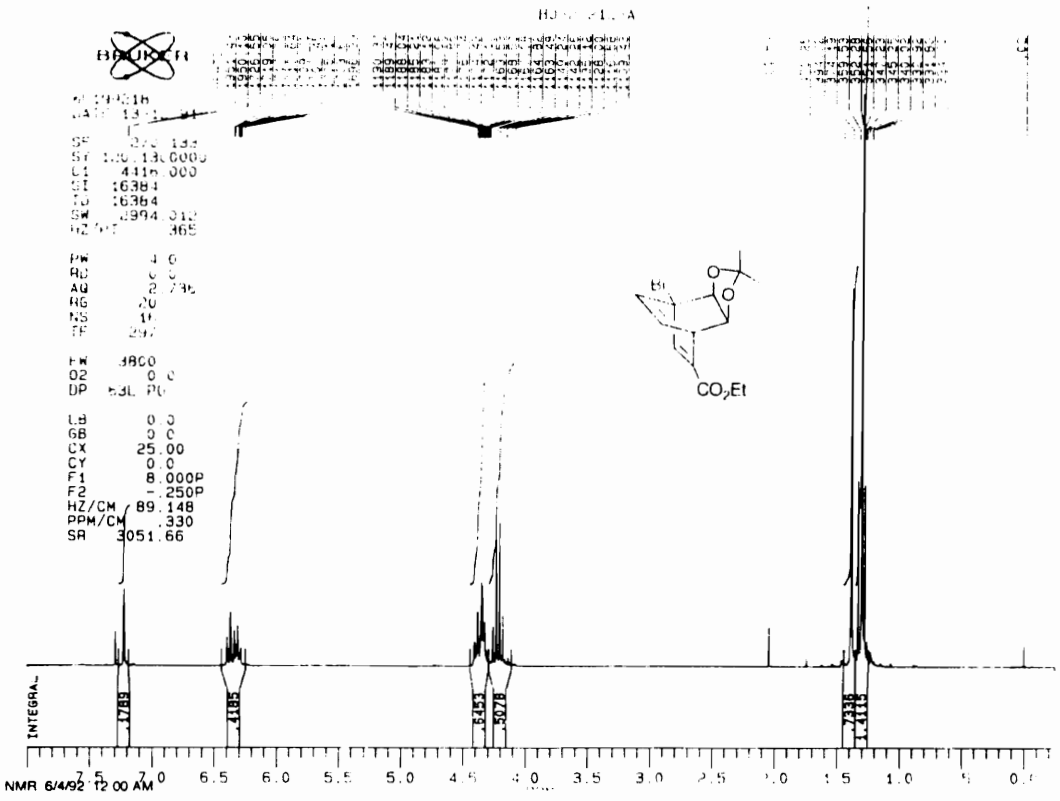

AQ 1.32H
RG 200
NS 334
TE 297
SW 15700
O2 3240.000
DP 5H DC
LB 2.000
GB 0.0
CX 25.00
CY 0.0
F1 219.996P
F2 -9.962P
HZ/CM 462.891
PPM/CM 9.198
SR -3678.13
200
180
160
140
120
100
80
60
40
20
0

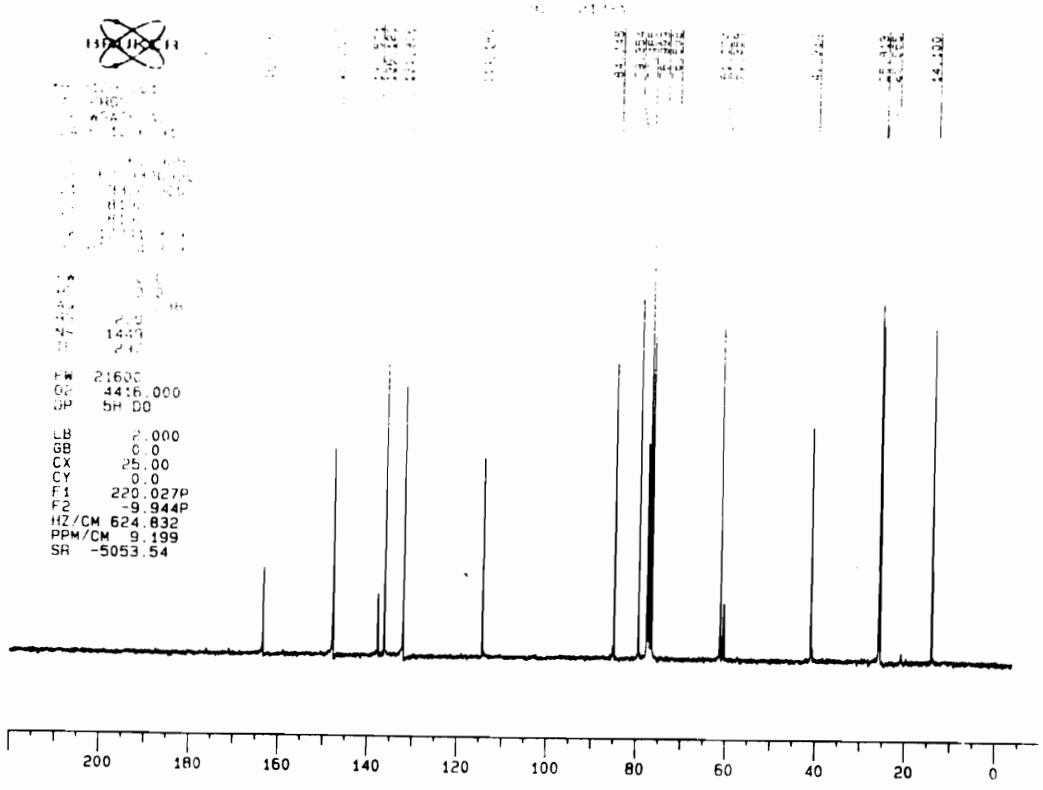


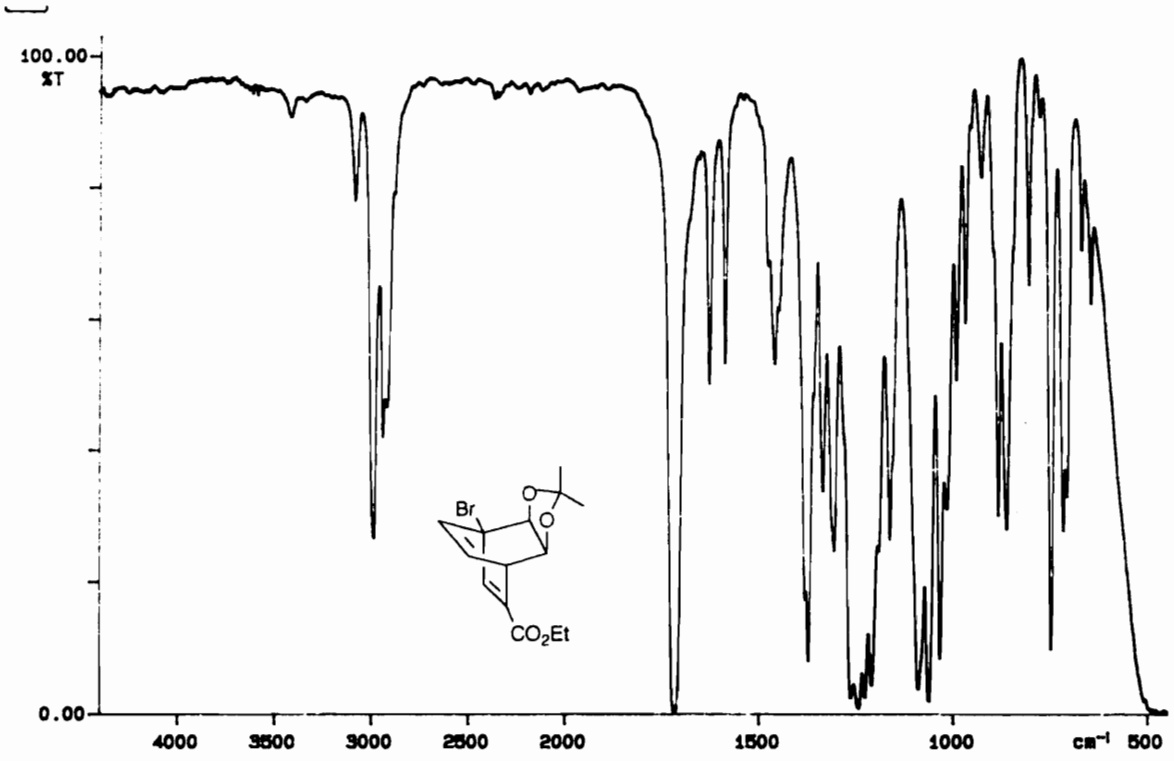
91/12/16 19:32
Y: 4 scans, 4.0cm-1, flat, abex

