Synthesis of (+)-Dynemicin A and Analogs of Wide Structural Variability. Establishment of the Absolute Configuration of Natural Dynemicin A.

Thesis by

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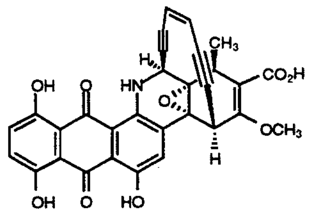
I am most grateful to my parents and Marion for their love, support and encouragement. I am forever indebted to Marion for her patience over the last five years.

Abstract

A highly convergent synthetic route to the potent natural antitumor agent (+)-dynemicin A (**1**) is described. Key features of the synthesis include: (1) the condensation of the potassium enolate of menthyl acetoacetate with *trans*-ethyl crotonate, providing the optically pure *trans*-disubstituted 1,3-cyclohexanedione **38**; (2) the palladium-catalyzed coupling of the enol triflate **37** with *t*-butyl 2-borono-4-methoxycarbanilate to furnish **35**, followed by the thermolysis of the latter to afford the quinolone **34**; (3) the stereoselective acetylide addition of the (*Z*)-enediyne bridge to an acylquinolinium intermediate derived from quinoline **60**, affording the addition product **61**; (4) the acetylide-mediated closure of the (*Z*)-enediyne bridge of ketone **65** to produce **66**; (5) the carboxylation and subsequent methylation of ketone **69**, providing the vinylogous carbonic acid **70**; (6) the oxidation of the phenol **73** to furnish the enone **74**, as well as the reductive deprotection of **75** to afford the quinone imine **77**; and (7) the Diels-Alder cycloaddition reaction of the quinone imine **77** with 1,4,7-tris(trimethylsiloxy)isobenzofuran, followed by the desilylation and oxidation of the resultant adduct to complete the synthesis of **1**. The preparation of structurally diverse analogs of **1** by late-stage modification of the synthetic route is detailed. The absolute configuration of natural **1** is determined to be 2*S*, 3*S*, 4*S*, 7*R*, 8*R*, by the comparison of circular dichroism spectra of synthetic and authentic **1**.



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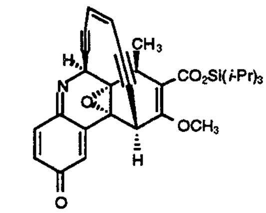

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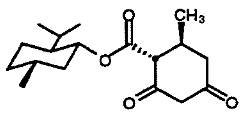

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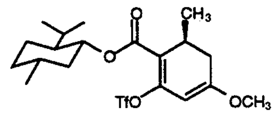

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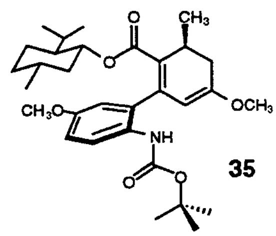

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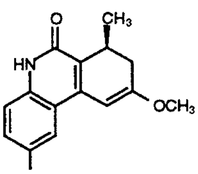

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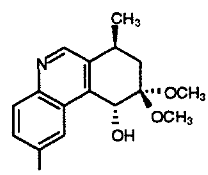

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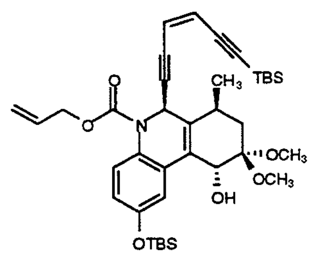

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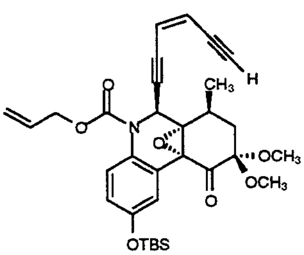

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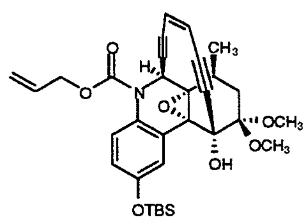

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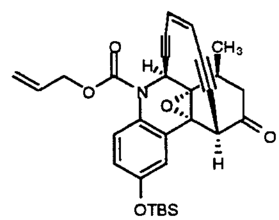

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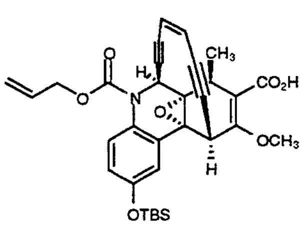

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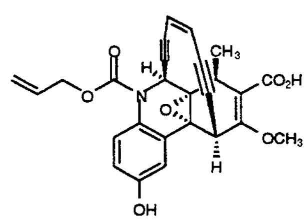

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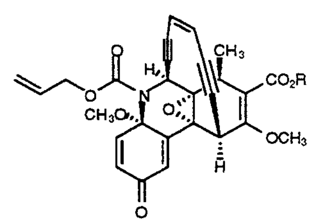

74 R = H
75 R = Si(*i*-Pr)$_3$

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Index of Figures and Schemes

List of Abbreviations

$[\alpha]_D^{22}$	optical rotation (589 nm, 22 °C)
Å	angstrom
Ac	acetyl
AIBN	2,2'-azobis(isobutyronitrile)
aq	aqueous
Boc	*t*-butyloxy carbonyl
bp	boiling point
Bu	butyl
°C	degrees Celsius
CAM	ceric ammonium molybdate
C_6D_6	hexadeuteriobenzene
CI	chemical ionization
cm^{-1}	reciprocal centimeters
CSA	10-camphorsulfonic acid
δ	chemical shift
DIBAL	diisobutylaluminum hydride
DMAP	4-dimethylaminopyridine
DMF	*N*,*N*-dimethylformamide
DMSO	dimethyl sulfoxide
DNA	deoxyribonucleic acid
E	entgegen

equiv	equivalent
EI	electron impact
Et	ethyl
EtOAc	ethyl acetate
FAB	fast atom bombardment
4Å MS	4 angstrom molecular sieves
FT	Fourier transform
g	gram
GSH	glutathione
h	hour
HMPA	hexamethylphosphoramide
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectroscopy
Hz	Hertz
i	iso
IR	infrared
J	coupling constant
L	liter
LTMP	lithium 2,2,6,6-tetramethylpiperdide
m	meta
M	molar
$[M]^+$	molecular ion
m-CPBA	*meta*-chloroperoxybenzoic acid
MeOH	methyl alcohol
mesitylene	1,3,5-trimethylbenzene
mg	milligram

MHz	megahertz
min	minute
mL	milliliter
mm Hg	millimeters of mercury
mmol	millimole
mol	mole
mp	melting point
Ms	methanesulfonyl
μL	microliter
n	normal
N	normal (concentration)
NADPH	nicotinamide adenine dinucleotide phosphate
NBS	*N*-bromosuccinimide
NIS	*N*-iodosuccinimide
nm	nanometer
NMR	nuclear magnetic resonance
o	ortho
p	para
PCC	pyridinium chlorochromate
PDC	pyridinium dichromate
pH	hydrogen ion concentration (log scale)
Ph	phenyl
ppm	parts per million
Pr	propyl
psi	pounds per square inch
Py	pyridine

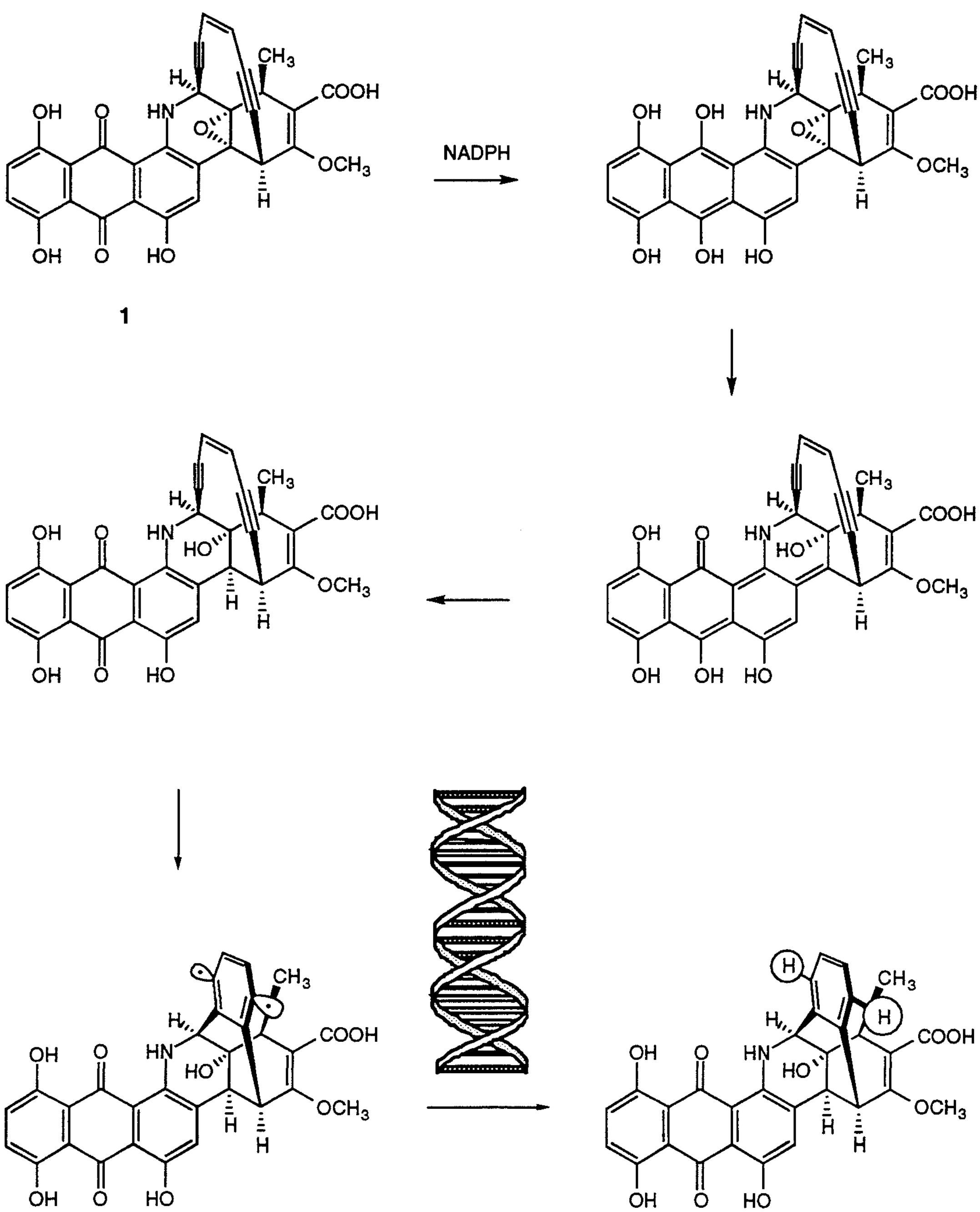
R	rectus
R_f	retention factor
s	seconds
S	sinister
SEM	2-(trimethylsilyl)ethoxymethyl
t	tertiary
TBAF	tetrabutylammonium fluoride
TBS	*tert*-butyldimethylsilyl
Tf	trifluoromethylsulfonyl
TFAA	trifluoroacetic anhydride
THF	tetrahydrofuran
3-N	three-necked
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TMS	trimethylsilyl
Ts	toluenesulfonyl
UV	ultraviolet
v/v	volume-to-volume ratio
w/v	weight-to-volume ratio
xs	excess
Z	zusammen

Chapter 1

Introduction

Dynemicin A (**1**) is a natural product isolated from the soil bacterium *Micromonospora chersina* and is unique among natural antitumor agents, possessing features of both the anthracycline and enediyne antibiotic families.[1] The highly reactive anthraquinone fragment imbues the molecule with its deep blue color and is characteristic of the anthracyclines,[2] while the (*Z*)-enediyne bridge and epoxide ring classify it among the enediyne antibiotics.[3] These same features are believed to be essential to the antitumor activity of **1**, the mechanism of which is proposed to involve an initial reduction of the anthraquinone moiety by NADPH or a thiol, leading to the opening of the epoxide through the intermediacy of a quinone methide (Scheme I).[4] Tautomerization of the latter intermediate greatly accelerates Bergman cyclization of the strained 10-membered (*Z*)-enediyne ring to form a 1,4-phenylene diradical intermediate, the proposed DNA cleaving agent. Hydrogen atom abstraction from the deoxyribose backbone of double helical DNA by this highly reactive intermediate is then believed to initiate the oxidative cleavage of DNA, leading ultimately to cell death. The slightly bowed anthraquinone fragment is not only proposed to facilitate the opening of the epoxide by means of bioreduction, but is believed to enhance the binding of dynemicin A to double helical DNA, by serving as an intercalating element.[5] Studies have shown that the nucleotide cleavage pattern induced by chemically activated **1** is significantly altered by the pretreatment of the DNA with distamycin A and anthramycin, suggesting an interaction between dynemicin A and the minor groove of the DNA helix. Dynemicin A cleaves double helical DNA with only modest sequence specificity, favoring attack adjacent to the 3' side of the purine bases such as 5'-GC, 5'-GT, 5'-AT, and 5'- AG.[6]

Scheme I



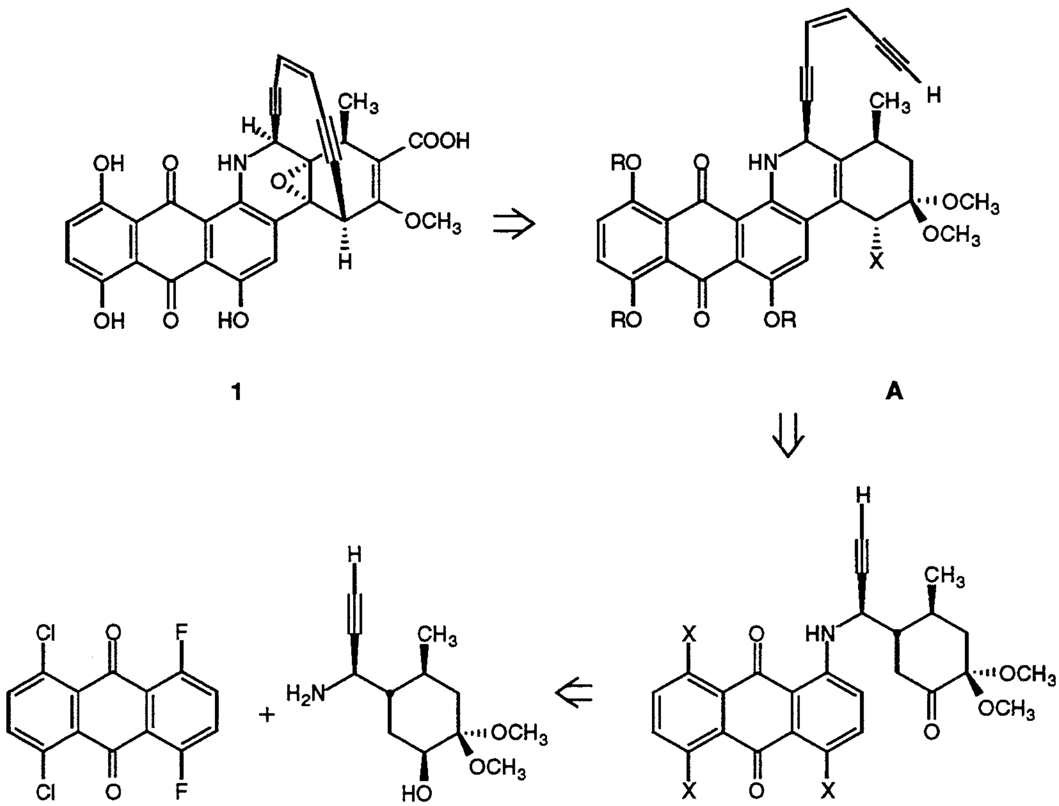
Dynemicin A demonstrates potent *in vitro* cytotoxicity against a variety of murine and human tumor cell lines, and *in vivo* antitumor activity in mice implanted with P388 and L1210 leukemias and B16 melanoma. Moreover, **1** exhibits broad antimicrobial activity, and is especially potent against Gram-positive bacteria.[7] These biological traits and the complex structure of dynemicin A have established it as an important target for chemical synthesis. This thesis describes the first and, at the time of this writing, only laboratory synthesis of a natural dynemicin.[8] The synthesis of (+)-dynemicin A is described in detail. This work has allowed the determination of the absolute configuration of **1**, and as well the preparation of diverse dynemicin analogs. The latter is anticipated to be of value for the development of dynemicins with improved therapeutic properties.

Initial Synthetic Plan

The primary challenge dynemicin A presents as a target for chemical synthesis is to assemble the anthraquinone, epoxide, and (*Z*)-enediyne groups under conditions where each is stable. In our initial synthetic plan, we decided to introduce the (*Z*)-enediyne bridge of **1** in the final stages of the route. Retrosynthetic disconnection of the bond anchoring the enediyne bridge to the densely functionalized cyclohexene ring of the right-hand half of dynemicin A led to the pentacyclic intermediate **A**, envisioned to be derived from the product of cyclization of intermediate **B** (Scheme II). Intermediate **B** was envisioned to arise by nucleophilic addition of the amine **2** to 1,4-dichloro-5,8-difluoroanthraquinone (**3**).

In order to determine in a timely manner the viability of the proposed strategy, a racemic synthesis of the amine **2** was developed. The first step involved a thermal Diels-Alder cycloaddition reaction which was conducted by heating a deoxygenated mixture of 2-(triisopropylsilyloxy)-1,3-butadiene[9] with crotonaldehyde (1.6 equiv) at 100 °C for 18 h, furnishing the racemic aldehyde **4** in 33% yield (Scheme III). Addition of lithium

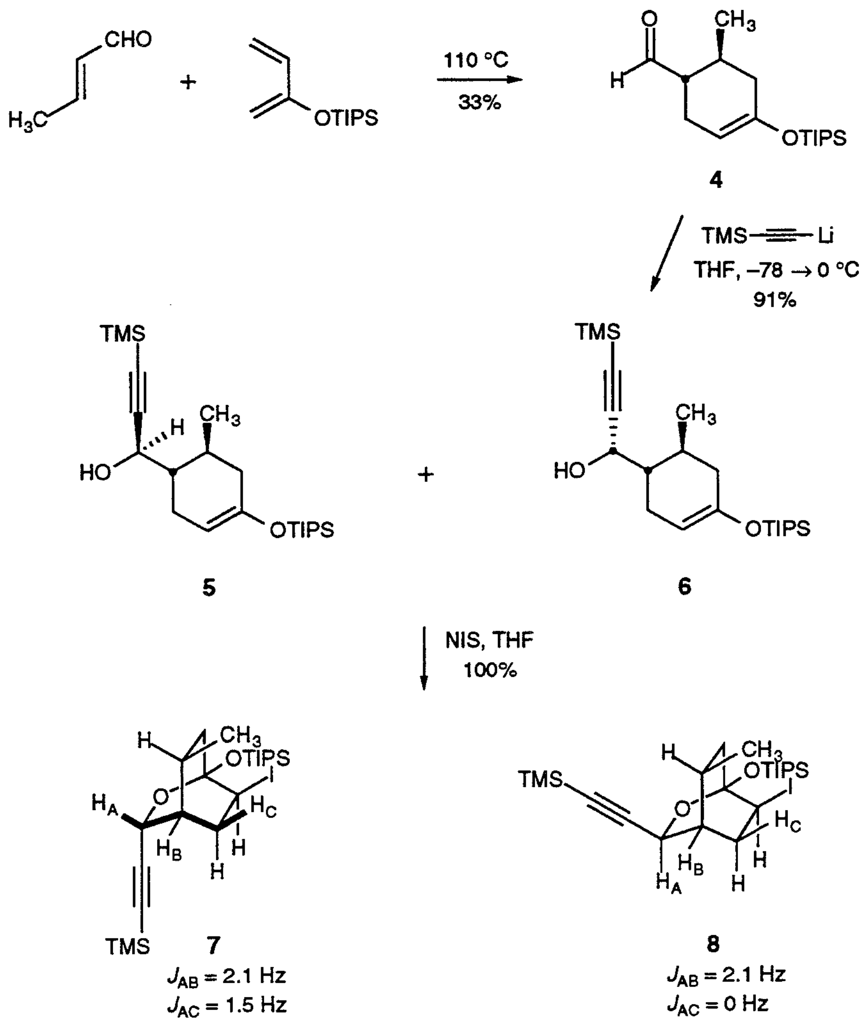
Scheme II



1 A 3 2 B

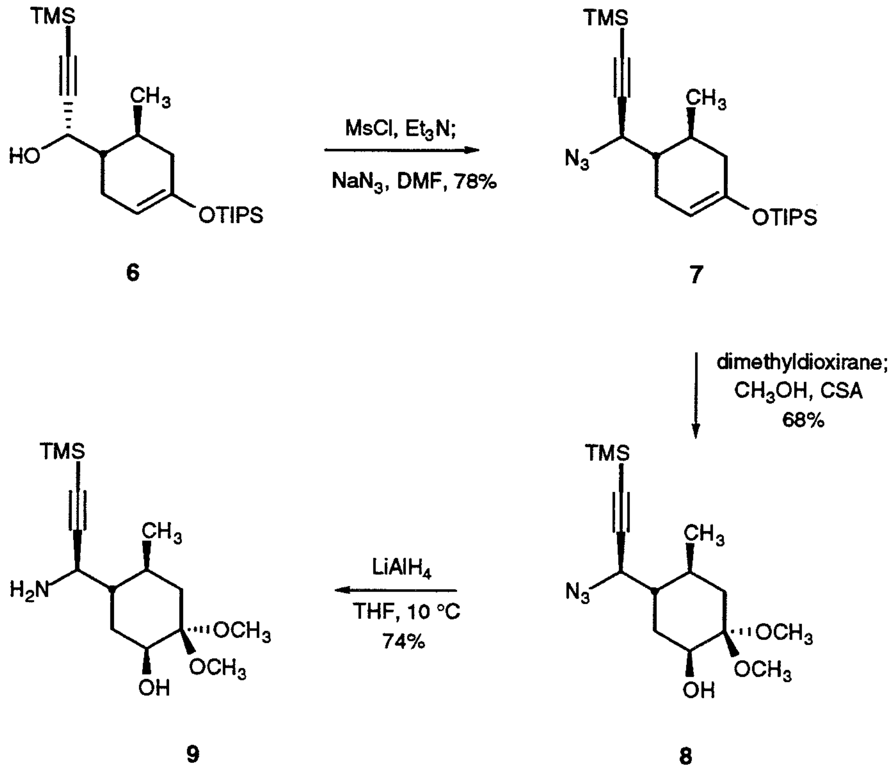
(trimethylsilyl)acetylide to aldehyde **4** proceeded in 91% yield to afford separately the alcohols **5** and **6** (ratio ca. 1:1) following flash column chromatography.[10] In order to establish the stereochemistry of the newly formed propargylic center, **5** and **6** were transformed into iodo ethers **7** and **8** in quantitative yield with *N*-iodosuccinimide (1.4 equiv) in tetrahydrofuran (THF). The stereochemical assignments of **7** and **8** were based on ^1H-^1H coupling constants obtained ^1H NMR spectral data. The signal for H_A of **7** showed a 1.5-Hz, four-bond coupling to H_C (W-coupling, depicted with bold bonds) in addition to a 2.1 Hz coupling to H_B, while H_A of **8** showed only a single coupling of 2.1 Hz to H_B. This data suggests an exo orientation for H_A of **7**, and an endo orientation for H_A of **8**. The stereochemistry of alcohol **6** is thus demonstrated to be that depicted within

Scheme III



Scheme III. Conversion of **6** to its mesylate proceeded smoothly and in high yield by the addition of excess triethylamine to a solution of **6** and methanesulfonyl chloride (1.2 equiv) in dichloromethane at 0 °C. Treatment of the unpurified mesylate with excess sodium azide (4.8 equiv) in *N,N*-dimethylformamide (DMF) at 23 °C furnished the propargylic azide **7** in 78% yield for the two-step sequence (Scheme IV). Epoxidation of the silyl enol ether double bond within **7** by the addition of a solution of dimethyldioxirane (0.05 M, excess) in acetone, followed by the treatment of the resultant epoxide with a catalytic amount of 10-

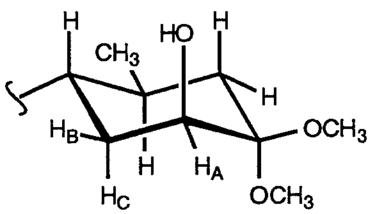
Scheme IV



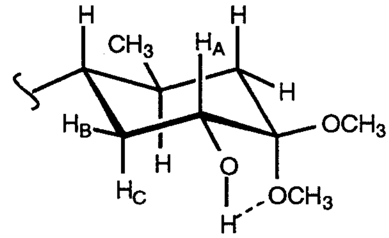
camphorsulfonic acid in methanol provided the β-oriented alcohol **8** as the predominant component of an epimeric mixture (68%, ratio ca. 3:1). The configuration of the alcohols was determined by the analysis of ^1H-^1H coupling constants obtained from ^1H NMR spectral data of the epimeric mixture (Figure 1). Reduction of the azide functionality within **8** was accomplished in 74% yield by the treatment of **8** with lithium aluminum hydride (3.3 equiv) in THF at 10 °C for 8 h, furnishing the amine **9** as a white solid (mp 79.5-80.5 °C) after purification by chromatography on silica gel.

With the amine **9** in hand, model studies were initiated to investigate the potential coupling of **9** with various haloanthraquinones. Because α-fluorinated anthraquinones were known to provide optimum results in aromatic displacement reactions with amine nucleophiles,[11] 1-fluoroanthraquinone was chosen as the initial coupling partner. This

Figure 1



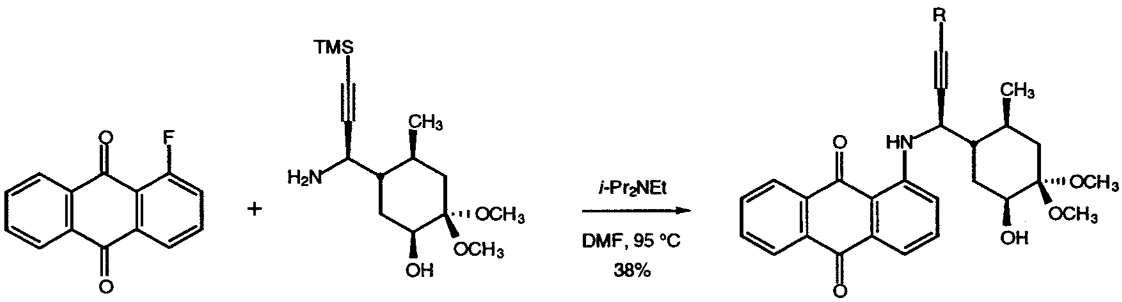
8: major epimer
J_{AOH} = <2 Hz
J_{AB} = <3 Hz
J_{AC} = <3 Hz



minor epimer
J_{AOH} = 8.0 Hz
J_{AC} = 11.7 Hz
J_{AB} = 4.4 Hz

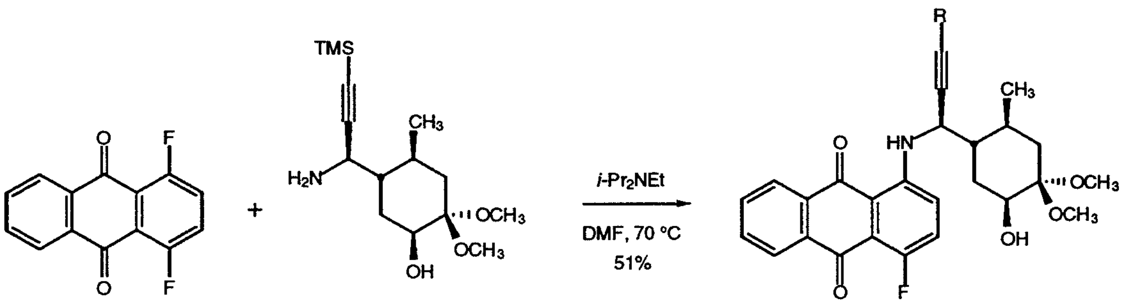
anthraquinone was prepared beginning with the diazotization of commercially available 1-aminoanthraquinone with sodium nitrite in concentrated sulfuric acid at 0 °C to afford the diazonium bisulfate salt as a tan precipitate in 68% yield. Exchange of the counter ion by the treatment of the product salt with silver tetrafluoroborate furnished the diazonium tetrafluoroborate salt in 69% yield. Heating a suspension of the latter in dichlorobenzene at 140 °C provided 1-fluoroanthraquinone as a yellow solid, following chromatography on silica gel and recrystallization from ethanol (39%, mp 210-212 °C; Lit. mp 234 °C).[12] Heating 1-fluoroanthraquinone with the amine **9** in DMF at 95 °C in the presence of excess *N,N*-diisopropylethylamine provided a separable mixture of **10** and **11** (1.2:1) in 38% yield. Likewise, the coupling of amine **9** with 1,4-difluoroanthraquinone[13] under similar conditions furnished **12** and **13** (4:1) in 51% yield.

