Enantioselective Synthesis of Neocarzinostatin Chromophore Aglycone

Thesis by

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Many thanks are owed to Mary Shepard for reading through this thesis so thoroughly.

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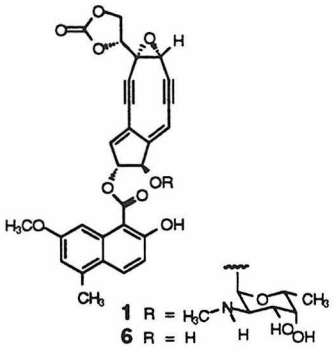
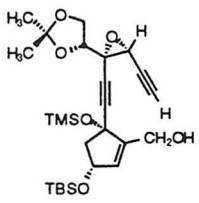
Abstract

An enantioselective synthesis of neocarzinostatin chromophore aglycone (**6**) is described. The key features of the synthesis include 1) Sharpless asymmetric epoxidation of the allylic alcohol **136** to produce epoxy alcohol **137**, 2) an intramolecular acetylide addition within the epoxy aldehyde **138** to furnish alcohol **139**, 3) esterification of the diol **171** with the acid **22** and in situ cleavage of the chloroacetate ester to provide ester **172**, 4) elimination of the C-1 alcohol of **175** to afford the olefin **176**, and 5) reductive opening of epoxy alcohol **120** with the combination of iodine, triphenylphosphine, and imidazole to afford neocarzinostatin chromophore aglycone (**6**). The synthetic pathway described is highly convergent, and should the supply quantities of **6** necessary for ongoing studies directed toward the completion of the total synthesis of neocarzinostatin chromophore (**1**), as well as the preparation of analogs bearing modified sugar residues.

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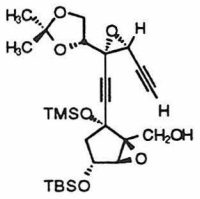
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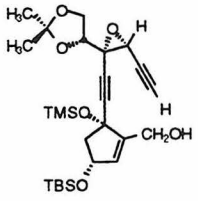
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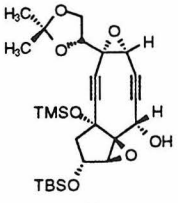
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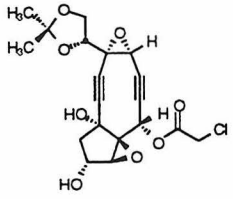
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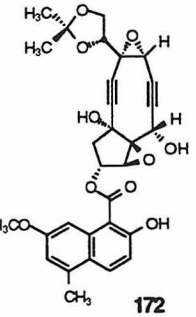
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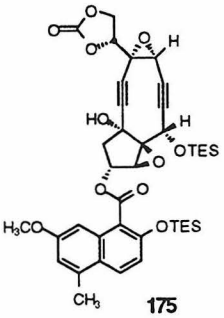
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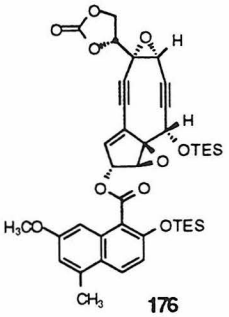
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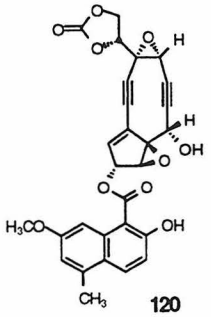
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List of Abbreviations

$[\alpha]_D^{20}$	optical rotation (589 nm, 20 °C)
A	adenine
Å	angstrom
Ac	acetyl
AIBN	2,2'-azobis(isobutyronitrile)
bp	base pair(s)
Bu	butyl
c	grams per 100 mL of solution
C	cytosine
℃	degrees Celsius
CAM	ceric ammonium molybdate
CD	circular dichroism
C_6D_6	hexadeuteriobenzene
CDI	1,1'-carbonyldiimidazole
CI	chemical ionization
cm^{-1}	reciprocal centimeters
Cp	cyclopentadienyl
CSA	camphorsulfonic acid
δ	chemical shift (parts per million)
DBU	1,8-diazabycyclo[5.4.0]undecene
DCC	1,3-dicyclohexylcarbodiimide
de	diastereomeric excess

DET	diethyl tartrate
DIBAL	diisobutylaluminum hydride
DMAP	4(*N*,*N*-dimethylamino)pyridine
DMF	*N*,*N*-dimethylformamide
DMSO	dimethylsulfoxide
DNA	deoxyribonucleic acid
E	entgegen
EDC	1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
ee	enantiomeric excess
EI	electron impact
equiv	equivalent
Et	ethyl
EtOAc	ethyl acetate
FAB	fast atom bombardment
FPLC	fast protein liquid chromatography
FT	Fourier transform
g	gram(s)
G	guanine
gc	gas chromatography
h	hour
*h*ν	light
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectroscopy
Hz	hertz
i	iso
IR	infrared

J	coupling constant
L	liter(s)
m	meta
M	molar
$[M]^+$	molecular ion
m-CPBA	meta-chloroperoxybenzoic acid
MEM	methoxyethoxymethyl
mesylate	methanesulfonate
mg	milligram(s)
MHz	megahertz
min	minute(s)
mL	milliliter(s)
mM	millimolar
mmol	millimole(s)
mol	mole(s)
mp	melting point
MS	molecular sieves
MS	mass spectroscopy
MW	molecular weight
µL	microliter(s)
n	normal
N	normal (concentration)
NCS	neocarzinostatin
nm	nanometer(s)
NMR	nuclear magnetic resonance
p	para
Ph	phenyl

pH	hydrogen ion concentration (log scale)
Piv	pivaloyl
ppm	parts per million
Pr	propyl
Py	pyridine
R, *Re*	rectus
R*f*	retention factor
rp	reverse-phase
S, *Si*	sinister
t	tertiary
T	thymine
TBAF	tetrabutylammonium fluoride
TBS	*tert*-butyldimethylsilyl
TBHP	*tert*-butyl hydroperoxide
TDS	*tert*-butyldiphenylsilyl
TES	triethylsilyl
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
TFE	2,2,2-trifluoroethanol
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TLC	thin-layer chromatography
TMGA	tetramethylguanidium azide
TMS	trimethylsilyl
TPS	triphenylsilyl
triflate	trifluoromethanesulfonate
p-Ts	*para*-toluenesulfonyl

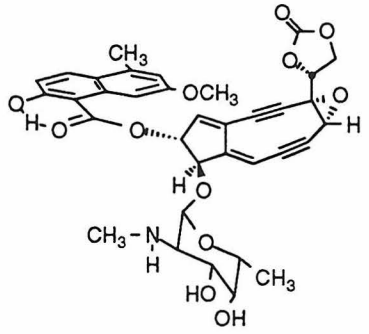
UV	ultraviolet
w	watt
w/v	weight/volume ratio (g/100 mL)
Z	zusammen

Chapter 1

Introduction and Background

Introduction

The chromoprotein neocarzinostatin, isolated from the soil bacterium *Streptomyces carzinostaticus*,[1] was the first of the enediyne family of antibiotics[2] to be isolated and is composed of a non-protein chromophore (**1**) bound to a 113-amino acid apoprotein (apo-NCS).[3] The antitumor activity of neocarzinostatin is believed to arise from the ability of the chromophore component **1** to damage double-stranded DNA in the presence of a thiol cofactor and oxygen.[4] This DNA-cleaving activity has been demonstrated to reside solely within the chromophore **1**, while the apoprotein is believed to function by imparting stability to the highly labile **1**.[5] The binding of **1** to apo-NCS has been elucidated by X-ray crystallographic analysis of the holo-NCS complex.[6] The epoxy nonadiyne ring was found to contact opposing phenylalanine benzene rings oriented perpendicular to the plane of the chromophore, as well as a disulfide bridge within the protein. It has also been suggested that apo-NCS may play a role in the transport of **1** across cell membranes.[6]



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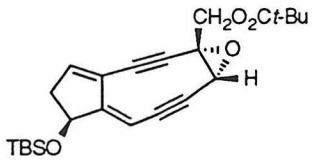
DNA cleavage by **1** shows little sequence selectivity, but exhibits the base selectivity T > A >>G > C.[7] The cleavage reaction has been extensively studied, and a substantial body of evidence has been compiled in support of the mechanism given in Scheme I.[3c,8,9] In the presence of the cofactor methyl thioglycolate at –70 °C, **1** is transformed into an intermediate whose ^{1}H NMR signals correspond to the cumulene-ene-

yne **2** (R = $CH_2CO_2CH_3$).[8b] Warming of the reaction mixture to –38 °C results in the further reaction of **2** to afford the rearranged indacene **4** (R = $CH_2CO_2CH_3$) through the proposed biradical species **3**. The cycloaromatized product **4** has been isolated and characterized for the reaction of **1** with methyl thioglycolate,[3c] as well as for the reactions of **1** with the biologically relevant thiols glutathione and cysteine.[9c] The biradical **3** is believed to abstract hydrogen atoms from the deoxyribose backbone of DNA, initiating a reaction cascade that, in the presence of oxygen, leads to single- and double-stranded DNA damage.

Based on the mechanism presented in Scheme I, it may be suggested that the epoxy [7.3.0]dodecadienediyne core of **1** functions as the pharmacophore of the drug. The 2-hydroxy-7-methoxy-5-methyl-1-naphthoate ester moiety is believed to serve as an intercalating agent[10] while the remainder of the drug is proposed to lie within the minor groove of double-stranded DNA.[11] The *N*-methylfucosamine substituent, largely protonated at physiological pH, is believed to provide a favorable electrostatic interaction with the negatively charged phosphate backbone of DNA.[12] It has further been proposed that the carbohydrate amino group functions as an internal base, catalyzing the addition of thiols to C-12 of the chromophore **1**.[13] The X-ray crystal structure of holo-NCS (the chromoprotein complex) reveals that, within the complex, the distance between the nitrogen of the aminosugar and the C-12 carbon is approximately 5 Å, or the van der Waals diameter of a sulfur atom.[6] Additional evidence to support this postulate has also been accrued, namely that the *N*-nitroso derivative of **1** and the simplified analog **5** both fail to add methyl thioglycolate in the absence of an external base.[13]



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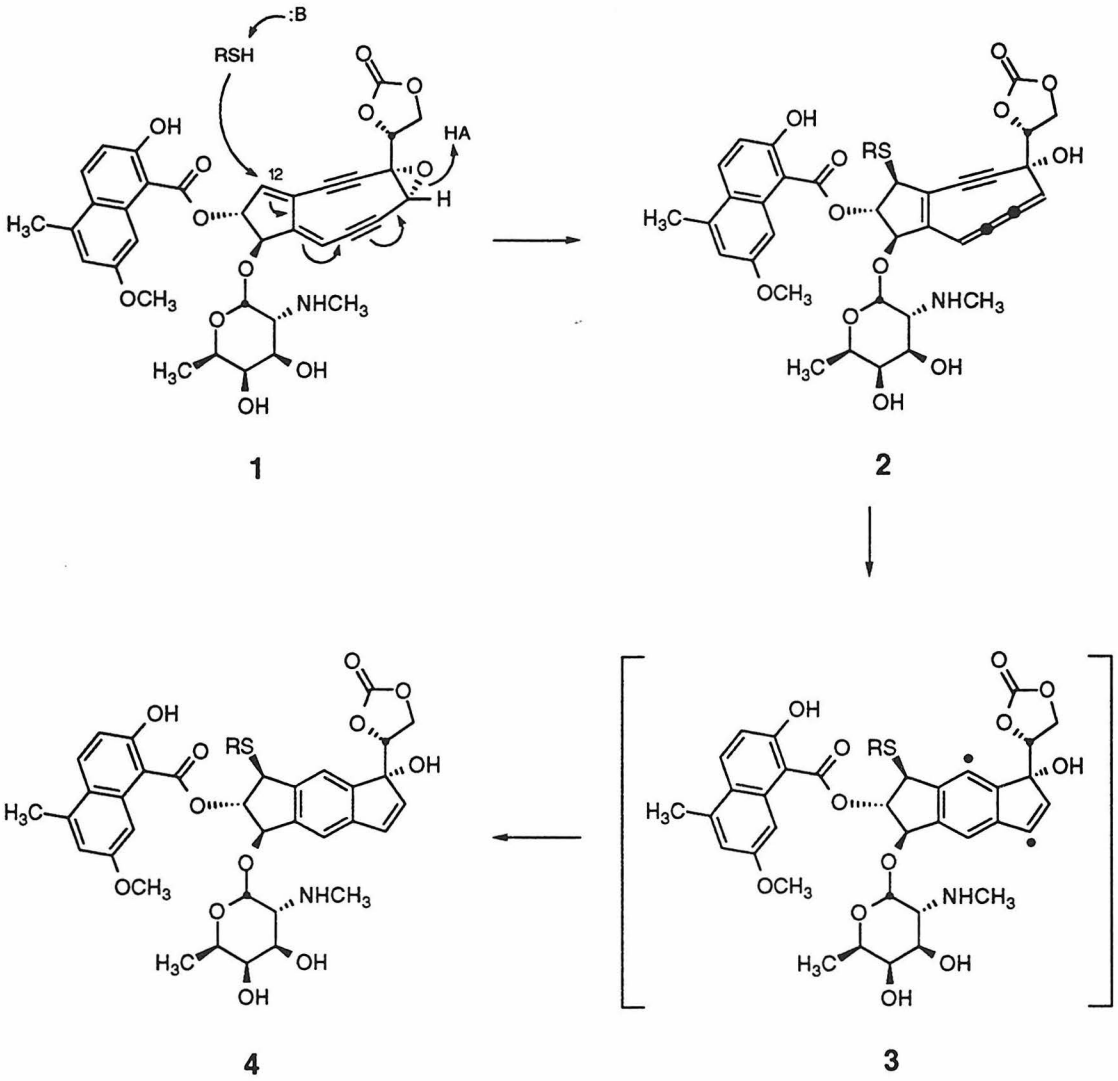
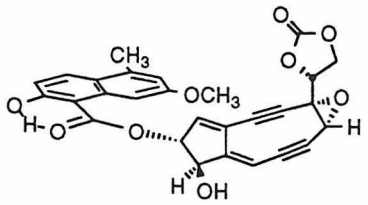
Scheme I Mechanism of Neocarzinostatin Chromophore Activation



The structural features of **1** alone define an intriguing synthetic target, with the high degree of unsaturation present within the bicyclic epoxydienediyne core and the strain of the 9-membered ring being exceptionally noteworthy. The degree of strain within the core is evidenced by the marked non-linearity of the acetylenic bonds in the crystal structure of holo-NCS, as the mean C–C≡C bond angle was determined to be 161.5 ± 1.2°.[6] The combination of these elements contributes to the instability of **1**, both neat and in solution,



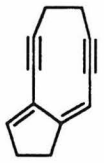
6

in the absence of the apoprotein. The proposal that the aminoglycoside functions as a component of the activation mechanism of **1** has provided additional impetus for the development of a synthesis of the aglycone portion of **1** (neocarzinostatin chromophore aglycone, **6**).[13] Such a synthesis would not only allow for the examination of the thiol addition chemistry and DNA-cleaving activity of **6** compared to **1**, but also the introduction of sugars lacking nitrogen substituents and other modified carbohydrate residues. Herein is described the first enantioselective synthesis of neocarzinostatin chromophore aglycone (**6**).[14]

Background

A variety of "model" studies, providing structures that little resemble **1** or the epoxydienediyne core, have been reported.[15] These systems generally were accessed by

construction of acyclic systems or analogs containing a less strained ten-membered ring in place of the nine-membered ring.[16] To date, the number of nine-membered ring-containing



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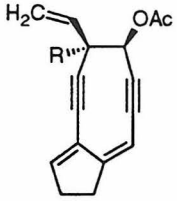
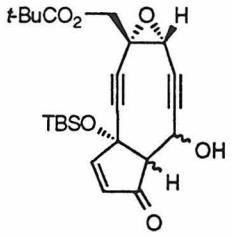


8 R = H
9 R = CH_3



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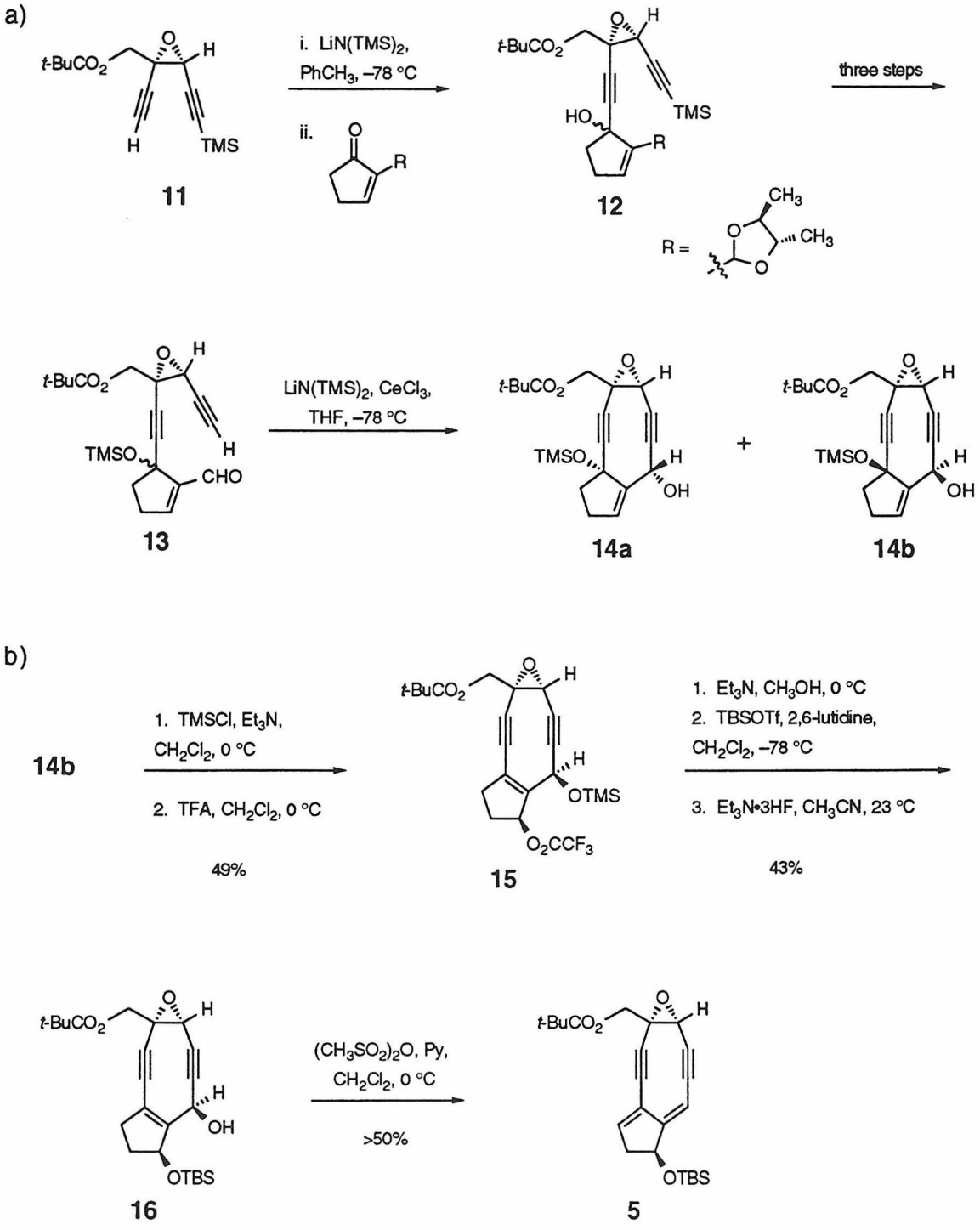
models reported is small.[17,18] Such systems, including representative structures **7-10**, lack critical structural elements found in the natural product **1** and were obtained through synthetic sequences that would prove difficult to extend to the synthesis of the fully elaborated epoxydienediyne core of **1**. A single highly functionalized model epoxydienediyne (**5**) has been prepared by Dr. P. M. Harrington of this research group.[13,19]

The synthesis of the epoxydienediyne pharmacophore of **1** involved three key transformations. First, an intramolecular acetylide addition within the α,β-unsaturated aldehyde **13** produced a separable mixture of diastereomeric nine-membered ring alcohols **14a** and **14b** (Scheme IIa).[13,19] Following this, silylation of the secondary alcohol of **14b** and exposure of the product to trifluoroacetic acid afforded the transposed trifluoroacetate **15** (Scheme IIb). After conventional functional group manipulation to produce **16**, extended elimination of the secondary alcohol of **16** produced the epoxydienediyne **5**.[13] It was this synthetic sequence that served as the platform for the studies that have resulted in the enantioselective synthesis of **6**.[14]

Scheme II


a)
t-BuCO2
H
TMS
11
i. LiN(TMS)2,
PhCH3, –78 °C
ii.
R
HO
12
three steps
R =
CH3
CH3
TMSO
CHO
13
LiN(TMS)2, CeCl3,
THF, –78 °C
OH
14a
14b
+
b)
14b
1. TMSCl, Et3N,
CH2Cl2, 0 °C
2. TFA, CH2Cl2, 0 °C
49%
OTMS
O2CCF3
15
1. Et3N, CH3OH, 0 °C
2. TBSOTf, 2,6-lutidine,
CH2Cl2, –78 °C
3. Et3N•3HF, CH3CN, 23 °C
43%
OTBS
16
(CH3SO2)2O, Py,
CH2Cl2, 0 °C
>50%
5

Chapter 2

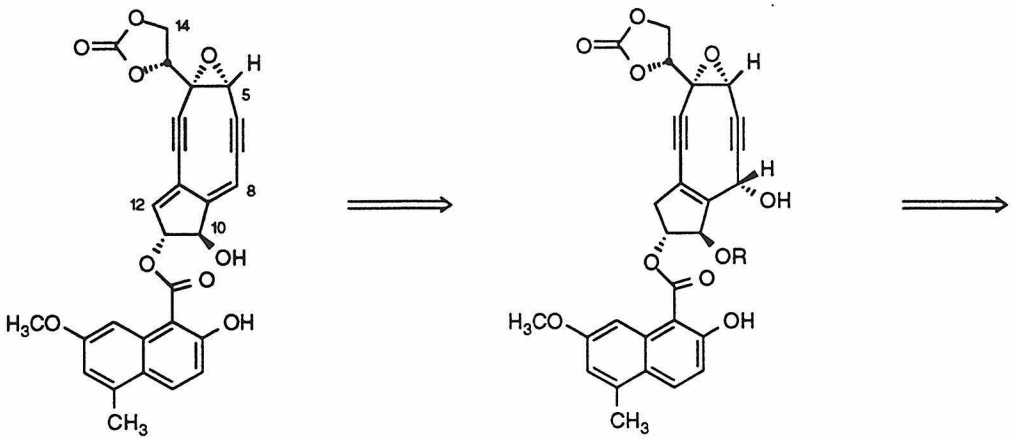
Initial Synthetic Plan

Initial Synthetic Plan

The strategy adopted at the outset of these studies was to apply the chemistry developed for the construction of the epoxydienediyne **5** to the synthesis of the more highly oxygenated core of **6**. It was expected that the final steps of the synthesis would include extended elimination of an allylic alcohol such as **17** and, if necessary, deprotection of the C-10 alcohol (Scheme III). Using the allylic transposition protocol given in Scheme IIb (Ch. 1), the alcohol **17** would be derived from the alcohol **18**, which would be the product of an intramolecular acetylide addition within the α,β-unsaturated aldehyde **19**. It was anticipated that the ring-closure substrate **19** could be constructed by the sequential coupling and elaboration of the epoxydiyne **20**, enone dimethyl acetal **21**, and the naphthoic acid **22**.

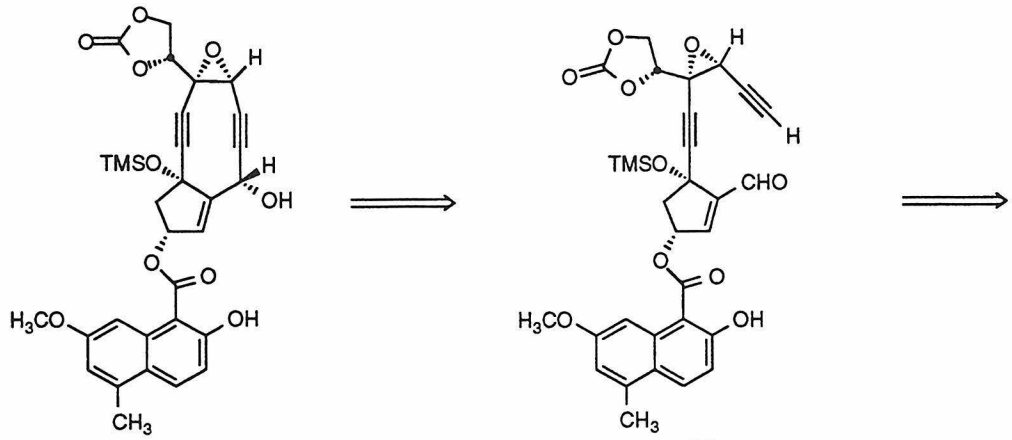
Accordingly, efficient syntheses of each of the component pieces **20**-**22** were developed. The synthesis of epoxydiyne **20** was initially optimized by E. Y. Kuo in this group, and is briefly summarized below.[14,20] Beginning with D-glyceraldehyde acetonide (Scheme IVa),[21] addition of lithium trimethylsilylacetylide in THF at –78 °C produced a 1.3:1 mixture of diastereomeric alcohols **23** in 81% yield.[22] The alcohols **23** were then oxidized to the propargylic ketone **24** with PDC and acetic acid in the presence of 3A molecular sieves in dichloromethane at 23 °C.[23] The ketone **24** was found to be unstable to concentration; consequently, the crude product was used directly in the next reaction without concentration or further purification. The *tert*-butyldimethylsilyl-protected propargyl alcohol **25**[24] was converted to the corresponding bromide,[25] which, after purification by reduced pressure distillation, was transformed to the Wittig salt **26** (Scheme IVb) by treatment with triphenylphosphine in benzene at 23 °C.[26] A solution of the ketone **24** in THF was added to the ylide derived from deprotonation of **26** with potassium hexamethyldisilazide ($KN(TMS)_2$) to produce the enediyne **28** as an approximately 3:1 mixture of olefin isomers in which the desired *E* isomer predominated. The isomers were

Scheme III



6

17



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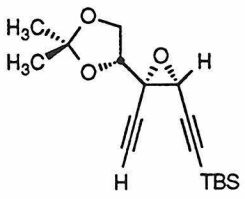
19



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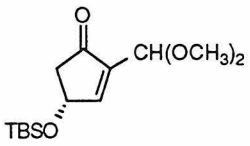

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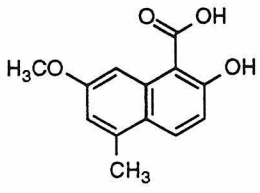

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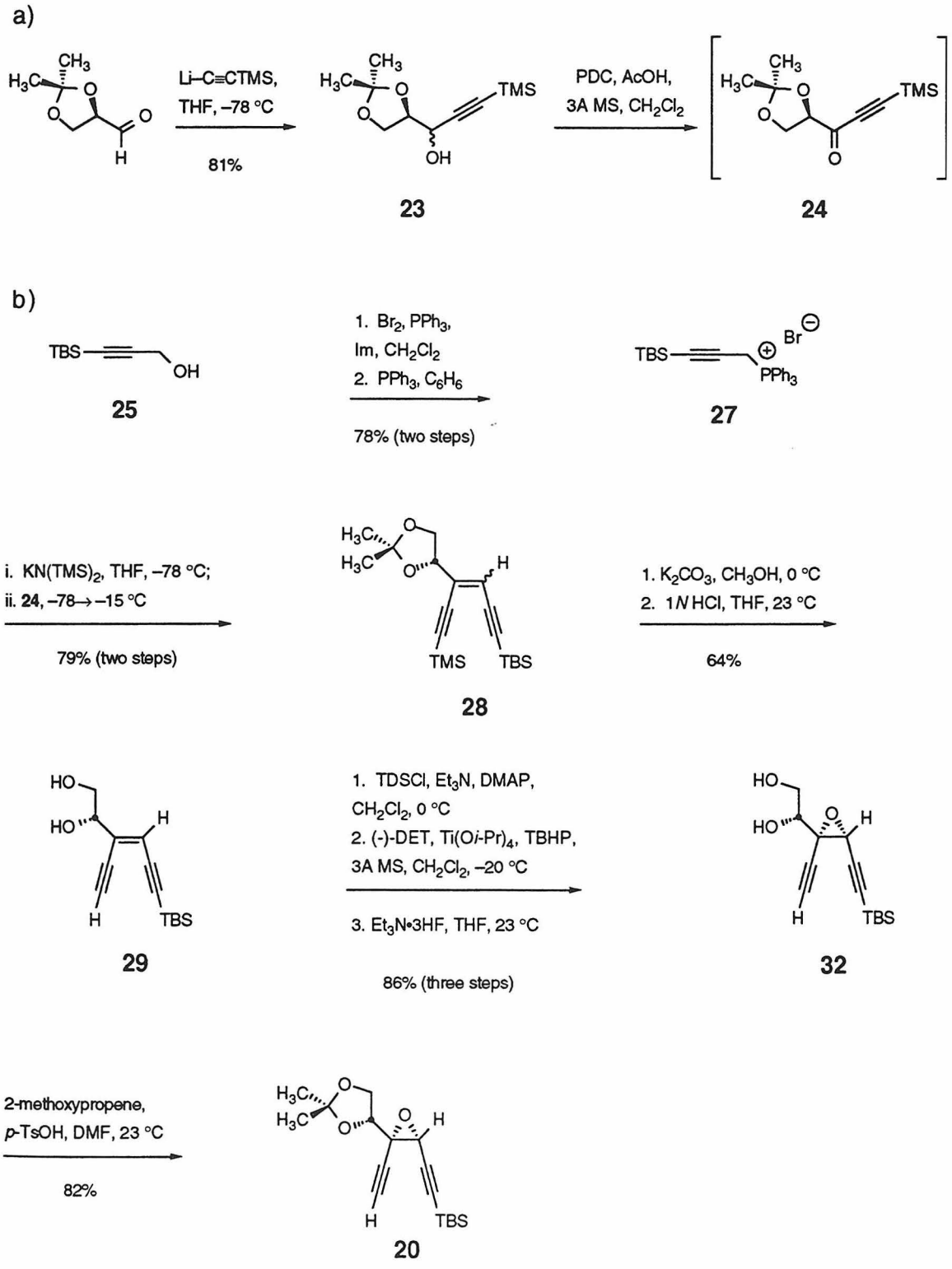
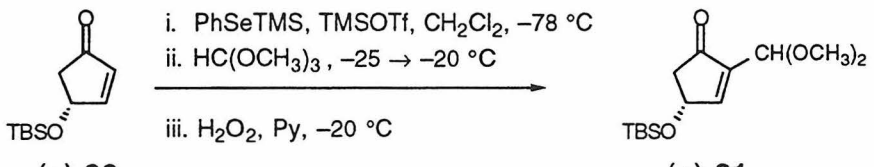
Scheme IV


a)
Li–C≡CTMS, THF, –78 °C
81%
PDC, AcOH, 3A MS, CH2Cl2
23
24
b)
25
1. Br2, PPh3, Im, CH2Cl2
2. PPh3, C6H6
78% (two steps)
27
i. KN(TMS)2, THF, –78 °C;
ii. 24, –78→–15 °C
79% (two steps)
28
1. K2CO3, CH3OH, 0 °C
2. 1N HCl, THF, 23 °C
64%
29
1. TDSCl, Et3N, DMAP, CH2Cl2, 0 °C
2. (-)-DET, Ti(Oi-Pr)4, TBHP, 3A MS, CH2Cl2, –20 °C
3. Et3N•3HF, THF, 23 °C
86% (three steps)
32
2-methoxypropene, p-TsOH, DMF, 23 °C
82%
20

not separated at this stage, but instead the acetylenic trimethylsilyl group was removed by treatment with potassium carbonate in methanol at 0 °C,[27] and the acetonide was cleaved by reaction with a mixture of 1N hydrochloric acid and THF (1:1) at 23 °C.[28] The olefin isomers proved to be separable at this stage, and flash column chromatography[29] provided the pure (*E*) isomer **29** as a pale yellow solid (mp 54 °C) in 64% yield from **28**. The primary alcohol of **29** was selectively protected as a TDS ether (**30**),[30] and the epoxide was introduced under the Sharpless asymmetric epoxidation conditions employing (–)-D-DET.[31] Cleavage of the TDS ether was carried out with triethylamine trihydrofluoride to provide epoxydiol **32** as a pale yellow solid (mp 78 °C).[32] The enantiomeric purity of intermediate **32** was established to be ≥95% ee by ^{1}H NMR analysis of both the mono- and the bis-Mosher ester derivatives of **32**.[33] The acetonide was re-introduced by the acid-catalyzed reaction of the epoxydiol **32** with 2-methoxypropene to provide epoxydiyne **20** as a pale yellow solid (mp 43-44 °C).[34]

The synthesis of the enone dimethyl acetal component (+)-**21** commenced with the well-known prostaglandin precursor (+)-**33**.[35] Application of chemistry developed by Noyori et al., involving the Michael addition of trimethylsilyl phenyl selenide into the enone followed by trapping of the intermediate enol with trimethyl orthoformate and in situ oxidation and elimination of the selenide, allowed for the introduction of the dimethyl acetal substituent in a single step.[36] The yield for the conversion of (+)-**33** to (+)-**21** was found to be highly dependent upon the exact conditions under which the reaction was carried out.

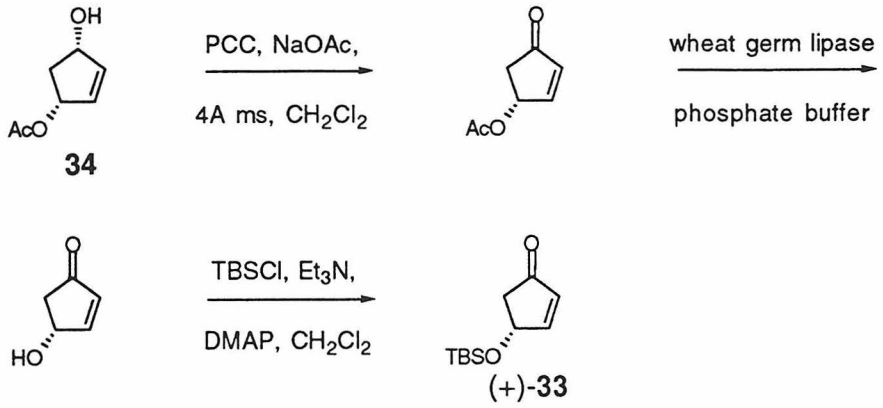


(+)-**33** 80% (+)-**21**

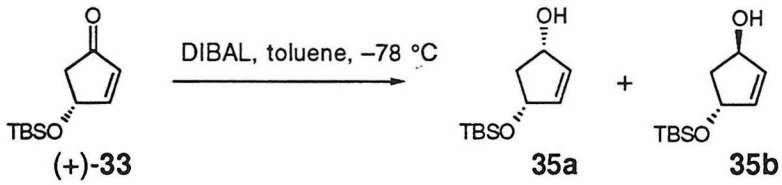
Formation of the initial Michael adduct between enone (+)-**33** and trimethylsilyl phenyl selenide with catalytic TMSOTf proceeded smoothly at –78 °C. The critical phase of the reaction was found to occur during the addition of trimethyl orthoformate and the subsequent warming. The highest yields of **21** were obtained when *freshly distilled* trimethyl orthoformate was added at –78 °C, and the reaction mixture was allowed to warm to –25 °C, and then to –20 °C over 45 minutes. Pyridine and hydrogen peroxide were added immediately after the reaction mixture turned from turbid to clear. When the reaction was carried out with careful monitoring of each stage, the enone dimethyl acetal **21** could be isolated in 80% yield as pale yellow needles (mp 29.5-30.5 °C).

At the outset of these studies the substrate for the above reaction, enone (+)-**33**, was prepared using the sequence shown in Scheme V. This route, the subject of an *Organic Syntheses* preparation,[37] was found to be both lengthy and inconvenient for large-scale material throughput. In particular the wheat germ lipase-catalyzed hydrolysis of an intermediate acetate ester required a total of ten days for completion: seven days for the hydrolysis and an additional three days for continuous extraction of the highly water-soluble product. Most importantly, it was determined that the enantiomeric excess (ee)

Scheme V



of the enone (+)-**33** was quite variable, and often unacceptably low. A method for the determination of the enantiomeric purity of (+)-**33** was developed, which involved the 1,2-reduction of (+)-**33** with DIBAL in toluene at –78 °C.[35] Separation of the diastereomers and preparation of the Mosher ester derivative[33] of the major diastereomer **35a** was followed by gas chromatographic analysis to determine the diastereomeric purity of the product ester.[38] The racemization was determined to be occurring during either the enzymatic hydrolysis or the subsequent silylation through analysis of the enantiomeric purity of (+)-**33** and each of the intermediates in the synthesis. Additionally, an improved synthesis of enone (+)-**33** was developed.[35]

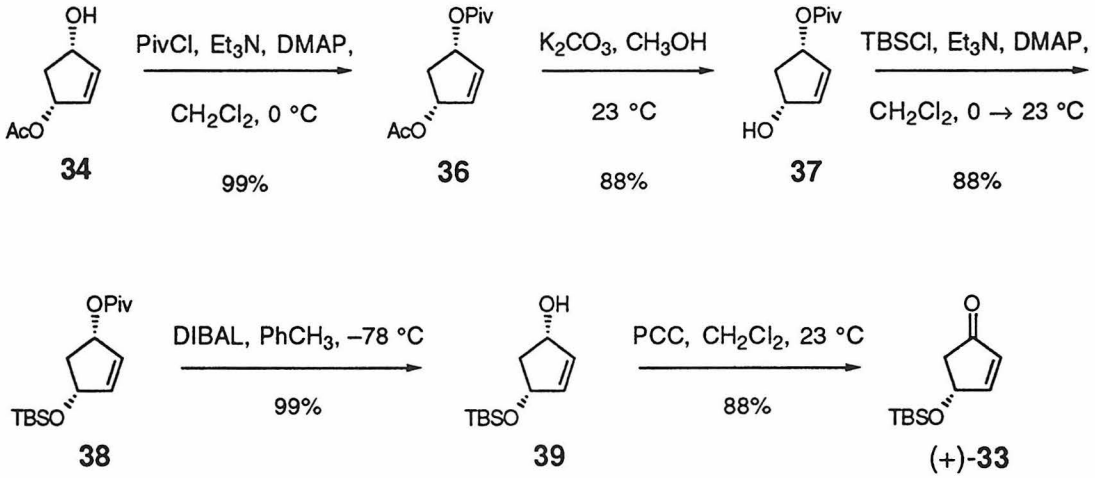


(+)-**33** **35a** **35b**

The modified synthesis of enone (+)-**33** is given in Scheme VI. The synthesis was initiated with the same starting material utilized in the aforementioned preparation of (+)-**33**. The highly enantiomerically enriched monoacetate **34**, prepared by the enzymatic hydrolysis of the corresponding meso diacetate,[40] was converted to the pivaloate ester **36** in 99% yield by treatment with pivaloyl chloride, triethylamine, and DMAP in dichloromethane at 0 °C. Selective hydrolysis of the acetate ester within **36** was accomplished using potassium carbonate in methanol to afford the hydroxy ester **37** in 88% yield and ≥99% ee, as determined by gas chromatographic (gc) analysis of the corresponding Mosher ester. Addition of TBSCl, triethylamine and DMAP to **37** produced the corresponding silyl ether **38** as a white solid (mp 64-66 °C) in 88% yield.[41] The pivaloate group of **38** was cleaved with DIBAL in toluene at –78 °C, affording the alcohol **39** in quantitative yield and ≥99% ee as determined by gc analysis[38] of the corresponding Mosher ester derivative.[33] The latter observation established that intramolecular migration

of the tert-butyldimethylsilyl group of **39** was not detectable under these conditions. Oxidation of **39** with pyridinium chlorochromate in dichloromethane[42] provided (+)-**33** in 88% yield after flash column chromatography. Reduction of (+)-**33** prepared this way with DIBAL and Mosher esterification[33] of the resulting major alcohol diastereomer **35a** afforded a Mosher ester of ≥99% diastereomeric excess (de), as determined by gc analysis.[38] To confirm the result, the minor diastereomer in the reduction, the trans alcohol **35b** was also transformed into its Mosher ester derivative.[33] The resulting Mosher ester was shown to be ≥99% de by gc analysis.[38] These results established that the synthetic (+)-**33** produced by the new route was of ≥99% ee and that the analytical method used proceeded without enantiomerization of **33** or any derivative in the sequence.

Scheme VI



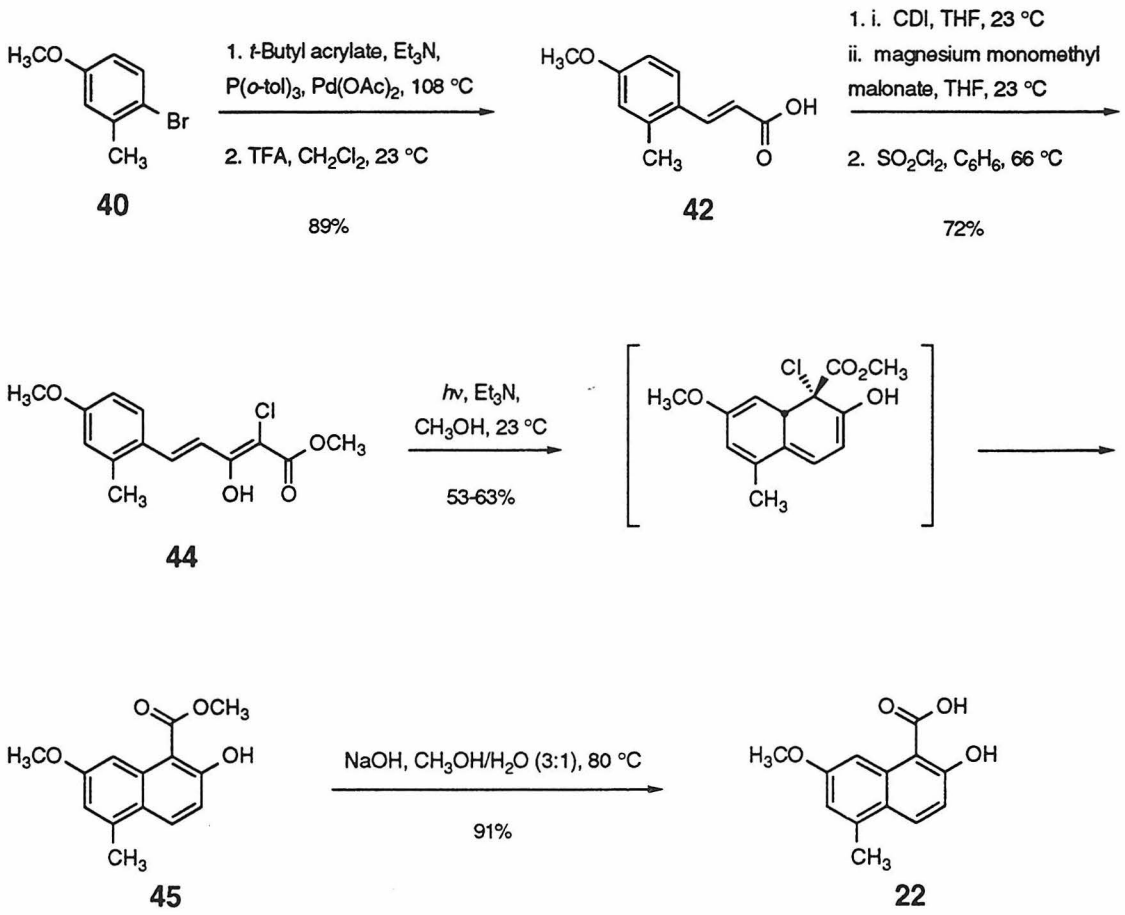
The enantiomeric purity of the enone dimethyl acetal **21**, prepared from the highly enantiomerically enriched (+)-**33**, was also determined by the 1,2-reduction – Mosher esterification sequence in analogy to (+)-**33**.[33] The diastereomeric Mosher esters, however, could not be effectively separated by gc, hence the de of these esters was

determined by the less accurate method of ^{1}H NMR analysis. By this technique the enantiomeric enrichment of **21** was found to be ≥90% ee.

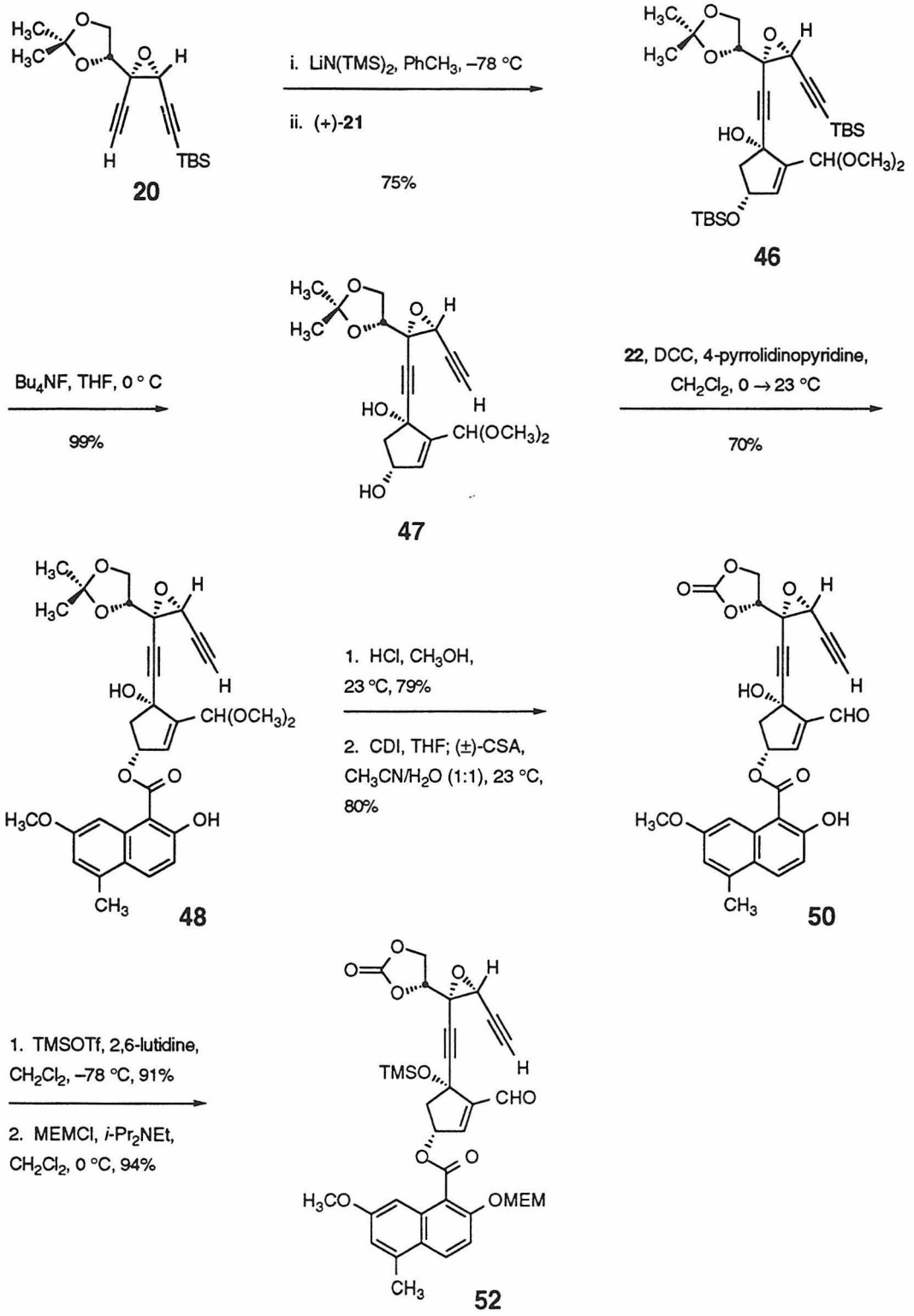
The synthesis of the 2-hydroxy-7-methoxy-5-methyl-1-naphthoic acid moiety **22** is given in Scheme VII. This sequence is the most efficient of several reported syntheses, and was developed within this research group by V. Subramanian.[44] Briefly, 4-bromo-3-methylanisole (**40**)[45] underwent Heck coupling[46] with *tert*-butyl acrylate, and the resultant ester (**41**) was hydrolyzed by treatment with trifluoroacetic acid (TFA) to provide the carboxylic acid **42** in 89% overall yield. Following a known acylation protocol,[47] the latter product was treated with carbonyldiimidazole in THF and the resulting acylimidazolide was trapped in situ with magnesium methyl malonate to provide a β-keto ester (**43**) which, when exposed to sulfuryl chloride in benzene at 66 °C,[48] produced the photocyclization precursor **44** in 72% yield for the two steps. Irradiation of a deoxygenated methanolic solution of **44** with a 450-watt Hanovia medium pressure mercury arc lamp (quartz immersion well) for 1 h at 23 °C produced methyl ester **45** in 53-63% yield after column chromatography. Saponification of ester **45** with sodium hydroxide in aqueous methanol afforded the naphthoic acid **22** in 91% yield. The acid **22** provided ^{1}H NMR, ^{13}C NMR, FTIR and mass spectroscopic data that was identical to the reported value,[49] and the combined yield of **22** from 4-bromo-3-methylanisole was 31-37%.

Having the components **20**-**22** in hand, the studies directed toward the synthesis of the nine-membered ring core of the aglycone **6** were initiated. First carried out by Dr. J.-N. Xiang in this group, the construction of the core followed closely the chemistry developed for the synthesis of model epoxydienediyne **5**.[13,19] Deprotonation of epoxydiyne **20** with lithium hexamethyldisilazide ($LiN(TMS)_2$) in toluene at –78 °C followed by addition of (+)-**21** afforded alcohol **46** in 75% yield and with ≥20:1 selectivity for the diastereomer shown (Scheme VIII).[50] The alcohol **46** was then treated with tetrabutylammonium fluoride (TBAF) to remove both silyl groups and provide diol **47** in

Scheme VII

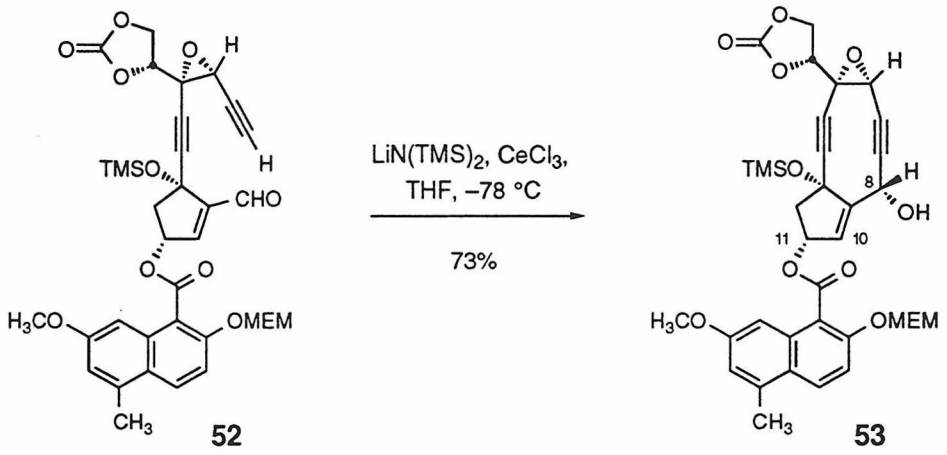

H3CO
Br
CH3
40
1. t-Butyl acrylate, Et3N,
P(o-tol)3, Pd(OAc)2, 108 °C
2. TFA, CH2Cl2, 23 °C
89%
H3CO
OH
O
CH3
42
1. i. CDI, THF, 23 °C
ii. magnesium monomethyl
malonate, THF, 23 °C
2. SO2Cl2, C6H6, 66 °C
72%
H3CO
Cl
OCH3
CH3
OH
O
44
hν, Et3N,
CH3OH, 23 °C
53-63%
Cl
CO2CH3
H3CO
OH
CH3
O
OCH3
H3CO
OH
CH3
45
NaOH, CH3OH/H2O (3:1), 80 °C
91%
O
OH
H3CO
OH
CH3
22

Scheme VIII


20
i. LiN(TMS)2, PhCH3, –78 °C
ii. (+)-21
75%
46
Bu4NF, THF, 0 ° C
99%
47
22, DCC, 4-pyrrolidinopyridine,
CH2Cl2, 0 → 23 °C
70%
48
1. HCl, CH3OH,
23 °C, 79%
2. CDI, THF; (±)-CSA,
CH3CN/H2O (1:1), 23 °C,
80%
50
1. TMSOTf, 2,6-lutidine,
CH2Cl2, –78 °C, 91%
2. MEMCl, i-Pr2NEt,
CH2Cl2, 0 °C, 94%
52

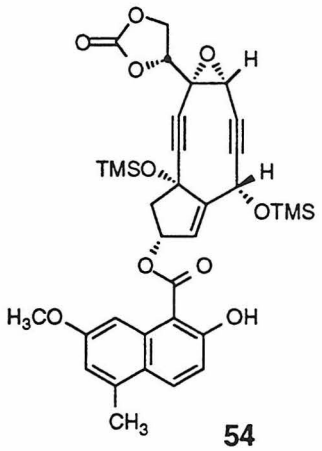
quantitative yield.[51] Esterification of the naphthoic acid **22** was then carried out using dicyclohexylcarbodiimide (DCC) and catalytic 4-pyrrolidinopyridine or DMAP in dichloromethane at 0 °C.[52] Under these conditions, ester **48** was obtained in 70% isolated yield. The acetonide protective group of **48** was removed by reaction with concentrated hydrochloric acid in methanol at 23 °C, and the ethylene carbonate group was introduced by treatment of the triol product with CDI.[53] Exposure of the crude reaction mixture to (±)-camphorsulfonic acid in a 1:1 mixture of acetonitrile and water at 23 °C afforded the α,β-unsaturated aldehyde **50** in 63% yield from the intermediate **48**. The tertiary alcohol of **50** was protected as a silyl ether by reaction with TMSOTf and 2,6-lutidine in dichloromethane at –78 °C,[54] and treatment of the intermediate with MEM chloride and diisopropylethylamine in dichloromethane at 0 °C[55] produced the protected ring-closure substrate **52** in 86% overall yield from intermediate **50**.

The conditions developed for the closure of the nine-membered ring in the synthesis of **5** found successful application for the acetylide addition into the aldehyde within substrate **52**.[13,19] Treatment of a premixed suspension of the intermediate **52** and cerium(III) chloride (3 equiv) in THF at –78 °C with $LiN(TMS)_2$ provided secondary

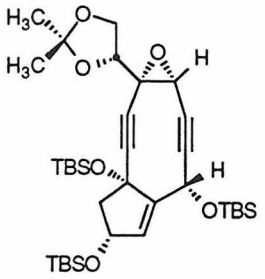


alcohol **53** as a pale yellow oil in 73% yield.[19] The reaction was found to be sensitive to the amount of base used; addition of excess base resulted in the cleavage of the ethylene

carbonate of both **52** and **53**. Previous studies carried out by Dr. J.-N. Xiang in this group indicated that the protocol employed for the transposition of the allylic alcohol, in analogy to the conversion of **14b** to **15** (Ch 1, Scheme II),[13] proved to be ineffective in this more highly oxygenated core system. Specifically, the exposure of silyl ethers such as **54** and **55** to trifluoroacetic acid in dichloromethane at 0 °C resulted in either recovery of unreacted starting material or simple cleavage of the silyl ethers.[50] As a result, it became necessary to explore alternative methodology for the transposition of the C-9 – C-10 olefin into the nine-membered ring and the introduction of the C-10 alcohol.



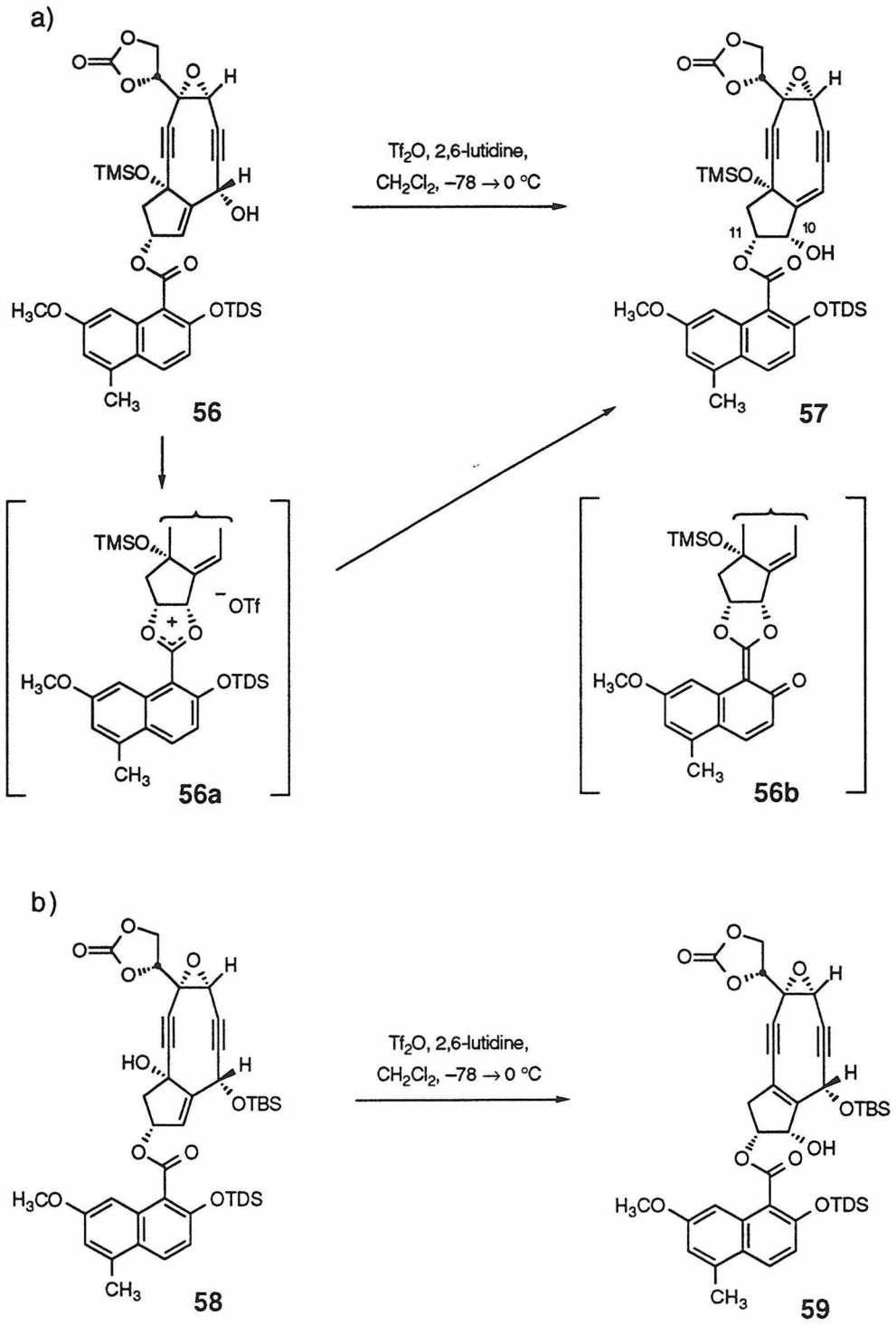
54



55

The studies carried out by Dr. J.-N. Xiang also revealed that, when the naphthoate ester was present within nine-membered ring intermediates such as **56**, reaction with trifluoromethanesulfonic anhydride (triflic anhydride) and 2,6-lutidine in dichloromethane at –78 °C followed by an aqueous work-up afforded the rearranged allylic alcohol **57** having cis stereochemistry relative to the naphthoate substituent (Scheme IXa).[50] The stereochemistry was assigned based on the coupling constant between the C-10 and C-11 protons,[56] found to be ca. 5.5 Hz, significantly larger than the 0 Hz coupling constant

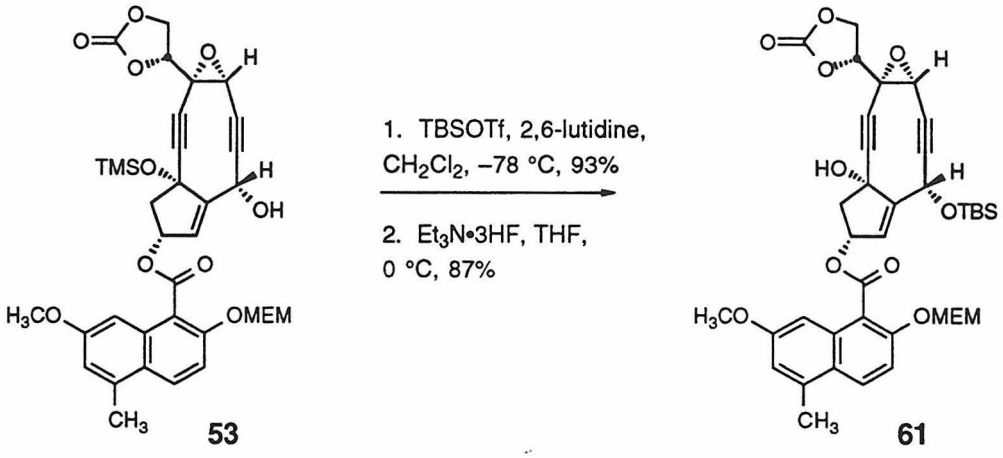
Scheme IX


a)
TMSO
H
OH
H3CO
OTDS
CH3
56
Tf2O, 2,6-lutidine,
CH2Cl2, –78 → 0 °C
TMSO
11
10
OH
H3CO
OTDS
CH3
57
TMSO
OTf
H3CO
OTDS
CH3
56a
TMSO
H3CO
O
CH3
56b
b)
HO
H
OTBS
H3CO
OTDS
CH3
58
Tf2O, 2,6-lutidine,
CH2Cl2, –78 → 0 °C
H
OTBS
OH
H3CO
OTDS
CH3
59

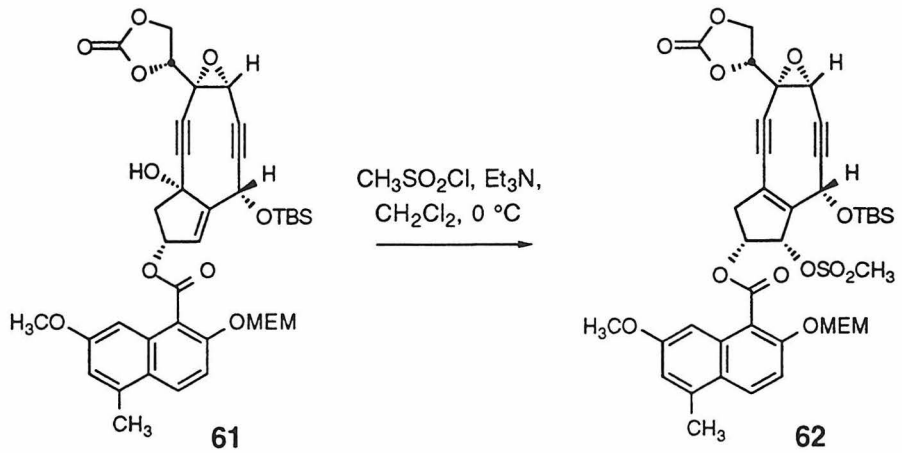
observed between the two corresponding protons in **1**.[3a] The mechanism proposed for this rearrangement involves activation of the secondary alcohol and neighboring group participation of the ester carbonyl in the allylic transposition via the dioxolenium ion intermediate **56a**.[57] Subsequent trapping of this intermediate with water at the carbonyl carbon, rather than at the C-10 position, would result in the formation of the cis alcohol **57**. Further evidence for the intermediacy of ion **56a** was found in the observation that a small amount of the rearranged product in which the naphthoate ester had migrated to the C-10 position was also formed. Additionally, substrates in which the hydroxyl group of the naphthoate ester had been protected with the labile TDS group afforded, in some cases, a rearranged product in which this protective group had been lost. The observation of this deprotected product suggested the further intermediacy of the neutral species **56b**. An analogous transposition was observed when the tertiary alcohol **58** (Scheme XIIb) was treated with triflic anhydride and 2,6-lutidine in dichloromethane at –78 °C, the transposition now occurring in the direction of the tertiary alcohol to provide the tetrasubstituted allylic alcohol **59**. While the nine-membered ring products corresponding to **53**, **56**, and **58** were found to be somewhat unstable, slowly decomposing over several hours when neat, the rearranged alcohols corresponding to **57** and **59** were significantly less stable, decomposing within minutes in neat form as well as when stored overnight at –20 °C in a frozen benzene matrix.

The replacement of the TDS protective group with the less labile MEM protective group in **53** was intended to suppress the loss of the naphthol protective group during the rearrangement reaction. Having substrate **53** in hand, the decision was made to protect the C-8 secondary alcohol and free the C-1 tertiary alcohol for rearrangement, as transposition in this direction would produce the relatively more stable tetrasubstituted olefin intermediate. With this in mind, treatment of alcohol **53** with TBSOTf and 2,6-lutidine in dichloromethane at –78 °C[58] followed by selective removal of the TMS group with triethylamine trihydrofluoride in THF at 0 °C[32] produced the tertiary alcohol **61** in 81%

overall yield. It was this alcohol that was employed as a substrate for the examination of many different conditions to effect allylic transposition and provide a rearrangement product having the requisite trans stereochemistry between the C-10 and C-11 substituents.



Reaction of the tertiary alcohol **61** with excess methanesulfonyl chloride and triethylamine in dichloromethane at 0 °C provided rearranged mesylate **62** directly.[59] The mesylate **62** appeared to be an ideal substrate for nucleophilic inversion, which would afford a product with trans relative stereochemistry between the C-10 and C-11 substituents. Table 1 summarizes many of the conditions examined to effect this inversion. Some conditions led to the formation of a new product (entries 6 and 7) that was



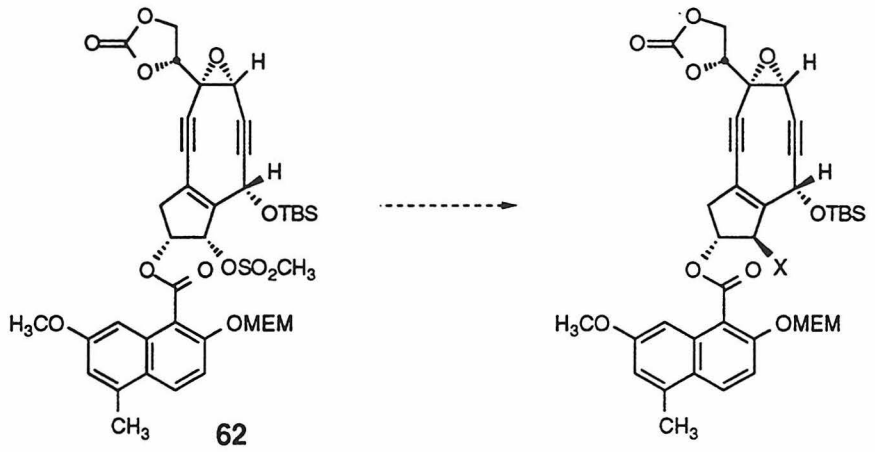


Table 1. Attempted Inversion of Mesylate **62**.

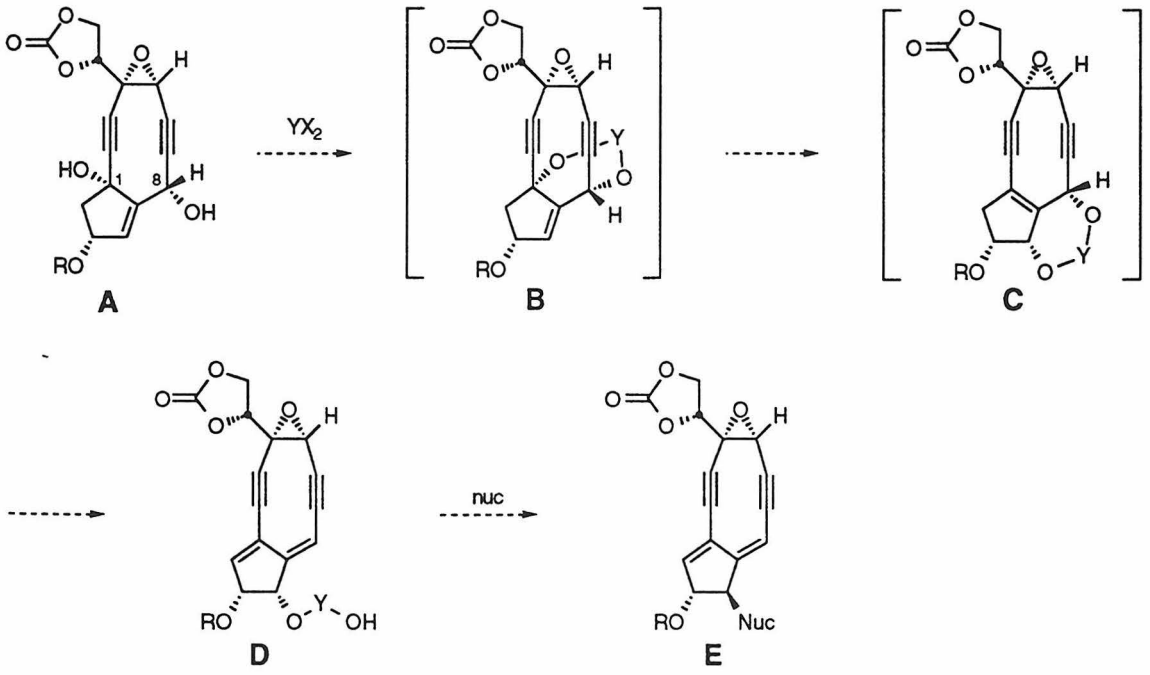
Entry	Conditions[a]	Result
1	NaOAc, TFE, 3A MS, 0 °C	no reaction
2	$NaOCCCl_3$, TFE, 3A MS, 0 °C	no reaction
3	KNO_2, DMF, 23 °C	decomposition of **62**
4	NaN_3, EtOH, –10 → 23 °C	decomposition of **62**
5	TMGA,[60] CH_2Cl_2, 23 °C	decomposition of **62**
6	H_2O, C_6H_6, 23 °C	"new" product
7	5% ethylene glycol, HMPA, 0 → 23 °C	"new" product

[a] TFE = 2,2,2-trifluoroethanol; DMF = *N,N*-dimethylformamide; TMGA = tetramethylguanidinium azide; HMPA = hexamethylphosphoramide

determined not to be the inverted alcohol. The structure of this product was not determined; however, the ^{1}H NMR and FTIR spectral data for this new product were consistent with the opening of the C-4 – C-5 epoxide. Because of the propensity of mesylate **62** to either decompose or undergo an unwanted side reaction, this approach was abandoned in favor of a new, but related, strategy.

With the idea of taking advantage of the ability of the tertiary alcohol to undergo facile allylic transposition, it was envisioned that cyclic, activated intermediate **B**, derived from diol **A** could be formed between the C-1 and the C-8 alcohols (Scheme X). The intermediate **B** could then rearrange to intermediate **C**, which then could eliminate, either spontaneously or in the presence of a base, to produce the epoxydienediyne **D** directly. In situ treatment with a nucleophile such as water would then yield the product **E**. With this in mind, nine-membered ring alcohol **53** was converted to diol **63** in 89% yield by reaction

Scheme X



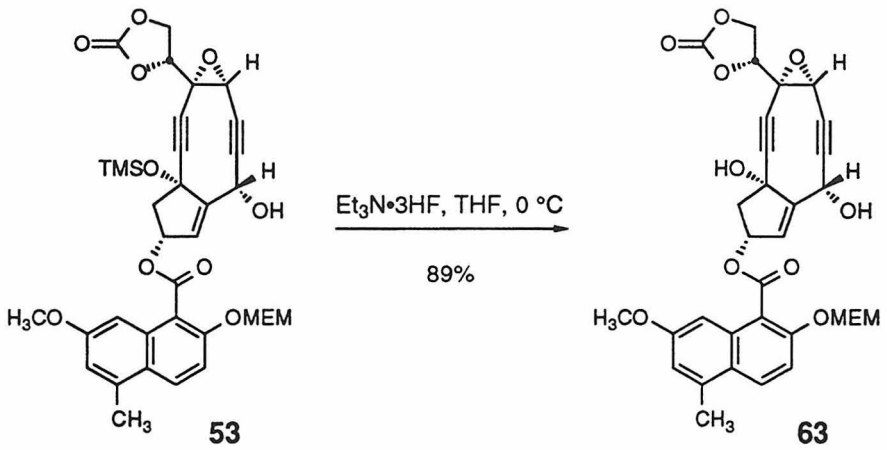
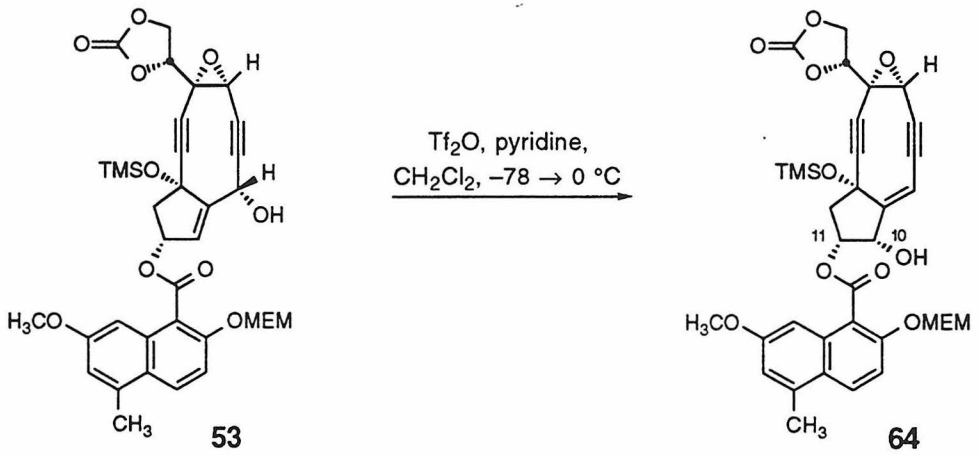


Table 2. Conditions Examined for Conversion of **63** to an Epoxydienediyne.

Entry	Conditions
1	Martin sulfurane,[61] CH_2Cl_2, 0 → 23 °C
2	Martin sulfurane,[61] CH_2Cl_2, –78 °C
3	SO_2Cl_2, Et_3N, CH_2Cl_2, 0 → 23 °C
4	SO_2Cl_2, pyridine, CH_2Cl_2, 0 °C
5	SO_2Cl_2, *i*-Pr_2NEt, CH_2Cl_2, 0 → 23 °C
6	SO_2Cl_2, CH_2Cl_2, –78 → 0 °C
7	$PhCl_2P$, pyridine, CH_2Cl_2, 0 → 23 °C
8	$PhCl_2P$, *i*-Pr_2NEt, CH_2Cl_2, 0 → 23 °C
9	$PhCl_2P$, CH_2Cl_2, 0 → 23 °C
10	(*i*-Pr)$_2$Si(OTf)$_2$, 2,6-lutidine, CH_2Cl_2, –78 °C

with triethylamine trihydrofluoride in THF at 0 °C. Table 2 provides a summary of conditions examined to carry out the conversion corresponding to **A** → **E**, all of which caused the decomposition of the diol **63** or resulted in the formation of complex reaction mixtures. Because of the lack of encouraging results, this approach was discontinued.

Hoping to make use of the triflic anhydride-mediated rearrangement of substrates such as **53** and **56**, which provided products having the requisite regiochemistry but incorrect stereochemistry, a study of the inversion of the resultant C-10 alcohol under Mitsunobu conditions was initiated.[62] Secondary alcohol **53**, upon treatment with excess triflic anhydride and pyridine, was converted to the highly unstable rearranged alcohol **64**, with the alcohol having the expected cis stereochemistry relative to the naphthoate ester.



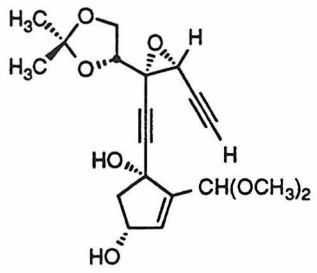
53 **64**

The alcohol **64** was then treated with either chloroacetic acid or *p*-nitrobenzoic acid under Mitsunobu conditions. Both chloroacetic acid[63] and *p*-nitrobenzoic acid[64] have been reported to be excellent nucleophiles under Mitsunobu conditions; however, none of the expected inverted ester product was isolated from any of the reaction mixtures. Mitsunobu inversions have also been found to be highly solvent dependent; accordingly, these reactions were examined in a variety of solvents, including benzene, THF, dichloromethane, and toluene. None of these solvents was found to be superior to any of the others and in all cases rapid decomposition of the substrate **64** was observed. The

conclusions reached from this series of experiments were two-fold: 1) the MEM group protecting the hydroxyl of the naphthoate ester may have been hydrogen bonding with the C-10 alcohol in the rearranged product and blocking it from further reactivation, and 2) the rearranged alcohol **64** was simply too unstable to be used as a synthetic intermediate. Consequently, this phase of synthetic studies was concluded.

The participation of the naphthoate ester in the triflic anhydride-induced rearrangement of alcohols **53**, **56**, and **58** prompted the consideration of setting the C-10 – C-11 trans stereochemistry prior to the introduction of the ester. To test the rearrangement behavior of nine-membered ring substrates lacking the naphthoate ester, the simplified intermediate **70** was constructed. Beginning with the known intermediate **47**, the C-10 alcohol was protected as a TBS ether by reaction with TBSCl, triethylamine, and catalytic DMAP in dichloromethane at 0 °C to afford the silyl ether (**65**) in 92% yield (Scheme XI).[41] The dimethyl acetal was then hydrolyzed with *p*-toluenesulfonic acid in acetone at 23 °C to provide α,β-unsaturated alcohol **66** as a white solid (mp 90-92 °C) in 90% yield.[64] Silylation of the tertiary alcohol **66** with TMSOTf and 2,6-lutidine in dichloromethane at –78 °C produced the silyl ether (**67**) in 88% yield,[54] which was subsequently treated with $LiN(TMS)_2$ in the presence of three equivalents of cerium(III) chloride to afford the ring-closed alcohol **68** in 82% yield.[13,19] The trimethylsilyl ether was selectively removed in 75% yield by treatment with potassium fluoride in methanol, and a triphenylsilyl (TPS) group was introduced by treatment with triphenylsilyl chloride, triethylamine, and DMAP in dichloromethane at 0 °C to provide TPS ether **70** in 66% yield.[66] The yield of this reaction was moderated by the formation of the product in which both the secondary and tertiary alcohols had been silylated. The tertiary alcohol **70** was examined as a substrate for allylic transposition reactions.

Scheme XI

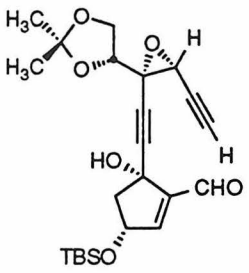


47

1. TBSCl, DMAP, Et_3N, CH_2Cl_2, 0 °C

2. *p*-TsOH, acetone, 23 °C

84%

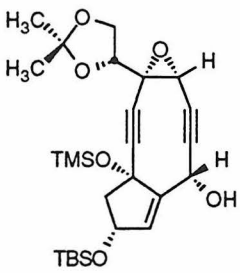


66

1. TMSOTf, 2,6-lutidine, CH_2Cl_2, –78 °C

2. $LiN(TMS)_2$, $CeCl_3$, THF, –78 °C

72%

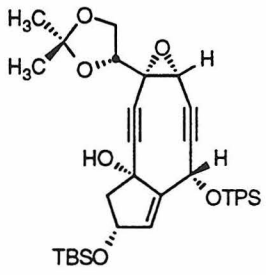


68

1. KF, CH_3OH, 23 °C

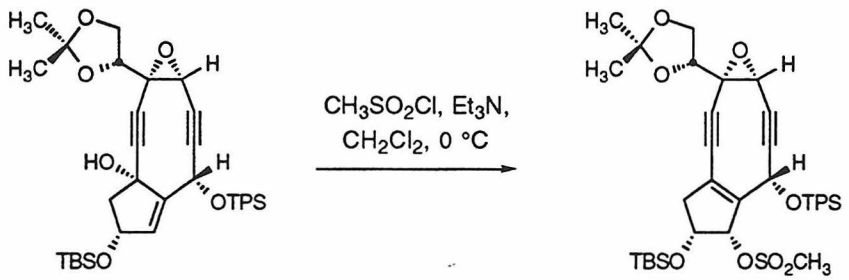
2. Ph_3SiCl, Et_3N, DMAP, CH_2Cl_2

50%



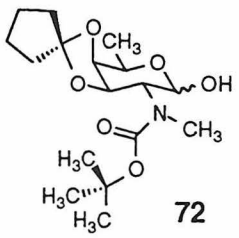
70

The absence of the C-11 ester functionality markedly changed the behavior of substrate **70** towards triflic anhydride. Treatment of **70** with triflic anhydride and pyridine in dichloromethane at –78 °C followed by warming to 0 °C resulted in nonspecific decomposition of the starting material. The reactivity of alcohol **70** toward methanesulfonyl chloride and triethylamine in dichloromethane at 0 °C,[59] on the other hand,



70 **71**

paralleled that of alcohol **61**, affording the unstable rearranged mesylate **71**. Attempted inversion of mesylate **71** with water and 2,6-di-*tert*-butylpyridine in 2,2,2-trifluoroethanol resulted in decomposition of the substrate. Introduction of the protected *N*-methylfucosamine sugar derivative **72** by displacement of the mesylate with the anomeric oxygen of the glycoside was also examined.[67] Neither treatment of the mesylate **71** with the glycoside **72** in trifluoroethanol in the presence of 2,6-lutidine and 3A molecular sieves at 23 °C nor treatment of **71** with the potassium salt of **72** in a 4:1 mixture of THF and HMPA at –40 °C produced the desired inverted product; in fact, these reactions only resulted in decomposition of the mesylate substrate.



72

The lack of success in obtaining products with the requisite trans relative stereochemistry between the C-10 and C-11 substituents using the strategies discussed above prompted the following conclusions: 1) the presence of oxygenation at the C-11 position greatly altered the rearrangement behavior of intermediates such as **53**, as the trifluoroacetic acid-mediated rearrangement of the corresponding trimethylsilyl ethers failed completely within this class of substrates, and 2) it was determined that rearranged intermediates **57**, **59**, **62**, **64**, and **71** were significantly less stable than even the non-rearranged nine-membered ring substrates. It was this instability that complicated all attempts to invert the C-10 center. In light of the findings discussed here, the decision was made to pursue strategies involving structurally and mechanistically different approaches to the stereoselective construction of the functionalized epoxydienediyne core of **6**.

Experimental Section

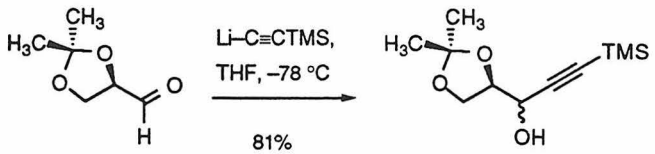
General procedures. All reactions were performed in flame-dried round bottom or modified Schlenk (Kjeldahl shape) flasks. The flasks were fitted with rubber septa and contained a positive pressure of argon unless otherwise stated. Stainless steel syringes or cannula were used to transfer air- and moisture-sensitive materials. Concentration in vacuo was accomplished by rotary evaporation at water aspirator pressure (approximately 25 torr). Flash chromatography was carried out as described by Still et al., employing 230-400 mesh silica gel.[29] Analytical thin-layer chromatography was performed using glass plates pre-coated with 0.25 mm 230-400 mesh silica gel impregnated with fluorescent indicator (254 nm). Thin-layer chromatography plates were visualized by exposure to ultraviolet light (noted as 'UV') and/or by exposure to an acidic solution of *p*-anisaldehyde (noted as 'anisaldehyde') or ethanolic phosphomolybdic acid (noted as 'PMA') followed by heating on a hot plate.

Materials. Commercial reagents were used as received, with the following exceptions. Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl. Dichloromethane, benzene, toluene, acetonitrile, N,N-diisopropylethylamine, hexamethyldisilazane, 2,6-lutidine, pyridine, and triethylamine were distilled from calcium hydride at 760 torr. Acetic acid was distilled from chromium trioxide at 760 torr and was stored over 4 Å molecular sieves. Anhydrous cerium(III) chloride was prepared from the

heptahydrate by heating at 100 °C and 1 torr for 12 h. Methanesulfonyl chloride was distilled from phosphorous pentoxide at 760 torr. Trifluoromethanesulfonic anhydride and trimethylsilyl trifluoromethanesulfonate were stored in a glove box in round bottom flasks fitted with polycarbonate or glass stoppers. The molarity of n-butyllithium solutions was determined by titration with 2,6-di-*tert*-butyl-4-methylphenol using fluorene as an indicator (average of three determinations). Where indicated, fresh solutions of lithium hexamethyldisilazide were prepared by the addition of a solution of n-butyllithium (1.0 eq) in hexanes to a solution of hexamethyldisilazane (1.0 eq) in hexanes at –20 °C, followed by warming to room temperature.

Instrumentation. Infrared (IR) spectra were obtained using a Perkin-Elmer 1600 FT-IR spectrophotometer referenced to a polystyrene standard. Data are presented as follows: frequency of absorption (cm^{-1}) intensity of absorption (v = very, s = strong, m = medium, w = weak) and assignment where appropriate. Proton nuclear magnetic resonance (^1H NMR) spectra and carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on either a General Electric QE-300 (300 MHz) or a JEOL GX-400 (400 MHz) NMR spectrometer; chemical shifts for protons are reported in parts per million downfield from tetramethylsilane and are referenced to residual protium in the NMR solvent ($CHCl_3$: δ 7.26, C_6D_5H: δ 7.20, $CDHCl_2$: δ 5.29, $SO(CD_3)(CD_2H)$: δ 2.49). Data are represented as follows: chemical shift, multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, complex = multiple resonances, app. = apparent), integration, coupling constant in Hertz (Hz), and assignment. Optical rotations were determined on a Jasco DIP-181 digital polarimeter equipped with a sodium lamp source. Melting points were determined on a Büchi SPM-20 melting point apparatus and are uncorrected. High resolution mass spectra were obtained either at the University of California, Riverside Mass Spectrometry Facility; the Midwest Center for Mass Spectroscopy, Lincoln, Nebraska; the University of California, Los Angeles Mass

Spectrometry Facility; or the California Institute of Technology Mass Spectrometry Facility.

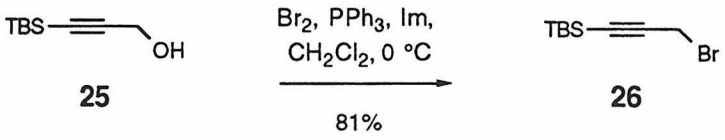


23

Propargylic alcohol **23**

Lithium hexamethyldisilazide (164 mL of a 1.0 M solution in THF, 0.164 mol, 1.20 equiv) was added in a dropwise manner over 30 min to a solution of trimethylsilylacetylene (25 mL, 17.6 g, 0.179 mol, 1.10 equiv) in tetrahydrofuran (720 mL) at –78 °C. The resultant solution was maintained at –78 °C for 30 min, and a solution of D-glyceraldehyde acetonide (19.4 g, 0.149 mol, 1.0 equiv) in tetrahydrofuran (225 mL) was added over a period of 30 min. The reaction mixture was maintained at –78 °C for 30 min, and excess base was quenched by the addition of saturated aqueous ammonium chloride (100 mL). The reaction mixture was concentrated in vacuo to a volume of approximately 300 mL, and then diluted with ethyl acetate (250 mL). The mixture was washed with water (200 mL) and saturated aqueous sodium chloride (200 mL). The combined aqueous layers were further extracted with ethyl acetate (100 mL), and the combined organics were dried over sodium sulfate and concentrated. Purification of the residue by flash column chromatography (20% ethyl acetate in hexanes grading to 40% ethyl acetate in hexanes) afforded alcohols **23** (inseparable 1.3:1 mixture of diastereomers, 27.6 g, 81%) as a pale yellow oil.

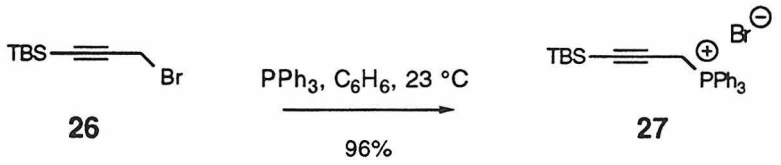
^{1}H NMR (400 MHz, C_6D_6), δ:	Major diastereomer: 4.35-3.80 (complex, 3H, OCH_2CHO), 2.22 (d, 1H, *J* = 5.48 Hz, CHOH), 1.36 (s, 3H, $C(CH_3)_2$), 1.24 (s, 3H, $C(CH_3)_2$), 0.17 (s, 9H, $Si(CH_3)_3$).
	Minor diastereomer: 4.35-3.80 (complex, 3H, OCH_2CHO), 2.09 (d, 1H, *J* = 5.84 Hz, CHOH), 1.42 (s, 3H, $C(CH_3)_2$), 1.26 (s, 3H, $C(CH_3)_2$), 0.17 (s, 9H, $Si(CH_3)_3$).
^{13}C NMR (100 MHz, C_6D_6), δ:	Major diastereomer: 110.4, 104.5, 90.40, 79.0, 66.4, 64.7, 26.9, 25.6, –0.1.
	Minor diastereomer: 110.2, 104.7, 90.3, 78.7, 65.9, 63.4, 26.6, 25.6, –0.1.
FTIR (thin film), cm^{-1}:	3439 (s, OH), 2960 (s), 2898 (s), 2174 (m, C≡C), 1374 (m), 1251 (s), 1215 (m), 1156 (m), 1068 (s), 884 (s), 761 (m).
HRMS (CI, CH_4):	Calc'd for $C_{11}H_{21}O_3Si$ $[MH]^+$: 229.1259982 Found: 229.1257000
TLC (20% EtOAc in Hexanes), R*f*:	glyceraldehyde acetonide: 0.24 (anisaldehyde) **23**: 0.59 (anisaldehyde)



3-*tert*-Butyldimethylsilylpropargyl bromide (**26**)

A solution of triphenylphosphine (56.8 g, 0.217 mol, 1.3 equiv), and imidazole (14.7 g, 0.217 mol, 1.3 equiv) in dichloromethane (350 mL) was cooled to 0 °C. Bromine (11.2 mL, 34.6 g, 0.217 mol, 1.3 equiv) was added in a dropwise manner over a period of 15 min. The resultant suspension was maintained at 0 °C for an additional 15 min, and then 3-*tert*-butyldimethylsilylpropargyl alcohol (**25**, 28.4 g, 0.167 mol, 1.0 equiv) in dichloromethane (150 mL) was added over a period of 30 min. The resultant suspension was maintained at 0 °C for an additional 15 min, and then pentane (500 mL) was added. The white suspension was filtered through a pad of Celite, and the filtrate was concentrated in vacuo. The residue was diluted with pentane (500 mL) and the filtration repeated. The filtrate was filtered through a plug of silica gel, and the silica was washed with 2:1 pentane/diethyl ether (2 400-mL portions). The combined filtrates were concentrated in vacuo to provide a pink oil. Distillation under reduced pressure provided 3-*tert*-butyldimethylsilylpropargyl bromide (**26**) (31.6 g, 81%, bp 102-103 °C/20 mm Hg) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$), δ:	3.92 (s, 2H, $BrCH_2$), 0.94 (s, 9H, $SiC(CH_3)_3(CH_3)_2$), 0.11 (s, 6H, $SiC(CH_3)_3(CH_3)_2$).
^{13}C NMR (75 MHz, $CDCl_3$), δ:	100.5, 90.8, 26.0, 16.6, 14.8, –4.9.
FTIR (thin film), cm^{-1}:	2953 (s), 2929 (s), 2857 (m), 2177 (w, C≡C), 1471 (m), 1363 (m), 1251 (m), 1204 (m), 1037 (m), 839 (s), 824 (s), 776 (s), 681 (m).
TLC (20% EtOAc in Hexanes), R*f*:	**25**: 0.30 (PMA) **26**: 0.34 (PMA)

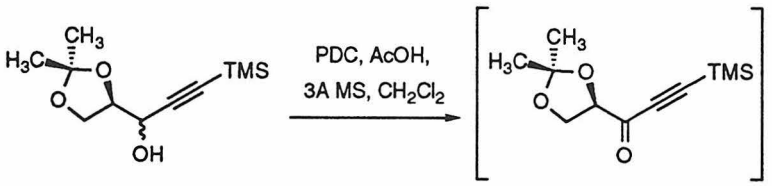


(3-*tert*-Butyldimethylsilyl)propargyltriphenylphosphonium bromide (**27**)

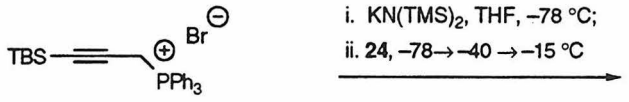
Triphenylphosphine (35.8 g, 0.137 mol, 1.3 equiv) was added in one portion to a solution of 3-*tert*-butyldimethylsilylpropargyl bromide (**26**, 24.5 g, 0.105 mol, 1.0 equiv) in benzene (180 mL). The resultant solution was stirred at 23 °C in the dark for 24 h, during which time a white precipitate formed. The precipitate was collected by filtration, washed with benzene (100 mL), and dried over phosphorous pentoxide to provide (3-*tert*-butyldimethylsilyl)propargyltriphenylphosphonium bromide (**27**) (49.8 g, 96%) as a white solid, mp 210 °C (dec).

^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.94 (m, 3H, $P(C_6\mathbf{H}_5)_3$), 7.81 (m, 12H, $P(C_6\mathbf{H}_5)_3$), 5.13 (d, 2H, J = 16.48 Hz, $PC\mathbf{H}_2$), 0.66 (s, 9H, $SiC(C\mathbf{H}_3)_3(CH_3)_2$), –0.05 (s, 6H, $SiC(CH_3)_3(C\mathbf{H}_3)_2$).

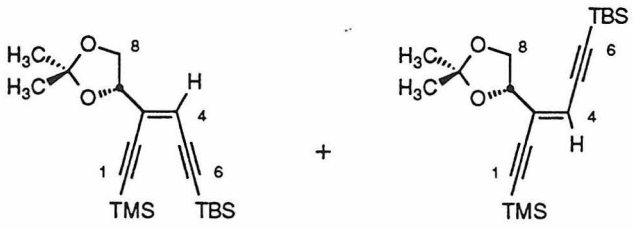
^{13}C NMR (100 MHz, DMSO-d_6), δ:	135.2 (s), 133.6 (d, *J* = 10.2 Hz), 130.0 (d, *J* = 12.2 Hz), 117.5 (d, *J* = 87.2 Hz), 95.3 (d, *J* = 13.0 Hz), 90.7 (d, *J* = 8.4 Hz), 25.4 (s), 16.4 (d, *J* = 53.3 Hz), 15.8 (s), –5.28 (s).
FTIR (thin film), cm^{-1}:	2982 (m), 2816 (m), 1439 (m), 1250 (m), 1113 (m), 919 (m).
HRMS (FAB):	Calc'd for $C_{27}H_{32}PSi$ $[M-Br]^+$: 415.2010931 Found: 415.2021000
TLC (20% EtOAc in Hexanes), R*f*:	**26**: 0.34 (PMA) **27**: 0.00 (UV, PMA)



23 **24**



27



28 (ca. 3:1)

Bis-silyl enediynes **28**

Pyridinium dichromate (43.0 g, 0.115 mol, 1.5 equiv) was added in one portion to a rapidly stirring suspension of propargylic alcohols **23** (17.46 g, 76.47 mmol, 1.0 equiv) in dichloromethane (380 mL) and crushed, activated 3A MS (52 g). Glacial acetic acid (7.4 mL, 7.8 g, 130 mmol, 1.7 equiv) was added via syringe, and the resultant brown suspension was stirred vigorously at 23 ℃ for 1.5 h. Celite (35g) was added, and the reaction mixture stirred for an additional 25 min. The reaction mixture was filtered through a plug of Celite and the filter cake washed with dichloromethane (400 mL). The filtrate

was diluted with heptane (1200 mL) and concentrated to a volume of ca. 300 mL. The concentrate was diluted with 2:1 pentane/diethyl ether (1200 mL) and filtered through a plug of anhydrous magnesium sulfate. The filtrate was washed with water (2 300-mL portions) and saturated aqueous sodium bicarbonate (2 300-mL portions). The organics were then dried over magnesium sulfate and concentrated to a volume of ca. 250 mL. Anhydrous tetrahydrofuran (400 mL) was added and the solution was again concentrated to ca. 250 mL. This procedure was repeated twice more, and the final concentrate was diluted to a volume of ca. 400 mL with anhydrous tetrahydrofuran. The crude propargylic ketone was stored at –20 °C under an argon atmosphere for later use.

A solution of potassium hexamethyldisilazide (17.7 g of 95% solid, 84.1 mmol, 1.1 equiv) in toluene (140 mL) was added over a period of 50 min to a suspension of 3-(*tert*-butyldimethylsilyl)propargyltriphenylphosphonium bromide (**27**, 43.6 g, 87.9 mmol, 1.15 equiv) in tetrahydrofuran (785 mL) at –78 °C. The resultant bright yellow suspension was held at –78 °C for an additional 15 min, and warmed to –40 °C. The suspension was kept at –40 °C for 2 h, and warmed to –15 °C. After five minutes at –15 °C, the crude propargylic ketone solution was added over a 45 min period, and the resultant orange solution was maintained at –15 °C for an additional 2 h. Excess base was quenched by addition of saturated aqueous ammonium chloride (200 mL), and the layers separated. The aqueous layer was extracted with pentane (2 250-mL portions), and the combined organics were washed with water (2 300-mL portions) and saturated aqueous sodium chloride (300 mL). The organics were dried over sodium sulfate and were concentrated. Purification of the residue by flash column chromatography (hexanes grading to 3% ethyl acetate in hexanes) afforded a ca. 3:1 mixture of enediynes **28** (22.38 g, 79%) as an orange oil.

^{1}H NMR (400 MHz, C_6D_6), δ:

Major diastereomer: 6.16 (s, 1H, C4 H), 4.34 (t, 1H, J = 6.96 Hz, C7 H), 3.90 (m, 2H, C8 CH_2), 1.39 (s, 3H, $C(CH_3)_2$), 1.29 (s, 3H, $C(CH_3)_2$), 1.11 (s, 9H, $SiC(CH_3)_3(CH_3)_2$), 0.25 (s, 9H, $Si(CH_3)_3$), 0.19 (s, 6H, $SiC(CH_3)_3(CH_3)_2$).

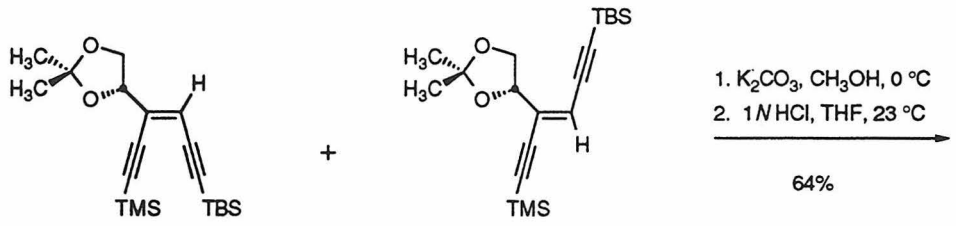
Minor diastereomer: 6.06 (s, 1H, C4 H), 5.55 (t, 1H, J = 6.60 Hz, C7 H), 4.13 (dd, 1H, J = 7.68, 6.96 Hz, C8 H), 4.02 (t, 1H, J = 7.72 Hz, C8 H), 1.62 (s, 3H, $C(CH_3)_2$), 1.44 (s, 3H, $C(CH_3)_2$), 0.98 (s, 9H, $SiC(CH_3)_3(CH_3)_2$), 0.24 (s, 9H, $Si(CH_3)_3$), 0.09 (s, 6H, $SiC(CH_3)_3(CH_3)_2$).

^{13}C NMR (100 MHz, C_6D_6), δ:

Major diastereomer: 134.9, 116.3, 116.2, 110.4, 104.0, 103.4, 101.5, 101.1, 77.6, 77.5, 68.2, 26.5, 26.3, 16.8, –0.0, –0.1.

Minor diastereomer: 130.1, 118.8, 118.7, 100.3, 105.5, 102.9, 101.7, 101.4, 75.1, 75.0, 68.4, 68.3, 26.1, –4.3, –4.4, –4.7.

FTIR (thin film), cm^{-1}:	2955 (s), 2931 (s), 2886 (m), 2858 (m), 2144 (m, C≡C), 1469 (m), 1372 (m), 1251 (s), 1154 (m), 1068 (s), 841 (s), 776 (m).
HRMS (CI, NH_3):	Calc'd for $C_{20}H_{35}O_2Si_2$ $[MH]^+$: 363.2175625 Found: 363.2177000
TLC (20% EtOAc in Hexanes), R*f*:	**27**: 0.20 (UV, anisaldehyde) **28**: *E*: 0.40 (UV, anisaldehyde) *Z*: 0.48 (UV, anisaldehyde)



28 (ca. 3:1)

29 (64%)

<u>*Z* and *E* Enediyne diols **29**</u>

Potassium carbonate (8.30 g, 59.8 mmol, 1.0 equiv) was added to a solution of bis silyl enediynes **28** (22.3 g, 59.8 mmol, 1.0 equiv) in methanol (300 mL) at 0 °C. The resultant yellow suspension was stirred vigorously at 0 °C for 45 min, and partitioned between pentane (500 mL) and water (200 mL). The layers were separated, and the aqueous layer was further extracted with pentane (3 200-mL portions). The combined organics were dried over sodium sulfate, and were concentrated. The residue was taken up in tetrahydrofuran (1500 mL) and 1N aqueous HCl (1200 mL) was added. Tetrahydrofuran (ca. 500 mL) was added until the mixture was homogeneous, and the solution was then stirred at 23 °C for 18 h. The reaction mixture was concentrated in vacuo

to remove most of the tetrahydrofuran, and the concentrate was extracted with ethyl acetate (3 300-mL portions). The combined organics were washed with saturated aqueous sodium bicarbonate (200 mL) and saturated aqueous sodium chloride (200 mL). The organics were dried over sodium sulfate and were concentrated. The residue was purified by careful flash column chromatography (25% ethyl acetate in hexanes grading to ethyl acetate) to afford a mixture of olefin isomers (5.78 g, 36%) as a yellow oil along with pure *E* isomer **29** (9.51 g, 64%) as an off-white solid, mp 54 °C.

For the *Z* isomer of 29:

^{1}H NMR (400 MHz, C_6D_6), δ:	5.93 (s, 1H, C4 H), 4.95 (br s, 1H, C7 H), 3.64 (m, 2H, C8 CH_2), 2.72 (s, 1H, C1 H), 2.04 (br s, 1H, OH), 1.52 (br s, 1H, OH), 1.00 (s, 9H, $OSiC(CH_3)_3(CH_3)_2$), 0.12 (s, 6H, $OSiC(CH_3)_3(CH_3)_2$).
^{13}C NMR (100 MHz, C_6D_6), δ:	136.5, 118.1, 106.0, 101.1, 85.6, 81.4, 72.0, 65.3, 26.3, 16.8, –4.6, –4.6.
$[\alpha]_D^{20}$:	+8.64° (*c* 0.88, C_6H_6)
FTIR (thin film), cm^{-1}:	3389 (s, OH), 3295 (s, C≡C-H), 2952 (s), 2930 (s), 2857 (s), 2123 (m, C≡C), 2092 (m, C≡C), 1467 (m), 1251 (s), 1676 (s), 892 (m), 825 (s), 777 (s), 685 (s).

TLC (30% EtOAc in Hexanes), R*f*: S. M.(after K_2CO_3): 0.62 (UV, anisaldehyde)

29: 0.14 (UV, anisaldehyde)

For the *E* isomer of 29:

^{1}H NMR (400 MHz, C_6D_6), δ: 6.17 (m, 1H, C4 H), 3.91 (m, 1H, C7 H), 3.53 (ddd, 1H, *J* = 10.96, 7.32, 3.64 Hz, C8 H), 3.31 (ddd, 1H, *J* = 11.72, 6.60, 5.12 Hz, C8 H), 2.98 (s, 1H, C1 H), 1.15 (dd, 1H, *J* = 7.72, 4.76 Hz, OH), 0.52 (br s, 1H, OH), 1.10 (s, 9H, $SiC(CH_3)_3(CH_3)_2$), 0.22 (s, 6H, $SiC(CH_3)_3(CH_3)_2$).

^{13}C NMR (100 MHz, C_6D_6), δ: 134.9, 117.8, 103.4, 101.4, 87.2, 80.4, 74.4, 65.5, 26.4, 16.8, –4.4, –4.5.

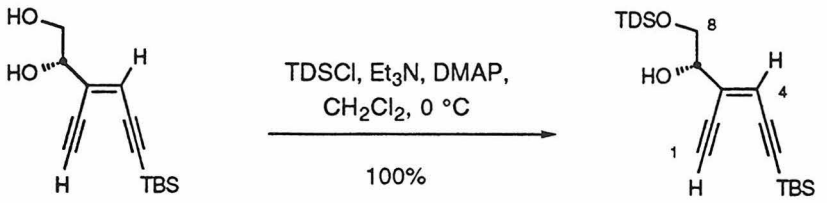
$[\alpha]_D^{20}$: +3.10° (*c* 0.71, C_6H_6)

FTIR ($CHCl_3$), cm^{-1}: 3599 (m, OH), 3401 (m, OH), 3301 (m, C≡C-H), 2954 (s), 2885 (m), 2857 (m), 2133 (m, C≡C), 1468 (m), 1252 (s), 1080 (s), 1039 (s), 839 (vs), 826 (vs), 650 (m).

HRMS (CI, NH_3): Calc'd for $C_{14}H_{23}O_2Si$ $[MH]^+$: 251.1467336

Found: 251.1466000

TLC (30% EtOAc in Hexanes), R*f*:	S. M.(after K_2CO_3): 0.62 (UV, anisaldehyde)
	29: 0.10 (UV, anisaldehyde)

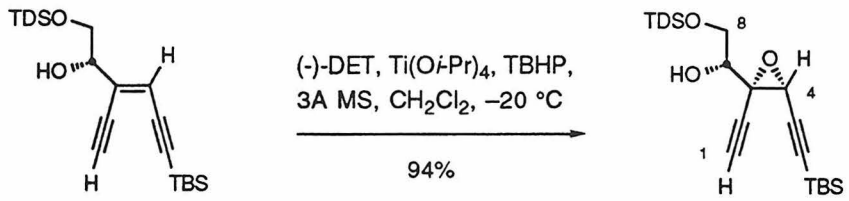


29 **30**

TDS ether **30**

tert-Butyldiphenylsilyl chloride (28.5 mL, 30.2 g, 0.122 mol, 2.4 equiv) was added via syringe to a solution of diol **29** (12.7 g, 50.8 mmol, 1.0 equiv), triethylamine (53.0 mL, 38.6 g, 0.381 mol, 7.5 equiv), and 4-dimethylaminopyridine (6.21 g, 50.8 mmol, 1.0 equiv) in dichloromethane (510 mL) at 0 °C. The resultant pale yellow solution was maintained at 0 °C for 1 h and excess silyl chloride was quenched by the addition of methanol (100 mL). The reaction mixture was poured into water (500 mL) and the layers were separated. The aqueous layer was further extracted with dichloromethane (200 mL) and the combined organics were dried over sodium sulfate and concentrated. Purification of the residue by flash column chromatography (25% ethyl acetate in hexanes) provided the TDS ether **30** (24.8 g, 100%) as a pale yellow oil.

^{1}H NMR (400 MHz, C_6D_6), δ:	7.73 (m, 4H, $OSiC(CH_3)_3(C_6\mathbf{H}_5)_2$), 7.25 (m, 6H, $OSiC(CH_3)_3(C_6\mathbf{H}_5)_2$), 6.33 (s, 1H, C4 H), 4.18 (m, 1H, C7 H), 3.88 (dd, 1H, *J* = 10.24, 4.04 Hz, C8 H), 3.72 (dd, 1H, *J* = 6.20, 4.04 Hz, C8 H), 2.90 (s, 1H, C1 H), 2.30 (d, 1H, *J* = 5.12 Hz, O**H**), 1.13 (s, 9H, $OSiC(C\mathbf{H}_3)_3(C_6H_5)_2$), 1.10 (s, 9H, $OSiC(C\mathbf{H}_3)_3(CH_3)_2$), 0.21 (s, 6H, $OSiC(CH_3)_3(C\mathbf{H}_3)_2$).
^{13}C NMR (100 MHz, C_6D_6), δ:	136.0, 135.9, 135.9, 135.2, 135.1, 133.9, 133.4, 130.1, 129.9, 128.1, 128.0, 117.3, 103.5, 101.1, 86.7, 80.4, 74.2, 66.9, 52.0, 27.0, 26.4, 19.4, 16.8, –4.4.
$[\alpha]_D^{20}$:	–4.70° (*c* 1.66, C_6H_6)
FTIR (thin film), cm^{-1}:	3552 (w, OH), 3447 (w, OH), 3296 (m, C≡C-H), 2951 (s), 2851 (s), 2135 (w, C≡C), 1470 (m), 1250 (m), 1111 (s), 824 (s), 702 (s).
HRMS (FAB):	Calc'd for $C_{30}H_{41}O_2Si_2$ $[MH]^+$: 489.2645127 Found: 489.2653000
TLC (30% EtOAc in Hexanes), R*f*:	**29**: 0.18 (UV, anisaldehyde) **30**: 0.78 (UV, anisaldehyde)

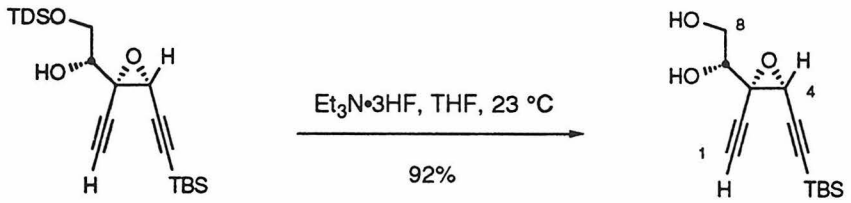


30 **31**

Epoxide **31**

Titanium(IV) isopropoxide (21.0 mL, 20.0 g, 70.5 mmol, 1.40 equiv) was added dropwise to a solution of D-(-)-diethyl tartrate (12.6 mL, 15.2 g, 73.5 mmol, 1.46 equiv) and powdered, activated 4A molecular sieves (6g) in dichloromethane (150 mL) at –20 °C. The resultant mixture was allowed to age at –20 °C for 50 min, and TDS ether **30** (24.6 g, 50.3 mmol, 1.0 equiv) in dichloromethane (60 mL) was added over a period of 15 min. The reaction mixture was allowed to stir at –20 °C for another 30 min, and *tert*-butyl hydroperoxide (31 mL of a 4.7 M solution in dichloromethane, 0.146 mol, 2.9 equiv) was added via gastight syringe/Teflon needle. The reaction mixture was held at –20 °C for an additional 20 h, and 10% aqueous D-tartaric acid (100 mL) was added. The resultant mixture was stirred vigorously at 23 °C for 30 min and filtered through a plug of celite. The filtrate layers were separated and the aqueous layer was further extracted with dichloromethane (3 50-mL portions). The combined organics were dried over sodium sulfate and concentrated. Purification of the residue by flash column chromatography (8% ethyl acetate in hexanes) afforded the epoxide **31** (24.0 g, 94%) as a pale yellow oil.

^{1}H NMR (400 MHz, C_6D_6), δ:	7.85 (m, 4H, $OSiC(CH_3)_3(C_6H_5)_2$), 7.28 (m, 6H, $OSiC(CH_3)_3(C_6H_5)_2$), 3.94 (dd, 1H, *J* = 11.00, 2.92 Hz, C8 H), 3.90 (s, 1H, C4 H), 3.84 (dd, 1H, *J* = 10.96, 2.56 Hz, C8 H), 3.60 (m, 1H, C7 H), 2.00 (s, 1H, C1 H), 1.79 (m, 1H, OH), 1.21 (s, 9H, $OSiC(CH_3)_3(C_6H_5)_2$), 1.05 (s, 9H, $OSiC(CH_3)_3(CH_3)_2$), 0.17 (s, 6H, $OSiC(CH_3)_3(CH_3)_2$).
^{13}C NMR (100 MHz, C_6D_6), δ:	136.1, 135.8, 135.2, 133.4, 133.3, 130.0, 129.8, 128.5, 128.1, 101.0, 90.5, 78.9, 75.7, 71.3, 64.3, 58.2, 48.7, 27.1, 26.3, 19.4, 16.6, –4.6.
$[\alpha]_D^{20}$:	+32.65° (*c* 5.28, C_6H_6)
FTIR (thin film), cm^{-1}:	3480 (m, OH), 3306 (m, C≡C-H), 2954 (s), 2930 (s), 2886 (m), 2857 (s), 2185 (w, C≡C), 2125 (w, C≡C), 1470 (m), 1427 (m), 1251 (m), 1113 (s), 12079 (s), 985 (m).
HRMS (FAB):	Calc'd for $C_{30}H_{41}O_3Si_2$ $[MH]^+$: 505.2594274 Found: 505.2581000
TLC (20% EtOAc in Hexanes), R*f*:	**30**: 0.49 (UV, anisaldehyde) **31**: 0.40 (anisaldehyde)



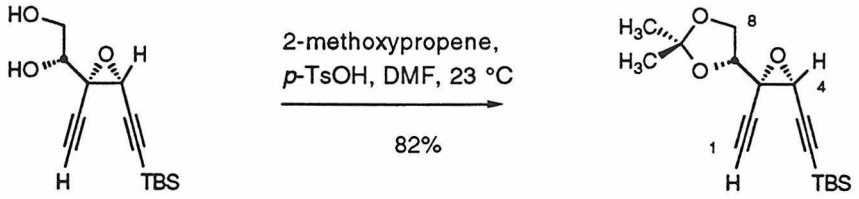
31 **32**

Diol epoxide **32**

Triethylamine trihydrofluoride (14.5 mL, 14.4 g, 89.0 mmol, 3 equiv) was added via syringe to a solution of epoxide **31** (15.0 g, 29.7 mmol, 1.0 equiv) in tetrahydrofuran (370 mL) at 23 °C. The solution was maintained at 23 °C for 20 h, and saturated aqueous sodium bicarbonate (300 mL) was added to quench excess acid. The layers were separated and the aqueous layer was further extracted with ethyl acetate (2 100-mL portions). The combined organics were washed with saturated aqueous sodium chloride (100 mL), dried over sodium sulfate and concentrated. Purification of the residue by flash column chromatography (10% ethyl acetate in hexanes grading to ethyl acetate) provided diol epoxide **32** (7.27 g, 92%) as a pale yellow solid, mp 78 °C.

^{1}H NMR (400 MHz, C_6D_6), δ: 3.66 (m, 1H, C8 H), 3.58 (s, 1H, C4 H), 3.51 (m, 2H, C7, C8 H), 1.97 (s, 1H, C1 H), 1.78 (br s, 1H, OH), 1.44 (br s, 1H, OH), 1.03 (s, 9H, $SiC(CH_3)_3(CH_3)_2$), 0.15 (s, 6H, $SiC(CH_3)_3(CH_3)_2$).

^{13}C NMR (100 MHz, C_6D_6), δ:	100.8, 90.7, 78.4, 76.2, 72.0, 63.4, 58.0, 48.8, 26.2, 16.6, –4.4.
$[\alpha]_D^{20}$:	+47.65° (*c* 1.62, C_6H_6)
FTIR (thin film), cm^{-1}:	3591 (m, OH), 3304 (s, C≡C-H), 3018 (m), 2931 (s), 2858 (m), 2190 (w, C≡C), 2131 (w, C≡C), 1468 (m), 1363 (m), 1252 (s), 1103 (s), 1079 (s), 1055 (s), 1038 (s), 828 (vs), 654 (m).
HRMS (CI, NH_3):	Calc'd for $C_{14}H_{23}O_3Si$ $[MH]^+$: 267.1416482 Found: 267.1427000
TLC (50% EtOAc in Hexanes), R*f*:	**31**: 0.56 (anisaldehyde) **32**: 0.19 (anisaldehyde)

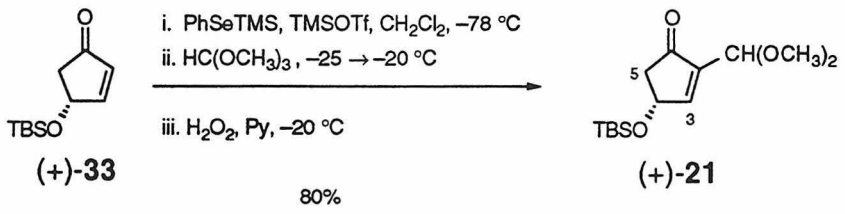


32 **20**

Acetonide **20**

2-Methoxypropene (2.15 mL, 1.62 g, 22.5 mmol, 1.2 equiv) and *p*-toluenesulfonic acid (500 mg) were added sequentially to a solution of diol epoxide **32** (5.00 g, 18.8 mmol, 1 equiv) in DMF (38 mL). The resultant pale yellow solution was maintained at 23 °C for 6 h and partitioned between hexanes (200 mL) and water (100 mL). The aqueous layer was extracted with hexanes (100 mL) and the combined organics were washed with water (3 100-mL portions) and saturated aqueous sodium chloride (100 mL). The organics were dried over sodium sulfate and concentrated. Purification of the residue by flash column chromatography (10% ethyl acetate in hexanes) provided the acetonide **20** (4.69 g, 82%) as a white solid, mp 43-44 °C.

^{1}H NMR (400 MHz, C_6D_6), δ:	3.99 (dd, 1H, *J* = 8.80, 6.24 Hz, C7 H), 3.79 (dd, 1H, *J* = 8.76, 6.60 Hz, C8 H), 3.64 (t, 1H, *J* = 6.60 Hz, C8 H), 3.47 (s, 1H, C4 H), 1.98 (s, 1H, C1 H), 1.37 (s, 3H, $C(CH_3)_2$), 1.19 (s, 3H, $C(CH_3)_2$), 1.03 (s, 9H, $SiC(CH_3)_3(CH_3)_2$), 0.15 (s, 3H, $SiC(CH_3)_3(CH_3)_2$), 0.14 (s, 3H, $SiC(CH_3)_3(CH_3)_2$).
^{13}C NMR (100 MHz, C_6D_6), δ:	110.7, 100.5, 90.6, 78.1, 76.7, 75.4, 66.8, 58.1, 50.1, 50.0, 26.2, 25.4, 16.7, –4.8.
$[\alpha]_D^{20}$:	+78.00° (*c* 1.00, C_6H_6)
FTIR (thin film), cm^{-1}:	3281 (m, C≡C-H), 2953 (s), 2931 (s), 2184 (w, C≡C), 2125 (w, C≡C), 1464 (m), 1374 (m), 1254 (s), 1215 (m), 1154 (m), 1076 (s), 828 (s).
HRMS (CI, NH_3):	Calc'd for $C_{17}H_{27}O_3Si$ $[MH]^+$: 307.1729484 Found: 307.1722000
TLC (20% EtOAc in Hexanes), R*f*:	**32**: 0.025 (anisaldehyde) **20**: 0.44 (anisaldehyde)



Enone (+)-**21**

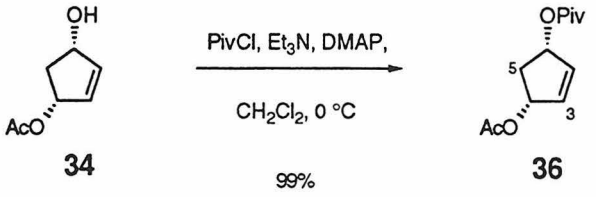
Trimethylsilyl phenylselenide (0.794 mL, 1.08 g, 4.71 mmol, 2 equiv) and trimethylsilyl trifluoromethanesulfonate (0.0910 mL, 0.105 g, 0.471 mmol, 0.2 equiv) were added sequentially to a solution of enone (+)-**33** (0.500 g, 2.35 mmol, 1 equiv) in dichloromethane (4.7 mL) at –78 °C. The colorless solution was maintained at –78 °C for an additional 20 min, and then *freshly distilled* trimethyl orthoformate (1.03 mL, 1.00 g, 9.42 mmol, 4 equiv) was added via syringe. After five min at –78 °C, the cloudy reaction mixture was warmed to –25 °C and allowed to warm to –20 °C over 45 min. During this time, examination of the reaction by thin-layer chromatography (20% ethyl acetate in hexanes) revealed the gradual disappearance of a spot at higher R*f* than (+)-**33** which was visible by *both* UV irradiation and anisaldehyde staining (a non-staining higher R*f* UV-active spot is unaffected). The complete disappearance of the spot and the return to clarity of the reaction mixture coincided (at approximately the 45 min mark), and at this juncture pyridine (0.050 mL) and 30% aqueous hydrogen peroxide (3 mL) were added to the reaction mixture at –20 °C. The reaction mixture darkened slightly over the next 3-5 min, at which time a rapid reaction occurred in which a precipitate formed and the reaction decolorized. The reaction mixture was warmed to 23 °C and diluted with 1:1 ethyl acetate/hexanes (10 mL). The mixture was washed with water (10 mL) and saturated

aqueous sodium chloride (10 mL). The organics were dried over sodium sulfate and concentrated. Purification of the residue by flash column chromatography (10% ethyl acetate in hexanes grading to 13% ethyl acetate in hexanes) afforded (+)-**21** (0.536 g, 80%) as pale yellow needles, mp 29.5-30.5 °C.

^{1}H NMR (400 MHz, C_6D_6), δ:	7.41 (d, 1H, J = 1.44 Hz, C3 H), 5.24 (s, 1H, C**H**$(OCH_3)_2$), 4.38 (m, 1H, C4 H), 3.21 (s, 3H, CH$(OCH_3)_2$), 3.14 (s, 3H, CH$(OCH_3)_2$), 2.42 (dd, 1H, J = 18.28, 6.20 Hz, C5 βH), 2.22 (dd, 1H, J = 17.92, 2.20 Hz, C12 αH), 0.89 (s, 9H, OSiC$(CH_3)_3(CH_3)_2$), –0.04 (s, 3H, OSiC$(CH_3)_3(CH_3)_2$), –0.06 (s, 3H, OSiC$(CH_3)_3(CH_3)_2$).
^{13}C NMR (100 MHz, $CDCl_3$), δ:	201.9, 159.2, 143.6, 97.6, 69.1, 53.6, 53.0, 46.0, 25.9, 18.1, –4.7.
$[\alpha]_D^{20}$:	+58.11° (*c* 2.64, C_6H_6)
FTIR (thin film), cm^{-1}:	2953 (m), 2930 (m), 2856 (m), 1718 (s, C=O), 1472 (w), 1388 (w), 1215 (m), 1059 (m), 835 (m).
HRMS (CI, NH_3):	Calc'd for $C_{14}H_{27}O_4Si$ $[MH]^+$: 287.1664000 Found: 287.1678630

TLC (20% EtOAc in Hexanes), R*f*: (+)-**33**: 0.31 (anisaldehyde)

(+)-**21**: 0.42 (anisaldehyde)

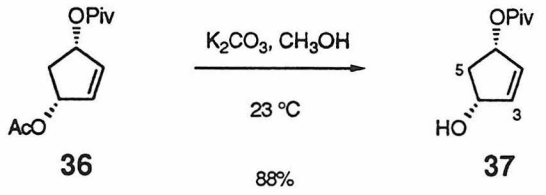


Pivaloate ester **36**

Pivaloyl chloride (8.45 mL, 8.27 g, 68.6 mmol, 1.5 equiv) was added dropwise via syringe to a solution of monoacetate **34** (6.50 g, 45.7 mmol, 1 equiv), triethylamine (32.0 mL, 23.0 g, 228 mmol, 5 equiv) and 4-dimethylaminopyridine (2.79 g, 22.8 mmol, 0.5 equiv) in dichloromethane (300 mL) at 0 °C. The resultant solution was stirred at 0 °C for an additional 2 h, and then poured into 1:1 ethyl acetate/hexanes (300 mL). The mixture was washed with water (300 mL) and saturated aqueous sodium chloride (300 mL), dried over sodium sulfate and concentrated. Purification of the residue by flash column chromatography (10% ethyl acetate in hexanes) provided pivaloate ester **36** (10.5 g, quantitative) as a colorless oil.

^{1}H NMR (400 MHz, C_6D_6), δ: 6.07 (s, 2H, C2, C3 H), 5.53 (m, 2H, C1, C4 H), 2.88 (dt, 1H, J = 15.04, 7.72 Hz, C5 H), 2.06 (s, 3H, O_2CCH_3), 1.67 (dt, 1H, J = 14.68, 4.04 Hz, C5 H), 1.19 (s, 9H, $O_2CC(CH_3)_3$).

^{13}C NMR (100 MHz, $CDCl_3$), δ:	177.6, 170.1, 134.4, 134.1, 76.3, 76.0, 38.2, 37.0, 26.8, 20.7.
FTIR (thin film), cm^{-1}:	2973 (m), 1728 (s, C=O), 1480 (w), 1367 (m), 1281 (m), 1238 (s), 1154 (s), 1026 (m).
$[\alpha]_D^{20}$:	–17.21° (*c* 1.36, CH_2Cl_2)
HRMS (FAB):	Calc'd for $C_{12}H_{19}O_4$ $[MH]^+$: 227.128334 Found: 227.127121
TLC (50% EtOAc in Hexanes), R*f*:	**34**: 0.20 (anisaldehyde) **36**: 0.60 (anisaldehyde)

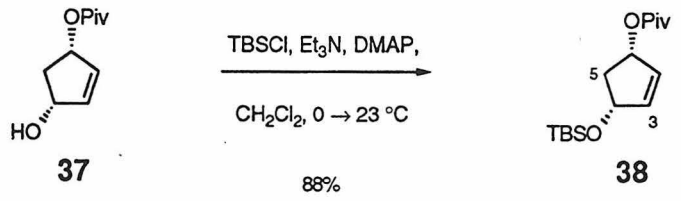


Allylic alcohol **37**

Potassium carbonate (1.94 g, 14.1 mmol, 1 equiv) was added in one portion to a solution of pivaloate ester **36** (3.18 g, 14.1 mmol, 1 equiv) in methanol (28 mL) at 23 °C. The resultant suspension was stirred vigorously for 15 min, and poured into water (50 mL). The mixture was extracted with ethyl acetate (3 50-mL portions). The combined extracts were washed with saturated aqueous sodium chloride (50 mL), dried over sodium sulfate and concentrated. Purification of the residue by flash column chromatography (30% ethyl acetate in hexanes) afforded allylic alcohol **37** (2.19 g, 85%) as a colorless oil.

^{1}H NMR (400 MHz, C_6D_6), δ: 5.79 (app. d, 1H, J = 5.48 Hz, C2 H), 5.75 (app. d, 1H, J = 5.84 Hz, C3 H), 5.47 (m, 1H, C1 H), 4.25 (br d, J = 5.12 Hz, C4 H), 2.53 (dt, 1H, J = 14.64, 7.32 Hz, C5 H), 1.57 (dt, 1H, J = 14.28, 4.76 Hz, C5 H), 1.24 (td, 1H, J = 6.92, 4.76 Hz, OH), 1.17 (s, 9H, $O_2CC(CH_3)_3$).

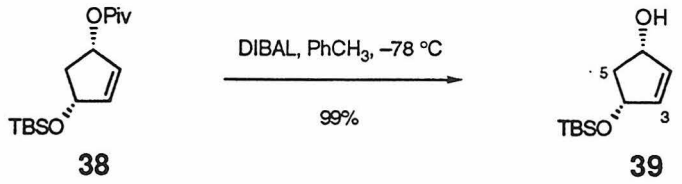
^{13}C NMR (100 MHz, $CDCl_3$), δ:	178.3, 138.2, 132.2, 76.8, 74.4, 40.4, 38.4, 26.9.
FTIR (thin film), cm^{-1}:	3408 (m, OH), 2975 (m), 1725 (s, C=O), 1480 (m), 1282 (s), 1157 (s), 1058 (m), 1031 (m).
$[\alpha]_D^{20}$:	–56.45° (*c* 2.31, CH_2Cl_2)
HRMS (EI):	Calc'd for $C_{10}H_{16}O_3$ $[M]^+$: 184.109945 Found: 184.109889
TLC (50% EtOAc in Hexanes), R*f*:	**36**: 0.58 (anisaldehyde) **37**: 0.35 (anisaldehyde)



TBS Ether **38**

tert-Butyldimethylsilyl chloride (4.20 g, 27.8 mmol, 2.5 equiv) was added in one portion to a solution of allylic alcohol **37** (2.05 g, 11.1 mmol, 1 equiv), triethylamine (7.75 mL, 5.63 g, 55.6 mmol, 5 equiv), and 4-dimethylaminopyridine (0.68 g, 5.56 mmol, 0.5 equiv) in dichloromethane (110 mL) at 0 °C. The resultant solution was allowed to gradually warm to 23 °C over 2 h and was stirred at 23 °C for an additional 12 h. The reaction mixture was diluted with 1:1 ethyl acetate/hexanes (100 mL), and washed with water (100 mL), aqueous 1N HCl (2 100-mL portions), saturated aqueous sodium bicarbonate (100 mL), and saturated aqueous sodium chloride (100 mL). The organics were dried over sodium sulfate and concentrated. Purification of the residue by flash column chromatography (10% ethyl acetate in hexanes) afforded TBS ether **38** (3.07 g, 92%) as a white solid, mp 64-66 °C.

^{1}H NMR (400 MHz, C_6D_6), δ:	5.84 (apparent qt, 2H, *J* = 8.44, 1.48 Hz, C2, C3 H), 5.57 (apparent t, 1H, *J* = 5.84 Hz, C1 H), 4.44 (apparent t, 1H, *J* = 5.48 Hz, C4 H), 2.66 (dt, 1H, *J* = 13.52, 7.32 Hz, C5 H), 1.77 (dt, 1H, *J* = 13.56, 5.48 Hz, C5 H), 1.19 (s, 9H, $O_2CC(CH_3)_3$), 0.97 (s, 9H, $OSiC(CH_3)_3(CH_3)_2$), 0.05 (s, 3H, $OSiC(CH_3)_3(CH_3)_2$), 0.04 (s, 3H, $OSiC(CH_3)_3(CH_3)_2$).
^{13}C NMR (100 MHz, $CDCl_3$), δ:	178.2, 138.5, 131.4, 76.6, 74.8, 41.2, 38.5, 27.0, 25.8, 18.1, –4.7.
FTIR (thin film), cm^{-1}:	2957 (m), 1728 (s, C=O), 1477 (w), 1371 (m), 1282 (m), 1254 (m), 1157 (s), 1050 (m), 837 (m).
$[\alpha]_D^{20}$:	–9.29° (*c* 1.27, CH_2Cl_2)
HRMS (EI):	Calc'd for $C_{16}H_{31}O_3Si$ $[MH]^+$: 299.204249 Found: 299.203845
TLC (50% EtOAc in Hexanes), R*f*:	**37**: 0.40 (anisaldehyde) **38**: 0.77 (anisaldehyde)

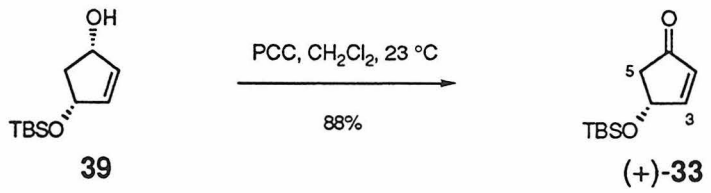


38 **39**

Allylic alcohol **39**

Diisobutylaluminum hydride (13.09 mL of a 1.5 M solution in toluene, 19.63 mmol, 2.0 equiv) was added via syringe to a solution of TBS ether **38** (2.93 g, 9.81 mmol, 1 equiv) in toluene (98 mL) at –78 °C. The resultant solution was maintained at –78 °C for an additional 10 min, and methanol (10 mL) was added and the solution warmed to 0 °C. After stirring at 0 °C for 20 min, 10% aqueous potassium sodium tartrate (20 mL) was added, and the reaction mixture was warmed to 23 °C and stirred vigorously for 25 min. The reaction mixture was diluted with water (30 mL) and extracted with ethyl acetate (3 30-mL portions). The combined extracts were washed with water (50 mL) and saturated aqueous sodium chloride (50 mL), dried over sodium sulfate, and concentrated. Purification of the residue by flash column chromatography (10% ethyl acetate in hexanes grading to 20% ethyl acetate in hexanes) provided allylic alcohol **39** (2.10 g, 100%) as a colorless oil.

^{1}H NMR (300 MHz, C_6D_6), δ:	5.76 (m, 2H, C2, C3 H), 4.43 (m, 2H, C1, C4 H), 2.46 (dt, 1H, *J* = 13.41, 7.12 Hz, C5 H), 1.56 (dt, 1H, *J* = 13.41, 5.01 Hz, C5 H), 1.41 (br s, 1H, OH), 0.99 (s, 9H, $OSiC(CH_3)_3(CH_3)_2$), 0.08 (s, 3H, $OSiC(CH_3)_3(CH_3)_2$), 0.07 (s, 3H, $OSiC(CH_3)_3(CH_3)_2$).
^{13}C NMR (100 MHz, $CDCl_3$), δ:	136.7, 135.7, 75.1, 74.9, 44.5, 25.8, 18.1, –4.7.
FTIR (thin film), cm^{-1}:	3353 (m, OH), 2955 (s), 2931 (s), 2857 (s), 1470 (m), 1365 (m), 1253 (m), 1071 (s), 1021 (m), 904 (m), 836 (m), 777 (s).
$[\alpha]_D^{20}$:	+23.39° (*c* 1.83, CH_2Cl_2)
HRMS (EI):	Calc'd for $C_{11}H_{23}O_2Si$ $[MH]^+$: 215.146734 Found: 215.146993
TLC (30% EtOAc in Hexanes), R*f*:	**38**: 0.67 (anisaldehyde) **39**: 0.33 (anisaldehyde)

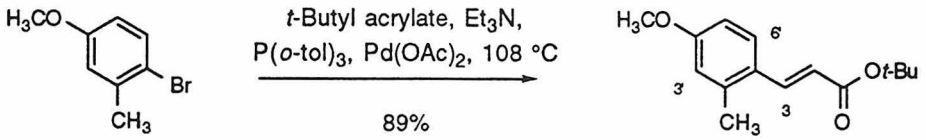


39 (+)-**33**

Enone (+)-**33**

A 250 mL round bottom flask was charged with allylic alcohol **36** (2.00 g, 9.33 mmol, 1.0 equiv) and dichloromethane (62 mL). Pyridinium chlorochromate (3.42 g, 15.9 mmol, 1.7 equiv) was added portionwise over a period of ca. 5 min. The resultant brown suspension was stirred at 23 °C for 1.5 h, and the reaction mixture was filtered through a plug of celite. The filtrate was concentrated, and the residue was purified by flash column chromatography (15% ethyl acetate in hexanes) to afford enone (+)-**33** (1.74 g, 88%) as a colorless solid, mp 30-31 °C. All analytical data were in accord with that previously reported, except the optical rotation.

$[\alpha]_D^{20}$: +68.00° (*c* 1.00, CH_3OH)

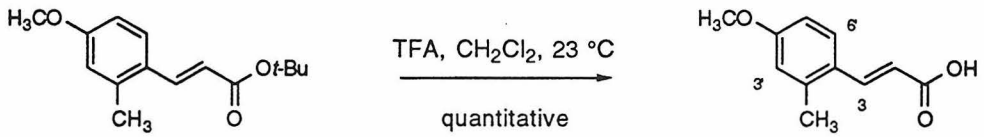


40 **41**

<u>*tert*-Butyl ester **41**</u>

tert-Butyl acrylate (37.0 mL, 32.0 g, 0.252 mol, 1.75 equiv), 4-bromo-3-methylanisole (**40**, 29 g, 0.144 mol, 1 equiv), triethylamine (35.0 mL, 25.5 g, 0.252 mol, 1.75 equiv), tri-*o*-tolylphosphine (10.5 g, 0.0340 mol, 0.24 equiv), and palladium diacetate (1.29 g, 5.76 mmol, 0.04 equiv) were combined in a 250 mL thick-walled flask. A stream of argon gas was bubbled through the solution for a period of 20 min, and the flask was sealed, covered with aluminum foil, and heated to 108 °C for 12 h. The reaction was cooled to 23 °C and dissolved in 10% aqueous sodium hydroxide (300 mL). The mixture was extracted with diethyl ether (2 450-mL portions) and the combined extracts were washed with saturated aqueous sodium chloride (300 mL). The organic layer was dried over sodium sulfate and was concentrated. Purification of the residue by flash column chromatography (2% ethyl acetate in hexanes grading to 20% ethyl acetate in hexanes) afforded ester **41** (32.0 g, 89%) as a pale yellow solid, mp 39 °C.

^{1}H NMR (400 MHz, C_6D_6), δ:	7.83 (d, 1H, J = 15.72 Hz, C3 H), 7.51 (d, 1H, J = 8.40 Hz, C6' H), 6.72 (m, 2H, C5', C3' H), 6.20 (d, 1H, J = 16.12 Hz, C2 H), 3.80 (s, 3H, C4' OCH_3), 2.42 (s, 3H, C2' CH_3), 1.53 (s, 9H, $OC(CH_3)_3$).
^{13}C NMR (100 MHz, $CDCl_3$), δ:	166.8, 160.8, 140.7. 139.5, 127.8, 126.2, 118.5, 115.8, 112.0, 80.1, 55.2, 28.2, 20.0.
FTIR (thin film), cm^{-1}:	2975 (m), 1704 (s, C=O), 1627 (m), 1603 (s), 1499 (m), 1366 (m), 1297 (m), 1256 (s), 1147 (s), 1046 (m), 980 (m), 863 (m).
HRMS (FAB):	Calc'd for $C_{15}H_{20}O_3$ $[M]^+$: 248.141245 Found: 248.140587
TLC (20% EtOAc in Hexanes), R*f*:	**41**: 0.27 (UV, anisaldehyde)



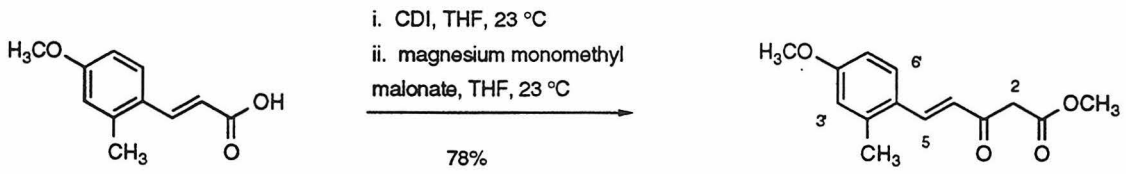
41 **42**

Acid **42**

Trifluoroacetic acid (35 mL) was added in one portion to a solution of ester **41** (16.9 g, 68.0 mmol, 1 equiv) in dichloromethane (145 mL). The resultant pale yellow solution was maintained at 23 °C for 5 h, during which time the solution darkened to red/brown. The solution was concentrated and the residual trifluoroacetic acid was removed by dissolution in toluene (100 mL) and concentration in vacuo. This procedure was repeated twice. The pale yellow solid remaining was examined by ^{1}H NMR and found to be ≥95% pure acid **42** (13.47 g, quantitative, mp 180 °C), and was used directly without further purification.

^{1}H NMR (400 MHz, C_6D_6), δ: 12.24 (s, 1H, OH), 7.73 (d, 1H, J = 16.08 Hz, C3 H), 7.66 (d, 1H, J = 8.44 Hz, C6' H), 6.82 (s, 1H, C3' H), 6.79 (d, 1H, J = 8.76 Hz, C5' H), 6.29 (d, 1H, J = 15.76 Hz, C2 H), 3.76 (s, 3H, C4' OCH_3), 2.36 (s, 3H, C2' CH_3).

^{13}C NMR (100 MHz, $CDCl_3$), δ:	167.7, 160.5, 140.7, 139.2, 128.1, 125.4, 117.4, 115.7, 112.3, 55.1, 19.4.
FTIR (thin film), cm^{-1}:	2931 (w), 2825 (s), 1686 (m, C=O), 1601 (s), 1334 (m), 1259 (s), 1102 (m), 937 (m), 807 (m).
HRMS (FAB):	Calc'd for $C_{11}H_{12}O_3$ $[M]^+$: 192.078644 Found: 192.078045
TLC (20% EtOAc in Hexanes), R*f*:	**41**: 0.27 (UV, anisaldehyde) **42**: 0.00 (UV, anisaldehyde)



42 **43**

β-Keto ester **43**

Carbonyldiimidazole (10.1 g, 62.4 mmol, 1.2 equiv) was added in one portion to a solution of acid **42** (10.0 g, 52.0 mmol, 1 equiv) in tetrahydrofuran (300 mL) at 23 °C. The solution was maintained at 23 °C for 8 h. At the same time, a separate flask was charged with monomethyl malonate (13.5 g, 0.114 mol, 2.2 equiv) and tetrahydrofuran and cooled to 0 °C. Magnesium ethoxide (13.1 g, 0.114 mmol, 2.2 equiv) was added portionwise over a 5 min period. After completion of the addition, the reaction mixture was warmed to 23 °C and stirred vigorously for 3 h. The reaction mixture was concentrated in vacuo to afford a gray solid, which was powdered in the same flask using a stainless steel spatula. At the appropriate time (after the acylimidazole solution had been allowed to react for 8 h), the magnesium monomethyl malonate was cooled to 0 °C, and the acylimidazole solution was added via cannula over a ten-minute period. Upon completion of the addition, the reaction mixture was warmed to 23 °C and stirred for an additional 15 h. The reaction mixture was partitioned between 1N hydrochloric acid (300 mL) and diethyl ether (300 mL). The aqueous layer was acidified to pH 1 with concentrated hydrochloric acid and the layers were separated. The aqueous layer was extracted with diethyl ether (2 100-mL portions), and the combined organics were washed with saturated aqueous sodium bicarbonate (250 mL), dried over sodium sulfate, and concentrated.

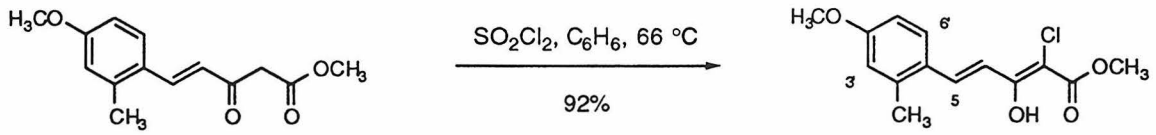
Purification of the residue by flash column chromatography (7% ethyl acetate in hexanes) afforded β-keto ester **43** (10.10 g, 78%) as a colorless oil.

^{1}H NMR (400 MHz, C_6D_6), δ: 11.96 (s, 1H, enol OH), 7.88 (d, 0.25 H, *J* = 16.12 Hz, C5 keto), 7.65 (d, 1H, *J* = 15.72 Hz, C5 enol), 7.57 (d, 0.25 H, *J* = 8.40 Hz, C6' keto), 7.50 (d, 1 H, *J* = 8.44 Hz, C6' enol), 6.80-6.70 (complex, 2.5 H, C3', C5' enol, C3', C5' keto), 6.64 (d, 0.25 H, *J* = 16.12 Hz, C4 keto), 6.27 (dd, 1H, *J* = 15.76, 1.88 Hz, C4 enol), 5.14 (s, 1H, C2 enol), 3.83 (s, 0.75 H, $COOCH_3$ keto), 3.82 (s, 3H, $COOCH_3$ enol), 3.77 (s, 3H, C4' OCH_3 enol), 3.76 (s, 0.75 H, C4' OCH_3 keto), 3.70 (s, 0.5 H, C2 keto), 2.44 (s, 0.75 Hz, C2' CH_3 keto), 2.42 (s, 3H, C2' CH_3 enol).

^{13}C NMR (100 MHz, $CDCl_3$), δ: 191.5, 173.2, 169.9, 167.9, 161.6, 141.8, 140.6, 139.0, 134.0, 128.2, 127.2, 125.5, 123.5, 120.4, 116.0, 115.8, 112.3, 112.0, 90.6, 55.2, 52.3, 51.1, 47.5, 19.9.

FTIR (thin film), cm^{-1}: 2950 (w), 1743 (w), 1632 (m, C=O), 1599 (s), 1498 (m), 1444 (s), 1313 (m), 1255 (s), 1102 (w), 1147 (s), 1102 (w), 1037 (m), 803 (m).

HRMS (FAB):	Calc'd for $C_{14}H_{17}O_4$ $[MH]^+$: 249.112684
	Found: 249.112953
TLC (20% EtOAc in Hexanes), R*f*:	**42**: 0.00 (UV, anisaldehyde)
	43: 0.45 (UV, anisaldehyde)



43 **44**

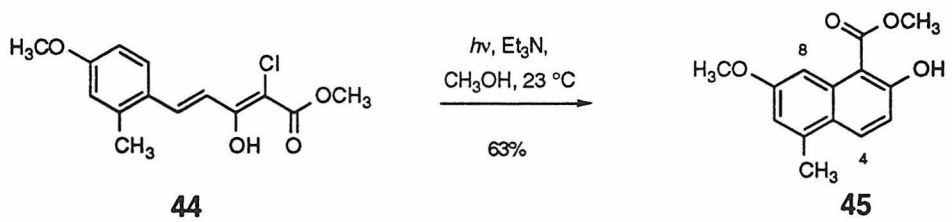
Chloro ester **44**

Sulfuryl chloride (3.47 mL, 5.84 g, 43.3 mmol, 1.1 equiv) was added to a solution of β-keto ester **43** (9.76 g, 39.3 mmol, 1 equiv) in benzene (240 mL). The yellow solution was heated to 66 °C for 50 min, and volatiles were removed in vacuo. Purification of the residue by flash column chromatography (20% ethyl acetate in hexanes) afforded chloro ester **44** (10.2 g, 92%) as a bright yellow solid, mp 93-96 °C.

^{1}H NMR (400 MHz, C_6D_6), δ: 12.31 (d, 1H, J = 1.80 Hz, OH), 7.76 (d, 1H, J = 15.40 Hz, C5 H), 7.61 (d, 1H, J = 8.80 Hz, C6' H), 7.03 (dd, 1H, J = 15.36, 1.44 Hz, C4 H), 6.76 (m, 2H, C3', C5' H), 3.89 (s, 3H, $COOCH_3$), 3.83 (s, 3H, C4' OCH_3), 2.44 (s, 3H, C2' CH_3).

^{13}C NMR (100 MHz, $CDCl_3$), δ: 170.2, 166.2, 160.9, 139.6, 136.8, 127.9, 126.9, 116.5, 115.9, 112.2, 96.6, 55.2, 52.8, 20.0.

FTIR (CH_2Cl_2), cm^{-1}:	2955 (m), 1638 (m), 1600 (s, C=O), 1560 (s), 1442 (s), 1355 (s), 1306 (s), 1208 (m), 1020 (m).
HRMS (FAB):	Calc'd for $C_{14}H_{15}ClO_4$ $[M]^+$: 283.073712 Found: 283.075798
TLC (40% EtOAc in Hexanes), R*f*:	**43**: 0.49 (UV, anisaldehyde) **44**: 0.58 (UV, anisaldehyde)



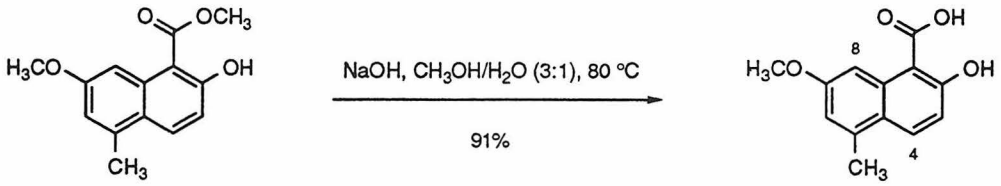
44 **45**

Methyl 2-hydroxy-7-methoxy-5-methyl-1-naphthoate (**45**)

A large Pyrex photoreaction vessel was charged with chloro ester **44** (1.20 g, 4.24 mmol, 1 equiv), triethylamine (15.0 mL, 10.7 g, 106 mmol, 25 equiv), and methanol (800 mL). The vessel was equipped with a quartz photowell containing a Hanovia 450 watt medium pressure mercury arc lamp. The solution was deoxygenated by passing argon through the solution with a needle for 20 min, and then irradiated at 23 °C for 1 h. Volatiles were removed in vacuo, and the residue was purified by flash column chromatography (50% dichloromethane in hexanes) to afford methyl 2-hydroxy-7-methoxy-5-methyl-1-naphthoate (**45**, 551 mg, 53%) as a white solid, mp. 103-104 °C.

^{1}H NMR (400 MHz, C_6D_6), δ: 12.12 (s, 1H, OH), 8.07 (s, 1H, C8 H), 8.03 (d, 1H, J = 9.16 Hz, C4 H), 7.04 (d, 1H, J = 9.16 Hz, C3 H), 6.89 (s, 1H, C6 H), 4.10 (s, 3H, CO_2CH_3), 3.92 (s, 3H, C7 OCH_3), 2.63 (s, 3H, C5 CH_3).

^{13}C NMR (100 MHz, $CDCl_3$), δ:	172.7, 164.3, 159.3, 136.8, 134.1, 132.3, 123.0, 116.0, 104.6, 104.2, 55.0, 52.3, 19.9.
FTIR (thin film), cm^{-1}:	2953 (w), 1641 (m, C=O), 1614 (m), 1436 (m), 1412 (m), 1318 (m), 1207 (s), 1171 (m), 1035 (m), 840 (m), 812 (m).
HRMS (FAB):	Calc'd for $C_{14}H_{14}O_4$ $[M]^+$: 246.089209 Found: 246.087196
TLC (25% EtOAc in Hexanes), R*f*:	**44**: 0.78 (UV, anisaldehyde) **45**: 0.83 (UV, anisaldehyde)



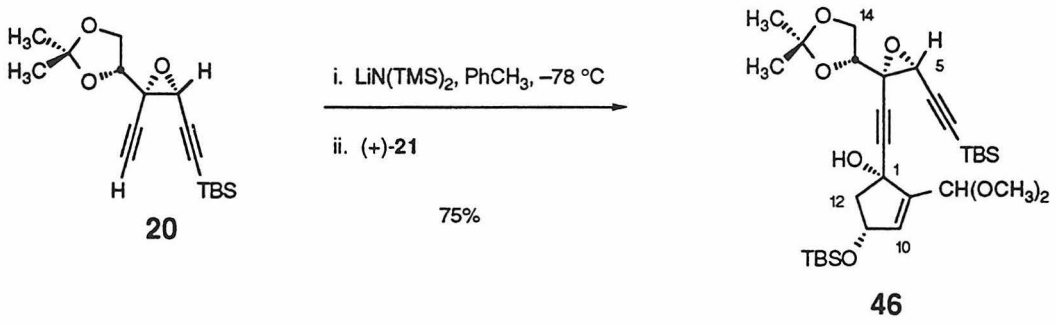
45 **22**

2-Hydroxy-7-methoxy-5-methyl-1-naphthoic acid (**22**)

Sodium hydroxide (30.0 g, 0.758 mol, 75 equiv) was added portionwise over a five minute period to a solution of methyl 2-hydroxy-7-methoxy-5-methyl-1-naphthoate (**45**, 2.49 g, 10.1 mmol, 1 equiv) in methanol (69 mL) and water (23 mL) at 0 °C. The resultant solution was warmed to 80 °C for 10.5 h and cooled to 23 °C. The reaction mixture was poured into 500 mL cold (0 °C) 6N hydrochloric acid, and the precipitate was collected by filtration and dried, leaving 2-hydroxy-7-methoxy-5-methyl-1-naphthoic acid (**22**) as a pale orange/red solid (2.15 g, 91%), mp 153-154 °C. The crude product could be recrystallized from toluene to afford yellow/orange needles.

^{1}H NMR (400 MHz, C_6D_6), δ: 7.97 (d, 1H, J = 9.12 Hz, C4 H), 7.68 (s, 1H, C8 H), 7.01 (d, 1H, J = 9.12 Hz, C3 H), 6.89 (s, 1H, C6 H), 3.80 (s, 3H, C7 OCH_3), 2.56 (s, 3H, C5 CH_3).

^{13}C NMR (100 MHz, DMSO-d_6), δ:	172.8, 160.1, 158.9, 137.1, 134.1, 130.7, 122.8, 116.3, 116.1, 109.4, 103.2, 55.4, 19.9.
FTIR (KBr), cm^{-1}:	2974 (m), 2618 (m), 1630 (s, C=O), 1444 (s), 1287 (s), 1247 (s), 1230 (s), 1022 (m), 850 (m).
HRMS (FAB):	Calc'd for $C_{13}H_{12}O_4$ $[M]^+$: 232.073559 Found: 232.074749
TLC (25% EtOAc in Hexanes), R*f*:	**45**: 0.83 (UV, anisaldehyde) **22**: 0.00 (UV, anisaldehyde)

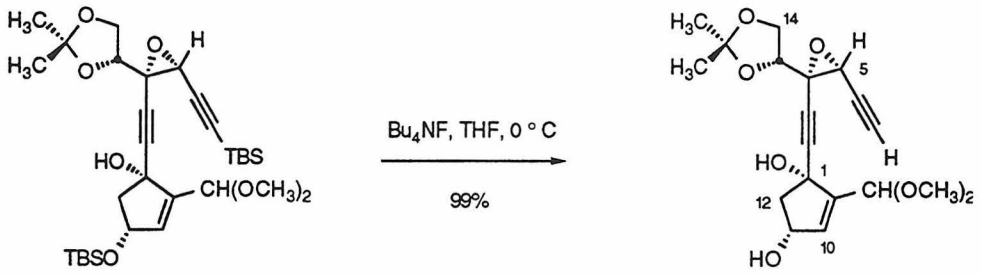


Alcohol **46**

Lithium hexamethyldisilazide (12.4 mL of a 1.0 M solution in hexanes, 12.4 mmol, 1.05 equiv) was added in a dropwise manner to a solution of epoxy diyne **20** (3.79 g, 12.4 mmol, 1.05 equiv) in toluene (82 mL) at –78 °C. The resultant solution was maintained at –78 °C for an additional 25 min, and a solution of enone (+)-**21** (3.37 g, 11.8 mmol, 1.0 equiv) in toluene (20 mL) was added over a 30 min period. The reaction mixture was maintained at –78 °C for an additional 10 min, and excess base was quenched by the addition of saturated aqueous ammonium chloride (40 mL). The reaction mixture was warmed to 23 °C and the layers were separated. The aqueous layer was extracted with 1:1 ethyl acetate/hexanes (3 50-mL portions), and the combined organics were washed with saturated aqueous sodium chloride (50 mL), dried over sodium sulfate, and concentrated. Purification of the residue by flash column chromatography (10% ethyl acetate in hexanes grading to 20% ethyl acetate in hexanes) afforded the tertiary alcohol **46** (5.20 g, 75%) as a pale yellow oil, along with recovered epoxy diyne (1.16 g, 30%).

^{1}H NMR (400 MHz, C_6D_6). δ:	6.19 (s, 1H, C10 H), 5.44 (s, 1H, C8 H), 4.89 (m, 1H, C11 H), 4.10 (dd, 1H, *J* = 8.40, 5.84 Hz, C13 H), 3.97 (s, 1H, OH), 3.85 (dd, 1H, *J* = 8.40, 6.56 Hz, C14 H), 3.63 (t, 1H, *J* = 6.24 Hz, C14 H), 3.50 (s, 1H, C5 H), 3.20 (s, 3H, $CH(OCH_3)_2$), 3.18 (obscured, 1H, C12 H), 3.17 (s, 3H, $CH(OCH_3)_2$), 2.55 (dd, 1H, *J* = 13.56, 5.12 Hz, C12 H), 1.45 (s, 3H, $C(CH_3)_2$), 1.19 (s, 3H, $C(CH_3)_2$), 1.06 (s, 9H, $SiC(CH_3)_3(CH_3)_2$), 0.97 (s, 9H, $SiC(CH_3)_3(CH_3)_2$), 0.21 (s, 3H, $SiC(CH_3)_3(CH_3)_2$), 0.20 (s, 3H, $SiC(CH_3)_3(CH_3)_2$), 0.090 (s, 3H, $SiC(CH_3)_3(CH_3)_2$), 0.076 (s, 3H, $SiC(CH_3)_3(CH_3)_2$).
^{13}C NMR (100 MHz, C_6D_6), δ:	142.8, 136.0, 110.7, 100.6, 99.8, 90.8, 90.2, 77.6, 77.4, 75.4, 73.4, 66.9, 58.3, 52.7, 50.6, 26.3, 26.2, 25.9, 25.3, 18.2, 16.6, –4.5, –4.7.
$[\alpha]_D^{20}$:	+107.83° (*c* 0.23, C_6H_6)
FTIR (thin film), cm^{-1}:	3520 (m, OH), 2955 (s), 2858 (s), 2252 (w, C≡C), 1463 (m), 1372 (m), 1252 (m), 1076 (s), 839 (s), 777 (m).

HRMS (FAB):	Calc'd for $C_{31}H_{52}O_7Si_2$ $[M]^+$: 591.320700
	Found: 591.3173363
TLC (30% EtOAc in Hexanes), R*f*:	**20**: 0.46 (anisaldehyde)
	(+)-**21**: 0.27 (anisaldehyde)
	46: 0.19 (anisaldehyde)

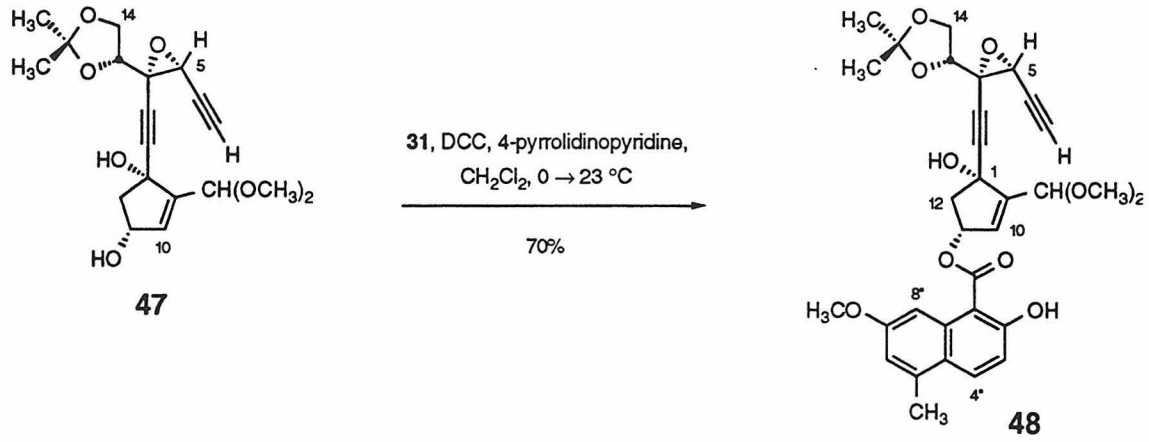


46 **47**

Diol **47**

Tetrabutylammonium fluoride (29.79 mL of a 1.0 M solution in tetrahydrofuran, 29.79 mmol, 3 equiv) was added over a 4 min period to a solution of alcohol **46** (5.88 g, 9.93 mmol, 1 equiv) in tetrahydrofuran (200 mL) at 0 °C. The resultant purple solution was stirred at 0 °C for an additional 30 min and poured into water (100 mL). The reaction mixture was extracted with ethyl acetate (3 75-mL portions), and the combined extracts were washed once with saturated aqueous sodium chloride (100 mL). The organics were dried over sodium sulfate and concentrated. Purification of the residue by flash column chromatography (50% ethyl acetate in hexanes grading to 80% ethyl acetate in hexanes) provided the diol **47** (3.62 g, quantitative) as a pale yellow oil.

^{1}H NMR (400 MHz, CD_2Cl_2), δ:	6.05 (t, 1H, *J* = 1.84 Hz, C10 H), 5.19 (t, 1H, *J* = 1.44 Hz, C8 H), 4.70 (br s, 1H, C11 H), 4.17 (dd, 1H, *J* = 7.68, 5.88 Hz, C13 H), 4.02 (m, 2H, C14 CH_2), 3.76 (br s, 1H, OH), 3.63 (d, 1H, *J* = 1.48 Hz, C5 H), 3.60 (s, 3H, $CH(OCH_3)_2$), 3.42 (s, 3H, $CH(OCH_3)_2$), 2.78 (dd, 1H, *J* = 14.28, 6.96 Hz, C12 βH), 2.54 (d, 1H, *J* = 1.48 Hz, C7 H), 2.09 (dd, 1H, *J* = 14.28, 3.64 Hz, C12 αH), 1.84 (br d, 1H, *J* = 8.44 Hz, OH), 1.43 (s, 3H, $C(CH_3)_2$), 1.32 (s, 3H, $C(CH_3)_2$).
^{13}C NMR (100 MHz, CD_2Cl_2), δ:	143.8, 135.4, 111.2, 100.7, 89.3, 78.2, 77.4, 76.3, 75.5, 75.0, 73.2, 67.1, 58.1, 54.4, 53.7, 51.1, 49.7, 26.2, 25.2.
$[\alpha]_D^{20}$:	+120.60° (*c* 0.33, CH_2Cl_2)
FTIR (thin film), cm^{-1}:	3418 (m, OH), 3281 (m, C≡C-H), 2947 (m), 2939 (m), 1374 (m), 1215 (m), 1106 (s), 1072 (s), 851 (m).
HRMS (FAB):	Calc'd for $C_{19}H_{23}O_7$ $[M-H]^+$: 363.1443000 Found: 363.1443784
TLC (50% EtOAc in Hexanes), R*f*:	**46**: 0.72 (anisaldehyde) **47**: 0.098 (anisaldehyde)

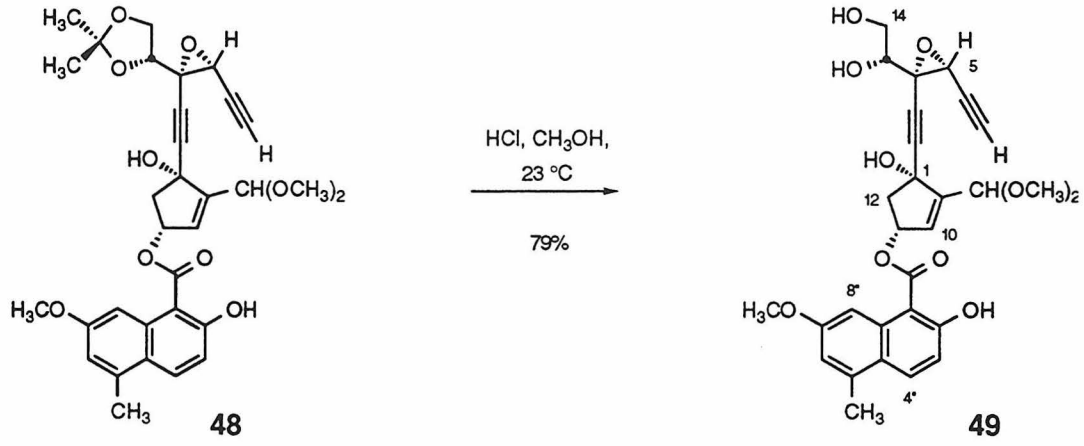


Naphthoate ester **48**

A solution of dicyclohexylcarbodiimide (200 mg, 0.972 mmol, 1.5 equiv) in dichloromethane (1 mL) was added via cannula to a solution of diol **47** (236 mg, 0.648 mmol, 1 equiv), naphthoic acid **22** (180 mg, 0.777 mmol, 1.2 equiv), and 4-pyrrolidinopyridine (19.0 mg, 0.129 mmol, 0.2 equiv) in dichloromethane (6.5 mL) at 0 °C. The resultant solution was allowed to warm to 23 °C over a 4 h period, and was maintained at 23 °C for an additional 8 h. The precipitated dicyclohexylurea was removed by filtration, and the filtrate was concentrated. The concentrate was purified by flash column chromatography (30% ethyl acetate in haxanes grading to 40% ethyl acetate in hexanes) to afford the ester **48** (262 mg, 70%) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$), δ:	12.12 (s, 1H, ArOH), 8.10 (s, 1H, C8" H), 8.02 (d, *J* = 9.3 Hz, 1H, C 4" H), 7.02 (d, 1H, *J* = 9.3 Hz, C3" H), 6.87 (s, 1H, C6" H), 6.28 (s, 1H, C10 H), 6.01 (td, 1H, *J* = 4.9, 4.0 Hz, C11 H), 5.29 (s, 1H, C8 H), 4.23-4.06 (m, 3H, C13, C14 H), 3.86 (s, 3H, C7" OCH_3), 3.77 (s, 1H, C5 H), 3.67 (s, 1H, OH), 3.46 (s, 3H, $CH(OCH_3)_2$), 3.42 (s, 3H, $CH(OCH_3)_2$), 3.11 (dd, 1H, *J* = 15.0, 7.3 Hz, C12 βH), 2.61 (s, 3H, C5" CH_3), 2.58 (dd, 1H, *J* = 15.0, 2.9 Hz, C12 αH), 2.52 (s, 1H, C7 H), 1.49 (s, 3H, $C(CH_3)_2$), 1.37 (s, 3H, $C(CH_3)_2$).
^{13}C NMR (100 MHz, $CDCl_3$), δ:	203.3, 171.9, 164.6, 159.5, 147.0, 136.8, 134.2, 132.6, 130.2, 123.0, 116.8, 115.9, 111.1, 104.4, 100.3, 88.5, 77.7, 76.3, 76.0, 75.1, 74.9, 74.8, 66.9, 57.8, 55.3, 54.3, 53.7, 49.6, 47.4, 26.2, 25.1, 19.9.
FTIR (thin film), cm^{-1}	3500(w, OH), 3281 (w, OH), 2990 (m), 2939 (m), 1644 (m, C=O), 1615 (m), 1207 (m), 1074 (m).
HRMS (FAB):	Calc'd for $C_{32}H_{34}O_{10}$ $[M]^+$: 578.2165 Found: 578.2152

TLC (20% EtOAc in Hexanes), R*f*:	**47**: 0.08 (anisaldehyde)
	48: 0.51 (fluoresces under UV, anisaldehyde)



Tetraol **49**

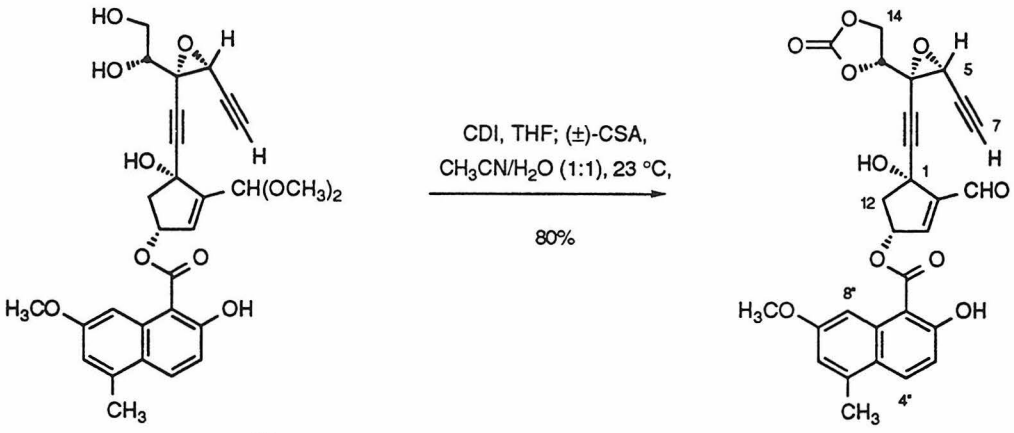
Concentrated HCl (68 μL) was added dropwise via syringe to a solution of acetonide **48** (488 mg, 0.843 mmol, 1 equiv) in methanol (75 mL) at 0 °C. The resultant solution was maintained at 0 °C for 2.5 h, and warmed to 23 °C for 9.5 h. The solution was cooled to 0 °C and quenched with saturated sodium bicarbonate (25 mL). The reaction was concentrated to approximately half volume and partitioned between 1:1 ethyl acetate/hexanes (50 mL) and water (50 mL). The aqueous layer was extracted with ethyl acetate (2 25-mL portions), and the combined extracts were washed once with saturated aqueous sodium chloride (50 mL). The organics were dried over sodium sulfate and concentrated. The residue was purified by flash column chromatography (40% ethyl acetate in hexanes grading to 100% ethyl acetate) to afford the tetraol **49** (360 mg, 79%) as a pale yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$), δ:	12.10 (s, 1H, ArO**H**), 8.08 (d, 1H, *J* = 2.4 Hz, C8" H), 8.02 (d, 1H, *J* = 9.2 Hz, C4" H), 7.01 (d, 1H, *J* = 9.2 Hz, C3" H), 6.86 (d, 1H, *J* = 2.4 Hz, C6" H), 6.29 (s, 1H, C10 H), 6.01 (td, 1H, *J* = 3.9, 2.9 Hz, C11 H), 5.26 (s, 1H, C8 H), 3.91 (m, 3H, C13, C14 H), 3.86 (s, 3H, C7" OC**H**$_3$), 3.83 (s, 1H, O**H**), 3.76 (d, 1H, *J* = 1.4 Hz, C5 H), 3.46 (s, 3H, CH(OC**H**$_3$)$_2$), 3.42 (s, 3H, CH(OC**H**$_3$)$_2$), 3.10 (dd, 1H, *J* = 14.6, 7.3 Hz, C12 βH), 2.60 (s, 3H, C5" C**H**$_3$), 2.58 (dd, 1H, *J* = 14.6, 3.4 Hz, C12 αH), 2.53 (d, 1H, *J* = 1.4 Hz, C7 H), 2.20 (br s, 1H, O**H**).
^{13}C NMR (100 MHz, $CDCl_3$), δ:	171.9, 164.6, 159.5, 146.8, 136.8, 134.2, 132.6, 130.6, 123.0, 116.7, 115.9, 104.3, 103.6, 100.2, 89.1, 78.1, 77.9, 77.5, 76.2, 75.1, 74.9, 71.4, 63.1, 57.5, 55.2, 54.4, 53.4, 48.5, 47.5.
FTIR (thin film), cm^{-1}:	3418 (s, OH), 3296 (s, OH), 2901 (m), 1644 (s, C=O), 1614 (s), 1207 (s), 1052 (s).
HRMS (FAB):	Calc'd for $C_{29}H_{30}O_{10}$ $[M]^+$: 538.1856 Found: 538.1839

TLC (75% EtOAc in Hexanes), R*f*:

48: 0.87 (fluoresces under UV, anisaldehyde)

49: 0.28 (fluoresces under UV, anisaldehyde)



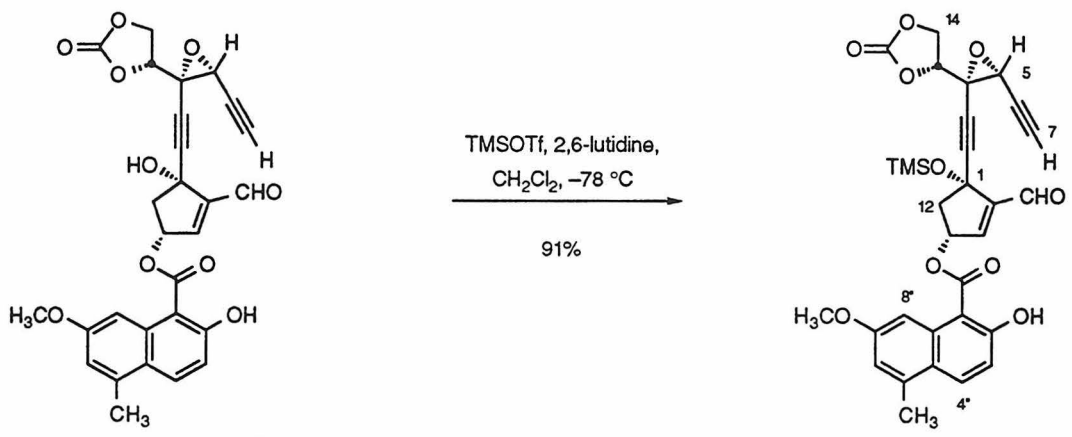
49 **50**

Carbonate **50**

Carbonyldiimidazole (38.0 mg, 0.232 mmol, 0.65 equiv) was added in one portion to a solution of tetraol **49** (192 mg, 0.357 mmol, 1 equiv) in dry THF (7 mL) at 0 °C. The resultant solution was stirred at 0 °C for 20 min, then another portion of carbonyldiimidazole (38.0 mg, 0.232 mmol, 0.65 equiv) was added. The reaction mixture was maintained at 0 °C for an additional 10 min, then warmed to 23 °C and held at that temperature for 2 h. The reaction mixture was diluted with ethyl acetate (25 mL) and washed with water (2 10-mL portions) and saturated aqueous sodium chloride (10 mL). The organics were dried over sodium sulfate and concentrated. The residue was dissolved in 1:1 acetonitrile/water (26 mL). (±)-Camphorsulfonic acid (325 mg) was added in one portion and the reaction mixture was stirred at 23 °C for 11 h. The reaction mixture was extracted with ethyl acetate (3 50-mL portions). The combined organics were washed with saturated aqueous sodium chloride (50 mL), dried over sodium sulfate and concentrated.

Purification of the residue by flash column chromatography (50% ethyl acetate in hexanes) provided the carbonate **50** (153 mg, 80%) as a colorless film.

^{1}H NMR (400 MHz, $CDCl_3$), δ:	12.00 (s, 1H, ArO**H**), 9.89 (s, 1H, C8 H), 8.05 (d, 1H, *J* = 9.3 Hz, C4" H), 7.98 (s, 1H, C8" H), 7.03 (d, 1H, *J* = 9.3 Hz, C3" H), 7.10 (d, 1H, *J* = 2.0 Hz, C10 H), 6.89 (s, 1H, C6" H), 6.22 (m, 1H, C11 H), 4.62 (m, 2H, C14 H), 4.35 (dd, 1H, *J* = 7.8, 4.9 Hz, C13 H), 3.85 (s, 3H, C7" OC**H**$_3$), 3.67 (d, 1H, *J* = 1.5 Hz, C5 H), 3.64 (s, 1H, OH), 3.30 (dd, 1H, *J* = 14.2, 7.8 Hz, C12 βH), 2.62 (d, 1H, *J* = 1.5 Hz, C7 H), 2.62 (s, 3H, C5" C**H**$_3$), 2.62 (dd, 1H, *J* = 14.2, 4.8 Hz, C12 αH).
FTIR (thin film), cm^{-1}:	3448 (w, OH), 3271 (w, OH), 2919 (w), 1818 (s, carbonate C=O), 1686 (m, C=O), 1616 (s, C=O), 1204 (s), 1084 (s).
HRMS (FAB):	Calc'd for $C_{28}H_{22}NaO_{10}$ $[M+Na]^+$: 541.1110 Found: 541.1094
TLC (50% EtOAc in Hexanes), R*f*:	**49**: 0.00 (fluoresces under UV, anisaldehyde) **50**: 0.31 (UV, anisaldehyde)



50 **51**

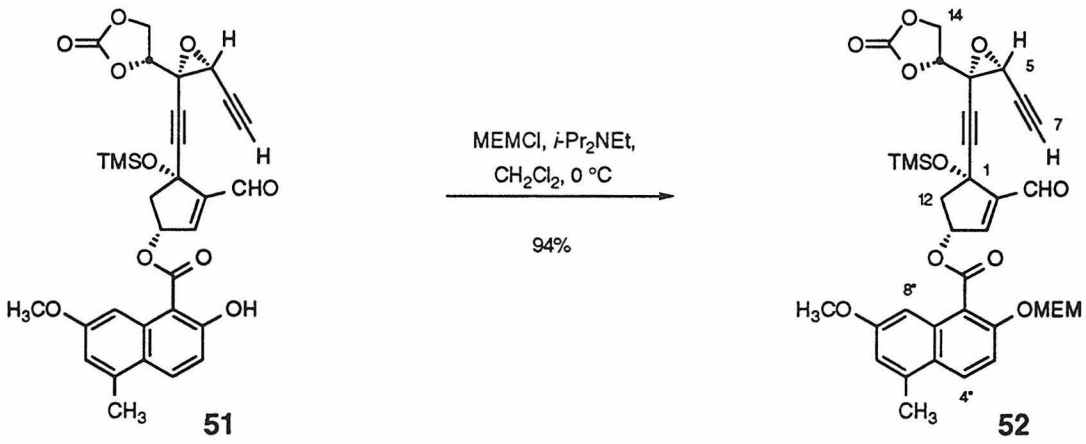
TMS ether **51**

2,6-Lutidine (0.573 mL, 527 mg, 4.92 mmol, 10 equiv) and trimethylsilyl trifluoromethanesulfonate (0.571 mL, 656 mg, 2.95 mmol, 6 equiv) were added sequentially via syringe to a solution of carbonate **50** (236 mg, 0.492 mmol, 1 equiv) in dichloromethane (30 mL) at –78 °C. The resultant solution was maintained at –78 °C for an additional 75 min, and excess trimethylsilyl trifluoromethanesulfonate was neutralized by the addition of triethylamine (0.1 mL) and methanol (0.1 mL). The reaction mixture was warmed to 23 °C and diluted with 1:1 ethyl acetate/hexanes (50 mL). The mixture was washed with water (50 mL), 5% aqueous citric acid (3 25-mL portions) and saturated aqueous sodium chloride (50 mL). The organics were then dried over sodium sulfate and concentrated. Purification of the residue by flash column chromatography (25% ethyl acetate in hexanes) afforded silyl ether **51** (264 mg, 91%) as a light orange oil.

^{1}H NMR (400 MHz, $CDCl_3$), δ:	11.95 (s, 1H, ArOH), 9.84 (s, 1H, C8 H), 8.04 (d, 1H, *J* = 9.2 Hz, C4" H), 7.99 (s, 1H, C8" H), 7.02 (d, 1H, *J* = 9.3 Hz, C3" H), 6.99 (d, 1H, *J* = 2.0 Hz, C10 H), 6.87 (s, 1H, C6" H), 6.15 (m, 1H, C11 H), 4.62 (m, 2H, C14 H), 4.37 (dd, 1H, *J* = 7.8, 5.4 Hz, C13 H), 3.83 (s, 3H, C7" OCH_3), 3.68 (d, 1H, *J* = 2.0 Hz, C5 H), 3.33 (dd, 1H, *J* = 14.1, 7.3 Hz, C12 βH), 2.61 (s, 3H, C5" CH_3), 2.61 (d, 1H, *J* = 2.0 Hz, C7 H), 2.51 (dd, 1H, *J* = 14.1, 4.9 Hz, C12 αH), 0.24 (s, 9H, $OSi(CH_3)_3$).
^{13}C NMR (100 MHz, $CDCl_3$), δ:	187.4, 171.8, 165.2, 159.8, 153.8, 149.3, 142.5, 137.3, 134.3, 133.3, 123.4, 116.8, 116.3, 104.3, 90.3, 77.1, 76.7, 76.3, 76.0, 75.8, 74.2, 66.9, 57.0, 55.2, 51.4, 51.1, 20.3, 1.9.
FTIR (thin film), cm^{-1}:	3289 (m, OH), 2957 (m), 1822 (s, Carbonate C=O), 1644 (m, C=O), 1615 (s, C=O), 1413 (m), 1206 (s).
HRMS (FAB):	Calc'd for $C_{31}H_{30}O_{10}Si$ $[M]^+$: 590.1627 Found: 590.1608

TLC (50% EtOAc in Hexanes), R*f*: **50**: 0.34 (UV, anisaldehyde)

51: 0.54 (UV, anisaldehyde)



51 52

Methoxyethoxymethyl ether **52**

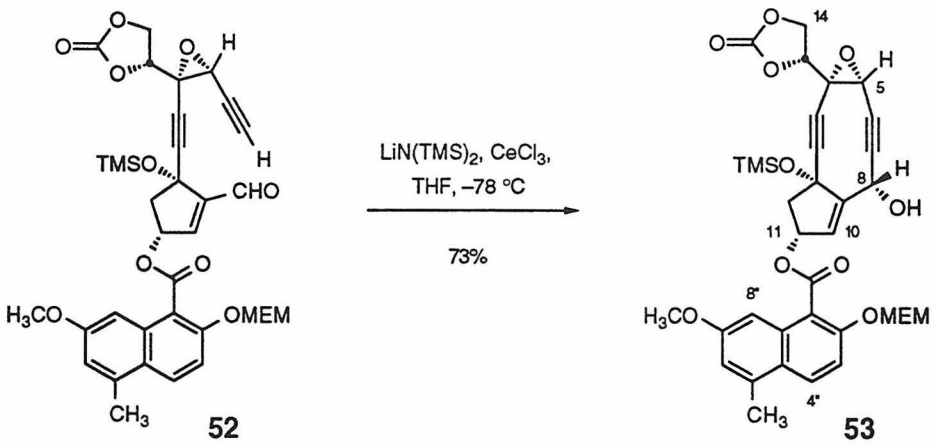
Methoxyethoxymethyl chloride (0.397 mL, 434 mg, 3.48 mmol, 15 equiv) was added to a solution of TMS ether **51** (137 mg, 0.232 mmol, 1 equiv) and diisopropylethylamine (1.21 mL, 899 mg, 6.96 mmol, 30 equiv) in dichloromethane (30 mL) at 0 °C. The reaction mixture was maintained at 0 °C for 1.5 h and partitioned between water (50 mL) and 1:1 ethyl acetate in hexanes (50 mL). The aqueous layer was extracted with 1:1 ethyl acetate in hexanes (50 mL) and the combined organics were washed with saturated aqueous sodium chloride (25 mL), dried over sodium sulfate and concentrated. Purification of the residue by flash column chromatography (50% ethyl acetate in hexanes) afforded the MEM ether **52** (145 mg, 94%) as a light orange oil.

^{1}H NMR (400 MHz, C_6D_6), δ: 9.48 (s, 1H, C8 H), 7.67 (d, 1H, *J* = 9.28 Hz, C4" H), 7.29 (d, 1H, *J* = 9.28 Hz, C3" H), 7.28 (s, 1H, C8" H), 7.02 (s, 1H, C6" H), 6.64 (d, 1H, *J* = 2.19 Hz, C10 H), 6.19 (m, 1H, C11 H), 5.17 (s, 2H, $ArOCH_2OCH_2CH_2OCH_3$), 3.97 (dd, 1H, *J* = 9.03, 5.13 Hz, C13 H), 3.76 (m, 2H, $ArOCH_2OCH_2CH_2OCH_3$), 3.65 (m, 1H, C14 H), 3.55 (s, 3H, C7" OCH_3), 3.42-3.31 (complex, 4H, $ArOCH_2OCH_2CH_2OCH_3$, C14 H, C12 βH), 3.15 (s, 3H, $ArOCH_2OCH_2CH_2OCH_3$), 2.86 (d, 1H, *J* = 1.47 Hz, C5 H), 2.58 (dd, 1H, *J* = 13.67, 5.37 Hz, C12 αH), 2.28(s, 3H, C5" CH_3), 2.23 (d, 1H, *J* = 1.50 Hz, C7 H), 0.32 (s, 9H, $OSi(CH_3)_3$).

FTIR (thin film), cm^{-1}: 2953 (m), 2120 (w, C≡C), 1821 (s, carbonate C=O), 1698 (s, C=O), 1254 (s), 1074 (s).

HRMS (FAB): Calc'd for $C_{35}H_{38}NaO_{12}Si$ $[M+Na]^+$: 701.2030
Found: 701.2007

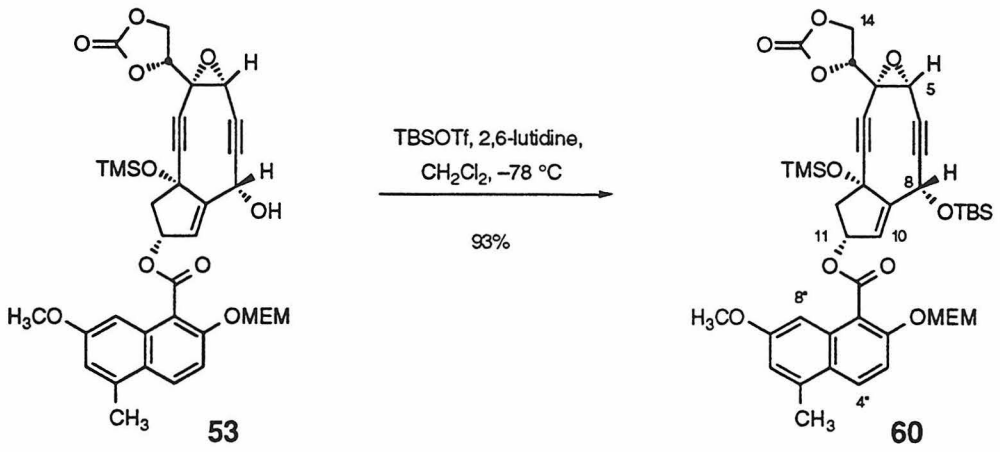
TLC (50% EtOAc in Hexanes), R*f*: **51**: 0.48 (UV, anisaldehyde)
52: 0.29 (UV, anisaldehyde)



Cyclic alcohol **53**

Lithium hexamethyldisilazide (0.262 mL of a 1.0 M solution in hexanes, 0.262 mmol, 1.02 equiv) was added over a two min period to a suspension of aldehyde **52** (175 mg, 0.258 mmol, 1 equiv) and anhydrous cerium(III) chloride (194 mg, 0.787 mmol, 3 equiv) in THF (20 mL) at –78 °C. After maintaining the reaction mixture at –78 °C for 10 min, excess base was quenched by addition of saturated aqueous ammonium chloride (10 mL) and the reaction mixture was warmed to 23 °C. The reaction mixture was partitioned between 1:1 ethyl acetate in hexanes (50 mL) and water (50 mL), and the layers were separated. The aqueous layer was further extracted with 1:1 ethyl acetate in hexanes (2 50-mL portions), and the combined organics were washed with saturated sodium chloride (25 mL), dried over sodium sulfate and concentrated. The residue was purified by flash column chromatography (50% ethyl acetate in hexanes) to provide the alcohol **53** (128 mg, 73%) as a light yellow oil.

^{1}H NMR (400 MHz, C_6D_6), δ:	7.66 (d, 1H, *J* = 9.24 Hz, C4" H), 7.33 (d, 1H, *J* = 2.30 Hz, C8" H), 7.20 (d, 1H, *J* = 9.24 Hz, C3" H), 7.00 (d, 1H, *J* = 2.25 Hz, C6" H), 6.42 (t, 1H, *J* = 1.83 Hz, C10 H), 6.07 (m, 1H, C11 H), 5.32 (d, 1H, *J* = 3.08 Hz, C8 H), 5.16 (abq, 2H, *J* = 6.82 Hz, $ArOCH_2OCH_2CH_2OCH_3$), 3.75 (m, 2H, $ArOCH_2OCH_2CH_2OCH_3$), 3.63 (m, 4H, C13, C14, and C12 βH), 3.57 (s, 2H, C7" OCH_3), 3.33 (m, 2H, $ArOCH_2OCH_2CH_2OCH_3$), 3.07 (s, 3H, $ArOCH_2OCH_2CH_2OCH_3$), 2.93 (s, 1H, C5 H), 2.41 (dd, 1H, *J* = 14.14, 4.63 Hz, C12 αH), 2.29 (s, 3H, C5" CH_3), 0.22 (s, 9H, $OSi(CH_3)_3$).
FTIR (thin film), cm^{-1}:	3474 (m, OH), 2924 (m), 1821 (s, carbonate C=O), 1722 (m, C=O), 1621 (m), 1254 (s), 1095 (s).
HRMS (FAB):	Calc'd for $C_{35}H_{38}NaO_{12}Si$ $[M+Na]^+$: 701.2030 Found: 701.2011
TLC (75% EtOAc in Hexanes), R*f*:	**52**: 0.58 (UV, anisaldehyde) **53**: 0.73 (fluoresces under UV, anisaldehyde)



Bis-silyl ether **60**

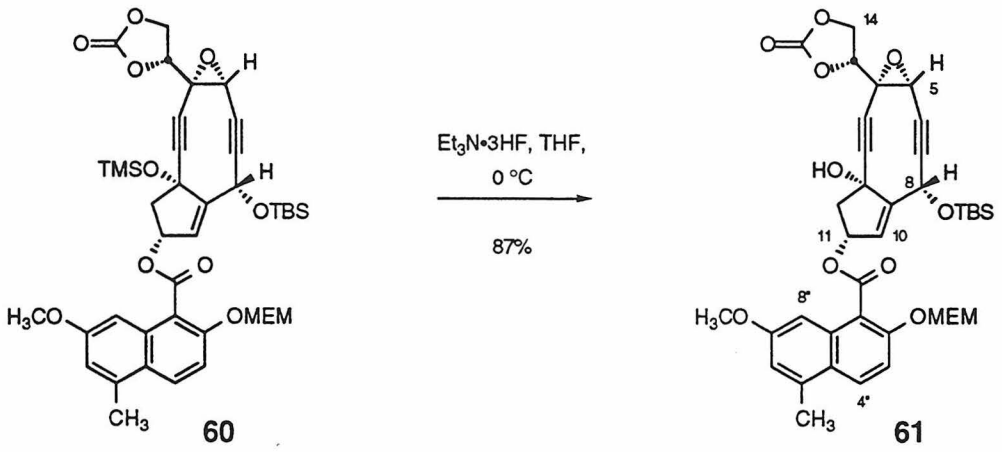
2,6-Lutidine (0.487 mL, 402 mg, 3.75 mmol, 20 equiv) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (0.431 mL, 496 mg, 1.87 mmol, 10 equiv) were added sequentially to a solution of alcohol **53** (125 mg, 0.187 mmol, 1 equiv) in dichloromethane (23 mL) at –78 °C. The reaction mixture was maintained at –78 °C for 30 min, and triethylamine (0.5 mL) and methanol (0.5 mL) were added and the reaction mixture was warmed to 23 °C. The reaction was partitioned between 1:1 ethyl acetate/hexanes (50 mL) and water (50 mL). The layers were separated, and the organic layer was washed with saturated aqueous sodium chloride (25 mL), dried over sodium sulfate and concentrated. The residue was purified by flash column chromatography (25% ethyl acetate in hexanes) to afford silyl ether **60** (138 mg, 93%) as a light yellow oil.

^{1}H NMR (400 MHz, C_6D_6), δ: 7.57 (d, 1H, *J* = 9.29 Hz, C4" H), 7.24 (d, 1H, *J* = 2.29 Hz, C8" H), 7.20 (d, 1H, *J* = 9.29 Hz, C3" H), 6.90 (m, 1H, C6" H), 6.42 (t, 1H, *J* = 1.85 Hz, C10 H), 6.03 (m, 1H, C11 H), 5.52 (t, 1H, *J* = 1.50 Hz, C8 H), 5.09 (s, 2H, $ArOCH_2OCH_2CH_2OCH_3$), 3.70 (m, 2H, $ArOCH_2OCH_2CH_2OCH_3$), 3.53 (dd, 1H, *J* = 6.30, 3.96 Hz, C13 H), 3.48 (s, 3H, C7" OCH_3), 3.35-3.24 (complex, 4H, $ArOCH_2OCH_2CH_2OCH_3$, C14 H), 3.16 (dd, 1H, *J* = 13.81, 7.29 Hz, C12 βH), 3.04 (s, 3H, $ArOCH_2OCH_2CH_2OCH_3$), 2.74 (d, 1H, *J* = 1.76 Hz, C5 H), 2.40 (dd, 1H, *J* = 13.86, 5.20 Hz, C12 αH), 2.20 (s, 3H, C5" CH_3), 0.90 (s, 9H, $OSiC(CH_3)_3(CH_3)_2$), 0.17 (s, 3H, $OSiC(CH_3)_3(CH_3)_2$), 0.16 (s, 9H, $OSi(CH_3)_3$), 0.02 (s, 3H, $OSiC(CH_3)_3(CH_3)_2$).

FTIR (thin film), cm^{-1}: 2942 (m), 2931 (m), 2214 (w, C≡C), 1823 (s, carbonate C=O), 1725 (m, C=O), 1622 (m), 1255 (s), 1096 (s).

TLC (50% EtOAc in Hexanes), R*f*: **53**: 0.15 (fluoresces under UV, anisaldehyde)

60: 0.43 (fluoresces under UV, anisaldehyde)



Alcohol **61**

Triethylamine trihydrofluoride (0.083 mL, 82.0 mg, 0.511 mmol, 3 equiv) was added via syringe to a solution of bis-silyl ether **60** (135 mg, 0.170 mmol, 1 equiv) in THF (25 mL) at 0 °C. The reaction was maintained at 0 °C for an additional 30 min, and saturated aqueous sodium bicarbonate (10 mL) was added. The reaction mixture was extracted with 1:1 ethyl acetate in hexanes (3 50-mL portions) and the combined extracts were washed with saturated aqueous sodium chloride, dried over sodium sulfate and concentrated. The residue was purified by flash column chromatography (50% ethyl acetate in hexanes) to provide the alcohol **61** (107 mg, 87%) as a light yellow oil.

^{1}H NMR (400 MHz, C_6D_6), δ: 7.64 (d, 1H, *J* = 9.28 Hz, C4" H), 7.37 (br s, 1H, C8" H), 7.16 (d, 1H, *J* = 9.27 Hz, C3" H), 7.00 (br s, 1H, C6" H), 6.44 (t, 1H, *J* = 2.0 Hz, C10 H), 5.90 (m, 1H, C11 H), 5.54 (s, 1H, C8 H), 5.11 (abq, 2H, *J* = 6.84 Hz, $ArOCH_2OCH_2CH_2OCH_3$), 3.72 (t, 2H, *J* = 4.88 Hz, $ArOCH_2OCH_2CH_2OCH_3$), 3.67 (m, 1H, C13 H), 3.52 (s, 3H, C7" OCH_3), 3.30-3.26 (complex, 4H, $ArOCH_2OCH_2CH_2OCH_3$, C14 H), 3.07 (s, 3H, $ArOCH_2OCH_2CH_2OCH_3$), 3.01 (dd, 1H, *J* = 15.13, 7.08 Hz, C12 βH), 2.80 (s, 1H, C5 H), 2.53 (dd, 1H, *J* = 14.89, 2.44 Hz, C12 αH), 2.27 (s, 3H, C5" CH_3), 1.00 (s, 9H, $OSiC(CH_3)_3(CH_3)_2$), 0.23 (s, 3H, $OSiC(CH_3)_3(CH_3)_2$), 0.06 (s, 3H, $OSiC(CH_3)_3(CH_3)_2$).

FTIR (thin film), cm^{-1}: 3461 (m, OH), 2928 (m), 2202 (w, C≡C), 1813 (s, carbonate C=O), 1725 (m, C=O), 1621 (m), 1257 (s), 1159 (s), 1096 (s).

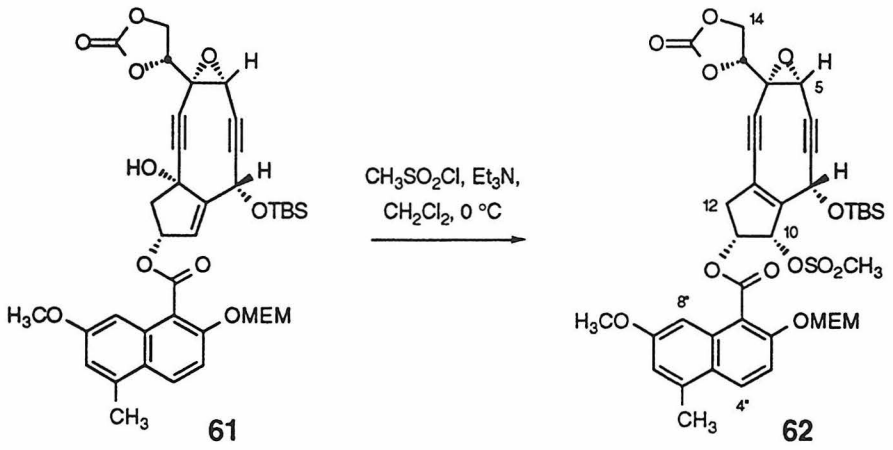
HRMS (FAB): Calc'd for $C_{38}H_{44}NaO_{12}Si$ $[M+Na]^+$: 743.2500

Found: 743.2477

TLC (50% EtOAc in Hexanes), R*f*:

60: 0.40 (fluoresces under UV, anisaldehyde)

61: 0.21 (fluoresces under UV, anisaldehyde)

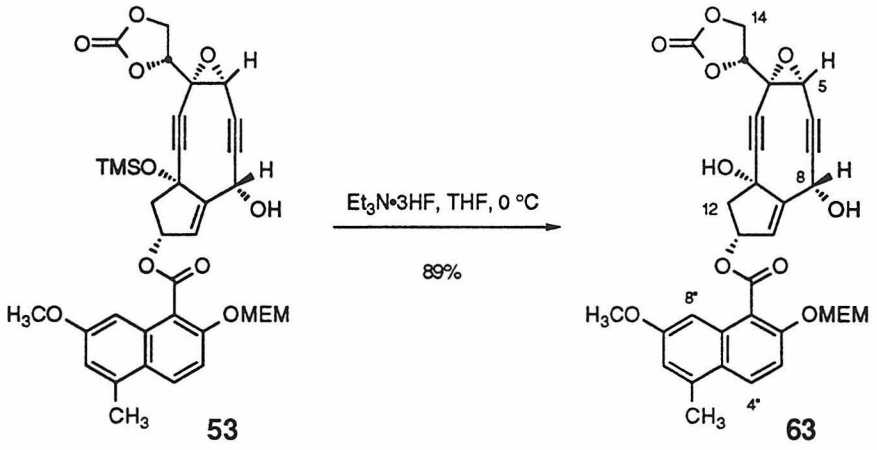


Mesylate **62**

Methanesulfonyl chloride (10.0 μL of a 0.323 M stock solution in dichloromethane, 3.23 x 10^{-3} mmol, 1.6 equiv) was added via syringe to a solution of alcohol **61** (2.00 mg, 2.77 x 10^{-3} mmol, 1 equiv) and triethylamine (10 μL, 7.00 mg, 0.0690 mmol, 25 equiv) in dichloromethane (0.5 mL) at 0 °C. The reaction mixture was held at 0 °C for an additional 10 min, and excess methanesulfonyl chloride was quenched by the addition of water (0.5 mL). The layers were separated, and the aqueous layer was further extracted with 1:1 ethyl acetate in hexanes (3 1-mL portions). The combined organic layers were dried over sodium sulfate and concentrated to a volume of ca. 0.1 mL. The concentrate was purified by flash column chromatography (dichloromethane grading to 10% ethyl acetate in dichloromethane). Fractions containing the mesylate were pooled and concentrated to a volume of ca. 0.1 mL. A 0.5 mL portion of deuteriated benzene (99.5 atom % D) was added and the resulting solution was concentrated to a volume of ca. 0.1 mL. This procedure was repeated 4 times. After the last iteration, the concentrated solution was taken up in approximately 0.4 mL deuteriated benzene (99.95 atom % D) for

^{1}H NMR analysis. Typically, the mesylate **62** was not subjected to column chromatography due to its instability, but was instead carried directly to the next reaction as the crude reaction mixture.

^{1}H NMR (400 MHz, C_6D_6), δ:	7.67 (d, 1H, J = 9.28 Hz, C4" H), 7.38 (m, 1H, C8" H), 7.30-7.00 (obscured, 1H, C3" H), 6.97 (m, 1H, C6" H), 6.12 (d, 1H, J = 5.86 Hz, C10 H), 5.57 (app. q, 1H, J = 5.86 Hz, C11 H), 5.35 (s, 1H, C8 H), 5.13 (abq, 2H, J = 7.08 Hz, $ArOCH_2OCH_2CH_2OCH_3$), 3.78-3.64 (complex, 3H, C13 and C14 H), 3.62 (s, 3H, C7" OCH_3), 3.32 (m, 4H, $ArOCH_2OCH_2CH_2OCH_3$), 3.11 (s, 3H, $ArOCH_2OCH_2CH_2OCH_3$), 2.87 (s, 1H, C5 H), 2.78 (dd, 1H, J = 15.38, 1.50 Hz, C12 αH), 2.55 (dd, 1H, J = 15.38, 6.35 Hz, C12 βH), 2.31 (s, 3H, C5" CH_3), 2.26 (s, 3H, SO_2CH_3), 1.15 (s, 9H, $OSiC(CH_3)_3(CH_3)_2$), 0.47 (s, 3H, $OSiC(CH_3)_3(CH_3)_2$), 0.43 (s, 3H, $OSiC(CH_3)_3(CH_3)_2$).
FTIR (thin film), cm^{-1}:	2923 (s), 1819 (m, carbonate C=O), 1731 (m, C=O), 1460 (m), 1255 (m).
TLC (10% EtOAc in CH_2Cl_2), R*f*:	**61**: 0.13 (fluoresces under UV, anisaldehyde) **62**: 0.39 (fluoresces under UV, anisaldehyde)



Diol **63**

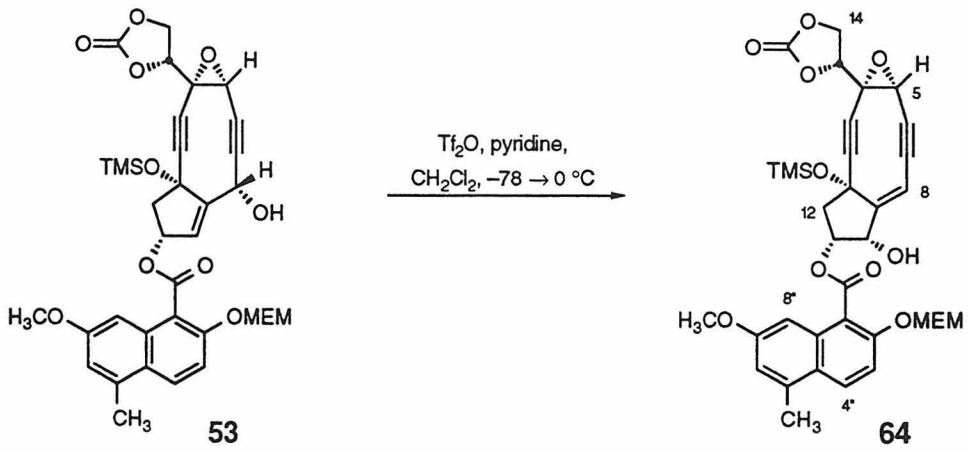
Triethylamine trihydrofluoride (34.0 μL, 34.0 mg, 0.211 mmol, 3 equiv) was added to a solution of alcohol **53** (47.0 mg, 0.0700 mmol, 1 equiv) in THF (0.2 mL) at 0 °C. The solution was kept at this temperature for 2 h, and saturated sodium bicarbonate (0.5 mL) was added. The reaction mixture was diluted with 1:1 ethyl acetate in hexanes (25 mL), dried over sodium sulfate and concentrated. Purification of the residue by flash column chromatography (75% ethyl acetate in hexanes) afforded the diol **63** (38.0 mg, 89%) as a pale yellow powder.

^{1}H NMR (400 MHz, C_6D_6), δ:	7.82 (d, 1H, *J* = 9.22 Hz, C8" H), 7.09 (d, 1H, *J* = 9.28 Hz, C6" H), 6.85 (d, 1H, *J* = 2.15 Hz, C3" H), 6.81 (d, 1H, *J* = 1.26 Hz, C4" H), 6.26 (t, 1H, *J* = 1.95 Hz, C10 H), 5.86 (m, 1H, C11 H), 5.34 (br s, 1H, C8 H), 5.25 (abq, 2H, *J* = 6.69 Hz, $ArOCH_2OCH_2CH_2OCH_3$), 4.51 (t, 1H, *J* = 8.85 Hz, C13 H), 4.42 (dd, 1H, *J* = 8.95, 5.58 Hz, C14 H), 3.77 (s, 3H, C7" OCH_3), 3.71 (m, 1H, $ArOCH_2OCH_2CH_2OCH_3$), 3.66 (m, 1H, $ArOCH_2OCH_2CH_2OCH_3$), 3.53 (s, 1H, C5 H), 3.43 (t, 2H, *J* = 5.09 Hz, $ArOCH_2OCH_2CH_2OCH_3$),3.35 (dd, 1H, *J* = 8.21, 5.58 Hz, C14 H), 3.25 (s, 3H, $ArOCH_2OCH_2CH_2OCH_3$), 3.00 (dd, 1H, *J* = 15.09, 7.07 Hz, C12 βH), 2.50 (s, 3H, C5" CH_3), 2.16 (dd, 1H, *J* = 15.00, 2.34 Hz, C12 αH).
FTIR (thin film), cm^{-1}:	3444 (s, OH), 2924 (s), 2214 (w, C≡C), 1816 (s, carbonate C=O), 1714 (s, C=O), 1621 (s), 1469 (m), 1257 (s), 1160 (s), 1035 (s) cm^{-1}
HRMS (FAB):	Calc'd for $C_{32}H_{30}NaO_{12}$ $[M+Na]^+$: 629.1635 Found: 629.1624

TLC (10% EtOAc in Hexanes), R*f*:

53: 0.58 (fluoresces under UV, anisaldehyde)

63: 0.35 (fluoresces under UV, anisaldehyde)

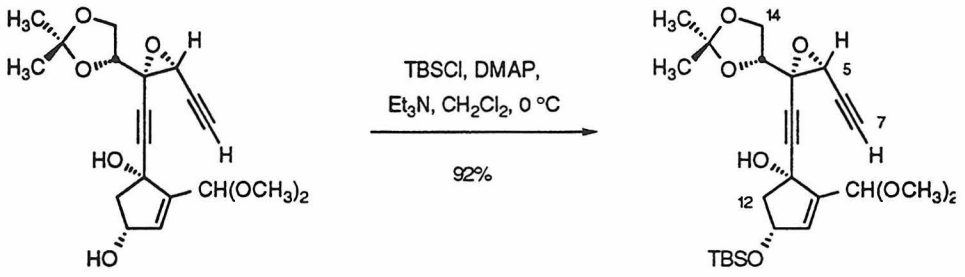


Alcohol **64**

Trifluoromethanesulfonic anhydride (7.60 μL, 12.7 mg, 4.50 x 10^{-3} mmol, 15 equiv) was added via syringe to a solution of alcohol **53** (2.00 mg, 3.00 x 10^{-2} mmol, 1 equiv) and pyridine (7.30 μL, 7.00 mg, 9.00 x 10^{-2} mmol, 30 equiv) in dichloromethane (0.3 mL) at –78 °C. After 30 min at –78 °C, the reaction mixture was warmed to 0 °C for 10 min. Water (0.3 mL) was added, and the reaction mixture was extracted with 1:1 ethyl acetate in hexanes (2 1-mL portions). The combined organics were washed with 10% aqueous hydrochloric acid (1 mL) and saturated aqueous sodium chloride (1 mL), dried over sodium sulfate and concentrated to ca. 0.1 mL. The concentrate was purified by flash column chromatography (25% ethyl acetate in hexanes), and fractions containing the product were pooled and concentrated to a volume of ca. 0.1 mL. A 0.5 mL portion of deuteriated benzene (99.5 atom % D) was added and the resulting solution was concentrated to a volume of ca. 0.1 mL. This procedure was repeated 4 times. After the last iteration, the concentrated solution was taken up in approximately 0.4 mL deuteriated benzene (99.95 atom % D) for ^{1}H NMR analysis. Typically, the alcohol **64** was not

subjected to column chromatography due to its instability, but was instead carried directly to the next reaction as the crude reaction mixture.

^{1}H NMR (400 MHz, C_6D_6), δ:	7.77 (s, 1H, C8" H), 7.64 (d, 1H, *J* = 9.23 Hz, C4" H), 7.50-6.90 (obscured by solvent, 2H, C6", C3" H), 5.46 (m, 1H, C11 H), 5.19 (abq, 2H, *J* = 6.83 Hz, $ArOCH_2OCH_2CH_2OCH_3$), 5.17 (d, 1H, *J* = 1.47 Hz, C8 H), 4.66 (dd, 1H, *J* = 10.50, 6.10 Hz, C10 H), 3.86-3.67 (complex, 4H, $ArOCH_2OCH_2CH_2OCH_3$,C13, C14 H), 3.73 (s, 3H, C7" OCH_3), 3.32 (t, 2H, *J* = 4.89 Hz, $ArOCH_2OCH_2CH_2OCH_3$), 3.25 (t, 1H, *J* = 8.3 Hz, C14 H), 3.18-3.04 (obscured, 1H, C12 βH), 3.10 (s, 3H, $ArOCH_2OCH_2CH_2OCH_3$), 2.76 (d, 1H, *J* = 1.47 Hz, C5 H), 2.36 (dd, 1H, *J* = 13.18, 2.64 Hz, C12 αH), 2.27 (s, 3H, C5" CH_3), 0.14 (s, 9H, $OSi(CH_3)_3$).
TLC (25% EtOAc in Hexanes), R*f*:	**53**: 0.41 (fluoresces under UV, anisaldehyde) **64**: 0.57 (fluoresces under UV, anisaldehyde)



47 **65**

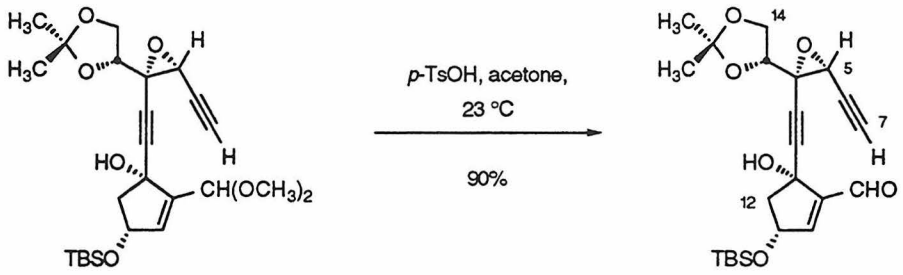
TBS Ether **65**

4-Dimethylaminopyridine (137 mg, 1.08 mmol, 0.5 equiv) was added in one portion to a solution of diol **47** (784 mg, 2.15 mmol, 1 equiv), triethylamine (1.50 mL, 1.09 g, 10.8 mmol, 5 equiv) and *tert*-butyldimethylsilyl chloride (486 mg, 3.23 mmol, 1.5 equiv) in dichloromethane (30 mL) at 0 °C. The reaction mixture was maintained at 0 °C for an additional 20 min, then warmed to 23 °C for 20 h. The reaction mixture was then partitioned between ethyl acetate (50 mL) and water (30 mL). The aqueous layer was extracted with ethyl acetate (2 20-mL portions), and the combined organics were washed with saturated aqueous sodium chloride (30 mL), dried over sodium sulfate and concentrated. Purification of the residue by flash column chromatography (30% ethyl acetate in hexanes) afforded TBS ether **65** (953 mg, 92%) as a colorless oil.

^{1}H NMR (400 MHz, C_6D_6), δ:	6.16 (s, 1H, C10 H), 5.42 (s, 1H, C8 H), 4.83 (m, 1H, C11 H), 4.09 (dd, 1H, *J* = 8.80, 5.84 Hz, C13 H), 3.95 (s, 1H, OH), 3.83 (dd, 1H, *J* = 8.80, 6.96 Hz, C14 H), 3.60 (t, 1H, *J* = 6.24 Hz, C14 H), 3.37 (d, 1H, *J* = 2.72 Hz, C5 H), 3.17 (s, 3H, $CH(OCH_3)_2$), 3.15 (s, 3H, $CH(OCH_3)_2$), 3.14 (dd, 1H, *J* = 13.56, 6.92 Hz, C12 H), 2.52 (dd, 1H, *J* = 13.16, 5.48 Hz, C12 H), 1.99 (d, 1H, *J* = 0.84 Hz, C7 H), 1.45 (s, 3H, $C(CH_3)_2$), 1.20 (s, 3H, $C(CH_3)_2$), 0.95 (s, 9H, $OSiC(CH_3)_3(CH_3)_2$)), 0.046 (s, 3H, $OSiC(CH_3)_3(CH_3)_2$)), 0.029 (s, 3H, $OSiC(CH_3)_3(CH_3)_2$)).
^{13}C NMR (100 MHz, C_6D_6), δ:	142.8, 136.1, 110.7, 99.8, 90.0, 78.5, 77.3, 77.2, 75.2, 74.9, 73.3, 66.8, 58.0, 52.8, 52.3, 50.0, 49.9, 26.4, 26.0, 25.3, 18.2, –4.6.
$[\alpha]_D^{20}$:	+116.31 ° (*c* 6.62, C_6H_6)
FTIR (thin film), cm^{-1}:	3496 (m, OH), 3279 (m, C≡C-H), 2933 (s), 2857 (s), 2127 (w, C≡C), 1469 (m), 1372 (s), 1256 (s), 1214 (s), 1154 (m), 1108 (s), 1074 (s), 838 (s).
HRMS (FAB):	Calc'd for $C_{25}H_{37}O_7Si$ $[M-H]^+$: 477.2309 Found: 477.2304

TLC (70% EtOAc in Hexanes), R*f*: **47**: 0.20 (anisaldehyde)

65: 0.95 (anisaldehyde)



65 66

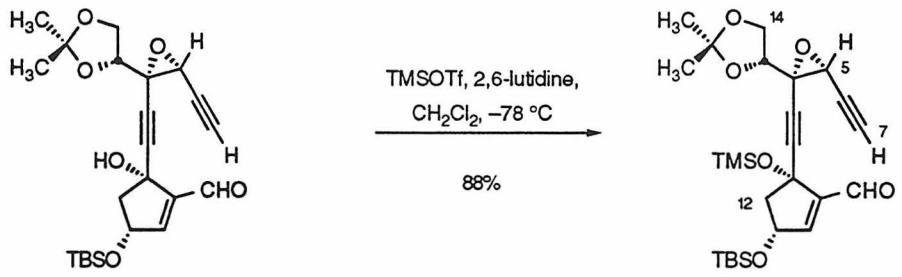
Aldehyde **66**

p-Toluenesulfonic acid (21 mg) was added in one portion to a solution of the dimethyl acetal **65** (248 mg, 0.518 mmol, 1 equiv) in acetone (7 mL). The resultant yellow solution was stirred at 23 °C for 15 min and then neutralized with saturated aqueous sodium bicarbonate (10 mL). The reaction mixture was extracted with 1:1 ethyl acetate/hexanes (3 10-mL portions), and the combined organics were washed with saturated sodium chloride (15 mL), dried over sodium sulfate and concentrated. Purification of the residue by flash column chromatography (5% ethyl acetate in dichloromethane) provided the aldehyde **66** (202 mg, 90%) as a colorless solid, mp 90-92 °C.