IR FRAME 6/25/92 10:28 AM



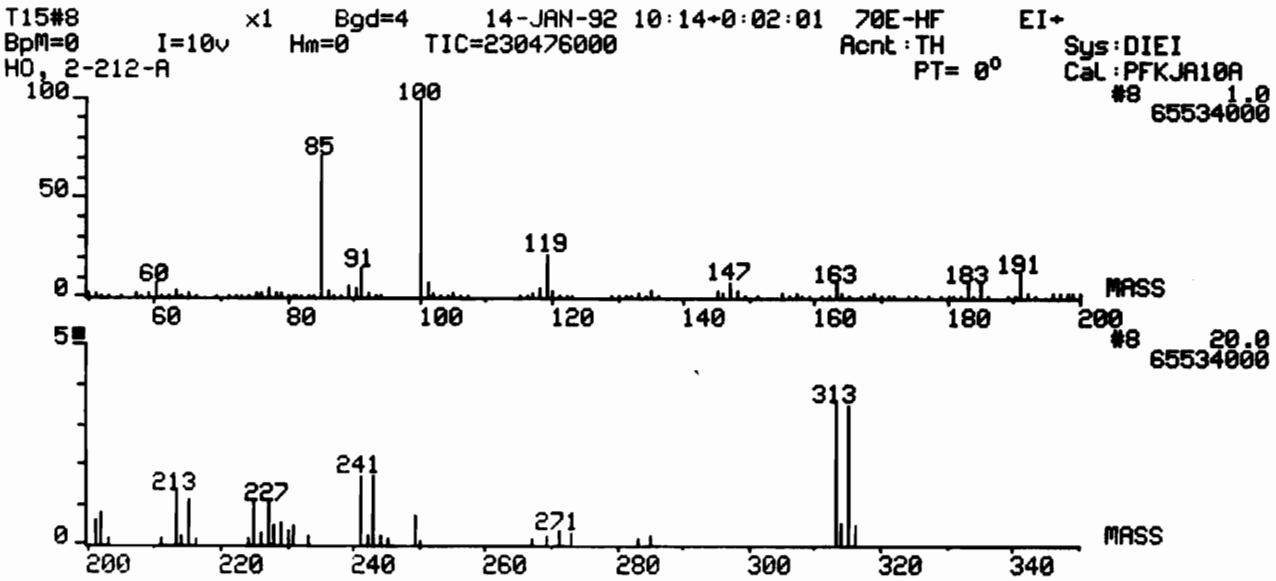

CO2Et
INTEGRAL
NMR 6/4/92 12:00 AM

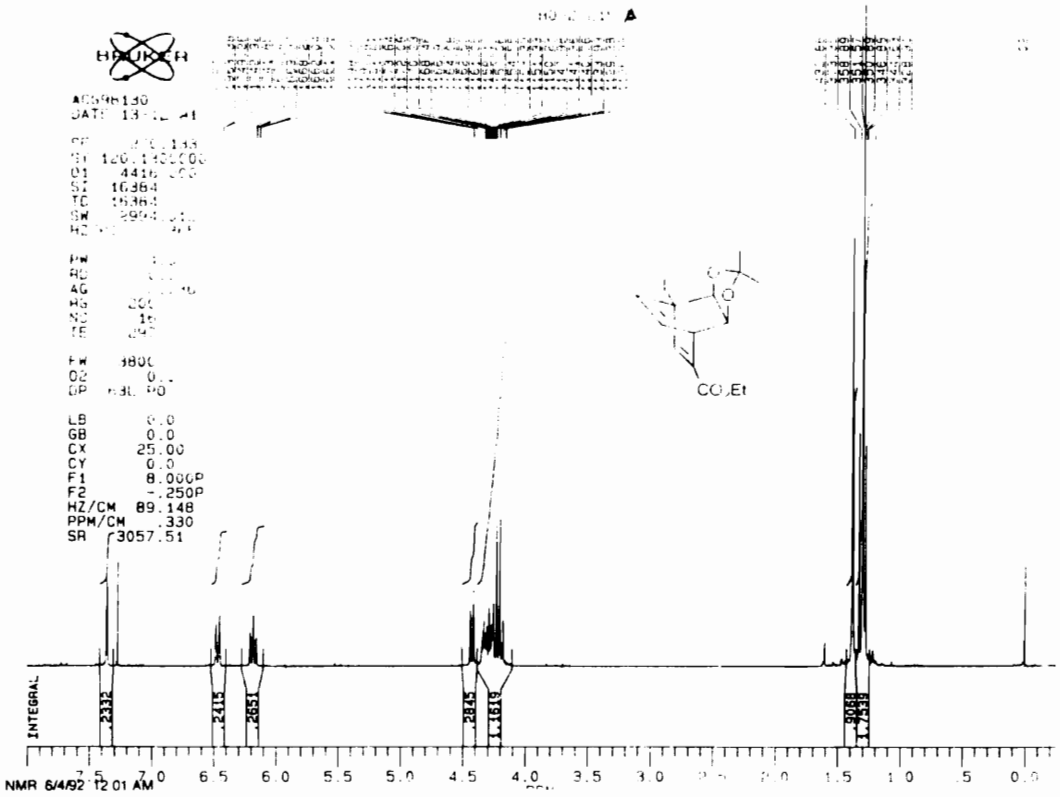


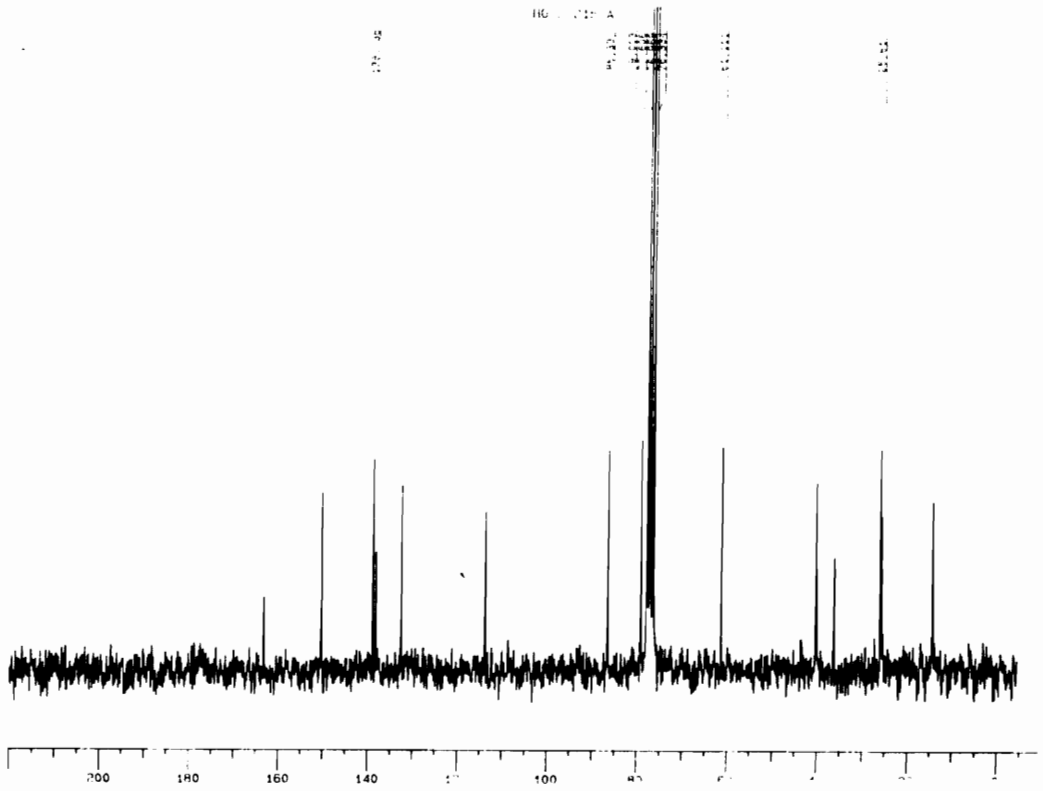


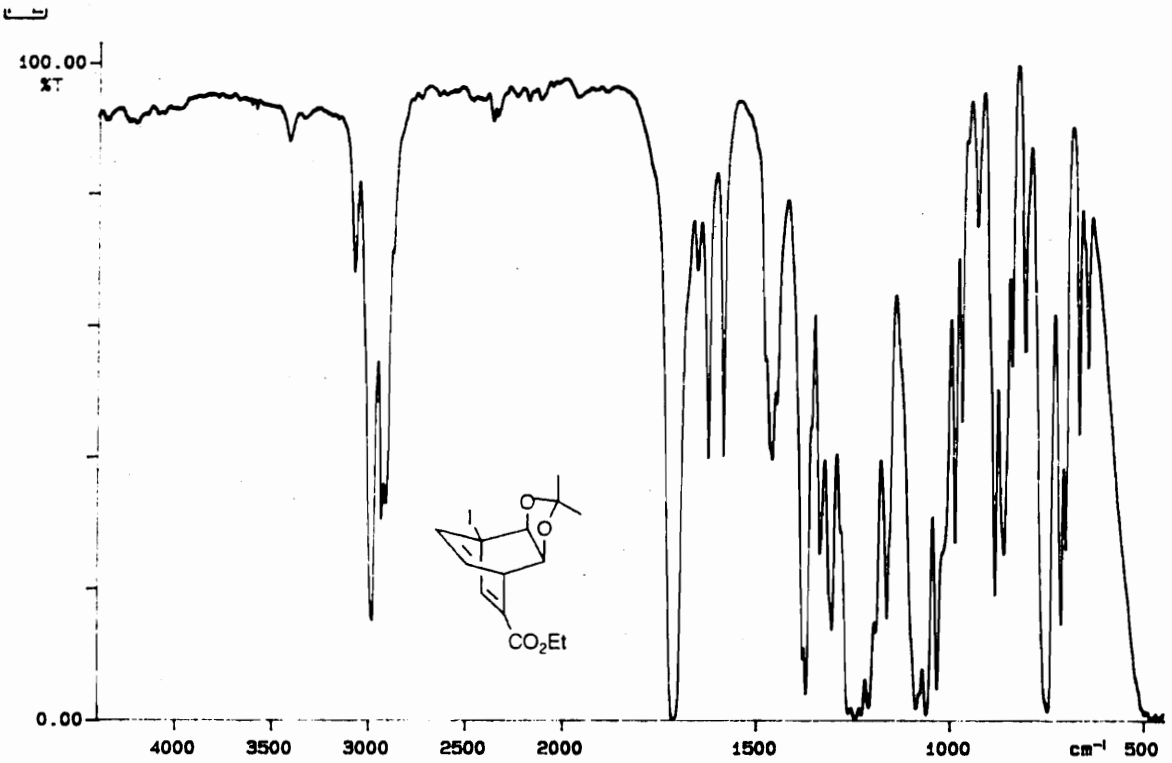
92/01/11 12:56
SCAN: 4 scans, 4.0cm-1, flat, abex

IR FRAME 6/25/92 10:33 AM



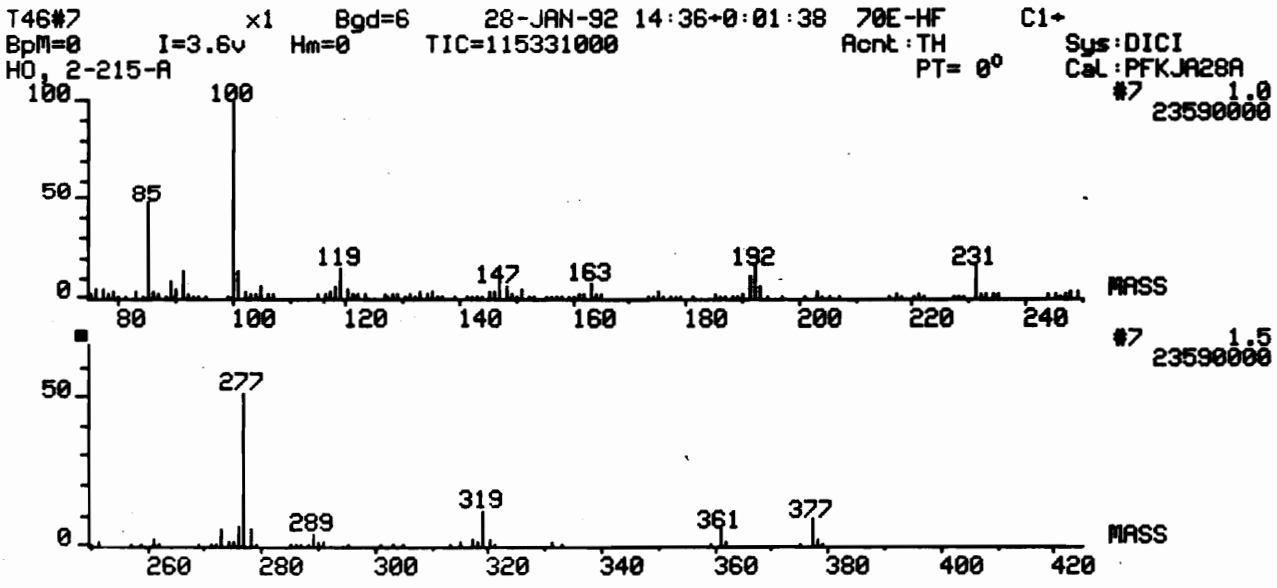

BRUKER
LB 0.0
GB 0.0
CX 25.00
CY 0.0
F1 8.000P
F2 -.250P
HZ/CM 89.148
PPM/CM .330
SR 3057.51
INTEGRAL
2332
2418
2651
2845
1.1619
3068
1.7539
CO2Et
NMR 6/4/92 12:01 AM

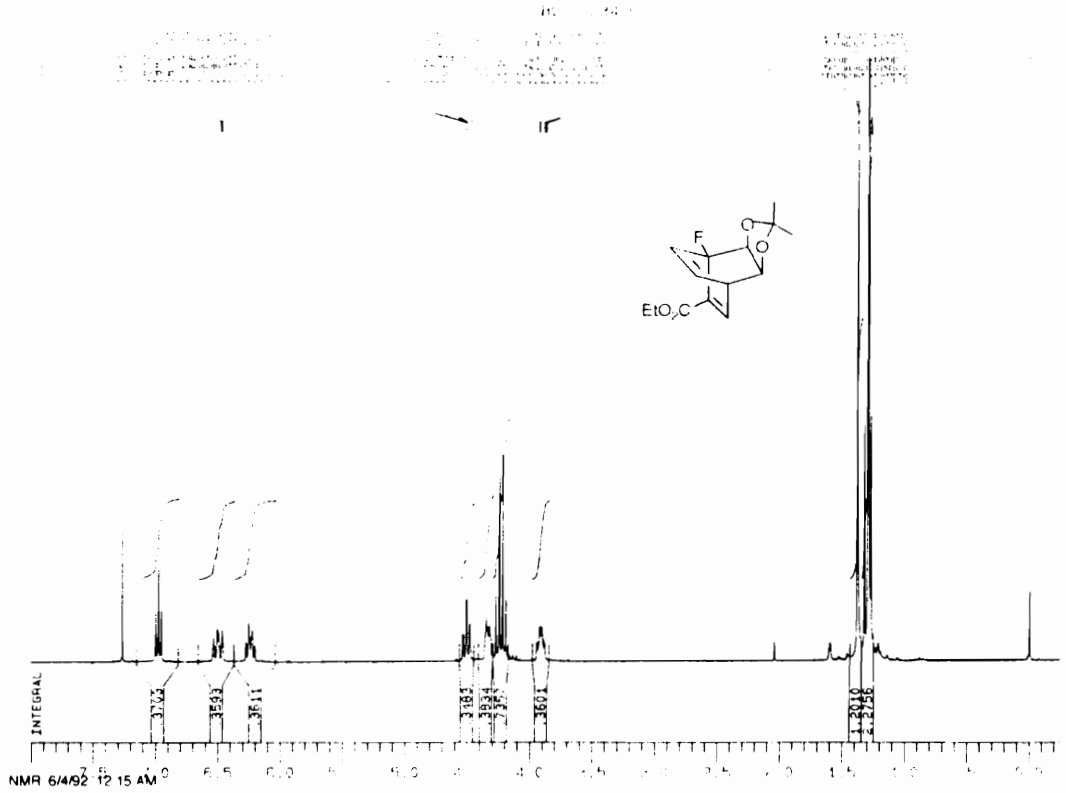


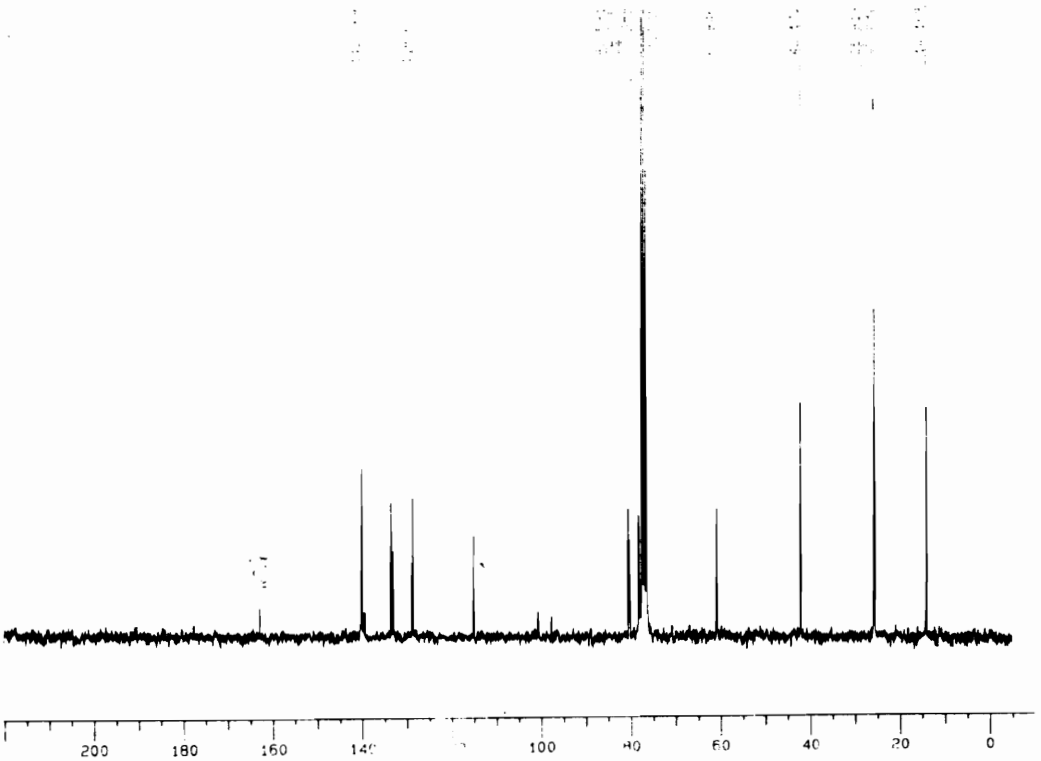


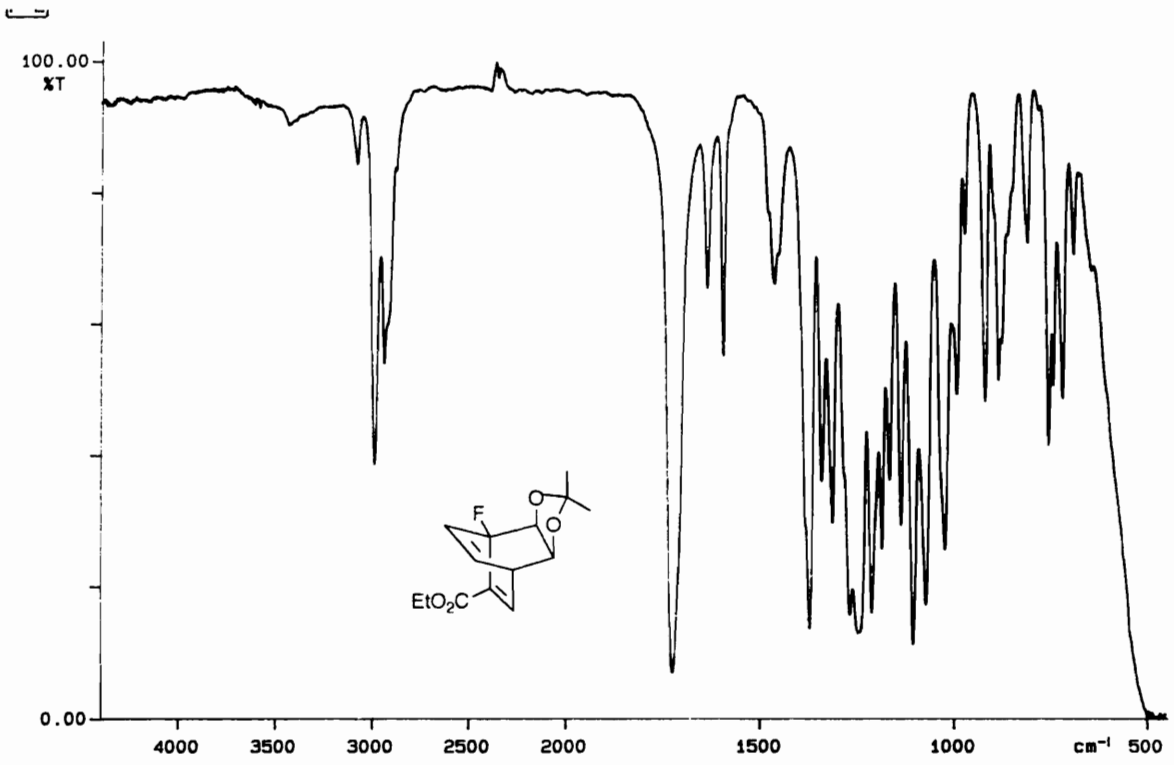
92/01/21 01:17
X: 4 scans, 4.0cm-1, abex