Because the addition of stabilized enolates of β-keto esters and nitronates to the *ortho* position of α,δ-dihydroxylated anthraquinones was precedented,[14] model studies were conducted to establish whether carbon-carbon bond formation *ortho* to an α-aminoanthraquinone would occur under similar conditions, and to determine the viability of this methodology for the cyclization of a derivative of compound **11**. 1-Amino-4-



9

10 R=H
11 R=TMS

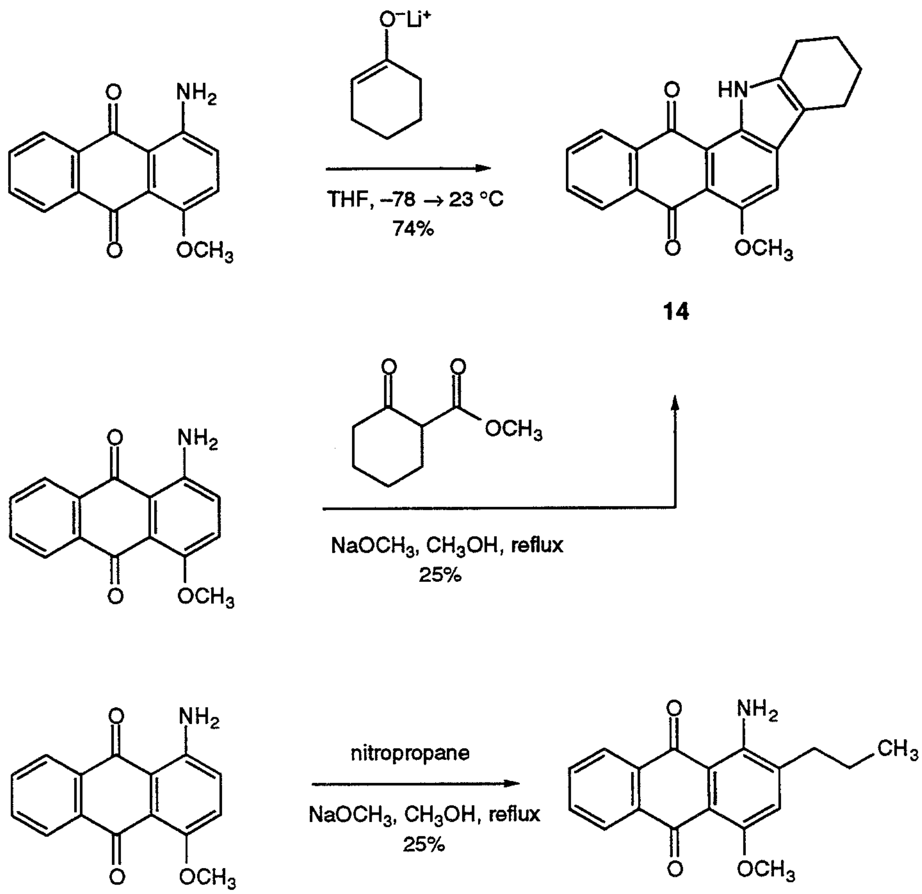


9

12 R=H
13 R=TMS

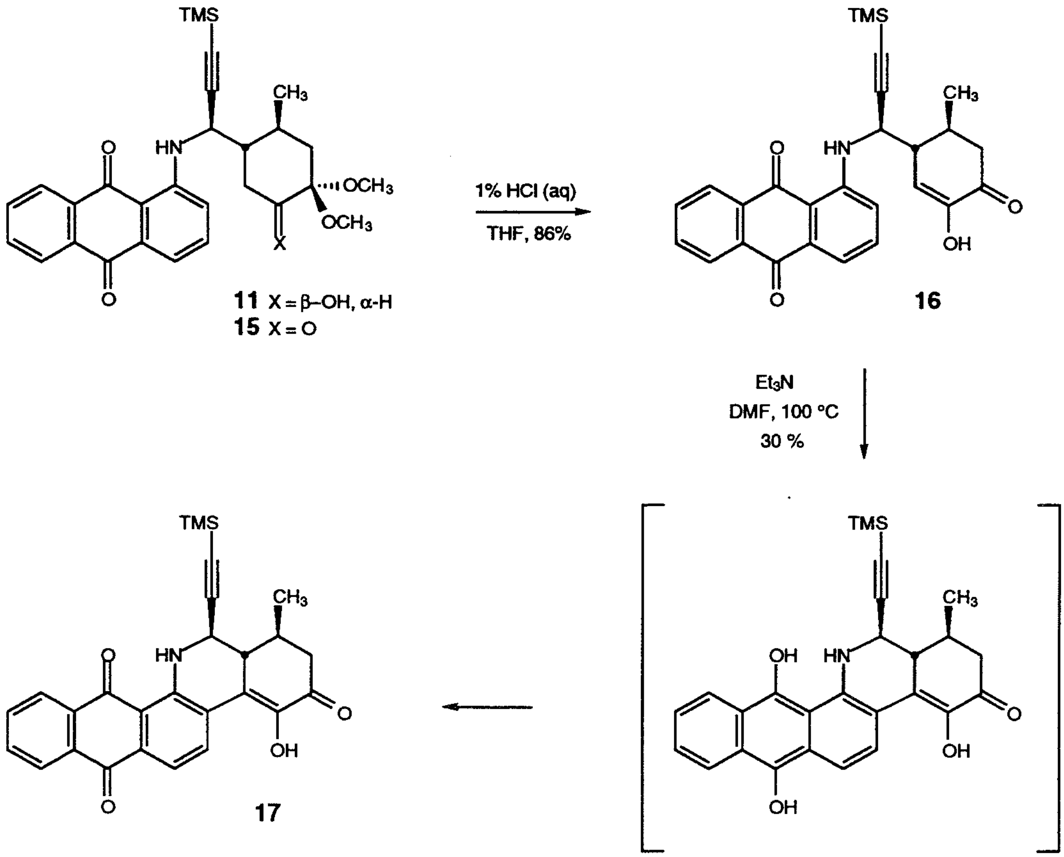
methoxyanthraquinone was chosen as the model substrate, as it was readily prepared by the alkylation of commercially available 1-amino-4-hydroxyanthraquinone with methyl iodide in the presence of potassium *t*-butoxide in DMF (52% yield). Addition of 1-amino-4-methoxyanthraquinone to a solution of the lithium enolate of cyclohexanone (5 equiv) at –78 °C, followed by warming of the reaction mixture to 23 °C afforded the indole product **14** as a red solid in 74% yield. Similarly, heating a solution of 1-amino-4-methoxyanthraquinone and methyl 2-oxo-1-cyclohexanonecarboxylate (12 equiv) or nitropropane (17 equiv) in methanol in the presence of excess sodium methoxide for 8 h provided the indole **14** (25%) and 1-amino-2-propyl-4-methoxyanthraquinone (25%), respectively.

With these encouraging results in mind, oxidation of **11** with pyridinium dichromate (PDC) furnished the ketone **15** in 77% yield (Scheme V). However, the



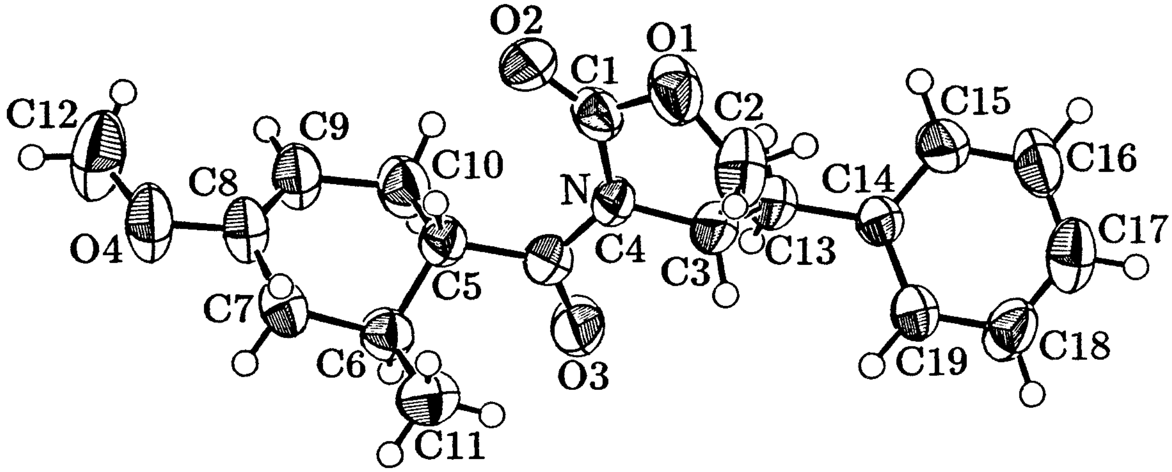
treatment of the ketone **15** with a variety of bases failed to produce cyclization products, but rather generated uncharacterizable decomposition products in each case. It was conjectured at this point that stabilization of the enolate would promote cyclization. Toward this end, the dimethyl ketal functionality within **15** was hydrolyzed, providing the diketone **16** as an orange solid in 90% yield. Heating **16** in the presence of excess triethylamine in DMF at 105 °C provided the pentacycle **17** as a purple solid in approximately 30% yield. The cyclization is believed to proceed through an anthracene intermediate which undergoes oxidation with molecular oxygen (or another anthraquinone) to give the product anthraquinone.

Scheme V

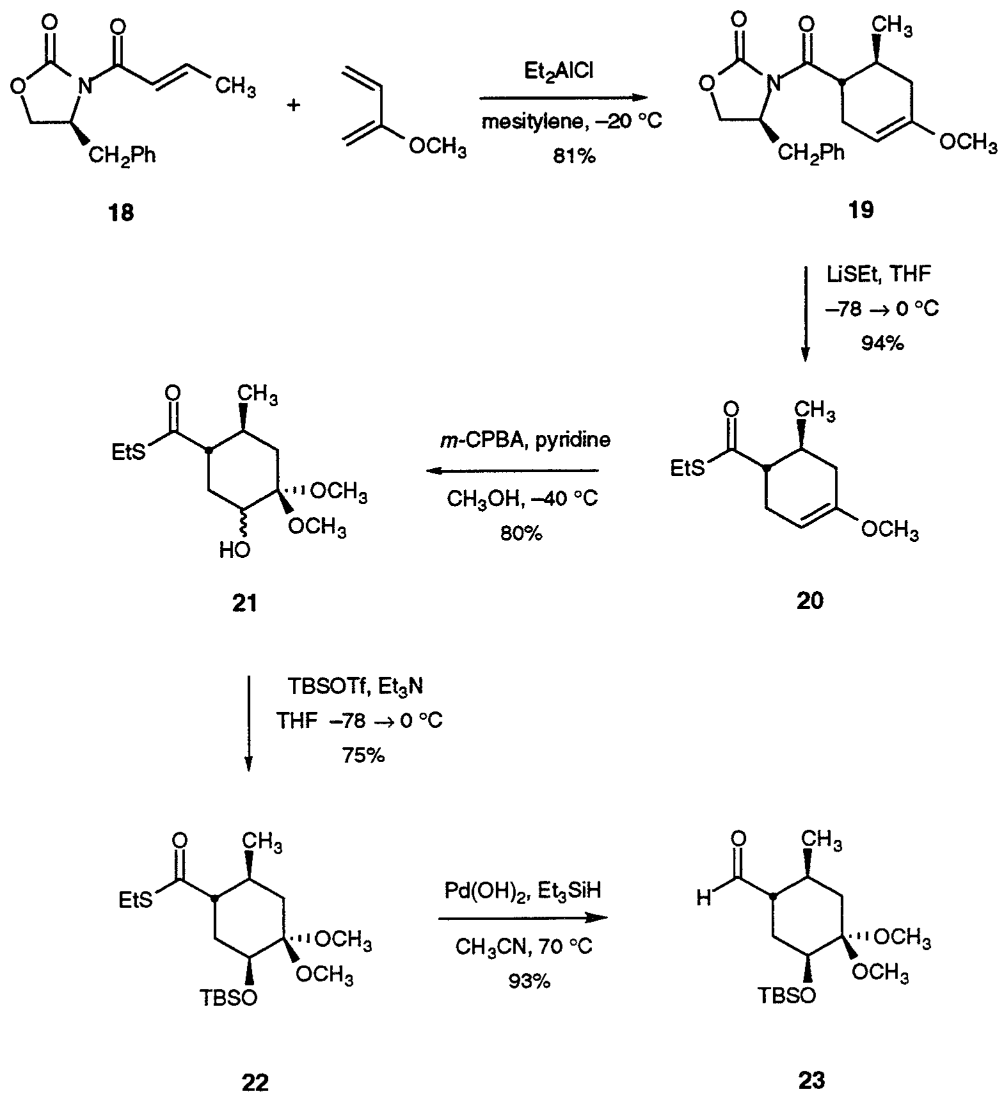


In response to the favorable results obtained from the preliminary coupling and cyclization studies, an enantioselective synthesis of the amine **2** was initiated. The first step involved the Lewis acid-catalyzed Diels-Alder cycloaddition reaction of the crotonyl imide **18** (derived from (*S*)-4-benzyl-2-oxazolidinone and (*E*)-crotonyl chloride)[15] with 2-methoxy-1,3-butadiene[16] in the presence of diethylaluminum chloride (0.4 equiv) in 1,3,5-trimethylbenzene at –20 °C, providing cycloadduct **19** as a single diastereomer in 81% yield (8-gram scale, Scheme VI).[17] . The stereochemistry of the product was determined by X-ray crystallographic analysis (Figure 2). Replacement of the oxazolidinone auxiliary with lithium ethylmercaptide in tetrahydrofuran at –78 °C, followed by warming of the reaction mixture to 23 °C, furnished the thioester **20** in 94% yield.[18] Epoxidation of **20**

Figure 2


O2
O1
C1
C2
C12
C9
C15
C10
C16
N
C14
C8
C17
O4
C4
C13
C5
C3
C7
C18
C19
C6
O3
C11

Scheme VI



with *m*-chloroperoxybenzoic acid (*m*-CPBA, 1.3 equiv) and pyridine (2.2 equiv) in anhydrous methanol at –40 °C afforded an epimeric mixture of axial and equatorial alcohols **21** (4.4:1, respectively) in 80% yield. The treatment of the alcohols **21** with *tert*-butyldimethylsilyl trifluoromethanesulfonate (1.3 equiv) in the presence of triethylamine (2.0 equiv) in THF at –78 °C, followed by warming of the reaction mixture to 0 °C, provided separately the axial TBS ether **22** (75%) as well as its equatorial epimer (17%),

Figure 3

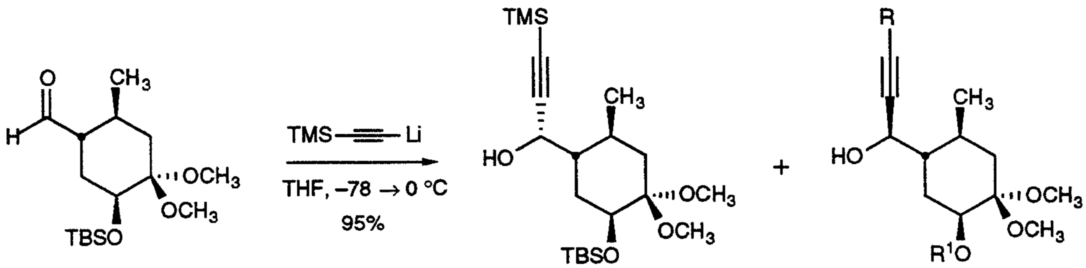
22: major epimer
$J_{AB} = 3.7$ Hz
$J_{AC} = 12.4$ Hz
$J_{AF} = 11.0$ Hz
$J_{BD} < 3$ Hz
$J_{CD} < 3$ Hz
$J_{DE} = 1.5$ Hz

minor epimer
$J_{AB} = 3.7$ Hz
$J_{AC} = 12.4$ Hz
$J_{AF} = 11.0$ Hz
$J_{CD} = 12.0$ Hz
$J_{BD} = 4.2$ Hz
$J_{DE} = 0$ Hz

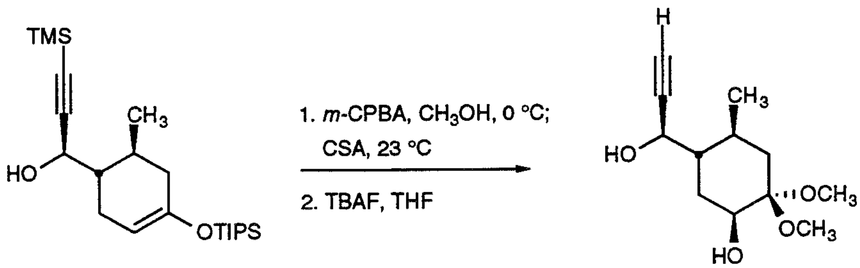
after chromatography on silica gel. The epimers were assigned by the analysis of ^{1}H-^{1}H coupling constants from ^{1}H NMR spectral data (Figure 3). Palladium-catalyzed reduction of the thioester group of **22** with triethylsilane and moist 20% palladium hydroxide on carbon furnished the aldehyde **23** in 93% yield.[19] This reaction was conducted in hot acetonitrile (70 °C) under a flow of argon in order to sweep away the liberated ethanethiol, which prevented the poisoning of the catalyst.

Addition of the aldehyde **23** to a solution of lithium (trimethylsilyl)acetylide at –78 °C provided a separable mixture of alcohols **24** and **25** (1:1.3, respectively) in 95% yield. The configuration of the newly formed stereocenter was determined by the following method. Alcohol **25** was first desilylated with tetrabutylammonium fluoride in THF, affording the diol **26.** Diol **26** was then compared with an authentic sample of **26,** prepared by the epoxidation of the racemic alcohol **5** with *m*-CPBA in methanol at 0 °C, followed by the acid-catalyzed (10-camphorsulfonic acid) internal opening of the resultant epoxide and desilylation with tetrabutylammonium fluoride in THF.

The poor stereoselectivity of the acetylide addition reaction was not of great concern because both products **24** and **25** were convertible to azide **27** (Scheme VII). Thus,



23 24 25 R = TMS, R¹ = TBS
26 R = H, R¹ = OH

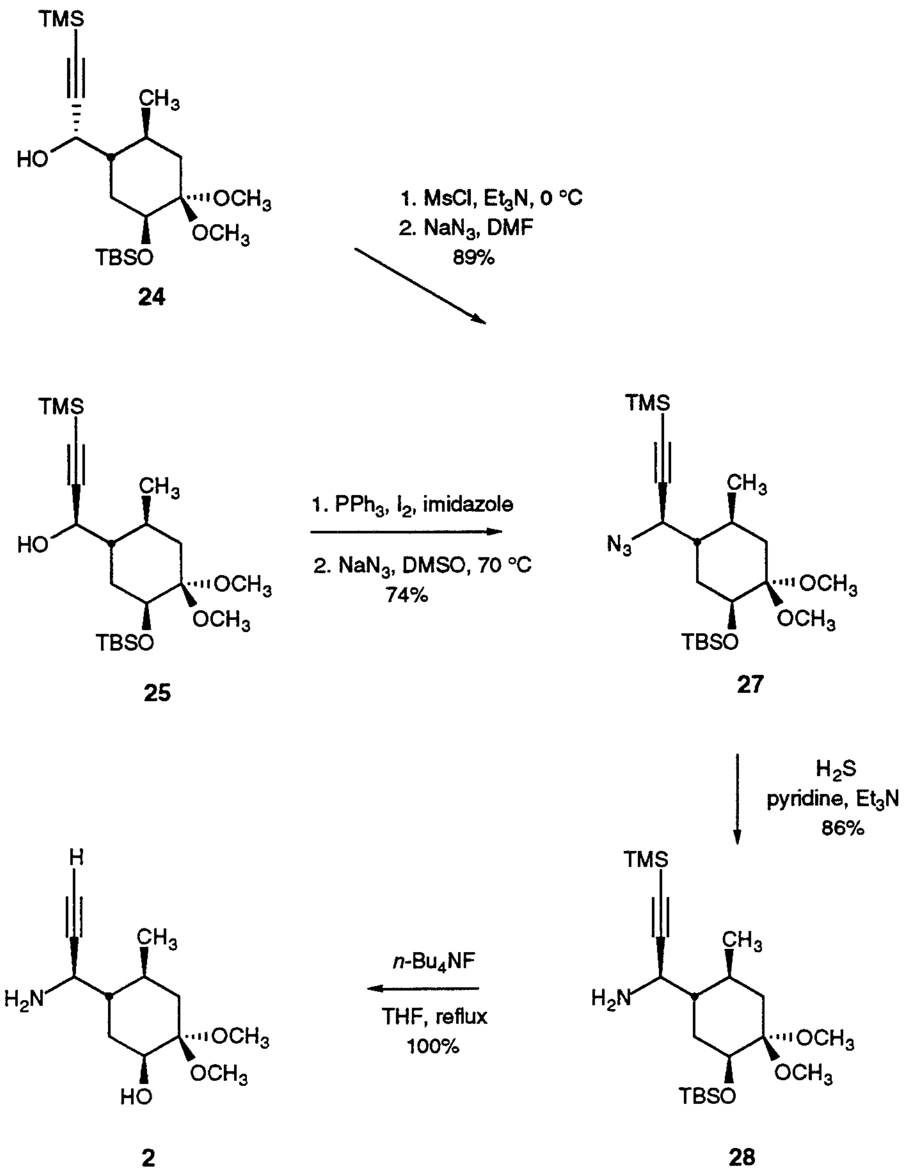


5 26

alcohol **24** was treated sequentially with triethylamine and methanesulfonyl chloride, and the resultant mesylate was stirred in a suspension of sodium azide in DMF at 23 °C, affording **27** in 89% yield. On the other hand, alcohol **25** was treated with iodine in the presence of triphenylphosphine and imidazole, and the resultant propargylic iodide was added to a hot solution of sodium azide in dimethylsulfoxide, furnishing **27** in 74% yield. Reduction of azide **27** with hydrogen sulfide provided amine **28** in 86% yield.[20] Desilylation of **28** with tetrabutylammonium fluoride in THF at reflux afforded the target amine **2** in quantitative yield.

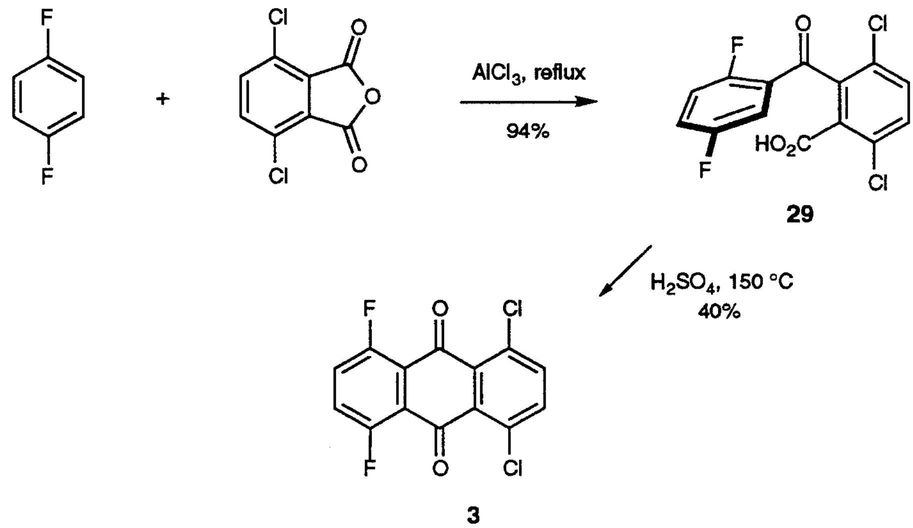
At this stage, 1,4-dichloro-5,8-difluoroanthraquinone (**3**) was chosen as a soluble and more highly oxidized partner for coupling with the amine **2**. This compound was prepared in two steps beginning with the reaction of 4,7-dichlorophthalic anhydride with 1,4-difluorobenzene under Friedel-Crafts conditions to furnish the acid **29** in 94%

Scheme VII



TMS
CH3
HO
OCH3
OCH3
TBSO
24
1. MsCl, Et3N, 0 °C
2. NaN3, DMF
89%
25
1. PPh3, I2, imidazole
2. NaN3, DMSO, 70 °C
74%
N3
27
H2S
pyridine, Et3N
86%
H2N
28
n-Bu4NF
THF, reflux
100%
H
HO
2

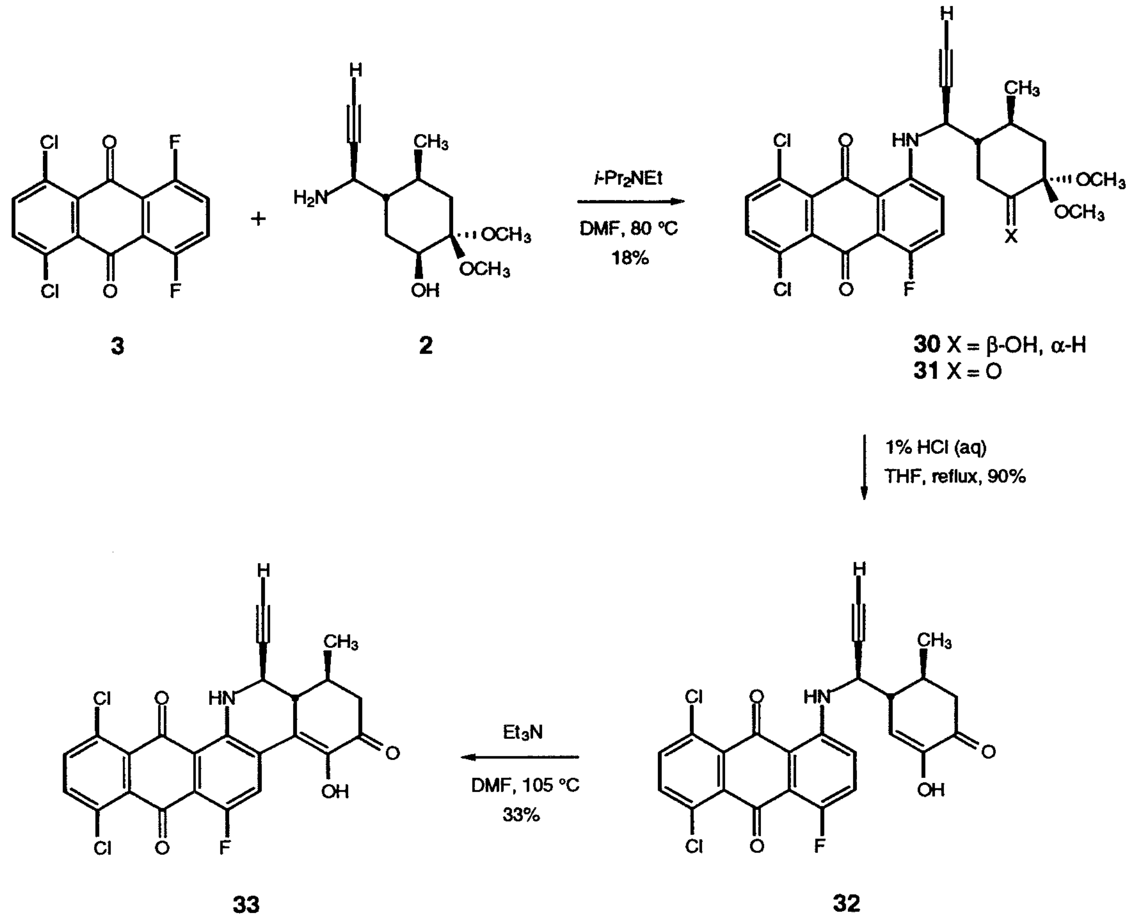
Scheme VIII



yield (Scheme VIII).[21] Cyclization of **29** in concentrated sulfuric acid at 150 °C then provided **3** (40% yield). The coupling of amine **2** with anthraquinone **3** proceeded in 18% yield, at best, by heating a solution of **2** and **3** in the presence of excess *N*,*N*-diisopropylethylamine in DMF at 80 °C for 26 h, producing **30** as a red oil (Scheme IX). In an attempt to increase the yield of the desired product **30**, various solvents and additives, higher temperatures, and longer periods of heating were employed; however, these measures resulted in lower yields and, oftentimes, decomposition of the coupled product. Oxidation of the alcohol **30** with PDC in dichloromethane formed the ketone **31** in 57% yield. Hydrolysis of the dimethyl ketal group of **31** with aqueous hydrochloric acid solution (1%, v/v) in THF at reflux provided the diketone **32** (90%). Cyclization of **32** proceeded in 33% yield in DMF at 105 °C, furnishing the pentacycle **33** as a purple solid.