^{1}H NMR (400 MHz, C_6D_6), δ:	9.28 (s, 1H, C8 H), 6.03 (d, 1H, *J* = 1.84 Hz, C10 H), 4.76 (td, 1H, *J* = 6.96, 1.84 Hz, C11 H), 4.08 (dd, 1H, *J* = 8.80, 5.88 Hz, C13 H), 3.85 (s, 1H, OH), 3.84 (dd, 1H, *J* = 8.76, 6.60 Hz, C14 H), 3.57 (t, 1H, *J* = 6.56 Hz, C14 H), 3.36 (d, 1H, *J* = 1.48 Hz, C5 H), 3.02 (dd, 1H, *J* = 12.80, 6.92 Hz, C12 H), 2.34 (dd, 1H, *J* = 12.44, 6.96 Hz, C12 H), 2.07 (d, 1H, *J* = 1.84 Hz, C7 H), 1.44 (s, 3H, $C(CH_3)_2$), 1.19 (s, 3H, $C(CH_3)_2$), 0.92 (s, 9H, $OSiC(CH_3)_3(CH_3)_2$)), –0.0035 (s, 3H, $OSiC(CH_3)_3(CH_3)_2$)), –0.0365 (s, 3H, $OSiC(CH_3)_3(CH_3)_2$)).
^{13}C NMR (100 MHz, C_6D_6), δ:	189.2, 151.8, 145.6, 110.8, 88.5, 78.3, 77.0, 75.0, 73.5, 73.3, 66.9, 57.9, 52.1, 50.1, 50.0, 26.4, 25.9, 25.4, 18.1, –4.7, –4.8.
$[\alpha]_D^{20}$:	+181.37 ° (*c* 2.04, C_6H_6)
FTIR (thin film), cm^{-1}:	3431 (m, OH), 3279 (m, C≡C-H), 2932 (s), 2857 (s), 2128 (w, C≡C), 1686 (s, C=O), 1471 (m), 1357 (m), 1258 (s), 1216 (m), 1119 (m), 1076 (s), 838 (s).
HRMS (FAB):	Calc'd for $C_{23}H_{31}O_6Si$ $(M-H)^+$: 431.1890 Found: 431.1888

TLC (30% EtOAc in Hexanes), R*f*: **65**: 0.28 (anisaldehyde)

66: 0.31 (UV, anisaldehyde)

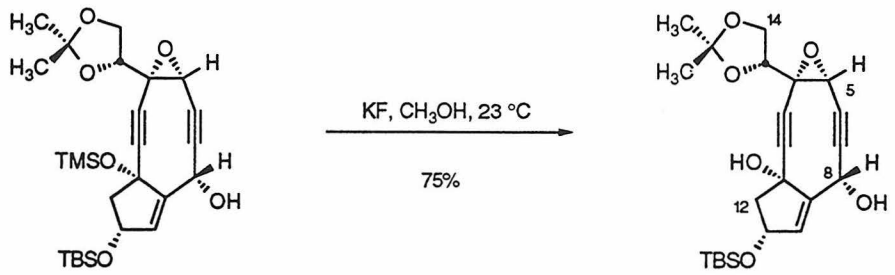


66 67

TMS Ether **67**

2,6-Lutidine (4.71 mL, 4.34 g, 40.5 mmol, 10 equiv) and trimethylsilyl trifluoromethanesulfonate (3.91 mL, 4.50 g, 20.2 mmol, 5 equiv) were added sequentially via syringe to a solution of aldehyde **66** (1.75 g, 4.05 mmol, 1 equiv) in dichloromethane (100 mL) at –78 °C. The resultant solution was maintained at –78 °C for an additional 20 min, and excess trimethylsilyl trifluoromethanesulfonate was quenched by the addition of triethylamine (5 mL) and methanol (5 mL). The reaction mixture was warmed to 23 °C and diluted with 1:1 ethyl acetate/hexanes (100 mL). The mixture was washed with water (2 50-mL portions) and saturated aqueous sodium chloride (50 mL). The organics were then dried over sodium sulfate and concentrated. Purification of the residue by flash column chromatography (20% ethyl acetate in hexanes) afforded the TMS ether **67** (1.79 g, 88%) as a pale yellow oil.

^{1}H NMR (400 MHz, C_6D_6), δ:	9.78 (s, 1H, C8 H), 6.37 (d, 1H, *J* = 1.44 Hz, C10 H), 4.74 (td, 1H, *J* = 6.96, 1.84 Hz, C11 H), 4.10 (dd, 1H, *J* = 8.76, 5.84 Hz, C13 H), 3.91 (dd, 1H, *J* = 8.76, 6.60 Hz, C14 H), 3.60 (t, 1H, *J* = 6.60 Hz, C14 H), 3.33 (d, 1H, *J* = 1.44 Hz, C5 H), 3.16 (dd, 1H, *J* = 12.84, 7.32 Hz C12 H), 2.40 (dd, 1H, *J* = 12.84, 6.60 Hz, C12 H), 2.07 (d, 1H, *J* = 1.44 Hz, C7 H), 1.43 (s, 3H, $C(CH_3)_2$), 1.18 (s, 3H, $C(CH_3)_2$), 0.94 (s, 9H, $OSiC(CH_3)_3(CH_3)_2$), 0.40 (s, 9H, $OSi(CH_3)_3$), 0.01 (s, 6H, $OSiC(CH_3)_3(CH_3)_2$).
^{13}C NMR (100 MHz, C_6D_6), δ:	187.5, 147.1, 146.6, 110.7, 88.5, 79.8, 78.2, 76.9, 75.3, 74.2, 73.3, 66.9, 57.8, 55.2, 50.0, 26.4, 25.8, 25.2, 18.1, 2.0, –4.8.
$[\alpha]_D^{20}$:	+91.02 ° (*c* 2.65, C_6H_6)
FTIR (thin film), cm^{-1}:	3281 (m, C≡C-H), 2954 (s), 2889 (s), 2857 (m), 2131 (w, C≡C), 1697 (s, C=O), 1470 (m), 1373 (s), 1256 (m), 1077 (s), 884 (m), 839 (s).
TLC (30% EtOAc in Hexanes), R*f*:	**66**: 0.37 (UV, anisaldehyde) **67**: 0.61 (UV, anisaldehyde)



68 **69**

Cyclic alcohol **68**

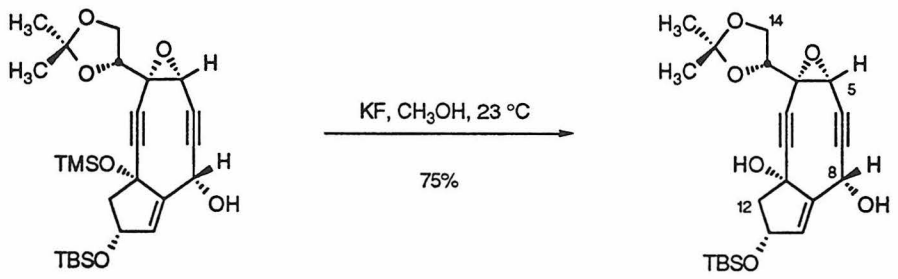
Lithium hexamethyldisilazide (0.560 mL of a 1.0 M solution in hexanes, 0.560 mmol, 1.2 equiv) was added over a 2 min period to a suspension of aldehyde **67** (223 mg, 0.467 mmol, 1 equiv) and anhydrous cerium(III) chloride (340 mg, 1.40 mmol, 3 equiv) in THF (25 mL) at –78 °C. After maintaining the reaction mixture at –78 °C for an additional 10 min, excess base was quenched by addition of saturated aqueous ammonium chloride (5 mL) and the reaction mixture was warmed to 23 °C. The reaction mixture was partitioned between 1:1 ethyl acetate/hexanes (25 mL) and water (25 mL), and the layers were separated. The aqueous layer was further extracted with 1:1 ethyl acetate/hexanes (2 25-mL portions), and the combined organics were washed with saturated sodium chloride (25 mL), dried over sodium sulfate and concentrated. The residue was purified by flash column chromatography (10% ethyl acetate in hexanes grading to 20% ethyl acetate in hexanes) to provide the alcohol **68** (183 mg, 82%) as a pale orange oil.

^{1}H NMR (400 MHz, C_6D_6), δ: 5.87 (t, 1H, *J* = 1.74 Hz, C10 H), 5.16 (m, 1H, C8 H), 4.67 (m, 1H, C11 H), 3.82 (dd, 1H, *J* = 8.56, 5.85 Hz, C13 H), 3.66 (dd, 1H, *J* = 8.54, 6.54 Hz, C14 H), 3.50 (t, 1H, *J* = 6.01 Hz, C14 H), 3.04 (s, 1H, C5 H), 2.95 (dd, 1H, *J* = 12.89, 6.97 Hz, C12 βH), 2.19 (dd, 1H, *J* = 12.87, 5.87 Hz, C12 αH), 1.40 (s, 3H, $C(CH_3)_2$), 1.13 (s, 3H, $C(CH_3)_2$), 0.86 (s, 9H, $OSiC(CH_3)_3(CH_3)_2$), 0.27 (s, 9H, $OSi(CH_3)_3$), –0.06 (s, 3H, $OSiC(CH_3)_3(CH_3)_2$), –0.07 (s, 3H, $OSiC(CH_3)_3(CH_3)_2$).

FTIR (thin film), cm^{-1}: 3428 (m, OH), 2953 (s), 2857 (m), 1467 (m), 1372 (m), 1254 (s), 1074 (s).

TLC (30% EtOAc in Hexanes), R*f*: **67**: 0.46 (anisaldehyde)

68: 0.38 (anisaldehyde)

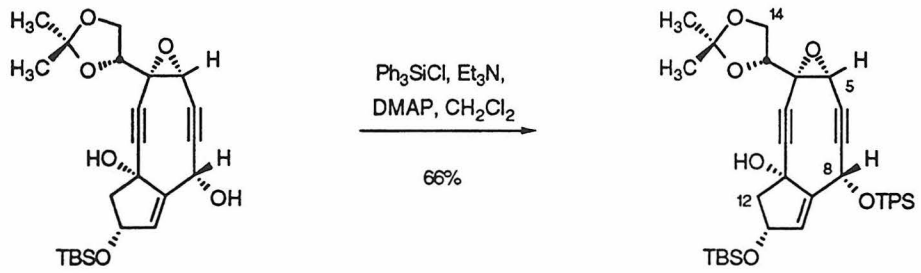


68 69

Diol **69**

Potassium fluoride (98.0 mg, 1.67 mmol, 10 equiv) was added in one portion to a solution of alcohol **68** (80.0 mg, 0.167 mmol, 1 equiv) in methanol (8 mL) at 23 °C. The solution was maintained at 23 °C for 2 h, then diluted with water (20 mL). The reaction mixture was extracted with ethyl acetate (3 25-mL portions), and the combined extracts were washed with saturated aqueous sodium chloride (25 mL), dried over sodium sulfate, and concentrated. The residue was purified by flash column chromatography (40% ethyl acetate in hexanes) to afford diol **69** (54 mg, 75%) as a pale orange oil.

^{1}H NMR (400 MHz, C_6D_6), δ:	6.01 (t, 1H, *J* = 1.81 Hz, C10 H), 5.28 (br s, 1H, C8 H), 4.61 (m, 1H, C11 H), 3.96 (dd, 1H, *J* = 8.74, 5.79 Hz, C13 H), 3.79 (dd, 1H, *J* = 8.70, 6.62 Hz, C14 H), 3.62 (t, 1H, *J* = 6.41 Hz, C14 H), 3.18 (s, 1H, C5 H), 2.87 (dd, 1H, *J* = 13.52, 6.96 Hz, C12 βH), 2.79 (br s, 1H, OH), 2.13 (dd, 1H, *J* = 13.56, 4.91 Hz, C12 αH), 2.03 (br s, 1H, OH), 1.51 (s, 3H, $C(CH_3)_2$), 1.24 (s, 3H, $C(CH_3)_2$), 0.93 (s, 9H, $OSiC(CH_3)_3(CH_3)_2$), 0.01 (s, 3H, $OSiC(CH_3)_3(CH_3)_2$), 0.00 (s, 3H, $OSiC(CH_3)_3(CH_3)_2$).
FTIR (thin film), cm^{-1}:	3422 (m, OH), 2929 (s), 2856 (m), 1458 (m), 1373 (s) 1256 (s), 1216 (m), 1074 (s).
TLC (40% EtOAc in Hexanes), R*f*:	**68**: 0.53 (anisaldehyde) **69**: 0.26 (anisaldehyde)

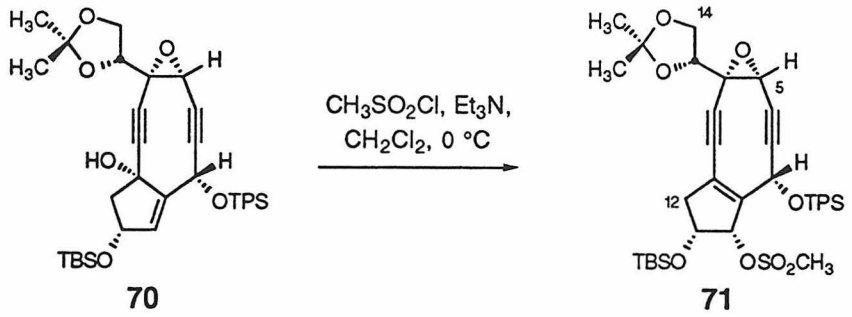


69 **70**

Tertiary alcohol **70**

Triphenylsilyl chloride (27.0 mg, 0.0902 mmol, 1.5 equiv) was added to a solution of diol **69** (26. mg, 6.0 x 10^{-2} mmol, 1 equiv), triethylamine (42 μL, 30 mg, 0.30 mmol, 5 equiv), and DMAP (4 mg, 3 x 10^{-2} mmol, 0.5 equiv) in dichloromethane (1.5 mL) at 23 °C. The reaction mixture was maintained at 23 °C for 2.5 h, and partitioned between water (5 mL) and 1:1 ethyl acetate in hexanes (5 mL). The aqueous layer was further extracted with 1:1 ethyl acetate/hexanes (2 5-mL portions) and the combined organics were washed with saturated aqueous sodium chloride (15 mL), dried over sodium sulfate, and concentrated. Purification of the residue by flash column chromatography (20% ethyl acetate in hexanes) afforded the alcohol **70** (28 mg, 66%) as a pale yellow powder.

^{1}H NMR (400 MHz, C_6D_6), δ:	7.87 (m, 6H, $OSi(C_6\mathbf{H}_5)_3$), 7.70 (m, 3H, $OSi(C_6\mathbf{H}_5)_3$), 7.25 (m, 6H, $OSi(C_6\mathbf{H}_5)_3$), 6.33 (t, 1H, *J* = 1.79 Hz, C10 H), 5.76 (t, 1H, J = 1.41 Hz, C8 H), 4.64 (m, 1H, C11 H), 3.92 (dd, 1H, *J* = 8.64, 5.69 Hz, C13 H), 3.74 (dd, 1H, *J* = 8.67, 6.60 Hz, C14 H), 3.54 (t, 1H, *J* = 6.30 Hz, C14 H), 3.05 (s, 1H, C5 H), 2.84 (dd, 1H, *J* = 13.45, 6.96 Hz, C12 βH), 2.08 (dd, 1H, *J* = 13.51, 5.00 Hz, C12 αH), 1.49 (s, 3H, $C(C\mathbf{H}_3)_2$), 1.22 (s, 3H, $C(C\mathbf{H}_3)_2$), 0.91 (s, 9H, $OSiC(C\mathbf{H}_3)_3(CH_3)_2$), 0.27 (s, 9H, $OSi(C\mathbf{H}_3)_3$), –0.04 (s, 6H, $OSiC(CH_3)_3(C\mathbf{H}_3)_2$).
FTIR (thin film), cm^{-1}:	3437 (m, OH), 2929 (m), 2856 (m), 1589 (m), 1428 (m), 1358 (m), 1255 (m), 1117(s), 1072 (s).
TLC (40% EtOAc in Hexanes), R*f*:	**69**: 0.21 (anisaldehyde) **70**: 0.55 (UV, anisaldehyde)



Mesylate **71**

Methanesulfonyl chloride (50 μL of a 1.3 mM stock solution in dichloromethane, 6.5 x 10^{-2} mmol, 22 equiv) was added via syringe to a solution of alcohol **70** (2.0 mg, 2.9 x 10^{-3} mmol, 1 equiv) and triethylamine (10 μL, 7.0 mg, 0.073 mmol, 25 equiv) in dichloromethane (0.2 mL) at 0 °C. The reaction mixture was held at 0 °C for an additional 10 min, and excess methanesulfonyl chloride was quenched by the addition of water (0.5 mL). The layers were separated, and the aqueous layer was further extracted with 1:1 ethyl/acetate in hexanes (3 1-mL portions). The combined organic layers were dried over sodium sulfate and concentrated to a volume of ca. 0.1 mL. The concentrate was purified by flash column chromatography (dichloromethane grading to 10% ethyl acetate in dichloromethane). Fractions containing mesylate **71** were pooled and concentrated to a volume of ca. 0.1 mL. A 0.5 mL portion of deuteriated benzene (99.5 atom % D) was added and the resulting solution was concentrated to a volume of ca. 0.1 mL. This procedure was repeated 4 times. After the last iteration, the concentrated solution was taken up in approximately 0.4 mL deuteriated benzene (99.95 atom % D) for ^{1}H NMR analysis. Typically, the mesylate **71** was not subjected to column chromatography due to

its instability, but was instead carried directly to the next reaction as the crude reaction mixture.

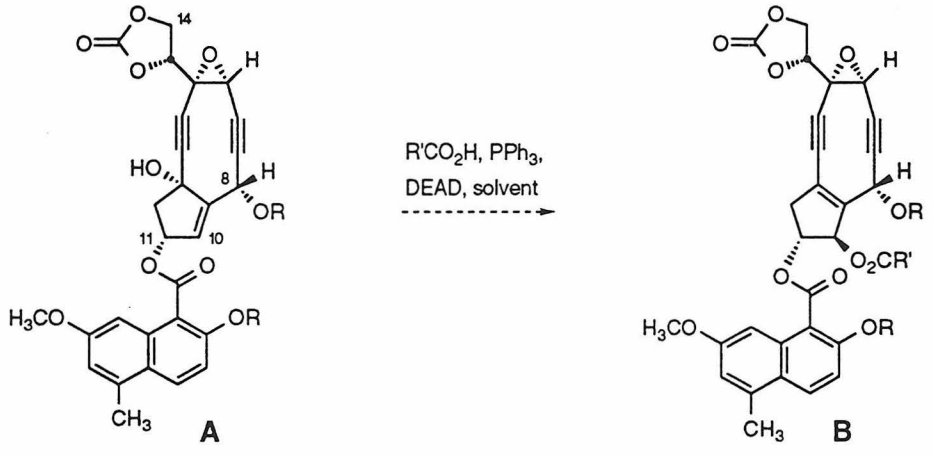
^{1}H NMR (400 MHz, C_6D_6), δ:	7.96 (d, 3H, *J* = 6.59 Hz, $OSi(C_6\mathbf{H}_5)_3$), 7.72 (dd, 2H, *J* = 7.08, 1.71 Hz, $OSi(C_6\mathbf{H}_5)_3$), 7.30-7.22 (complex, 10H, $OSi(C_6\mathbf{H}_5)_3$), 5.81 (d, 1H, *J* = 7.08 Hz, C10 H), 5.48 (d, 1H, *J* = 2.69 Hz, C8 H), 3.97 (dd, 1H, *J* = 8.79, 5.86 Hz, C13 H), 3.91 (d, 1H, *J* = 6.84 Hz, C11 H), 3.79 (dd, 1H, *J* = 8.79, 6.59 Hz, C14 H), 3.57 (t, 1H, *J* = 6.10 Hz, C14 H), 3.06 (s, 1H, C5 H), 2.51 (ddd, 1H, *J* = 12.94, 7.08, 2.69 Hz, C12 βH), 2.24 (dd, 1H, *J* = 15.86, 6.83 Hz, C12 αH), 2.20 (s, 3H, $OSO_2C\mathbf{H}_3$), 1.54 (s, 3H, $C(C\mathbf{H}_3)_2$), 1.24 (s, 3H, $C(C\mathbf{H}_3)_3$), 0.95 (s, 9H, $OSiC(C\mathbf{H}_3)(CH_3)_2$), 0.14 (s, 3H, $OSiC(CH_3)_3(C\mathbf{H}_3)_2$), 0.03 (s, 3H, $OSiC(CH_3)_3(C\mathbf{H}_3)_2$).
TLC (40% EtOAc in CH_2Cl_2), R*f*:	**70**: 0.85 (UV, anisaldehyde) **71**: 0.74 (UV, anisaldehyde)

Chapter 3

Intermediate Synthetic Strategies

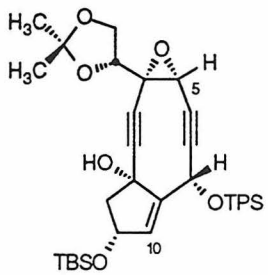
An Allylic Mitsunobu Inversion Approach

Drawing upon the observations made about the rearrangement behavior of the substrates discussed in Chapter 2, it was envisioned that the stereoselectivity necessary for a successful allylic transposition reaction might be achieved under Mitsunobu conditions.[62] Although little precedent exists for the application of the Mitsunobu esterification to either the inversion of tertiary alcohols or allylic transposition reactions, it was anticipated that the desired transformation would be favorable using a substrate having the general structure **A**. Activation of the tertiary alcohol would be assisted by its being both allylic and propargylic; however, the steric demands of the C-1 oxyphosphonium intermediate should disfavor direct inversion and instead favor attack of the nucleophile at the C-10 position to afford a product having the general structure **B**. The stereoselectivity of the reaction would also be expected to proceed in the requisite sense, with the naphthoate ester effectively blocking attack from the bottom face of **A** (as drawn). Finally, it was predicted that the mechanism of the Mitsunobu inversion, known to disfavor the formation of carbocationic intermediates, would preclude the formation of the dioxolenium intermediates that were observed previously (cf. Ch. 2, Scheme IX).

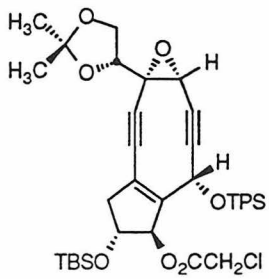


Preliminary studies of this reaction sequence were carried out with the tertiary alcohol **70**. Reaction of this intermediate with chloroacetic acid (25 equiv),

triphenylphosphine (25 equiv), and diethyl azodicarboxylate (DEAD, 25 equiv) in benzene at 23 °C[63] afforded a product that was initially assigned as the desired rearranged ester **73** (in 16-18% yield as determined by ^{1}H NMR integration against trans-1,2-dichloroethylene added as an internal standard). This structural assignment was based on several considerations, including the observation that the components of both substrate **70** and chloroacetic acid were visible in a 1:1 ratio in the ^{1}H NMR spectrum of the product. Furthermore, comparison of the changes in the proton chemical shifts and the coupling constants of the alcohol **70** and the product were consistent with the formation of ester **73**.[56] Comparison of the ^{1}H NMR spectrum of the reaction product with the spectra of other well-characterized intermediates, both rearranged and non-rearranged, also supported the assignment of the product as ester **73**. For further assistance in the determination of the regiochemistry of the product, the C-H coupling constant at C-10 was determined. The magnitude of this coupling constant, generally indicative of the hybridization of the carbon center,[68] was found to be borderline between the values expected for sp^2 and sp^3 centers and consequently of little aid in the assignment of the structure. Believing that the desired transformation had taken place, studies to optimize both the degree of functionalization of the reaction substrate and the yield of the product were initiated.



70

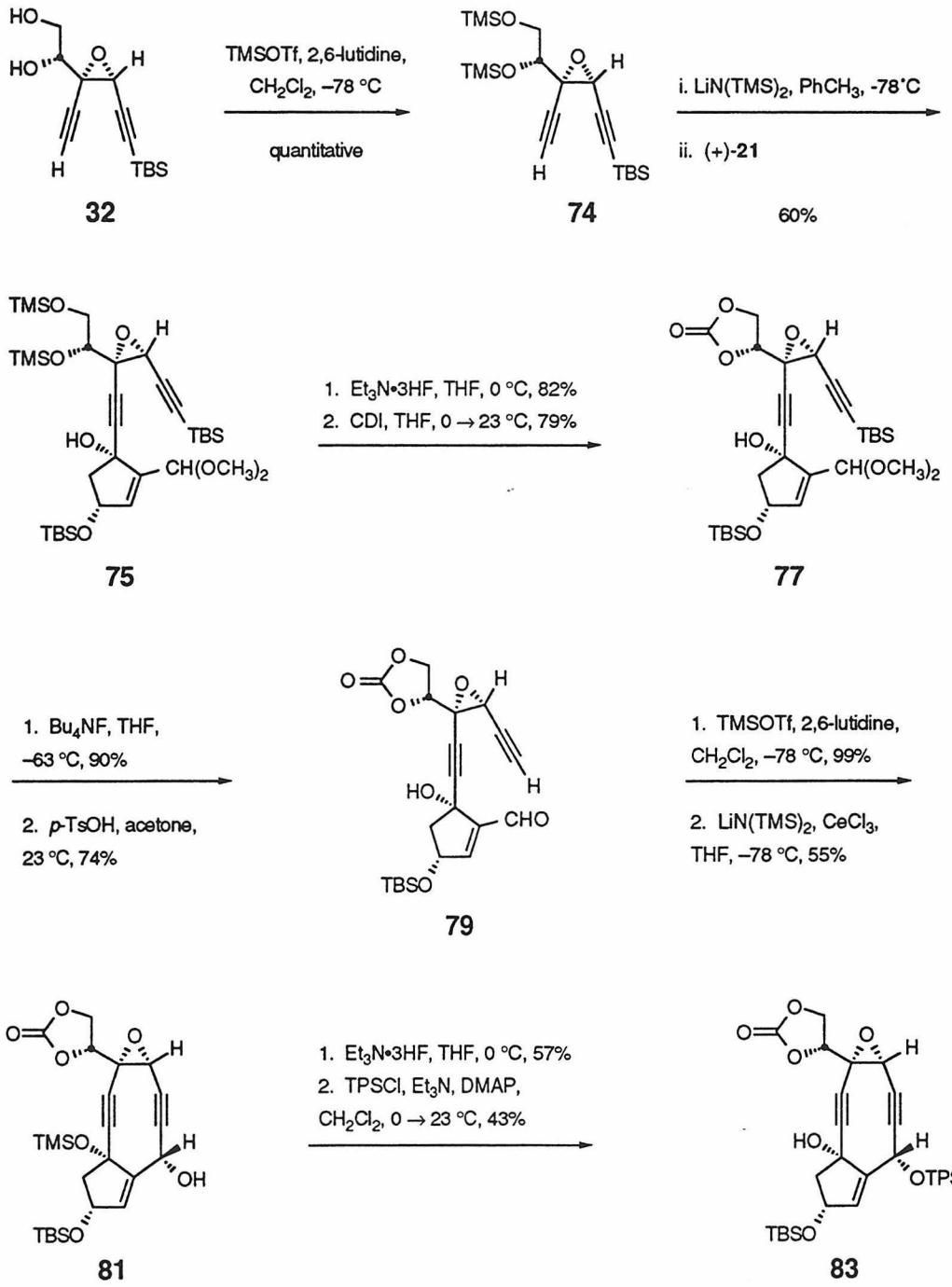


73

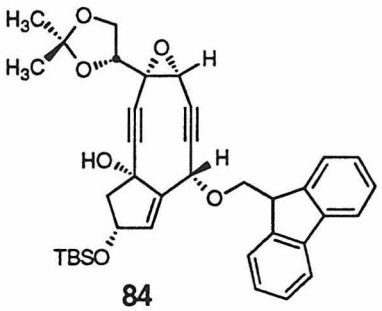
With the intention of carrying out this reaction on a system bearing more of the functionalization present within the aglycone **6**, an ethylene carbonate-containing intermediate was prepared (Scheme XII). In anticipation of the selective removal of the

C-13 – C-14 diol protecting groups in the presence of the C-10 TBS ether, the diol **32** was treated with TMSOTf (12 equiv) and 2,6-lutidine (20 equiv) in dichloromethane at –78 °C to afford the epoxydiyne intermediate **74** in quantitative yield.[54] Deprotonation of **74** (1.02 equiv) with $LiN(TMS)_2$ (1.05 equiv) in toluene at –78 °C was followed by addition of the enone dimethyl acetal (+)-**21** (1.0 equiv) to provide the coupled tertiary alcohol **75** in 60% yield after flash column chromatography. The trimethylsilyl groups were selectively cleaved by treatment of intermediate **75** with triethylamine trihydrofluoride (3 equiv) in THF at 0 °C.[32] The carbonate group was then introduced by treatment with carbonyldiimidazole (1.2 equiv) in THF, affording carbonate **77** in 65% overall yield from **75**.[53] Selective removal of the acetylenic TBS proved to be nontrivial, as both the C-10 TBS ether and the ethylene carbonate were found to be labile under many of the deprotection conditions examined. After extensive investigation, it was determined that treatment of **77** with TBAF (2 equiv) in THF at –63 °C selectively cleaved the acetylenic TBS group to provide the free acetylene (**78**) in 90% yield. Subsequent hydrolysis of the dimethyl acetal with *p*-toluenesulfonic acid in acetone at 23 °C afforded the α,β-unsaturated aldehyde **79** in 74% yield.[65] The tertiary alcohol of **79** was silylated in 99% yield with TMSOTf (5 equiv) and 2,6-lutidine (10 equiv) in dichloromethane at –78 °C.[54] Closure of the nine-membered ring was effected with $LiN(TMS)_2$ (1 equiv) and cerium(III) chloride (3 equiv) in THF at –78 °C, producing secondary alcohol **81** in 55% yield.[13,19] Removal of the TMS group with triethylamine trihydrofluoride (3 equiv) in THF at 0 °C[32] was followed by selective silylation of the secondary alcohol (**82**) with TPSCl (1.3 equiv), triethylamine (5 equiv), and DMAP (0.5 equiv) in dichloromethane at 0 °C[66] to provide the carbonate-containing intermediate **83** in 25% overall (unoptimized) yield from **81**. Surprisingly, the tertiary alcohol **83** was inert to the Mitsunobu conditions utilized for the transformation of **70**, indicating that the ethylene carbonate was deactivating the tertiary alcohol, likely through an inductive effect.

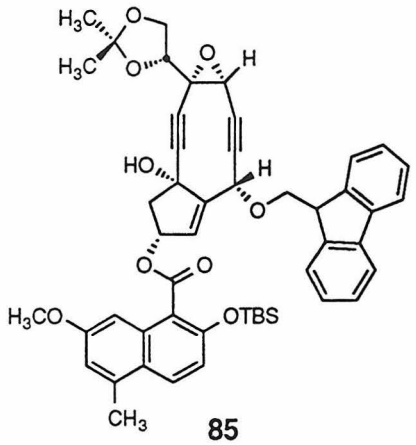
Scheme XII


HO
HO
O
H
H
TBS
32
TMSOTf, 2,6-lutidine,
CH_2Cl_2, –78 °C
quantitative
TMSO
TMSO
O
H
H
TBS
74
i. $LiN(TMS)_2$, $PhCH_3$, -78°C
ii. (+)-21
60%
TMSO
TMSO
O
H
HO
TBS
$CH(OCH_3)_2$
TBSO
75
1. $Et_3N{\bullet}3HF$, THF, 0 °C, 82%
2. CDI, THF, 0 → 23 °C, 79%
O
O
O
O
H
HO
TBS
$CH(OCH_3)_2$
TBSO
77
1. Bu_4NF, THF,
–63 °C, 90%
2. p-TsOH, acetone,
23 °C, 74%
O
O
O
O
H
HO
H
CHO
TBSO
79
1. TMSOTf, 2,6-lutidine,
CH_2Cl_2, –78 °C, 99%
2. $LiN(TMS)_2$, $CeCl_3$,
THF, –78 °C, 55%
O
O
O
O
H
TMSO
H
OH
TBSO
81
1. $Et_3N{\bullet}3HF$, THF, 0 °C, 57%
2. TPSCl, Et_3N, DMAP,
CH_2Cl_2, 0 → 23 °C, 43%
O
O
O
O
H
HO
H
OTPS
TBSO
83

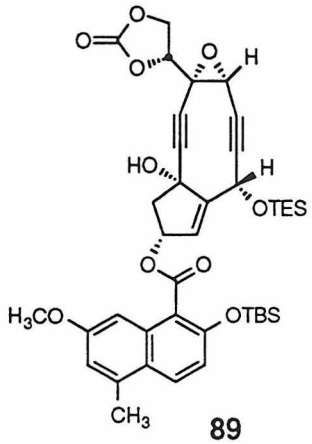
Concurrent with these efforts, additional studies carried out by Dr. Y. Wu in this research group indicated that methyl diphenylphosphine was superior to triphenylphosphine in effecting the esterification of structurally similar substrates. When the reaction was carried out with the alcohol **84** and 4-azidobutyric acid (10 equiv), methyl diphenylphosphine (10 equiv), and DEAD (10 equiv) in benzene at 5 °C, the coupled product was obtained in 67% yield as determined by ^{1}H NMR integration against an internal standard.[69] Subsequently, the incrementally more functionalized intermediates **85**, having the naphthoate ester in place, and **89**, having both the ethylene carbonate and the naphthoate ester present, were found to undergo the esterification reaction with the 2-nitrobenzyl protected hydroxy acid **91** under the new conditions.[70]



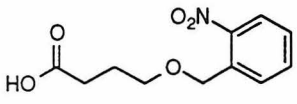
84



85

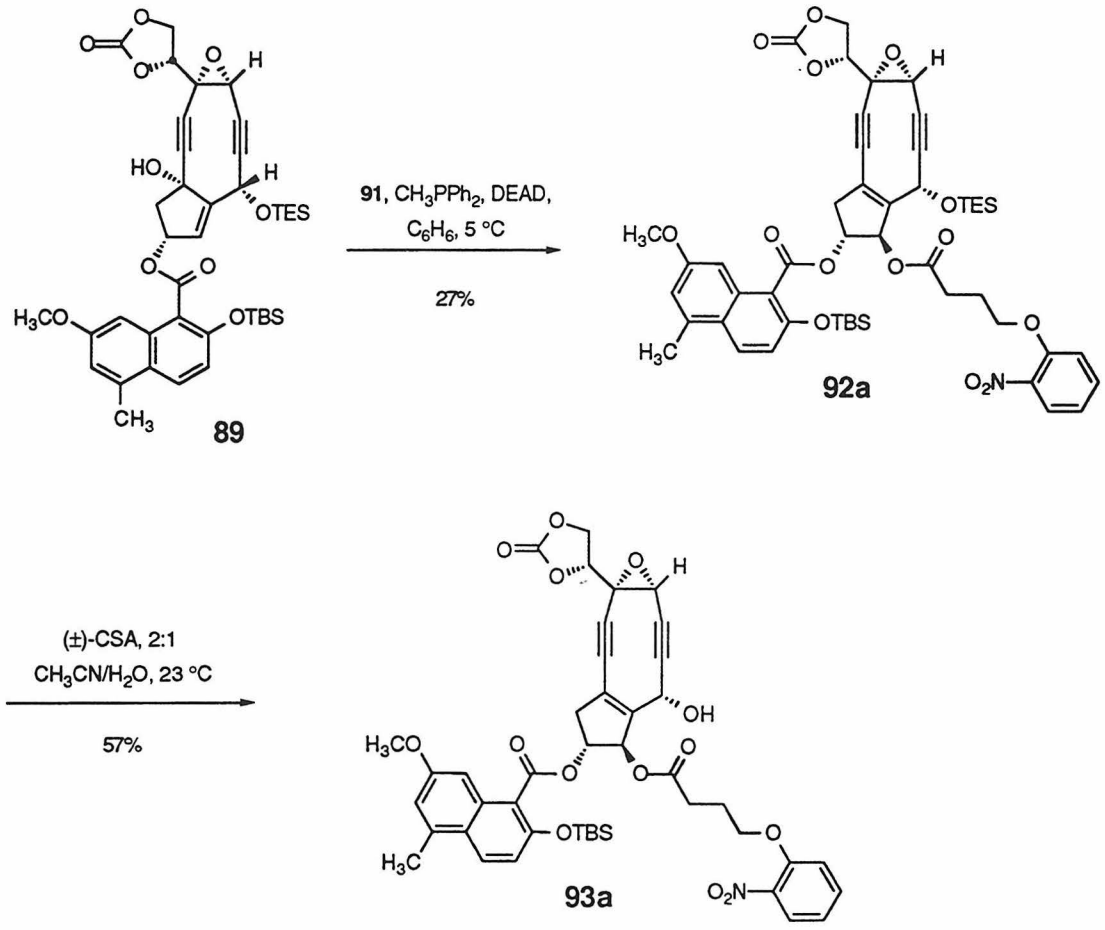


89



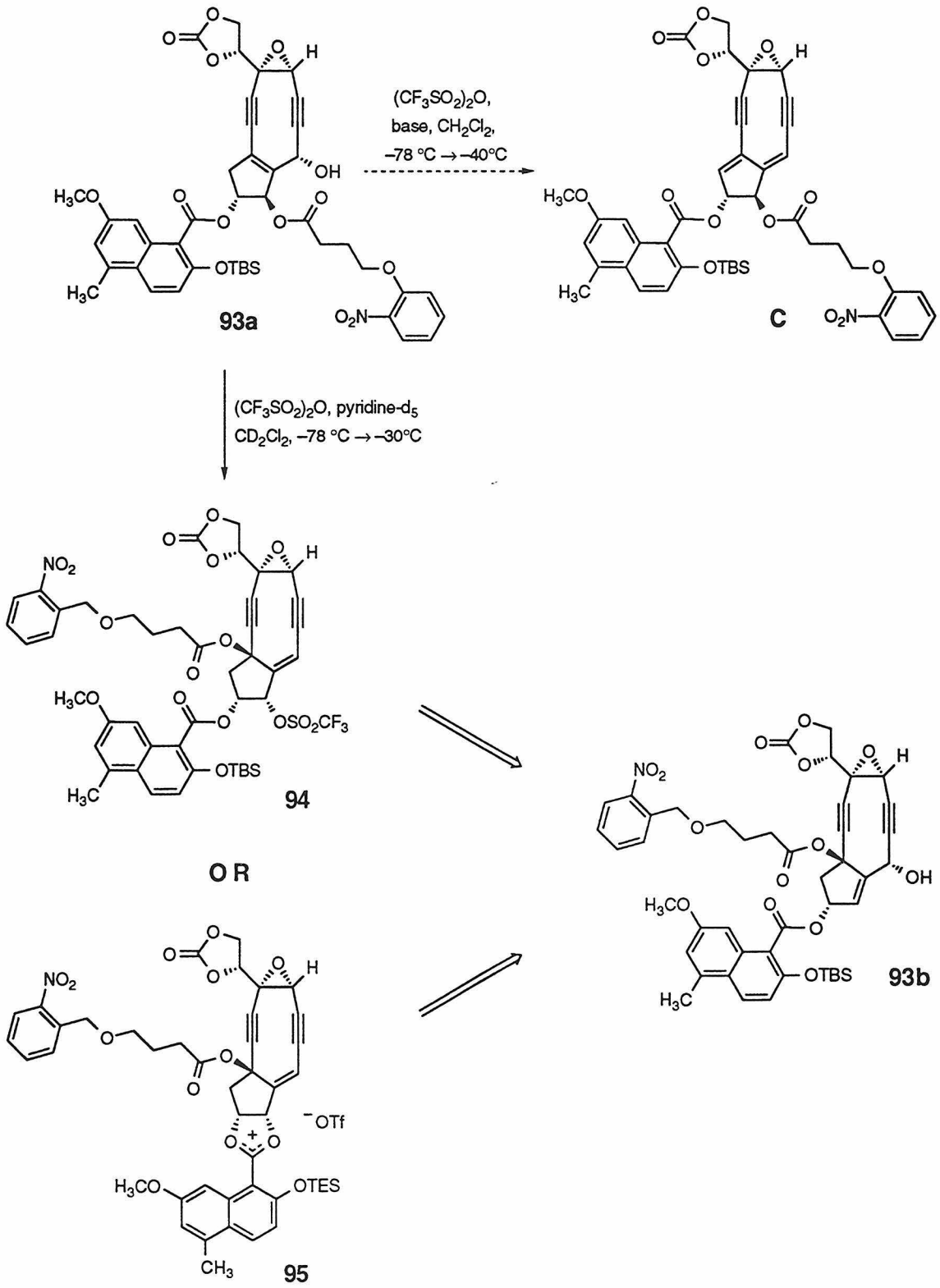
91

Scheme XIII



The product derived from the coupling of **89** and **91**, assigned as structure **92a** (Scheme XIII), was quantitated (27% yield from **89**) and purified by reverse-phase HPLC.[72] The diester (**92a**) was next subjected to deprotection-elimination studies. Treatment of the esterification product **92a** with (±)-camphorsulfonic acid (5 equiv) in a 2:1 mixture of acetonitrile and water at 23 °C provided the corresponding alcohol in 57% yield, assigned as structure **93a**. A number of elimination conditions were examined for the conversion of **93a** to the epoxydienediyne (**C**, Scheme XIV), most notably triflic anhydride and pyridine in dichloromethane at –78 °C. Under these conditions, conversion

Scheme XIV


(CF3SO2)2O,
base, CH2Cl2,
–78 °C → –40°C
93a
C
(CF3SO2)2O, pyridine-d5
CD2Cl2, –78 °C → –30°C
94
O R
95
93b
OTBS
OTES
OTf
OSO2CF3
NO2
OH

to a new product could be observed by thin-layer chromatography, but could not be isolated after aqueous work-up of the reaction mixture. The lack of success in isolating the supposed dienediyne **C** prompted a low-temperature study of the elimination reaction. Accordingly, the alcohol assigned as **93a** was taken up in deuteriated dichloromethane and placed in an NMR tube, where it was cooled to –78 °C. Deuteriated pyridine (20 equiv) and triflic anhydride (10 equiv) were added to the cold reaction mixture, and the NMR tube was quickly inserted into an NMR spectrometer whose probe had been cooled to –70 °C. Unreacted starting material was observed by ^{1}H NMR at this temperature, so the reaction was gradually warmed in the probe of the instrument and the progress of the reaction was monitored by ^{1}H NMR spectroscopy. When the temperature of the probe reached –30 °C, clean conversion to a new product was observed. The signals for this product did not correspond to the expected dienediyne **C**, but instead were consistent with either triflate **94** or dioxolenium ion **95**, neither of which could have been derived from the alcohol **93a**. The origin of the product (**94** or **95**) could best be explained by the triflic anhydride-induced rearrangement of a substrate having the structure **93b**, which would result from the direct inversion of the tertiary alcohol of Mitsunobu substrate **89**.

It appeared as though the same structural and electronic features that were expected to favor the allylic transposition during the Mitsunobu reaction of this substrate, namely the coupling of the allylic and propargylic natures of the C-1 alcohol, served to activate the alcohol for direct displacement. Once the regiochemistry of the esterification reaction was unequivocally assigned, this strategy was discontinued.

Revisitation of an Alternate Ring Closure Strategy

Within this research group, early studies directed toward the preparation of the epoxydienediyne core of neocarzinostatin chromophore had shown that the α,β-unsaturated aldehyde **96** (Figure 1) failed to cyclize to the desired nine-membered ring alcohol upon treatment with $LiN(TMS)_2$ in THF at –78 °C.[67] The α,β-unsaturated aldehyde **13**, however, proved to be an excellent substrate for the ring-closure reaction, and eventually served as an intermediate in the synthetic sequence providing the functionalized core structure **5** (cf. Ch. 1, Scheme II).[13,19] A rationale for the differential behavior under the ring-closure was developed upon inspection of molecular models of **96** and **13**. The C-7 carbon of **96** is thought to be nearly coplanar with the C-8 carbonyl group, rendering the trajectory necessary for nucleophilic addition of the acetylide into the aldehyde carbonyl inaccessible without significant distortion of the molecule. On the other hand, the C-7 carbon of enal **13** can be positioned within a more favorable trajectory for nucleophilic addition into the C-8 carbonyl.

The enal **96** bore no substitution at the C-10 and C-11 positions, and the possibility of using substituents at these positions to bend the C-8 carbonyl out of plane to favor the proper trajectory for acetylide addition was considered. Accordingly, a direct synthesis of the α,β-unsaturated aldehyde **103**, having bulky triisopropylsilyl and *tert*-butyldimethylsilyl ethers at C-10 and C-11, respectively, was developed.

Reaction of the tertiary alcohol **65** under Mitsunobu conditions (chloroacetic acid (10 equiv), triphenylphosphine (10 equiv), and DEAD (10 equiv) in benzene at 23 °C) afforded a mixture of two products (Scheme XV).[63] In contrast to the chemistry described in Section I of this chapter, the ester product in which the allylic transposition was effected (**97**), along with the inseparable direct inversion product **98**, were obtained in an approximately 2:3 ratio. The mixture of products was then subjected to the saponification conditions of potassium carbonate in methanol at 0 °C to provide an inseparable mixture of alcohols **99** and **100** in 80% yield from the alcohol **65**. Treatment of the mixture of

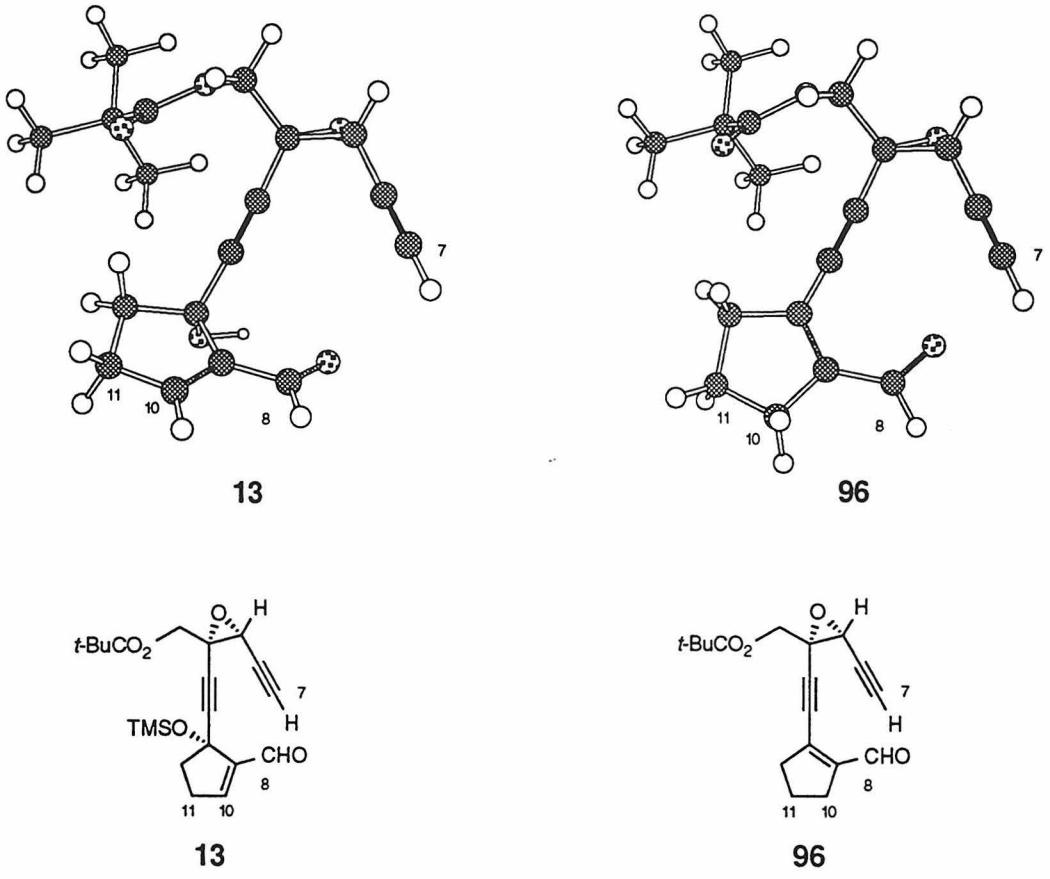
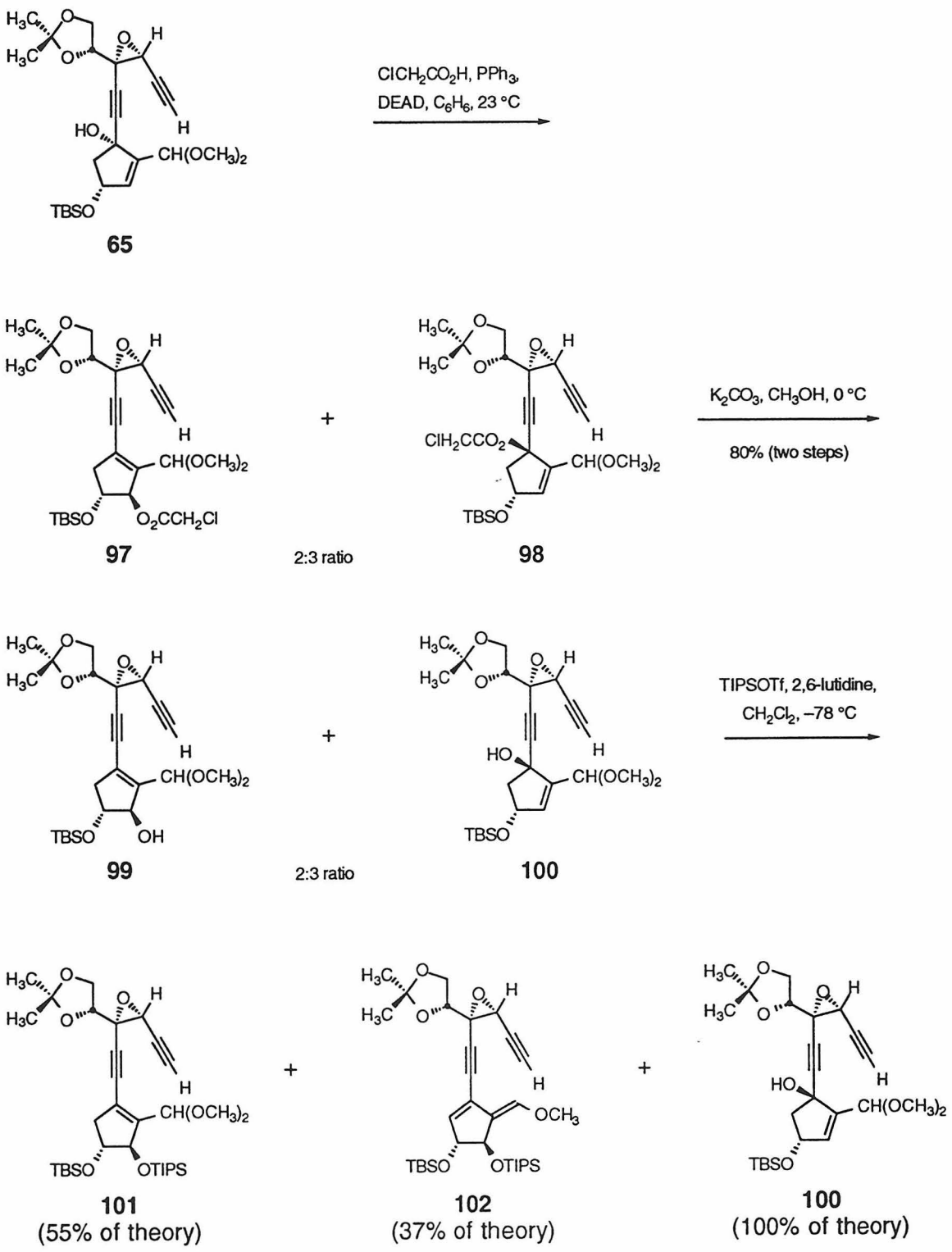


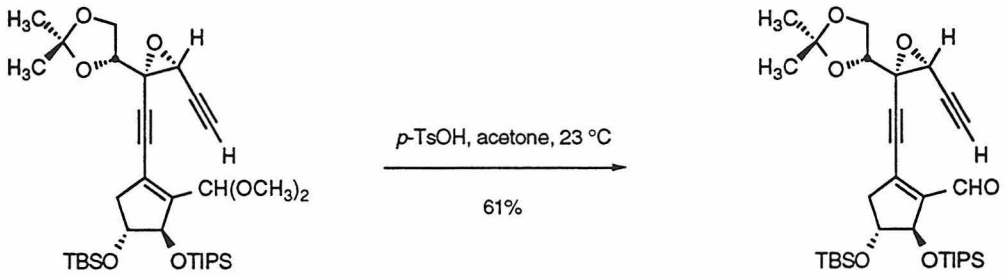
Figure 1. Ball and Stick Depictions of Ring-Closure Substrates 13 and 96.

Scheme XV


ClCH2CO2H, PPh3,
DEAD, C6H6, 23 °C
65
97
2:3 ratio
98
K2CO3, CH3OH, 0 °C
80% (two steps)
99
2:3 ratio
100
TIPSOTf, 2,6-lutidine,
CH2Cl2, –78 °C
101
(55% of theory)
102
(37% of theory)
100
(100% of theory)

alcohols with triisopropylsilyl trifluoromethanesulfonate (TIPSOTf, 10 equiv) and 2,6-lutidine (20 equiv) in dichloromethane at –78 °C afforded a now separable mixture of three products.[73] The unreacted tertiary alcohol **100** was recovered quantitatively, and the TIPS ether **101**, derived from the rearranged alcohol **99**, was isolated in 55% yield. In addition, the methyl dienol ether **102** was obtained in 37% yield. The dimethyl acetal of purified TIPS ether **101** was hydrolyzed by reaction with *p*-TsOH in acetone at 23 °C to afford the α,β-unsaturated aldehyde **103** in 61% yield.[65]

Intramolecular acetylide addition within **103** was attempted using both $LiN(TMS)_2$ (16 equiv) and $CeCl_3$ (3 equiv) in THF at –78 °C[13,19] and $KN(TMS)_2$ (6 equiv) and LiBr (0.5 equiv) in THF at –78 °C. Neither of these sets of reaction conditions provided any of the desired nine-membered ring product. Accordingly, this approach was abandoned.

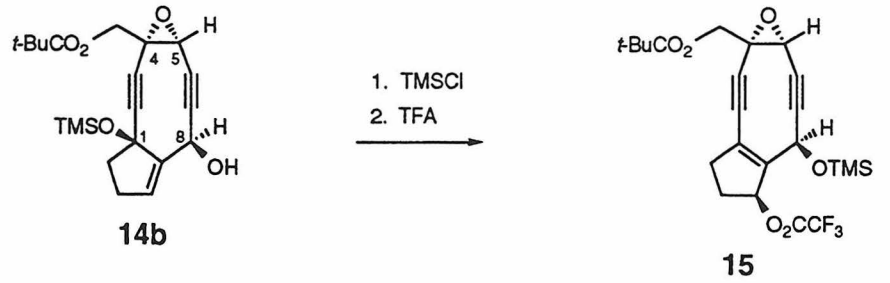


101 **103**

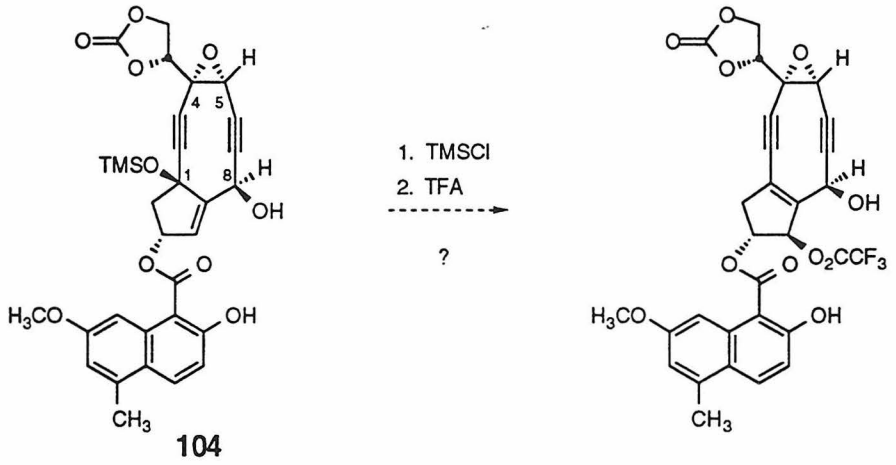
Studies with Diastereomeric Nine-Membered Ring Intermediates

A potentially significant difference between the allylic transposition substrates used for the preparation of model system **5**[13] and those employed in the studies described in Chapter 2 is the stereochemistry at C-1 and C-8 relative to the stereochemistry of the C-4 – C-5 epoxide (cf. **14b** and **54**, Ch. 1 and Ch. 2). As the allylic rearrangement in the conversion of **14b** to **15** proceeded in a suprafacial manner, it was of interest to determine whether a correspondingly more functionalized intermediate such as **104** would be a substrate for the trifluoroacetic acid-mediated allylic transposition. To examine this

possibility, the synthesis of intermediates possessing this stereochemical framework was initiated.



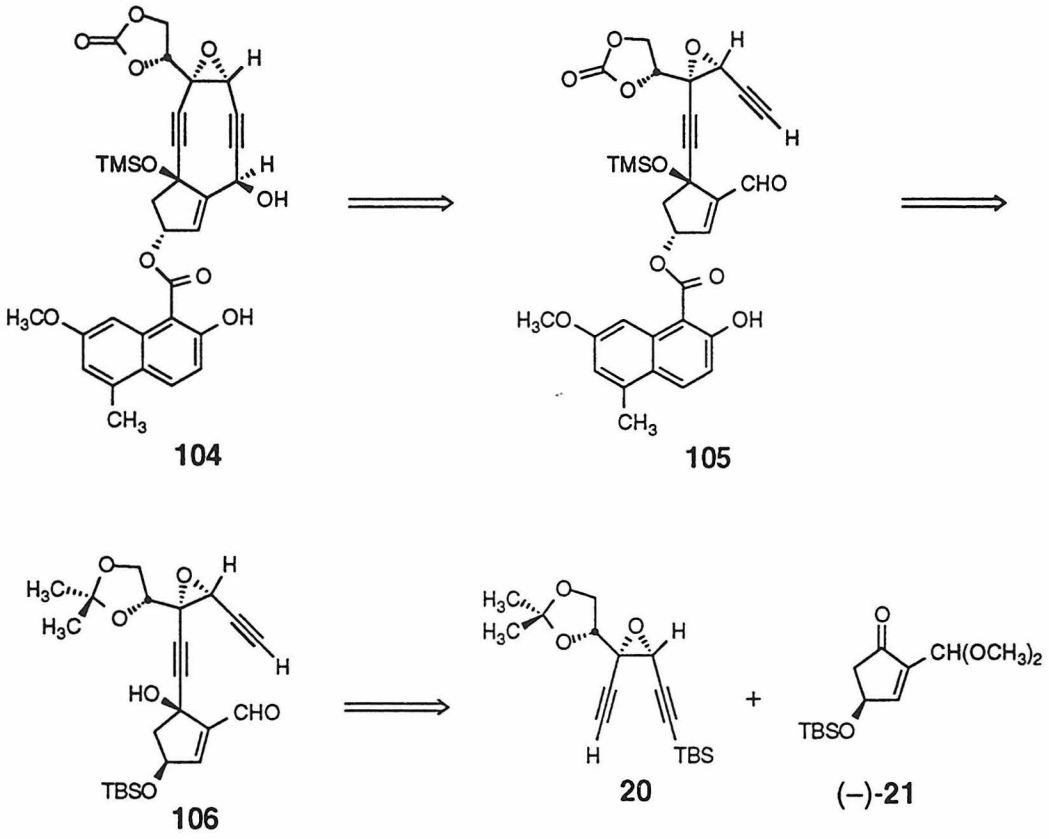
14b **15**



104

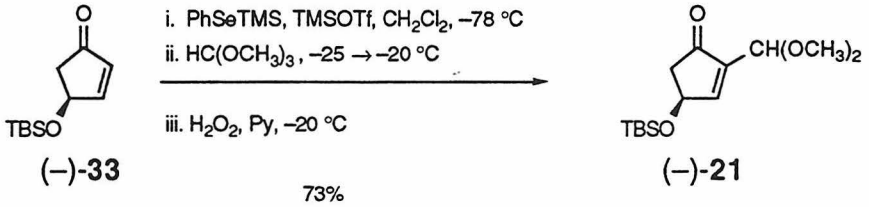
The strategy employed for the preparation of this series of compounds is given in Scheme XVI. Alcohol **104** was envisioned as being the product of the previously developed intramolecular acetylide addition chemistry within an α,β-unsaturated alcohol such as **105**. A key step in the preparation of **105** would be a Mitsunobu inversion[62] of the C-11 secondary alcohol derived from **106** using the naphthoic acid **22** as the nucleophile. Intermediate **106** was envisioned as arising from the diastereoselective

Scheme XVI

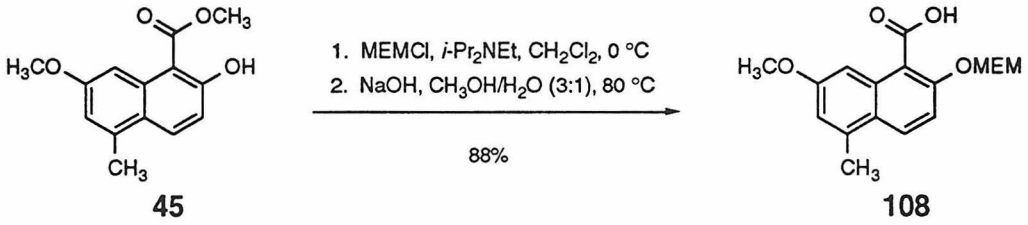

TMSO
H
OH
O
O
H3CO
OH
CH3
104
TMSO
CHO
H
105
H3C
H3C
HO
CHO
TBSO
106
H
TBS
20
CH(OCH3)2
TBSO
(–)-21

coupling of the epoxydiyne **20** and the enone dimethyl acetal (–)-**21**, the enantiomer of the enone (+)-**21** employed for the synthesis of the substrates discussed in Chapter 2 and the first two sections of this chapter.

To gain entry into this series of compounds, the preparation of the enone dimethyl acetal (–)-**21** was prepared from the known enantiomer of (+)-**33**,[35] enone (–)-**33**.[39] Treatment of (–)-**33** with trimethylsilyl phenyl selenide (1.5 equiv) and catalytic TMSOTf (0.2 equiv) followed by addition of freshly distilled trimethyl orthoformate (4 equiv) and in situ oxidation and elimination with hydrogen peroxide and pyridine afforded (–)-**21** in 73% yield.[36]

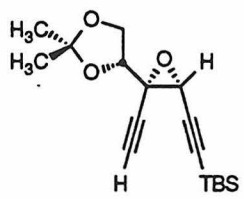


It was necessary to protect the 2-hydroxy group of the naphthoic acid **22** prior to its employment as a nucleophile in the planned Mitsunobu inversion. Accordingly, the methyl ester **45** was treated with MEM chloride (10 equiv) and diisopropylethylamine (20 equiv) in dichloromethane at 0 °C to provide the MEM ether in 98% yield.[55] The ester was subsequently saponified with sodium hydroxide (75 equiv) in a (3:1) mixture of methanol and water at 80 °C to afford the acid **108** in 90% yield.



Treatment of epoxydiyne **20** (1.05 equiv) with $LiN(TMS)_2$ (1.05 equiv) in toluene at –78 °C followed by addition of enone dimethyl acetal (–)-**21** (1 equiv) afforded the tertiary alcohol **109** as a single diastereomer in 54% yield (Scheme XVII). Removal of the TBS groups by treatment with TBAF (3 equiv) in THF at 0 °C afforded diol **110**.[51] Selective inversion of the secondary alcohol under Mitsunobu conditions utilizing acid **108** (1.2 equiv), triphenylphosphine (1.2 equiv), and DEAD (1.2 equiv) in benzene at 23 °C provided ester **111** in 70% yield.[62] As it was not clear at this juncture whether the formation of the nine-membered ring would occur in analogy to the other systems, the introduction of the ethylene carbonate was forgone in favor of arriving more directly at a ring-closure substrate. The dimethyl acetal of **111** underwent hydrolysis with *p*-TsOH in acetone at 23 °C to afford the α,β-unsaturated aldehyde, and the tertiary alcohol was protected as a trimethylsilyl ether with TMSOTf (5 equiv) and 2,6-lutidine (10 equiv) in dichloromethane at –78 °C to provide the ring-closure substrate **113** in 77% overall yield from **111**.[54] Treatment of a suspension of the intermediate **113** and cerium(III) chloride (3 equiv) in THF at –78 °C with $LiN(TMS)_2$ afforded the ring-closed secondary alcohol **114** in 59% yield, in complete analogy to prior substrates;[13,19] however, a large excess of the base (9 equiv) was required for the reaction to proceed to completion. The nine-membered ring-containing product **114** as well as subsequent intermediates in this diastereomeric series, were found to be more unstable than the corresponding intermediates having the opposite stereochemistry at C-1 and C-8 (cf. Ch. 2 and Ch. 3, Section I). Even when stored in a solid benzene matrix (–20 °C) and in the presence of the radical inhibitor 5-hydroxy-4-*tert*-butyl-2-methylphenyl sulfide (BHMS),[74] noticeable decomposition occurred in a matter of days.

Scheme XVII

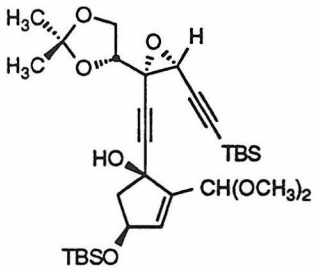


20

i. $LiN(TMS)_2$, $PhCH_3$, –78 °C

ii. (–)-**21**

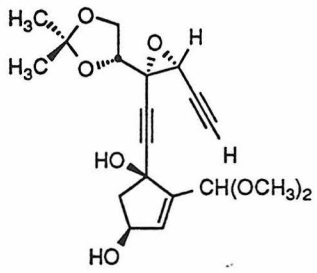
54%



109

Bu_4NF, THF, 0 ° C

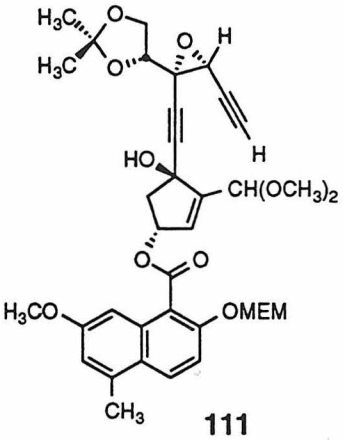
99%



110

108, PPh_3, DEAD, C_6H_6, 23 °C

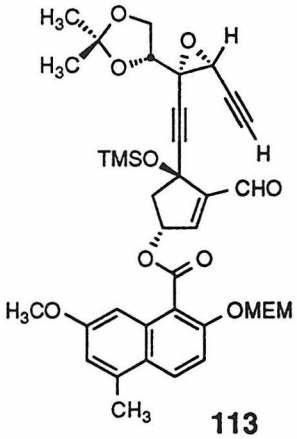
70%



111

1. *p*-TsOH, acetone, 23 °C
2. TMSOTf, 2,6-lutidine, CH_2Cl_2, –78 °C

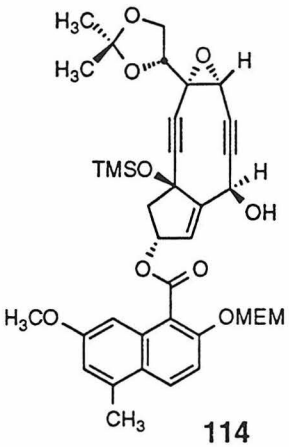
77%



113

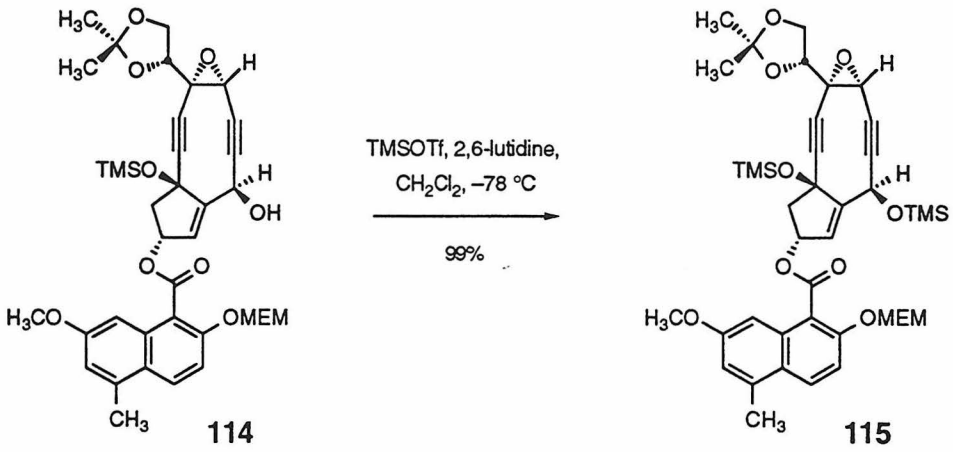
$LiN(TMS)_2$, $CeCl_3$, THF, –78 °C

59%



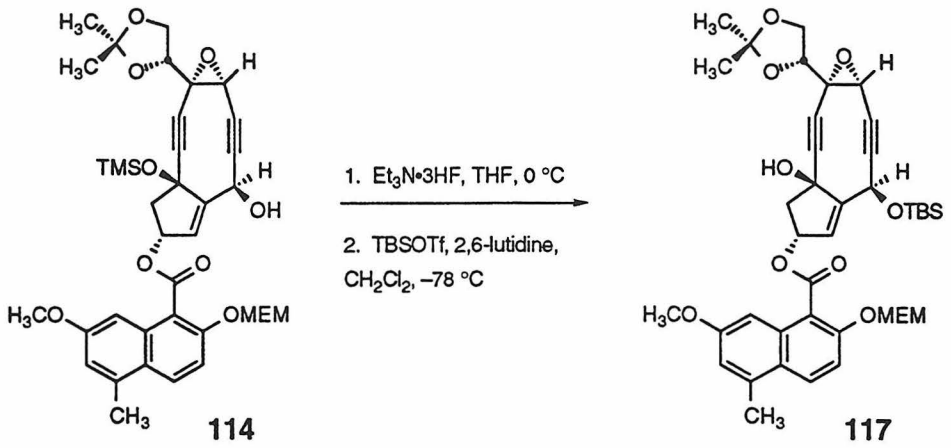
114

Conversion of the cyclized product **114** to its bis-TMS derivative **115** was accomplished in quantitative yield by treatment with TMSOTf (10 equiv) and 2,6-lutidine (20 equiv) in dichloromethane at –78 °C.[54] Reaction of the ether **115** with trifluoroacetic acid in dichloromethane (1:5) at 0 °C,[13] however, did not product the desired allylic transposition product. Simple desilylation of the secondary alcohol was observed instead.

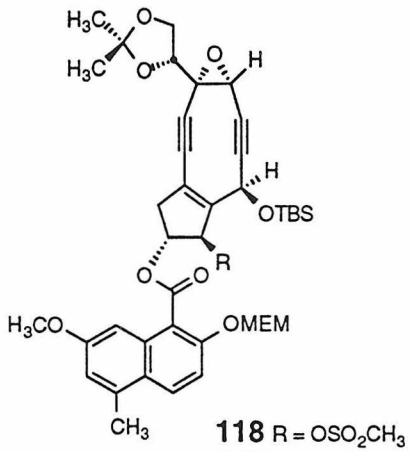


The rearrangement chemistry of intermediates in this series was also examined by alternative activation of the C-1 tertiary alcohol. Alcohol **114** was desilylated by treatment with triethylamine trihydrofluoride (3 equiv) in THF at 0 °C,[32] and the product diol (**116**) was selectively silylated with TBSOTf (10 equiv) and 2,6-lutidine (20 equiv) in dichloromethane at –78 °C to provide intermediate **117**.[58]

Treatment of alcohol **117** with triflic anhydride and pyridine in dichloromethane at –78 °C resulted in decomposition of the substrate. Reaction of **117** with methanesulfonic anhydride (10 equiv, 25 equiv Et_3N, dichloromethane, 0 °C) and methanesulfonyl chloride (6 equiv, 25 equiv Et_3N, dichloromethane, 0 °C)[59] afforded the rearranged mesylate **118** and chloride **119**, respectively, each having trans stereochemistry between the C-10 and C-11 centers. Neither of these rearranged products, however, could be converted to a



useful intermediate to complete the synthesis of **6**. The tertiary alcohol of intermediate **117** could also be functionalized as a trifluoroacetate, trichloroacetate, acetate, or *p*-toluenesulfinate (1:1 mixture of diastereomers). Attempted rearrangement of these activated intermediates under thermal conditions resulted in decomposition of the substrate in all cases examined, and attempted Lewis-acid catalyzed rearrangement of the derived acetate resulted in either loss of the silyl protecting group ($EtAlCl_2$, dichloromethane, –78 °C)[75] or recovery of the starting acetate ($BF_3•OEt_2$, dichloromethane, –78 → 23 °C; TMSOTf, dichloromethane, –78 → 23 °C).[76]



118 R = OSO_2CH_3
119 R = Cl

The inability to effect the requisite stereoselective allylic rearrangement of any of the intermediates prepared in this series prompted the discontinuation of this approach in favor of an alternative approach to the introduction of the C-10 and C-11 substituents with the proper stereochemistry.

Experimental Section

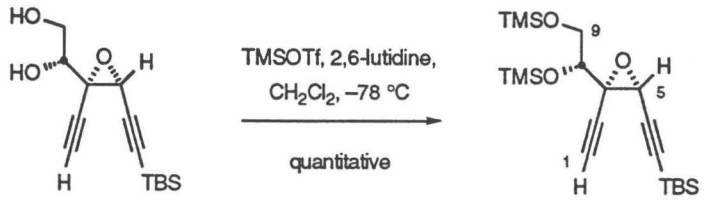
General procedures. All reactions were performed in flame-dried round bottom or modified Schlenk (Kjeldahl shape) flasks. The flasks were fitted with rubber septa and contained a positive pressure of argon unless otherwise stated. Stainless steel syringes or cannula were used to transfer air- and moisture-sensitive materials. Concentration in vacuo was accomplished by rotary evaporation at water aspirator pressure (approximately 25 torr). Flash chromatography was carried out as described by Still et al., employing 230-400 mesh silica gel.[29] Analytical thin-layer chromatography was performed using glass plates pre-coated with 0.25 mm 230-400 mesh silica gel impregnated with fluorescent indicator (254 nm). Thin-layer chromatography plates were visualized by exposure to ultraviolet light (noted as 'UV') and/or by exposure to an acidic solution of *p*-anisaldehyde (noted as 'anisaldehyde') followed by heating on a hot plate.

Materials. Commercial reagents were used as received, with the following exceptions. Ethyl ether and tetrahydrofuran (THF) were distilled from sodium benzophenone ketyl. Dichloromethane, benzene, toluene, acetonitrile, N,N-diisopropylethylamine, hexamethyldisilazane, 2,6-lutidine, pyridine, and triethylamine were distilled from calcium hydride at 760 torr. Anhydrous cerium(III) chloride was prepared from the heptahydrate by heating at 100 °C and 1 torr for 12 hours. Methanesulfonyl chloride was distilled from phosphorous pentoxide at 760 torr.

Trifluoromethanesulfonic anhydride and trimethylsilyl trifluoromethanesulfonate were stored in a glove box in round bottom flasks fitted with polycarbonate or glass stoppers. The molarity of n-butyllithium solutions was determined by titration with 2,6-di-*tert*-butyl-4-methylphenol using fluorene as an indicator (average of three determinations). Where indicated, fresh solutions of lithium hexamethyldisilazide were prepared by the addition of a solution of n-butyllithium (1.0 eq) in hexanes to a solution of hexamethyldisilazane (1.0 eq) in hexanes at -20 °C, followed by warming to room temperature.

Instrumentation. Infrared (IR) spectra were obtained using a Perkin-Elmer 1600 FT-IR spectrophotometer referenced to a polystyrene standard. Data are presented as follows: frequency of absorption (cm^{-1}), intensity of absorption (v = very, s = strong, m = medium, w = weak) and assignment where appropriate. Proton nuclear magnetic resonance (^1H NMR) spectra and carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on either a General Electric QE-300 (300 MHz), a JEOL GX-400 (400 MHz) or a Bruker AM-500 (500 MHz) NMR spectrometer; chemical shifts for protons are reported in parts per million downfield from tetramethylsilane and are referenced to residual protium in the NMR solvent ($CHCl_3$: δ 7.26, C_6D_5H: δ 7.20, $CDHCl_2$: δ 5.29, CD_2HOD: δ 3.30). Data are represented as follows: chemical shift, multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, obscured = obscured by solvent or other signals, abq = ab quartet), integration, coupling constant in Hertz (Hz), and assignment. Optical rotations were determined on a Jasco DIP-181 digital polarimeter equipped with a sodium lamp source. HPLC purification was carried out on a Waters Delta Prep 3000 HPLC equipped with a Waters 994 programmable photodiode array detector set at 240 nm and either a Beckman ODS C18 column (10 mm x 25 cm, for analytical HPLC) or a Vydac 201HS1022 C18 reverse-phase column (22 mm x 25 cm, for preparative HPLC). Melting points were determined on a Büchi SMP-20 melting point apparatus, and are uncorrected. High resolution mass spectra were obtained either at the University of California, Riverside Mass Spectrometry Facility; the Midwest Center for Mass

Spectroscopy, Lincoln, Nebraska; the University of California, Los Angeles Mass Spectrometry Facility; or the California Institute of Technology Mass Spectrometry Facility.

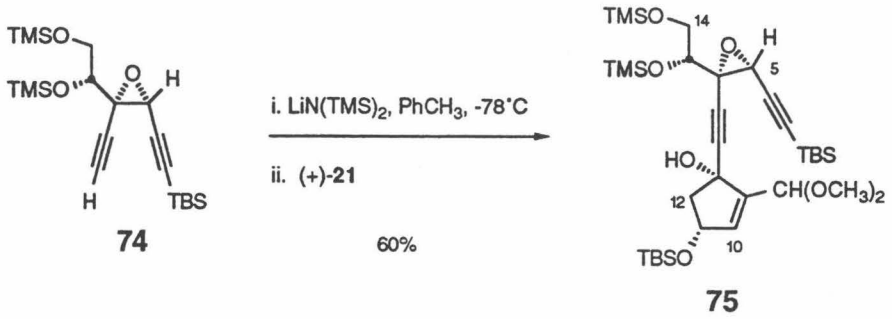


32 **74**

Bis-TMS ether **74**

2,6-Lutidine (8.75 mL, 8.04 g, 75.1 mmol, 20 equiv) and trimethylsilyl trifluoromethanesulfonate (8.71 mL, 10.0 g, 45.0 mmol, 12 equiv) were added sequentially via syringe to a solution of diol **32** (1.00 g, 3.75 mmol, 1 equiv) in dichloromethane (100 mL) at –78 °C. The reaction was maintained at –78 °C for 1.5 h. Triethylamine (10 mL) and methanol (10 mL) were added, and the reaction mixture was warmed to 23 °C and partitioned between water (50 mL) and hexanes (50 mL). The layers were separated, and the aqueous layer was further extracted with hexanes (2 25-mL portions). The combined organics were washed with saturated sodium chloride (50 mL), and were dried over sodium sulfate and concentrated. Purification of the residue by flash column chromatography (10% ethyl acetate in hexanes) afforded the bis-TMS ether **74** (1.49 g, quantitative) as a pale yellow solid, mp 59.5-60.5 °C.

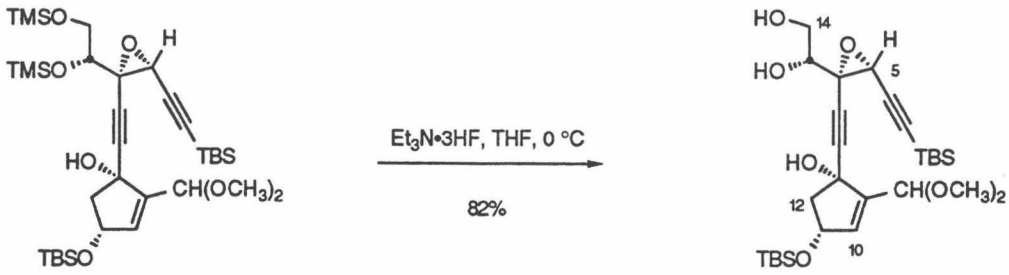
^{1}H NMR (300 MHz, C_6D_6), δ:	3.98-3.93 (m, 2H, C9 H), 3.84 (s, 1H, C5 H), 3.80 (dd, 1H, *J* = 11.0, 6.2 Hz, C8 H), 2.03 (s, 1H, C1 H), 1.04 (s, 9H, $OSiC(CH_3)_3(CH_3)_2$), 0.16-0.12 (complex, 24 H, $OSiC(CH_3)_3(CH_3)_3$, 2 x $OSi(CH_3)_3$).
FTIR (thin film), cm^{-1}:	3432 (m, C≡C-H), 2956 (m), 2840 (m), 2120 (w, C≡C), 1249 (s), 1149 (s).
TLC (20% EtOAc in Hexanes) R*f*:	**74**: 0.61 (anisaldehyde)



Alcohol **75**

Epoxydiyne **74** (2.78 g, 6.76 mmol, 1.05 equiv) in toluene (20 mL) was added over a 25 min period to a solution of lithium hexamethyldisilazide (6.96 mL of a 1.0 M solution in hexanes, 6.96 mmol, 1.05 equiv) in toluene (20 mL) at –78 °C. The resultant solution was maintained at –78 °C for an additional 20 min, and a solution of enone (+)-**21** (1.90 g, 6.64 mmol, 1.0 equiv) in toluene (20 mL) was added over a 10 min period. The reaction mixture was stirred at –78 °C for 10 min, and saturated aqueous ammonium chloride (50 mL) was added to quench excess base. The reaction mixture was warmed to 23 °C and partitioned between water (50 mL) and 1:1 ethyl acetate/hexanes (50 mL). The layers were separated and the aqueous layer was further extracted with 1:1 ethyl acetate/hexanes (2 25-mL portions). The combined organics were washed with saturated aqueous sodium chloride (25 mL), dried over sodium sulfate and concentrated. Purification of the residue by flash column chromatography (5% ethyl acetate in hexanes) provided the alcohol **75** (2.76 g, 60%) as a yellow oil, along with recovered epoxydiyne (785 mg, 25%).

^{1}H NMR (400 MHz, C_6D_6), δ:	6.17 (t, 1H, *J* = 1.71 Hz, C-10 H), 5.42 (t, 1H, *J* = 1.46 Hz, C8 H), 4.88 (m, 1H, C11 H), 4.05-4.02 (m, 1H, C13 H), 3.92-3.95 (m, 1H, C14 H), 3.93 (s, 1H, C5 H), 3.85 (dd, 1H, *J* = 10.99, 6.11 Hz, C14 H), 3.22 (s, 3H, $CH(OC\mathbf{H}_3)_2$), 3.21 (s, 3H, $CH(OC\mathbf{H}_3)_2$), 3.18 (dd, 1H, *J* = 13.43, 7.08 Hz, C12 βH), 2.55 (dd, 1H, *J* = 13.43, 5.13 Hz, C12 αH), 1.06 (s, 9H, $SiC(C\mathbf{H}_3)_3(C\mathbf{H}_3)_2$), 0.97 (s, 9H, $SiC(CH_3)_3(C\mathbf{H}_3)_2$), 0.21 (s, 6H, $SiC(CH_3)_3(C\mathbf{H}_3)_2$), 0.17 (s, 9H, $OSi(C\mathbf{H}_3)_3$), 0.14 (s, 9H, $OSi(C\mathbf{H}_3)_3$), 0.09 (s, 3H, $SiC(CH_3)_3(C\mathbf{H}_3)_2$), 0.07 (s, 3H, $SiC(CH_3)_3(C\mathbf{H}_3)_2$).
FTIR (thin film), cm^{-1}:	3521 (w, OH), 2955 (s), 2184 (w, C≡C), 1464 (m), 1360 (m), 1252 (s), 1080 (s), 964 (m).
TLC (20% EtOAc in Hexanes) R*f*:	**74**: 0.65 (anisaldehyde) (+)-**21**: 0.31 (anisaldehyde) **75**: 0.50 (anisaldehyde)

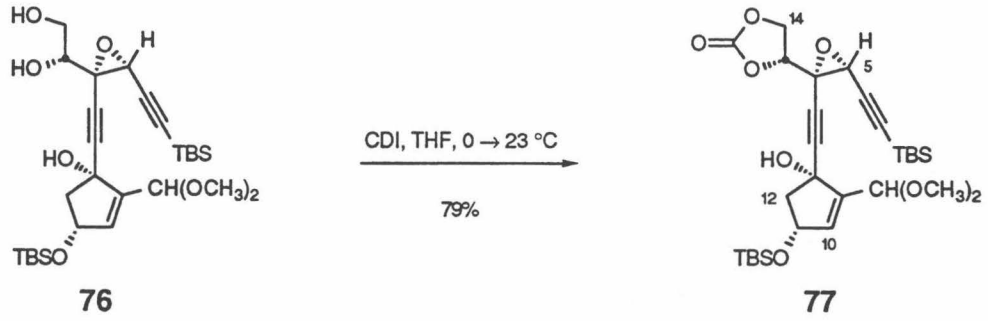


75 **76**

Triol **76**

Triethylamine trihydrofluoride (1.91 mL, 1.89 g, 11.8 mmol, 3 equiv) was added via syringe to a solution of alcohol **75** (2.73 g, 3.92 mmol, 1 equiv) in THF (228 mL) at 0 °C. The reaction was kept at 0 °C for 15 min, and saturated aqueous sodium bicarbonate (50 mL) was added. The reaction mixture was warmed to 23 °C and the layers were separated. The aqueous layer was extracted with ethyl acetate (2 25-mL portions). The combined organics were washed with saturated aqueous sodium chloride (50 mL), dried over sodium sulfate, and concentrated. The residue was purified by flash column chromatography (50% ethyl acetate in hexanes grading to ethyl acetate) to provide the triol **76** (1.79g, 82%) as a pale yellow oil.

^{1}H NMR (300 MHz, C_6D_6), δ:	6.16 (t, 1H, *J* = 1.3 Hz, C10 H), 5.36 (m, 1H, C-8 H), 4.85 (m, 1H, C11 H), 4.36 (br s, 1H, C1 O**H**), 3.92-3.63 (complex, 3H, C13 and C14 H), 3.65 (s, 1H, C5 H), 3.23 (s, 3H, $CH(OCH_3)_2$), 3.21 (s, 3H, $CH(OCH_3)_2$), 3.85 (dd, 1H, *J* = 10.99, 6.11 Hz, C14 H), 3.13 (dd, 1H, *J* = 13.4, 7.2 Hz, C12 βH), 2.80 (br s, 1H, O**H**), 2.48 (dd, 1H, *J* = 13.5, 5.1 Hz, C12 αH), 2.22 (br s, 1H, O**H**), 1.06 (s, 9H, $SiC(CH_3)_3(CH_3)_2$), 0.97 (s, 9H, $SiC(CH_3)_3(CH_3)_2$), 0.22 (s, 3H, $SiC(CH_3)_3(CH_3)_2$), 0.21 (s, 3H, $SiC(CH_3)_3(CH_3)_2$), 0.09 (s, 3H, $SiC(CH_3)_3(CH_3)_2$), 0.08 (s, 3H, $SiC(CH_3)_3(CH_3)_2$).
FTIR (thin film), cm^{-1}:	3337 (m, OH), 2930 (s), 2857 (m), 2178 (w, C≡C), 1463 (m), 1360 (m), 1252 (m), 1193 (m), 1109 (s), 1049 (s).
TLC (50% EtOAc in Hexanes) R*f*:	**75**: 0.97 (anisaldehyde) **76**: 0.067 (anisaldehyde)



76 **77**

Carbonate **77**

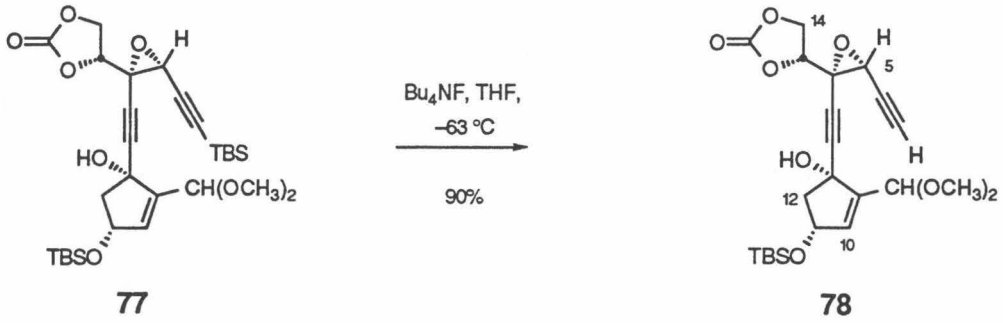
Carbonyldiimidazole (313 mg, 1.94 mmol, 0.6 equiv) was added in one portion to a solution of triol **76** (1.78 g, 3.22 mmol, 1 equiv) in dry THF (66 mL) at 0 °C. The resultant solution was stirred at 0 °C for 20 min, and another portion of carbonyldiimidazole (313 mg, 1.94 mmol, 0.6 equiv) was added. The reaction mixture was maintained at 0 °C for an additional 10 min, warmed to 23 °C and held at that temperature for 2.25 h. The reaction mixture was partitioned between water (50 mL) and ethyl acetate (50 mL). The layers were separated, and the aqueous layer was further extracted with ethyl acetate (2 30-mL portions). The combined organics were washed with saturated aqueous sodium chloride (50 mL), dried over sodium sulfate and concentrated. The residue was purified by flash column chromatography (50% ethyl acetate in hexanes) to afford carbonate **77** (1.47 g, 79%) as a colorless foam.

^{1}H NMR (300 MHz, C_6D_6), δ: 6.17 (br s, 1H, C10 H), 5.38 (br s, 1H, C8 H), 4.90 (m, 1H, C11 H), 4.08 (br s, 1H, C1 O**H**), 3.94 (dd, 1H, *J* = 8.9, 4.8 Hz, C13 H), 3.37 (t, 1H, *J* = 8.4 Hz, C14 H), 3.24 (s, 3H, $CH(OCH_3)_2$), 3.21 (s, 3H, $CH(OCH_3)_2$), 3.19-3.10 (m, 2H, C14 H and C12 βH), 3.02 (s, 1H, C5 H), 2.50 (dd, 1H, *J* = 13.3, 5.5 Hz, C12 αH), 1.05 (s, 9H, $SiC(CH_3)_3(CH_3)_2$), 0.96 (s, 9H, $SiC(CH_3)_3(CH_3)_2$), 0.21 (s, 3H, $SiC(CH_3)_3(CH_3)_2$), 0.20 (s, 3H, $SiC(CH_3)_3(CH_3)_2$), 0.10 (s, 3H, $SiC(CH_3)_3(CH_3)_2$), 0.089 (s, 3H, $SiC(CH_3)_3(CH_3)_2$).

FTIR (thin film), cm^{-1}: 3498 (m, OH), 2954 (s), 2857 (m), 2178 (w, C≡C), 1823 (s, C=O), 1727 (m), 1468 (m), 1382 (m), 1361 (m), 1253 (m), 1082 (s).

TLC (50% EtOAc in Hexanes) R*f*: **76**: 0.04 (anisaldehyde)

77: 0.48 (anisaldehyde)

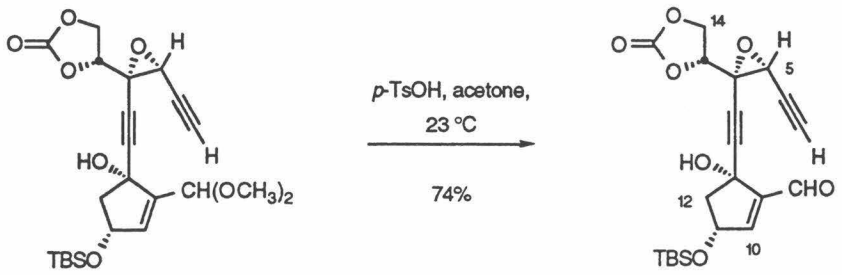


77 **78**

Free acetylene **78**

Tetrabutylammonium fluoride (2.53 mL of a 1.0 M solution in THF, 2.53 mmol, 2 equiv) was added via syringe to a solution of carbonate **77** (735 mg, 1.26 mmol, 1 equiv) in THF (85 mL) at –63 °C. The pale purple suspension was stirred at –63 °C for 30 min, pH 7.2 phosphate buffer (20 mL) was added, and the reaction mixture was warmed to 23 °C. The reaction mixture was partitioned between water (50 mL) and ethyl acetate (50 mL). The aqueous layer was further extracted with ethyl acetate (2 25-mL portions), and the combined organics were washed with saturated aqueous sodium chloride (50 mL), dried over sodium sulfate and concentrated. The residue was purified by flash column chromatography (25% ethyl acetate in hexanes grading to 50% ethyl acetate in hexanes), providing the free acetylene **78** (1.06 g, 90%) as a colorless oil.

^{1}H NMR (400 MHz, C_6D_6), δ:	6.13 (t, 1H, *J* = 1.7 Hz, C10 H), 5.35 (t, 1H, *J* = 1.7 Hz, C8 H), 4.91 (m, 1H, C11 H), 4.10 (s, 1H, C1 OH), 3.91 (dd, 1H, *J* = 9.0, 4.4 Hz, C13 H), 3.33 (t, 1H, *J* = 8.7 Hz, C14 H), 3.23-3.15 (obscured, 1H, C12 βH), 3.19 (s, 3H, $CH(OCH_3)_2$), 3.17 (s, 3H, $CH(OCH_3)_2$), 3.09 (dd, 1H, *J* = 8.2, 4.5 Hz, C14 H), 2.86 (d, 1H, *J* = 1.6 Hz, C5 H), 2.50 (dd, 1H, *J* = 13.2, 5.6 Hz, C12 αH), 1.98 (d, 1H, *J* = 1.6 Hz, C7 H), 0.96 (s, 9H, $OSiC(CH_3)_3(CH_3)_2$), 0.10 (s, 6H, $OSiC(CH_3)_3(CH_3)_2$)
FTIR (thin film), cm^{-1}:	3471 (m, OH), 3277 (w, C≡C-H), 2932 (m), 2856 (m), 1820 (s, C=O), 1470 (w), 1360 (m), 1159 (m), 1080 (s).
TLC (50% EtOAc in Hexanes) R*f*:	**77**: 0.48 (anisaldehyde) **78**: 0.40 (anisaldehyde)



78 **79**

Aldehyde **79**

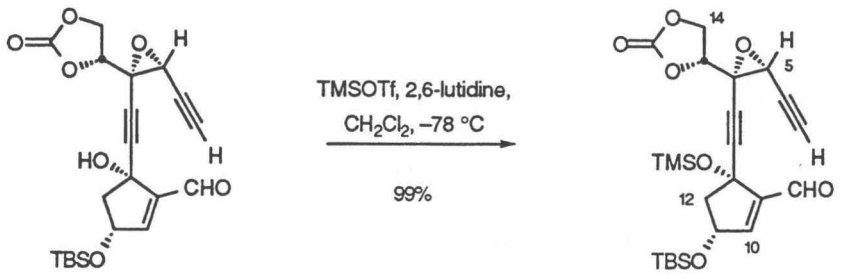
p-Toluenesulfonic acid (75 mg) was added in one portion to a solution of dimethyl acetal **78** (900 mg, 1.94 mmol, 1 equiv) in acetone (30 mL). The resultant yellow solution was stirred at 23 °C for 15 min and the *p*-toluenesulfonic acid was neutralized with saturated aqueous sodium bicarbonate (30 mL). The reaction mixture was extracted with 1:1 ethyl acetate/hexanes (3 30-mL portions), and the combined organics were washed with saturated sodium chloride (50 mL), dried over sodium sulfate and concentrated. Purification of the residue by flash column chromatography (30% ethyl acetate in hexanes grading to 50% ethyl acetate in hexanes) provided aldehyde **79** (602 mg, 74%) as a colorless solid.

^{1}H NMR (400 MHz, C_6D_6), δ: 9.22 (s, 1H, C8 H), 6.08 (t, 1H, *J* = 1.7 Hz, C10 H), 5.02 (t, 1H, *J* = 1.7 Hz, C11 H), 3.91 (s, 1H, C1 O**H**), 3.85 (dd, 1H, *J* = 9.2, 4.0 Hz, C13 H), 3.30 (dd, 1H, *J* = 9.2, 8.1 Hz, C14 H), 3.10 (dd, 1H, *J* = 12.7, 6.9 Hz, C12 βH), 3.02 (dd, 1H, *J* = 8.1, 4.0 Hz, C14), 2.78 (d, 1H, *J* = 1.7 Hz, C5 H), 2.36 (dd, 1H, *J* = 12.7, 7.3 Hz, C12 αH), 2.15 (d, 1H, *J* = 1.7 Hz, C7 H), 0.98 (s, 9H, $OSiC(CH_3)_3(CH_3)_2$), 0.19 (s, 3H, $OSiC(CH_3)_3(CH_3)_2$), 0.17 (s, 3H, $OSiC(CH_3)_3(CH_3)_2$).

FTIR (thin film), cm^{-1}: 3507 (w, OH), 3285 (m, C≡C-H), 2953 (m), 2857 (m), 2130 (w, C≡C), 1819 (s, carbonate C=O), 1684 (m, aldehyde C=O), 1472 (w), 1359 (m), 1084 (s).

TLC (50% EtOAc in Hexanes) R*f*: **78**: 0.34 (anisaldehyde)

79: 0.42 (UV, anisaldehyde)

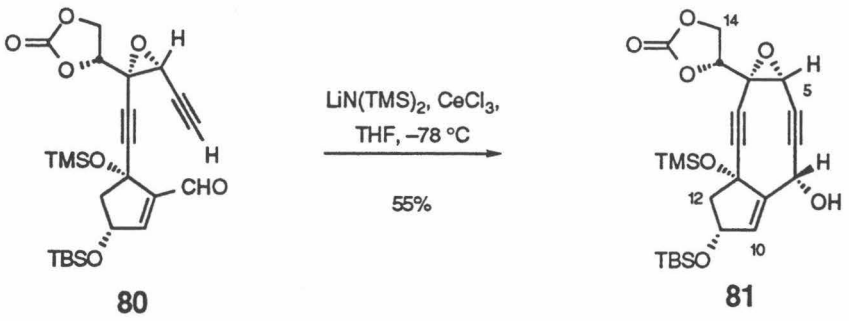


79 **80**

TMS ether **80**

2,6-Lutidine (1.38 mL, 1.27 g, 11.8 mmol, 10 equiv) and trimethylsilyl trifluoromethanesulfonate (1.14 mL, 1.31 g, 5.91 mmol, 5 equiv) were added sequentially via syringe to a solution of aldehyde **79** (495 mg, 1.18 mmol, 1 equiv) in dichloromethane (28 mL) at –78 °C. The resultant solution was maintained at –78 °C for an additional 1 h, and then excess trimethylsilyl trifluoromethanesulfonate was quenched by the addition of triethylamine (6 mL) and methanol (6 mL). The reaction mixture was partitioned between water (25 mL) and 1:1 ethyl acetate/hexanes (25 mL). The layers were separated, and the aqueous layer was further extracted with 1:1 ethyl acetate/hexanes (2 25-mL portions). The combined organics were washed with saturated aqueous sodium chloride (50 mL), dried over sodium sulfate and concentrated. Purification of the residue by flash column chromatography (25% ethyl acetate in hexanes) provided the TMS ether **80** (575 mg, 99%) as a pale yellow oil.

^{1}H NMR (400 MHz, C_6D_6), δ:	9.61 (s, 1H, C8 H), 6.29 (d, 1H, *J* = 1.6 Hz, C10 H), 4.94 (td, 1H, *J* = 8.3, 1.4 Hz, C11 H), 4.00 (dd, 1H, J = 9.1, 4.1 Hz, C13 H), 3.38 (t, 1H, J = 8.7 Hz, C14 H), 3.23 (dd, 1H, *J* = 12.7, 7.1 Hz, C12 βH), 3.07 (m, 1H, C14), 2.80 (s, 1H, C5 H), 2.39 (dd, 1H, *J* = 12.7, 6.6 Hz, C12 αH), 2.18 (d, 1H, *J* = 1.4 Hz, C7 H), 0.98 (s, 9H, $OSiC(C\mathbf{H}_3)_3(CH_3)_2$), 0.37 (s, 9H, $OSi(C\mathbf{H}_3)_3$), 0.19 (s, 3H, $OSiC(CH_3)_3(C\mathbf{H}_3)_2$), 0.17 (s, 3H, $OSiC(CH_3)_3(C\mathbf{H}_3)_2$).
FTIR (thin film), cm^{-1}:	3285 (w, C≡C-H), 2955 (m), 2857 (m), 2237 (w, C≡C), 2131 (w, C≡C), 1822 (s, carbonate C=O), 1696 (m, aldehyde C=O), 1254 (s), 1130 (m), 1084 (s).
TLC (50% EtOAc in Hexanes) R*f*:	**79**: 0.47 (UV, anisaldehyde) **80**: 0.64 (UV, anisaldehyde)



80 **81**

Cyclic alcohol **81**

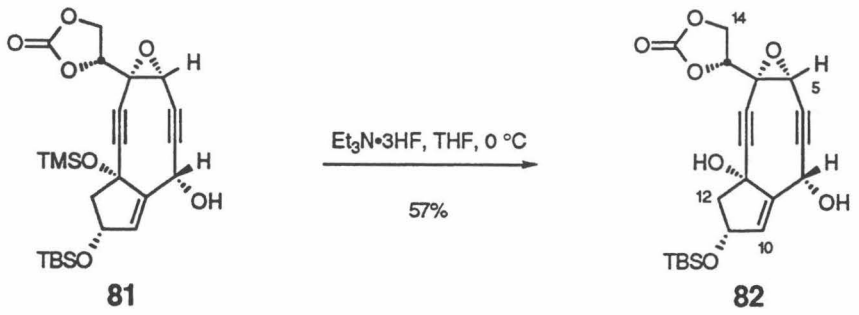
A suspension of aldehyde **80** (116 mg, 0.236 mmol, 1 equiv) and anhydrous cerium(III) chloride (175 mg, 0.709 mmol, 3 equiv), in THF (15 mL) was stirred vigorously under argon at 23 °C for 10 min. The mixture was cooled to –78 °C, and freshly prepared lithium hexamethyldisilazide (0.236 mL of a 1.0 M solution in hexanes, 0.236 mmol, 1.0 equiv) was added dropwise via syringe. The reaction was stirred at –78 °C for 10 min, and excess base was quenched with saturated aqueous ammonium chloride (5 mL). The reaction mixture was warmed to 23 °C and partitioned between water (25 mL) and 1:1 ethyl acetate/hexanes (25 mL). The layers were separated and the aqueous layer was further extracted with 1:1 ethyl acetate/hexanes (2 25-mL portions). The combined organics were dried over sodium sulfate and concentrated The residue was purified by flash column chromatography (25% ethyl acetate in hexanes) to afford cyclic alcohol **81** (64 mg, 55%) as a pale orange oil.

^{1}H NMR (300 MHz, C_6D_6), δ: 5.95 (t, 1H, *J* = 1.66 Hz, C10 H), 5.17 (m, 1H, C8 H), 4.67 (m, 1H, C11 H), 3.68 (m, 1H, C13 H), 3.22 (m, 2H, C14 H), 2.94 (dd, 1H, *J* = 13.08, 7.03 Hz, C12 βH), 2.78 (s, 1H, C5 H), 2.18 (dd, 1H, *J* = 13.06, 5.59 Hz, C12 αH), 0.93 (s, 9H, $OSiC(CH_3)_3(CH_3)_2$), 0.30 (s, 9H, $OSi(CH_3)_3$), 0.00 (s, 3H, $OSiC(CH_3)_3(CH_3)_2$), -0.01 (s, 3H, $OSiC(CH_3)_3(CH_3)_2$).

FTIR (thin film), cm^{-1}: 3446 (w, OH), 2954 (m), 2857 (m), 2202 (w, C≡C), 1822 (s, carbonate C=O), 1361 (m), 1253 (m), 1080 (s) cm^{-1}

TLC (50% EtOAc in Hexanes) R*f*: **80**: 0.62 (UV, anisaldehyde)

81: 0.54 (anisaldehyde)

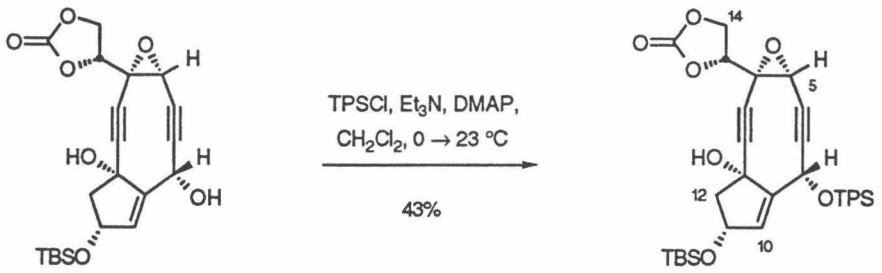


81 **82**

Diol **82**

Triethylamine trihydrofluoride (0.058 mL, 57 mg, 0.35 mmol, 3 equiv) was added via syringe to a solution of cyclic alcohol **81** (58 mg, 0.118 mmol, 1 equiv) in THF (5 mL) at 0 °C. The resultant solution was held at 0 °C for an additional 2 h, and saturated aqueous sodium bicarbonate (3 mL) was added. The reaction mixture was warmed to 23 °C and extracted with ethyl acetate (3 25-mL portions). The combined organics were washed with saturated aqueous sodium chloride (25 mL), dried over sodium sulfate and concentrated. Purification of the residue by flash column chromatography (50% ethyl acetate in hexanes grading to ethyl acetate) afforded diol **82** (28 mg, 57%) as a yellow powder.

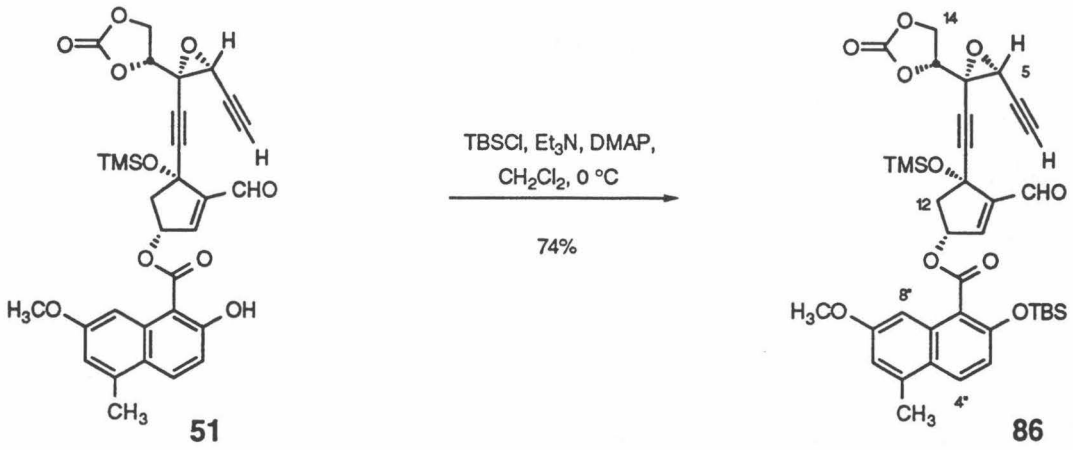
^{1}H NMR (500 MHz, CD_3OD), δ:	5.86 (t, 1H, *J* = 1.80 Hz, C10 H), 5.83 (t, 1H, *J* = 1.57 Hz, C8 H), 5.23 (m, 1H, C11 H), 4.38 - 4.19 (complex, 2H, C13 H, one C14 H), 3.79 (m, 1H, C14 H), 3.64 (s, 1H, C5 H), 2.85 (dd, 1H, *J* = 13.27, 7.07 Hz, C12 βH), 1.87 (dd, 1H, *J* = 13.34, 5.42 Hz, C12 αH), 0.89 (s, 9H, $OSiC(\mathbf{CH_3})_3(CH_3)_2$), 0.09 (s, 3H, $OSiC(CH_3)_3(\mathbf{CH_3})_2$), 0.08 (s, 3H, $OSiC(CH_3)_3(\mathbf{CH_3})_2$).
FTIR (thin film), cm^{-1}:	3421 (s, OH), 2929 (s), 2860 (m), 1750 (s, carbonate C=0), 1360 (m), 1290 (m), 1080 (s).
TLC (50% EtOAc in Hexanes) R*f*:	**81**: 0.51 (anisaldehyde) **82**: 0.30 (anisaldehyde)



Tertiary alcohol **83**

Triphenylsilyl chloride (23 mg, 0.078 mmol, 1.3 equiv) was added in one portion to a solution of the diol **82** (25 mg, 0.060 mmol, 1 equiv), triethylamine (0.042 mL, 30 mg, 0.30 mmol, 5 equiv) and 4-dimethylaminopyridine (4 mg, 0.030 mmol, 0.5 equiv) in dichloromethane (2 mL) at 0 °C. The reaction mixture was maintained at 0 °C for 10 min and warmed to 23 °C for 2.5 h. The reaction mixture was partitioned between water (5 mL) and ethyl acetate (5 mL). The layers were separated, and the aqueous layer was further extracted with ethyl acetate (2 5-mL portions). The combined organics were washed with saturated aqueous sodium chloride (15 mL), dried over sodium sulfate and concentrated. The residue was purified by flash column chromatography (20% ethyl acetate in hexanes grading to 50% ethyl acetate in hexanes) to afford the triphenylsilyl ether **83** (17 mg, 43%) as a pale yellow powder.

^{1}H NMR (300 MHz, C_6D_6), δ:	7.85 (m, 4H, $OSi(C_6\mathbf{H}_5)_3$), 7.73 (m, 4H, $OSi(C_6\mathbf{H}_5)_3$),7.23 (m, 7H, $OSi(C_6\mathbf{H}_5)_3$), 5.86 (t, 1H, *J* = 1.80 Hz, C10 H), 5.83 (t, 1H, *J* = 1.57 Hz, C8 H), 5.23 (m, 1H, C11 H), 4.38 - 4.19 (complex, 2H, C13 H and one C14 H), 3.79 (m, 1H, C14 H), 3.64 (s, 1H, C5 H), 2.85 (dd, 1H, *J* = 13.27, 7.07 Hz, C12 βH), 1.87 (dd, 1H, *J* = 13.34, 5.42 Hz, C12 αH), 0.89 (s, 9H, $OSiC(C\mathbf{H}_3)_3(CH_3)_2$), 0.09 (s, 3H, $OSiC(CH_3)_3(C\mathbf{H}_3)_2$), 0.08 (s, 3H, $OSiC(CH_3)_3(C\mathbf{H}_3)_2$).
FTIR (thin film), cm^{-1}:	3421 (s, OH), 2929 (s), 2860 (m), 1750 (s, carbonate C=O), 1360 (m), 1290 (m), 1080 (s).
TLC (50% EtOAc in Hexanes) R*f*:	**82**: 0.42 (anisaldehyde) **83**: 0.66 (UV, anisaldehyde)



Aldehyde **86**

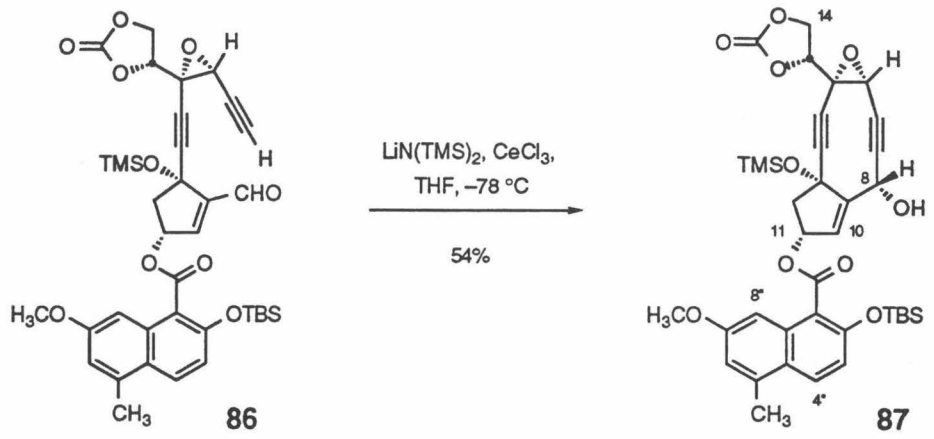
tert-Butyldimethylsilyl chloride (112 mg, 0.742 mmol, 2 equiv) was added in one portion to a solution of aldehyde **51** (220 mg, 0.371 mmol, 1 equiv), triethylamine (1.03 mL, 7.42 mmol, 20 equiv), and 4-dimethylaminopyridine (30 mg) in dichloromethane (25 mL) at 0 °C. The solution was stirred at 0 °C for 2.5 h and partitioned between 1:1 ethyl acetate/hexanes (50 mL) and water (50 mL). The layers were separated, and the aqueous layer was further extracted with 1:1 ethyl acetate/hexanes (2 25-mL portions). The combined organics were washed with saturated aqueous sodium chloride (50 mL), dried over sodium sulfate and concentrated. The residue was purified by flash column chromatography (20% ethyl acetate in hexanes grading to 50% ethyl acetate in hexanes) to afford aldehyde **86** (195 mg, 74%) as a colorless oil.

^{1}H NMR (400 MHz, C_6D_6), δ: 9.59 (s, 1H, C8 H), 7.61 (d, 1H, *J* = 9.08 Hz, C4" H), 7.19 (obscured, 1H, C8" H), 7.01 (s, 1H, C6" H), 6.91 (d, 1H, *J* = 9.13 Hz, C3" H), 6.69 (s, 1H , C10 H), 6.15 (m, 1H, C11 H), 3.97 (dd, 1H, *J* = 8.86, 4.82 Hz, C13 H), 3.57 (s, 3H, C7" OC**H**$_3$), 3.41 (m, 2H, C14 H and C12 βH), 3.13 (dd, 1H, *J* = 7.96, 4.92 Hz, C14 H), 2.86 (d, 1H, *J* = 1.29 Hz, C5 H), 2.31 (s, 3H, C5" C**H**$_3$), 2.25 (d, 1H, *J* = 1.27 Hz, C7 H), 1.13 (s, 9H, OSiC(C**H**$_3$)$_3$(CH$_3$)$_2$), 0.31 (s, 9H, OSi(C**H**$_3$)$_3$), 0.29 (s, 3H, OSiC(CH$_3$)$_3$(C**H**$_3$)$_2$), 0.27 (s, 3H, OSiC(CH$_3$)$_3$(C**H**$_3$)$_2$).

FTIR (thin film), cm^{-1}: 3281(w, C≡C-H), 2955 (m), 2857 (m), 2131 (w, C≡C), 1823 (s, carbonate C=O), 1728 (m, ester C=O), 1699 (m, aldehyde C=O), 1621 (m), 1410 (m), 1256 (s), 1094 (m).

TLC (50% EtOAc in Hexanes), R*f*: **51**: 0.36 (UV, anisaldehyde)

86: 0.50 (UV, anisaldehyde)



Cyclic alcohol **87**

A suspension of aldehyde **86** (87 mg, 0.12 mmol, 1 equiv) and cerium(III) chloride (91 mg, 0.37 mmol, 3 equiv) in THF (6 mL) was stirred vigorously at 23 °C for 10 min and cooled to –78 °C. Lithium hexamethyldisilazide (136 μL of a freshly prepared 1.0 M solution in hexanes, 0.136 mmol, 1.1 equiv) was added dropwise via syringe over 2 min. After maintaining the reaction at –78 °C for an additional 10 min, excess base was quenched by addition of saturated aqueous ammonium chloride (10 mL) and the reaction mixture was warmed to 23 °C. The reaction mixture was partitioned between 1:1 ethyl acetate/hexanes (15 mL) and water (10 mL). The layers were separated, and the aqueous layer was further extracted with 1:1 ethyl acetate/hexanes (2 15-mL portions). The combined organics were washed with saturated aqueous sodium chloride (15 mL), and were dried over sodium sulfate and concentrated. The residue was purified by flash column chromatography (25% ethyl acetate in hexanes) to afford the cyclic alcohol **87** (47 mg, 54%) as a colorless oil.

^{1}H NMR (400 MHz, C_6D_6), δ: 7.57 (d, 1H, *J* = 9.16 Hz, C4" H), 7.17 (s, 1H, C8" H), 6.99 (m, 1H, C6" H), 6.88 (d, 1H, *J* = 9.16 Hz, C3" H), 6.36 (t, 1H, *J* = 1.80 Hz, C10 H), 6.02 (m, 1H, C11 H), 5.14 (br s, 1H, C8 H), 3.56 (m, 1H, C13 H), 3.55 (s, 3H, C7" OCH_3), 3.37 (dd, 1H, *J* = 8.40, 5.84 Hz, C14 H), 3.23 (t, 1H, *J* = 8.76 Hz, C14 H), 3.14 (dd, 1H, *J* = 13.92, 7.32 Hz, C12 βH), 2.85 (s, 1H, C5 H), 2.41 (dd, 1H, *J* = 13.92, 4.76 Hz, C12 αH), 2.28 (s, 3H, C5" CH_3), 1.09 (s, 9H, $OSiC(CH_3)_3(CH_3)_2$), 0.26 (s, 3H, $OSiC(CH_3)_3(CH_3)_2$), 0.24 (s, 3H, $OSiC(CH_3)_3(CH_3)_2$), 0.20 (s, 9H, $OSi(CH_3)_3$).

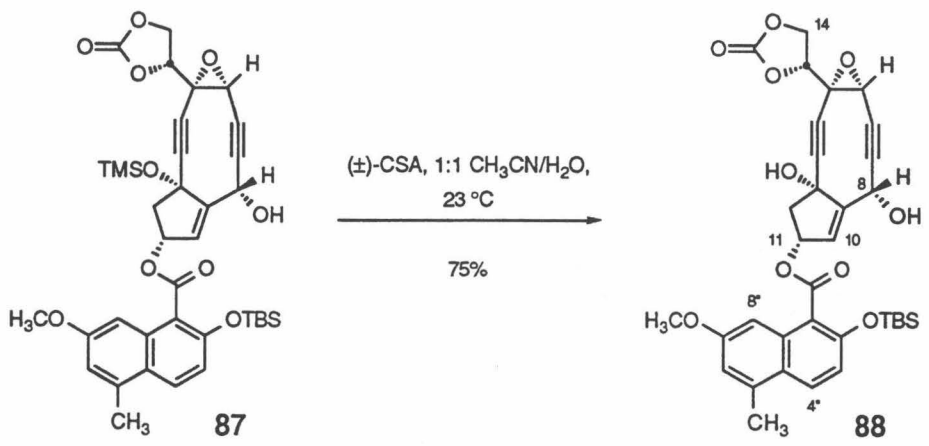
^{13}C NMR (100 MHz, C_6D_6) δ: 168.1, 158.9, 157.1, 153.5, 151.3, 136.5, 133.6, 127.2, 125.9, 123.9, 120.9, 118.1, 117.2, 101.0, 96.8, 87.9, 86.4, 85.0, 76.7, 76.2, 73.7, 65.6, 60.3, 58.6, 54.7, 52.5, 48.2, 25.7, 19.1, 18.3, 1.4, –4.2.

FTIR (thin film), cm^{-1}: 3459 (w, OH), 2954 (m), 1822 (s, carbonate C=O), 1724 (ester C=O), 1620 (m), 1409 (m), 1256 (s), 1096 (s), 842 (s).

TLC (50% EtOAc in Hexanes), R*f*:

86: 0.57 (UV, anisaldehyde)

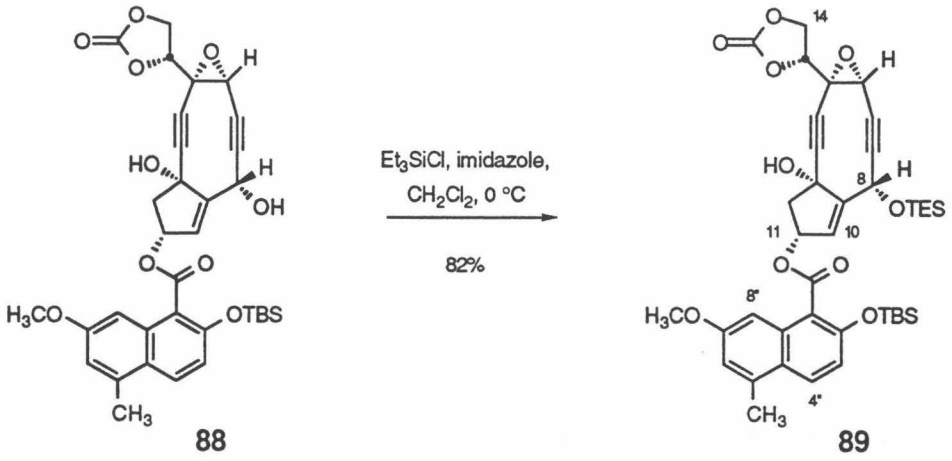
87: 0.47 (fluoresces under UV, anisaldehyde)



Diol **88**

(±)-Camphorsulfonic acid (163 mg, 0.702 mmol, 5 equiv) was added in one portion to a solution of the cyclic alcohol **87** (99 mg, 0.140 mmol, 1 equiv) in 1:1 acetonitrile/water (26 mL) at 23 °C. The solution was stirred at 23 °C for 1 h, and extracted with 1:1 ethyl acetate/hexanes (3 25-mL portions). The combined organics were washed once with saturated aqueous sodium chloride (25 mL), dried over sodium sulfate and concentrated. Purification of the residue by flash column chromatography (50% ethyl acetate in hexanes) afforded diol **88** (67 mg, 75%) as a yellow oil that rapidly darkened upon standing.

^{1}H NMR (400 MHz, C_6D_6), δ:	7.59 (d, 1H, *J* = 8.60 Hz, C4" H), 7.14 (s, 1H, C8" H), 7.01 (s, 1H, C6" H), 6.90 (d, 1H, *J* = 8.96 Hz, C3" H), 6.28 (s, 1H, C10 H), 5.78 (m, 1H, C11 H), 4.99 (br s, 1H, C8 H), 3.64 (m, 1H, C13 H), 3.54 (s, 3H, C7" OCH_3), 3.26 (m, 3H, C14 H, C12 αH), 2.94 (dd, 1H, *J* = 15.20, 7.40 Hz, C12 βH), 2.81 (s, 1H, C5 H), 2.30 (s, 3H, C5" CH_3), 1.10 (s, 9H, $OSiC(CH_3)_3(CH_3)_2$), 0.26 (s, 6H, $OSiC(CH_3)_3(CH_3)_2$).
^{13}C NMR (100 MHz, C_6D_6), δ:	167.7, 158.5, 156.1, 150.8, 135.9, 135.2, 133.1, 123.5, 119.8, 117.8, 117.7, 116.8, 100.5, 96.3, 89.5, 86.0, 83.3, 75.7, 75.5, 73.6, 65.4, 60.1, 59.5, 58.2, 54.4, 52.5, 46.6, 25.3, 19.9, 18.7, 17.8, 13.5, -4.6, -4.7.
$[\alpha]_D^{20}$:	+50.93° (*c* 0.23, C_6D_6)
TLC (50% EtOAc in Hexanes), R*f*:	**87**: 0.43 (fluoresces under UV, anisaldehyde) **88**: 0.25 (fluoresces under UV, anisaldehyde)



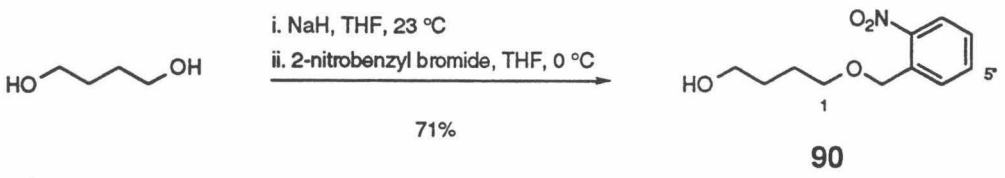
Triethylsilyl ether **89**

Imidazole (57 mg, 0.84 mmol, 5 equiv) was added in one portion to a solution of the diol **88** (106 mg, 0.17 mmol, 1 equiv) in dichloromethane (8 mL) at 0 °C. Triethylsilyl chloride (31 μL, 28 mg, 0.18 mmol, 1.1 equiv) was added dropwise via syringe. The reaction was checked by thin layer chromatography (TLC, 50% ethyl acetate/hexanes), which indicated approximately 50% conversion. An additional portion of triethylsilyl chloride (16 μL, 14 mg, 0.094 mmol, 0.55 equiv) was added via syringe. The reaction was determined to be complete by TLC, and was diluted with 1:1 ethyl acetate/hexanes (30 mL). The reaction mixture was then washed with water (2 15-mL portions). The combined aqueous layers were further extracted with 1:1 ethyl acetate/hexanes (2 25-mL portions). The combined organics were washed with saturated aqueous sodium chloride (30 mL), dried over sodium sulfate and concentrated. Purification of the residue by flash column chromatography (40% ethyl acetate in hexanes) afforded triethylsilyl ether **89** (103 mg, 82%) as a pale yellow oil.

^{1}H NMR (400 MHz, C_6D_6), δ: 7.58 (d, 1H, *J* = 9.16 Hz, C4" H), 7.22 (s, 1H, C8" H), 6.99 (m, 1H, C6" H), 6.88 (d, 1H, *J* = 9.16 Hz, C3" H), 6.51 (t, 1H, *J* = 1.84 Hz, C10 H), 5.93 (m, 1H, C11 H), 5.49 (t, 1H, *J* = 1.44 Hz, C8 H), 3.64 (dd, 1H, *J* = 8.80, 5.48 Hz, C13 H), 3.59 (s, 3H, C7" OCH_3), 3.42 (dd, 1H, *J* = 8.44, 5.52 Hz, C14 H), 3.34 (t, 1H, *J* = 8.40 Hz, C14 H), 3.17 (dd, 1H, *J* = 14.64, 7.68 Hz, C12 βH), 2.82 (s, 1H, C5 H), 2.43 (dd, 1H, *J* = 14.64, 3.64 Hz, C12 αH), 2.31 (s, 3H, C5" CH_3), 1.11 (s, 9H, $OSiC(CH_3)_3(CH_3)_2$), 1.03 (t, 9H, J = 8.04 Hz, $OSi(CH_2CH_3)_3$), 0.69 (m, 6H, $OSi(CH_2CH_3)_3$), 0.27 (s, 3H, $OSiC(CH_3)_3(CH_3)_2$), 0.26 (s, 3H, $OSiC(CH_3)_3(CH_3)_2$).

^{13}C NMR (75 MHz, C_6D_6) δ: 168.2, 159.1, 157.0, 153.8, 151.6, 136.5, 133.8, 128.5, 127.4, 124.1, 120.3, 118.3, 117.4, 101.1, 97.0, 90.3, 86.2, 84.0, 76.1, 75.6, 74.0, 65.8, 60.6, 59.4, 54.9, 53.0, 47.8, 25.9, 19.3, 18.4, 7.0, 6.9, 4.9, -4.0, -4.1.

FTIR (thin film), cm^{-1}:	3448 (m, OH), 2955 (s), 1821 (s, carbonate C=O), 1723 (s, ester C=O), 1620 (s), 1409 (s), 1260 (s), 1081 (s), 865 (s).
$[\alpha]_D^{20}$:	+31.58° (*c* 0.19, C_6H_6)
TLC (50% EtOAc in Hexanes), R*f*:	**88**: 0.29 (fluoresces under UV, anisaldehyde) **89**: 0.69 (fluoresces under UV, anisaldehyde)

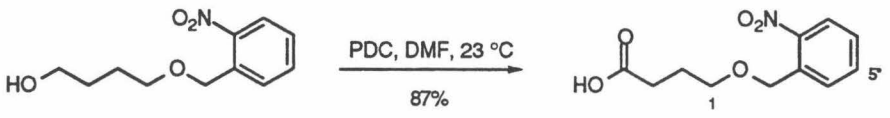


90

1-(2-Nitrobenzyl)-1,4-butanediol (**90**)

Sodium hydride (222 mg of a 60% dispersion in mineral oil, 5.55 mmol, 1 equiv) was added to a flame dried 25 mL flask under argon atmosphere. The solid was washed with dry hexanes (3 1-mL portions), and THF (11 mL) was introduced into the flask. 1,4-Butanediol (490 μL, 5.55 mmol, 1 equiv) was added dropwise via syringe to the suspension, and gas evolution was observed. After 1 h of stirring at 23 °C, the yellow suspension was cooled to 0 °C and a solution of 2-nitrobenzyl bromide (1.20 g, 5.55 mmol, 1 equiv) in THF (1 mL) was added dropwise via cannula over 2 min. The resultant yellow suspension was maintained at 0 °C for 7 h, and excess sodium hydride was quenched by the addition of water (10 mL). The reaction mixture was extracted with ethyl acetate (3 25-mL portions). The combined organics were washed with saturated aqueous sodium chloride (25 mL), dried over sodium sulfate and concentrated. The residue was purified by flash column chromatography (50% ethyl acetate in hexanes) to provide the alcohol **90** (883 mg, 71%) as a pale yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$), δ:	8.03 (d, 1H, J = 8.3 Hz, C3' H), 7.75 (d, 1H, *J* = 7.8 Hz, C4' H), 7.63 (t, 1H, *J* = 6.1 Hz, C6' H), 7.42 (t, 1H, *J* = 7.33 Hz, C5' H), 4.86 (s, 2H, *o*-$NO_2C_6H_4CH_2O$), 3.67 (t, 2H, *J* = 6.1 Hz, C1 H), 3.60 (t, 2H, *J* = 6.1 Hz, C4 H), 2.09 (br s, 1H OH), 1.70 (m, 4 H, C2, C3 H)
FTIR (thin film), cm^{-1}:	3386 (m, OH), 2942 (m), 2869 (m), 1523 (s, N-O), 1341 (s, N-O), 1109 (m), 1067 (m), 858 (w).
TLC (50% EtOAc in Hexanes), R*f*:	2-nitrobenzyl bromide: 0.65 (UV, anisaldehyde) **90**: 0.33 (UV, anisaldehyde)



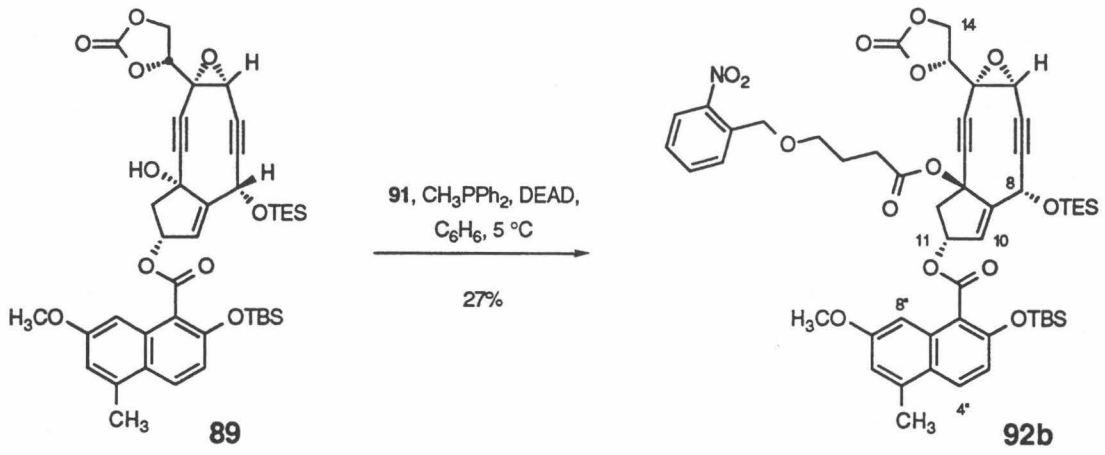
90 **91**

Acid **91**

Pyridinium dichromate (3.34 g, 8.92 mmol, 10 equiv) was added in one portion to a solution of alcohol **90** (200 mg, 0.892 mmol, 1 equiv) in N,N-dimethylformamide (5 mL) at 23 °C. The reaction mixture was kept in the dark at 23 °C for 15 h, and diluted with water (50 mL). The reaction mixture was acidified to pH 3 with 10% aqueous hydrochloric acid (10 mL) and extracted with diethyl ether (3 20-mL portions). The combined organics were washed with saturated aqueous sodium chloride (30 mL), dried over sodium sulfate and concentrated. Purification of the residue by flash column chromatography (10% methanol in dichloromethane) afforded acid **91** (186 mg, 87%) as a pale yellow oil that solidified upon standing.

^{1}H NMR (300 MHz, $CDCl_3$), δ: 8.05 (d, 1H, *J* = 8.2 Hz, C3' H), 7.75 (d, 1H, *J* = 7.6 Hz, C6' H), 7.64 (t, 1H, *J* = 7.3 Hz, C5' H), 7.42 (t, 1H, *J* = 7.6 Hz, C4' H), 4.86 (s, 2H, *o*- $NO_2C_6H_4CH_2O$), 3.63 (t, 2H, *J* = 6.1 Hz, C1 H), 2.50 (t, 2H, J = 7.2 Hz, C3 H), 2.02 (m, 2 H, C2 H).

FTIR (thin film), cm^{-1}:	3083 (m, OH), 2939 (m), 2872 (m), 1707 (s, C=O), 1525 (s, N-O), 1342 (s, N-O), 1112 (m), 729 (w).
TLC (10% CH_3OH in CH_2Cl_2), R*f*:	**90**: 0.43 (UV, anisaldehyde) **91**: 0.32 (UV, anisaldehyde)



Mitsunobu diester **92b**

A flame-dried 10-mL Schlenk flask under an argon atmosphere was charged with 1.5 mL of a 10 mg/mL stock solution in benzene containing the alcohol **89** (15 mg, 2.0 x 10^{-2} mmol, 1 equiv). The solvent was removed in vacuo, and 1.13 mL freshly distilled benzene was added. Acid **91** (72 mg, 0.30 mmol, 15 equiv) was added in one portion, and the resultant pale yellow solution was cooled to 5 °C in an ice/water bath. Methyl diphenylpholsphine (56 μL, 60 mg, 0.30 mmol, 15 equiv) and a solution of diethyl azodicarboxylate (31 μL, 0.20 mmol, 15 equiv) in anhydrous benzene (375 μL) were added sequentially over 1 min via syringe to the cooled solution. The resultant orange solution was maintained at 5 °C for a period of 15 min. At this point, the reaction was judged to be complete by TLC analysis.

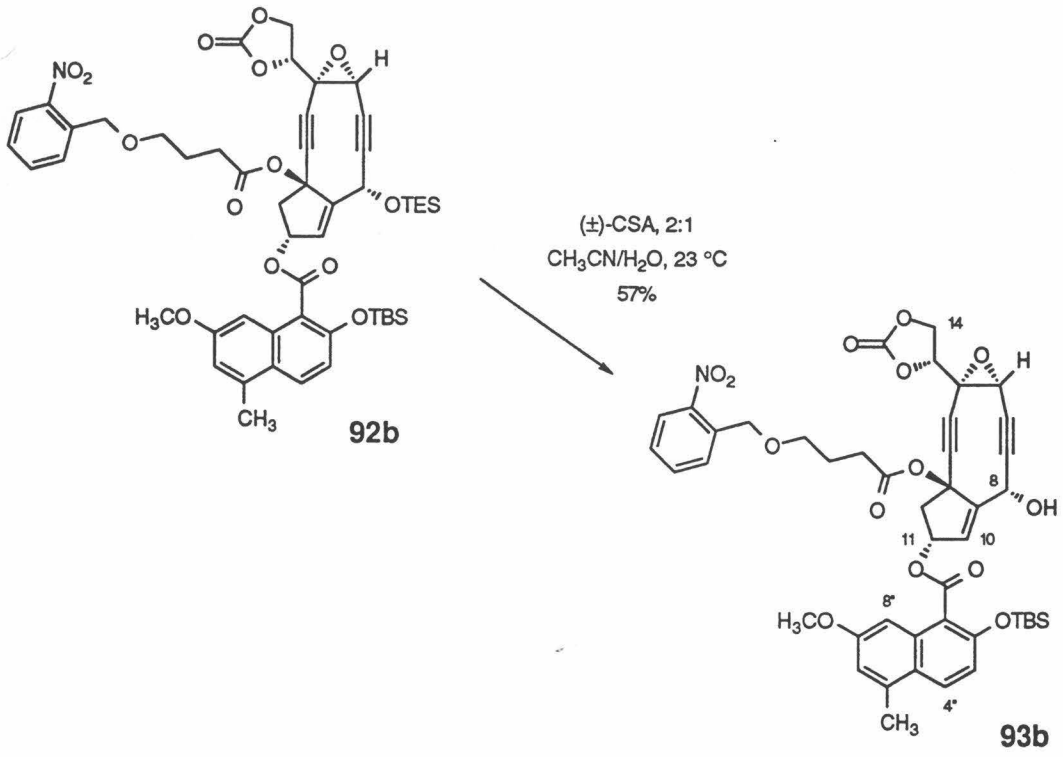
Determination of the HPLC yield of the reaction and preparatory purification of the product was accomplished as follows: A solution of 1,3,5-trimethoxybenzene in acetonitrile (200 μL of a 1.0 M solution, 0.20 mmol) was added to the crude reaction mixture as an internal standard, and the resultant solution was filtered through a small plug

of cotton in the tip of a Pasteur pipet. Two 1-mL benzene washings of the pipet were also made, bringing the final volume of the crude reaction solution to approximately 3.3 mL. For analytical HPLC: 10 μL of this solution was removed and placed in a half-dram vial. The solution was briefly concentrated to near dryness on a rotary evaporator, and quickly diluted with 100 μL acetonitrile. Injections of 100 μL were made onto the HPLC (Beckman ODS C18 semi-prep column (10 mm x 25 cm) with a solvent system comprising 65% 10 mM pH 5.5 sodium acetate/ 35% acetonitrile grading to 100% acetonitrile over 20 min at a flow rate of 2.0 mL/min, monitoring at 240 nm. Retention times: 1,3,5-trimethoxybenzene: 19 min; Mitsunobu product: 37 min.). The yield was based on the average of two injections, and was found to be 8.75×10^{-3} mmol (44%). For preparatory HPLC: 600-900 μL of the stock solution was removed and added to a half-dram vial. The solution was concentrated to near dryness on a rotary evaporator and rapidly diluted with 500 μL acetonitrile. The entire sample was injected onto the HPLC (Vydac 201HS1022 C18 column (22 mm x 25 cm) and an isocratic solvent system comprising 14% 10 mM aqueous ammonium acetate (pH 5.5)/86% acetonitrile at a flow rate of 7.0 mL/minute, monitoring at 240 nm. The retention time of the Mitsunobu product was approximately 30 minutes.). As the peak was eluting, collections were made in a test tube just outside of the detector on the HPLC. The acetonitrile/buffer solution was concentrated in vacuo to remove acetonitrile, and the concentrate was diluted with benzene and stored in the freezer until all injections were complete. Subsequent collections were handled identically and pooled with previous collections. After the final collection and pooling, the layers were separated, and the aqueous layer further extracted with benzene (2 0.5-mL portions). The combined organics were dried over sodium sulfate and were concentrated to a volume of ca. 0.1 mL. Quantitation of the isolated product was performed as described in the next paragraph. Following this protocol, the reaction product could be cleanly isolated in approximately 13 runs on the HPLC.

Quantitation of the isolated product was accomplished as follows: A 0.5 mL portion of deuteriated benzene (99.5 atom % D) was added to the concentrated benzene solution, and the resultant solution was concentrated to a volume of ca. 0.1 mL. This procedure was repeated 4 times. After the last iteration, the concentrated solution was taken up in approximately 0.4 mL deuteriated benzene (99.95 atom % D). *trans*-Dichloroethylene (5 μL of a 0.0648 M solution in deuteriated chloroform (5 μL dichloroethylene diluted to 1.0 mL)) was added as an internal standard. Analysis of **92b** by ^{1}H NMR and integration of the internal standard against the C8 proton provided the isolated yield of the product (5.39×10^{-3} mmol, 27%).

^{1}H NMR (400 MHz, C_6D_6), δ: 7.73 (d, 1H, *J* = 8.40 Hz, $NO_2C_6\mathbf{H}_4CH_2O$), 7.60 (d, 2H *J* = 9.20 Hz, C3" and C4" H), 7.30-7.18 (1H, obscured, C8" H), 7.12 (t, 1H *J* = 8.00 Hz, $NO_2C_6\mathbf{H}_4CH_2O$), 7.02 (s, 1H, C6" H), 6.91 (d, 1H, *J* = 8.80 Hz, $NO_2C_6\mathbf{H}_4CH_2O$), 6.77 (t, 1H, *J* = 8.00 Hz, $NO_2C_6\mathbf{H}_4CH_2O$), 6.33 (m, 1H, C11 H), 6.31 (d, 1H, *J* = 2.20 Hz, C10 H), 5.16 (s, 1H, C8 H), 4.70 (s, 2H, 2- $NO_2C_6H_4C\mathbf{H}_2O$), 3.63 (s, 3H, C7" $OC\mathbf{H}_3$), 3.58 (dd, 1H, *J* = 8.40, 6.00 Hz, C13 H), 3.42-3.36 (complex, 2H, C14 H), 3.31-3.22 (complex, 3H, C12 βH and $O_2CCH_2CH_2C\mathbf{H}_2O$), 3.07 (dd, 1H, *J* = 15.30, 4.00 Hz, C12 αH), 2.96 (s, 1H, C5 H), 2.38 (td, 2H, *J* = 7.20, 2.80 Hz, $O_2CC\mathbf{H}_2CH_2CH_2O$), 2.32 (s, 3H, C5" $C\mathbf{H}_3$), 1.89 (m, 2H, $O_2CCH_2C\mathbf{H}_2CH_2O$), 1.13 (s, 9H, $OSiC(C\mathbf{H}_3)_3(CH_3)_2$), 1.07 (t, 9H, *J* = 8.00 Hz, $OSi(CH_2C\mathbf{H}_3)_3$), 0.93 (m, 6H, $OSi(C\mathbf{H}_2CH_3)_3$), 0.30 (s, 3H, $OSiC(CH_3)_3(C\mathbf{H}_3)_2$), 0.27 (s, 3H, $OSiC(CH_3)_3(C\mathbf{H}_3)_2$).

TLC (5% EtOAc in CH_2Cl_2), R*f*: **89**: 0.38 (fluoresces under UV, anisaldehyde)
92b: 0.54 (fluoresces under UV, anisaldehyde)



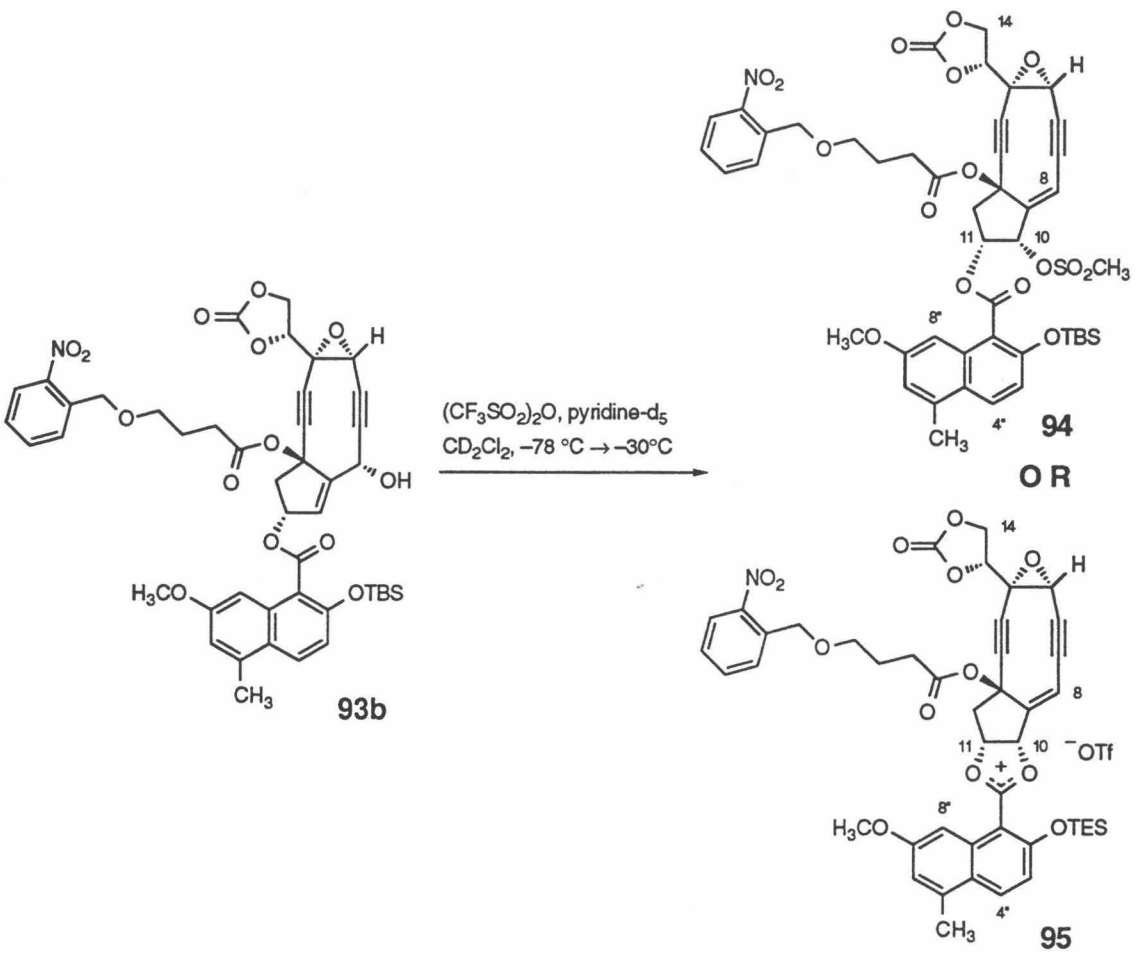
Secondary alcohol **93b**

(±)-Camphorsulfonic acid (2.3 mg, 0.0098 mmol, 5 equiv) was added in one portion to a solution of the Mitsunobu diester **92b** (0.0020 mmol, 1 equiv) in 2:1 acetonitrile/water (325 μL). The solution was held at 23 °C for 40 min, then extracted with 1:1 ethyl acetate/hexanes (3 5-mL portions). The combined organics were washed with saturated aqueous sodium chloride (5 mL), and were dried over sodium sulfate and concentrated. Purification of the residue by flash column chromatography (50% ethyl acetate in hexanes) was followed by pooling the fractions containing the alcohol and concentrating to approximately 100 μL. A 0.5 mL portion of deuteriated benzene (99.5 atom % D) was added to the concentrated solution, and the resultant solution was concentrated to a volume of ca. 0.1 mL. This procedure was repeated 4 times. After the

last iteration, the concentrated solution was taken up in approximately 0.4 mL deuteriated benzene (99.95 atom % D). *trans*-Dichloroethylene (5 μL of a 0.0648 M solution in deuteriated chloroform (5 μL dichloroethylene diluted to 1.0 mL)) was added as an internal standard. Analysis of the sample by ^{1}H NMR and integration of the internal standard against the C-8 proton provided the isolated yield of the **93b** (1.11×10^{-3} mmol, 57%).

^{1}H NMR (400 MHz, C_6D_6), δ: 7.65 (dd, 1H, *J* = 8.40, 1.08 Hz, 2-$NO_2C_6\mathbf{H}_4CH_2O$), 7.57 (d, 1H, *J* = 9.16 Hz, C4" H), 7.47 (d, 1H, *J* = 7.72 Hz, $NO_2C_6\mathbf{H}_4CH_2O$), 7.13 (d, 1H, *J* = 2.20 Hz, C8" H), 7.08 (td, 1H *J* = 7.68, 1.12 Hz, $NO_2C_6\mathbf{H}_4CH_2O$), 7.00 (br s, 1H, C6" H), 6.87 (d, 1H, *J* = 8.80 Hz, C3" H), 6.74 (t, 1H, *J* = 7.32 Hz, $NO_2C_6\mathbf{H}_4CH_2O$), 6.12 (d, 1H, *J* = 1.84 Hz, C10 H), 6.11 (m, 1H, C11 H), 4.18 (d, 1H, *J* = 9.52 Hz, C8 H), 4.71 (abq, 2H, *J* = 14.64 Hz, Δν = 35.52 Hz, 2-$NO_2C_6H_4C\mathbf{H}_2O$), 3.64 (m, 1H, C13 H), 3.62 (s, 3H, C7" $OC\mathbf{H}_3$), 3.48 (d, 1H, *J* = 9.52 Hz, O**H**), 3.26 (m, 2H, $O_2CCH_2CH_2C\mathbf{H}_2O$), 3.23 (dd, 2H, *J* = 2.56, 1.84 Hz, C14 H), 3.00 (d, 2H, *J* = 5.48 Hz, C12 H), 2.91 (s, 1H, C5 H), 2.30 (s, 3H, C5" $C\mathbf{H}_3$), 2.12 (m, 2H, $O_2C\mathbf{H}_2CH_2CH_2O$), 1.73 (m, 2H, $O_2CCH_2C\mathbf{H}_2CH_2O$), 1.10 (s, 9H, $OSiC(C\mathbf{H}_3)_3(CH_3)_2$), 0.27 (s, 3H, $OSiC(CH_3)_3(C\mathbf{H}_3)_2$), 0.24 (s, 3H, $OSiC(CH_3)_3(C\mathbf{H}_3)_2$).

TLC (50% EtOAc in Hexanes), R*f*:	**92b**: 0.53 (fluoresces under UV, anisaldehyde) **93b**: 0.22 (fluoresces under UV, anisaldehyde)



Rearranged trifluoromethanesulfonate **94** or dioxolenium ion **95**

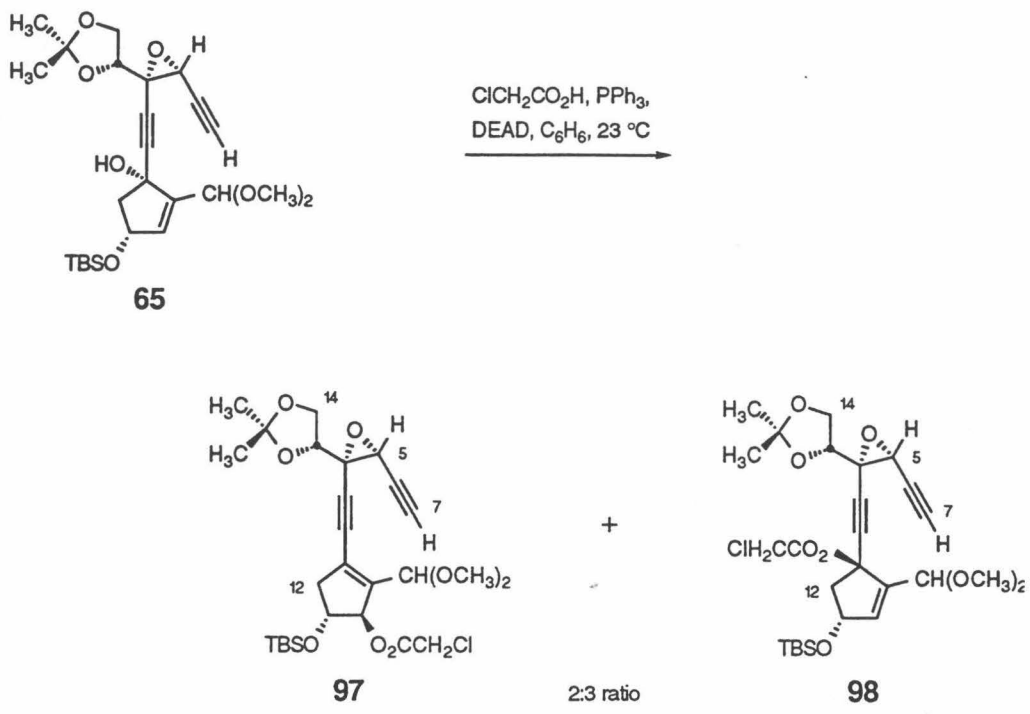
A solution the alcohol **93b** (1.9 x 10^{-3} mmol, 1 equiv) in CD_2Cl_2 (99.95 atom % D, 400 μL) was placed in an NMR tube, which was sealed with a septum and cooled to –78 °C. Pyridine-d_5 (3.0 μL, 3.2 mg, 3.8 x 10^{-2} mmol, 20 equiv) was added via syringe. The tube was tilted carefully to wash the pyridine into solution, and the reaction mixture was re-cooled to –78 °C. Trifluoromethanesulfonic anhydride (3.0 μL, 5.4 mg, 1.9 x 10^{-2} mmol, 10 equiv) was added to the cold reaction mixture via syringe. Keeping the solution as cold

as possible, the NMR tube was inserted quickly into the probe of a JEOL GX-400 spectrometer that had been pre-cooled to –70 °C. After obtaining a spectrum of unreacted diester alcohol at –70 °C, the probe was warmed to –30 °C. After adjusting the shims, a new spectrum was obtained which indicated complete and clean conversion to a product corresponding to either trifluoromethanesulfonate **94** or dioxolenium ion **95**. The probe was also warmed to 0 °C, and the spectrum obtained at this temperature was identical to that obtained at –30 °C.

^{1}H NMR (400 MHz, CD_2Cl_2), δ: 8.40 Hz (d, 1H, *J* = 9.12 Hz, C4" H), 8.00 (d, 1H, *J* = 8.08 Hz, $NO_2C_6\mathbf{H}_4CH_2O$), 7.79 (s, 1H, C8" H), 7.72 (d, 1H, *J* = 7.68 Hz, $NO_2C_6\mathbf{H}_4CH_2O$), 7.67 (t, 1H, *J* = 7.32 Hz, $NO_2C_6\mathbf{H}_4CH_2O$), 7.45 (t, 1H, *J* = 7.32 Hz, $NO_2C_6\mathbf{H}_4CH_2O$), 7.03 (s, 1H, C6" H), 6.92 (d, 1H, *J* = 9.16 Hz, C3" H), 6.85 (d, 1H, *J* = 7.68 Hz, C10 H), 6.40 (app. q, 1H, *J* = 7.68 Hz, C11 H), 6.25 (s, 1H, C8 H), 4.81 (s, 3H, $NO_2C_6H_4C\mathbf{H}_2O$), 4.80 (dd, 1H, *J* = 8.40, 5.48 Hz, C13 H), 4.60 (t, 1H, *J* = 8.80 Hz, C14 H), 4.37 (dd, 1H, *J* = 9.16, 5.88 Hz, C14 H), 3.94 (s, 3H, C7" $OC\mathbf{H}_3$), 3.93 (s, 1H, C5 H), 3.55 (t, 2H, *J* = 5.84 Hz, $O_2CCH_2CH_2C\mathbf{H}_2O$), 3.47 (dd, 1H, *J* = 15.00, 7.32 Hz, C12 βH), 2.64 (s, 3H, C5" $C\mathbf{H}_3$), 2.54 (dd, 1H, *J* = 15.76, 6.24 Hz, C12 αH), 2.48 (t, 2H, *J* = 7.32 Hz, $O_2CC\mathbf{H}_2CH_2CH_2O$), 1.91 (app. t, 2H, *J* = 6.20 Hz, $O_2CCH_2C\mathbf{H}_2CH_2O$), 1.01 (s, 9H, $OSiC(C\mathbf{H}_3)_3(CH_3)_2$), 0.41 (s, 6H, $OSiC(CH_3)_3(C\mathbf{H}_3)_2$).

TLC (50% EtOAc in Hexanes), R*f*: **93b**: 0.21 (fluoresces under UV, anisaldehyde)

94 or **95**: 0.37 (fluoresces under UV, anisaldehyde)



Esters **97** and **98**

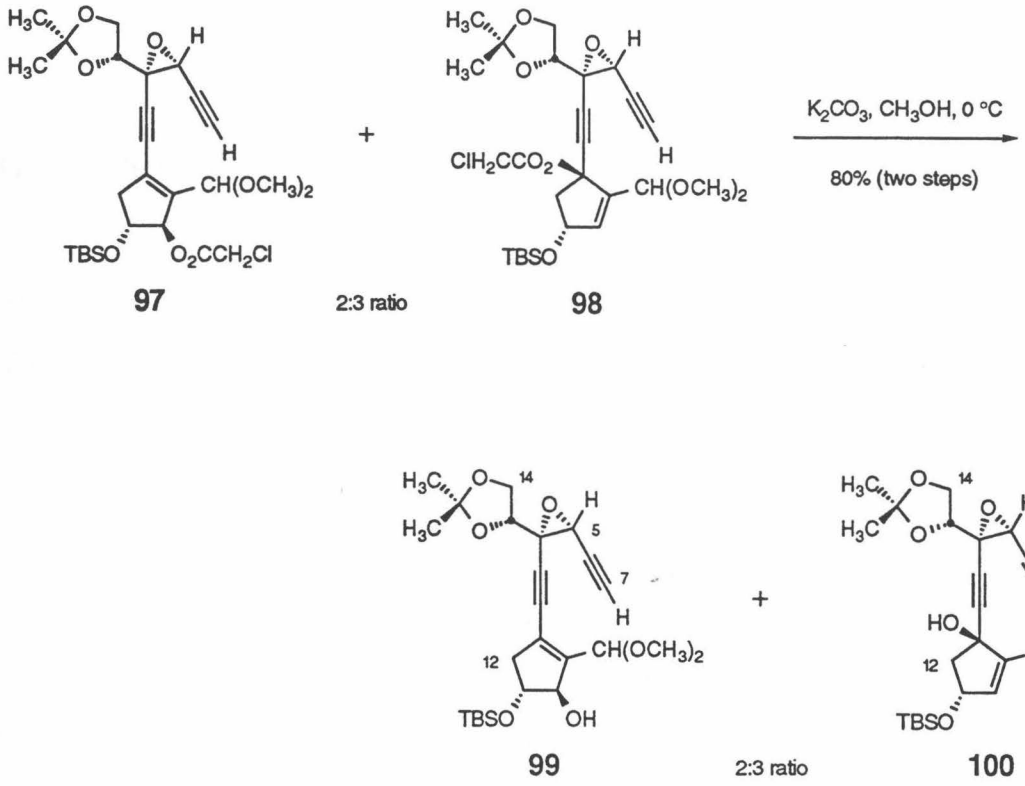
Diethyl azodicarboxylate (237 mL, 1.50 mmol, 10 equiv) was added dropwise via syringe over 3 min to a solution of alcohol **65** (72 mg, 0.15 mmol, 1 equiv), triphenylphosphine (395 mg, 1.50 mmol, 10 equiv), and chloroacetic acid (142 mg, 1.50 mmol, 10 equiv) in benzene (8 mL) at 23 °C. The orange reaction mixture was stirred at 23 °C for 10 h, then volatiles were removed in vacuo. The residue was purified by flash column chromatography (10% ethyl acetate in hexanes grading to 30% ethyl acetate in hexanes) to provide an inseparable mixture of esters **97** and **98** as well as a small amount of the chloroacetic acid-diethyl azodicarboxylate adduct. The yield was not determined at this point, but the mixture of esters was instead carried directly to the next step.

For 97:

^{1}H NMR (400 MHz, C_6D_6), δ: (Diagnostic peaks only)	6.18 (s, 1H, C10 H), 5.30 (s, 1H, C8 H), 4.27 (m, 1H, C11 H), 4.08 (dd, 1H, *J* = 8.79, 5.68 Hz, C13 H), 2.83 (dd, 1H, *J* = 16.36, 6.11 Hz, C12 βH), 2.44 (dd, 1H, *J* = 16.36, 2.44 Hz, C12 αH), 1.98 (d, 1H, *J* = 1.71 Hz, C7 H), 1.41 (s, 3H, $C(C\mathbf{H}_3)_2$), 1.21 (s, 3H, $C(C\mathbf{H}_3)_2$), 0.94 (s, 9H, $OSiC(C\mathbf{H}_3)_3(CH_3)_2$), 0.15 (s, 3H, $OSiC(CH_3)_3(C\mathbf{H}_3)_2$), 0.06 (s, 3H, $OSiC(CH_3)_3(C\mathbf{H}_3)_2$).
TLC (10% EtOAc in CH_2Cl_2), R*f*:	**65**: 0.29 (UV, anisaldehyde) **97**: 0.68 (UV, anisaldehyde)

For 98:

^{1}H NMR (400 MHz, C_6D_6), δ: (Diagnostic peaks only)	6.53 (s, 1H, C10 H), 5.55 (s, 1H, C8 H), 4.99 (m, 1H, C11 H), 4.17 (dd, 1H, *J* = 9.04, 5.86 Hz, C13 H), 3.93 (dd, 1H, *J* = 8.79, 6.84 Hz, C14 H), 3.09 (dd, 1H, *J* = 14.65, 6.35 Hz, C12 βH), 2.72 (dd, 1H, *J* = 14.65, 4.39 Hz, C12 αH), 2.13 (d, 1H, *J* = 1.71 Hz, C7 H), 1.44 (s, 3H, $C(CH_3)_2$), 1.18 (s, 3H, $C(CH_3)_2$), 0.92 (s, 9H, $OSiC(CH_3)_3(CH_3)_2$), 0.00 (s, 3H, $OSiC(CH_3)_3(CH_3)_2$), -0.01 (s, 3H, $OSiC(CH_3)_3(CH_3)_2$).
TLC (10% EtOAc in CH_2Cl_2), R*f*:	**65**: 0.29 (UV, anisaldehyde) **98**: 0.68 (UV, anisaldehyde)



Alcohols **99** and **100**

Potassium carbonate (10 mg) was added in one portion to a 0 ℃ solution of esters **97** and **98** (19 mg, 0.034 mmol, 1 equiv) in methanol (1 mL). After maintaining the solution at 0 ℃ for 10 min, the reaction mixture was partitioned between 1:1 ethyl acetate/hexanes (2 mL) and pH 7.2 phosphate buffer (2 mL). The layers were separated and the aqueous layer was further extracted with 1:1 ethyl acetate/hexanes (2 2-mL portions). The combined organics were washed with saturated aqueous sodium chloride (5 mL), dried over sodium sulfate and concentrated. Purification of the residue by flash

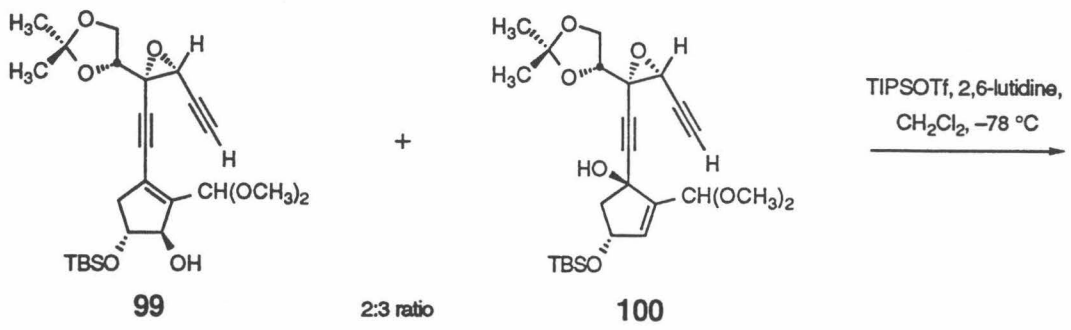
column chromatography (20% ethyl acetate in hexanes) afforded inseparable alcohols **99** and **100** (13 mg combined, 80%) as an approximately 2:3 mixture.

For alcohol 99:

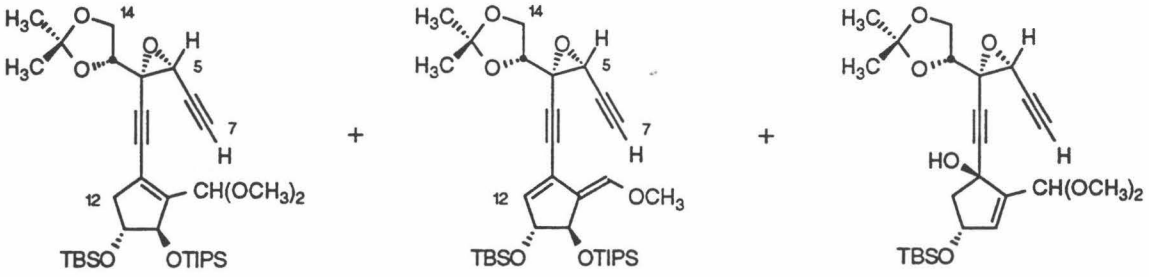
^{1}H NMR (400 MHz, C_6D_6), δ: (Diagnostic peaks only)	6.21 (t, 1H, *J* = 1.47 Hz, C10 H), 5.48 (s, 1H, C8 H), 5.11 (m, 1H, C11 H), 2.96 (dd, 1H, *J* = 13.92, 6.89 Hz, C12 βH), 2.57 (dd, 1H, *J* = 13.56, 5.13 Hz, C12 αH), 1.44 (s, 3H, $C(C\mathbf{H}_3)_2$), 1.19 (s, 3H, $C(C\mathbf{H}_3)_2$), 0.93 (s, 9H, $OSiC(C\mathbf{H}_3)_3(CH_3)_2$), 0.01 (s, 3H, $OSiC(CH_3)_3(C\mathbf{H}_3)_2$), 0.00 (s, 3H, $OSiC(CH_3)_3(C\mathbf{H}_3)_2$).
TLC (10% EtOAc in CH_2Cl_2), R*f*:	**97** and **98**: 0.80 (UV, anisaldehyde) **99**: 0.60 (UV, anisaldehyde)

For alcohol 100:

^{1}H NMR (400 MHz, C_6D_6), δ: (Diagnostic peaks only)	5.34 (s, 1H, C8 H), 5.07 (s, 1H, C10 H), 4.44 (m, 1H, C11 H), 2.90 (dd, 1H, *J* = 16.49, 5.50 Hz, C12 βH), 2.52 (dd, 1H, *J* = 16.48, 4.03 Hz, C12 αH), 1.40 (s, 3H, $C(CH_3)_2$), 1.21 (s, 3H, $C(CH_3)_2$), 1.00 (s, 9H, $OSiC(CH_3)_3(CH_3)_2$), 0.19 (s, 3H, $OSiC(CH_3)_3(CH_3)_2$), 0.13 (s, 3H, $OSiC(CH_3)_3(CH_3)_2$).
TLC (10% EtOAc in CH_2Cl_2), R*f*:	**97** and **98**: 0.80 (UV, anisaldehyde) **100**: 0.60 (UV, anisaldehyde)



99 **100**



101 (55% of theory) **102** (37% of theory) **100** (100% of theory)

Triisopropylsilyl ethers **101** and **102**

2,6-Lutidine (24 μL, 0.21 mmol, 20 equiv) and triisopropylsilyl trifluoromethanesulfonate (28 μL, 0.10 mmol, 10 equiv) were added sequentially via syringe to a solution of alcohols **99** and **100** (13 mg of the mixture, assume 5 mg **99**, 0.010 mmol, 1 equiv) in dichloromethane (1 mL) at –78 °C. After 15 min at –78 °C, the solution was warmed to 0 °C. After 3.5 h at 0 °C, excess triisopropylsilyl trifluoromethanesulfonate was quenched by addition of triethylamine (0.5 mL) and methanol (0.5 mL). The resultant solution was warmed to 23 °C and partitioned between

1:1 ethyl acetate/hexanes (2 mL) and pH 7.2 phosphate buffer (2 mL). The layers were separated and the aqueous layer was further extracted with 1:1 ethyl acetate/hexanes (2 2-mL portions). The combined organics were washed with saturated aqueous sodium chloride (3 mL), dried over sodium sulfate and concentrated. Purification of the residue by flash column chromatography (hexanes grading to 20% ethyl acetate in hexanes) afforded dimethyl acetal **101** (6.6 mg, 55%) as a colorless oil, methyl enol ether **102** (6.2 mg, 37%) as a colorless oil, and recovered alcohol **100** (8.3 mg, 100% recovery) as a colorless oil.

For 101:

^{1}H NMR (400 MHz, C_6D_6), δ: 5.45 (s, 1H, C8 H), 5.07 (s, 1H, C10 H), 4.29 (m, 1H, C11 H), 4.15 (dd, 1H, J = 8.55, 6.11 Hz, C13 H), 3.93 (dd, 1H, J = 8.55, 6.84 Hz, C14 H), 3.77 (t, 1H, J = 6.35 Hz, C14 H), 3.54 (d, 1H, J = 1.71 Hz, C5 H), 3.34 (s, 3H, $CH(OCH_3)_2$), 3.33 (s, 3H, $CH(OCH_3)_2$), 2.82-2.62 (obscured, 1H, C12 βH), 2.42 (br d, 1H, J = 15.87 Hz, C12 αH), 2.00 (d, 1H, J = 1.46 Hz, C7 H), 1.48-0.95 (complex, 21H, $OSi(CH(CH_3)_2)_3$), 0.91 (s, 9H, $OSiC(CH_3)_3(CH_3)_2$), 0.12 (s, 3H, $OSiC(CH_3)_3(CH_3)_2$), 0.05 (s, 3H, $OSiC(CH_3)_3(CH_3)_2$).

TLC (2% EtOAc in CH_2Cl_2), R*f*: **99** and **100**: 0.13 (UV, anisaldehyde)

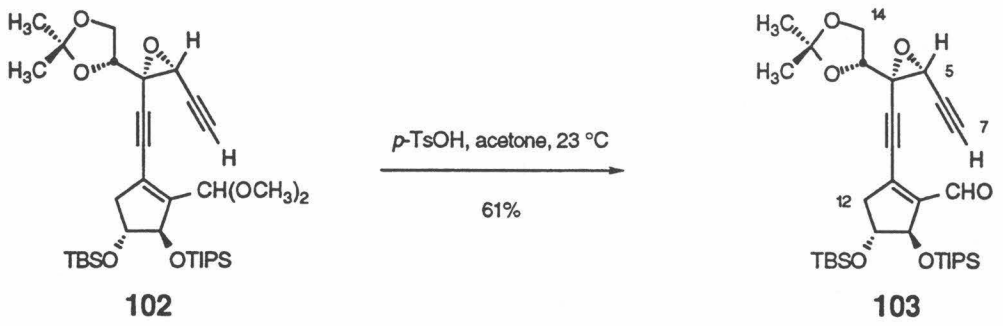
101: 0.56 (UV, anisaldehyde)

For 102:

^{1}H NMR (400 MHz, C_6D_6), δ: 6.66 (d, 1H, J = 0.74 Hz, C12 H), 6.14 (d, 1H, *J* = 2.19 Hz, C10 H), 5.21 (s, 1H, C8 H), 4.90 (d, 1H, J = 2.45 Hz, C11 H), 4.05 (dd, 1H, *J* = 8.79, 5.61 Hz, C13 H), 3.79 (dd, 1H, *J* = 8.79, 6.83 Hz, C14 H), 3.62 (t, 1H, *J* = 5.62 Hz, C14 H), 3.44 (d, 1H, *J* = 1.71 Hz, C5 H), 3.13 (s, 3H, CHOC**H**$_3$), 1.95 (d, 1H, *J* = 1.70 Hz, C7 H), 1.45-1.16 (complex, 21H, OSi(C**H**(C**H**$_3$)$_2$)$_3$), 0.96 (s, 9H, OSiC(C**H**$_3$)$_3$(CH$_3$)$_2$), 0.17 (s, 3H, OSiC(CH$_3$)$_3$(C**H**$_3$)$_2$), 0.08 (s, 3H, OSiC(CH$_3$)$_3$(C**H**$_3$)$_2$).

TLC (2% EtOAc in CH_2Cl_2), R*f*: **99** and **100**: 0.13 (UV, anisaldehyde)

102: 0.67 (UV, anisaldehyde)



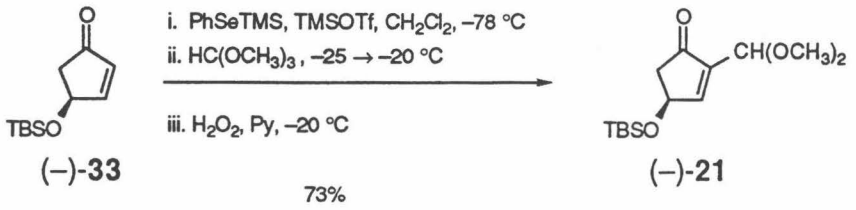
Aldehyde **103**

p-Toluenesulfonic acid (1 mg) was added in one portion to a solution of dimethyl acetal **101** (3.0 mg, 4.72 x 10^{-3} mmol, 1 equiv) in acetone (0.5 mL) at 23 °C. The resultant pale yellow solution was maintained at 23 °C for 45 min, and was partitioned between saturated aqueous sodium bicarbonate (2 mL) and hexanes (2 mL). The layers were separated and the aqueous layer was further extracted with hexanes (2 2-mL portions). The combined organic extracts were dried over sodium sulfate and concentrated. The crude aldehyde **103** (1.7 mg, 61%) was examined by ^{1}H NMR and judged to be sufficiently pure to proceed without further purification.

^{1}H NMR (400 MHz, C_6D_6), δ: 10.43 (s, 1H, C8 H), 5.28 (s, 1H, C10 H), 4.31 (d, 1H, *J* = 4.76 Hz, C11 H), 3.89 (dd, 1H, *J* = 8.79, 5.50 Hz, C13 H), 3.69 (dd, 1H, *J* = 8.79, 6.97 Hz, C14 H), 3.52 (t, 1H, *J* = 6.59 Hz, C14 H), 3.33 (d, 1H, *J* = 1.46 Hz, C5 H), 3.07 (dd, 1H, *J* = 17.96, 5.13 Hz, C12 βH), 2.45 (d, 1H, *J* = 18.31 Hz, C12 αH), 1.88 (d, 1H *J* = 1.83 Hz, C7 H), 1.60-1.11 (complex, 21H, $OSi(C\mathbf{H}(C\mathbf{H}_3)_2)_3$), 0.91 (s, 9H, $OSiC(C\mathbf{H}_3)_3(CH_3)_2$), 0.09 (s, 3H, $OSiC(CH_3)_3(C\mathbf{H}_3)_2$), 0.02 (s, 3H, $OSiC(CH_3)_3(C\mathbf{H}_3)_2$).

TLC (20% Hexanes in CH_2Cl_2), R*f*: **101**: 0.25 (UV, anisaldehyde)

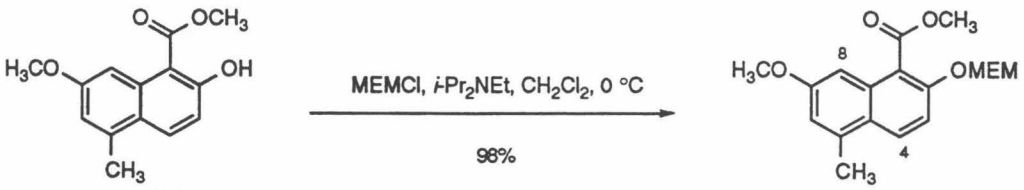
103: 0.37 (UV, anisaldehyde)



Enone (–)-**21**

Trimethylsilyl phenylselenide (4.76 mL, 28.3 mmol, 1.5 equiv) was added dropwise over 4 min to a solution of enone (–)-**33** (4.0 g, 19 mmol, 1.0 equiv) in dichloromethane (80 mL) at –78 °C. This was followed by dropwise addition of trimethylsilyl trifluoromethanesulfonate (1.11 mL, 5.65 mmol, 0.30 equiv). The resultant yellow solution was stirred at –78 °C for 10 min, and warmed to –20 °C for an additional hour. Freshly distilled trimethyl orthoformate (8.24 mL, 75.4 mmol, 4.0 equiv) was added dropwise via syringe over a 5 min period. The slightly darker yellow solution was maintained at –20 °C for an additional 20 min, and pyridine (2.4 mL) and 30% hydrogen peroxide (11.4 mL) were added sequentially through the top of the flask. The reaction mixture was kept at –20 °C for 15 min, during which time the yellow color faded to a pale yellow. After warming to 23 °C, the reaction mixture was diluted with 1:1 ethyl acetate/hexanes (200 mL). The layers were separated, and the organic layer was washed with water (100 mL) and saturated aqueous sodium chloride (100 mL), then was dried over sodium sulfate and concentrated. The residue was purified by flash column chromatography (10% ethyl acetate in hexanes grading to 15% ethyl acetate in hexanes) to provide enone (–)-**21** (3.9 g, 73%) as a pale yellow oil.

^{1}H NMR (300 MHz, C_6D_6), δ:	7.41 (s, 1H, vinylic **H**), 5.10 (s, 1H, **CH**$(OCH_3)_2$, 4.92 (m, 1H, **CH**OTBS), 3.32 (s, 6H, CH$(OCH_3)_2$), 2.78 (dd, 1H, J = 18.2, 5.5 Hz, methylene βH), 2.32 (dd, 1H, J = 18.2, 1 Hz, methylene αH), 0.90 (s, 9H, OSiC$(CH_3)_3(CH_3)_2$), 0.12 (s, 3H, OSiC$(CH_3)_3(CH_3)_2$), 0.10 (s, 3H, OSiC$(CH_3)_3(CH_3)_2$).
FTIR (thin film), cm^{-1}:	2953 (m), 2930 (m), 2856 (m), 1718 (s, C=O), 1059 (m).
TLC (20% EtOAc in Hexanes), R*f*:	(–)-**33**: 0.39 (UV, anisaldehyde) (–)-**21**: 0.30 (UV, anisaldehyde)

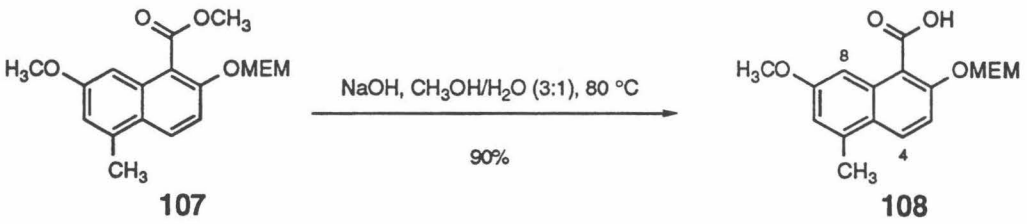


45 **107**

Naphthoate ester **107**

Diisopropylethylamine (7.06 mL, 40.6 mmol, 20 equiv) and MEM chloride (2.32 mL, 20.3 mmol, 10 equiv) were added sequentially via syringe to a solution of naphthoate ester **45** (1.00 g, 4.06 mmol, 1 equiv) in dichloromethane (100 mL) at 0 °C. The resultant yellow solution was maintained at 0 °C for 2 h, and partitioned between 1:1 ethyl acetate/hexanes (100 mL) and water (100 mL). The layers were separated and the aqueous layer was further extracted with ethyl acetate (2 30-mL portions). The combined organics were dried over sodium sulfate and concentrated. Purification of the residue by flash column chromatography (25% ethyl acetate in hexanes grading to 30% ethyl acetate in hexanes) afforded naphthoate ester **107** (1.33 g, 98%) as a colorless oil.

^{1}H NMR (400 MHz, C_6D_6), δ:	7.68 (d, 1H, *J* = 9.26 Hz, C4 H), 7.32 (d, 1H, *J* = 9.26 Hz, C3 H), 7.27 (s, 1H, C8 H), 7.00 (s, 1H, C6 H), 5.16 (s, 2H, $OCH_2OCH_2CH_2OCH_3$), 3.81 (s, 3H, CO_2CH_3), 3.73 (t, 2H, *J* = 5.89 Hz, $OCH_2OCH_2CH_2OCH_3$), 3.46 (s, 3H, C7 OCH_3), 3.31 (t, 2H, *J* = 5.89 Hz, $OCH_2OCH_2CH_2OCH_3$, 3.07 (s, 3H, $OCH_2OCH_2CH_2OCH_3$, 2.28 (s, 3H, C5 CH_3).
^{13}C NMR (100 MHz, C_6D_6) δ:	168.7, 159.2, 153.4, 136.6, 133.6, 127.5, 124.7, 119.7, 118.6, 113.4, 101.3, 94.4, 71.9, 68.3, 58.5, 54.6, 51.9, 19.2.
FTIR (thin film), cm^{-1}:	2916 (s), 1725 (m, C=O), 1619 (m), 1028 (m).
TLC (20% EtOAc in Hexanes), R*f*:	**45**: 0.38 (fluoresces under UV, anisaldehyde) **107**: 0.09 (fluoresces under UV, anisaldehyde)

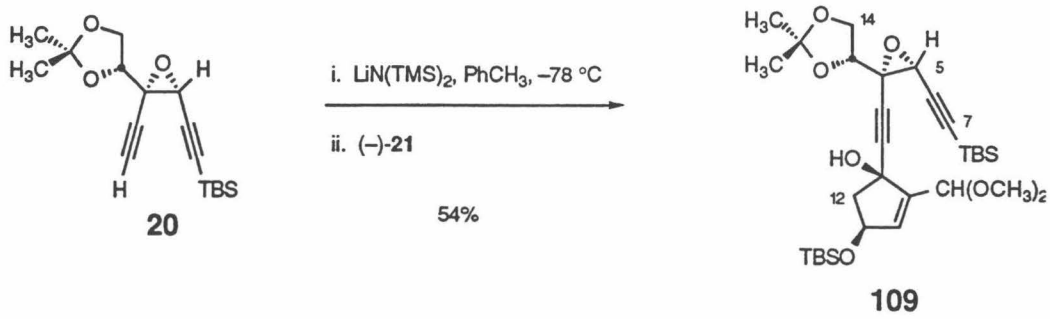


107 **108**

Acid **108**

Sodium hydroxide (11.9 g, 298 mmol, 75 equiv) was added in portions over a 5 min period to a solution of the naphthoate ester **107** (1.33 g, 3.98 mmol, 1 equiv) in 1:1 methanol/water (40 mL). The resultant solution was heated to 80 °C for 20 h and cooled to 23 °C. The reaction mixture was acidified to pH 3 with 1N hydrochloric acid (400 mL) and extracted with ethyl acetate (3 100-mL portions). The combined organic extracts were washed with saturated aqueous sodium chloride (100 mL), dried over sodium sulfate and concentrated. The crude acid **108** (1.14 g, 90%) solidified from a pink oil to a pink solid, and was used without further purification.

^{1}H NMR (300 MHz, C_6D_6), δ:	9.50 (br s, 1H, $CO_2\mathbf{H}$), 7.62 (d, 1H, J = 8.73 Hz, C4 H), 7.62 (s, 1H, C8 H), 7.18 (d, 1H, J = 9.42 Hz, C3 H), 6.95 (m, 1H, C6 H), 5.07 (s, 2H, $OC\mathbf{H}_2OCH_2CH_2OCH_3$), 3.61 (dd, 2H, J = 6.10, 4.50 Hz, $OCH_2OC\mathbf{H}_2CH_2OCH_3$), 3.44 (s, 3H, C7 $OC\mathbf{H}_3$), 3.16 (dd, 2H, J = 4.71, 3.18 Hz, $OCH_2OCH_2C\mathbf{H}_2OCH_3$), 2.92 (s, 3H, $OCH_2OCH_2CH_2OC\mathbf{H}_3$), 2.25 (s, 3H, C5 $OC\mathbf{H}_3$).
TLC (50% EtOAc in Hexanes), R*f*:	**107**: 0.47 (fluoresces under UV, anisaldehyde) **108**: 0.00 (fluoresces under UV, anisaldehyde)



Alcohol **109**

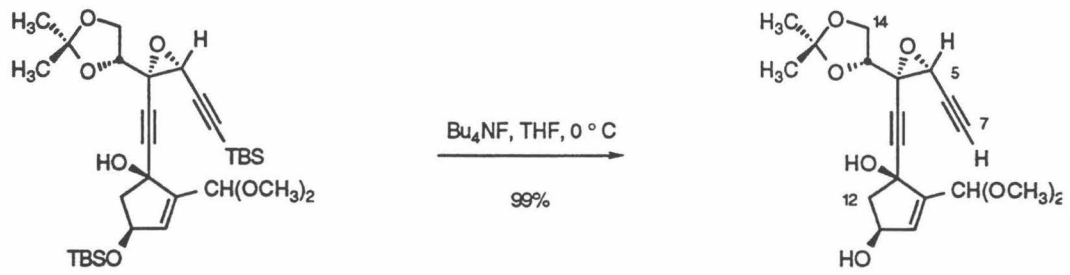
Lithium hexamethyldisilazide (3.25 mL of a 1.0 M solution in hexanes, 3.25 mmol, 1.05 equiv) was added dropwise over 4 min to a –78 °C solution of epoxy diyne **20** (996 mg, 3.25 mmol, 1.05 equiv) in toluene (23 mL). The resultant pale yellow solution was stirred at –78 °C for 30 min, then a solution of enone (–)-**21** (887 mg, 3.10 mmol, 1.0 equiv) in toluene (10 mL) was added dropwise via cannula over 10 min. The transfer was quantitated with toluene (2 x 3 mL). The reaction mixture was maintained at –78 °C for an additional 15 min, then excess lithium hexamethyldisilazide was quenched by the addition of saturated aqueous ammonium chloride (30 mL). The mixture was warmed to 23 °C and partitioned between 1:1 ethyl acetate in hexanes (50 mL) and water (50 mL). The layers were separated and the aqueous layer was further extracted with 1:1 ethyl acetate/hexanes (2 50-mL portions). The combined organic extracts were washed with saturated aqueous sodium chloride (50 mL), dried over sodium sulfate and concentrated. Purification of the residue was accomplished by flash column chromatography (10% ethyl acetate in hexanes) to afford alcohol **109** (1.0 g, 54%) as a pale yellow oil.

^{1}H NMR (400 MHz, C_6D_6), δ: 6.18 (s, 1H, C10 H), 5.45 (s, 1H, C8 H), 4.88 (m, 1H, C11 H), 4.08 (dd, 1H, *J* = 8.79, 5.86 Hz, C13 H), 3.89 (s, 1H, OH), 3.84 (dd, 1H, *J* = 8.55, 6.83 Hz, C14 H), 3.58 (t, 1H, *J* = 5.86 Hz, C14 H), 3.46 (s, 1H, C5 H), 3.21 (s, 3H, $CH(OCH_3)_2$), 3.17 (s, 3H, $CH(OCH_3)_2$), 3.21-3.14 (obscured, 1H, C12 βH), 2.50 (dd, 1H, *J* = 13.43, 5.37 Hz, C12 αH), 1.43 (s, 3H, $C(CH_3)_2$), 1.18 (s, 3H, $C(CH_3)_2$), 1.04 (s, 9H, $SiC(CH_3)_3(CH_3)_2$), 0.95 (s, 9H, $SiC(CH_3)_3(CH_3)_2$), 0.19 (s, 6H, $SiC(CH_3)_3(CH_3)_2$), 0.08 (s, 3H, $SiC(CH_3)_3(CH_3)_2$), 0.06 (s, 3H, $SiC(CH_3)_3(CH_3)_2$).

FTIR (thin film), cm^{-1}: 3509 (m, OH), 2953 (s), 2931 (s), 2888 (s), 2857 (s), 2182 (w, C≡C), 1464 (m), 1361 (m), 1254 (s), 1213 (m), 1109 (s).

TLC (20% EtOAc in Hexanes), R*f*: (–)-**21**: 0.38 (UV, anisaldehyde)

109: 0.19 (anisaldehyde)

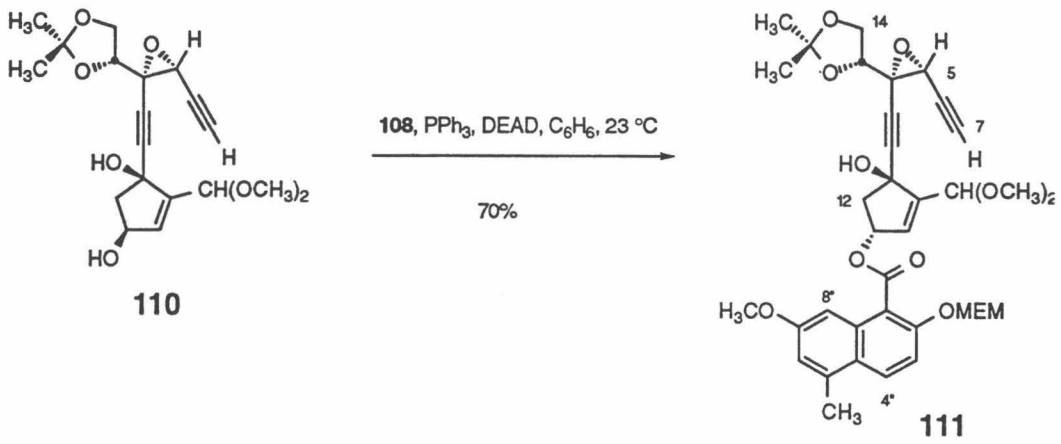


109 **110**

Diol **110**

Tetrabutylammonium fluoride (709 μL of a 1.0 M solution in THF, 0.709 mmol, 3 equiv) was added dropwise via syringe to a solution of alcohol **109** (140 mg, 0.236 mmol, 1 equiv) in THF (5 mL) at 0 °C. The resultant deep purple solution was maintained at 0 °C for 20 min, and poured into water (35 mL). The mixture was extracted with ethyl acetate (4 15-mL portions). The combined extracts were washed with saturated aqueous sodium chloride (30 mL), dried over sodium sulfate and concentrated. The residue was purified by flash column chromatography (50% ethyl acetate in hexanes grading to 100% ethyl acetate) to afford diol **110** (90 mg, 99%) as a pale yellow oil.

^{1}H NMR (400 MHz, C_6D_6), δ:	6.06 (br s, 1H, C10 H), 5.38 (t, 1H, *J* = 1.71 Hz, C8 H), 4.49 (br s, 1H, C11 H), 4.09 (dd, 1H, *J* = 8.78, 5.85 Hz, C13 H), 3.83 (dd, 1H, *J* = 8.55, 6.59 Hz, C14 H), 3.62 (t, 1H, *J* = 6.35 Hz, C14 H), 3.40 (d, 1H, *J* = 1.71 Hz, C5 H), 3.18 (s, 3H, $CH(OC\mathbf{H}_3)_2$), 3.17 (s, 3H, $CH(OC\mathbf{H}_3)_2$), 2.87 (dd, 1H, *J* = 13.92, 7.08 Hz, C12 αH), 2.31 (dd, 1H, *J* = 13.67, 3.90 Hz, C12 βH), 1.98 (d, 1H, *J* = 1.71 Hz, C7 H), 1.41 (s, 3H, $C(C\mathbf{H}_3)_2$), 1.19 (s, 3H, $C(C\mathbf{H}_3)_2$).
FTIR (thin film), cm^{-1}:	3418 (s, OH), 3260 (s, C≡C-H), 2931 (s), 2131 (w, C≡C), 1108 (m), 1070 (s).
TLC (20% EtOAc in Hexanes), R*f*:	**109**: 0.19 (anisaldehyde) **110**: 0.00 (anisaldehyde)
TLC (50% EtOAc in Hexanes), R*f*:	**110**: 0.10 (anisaldehyde)



Ester **111**

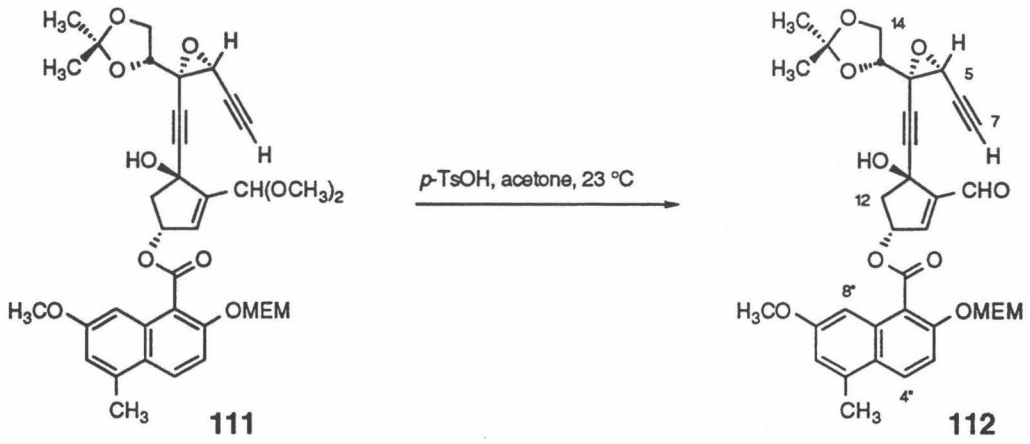
Diethyl azodicarboxylate (40 mL, 0.26 mmol, 1.2 equiv) was added dropwise via syringe over 2 min to a solution of diol **110** (65 mg, 0.21 mmol, 1 equiv), triphenylphosphine (67 mg, 0.26 mmol, 1.2 equiv), and acid **108** (82 mg, 0.26 mmol, 1.2 equiv) in benzene (5 mL) at 23 °C. The resultant yellow solution was stirred for 15 min, and volatiles were removed in vacuo. The residue was purified by flash column chromatography (25% ethyl acetate in hexanes grading to 100% ethyl acetate) to provide ester **111** (99 mg, 70%) as a viscous, colorless oil.

^{1}H NMR (400 MHz, C_6D_6), δ: 7.67 (d, 1H, *J* = 9.28 Hz, C4" H), 7.29 (d, 1H, *J* = 9.28 Hz, C3" H), 7.28 (m, 1H, C8" H), 7.00 (m, 1H, C6" H), 6.49 (d, 1H, *J* = 1.47 Hz, C10 H), 6.45 (m, 1H, C11 H), 5.47 (s, 1H, C8 H), 5.21 (s, 2H, $OCH_2OCH_2CH_2OCH_3$), 3.97-3.91 (complex, 2H, C13, C14 H), 3.79 (m, 2H, $OCH_2OCH_2CH_2OCH_3$), 3.72 (m, 1H, C14 H), 3.57 (s, 3H, C7" OCH_3), 3.37 (m, 2H, $OCH_2OCH_2CH_2OCH_3$), 3.19-3.12 (obscured, 1H, C12 βH), 3.14 (s, 3H, $CH(OCH_3)_2$), 3.13 (s, 3H, $OCH_2OCH_2CH_2OCH_3$), 3.12 (s, 3H, $CH(OCH_3)_2$), 3.04 (s, 1H, C5 H), 2.92 (dd, 1H, *J* = 14.40, 3.90 Hz, C12 αH), 2.29 (s, 3H, C5" CH_3), 1.97 (d, 1H, *J* = 1.71 Hz, C7 H), 1.34 (s, 3H, $C(CH_3)_2$), 1.12 (s, 3H, $C(CH_3)_2$).

FTIR (thin film), cm^{-1}: 3483 (m, OH), 3278 (w, C≡C-H), 2936 (s), 1724 (s, C=O), 1622 (s), 1466 (m), 1157 (s), 1099 (s).

TLC (50% EtOAc in Hexanes), R*f*: **110**: 0.10 (anisaldehyde)

111: 0.21 (fluoresces under UV, anisaldehyde)



Aldehyde **112**

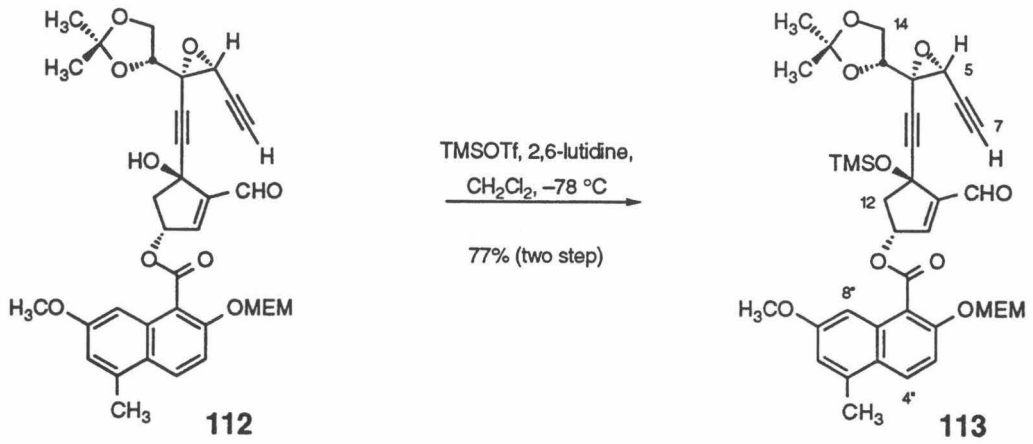
p-Toluenesulfonic acid (140 mg) was added to a solution of dimethyl acetal **111** (522 mg, 0.842 mmol) in acetone (25 mL) at 23 °C. The resultant pale yellow solution was stirred for 40 min and poured into saturated sodium bicarbonate (25 mL). The mixture was extracted with 1:1 ethyl acetate/hexanes (3 25-mL portions). The combined organic extracts were washed with saturated aqueous sodium chloride (50 mL), and were dried over sodium sulfate and concentrated. The crude aldehyde **112** was carried directly to the next reaction without further purification.

^{1}H NMR (400 MHz, C_6D_6), δ: 9.36 (s, 1H, C8 H), 7.67 (d, 1H, *J* = 9.27 Hz, C4" H), 7.31 (d, 1H, *J* = 9.28 Hz, C3" H), 7.22 (d, 1H, *J* = 2.20 Hz, C8" H), 7.00 (s, 1H, C6" H), 6.50 (d, 1H, *J* = 2.44 Hz, C10 H), 6.16 (m, 1H, C11 H), 5.25 (s, 2H, $OCH_2OCH_2CH_2OCH_3$), 3.95 (dd, 1H, *J* = 8.54, 6.10 Hz, C13 H), 3.80 (t, 2H, *J* = 4.88 Hz, $OCH_2OCH_2CH_2OCH_3$), 3.76 (dd, 1H, *J* = 8.78, 6.83 Hz, C14 H), 3.60 (t, 1H, *J* = 6.35 Hz, C14 H), 3.57 (s, 3H, C7" OCH_3), 3.37 (m, 3H, C12 H, $OCH_2OCH_2CH_2OCH_3$), 3.13 (s, 3H, $OCH_2OCH_2CH_2OCH_3$), 2.89-2.85 (complex, 2H, C12 H, C5 H), 2.28 (s, 3H, C5" CH_3), 1.95 (d, 1H, *J* = 1.46 Hz, C7 H), 1.33 (s, 3H, $C(CH_3)_2$), 1.12 (s, 3H, $C(CH_3)_2$).

FTIR (thin film), cm^{-1}: 3463 (m, OH), 3282 (m, C≡C-H), 2932 (m), 2131 (w, C≡C), 1728 (s, ester C=O), 1693 (s, aldehyde C=O), 1622 (s), 1514 (m), 1411 (m), 1334 (m), 1257(s).

TLC (30% EtOAc in Hexanes), R*f*: **111**: 0.26 (fluoresces under UV, anisaldehyde)

112: 0.17 (fluoresces under UV, anisaldehyde)



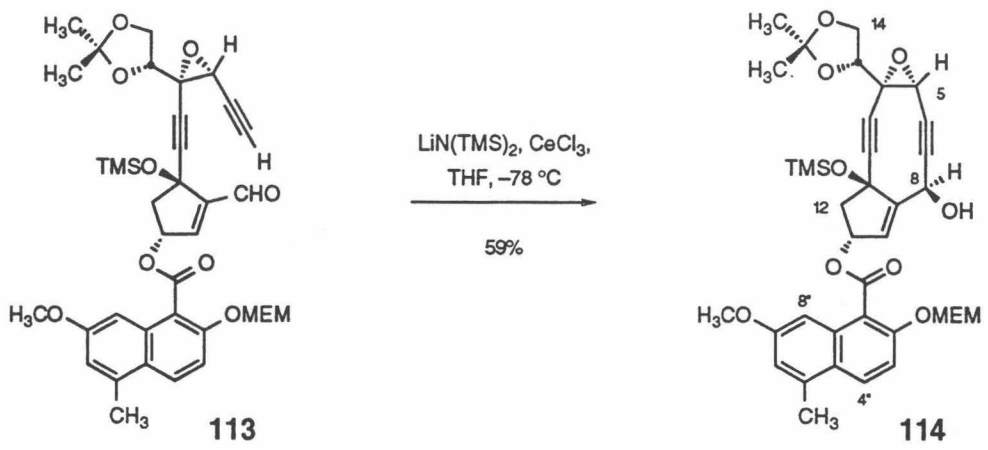
Trimethylsilyl ether **113**

A flame-dried 50-mL round bottom flask was charged with aldehyde **112** (crude residue from previous reaction, assume 0.842 mmol, 1 equiv) and dichloromethane (21 mL). The solution was cooled to –78 °C, and 2,6-lutidine (981 μL, 8.42 mmol, 10 equiv) and trimethylsilyl trifluoromethanesulfonate (814 μL, 4.21 mmol, 5 equiv) were added sequentially via syringe. The solution was maintained at –78 °C for 20 min, and excess trimethylsilyl trifluoromethanesulfonate was quenched by the addition of triethylamine (1 mL) and methanol (1 mL). The reaction mixture was warmed to 23 °C and partitioned between 1:1 ethyl acetate/hexanes (50 mL) and water (50 mL). The layers were separated and the aqueous layer was further extracted with 1:1 ethyl acetate/hexanes (2 50-mL portions). The combined extracts were washed with saturated aqueous sodium chloride (50 mL), dried over sodium sulfate and concentrated. The residue was purified by flash column chromatography (10% ethyl acetate in dichloromethane) to afford trimethylsilyl ether **113** (318 mg, 77% two-step yield) as a colorless oil.

^{1}H NMR (400 MHz, C_6D_6), δ: 9.38 (s, 1H, C8 H), 7.67 (d, 1H, *J* = 9.28 Hz, C4" H), 7.30 (d, 1H, *J* = 9.28 Hz, C3" H), 7.25 (d, 1H, *J* = 2.20 Hz, C8" H), 7.00 (br s, 1H, C6" H), 6.60 (d, 1H, *J* = 2.19 Hz, C10 H), 6.35 (m, 1H, C11 H), 5.22 (s, 2H, $OCH_2OCH_2CH_2OCH_3$), 4.02 (d , 1H, *J* = 8.79, 6.11 Hz, C13 H), 3.88 (dd, 1H, *J* = 8.79, 6.83 Hz, C14 H), 3.78 (dd, 2H, *J* = 6.10, 4.64 Hz, $OCH_2OCH_2CH_2OCH_3$), 3.72 (t, 1H, *J* = 6.35 Hz, C14 H), 3.56 (s, 3H, C7" OCH_3), 3.36 (m, 3H, C5 H, $OCH_2OCH_2CH_2OCH_3$), 3.12 (s, 3H, $OCH_2OCH_2CH_2OCH_3$), 3.01 (dd, 1H, *J* = 14.16, 7.08 Hz, C12 βH), 2.87 (dd, 1H, *J* = 14.16, 4.88 Hz, C12 αH), 2.27 (s, 3H, C5" CH_3), 2.01 (d, 1H, *J* = 1.71 Hz, C7 H), 1.28 (s, 3H, $C(CH_3)_2$), 1.12 (s, 3H, $C(CH_3)_2$), 0.40 (s, 9H, J = 7.69 Hz, $OSi(CH_3)_3$).

FTIR (thin film), cm^{-1}: 3279 (m, C≡C-H), 2953 (m), 2127 (w, C≡C), 1728 (s, ester C=O), 1698 (s, aldehyde C=O), 1622 (s), 1514 (m), 1411 (m), 1254 (s), 1093 (s), 959 (m).

TLC (30% EtOAc in Hexanes), R*f*:	**112**: 0.29 (fluoresces under UV, anisaldehyde) **113**: 0.64 (fluoresces under UV, anisaldehyde)



113 114

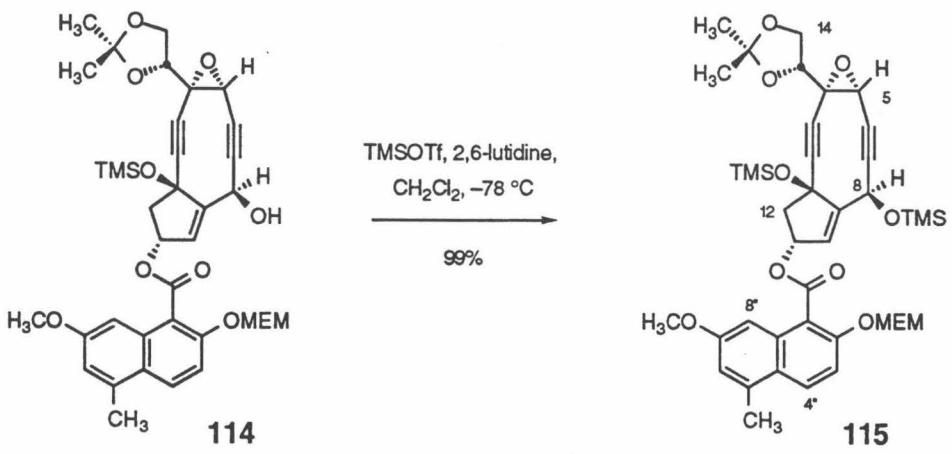
Cyclic alcohol **114**

A suspension of aldehyde **113** (100 mg, 0.144 mmol, 1 equiv) and cerium(III) chloride (107 mg, 0.433 mmol, 3 equiv) in THF (7 mL) was stirred at 23 °C for 10 min and cooled to –78 °C. Lithium hexamethyldisilazide (721 μL of a 1.0 M solution in hexanes, 0.721 mmol, 5 equiv) was added dropwise via syringe over 2 min. The reaction was checked by thin-layer chromatography (TLC) (50% ethyl acetate in hexanes) and found to be incomplete. Additional lithium hexamethyldisilazide (288 μL of a 1.0 M solution in hexanes, 0.288 mmol, 2 equiv) was added from a syringe, and the TLC of the reaction re-examined. One last portion of lithium hexamethyldisilazide (288 μL of a 1.0 M solution in hexanes, 0.288 mmol, 2 equiv) was added via syringe. After maintaining the reaction mixture at –78 °C for an additional 10 min, excess base was quenched by the addition of saturated aqueous ammonium chloride (10 mL). The reaction mixture was warmed to 23 °C and partitioned between 1:1 ethyl acetate/hexanes (30 mL) and water (30 mL). The aqueous layer was further extracted with 1:1 ethyl acetate/hexanes (2 30-mL portions). The combined organic extracts were washed once with saturated aqueous

sodium chloride (50 mL), and were dried over sodium sulfate and concentrated. The residue was purified by flash column chromatography (25% ethyl acetate in hexanes grading to 40% ethyl acetate in hexanes) to provide cyclic alcohol **114** (59 mg, 59%) as a yellow oil.

^{1}H NMR (400 MHz, C_6D_6), δ: 7.63 (d, 1H, *J* = 9.28 Hz, C4" H), 7.45 (br s, 1H, C8" H), 7.18 (d, 1H, *J* = 9.28 Hz, C3" H), 7.01 (br s, 1H, C6" H), 6.50 (t, 1H, *J* = 2.20 Hz, C10 H), 6.27 (m, 1H, C11 H), 5.36 (d, 1H, J = 8.30 Hz, C8 H), 5.30 (abq, 2H, *J* = 6.96 Hz, Δν = 9.52 Hz, $OCH_2OCH_2CH_2OCH_3$), 3.96-3.84 (complex, 3H, C13 H and $OCH_2OCH_2CH_2OCH_3$), 3.78 (dd, 1H, *J* = 8.54, 6.59 Hz, C14 H), 3.60 (s, 3H, C7" OCH_3), 3.50 (m, 2H, $OCH_2OCH_2CH_2OCH_3$), 3.42 (dd, 1H, *J* = 6.10, 4.64 Hz, C14 H), 3.14 (s, 3H, $OCH_2OCH_2CH_2OCH_3$), 3.11 (s, 1H, C5 H), 3.05 (d, 1H, J = 8.05 Hz, OH), 2.90 (dd, 1H, *J* = 14.64, 2.93 Hz, C12 αH), 2.76 (dd, 1H, *J* = 14.65, 7.32 Hz, C12 βH), 2.27 (s, 3H, C5" CH_3), 1.44 (s, 3H, $CH(CH_3)_2$), 1.22 (s, 3H, $CH(CH_3)_2$), 0.31 (s, 9H, $OSi(CH_3)_3$).

FTIR (thin film), cm^{-1}:	3457 (m, OH), 2950 (m), 1722 (m, C=O), 1621 (s), 1411 (m), 1255 (s), 1207 (m), 1158 (m), 1092 (s), 960 (m).
TLC (50% EtOAc in Hexanes), R*f*::	**113**: 0.43 (fluoresces under UV, anisaldehyde) **114**: 0.33 (fluoresces under UV, anisaldehyde)



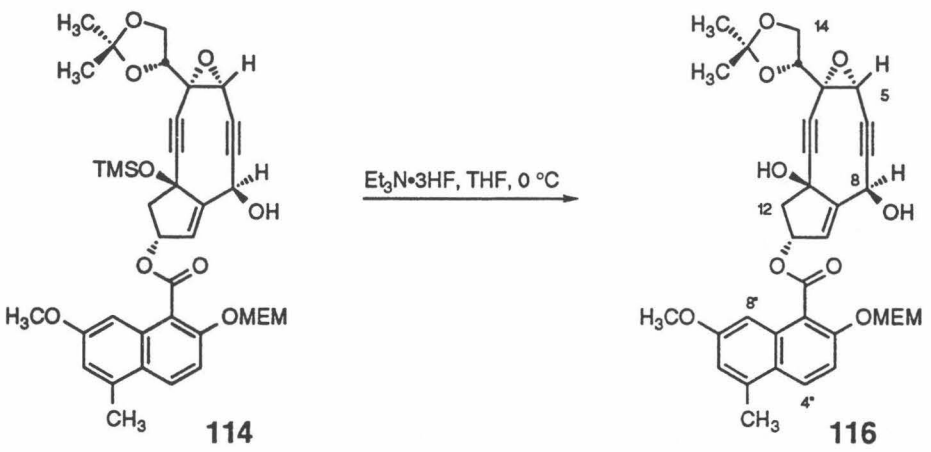
Bis-TMS ether **115**

2,6-Lutidine (17 μL, 0.14\ mmol, 20 equiv) and trimethylsilyl trifluoromethanesulfonate (14 μL, 0.072 mmol, 10 equiv) were added sequentially via syringe to a solution of alcohol **114** (5.0 mg, 0.0072 mmol, 1 equiv) in dichloromethane (1 mL) at –78 °C. The resultant pale yellow solution was maintained at –78 °C for 20 min, and excess silylating reagent was quenched by the addition of triethylamine (0.1 mL) and methanol (0.1 mL). The reaction mixture was warmed to 23 °C and partitioned between 1:1 ethyl acetate/hexanes (5 mL) and water (10 mL). The layers were separated and the aqueous layer was further extracted with 1:1 ethyl acetate/hexanes (2 5-mL portions). The combined organics were dried over sodium sulfate and concentrated. Purification of the residue by flash column chromatography (25% ethyl acetate in hexanes) afforded Bis-TMS ether **115** (5.5 mg, 99%) as a colorless oil.