IR FRAME 6/25/92 10:37 AM



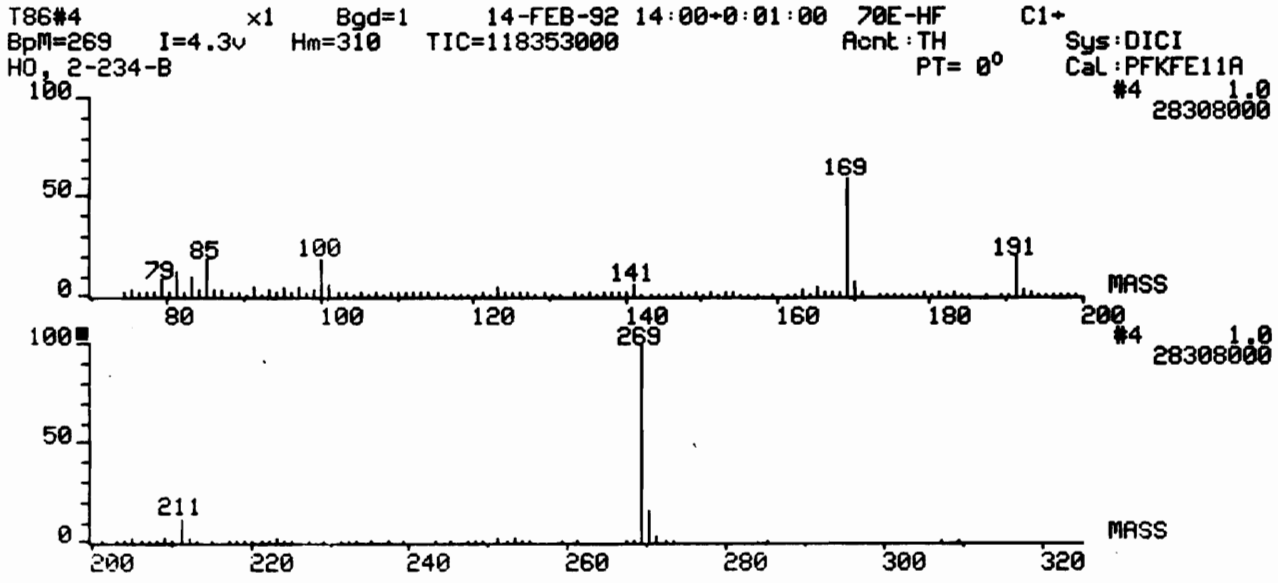

F
O
O
EtO2C
INTEGRAL
NMR 6/4/92 12:15 AM

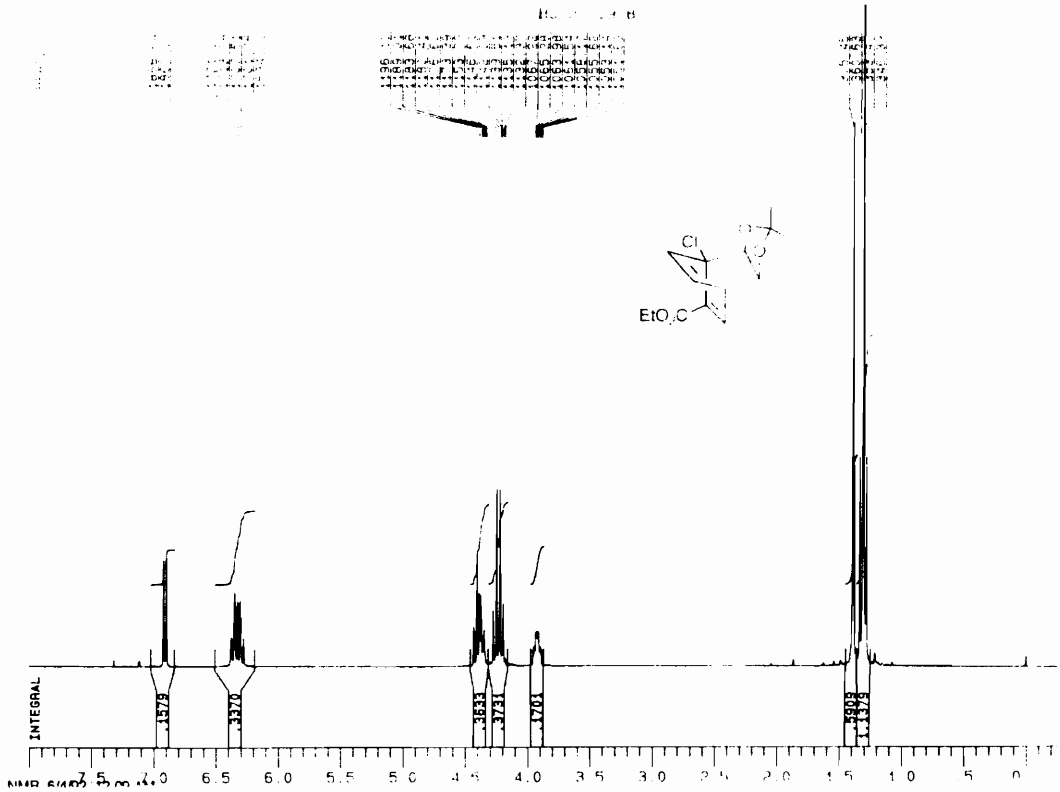

200
180
160
140
100
80
60
40
20
0

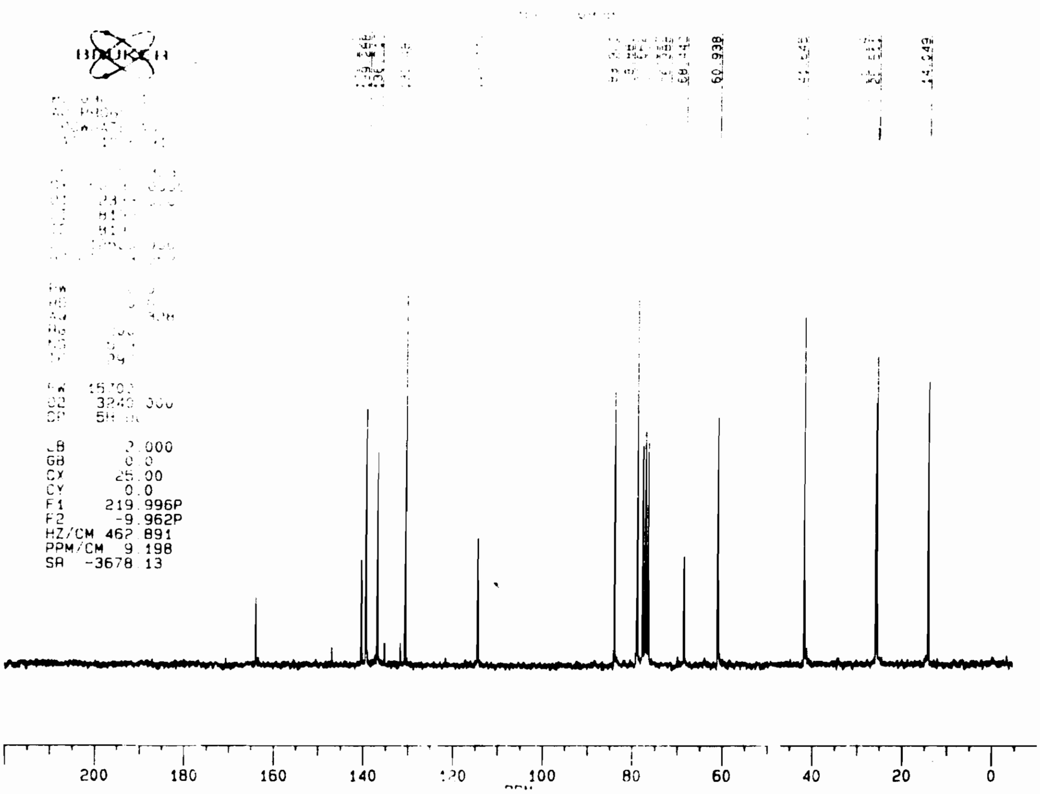


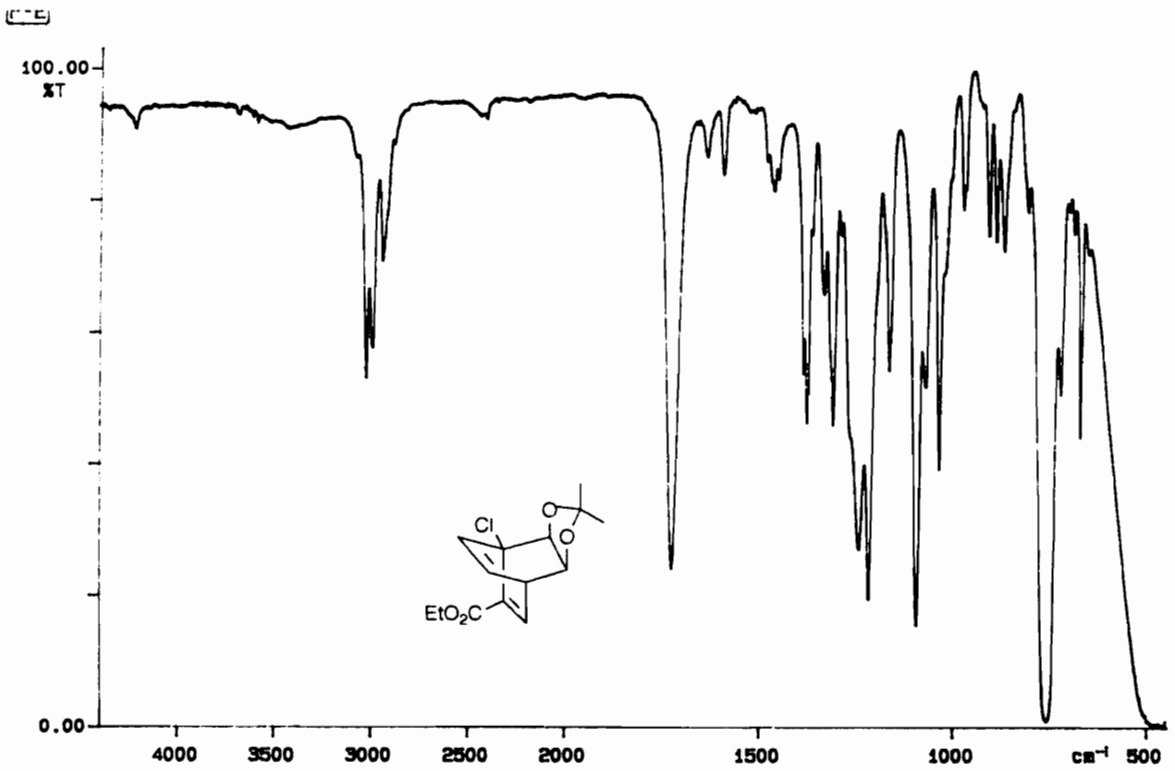
92/02/12 01:27
Y: 4 scans, 4.0cm-1, flat, abex

IR FRAME 6/25/92 10:43 A



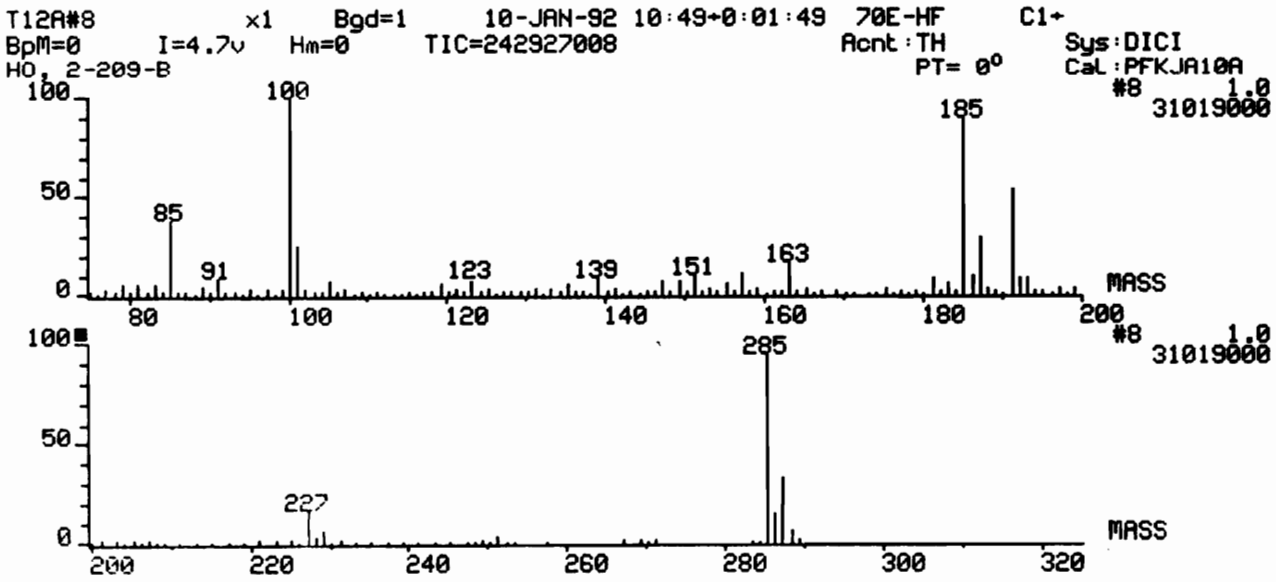

Cl
EtO₂C
INTEGRAL
.1579
.3370
.3633
.3731
.1701
.5909
1.1379

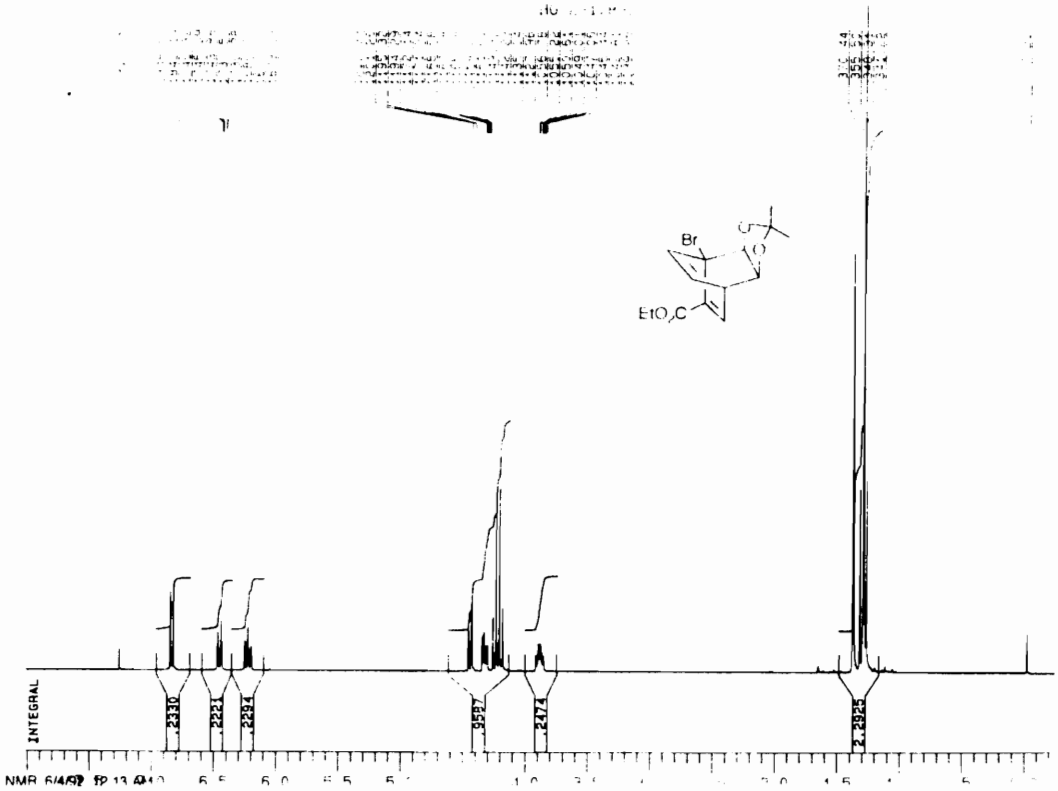

60.938
14.249
LB 2.000
GB 0.0
CX 25.00
CY 0.0
F1 219.996P
F2 -9.962P
HZ/CM 462.891
PPM/CM 9.198
SR -3678.13
200
180
160
140
120
100
80
60
40
20
0