Although the pentacyclic carbon framework of dynemicin A was realized with the synthesis of **33**, this exploratory approach was abandoned as the result of the low yields late in the synthesis and for several reasons which were not apparent at the outset of our

Scheme IX



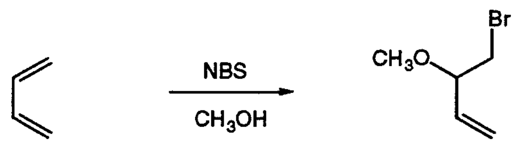
study, namely: (1) the reactivity of the anthraquinone ring was unpredictable and varied according to substitution; (2) the problem of converting the halogen substituents of the anthraquinone to hydroxyl groups had not been addressed, and it was doubtful that the functionality present within the pentacycle could withstand the conditions for such a transformation; and (3) the remaining manipulations needed to construct the (*Z*)-enediyne bridge and complete the functionalization of the right half of the molecule would most likely be incompatible with the reactive anthraquinone. The third claim is supported by our unsuccessful attempts to cyclize ketones **15** and **31**, and by a contemporaneous observation by another group member in which an anthraquinone ring had undergone nucleophilic addition at the carbonyl positions by an acetylide.[22] Because the anthraquinones within our advanced intermediates were much more reactive and capricious in their reactivity than was anticipated at the beginning of our studies, it became clear that the optimum order of assembly of dynemicin A would place the synthesis of the anthraquinone last.

Experimental Section

General Procedure. All reactions were performed in flame-dried round bottom or modified Schlenk (Kjeldahl shape) flasks fitted with rubber septa under a positive pressure of argon, unless otherwise noted. Air- and moisture-sensitive liquids and solutions were transferred via syringe or stainless steel cannula. Where necessary (so noted), solutions were deoxygenated by alternate evacuation for 10-15 seconds and flushing with argon (≥ 5 iterations). Organic solutions were concentrated by rotary evaporation below 30 °C at ca. 25 Torr (water aspirator). Flash column chromatography was performed as described by Still et al.,[10] employing 230-400 mesh silica gel. Analytical and preparative thin layer chromatography were performed using glass plates pre-coated with 0.25 mm 230-400 mesh silica gel impregnated with a fluorescent indicator (254 nm). Thin-layer chromatography plates were visualized by exposure to ultraviolet light (noted as 'UV') and/or by immersion in an acidic staining solution (*p*-anisaldehyde, unless otherwise noted) followed by heating on a hot-plate.

Materials. Commercial reagents and solvents were used as received with the following exceptions. Tetrahydrofuran and diethyl ether were distilled from sodium benzophenone ketyl. Methanol was distilled from magnesium turnings. Dichloromethane, *N,N*-diisopropylethylamine, triethylamine, and hexamethyldisilazane were distilled from calcium hydride. Dimethyl sulfoxide and *N,N*-dimethylformamide were distilled from calcium hydride at reduced pressure and stored over 4Å molecular sieves. Methanesulfonyl chloride was distilled from phosphorous pentoxide at atmospheric pressure. The molarity of *n*-butyllithium solutions was determined by titration using diphenylacetic acid as an indicator (average of three determinations).

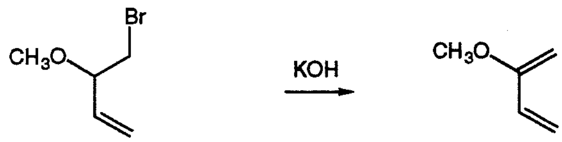
Instrumentation. Infrared spectra were obtained using a Perkin-Elmer 1600 FT-IR spectrophotometer referenced to a polystyrene standard. Data are presented as follows: frequency of adsorption (cm^{-1}), intensity of adsorption (vs = very strong, s = strong, m = medium, w = weak, br = broad, sh = shoulder) and assignment (when appropriate). Proton magnetic resonance (^1H NMR) spectra were recorded with a JEOL JX-400 (400 MHz) NMR spectrometer; chemical shifts are expressed in parts per million (δ scale) downfield from tetramethylsilane and are referenced to residual protium in the NMR solvent ($CHCl_3$: δ 7.26, C_6HD_5: δ 7.20, CD_2HOD: δ 3.30). Data are presented as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet and/or multiple resonances, app = apparent), integration, coupling constant in Hertz (Hz), and assignment. High resolution mass spectra were obtained from the University of California, Riverside Mass Spectrometry Facility. Melting points were recorded with a Büchi SMP-20 melting point apparatus and are uncorrected.



1-Bromo-2-methoxy-3-butene

1,3-Butadiene (125 mL, 1.50 mol, 4.35 equiv) was condensed into a 250-mL Erlenmeyer flask immersed in a dry ice/acteone bath. The cold 1,3-butadiene was then transferred via cannula to a 1-L round bottom containing anhydrous methanol (600 mL) cooled to –10 °C. *N*-Bromosuccinimide (recrystallized from water, 61.45 g, 345.2 mmol, 1 equiv) was added in four equal portions to the solution over 2 h, and the resulting suspension was stirred at –10 °C for 10 h. The cold bath was removed, and the suspension was warmed to reflux (–4.5 °C) and was held at this temperature for 12 h by the use of a dry ice/acetone-cooled cold finger condenser. The reaction mixture became homogeneous during this period of time. The condenser was removed, and butadiene was allowed to evaporate over 4 h. The reaction mixture was partitioned between water (2 L) and pentane (500 mL), causing the remaining 1,3-butadiene to boil vigorously. The aqueous layer was separated and extracted further with pentane (500 mL). The combined organic layers were washed with water (1 L), then were dried over magnesium sulfate and were concentrated at 0 °C (the receiving flask was immersed in a dry ice/acetone bath to aid in the removal of the volatiles) to provide 1-bromo-2-methoxy-3-butene as a low-boiling colorless liquid (47.1 g, 83%).

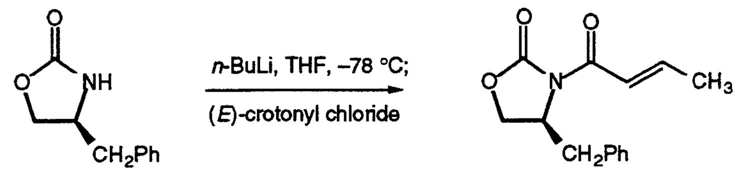
^1H NMR (400 MHz, C_6D_6), δ:	5.46 (ddd, 1H, *J* = 17.4, 10.2, 7.2 Hz, H_2C=C**H**), 5.04 (ddd, 1H, *J* = 17.4, 1.7, 1.0 Hz, **H_2**C=CH), 5.01 (ddd, 1H, *J* = 10.2, 1.7, 1.0 Hz, **H_2**C=CH), 3.43 (m, 1H, C**H**OCH$_3$), 3.11 (dd, 1H, *J* = 10.4, 6.5 Hz, C**H$_2$**Br), 3.04 (s, 3H, OC**H$_3$**), 3.02 (dd, 1H, *J* = 10.4, 5.0 Hz, C**H$_2$**Br).



2-Methoxy-1,3-butadiene

A 250-mL, 3-N round bottom fitted with a short path distillation apparatus and two rubber septa was charged with potassium hydroxide (20.8 g, 371 mmol, 1.51 equiv) and diethylene glycol (150 mL), and the resulting mixture was heated to 100 °C. 1-Bromo-2-methoxy-3-butene (40.5 g, 245 mmol, 1 equiv) was added in 4-mL portions by pipet over 2 h to the hot solution, causing 2-methoxy-1,3-butadiene to distill into the recieving flask (bp 50-60 °C). After the addition was completed, the temperature of the solution was increased to 130 °C, and more 2-methoxy-1,3-butadiene was collected as distillate over 3 h. Water (15 mL) was then added to the hot reaction mixture and more distillate of boiling range 50-60 °C was collected. The combined distillates were dried over anhydrous sodium sulfate, and the drying agent was removed by filtration through filter paper to afford 2-methoxy-1,3-butadiene as a colorless liquid (12.0 g, 58%).

^{1}H NMR (400 MHz, C_6D_6), δ: 6.17 (dd, 1H, J = 17.3, 10.6 Hz, $CH{=}CH_2$), 5.83 (br d, 1H, J = 17.3 Hz, $CH{=}CH_2$), 5.06 (br d, 1H, J = 10.6 Hz, $CH{=}CH_2$), 4.09 (br s, 1H, $CH_3OC{=}CH_2$), 4.03 (br s, 1H, $CH_3OC{=}CH_2$), 3.26 (s, 3H, OCH_3).

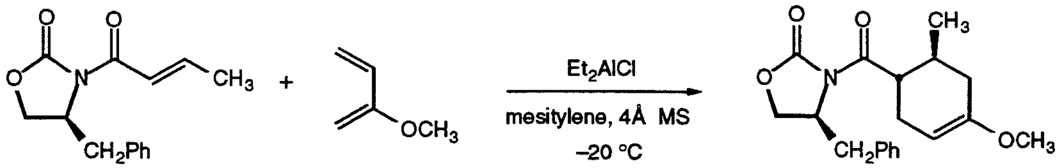


18

(4*S*)-3-((*E*)-2-Butenoyl)-4-(phenylmethyl)-2-oxazolidinone (18)

A solution of *n*-butyllithium (1.6 M, 21.2 mL, 33.9 mmol, 1.20 equiv) was added to a solution of (*S*)-(-)-4-benzyl-2-oxazolidinone (5.00 g, 28.2 mmol, 1 equiv) in tetrahydrofuran (100 mL) at –78 °C, and the resulting orange solution was stirred for 15 min. (*E*)-Crotonyl chloride (distilled from 90% technical grade, 4.05 mL, 42.3 mmol, 1.50 equiv) was added via syringe over 2 min, causing a mild exotherm and the solution to become yellow. The reaction solution was stirred at –78 °C for 30 min, then was warmed to 0 °C and was stirred at that temperature for 1 h. The product solution was then partitioned between aqueous saturated sodium bicarbonate solution (400 mL) and ethyl acetate (200 mL). The aqueous layer was separated and extracted further with ethyl acetate (2 x 200 mL). The combined organic extracts were washed with saturated sodium chloride solution (300 mL), then were dried over sodium sulfate and were concentrated. The residue was passed through a short plug of flash grade silica gel (200 g) using a 1:1 mixture of diethyl ether and petroleum ether as eluent. Concentration of the appropriate fractions provided predominantly the desired product (**18**), which was further purified by recrystallization from petroleum ether and a minimal amount of dichloromethane to furnish (4*S*)-3-((*E*)-2-butenoyl)-4-(phenylmethyl)-2-oxazolidinone (**18**) as fine white needles (mp 84.5-85.0 °C; Lit. mp 85.0-86.0 °C, 6.01 g, 87%).

^1H NMR (400 MHz, $CDCl_3$), δ:	7.36-7.18 (m, 7H, C_6**H_5**, **CH**=**C**H**C**H₃), 4.73 (m, 1H, NC**H**), 4.21 (br t, 1H, *J* = 9.0 Hz, OC**H**$_2$), 4.17 (dd, 1H, *J* = 9.0, 3.2 Hz, OC**H**$_2$), 3.33 (dd, 1H, *J* = 13.3, 3.3 Hz, C**H**$_2$Ph), 2.80 (dd, 1H, *J* = 13.3, 9.6 Hz, C**H**$_2$Ph), 1.99 (d, 3H, *J* = 5.4 Hz, CH=C**H**$_3$).
FTIR (neat), cm^{-1}:	3031 (w), 2969 (w), 2919 (w), 1775 (vs, C=O), 1685 (m, C=O), 1637 (m, C=C), 1493 (w), 1388 (m), 1353 (m), 1292 (m), 1211 (m), 1125 (w), 1095 (w), 1051 (w), 1005 (w), 969 (w), 761 (w), 701 (m).
TLC (30% diethyl ether-hexanes), R_f:	**18**: 0.17



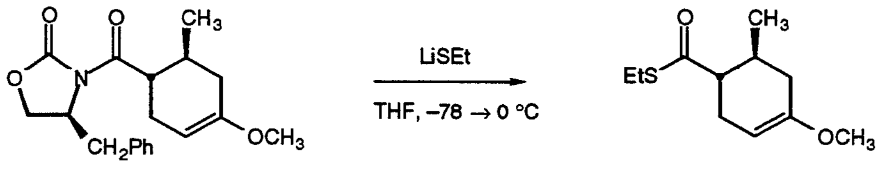
18 19

Diels-Alder Adduct 19

A mixture of (4*S*)-3-((*E*)-2-butenoyl)-4-(phenylmethyl)-2-oxazolidinone (**18**, 7.845 g, 31.98 mmol, 1 equiv) and partially crushed and activated 4Å molecular sieves (3.938 g) in 1,3,5-trimethylbenzene (150 mL) at -15 °C (ice/salt bath) was deoxygenated by alternately evacuating the reaction vessel and flushing with argon (5x). A solution of diethylaluminum chloride in toluene (1.8 M, 7.1 mL, 13 mmol, 0.040 equiv) was added via syringe over 1 min, causing the reaction mixture to become light yellow. The resulting mixture was deoxygenated as described above (5x), and was stirred at –15 °C for 10 min. 2-Methoxy-1,4-butadiene (5.325 g, 63.30 mmol, 1.979 equiv) was added, and the resulting mixture was cooled to –20 °C, and was stirred at that temperature for 12 h. Triethylamine (5.0 mL, 36 mmol, 1.1 equiv) was added, and the resulting mixture was stirred for 10 min at –20 °C, then was partitioned between a 1:1 mixture of aqueous saturated sodium bicarbonate solution and saturated sodium chloride solution (800 mL) and diethyl ether (300 mL). The aqueous layer was separated and extracted further with diethyl ether (2 x 300 mL). The combined organic extracts were washed with saturated sodium chloride solution (500 mL), then were dried over sodium sulfate and were concentrated. The residue was purified by flash column chromatography (2% triethylamine in 30% diethyl ether-hexanes) to afford the adduct **19** as a colorless oil (8.502 g, 81%).

^1H NMR (400 MHz, $CDCl_3$), δ:	7.36-7.21 (m, 5H, $C_6\mathbf{H}_5$), 4.72 (m, 1H, NC**H**), 4.61 (m, 1H, C**H**=$COCH_3$), 4.22 (br t, 1H, J = 9.0 Hz, $OC\mathbf{H}_2$), 4.18 (dd, 1H, J = 9.0, 3.0 Hz, $OC\mathbf{H}_2$), 3.60 (td, 1H, J = 10.3, 5.1 Hz, COC**H**), 3.52 (s, 3H, $OC\mathbf{H}_3$), 3.26 (dd, 1H, J = 13.3, 3.3 Hz, $C\mathbf{H}_2Ph$), 2.79 (dd, 1H, J = 13.3, 9.4 Hz, $C\mathbf{H}_2Ph$), 2.47 (br dt, 1H, J = 15.6, 5.1 Hz, $CHC\mathbf{H}_2CH{=}COCH_3$), 2.32-2.13 (m, 3H, $CH_3C\mathbf{H}C\mathbf{H}_2COCH_3$), 1.91 (br t, 1H, J = 15.6 Hz, $CHC\mathbf{H}_2CH{=}COCH_3$), 0.99 (d, 3H, J = 6.3 Hz, $CHC\mathbf{H}_3$).
FTIR (neat), cm^{-1}:	2919 (m), 1779 (vs, C=O), 1695 (s, C=O), 1674 (sh, C=C), 1454 (m), 1385 (s), 1350 (m), 1321 (w), 1284 (w), 1241 (w), 1211 (s), 1090 (w), 1016 (w), 914 (w), 802 (w), 763 (w), 702 (m).
HRMS (FAB):	Calcd for $C_{19}H_{24}NO_4$ $[M+H]^+$: 330.1705 Found: 330.1720

TLC (50% diethyl ether-hexanes), R_f:	**19**: 0.29
(Note: TLC plates were immersed in 5% Et_3N in hexanes, then air dried for 1 min prior to spotting)	**18**: 0.25

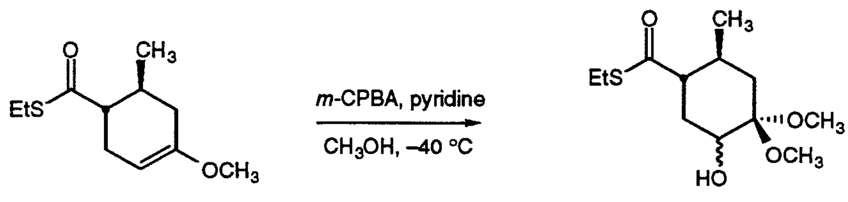


19 **20**

Thioester 20

A solution of *n*-butyllithium in hexanes (1.4 M, 17 mL, 24 mmol, 1.3 equiv) was added to a solution of ethanethiol (2.7 mL, 36 mmol, 2.0 equiv) in tetrahydrofuran (100 mL) at –78 °C, and the resulting light yellow solution was stirred for 10 min. The cold bath was removed, and the reaction flask was immersed in an ice bath for 10 min, causing the reaction mixture to become milky white. The suspension was cooled to –78 °C, and a solution of the Diels-Alder adduct **19** (6.07 g, 18.4 mmol, 1 equiv) in tetrahydrofuran (50 mL) was added over 1 min via cannula. The resulting suspension was stirred for 15 min, then was warmed to 0 °C, and was stirred at that temperature for 30 min, causing the reaction mixture to become clear. The product solution was partitioned between saturated aqueous sodium bicarbonate solution (250 mL) and diethyl ether (200 mL). The aqueous layer was separated and extracted further with diethyl ether (200 mL). The combined organic extracts were dried over sodium sulfate, then were concentrated within a fume hood. The residue was purified by flash column chromatography (2% triethylamine in 25% diethyl ether-hexanes) to yield the thioester **20** as a colorless oil (3.72 g, 94 %).

^1H NMR (400 MHz, $CDCl_3$), δ:	4.57 (m, 1H, **CH**=$COCH_3$), 3.49 (s, 3H, OCH_3), 2.88 (m, 2H, CH_3**CH_2**S), 2.41 (td, 1H, *J* = 9.5, 6.3 Hz, COC**H**), 2.36-2.28 (m, 2H, CHC**H_2**CH=$COCH_3$, C**H**CH_3), 2.19-2.05 (m, 2H, CH_3CHC**H_2**$COCH_3$), 1.85 (br m, 1H, CHC**H_2**CH=$COCH_3$), 1.25 (t, 3H, *J* = 7.4 Hz, **CH_3**CH_2S), 0.99 (d, 3H, *J* = 6.1 Hz, **CH_3**CH).
FTIR (neat), cm^{-1}:	2925 (m), 2842 (w), 1683 (s, C=O), 1453 (m), 1379 (m), 1266 (w), 1214 (s), 1168 (m), 1096 (m), 1011 (m), 911 (w), 860 (w), 825 (m), 746 (w).
HRMS (EI):	Calcd for $C_{11}H_{18}O_2S$ $[M]^+$: 214.1028 Found: 214.1019
TLC (30% diethyl ether-hexanes), R_f:	**20**: 0.56 **19**: 0.17



20 21

Alcohols 21

A solution of 55% *m*-chloroperoxybenzoic acid (5.3 g, 17 mmol, 1.3 equiv) in methanol (60 mL) was added dropwise via addition funnel over 20 min to a solution of the thioester **20** (2.840 g, 13.25 mmol, 1 equiv) and pyridine (2.7 mL, 33 mmol, 2.2 equiv) in methanol (60 mL) at –40 °C. After the addition was completed, the reaction mixture was stirred at –40 °C for 5.7 h, then was warmed slowly to –20 °C over 1 h, and was held at that temperature for 9.8 h. The cold bath was removed and the reaction mixture was allowed to warm to 23 °C, and was stirred at that temperature for 6 h. The reaction mixture was partitioned between saturated aqueous thiosulfate solution (200 mL) and ethyl acetate (200 mL). The aqueous layer was separated and extracted further with ethyl acetate (200 mL). The combined organic layers were washed successively with saturated sodium bicarbonate solution (200 mL) and saturated sodium chloride solution (200 mL), then were dried over sodium sulfate and were concentrated. The residue was purified by flash column chromatography (20% ethyl acetate in hexanes) to furnish an epimeric mixture of axial and equatorial alcohols **21** (ratio 4.4:1, respectively) as a colorless oil (2.796 g, 80%).

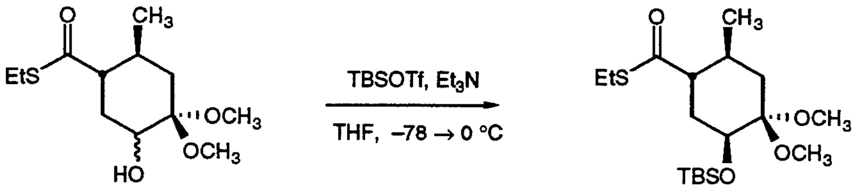
Axial epimer 21:

^1H NMR (400 MHz, $CDCl_3$), δ: 3.91 (m, 1H, **CH**OH), 3.22 (s, 3H, OC**H**$_3$), 3.20 (s, 3H, OC**H**$_3$), 2.87 (m, 2H, CH_3C**H**$_2$S), 2.61 (ddd, 1H, J = 12.6, 11.0, 3.8 Hz, COC**H**), 1.98 (dt, 1H, J = 13.7, 3.4 Hz, CHC**H**$_2$CHOH), 1.94 (m, 1H, C**H**CH_3), 1.84 (td, 1H, J = 13.7, 2.6 Hz, CHC**H**$_2$CHOH), 1.78 (ddd, 1H, J = 13.7, 3.8, 1.7 Hz, $(CH_3O)_2$CC**H**$_2$), 1.39 (t, 1H, J = 13.3 Hz, $(CH_3O)_2$CC**H**$_2$), 1.24 (t, 3H, J = 7.4 Hz, C**H**$_3$$CH_2$S), 0.91 (d, 3H, J = 6.6 Hz, C**H**$_3$CH).

FTIR (neat), cm^{-1}: 3482 (br m, OH), 2958 (s), 2832 (w), 1684 (vs, C=O), 1458 (m), 1376 (w), 1302 (w), 1218 (w), 1195 (w), 1118 (m), 1061 (vs), 973 (s), 898 (w), 824 (m).

HRMS (FAB): Calcd for $C_{12}H_{21}O_4S$ $[M{-}H]^+$: 261.1161
Found: 261.1155

TLC (40% ethyl acetate-hexanes), R_f: **21**: 0.41
20: 0.75



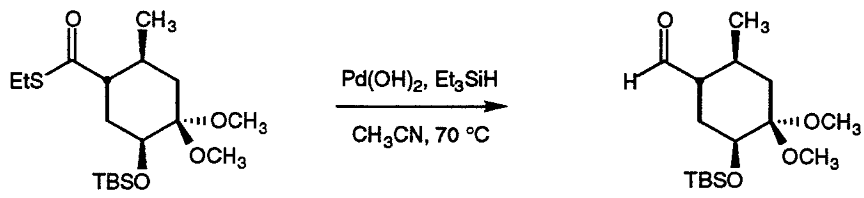
21 22

TBS Ether 22

tert-Butyldimethylsilyl trifluoromethanesulfonate (2.85 mL, 12.4 mmol, 1.3 equiv) was added to a solution of the alcohols **21** (2.50 g, 9.53 mmol, 1 equiv) and triethylamine (2.65 mL, 19.0 mmol, 1.99 equiv) in tetrahydrofuran (40 mL) at -78 °C. The resulting reaction mixture was warmed to 0 °C and was stirred at that temperature for 3.8 h. The product solution was partitioned between saturated aqueous sodium bicarbonate solution (200 mL) and ethyl acetate (200 mL). The aqueous layer was separated and extracted further with ethyl acetate (200 mL). The combined organic layers were dried over sodium sulfate and then were concentrated. The residue was purified by flash column chromatography (1% ethyl acetate in petroleum ether initially, then 5% ethyl acetate in petroleum ether) to afford separately the TBS ether **22** as a colorless oil (2.69 g, 75.0%) as well as its equatorial diastereomer as a colorless oil (616 mg, 17.2%), which crystallized upon standing.

