Chemistry of Oxa- and Aza-bicyclic[4.1.0]heptenes Total Synthesis of (+)-Pancratistatin

by

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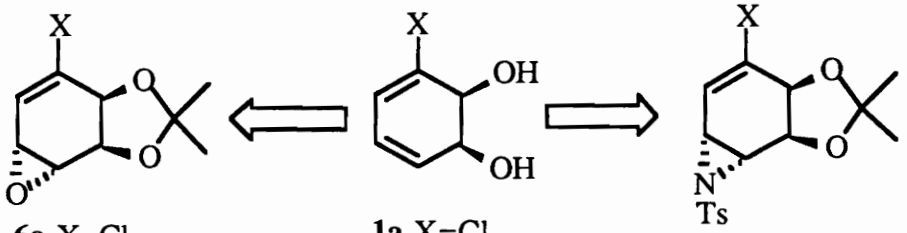
(Abstract)

Vinyloxiranes **6a-b** and vinylaziridines **7a-b** were prepared efficiently from halo-cyclohexadiene-*cis*-diols **1**. Reactions of **6** and **7** with a variety of organometallic reagents were investigated in order to determine the stereo- and regiochemistry of ring opening with carbon nucleophiles. The results indicate that **6** and **7** could serve as useful new synthons for C-disaccharides and *Amaryllidaceae* alkaloid syntheses.

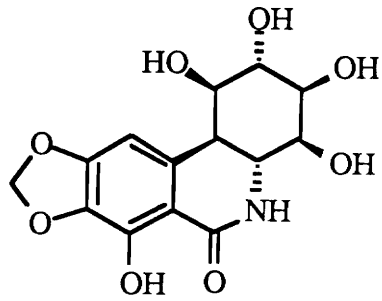


6a X=Cl
6b X=H

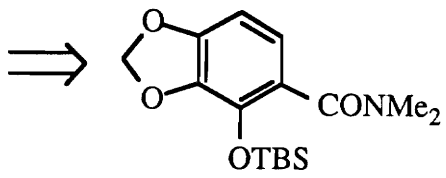
1a X=Cl
1b X=Br

7a X=Cl
7b X=H

The utility of synthon **7b** has been demonstrated by a concise enantiocontrolled synthesis of (+)-pancratistatin (**9**). The key step involved the S_N2 opening of **7b** with the aryl cyanocuprate derived from amide **217** to generate the pivotal cyclization precursor.



9 pancratistatin



217

+ **7b**

Acknowledgments

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To my mother.

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF SCHEMES

LIST OF TABLES

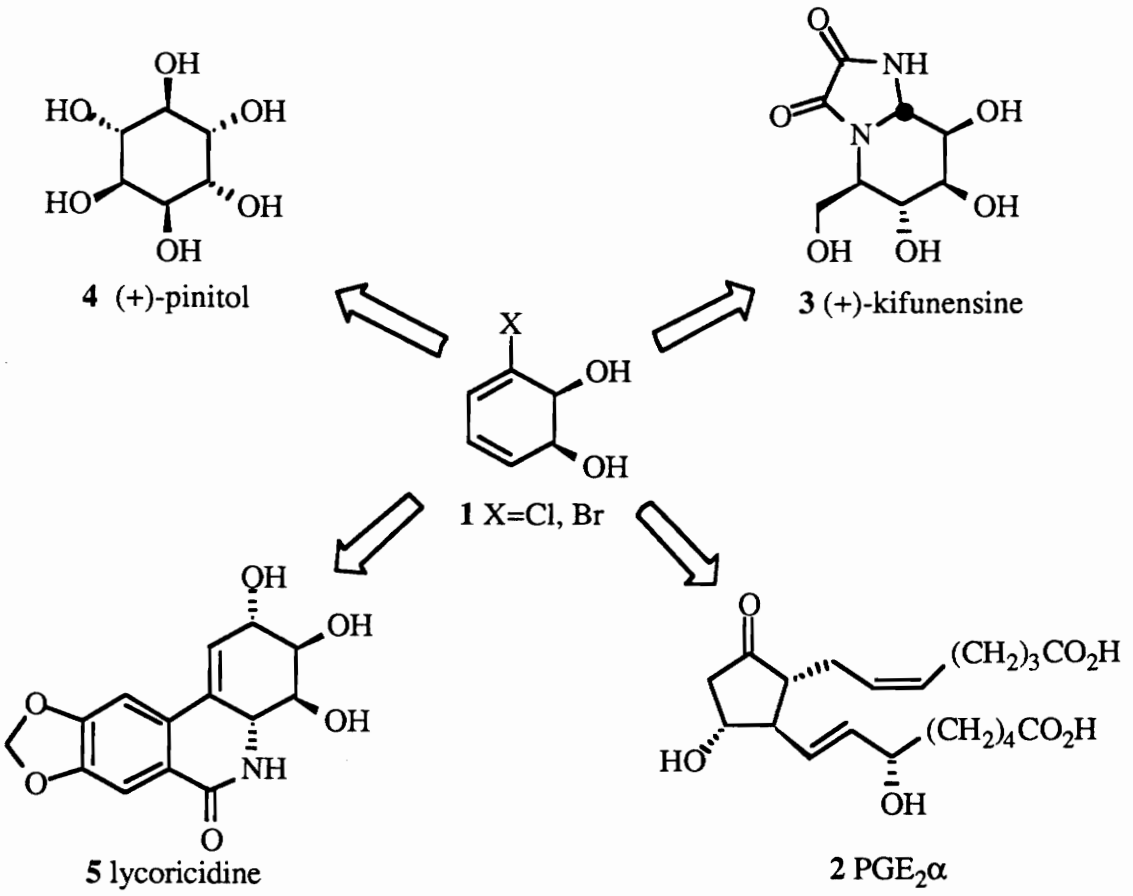
I. INTRODUCTION

Epoxides are versatile intermediates in organic synthesis. These three-membered heterocyclic compounds can be prepared easily in homochiral form by highly efficient procedures. Because of the inherent polarity and the ring strain, epoxides are susceptible to reactions with a large number of reagents, the reactions usually proceeding in a stereospecific and often highly regioselective fashion. Among these reactions, ring opening by carbon nucleophiles represents a very useful transformation, resulting in the formation of new carbon-carbon bonds. For this purpose, a variety of organometallic reagents have been employed. The available data shows that organocuprates seem to be the most appropriate choice, since Grignard reagents and organolithium reagents often result in side reactions, such as elimination and rearrangement, promoted by either the basicity of the nucleophile or Lewis acidity of the counterion.

Aziridines, the nitrogenenous epoxide counterparts, are also attractive building blocks for organic synthesis, and the last decade witnessed a rapid development of aziridine chemistry. A variety of procedures has been designed for the preparation of aziridines in enantiomerically pure form. The reactions of activated aziridines with heteroatom-nucleophiles and carbon nucleophiles, such as organocopper reagents and Grignard reagents, have been extensively investigated. In contrast, the chemistry of vinylaziridines escaped attention for years. By the time of the initiation of our effort, no literature precedent on the nucleophilic ring opening of vinylaziridines existed.

Halocyclohexadiene-*cis*-diols **1**, prepared by whole-cell oxidation of halobenzene with *Pseudomonas putida* 39/D,[2] have proved to be very useful chiral synthons. Starting from **1**, a structurally diverse set of natural products have been synthesized enantioselectively, such as $PGE_2\alpha$ (**2**),[3] (+)-kifunensine (**3**),[4] (+)-pinitol (**4**),[5] and lycoricidine (**5**),[6] Scheme 1. One remarkable property associated with diol **1** is the

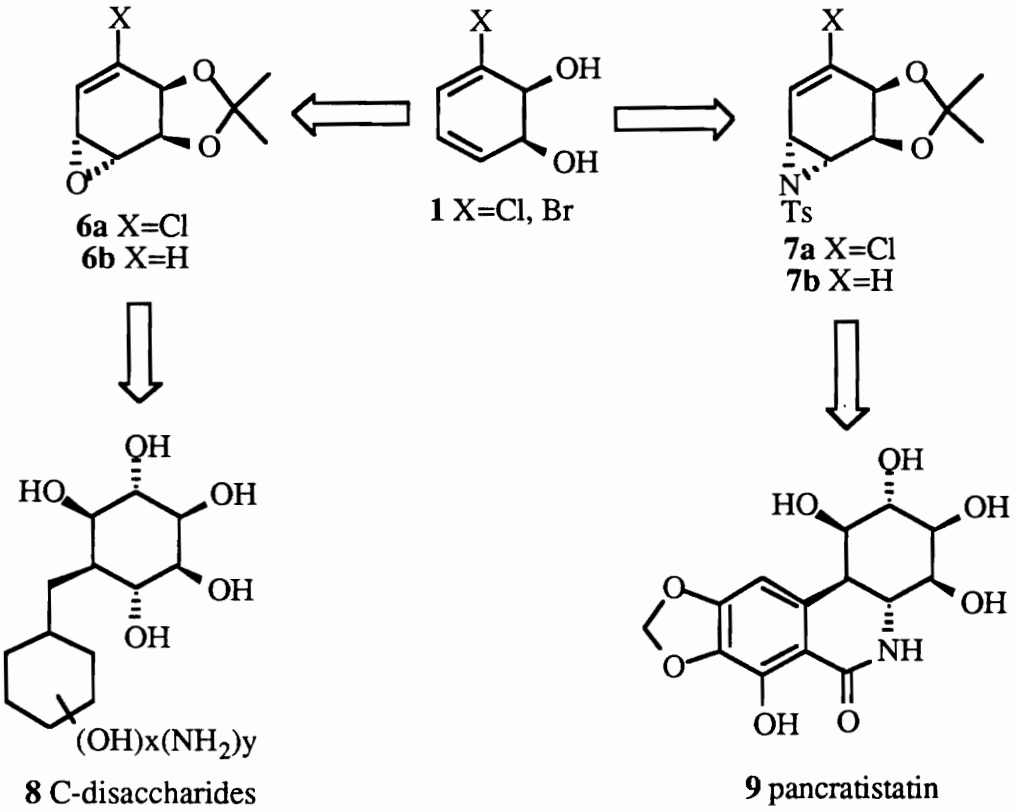
possibility to introduce functionality regio- and stereospecifically by taking advantage of the steric and stereoelectronic effects exerted by the substituent on C-1 and the appropriately selected protection group of the diol.



Scheme 1

In the continuing effort to explore the utility of **1** in the syntheses of C-disaccharides and *Amaryllidaceae* alkaloids, it became necessary to understand the regio- and stereoselectivity of ring opening of vinyloxiranes **6** and vinylaziridines **7** with carbon nucleophiles, Scheme 2. Vinyloxirane **6a** has previously been opened by non-carbon nucleophiles such as alkoxide, azide, and halide, to give exclusively S_N2 products with

the inversion of configuration, while the addition of carbon nucleophiles has not been examined. No data concerning the ring opening of **7** with either non-carbon or carbon nucleophiles was available.



Scheme 2

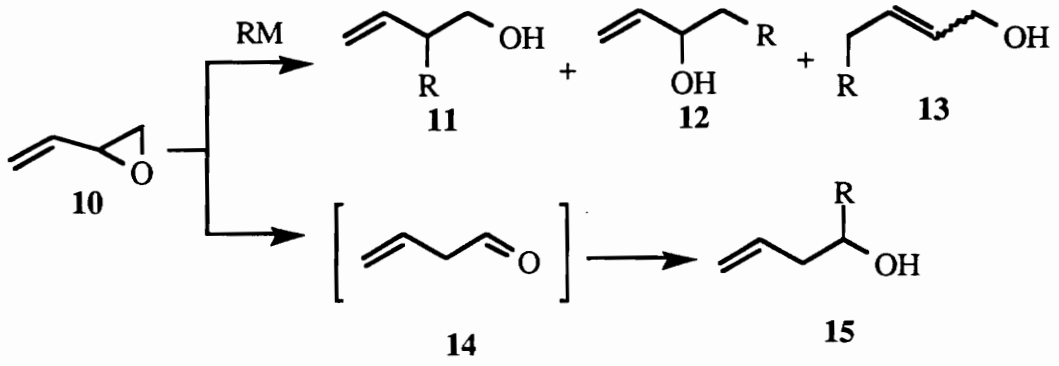
This thesis will discuss the initial findings on the reactive tendencies of both **6** and **7** toward a series of organometallic reagents. A total synthesis of (+)-pancratistatin designed to capitalize on the newly developed methodology will also be described.

II.HISTORICAL

1. Chemistry of Vinyloxiranes

Vinyloxiranes, also called monoepoxides of 1,3-dienes, constitute a special subset of allylic systems. Four contiguously functionalized carbons contained in these compounds render them versatile intermediates in organic synthesis, because nucleophiles can be introduced at different positions with particular reagents. Nucleophilic additions to vinyloxiranes have been extensively studied and have been discussed in several reviews.[6] In this section, emphasis will be placed on the nucleophilic ring opening of vinyloxiranes, especially cyclic vinyloxiranes, by organometallic reagents.

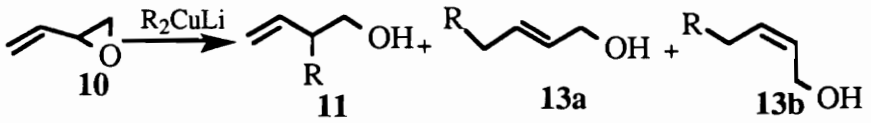
Early examination of the reaction of the monoepoxide of 1,3-butadiene (**10**) with organometallic compounds revealed four theoretically possible products **11**, **12**, **13**, and **15**,[7] Scheme 3. Direct 1,2- or 1,4- addition to **10** gave **11-13**. With organometallic reagents possessing sufficient Lewis acidity, the rearrangement of epoxide to a carbonyl compound **14** would be followed by addition, affording **15.**



Scheme 3

Conditions have been developed to produce preferentially each of these four products. In general, the organocopper reagents prefer S_N2' addition to give **13**,[8] while the organomagnesium and organolithium reagents tend to produce **11**.[9] The hard and soft acid-base principle has been proposed to account for this reactivity difference.[10] The hardness of the organometallic reagent (RLi>RMgBr>R_2CuLi or RCu) is directly related to the nature of metal atom.[11] Organocopper reagents are soft bases and prefer to react with the soft acid site, i.e., olefin C-4, leading to 1,4-addition products, whereas organomagnesium and organolithium reagents are harder bases and prefer to attack the hard acid site, i.e. C-2, giving 1,2-addition products. Reaction of 1,3-butadiene monoepoxide **10** with the Gilman reagent proceeded regiospecifically and stereospecifically to yield 1,4-adducts, **13a** and **13b**, Table 1.

Table 1. Reaction of Gilman Reagents with 1,3-Butadiene Monoepoxide[a]

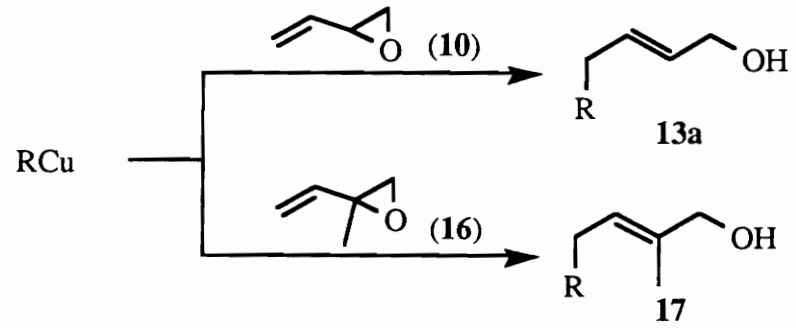


R	11	13a	13b	E:Z
Bu	4	80	14	86:14
Ph	15	76	8	90:10

a, ref.8.

Ring opening studies of butadiene monoepoxide **10** and isoprene epoxide **16** conducted by Normant[12] further complemented these initial findings. The copper(I)-catalyzed Grignard reaction also provided S_N2' products exclusively, Table 2.

Table 2. Additions of Cuprates to Butadiene and Isoprene Epoxides[a]

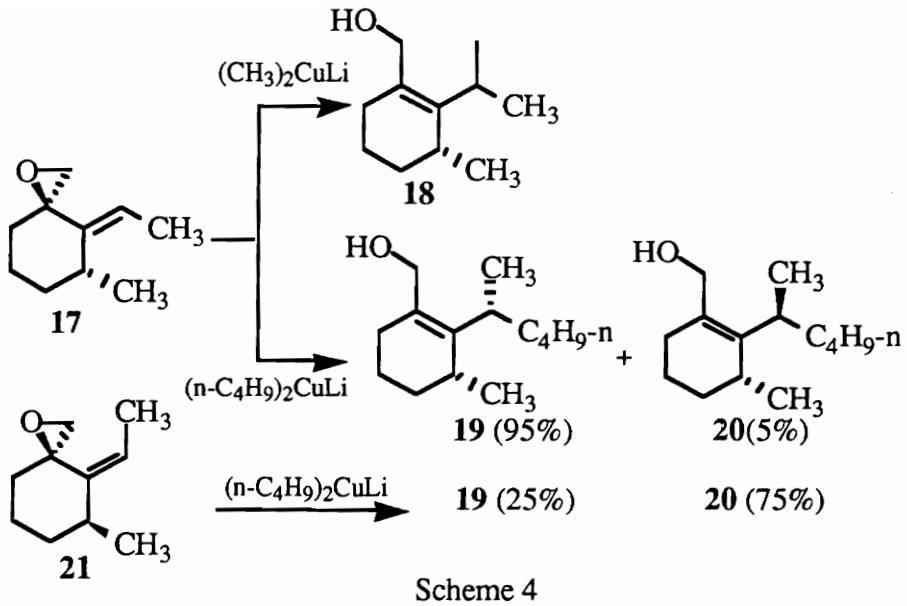


R	Epoxide	Product	Yield (%)	E:Z
$((Z)\text{-}EtCH{=}CH)_2CuLi$	**10**	**13a**	70	96:4
	16	**17**	82	86:14
$((CH_3)_2C{=}CH)_2CuLi$	**10**	**13a**	82	96:4
	16	**17**	95	92:8
$(Bu(CH_3)C{=}CH)_2CuLi$	**16**	**17**	91	91:9
$(Me_2C{=}CH)_2Cu{\cdot}MgBr$	**16**	**17**	34	97:3
$CH_2{=}CHCH_2MgBr{\cdot}CuBr$[b]	**16**	**17**	90	92:8
$(Z)\text{-}MeCH{=}CHCH_2MgBr{\cdot}CuBr$[b]	**16**	**17**	95	95:5

a, ref. 12. b, 5% CuBr was used.

Similarly, exocyclic epoxides underwent S_N2' alkylation by organocuprates preferentially.[13] Reaction of **17** with Gilman type methyl- or butylcuprates produced only S_N2' products **18**. With butylcuprate, a 95:5 mixture of *syn* and *anti* adducts **19** and **20** was obtained from **17**, while the (Z)-oxirane **21** furnished a 25:75 mixture of *syn* and *anti* S_N2' products **19** and **20**. This contrasting behavior could be attributed to the hindrance by the ring methyl group.

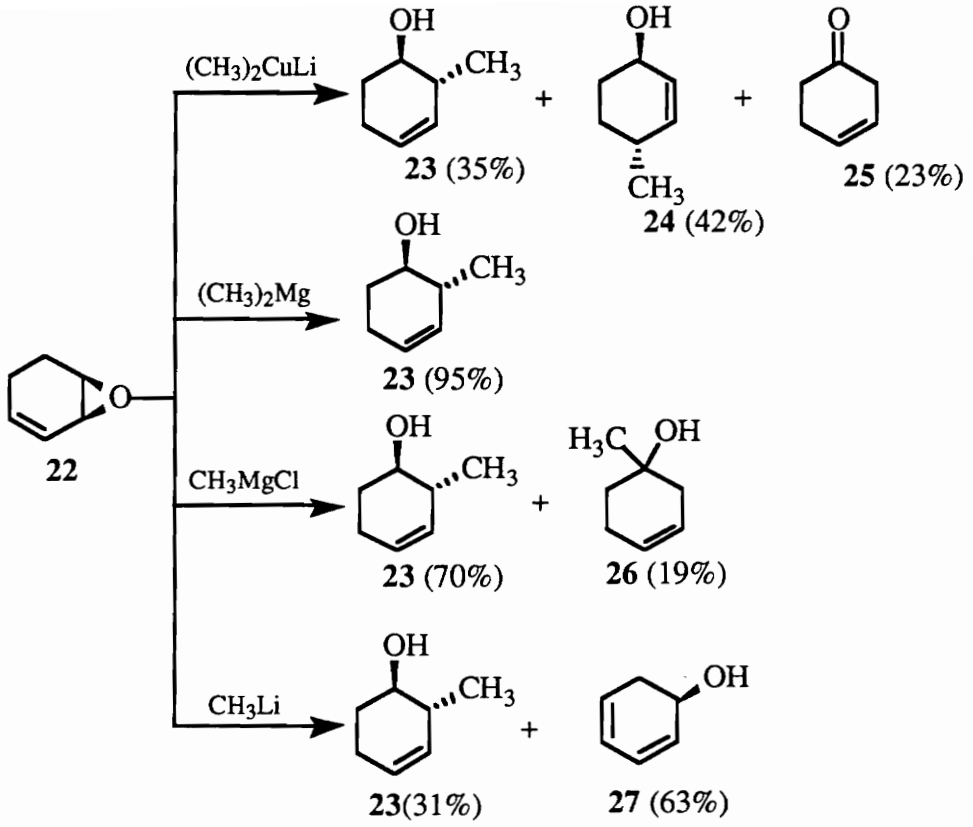
The reaction of monoepoxides of cyclic 1,3-dienes with organometallic reagents show similar, but not identical, trends. Rickborn first reported a systematic study of the reactivity of the mono-epoxide of 1,3-cyclohexadiene with methyl-metal reagents,[14]



Scheme 4

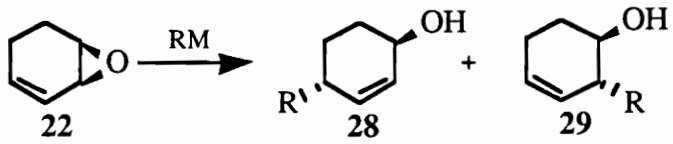
as shown in Scheme 5.

In contrast to the high regioselectivity exhibited in the reactions of the monoepoxide of 1,3-butadiene, treatment of **22** with lithium dimethylcuprate gave both S_N2 and S_N2' products with complete *trans*-stereospecificity. No S_N2' products were formed with Grignard or organolithium reagents. Meanwhile, Johnson reported a similar ring opening study of **22** with organolithium and organocuprate reagents.[15] The methyl and phenyl reagents displayed high *trans*-stereoselectivity in both 1,2-and 1,4-additions, Table 3. On the other hand, lithium *tert*-butylcuprate showed decreased stereoselectivity in conjugate addition and favored the *cis*-product in 1,2-addition. This low stereoselectivity was rationalized by a mechanism involving an intermediate radical anion **30**, as depicted in Scheme 6.



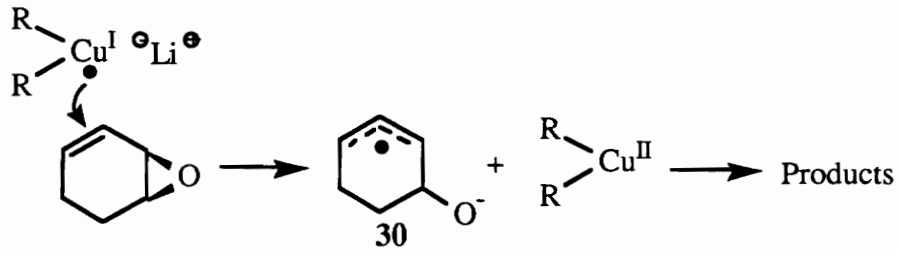
Scheme 5

Table 3. Reaction of Gilman Reagents with 1,3-Cyclohexadiene Monoepoxide[a]



RM	yield (%)	**28:29**
Me_2CuLi	91	54:46
Ph_2CuLi	87	69:31
$(t\text{-}Bu)_2CuLi$	72	65:35

a, ref. 15.

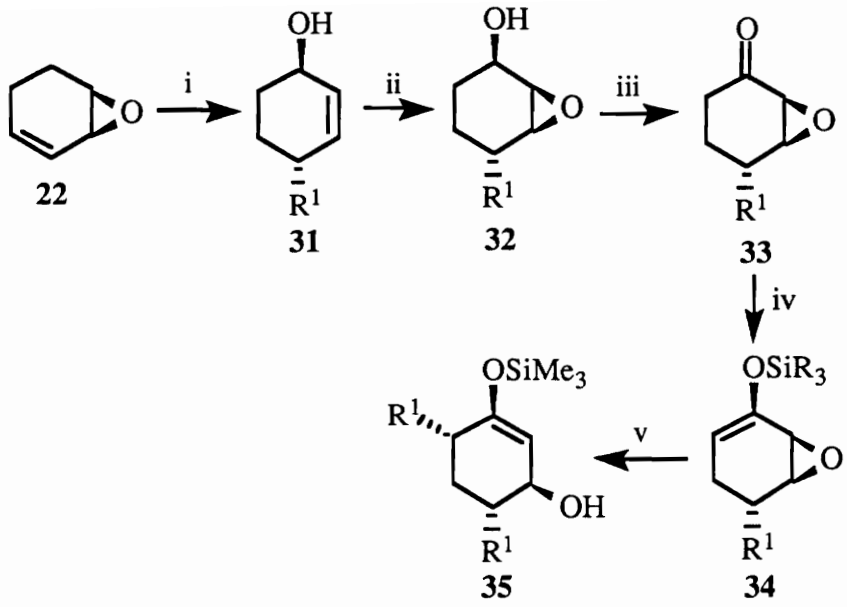


Scheme 6

In contrast to the behavior of the Gilman reagent, mixed cyanocuprates added stereospecificially (100% *trans*) and regiospecifically (1,4-addition >95%) to **22**.[16] Based on this finding, Marino devised an efficient approach to introduce multiple stereocenters into cyclohexane systems by the stereoselective tandem 1,4-opening of cyclohexene epoxide, as shown in Scheme 7.

The high regioselectivity was also observed in the reaction of the monoepoxide of 1,3-cycloheptadiene **36** with mixed cuprates,[16] Table 4. The mixed cuprate derived from the acrylate gave the highest regioselectivity, followed closely by cyanocuprate.

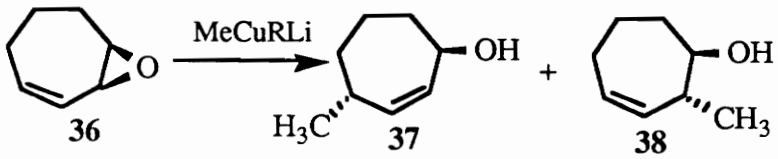
The regio- and stereochemistry of cyanocuprate addition to cyclopentene epoxides has also been studied.[17] Reaction of alkylcyanocuprate with **39** proceeded with complete regio- and stereoselectivity to provide *trans*-4-alkylcyclopenta-2-enols **40** in excellent yields, Table 5. However, sp^2-hybridized (vinyl-, allyl-, and phenyl-) cyanocuprates afforded mixtures of 1,2- and trans-1,4 adducts. In sharp contrast with the high regioselectivity observed with cyclohexadiene monoepoxide, phenylcyanocuprate addition provides both regioisomers in a surprisingly low ratio.



(i) $R^1Cu(CN)Li$; R^1=Me, 95%; R^1=Ph. 60%; (ii) $ArCO_3H$; (iii) $CrO_3 \cdot py_2$; (iv) LDA, R_3SiCl; (v) $R^2Cu(CN)Li$.

Scheme 7

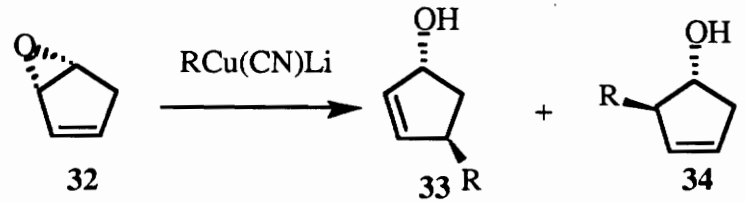
Table 4. Reactions of 1,3-Cycloheptadiene Monoepoxide and the Mixed Cuprates[a]



R	yield (%)	37:38
Me	91	70:30
BuC≡C	95	85:15
CN	95	90:10
CH_2=CCO_2Me	98	97:3

a, ref. 16a.

Table 5. Reaction of Cyanocuprates with Cyclopentadiene Monoeppoxide[a]



32 33 34

Cyanocuprate	yield (%)	33:34
Me	78	
n-Bu	95	
t-Bu	88	
EtO_2CCH_2	17	
$(n\text{-}Bu)_3SnCH_2$	5	
CH_2=CH	75	1:1
(E)-C_5H_{11}CH(OTBDMS)CH=CH	80	4:1
Ph	50	2:1

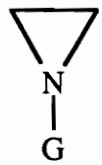
a, ref. 17.

In summary, this section highlights some of the general reaction trends of both acyclic and cyclic vinyloxiranes with organometallic reagents. The next section will present some chemistry on the ring opening of aziridines and vinylaziridines by carbon nucleophiles.

2. Chemistry of Aziridines and Vinylaziridines

In analogy to their epoxide counterparts, aziridines are also highly strained and susceptible to the ring-opening reactions that constitute the major part of their chemistry. Aziridines have also emerged as versatile chiral synthons for the synthesis of biologically important cyclic and acyclic compounds.[18]

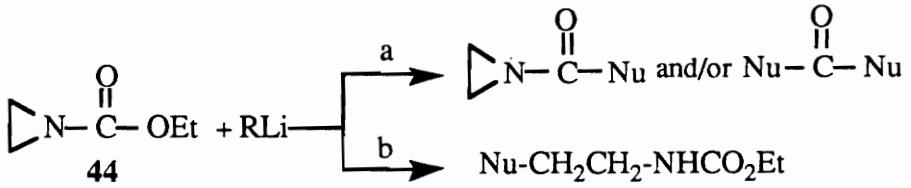
Aziridines can be divided broadly into two groups based on the nature of the substituents on nitrogen.[19] "Activated' aziridines **42** contain an electron-withdrawing substituent which can stabilize the negative charge formed on the nitrogen in the transition state of the nucleophilic ring-opening by resonance. "Nonactivated" aziridines **43** contain no such substituent, and their ring-opening usually requires protonation, quaternization, or the complexation with a Lewis acid.



42 G=COR, CO_2R, SO_2R
43 G=H, alkyl, aryl

Both activated and nonactivated aziridines undergo ring-opening reactions with noncarbon nucleophiles, such as oxygen nucleophiles,[20] halide ions,[21] nitrogen nucleophiles[22] and phosphine nucleophiles.[23] These reaction have been covered in two reviews[24] and will not be discussed here. Instead, this section will focus on the reactions of aziridines with the organometallic reagents.

Early work by Hassner and Kascheres[25] demonstrated that aziridine-carbamates **44** performed as ambident electrophiles, with the nucleophile attacking the carbonyl group (path a) or the ring carbon (path b), Scheme 8.



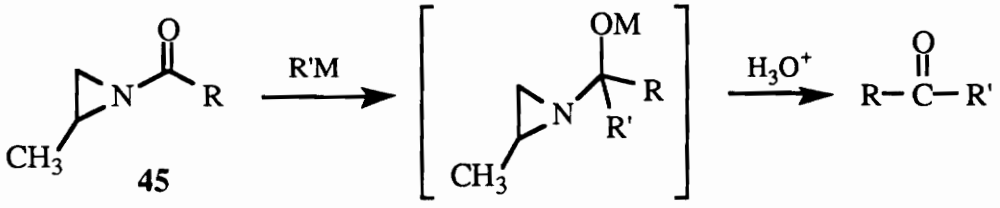
44

R=$PhCH_2$, Ph_2CH, Ph_3C, t-Bu, Ph-C≡C

Scheme 8

Benzyllithium and the bulky *t*-butyllithium produced only products of carbonyl attack (path a). However, trityllithium afforded solely ring opening product (path b), while diphenylmethyllithium gave both 1-(diphenylacetyl)aziridine (path a, 33%) and allyl *N*-(3,3-diphenylpropyl)carbamate (path b, 66%). It appears that the phenyl substitution in the alkyllithium enhances the tendency for ring opening over carbonyl attack. These results also indicate that the reaction course is controlled by nucleophilicity rather than basicity; strong nucleophiles attack the carbonyl function and weak ones attack the ring carbon.

Wattanasin and Kathawala[26] also found that N-acylaziridines reacted cleanly with both organolithium and Grignard reagents to furnish the corresponding ketones, Scheme



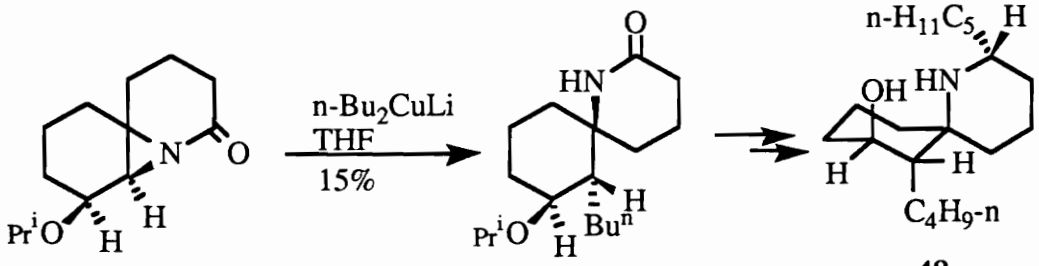
45

R=CH_3, *t*-Bu, Ph

Scheme 9

9. The reaction worked well with both aliphatic and aromatic acylaziridines. Even the bulky secondary organolithium and secondary Grignards gave good yields as well.

The successful ring opening of an acylaziridine using an organocuprate was first reported by Kishi[27] in 1975. The key step in the stereocontrolled synthesis of (±)-perhydrohistrionicotoxin **48** was the reaction of acylaziridine **46** with dibutylcopper lithium to afford lactam **47**, which was converted to **48** in four steps.

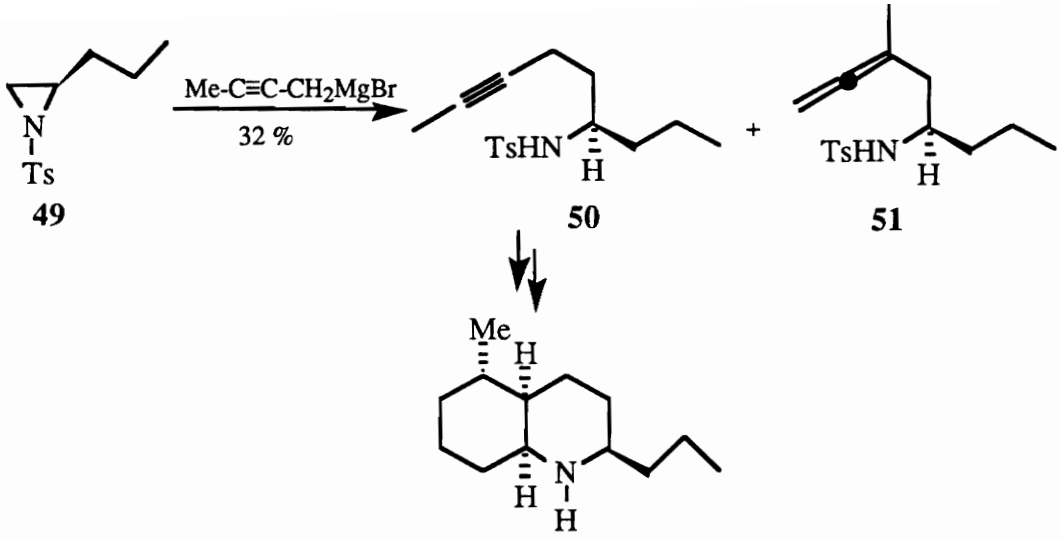


46 **47** **48**

Scheme 10

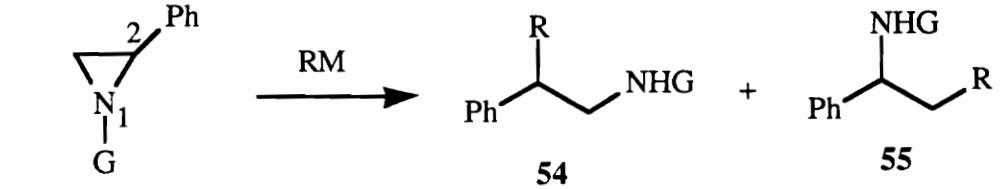
The aziridine ring opening strategy was also used by Oppolzer and Flaskamp[28] who achieved an enantioselective total synthesis of pumiliotoxin-C. In this work, *N*-tosylaziridine **49** was reacted with 2-butynylmagnesium bromide to give two ring-opened products, acetylene **50** and allene **51**, Scheme 11. Subsequent manipulations of **50** led to the target compound. This synthesis also allowed unambiguous assignment of the absolute configuration of the natural product.

The reactions of *N*-substituted derivatives of 2-phenylaziridine **52** with organolithium, organocuprate and the Grignard reagents have been investigated by Kozikowski,[29] Scheme 12. It was found that the regioselectivity of the reaction depended on the reagents and reaction conditions. In general, less bulky methyl-metal reagents, such as MeMgBr, Me_2CuLi and $MeCu{\cdot}BF_3$, preferred to attack the C-2 of **53** to



52 pumiliotoxin-C

Scheme 11

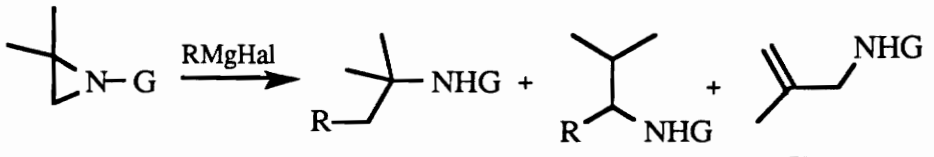


53a R=Ts
53b R=CO_2Et
53c R=CH_3

Scheme 12

give **54**. Tosylaziridine **53a** was more reactive than acylaziridine **53b**, while aziridine **53c** without an electron-withdrawing group proved unstable, and suffered decomposition even with mild cuprate reagents, Me_2CuLi and $MeCu{\cdot}BF_3$. Of the three reagents examined, organocuprate proved most effective for the ring opening of three aziridines. Grignard reagents also reacted with aziridines **53a** and **53b**, giving phenylethylamines in somewhat lower yields than the cuprates. By contrast, organolithium reagents caused either the decomposition of the aziridines or the displacement of the *N*-substituent.

In a mechanistic study[30], activated 2, 2-dimethylaziridines **56** were reacted with Grignard reagents in boiling THF to yield products of normal aziridine ring opening, i.e. **57**, the rearranged product **58**, and the methallylamides **59,** Scheme 13. The product distribution depended on the nature of the nucleophiles and the halide, as well as on the



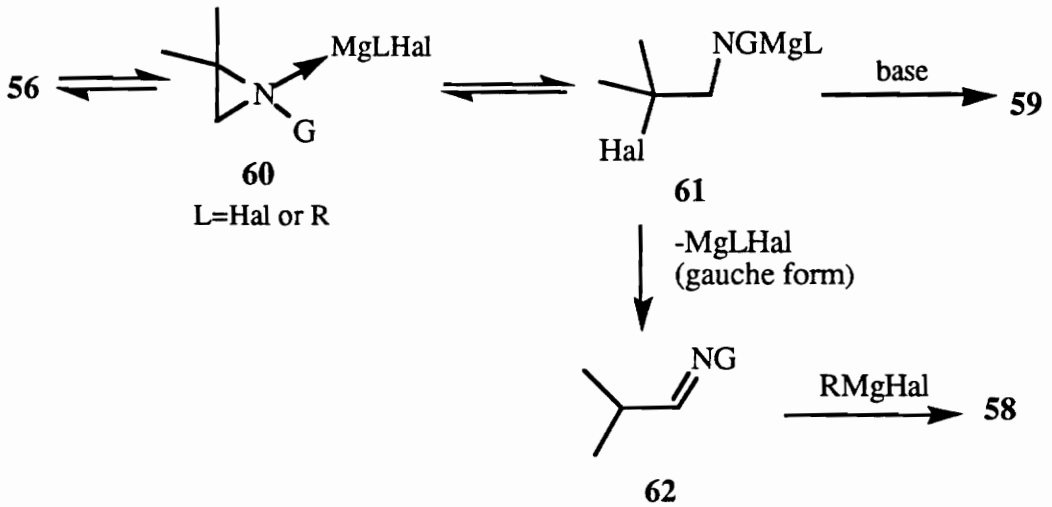
57 **58** **59**

56a G=Ts
56b G=2,5-dichlorobenzensulfonyl
56c G=$COCMe_3$
56d G=COPh
56e G=$POPh_2$

R=benzyl, methyl, phenyl

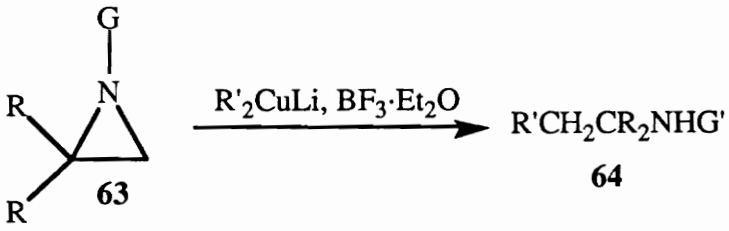
Scheme 13

nature of the acitivating groups. Control experiments indicated that **58** and **59** arose from **61,** which was formed through Lewis acid assisted aziridine opening by the halide ion, as illustrated in Scheme 14.



Scheme 14

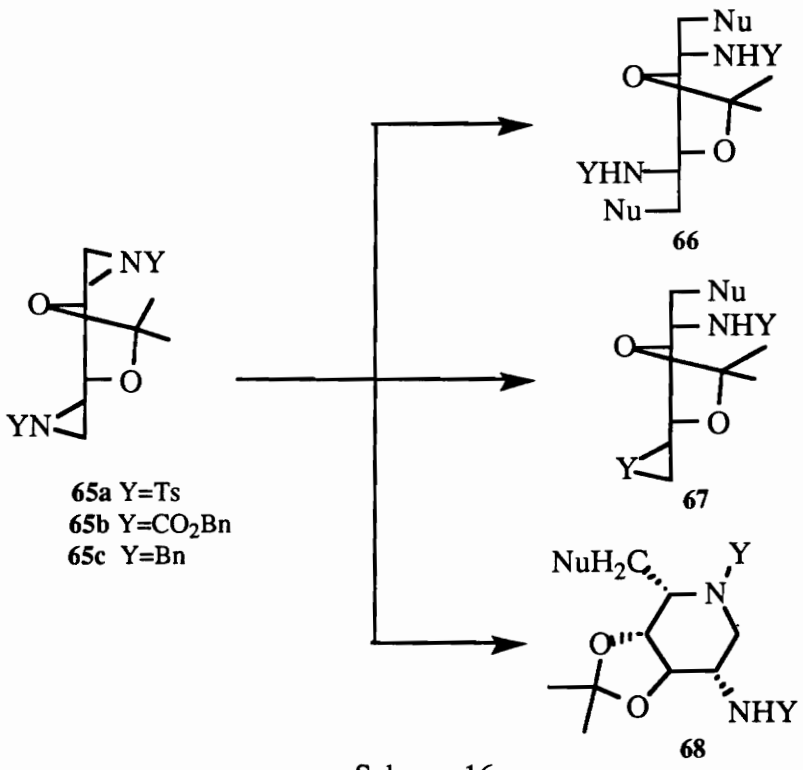
The use of $BF_3{\cdot}Et_2O$ proved to be uniquely effective in activating epoxides toward nucleophilic attack by organocuprate reagents.[31] The nucleophilic ring opening of nonactivated aziridines with Gilman reagents can similarly be facilitated by $BF_3{\cdot}Et_2O$ leading to both primary and secondary amines in moderate to high yields,[32] Scheme 15.



G=Me, Bu, Bn, TBDMS, DMB
R=H, Me
R'=CH_3, Bu, Ph

Scheme 15

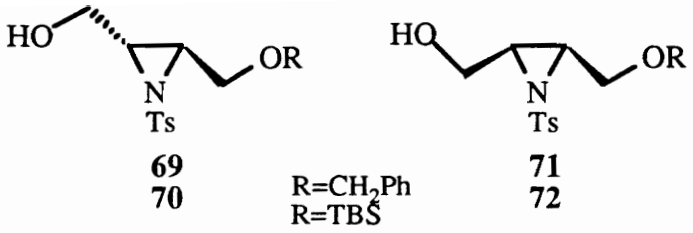
In an effort to synthesize α-aminoaldehydes or α-aminoacids from *N*, *N'*-disubstituted bis(aziridine) derived from D-mannitol, Duréault and co-workers[33] systematically studied the ring opening of bis(aziridines) **65** with a wide range of organometallic and heteroatom-nucleophilic reagents, Scheme 16. The results have shown that among the three different *N*-protected bis-(aziridines) tested, *N*-tosyl bis-(aziridine) **65a** is most appropriate for the ring-opening addition by organometallic reagents. The reaction of **65a** with methyl or n-butyl Gilman reagent produced regiospecifically diamine derivatives **66** in good yields. With lithium divinylcuprate, only a low yield of a single addition product **67** was obtained, however, the use of higher-order cuprate, $(CH_2{=}CH)_2CuCNLi_2$, led to diamine in 80% yield. Lithium heptynide addition in the presence of HMPA gave the 2-alkylpiperidine **68** in 50 % yield. With the methyl and n-butyl Gilman reagents, *N*, *N'*-bis(benzyloxycarbonyl)bis(aziridine) **65b** also underwent bis opening to give a disubstituted derivative, albeit in a moderate yield.



Scheme 16

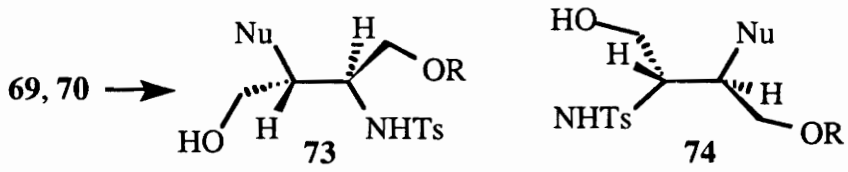
This lower yield was attributed to the partial decomposition of the intermediate metallic amide. Reaction of the poorly reactive *N*, *N'*-dibenzylbis(aziridine) **65c** with Me_2CuLi in the presence of $BF_3{\cdot}Et_2O$ afforded monobenzylamine **67**.

The ring opening of aziridino alcohols **69-72** by organometallic reagents was systematically examined by Tanner.[34] The free hydroxyl group in these compounds was expected to effect the regioselectivity of nucleophilic opening by complexation with organometallic reagents. The results of reactions of the trans aziridine **69** and **70** are shown in Table 6. Gilman cuprate as well as higher-order cyanocuprate exhibited very high C-2 selectivity irrespective of the substituent on C-4, and gave ring opening products in good yields. On the other hand, trimethylaluminum showed good to excellent C-3 selectivity. This abnormal result was accounted for as follows; initial deprotonation



69 **71**
70 R=CH_2Ph **72**
R=TBS

Table 6. Ring Opening of **69** and **70** by Methyl-Transfer Reagents[a]



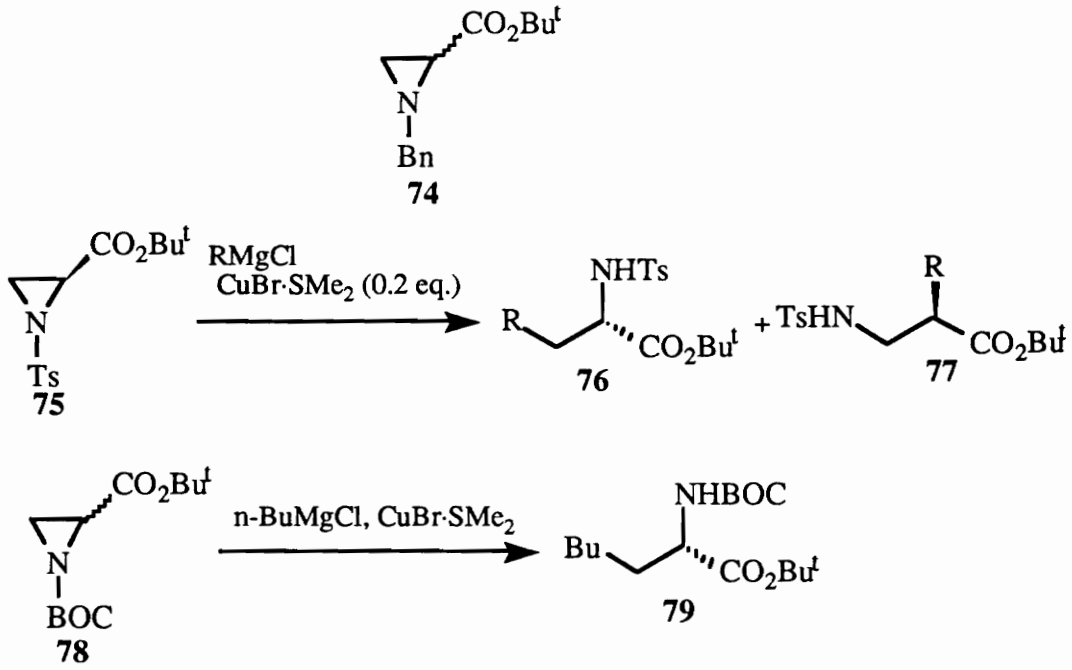
Substrate	Reagent/Conditions	**73;74**	yield, %
69	$LiMe_2Cu$, Et_2O, -20 °C	>99:1	80
70	$LiMe_2Cu$, Et_2O, -20 °C	>99:1	98
69	Li_2Me_2CuCN, THF, -20 °C	92:8	81
70	Li_2Me_2CuCN, THF, -20 °C	>99:1	71
70	$AlMe_3$, toluene, 75 °C	15:85	82

a, ref. 34.

of the hydroxyl group resulted in the formation of aluminum alkoxide, which was expected to transfer a methyl group more slowly than a trialkylaluminum species. Then second equivalent of $AlMe_3$ formed a Lewis acid-base complex with the benzyloxy group, followed by intramolecular delivery of a methyl group to the proximal (C-3) carbon. The reactions of *cis*-aziridines **71** and **72** with the same reagents used for trans-aziridine showed less regioselectivity, presumably due to steric effects that prevent the complexation between the organometallic reagent and free hydroxyl group.

The ring opening of aziridine-2-carboxylate esters with organometallic reagents was investigated by Baldwin.[35] Treatment of *t*-butyl *N*-benzylaziridinecarboxylate **74** with higher-order di-*n*-butylcuprate in the presence of $BF_3{\cdot}Et_2O$ gave a mixture of

products from reaction at the *t*-butyl ester as well as attack at C2 and C3, Scheme 17. In the absence of $BF_3{\cdot}Et_2O$, however, CuBr catalyzed Grignard addition to tosyl aziridine

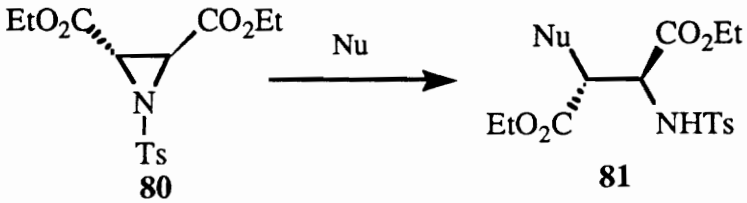


Scheme 17

75 proceeded smoothly to give **76** and **77**. *t*-Butyl *N*-*t*-butoxycarbonyl aziridine carboxylate **78** also reacted with *n*-BuMgCl in the presence of 20% $CuBr{\cdot}SMe_2$ affording C-3 opened product **79** in high yield.

Tanner[36] has described the ring opening of axially symmetric aziridine **80** with organocopper reagents. The results are shown in Table 7. Owing to the activation by three electron-withdrawing groups, aziridine **80** proved to be very susceptible to nucleophilic attack. Gilman cuprate reagents produced ring-opened products in moderate yields. In contrast, the use of Lipshutz cyanocuprate resulted in the decomposition of the aziridine. Non-carbon nucleophiles, such as azide, iodide and bromide, gave ring-opening products under mild conditions and in high yields.

Table 7. Ring Opening of Aziridine **80**[a]

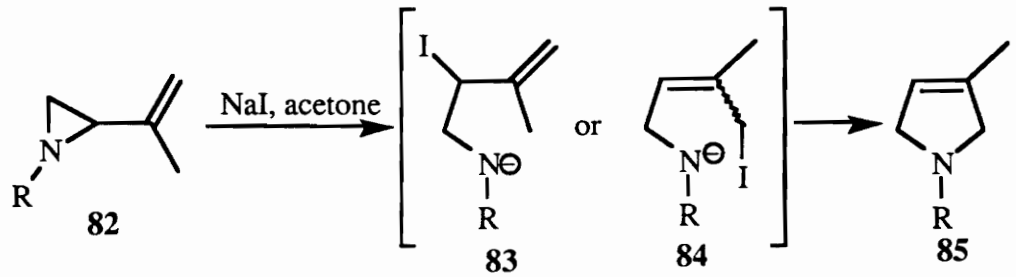


80 **81**

Entry	Reagent	Nu	Yield (%)
1	$LiMe_2Cu$	Me	68
2	$LiBu_2Cu$	Bu	54
3	$Bu_2Cu(CN)Li_2$		b
4	NaN_3	N_3	81
5	MgI_2	I	72
6	$MgBr_2$	Br	76

a, ref. 36; b, Decomposition.

Reports on the chemistry of ring opening of vinylaziridines are very rare. In the same year as our own work published in 1994[37] (see also discussion section), only two articles dealing with the systematic investigation of the chemistry of vinylaziridines appeared.[38,39] Before 1994, the only documented use of vinylazirdines and their interaction with nucleophiles was the iodide-mediated transformation to pyrrolines,[40] as shown in Scheme 18.

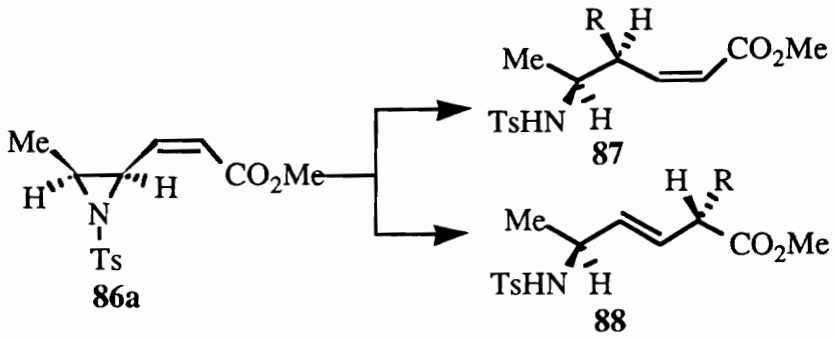


82 **83** **84** **85**

Scheme 18

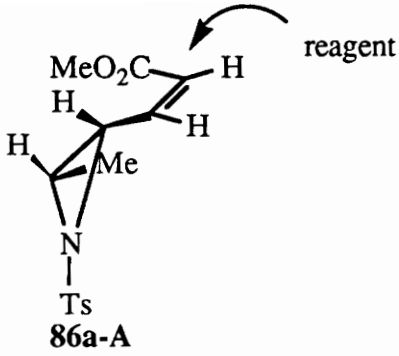
Ibuka first reported the reaction of the four isomers of **86** with the organometallic reagents.[38] Aziridine **86a** was reacted with a variety of organozinc reagents in the presence of CuCN or lower order cyanocuprates. These reactions proceeded with high regio- and stereoselectivity to give *anti* S_N2' product **87** as the major product, Table 8. The ^1H-^1H COSY and selective decoupling experiments suggest that the preferred conformation of **86a** is **86aA**, and the cuprate attack at a position *anti* to the C_γ-N bond gives the observed *anti* SN2' product. The other three isomers **86b**, **86c** and **86d**, when allowed to react with either Me_2Zn in the presence of 20% CuCN or MeCu(CN)Li, also provided *anti* S_N2' products preferentially .

Table 8. Reaction of Aziridine **86a** with Organometallic Reagents[a]

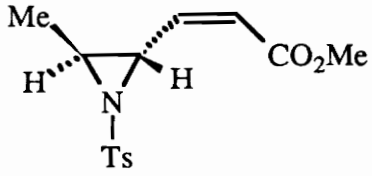


RM	**87** (%)	**88** (%)
Me_3ZnLi, 30% CuCN	4	90
Me_3ZnLI, 3% CuCN	3	81
Me_2Zn, 20% CuCN	4	94
MeCu(CN)Li	6	93
n-Bu_3ZnLi, 30% CuCN	1	97
i-PrCu(CN)MgCl·2LiCl	2	98
i-PrOSiMe_2CH_2Cu(CN)MgCl·2LiCl	b	75
p-F-$C_6H_4CH_2$Cu(CN)MgCl·2LiCl	b	98

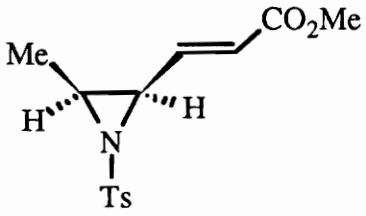
a, ref. 38; b. decomposition.