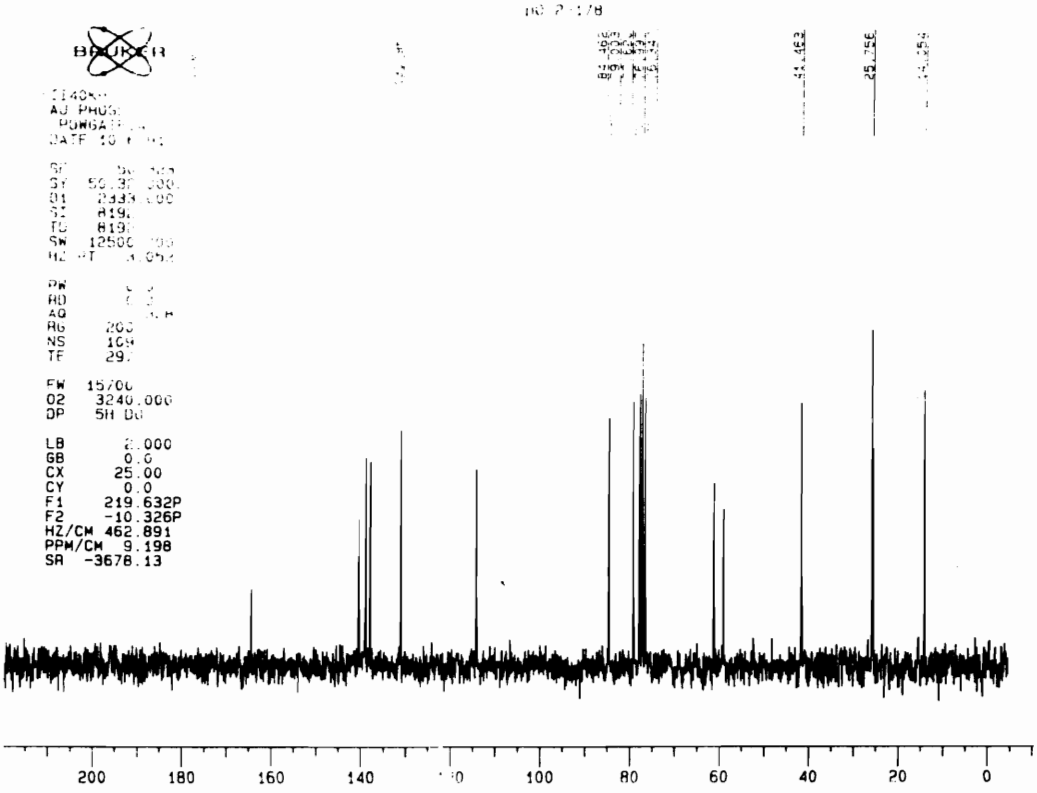


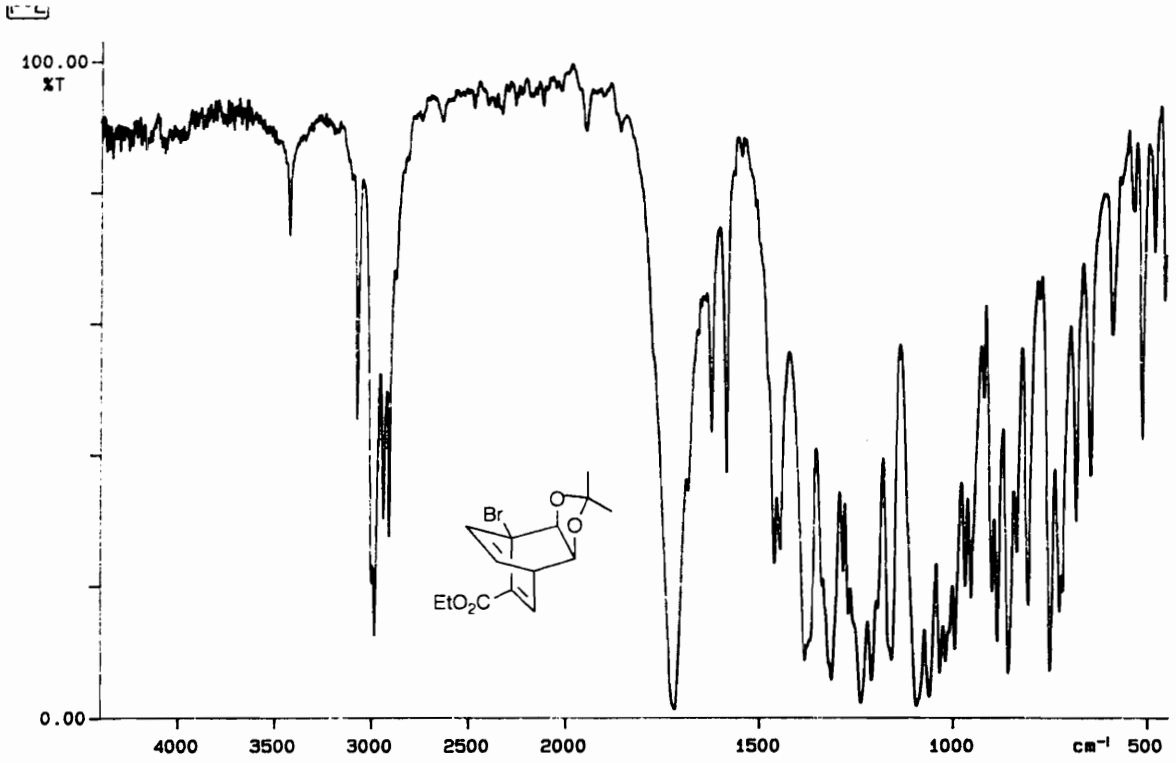
91/12/16 19:58
SCAN: 4 scans, 4.0cm-1, flat, abex

IR FRAME 6/25/92 10:47 AM



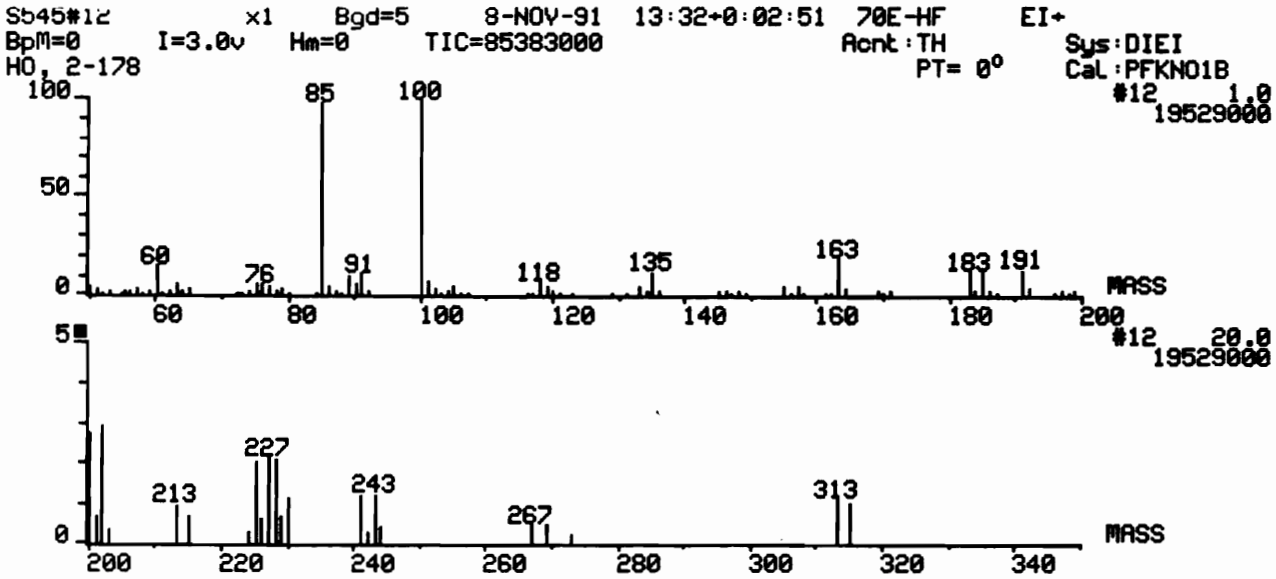

Br
EtO2C
INTEGRAL
2.330
2.221
2.294
3.927
2.474
2.000

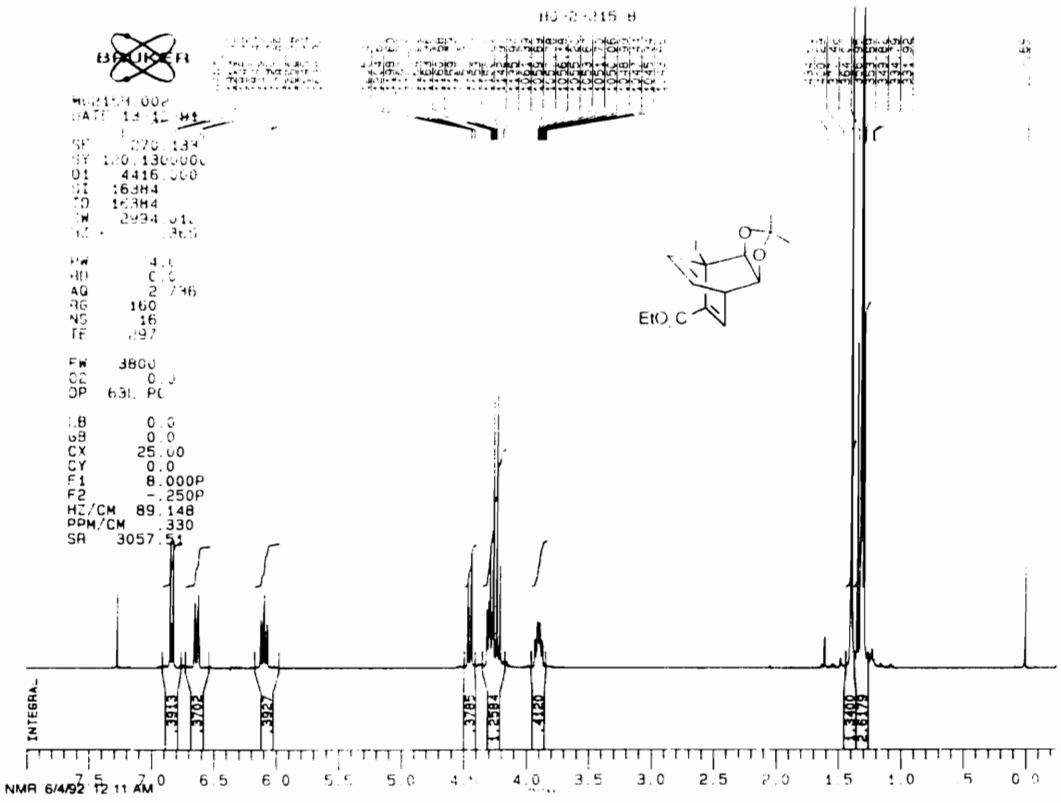

BRUKER
AQ PHOS
PUNGA
DATE 10
SF
SI 8192
TD 8192
SW 12500.000
PW
RD
AQ
RG 203
NS 109
TF 29
FW 15700
O2 3240.000
DP 5H D0
LB 2.000
GB 0.0
CX 25.00
CY 0.0
F1 219.632P
F2 -10.326P
HZ/CM 462.891
PPM/CM 9.198
SR -3678.13
200
180
160
140
100
80
60
40
20
0

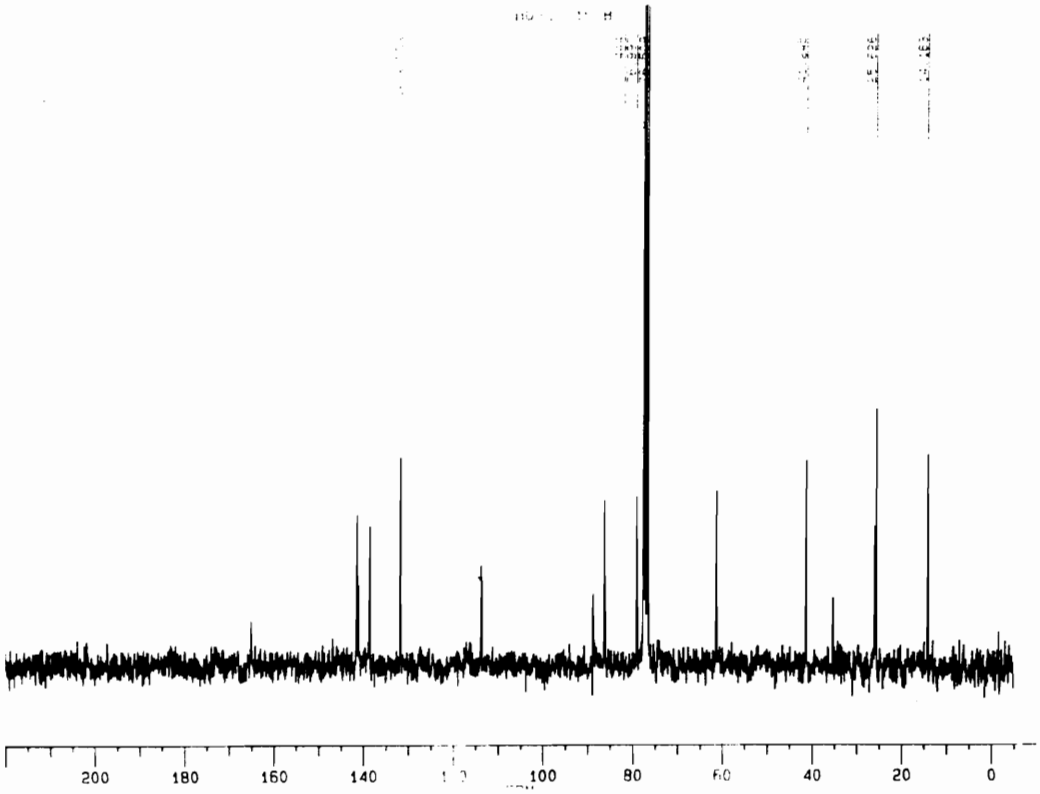


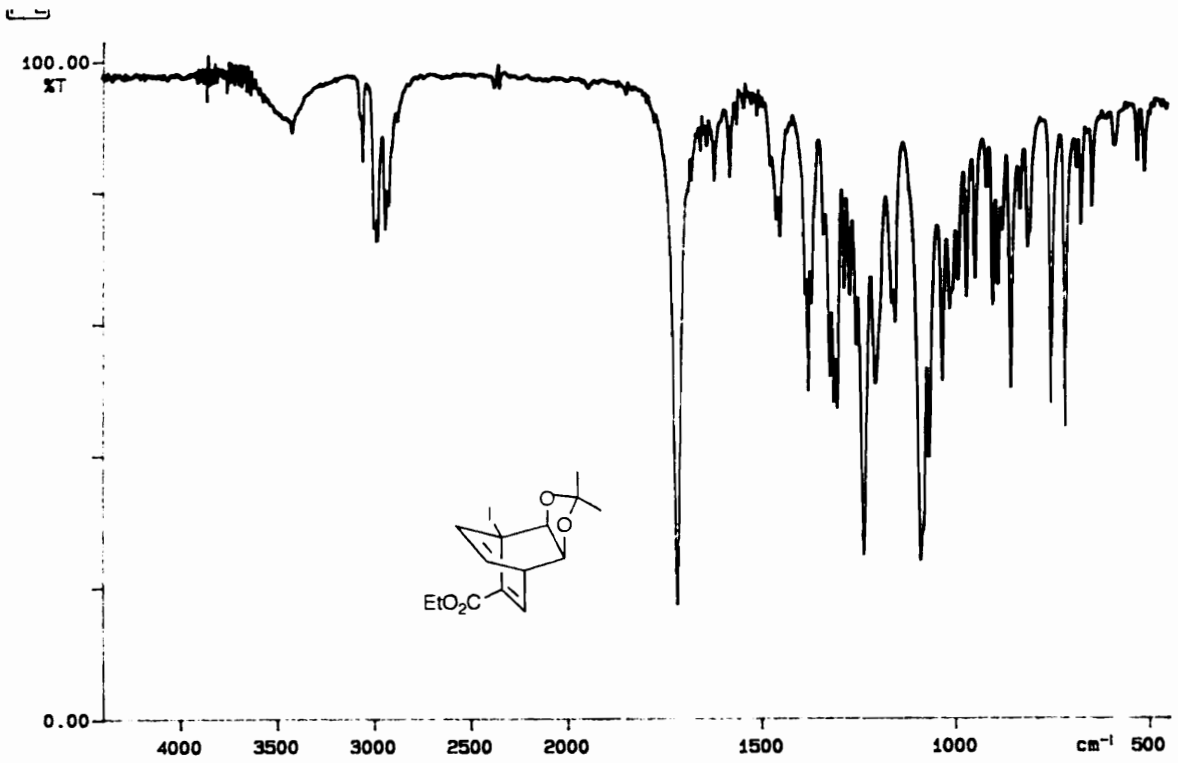
91/11/02 18:59
SCAN: 4 scans, 4.0cm-1, flat, abex