TBS ether 22:

^1H NMR (400 MHz, $CDCl_3$), δ:	3.91 (m, 1H, **CH**OTBS), 3.17 (s, 3H, OC**H**$_3$), 3.15 (s, 3H, OC**H**$_3$), 2.86 (m, 2H, CH_3C**H**$_2$S), 2.56 (ddd, 1H, *J* = 12.4, 11.0, 3.7 Hz, COC**H**), 1.91 (m, 1H, C**H**CH_3), 1.90 (td, 1H, *J* = 13.0, 2.2 Hz, CHC**H**$_2$CHOTBS), 1.78 (dt, 1H, *J* = 13.4, 3.7 Hz, CHC**H**$_2$CHOTBS), 1.71 (ddd, 1H, *J* = 13.7, 3.6, 1.5 Hz, $(CH_3O)_2$C**H**$_2$), 1.45 (t, 1H, *J* = 13.3 Hz, $(CH_3O)_2$C**H**$_2$), 1.24 (t, 3H, *J* = 7.4 Hz, C**H**$_3$$CH_2$S), 0.92 (s, 9H, (C**H**$_3$)$_3$CSi), 0.90 (d, 3H, *J* = 6.6 Hz, C**H**$_3$CH), 0.13 (s, 3H, (C**H**$_3$)$_2$Si), 0.08 (s, 3H, (C**H**$_3$)$_2$Si).
FTIR (neat), cm^{-1}:	2955 (s), 2930 (s), 2856 (w), 2830 (w), 1689 (s, C=O), 1461 (m), 1361 (w), 1299 (w), 1256 (m), 1197 (m), 1139 (m), 1120 (w), 1099 (s), 1082 (m, sh), 1052 (m), 971 (m), 900 (w), 836 (vs), 775 (m), 676 (w).
HRMS (FAB):	Calcd for $C_{18}H_{35}O_4SiS$ $[M–H]^+$: 375.2025 Found: 375.2038
TLC (20% ethyl acetate-hexanes), R_f:	**22**: 0.53, equatorial diastereomer: 0.62 **21**: 0.12



22 23

Aldehyde 23

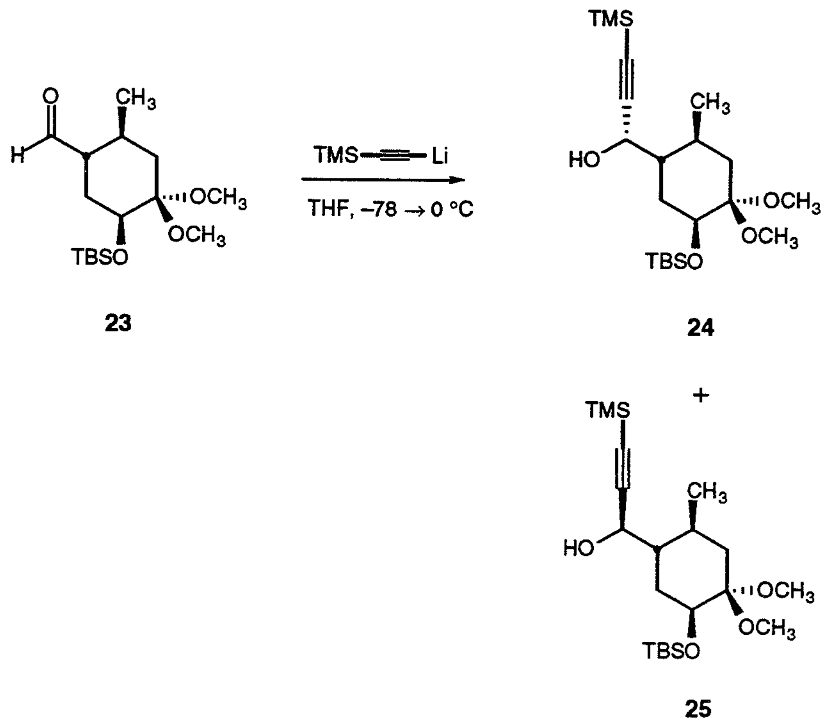
A 250-mL, 3-N round bottom flask equipped with two rubber septum and an open joint was charged with the thioester **22** (1.60 g, 4.25 mmol, 1 equiv), 20% palladium hydroxide on carbon (0.960 g, 1.31 mmol, 0.322 equiv) and acetonitrile (100 mL). A steady stream of argon was passed over the resulting suspension (via an inlet needle) and was allowed to exit through the open joint. The reaction flask was immersed in an oil bath heated to 70 °C, and then triethylsilane (2.7 mL, 17 mmol, 4.0 equiv) was added, causing gas evolution and the liberation of ethanethiol (bp 35 °C). More triethylsilane (4.0 mL, 25 mmol, 5.9 equiv) was added in four 1-mL portions to the reaction suspension over 20 min. The product suspension was allowed to cool to 23 °C, and the catalyst was removed by vacuum filtration (water aspirator) through a pad of Celite using dichloromethane as eluent (300 mL). The filtrate was concentrated within a fume hood, and then the residue was placed under high vacuum for 8 h to remove silane by-products. The residue was purified by flash column chromatography (3% ethyl acetate in hexanes initially, grading to 10% ethyl acetate in hexanes) to provide the aldehyde **23** as a colorless oil (1.249 g, 93%).

^{1}H NMR (400 MHz, $CDCl_3$), δ: 9.62 (d, 1H, J = 3.5 Hz, **CHO**), 3.95 (br s, 1H, **CH**OTBS), 3.17 (s, 6H, O**CH**$_3$), 2.30 (m, 1H, COC**H**), 1.83 (m, 1H, **CH**CH_3), 1.80-1.67 (m, 3H, $(CH_3O)_2C$**H**$_2$, CHC**H**$_2$CHOTBS), 1.50 (t, 1H, J = 13.0 Hz, $(CH_3O)_2C$**H**$_2$), 0.96 (d, 3H, J = 6.4 Hz, **CH**$_3$CH), 0.90 (s, 9H, (**CH**$_3$)$_3$CSi), 0.08 (s, 6H, (**CH**$_3$)$_2$Si).

FTIR (neat), cm^{-1}: 2954 (m), 2930 (m), 2856 (w), 2831 (w), 2707 (w), 1728 (s, C=O), 1465 (m), 1434 (w), 1361 (w), 1300 (w), 1254 (m), 1200 (m), 1139 (m), 1119 (w, sh), 1089 (vs), 1053 (m), 1006 (w), 972 (w), 835 (s), 775 (m).

HRMS (FAB): Calcd for $C_{16}H_{31}O_4Si$ $[M-H]^+$: 315.1992
Found: 315.1996

TLC (10% ethyl acetate-hexanes), R_f: **23**: 0.28 (black-green, anisaldehyde)
22: 0.36 (brown, anisaldehyde)



Alcohols 24 and 25

A solution of lithium hexamethyldisilazide in tetrahydrofuran (1.0 M, 3.3 mL, 3.3 mmol, 1.2 equiv) was added to a solution of trimethylsilylacetylene (500 µL, 3.5 mmol, 1.3 equiv) in tetrahydrofuran (50 mL) at –78 °C, and the resulting solution was stirred for 30 min. A solution of the aldehyde **23** (866 mg, 2.74 mg, 1 equiv) in tetrahydrofuran (20 mL) was added via cannula, and the resulting reaction mixture was stirred at –78 °C for 1.5 h, then was warmed to 0 °C and was stirred at that temperature for 30 min. The product solution was partitioned between aqueous phosphate buffer solution (pH 7, 0.05 M in sodium hydrogen phosphate and 0.05 M in potassium dihydrogen phosphate, 200 mL) and a 1:1 mixture of ethyl acetate and hexanes (200 mL). The aqueous layer was separated and extracted further with one 200-mL portion of a 1:1 mixture of ethyl acetate and hexanes. The combined organic layers were dried over sodium sulfate and then were concentrated.

The residue was purified by flash column chromatography (5% ethyl acetate in hexanes initially, then 15% ethyl acetate in hexanes) to provide separately the alcohol **24** as a colorless oil (458 mg, 40.4%) as well as the alcohol **25** as a colorless oil (618 mg, 54.4 %).

Alcohol 24:

^{1}H NMR (400 MHz, $CDCl_3$), δ: 4.63 (m, 1H, C≡CC**H**OH), 3.97 (br s, 1H, C**H**OTBS), 3.17 (s, 6H, OC**H**$_3$), 1.87 (br ddd, 1H, *J* = 20.2, 10.6, 3.4 Hz, CHC**H**$_2$CHOTBS), 1.75 (br t, 1H, *J* = 12.0 Hz, CH(OH)C**H**CH$_2$), 1.73 (m, 1H, CHC**H**$_2$CHOTBS), 1.67 (d, 1H, *J* = 5.6 Hz, O**H**), 1.66 (br d, 1H, *J* = 11.4 Hz, $(CH_3O)_2$CC**H**$_2$), 1.56 (t, 1H, *J* = 11.4 Hz, $(CH_3O)_2$CC**H**$_2$), 1.53 (m, 1H, C**H**CH$_3$), 0.93 (d, 3H, *J* = 5.4 Hz, C**H**$_3$CH), 0.89 (s, 9H, (C**H**$_3$)$_3$CSi), 0.17 (s, 9H, (C**H**)$_3$Si), 0.09 (s, 3H, (C**H**$_3$)$_2$Si), 0.08 (s, 3H, (C**H**$_3$)$_2$Si).

FTIR (neat), cm^{-1}: 3448 (m br, OH), 2955 (s), 2899 (m), 2857 (w), 2168 (w, C≡C), 1463 (m), 1374 (w), 1251 (m), 1200 (w), 1139 (m), 1090 (s), 1051 (m), 982 (m), 971 (m), 915 (m), 839 (vs), 774 (m).

HRMS (FAB): Calcd for $C_{21}H_{41}O_4Si_2$ $[M-H]^+$: 413.2543

Found: 413.2558

TLC (10% ethyl acetate-hexanes), R_f: **24**: 0.38 (black, anisaldehyde)

23: 0.28 (black-green, anisaldehyde)

Alcohol 25:

^{1}H NMR (400 MHz, $CDCl_3$), δ: 4.69 (dd, 1H, J = 5.9, 2.2 Hz, C≡CC**H**OH), 3.98 (br s, 1H, C**H**OTBS), 3.16 (s, 6H, OC**H**$_3$), 1.94 (dt, 1H, J = 13.2, 3.4 Hz, CHC**H**$_2$CHOTBS), 1.71 (br ddd, 1H, J = 13.2, 12.7, 2.6 Hz, CHC**H**$_2$CHOTBS), 1.68-1.47 (m, 5H), 1.51 (d, 1H, J = 2.2 Hz, O**H**), 0.95 (d, 3H, J = 5.9 Hz, C**H**$_3$CH), 0.90 (s, 9H, (C**H**$_3$)$_3$CSi), 0.16 (s, 9H, (C**H**)$_3$Si), 0.11 (s, 3H, (C**H**$_3$)$_2$Si), 0.09 (s, 3H, (C**H**$_3$)$_2$Si).

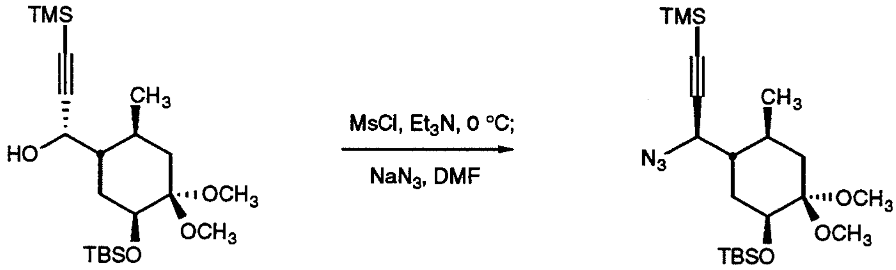
FTIR (neat), cm^{-1}: 3447 (m br, OH), 2955 (s), 2898 (m), 2857 (w), 2169 (w, C≡C), 1464 (m), 1376 (w), 1251 (m), 1198 (w), 1138 (m), 1087 (s), 1052 (w), 1026 (w), 982 (m), 971 (m), 910 (w), 880 (m), 837 (vs), 774 (m), 760 (w).

HRMS (FAB): Calcd for $C_{21}H_{41}O_4Si_2$ $[M-H]^+$: 413.2543

Found: 413.2541

TLC (10% ethyl acetate-hexanes), R_f: **25**: 0.15 (black, anisaldehyde)

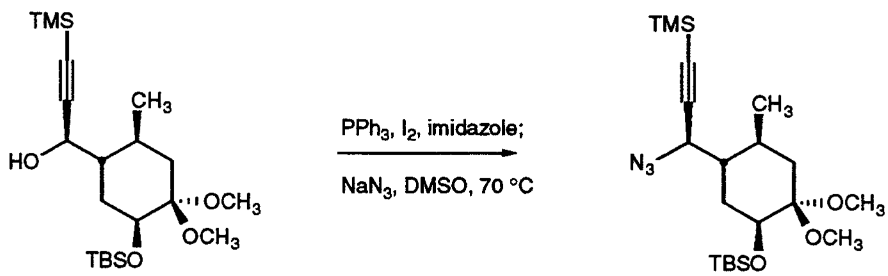
23: 0.28 (black-green, anisaldehyde)



24 27

Azide 27 from Alcohol 24

Methanesulfonyl chloride (230 μL, 2.97 mmol, 1.30 equiv) was added to an ice-cooled solution of the alcohol **24** (944 mg, 2.28 mmol, 1 equiv) and triethylamine (1.6 mL, 11.5 mmol, 5.04 equiv) in dichloromethane (25 mL). The resulting light yellow reaction mixture was stirred at 0 °C. The product solution was partitioned between aqueous phosphate buffer solution (pH 7, 0.05 M in sodium hydrogen phosphate and 0.05 M in potassium dihydrogen phosphate, 200 mL) and a 1:1 mixture of ethyl acetate and hexanes (150 mL). The aqueous layer was separated and extracted further with two 150-mL portions of a 1:1 mixture of ethyl acetate and hexanes. The combined organic layers were dried over sodium sulfate and then were concentrated to leave the product mesylate as a light yellow oil [TLC (10% ethyl acetate in hexanes), R_f : 0.26 (black, anisaldehyde)]. Sodium azide (1.06 g, 16.3 mmol, 7.16 equiv) was added to a solution of the unpurified mesylate in *N*,*N*-dimethylformamide (10 mL), and the resulting suspension was stirred at 23 °C for 20 h. The product suspension was partitioned between saturated sodium chloride solution (200 mL) and a 1:1 mixture of ethyl acetate and hexanes (100 mL). The aqueous layer was separated and extracted further with two 100-mL portions of a 1:1 mixture of ethyl acetate and hexanes. The combined organic layers were dried over sodium sulfate and then were concentrated. The residue was purified by flash column chromatography (5% ethyl acetate in hexanes) to afford the azide **27** as a colorless oil (857 mg, 86%).

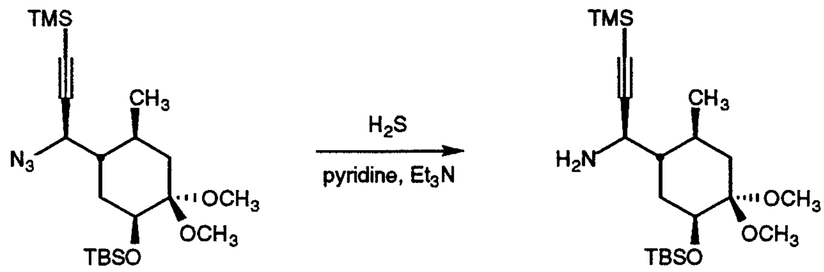


25 **27**

Azide 27 from Alcohol 25

Iodine (175 mg, 0.689 mmol, 2.75 equiv) was added to a solution of the alcohol **25** (104 mg, 0.251 mmol, 1 equiv), triphenylphosphine (197 mg, 0.751 mmol, 2.99 equiv), and imidazole (53 mg, 0.78, 3.1 equiv) in dichloromethane (10 mL), and the resulting reaction mixture was stirred at 23 °C for 50 min. The reaction solution was then added via cannula into a solution of sodium azide (168 mg, 2.58, 10.3 equiv) in dimethyl sulfoxide (7 mL) at 70 °C open to the atmosphere. The resulting solution was heated at that temperature for 20 min, causing the dichloromethane to boil away. The product solution was allowed to cool to 23 °C, then was partitioned between water (200 mL) and a 4:1 mixture of hexanes and ethyl acetate (75 mL). The aqueous layer was separated and extracted further with one 75-mL portion of a 4:1 mixture of hexanes and ethyl acetate. The combined organic layers were dried over sodium sulfate and then were concentrated. The residue was purified by flash column chromatography (20% ethyl acetate in hexanes) to provide the azide **27** as a colorless oil (82 mg, 74%).

^{1}H NMR (400 MHz, $CDCl_3$), δ:	4.51 (br s, 1H, C≡CC**H**N_3), 3.94 (br s, 1H, C**H**OTBS), 3.16 (s, 3H, OC**H**$_3$), 3.15 (s, 3H, OC**H**$_3$), 1.93 (br ddd, 1H, *J* = 21.3, 11.7, 2.9 Hz, CHC**H**$_2$CHOTBS), 1.72-1.59 (m, 3H, CHC**H**$_2$CHOTBS, CH(N_3)C**H**CH$_2$, $(CH_3O)_2$CC**H**$_2$), 1.54 (m, 1H, C**H**CH_3), 1.47 (t, 1H, *J* = 12.6 Hz, $(CH_3O)_2$CC**H**$_2$), 0.89 (s, 9H, (C**H**$_3$)$_3$CSi), 0.88 (d, 3H, *J* = 7.0 Hz, C**H**$_3$CH), 0.19 (s, 9H, (C**H**$_3$)$_3$Si), 0.11 (s, 3H, (C**H**$_3$)$_2$Si), 0.08 (s, 3H, (C**H**$_3$)$_2$Si).
FTIR (neat), cm^{-1}:	2955 (s), 2931 (s), 2900 (m), 2856 (m), 2830 (w), 2176 (w, C≡C), 2110 (vs, N_3), 1464 (m), 1375 (w), 1252 (s), 1198 (m), 1139 (m), 1105 (m), 1086 (s), 1053 (m), 1017 (w), 984 (m), 971 (m), 941 (w), 862 (s sh), 843 (vs), 775 (m), 662 (w sh).
HRMS (FAB):	Calcd for $C_{21}H_{40}O_3Si_2N_3$ [M–H]$^+$: 438.2608 Found: 438.2602
TLC (5% ethyl acetate-hexanes), R_f:	**27**: 0.31 (brown, anisaldehyde)
(10% ethyl acetate-hexanes), R_f:	**24**: 0.38 (black, anisaldehyde) **25**: 0.15 (black, anisaldehyde)

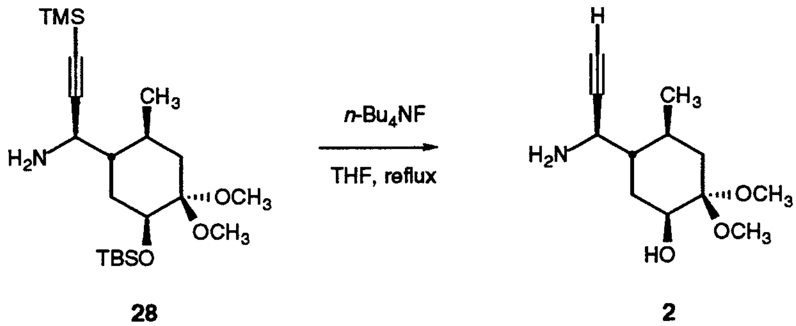


27 28

Amine 28

A 50-mL, 3-N round bottom flask fitted with glass inlet and outlet tubes was charged with the amine **27** (840 mg, 1.91 mmol, 1 equiv), pyridine (15 mL), and triethylamine (7 mL). Hydrogen sulfide was sparged at a moderate rate through the resulting solution; the gas exiting the flask was sparged through an aqueous sodium hydroxide solution (15% w/v). After 7 h, the product solution was partitioned between water (500 mL) and ethyl acetate (100 mL). The aqueous layer was separated and extracted further with ethyl acetate (2 x 100 mL). The combined organic layers were dried over sodium sulfate and then were concentrated. The residue was purified by flash column chromatography (30% ethyl acetate in hexanes) to provide separately the amine **28** as a colorless oil (700 mg, 89%) as well as the starting azide **27** as a colorless oil (40 mg, 5%).

^{1}H NMR (400 MHz, $CDCl_3$), δ:	3.97 (br s, 1H, C**H**OTBS), 3.91 (br s, 1H, C≡CC**H**NH_2), 3.16 (s, 6H, OC**H**$_3$), 1.90 (br m, 1H, CHC**H**$_2$CHOTBS), 1.71-1.48 (m, 5H), 1.18 (br s, 2H, N**H**$_2$), 0.90 (br s, 12H, (C**H**$_3$)$_3$Si, C**H**$_3$CH), 0.14 (s, 9H, (C**H**$_3$)$_3$Si), 0.12 (s, 3H, (C**H**$_3$)$_2$Si), 0.08 (s, 3H, (C**H**$_3$)$_2$Si).
FTIR (neat), cm^{-1}:	3382 (w, NH_2), 3318 (w, NH_2), 2954 (s), 2856 (m), 2830 (w), 2161 (m, C≡C), 1600 (br w), 1463 (m), 1374 (w), 1360 (w), 1250 (s), 1200 (m), 1136 (m), 1094 (vs), 1050 (m), 1022 (w), 980 (m), 922 (vw), 878 (m), 838 (vs), 774 (m), 760 (sh w), 698 (w), 657 (w).
HRMS (FAB):	Calcd for $C_{21}H_{42}O_3Si_2N$ $[M-H]^+$: 412.2703 Found: 412.2715
TLC (40% ethyl acetate-hexanes), R_f:	**28**: 0.33 (yellow, ninhydrin) **27**: 0.80 (brown, anisaldehyde)



Amine 2

A solution of tetrabutylammonium fluoride in tetrahydrofuran (1.0 M, 2.5 mL, 2.5 mmol, 2.8 equiv) was added to a solution of the amine **28** (368 mg, 0.889 mmol, 1 equiv) in tetrahydrofuran (20 mL) at 23 °C. The reaction mixture was heated to 70 °C and was stirred at that temperature for 3 h. The reaction mixture was allowed to cool to 23 °C and then was concentrated. The residue was purified by flash column chromatography (10% 2-propanol in ethyl acetate) to yield the amine **2** as a colorless oil (202 mg, 100%).

^{1}H NMR (400 MHz, $CDCl_3$), δ:	3.98 (br s, 1H, **CH**OTBS), 3.90 (br s, 1H, C≡C**CH**NH_2), 3.23 (s, 3H, OCH_3), 3.20 (s, 3H, OCH_3), 2.27 (d, 1H J = 2.4 Hz, C≡**CH**), 2.09 (br d, 1H, J = 12.7 Hz, $CHCH_2CHOTBS$), 1.98 (br s, 1H, **OH**), 1.76 (br d, 1H, J = 13.7 Hz, $(CH_3O)_2CCH_2$), 1.72-1.50 (m, 2H, **CH**CH_3, $CH(NH_2)$**CH**CH_2), 1.58 (br td, 1H, J = 13.0, 2.4 Hz, $CHCH_2CHOTBS$), 1.45 (dd, 1H, J = 13.7, 12.2 Hz, $(CH_3O)_2CCH_2$), 1.23 (br s, 2H, NH_2), 0.95 (d, 3H, J = 5.9 Hz, CH_3CH).
FTIR (neat), cm^{-1}:	3467 (s br, OH), 3284 (s, C≡CH), 2955 (s), 2825 (w), 1595 (br w), 1461 (m), 1437 (w), 1373 (w), 1302 (w), 1226 (w), 1196 (w), 1107 (m), 1061 (s), 967 (m), 879 (w), 791 (w).
HRMS (FAB):	Calcd for $C_{12}H_{22}O_3N$ $[M+H]^+$: 228.1600 Found: 228.1592
TLC (ethyl acetate), R_f:	**2**: 0.16 (yellow, ninhydrin)

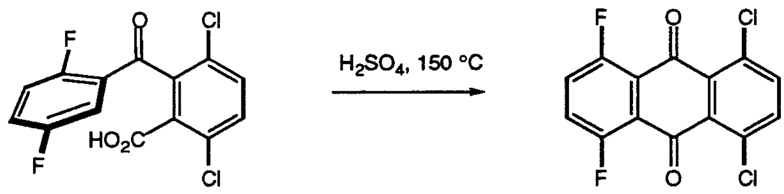
29

Carboxylic Acid 29

A suspension of 3,6-dichlorophthalic anhydride (1.337 g, 6.161 mmol, 1 equiv) and aluminum trichloride (2.3 g, 17 mmol, 2.8 equiv) in 1,4-difluorobenzene (15 mL, 150 mmol, 24 equiv) was heated at reflux for 21.5 h. The cloudy yellow reaction mixture was allowed to cool to 23 °C, then was poured over a mixture of ice (200 g) and aqueous hydrochloric acid solution (1% v/v, 200 mL). The white precipitate which formed was removed by vacuum filtration (water aspirator) and was allowed to air dry, providing the carboxylic acid **29** as an off-white solid (1.825 g, 89.5%). The filtrate was extracted with dichloromethane (2 x 200 mL), and the combined organic layers were dried over sodium sulfate and then were concentrated to furnish additional acid **29** as an off-white solid (0.101 g, 4.95%; combined yield: 94.4%).

^{1}H NMR (400 MHz, CD_3OD), δ: 7.76 (m, 1H, FCC**H**=CHCF), 7.65 (d, 1H, *J* = 8.6 Hz, ClCC**H**=CHCCl), 7.63 (d, 1H, *J* = 8.6 Hz, ClCCH=C**H**CCl), 7.20 (m, 1H, FCCH=C**H**CF), 7.05 (m, 1H, COC=C**H**CF).

FTIR (neat), cm^{-1}:	3382 (s, vbr, COOH), 1747 (vs, C=O), 1590 (w, C=C), 1494 (s), 1459 (m), 1297 (m), 1251 (m), 1224 (s), 1197 (m), 1158 (m), 1114 (m), 1080 (m), 997 (w), 936 (m), 864 (m), 824 (m), 756 (m).
TLC (40% ethyl acetate-hexanes), R_f:	**29**: 0.14



29

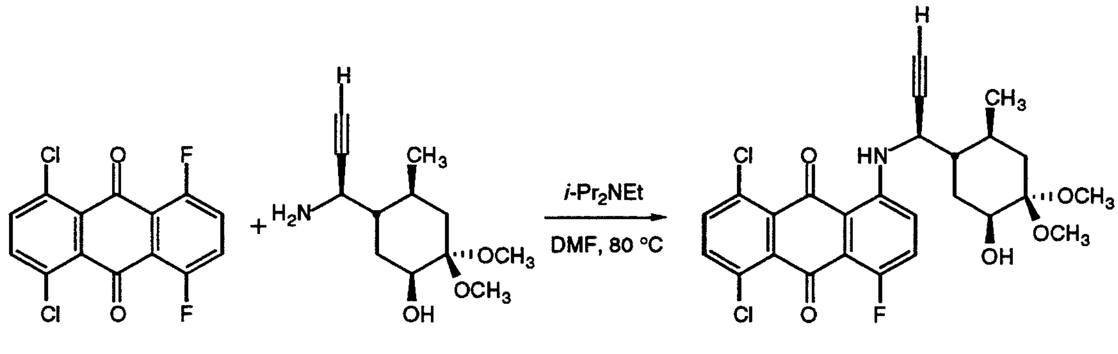
3

1,4-Dichloro-5,8-difluoroanthraquinone

A solution of the acid **29** (398 mg, 1.20 mmol, 1 equiv) in concentrated sulfuric acid (5 mL) was heated at 145 °C for 7 h. The reaction mixture was allowed to cool to 23 °C, then was poured over ice (50 g). The transfer was quantitated with water (20 mL), and the resulting mixture was extracted with ethyl acetate (3 x 50 mL). The combined organic layers were dried over sodium sulfate and were concentrated. The residue was dissolved in ethyl acetate (50 mL), then flash grade silica gel (15 mL) was added to the product solution. The resulting suspension was concentrated, and the remaining mixture of fine solid was loaded onto a column of solvated (20% ethyl acetate in hexanes) flash grade silica gel (150 mL). Elution (20% ethyl acetate in hexanes) provided 1,4-dichloro-5,8-difluoroanthraquinone (**3**) as a pale yellow solid (149 mg, 40%).

^{1}H NMR (400 MHz, C_6D_6), δ: 6.72 (s, 2H, ClCCH=CHCCl), 6.34 (dd, 2H, J = 7.0, 6.2 Hz, FCCH=CHCF).