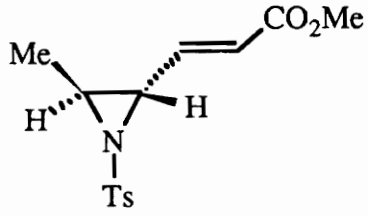
86a-A



86b

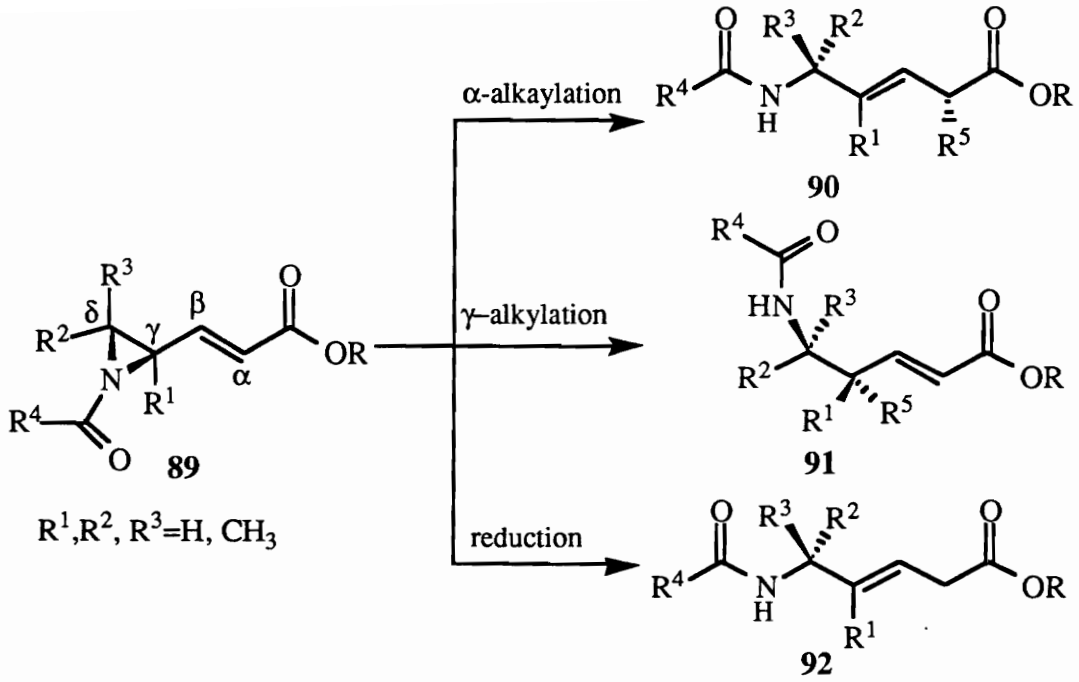


86c



86d

Wipf also reported a ring opening study of aziridines **89**.[39] The organocuprates examined in this study included R_2CuLi, $R_2Cu(CN)Li_2$, RCu, RCu(CN)Li. Treatment of **89** with cuprates in the presence of $BF_3{\cdot}Et_2O$ provided anti S_N2' product **90** as the major product, accompanied by S_N2 and reduction products **91** and **92**, Scheme 19. The product distribution depended on the type of the cuprate reagent. The best yields of *anti* S_N2' products were obtained with the cuprates derived from CuI or CuCN and alkyllithium in the presence of $BF_3{\cdot}Et_2O$. The nature of the electron-withdrawing group on the aziridine ring nitrogen also had a profound effect on the efficiency and the regioselectivity of the nucleophilic ring opening. The *N*-sulfonated or BOC-protected aziridines produced the highest yields of S_N2' products. The stereoselectivity of S_N2' alkylation of aziridine **89** appeared uniformly in favor of *anti* attack.



Scheme 19

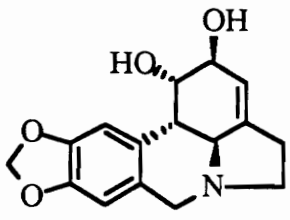
In summary, the chemistry of ring opening of aziridines and vinylaziridines has been briefly discussed. In general, activated aziridines undergo ring opening by organometallic reagents in S_N2 fashion with inversion of stereochemistry. The reactivity of aziridines depends on the substituent on the nitrogen atom. In the case of vinylaziridines, the regio- and stereospecificities are controlled by the type of organometallic reagent and the activating groups. Organocuprates appear to favor the *anti* S_N2' addition. Two articles discussed above reported only the reactions of acyclic vinylaziridines with organocuprates. The question remains of whether these reaction trends also apply to cyclic vinylaziridines. This issue will be discussed in section III.2 of this thesis.

II. HISTORICAL

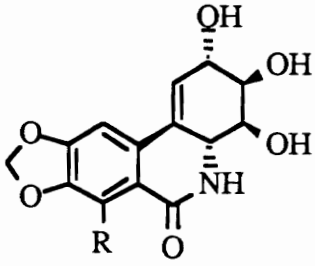
3. Amaryllidaceae Alkaloids

3.1. Isolation and Structure Determination

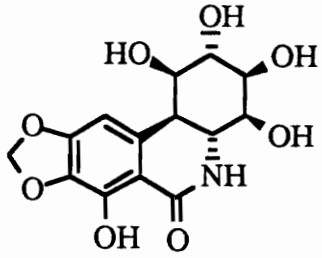
The use of *Amaryllidaceae* family plants as medicinal agents may be dated back to ancient Grecian times. By that time, oil of the daffodil *Narcissus poeticus L.* was already known to physician Hippocrates of Cos for the treatment of cancer.[41] More than thirty other plants of the *Amaryllidaceae* familiy have found use in primitive treatment of cancer. The study of *Amaryllidaceae* alkaloids started with the isolation of lycorine (**93**), the most common alkaloid of this family, from *Narcissus pseudonarcissus* in 1877.[42] Later, it was found to be able to inhibit the growth of murine P-388 lymphocytic leukemia.[43] Since then, more than 100 structurally different alkaloids have been isolated from *Amaryllidaceae* species. In 1968, Okamoto[44] reported the isolation of two non-basic constituents of *Amaryllidaceae* plants, lycoricidine (**5**) and narciclasine (**94**), from the methanolic extract of the bulbs of *Lycoris radiata*, and determined their structures as shown. In 1984, during the reexamination of alkaloid components from *Pancratium littorale*, a plant whose root extracts possessed a confirmed level of activity against the



93 lycorine



5 R=H lycoricidine
94 R=OH narciclasine



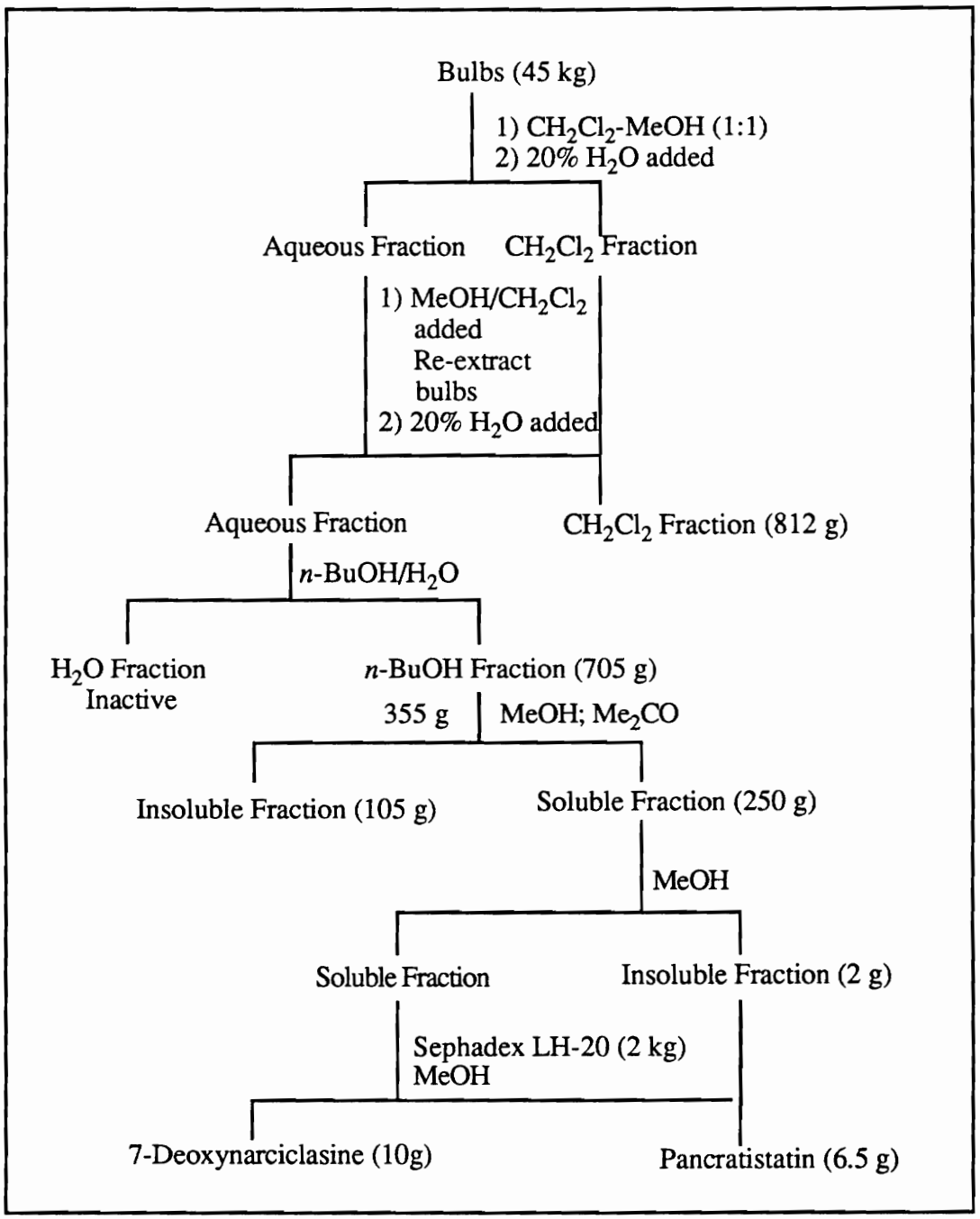
9 pancratistatin

PS lymphocytic leukemia, Pettit and coworkers[45] found that the antineoplastic activity was present in the *n*-BuOH fraction rather than the CH_2Cl_2 residue where lycorine (**93**) resided, Scheme 20. Further separation of the *n*-BuOH extract produced two principal antineoplastic components. One of them was determined by X-ray crystallography method to be lycoricidine (7-deoxynarciclasine) (**5**). Another one was extensively characterized (NMR, MS, X-ray) and found to be a new phenanthridone alkaloid, which was then designated pancratistatin (**9**).

3.2. Biological Activity

A number of *Amaryllidaceae* alkaloids, such as lycoricidine, narciclasine and pancratistatin, exhibited a wide range of biological activity. Lycoricidine and narciclasine have shown growth-inhibiting activity on *Avana coleoptitle* sections and rice seedling test, and murine Ehrlich carcinoma,[44] and shown marked inhibition of cell division on tobacco plant tissue culture.[46] Pancratistatin has been found active against *in vivo* murine M-5076 ovarian sarcoma and murine P-388 lymphocytic leukemia[47] and has demonstrated significantly higher therapeutic indices than its congeners lycoricidine (**5**) and narciclasine (**94**).

Although no data is currently available on the mechanism of the antineoplastic action of pancratistatin, the mode of action of narciclasine has been extensively studied.[48] The results indicate that the mechanism of action of narciclasine involves the inhibition of the growth of eukaryotic cells by the disruption of protein biosynthesis. This inhibition has been demonstrated both in cell-free systems and in intact cells. It has been concluded that narciclasine inhibits binding of RNA to the peptidal transferase center of the 60s ribosomal subunit. Whether pancratistatin inhibits protein synthesis by the same mechanism remains to be determined.

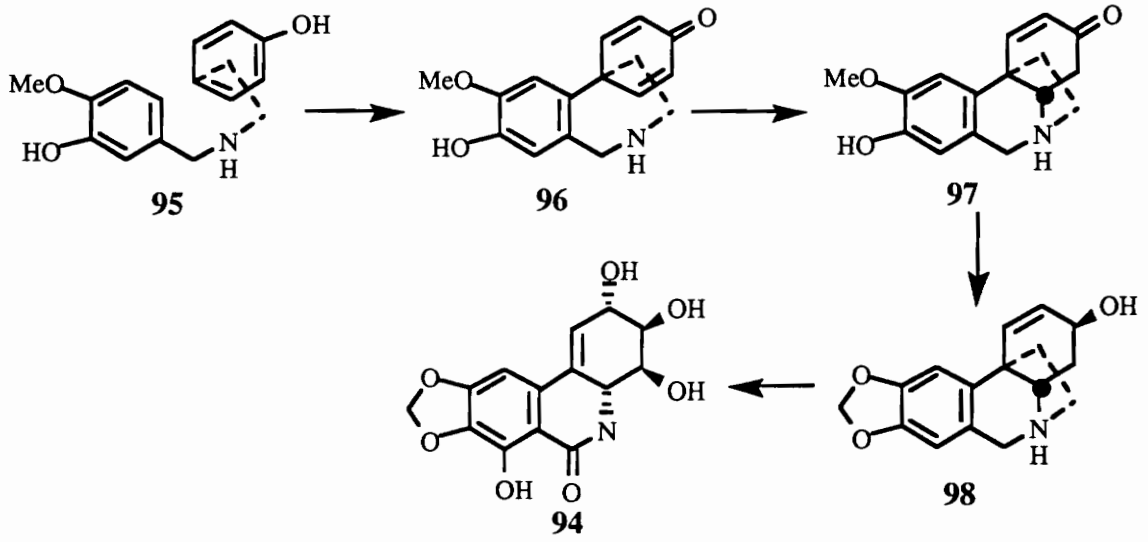


Scheme 20. Isolation of 7-deoxynarciclasine (**5**) and pancratistatin (**9**)[47]

3.3 Biosynthesis

The biosynthesis of lycoricidine and pancratistatin has not yet been explored. However, considerable research aimed at defining the biosynthesis of their congener narciclasine has been conducted by Fuganti.[49]

Narciclasine is biosynthesized from O-methyl-norbelladine (**95**) by a *para-para* phenol-coupling, as shown in Scheme 21. This biosynthetic pathway was first established by radioactive feeding experiments of ^{3}H and ^{14}C labeled compounds, and later supported by the conversion of **95** to **98** by *Pancratium maritimum* .



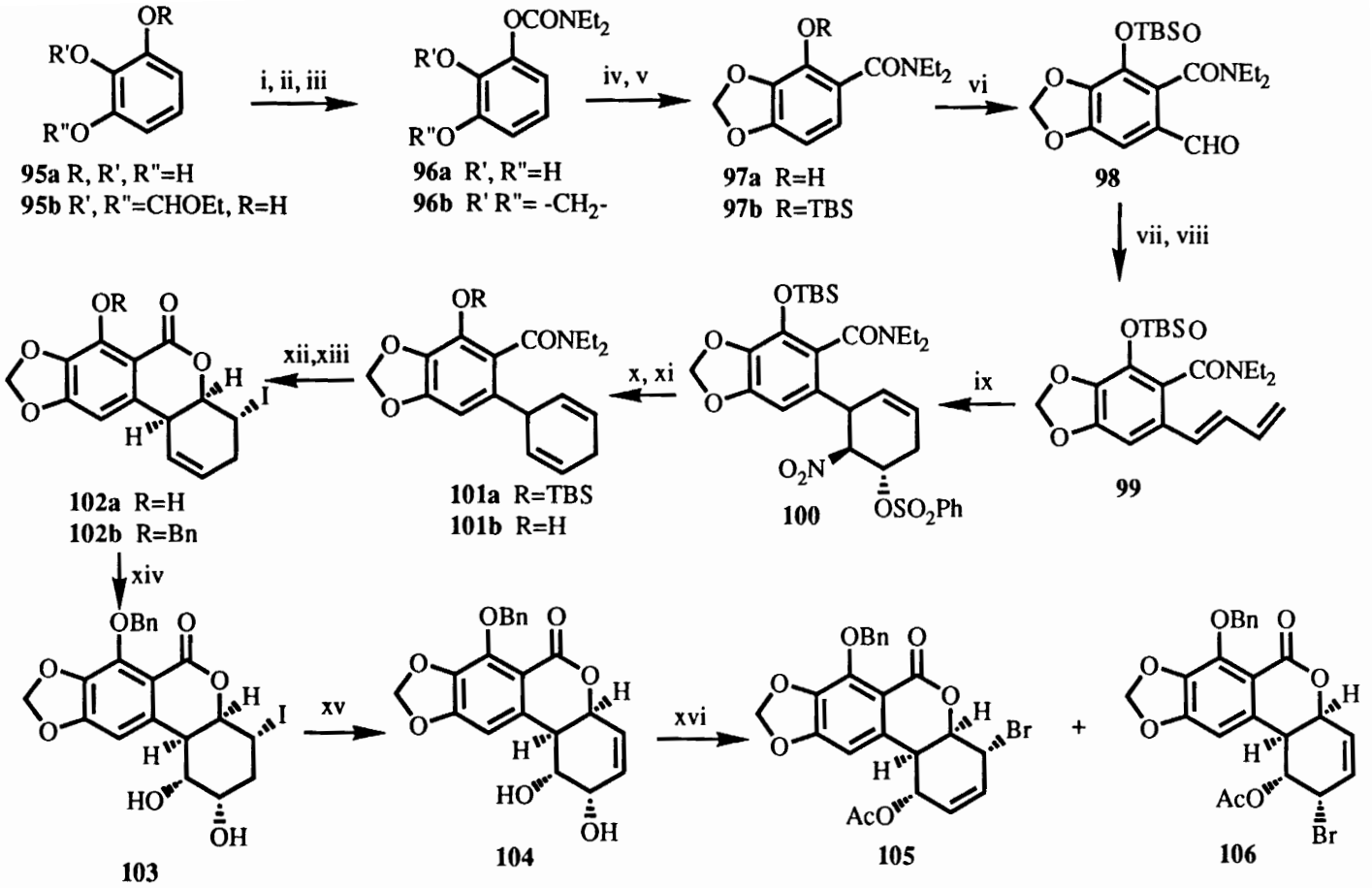
Scheme 21. Biogenesis of Narciclasine

3.4. Total Synthesis and Synthetic Approaches

The wide range of biological activity associated with the phenanthridone plant alkaloids, exemplified by lycoricidine (**5**), narciclasine (**94**) and pancratistatin (**9**), has stimulated considerable interest of synthetic chemists. To date, three total syntheses of

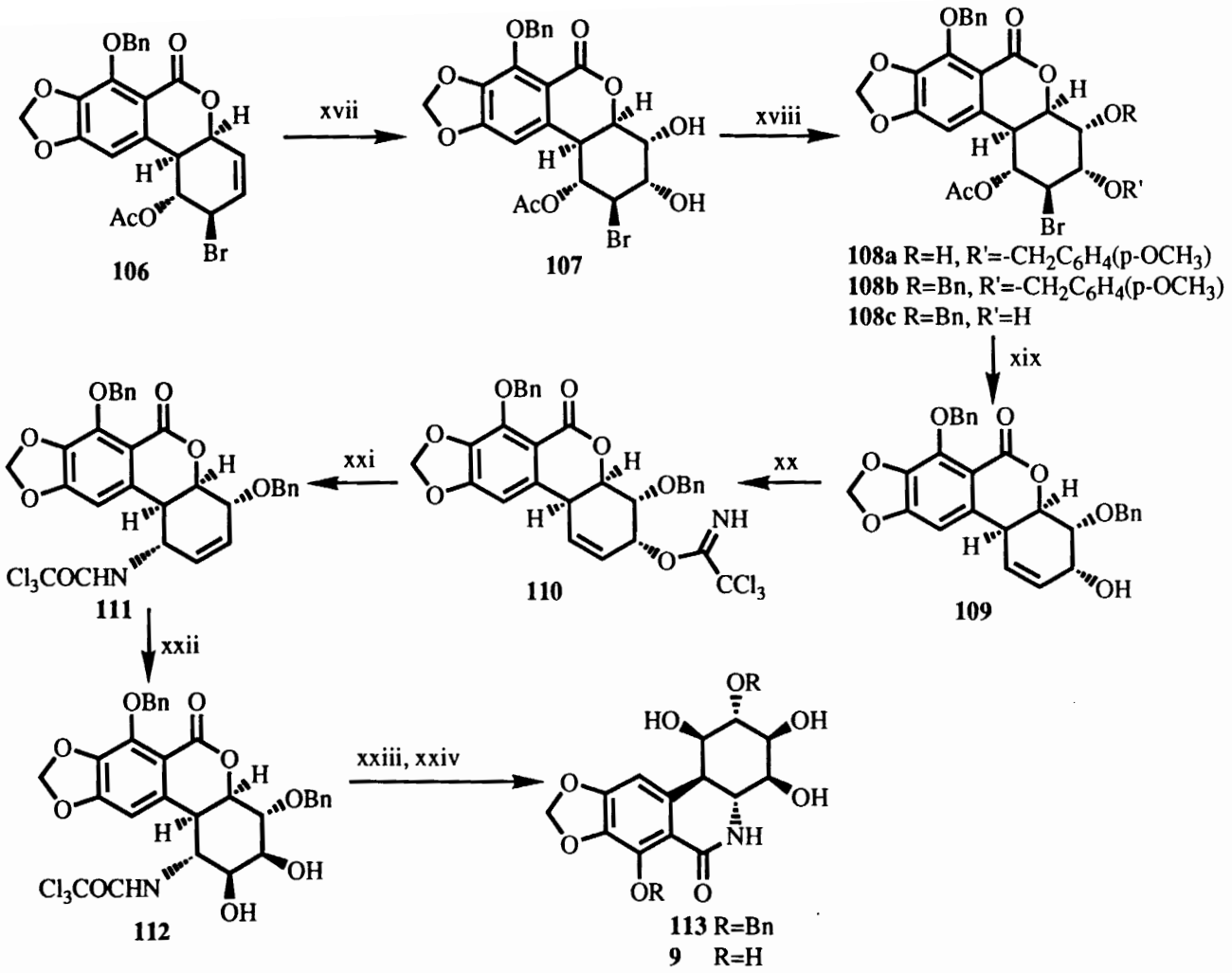
(+)-lycoricidine (Hudlicky and Olivo,[50] Ogawa et al.,[51] Paulsen and Stubbe[52]) and two of racemic lycoricidine (Ohta and Kimoto,[53] Martin and Tso[54]) have been completed. In contrast, only one total synthesis of racemic pancratistatin was reported by Danishefsky and Lee,[55] although several synthetic approaches have appeared.[56-60] The synthesis of narciclasine has not been achieved so far. The review of this section will focus on the total synthesis and synthetic approaches to the most interesting target, pancratistatin.

Total synthesis. The total synthesis reported by Danishefsky[55] started with pyrogallol (**99a**), Figure 2. Protection with triethyl orthoformate and carbamolylation followed by the formation of the methylenedioxy linkage gave **99b**. Anionic Fries rearrangement of **99b** produced the tetrasubstituted system **101a** in modest yield. Protection with TBSCl and ortho-lithiation followed by the addition of dimethylformamide afforded **102**. Conversion of **102** to diene **103** was accomplished by treatment of **102** with allylmagnesium bromide followed by mesylation and elimination with DBU. The reaction of **103** with an acetylenic dienophile and Bu_3SnH reduction led to the construction of ring C. With **105a** attained, the introduction of functionalities into C-ring was pursued. The initial attempt at halolactonization of **105a** failed. Finally, the goal was realized by deprotection of **105a** with TBAF followed by treatment with bis(tributyltin) oxide and the reaction of stannyl ether with iodine to furnish lactone **106a**, which was protected as benzyl ether **106b**. Osmylation of **106b** followed by elimination with DBU produced diol **108**. Treatment of **108** with 2-acetoxylisobutyryl bromide in a Moffatt-like transformation gave **110**, which was osmylated to **111** containing a fully functionalized C-ring. Selective protection of two hydroxyl groups in **108** was achieved though a three-step sequence to give monoalcohol **112c**. Reductive elimination of **112c**



(i) $HC(OEt)_3$, Amberlyst-15, benzene, reflux; (ii) NaH, THF, Et_2NCOCl, DMAP, 0 °C; (iii) K_2CO_3, CH_2Br_2, CuO, DMF, reflux; (iv) (a) s-BuLi, TMEDA, THF, -78 °C; (b)NH_4Cl; (v) TBSCl, imidazole, CH_2Cl_2; (vi) (a) s-BuLi, TMEDA, -78 °C; (b) DMF; (vii) allylmagnesiumbromide, Et_2O, -78 °C; (viii) (a) MsCl, Et_3N; (b) DBU; (ix) 1-(benzenesulfonyl)-2-nitroethene, $CHCl_3$, reflux; (x) Bu_3SnH, AIBN, toluene, reflux; (xi) TBAF, THF, 0 °C; (xii) $(Bu_3SnO)_2$, toluene, reflux; (xiii) BnBr, Ag_2O, DMF; (xiv) OsO_4, NMO, THF; (xv) DBU, benzene, reflux; (xvi) 2-acetoxyisobutyryl bromide, CH_3CN, 0 °C.

Scheme 22. First Total Synthesis of Pancratistatin (part A)[55]



(xvii) OsO_4, NMO, THF; (xviii) (a) Bu_2SnO, toluene, reflux; then p-methoxybenzyl bromide; (b) BnBr, Ag_2O, DMF; (c) DDQ, CH_2Cl_2, H_2O; (xix) Zn dust, AcOH, CH_2Cl_2; (xx) NaH, CCl_3CN, THF, 0 °C; (xxi) 105 °C, 0.1 mmHg; (xxii) OsO_4, NMO, THF; (xxiii) K_2CO_3, CH_2Cl_2, reflux; (xxiv) $Pd(OH)_2$, H_2.

Scheme 22. First Total Synthesis of Pancratistatin (part B)[55]

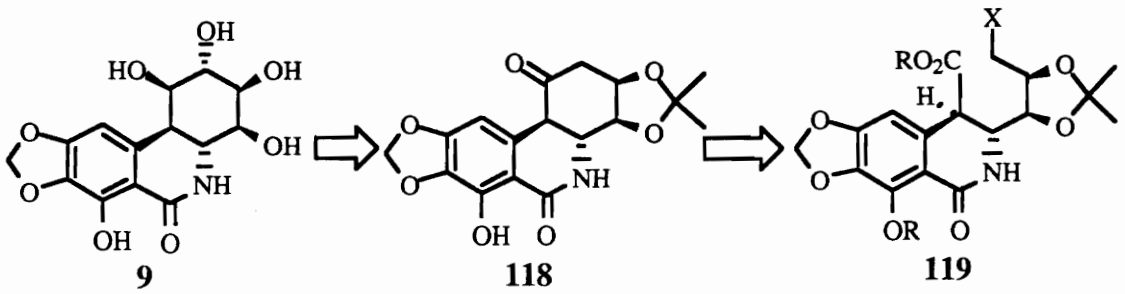
furnished **113**, which was then converted to the imidate **114**. The Overman rearrangement of **114** followed by osmylation produced diol **114**. Upon treatment with potassium carbonate in refluxing methanol, **116** was transformed to benzyl protected pancratistatin **117**, which was hydrogenated to the target molecule **9**.

This synthesis produced a racemic mixture of pancratistatin in 26 steps with a 0.13% overall yield. In this pioneering work, the highly oxygenated C-ring was successfully established through a series of *cis*-directed vicinal functionalization reactions.

Synthetic Approaches. Following the first total synthesis achieved by Danishefsky,[55] several synthetic approaches have appeared. These are chronologically reviewed below. It should be noted that synthetic approaches to lycoricidine developed by Paulsen[52] and by Ohta[53] should also serve as the model studies of pancratistatin synthesis, even though these two syntheses were published before the isolation of pancratistatin (1984). In each case, a derivatized 7-deoxypancratistatin was synthesized and dehydrated to lycoricidine.

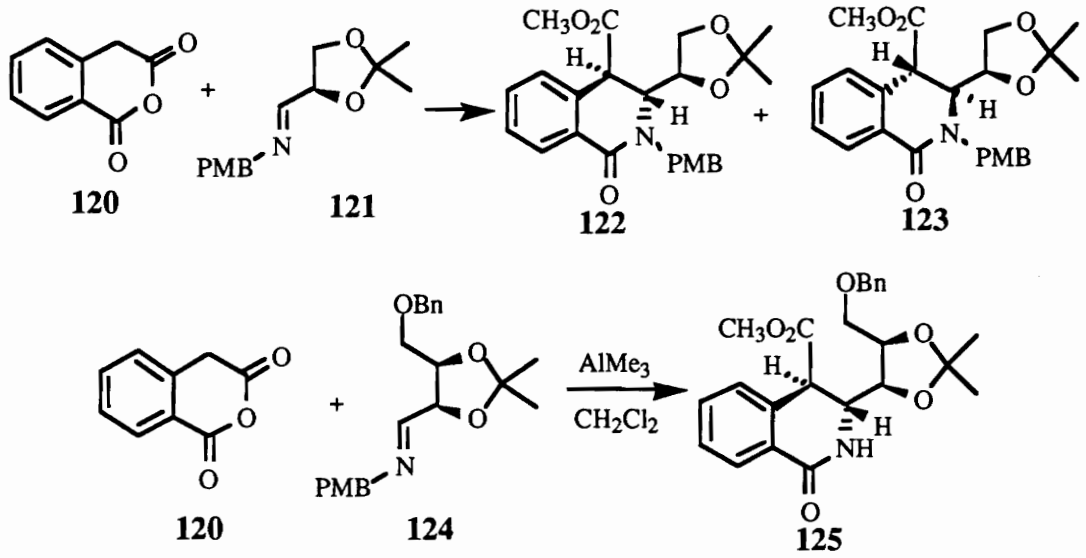
Clark's Approach (1990)

The general retrosynthetic strategy reported by Clark[56] is shown in Scheme 23. It was assumed that pancratistatin could be synthesized from ketone **118** which, in turn, could be available from a seco- derivative **119**. The stereocontrolled synthesis of **119** from a chiral imine and a suitably functionalized homophthalic anhydride was investigated. It was found that the distereoselectivity of condensation between **120** and imine **121** could be enhanced dramatically with the addition of Lewis acid, such as magnesium iodide and trimethylaluminium, resulting in preferred formation of desired adduct **122**. This enhancement stems from the Lewis acids complexation between the nitrogen and α-alkoxy group of the imine. Similarly, condensation of **120** and **124** in the



Scheme 23. Retrosynthetic Analysis by Clark[56]

presence of trimethylaluminum furnished the major product **125**, which possesses four asymmetric centers with the correct stereochemistry for pancratistatin. The effort to apply this method to other imine addition processes and to the preparation of more advanced pancratistatin precursor is underway.[56]

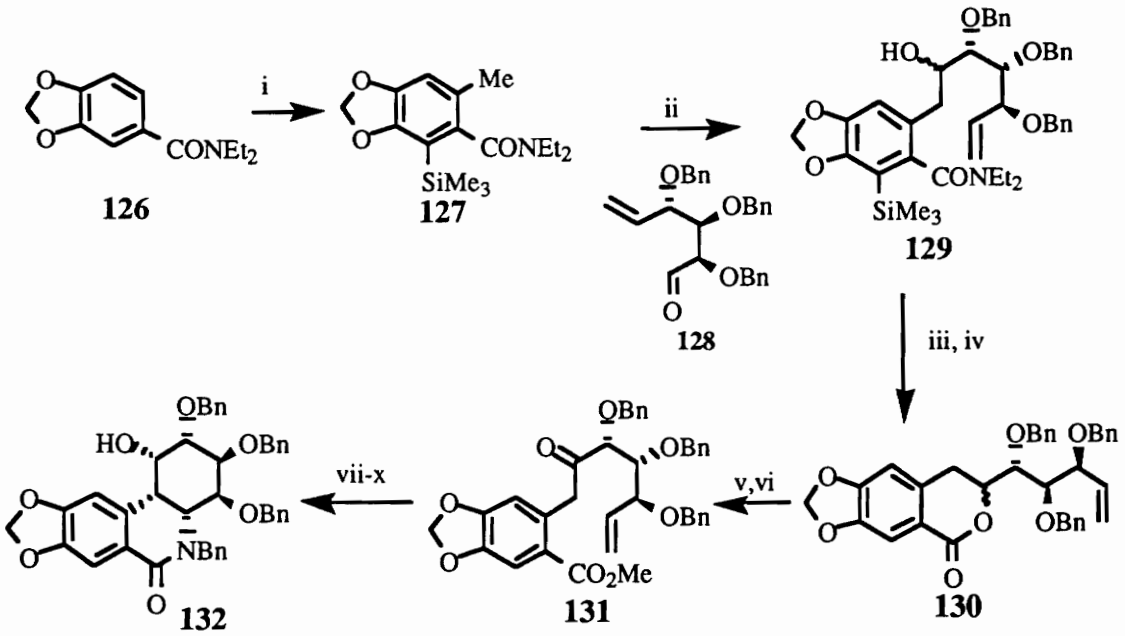


Scheme 24. Lewis Acid Mediated Condensation[56]

Kallmerten's Approach (1990)

Kallmerten[57] reported a convergent strategy, the addition of a nucleophilic aryl subunit to a dialdehyde synthon, for the construction of pancratistatin-type phenanthridone system.

N,*N*-diethylamide **126** was converted to **127** by a two-step *ortho*-lithiation /electrophilic quench sequence. The condensation of the anion derived from **127** and aldehyde **128** gave adduct **129**. Desilylation and acid-catalyzed cyclization produced



(i) s-BuLi, Me_3SiCl, THF, TMEDA, -78 °C; s-BuLi, THF, TMEDA, MeI; (ii) s-BuLi, THF, -78 °C, **128**; (iii) Bu_4NF, THF; (iv) CSA, PhH, 90 °C; (v) LiOH, THF-MeOH, then CH_2N_2, Et_2O; (vi) $(COCl)_2$, DMSO, NEt_3, CH_2Cl_2; (vii) O_3, MeOH, -78 °C, then, Me_2S; (viii) DBU, THF; (ix) $PhCh_2NH_2$, PPTs; (x) $NaCNBH_3$, MEOH-10% aqueous HCl.

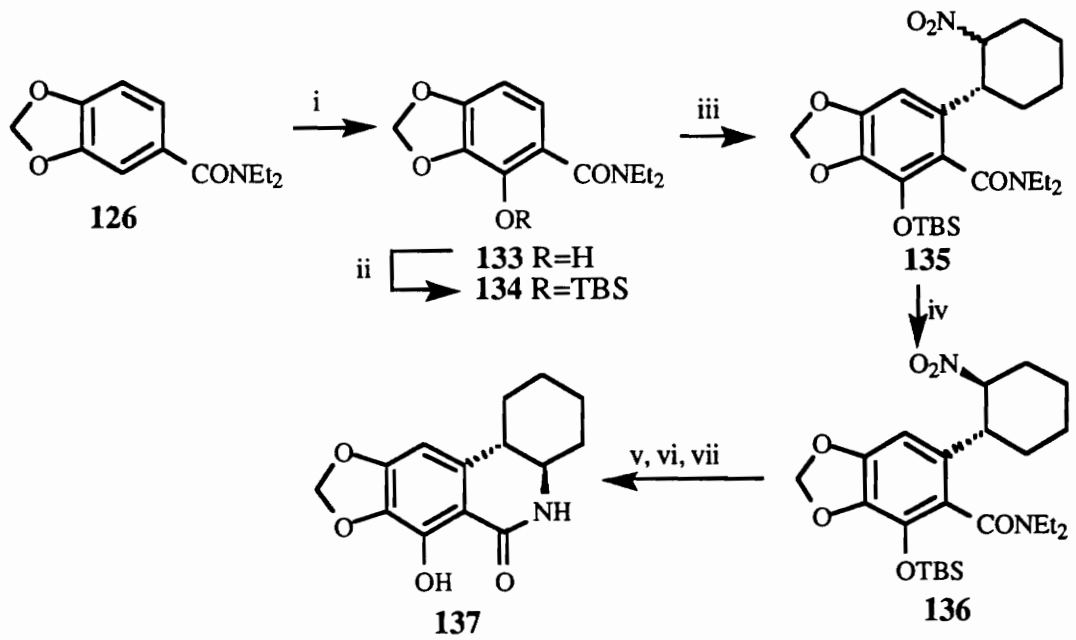
Scheme 25. Kallmerten's Model Study[57]

lactone **130**, which, upon hydrolysis followed by esterification and oxidation, was converted to ketone **131**. Subsequent ozonolysis and DBU-mediated intramolecular aldol reaction resulted in the closure of C-ring. Further treatment with benzylamine and cyanoborohydride reduction established phenanthridone **132**, which contains four of six

stereogenic centers of the pancratistatin C-ring. The attempt to establish a *trans*-fused phenanthridone required for pancratistatin by the epimeriztion of ketone from the oxidation of **132** failed.

Heathcock's Approach (1992)

Another expedient approach to synthesizing the tetracyclic phenanthridone nucleus has been reported by Heathcock.[58] The synthesis started with *N*,*N*' -diethyl piperonylamide. Lithiation **126** and treatment of aryllithium with trimethyl borate, followed by the oxidation with hydrogen peroxide gave phenol **133**, which was protected with TBSCl to **134**. Lithiation of **134** and exposure of lithiated species to



(i) (a) s-BuLi, TMEDA, THF; (b) $(MeO)_3B$; (c) H_2O_2, HOAc; (ii) TBSCl, imidazole, CH_2Cl_2; (iii) (a) s-BuLi, TMEDA, THF, -78 °C; (b) 1-nitrocyclohexene; (c) HOAc; (iv) Et_3N, EtOH; (v) $NaBH_4$, $NiCl_2 \cdot 6H_2O$, MeOH, sonication; (vi) s-BuLi, THF, -15 °C (vii) HCl.

Scheme 26. Heathcock's Model Study[58]

1-nitrocyclohexene generated a mixture of *cis* and *trans* **135**. Then conversion of **135** to the tetracyclic system **137** was accomplished by first epimerization with triethylamine to

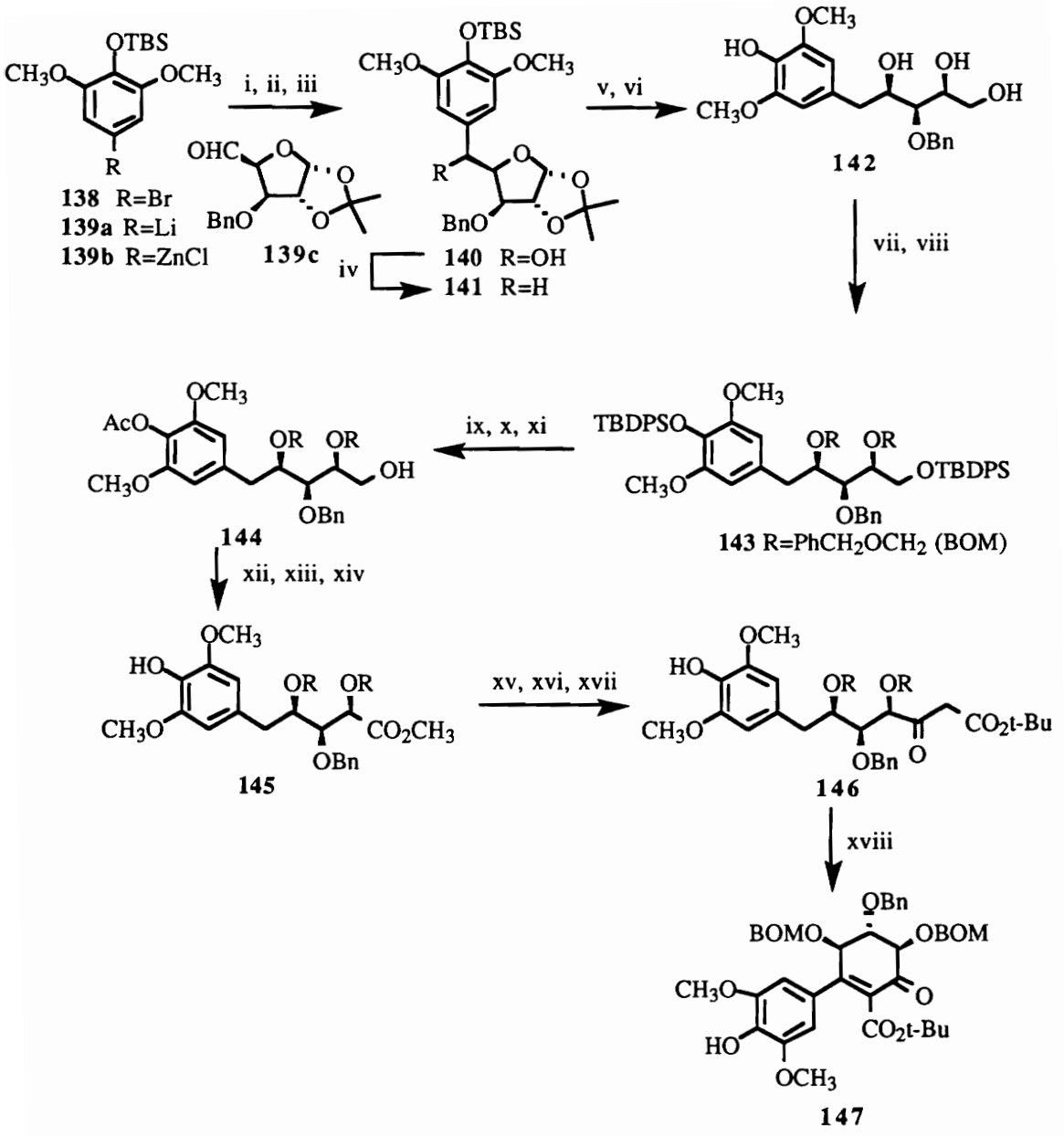
136 followed by $NaBH_4$ reduction and ring closure with *s*-BuLi at low temperature. Application of this model study to the total synthesis of pancratistatin requires a suitably functionalized 1-nitrocyclohexene.

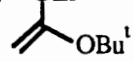
Angle's Approach (1993)

Angle[59] reported the synthesis of the possible pancratistatin precursor **147** *via* a quinone methide initiated cyclization reaction. The starting aryl bromide **138** underwent halogen-metal exchange, followed by transmetallation to give the arylzinc species **139b**, which added to aldehyde **139c** to yield alcohol **140** as a single diastereomer, Scheme 27. Deoxygenation of **140** was effected by formation of the methanesulfonate followed by LAH reduction to afford **141**. Hydrolysis of the acetonide and $NaBH_3CN$ reduction gave **142**, which was protected to **143**. Selective deprotection of **143** and subsequent treatment with acetyl chloride led to the acetate which was converted to primary alcohol **144** with TBAF. Oxidation followed by hydrolysis and esterification afforded **145**. Protection of **145** with TBSCl, then homologization and deprotection gave phenol **146**, which, upon Ag_2O oxidation, was converted to **147** in good yield. The effort is currently focused on the modification of this approach to allow the synthesis of a cyclohexanone with five stereogenic centers in the proper orientation required for pancratistatin.

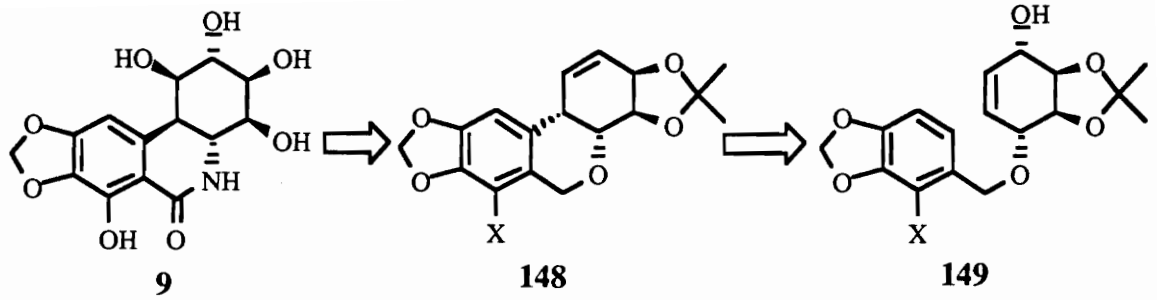
Haseltine's Approach (1994)

Recently, Haseltine[60] disclosed another synthetic approach, as outlined in Scheme 28. The feasibility of formation of the central C-C bond of the target skeleton by intramolecular electrophilic aromatic substitution (**149** to **148**) was examined first. **150**



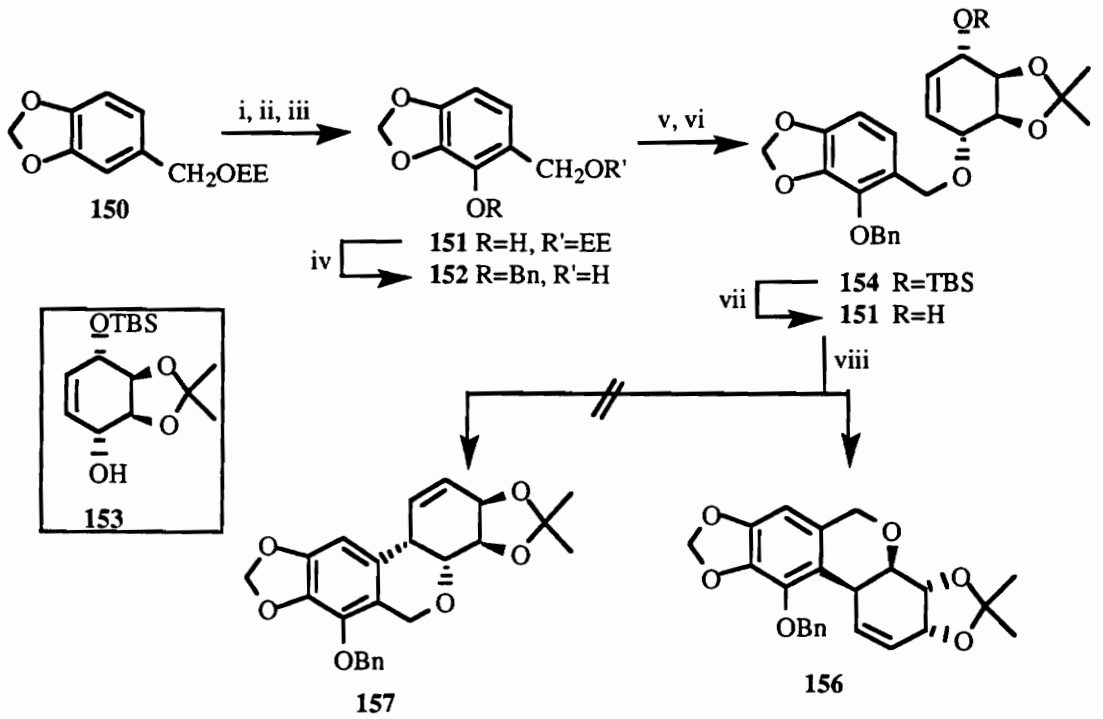
(i) t-BuLi; (ii) $ZnCl_2$; (iii) aldehyde **139c**; (iv) MsCl, Et_3N, then LAH; (v) HNO_3, H_2O; (vi) $NaBH_3CN$, CF_3CO_2H; (vii) TBDPSCl, imidazole; (viii) BOMCl, $(i\text{-}Pr)_2NEt$; (ix) TBAF; (x) AcCl, Et_3N, DMAP; (xi) TBAF; (xii) PDC; (xiii) NaOH; (xiv) CH_2N_2; (xv) TBSCl; (xvi)  ; (xvii) TBAF; (xviii) Ag_2O.

Scheme 27. Angle's Model Study[59]



Scheme 28. Retrosynthetic Analysis by Haseltine[60]

was metallated and the resulting lithiated species was quenched with trimethyl borate followed by H_2O_2 oxidation to give phenol **151**, Scheme 29. Protection of the phenol as



(i) (a) n-BuLi; (b)BH_3·THF; (c) H_2O_2, NaOH; (ii) KH, BnBr, DMF; (iii) H_3O^+; (iv) BnBr; (v) Cl_3CCN, cat. KH, THF, -78 °C to rt; (vi) CSA, CH_2Cl_2, **153**; (vii) TBAF; (viii) Tf_2O, 2,6-di-t-butyl-pyridine.

Scheme 29. Unexpected Cationic Rearrangment[60]

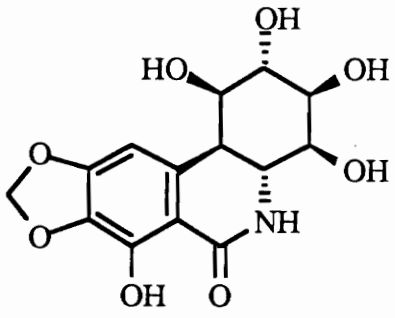
a benzyl ether and removal of the EE group yielded **152**, which was coupled to conduritol **153** to generate **154**. Desilylation produced cyclization precursor **155**. Unfortunately, exposure of **155** to trifluoromethanesulfonic anhydride and 2, 6-di-*tert*-butylpyridine yielded **156** *via* a cationic rearrangement instead of the expected pentacycle **157**.

In summary, one total synthesis and several synthetic approaches have been briefly reviewed. It is easy to see that all these synthetic efforts have been challenged by the complex stereochemistry and high degree of oxygenation of pancratistatin C-ring, and in some instances by non-stereoselective reductions. A lot of work remains to apply any of above synthetic approaches to the total synthesis of pancratistatin itself. Clearly a concise and practical synthesis largely relies on the development of a novel method to efficiently construct six asymmetric centers. Our efforts directed toward this goal will be discussed in the next section.

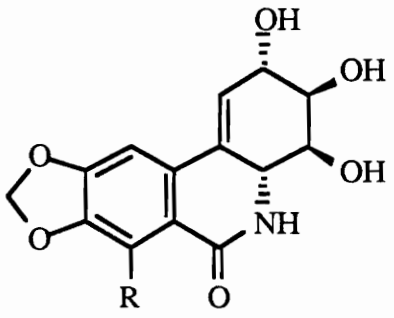
III. DISCUSSION

1. Introduction

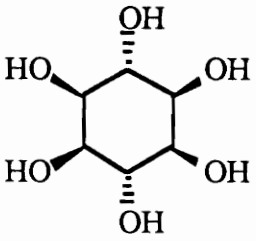
Pancratistatin (**9**) has shown pronounced *in vivo* antineoplastic activity in animal model and demonstrated significiantly higher therapeutic indices than its congeners lycoricidine (**5**) and narciclasine (**94**).[47] However, the preclinical development of pancratistatin has been impeded by the small amounts of the natural product available for testing and the difficulties in its purification by conventional procedures.[47] The limited availability of this compound for further biological evaluation as well as its greater structural complexity have prompted significant efforts directed toward the total synthesis of pancratistatin.



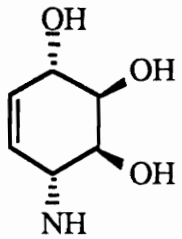
9 pancratistatin



5 lycoricidine
94 narciclasine



158 D-*chiro*-inositol



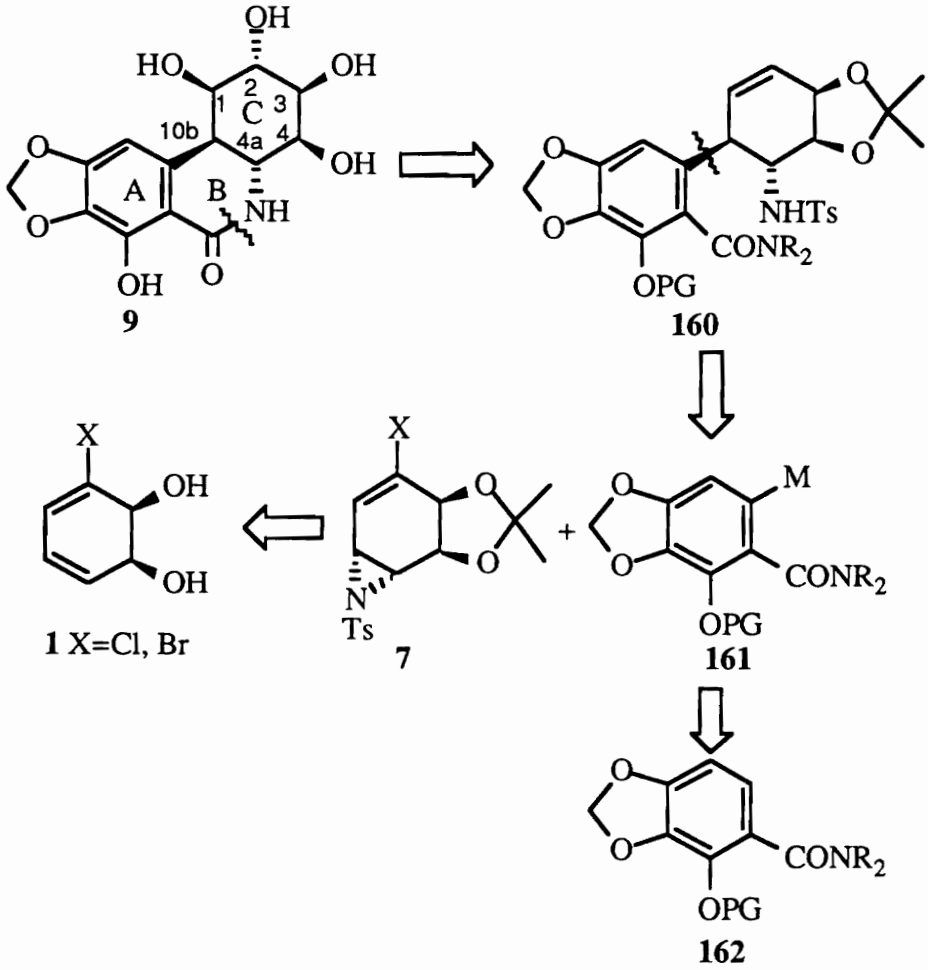
159 conduramine A-1

The synthetic challenge posed by any approach to pancratistatin is the construction of six contiguous asymmetric centers on the highly oxygenated C-ring. The first total synthesis reported by Danishefsky[55] gave a racemic mixture of pancratistatin in 26 steps and with a 0.13% overall yield. A lengthy process and several low-yielding steps leave much room for an economical, 'low-tech' route. Heathcock et al.[58] published an elegant procedure to elaborate the phenanthridone nucleus in 1992. However, the application of this model study to the total synthesis of pancratistatin itself was challenged by the incorporation of suitably protected 3,4,5,6-tetrahydroxyl-1-nitrocyclohexene, a C-ring precursor.

Our approach to the synthesis of pancratistatin was based on the recognition of configurational similarity between the C-ring and both D-*chiro*-inositol **158**[61] and conduramine **159**,[62] as well as lycoricidine **5**.[50] All these three have been synthesized in our laboratories starting from the protected diene diol **1**, which contains the *cis*-diol unit common to all of the compounds. The *trans*-diol unit at C-1 and C-2 in **9** could be reliably introduced *via* epoxide hydrolysis as demonstrated in the synthesis of D-*chiral*-inositol.[61] Thus the synthetic challenge reduced to introduction of the aryl moiety at C-10b and the amino group at C-4b in a stereocontolled manner. We expected that this goal could be realized through the regioselective ring opening at C-10b of vinylaziridine **7** by a suitable aryl nucleophile. With these considerations in mind, a synthetic approach to (+)-pancratistatin, starting from diol **1**, was conceived, as retrosynthetically depicted in Scheme 30.

Disconnection of lactam ring leads to **160.** The *trans*-diol at C-1 and C-2 could be introduced by epoxidation and subsequent opening of epoxide. We regarded **160** as a critical intermediate because its transformation to the target compound required only seemingly trivial functional group transformations. Further disconnection of C-10b and C-4 in **160** revealed two intermediates, vinylaziridine **7** and aromatic species **161.**

Lithiated species **161** could arise from the ortho-metalation of the corresponding amide **162**, as previously reported,[63] which could then be transmetallated into other organometallic forms. It was envisaged that aziridine **7** could be available from diol **1**. Therefore, the reduction of this plan to practice appeared to depend solely on the successful union of aziridine **7** and aromatic species **161** in a stereo- and regioselective fashion.



Scheme 30. Retrosynthetic Analysis

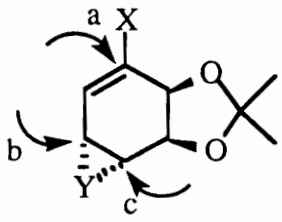
Because of the absence of data in the literature concerning the ring-opening of vinylepoxides **6** and vinylaziridines **7** with carbon nucleophiles, a model study intended

to probe the regio- and stereochemistry of ring opening was performed prior to the execution of the above synthetic strategy. Compounds **6** and **7** were reacted with a series of organometallic reagents, and it was hoped that this study would provide the foundation necessary for the exploration of the application of these chiral synthons in the synthesis to C-disaccharides and their amino derivatives, as well as *Amaryllidaceae* alkaloids. The results of this preliminary study will be detailed in the next section.