IR FRAME 6/25/92 10 49 AM



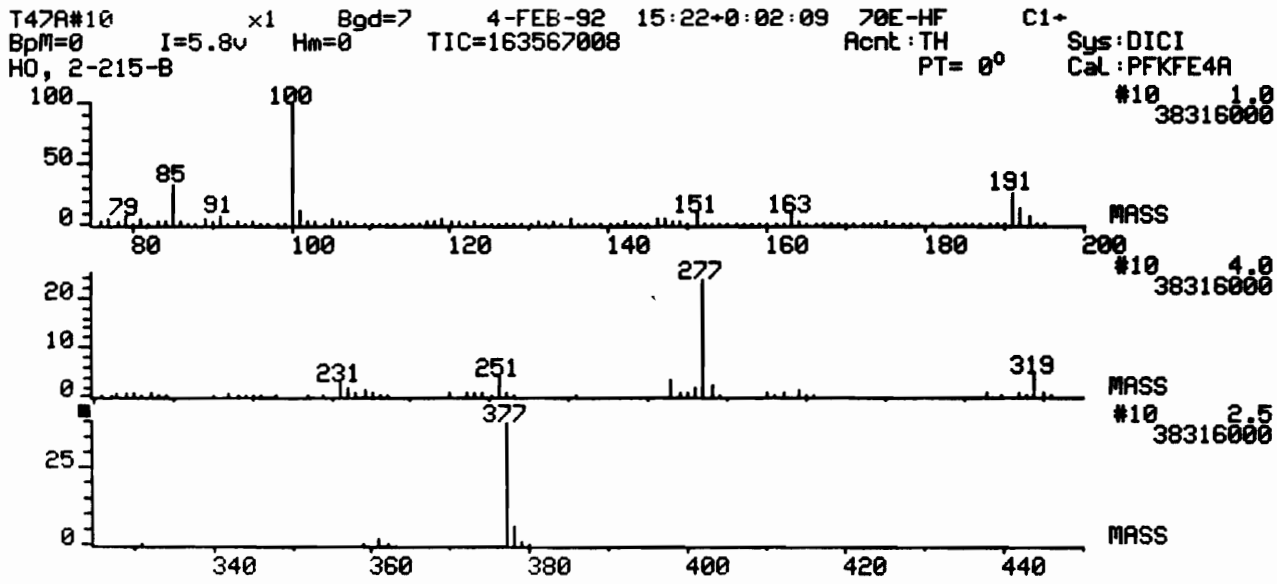

BRUKER
EtO2C
INTEGRAL
NMR 6/4/92 12 11 AM

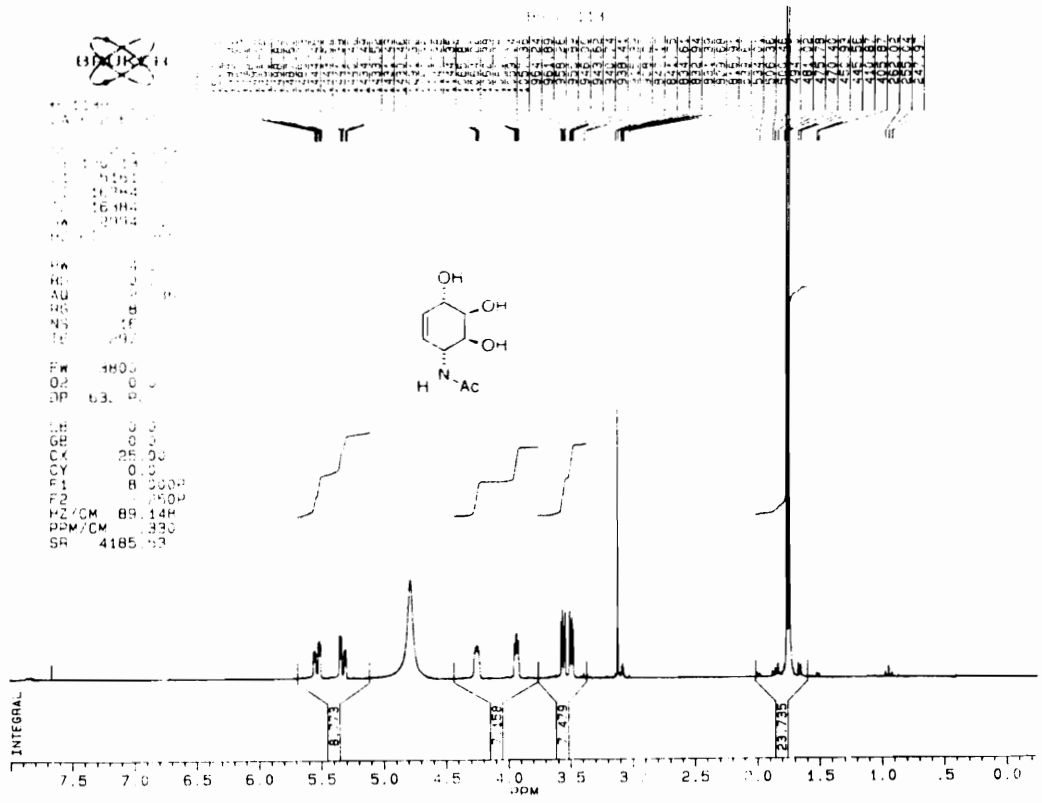


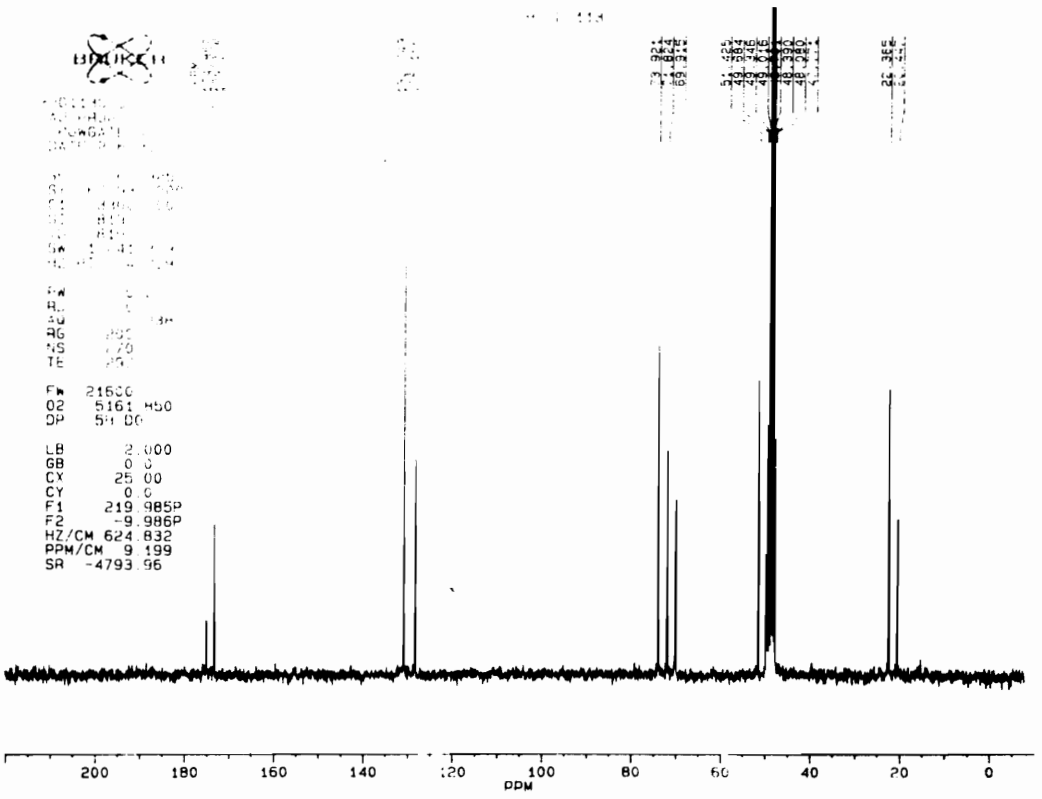


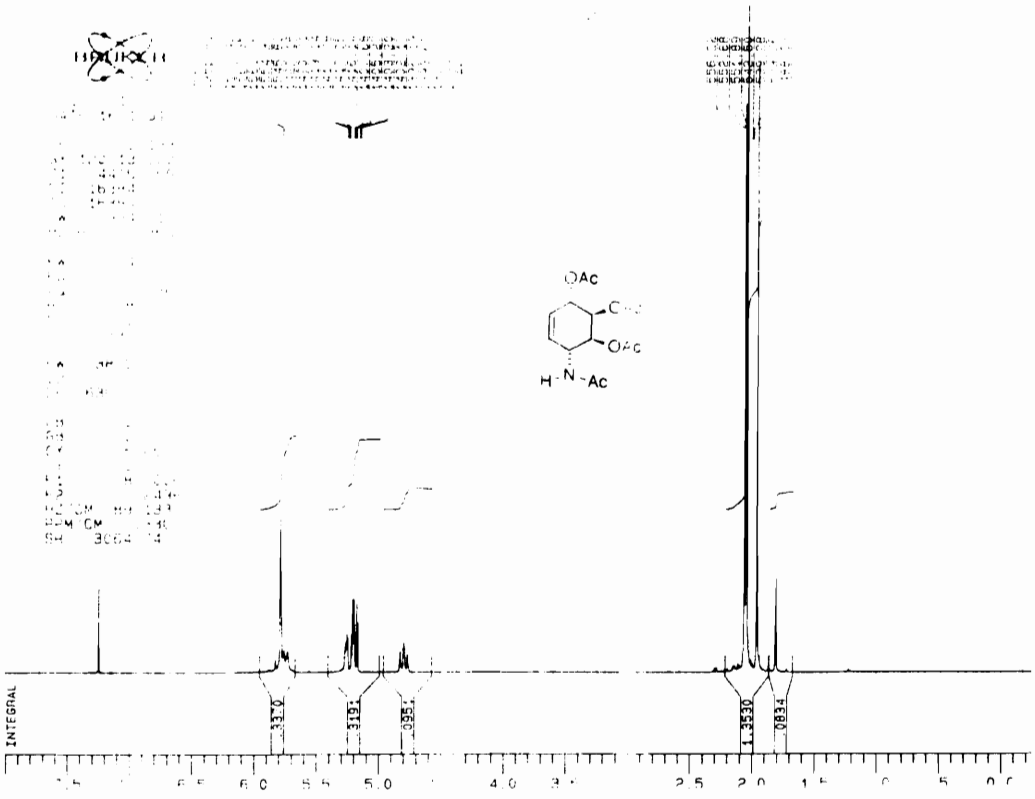
92/01/20 21:10
Y: 4 scans, 4.0cm-1, flat, abex

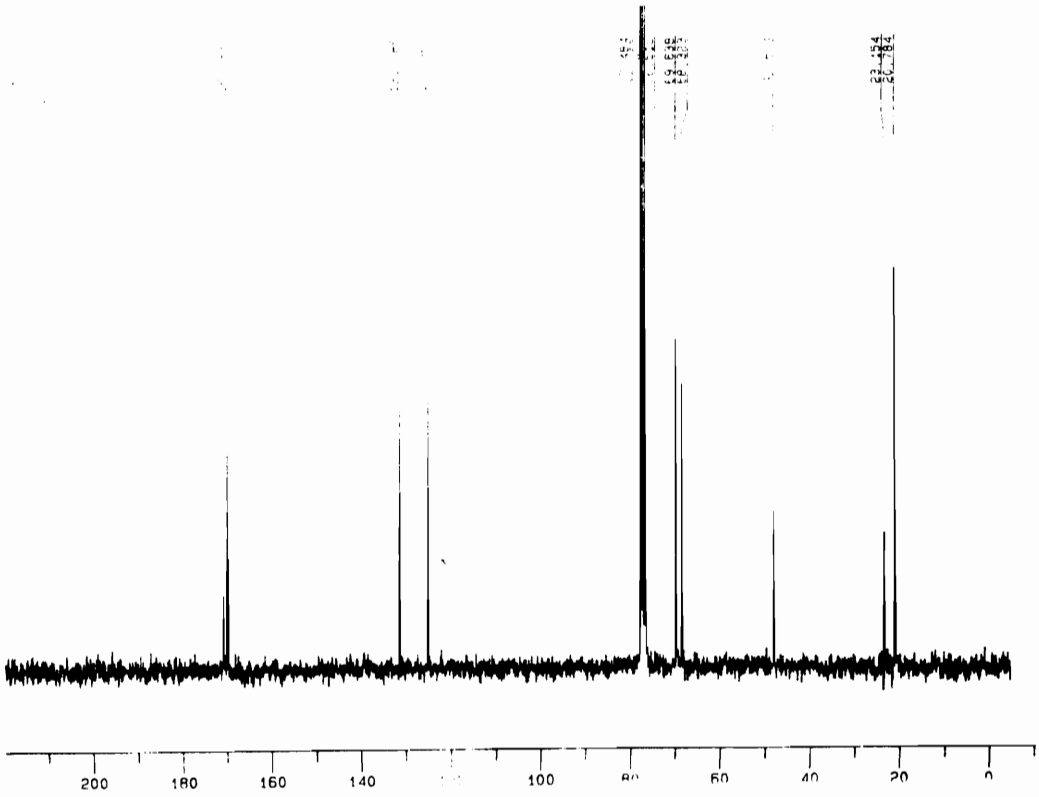
IR FRAME 6/25/92 10:52 AM

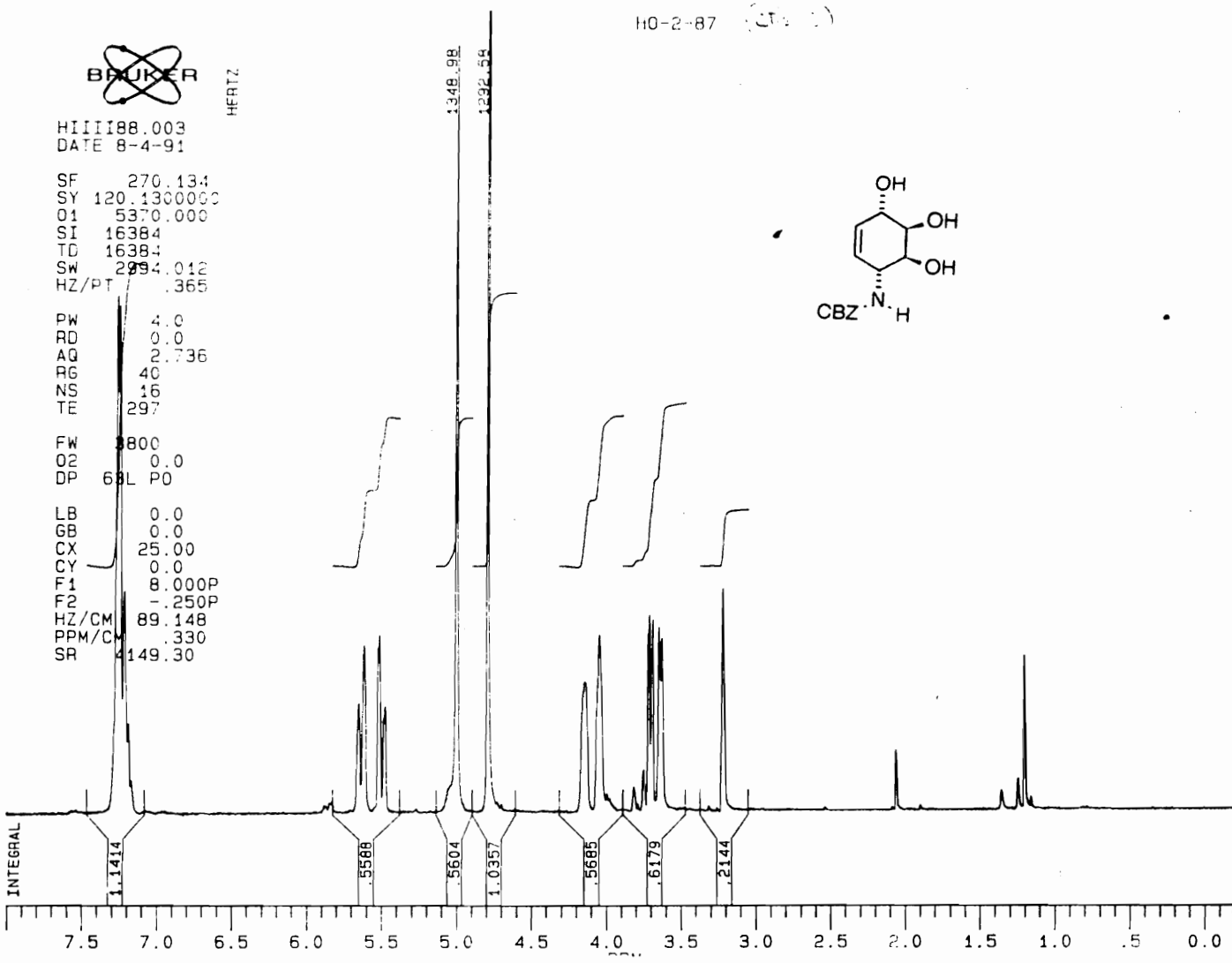


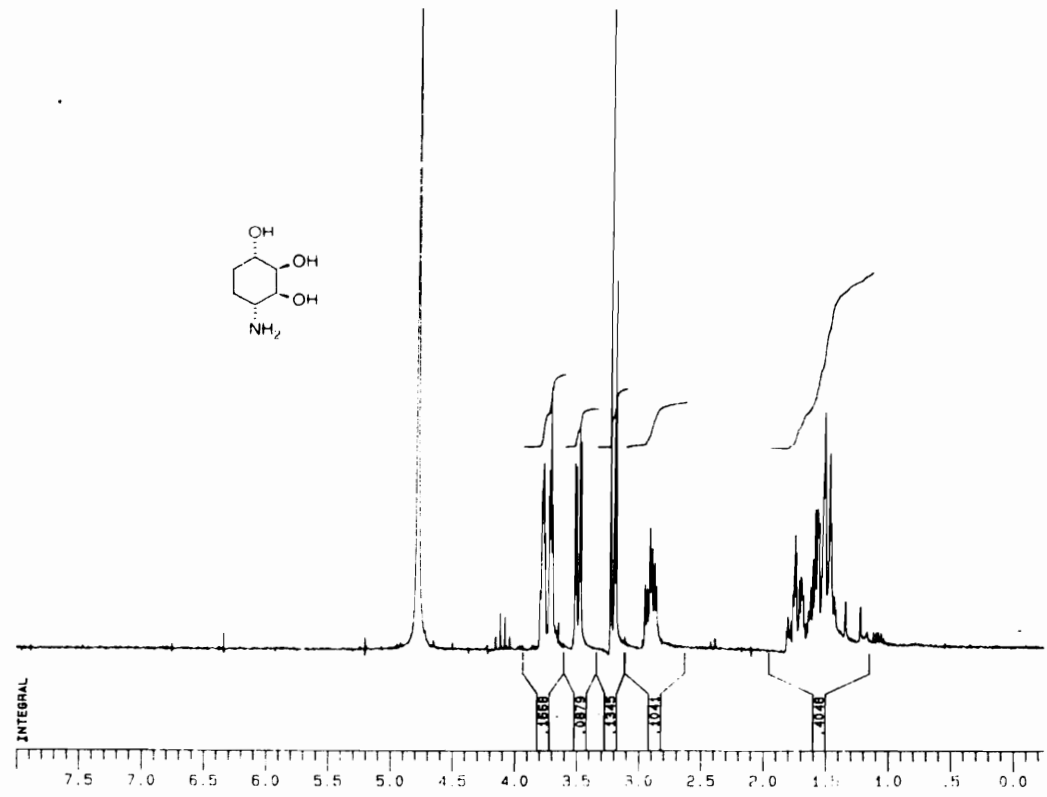

OH
OH
OH
H
N
Ac
INTEGRAL
6.723
4.479
23.735
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
.5
0.0
PPM