FTIR (neat), cm^{-1}:	3096 (w), 1690 (s, C=O), 1600 (w, C=C), 1560 (w), 1477 (m), 1438 (m), 1379 (w), 1325 (m), 1300 (m), 1271 (w), 1251 (w), 1212 (vs), 1143 (m), 937 (w), 897 (w), 843 (m).
TLC (40% ethyl acetate-hexanes), R_f:	**3**: 0.44 **29**: 0.14



Coupled Product 30

A solution of the amine **2** (17 mg, 0.075 mmol, 1 equiv) and 1,4-dichloro-5,8-difluoroanthraquinone (**3**, 35 mg, 0.11 mmol, 1.5 equiv) and *N*,*N*-diisopropylethylamine (50 μL, 0.29 mmol, 2.6 equiv) in *N*,*N*-dimethylformamide (1.5 mL) at 23 °C was deoxygenated by alternately evacuating the reaction vessel and flushing with argon (5x). The reaction mixture was heated at 80 °C under a positive pressure of argon (5 psi) for 26 h. The red product solution was allowed to cool to 23 °C, and the volatiles were removed in vacuo. The residue was purified by flash column chromatography (40% ethyl acetate in hexanes) to afford the coupled product **30** as a red oil (7 mg, 18%) as well as the starting amine **2** and 1,4-dichloro-5,8-difluoroanthraquinone (**3**).

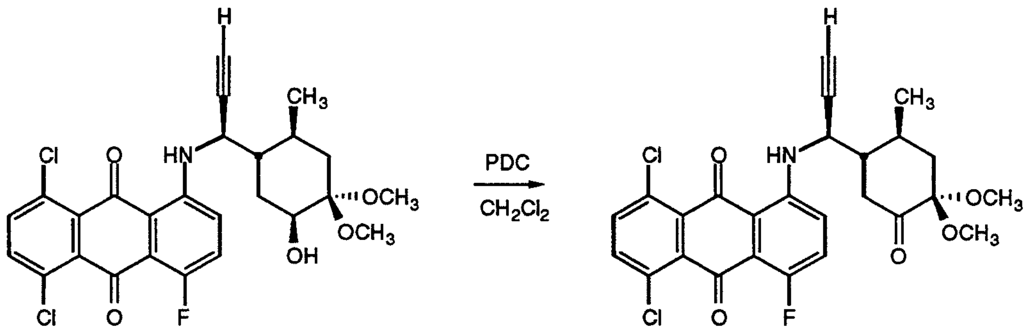
^1H NMR (400 MHz, $CDCl_3$), δ:	9.33 (d, 1H, *J* = 6.4 Hz, N**H**), 7.61 (d, 1H *J* = 8.6 Hz, ClCCH=C**H**CCl), 7.58 (d, 1H, *J* = 8.6 Hz, ClCC**H**=CHCCl), 7.35 (t, 1H, *J* = 9.8 Hz, FCC**H**=CHCN), 7.21 (dd, 1H, *J* = 9.4, 4.1 Hz, FCCH=C**H**CN), 4.48 (m, 1H, C≡CC**H**N), 4.10 (br s, 1H, C**H**OTBS), 3.30 (s, 3H, OCH_3), 3.27 (s, 3H, OCH_3), 2.34 (d, 1H, *J* = 2.4 Hz, C≡C**H**), 2.29 (dt, 1H, *J* = 13.2, 3.2 Hz, CHCH_2CHOTBS), 2.10-2.00 (m, 2H, O**H**, C≡CCH(N)CHCH_2), 1.95 (br t, 1H, *J* = 12.9 Hz, CHCH_2CHOTBS), 1.84 (m, 1H, C**H**CH_3), 1.83 (br d, 1H, *J* = 13.7 Hz, $(CH_3O)_2CCH_2$), 1.55 (t, 1H, *J* = 13.7 Hz, $(CH_3O)_2CCH_2$), 0.96 (d, 3H, *J* = 6.4 Hz, CH_3CH).
FTIR (neat), cm^{-1}:	3490 (m br, OH), 3300 (m, C≡CH), 2251 (vw, C≡C), 1682 (s, C=O), 1643 (s, C=O), 1600 (m, C=C), 1506 (s), 1434 (w), 1383 (w), 1299 (m), 1210 (vs), 1138 (m), 1066 (s), 962 (w), 912 (w), 897 (w), 827 (w), 771 (w), 731 (w).

HRMS (FAB): Calcd for $C_{12}H_{21}O_4S$ $[M]^+$: 519.1016

Found: 519.1035

TLC (40% ethyl acetate-hexanes), R_f: **30**: 0.17 (red, visible)

3: 0.44 (UV)

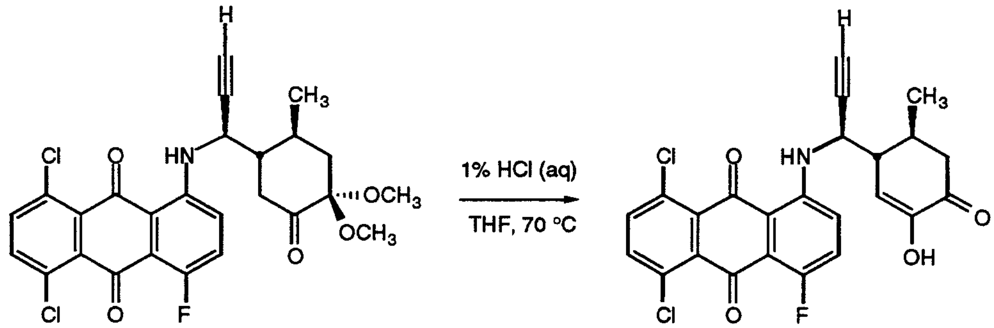


30 31

Ketone 31

A solution of the alcohol **30** (7 mg, 0.01 mol, 1 equiv) in dichloromethane (5 mL) was stirred at 23 °C in the presence of partially crushed and activated 4Å molecular sieves for 45 min. Pyridinium dichromate (25 mg, 0.066 mmol, 4.9 equiv) was added to the solution, and the resulting suspension was stirred at 23 °C for 1.25 h. Diethyl ether (5 mL) was added to the brown product suspension followed by Celite (100 mg). The resulting suspension was stirred for 5 min, then the solids were removed by vacuum filtration (water aspirator) through a small plug of Celite using diethyl ether (20 mL) initially, then dichloromethane (20 mL) as eluent. The filtrate was concentrated, and the residue was purified by flash column chromatography (50% ethyl acetate in hexanes) to afford the ketone **31** as an orange oil (4 mg, 60%).

^{1}H NMR (400 MHz, $CDCl_3$), δ:	9.47 (d, 1H, *J* = 6.4 Hz, N**H**), 7.63 (d, 1H *J* = 8.6 Hz, ClCCH=C**H**CCl), 7.60 (d, 1H, *J* = 8.6 Hz, ClCC**H**=CHCCl), 7.38 (t, 1H, *J* = 9.7 Hz, FCC**H**=CHCN), 7.19 (dd, 1H, *J* = 9.4, 4.1 Hz, FCCH=C**H**CN), 4.48 (m, 1H, C≡CC**H**N), 3.37 (s, 3H, OC**H**$_3$), 3.33 (s, 3H, OC**H**$_3$), 2.98 (t, 1H, *J* = 12.9 Hz, CHC**H**$_2$CO), 2.88 (dd, 1H, *J* = 12.9, 4.1 Hz, CHC**H**$_2$CO), 2.41 (dd, 1H, *J* = 14.1, 3.0 Hz, $(CH_3O)_2$CC**H**$_2$), 2.38 (d, 1H, *J* = 2.4 Hz, C≡C**H**), 2.35 (m, 1H, C**H**CH$_3$), 2.01 (m, 1H, C≡CCH(N)C**H**CH$_2$),1.41 (dd, 1H, *J* = 14.1, 12.6 Hz, $(CH_3O)_2$CC**H**$_2$), 1.03 (d, 3H, *J* = 6.4 Hz, C**H**$_3$CH).
FTIR (neat), cm^{-1}:	3287 (m, C≡CH), 2961 (m), 2252 (vw, C≡C), 1735 (s, C=O), 1685 (s, C=O), 1638 (s, C=O), 1599 (C=C), 1508 (s), 1298 (m), 1211 (vs), 1139 (s), 1047 (s), 916 (w), 826 (m), 730 (m).
TLC (40% ethyl acetate-hexanes), R_f:	**31**: 0.30 (orange, visible) **30**: 0.17 (red, visible)



31 32

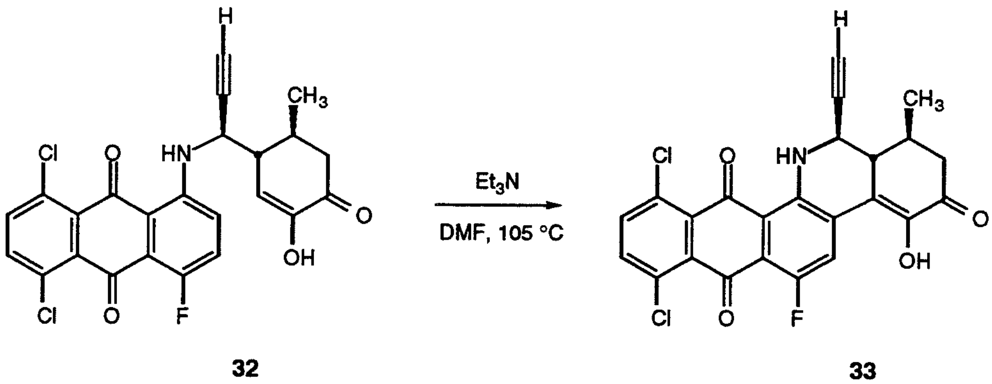
Diketone 32

A homogeneous solution of the ketone **31** (7 mg, 0.01 mmol, 1 equiv) in tetrahydrofuran (3 mL) saturated with aqueous hydrochloric acid solution (1% v/v) was heated at 70 °C for 5.75 h. The product solution was allowed to cool to 23 °C, and the volatiles were removed in vacuo. The residue was purified by flash column chromatography (40% ethyl acetate in hexanes initially, grading to 20% hexanes in ethyl acetate) to afford the diketone **32** as an orange solid (6 mg, 90%).

^{1}H NMR (400 MHz, $CDCl_3$), δ: **major enol regioisomer**:

9.13 (d, 1H, *J* = 7.0 Hz, N**H**), 7.61 (d, 1H *J* = 8.6 Hz, ClCCH=C**H**CCl), 7.58 (d, 1H, *J* = 8.6 Hz, ClCC**H**=CHCCl), 7.37 (t, 1H, *J* = 9.7 Hz, FCC**H**=CHCN), 7.19 (dd, 1H, *J* = 9.7, 4.1 Hz, FCCH=C**H**CN), 6.38 (d, 1H, *J* = 3.5 Hz, C**H**=COH), 6.21 (s, 1H, O**H**), 4.54 (m, 1H, C≡CC**H**N), 2.87 (m, 1H, C≡CCH(N)C**H**CH=COH), 2.78 (dd, 1H, *J* = 16.6, 4.0 Hz, COC**H**$_2$CHCH$_3$), 2.47 (m, 1H, C**H**CH$_3$), 2.41 (d, 1H, *J* = 2.1 Hz, C≡C**H**), 2.38 (dd, 1H, *J* = 16.6, 10.6 Hz, COC**H**$_2$CHCH$_3$), 1.15 (d, 3H, *J* = 6.4 Hz, C**H**$_3$CH).

^1H NMR (400 MHz, $CDCl_3$), δ:	**minor enol regioisomer**: 9.24 (d, 1H, *J* = 7.3 Hz, N**H**), 7.63 (d, 1H *J* = 8.8 Hz, ClCCH=C**H**CCl), 7.60 (d, 1H, *J* = 8.8 Hz, ClCC**H**=CHCCl), 7.37 (t, 1H, *J* = 9.7 Hz, FCC**H**=CHCN), 7.16 (dd, 1H, *J* = 9.7, 4.1 Hz, FCCH=C**H**CN), 6.00 (d, 1H, *J* = 3.8 Hz, C**H**=COH), 5.93 (s, 1H, O**H**), 4.49 (m, 1H, C≡CC**H**N), 3.07 (dd, 1H, *J* = 17.0, 4.1 Hz, COC**H**$_2$CHCH(N)), 3.02 (m, 1H, C**H**CH$_3$), 2.80 (dd, 1H, *J* = 17.0, 10.8 Hz, COC**H**$_2$CHCH(N)), 2.87 (m, 1H, C≡CCH(N)C**H**CH=COH), 2.41 (d. 1H, *J* = 2.3 Hz, C≡C**H**), 2.38 (m. 1H, C≡CCH(N)C**H**CH$_2$), 1.27 (d, 3H, *J* = 7.0 Hz, C**H**$_3$CH).
FTIR (neat), cm^{-1}:	3433 (br w, OH), 3283 (m, C≡CH), 2962 (w), 2260 (vw, C≡C), 1682 (s, C=O), 1644 (C=O), 1599 (C=C), 1505 (s), 1409 (w), 1384 (w), 1298 (m), 1253 (w), 1208 (vs), 1163 (w), 1138 (m), 1063 (m), 953 (m), 913 (w), 828 (m), 772 (w), 732 (m).
TLC (40% ethyl acetate-hexanes), R_f:	**32**: 0.28 (orange, visible) **31**: 0.30 (orange, visible)



Cyclized Product 33

A solution of the diketone **32** (3 mg, 0.006 mmol, 1 equiv) and triethylamine (100 µL, 0.72 mmol, 110 equiv) in *N,N*-dimethylformamide (2 mL) in a treaded reaction tube fitted with a Teflon screw plug was deoxygenated by alternately evacuating the reaction tube and flushing with argon (5x). The reaction tube was evacuated a final time, then was screwed closed. The reaction tube was immersed in an oil bath heated to 105 °C for 3.75 h, causing the reaction mixture to darken. The reaction tube was allowed to cool to 23 °C, then was opened under a positive pressure of argon (5 psi). Volatiles were removed in vacuo, and the red residue was purified by preparative thin layer chromatography (2% ethyl acetate in methylene chloride) to yield the cyclized product **33** as a purple solid (1 mg, 33%).

^1H NMR (400 MHz, $CDCl_3$), δ:	9.65 (br s, 1H, N**H**), 8.20 (d, 1H, *J* = 12.3 Hz, FCC**H**=C), 7.63 (d, 1H *J* = 8.8 Hz, ClCCH=C**H**CCl), 7.61 (d, 1H, *J* = 8.8 Hz, ClCC**H**=CHCCl), 7.10 (s, 1H, O**H**), 4.38 (dd, 1H, *J* = 11.3, 2.2 Hz, C≡CC**H**N), 2.73 (dd, 1H, *J* = 11.3, 4.8 Hz, C**H**C=COH), 2.69 (dd, 1H, *J* = 19.8, 7.6 Hz, COC**H**$_2$CHCH$_3$), 2.64 (d, 1H, *J* = 2.4 Hz, C≡C**H**), 2.54 (dd, 1H, *J* = 19.8, 7.3 Hz, COC**H**$_2$CHCH$_3$), 2.53 (m, 1H, C**H**CH$_3$), 1.41 (d, 3H, *J* = 6.7 Hz, C**H**$_3$CH).
FTIR (neat), cm^{-1}:	3354 (m, OH), 3265 (m, C≡CH), 2928 (vw), 1669 (vs, C=O), 1625 (C=C), 1506 (s), 1377 (m), 1321 (s), 1293 (m), 1243 (m), 1218 (m), 1204 (m), 1144 (m), 1085 (w), 946 (w), 906 (m), 767 (w).
HRMS (FAB):	Calcd for $C_{24}H_{15}O_4NCl_2F$ $[M+H]^+$: 470.0362 Found: 470.0366
TLC (40% ethyl acetate-hexanes), R_f:	**33**: 0.38 (purple, visible) **32**: 0.28 (orange, visible)

Chapter 2

Synthesis of (+)-Dynemicin A

With the benefit of retrospection, a new retrosynthetic plan was devised where the intermediate **C** was targeted as a late-stage intermediate, derivable from precursor **D** (Scheme X). Compound **C** was envisioned to arise from the pyridone **34**, the latter the product of cyclization of the intermediate **35**. Intermediate **35** was obtained from the palladium-catalyzed coupling of the aryl boronic acid **36** and the enantiomerically pure enol triflate **37**.

Enantiodifferentiation was achieved at the outset of our synthetic route by employing menthol as a chiral auxiliary/resolving agent. Menthyl acetoacetate (1.06 equiv, prepared on the half-kilo scale in 94% yield by thermal transesterification[23] of *t*-butyl acetoacetate with (–)-menthol) was condensed with *trans*-ethyl crotonate (1 equiv) in the presence of potassium *t*-butoxide (1.04 equiv) in *t*-butyl alcohol, forming the two possible *trans*-disubstituted 1,3-cyclohexanediones as a 1:1 mixture (Scheme XI).[24] A single recrystallization of the unpurified product mixture (benzene) afforded diastereomerically pure **38** (mp 180-181 °C, $[\alpha]_D^{22}$ = +66.9°, C = 0.77, CH_3OH) in 36% yield. The diastereomer of **38** (mp 140-141 °C) was isolated in pure form by recrystallization of the concentrated mother liquors from a mixture of ethyl acetate and hexanes (ratio 4:1, respectively).[25] The stereochemistry of the latter product was determined unequivocally by X-ray crystallographic analysis (Figure 4), and thereby established the configuration of **38** as shown. In a typical procedure, 150 g of menthyl acetoacetate was transformed into 65 g of the optically pure, crystalline diketone **38**. Treatment of **38** with anhydrous methanol

Scheme X

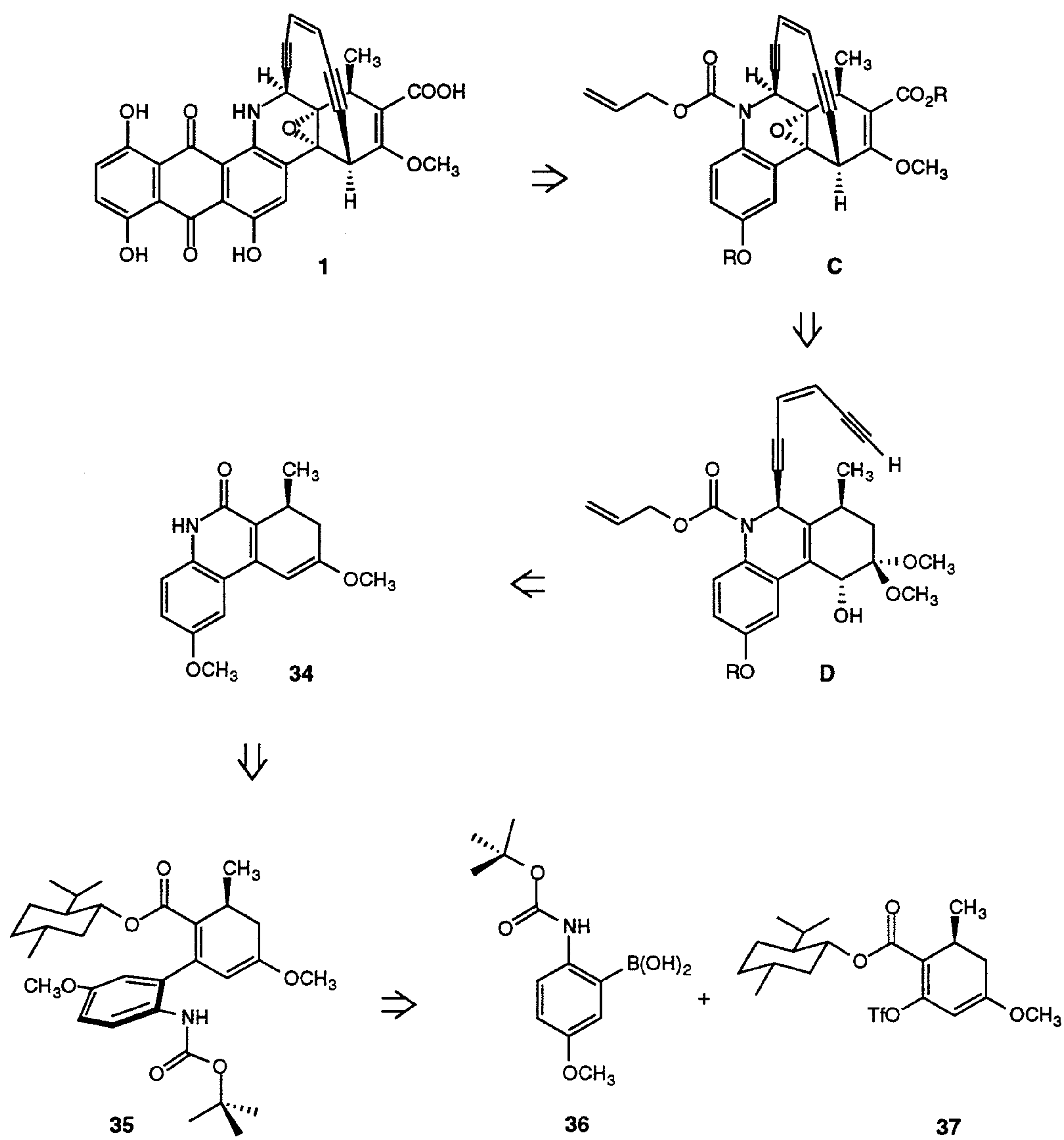


Figure 4

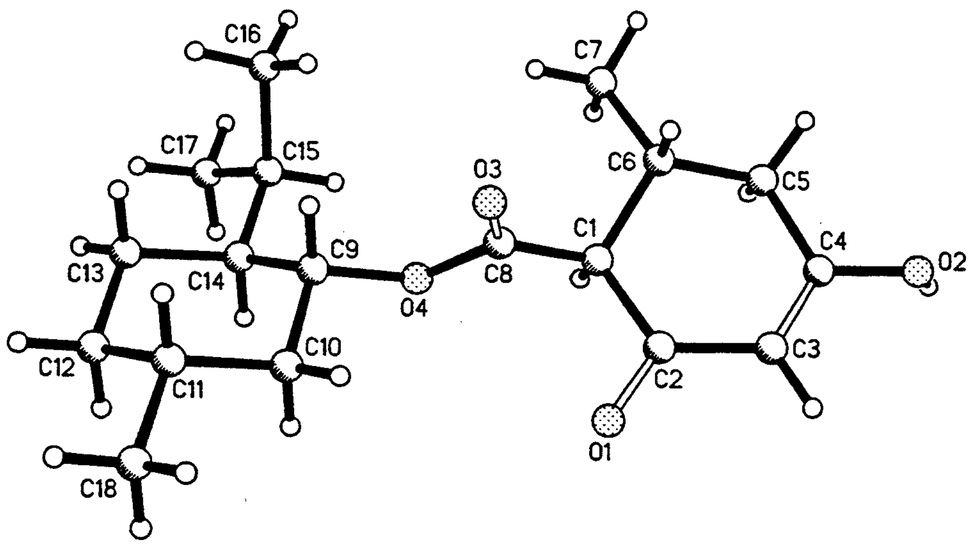
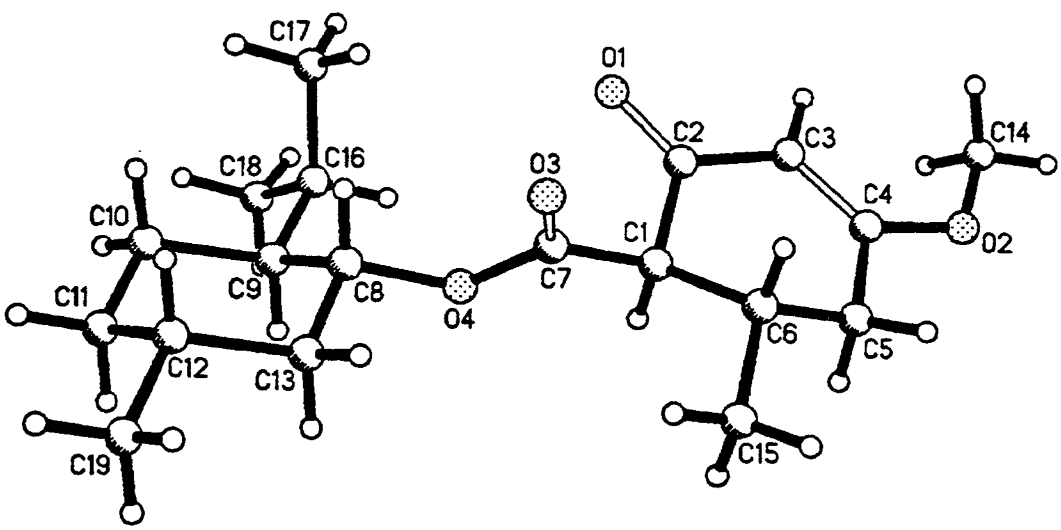
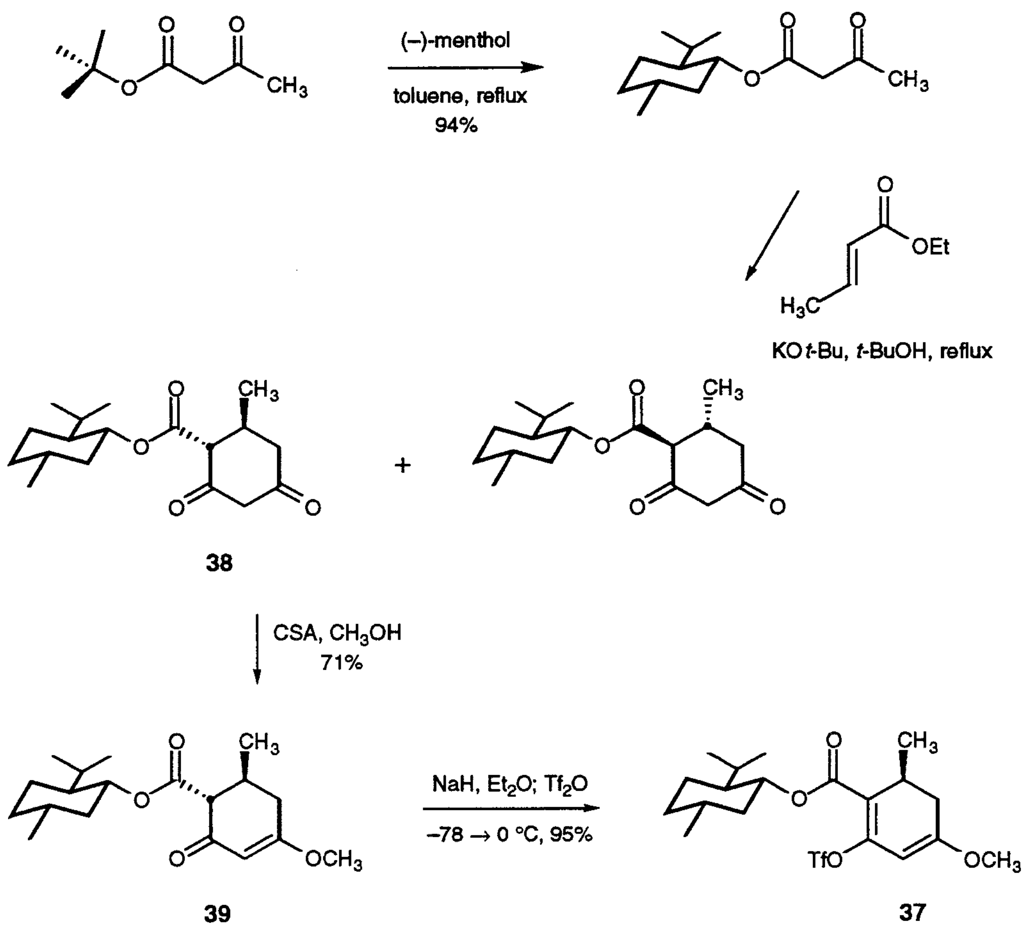


Figure 5



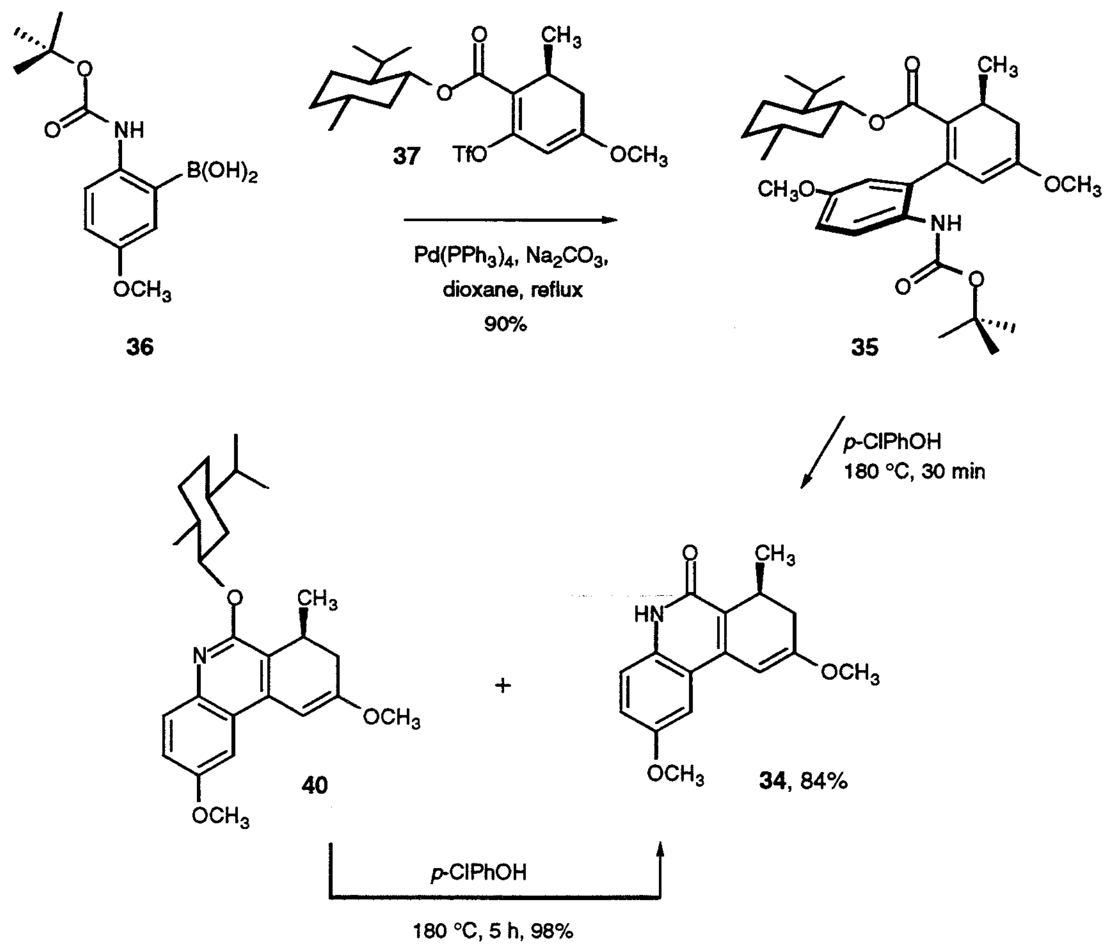
Scheme XI



and catalytic 10-camphorsulfonic acid provided regioselectively the methyl enol ether **39** in 71% yield. The regio- and stereochemistry of methyl enol ether **39** was established by X-ray crystallographic analysis (Figure 5). Deprotonation of **39** with sodium hydride in diethyl ether and trapping of the resultant enolate with triflic anhydride at low temperature afforded the corresponding enol triflate **37** in 95% yield.