2. Methodology Study—Ring Opening with Organometallic Reagents

2. 1. Preparation of Vinyloxiranes and Vinylaziridines

Ring opening of vinyloxiranes has been well studied and a wealth of parameters associated with the regio- and stereoselectivity of such openings are available.[6] Conversely, the chemistry of ring opening of vinylaziridines with nucleophiles was absent before the initiation of our study, save for the case of iodide-mediated vinylaziridine-pyrroline rearrangement.[40] In principle, there are three reaction centers in vinyloxiranes **6a** and **6b**, and vinylaziridines **7a** and **7b** that are available for nucleophilic attack, as denoted by a, b and c.

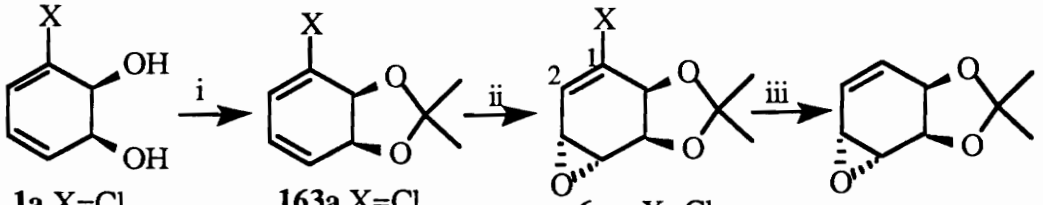


6a X=Cl, Y=O
6b X=H, Y=O
7a X=Cl, Y=NTs
7b X=H, Y=NTs

A detailed study should allow insight into the following issues: (1) selectivity of S_N2 vs. S_N2' opening as a function of the nature of the metal; (2) the electronic influence

of the halogen atom and the steric influence of the acetonide on the outcome of the ring opening; (3) steric and stereoelectronic requirements for different nucleophiles; (4) potential application of these vinyloxiranes and vinylaziridines as chiral synthons in the synthesis of disaccharides and alkaloids.

Chlorovinyloxirane **6a** and vinyloxirane **6b** were readily prepared following known procedures,[64] as shown in Scheme 31. Protection of halodiene diols **1** with



1a X=Cl
1b X=Br

163a X=Cl
163b X=Br

6a X=Cl
164 X=Br

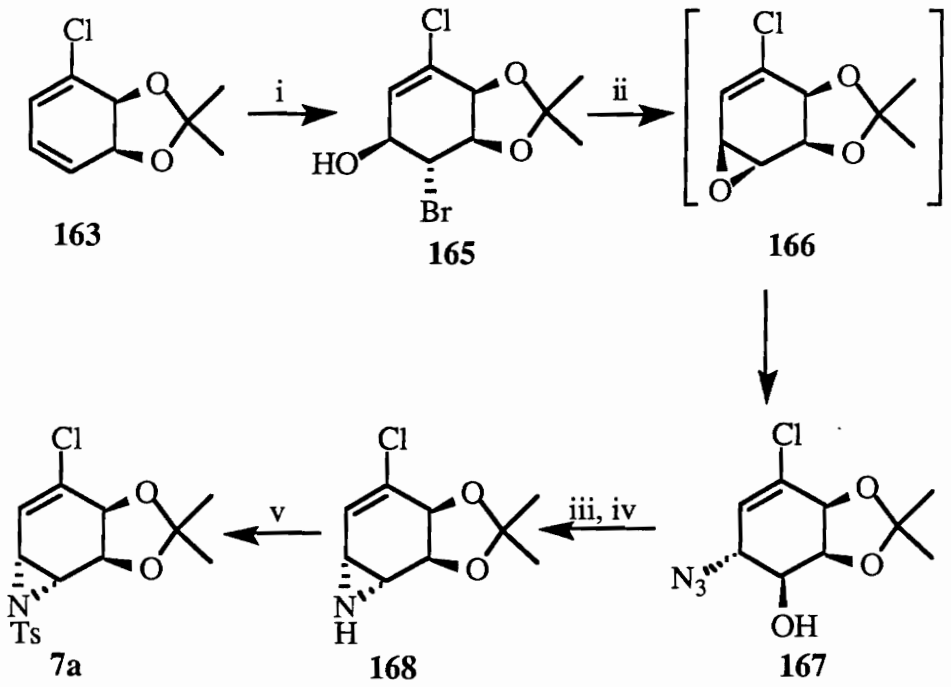
6b

(i) 2,2-dimethoxypropane, TsOH, CH_2Cl_2; (ii) m-CPBA, CH_2CH_2;
(iii) Bu_3SnH, AIBN, C_6H_6, pyridine, hυ.

Scheme 31. Preparation of Vinyloxiranes[64]

2,2-dimethoxypropane in the presence of a catalytic amount of *p*-toluenesulfonic acid produced acetonides **163** in nearly quantitative yield. Stereospecific epoxidation with *m*-chloroperoxybenzoic acid (m-CPBA) afforded the α-epoxides **6a** and **164** as single diastereomers. This stereoselectivity arises from the efficient shielding of the β-face by the endo methyl group of the aceonide and deactivation of the inductive effect of C1-C2 olefin by the halogen. Vinylic bromide **164** was subsequently reduced to **6b** in 50% yield by the use of Carless' photochemical procedure[64b] (Bu_3SnH, AIBN, C_6H_6, pyridine, hυ). This debromination could not be successfully achieved by normal thermal conditions (Bu_3SnH, AIBN, benzene, reflux), due to the sensitivity of **164** toward electrophilic ring opening.

Unlike vinyloxiranes **6a** and **6b,** the syntheses of vinylaziridines **7a** and **7b** have not been precedented. Initially, aziridine **7a** was prepared through a six step sequence starting from protected diol **163**, as depicted in Scheme 32.



163 **165** **166** **167** **168** **7a**

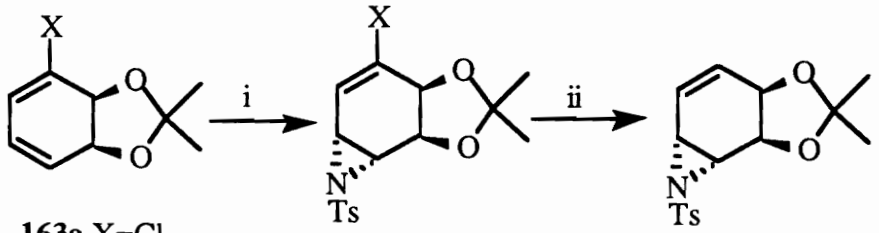
(i) NBS, DME, H_2O; (ii) NaN_3, DMSO; (iii) MsCl, Et_3N, CH_2Cl_2; (iv) $LiAH_4$, THF; (v) TsCl, Et_3N, CH_2Cl_2.

Scheme 32. Initial Approach to Chlorovinylaziridine **7a**

The reaction of acetonide **163a** with *N*-bromosuccinimide in wet DMSO gave bromohydrin **165**. Upon treatment with sodium azide in DMSO, **165** underwent ring closure to afford β-epoxide **166**, which was opened immediately by azide to furnish the azido alcohol **167**. Protection with methylsulfonyl chloride followed by LAH reduction of the resulting mesylate produced aziridine **168**, which was subsequently transformed to tosyl aziridine **7a** with TsCl. The corresponding bromoaziridine **169** was also attained by the same procedure. However, the low overall yield associated with this process

promoted us to seek a short and efficient synthetic route. A literature search revealed several procedures of olefin aziridination.[65]

Owing to its simplicity, Evans' procedure[65a] was first attempted. Accordingly, diene **163a** was treated with iodonium ylide **170**[66] in the presence of a catalytic amount of $Cu(acac)_2$. Indeed, chloroaziridine **168** was generated in 20% yield based on iodonium ylide **170**. With bromodiene **163b**, aziridine **169** was formed in 59% yield. This reactivity difference could be accounted for by the fact that the nucleophilicity and reactivity of the C3-C4 olefin in **163b** is greater than that of **163a**. In contrast to bromo-epoxide **164**, the debromination of **169** under the normal conditions (Bu_3SnH, AIBN, toluene, reflux) proceeded smoothly to afford aziridine **7b** in 59% yield. It was later found that the yield could be greatly improved (to 78 %) by the use of THF as the solvent instead of toluene.



163a X=Cl
163b X=Br

7a X=Cl
169 X=Br

7b

(i) PhI=NTs (**170**), $Cu(acac)_2$, CH_3CN, 59%; (ii) Bu_3SnH, AIBN, THF, 78%.

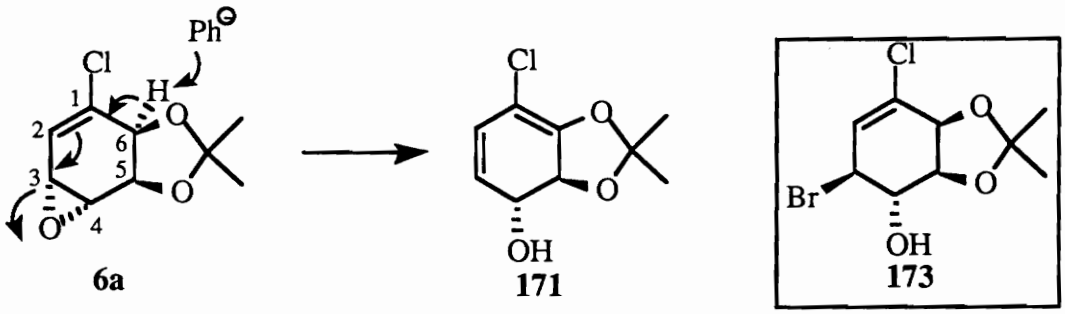
Scheme 33. Short Synthesis of Vinylaziridines **7a** and **7b**

With an efficient access to vinyloxiranes and vinylaziridines secured, their ring opening with organometallic reagents was investigated. Three nucleophiles were employed in this study: methyl, cyclohexylmethyl and phenyl. Commercially available phenyllithium and methylmagnesium bromide, as well as freshly prepared cyclohexyl-

methyllithium[67] and cyclohexylmethylmagnesium bromide were either used directly or converted into different cuprate reagents.

2.2. Reactions of Chlorovinyloxirane 6a

Initial attempts at ring opening with phenyllithium met with little success. Treatment of **6a** with phenyllithium at -78 °C gave diene **171** in 55% yield (Table 9, entry 1). No nucleophilic opening product was detected. The formation of **171** could be explained by the deprotonation at C-6 followed by ring opening, as shown in Scheme 34. The aromatic products derived from the extensive elimination of **6a** constituted the remaining mass balance.

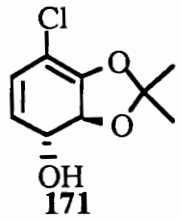
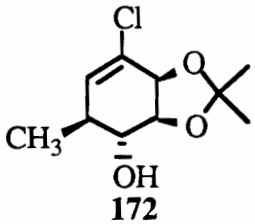
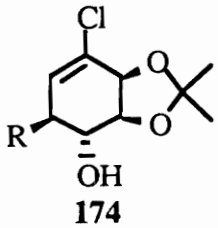
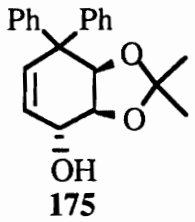
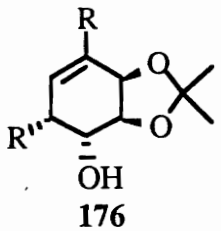


Scheme 34

Reaction of methylmagnesium bromide in the presence of 10% CuI gave normal S_N2 product **172** in 58% yield (entry 2). A byproduct of this reaction was bromohydrin **173** from epoxide opening by the bromide ion of the Grignard reagent.

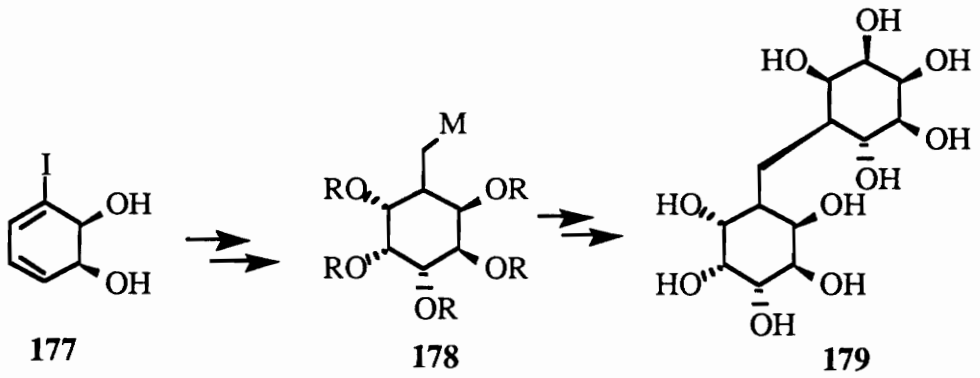
Similarly, CuI-catalyzed cyclohexylmethylmagnesium bromide addition gave S_N2 product **174** in 39% yield in addition to bromohydrin **173**. The lower yield in the latter case may be due to the increased size of the cyclohexylmethyl group which commends more steric hindrance than methyl. Thus the competitive epoxide opening by bromide becomes predominant. This reaction serves as a suitable model study for the synthesis

Table 9. Reactions of Chlorovinyloxirane **6a**

Entry	Nucleophile/Conditions[a]	Product (s) (yield, %)
1	PhLi/THF/-78 °C	 (55) **171**
2	CH_3MgBr/10% CuI THF/ -78 °C to -40 °C	 (58) **172**
3	RMgBr/10% CuI THF/-78 °C to 0 °C	 (39) **174**
4	Ph_2CuLi/Et_2O/0 °C	 (8) **175**
5	R_2CuLi/Et_2O THF/-78 °C to -40 °C	 (14) + **174** (4) **176**

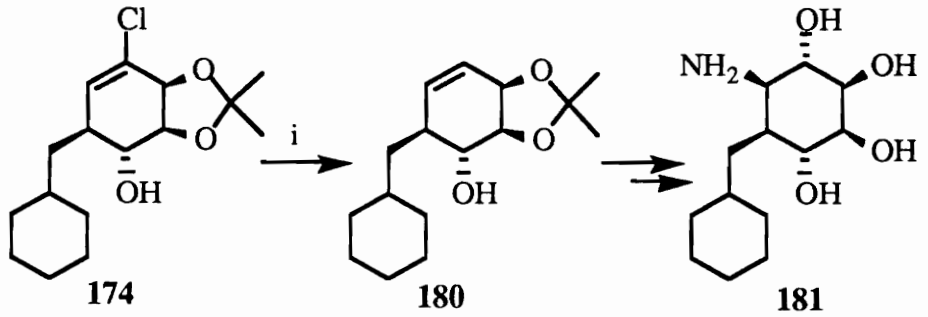
a, R=cyclohexylmethyl

of C-disaccharides and cyclitol conjugates. An effort is underway to replace the cyclohexylmethyl moiety with **178** derived from iodo diol **177**[68] (Scheme 35). In an attempt to functionalize the C1-C2 olefin, **174** was reductively dechlorinated with sodium in refluxing absolute ethanol,[69] giving rise in 73% yield to **180**, which has been converted to **181**,[70] Scheme **36**. The use of Bu_3SnH (AIBN, toluene, refluxing) for the dehalogenation only led to the recovery of most of the starting material accompanied by some decomposition products.



177 **178** **179**

Scheme 35



174 **180** **181**

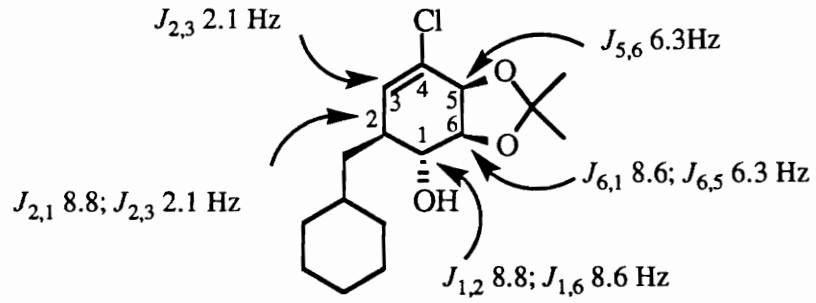
(i) Na, C_2H_5OH, refulx, 73%.

Scheme 36. Reductive Dechlorination

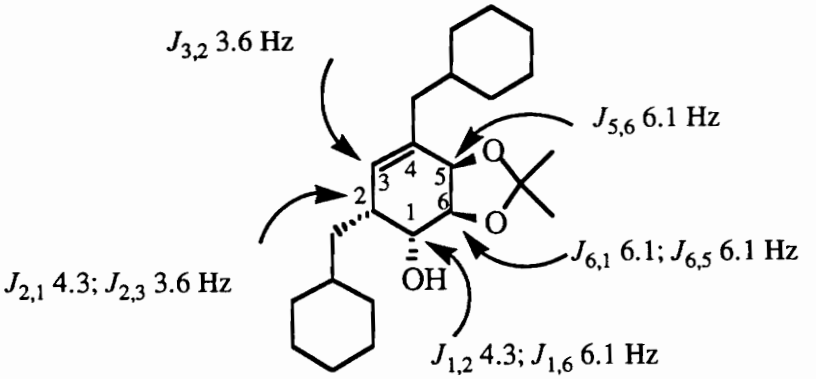
As with phenyllithium, the phenyl Gilman reagent Ph_2CuLi, prepared *in situ* from phenyllithium and CuI,[71] also afforded predominantly aromatic products. However, the isolation of the minor product **175** was noteworthy. Considering the steric crowding on C-4, the formation of this compound is rather unexpected. Likewise, the use of lithium dicyclohexylmethyl cuprate also produced significant amounts of aromatic products. In addition, two minor products, **174** and **176**, were isolated in 14% and 4% yield (entry 5), respectively.

The stereochemistry of **176** was established based on the extensive decoupling experiments and by comparison with similar system, like **174**. The key coupling constants thus observed are illustrated in Figure 1. For the sake of comparison, those of **174** are also listed. A small coupling constant $J_{1,2}$ (4.3 Hz) is indicative of the *cis*-relationship between H-1 and H-2 in **176**, while the *trans*-diaxial relationship between H-1 and H-2 in **174** is confirmed by a large coupling constant ($J_{1,2}$ 8.8 Hz).

A plausible mechanism is proposed to rationalize the formation of **175** and **176**, as delineated in Scheme 37. Initial addition of the nucleophile to C-1 in a *syn* S_N2' manner gives **182**. This is a reactive species because there is a strong driving force for the elimination of chloride, diminishing the steric crowding at C-4. There are two options for this to occur. The intermediate alkoxide **182** could undergo ring closure through the intramolecular allylic attack by the alkoxy anion to form vinyloxirane **183** (path a), which is then converted to a 4,4-disubstituted adduct, **175**, by a second *syn* S_N2' addition. Alternatively, nucleophilic displacement at C-2 in *anti* S_N2' fashion will afford a 2,4-disubstituted product (path b), **176**. It should be pointed out that the first *syn* S_N2' addition is unexpected, because all the known vinyloxiranes derived from cyclohexane systems have been found to undergo highly stereoselective *anti* S_N2' addition by organocuprates.[6b] This abnormal result could be rationalized in terms of the blocking



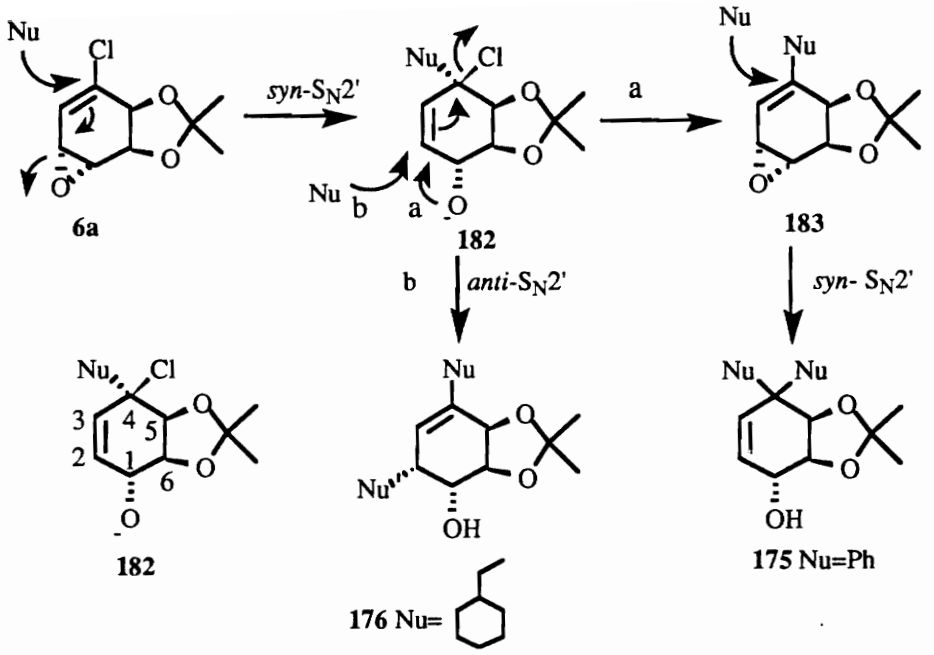
174



176

Figure 1. Key Coupling Constants of **174** and **176**.

effect exerted by the acetonide moiety, which directs the nucleophile to attack form the less hindered α-face. This rationale is also supported by the results of reactions of vinyloxirane **6b** and vinylaziridine **7b** with organocuprates, which will be discussed in the next section.



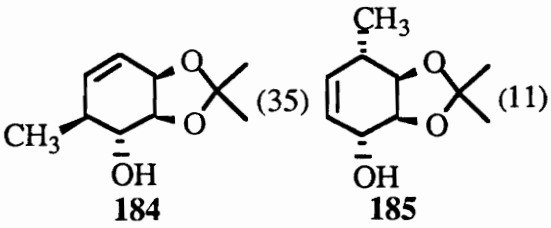
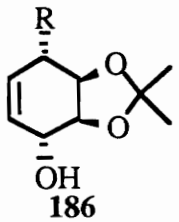
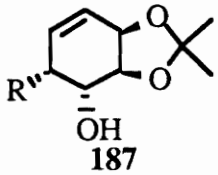
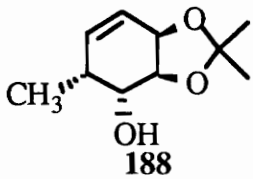
Scheme 37. Proposed Mechanism for the Formation of **175** and **176**

2.3. Reactions of Vinyloxirane 6b

CuI-catalyzed addition of methylmagnesium bromide to vinyloxirane **6b** proceeded smoothly to yield *syn* S_N2 (**184**) and S_N2' (**185**) products in 35% and 11% yields (Table 10, entry 1), respectively. In contrast, under similar conditions, the reaction with a cyclohexylmethyl Grignard reagent showed high regioselectivity and produced exclusively *syn* S_N2' product **186** in 83% yield (entry 2). It is rationalized that the efficient shielding of the β-face by the endo methyl group of the acetonide is responsible for the *syn* S_N2' addition.

Treatment of **6b** with lithium dicyclohexylmethylcuprate at -78 °C and then -40 °C led to ring-opened products **186** and **187** (entry 3). Alcohol **186** was previously isolated from the Grignard reaction (entry 2). However, the formation of **187**, in which nucleophile and hydroxyl group have a *cis*-relationship, was quite unusual. The

Table 10. Reactions of Vinyloxirane **6b**

Entry	Nucleophile/conditions[a]	Product(s) (yield, %)
1	CH_3MgBr/10% CuI THF/Et_2O/-40 °C	 (35) (11) **184** **185**
2	RMgBr/10% CuI THF/-78 °C to -10 °C	 (83) **186**
3	R_2CuLi/Et_2O/THF -78 °C to -40 °C	 (37) + **186** (5) **187**
4	Me_2CuLi/Et_2O THF/-78 °C	 (30) **188**

a, R=cyclohexylmethyl.

stereochemistry of regioisomers **186** and **187** could easily be assigned on the basis of coupling constants (Figure 2) and NOE experiments. The *trans* arrangement between H-1 and H-2 in **187** is evidenced by a small coupling constant ($J_{1,2}$ 4.4 Hz). In **186**, irradiation of H-4 effected NOE enhancement of H-1 and H-5, with no enhancement at H-6. This observation confirms that H-1 and H-4 have a *cis* relationship and both are positioned on the β-face.

The formation of **187** presumably proceeded through a single electron transfer (SET) or S_N1-type mechanism. At this point, it is still difficult to differentiate these mechanistic possibilities before additional work is carried out. Similarly, with the methyl Gilman reagent, **188** was obtained in 30% yield (entry 5).

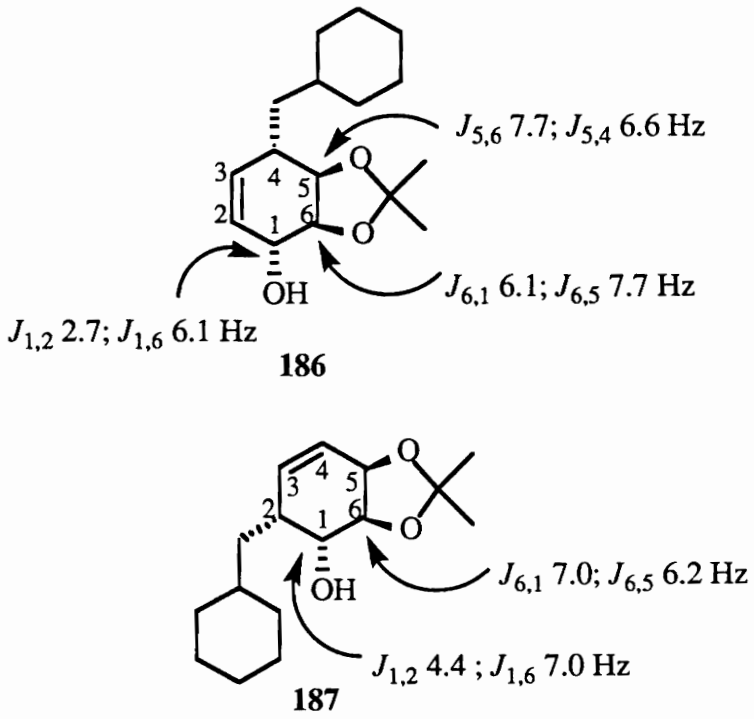
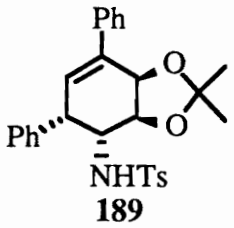
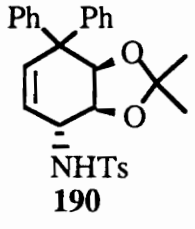
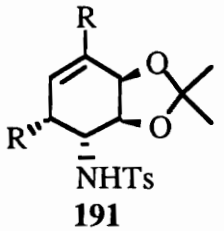
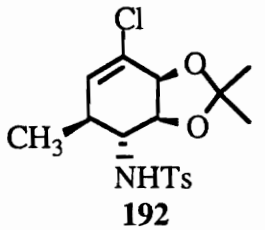


Figure 2. Key Coupling Constants of **186** and **187**

2.4. Reactions of Chlorovinylaziridine 7a

This series was examined in parallel with vinyloxiranes **6a** and **6b**. Moreover, in order to probe the influence of the nature of the metal on the ring opening of vinylaziridines and to further define the suitable conditions for pancratistatin synthesis, zinc and cadmium reagents, in addition to cuprates, were examined as well. To this end, aziridine **7a** was first reacted with lithium diphenylcuprate in the presence of 1 equivalent. of $BF_3{\cdot}Et_2O$ initially at -78 °C, then the reaction was warmed to room

Table 11. Reactions of Chlorovinylaziridine **7a**

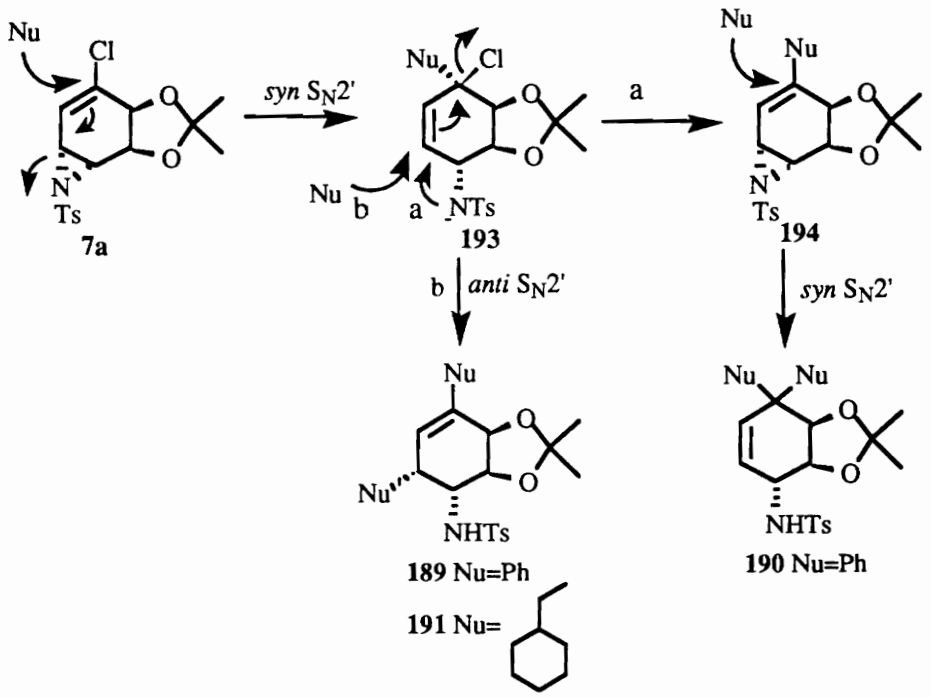
Entry	Nucleophile/conditions[a]	Product(s) (yield, %)
1	Ph_2CuLi/THF -78 °C to rt	 **189** (57)
2	Ph_2Cd/THF/50 °C	 **190** (50)
3	Ph_2Zn/THF Et_2O/rt	**189** + **190** 3 : 1 (36)
4	R_2CuLi/Et_2O THF/-78 °C to -40 °C	 **191** (89)
5	MeMgBr/CuI THF/Et_2O/-45 °C	 **192** (53)

a, R=cyclohexylmethyl

temperature. Thus, compound **189** containing the 1,3-diphenyl substitution (Table 11, entry 1) was formed in 57% yield. In contrast, diphenylcadmium,[72] prepared *in situ* from phenyllithium and cadmium chloride, afforded only 4,4-diphenyl adduct **190** (entry 2).

Furthermore, with diphenyl zinc,[73] a 3:1 mixture of **189** and **190** was afforded in 36% yield. This mixture proved to be inseparable by column chromatography.

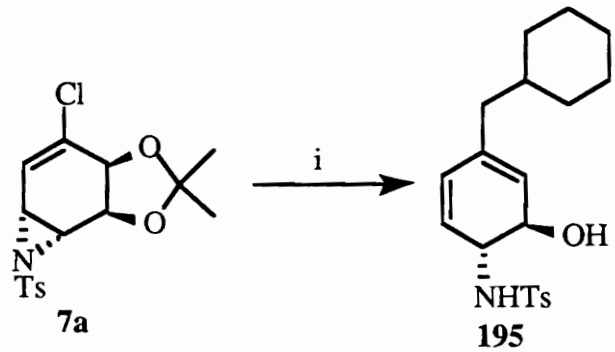
Moreover, the reactions of **7a** with methyl and cyclohexylmethyl Grignard reagents and with cyclohexylmethyl Gilman reagent were also examined. When **7a** was treated with lithium dicyclohexylmethylcuprate at -78 °C, and the reaction allowed to warm to -40 °C, compound **191** containing 1,3-dicyclohexylmethyl substitution was isolated in 89% yield. This result is in sharp contrast with the observation from the corresponding experiments with chlorovinyloxirane **6a**, which gave a mixture of ring opened products in a low combined yield. The formation of **189, 190** and **191** probably could be accounted for by a mechanism similar to that advanced for **175** and **176**, Scheme 38.



Scheme 38. Proposed Mechanism for the Formation of **189, 190** and **191**

The lack of reactivity of **7a** toward cyclohexylmethylmagnesium bromide/CuI was unexpected. Treatment of **7a** with excess cyclohexylmethylmagnesium bromide in

the presence of 10% CuI at room temperature resulted only in the recovery of the starting material. Prolonged reaction time in refluxing THF produced only a low yield (< 5%) of **195**. Under the same conditions, chlorovinyloxirane **6a** smoothly underwent ring opening, leading to a *syn* S_N2' product **186** in good yield. Interestingly, CuI-catalyzed methyl Grignard addition at -45 °C gave S_N2 product **192** in 53% yield. This disparity may lie in the nature of methylmagnesium bromide, which is less sterically demanding than the corresponding cyclohexylmethyl reagent.



7a **195**

(i) cyclohexylmethylmagnesium bromide, 10% CuI.

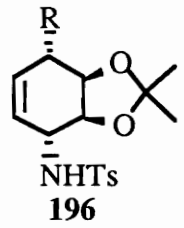
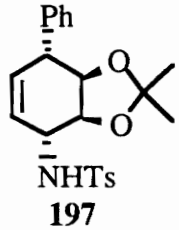
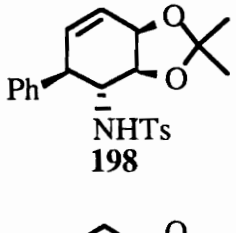
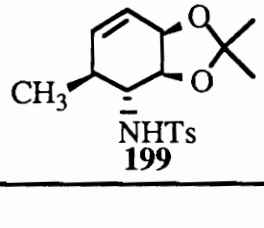
Scheme 39

2.5. Reactions of Vinyaziridine 7b

When exposed to lithium dicyclohexylmethylcuprate warming up from -78 °C -40 °C, vinylaziridine **7b** underwent ring opening exclusively in a *syn* S_N2' sense, and **196** was produced in 76% yield (Table 12, entry 1). This behavior is strikingly different from that of the corresponding vinyloxirane **6b**, which, under similar conditions, underwent extensive elimination.

In contrast with the high regioselectivity shown by the cyclohexylmethyl Grignard reagent, the phenyl Gilman reagent afforded *syn* S_N2' product **197** in 36% yield, along with S_N2 product **198** in 6% yield (entry 2). Tosylamide **198** represented the

Table 12. Reactions of Vinylaziridine **7b**

Entry	Nucleophile/conditions[a]	Product (s) (yield, %)
1	R_2CuLi/THF -78 °C to -40 °C	 (76) **196**
2	$Ph_2CuLi/BF_3{\cdot}Et_2O$ THF/-78 °C to RT	 (38) + **198** (6) **197**
3	$Ph_2Cu(CN)Li/BF_3{\cdot}Et_2O$ THF/-78 °C to RT	 (70) **198**
4	MeMgBr/CuI THF/Et_2O/-45 °C	 (29) **199**

a, R=cyclohexylmethyl.

desired model compound for eventual synthesis of pancratistatin and has the crucial *trans* substitution pattern on C-1 and C-2. The stereochemical elucidation of **198** was made based on NMR analysis. The ^1H NMR spectrum displayed two large coupling constants $J_{1,2}$ (8.4 Hz) and $J_{1,6}$ (8.9 Hz) (Figure 3).

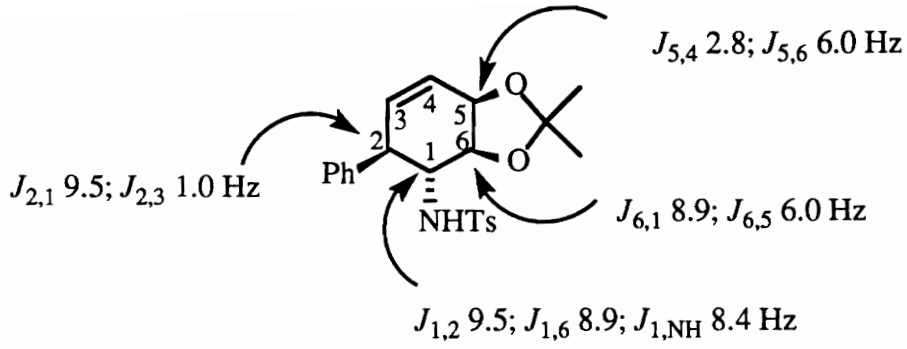


Figure 3. Key Coupling Constants of **198**

These values are consistent with *trans* relationship of H-1 with both H-2 and H-6. In an attempt to improve the yield of **198**, other conditions were also investigated. Lipshutz[74] has found that higher-order cyanocuprates, $R_2Cu(CN)Li_2$, are particularly efficient for effecting epoxide ring opening under milder conditions. To this end, the reaction of **7b** with $Ph_2Cu(CN)Li$, prepared from phenyllithium and copper(I) cyanide, was examined. Surprisingly, this reagent showed excellent regioselectivity to afford **198** in 70% yield (entry 3). These conditions were later adapted for the total synthesis of pancratistatin. When this reaction was kept at -78 °C until starting **7b** was consumed, **198** was isolated in 23% yield. Finally, methylmagnesium bromide addition in the presence of 10% CuI gave the normal S_N2 product **199** in 29 % yield (entry 4).

In summary, several reactivity trends of homochiral vinyloxiranes and vinylaziridines could be derived from the results described above. (a) In general, vinyloxiranes appear to be more reactive than the corresponding vinylaziridines without activation by Lewis acid. This can be clearly seen by the comparison of the results from the Grignard reactions. Vinyloxiranes reacted smoothly with the Grignard reagents,

giving rise to the S_N2 or S_N2' product in moderate to good yields, whereas vinylaziridines showed poor reactivity under the same conditions. (b) Vinyloxiranes were quite sensitive to cuprate reagents. Because of extensive elimination, the ring opened products were formed in low yields. In contrast, under the same conditions, vinylaziridines afforded ring opening products in moderate to good yields. (c) The efficient shielding of the β-face by the acetonide moiety precludes the preferred *anti* S_N2' fashion exhibited by organocuprates. Both the Gilman and the Grignard reagents preferentially produced *syn* S_N2' products, except methylmagnesium bromide. (d) In the case of vinylaziridine **7b,** the Lipshutz reagent, $Ph_2Cu(CN)Li_2$, demonstrated higher regioselectivity than the Gilman reagent, giving rise exclusively to S_N2 product in good yield. This reaction serves as a remarkably useful model study for the pancratistatin synthesis. A thorough study would be required to ascertain the mechanism of the formation of several abnormal compounds isolated from some of the aforementioned reactions. Nevertheless, a logical foundation has been developed to proceed to the application of this new method and to exploit it in the synthesis of pancratistatin. The pursuit of this goal will be detailed in the next section.

III. DISCUSSION

3. Total Synthesis of (+)-Pancratistatin

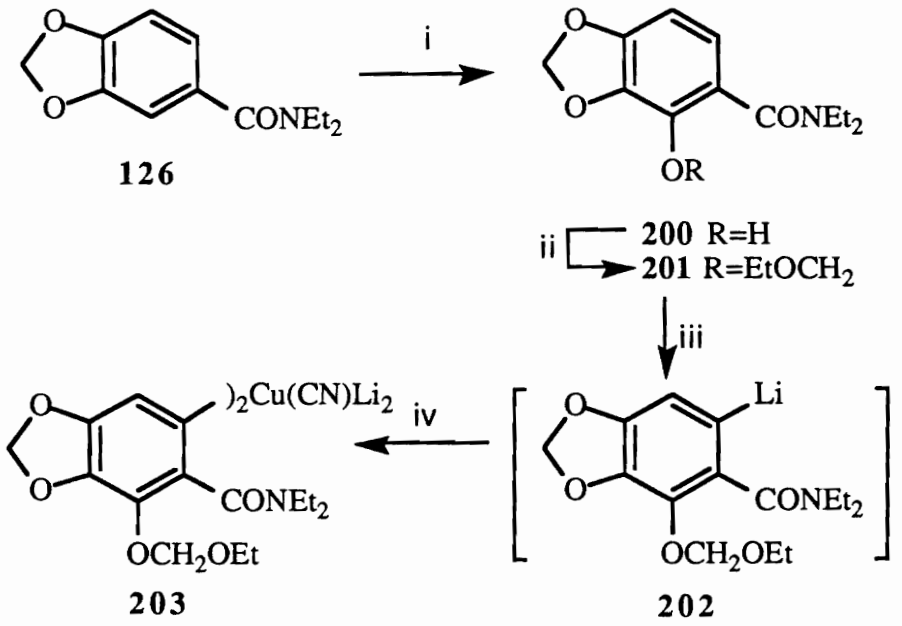
With the completion of the methodology study, effort was directed toward the total synthesis of pancratistatin. As described in section III.1, a method to affect the regioselective S_N2 opening of aziridine **7** with organometallic reagents was required for our approach. It was found that only the reaction of aziridine **7a** with higher-order cyanocuprates generated exclusively the desired S_N2 opening product **198**. With aziridine **7a**, readily available in gram quantities using a three step sequence, the first objective toward the synthesis of pancratistatin became the generation of an appropriate higher-order cuprate from lithiated species **161**.

3.1. First Approach

At the outset of our studies, *N*, *N*-diethylamide **126** (Scheme 40) was chosen as a substrate for the cuprate addition since the *ortho*-metalation of *N*, *N*-diethylamides is easy and the lithiated species of this type have been used by Heathcock in his model studies.[58]

First, amide **201** was synthesized from **126** by means of a known *ortho*-lithiation procedure.[63] Subjecting **126** to 1.1 equivalents of *s*-BuLi in the presence of 1.1 equivalents of *N*, *N*, *N'*, *N'*-tetramethylethylenediamine (TMEDA) at -78 °C gave the *ortho*-lithiated derivative, which was quenched with trimethylborate, followed by acidic hydrolysis and hydrogen peroxide oxidation to produce phenol **200**. Protection with chloromethyl ethyl ether in the presence of a phase-transfer catalyst[75] provided amide **201**. Similarly, **201** was lithiated to **202**, a highly unstable species, which was converted *in situ* into higher-order cuprate by adopting Lipshutz's protocol.[74] Unlike lower-order cuprates (Gilman reagent, R_2CuLi), which can be generated from organolithium and copper(I)

halide at low temperature (-78°C or lower), the formation of higher-order cyanocuprate requires higher temperature. Thus **202** was treated with 0.5 equivalent of copper(I) cyanide initially at -78 °C; then the reaction mixture was warmed slowly to -20 °C. During this process, CuCN dissolved gradually and a deep purple homogeneous solution of **203** resulted.

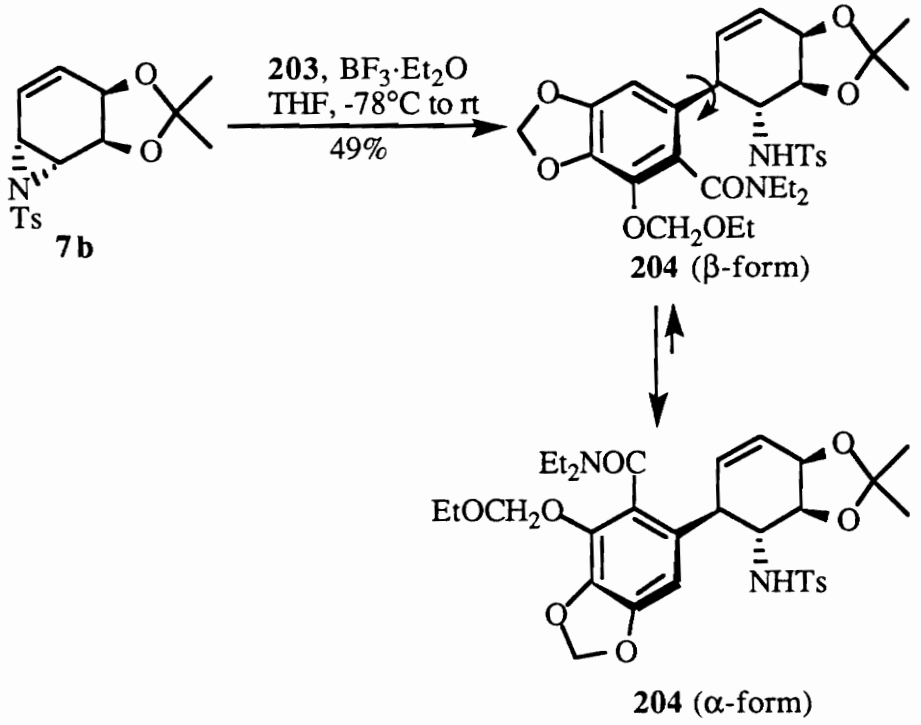


(i) (a) *s*-BuLi, TMEDA, THF, -78 °C; (b) $B(OMe)_3$; (c) AcOH, H_2O_2: (ii) $EtOCH_2Cl$, NaOH, Adogen,CH_2Cl_2, H_2O; (iii) *s*-BuLi, TMEDA, THF, -78°C; (iv) CuCN, -78 °C to -20 °C.

Scheme 40. Preparation of Higher-Order Cuprate

With the higher-order cyanocuprate obtained, as evidenced by the complete disappearance of CuCN, the crucial ring opening of vinylaziridine **7b** was examined. The conditions developed during the methodology study were first tested. To that end aziridine **7b** was exposed to 1.7 equivalents of cuprate **203** in the presence of boron trifluoride etherate in THF at -78 °C, Scheme 41. The stirred reaction mixture was warmed slowly to room temperature. As expected, this reaction produced the desired S_N2 opening product

204, a pivotal cyclization precursor, in 49% yield. The moderate yield of **204** was due to difficulties in the purification, also partially attributed to atropisomerism. The coupling reaction initially provided **204** exclusively as one atropisomer, as demonstrated by TLC



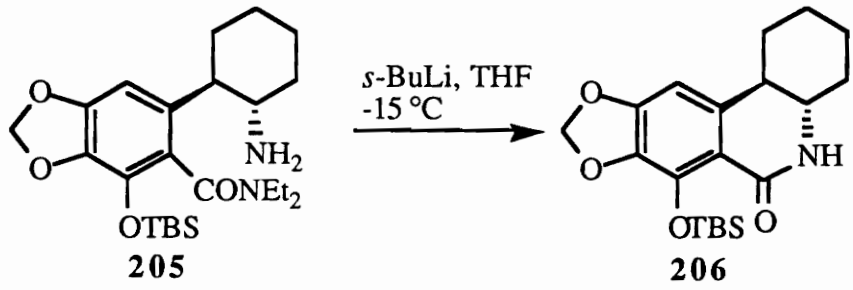
Scheme 41. Coupling of Aziridine and Higher-order Cyanocuprate

and ^1H NMR analysis. Upon chromatographic purification, it equilibrated to the more stable and less polar α-form, which was only partially separable from starting amide **201**. In fact, this conversion, although sluggish, was also observed when **204** was kept at 0 °C. The configurational assignment was based on the ^1H NMR analysis of the two atropisomers. In the ^1H NMR spectrum of the α-form, the resonance due to NH group of tosylamide appears at 7.67 ppm, as opposed to the 5.50 ppm of the β-form. It is reasoned that this downfield shift stems from the hydrogen bonding between the NH group and

carbonyl group of the benzamide, which is impossible in the β-form, due to the large separation of two groups.

With the successful coupling secured, we anticipated that our synthetic effort would be close to an end, since what remained to complete the synthesis of target compound seemed to be only simple functional group transformations, which involved detosylation to cyclize the lactam ring, functionalization of C2-C3 olefin to introduce the *trans*-diol and the final removal of protecting groups.

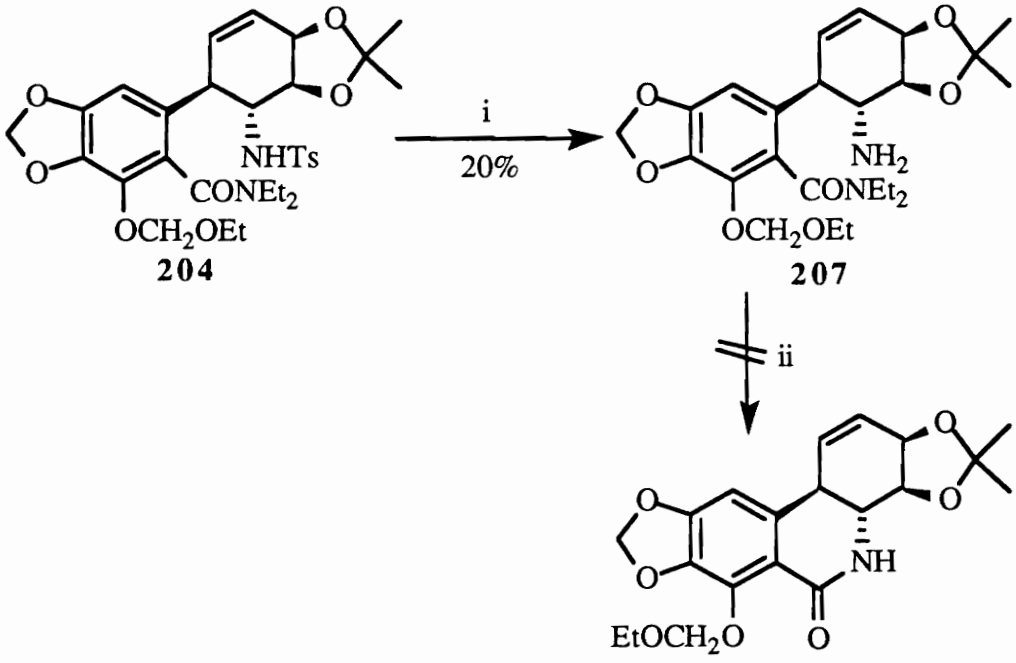
As originally planned, the next objective was the construction of the lactam B-ring. Since initial attempts to achieve direct cyclization of **204** by use of base (NaH, BuLi) met with failure, it was essential to transform either tosylamide into an amine or benzamide to a more reactive carboxylic acid derivative, such as an ester. At this point, Heathcock's



Scheme 42. Heathcock's Cyclization Strategy

cyclization strategy reported in the model study[58] appeared attractive. Upon treatment with *s*-BuLi at -15 °C, compound **205** underwent smooth cyclization to give lactam **206**, Scheme 42. To evaluate this method the tosylamide in **204** had to be reduced to an amine. The tosyl group is an effective protecting group for amines because it can survive various basic and acidic conditions. However, this stability often causes problems in deprotection. Among the various methods of sulfonamide cleavage[76] that have appeared in the literature, reductive methods were the most widely used, although a general one applicable to all tosylamides is still lacking. To this end we decided to first assess the use of

sodium/ammonia[76c] and sodium/naphthalene.[76d] Disappointingly, tosylamide **204**, when treated with sodium/ammonia at -78 °C, underwent extensive decomposition, resulting in a complex mixture. With excess sodium/naphthalene at -78 °C, only epimerization at C-1 was observed. Finally, the adoption of buffered sodium amalgam procedure developed by Trost[76f] afforded desired amine **207**, albeit in low yield.

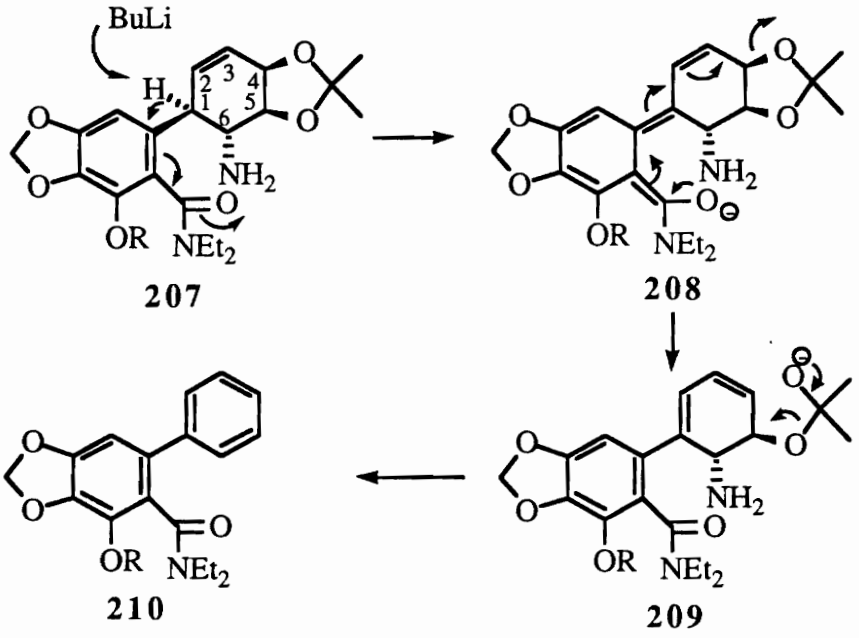


(i) 6% Na(Hg), Na_2HPO_4, CH_3OH; (ii) *s*-BuLi, THF.

Scheme 43. Attempted Lactam Formation

With sufficient **207** in hand, the stage was set to attempt the final lactam ring closure. Accordingly, amine **207** was treated with 1.1 equivalents of *s*-BuLi in THF at -15 °C. However, no reaction occurred under these conditions. The reaction mixture was then slowly warmed to room temperature; still no reaction was observed. Prolonged reaction time only led to a product derived form the epimerization at C-1. It was reasoned that this was caused by the greatly enhanced acidity of the C-1 proton, which was

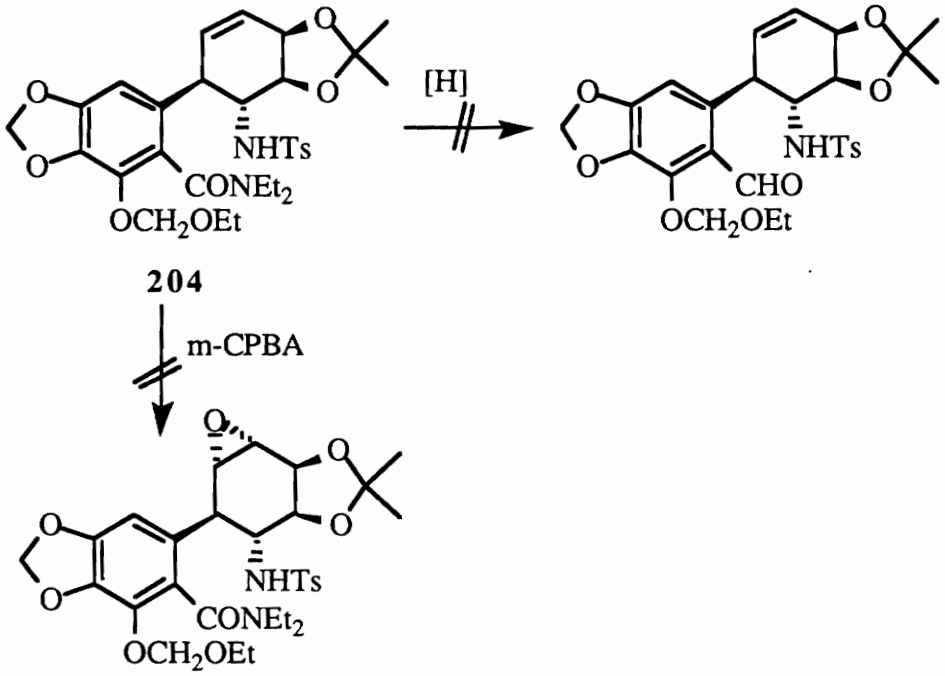
inductively and electronically affected by aromatic ring as well as double bond. Moreover, this proton is a part of a deconjugated sorbyl amide unit. The formation of the expended dienolate would then lead to the elimination of C-4 alkoxide, collapse of the acetonide and eventual formation of **210**, Scheme 44.



Scheme 44

This unexpected failure forced us to consider the manipulation of the benzamide functionality. It was rationalized that if the benzamide could be converted into carboxylic acid, ring closure to tosyllactam should be feasible by activating acid group with DCC[77] or *N*-methylmorpholine/EtOCOCl.[78] Mild hydrolysis of **204** under Gassman's conditions[79] was explored first, since the base liability of C-ring was of some concern to us. Unfortunately, treatment of **204** with KO^{t}Bu and water in THF at reflux only caused the elimination of alkaoxides on the C-ring, and no trace of desired acid was detected. A stepwise route was then pursued, which involved the reduction of amide to aldehyde followed by the oxidation to acid. For this purpose, four reducing reagents, LAH,[80] DIBAL-BuLi,[81] SMEAH (sodium bis(methoxyethoxy)aluminiumhydride),[80,82] super-

hydride[83] were examined. Surprisingly, none of them were successful in reducing diethylamide at room temperature, or in refluxing THF, leading to only complete recovery of most of the starting material. Presumably, the lack of the reactivity of the diethylamide moiety is due to the efficient blocking by two bulky *ortho*-substituents. This postulation was supported by later experiments.



Scheme 45. Attempted Reduction and Epoxidation

Even more puzzling was the unexpected difficulty encountered in the functionalization of the C2-C3 olefin. Treatment of **204** with excess m-CPBA at room temperature resulted only in recovery of starting material. Under Kishi's conditions[84] (m-CPBA, 4,4'-thiobis-(6-*t*-butyl-3-methylphenol), 1,2-dichloroethane, 90 °C), **204** underwent decomposition to give a complex mixture. The unreactivity of the olefin is probably due to a combination of two factors. First, the α-face of the olefin is blocked by the diethylamide group and the β-face by the acetonide moiety. Second, the olefin is inductively affected by the flanking allylic ether and aromatic moiety.