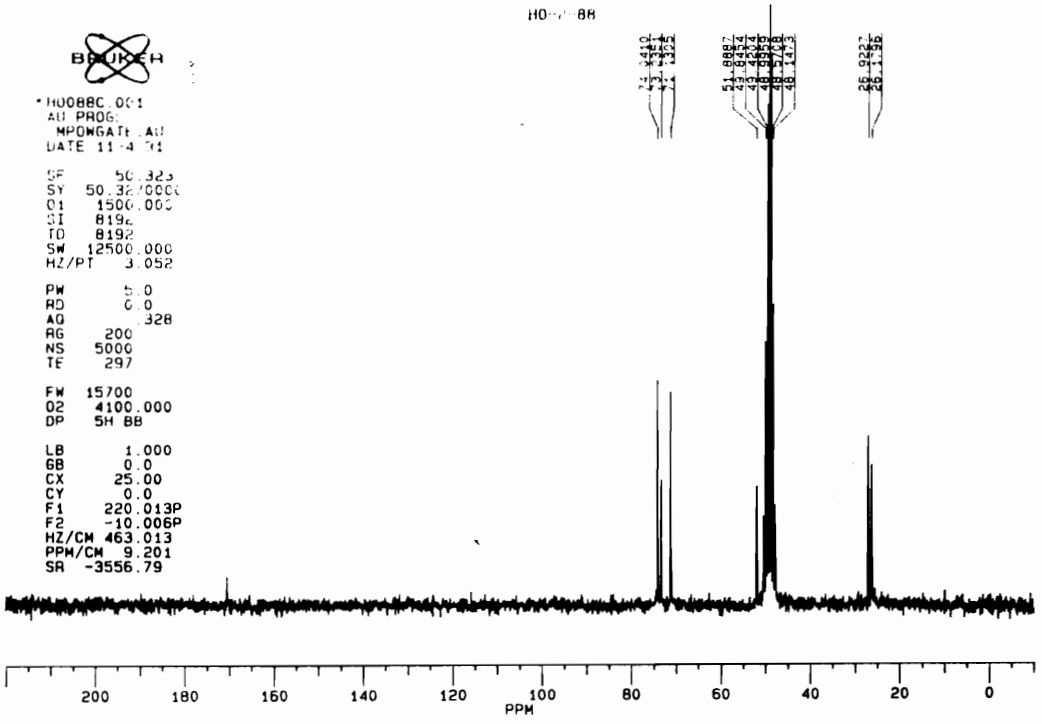

200
180
160
140
120
100
80
60
40
20
0
PPM

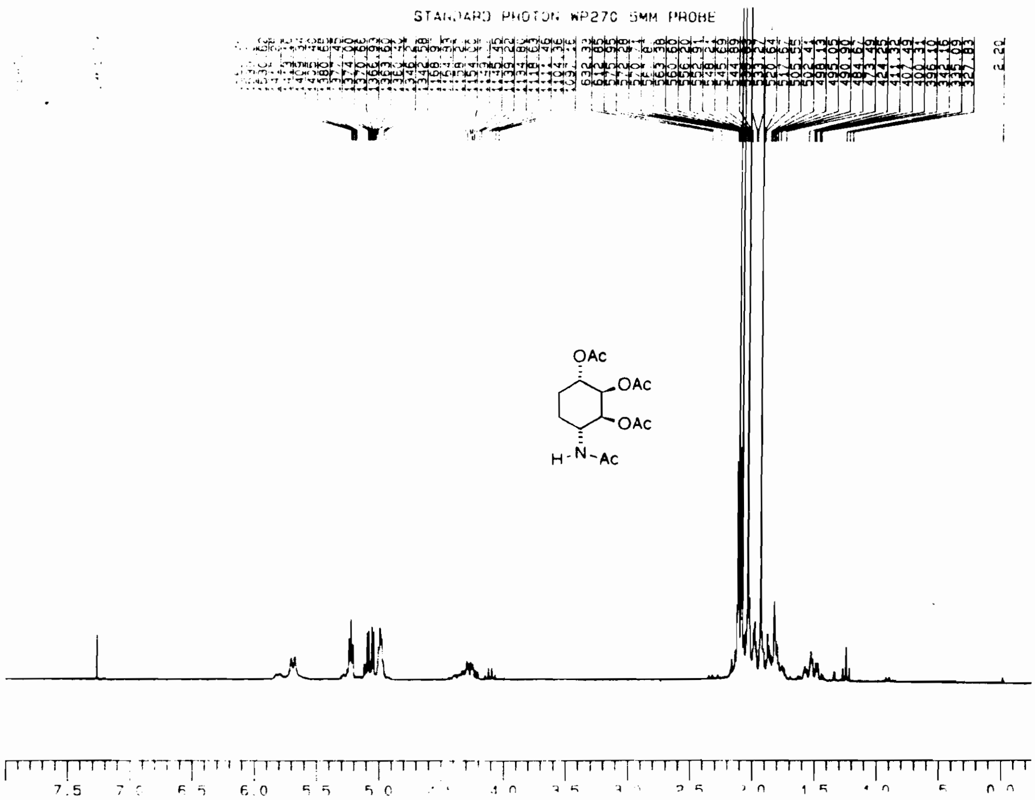

OAc
OAc
H-N-Ac
INTEGRAL
3.170
3.191
.985
1.3530
.0834


77.451
69.648
22.454
20.784


BRUKER
HERTZ
HIIII88.003
DATE 8-4-91
SF 270.134
SY 120.1300000
O1 5370.000
SI 16384
TD 16384
SW 2994.012
HZ/PT .365
PW 4.0
RD 0.0
AQ 2.736
RG 40
NS 16
TE 297
FW 3800
O2 0.0
DP 68L PO
LB 0.0
GB 0.0
CX 25.00
CY 0.0
F1 8.000P
F2 -.250P
HZ/CM 89.148
PPM/CM .330
SR 4149.30
HO-2-87
1348.98
1232.55
OH
OH
OH
CBZ
N
H
INTEGRAL
1.1414
.5588
.5604
1.0357
.5685
.6179
.2144
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
.5
0.0


OH
OH
OH
NH2
INTEGRAL
1868
0879
1345
1041
2048
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
.5
0.0


BRUKER
*H0088C.001
AU PROG:
MPDWGATE.AU
DATE 11-4-01
SF 50.323
SY 50.32[illegible]0000
01 1500.000
SI 819[illegible]
TD 8192
SW 12500.000
HZ/PT 3.052
PW 5.0
RD 0.0
AQ .328
RG 200
NS 5000
TE 297
FW 15700
O2 4100.000
DP 5H BB
LB 1.000
GB 0.0
CX 25.00
CY 0.0
F1 220.013P
F2 -10.006P
HZ/CM 463.013
PPM/CM 9.201
SR -3556.79
H0-[illegible]88
200
180
160
140
120
100
80
60
40
20
0
PPM


STANDARD PHOTON WP270 5MM PROBE
OAc
OAc
OAc
H-N-Ac
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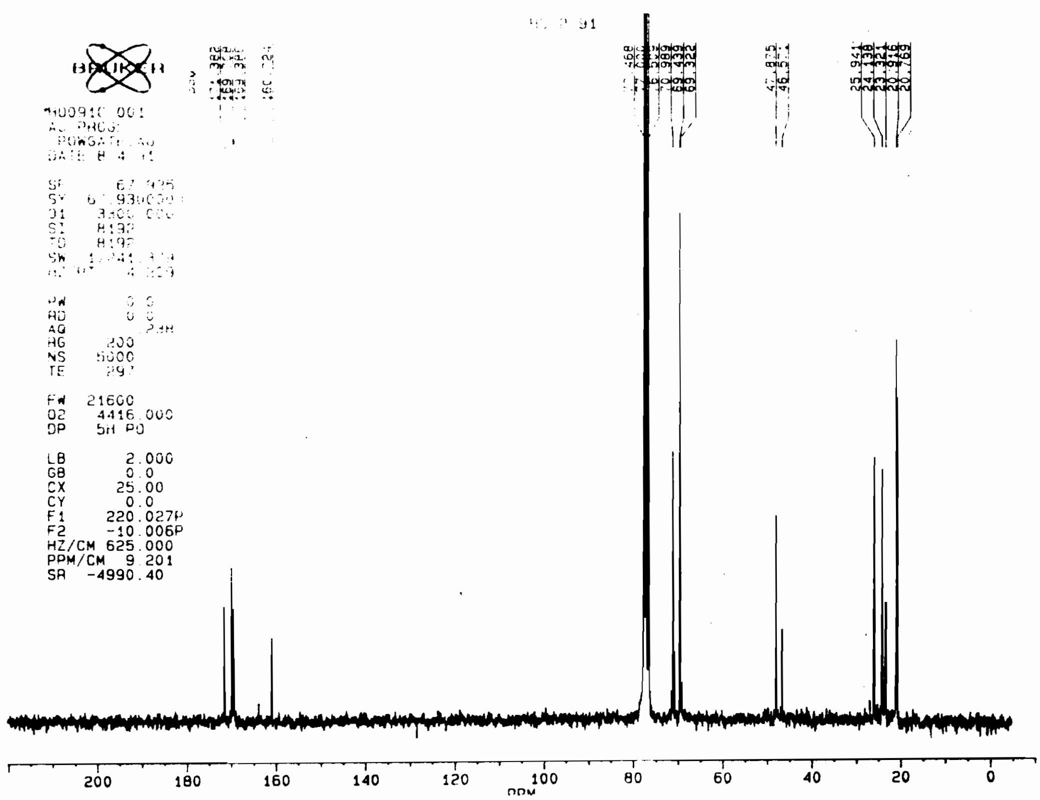
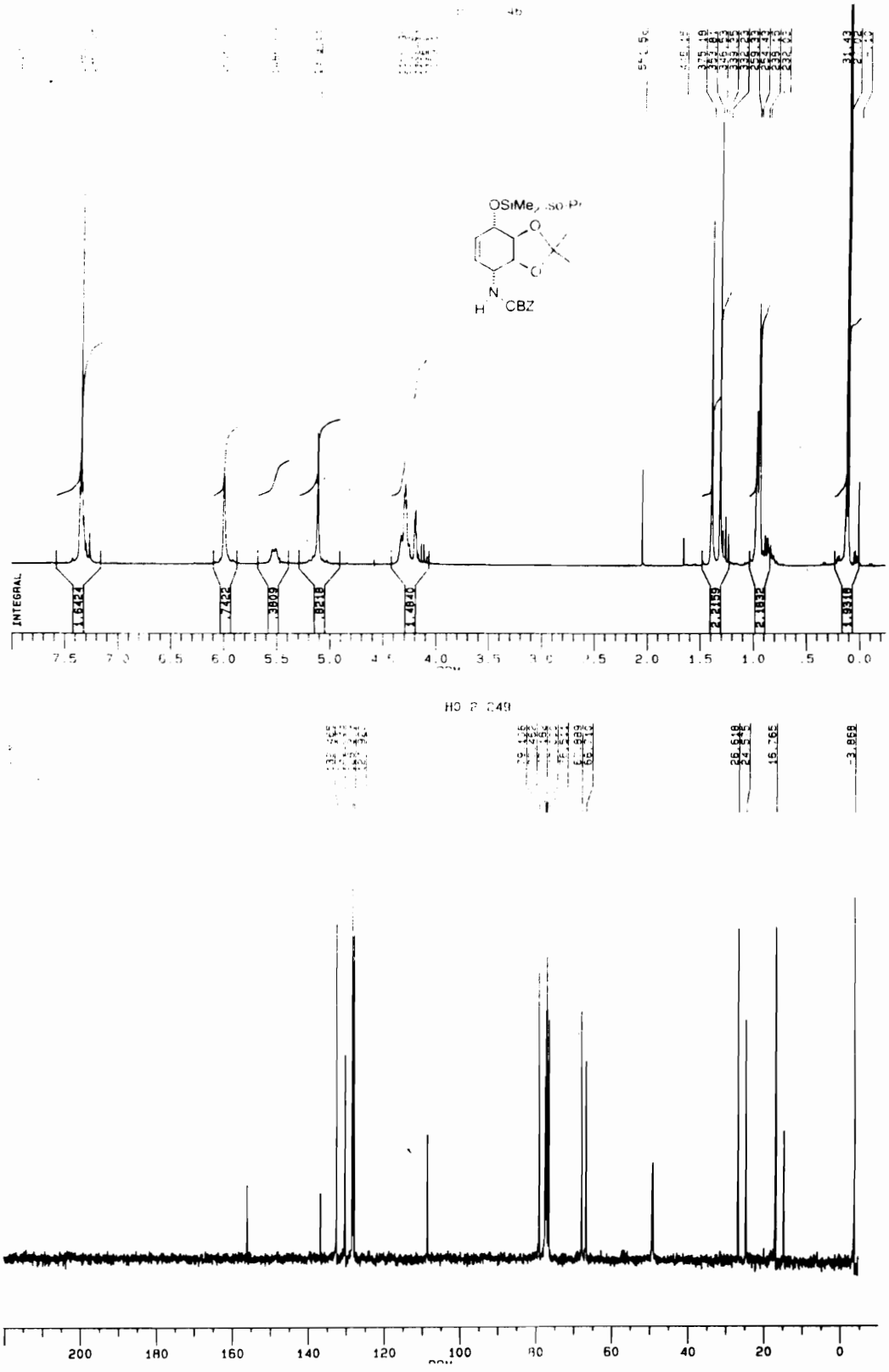
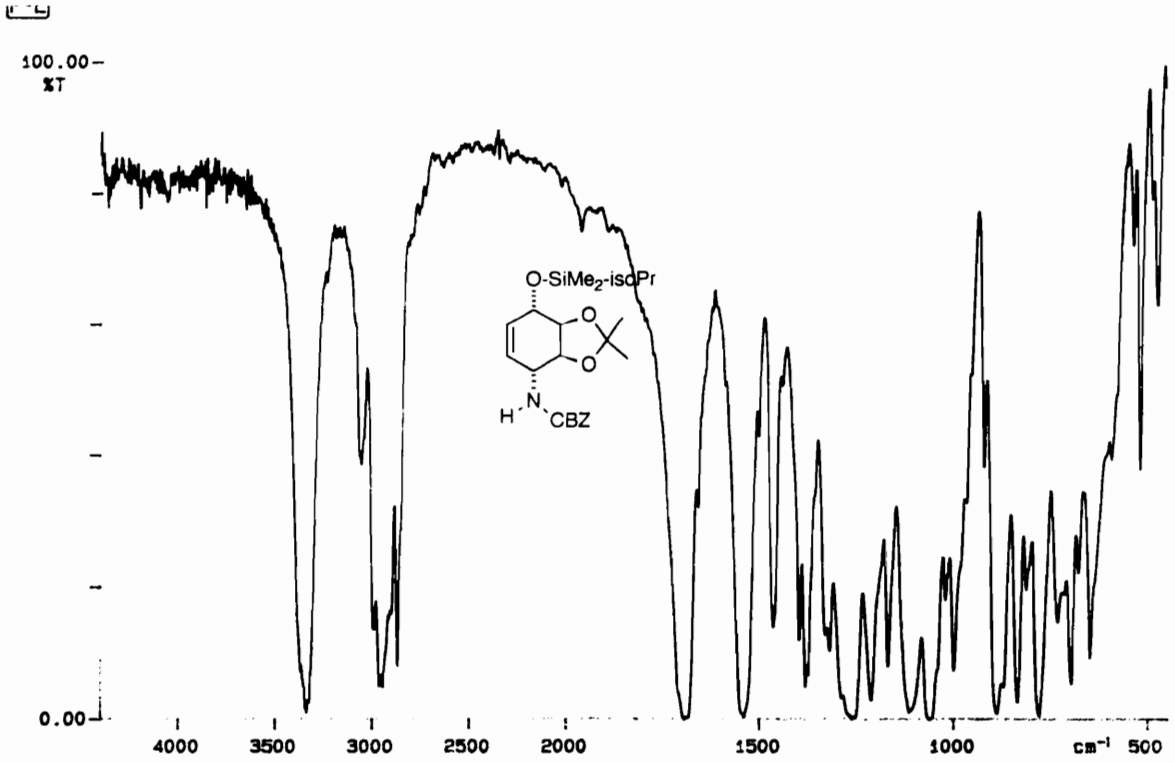
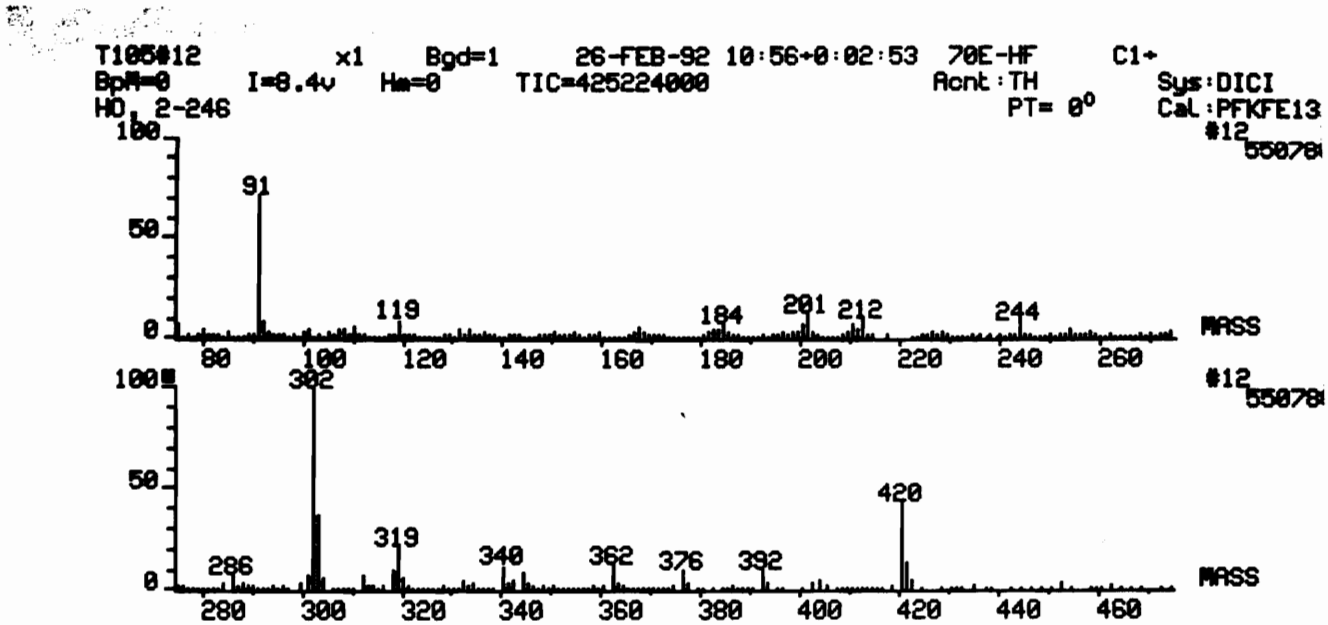
7.0
6.5
6.0
5.5
5.0
4.0
3.5
2.5
2.0
1.5
1.0
.5
0.0