Enol triflate **37** was efficiently coupled with *t*-butyl 2-borono-4-methoxycarbanilate (**36**, prepared by dilithiation of *t*-butyl 4-methoxycarbanilate with *t*-butyllithium in diethyl ether at –78 °C and subsequent trapping of the resultant dianion with trimethylborate)[26] in the presence of catalytic tetrakis(triphenylphosphine)palladium(0) (0.04 equiv) and sodium

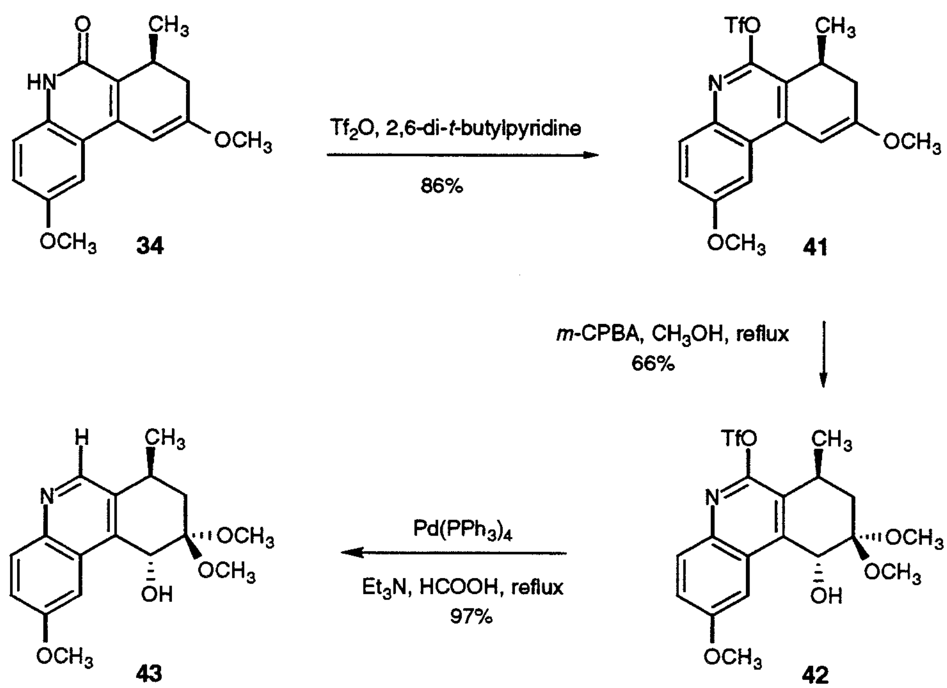
Scheme XII



carbonate (1.4 equiv) in dioxane to furnish the coupling product **35** (mp 141-142 °C) in 90% yield after recrystallization from a mixture of ethyl acetate and hexanes (4:1, respectively, Scheme XII).[27] Alternatively, **35** was obtained in 81% yield by the coupling of **37** and *t*-butyl 2-(trimethylstannyl)-4-methoxycarbanilate in the presence of catalytic tetrakis(triphenylphosphine)palladium(0) (0.05 equiv), cuprous iodide (0.04 equiv), and excess lithium chloride (4.4 equiv) in dioxane at reflux.[28] A high barrier to rotation about the newly formed carbon-carbon bond was evidenced by the observation of two distinct sets of peaks in the ^1H NMR spectrum, corresponding to the atropisomers of **35**.

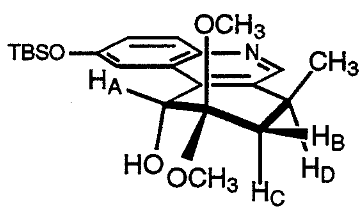
Thermolysis of **35** for 30 min in 4-chlorophenol at 180 °C afforded quinolone **34** in 84% yield after flash column chromatography.[29] The by-product **40** was obtained in separate fractions, and could be converted to desired product **34** in 98% yield by its resubjection to the reaction conditions for 5 h. The solvent is believed to play an important role in the former reaction, perhaps acting as a weak Bronsted acid. Reactions conducted in *o*-dichlorobenzene at the same temperature, for example, did not proceed to any appreciable extent.

Scheme XIII

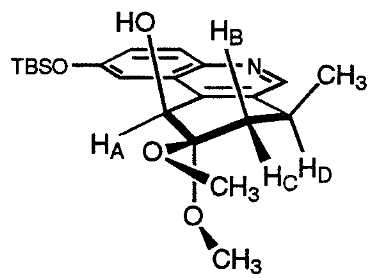


Quinolone **34** was transformed into the corresponding trifluoromethanesulfonate derivative **41** (86%) by warming a solution of the former from –78 °C in the presence of triflic anhydride and 2,6-di-*t*-butylpyridine in dichloromethane (Scheme XIII). Epoxidation of the methyl enol ether double bond using *m*-CPBA in methanol at reflux and chromtography of the product on silica gel afforded separately the α-oriented alcohol **42** (66%) and the β-oriented alcohol epimer (16%). The epimers were assigned by the analysis of ^{1}H-^{1}H coupling constants from ^{1}H NMR spectral data (Figure 6). Reductive cleavage of the trifluoromethanesulfonate group to form the quinoline **43** was accomplished in 97% yield by heating **42** with formic acid (2.6 equiv), excess triethylamine (4.0 equiv) and catalytic tetrakis(triphenylphosphine)palladium(0) (0.04 equiv) in dioxane at reflux.[30]

Figure 6

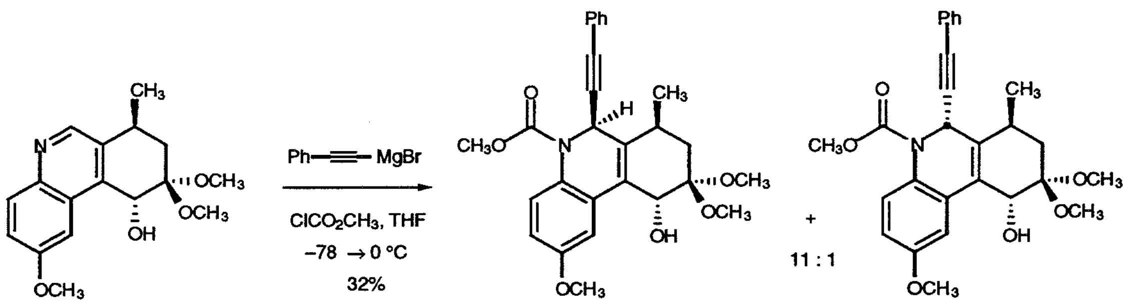


42: major epimer
J_{AB} = 2.0 Hz
J_{BD} = 2.0 Hz
J_{CD} = 7.6 Hz

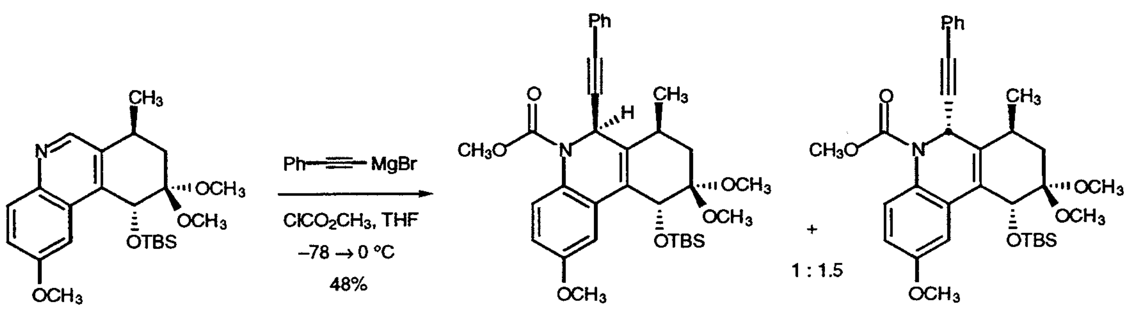


minor epimer
J_{AC} = 2.0 Hz
J_{BD} = 10.0 Hz
J_{CD} = 7.2 Hz

At this juncture, the protocol of Yamaguchi and co-workers,[31] involving acetylide addition to *N*-acylpyridinium intermediates, was investigated as a method for the introduction of the (*Z*)-enediyne bridge. In our initial studies, phenylacetylene was employed as a model for the acetylene component. A critical feature of this addition reaction concerns the stereochemistry of the carbon-carbon bond formation, where the desired product must result from addition of the acetylide to the same face of the *N*-acylquinolinium intermediate as that occupied by the methyl group. In our first experiment, the sequential addition of excess 1-bromomagnesio-2-phenylacetylene (prepared by the addition of ethylmagnesium bromide (4.0 equiv) to phenylacetylene (4.4 equiv) in THF at 0 °C and warming of the mixture to 23 °C) and methyl chloroformate (3.2 equiv) to a solution of **43** in THF at –78 °C, followed by warming of the reaction mixture to 0 °C for 3 h furnished separately **44** and **45** (11:1, respectively, 32% yield) after chromatography on silica gel. Interestingly, a modest reversal of diastereoselectivity was observed when the *tert*-butyldimethylsilyl ether of **43** was treated with 1-bromomagnesio-2-phenylacetylene (6.1 equiv) in the presence of methyl chloroformate (8.6 equiv) in THF at 0 °C for 6 h, suggesting that the presence of the hydroxy group within **43** is critical for obtaining high stereoselectivity favoring the desired acetylide addition product.

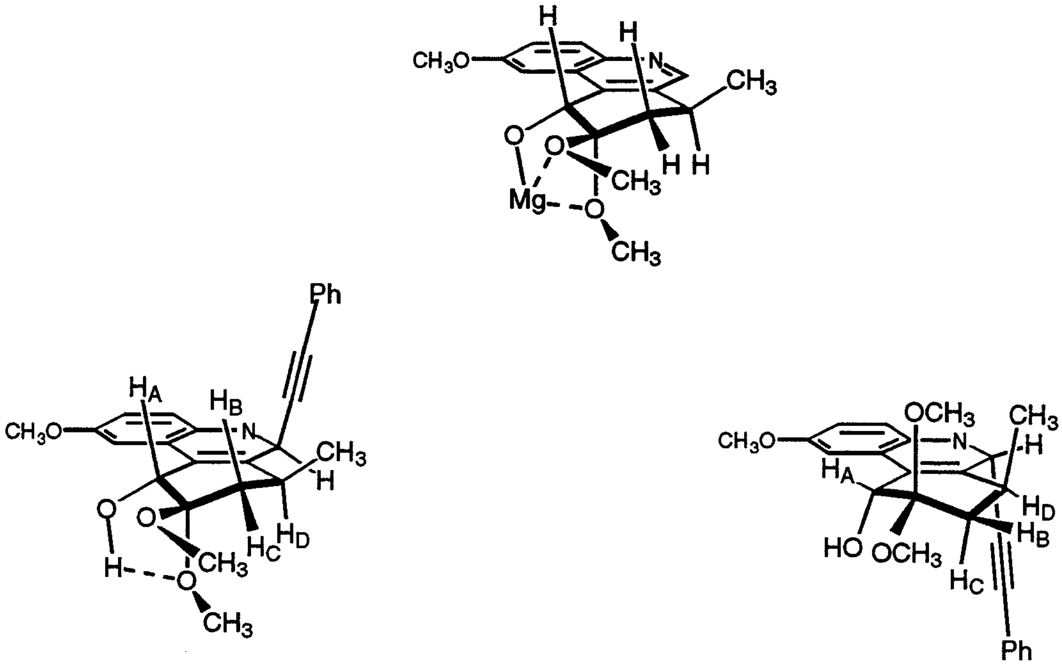


43 **44** **45**



The high stereoselectivity of the acetylide addition to **43** is believed to be due to the involvement of a magnesium alkoxide intermediate occupying a reactive half-chair conformation in which magnesium is chelated to the alkoxide and one or both methoxyl oxygens, placing the methyl group in a pseudoequatorial orientation (Figure 7). The

Figure 7



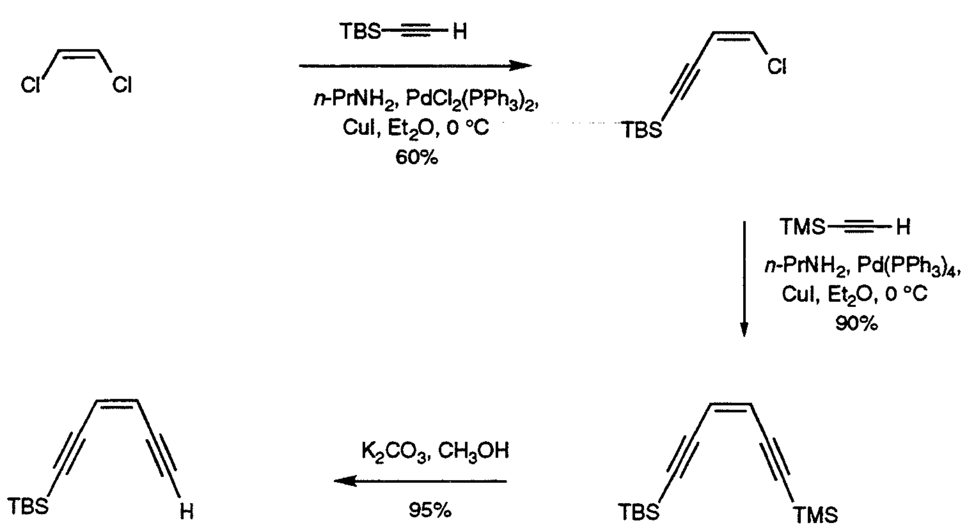
44, major diastereomer
J_{AOH} = 8.5 Hz
J_{AD} = 1.7 Hz
J_{BD} = 7.9 Hz
J_{CD} = 5.7 Hz

45, minor diastereomer
J_{AOH} = 3.0 Hz
J_{AD} = 0 Hz
J_{BD} < 2 Hz
J_{CD} = 7.1 Hz

assignment of the stereochemistry of the products of the addition reaction was aided by the use of molecular modeling. A Monte Carlo conformational search (MM2 force field) of each diastereomer suggested that the lowest energy conformation of each involved different half-chair conformers.[32] Tentative assignments were made by comparing calculated ^{1}H-^{1}H coupling constants of the lowest energy conformation of each diastereomer with those obtained from ^{1}H NMR spectral data (Figure 7). The calculated ^{1}H-^{1}H coupling constants of the desired product were nearly identical to those obtained from the ^{1}H NMR spectrum of the major product. Likewise, the calculated ^{1}H-^{1}H coupling constants of the undesired product matched those observed in the ^{1}H NMR spectrum of the minor product. Thus, the stereochemistry of products **44** and **45** were tentatively assigned as that depicted in Figure 7. This assignment was confirmed in studies with subsequent intermediates, most significantly with the preparation of **1**, for which X-ray crystallographic confirmation of structure exists.

Encouraged by the preliminary results of the acetylide addition reaction of 1-bromomagnesio-2-phenylacetylene with compound **43**, we synthesized (*Z*)-1-(*t*-butyldimethylsilyl)hex-3-ene-1,5-diyne in order to investigate the addition reaction of its derivable magnesium acetylide with quinoline **43**. (*Z*)-1-(*t*-Butyldimethylsilyl)hex-3-ene-1,5-diyne was prepared starting with a palladium and copper catalyzed coupling of (*t*-

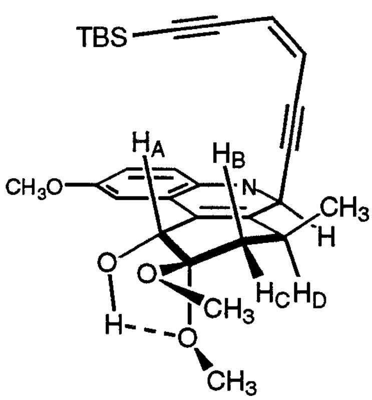
Scheme XIV



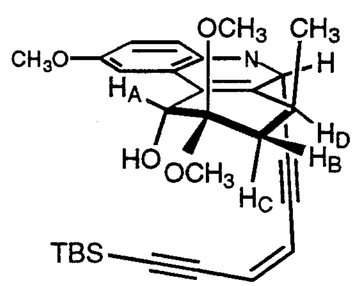
butyldimethylsilyl)acetylene and 1,2-*cis*-dichloroethylene in diethyl ether in the presence of *n*-propylamine to give (*Z*)-1-chloro-4-(*t*-butyldimethylsilyl)-1-buten-3-yne in 60% yield (12-g scale) after distillation under reduced pressure (Scheme XIV).[33] A similar coupling with the latter and (trimethylsilyl)acetylene in diethyl ether afforded (*Z*)-1-(*t*-butyldimethylsilyl)-6-(trimethylsilyl)-3-hexen-1,5-diyne after distillation under reduced pressure in 90% yield (20-g scale). Deprotection of the TMS group with potassium carbonate in methanol furnished (*Z*)-1-(*t*-butyldimethylsilyl)hex-3-ene-1,5-diyne in 95% yield which was not stored, but was carried on immediately to the acetylide addition step.

Treatment of the alcohol **43** with excess (*Z*)-1-bromomagnesio-6-(*t*-butyldimethylsilyl)hex-3-ene-1,5-diyne (2.3 equiv) at 0 °C and the subsequent addition of methyl chloroformate (1.6 equiv) provided separately the desired product **46** and its diastereomer (6:1, respectively, 41% yield) following chromatography on silica gel. As an improvement to the procedure, the alcohol **43** was treated with ethylmagnesium bromide (0.7 equiv) in THF at 0 °C, and the resulting magnesium alkoxide was combined with (*Z*)-1-bromomagnesio-6-(*t*-butyldimethylsilyl)hex-3-ene-1,5-diyne (2.4 equiv) in the presence of allyl chloroformate (2.0 equiv) to form the desired addition product **47** in 69% yield as well as small amounts of the undesired diastereomer **48** (3%). Conformationally, products

Figure 8



47, major diastereomer
J_{AOH} = 8.5 Hz
J_{AD} = 1.9 Hz
J_{BD} = 8.6 Hz
J_{CD} = 5.3 Hz

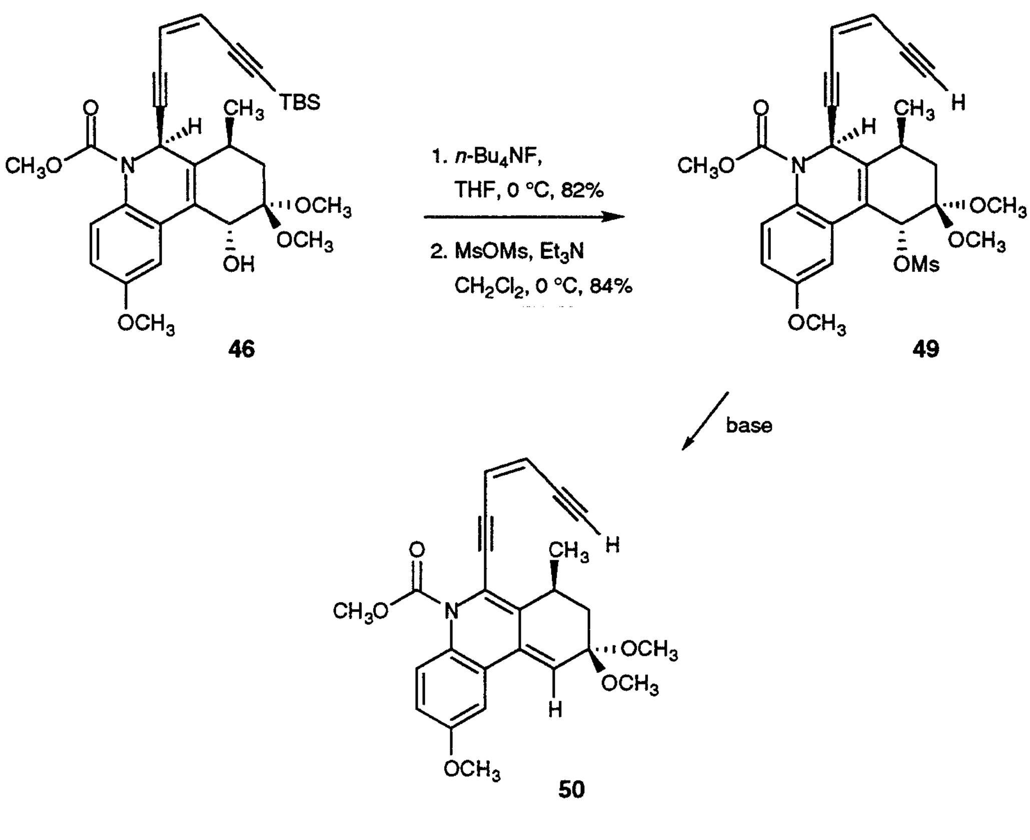


48, minor diastereomer
J_{AOH} < 3 Hz
J_{AD} = 0 Hz
J_{BD} < 2 Hz
J_{CD} = 7.3 Hz

47 and **48** were similar to the phenyl acetylide addition products **44** and **45** and, as a result, were assigned accordingly (Figure 8).