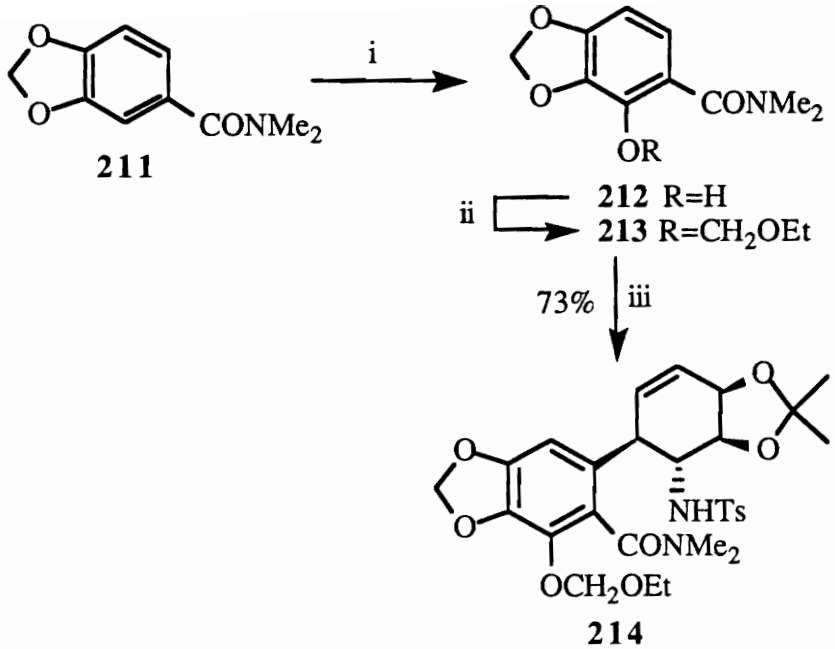
All these quite discouraging results to manipulate **204** suggest that we have reached a temporary dead end. In order to salvage this approach, the functional groups introduced in the coupled product **204** must be redesigned, since they are too resistant to further transformations. Failed epoxidation of **204** and cyclization of **207** indicated that the use of the *N*, *N*-diethylamide must be addressed in order to accomplish ring closure.

3.2. Modified Approach

Previous work reported by Brown demonstrated that a *N*, *N*-dimethylamide is much easier to reduce than a *N*, *N*-diethylamide.[85] Accordingly, the coupled adduct **212** was prepared from aziridine **7b** and amide **211** in a fashion similar to that of **204** except that the ortho-lithiation was performed at -90 °C, because the lithiated **211** underwent dimerization above that temperature. This time, the coupling reaction produced **212** in 73% yield (Scheme 46).

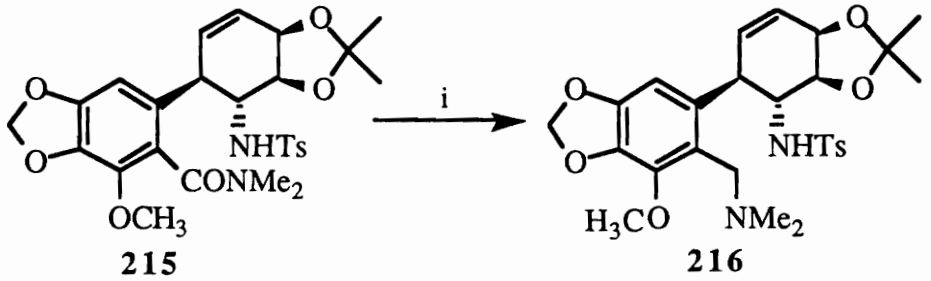
With **214** in hand, the reduction of the *N*, *N*-dimethylamide moiety to an aldehyde was examined. As in the case of **204**, four potential reducing reagents (LAH, DIBAL-BuLi, SMEAH and super-hydride) were evaluated. Once again, all of these reagents failed to reduce **214** under various conditions. In an attempt to clarify the effect of the protection group of the phenol on the reactivity of the benzamide, the coupled product **215** was prepared by use of the same procedure as described above (Scheme 47).

Attempted reduction finally produced a positive result. LAH reduction of **215** proceeded smoothly to give dimethylamine **216.** This observation revealed that the nature of the protecting group on the phenol influences the reactivity of the neighboring benzamide moiety. Therefore, it was decided to explore the reduction of the *N*, *N*-dimethyl amide moiety on free phenol form of **214**. However, selective cleavage of the ethoxymethyl group in the presence of the acetonide was a challenge, since both groups



(i) (a) s-BuLi, TMEDA, THF, -90 °C; (b) $B(OMe)_3$; (c) AcOH, H_2O_2;
(ii) NaH, $EtOCH_2Cl$, THF, 81%; (iii) (a) s-BuLi, TMEDA, THF, -90 °C;
(b) CuCN, -90 °C to -20 °C; (c) aziridine **7b**; (d) $BF_3{\cdot}Et_2O$, -78 °C to rt.

Scheme 46. Coupling of Aziridine and Higher-Order Cuprate

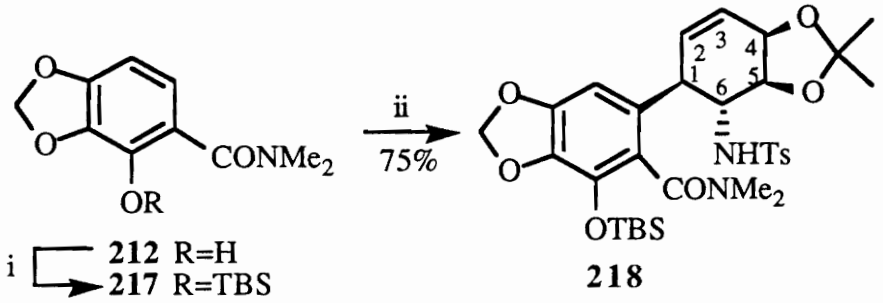


(i) LAH, THF, rt.

Scheme 47. LAH Reduction of Dimethylamide

were quite acid sensitive. Several attempts under various conditions only produced complex mixtures derived from the loss of either protecting group. We abandoned the use of **214** and the focus was then directed toward the preparation of the coupled product **218** with TBS protected phenol moiety. It was assumed that TBS group could be safely removed in the presence of the acetonide group. Toward this end, the coupled product

218 was generated from aziridine **7b** and amide **217** in the manner similar to that of **214**, as shown in scheme 48. Protection of phenol **212** with TBSCl delivered **217**, which was lithiated at -90 °C and converted to a higher-order cuprate by treatment with CuCN. Then, aziridine **7b** was reacted with cyanocuprate in the presence of $BF_3{\cdot}Et_2O$ to furnish **218** in 75% yield.



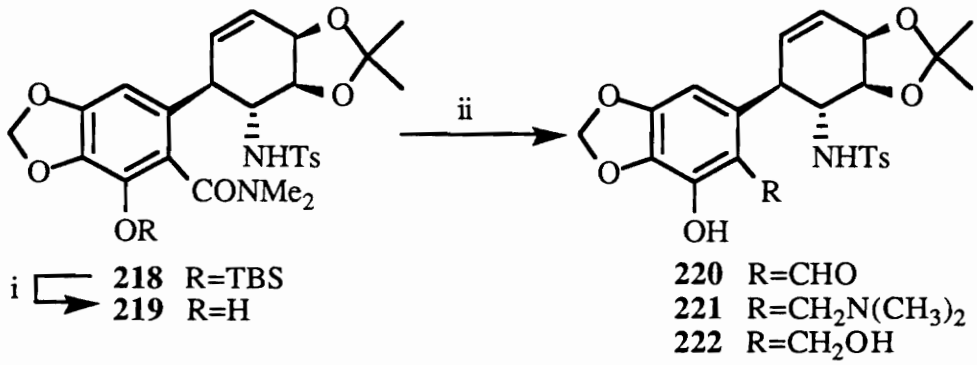
(i) TBSCl, imidazole, CH_2Cl_2, 82%; (ii) (a) *s*-BuLi, TMEDA, THF, -90 °C; (b) CuCN, -90 °C to -20 °C then to -78 °C; (c) azridine **7b**; (d) $BF_3{\cdot}Et_2O$, -78 °C to rt.

Scheme 48. Coupling of Aziridine and Higher-Order Cuprate

As in the case of **214**, atropisomerism was again observed with **218**. The initially formed β-atropisomer equilibrated to the more stable α-form. The structural assignment of **218** was based on detailed NMR analysis. The large coupling constant of $J_{5,6}$ (10.1 Hz) and the lack of coupling between H-1 and H-6 confirmed the essential *trans*-diaxial relationship between H-5 and H-6.

With sufficient **218** in hand, reduction of the amide moiety was examined. Upon treatment with TBAF, **218** was desilylated readily to give phenol **219** in 80% yield. The next objective was to affect the transformation of the *N*, *N*-dimethylamide moiety to the aldehyde. Once again, initial effort met with failure, and the use of super-hydride led only to the recovery of the starting material even in THF at reflux. However, SMEAH reduction

of **219** proceeded very smoothly at room temperature, giving a mixture of desired aldehyde **220** and two unwanted over reduction products, dimethylamine **221** and benzyl alcohol **222** (Scheme 49). At lower temperature (-45 °C), the formation of **221** and **222** could be suppressed to some degree, but could not be entirely avoided. Later, it was found that this problem could be solved by simply modifying SMEAH with 1 equivalent of morpholine.[86]

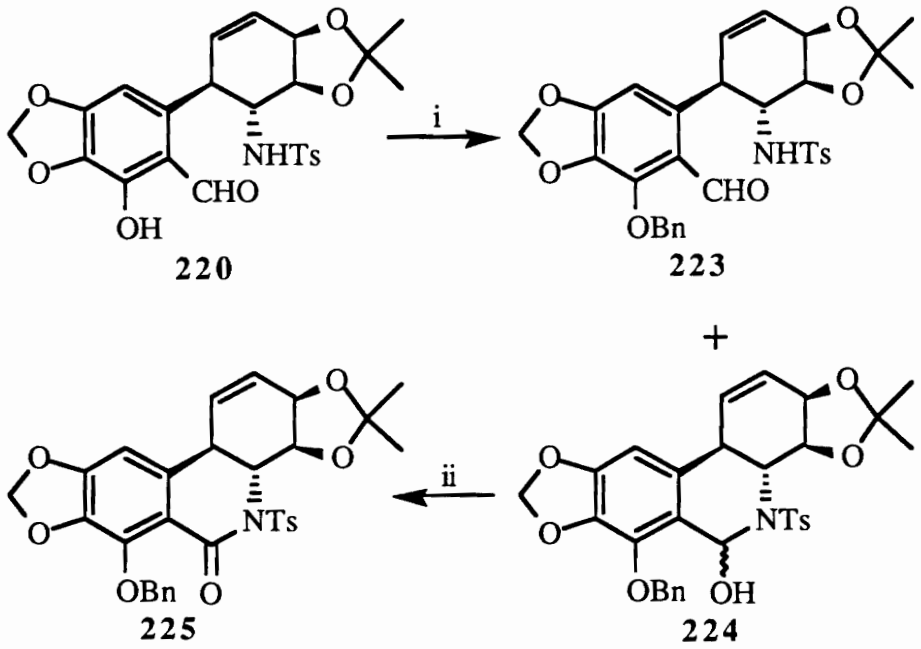


(i) TBAF, THF, 73%; (ii) Morpholine-SMEAH.

Scheme 49. Reduction of *N,N*-Dimethylamide

The use of excess morpholine-SMEAH at -45 °C afforded exclusively aldehyde **220**, along with trace amount of **221.** However, the frustrating aspect of this work was our inability to drive this reaction to completion under these conditions even with a large excess of the reducing reagent. At this point, we just recycled the starting material and prepared enough aldehyde to press on to test the feasibility of the ring closure. In order to protect the phenol against the oxidant to be used in the oxidation of aldehyde, **220** was treated with benzyl bromide and potassium carbonate in DMF to give a mixture of **223** and unexpected hemiaminal **224** in a 2:1 ratio, as judged by the integration of the ^{1}H NMR spectrum (Scheme 50). We rationalized that aldehyde **223** and hemiaminal **224** should be interconvertiable under acidic or basic conditions. Moreover, direct conversion of **224** to

lactam **225** should be feasible, using Jones reagent, as previously described.[87] Fortunately, careful treatment of **224** with Jones reagent in acetone at 0 °C produced crucial pentacyclic compound **225**, albeit in low yield.



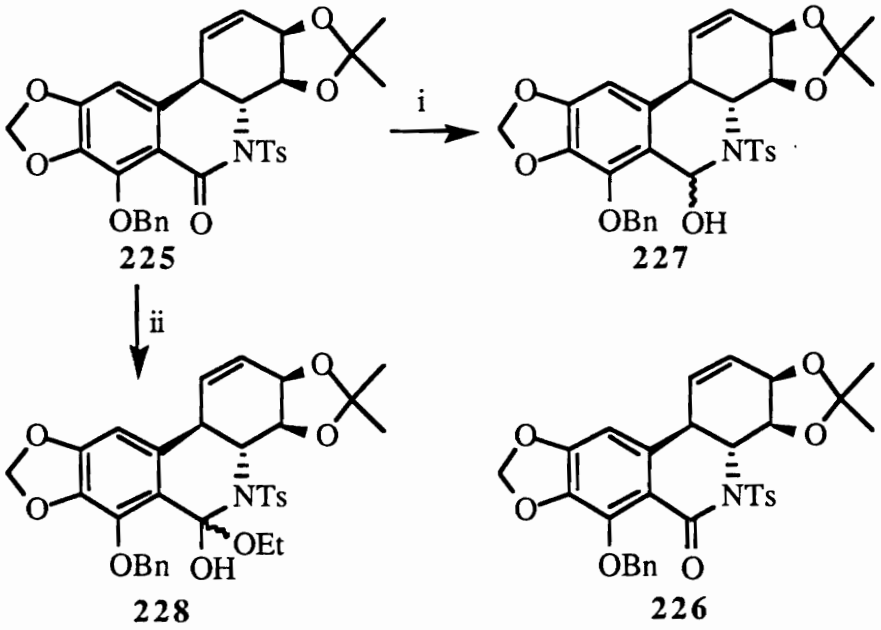
(i) BnBr, K_2CO_3, DMF; (ii) Jones reagent, acetone, 0 °C.

Scheme 50. Successful Ring Closure with Jones Reagent

With the successful arrival at the lactam stage, focus was then shifted to the final transformations required to complete the synthesis. Detosylation became the immediate objective. Although the tosyl group has caused a lot of trouble, previous work demonstrated that the cleavage of tosyl group of tosylamide or tosyllactam could be reliably achieved by using sodium naphthalenide.[88] However, subjecting **225** to excess sodium naphthalene in DME at -75 °C clearly produced hemiaminal **227** rather than the expected lactam **226**, which was derived from the reduction of carbonyl group of the tosyllactam. Interestingly, hemiaminal **227** is more polar than **224**, as evidenced by TLC, probably

due to the different stereochemistry at hemiaminal carbon. With the Trost's conditions[76f] (Na/Hg, Na_2HPO_4, CH_3OH), the same result was obtained. It appears that the carbonyl group of the lactam is much more reactive than the tosylamide. Presumably, this tendency arises from the relief of the ring strain by rehybridization of the sp^2 carbon. The use of SmI_2 resulted only in inseparable mixtures of unknown compounds.

Examination of the literature suggested that alcoholysis could be an alternative solution to this problem. Interestingly, heating of **225** with freshly prepared potassium



(i) Na/naphthalene, DME, -75 °C; or Na/Hg, Na_2HPO_4, CH_3OH;
(ii) KOC_2H_5, C_2H_5OH.

Scheme 51. Attempted Detosylation

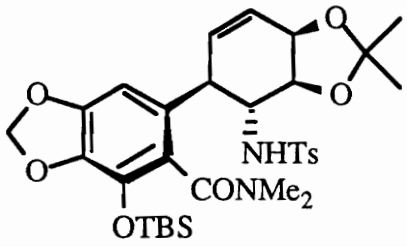
ethoxide in absolute ethanol produced only **228**, which collapsed to **225** upon working up of reaction, as indicated by TLC and NMR analysis. This result also suggested that the lactam carbonyl carbon prefers sp^3 hybridization to achieve more flexibility in pentacyclic

system. At this point, it became apparent that the tosyl group must be removed prior to ring closure of the lactam.

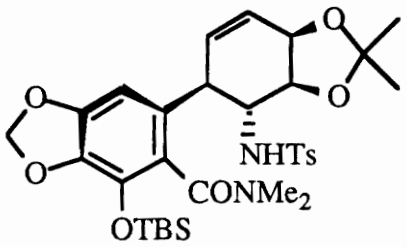
3.3. Final Transformations

After the abortive attempts at detosylation, we returned to the coupled product **218**. Once again, all efforts to effect detosylation of **218** failed. Of the three reducing reagents (Na/naphthalene, SmI_2, Na/Hg) assayed, none of them gave the desired amine; instead, only an inseparable mixture of products was obtained in each case.

It is known that electron-withdrawing groups on aromatic sulfonamides decrease the reduction potential.[89] The precedent established by Sharpless[90] also suggested that acylation of tosylamide **218** would facilitate the reductive removal of the tosyl group. Thus a two-step sequence was then pursued to convert the tosylamide group to a more liable group, specifically, *N*-tosyl-*N*-*t*-BOC amide, since the latter could be removed under mild acidic conditions. Accordingly, **218** was deprotonated with *s*-BuLi at 0 °C, and the resulting anion was quenched with excess di-*tert*-butyl dicarbonate to give a mixture of three atropisomers of *t*-BOC tosylamide **229**, as evidenced by TLC and ^{1}H NMR analysis (Scheme 52). Among these, one α-atropisomer could be rendered pure by column chromatography, but it equilibrated slowly to the β-isomer during the removal of solvent. In contrast, the two β-isomers were inseparable. It is interesting to note that the two atropisomers of **218** exhibited different reactivity toward acylation under the conditions described above, with the α-isomer (**218b**) being extremely sluggish. Presumably, the robustness toward acylation shown by the α-isomer stems from steric congestion. Inspection of models reveals that the tosylamide group is efficiently blocked by the bulky dimethylamide moiety.



218a (β)

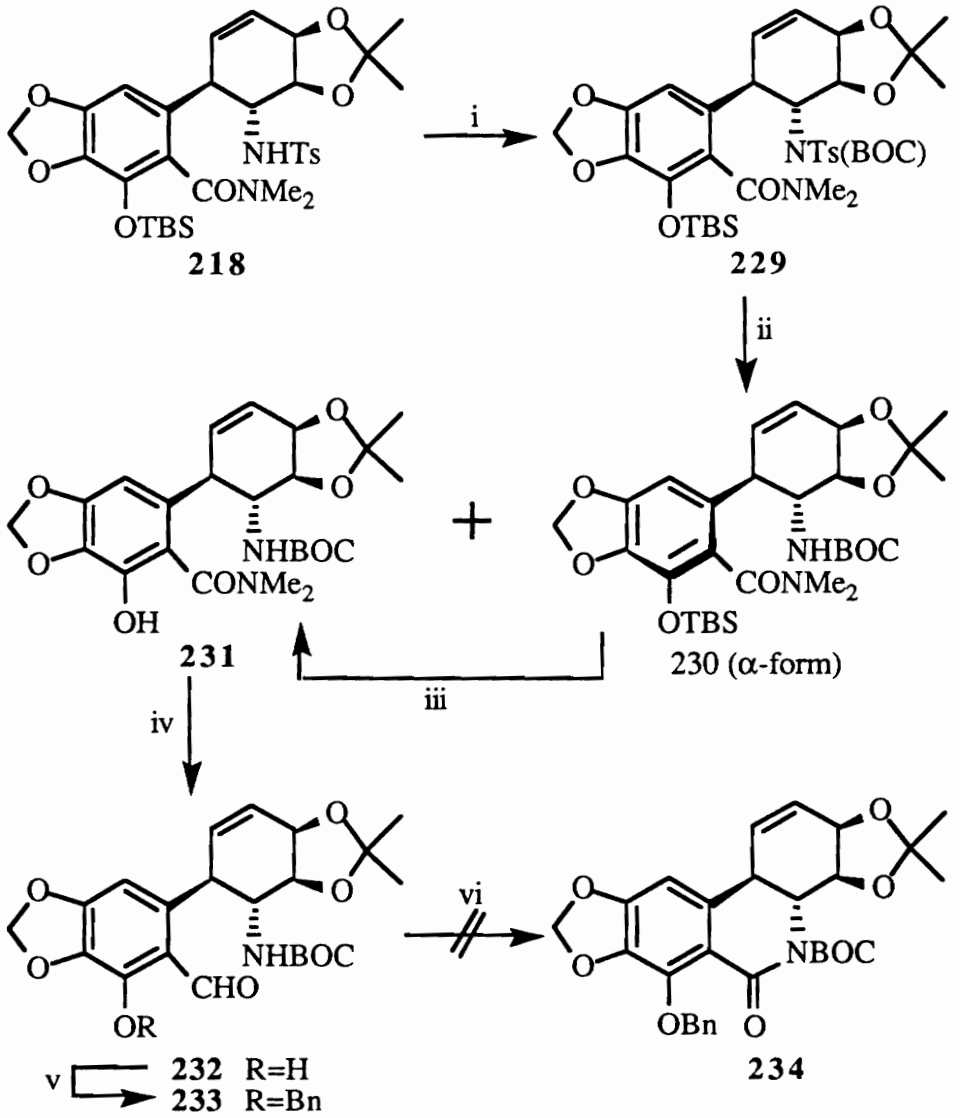


218b (α)

With **229** obtained, conditions for the reductive detosylation were then examined. This time, the mild Na/anthracene reagent,[91] which could be conveniently prepared from sodium and anthracene in DME, was employed first. Toward this end, a stirred solution of **229** in DME was treated with Na/anthracene at -78 °C until the blue color persisted for 15 min, affording a mixture of two detosylated products, **230** and **231**, in 82% yield, the latter being desired for dimethylamide reduction (Scheme 52). The ratio of these two compounds depended on the ratio between α and β-atropisomers of **229**, under these conditions, the α-atropisomer underwent simultaneous detosylation and unexpected desilylation to give **241** while the β-isomer underwent only detosylation to afford **230**. The reactivity difference between the two atropisomers must have originated in the steric factors, as in the case of acylation of **218**. Because the conversion of the β-isomer to the α-isomer was tremendously slow at -75 °C, addition of excess reducing agent could not accomplish the desilylation of **230**, which had to be isolated and reacted with TBAF in THF to give **231** in 93% yield.

Encouraged by the successful removal of the tosyl group, we embarked on the next objective, the cyclization to the pentacyclic system, by following reaction sequences which led to **225**. Morpholine-SMEAH reduction of **231** at -45 °C proceeded smoothly to give aldehyde **232**. Again, problems were encountered here, and we were not able to drive this reaction to completion. Under the optimum conditions, **232** was formed in 67% yield

accompanied by **231**. Upon treatment with benzyl bromide and potassium carbonate in DMF, **232** was protected to benzyl ether **233** in 83% yield.



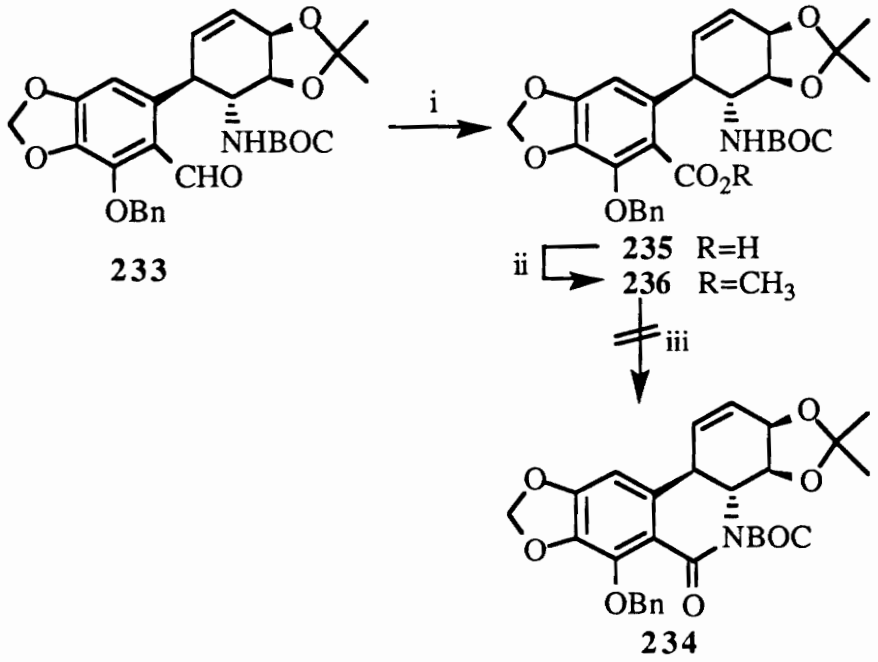
(i) s-BuLi, THF; then $(BOC)_2O$; (ii) sodium anthracenide, DME, -78 C; (iii) TBAF, THF; (iv) Morpholine-SMEAH, -45 °C; (v) BnBr, K_2CO_3, DMF; (vi) Jones reagent, acetone, 0 °C.

Scheme 52. Attempted Lactam Formation

Unlike the benzylation of **220**, the hemiaminal was not formed this time, probably because of the conformational constraint of the bulky BOC group. Cyclization was then attempted by means of the Jones reagent which proved effective in the case of **223**. However, addition of 3.5 equivalents of Jones reagent to a stirred solution of **233** in acetone at 0 °C generated a complex mixture. The isolation and ^{1}H NMR analysis of products did not reveal any trace amount of desired lactam **234**. Instead, the A-ring appeared to have undergone oxidation under these conditions, as evidenced by the disappearance of the resonance attributed to the aldehyde in the ^{1}H NMR spectrum. It is not clear why **223** and **233** exhibited markedly different behavior toward the Jones oxidation and what really happened in the case of **233**.

This unexpected and disappointing result forced us to devise an alternative strategy to affect the desired cyclization. It was rationalized that this goal probably could be realized by conversion of the aldehyde to the ester **236**, followed by the deprotonation of BOC-amide with base, as shown in Scheme 53. The execution of this sequence first required a mild oxidation method to accommodate the liable functionalities on C-ring, namely the olefin and the acetonide. Known for its mildness, Ag_2O[92] seemed to be a suitable choice. However, Ag_2O oxidation of **233** turned out to be very sluggish. Prolonged reaction time gave only a very low yield of acid, which suffered further decomposition. A literature search suggested that oxidation with sodium chlorite under Pinnick's conditions[93] could provide the desired aldehyde; this has proved to be a satisfactory reagent for sensitive aldehydes.[94] To our surprise, subjecting **233** to a solution of $NaClO_2/K_2HPO_4$/2-methyl-2-butene in *t*-BuOH and H_2O furnished acid **235** in almost quantitative yield, Scheme 53. Because of its instability, the crude acid **235** was directly esterified with diazomethane without purification to give methyl ester **236** in 98% overall yield from **233**. With sufficient quantities of **236** in hand, a variety of attempts were directed toward the cyclization. Unfortunately, all attempts to affect the cyclization under basic conditions were

were unsuccessful. Under forcing conditions, treatment of **236** with a series of bases (*s*-BuLi, $NaN(TMS)_2$, K_2CO_3) only resulted in the elimination on the C-ring under the forcing conditions. At room temperature, no reaction was observed, presumably

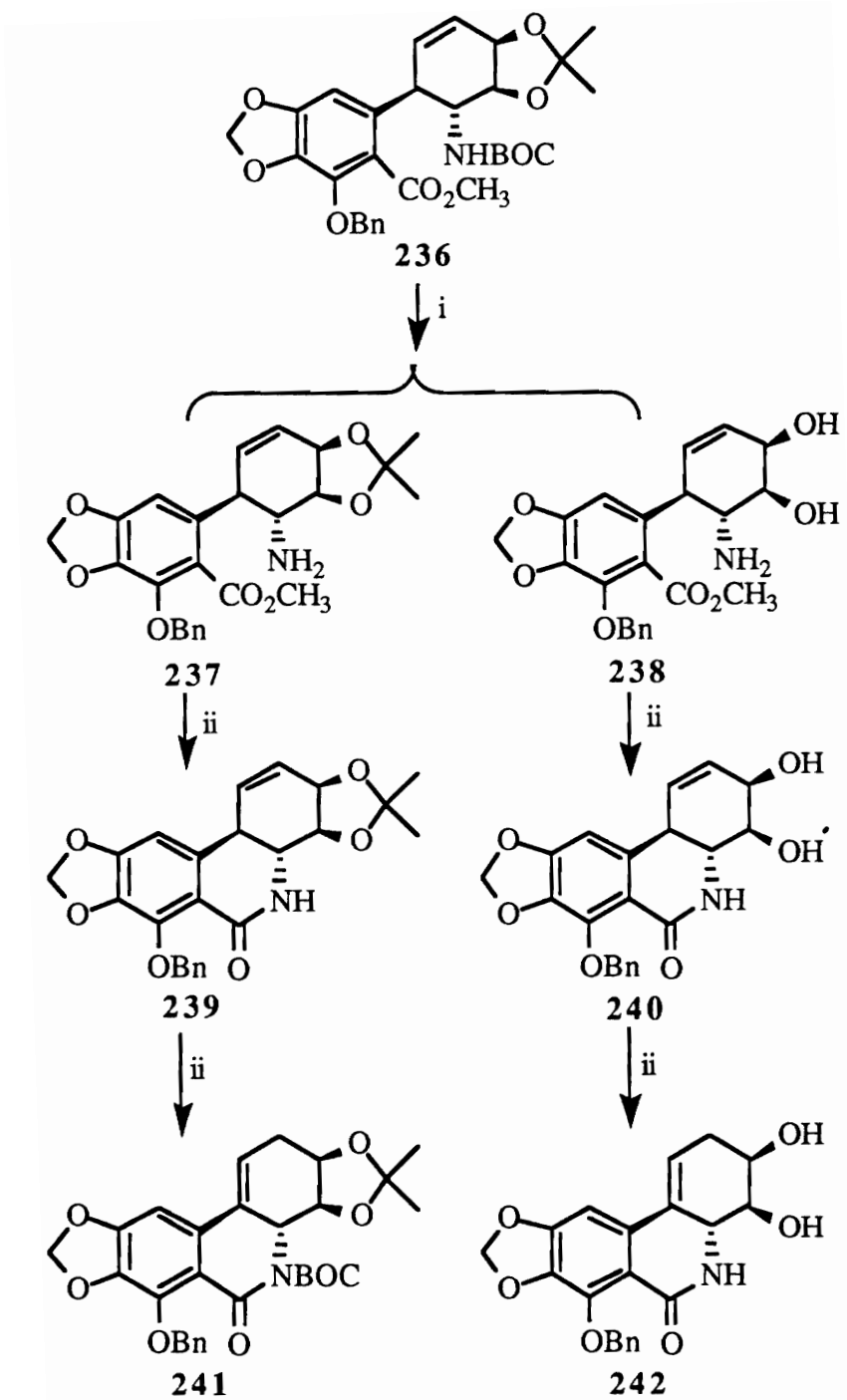


(i) $NaClO_2$, K_2HPO_4, 2-methyl-2-butene, *t*-BuOH, H_2O; (ii) CH_2N_2; (iii) $NaN(TMS)_2$; or *s*-BuLi; or K_2CO_3; (iv) m-CPBA.

Scheme 53. Attempted Lactam Formation and Epoxidation

because of the considerable steric interaction between the bulky BOC group and the methyl ester, which precluded the attack of the nitrogen anion on the ester group.

A stepwise route was then considered, which involved removal of the BOC group, followed by treatment of the resulting amine with potassium carbonate in methanol to accomplish cyclization, as precedented by literature.[52] However, selective removal of the BOC group in the presence of the acetonide did not appear feasible, since the employment of traditional methods (CF_3CO_2H, CH_2Cl_2, 0 °C) for the cleavage of BOC would also remove the acetonide. At this point, loss of the acetonide was not our major concern,



(i) CF_3CO_2H, CH_2Cl_2, 0 °C; (ii) K_2CO_3, CH_3OH.

Scheme 54. Attempted Cyclization

because the diol could be reprotected readily after ring closure. Accordingly, the methyl ester **236** was treated with trifluoroacetic acid in methylene chloride at 0 °C. Careful monitoring of reaction progress with TLC and ^{1}H NMR indicated that cleavage of BOC was always accompanied, as anticipated, by the loss of acetonide, leading to a mixture of **237** and **238**, the ratio varying with reaction time (Scheme 54). After 2h, this reaction gave exclusively **238**. The crude mixture was then treated with K_2CO_3 in methanol at rt, and the cyclization of **237** and **238** proceeded smoothly to give lactams **239** and **240**. Unfortunately, these lactams underwent further isomerization by olefin migration to the benzylic position, giving **241** and **242**. All attempts to avoid the unwanted isomerization were unsuccessful.

These results suggested that the olefin of C-ring should be functionalized prior to the ring closure. We postulated that this could be realized by the epoxidation followed by the ring opening of epoxide. However, the epoxidation of the olefin turned out to be unexpectedly problematic again. The initial attempts with m-CPBA at room temperature or Kishi's condition failed to give desired epoxide, but rather furnished a complex mixture. Subjecting **236** to excess dimethyldioxirane caused only the removal of the acetonide. Strangely enough, treatment of **236** with trifluoroperacetic acid, prepared from UHP (urea-hydrogen peroxide complex) and trifluoroacetic anhydride,[95] gave clearly one product derived from the oxidation of methylenedioxy group. Moreover, reaction of *tert*-butyl hydroperoxide catalyzed by molybenum hexacarbonl in refluxing benzene[96] also gave a complex mixture.

It was reasoned that the unreactivity of double bond toward epoxidation probably arose, as in the case of **204**, from a combination of steric hindrance caused by the BOC and methyl ester groups, and the inductive effect from the flanking allylic ethyl ether and aromatic moiety.

Following the repeated failure of the epoxidation from the α-face of **236**, our efforts were redirected toward the elaboration of the β-epoxide by the directed epoxidation under the Sharpless' conditions[97] (*t*-BuOOH, $VO(acac)_2$). Methyl ester **236** was heated in a HOAc/THF/H_2O (2:1:1) mixture at 60 °C without incident to provide diol **243** in 73% yield (Scheme 54). As expected, subsequent treatment of **243** with excess *t*-BuOOH in the presence of a catalytic amount of vanadyl acetylaceonate in benzene at 60 °C afforded the desired β-epoxide **244**. A frustrating aspect of this transformation was the competitive cleavage of BOC group, giving a polar complex compound. In order to avoid the considerable decomposition of the β-epoxide, the reaction had to be stopped before the starting material was consumed. In this way, a best yield of 52% was obtained based on recovered diol **243**, which was readily recycled.

With epoxide **244** in hand, the next step was to affect the regioselective ring opening of epoxide to set the *trans*-diol functionality on C-2 and C-3. An inspection of a model of **244** showed that only C-3 should be available for *trans*-diaxial opening by nucleophile attack to give ring opened product **245**. This theoretical mode of opening, if mirrored in practice, would give the correct stereochemistry of C-2 and C-3 required for pancratistatin, as illustrated in Figure 4. In the case of α-epoxide **246** , nucleophile (H_2O) would attack C-2 to achieve the *trans*-diaxal opening, giving also the *trans* diol product with correct stereochemistry. Unfortunately, **246** could not be formed by the epoxidation of **236**.

To explore this possibility, we subjected epoxide **244** to the conditions (H_2O, BzONa (cat.), 100 °C) adapted from *chiro*-inositol synthesis.[61] Amazingly, this operation led to a series of rather unexpected but fortuitous events, as indicated by careful TLC and ^1H NMR analysis.

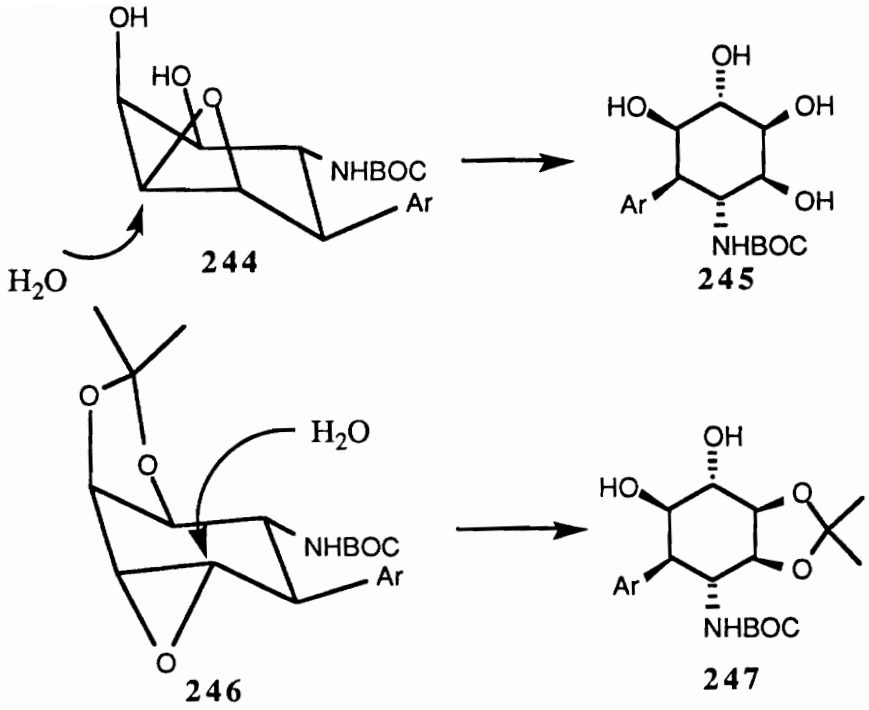
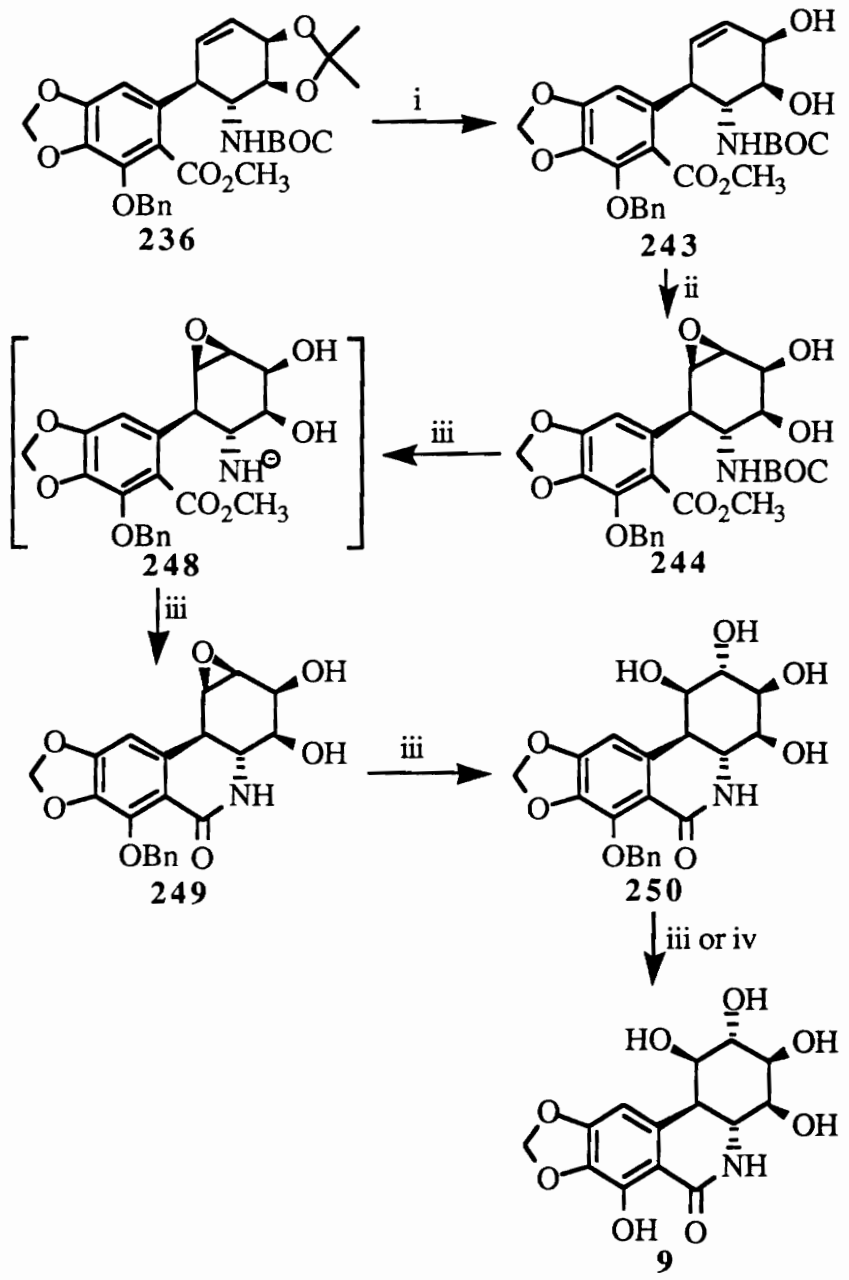


Figure 4. *Trans* Diaxial Opening of Epoxides

When epoxide **244** was heated in boiling H_2O in the presence of a catalytic amount of sodium benzoate, cleavage of the BOC group, instead of opening of the epoxide, occurred first under the thermal condition to give intermediate **248**, which cyclized immediately to lactam **249**, as evidenced by the disappearance of peaks attributed to BOC and methyl ester in the ^1H NMR (Scheme 55). Although the thermal cleavage of BOC has been reported,[98] to our knowledge, this is the first example to affect BOC cleavage in boiling H_2O. After 2h, almost all starting material **244** was consumed. It was at this time that **249** started to undergo sluggish epoxide ring opening with desired regioselectivity to generate benzyl protected pancratistatin **250**, whose structure was identified by NMR analysis. The ^1H NMR spectrum clearly showed four doublets (4.77, 5.36, 5.10, 5.01 ppm), being assigned to four hydroxyl groups. In addition, six signals attributed to six

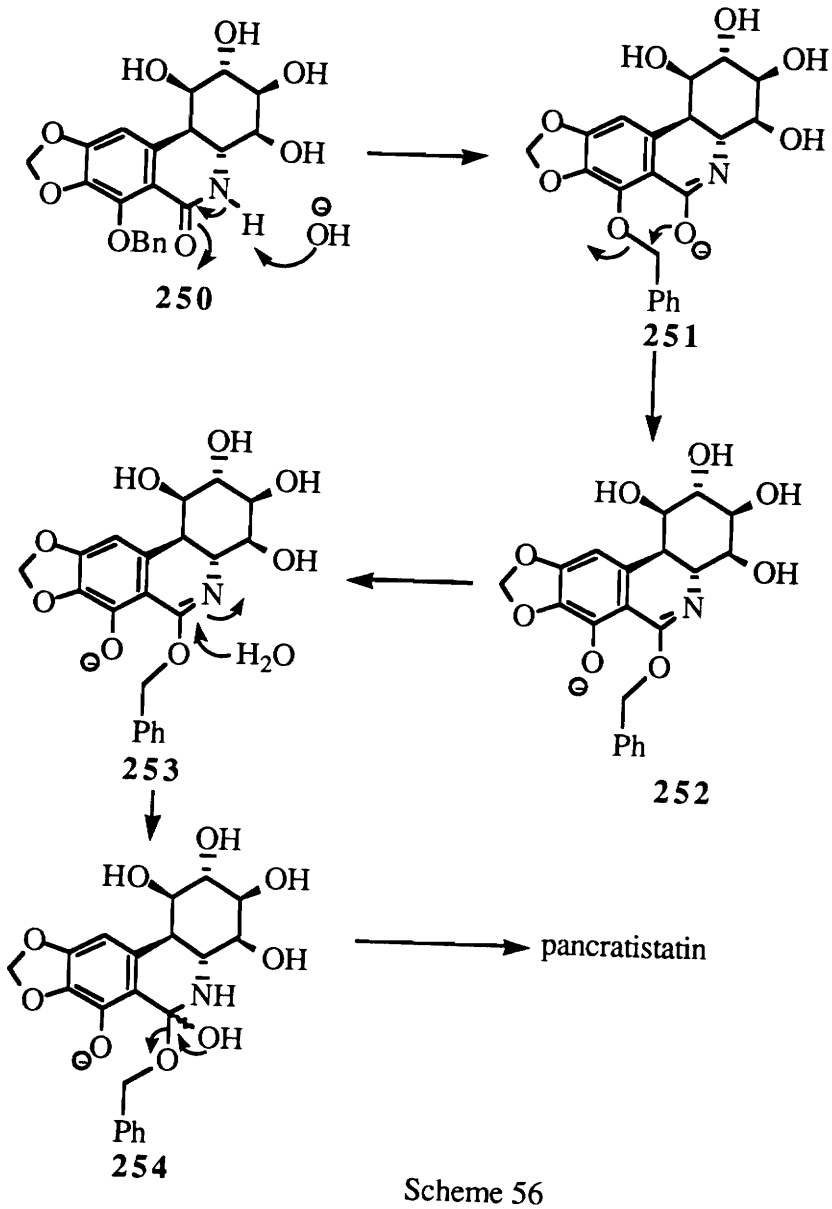


(i) HOAc-THF-H_2O (2:1:1), 60 °C, 73%; (ii) t-BuOOH, $VO(acac)_2$, benzene, 60 °C, 52%; (iii) H_2O, BzONa(cat.), 100 °C, 51%; (iv) H_2, $Pd(OH)_2/C$, EtOAc.

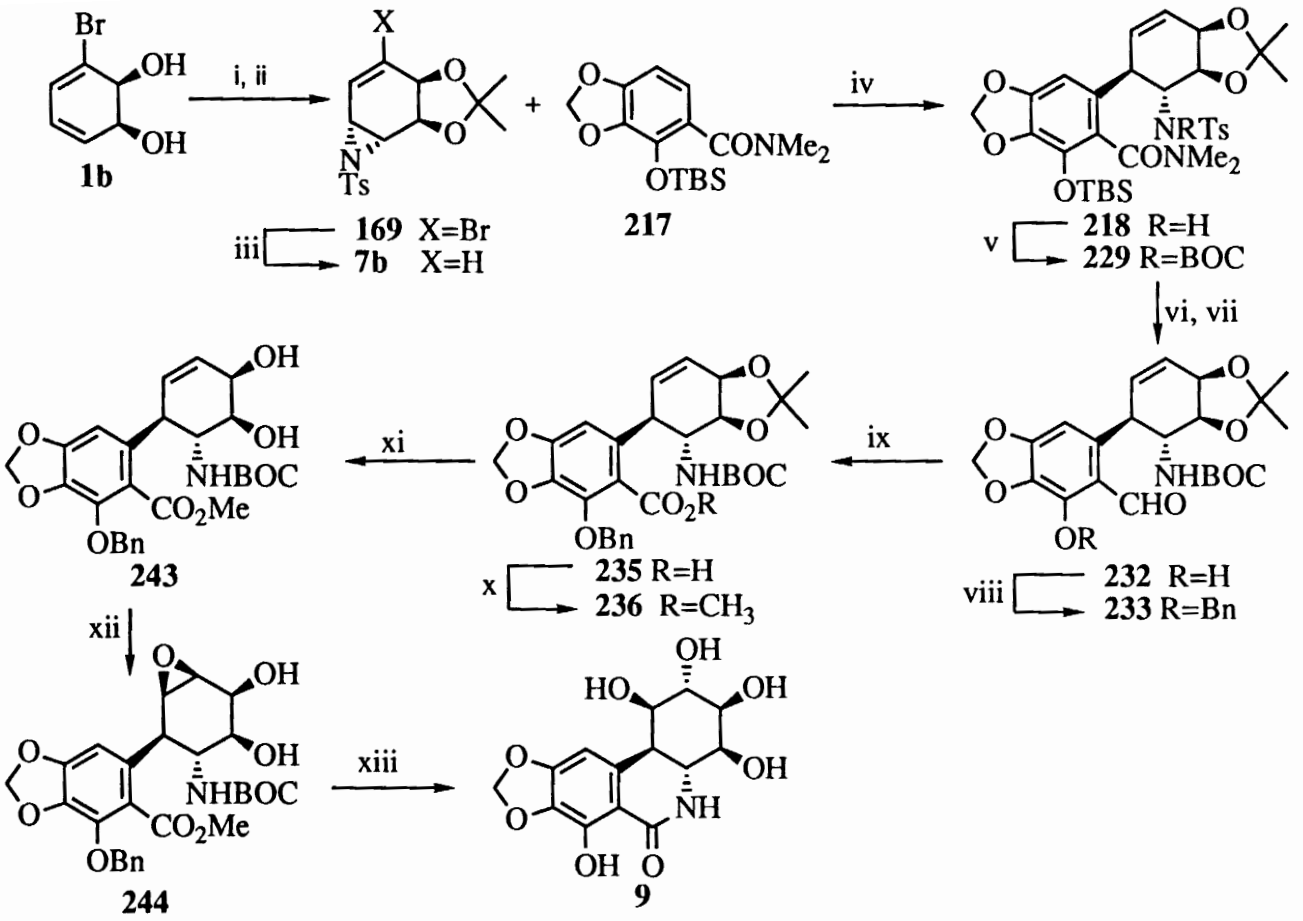
Scheme 55. Remarkable Final Transformations

aliphatic protons on C-ring also appeared. Most indicative of these signals was the doublet (*J* 11.0 Hz) due to H-10b, suggesting the required *trans*-relationship between H-10b and H-4b. Even more surprisingly, upon prolonged heating, **250** underwent slow debenzylation to give the long sought-after pancratistatin. After 6 days, this series of transformations finished, with the disappearance of all starting material to afford pancratistatin in 51% yield from **244**. This was really a remarkable result, since this operation achieved at least four transformations in one pot; moreover, these took place in a seemingly well designed sequence, *i.e.*, cleavage of the BOC group, followed by ring closure to lactam, then epoxide ring opening, and final debenzylation, to ensure a clean conversion to pancrastitatin. Since the benzyl ether is quite stable to the acidic and basic conditions, the debenzylation in H_2O as observed here is really unusual. A plausible mechanism is proposed to account for this result, Scheme 56. When this reaction was stopped after 48h, **250** was isolated in 80% yield, and could be quantitatively hydrogenated (H_2, $Pd(OH)_2$, EtOAc) to pancratistatin.

The R_fs in several solvent systems and ^1H NMR spectrum of synthesized pancratistatin were identical to those of natural material, kindly provided by Professor Pettit. Optical rotation (α_D^{26}=+41°, c 1.0, DMSO) is also in good agreement with literature value (α_D^{34}=+48°, c 1.0, DMSO). Thus a total synthesis of (+)-pancratistatin has been achieved in 13 steps and with a 2% overall yield, which is summarized in Scheme 57.


OH
HO
OH
OH
O
O
N
H
OBn
O
OH
250
251
Ph
252
253
H_2O
254
NH
pancratistatin

Scheme 56



(i) DMP, TsOH, CH_2Cl_2,95%; (ii) PhI=NTs, $Cu(acac)_2$, CH_3CN, 59%; (iii) $BuSnH_3$, AIBN, THF, 78%; (iv)(a)s-BuLi, TMEDA, THF, -90 °C;(b)CuCN; (c)aziridine **7b**; (c) $BF_3{\cdot}Et_2O$, 75%; (v) (a)*s*-BuLi; (b) $(BOC)_2O$, 68%; (vi) Na/anthracene, -78 °C, 81%; (vii) Morpholine-SMEAH, -45 °C, 72%; (viii)BnBr, K_2CO_3, DMF, 83%; (ix) $NaClO_2$, K_2HPO_4, 2-methyl-2-butene, *t*-BuOH, H_2O; (x) CH_2N_2, 98%; (xi)HOAc-THF-H_2O, 60 °C, 73%; (xii)BuOOH, $VO(acac)_2$, benzene, 60 °C, 53%; (xiii) H_2O, BzONa (cat.), 100 °C, 51%.

Scheme 57. Total Synthesis of (+)-Pancratistatin

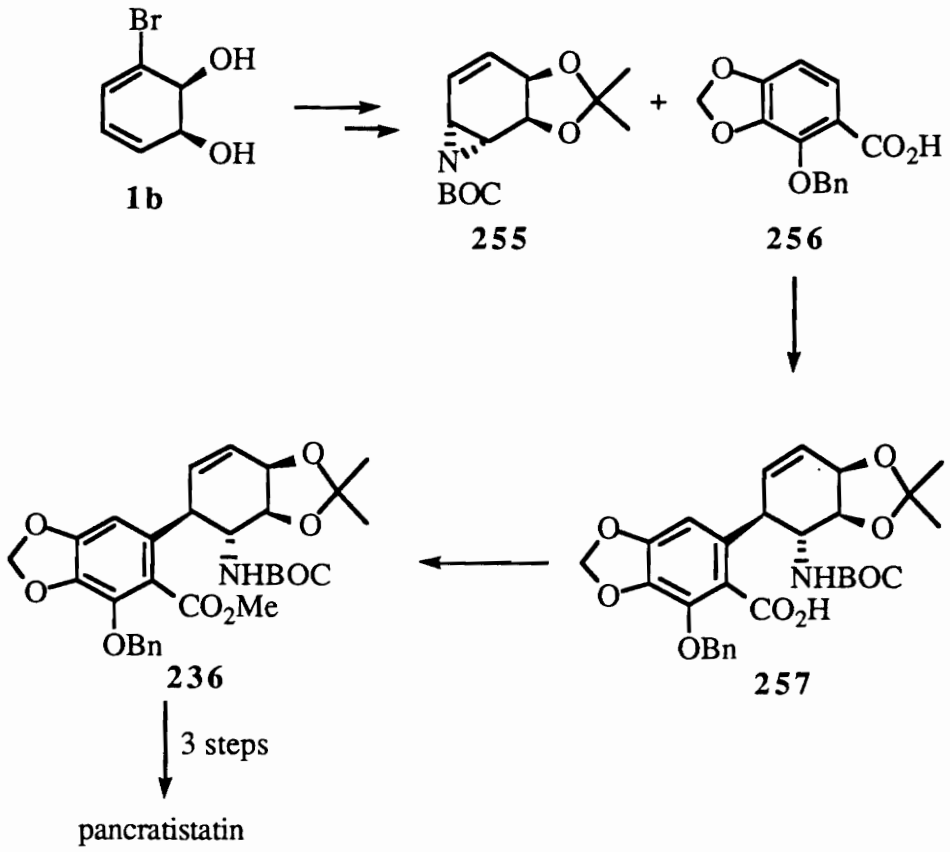
IV.CONCLUSION

At long last, a novel total synthesis of (+)-pancratistatin has been completed in 13 steps and with a 2% overall yield. This synthesis is superior to the first one reported by Danishefsky in both number of steps and overall yield. In fact, this work constitutes the first enatiocontrolled synthesis, since the reported one gave rise to a racemic mixture.

The key features of our synthesis include: (a) the use of vinylaziridine **7b** as a fully functionalized chiral synthon which proved to be quite a suitable precursor for rapid construction of highly oxygenated C-ring. Two of the six asymmetric centers have already been present and the remaining four could be established by the elaboration of the masked functionality of the olefin and the aziridine. (b) highly regioselective S_N2 ring opening of vinylaziridine **7b** with a higher-order cuprate derived from *ortho*-lithiation. This desired ring opening provided a key cyclization precursor in which sufficient functionality was present for further elaboration to target molecule. (c) ring opening of epoxide **244** with water in the presence of a catalytic amount of sodium benzoate. Originally intended to introduce oxygenation of C-1 and C-2, this reaction accomplished a series of remarkable transformations to give pancratistation in one pot from epoxide **244**.

On the other hand, difficulties were encountered in the manipulation of benzamide and tosylamide to close B-ring, because of absence of efficient methods for the further transformations of these groups and interaction between the different groups. These problems were finally solved at the expense of increased synthetic steps. Obviously, in the second generation synthesis, the dimethylamide issue must be addressed. The solution of this problem will lead to a more efficient synthesis. The effort is underway to replace the dimethylamide with the carboxylic acid group, as shown in Scheme 58. Also, the *t*-BOC

aziridine will be used in place of the tosylaziridine. The key step in this envisioned second generation synthesis is still the coupling between *t*-BOC aziridine **255** and a higher order



Scheme 58. Proposed Second Generation Synthesis of (+)-Pancratistatin

cyanocuprate derived from acid **256**. Recently, the *ortho*-metallation of benzoic acid has been reported.[99] This procedure will be adapted for the lithiation of acid **256** to generate a high order cyanocuprate for the coupling reaction.

This synthesis demonstrates the utility of vinylaziridine **7** as a new chiral synthon. It is believed that the newly developed methods in this work will find extensive application in the syntheses of C-disaccharides and *Amaryllidaceae* alkaloids.