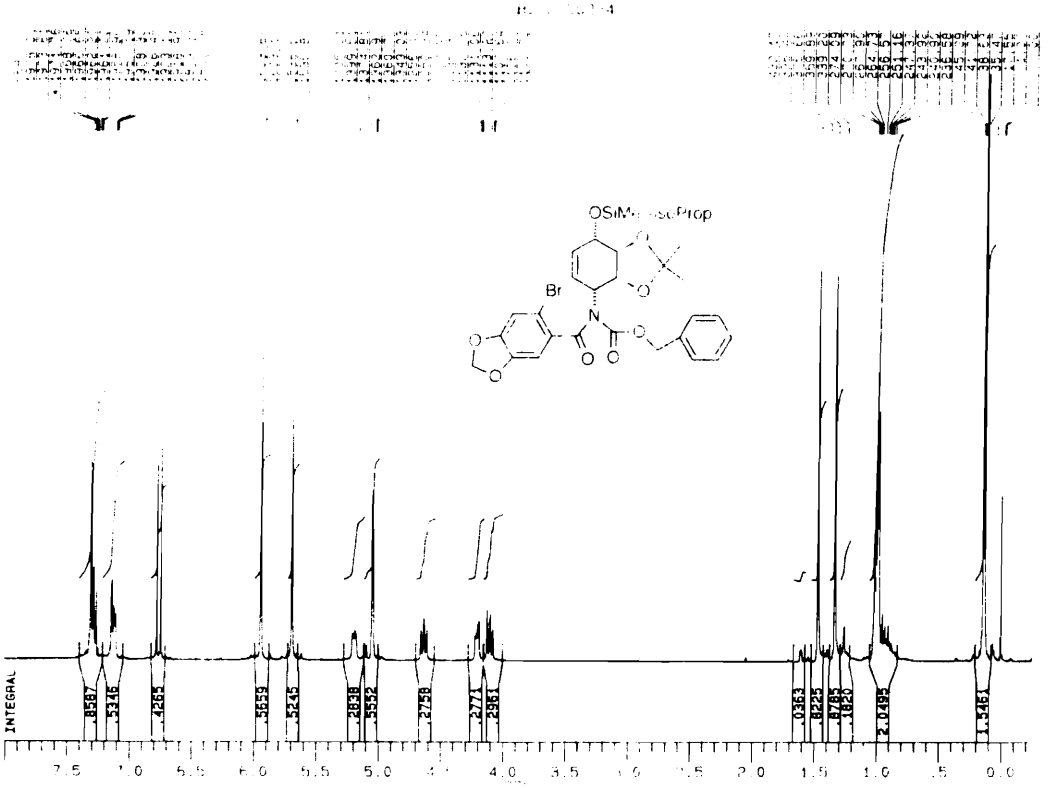

BRUKER
LB 2.000
GB 0.0
CX 25.00
CY 0.0
F1 220.027P
F2 -10.006P
HZ/CM 625.000
PPM/CM 9.201
SR -4990.40
FW 21600
O2 4416.000
DP 5H PO
RG 200
NS 5000
TE 297
47.875
46.514
25.941
24.138
23.321
20.916
20.469
200
180
160
140
120
100
80
60
40
20
0
PPM

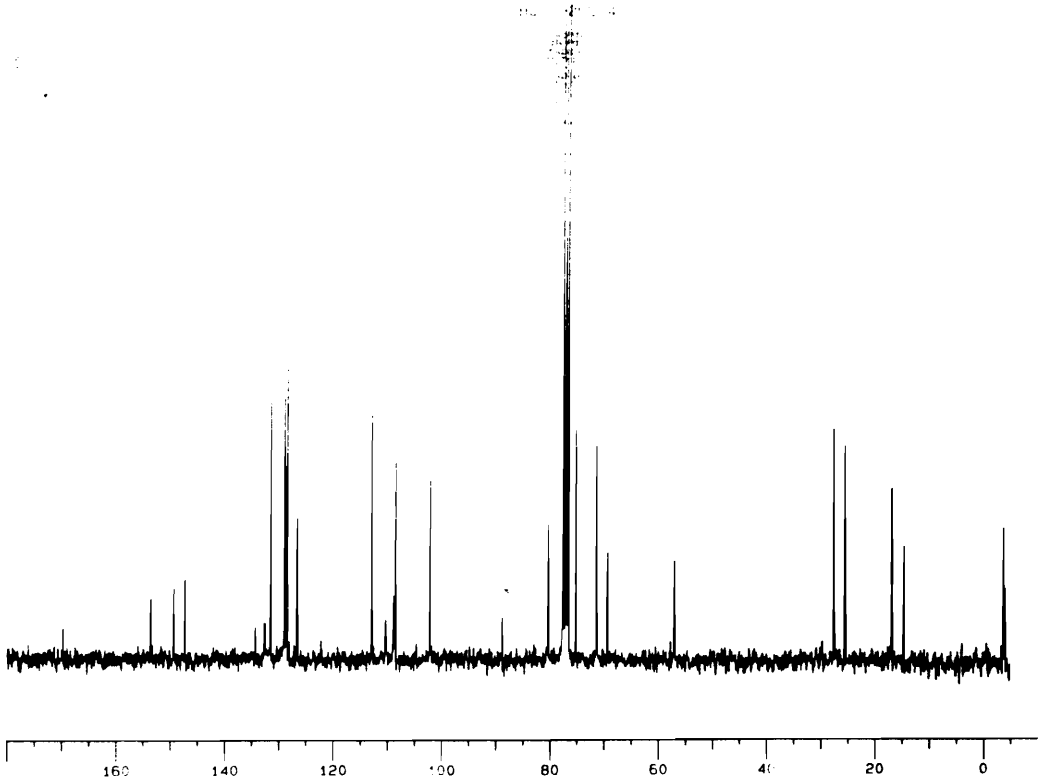

OSiMe2 iso-Pr
O
O
N
H
CBZ
INTEGRAL
1.6421
.7422
.3809
.8218
1.4840
2.2159
2.1832
1.8310
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
.5
0.0
HO P 249
200
180
160
140
120
100
80
60
40
20
0

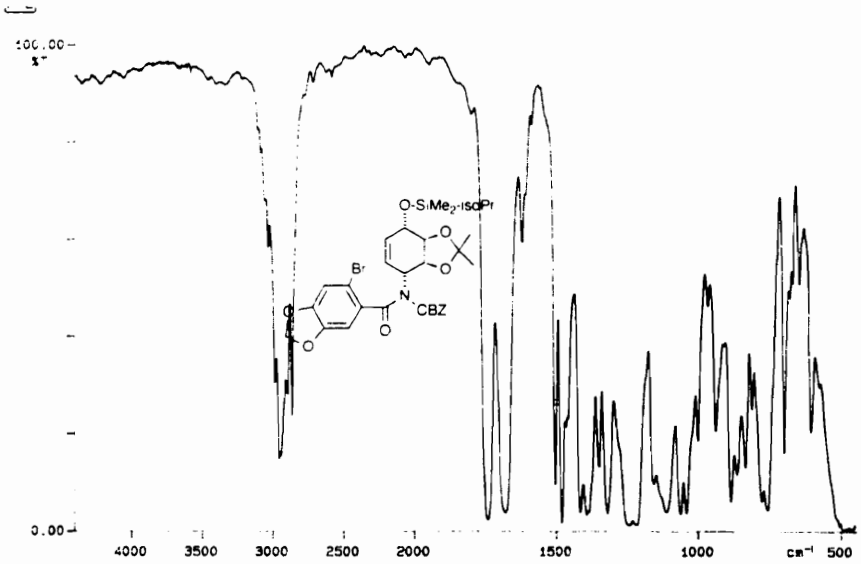


92/02/22 14:59
Y: 4 scans, 4.0cm-1, flat, abex

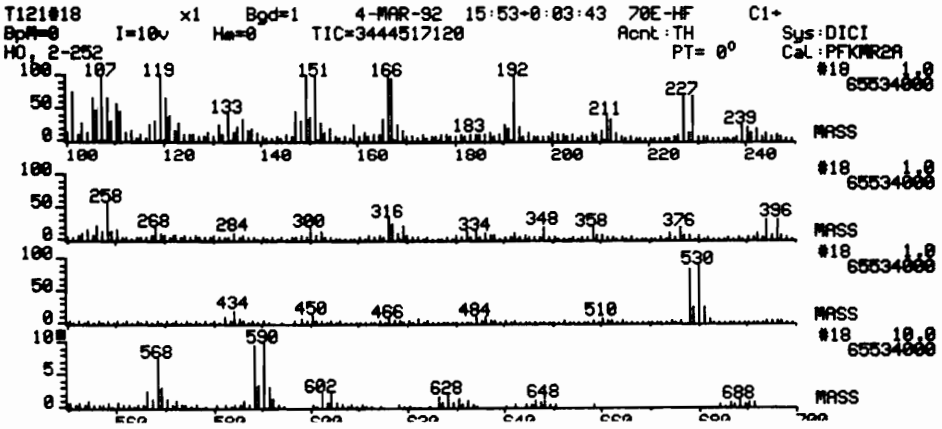


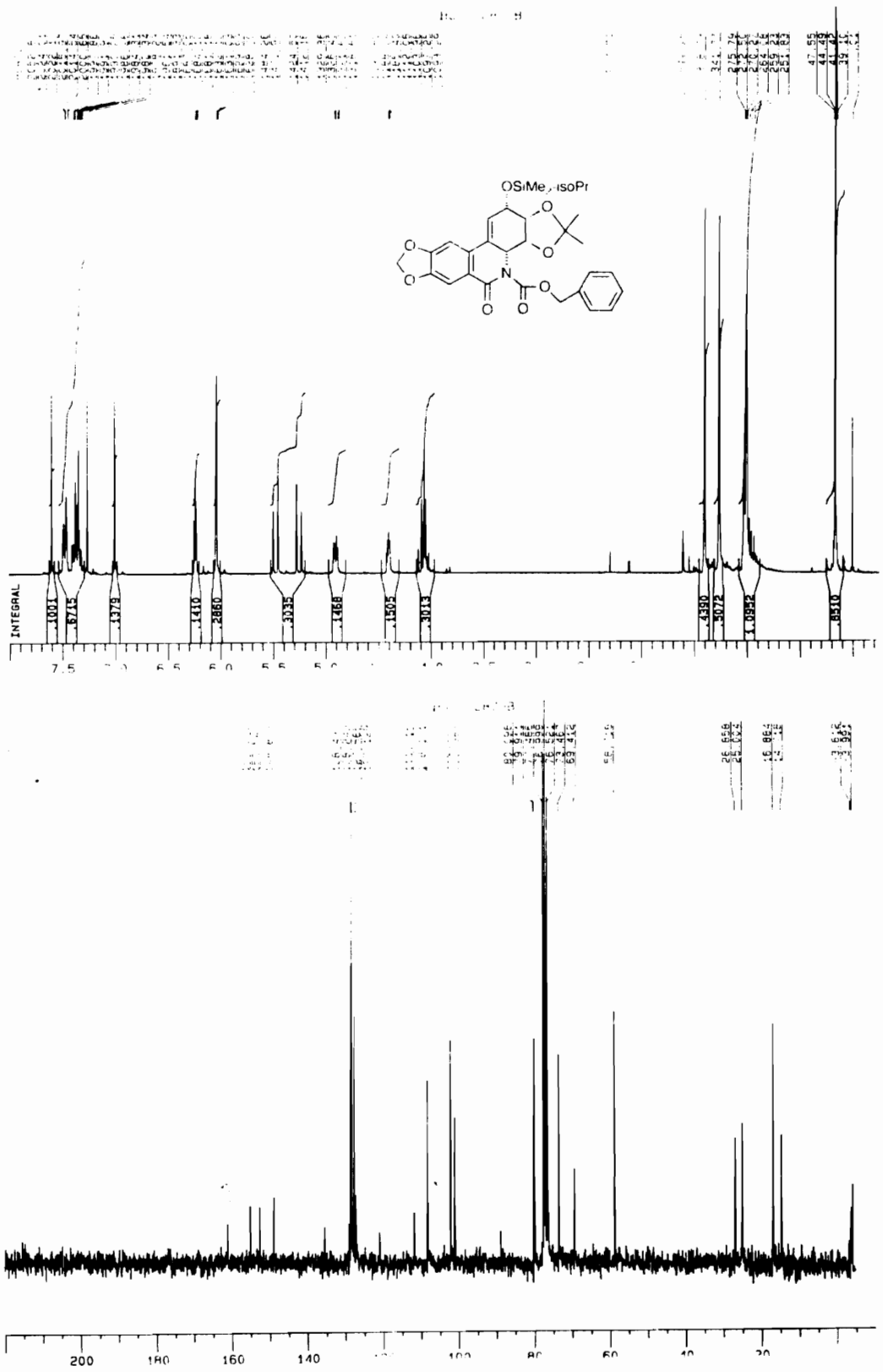

OSiMe2tBuPhop
Br
N
O
O
O
O
O
O
INTEGRAL
.8587
.5216
.4265
.5659
.5245
.2838
.5552
.2758
.2771
.2961
.0363
.8225
.8785
.1820
2.0495
1.5461
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
.5
0.0