^{1}H NMR (400 MHz, C_6D_6), δ: 7.65 (d, 1H, *J* = 9.28 Hz, C4" H), 7.40 (s, 1H, C8" H), 7.34 (d, 1H, *J* = 9.28 Hz, C3" H), 7.09 (s, 1H, C6" H), 6.65 (t, 1H, *J* = 1.95 Hz, C10 H), 6.37 (m, 1H, C11 H), 5.63 (s, 1H, C8 H), 5.27 (abq, 2H, *J* = 7.08 Hz, Δν =14.64 Hz, $OCH_2OCH_2CH_2OCH_3$), 3.88 (dd, 2H, *J* = 9.52, 4.15 Hz, $OCH_2OCH_2CH_2OCH_3$), 3.85 (dd, 1H, *J* = 8.54, 6.83 Hz, C13 H), 3.76 (dd, 1H, *J* = 8.55, 6.59 Hz, C14 H), 3.68 (s, 3H, C7" OCH_3), 3.48-3.43 (complex, 3H, C14 H and $OCH_2OCH_2CH_2OCH_3$), 3.16 (s, 3H, $OCH_2OCH_2CH_2OCH_3$), 3.08 (s, 1H, C5 H), 2.93 (dd, 1H, *J* = 14.65, 3.18 Hz, C12 αH), 2.81 (dd, 1H, *J* = 14.65, 7.33 Hz, C12 βH), 2.27 (s, 3H, C5" CH_3), 1.44 (s, 3H, $CH(CH_3)_2$), 1.21 (s, 3H, $CH(CH_3)_2$), 0.33 (s, 9H, $OSi(CH_3)_3$), 0.21 (s, 9H, $OSi(CH_3)_3$).

TLC (30% EtOAc in Hexanes), R*f*: **114**: 0.38 (fluoresces under UV, anisaldehyde)

115: 0.55 (fluoresces under UV, anisaldehyde)



114 116

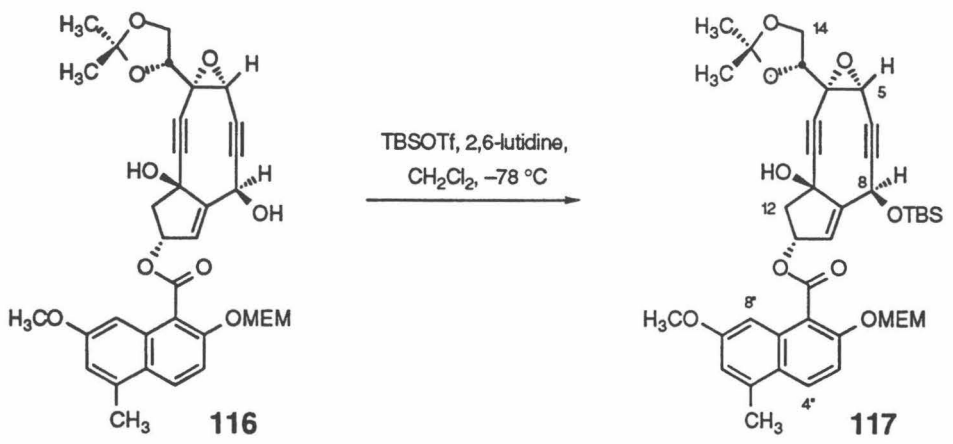
Diol **116**

Triethylamine trihydrofluoride (37 μL, 0.30 mmol, 3 equiv) was added via syringe to a solution of alcohol **114** (70 mg, 0.101 mmol, 1 equiv) in THF (7 mL) at 0 °C. The resultant solution was maintained at 0 °C for 40 min, and excess acid was quenched by the addition of saturated aqueous sodium bicarbonate (5 mL). The reaction mixture was then partitioned between 1:1 ethyl acetate in hexanes (10 mL) and water (10 mL). The layers were separated, and the aqueous layer was further extracted with 1:1 ethyl acetate/hexanes (2 10-mL portions). The combined organics were dried over sodium sulfate and concentrated. The diol **116** was carried directly to the next reaction without further purification.

^{1}H NMR (400 MHz, C_6D_6), δ: 7.65 (d, 1H, *J* = 9.28 Hz, C4" H), 7.41 (s, 1H, C8" H), 7.21 (d, 1H, *J* = 9.28 Hz, C3" H), 7.01 (s, 1H, C6" H), 6.60 (s, 1H, C10 H), 6.30 (br s, 1H, C11 H), 5.45 (br s, 1H, C8 H), 5.32 (m, 2H, $OCH_2OCH_2CH_2OCH_3$), 3.94-3.87 (complex, 3H, C13 H and $OCH_2OCH_2CH_2OCH_3$), 3.78 (dd, 1H, *J* = 9.03, 6.83 Hz, C14 H), 3.64 (s, 3H, C7" OCH_3), 3.61 (m, 1H, C14 H), 3.45 (m, 2H, $OCH_2OCH_2CH_2OCH_3$), 3.29 (s, 1H, C5 H), 3.16 (s, 3H, $OCH_2OCH_2CH_2OCH_3$), 2.90 (dd, 1H, *J* = 14.89, 3.42 Hz, C12 αH), 2.79 (dd, 1H, *J* = 14.86, 7.08 Hz, C12 βH), 2.29 (s, 3H, C5" CH_3), 1.49 (s, 3H, $CH(CH_3)_2$), 1.23 (s, 3H, $CH(CH_3)_2$).

TLC (30% EtOAc in CH_2Cl_2), R*f*: **114**: 0.68 (fluoresces under UV, anisaldehyde)

116: 0.08 (fluoresces under UV, anisaldehyde)

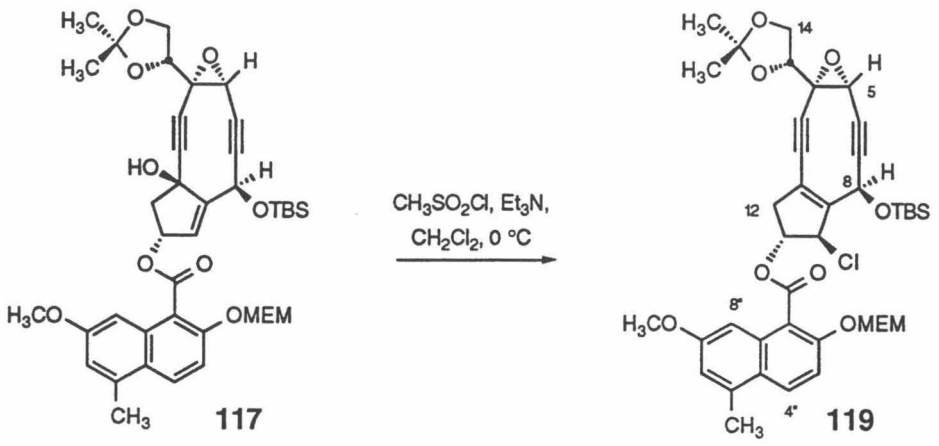


TBS ether **117**

2,6-Lutidine (235 μL, 2.02 mmol, 20 equiv) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (232 μL, 1.01 mmol, 10 equiv) were added sequentially via syringe to a solution of diol **116** (crude from previous reaction, assume 0.10 mmol, 1 equiv) in dichloromethane (10 mL) at –78 °C. The resultant pale yellow solution was maintained at –78 °C for 40 min, and excess silylating reagent was quenched by the addition of triethylamine (1 mL) and methanol (1 mL). The reaction mixture was warmed to 23 °C and partitioned between 1:1 ethyl acetate/hexanes (50 mL) and water (50 mL). The layers were separated and the aqueous layer was further extracted with 1:1 ethyl acetate/hexanes (2 50-mL portions). The combined organics were dried over sodium sulfate and concentrated. Purification of the residue by flash column chromatography (25% ethyl acetate in hexanes grading to 40% ethyl acetate in hexanes) afforded TBS ether **117** (43 mg, 58% over two steps) as a colorless oil.

^{1}H NMR (400 MHz, C_6D_6), δ: 7.62 (d, 1H, *J* = 9.28 Hz, C4" H), 7.37 (s, 1H, C8" H), 7.30 (d, 1H, *J* = 9.28 Hz, C3" H), 7.21-6.98 (obscured, 1H, C6" H), 6.65 (t, 1H, *J* = 2.20 Hz, C10 H), 6.27 (m, 1H, C11 H), 5.45 (s, 1H, C8 H), 5.26 (abq, 2H, *J* = 7.08 Hz, Δν =14.16 Hz, $OCH_2OCH_2CH_2OCH_3$), 3.96-3.88 (complex, 3H, C13 H and $OCH_2OCH_2CH_2OCH_3$), 3.76 (dd, 1H, *J* = 8.79, 6.59 Hz, C14 H), 3.69 (s, 3H, C7" OCH_3), 3.55 (t, 1H, *J* = 6.10 Hz, C14 H), 3.45 (m, 2H, $OCH_2OCH_2CH_2OCH_3$), 3.16 (s, 3H, $OCH_2OCH_2CH_2OCH_3$), 3.15 (s, 1H, C5 H), 2.86 (dd, 1H, *J* = 14.90, 3.18 Hz, C12 αH), 2.64 (dd, 1H, *J* = 14.89, 7.32 Hz, C12 βH), 2.27 (s, 3H, C5" CH_3), 1.47 (s, 3H, $CH(CH_3)_2$), 1.21 (s, 3H, $CH(CH_3)_2$), 0.98 (s, 9H, $OSiC(CH_3)_3(CH_3)_2$), 0.23 (s, 3H, $OSiC(CH_3)_3(CH_3)_2$), 0.12 (s, 3H, $OSiC(CH_3)_3(CH_3)_2$).

TLC (50% EtOAc in Hexanes), R*f*: **117**: 0.34 (fluoresces under UV, anisaldehyde)



Chloride **119**

Triethylamine (14 μL, 0.10 mmol, 25 equiv) and methanesulfonyl chloride (20 μL of a 1.3 M solution in dichloromethane, 0.026 mmol, 6 equiv) were added sequentially via syringe to a solution of TBS ether **117** (3.0 mg, 4.1 x 10^{-3} mmol, 1 equiv) in dichloromethane (0.5 mL) at 0 °C. After 10 min at 0 °C, the reaction mixture was partitioned between hexanes (2 mL) and water (2 mL). The layers were separated and the aqueous layer was further extracted with hexanes (2 2-mL portions). The combined organics were dried over sodium sulfate, and concentrated to a volume of approximately 0.1 mL. Purification of the concentrate by flash column chromatography (40% ethyl acetate in hexanes) was followed by pooling the fractions containing the product. The pooled fractions were concentrated to a volume of ca. 0.1 mL. A 0.5 mL portion of deuteriated benzene (99.5 atom % D) was added to the concentrated solution, and the resultant solution was concentrated to a volume of ca. 0.1 mL. This procedure was repeated 4 times. After the last iteration, the concentrated solution was taken up in

approximately 0.4 mL deuteriated benzene (99.95 atom % D). Analysis of the sample by ^{1}H NMR indicated it to be chloride **119** (yield not determined).

^{1}H NMR (400 MHz, C_6D_6), δ: 7.64 (d, 1H, *J* = 9.28 Hz, C4" H), 7.41 (s, 1H, C8" H), 7.31 (d, 1H, *J* = 9.28 Hz, C3" H), 7.00 (s, 1H, C6" H), 5.82 (d, 1H, *J* = 6.11 Hz, C10 H), 5.46 (s, 1H, C8 H), 5.32 (m, 1H, C11 H), 5.25 (s, 2H, $OCH_2OCH_2CH_2OCH_3$), 4.00 (dd, 1H, *J* = 8.45, 5.37 Hz, C13 H), 3.91 (m, 2H, $OCH_2OCH_2CH_2OCH_3$), 3.81 (dd, 1H, *J* = 8.79, 6.59 Hz, C14 H), 3.60 (s, 3H, C7" OCH_3), 3.56 (t, 1H, *J* = 6.35 Hz, C14 H), 3.51 (m, 2H, $OCH_2OCH_2CH_2OCH_3$), 3.21 (d, 1H, *J* = 1.46 Hz, C5 H), 3.20 (s, 3H, $OCH_2OCH_2CH_2OCH_3$), 2.93 (dm, 1H, *J* = 17.09 Hz, C12 βH), 2.68 (d, 1H, *J* = 17.82 Hz, C12 αH), 2.26 (s, 3H, C5" CH_3), 1.51 (s, 3H, $CH(CH_3)_2$), 1.23 (s, 3H, $CH(CH_3)_2$), 0.90 (s, 9H, $OSiC(CH_3)_3(CH_3)_2$), 0.23 (s, 3H, $OSiC(CH_3)_3(CH_3)_2$), 0.19 (s, 3H, $OSiC(CH_3)_3(CH_3)_2$).

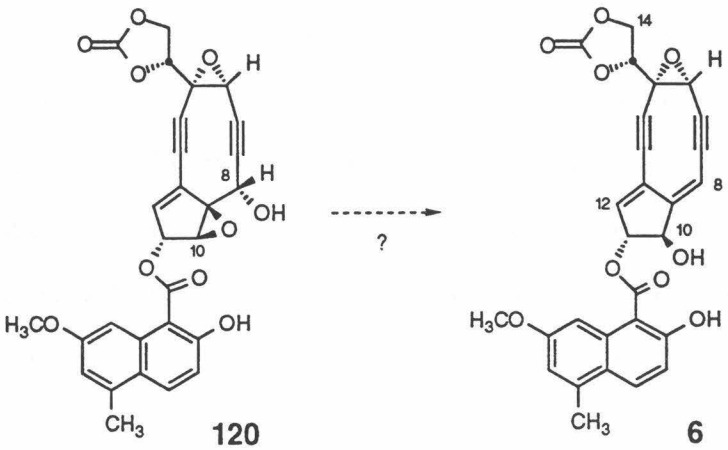
TLC (50% EtOAc in Hexanes), R*f*:	**117**: 0.30 (fluoresces under UV, anisaldehyde) **119**: 0.51 (fluoresces under UV, anisaldehyde)

Chapter 4

Enantioselective Synthesis of Neocarzinostatin Chromophore Aglycone

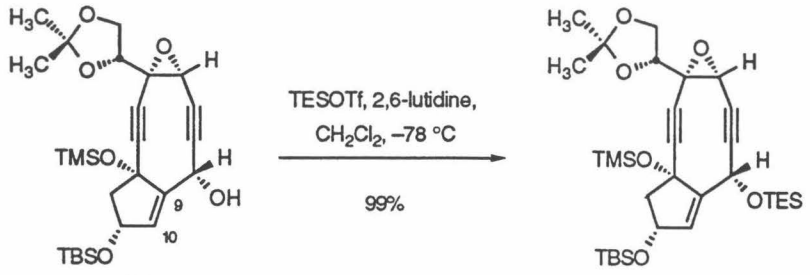
Synthetic Plan

Having exhausted many potential routes for the preparation of the conjugated dienediyne core of neocarzinostatin chromophore by the transposition of the allylic alcohols discussed in the previous chapters, attention was turned to a new strategy. It was anticipated that epoxidation of the C-9 – C-10 olefin (see **120**) would furnish an intermediate that, upon activation of the C-8 alcohol, would be stereoselectively transformed into the C-10 allylic alcohol under radical-mediated or reductive conditions. Such a process conducted within the epoxy alcohol **120** would produce neocarzinostatin chromophore aglycone (**6**) directly. This chapter describes the diastereoselective introduction of the C-9 – C-10 epoxide, optimization of the synthetic sequence for the preparation of epoxy alcohol **120**, and its successful conversion into neocarzinostatin chromophore aglycone (**6**).



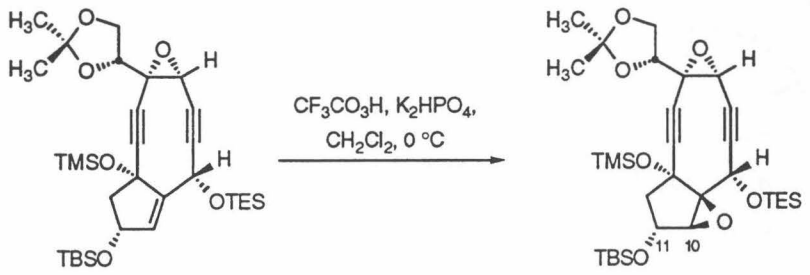
120 **6**

The most direct means by which to access C-9 – C-10 epoxide-containing intermediates, the epoxidation of known nine-membered ring-containing substrates, was studied extensively. The nine-membered ring alcohol **68** was silylated by treatment with TESOTf (6 equiv) and 2,6-lutidine (10 equiv) in dichloromethane at –78 °C to provide the tris-silyl ether **121** in quantitative yield.[77] A number of conditions were examined for the

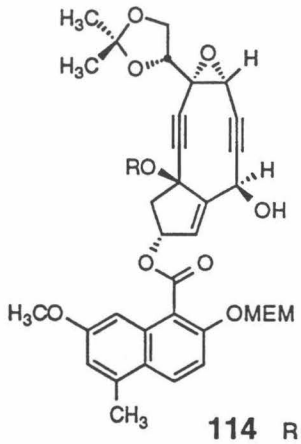


68 **121**

introduction of the epoxide into **121**, including *m*-chloroperoxybenzoic acid (*m*-CPBA, 94% purity, both with and without sodium carbonate), dimethyldioxirane,[78] methyl(trifluoromethyl) dioxirane,[79] 4-nitroperoxybenzoic acid,[80] and the peroxycarboximidic acid derived from the combination of 90% hydrogen peroxide and acetonitrile,[81] all of which resulted in recovery of **121**, decomposition of **121**, or the formation of a complex mixture of products. A single set of conditions, trifluoroperoxyacetic acid (6 equiv) buffered with solid dibasic potassium phosphate (20 equiv) in dichloromethane at 0 °C, afforded the desired epoxidized product **122**. The stereochemistry of the product was determined by inspection of the coupling constant between H-10 and H-11, in this case 0 Hz, which indicated a trans substitution pattern, the result of epoxidation from the least hindered face of **121**. Unfortunately, significant decomposition of the substrate and/or product occurred under the reaction conditions, necessitating the development of an alternative method for introduction of the epoxide.

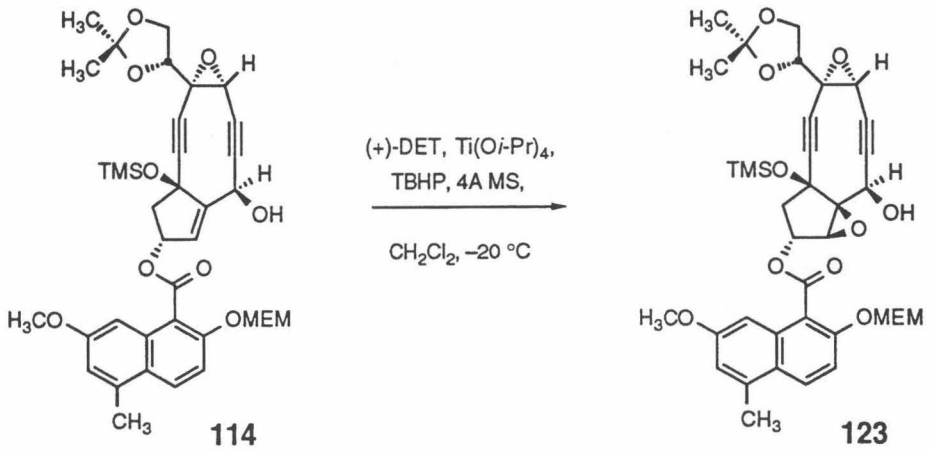


121 **122**



114 R = TMS
116 R = H

Use of the C-8 alcohol to direct the epoxidation reaction was next examined. Both the known alcohol **114** and diol **116** were subjected to conditions known to effect directed epoxidations. These conditions included *m*-CPBA, the combination of Ti(O*i*-Pr)$_4$ and *tert*-butyl hydroperoxide (TBHP),[83] and the combination of VO(acac)$_2$ and TBHP.[84] In each case either unreacted starting material was recovered or the substrate slowly underwent nonspecific decomposition. The ligand-accelerated conditions of the Sharpless asymmetric epoxidation were also examined using both (+)- and (–)-DET and employing both stoichiometric and suprastoichiometric amounts of reagents.[31] The reaction of TMS

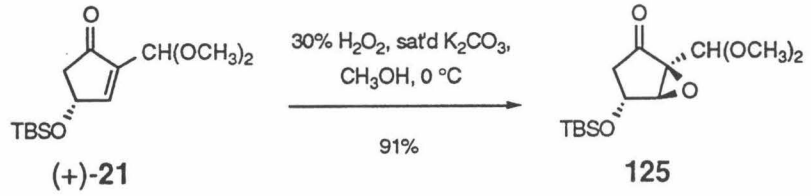


114 **123**

ether **114** with (+)-DET (12 equiv), Ti(O*i*-Pr)$_4$ (10 equiv), and TBHP (5 equiv) with 4A MS in dichloromethane at –20 °C afforded a product whose ^{1}H NMR spectrum was consistent with the formation of the epoxy alcohol **123**.[31] The purification of epoxide **123** was complicated by the laborious separation of the product **123** from the residual (+)-DET. More importantly, the instability of this diastereomeric series (cf. Ch. 2) made manipulation of the starting olefin **114** and the product **123** difficult. This instability provided cause for concern when the further transformations required for completion of the synthesis were considered. Consequently, the alternative strategy of introducing the C-9 – C-10 epoxide prior to closure of the nine-membered ring was investigated.

Although unclear at the outset, it was not expected that the introduction of the C-9 – C-10 epoxide prior to the closure of the nine-membered ring would have a marked effect on the ring-closure reaction. Based on inspection of molecular models, it was concluded that the geometry of an epoxy aldehyde having a structure such as **124** should not differ significantly from the corresponding α,β-unsaturated aldehyde intermediates (e.g., **13**) known to favor intramolecular acetylide addition, and should provide the cyclized alcohol upon treatment with base (Figure 2).

The first approach to accessing an epoxy aldehyde intermediate such as **124** involved the coupling of the epoxydiyne component **20** with an epoxide-containing ketone corresponding to the enone dimethyl acetal (+)-**21**. Accordingly, the enone dimethyl acetal (+)-**21** was epoxidized to afford ketone **125** in 91% yield and ≥95% diastereomeric



(+)-**21** **125**

enrichment (^{1}H NMR analysis) by treatment with 30% hydrogen peroxide (2 equiv) in a 15:1 mixture of methanol and saturated aqueous potassium carbonate at 0 °C.[85] Removal

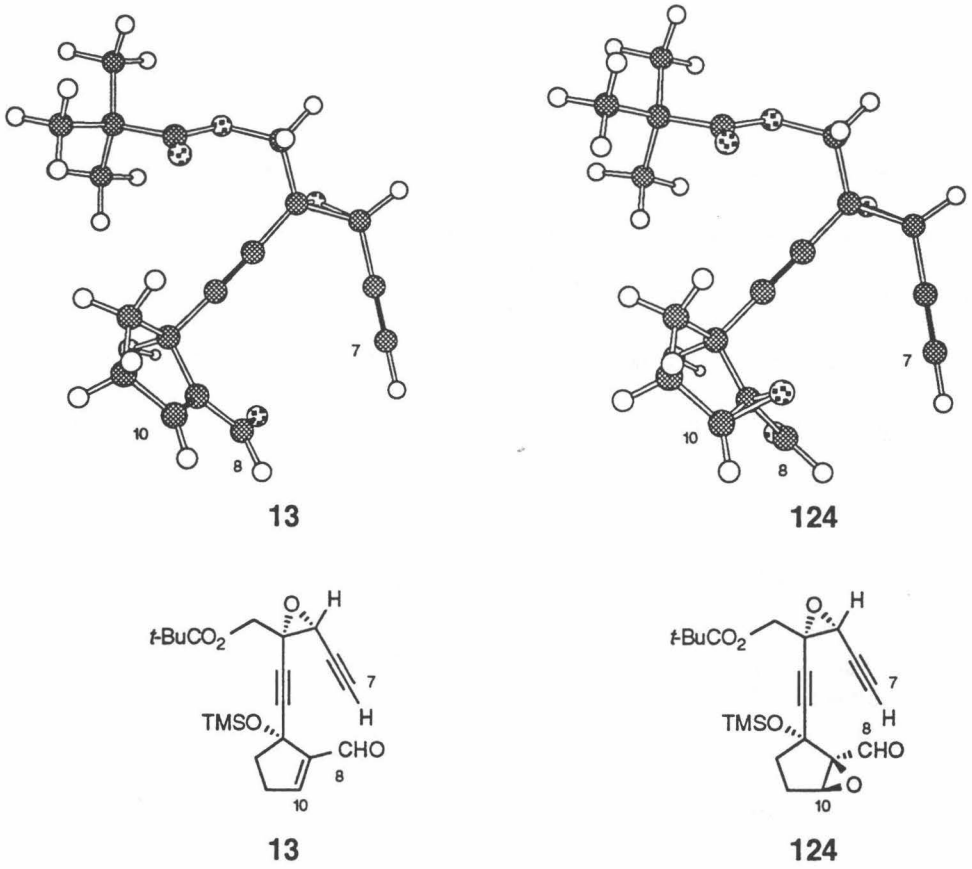
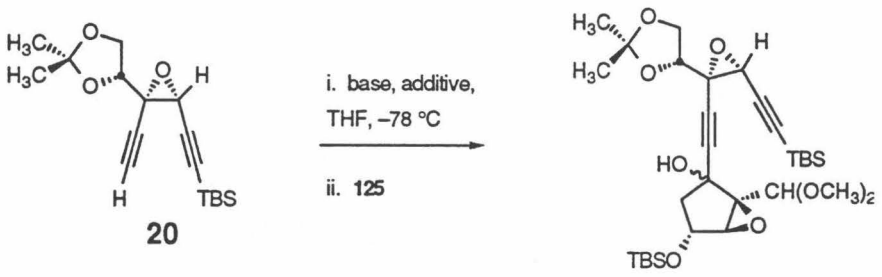


Figure 2. Ball and Stick Depictions of Ring-Closure Substrates 13 and 124.

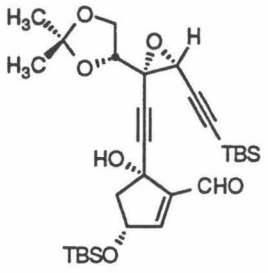
of the TBS group of **125** followed preparation of the Mosher ester and ^{1}H NMR analysis indicated that the epoxy ketone was of ≥85% ee. The epoxy ketone **125** was then examined as a substrate for addition of the epoxydiyne component **20**. Deprotonation of epoxydiyne **20** with a base such as $LiN(TMS)_2$ in THF at –78 °C followed by addition of the ketone **125** afforded a mixture of diastereomers **126** in low yield (10-15%). Subsequent studies carried out by Dr. Y. Wu in this group to optimize both the yield and the diastereoselectivity of this coupling did afford some improvement in the yield of the reaction. An approximately 70% combined yield was obtained when the reaction was carried out with $LiN(TMS)_2$ in the presence of the crown ether 12-C-4, but the diastereoselectivity remained unacceptable (ca. 3:1, absolute stereochemistry of the individual diastereomers not assigned), and so this strategy was discontinued.



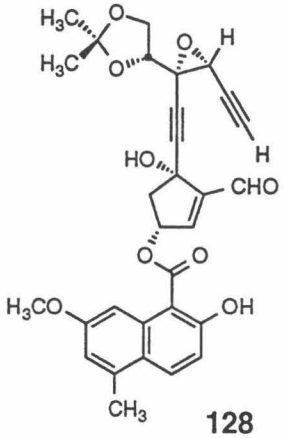
20 **126**

The epoxidation of α,β-unsaturated aldehyde intermediates obtained subsequent to the coupling of the epoxydiyne **20** and the enone dimethyl acetal (+)-**21** was next examined. Enal **127**, obtained by hydrolysis of known dimethyl acetal **46**, was inert to epoxidation under the conditions used to prepare ketone **125**. Use of stronger bases, such as DBU,[86] Triton B,[87] or sodium hydroxide,[88] resulted in the formation of complex reaction mixtures. Treatment of either enal **128** or enal **50** with 30% hydrogen peroxide (2 equiv) in a mixture of saturated sodium bicarbonate in THF (1:40) at 0 °C produced, in all cases, mixtures of epoxy aldehyde diastereomers.[89] These diastereomers could be separated and purified, but this methodology was not considered to be preparatively useful,

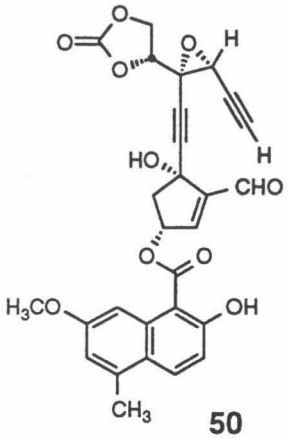
as both the yields and the diastereoselectivities observed in these reactions were low. Accordingly, alternative means were pursued for the introduction of the C-9 – C-10 epoxide with a higher degree of stereocontrol.



127

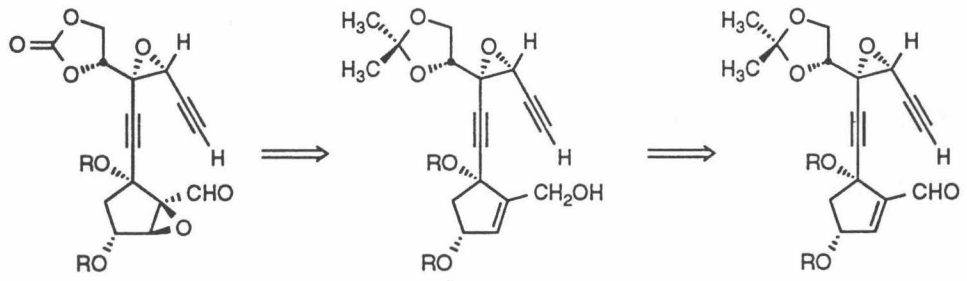


128



50

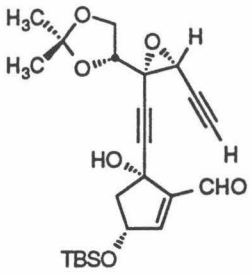
The final strategy involved the application of the Sharpless asymmetric epoxidation to diastereoselectively incorporate the epoxide.[31] With the goal remaining the preparation of a ring-closure substrate having the general structure **A**, it was anticipated that the epoxy aldehyde could be prepared from the allylic alcohol **B**, which was expected to be a suitable substrate for the epoxidation reaction. The intermediate **B** could be obtained by the 1,2-reduction of an α,β-unsaturated aldehyde having the general structure **C**, which should be readily accessible through known methodology.



A **B** **C**

Following this strategy, studies directed toward the preparation of a ring-closure intermediate commenced with the known α,β-unsaturated aldehyde **66**. Silylation of the tertiary alcohol with TESOTf (6 equiv) and 2,6-lutidine (10 equiv) in dichloromethane at –78 °C afforded the enal (**129**) in 85% yield (Scheme XVIII).[77] The aldehyde was then reduced by treatment of the enal with DIBAL (1.1 equiv) in toluene at –78 °C, to afford the allylic alcohol **130** in 81% yield. Sharpless asymmetric epoxidation employing (+)-diethyl tartrate (6 equiv), $Ti(O\textit{i}\text{-}Pr)_4$ (5 equiv), and TBHP (5 equiv) with 4A MS in dichloromethane at –20 °C produced the expected epoxy alcohol **131** in 88% yield.[31] The stereoselectivity of the epoxidation proceeded in the requisite sense, as evidenced by the 0 Hz coupling constant between H-10 and H-11 in the product **131**.[56] Oxidation of the epoxy alcohol under Swern conditions provided the epoxy aldehyde **132** in 86% yield.[90] Although the aldehyde was observed to streak considerably when examined by thin-layer chromatography on silica gel (presumed hydrate), no hydrate was observed by ^1H NMR analysis of **132** in deuteriated benzene. The key step, the closure of the nine-membered ring, was effected by treatment of a suspension of the epoxy aldehyde **132** and cerium(III) chloride in THF at –78 °C with $LiN(TMS)_2$ (12 equiv), affording an approximately 50% yield of the cyclized epoxy alcohol **133**.[13,19] An improvement in the yield of the reaction was realized by the substitution of dry lithium chloride for the cerium(III) chloride. Under these modified conditions (50 equiv LiCl, 10 equiv $LiN(TMS)_2$, THF, –78 °C), the cyclized product **133** could be obtained in 67% yield. The ring-closure reaction also proceeded in the absence of any additive ($LiN(TMS)_2$, THF –78 °C), but the reaction was not as clean, and the conversion was low (TLC analysis). It should be noted that the cyclization product **133** was found to be remarkably stable both in neat form and in solution, especially relative to many of the other nine-membered ring intermediates prepared during the studies discussed in Chapters 2 and 3.

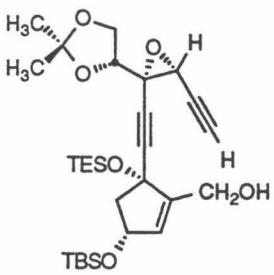
Scheme XVIII



66

1. TESOTf, 2,6-lutidine, CH_2Cl_2, –78 °C, 85%

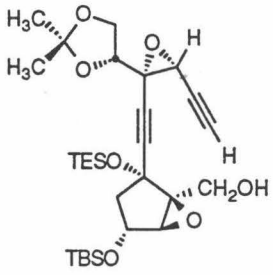
2. DIBAL, $PhCH_3$, –78 °C, 81%



130

(+)-DET, $Ti(O\textit{i}\text{-}Pr)_4$, TBHP, 4A MS, CH_2Cl_2, –20 °C

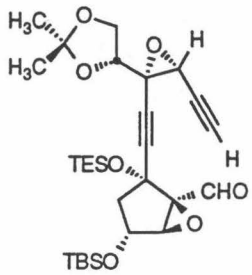
88%



131

$(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, –78 → 0 °C

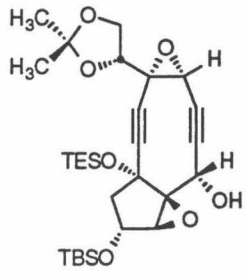
86%



132

$LiN(TMS)_2$, LiCl, THF, –78 °C

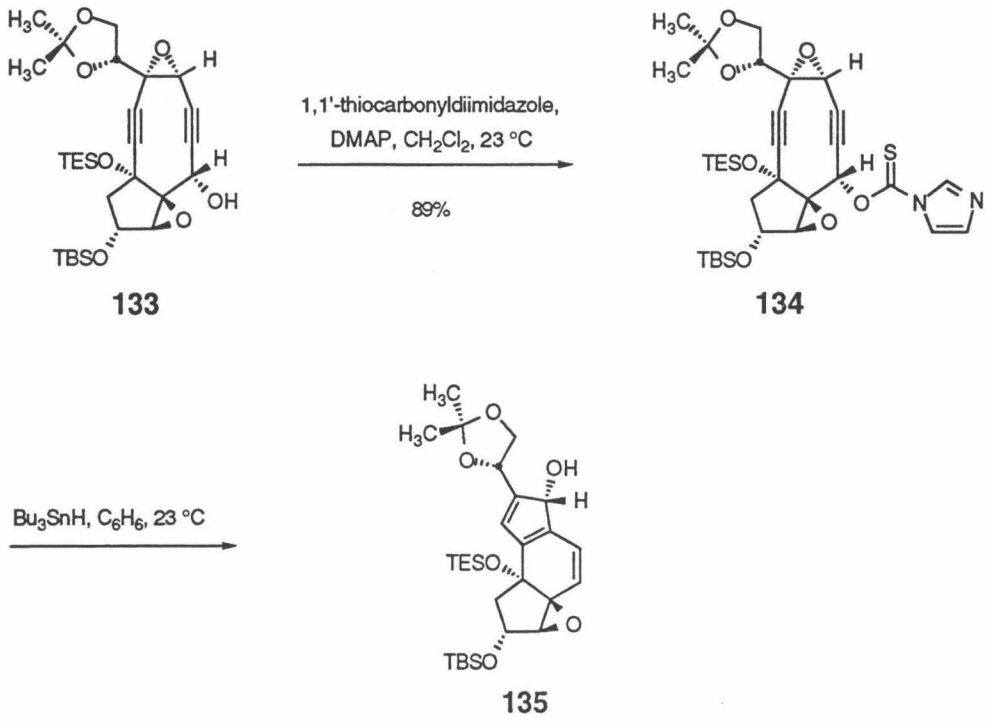
67%



133

The alcohol **133** was next examined as a substrate for conversion of the epoxy alcohol into the desired allylic alcohol. Reaction of alcohol **133** with thiocarbonyldiimidazole ($CS(Im)_2$, 10 equiv) and DMAP (5 equiv) in dichloromethane at 23 °C afforded thiocarbonylimidazolide **134** in 89% yield (Scheme XIX). Treatment of a deoxygenated solution of **134** in benzene with tributyltin hydride (10 equiv) at 23 °C[92] afforded a product whose ^1H NMR spectrum indicated that the epoxide-containing five-membered ring substructure remained intact (no added radical initiator was necessary for this reaction to occur). A set of olefinic doublets was also visible by analysis of the ^1H NMR spectrum, and suggesting the presence of a double bond within a five- or six-membered ring.[93] The C-13 – C-14 substructure, complete with the acetonide was also

Scheme XIX

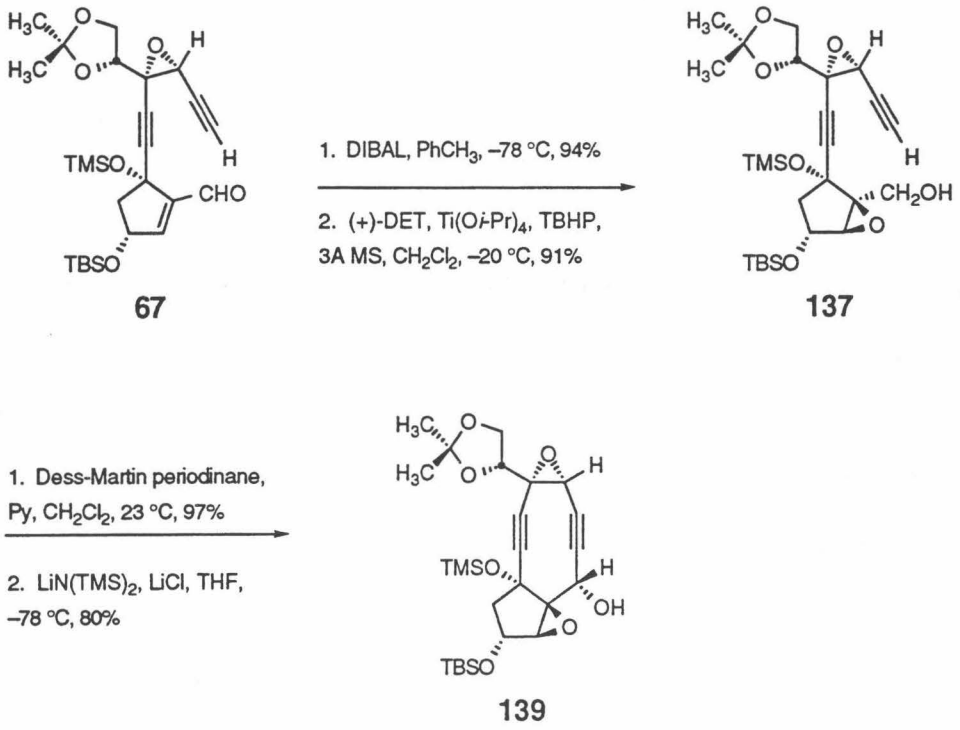


133 **134** **135**

visible within the ^1H NMR spectrum. The high-resolution mass spectrum of the product was consistent with the loss of the thiocarbonylimidazolide (including the oxygen) and the addition of two hydrogen atoms. Although the structure was not rigorously proven, the data are all consistent with the formation of a structure such as **135**, resulting from generation of the carbon-centered radical at C-8 and subsequent opening of the C-4 – C-5 epoxide.

In order to obtain a substrate analogous to **133** in which the C-1 alcohol protecting group could be selectively removed in the presence of the C-11 TBS ether, the analogous TMS-containing substrate **139** was prepared (Scheme XX). In this sequence, the oxidation of the Sharpless epoxidation product, epoxy alcohol **137**, was accomplished with the Dess-Martin periodinane (2 equiv) buffered with pyridine (20 equiv) in

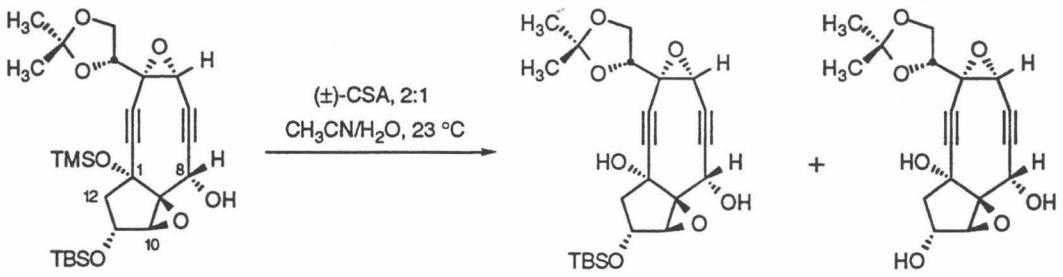
Scheme XX



67 **137** **139**

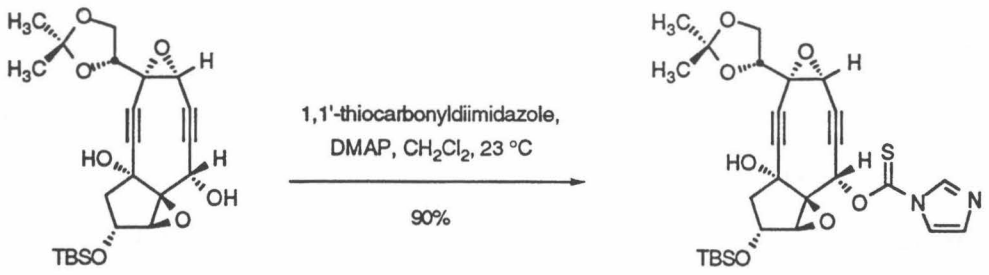
dichloromethane at 23 °C, affording the epoxy aldehyde in 97% yield.[94] The closure of the nine-membered ring, effected by the addition of $LiN(TMS)_2$ (5 equiv) to a suspension of LiCl (50 equiv) and the epoxy aldehyde in THF at –78 °C, proceeded quite cleanly, providing the alcohol **139** in 80% yield.

The TMS group of intermediate **139** could be removed by treatment with (±)-camphorsulfonic acid (5 equiv) in a 2:1 mixture of acetonitrile and water at 23 °C to afford the diol **140** in 47% yield, along with the triol **141**, resulting from cleavage of both silyl groups (24% yield). In an effort to favor the reactivity of the C-9 – C-10 epoxide, attempts were made to prepare a thiocarbonate between the C-1 and C-8 alcohols. Accordingly, diol



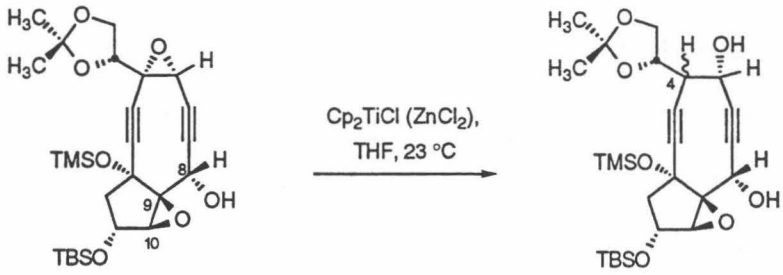
139 → **140** (47%) + **141** (24%)

140 was treated with thiocarbonyldiimidazole (10 equiv) and DMAP (5 equiv) in dichloromethane at 23 °C. Under these conditions, the acyclic thiocarbonylimidazolide **142** was isolated in 90% yield. All attempts to effect the intramolecular cyclization of this intermediate, including addition of base (20 equiv DBU in toluene), heating to 50 °C in the polar solvent DMF, or activation of the imidazole ring by the addition of methyl triflate,[95] failed to provide the desired thiocarbonate.

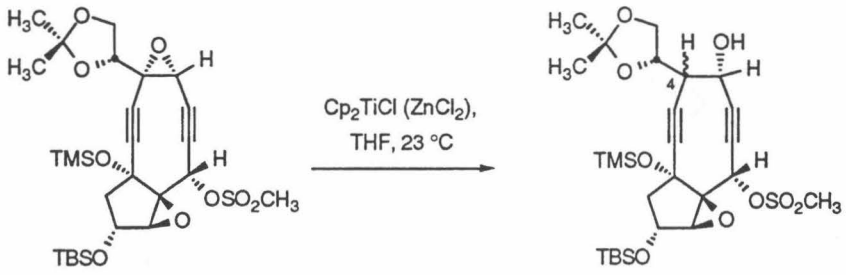


140 **142**

The reaction of alcohol **139** with the one-electron reductant dicyclopentadienyl titanium(III) chloride was also examined.[96] This reagent, prepared by in situ reduction of dicyclopentadienyl titanium(IV) chloride with granular zinc in THF at 23 °C, is known to convert epoxides to the corresponding alcohols in which the most substituted C-O bond has been cleaved.[96] In the case of epoxy alcohol **139**, this would correspond to the cleavage of the C-9 – O bond, producing a secondary alcohol at C-10. The C-8 mesylate **143** was prepared in 78% yield from intermediate **139** (10 equiv methanesulfonyl chloride, 25 equiv



139 **144**

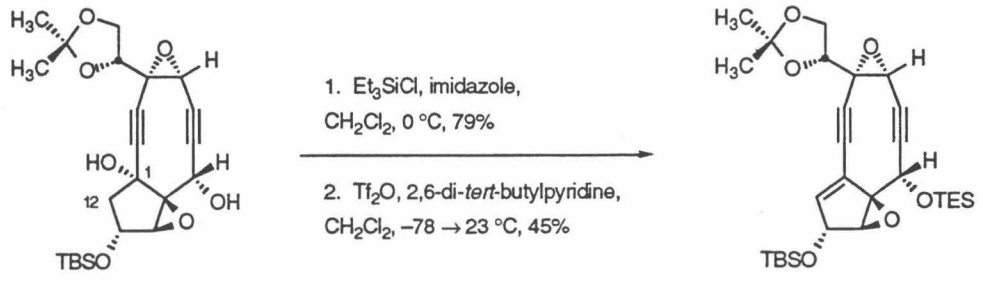


143 **145**

Et_3N, dichloromethane, 0 °C)[59] with the hope of effecting reductive opening of the C-9 – C-10 epoxide and elimination of the C-8 mesylate concurrently. Treatment of either the alcohol **139** or the mesylate **143** with dicyclopentadienyl titanium(III) chloride (3 equiv) in THF at 23 °C afforded products in which the C-4 – C-5 epoxides had been selectively opened. The products, diol **144** (from alcohol **139**) and mesylate **145** (from mesylate **143**) were each isolated as a single diastereomer having undetermined stereochemistry at C-4.

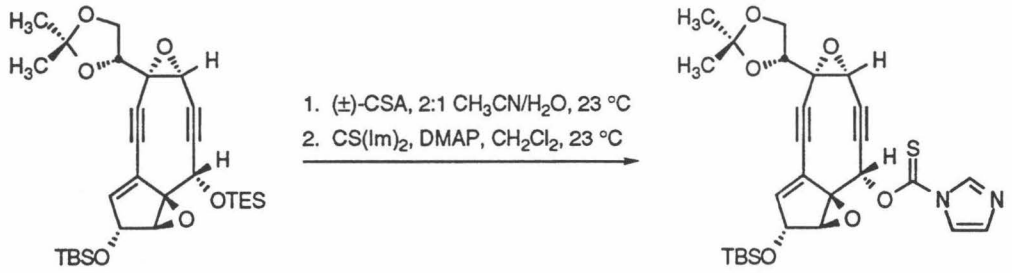
In order to favor reactivity at the C-9 – C-10 epoxide, studies were initiated to introduce the C-1 – C-12 olefin. The presence of this double bond would increase the reactivity of the desired epoxide in two ways: 1) the strain within both the five-membered ring and the epoxide would be increased, and the relief of this strain would be a driving force for epoxide opening; and 2) with the olefin in place, cleavage of the C-9 – O bond should be favored by the production of either a stabilized allylic radical or an allyl cation, depending upon the reaction conditions.

Preliminary studies of the elimination of the C-1 alcohol were conducted with the triethylsilyl ether derived in 79% yield by treatment of the diol **140** with triethylsilyl chloride (5 equiv) and imidazole (5 equiv) in dichloromethane at 0 °C. Elimination occurred upon treatment of the product tertiary alcohol with triflic anhydride (100 equiv) and 2,6-di-*tert*-butylpyridine (200 equiv) in dichloromethane (–78 °C and warming to 23 °C) to afford the olefin **147** in 45% yield.



140 **147**

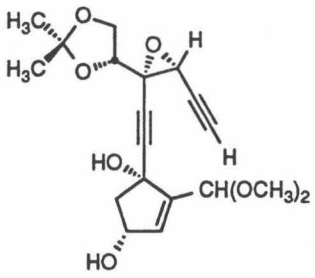
The presence of the C-1 – C-12 olefin markedly changed the reactivity of the substrate under radical conditions. The thiocarbonylimidazolide **149** could be prepared by removal of the TES group of olefin **147** with (±)-camphorsulfonic acid (5 equiv) in 2:1 acetonitrile/water at 23 °C followed by reaction of the resultant secondary alcohol with thiocarbonyldiimidazole (10 equiv) and DMAP (5 equiv) in dichloromethane at 23 °C. In contrast to thiocarbonylimidazolide **134**, no reaction was observed upon treatment of a deoxygenated solution of the thiocarbonylimidazolide **149** in benzene with tributyltin hydride (20 equiv).[92] Addition of a catalytic amount of triethylborane (Et_3B) and oxygen resulted in the formation of a complex reaction mixture.[97] The bis-silyl ether **147** was also reacted with tributyltin hydride (20 equiv) and catalytic Et_3B and oxygen in benzene at 23 °C and once again multiple products were observed to form.[97] Additionally, reaction of the intermediate **147** with the one-electron reductant dicyclopentadienyl titanium(III) chloride afforded a complex mixture of products.[96]



147 **149**

With an eye directed toward the preparation of intermediates bearing additional functionalization, and with the prospect of deactivating the C-4 – C-5 epoxide, a synthetic route to an olefin-containing intermediate that also incorporated the ethylene carbonate was developed. The known intermediate diol **47** was silylated with TIPS triflate (5 equiv) and 2,6-lutidine (10 equiv) in dichloromethane at –78 °C to provide the TIPS ether **150** in 89% yield (Scheme XXI).[73] As before, the dimethyl acetal was hydrolyzed with *p*-TsOH in methanol at 23 °C,[65] and the tertiary alcohol was silylated with TMSOTf (6 equiv) and

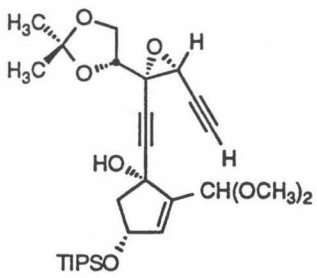
Scheme XXI



47

TIPSOTf, 2,6-lutidine,
CH_2Cl_2, –78 → 0 °C

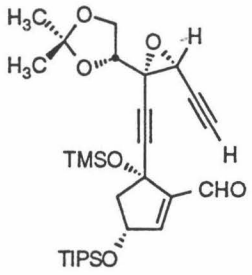
89%



150

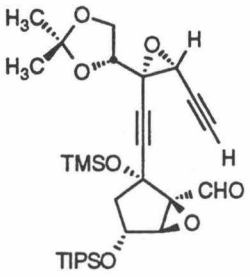
1. *p*-TsOH, acetone, 23 °C
2. TMSOTf, 2,6-lutidine,
CH_2Cl_2, –78 °C

93%



152

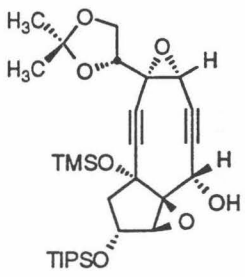
1. DIBAL, $PhCH_3$, –78 °C, 96%
2. (+)-DET, Ti(*i*-Pr)$_4$, TBHP,
4A MS, CH_2Cl_2, –78 C, 89%
3. Dess-Martin periodinane,
Py, CH_2Cl_2, 23 °C, 94%



155

$LiN(TMS)_2$, LiCl,
THF, –78 °C

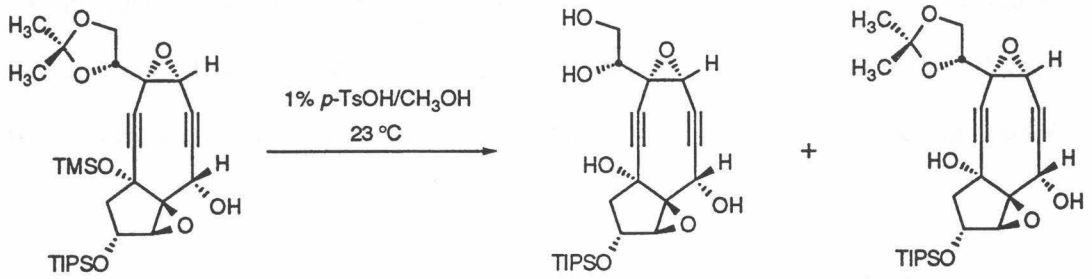
62%



156

2,6-lutidine (10 equiv) in dichloromethane at –78 °C,[54] affording TMS ether **152** in 93% overall yield from **150**. Introduction of the C-9 – C-10 epoxide was accomplished in analogy to other systems: 1,2-reduction with DIBAL (1.2 equiv) in toluene at –78 °C provided the allylic alcohol (**153**) in 96% yield, epoxidation under Sharpless conditions produced the epoxy alcohol (**154**) in 89% yield,[31] and oxidation with Dess-Martin periodinane (2 equiv) buffered with pyridine (10 equiv) in dichloromethane at 23 °C afforded the epoxy aldehyde **155** in 94% yield.[94] Closure of the nine-membered ring was effected as before, as addition of $LiN(TMS)_2$ (5 equiv) to a suspension of **155** and LiCl (50 equiv) in THF at –78 °C produced the ring-closed alcohol **156** in 62% yield.[91]

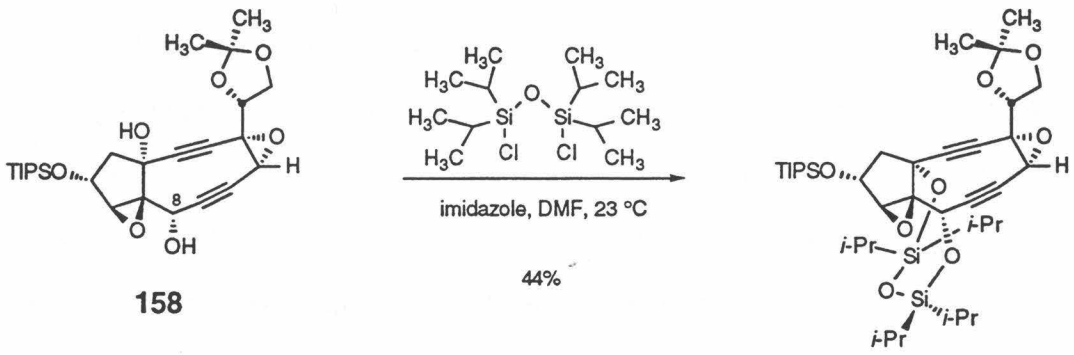
Protection of the C-11 alcohol of **156** as a TIPS ether was intended to allow for selective removal of the C-13 – C-14 acetonide and subsequent introduction of the ethylene carbonate. Accordingly, treatment of the alcohol **156** with 1% *p*-TsOH in methanol at 23 °C afforded the tetraol **157** in 62% yield and the incompletely deprotected diol **158** in 10% yield. The reaction was generally not allowed to proceed until complete conversion of **156** to **157** had occurred, as by that time a substantial amount of very polar material, possibly from the cleavage of the TIPS ether, would form (TLC analysis).



156 **157** (62%) **158** (10%)

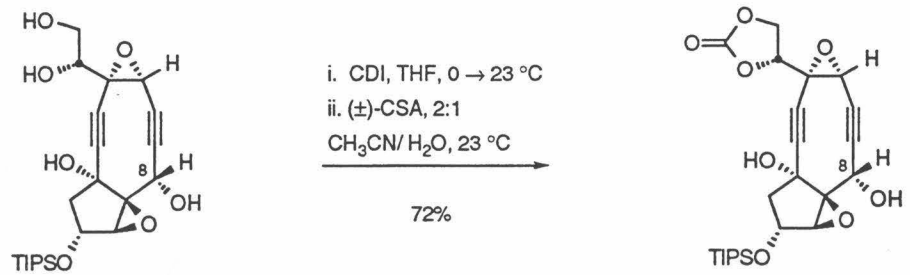
The stereochemistry of the C-8 alcohol center formed during the closure of the nine-membered ring (**155** → **156**) was established by the preparation of a cyclic disiloxane derivative of the diol **158**.[19] Accordingly, treatment of **158** with 1,3-dichloro-1,1,3,3-

tetra-*iso*-propyldisiloxane (5 equiv) and imidazole (20 equiv) in DMF at 23 °C afforded a single product after silica gel and Sephadex chromatographies. The ^{1}H NMR, FTIR, and high-resolution mass spectrum of the product were in full accord with the formation of the cyclic disiloxane **159**, thereby verifying that the stereochemical outcome of the acetylide addition into the epoxy aldehyde proceeded in analogy to the ring-closure of the related α,β–unsaturated aldehydes (cf. **13** → **14** and **52** → **53**).



158 **159**

The tetraol **157** was next treated with carbonyldiimidazole (1.5 equiv, added in two 0.75 equiv portions at 15 min intervals) in THF starting at 0 °C, then warming to 23 °C.[53] At least three products were obtained from the reaction mixture. Isolation and characterization of these products showed them to include not only the desired carbonate **160**, but also the intermediate C-8 carbonylimidazolides of both the starting tetraol **157**

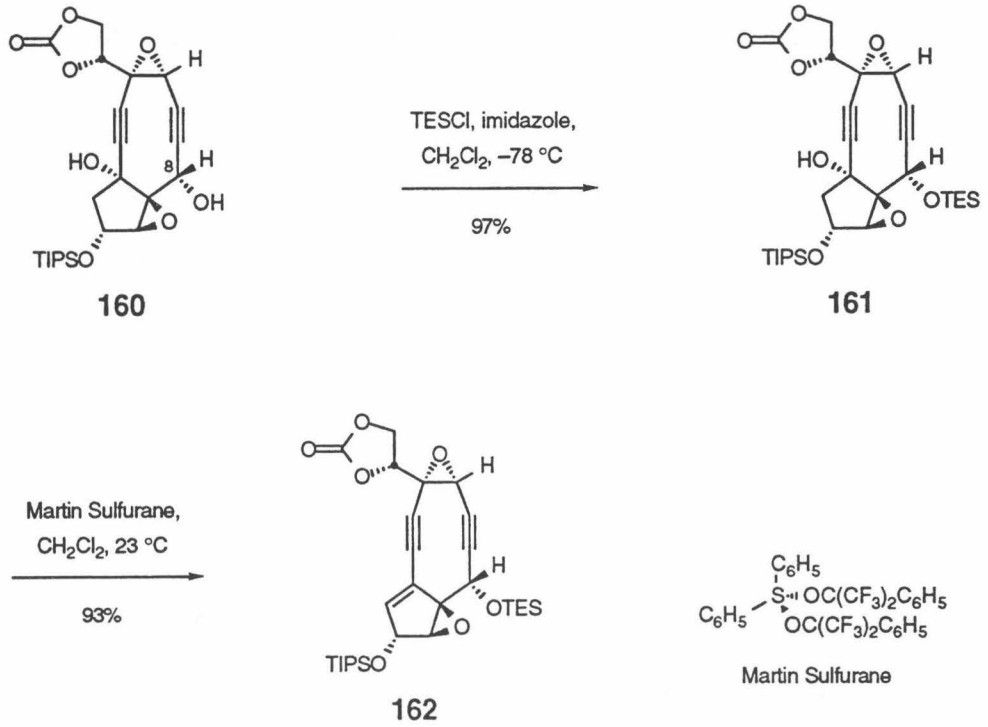


157 **160**

and the product **160**. Although these intermediates were expected to hydrolyze upon aqueous work-up of the reaction mixture, they were found to be surprisingly stable to even silica gel chromatographic purification. Subsequent to this finding, the crude reaction mixture obtained from the aqueous work-up was treated directly with (±)-camphorsulfonic acid in a 2:1 mixture of acetonitrile and water to provide the carbonate **160** in 72% yield along with unreacted tetraol **157** (23%).

In order to selectively activate and eliminate the C-1 alcohol, the C-8 alcohol of diol **160** was selectively protected by reaction with triethylsilyl chloride (7 equiv) and imidazole (20 equiv) in dichloromethane at 0 °C, affording the TES ether **161** in 97% yield (Scheme XXII). The first attempts to carry out the elimination of the C-1 alcohol employed triflic anhydride and the bulky base 2,6-di-*tert*-butylpyridine in dichloromethane (–78 → 0 °C), but the reaction was complicated by the formation of decomposition products, and the

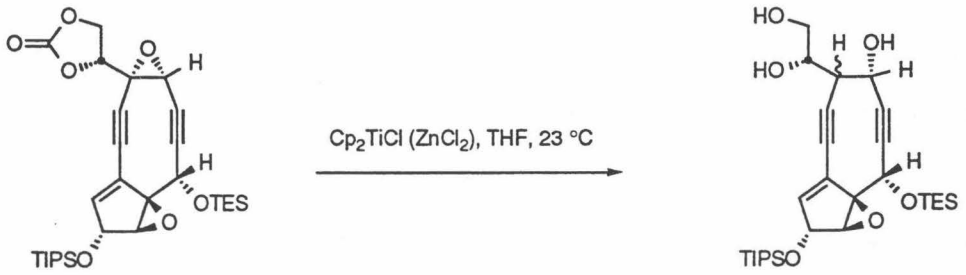
Scheme XXII



160 **161** **162**

yield of the olefin **162** was low (30-50%). Changing the base from 2,6-di-*tert*-butylpyridine to 2,6-dichloropyridine caused complete decomposition of the substrate, while substitution of the 2,6-di-*tert*-butylpyridine with 2-chloropyridine neither improved nor worsened the yield.[98] The optimal set of conditions for dehydration of the C-1 alcohol was found to be use of the Martin sulfurane dehydrating reagent (5 equiv) in dichloromethane at 23 °C.[61] Under these conditions, the olefin **162** could be isolated in 93% yield. The double bond-containing product **162** was found to be considerably less stable than the corresponding saturated intermediates, darkening within minutes upon concentration. Despite this instability, the product **162** could be concentrated to neatness for brief periods, and was stable to storage at –20 °C in a frozen benzene matrix for several days.

Continued exploration of conditions by which to effect the selective opening of the C-9 – C-10 epoxide of **162** began with a reexamination of the dicyclopentadienyl titanium(III) chloride reagent.[96] Reaction of the olefin-containing intermediate **162** with this reagent (3 equiv) in THF at 23 °C afforded the product **163**, which resulted from opening of the C-4 – C-5 epoxide and concomitant cleavage of the ethylene carbonate.



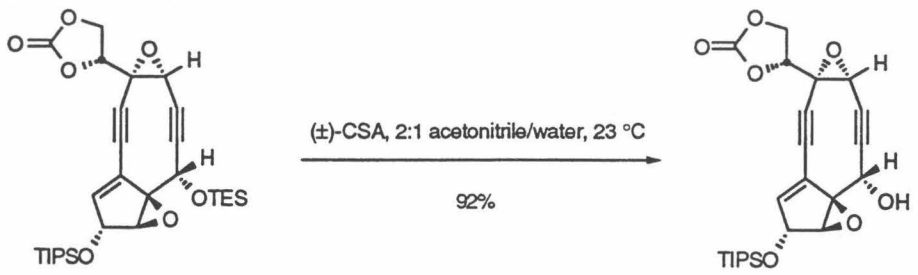
162 **163**

It was anticipated that selective opening of the C-9 – C-10 epoxide could be carried out under conditions that favored the formation of the allylic cation spanning the region defined by C-12, C-1, and C-9. Acidic halohydrin-forming conditions were examined to carry out this transformation, with the expectation that the halogen would be reductively

removed at a later stage. Toward this end, the olefin **162** was treated with lithium iodide (16 equiv) and acetic acid (30 equiv) in THF at 0 °C.[100] Aside from unreacted **162** and material corresponding to the cleavage of the TES ether of **162**, the signals for an additional product observed in the ^{1}H NMR spectrum of the crude reaction mixture were consistent with an iodohydrin being formed at the C-4 – C-5 epoxide. The more strongly Lewis acidic conditions of magnesium iodide (10 equiv) in toluene starting at –78 °C and warming to 0 °C provided a highly unstable product in which the C-1 – C-12 olefin had reacted, although it appeared by ^{1}H NMR analysis that the C-9 – C-10 epoxide was still intact. The ^{1}H NMR spectrum of this new product was also indicative of C-4 – C-5 iodohydrin formation.

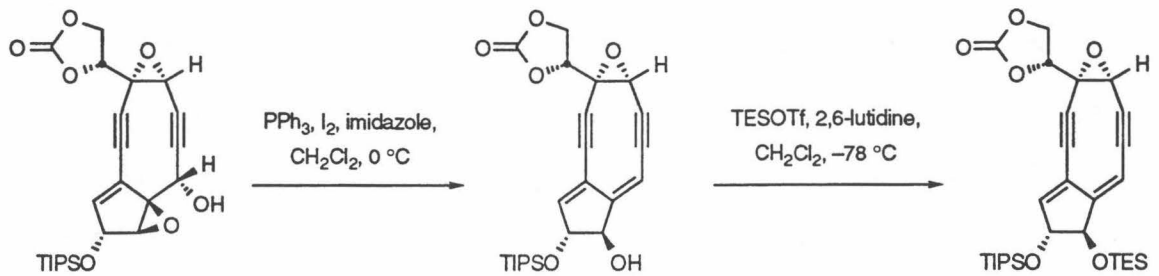
A thorough study of the opening of the C-9 – C-10 epoxide under ionic hydrogenation conditions was also conducted.[102] Exposure of the substrate **162** to triethylsilane (50 equiv) and various concentrations (0.04-1.8 M) of trifluoroacetic acid (TFA) in dichloromethane at either –78 °C or –40 °C followed by gradual warming generally resulted in loss of the C-8 TES group and no further reaction. Reaction of **162** with triethylsilane (50 equiv) and boron trifluoride etherate (25 equiv) in dichloromethane at 0 °C[103] produced a complex mixture of products, as did treatment of **162** with sodium cyanoborohydride (50 equiv) and boron trifluoride etherate (100 equiv) in THF at 0 °C.[104]

An additional strategy for the transformation of the epoxy alcohol to an allylic alcohol was the conversion of the alcohol to an iodide or a bromide and subsequent treatment with an alkyllithium to effect a reductive opening. Accordingly, the TES ether of intermediate **162** was cleaved with (±)-camphorsulfonic acid (5 equiv) in 2:1 acetonitrile/water at 23 °C to provide the alcohol **164** in 92% yield. Reaction of the alcohol **164** with the combination of triphenylphosphine (10 equiv), iodine (10 equiv), and imidazole (10 equiv) in dichloromethane at 23 °C[25] resulted in the formation of a mixture of several unstable products, and attempted isolation of the major component by



162 **164**

chromatography on silica gel was not successful, likely due to its rapid decomposition. When the same reaction was carried out at a temperature of 0 °C and with a modification of the stoichiometry of the reagents (12 equiv PPh_3, 10 equiv I_2, 20 equiv imidazole), clean conversion to a single, slightly less polar, significantly more UV-active product was observed within 7-10 minutes. Again, difficulties were encountered in the attempted purification of the product, with the continued conversion of the single product to several new products by the time a silica gel column had been prepared. Finally, pre-packing of the column with silica and the eluant (20% ethyl acetate in hexanes) was followed by direct loading of the concentrated reaction mixture directly onto the column as soon as completion of the reaction was indicated by TLC. This practice allowed for isolation of the new, unstable product. Extensive ^1H NMR analysis of the product, including a deuterium-exchange experiment (D_2O), indicated that the product was not the expected iodide, but in



164 **165** **166**

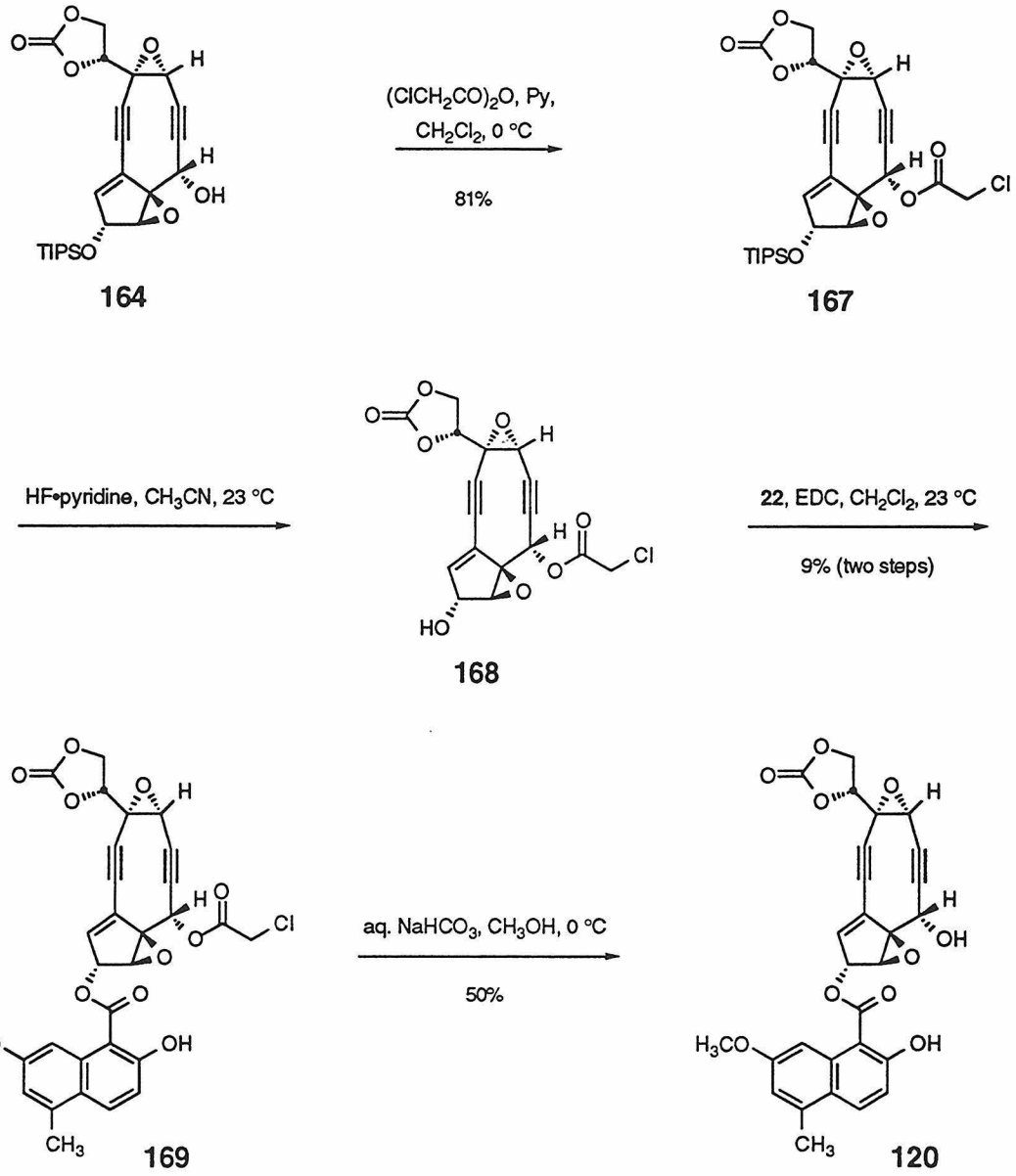
fact the epoxydienediyne **165**. Further support for the assignment of structure **165** was gained by the reaction of the alcohol **165** with TESOTf (50 equiv based on **164**) and 2,6-

lutidine (100 equiv based on **164**) in dichloromethane at –78 °C[77] to produce the silyl ether **166**, which was found to be slightly more stable than **165** (stable at –20 °C in solid deuteriated benzene matrix for 12 hours) and also displayed more well resolved signals in the ^{1}H NMR spectrum. The sharpness of these peaks allowed for a complete series of ^{1}H NMR decoupling experiments and a comprehensive assignment of the signals. The preparation of the dienediyne **165** marked the first synthesis of the fully substituted epoxydienediyne core of neocarzinostatin chromophore, including substituents having the proper stereochemistry at the C-10 and C-11 positions.

Having the model dienediyne **165** in hand, the goal now became the incorporation of the naphthoate ester at the C-11 position. Based on the instability of the dienediyne **165**, the possibility of appending the ester at this stage or beyond was not considered. Instead, a naphthoate-containing epoxy alcohol in analogy to **164** was targeted as a substrate for the PPh_3/I_2/imidazole reaction. In order to arrive at this substrate as directly as possible, a four-step preparation from the epoxy alcohol **164** was developed.

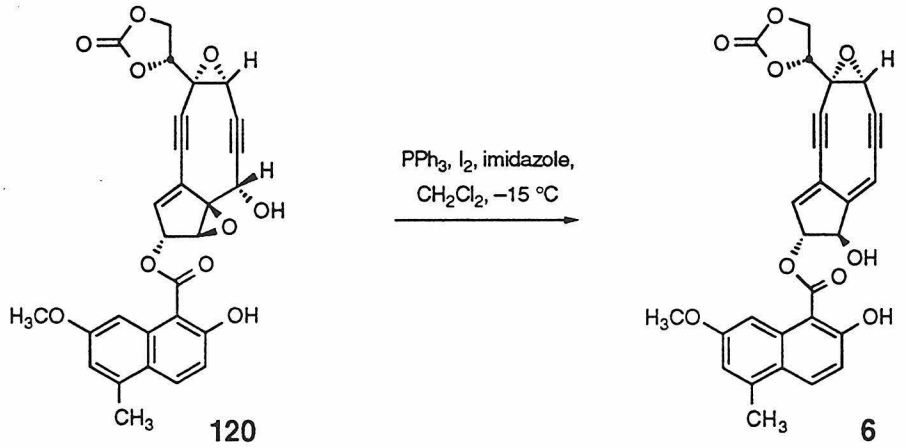
The C-8 alcohol of intermediate **164** was protected as a chloroacetate ester by reaction with chloroacetic anhydride (10 equiv) and pyridine (20 equiv) in dichloromethane at 0 °C, affording chloroacetate **167** in 81% yield (Scheme XXIII).[105] The cleavage of the TIPS ether proved to be a difficult task, attributable to the instability of both the starting TIPS ether **167** and the product allylic alcohol **168**. Initially, the best conditions were thought to be exposure of the substrate to a 6:1 mixture of methanol and 1 N aqueous hydrochloric acid. The yield of allylic alcohol **168**, however, was found to be highly variable under these conditions, due in part to concurrent cleavage of the chloroacetate ester. Cleaner conversion was observed when a 1:9 mixture the hydrofluoric acid-pyridine complex and acetonitrile at 23 °C was employed for this deprotection. Because of the instability of the alcohol **168**, it was generally carried directly to the next reaction without storage. The coupling of the naphthoate ester was accomplished using the naphthoic acid **22** (6 equiv) and the coupling agent 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide

Scheme XXIII



hydrochloride (EDC, 9 equiv) in dichloromethane at 23 °C. Due to the instability of the intermediate **168** and the inefficiency of the coupling, the product diester **169** could only be isolated in 9% overall yield from TIPS ether **167**. It appeared that the allylic alcohol **168** was the most unstable compound in the series, as the esterification product **169** was found to be considerably more stable, and could be stored at –20 °C for several days without significant decomposition. The chloroacetate protecting group was removed by treatment of a solution of the diester **169** in toluene at 0 °C with saturated aqueous sodium bicarbonate in methanol at 0 °C to provide the targeted epoxy alcohol **120** in 50% yield. The epoxy alcohol **120** was also found to be remarkably stable, and could be stored in neat form (pale yellow film) for several weeks at –20 °C.

Addition of a solution of the epoxy alcohol **120** in dichloromethane/acetonitrile (10:1) to a premixed suspension of triphenylphosphine (27 equiv), iodine (24 equiv), and imidazole (50 equiv) in dichloromethane at –15 °C produced the highly unstable neocarzinostatin chromophore aglycone (**6**).[25] This conversion was found to be highly dependent upon the initial mixing of the triphenylphosphine, iodine, and imidazole reagents, as evidenced by the failure of the reaction the first several times it was conducted. It was later determined that the color of the suspension formed upon the mixing of the reagents PPh_3, I_2, and imidazole was critical: the reaction failed when the initial suspension



was white and was successful when the suspension was yellow. It is unclear as to what the nature of this difference was, but the reaction has never failed when starting with a yellow or pale orange suspension. It is also not known what the mechanism of the transformation of **120** to **6** is. The formation of an epoxy iodide intermediate followed by in situ reduction by iodide ion cannot be excluded, although no intermediate species were observed by thin-layer chromatographic monitoring of the reaction. Such nucleophilic conversions of epoxy iodides to allylic alcohols are known, but generally require more forcing conditions.[106] It is possible that in this system the strain imposed by the adjacent cyclopentene facilitated the conversion of **120** to **6**.

Characterization of the aglycone **6** proved to be quite challenging. The aglycone **6** is not a known degradation product of **1**, and as a result, no authentic sample was available for comparison. Additionally, the aglycone **6** was found to be highly unstable, further complicating the structural proof. Although an NMR sample could be prepared from the chromatographic eluant without concentration to neatness, and good-quality ^{1}H NMR spectra, complete with decoupling, could be obtained, the sample was found to decompose at a rate such that, after 8 hours at –20 °C, less than half of the aglycone **6** remained (^{1}H NMR analysis). Such instability also precluded the accumulation of aglycone **6** through multiple reactions and rendered the acquisition of a ^{13}C NMR spectrum implausible. A circular dichroism (CD) spectrum of **6** was obtained as a solution in acetonitrile, and displayed the same general characteristics as a CD spectrum of **1** obtained in 0.5 M acetic acid in methanol.

The instability of **6** also precluded the procurement of its mass spectrum in isolation using the soft ionization techniques of FAB or electrospray. Anticipating that the structural components present in **6** were sufficient to bind to apo-NCS, the protein that imparts the stability necessary for **1** to exist in nature, efforts were directed toward obtaining a mass spectrum of **6** complexed to the apoprotein. Initial studies revealed that analysis of an aqueous solution of holo-NCS (pH 7) by electrospray MS provided peaks consistent with

the free apoprotein in the +6 and +7 charge states and a strong signal corresponding to free protonated **1** (mass 651). An FPLC-purified[107] and dialyzed sample of apo-NCS in aqueous solution (pH 7) also displayed peaks consistent with its +6 and +7 charge states. The molecular weight of apo-NCS was determined from the spectrum to be 11,095, fully consistent with the molecular weight expected as calculated from its amino acid sequence. Addition of a solution of **6** in acetonitrile to an aqueous solution of apo-NCS (pH 7) followed by electrospray mass spectral analysis of the mixture provided peaks consistent with the free apo-NCS in the +7 and +8 charge states, as well as the complex between apo-NCS and **6** in the +7 and +8 charge states (Figure 3).[108] It should be noted that the spectra

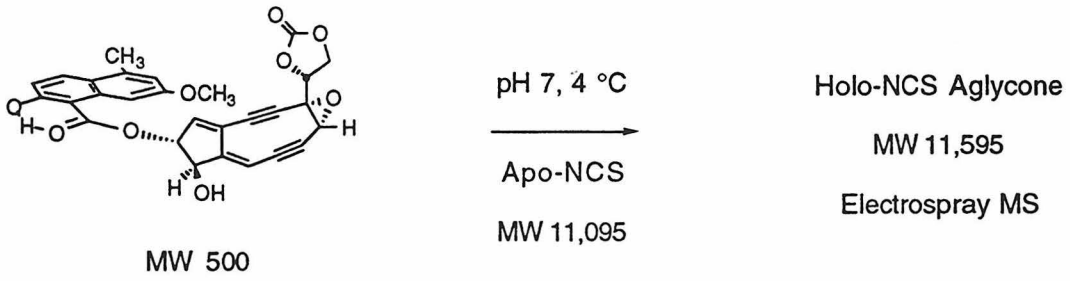


Figure 3. Complexation of 6 with apo-NCS.

for holo-NCS and the apo-NCS complex with **6** were obtained using different instruments. The analysis of **6** complexed with apo-NCS using the same instrument employed to obtain the spectrum of holo-NCS provided only peaks corresponding to apo-NCS. This result would appear to provide further support for the reduced stability of **6** relative to **1**, as the conditions of this analysis were sufficient to decomplex both **1** and **6** from the apoprotein, and while **1** was able to survive the analysis, no peaks corresponding to **6** could be observed.

The yield for the conversion of the epoxy alcohol **120** to **6** could be determined by UV spectroscopy, assuming an extinction coefficient of 7040 cm^{-1} M^{-1} at 302 nm, which

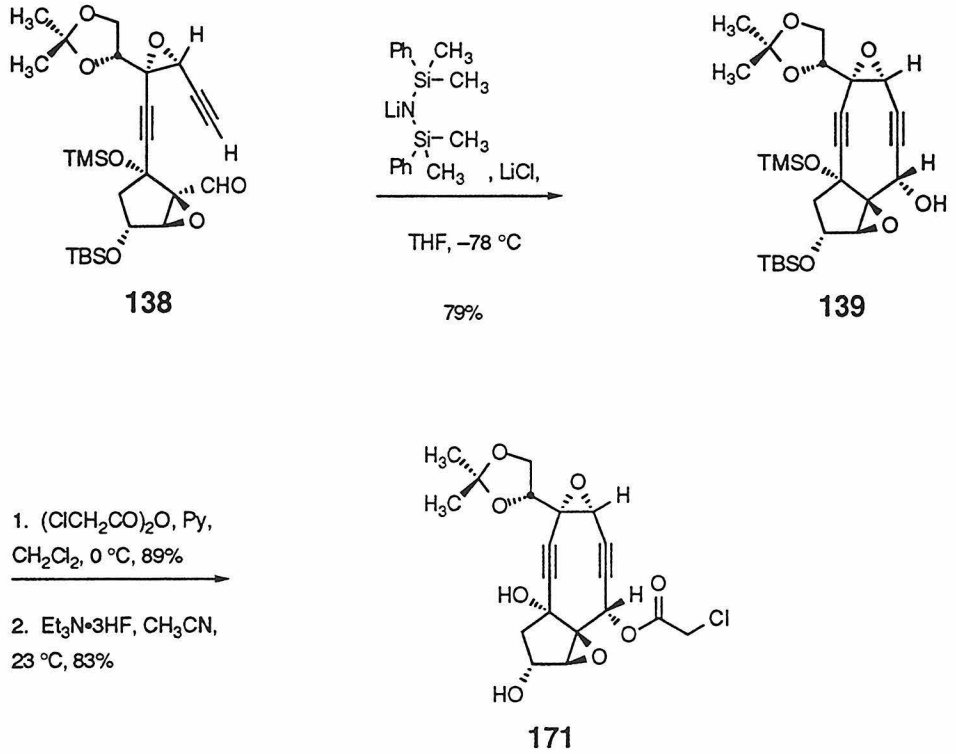
corresponds to the epoxydienediyne core of **1** as determined in these laboratories.[109] As the carbohydrate group of **1** is expected to contribute little to the UV activity of **1**, it was anticipated that the extinction coefficients of **1** and **6** should be very similar. Samples were generally prepared for quantitation by the concentration of column fractions containing **6** to a volume of ca. 0.1 mL followed by dissolution of the concentrate into the appropriate amount of methanol. Precise dilutions were made in order to obtain an absorbance at 302 nm of less than one unit. Further testimony to the instability of **6** may be gleaned from the information that the yields determined for the reaction producing **6** covered the full spectrum between 13% and 75%.

Having completed the enantioselective synthesis and characterization of the aglycone **6**, the next task became the preparation of sufficient quantities of **6** for the investigation of the thiol addition chemistry and DNA cleavage activity of **6** in comparison to **1**. As the synthetic sequence developed for the preparation of the direct precursor of **6**, epoxy alcohol **120**, contained several poor-yielding steps, studies of the optimization of the route were initiated. The lowest-yielding series involved conversion of the chloroacetate **167** to the epoxy alcohol **120**. These three steps were found to proceed in 4.5% overall yield *at best.* A significant portion of this low yield could be attributed to the instability of allylic alcohol **168**, both in its preparation and in its further reaction with the naphthoic acid **22**. It was expected that the introduction of the naphthoate ester prior to dehydration of the C-1 alcohol would circumvent this problem and perhaps provide more stable intermediates in the later stages of the synthesis.

Implementation of the new synthetic strategy involved an older intermediate: nine-membered ring alcohol **139**. This alcohol was chosen with the expectation that, upon orthogonal protection of the C-8 alcohol, the C-10 TBS group could be removed under mild conditions to provide the free alcohol required for the incorporation of the naphthoate ester. One of the complications observed in the preparation of **139** from the epoxy aldehyde **138** using the standard conditions of excess $LiN(TMS)_2$ and LiCl in THF at –78

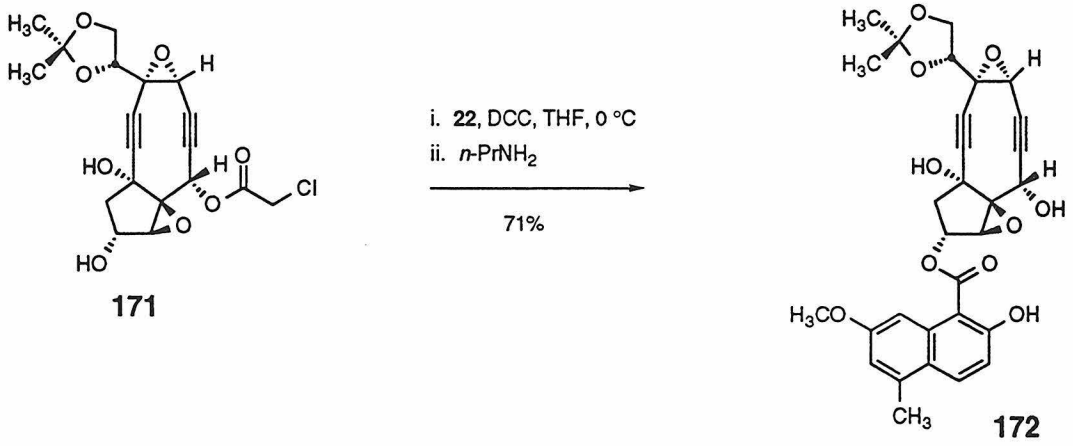
°C was the capricious formation of a cyclized product in which the C-8 alcohol had been converted to a TMS ether. The formation of this by-product was attributed to the requirement for excess $LiN(TMS)_2$ in the ring-closure reaction. Upon aqueous work-up of the reaction mixture, neutralization of excess $LiN(TMS)_2$ generated hexamethyldisilazane, which in turn silylated the C-8 alcohol. Quenching of the excess base with pH 7.2 phosphate buffer was of no assistance in alleviating this problem; however, substitution of $LiN(TMS)_2$ with the bulkier base lithium diphenyltetramethyldisilazide not only suppressed side product formation, but also was more efficient, as only 2 equivalents of base were required for the reaction to proceed to completion, as opposed to 5 equivalents of $LiN(TMS)_2$ (Scheme XXIV).[110] Treatment of alcohol **139** with chloroacetic anhydride (5 equiv) and pyridine (10 equiv) in dichloromethane at 0 °C produced the chloroacetate ester

Scheme XXIV



in 89% yield,[105] and subsequent exposure of the chloroacetate to triethylamine trihydrofluoride (5 equiv) in acetonitrile at 23 °C afforded chloroacetate diol **171** as a white foam in 83% yield.[32]

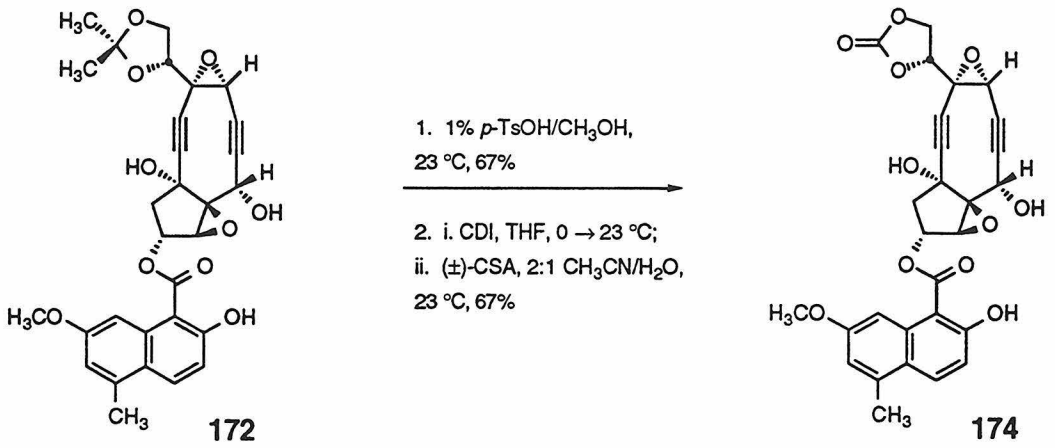
The esterification of diol **171** with the naphthoate ester **22** (3 equiv) was carried out with DCC (5 equiv) in THF at 0 °C. In situ cleavage of the chloroacetate was effected by addition of *n*-propylamine (10 equiv). Considerable effort was required for the optimization of this reaction, as the naphthoate ester **22** displayed a tendency to couple with itself at the naphthol position and even with the tertiary alcohol of **171** to form oligomeric products. A survey of conditions for the introduction of the ester group, including use of the pentafluorophenyl and 4-nitrophenyl activated esters of **22**, mixed anhydrides of **22**, and the coupling reagents EDC and DCC indicated that DCC was the most effective reagent for this reaction. Selection of THF as the solvent for the DCC-mediated coupling proved to be critical; couplings carried out in either dichloromethane or DMF resulted in markedly diminished yields of ester **172**.



171 **172**

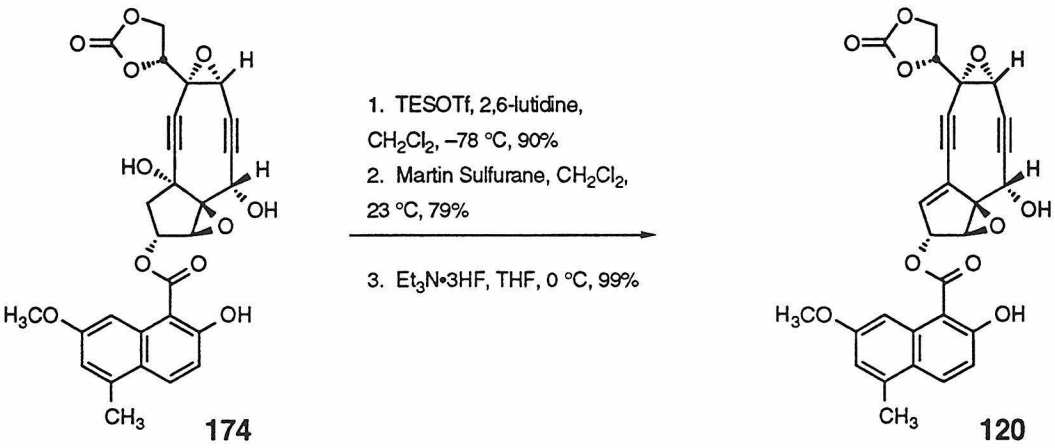
The acetonide of ester **172** was removed by exposure to 1% *p*-TsOH in methanol at 23 °C to provide the pentaol intermediate in 67% yield.[111] Introduction of the ethylene carbonate was accomplished with carbonyldiimidazole in THF,[53] and the intermediate carbonylimidazolides were hydrolyzed by treatment of the crude reaction mixture with (±)-

camphorsulfonic acid in 2:1 acetonitrile/water at 23 °C to afford diol **174** in 67% yield. Unreacted starting pentaol (29%) could also be recovered from this reaction.



172 **174**

The C-8 alcohol and the hydroxyl group of the naphthoate ester of **174** were protected as triethylsilyl ethers by reaction with TESOTf (5 equiv) and 2,6-lutidine (12 equiv) in dichloromethane at –78 °C[77] to provide the bis-silyl ether in 90% yield. The tertiary alcohol was cleanly dehydrated using the Martin sulfurane dehydrating agent (5 equiv) in dichloromethane at 23 °C,[61] affording the olefinic product in 79% yield. The triethylsilyl ethers were then cleaved by treatment with triethylamine trihydrofluoride (5 equiv) in THF at 0 °C[32] to produce the epoxy alcohol **120** in quantitative yield. Application of this improved sequence for the preparation of the epoxy alcohol **120** provided a several-



174 **120**

fold increase in the amount of this intermediate that could be amassed relative to the pathway summarized in Scheme XXIII. The revised synthetic pathway should supply the necessary quantities of intermediates for the ongoing studies directed toward the completion of the total synthesis of neocarzinostatin chromophore (**1**), as well as the synthesis of analogs bearing modified sugar residues.[112]

Experimental Section

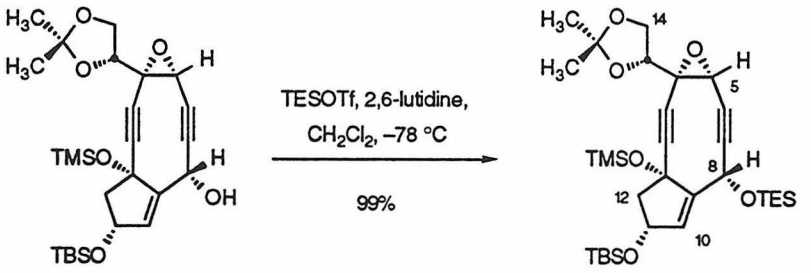
General procedures. All reactions were performed in flame-dried round bottom or modified Schlenk (Kjeldahl shape) flasks. The flasks were fitted with rubber septa and contained a positive pressure of argon unless otherwise stated. Stainless steel syringes or cannula were used to transfer air- and moisture-sensitive materials. Concentration in vacuo was accomplished by rotary evaporation at water aspirator pressure (approximately 25 torr). Flash chromatography was carried out as described by Still et al., employing 230-400 mesh silica gel.[29] Analytical thin-layer chromatography was performed using glass plates pre-coated with 0.25 mm 230-400 mesh silica gel impregnated with fluorescent indicator (254 nm). Thin-layer chromatography plates were visualized by exposure to ultraviolet light (noted as 'UV') and/or by exposure to an acidic solution of *p*-anisaldehyde (noted as 'anisaldehyde') or ethanolic ceric ammonium molybdate (noted as 'CAM'), followed by heating on a hot plate.

Materials. Commercial reagents were used as received, with the following exceptions. Ethyl ether and tetrahydrofuran (THF) were distilled from sodium benzophenone ketyl. Dichloromethane, benzene, toluene, acetonitrile, N,N-diisopropylethylamine, hexamethyldisilazane, 2,6-lutidine, pyridine, and triethylamine were distilled from calcium hydride at 760 torr. Diphenyltetramethyldisilazane was distilled from calcium hydride at 0.1 torr, and was stored under an atmosphere of argon. Acetic

acid was distilled from chromium trioxide at 760 torr and was stored over 4 Å molecular sieves. Methanesulfonyl chloride was distilled from phosphorous pentoxide at 760 torr. Trifluoromethanesulfonic anhydride and trimethylsilyl trifluoromethanesulfonate were stored in a glove box in round bottom flasks fitted with polycarbonate or glass stoppers. The molarity of n-butyllithium solutions was determined by titration with 2,6-di-*tert*-butyl-4-methylphenol using fluorene as an indicator (average of three determinations). Anhydrous lithium chloride was prepared by heating at 100 °C at 1 torr for 24 h. Fresh solutions of lithium hexamethyldisilazide were prepared by the addition of a solution of n-butyllithium (1.0 eq) in hexanes to a solution of hexamethyldisilazane (1.0 eq) in hexanes at -20 °C, followed by warming to room temperature. Fresh solutions of lithium diphenyltetramethyldisilazide were prepared by the addition of a solution of n-butyllithium (1.0 eq) in hexanes to a solution of hexamethyldisilazane (1.0 eq) in tetrahydrofuran at -20 °C, followed by warming to room temperature.

Instrumentation. Infrared (IR) spectra were obtained using a Perkin-Elmer 1600 FT-IR spectrophotometer referenced to a polystyrene standard. Data are presented as follows: frequency of absorption (cm^{-1}), intensity of absorption (v = very, s = strong, m = medium, w = weak) and assignment where appropriate. Proton nuclear magnetic resonance (^1H NMR) spectra and carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on either a General Electric QE-300 (300 MHz) or a JEOL GX-400 (400 MHz) NMR spectrometer; chemical shifts for protons are reported in parts per million downfield from tetramethylsilane and are referenced to residual protium in the NMR solvent (C_6D_5H: δ 7.20, $CDHCl_2$: δ 5.29, CD_2HCN: δ 1.93, $SO(CD_3)(CD_2H)$: δ 2.49). Data are represented as follows: chemical shift, multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, complex = multiple resonances, app. = apparent, abq = ab quartet), integration, coupling constant in Hertz (Hz), and assignment. FPLC was conducted on a Beckman System Gold HPLC equipped with a Pharmacia Mono-Q HR 5/5 anion exchange FPLC column and a Beckman 168 Programmable

Photodiode Detector set at 280 nm. Optical rotations were determined on a Jasco DIP-181 digital polarimeter equipped with a sodium lamp source. Circular dichroism spectra were obtained on a Jasco J-600 spectrophotometer using a solution cell with a path length of 1 cm. High resolution mass spectra were obtained either at the University of California, Riverside Mass Spectrometry Facility; the Midwest Center for Mass Spectroscopy, Lincoln, Nebraska; the University of California, Los Angeles Mass Spectrometry Facility; orthe California Institute of Technology Mass Spectrometry Facility. Electrospray mass spectra were obtained at Beckman Research Institute of the City of Hope, Duarte, California, on a Finnigan LCQ ion trap mass spectrometer equipped with a Finnigan-MAT electrospray ion source modified for microspray as previously described.[108]



68 **121**

Tris-silyl ether **121**

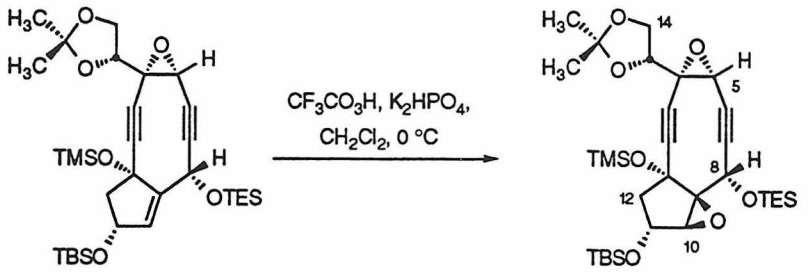
2,6-Lutidine (205 μL, 189 mg, 1.76 mmol, 10 equiv) and triethylsilyl trifluoromethanesulfonate (239 μL, 280 mg, 1.06 mmol, 6 equiv) were added sequentially to a solution of alcohol **68** (84.0 mg, 0.176 mmol, 1 equiv) in dichloromethane (9 mL) at –78 °C. The resultant yellow solution was maintained at –78 °C for 20 min, then excess triethylsilyl trifluoromethanesulfonate was quenched by the addition of triethylamine and methanol (0.5 mL each). The reaction mixture was partitioned between hexanes (20 mL) and water (20 mL). The layers were separated and the aqueous layer was further extracted with hexanes (2 x 20 mL). The combined organics were washed once with brine (25 mL), dried over sodium sulfate and concentrated. Purification of the residue by flash column chromatography (20% ethyl acetate in hexanes) provided tris-silyl ether **121** (109 mg, 99%) as a pale yellow oil.

^{1}H NMR (400 MHz, C_6D_6), δ: 6.22 (t, 1H, *J* = 1.84 Hz, C10 H), 5.71 (t, 1H, *J* = 1.44 Hz, C8 H), 4.82 (m, 1H, C11 H), 3.91 (dd, 1H, *J* = 8.40, 5.84 Hz, C13 H), 3.75 (dd, 1H, *J* = 8.80, 6.60 Hz, C14 H), 3.59 (t, 1H, *J* = 6.24 Hz, C14 H), 3.11 (s, 1H, C5 H), 3.08 (dd, 1H, *J* = 13.20, 6.96 Hz, C12 βH), 2.34 (dd, 1H, *J* = 12.80, 5.88 Hz, C12 αH), 1.51 (s, 3H, $C(CH_3)_2$), 1.23 (s, 3H, $C(CH_3)_2$), 1.09 (m, 9H, $OSi(CH_2CH_3)_3$), 0.95 (s, 9H, $OSiC(CH_3)_3(CH_3)_2$), 0.73 (m, 2H, $OSi(CH_2CH_3)_3$), 0.61 (m, 4H, $OSi(CH_2CH_3)_3$), 0.37 (s, 9H, $OSi(CH_3)_3$), 0.046 (s, 3H, $OSiC(CH_3)_3(CH_3)_2$), 0.032 (s, 3H, $OSiC(CH_3)_3(CH_3)_2$).

FTIR (thin film), cm^{-1}: 2955 (m), 2878 (m), 1461 (w), 1372 (w), 1252 (m), 1075 (m), 1005 (m), 844 (m), 741 (m).

TLC (25% EtOAc in Hexanes), R*f*: **68**: 0.46 (anisaldehyde)

121: 0.71 (anisaldehyde)



Bis-epoxide **122**

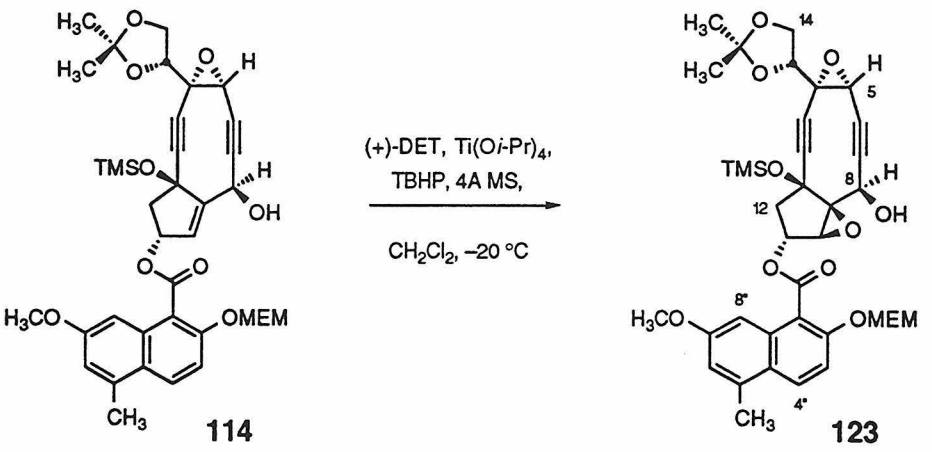
Peroxytrifluoroacetic acid (3 drops from a Pasteur pipet of a solution prepared in situ by dropwise addition of trifluoroacetic anhydride (2.12 mL, 3.15 g, 15.0 mmol, 1.2 equiv relative to H_2O_2) to a solution of hydrogen peroxide (340 μL of a 90% solution, 12.5 mmol, 1 equiv) in dichloromethane (2.5 mL)) was added to a solution of tris-silyl ether **121** (5.0 mg, 8.1 x 10^{-3} mmol, 1 equiv) and anhydrous K_2HPO_4 (28 mg, 0.16 mmol, 20 equiv) in dichloromethane (100 μL) at 0 °C. The yellow solution was maintained at 0 °C for an additional 5 min, then diluted with 1:1 ethyl acetate/hexanes (2 mL). The solution was washed with water (3 x 1 mL) and brine (1 mL), dried over sodium sulfate and concentrated to approximately 0.1 mL. The concentrated sample was applied to a flash chromatography column loaded with 10% ethyl acetate in hexanes, and the product was eluted with a solvent system of 10% ethyl acetate in hexanes grading to 20% ethyl acetate in hexanes. Fractions containing the product were pooled and concentrated to a volume of ca. 0.1 mL. A 0.5 mL portion of deuteriated benzene (99.5 atom % D) was added and the resulting solution was concentrated to a volume of ca. 0.1 mL. This procedure was repeated 4 times. After the last iteration, the concentrated solution was taken up in

approximately 0.4 mL deuteriated benzene (99.95 atom % D). Analysis of the sample by ^{1}H NMR showed it to contain a small amount (not quantitated) of bis-epoxide **122.**

^{1}H NMR (400 MHz, C_6D_6), δ: 5.17 (s, 1H, C8 H), 4.29 (t, 1H, *J* = 7.32 Hz, C11 H), 4.03 (dd, 1H, *J* = 9.16, 5.12 Hz, C13 H), 3.86 (s, 1H, C10 H), 3.80 (dd, 1H, *J* = 8.76, 6.60 Hz, C14 H), 3.44 (dd, 1H, *J* = 6.60, 5.12 Hz, C14 H), 3.15 (s, 1H, C5 H), 2.24 (dd, 1H, *J* = 11.36, 6.60 Hz, C12 H), 1.94 (dd, 1H, *J* = 12.08, 9.12 Hz, C12 H), 1.58 (s, 3H, $C(CH_3)_2$), 1.27 (s, 3H, $C(CH_3)_2$), 1.08 (t, 9H, *J* = 8.08 Hz, $OSi(CH_2CH_3)_3$), 0.91 (s, 9H, $OSiC(CH_3)_3(CH_3)_2$), 0.67 (q, 6H, *J* = 7.72 Hz, $OSi(CH_2CH_3)_3$), 0.44 (s, 9H, $OSi(CH_3)_3$), –0.014 (s, 3H, $OSiC(CH_3)_3(CH_3)_2$), –0.026 (s, 3H, $OSiC(CH_3)_3(CH_3)_2$).

TLC (25% EtOAc in Hexanes), R*f*: **121**: 0.59 (anisaldehyde)

122: 0.41 (anisaldehyde)



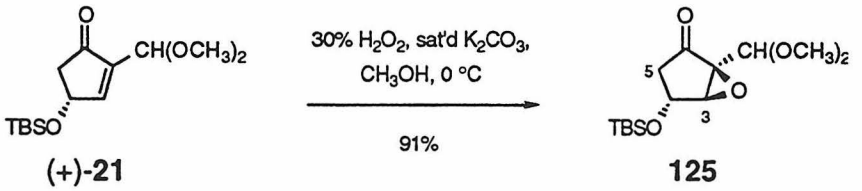
Epoxy alcohol **123**

A suspension of 4Å molecular sieves (approx. 0.1g, powdered, activated) in dichloromethane (0.7 mL) was cooled to –20 °C. (+)-Diethyl-L-tartrate (30 μL, 37 mg, 0.17 mmol, 12 equiv) and titanium isopropoxide (43 μL, 41 mg, 0.14 mmol, 10 equiv) were added sequentially via syringe. The mixture was allowed to stir at –20 °C for an additional 15 min, and alcohol **114** (10 mg, 0.014 mmol, 1 equiv) in dichloromethane (0.3 mL) was added via cannula. The resultant mixture was stirred at –20 °C for another 30 min, then *tert*-butyl hydroperoxide (15 μL of a 4.7 M solution in dichloromethane, 0.0722 mmol, 5 equiv) was added with a Teflon needle through a slit in the septum at the neck of the flask. The reaction was maintained at –20 °C for 11 h, then the catalyst was quenched with 10% aqueous D-tartaric acid (5 mL) and stirred vigorously for 30 min. The layers were separated, and the aqueous layer was further extracted with dichloromethane (3 2-mL portions). The combined organics were dried over sodium sulfate and concentrated. Purification of the residue by flash column chromatography (5% ethyl acetate in dichloromethane grading to 10% ethyl acetate in dichloromethane) was followed by pooling

fractions containing the product and concentration to ca. 0.1 mL. A 0.5 mL portion of deuteriated benzene (99.5 atom % D) was added, and the resultant solution was concentrated to a volume of ca. 0.1 mL. This procedure was repeated 4 times. After the final concentration, the concentrate was taken up in ca. 0.4 mL deuteriated benzene (99.95 atom % D) and analyzed by ^{1}H NMR to confirm the formation of epoxy alcohol **123**.

^{1}H NMR (400 MHz, C_6D_6), δ: 7.63 (d, 1H, *J* = 9.16 Hz, C4" H), 7.36 (d, 1H, *J* = 2.20 Hz, C8" H), 7.20 (d, 1H, *J* = 9.16 Hz, C3" H), 6.96 (br s, 1H, C6" H), 5.85 (d, 1H, *J* = 5.48 Hz, C11 H), 5.21 (abq, 2H, Δν = 53.08 Hz, *J* = 6.96 Hz, $OCH_2OCH_2CH_2OCH_3$), 4.89 (d, 1H, *J* = 6.5 Hz, C8 H), 4.25 (s, 1H, C10 H), 3.93-3.24 (complex, 7 H, $OCH_2OCH_2CH_2OCH_3$, C13, C14 H), 3.53 (s, 3H, C7" OCH_3), 3.13 (d, 1H, *J* = 16.12 Hz, C12 αH), 3.06 (s, 3H, $OCH_2OCH_2CH_2OCH_3$), 2.79 (s, 1H, C5 H), 2.48 (dd, 1H, *J* = 16.12, 5.48 Hz, C12 βH), 2.36 (d, 1H, *J* = 6.56 Hz, C8 OH), 2.23 (s, 3H, C5" CH_3), 1.47 (s, 3H, $C(CH_3)_2$), 1.34 (s, 3H, $C(CH_3)_2$), 0.25 (s, 9H, $OSi(CH_3)_3$).

FTIR (thin film), cm^{-1}:	3401 (m, OH), 3283 (m, OH), 2923 (s), 1828 (m), 1724 (s, ester C=O), 1622 (m), 1466 (m), 1255 (vs), 1159 (m), 1083 (s), 1035 (s), 842 (m)
HRMS (FAB):	Calc'd for $C_{37}H_{44}O_{12}Si$ $[M]^+$: 708.260216 Found: 708.264496
TLC (30% EtOAc/30% Hexanes/40% CH_2Cl_2), R*f*:	**114**: 0.32 (fluoresces under UV, anisaldehyde) **123**: 0.41 (fluoresces under UV, anisaldehyde)

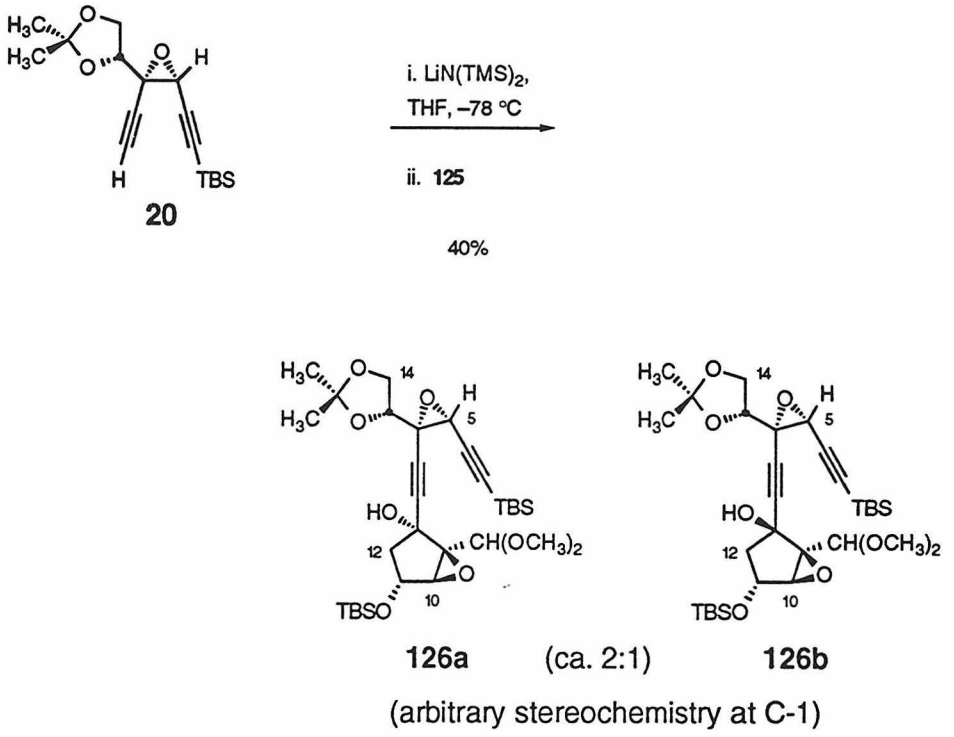


(+)-21 **125**

Epoxy ketone **125**

A solution of enone (+)-**21** (275 mg, 0.960 mmol, 1.0 equiv) in methanol (1.60 mL) was cooled to 0 °C. Hydrogen peroxide (205 μL of a 30% solution, 1.92 mmol, 2 equiv) was added via syringe, followed by dropwise addition of saturated aqueous potassium carbonate (110 μL). The reaction mixture was maintained at 0 °C for an additional 30 min, then diluted with H_2O (10 mL). The solution was extracted with three 25-mL portions of ethyl acetate and the combined organics were washed once with brine (25 mL), dried over sodium sulfate and concentrated. Purification of the residue by flash column chromatography (50% ethyl acetate in hexanes) afforded epoxy ketone **125** (263 mg, 91%) as a colorless oil.

^{1}H NMR (400 MHz, C_6D_6), δ:	4.98 (s, 1H, $CH(OCH_3)_2$), 4.14 (d, 1H, J = 5.48 Hz, C4 H), 4.13 (s, 1H, C3 H), 3.23 (s, 3H, $CH(OCH_3)_2$), 3.20 (s, 3H, $CH(OCH_3)_2$), 2.44 (dd, 1H, *J* = 18.30, 5.49 Hz, C5 βH), 1.98 (d, 1H, *J* = 18.30 Hz, C5 αH), 0.81 (s, 9H, $OSiC(CH_3)_3(CH_3)_2$), –0.11 (s, 3H, $OSiC(CH_3)_3(CH_3)_2$), –0.14 (s, 3H, $OSiC(CH_3)_3(CH_3)_2$).
FTIR (thin film), cm^{-1}:	2954 (s), 2858 (s), 1753 (s, C=O), 1469 (m), 1369 (m), 1085 (s), 837 (s).
$[\alpha]_D^{20}$:	+6.86° (*c* 0.52, C_6H_6)
TLC (50% EtOAc in Hexanes s), R*f*:	(+)-**21**: 0.63 (anisaldehyde) **125**: 0.70 (anisaldehyde)



Diepoxydiynes **126a** and **126b**

Lithium hexamethyldisilazide (258 μL of a 1.0 M solution in hexanes, 0.258 mmol, 3.0 equiv) was added dropwise over a two minute period to a solution of epoxydiyne **20** (79 mg, 0.26 mmol, 3.0 equiv) in toluene (2.0 mL) at –78 °C. The resultant pale yellow solution was stirred at –78 °C for an additional 20 min, and epoxy ketone **125** (26 mg, 0.086 mmol, 1.0 equiv) in toluene (150 μL) was added dropwise via cannula over a four minute period. The reaction mixture was maintained at –78 °C for another 90 min, then excess base was quenched by the addition of saturated aqueous ammonium chloride. The reaction was allowed to warm to 23 °C and was extracted with 1:1 ethyl acetate/hexanes (3 15-mL portions). The combined organics were washed with brine (20 mL), dried over

sodium sulfate and concentrated. Purification of the residue by flash column chromatography (5% ethyl acetate in dichloromethane) provided diastereomers **126a** (14 mg, 27%) and **126b** (7 mg, 13%), each as colorless oils.

For 126a:

^{1}H NMR (400 MHz, C_6D_6), δ: 5.27 (s, 1H, C**H**$(OCH_3)_2$), 4.21 (m, 2H, C11 H, C13 H), 3.95 (dd, 1H, *J* = 8.80, 6.60 Hz, C14 H), 3.85 (s, 1H, C10 H), 3.77 (t, 1H, *J* = 6.56 Hz, C14 H), 3.72 (s, 1H, O**H**), 3.62 (s, 1H, C5 H), 3.37 (s, 3H, CH$(OCH_3)_2$), 3.22 (s, 3H, CH$(OCH_3)_2$), 2.39 (dd, 1H, *J* = 14.28, 5.12 Hz, C12 βH), 2.19 (d, 1H, *J* = 14.28 Hz, C12 αH), 1.48 (s, 3H, C$(CH_3)_2$), 1.21 (s, 3H, C$(CH_3)_2$), 1.07 (s, 9H, SiC$(CH_3)_3(CH_3)_2$), 0.90 (s, 9H, SiC$(CH_3)_3(CH_3)_2$), 0.23 (s, 6H, SiC$(CH_3)_3(CH_3)_2$), –0.025 (s, 3H, SiC$(CH_3)_3(CH_3)_2$), –0.049 (s, 3H, SiC$(CH_3)_3(CH_3)_2$).

TLC (5% EtOAc in CH_2Cl_2), R*f*: **20**: 0.64 (anisaldehyde)

125: 0.52 (anisaldehyde)

126a: 0.25 (anisaldehyde)

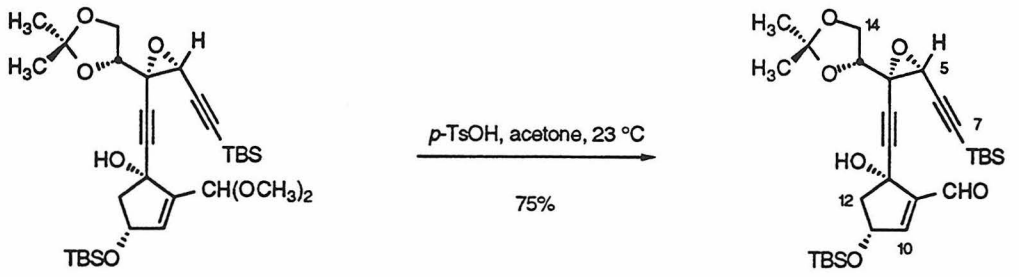
For 126b:

^{1}H NMR (400 MHz, C_6D_6), δ: 5.78 (s, 1H, $CH(OCH_3)_2$), 4.21 (d, 1H, *J* = 4.40 Hz, C11 H), 4.13 (dd, 1H, *J* = 8.80, 5.84 Hz, C13 H), 3.95 (dd, 1H, *J* = 8.76, 6.60 Hz, C14 H), 3.80 (t, 1H, *J* = 5.84 Hz, C14 H), 3.56 (s, 1H, C10 H), 3.53 (s, 1H, C5 H), 3.41 (s, 1H, OH), 3.37 (s, 3H, $CH(OCH_3)_2$), 3.32 (s, 3H, $CH(OCH_3)_2$), 2.37 (m, 2H, C12 H), 1.46 (s, 3H, $C(CH_3)_2$), 1.21 (s, 3H, $C(CH_3)_2$), 1.07 (s, 9H, $SiC(CH_3)_3(CH_3)_2$)), 0.97 (s, 9H, $OSiC(CH_3)_3(CH_3)_2$), 0.23 (s, 3H, $OSiC(CH_3)_3(CH_3)_2$), 0.22 (s, 3H, $OSiC(CH_3)_3(CH_3)_2$), 0.058 (s, 3H, $OSiC(CH_3)_3(CH_3)_2$), 0.011 (s, 3H, $OSiC(CH_3)_3(CH_3)_2$).

TLC (5% EtOAc in CH_2Cl_2), R*f*: **20**: 0.64 (anisaldehyde)

125: 0.52 (anisaldehyde)

126b: 0.18 (anisaldehyde)

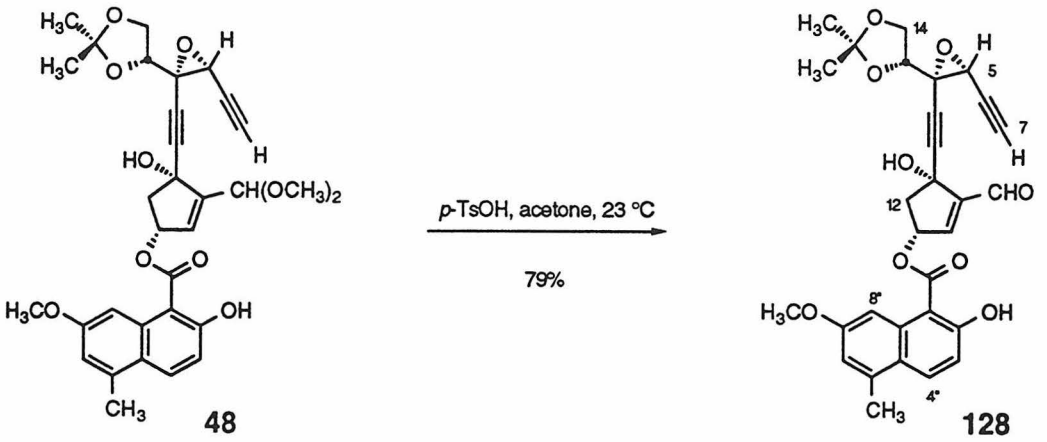


46 **127**

Aldehyde **127**

p-Toluenesulfonic acid (4.0 mg, 0.021 mmol, 0.2 equiv) was added in one portion to a solution of dimethyl acetal **46** (63 mg, 0.11 mmol, 1 equiv) in acetone (1.5 mL). The yellow solution was stirred at 23 °C for 10 min, and excess *p*-toluenesulfonic acid was neutralized by addition of saturated sodium bicarbonate (1 mL). The cloudy mixture was extracted with 1:1 ethyl acetate/hexanes (3 x 5 mL), and the combined organics were dried over sodium sulfate and concentrated. Purification of the residue by flash column chromatography (5% ethyl acetate in dichloromethane) afforded aldehyde **127** (44 mg, 75%) as a pale yellow oil.

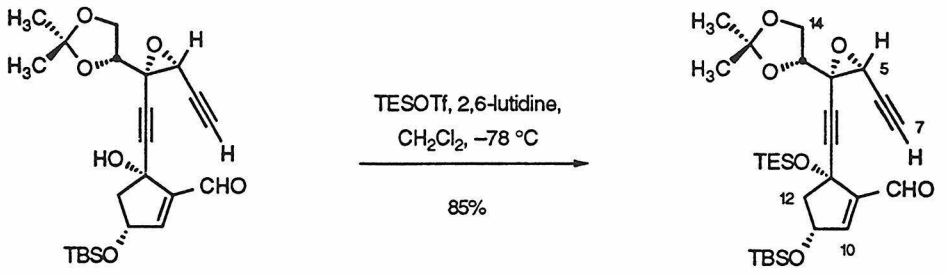
^{1}H NMR (400 MHz, C_6D_6), δ:	9.33 (s, 1H, CHO), 6.09 (d, 1H, *J* = 1.8 Hz, C10 H), 4.81 (td, 1H, *J* = 6.92, 1.80 Hz, C11 H), 4.10 (dd, 1H, *J* = 8.80, 5.84 Hz, C13 H), 3.87 (m, 2H, C14 H and OH), 3.61 (t, 1H, *J* = 6.20 Hz, C14 H), 3.49 (s, 1H, C5 H), 3.10 (dd, 1H, *J* = 12.80, 6.92 Hz, C12 H), 2.40 (dd, 1H, *J* = 12.80, 6.56 Hz, C12 H), 1.42 (s, 3H, $C(CH_3)_2$), 1.18 (s, 3H, $C(CH_3)_2$), 1.07 (s, 9H, $SiC(CH_3)_3(CH_3)_2$), 0.95 (s, 9H, $SiC(CH_3)_3(CH_3)_2$), 0.23 (s, 3H, $SiC(CH_3)_3(CH_3)_2$), 0.22 (s, 3H, $SiC(CH_3)_3(CH_3)_2$), 0.038 (s, 3H, $SiC(CH_3)_3(CH_3)_2$), 0.015 (s, 3H, $SiC(CH_3)_3(CH_3)_2$).
TLC (10% EtOAc in CH_2Cl_2), R*f*:	**46**: 0.29 (anisaldehyde) **127**: 0.51 (UV, anisaldehyde)



Aldehyde **128**

p-Toluenesulfonic acid (110 mg) was added in one portion to a solution of dimethyl acetal **48** (390 mg, 0.674 mmol, 1 equiv) in acetone (20 mL) at 23 °C. The reaction was maintained at 23 °C for 55 min, then poured into saturated aqueous sodium bicarbonate (40 mL). The mixture was extracted with 1:1 ethyl acetate/hexanes (3 25-mL portions), and the combined organics were washed with saturated aqueous sodium chloride (35 mL), dried over sodium sulfate and concentrated. The residue was purified by flash column chromatography (30% ethyl acetate in hexanes) to afford the aldehyde **128** (285 mg, 79%) as a pale yellow oil.

^{1}H NMR (300 MHz, C_6D_6), δ:	12.72 (s, 1H, C2" OH), 9.24 (s, 1H, C8 H), 8.13 (d, 1H, *J* = 2.0 Hz, C8" H), 7.71 (d, 1H, *J* = 9.18 Hz, C4" H), 7.18 (d, 1H, *J* = 9.46 Hz, C3" H), 6.98 (m, 1H, C6" H), 6.07 (t, 1H, *J* = 2.2 Hz, C10 H), 5.71 (m, 1H, C11 H), 4.12 (dd, 1H, *J* = 8.15, 5.14 Hz, C13 H), 3.84 (m, 1H, C14 H), 3.66 (s, 3H, C7" OCH_3), 3.38 (d, 1H, *J* = 1.03 Hz, C5 H), 2.98 (dd, 1H, *J* = 14.03, 7.42 Hz, C12 βH), 2.46 (dd, 1H, *J* = 14.09, 5.28 Hz, C12 αH), 2.24 (s, 3H, C5" CH_3), 2.20 (d, 1H, *J* = 1.11 Hz, C7 H), 1.47 (s, 3H, $C(CH_3)_2$), 1.21 (s, 3H, $C(CH_3)_2$).
TLC (10% EtOAc in CH_2Cl_2), R*f*:	**48**: 0.46 (fluoresces under UV, anisaldehyde) **128**: 0.37 (fluoresces under UV, anisaldehyde)



66 **129**

TES ether **129**

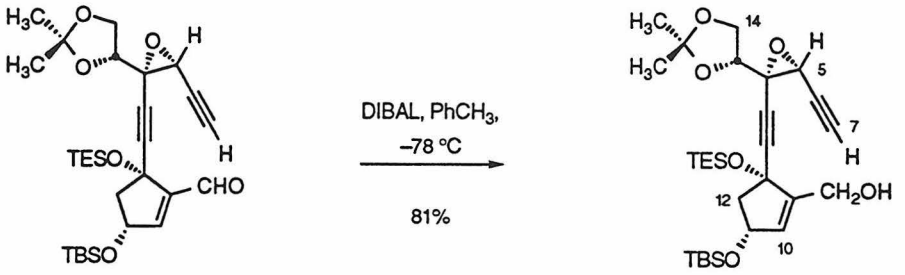
2,6-Lutidine (0.471 mL, 434 mg, 4.04 mmol, 10 equiv) and triethylsilyl trifluoromethanesulfonate (0.549 mL, 642 mg, 2.43 mmol, 6 equiv) were added sequentially to a solution of enal **66** (175 mg, 0.404 mmol, 1 equiv) in dichloromethane (15 mL) at –78 °C. The reaction mixture was maintained at –78 °C for an additional 50 min, and triethylamine (1 mL) and methanol (1 mL) were added. The mixture was warmed to 23 °C, diluted with 1:1 ethyl acetate in hexanes (30 mL), and washed with water (15 mL) and saturated aqueous sodium chloride (15 mL). The organics were dried over sodium sulfate and concentrated. The residue was purified by flash column chromatography (10% ethyl acetate in hexanes) to provide the TES ether **129** (188 mg, 85%) as a pale yellow oil.

^{1}H NMR (400 MHz, C_6D_6), δ: 9.82 (s, 1H, CHO), 6.39 (d, 1H, *J* = 1.84 Hz, C10 H), 4.75 (td, 1H, *J* = 6.60, 1.84 Hz, C11 H), 4.11 (dd, 1H, *J* = 8.80, 5.88 Hz, C13 H), 3.94 (m, 1H, C14 H), 3.63 (t, 1H, *J* = 6.20 Hz, C14 H), 3.34 (d, 1H, *J* = 1.44 Hz, C5 H), 3.18 (dd, 1H, *J* = 12.80, 6.96 Hz, C12 H), 2.38 (dd, 1H, *J* = 12.80, 6.24 Hz, C12 H), 2.11 (s, 1H, *J* = 1.84 Hz, C7 H), 1.43 (s, 3H, $C(CH_3)_2$), 1.18 (s, 3H, $C(CH_3)_2$), 1.12 (t, 9H, *J* = 7.68 Hz, $OSi(CH_2CH_3)_3$), 0.98 (m, 2H, $OSi(CH_2CH_3)_3$), 0.94 (s, 9H, $OSiC(CH_3)_3(CH_3)_2$), 0.86 (m, 2H, $OSi(CH_2CH_3)_3$), 0.53 (q, 2H, *J* = 8.08 Hz, $OSi(CH_2CH_3)_3$), 0.016 (s, 3H, $OSiC(CH_3)_3(CH_3)_2$), 0.012 (s, 3H, $OSiC(CH_3)_3(CH_3)_2$).

FTIR (thin film), cm^{-1}: 3277 (w, C≡C-H), 2955 (s), 1699 (s, C=O), 1463 (w), 1256 (m), 1079 (s), 838 (s).

TLC (25% EtOAc in Hexanes), R*f*: **66**: 0.26 (UV, anisaldehyde)

129: 0.62 (UV, anisaldehyde)



129 **130**

Allylic alcohol **130**

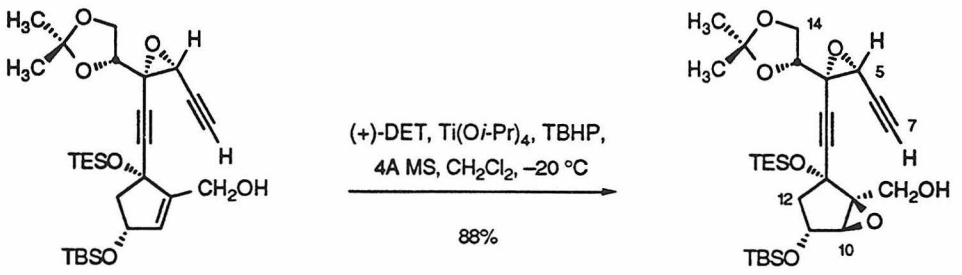
Diisobutylaluminum hydride (170 μL of a 1.5 M solution in toluene, 0.255 mmol, 1.1 equiv) was added dropwise via syringe to a solution of aldehyde **129** (127 mg, 0.232 mmol, 1 equiv) in toluene (5 mL) at –78 °C. The reaction was maintained at –78 °C for an additional 10 min, then excess reducing agent was quenched by the addition of methanol (1 mL). The reaction mixture was then warmed to 0 °C, and a 10% aqueous solution of potassium sodium tartrate (5 mL) was added. The mixture was warmed to 23 °C and stirred vigorously for 20 min. The reaction mixture was poured into water (20 mL) and extracted with ethyl acetate (3 x 15 mL). The combined organics were washed with 1N HCl (10 mL), water (10 mL), and saturated aqueous sodium chloride (10 mL), dried over sodium sulfate and concentrated. Purification of the residue by flash column chromatography (20% ethyl acetate in hexanes) provided allylic alcohol **130** (103 mg, 81%) as a colorless oil.

^{1}H NMR (400 MHz, C_6D_6), δ: 5.84 (d, 1H, *J* = 1.48 Hz, C10 H), 4.90 (m, 1H, C11 H), 4.54 (abq, 2H, *J* = 14.64, Δν = 23.04 Hz, C8 CH_2), 4.04 (dd, 1H, *J* = 8.76, 5.84 Hz, C13 H), 3.80 (dd, 1 H, *J* = 8.40, 6.60 Hz, C14 H), 3.51 (t, 1H, *J* = 5.88 Hz, C14 H), 3.22 (d, 1H, *J* = 1.84 Hz, C5 H), 3.19 (dd, 1H, *J* = 12.44, 6.96 Hz, C12 H), 2.38 (dd, 1H, *J* = 12.44, 6.24 Hz, C12 H), 2.08 (d, 1H, *J* = 1.84 Hz, C7 H), 1.47 (s, 3H, $C(CH_3)_2$), 1.18 (s, 3H, $C(CH_3)_2$), 1.09 (t, 9H, *J* = 7.68 Hz, $OSi(CH_2CH_3)_3$), 1.00 (s, 9H, $OSiC(CH_3)_3(CH_3)_2$), 0.84 (m, 6H, $OSi(CH_2CH_3)_3$), 0.10 (s, 3H, $OSiC(CH_3)_3(CH_3)_2$), 0.09 (s, 3H, $OSiC(CH_3)_3(CH_3)_2$).

FTIR (thin film), cm^{-1}: 3448 (m, OH), 3309 (m, C≡C–H), 2955 (s), 2878 (s), 1461 (m), 1075 (vs), 837 (s).

TLC (50% EtOAc in Hexanes), R*f*: **129**: 0.68 (UV, anisaldehyde)

130: 0.59 (anisaldehyde)

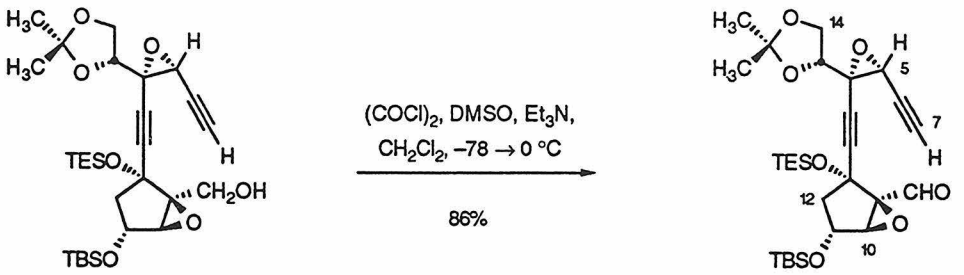


130 **131**

Bisepoxide **131**

A suspension of 4Å molecular sieves (approx. 1g, powdered, activated) in dichloromethane (7.0 mL) was cooled to –20 °C. (+)-Diethyl-L-tartrate (262 μL, 316 mg, 1.53 mmol, 6 equiv) and titanium isopropoxide (380 μL, 363 mg, 1.28 mmol, 5 equiv) were added sequentially via syringe. The mixture was allowed to stir at –20 °C for an additional 15 min, then alcohol **130** (140 mg, 0.255 mmol, 1 equiv) in dichloromethane (5 mL) was added via cannula. The resultant mixture was stirred at –20 °C for another 30 min, then *tert*-butyl hydroperoxide (271 μL of a 4.7 M solution in dichloromethane, 1.28 mmol, 5 equiv) was added through a slit in the septum at the neck of the flask via a gastight syringe equipped with a Teflon needle. The reaction was maintained at –20 °C for 20 h, and the catalyst was quenched with 10% aqueous D-tartaric acid (5 mL) and stirred vigorously for 30 min. The layers were separated and the aqueous layer was further extracted with dichloromethane (2 10-mL portions). The combined organics were dried over sodium sulfate and were concentrated. Purification of the residue by flash column chromatography (5% ethyl acetate in dichloromethane grading to 10% ethyl acetate in dichloromethane) afforded the bisepoxide **131** (127 mg, 88%) as a colorless oil.

^{1}H NMR (400 MHz, C_6D_6), δ:	4.38 (d, 2H, *J* = 5.06 Hz, C8 H), 4.30 (d, 1H, *J* = 6.10 Hz, C11 H), 4.10 (dd, 1H, *J* = 8.73, 5.75 Hz, C13 H), 3.87 (dd, 1 H, *J* = 8.73, 6.93 Hz, C14 H), 3.64 (t, 1H, *J* = 5.88 Hz, C14 H), 3.62 (s, 1H, C10 H), 3.33 (d, 1H, *J* = 1.58 Hz, C5 H), 2.50 (dd, 1H, *J* = 14.56, 6.04 Hz, C12 βH), 2.13 (d, 1H, *J* = 14.00 Hz, C12 αH), 2.10 (d, 1H, *J* = 1.60 Hz, C7 H), 1.92 (t, 1H, *J* = 5.23 Hz, OH), 1.49 (s, 3H, $C(CH_3)_2$), 1.19 (s, 3H, $C(CH_3)_2$), 1.12 (t, 9H, *J* = 7.59 Hz, $OSi(CH_2CH_3)_3$), 0.94 (s, 9H, $OSiC(CH_3)_3(CH_3)_2$), 0.91 (m, 6H, $OSi(CH_2CH_3)_3$), 0.11 (s, 6H, $OSiC(CH_3)_3(CH_3)_2$).
FTIR (thin film), cm^{-1}:	3448 (m, OH), 3271 (m, C≡C-H), 2954 (s), 1454 (m), 1373 (m), 1256 (m), 1134 (s), 1075 (m), 839 (m).
TLC (10% EtOAc in CH_2Cl_2), R*f*:	**130**: 0.54 (anisaldehyde) **131**: 0.47 (anisaldehyde)



131 **132**

Epoxy aldehyde **132**

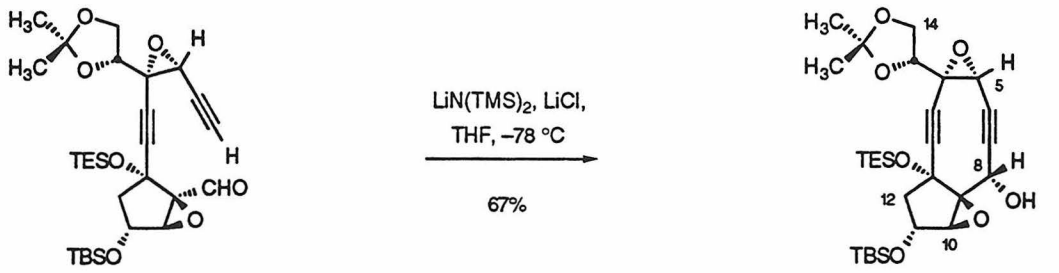
Dimethylsulfoxide (247 μL, 272 mg, 3.48 mmol, 15 equiv) was added dropwise to a solution of oxalyl chloride (203 μL, 295 mg, 2.32 mol, 10 equiv) in dichloromethane (4.5 mL) at –78 °C. The resultant solution was maintained at –78 °C for 15 min, and epoxy alcohol **131** (127 mg, 0.225 mmol, 1 equiv) in dichloromethane (4.5 mL) was added in a dropwise manner. The solution was then warmed to –40 °C and was held at this temperature for 20 min. The reaction mixture was then cooled to –78 °C, triethylamine (971 μL, 705 mg, 6.96 mmol, 30 eq) was added, and the solution was stirred at 0 °C for 40 min. The reaction mixture was diluted with pH 7.2 phosphate buffer (10 mL) and extracted with dichloromethane (2 x 10 mL). The combined organics were dried over sodium sulfate and concentrated. Purification of the residue by flash column chromatography (10% ethyl acetate in hexanes) provided epoxy aldehyde **132** (109 mg, 86%) as a pale yellow oil.

^{1}H NMR (400 MHz, C_6D_6), δ: 10.02 (s, 1H, CHO), 4.14 (d, 1H, *J* = 6.24 Hz, C11 H), 4.05 (dd, 1H, *J* = 8.44, 5.88 Hz, C13 H), 3.86 (dd, 1 H, *J* = 8.80, 6.56 Hz, C14 H), 3.68 (s, 1H, C10 H), 3.61 (t, 1H, *J* = 6.24 Hz, C14 H), 3.31 (d, 1H, *J* = 1.48 Hz, C5 H), 2.37 (dd, 1H, *J* = 14.64, 5.88 Hz, C12 βH), 2.12 (d, 1H, *J* = 14.64 Hz, C12 αH), 2.12 (d, 1H, *J* = 1.60 Hz, C7 H), 1.46 (s, 3H, $C(CH_3)_2$), 1.18 (s, 3H, $C(CH_3)_2$), 1.13 (t, 9H, *J* = 7.72 Hz, $OSi(CH_2CH_3)_3$), 0.93 (m, 6H, $OSi(CH_2CH_3)_3$), 0.89 (s, 9H, $OSiC(CH_3)_3(CH_3)_2$), –0.046 (s, 3H, $OSiC(CH_3)_3(CH_3)_2$), –0.059 (s, 3H, $OSiC(CH_3)_3(CH_3)_2$).

FTIR (thin film), cm^{-1}: 3301 (m, C≡C–H), 2954 (s), 1730 (m, C=O), 1374 (m), 1256 (m), 1137 (s), 1074 (s), 836 (m).

TLC (40% EtOAc in Hexanes), R*f*: **131**.: 0.50 (anisaldehyde)

132: 0.61 (anisaldehyde)

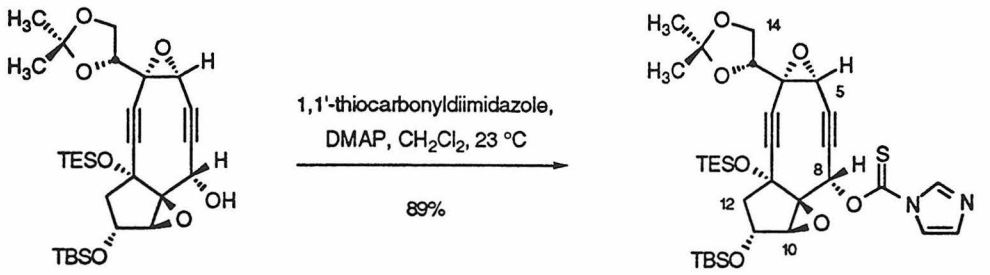


132 **133**

Cyclic alcohol **133**

Lithium hexamethyldisilazide (320 μL of a freshly prepared 1.0 M solution in hexanes, 0.32 mmol, 10 equiv) was added dropwise over a 2 minute period to a vigorously stirring suspension of epoxy aldehyde **132** (18 mg, 3.2×10^{-2} mmol, 1 equiv) and lithium chloride (68 mg, 1.6 mmol, 50 equiv) in tetrahydrofuran (1.6 mL) at –78 °C. The suspension was allowed to stir at –78 °C for an additional 10 min, then excess base was quenched by the addition of saturated aqueous ammonium chloride (2 mL). The mixture was warmed to 23 °C and partitioned between water (10 mL) and 1:1 ethyl acetate/hexanes (10 mL). The layers were separated and the aqueous layer was further extracted with 1:1 ethyl acetate/hexanes (2 10-mL portions). The combined organics were washed once with saturated aqueous sodium chloride (15 mL), dried over sodium sulfate and concentrated. Purification of the residue by flash column chromatography (2% ethyl acetate in dichloromethane grading to 10% ethyl acetate in dichloromethane) afforded cyclic alcohol **133** (12 mg, 67%) as a colorless oil.

^{1}H NMR (400 MHz, C_6D_6), δ:	5.41 (d, 1H, *J* = 9.52 Hz, C8 H), 4.22 (d, 1H, J = 5.84 Hz, C11 H), 3.90 (dd, 1H, *J* = 8.44, 5.88 Hz, C13 H), 3.74 (dd, 1 H, *J* = 8.80, 6.56 Hz, C14 H), 3.68 (s, 1H, C10 H), 3.63 (t, 1H, *J* = 5.88 Hz, C14 H), 3.17 (s, 1H, C5 H), 2.34 (dd, 1H, *J* = 14.28 5.88 Hz, C12 βH), 1.98 (d, 1H, *J* = 14.64 Hz, C12 αH), 1.82 (d, 1H, *J* = 9.52 Hz, OH), 1.48 (s, 3H, $C(CH_3)_2$), 1.23 (s, 3H, $C(CH_3)_2$), 1.11 (t, 9H, J = 8.08 Hz, $OSi(CH_2CH_3)_3$), 0.92 (m, 6H, $OSi(CH_2CH_3)_3$), 0.91 (s, 9H, $OSiC(CH_3)_3(CH_3)_2$), –0.012 (s, 3H, $OSiC(CH_3)_3(CH_3)_2$), –0.018 (s, 3H, $OSiC(CH_3)_3(CH_3)_2$).
FTIR (thin film), cm^{-1}:	3447 (m, OH), 2954 (s), 2933 (s), 1460 (m), 1257 (m), 1134 (s), 1075 (s), 836 (m).
TLC (40% EtOAc in Hexanes), R*f*:	**132**: 0.56 (anisaldehyde) **133**: 0.48 (anisaldehyde)



133 **134**

Thiocarbonylimidazolide **134**

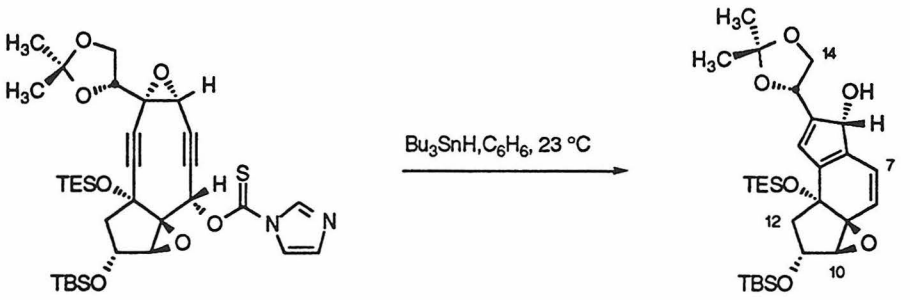
Thiocarbonyldiimidazole (84 mg of 90% pure, 0.43 mmol, 10 equiv) and 4-dimethylaminopyridine (26 mg, 0.21 mmol, 5 equiv) were added sequentially to a solution of alcohol **133** (24 mg, 4.3 x 10^{-2} mmol, 1 equiv) in dichloromethane (2.5 mL). The resultant orange solution was stirred at 23 °C for 25 min and concentrated. Purification of the residue by flash column chromatography (4% ethyl acetate in hexanes grading to 10% ethyl acetate in hexanes) afforded thiocarbonylimidazolide **134** (24 mg, 89%) as a yellow oil.

^{1}H NMR (400 MHz, C_6D_6), δ: 8.25 (s, 1H, imidazole), 7.26 (s, 1H, imidazole), 7.23 (s, 1H, C8 H), 6.86 (s, 1H, imidazole), 4.29 (d, 1H, *J* = 5.84 Hz, C11 H), 3.91 (dd, 1H, *J* = 8.80, 5.88 Hz, C13 H), 3.76 (dd, 1 H, *J* = 8.80, 6.60 Hz, C14 H), 3.69 (s, 1H, C10 H), 3.63 (t, 1H, *J* = 5.84 Hz, C14 H), 3.13 (s, 1H, C5 H), 2.39 (dd, 1H, *J* = 14.64, 5.84 Hz, C12 βH), 2.05 (d, 1H, *J* = 14.64 Hz, C12 αH), 1.52 (s, 3H, $C(CH_3)_2$), 1.26 (s, 3H, $C(CH_3)_2$), 1.23 (t, 9H, *J* = 8.04 Hz, $OSi(CH_2CH_3)_3$), 1.02 (m, 6H, $OSi(CH_2CH_3)_3$), 0.91 (s, 9H, $OSiC(CH_3)_3(CH_3)_2$), 0.001 (s, 3H, $OSiC(CH_3)_3(CH_3)_2$), –0.024 (s, 3H, $OSiC(CH_3)_3(CH_3)_2$).

FTIR (thin film), cm^{-1}: 2953 (s), 1463 (m), 1394 (m), 1286 (m), 1135 (s), 1073 (s), 835 (m), 744 (m).

HRMS (FAB): Calc'd for $C_{29}H_{49}N_2O_7SSi_2$ $[MH]^+$: 625.2799
Found: 625.2849

TLC (10% EtOAc in CH_2Cl_2), R*f*: **133**: 0.34 (anisaldehyde)
134: 0.46 (UV, anisaldehyde)



134 **135**

Rearrangement product (suggested structure **135**)

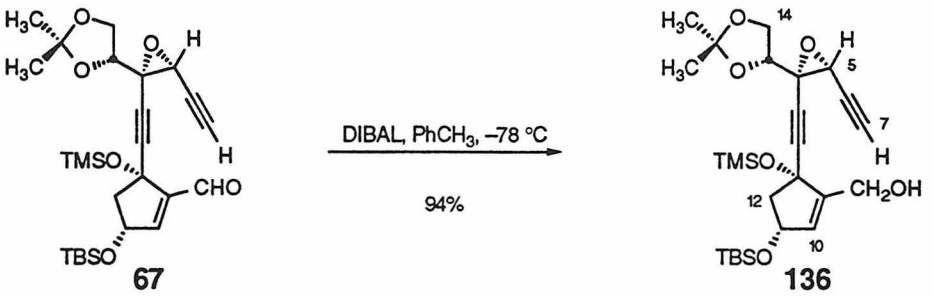
Tributyltin hydride (0.0107 mL, 11.6 mg, 4.00 x 10^{-2} mmol, 10 equiv) was added to a solution of thiocarbonylimidazolide **134** (2.5 mg, 4.0 x 10^{-3} mmol, 1 equiv) in benzene (0.4 mL) at 23 °C. The solution was deoxygenated by five freeze-pump-thaw cycles and then stirred at 23 °C under an atmosphere of argon for 20 min. The reaction mixture was concentrated to a volume of ca. 0.1 mL and applied directly to a silica gel column packed with dichloromethane. Chromatography (dichloromethane grading to 10% ethyl acetate in dichloromethane) was followed by pooling of the fractions containing the product and concentration to ca. 0.1 mL. Deuteriated benzene (99.5 atom % D, 0.4 mL) was added to the concentrate and the solution concentrated to ca. 0.1 mL. This process was repeated four times. The concentrate was taken up in deuteriated benzene (99.95 atom % D, 0.4 mL). Although not unequivocally assigned, all spectral data corresponded to a product having the structure **135**.

^{1}H NMR (400 MHz, CD_2Cl_2), δ: 6.71 (d, 1H, *J* = 5.52 Hz, C7 H), 6.54 (d, 1H, *J* = 5.88 Hz, C8 H), 5.47 (s, 1H, C3 H), 5.33 (s, 1H, C5 H), 4.78 (dd, 1H *J* = 5.84, 2.92 Hz, C11 H), 4.73 (t, 1H, *J* = 6.20 Hz, C13 H), 4.01 (dd ,1H, *J* = 1.84, 1.08 Hz, C10 H), 3.91 (dd, 1H, *J* = 8.40, 6.96 Hz, C14 H), 3.48 (dd, 1H, *J* = 8.76, 6.20 H, C14 H), 3.44 (s, 1H, OH), 2.78 (dd, 1H, *J* = 15.72, 2.92 Hz, C12 βH), 2.43 (ddd, 1H, *J* = 15.84, 2.92, 1.08 Hz, C12 αH), 1.43 (s, 3H, $C(CH_3)_2$), 1.35 (s, 3H, $C(CH_3)_2$), 1.30-0.83 (complex, 15H, $OSi(CH_2CH_3)_3$), 0.82 (s, 9H, $OSiC(CH_3)_3(CH_3)_2$), 0.10 (s, 3H, $OSiC(CH_3)_3(CH_3)_2$), 0.09 (s, 3H, $OSiC(CH_3)_3(CH_3)_2$).

FTIR (thin film), cm^{-1}: 3448 (m, OH), 2923 (s) , 1736 (m), 1637 (m), 1366 (m), 1460 (m), 1078 (m).

HRMS (FAB): Calc'd for $C_{29}H_{49}O_6Si_2$ $[MH]^+$: 549.306772
Found: 549.305561

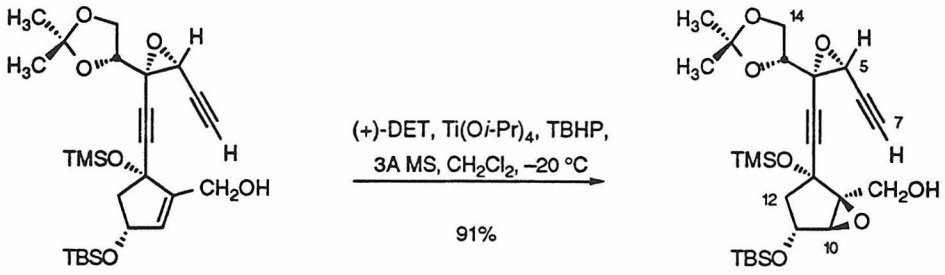
TLC (10% EtOAc in CH_2Cl_2), R*f*: **134**: 0.34 (UV, anisaldehyde)
135: 0.46 (UV, anisaldehyde)



Allylic alcohol **136**

Diisobutylaluminum hydride (0.662 mL of a 1.5 *M* solution in toluene, 0.992 mmol, 1.1 equiv) was added in a dropwise manner to a solution of the enal **67** (1.78 g, 3.53 mmol, 1 equiv) in toluene (18 mL) at –78 °C. The reaction mixture was allowed to stir at –78 °C for an additional 10 min, and excess diisobutylaluminum hydride was quenched by the addition of methanol (10 mL), and the reaction warmed to 0 °C. After 20 minutes at 0 °C, 10% aqueous potassium sodium tartrate (20 mL) was added, and the mixture was warmed to 23 °C and stirred vigorously for an additional 30 minutes. The layers were then separated, and the aqueous layer was extracted with ethyl acetate (3 20-mL portions). The combined organics were washed with saturated aqueous sodium chloride (25 mL) and were dried over sodium sulfate and concentrated. Purification of the residue by flash column chromatography (30% ethyl acetate in hexanes) provided the allylic alcohol **136** (405 mg, 94%) as a colorless oil.

^{1}H NMR (400 MHz, C_6D_6), δ:	5.85 (d, 1H, *J* = 1.44 Hz, C10 H), 4.88 (tdd, 1H, *J* = 6.60, 4.88, 1.84 Hz, C11 H), 4.53 (m, 2H, C8 H), 4.04 (dd, 1H, *J* = 8.44, 5.48 Hz, C13 H), 3.78 (dd, 1H, *J* = 8.80, 6.96 Hz, C14 H), 3.48 (dd, 1H, *J* = 6.96, 5.48 Hz, C14 H), 3.22 (d, 1H, *J* = 1.80 Hz, C5 H), 3.18 (dd, 1H, *J* = 12.44, 6.96 Hz, C12 H), 2.39 (dd, 1H, *J* = 12.48, 6.24 Hz, C12 H), 2.07 (s, 1H, *J* = 1.48 Hz, C7 H), 1.47 (s, 3H, $C(CH_3)_2$), 1.18 (s, 3H, $C(CH_3)_2$), 0.99 (s, 9H, $OSiC(CH_3)_3(CH_3)_2$), 0.33 (s, 9H, $OSi(CH_3)_3$), 0.09 (s, 3H, $OSiC(CH_3)_3(CH_3)_2$), 0.08 (s, 3H, $OSiC(CH_3)_3(CH_3)_2$).
^{13}C NMR (100 MHz, C_6D_6) δ:	148.6, 131.0, 110.7, 89.3, 78.8, 78.2, 77.4, 76.9, 75.3, 73.9, 66.7, 58.9, 57.8, 54.5, 50.4, 26.4, 26.0, 25.0, 18.2, 1.9, –4.6 (2).
$[\alpha]_D^{20}$	+113.91° (*c* 1.84, C_6H_6)
FTIR (thin film), cm^{-1}:	3448 (m, OH), 3309 (m, C≡C-H), 2954 (s), 2857 (m), 2128 (w, C≡C), 1462 (m), 1372 (m), 1253 (s), 1110 (s), 1075 (s), 839 (s).
TLC (10% EtOAc in CH_2Cl_2), R*f*:	**67**: 0.88 (UV, anisaldehyde) **136**: 0.46 (anisaldehyde)



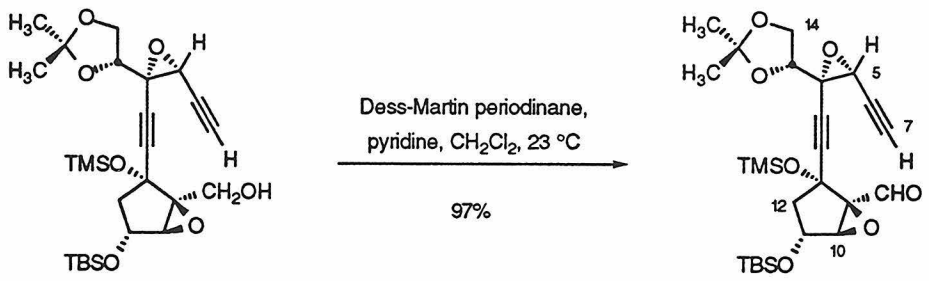
136 137

Epoxy alcohol **137**

A suspension of 3Å molecular sieves (approx. 0.5g, crushed and flame-dried under vacuum in the reaction flask) in dichloromethane (80 mL) was cooled to –20 °C. (+)-Diethyl-L-tartrate (2.84 mL, 3.42 g, 16.6 mmol, 6 equiv) and titanium(IV) isopropoxide (4.11 mL, 3.93 g, 13.8 mmol, 5 eq) were added sequentially via syringe. The mixture was allowed to stir at –20 °C for an additional 15 min, and the allylic alcohol **136** (1.40 g, 2.76 mmol, 1 eq) in dichloromethane (60 mL) was added via cannula. The resultant mixture was stirred at –20 °C for another 30 min, and *tert*-butyl hydroperoxide (5.88 of a 4.7 M solution in dichloromethane, 27.6 mmol, 10 eq) was added through a slit in the septum at the neck of the flask via a gastight syringe equipped with a Teflon needle. The reaction was maintained at –20 °C for 15 h, and the catalyst was quenched with 10% aqueous D-tartaric acid (50 mL) and stirred vigorously at 23 °C for 30 min. The reaction mixture was filtered, the layers were separated, and the aqueous layer was further extracted with dichloromethane (2 50-mL portions). The combined organics were dried over sodium sulfate and concentrated. Purification of the residue by flash column chromatography (15% ethyl acetate in hexanes grading to 20% ethyl acetate in hexanes) afforded epoxy alcohol **137** (1.31 g, 91%) as a colorless oil.

^{1}H NMR (400 MHz, C_6D_6), δ:	4.31 (m, 2H, C8 H), 4.22 (d, 1H, *J* = 5.84 Hz, C11 H), 4.06 (dd, 1H, *J* = 8.80, 5.48 Hz, C13 H), 3.80 (dd, 1H, *J* = 8.44, 6.60 Hz, C14 H), 3.55 (complex, 2H, C10 and C14 H), 3.28 (d, 1H, *J* = 1.48 Hz, C5 H), 2.38 (dd, 1H, *J* = 14.28, 5.84 Hz, C12 βH), 2.06 (d, 1H, *J* = 14.64 Hz, C12 αH), 2.01 (d, 1H, *J* = 1.80 Hz, C7 H), 1.46 (s, 3H, $C(CH_3)_2$), 1.14 (s, 3H, $C(CH_3)_2$), 0.90 (s, 9H, $OSiC(CH_3)(CH_3)_2$), 0.33 (s, 9H, $OSi(CH_3)_3$), –0.045 (s, 6H, $OSiC(CH_3)(CH_3)_2$).
^{13}C NMR (100 MHz, C_6D_6) δ:	110.8, 87.7, 79.9, 78.3, 77.1, 75.4, 74.7, 71.8, 71.4, 66.7, 63.6, 58.0, 50.5, 50.0, 26.3, 25.9, 25.1, 18.2, 1.9, –4.8.
$[\alpha]_D^{20}$:	+65.04° (*c* 1.23, C_6H_6)
FTIR (thin film), cm^{-1}:	3486 (m, OH), 3267 (m, C≡C–H), 2955 (s), 2893 (s), 2859 (s), 2131 (w, C≡C), 1373 (m), 1253 (s), 1214 (m), 1135 (s), 1075 (s), 945 (m), 843 (s).

HRMS (FAB):	Calc'd for $C_{26}H_{41}O_7Si_2$ $[M-1]^+$: 521.239086
	Found: 521.239042
TLC (10% EtOAc in CH_2Cl_2), R*f*:	**136**: 0.41 (anisaldehyde)
	137: 0.38 (anisaldehyde)



137 138

Epoxy aldehyde **138**

Dess-Martin periodinane (2.03 g, 4.78 mmol, 2 equiv) was added portionwise to a solution of epoxy alcohol **137** (1.25 g, 2.39 mmol, 1 equiv) and pyridine (1.93 mL, 1.89 g, 23.9 mmol, 10 equiv) in dichloromethane (24 mL) at 23 °C. The resultant solution was stirred at 23 °C for 40 minutes, then diluted with diethyl ether (20 mL). Saturated aqueous sodium bicarbonate (10 mL) and saturated aqueous sodium thiosulfate (10 mL) were added, and the reaction mixture was stirred vigorously until the organic layer was clear (approximately 5-10 minutes). The layers were separated and the aqueous later was extracted with diethyl ether (2 20-mL portions). The combined organics were washed with saturated aqueous sodium chloride (20 mL), dried over sodium sulfate and concentrated. Purification of the residue by flash column chromatography (15% ethyl acetate in hexanes) afforded the epoxy aldehyde **138** (1.21 g, 97%) as a pale yellow oil.

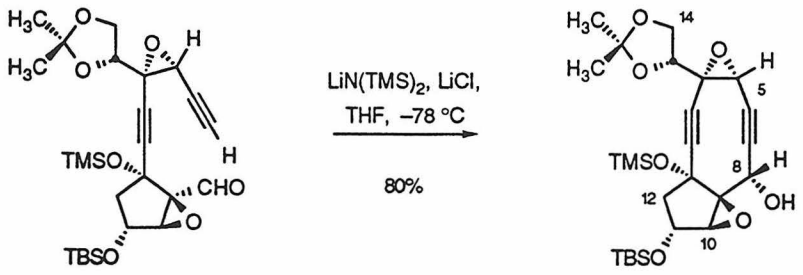
^{1}H NMR (400 MHz, C_6D_6) δ: 9.87 (s, 1H, C8 H), 4.10 (d, 1H, J = 5.84 Hz, C11 H), 4.05 (dd, 1H, J = 8.80, 5.84 Hz, C13 H), 3.85 (dd, 1H, J = 8.76, 6.56 Hz, C14 H), 3.65 (s, 1H, C10 H), 3.60 (t, 1H, J = 6.24 Hz, C14 H), 3.32 (d, 1H, J = 1.48 Hz, C5 H), 2.28 (dd, 1H, J = 14.64, 5.84 Hz, C12 βH), 2.08 (d, 1H, J = 1.80 Hz, C7 H), 2.06 (d, 1H, J = 14.64 Hz, C12 αH), 1.45 (s, 3H, $C(CH_3)_2$), 1.18 (s, 3H, $C(CH_3)_2$), 0.90 (s, 9H, $OSiC(CH_3)_3(CH_3)_2$), 0.42 (s, 9H, $OSi(CH_3)_3$), –0.056 (s, 6H, $OSiC(CH_3)_3(CH_3)_2$), –0.071 (s, 6H, $OSiC(CH_3)_3(CH_3)_2$).

^{13}C NMR (100 MHz, C_6D_6) δ: 193.1, 110.8, 86.4, 80.8, 78.0, 76.8, 75.5, 73.0, 71.0, 70.7, 66.8 (2), 57.8, 50.4, 49.9, 26.3, 25.9, 25.2, 18.1, 2.0, –4.9.

$[\alpha]_D^{20}$: +39.72° (*c* 2.16, C_6H_6)

FTIR (thin film), cm^{-1}: 3270 (m, C≡C-H), 2955 (s), 2851 (s), 2131 (w, C≡C), 1730 (s, C=O), 1374 (m), 1253 (s), 1215 (m), 1138 (s), 1074 (s), 945 (m), 845 (s).

HRMS (FAB):	Calc'd for $C_{26}H_{39}O_7Si_2$ $[M-1]^+$: 519.223436
	Found: 519.223453
TLC (10% EtOAc in CH_2Cl_2), R*f*:	**137**: 0.50 (anisaldehyde)
	138: 0.68 (anisaldehyde)



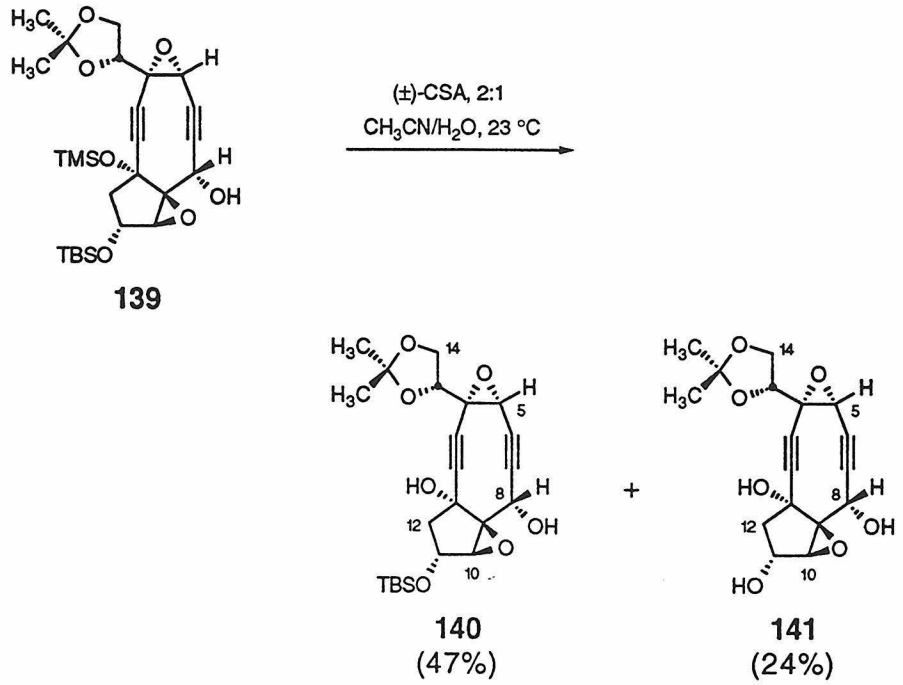
138 **139**

Cyclized bisepoxide **139** (for improved procedure, see p. 387)

Lithium hexamethyldisilazide (1.36 mL of a 1.0 M solution in hexanes, 1.36 mmol, 5 equiv) was added dropwise over a 2 minute period to a vigorously stirring suspension of the epoxy aldehyde **138** (142 mg, 0.272 mmol, 1 equiv) and dry lithium chloride (578 mg, 13.6 mmol, 50 equiv) in tetrahydrofuran (14 mL) at –78 °C. The suspension was allowed to stir at –78 °C for an additional 10 min, and excess base was quenched by the addition of saturated aqueous ammonium chloride (5 mL). The mixture was warmed to 23 °C and partitioned between water (10 mL) and 1:1 ethyl acetate/hexanes (10 mL). The layers were separated and the aqueous layer was further extracted with 1:1 ethyl acetate/hexanes (2 10-mL portions). The combined organics were washed once with saturated aqueous sodium chloride (25 mL), dried over sodium sulfate and concentrated. Purification of the residue by flash column chromatography (20% ethyl acetate in hexanes) afforded cyclized bisepoxide **139** (113 mg, 80%) as a yellow oil.

^{1}H NMR (400 MHz, C_6D_6), δ:	5.35 (d, 1H, *J* = 10.60 Hz, C8 H), 4.18 (d, 1H, *J* = 5.84 Hz, C11 H), 3.88 (dd, 1H, *J* = 8.40, 6.60 Hz, C13 H), 3.74 (dd, 1 H, *J* = 8.40, 5.84 Hz, C14 H), 3.66 (s, 1H, C10 H), 3.65 (t, 1H, *J* = 6.20 Hz, C14 H), 3.18 (s, 1H, C5 H), 2.27 (dd, 1H, *J* = 14.28, 5.84 Hz, C12 βH), 1.93 (d, 1H, *J* = 14.28 Hz, C12 αH), 1.87 (d, 1H, *J* = 11.00 Hz, OH), 1.48 (s, 3H, $C(CH_3)_2$), 1.23 (s, 3H, $C(CH_3)_2$), 0.91 (s, 9H, $OSiC(CH_3)_3(CH_3)_2$), 0.36 (s, 9H, $Si(CH_3)_3$), –0.023 (s, 3H, $OSiC(CH_3)_3(CH_3)_2$), –0.026 (s, 3H, $OSiC(CH_3)_3(CH_3)_2$).
^{13}C NMR (100 MHz, C_6D_6), δ:	110.7, 92.9, 88.3, 87.6, 86.7, 80.8, 75.1, 70.7, 66.8, 64.0, 61.8, 57.2, 52.5, 48.2, 26.3, 25.9, 25.5, 18.1, 1.8, –4.8
$[\alpha]_D^{20}$:	+13.91° (*c* 1.51, C_6H_6)
FTIR (thin film), cm^{-1}:	3448 (m, OH), 2954 (s), 2860 (m), 2214 (w, C≡C), 1373 (m), 1253 (s), 1135 (s), 1075 (s), 953 (m), 843 (s).
HRMS (FAB):	Calc'd for $C_{26}H_{39}O_7Si_2$ [M–1]+: 519.223436 Found: 519.222949.

TLC (10% EtOAc in CH_2Cl_2), R*f*:	**138**:	0.69 (anisaldehyde)
	139:	0.60 (anisaldehyde)



Diol **140** and triol **141**

(±)-Camphorsulfonic acid (83 mg, 0.36 mmol, 5 equiv) was added in one portion to a solution of alcohol **139** (37 mg, 7.1 x 10^{-2} mmol, 1 equiv) in 2:1 acetonitrile/water (7.1 mL) at 23 °C. The resultant pale yellow solution was maintained at 23 °C for 40 min, poured into water (20 mL), and extracted with 1:1 ethyl acetate/hexanes (3 25-mL portions). The combined organic layers were washed once with brine (20 mL), and were dried over sodium sulfate and concentrated. Purification of the residue by flash column chromatography (5% ethyl acetate in hexanes to elute **140**, followed by 100% ethyl acetate to elute **141**) afforded diol **140** (15 mg, 47%) as a pale yellow oil and triol **141** (5.7 mg, 24%), also as a pale yellow oil.

For 140:

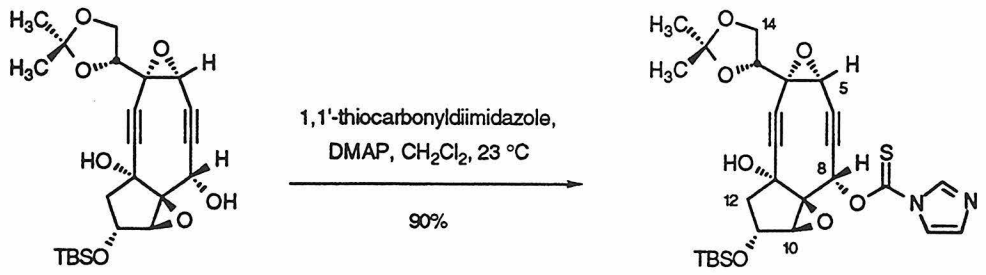
^{1}H NMR (400 MHz, C_6D_6), δ: 5.40 (br s, 1H, C8 H), 3.99 (d, 1H, *J* = 5.12 Hz, C11 H), 3.94 (dd, 1H, *J* = 8.76, 5.48 Hz, C13 H), 3.75 (dd, 1 H, *J* = 8.76, 6.96 Hz, C14 H), 3.62 (t, 1H, *J* = 6.24 Hz, C14 H), 3.57 (s, 1H, C10 H), 3.20 (s, 1H, C5 H), 2.94 (br s, 1H, OH), 2.15 (dd, 1H, *J* = 14.28, 4.76 Hz, C12 βH), 1.93 (br s, 1H, OH), 1.75 (d, 1H, *J* = 14.68 Hz, C12 αH), 1.52 (s, 3H, $C(CH_3)_2$), 1.25 (s, 3H, $C(CH_3)_2$), 0.78 (s, 9H, $OSiC(CH_3)_3(CH_3)_2$), –0.15 (s, 3H, $OSiC(CH_3)_3(CH_3)_2$), –0.16 (s, 3H, $OSiC(CH_3)_3(CH_3)_2$).

TLC (10% EtOAc in CH_2Cl_2), R*f*: **139**: 0.49 (anisaldehyde)

140: 0.31 (anisaldehyde)

For 141:

^{1}H NMR (400 MHz, C_6D_6), δ:	5.10 (d, 1H, *J* = 11.00 Hz, C8 H), 3.80 (dd, 1H, *J* = 7.96, 5.84 Hz, C13 H), 3.76 (dd, 1H, *J* = 8.44, 4.76 Hz, C11 H), 3.69 (dd, 1 H, *J* = 8.44, 6.60 Hz, C14 H), 3.57 (t, 1H, *J* = 5.84 Hz, C14 H), 3.38 (s, 1H, C10 H), 3.08 (s, 1H, C5 H), 1.96 (dd, 1H, *J* = 14.64, 5.12 Hz, C12 βH), 1.71 (d, 1H, *J* = 10.96 Hz, C8 OH), 1.55 (d, 1H, *J* = 14.64 Hz, C12 αH), 1.41 (s, 3H, $C(CH_3)_2$), 1.19 (s, 3H, $C(CH_3)_2$).
TLC (10% EtOAc in CH_2Cl_2), R*f*:	**139**: 0.49 (anisaldehyde) **141**: 0.00 (anisaldehyde)

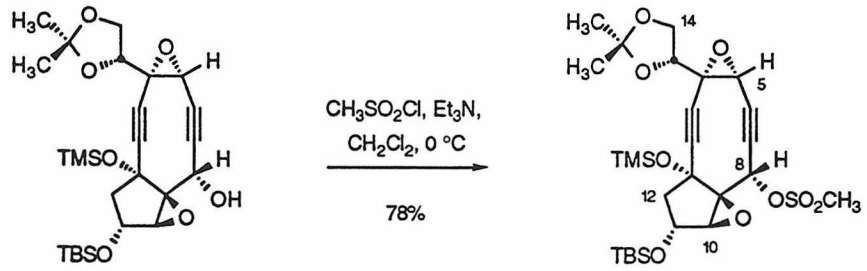


140 **142**

Thiocarbonylimidazolide **142**

Thiocarbonyldiimidazole (106 mg of 90% pure, 0.54 mmol, 10 equiv) and 4-dimethylaminopyridine (33 mg, 0.27 mmol, 5 equiv) were added sequentially to a solution of diol **140** (24 mg, 0.054 mmol, 1 equiv) in dichloromethane (2.7 mL). The resultant orange solution was placed in a 40 °C oil bath and heated to a gentle reflux for 25 min. The reaction mixture was cooled to 23 °C and concentrated. Purification of the residue by flash column chromatography (25% ethyl acetate in hexanes) afforded thiocarbonylimidazolide **142** (26 mg, 90%) as a yellow oil.

^{1}H NMR (400 MHz, C_6D_6), δ:	8.23 (s, 1H, imidazole), 7.29 (s, 1H, C8 H), 7.23 (s, 1H, imidazole), 6.84 (s, 1H, imidazole), 3.99 (d, 1H, *J* = 5.12 Hz, C11 H), 3.93 (dd, 1H, *J* = 8.76, 5.52 Hz, C13 H), 3.75 (dd, 1 H, *J* = 8.80, 6.56 Hz, C14 H), 3.60 (t, 1H, *J* = 5.52 Hz, C14 H), 3.39 (s, 1H, C10 H), 3.36 (br s, 1H, OH), 3.13 (s, 1H, C5 H), 2.15 (dd, 1H, *J* = 14.28, 4.76 Hz, C12 βH), 1.77 (d, 1H, *J* = 14.64 Hz, C12 αH), 1.53 (s, 3H, $C(CH_3)_2$), 1.25 (s, 3H, $C(CH_3)_2$), 0.78 (s, 9H, $OSiC(CH_3)_3(CH_3)_2$), –0.17 (s, 3H, $OSiC(CH_3)_3(CH_3)_2$), –0.18 (s, 3H, $OSiC(CH_3)_3(CH_3)_2$).
TLC (50% EtOAc in Hexanes), R*f*:	**140**: 0.48 (anisaldehyde) **142**: 0.40 (UV, anisaldehyde)



139 **143**

Methanesulfonate ester **143**

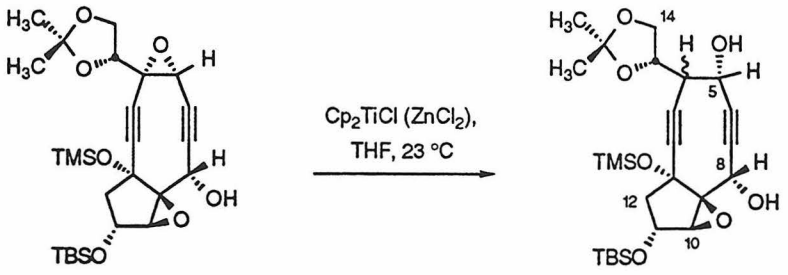
Methanesulfonyl chloride (9.0 μL, 13 mg, 0.12 mmol, 10 equiv) was added to a solution of alcohol **139** (6.0 mg, 1.2 x 10^{-2} mmol, 1 equiv) and triethylamine (40 μL, 29 mg, 0.29 mmol, 25 equiv) in dichloromethane (0.6 mL) at 0 °C. The resultant pale yellow solution was stirred at 0 °C for an additional 5 min, and diluted with hexanes (10 mL) and washed with water (3 5-mL portions) and brine (5 mL). The organics were dried over sodium sulfate and concentrated. Purification of the residue by flash column chromatography (4% ethyl acetate in dichloromethane) afforded methanesulfonate ester **143** (5.4 mg, 78%) as a colorless oil.

^{1}H NMR (400 MHz, C_6D_6), δ: 6.47 (s, 1H, C8 H), 4.09 (d, 1H, *J* = 5.52 Hz, C11 H), 3.93 (s, 1H, C10 H), 3.81 (dd, 1H, *J* = 8.80, 5.52 Hz, C13 H), 3.68 (dd, 1 H, *J* = 8.80, 6.60 Hz, C14 H), 3.59 (t, 1H, *J* = 5.84 Hz, C14 H), 3.07 (s, 1H, C5 H), 2.28 (s, 3H, OSO_2CH_3), 2.19 (dd, 1H, *J* = 14.64, 5.88 Hz, C12 βH), 1.89 (d, 1H, *J* = 14.64 Hz, C12 αH), 1.43 (s, 3H, $C(CH_3)_2$), 1.19 (s, 3H, $C(CH_3)_2$), 0.88 (s, 9H, $OSiC(CH_3)_3(CH_3)_2$), 0.30 (s, 9H, $OSi(CH_3)_3$), –0.052 (s, 3H, $OSiC(CH_3)_3(CH_3)_2$), –0.093 (s, 3H, $OSiC(CH_3)_3(CH_3)_2$).

FTIR (thin film), cm^{-1}: 2954 (s), 2930 (s), 2884 (m), 1460 (m), 1413 (m), 1371 (s), 1258 (s), 1180 (s), 1135 (s), 1074 (s), 1108 (m), 963 (m), 835 (m).

TLC (10% EtOAc in CH_2Cl_2), R*f*: **139**: 0.41 (anisaldehyde)

143: 0.66 (anisaldehyde)



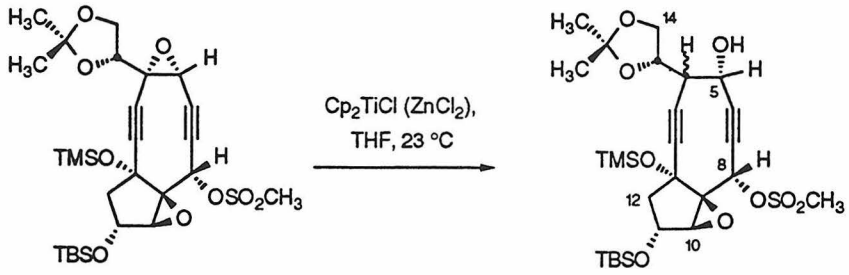
139 **144**

Diol **144**

Alcohol **139** (2.0 mg, 3.8 x 10^{-3} mmol, 1 equiv) in tetrahydrofuran (0.1 mL) was added dropwise via cannula to a green solution of dicyclopentadienyl titanium (III) chloride (29 μL of a 0.4 M stock solution in tetrahydrofuran prepared by the in situ method of RajanBabu and Nugent,[96] 0.012 mmol, 3 equiv) in tetrahydrofuran (0.1 mL) at 23 °C. The reaction mixture turned orange upon addition of the alcohol. The solution was maintained at 23 °C for an additional 2 min, and pH 7.2 phosphate buffer (1 mL) was added. The mixture was extracted with ethyl acetate (3 1-mL portions), and the combined organics were washed with saturated aqueous sodium bicarbonate (2 mL) and saturated aqueous sodium chloride (2 mL). The organics were dried over sodium sulfate and were concentrated to ca. 0.1 mL. Purification of the concentrate by flash column chromatography (dichloromethane grading to 20% ethyl acetate in dichloromethane) was followed by pooling the fractions containing the product and concentrating to a volume of ca. 0.1 mL. A 0.5 mL portion of deuteriated benzene (99.5 atom % D) was added and the resulting solution was concentrated to a volume of ca. 0.1 mL. This procedure was repeated 4 times. After the last iteration, the concentrated solution was taken up in

approximately 0.4 mL deuteriated benzene (99.95 atom % D). Analysis of the sample by ^{1}H NMR showed it to contain diol **144**.

^{1}H NMR (400 MHz, C_6D_6), δ:	5.42 (d, 1H, *J* = 9.60 Hz, C8 H), 4.39 (t, 1H, *J* = 6.24 Hz, C5 H), 4.21 (m, 2H, C11, C13 H), 4.02 (dd, 1H, *J* = 8.44, 6.24 Hz, C14 H), 3.85 (dd, 1H, *J* = 8.40, 6.20 Hz, C14 H), 3.68 (s, 1H, C10 H), 2.99 (dd, 1H, *J* = 8.08, 6.24 Hz, C4 H), 2.31 (dd, 1H, *J* = 12.08, 5.48 Hz, C12 βH), 1.91 (d, 1H, *J* = 12.08 Hz, C12 αH), 1.84 (d, 1H, *J* = 9.60 Hz, C8 OH), 1.77 (m, 1H, C5 OH), 1.33 (s, 3H, $C(CH_3)_2$), 1.20 (s, 3H, $C(CH_3)_2$), 0.89 (s, 9H, $OSiC(CH_3)_3(CH_3)_2$), 0.31 (s, 9H, $OSi(CH_3)_3$), -0.06 (s, 6H, $OSiC(CH_3)_3(CH_3)_2$).
FTIR (thin film), cm^{-1}:	3421 (m, OH), 2928 (s), 2860 (m), 1460 (w), 1372 (m), 1252 (s), 1130 (s), 1076 (m), 843 (s).
TLC (50% EtOAc in Hexanes), R*f*:	**139**: 0.52 (anisaldehyde) **144**: 0.34 (anisaldehyde)



143 **145**

Alcohol **145**

Methanesulfonate ester **143** (2.0 mg, 3.3 x 10^{-3} mmol, 1 equiv) in tetrahydrofuran (0.1 mL) was added dropwise via cannula to a green solution of dicyclopentadienyl titanium (III) chloride (25 μL of a 0.4 M stock solution in tetrahydrofuran prepared by the in situ method of RajanBabu and Nugent,[96] 0.010 mmol, 3 equiv) in tetrahydrofuran (0.1 mL) at 23 °C. The reaction mixture turned orange upon addition of the alcohol. The solution was maintained at 23 °C for an additional 10 min and pH 7.2 phosphate buffer (1 mL) was added. The mixture was extracted with ethyl acetate (3 1-mL portions), and the combined organics were washed with saturated aqueous sodium bicarbonate (2 mL) and saturated aqueous sodium chloride (2 mL). The organics were dried over sodium sulfate and were concentrated to ca. 0.1 mL. Purification of the concentrate by flash column chromatography (4% ethyl acetate in dichloromethane grading to 20% ethyl acetate in dichloromethane) was followed by pooling the fractions containing the product and concentrating to a volume of ca. 0.1 mL. A 0.5 mL portion of deuteriated benzene (99.5 atom % D) was added and the resulting solution was concentrated to a volume of ca. 0.1 mL. This procedure was repeated 4 times. After the last iteration, the concentrated

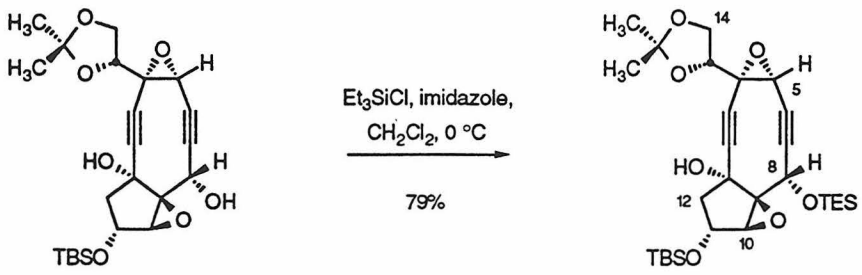
solution was taken up in approximately 0.4 mL deuteriated benzene (99.95 atom % D). Analysis of the sample by ^{1}H NMR showed it to contain alcohol **145**.

^{1}H NMR (400 MHz, C_6D_6), δ: 6.60 (s, 1H, C8 H), 4.40 (t, 1H, J = 4.40 Hz, C5 H), 4.18 (m, 2H, C11, C13 H), 3.98 (s, 1H, C10 H), 3.96 (dd, 1H, J = 8.76, 6.20 Hz, C14 H), 3.78 (dd, 1H, J = 8.44, 5.88 Hz, C14 H), 2.87 (dd, 1H, J = 8.40, 5.48 Hz, C4 H), 2.32 (s, 3H, OSO_2CH_3), 2.29 (dd, 1H, J = 14.64, 5.88 Hz, C12 βH), 1.98 (d, 1H, J = 5.12 Hz, OH), 1.93 (d, 1H, J = 14.28 Hz, C12 αH), 1.28 (s, 3H, $C(CH_3)_2$), 1.18 (s, 3H, $C(CH_3)_2$), 0.90 (s, 9H, $OSiC(CH_3)_3(CH_3)_2$), 0.30 (s, 9H, $OSi(CH_3)_3$), -0.022 (s, 3H, $OSiC(CH_3)_3(CH_3)_2$), -0.071 (s, 3H, $OSiC(CH_3)_3(CH_3)_2$).

FTIR (thin film), cm^{-1}: 3424 (m, OH), 2928 (s), 2856 (m), 1460 (w), 1367 (s), 1253 (s), 1179 (s), 1132 (s), 962 (m), 843 (s).

TLC (50% EtOAc in Hexanes), R*f*: **143**: 0.59 (anisaldehyde)

145: 0.41 (anisaldehyde)



140 **146**

TES ether **146**

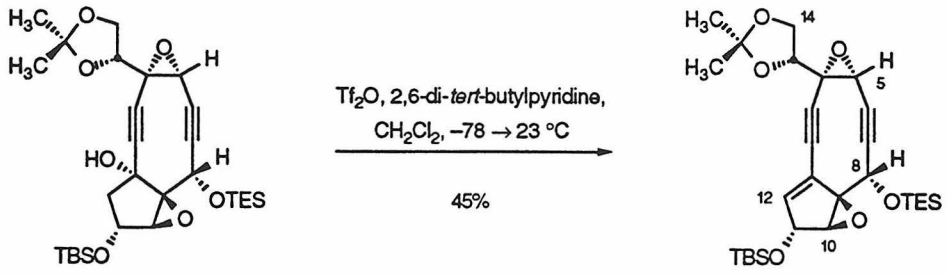
Triethylsilyl chloride (22.6 μL, 19.8 mg, 0.131 mmol, 3.9 equiv) was added via syringe to a solution of diol **140** (15 mg, 3.3 x 10^{-2} mmol, 1 equiv) and imidazole (11 mg, 0.17 mmol, 5 equiv) in dichloromethane (1.7 mL) at 0 °C. The resultant solution was maintained at 0 °C for an additional 10 min, diluted with hexanes (5 mL), and washed with water (3 5-mL portions) and saturated aqueous sodium chloride (5 mL). The organics were dried over sodium sulfate and concentrated. Purification of the residue by flash column chromatography (5% ethyl acetate in hexanes grading to 15% ethyl acetate in hexanes) provided the triethylsilyl ether **146** (15 mg, 79%) as a colorless oil.

^{1}H NMR (400 MHz, C_6D_6), δ: 5.82 (s, 1H, C8 H), 4.02 (d, 1H, *J* = 4.40 Hz, C11 H), 3.91 (dd, 1H, *J* = 8.40, 5.48 Hz, C13 H), 3.78 (s, 1H, C10 H), 3.74 (dd, 1 H, *J* = 8.80, 6.60 Hz, C14 H), 3.64 (t, 1H, *J* = 5.88 Hz, C14 H), 3.13 (s, 1H, C5 H), 3.00 (s, 1H, OH), 2.24 (dd, 1H, *J* = 14.28, 4.40 Hz, C12 βH), 1.77 (d, 1H, *J* = 14.28 Hz, C12 αH), 1.52 (s, 3H, $C(CH_3)_2$), 1.26 (s, 3H, $C(CH_3)_2$), 1.06 (t, 9H, *J* = 7.68 Hz, $OSi(CH_2CH_3)_3$), 0.81 (s, 9H, $OSiC(CH_3)_3(CH_3)_2$), 0.69 (m, 6H, $OSi(CH_2CH_3)_3$), –0.012 (s, 3H, $OSiC(CH_3)_3(CH_3)_2$), –0.14 (s, 3H, $OSiC(CH_3)_3(CH_3)_2$).

FTIR (thin film), cm^{-1}: 3490 (m, OH), 2954 (s), 1462 (m), 1373 (m), 1256 (m), 1104 (s), 1070 (s), 1004 (m), 908 (m), 837 (m).

TLC (20% EtOAc in Hexanes), R*f*: **140**: 0.06 (anisaldehyde)

146: 0.38 (anisaldehyde)



146 **147**

Olefin **147**

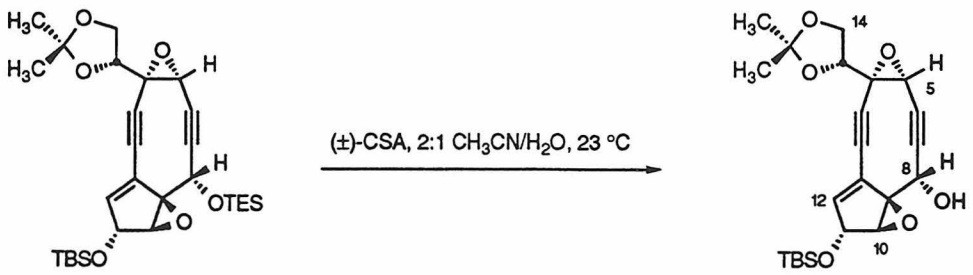
Trifluoromethanesulfonic anhydride (150 μL, 251 mg, 0.888 mmol, 100 equiv) was added dropwise via syringe to a solution of the alcohol **146** (5.0 mg, 8.9 x 10^{-3} mmol, 1 equiv) and 2,6-di-*tert*-butylpyridine (400 μL, 340 mg, 1.78 mmol, 200 equiv) in dichloromethane (440 μL) at –78 °C. The resultant colorless solution with a white precipitate was immediately warmed to 23 °C and maintained at this temperature for 2 hours. During the course of the reaction, the precipitate went into solution and the color of the reaction changed from colorless to pale yellow, light brown, and finally to brown. The reaction mixture was diluted with hexanes (3 mL) and washed with water (3 1-mL portions) and saturated aqueous sodium chloride (1 mL). The organics were dried over sodium sulfate and concentrated to ca. 0.1 mL. Purification of the concentrate (100% hexanes initially to flush through residual 2,6-di-*tert*-butylpyridine, then 10% ethyl acetate in hexanes) was followed by pooling fractions containing the product and concentrating to a volume of ca. 0.1 mL. A 0.5 mL portion of deuteriated benzene (99.5 atom % D) was added and the resulting solution was concentrated to a volume of ca. 0.1 mL. This procedure was repeated 4 times. After the last iteration, the concentrated solution was taken up in approximately 0.4 mL deuteriated benzene (99.95 atom % D). *trans*-

Dichloroethylene (10 μL of a 0.130 M solution in deuteriated chloroform (10 μL dichloroethylene diluted to 1.0 mL)) was added as an internal standard. Analysis of the sample by ^{1}H NMR showed it to contain 4.00 x 10^{-3} mmol (45%) of bisepoxy enediyne **147** as determined by integration of the internal standard against the C-12 proton.

^{1}H NMR (400 MHz, C_6D_6), δ: 5.88 (t, 1H, *J* = 2.56 Hz, C12 H), 5.14 (s, 1H, C8 H), 4.49 (d, 1H, *J* = 2.20 Hz, C11 H), 3.90 (m, 2H, C10 and C13 H), 3.78 (dd, 1H, *J* = 8.80, 6.60 Hz, C14 H), 3.69 (t, 1H, *J* = 5.84 Hz, C14 H), 3.15 (s, 1H, C5 H), 1.49 (s, 3H, $C(CH_3)_2$), 1.25 (s, 3H, $C(CH_3)_2$), 1.04 (t, 9H, *J* = 8.04 Hz, $OSi(CH_2CH_3)_3$), 0.92 (s, 9H, $OSiC(CH_3)_3(CH_3)_2$), 0.69 (m, 6H, $OSi(CH_2CH_3)_3$), –0.027 (s, 3H, $OSiC(CH_3)_3(CH_3)_2$), –0.050 (s, 3H, $OSiC(CH_3)_3(CH_3)_2$).

TLC (20% EtOAc in Hexanes), R*f*: **146**: 0.21 (anisaldehyde)

147: 0.33 (UV, anisaldehyde)



147 148

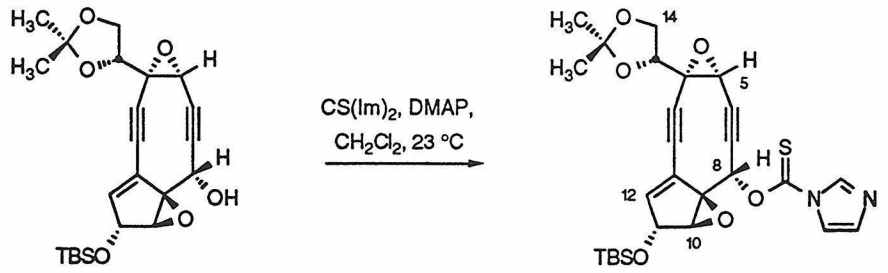
Secondary alcohol **148**

(±)-Camphorsulfonic acid (4.0 mg, 1.8 x 10^{-2} mmol, 5 equiv) was added in one portion to a solution of bisepoxy enediyne **147** (2.0 mg, 3.7 x 10^{-3} mmol, 1 equiv) in 2:1 acetonitrile/water (0.37 mL) at 23 °C. The resultant pale yellow solution was maintained at 23 °C for 15 min and extracted with 1:1 ethyl acetate/hexanes (3 2-mL portions). The combined organic layers were washed once with brine (2 mL), dried over sodium sulfate and concentrated to a volume of ca. 0.1 mL. Purification of the residue by flash column chromatography (10% ethyl acetate in hexanes grading to 20% ethyl acetate in hexanes) was followed by pooling fractions containing the product and concentrating to a volume of ca. 0.1 mL. A 0.5 mL portion of deuteriated benzene (99.5 atom % D) was added and the resulting solution was concentrated to a volume of ca. 0.1 mL. This procedure was repeated 4 times. After the last iteration, the concentrated solution was taken up in approximately 0.4 mL deuteriated benzene (99.95 atom % D). *trans*-Dichloroethylene (10 μL of a 0.130 M solution in deuteriated chloroform (10 μL dichloroethylene diluted to 1.0 mL)) was added as an internal standard. Analysis of the sample by ^{1}H NMR showed it to contain 3.2 x 10^{-3} mmol (87%) of secondary alcohol **148** as determined by integration of the internal standard against the C-12 proton.

^{1}H NMR (400 MHz, C_6D_6), δ: 5.82 (t, 1H, J = 2.56 Hz, C12 H), 5.14 (d, 1H, *J* = 10.60 Hz, C8 H), 4.42 (d, 1H, *J* = 2.20 Hz, C11 H), 3.95 (dd, 1H, *J* = 8.80, 5.48 Hz, C13 H), 3.79 (dd, 1H, *J* = 8.80, 6.60 Hz, C14 H), 3.66 (m, 2H, C10, C14 H), 3.15 (s, 1H, C5 H), 2.02 (d, 1H, *J* = 11.00 Hz, C8 OH), 1.51 (s, 3H, $C(CH_3)_2$), 1.24 (s, 3H, $C(CH_3)_2$), 0.89 (s, 9H, $OSiC(CH_3)_3(CH_3)_2$), –0.067 (s, 3H, $OSiC(CH_3)_3(CH_3)_2$), –0.087 (s, 3H, $OSiC(CH_3)_3(CH_3)_2$).

TLC (20% EtOAc in Hexanes), R*f*: **147**: 0.38 (UV, anisaldehyde)

148: 0.15 (UV, anisaldehyde)

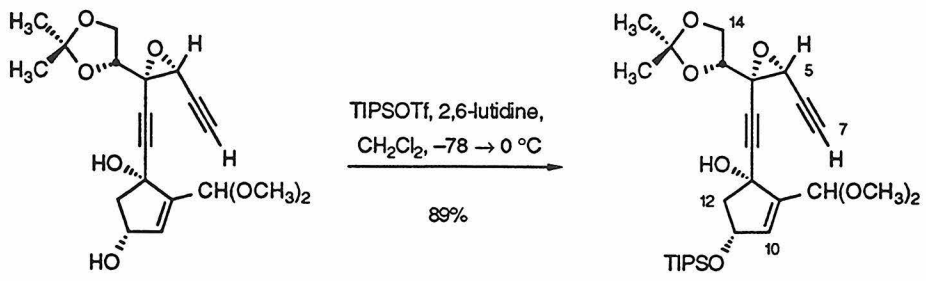


148 **149**

Thiocarbonylimidazolide **149**

Thiocarbonyldiimidazole (3.2 mg of 90% pure, 1.63 x 10^{-2} mmol, 10 equiv) and 4-dimethylaminopyridine (1.0 mg, 8.1 x 10^{-3} mmol, 5 equiv) were added sequentially to a solution of secondary alcohol **148** (0.70 mg, 1.6 x 10^{-3} mmol, 1 equiv) in dichloromethane (0.1 mL). The resultant orange solution was stirred at 23 °C for 5 min, and loaded directly onto a column packed with silica gel and 25% ethyl acetate in hexanes. Elution of the product with the same solvent system was followed by pooling fractions containing the product and concentrating to a volume of ca. 0.1 mL. A 0.5 mL portion of deuteriated benzene (99.5 atom % D) was added and the resultant solution concentrated to a volume of ca. 0.1 mL. This procedure was repeated 4 times. After the last iteration, the concentrated solution was taken up in approximately 0.4 mL deuteriated benzene (99.95 atom % D). Analysis of the sample by ^{1}H NMR showed it to contain thiocarbonylimidazolide **149**.

^{1}H NMR (400 MHz, C_6D_6), δ:	8.23 (s, 1H, imidazole), 7.26 (s, 1H, imidazole), 6.82 (s, 1H, imidazole), 6.38 (s, 1H, C8 H), 5.85 (t, 1H, *J* = 2.20 Hz, C12 H), 4.42 (d, 1H, *J* = 2.56 Hz, C11 H), 3.95 (dd, 1H, *J* = 8.80, 5.48 Hz, C13 H), 3.79 (dd, 1H, *J* = 8.76, 6.56 Hz, C14 H), 3.66 (d, 1H, *J* = 2.56 Hz, C10 H), 3.62 (t, 1H, *J* = 5.52 Hz, C14 H), 3.09 (s, 1H, C5 H), 1.53 (s, 3H, $C(CH_3)_2$), 1.24 (s, 3H, $C(CH_3)_2$), 0.88 (s, 9H, $OSiC(CH_3)_3(CH_3)_2$), –0.063 (s, 3H, $OSiC(CH_3)_3(CH_3)_2$), –0.079 (s, 3H, $OSiC(CH_3)_3(CH_3)_2$).
TLC (50% EtOAc in Hexanes), R*f*:	**148**: 0.48 (UV, anisaldehyde) **149**: 0.36 (UV, anisaldehyde)



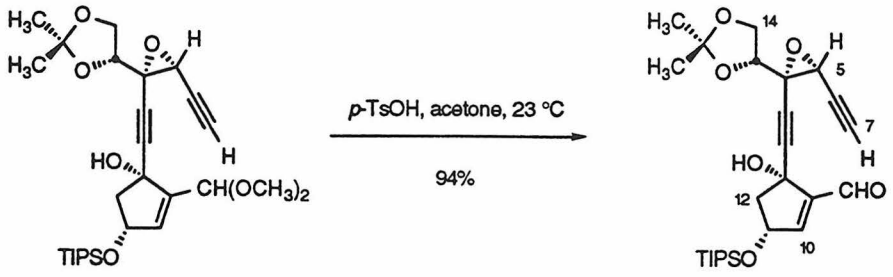
47 150

TIPS ether **150**

2,6-Lutidine (4.09 mL, 3.76 g, 35.1 mmol, 10 equiv) and triisopropylsilyl trifluoromethanesulfonate (4.72 mL, 5.38 g, 17.6 mmol, 5 equiv) were added sequentially via syringe to a solution of diol **47** (1.28 g, 3.51 mmol, 1 equiv) in dichloromethane (87 mL) at –78 °C. The resultant pale yellow solution was maintained at this temperature for an additional 20 min before warming to 0 °C for 5 min. Excess silyl triflate was quenched by the addition of triethylamine and methanol (10 mL each), and the reaction mixture was poured into 1:1 ethyl acetate/hexanes (75 mL). The resultant solution was washed twice with water (50 mL) and once with saturated aqueous sodium chloride (50 mL). The organics were dried over sodium sulfate and concentrated. Purification of the residue by flash column chromatography (10% ethyl acetate in hexanes grading to 30% ethyl acetate in hexanes) afforded triisopropylsilyl ether **150** (1.63 g, 89%) as a pale yellow oil.

^{1}H NMR (400 MHz, C_6D_6), δ:	6.25 (m, 1H, C10 H), 5.44 (m, 1H, C8 H), 4.92 (m, 1H, C11 H), 4.09 (dd, 1H, *J* = 8.76, 5.84 Hz, C13 H), 3.97 (s, 1H, OH), 3.84 (m, 1H, C14 H), 3.60 (t, 1H, *J* = 5.88 Hz, C14 H), 3.37 (d, 1H, *J* = 1.48 Hz, C5 H), 3.20 (dd, 1H, *J* = 12.80, 7.32 Hz, C12 βH), 3.19 (s, 3H, $CH(OCH_3)_2$), 3.16 (s, 3H, $CH(OCH_3)_2$), 2.56 (dd, 1H, *J* = 13.20, 5.12 Hz, C12 αH), 2.03 (d, 1H, *J* = 1.48 Hz, C7 H), 1.46 (s, 3H, $C(CH_3)_2$), 1.20 (s, 3H, $C(CH_3)_2$), 1.10-0.90 (complex, 21H, $OSi(CH(CH_3)_2)_3$).
^{13}C NMR (100 MHz, C_6D_6) δ:	142.8, 136.1, 110.7, 99.8, 90.1, 78.5, 77.2, 75.2, 74.8, 73.4, 66.9, 58.0, 52.7, 52.5, 52.2, 50.1, 26.3, 25.3, 18.1, 12.3.
$[\alpha]_D^{20}$:	+140.00° (*c* 0.55, C_6H_6)
FTIR (thin film), cm^{-1}:	3487 (m, OH), 3309 (m, C≡C-H), 2943 (s), 2866 (s), 2237 (w, C≡C), 2131 (w, C≡C), 1462 (m), 1372 (m), 1191 (m), 1069 (s), 884 (m).
HRMS (FAB):	Calc'd for $C_{28}H_{43}O_7Si$ $[M-H]^+$: 519.279800 Found: 519.277808

TLC (40% EtOAc in Hexanes), R*f*:	**47**: 0.05 (anisaldehyde)
	150: 0.44 (anisaldehyde)



Enal **151**

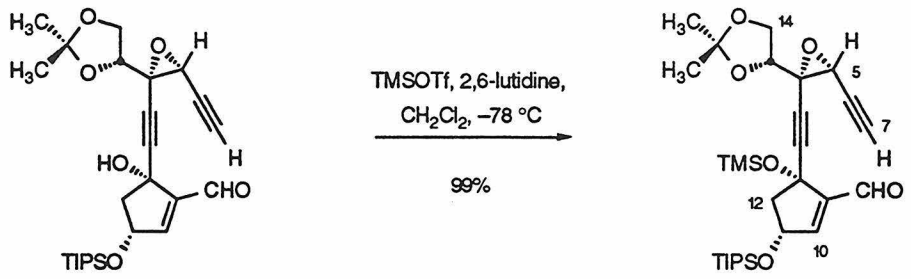
p-Toluenesulfonic acid (65 mg) was added in one portion to a solution of triisopropylsilyl ether **150** (191 mg, 0.366 mmol, 1 equiv) in acetone (9 mL) at 23 °C. The resultant pale yellow solution was maintained at 23 °C for 10 min and poured into water (20 mL). The reaction mixture was extracted with 1:1 ethyl acetate/hexanes (3 20-mL portions), and the combined organics were washed once with saturated aqueous sodium chloride (25 mL), dried over sodium sulfate and concentrated. Purification of the residue by flash column chromatography (20% ethyl acetate in hexanes) afforded enal **151** (164 mg, 94%) as a colorless oil.

^{1}H NMR (400 MHz, C_6D_6), δ:	9.29 (s, 1H, C8 H), 6.20 (d, 1H, *J* = 1.44 Hz, C10 H), 4.91 (td, 1H, *J* = 6.96, 1.44 Hz, C11 H), 4.09 (dd, 1H, *J* = 8.76, 5.84 Hz, C13 H), 3.87 (s, 1H, OH), 3.84 (dd, 1H, *J* = 8.76, 6.96 Hz, C14 H), 3.57 (t, 1H, *J* = 6.20 Hz, C14 H), 3.36 (d, 1H, *J* = 1.80 Hz, C5 H), 3.11 (dd, 1H, *J* = 12.84, 6.96 Hz, C12 H), 2.41 (dd, 1H, *J* = 12.84, 6.96 Hz, C12 H), 2.09 (d, 1H, *J* = 1.84 Hz, C7 H), 1.44 (s, 3H, $C(CH_3)_2$), 1.19 (s, 3H, $C(CH_3)_2$), 1.12-0.91 (complex, 21 H, $OSi(CH(CH_3)_2)_3$).
^{13}C NMR (100 MHz, C_6D_6) δ:	189.2, 151.8, 145.6, 110.7, 88.5, 78.4, 78.3, 77.1, 74.8, 73.6, 73.4, 66.9, 57.9, 52.3, 50.1, 26.3, 25.3, 18.0, 12.2.
$[\alpha]_D^{20}$:	+164.87° (*c* 0.78, C_6H_6)
FTIR (thin film), cm^{-1}:	3448 (m, OH), 3278 (m, C≡C-H), 2943 (s), 2866 (s), 2131 (w, C≡C), 1686 (s, C=O), 1461 (m), 1352 (m), 1259 (m), 1121 (m), 1071 (s), 882 (m).
HRMS (FAB):	Calc'd for $C_{26}H_{37}O_6Si$ $[M-H]^+$: 473.2346000 Found: 473.255943

TLC (40% EtOAc in Hexanes), R*f*:

150: 0.40 (anisaldehyde)

151: 0.45 (UV, anisaldehyde)



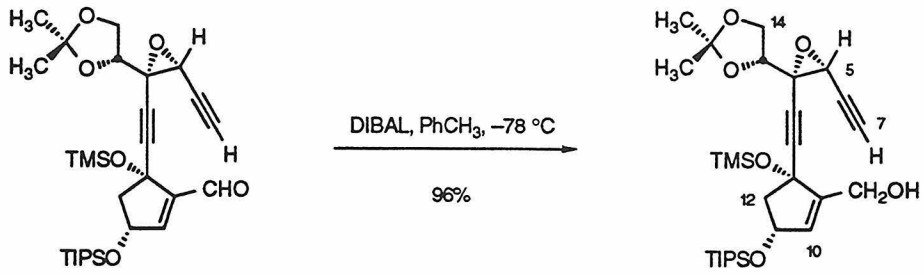
151 **152**

TMS ether **152**

2,6-Lutidine (2.99 mL, 2.75 g, 25.7 mmol, 10 equiv) and trimethylsilyl trifluoromethanesulfonate (2.48 mL, 2.86 g, 12.9 mmol, 5 equiv) were added sequentially via syringe to a solution of enal **151** (1.22 g, 2.57 mmol, 1 equiv) in dichloromethane (51 mL) at –78 °C. The resultant pale yellow solution was maintained at this temperature for an additional 15 min before the excess silyl triflate was quenched by the addition of triethylamine and methanol (10 mL each). The reaction mixture was poured into 1:1 ethyl acetate/hexanes (50 mL) and was washed with water (2 50-mL portions) and saturated aqueous sodium chloride (50 mL). The organics were dried over sodium sulfate and concentrated. Purification of the residue by flash column chromatography (5% ethyl acetate in hexanes grading to 10% ethyl acetate in hexanes) afforded TMS ether **152** (1.40 g, 99%) as a pale yellow oil.

^{1}H NMR (400 MHz, C_6D_6), δ:	9.80 (s, 1H, C8 H), 6.53 (d, 1H, *J* = 1.87 Hz, C10 H), 4.89 (td, 1H, *J* = 6.56, 1.85 Hz, C11 H), 4.10 (dd, 1H, *J* = 8.69, 5.92 Hz, C13 H), 3.91 (m, 1H, C14 H), 3.60 (t, 1H, *J* = 6.16 Hz, C14 H), 3.32 (d, 1H, *J* = 1.62 Hz, C5 H), 3.26 (dd, 1H, *J* = 12.78, 6.96 Hz, C12 H), 2.47 (dd, 1H, *J* = 12.76, 6.24 Hz, C12 H), 2.08 (d, 1H, *J* = 1.58 Hz, C7 H), 1.44 (s, 3H, $C(CH_3)_2$), 1.18 (s, 3H, $C(CH_3)_2$), 1.10-0.92 (complex, 21H, $OSi(CH(CH_3)_2)_3$), 0.41 (s, 9H, $OSi(CH_3)_3$).
^{13}C NMR (100 MHz, C_6D_6) δ:	187.5, 146.8, 146.6, 110.7, 88.5, 79.9, 78.2, 76.9, 75.2, 74.2, 73.5, 66.9, 57.9, 55.6, 50.0, 26.4, 25.1, 18.1, 12.3, 2.0.
$[\alpha]_D^{20}$:	+110.95° (*c* 0.95, C_6H_6)
FTIR (thin film), cm^{-1}:	3309, (m, C≡C-H), 2945 (s), 2867 (s), 2129 (w, C≡C), 1699 (s, C=O), 1463 (m), 1350 (m), 1253 (m), 1190 (m), 1073 (s), 882 (s), 846 (s), 684 (m).
HRMS (FAB):	Calc'd for $C_{29}H_{46}O_6Si_2$ $[M]^+$: 546.283296 Found: 546.285721

TLC (20% EtOAc in Hexanes), R*f*:	**151**:	0.15 (UV, anisaldehyde)
	152:	0.36 (UV, anisaldehyde)



152 **153**

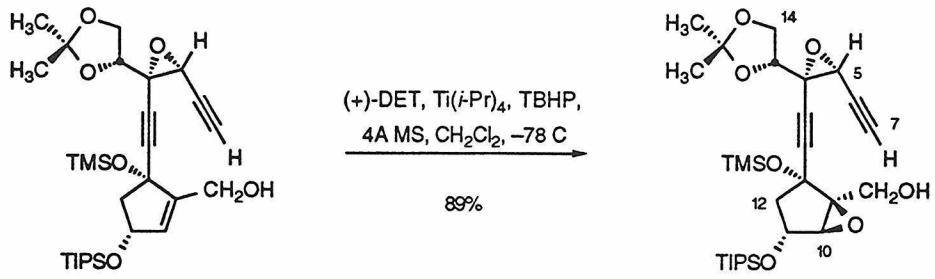
Allylic alcohol **153**

Diisobutylaluminum hydride (390 μL of a 1.5 M solution in toluene, 0.585 mmol, 2 equiv) was added dropwise via syringe to a solution of aldehyde **152** (160 mg, 0.293 mmol, 1 equiv) in toluene (6 mL) at –78 °C. The reaction was maintained at –78 °C for an additional 10 min, and excess reducing agent was quenched by the addition of methanol (1 mL). The reaction mixture was warmed to 0 °C and stirred for 20 min. A 10% aqueous solution of potassium sodium tartrate (5 mL) was added, and the mixture was warmed to 23 °C and stirred vigorously for 20 min. The reaction mixture was poured into water (15 mL) and extracted with ethyl acetate (3 20-mL portions). The combined organics were washed with saturated aqueous sodium chloride (25 mL), dried over sodium sulfate and concentrated. Purification of the residue by flash column chromatography (15% ethyl acetate in hexanes) provided allylic alcohol **153** (155 mg, 96%) as a colorless oil.