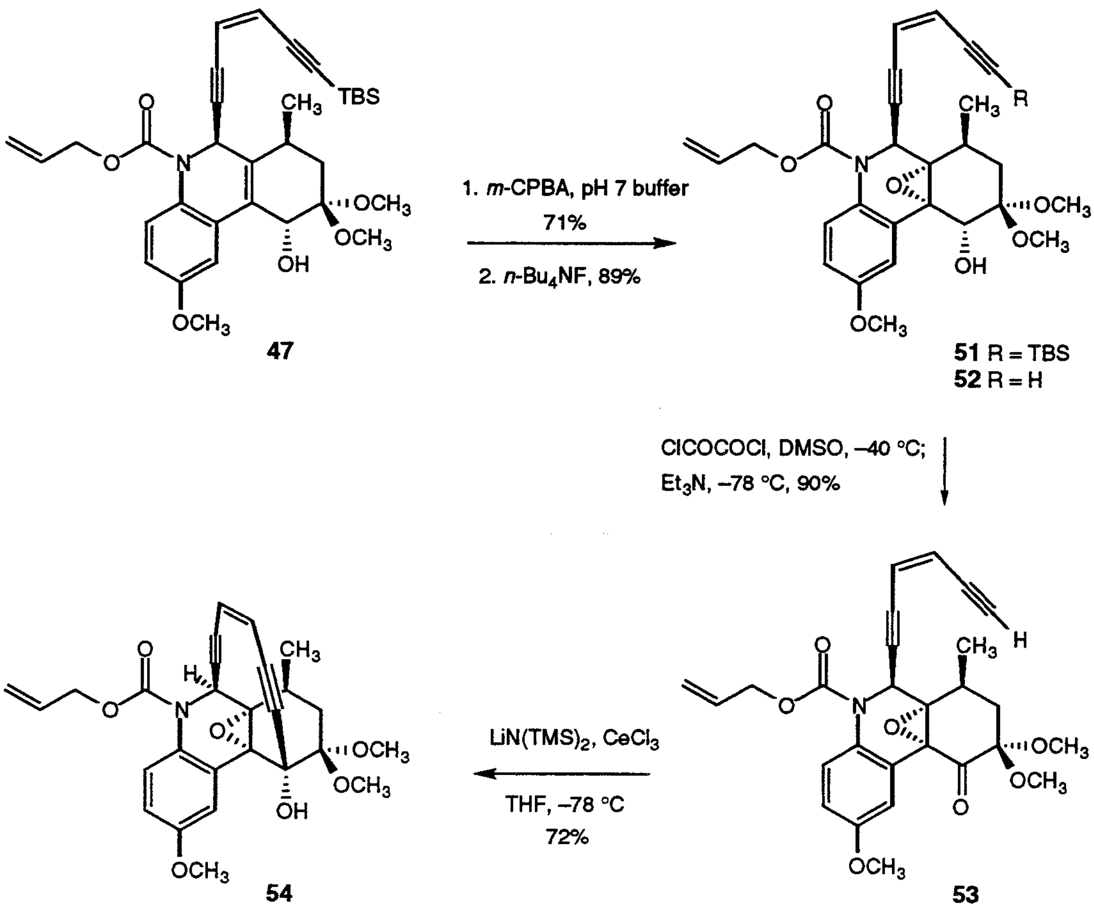
With the key intermediate **46** in hand, the next critical stage for our synthesis, ring closure to form the strained (Z)-enediyne bridge, was investigated. Desilylation of **46** followed by treatment of the allylic alcohol with methanesulfonic anhydride in the presence

Scheme XV



of triethylamine at 0 °C furnished the sensitive allylic mesylate **49** in good yield for the two-step sequence (Scheme XV). Exposure of **49** to base, in an effort to induce acetylide formation and ring closure, brought about a facile elimination reaction to afford the diene **50** in quantitative yield. Epoxidation of the tetrasubstituted double was therefore examined as a means to prevent the competing elimination reaction. Allylic alcohol **47** was treated

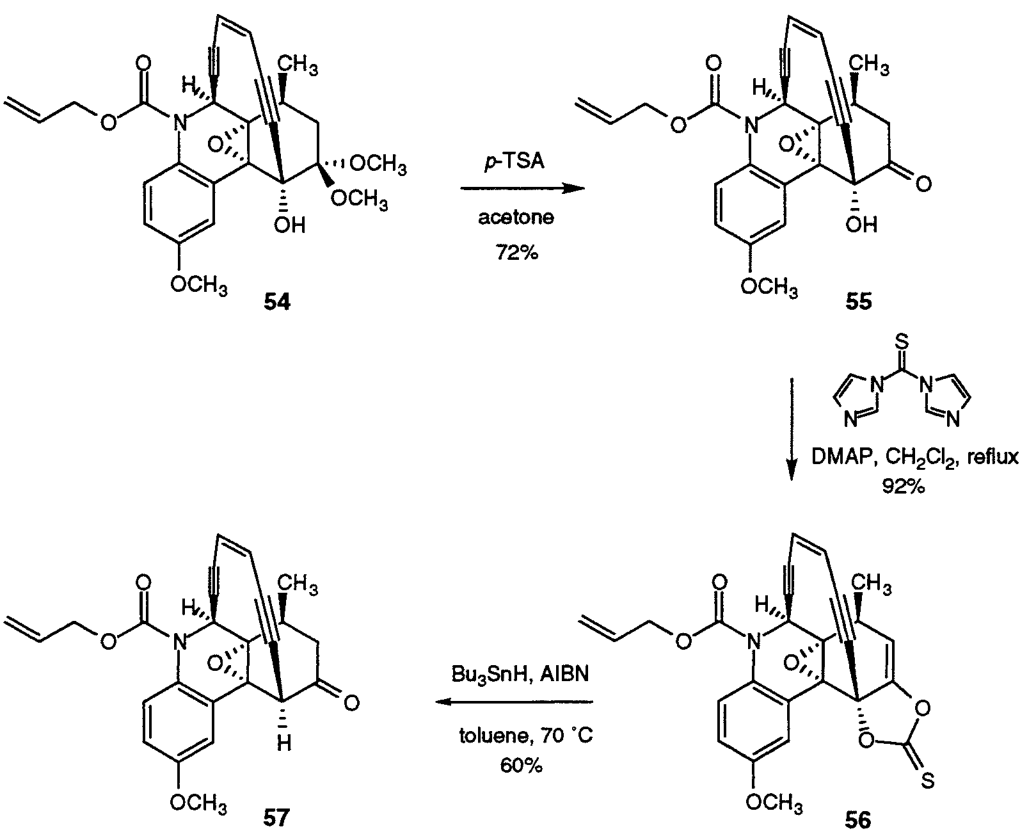
Scheme XVI



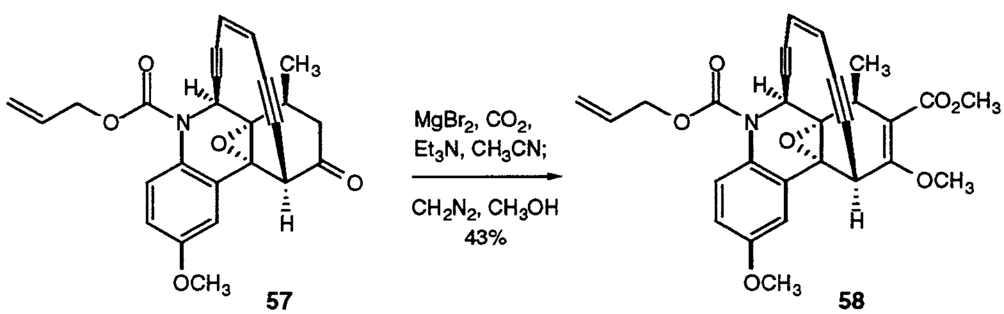
with *m*-CPBA in a biphasic mixture of dichloromethane and aqueous phosphate buffer solution (pH 7) to provide the α-oriented epoxide **51** in 71% yield (Scheme XVI). Desilylation proceeded smoothly by treatment of **51** with tetrabutylammonium fluoride to furnish compound **52** in 89% yield. Alcohol **52** was converted to its corresponding mesylate in ca. 60% yield through the slow, dropwise addition of triethylamine to a solution of **52** and excess methanesulfonyl chloride in dichloromethane. Attempted ring closure of the product mesylate failed under a variety of conditions, including those which employed copper acetylides. Intramolecular acetylide addition to a ketone was next pursued for the closure of the (*Z*)-enediyne bridge.[34] Swern oxidation[35] of alcohol **52** afforded ketone **53** in high yield (90%) and set the stage for the completion of the enediyne bridge. Toward this end, addition of lithium hexamethyldisilazide (1.06 equiv) to a solution of ketone **53** in THF at –78 °C containing cerium(III) chloride[36] (4.9 equiv) produced the strained ring closed product **54** in 72% yield as a stable, colorless oil after purification by chromatography on silica gel.

With the (*Z*)-enediyne bridge intact, our next objective was to complete the right-hand portion of dynemicin A, a task which required the deoxygenation of the bridgehead alcohol and introduction of the carboxylic acid. The first requirement was met beginning with the hydrolysis of the dimethyl ketal group in acetone in the presence of *para*-toluenesulfonic acid monohydrate, providing hydroxy ketone **55** in 72% yield (Scheme

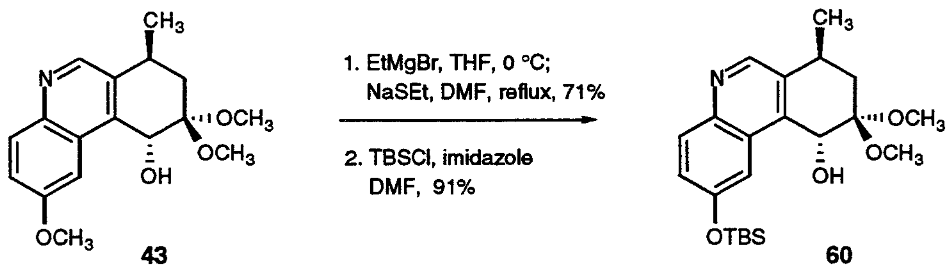
Scheme XVII



XVII). Heating a solution of the hydroxy ketone and 1,1'-thiocarbonyldiimidazole (8.0 equiv) in the presence of 4-dimethylaminopyridine (DMAP, 3.7 equiv) in dichloromethane at reflux furnished thiocarbonate **56** as a colorless oil (92%). Deoxygenation of the bridgehead oxygen within thiocarbonate **56** was accomplished with tributyltin hydride (1.7 equiv) in the presence of a catalytic amount of azobisisobutylnitrile (AIBN) in toluene at 70 °C, affording ketone **57** in 60% yield.[37] Carboxylation α to the ketone within **57** proved to be difficult. After extensive experimentation, it was discovered that mild conditions for carboxylation,[38] involving stirring a solution of **57** in the presence of magnesium bromide (5.5 equiv) and excess triethylamine (12 equiv) in acetonitrile under a dry carbon dioxide atmosphere, led to the efficient conversion of **57** to the α-keto acid. Addition of excess diazomethane to a solution of the decarboxylation-prone acid in methanol provided the vinylogous methyl carbonate **58** in 43% yield for the two-step sequence.[39]

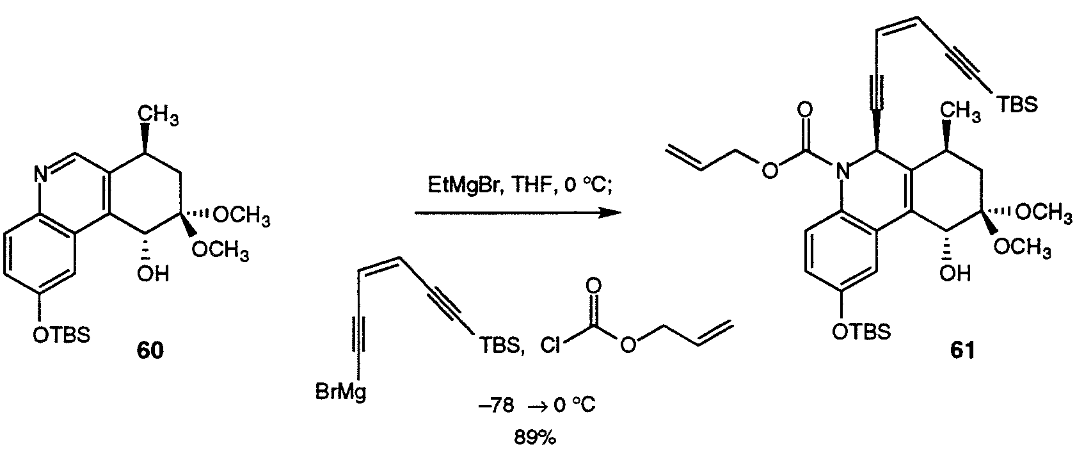


With the synthesis of the right-hand portion of dynemicin A secured, we focused our attention on the construction of the anthraquinone. It was conjectured at this time that oxidation of the aniline ring of **58** to the quinone oxidation state might enable the use of a Diels-Alder cycloaddition reaction or, alternatively, a related phthalide anion addition reaction for the completion of the anthraquinone. The aryl methyl ether group was exchanged for the more labile *t*-butyldimethylsilyl (TBS) group in order to facilitate liberation of the phenol late in the synthesis, as required for preparation of the quinone



43 60

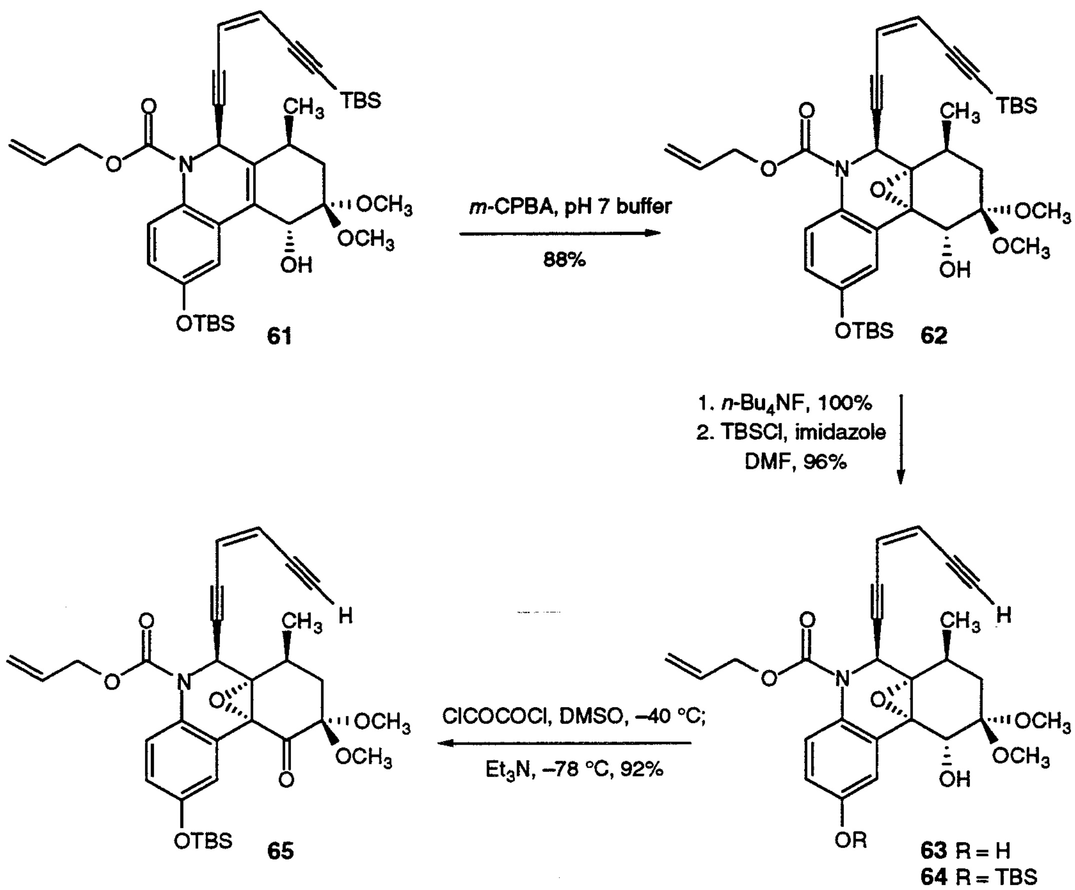
imine. Toward this end, the following demethylation procedure was developed by another group member, Norma J. Tom, using a modification of existing methodology.[40] Compound **43** was initially treated with ethylmagnesium bromide (1.1 equiv) in tetrahydrofuran at 0 °C (to prevent nucleophilic attack on the dimethyl ketal group), and the resultant magnesium alkoxide was heated with excess sodium ethylmercaptide in DMF at reflux for 1.5 h. The diol product **59** of the latter reaction was isolated in 71% yield; protection of the phenol (TBSCl, imidalzole, DMF)[41] afforded the silyl ether **60** (91%).



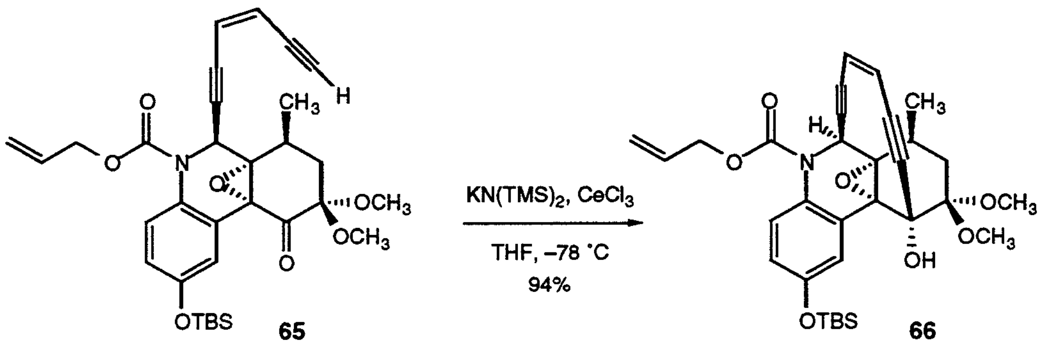
60 61

The addition reaction of (*Z*)-1-bromomagnesio-6-(*t*-butyldimethylsilyl)hex-3-ene-1,5-diyne with quinoline **60** proceeded in even higher yield and stereoselectivity than that of quinoline **43**. When alcohol **60** was treated with ethylmagnesium bromide (0.9 equiv) in THF at 0 °C and the resultant alkoxide was combined with (*Z*)-1-bromomagnesio-6-(*t*-

Scheme XVIII

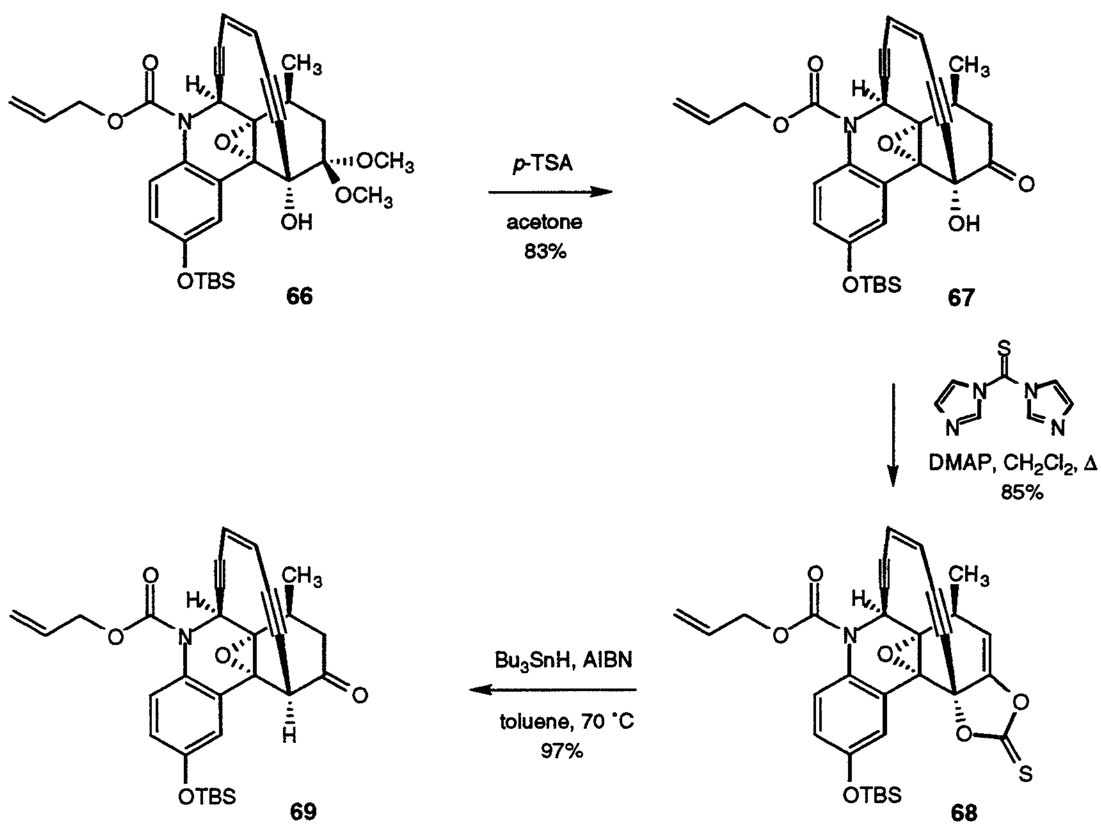


butyldimethylsilyl)hex-3-ene-1,5-diyne (2.0 equiv) in the presence of allyl chloroformate (1.6 equiv), addition product **61** was formed in 89% yield (9-g scale) and with greater than 25:1 diastereoselectivity. Selective epoxidation of the allylic alcohol **61** proceeded smoothly with *m*-CPBA in a two-phase mixture of dichloromethane and pH 7 aqueous phosphate buffer to provide the α-epoxide **62** in 88% yield (Scheme XVIII). Removal of both TBS groups occurred upon treatment of **62** with tetrabutylammonium fluoride in THF to furnish the phenol **63** in quantitative yield. Reprotection of the phenol by the treatment of **63** with TBSCl and imidazole in DMF then provided alcohol **64** (96%). Oxidation of **64** under Swern conditions afforded ketone **65** in 92% yield. Ring closure was accomplished in 94% yield by the addition of 1.1 equiv of potassium hexamethyldisilazide to a solution of ketone **65** in THF at –78 °C containing 3 equiv of cerium (III) chloride, producing the ring closed product **66** as a light yellow foam.

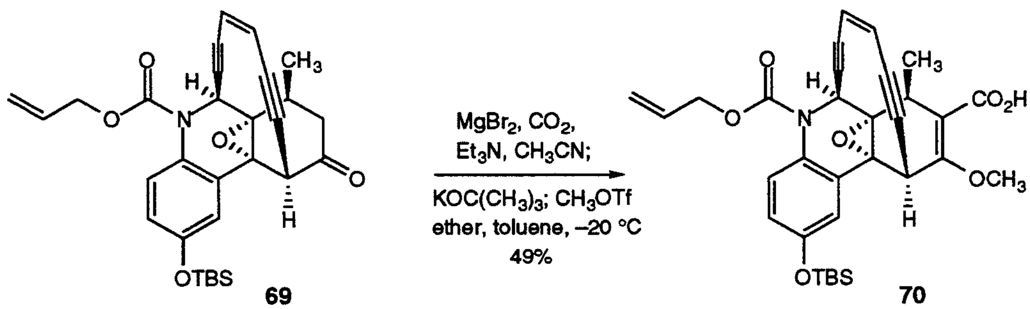


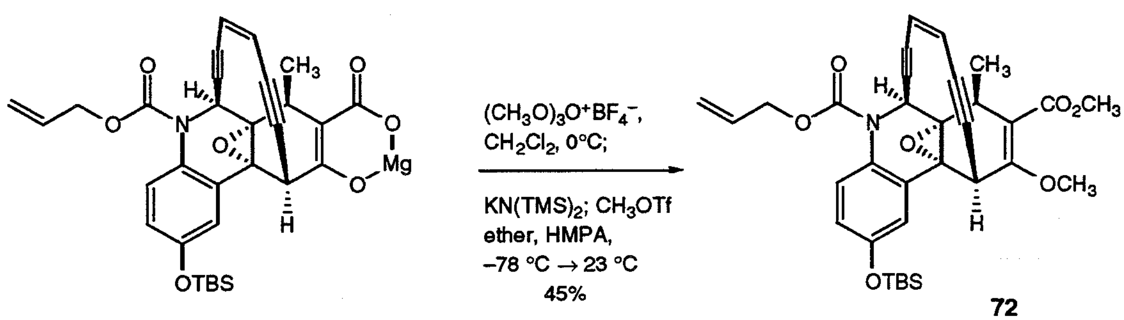
Completion of the right-most ring was initiated by hydrolysis of the dimethyl ketal group of **66** with *p*-toluenesulfonic acid hydrate in acetone at 23°C, furnishing the ketone **67** in 83% yield (Scheme XIX). Exposure of the latter product to excess 1,1'-thiocarbonyldiimidazole and DMAP (1.5 equiv) in dichloromethane at reflux produced cyclic thionocarbonate **68** in 85% yield. Heating a solution of **68** with tributyltin hydride and a catalytic amount of AIBN in deoxygenated toluene at 70°C afforded ketone **69** in 97% yield. Although conditions for carboxylation α to the ketone within **69** had been established, transformation of the intermediate carboxylic acid into the methyl enol ether **70** proved to be one of the most difficult operations in the route. The following procedure was developed by Norma J. Tom after extensive investigation: The α-keto acid was formed in high yield by stirring a solution of **69** in the presence of magnesium bromide (2.5 equiv) and excess triethylamine (15 equiv) in acetonitrile under a dry carbon dioxide atmosphere. Addition of a solution of the sensitive α-keto acid in diethyl ether to a suspension of potassium *t*-butoxide (4 equiv) in diethyl ether at –78 °C, followed by the transfer of the cold solution to a solution of freshly distilled methyl triflate (5 equiv) in toluene at –20 °C, afforded the vinylogous carbonic acid **70** in 49% yield for the two-step sequence. The

Scheme XIX



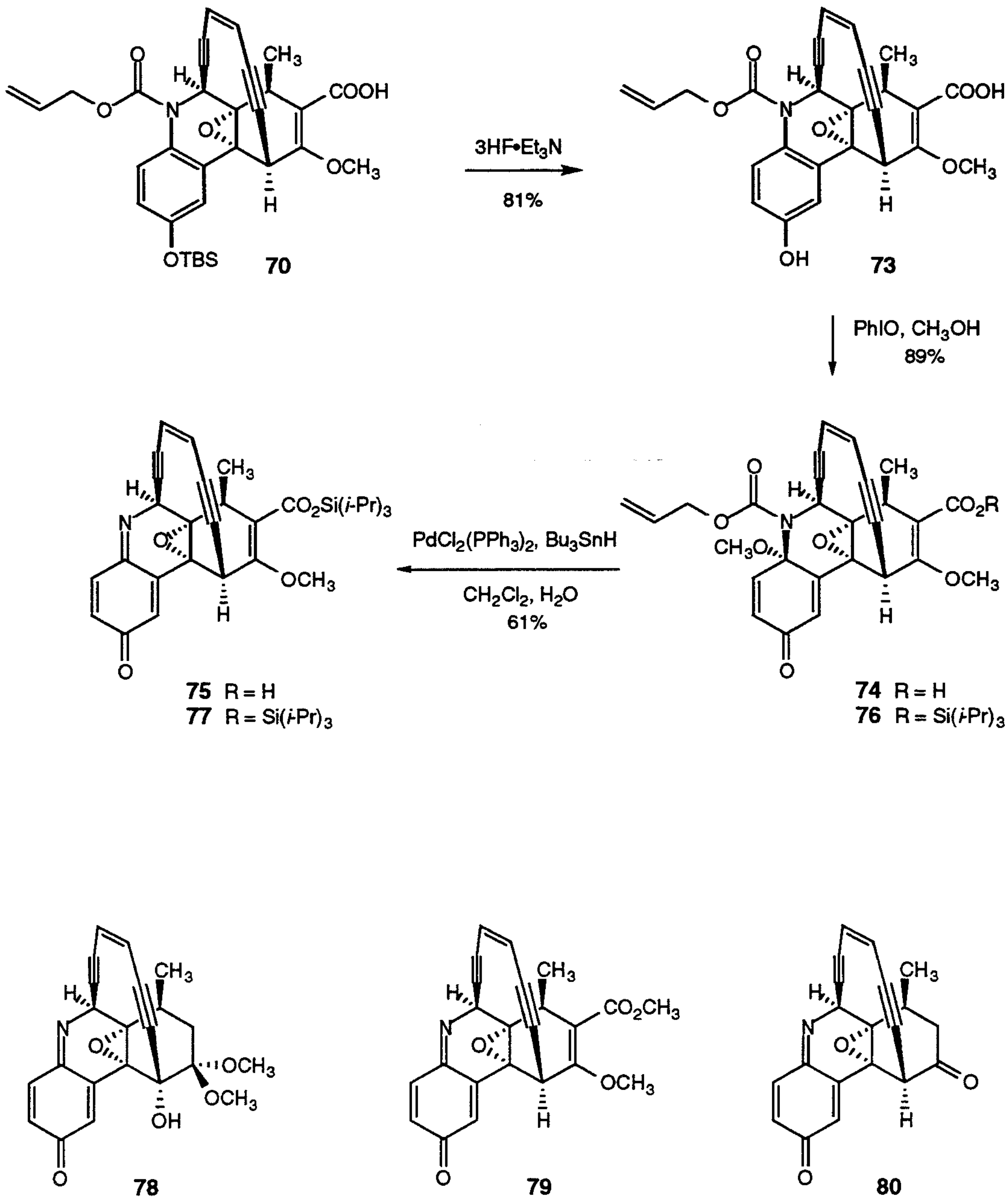
vinylogous methyl carbonate **72** was prepared beginning with the alkylation of the magnesium carboxylate (direct product of the carboxylation reaction, excess trimethyloxonium tetrafluoroborate in dichloromethane at 0 °C), providing the β-keto methyl ester **71** in 73% yield. Conversion of the latter to **72** was accomplished in 61% yield by the addition of a solution of potassium hexamethyldisilazide (3 equiv) to a solution of **71** in the presence of hexamethylphosphoramide (HMPA) in diethyl ether at –78 °C, followed by the addition of methyl triflate (3 equiv) and warming of the reaction mixture to 23 °C. Cleavage of the *t*-butyldimethylsilyl ether group of **70** with triethylamine hydrogen fluoride complex in acetonitrile afforded the phenol **73** in 81% yield, and oxidation of the latter with iodosobenzene in methanol at 23 °C provided the protected quinone imine **74** in