V. EXPERIMENTAL

All reactions were carried out in an argon atmosphere with standard techniques for the exclusion of air and moisture. Glassware used for moisture sensitive reactions was flame dried under vacuum. Tetrahydrofuran and ether were distilled from Na benzophenone ketyl. Dichloromethane, DMF, toluene and TMEDA were distilled from calcium hydride. Flash column chromatography was performed on Merck silica gel (grade 60, 230–400 mesh). Infrared spectra were recorded on a Perkin Elmer 283B or 1600 FTIR. ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker WP-270 MHz or Varian NR-400 instruments. Proton chemical shifts are reported in parts per million (ppm) relative to TMS as an internal reference (0.00). Carbon chemical shifts are reported in ppm relative to the center line of the $CHCl_3$ triplet (77.0 ppm) and the multiplicity is indicated by CH_3, CH_2, CH, C (DEPT experiments). Melting points were determined on a Thomas Hoover capillary apparatus and are uncorrected. Optical rotations were measured on a Perkin-Elmer 241 digital polarimeter. Elemental analyses were performed by Atlantic Microlabs, Norcross, GA.

General procedure for the formation of aziridines 7a and 169. A mixture of 5 equivalents (eq.) of (1*S*, 2*S*)-3-halo-1,2-isopropylidenedioxycyclohexa-3,5-diene, 1 eq. of *p*-tosyliminophenyliodinane (PhI=NTs) and 0.08 eq. of $Cu(acac)_2$ in 10 mL $mmol^{-1}$ of CH_3CN was stirred at rt. After consumption of PhI=NTs, the mixture was filtered through a pad of silica gel and concentrated in vacuo. The crude product was recrystallized from hexane/ethyl acetate.

(1*R*,4*S*,5*S*,6*R*)-3-Chloro-4,5-isopropylidenedioxy-7-(4'-methylphenylsulfonyl)7-azabicyclo[4.1.0]hept-2-ene (7a). The compound was obtained in 20.5% yield from (1*S*,2*S*)-3-chloro-1,2-isopropylidenedioxycyclohexa-3,5-diene following the general procedure (reaction time 18h): R_f 0.43 (hexane/ethyl acetate, 3:1); white solid; mp 202–203 °C; $[\alpha]_D^{25}$ –75.5° (c 1.54, $CHCl_3$); IR (KBr) 3060, 2980, 2910, 1645, 1590, 1410, 1375, 1330, 1255, 1210, 1155, 1060, 1000, 865, 800, 740 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.82 (dm, *J* = 8.2 Hz, 2H), 7.37 (dm, *J* = 8.2 Hz, 2H), 6.09 (dd, *J* = 4.9, 1.2 Hz, 1H), 4.65 (ddd, *J* = 6.6, 1.8, 0.7 Hz, 1H), 4.30 (dd, *J* = 6.6, 1.0 Hz, 1H), 3.44 (dd, *J* = 6.5, 1.8 Hz, 1H), 3.34 (dt, *J* = 0.6, 6.5 Hz, 1H), 2.46 (s, 3H), 1.41 (s, 3H), 1.38 (s, 3H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 145.3 (C), 138.06 (C), 134.41 (C), 130.06 (2CH), 128.07 (2CH), 119.96 (CH), 111.72 (C), 73.04 (CH), 71.68 (CH), 37.17 (CH), 36.74 (CH), 27.51 (CH_3), 26.07 (CH_3), 21.74 (CH_3); MS (CI+) *m/z* (rel. intensity) 356 ($(M+H)^+$, 3), 340 (6), 298 (27), 262 (23), 200 (36), 155 (100), 142 (36), 114 (60), 91 (43). Anal. Calcd for $C_{16}H_{18}ClNO_4$: C, 54.00; H, 5.12; N, 3.94. Found: C, 53.92; H, 5.12; N, 3.86.

(1*R*,4*S*,5*S*,6*R*)-3-Bromo-4,5-isopropylidenedioxy-7-(4'-methylphenylsulfonyl)-7-azabicyclo[4.1.0]hept-2-ene (169). From 10.52 g (45.52 mmol) of (1*S*,2*S*)-3-bromo-1,2-isopropylidenedioxycyclohexa-3,5-diene **163b**, **169** (1.97g, 54% yield) was obtained following the general procedure (reaction time 1 h): white solid; R_f 0.48 (hexane/ethyl acetate, 3:1); mp 206–207 °C; $[\alpha]_D^{25}$ –33.7° (c 1.05, $CHCl_3$); IR (KBr) 3060, 2980, 2900, 1640, 1590, 1440, 1400, 1370, 1325, 1290, 1210, 1150, 1060, 990, 860, 800 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.82 (dm, *J* = 8.2 Hz, 2H), 7.37 (dm, *J* = 8.2 Hz, 2H), 6.35 (dd, *J* = 5.0, 1.2 Hz, 1H), 4.64 (ddd, *J* = 6.5, 1.7, 0.6 Hz, 1H), 4.34 (dd, *J* = 6.5, 1.2 Hz, 1H), 3.44 (dd, *J* = 6.5, 1.7 Hz, 1H), 3.28 (dd, *J* = 6.5, 5.0 Hz, 1H), 2.46 (s, 3H), 1.42 (s, 3H), 1.38 (s, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 145.1 (C), 134.1 (C), 129.92

(2CH), 129.89 (C), 127.9 (2CH), 123.9 (CH), 111.5 (C), 73.8 (CH), 71.4 (CH), 37.4 (CH), 36.4 (CH), 27.4 (CH_3), 26.1 (CH_3), 21.6 (CH_3); MS (CI+) *m/z* (rel. intensity) 400 ($(M+H)^+$, 2), 384 (1.5), 372 (1.5), 344 (23), 314 (12), 262 (29), 244 (11), 228 (7), 187 (29), 155 (100), 108 (60), 91 (31); HRMS (CI+) calcd for ($C_{16}H_{18}BrNO_4S$+H) 400.0218, found 400.0231.

(1*R*,4*R*,5*S*,6*R*)-4,5-Isopropylidenedioxy-7-(4'-methylphenylsulfonyl) 7a-zabicyclo [4.1.0]hept-2-ene (7b). A mixture of **169** (10.1g, 25.23 mmol), tributyltin hydride (11.6 g, 39.85 mmol) and AIBN (413 mg) in THF (200 mL) was stirred at reflux. After 2h, the mixture was washed with excess saturated KF aqueous solution, and the organic layer was dried over Na_2SO_4. Removal of solvent and column chromatography (silica gel, hexane/EtOAc, 3:1) afforded **7b** (6.32g, 78%): R_f 0.37 (hexane/ethyl acetate, 3:1); white solid; m.p 106-107 °C; $[\alpha]_D^{25}$ -183° (c 2.3, $CHCl_3$); IR (KBr) 3040, 2970, 1601, 1375, 1365, 1325, 1150, 1060, 980, 840 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.82 (dm, *J* = 8.2 Hz, 2H), 7.35 (bd, *J* = 8.0 Hz, 2H), 5.95 (ddd, *J* = 10.2, 4.4, 1.7 Hz, 1H), 5.76 (dd, *J* = 10.2, 2.4 Hz, 1H), 4.54 (dd, *J* = 6.7, 1.5 Hz, 1H), 4.39 (dt, *J* = 6.7, 1.0 Hz, 1H), 3.37 (dd, *J* = 6.5, 1.8 Hz, 1H), 3.27 (dd, *J* = 6.5, 4.7 Hz, 1H), 2.46 (s, 3H), 1.37 (s, 3H), 1.34 (s, 3H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 144.8, 134.6, 132.4, 129.8 (2C), 127.9 (2C), 120.9, 110.7, 70.6, 69.3, 36.4, 35.5, 27.8, 26.1, 21.6; MS (CI+) *m/z* (rel. intensity) 322 ($(M+H)^+$, 12), 292 (11), 264 (100), 236 (44), 155 (80), 109 (84), 80 (78); HRMS (CI+) calcd for ($C_{16}H_{19}O_4NS$+H) 322.1113, found 322.1106. Anal. Calcd for $C_{16}H_{19}O_4NS$ C, 59.80; H, 5.96; N, 4.36. Found: C, 59.90; H, 5.99; N, 4.36.

(1R, 6S)-4-chloro-5,6-isopropylidenedioxy-cyclohex-2-enol (171). Phenyllithium solution in hexane/ether (1.7 M, 3.6 mL) was added dropwise to a solution of epoxide **6a** (821 mg, 4.05 mmol) in THF (10 mL) at -78 °C. The reaction mixture was stirred at -78 °C for 4h, quenched with H_2O (2 mL). The reaction mixture was extracted with ethyl acetate (3x10 mL), combined extract was dried over Na_2SO_4. Column chromatography (silica gel, hexane/ethyl acetate, 3:1) gave **171** (451 mg, 55%) as a colorless oil: R_f 0.37 (hexane/ethyl acetate, 3:1); IR (neat) 3418, 2991, 2859, 1697, 1387, 1300 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 5.68 (dd, *J* =9.9, 2.9 Hz, 1H), 5.38 (bd, *J* =9.9 Hz, 1H), 4.87 (d, *J* =12.8, 1H), 4.71 (dt, *J* =12.8, 2.3 Hz, 1H), 3.60 (s, 1H), 1.52 (s, 3H), 1.44 (s, 3H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 147.83 (C), 127.12 (CH), 124.72 (CH), 116.29 (C), 92.99 (C), 82.94 (CH), 73.46 (CH), 26.49 (CH_3), 24.45 (CH_3); MS (CI+) *m/z* (rel. intensity) 203 ($(M+H)^+$, 4), 185 (6), 163 (17), 145 (56), 117 (35), 59 (100); HRMS (CI+) calcd for ($C_9H_{11}O_3Cl$+H) 203.0480, found 203.0474.

(1*R*,2*S*,5*S*,6*S*)-4-Chloro-5,6-isopropylidenedioxy-2-methylcyclohex-3-enol (172). Methylmagnesium bromide in ether (3M, 0.65 mL, 1.95 mmol) was added to a suspension of CuI (39 mg, 0.20 mmol) in ether (7 mL) at –40 °C. The mixture was stirred for 15 min before it was cooled to –78 °C. A solution of **6a** (307 mg, 1.52 mmol) in ether (3 mL) was added and the mixture was stirred at –78 °C for 2.5 h, then warmed slowly to –40 °C. After 2h, the reaction was quenched with saturated ammonium chloride solution (3 mL), and the reaction mixture was extracted with ether (3x20 mL). The combined ether layers were dried over Na_2SO_4, and concentrated in vacuo. The residue was chromatographed on silica gel eluting with 2:1 hexane/ethyl acetate to afford **172** (293 mg, 58%) as colorless oil: bp 100–110 °C (0.1 mm, Kugelrohr); $[\alpha]_D^{25}$ –21° (c 1.74, $CHCl_3$); IR (neat) 3460, 2990, 2930, 2880, 1375, 1240, 1210, 1160, 1080, 1065,

1050, 925, 870 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 5.79 (d, *J* = 2.0 Hz, 1H), 4.60 (dd, *J* = 6.4, 1.4 Hz, 1H), 4.05 (dd, *J* = 8.9, 6.3 Hz, 1H), 3.34 (dt, *J* =9.0, 1.8 Hz, 1H), 2.55 (d, *J* = 2.3 Hz, 1H), 2.26 (m, 1H), 1.57 (s, 3H), 1.45 (s, 3H), 1.18 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 145.3 (C), 138.06 (C), 134.41 (C), 130.06 (2CH), 128.07 (2CH), 119.96 (CH), 111.72 (C), 73.04 (CH), 71.68 (CH), 37.17 (CH), 36.74 (CH), 27.51 (CH_3), 26.07 (CH_3), 21.74 (CH_3); MS (EI) *m/z* (el. intensity) 203 (M^+–CH_3) (100), 143 (87), 115 (81), 79 (54); HRMS (CI+) calcd for ($C_{10}H_{15}ClO_3$+H) 219.0788, found 219.0794.

(1*R*,2*S*,5*S*,6*S*)-4-Chloro-5,6-isopropylidenedioxy-2-cyclohexylmethylcyclohex-3-enol (174). To a suspension of Mg (364 mg, 14.97 mmol) and a small crystal of iodine in THF (3 mL) cyclohexylmethyl bromide (1.6 mL in 15 mL of THF) was added over 1h and the mixture was stirred at rt for 1.5 h. The resulting Grignard reagent was added into a suspension of CuI (160 mg, 0.84 mmol) in THF (4 mL) at –40 °C. The mixture was stirred for 15 min, then cooled to –78 °C, and a solution of **6a** (1.707g, 8.42 mmol) in THF (8 mL) was added dropwise. The reaction mixture was warmed slowly to 0 °C and stirred at 0 °C for 3 h. The reaction was quenched with saturated NH_4Cl solution (5 mL) and the mixture was extracted with ethyl acetate (3x15 mL). The combined organic layers were dried over Na_2SO_4. Evaporation of the solvent and chromatography (3:1 hexane/ethyl acetate) afforded **174** (995 mg, 39%) as a white solid: R_f 0.40 (hexane/ethyl acetate, 3:1); mp 80-82 °C; $[\alpha]_D^{25}$ +16.9° (c 0.94, $CHCl_3$); IR (KBr) 3490, 2980, 2920, 1640, 1450, 1370, 1250, 1200, 1060 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 5.91 (d, *J* =2.1 Hz, 1H), 4.59 (dd, *J* =6.3, 1.2 Hz, 1H), 4.05 (dd, *J* =8.6, 6.3 Hz, 1H), 3.38 (dt, *J* =8.8, 2.8 Hz, 1H), 2,28 (bs, 1H), 2.24 (m, 1H), 1.53 (s, 3H), 1.42 (s, 3H), 0.70~1.90 (m, 13H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 131.41 (CH), 127.75 (C), 110.34

(C), 79.91 (CH), 75.89 (CH), 72.97 (CH), 38.64 (CH), 38.39 (CH_2), 34.73 (CH), 34.43 (CH_2), 32.50 (CH_2), 28.29 (CH_3), 26.56 (CH_2), 26.31 (CH_2), 26.12 (CH_2), 25.99 (CH_3); MS (CI+) *m/z* (rel. intensity) ($(M+H)^+$ not found), 285 (25), 225 (15), 207 (29), 95 (20), 59 (100); HRMS (CI+) calcd for ($C_{16}H_{25}O_3Cl$+H) 301.1570, found 301.1574.

(1*R*,5*R*,6*S*)-5,6-Isopropylidenedioxy-4,4-diphenylcyclohex-2-enol (175). To a suspension of CuI (596 mg, 3.12 mmol) in ether (5 mL) was added phenyllithium solution (1.8 M, 3.5 ml) at 0 °C. The mixture was stirred for 30 min and then a solution of **6a** (634 mg, 3.13 mmol) in ether (5 mL) was added. The mixture was stirred at 0 °C for 2h and at rt for 8h before the reaction was quenched with ice water (5 mL). The aqueous layer was extracted with ethyl acetate (3x15 mL), and the combined organic layers were dried over Na_2SO_4. Removal of solvent and column chromatography (silica gel, 2:1 hexane/ethyl acetate) gave **175** (80 mg, 8% yield) as a colorless oil: R_f 0.24 (hexane/ethyl acetate, 2:1); $[\alpha]_D^{28}$ +65.9° (c 1.22, $CHCl_3$); IR (neat) 3420, 3040, 3020, 2970, 2920, 2890, 1590, 1485, 1440, 1375 cm-1; ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.10~7.40 (m, 10H), 6.38 (d, *J* =9.9 Hz, 1H), 6.11 (dd, *J* =9.9, 3.6 Hz, 1H), 5.01 (d, *J* =6.8 Hz, 1H), 4.41 (dd, *J* =6.8, 3.7 Hz, 1H), 4.29 (m, 1H), 1.93 (d, *J* =6.8 Hz, 1H), 1.36 (s, 3H), 1.27 (s, 3H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 147.77 (c), 143.43 (C), 136.12 (CH), 129.86 (CH), 129.49 (2CH), 128.56 (2CH), 127.69 (CH), 127.50 (2CH), 126.64 (CH), 126.20 (CH), 108.79 (C), 81.05 (CH), 79.90 (CH), 69.70 (CH), 52.39 (C), 26.62 (CH_3), 25.14 (CH_3); MS (EI) *m/z* (rel. intensity) 323 ($(M+H)^+$, 5), 275 (4), 265 (6), 247 (100), 219 (15); HRMS (EI) calcd for ($C_{27}H_{22}O_3$+H) 323.1647, found 323.1638.

(1*R*,2*R*,5*R*,6*S*)-2,4-Di(cyclohexylmethyl)-5,6-isopropylidenedioxy-cyclohex-3-enol (176). To a suspension of lithium (215 mg, 31 mmol) in THF (12 mL) at –30 °C was

added cyclohexylmethyl bromide (0.865 mL, 6.2 mmol) at –30 °C. The mixture was stirred 2h before it was was cannulated to a suspension of cuprous iodide (590 mg, 3.10 mmol) in ether (3 mL) pecooled to –35 °C. The mixture was stirred at –40 °C for 40 min and cooled to –78 °C, and a solution of **6a** (203 mg, 1.00 mmol) in THF (3 mL) was added. The resulting mixture was stirred at –78 °C for 2h and then allowed to warm up to –40 °C before the reaction was quenched with saturated aqueous NH_4Cl solution (5 mL). The aqueous layer was extracted with ethyl acetate (3x10 mL), and the combined organic phases were dried over Na_2SO_4. Removal of solvent and flash column chromatography (silica gel, hexane/ethyl acetate, 4:1) afforded **176** (52 mg, 14%) and **174** (12 mg, 4%) as colorless oils: **176,** R_f 0.42 (hexane/ethyl acetate, 3:1); $[\alpha]_D^{28}$ -62.0° (c 1.1, $CHCl_3$); IR (neat) 3460, 2920, 2840, 1445, 1378, 1370, 1230 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 5.35 (d, *J* =3.6 Hz,1H), 4.47 (d, *J* =6.1 Hz, 1H), 4.24 (t, *J* =6.1 Hz, 1H), 3.90 (bs, 1H), 2.52 (bs, 1H), 2.19 (dd, *J* =14.0, 5.4 Hz, 1H), 1.41 (s, 3H), 1.39 (s, 3H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 134.32 (C), 127.94 (CH), 108.85 (C), 76.51 (CH), 73.96 (CH), 71.05 (CH), 41,99 (CH_2), 38.02 (CH_2), 35.29 (CH), 34.98 (CH), 34.99 (CH), 33.87 (CH_2), 33.25 (CH_2), 32.81 (CH_2), 27.73 (CH_3), 26.62 ($2CH_2$), 26.32 ($2CH_2$), 25.94 (CH_3); MS (EI) *m/z* (rel. intensity) 363 ($(M+H)^+$, 14), 345 (24), 330 (31), 305 (32), 287 (100), 269 (12), 253 (9), 197 (7); HRMS (EI) calcd for ($C_{23}H_{38}O_3$+H) 363.2899, found 363.2885. Anal. Calcd for $C_{23}H_{38}O_3$: C, 76.20; H, 10.56. Found: C, 75.76; H, 10.67.

(1*R*,4*S*,5*R*,6*S*)-4-Cyclohexylmethyl-5,6-isopropylidenedioxycyclohex-2-enol (186). To a suspension of cuprous iodide (39 mg, 0.20 mmol) in THF (3 mL) cooled to –40 °C was added cyclohexylmethyl magnesium bromide (2.69 mmol). The mixture was stirred at –40 °C for 15 min, then cooled to –78 °C, when solution of **6b** (334 mg, 1.99 mmol) in THF (4 mL) was added. The mixture was warmed to –10 °C with stirring before the

reaction was quenched with saturated NH_4Cl solution (5 mL). The aqueous layer was extracted with ethyl acetate (3x15 mL), and the combined organic layers were dried over Na_2SO_4. The product was purified using column chromatography (silica gel, hexane/ethyl acetate, 3:1) to give **186** (439 mg, 83%) as a colorless oil: R_f 0.28 (hexane/ethyl acetate, 3:1); $[\alpha]_D^{26}$ +8.4°(c 1.76, $CHCl_3$); IR (neat) 3443, 2992, 1449, 1374 cm^{-1}; IR (neat) 3443, 2992, 1449, 1374 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 5.76 (dt, *J* =9.7, 2.6 Hz, 1H), 5.61 (dt, *J* =9.7, 2.8 Hz, 1H), 4.21 (m, 1H), 3.97 (dd, *J* =7.6, 6.1 Hz, 1H), 3.83 (dd, *J* =7.6, 6.6 Hz, 1H), 2.58 (bs, 1H), 2.19 (m, 1H), 1.47 (s, 3H), 1.36 (s, 3H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 130.74 (CH), 130.54 (CH), 108.67 (C), 81.40 (CH), 78.30 (CH), 71.61 (CH), 41.42 (CH_2), 37.40 (CH), 35.10 (CH), 33.94 (CH_2), 32,81 (CH_2), 27.30 (CH_3), 26.56 (CH_2), 26.25 (CH_2), 26.12 (CH_2), 24.88(CH_3); MS (EI) *m/z* (rel. intensity) 251 (16), 208 (31), 179 (77), 112 (43), 83 (100), 55 (70). Anal. Calcd for $C_{16}H_{26}O_3$: C, 72.14; H, 9.84. Found: C, 72.13; H, 9.83.

(1*R*,2*R*,5*R*,6*S*)-2-Cyclohexylmethyl-5,6-isopropylidenedioxycyclohex-3-enol (187). To a suspension of lithium (350 mg, 50.4 mmol) in ether (17 mL) at –30 °C was added cyclohexylmethyl bromide (1.395 mL, 10.0 mmol) at –30 °C. The mixture was stirred at –30 °C for 2h before it was was cannulated to a suspension of cuprous iodide (952 mg, 5.00 mmol) in ether (5 mL) pecooled to –40 °C. The mixture was stirred at –40 °C for 40 min and cooled to –78 °C, when a solution of **6b** (279 mg, 1.66 mmol) in THF (4 mL) was added. The resulting mixture was stirred at –78 °C for 2h before the reaction was quenched by saturated aqueous NH_4Cl solution (5 mL). The aqueous layer was extracted with ethyl acetate (3x15 mL), and the combined organic phases were dried over Na_2SO_4. Removal of sovent and column chromatography (silica gel, CH_2Cl_2/acetone, 5:1) afforded **187** (165 mg, 37%) and **186** (25 mg, 5%) as colorless oils: **187**: R_f 0.28

(hexane/ethyl acetate, 3:1); $[\alpha]_D^{28}$ –159.2° (c 1.51, $CHCl_3$); IR (neat) 3450, 2980, 2920, 2850, 1445, 1368, 1235, 1210 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 5.80 (m, 2H), 4.62 (m, 1H), 4.23 (t, *J* =6.6 Hz, 1H), 3.91 (m, 1H), 2.52 (m, 1H), 2.09 (d, *J* =4.7 Hz, 1H), 0.80~1.80 (m, 19H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 133.46 (CH), 124.46 (CH), 108.98 (C), 76.50 (CH), 72.04 (CH), 71.11 (CH), 37.46 (CH_2), 34.98 (CH), 34.86 (CH), 34.12 (CH_2), 33.00 (CH_2), 27.92 (CH_3), 26.62 (CH_2), 26.27 (CH_3), 25.81 (CH_3); MS (EI) *m/z* (rel. intensity) 267 ($(M+H)^+$, 5), 191 (11), 173 (5), 107 (31), 89 (100), 61 (12); HRMS (CI+) calcd for ($C_{16}H_{26}O_3$+H) 267.1960, found 267.1974.

(1*R*,2*S*,5*R*,6*S*)-*N*-(5,6-Isopropylidenedioxy-2,4-diphenylcyclohex-3-enyl)-(4'-methylphenyl)sulfonamide (189). Phenyllithium (0.47 mL, 0.84 mmol) was added to a suspension of CuI (80 mg, 0.42 mmol) in anhydrous THF at –40 °C and stirred for 15 min. Compound **7a** (50 mg, 0.14 mmol) in anhydrous THF (2 mL) was added precooled by cannula, followed by $BF_3{\cdot}Et_2O$ (60 mg, 0.42 mmol), and the mixture was stirred and allowed to warm to rt over 12 h. The reaction was quenched using NH_4OH solution, solid NH_4Cl was added and the mixture was extracted with ether (5x). The combined extracts were washed with brine, dried over $MgSO_4$ and concentrated in vacuo. Chromatography afforded **189** (35 mg, 52%) as a white solid; R_f 0.39 (hexane/ethyl acetate, 3:1); mp 268–270 °C; $[\alpha]_D^{25}$ –105.2° (c 0.50, $CHCl_3$); IR (KBr) 3315, 3020, 2980, 1595, 1490, 1375, 1330, 1240, 1215, 1155, 1085, 1075, 890, 860, 810 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.59 (m, 4H), 7.08–7.41 (m, 10H), 6.34 (d, *J* = 4.8 Hz, 1H), 5.19 (d, *J* = 5.7 Hz, 1H), 4.37 (d, *J* = 6.6 Hz, 1H), 4.27 (dd, *J*= 8.3, 5.5 Hz, 1H), 4.14 (t, *J* = 5.1 Hz, 1H), 3.62 (ddd, *J* = 8.1, 6.6, 5.2 Hz, 1H), 2.40 (s, 3H), 1.38 (s, 3H), 1.14 (s, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 143.19 (C), 138.66 (C), 136.96 (C), 136.45 (C), 136.26 (C), 129.62 (2CH), 129.51 (2CH), 128.63 (2CH), 128.61 (2CH), 128.00 (CH),

127.35 (4CH), 125.97 (2CH), 109.56 (C), 74.21 (CH), 72.98 (CH), 55.26 (CH), 43.92 (CH), 27.28 (CH_3), 25.95 (CH_3), 21.45 (CH_3); MS (CI+) *m/z* (rel. intensity) ($(M+H)^+$ not found), 418 (7), 400 (18), 247 (82), 222 (87), 139 (30), 98 (68), 91 (100). Anal. Calcd for $C_{28}H_{29}NO_4S$: C, 70.71; H, 6.14; N, 2.94. Found: C, 70.65; H, 6.12; N, 2.90.

(1*R*,2*R*,5*R*,6*S*)-*N*-[2,4-Di(cyclohexylmethyl)-5,6-isopropylidenedioxycyclohex-3-enyl]-(4'-methylphenyl)sulfonamide (191). To a suspension of lithium (193 mg, 27.8 mmol) in ether (12 mL) cooled to –30 °C was added cyclohexylmethyl bromide (0.766 mL, 5.56 mmol). The mixture was stirred at –30 °C for 2h and cannulated to a suspension of cuprous iodide (529 mg, 2.78 mmol) in ether (3 mL) precooled to –40 °C. After the mixture was stirred at –40 °C for 40 min, it was cooled to –78 °C and a solution of **7a** (329 mg, 0.92 mmol) in THF (5 mL) was added. The mixture was stirred at –78 °C for 2h, then slowly warmed to –40 °C and stirred at –40 °C for 2h, then quenched with saturated aqueous ammonium chloride (5 mL) and extracted with ethyl acetate (3x5 mL). The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. The residue was chromatographed (silica gel, hexane/ethyl acetate, 4:1) to give **191** (433 mg, 89%) as a white solid; R_f 0.48 (hexane/ethyl acetate, 3:1); mp 192-193 °C; $[\alpha]_D^{25}$ –55.4° (c 0.90, $CHCl_3$); IR (KBr) 3300, 2910, 2840, 1595, 1440, 1370, 1325, 1155 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.76 (d, *J* =8.3 Hz, 2H), 7.29 (d, *J* =8.1, 2H), 5.29 (bs, 1H), 4.46 (d, *J* =6,3 Hz, 1H), 4.40 (d, *J* =5.8 Hz, 1H), 4.28 (t, *J* =6.0 Hz, 1H), 3.38 (q, *J* =4.5 Hz, 1H), 2.65 (bs, 1H), 2.41 (s, 3H), 2.11 (dd, *J* =14.2, 5.5 Hz, 1H), 1.82 (dd, *J* =14.2, 8.6 Hz,1H), 1.31 (s, 3H), 1.14 (s, 3H), 0.50~1.72 (m, 24H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 143.43 (C), 137.54 (C), 135.44 (C), 129.65 (2CH), 128.19 (CH), 127.39 (2CH), 109.28 (C), 75.01 (CH), 73.59 (CH), 55.06 (CH), 42.10 (CH_2), 38.20 (CH_2), 35.29 (CH), 34.55 (CH), 33.87 (CH_2), 33.62 (CH_2), 33.02 ($2CH_2$), 32.06 (CH), 27.30 (CH_3), 26.62

($2CH_2$), 26.26 ($2CH_2$), 26.06 (CH_2), 25.93 (CH_3), 21.41 (CH_3); MS (FAB) *m/z* (rel. intensity) 538 ($(M+Na)^+$, 23), 458 (29), 440 (24), 302 (100), 287 (38), 5 (74). Anal. Calcd for $C_{30}H_{45}O_4NS$: C, 69.86; H, 8.79; N, 2.72. Found: C, 69.92; H, 8.81; N, 2,69.

(1*R*,2*S*,5*S*,6*S*)-*N*-(4-Chloro-5,6-isopropylidenedioxy-2-methylcyclohex-3-enyl)-(4'-methylphenyl)sulfonamide (192). To a suspension of CuI (14 mg, 0.073 mmol) in anhydrous ether was added a solution of methylmagnesium bromide (MeMgBr) (0.050 mL, 0.15 mmol) at –45 °C and stirred for 30 min. Compound **7a** (200 mg, 0.56 mmol) in anhydrous THF (5 mL) was added precooled via cannula and MeMgBr (0.40 mL, 1.20 mmol) was added over 60 min. After 7h the white suspension was quenched using saturated NH_4Cl solution (containing NH_3, pH 9) (30 mL) and the mixture was extracted with ether (4x).The combined organic phases were washed with brine, dried over Na_2SO_4 and concentrated in vacuo. Chromatography (toluene/ethyl acetate, 4:1) afforded **192** (111 mg, 53%) as a white solid: mp 65-66 °C; $[\alpha]_D^{20}$ –15.6 (c 1.035, $CHCl_3$); IR (KBr) 3270, 2980, 2940, 1600, 1500, 1380, 1325, 1155, 1090, 870 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.79 (dm, *J* = 8.2 Hz, 2H), 7.29 (dm, *J* = 8.7 Hz, 2H), 5.79 (d, *J* = 3.0 Hz, 1H), 5.02 (d, *J* = 8.5 Hz, 1H), 4.50 (dd, *J* = 6.0, 1.4 Hz, 1H), 4.08 (dd, *J* = 7.9, 6.0 Hz, 1H), 3.28 (q, *J* = 8.0 Hz, 1H), 2.45 (s, 1H), 2.19 (ddquintett, *J* = 1.4, 3.1, 7.3 Hz, 1H), 1.282 (s, 3H), 1.258 (s, 3H), 1.13 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 143.2, 138.3, 132.1, 129.3 (2C), 128.4, 127.2 (2C), 110.3, 77.7, 75.2, 57.2, 36.5, 27.4, 25.8, 21.5, 18.0; MS (CI+), *m/z* (rel. intensity) 372 ($(M+H)^+$, 15), 342 (17), 314 (100), 296 (30), 278 (27), 172 (22), 143 (51); HRMS calcd for ($C_{17}H_{22}O_4NSCl$+H) 372.1036, found 372.1019. Anal. Calcd for $C_{17}H_{22}O_4NSCl$ C, 54.91; H, 5.96; N, 3.77. Found: C, 54.79; H, 5.94; N, 3.70.

***(1R,4S,5R,6S)*-*N*-(4-Cyclohexylmethyl-5,6-isopropylidenedioxycyclohex-2-enyl)-(4'-methylphenyl)sulfonamide (196).** To a suspension of lithium (187 mg, 26.94 mmol) in ether (12 mL) at –30 °C was added cyclohexylmethyl bromide (0.726 mL, 5.20 mmol) at –30 °C. The mixture was stirred at –30 °C for 2h before it was was cannulated to a suspension of cuprous iodide (495 mg, 2.60 mmol) in ether (3 mL) pecooled to –40 °C. The mixture was stirred at –40 °C for 40 min and cooled to –78 °C, when a solution of **7b** (281 mg, 0.87 mmol) in THF (4 mL) was added. The resulting mixture was stirred at –78 °C for 2h, and then allowed to warm to –40 °C before the reaction was quenched with saturated aqueous NH_4Cl solution (5 mL). The aqueous layer was extracted with ethyl acetate (3x15 mL), and the combined organic phases were dried over Na_2SO_4. Removal of sovent and column chromatography (silica gel, hexanes/ethyl acetate, 3:1) afforded **196** (276 mg, 76%); white solid; R_f 0.30 (hexane/ethyl acetate, 3:1); mp 138-139 °C; $[\alpha]_D^{25}$ –40.4° (c 0.96, $CHCl_3$); IR (KBr) 3290, 2980, 2920, 2860, 1590, 1440, 1405, 1370, 1325, 1280, 1235, 1215, 1150, 1045, 900, 875, 855, 805 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.79 (d, *J* =8.25 Hz, 2H), 7.30 (d, *J* =8.21 Hz, 2H), 5.66 (m, 2H), 4.70 (d, *J* =5.58 Hz, 1H), 3.81 (m, 2H), 3.58 (m, 1H), 2,42 (s, 3H), 2.22 (bs, 1H), 1.23 (s, 3H), 1.16 (s, 3H), 0.71~1.80 (m, 13H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 143.30 (C), 137.48 (C), 132.34 (CH), 132.34 (CH), 129.49 (CH), 128.00 (CH), 127. 51 (CH), 108.79 (C), 78.36 (CH), 78.18 (CH), 54.81 (CH), 41.74 (CH_2), 37.03 (CH), 35.10 (CH), 33.80 (CH_2), 32.99 (CH_2), 27.24 (CH_3), 26.55 (CH_2), 26.23 (CH_2), 25.19 (CH_3), 21.30 (CH_3); MS (CI+) *m/z* (rel. intensity) ($(M+H)^+$ not found), 363 (20), 319 (46), 206 (38), 191 (76), 91 (99), 59 (100). Anal. Calcd for $C_{23}H_{33}O_4NS$: C, 65.84; H, 7.93. Found: C, 65.68; H, 7.97.

(1*R*,4*R*,5*R*,6*S*)-*N*-(5,6-Isopropylidenedioxy-4-phenylcyclohex-2-enyl)-(4'-methylphenyl)sulfonamide (197) and (1*R*,2*R*,5*R*,6*S*)-*N*-(5,6-Isopropylidenedioxy-2-phenylcyclohex-3-enyl)-(4'-methylphenyl)sulfon-amide (198). with lithium diphenylcuprate: phenyllithium solution (1.8 M, 2.36 mL) was added slowly at –35 °C to a suspension of cuprous iodide (224 mg, 1.18 mmol) in THF (8 mL). The resulting mixture was stirred for 30 min, and a solution of (125 mg, 0.39 mmol) of **7b** in THF (2 mL) was added, followed by $BF_3 \cdot Et_2O$ (0.145 mL) . The mixture was warmed over 5h to rt with stirring, quenched with saturated aqueous ammonium chloride solution (5 mL) and extracted with ethyl acetate (3x10 mL). The combined organic phases were dried over Na_2SO_4, removal of solvent and column chromatography afforded (54 mg, 38%) of **197** and (10 mg, 6%) of **198**:

197: white solid; mp 159-160 °C; R*f* 0.21 (hexanes/ethyl acetate, 3:1); $[\alpha]_D^{25}$ -16.2° (c 1.30, $CHCl_3$); IR (KBr) 3300, 3020, 2980, 2920, 2880, 1592, 1320, 1148, 1370, 1080, 1055, 850, 740, 655, 690 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.83 (d, *J* =8.1 Hz, 2H), 7.10~7.40 (m, 7H), 5.81 (m, 2H), 4.95 (d, J =6.0 Hz, 1H), 4.09 (t, *J* =6.3 Hz, 1H), 3.93 (t, *J* =6.6 Hz, 1H), 3.77 (m, 1H), 3.34 (m, 1H), 1.18 (s, 3H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 143.37 (C), 142.50 (C), 137.54 (C), 131.41 (CH), 129.48 (CH), 129.12 (CH), 128.75 (CH), 128.06 (CH), 127.50 (CH), 126.88 (CH), 109.04 (C), 79.11 (CH), 78.06 (CH), 54.75 (CH), 46.39 (CH), 27.30 (CH_3), 25.13 (CH_3), 21.36 (CH_3); MS (FAB) *m/z* (rel. intensity) 400 ($(M+H)^+$, 15), 342 (43), 323 (36), 247 (24), 171 (100), 91 (51); HRMS calcd for ($C_{22}H_{25}O_4NS$+H) 400.1582, found 400.1581. Anal. Calcd for $C_{22}H_{25}O_4NS$: C, 66.14; H, 6.31; N, 3.51. Found: C, 66.20; H, 6.31; N, 3.28.

198: R_f 0.36 (hexanes/ethyl acetate); white solid; mp 165–167 °C; $[\alpha]_D^{25}$ –17.8° (c 1.07, $CHCl_3$); IR (KBr) 3300, 3030, 2890, 1580, 1495, 1435, 1370, 1320, 1250, 1160, 1085, 1060, 810 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.42 (dm, *J* = 8.3 Hz, 2H), 7.26 (dm, *J* = 8.3 Hz, 2H), 7.23 (m, 1H), 7.09 (m, 4H), 6.00 (ddd, *J* = 9.9, 3.5, 2.7 Hz, 1H),

5.87 (dt, J = 9.9, 1.5 Hz, 1H), 4.67 (brt, J = 4.7 Hz, 1H), 4.52 (d, J = 8.2 Hz, 1H), 4.14 (dd, J = 9.0, 6.0 Hz, 1H), 3.65 (q, J = 9.0 Hz, 1H), 3.24 (dq, J = 8.6,1.9 Hz, 1H), 2.38 (s, 3H), 1.44 (s, 3H), 1.33 (s, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 142.4 (C), 140.1 (C), 138.6 (C), 134.6 (CH), 129.1 (2CH), 128.61 (2CH), 128.57 (2CH), 127.14 (CH), 126.96 (2CH), 124.2 (CH), 109.93 (C), 77.58 (CH), 72.16 (CH), 58.95 (CH), 47.70 (CH), 27.79 (CH_3), 25.83 (CH_3), 21.41 (CH_3); MS(CI+) *m/z* (rel. intensity) 400 ($(M+H)^+$, 15), 386 (13), 370 (23), 342 (99), 312 (19), 171 (100), 143 (19); HRMS calcd for ($C_{22}H_{25}O_4NS$+H) 400.1582, found 400.1568. Anal. Calcd for $C_{22}H_{25}O_4NS$: C, 66.14; H, 6.31; N, 3.51. Found: C, 66.05; H, 6.36; N, 3.49.

198 with dilithium diphenylcyanocuprate: a suspension of (161 mg, 1.80 mmol) of dry CuCN in THF (2 mL) was treated with phenyllithium solution (1.8M, 2.0 mL) at –78 °C. The mixture was warmed to –10 °C with stirring to dissolve CuCN, and then cooled to –78 °C, a solution of **7b** (182 mg, 0.57 mmol) was added, followed by $BF_3{\cdot}Et_2O$ (0.221 mL). The mixture was stirred at –78 °C for 3h and then quenched with aqueous NH_4Cl solution (5 mL, containing NH_3, pH 8). After stirring at rt for 30 min, the mixture was extracted with ethyl acetate (3x15 mL), the combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. The residue was chromatographed on silica gel eluting with 10:1 $CHCl_3$/acetone to give **198** (52 mg, 23 %) .

***N,N*-Dimethyl-4-(*tert*-butyldimethylsilyl)oxy-1,3-benzodioxole-5-carboxamide (217).** *t*-Butyldimethylsilyl chloride (1.73 g, 11.5 mmol) in CH_2Cl_2 (10 mL) was added to a solution of *N,N*-dimethyl-4-hydroxy-1,3-benzodioxole-5-carboxamide (**216**) (2.0 g, 9.56 mmol) and imidazole (2.0 g, 29 mmol) in CH_2Cl_2 (60 mL). The solution was stirred for

12 h at rt, during which time a white solid precipitated. The mixture was washed with brine, dried over $MgSO_4$ and concentrated. Chromatography on silica (hexane/ethyl acetate, 1:1) afforded **217** (2.95 g, 95%) as a crystalline solid: R_f 0.60 (hexane/ethyl acetate, 1:1); IR (KBr) 2920, 2870, 2840, 1610, 1460, 1380, 1260, 1050, 1030, 840, 825, 770 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 6.75 (d, J = 8.0 Hz, 1H), 6.50 (d, J = 8.0 Hz, 1H), 5.92 (s, 2H), 3.03 (s, 3H), 2.87 (s, 3H), 0.94 (s, 9H), 0.16 (bs, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.9 (C), 149.3 (C), 137.0 (C), 135.5 (C), 124.9 (C), 121.4 (CH), 102.8 (CH), 101.0 (CH_2), 38.2 (CH_3), 34.9 (CH_3), 25.4 ($3CH_3$), 18.1 (C), –4.6 ($2CH_3$); MS (CI+) m/z (rel. intensity) 423 ($(M+H)^+$, 52), 308 (40), 279 (12), 266 (100), 59 (8); HRMS calcd for ($C_{16}H_{25}O_4NSI+H$) 324.1631, found 324.1623.

***N,N*-Dimethyl-4-[(*tert*-butyldimethylsilyl)oxy]-6-[(1R,4R,5S,6R)-4,5-isopropylidenedioxy-6-(4-methylphenylsulfonylamino)-2-cyclohexen-1-yl]-1,3-benzodioxole-5-carboxamide (218).** *s*-BuLi in hexane (1.28 M, 40 mL) was added to a solution of TMEDA (7.68 mL) in THF (160 mL) at -78 °C, the yellow mixture was stirred for 10 min before cooling to –90 °C, and a solution of amide **217** (14.71 g, 45.47 mmol) in THF (60 mL) was added precooled by cannula. The resulting deep red solution was stirred at –90 °C for 1.5 h and transferred to a round bottom flask charged with CuCN (2.08 g, 22.75 mmol). The tannish solution was warmed to –20 °C furnishing a dark purple solution, which was recooled to –78 °C, and a solution of vinylaziridine **7b** (4.81 g 14.96 mmol) in THF (40 mL) was added, followed by $BF_3{\cdot}Et_2O$ (2.8 mL). The reaction mixture was then warmed slowly to rt and saturated aqueous NH_4Cl solution (10 mL, containing NH_4OH, pH 8) was added. The mixture was stirred at rt for 30 min, the organic layer was separated and the aqueous layer was extracted with EtOAc (3x25 mL). The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. The

residue was chromatographed on silica gel eluting with hexanes/EtOAc (3:2) (for one atropisomer) followed by hexane/EtOAc (2:3) (for the other atropisomer) to give 6.88 g (75%) of **218** as a glassy solid; β-atropisomer; R_f 0.21 (hexane/ethyl acetate, 1:1); IR (KBr) 3422, 2930, 2859, 1622, 1479, 1432, 1400, 1371, 1325, 1252, 1218, 1160, 1094, 1031, 864, 843, 815, 788 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.62 (d, *J* = 8.1 Hz, 2H), 7.09 (d, *J* = 8.1 Hz, 2H), 6.26 (s, 1H), 5.9~6.05 (m, 3H), 5.79 (d, *J* = 9.8 Hz, 1H), 4.58 (m, 1H), 3.99 (dd, *J* = 9.5, 6.2 Hz, 1H), 3.34 (td, *J* = 10.1, 6.43 Hz, 1H), 3.10 (d, *J* = 10.1 Hz, 1H), 3.08 (s, 3H), 2.87 (s, 3H), 2.36 (s, 3H), 1.45 (s, 3H), 1.29 (s, 3H), 0.97 (s, 9H), 0.27 (s, 3H), 0.23 (s. 3H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 169.08 (C), 149.68 (C), 141.14 (C), 139.89 (C), 135.93 (C), 134.58 (CH), 132.21 (C), 128.25 (2xCH), 127.00 (2xCH), 125.16 (CH), 123.66 (C), 109.28 (C), 101.66 (CH), 101.11 (C), 79.11 (CH), 72.53 (CH), 58.59 (CH), 42.91 (CH), 37.77 (CH), 34.90 (CH), 27.68 (CH_3), 25.80 (CH_3), 25.44 (3xCH_3), 21.94 (CH_3), 17.94 (C), –4.57 (2xCH_3); MS (EI), *m/z* (rel. intensiry) 644 (M^+, 17), 629 (27), 587 (58), 473 (6), 391 (100), 261 (28), 187 (7), 159 (13), 91(35); HRMS calcd for $C_{32}H_{44}O_8N_2SSi$ 644.2588, found 644.2591.

***N*,*N*-Dimethyl-4-[(*tert*-butyldimethylsilyl)oxy]-6-{(1R,4R,5S,6R)-6-[*N*-(*tert*-butyloxycarbonyl)-*N*-(4-methylphenylsulfonyl)amino]-4,5-isopropylidenedioxy-2-cyclohexen-1-yl}-1,3-benzodioxole-5-carboxamide (229).** *s*-BuLi in hexane (1.28 M, 7.02 mL) was added to a solution of tosylamide **218** (5.04 g, 8.17 mmol) in THF (25 mL) at 0 °C. The mixture was stirred at 0 °C for 15 min and di-*tert*-butyl dicarbonate (7.13 g, 32.67 mmol) was added. After refluxing for 4 days the reaction mixture was quenched with 10 mL of brine, the organic layer was separated and the aqueous phase was extracted with EtOAc (3x20 mL). The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. Chromtography of the residue (silica gel, hexane/ethyl acetate,

3:2) afforded 4.14 g (68%) of a mixture of atropisomers, **229**. (pure sample for analysis could not be obtained due to atropisomerism)

***N,N*-Dimethyl-6-[(1R,4R,5S,6R)-6-(*tert*-butyloxycarbonylamino)-4,5-isopropylidene-dioxy-2-cyclohexen-1-yl]-4-hydroxy-1,3-benzodioxole-5-carboxamide (231).** A solution of sodium anthracenide (ca. 0.6 N) was added dropwise under Ar at -78 °C to a stirred solution of **229** (5.68 g, 7.62 mmol) in DME (30 mL), until a blue color persisted for 15 min. The reaction mixture was quenched with saturated NH_4Cl solution (5 mL) and the solvent was removed in vacuo. The residue was taken up in ethyl acetate and filtered. Concentration and chromatography of the residue (silica gel, hexane/ethyl acetate, 2:3) gave **230** (2.81 g, 62%) and **231** (0.75, 20 %) as glassy solids.

A solution of tetrabutylammonium fluoride in THF (1 M, 9.8 mL) was added to a solution of **230** (2.81 g, 4.76 mmol) in THF (35 mL) at 0 °C. The resulting brown solution was stirred at 0°C for 1.5 h, the solvent was removed in vacuo and the residue was chromatographed (silica, ethyl acetate) to furnish **231** (2.11 g, 93 %) .

230, R_f 0.43 (hexanes/ethyl acetate, 1:1); α_D^{26} +46.2° (c 1.27, $CHCl_3$); IR (KBr) 3280, 2140, 1710, 1620, 1475, 1365, 1388, 1215, 1245, 1170, 1070, 835 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 6.48 (s, 1H), 6.13 (bd, *J* =9.0 Hz, 1H), 5.98 (dt, *J* =9.7, 3.2 Hz, 1H), 5.93 (m. 2H), 5.84 (m, 2H), 4.62 (m, 2H), 3.95 (dd, *J* =10.1, 5.9 (m, 3H), 3.73 (q, *J* =10.0 Hz, 1H), 3.07 (bs, 4H), 2.85 (s, 3H), 1.61 (s, 3H), 1.39 (s, 3H), 1.24 (s, 9H), 0.96 (s, 9H), 0.23 (s, 3H), 0.15 (s, 3H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 168.61 (C), 156.31 (C), 149.50 (C), 135.74 (C), 135.24 (CH), 134.44 (C), 132.78 (C), 125.03 (CH), 124.28 (C), 109.46 (C), 101.91 (CH), 101.04 (CH_2), 78.68 (CH), 77.80 (C), 72.89 (CH), 55.34 (CH), 43.41

(CH), 37.77 (CH_3), 34.81 (CH_3), 28.16 ($3CH_3$), 28.05 (CH_3), 26.19 (CH_3), 25.50 ($3CH_3$), 18.07 (C), -4.30 (CH_3), -4.55 (CH_3); MS (EI) *m/z* (rel. intensity) 591 (M^+, 100), 533 (8), 491 (2), 358 (3); HRMS calcd for $C_{30}H_{47}O_8N_2Si$ 591.3102, found 591.3143.

231, R_f 0.41 (ethyl acetate); $[\alpha]_D^{26}$ – 17.1° (c 1.31, $CHCl_3$); mp 133 °C (decomp.); IR (KBr) 3270 (broad), 2970, 2930, 1710, 1630, 1480, 1365 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 9.73 (bs, 1H), 6.39 (bs, 2H), 5.98 (d, *J* = 9.6 Hz, 1H), 5.82 (d, *J* = 5.6 Hz, 1H), 4.59 (t, *J* = 4.2 Hz, 1H), 3.60~4.40 (m, 3H), 2.98~3.40 (m, 7H), 1.53 (s, 3H), 1.38 (s, 3H), 1.20 (s, 9H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 169.72 (C), 155.38 (C), 149.26 (C), 136.24 (CH), 134.94 (C), 133.37 (C), 122.87 (C), 121.13 (C), 109.35 (C), 102.08 (C), 102.08 (CH), 101.27 (C), 78.94 (C), 77.49 (CH), 72.35 (CH), 55.86 (CH), 44.32 (CH), 37.37 (CH), 35.55 (CH), 27.91 (CH_3), 26.06 (CH_3); MS (EI, 70ev) *m/z* (rel. intensity) 476 (M^+, 6), 376 (16), 318 (30), 277 (59), 256 (20), 83 (100); HRMS calcd for $C_{24}H_{32}O_8N_2$ 476.2158, found 476.2153.

6-[(1R,4R,5S,6R)-6-(*tert*-Butyloxycarbonylamino)-4,5-isopropylidenedioxy-2-cyclohexen-1-yl]-4-hydroxy-1,3-benzodioxole-5-carbaldehyde (232).

Modified sodium bis(2-methoxyethoxy)alumium hydride (SMEAH) in toluene (1.02 M solution, 20 mL) was added to a stirred solution of **231** (2.82 g) in THF (80 mL) at -45 °C. After 9 h, additional SMEAH solution (9 mL) was added, and the mixture was stirred for another 22 h. The reaction was then quenched with saturated NH_4Cl solution (10 mL) and brine (10 mL). The organic phase was separated and the aqueous layer was extracted with ethyl acetate (3x50 mL). Drying of the combined organic layers, concentration and

chromatography (silica gel, ethyl acetate) of the residue gave aldehyde **232** as a white solid (853 mg, 72 %, based on recovered **231**) and recovered starting material (1.52 g): R_f 0.36 (hexane/ethyl acetate, 3:2); mp 168 °C (decomp.); $[\alpha]_D^{25}$ +5.9° (c 1.04, $CHCl_3$); IR (KBr) 3360, 2980, 1650, 1430, 1340, 1230 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 10.18 (s, 1H), 6.45 (s, 1H), 6.07 (bs, 3H), 5.93 (d, *J* = 10.0 Hz, 1H), 4.68 (m, 2H), 4.50 (bs, 1H), 4.36 (bs, 1H), 3.31 (bs, 1H), 1.51 (s, 3H), 1.41 (s, 3H), 1.32 (s, 9H); ^{13}C NMR δ 193.45 (CH), 155.20 (C), 154.83 (C), 147.20 (C), 143.01 (C), 134.64 (CH), 133.02 (C), 124.62 (CH), 116.16 (C), 109. 78 (C), 102.66 (C), 102.15 (CH), 79.85 (CH), 75.85 (CH), 75.51 (CH), 72. 23 (CH), 57.84 (CH), 28.10 (CH_3), 28.22 (CH_3), 25.81 (CH_3); MS (FAB) *m/z* (rel. intensity) 434 ($(M+H)^+$, 46), 378 (16), 320 (50), 258 (46), 240 (100), 135 (54), 85 (68). Anal. Calcd for $C_{22}H_{27}O_8N$: C, 60.96; H, 6.28. Found: C, 60.91; H, 6,27.

6-[(1R,4R,5S,6R)-6-(*tert*-Butyloxycarbonylamino)-4,5-isopropylidenedioxy-2-cyclohexen-1-yl]-4-(phenylmethoxy)-1,3-benzodioxole-5-carbaldehyde (233). Benzyl bromide (0.351 mL) was added to a suspension of phenol **232** (853 mg, 1.97 mmol) and K_2CO_3 (544 mg, 3.94 mmol) in DMF (8 mL). The reaction mixture was stirred at rt for 4h and then quenched with saturated $CuSO_4$ aqueous solution (5 mL) and brine (5 mL). The aqueous layer was extracted with ethyl acetate (3x15 mL), and the combined organic layers were dried over Na_2SO_4. Removal of the solvent and chromatography (silica gel, hexane/ethyl acetate, 3:1) of the residue afforded **233** (869 mg, 83%) as a glassy solid: R_f 0.48 (hexane/ethyl acetate, 3:2); α_D^{25} –86.4° (c 1.14, $CHCl_3$); IR (KBr) 3370 (broad), 3030, 2970, 2920, 1710, 1670, 1605, 1475, 1500, 1360, 1280, 1212, 1240, 1160, 1065, 1030 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 10.38 (s, 1H), 7.37 (m, 5H), 6.63 (s, 1H), 6.02 (d, *J* = 12.6 Hz, 2H), 6.00 (m, 1H), 5.82 (d, *J* = 9.9 Hz, 1H), 5.34 (s, 2H), 4.83 (d, *J*

= 10.8 Hz, 1H), 4.65 (m, 2H), 4.06 (dd, J = 10.3, 5.1 Hz, 1H), 3.71 (q, J = 10.4 Hz, 1H), 1.54 (s, 3H), 1.40 (s, 3H), 1.23 (s, 9H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 192.83 (CHO), 155.54 (C), 153.82 (C), 145.59 (C), 140.88 (C), 136.30 (C), 135.69 (CH), 135.13 (C), 128.62 (2xCH), 128.50 (2xCH), 127.94 (CH), 124.10 (CH), 121.52 (C), 109.60 (C), 104.52 (CH), 101.85 (CH_2), 78.57 (C), 77.87 (CH), 74.58 (CH), 72.80 (CH), 56.48 (CH), 40.87 (CH), 28.15 (3xCH_3), 26.19 (2xCH_3); MS (FAB) m/z (rel. intensity) 524 ($(M+H)^+$, 76), 506 (82), 466 (61), 438 (10), 406 (100), 348 (25), 330 (34); HRMS calcd for ($C_{29}H_{34}O_8N$+H) 524.2284, found 524.2263. Anal. Calcd for $C_{29}H_{33}O_8N$: C, 66.53; H, 6.35; N, 2.67. Found: C, 66.57; H, 6.51; N, 2.54.

Methyl 6-[(1R.4R,5S,6R)-6-(*tert*-butyloxycarbonylamino)-4,5-isopropylidenedioxy-2-cyclohexen-1-yl]-4-(phenylmethoxy)-1,3-benzodioxole-5-carboxylate (235). Aldehyde **233** (507 mg, 0.97 mmol) was dissolved in *t*-BuOH (24 mL) and 2-methyl-2-butene (6.6 mL, 85% purity). A solution of sodium chlorite (1.18 g, 10.43 mmol) and potassium dihydrogen phosphate (1.07 g, 7.86 mmol) in H_2O (10 mL) was added dropwise over a 10 min period. The yellow solution was stirred at rt overnight. Volatiles were removed under high vacuum, brine (3 mL) was added to the residue, and the aqueous layer was extracted with ethyl acetate (4x20 mL). The organic extract was dried over Na_2SO_4 and the crude acid **234** was then treated with excess diazomethane. Removal of the solvent and chromatography (silica gel, hexane/ethyl acetate, 3:2) gave the methyl ester **235** (526 mg, 98%) as a glassy solid: R_f 0.40 (hexane/ethyl acetate, 3:2); α_D^{25} +17.1° (c 1.07, $CHCl_3$); IR (KBr) 3370, 2980, 1715, 1620, 1500, 1480, 1370, 1280, 1240, 1160, 1070, 1030; ^1H NMR (270 MHz, $CDCl_3$) δ 7.26~7.39 (m, 5H), 6.54 (s, 1H), 5.84~5.99 (4H, m), 5.21 (s, 2H), 4.94 (bs, 1H), 4.63 (t, J = 4.4 Hz, 1H), 4.01 (bs, 1H), 3.79 (s, 3H), 3.73 (q, J = 10.1 Hz, 1H), 3.36 (bs, 1H), 1.61 (s, 3H), 1.40 (s, 3H), 1.27 (s, 9H); ^{13}C NMR

(68 MHz, $CDCl_3$) δ 168.14 (C), 155.51 (C), 150. 56 (C), 139.46 (C), 136.99 (C), 127.63 (2CH), 135.19 (CH), 134.01 (C), 128.29 (CH), 127.94 (2CH), 127.63 (2CH), 124.22 (CH), 121.42 (CH), 109.56 (CH_2), 103.29 (CH), 101.48 (C), 78.67 (C), 77.37 (CH), 72.27 (CH_2), 72.54 (CH), 55.52 (CH), 52.09 (CH_3), 43.84 (CH), 29.58 ($3CH_3$), 26.06 ($2CH_3$); MS (FAB) *m/z* (rel. intensity) 554 ($(M+H)^+$, 8), 496 (4), 454 (6), 440 (19), 396 (10), 346 (13), 144 (9), 121 (11), 91 (100). Anal. Calcd for $C_{30}H_{35}O_9N$: C, 65.09; H, 6.37; N, 2.53. Found: C, 65.29; H, 6.61; N, 2.34.