^{1}H NMR (400 MHz, C_6D_6), δ:	5.96 (m, 1H, C10 H), 4.98 (m, 1H, C11 H), 4.54 (m, 2H, C8 H), 4.04 (dd, 1H, *J* = 8.76, 5.48 Hz, C13 H), 3.78 (dd, 1 H, *J* = 8.40, 6.56 Hz, C14 H), 3.47 (dd, 1H, *J* = 6.96, 5.84 Hz, C14 H), 3.27 (dd, 1H, *J* = 12.44, 6.96 Hz, C12 βH), 3.21 (d, 1H, *J* = 1.44 Hz, C5 H), 2.45 (dd, 1H, *J* = 12.44, 5.84 Hz, C12 αH), 2.09 (d, 1H, *J* = 1.80 Hz, C7 H), 1.48 (s, 3H, $C(CH_3)_2$), 1.18 (s, 3H, $C(CH_3)_2$), 1.13-0.94 (complex, 21H, $OSi(CH(CH_3)_2)_3$), 0.33 (s, 9H, $OSi(CH_3)_3$).
^{13}C NMR (100 MHz, C_6D_6) δ:	148.5, 131.3, 110.7, 89.4, 78.8, 78.3, 77.4, 76.9, 75.2, 73.9, 66.7, 59.0, 57.9, 54.9, 50.3, 26.4, 25.0, 18.2, 12.4, 1.9.
$[\alpha]_D^{20}$:	+140.63° (*c* 0.32, C_6H_6)
FTIR (thin film), cm^{-1}:	3447 (m, OH), 3310 (m, C≡C–H), 2945 (s), 2867 (m), 2133 (w, C≡C), 1436 (m), 1372 (m), 1253 (s), 1216 (m), 1075 (s), 881 (s), 846 (s).
HRMS (FAB):	Calc'd for $C_{29}H_{48}O_6Si_2$ $[M]^+$: 548.298947 Found: 548.295807

TLC (20% EtOAc in Hexanes), R*f*: **152**: 0.38 (UV, anisaldehyde)

153: 0.31 (anisaldehyde)



153 154

Epoxy alcohol **154**

A suspension of 4Å molecular sieves (ca. 5 g, powdered, activated) in dichloromethane (65 mL) was cooled to –20 °C. (+)-Diethyl-L-tartrate (5.65 mL, 6.81 g, 33.01 mmol, 12 equiv) and titanium(IV) isopropoxide (8.19 mL, 7.82 g, 27.51 mmol, 10 equiv) were added sequentially via syringe. The mixture was allowed to stir at –20 °C for an additional 50 min, and allylic alcohol **153** (1.51 g, 2.75 mmol, 1 equiv) in dichloromethane (50 mL) was added via cannula over a 10 min period. The resultant mixture was stirred at –20 °C for another 40 min, and *tert*-butyl hydroperoxide (5.85 mL of a 4.7 M solution in dichloromethane, 27.5 mmol, 10 equiv) was added dropwise through a slit in the septum at the neck of the flask via a gastight syringe equipped with a Teflon needle. The reaction was maintained at –20 °C for 24 h, and the catalyst was quenched by addition of 10% aqueous D-tartaric acid (150 mL). The reaction mixture was warmed to 23 °C and stirred vigorously for 20 min. The reaction mixture was filtered through a plug of celite. The filtrate layers were separated and the aqueous layer was further extracted with dichloromethane (2 100-mL portions). The combined organics were dried over sodium sulfate and concentrated. Purification of the residue by flash column chromatography

(10% ethyl acetate in dichloromethane grading to 20% ethyl acetate in dichloromethane) afforded epoxy alcohol **154** (1.38 g, 89%) as a colorless oil.

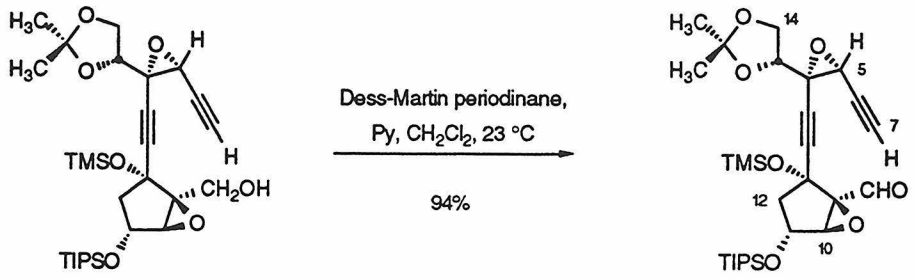
^{1}H NMR (400 MHz, C_6D_6), δ:	4.41 (d, 1H, *J* = 5.84 Hz, C11 H), 4.38 (br s, 2H, C8 H), 4.10 (dd, 1H, *J* = 8.80, 5.52 Hz, C13 H), 3.85 (dd, 1 H, *J* = 8.80, 6.96 Hz, C14 H), 3.73 (s, 1H, C10 H), 3.63 (dd, 1H, *J* = 6.60, 5.88 Hz, C14 H), 3.45 (d, 1H, *J* = 1.84 Hz, C5 H), 2.51 (dd, 1H, *J* = 14.28, 5.84 Hz, C12 βH), 2.21 (d, 1H, *J* = 14.64 Hz, C12 αH), 2.06 (d, 1H, *J* = 1.80 Hz, C7 H), 1.89 (br s, 1H, OH), 1.50 (s, 3H, $C(CH_3)_2$), 1.28 (s, 3H, $C(CH_3)_2$), 1.15-0.92 (complex, 21H, $OSi(CH(CH_3)_2)_3$), 0.40 (s, 9H, $OSi(CH_3)_3$).
^{13}C NMR (100 MHz, C_6D_6) δ:	110.8, 87.8, 80.1, 78.3, 77.1, 75.4, 74.8, 71.7, 71.6, 66.7, 63.8, 58.0, 57.9, 51.2, 49.9, 26.3, 25.1, 18.1, 12.3, 1.9.
$[\alpha]_D^{20}$:	+63.08 ° (*c* 0.78, C_6H_6)
FTIR (thin film), cm^{-1}:	3483 (m, OH), 3271 (m, C≡C–H), 2944 (s), 2866 (s), 1462 (m), 1373 (m), 1252 (s), 1213 (m), 1137 (s), 1073 (s), 883 (m), 846 (s).

HRMS (FAB): Calc'd for $C_{29}H_{49}O_7Si_2$ $[MH]^+$: 565.301686

Found: 565.301025

TLC (10% EtOAc in CH_2Cl_2), R*f*: **153**: 0.57 (anisaldehyde)

154: 0.52 (anisaldehyde)



154 155

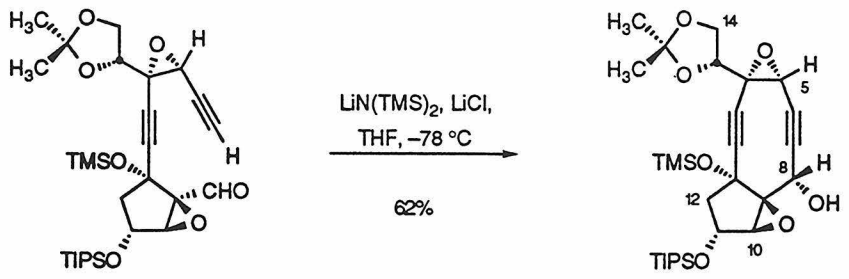
Epoxy aldehyde **155**

Dess-Martin periodinane (243 mg, 0.574 mmol, 3 equiv) was added in one portion to a solution of epoxy alcohol **154** (108 mg, 0.191 mmol, 1 equiv) and pyridine (155 μL, 151 mg, 1.91 mmol, 10 equiv) in dichloromethane (3 mL). The resultant pale yellow solution was maintained at 23 °C for 1 h, and the reaction mixture was diluted with diethyl ether (5 mL). Saturated aqueous sodium bicarbonate (5 mL) and saturated aqueous sodium thiosulfate (5 mL) were added sequentially, and the mixture was stirred vigorously until the organic layer was clear (approximately 5 min). The mixture was poured into water (20 mL) and extracted with diethyl ether (3 25-mL portions). The combined organics were washed once with saturated aqueous sodium chloride (30 mL), and were dried over sodium sulfate and concentrated. Purification of the residue by flash column chromatography (15% ethyl acetate in hexanes) afforded epoxy aldehyde **155** (101 mg, 94%) as a colorless oil.

^{1}H NMR (400 MHz, C_6D_6), δ:	9.91 (s, 1H, C8 H), 4.26 (d, 1H, *J* = 5.52 Hz, C11 H), 4.05 (dd, 1H, *J* = 8.80, 5.88 Hz, C13 H), 3.85 (dd, 1 H, *J* = 8.80, 6.96 Hz, C14 H), 3.82 (s, 1H, C10 H), 3.61 (t, 1H, *J* = 6.24 Hz, C14 H), 3.33 (d, 1H, *J* = 1.48 Hz, C5 H), 2.38 (dd, 1H, *J* = 14.64, 5.88 Hz, C12 βH), 2.19 (d, 1H, *J* = 14.28 Hz, C12 αH), 2.08 (d, 1H, *J* = 1.48 Hz, C7 H), 1.46 (s, 3H, $C(CH_3)_2$), 1.18 (s, 3H, $C(CH_3)_2$), 1.10-0.91 (complex, 21H, $OSi(CH(CH_3)_2)_3$), 0.45 (s, 9H, $OSi(CH_3)_3$).
^{13}C NMR (100 MHz, C_6D_6) δ:	193.1, 110.8, 86.4, 81.0, 78.0, 76.8, 75.5, 73.1, 71.3, 70.7, 67.0, 66.8, 57.9, 51.1, 49.9, 26.3, 25.2, 18.1, 12.2, 1.9.
$[\alpha]_D^{20}$:	+44.44° (*c* 0.72, C_6H_6)
FTIR (thin film), cm^{-1}:	3274 (m, C≡C–H), 2946 (s), 2867 (s), 2131 (w, C≡C), 1730 (s, C=O), 1462 (m), 1381 (m), 1252 (s), 1141 (s), 1073 (s), 884 (m), 846 (s).
HRMS (FAB):	Calc'd for $C_{29}H_{47}O_7Si_2$ $[MH]^+$: 563.286036 Found: 563.288330

TLC (10% EtOAc in CH_2Cl_2), R*f*: **154**: 0.51 (anisaldehyde)

155: 0.63 (anisaldehyde)

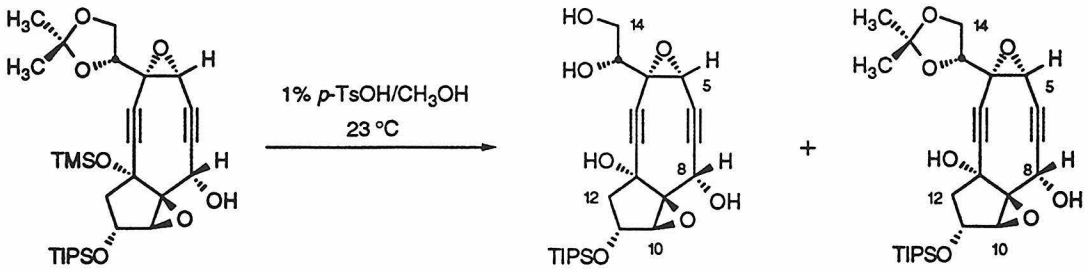


155 156

Cyclic alcohol **156**

A suspension of dry lithium chloride (2.03 g, 47.9 mmol, 50 equiv) and epoxy alcohol **155** (539 mg, 0.958 mmol, 1 equiv) in tetrahydrofuran (48 mL) was stirred vigorously at 23 °C for 5 min and cooled to –78 °C. Lithium hexamethyldisilazide (2.87 mL of a 1.0 M solution in hexanes, 2.87 mmol, 3 equiv) was added dropwise over a 5 min period to the suspension and the reaction mixture was allowed to stir at –78 °C for an additional 10 min. Excess base was quenched by the addition of pH 7.2 phosphate buffer (10 mL). The mixture was warmed to 23 °C and partitioned between water (20 mL) and 1:1 ethyl acetate/hexanes (20 mL). The layers were separated and the aqueous layer was further extracted with 1:1 ethyl acetate/hexanes (2 25-mL portions). The combined organics were washed once with saturated aqueous sodium chloride (25 mL), and were dried over sodium sulfate and concentrated. Purification of the residue by flash column chromatography (4% ethyl acetate in dichloromethane) afforded cyclic alcohol **156** (335 mg, 62%) as a yellow oil.

^{1}H NMR (400 MHz, C_6D_6), δ:	5.36 (d, 1H, *J* = 11.00 Hz, C8 H), 4.18 (d, 1H, *J* = 5.84 Hz, C11 H), 3.89 (dd, 1H, *J* = 8.44, 5.52 Hz, C13 H), 3.79 (s, 1H, C10 H), 3.74 (dd, 1H, *J* = 8.44, 6.60 Hz, C14 H), 3.64 (t, 1H, *J* = 5.88 Hz, C14 H), 3.18 (s, 1H, C5 H), 2.35 (dd, 1H, *J* = 14.28, 5.88 Hz, C12 βH), 2.04 (d, 1H, *J* = 14.64 Hz, C12 αH), 1.89 (d, 1H, *J* = 10.96 Hz, OH), 1.48 (s, 3H, $C(CH_3)_2$), 1.23 (s, 3H, $C(CH_3)_2$), 1.09-0.92 (complex, 21H, $OSi(CH(CH_3)_2)_3$), 0.36 (s, 9H, $C(CH_3)_3$).
^{13}C NMR (100 MHz, C_6D_6) δ:	127.5, 110.7, 92.9, 88.4, 87.6, 86.7, 80.9, 75.2, 70.9, 66.8, 64.1, 61.8, 57.2, 52.5, 48.7, 26.4, 25.5, 18.1, 12.2, 1.8.
$[\alpha]_D^{20}$:	+13.09° (*c* 1.10, C_6H_6)
FTIR (thin film), cm^{-1}:	3448 (m, OH), 2945 (s), 2867 (s), 2214 (w, C≡C), 1463 (m), 1381 (m), 1252 (s), 1217 (m), 1074 (s), 953 (m), 846 (s), 680 (m).
HRMS (FAB):	Calc'd for $C_{29}H_{47}O_7Si_2$ $[MH]^+$: 563.286036 Found: 563.285300
TLC (10% EtOAc in CH_2Cl_2), R*f*:	**155**: 0.81 (anisaldehyde) **156**: 0.75 (anisaldehyde)



Tetraol **157** and diol **158**

Cyclic alcohol **156** (290 mg, 0.515 mmol, 1 equiv) was dissolved in a 1% solution of *p*-toluenesulfonic acid in methanol (26 mL) at 23 °C. The resultant solution was maintained at 23 °C for an additional 80 min, during which time the solution gradually became pale yellow. The reaction mixture was neutralized with saturated aqueous sodium bicarbonate (25 mL) and poured into water (20 mL). The mixture was extracted with ethyl acetate (3 15-mL portions). The combined organics were washed with saturated aqueous sodium chloride (20 mL), dried over sodium sulfate and concentrated. Purification of the residue by flash column chromatography (30% ethyl acetate in hexanes grading to 70% ethyl acetate in hexanes) provided tetraol **157** (144 mg, 62%) as a colorless foam and diol **158** (36 mg, 10%) as a yellow oil.

For tetraol 157:

^{1}H NMR (400 MHz, CD_2Cl_2) δ:	5.29 (d, 1H, *J* = 10.96 Hz, C8 H), 4.54 (d, 1H, *J* = 4.36 Hz, C11 H), 3.86 (br m, 2H, C13, C 14 H), 3.71 (m, 3H, C14 H, C10 H, OH), 3.08 (s, 1H, C5 H), 2.42 (br s, 1H, OH), 2.21 (br d, 1H, *J* = 10.80 Hz, OH), 2.18 (dd, 1H, *J* = 14.64, 4.76 Hz, C12 βH), 2.01 (br s, 1H, OH), 1.98 (d, 1H, J = 14.64 Hz, C12 αH), 1.21-1.02 (complex, 21H, $OSi(CH(CH_3)_2)_3$).
^{13}C NMR (100 MHz, CD_3CN) δ:	92.5, 88.5, 87.2, 87.1, 80.0, 74.8, 71.8, 71.5, 64.1, 63.4, 62.3, 57.0, 52.3, 46.9, 18.3, 12.7.
$[\alpha]_D^{20}$:	+48.57° (*c* 0.28, CH_3CN)
FTIR (thin film), cm^{-1}:	3380 (s, OH), 2943 (s), 2866 (s), 2214 (w, C≡C), 1462 (m), 1384 (m), 1131 (m), 1067 (m), 882 (m), 745 (m).
HRMS (FAB):	Calc'd for $C_{23}H_{35}O_7Si$ $[MH]^+$: 451.215207 Found: 451.213867
TLC (70% EtOAc in Hexanes), R*f*:	**156**: 0.77 (anisaldehyde) **157**: 0.23 (anisaldehyde)

For diol 158:

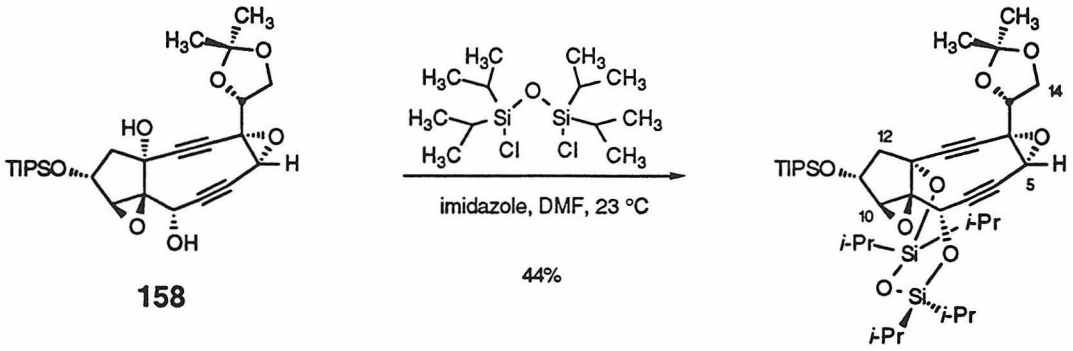
^{1}H NMR (400 MHz, C_6D_6), δ: 5.41 (d, 1H, *J* = 10.64 Hz, C8 H), 4.13 (d, 1H, *J* = 4.4 Hz, C11 H), 3.95 (dd, 1H, *J* = 8.80, 5.48 Hz, C13 H), 3.75 (dd, 1H, *J* = 8.80, 6.60 Hz, C14 H), 3.68 (s, 1H, C10 H), 3.61 (t, 1H, *J* = 6.20 Hz, C14 H), 3.18 (s, 1H, C1 OH), 3.02 (s, 1H, C5 H), 2.21 (dd, 1H, *J* = 14.28, 4.40 Hz, C12 βH), 1.87 (d, 1H, *J* = 14.28 Hz, C12 αH), 1.79 (d, 1J, *J* = 10.60 Hz, C8 OH), 1.53 (s, 3H, $C(CH_3)_2$), 1.25 (s, 3H, $C(CH_3)_2$), 0.95-0.80 (complex, 21H, $OSi(CH(CH_3)_2)_3$).

^{13}C NMR (100 MHz, C_6D_6) δ: 110.8, 91.7, 88.4, 87.0, 79.0, 75.5, 74.7, 71.4, 67.0, 62.4, 61.8, 57.0, 52.8, 45.8, 26.4, 25.5, 17.9, 12.1.

FTIR (thin film), cm^{-1}: 3441 (m. OH), 2943 (m), 2867 (m), 2279 (w, C≡C), 2220 (w, C≡C), 1729 (w), 1620 (w), 1463 (m), 1382 (m), 1257 (m), 1217 (m), 1134 (m), 1107 (m), 1070 (m), 882 (m), 682 (m).

TLC (70% EtOAc in Hexanes), R*f*: **156**: 0.73 (anisaldehyde)

158: 0.65 (anisaldehyde)



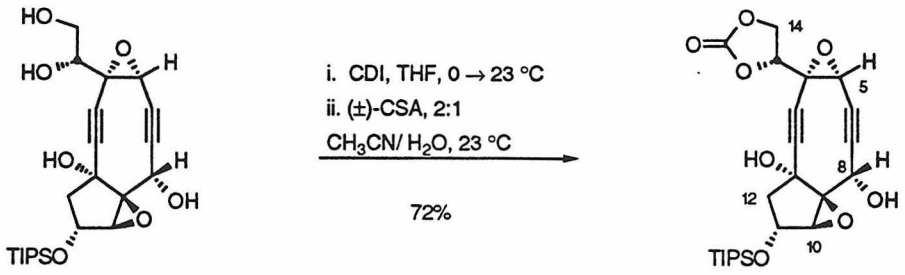
158

159

Disiloxane **159**

1,3-Dichloro-1,1,3,3-tetraisopropyldisiloxane (0.026 mL, 26 mg, 0.082 mmol, 5 equiv) was added via syringe to a solution of diol **158** (8.0 mg, 0.016 mmol, 1 equiv) and imidazole (22 mg, 0.33 mmol, 20 equiv) in DMF (0.8 mL) at 23 °C. The reaction mixture was held at 23 °C for an additional 3 h. The solution was poured into saturated aqueous sodium chloride (5 mL) and extracted with 1:1 ethyl acetate/hexanes (3 5-mL portions). The combined organics were dried over sodium sulfate and were concentrated. Purification of the residue by flash column chromatography (10% ethyl acetate in hexanes) was followed by chromatography over Sephadex LH-20 (dichloromethane) to afford the disiloxane **159** (5.3 mg, 44%) as a colorless oil.

^{1}H NMR (400 MHz, C_6D_6), δ:	6.07 (s, 1H, C8 H), 4.19 (d, 1H, *J* = 4.76 Hz, C11 H), 3.91 (dd, 1H, *J* = 8.80, 5.84 Hz, C13 H), 3.74 (dd, 1H, *J* = 8.44, 6.96 Hz, C14 H), 3.63 (t, 1H, *J* = 6.20 Hz, C14 H), 3.36 (s, 1H, C10 H), 3.16 (s, 1H, C5 H), 2.31 (dd, 1H, *J* = 14.28, 4.76 Hz, C12 βH), 1.92 (d, 1H, *J* = 14.28 Hz, C12 αH), 1.51 (s, 3H, $C(CH_3)_2$), 1.30-0.84 (complex, 52H, $C(CH_3)_2$, $OSi(CH(CH_3)_2)_3$, and 2 x $Si(CH(CH_3)_2)_2$).
HRMS (FAB):	Calc'd for $C_{38}H_{65}O_8Si_3$ $[MH]^+$: 733.3987 Found: 733.3991
TLC (30% EtOAc in Hexanes), R*f*:	**158**: 0.22 (anisaldehyde) **159**: 0.49 (anisaldehyde)

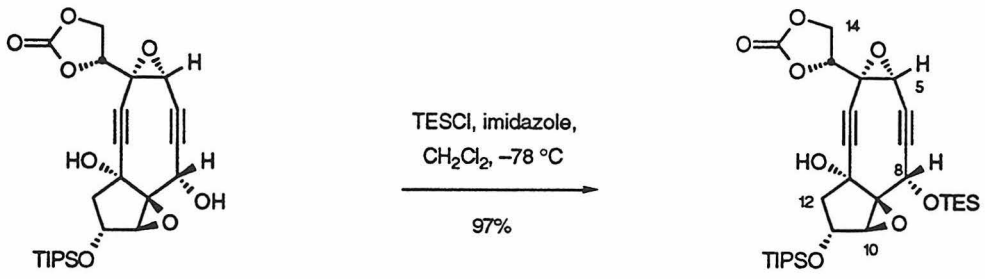


157 **160**

Carbonate **160**

Carbonyldiimidazole (37 mg, 0.23 mmol, 0.75 equiv) was added in one portion to a solution of tetraol **157** (135 mg, 0.300 mmol, 1 equiv) in tetrahydrofuran (10 mL) at 0 °C. After stirring for an additional 20 min, another portion of carbonyldiimidazole (37 mg, 0.23 mmol, 0.75 equiv) was added. The reaction was kept at 0 °C for an additional 10 min, and warmed to 23 °C for 2.5 h. The reaction mixture was poured into water (10 mL) and extracted with ethyl acetate (3 20-mL portions). The combined organics were dried over sodium sulfate and concentrated. The residue was then taken up in 2:1 acetonitrile/water (12 mL), and (±)-camphorsulfonic acid (150 mg) was added. The resultant pale yellow solution was maintained at 23 °C for 30 min, and poured into water (20 mL) and extracted with ethyl acetate (3 20-mL portions). The combined organics were washed with saturated aqueous sodium chloride (25 mL) and were dried over sodium sulfate and concentrated. Purification of the residue by flash column chromatography (50% ethyl acetate in hexanes grading to ethyl acetate) provided carbonate **160** (103 mg, 72%) as a colorless foam along with recovered tetraol (31 mg, 23%).

^{1}H NMR (400 MHz, C_6D_6), δ:	5.36 (d, 1H, *J* = 10.24 Hz, C8 H), 4.07 (d, 1H, *J* = 4.76 Hz, C11 H), 3.69 (dd, 1H, *J* = 7.68, 4.04 Hz, C13 H), 3.65 (s, 1H, C10 H), 3.26 (m, 2H, C14 H), 3.06 (s, 1H, OH), 2.86 (s, 1H, C5 H), 2.04 (dd, 1H, *J* = 14.64, 4.76 Hz, C12 βH), 1.88 (d, 1H, *J* = 10.60 Hz, OH), 1.74 (d, 1H, *J* = 14.28 Hz, C12 αH), 0.98-0.76 (complex, 21H, $OSi(CH(CH_3)_2)_3$).
^{13}C NMR (100 MHz, C_6D_6) δ:	153.9, 94.2, 89.3, 85.9, 84.1, 79.0, 74.8, 74.1, 71.3, 66.2, 62.2, 60.7, 56.9, 53.1, 45.4, 17.9, 12.0.
$[\alpha]_D^{20}$:	+65.26° (*c* 0.76, C_6H_6)
FTIR (thin film), cm^{-1}:	3482 (m, OH), 2944 (s), 2866 (s), 1816 (s, C=O), 1367 (m), 1082 (s), 881 (s).
HRMS (FAB):	Calc'd for $C_{24}H_{32}O_8Si$ $[M]^+$: 476.186647 Found: 476.184998
TLC (70% EtOAc in Hexanes), R*f*:	**157**: 0.30 (anisaldehyde) **160**: 0.65 (anisaldehyde)

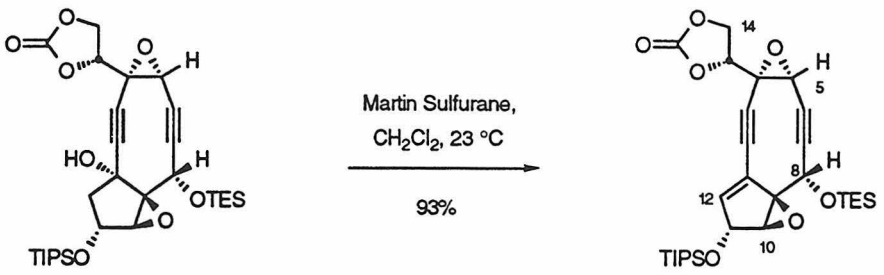


160 **161**

Triethylsilyl ether **161**

Triethylsilyl chloride (313 μL, 274 mg, 1.82 mmol, 7 equiv) was added dropwise via syringe to a solution of carbonate **160** (124 mg, 0.260 mmol, 1 equiv) and imidazole (354 mg, 5.20 mmol, 20 equiv) in dichloromethane (13 mL) at 0 °C. The resultant solution was maintained at 0 °C for 10 min and partitioned between 1:1 ethyl acetate/hexanes (25 mL) and water (15 mL). The aqueous layer was further extracted with 1:1 ethyl acetate/hexanes (2 20-mL portions), and the combined organics were washed with saturated aqueous sodium chloride (25 mL), dried over sodium sulfate, and concentrated. Purification of the residue by flash column chromatography (20% ethyl acetate in hexanes) afforded triethylsilyl ether **161** (148 mg, 97%) as a pale yellow oil.

^{1}H NMR (400 MHz, C_6D_6) δ:	5.79 (s, 1H, C8 H), 4.09 (d, 1H, *J* = 4.40 Hz, C11 H), 3.87 (s, 1H, C10 H), 3.65 (dd, 1H, J = 6.96, 3.68 Hz, C13 H), 3.26 (m, 2H, C14 H), 3.13 (s, 1H, OH), 2.78 (s, 1H, C5 H), 2.14 (dd, 1H, *J* = 14.28, 4.40 Hz, C12 βH), 1.76 (d, 1H, *J* = 14.64 Hz, C12 αH), 1.06 (t, 9H, *J* = 8.04 Hz, $OSi(CH_2CH_3)_3$), 0.95-0.81 (complex, 21H, $OSi(CH(CH_3)_2)_3$), 0.69 (m, 6H, $OSi(CH_2CH_3)_3$).
^{13}C NMR (100 MHz, C_6D_6) δ:	153.5, 90.4, 89.8, 85.7, 80.4, 80.0, 74.8, 73.9, 71.6, 65.8, 62.5, 60.4, 57.5, 53.2, 45.7, 17.9, 12.0, 6.9, 5.0.
$[\alpha]_D^{20}$:	+39.45 ° (*c* 0.73, C_6H_6)
FTIR (thin film), cm^{-1}:	3490 (m, OH), 2954 (s), 2870 (s), 2214 (w, C≡C), 1822 (s, C=O), 1469 (m), 1240 (m), 1148 (s), 1104 (s), 881 (m), 727 (m).
HRMS (FAB):	Calc'd for $C_{30}H_{47}O_8Si_2$ $[MH]^+$: 591.2810 Found: 591.2809
TLC (10% EtOAc in CH_2Cl_2), R*f*:	**160**: 0.28 (anisaldehyde) **161**: 0.83 (anisaldehyde)

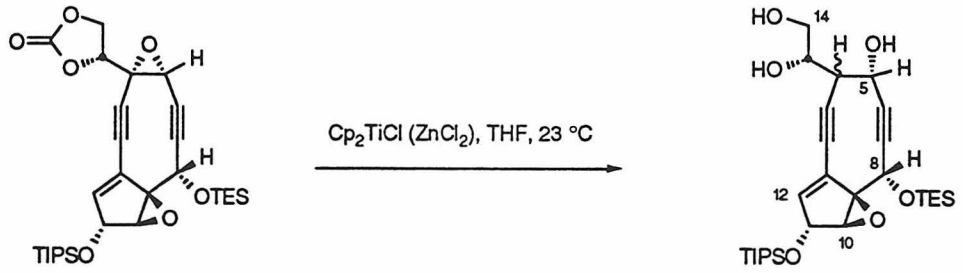


161 **162**

Olefin **162**

A solution of triethylsilyl ether **161** (20 mg, 0.034 mmol, 1 equiv) in dichloromethane (0.85 mL) was added via cannula to a solution of Martin sulfurane dehydrating agent (114 mg, 0.169 mmol, 5 equiv) in dichloromethane (0.85 mL) at 0 °C. The resultant yellow solution was warmed to 23 °C, allowed to stand at that temperature for 1 h, and concentrated. Purification of the residue by flash column chromatography (2% ethyl acetate in dichloromethane) afforded enediyne along with a close running by-product of the sulfurane. A second flash purification by flash column chromatography (20% ethyl acetate in hexanes) afforded pure olefin **162** (18 mg, 93%) as a pale yellow oil.

^{1}H NMR (400 MHz, C_6D_6) δ:	5.94 (t, 1H, *J* = 2.56 Hz, C12 H), 5.07 (s, 1H, C8 H), 4.59 (d, 1H, *J* = 2.20 Hz, C11 H), 3.96 (d, 1H, *J* = 2.56 Hz, C10 H), 3.58 (dd, 1H, *J* = 8.44, 5.48 Hz, C13 H), 3.39 (dd, 1H, *J* = 8.04, 5.48 Hz, C14 H), 3.27 (t, 1H, *J* = 8.40 Hz, C14 H), 2.76 (s, 1H, C5 H), 1.07-0.90 (complex, 30H, $OSi(CH_2CH_3)_3$ and $OSi(CH(CH_3)_2)_3$), 0.67 (m, 6H, $OSi(CH_2CH_3)_3$).
^{13}C NMR (100 MHz, C_6D_6) δ:	153.5, 143.5, 96.7, 90.4, 88.4, 86.1, 77.2, 73.6, 65.8, 62.9, 61.4, 58.6, 52.7, 18.0, 12.3, 6.9, 5.1.
$[\alpha]_D^{20}$:	–26.00 ° (*c* 0.10, C_6H_6)
FTIR (thin film), cm^{-1}:	2953 (s), 2870 (s), 2190 (w, C≡C), 1823 (s, C=O), 1462 (m), 1323 (m), 1154 (s), 1091 (s), 879 (m), 747 (m).
HRMS (FAB):	Calc'd for $C_{30}H_{45}O_7Si_2$ $[MH]^+$: 573.2704 Found: 573.2709
TLC (25% EtOAc in Hexanes), R*f*:	**161**: 0.14 (anisaldehyde) **162**: 0.25 (UV, anisaldehyde)



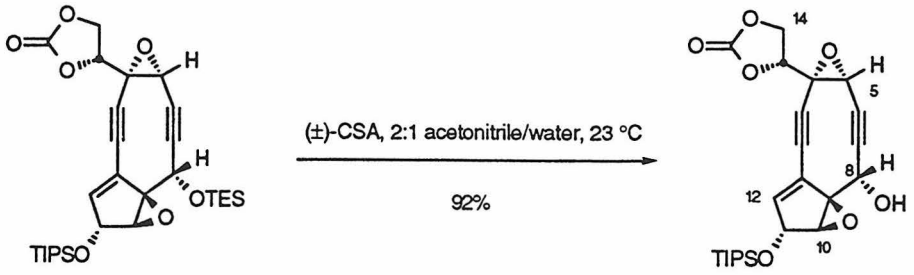
162 **163**

Triol **163**

A solution of bis-epoxide **162** (1.0 mg, 1.7 x 10^{-3} mmol, 1 equiv) in tetrahydrofuran (0.1 mL) was added dropwise via cannula to a green solution of dicyclopentadienyltitanium(III) chloride (13 μL of a 0.4 M stock solution in tetrahydrofuran prepared by the in situ method of RajanBabu and Nugent,[96] 5.2 x 10^{-3} mmol, 3 equiv) in tetrahydrofuran (0.1 mL) at 23 °C. The reaction mixture turned orange upon addition of the alcohol. The solution was maintained at 23 °C for an additional 10 min and pH 7.2 phosphate buffer (1 mL) was added. The mixture was extracted with ethyl acetate (3 1-mL portions) and the combined organics were washed with saturated aqueous sodium bicarbonate (2 mL) and saturated aqueous sodium chloride (2 mL). The organics were dried over sodium sulfate and concentrated to ca. 0.1 mL. Purification of the concentrate by flash column chromatography (20% ethyl acetate in hexanes grading to 50% ethyl acetate in hexanes) was followed by pooling the fractions containing the product and concentrating to a volume of ca. 0.1 mL. A 0.5 mL portion of deuteriated benzene (99.5 atom % D) was added and the resulting solution was concentrated to a volume of ca. 0.1 mL. This procedure was repeated 4 times. After the last iteration, the concentrated

solution was taken up in approximately 0.4 mL deuteriated benzene (99.95 atom % D). Analysis of the sample by ^{1}H NMR showed it to contain triol **163**.

^{1}H NMR (400 MHz, C_6D_6) δ:	6.00 (t, 1H, *J* = 2.56 Hz, C12 H), 5.97 (complex, 2H, C4, C5 H), 5.40 (d, 1H, *J* = 2.60 Hz, C8 H), 4.73 (br m, 1H, C13 H), 4.62 (d, 1H, *J* = 2.56 Hz, C11 H), 4.16 (br m, 2H, C14 H), 4.11 (d, 1H, *J* = 2.56 Hz, C10 H), 1.08-0.71 (complex, 36 H, $OSi(CH(CH_3)_2)_3$) and $OSi(CH_2CH_3)_3$).
FTIR (thin film), cm^{-1}:	3364 (m, OH), 2924 (s), 1723 (w), 1461 (m), 1093 (m).
TLC (50% EtOAc in Hexanes), R*f*:	**162**: 0.61 (UV, anisaldehyde) **163**: 0.29 (UV, anisaldehyde)

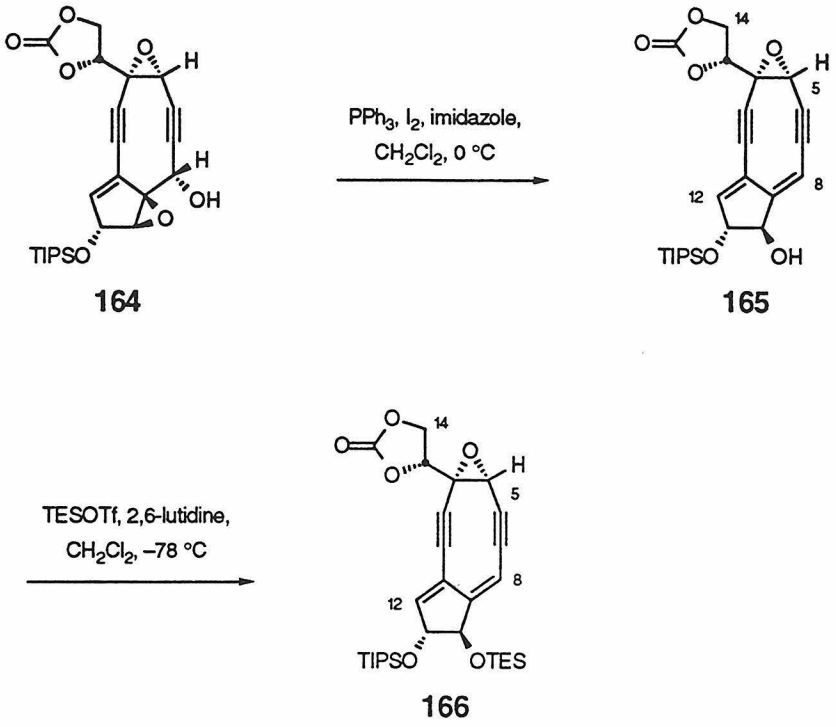


162 **164**

Alcohol **164**

(±)-Camphorsulfonic acid (214 mg, 0.920 mmol, 5 equiv) was added in one portion to a solution of olefin **162** (105 mg, 0.184 mmol, 1 equiv) in 2:1 acetonitrile/water (6 mL). The resultant yellow solution was stirred at 23 °C for 15 min, and poured into water (15 mL). The mixture was then extracted with ethyl acetate (3 25-mL portions) and the combined organics were washed once with saturated aqueous sodium chloride (30 mL), dried over sodium sulfate and concentrated. Purification of the residue by flash column chromatography (20% ethyl acetate in hexanes grading to 40% ethyl acetate in hexanes) afforded alcohol **164** (77 mg, 92%) as a colorless oil.

^{1}H NMR (400 MHz, C_6D_6) δ:	5.89(t, 1H, *J* = 2.20 Hz, C12 H), 4.54 (d, 1H, *J* = 2.20 Hz, C11 H), 4.13 (d, 1H, *J* = 9.12 Hz, C8 H), 3.76 (d, 1H, *J* = 2.20 Hz, C10 H), 3.66 (dd, 1H, *J* = 8.80, 5.12 Hz, C13 H), 3.37 (dd, 1H, *J* = 8.08, 5.12 Hz, C14 H), 3.31 (t, 1H, *J* = 8.44 Hz, C14 H), 2.82 (s, 1H, C5 H), 2.14 (d, 1H, *J* = 9.88 Hz, OH), 1.13-0.48 (complex, 21 H, OSi(CH(CH$_3$)$_2$)$_3$).
^{13}C NMR (100 MHz, C_6D_6) δ:	153.3, 143.7, 126.6, 96.1, 89.8, 88.0, 85.3, 76.2, 73.6, 73.4, 65.7, 63.5, 61.2, 56.9, 52.7, 17.7, 11.8.
$[\alpha]_D^{20}$:	–119.76° (*c* 0.167, C_6H_6)
FTIR (thin film), cm^{-1}:	3448 (m, OH),2943 (s), 2866 (s), 2202 (w, C≡C), 1818 (s, C=O), 1463 (m), 1321 (m), 1154 (s), 1082 (s), 881 (m).
HRMS (FAB):	Calc'd for $C_{24}H_{30}O_7Si$ $[M]^+$: 458.176082 Found: 458.177483
TLC (50% EtOAc in Hexanes), R*f*:	**162**: 0.66 (UV, anisaldehyde) **164**: 0.44 (UV, anisaldehyde)



164 165 166

Dienediynes **165** and **166**

Iodine (3.0 mg, 2.2 x 10^{-2} mmol, 10 equiv) was added in one portion to a solution of triphenylphosphine (7.0 mg, 2.7 x 10^{-2} mmol, 12 equiv) and imidazole (3.0 mg, 4.4 x 10^{-2} mmol, 20 equiv) in dichloromethane (0.05 mL) at 0 °C. The resultant pale yellow suspension was stirred at 0 °C for an additional 5 min, and a solution of alcohol **164** (1 mg, 2.2 x 10^{-3} mmol, 1 equiv) in dichloromethane (0.2 mL) was added in a dropwise manner. The reaction was monitored by thin-layer chromatography (silica, 50% ethyl acetate in hexanes), and was judged to be complete in 7 min. The reaction mixture was concentrated to ca. one-third of the original volume. The concentrated sample was applied directly to a pipet column packed with 20% ethyl acetate in hexanes, and the product was

eluted with a solvent system of 20% ethyl acetate in hexanes grading to 30% ethyl acetate in hexanes. Fractions containing the product were pooled and concentrated to a volume of ca. 0.1 mL. A 0.5 mL portion of deuteriated benzene (99.5 atom % D) was added and the resulting solution was concentrated to a volume of ca. 0.1 mL. This procedure was repeated 4 times. After the last iteration, the concentrated solution was taken up in approximately 0.4 mL deuteriated benzene (99.95 atom % D). Analysis of the sample by ^{1}H NMR showed it to contain dienediyne **165**.

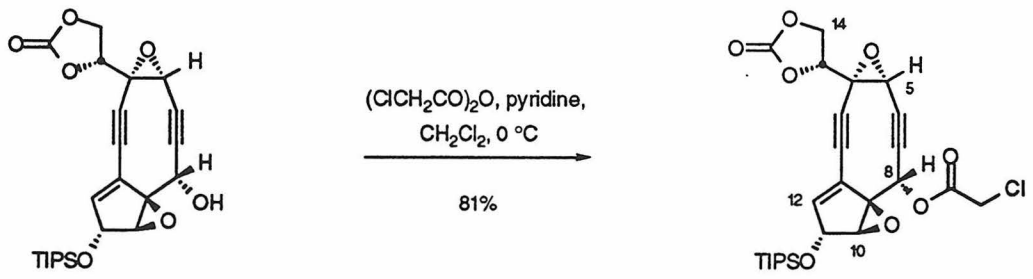
The NMR sample was placed in a 10 mL round-bottom flask and concentrated to approximately 0.05 mL. The concentrate was diluted with dry dichloromethane (0.1 mL) and cooled to –78 °C. 2,6-Lutidine (13 μL, 12 mg, 0.11 mmol, 50 equiv) and triethylsilyl trifluoromethanesulfonate (12.5 μL, 15 mg, 5.6 x 10^{-2} mmol, 25 equiv) were added sequentially via syringe. The reaction was held at –78 °C for an additional 15 min, and warmed to 0 °C. After 10 min at 0 °C, the reaction was diluted with hexanes (2 mL) and washed with water (3 1-mL portions). The organics were dried over sodium sulfate and were concentrated to a volume of ca. 0.1 mL. A 0.5 mL portion of deuteriated benzene (99.5 atom % D) was added and the resulting solution was concentrated to a volume of ca. 0.1 mL. This procedure was repeated 4 times. After the last iteration, the concentrated solution was taken up in approximately 0.4 mL deuteriated benzene (99.95 atom % D). Analysis of the sample by ^{1}H NMR showed it to contain dienediyne **166**.

For 165:

^{1}H NMR (400 MHz, C_6D_6), δ:	5.88 (t, 1H, *J* = 1.6 Hz, C12 H), 5.16 (br s, 1H, C8 H), 4.37 (t, 1H, *J* = 2.4 Hz, C11 H), 4.08 (br S, OH), 4.06 (br s, 1H, C10 H), 3.75 (dd, 1H, *J* = 8.40, 4.76 Hz, C13 H), 3.30 (t, 1H, *J* = 8.44 Hz, C14 H), 3.25 (dd, 1H, *J* = 8.40, 4.76 Hz, C14 H), 3.18 (d, 1H, *J* = 1.3 Hz, C5 H), 1.10-0.82 (complex, 21 H, $OSi(CH(CH_3)_2)_3$).
FTIR (thin film), cm^{-1}:	3401 (m, OH), 2923 (s), 1807 (m, C=O), 1530 (m), 1085 (m).
TLC (50% EtOAc in Hexanes), R*f*:	**164**: 0.40 (UV, anisaldehyde) **165**: 0.49 (UV, anisaldehyde)

For 166:

^{1}H NMR (400 MHz, C_6D_6), δ:	6.04 (br s, 1H, C12 H), 5.51 (br s, 1H, C8 H), 4.67 (t, 1H, J = 2.6 Hz, C11 H), 4.47 (t, 1H, J = 2.6 Hz, C10 H), 3.73 (m, 1H, C13 H), 3.28 (m, 2H, C14 H), 3.10 (d, 1H, J = 1.7 Hz, C5 H), 1.12-0.50 (complex, 21 H, $OSi(CH(CH_3)_2)_3$).
TLC (50% EtOAc in Hexanes), R*f*:	**165**.: 0.49 (UV, anisaldehyde) **166**: 0.61 (UV, anisaldehyde)

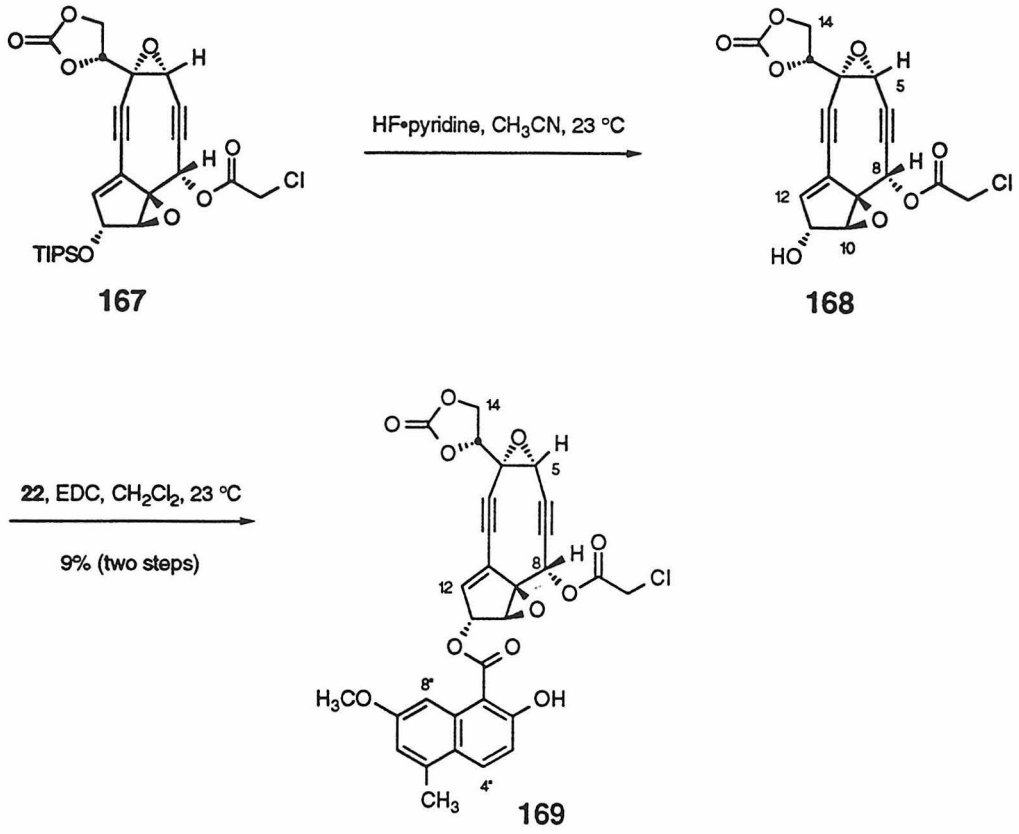


164 **167**

Chloroacetate **167**

Chloroacetic anhydride (216 mg, 1.26 mmol, 10 equiv) was added in one portion to a solution of alcohol **164** (58 mg, 0.13 mmol, 1 equiv) and pyridine (205 μL, 200 mg, 2.538 mmol, 20 equiv) in dichloromethane (3.0 mL) at 0 °C. The reaction was maintained at 0 °C for an additional 10 min, diluted with 1:1 ethyl acetate/hexanes (10 mL) and washed with water (3 5-mL portions) and saturated aqueous sodium chloride (5 mL). The organics were dried over sodium sulfate and concentrated. Purification of the residue by flash column chromatography (5% ethyl acetate in hexanes grading to 50% ethyl acetate in hexanes) provided chloroacetate ester **167** (54 mg, 81%) as a yellow oil.

^{1}H NMR (400 MHz, C_6D_6), δ:	5.91 (t, 1H, *J* = 2.60 Hz, C12 H), 5.68 (s, 1H, C8 H), 4.56 (d, 1H, *J* = 2.56 Hz, C11 H), 3.89 (d, 1H, *J* = 2.56 Hz, C10 H), 3.61 (dd, 1H, *J* = 8.40, 5.12 Hz, C13 H), 3.37 (dd, 1H, *J* = 8.44, 5.12 Hz, C14 H), 3.30 (t, 1H, *J* = 8.40 Hz, C14 H), 3.18 (abq, 2H, *J* = 15.97 Hz, Δν = 17.28 Hz, $COCH_2Cl$), 2.73 (s, 1H, C5 H), 1.02-0.91 (complex, 21H, $OSi(CH(CH_3)_2)_3$).
^{13}C NMR (100 MHz, C_6D_6), δ:	165.4, 153.4, 144.3, 127.1, 96.5, 88.9, 88.1, 85.6, 74.2, 73.8, 73.6, 65.9, 64.1, 61.5, 59.6, 52.7, 39.8, 17.6, 12.3.
$[\alpha]_D^{20}$:	–82.78° (*c* 0.72, C_6H_6)
FTIR (thin film), cm^{-1}:	2944 (m), 2872 (m), 2202 (w, C≡C), 1819 (s, carbonate C=O), 1772 (m, ester C=O), 1466 (w), 1325 (w), 1249 (w), 1151 (s), 1078 (s), 996 (m), 881 (m).
HRMS (FAB):	Calc'd for $C_{26}H_{32}ClO_8Si$ $[MH]^+$: 535.155500 Found: 535.153870
TLC (40% EtOAc in Hexanes), R*f*:	**164**: 0.32 (UV, anisaldehyde) **167**: 0.43 (UV, anisaldehyde)



167 168 169

Allylic alcohol **168** and naphthoate ester **169**

Hydrogen fluoride - pyridine complex (1 mL) was added to a solution of chloroacetate ester **167** (110 mg, 0.206 mmol, 1 equiv) in acetonitrile (9 mL) at 23 °C. The resultant orange-brown solution was stirred at 23 °C for an additional 2 h, during which time the solution darkened considerably. The reaction mixture was poured into water (25 mL) and extracted with ethyl acetate (3 20-mL portions). The combined organics were dried over sodium sulfate and concentrated to a volume of ca. 3 mL. The crude alcohol **168** was taken up in dichloromethane (21 mL) and cooled to 0 °C. 2-Hydroxy-7-methoxy-5-methyl-1-naphthoic acid (**22**, 287 mg, 1.24 mmol, 6 eq) was added in one

portion followed by 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (EDC) (355 mg, 1.85 mmol, 9 equiv), also in one portion. The reaction was maintained at 0 °C for 30 min, then another portion of EDC (150 mg, 0.782 mmol, 3.7 equiv) was added. Stirring was continued for an additional 30 min, and the reaction mixture was poured into a bilayer of ethyl acetate (10 mL) and water (10 mL). The layers were separated and the aqueous layer was further extracted with ethyl acetate (2 10-mL portions). The combined organics were washed with saturated aqueous sodium chloride (25 mL), and were dried over sodium sulfate and concentrated. Purification of the residue by flash column chromatography (25% ethyl acetate in hexanes grading to 50% ethyl acetate in hexanes) provided naphthoate ester **169** (11.2 mg, 9% two-step yield) as a colorless film along with recovered alcohol **168** (17 mg, 23%) as an orange oil.

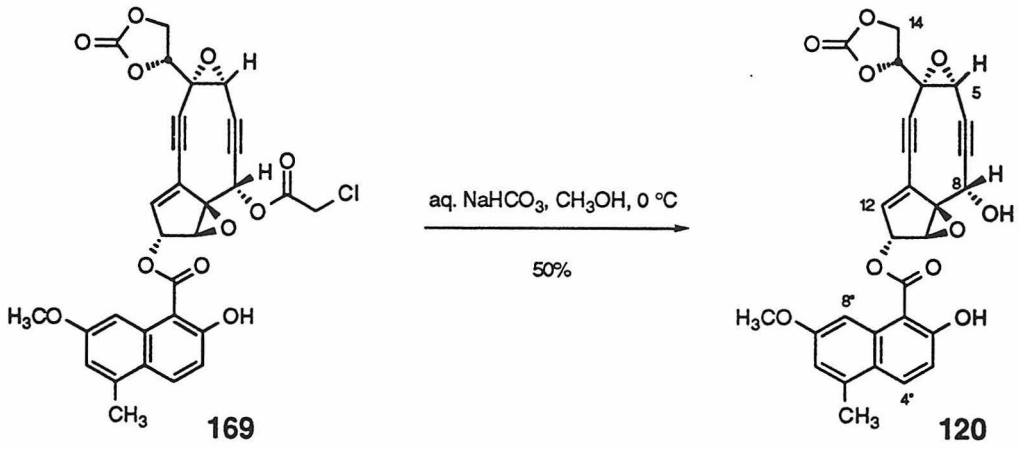
For alcohol 168:

^{1}H NMR (400 MHz, C_6D_6), δ:	5.83 (s, 1H, C8 H), 5.58 (t, 1H, *J* = 2.56 Hz, C12 H), 3.99 (br s, 1H, C11 H), 3.51 (dd, 1H, *J* = 8.80, 5.48 Hz, C13 H), 3.45 (d, 1H, *J* = 2.56 Hz, C10 H), 3.37 (dd, 1H, *J* = 8.04, 5.48 Hz, C14 H), 3.23 (m, 3H, C14 H and CH_2Cl), 2.71 (s, 1H, C5 H).
FTIR (thin film), cm^{-1}:	3448 (m, OH), 2919 (m), 2202 (w, C≡C), 1813 (s, carbonate C=O), 1791 (s, ester C=O), 1401 (w), 1307 (m), 1249 (w), 1154 (s), 1080 (s), 995 (m) 868 (m), 767 (m).
HRMS (FAB):	Calc'd for $C_{17}H_{12}ClO_7$ $[M]^+$: 363.027156 Found: 363.027054
TLC (70% EtOAc in Hexanes), R*f*:	**167**: 0.66 (UV, anisaldehyde) **168**.: 0.41 (fluoresces under UV, anisaldehyde)

For 169:

^{1}H NMR (400 MHz, C_6D_6), δ:	12.58 (s, 1H, C2" OH), 8.00 (s, 1H, C8" H), 7.70 (d, 1H, *J* = 9.16 Hz, C4" H), 7.14 (d, 1H, *J* = 9.16 Hz, C3" H), 6.99 (s, 1H, C6" H), 5.75 (t, 1H, *J* = 2.20 Hz, C12 H), 5.69 (s, 1H, C8 H), 5.47 (d, 1H, *J* = 2.20 Hz, C11 H), 3.72 (d, 1H, *J* = 2.56 Hz, C10 H), 3.66 (s, 3H, C7" OCH_3), 3.49 (dd, 1H, *J* = 8.80, 5.52 Hz, C13 H), 3.36 (dd, 1H, *J* = 8.04, 5.48 Hz, C14 H), 3.23 (t, 1H, *J* = 8.76 Hz, C14 H), 3.18 (abq, 2H, *J* = 14.64 Hz, Δν = 23.80 Hz, $COCH_2Cl$), 2.71 (s, 1H, C5 H), 2.23 (s, 3H, C5" CH_3).
^{13}C NMR (100 MHz, CD_2Cl_2), δ:	171.7, 166.1, 165.5, 160.0, 153.7, 139.9, 137.8, 134.2, 133.9, 130.6, 123.4, 117.0, 116.2, 104.1, 97.9, 89.0, 87.1, 84.8, 75.1, 74.3, 67.0, 61.6, 61.4, 61.3, 59.4, 55.4, 53.0, 40.9, 30.0, 20.1.
$[\alpha]_D^{20}$:	–126.90° (*c* 0.29, CH_3CN)
FTIR (thin film), cm^{-1}:	2927 (m), 1819 (s, C=O), 1648 (m), 1616 (s), 1411 (m), 1257 (m), 1201 (s), 1150 (s), 1079 (m).

HRMS (FAB):	Calc'd for $C_{30}H_{22}ClO_{11}$ $[MH]^+$: 593.085065 Found: 593.084457
TLC (70% EtOAc in Hexanes), R*f*:	**168**: 0.46 (UV, anisaldehyde) **169**: 0.68 (fluoresces under UV, anisaldehyde)

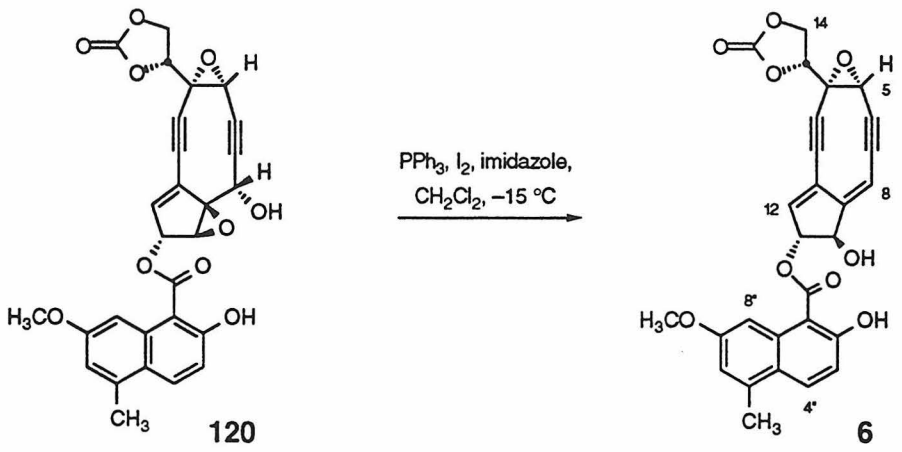


Epoxy alcohol **120**

Sodium bicarbonate (13 mg, 0.16 mmol, 10 equiv) was added to a solution of ester **169** (9.2 mg, 0.016 mmol, 1 equiv) in methanol (1.6 mL) at 0 °C. The resultant suspension was stirred at 0 °C for an additional 60 minutes, then was diluted with ethyl acetate (10 mL). The reaction mixture was washed with water (3 5-mL portions) and saturated aqueous sodium chloride (5 mL). The organics were dried over sodium sulfate and were concentrated. Purification of the residue by flash column chromatography (10% ethyl acetate in dichloromethane grading to 20% ethyl acetate in dichloromethane) afforded the epoxy alcohol **120** (4.1 mg, 50%) as a yellow film.

^{1}H NMR (400 MHz, C_6D_6) δ:	12.57 (s, 1H, C2" OH), 7.98 (s, 1H, C8" H), 7.70 (d, 1H, *J* = 9.16 Hz, C4" H), 7.15 (d, 1H, *J* = 9.52 Hz, C3" H), 6.98 (s, 1H, C6" H), 5.69 (t, 1H, *J* = 2.56 Hz, C12 H), 5.47 (d, 1H, *J* = 2.56 Hz, C11 H), 4.40 (d, 1H, *J* = 10.28 Hz, C8 H), 3.64 (d, 1H, *J* = 2.56 Hz, C10 H), 3.53 (dd, 1H, *J* = 8.80, 5.48 Hz, C13 H), 3.50 (s, 3H, C7" OCH_3), 3.34 (dd, 1H, *J* = 8.04, 5.48 Hz, C14 H), 3.23 (t, 1H, *J* = 8.40 Hz, C14 H), 2.77 (s, 1H, C5 H), 2.24 (s, 3H, C5" CH_3), 1.84 (d, 1H, *J* = 10.28 Hz, OH).
^{13}C NMR (100 MHz, CD_3CN), δ:	171.8, 164.3, 160.5, 155.0, 140.1, 138.4, 134.9, 134.0, 131.7, 123.9, 117.7, 116.4, 105.7, 104.4, 99.1, 90.2, 86.9, 86.2, 77.6, 75.9, 75.3, 67.1, 61.8, 61.2, 57.6, 57.2, 53.5, 19.9.
$[\alpha]_D^{20}$:	–50.00° (*c* 0.20, C_6H_6)
FTIR (CH_2Cl_2), cm^{-1}:	3684 (m, OH), 3070 (m), 3036 (m), 2957 (m), 1823 (s, C=O), 1732 (w), 1649 (w), 1611 (m), 1478 (s), 1199 (m), 1035 (m).

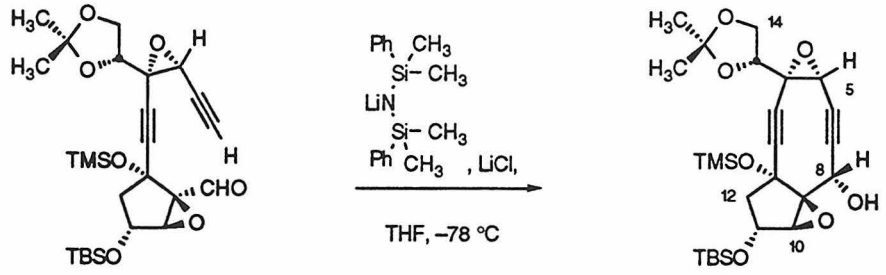
HRMS (FAB):	Calc'd for $C_{28}H_{21}O_{10}$ $[MH]^+$: 517.1135 Found: 517.1137
TLC (40% EtOAc in CH_2Cl_2), R*f*:	**169**: 0.71 (fluoresces under UV, anisaldehyde) **120**: 0.49 (fluoresces under UV, anisaldehyde)



Neocarzinostatin chromophore aglycone (**6**)

Epoxy alcohol **120** (0.6 mg, 1 x 10^{-3} mmol, 1 equiv) in dichloromethane (0.1 mL) was added via cannula to a pale yellow suspension of triphenylphosphine (7.5 mg, 2.9 x 10^{-2} mmol, 25 equiv), imidazole (3.9 mg, 5.7 x 10^{-2} mmol, 50 equiv) and iodine (7.2 mg, 2.9 x 10^{-2} mmol, 25 equiv) in dichloromethane (0.1 mL) at –15 °C. The reaction mixture was maintained at –15 °C for an additional 30 min, and the reaction mixture was loaded directly onto a pipet column packed with silica gel and 20% ethyl acetate in dichloromethane. Elution with the same solvent system was followed by pooling the fractions containing the aglycone **6**. The collected fractions were concentrated to a small volume (ca. 0.1 mL), and the concentrate taken up in methanol (1.0 mL). The yield of neocarzinostatin chromophore aglycone was determined by UV absorption using the extinction coefficient determined for neocarzinostatin chromophore (ε_{302} = 7040 M^{-1} cm^{-1}). By this method, the amount of neocarzinostatin chromophore aglycone (**6**) isolated was 3 x 10^{-4} mmol, or 22% of theoretical.

^{1}H NMR (400 MHz, C_6D_6) δ:	11.69 (s, 1H, C2" OH), 8.14 (d, 1H, *J* = 9.52 Hz, C4" H), 7.99 (br s, 1H, C8" H), 7.07 (d, 1H, *J* = 9.16 Hz, C3" H), 6.95 (br s, 1H, C6" H), 6.65 (br s, 1H, C12 H), 6.30 (t, 1H, *J* = 2.56 Hz, C11 H), 5.69 (br s, 1H, C8 H), 4.92 (m, 1H, C10 H), 4.90 (dd, 1H, *J* = 8.44, 5.48 Hz, C13 H), 4.62 (t, 1H, *J* = 8.80 Hz, C14 H), 4.39 (dd, 1H, *J* = 8.76, 5.12 Hz, C14 H), 4.24 (d, 1H, *J* = 5.16 Hz, OH), 4.06 (d, 1H, *J* = 1.44 Hz, C5 H), 3.85 (s, 3H, C7" OCH_3), 2.62 (s, 3H, C5" CH_3).
$[\alpha]_D^{20}$:	–58.90° (*c* 0.146, CH_3OH)
FTIR (CH_2Cl_2), cm^{-1}:	3684 (m, OH), 3624 (w, OH), 3060 (m), 2938 (m), 2178 (w, C≡C), 1820 (s, carbonate C=O), 1733 (m, ester C=O), 1614 (s), 1466 (m), 1413 (m), 1376 (m), 1309 (m), 1244 (m), 1203 (vs), 1082 (s), 1018 (s).
TLC (25% EtOAc in CH_2Cl_2), R*f*:	**120**: 0.49 (fluoresces under UV, anisaldehyde) **6**: 0.60 (UV, anisaldehyde)



138 79% **139**

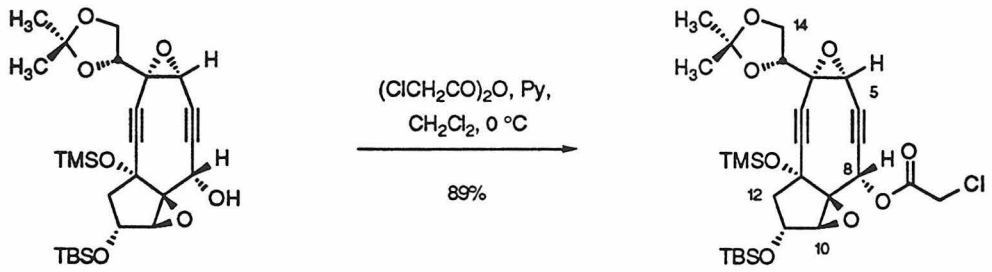
Cyclic alcohol **139** (improved procedure)

Lithium diphenyltetramethyldisilazide (1.78 mL of a 1.0 M solution in hexanes/THF, 1.78 mmol, 2.0 equiv) was added dropwise via syringe to a rapidly stirring suspension of epoxy aldehyde **138** (463 mg, 0.891 mmol, 1 equiv) and lithium chloride (1.89 g, 44.53 mmol, 50 equiv) in tetrahydrofuran (45 mL) at –78 °C. The reaction mixture was stirred at –78 °C for 5 min, and excess base was quenched by the addition of aqueous pH 7.2 phosphate buffer (20 mL). The reaction was warmed to 23 °C, the layers were separated, and the aqueous layer was further extracted with 1:1 ethyl acetate/hexanes (2 20-mL portions). The combined organics were washed with saturated aqueous sodium chloride (20 mL), dried over sodium sulfate and concentrated. Purification of the residue by flash column chromatography (20% ethyl acetate in hexanes) provided cyclic alcohol **139** (368 mg, 79%) as a yellow oil.

^{1}H NMR (400 MHz, C_6D_6) δ:	5.35 (d, 1H, *J* = 10.60 Hz, C8 H), 4.18 (d, 1H, *J* = 5.84 Hz, C11 H), 3.88 (dd, 1H, *J* = 8.76, 5.84 Hz, C13 H), 3.74 (dd, 1H, *J* = 8.40, 6.60 Hz, C14 H), 3.66 (s, 1H, C10 H), 2.65 (t, 1H, *J* = 6.20 Hz, C14 H), 3.18 (s, 1H, C5 H), 2.27 (dd, 1H, *J* = 14.28, 5.84 Hz, C12 βH), 1.93 (d, 1H, *J* = 14.28 Hz, C12 αH), 1.87 (d, 1H, *J* = 11.00 Hz, OH), 1.48 (s, 3H, $C(CH_3)_2$), 1.23 (s, 3H, $C(CH_3)_2$), 0.91 (s, 9H, $OSiC(CH_3)_3(CH_3)_2$), 0.36 (s, 9H, $OSi(CH_3)_3$), –0.023 (s, 6H, $OSiC(CH_3)_3(CH_3)_2$), –0.026 (s, 6H, $OSiC(CH_3)_3(CH_3)_2$).
^{13}C NMR (100 MHz, C_6D_6), δ:	100.7, 92.9, 88.3, 87.6, 86.7, 80.8, 75.1, 70.68, 66.8, 64.0, 61.8, 57.2, 52.4, 48.2, 26.3, 25.9, 25.5, 18.2, 1.8, –4.8.
$[\alpha]_D^{20}$:	+13.91° (*c* 1.51, C_6H_6)
FTIR (thin film), cm^{-1}:	3448 (m, OH), 2954 (s), 2860 (m), 2214 (w, C≡C), 1373 (m), 1252 (s), 1135 (s), 1075 (s), 953 (m), 843 (s).
HRMS:	Calc'd for $C_{26}H_{39}O_7Si_2$ $[M-H]^+$: 519.223436 Found: 519.222949

TLC (10% EtOAc in CH_2Cl_2), R*f*: **138**: 0.69 (anisaldehyde)

139: 0.60 (anisaldehyde)



139 **170**

Chloroacetate **170**

Chloroacetic anhydride (706 mg, 4.12 mmol, 5 equiv) was added in one portion to a solution of cyclic alcohol **139** (430 mg, 0.826 mmol, 1 equiv) and pyridine (0.688 mL, 653 mg, 8.26 mmol, 10 equiv) in dichloromethane (17 mL) at 0 °C. The resultant pale yellow solution was stirred at 0 °C for 10 minutes, then diluted with 1:1 ethyl acetate/hexanes (20 mL). The mixture was washed with water (20 mL) and saturated aqueous sodium chloride (20 mL). The organics were dried over sodium sulfate and concentrated. Purification of the residue by flash column chromatography (15% ethyl acetate in hexanes) provided chloroacetate ester **170** (440 mg, 89%) as a yellow oil.

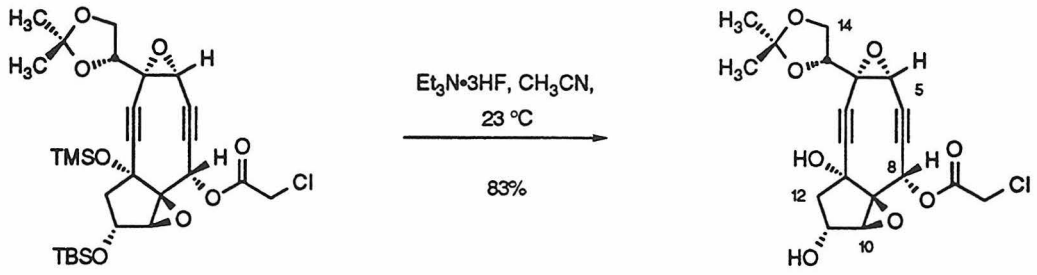
^{1}H NMR (400 MHz, C_6D_6) δ:	6.59 (s, 1H, C8 H), 4.22 (d, 1H, *J* = 5.88 Hz, C11 H), 3.83 (dd, 1H, *J* = 8.76, 5.84 Hz, C13 H), 3.80 (s, 1H, C10 H), 3.70 (dd, 1H, *J* = 8.44, 6.56 Hz, C14 H), 3.62 (t, 1H, *J* = 6.24 Hz, C14 H), 3.17 (abq, 2H, Δν = 14.32 Hz, *J* = 14.64 Hz, CH_2Cl), 3.06 (s, 1H, C5 H), 2.30 (dd, 1H, *J* = 14.28, 5.88 Hz, C12 βH), 1.96 (d, 1H, *J* = 14.28 Hz, C12 αH), 1.48 (s, 3H, $C(CH_3)_2$), 1.24 (s, 3H, $C(CH_3)_2$), 0.92 (s, 9H, $OSiC(CH_3)_3(CH_3)_2$), 0.38 (s, 9H, $OSi(CH_3)_3$), 0.012 (s, 3H, $OSiC(CH_3)_3(CH_3)_2$), –0.012 (s, 3H, $OSiC(CH_3)_3(CH_3)_2$).
^{13}C NMR (100 MHz, C_6D_6), δ:	165.2, 110.7, 92.1, 89.6, 87.5, 84.1, 79.2, 75.4, 75.0, 70.9, 66.6, 64.7, 61.5, 59.8, 52.2, 48.0, 40.0, 26.3, 25.9, 25.5, 18.1, 1.7, –4.7, –4.8.
$[\alpha]_D^{20}$:	–55.14° (*c* 0.37, C_6H_6)
FTIR (thin film), cm^{-1}:	2954 (m), 2895 (m), 1775 (m, C=O), 1372 (w), 1253 (s), 1216 (m), 1138 (s), 1074 (s), 955 (m), 843 (s).

HRMS (FAB): Calc'd for $C_{28}H_{40}ClO_8Si_2$ $[M-H]^+$: 595.195028

Found: 595.196716

TLC (30% EtOAc in Hexanes), R*f*: **139**: 0.37 (anisaldehyde)

170: 0.46 (anisaldehyde)

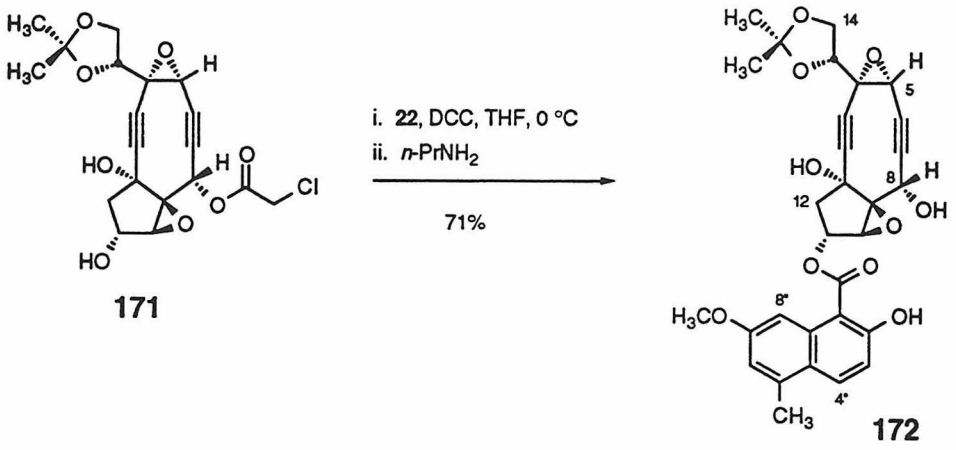


170 171

Diol **171**

Triethylamine trihydrofluoride (0.668 mL, 661 mg, 4.10 mmol, 10 equiv) was added via syringe to a solution of chloroacetate ester **170** (245 mg, 0.410 mmol, 1 equiv) in acetonitrile (8 mL) at 23 °C. The reaction was maintained at 23 °C for an additional 2 h, and then partitioned between 1:1 ethyl acetate/hexanes (20 mL) and water (20 mL). The aqueous layer was further extracted with 1:1 ethyl acetate/hexanes (2 15-mL portions) and the combined organics were washed with saturated aqueous sodium chloride (20 mL), dried over sodium sulfate and concentrated. Purification of the residue by flash column chromatography (50% ethyl acetate in hexanes) afforded diol **171** (140 mg, 83%) as a white foam.

^{1}H NMR (400 MHz, CD_2Cl_2) δ:	6.31 (s, 1H, C8 H), 4.40 (d, 1H, *J* = 5.16 Hz, C11 H), 4.15 (dd, 1H, *J* = 8.44, 6.24 Hz, C13 H), 4.13 (s, 2H, CH_2Cl), 4.03 (t, 1H, *J* = 6.24 Hz, C14 H), 3.98 (dd, 1H, *J* = 8.44, 5.12 Hz, C14 H), 3.70 (s, 1H, C10 H), 3.63 (s, 1H, C5 H), 2.16 (dd, 1H, *J* = 15.00, 5.12 Hz, C12 βH), 1.98 (d, 1H, *J* = 14.68 Hz, C12 αH), 1.45 (s, 3H, $C(CH_3)_2$), 1.33 (s, 3H, $C(CH_3)_2$).
^{13}C NMR (100 MHz, C_6D_6), δ:	166.6, 111.0, 91.3, 89.8, 87.2, 84.4, 77.5, 74.8, 74.3, 70.4, 66.5, 63.3, 61.7, 59.8, 52.6, 45.1, 40.6, 26.3, 25.4.
$[\alpha]_D^{20}$:	–32.43° (*c* 1.03, C_6H_6)
FTIR (thin film), cm^{-1}:	3440 (s, OH), 2989 (m), 2951 (m), 2222 (w, C≡C), 1767 (s, C=O), 1381 (m), 1256 (m), 1217 (m), 1150 (s), 1072 (s), 952 (m), 848 (m).
TLC (70% EtOAc in Hexanes), R*f*:	**170**: 0.74 (anisaldehyde) **171**: 0.36 (anisaldehyde)

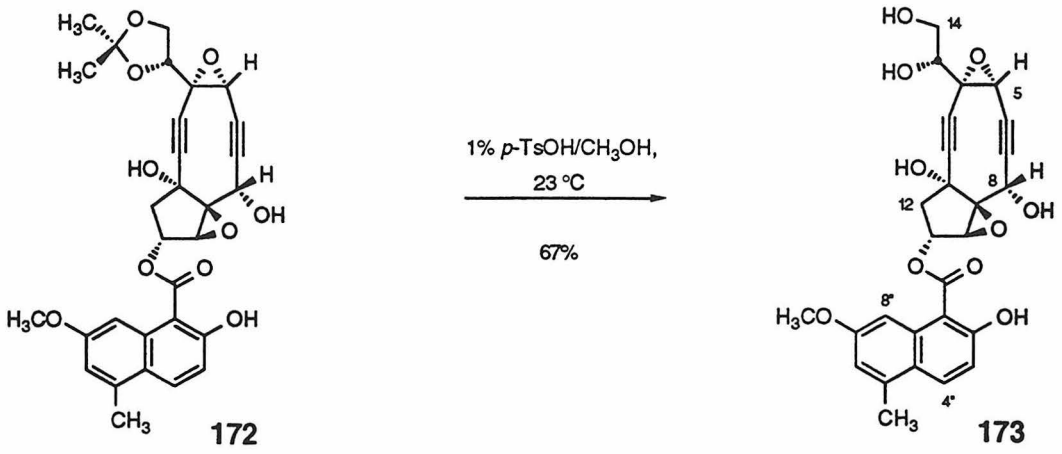


Naphthoate ester **172**

Dicyclohexylcarbodiimide (414 mg, 2.01 mmol, 5 equiv) was added in one portion to a solution of diol **171** (165 mg, 0.402 mmol, 1 equiv) and naphthoate **22** (280 mg, 1.20 mmol, 3 equiv) in tetrahydrofuran (8 mL) at 0 °C. The solution was maintained at this temperature for 1 h, and precipitated dicyclohexylurea was removed by filtration, and the filtrate concentrated in vacuo. Purification of the residue by flash column chromatography (10% ethyl acetate in hexanes grading to 50% ethyl acetate in hexanes) afforded naphthoate ester and naphthoate diester (194 mg) as a 6:1 mixture as determined by integration of the ^{1}H NMR spectrum (158 mg monoester, 71%, and 36 mg diester, 12%). The monoester could be isolated cleanly as a pale yellow film after a second chromatography (10% ethyl acetate in hexanes grading to 50% ethyl acetate in hexanes), but purification could be more easily accomplished subsequent to the next reaction.

^{1}H NMR (400 MHz, DMSO-d_6) δ:	10.56 (s, 1H, C2" OH), 7.94 (d, 1H, *J* = 9.16 Hz, C4" H), 7.18 (d, 1H, *J* = 2.16 Hz, C8" H), 7.02 (d, 1H, *J* = 9.16 Hz, C3" H), 6.87 (s, 1H, C6" H), 6.42 (s, 1H, C11 H), 5.52 (d, 1H, *J* = 6.24 Hz, C8 H), 5.15 (br d, 1H, *J* = 3.64 Hz, OH), 4.09 (dd, 1H, *J* = 8.80, 6.96 Hz, C13 H), 4.02 (dd, 1H, *J* = 6.96, 4.40 Hz, C14 H), 3.90 (s, 2H, C5, C10 H), 3.80 (s, 3H, C7: OCH_3), 3.76 (dd, 1H, *J* = 8.76, 3.96 Hz, C14 H), 2.54 (s, 3H, C5" H), 2.24 (dd, 1H, *J* = 15.40, 6.24 Hz, C12 βH), 2.13 (d, 1H, *J* = 15.36 Hz, C12 αH), 1.41 (s, 3H, $C(CH_3)_2$), 1.27 (s, 3H, $C(CH_3)_2$).
^{13}C NMR (100 MHz, DMSO-d_6), δ:	168.0, 158.4, 156.5, 136.5, 133.0, 129.4, 122.0, 116.5, 115.2, 110.3, 109.8, 101.1, 92.7, 88.8, 85.5, 85.2, 80.2, 74.4, 72.3, 72.0, 67.8, 61.0, 60.5, 55.2, 43.1, 26.0, 25.0, 19.1.
$[\alpha]_D^{20}$:	+32.58° (*c* 0.85, CH_3OH)
FTIR (thin film), cm^{-1}:	3201 (m, OH), 2979 (m), 2931 (m), 1639 (m), 1614 (s, C=O), 1411 (m), 1375 (m), 1250 (m), 1206 (vs), 1024 (s), 847 (m) cm^{-1}

HRMS (FAB):	Calc'd for $C_{30}H_{29}O_{10}$ $[MH]^+$: 549.1761 Found: 549.1755
TLC (50% EtOAc in Hexanes), R*f*:	**171**: 0.55 (anisaldehyde) **172**: 0.40 (fluoresces under UV, anisaldehyde)



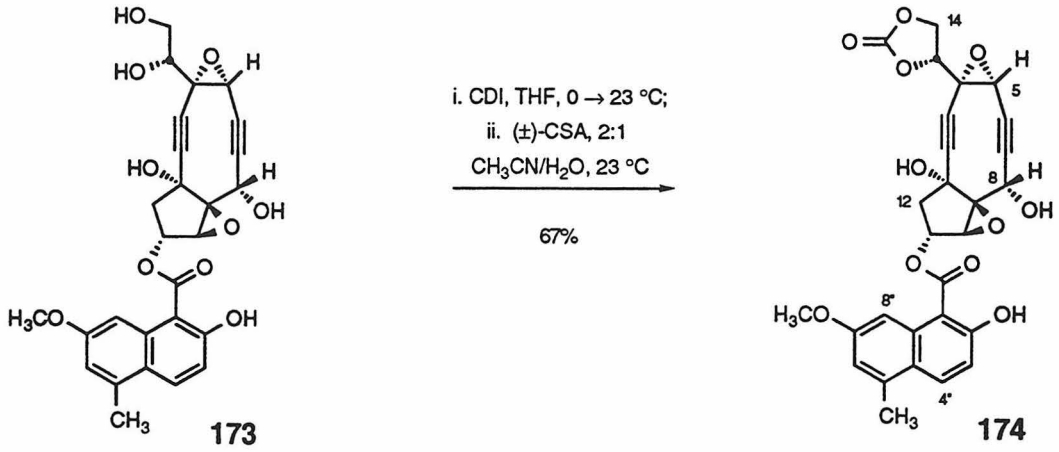
172 173

Pentaol **173**

p-Toluenesulfonic acid (30 mg, 1% w/v relative to CH_3OH) was added in one portion to a solution of ester **172** (33 mg, 0.0602 mmol, 1 equiv) in methanol (3 mL). The resultant yellow solution was stirred at 23 °C for an additional 1.5 h and then diluted with ethyl acetate (5 mL). The reaction mixture was washed with water (2 5-mL portions) and saturated aqueous sodium chloride (5 mL), dried over sodium sulfate, and concentrated in vacuo. Purification of the residue by flash column chromatography (2% methanol in dichloromethane grading to 10% methanol in dichloromethane) afforded the pentaol **173** (20 mg, 67%) as a colorless film as well as recovered ester (7 mg, 23%).

^{1}H NMR (400 MHz, CD_3CN) δ:	8.05 (d, 1H, *J* = 9.12 Hz, C4" H), 8.01 (s, 1H, C8" H), 6.97 (d, 1H, *J* = 9.16 Hz, C3" H), 6.86 (s, 1H, C6" H), 5.60 (d, 1H, *J* = 5.88 Hz, C11 H), 5.20 (s, 1H, C8 H), 3.99 (s, 1H, C10 H), 3.84 (s, 3H, C7" OCH_3), 3.68 (s, 1H, C5 H), 3.67-3.49 (complex, 4H, C13, C14 H, OH), 3.26 (s, 1H, OH), 2.55 (s, 3H, C5" CH_3), 2.37 (dd, 1H, *J* = 15.76, 5.88 Hz, C12 βH), 2.25 (d, 1H, *J* = 15.76 Hz, C12 αH).
^{13}C NMR (100 MHz, CD_3CN), δ:	171.6, 164.3, 160.6, 138.2, 135.2, 133.7, 117.8, 116.6, 106.0, 104.3, 92.1, 88.1, 87.7, 87.5, 80.7, 74.0, 71.5, 64.0, 62.3, 61.5, 61.0, 57.0, 56.1, 52.3, 44.0, 19.9, 14.5.
$[\alpha]_D^{20}$:	+44.99° (*c* 1.067, CH_3CN)
FTIR (thin film), cm^{-1}:	3382 (m, OH), 2931 (m), 1614 (s, C=O), 1410 (m), 1378 (m), 1307 (m), 1246 (m), 1206 (s), 1092 (m).
HRMS (FAB):	Calc'd for $C_{27}H_{25}O_{10}$ $[MH]^+$: 509.1448 Found: 509.1443

TLC (70% EtOAc in Hexanes), R*f*:	**172**: 0.66 (fluoresces under UV, anisaldehyde)
	173: 0.17 (fluoresces under UV, anisaldehyde)



173 174

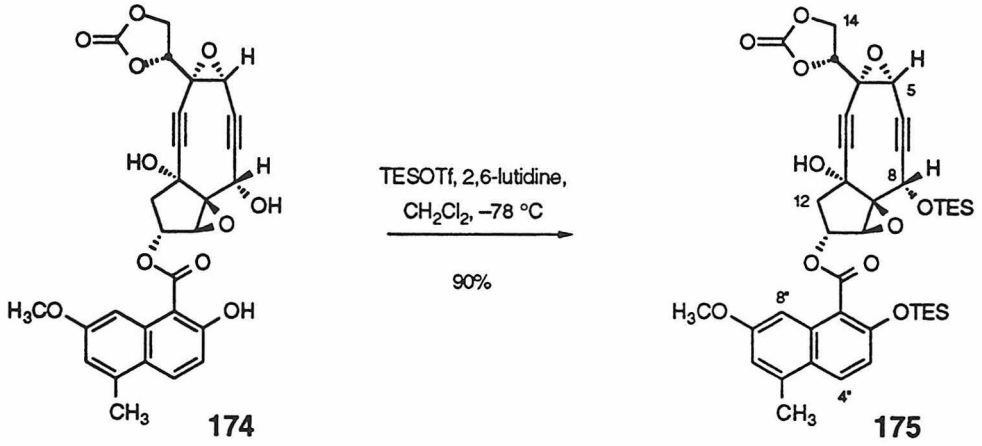
Carbonate **174**

Carbonyldiimidazole (19 mg, 0.011 mmol, 1 equiv) was added in one portion to a solution of pentaol **173** (58 mg, 0.011 mmol, 1 equiv) in dry THF (3.8 mL) at 0 °C. The resultant solution was stirred at 0 °C for 20 min, and then another portion of carbonyldiimidazole (19 mg, 0.011 mmol, 1 equiv) was added. The reaction mixture was maintained at 0 °C for an additional 10 min, then warmed to 23 °C and held at that temperature for 2 h. The reaction mixture was then diluted with ethyl acetate (10 mL) and washed with water (2 5-mL portions) and saturated aqueous sodium chloride (5 mL). The organics were dried over sodium sulfate and concentrated. The residue was then dissolved in 2:1 acetonitrile/water (2 mL). (±)-Camphorsulfonic acid (20 mg) was added in one portion, and the reaction mixture stirred at 23 °C for 30 min. The reaction mixture was then diluted with ethyl acetate (15 mL) and washed with water (3 5-mL portions) and saturated aqueous sodium chloride (5 mL). The organics were dried over sodium sulfate and concentrated. Purification of the residue by flash column chromatography (40% ethyl

acetate in hexanes grading to 100% ethyl acetate) provided the carbonate **174** (41 mg, 67%) as a colorless film as well as recovered pentaol **173** (17 mg, 29%).

^{1}H NMR (400 MHz, CD_3CN) δ:	8.07 (d, 1H, *J* = 9.12 Hz, C4" H), 8.01 (s, 1H, C8" H), 6.99 (d, 1H, *J* = 9.16 Hz, C3" H), 6.88 (s, 1H, C6" H), 5.63 (d, 1H, *J* = 5.84 Hz, C11 H), 5.23 (s, 1H, C8 H), 4.78 (dd, 1H, *J* = 8.40, 5.48 Hz, C13 H), 4.56 (t, 1H, *J* = 8.40 Hz, C14 H), 4.30 (dd, 1H, *J* = 8.80, 5.16 Hz, C14 H), 4.03 (s, 1H, C10 H), 3.85 (s, 3H, C7" OCH_3), 3.84 (s, 1H, C5 H), 2.56 (s, 3H, C5" CH_3), 2.38 (dd, 1H, *J* = 15.36, 5.48 Hz, C12 βH), 2.29 (d, 1H, *J* = 15.36 Hz, C12 αH), 2.18 (br s, 1H, OH)
^{13}C NMR (100 MHz, CD_3CN), δ:	171.6, 164.4, 160.6, 155.1, 138.2, 135.1, 133.7, 123.9, 117.8, 116.6, 105.9, 104.3, 94.4, 89.3, 86.0, 84.8, 80.8, 75.4, 73.9, 73.8, 67.1, 61.7, 61.1, 56.9, 56.1, 53.6, 43.9, 19.9.
$[\alpha]_D^{20}$:	+18.22° (*c* 0.933, CH_3CN)

FTIR (thin film), cm^{-1}:	3410 (m, OH), 2926 (m), 1817 (s carbonate C=O), 1641 (s), 1615 (s, ester C=O), 1412 (m), 1376 (m), 1310 (m), 1250 (m), 1206 (s), 1081 (s), 962 (w), 847 (m).
HRMS (FAB):	Calc'd for $C_{28}H_{23}O_{11}$ $[MH]^+$: 535.1240 Found: 535.1234
TLC (70% EtOAc in Hexanes), R*f*:	**173**: 0.14 (fluoresces under UV, anisaldehyde) **174**: 0.46 (fluoresces under UV, anisaldehyde)



Bis-TES ether **175**

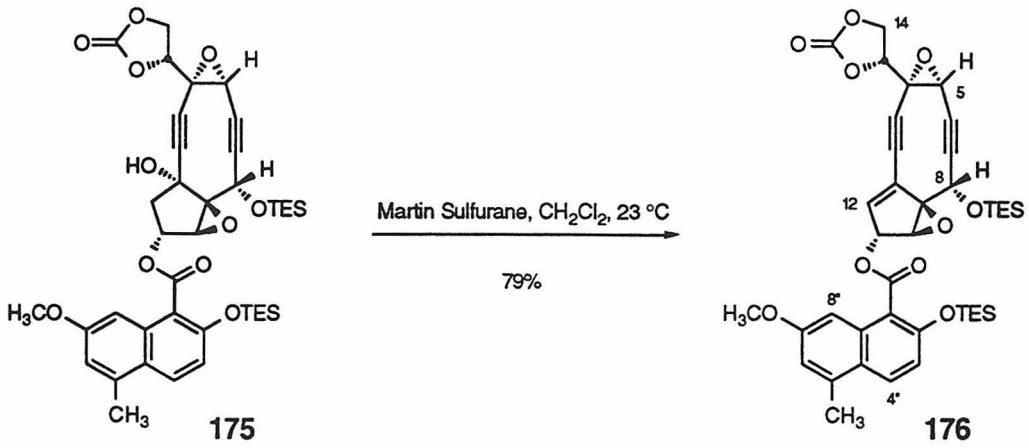
2,6-Lutidine (0.229 mL, 210 mg, 1.96 mmol, 12 equiv) and triethylsilyl trifluoromethanesulfonate (0.185 mL, 216 mg, 0.818 mmol, 5 equiv) were added sequentially via syringe to a solution of carbonate **174** (87.5 mg, 0.163 mmol, 1 equiv) in dichloromethane (8 mL) at –78 °C. The resultant solution was stirred at –78 °C for 10 min, and then excess triethylsilyl trifluoromethanesulfonate was quenched by the addition of triethylamine (1 mL) and methanol (1 mL). The reaction mixture was warmed to 23 °C, diluted with 1:1 ethyl acetate/hexanes (25 mL), and washed with water (10 mL) and saturated aqueous sodium chloride (10 mL). The organics were dried over sodium sulfate and were concentrated. Purification of the residue by flash column chromatography (20% ethyl acetate in hexanes grading to 50% ethyl acetate in hexanes) afforded bis-TES ether **175** (112 mg, 90%) as a colorless oil.

^{1}H NMR (400 MHz, C_6D_6) δ: 7.57 (d, 1H, *J* = 9.16 Hz, C4" H), 7.23 (s, 1H, C8" H), 6.98 (s, 1H, C6" H), 6.86 (d, 1H, *J* = 9.12 Hz, C3" H), 5.73 (d, 1H, *J* = 5.88 Hz, C11 H), 5.57 (s, 1H, C8 H), 4.20 (s, 1H, C10 H), 3.60 (s, 3H, C7" OCH_3), 3.52 (dd, 1H, *J* = 8.44, 5.84 Hz, C13 H), 3.47 (dd, 1H, *J* = 8.04, 5.84 Hz, C14 H), 3.30 (t, 1H, *J* = 8.04 Hz, C14 H), 2.77 (s, 1H, C5 H), 2.49 (dd, 1H, *J* = 15.76, 5.84 Hz, C12 βH), 2.30 (s, 3H, C5" CH_3), 2.28 (d, 1H, *J* = 15.76 Hz, C12 αH), 1.04 (t, 9H, *J* = 8.04 Hz, $OSi(CH_2CH_3)_3$), 0.97 (t, 9H, *J* = 8.04 Hz, $OSi(CH_2CH_3)_3$), 0.81 (m, 6H, $OSi(CH_2CH_3)_3$), 0.64 (m, 6H, $OSi(CH_2CH_3)_3$).

^{13}C NMR (100 MHz, C_6D_6), δ: 167.4, 159.3, 153.4, 152.0, 136.6, 133.7, 124.1, 119.7, 118.2, 117.3, 101.3, 93.9, 89.3, 85.9, 84.2, 80.7, 74.0, 73.6, 72.7, 72.6, 65.3, 65.2, 61.7, 61.6, 60.2, 57.5, 57.4, 55.1, 54.9, 54.8, 52.7, 44.2, 19.3, 7.6, 5.9, 5.2, 1.4.

$[\alpha]_D^{20}$: +8.43° (*c* 1.07, C_6H_6)

FTIR (thin film), cm^{-1}:	3463 (m, OH), 2956 (s), 2877 (m), 2214 (w, C≡C), 1821 (s, carbonate C=O), 1728 (m, ester C=O), 1620 (m), 1151 (m), 1465 (m), 1410 (m), 1264 (s), 1205 (s), 1150 (s), 1082 (s), 859 (m).
HRMS (FAB):	Calc'd for $C_{40}H_{51}O_{11}Si_2$ $[MH]^+$: 763.2970 Found: 763.2968
TLC (50% EtOAc in Hexanes), R*f*:	**174**: 0.32 (fluoresces under UV, anisaldehyde) **175**: 0.64 (fluoresces under UV, anisaldehyde)

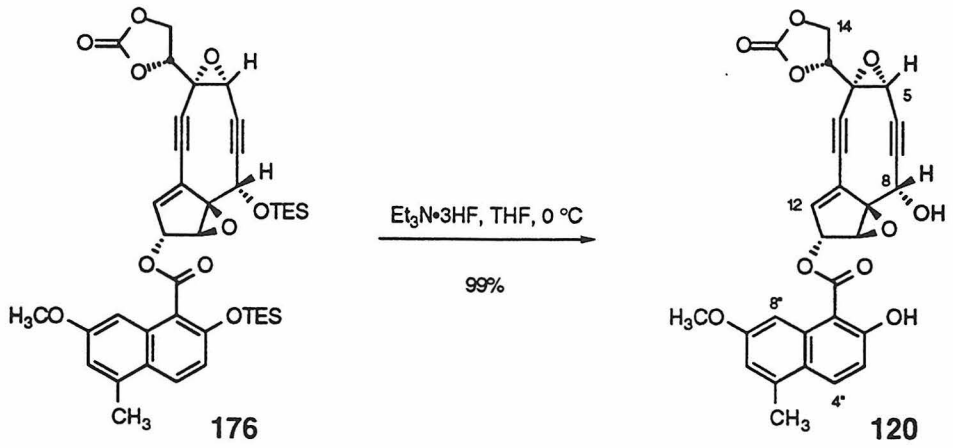


Olefin **176**

A solution of bis-TES ether **175** (17.6 mg, 0.0231 mmol, 1 equiv) in dichloromethane (1.2 mL) was added via cannula to Martin sulfurane dehydrating agent (78 mg, 0.12 mmol, 5 equiv). The resultant pale yellow solution was stirred at 23 °C for 1.5 h, during which time the solution darkened to light brown. The volatiles were removed in vacuo and the residue was purified by flash column chromatography (dichloromethane) to provide olefin **176** (13.6 mg, 79%) as a pale yellow oil that darkened upon standing.

^{1}H NMR (400 MHz, C_6D_6) δ:	7.60 (d, 1H, *J* = 9.16 Hz, C4" H), 7.21 (s, 1H, C8 " H), 6.99 (s, 1H, C6" H), 6.89 (d, 1H, *J* = 9.16 Hz, C3" H), 6.23 (t, 1H, *J* = 2.20 Hz, C12 H), 6.01 (d, 1H, *J* = 1.80 Hz, C11 H), 5.07 (s, 1H, C8 H), 4.18 (d, 1H, *J* = 2.20 Hz, C10 H), 3.52 (s, 3H, C7" OCH_3), 3.46 (m, 2H, C13, C14 H), 3.25 (m, 1H, C14 H), 2.77 (s, 1H, C5 H), 2.30 (s, 3H, C5" CH_3), 1.03 (m, 18 H, 2 x $OSi(CH_2CH_3)_3$), 0.80 (m, 6H, $OSi(CH_2CH_3)_3$), 0.68 (m, 6H, $OSi(CH_2CH_3)_3$).
^{13}C NMR (100 MHz, C_6D_6), δ:	167.4, 159.4, 152.1, 139.7, 139.6, 136.7, 133.8, 131.1, 124.1, 119.4, 118.3, 117.2, 101.2, 97.9, 89.9, 87.6, 86.6, 77.2, 74.9, 74.8, 73.1, 65.5, 65.4, 60.5, 60.3, 58.4, 58.3, 54.8, 54.7, 52.3, 52.2, 30.2, 19.3, 6.9, 5.7, 5.4, 1.4.
$[\alpha]_D^{20}$:	–14.99° (*c* 1.467, C_6H_6)
FTIR (thin film), cm^{-1}:	2922 (s), 1822 (s, carbonate C=O), 1735 (m, ester C=O), 1620 (m), 1511 (m), 1464 (m), 1264 (s), 1150 (s), 1079 (s), 1037 (m), 863 (m).

HRMS (FAB):	Calc'd for $C_{40}H_{49}O_{10}Si_2$ $[MH]^+$: 745.2864 Found: 745.2869
TLC (8% EtOAc in CH_2Cl_2), R*f*:	**175**: 0.49 (fluoresces under UV, anisaldehyde) **176**.: 0.61 (fluoresces under UV, anisaldehyde)



Epoxy alcohol **120**

Triethylamine trihydrofluoride (0.015 mL, 15 mg, 0.091 mmol, 5 equiv) was added via syringe to a solution of olefin **176** (13.6 mg, 0.0183 mmol, 1 equiv) in THF (0.91 mL) at 0 °C. The resultant yellow solution was stirred at 0 °C for 1 h, and then diluted with ethyl acetate (10 mL). The reaction mixture was washed with water (3 5-mL portions) and saturated aqueous sodium chloride (5 mL), dried over sodium sulfate and concentrated. Purification of the residue by flash column chromatography (2% methanol in dichloromethane) provided epoxy alcohol **120** (13.5 mg, quantitative) as a pale yellow film.

^{1}H NMR (400 MHz, C_6D_6) δ:	12.57 (s, 1H, C2" OH), 7.98 (s, 1H, C8" H), 7.70 (d, 1H, *J* = 9.16 Hz, C4" H), 7.15 (d, 1H, *J* = 9.52 Hz, C3" H), 6.98 (s, 1H, C6" H), 5.69 (t, 1H, *J* = 2.56 Hz, C12 H), 5.47 (d, 1H, *J* = 2.56 Hz, C11 H), 4.40 (d, 1H, *J* = 10.28 Hz, C8 H), 3.64 (d, 1H, *J* = 2.56 Hz, C10 H), 3.53 (dd, 1H, *J* = 8.80, 5.48 Hz, C13 H), 3.50 (s, 3H, C7" OCH_3), 3.34 (dd, 1H, *J* = 8.04, 5.48 Hz, C14 H), 3.23 (t, 1H, *J* = 8.40 Hz, C14 H), 2.77 (s, 1H, C5 H), 2.24 (s, 3H, C5" CH_3), 1.84 (d, 1H, *J* = 10.28 Hz, OH).
^{13}C NMR (100 MHz, CD_3CN), δ:	171.8, 164.3, 160.5, 155.0, 140.1, 138.4, 134.9, 134.0, 131.7, 123.9, 117.7, 116.4, 105.7, 104.4, 99.1, 90.2, 86.9, 86.2, 77.6, 75.9, 75.3, 67.1, 61.8, 61.2, 57.6, 57.2, 53.5, 19.9.
$[\alpha]_D^{20}$:	–50.00° (*c* 0.20, C_6H_6)
FTIR (CH_2Cl_2), cm^{-1}:	3684 (m, OH), 3070 (m), 3036 (m), 2957 (m), 1823 (s, C=O), 1732 (w), 1649 (w), 1611 (m), 1478 (s), 1199 (m), 1035 (m).

HRMS (FAB): Calc'd for $C_{28}H_{21}O_{10}$ $[MH]^+$: 517.1135

Found: 517.1137

Enantioselective Synthesis of Neocarzinostatin Chromophore Aglycone

Volume II

Thesis by

Marlys Hammond

In Partial Fulfillment of the Requirements

for the Degree of

Doctor of Philosophy

California Institute of Technology

Pasadena, California

1997

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Volume II

List of Schemes, Figures, and Tables

Chapter 5

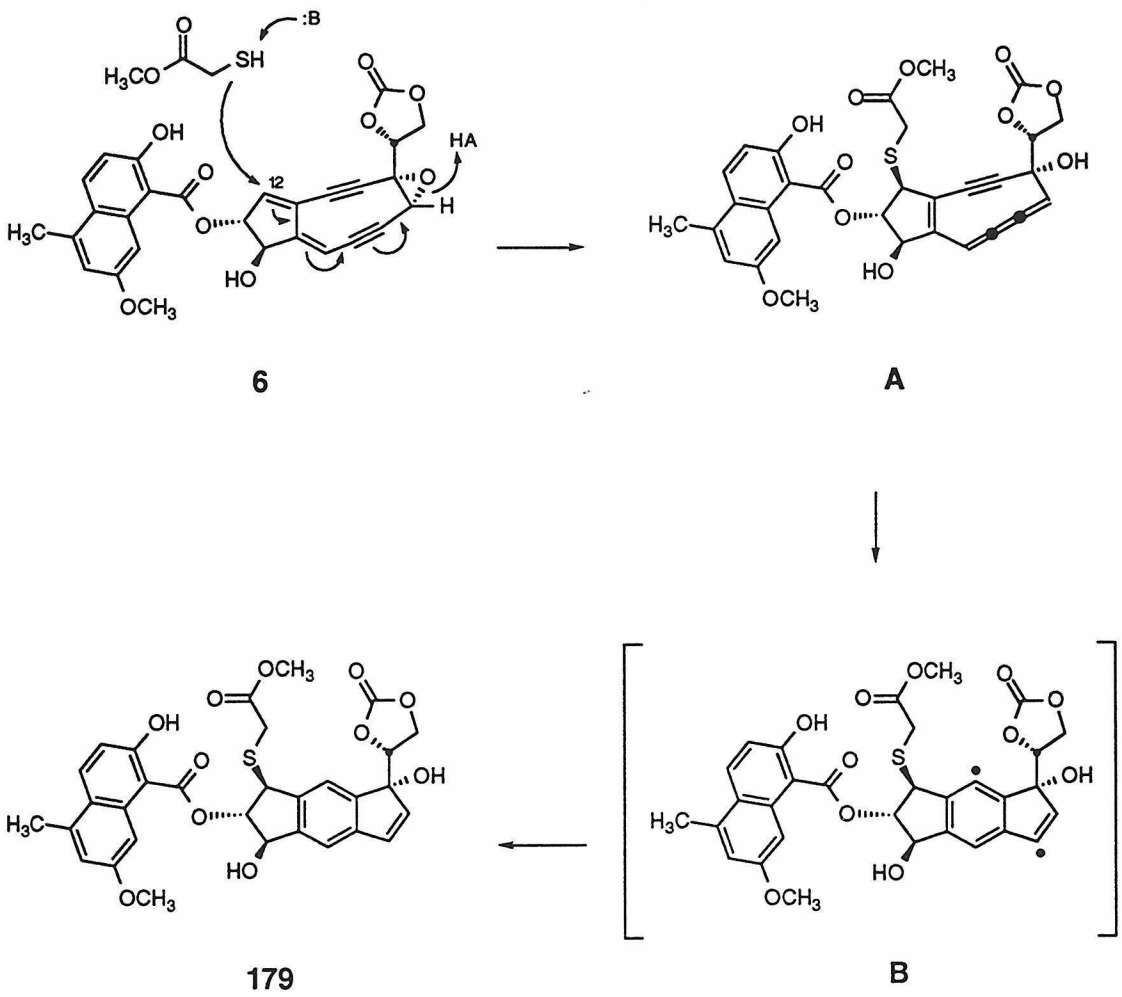
Thiol Addition Chemistry and DNA Cleavage Behavior of Neocarzinostatin Chromophore Aglycone

Thiol Addition Chemistry

With the development of a concise route to enantiomerically pure **6**, the course of these studies shifted next to the investigation of the thiol addition chemistry of **6**. As with the epoxy bicyclononadienediyne **5**[13] and the chromophore **1**[9c] (Ch. 1), initial thiol addition experiments were conducted with a large excess of methyl thioglycolate (0.3 M) and 1,4-cyclohexadiene (0.6 M) in a mixture of THF and acetic acid (9:1) at 23 °C. It was soon noted that the aglycone **6** was not stable in the 9:1 THF/acetic acid solvent mixture, as extensive decomposition of the substrate was noted prior to the addition of methyl thioglycolate (TLC analysis). The nature of this decomposition was not determined and no characterizable products were isolated from the reaction mixtures under these conditions; however, it was apparent that acetic acid, known to assist in the stabilization of the parent chromophore **1**, was in fact hastening the decomposition of the aglycone **6**. Consequently, further thiol addition studies with **6** were conducted with the omission of acetic acid from the reaction medium.

In addition to changing the reaction solvent, further investigations were carried out in the presence of the radical inhibitor BHMS,[74] added to solutions of **6** immediately subsequent to chromatographic purification. The inhibitor was found to prolong the lifetime of **6** in solution and during the repeated concentration-dilution processes necessary for the transfer of **6** from the flash column chromatographic eluant solution to the thiol addition reaction conditions. Addition of a deoxygenated solution of methyl thioglycolate (final concentration 0.5 M) to a deoxygenated solution of **6** and 1,4-cyclohexadiene (final concentration 1.0 M) in THF at 23 °C was followed by incubation at 23 °C for 3 hours. Removal of the volatiles in vacuo and ^{1}H NMR analysis of the crude reaction mixture showed no evidence for the formation of the expected cycloaromatized thiol adduct **179** (Scheme XXV). In fact, the only identifiable signals in the spectrum were those corresponding to unreacted aglycone **6**. Repetition of the reaction in the presence of

Scheme XXV

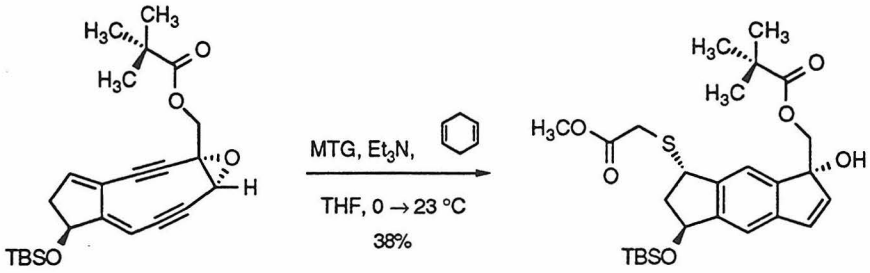


6 A

B 179

triethylamine (0.5 M, equimolar with MTG) followed by removal of volatiles after 55 minutes and ^{1}H NMR analysis of the crude reaction mixture this time provided spectroscopic evidence for the formation of the adduct **179**. Purification of the reaction mixture by flash column chromatography proved to be difficult and appeared to be complicated by the instability of the adduct **179**, which may be prone to air oxidation. A superior purification was achieved using reverse-phase HPLC (40% 10 mM aqueous ammonium acetate (pH 5.5)/60% acetonitrile), keeping the crude reaction mixture and column eluant under an argon atmosphere.[113] In this manner, the thiol adduct **179** was obtained in ≥90% purity (^{1}H NMR analysis).

The ^{1}H NMR data for the adduct **179** showed a remarkable homology with that of the methyl thioglycolate adducts **4** (Ch. 1) and **180** (from neocarzinostatin chromophore (**1**) and the model epoxydienediyne **5**, respectively) (Table 3). The trans relative stereochemistry between the C-12 thioether and C-11 naphthoate ester groups of the adduct **179** was assigned based on the ^{1}H-^{1}H coupling constant between these two centers, and was in full accord with the stereochemistry observed in the adduct **4**. Electrospray mass spectral analysis of the cycloaromatized product **179** provided peaks corresponding to adducts of **179** with both sodium and potassium.[108]



5 **180**

The yield for the formation of thiol adduct **179** was determined to be 13% by reverse-phase HPLC using 2,5-dimethoxybenzyl alcohol as an internal standard. Interestingly, when two parallel thiol addition reactions were conducted, one in the

presence of triethylamine and one in the absence of triethylamine, both showed complete conversion to the thiol adduct **179** within 35 minutes by rp-HPLC analysis. However, after incubation of both reactions at 23 °C for 1 hour, removal of volatiles, and repeat rp-HPLC analysis, the reaction conducted in the presence of triethylamine showed complete conversion to the thiol adduct **179**, while the reaction conducted in the absence of triethylamine showed no indication of formation of adduct **179**, and in fact 58% of the starting aglycone **6** remained (vide infra).

The formation of the indacene **179** is believed to occur via the pathway **6** → **A** → **B** → **179** (Scheme XXV), in a manner analogous to that proposed for the formation of adduct **4** from the chromophore **1** (Ch. 1, Scheme I).[8] In addition, the thiol addition chemistry of **6** is fully consistent with the earlier findings regarding the thiol addition characteristics displayed by the model epoxydienediyne **5**.[13] Both **5** and **6** failed to add MTG in the absence of an added external base. In fact, the epoxy cyclononadiyne **5** failed to add MTG up to a temperature of 60 °C (^{1}H NMR analysis), a temperature at which significant decomposition of **5** ensued.[13] To contrast this behavior, the chromophore **1** undergoes facile thiol addition at –70 °C in the absence of added base.[8b] In the presence of added triethylamine (equimolar to MTG), both **5** and **6** undergo addition of MTG at 23 °C to provide the cycloaromatized indacenes **180** (38%)[13] and **179** (13%), respectively. The initial misleading rp-HPLC analysis of the reaction between MTG and **6** in the absence of triethylamine was presumably the result of the buffer used in the HPLC mobile phase (40% pH 5.5 aqueous ammonium acetate (10 mM)/60% acetonitrile) catalyzing the addition of methyl thioglycolate into **6**, as evidenced by the reappearance of the aglycone **6** upon removal of the excess MTG.

The above results lend further support to the mechanistic postulate implicating the participation of the aminoglycoside as an internal base in the thiol activation of the chromophore **1**.[13] The positioning of the sugar residue in the crystal structure of holo-NCS such that the distance between the nitrogen of the aminoglycoside and the C-12

Adduct (Solvent)	**4** ($CDCl_3$)	**179** (CD_3CN)	**180** ($CDCl_3$)
C2	7.71 (s)	7.57 (s)	7.40 (s)
C5	6.31 (d, J = 5.81)	6.26 (d, J = 5.84)	6.33 (d, J = 5.86)
C6	6.95 (d, J = 5.48)	6.92 (d, J = 5.88)	6.70 (d, J = 5.86)
C8	7.23 (s)	7.35 (s)	7.12 (s)
C10	5.26 (s)	5.34 (br m)	5.39 (m)
C11	5.83 (s)	5.75 (t, J = 3.32)	2.5 (m)
C12	4.63 (s)	4.60 (d, J = 3.28)	4.52 (d, J = 6.10)
C13	4.86 (dd, J = 8.56, 6.16)	4.67 (dd, J = 8.44, 5.52)	–
C14	4.43 (dd, J = 8.90, 8.55)	4.43 (t, J = 9.16)	–
C14	4.16 (dd, J = 8.89, 6.16)	4.27 (dd, J = 8.76, 5.84)	–
C3"	7.03 (d, J = 9.24)	7.04 (d, J = 9.16)	–
C4"	8.03 (d, J = 9.23)	8.10 (d, J = 9.53)	–
C5"	2.57 (s)	2.57 (s)	–
C6"	6.78 (br s)	6.84 (br s)	–
C7"	3.76 (s)	3.59 (s)	–
C8"	7.53 (br s)	7.78 (br s)	–
SCH_2	3.54 (abq, J = 15.14, $\Delta\nu$ = 78.55)	3.54 (abq, J = 15.36, $\Delta\nu$ = 46.97)	3.22 (abq, J = 14.90, $\Delta\nu$ = 13.02)
CO_2CH_3	3.32 (s)	3.48 (s)	3.72 (s)

Table 3. Comparison of ^1H NMR Data for Thiol Adducts **4**, **179**, and **180**.

carbon of **1** is ~5Å, or approximately the van der Waals diameter of a sulfur atom, indicating that the sugar residue is suitably disposed for this type of assistance. It should be noted, however, that the C-12 position remains the preferred site of thiol addition even in the absence of the aminoglycoside, as the C-12 thiol adducts **179** and **180** were the major products obtained from the reactions of **5** and **6**, respectively, with MTG.

DNA Cleavage by Neocarzinostatin Chromophore Aglycone

The efficacy of neocarzinostatin chromophore aglycone (**6**) in the cleavage of single-stranded DNA relative to that of the parent neocarzinostatin chromophore (**1**) was evaluated in this group by Dr. M. E. Kort. The results are briefly summarized below.[109]

The DNA cleavage by **6** and the cofactor methyl thioglycolate (MTG) was evaluated using a 3′-^{32}P-labeled 193-base pair restriction fragment (*Eco* RI/*Ssp* I) from plasmid pBR322, and results are given in Figure 4. The aglycone **6** displayed essentially the same relative cleavage pattern as that of the chromophore **1**, but the observed efficiency of **6** relative to **1** was markedly lower. Cleavage reactions conducted with the same concentration of drug showed a much higher level of cleavage for **1** (lane 9 vs. lane 11), while a ten-fold higher concentration of **6** was required to effect the same relative amount of cleavage as **1** (lane 7 vs. lane 11). The DNA cleavage by either **1** or **6** could be effectively suppressed at 2 °C by the addition of 1.8 equivalents of apo-NCS (lanes 8, 10, and 12), providing further evidence for the binding of **6** to apo-NCS.

The aglycone **6** was found to cleave DNA with little sequence specificity, in full accord with the behavior of the parent chromophore **1**. Inspection of histograms prepared by quantitative phosphorimaging of the gel in Figure 4 reveals considerable similarity in the base specificities of **1** and **6** (Figure 5). Both drugs cleave primarily at T and A residues, and the calculated base specificities for **1** and **6** at 2 °C are T (63%) >> A (24%) > C(11%) >> G(2%), and T (65%) >> A (22%) > C (10%) >> G (3%), respectively.[7a]

Figure 4

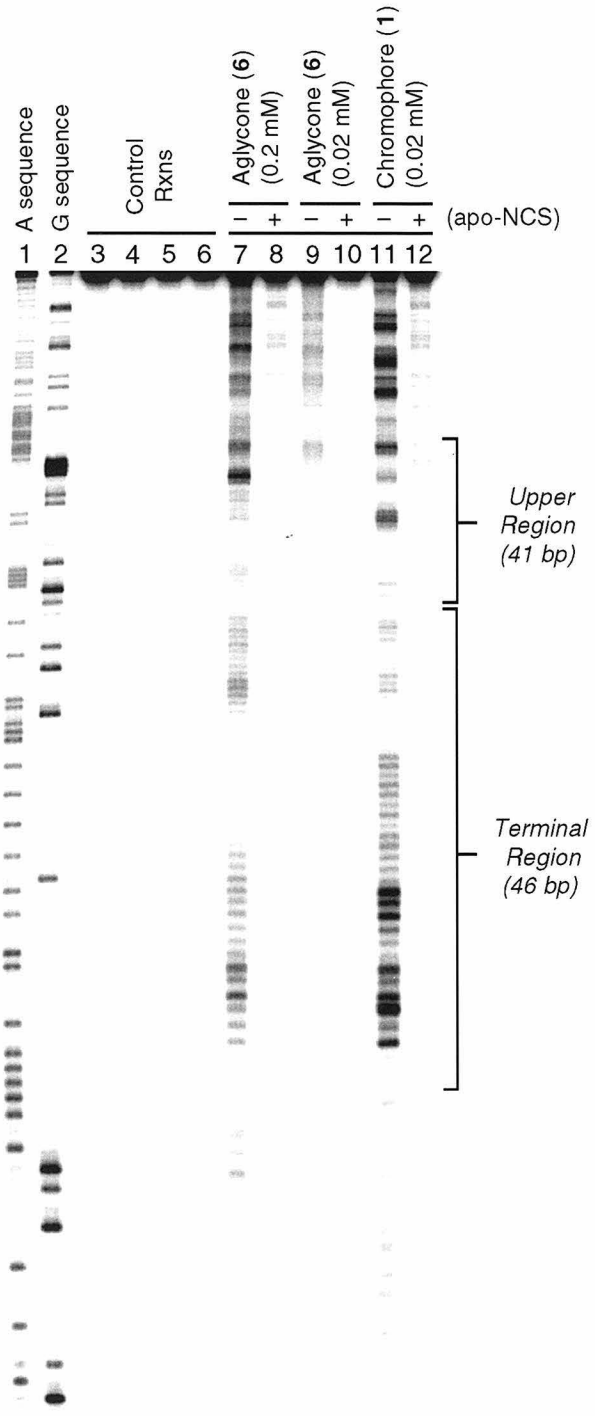

A sequence
G sequence
Control Rxns
Aglycone (6) (0.2 mM)
Aglycone (6) (0.02 mM)
Chromophore (1) (0.02 mM)
– + – + – + (apo-NCS)
1 2 3 4 5 6 7 8 9 10 11 12
Upper Region (41 bp)
Terminal Region (46 bp)

Figure 4. Thiol-dependent DNA cleavage (2 °C, 30 min) by NCS chromophore (**1**) and aglycone (**6**). Storage phosphor autoradiogram of an 8% denaturing polyacrylamide gel. All reaction mixtures contained calf thymus DNA (1 mM bp), 3′-labeled 193 bp restriction fragment (~50 kcpm), and NaCl (20 mM) in tris-HCl (50 mM, pH 7.6) with 5% methanol by volume. Lanes 1 and 2: Maxam-Gilbert sequencing reactions; lanes 3 and 4: **6** (0.2 mM) and **1** (0.02 mM), respectively, no added thiol; lanes 5 and 6: apo-NCS (0.036 mM and 0.36 mM, respectively) and methyl thioglycolate (MTG, 2 mM); lanes 7-12: **1** or **6** (at the indicated concentration) and MTG (2 mM) in the absence (–) or presence (+) of 1.8 equiv (with respect to drug) of purified apo-NCS.

Figure 5

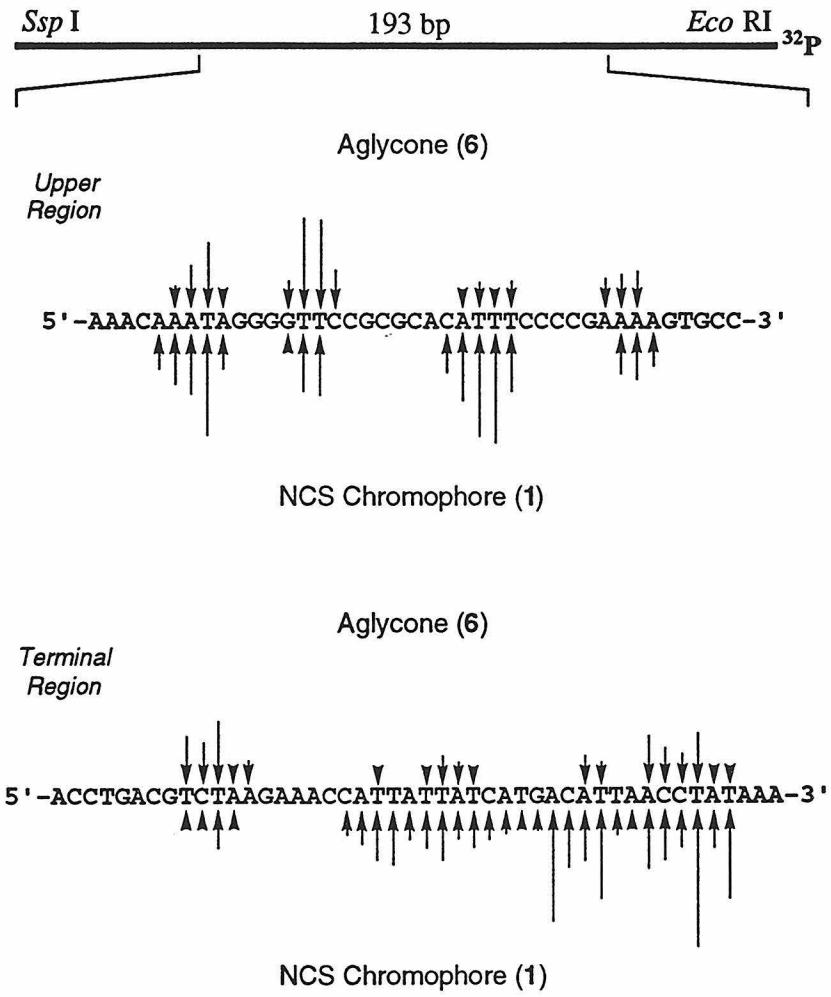

Ssp I
193 bp
Eco RI
32P
Aglycone (6)
Upper Region
5'-AAACAAATAGGGGTTCCGCGCACATTTCCCCGAAAAGTGCC-3'
NCS Chromophore (1)
Aglycone (6)
Terminal Region
5'-ACCTGACGTCTAAGAAACCATTATTATCATGACATTAACCTATAAA-3'
NCS Chromophore (1)

Figure 5. Observed patterns of single-stranded DNA cleavage arising from treatment of **1** or **6** with MTG at 2 °C as described for Figure 4; consecutive 41 bp ("upper") and 47 bp ("terminal") regions within the 3′-end-labeled 193-bp restriction fragment. Arrow lengths are proportional to the amount of cleavage of the indicated base.

Figure 6

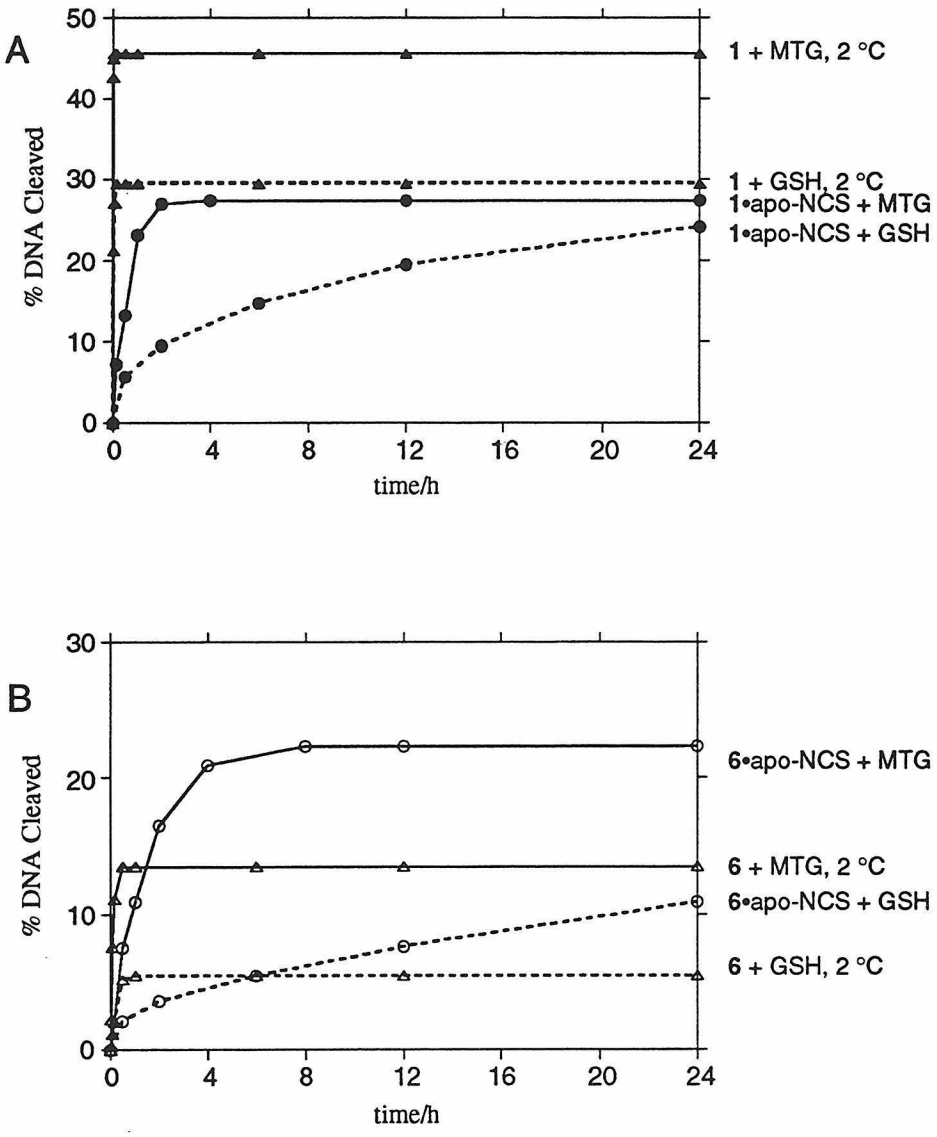

A
% DNA Cleaved
time/h
1 + MTG, 2 °C
1 + GSH, 2 °C
1•apo-NCS + MTG
1•apo-NCS + GSH
B
% DNA Cleaved
time/h
6•apo-NCS + MTG
6 + MTG, 2 °C
6•apo-NCS + GSH
6 + GSH, 2 °C

Figure 6. Kinetics of thiol-dependent DNA cleavage at 37 °C by (A) NCS chromophore (**1**, 0.02 mM) and (B) aglycone (**6**, 0.2 mM) using methyl thioglycolate (MTG) or glutathione (GSH) in the absence or presence of 1.8 equiv of apo-NCS. Reactions were performed in tris-HCl (50 mM, pH 7.6) containing NaCl (20 mM), calf thymus DNA (1 mM bp), and 3'-labeled 193 bp restriction fragment (~150 kcpm) with 5% methanol by volume: (●) **1** (0.02 mM), apo-NCS (0.036 mM); (○) **6** (0.2 mM), apo-NCS (0.36 mM); —— reactions containing MTG (2 mM); ----- reactions containing GSH (2 mM). Reactions conducted at 2 °C in the absence of apo-NCS are shown for comparison: (▲) **1** (0.02 mM); (Δ) **6** (0.2 mM).

The kinetics of thiol-dependent DNA damage by **1** and **6** were also investigated. These experiments were conducted using both MTG and glutathione (GSH) cofactors, and in the absence and presence of 1.8 equivalents of apo-NCS. The accumulated data, plotted in Figure 6, indicated that the DNA cleavage by **1** was in all cases faster than that of the corresponding reactions carried out with **6**. With GSH, both **1** and **6** show similar or greater cleavage efficiency with apo-NCS than without. This is also the case for **6** and MTG, but not for **1** and MTG, where the cleavage efficiency is significantly lower in the presence of apo-NCS than in its absence. This has been attributed to the ability of **1** to undergo a competitive protein-directed thiol addition which reduces the overall efficiency of the DNA cleavage reaction.[114] That the aglycone **6** does not show this reduced efficiency with MTG in the presence of apo-NCS may be interpreted to mean that **6** does not undergo the parallel protein-directed thiol addition reaction. It is proposed that the aminoglycoside of **1** again functions as an internal base, this time catalyzing the protein-directed thiol addition reaction.

The findings from these studies suggest that the aminoglycoside of **1** both accelerates the rate and improves the efficiency of DNA cleavage versus the aglycone **6**, but does not appear to be a major determinant of the base specificity of DNA cleavage by **1**. These results emphasize the need for further investigations into the role of the carbohydrate residue of **1** in damaging DNA, and investigations of the DNA-cleaving activity of analogs of **1** bearing modified carbohydrate residues (i.e., non-aminoglydosides) should provide additional insight. The availability of the aglycone **6** in enantiomerically pure form should provide the necessary entry into the preparation of such analogs.

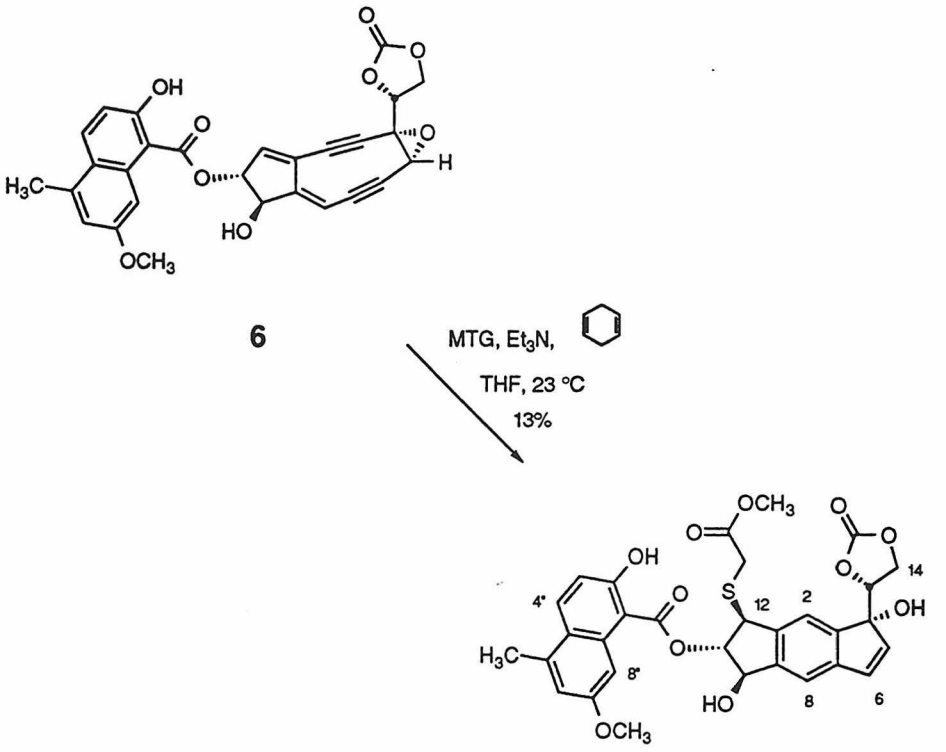
Experimental Section

General procedures. All reactions were performed in flame-dried round bottom or modified Schlenk (Kjeldahl shape) flasks. The flasks were fitted with rubber septa and contained a positive pressure of argon unless otherwise stated. Stainless steel syringes or cannula were used to transfer air- and moisture-sensitive materials. Concentration in vacuo was accomplished by rotary evaporation at water aspirator pressure (approximately 25 torr). Analytical thin-layer chromatography was performed using glass plates pre-coated with 0.25 mm 230-400 mesh silica gel impregnated with fluorescent indicator (254 nm). Thin-layer chromatography plates were visualized by exposure to ultraviolet light (noted as 'UV') and by exposure to an acidic solution of *p*-anisaldehyde (noted as 'anisaldehyde') followed by heating on a hot plate.

Materials. Commercial reagents were used as received, with the following exceptions. Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl. Acetonitrile, toluene, and triethylamine were distilled from calcium hydride at 760 torr. Methyl thioglycolate was distilled at 760 torr. 1,4-cyclohexadiene was filtered through a plug of basic alumina immediately prior to use.

Instrumentation. Infrared (IR) spectra were obtained using a Perkin-Elmer 1600 FT-IR spectrophotometer referenced to a polystyrene standard. Data are presented as follows: frequency of absorption (cm^{-1}) intensity of absorption (v = very, s = strong, m =

medium, w = weak) and assignment where appropriate. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on a JEOL GX-400 (400 MHz) NMR spectrometer; chemical shifts for protons are reported in parts per million downfield from tetramethylsilane and are referenced to residual protium in the NMR solvent (CD_2HCN: δ 1.93). Data are represented as follows: chemical shift, multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, abq = ab quartet), integration, coupling constant in Hertz (Hz), and assignment. HPLC was conducted on a Beckman System Gold HPLC equipped with a Beckman ODS C18 reverse-phase column (10 mm x 25 cm) and a Beckman 168 Programmable Photodiode Detector set a 280 nm. Mass spectra were obtained at Beckman Research Institute of the City of Hope, Duarte, California on a Finnigan LCQ ion trap mass spectrometer equipped with a Finnigan-MAT electrospray ion source modified for microspray as previously described.[108]



Thiol adduct **179**

2,5-Dimethoxybenzyl alcohol (ca. 0.6 mg) was added as an internal standard to a deoxygenated solution of the aglycone **6** in methanol (0.5 mL of a solution ~2 mg/mL) containing BHMS (ca. 0.05 mg), and the ratio of aglycone/internal standard was determined by rp-HPLC analysis (ODS C18 column, 10 mm x 25 cm, isocratic solvent system of 40% 10 mM ammonium acetate (pH 5.5)/60% acetonitrile, flow rate of 2.0 mL/min, monitoring at 240 nm; retention times: **6**, 25.0 min; **179**, 14.1 min; 2,5-dimethoxybenzyl alcohol, 7.3 min). The solution was concentrated to a volume of ca. 0.1 mL, the concentrate was diluted with toluene (0.5 mL), and the resulting solution was

concentrated to a volume of ca. 0.1 mL. This procedure was repeated twice. Tetrahydrofuran (0.2 mL) and 1,4-cyclohexadiene (24 mg, 0.028 mL, 0.30 mmol, final concentration 1.0 M) were added to the concentrate, and the solution was deoxygenated. A deoxygenated solution of methyl thioglycolate (16 mg, 0.013 mL, 0.15 mmol, final concentration 0.5 M), and triethylamine (15 mg, 0.021 mL, 0.15 mmol, final concentration 0.5 M) in tetrahydrofuran (0.1 mL) was added and, after 55 minutes, the volatiles were removed in vacuo. The residue was dissolved in toluene and the resulting solution was concentrated to ca. 0.1 mL. This procedure was repeated twice. The residue was then taken up in acetonitrile (0.3 mL), and the yield of **179** was determined by rp-HPLC analysis (as above, 13%). This procedure was repeated on two-fold larger scale and the product was isolated by rp-HPLC (as above) to afford the adduct **179** as a pale yellow oil (ca. 0.2 mg).

^{1}H NMR (400 MHz, CD_3CN), δ:	8.10 (d, 1 H, *J* = 9.53 Hz, C4" H), 7.78 (br s, 1 H, C8" H), 7.57 (s, 1 H, C2 H), 7.35 (s, 1 H, C8 H), 7.04 (d, 1 H, *J* = 9.16 Hz, C3" H), 6.92 (d, 1 H, *J* = 5.88 Hz, C6 H), 6.84 (br s, 1 H, C6" H), 6.26 (d, 1 H, *J* = 5.84 Hz, C5 H), 5.75 (t, 1 H, *J* = 3.32 Hz, C11 H), 5.34 (br m, 1 H, C10 H), 4.67 (dd, 1 H, *J* = 8.44, 5.52 Hz, C13 H), 4.60 (d, 1 H, *J* = 3.28 Hz, C12 H), 4.43 (t, 1 H, *J* = 9.16 Hz, C14 H), 4.27 (dd, 1H, *J* = 8.76, 5.84 Hz, C14 H), 3.59 (s, 3 H, C7" OCH_3), 3.54 (abq, 2 H, *J* = 15.36 Hz, Δν = 46.97 Hz, SCH_2), 3.48 (s, 3 H, CO_2CH_3), 2.57 (s, 3 H, C5" CH_3).
FTIR (CH_3CN), cm^{-1}:	3628 (s, OH), 3542 (s, OH), 2932 (m), 1732 (m, C=O), 1631 (m, C=O), 1278 (m), 1204 (m), 1009 (w).
MS (electrospray):	631 $[M+Na]^+$, 647 $[M+K]^+$
TLC (10% CH_3OH/CH_2Cl_2), R*f*:	**179**: 0.42 (fluoresces under UV, anisaldehyde)

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98. Little to no difference has been observed in reactions utilizing trifluoromethanesulfonic anhydride when the expensive 2,6-di-*tert*-butylpyridine is replaced with the moderately priced 2-chloropyridine. The 2-chloropyridine also does not react with trifluoromethanesulfonic anhydride, as is observed with pyridine and 2,6-lutidine.[99] Myers, A. G.; Tom, N. J.; Hammond, M., California Institute of Technology, unpublished results.

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108. Mass spectra were obtained on a Finnigan LCQ ion trap mass spectrometer equipped with a Finnigan-MAT electrospray ion source modified for microspray as previously described. Davis, M. T.; Stahl, D. C.; Hesta, S. A.; Lee, T. D. *Anal. Chem.* **1995**, *67*, 4549.

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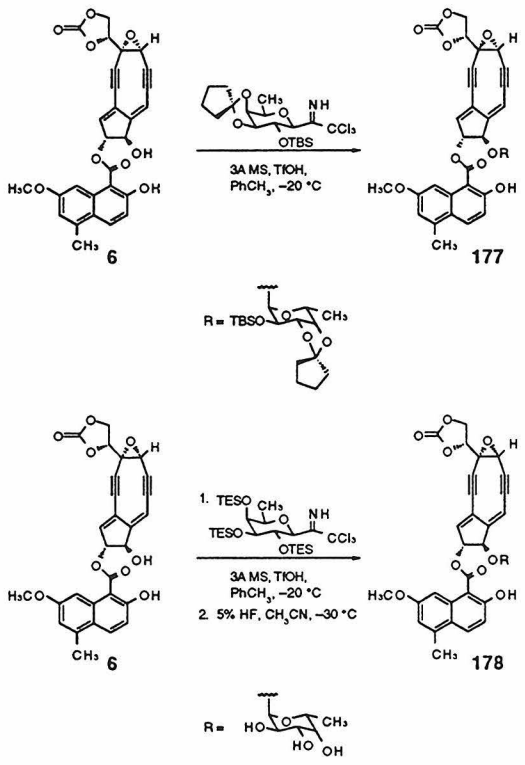
112. The aglycone **6** has been successfully glycosylated with a protected fucosamine derivative to provide the neocarzinostatin chromophore analog **177**.[112a] Additionally, the fucose analog **178** has been prepared.[112b] (a) Myers, A. G.; Wu, Y.; Hammond, M., California Institute of Technology, unpublished results. (b) Myers, A. G.; Liang, J.; Hammond, M., California Institute of Technology, unpublished results.

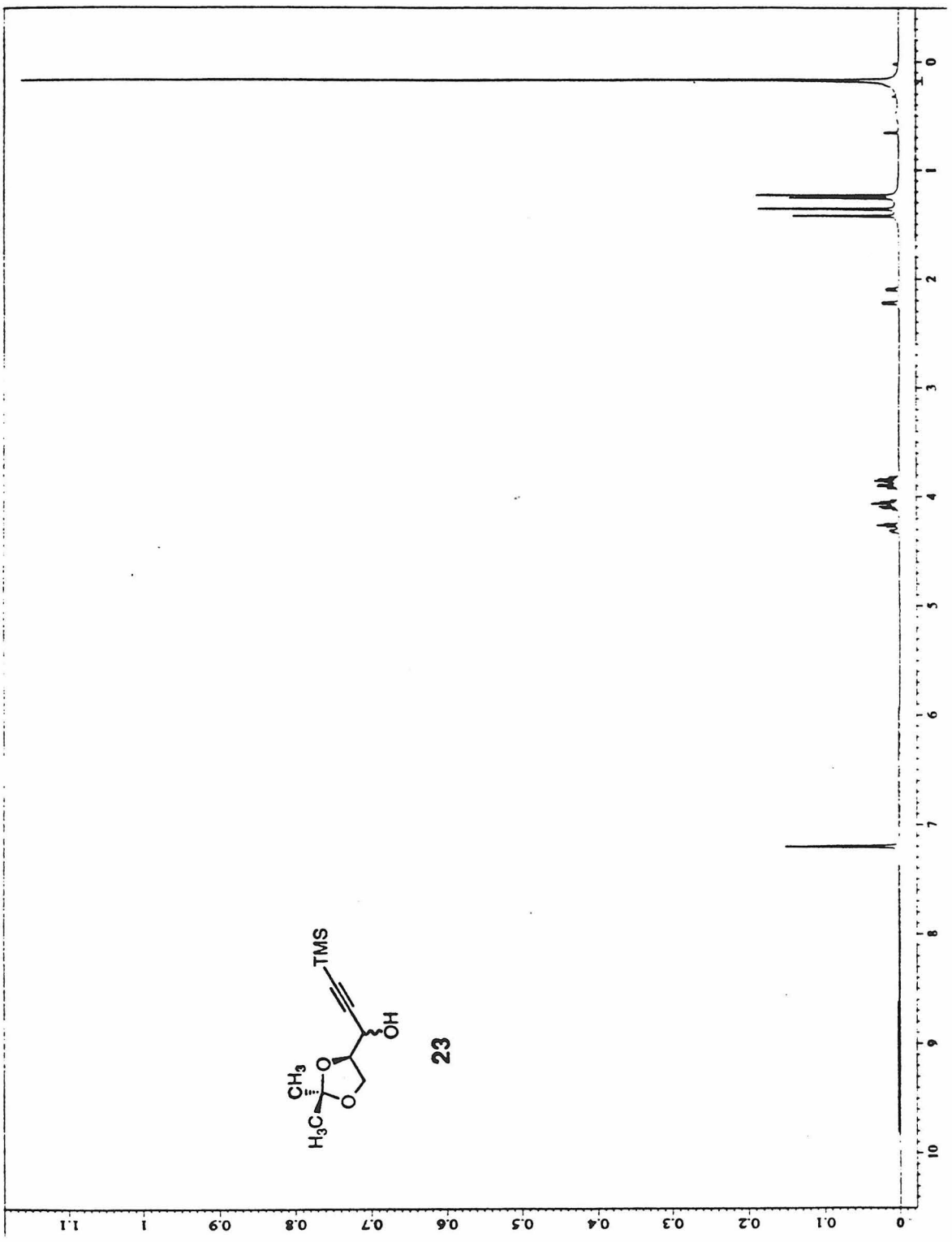


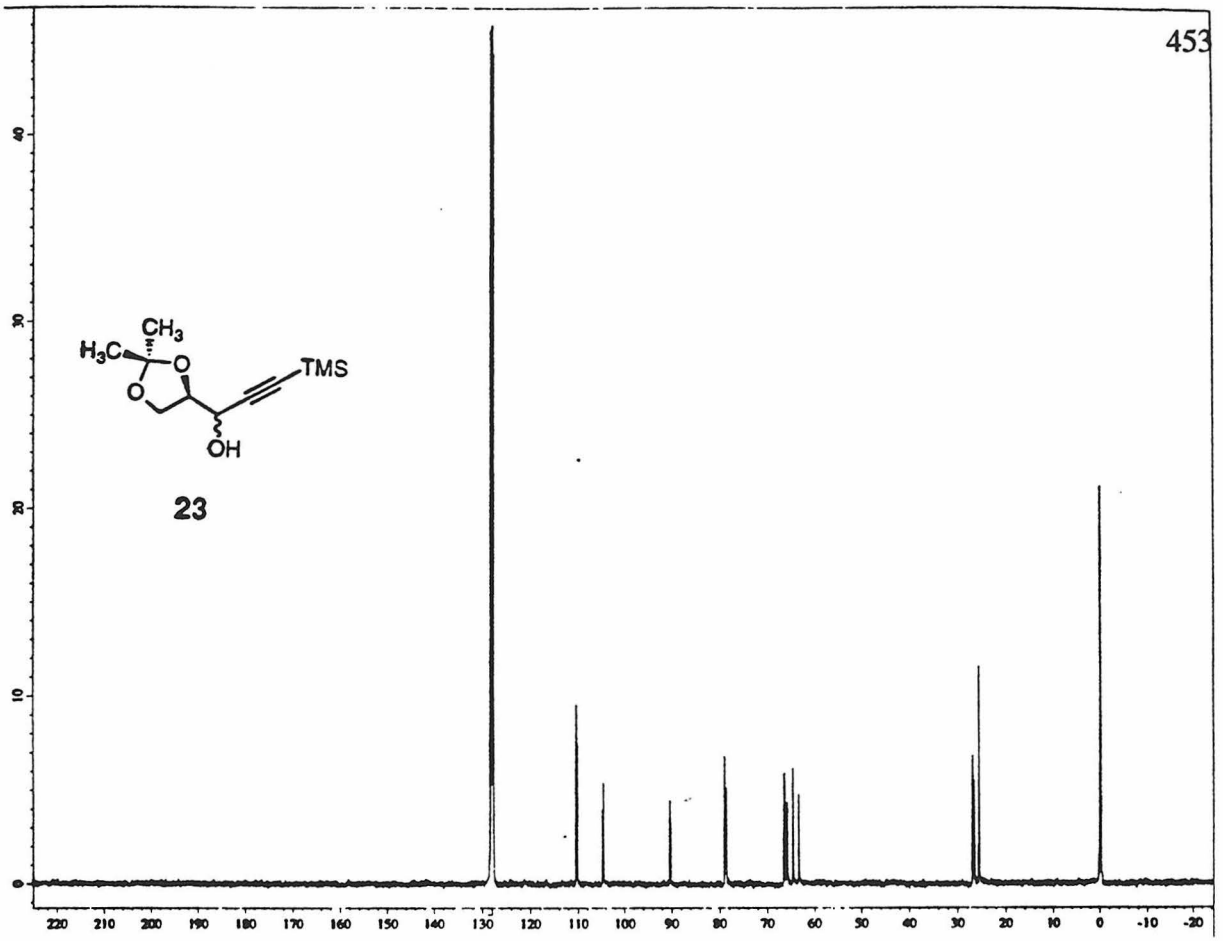
113. HPLC purification of the adduct **179** was carried out on a Beckman System Gold HPLC equipped with a Beckman 168 diode array detector set at 240 nm and a Beckman ODS C18 reverse-phase column (10 mm x 25 cm). The system utilized an isocratic solvent system comprising 40% 10 mM aqueous ammonium acetate (pH 5.5)/60% acetonitrile at a flow rate of 2.0 mL/minute. Retention times are as follows: **6**, 25 min; 2,5-dimethoxybenzyl alcohol, 7.3 min; **179**, 14.1 min.

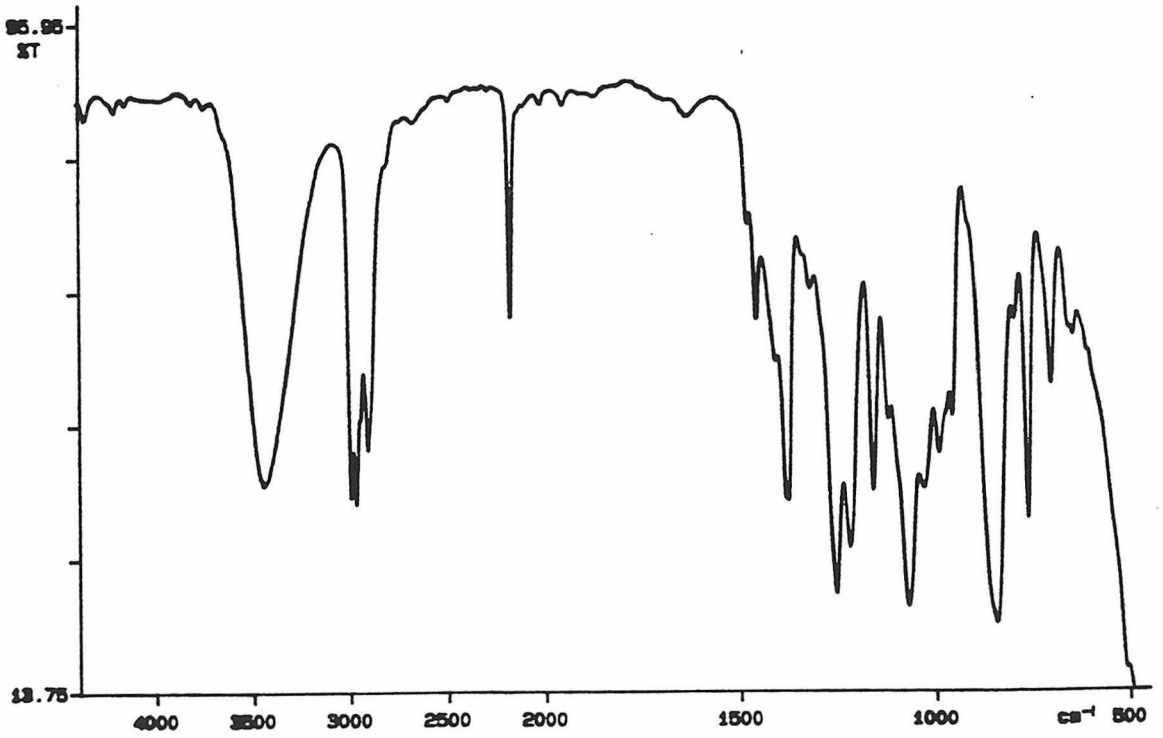
114. Myers, A. G.; Arvedson, S. P.; Lee, R. W. *J. Am. Chem. Soc.* **1996**, *118*, 4725.

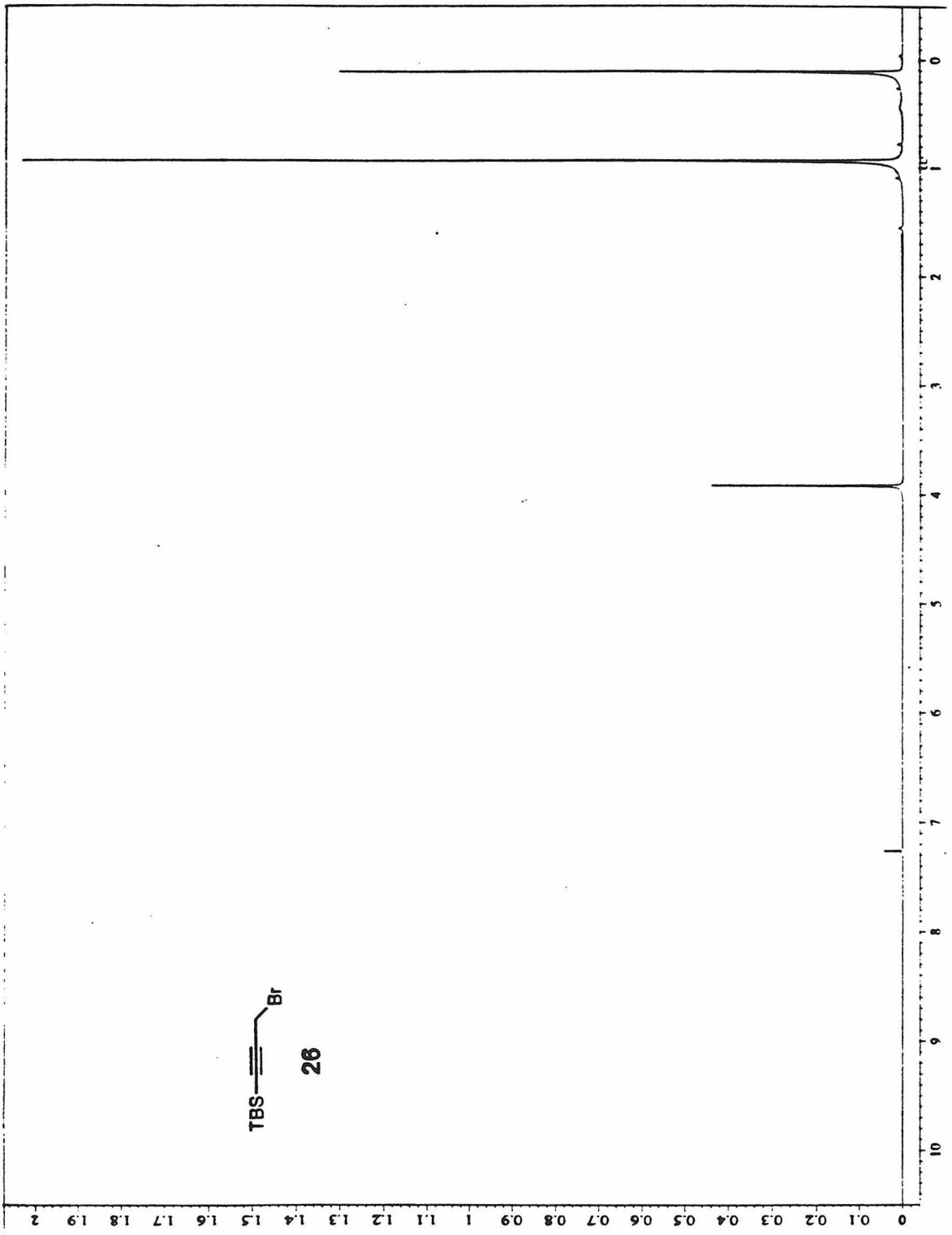
Appendix

Catalog of Spectra


TMS
OH
CH3
H3C
O
O
23


CH3
H3C
O
O
TMS
OH
23
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20

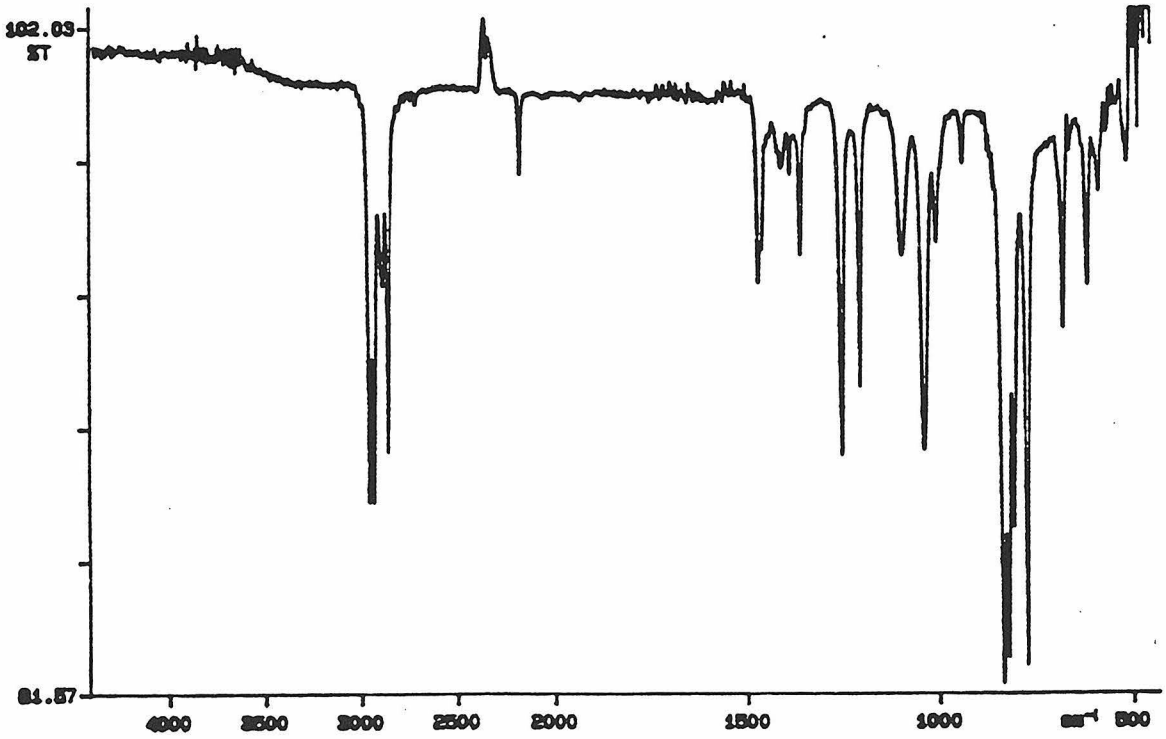

95.95
%T
13.75
4000
3500
3000
2500
2000
1500
1000
cm-1
500


TBS
Br
26


TBS
Br

26

200
150
100
50
0
PPM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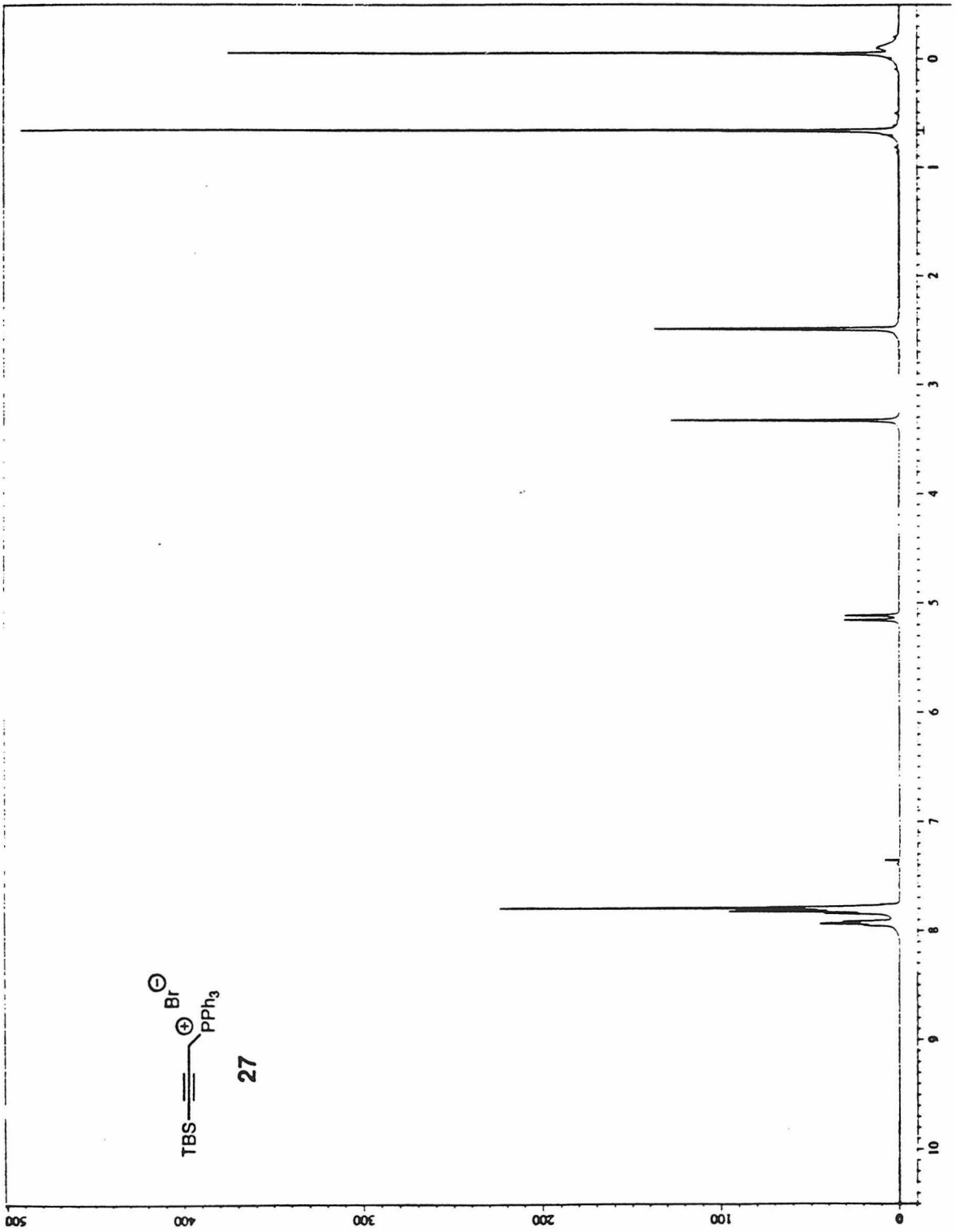
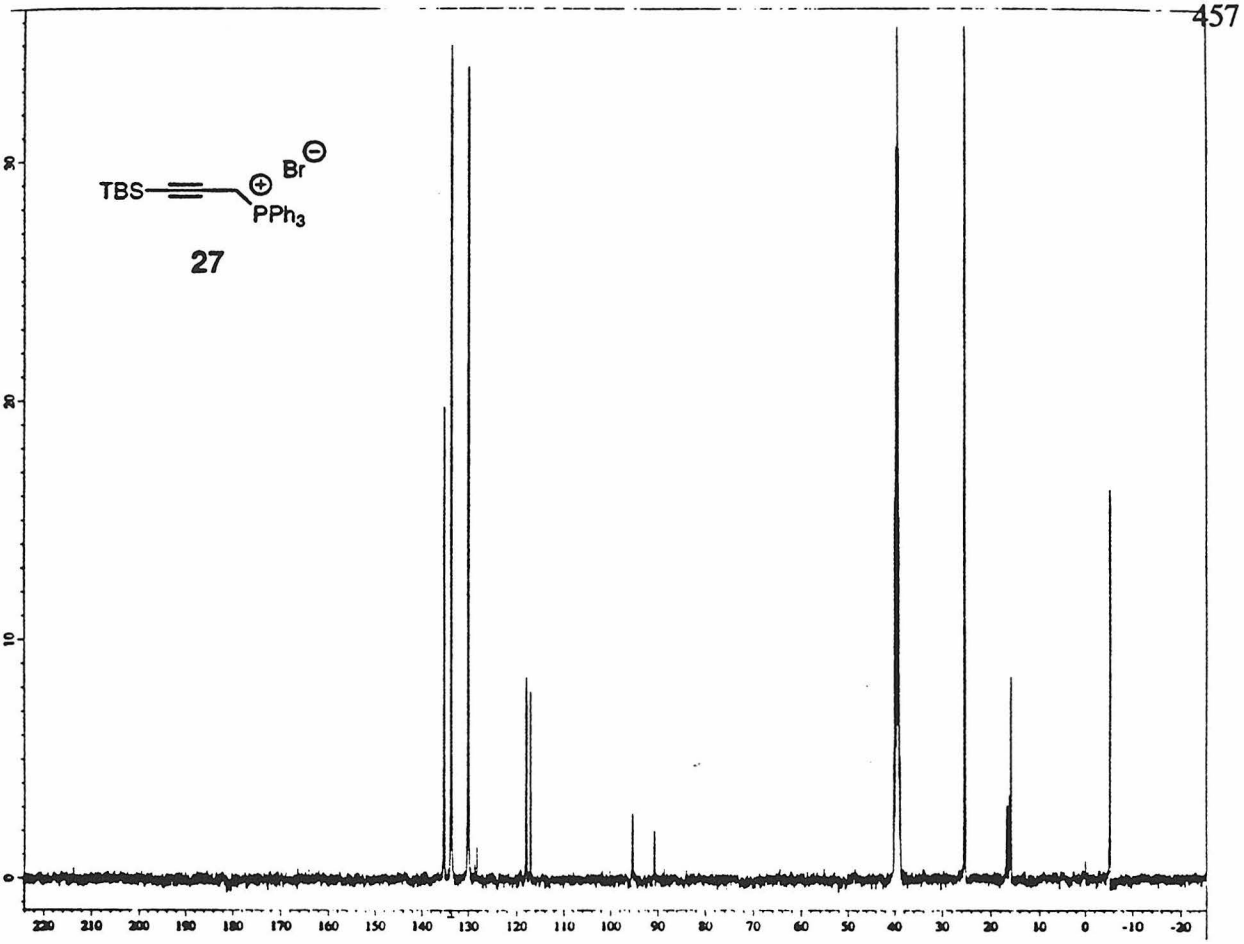
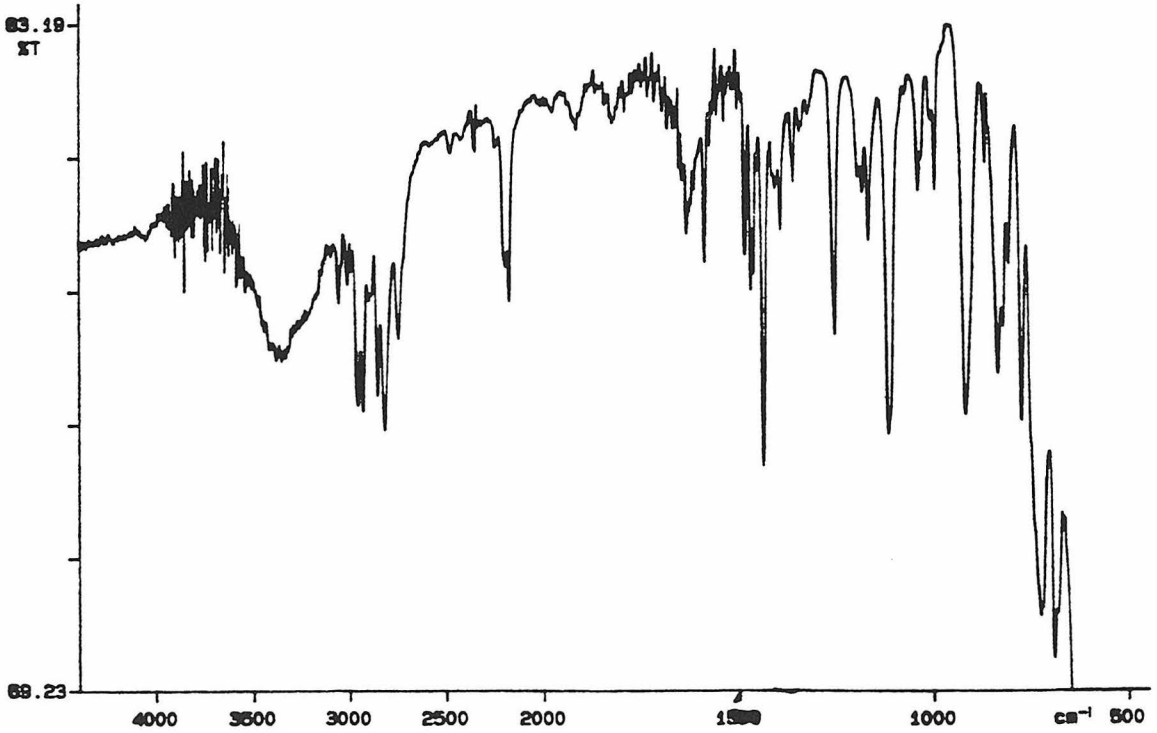
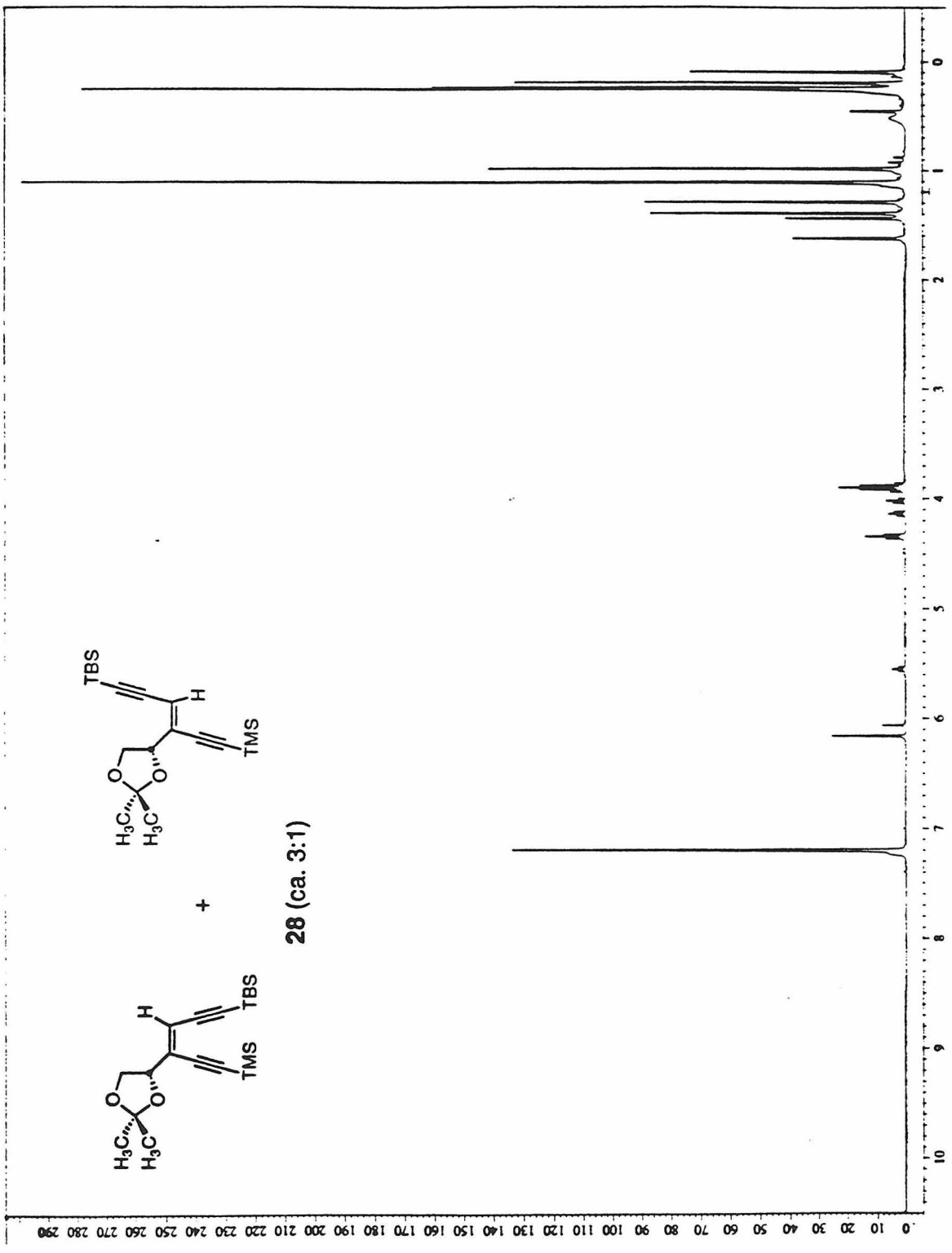
%T
81.57
4000
3500
3000
2500
2000
1500
1000
cm-1
500

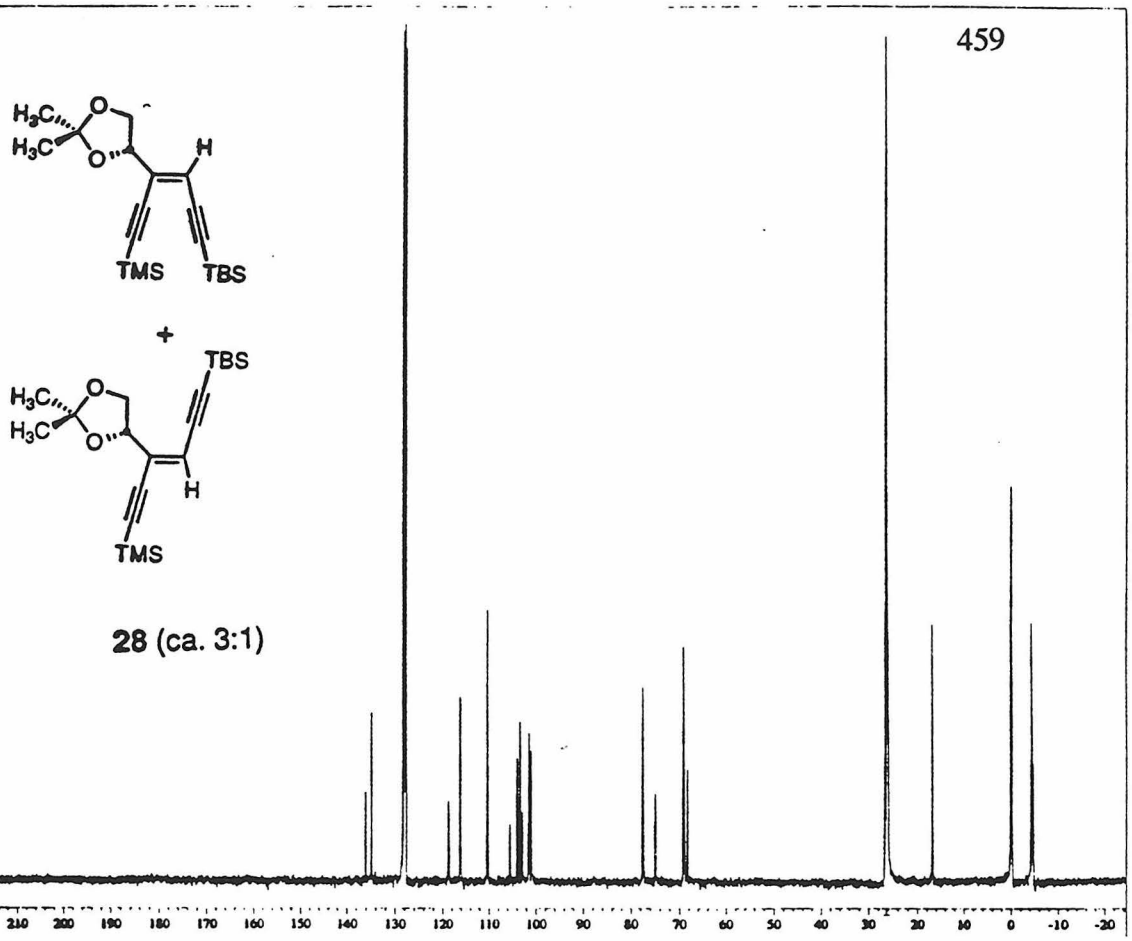

TBS
PPh3
Br
27


TBS
Br
PPh3
27
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20

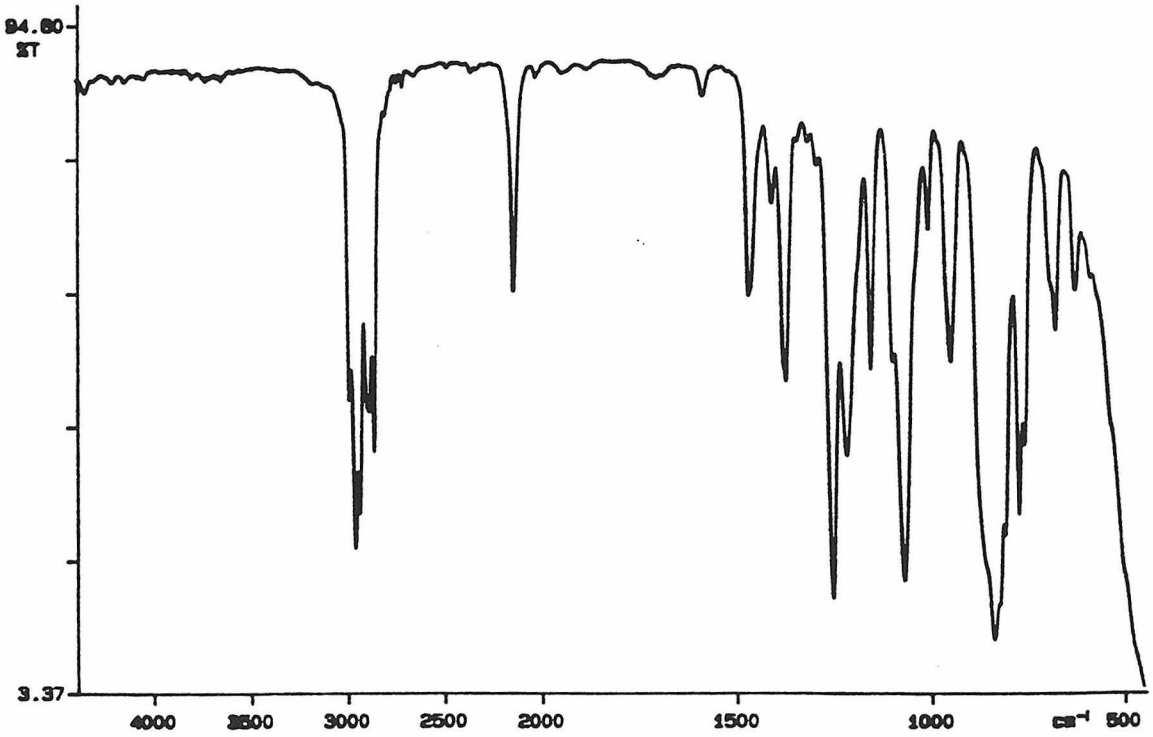

83.19
%T
69.23
4000 3500 3000 2500 2000 1000 cm-1 500


TBS
H
TMS
O
O
H3C
H3C
+
TMS
TBS
H
O
O
H3C
H3C
28 (ca. 3:1)

459


TMS
TBS
+
TBS
TMS

28 (ca. 3:1)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%T
3.37
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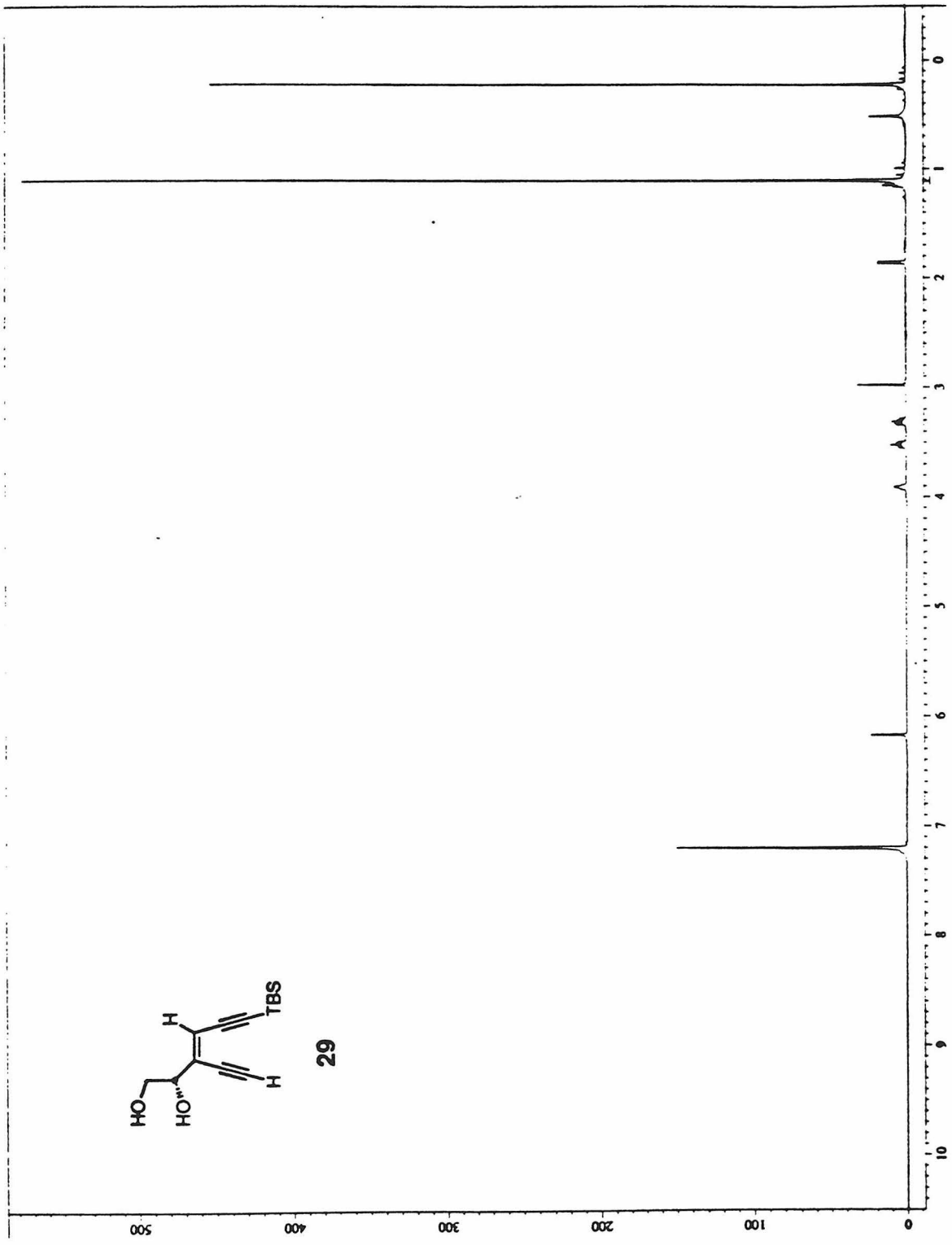
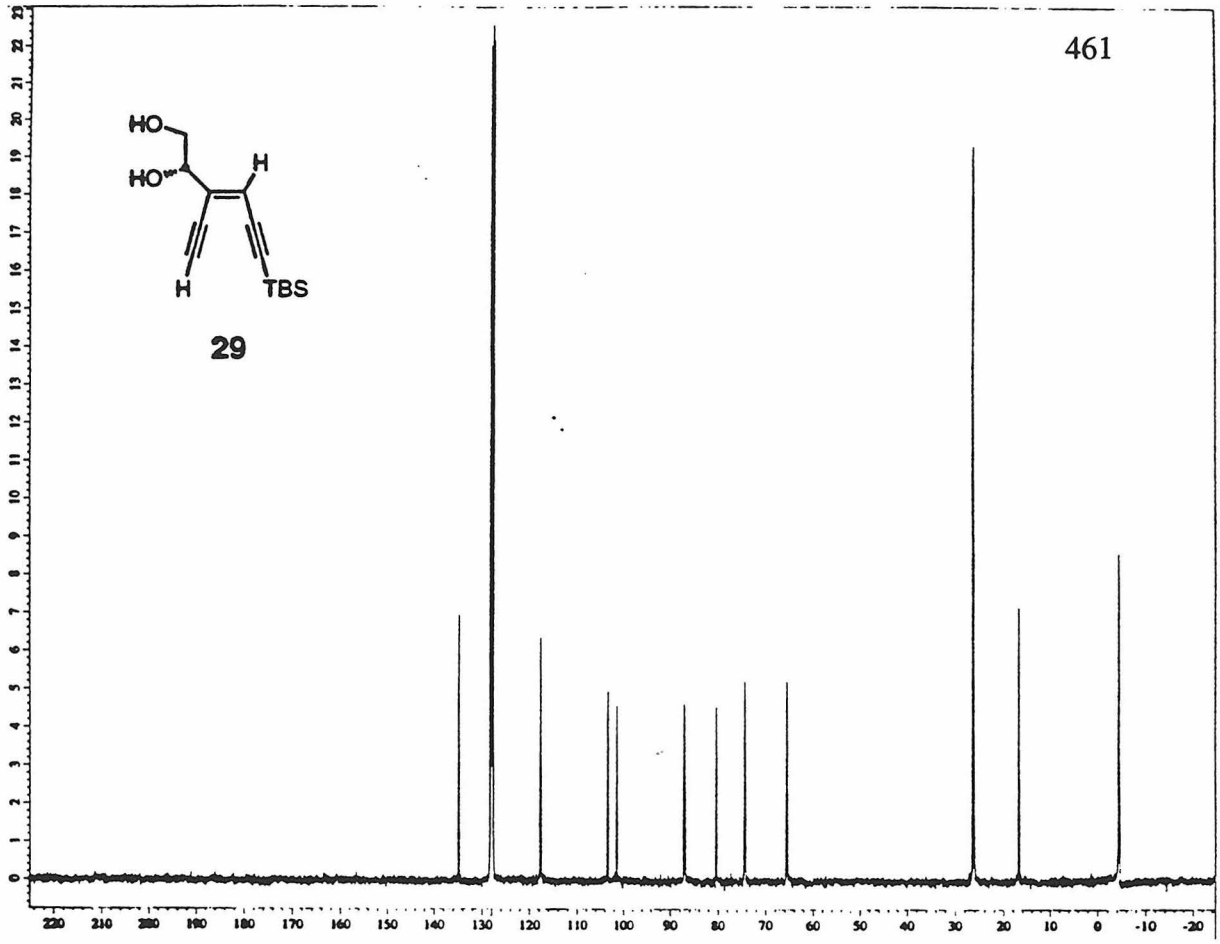
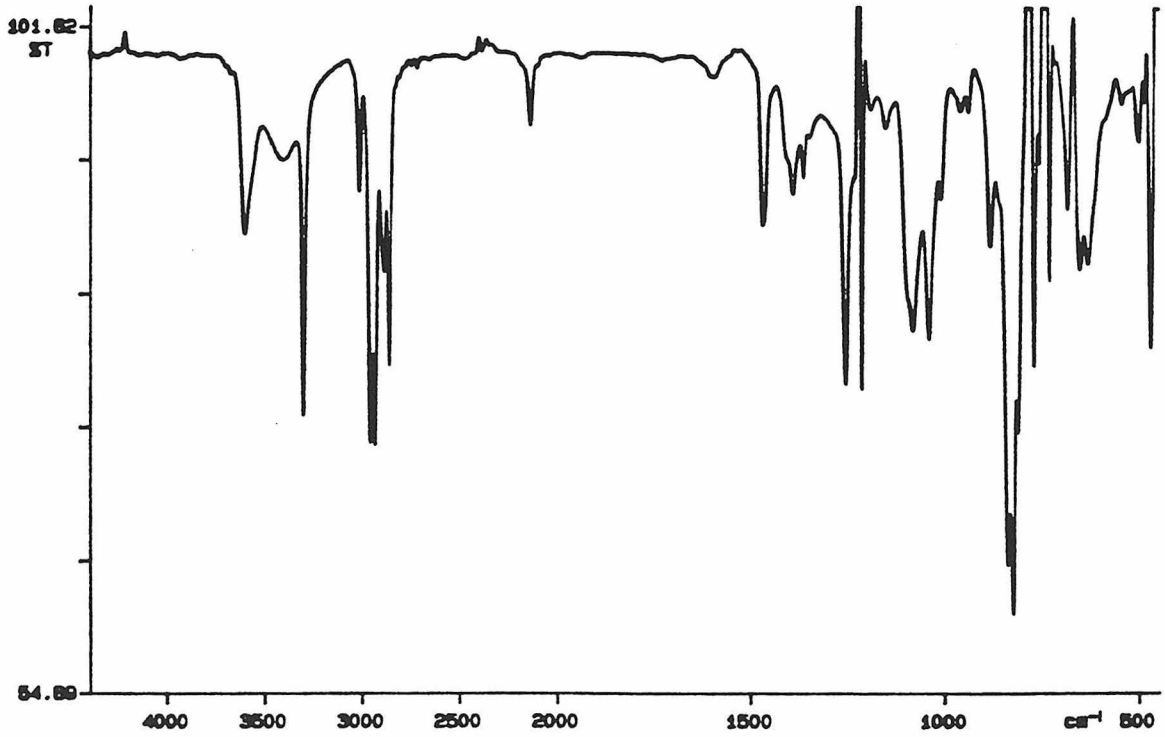
3500
3000
2500
2000
1500
1000
cm⁻¹
500


TBS
H
H
HO
HO
29


HO
HO
H
H
TBS

29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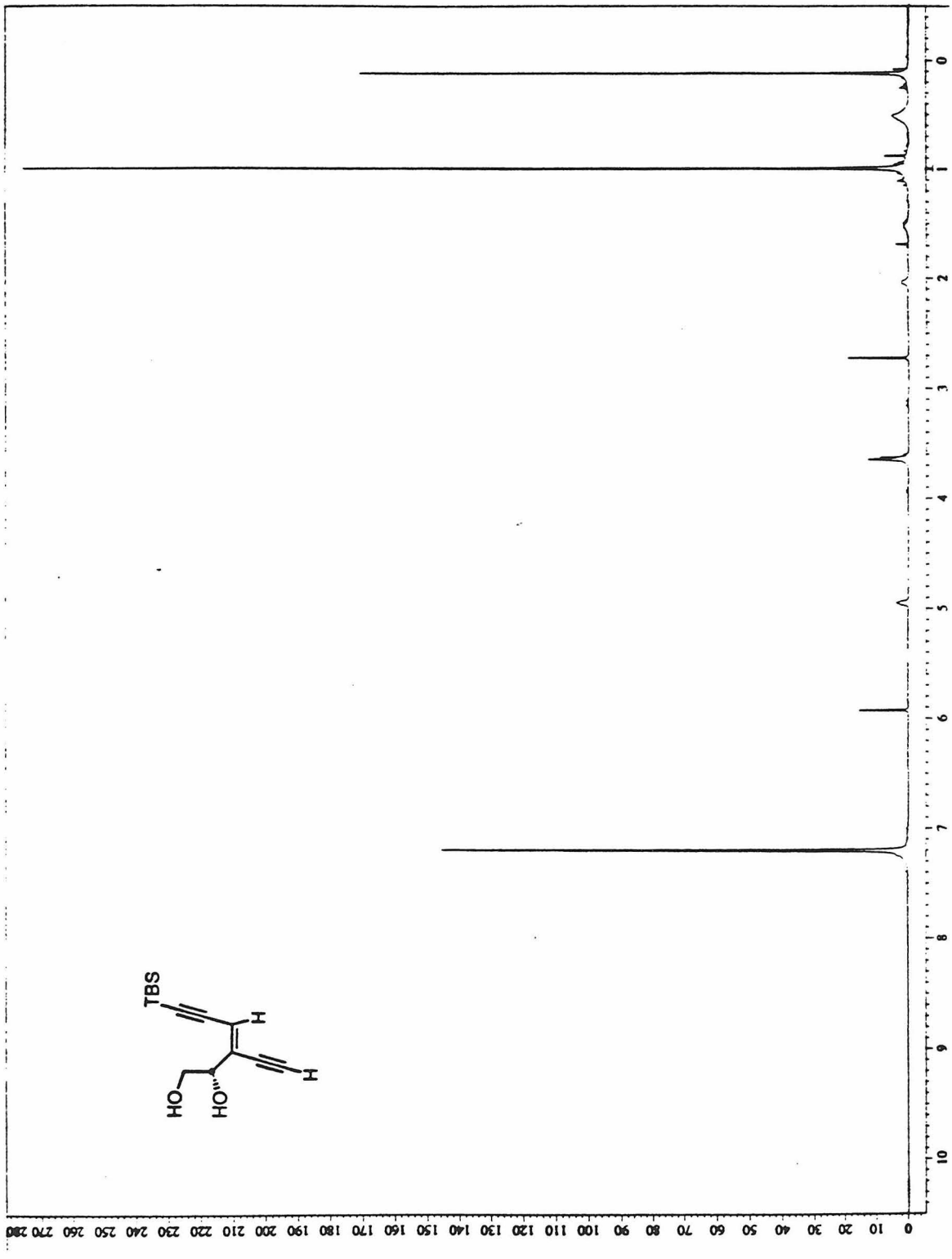
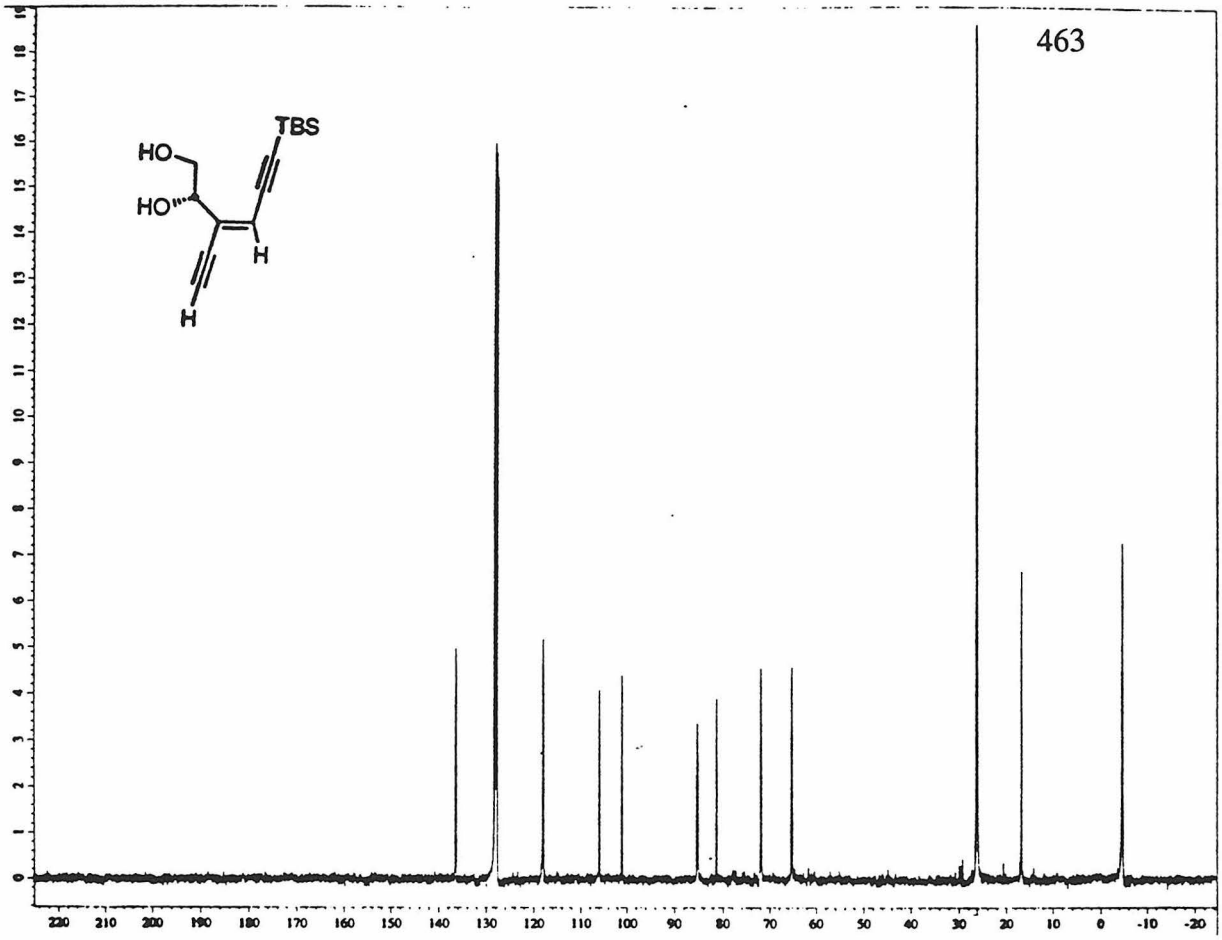
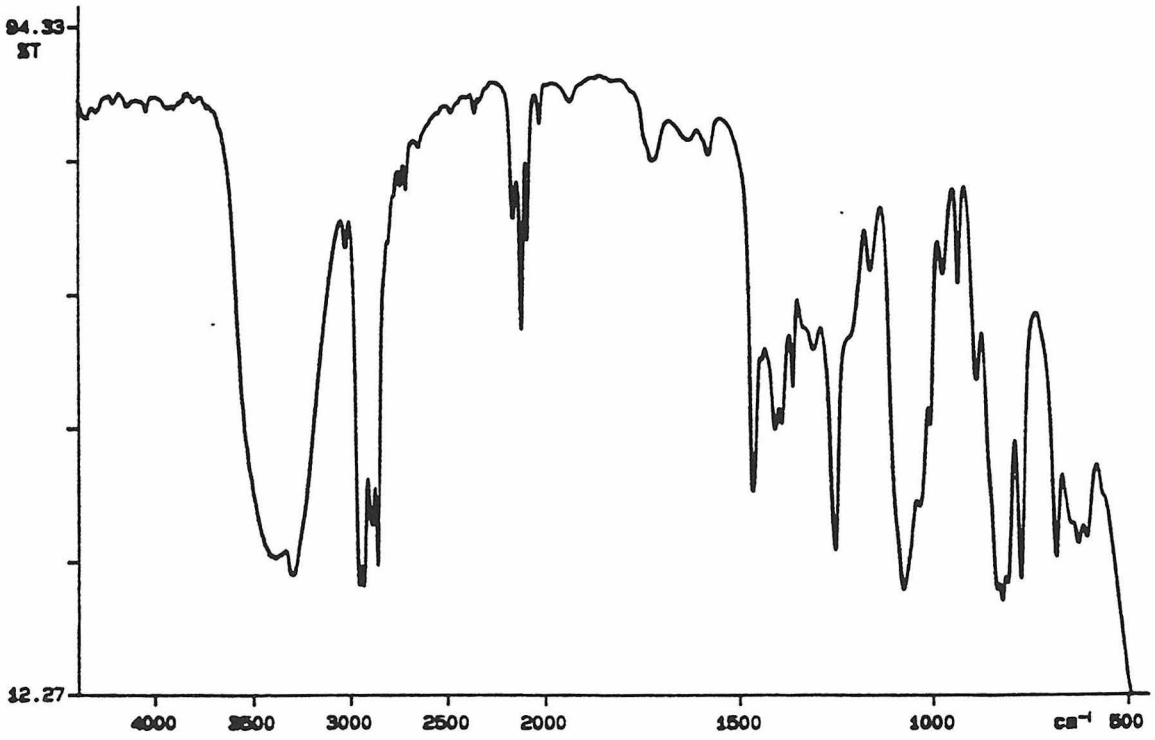
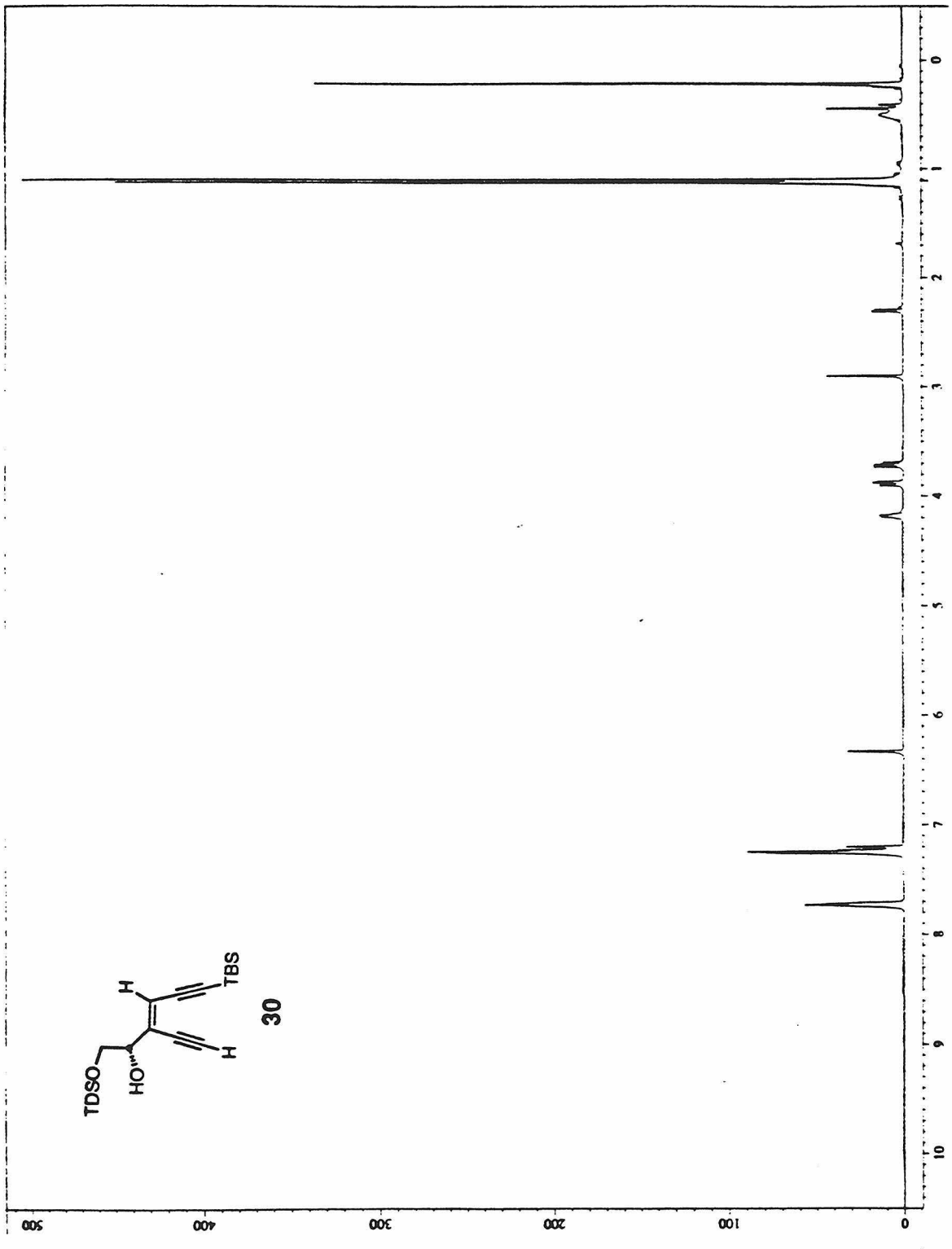
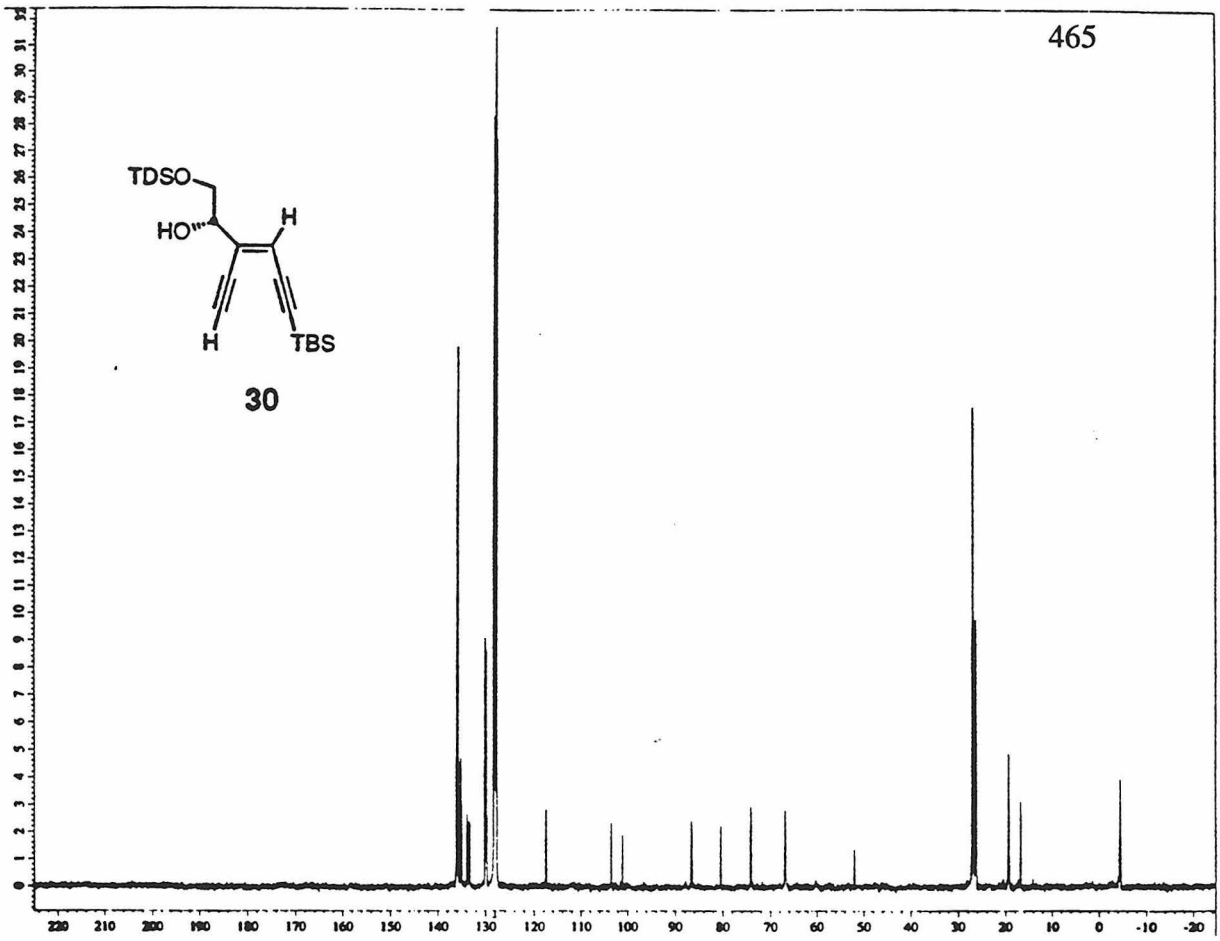
%T
54.89
4000
3500
3000
2500
2000
1500
1000
cm-1
500


TBS
H
H
HO
HO

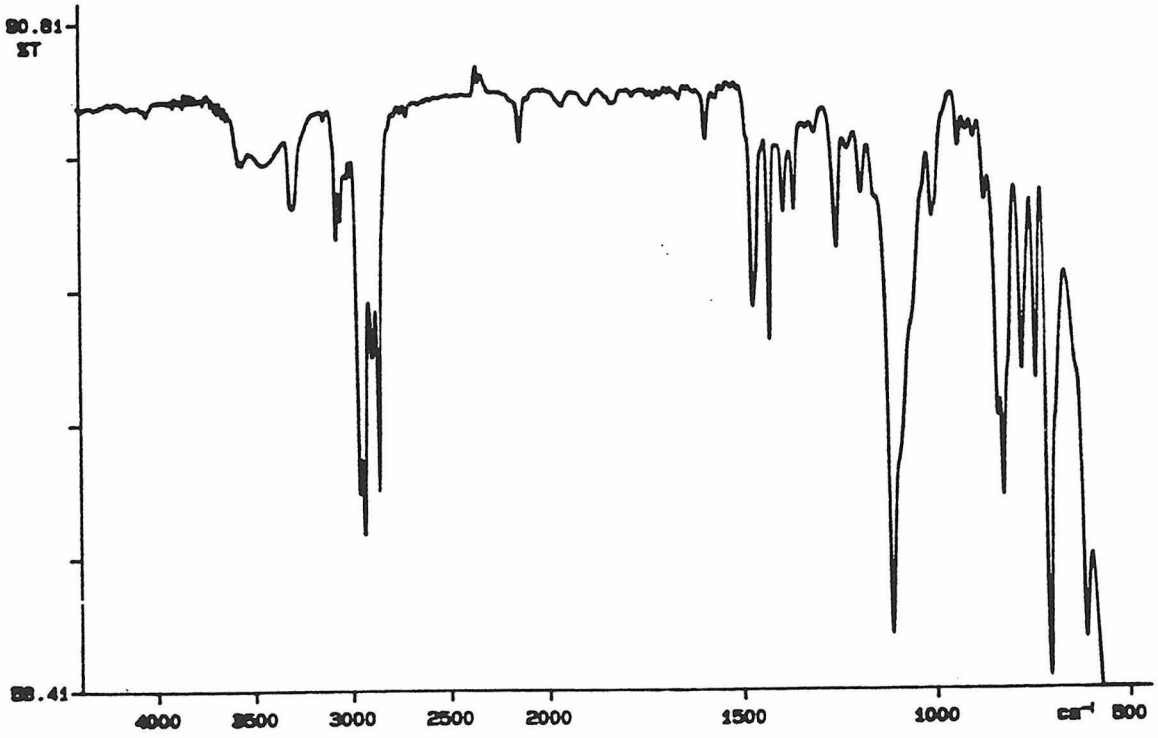

TBS
HO
HO
H
H


94.33
%T
12.27
4000
3500
3000
2500
2000
1500
1000
cm⁻¹
500


TDSO
HO
H
TBS
H
30


TDSO
HO
H
H
TBS

30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%T
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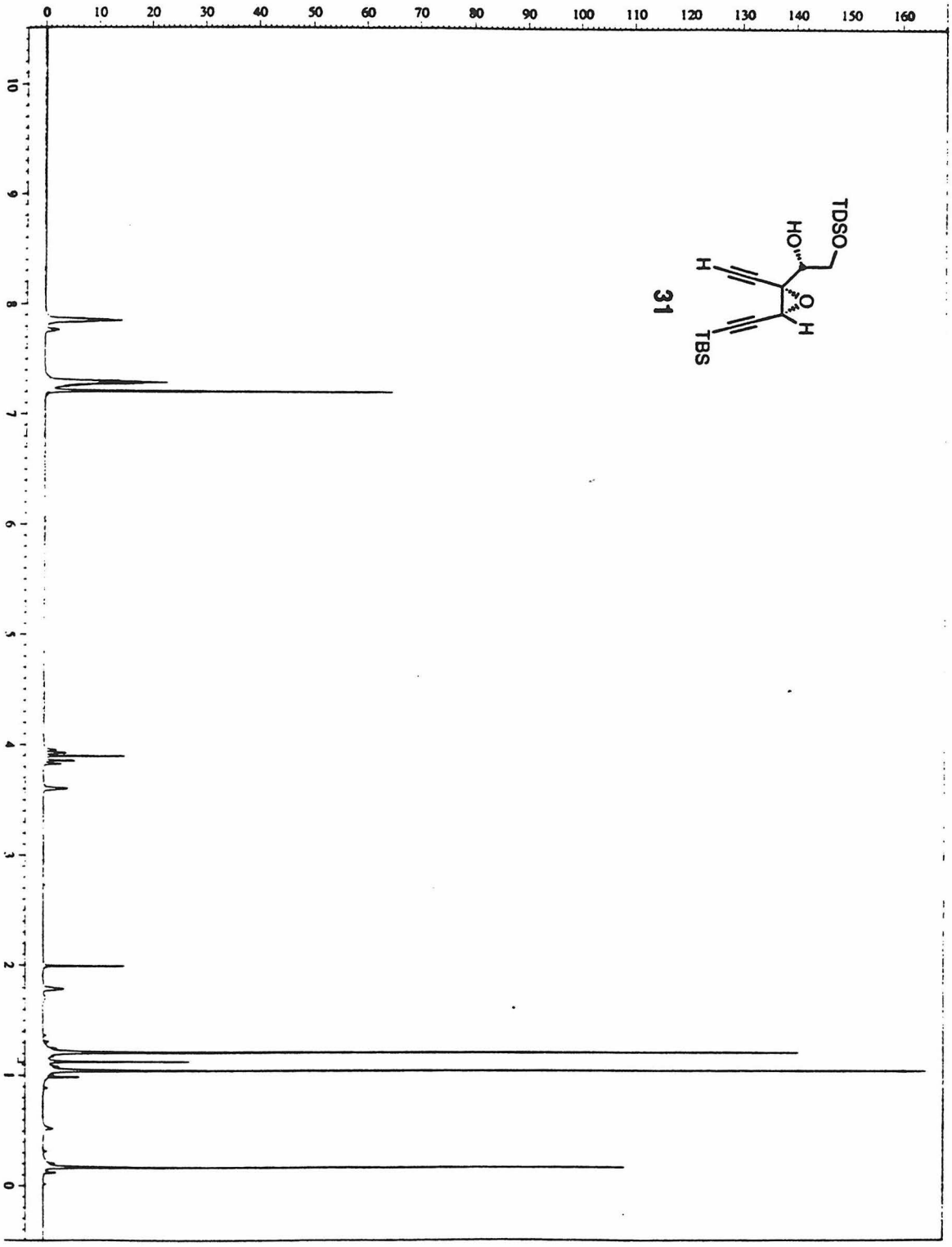
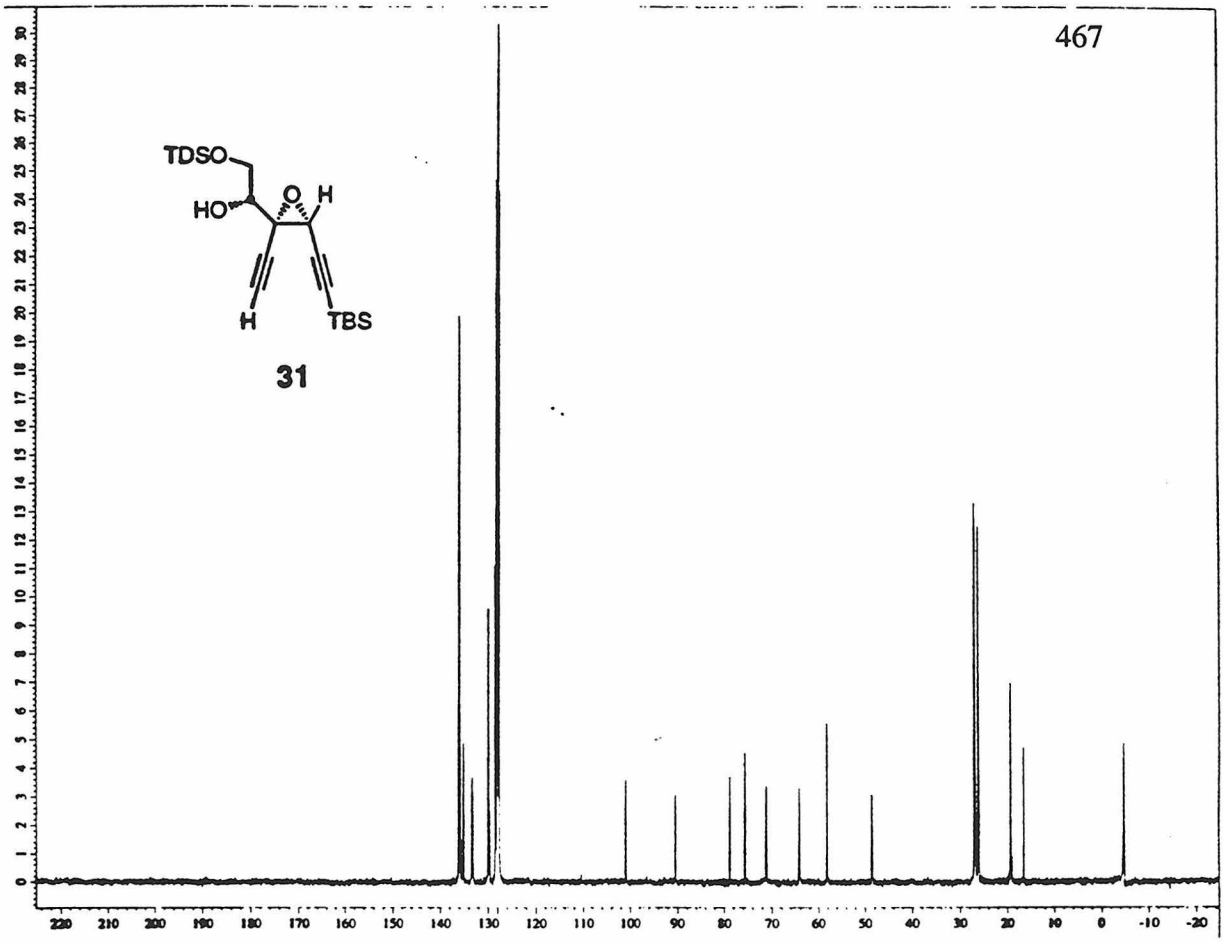
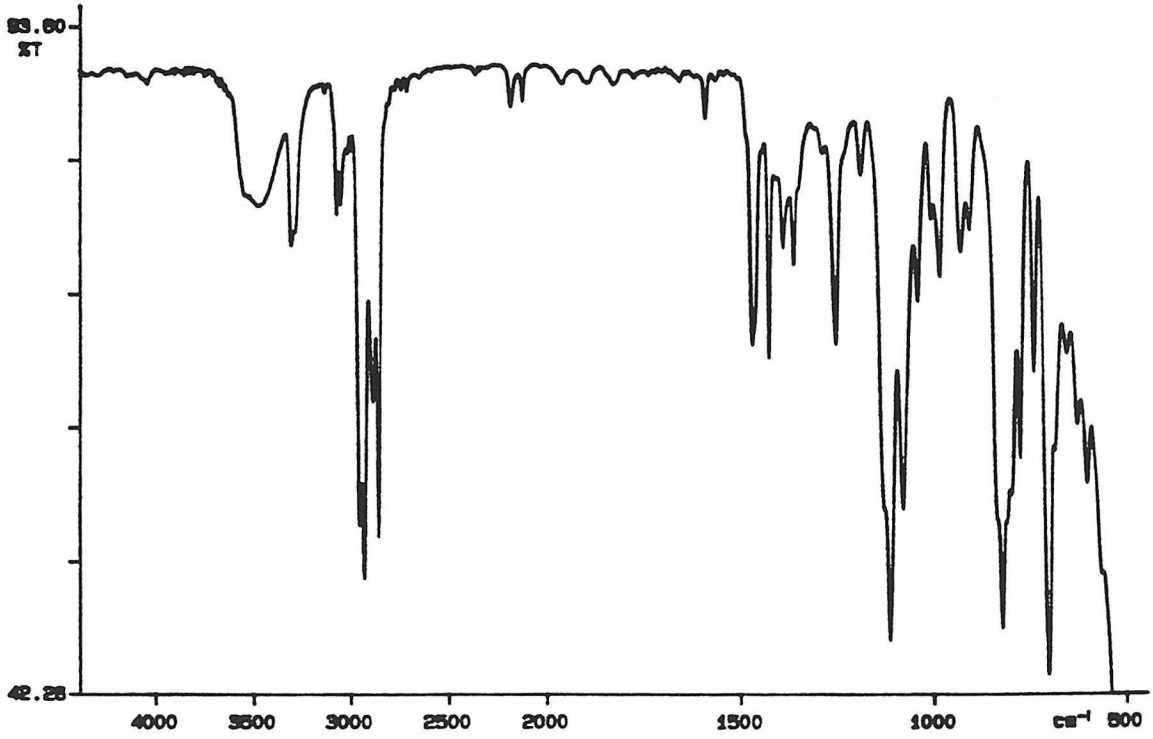
3500
3000
2500
2000
1500
1000
cm-1
500