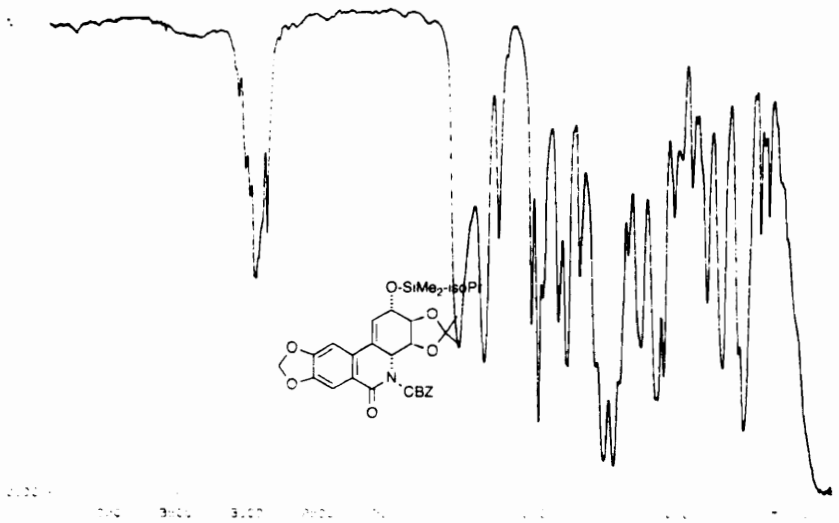

160
140
120
100
80
60
40
20
0

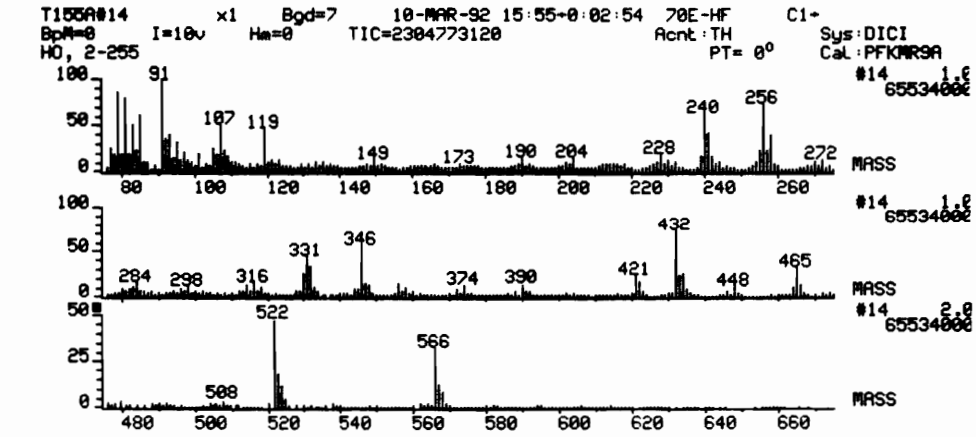


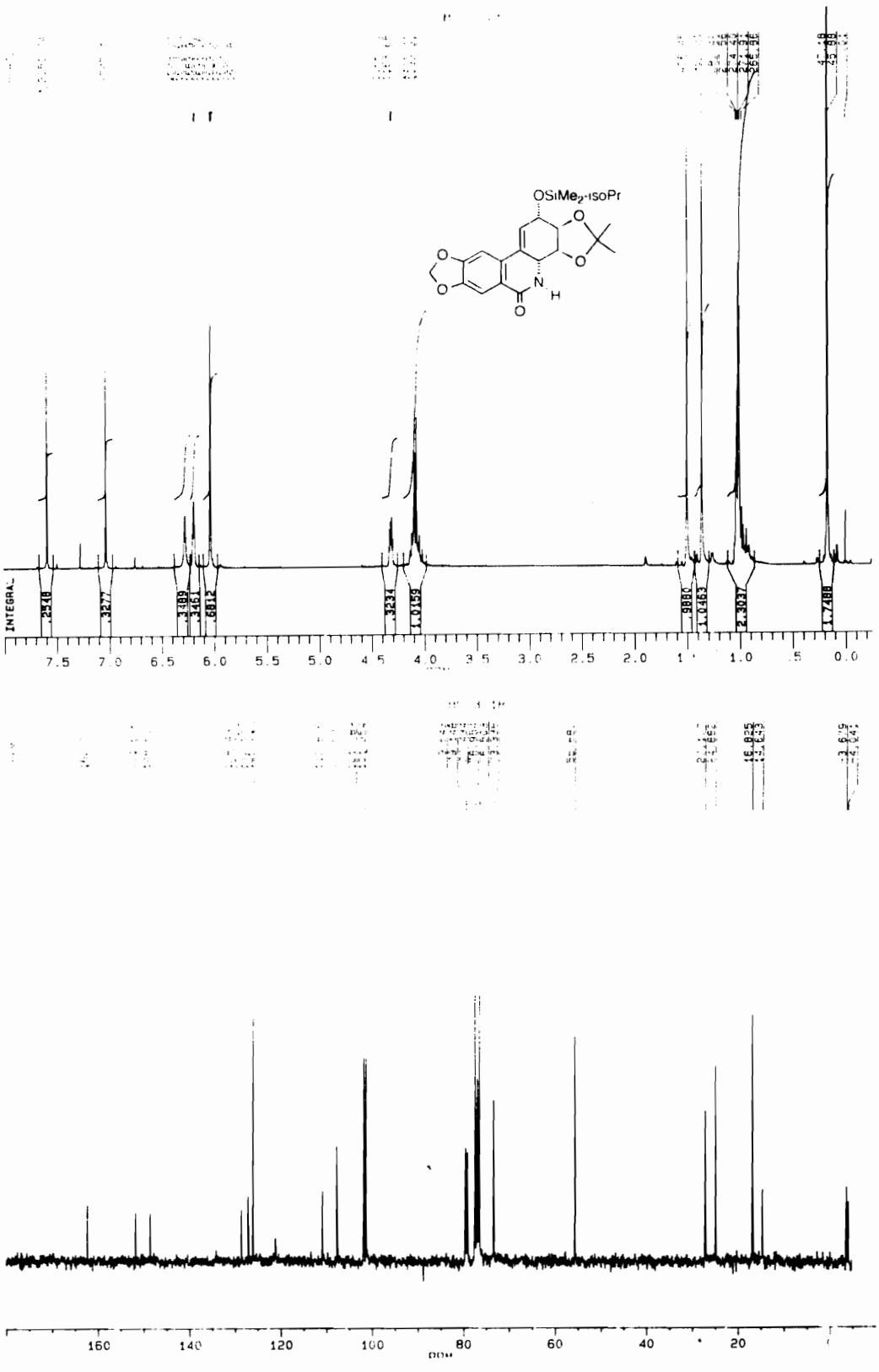
92/03/02 21:11
2: 4 scans, 4.0cm-1, abex

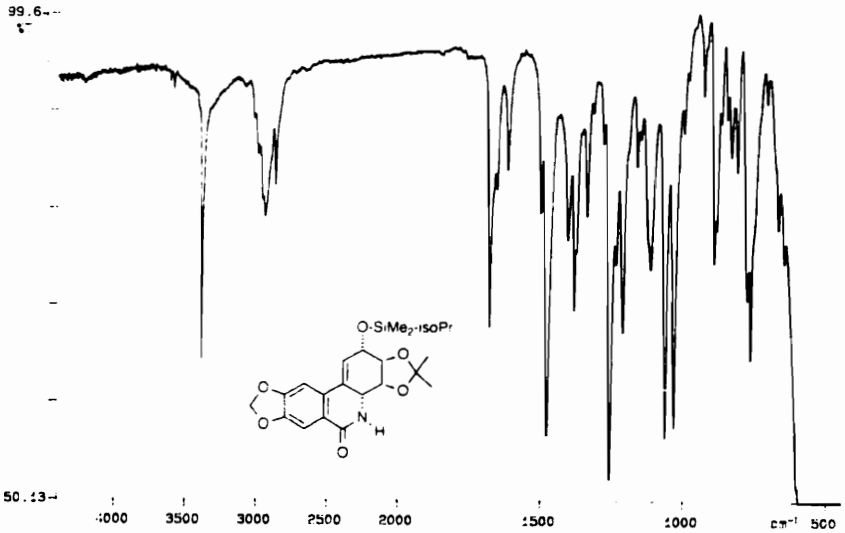



OSiMe2tBuPr
INTEGRAL
1.001
6.745
1.379
1.410
2.860
3.035
1.468
1.505
3.013
4.390
3.072
11.092
8.510


O-SiMe2-isoPr
O
O
O
O
N
CBZ
O

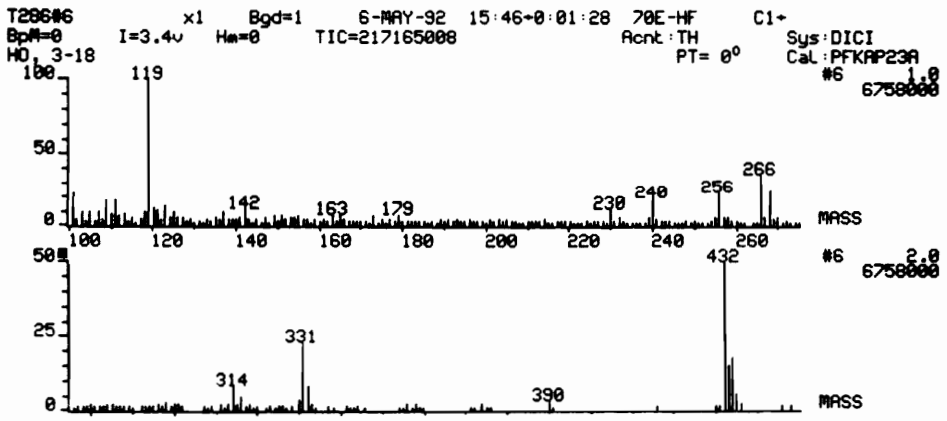

T155A#14 x1 Bgd=7 10-MAR-92 15:55+0:02:54 70E-HF C1+
BpM=0 I=10v Hm=0 TIC=2304773120 Acnt:TH Sys:DICI
HO, 2-255 PT= 0° CaL:PFKMR9A
#14
MASS
91
107
119
149
173
190
204
228
240
256
272
284
298
316
331
346
374
390
421
432
448
465
508
522
566

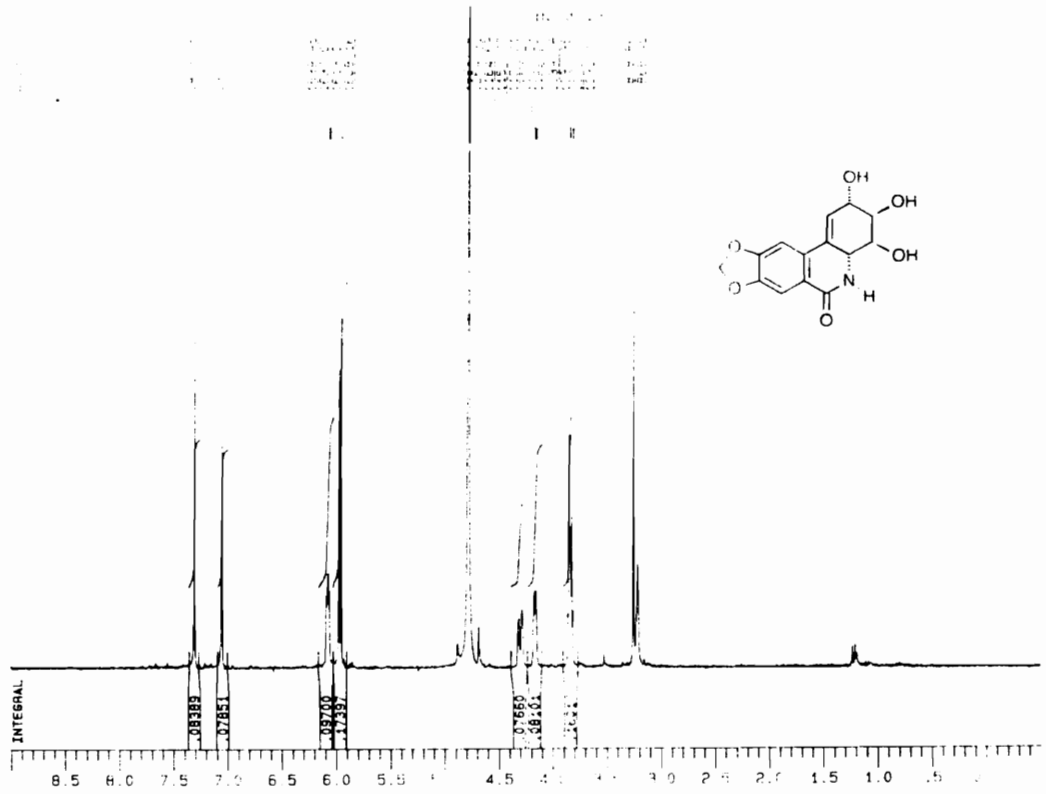

OSiMe2-isoPr
O
O
O
O
N
H
O
INTEGRAL
2.518
3.277
3.489
3.467
6.812
3.234
1.0159
.9886
1.0363
2.3037
1.7488
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
.5
0.0
160
140
120
100
80
60
40
20
PPM

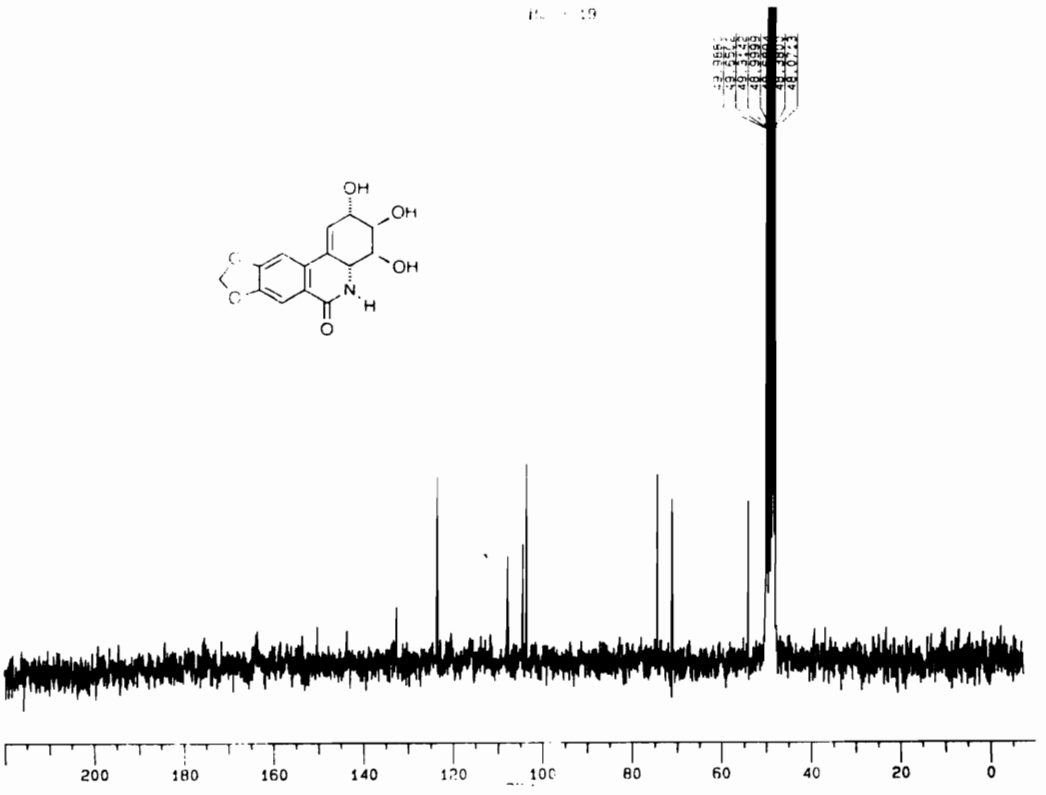


92.05.03 21:38
SCAN: 4 scans, 4.0cm-1, flat, abs.

B FRAME 6/25/92 10:21 AM




OH
OH
OH
O
O
N
H
O
INTEGRAL
8.5
6.0
6.5
6.0
4.5


OH
OH
OH
O
O
N
H
O
200
180
160
140
120
100
80
60
40
20
0

VII. VITA

Horacio Olivo was born in Mexico City, on February 2, 1962, to David Olivo and Maria Teresa Hernandez. He received his bachelor's degree in Chemical Engineering at Universidad La Salle (ULSA, Mexico) in 1984. He worked as a process engineer at CIDESI (Centro de Ingenieria y Desarrollo Industrial) for two years. He started graduate studies at the Division de Estudios de Posgrado at the National University of Mexico (UNAM) in 1986. During his graduate studies at UNAM in Dr. Martha Albores' group, he worked as an organic chemistry lab instructor at UNAM and also as a FTIR instructor in Perkin-Elmer de Mexico. In August 1988, he moved to Blacksburg, Virginia to continue his studies in Organic Chemistry at Virginia Tech under the supervision of Professor Tomas Hudlicky.