Methyl 6-[(1R,4R,5S,6R)-6-(*tert*-Butyloxycarbonylamino)-4,5-dihydroxy-2-cyclohexen-1-yl]-4-(phenylmethoxy)-1,3-benzodioxole-5-carboxylate (243). Methyl ester **235** (488 mg, 0.88 mmol) was dissolved in a mixture of acetic acid, THF and H_2O (2:1:1) (8 mL) and the solution was heated to 60 °C for 3 h. The solvent was removed in vacuo and the residue was subjected to chromatography (hexane/ethyl acetate, 1:4) to afford 4,5-diol (324 mg, 73%) as a white solid: R_f 0.19 (hexane/ethyl acetate, 2:3); mp 129-131 °C; α_D^{25} +73.7° (c 0.91, $CHCl_3$); ^1H NMR (270 MHz, $CDCl_3$), δ 7.27~7.40 (m, 5H), 6.61 (s, 1H), 6.15 (bs, 1H), 5.97 (m, 3H), 5.59 (d, J = 9.1 Hz, 1H), 5.23 (AB, J = 11.3 Hz, Δν = 25.1 Hz, 2H), 4.83 (bs, 1H), 4.23 (t, J = 3.3 Hz, 1H), 3.87 (m, 1H), 3.73 (s, 3H), 3.61 (m, 1H), 3.31 (bs, 1H), 3.29 (d, J = 10.2 Hz, 1H), 1.38 (s, 9H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 168.83 (C), 158.68 (C), 151.08 (C), 139.38 (C), 136.92 (C), 136.10 (C), 134.91 (C), 132.75 (CH), 128.40 (CH), 128.13 (CH), 127.80 (CH), 126.98 (CH), 120.88 (C), 103.60 (CH), 101.72 (CH_2), 80.03 (C), 74.86 (CH), 74.39 (CH), 66.68 (CH), 54.66 (CH), 52.50 (CH_3), 45.02 (CH), 28.29 ($3xCH_3$); MS (FAB) *m/z* (rel. intensity) 514 ($(M+H)^+$, 6), 414 (40), 382 (6), 256 (7), 91 (100); HRMS calcd for ($C_{27}H_{31}O_9N$+H) 514.2077, found 514.2165. Anal. Calcd for $C_{27}H_{31}O_9N$: C, 63.15; H, 6.08; N, 2.73. Found: C, 62.48; H, 6.19; N, 2.57.

Methyl 6-[(1R,2R,3S,4S,5S,6R)-6-(*tert*-Butyloxycarbonylamino)-5,6-epoy-3,4-dihydroxycyclohex-1-yl]-4-(phenylmethoxy)-1,3-benzodioxole-5-carboxylate (244). *t*-Butyl hydroperoxide in decane (5 M, 0.45 mL) was added to a solution of **243** (280 mg, 0.55 mmol) and vanadyl acetylacetonate (7 mg, 0.026 mmol) in benzene (10 mL). After stirring for 2 h at 60 °C, the reaction mixture was concentrated under reduced pressure and subjected to chromatography (hexane/ethyl acetate, 1:5) to afford epoxide **16** (129 mg, 53% yield based on recovered starting material) as a glassy solid and recovered starting material (42 mg): R_f 0.18 (hexane/ethyl acetate, 1:4); $[\alpha]_D^{25}$ +28.6° (c 1.48, $CHCl_3$); IR (KBr) 3380, 1705, 1615, 1475, 1360, 1280, 1260, 1240, 1080 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.27~7.40 (m, 5H), 7.04 (s, 1H), 5.99 (d, J = 2.3 Hz, 2H), 5.68 (bd, J = 7.3 Hz, 1H), 5.24 (AB, J = 11.3 Hz, Δν = 16.5 Hz, 2H), 4.28 (t, J = 5.0 Hz, 1H), 3.83 (m, 4H), 3.35~3.46 (m, 3H), 3.07 (d, J = 10.9 Hz, 1H), 1.33 (s, 9H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 168.72 (C), 158.06 (C), 151.18 (C), 139.47 (C), 136.86 (C), 136.42 (C), 132.46 (C), 128.37 (2CH), 128.12 (CH), 127.82 (2CH), 121.31 (C), 103.52 (CH), 101.73 (CH_2), 79.85 (C), 74.46 (CH), 74.39 (CH_2), 66.28 (CH), 58.09 (CH), 52.70 (CH), 52.46 (CH_3), 50.49 (CH), 43.29 (CH), 29.23 ($3CH_3$); MS (FAB) *m/z* (rel. intensity) 530 ($(M+H)^+$, 17), 474 (6), 430 (53), 151 (42), 135 (70), 119 (100); HRMS calcd for ($C_{27}H_{31}O_{10}N$+H) 530.2026, found 530.2050.

Pancratistatin (9) A suspension of epoxide **244** (109 mg, 0.21 mmol) and sodium benzoate (1mg) in water (8mL) was stirred at 100 °C for 6 days. The mixture was then concentrated and subjected to chromatography (chloroform/methanol, 4:1) to afford 35 mg (51 %) of pancratistatin: R_f 0.40 (chloroform/methanol, 4:1); mp 260 °C (starts to

decompose); $[\alpha]_D^{26}$ +40.9° (c 1.0, DMSO); ^{1}H NMR (400 MHz, DMSO-d6) δ 13.06 (s, 1H), 7.51 (s, 1H), 6.48 (s, 1H), 6.05 (d, *J* =1.0Hz), 6.02 (d, *J* =1.0 Hz), 5.35 (bs, 1H), 5.35 (bs, 1H), 5.04 (bs, 2H), 4.84 (bs, 1H), 4.27 (bs, 1H), 3.95 (bs, 1H), 3.84 (bs, 1H), 3.74 (m, 2H), 2.96 (d, *J* =11.5 Hz, 1H).

VI. SPECTRA

1. (1*R*,4*S*,5*S*,6*R*)-3-Chloro-4,5-isopropylidenedioxy-7-(4'-methylphenylsulfonyl) azabicyclo[4.1.0]hept-2-ene (**7a**).
   ^{1}H NMR (270 MHz, $CDCl_3$), ^{13}C NMR (68 MHz, $CDCl_3$)

2. (1*R*,4*S*,5*S*,6*R*)-3-Bromo-4,5-isopropylidenedioxy-7-(4'-methylphenylsulfonyl)-7-azabicyclo[4.1.0]hept-2-ene (**169**).
   ^{1}H NMR (270 MHz, $CDCl_3$), ^{13}C NMR (100 MHz, $CDCl_3$)

3. (1*R*,4*R*,5*S*,6*R*)-4,5-Isopropylidenedioxy-7-(4'-methylphenylsulfonyl)7a-zabicyclo [4.1.0]hept-2-ene (**7b**).
   ^{1}H NMR (270 MHz, $CDCl_3$), ^{13}C NMR (68 MHz, $CDCl_3$)

4. (1R, 6S)-4-chloro-5,6-isopropylidenedioxy-cyclohex-2-enol (**171**).
   ^{1}H NMR (270 MHz, $CDCl_3$), ^{13}C NMR (68 MHz, $CDCl_3$)

5. (1*R*,2*S*,5*S*,6*S*)-4-Chloro-5,6-isopropylidenedioxy-2-methylcyclohex-3-enol (**172**).
   ^{1}H NMR (270 MHz, $CDCl_3$), ^{13}C NMR (68 MHz, $CDCl_3$)

6. (1*R*,2*S*,5*S*,6*S*)-4-Chloro-5,6-isopropylidenedioxy-2-cyclohexylmethylcyclohex-3-enol (**174**).
   ^{1}H NMR (270 MHz, $CDCl_3$), ^{13}C NMR (68 MHz, $CDCl_3$)

7. (1*R*,5*R*,6*S*)-5,6-Isopropylidenedioxy-4,4-diphenylcyclohex-2-enol (**175**).
   ^{1}H NMR (270 MHz, $CDCl_3$), ^{13}C NMR (68 MHz, $CDCl_3$)

8. (1*R*,2*R*,5*R*,6*S*)-2,4-Di(cyclohexylmethyl)-5,6-isopropylidenedioxy-cyclohex-3-enol (**176**).
   ^{1}H NMR (270 MHz, $CDCl_3$), ^{13}C NMR (68 MHz, $CDCl_3$)

9. (1*R*,2*S*,5*R*,6*S*)-5,6-Isopropylidenedioxy-2-methylcyclohex-3-enol (**184**).
   ^{1}H NMR (270 MHz, $CDCl_3$), ^{13}C NMR (68 MHz, $CDCl_3$)

10. (1*R*,4*S*,5*R*,6*S*)-5,6-Isopropylidenedioxy-4-methylcyclohex-2-enol (**185**).
^{1}H NMR (270 MHz, $CDCl_3$), ^{13}C NMR (100 MHz, $CDCl_3$)

11. (1*R*,4*S*,5*R*,6*S*)-4-Cyclohexylmethyl-5,6-isopropylidenedioxycyclohex-2-enol (**186**).
^{1}H NMR (270 MHz, $CDCl_3$), ^{13}C NMR (68 MHz, $CDCl_3$)

12. (1*R*,2*R*,5*R*,6*S*)-2-Cyclohexylmethyl-5,6-isopropylidenedioxycyclohex-3-enol (**187**).
^{1}H NMR (270 MHz, $CDCl_3$), ^{13}C NMR (68 MHz, $CDCl_3$)

13. (1*R*,2*R*,5*R*,6*S*)-5,6-Isopropylidenedioxy-2-methylcyclohex-3-enol (**188**).
^{1}H NMR (270 MHz, $CDCl_3$), ^{13}C NMR (100 MHz, $CDCl_3$)

14. (1*R*,2*S*,5*R*,6*S*)-*N*-(5,6-Isopropylidenedioxy-2,4-diphenylcyclohex-3-enyl)-(4'-methylphenyl)sulfonamide (**189**).
^{1}H NMR (400 MHz, $CDCl_3$), ^{13}C NMR (100 MHz, $CDCl_3$)

15. (1*R*,5*R*,6*S*)-*N*-(4,4-Diphenyl-5,6-isopropylidenedioxycyclohex-2-enyl)-(4'-methylphenyl)sulfonamide (**190**).
^{1}H NMR (400 MHz, $CDCl_3$), ^{13}C NMR (100 MHz, $CDCl_3$)

16. (1*R*,2*R*,5*R*,6*S*)-*N*-[2,4-Di(cyclohexylmethyl)-5,6-isopropylidenedioxycyclohex-3-enyl]-(4'-methylphenyl)sulfonamide (**191**).
^{1}H NMR (270 MHz, $CDCl_3$), ^{13}C NMR (68 MHz, $CDCl_3$)

17. (1*R*,2*S*,5*S*,6*S*)-*N*-(4-Chloro-5,6-isopropylidenedioxy-2-methylcyclohex-3-enyl)-(4'-methylphenyl)sulfonamide (**192**).
^{1}H NMR (400 MHz, $CDCl_3$), ^{13}C NMR (100 MHz, $CDCl_3$)

18. (1*R*,4*S*,5*R*,6*S*)-*N*-(4-Cyclohexylmethyl-5,6-isopropylidenedioxycyclohex-2-enyl)-(4'-methylphenyl)sulfonamide (**196**).
^{1}H NMR (270 MHz, $CDCl_3$), ^{13}C NMR (68 MHz, $CDCl_3$)

19. (1*R*,4*R*,5*R*,6*S*)-*N*-(5,6-Isopropylidenedioxy-4-phenylcyclohex-2-enyl)-(4'-methylphenyl)sulfonamide (**197**).
^{1}H NMR (270 MHz, $CDCl_3$), ^{13}C NMR (68 MHz, $CDCl_3$)

20. (1*R*,2*R*,5*R*,6*S*)-*N*-(5,6-Isopropylidenedioxy-2-phenylcyclohex-3-enyl)-(4'-methylphenyl)sulfon-amide (**198**).
^{1}H NMR (270 MHz, $CDCl_3$), ^{13}C NMR (68 MHz, $CDCl_3$)

21. (1*R*,2*S*,5*R*,6*S*)-*N*-(5,6-Isopropylidenedioxy-2-methylcyclohex-3-enyl)-(4'-methylphenyl)sulfonamide (**199**).
^{1}H NMR (270 MHz, $CDCl_3$), ^{13}C NMR (68 MHz, $CDCl_3$)

22. *N*,*N*-Diethyl-4-ethoxymethoxy-6-[4,5-isopropylidenedioxy-6-(4-methylphenyl-sulfonylamino)-2-cyclohexen-1-yl]-1,3-benzodioxole-5-carboxamide (**204**).
^{1}H NMR (270 MHz, $CDCl_3$), ^{13}C NMR (68 MHz, $CDCl_3$)

23. *N*,*N*-Diethyl-6[(1*R*,4*R*,5*S*,6*R*)-(6-amino-4,5-isopropylidenedioxy-2-cyclohexen-1-yl)]-4-(ethoxymethoxy)-1,3-benzodioxole-5-carboxamide (**207**).
^{1}H NMR (270 MHz, $CDCl_3$)

24. *N*,*N*-Dimethyl-4-(*tert*-butyldimethylsilyl)oxy-1,3-benzodioxole-5-carboxamide (**217**).
^{1}H NMR (270 MHz, $CDCl_3$), ^{13}C NMR (68 MHz, $CDCl_3$)

25. *N*,*N*-Dimethyl-4-[(*tert*-butyldimethylsilyl)oxy]-6-[(1*R*,4*R*,5*S*,6*R*)-4,5-isopropylidenedioxy-6-(4-methylphenylsulfonylamino)-2-cyclohexen-1-yl]-1,3-benzodioxole-5-carboxamide (**218**).
^{1}H NMR (270 MHz, $CDCl_3$), ^{13}C NMR (68 MHz, $CDCl_3$)

26. *N*,*N*-Dimethyl-6-[(1*R*,4*R*,5*S*,6*R*)-6-(*tert*-butyloxycarbonylamino)-4,5-isopropylidene-dioxy-2-cyclohexen-1-yl]-4-hydroxy-1,3-benzodioxole-5-carboxamide (**231**).
^{1}H NMR (270 MHz, $CDCl_3$), ^{13}C NMR (68 MHz, $CDCl_3$)

27. 6-[(1*R*,4*R*,5S,6*R*)-6-(*tert*-Butyloxycarbonylamino)-4,5-isopropylidenedioxy-2-cyclohexen-1-yl]-4-hydroxy-1,3-benzodioxole-5-carbaldehyde (**232**).
^{1}H NMR (270 MHz, $CDCl_3$), ^{13}C NMR (68 MHz, $CDCl_3$)

28. 6-[(1R,4R,5S,6R)-6-(*tert*-Butyloxycarbonylamino)-4,5-isopropylidenedioxy-2-cyclohexen-1-yl]-4-(phenylmethoxy)-1,3-benzodioxole-5-carbaldehyde (**233**).
^{1}H NMR (270 MHz, $CDCl_3$), ^{13}C NMR (68 MHz, $CDCl_3$)

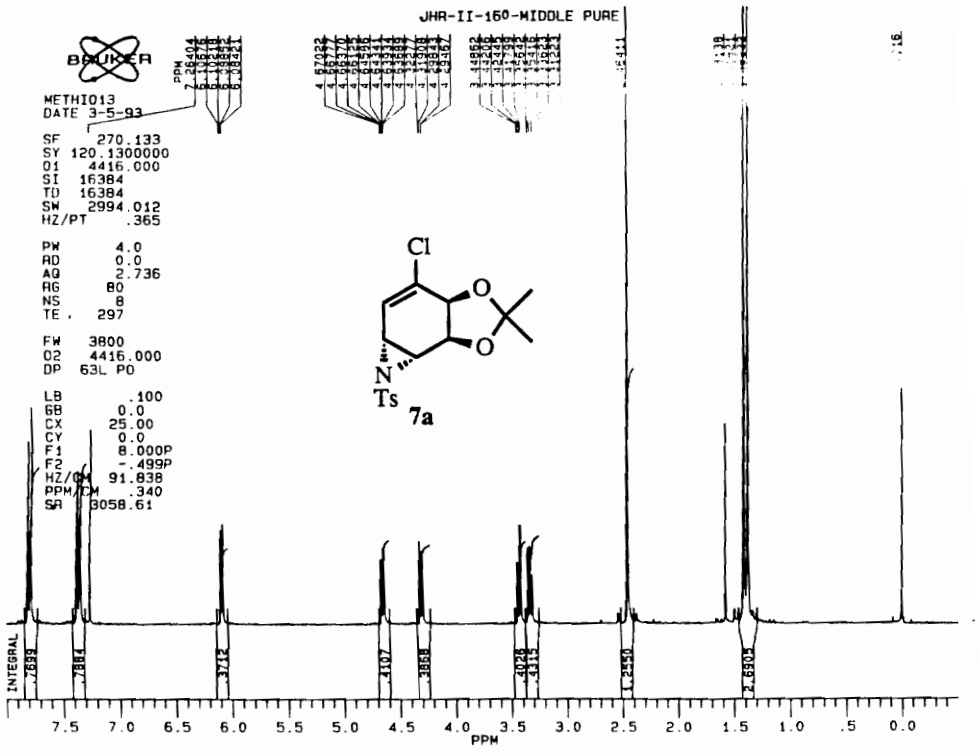
29. Methyl 6-[(1R.4R,5S,6R)-6-(*tert*-butyloxycarbonylamino)-4,5-isopropylidene-dioxy-2-cyclohexen-1-yl]-4-(phenylmethoxy)-1,3-benzodioxole-5-carboxylate (**235**).
^{1}H NMR (270 MHz, $CDCl_3$)

30. Methyl 6-[(1*R*,4*R*,5*S*,6*R*)-6-(*tert*-Butyloxycarbonylamino)-4,5-dihydroxy-2-cyclohexen-1-yl]-4-(phenylmethoxy)-1,3-benzodioxole-5-carboxylate (**243**).
^{1}H NMR (270 MHz, $CDCl_3$), ^{13}C NMR (68 MHz, $CDCl_3$)

31. Methyl 6-[(1*R*,2*R*,3*S*,4*S*,5*S*,6*R*)-6-(*tert*-Butyloxycarbonylamino)-5,6-epoy-3,4-dihydroxy-cyclohex-1-yl]-4-(phenylmethoxy)-1,3-benzodioxole-5-carboxylate (**244**).
^{1}H NMR (270 MHz, $CDCl_3$), ^{13}C NMR (68 MHz, $CDCl_3$)

32. (1β,2α,3β,4β,4aβ,11bα)-1,2,3,4-Tetrahydroxy-8,9-methylenedioxy-7-phenyl-methoxy-1,3,4,4a,5,10b-hexahydro-1,3-dioxolo[4,5-j]phenanthridin-6-(2H)-one (**250**).
^{1}H NMR (270 MHz, DMSO-d_6)

33. Pancratistatin (**9**).
^{1}H NMR (400 MHz, DMSO-d_6)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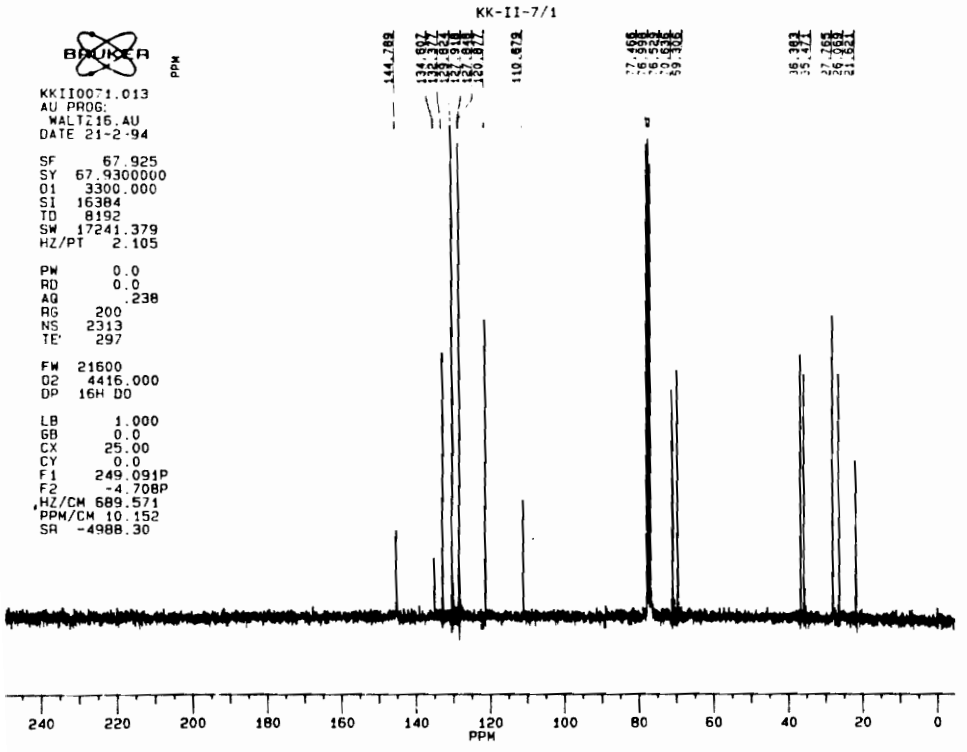
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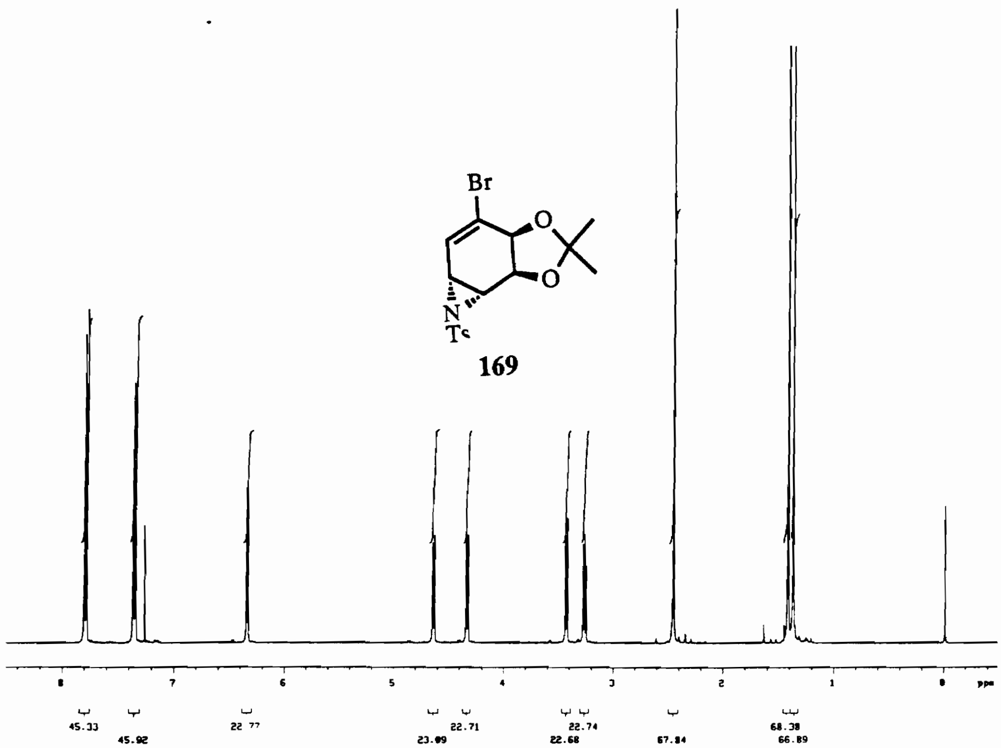
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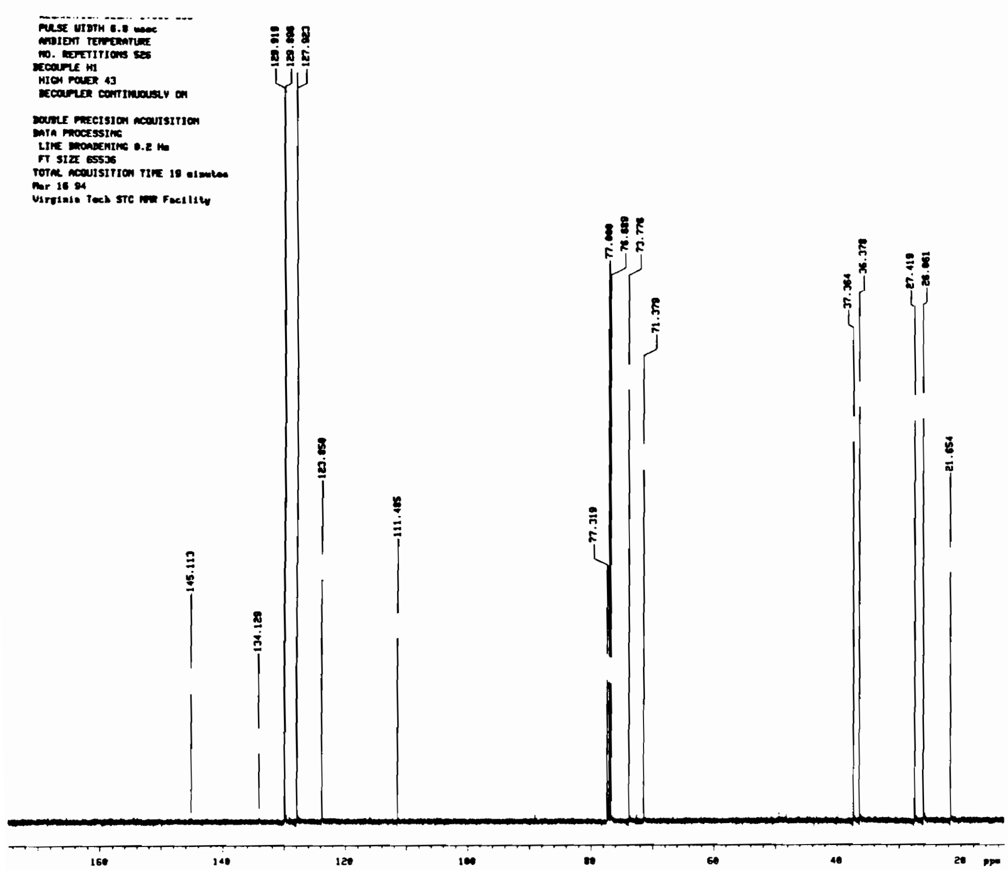
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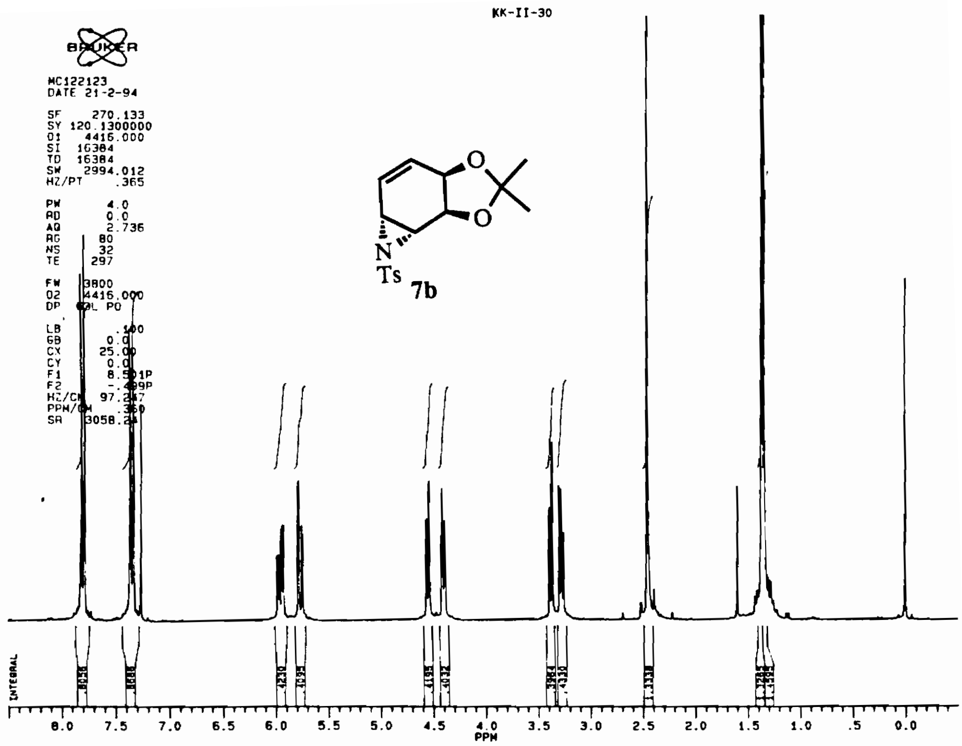
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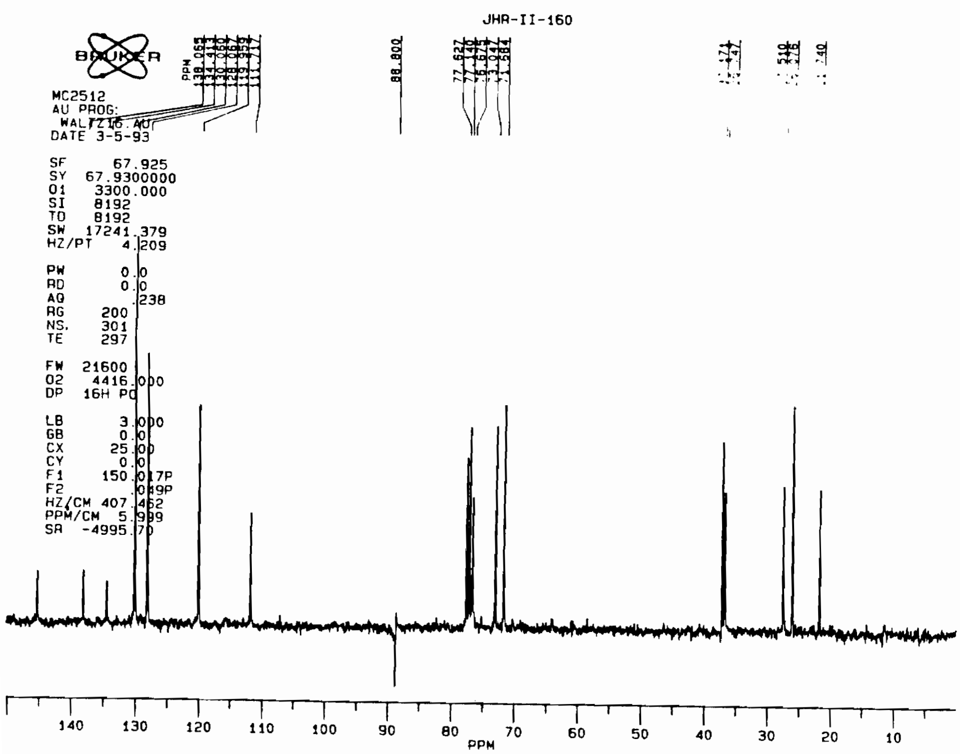
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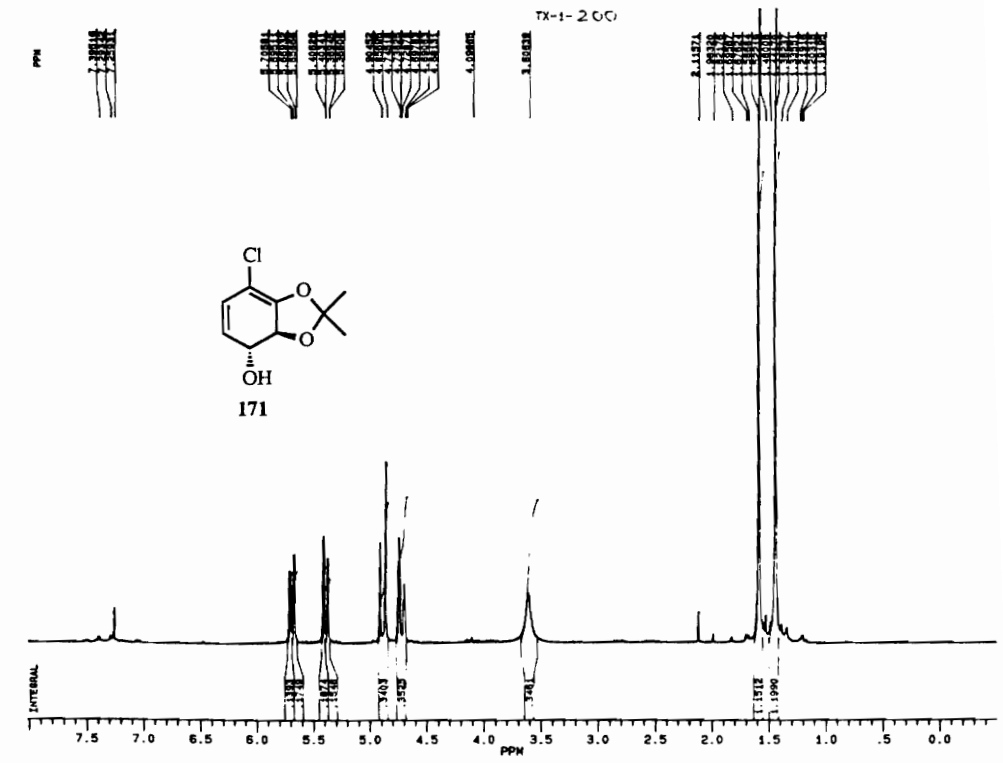
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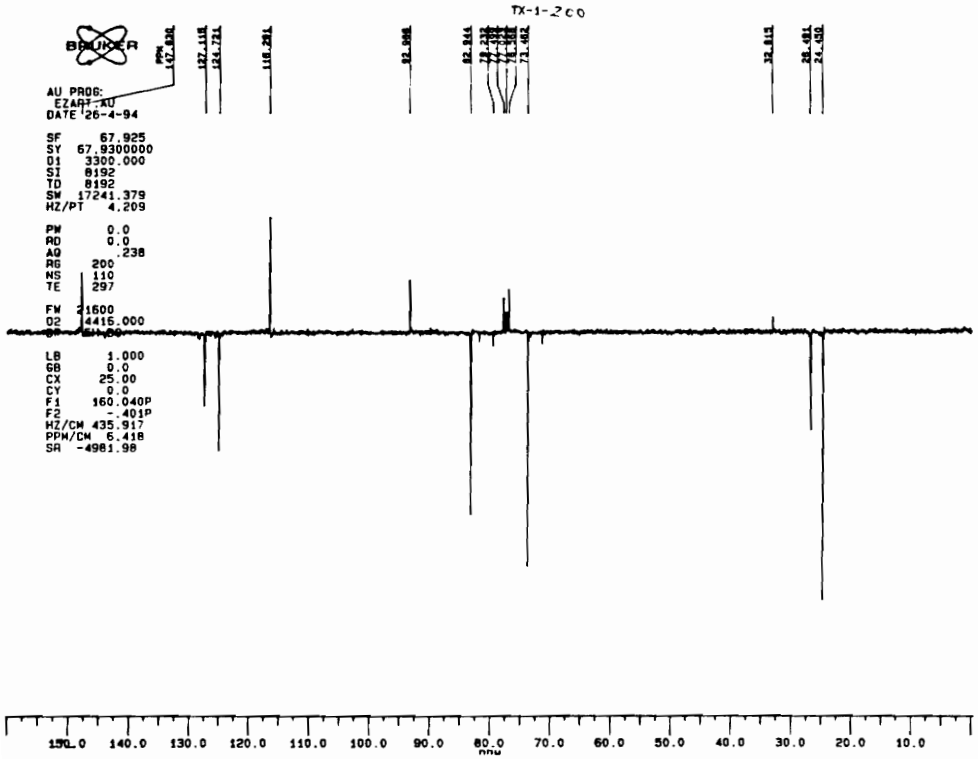
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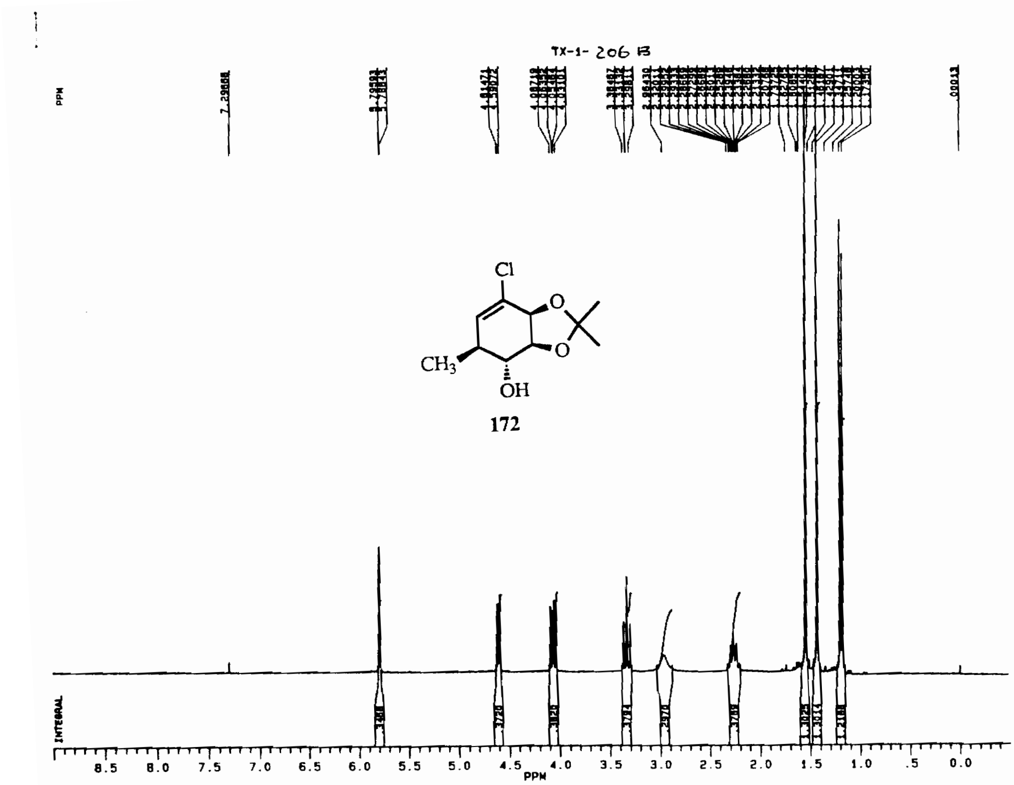
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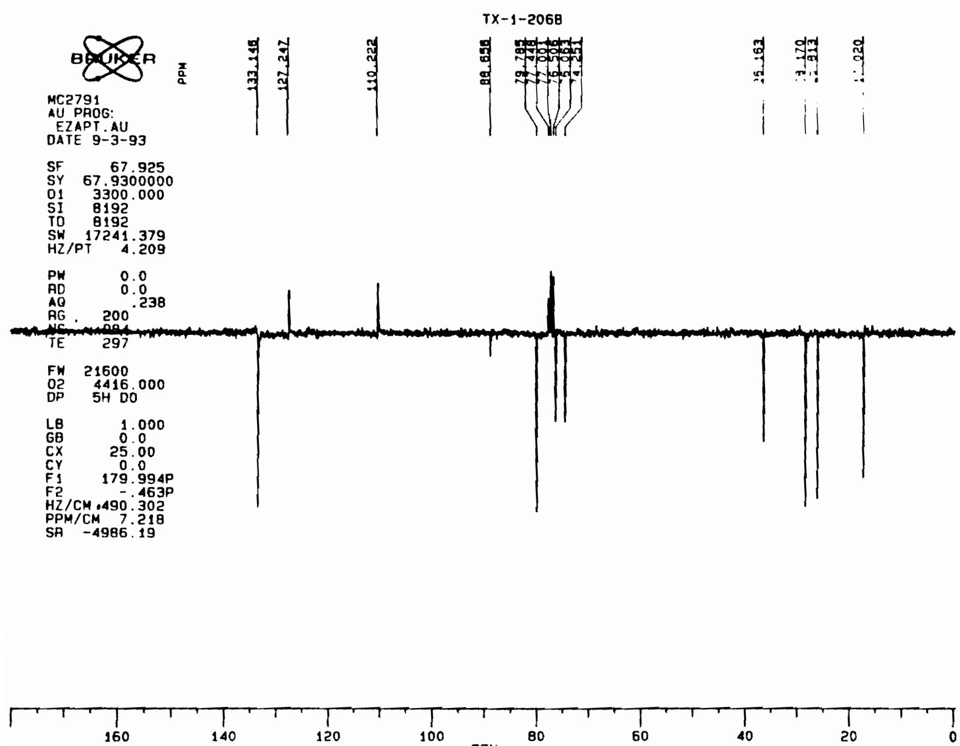
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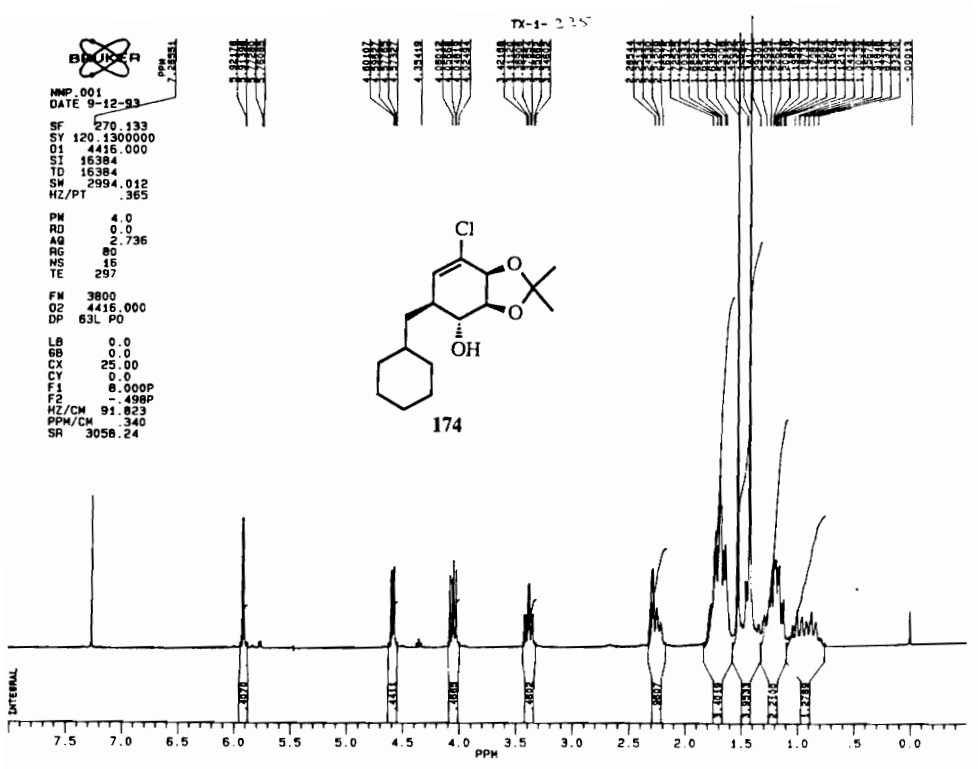
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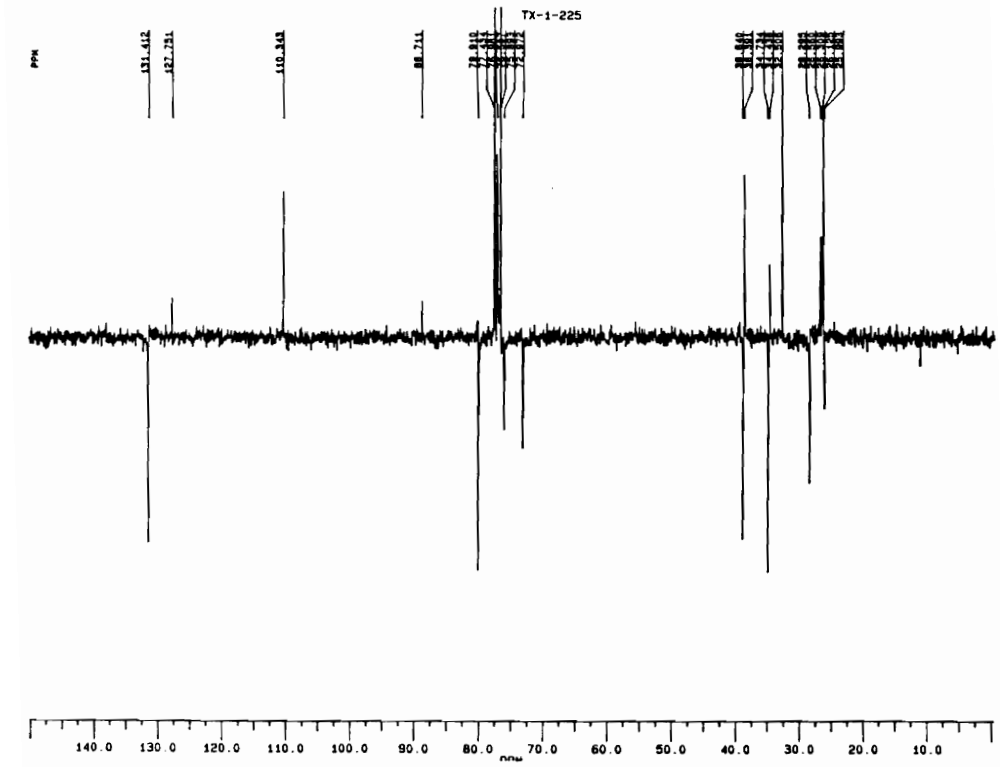
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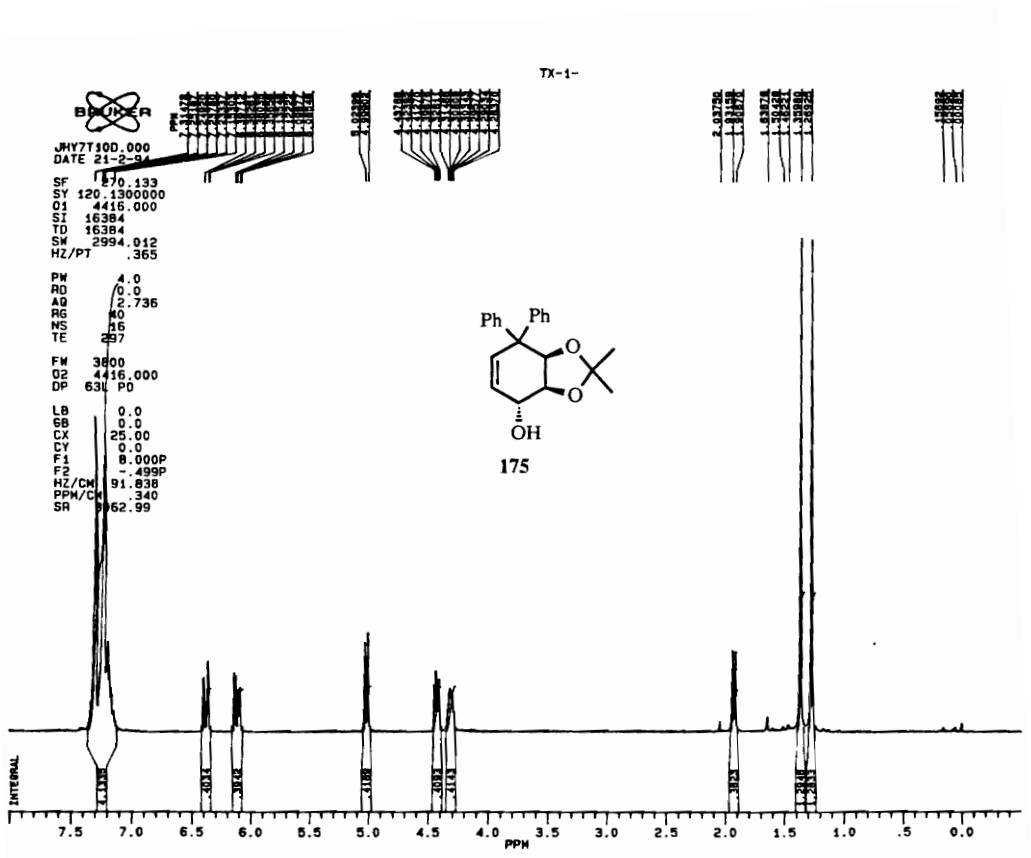
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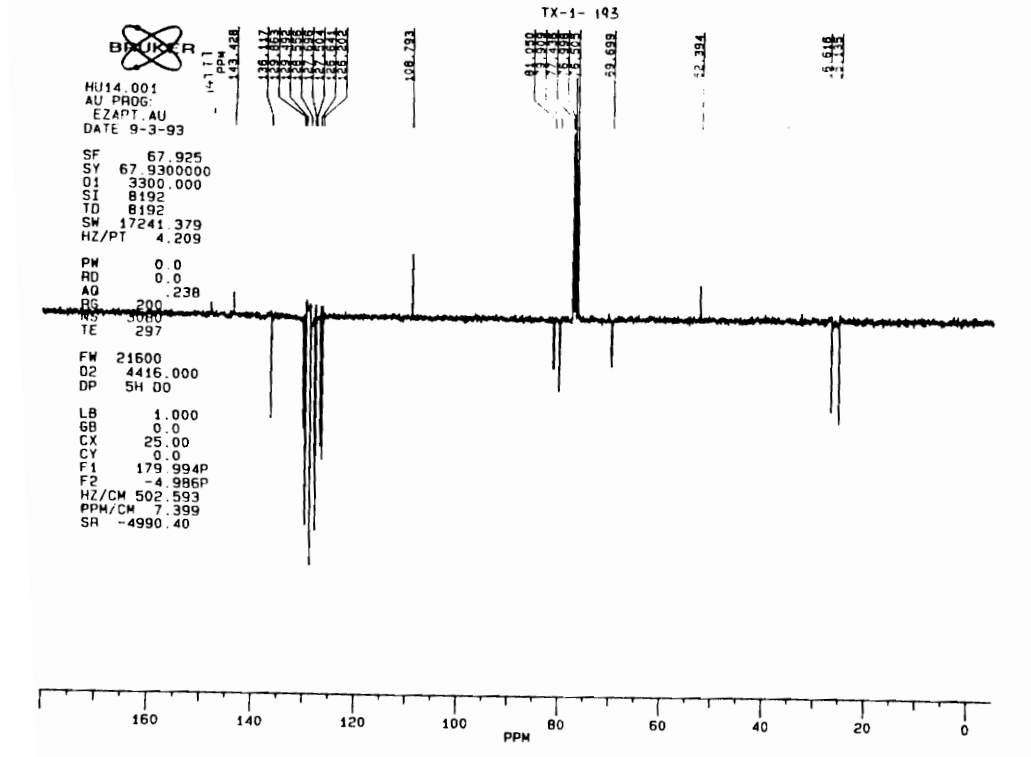
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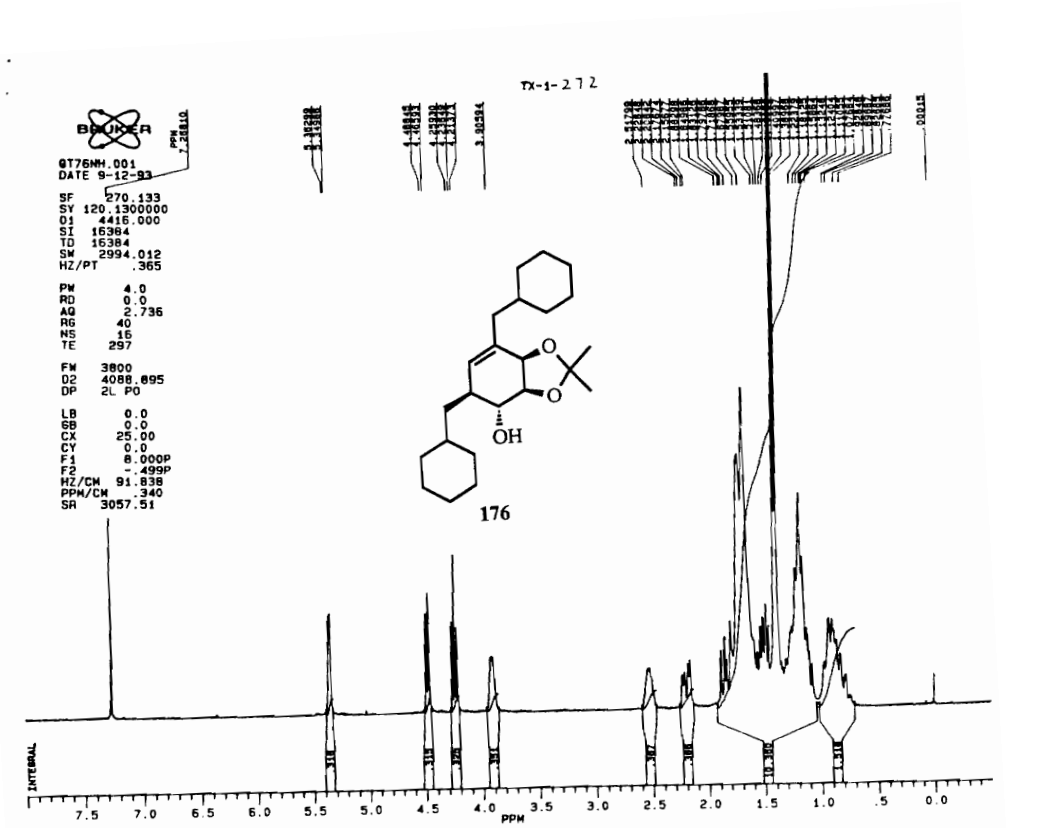
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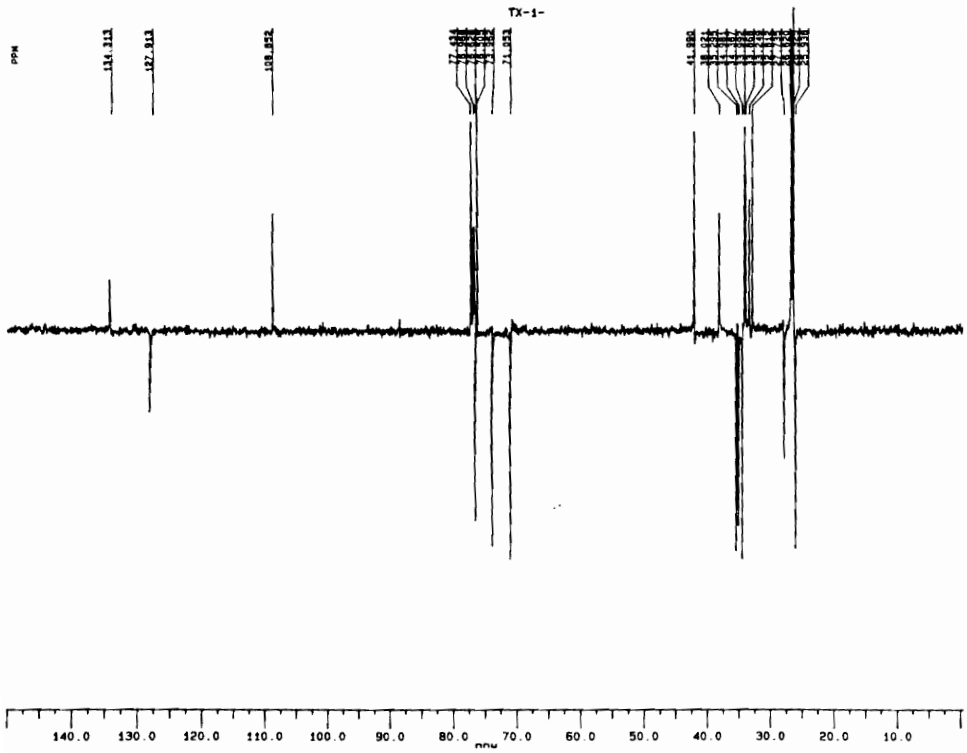
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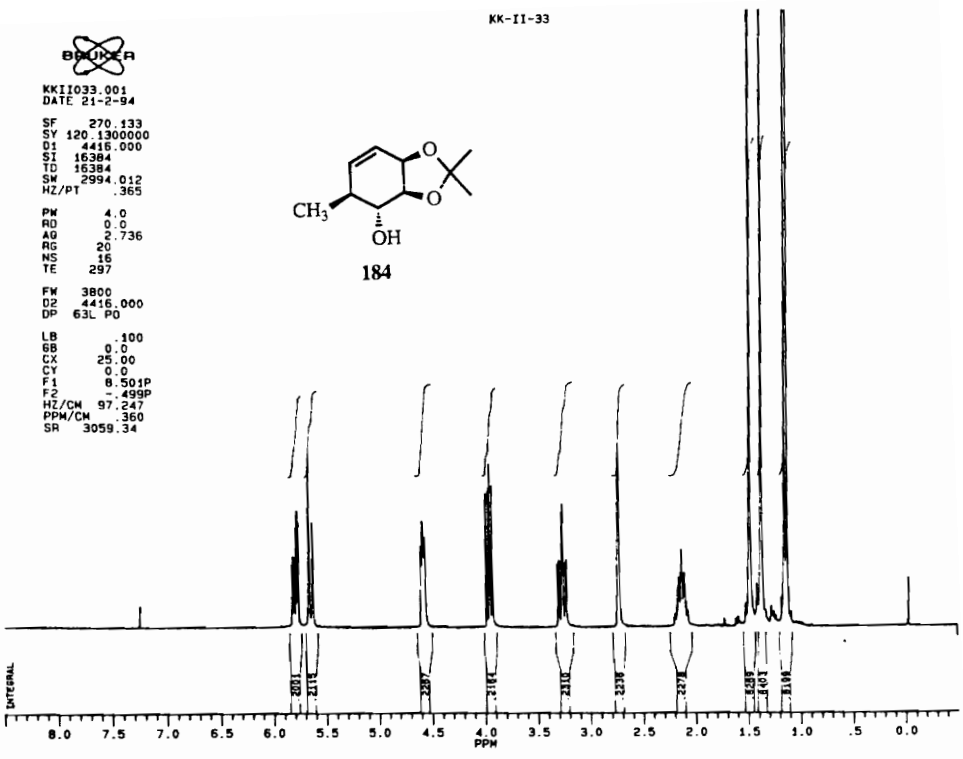
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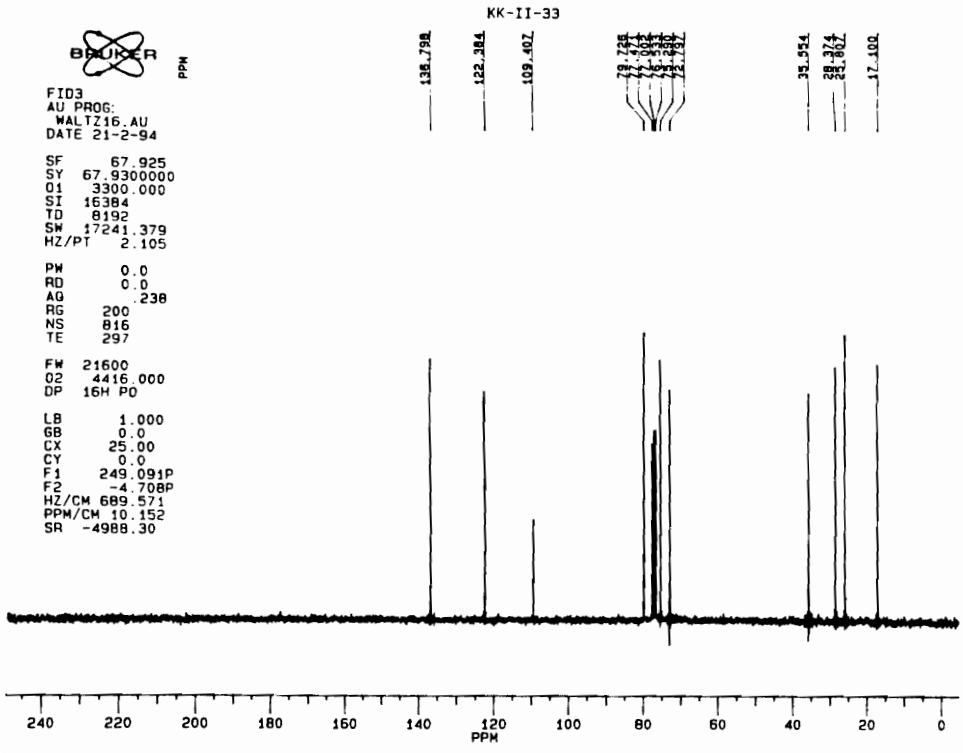
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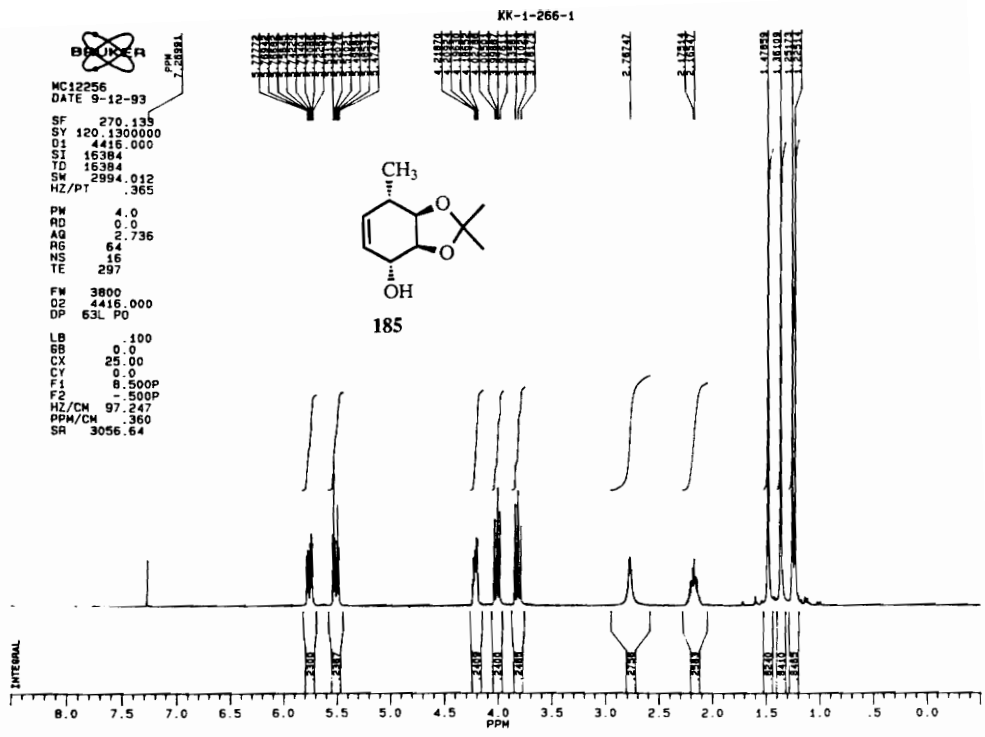
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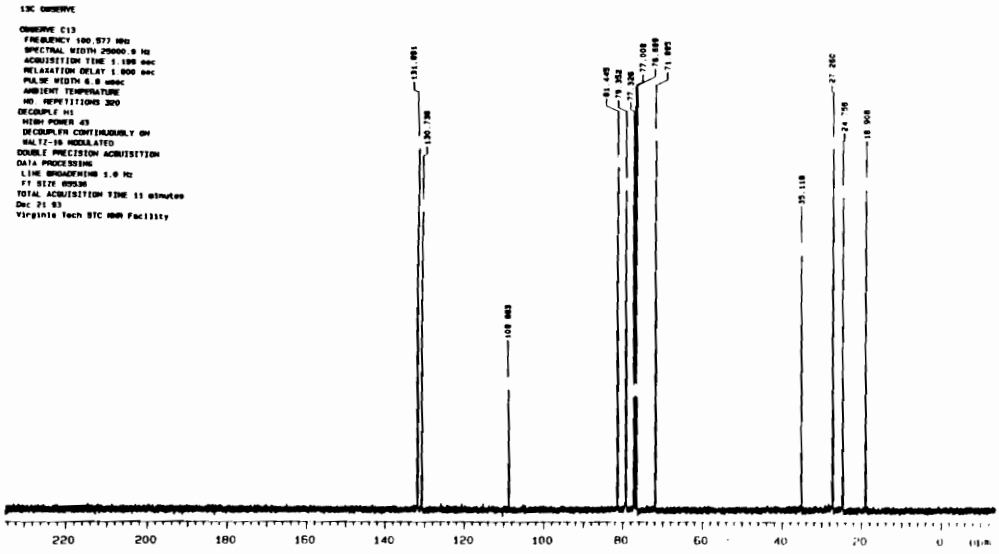
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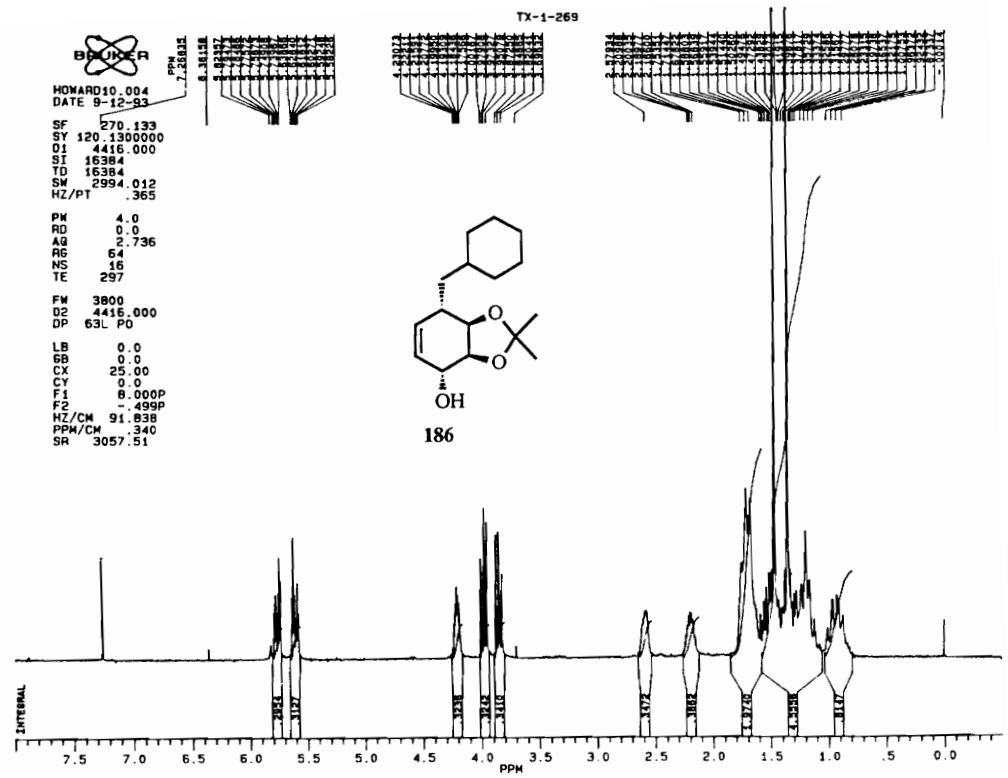
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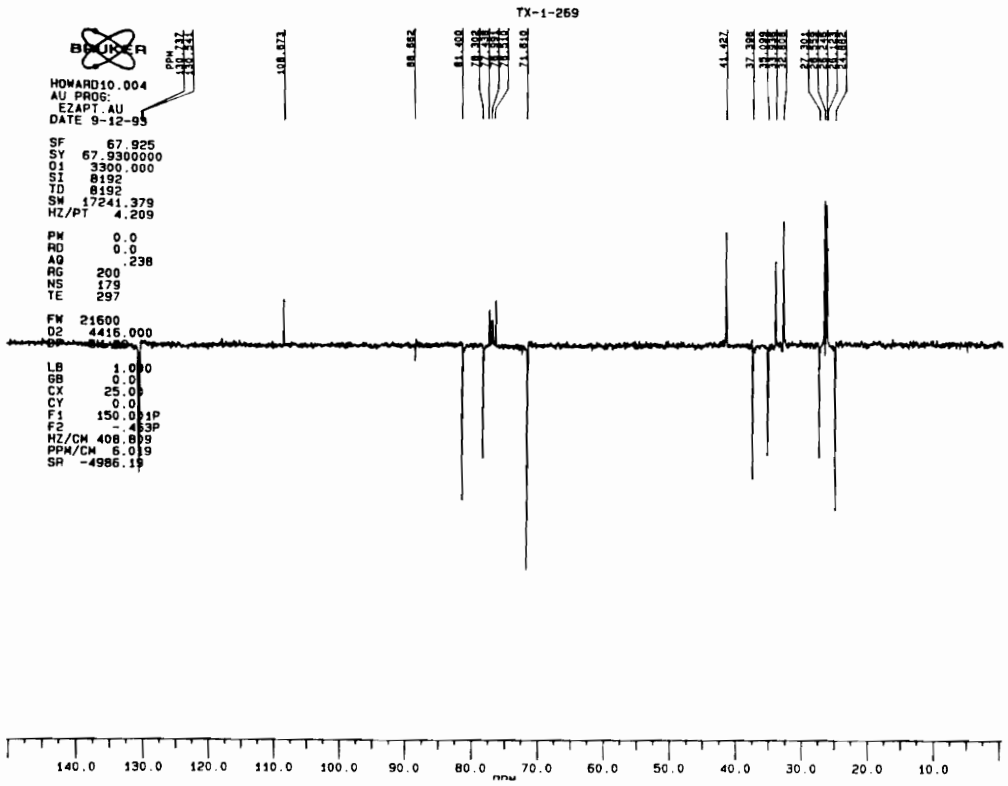
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HZ/PT 4.209
PW 0.0
RD 0.0
AQ .238
RG 200
NS 179
TE 297
FW 21600
D2 4416.000
LB 1.000
GB 0.0
CX 25.00
CY 0.0
F1 150.001P
F2 -.463P
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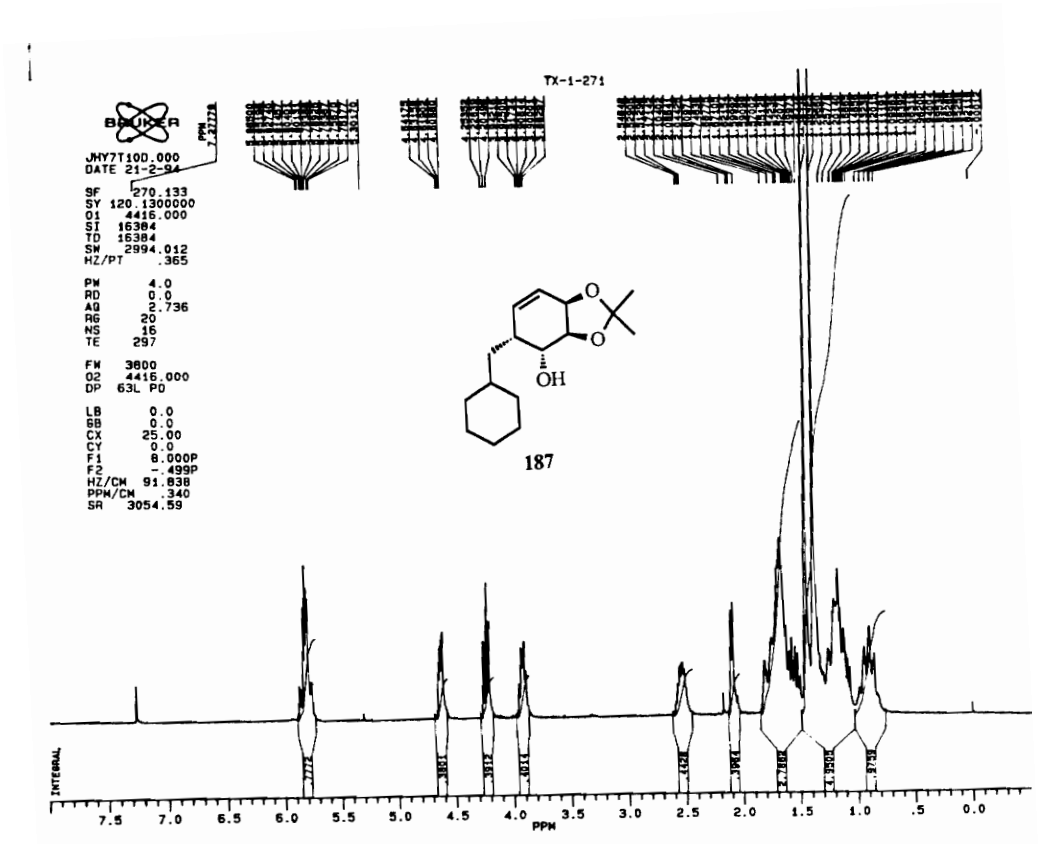
SR -4986.19
PPM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BRUKER
JHY7T10D.000
DATE 21-2-94
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RG 20
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TE 297
FW 3800
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DP 63L P0
LB 0.0
GB 0.0
CX 25.00
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PPM/CM .340
SR 3054.59
OH
187
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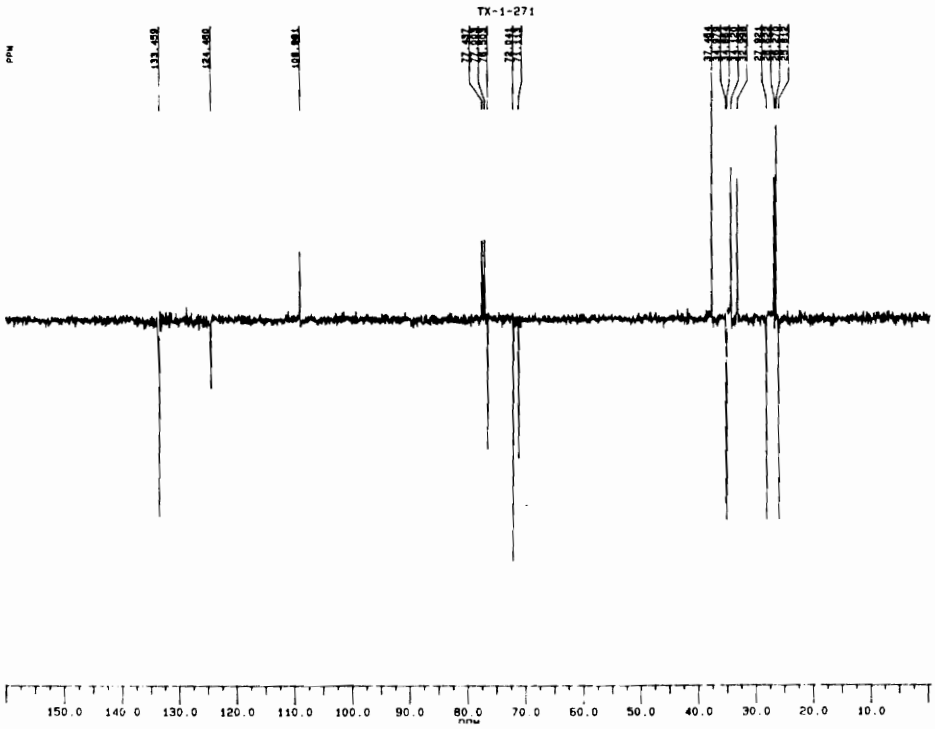
PPM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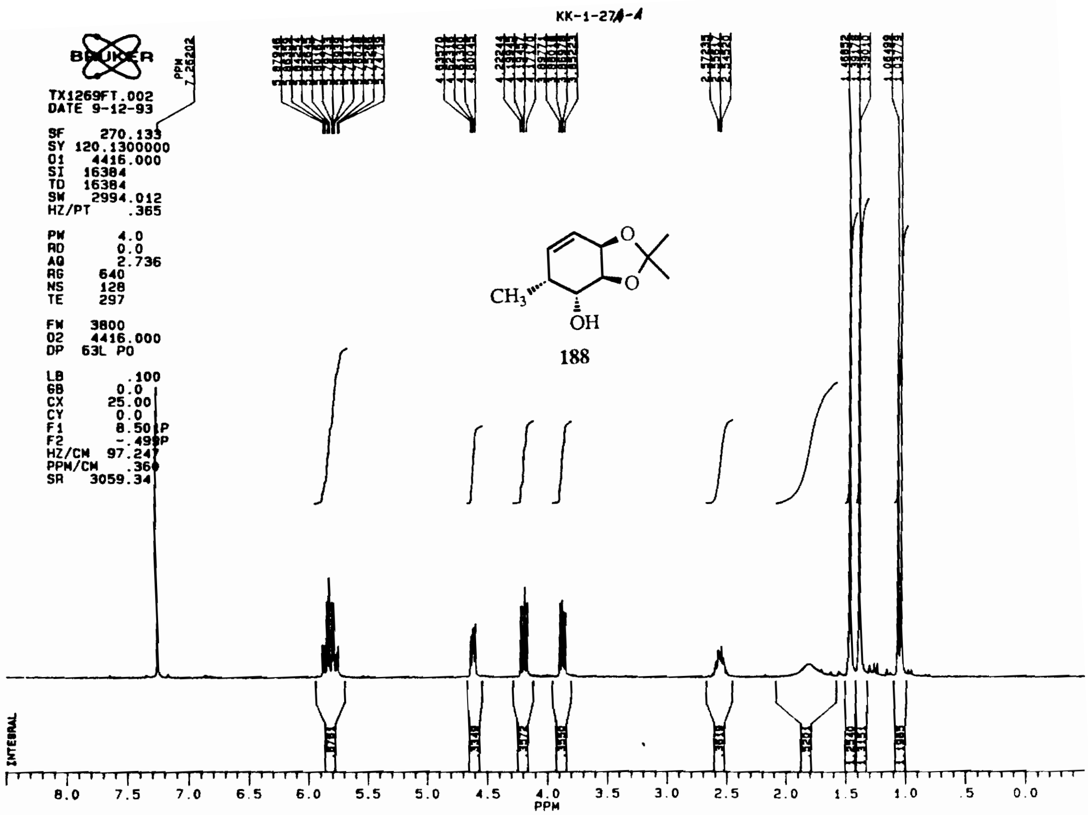
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DATE 9-12-93
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RD 0.0
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NS 128
TE 297
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O2 4416.000
DP 63L PO
LB .100
GB 0.0
CX 25.00
CY 0.0
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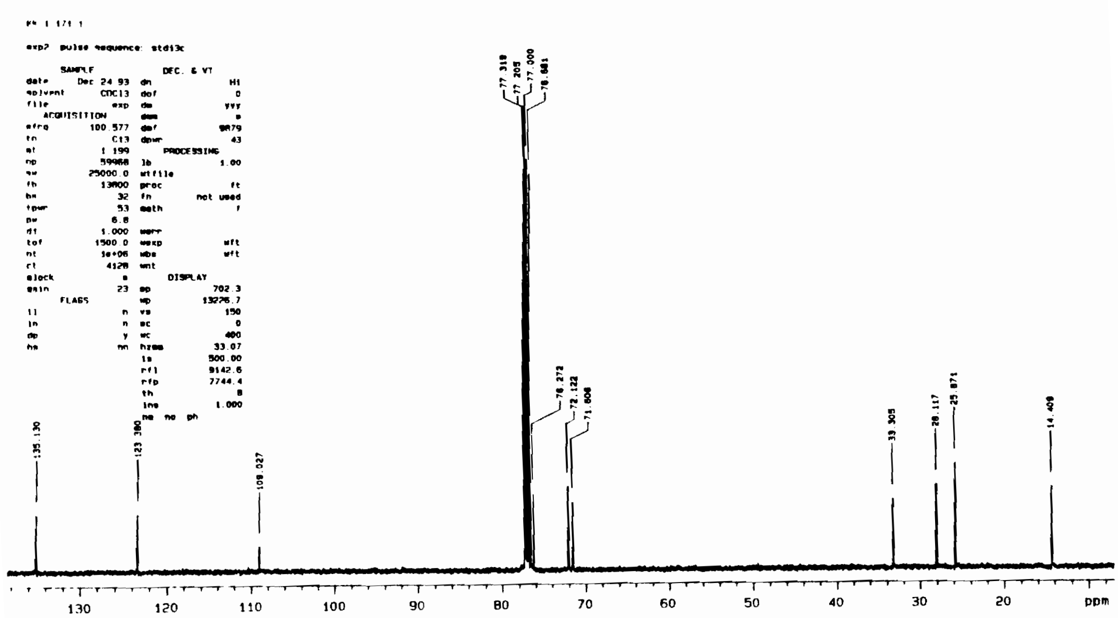
OH
188
INTEGRAL
PPM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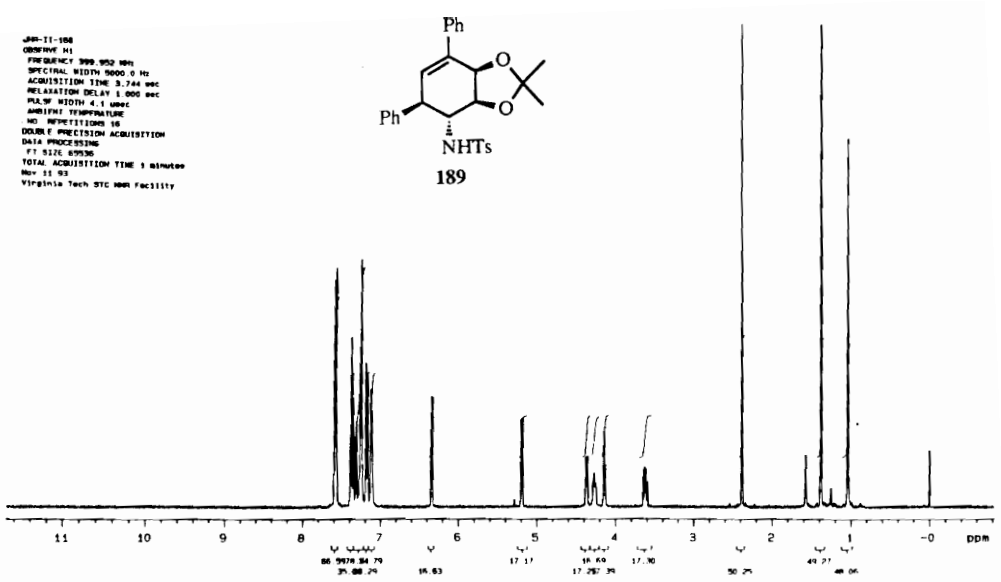
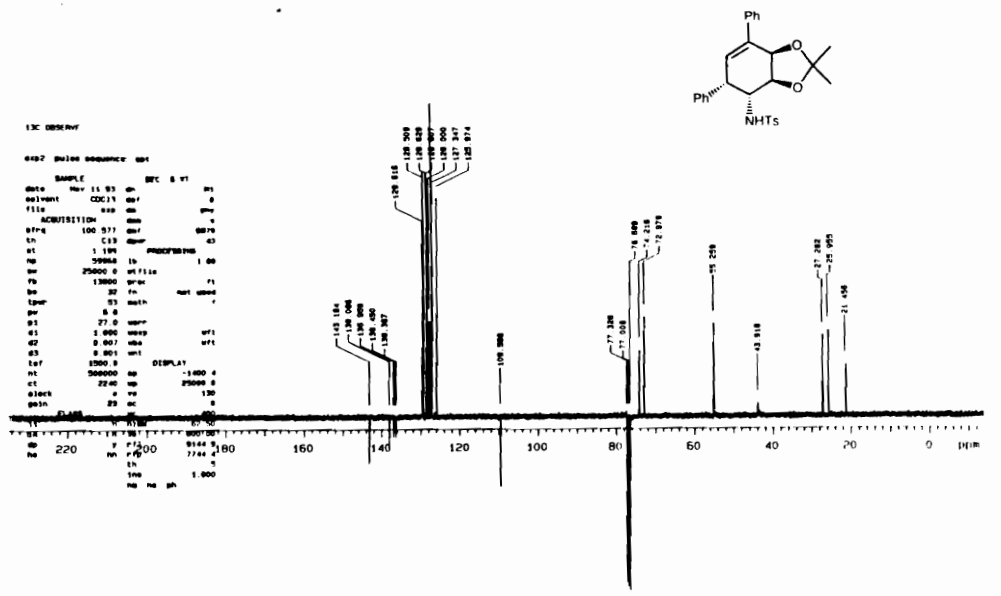
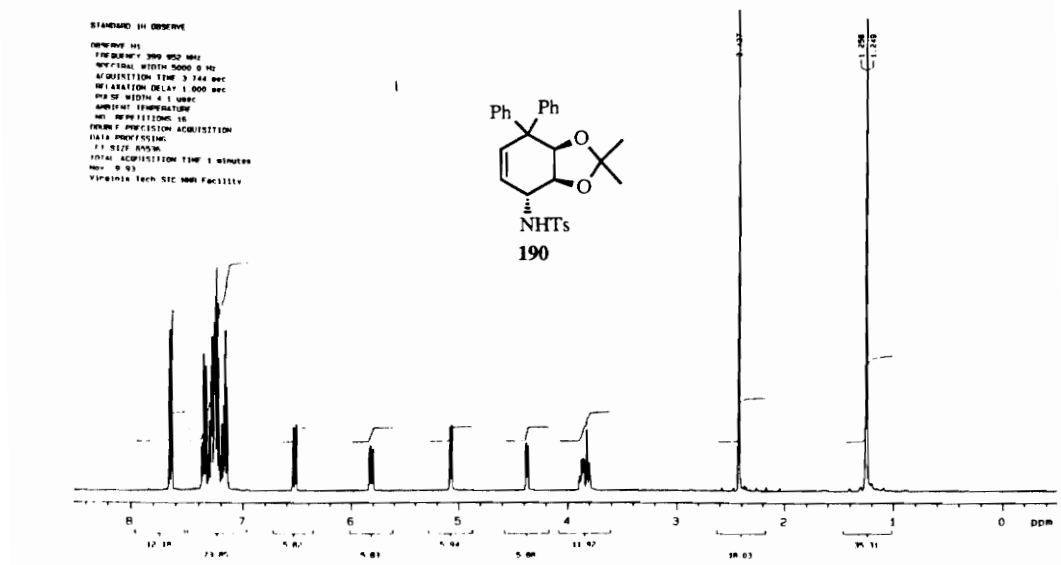