TDSO
HO
H
O
H
TBS
31


TDSO
HO
O
H
H
TBS

31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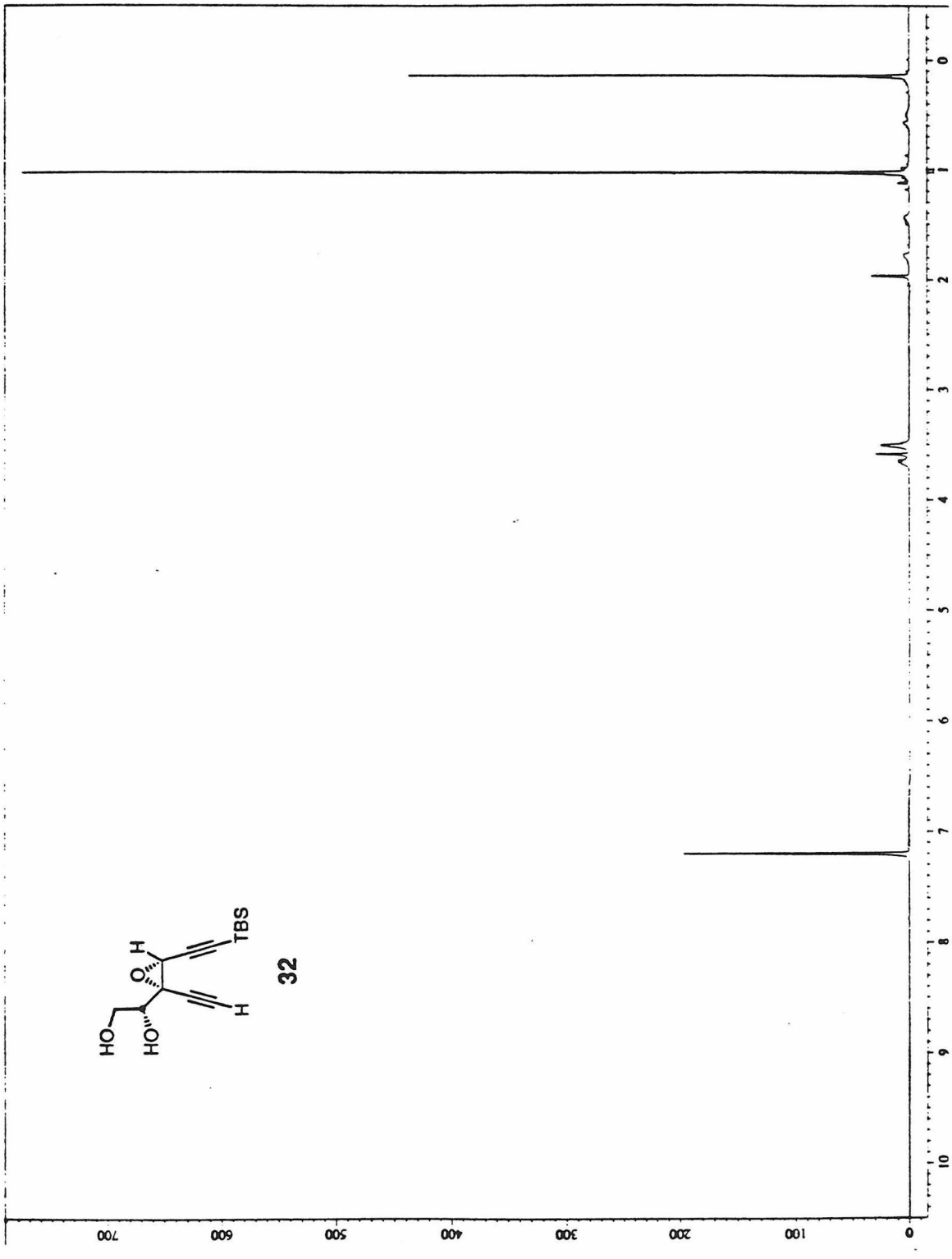
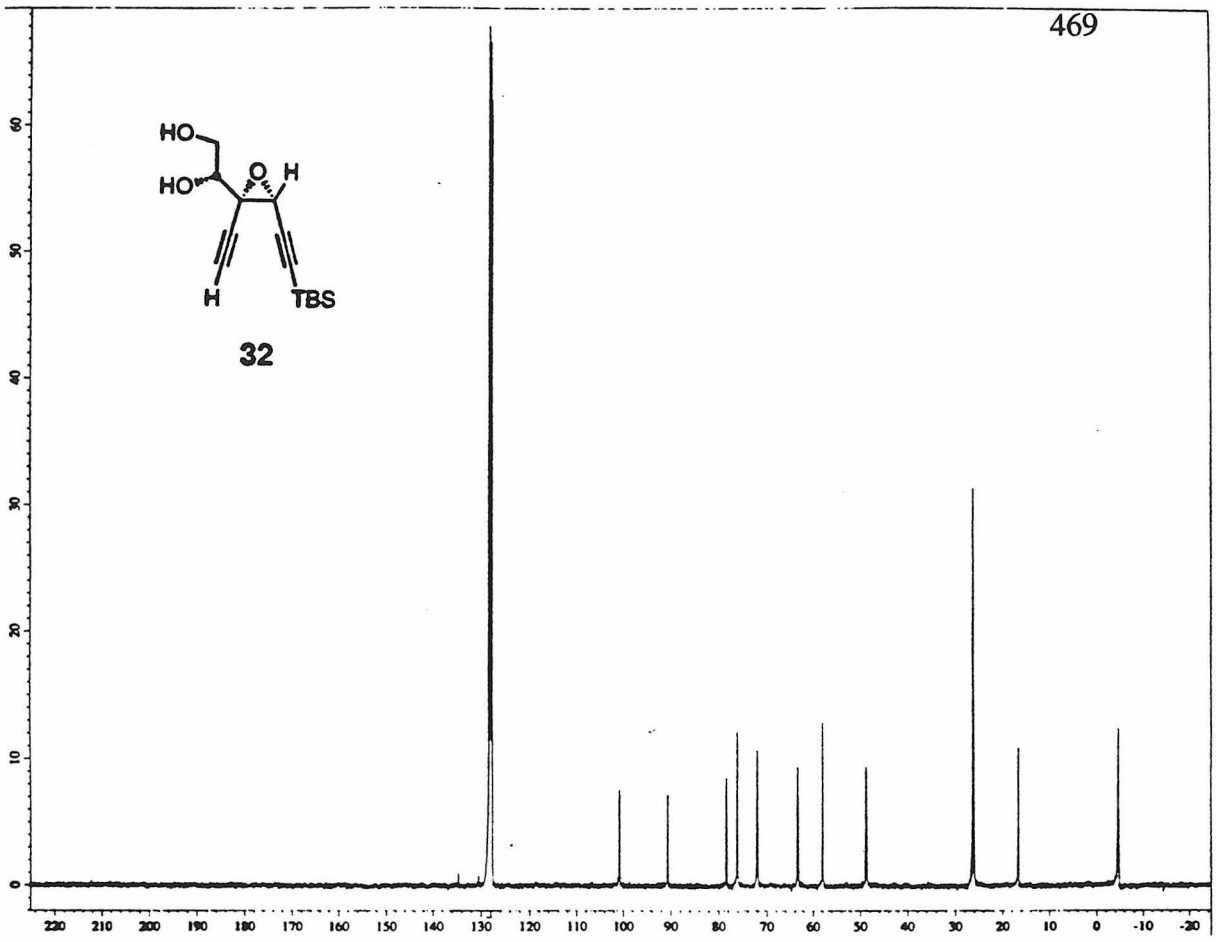
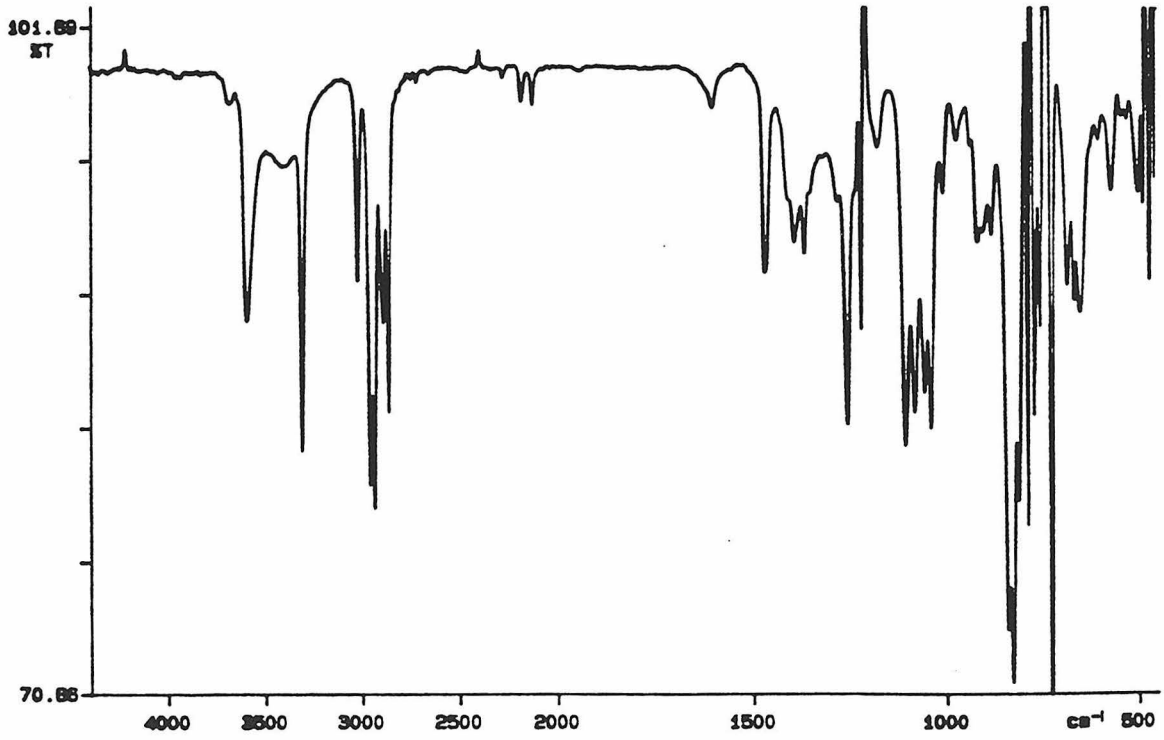
3500
3000
2500
2000
1500
1000
cm⁻¹
500


TBS
H
O
H
HO
HO
32


HO
HO
O
H
H
TBS

32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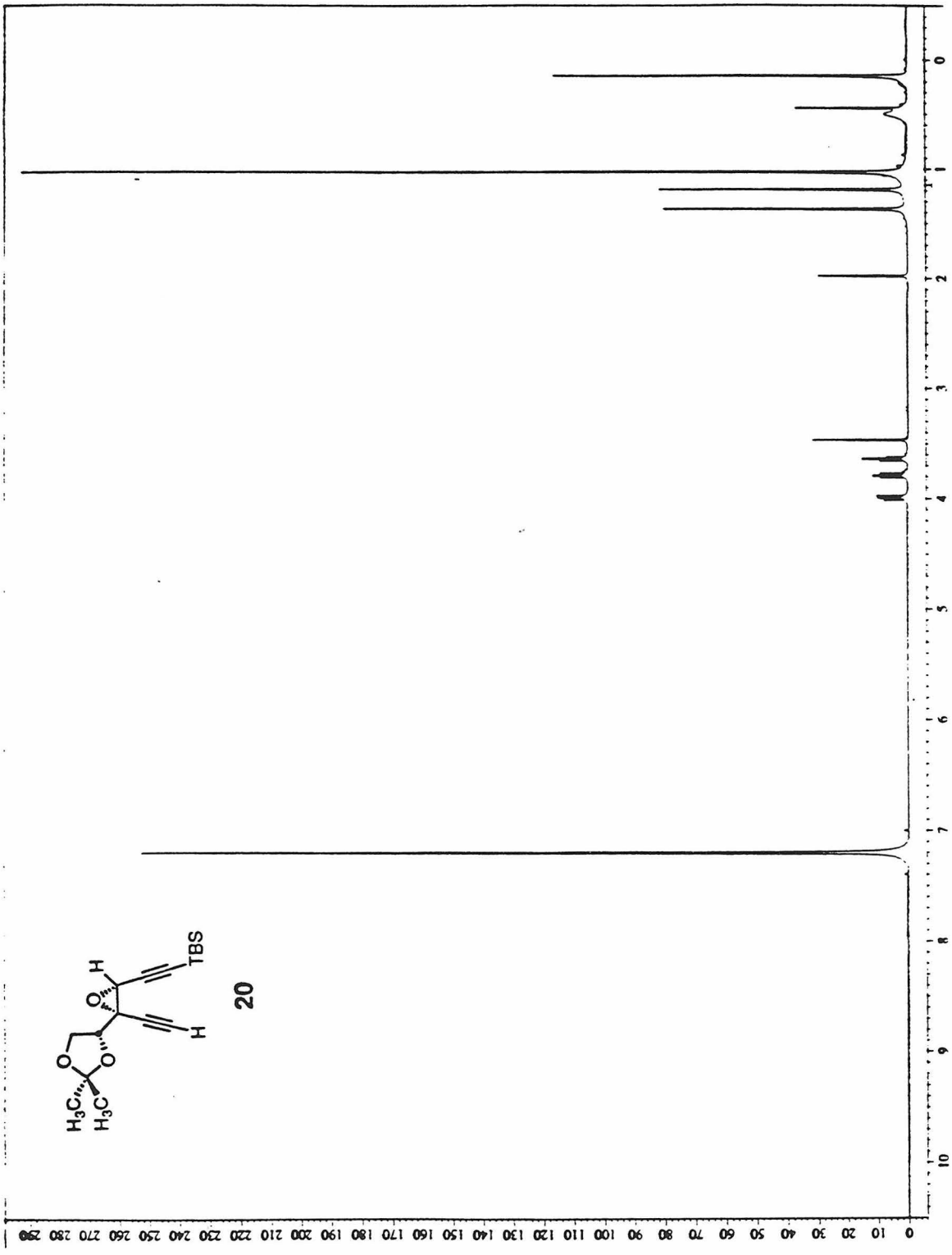
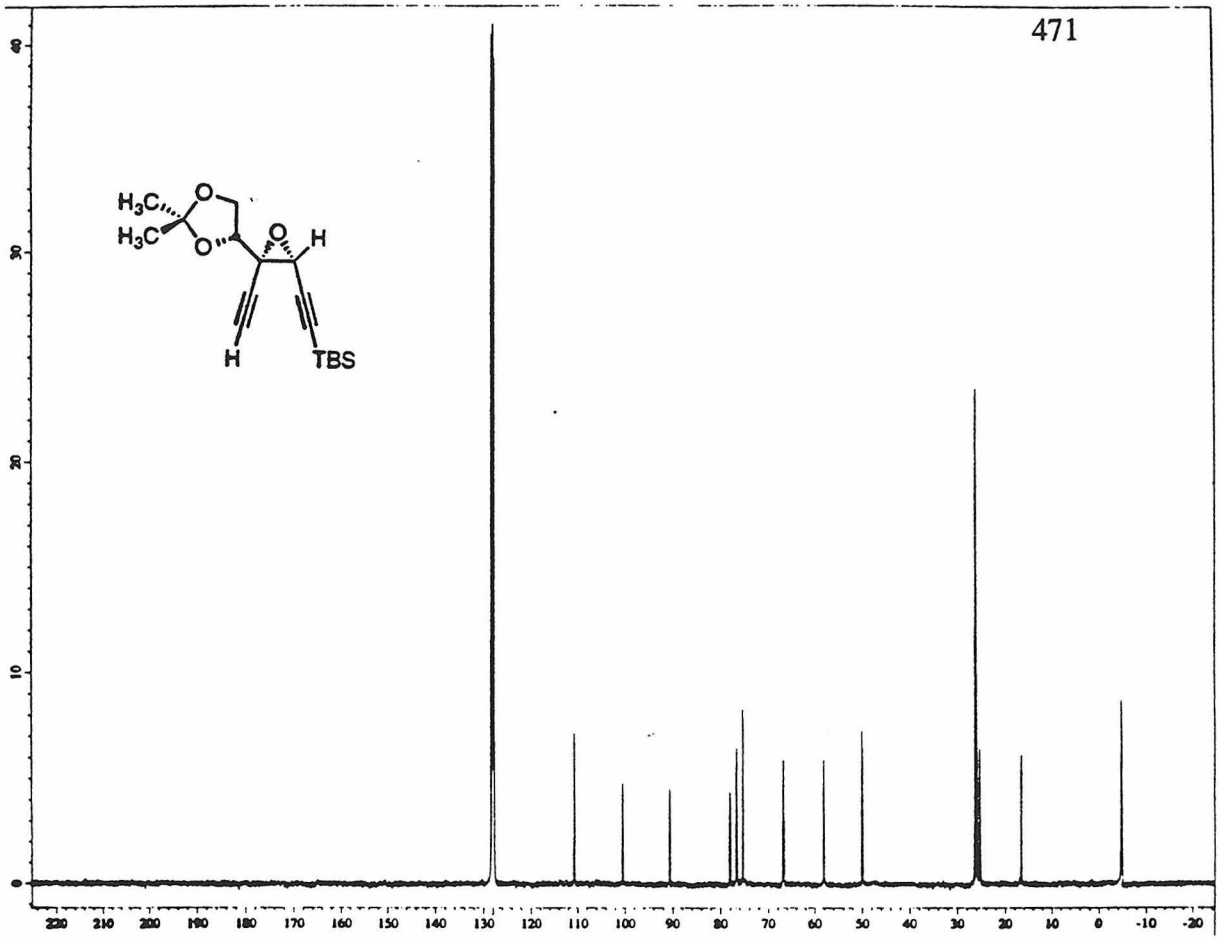
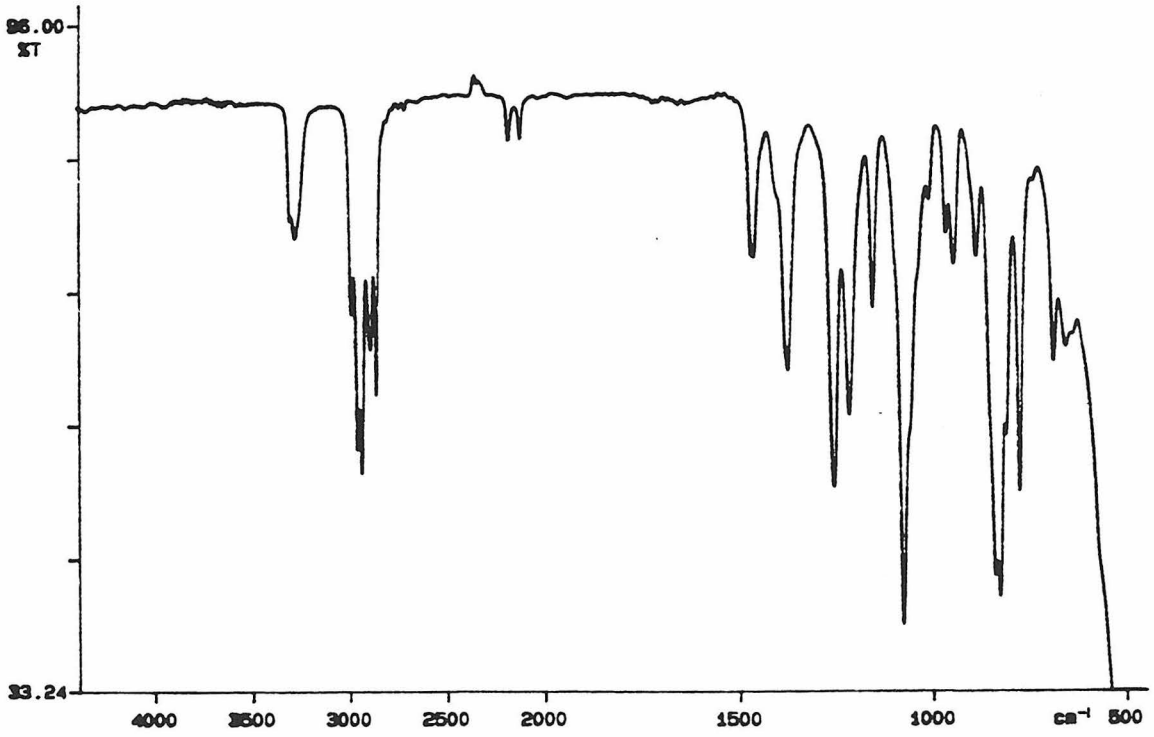
1500
1000
cm-1
500


TBS
H
O
H
O
O
H3C
H3C
20


H3C
H3C
O
O
O
H
H
TBS
40
30
20
10
0
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20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%T
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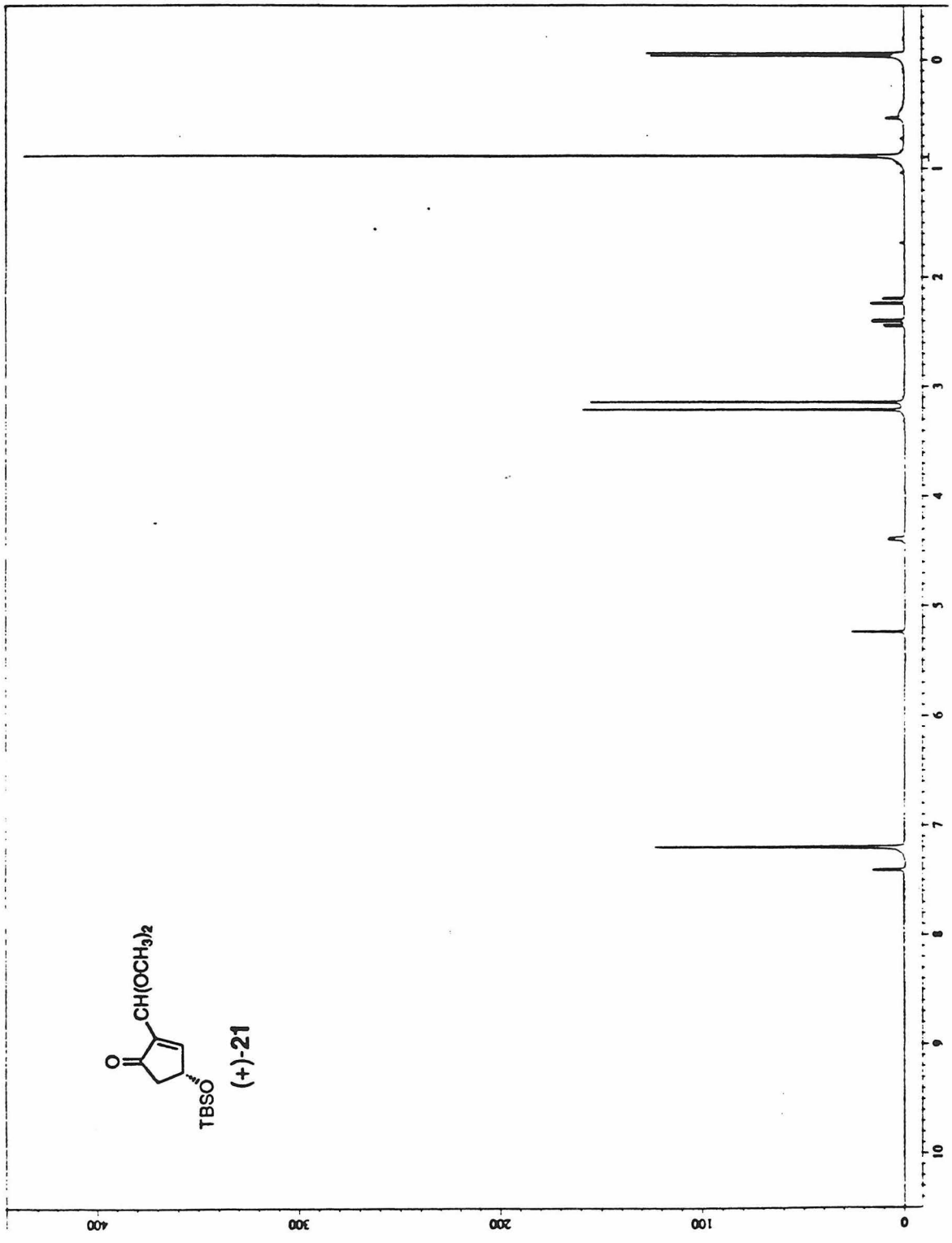
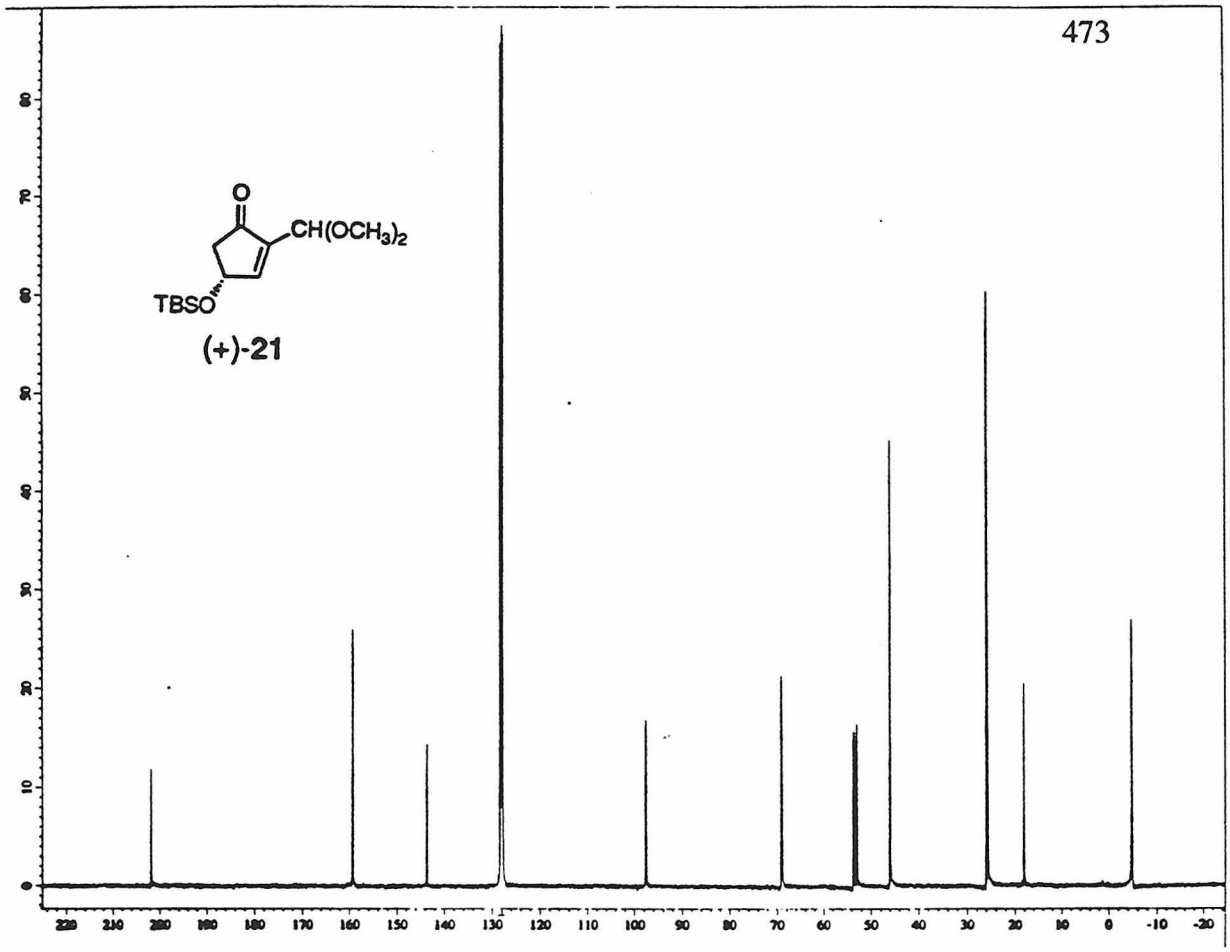
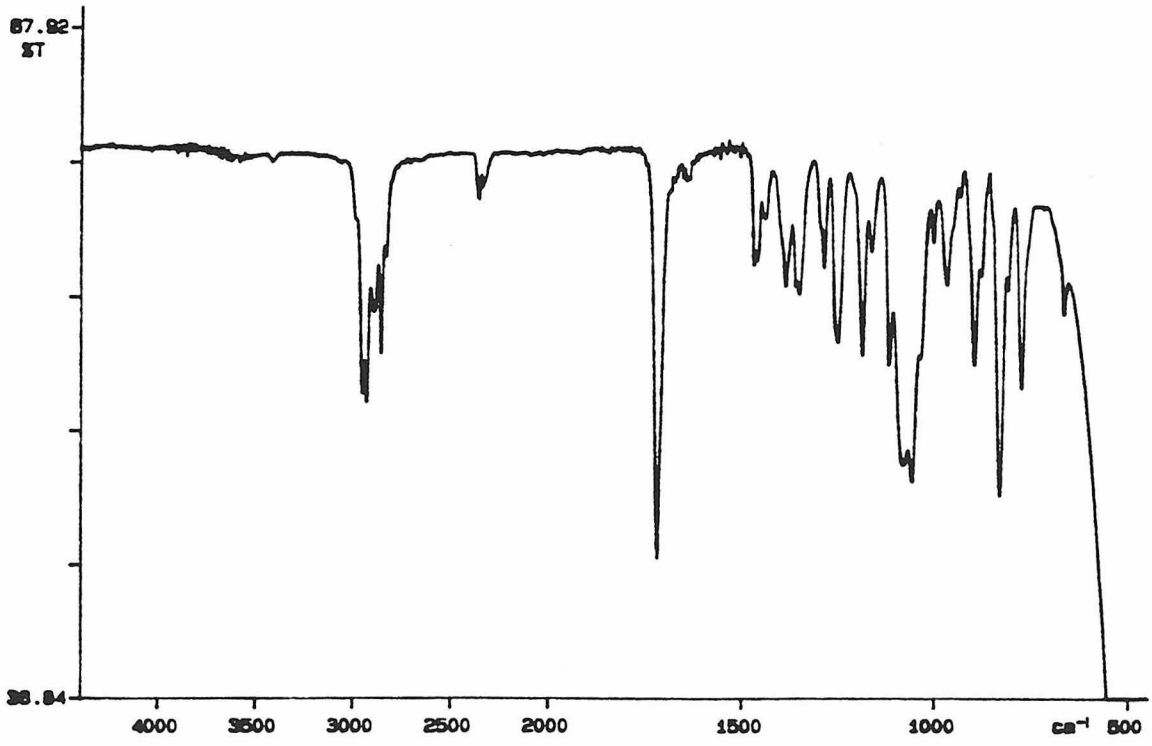
3500
3000
2500
2000
1500
1000
cm-1
500

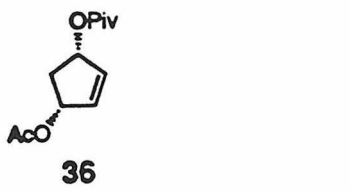

CH(OCH3)2
O
TBSO
(+)-21


O
CH(OCH3)2
TBSO

(+)-21

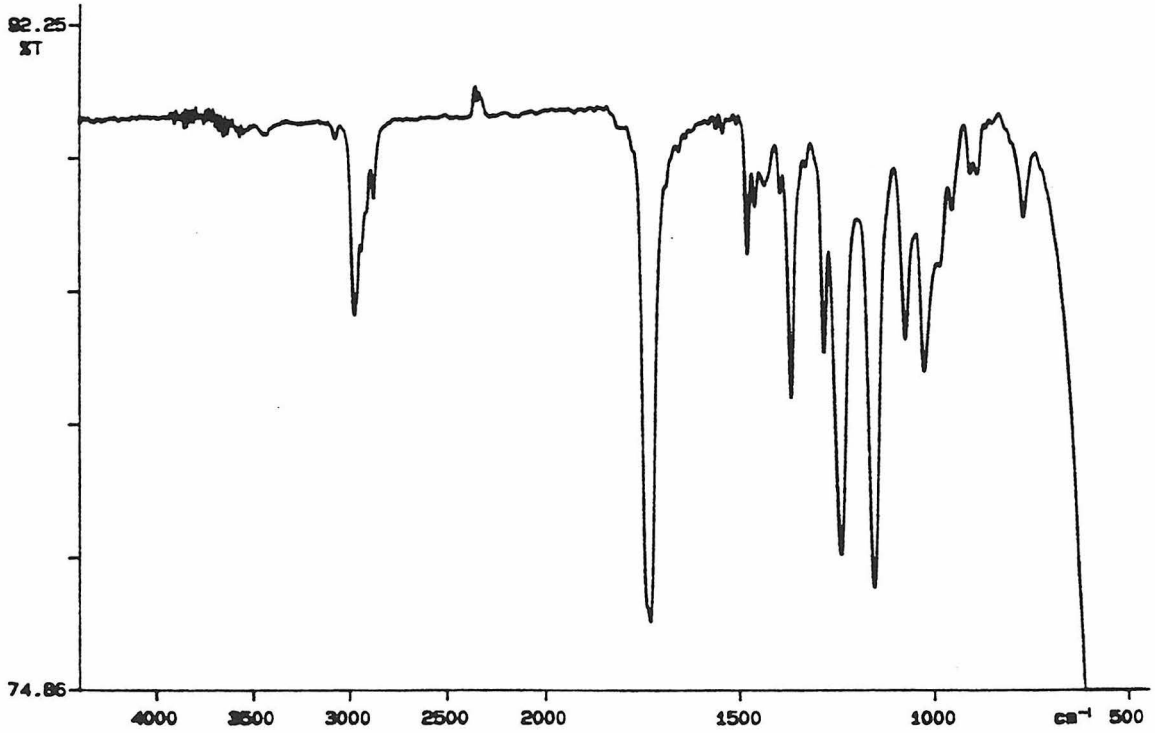

87.92
%T
38.84
4000
3500
3000
2500
2000
1500
1000
cm-1
500

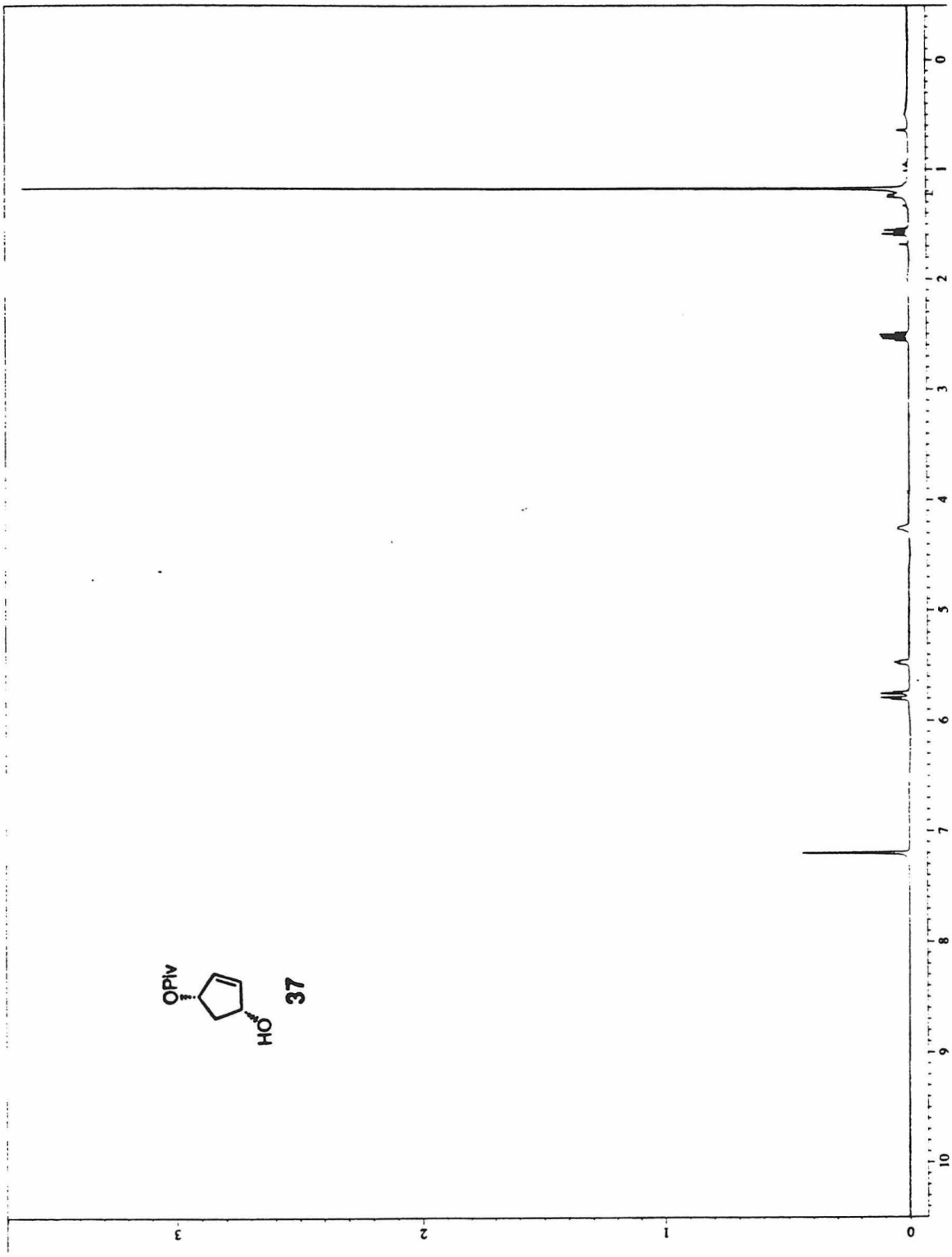

OPiv
AcO
36

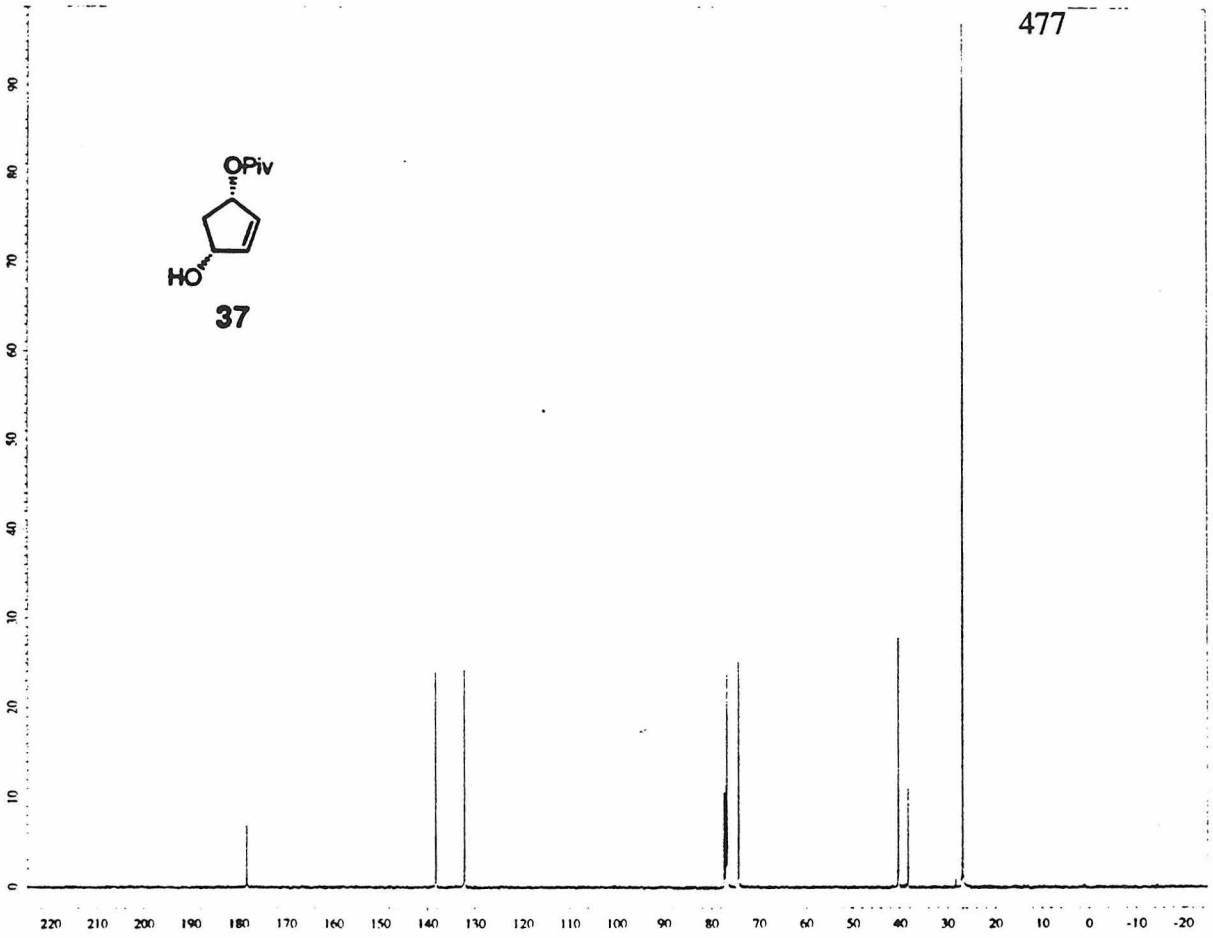

OPiv
AcO

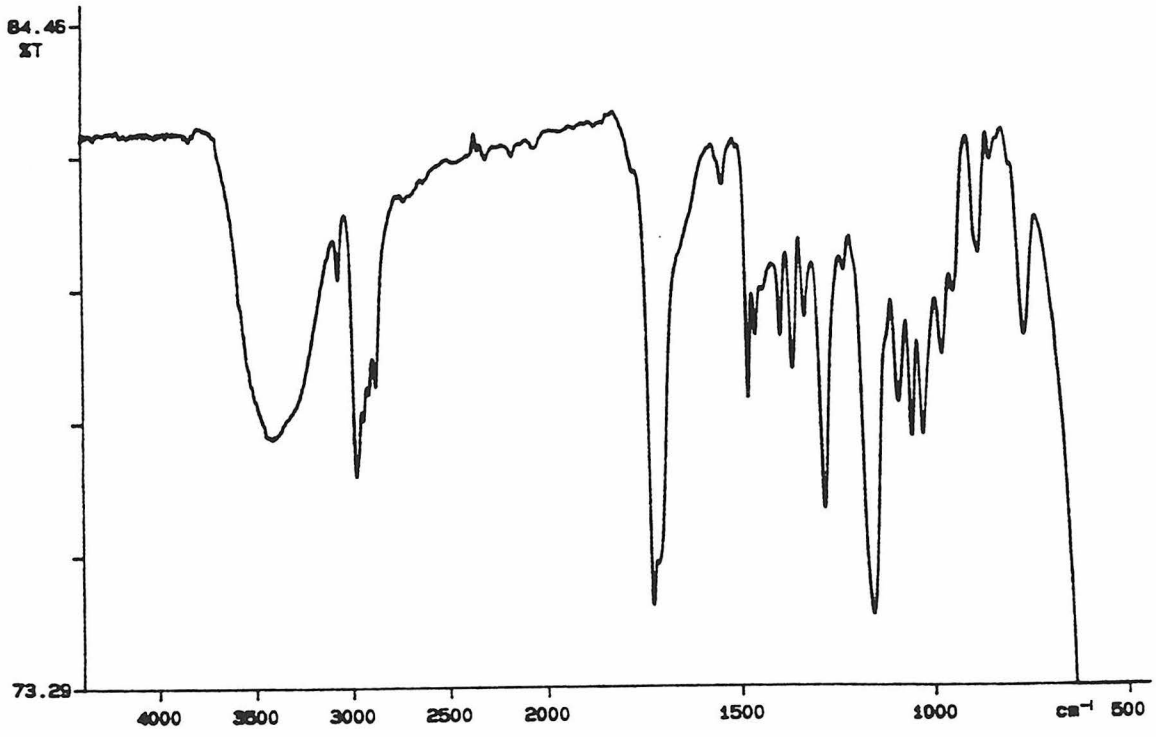
36

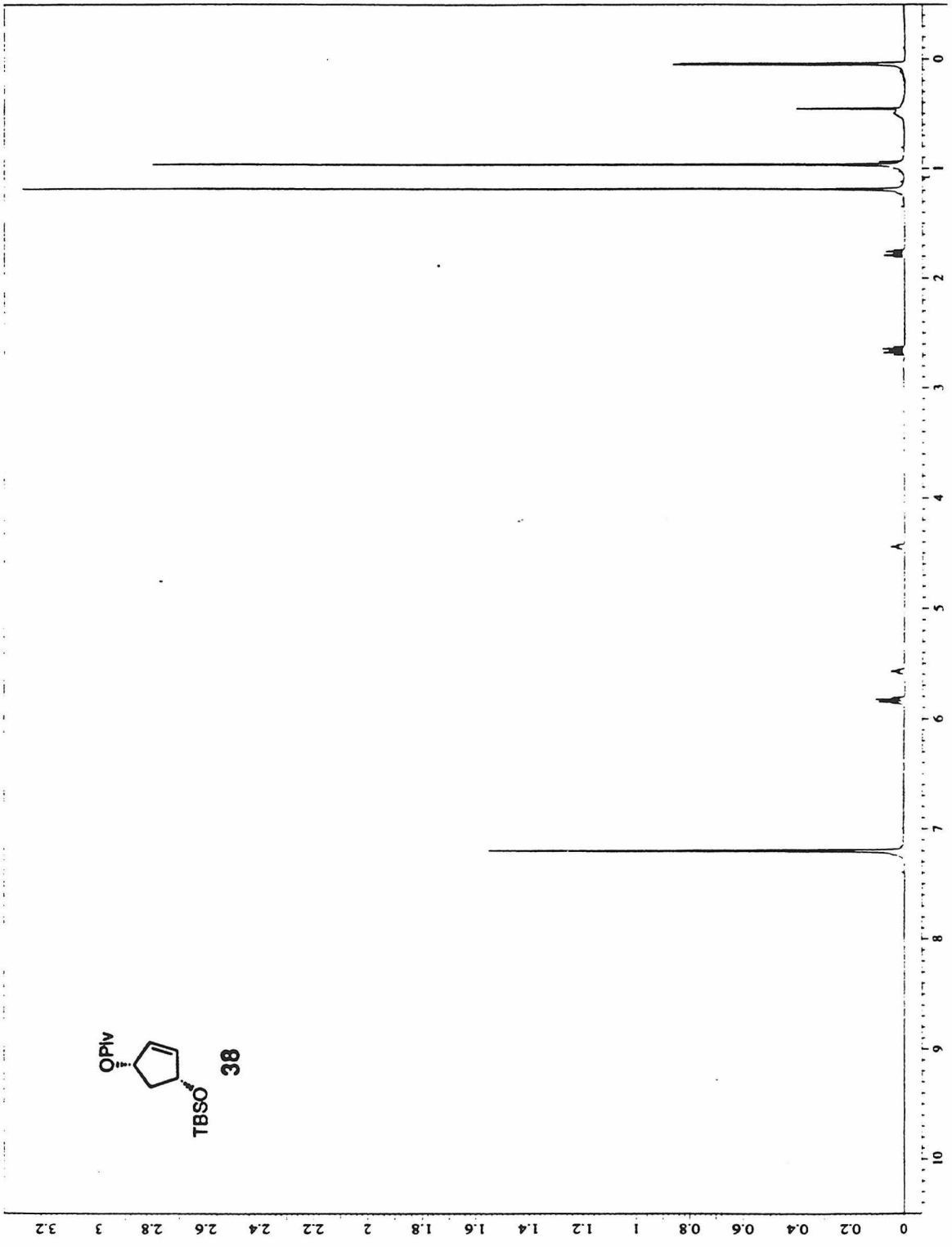
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20

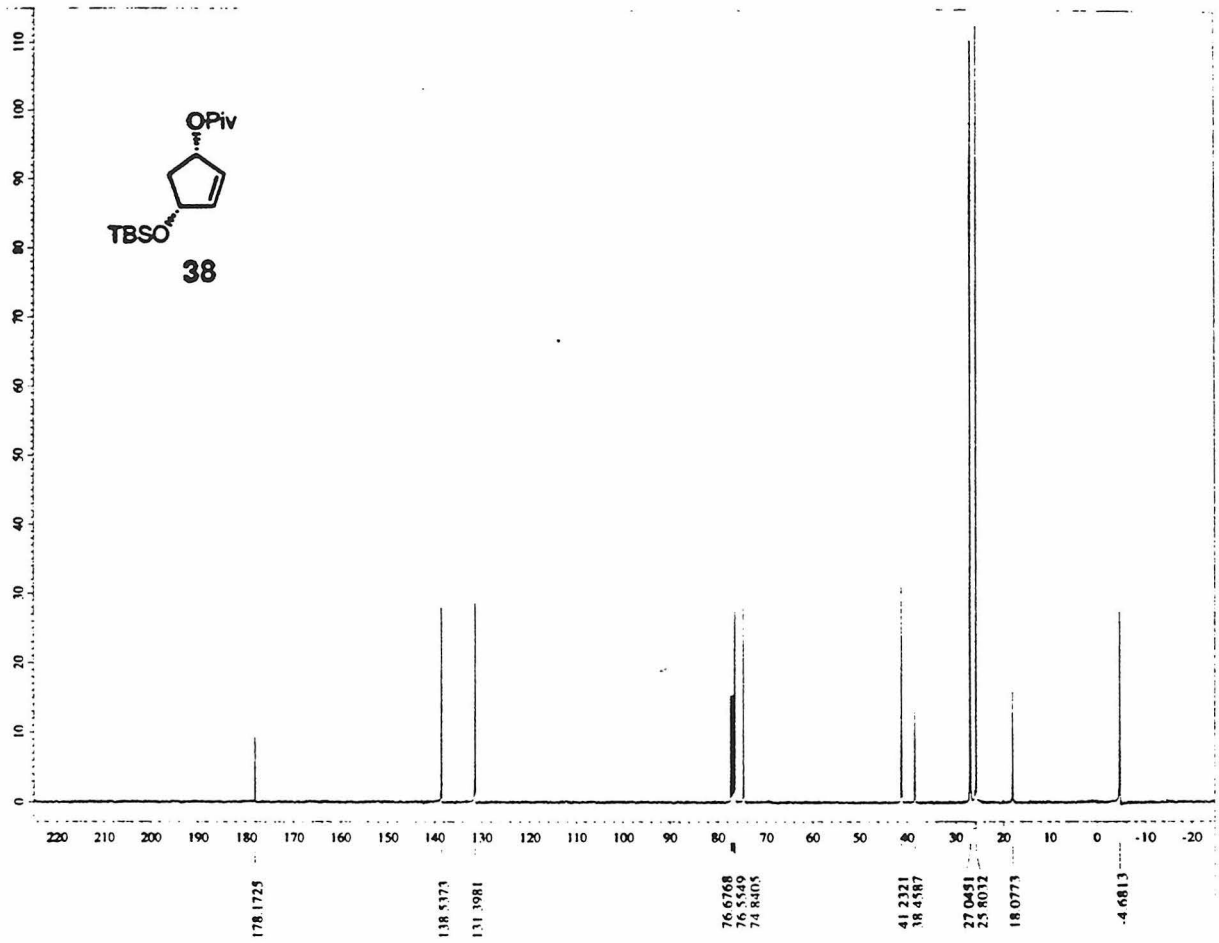

92.25
%T
74.86
4000 3500 3000 2500 2000 1500 1000 cm⁻¹ 500

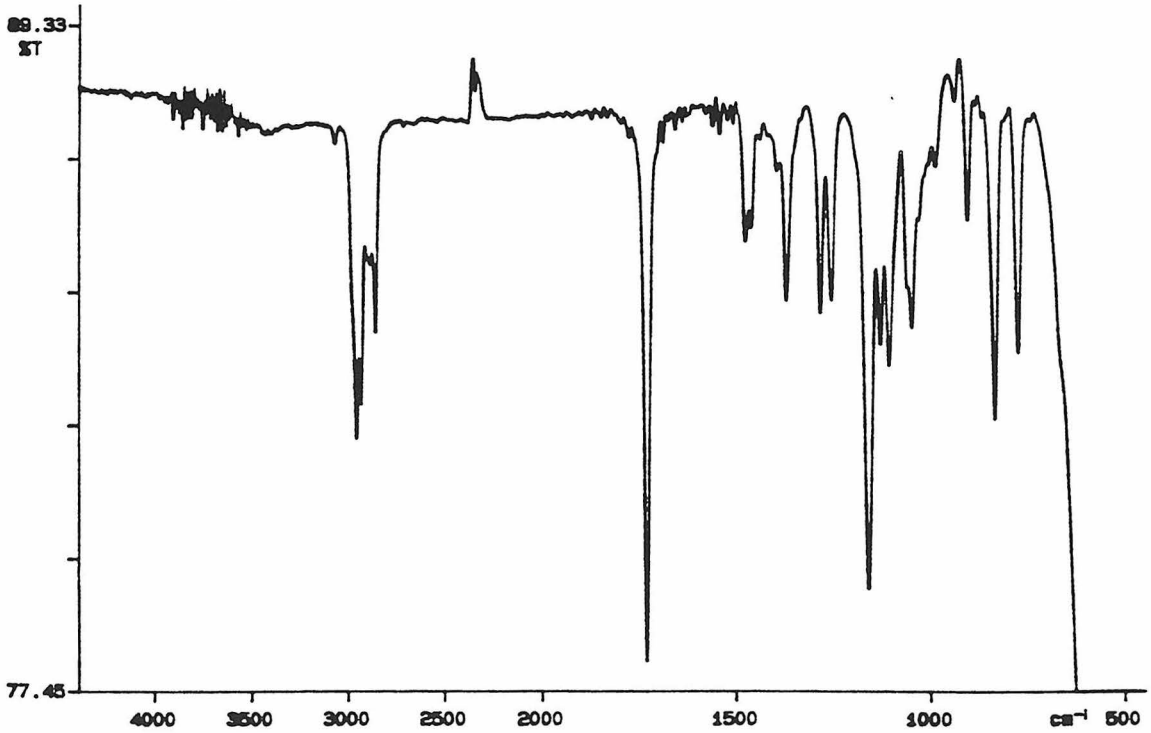

OPiv
HO
37

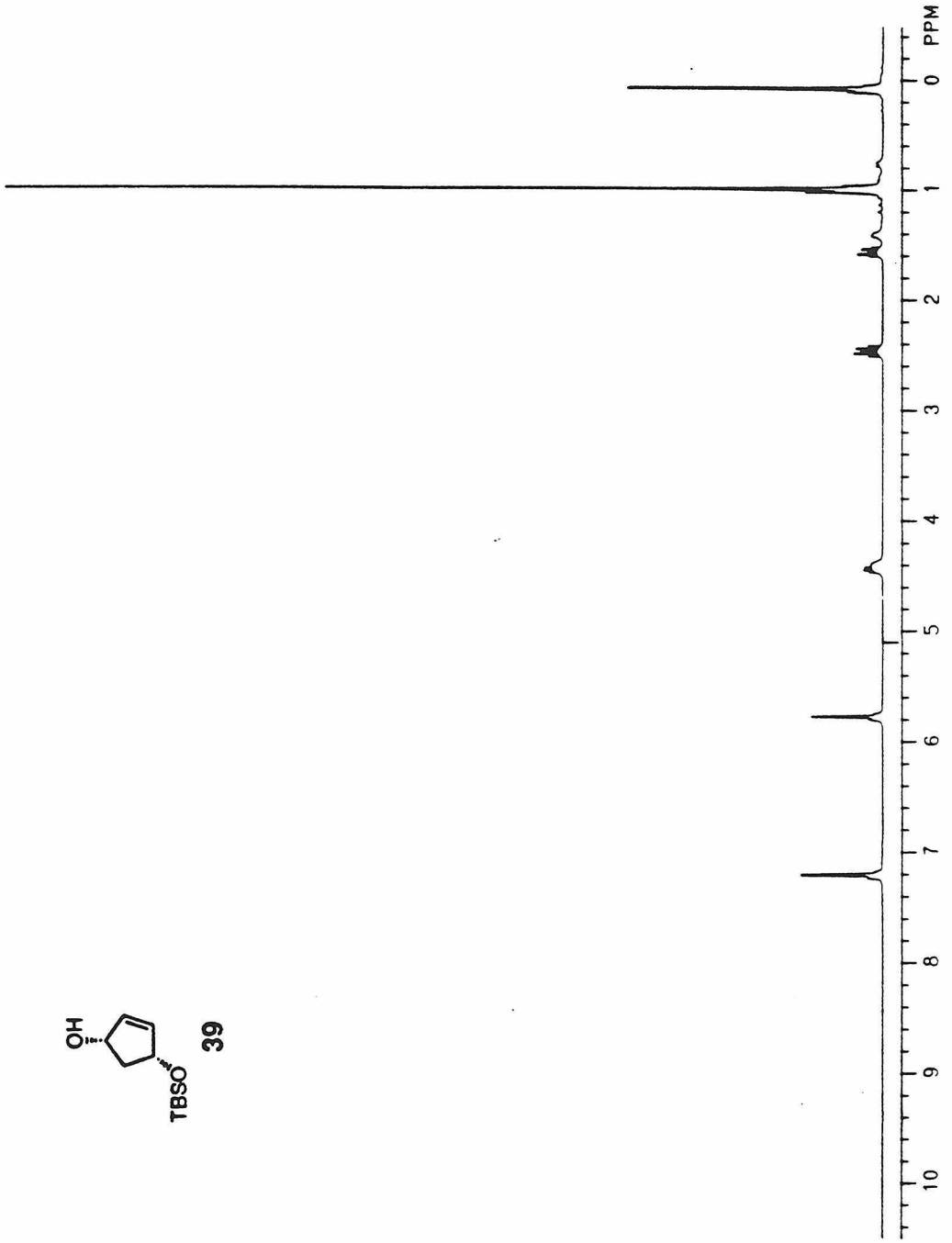

OPiv
HO
37
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20

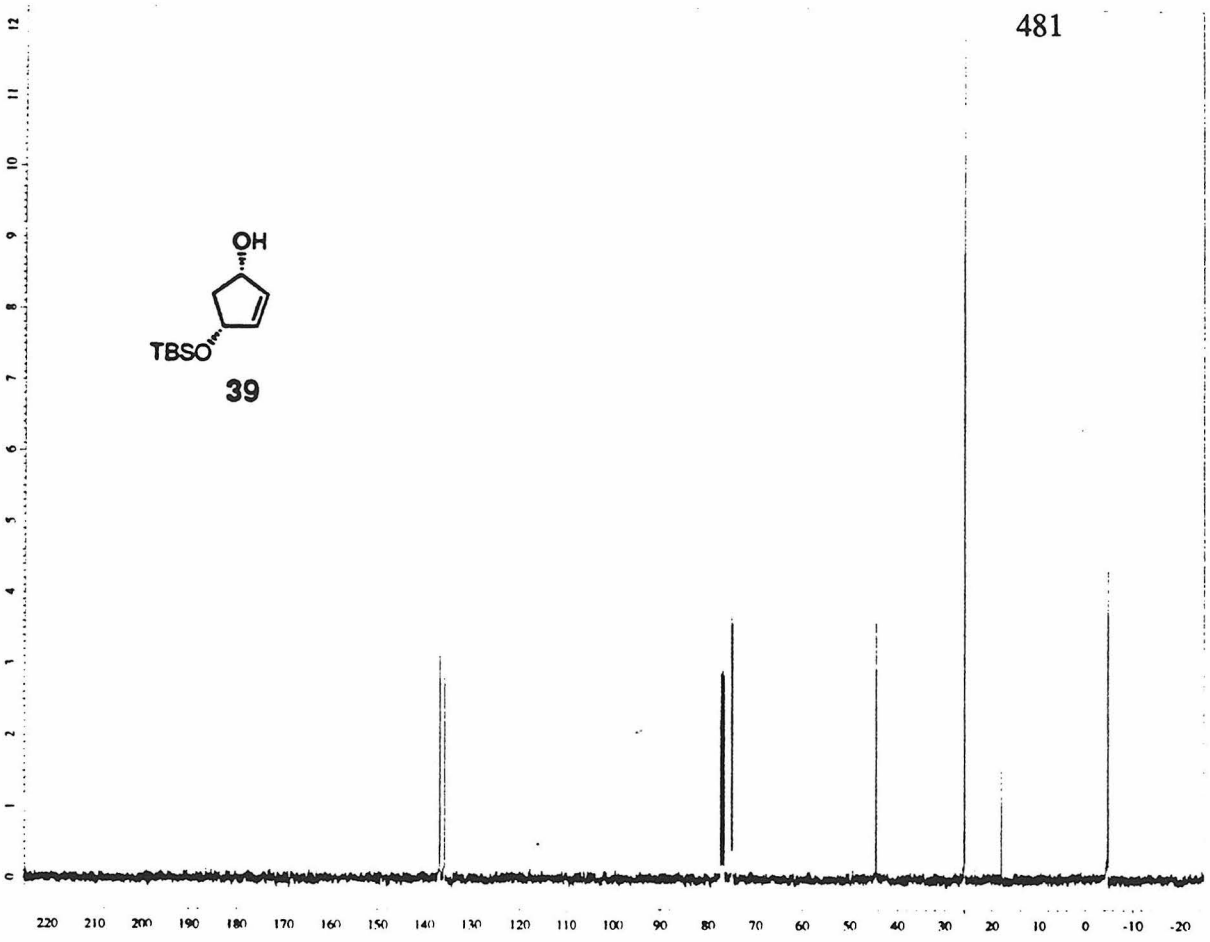

84.46
%T
73.29
4000 3500 3000 2500 2000 1500 1000 cm⁻¹ 500

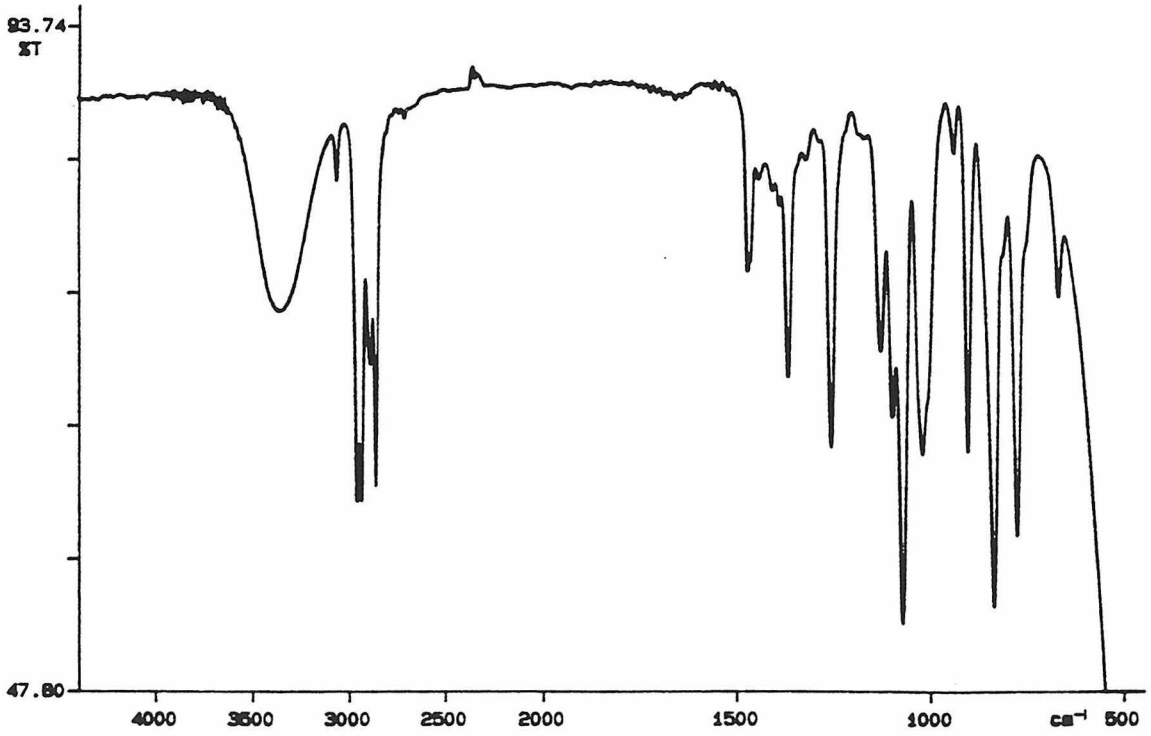

OPiv
TBSO
38

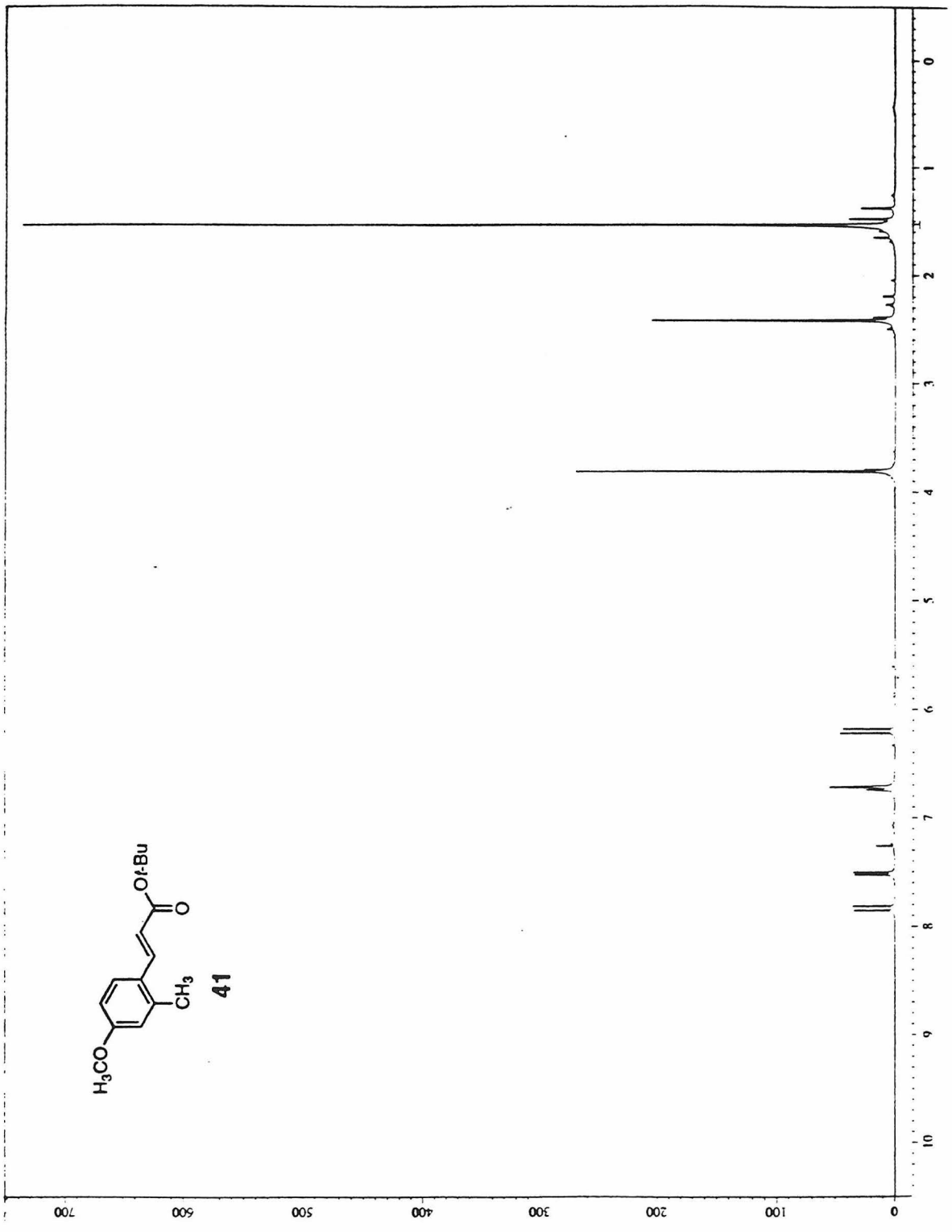

OPiv
TBSO
38
178.1725
138.5373
131.3981
76.6768
76.5549
74.8405
41.2321
38.4587
27.0451
25.8032
18.0773
-4.6813

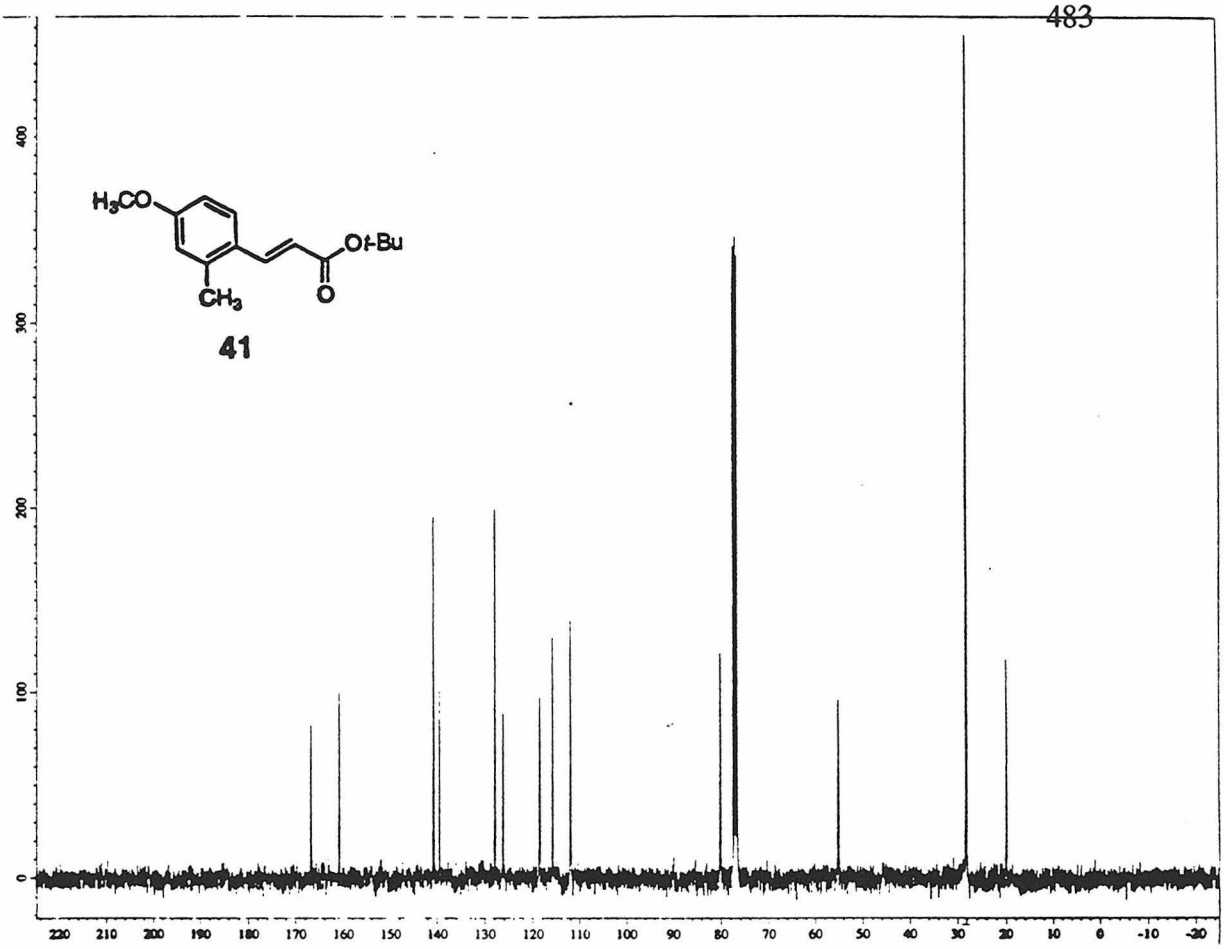

89.33
%T
77.45
4000
3500
3000
2500
2000
1500
1000
cm-1
500

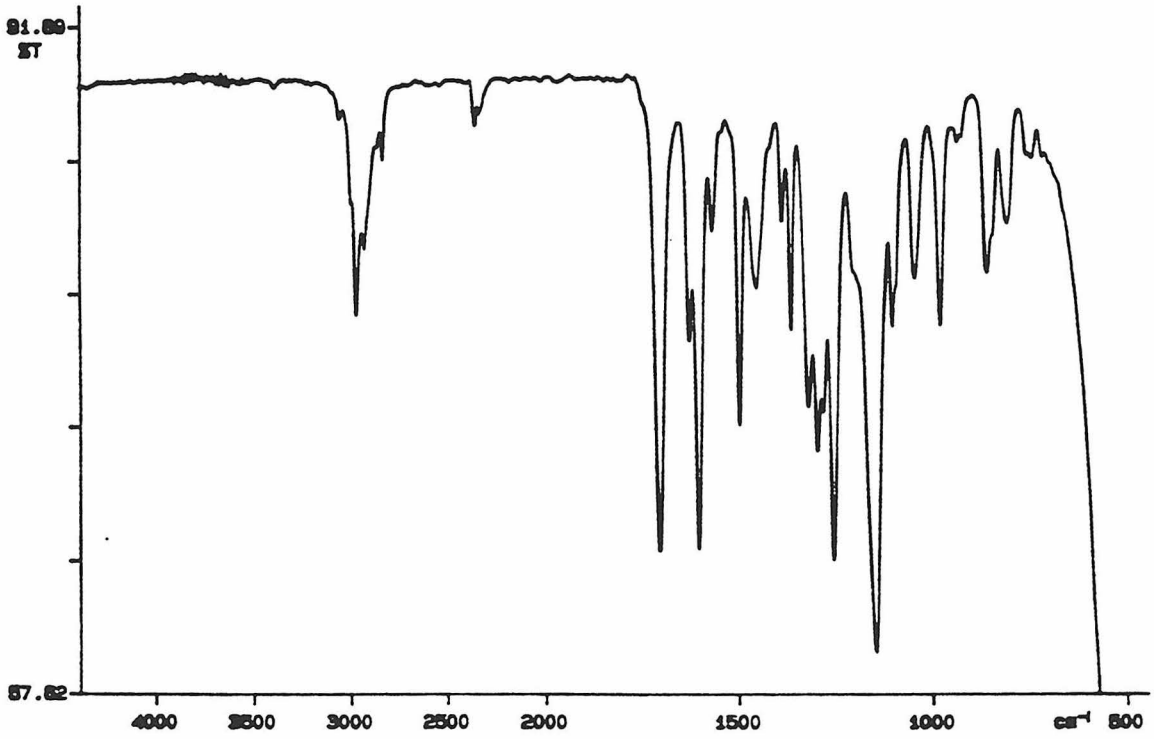

OH
TBSO
39
PPM
0
1
2
3
4
5
6
7
8
9
10

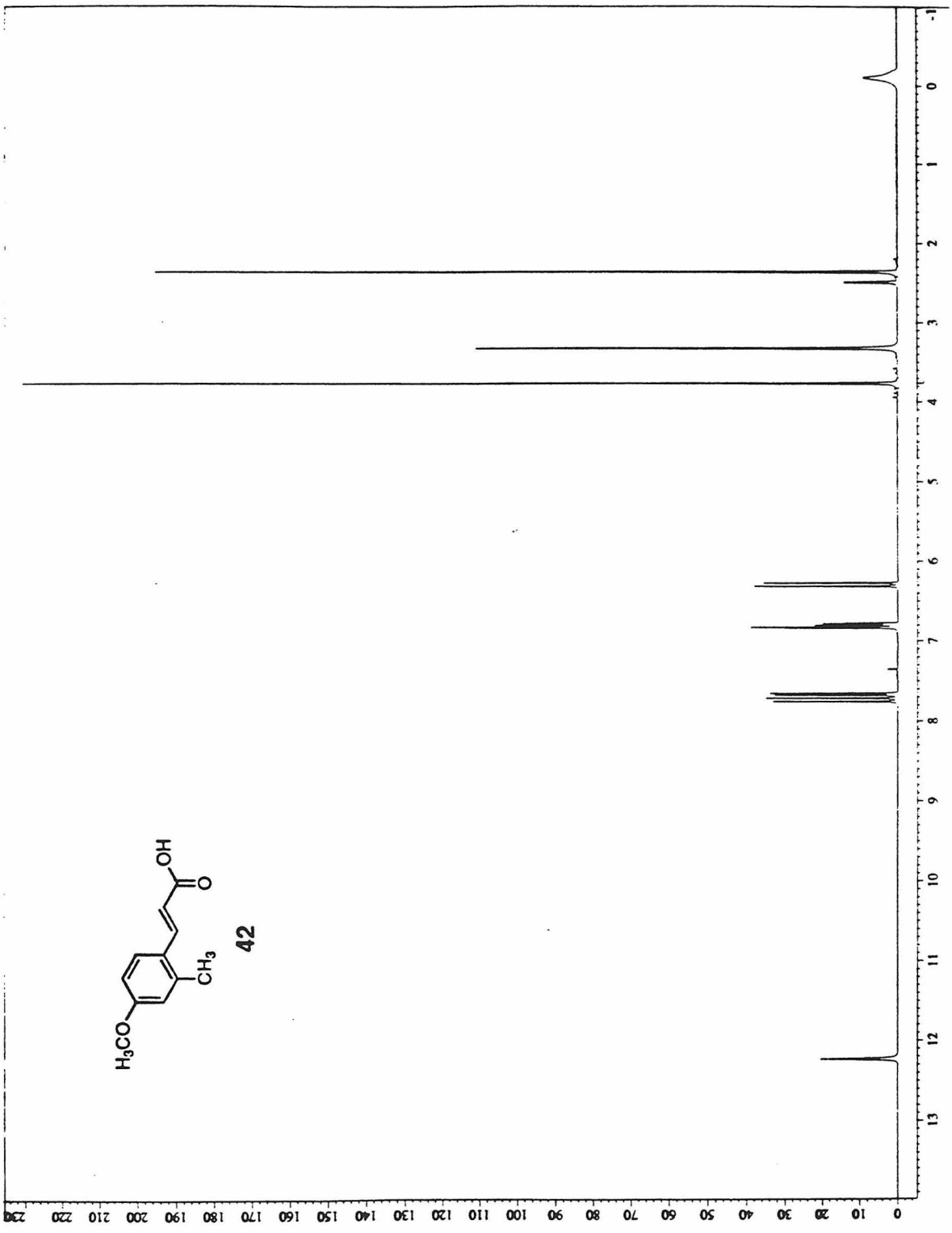

OH
TBSO
39
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20


93.74
%T
47.80
4000 3500 3000 2500 2000 1500 1000 cm⁻¹ 500

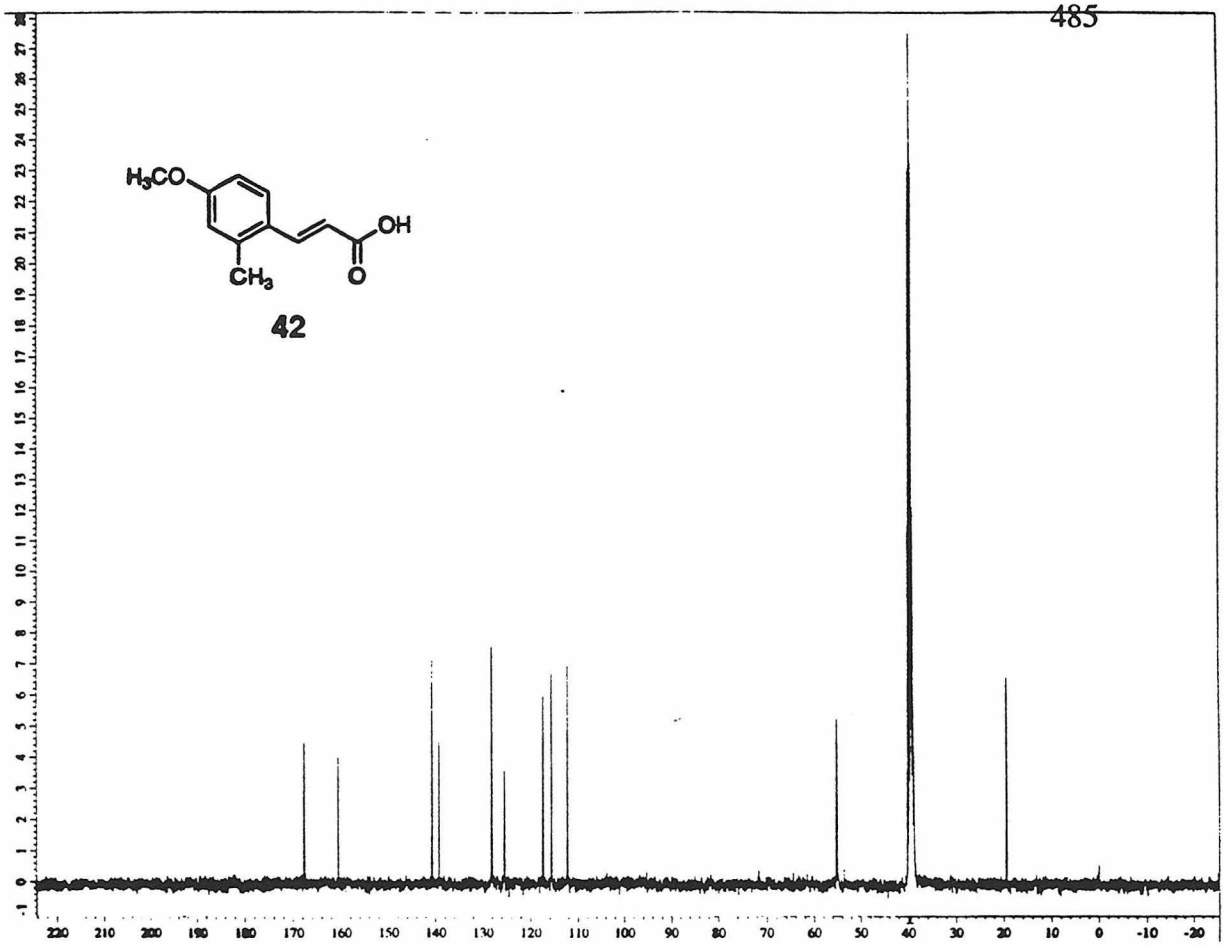

O-t-Bu
O
CH3
H3CO
41


H3CO
Ot-Bu
CH3
O
41
400
300
200
100
0
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20

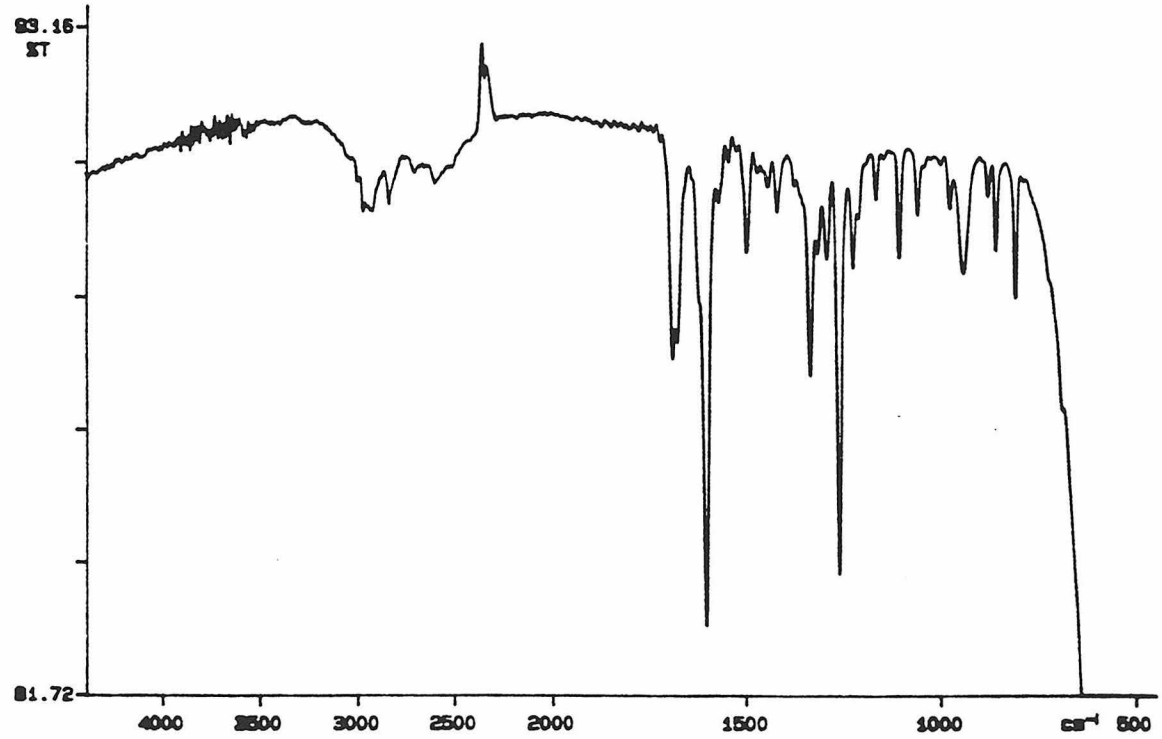

91.89
%T
57.62
4000 3500 3000 2500 2000 1500 1000 cm-1 500

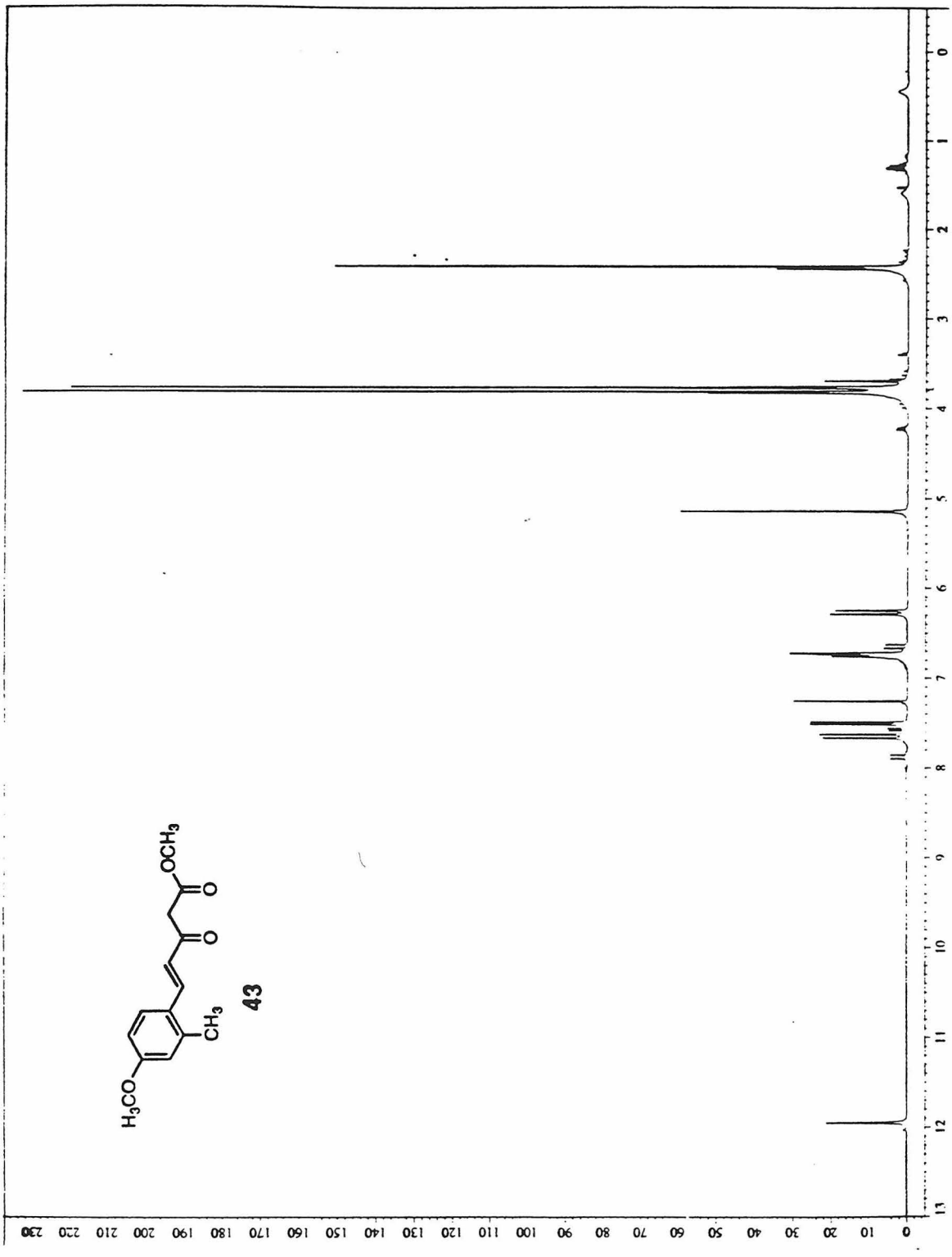


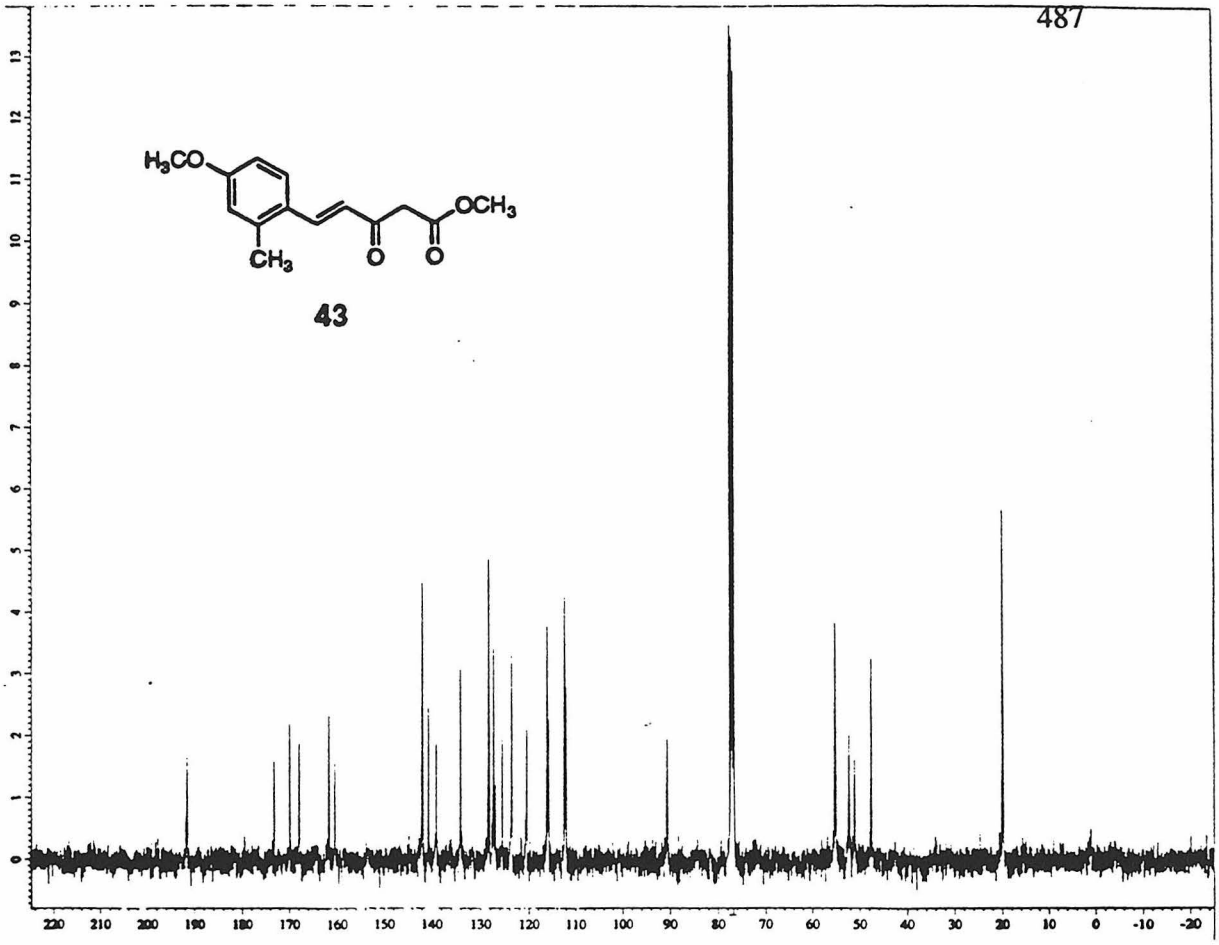
42


H3CO
OH
O
CH3

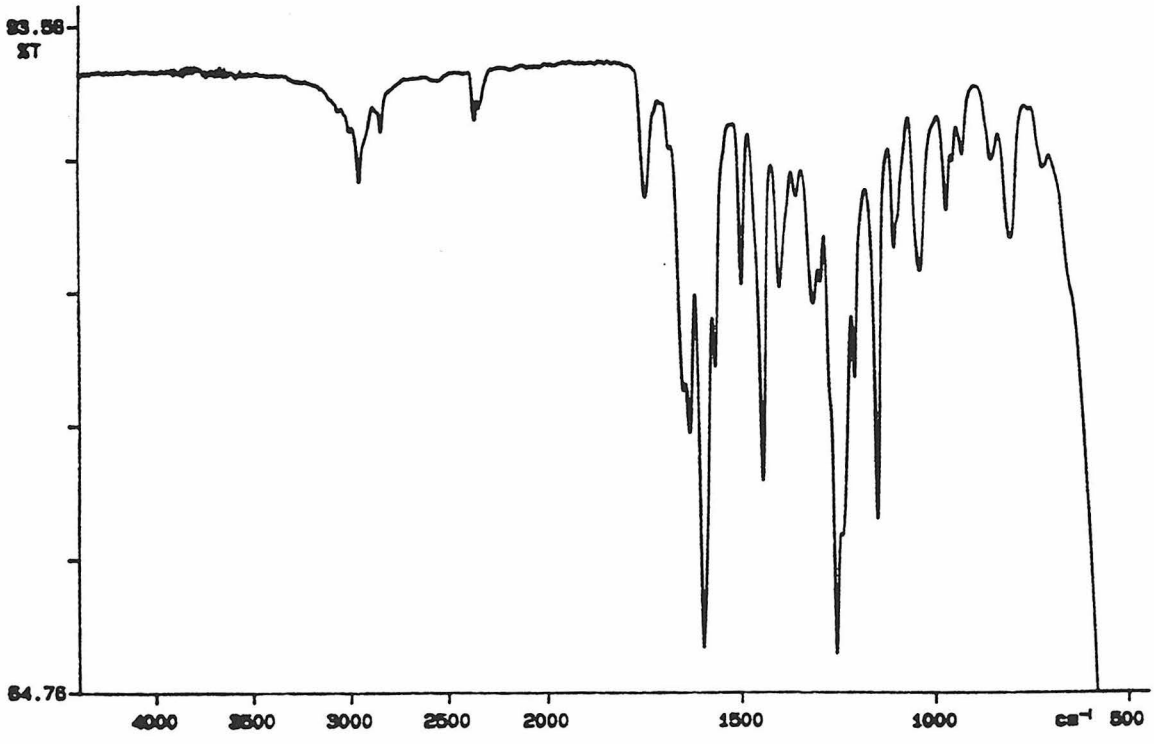
42

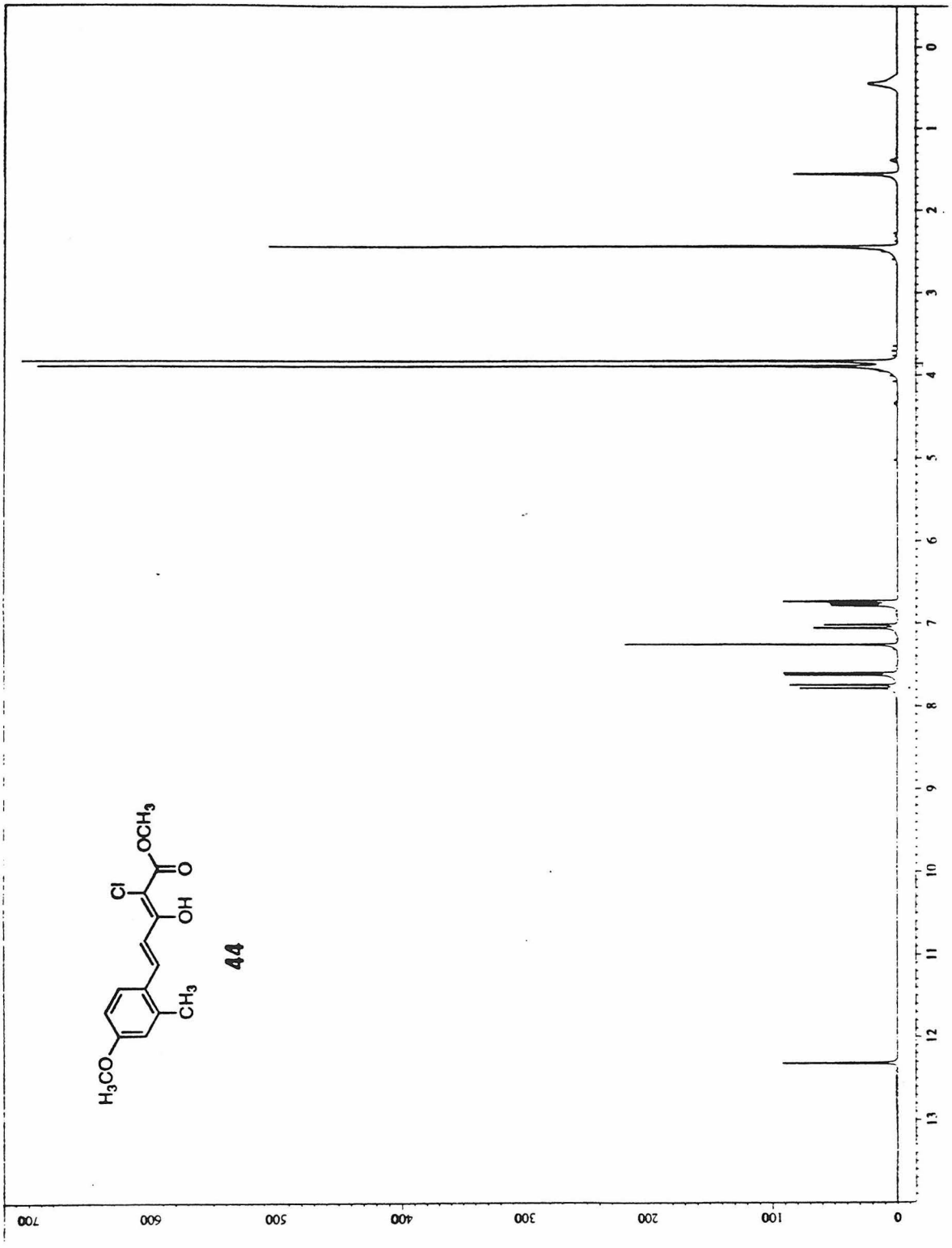

93.16
%T
81.72
4000
3500
3000
2500
2000
1500
1000
cm-1
500

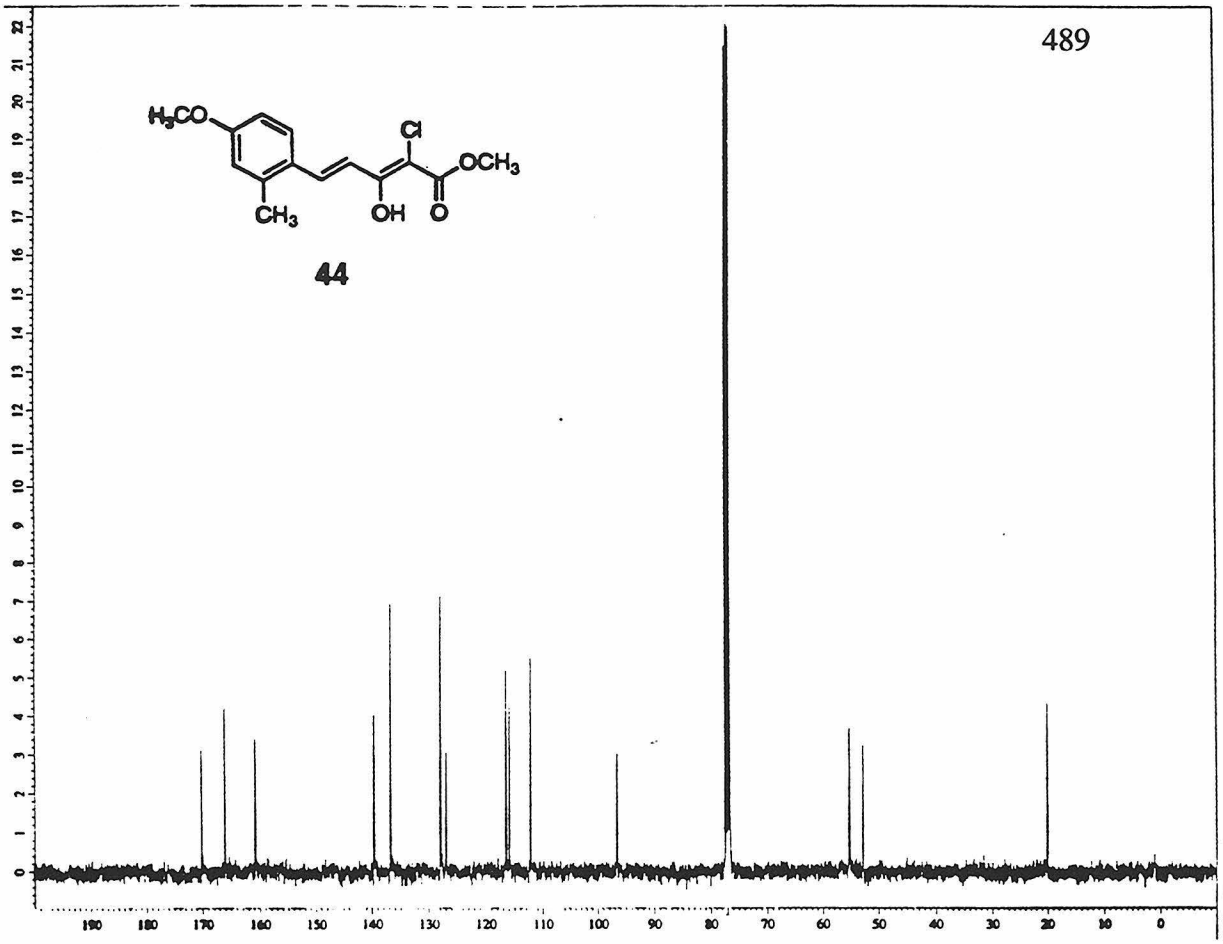

H3CO
CH3
OCH3
O
O
43


H3CO
OCH3
CH3
O
O

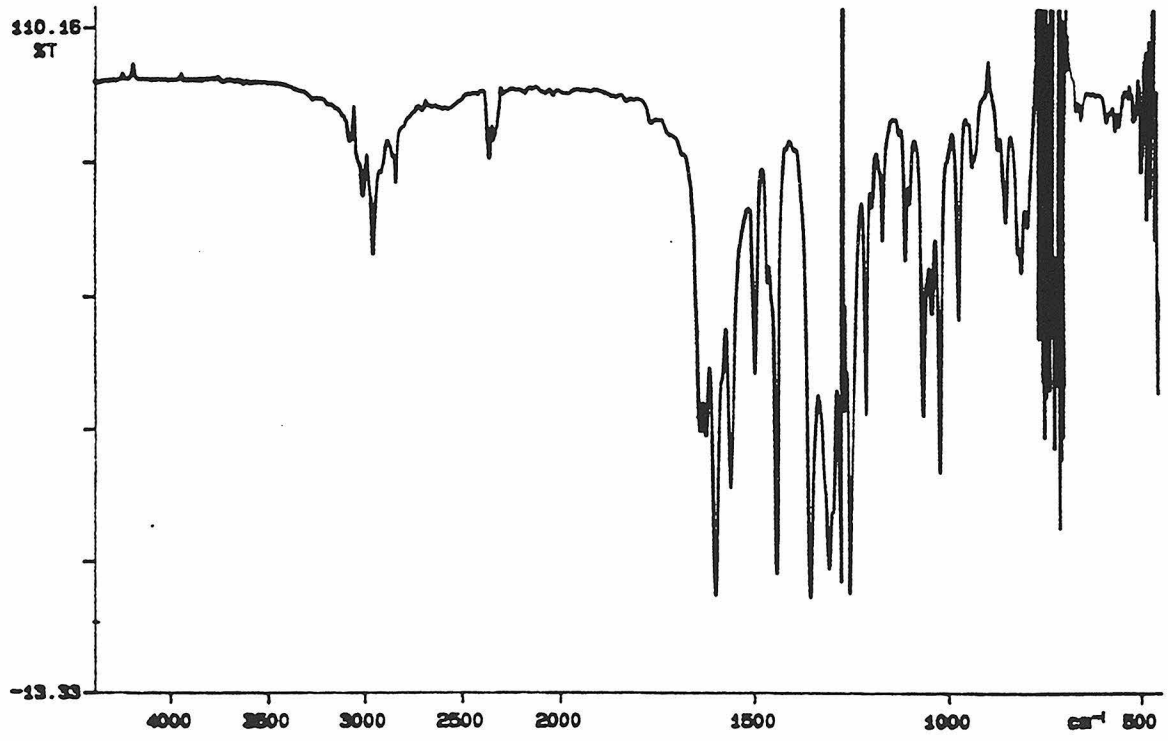
43

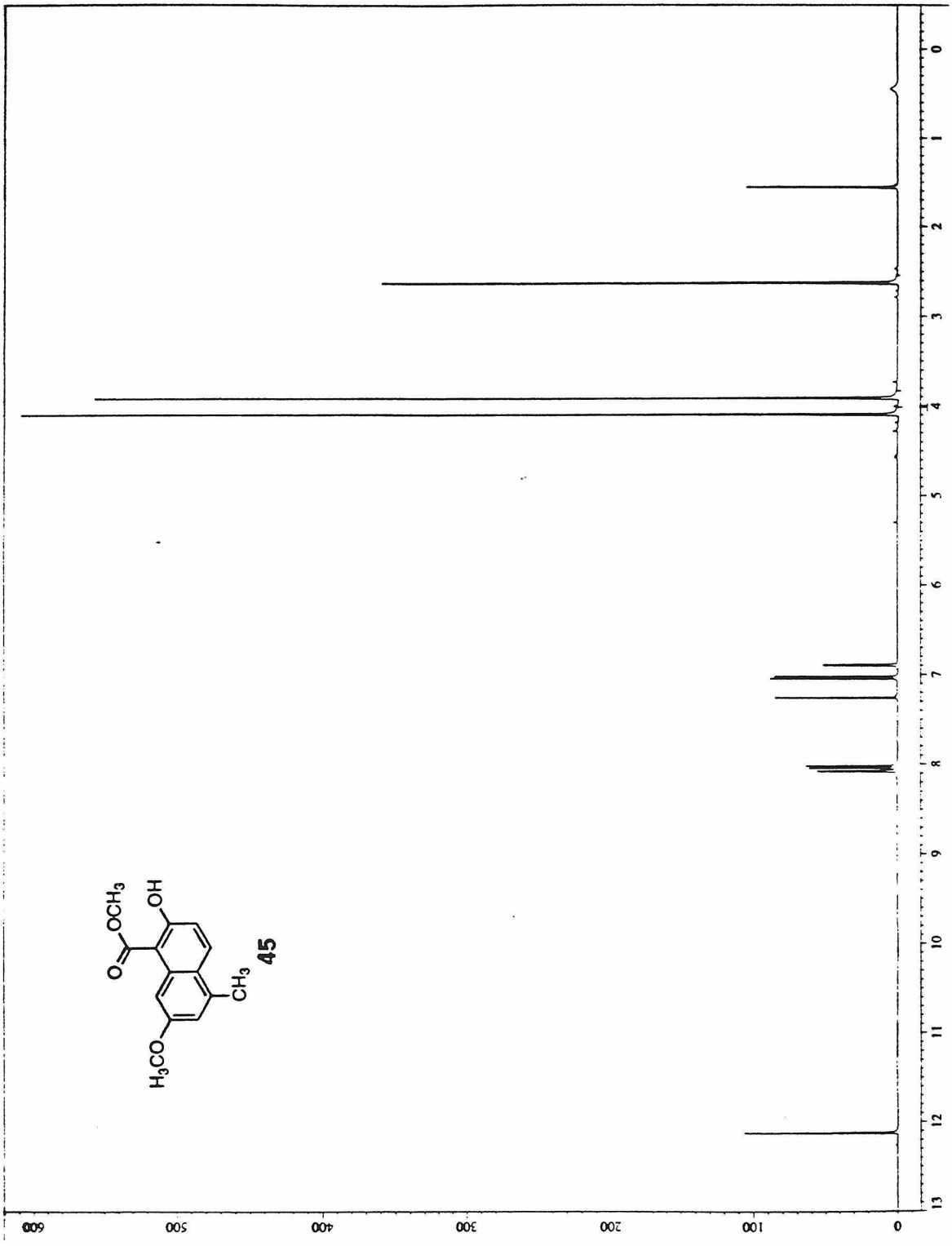

93.58
%T
64.78
4000
3500
3000
2500
2000
1500
1000
cm-1
500

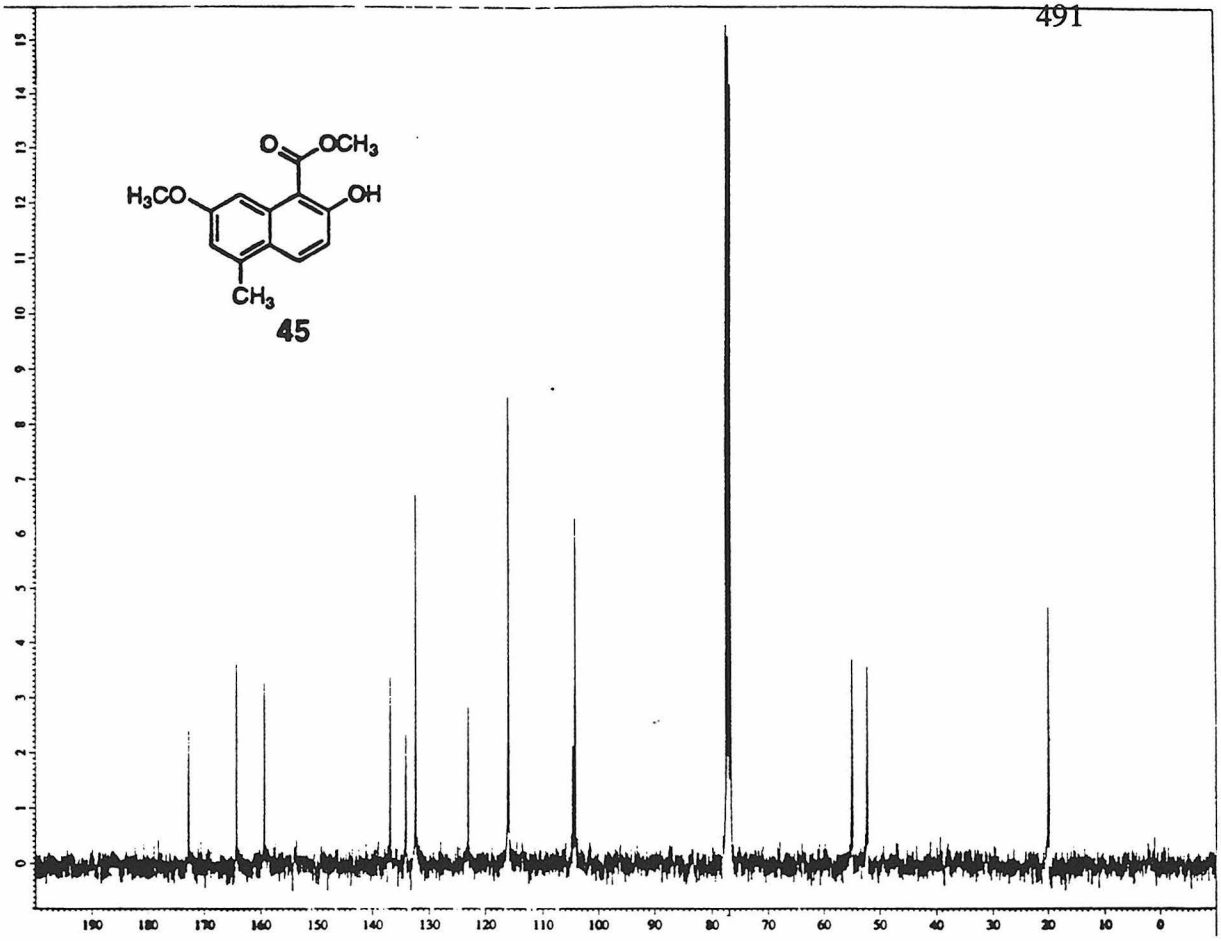

OCH3
Cl
O
OH
CH3
H3CO
44


H3CO
Cl
OCH3
CH3
OH
O

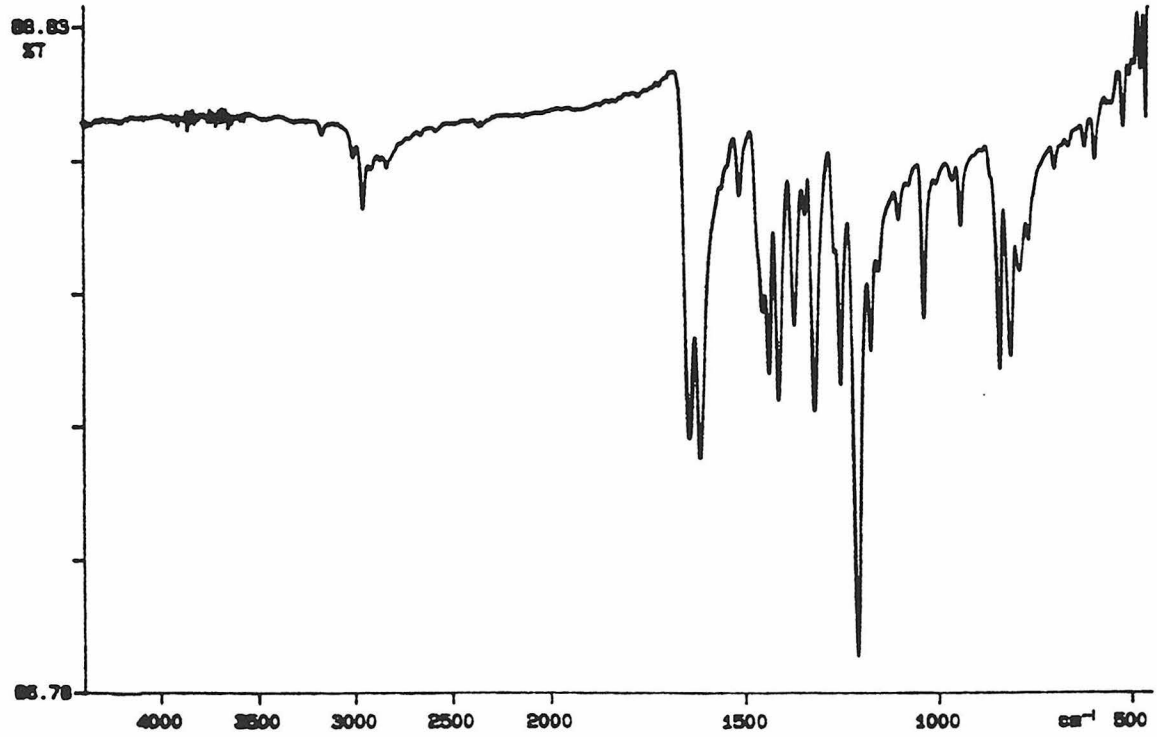
44


110.16
%T
-13.33
4000
3500
3000
2500
2000
1500
1000
cm-1
500

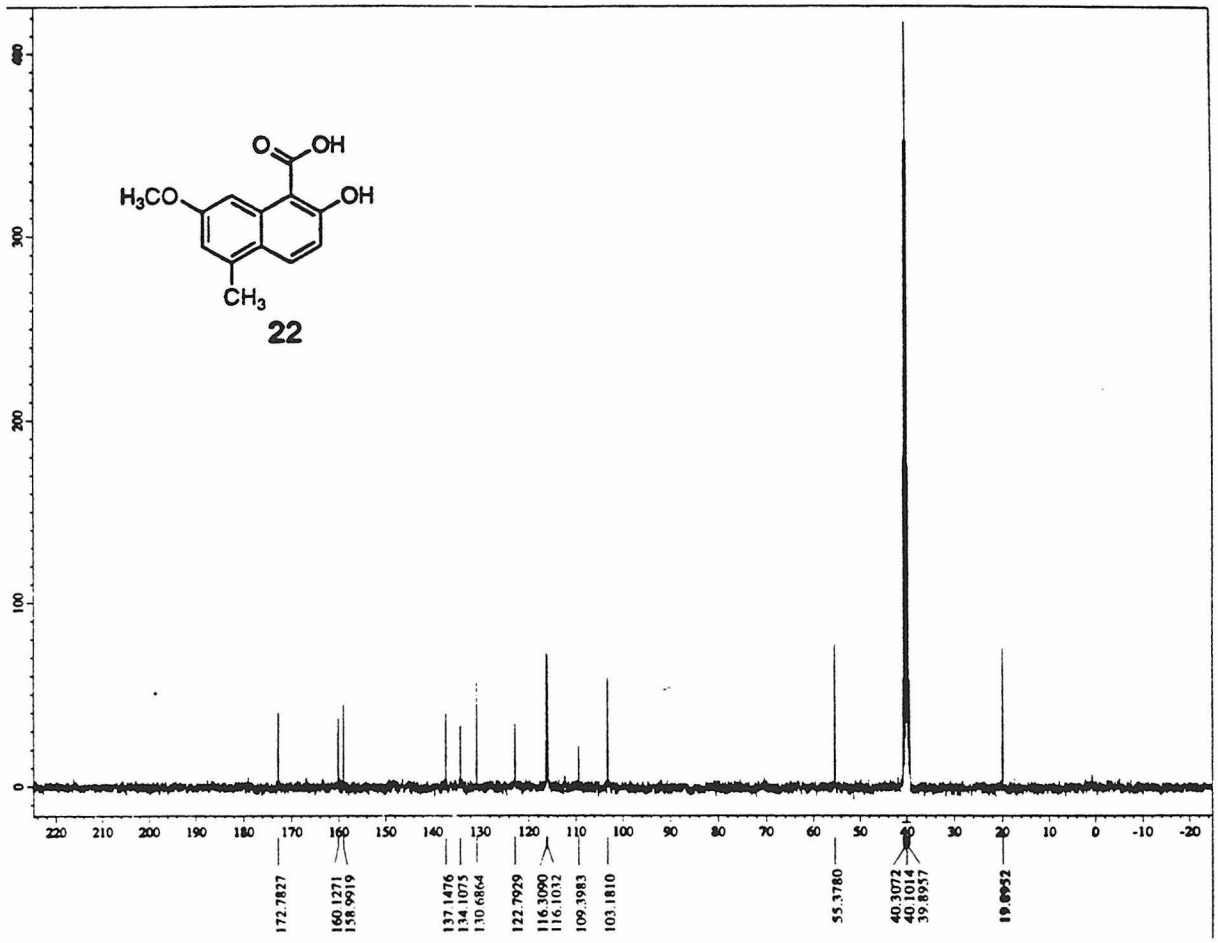

OCH3
OH
O
CH3
H3CO
45

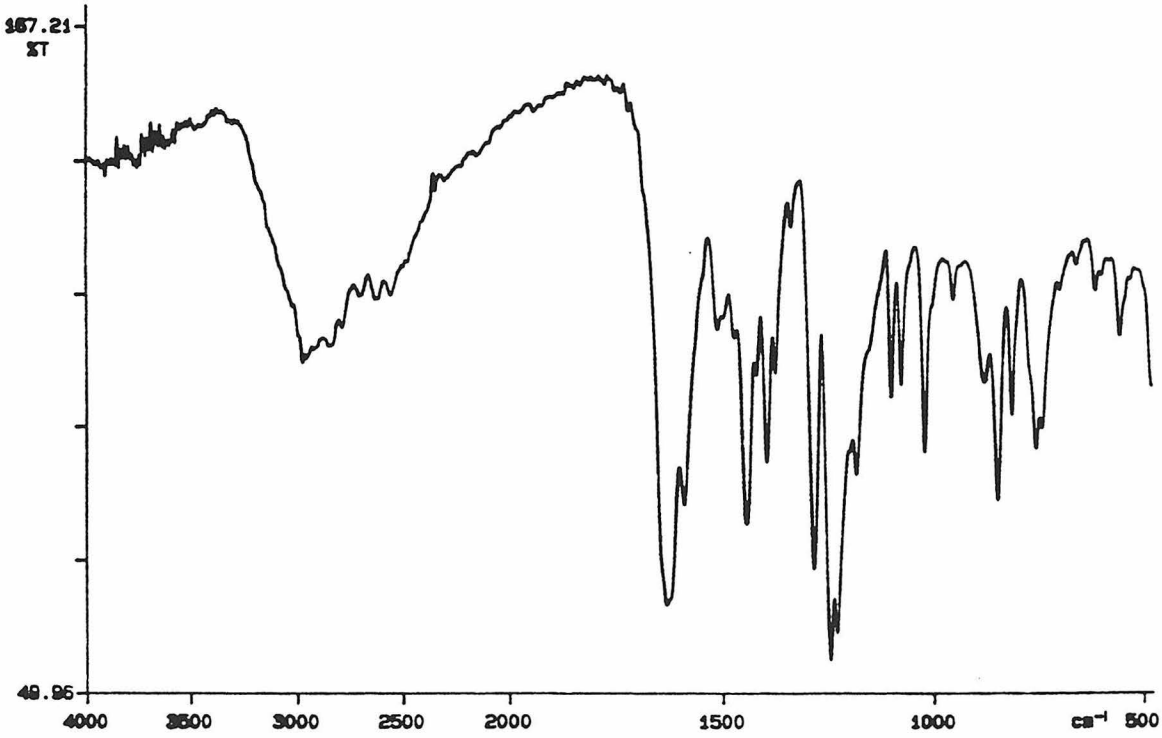

O
OCH3
H3CO
OH
CH3

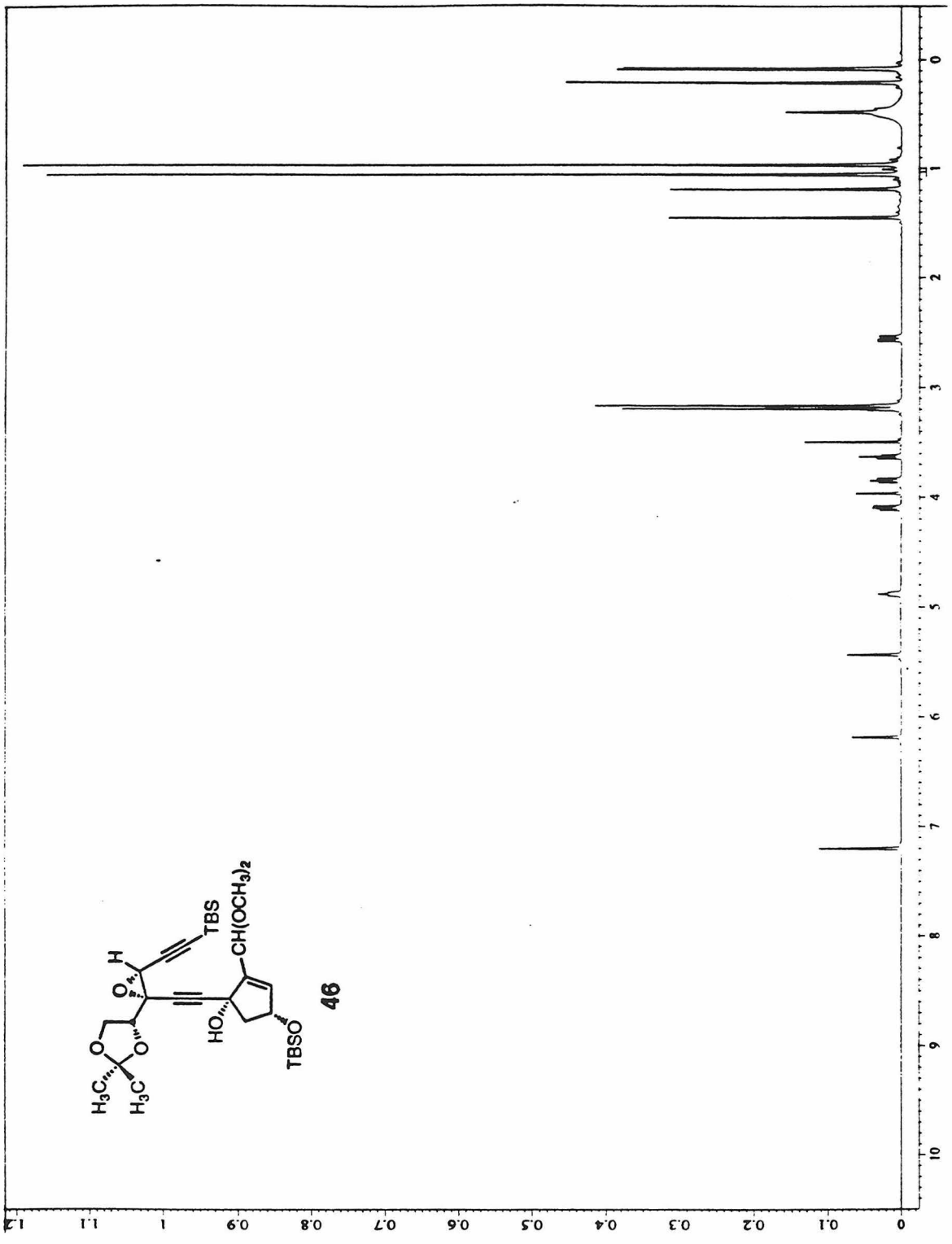
45

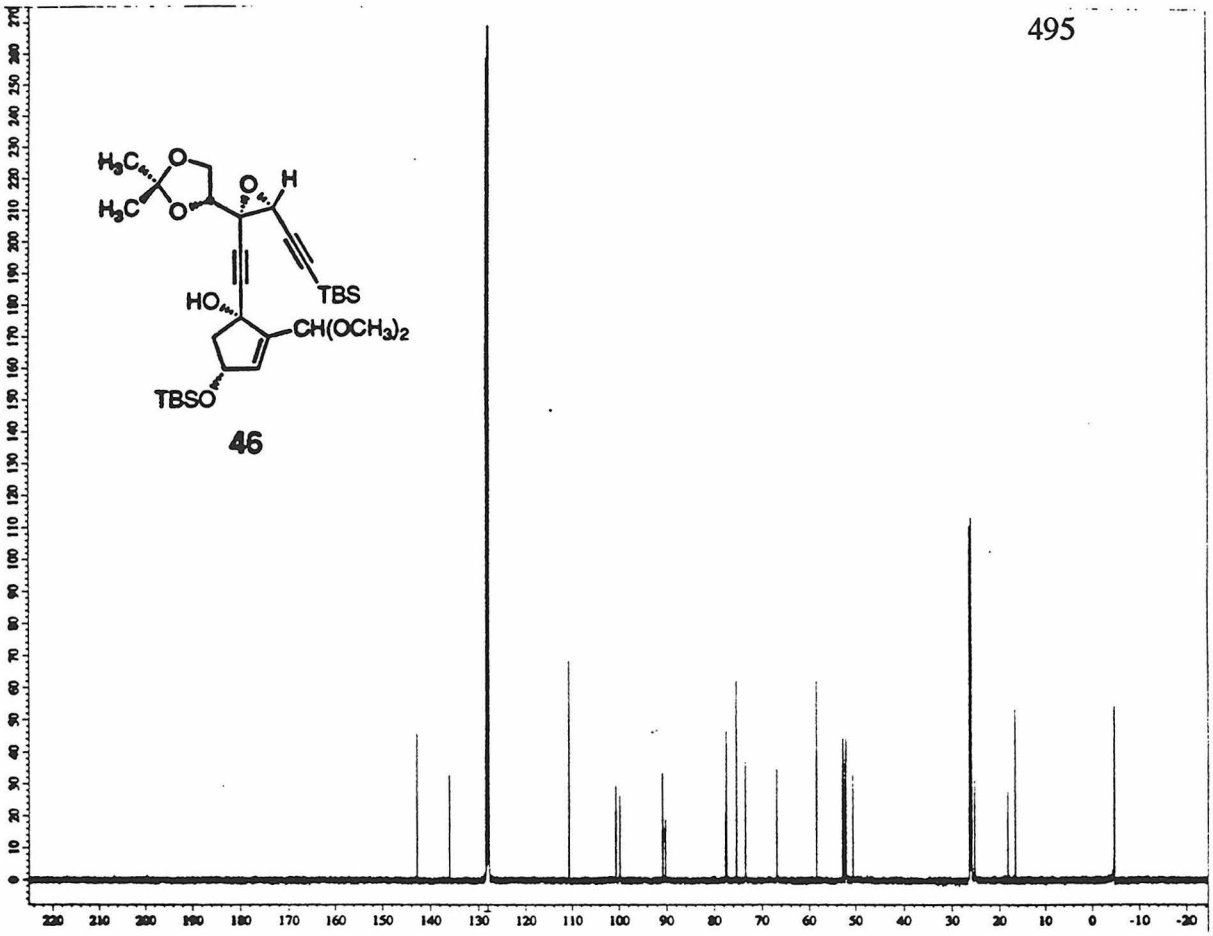

88.83
%T
85.78
4000
3500
3000
2500
2000
1500
1000
cm-1
500


OH
O
OH
CH3
H3CO
22

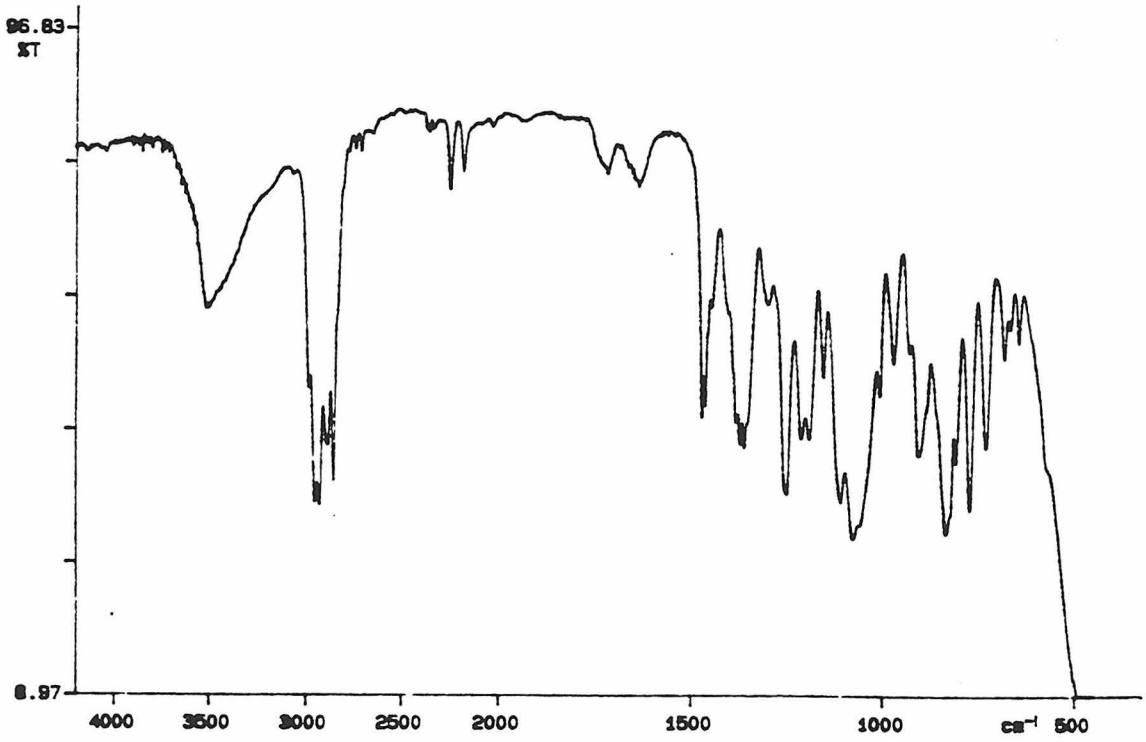

O
OH
H3CO
OH
CH3
22
172.7827
160.1271
158.9919
137.1476
134.1075
130.6864
122.7929
116.3090
116.1032
109.3983
103.1810
55.3780
40.3072
40.1014
39.8937
19.8932

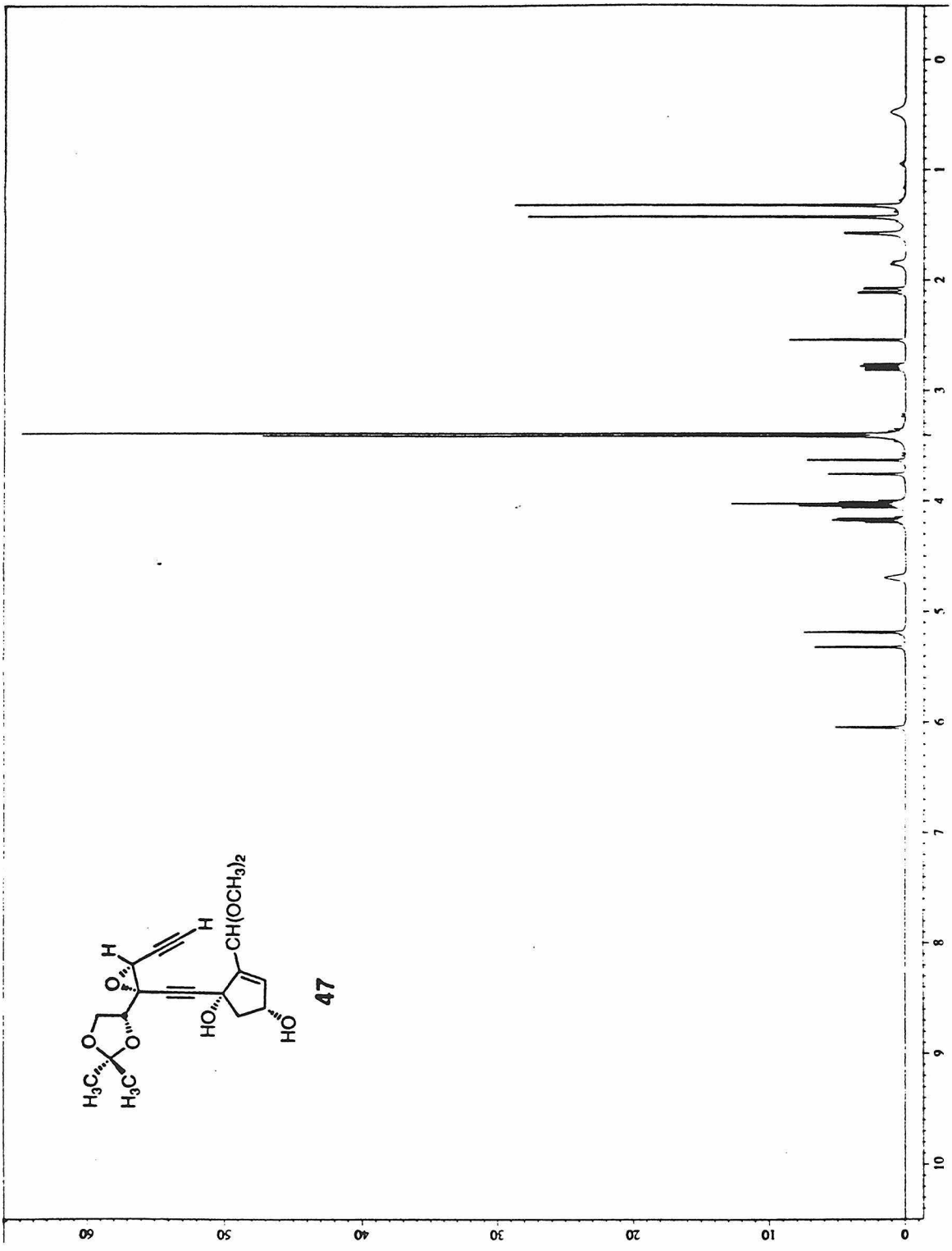

167.21
%T
49.96
4000
3500
3000
2500
2000
1500
1000
cm-1
500


TBS
CH(OCH3)2
H
O
HO
TBSO
H3C
H3C
O
O
46

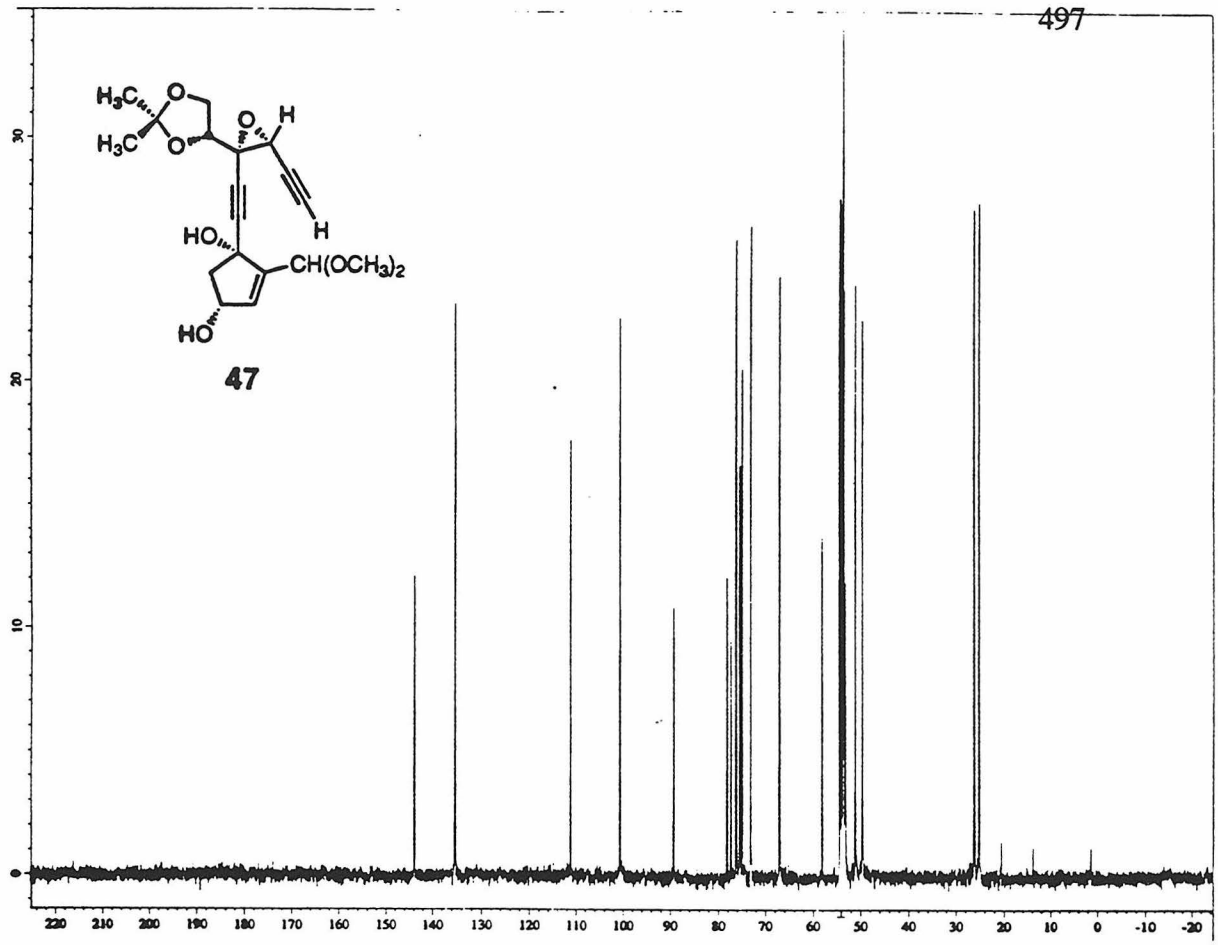

H3C
O
H3C
O
O
H
TBS
HO
CH(OCH3)2
TBSO

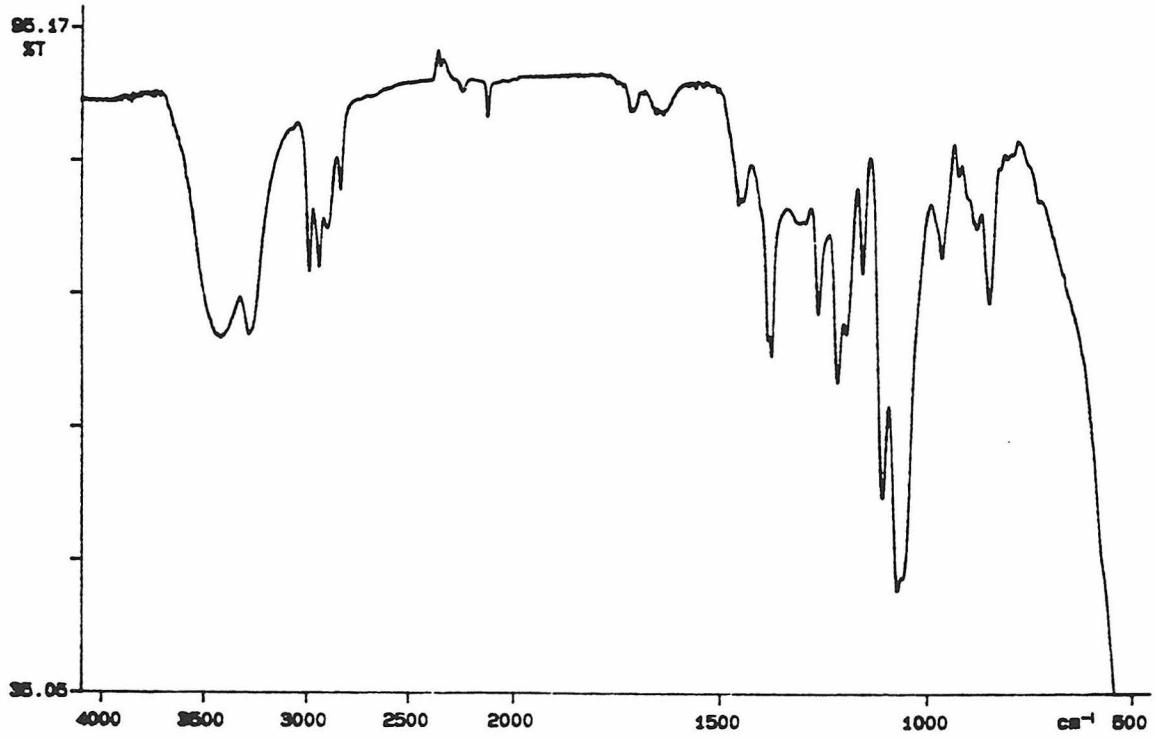
46

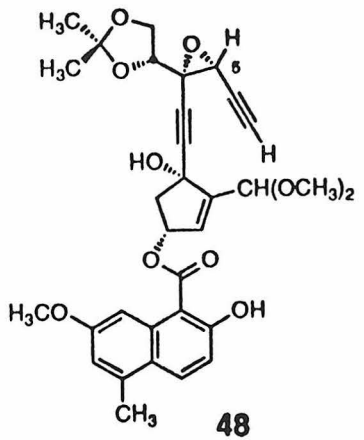

96.83
%T
8.97
4000
3500
3000
2500
2000
1500
1000
cm-1
500



47

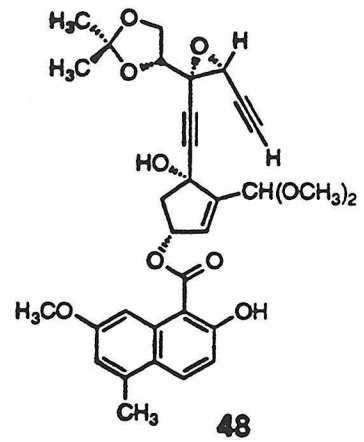

H_3C
H_3C
O
O
O
H
HO
H
$CH(OCH_3)_2$
HO
47
30
20
10
0
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20


95.17
%T
95.05
4000
3500
3000
2500
2000
1500
1000
cm^{-1}
500


H3C
O
H3C
O
O
H
6
HO
H
CH(OCH3)2
O
O
H3CO
OH
CH3

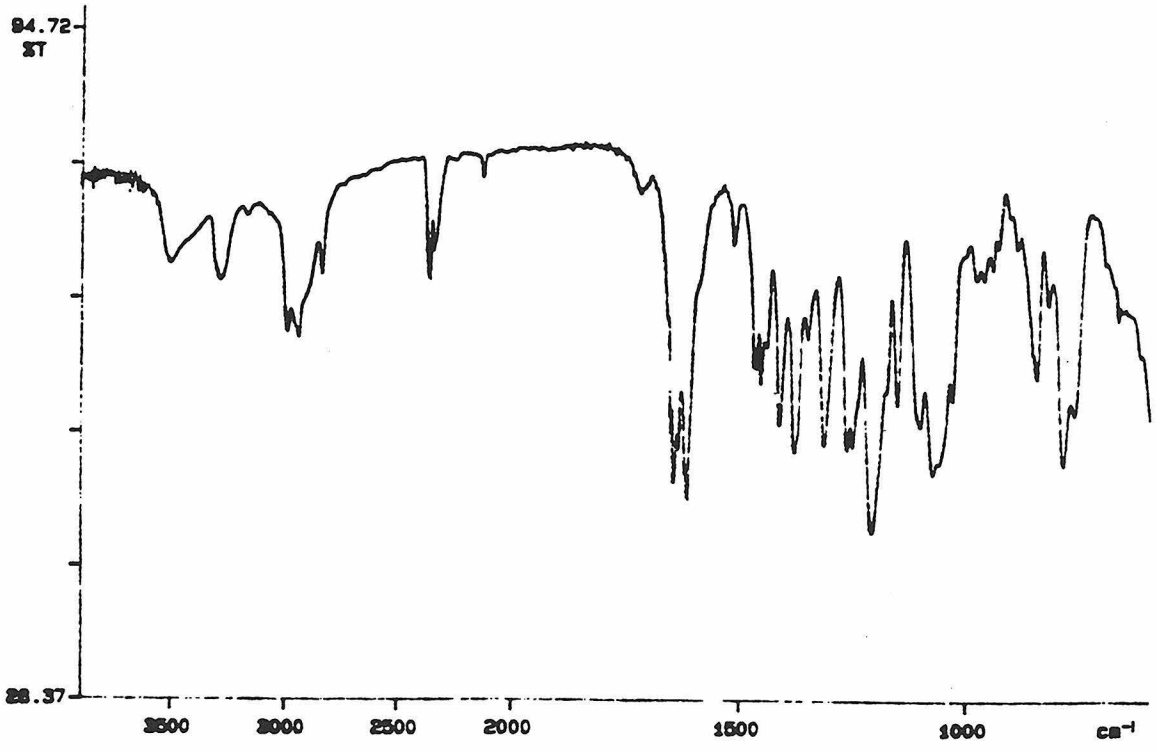
48

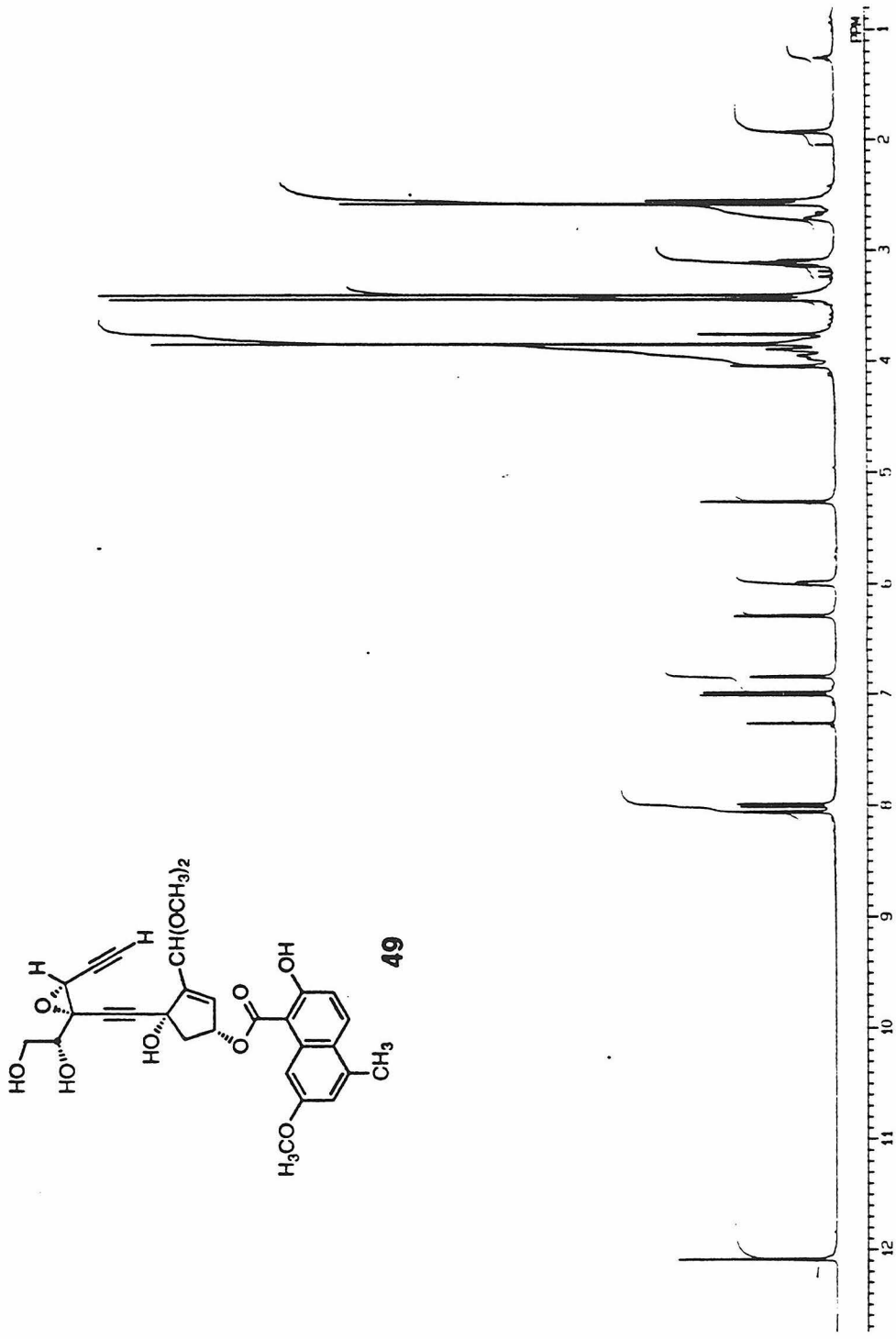
PPM
12
11
10
9
8
7
6
5
4
3
2
1

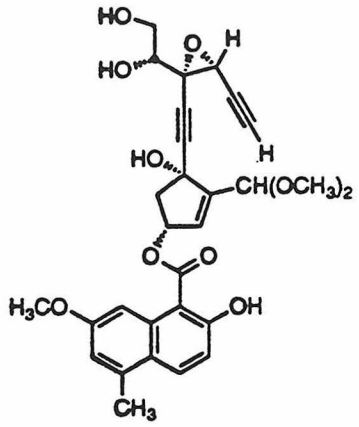

H3C
O
O
H3C
O
H
HO
H
CH(OCH3)2
O
O
H3CO
OH
CH3

48

210 205 200 195 190 185 180 175 170 165 160 155 150 145 140 135 130 125 120 115 110 105 100 95 90 85 80 75 70 65 60 55 50 45 40 35 30 25 20 15

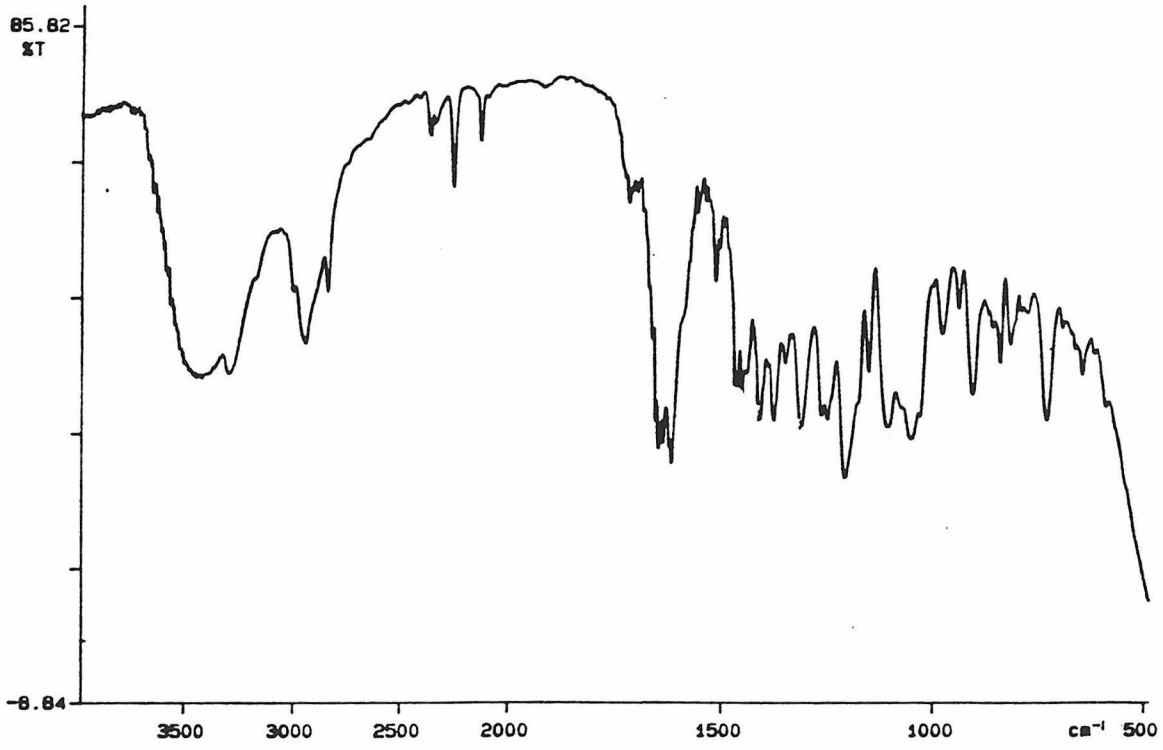

94.72
%T
28.37
3500
3000
2500
2000
1500
1000
cm-1

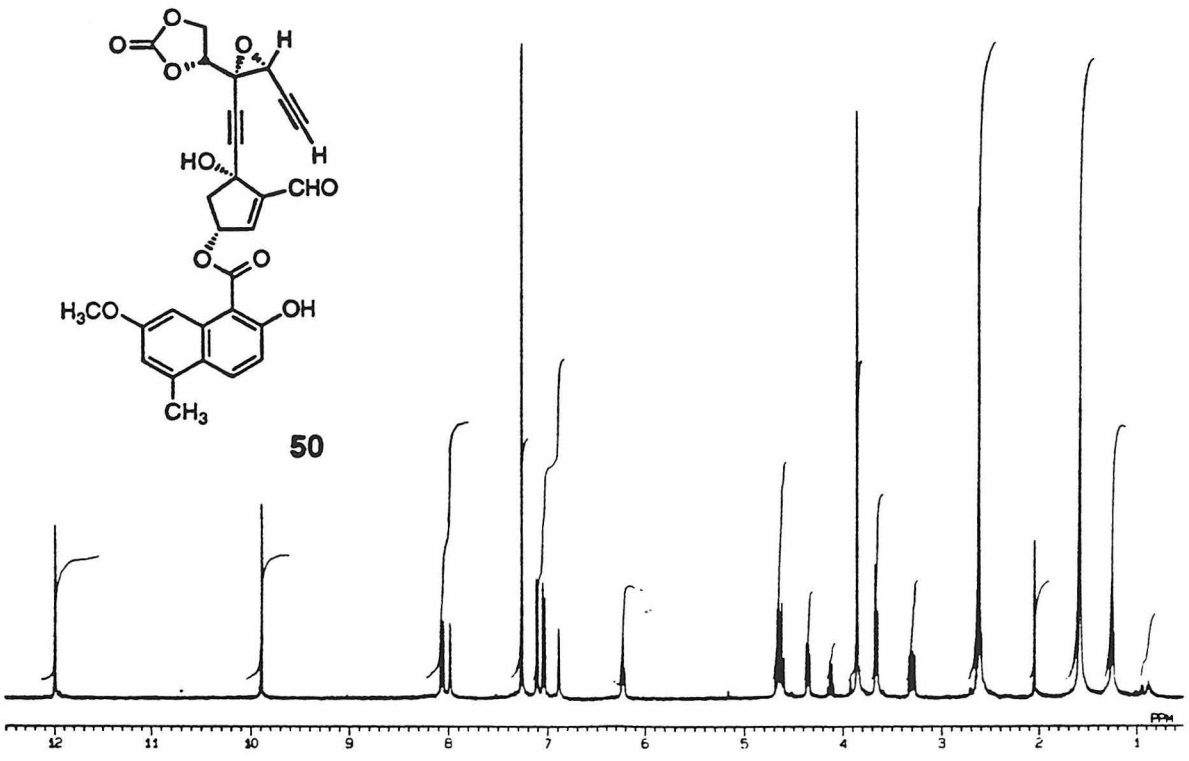

HO
HO
H
O
H
HO
CH(OCH3)2
O
O
OH
H3CO
CH3
49
PPM
1
2
3
4
5
6
7
8
9
10
11
12

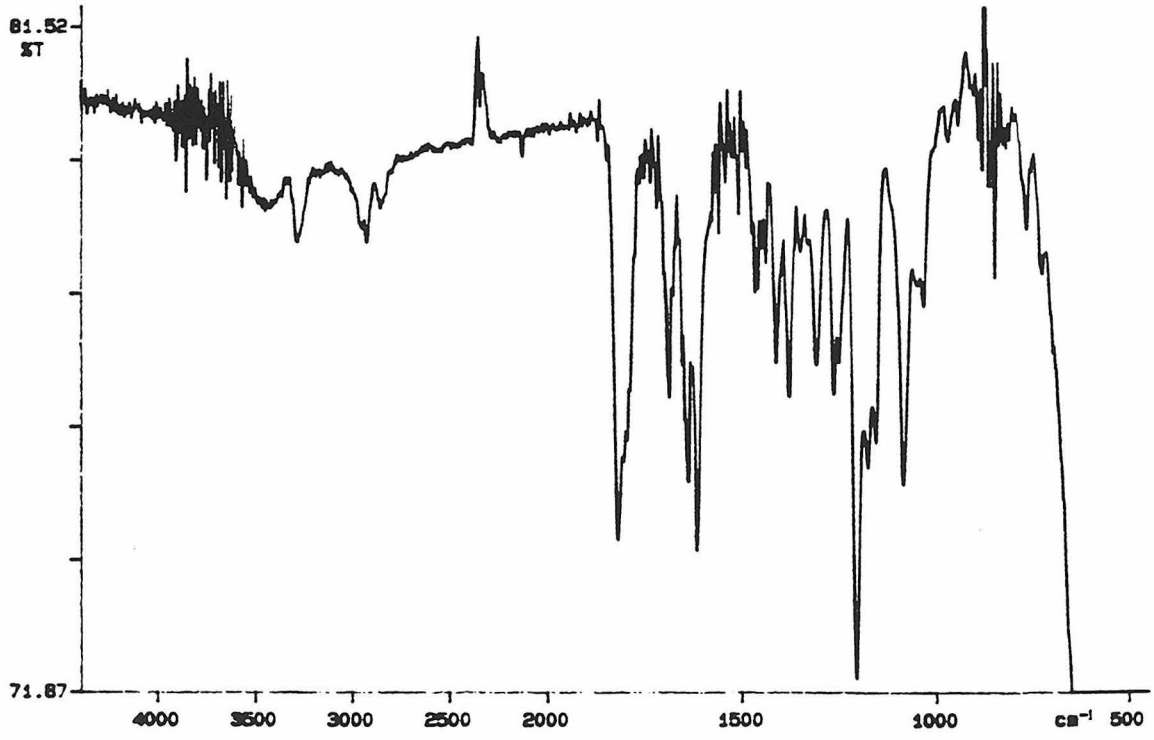

HO
HO
O
H
HO
H
CH(OCH3)2
O
O
H3CO
OH
CH3

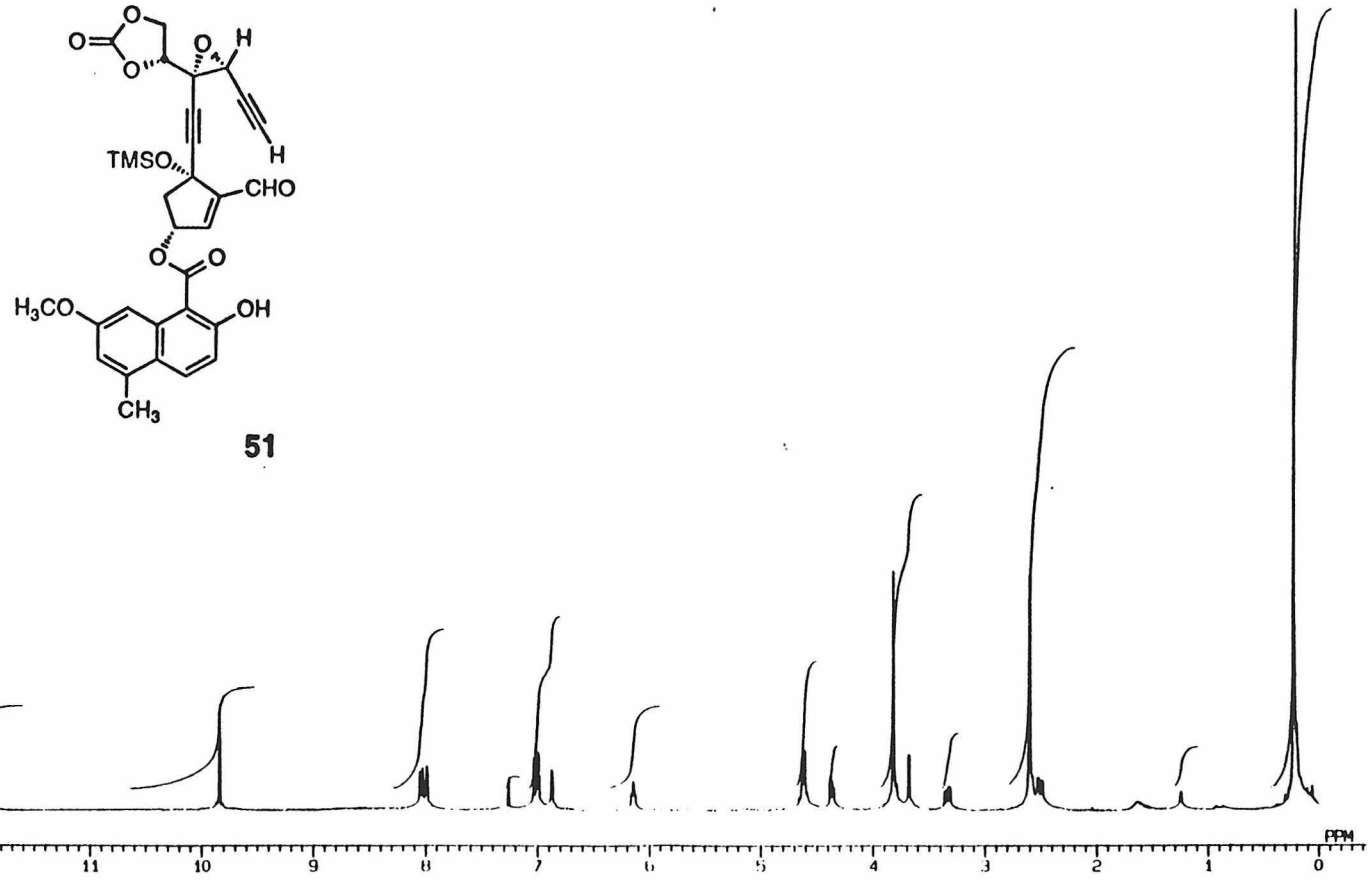
49

175 170 165 160 155 150 145 140 135 130 125 120 115 110 105 100 95 90 85 80 75 70 65 60 55 50 45

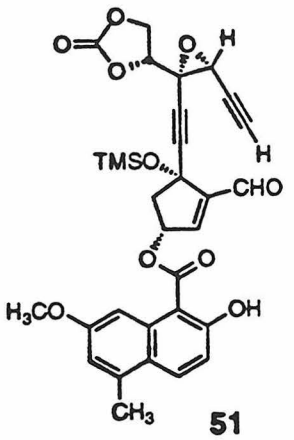

85.82
%T
-8.84
3500
3000
2500
2000
1500
1000
cm-1
500


O
O
O
O
H
HO
H
CHO
O
O
H3CO
OH
CH3
50
12
11
10
9
8
7
6
5
4
3
2
1
PPM

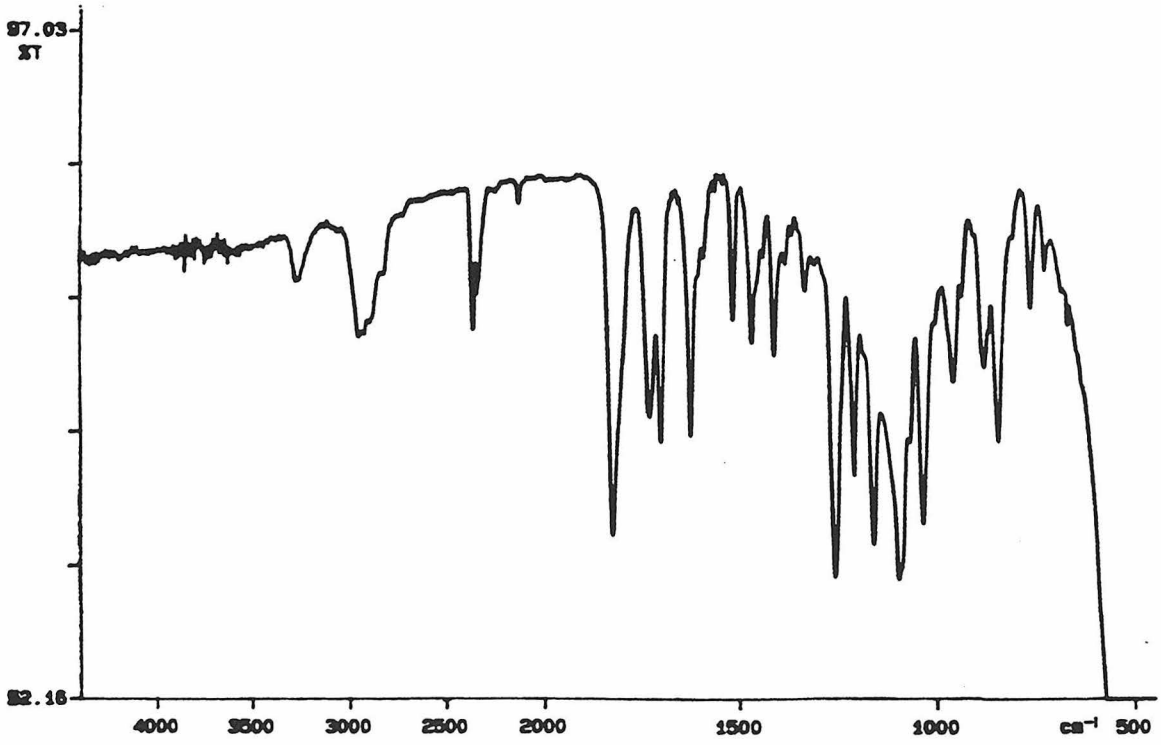

81.52
%T
71.87
4000
3500
3000
2500
2000
1500
1000
cm-1
500



51


O
O
O
O
H
TMSO
H
CHO
O
O
H3CO
OH
CH3

51


97.03
%T
92.16
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3500
3000
2500
2000
1500
1000
cm-1
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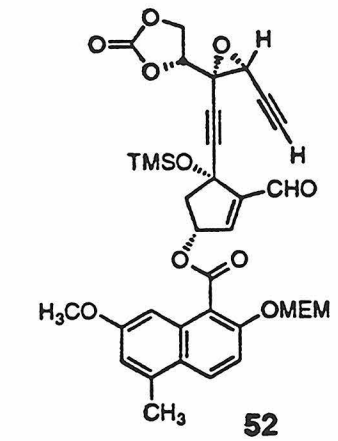
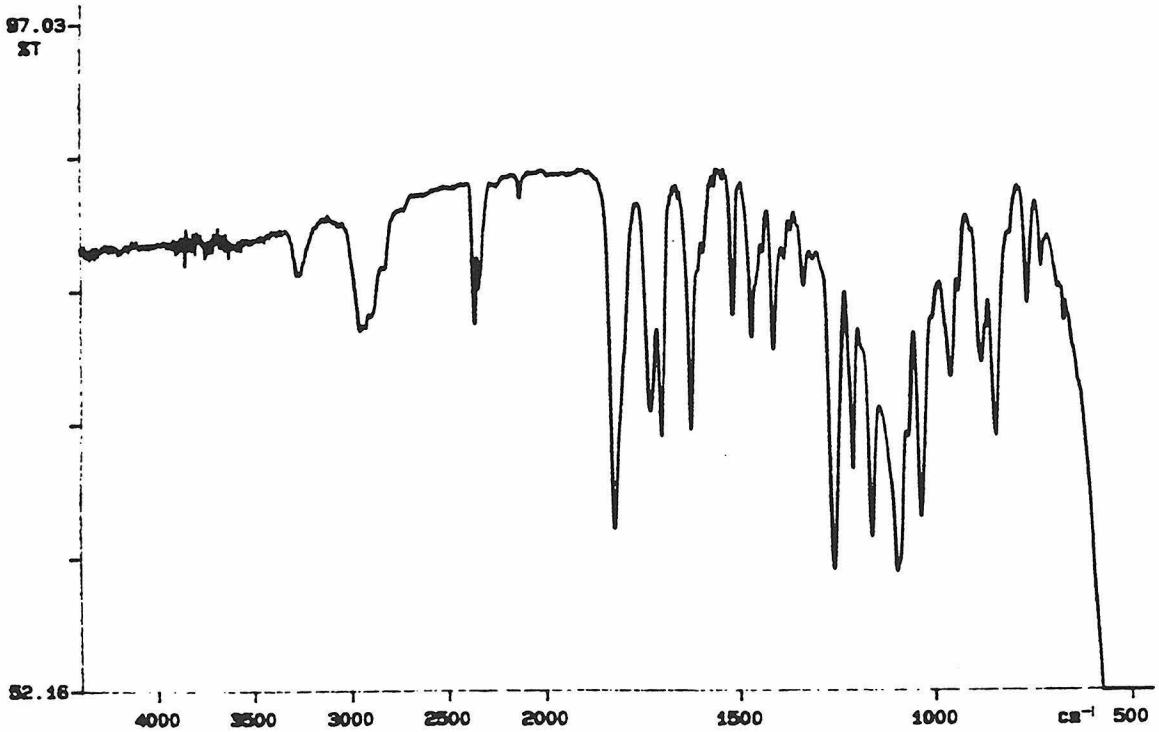

O
O
O
O
H
TMSO
H
CHO
O
O
H3CO
OMEM
CH3

52

11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
PPM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52.16
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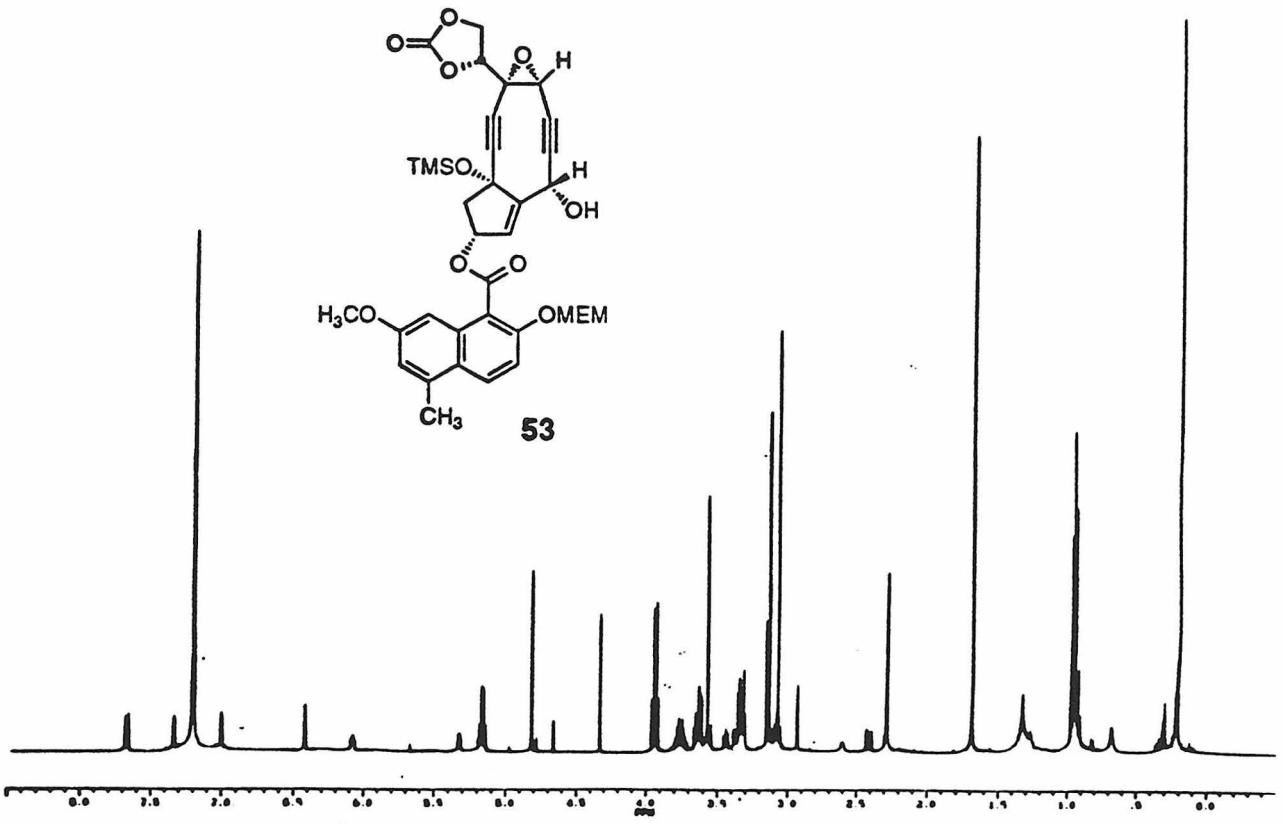
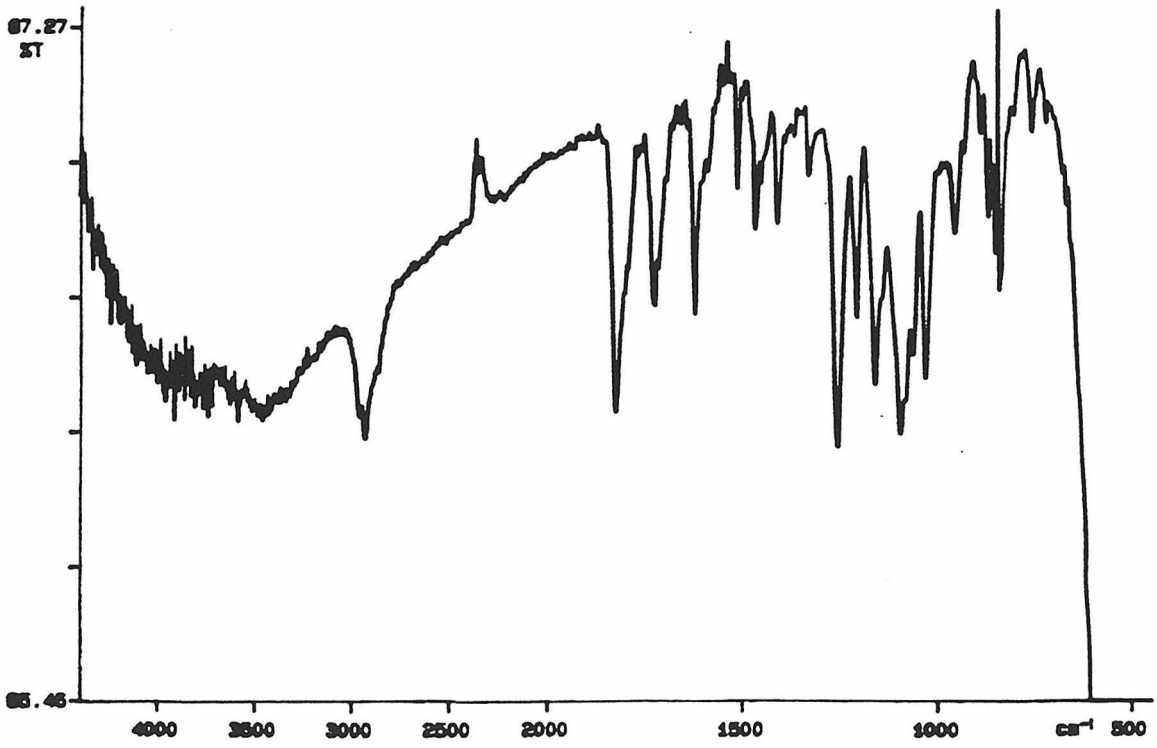
cm-1
500


TMSO
H
OH
H3CO
OMEM
CH3

53


87.27
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85.46
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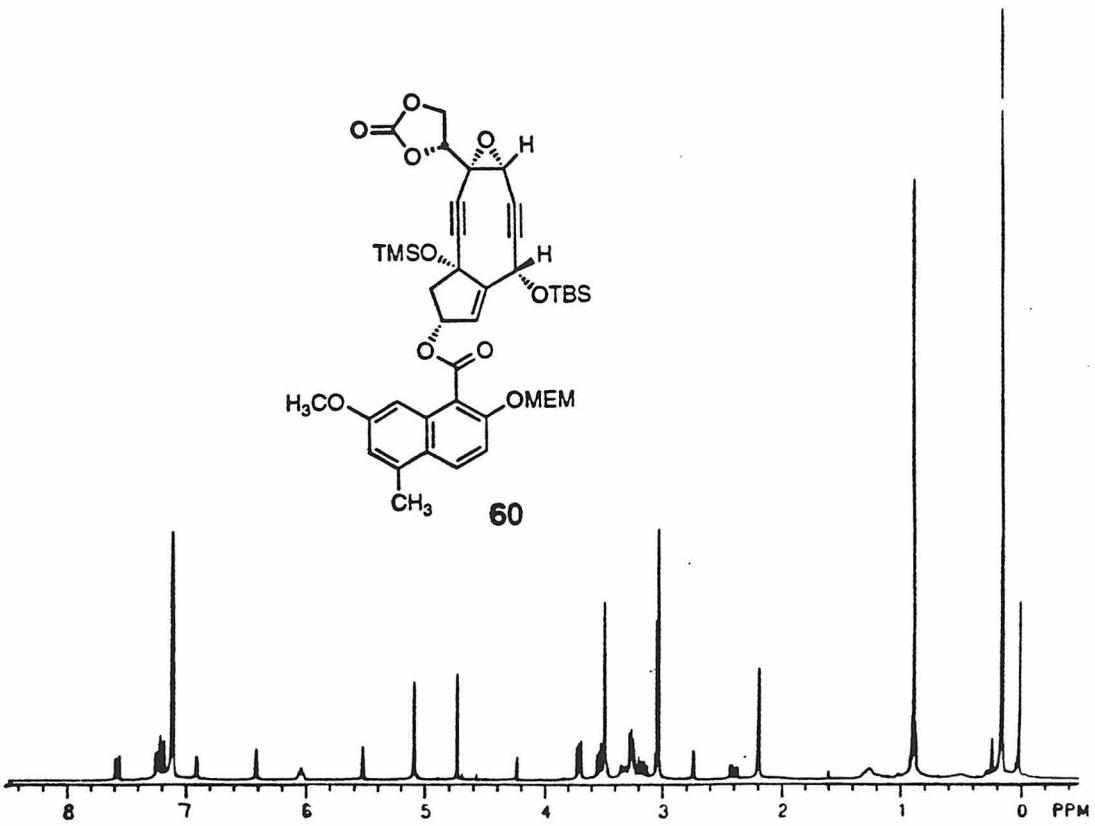
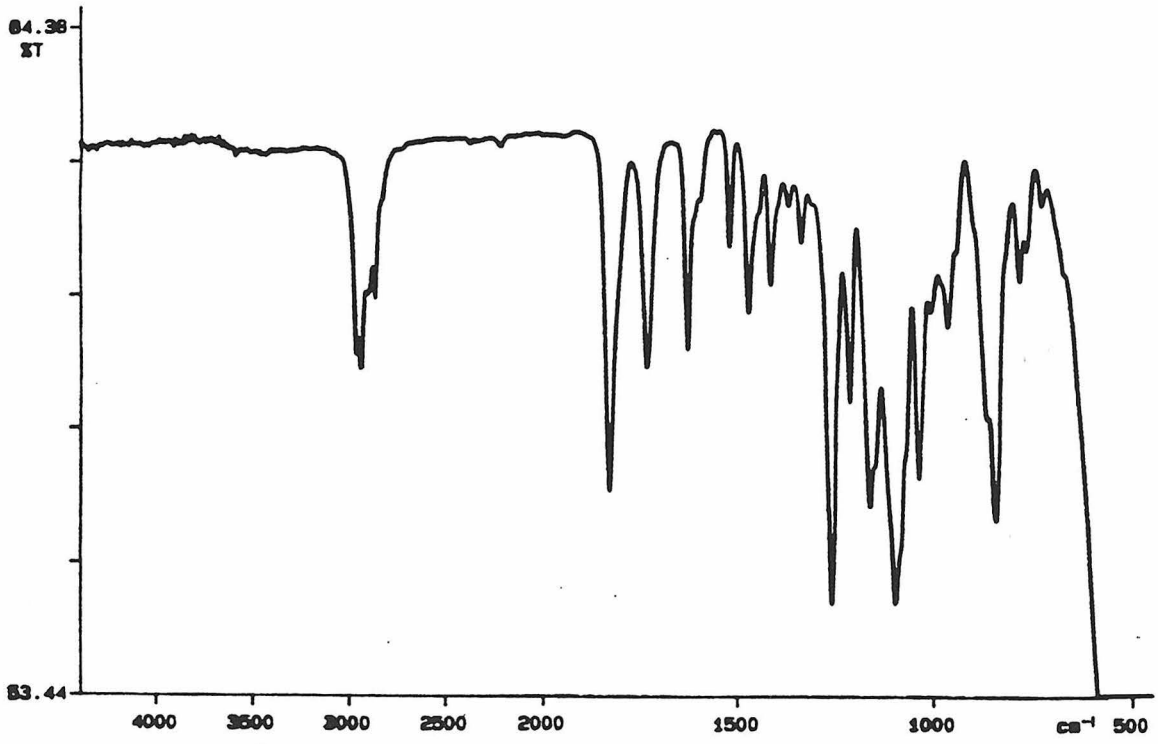
1500
1000
cm-1
500


TMSO
H
OTBS
H3CO
OMEM
CH3
8
7
6
5
4
3
2
1
0
PPM

60


84.38
%T
83.44
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3500
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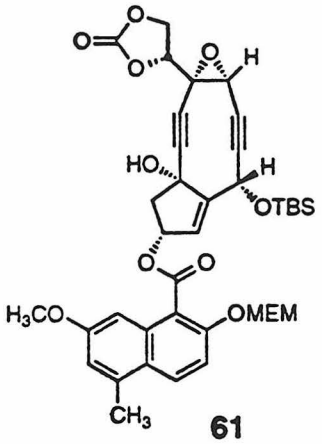
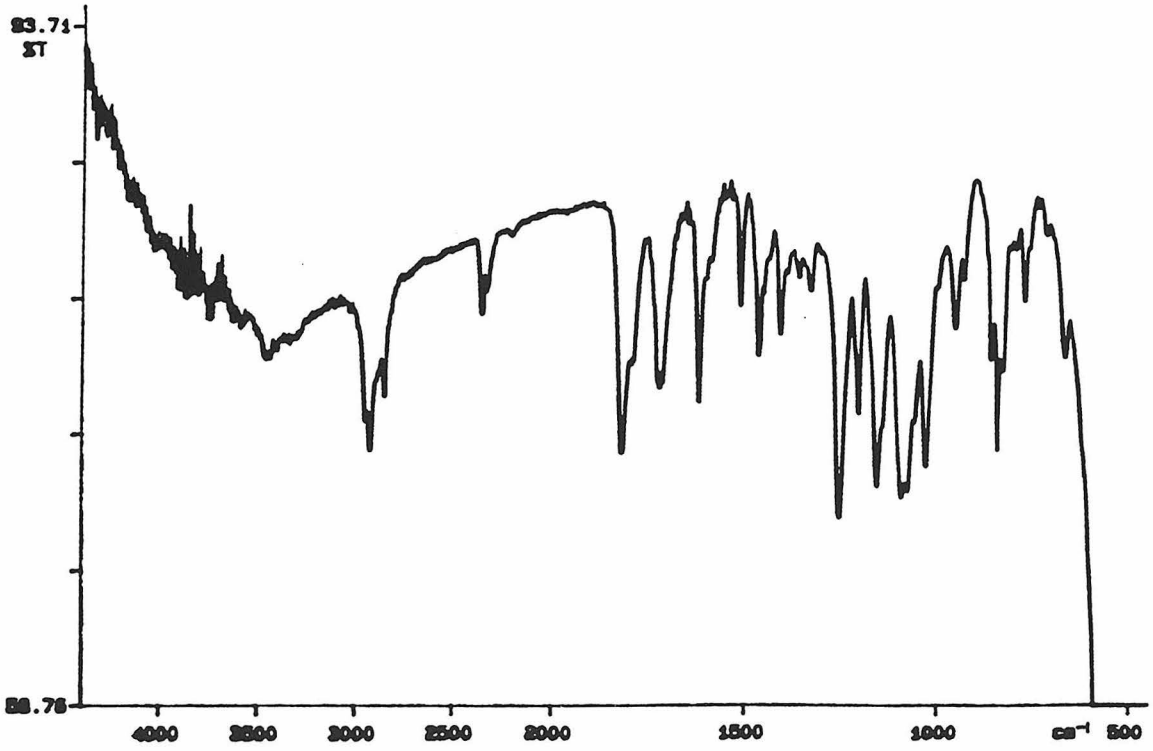
1500
1000
cm-1
500


O
O
O
O
H
HO
H
OTBS
O
O
H3CO
OMEM
CH3

61

9
8
7
6
5
4
3
2
1
0
PPM


93.71
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58.76
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2000
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1000
cm-1
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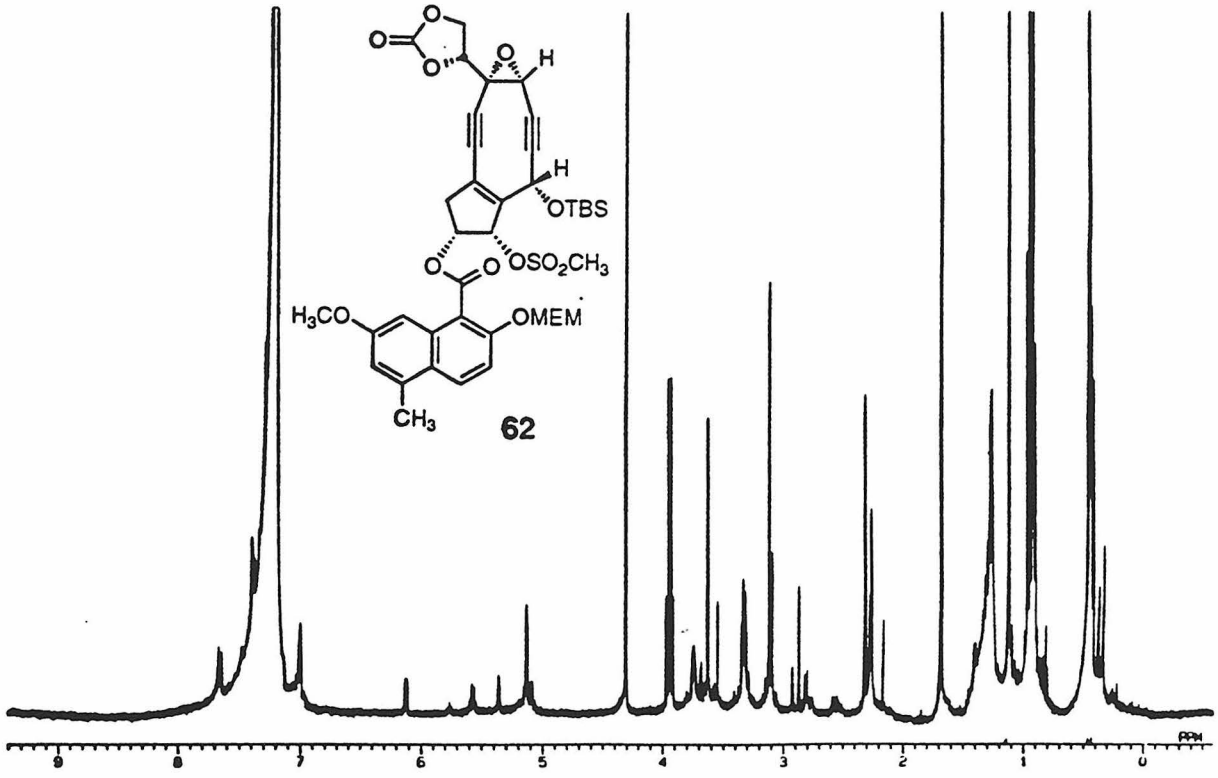
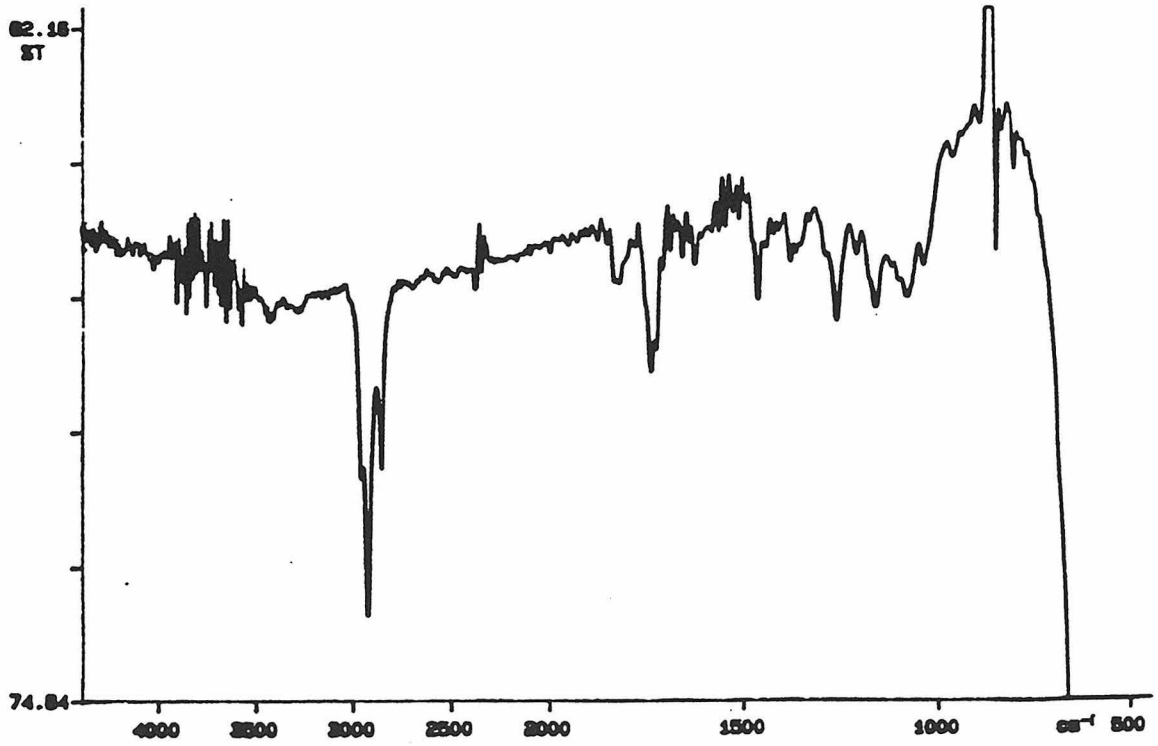
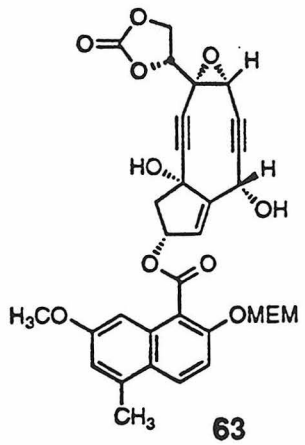
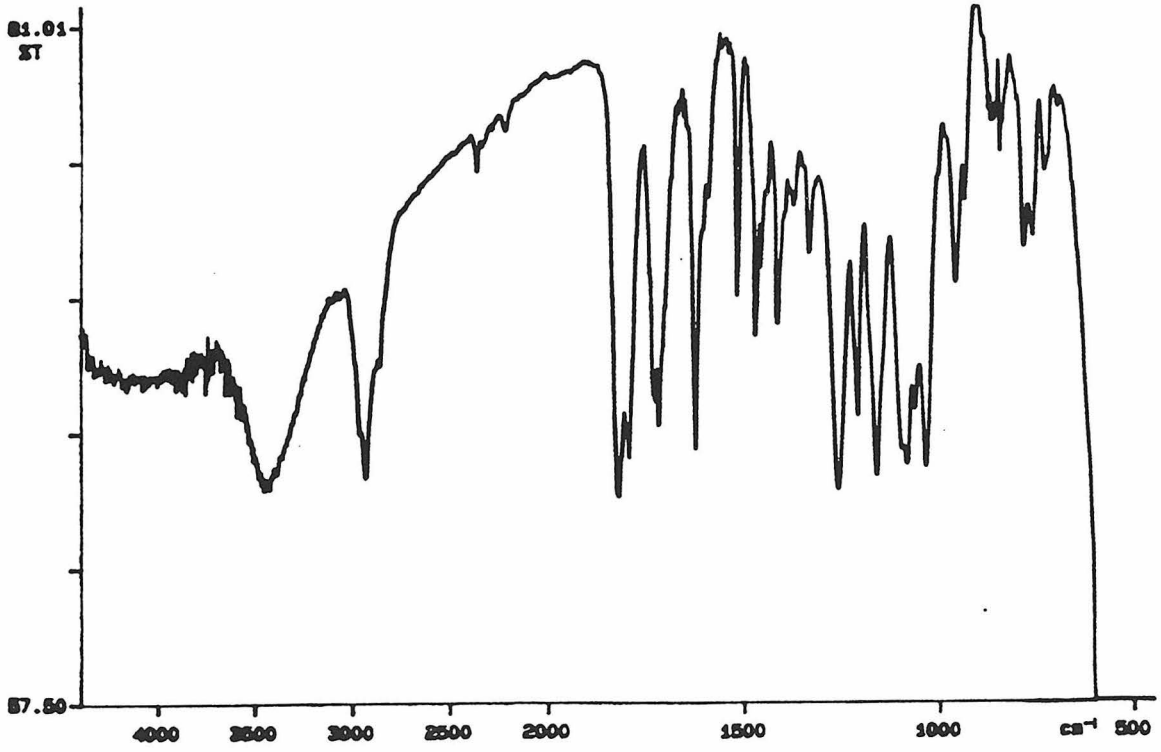

H
H
OTBS
OSO2CH3
H3CO
OMEM
CH3
62
PPM


82.16
ST
74.84
4000
3500
3000
2500
2000
1500
1000
500


O
O
O
O
H
HO
H
OH
O
O
H3CO
OMEM
CH3

63


81.01
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57.50
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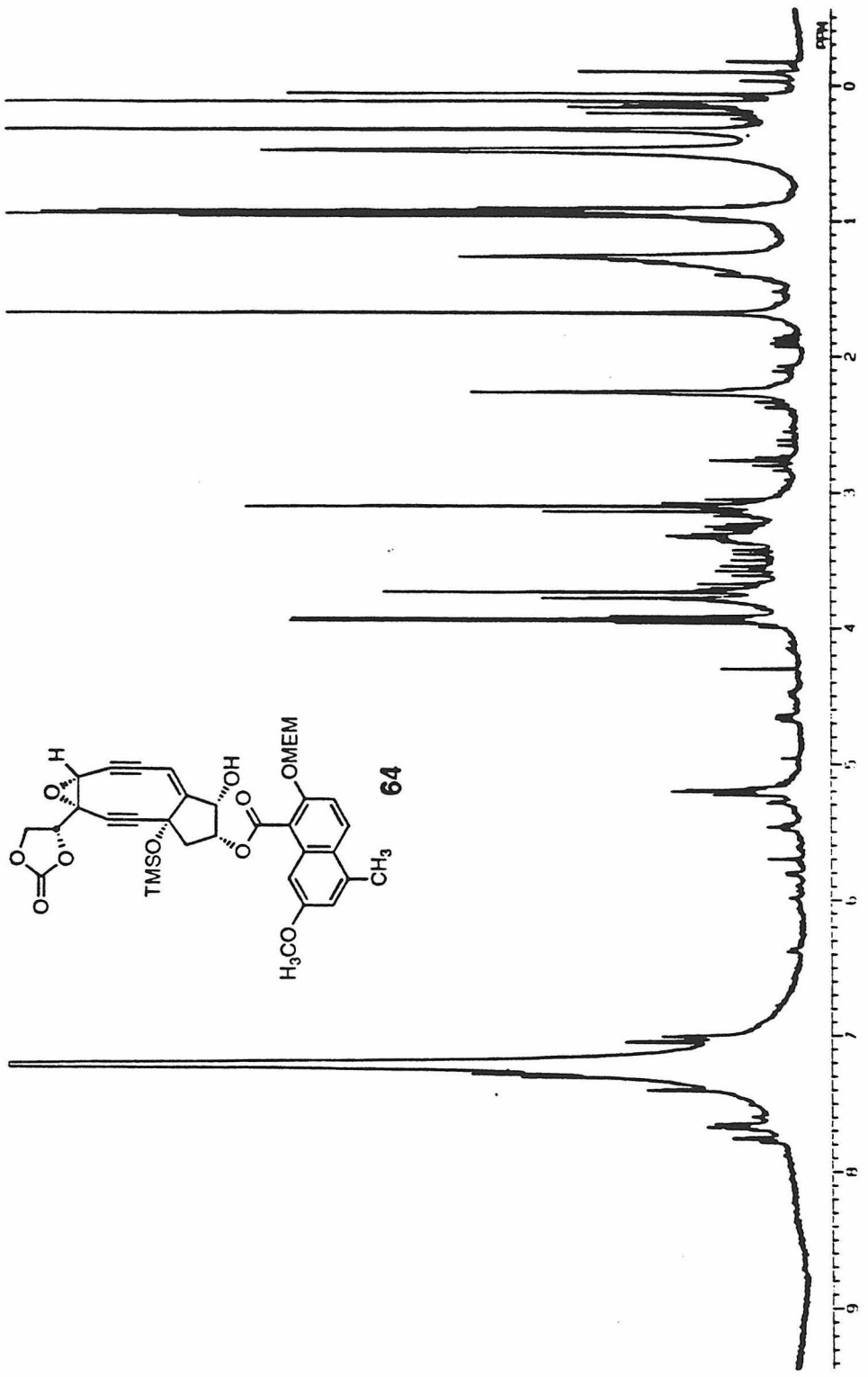
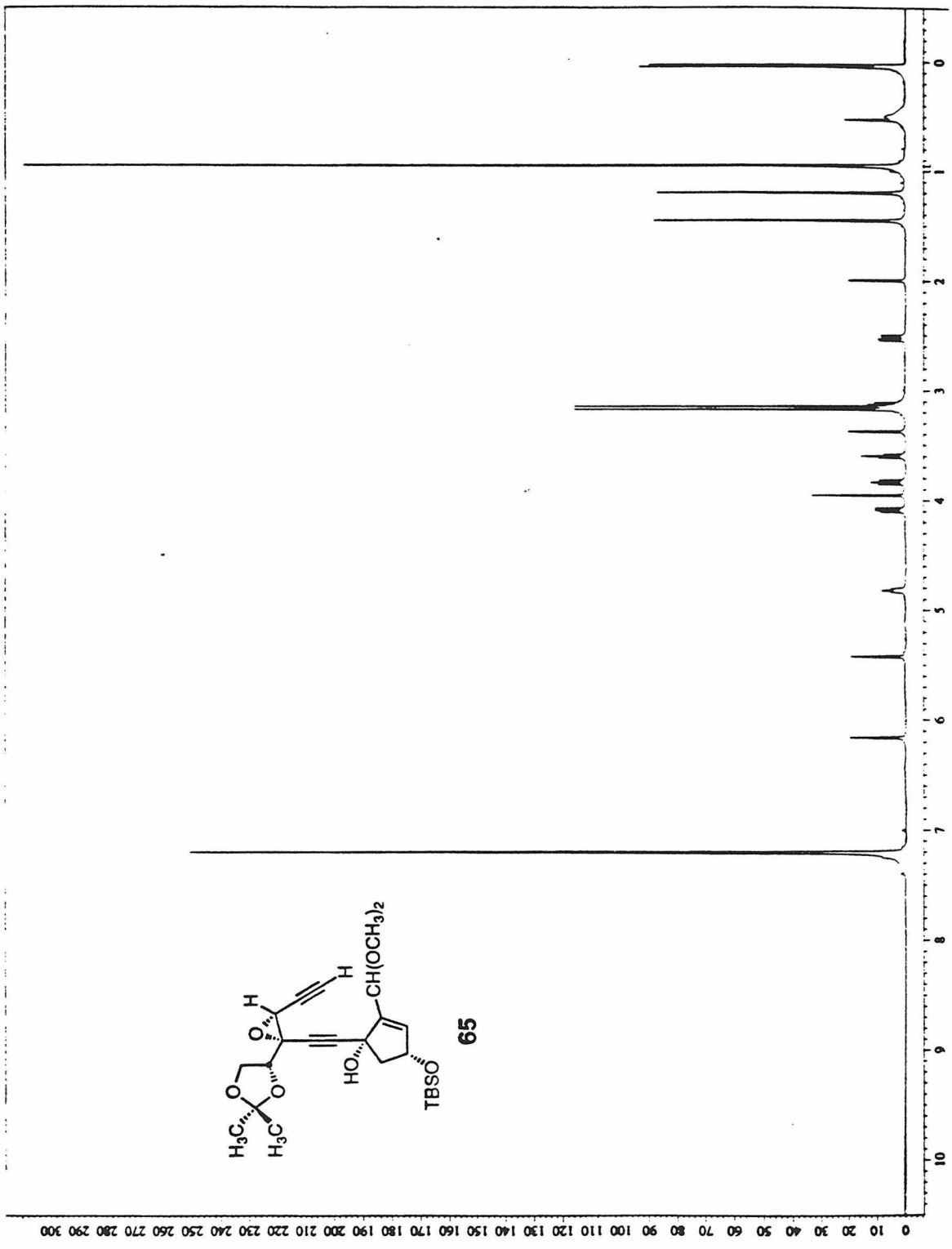
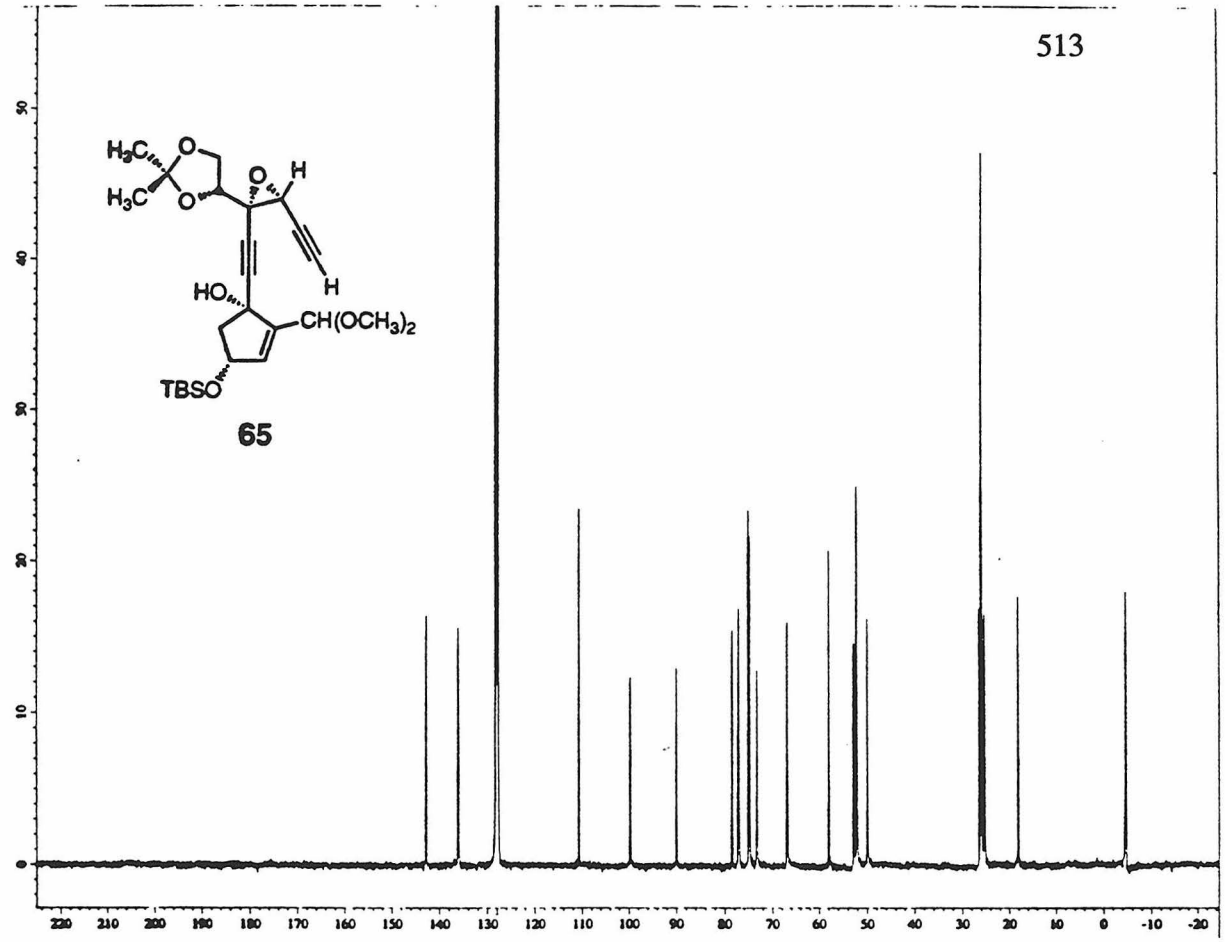
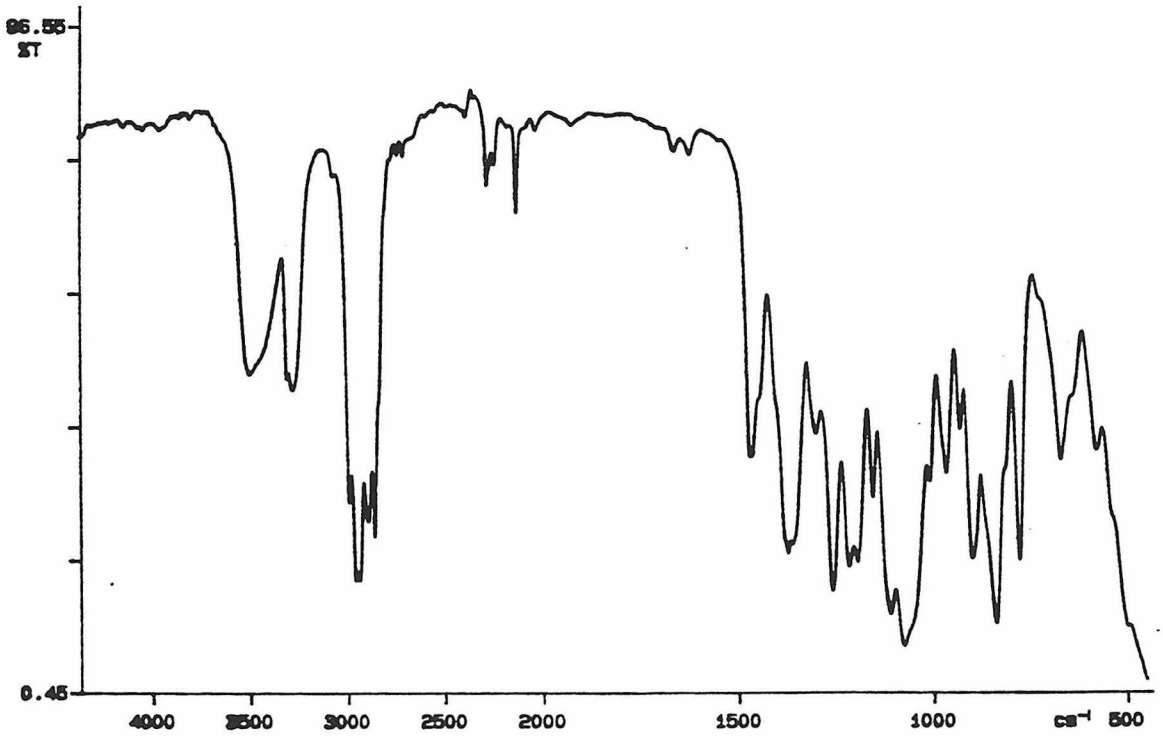
3500
3000
2500
2000
1500
1000
cm-1
500

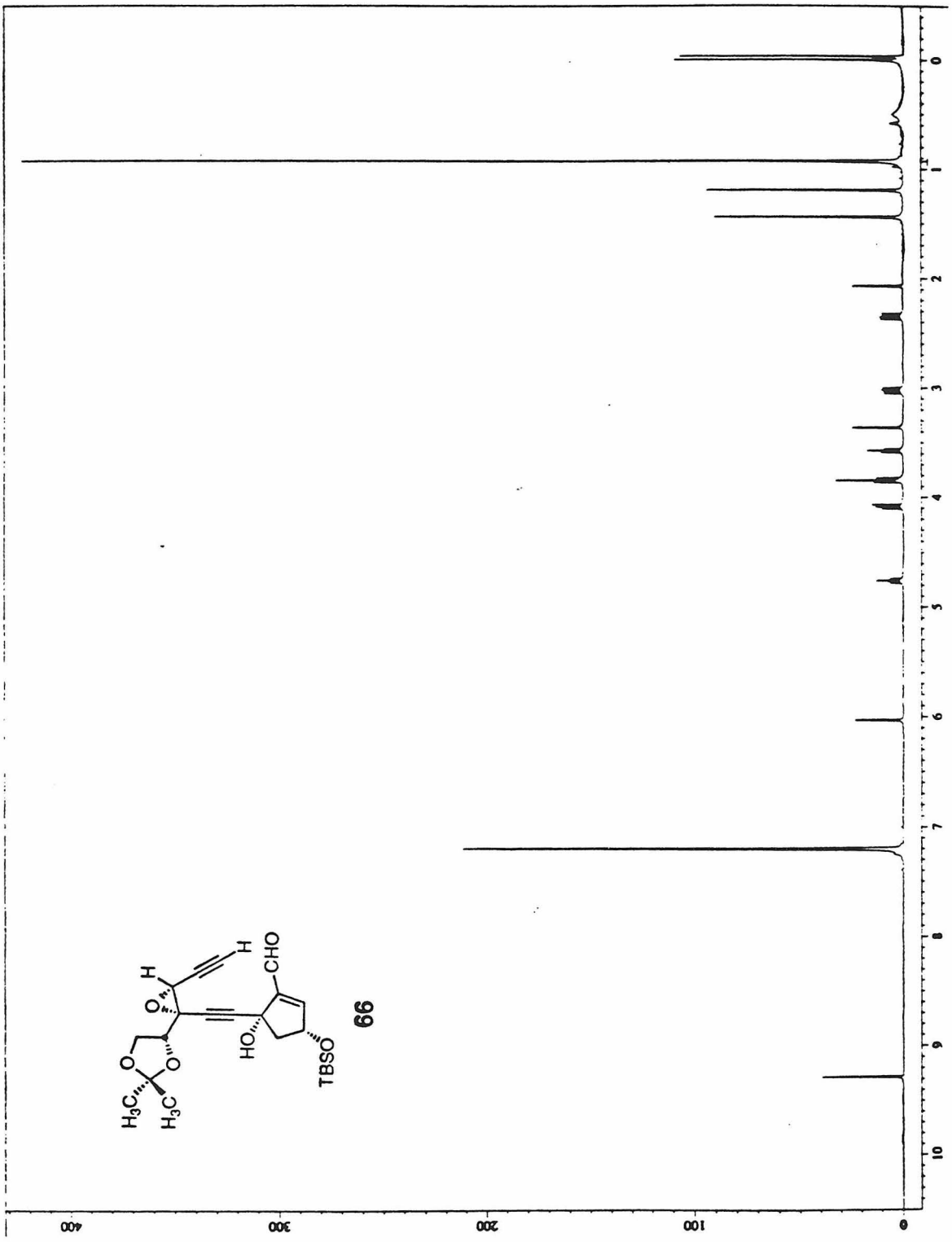

H
O
O
O
O
TMSO
OH
O
O
OMEM
CH3
H3CO
64
PPM
0
1
2
3
4
5
6
7
8
9

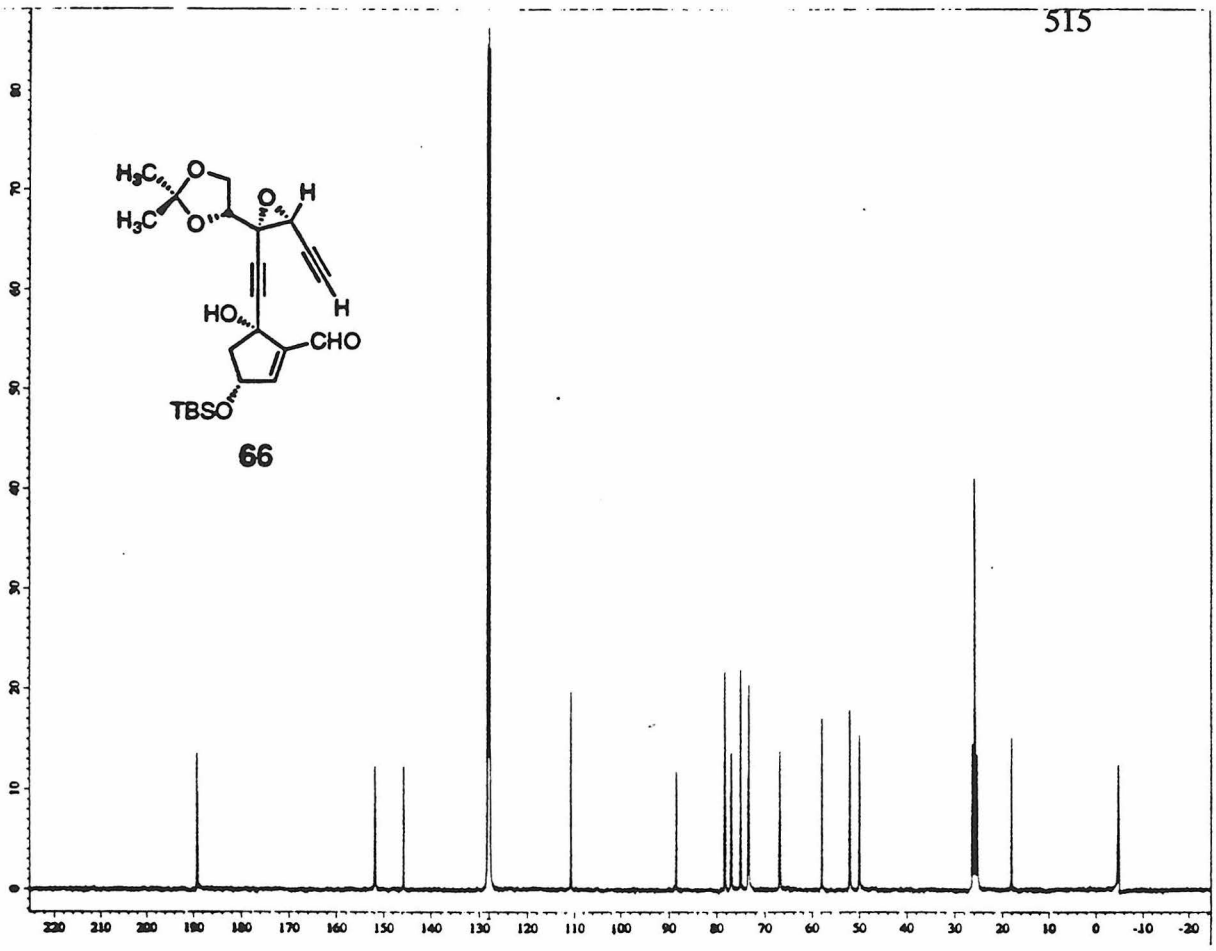

H
O
H
CH(OCH3)2
HO
TBSO
O
O
H3C
H3C
65


H3C
O
O
O
H
H3C
HO
H
CH(OCH3)2
TBSO

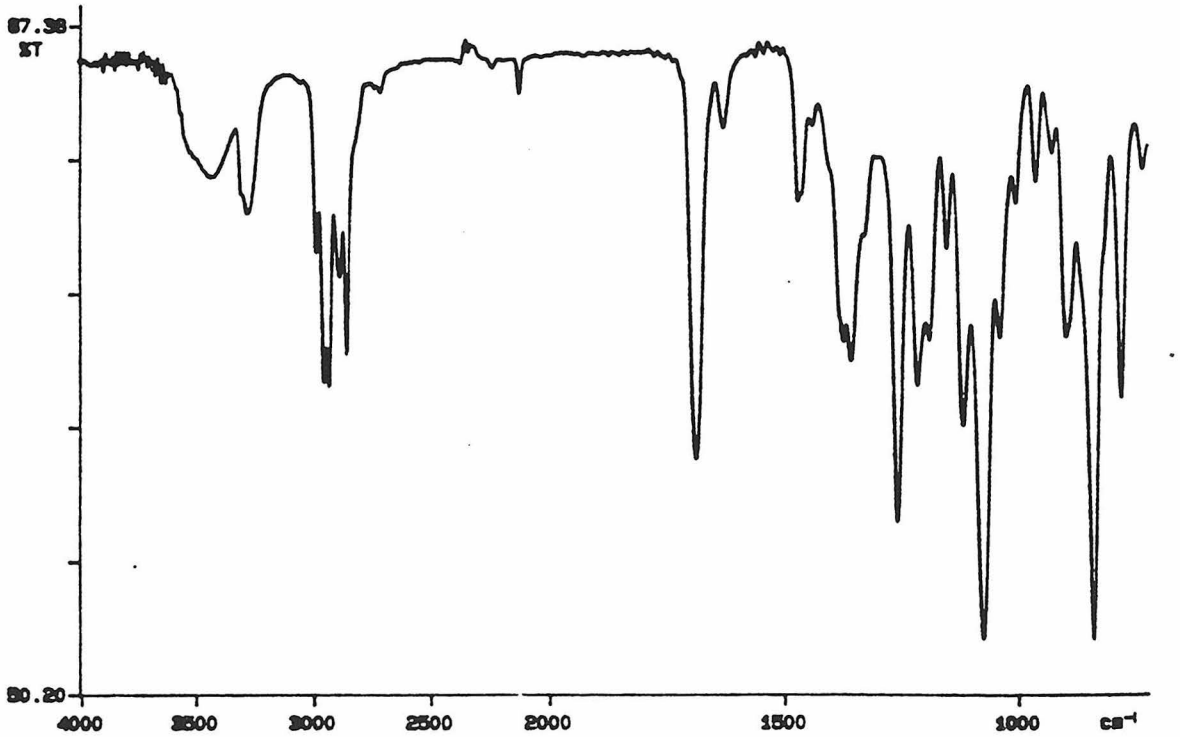
65


96.55
%T
0.45
4000
3500
3000
2500
2000
1500
1000
cm-1
500


H
CHO
O
HO
O
TBSO
O
H3C
H3C
66


H3C
O
H3C
O
O
H
HO
H
CHO
TBSO

66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%T
80.20
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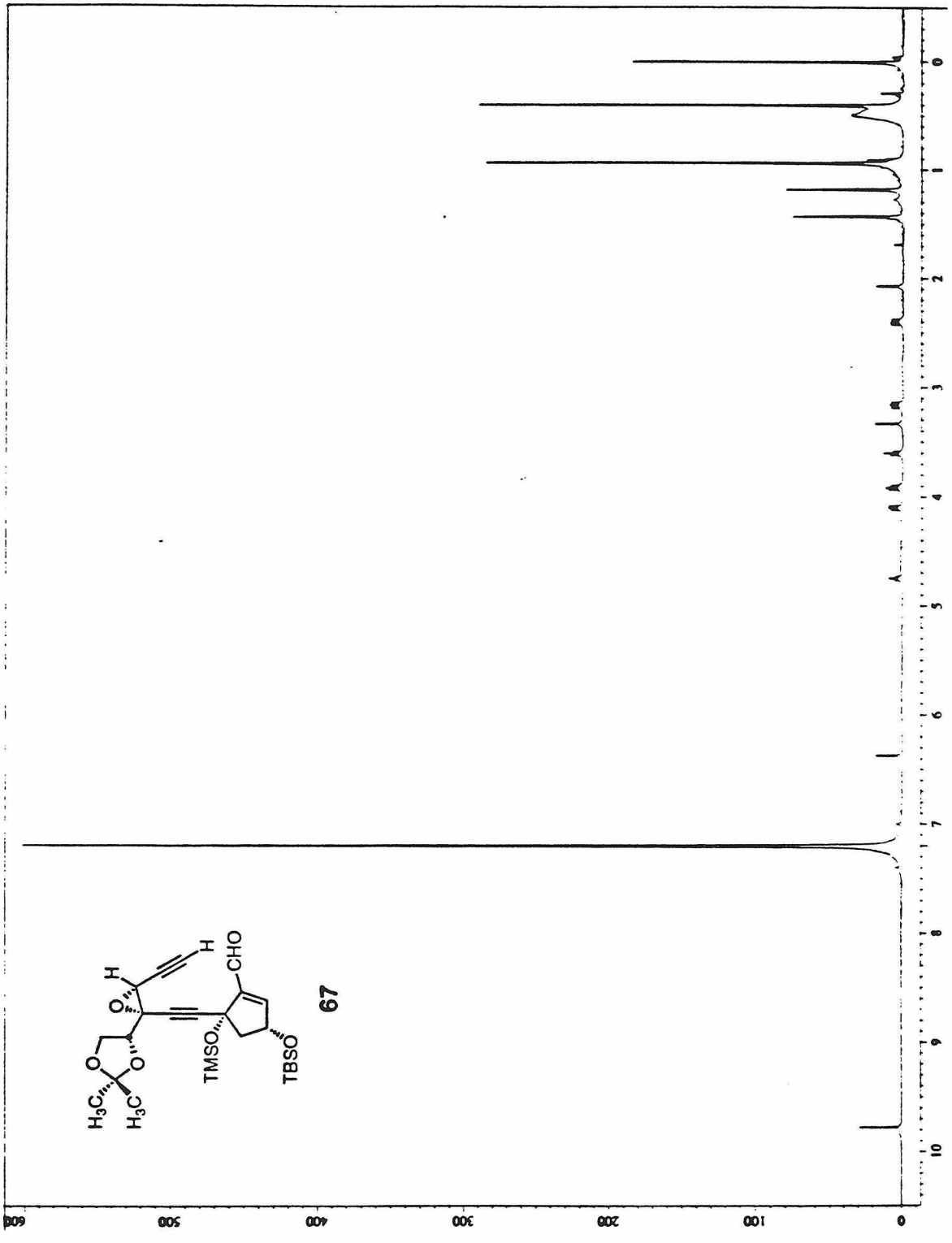
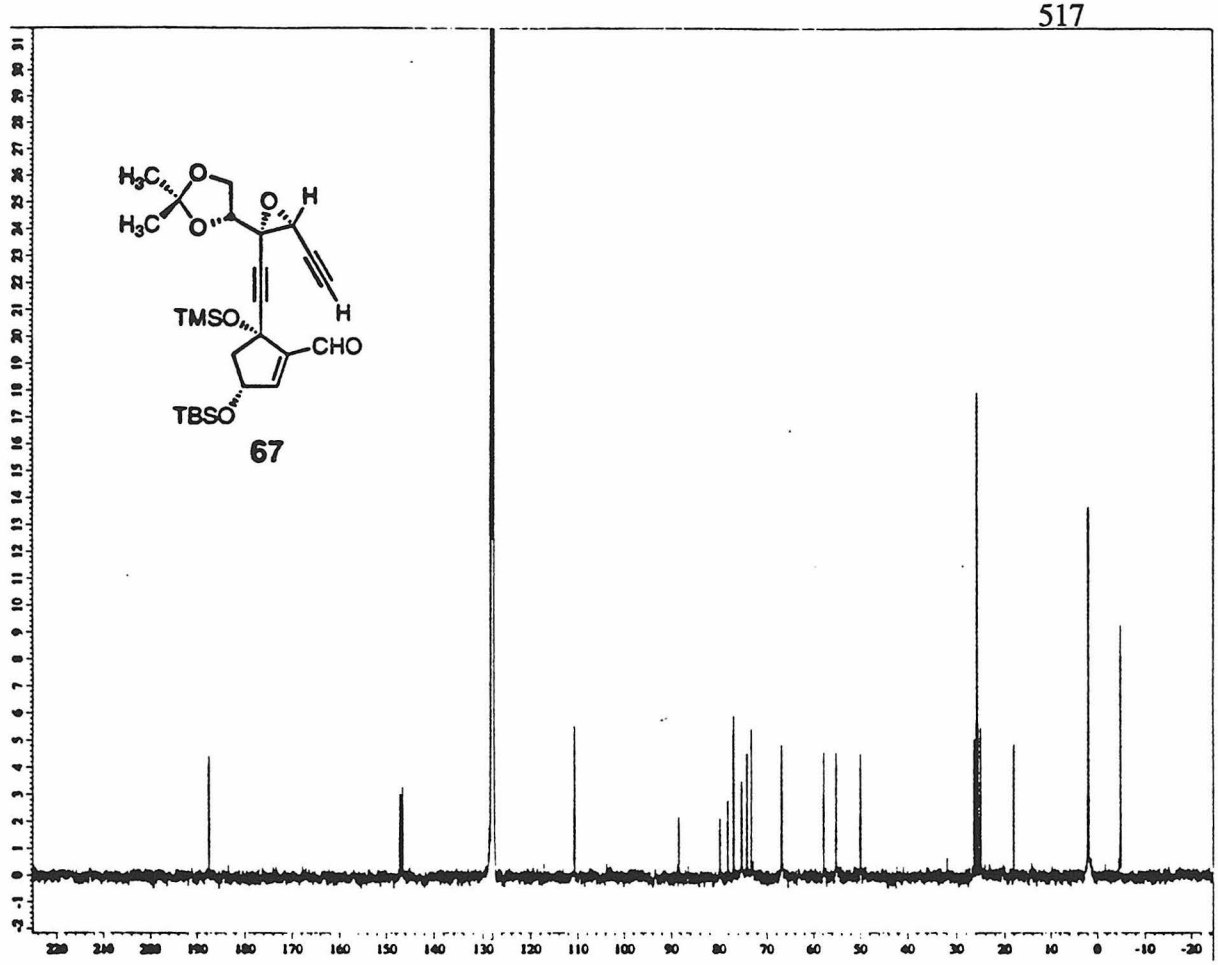
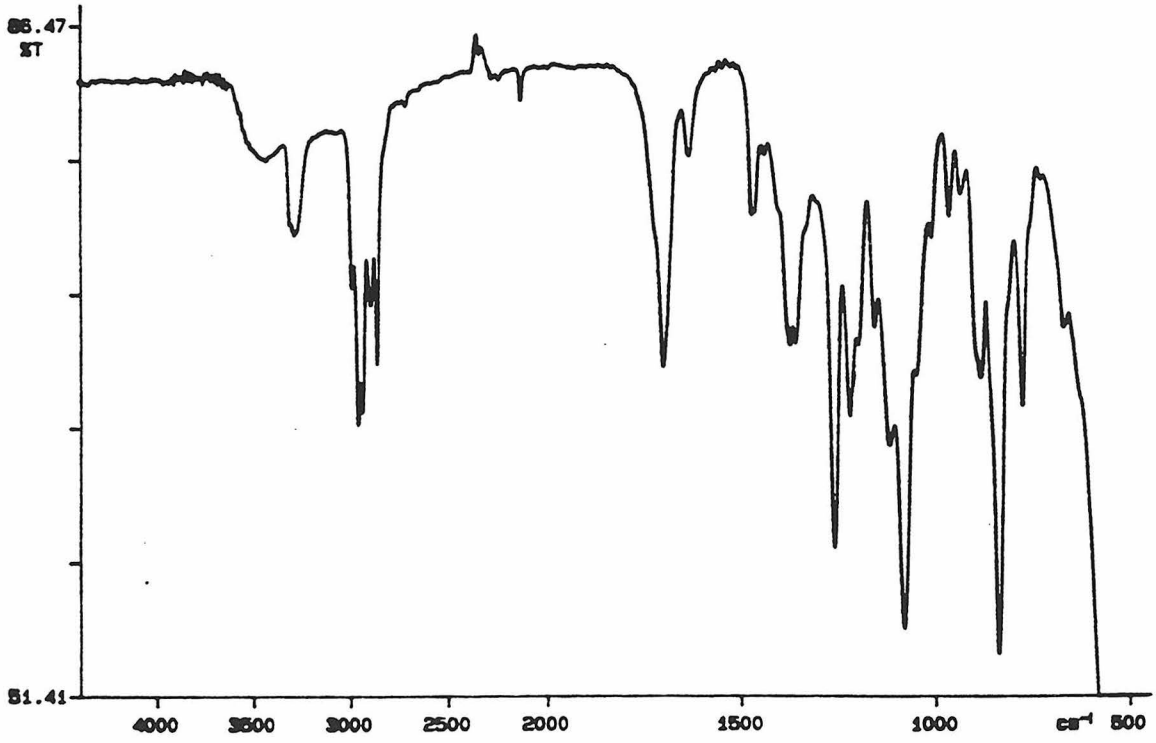
3500
3000
2500
2000
1500
1000
cm-1


H
CHO
O
H
O
O
O
H3C
H3C
TMSO
TBSO
67


H3C
O
H3C
O
O
H
H
TMSO
CHO
TBSO

67


86.47
%T
51.41
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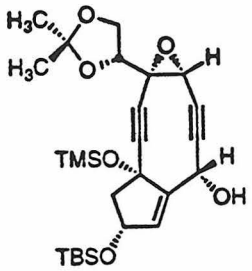
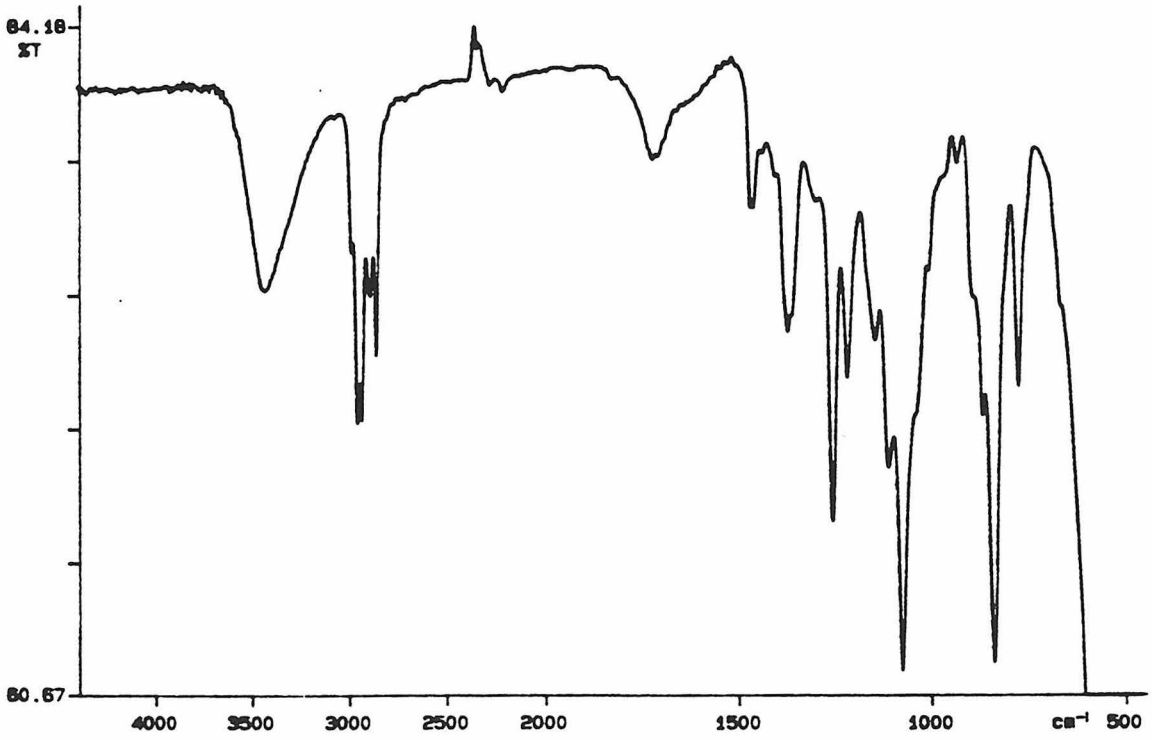
3500
3000
2500
2000
1500
1000
cm-1
500


H3C
O
H3C
O
O
H
TMSO
H
OH
TBSO

68

10
9
8
7
6
5
4
3
2
1
0
PPM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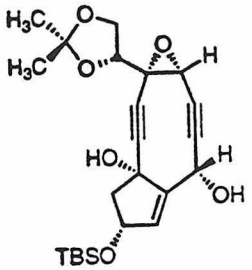
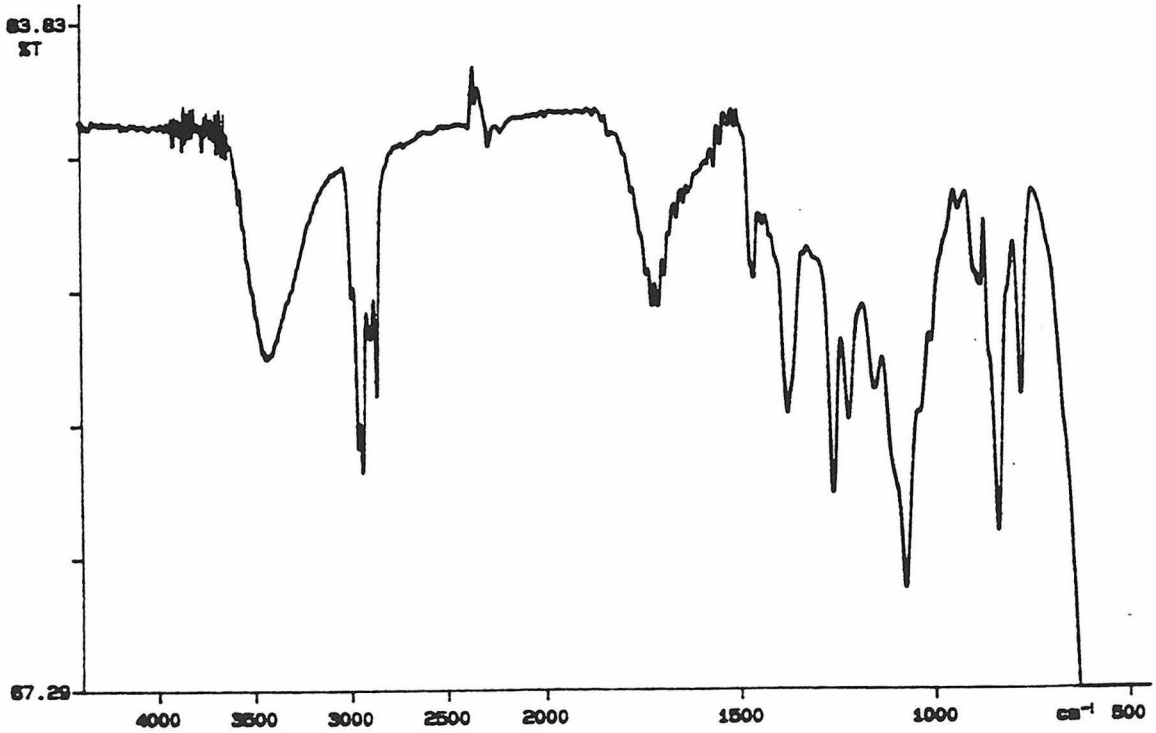
1500
1000
cm-1
500


H3C
O
H3C
O
O
H
HO
H
OH
TBSO

69

10
8
6
4
2
0
PPM


83.83
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67.29
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3000
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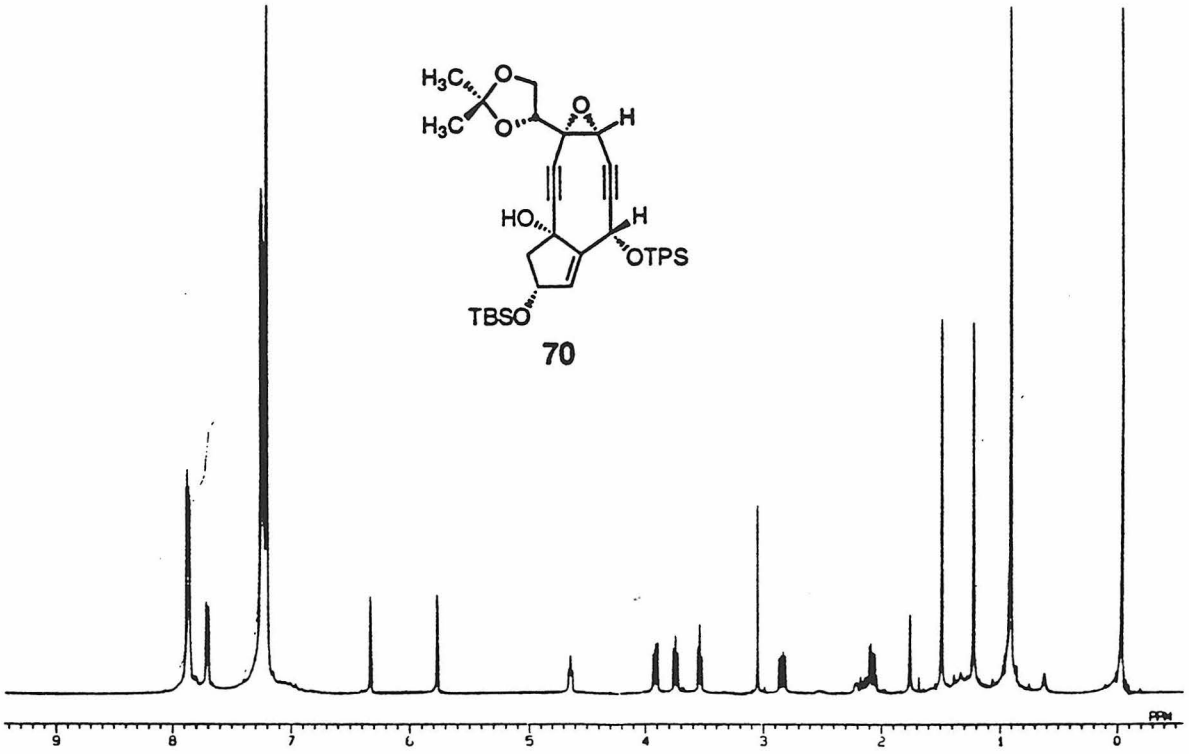
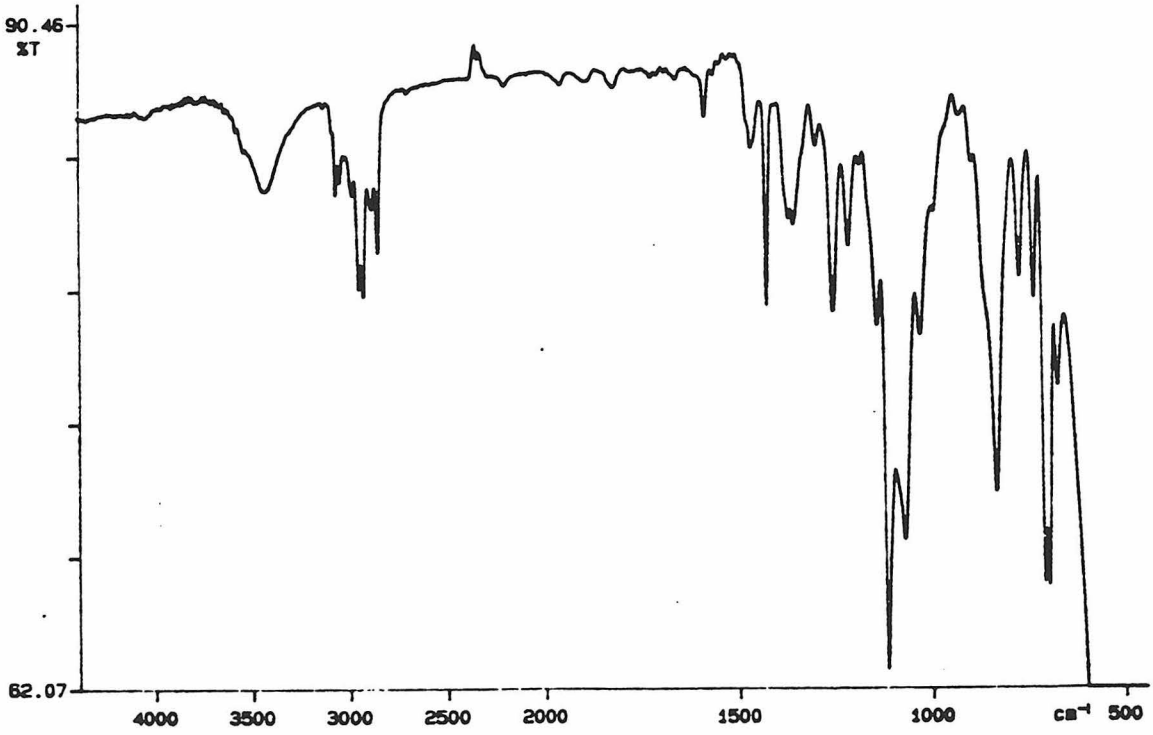
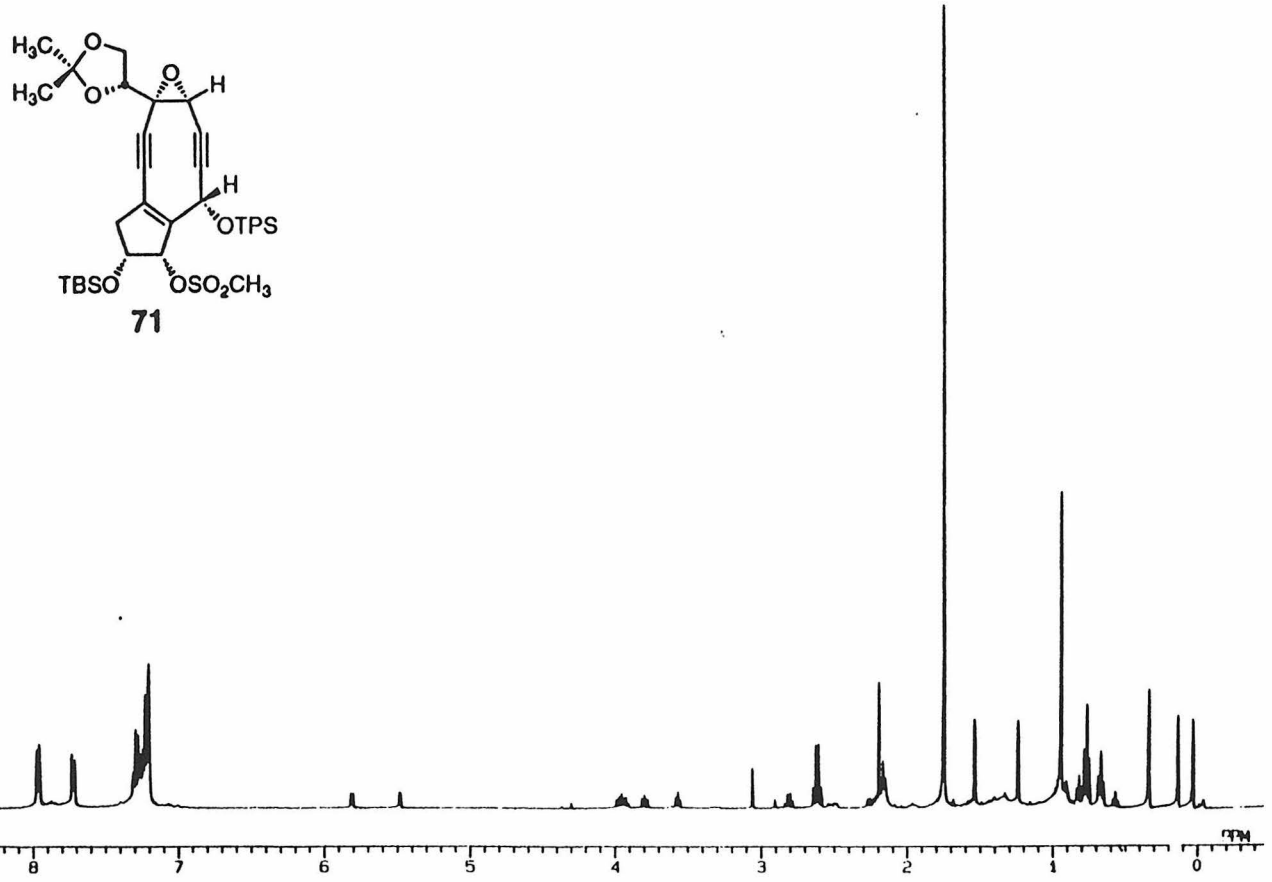
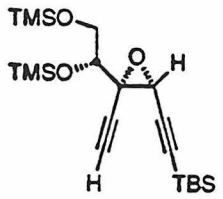
2000
1500
1000
cm-1
500


H3C
O
H3C
O
O
H
HO
H
OTPS
TBSO
9
8
7
6
5
4
3
2
1
0
PPM

70

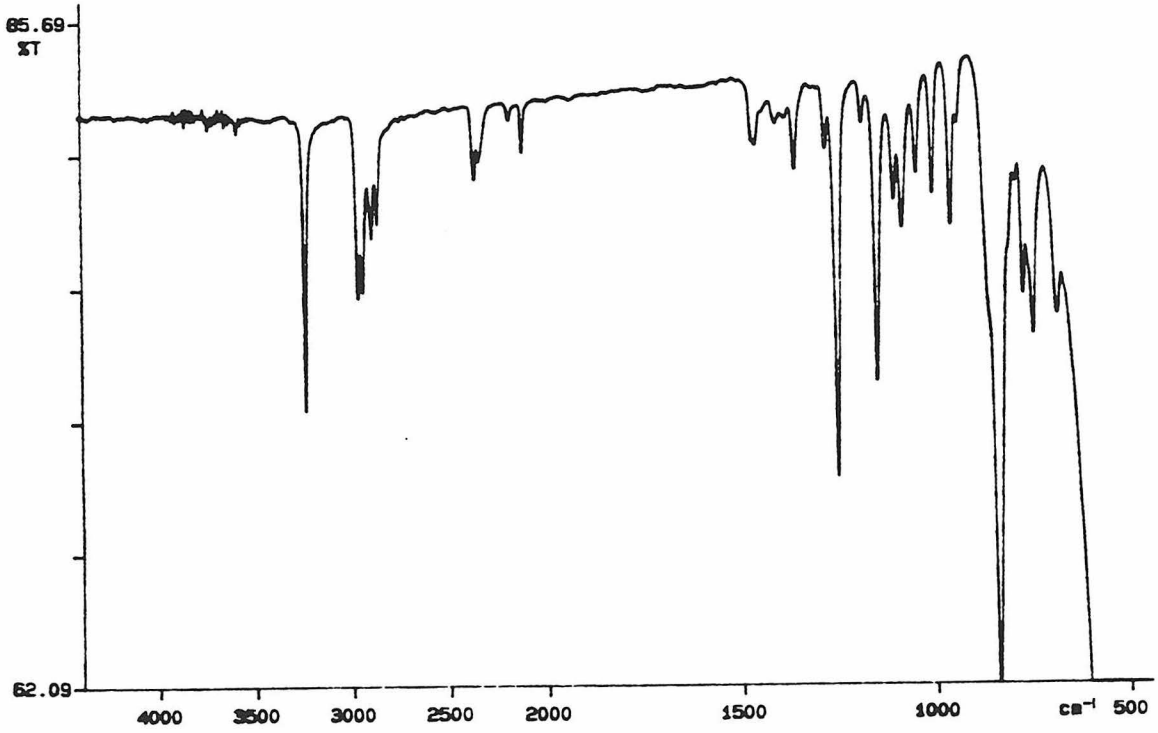

90.46
%T
62.07
4000
3500
3000
2500
2000
1500
1000
cm-1
500

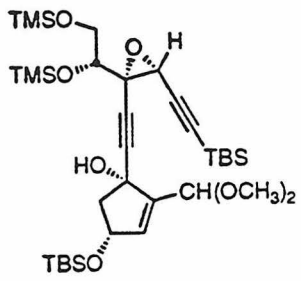

H3C
O
H3C
O
O
H
H
OTPS
TBSO
OSO2CH3
71
9
8
7
6
5
4
3
2
1
0
PPM


TMSO
TMSO
O
H
H
TBS

74

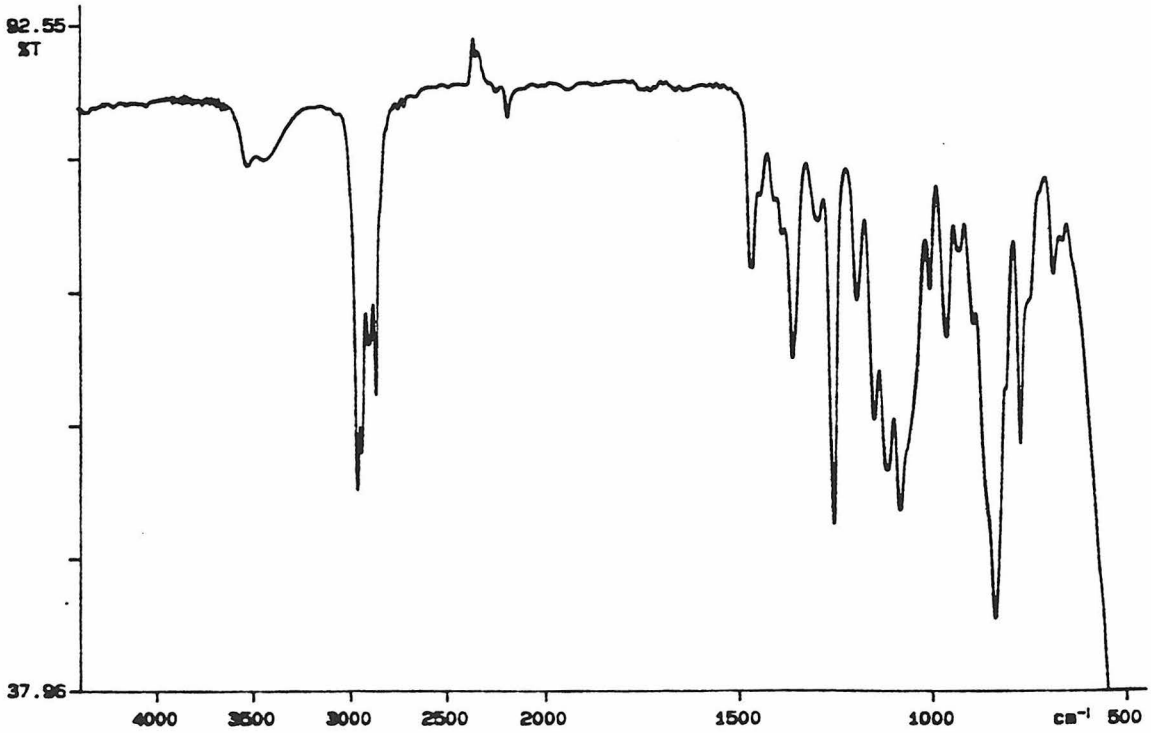
7
6
5
4
3
2
1
0
PPM


85.69
%T
62.09
4000
3500
3000
2500
2000
1500
1000
cm⁻¹
500


TMSO
TMSO
O
H
HO
TBS
CH(OCH3)2
TBSO

75

10
9
8
7
6
5
4
3
2
1
0
PPM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37.96
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3000
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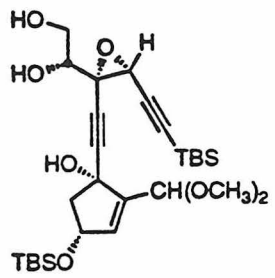
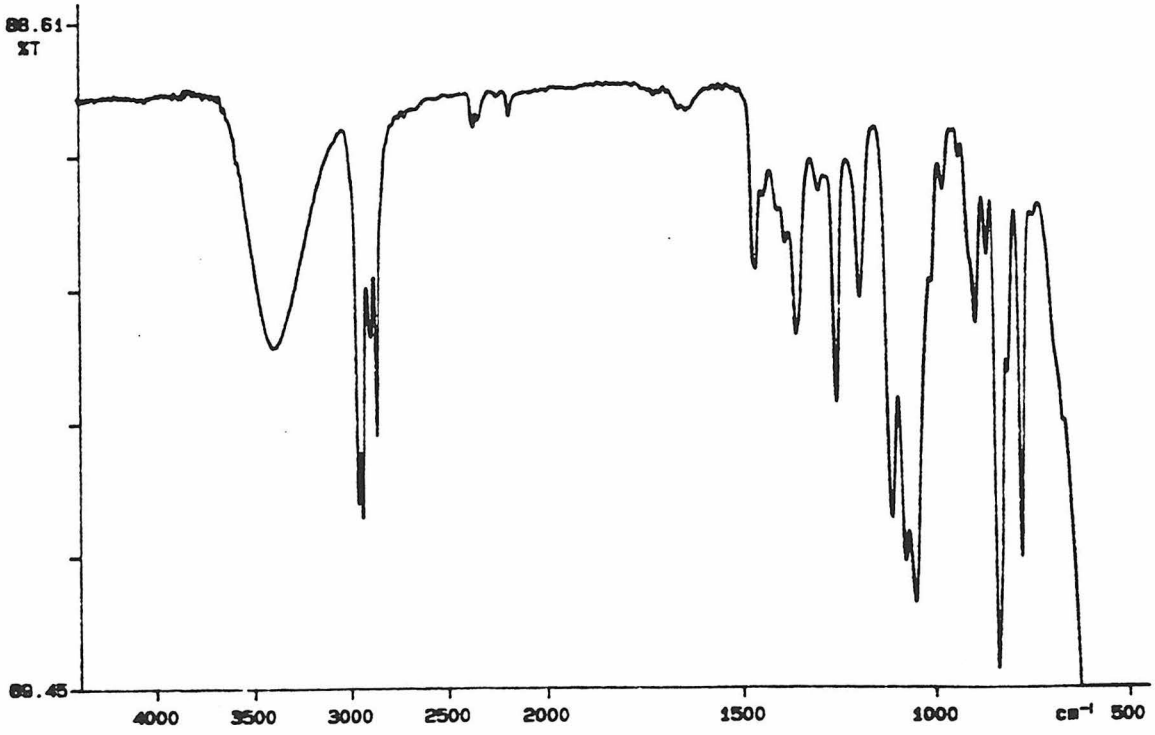
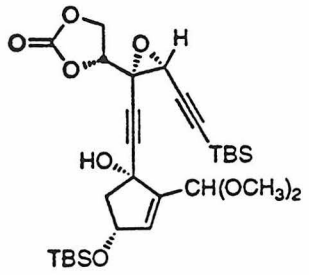
2000
1500
1000
cm-1
500


HO
HO
O
H
TBS
HO
CH(OCH3)2
TBSO

76

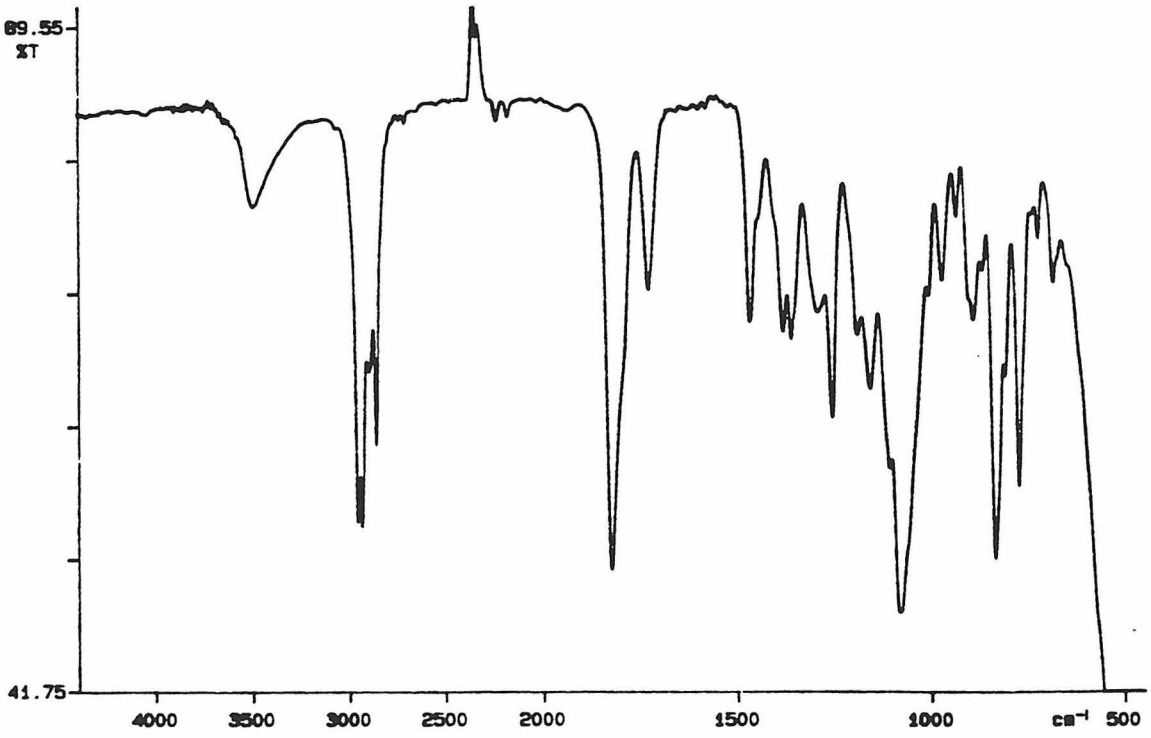
8
7
6
5
4
3
2
1
0
PPM

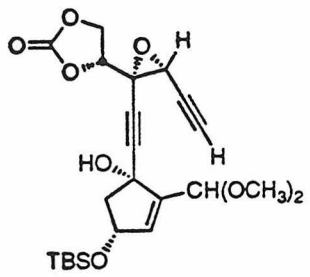

88.61
%T
69.45
4000
3500
3000
2500
2000
1500
1000
cm-1
500


O
O
O
O
H
TBS
HO
CH(OCH3)2
TBSO

77

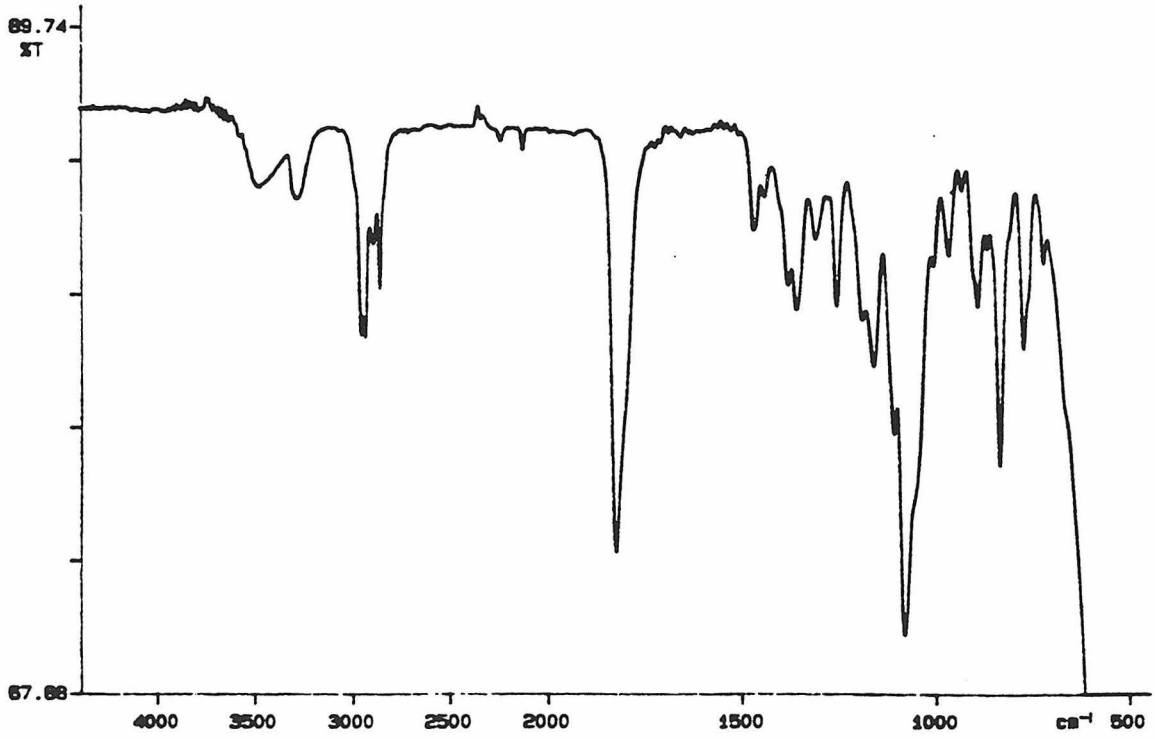
8
7
6
5
4
3
2
1
0
PPM

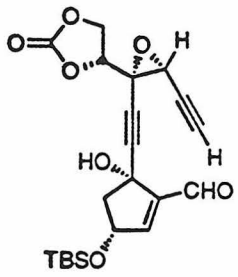

89.55
%T
41.75
4000
3500
3000
2500
2000
1500
1000
cm-1
500


O
O
O
O
H
HO
H
CH(OCH3)2
TBSO

78

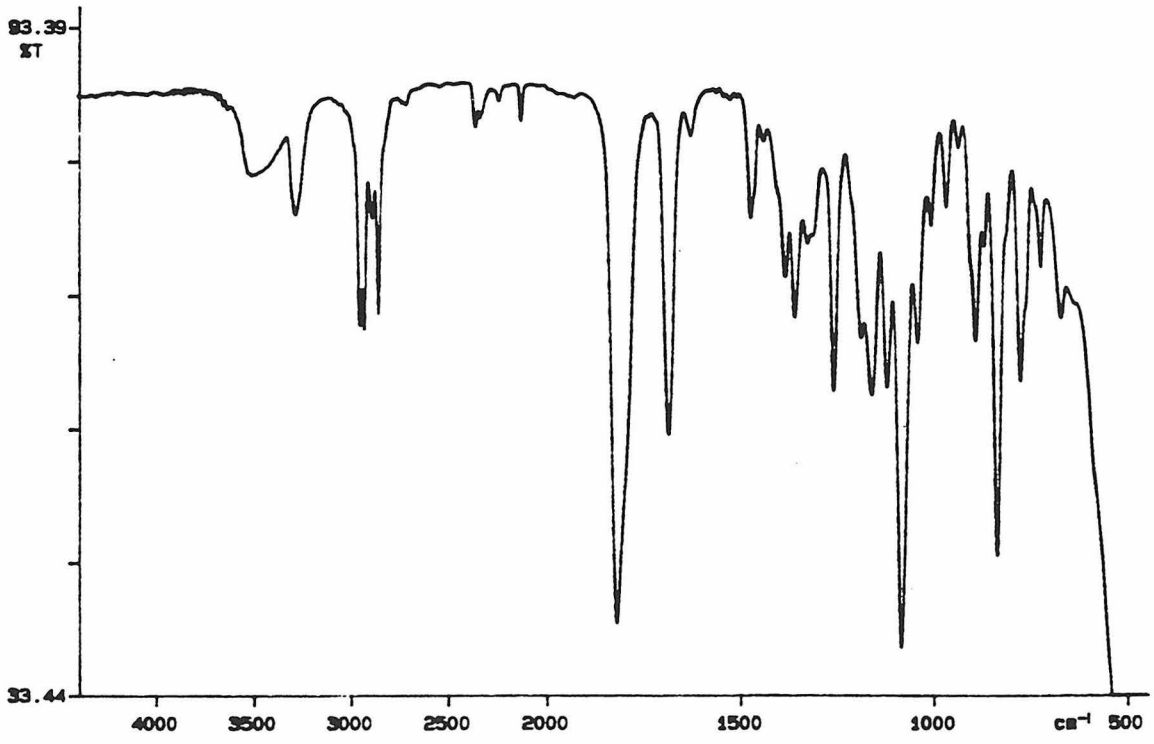
9
8
7
6
5
4
3
2
1
0
PPM

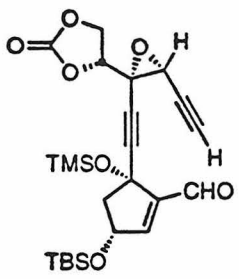

89.74
%T
67.88
4000
3500
3000
2500
2000
1500
1000
cm-1
500


O
O
O
O
H
HO
H
CHO
TBSO

79

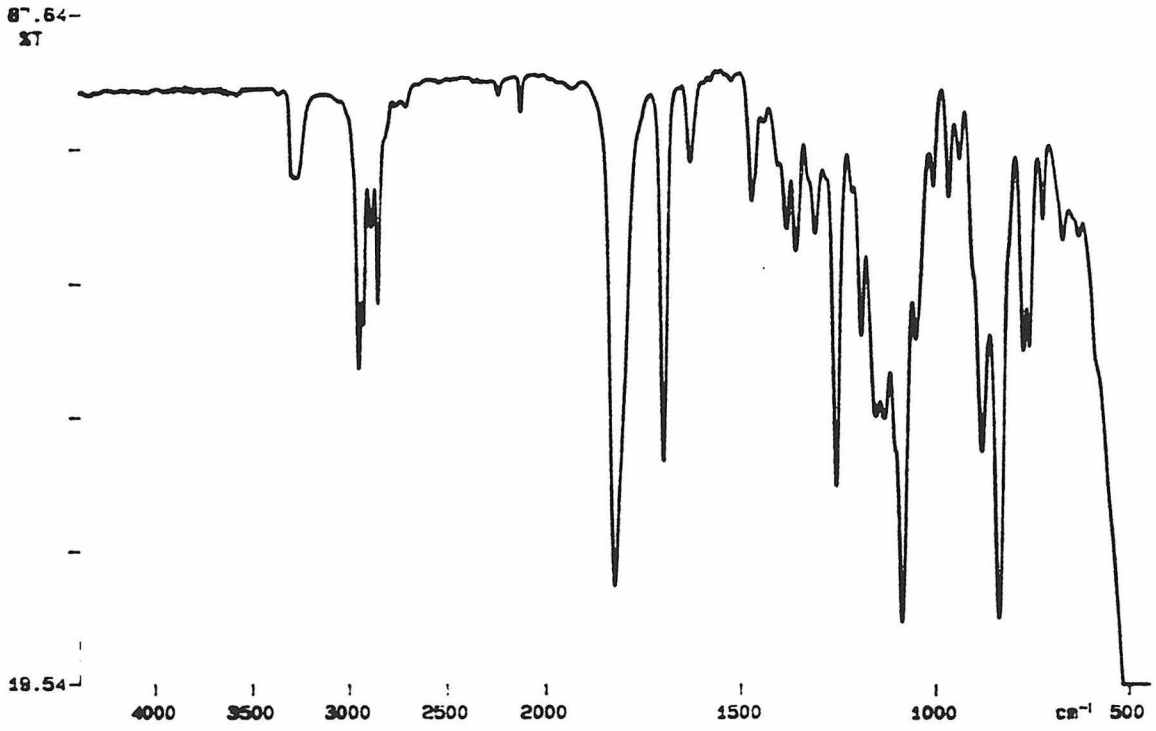
10
9
8
7
6
5
4
3
2
1
0
PPM

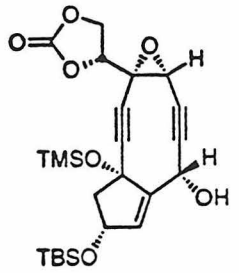

93.39
%T
93.44
4000
3500
3000
2500
2000
1500
1000
cm⁻¹
500


O
O
O
O
H
H
TMSO
CHO
TBSO

80

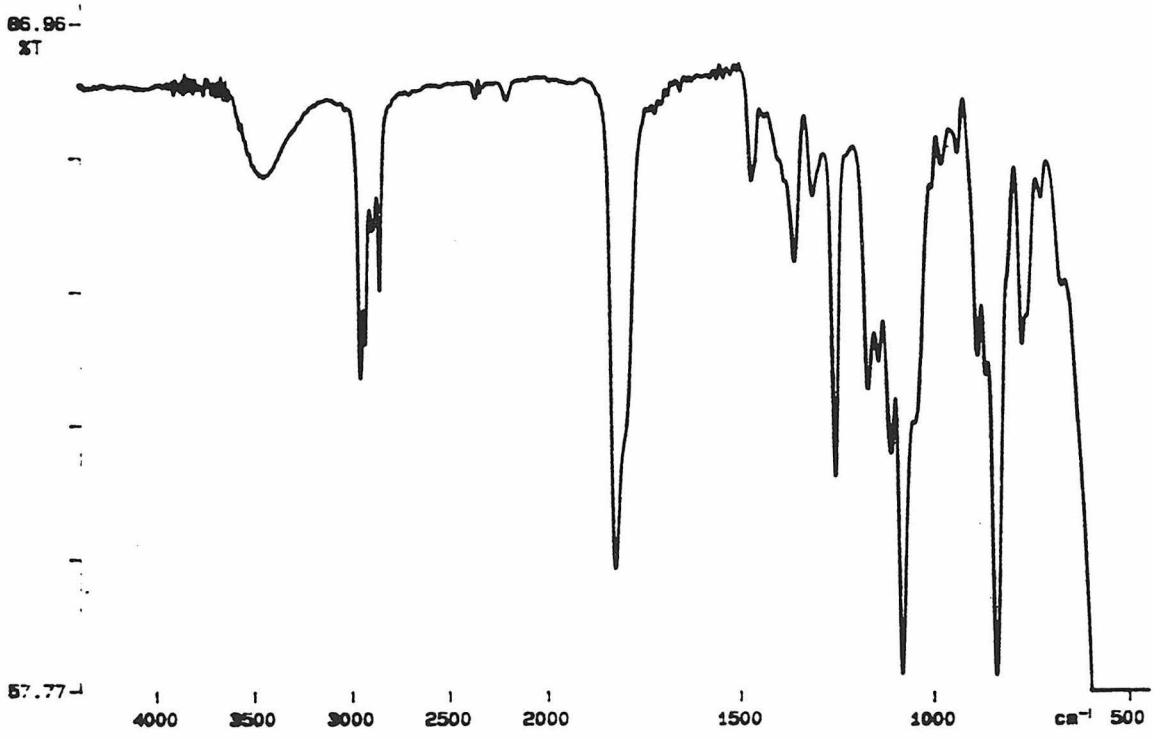
10
9
8
7
6
5
4
3
2
1
0
PPM

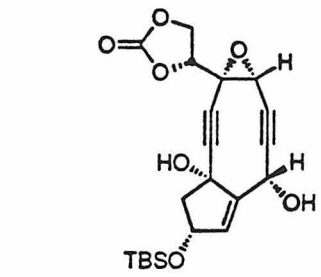

%T
19.54
4000
3500
3000
2500
2000
1500
1000
cm-1
500


O
O
O
O
H
TMSO
H
OH
TBSO

81

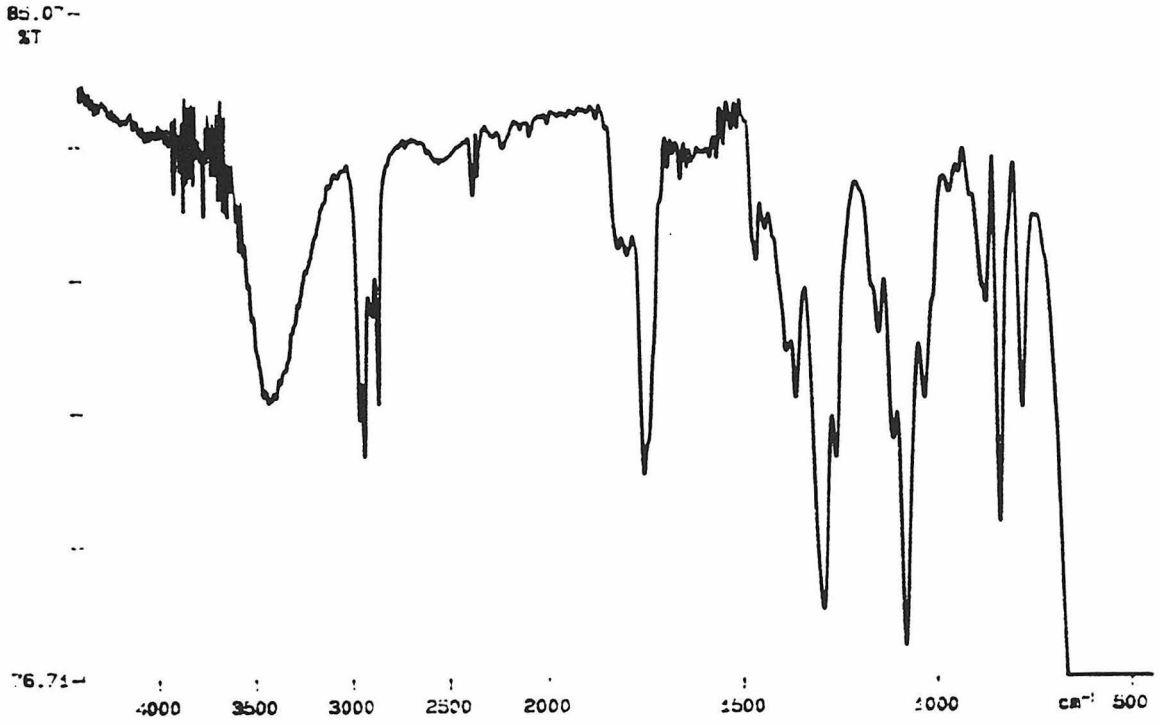
10
9
8
7
6
5
4
3
2
1
0
PPM

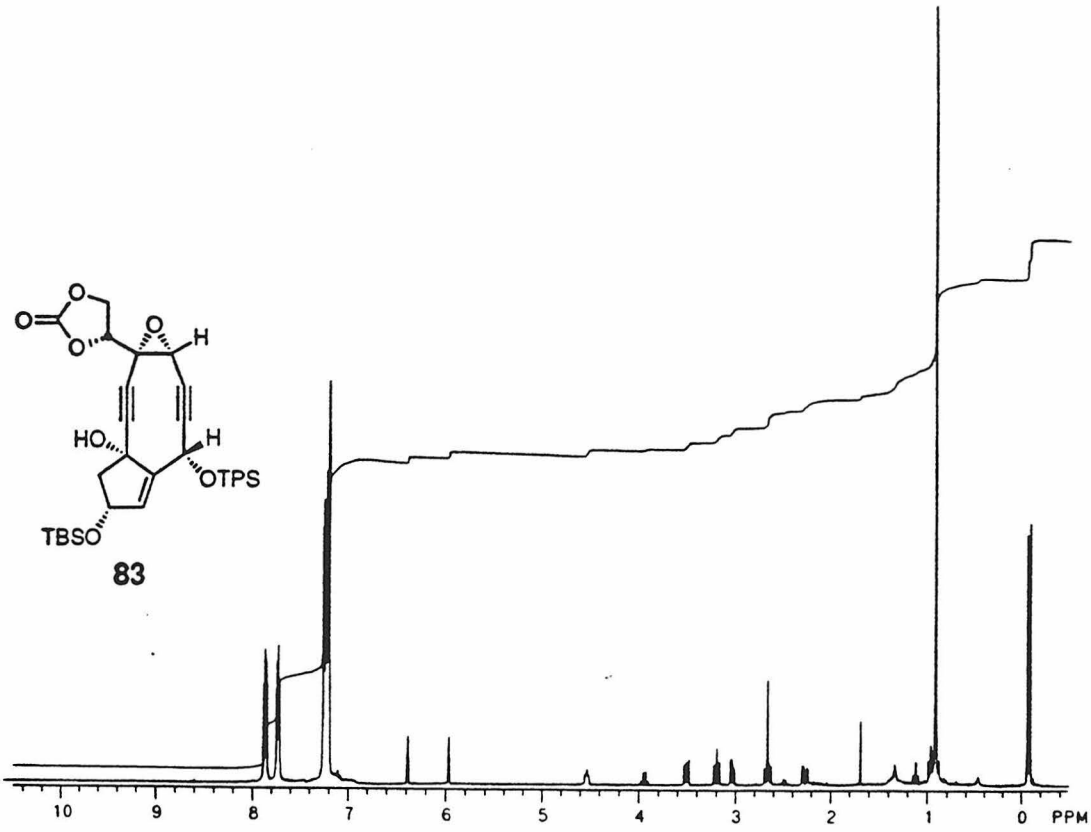

86.96
%T
57.77
4000
3500
3000
2500
2000
1500
1000
cm⁻¹
500


O
O
O
O
H
HO
H
OH
TBSO

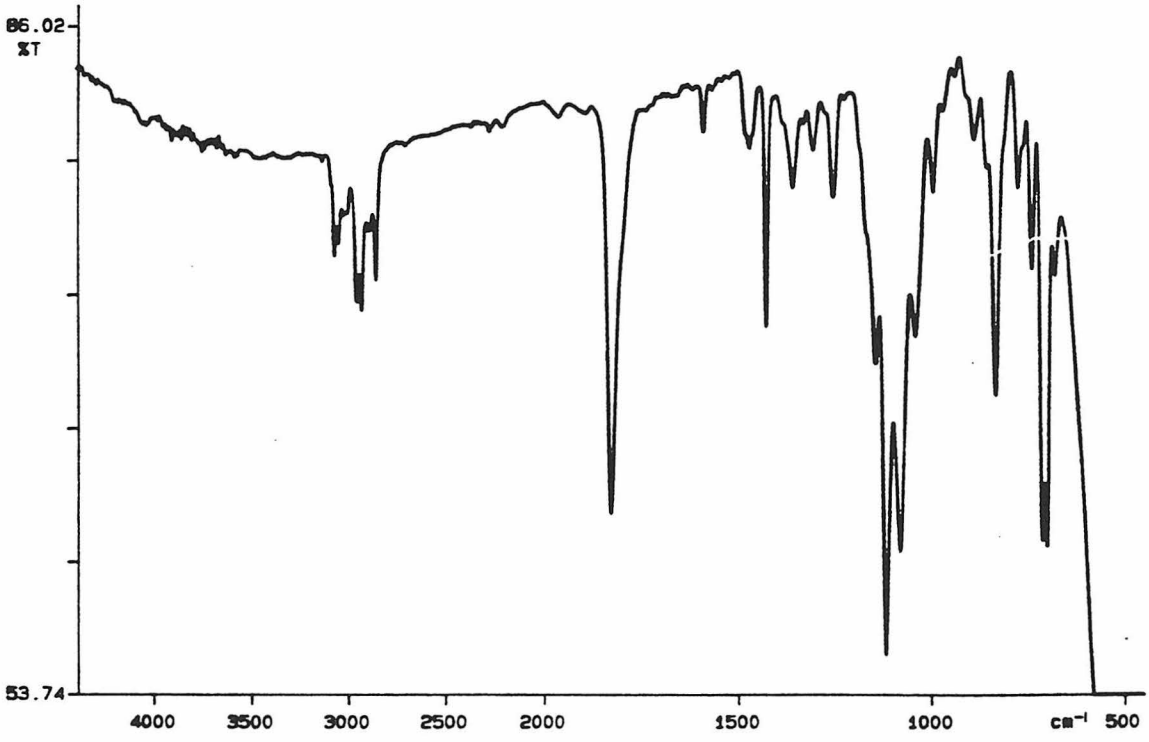
82

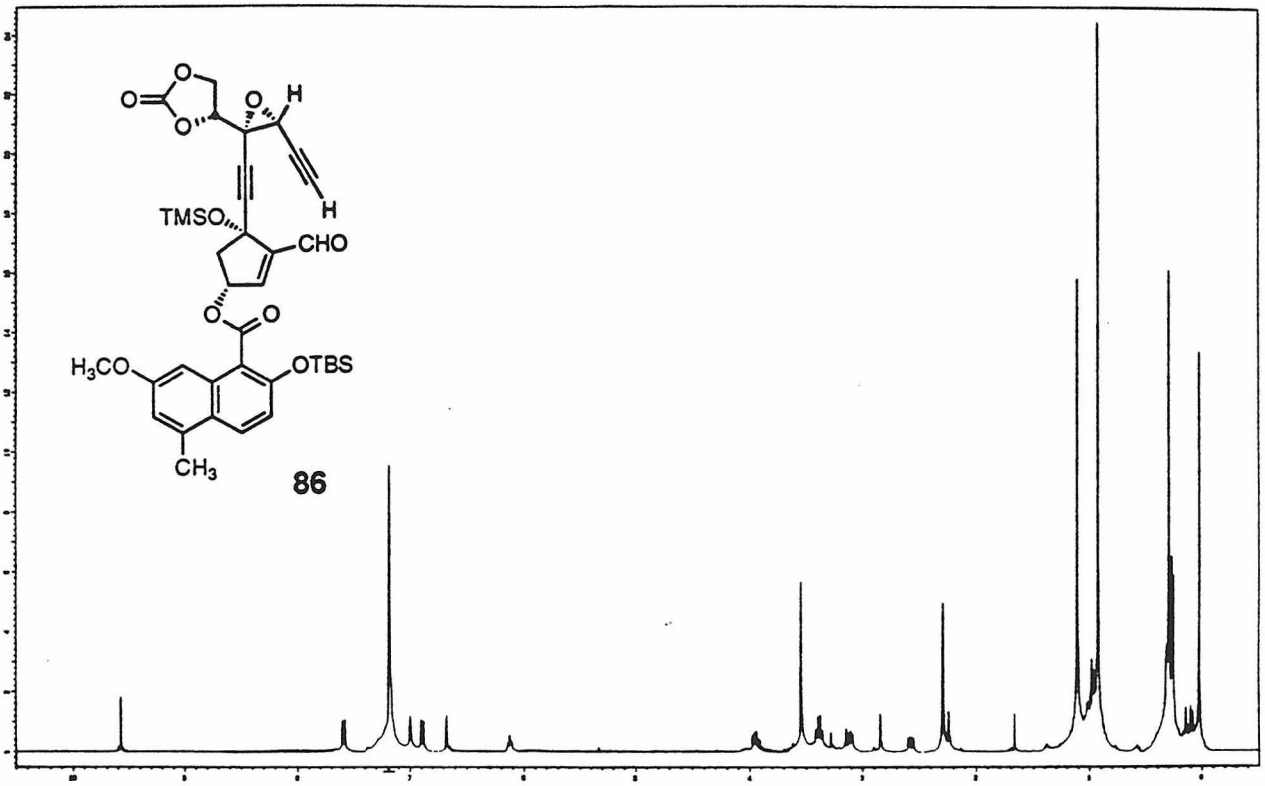
PPM
9
8
7
6
5
4
3
2
1
0


%T
4000
3500
3000
2500
2000
1500
1000
cm⁻¹
500

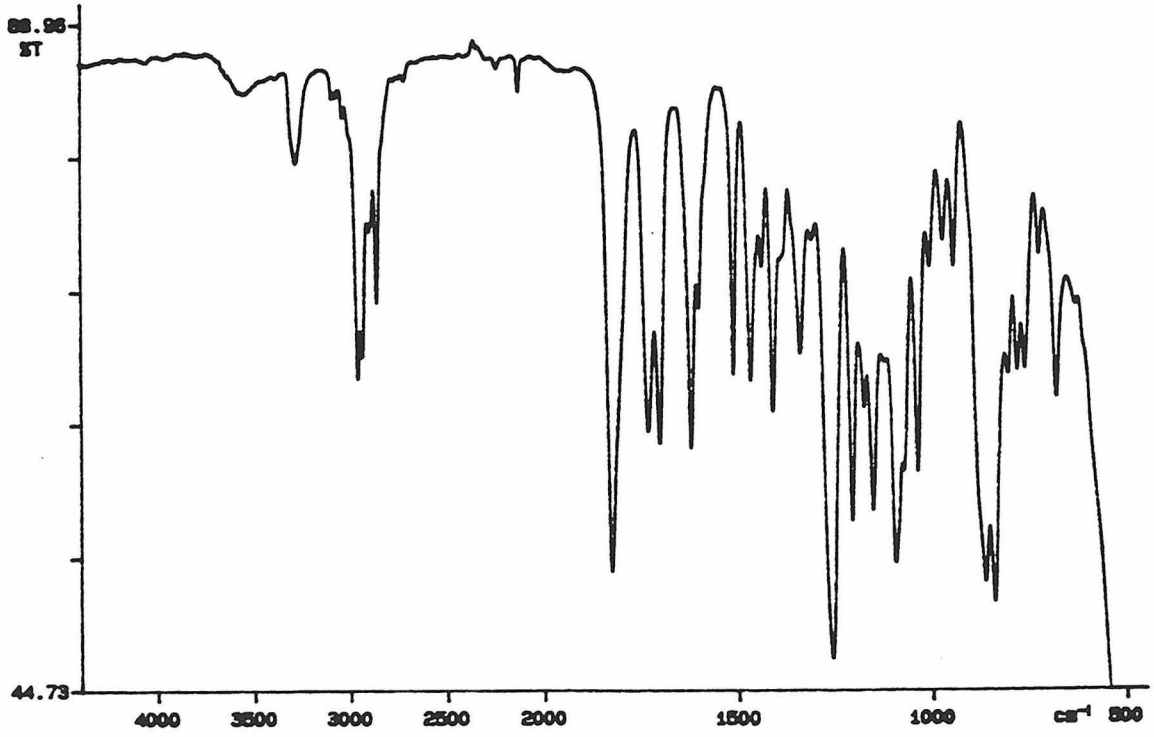

HO
H
OTPS
TBSO
10
9
8
7
6
5
4
3
2
1
0
PPM

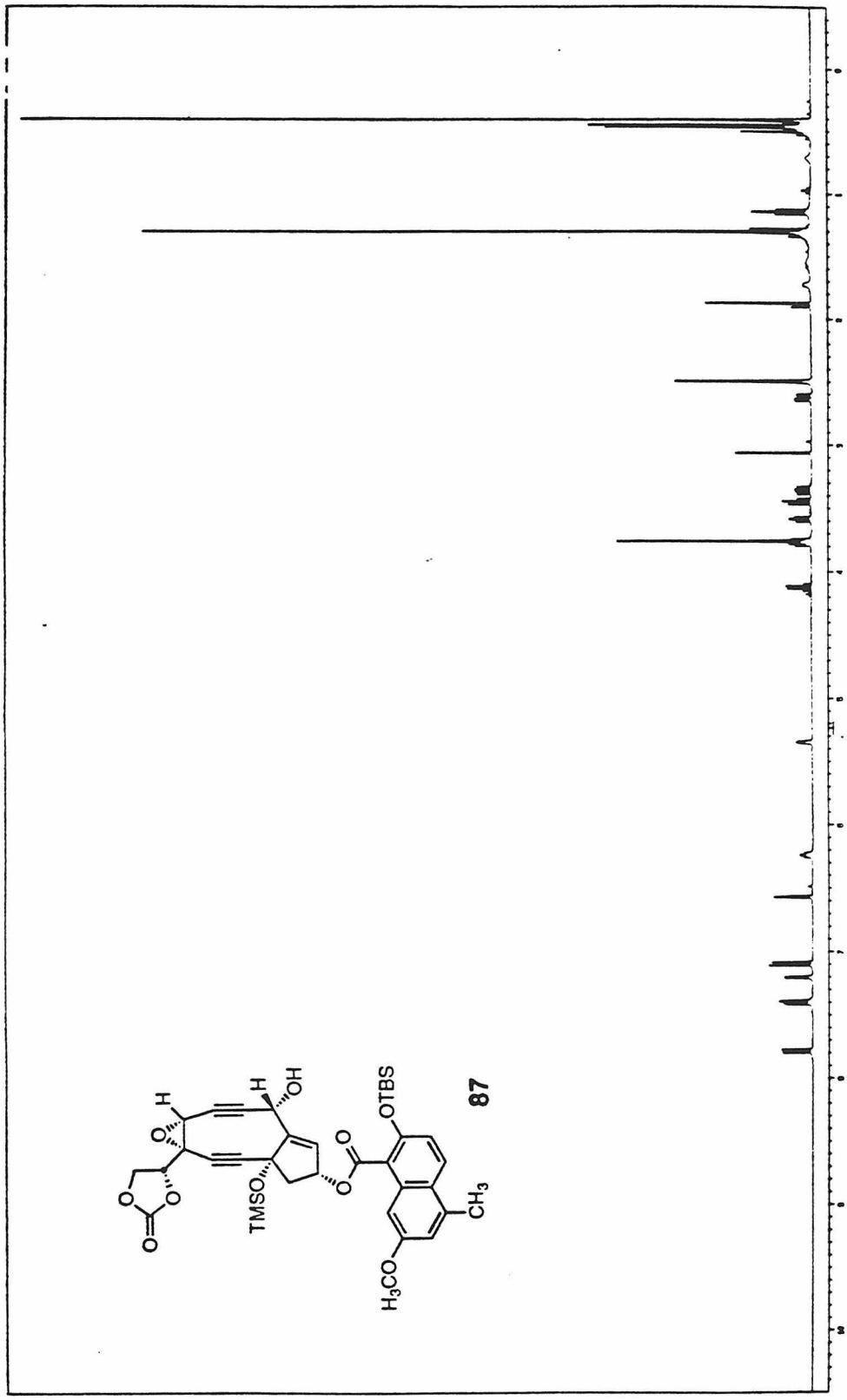
83


86.02
%T
53.74
4000
3500
3000
2500
2000
1500
1000
cm⁻¹
500

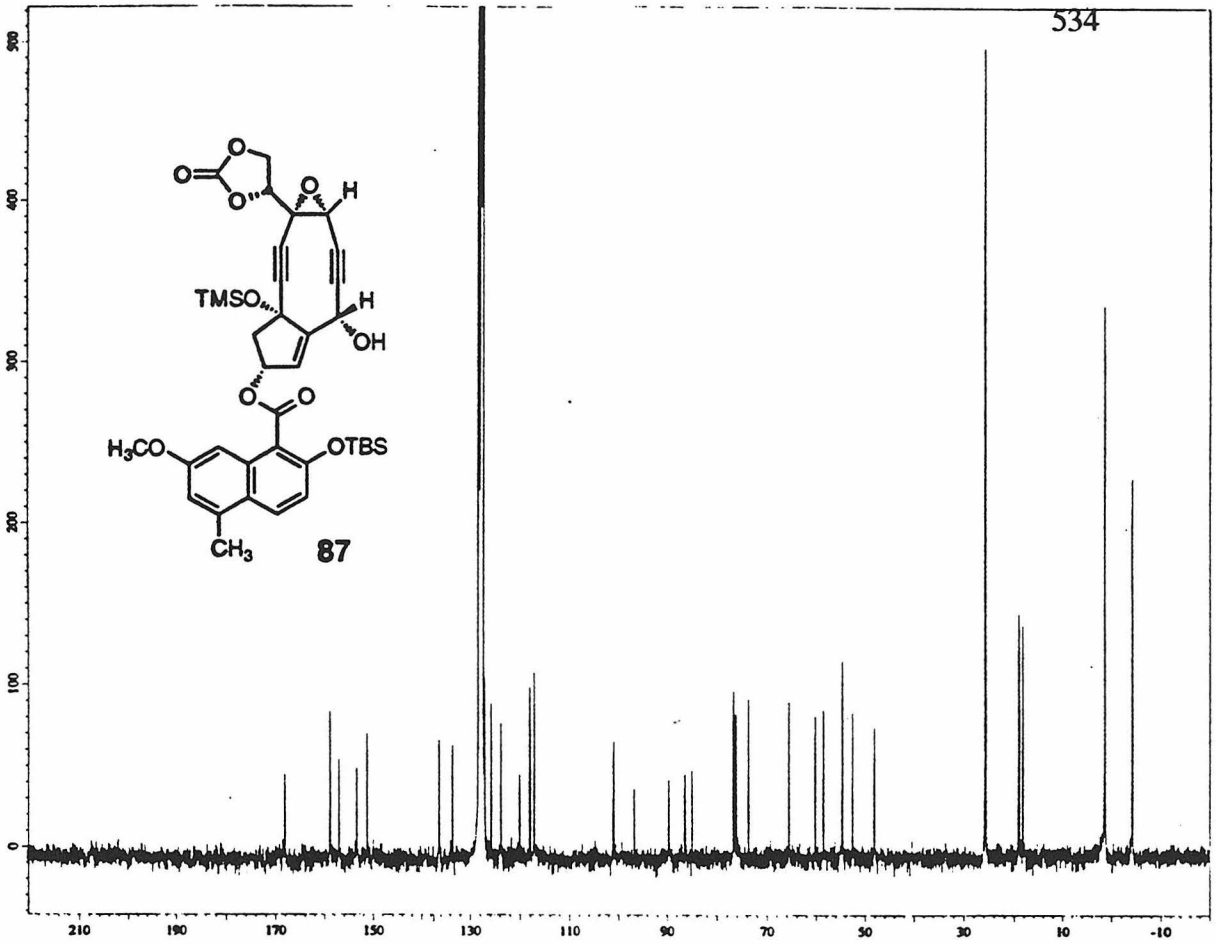

TMSO
CHO
H
H3CO
OTBS
CH3

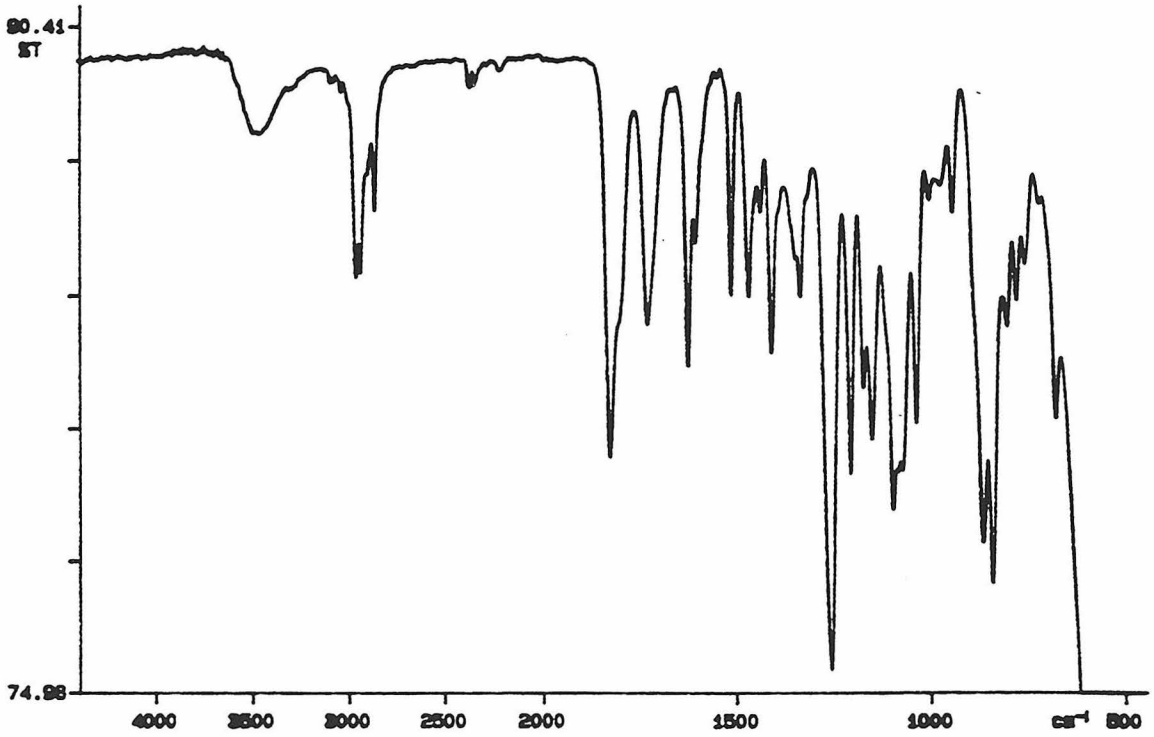
86

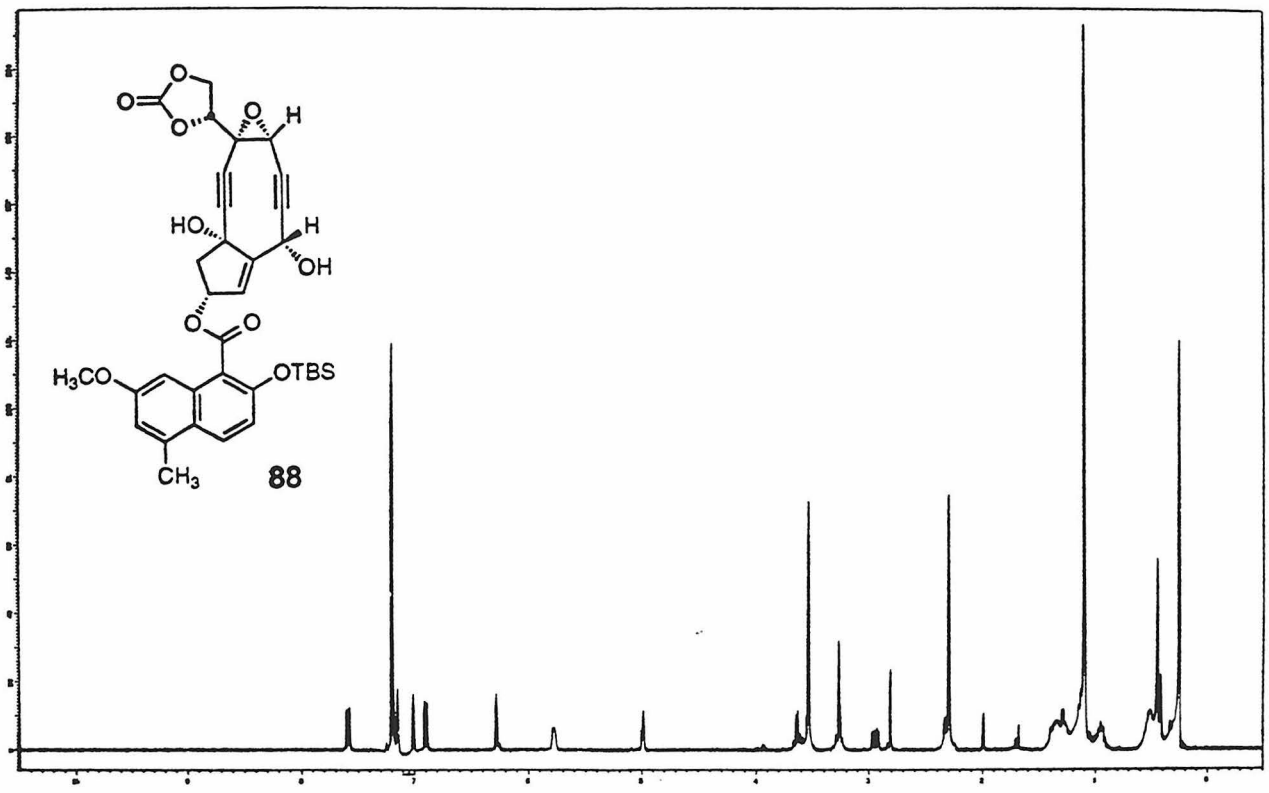

88.96
%T
44.73
4000
3500
3000
2500
2000
1500
1000
cm-1
500



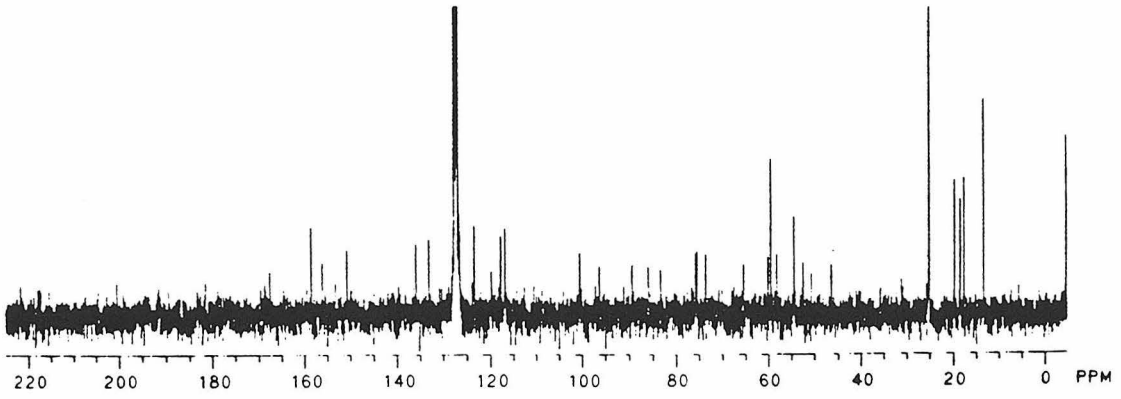
87

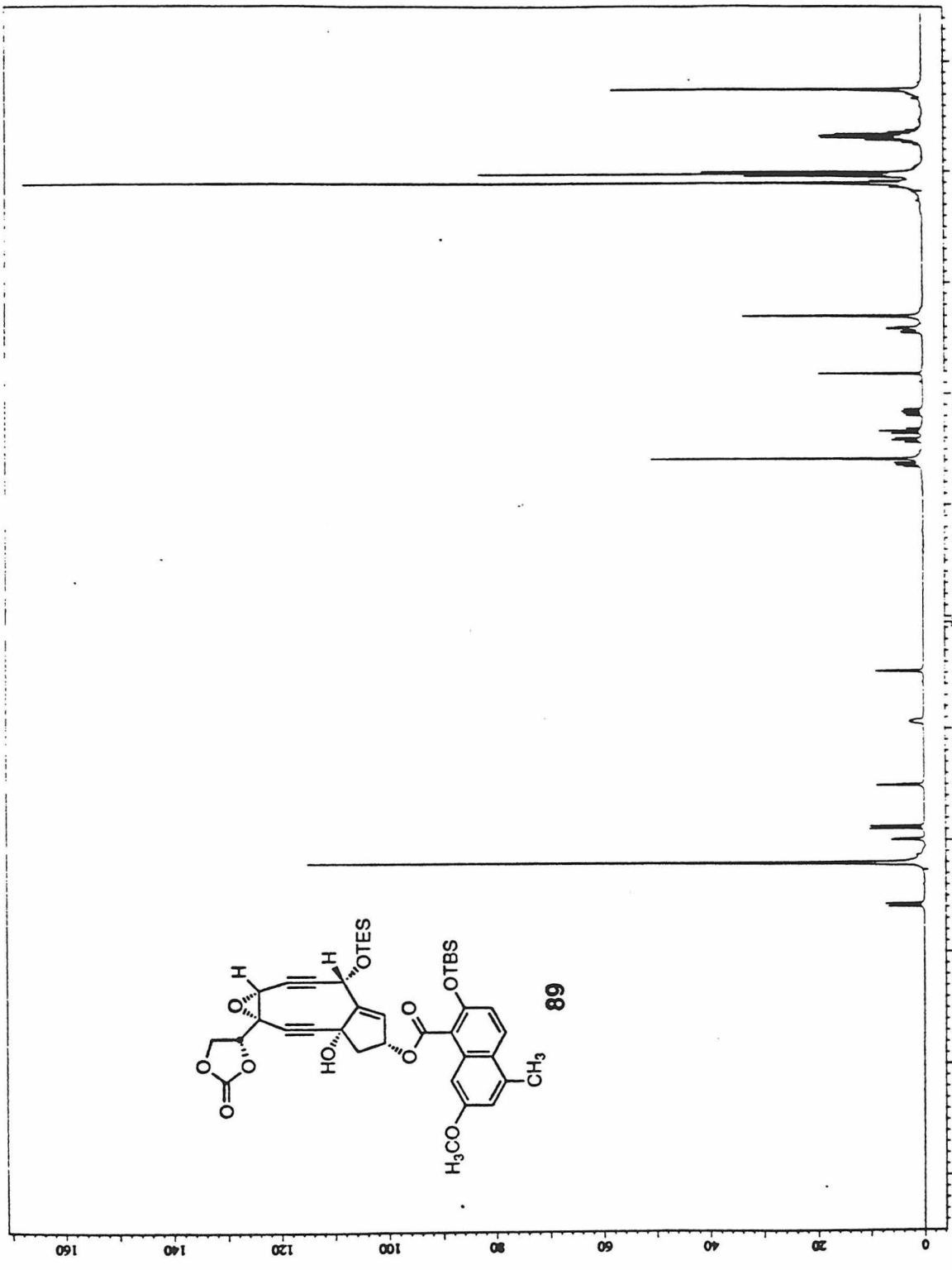

TMSO
H
OH
H3CO
OTBS
CH3
87
500
400
300
200
100
0
210
190
170
150
130
110
90
70
50
30
10
-10

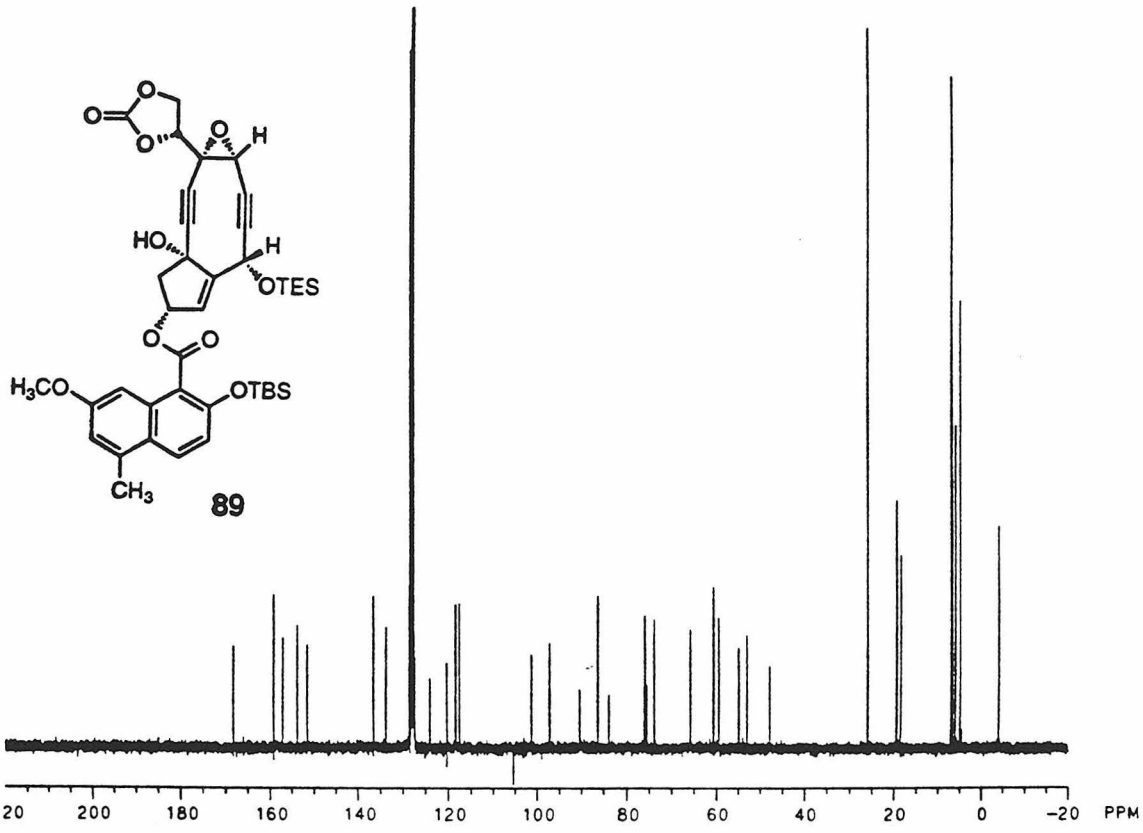

90.41
%T
74.98
4000
3500
3000
2500
2000
1500
1000
cm-1
500


O
O
O
O
H
HO
H
OH
O
O
H3CO
OTBS
CH3

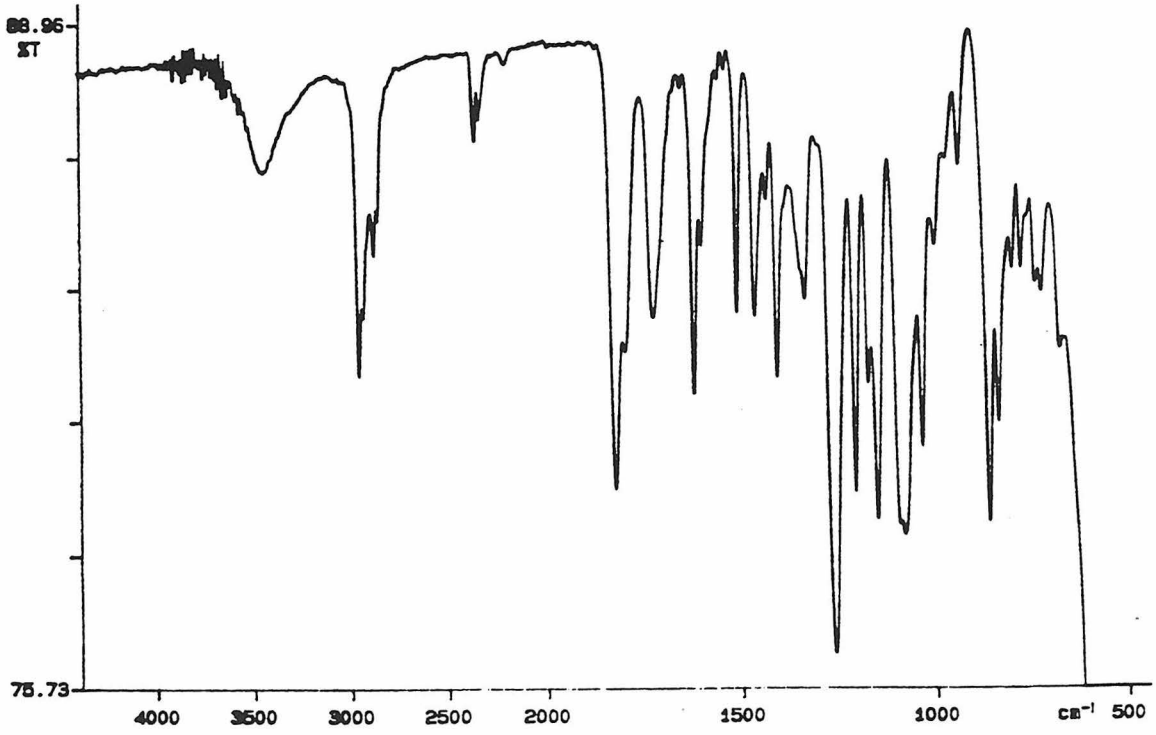
88

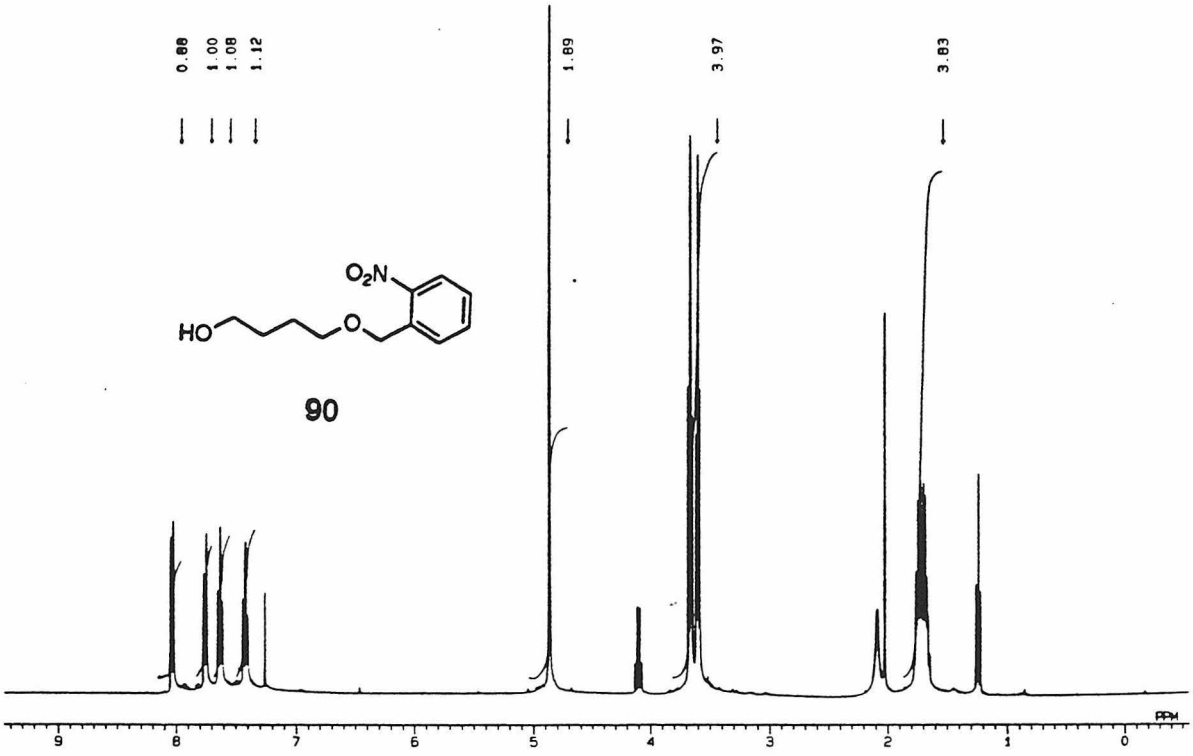

220
200
180
160
140
120
100
80
60
40
20
0
PPM


OTES
H
H
OTBS
HO
O
O
O
O
O
O
CH3
H3CO
89

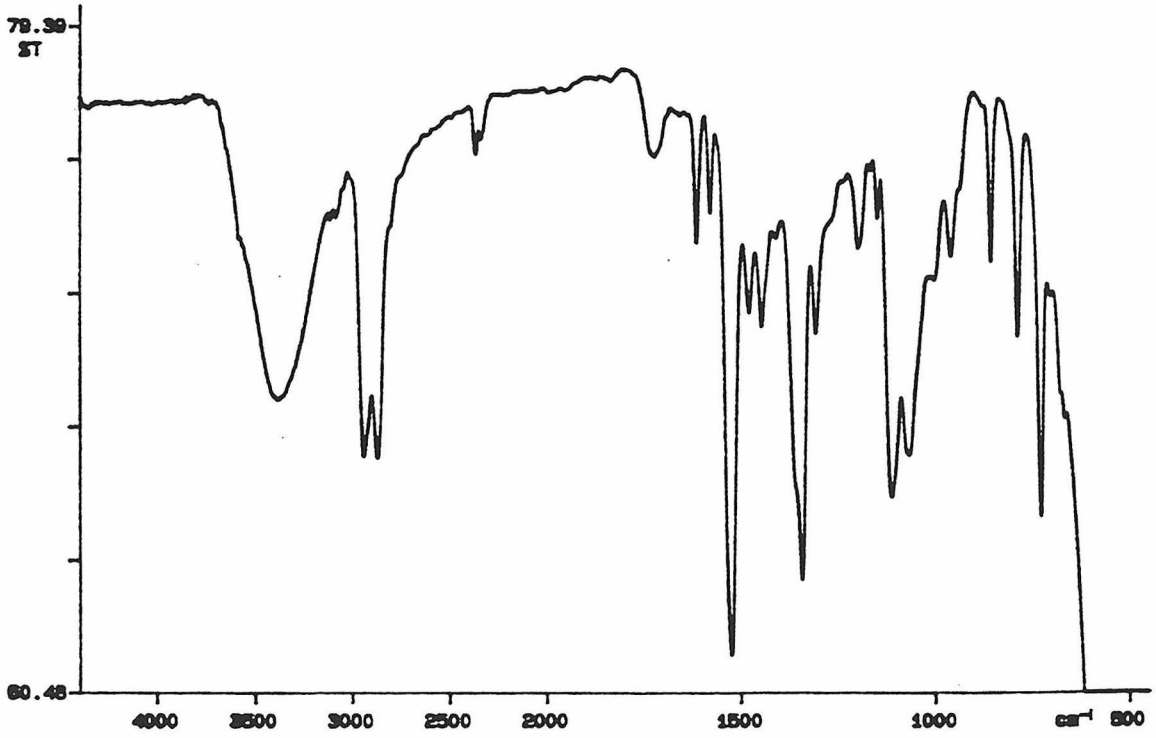

O
O
O
O
H
HO
H
OTES
O
O
H3CO
OTBS
CH3
220
200
180
160
140
120
100
80
60
40
20
0
−20
PPM

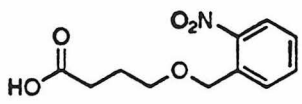
89


88.96
%T
75.73
4000
3500
3000
2500
2000
1500
1000
cm-1
500


0.88
1.00
1.08
1.12
1.89
3.97
3.83
O_2N
HO
O
PPM
9
8
7
6
5
4
3
2
1
0

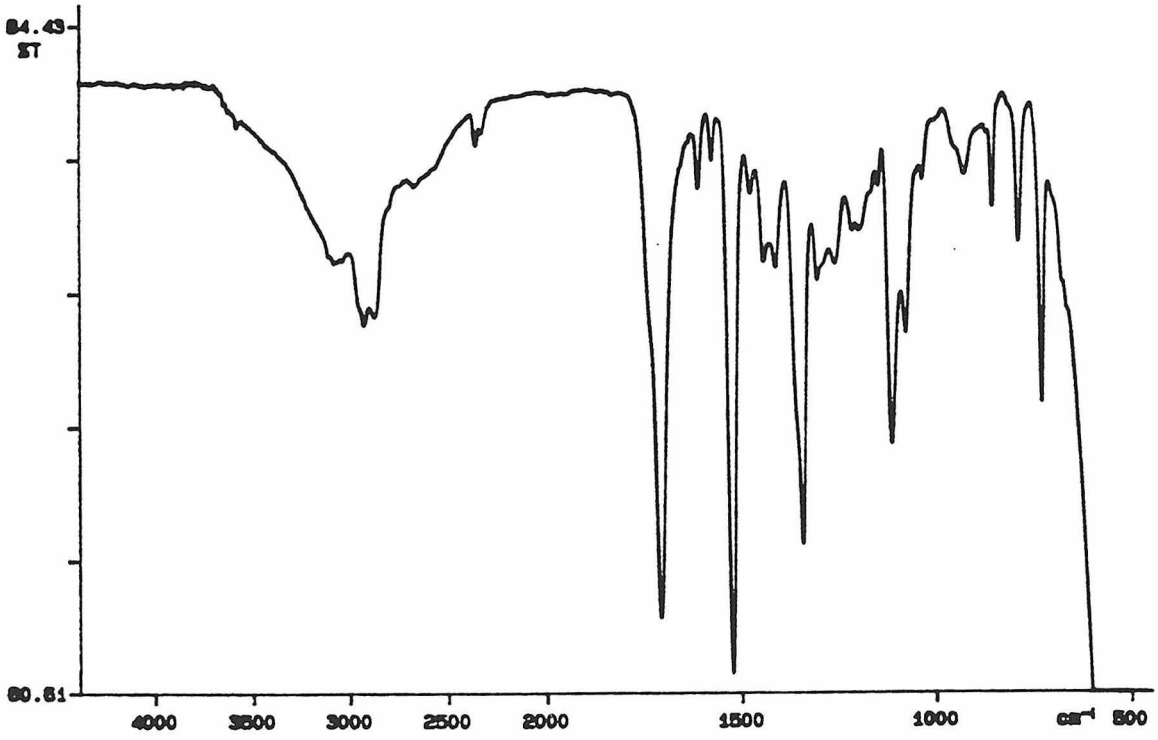
90

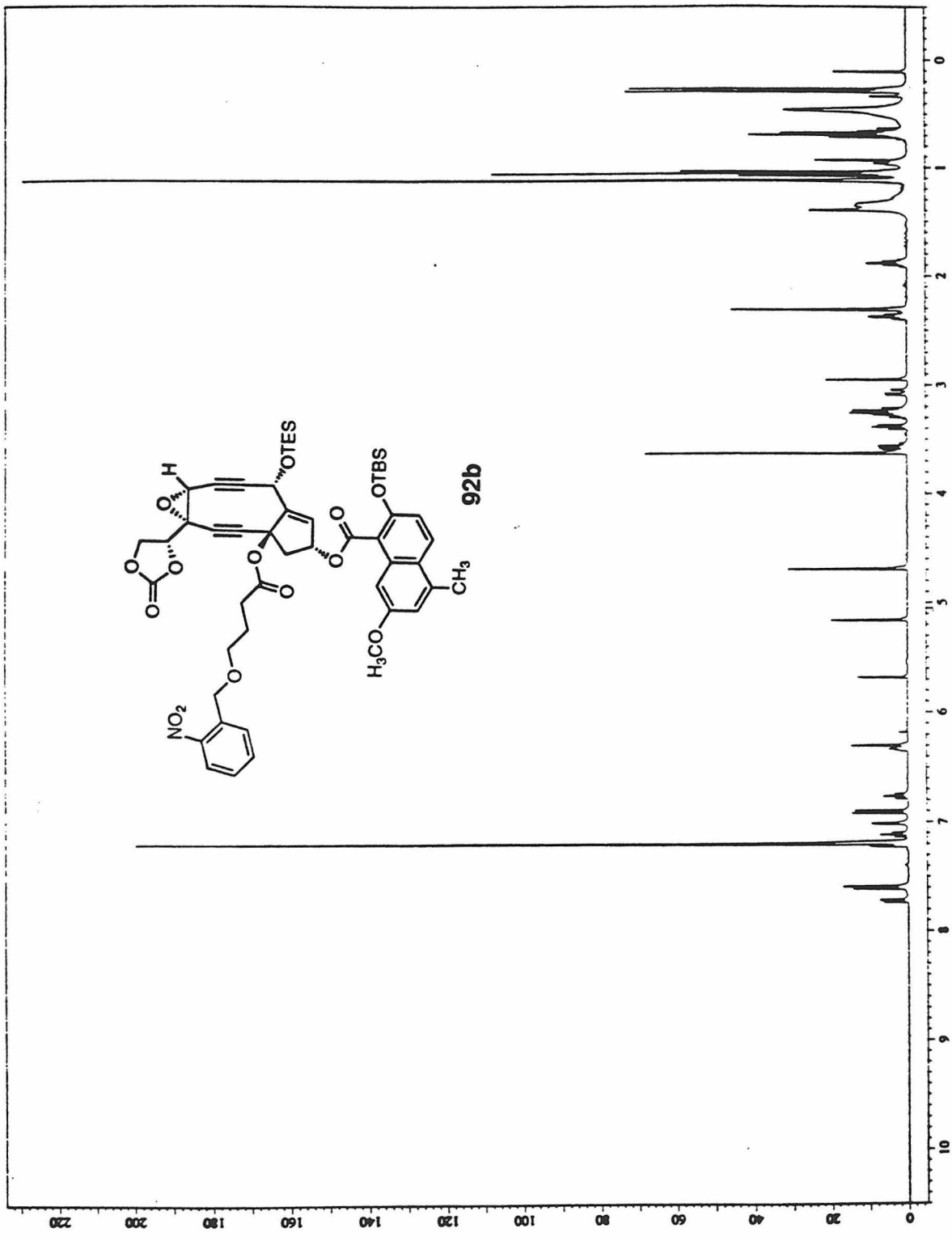

79.39
%T
60.48
4000
3500
3000
2500
2000
1500
1000
cm^{-1}
500

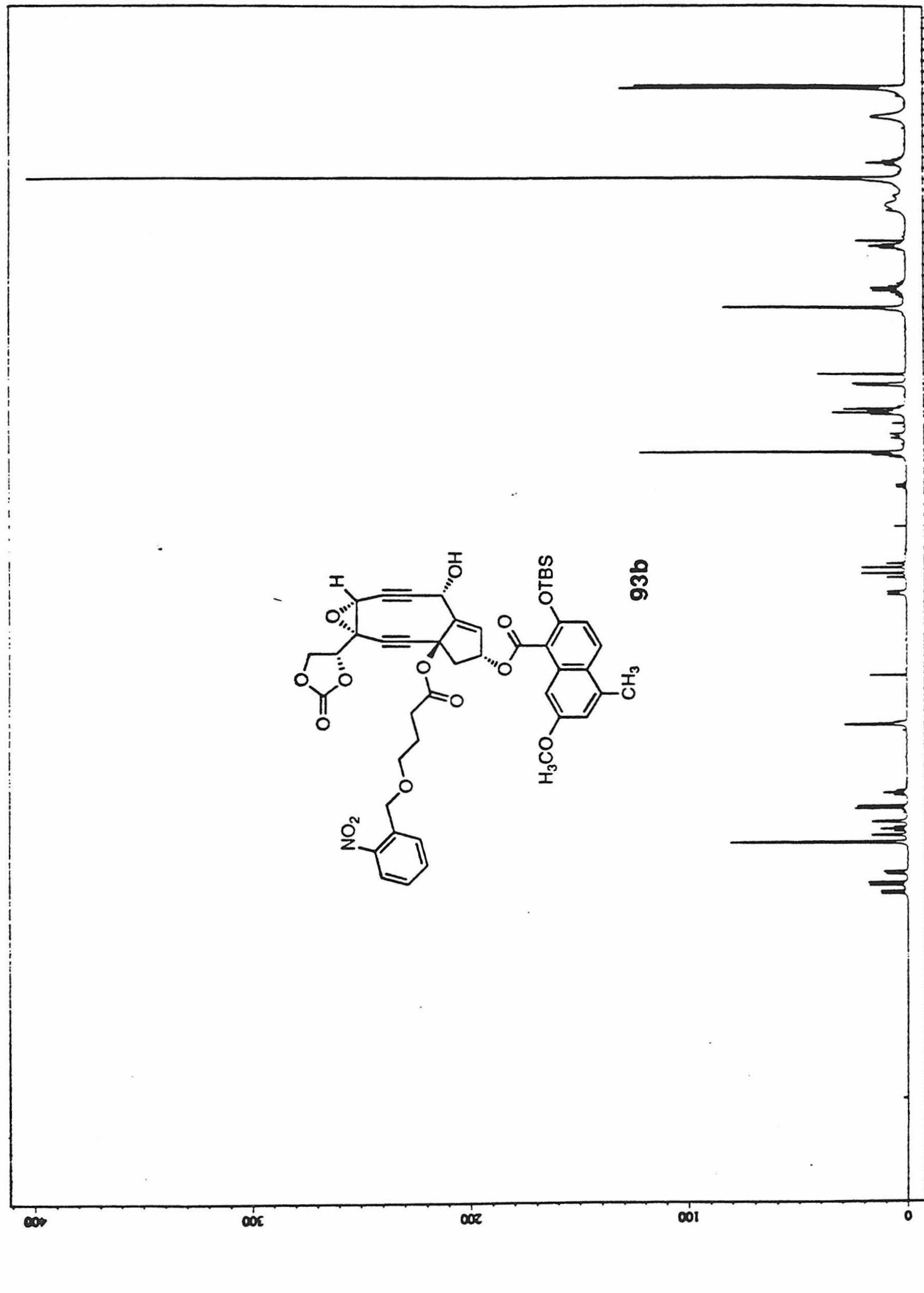

O
HO
O
O_2N

91

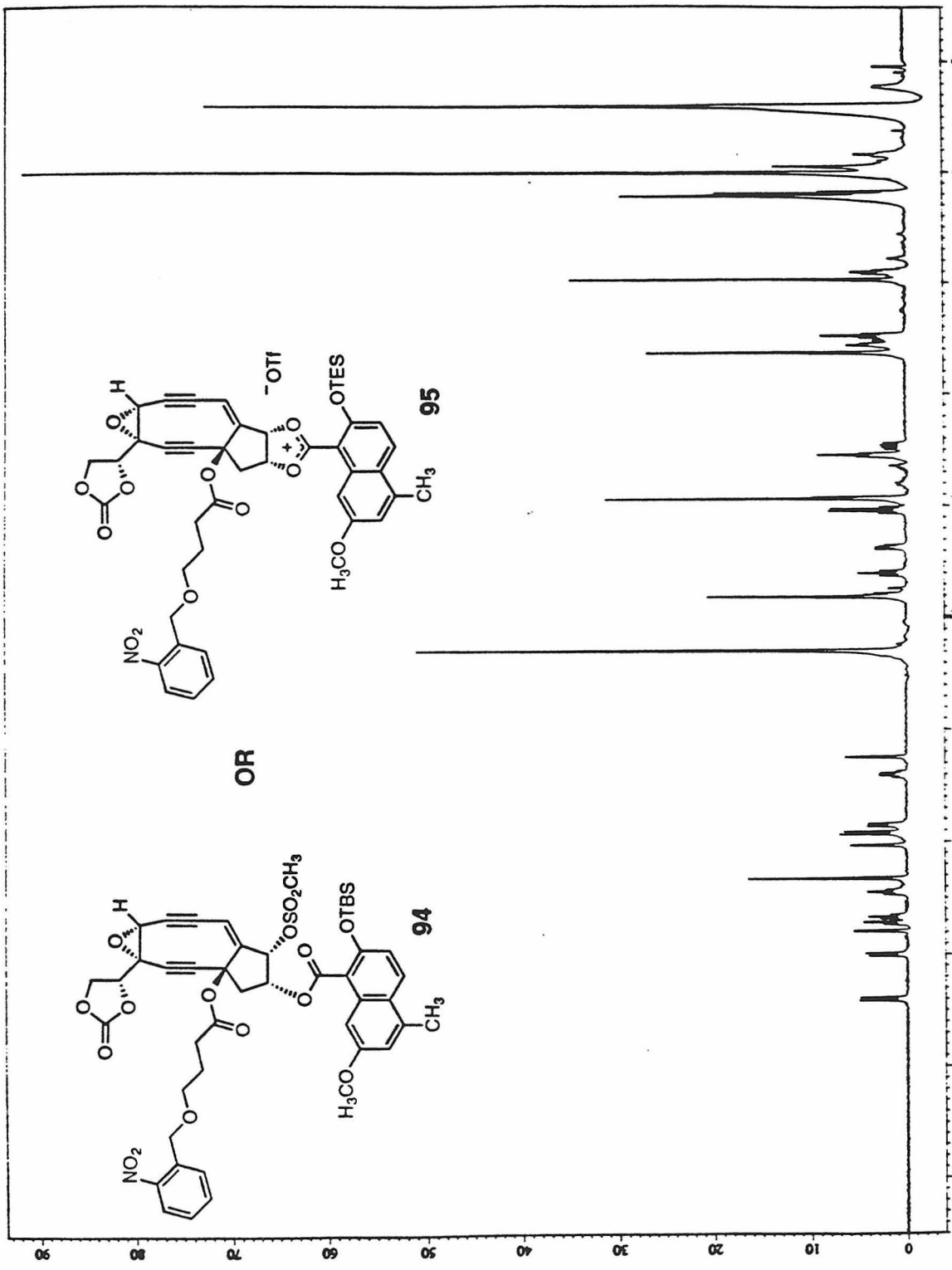
10
9
8
7
6
5
4
3
2
1
0
PPM

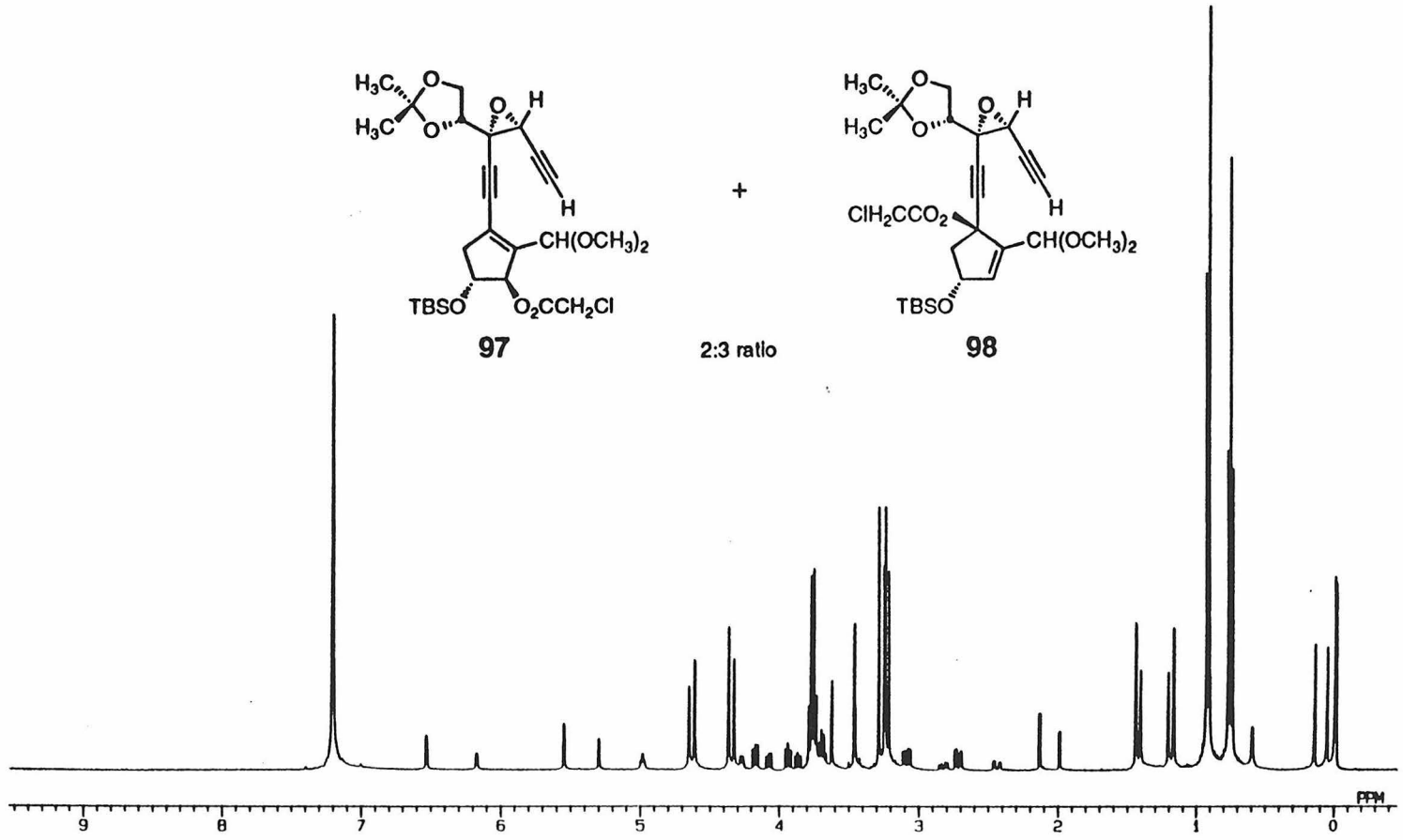

84.43
%T
60.61
4000
3500
3000
2500
2000
1500
1000
cm⁻¹
500

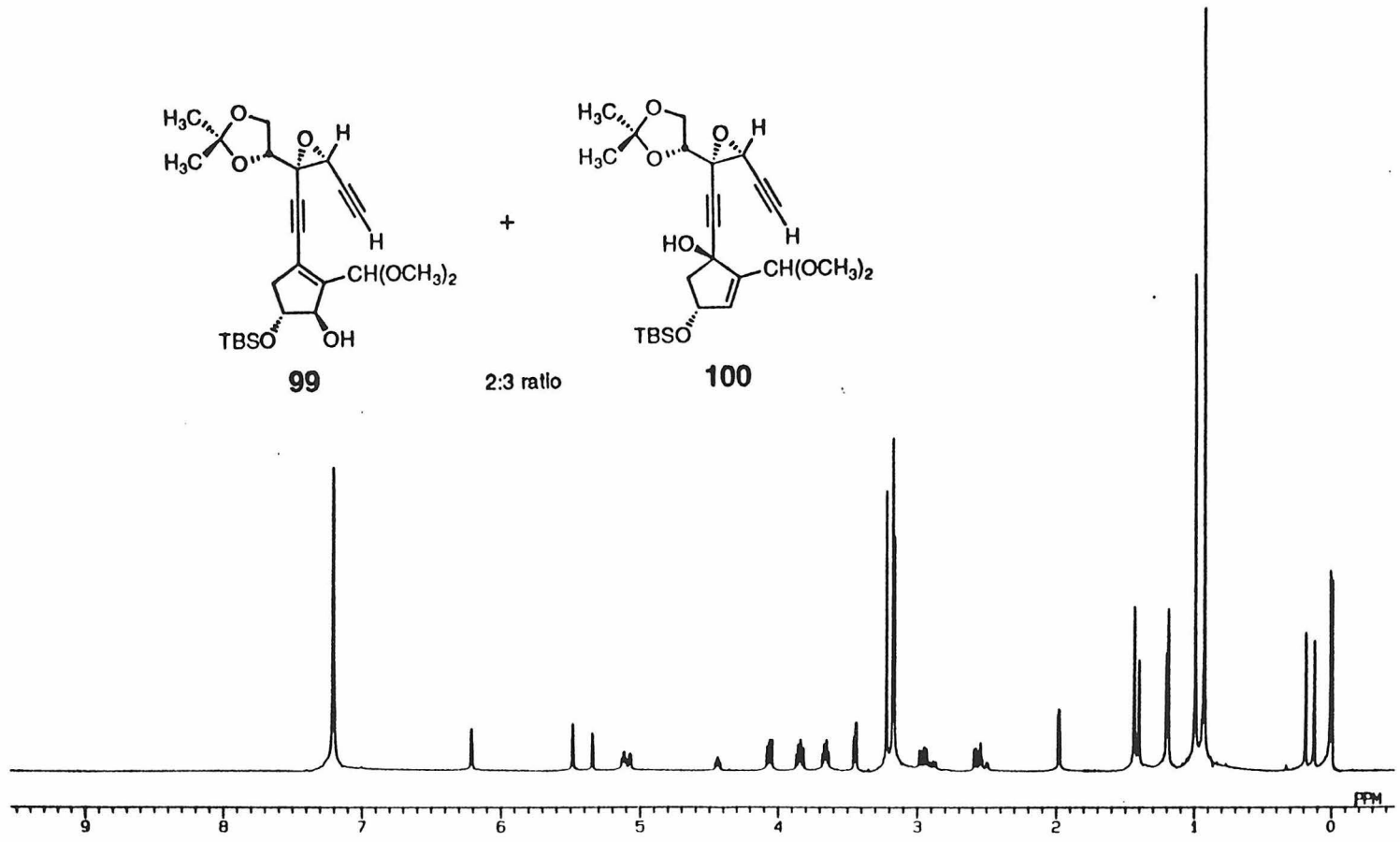

OTES
H
OTBS
92b
CH_3
H_3CO
NO_2

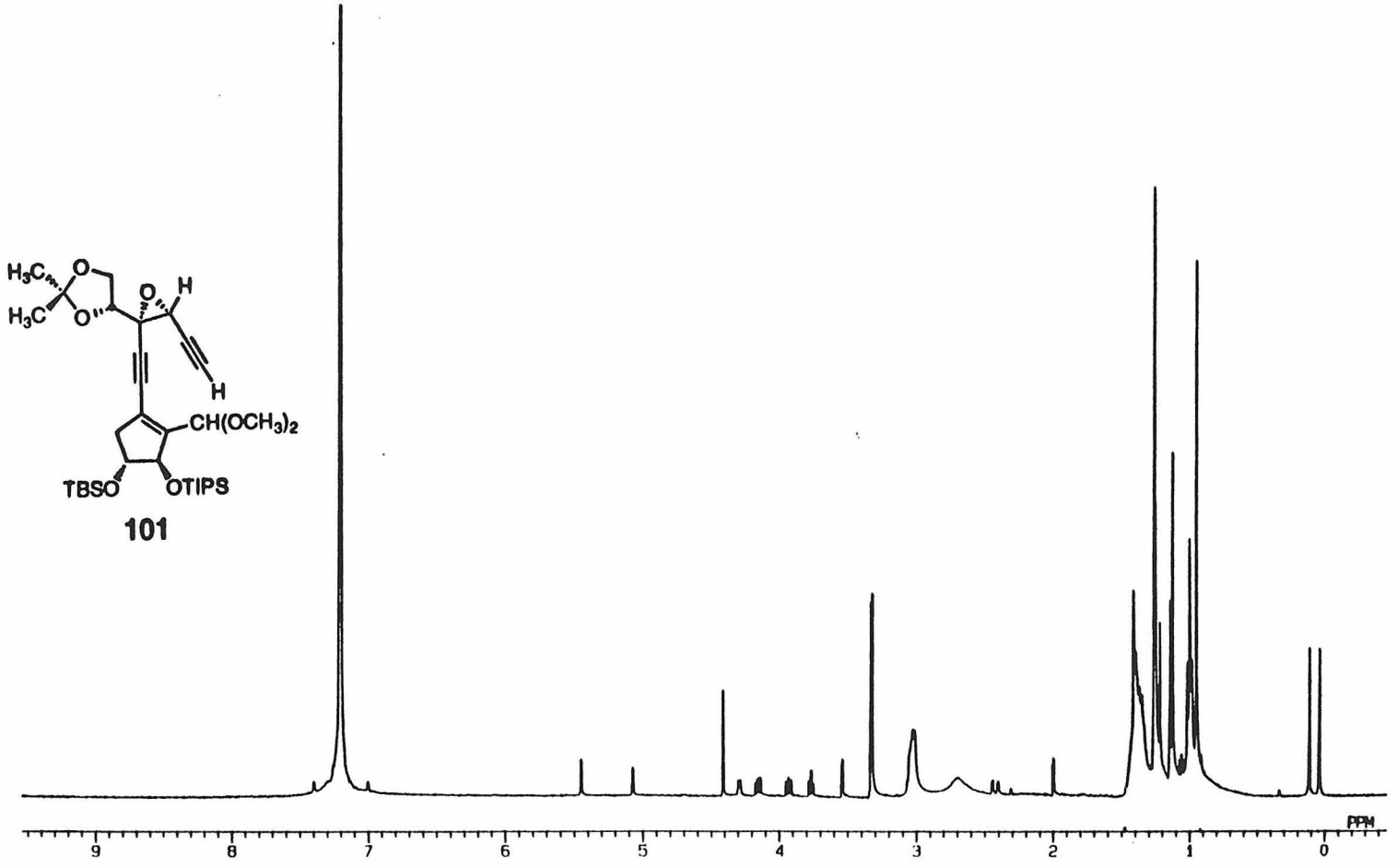


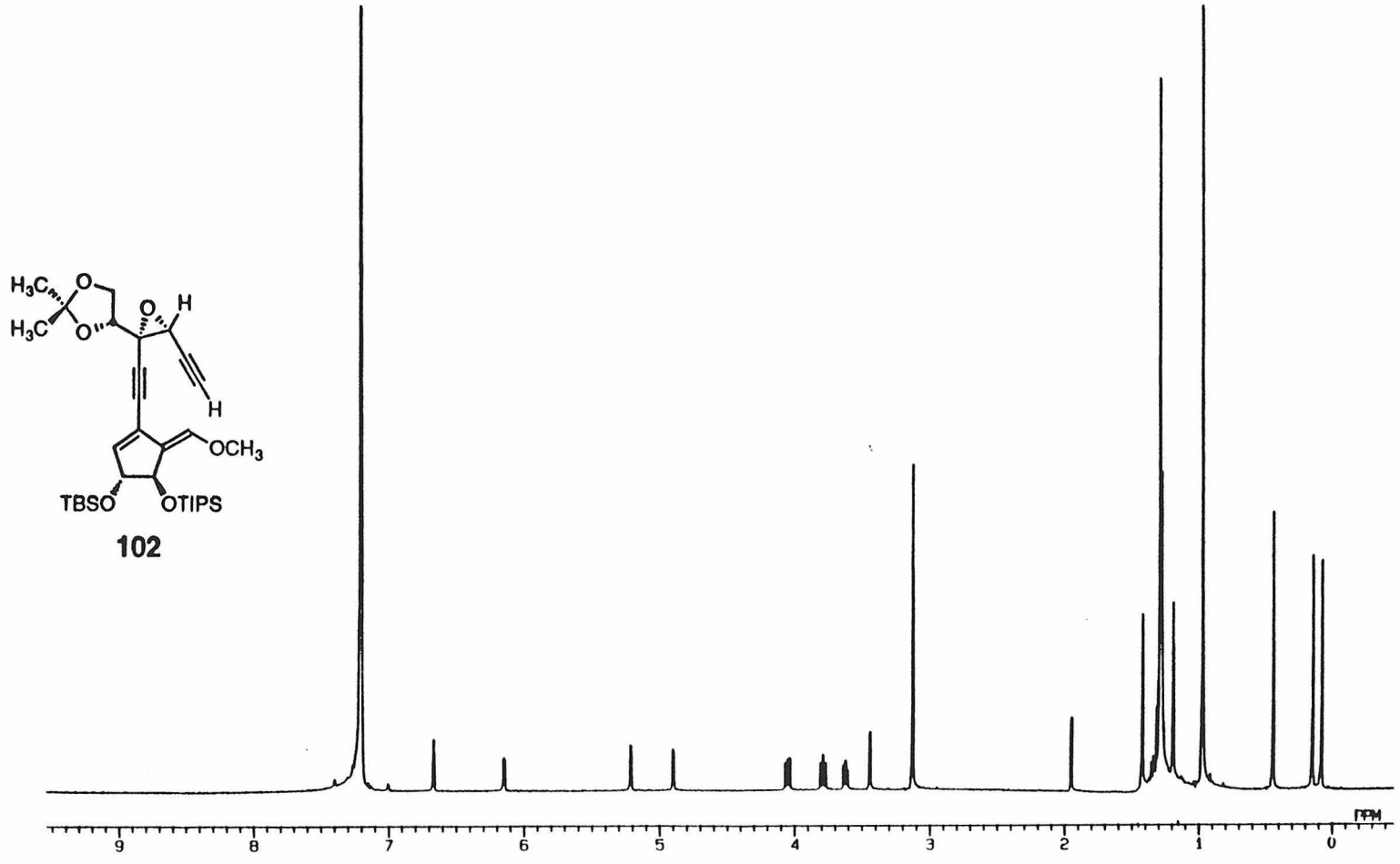
NO$_2$
OTBS
OH
H
H$_3$CO
CH$_3$
93b
0
1
2
3
4
5
6
7
8
9
10
0
100
200
300
400

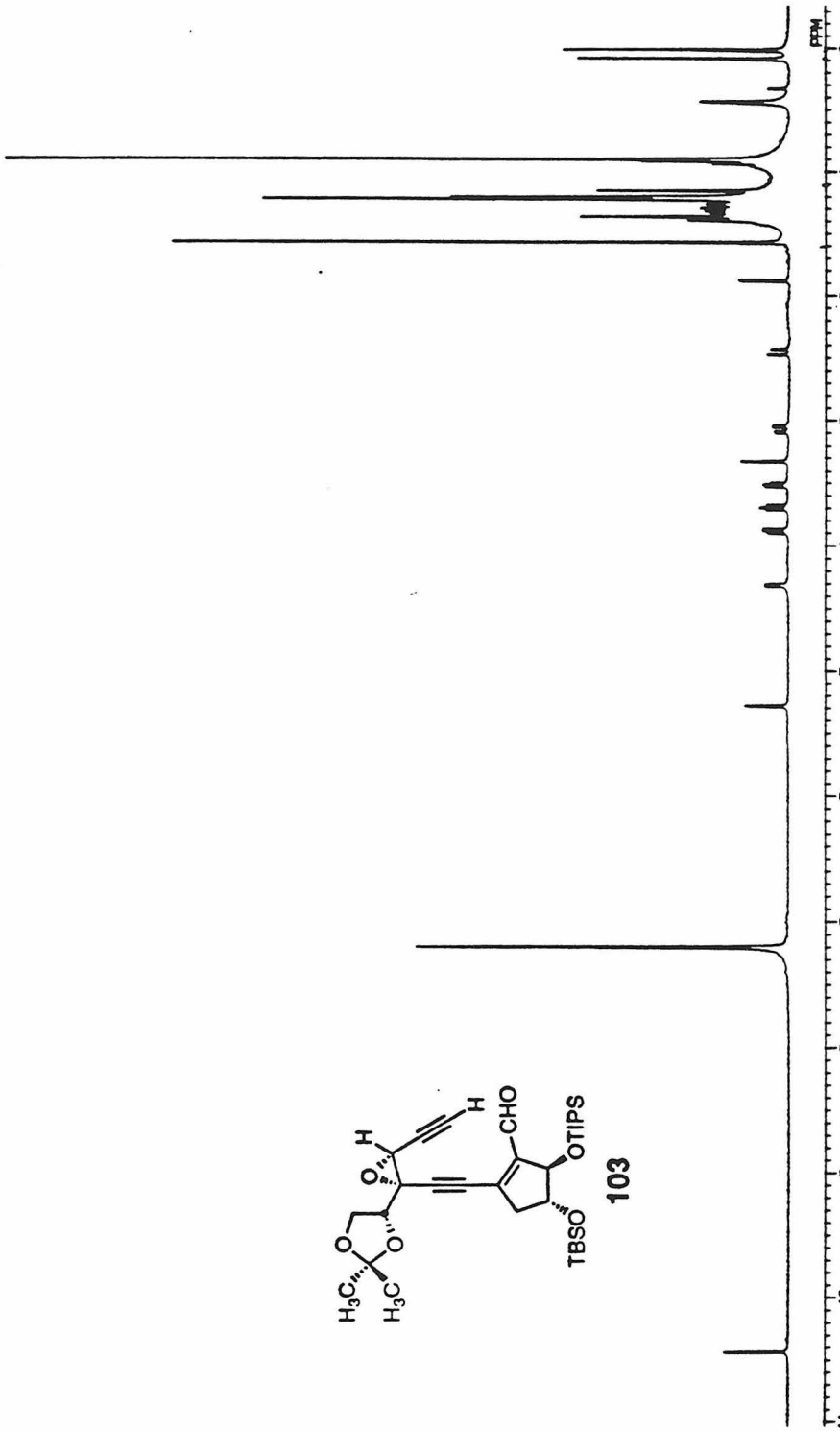

OR
94
95
OTBS
OTES
OSO2CH3
−OTf
H3CO
CH3
NO2

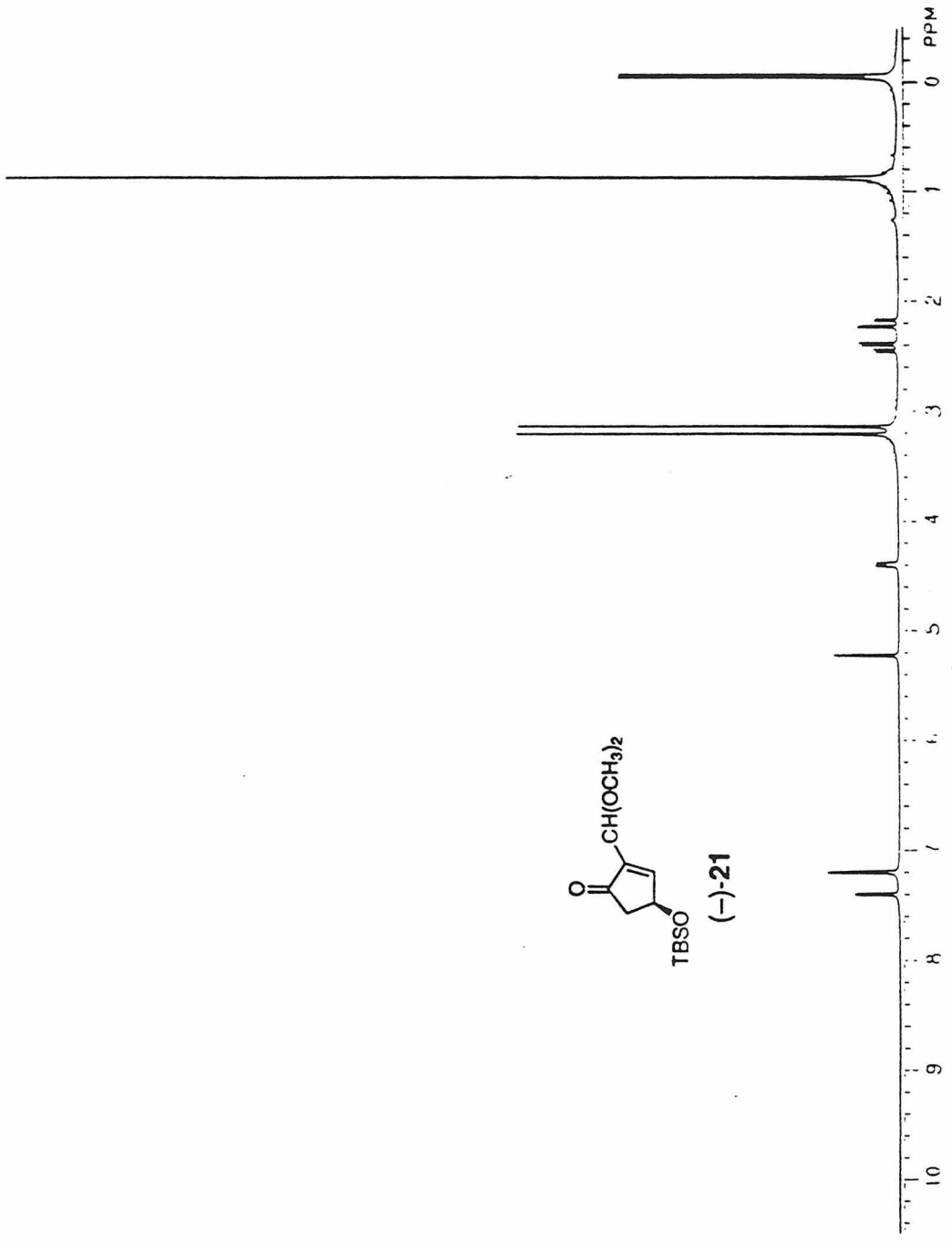

97
2:3 ratio
98
PPM

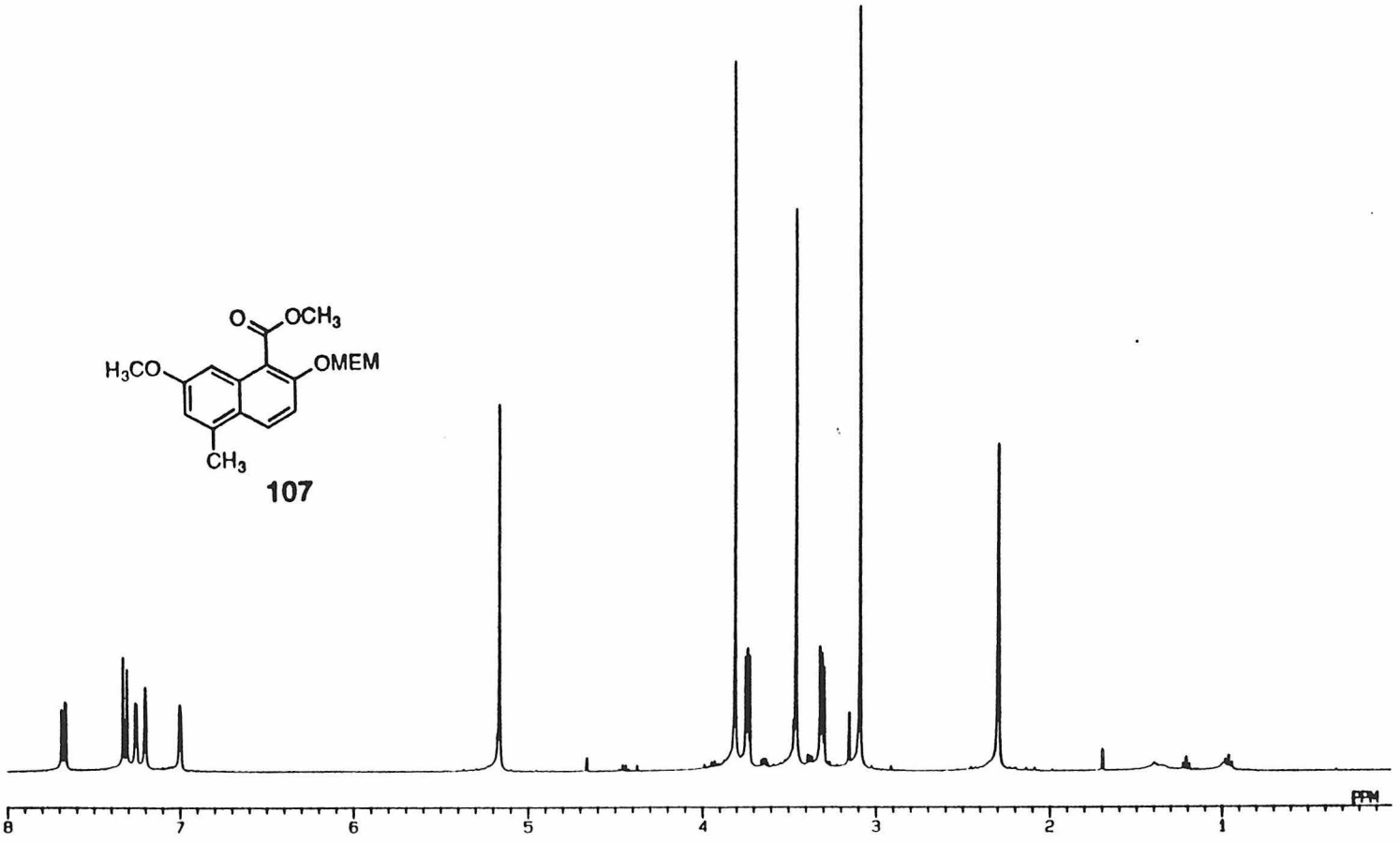

H3C
H3C
O
O
O
H
H
CH(OCH3)2
TBSO
OH
99
+
2:3 ratio
HO
100
PPM
9
8
7
6
5
4
3
2
1
0


H3C
O
H3C
O
O
H
H
CH(OCH3)2
TBSO
OTIPS
101
9
8
7
6
5
4
3
2
1
0
PPM

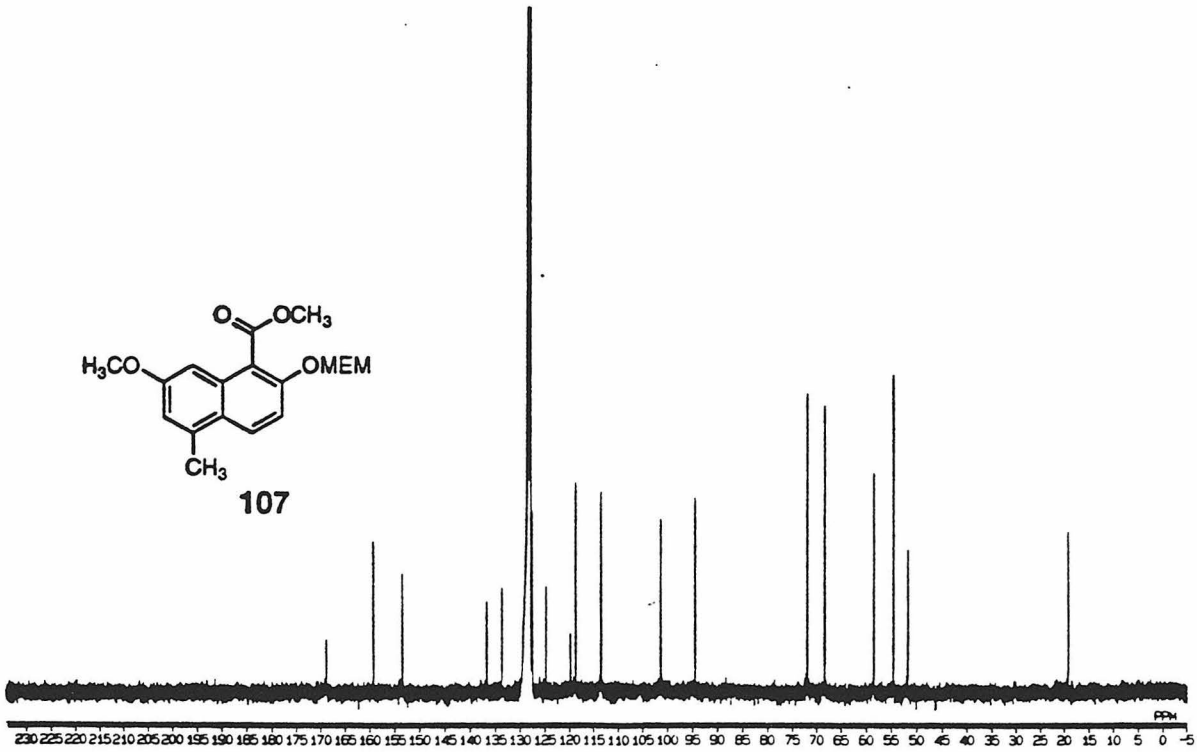

H3C
H3C
O
O
O
H
H
OCH3
TBSO
OTIPS
102
9
8
7
6
5
4
3
2
1
0
PPM


H
O
CHO
OTIPS
TBSO
H_3C
H_3C
O
O
103
PPM
0
1
2
3
4
5
6
7
8
9
10
11

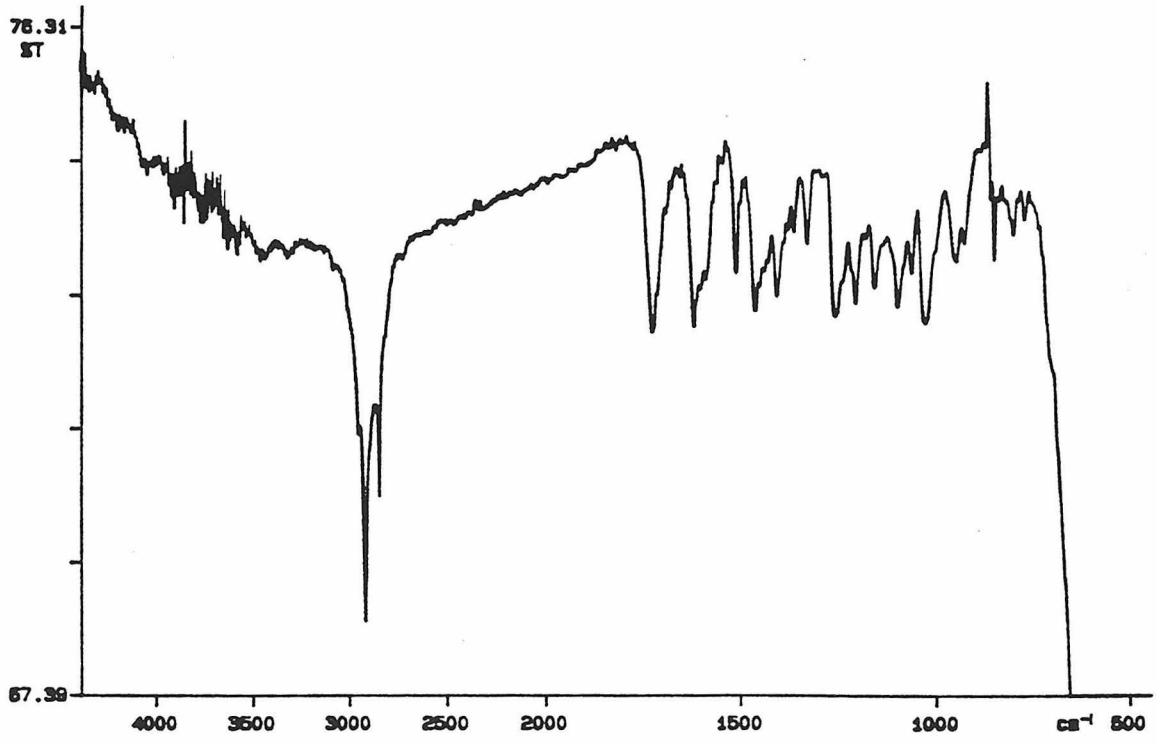

CH(OCH3)2
O
TBSO
(−)-21
PPM
0
1
2
3
4
5
6
7
8
9
10

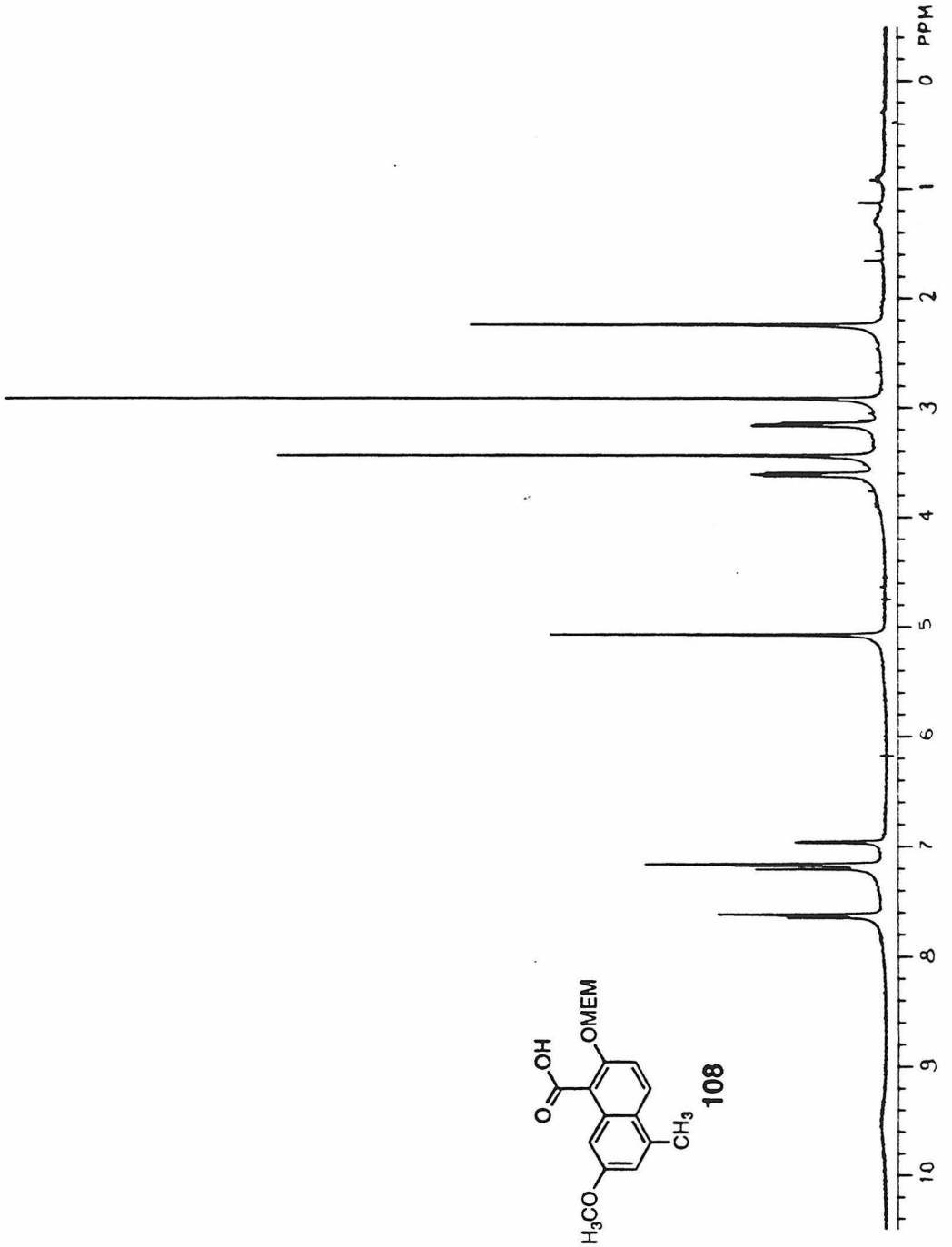


107

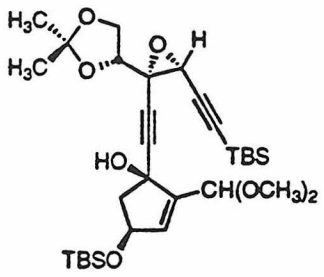

O
OCH3
H3CO
OMEM
CH3
PPM
230 225 220 215 210 205 200 195 190 185 180 175 170 165 160 155 150 145 140 135 130 125 120 115 110 105 100 95 90 85 80 75 70 65 60 55 50 45 40 35 30 25 20 15 10 5 0 -5

107


76.31
%T
57.39
4000
3500
3000
2500
2000
1500
1000
cm-1
500

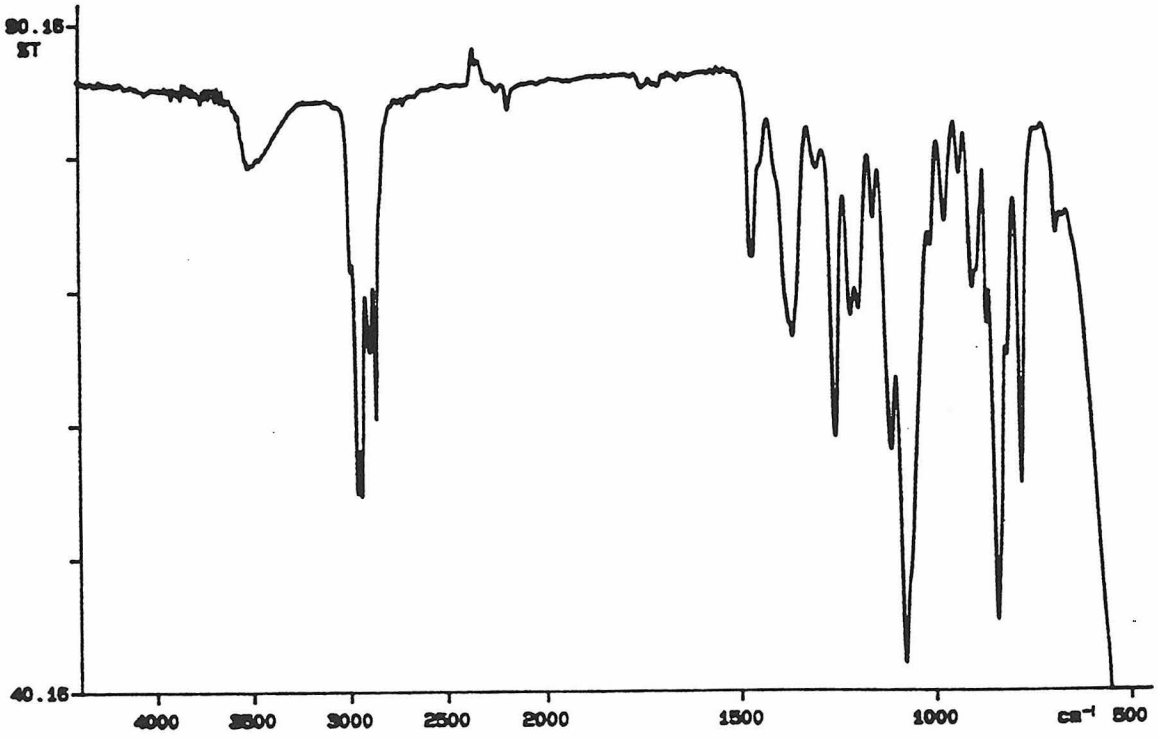


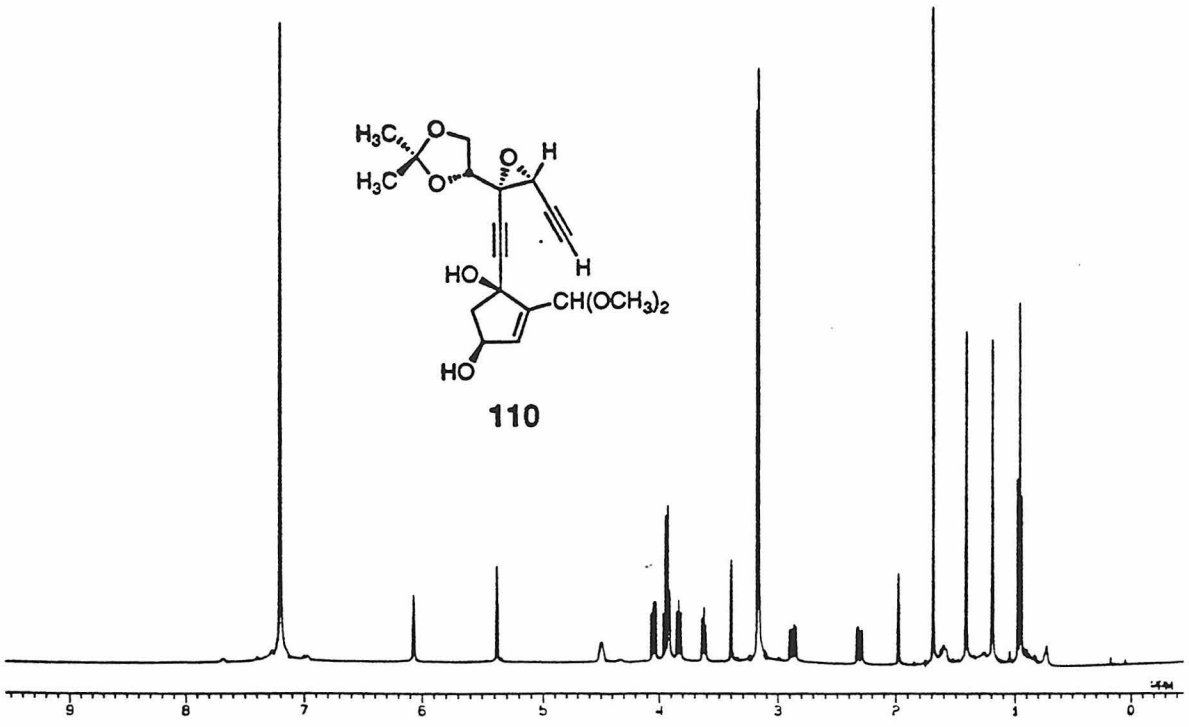
108


H3C
O
H3C
O
O
H
TBS
HO
CH(OCH3)2
TBSO

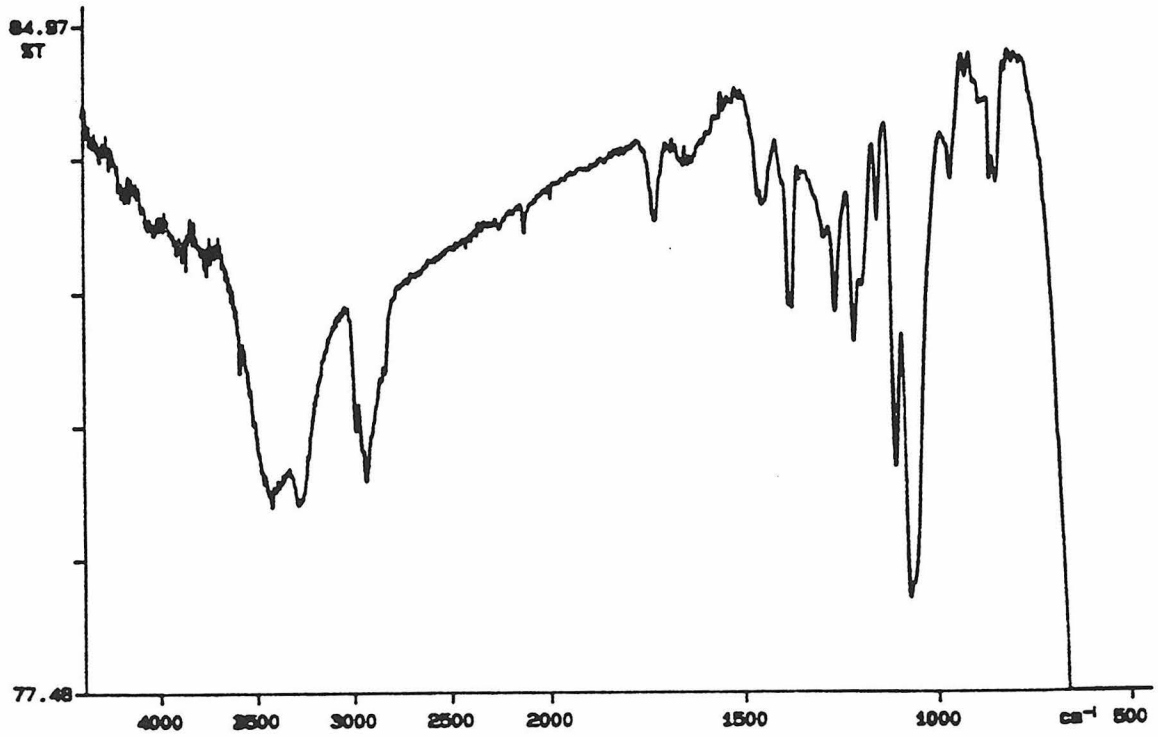
109

9
8
7
6
5
4
3
2
1
0
PPM


90.16
%T
40.16
4000
3500
3000
2500
2000
1500
1000
cm-1
500


H3C
O
O
O
H
H3C
HO
H
CH(OCH3)2
HO
9
8
7
6
5
4
3
2
1
0

110


84.87
%T
77.48
4000
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3000
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1000
cm-1
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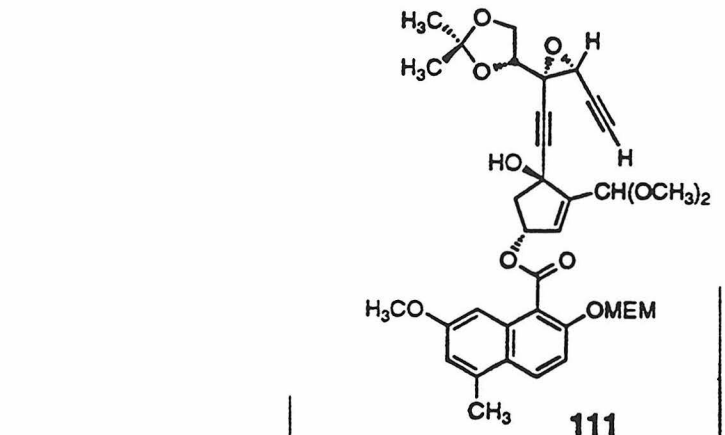
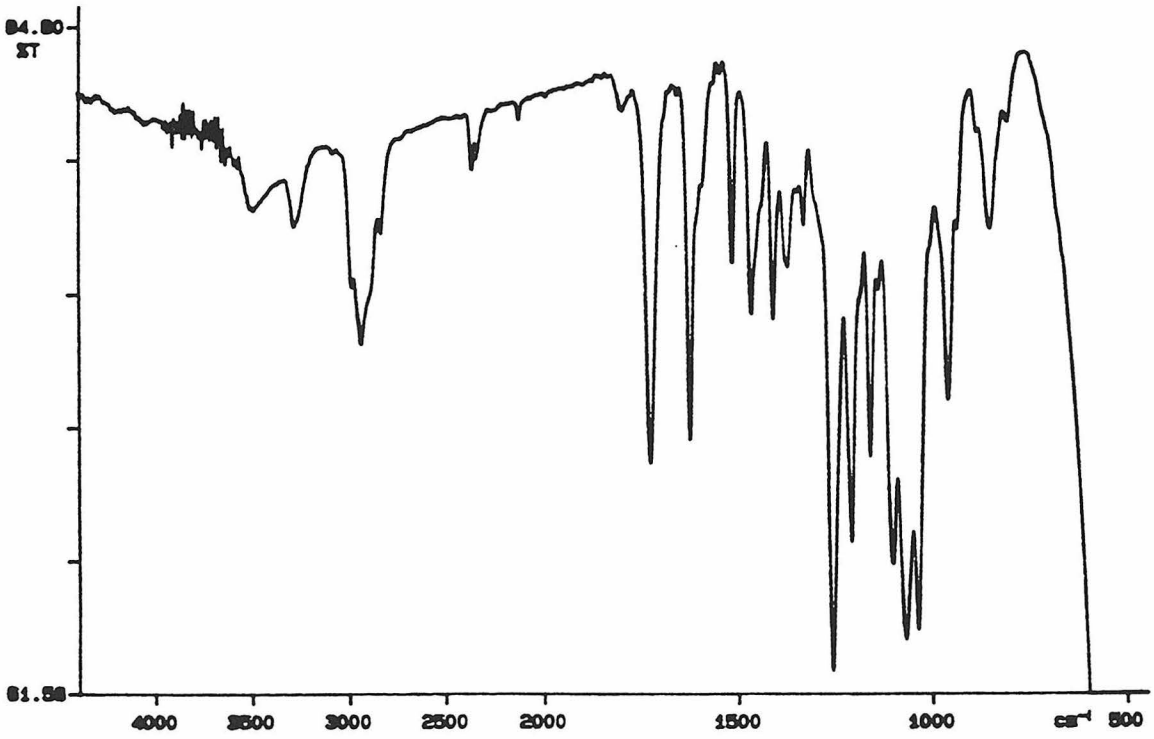

H3C
H3C
O
O
O
H
HO
H
CH(OCH3)2
O
O
H3CO
OMEM
CH3

111

PPM
9
8
7
6
5
4
3
2
1
0


84.80
%T
61.58
4000
3500
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2000
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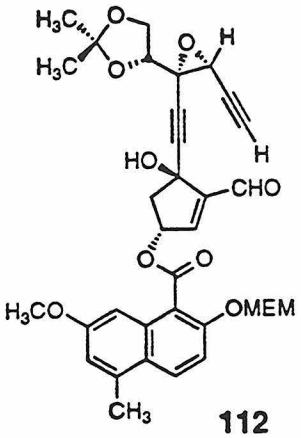
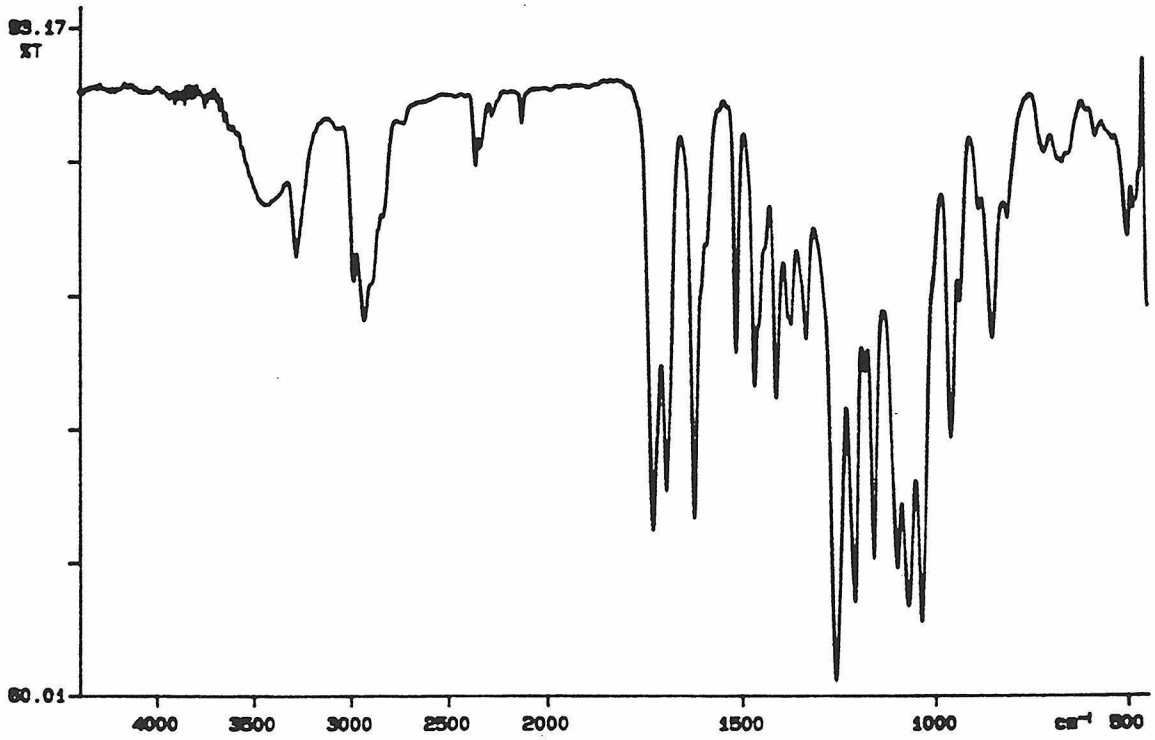
1000
cm-1
500


H3C
H3C
O
O
O
H
HO
H
CHO
O
O
H3CO
OMEM
CH3

112

9
8
7
6
5
4
3
2
1
0
PPM


93.17
%T
60.01
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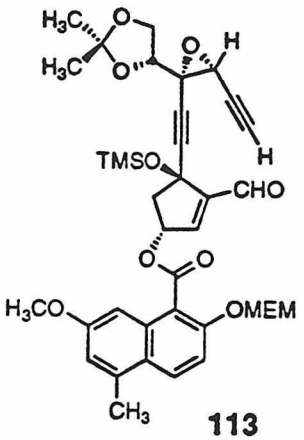
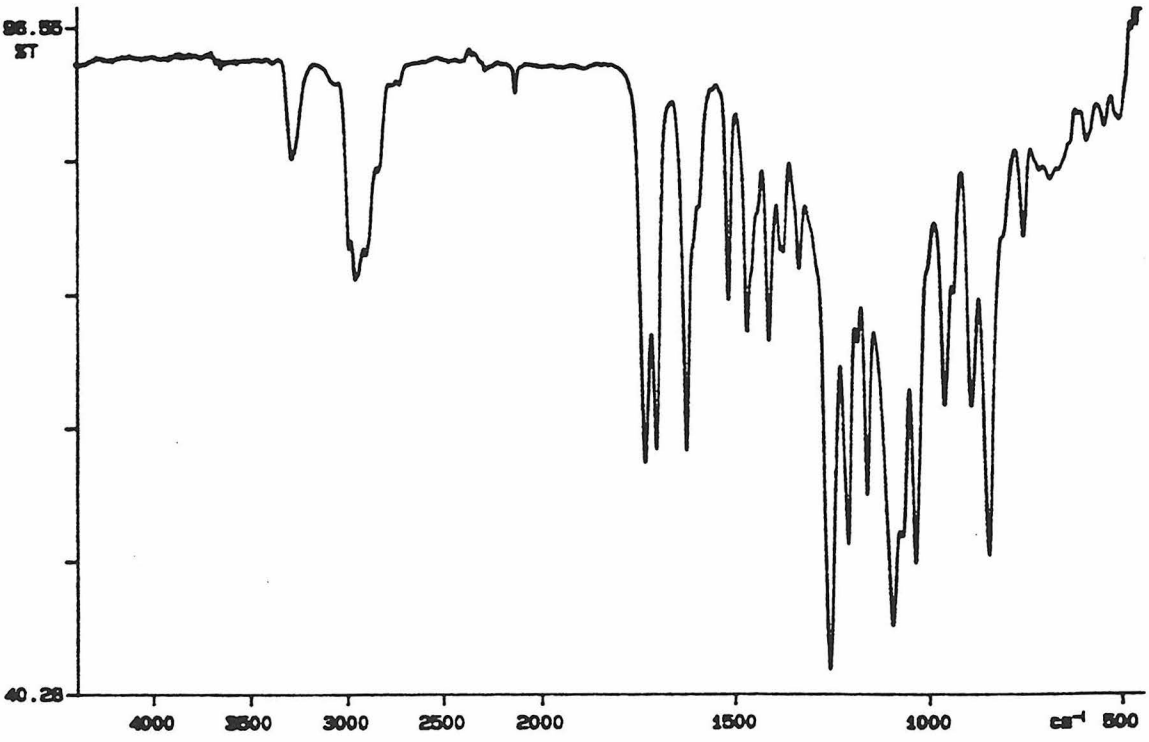
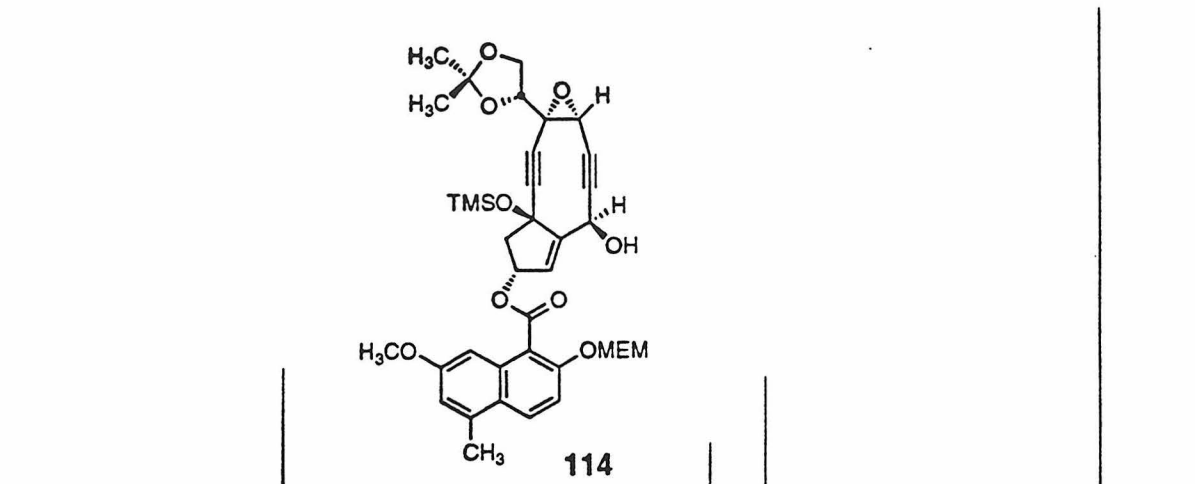
3500
3000
2500
2000
1500
1000
cm-1
500