Ph
Ph
NHTs
189


Ph
Ph
NHTs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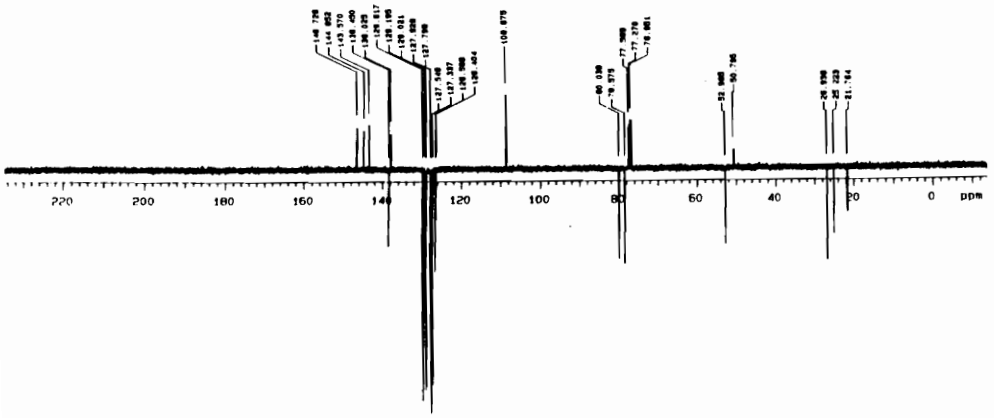
Ph
O
O
NHTs
190
8
7
6
5
4
3
2
1
0
ppm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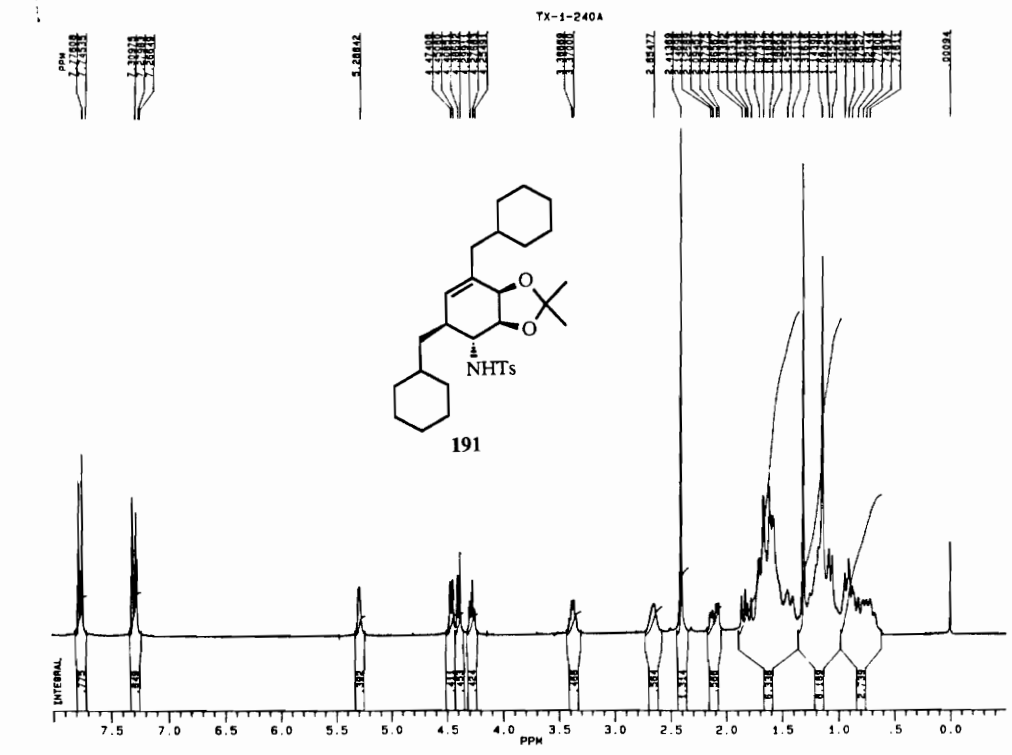
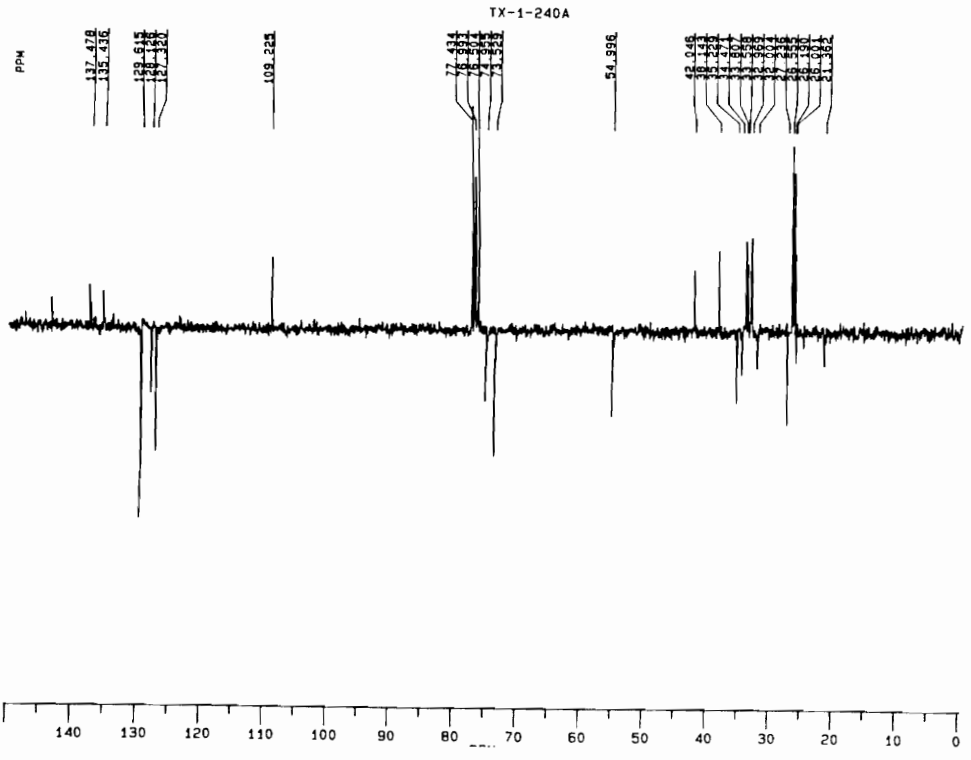
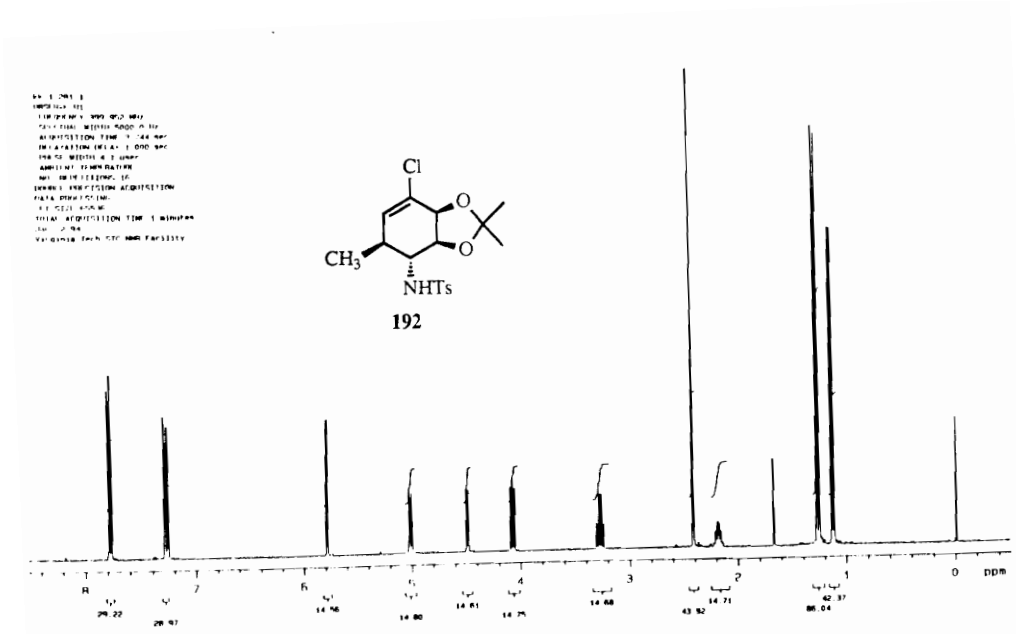


191

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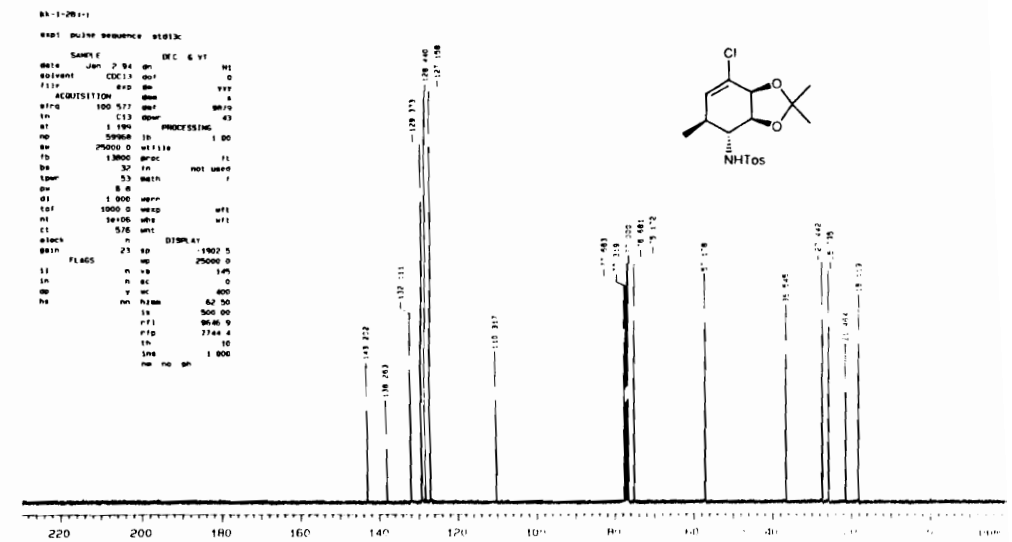
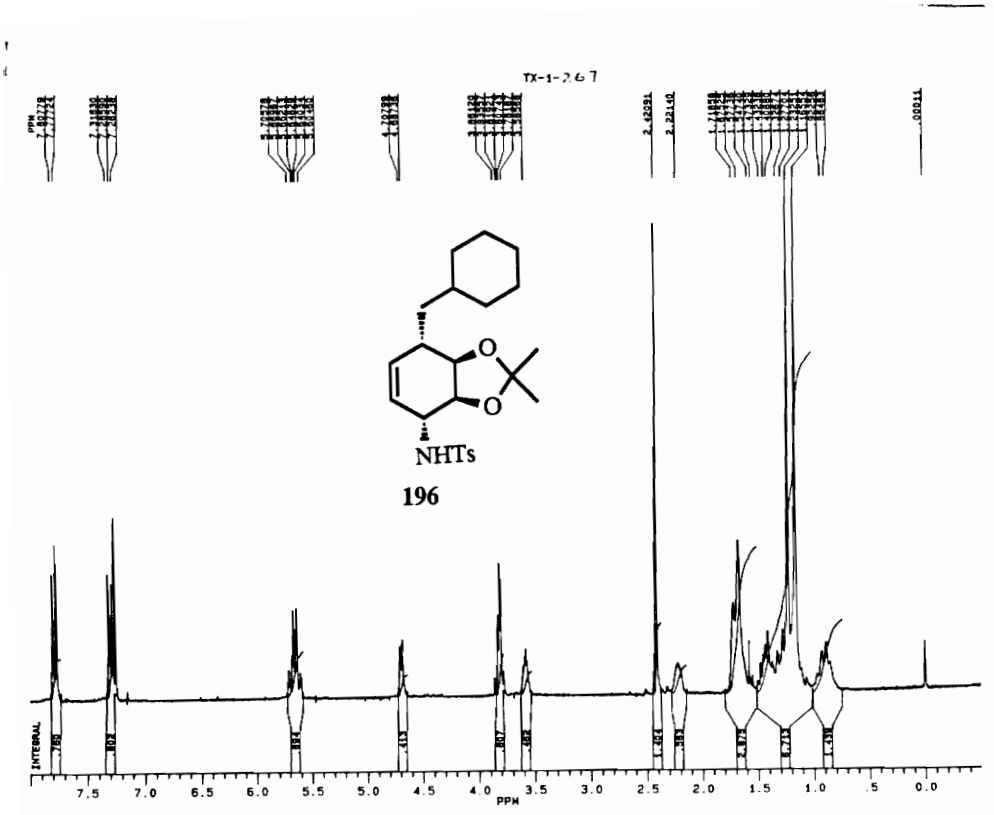
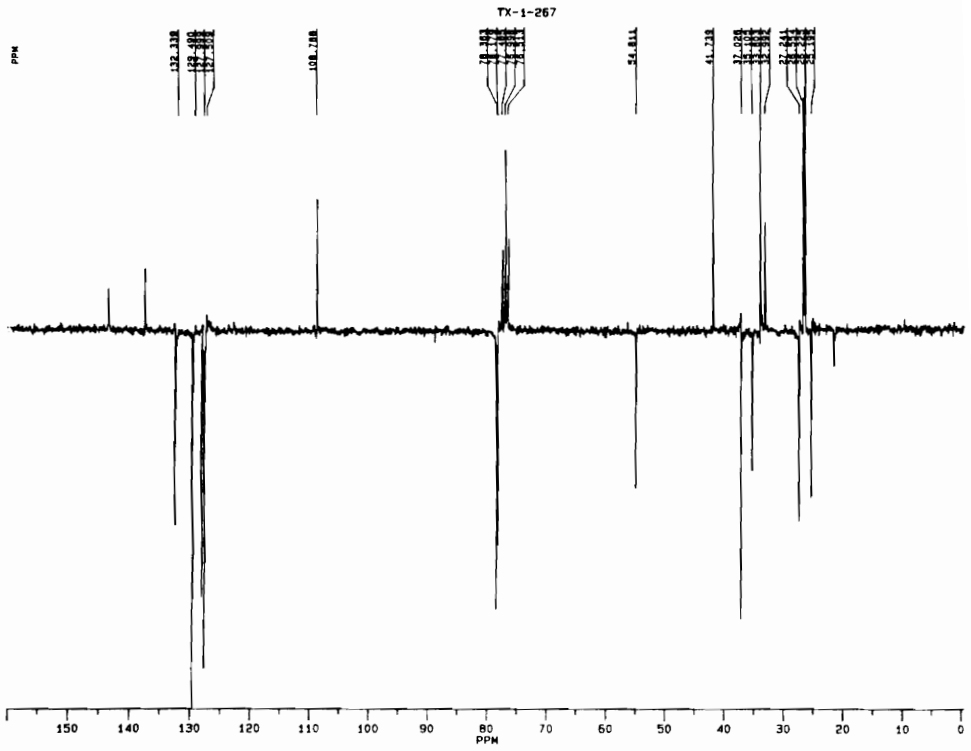
O
O
CH3
NHTs
192
ppm


Cl
O
O
NHTos


TX-1-267
NHTs
196
INTEGRAL
PPM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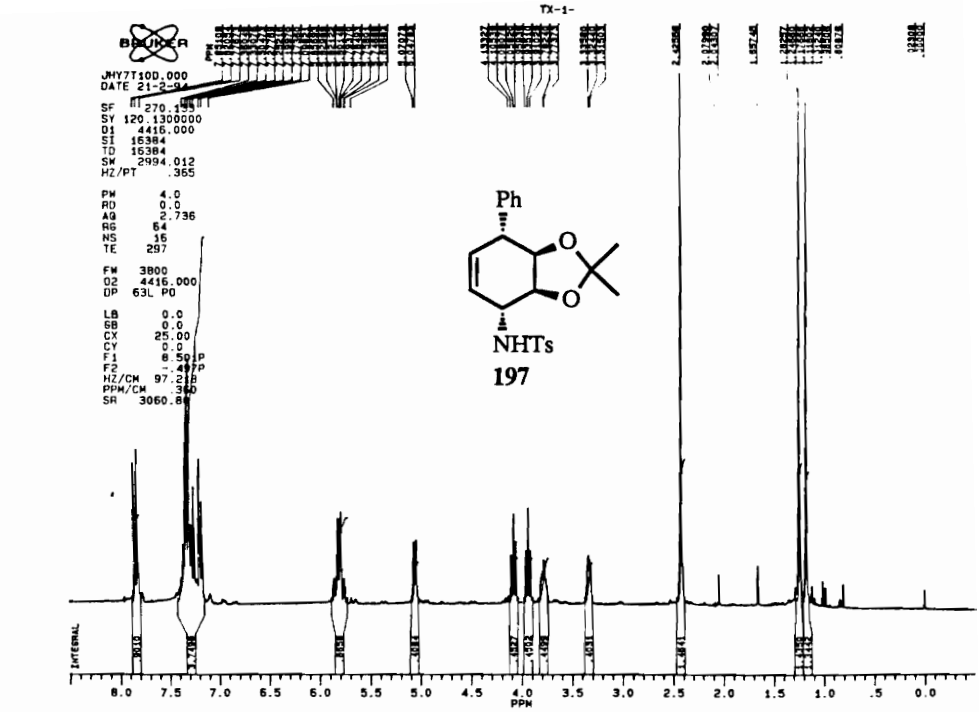
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DATE 21-2-94
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TD 16384
SW 2994.012
HZ/PT .365
PW 4.0
RD 0.0
AQ 2.736
RG 64
NS 16
TE 297
FW 3800
O2 4416.000
DP 63L PO
LB 0.0
GB 0.0
CX 25.00
CY 0.0
F1 8.59
F2 -.49
HZ/CM 97.21
PPM/CM .36
SR 3060.86
Ph
O
O
NHTs
197
INTEGRAL
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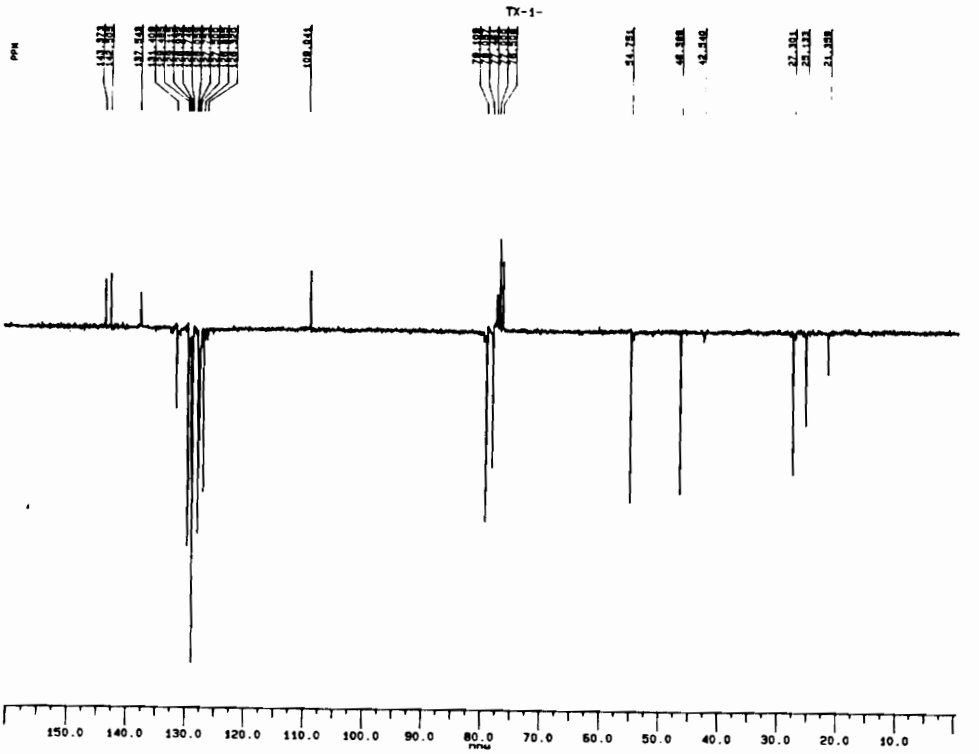
PPM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PPM
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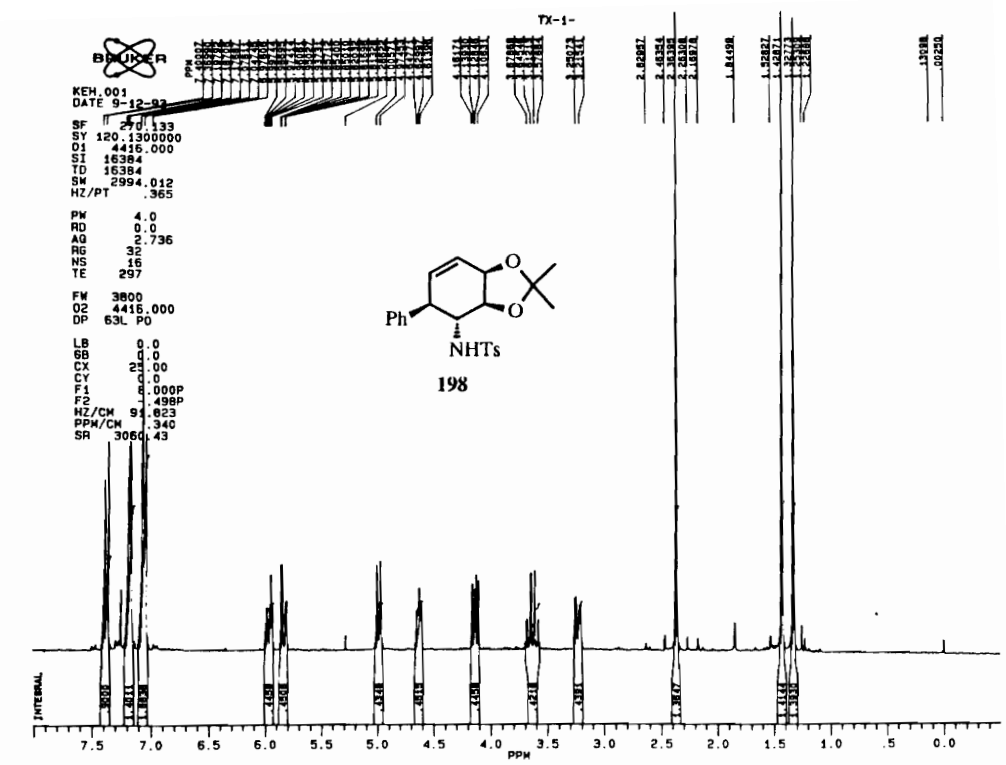
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DATE 9-12-02
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TD 16384
SW 2994.012
HZ/PT .365
PW 4.0
RD 0.0
AQ 2.736
RG 32
NS 16
TE 297
FW 3800
O2 4416.000
DP 63L PO
LB 0.0
GB 0.0
CX 25.00
CY 0.0
F1 6.000P
F2 -1.498P
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PPM/CM .340
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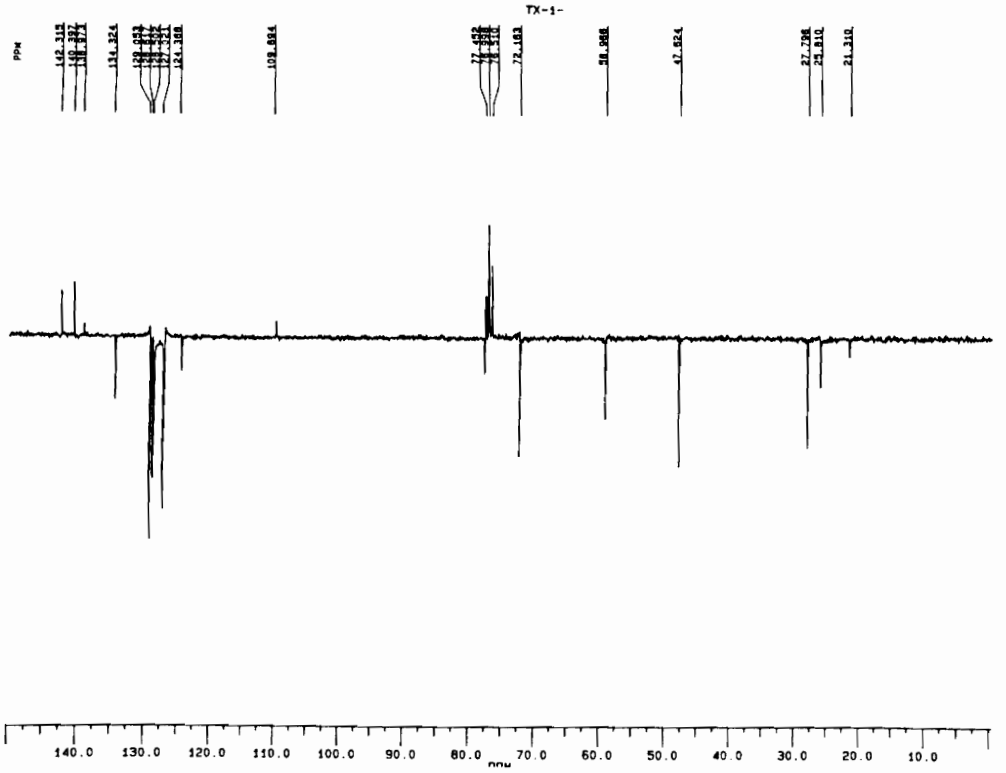
Ph
NHTs
O
O
INTEGRAL
PPM