H3C
H3C
O
O
O
H
TMSO
H
CHO
O
O
H3CO
OMEM
CH3

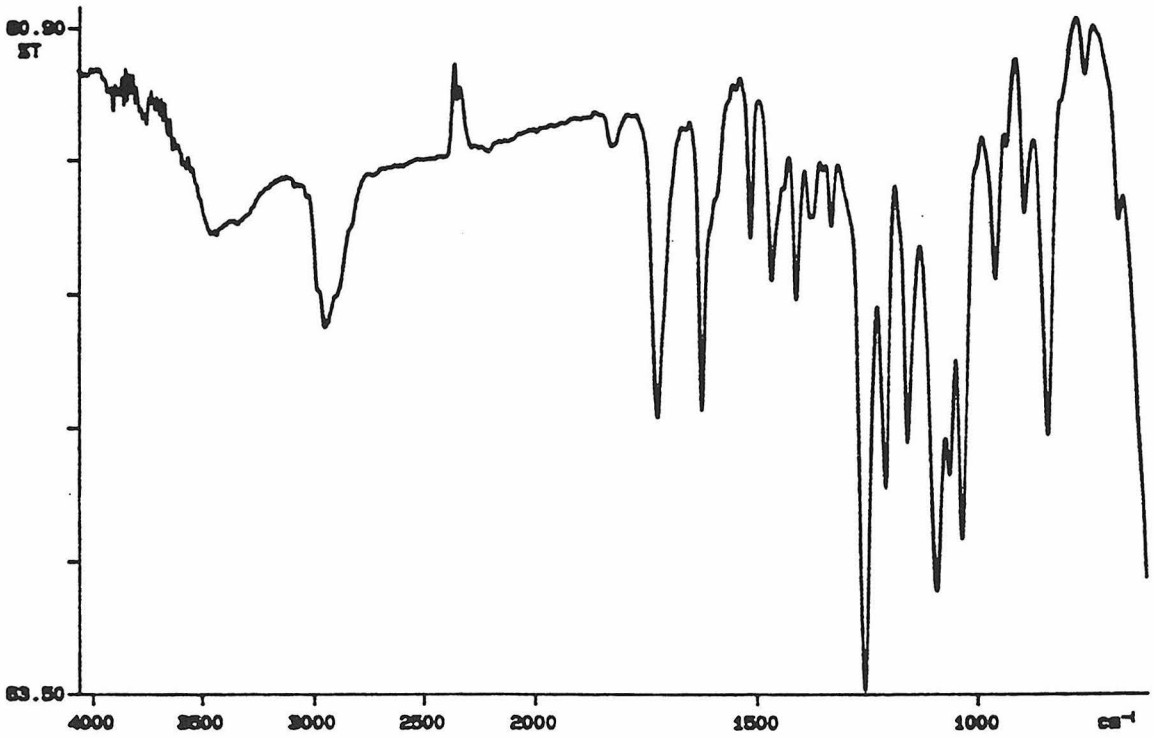
113

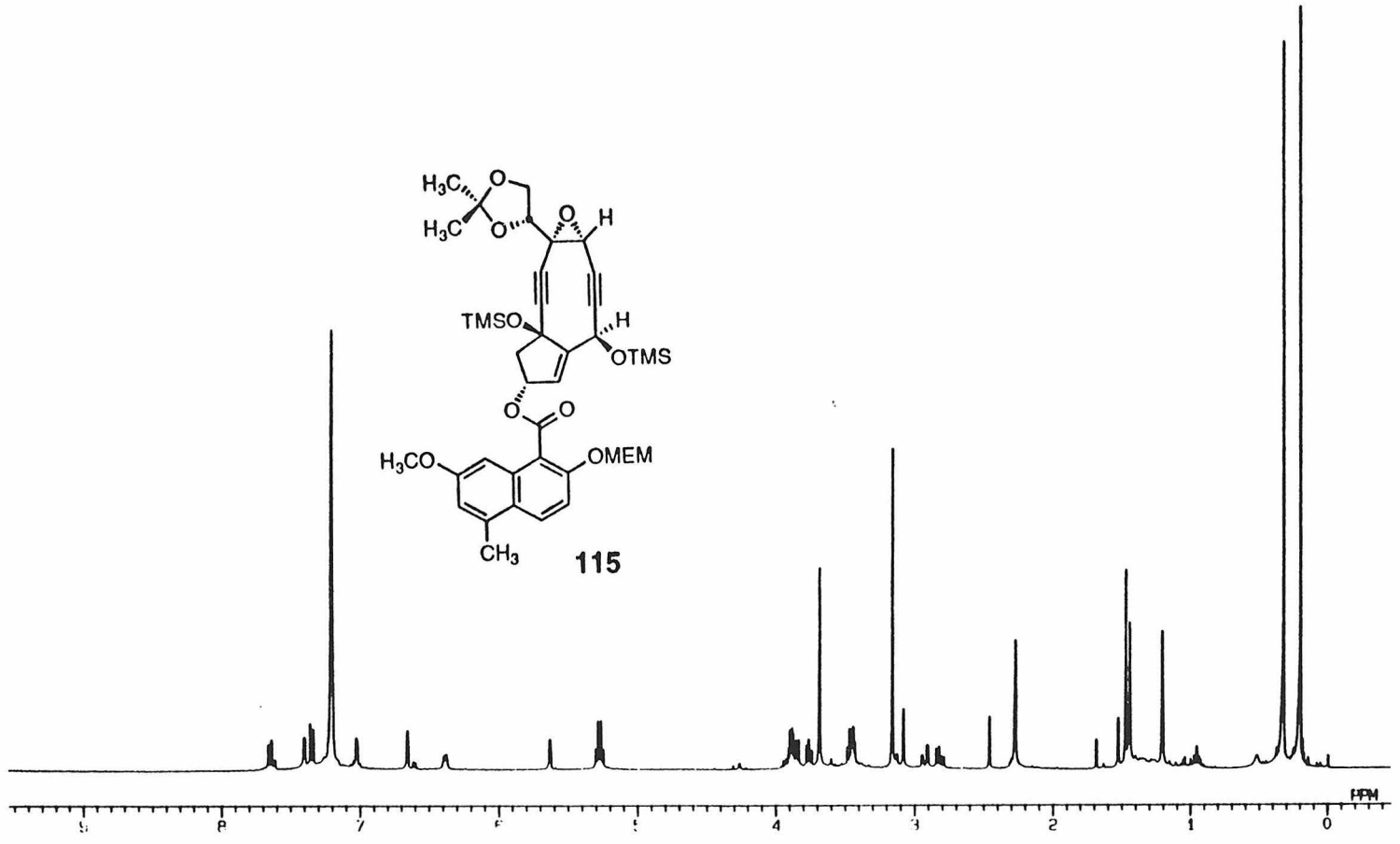
9
8
7
6
5
4
3
2
1
0
PPM

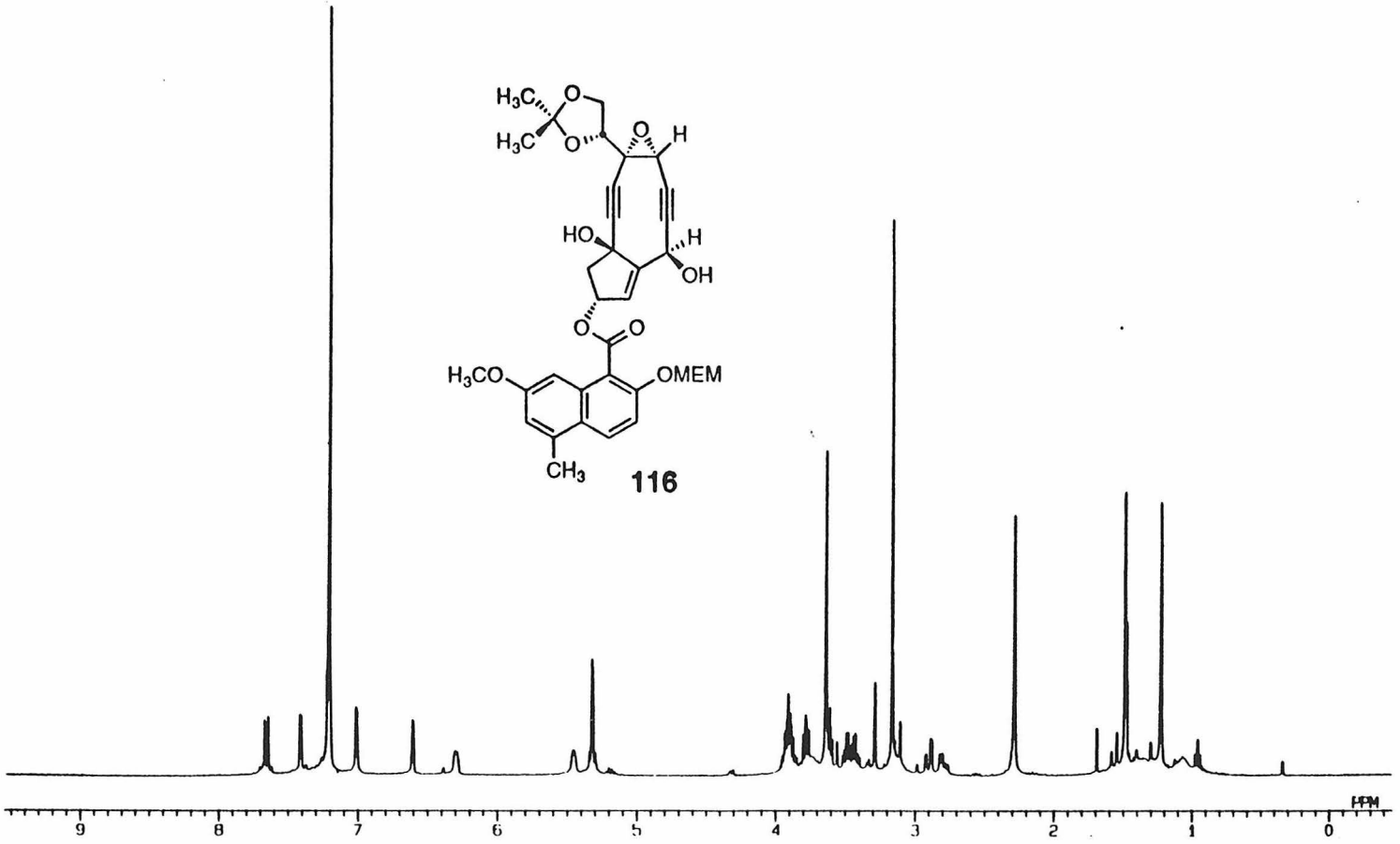

96.55
%T
40.28
4000
3500
3000
2500
2000
1500
1000
cm-1
500

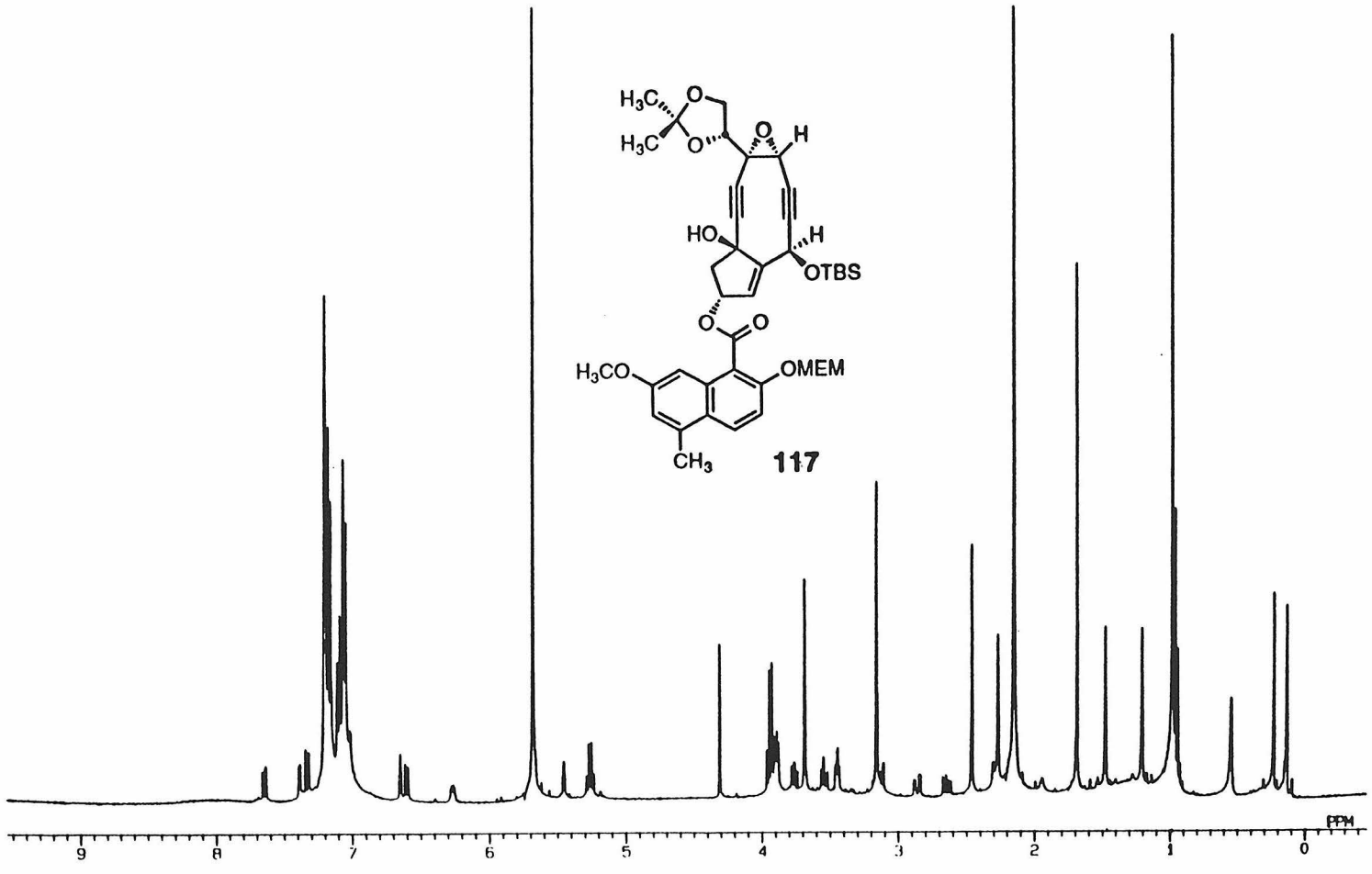

H3C
O
H3C
O
O
H
TMSO
H
OH
O
O
H3CO
OMEM
CH3
9
8
7
6
5
4
3
2
1
0
PPM

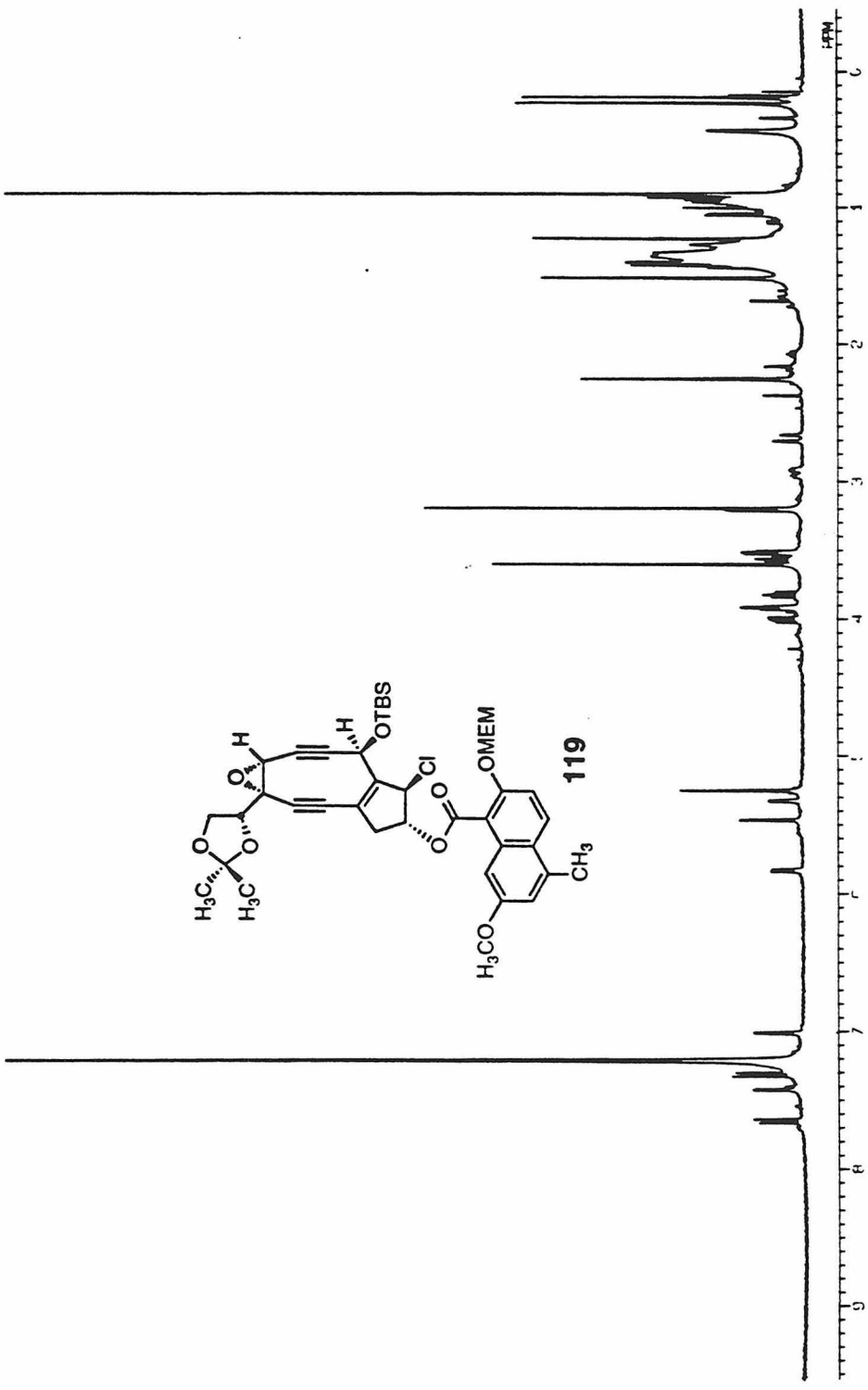
114

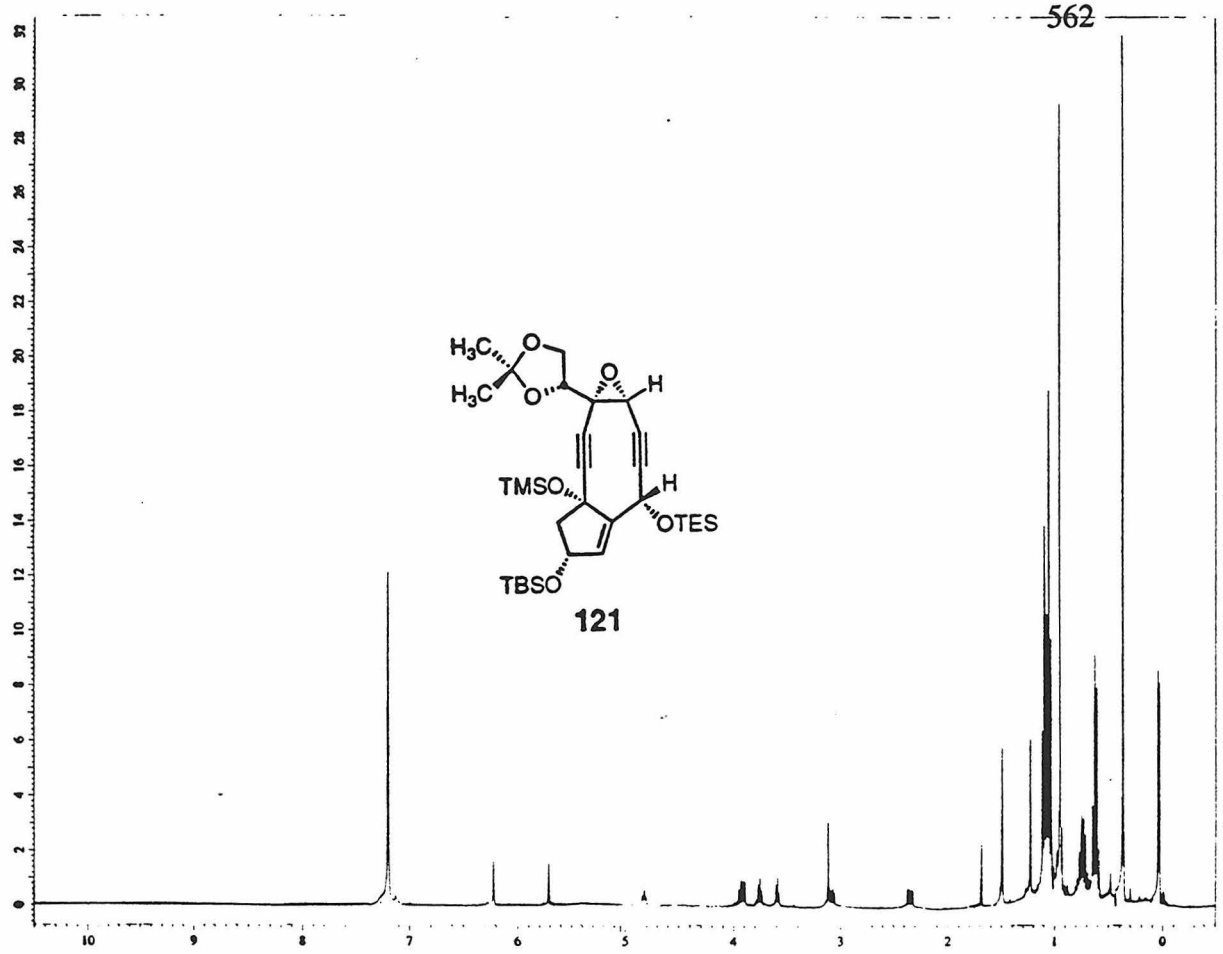

80.90
%T
63.50
4000
3500
3000
2500
2000
1500
1000
cm-1


H3C
O
H3C
O
O
H
TMSO
H
OTMS
O
O
H3CO
OMEM
CH3
115
PPM
1
0

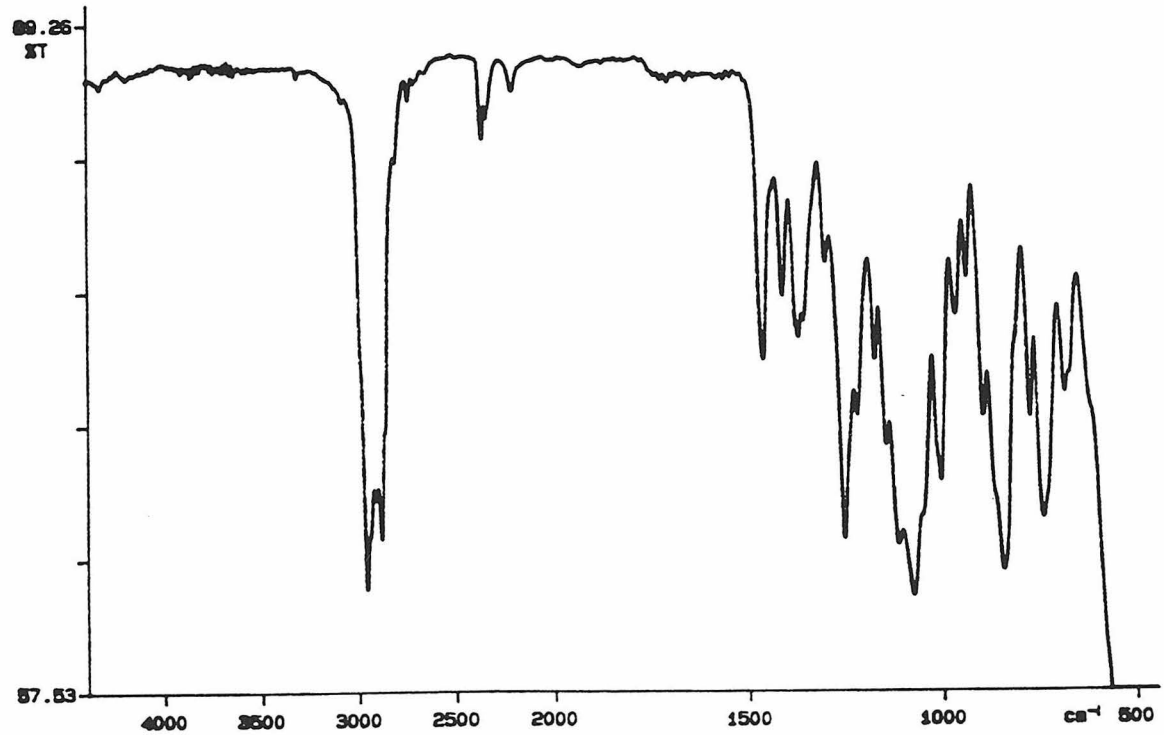

H3C
H3C
O
O
O
H
HO
H
OH
O
O
H3CO
OMEM
CH3
116
9
8
7
6
5
4
3
2
1
0
PPM

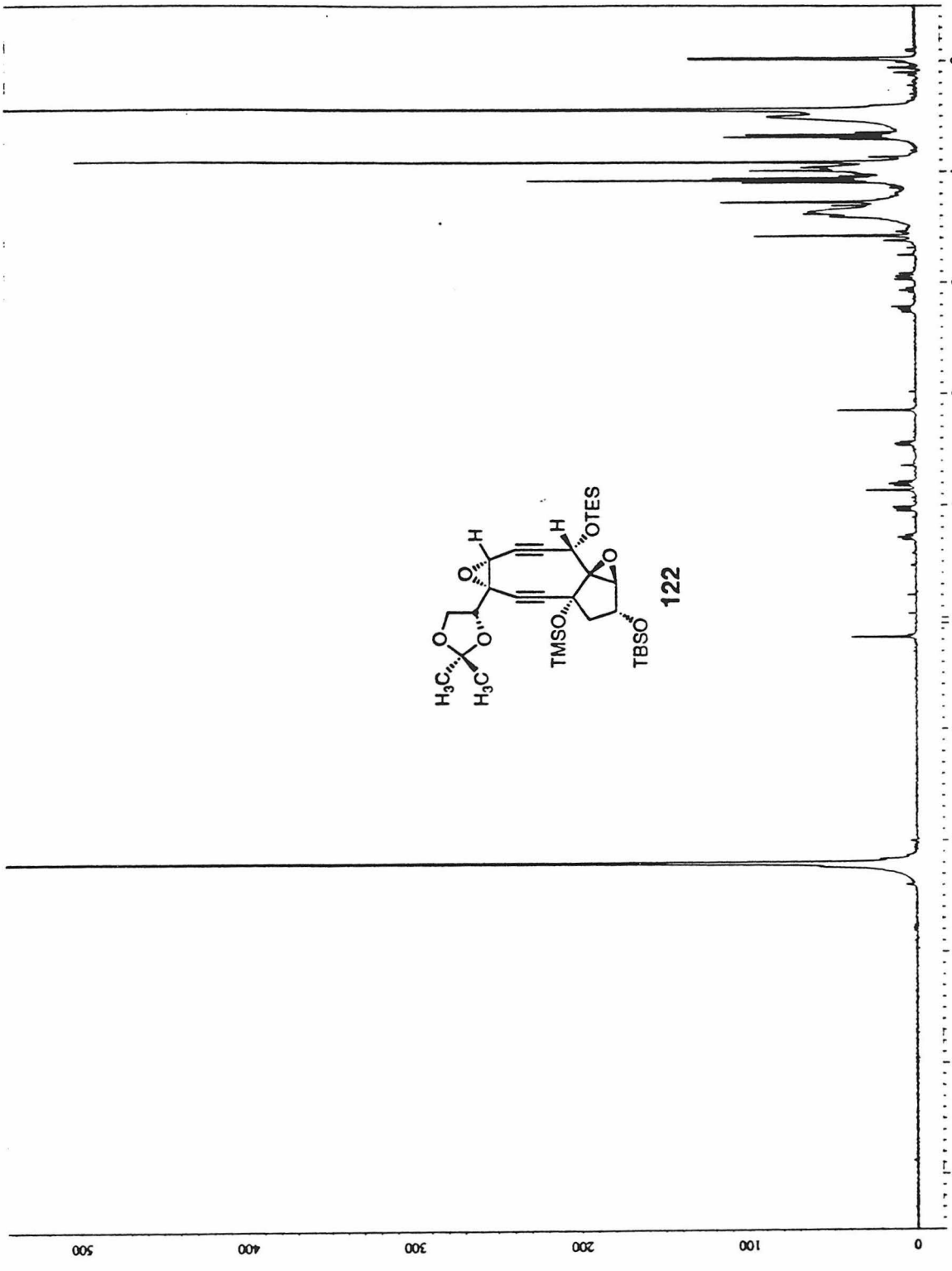

H3C
O
H3C
O
O
H
HO
H
OTBS
O
O
H3CO
OMEM
CH3
117
PPM
9
8
7
6
5
4
3
2
1
0

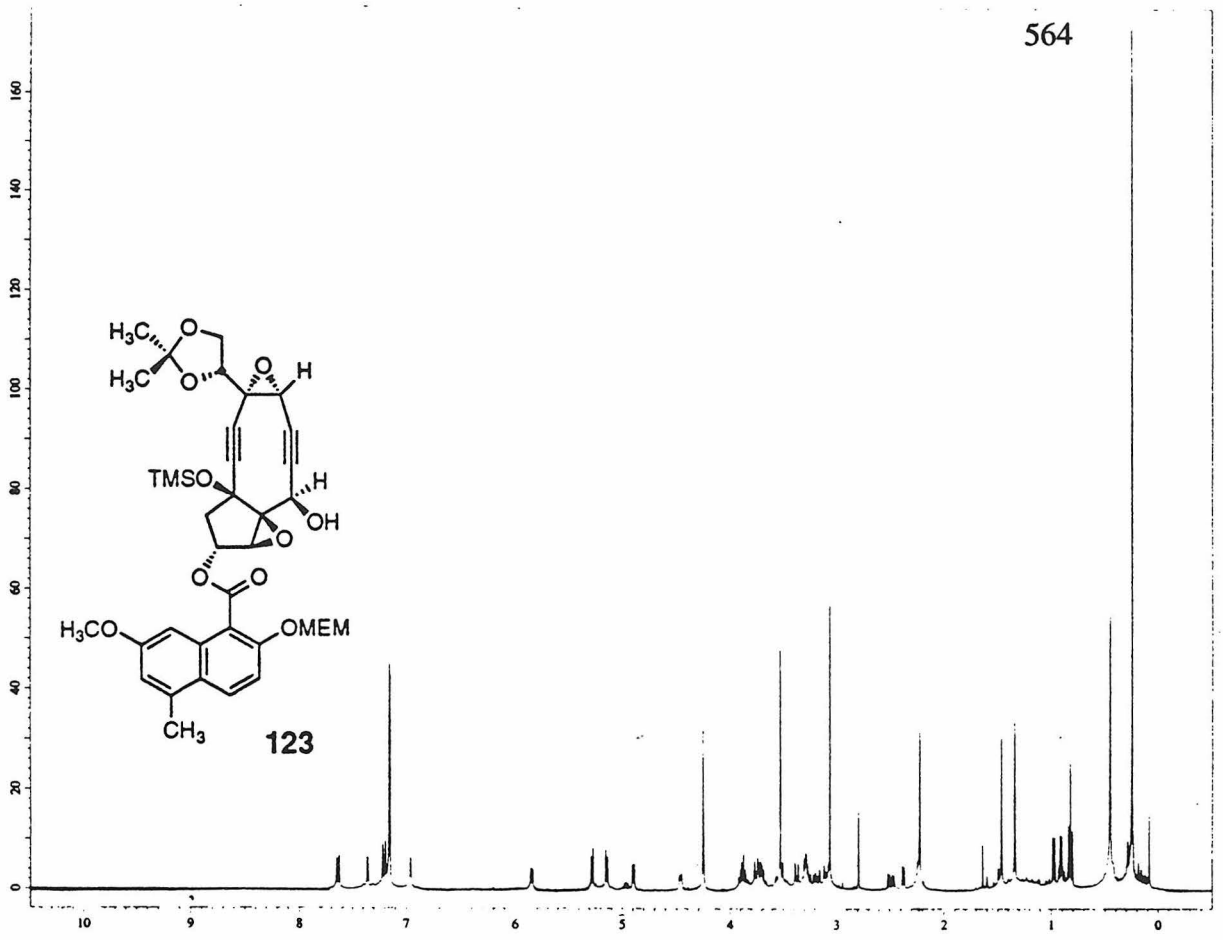

OTBS
Cl
OMEM
CH_3
H_3CO
H_3C
H_3C
119
PPM

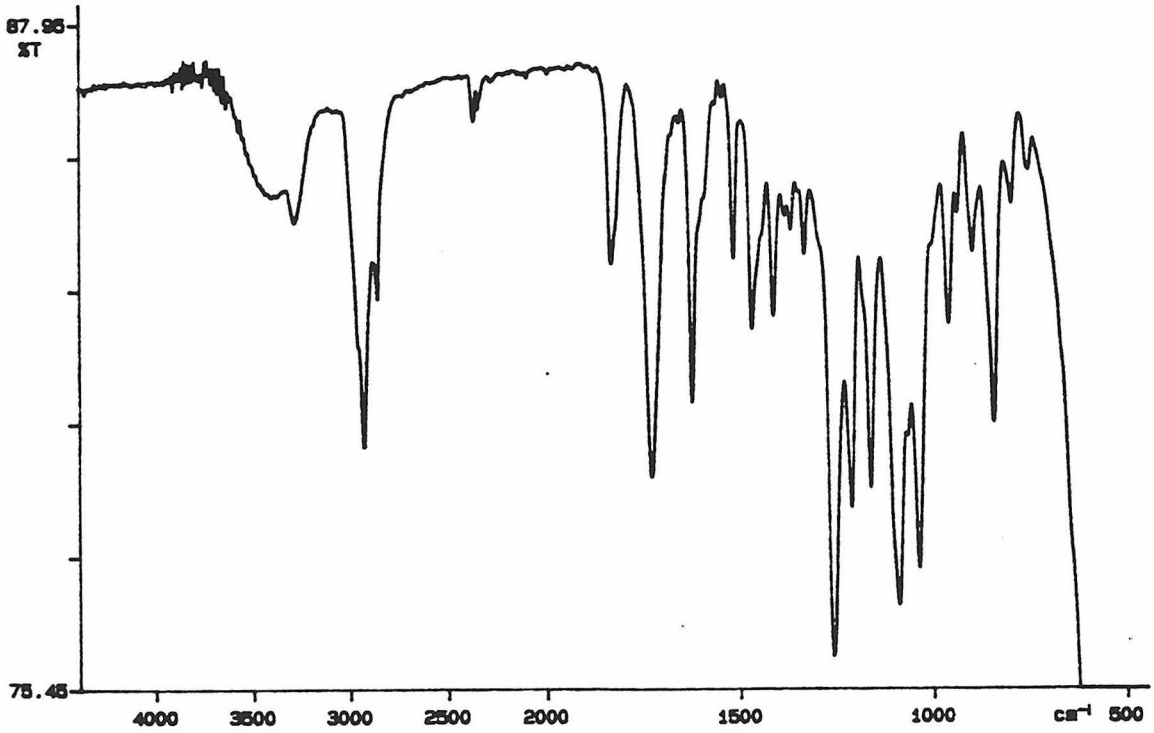

H3C
O
H3C
O
O
H
TMSO
H
OTES
TBSO

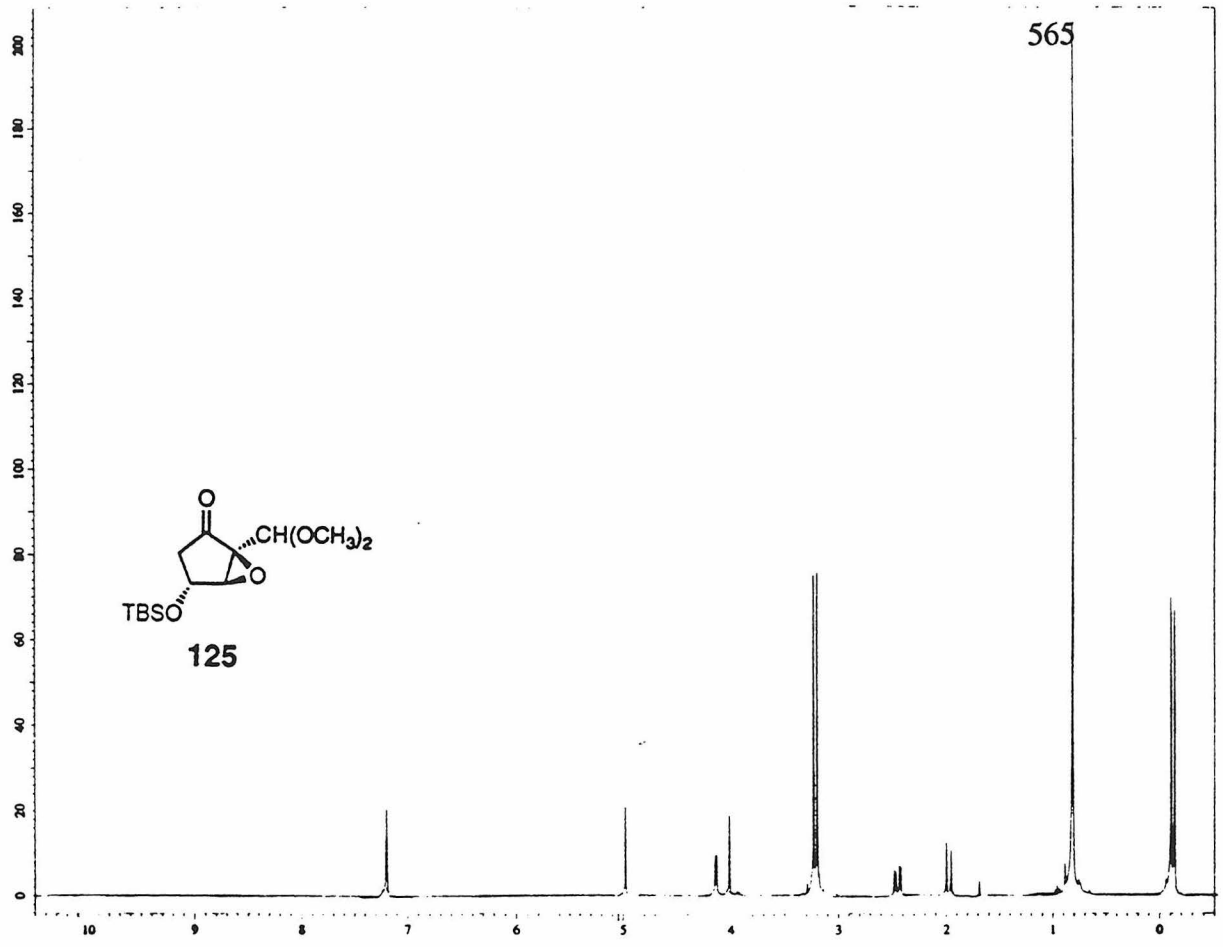
121

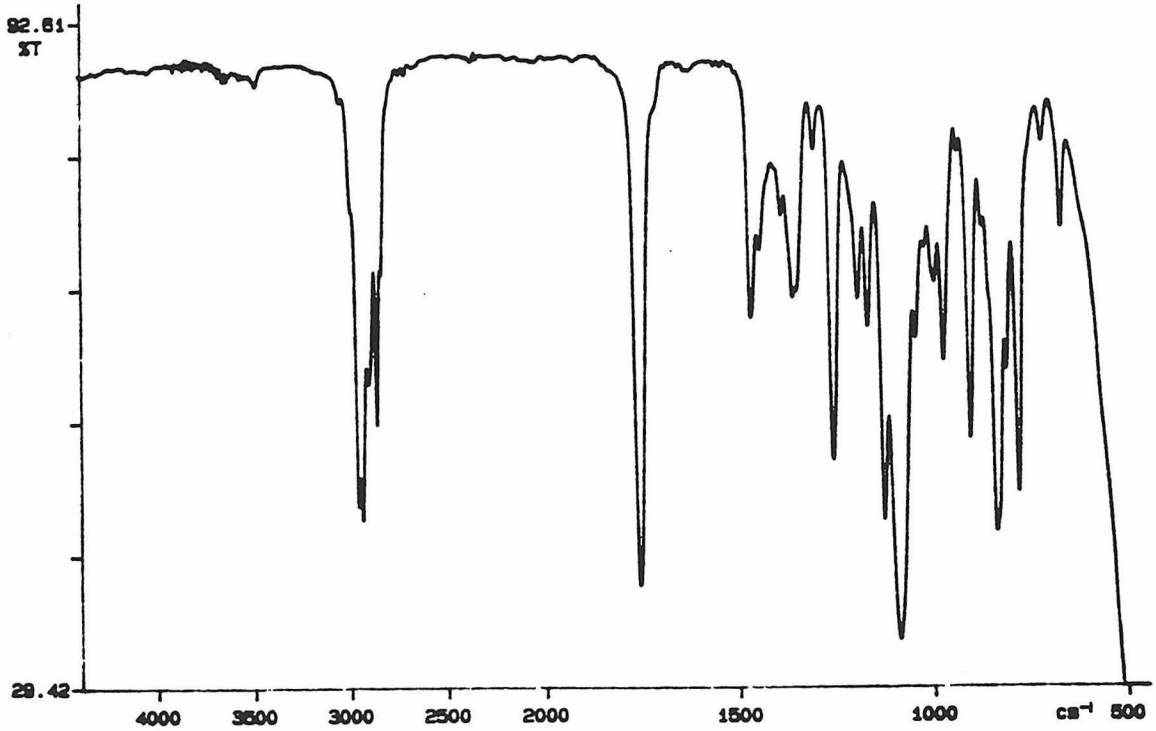

89.26
%T
57.53
4000
3500
3000
2500
2000
1500
1000
cm-1
500

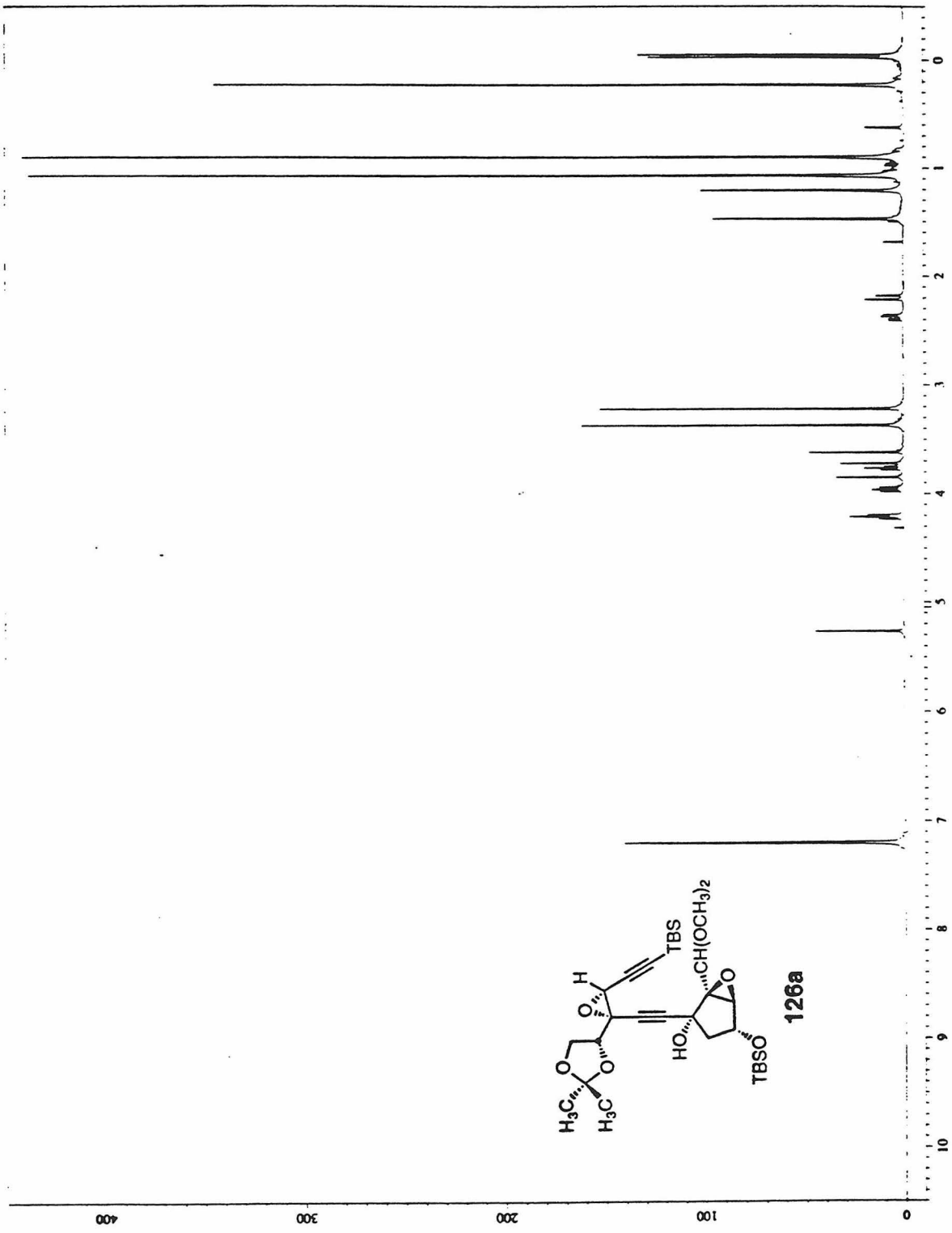

H
O
O
O
H3C
H3C
H
OTES
O
TMSO
TBSO
122

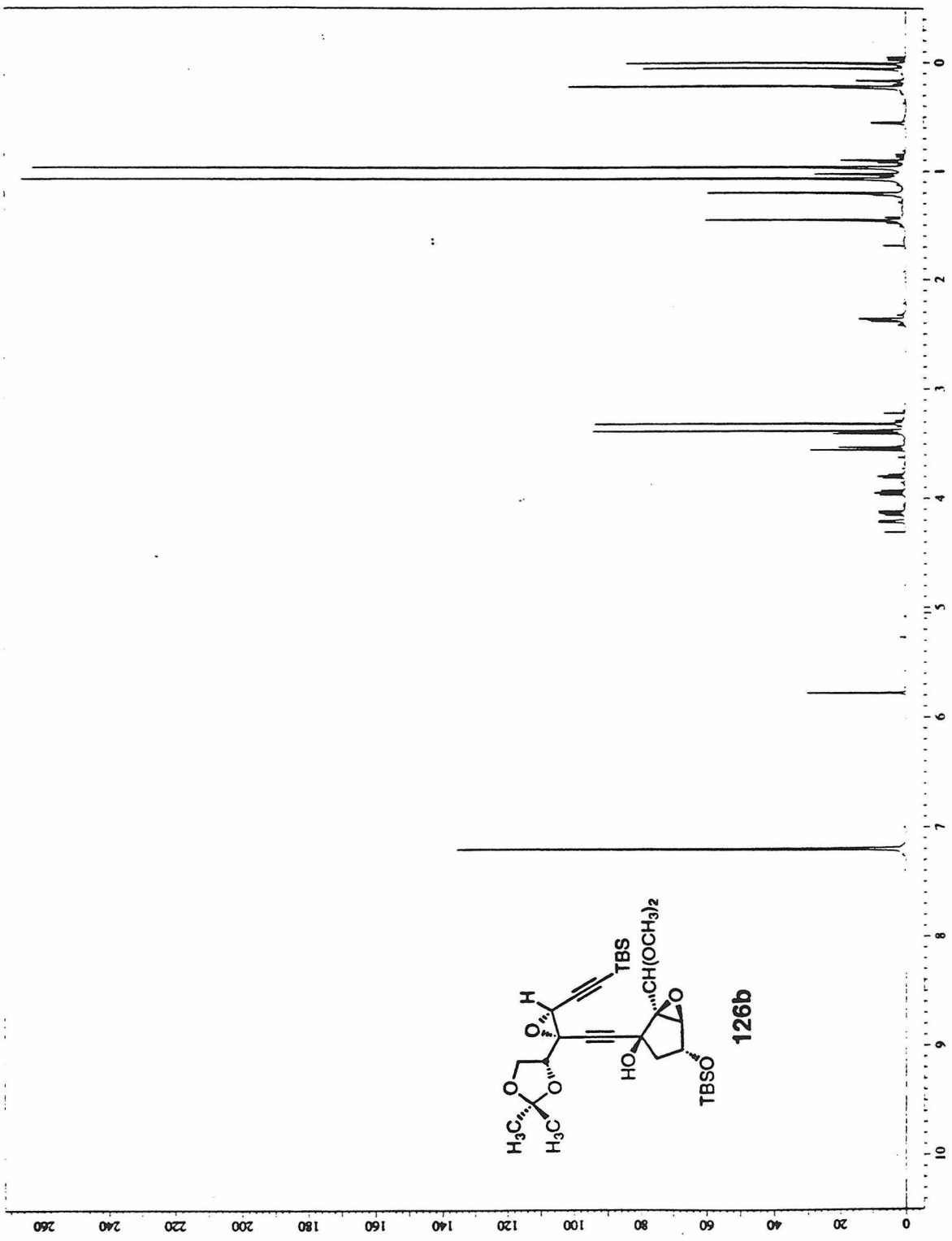

H3C
O
H3C
O
O
H
TMSO
H
OH
O
O
O
H3CO
OMEM
CH3
123

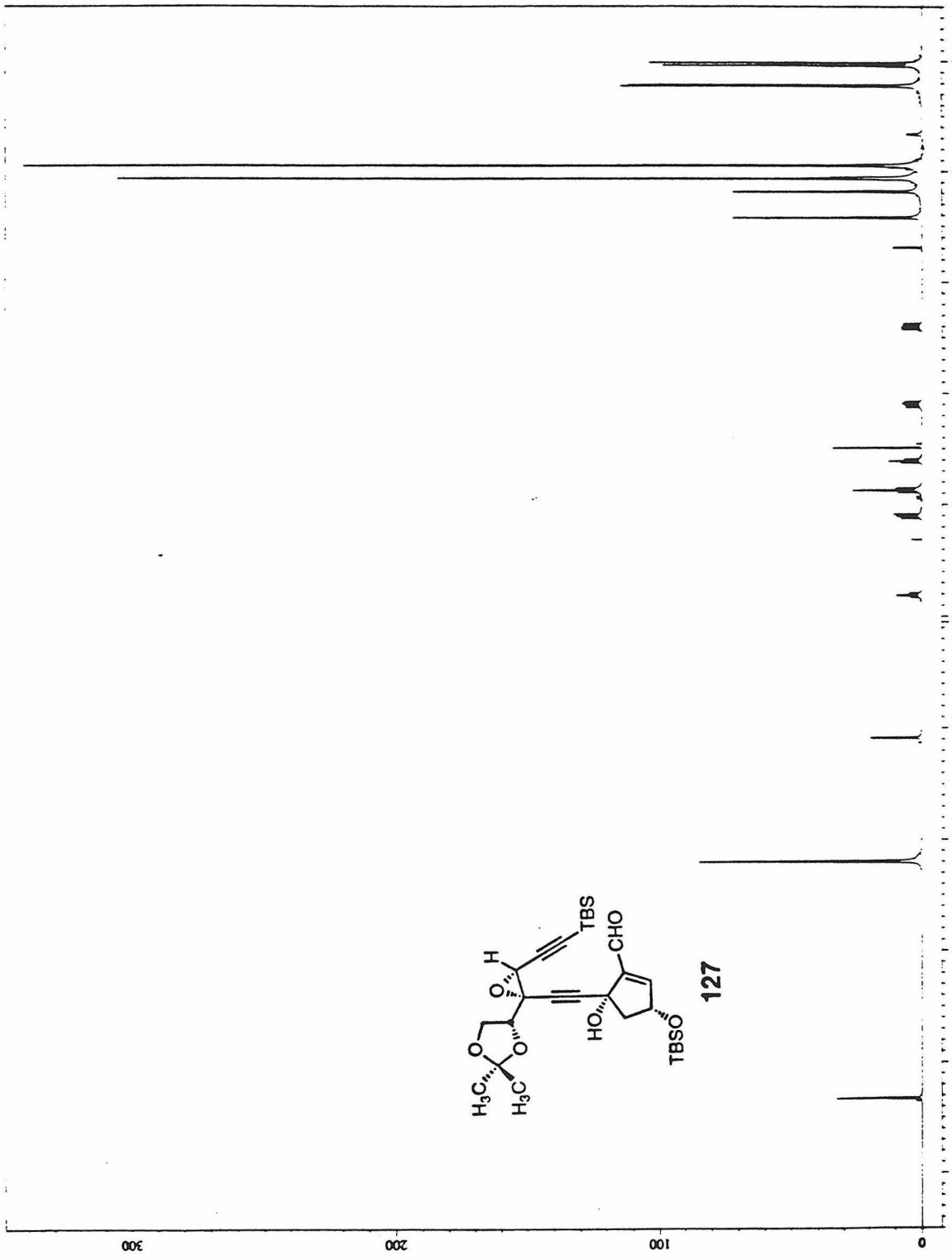

87.96
%T
75.45
4000
3500
3000
2500
2000
1500
1000
cm-1
500

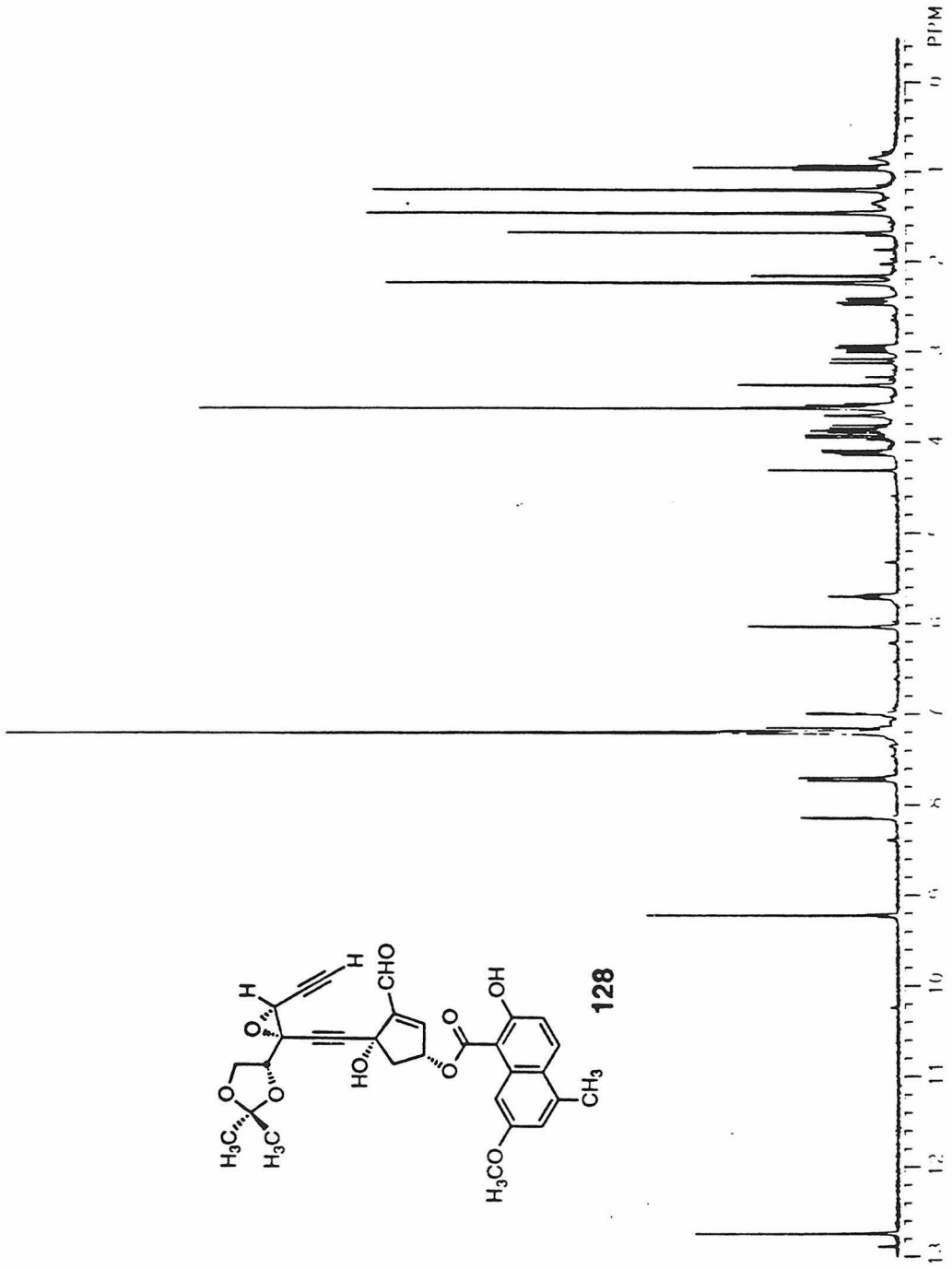

565
CH(OCH3)2
O
O
TBSO
125
200
180
160
140
120
100
80
60
40
20
0
10
9
8
7
6
5
4
3
2
1
0

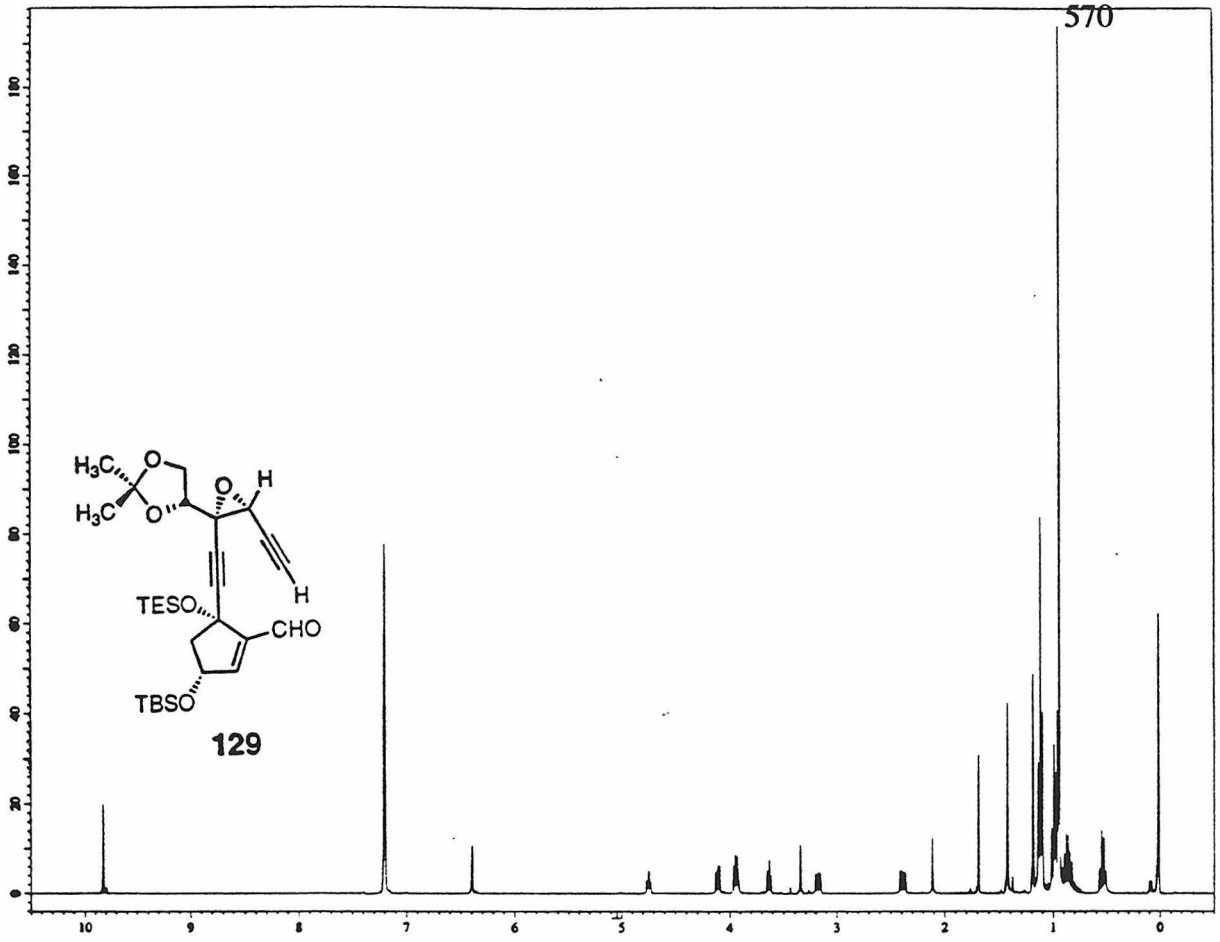

92.61
%T
29.42
4000
3500
3000
2500
2000
1500
1000
cm-1
500


TBS
CH(OCH3)2
H
O
HO
TBSO
H3C
H3C
126a

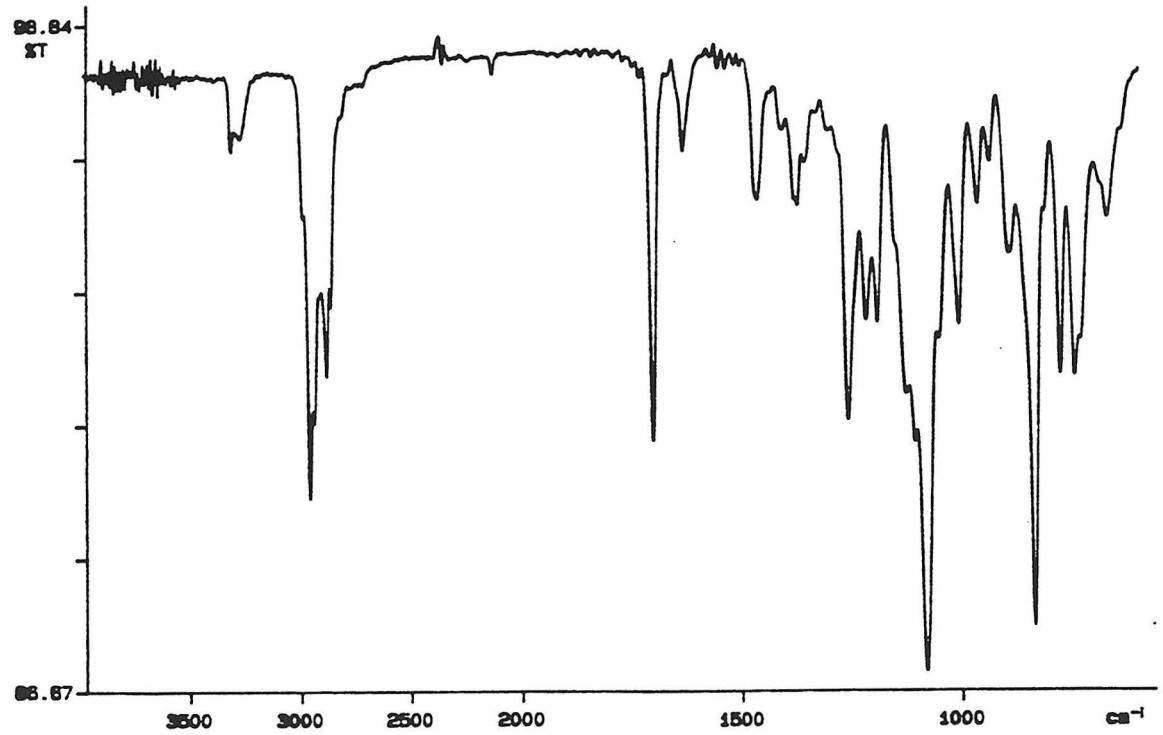

TBS
CH(OCH3)2
H
O
HO
TBSO
H3C
H3C
126b

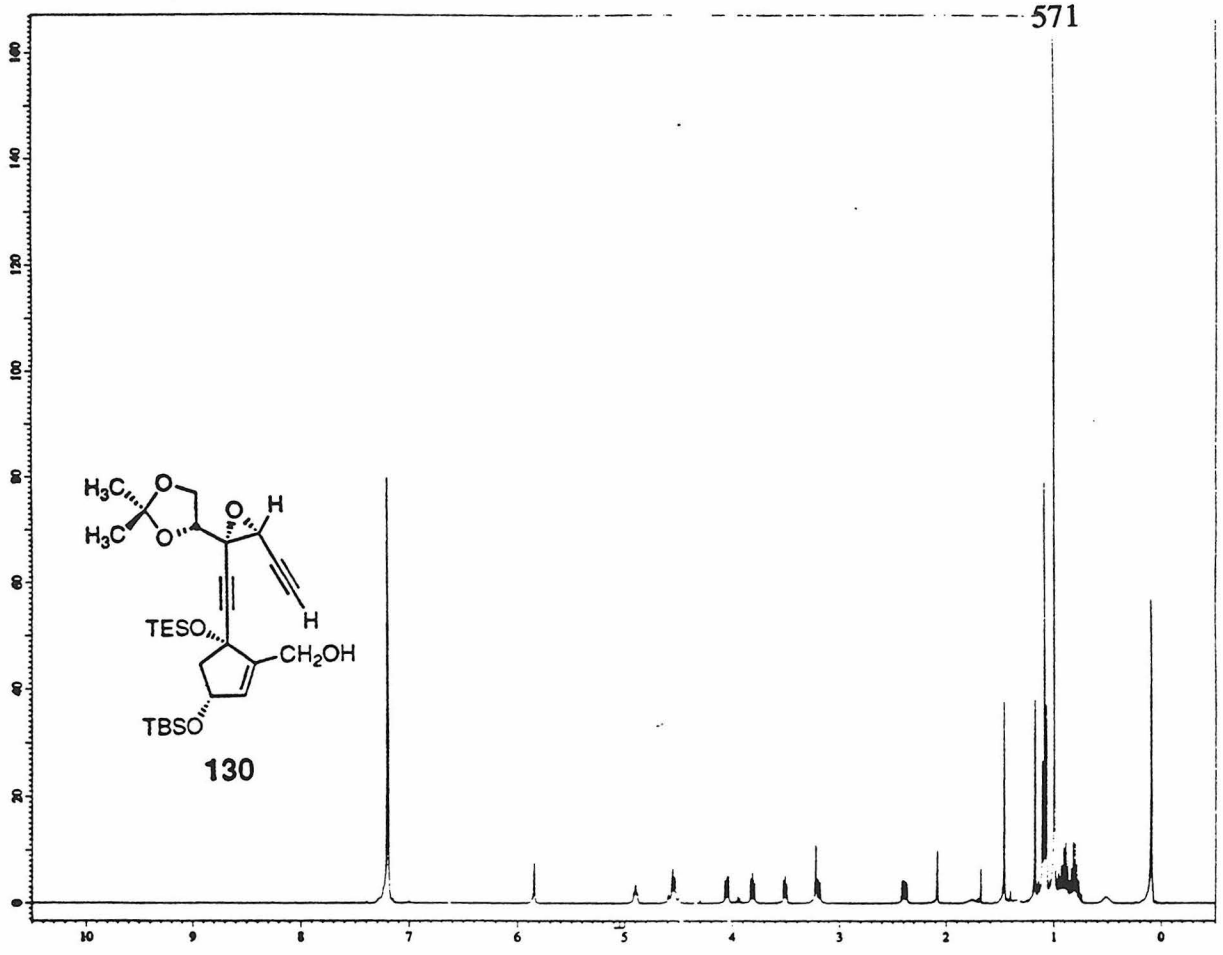

TBS
CHO
H
O
HO
TBSO
O
O
H_3C
H_3C
127

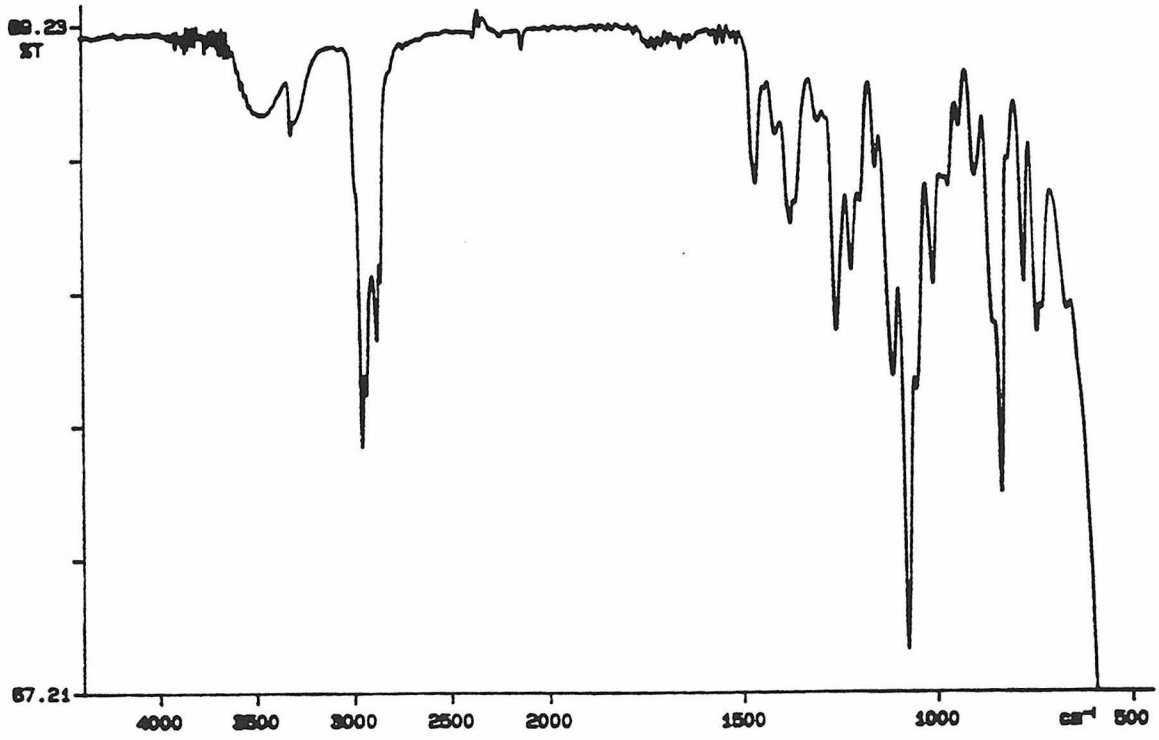

H
CHO
O
OH
O
HO
O
O
H3C
H3C
CH3
H3CO
128
PPM


H3C
O
H3C
O
O
H
H
TESO
CHO
TBSO

129


98.84
%T
86.67
3500
3000
2500
2000
1500
1000
cm-1


H3C
O
H3C
O
O
H
TESO
H
CH2OH
TBSO
130


89.23
%T
67.21
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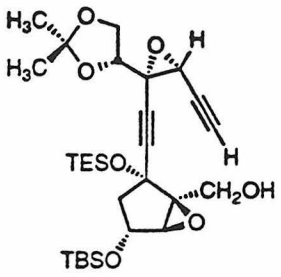
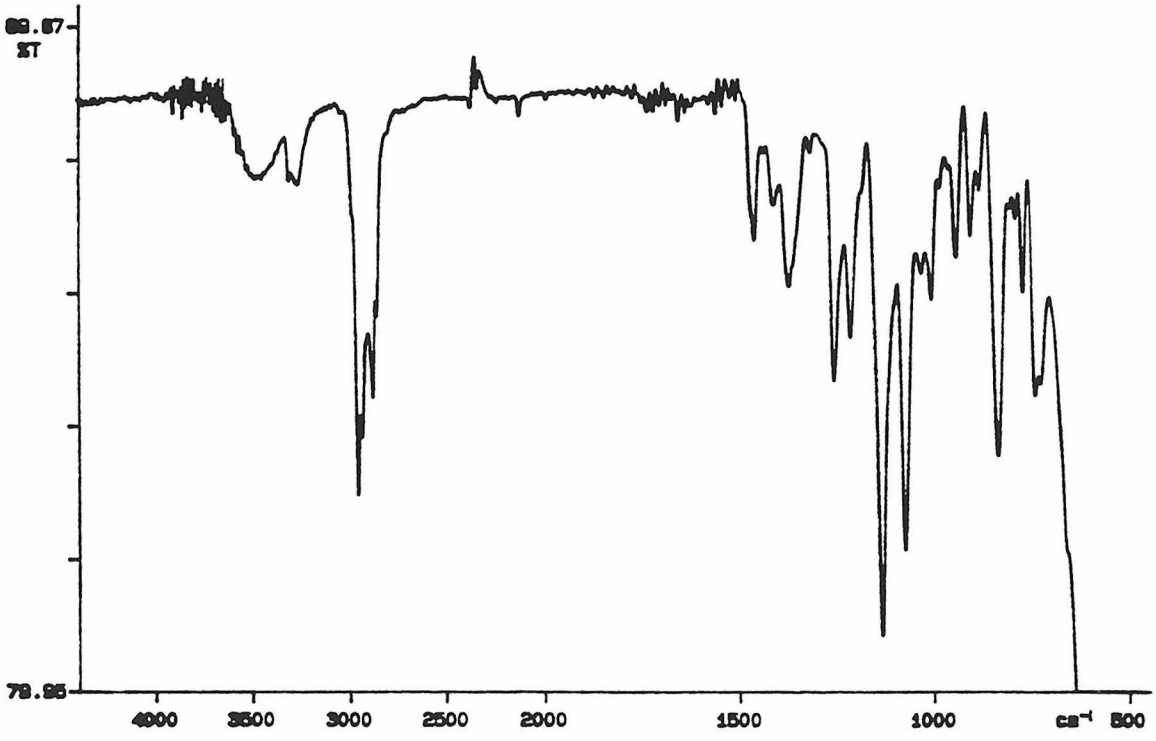
3500
3000
2500
2000
1500
1000
cm-1
500


H3C
O
H3C
O
O
H
H
TESO
CH2OH
O
TBSO

131

10
9
8
7
6
5
4
3
2
1
0
PPM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79.95
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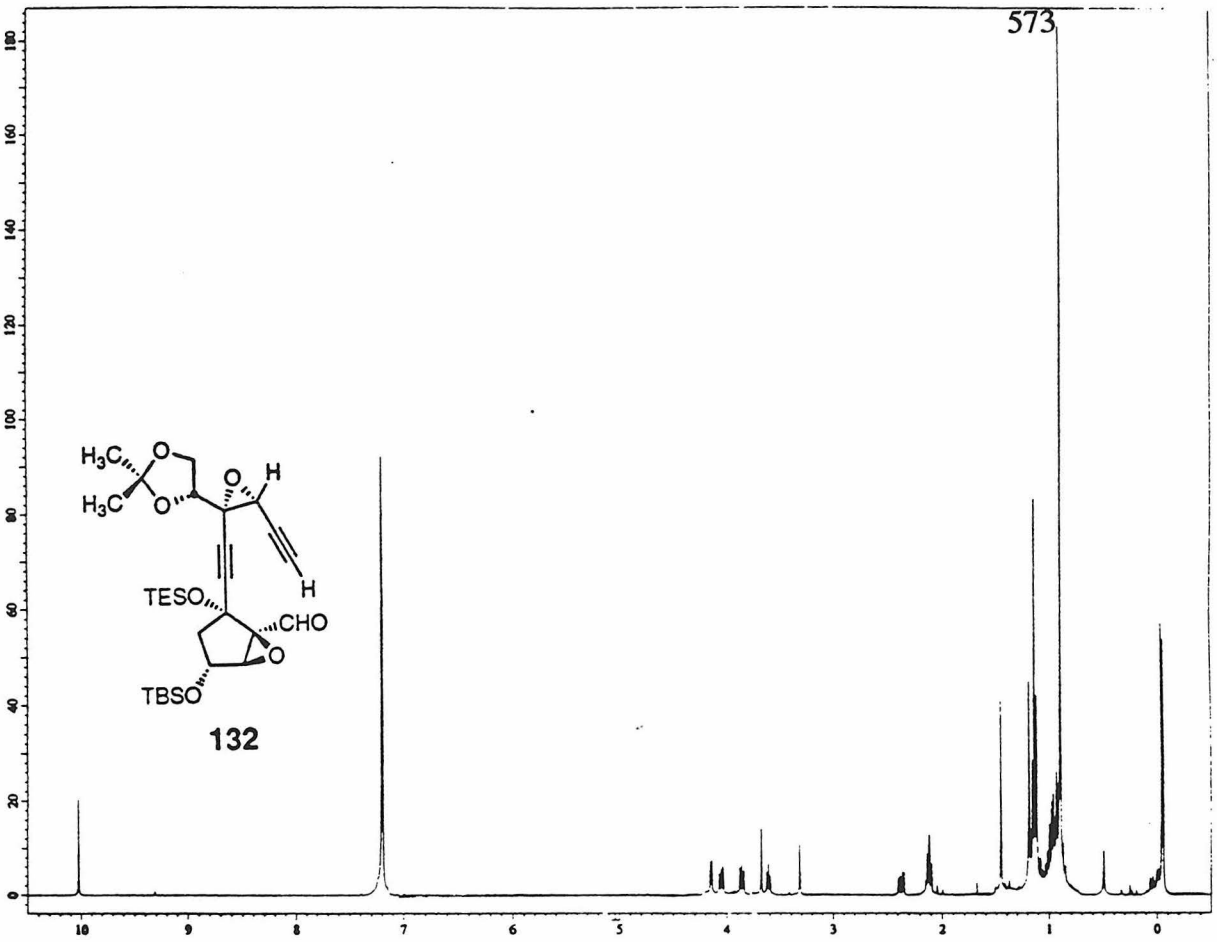
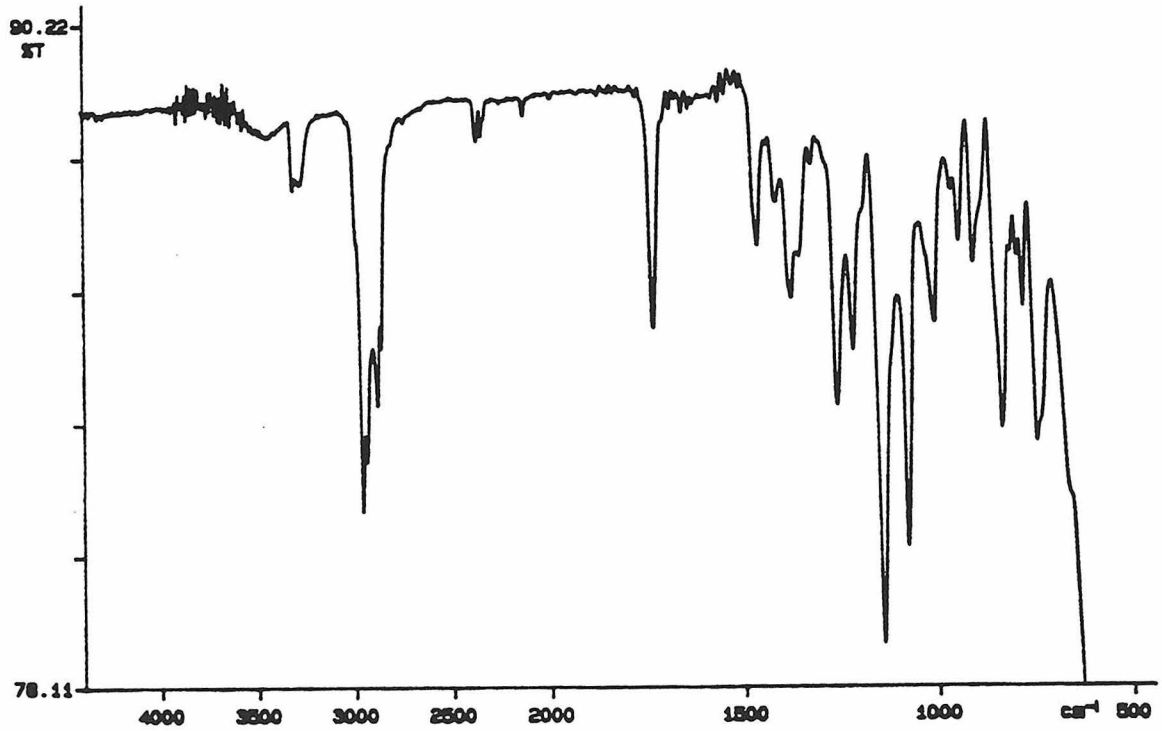
2500
2000
1500
1000
cm-1
500


573
H3C
O
H3C
O
O
H
H
TESO
CHO
O
TBSO
132


90.22
%T
78.11
4000
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3000
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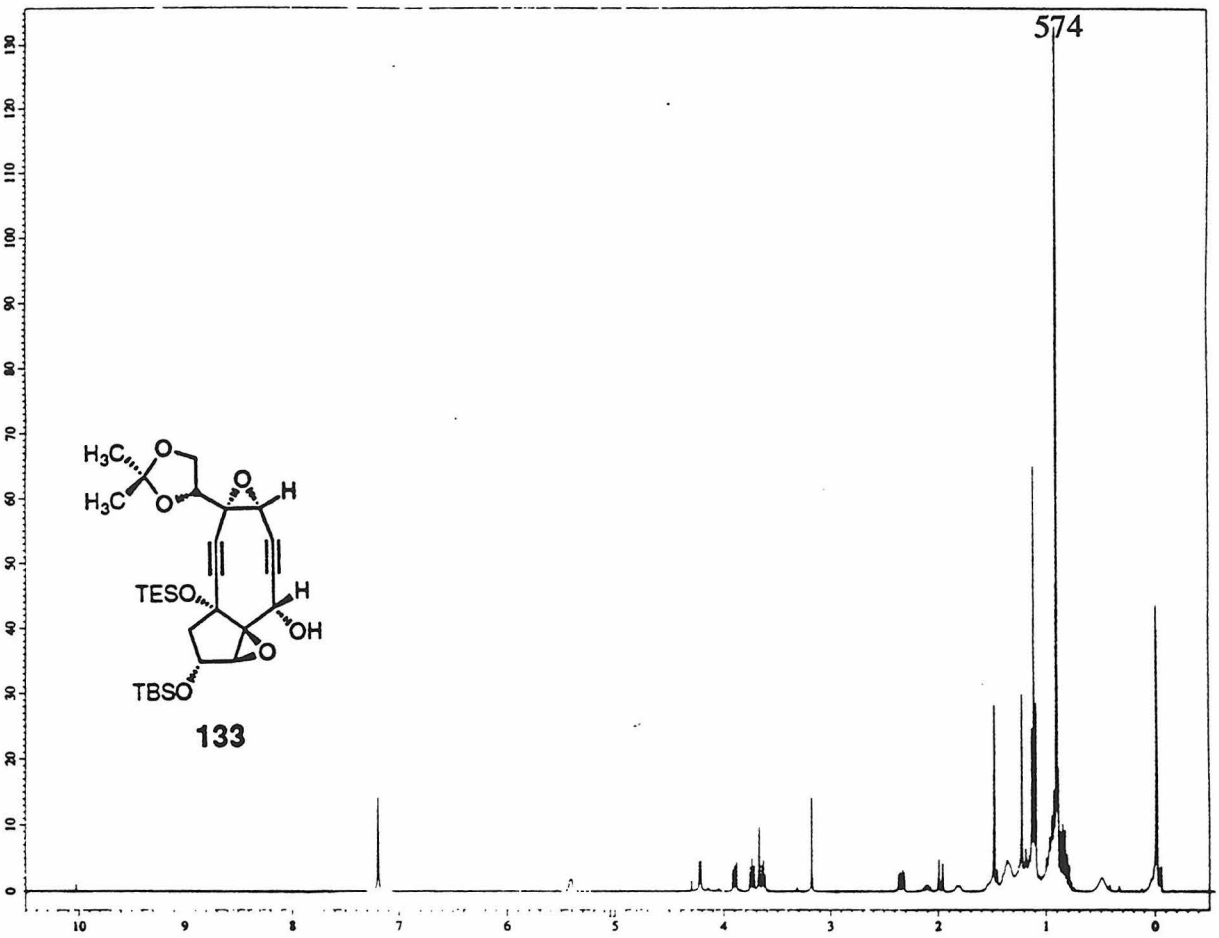
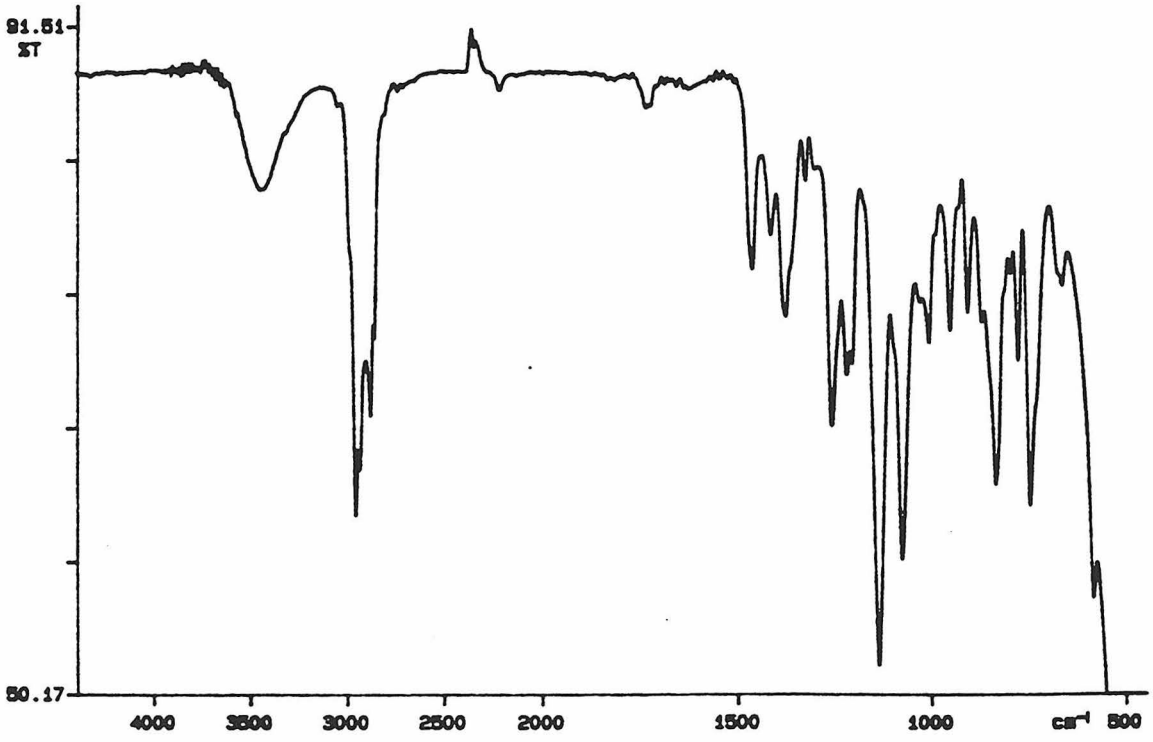
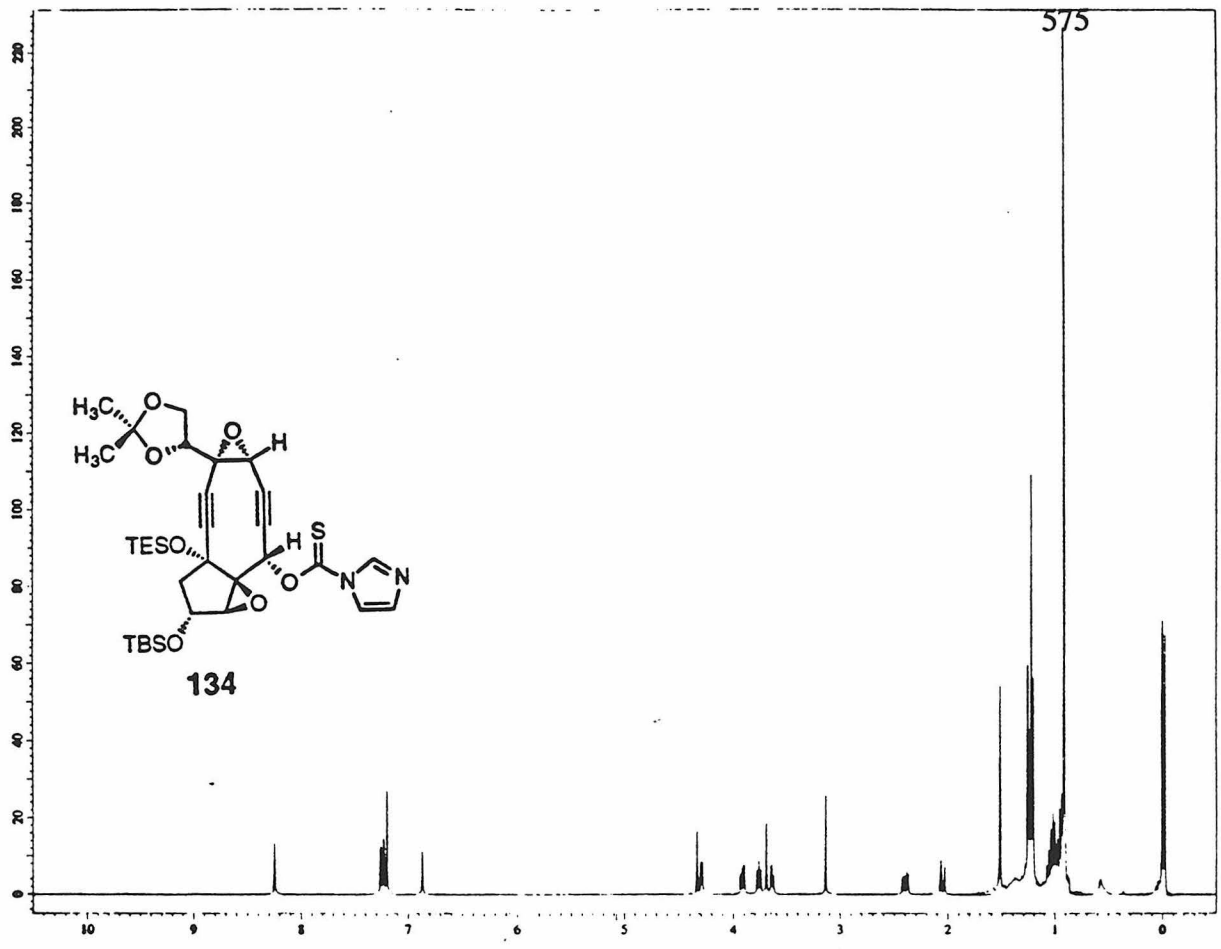
2000
1500
1000
cm-1
500

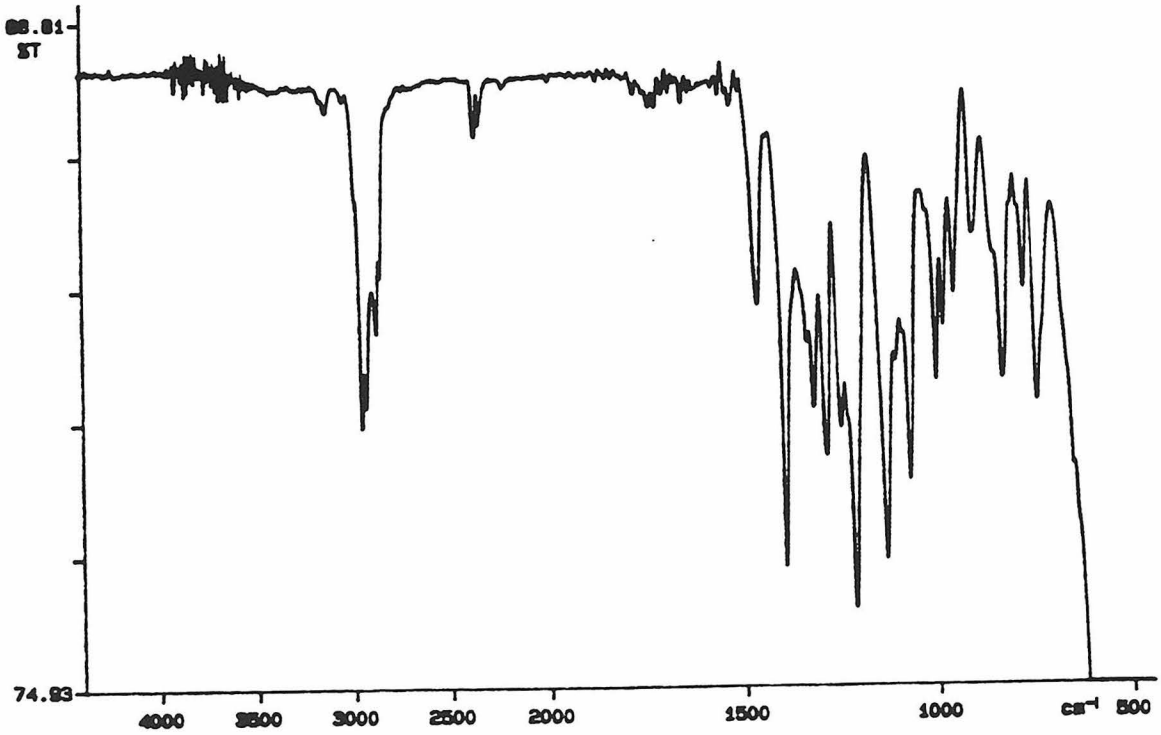

H3C
O
H3C
O
O
H
TESO
H
OH
O
TBSO

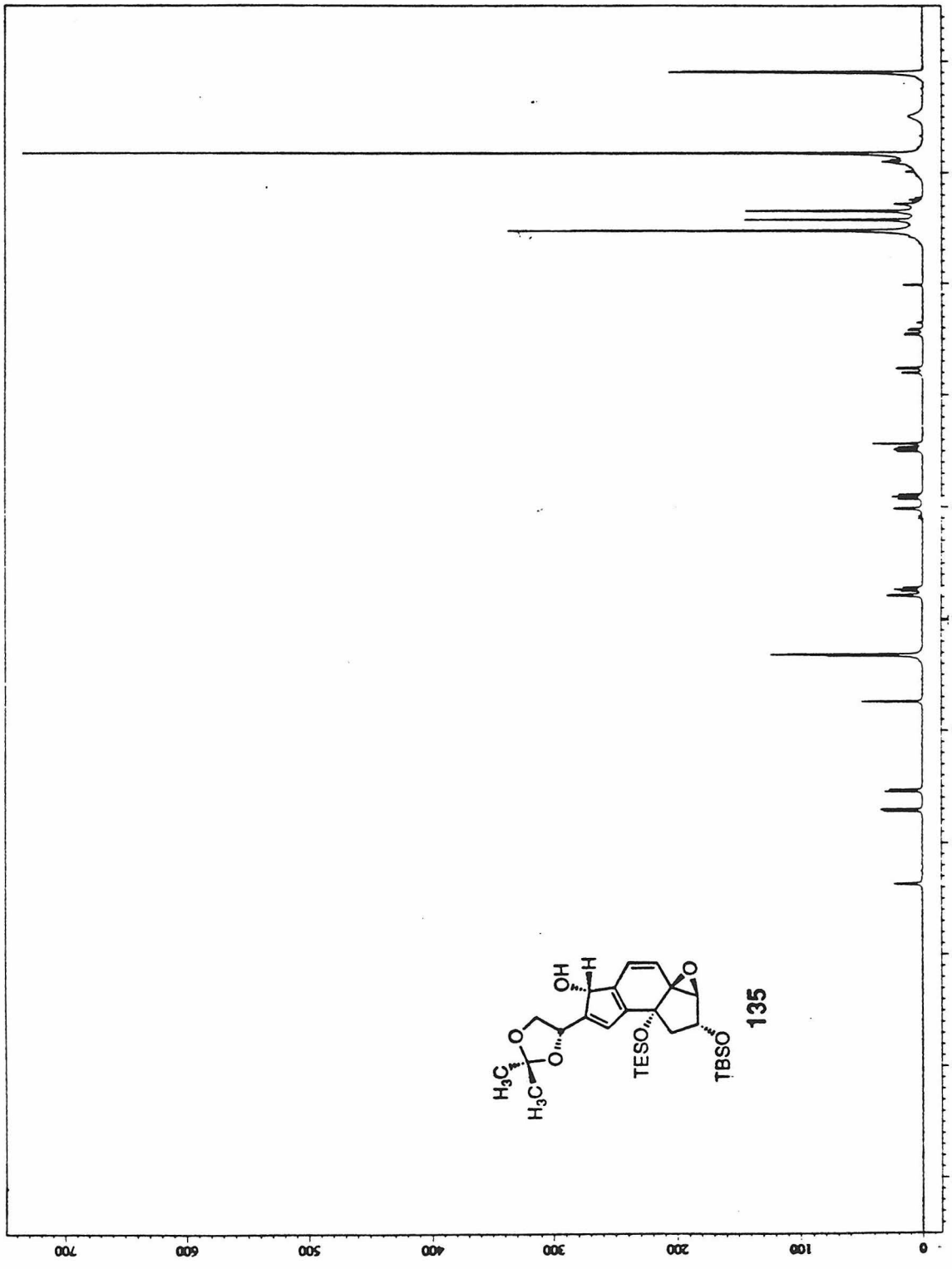
133

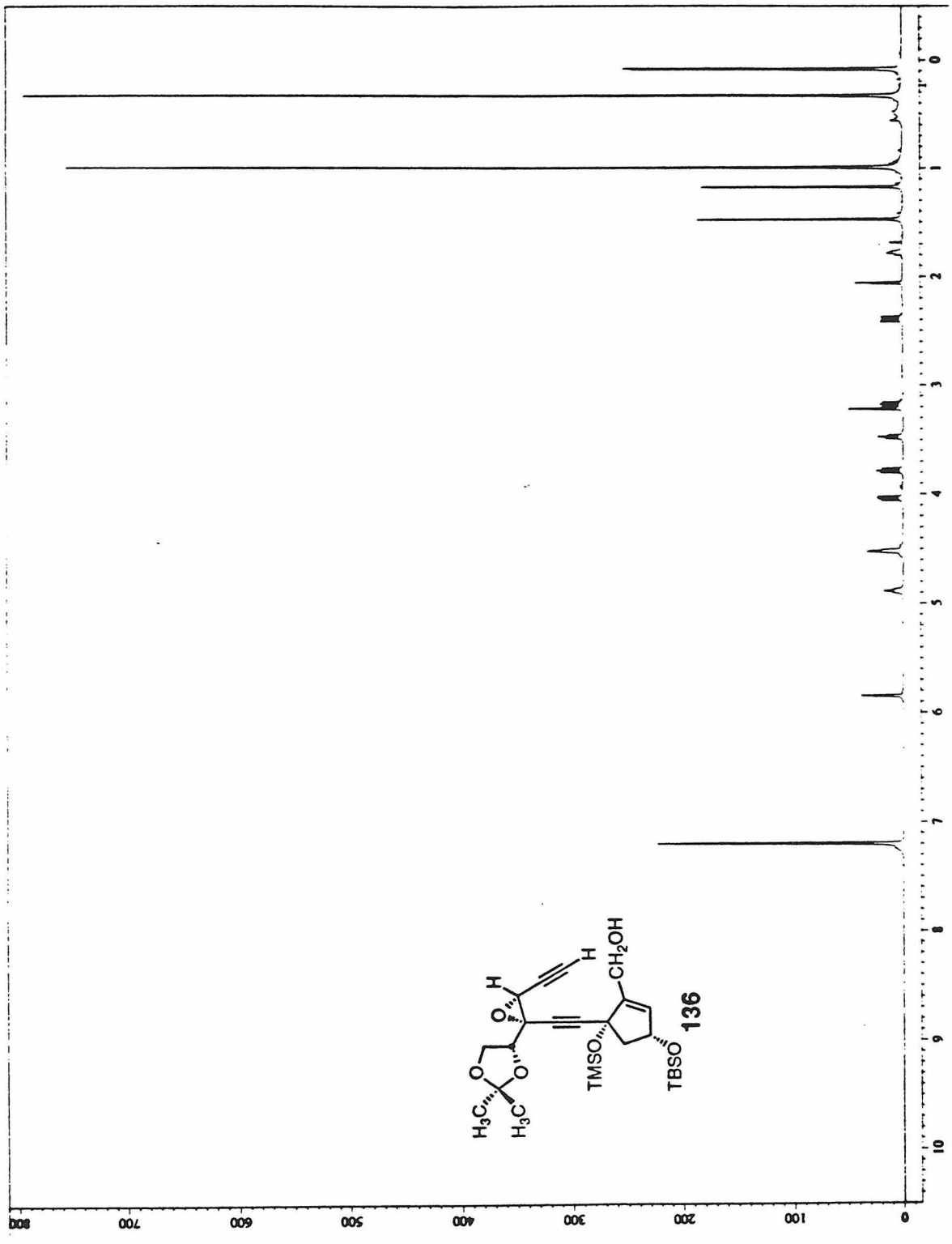

91.51
%T
50.17
4000
3500
3000
2500
2000
1500
1000
cm-1
500

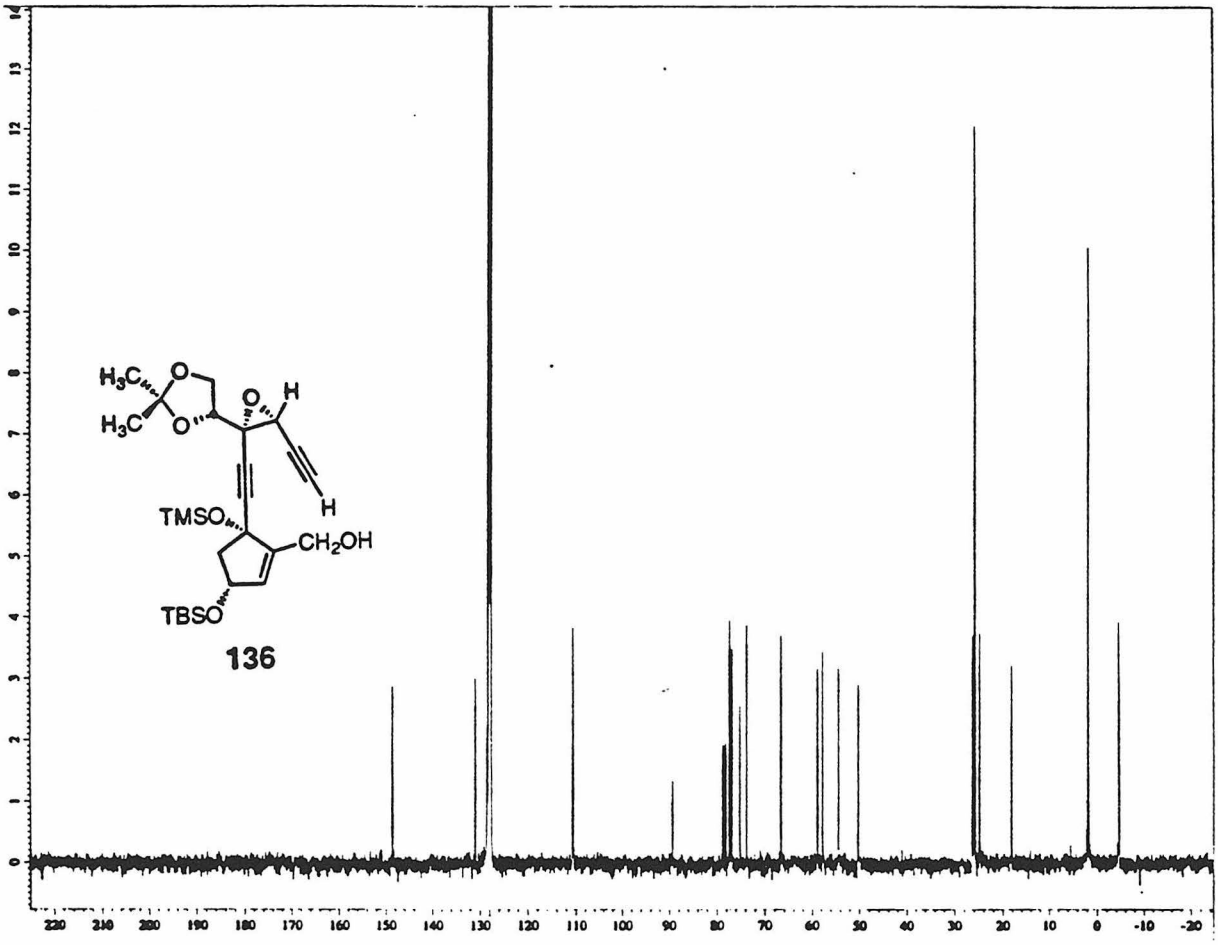

H3C
O
H3C
O
O
H
TESO
H
S
O
N
N
O
TBSO

134

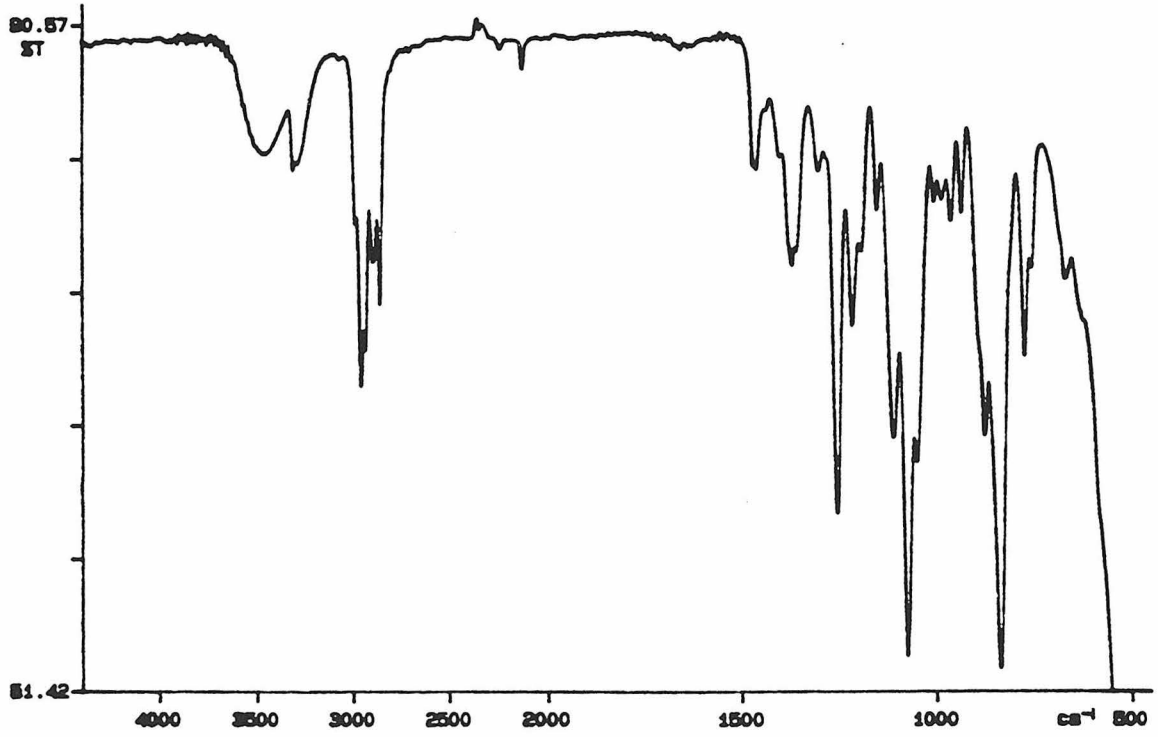

88.81
%T
74.83
4000
3500
3000
2500
2000
1500
1000
cm-1
500

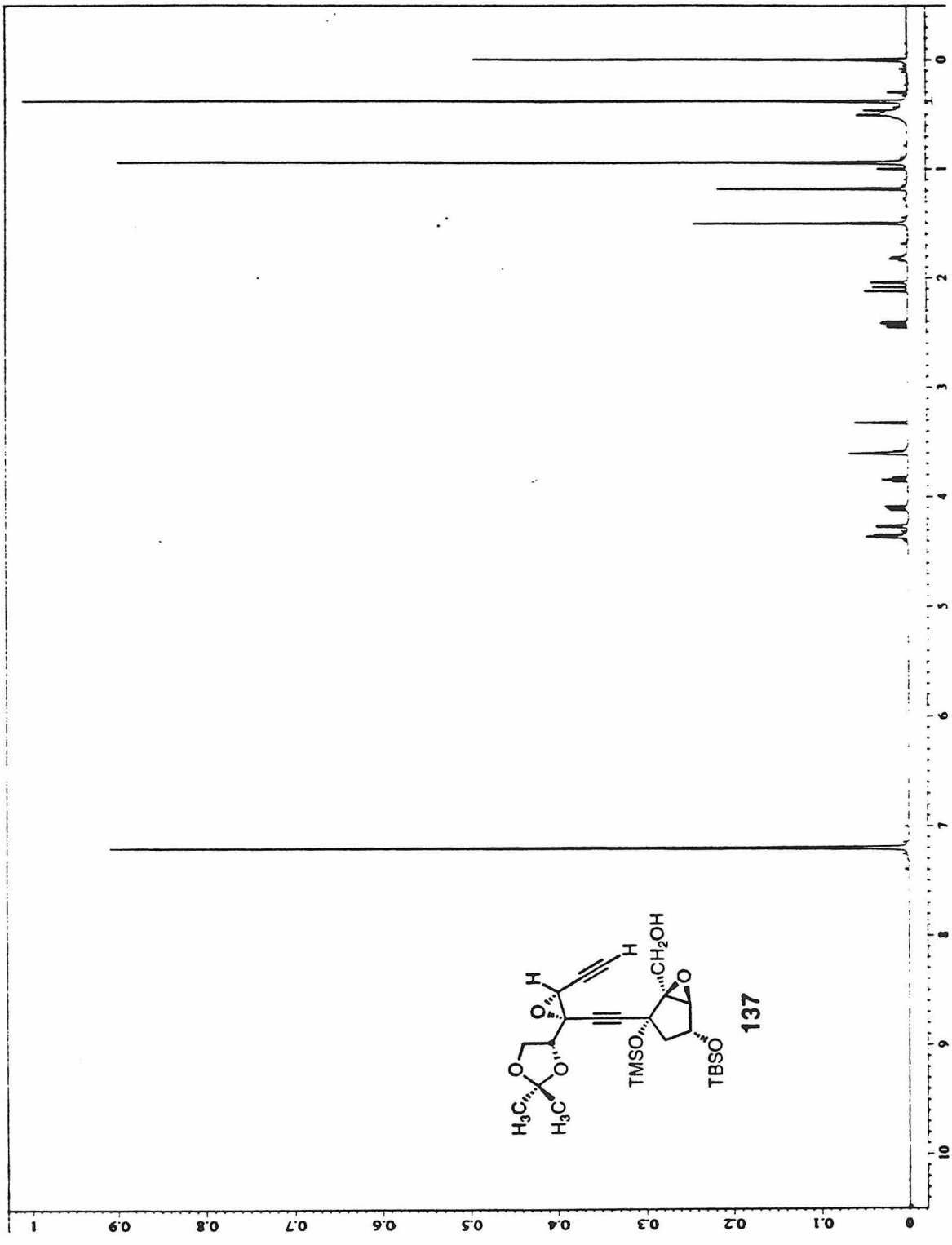

OH
H
O
O
O
H3C
H3C
TESO
TBSO
135

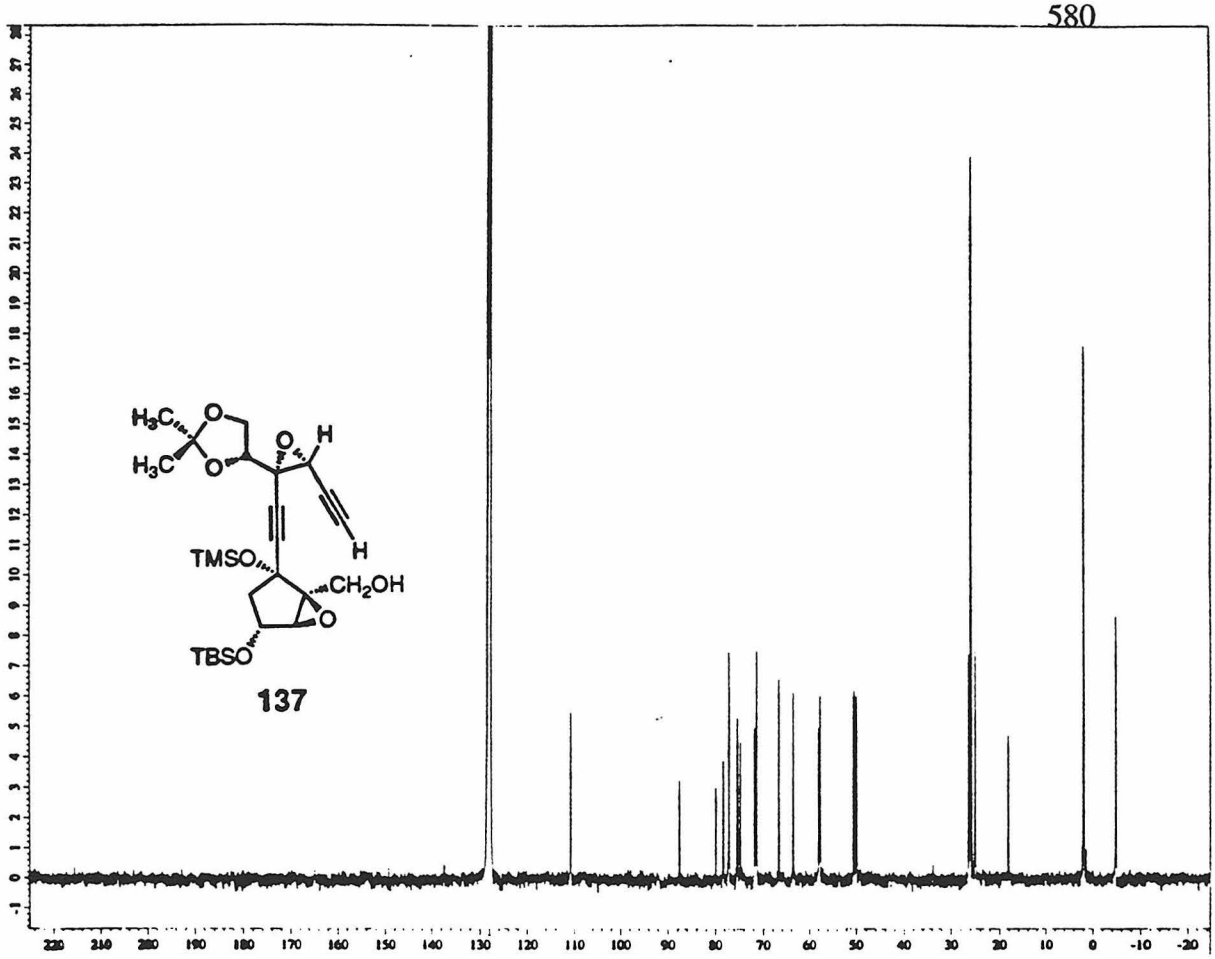

H
O
O
O
H3C
H3C
TMSO
CH2OH
TBSO
136


H3C
O
H3C
O
O
H
H
TMSO
CH2OH
TBSO

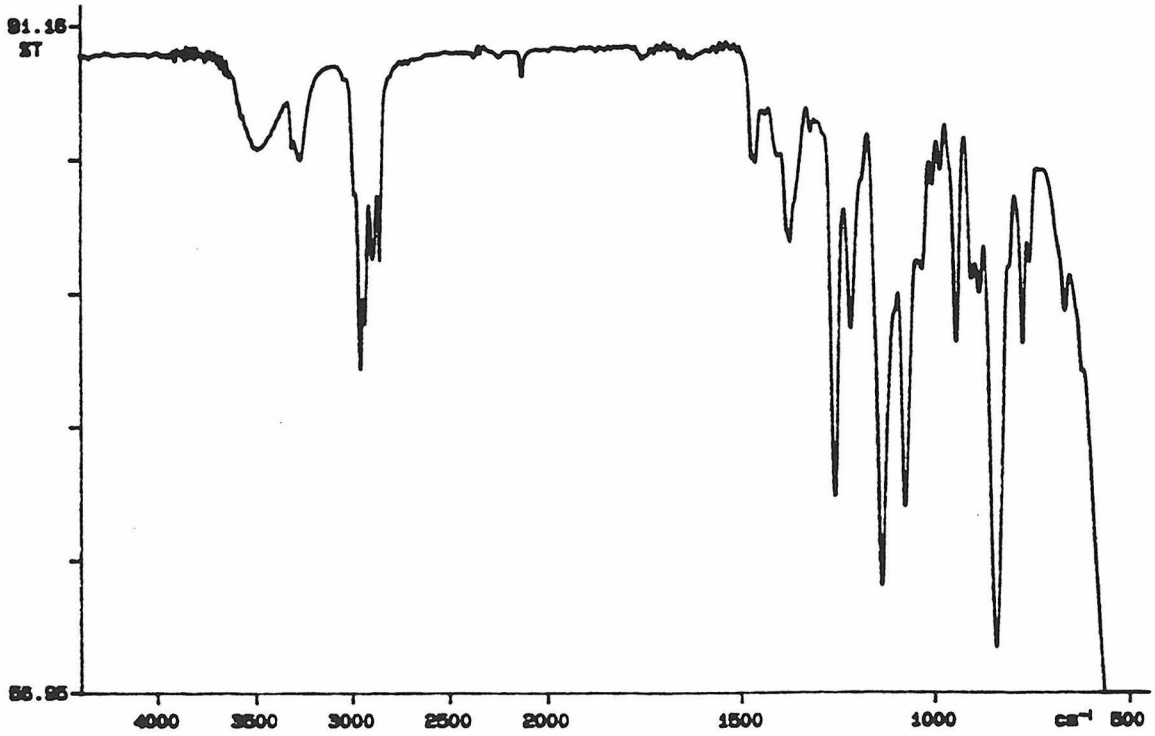
136

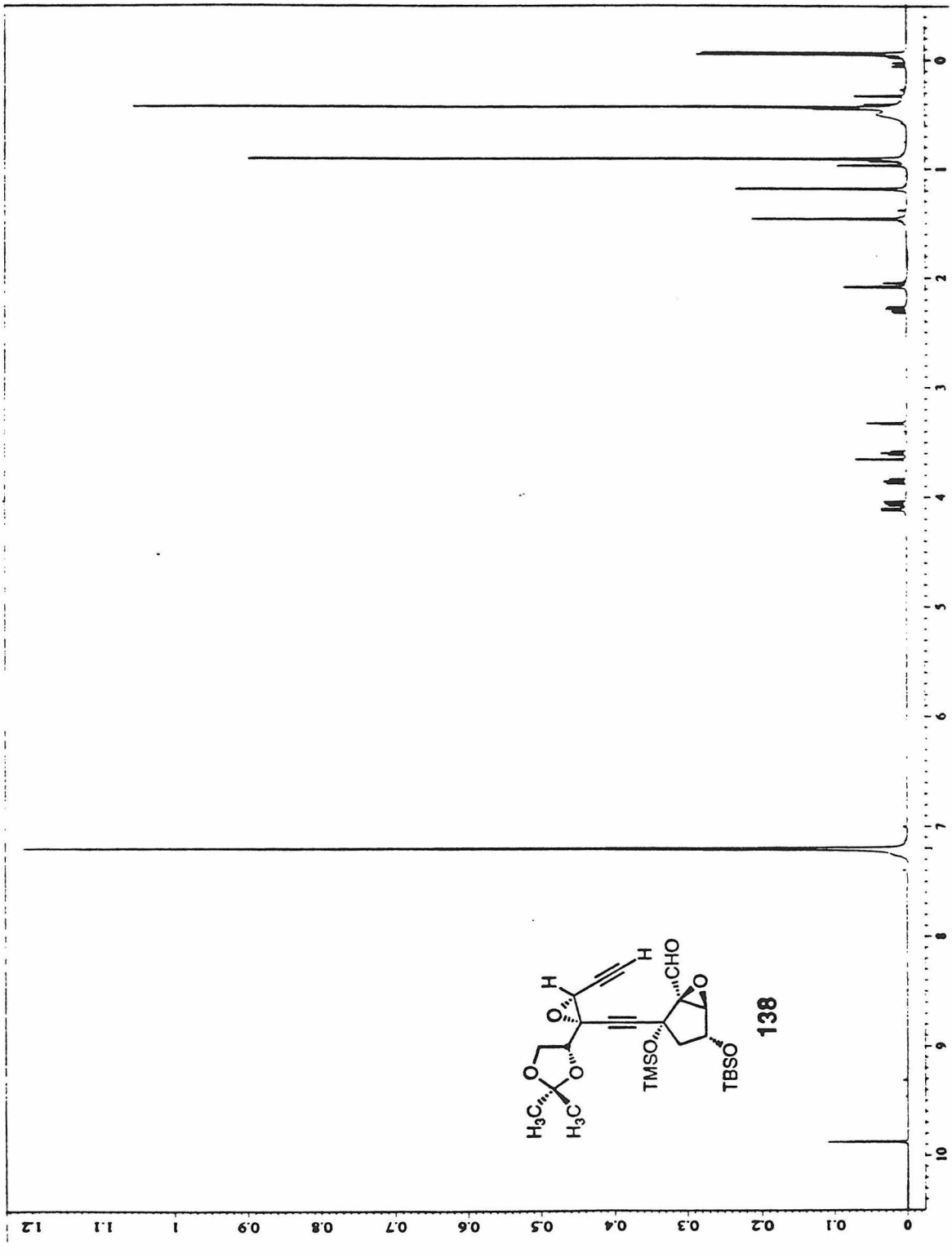

80.57
%T
51.42
4000
3500
3000
2500
2000
1500
1000
cm-1
500

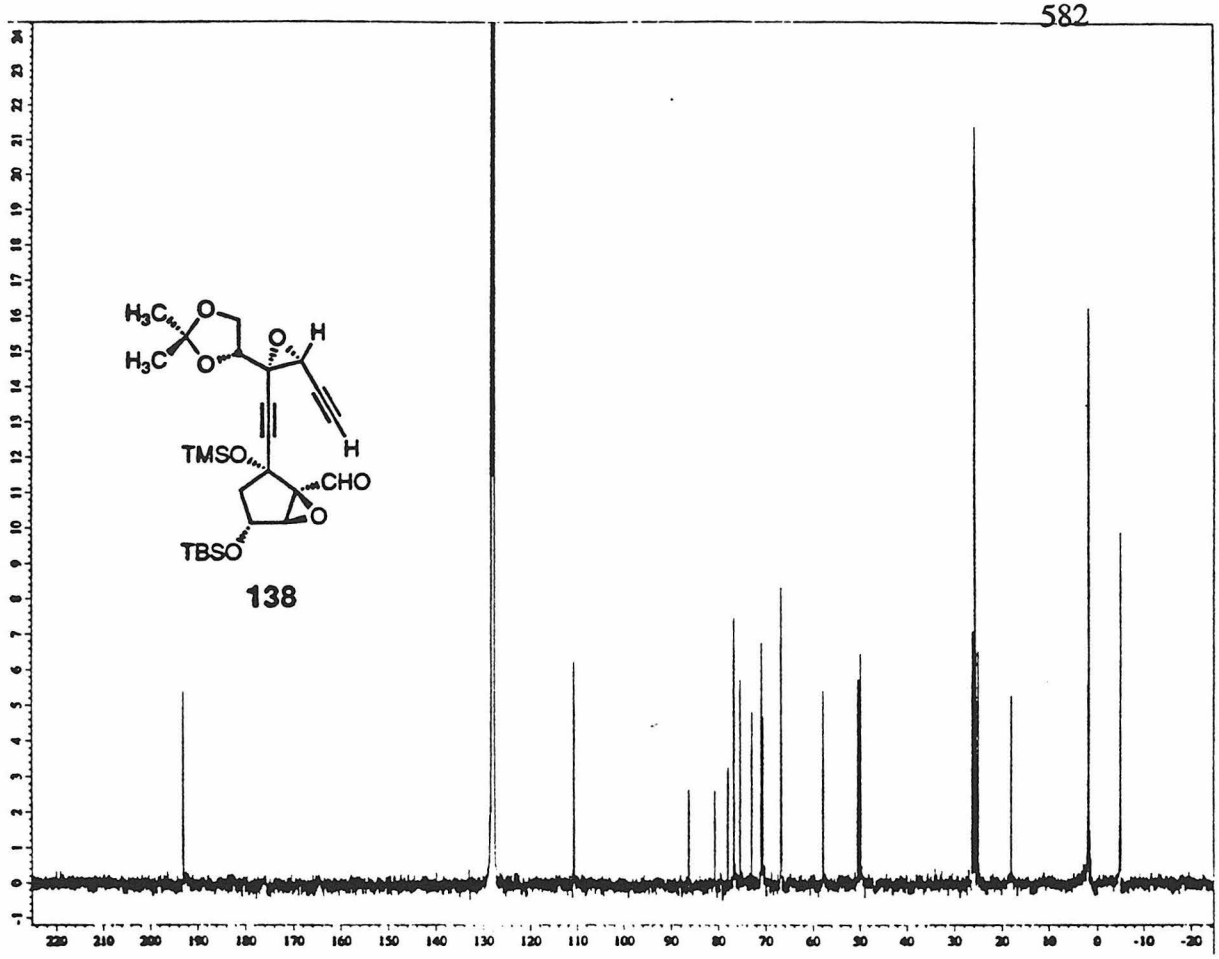

H
O
H
O
O
H3C
H3C
TMSO
CH2OH
O
TBSO
137


H3C
H3C
O
O
O
H
H
TMSO
CH2OH
O
TBSO

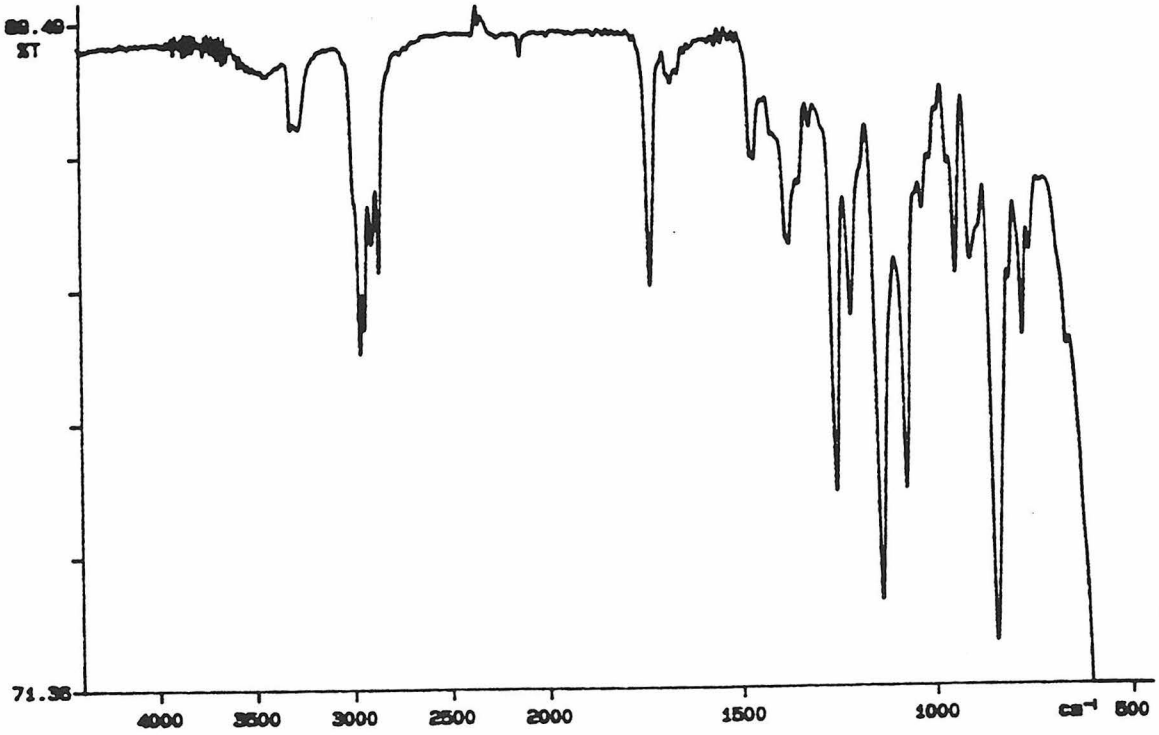
137

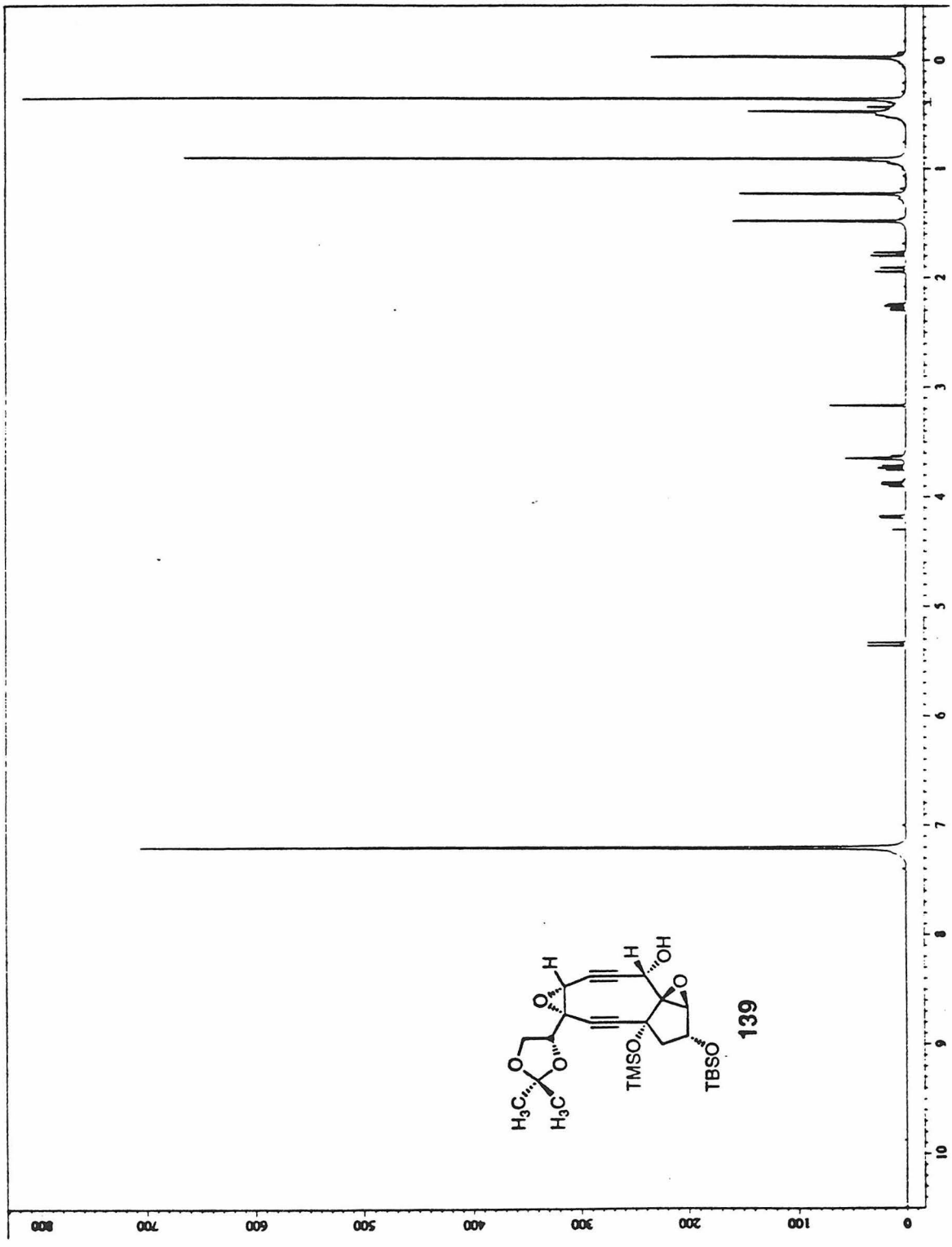

91.16
%T
55.95
4000
3500
3000
2500
2000
1500
1000
cm-1
500

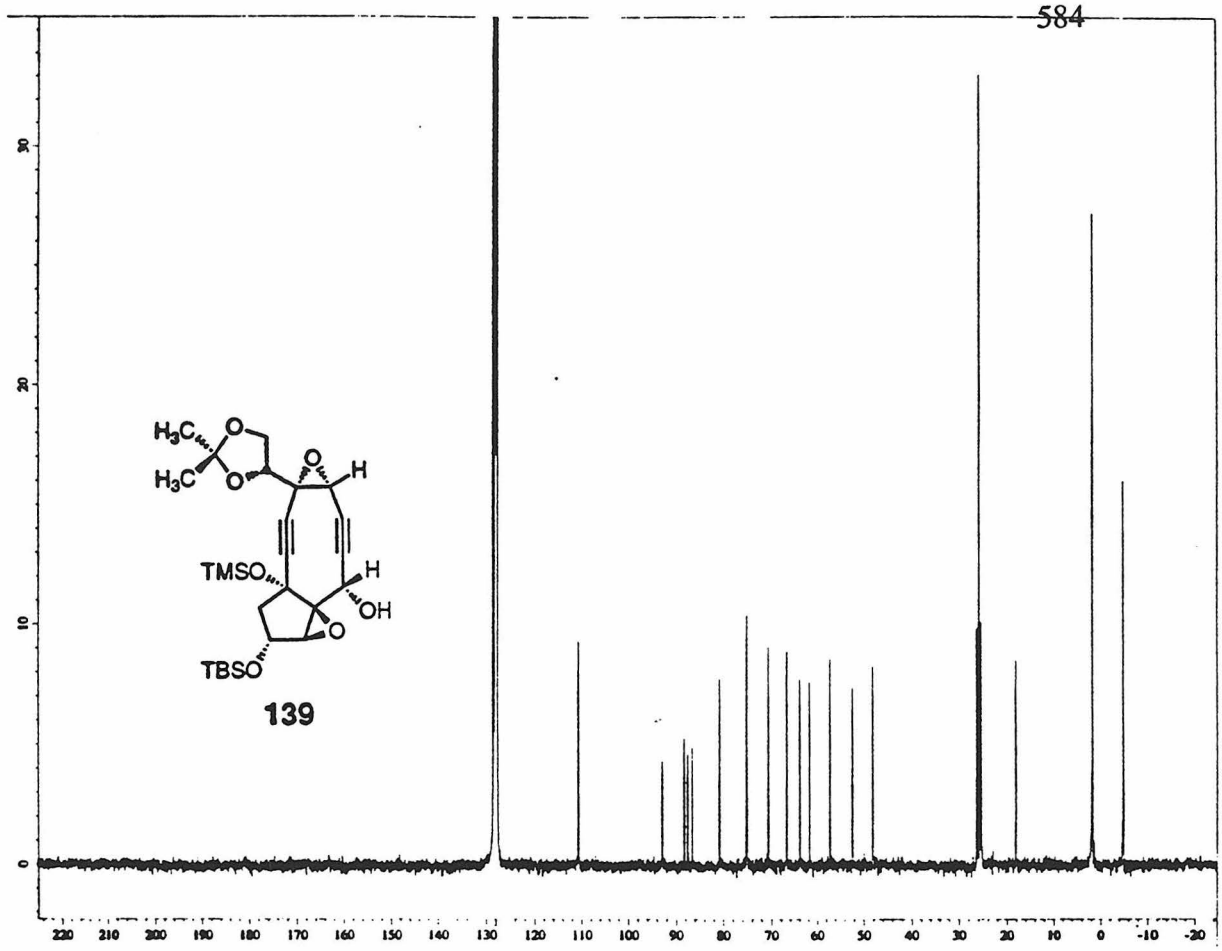

H
CHO
O
TMSO
TBSO
O
O
O
H
H3C
H3C
138

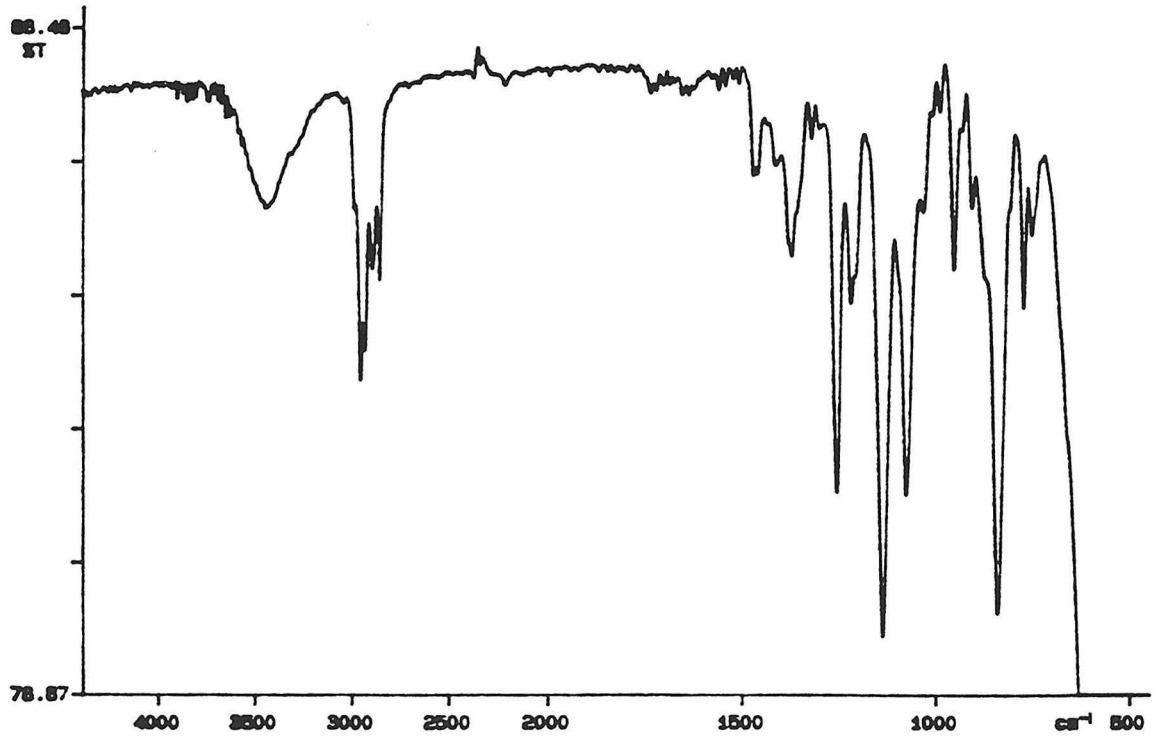

H3C
O
H3C
O
O
H
H
TMSO
CHO
O
TBSO

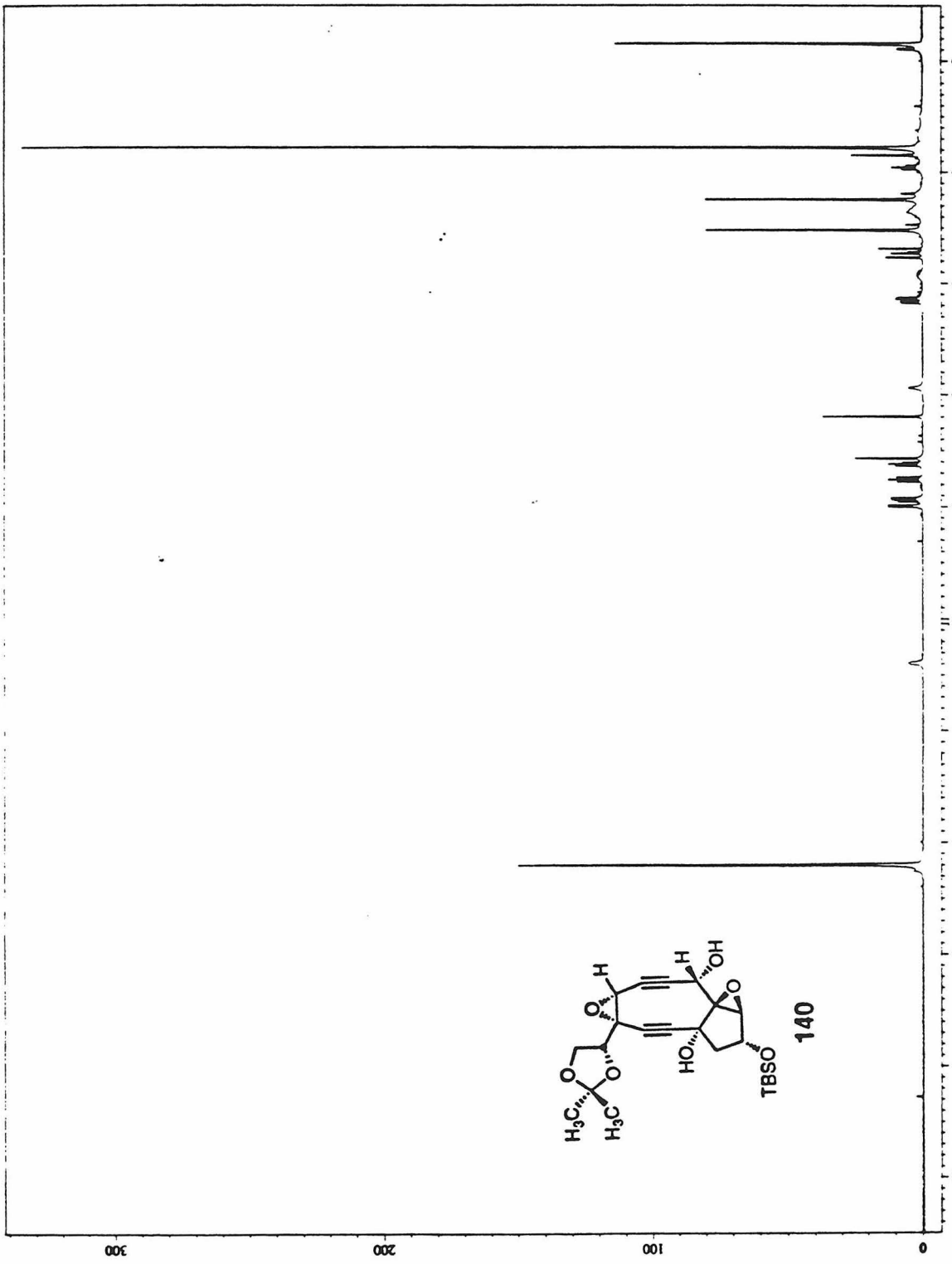
138

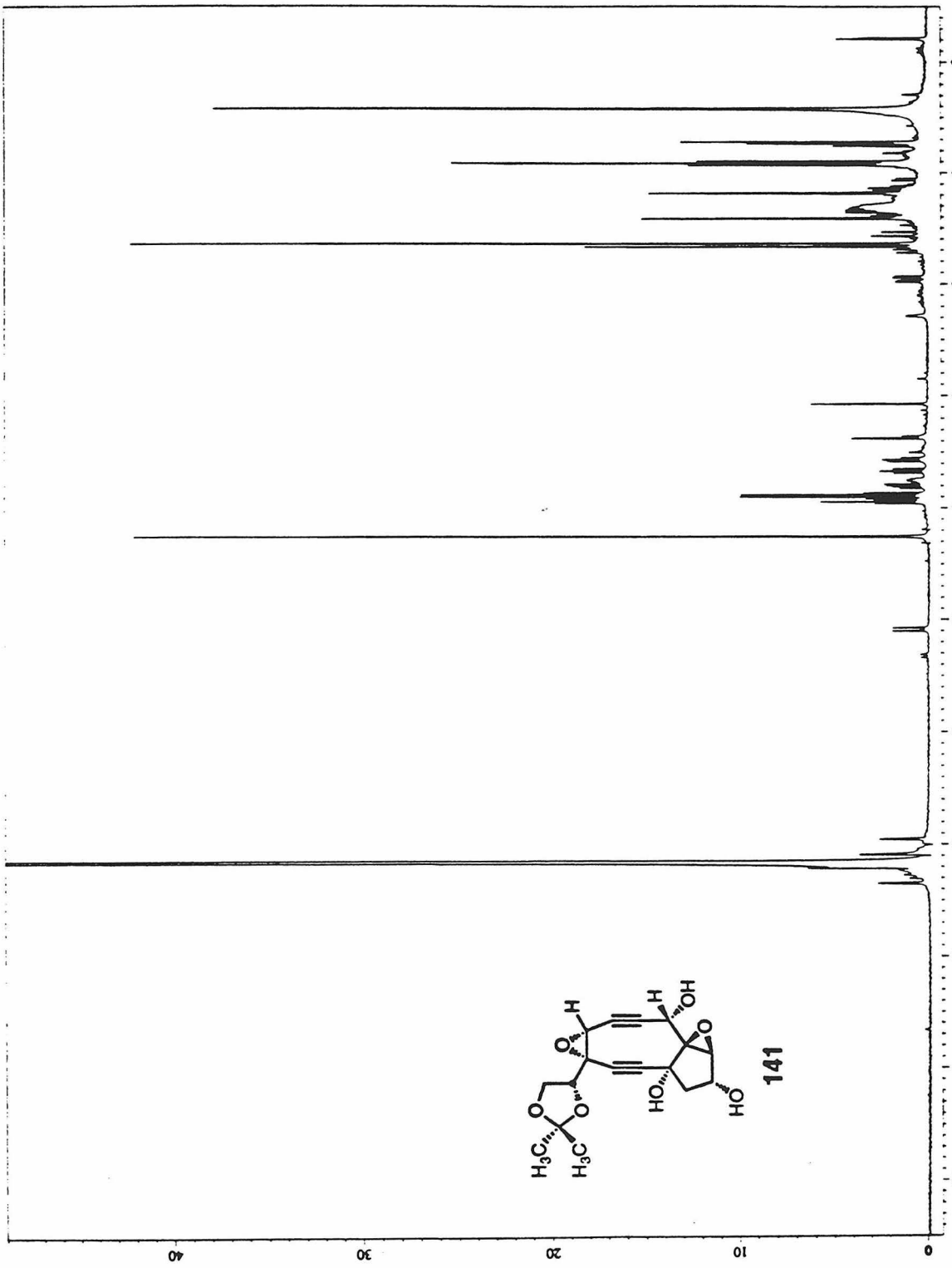

88.49
%T
71.36
4000
3500
3000
2500
2000
1500
1000
cm-1
500

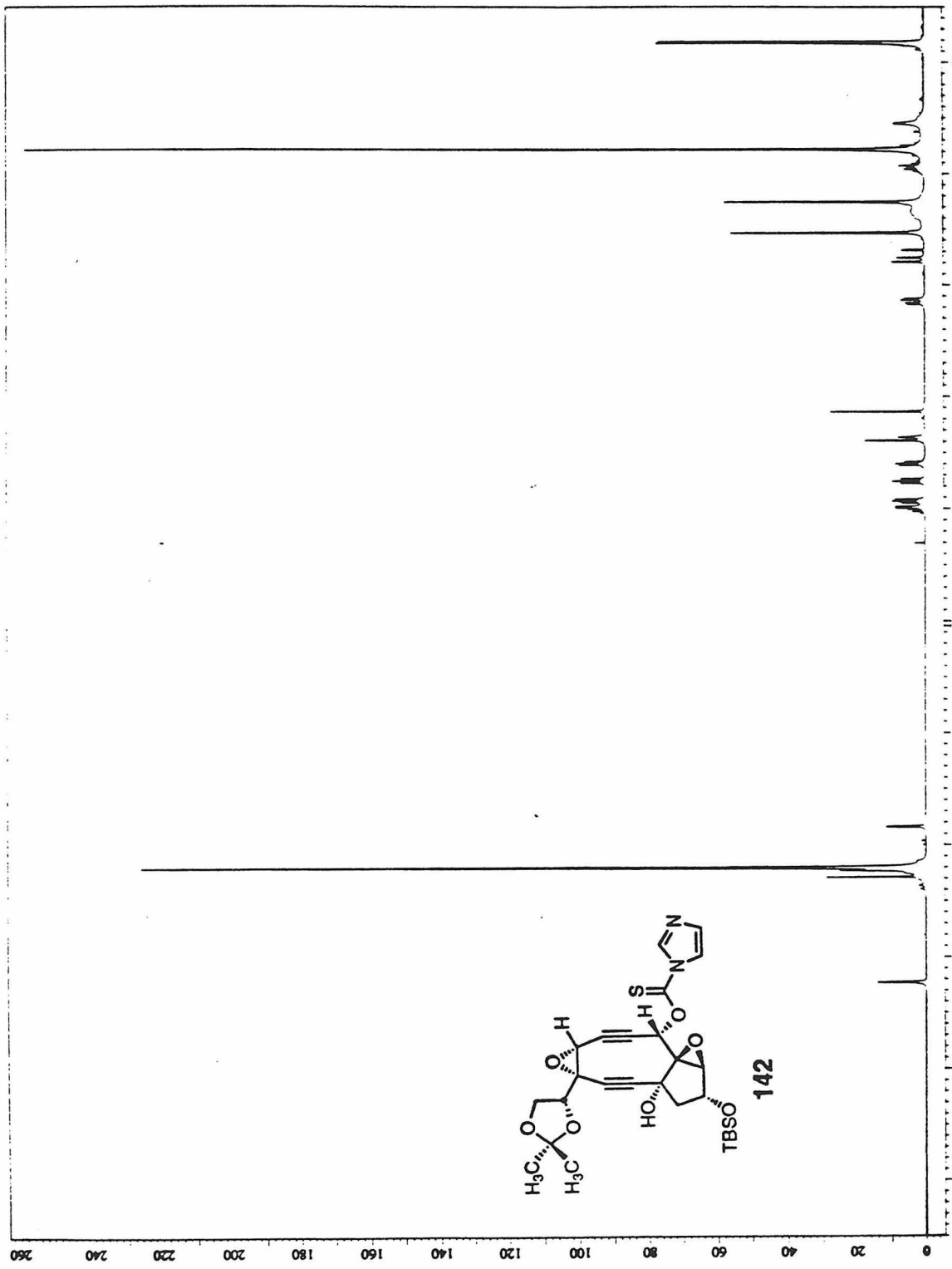

H
O
H
OH
O
O
O
H3C
H3C
TMSO
TBSO
139

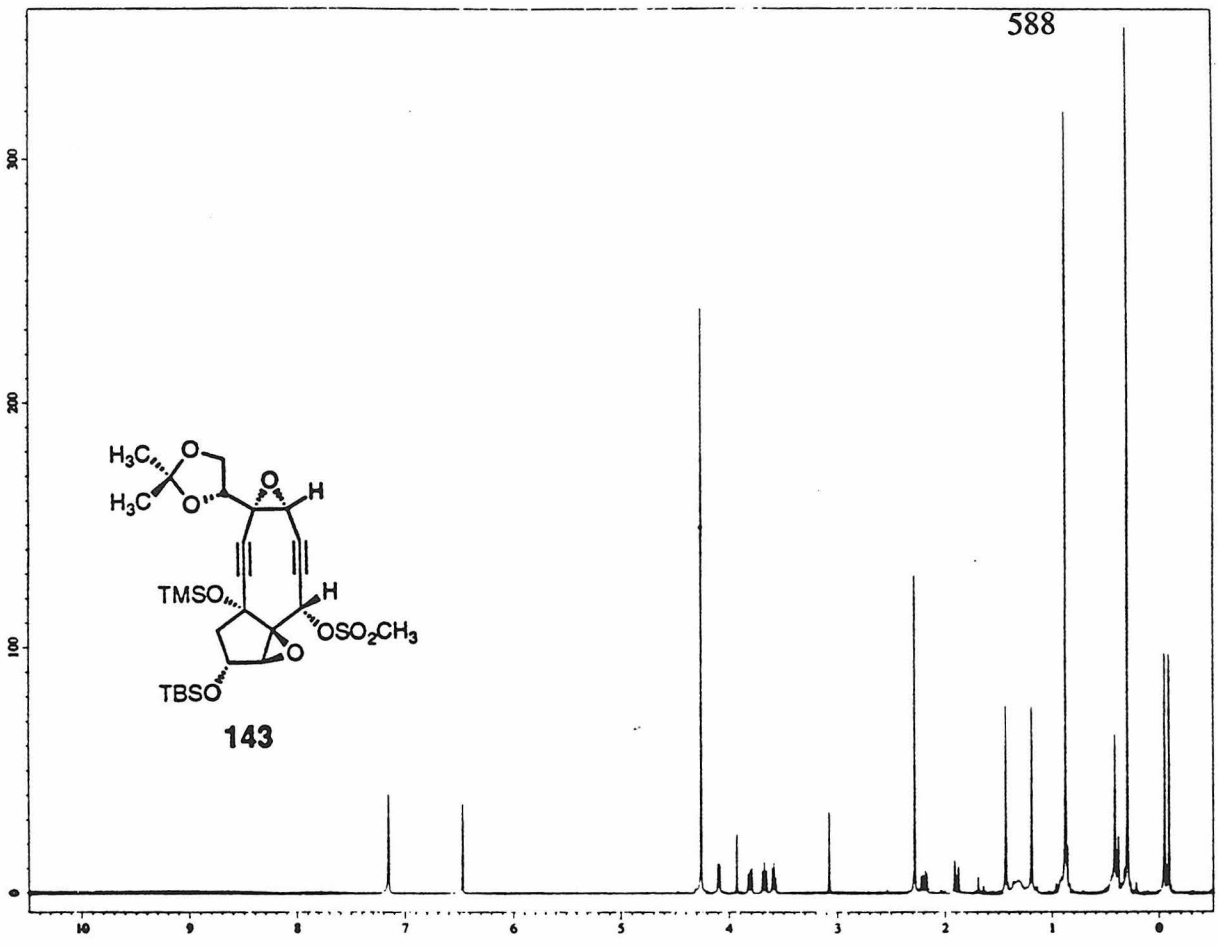

H3C
O
H3C
O
O
H
TMSO
H
OH
O
TBSO
139
30
20
10
0
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20