198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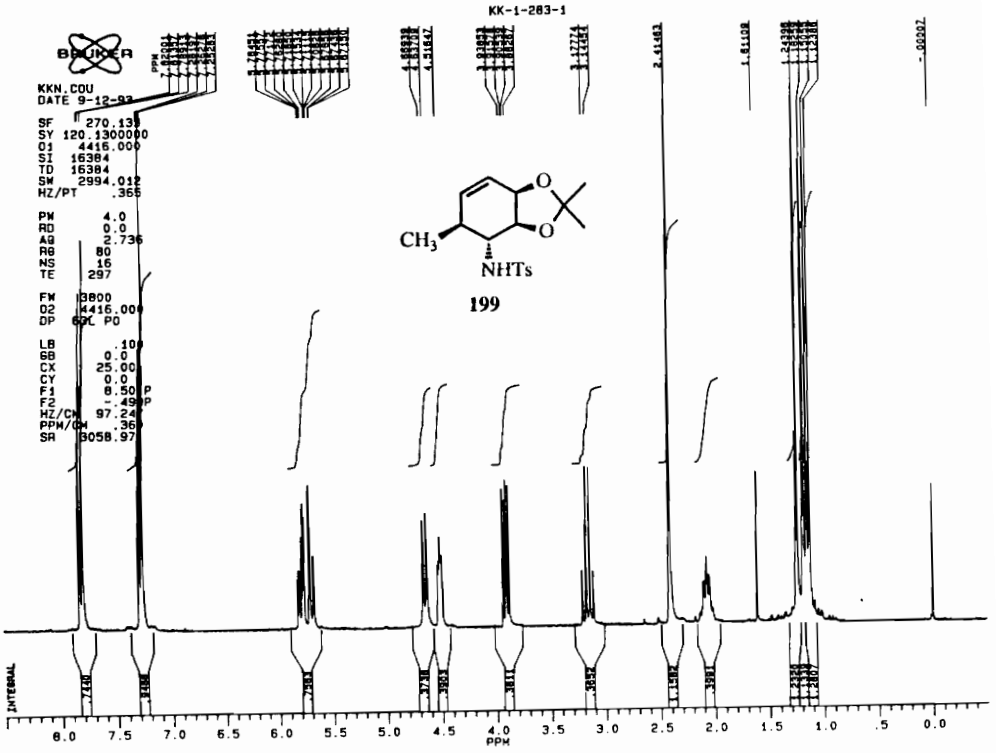
PPM
ppm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KKN.COU
DATE 9-12-93
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TD 16384
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PW 4.0
RD 0.0
AQ 2.736
RG 80
NS 16
TE 297
FW 13800
O2 4416.000
LB .100
GB 0.0
CX 25.00
CY 0.0
F1 8.50 P
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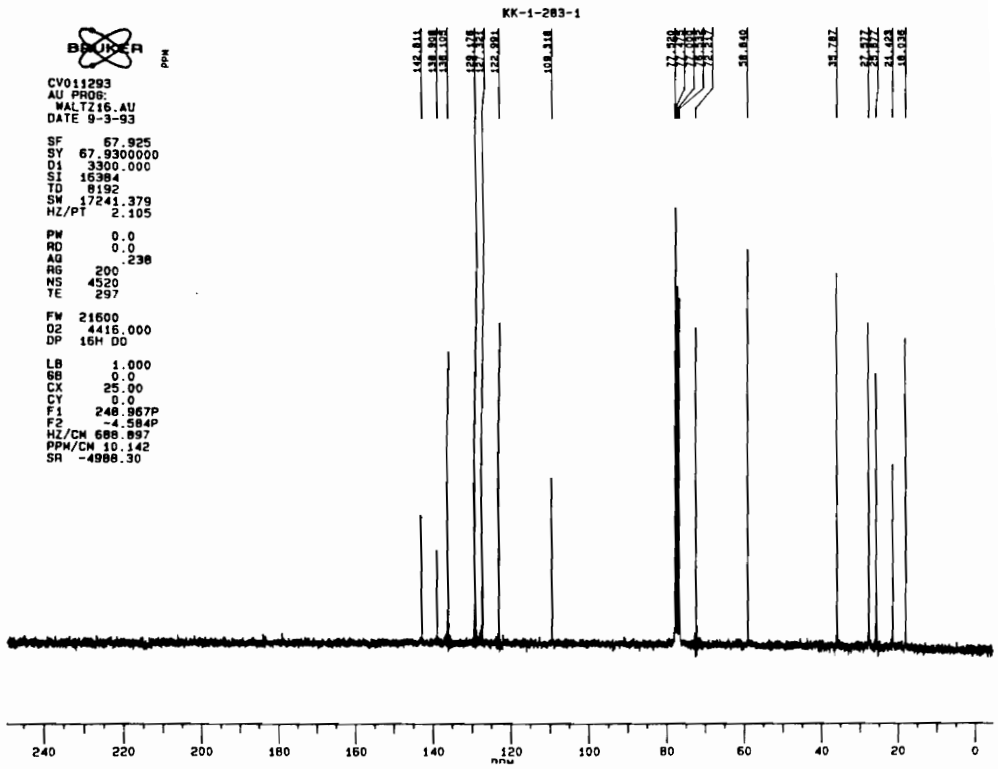
PPM/CM .359
SR 3058.97
INTEGRAL
PPM

O
O
CH3
NHTs

199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DATE 9-3-93
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RG 200
NS 4520
TE 297
FW 21600
O2 4416.000
DP 16H DD
LB 1.000
GB 0.0
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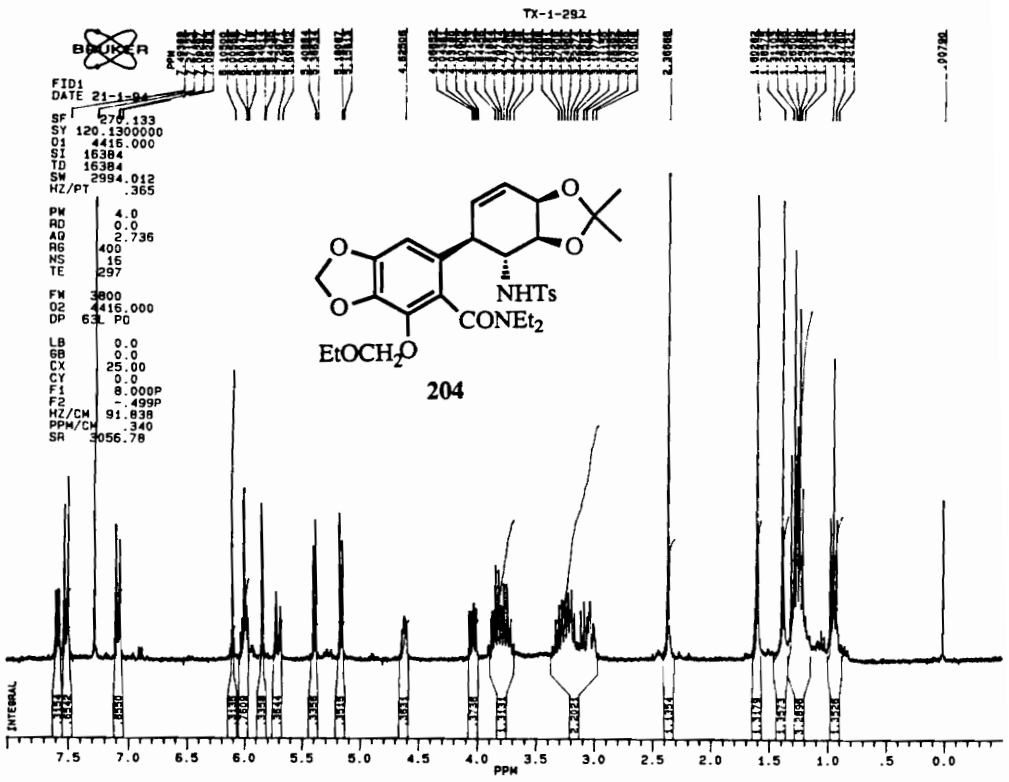
PPM


TX-1-292
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TD 16384
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HZ/PT .365
PW 4.0
RD 0.0
AQ 2.736
RG 400
NS 16
TE 297
FW 3800
O2 4416.000
DP 63L PO
LB 0.0
GB 0.0
CX 25.00
CY 0.0
F1 8.000P
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PPM/CM .340
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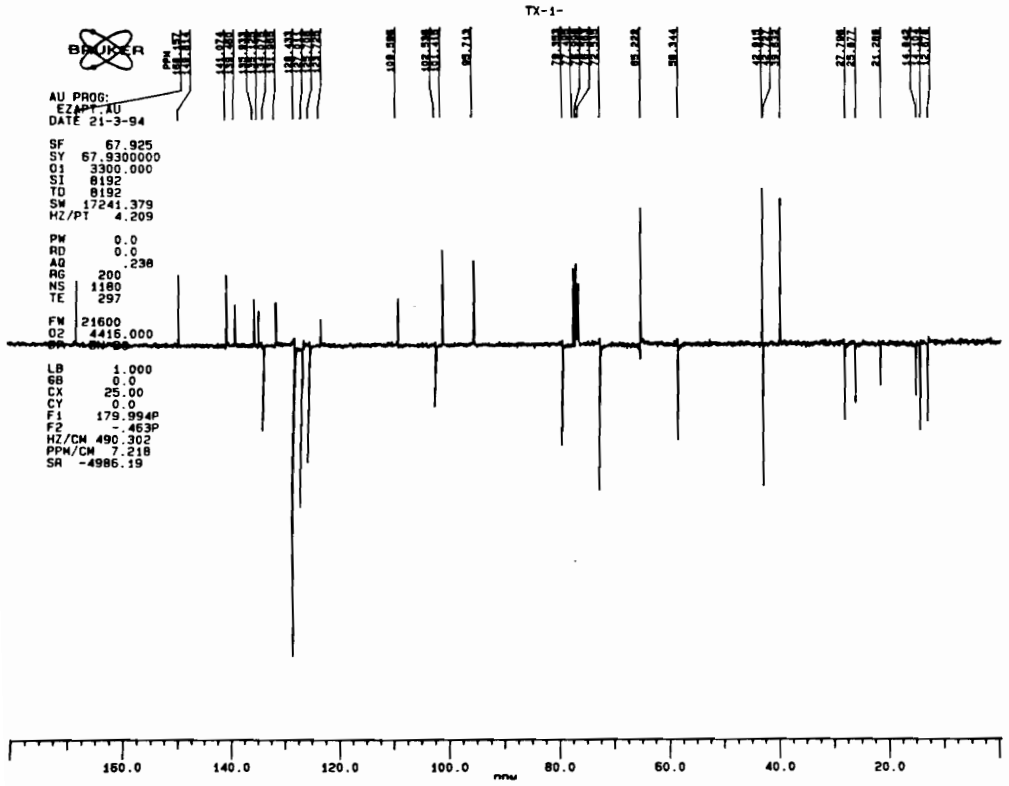
CONEt2
EtOCH2O
204
INTEGRAL
PPM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TD 8192
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HZ/PT 4.209
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AQ .238
RG 200
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TE 297
FW 21600
O2 4416.000
LB 1.000
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CY 0.0
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PPM/CM 7.218
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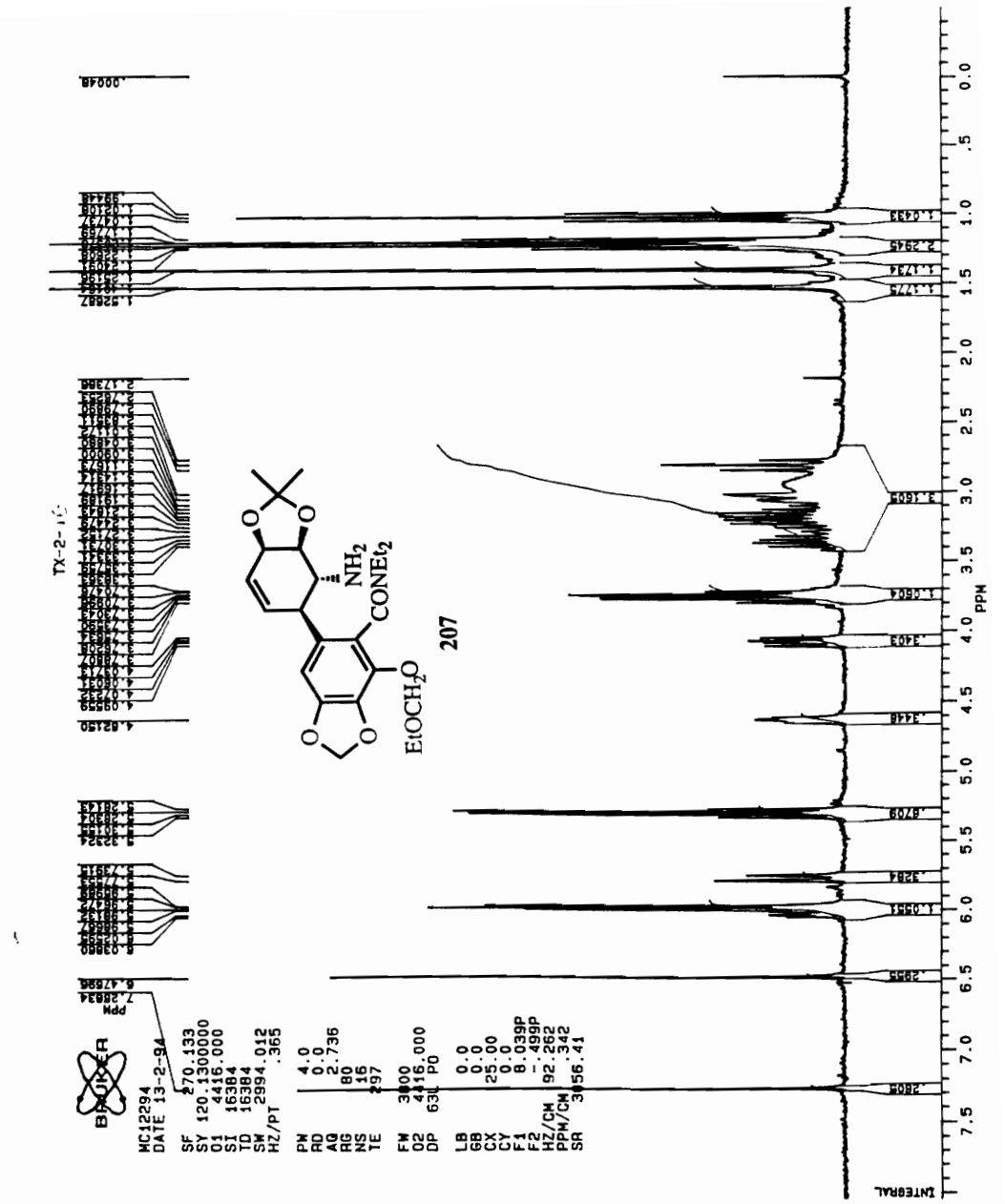
PPM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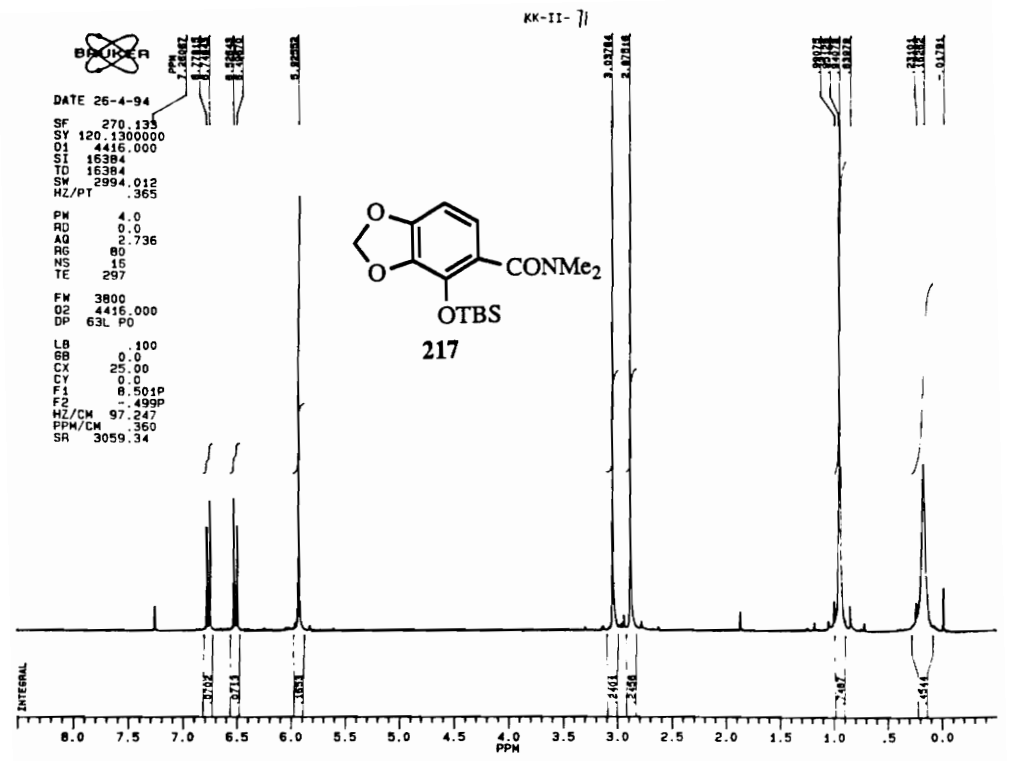
EtOCH2O
207
PPM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DATE 26-4-94
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SW 2994.012
HZ/PT .365
PW 4.0
RD 0.0
AQ 2.736
RG 80
NS 16
TE 297
FW 3800
O2 4416.000
DP 63L PO
LB .100
GB 0.0
CX 25.00
CY 0.0
F1 8.501P
F2 -.499P
HZ/CM 97.247
PPM/CM .360
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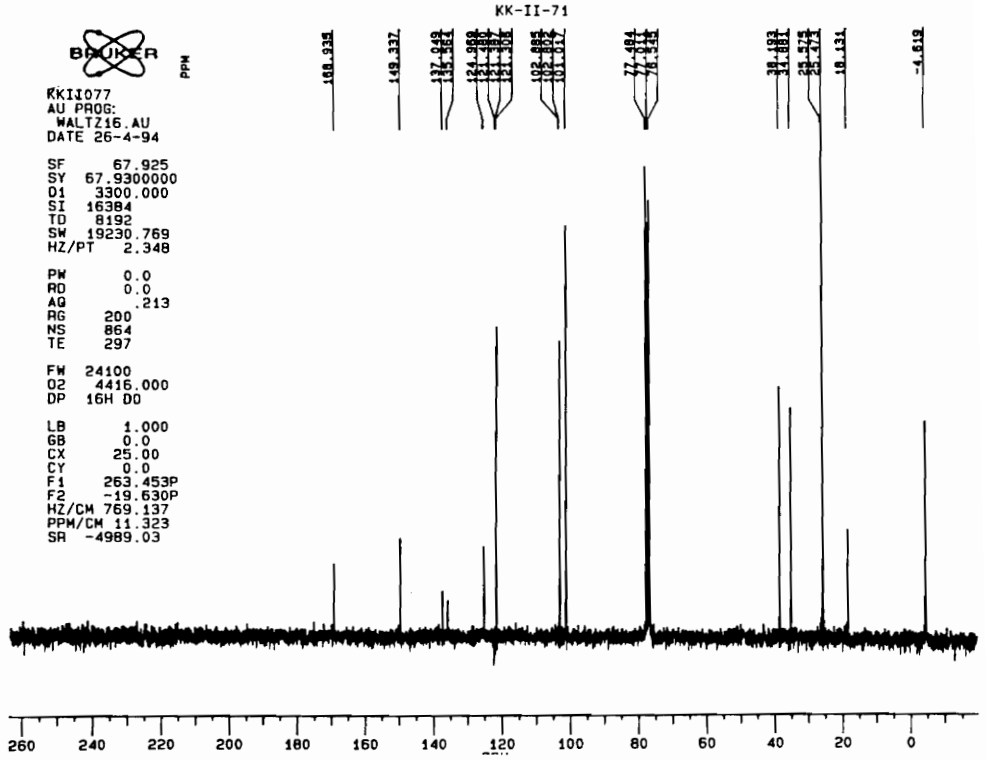
CONMe2
OTBS
217
INTEGRAL
PPM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KKII077
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HZ/PT 2.348
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AQ .213
RG 200
NS 864
TE 297
FW 24100
O2 4416.000
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LB 1.000
GB 0.0
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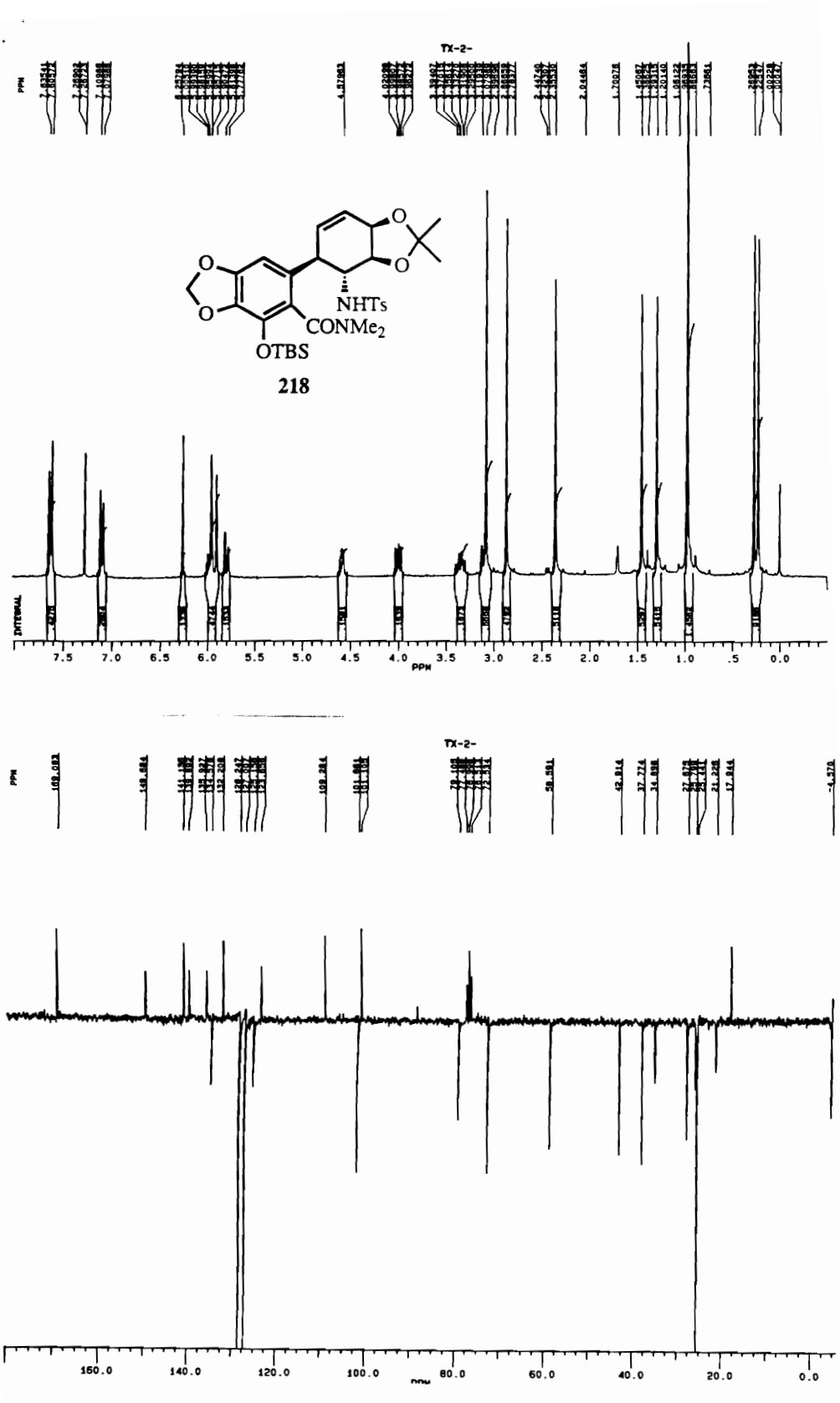
SR -4989.03
PPM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NHTs
CONMe2
OTBS
218
PPM
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7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
.5
0.0
TX-2-
PPM
169.033
148.884
58.591
52.814
37.724
34.858
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80.0
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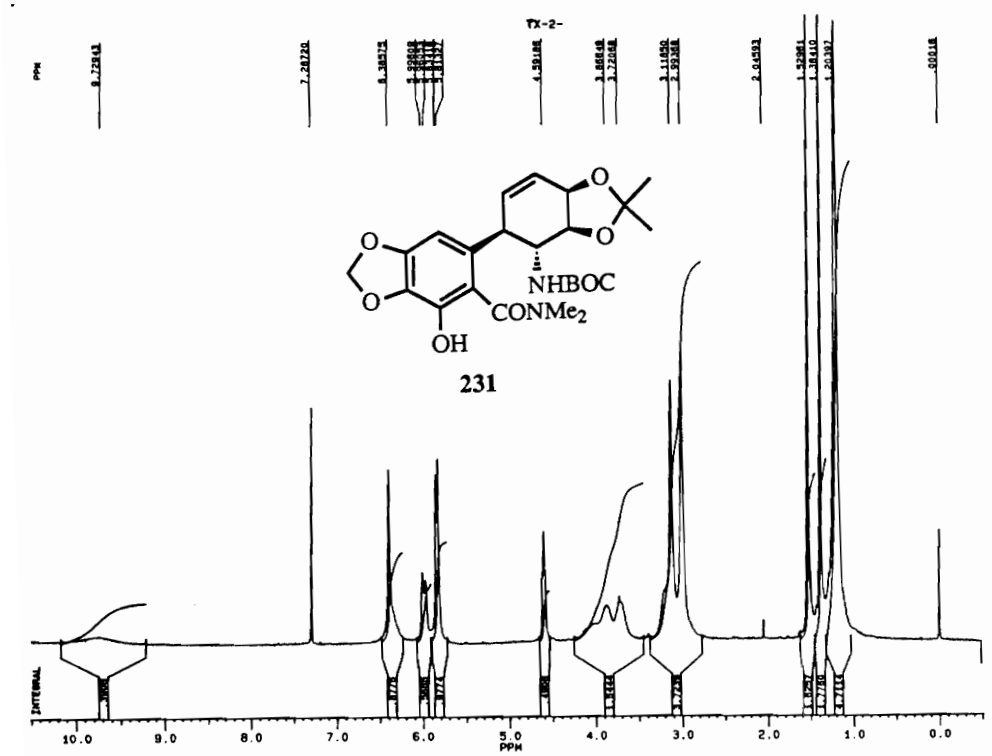

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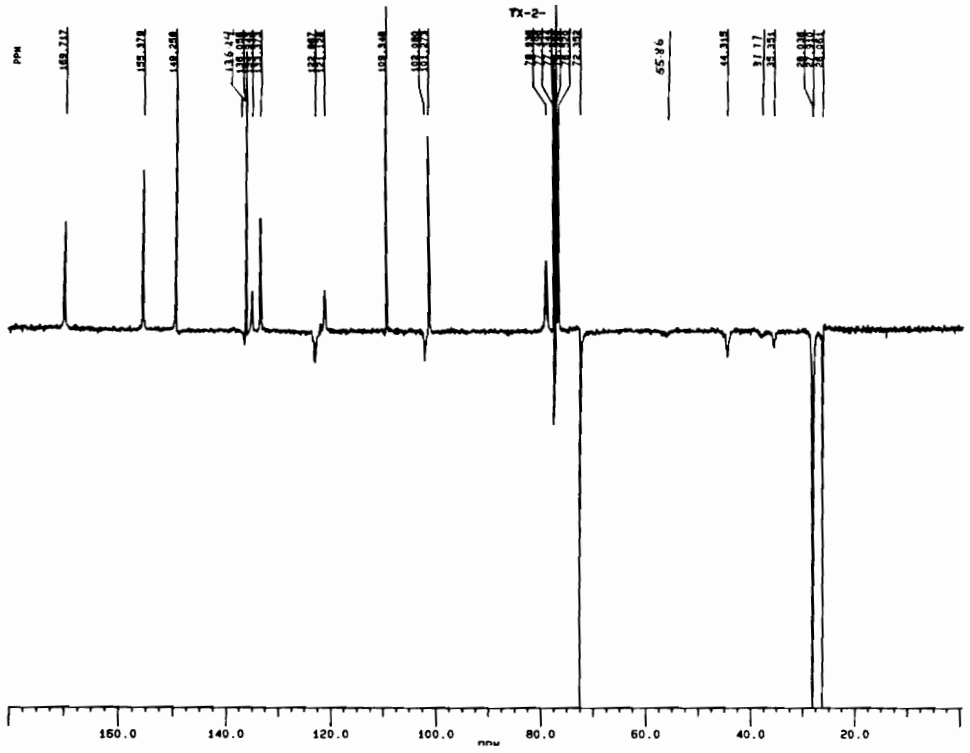
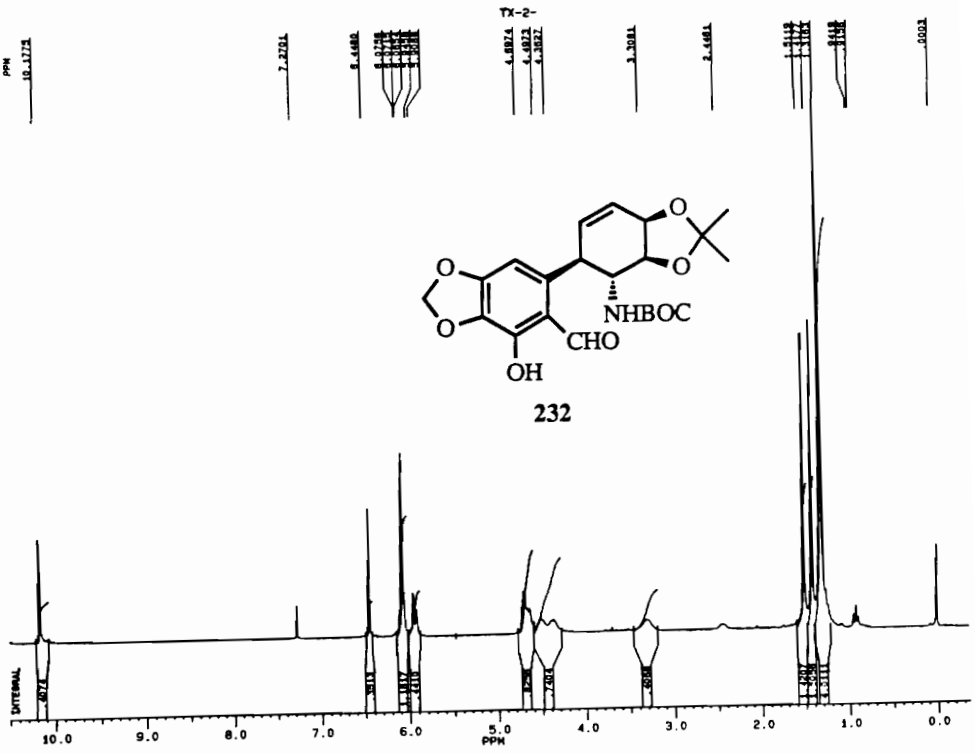
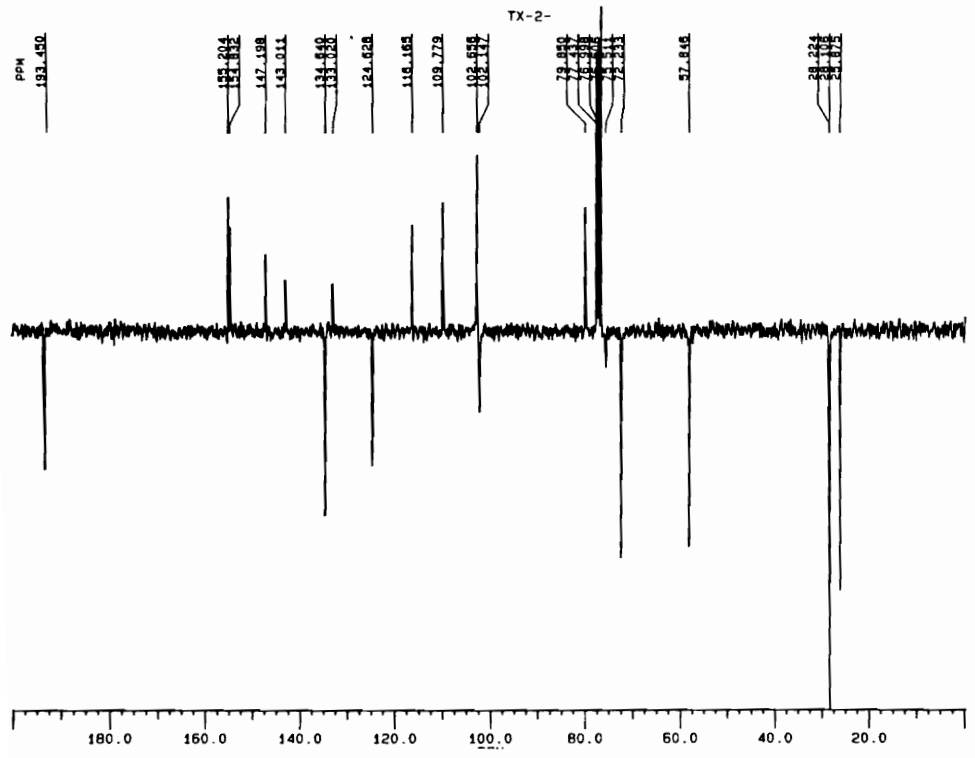
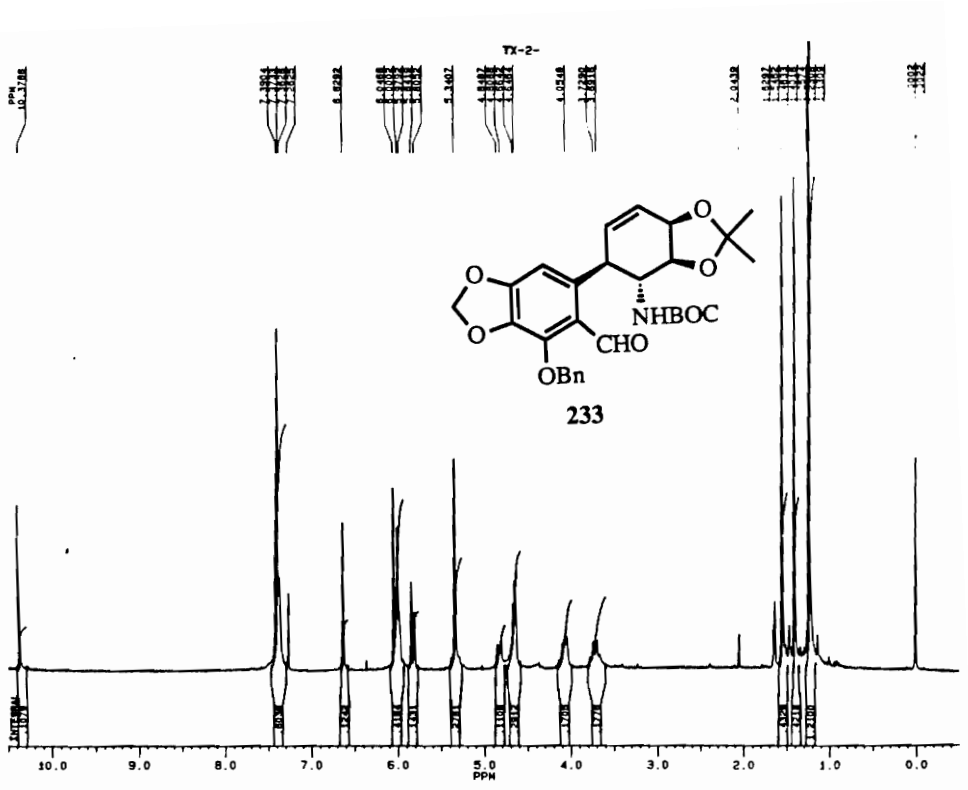
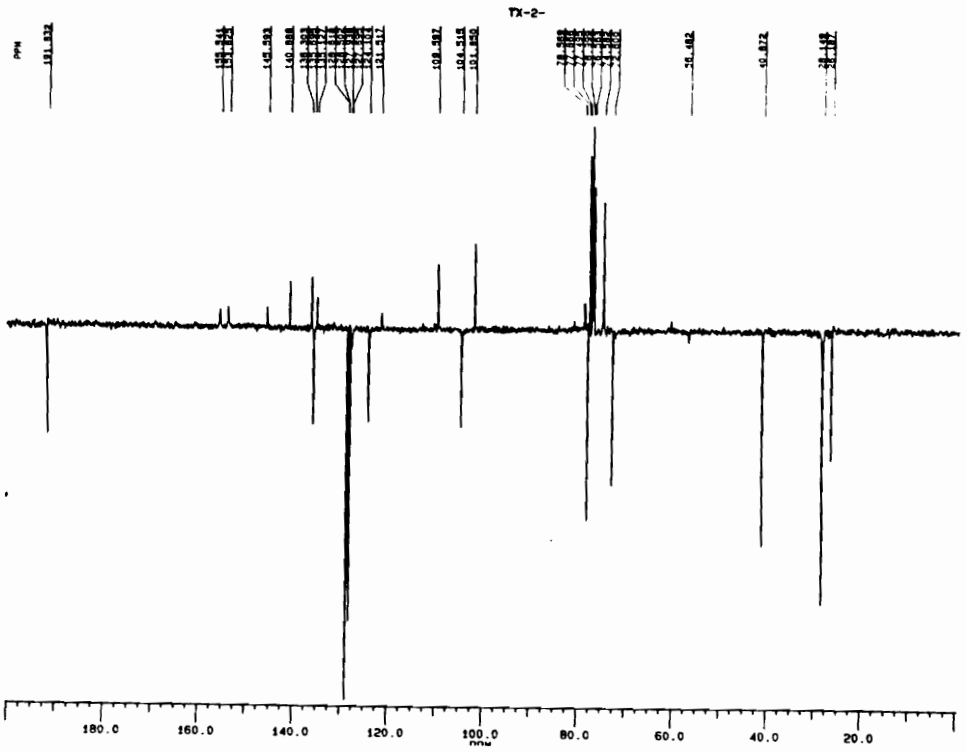


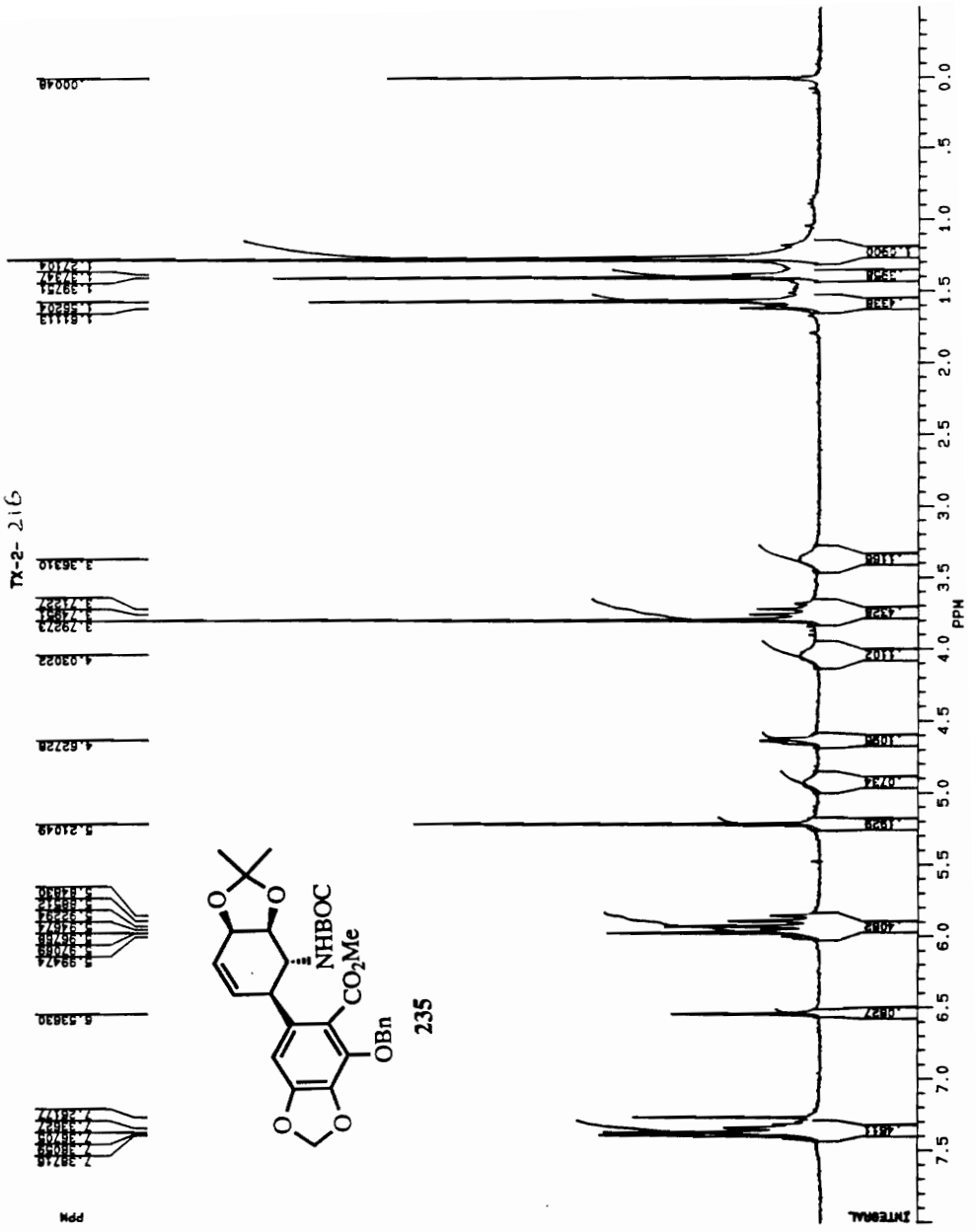


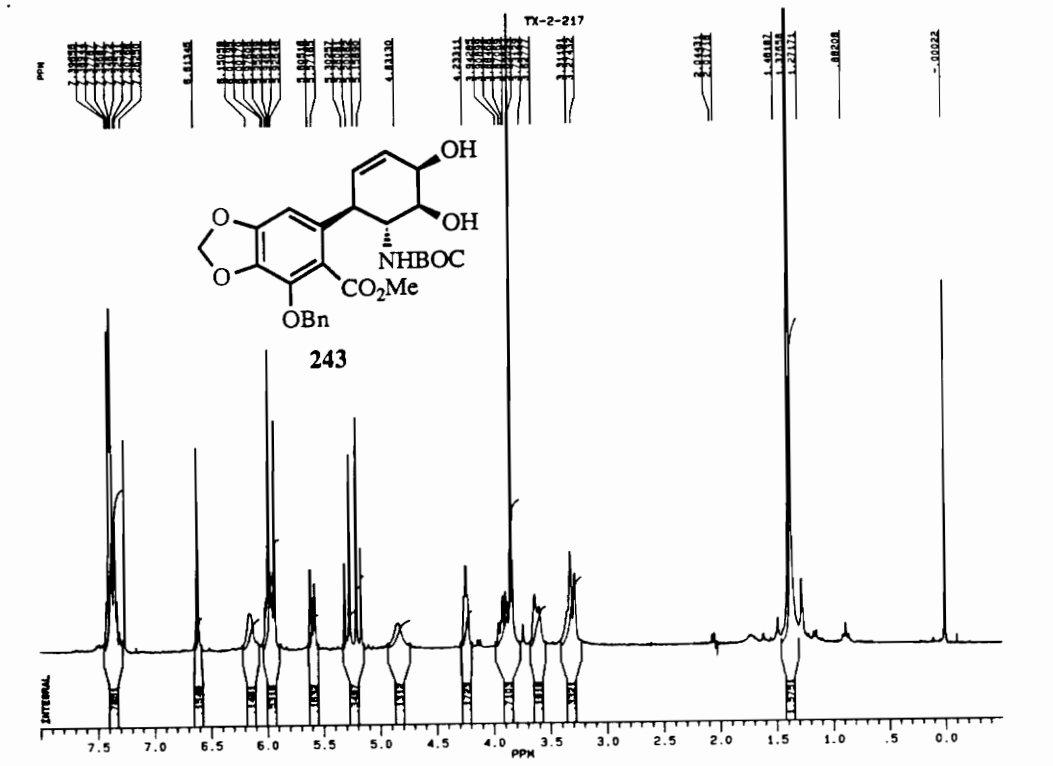
232

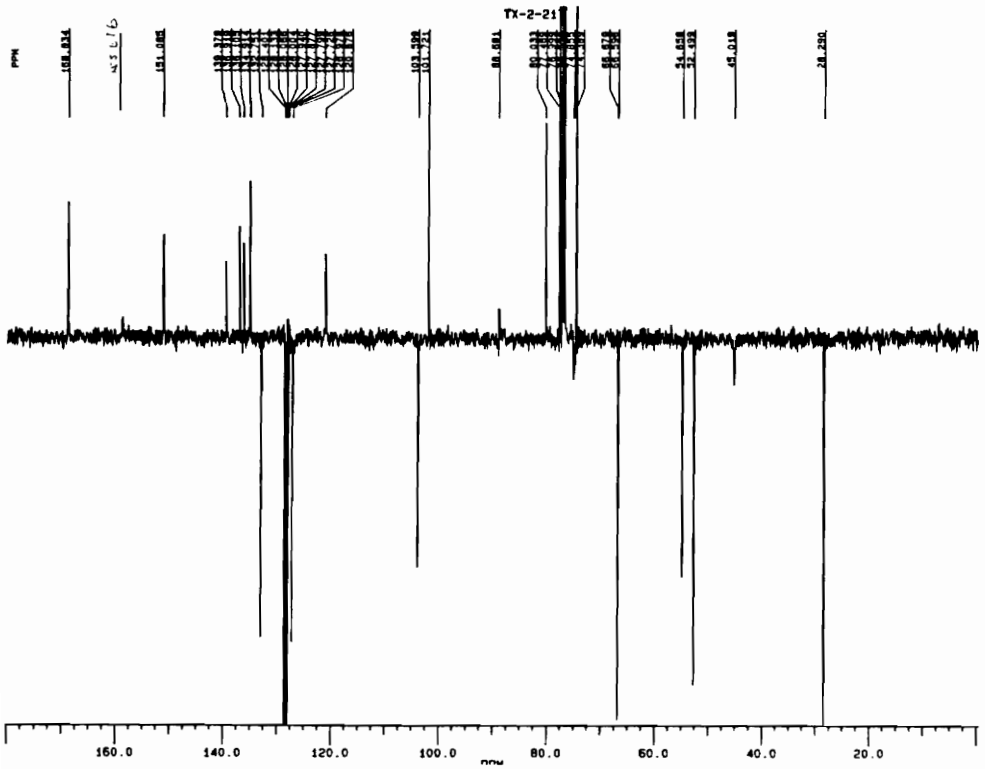


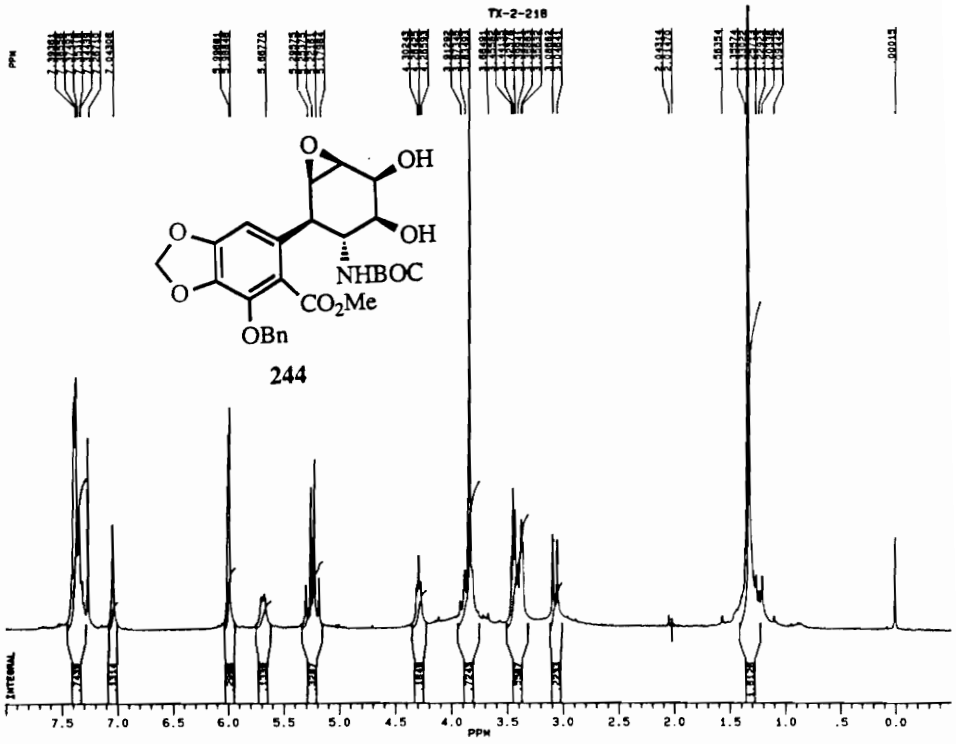

TX-2-
NHBOC
CHO
OBn
233
PPM


TX-2-
PPM


TX-2- 216
NHBOC
CO_2Me
OBn
235
PPM


TX-2-217
OH
OH
NHBOC
CO_2Me
OBn
243
PPM


TX-2-21
PPM


TX-2-218
OH
OH
NHBOC
CO_2Me
OBn
244
7.5
7.0
6.5
6.0
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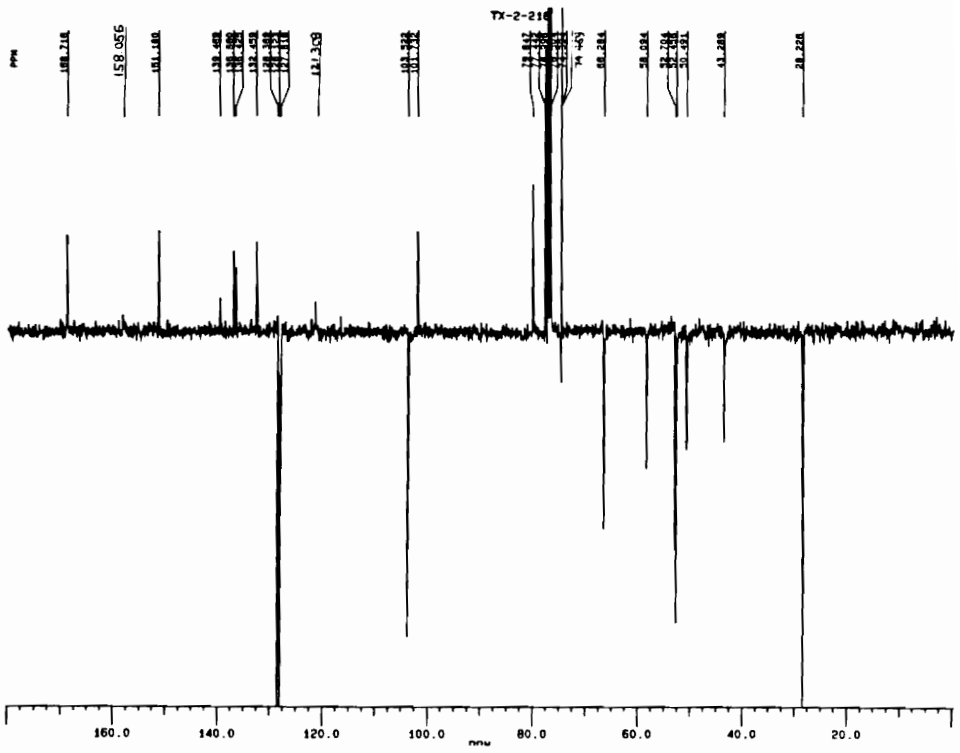
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
.5
0.0
PPM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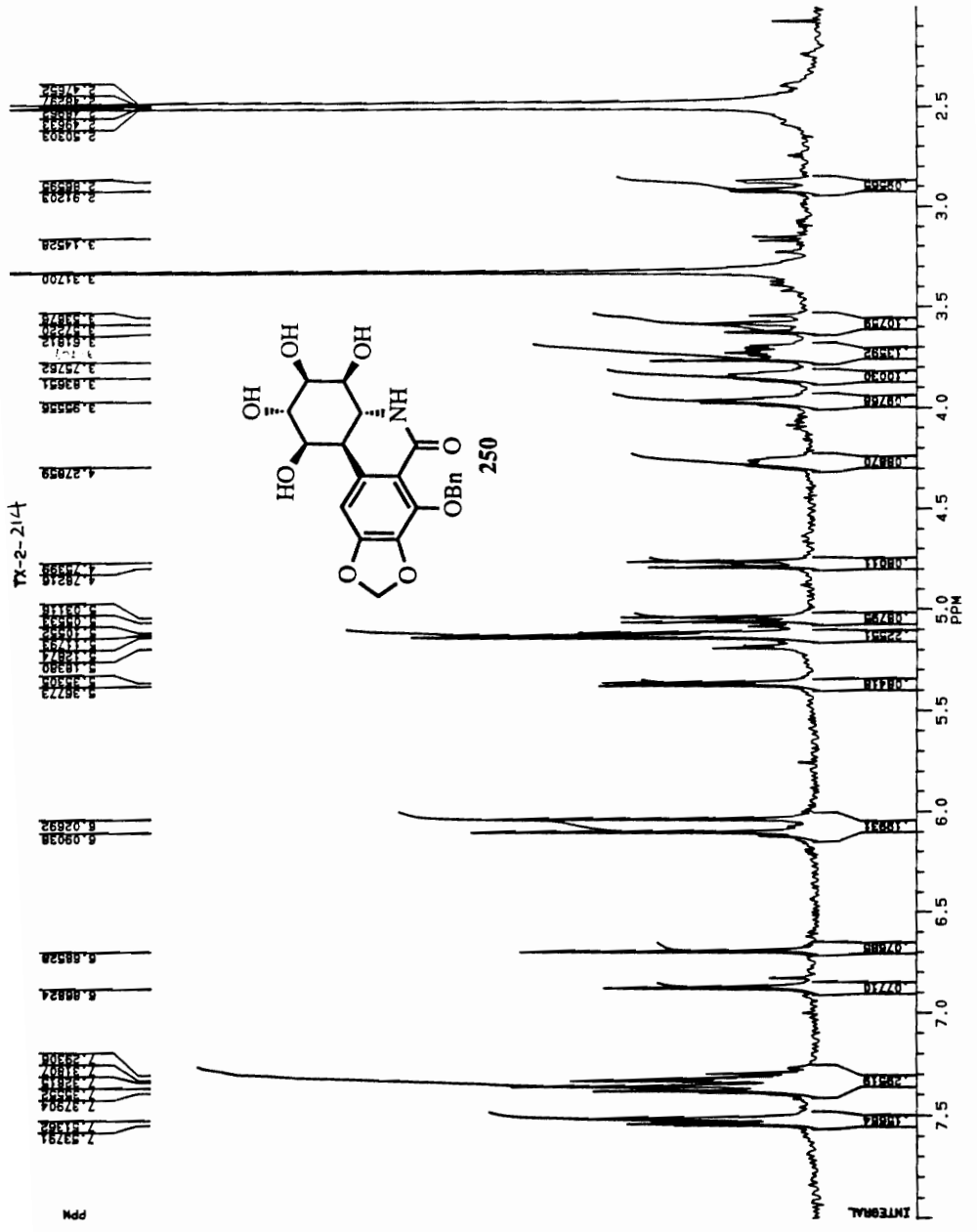
60.0
40.0
20.0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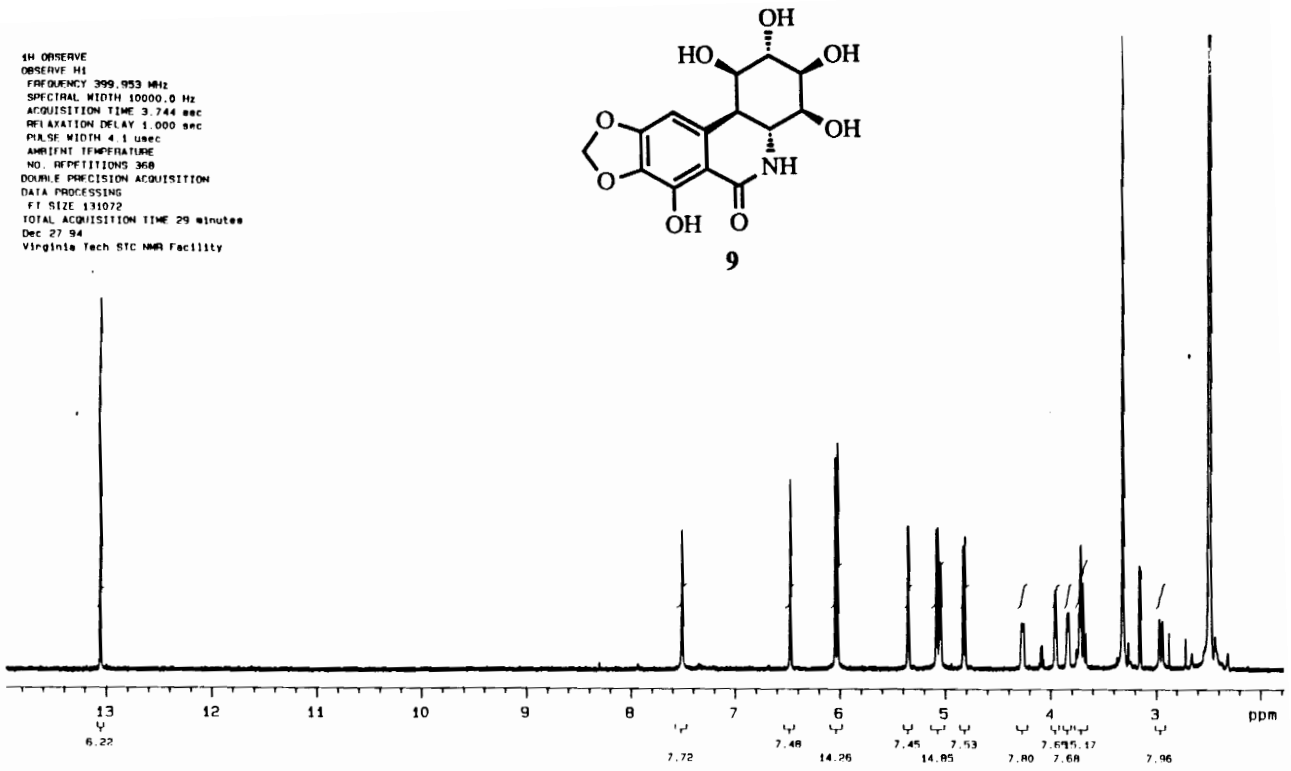
OH
OH
NH
HO
OBn
O
O
O
O
250
TX-2-214
PPM
INTEGRAL


1H OBSERVE
OBSERVE H1
FREQUENCY 399.953 MHz
SPECTRAL WIDTH 10000.0 Hz
ACQUISITION TIME 3.744 sec
RELAXATION DELAY 1.000 sec
PULSE WIDTH 4.1 usec
AMBIENT TEMPERATURE
NO. REPETITIONS 360
DOUBLE PRECISION ACQUISITION
DATA PROCESSING
FT SIZE 131072
TOTAL ACQUISITION TIME 29 minutes
Dec 27 94
Virginia Tech STC NMR Facility
OH
HO
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3
ppm
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7.48
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7.68
15.17
7.96

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