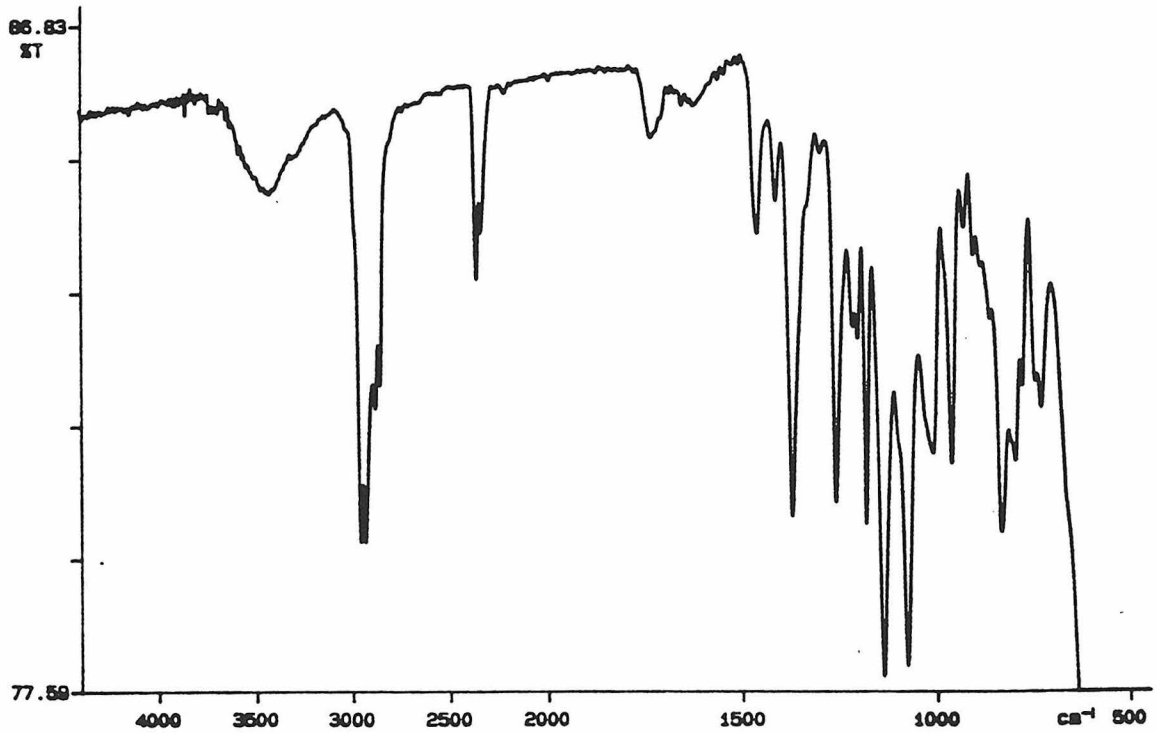

88.48
%T
78.87
4000
3500
3000
2500
2000
1500
1000
cm-1
500


H
H
OH
O
HO
TBSO
O
O
H3C
H3C
140

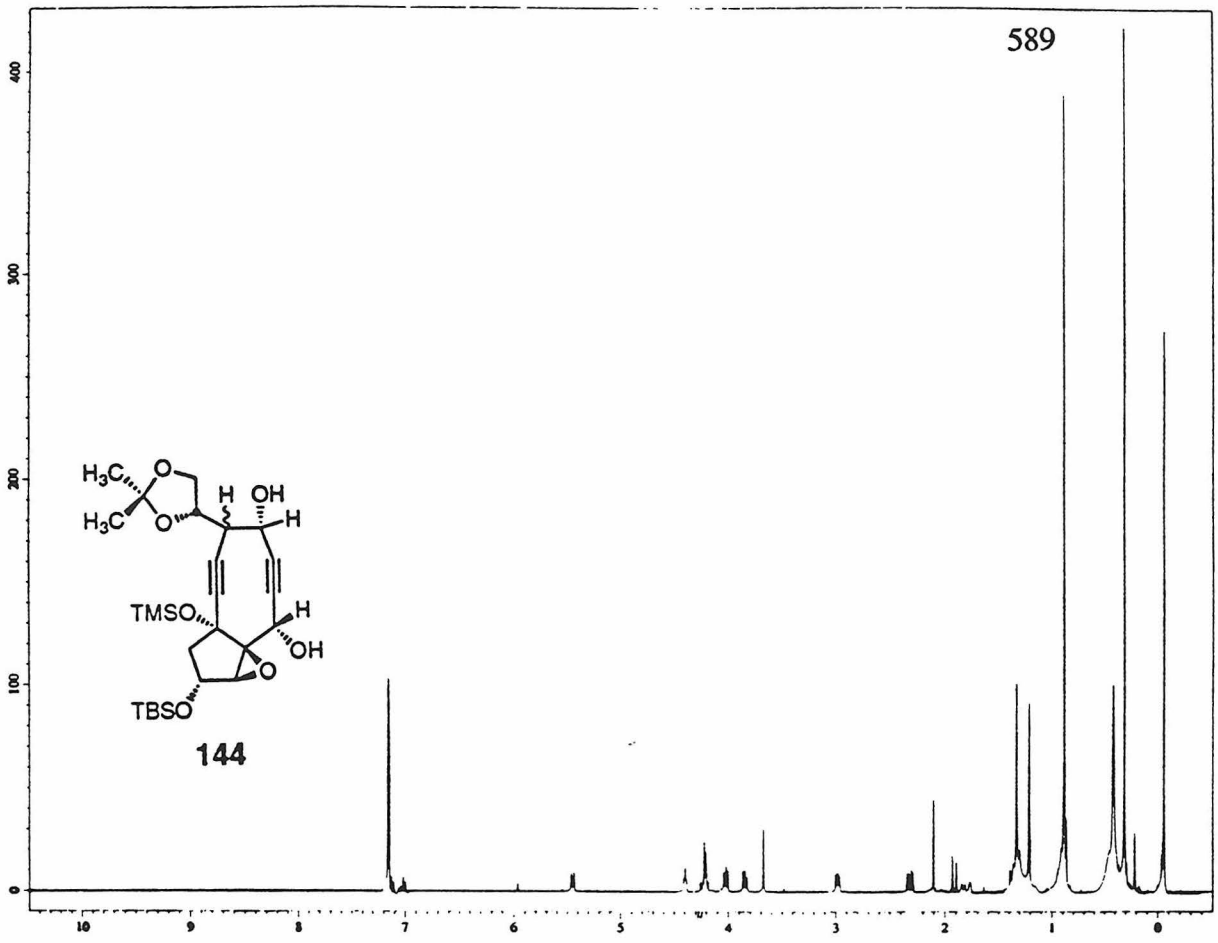

141

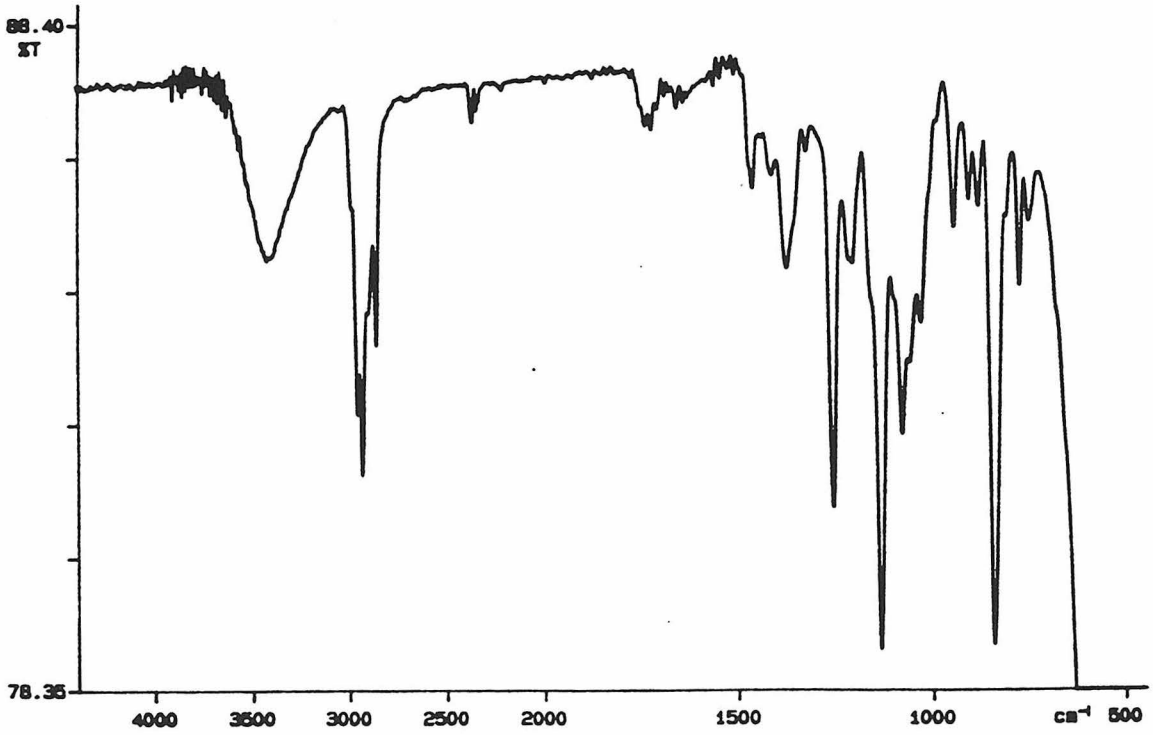

142

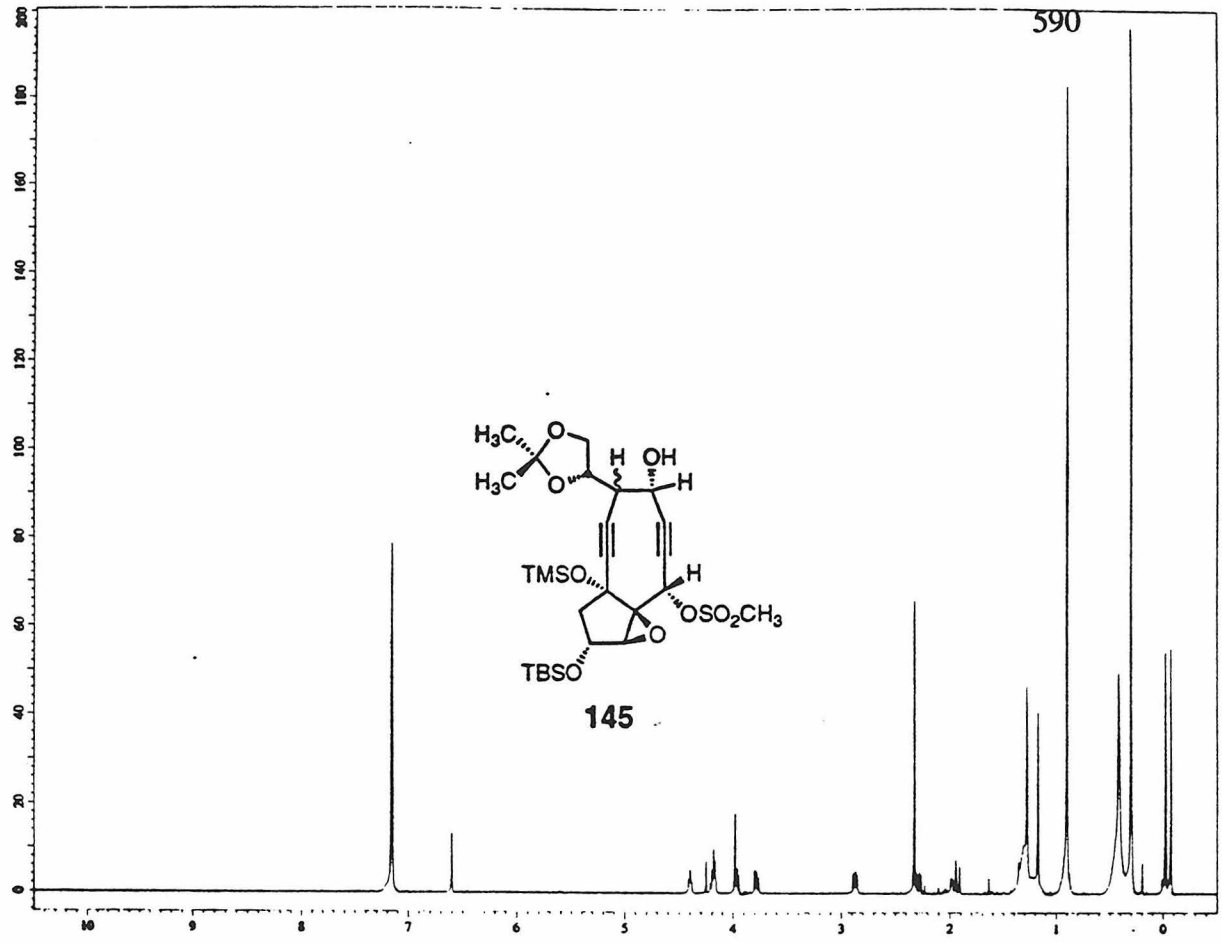

H3C
O
H3C
O
O
H
TMSO
H
OSO2CH3
O
TBSO
143
300
200
100
0
10
9
8
7
6
5
4
3
2
1
0


86.83
%T
77.59
4000
3500
3000
2500
2000
1500
1000
cm-1
500

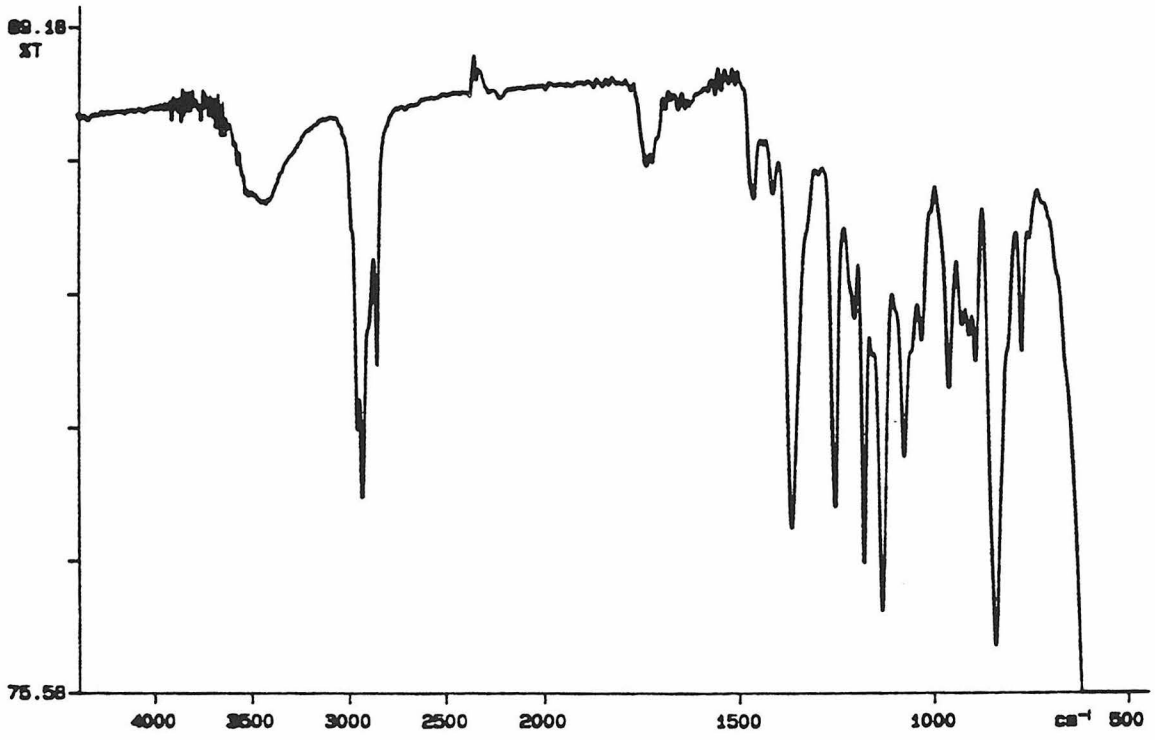
589

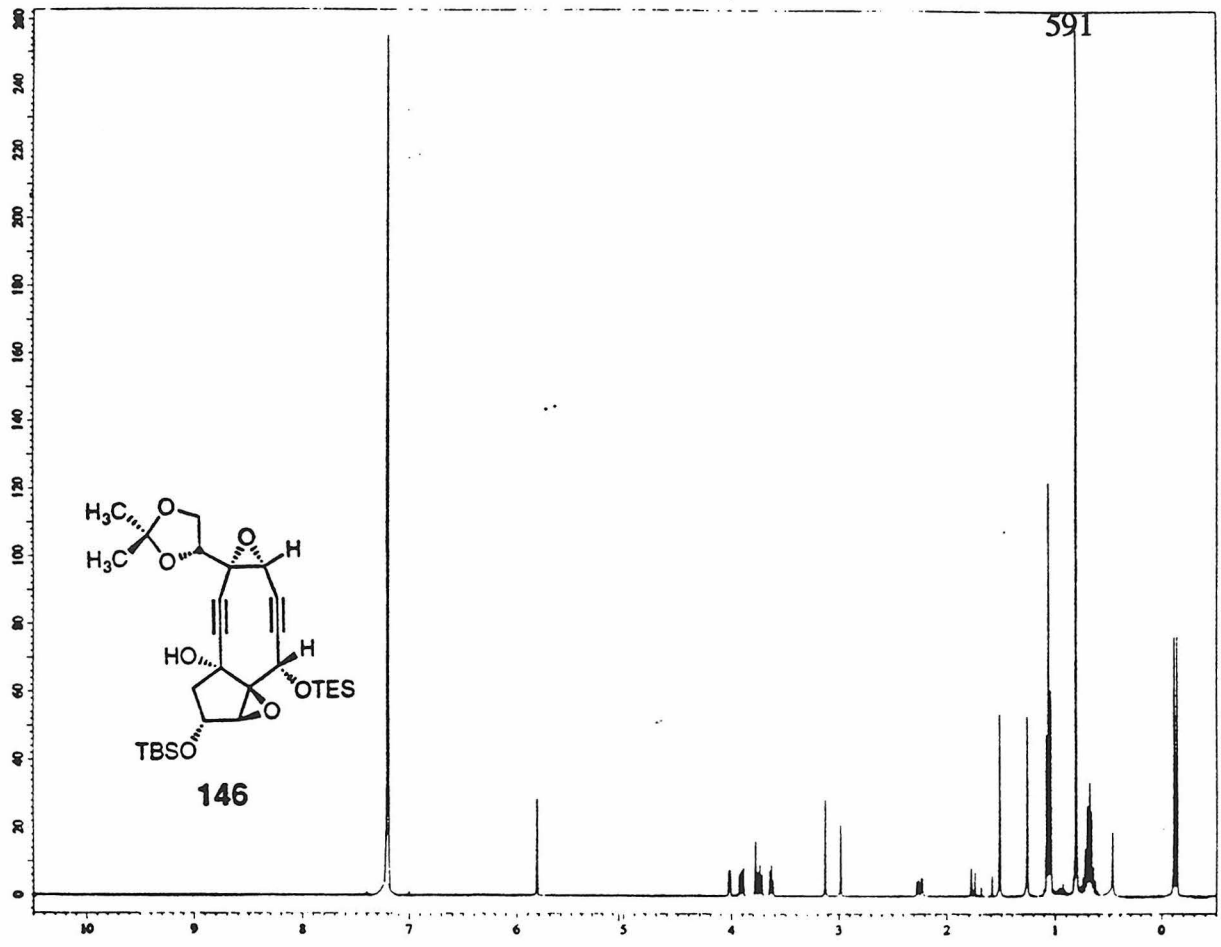

H3C
O
H3C
O
H
OH
H
TMSO
H
OH
O
TBSO
144


88.40
%T
78.35
4000
3500
3000
2500
2000
1500
1000
cm-1
500

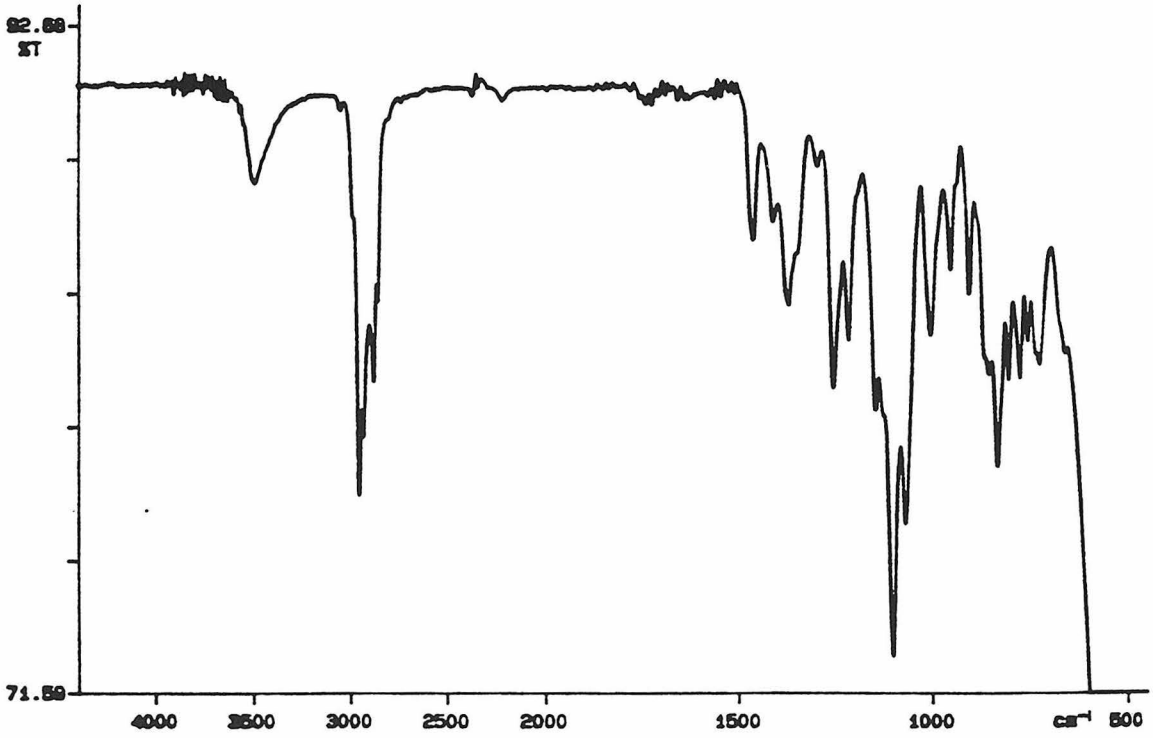

H3C
O
H
OH
H3C
O
H
TMSO
H
OSO2CH3
O
TBSO

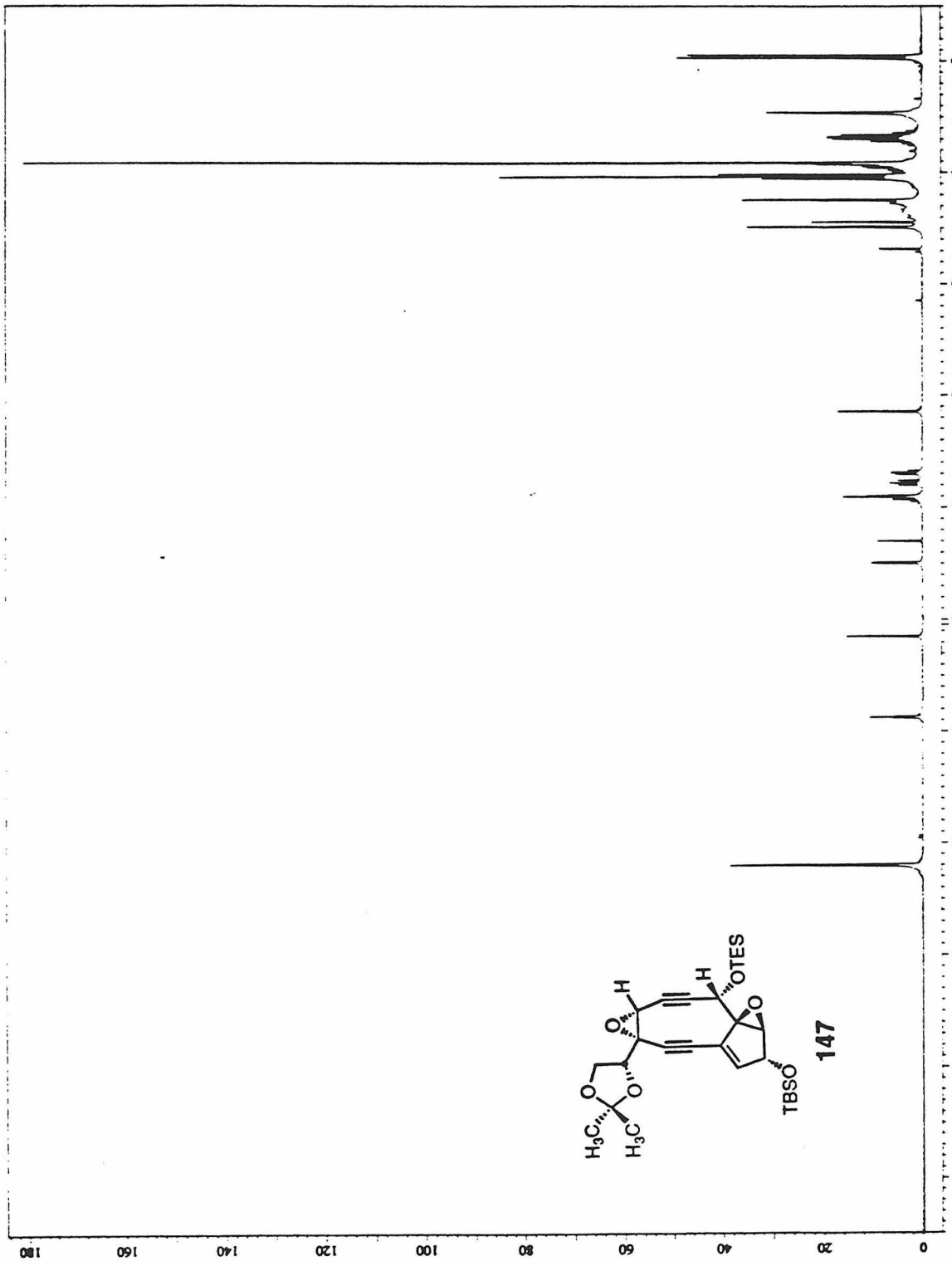
145

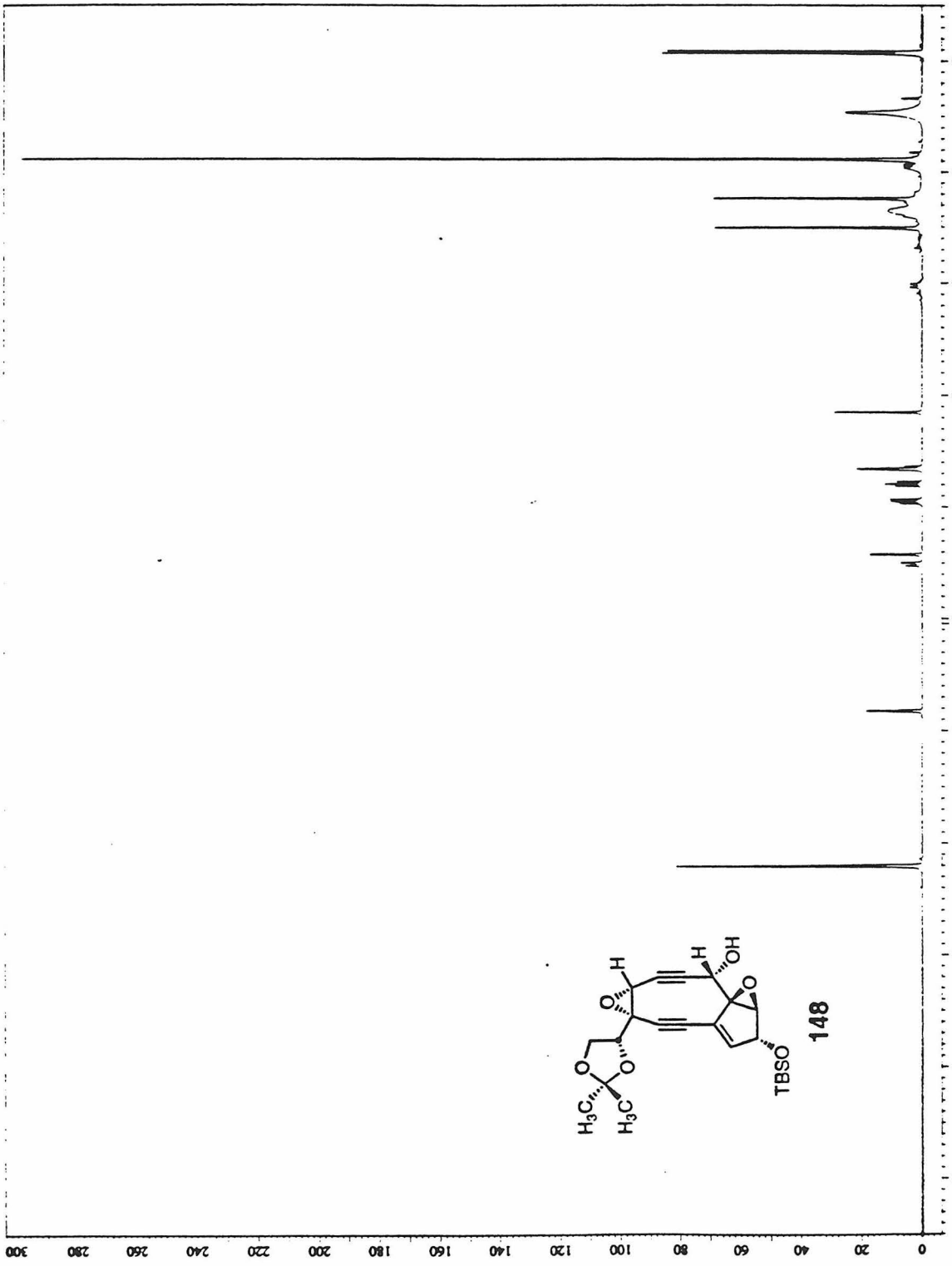

89.18
%T
75.58
4000
3500
3000
2500
2000
1500
1000
cm-1
500

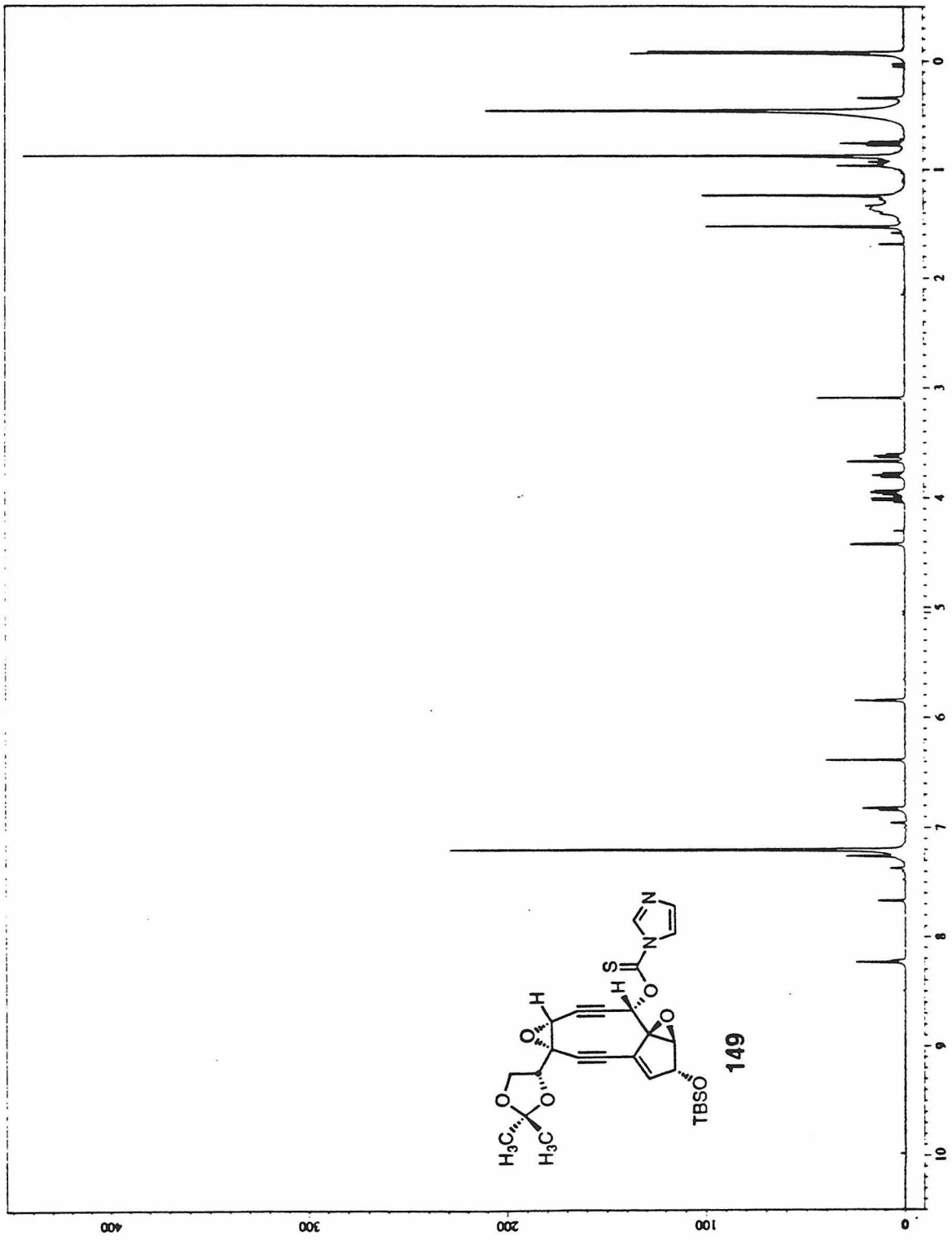

H3C
O
H3C
O
O
H
HO
H
OTES
O
TBSO

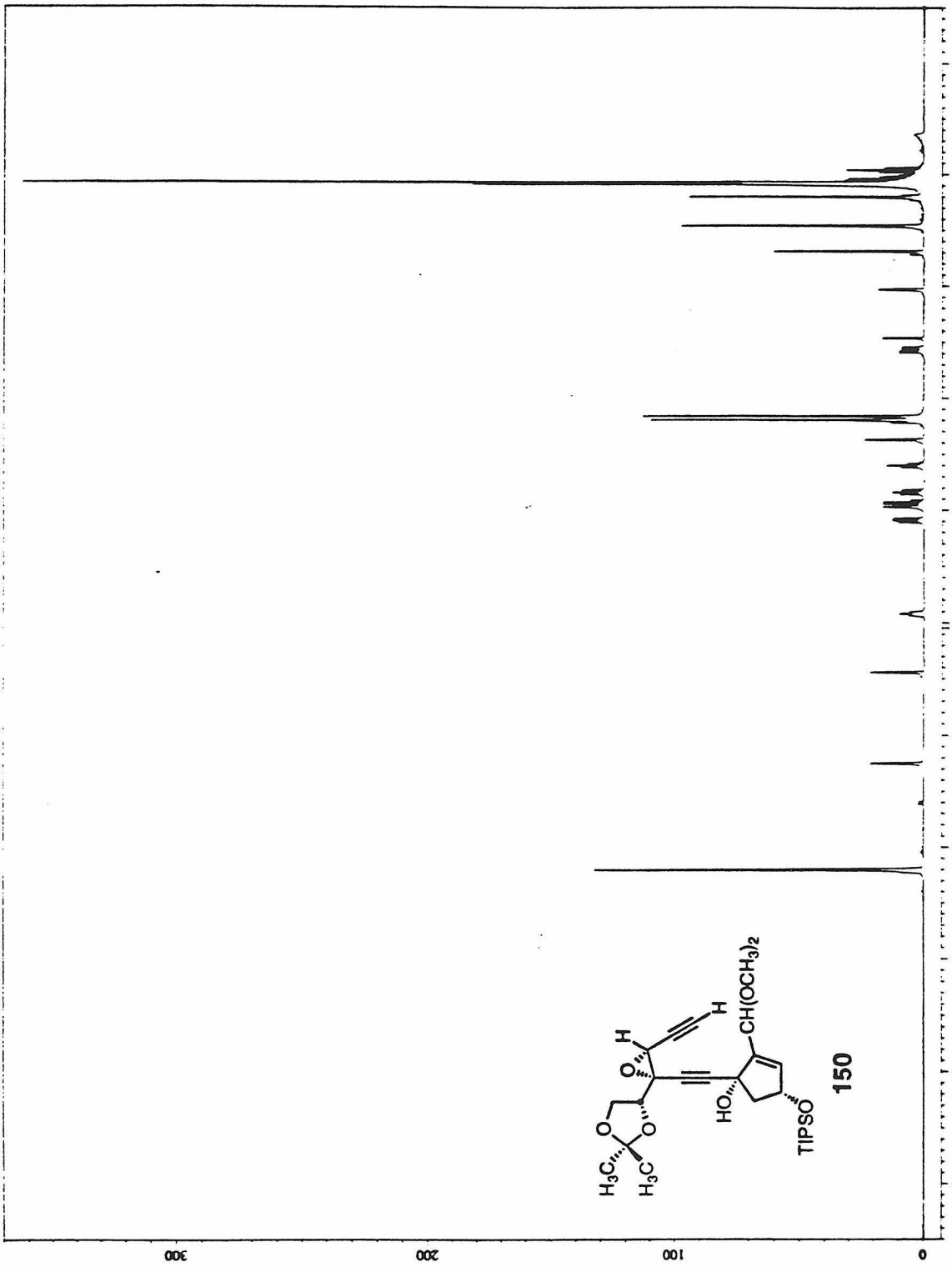
146

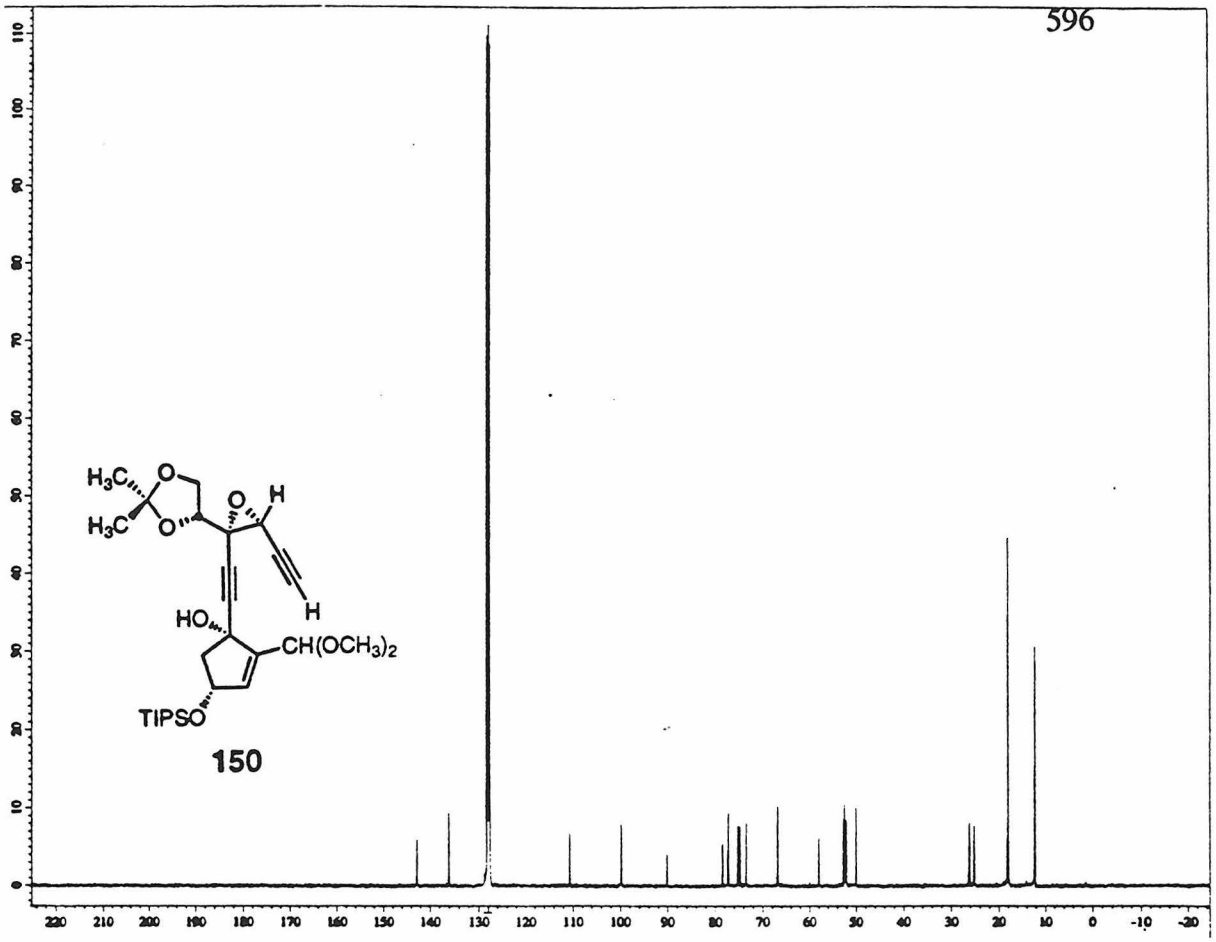

92.68
%T
71.59
4000
3500
3000
2500
2000
1500
1000
cm-1
500


H
H
OTES
O
O
O
O
H3C
H3C
TBSO
147

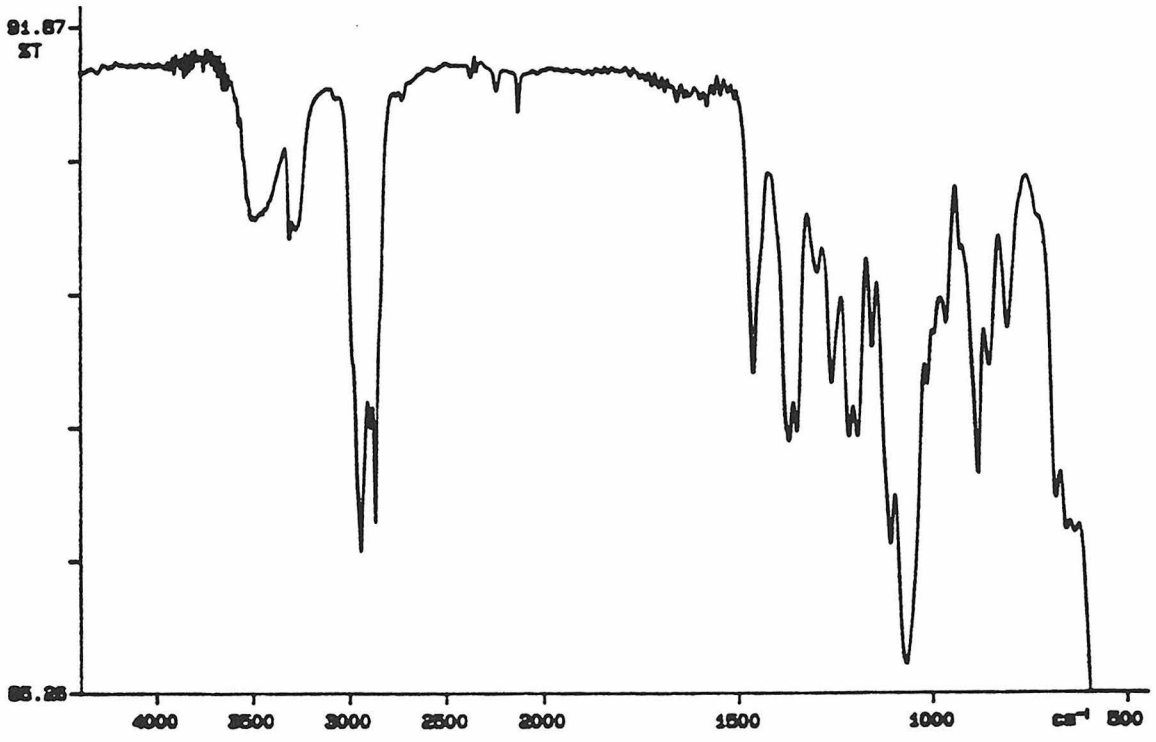

H
H
OH
O
O
O
O
H3C
H3C
TBSO
148

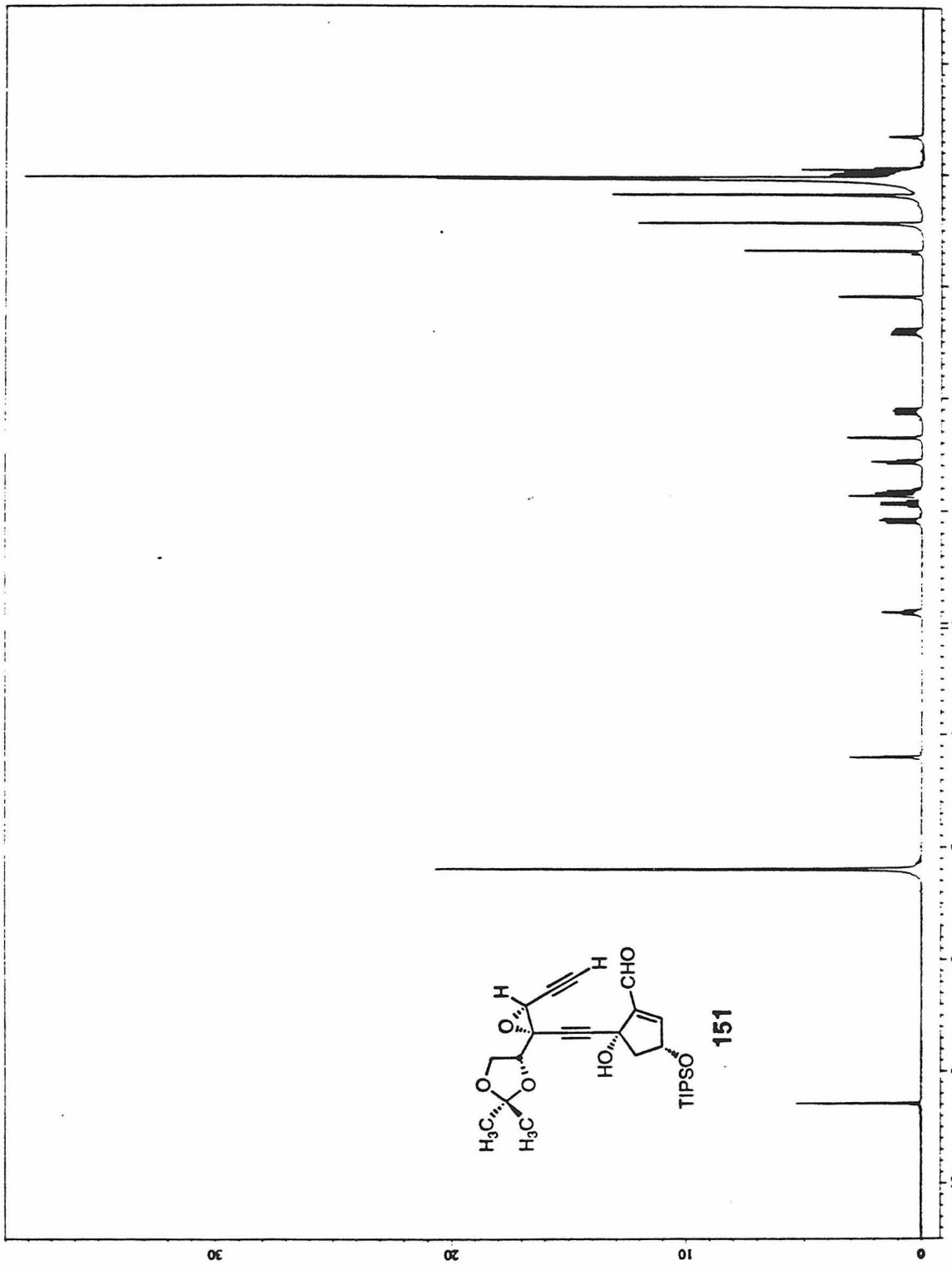

149
TBSO
H3C
H3C

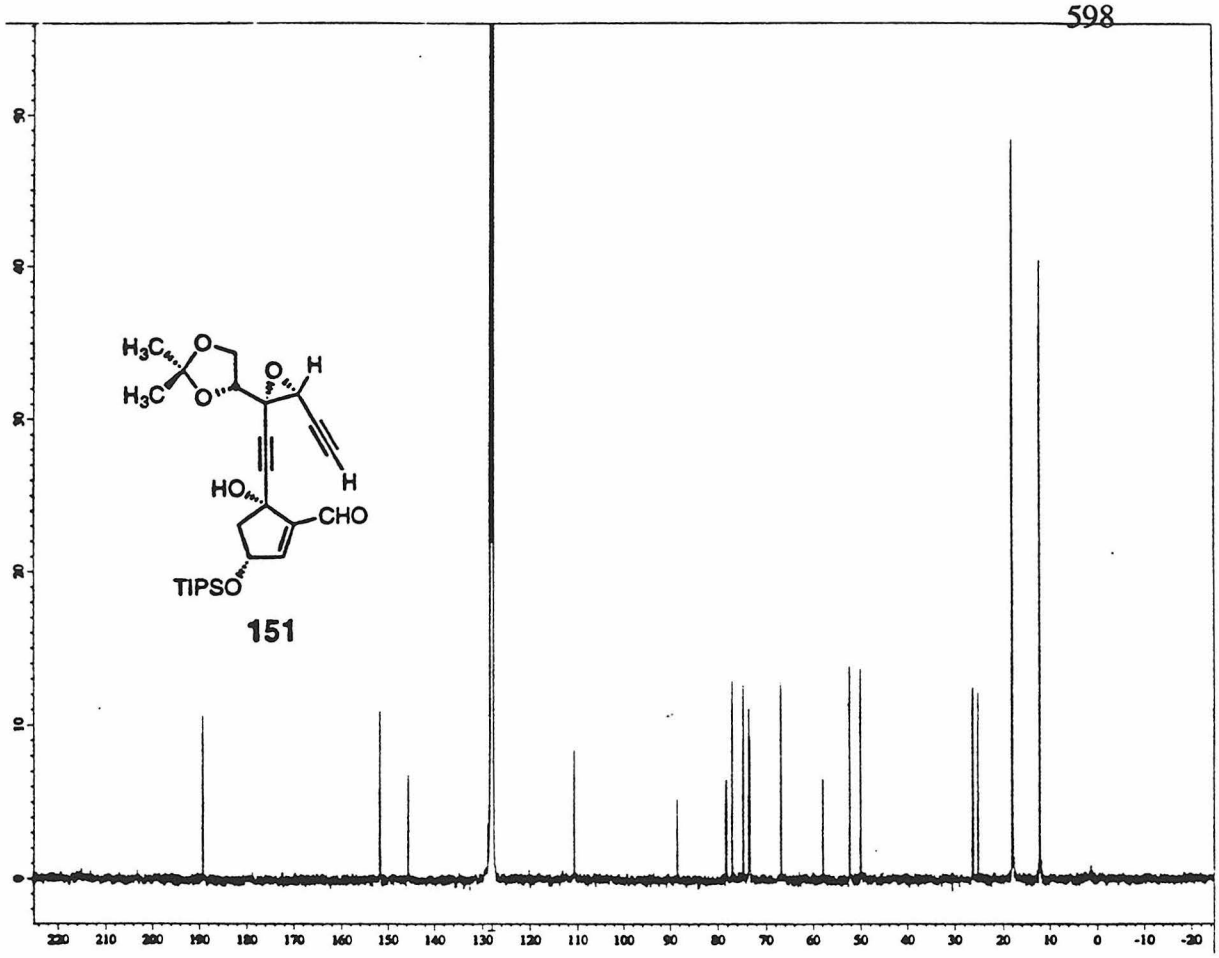

H
O
H
CH(OCH3)2
HO
TIPSO
150
H3C
H3C
O
O
0
100
200
300
1
2
3
4
5
6
7
8
9
10


H3C
O
H3C
O
O
H
HO
H
CH(OCH3)2
TIPSO

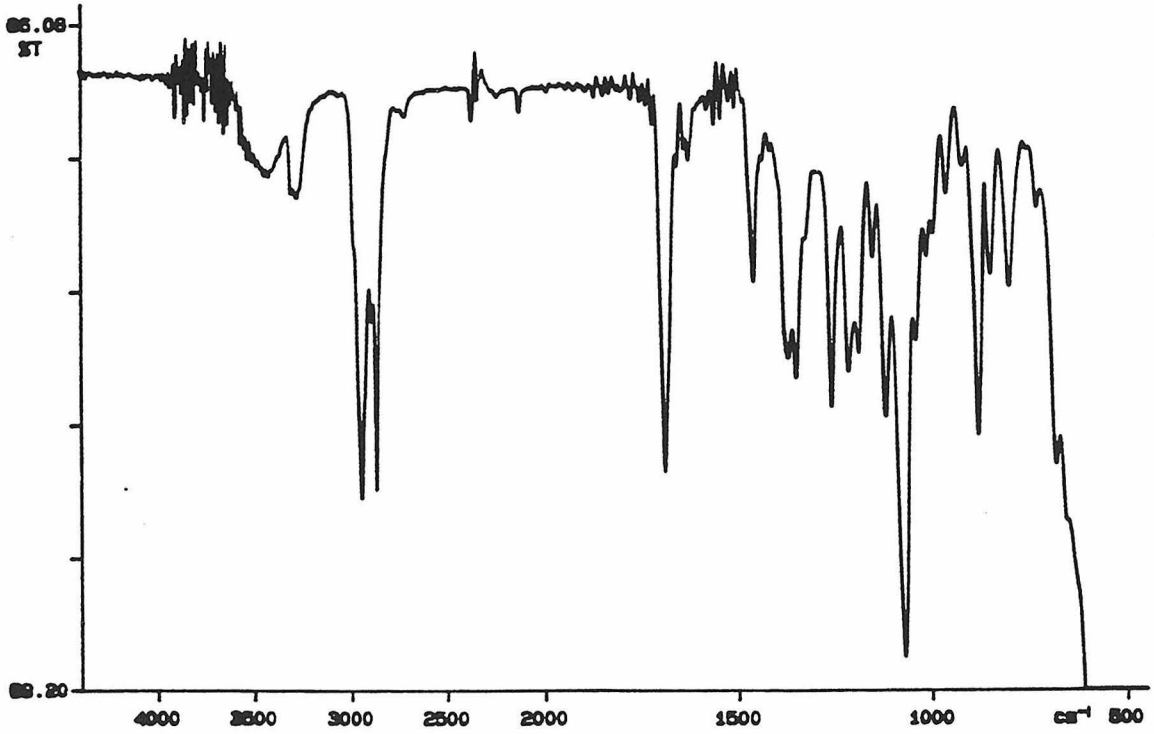
150

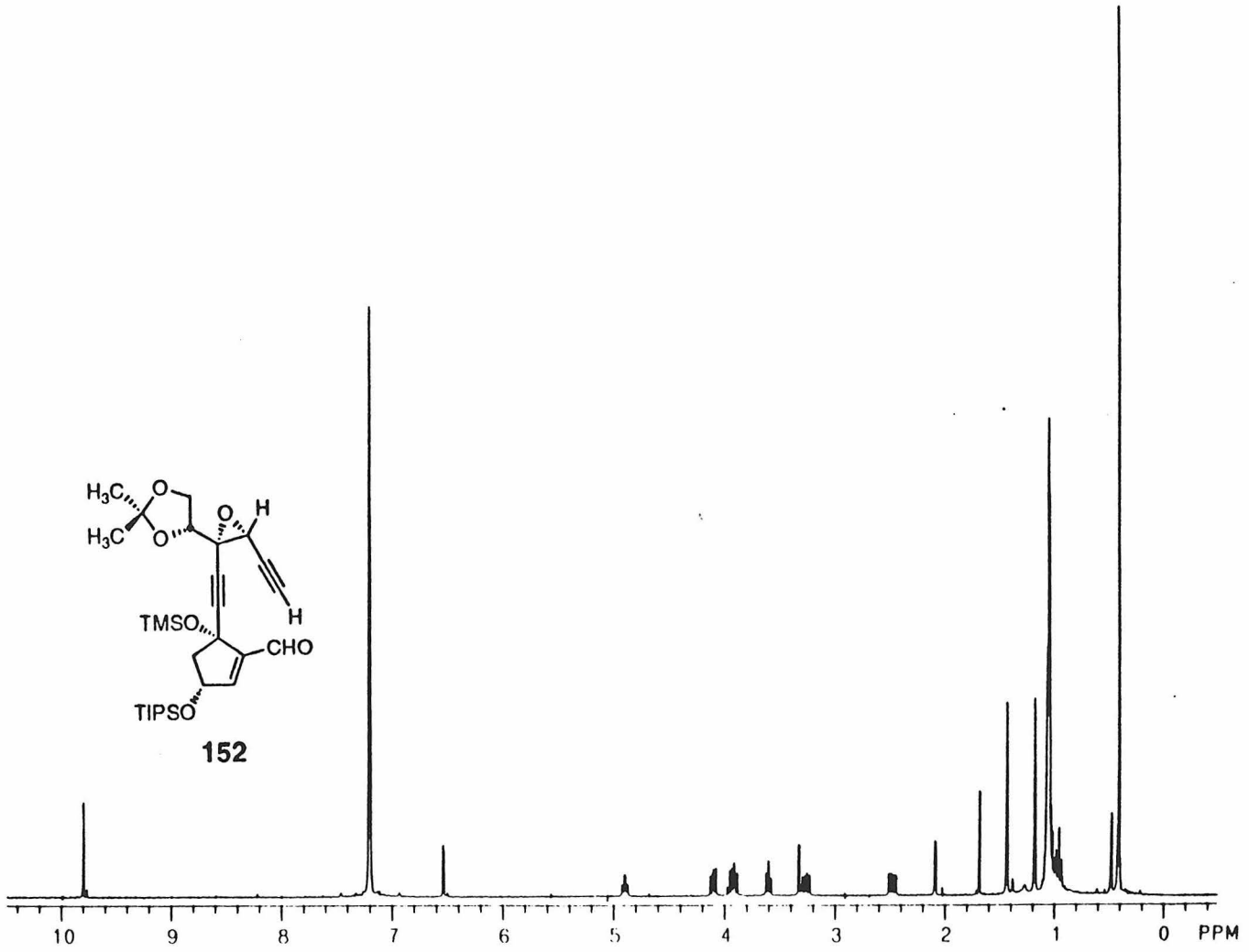

91.67
%T
85.28
4000
3500
3000
2500
2000
1500
1000
cm-1
500


H
O
O
O
H3C
H3C
CHO
HO
TIPSO
151

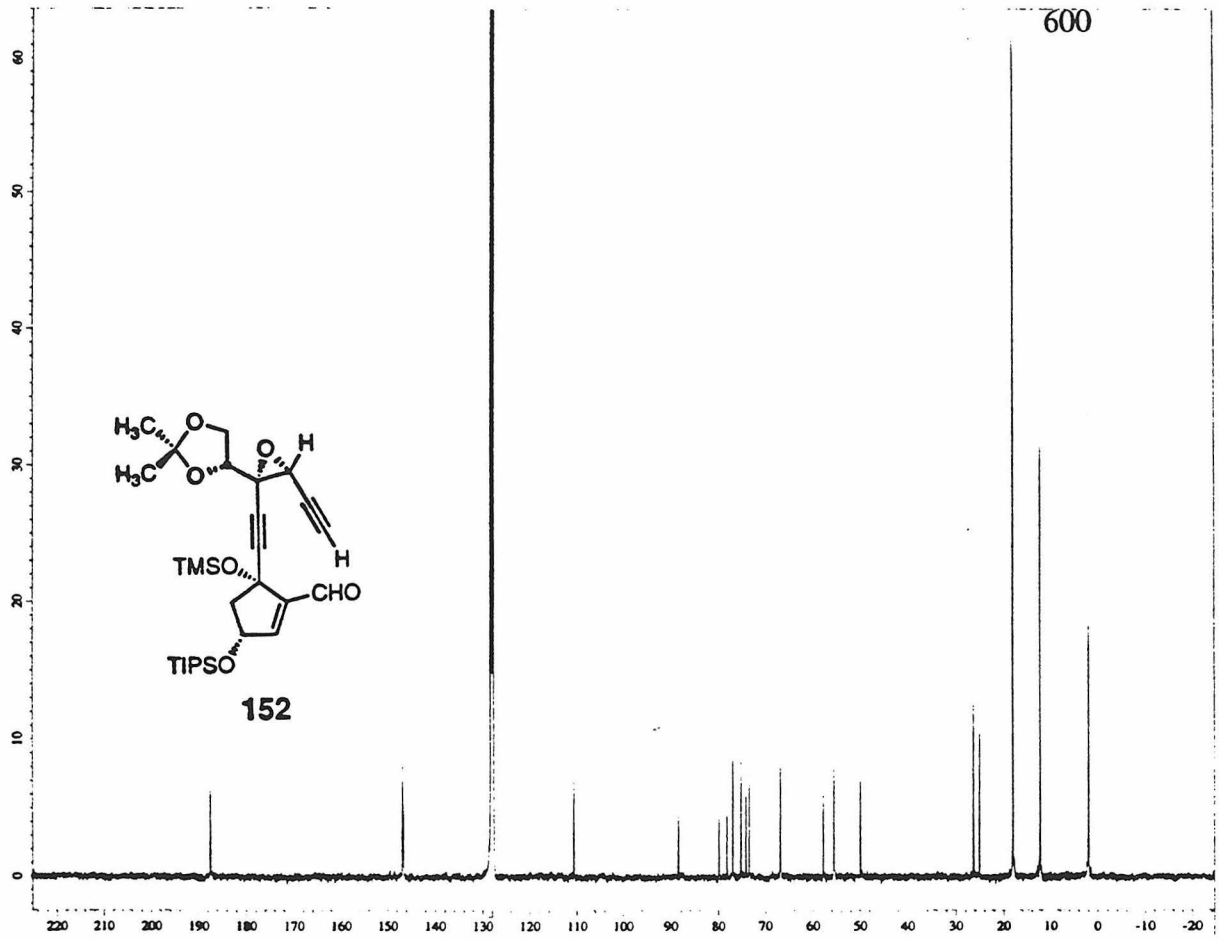

H3C
O
H3C
O
O
H
H
HO
CHO
TIPSO

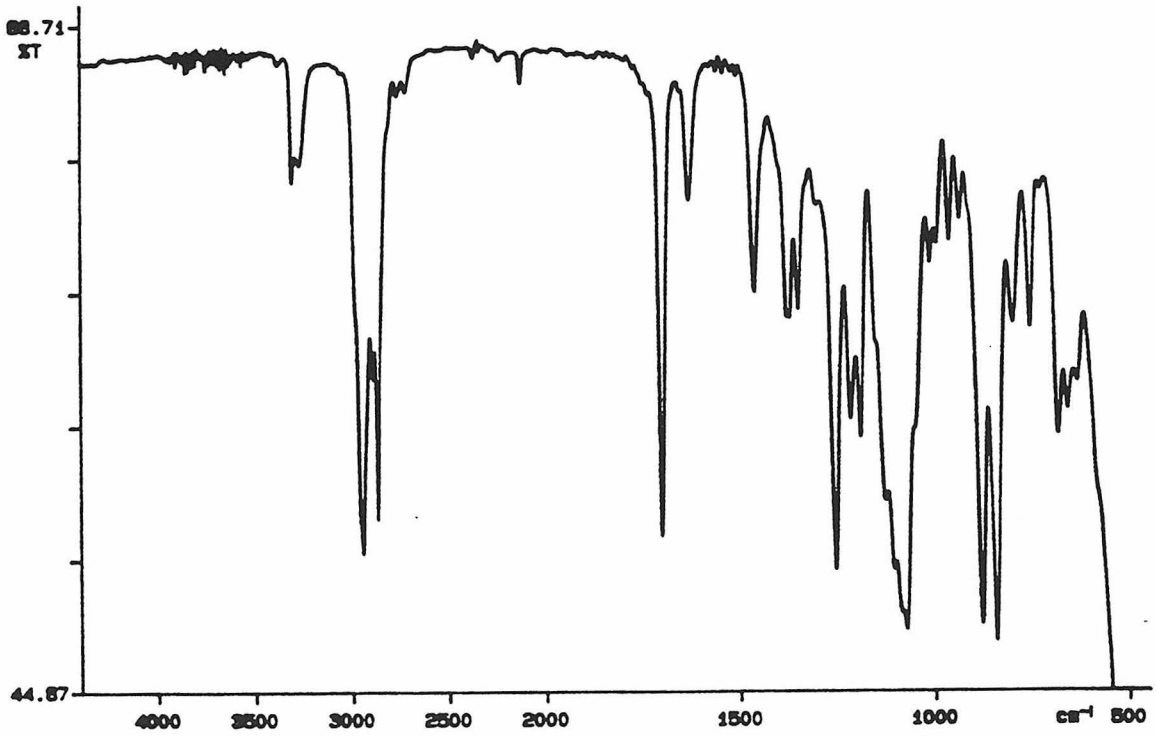
151

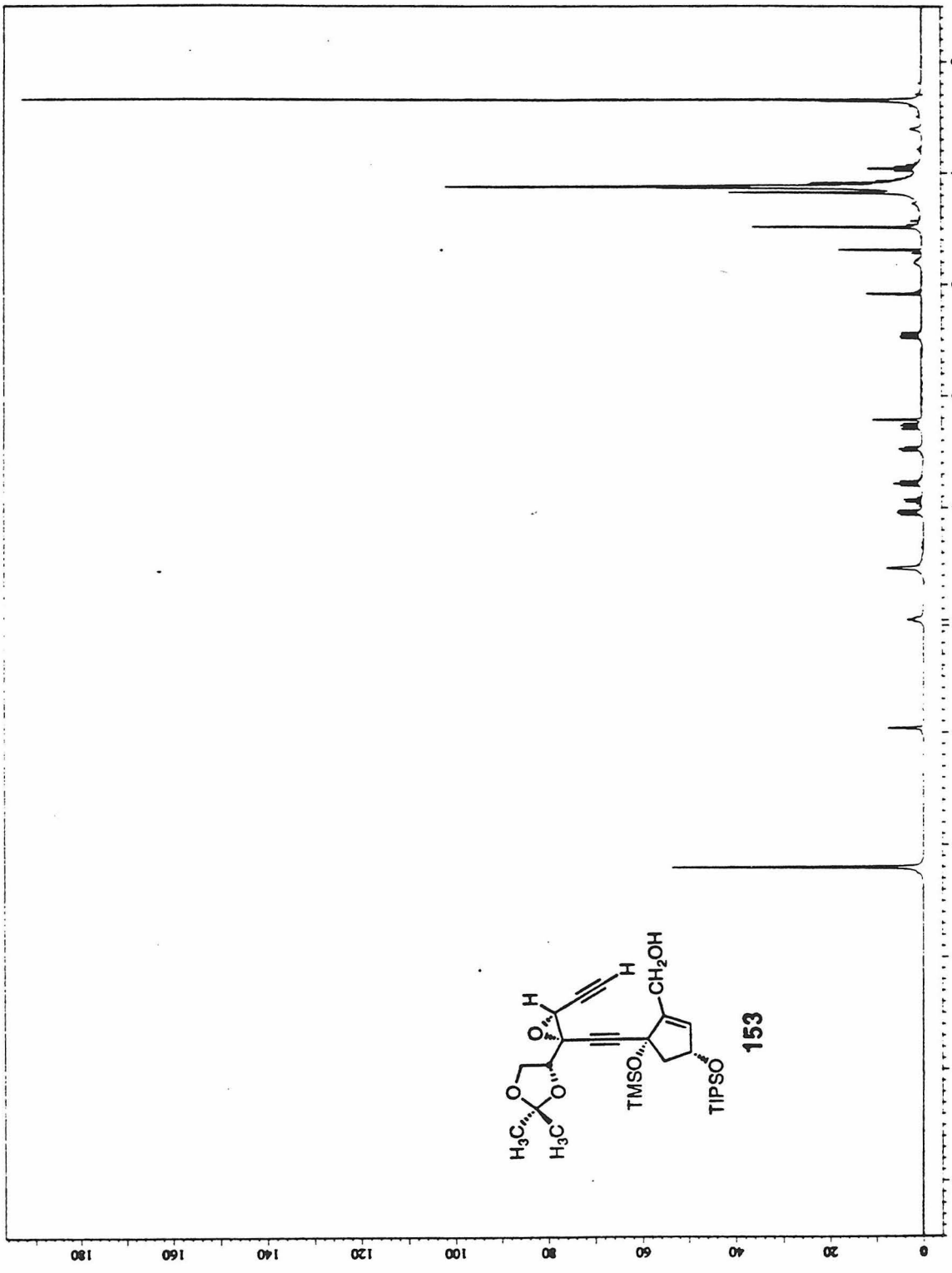

86.08
%T
89.20
4000
3500
3000
2500
2000
1500
1000
cm-1
500



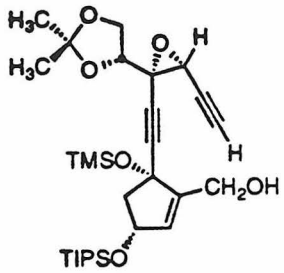
152


600
H3C
O
O
H
H3C
O
H
TMSO
CHO
TIPSO
152
60
50
40
30
20
10
0
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20

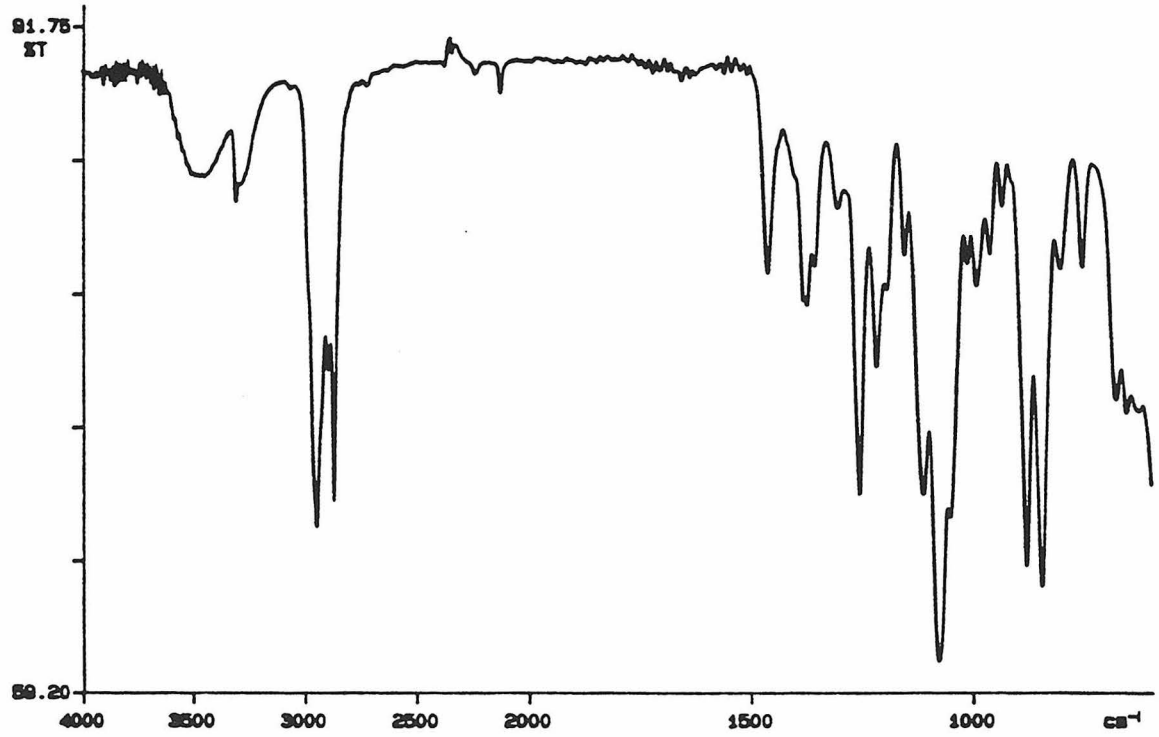

88.71
%T
44.67
4000
3500
3000
2500
2000
1500
1000
cm-1
500

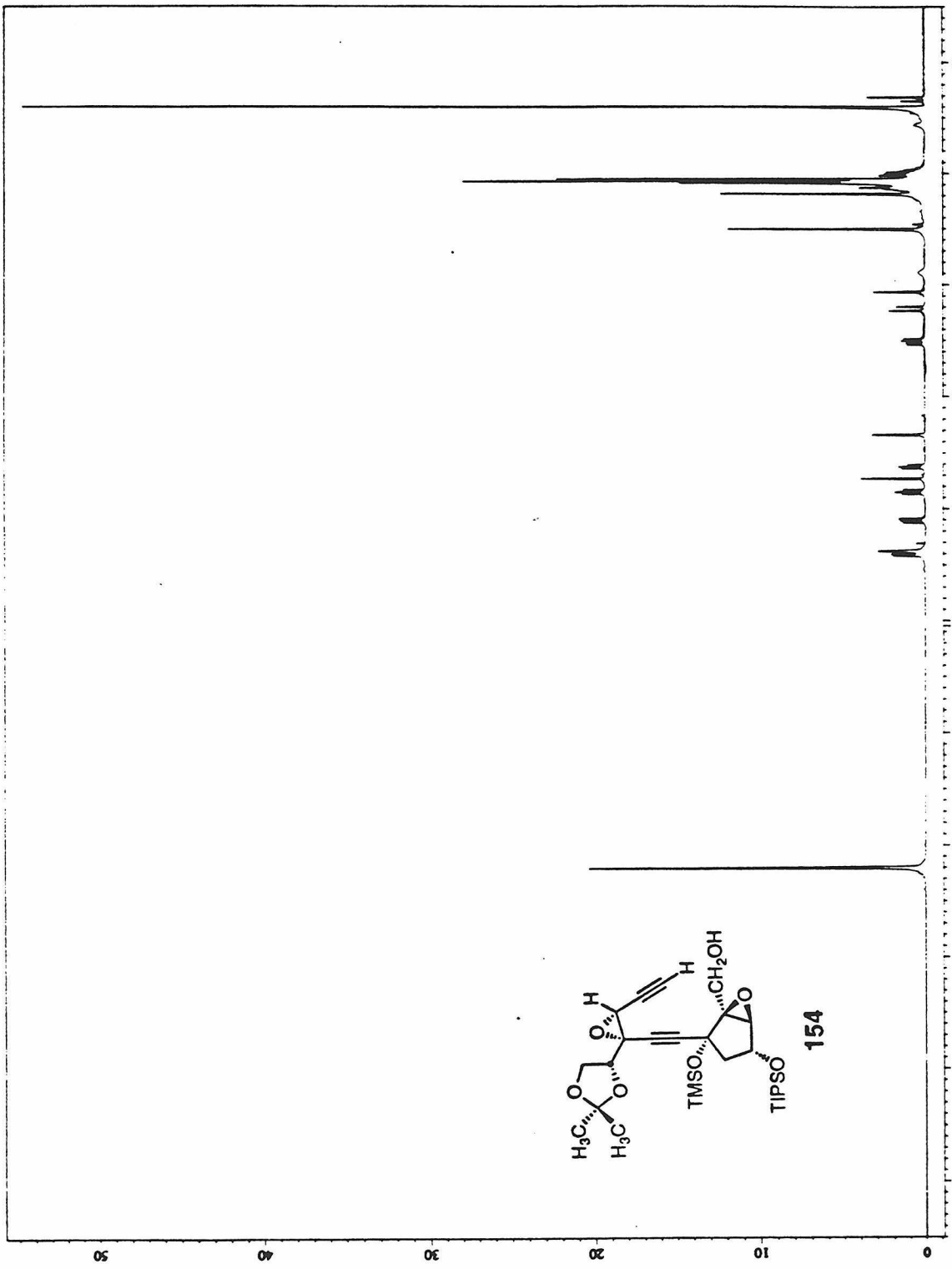

H
O
O
O
H3C
H3C
CH2OH
TMSO
TIPSO
153

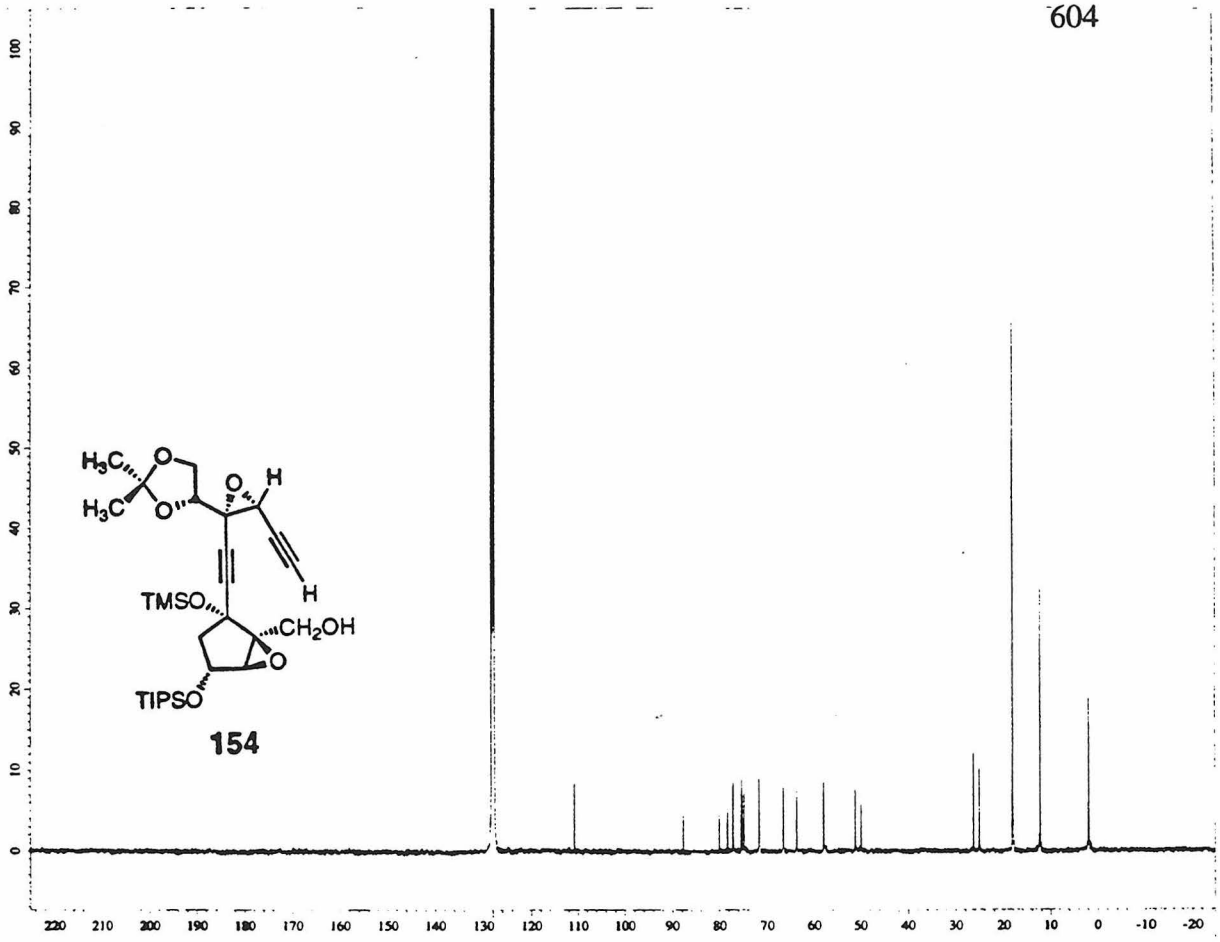
602


H3C
O
H3C
O
O
H
TMSO
H
CH2OH
TIPSO

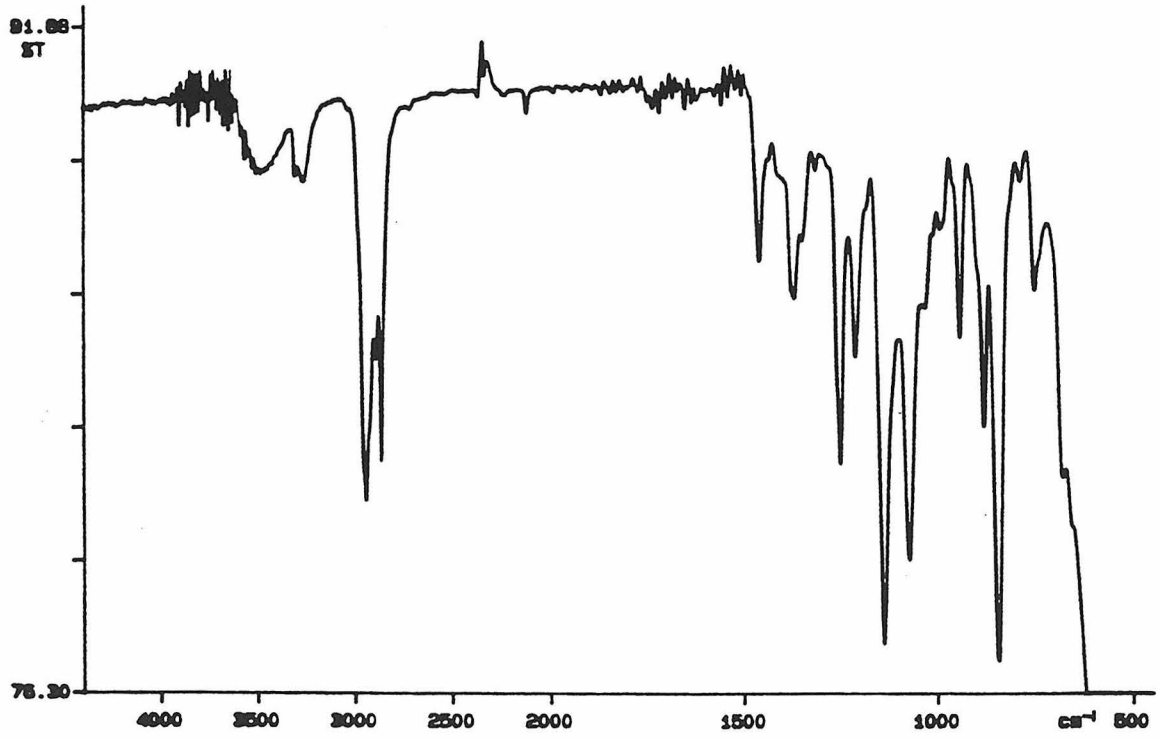
153

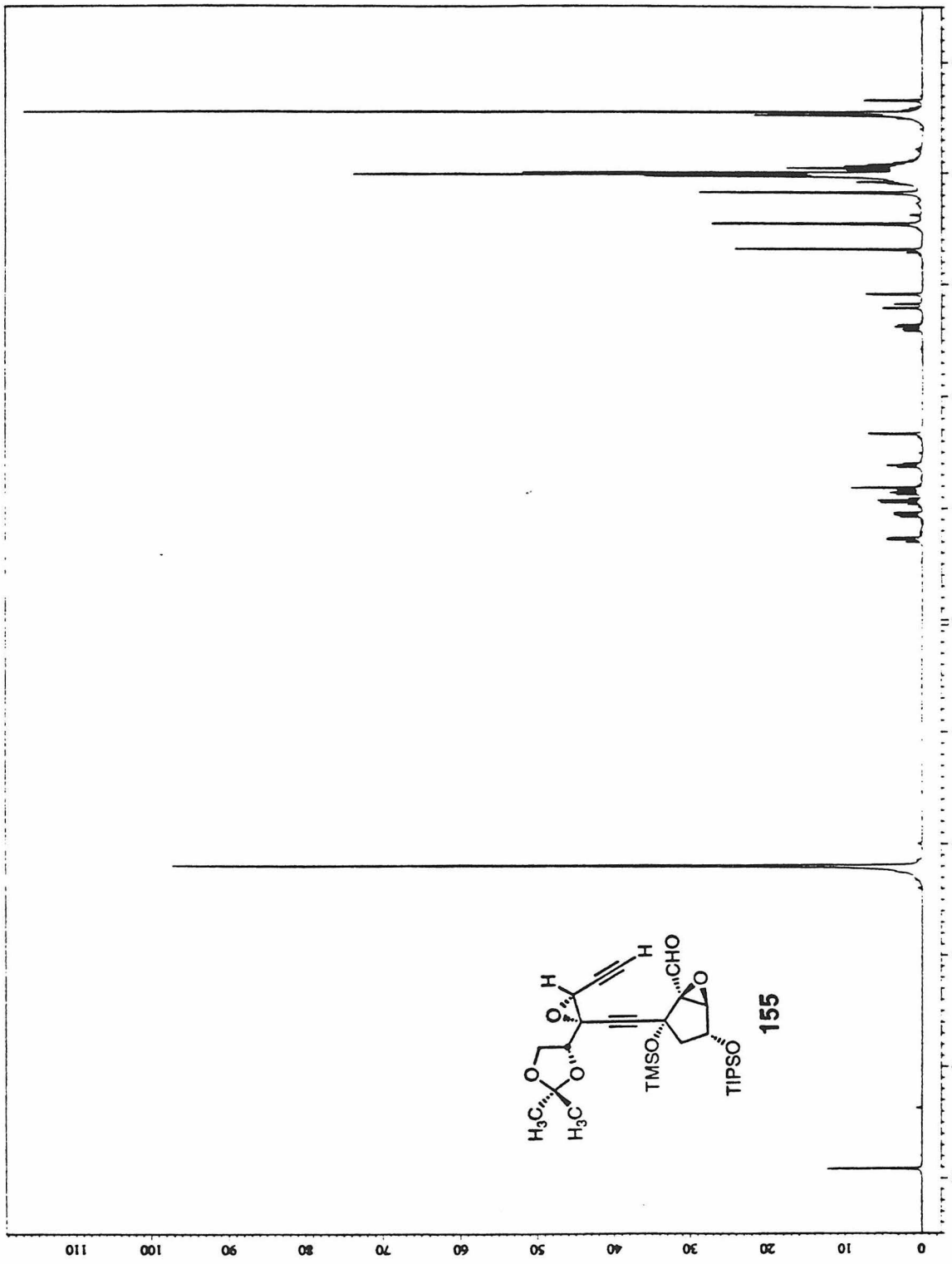

91.75
%T
59.20
4000
3500
3000
2500
2000
1500
1000
cm-1

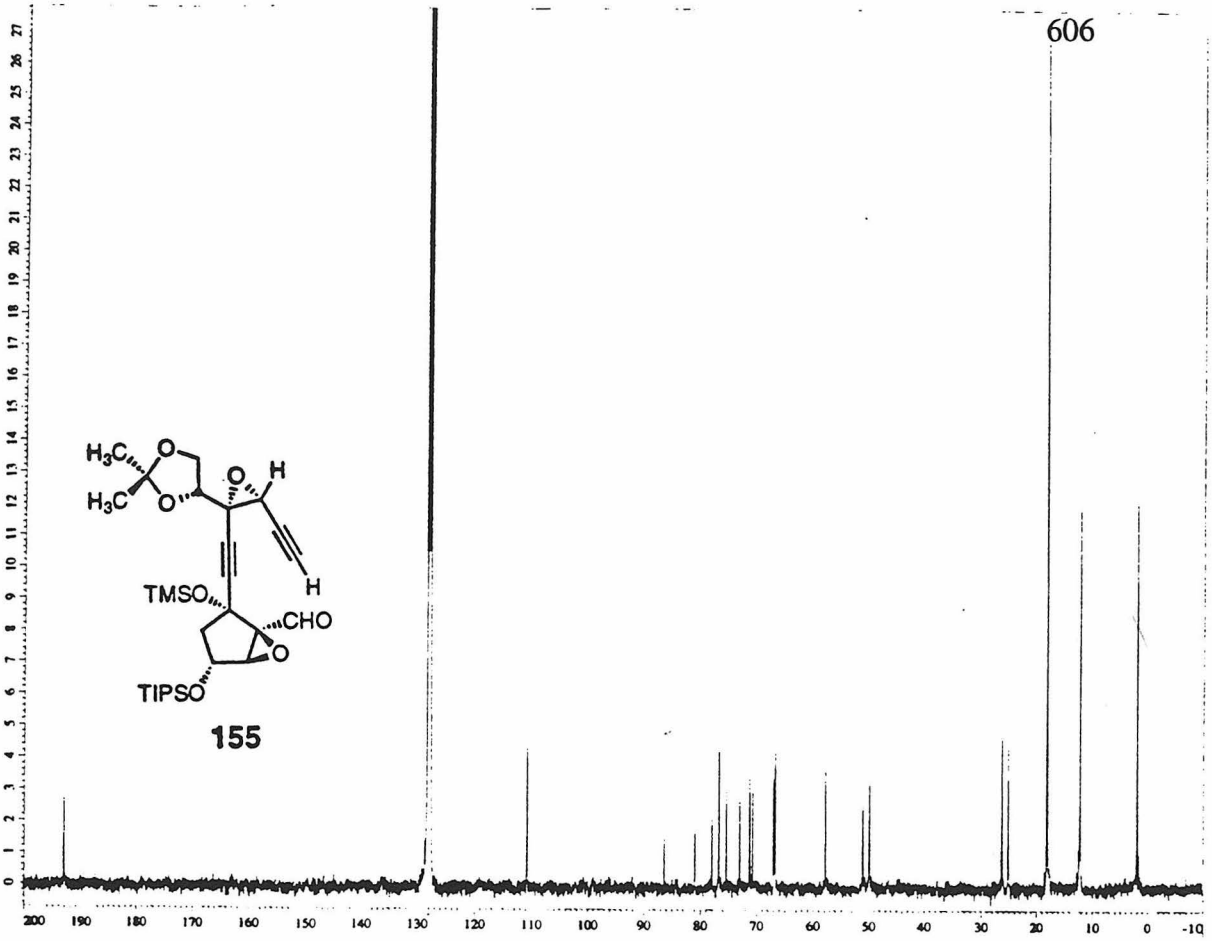

H
O
CH2OH
O
TMSO
TIPSO
H3C
H3C
O
O
154


H3C
O
H3C
O
O
H
H
TMSO
CH2OH
O
TIPSO

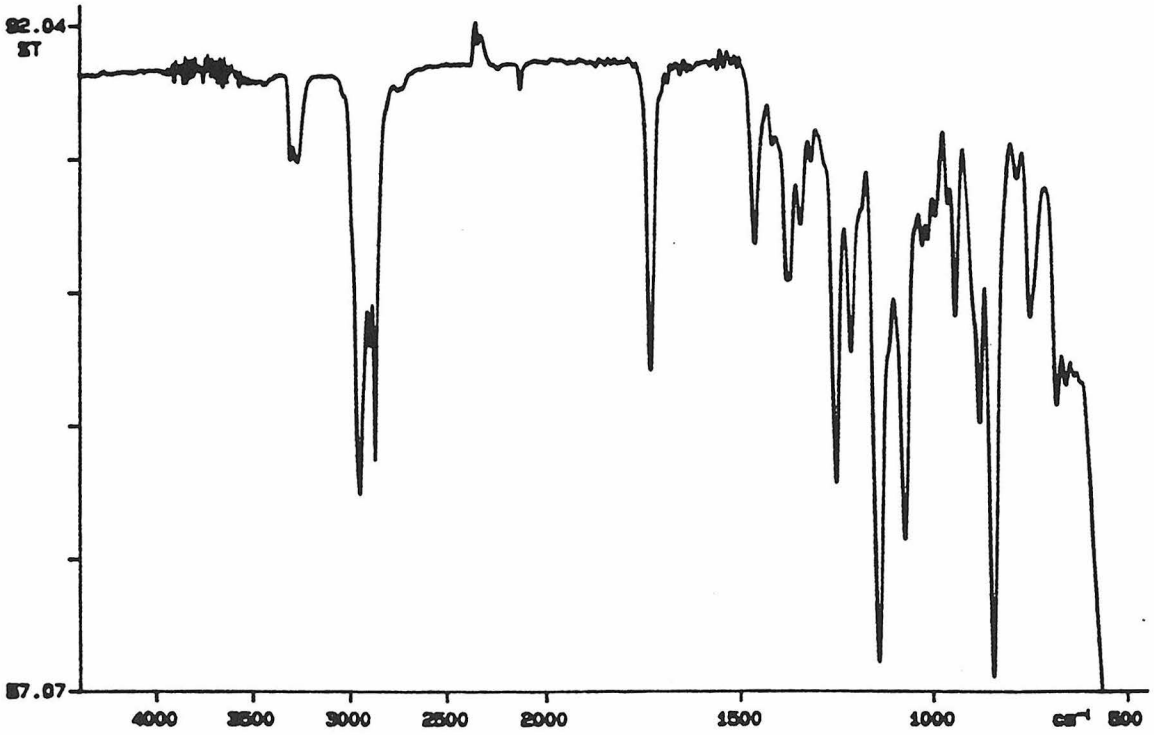
154

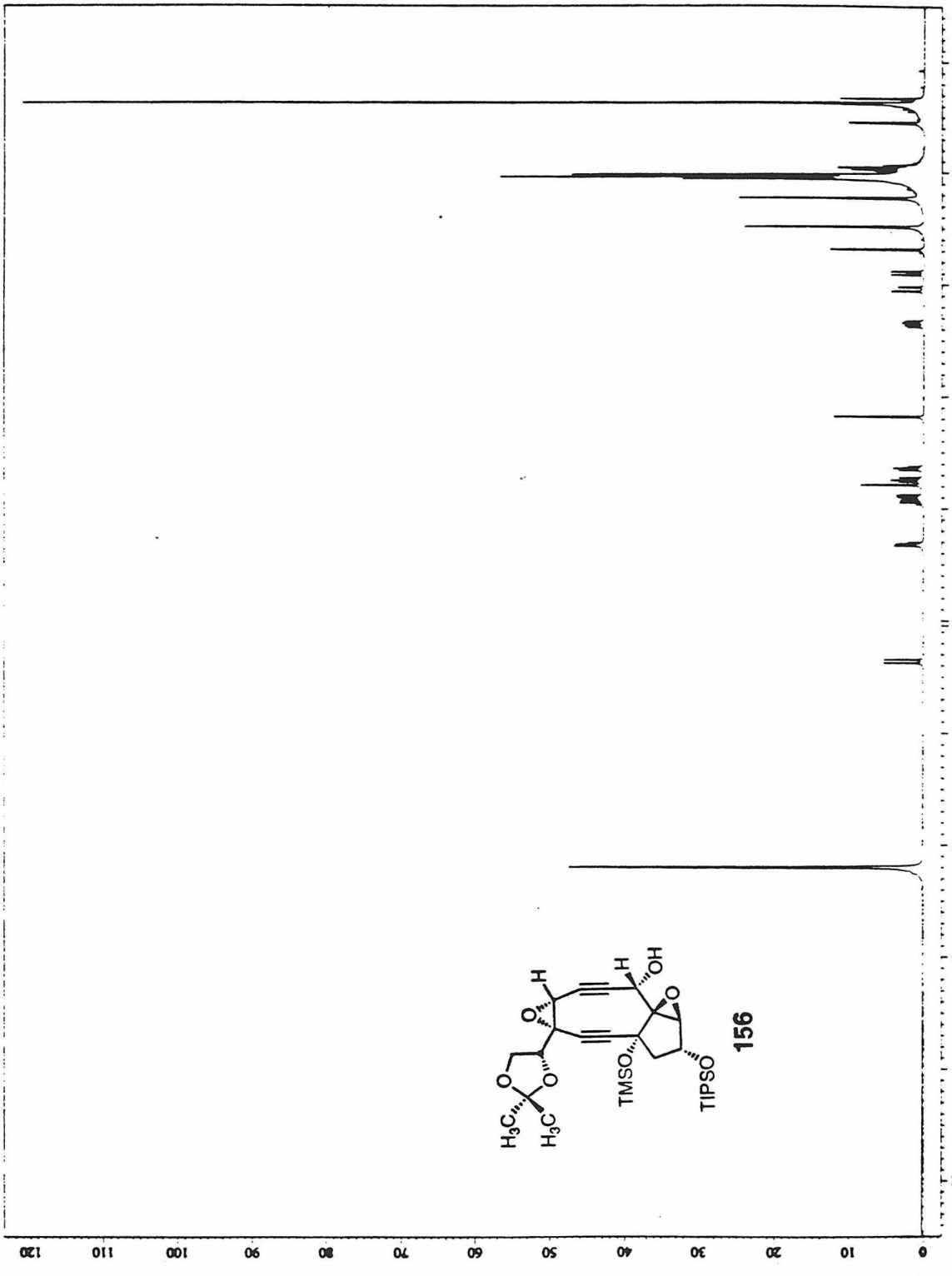

91.68
%T
76.30
4000
3500
3000
2500
2000
1500
1000
cm-1
500


H
O
H
CHO
O
TMSO
TIPSO
O
O
H3C
H3C
155

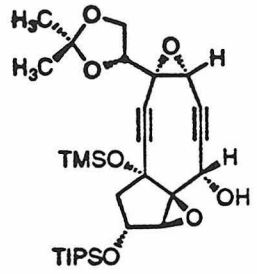

H3C
O
H3C
O
O
H
H
TMSO
CHO
O
TIPSO

155

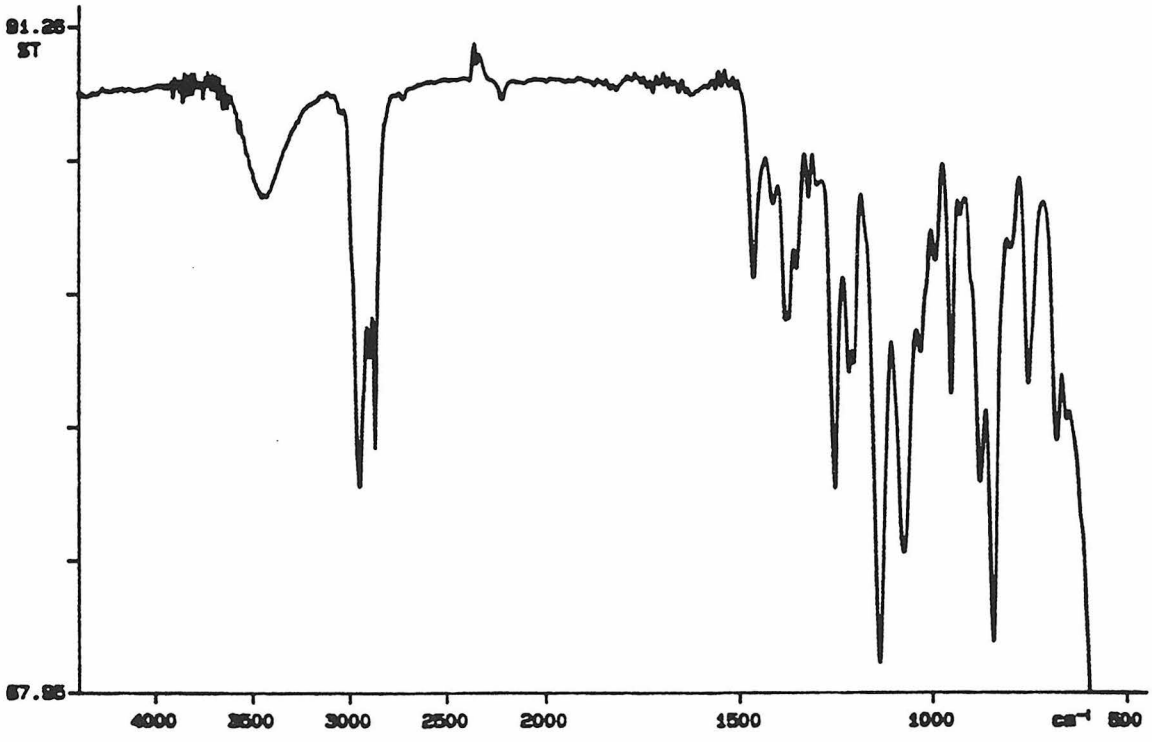

92.04
%T
87.07
4000
3500
3000
2500
2000
1500
1000
cm-1
500

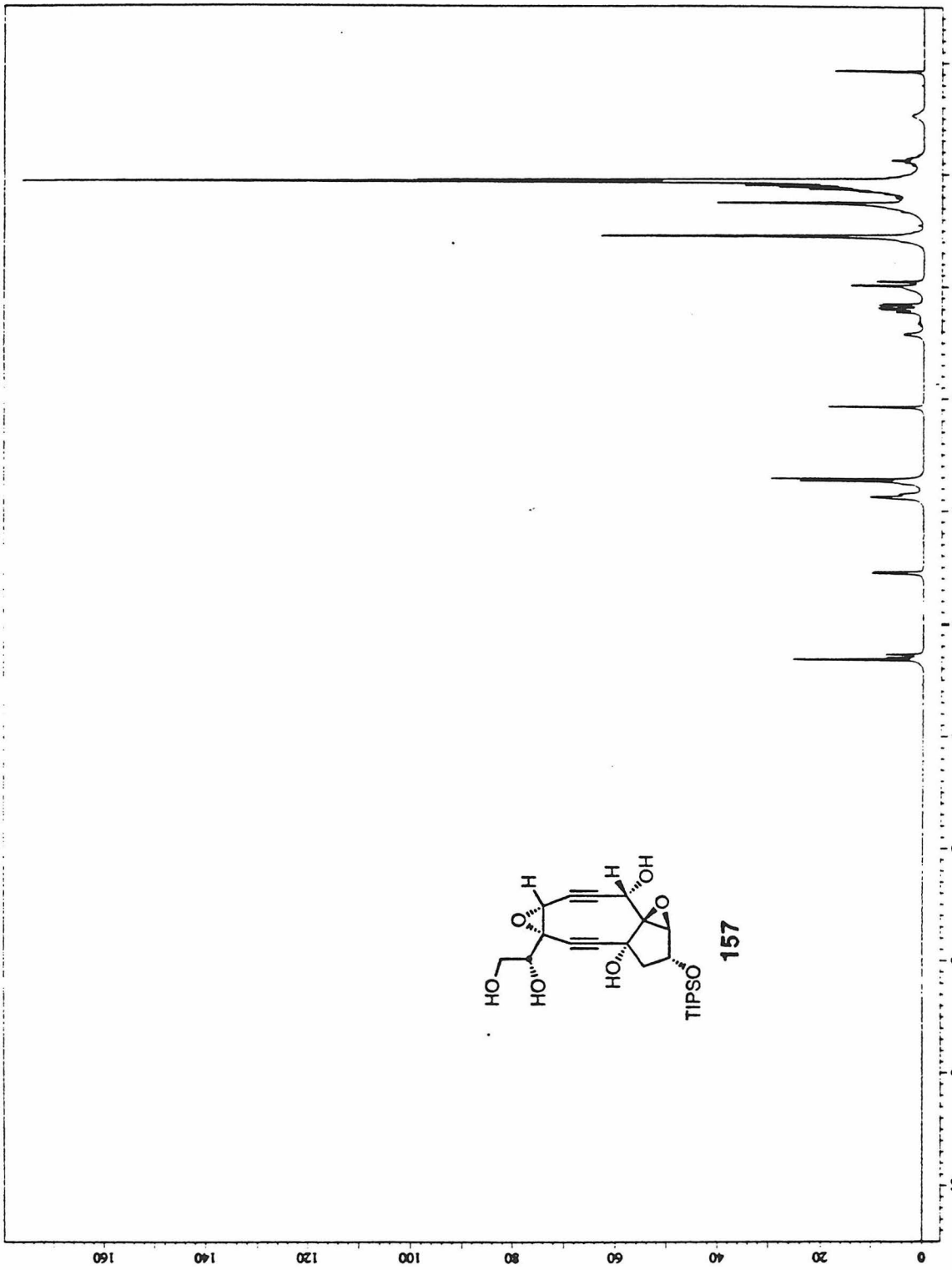

H
O
H
OH
O
TMSO
TIPSO
O
O
H3C
H3C
156

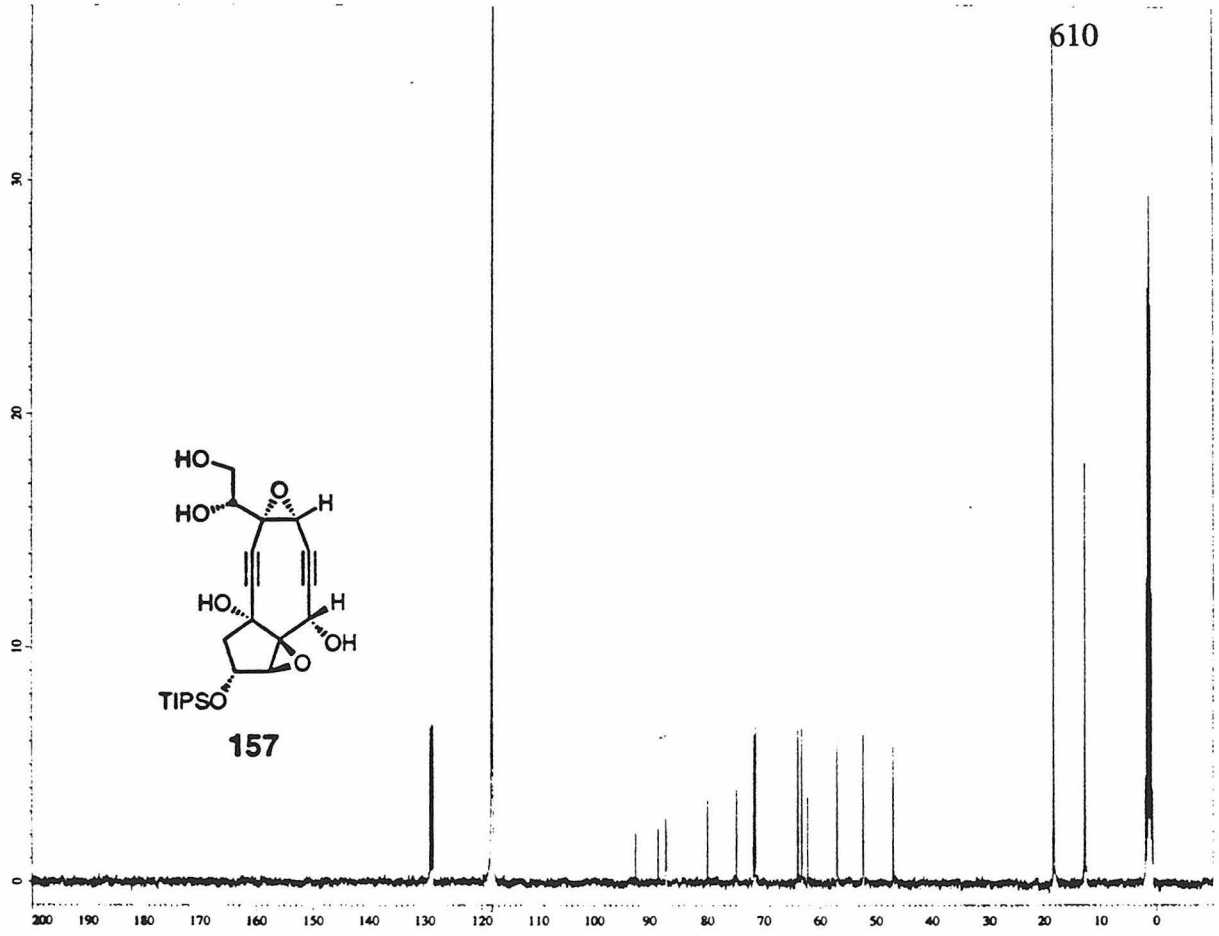
608

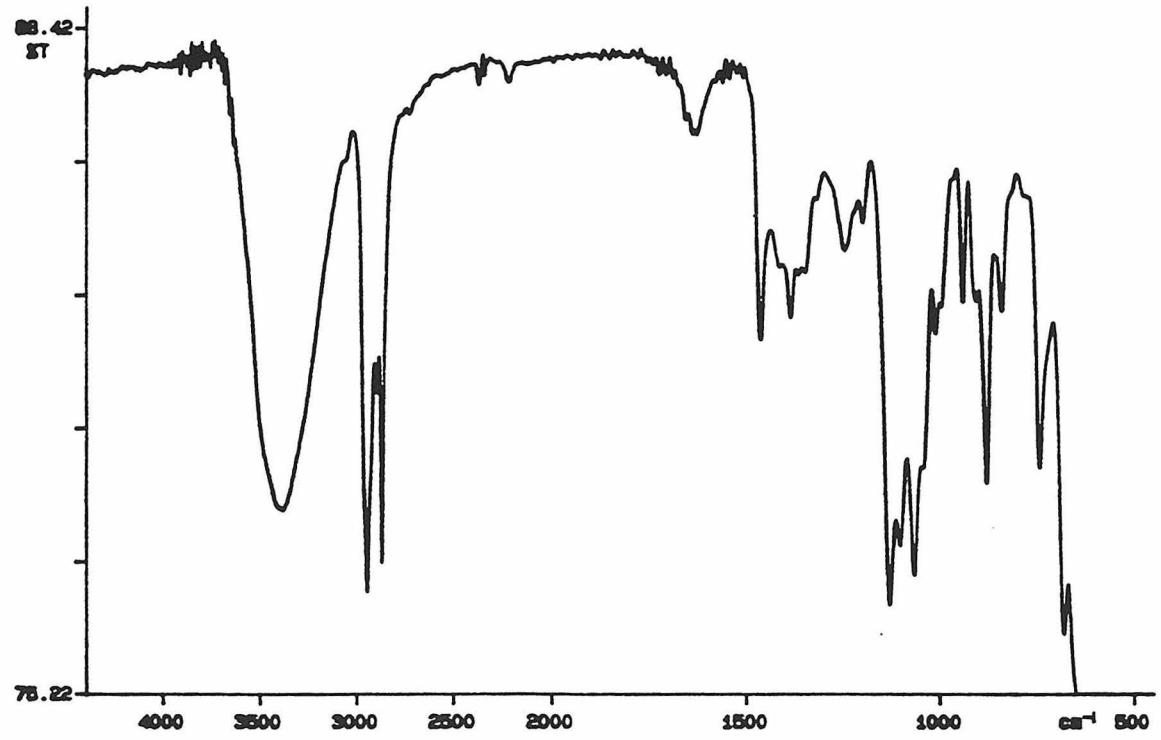

H3C
O
H3C
O
O
H
TMSO
H
OH
O
TIPSO

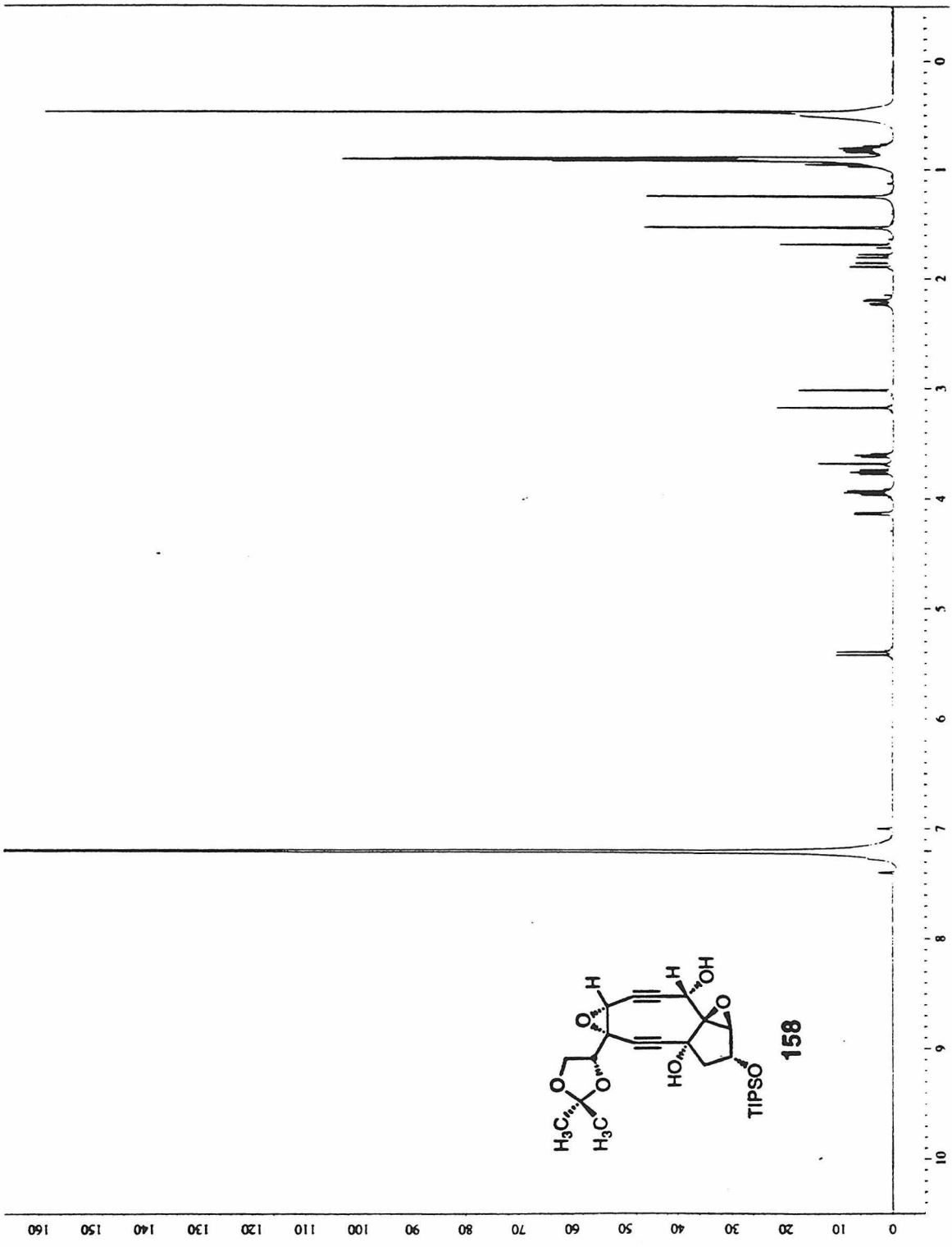
156

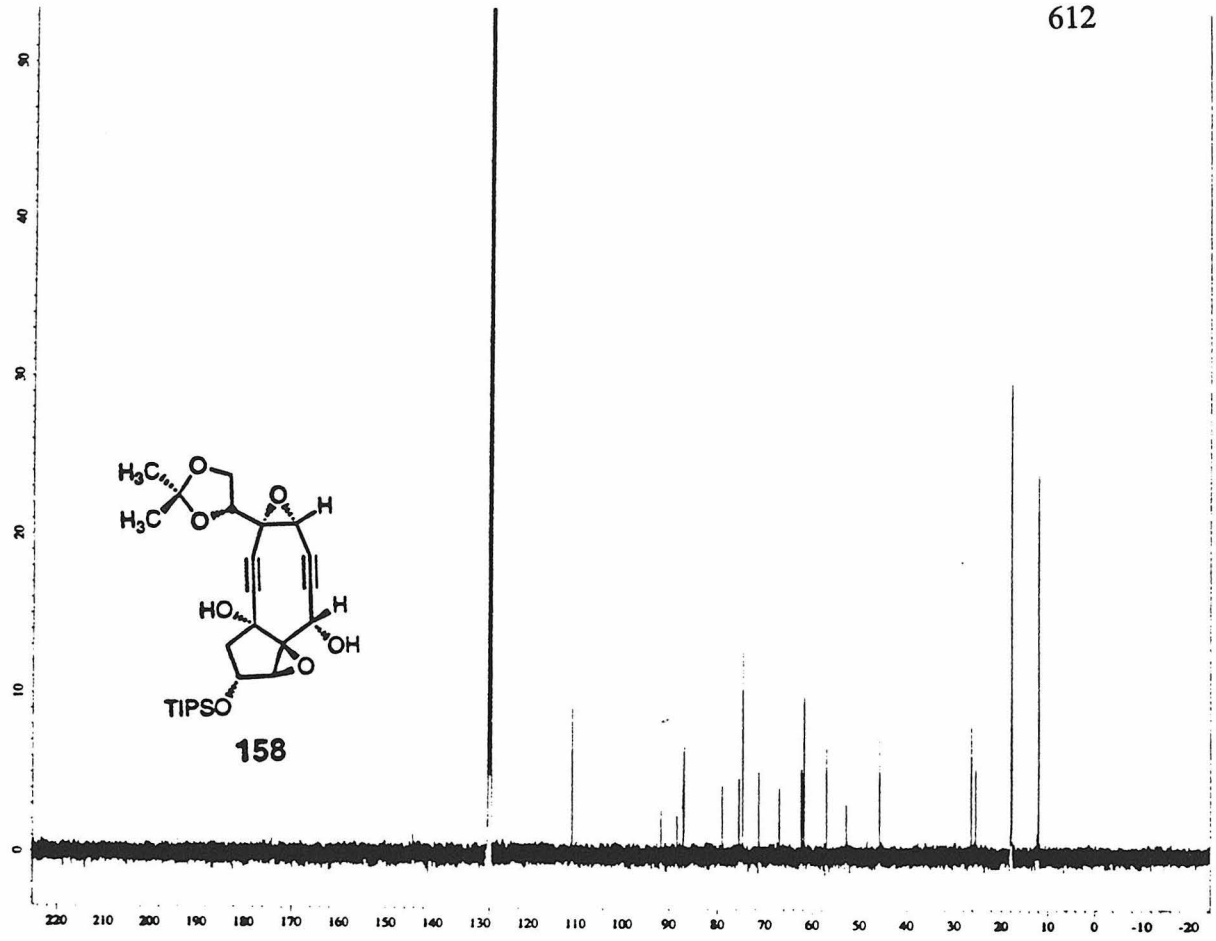

91.26
ST
67.95
4000
3500
3000
2500
2000
1500
1000
cm-1
500

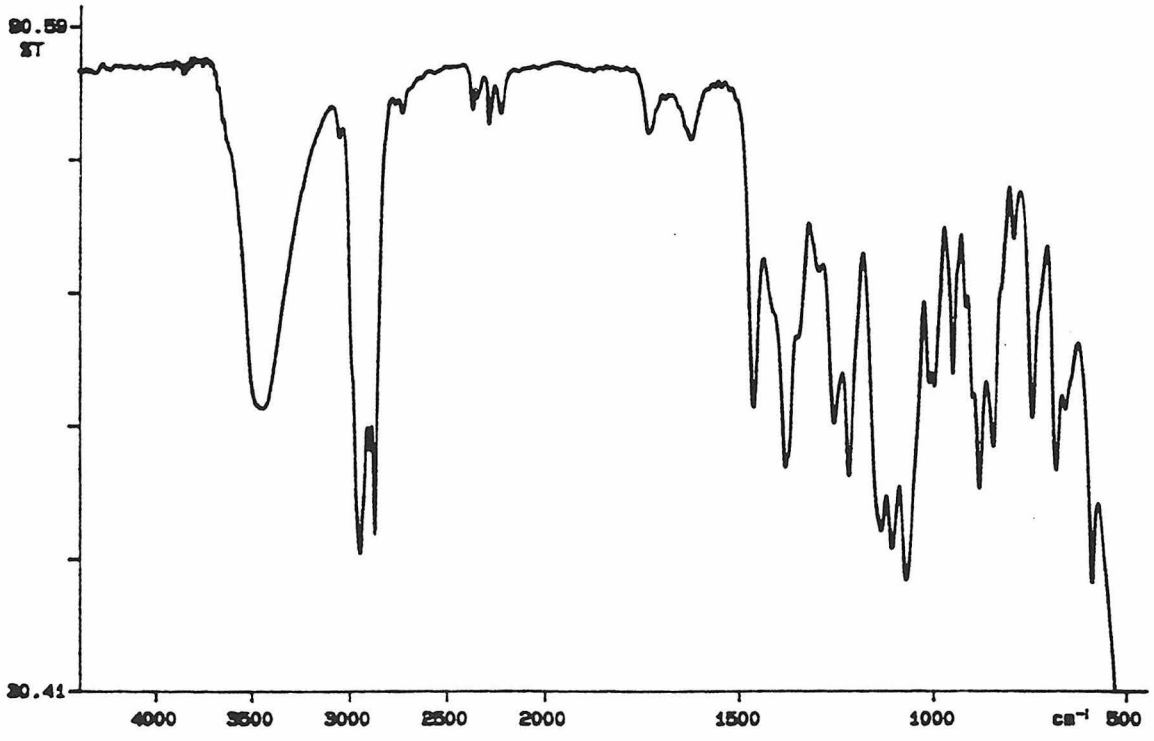

HO
HO
O
H
H
OH
HO
O
TIPSO
157

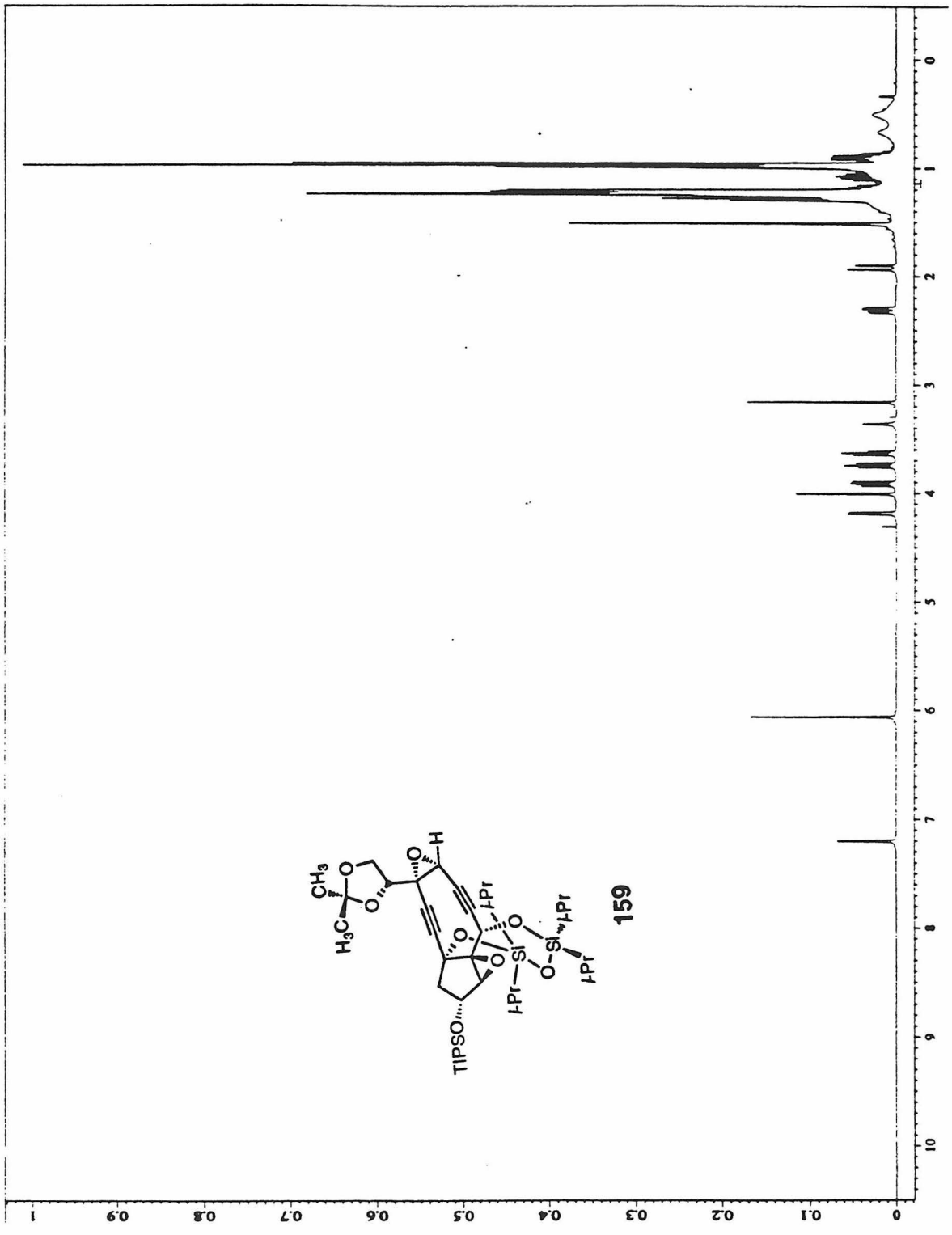

HO
HO
O
H
HO
H
OH
O
TIPSO
157
30
20
10
0
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

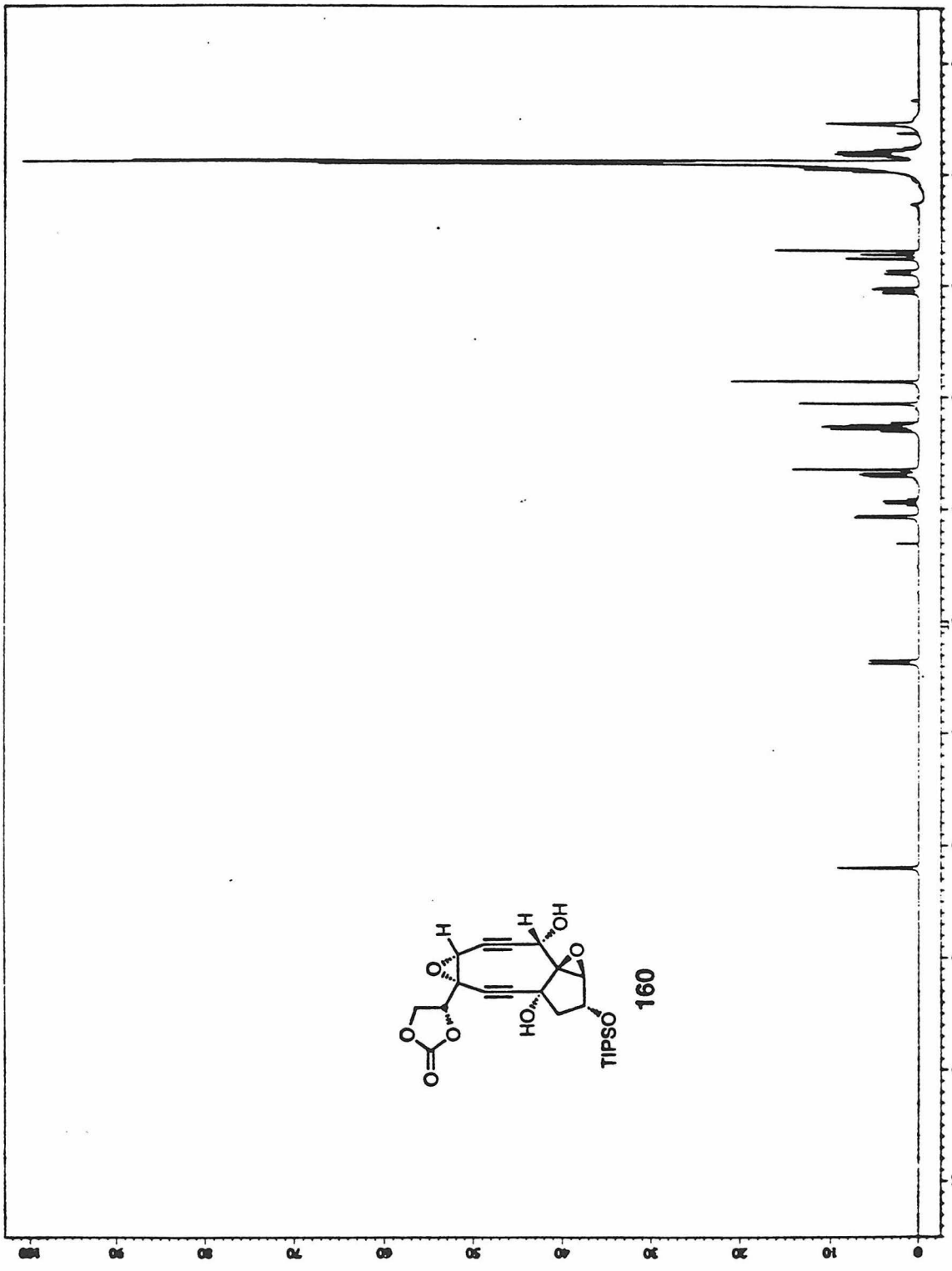

88.42
ST
75.22
4000 3500 3000 2500 2000 1500 1000 cm⁻¹ 500

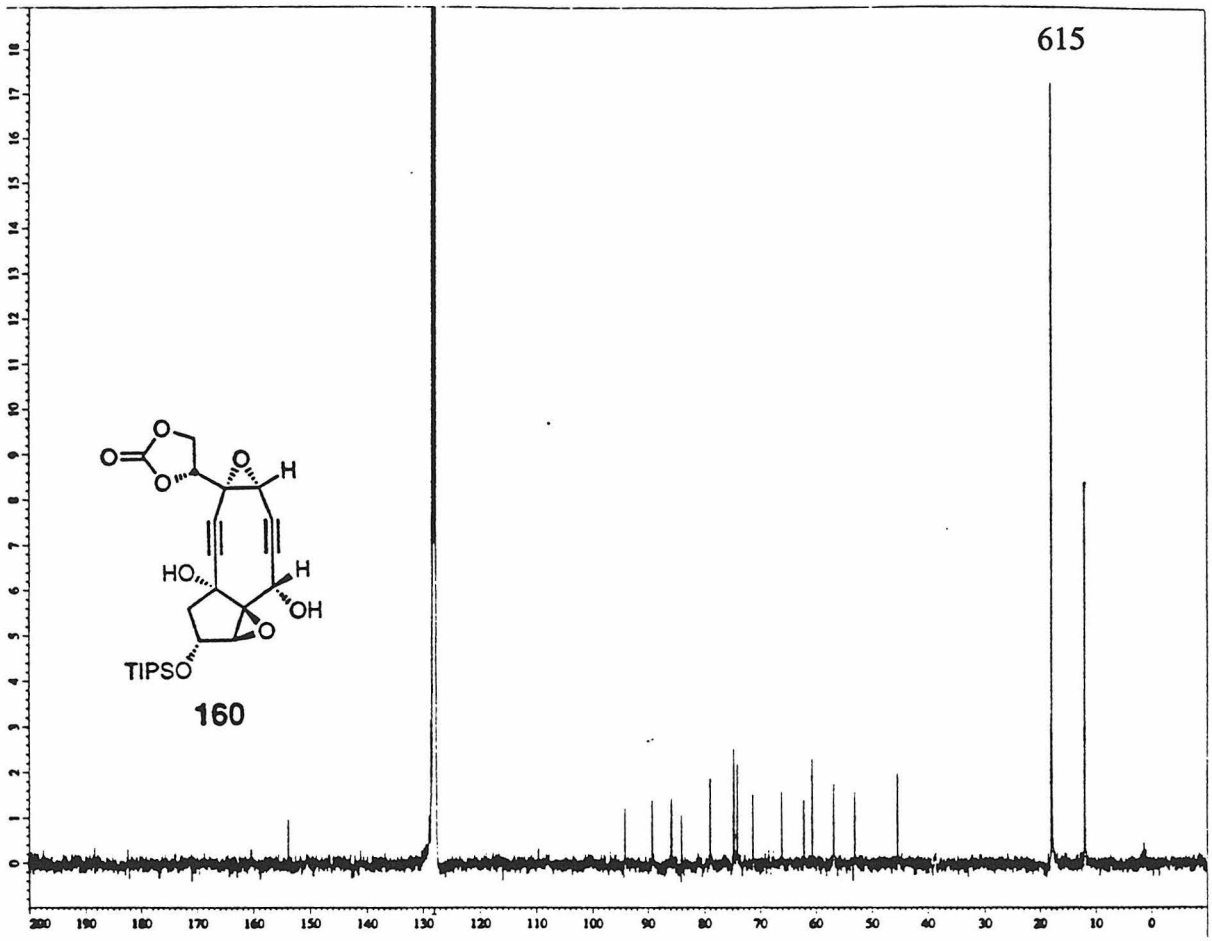

158


H3C
H3C
O
O
O
H
HO
H
OH
O
TIPSO
158
90
40
30
20
10
0
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20

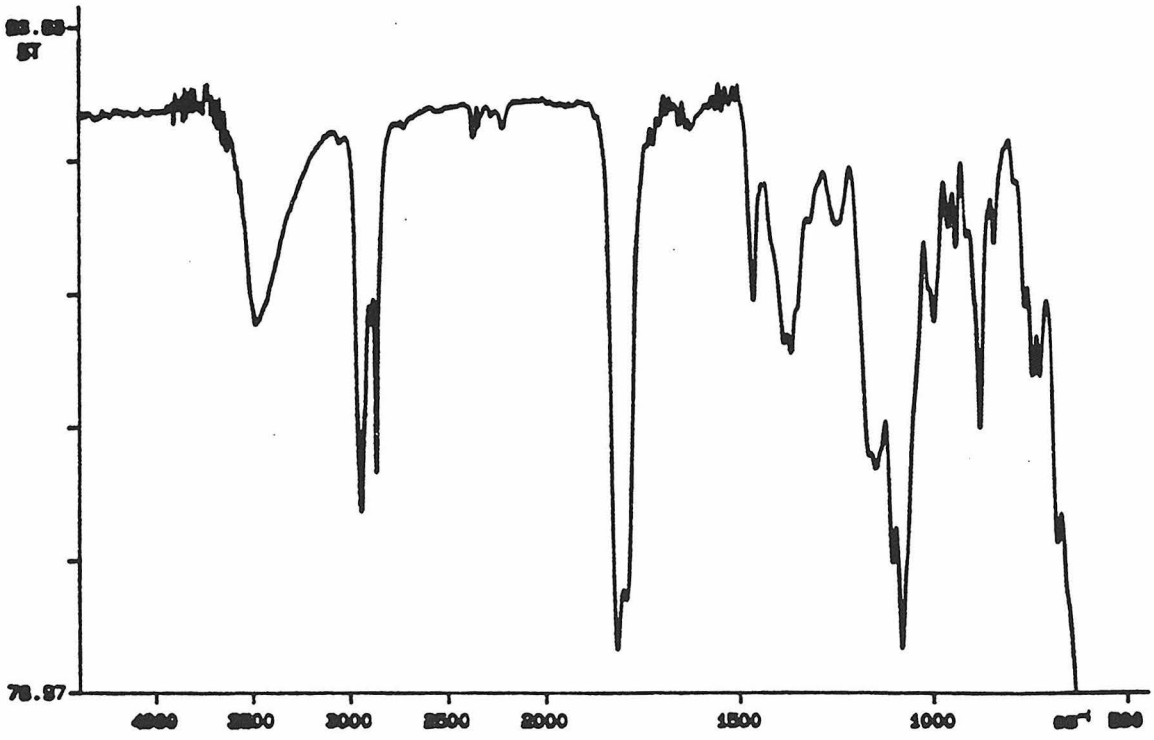

90.59
%T
30.41
4000 3500 3000 2500 2000 1500 1000 cm-1 500

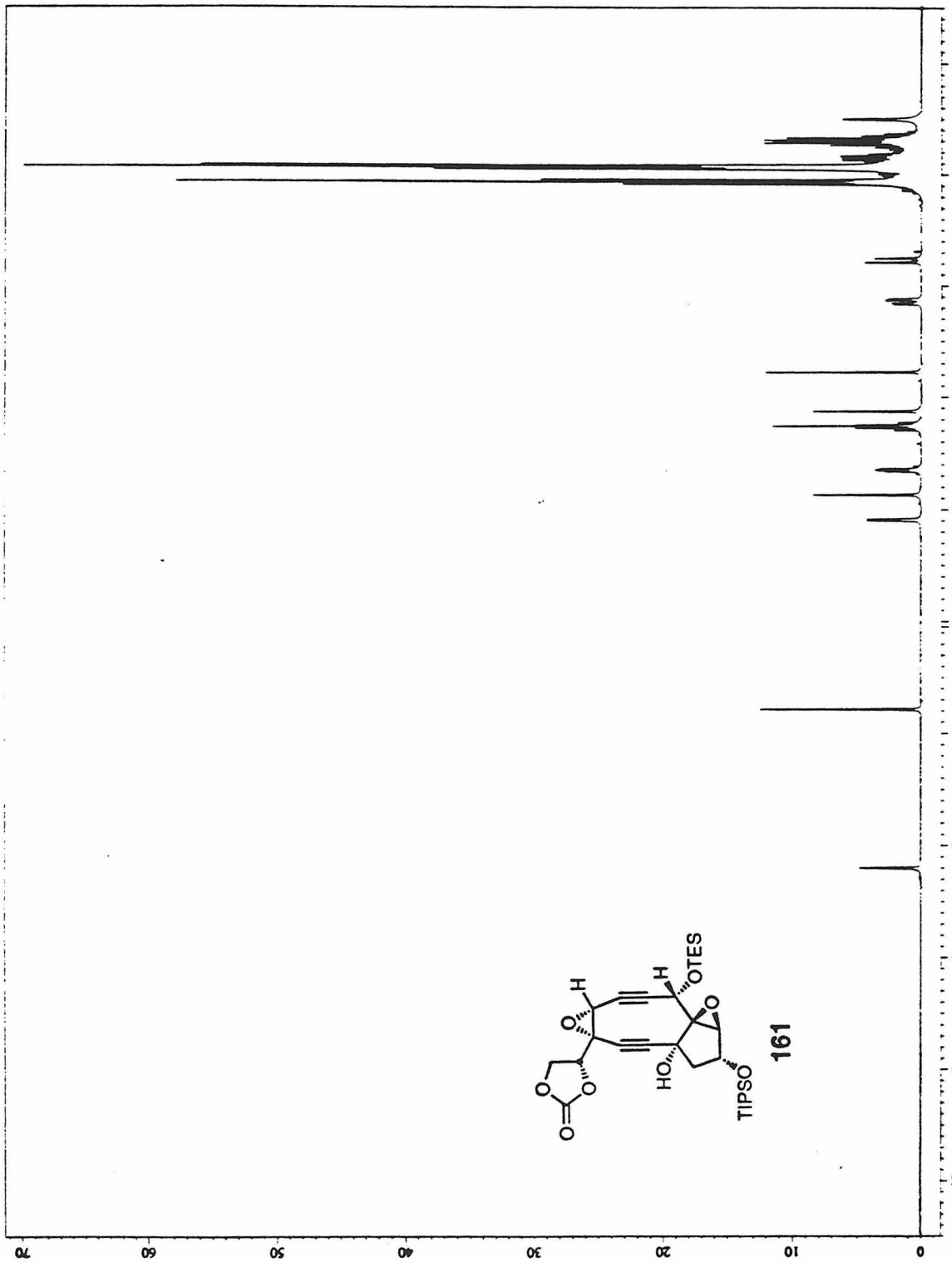

H
O
CH3
H3C
O
O
O
i-Pr
Si
O
i-Pr
O
Si
i-Pr
i-Pr
TIPSO
159


H
O
H
OH
O
HO
TIPSO
O
O
O
160

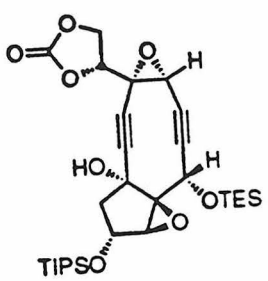

615
O
O
O
O
H
HO
H
OH
O
TIPSO

160


88.88
ST
78.97
4000
3500
3000
2500
2000
1500
1000
cm-1
500

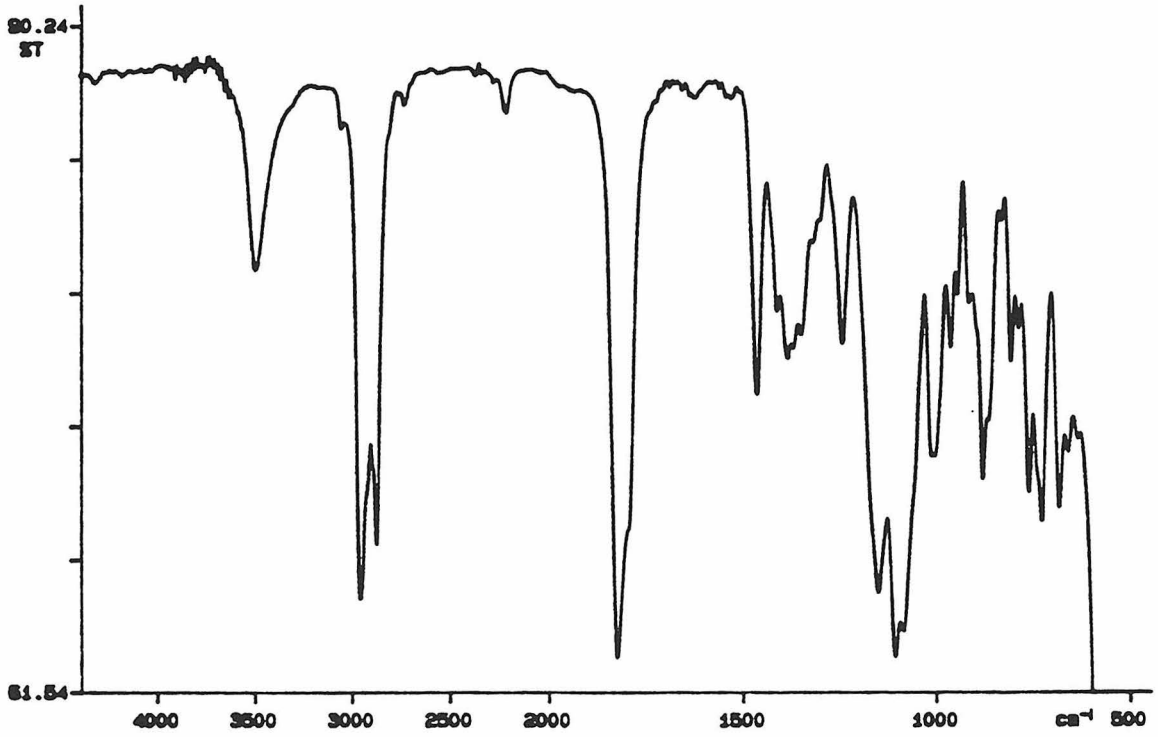

OTES
H
H
O
O
HO
TIPSO
O
O
O
161

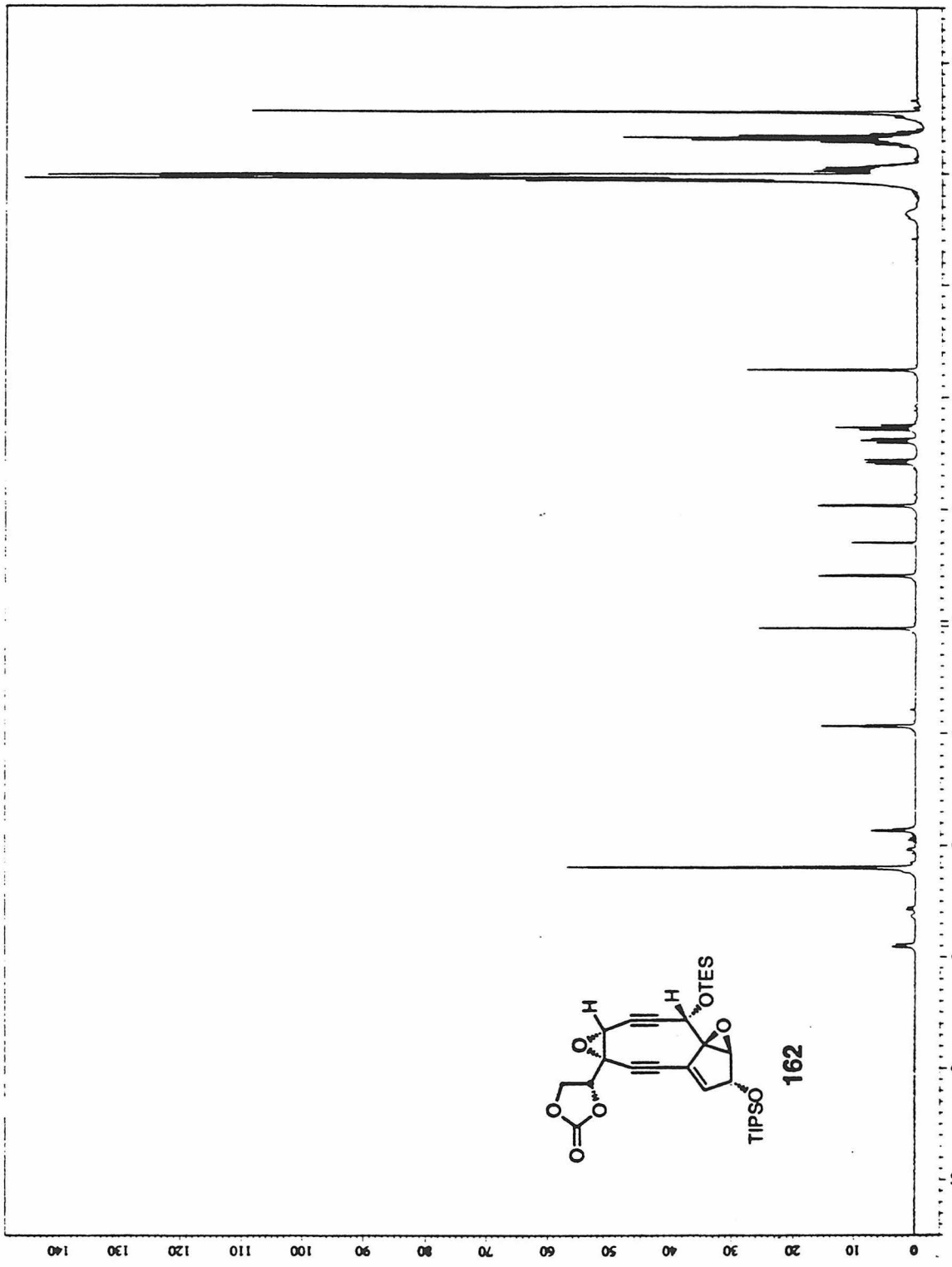
617

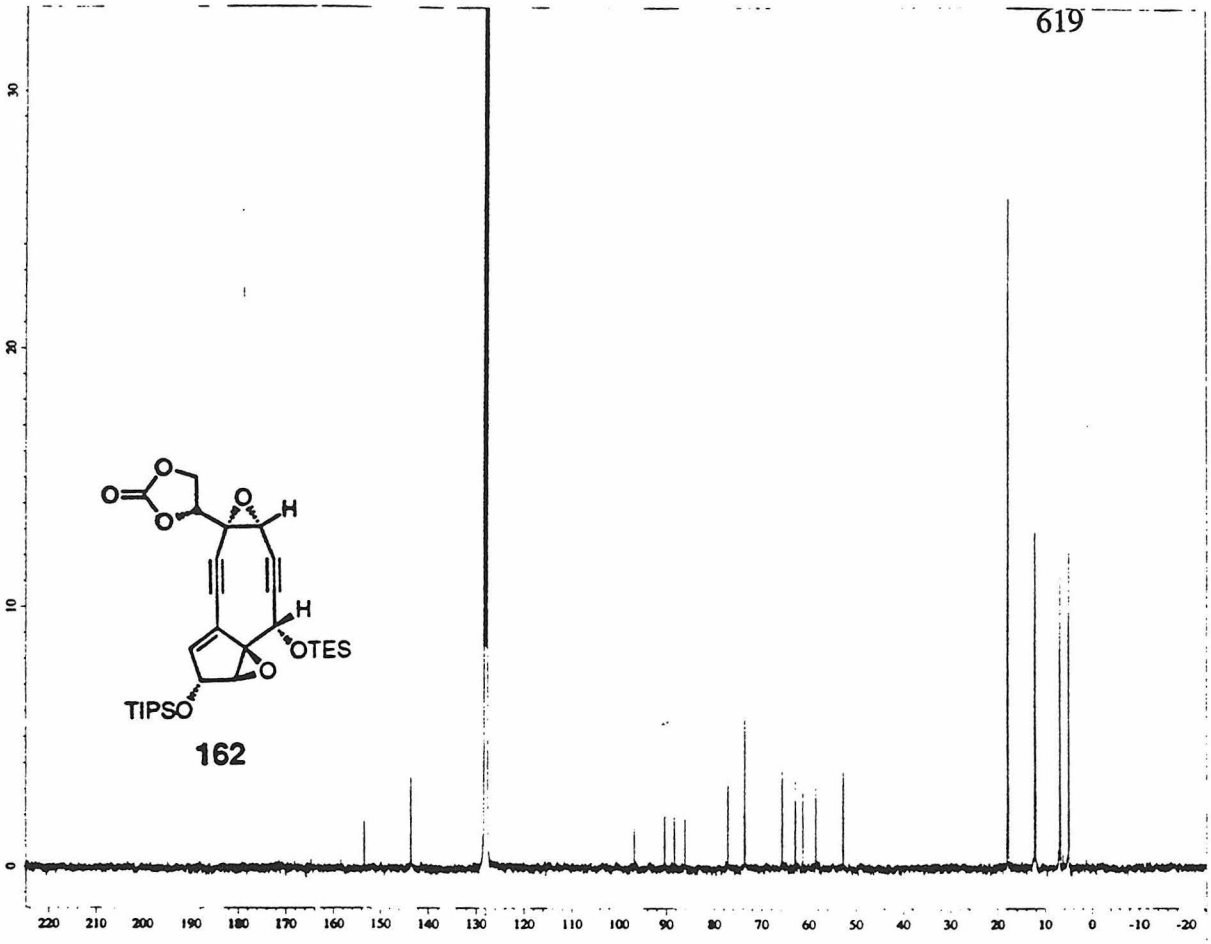

O
O
O
O
H
HO
H
OTES
O
TIPSO

161

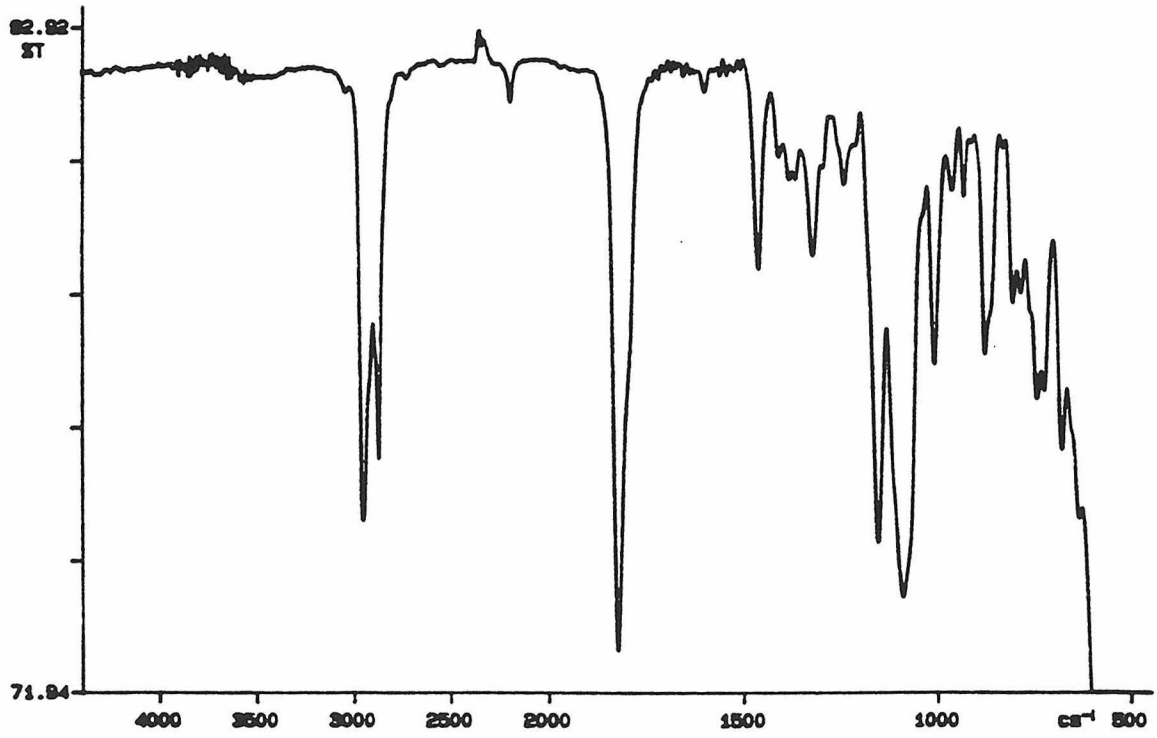
300
200
100
0
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

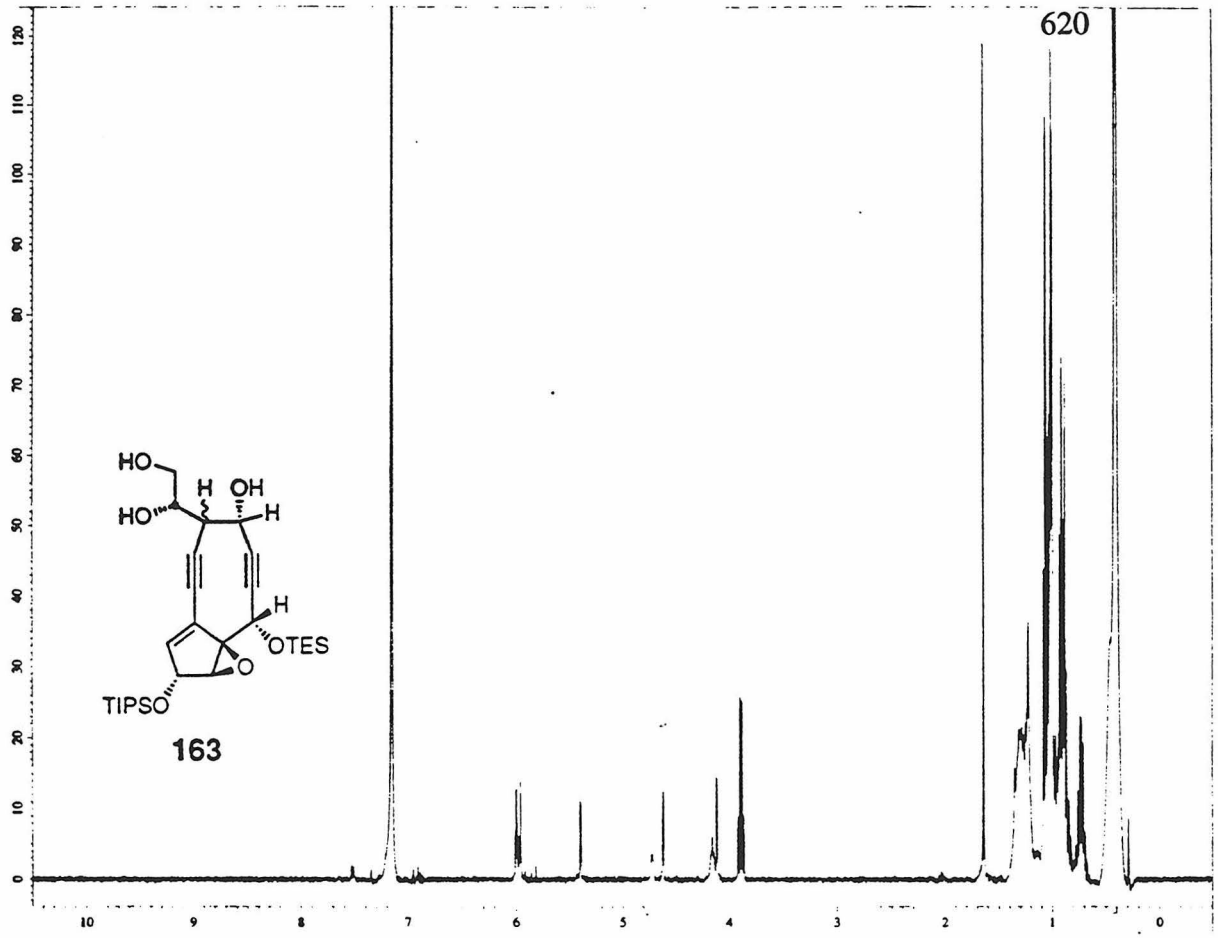

90.24
%T
61.54
4000 3500 3000 2500 2000 1500 1000 cm⁻¹ 500

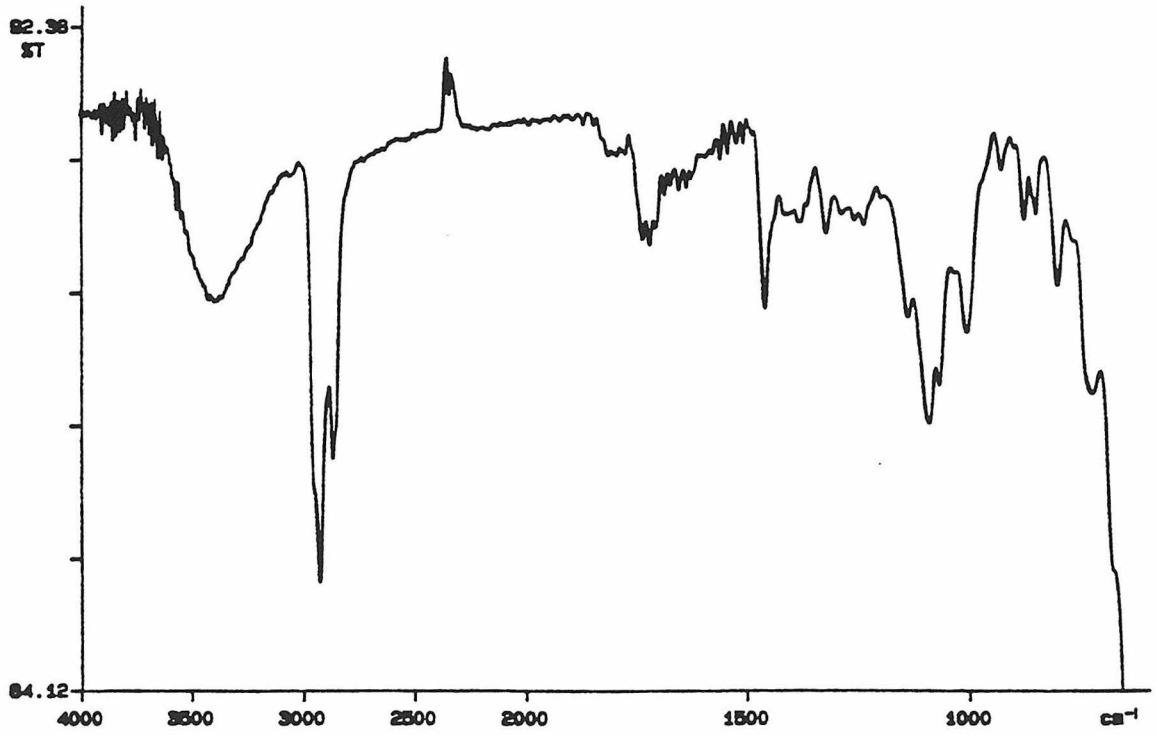

OTES
H
H
O
O
O
O
O
TIPSO
162

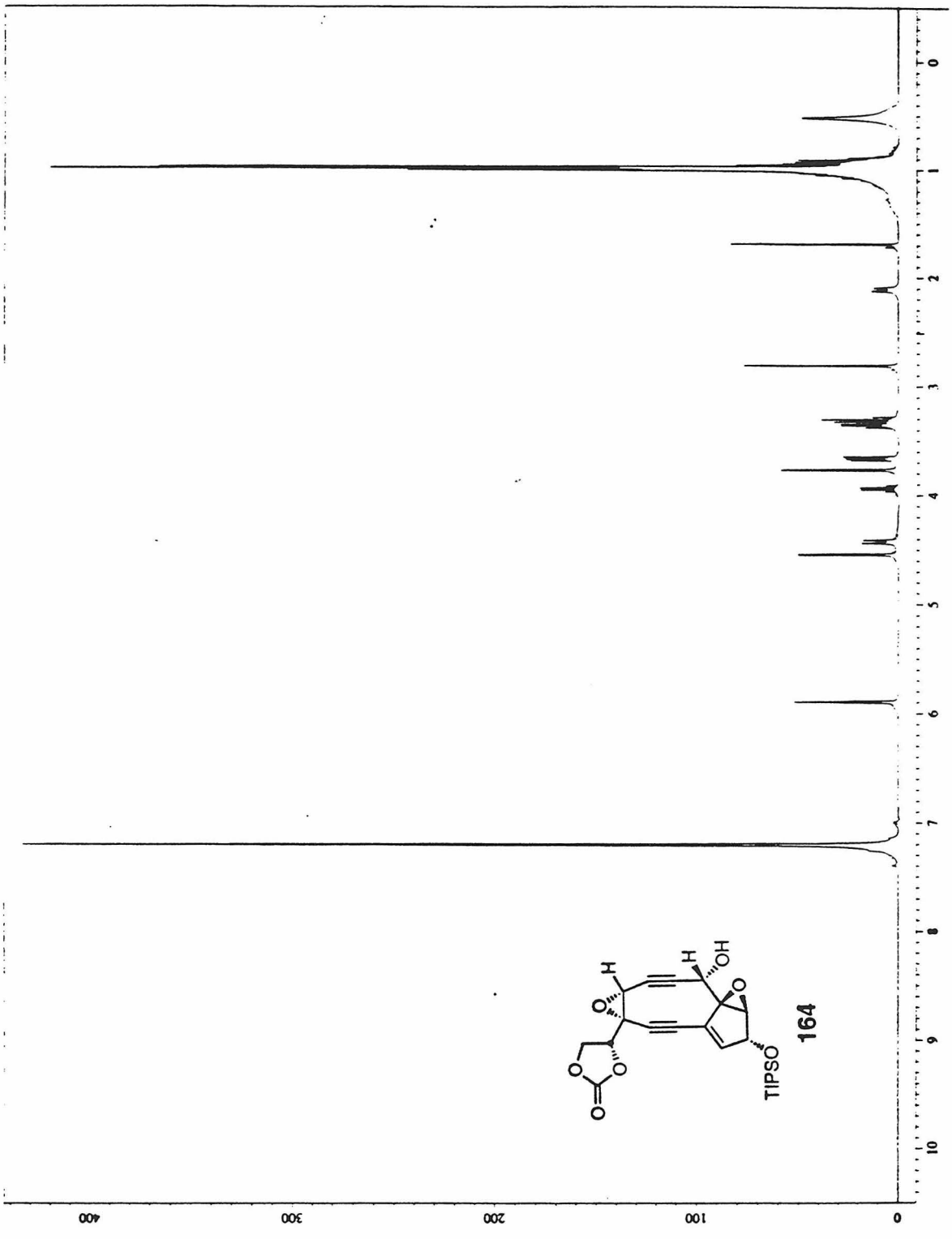

O
O
O
O
H
H
OTES
O
TIPSO
30
20
10
0
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20

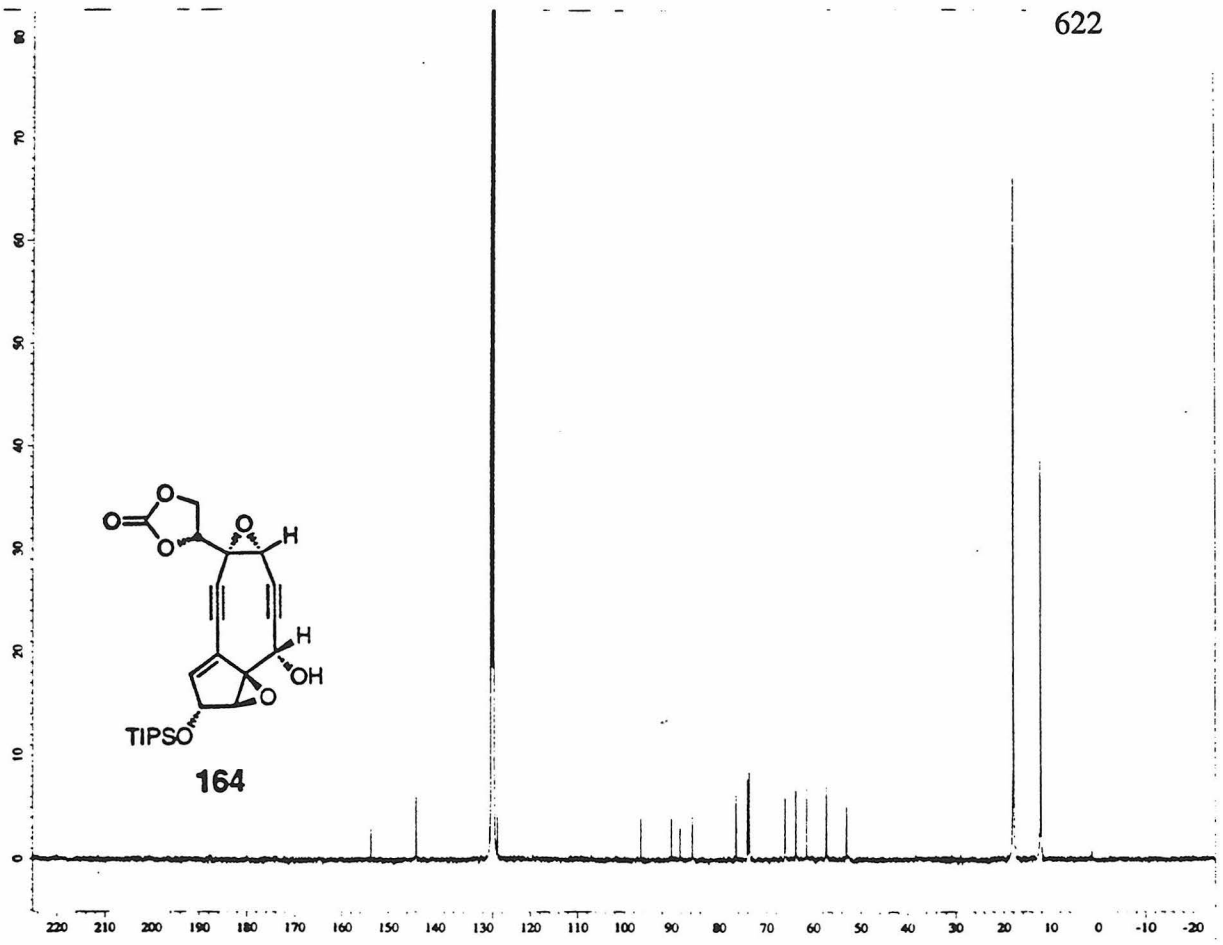
162


92.92
%T
71.94
4000
3500
3000
2500
2000
1500
1000
cm⁻¹
500


620
HO
H
OH
HO
H
H
OTES
O
TIPSO
163

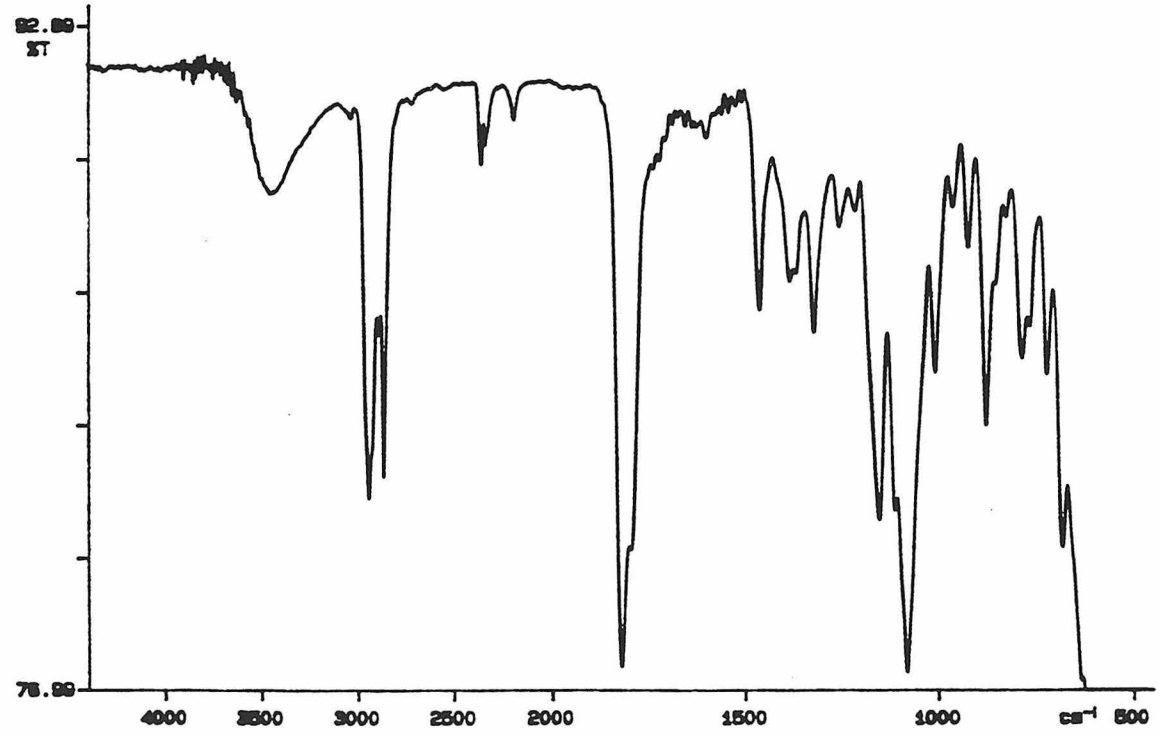

92.38
%T
84.12
4000
3500
3000
2500
2000
1500
1000
cm⁻¹

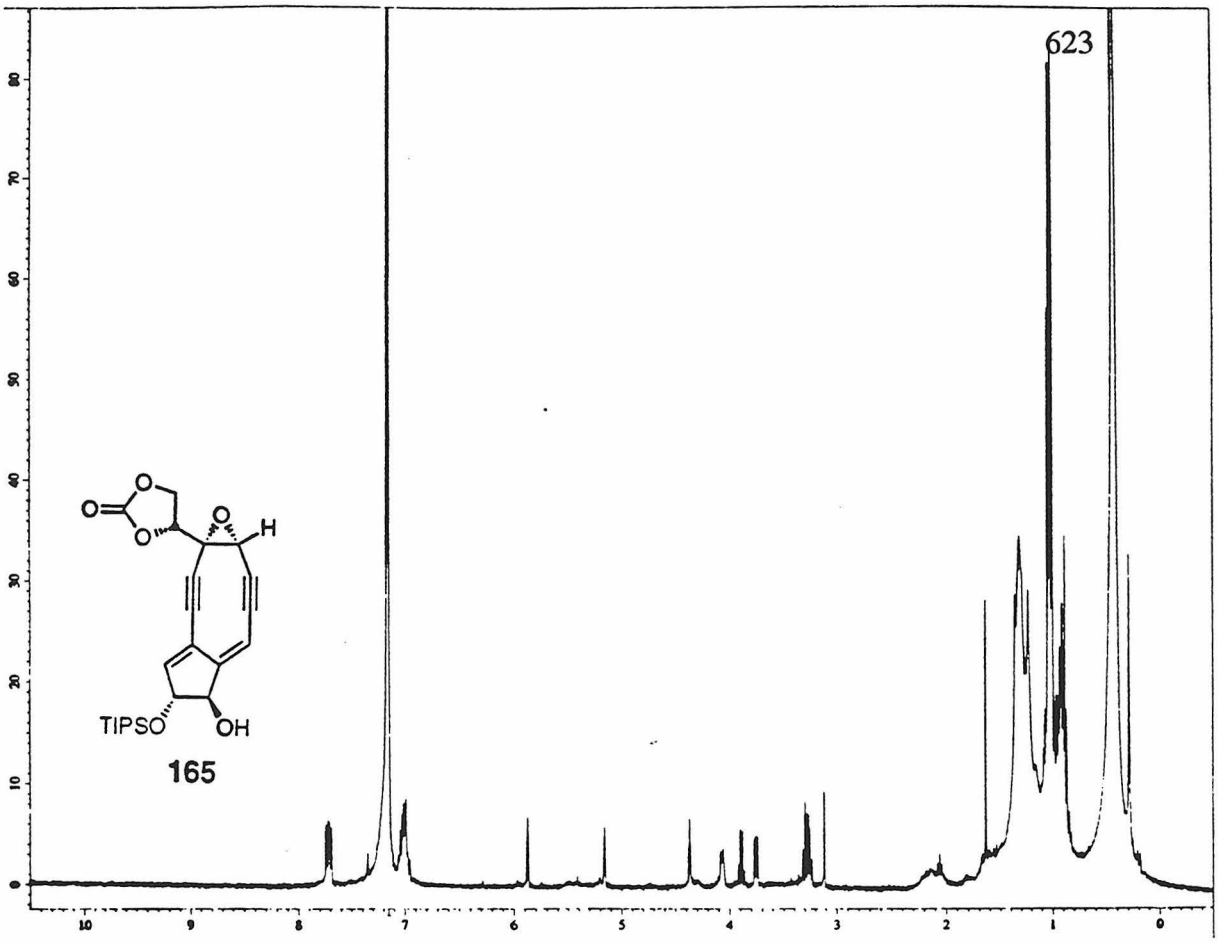

H
H
OH
O
O
O
O
O
TIPSO
164


O
O
O
O
H
H
OH
O
TIPSO

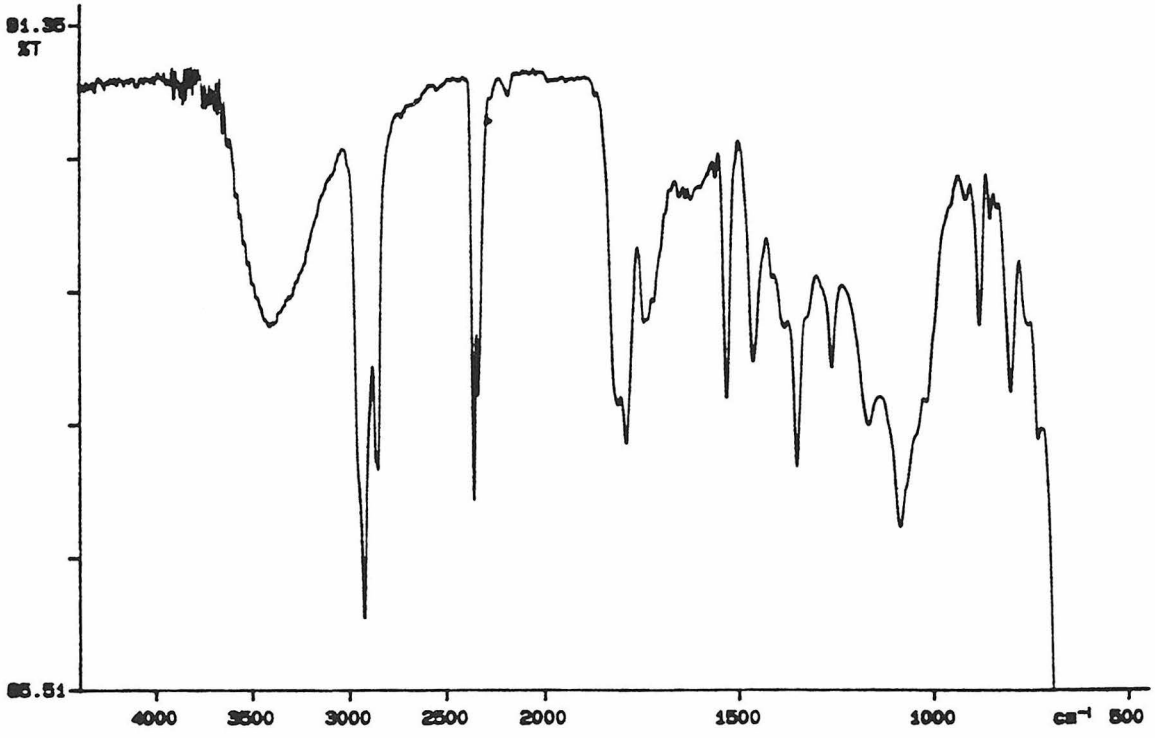
164

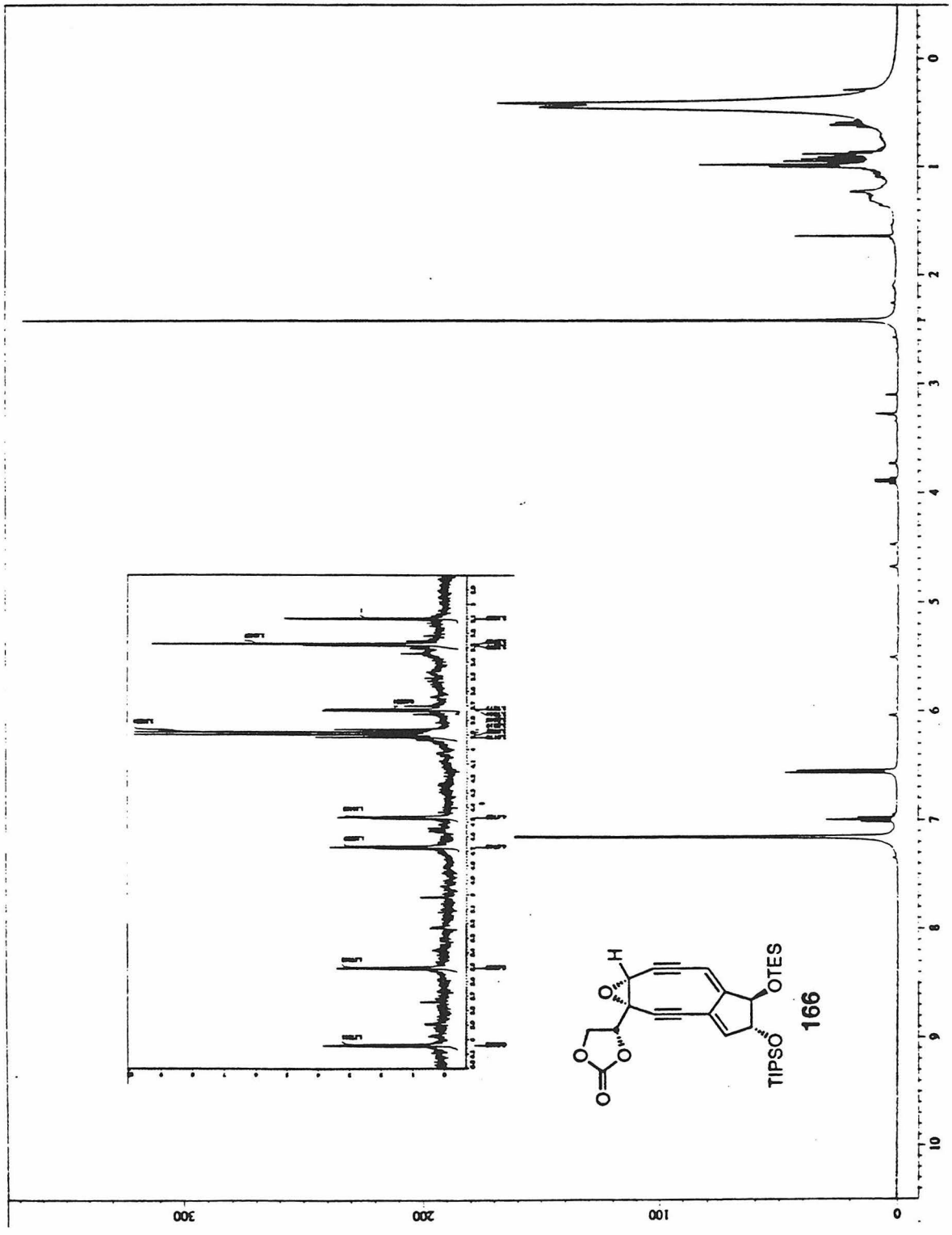
80
70
60
50
40
30
20
10
0
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20

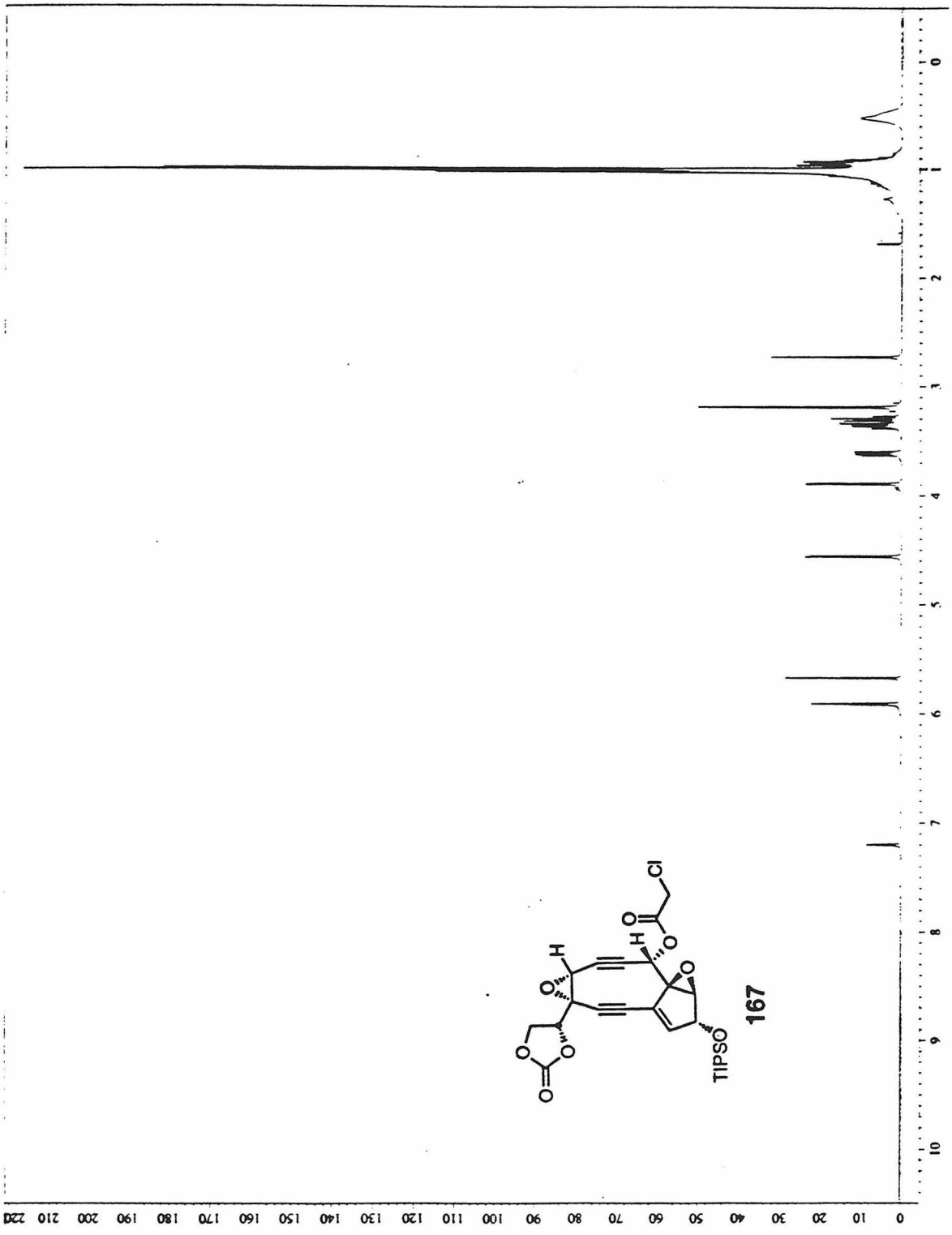

92.89
%T
78.99
4000
3500
3000
2500
2000
1500
1000
cm-1
500

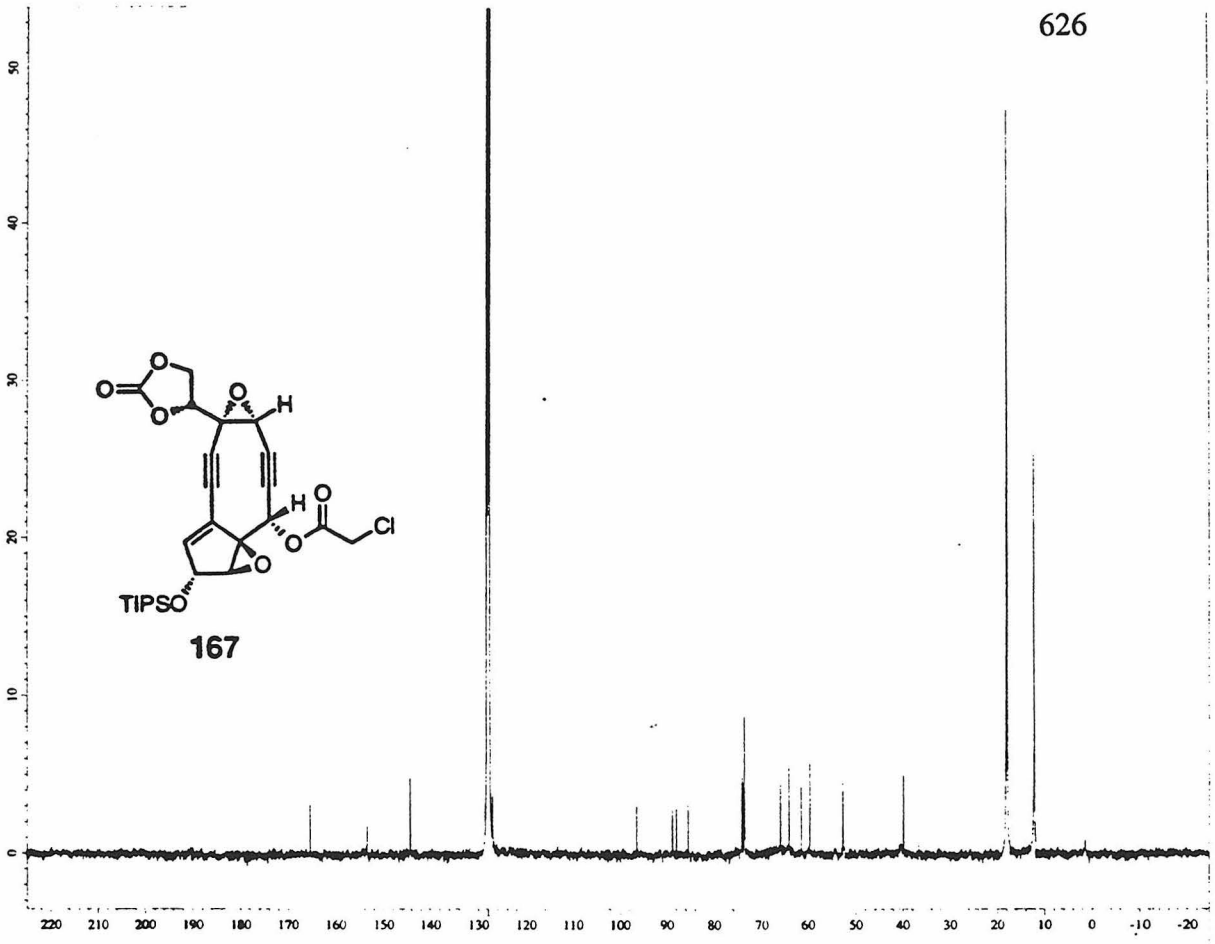

623
O
O
O
O
H
TIPSO
OH

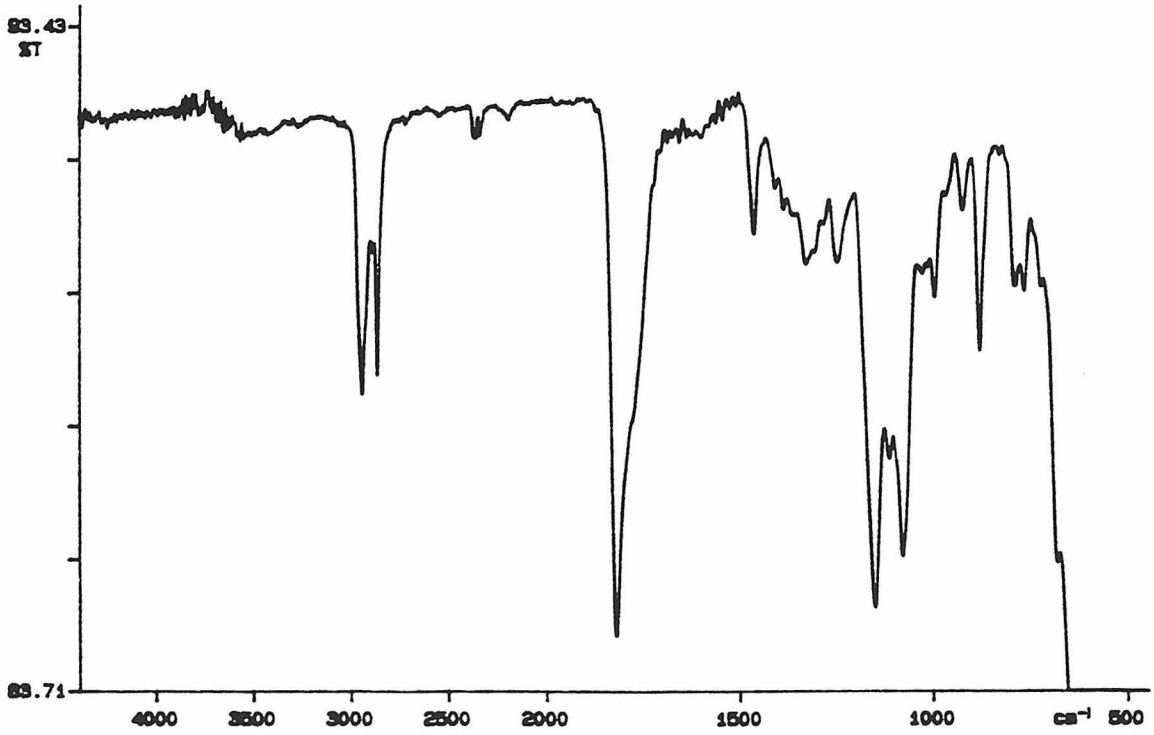
165


91.35
%T
85.51
4000
3500
3000
2500
2000
1500
1000
cm⁻¹
500

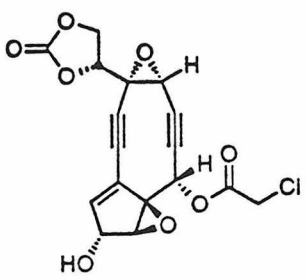

H
O
OTES
TIPSO
166


Cl
O
H
O
O
O
O
H
O
O
O
TIPSO
167


TIPSO
167

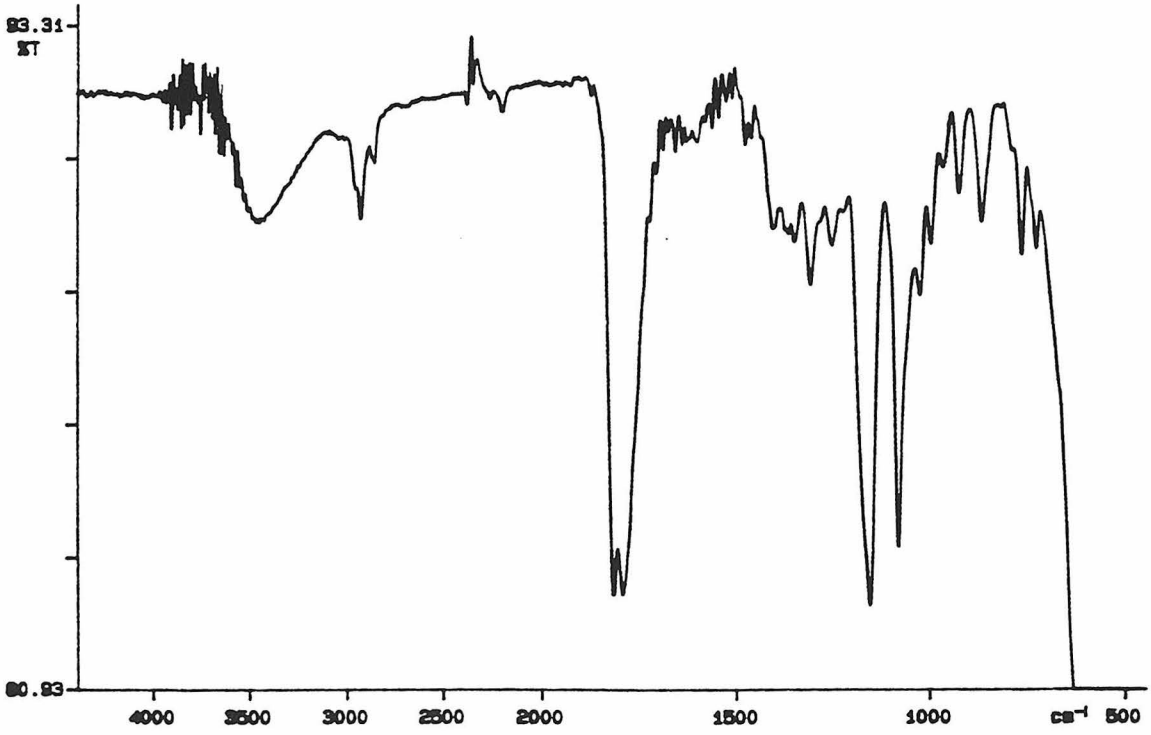

93.43
%T
89.71
4000
3500
3000
2500
2000
1500
1000
cm⁻¹
500

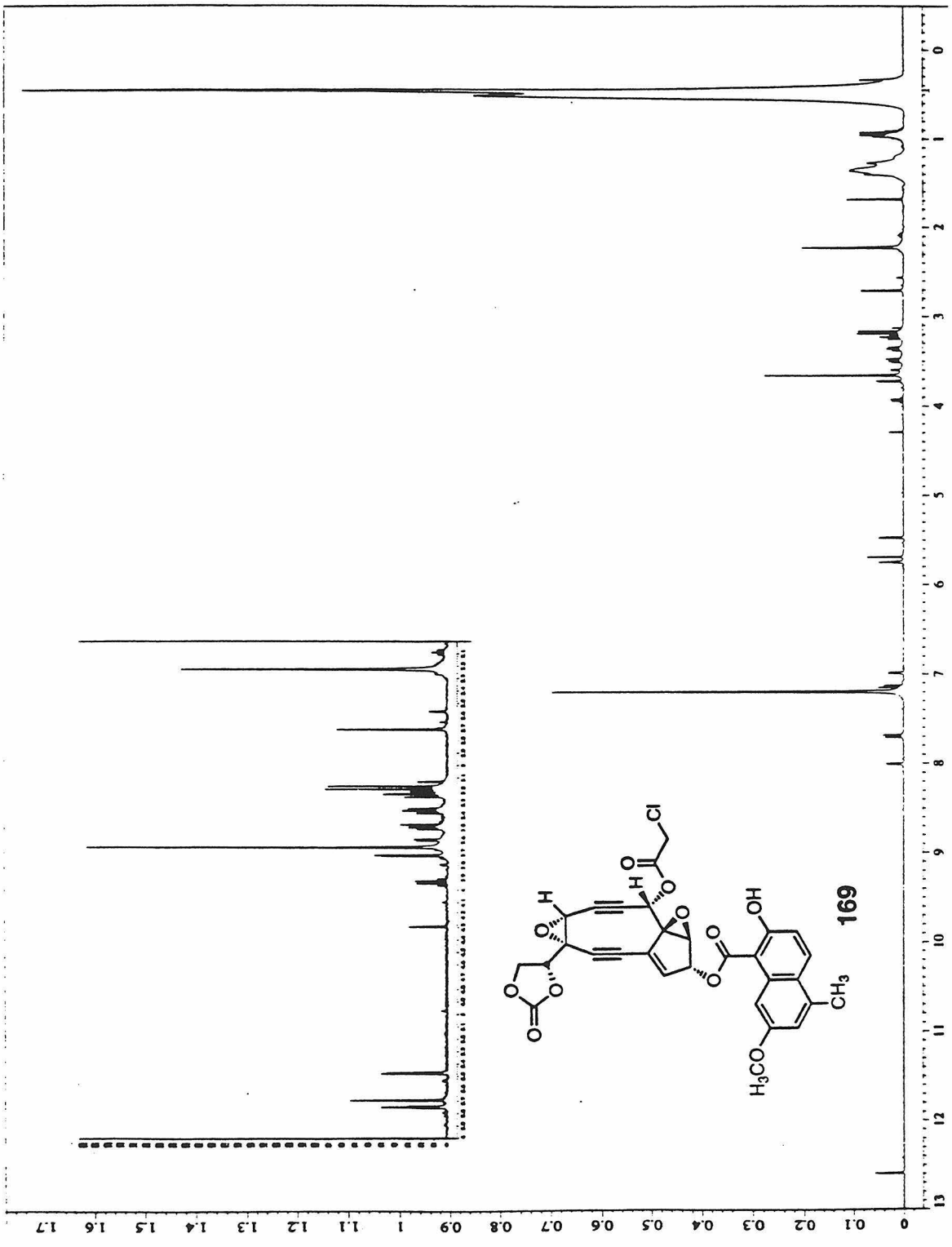
627

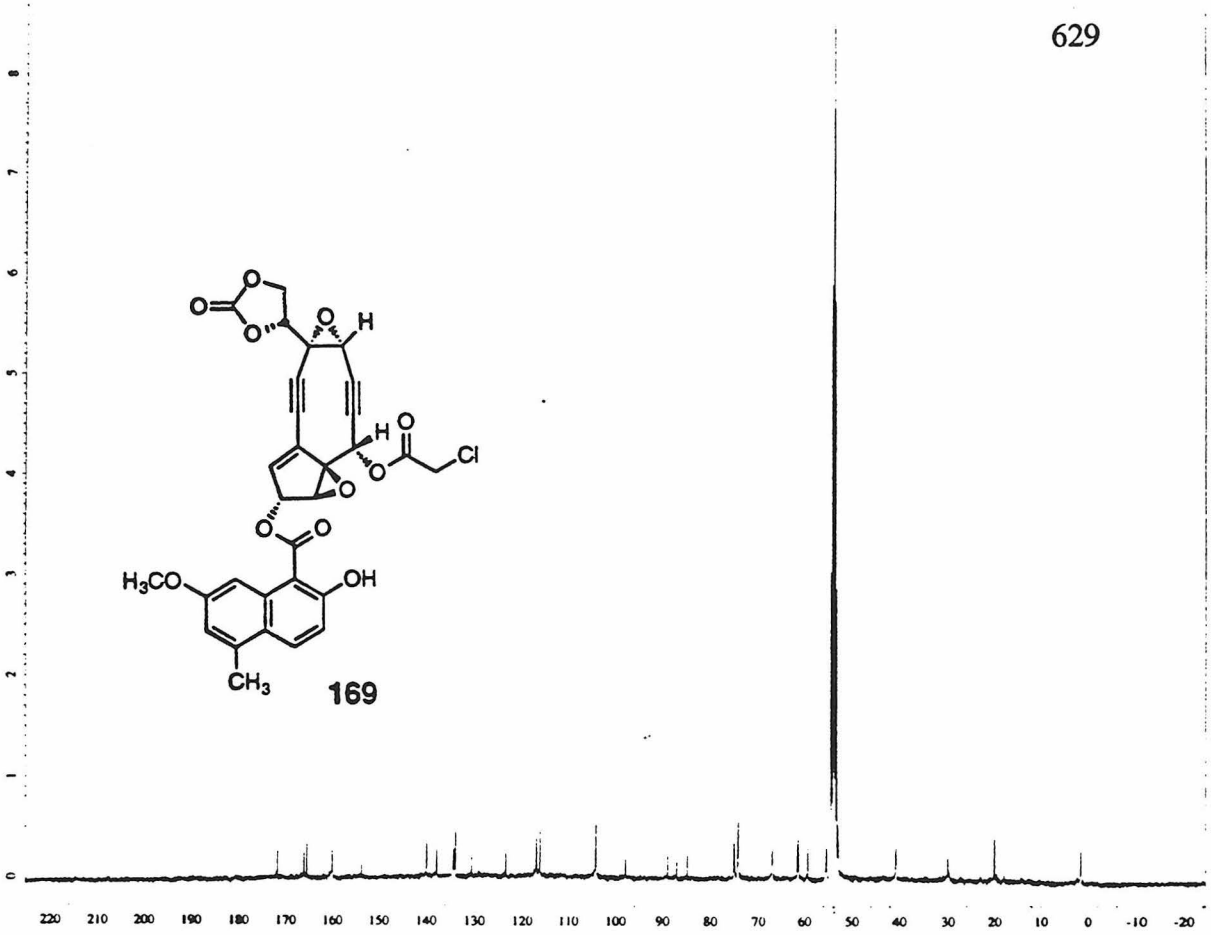


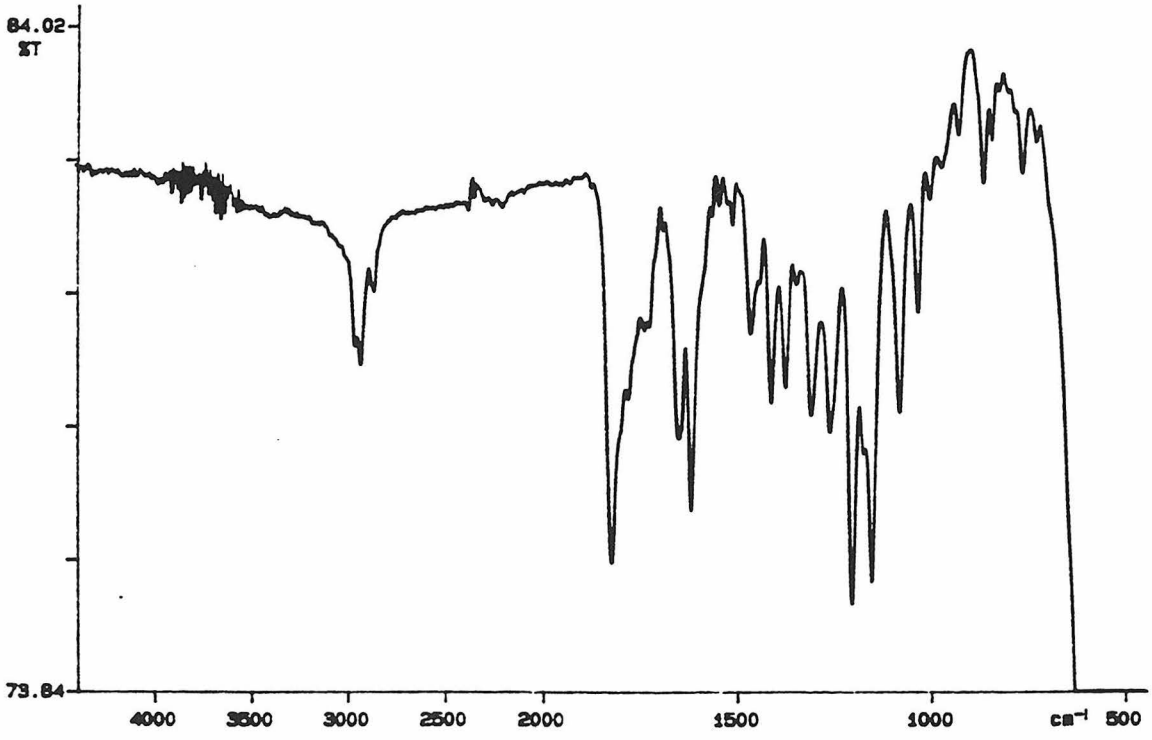
168

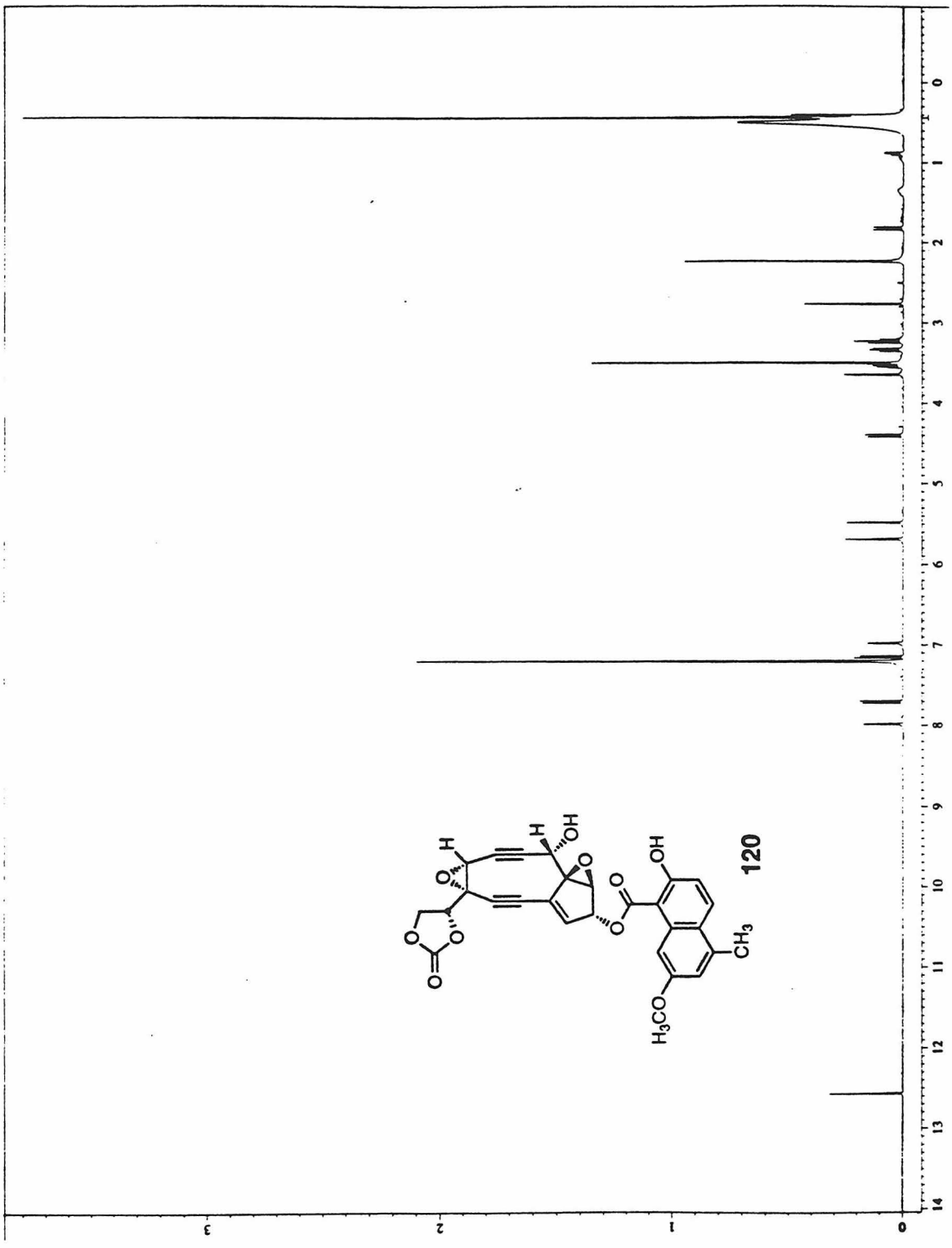
400
300
200
100
0
10
9
8
7
6
5
4
3
2
1
0

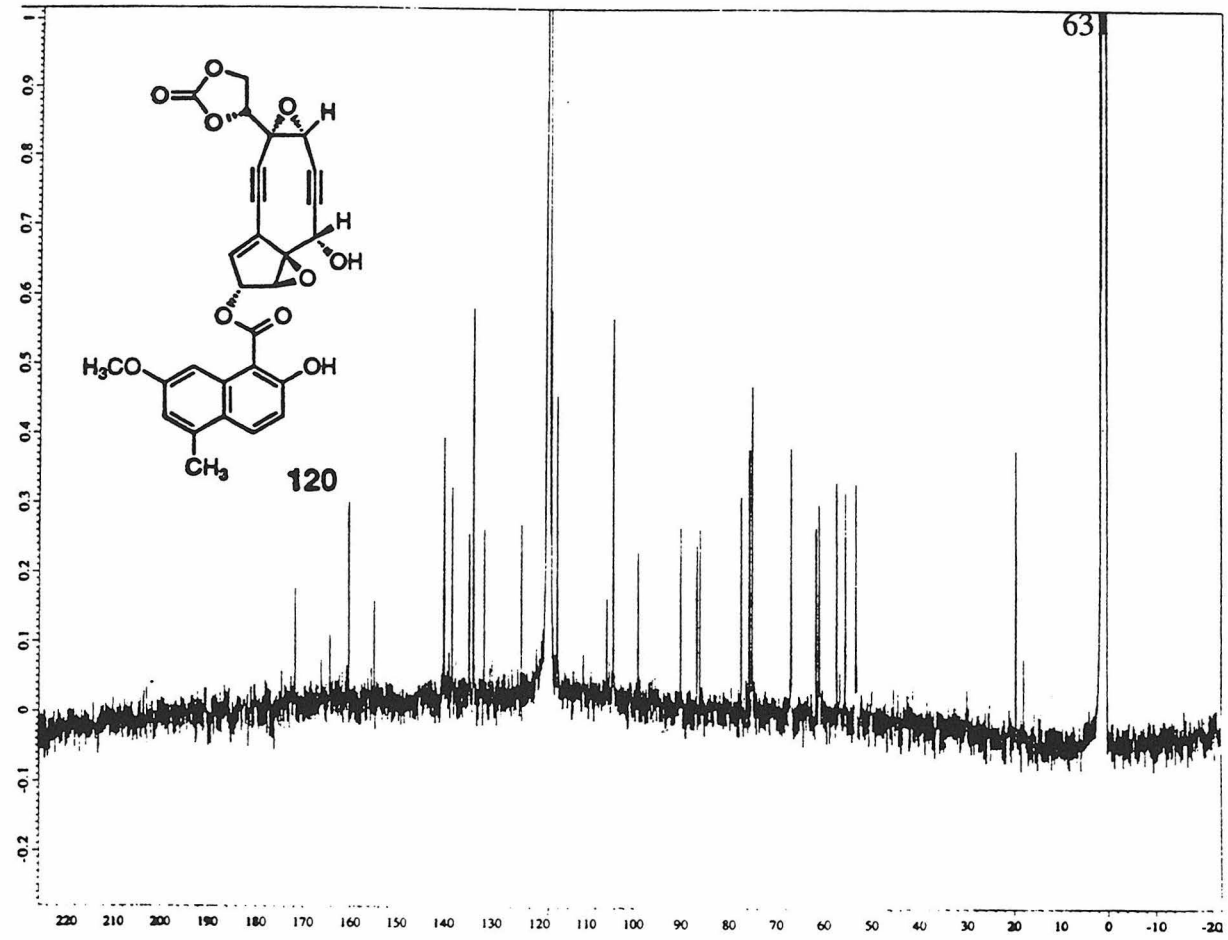

93.31
%T
80.93
4000
3500
3000
2500
2000
1500
1000
cm⁻¹
500

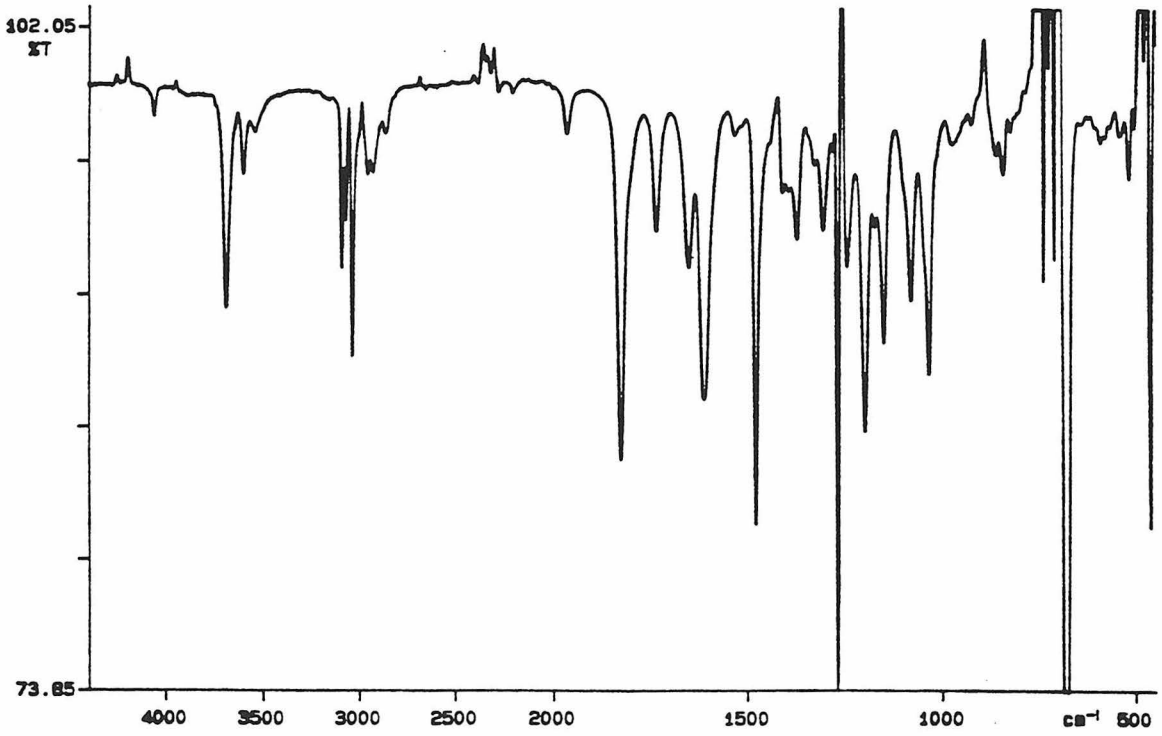

169

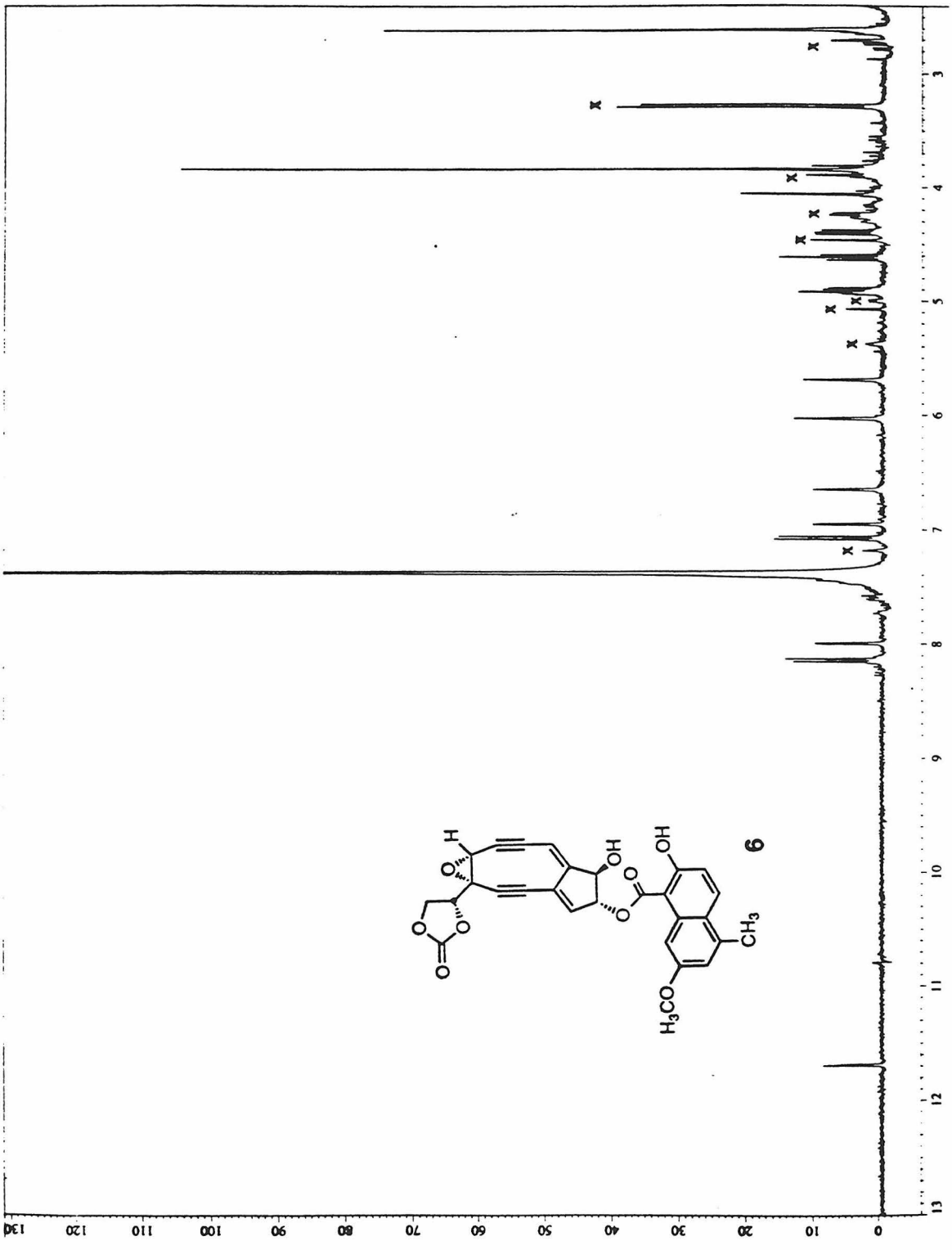

H
O
Cl
H_3CO
OH
CH_3
169
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20

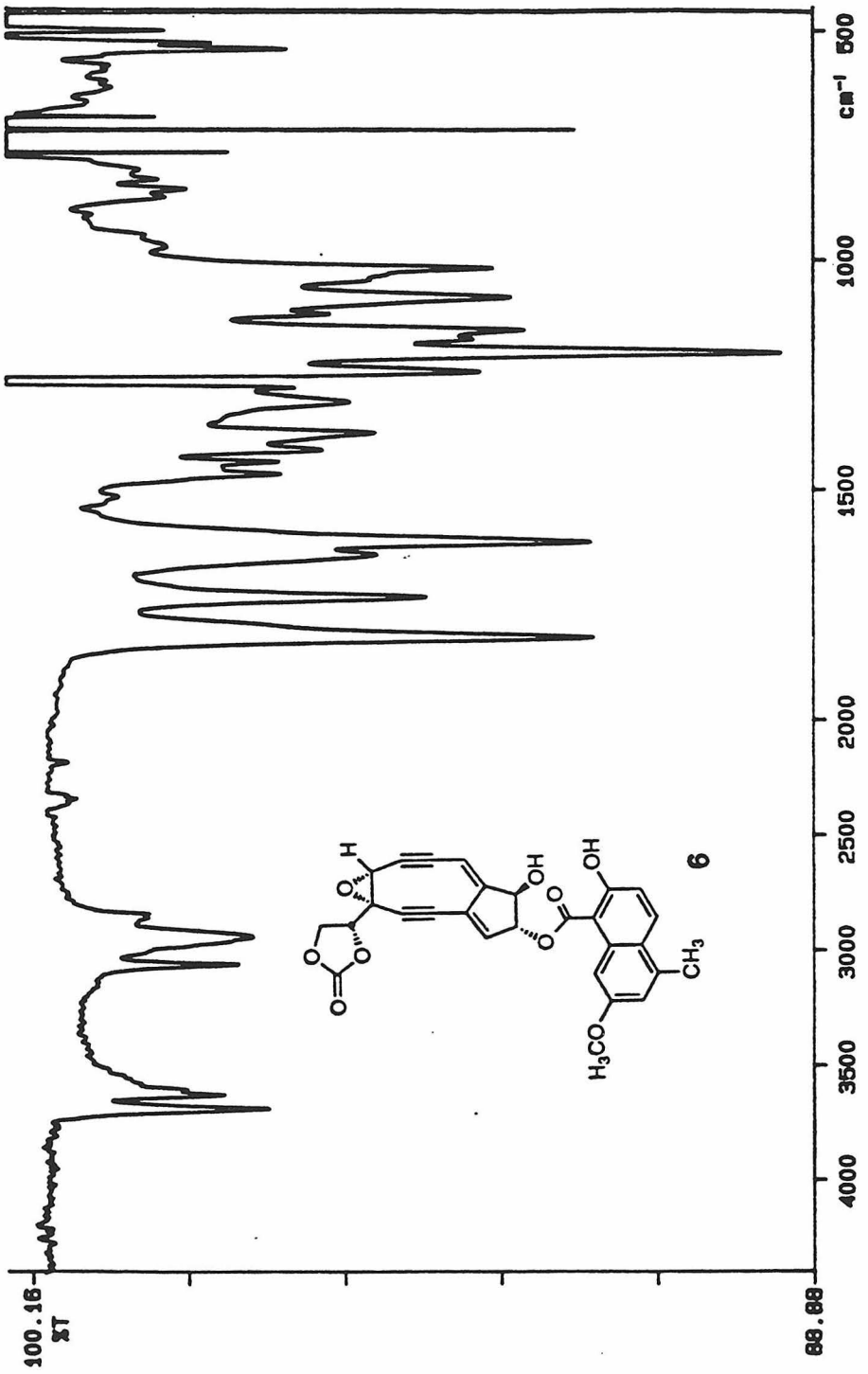

84.02
%T
73.84
4000 3500 3000 2500 2000 1500 1000 cm^{-1} 500

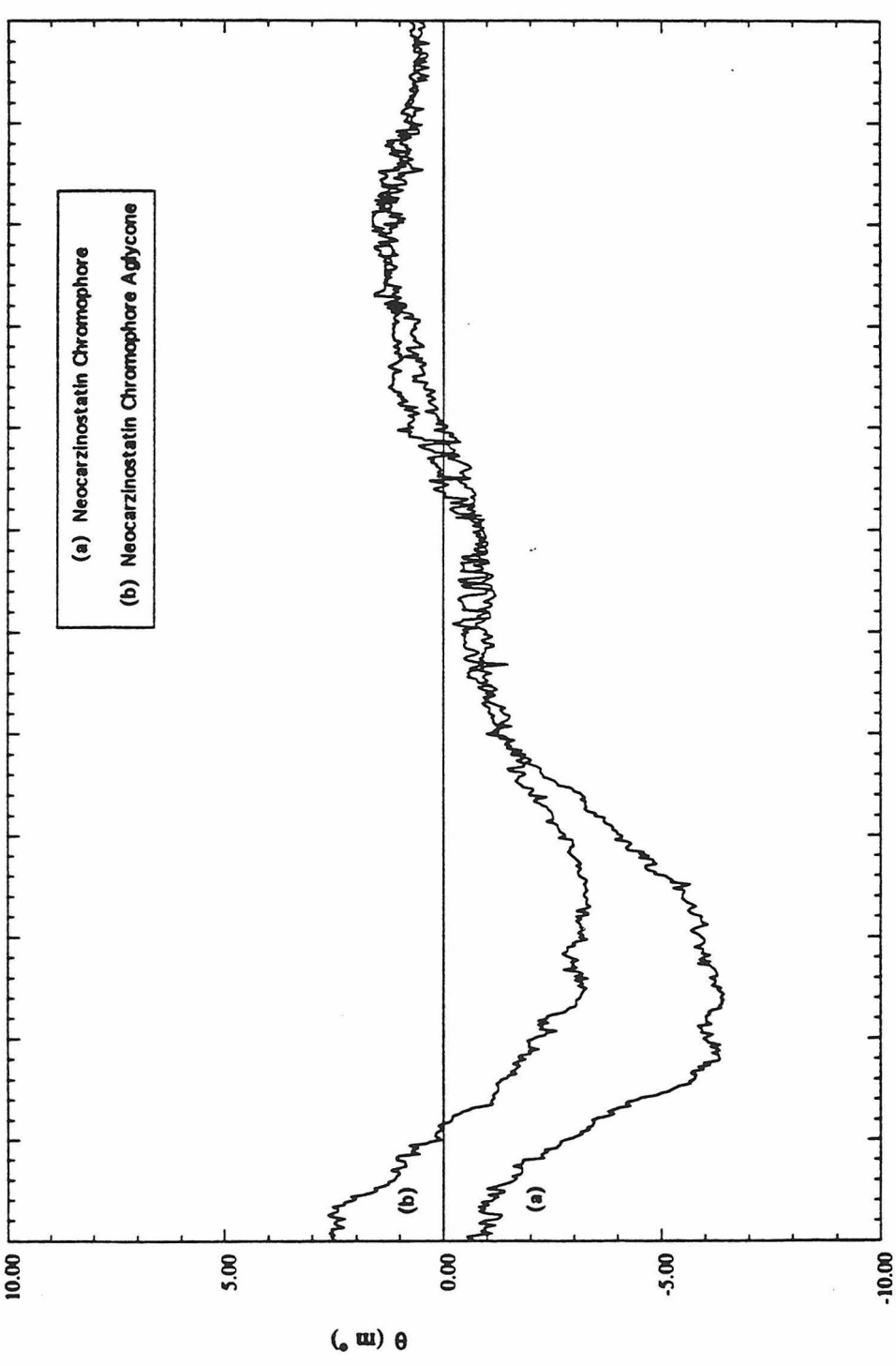

H
OH
O
O
O
O
O
O
OH
CH3
H3CO
120


63
H
H
OH
O
O
O
O
O
O
O
H3CO
OH
CH3
120
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20

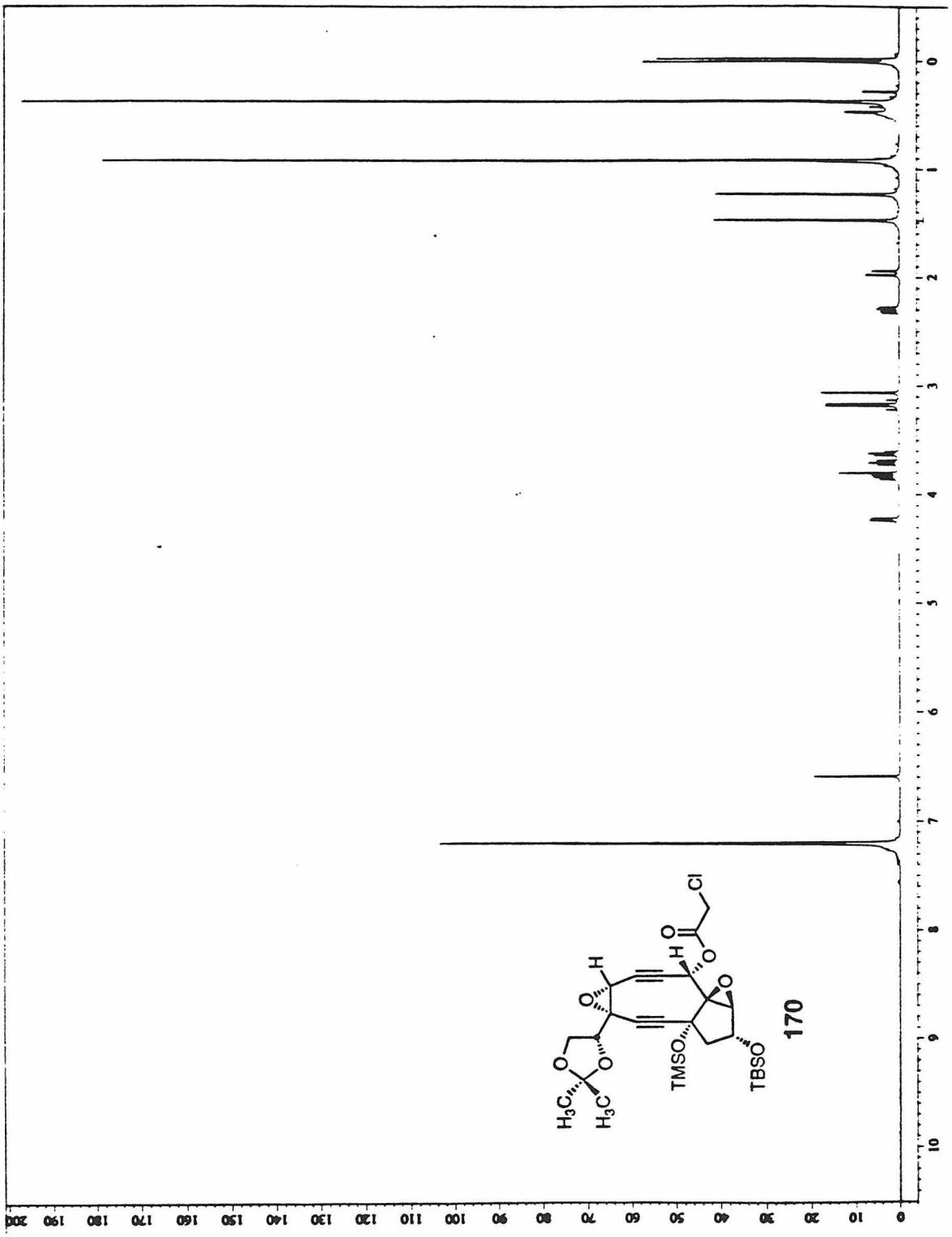

102.05
%T
73.85
4000
3500
3000
2500
2000
1500
1000
cm-1
500

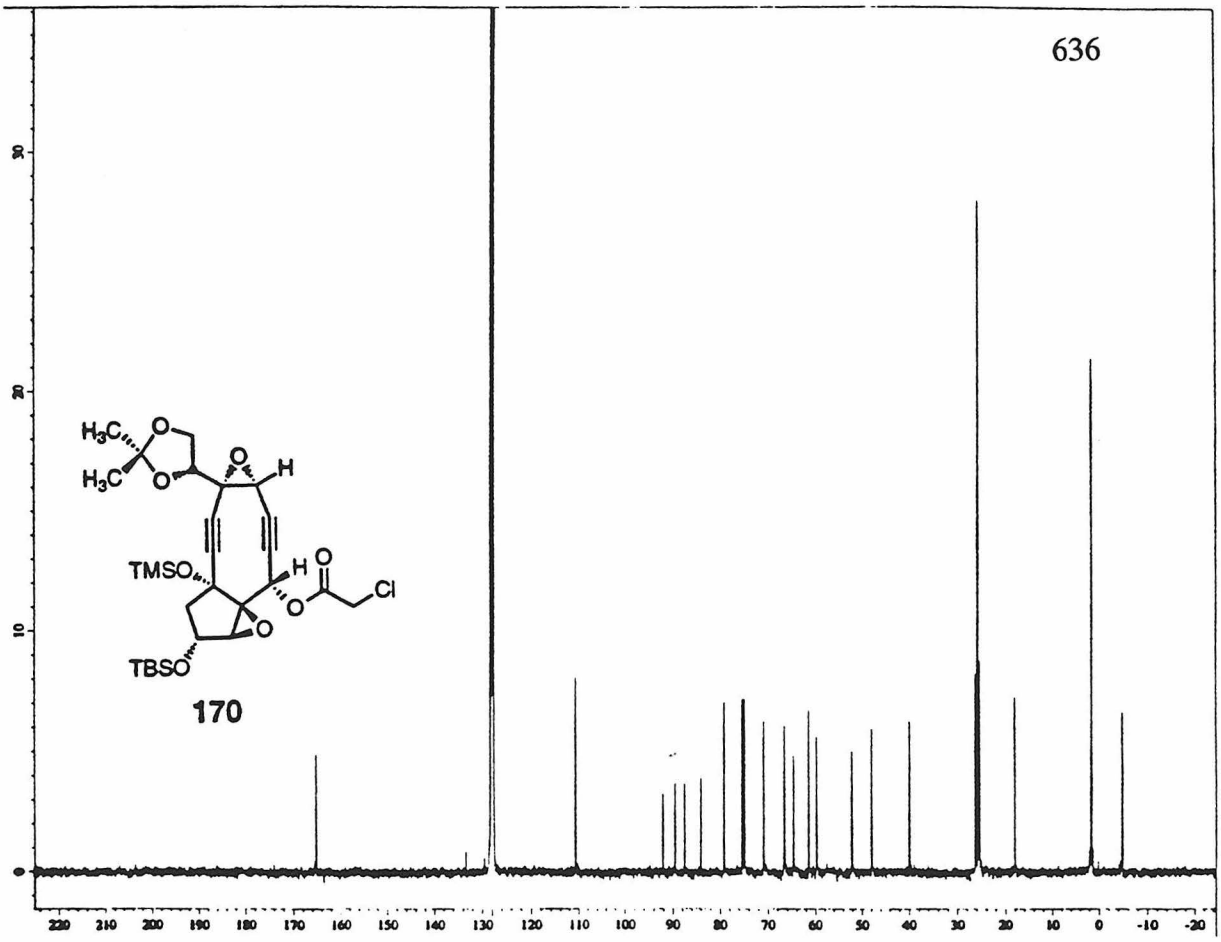

H
O
OH
O
O
O
O
O
OH
CH3
H3CO
6


100.16
%T
88.88
4000
3500
3000
2500
2000
1500
1000
500
cm⁻¹
OH
OH
H
O
O
O
O
O
O
CH3
H3CO
6

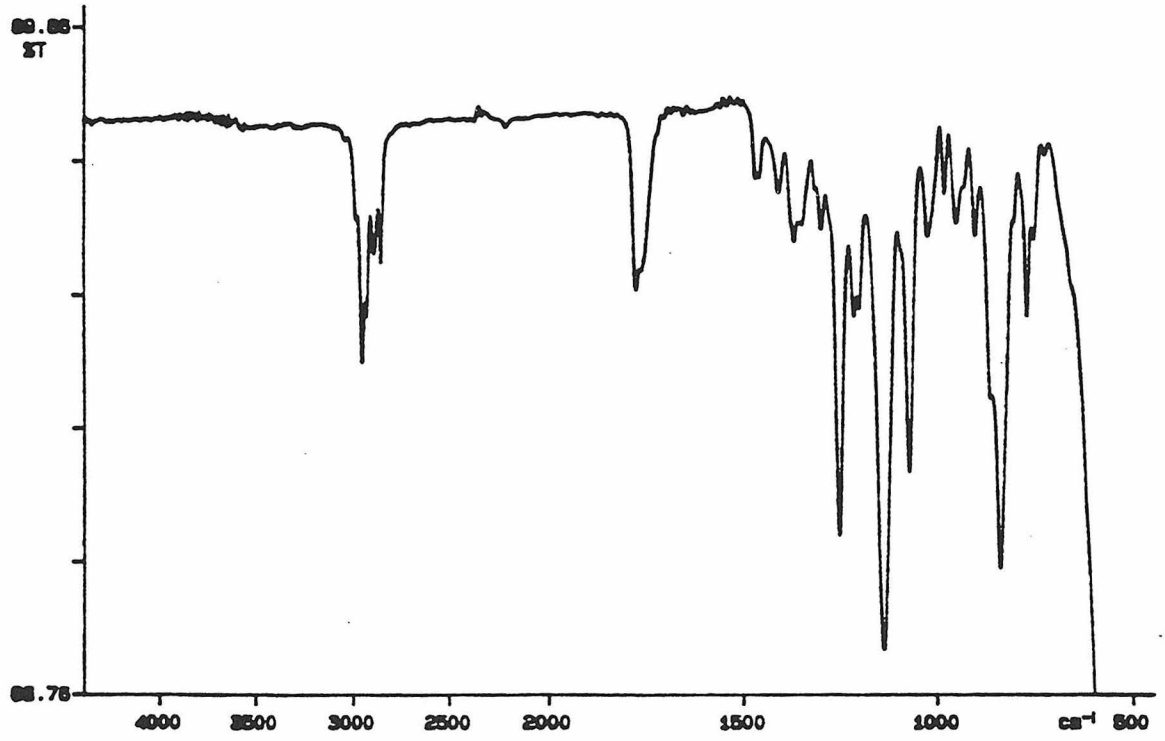


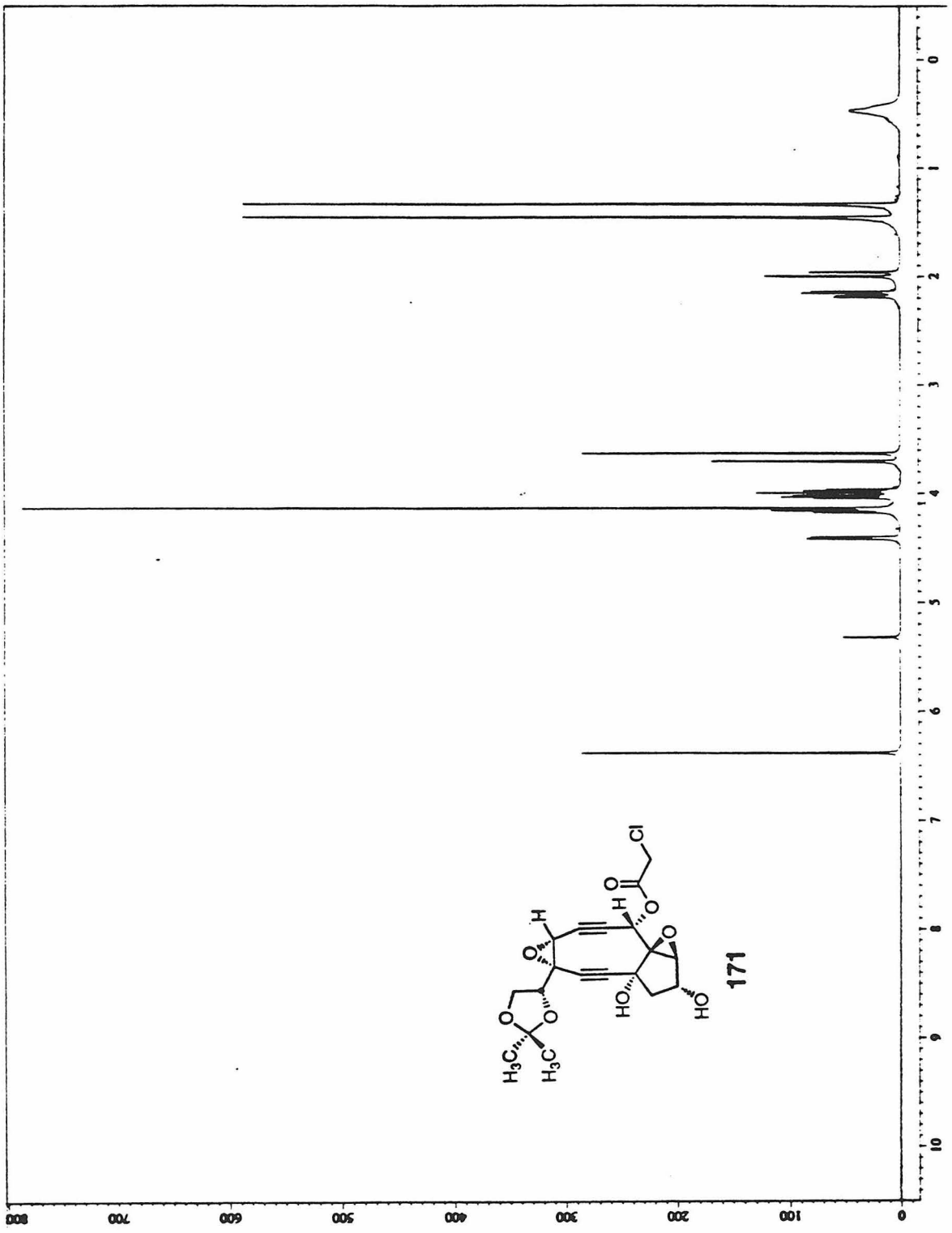
Neocarzinostatin Chromophore overlay with
Neocarzinostatin Chromophore Aglycone

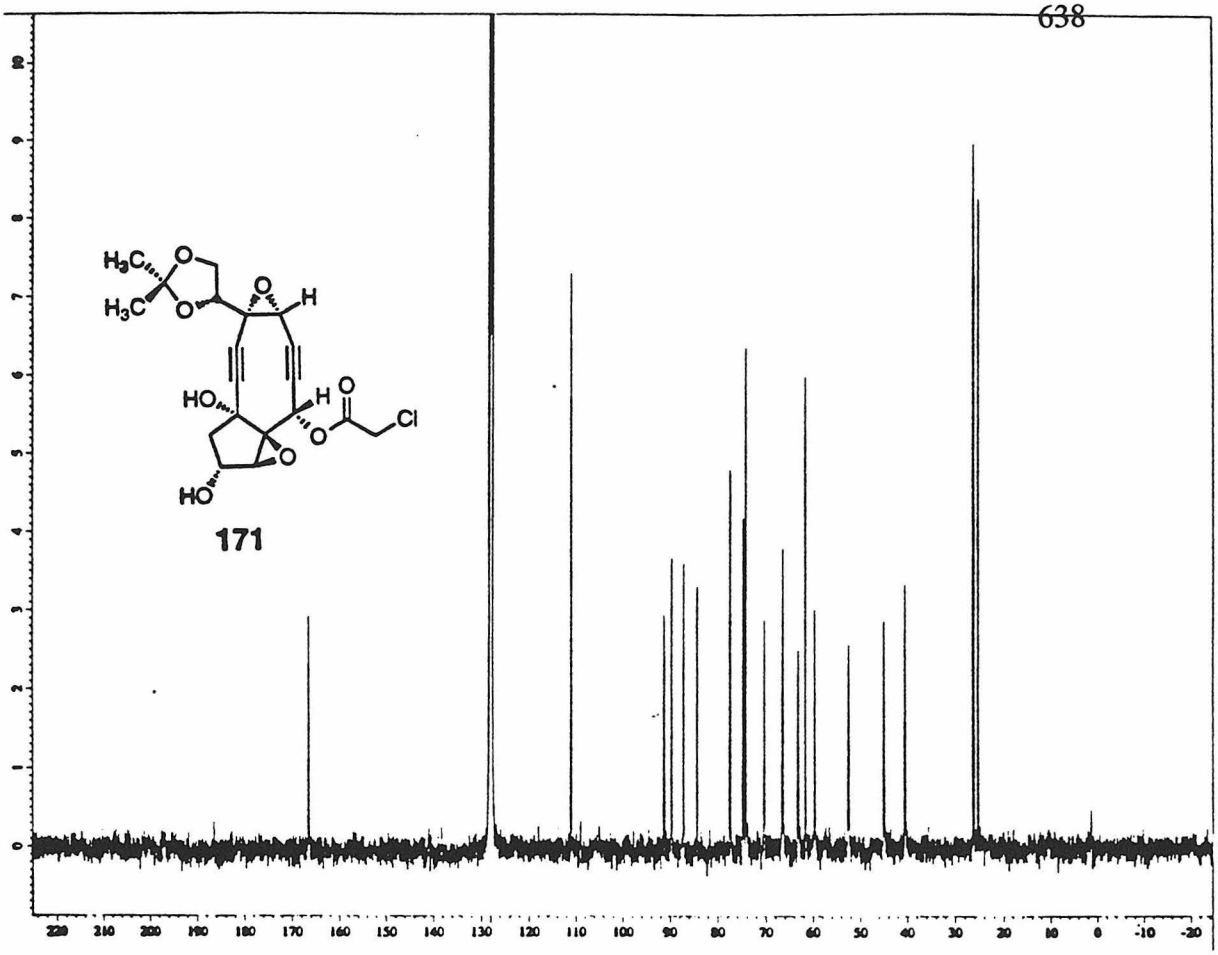

H3C
H3C
TMSO
TBSO
Cl
170


H3C
H3C
O
O
O
H
TMSO
H
O
O
Cl
O
TBSO

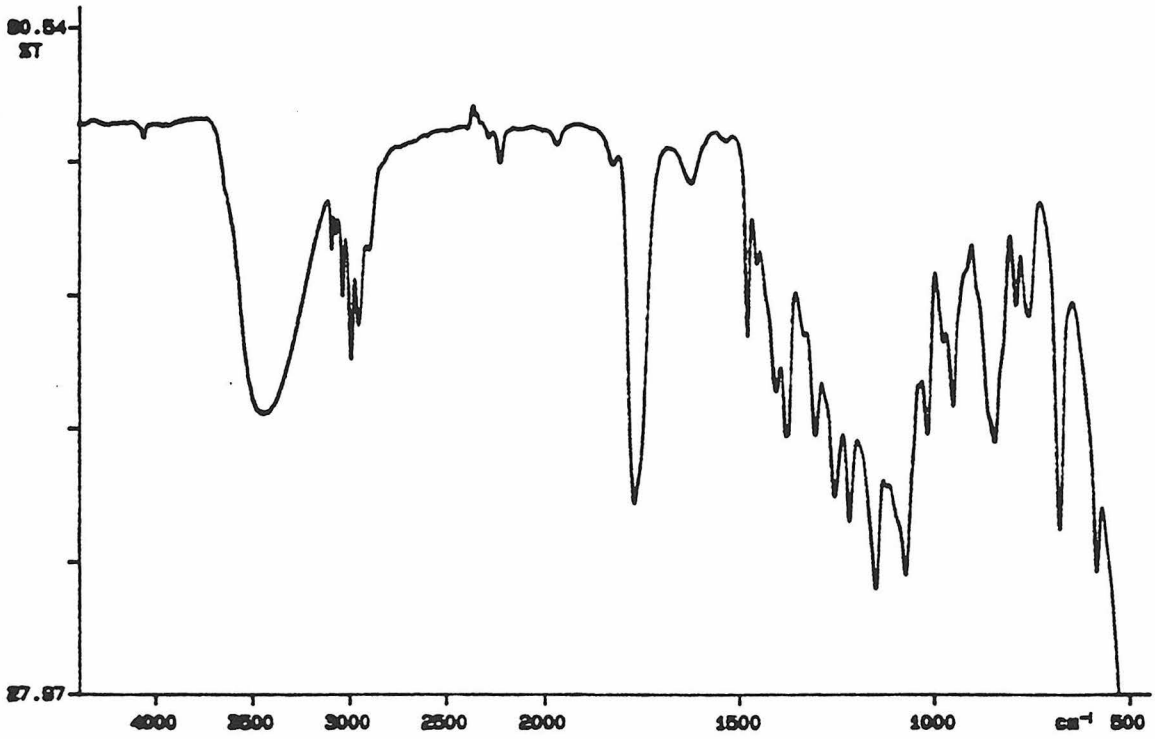
170

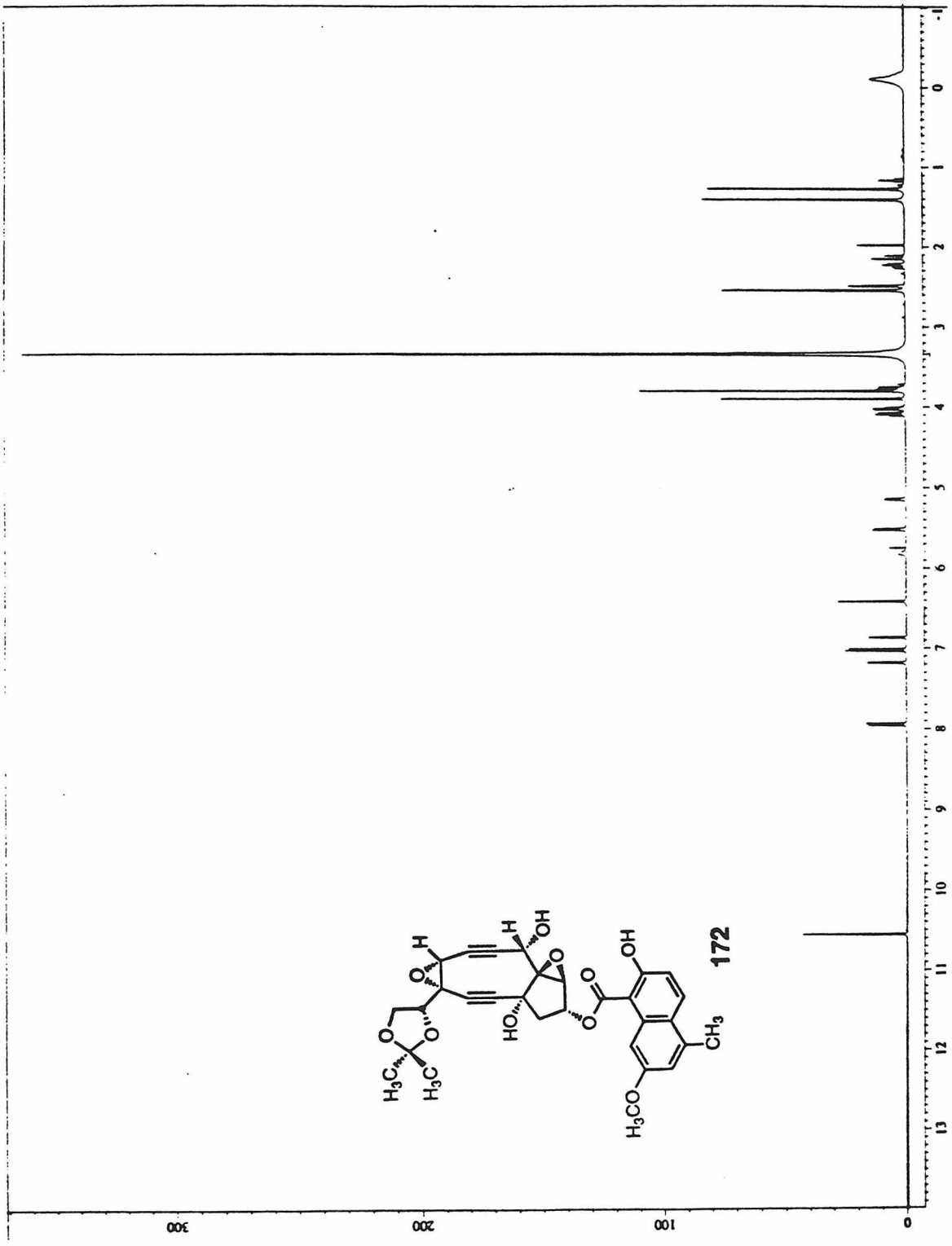

%T
4000
3500
3000
2500
2000
1500
1000
cm-1
500

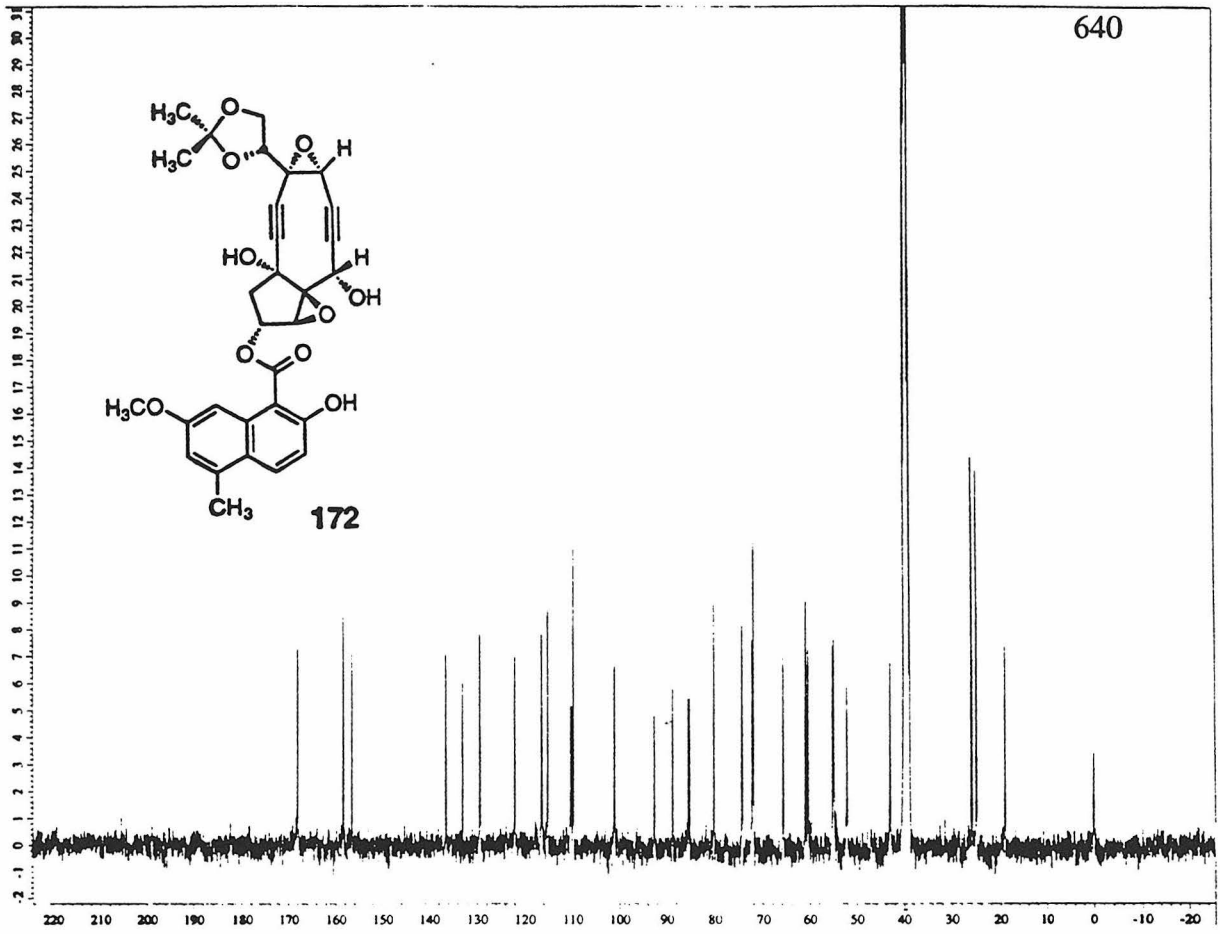

171

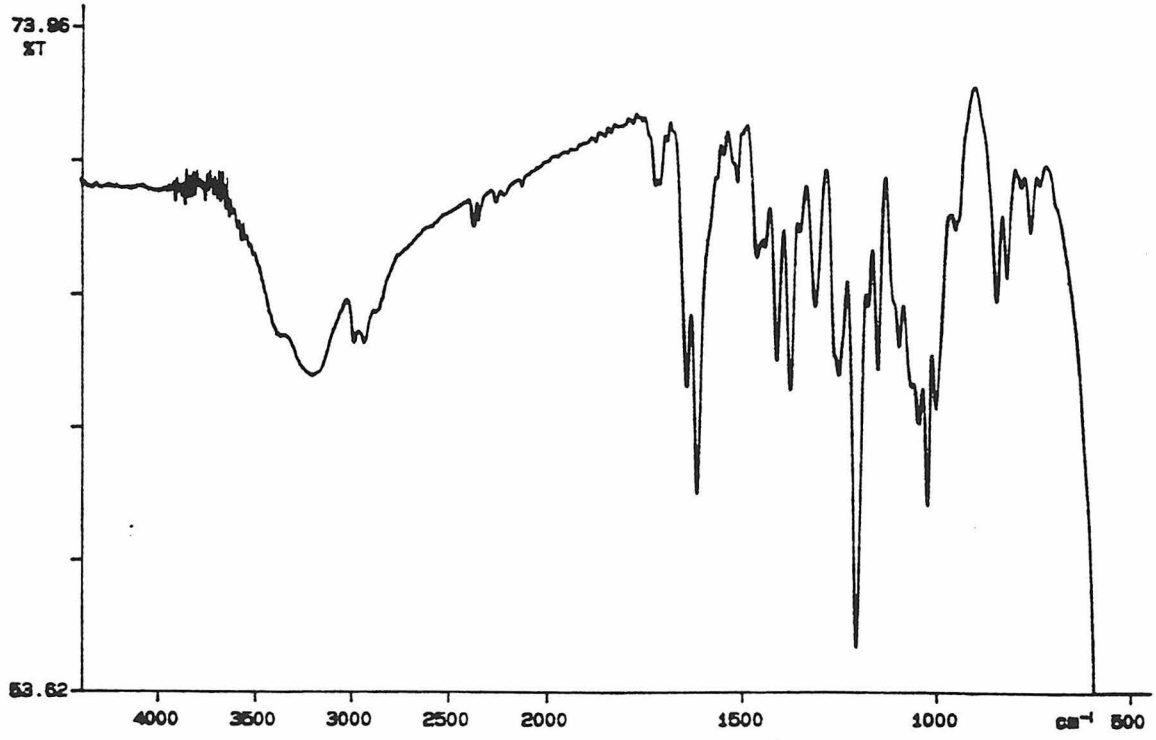

H3C
H3C
O
O
O
H
HO
H
O
Cl
O
O
HO

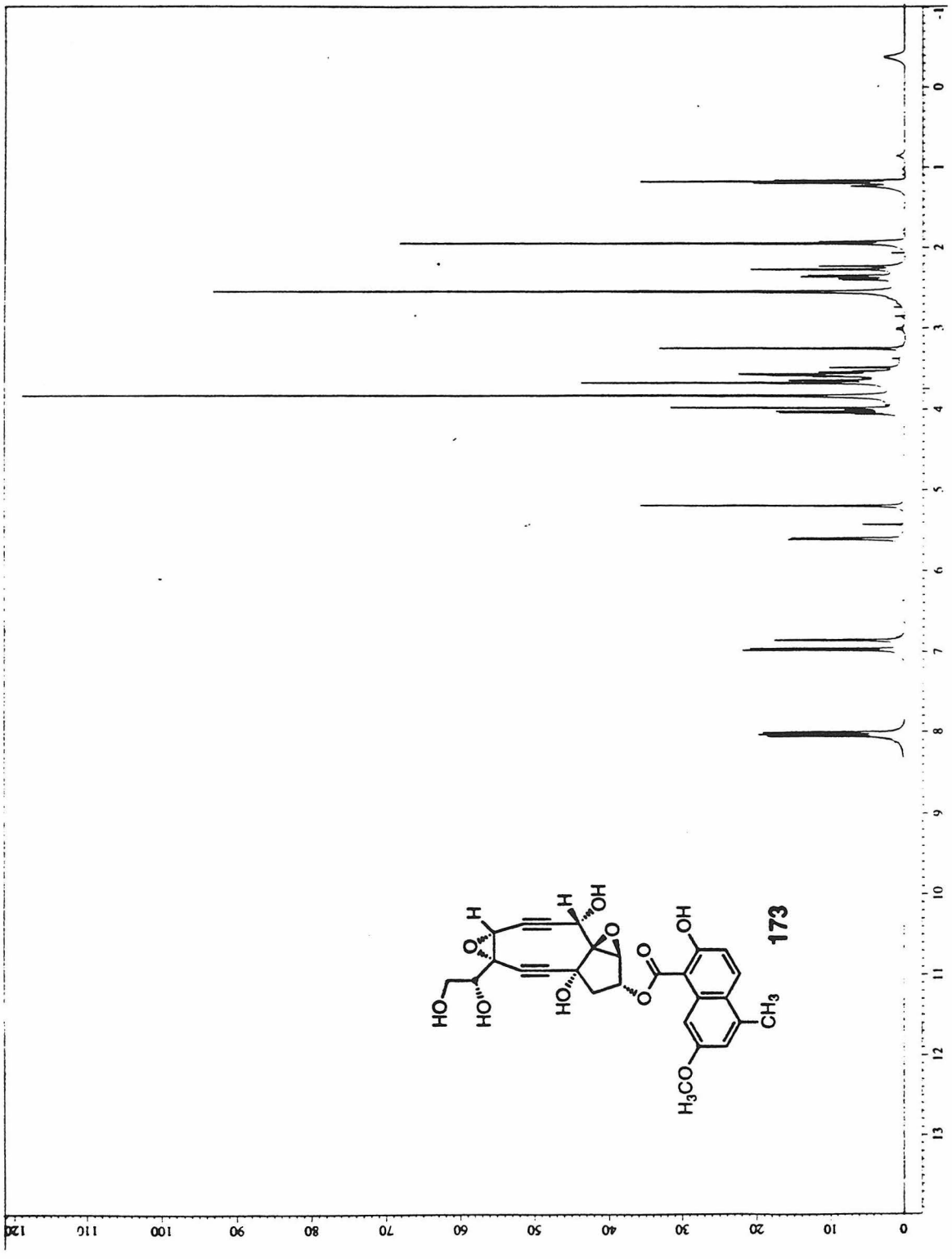
171


80.54
%T
27.97
4000
3500
3000
2500
2000
1500
1000
cm-1
500

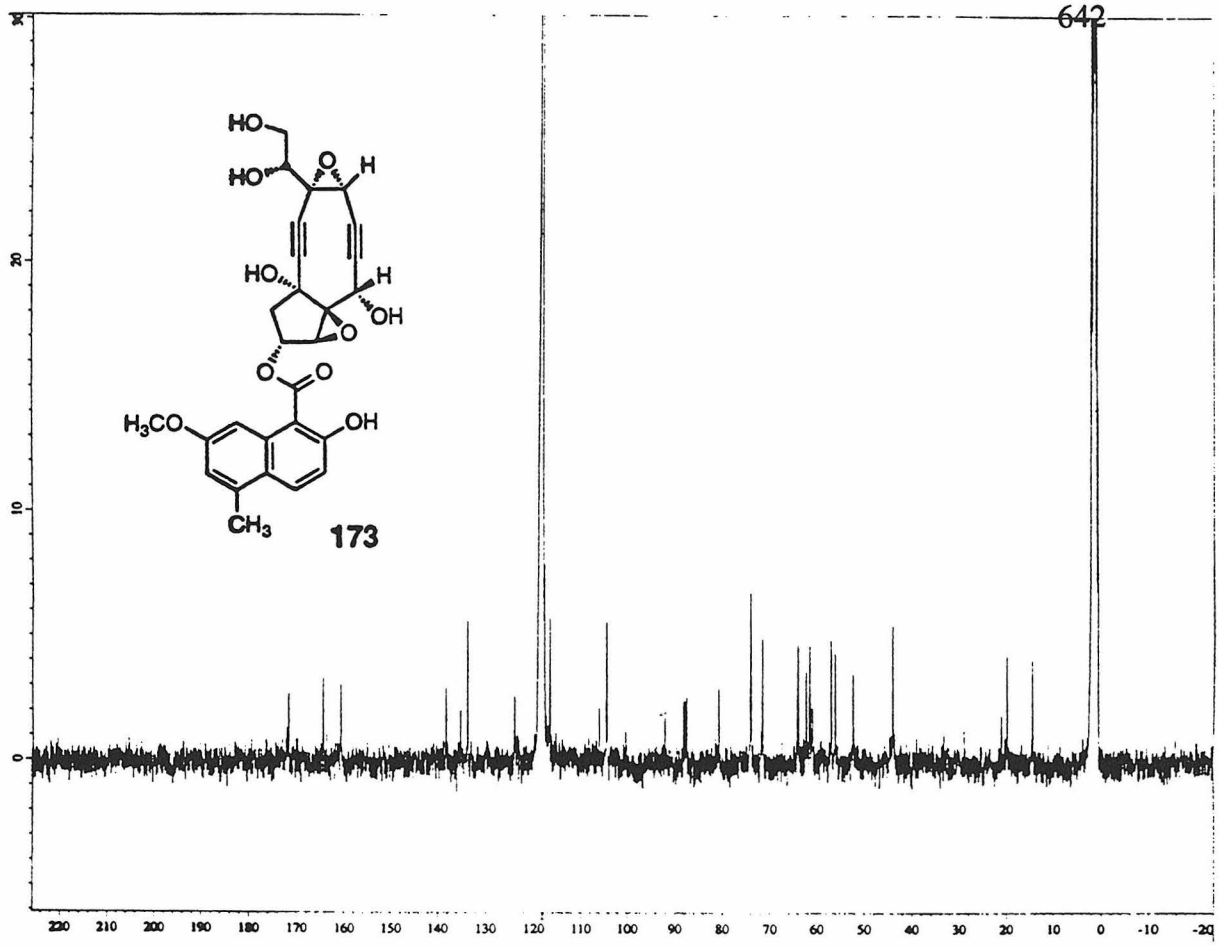

172

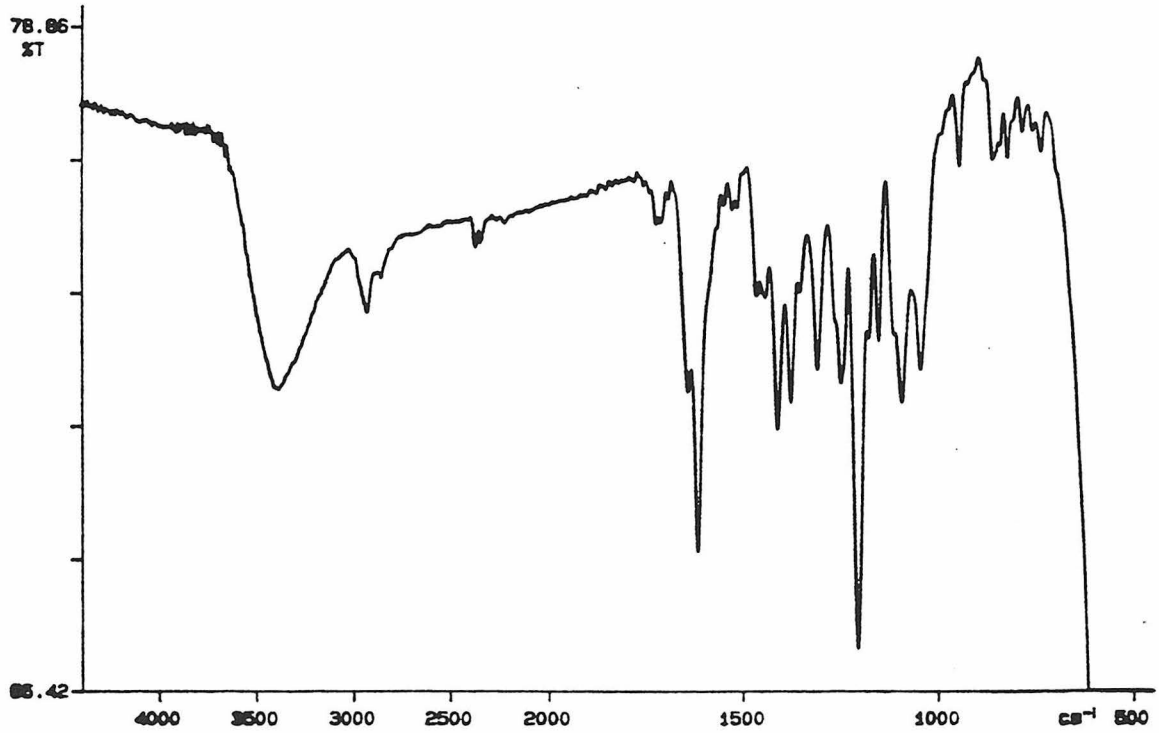

640
H3C
O
H3C
O
O
H
HO
H
OH
O
O
O
H3CO
OH
CH3
172
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20

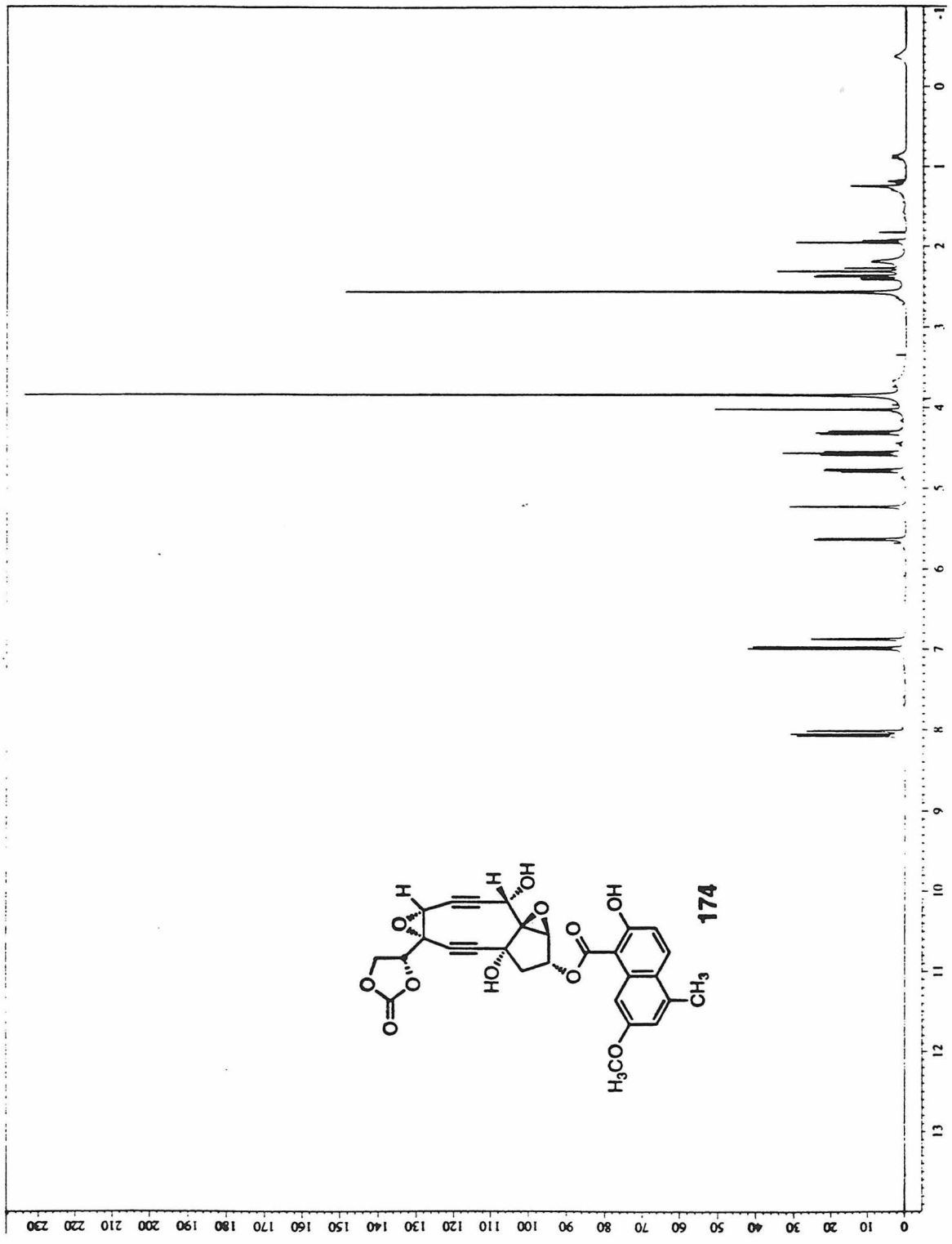

73.86
%T
53.62
4000 3500 3000 2500 2000 1500 1000 cm-1 500

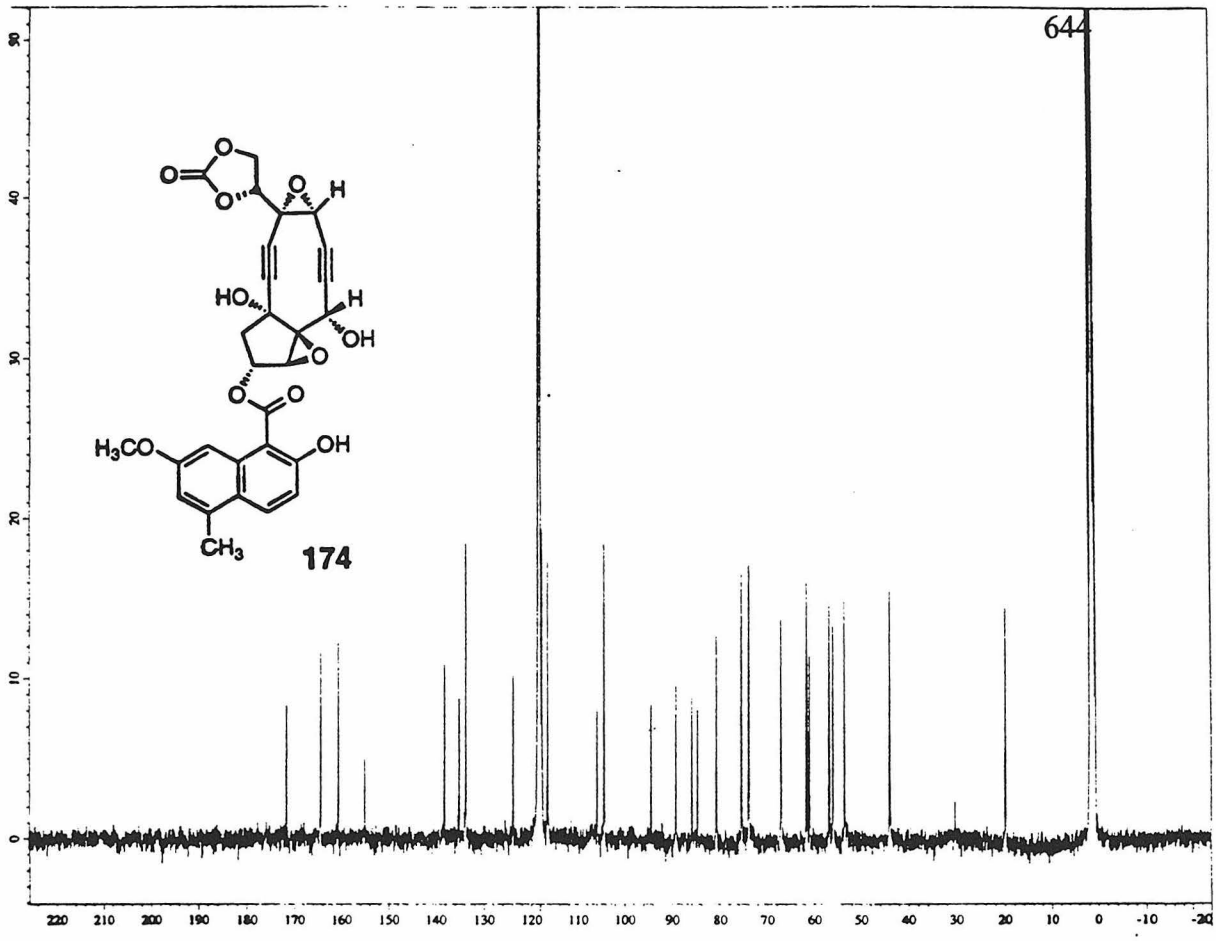


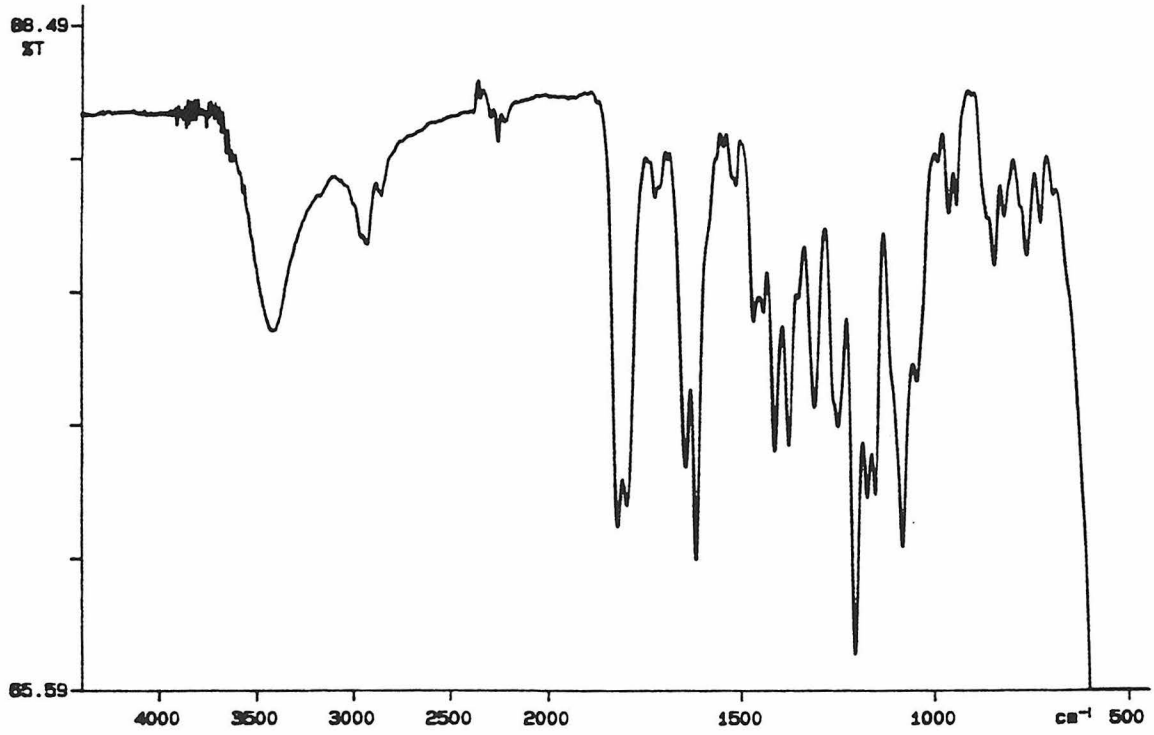
173

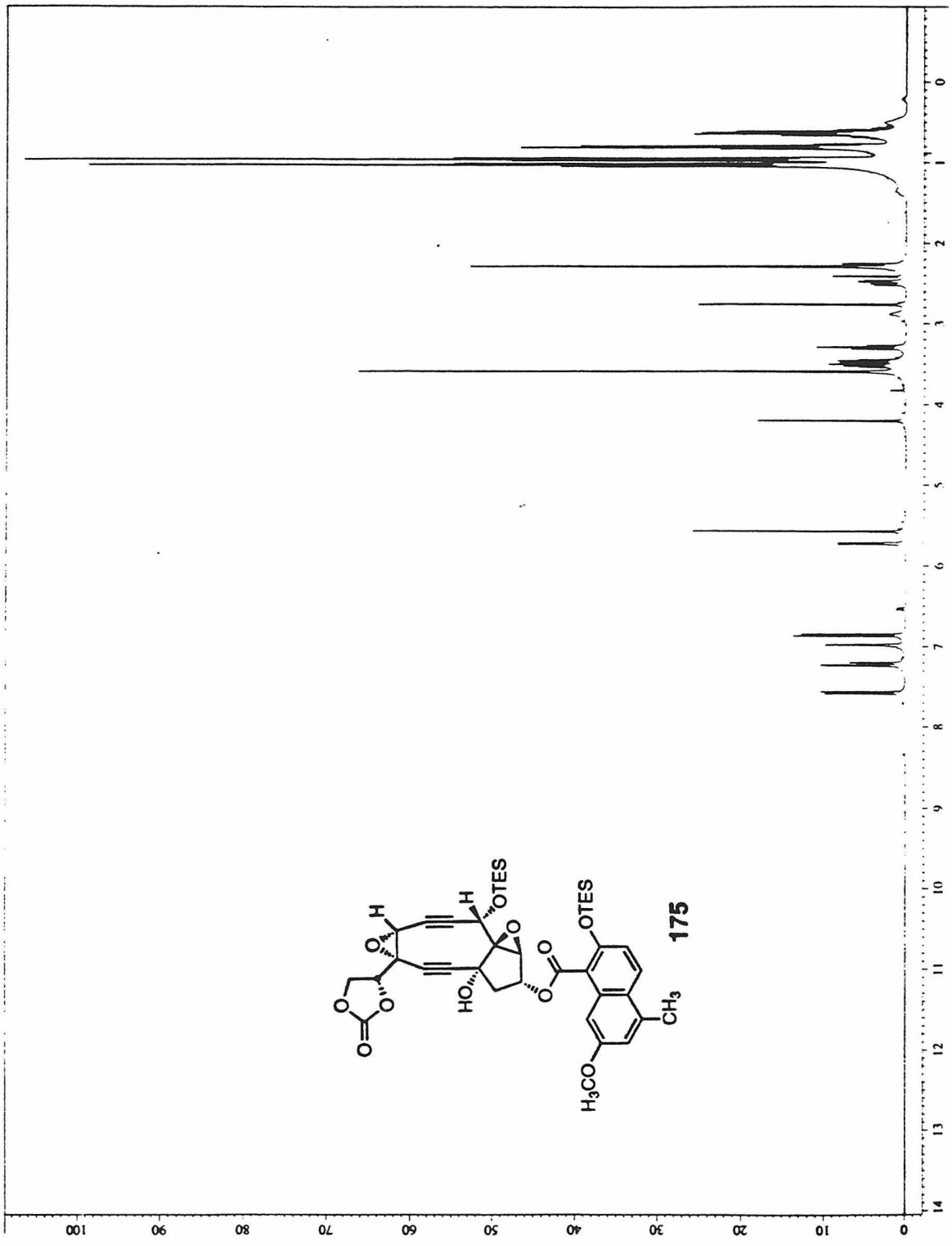

HO
HO
O
H
HO
H
OH
O
O
O
H3CO
OH
CH3
173
30
20
10
0
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20

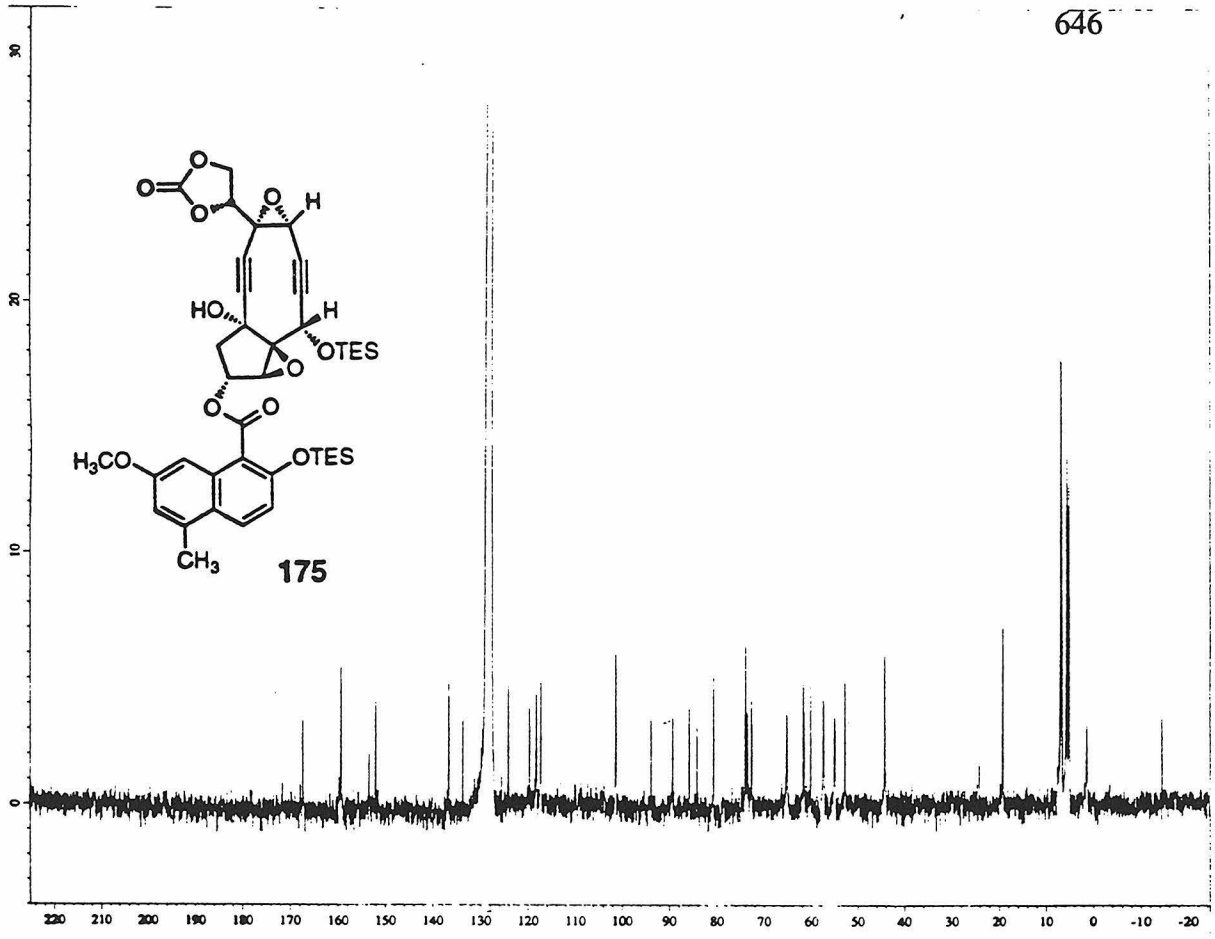

78.86
%T
65.42
4000
3500
3000
2500
2000
1500
1000
cm-1
500

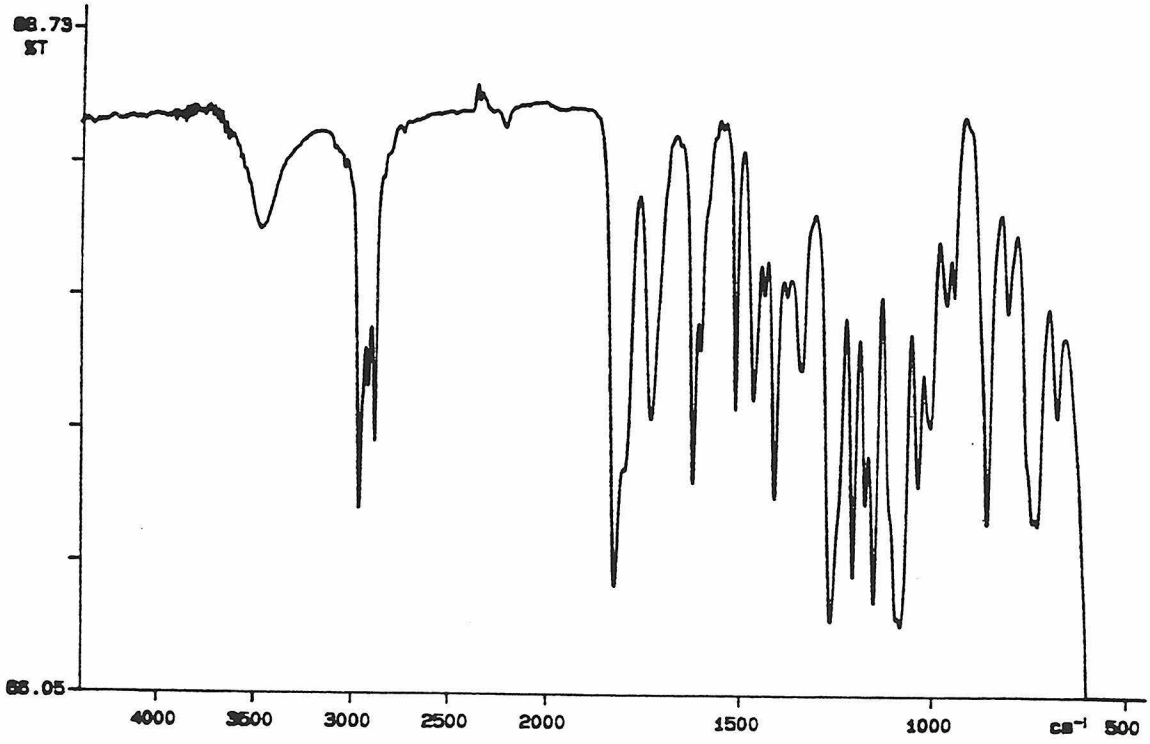

174

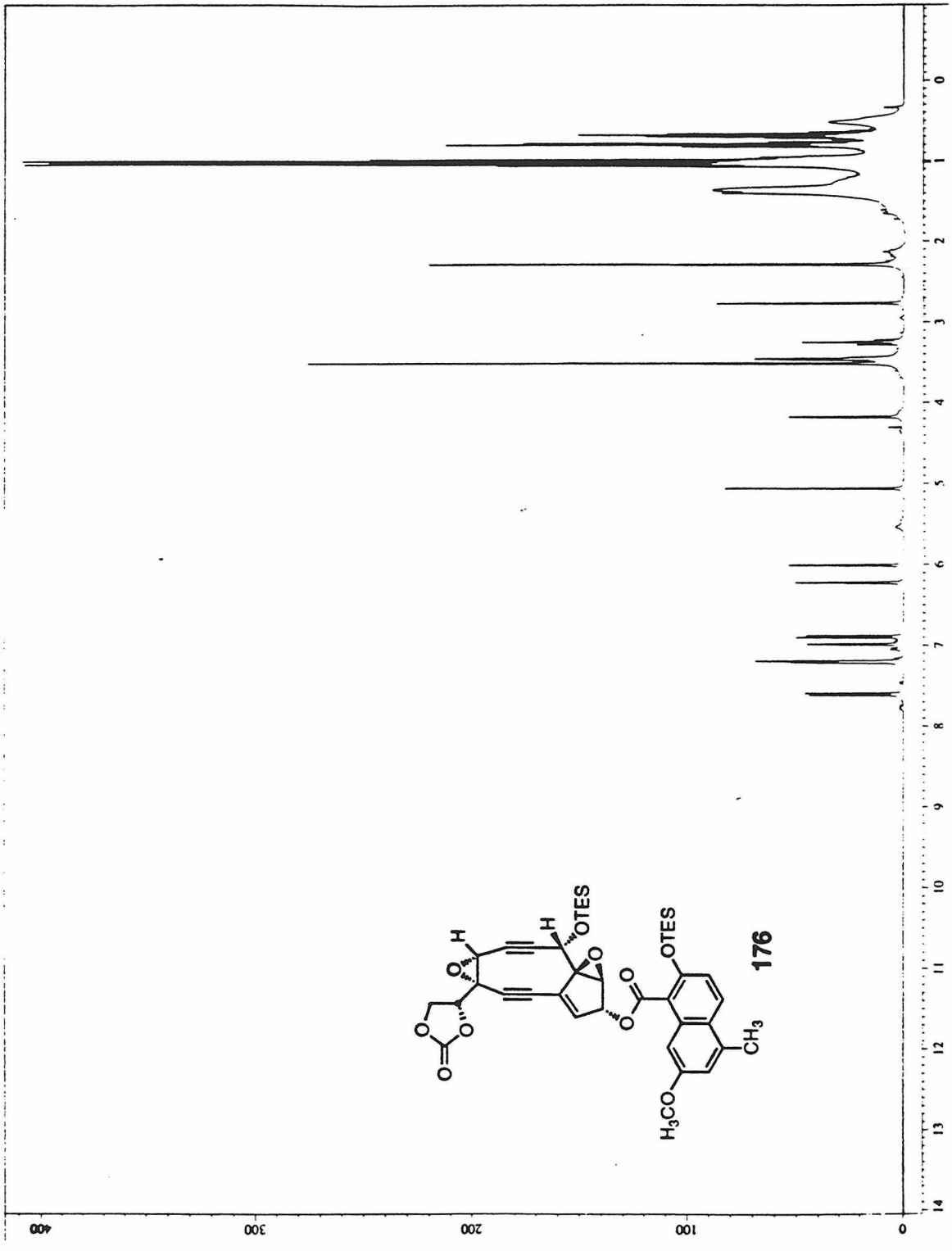

644
174

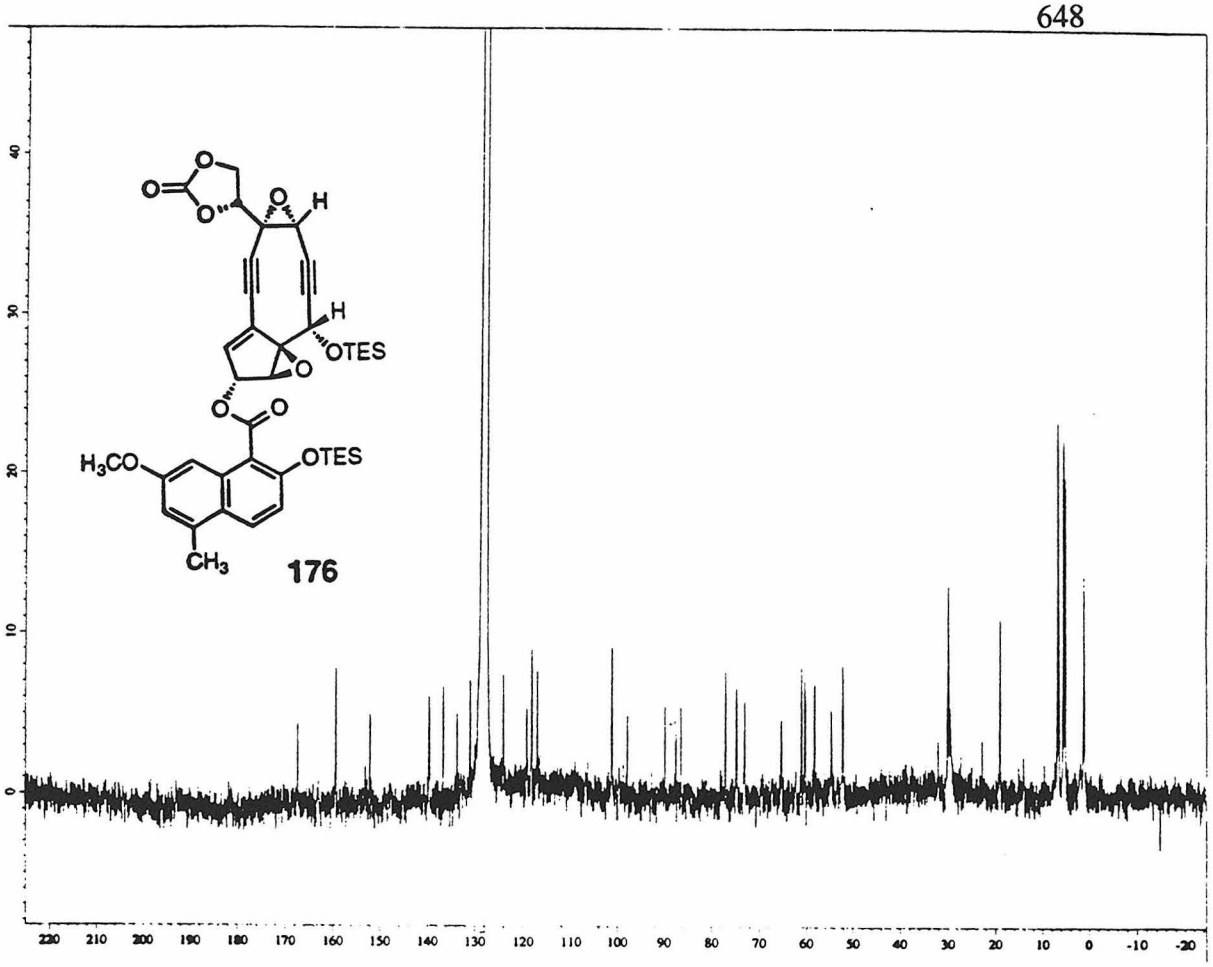

88.49
%T
65.59
4000
3500
3000
2500
2000
1500
1000
cm⁻¹
500

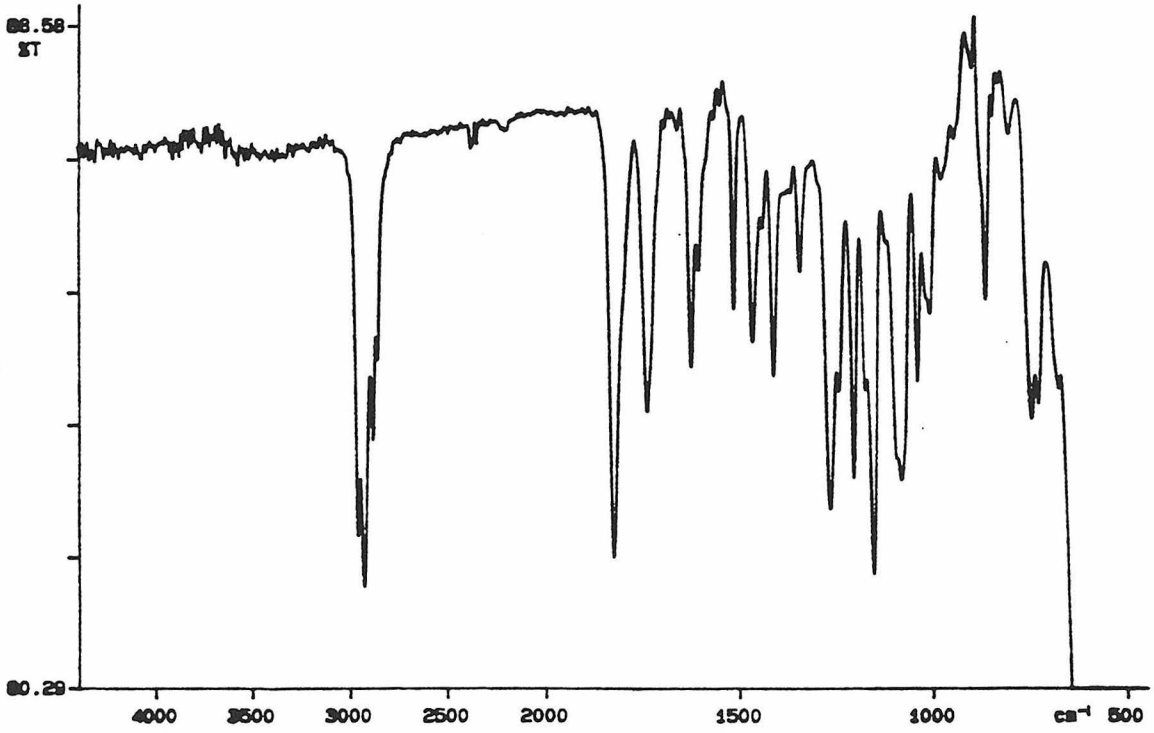

H
OTES
H
O
HO
O
O
O
O
OTES
CH3
H3CO
175

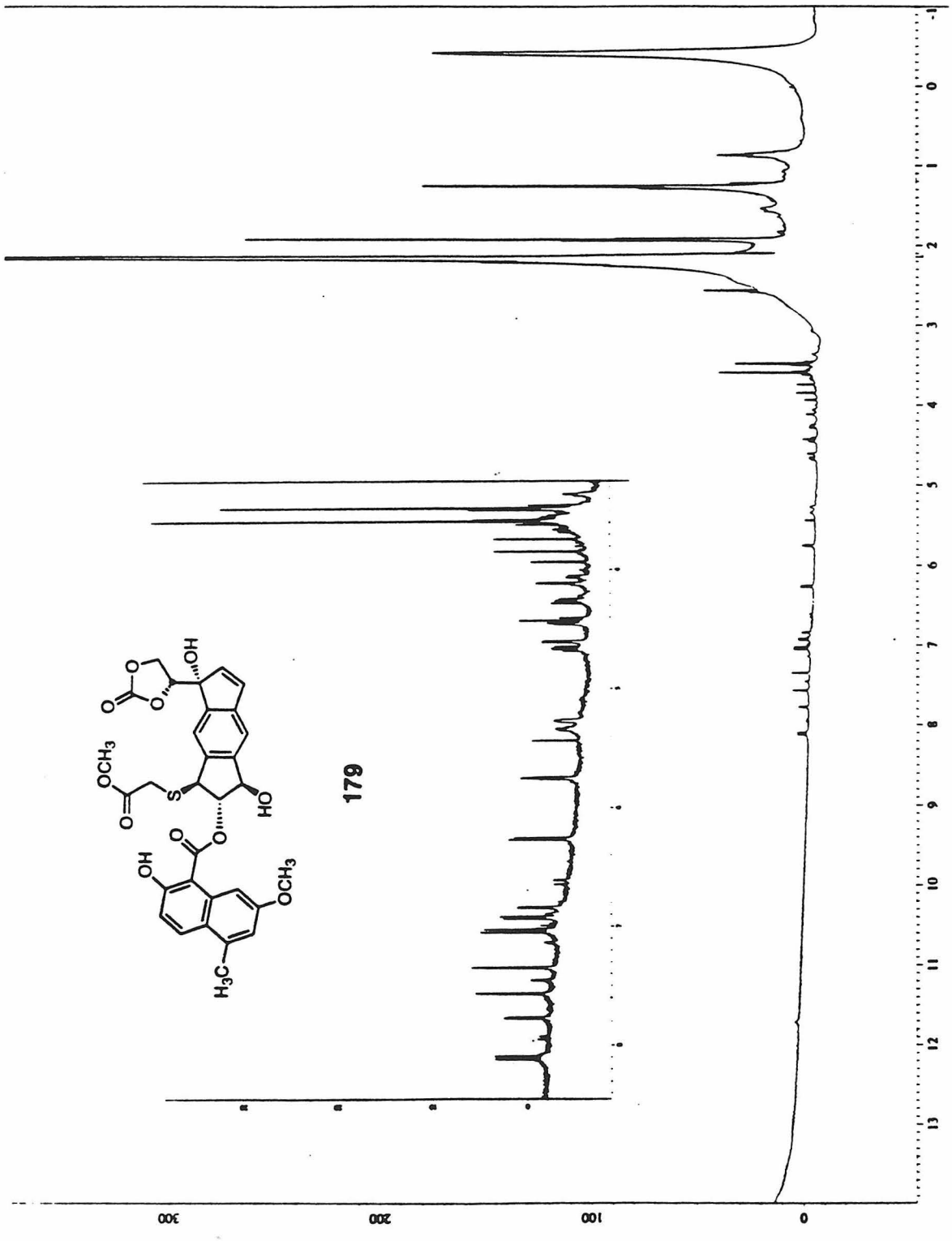

HO
H
OTES
O
O
O
O
O
H3CO
OTES
CH3
175
30
20
10
0
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20

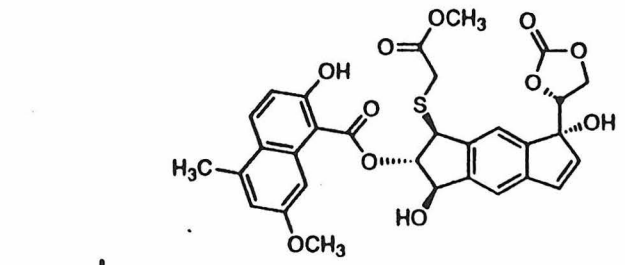

88.79
%T
88.05
4000
3500
3000
2500
2000
1500
1000
cm-1
500

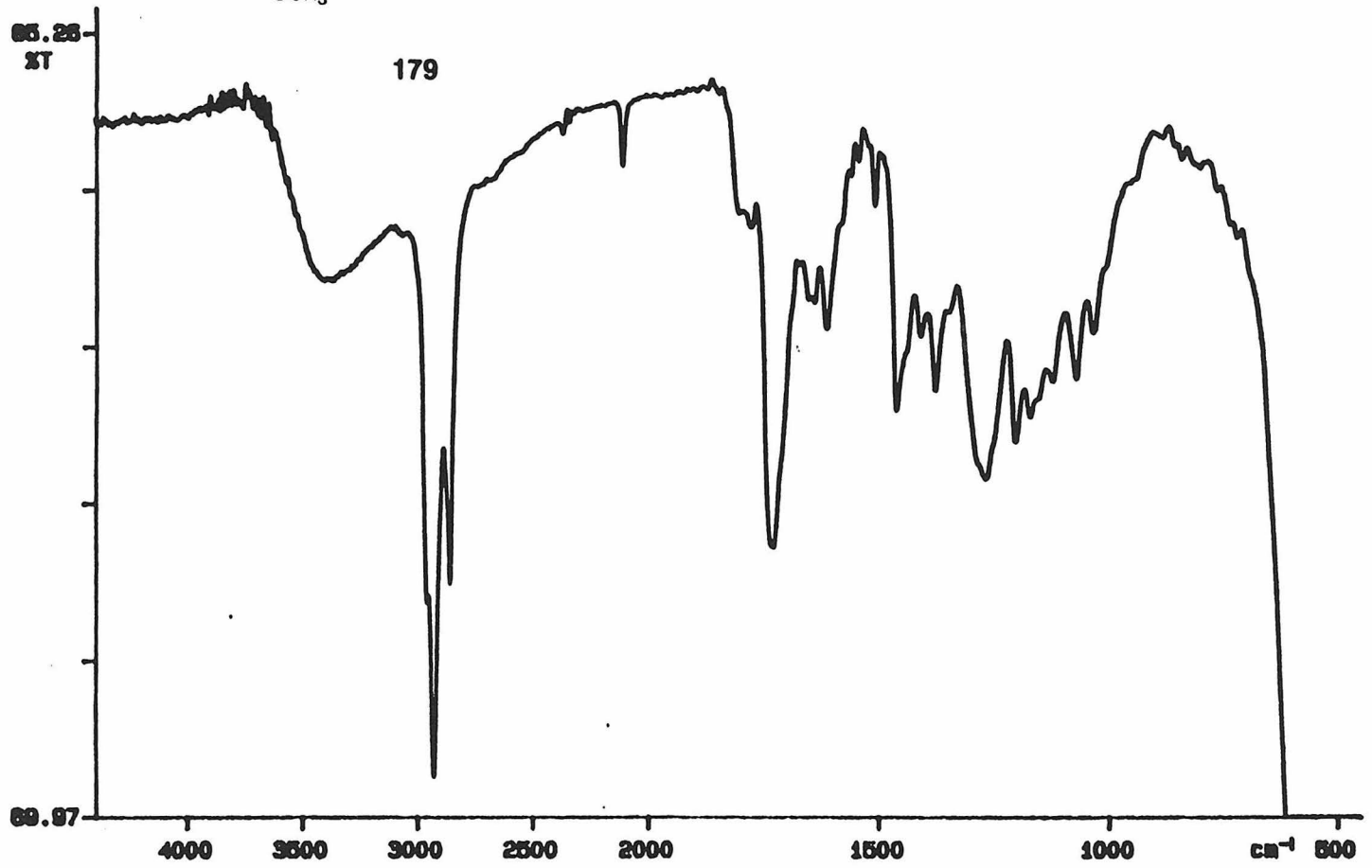

OTES
OTES
H
H
O
O
O
O
O
O
O
CH_3
H_3CO
176


H
OTES
O
O
O
O
O
H3CO
OTES
CH3
176
40
30
20
10
0
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20


88.58
%T
80.29
4000
3500
3000
2500
2000
1500
1000
cm-1
500


179
OCH3
OH
HO
OCH3
H3C
O
S


OCH3
O
O
O
O
OH
S
OH
H3C
O
HO
OCH3


95.26
%T
179
69.97
4000
3500
3000
2500
2000
1500
1000
cm-1
500