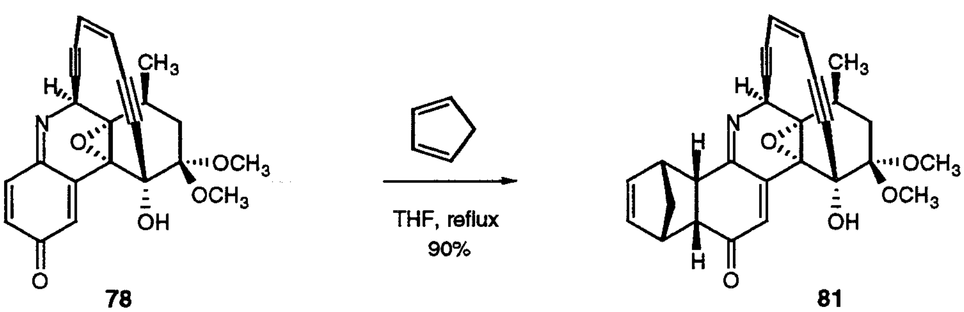


89% yield (Scheme XX).[42] Removal of the allyl carbamate group of **74** to reveal the quinone imine **75** was found to proceed with greater efficiency when the carboxyl group was protected as the corresponding triisopropyl ester **76**, prepared in 85% yield by the sequential treatment of the acid **74** with triethylamine and triisopropyl triflate in THF at –78 °C and warming of the reaction mixture to 0 °C. Treatment of **76** with 1.0 equiv of tributyltin hydride in wet dichloromethane containing bis(triphenylphosphine)palladium(II) chloride as catalyst then afforded the quinone imine **77** in 61% yield.[43] As anticipated, the quinone imine **77** proved to be stable to chromatography on silica gel, to routine manipulations, and to storage. The same sequence of steps, desilylation, oxidation, and deprotection, transformed intermediates **66** and **72** into the analogous quinone imines **78** and **79** in 73%, and 62% yield, respectively, for the sequence. Likewise, quinone imine **80** was prepared from ketone **69**, albeit in lower yield.[44]

Scheme XX


3HF•Et3N
81%
70
73
PhIO, CH3OH
89%
PdCl2(PPh3)2, Bu3SnH
CH2Cl2, H2O
61%
75 R = H
77 R = Si(i-Pr)3
74 R = H
76 R = Si(i-Pr)3
78
79
80

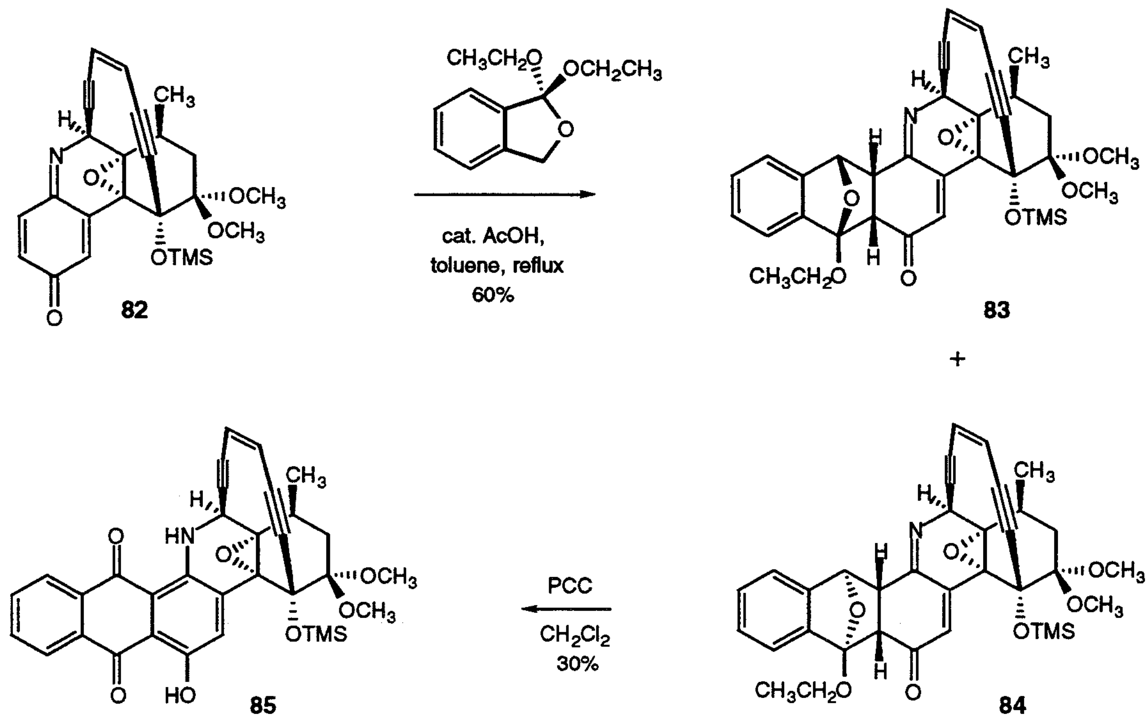
The synthesis of the anthraquinone was envisioned to arise at this juncture employing a Diels-Alder cycloaddition reaction. Because the quinone imine **78** could be prepared in fewer steps than **77**, it served as a useful model compound for our studies. In order to gauge the reactivity of the quinone imine **78** as a dienophile in the Diels-Alder reaction, a solution of **78** in THF containing excess cyclopentadiene (2 M) was heated at reflux for 30 min, whereupon cycloadduct **81** was formed as a single diastereomer in 90% yield. This product is believed to arise by endo addition of cyclopentadiene to the face of the quinone imine opposite the (Z)-enediyne bridge (α-face), a tentative assignment that is



supported by the observation of a 4-Hz coupling between protons vicinal by virtue of the newly formed carbon-carbon bonds. Two features of this reaction are noteworthy. First, the stability of the (Z)-enediyne group to the temperature of this and subsequently described thermal Diels-Alder reactions attests to the effectiveness of the epoxide ring in providing a structural barrier to Bergman cyclization in this system. Opening of the epoxide ring (formally by hydride addition), in contrast, leads to rapid Bergman cyclization of the (Z)-enediyne at ambient temperature, as demonstrated with the natural product (**1**).[45] It is also noteworthy that the Diels-Alder adduct **81** is sufficiently stable as to allow for its isolation. This is of no small concern, for aromatization of **81** is anticipated to facilitate epoxide opening, and thus biradical formation. Any Diels-Alder adduct of quinone imines **77-80** is conceivably a latent DNA cleaving agent, activated by tautomerization. It is perhaps not surprising, then, that **81** was found to bring about pH-dependent cleavage of a ^{32}P-labeled 193-base pair restriction fragment duplex DNA from pBR322 (Eco RI/Ssp I digest), albeit non-sequence specifically, and with poor efficiency (2% yield cleaved DNA (bp)/mol **81**).[46] Although the nature of the cleavage bands was suggestive of free-radical damage, the cleavage mechanism had not been established at the time of this writing. The quinone imines **77-80** themselves are also potential DNA-cleaving agents; however, these substrates have thus far not revealed any significant DNA-cleaving activity upon attempted activation with glutathione (GSH) or NADPH.

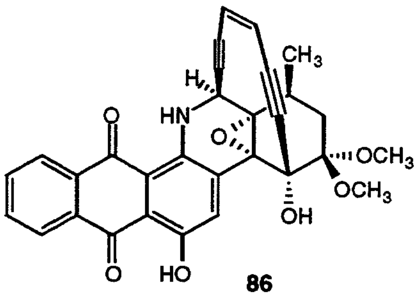
To synthesize the anthraquinone fragment by a Diels-Alder cycloaddition, we utilized the highly reactive isobenzofurans as dienes. The use of isobenzofurans to deliver an 8-carbon fragment to a quinone as a dienophile is precedented in anthracycline synthetic studies; however, in those cases several steps were necessary to transform the cycloadducts into the product anthraquinones, and these involved intermediates or reaction conditions that are incompatible with the sensitive functionality of **1**.[47] We initially synthesized anthraquinones in the dideoxydynemicin series, utilizing 1,1-diethoxyphthalan as the isobenzofuran precursor.[48] Heating a solution of **78** trimethylsilyl ether (**82**, prepared by silylation of the protected quinone imine precursor to **78** and subsequent removal of the allyl carbamate group), excess 1,1-diethoxyphthalan (22 equiv), and glacial acetic acid (1.6 equiv) in toluene at reflux for 20 min afforded a 1:1 mixture of endo and exo adducts **83** and **84**, respectively, in 60% yield (Scheme XXI). Both adducts **83** and **84** are believed to arise by attack on the α-face of the quinone imine. When exo adduct **84** was stirred with excess pyridinium chlorochromate (PCC, 11 equiv) in dichloromethane at 23 °C, the deep red anthraquinone **85** was obtained in 30% yield after purification by chromatography on silica gel. Desilylation of **85** with triethylamine trihydrofluoride in acetonitrile at 23 °C afforded the anthraquinone **86**; treatment of the latter product with *p*-toluenesulfonic acid in

Scheme XXI

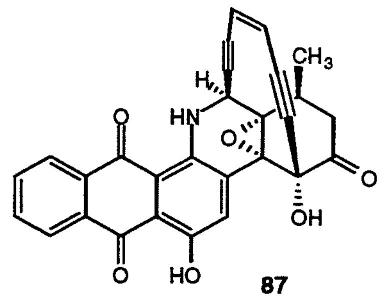


acetone at 23 °C produced dynemicin analog **87** as a dark red oil in 50% yield. This Diels-Alder/oxidation reaction sequence provides a general route to dideoxydynemicin analogs. Thus, quinone imine **80** afforded the anthraquinone **88** in 10% yield for the two steps, while **79** provided dideoxydynemicin methyl ester (**89**) in 6% yield.[49] The latter products (**88** and **89**) were too unstable to isolation by chromatography on silica gel, but could be purified by reverse-phase HPLC. The poor isolated yields of these products is believed to be due in large part to their instability.

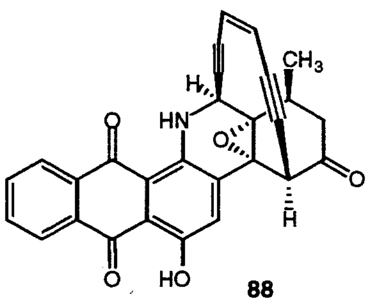
The synthesis of the more highly oxygenated anthraquinones, to include dynemicin A itself, proved more difficult. The oxygenated phthalides **90** and **91** served as precursors to the requisite isobenzofurans using a deprotonation-silylation sequence,[50] and were prepared in quantity by the simple synthetic route shown in Scheme XXII. Thus, 2,5-bis[[2-(trimethylsilyl)ethoxy]methoxy]benzoic acid *N*,*N*-diethylamide was formed in 76%



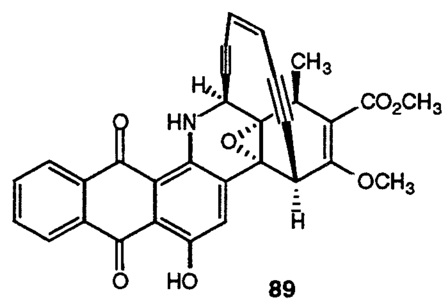
86



87



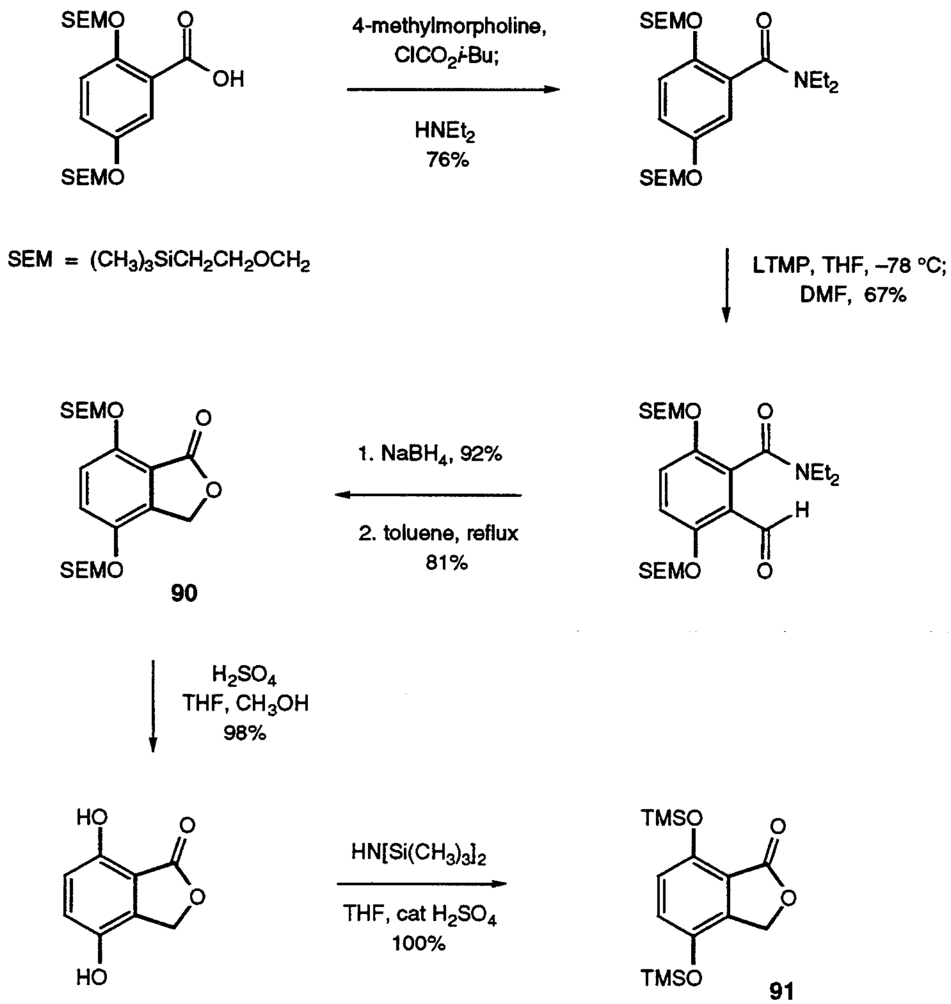
88



89

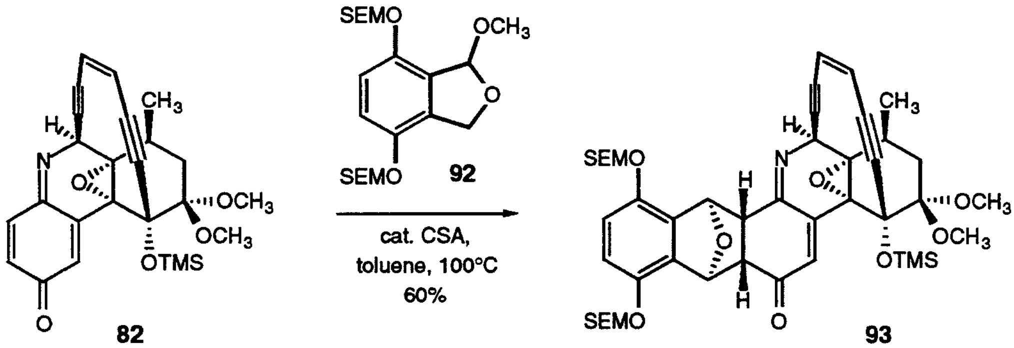
yield by addition of excess diethylamine to the preformed mixed anhydride intermediate (4-methylmorpholine, isobutyl chloroformate, THF, 0 °C) derived from 2,5-bis[[2-(trimethylsilyl)ethoxy]methoxy]benzoic acid. Treatment of the amide with lithium tetramethylpiperdide (1.4 equiv) in THF at –78 °C followed by the sequential addition of excess DMF and warming to 23°C provided 2-formyl-3,6-bis[[2-(trimethylsilyl)ethoxy]methoxy]benzoic acid *N,N*-diethylamide in 67% yield. Reduction of the aldehyde group with sodium borohydride in ethanol furnished 2-(hydroxymethyl)-3,6-bis[[2-(trimethylsilyl)ethoxy]methoxy]benzoic acid *N,N*-diethylamide (92%). Cyclization of the latter occurred in toluene at reflux in the presence of solid potassium carbonate (0.05 equiv), affording 2,5-bis[[2-(trimethylsilyl)ethoxy]methoxy]phthalide (**90**, 81%). Phthalide **90** was treated with excess concentrated sulfuric acid in a 1:1 mixture of methanol and THF at 23 °C to provide 4,7-dihydroxy phthalide in 98% yield.[51] Lastly, heating 4,7-dihydroxyphthalide with hexamethyldisilazane in the presence of catalytic

Scheme XXII



sulfuric acid in THF at reflux (30 min), followed by the removal of the volatiles in vacuo afforded 4,7-bis(trimethylsiloxy)phthalide (**91**) as a hydrolytically sensitive oil in quantitative yield.[52]

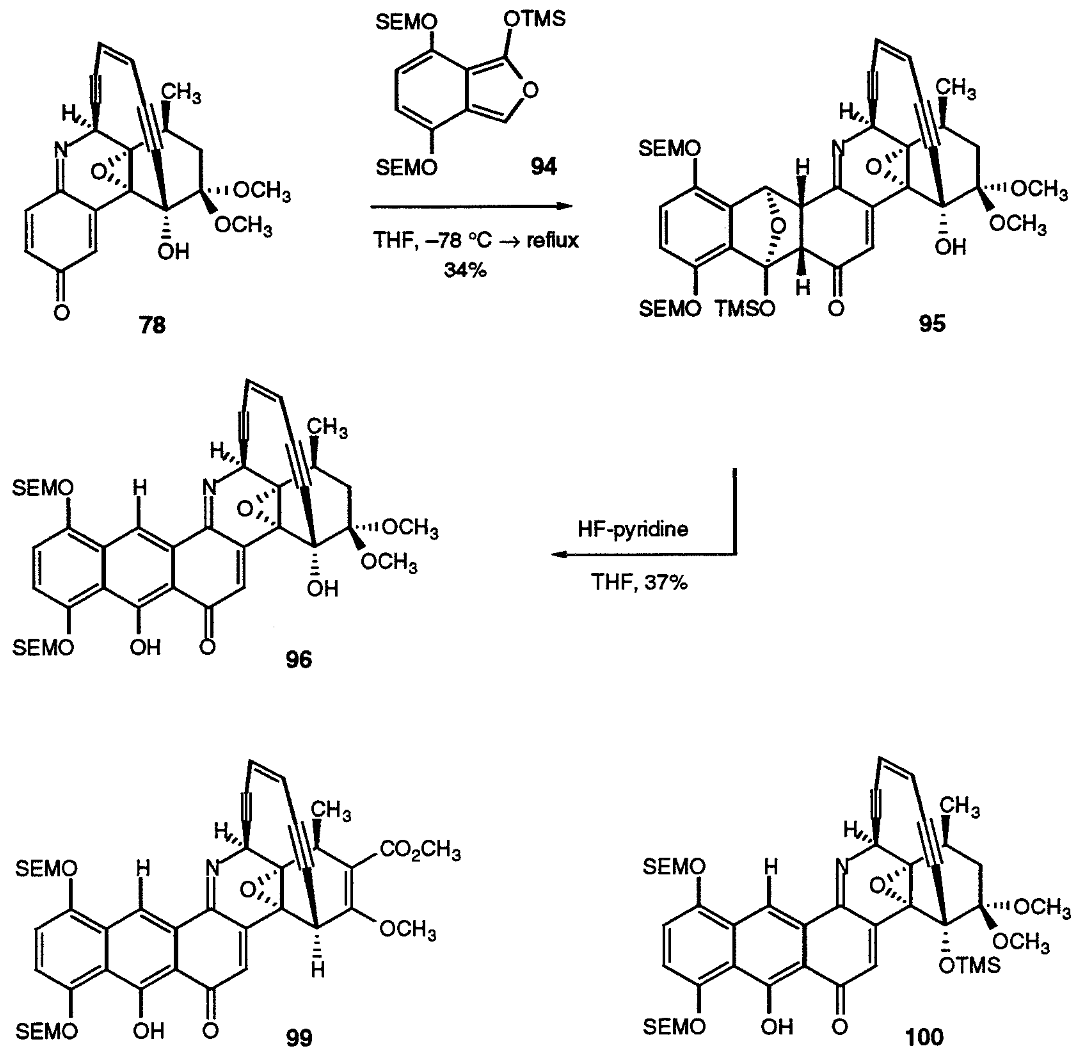
A preliminary experiment was conducted to determine how the 4,7-bis[[2-(trimethylsilyl)ethoxy]methoxy substituents of phthalide **90** would affect the reactivity of a derivable isobenzofuran and the stereochemical outcome of a Diels-Alder cycloaddition reaction. Heating 1-methoxy-4,7-bis[[2-(trimethylsilyl)ethoxy]methoxy]phthalan (**92**)



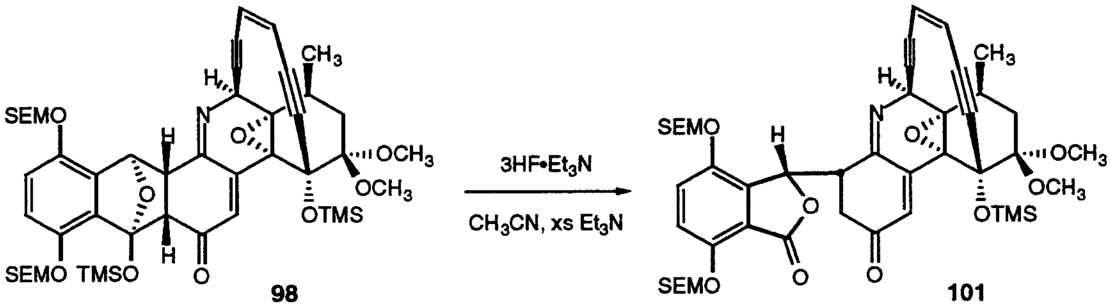
(prepared by reduction of phthalide **90** with diisobutylaluminum hydride (DIBAL), followed by etherification of the product lactol in acidic methanol) with quinone imine **82** in toluene at 100 °C in the presence of catalytic 10-camphorsulfonic acid provided exclusively the exo adduct **93** in 60% yield.[53] Apparently, the large size of the 2,5-bis[[2-(trimethylsilyl)ethoxy]methoxy groups in combination with the bulk of the trimethylsilyl ether and dimethylketal functionality allow only the exo adduct to be formed.

Treatment of phthalide **90** with a solution of lithium hexamethyldilazide in THF at –78 °C, followed by trapping the resultant anion with trimethylsilyl chloride afforded the isobenzofuran **94**, which formed the exo-oriented cycloadduct **95** exclusively in 34% yield upon warming with quinone imine **78** (Scheme XXIII). Under carefully defined conditions, employing hydrogen fluoride-pyridine complex in THF buffered with pyridine at 23°C,[54] the sensitive adduct **95** was transformed to the red naphthalenol derivative **96** in 37% yield. Similarly, Diels-Alder addition reaction of **94** with quinone imine **79** provided the exo and endo adducts **97** (ratio ca. 3:1, 30% yield), and cycloaddition of **94** with quinone imine **82** furnished the exo adduct **98** (32%). Napthalenol **99** was then obtained in 30% yield by the treatment of the adducts **97** with the HF-pyridine solution. Treatment of **98** with trihydrogen fluoride-triethylamine complex in acetonitrile at 23°C, followed by the addition of silica gel afforded the naphthalenol **100** in 44% yield. However, under more basic desilylation conditions (trihydrogen fluoride-triethylamine in the presence of

Scheme XXIII



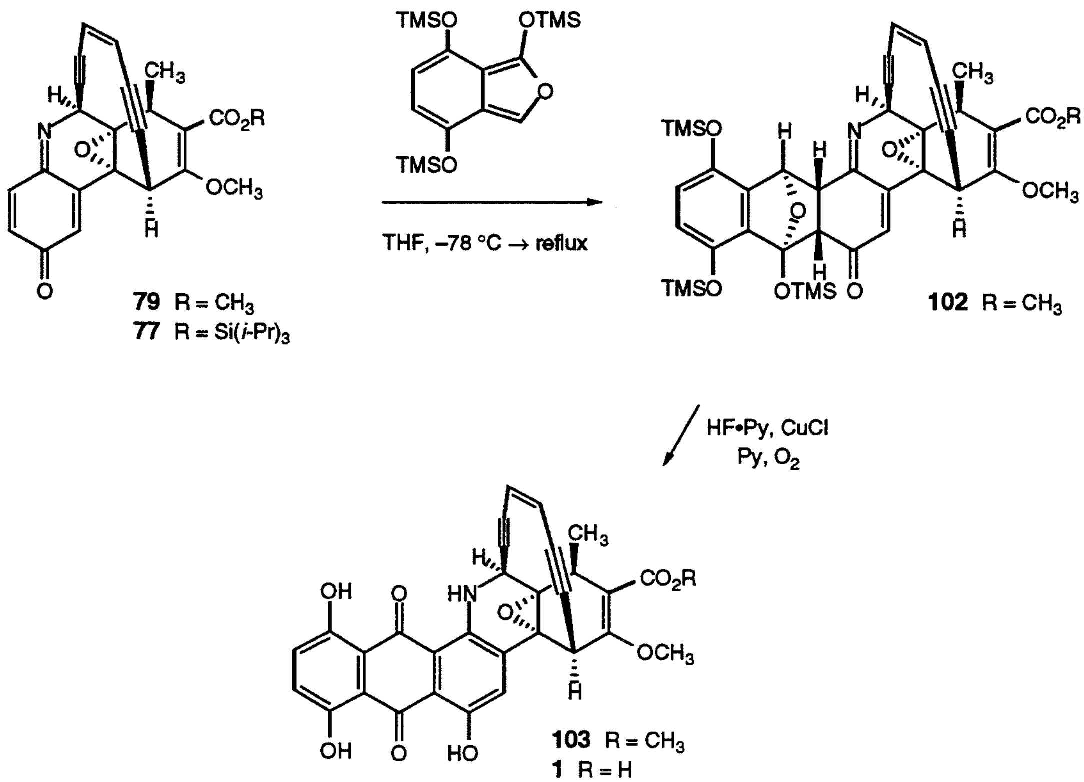
excess triethylamine in acetonitrile) adduct **98** was converted quantitatively to the phthalide **101**. This result is reminiscent of the transformations occurring within the tetracycline antibiotics,[55] and suggests that routes to adducts such as **95** or **96** that employ one of the many methods involving phthalide anions may suffer from unfavorable thermodynamics in the Dieckman closure step. Indeed this has been our experience, for the addition of lithiated phthalide **90** to a solution of quinone imine **82** in THF at –78 °C afforded phthalide **101** as the major component of a 1.3:1 diastereomeric mixture (64% yield).



98 101

Although the naphthalenols **96**, **99**, and **100** lie one oxidation state from the desired anthraquinone, a series of oxidants, including Fremy's salt, PCC, PDC, chromium trioxide, ozone, hydrogen peroxide, singlet oxygen, ceric ammonium nitrate, iodosobenzene, dimethyldioxirane, 2,3-dichloro-4,5-dicyano-1,4-benzoquinone and lead tetraacetate, failed absolutely to bring about this conversion. In considering the problem, it was recognized that the oxidation of the left-most ring of Diels-Alder adduct **95** from the hydroquinone to the quinone level would place the resultant intermediate at the same level of oxidation as the desired anthraquinone, and one removed from that product only by the opening of the bicyclic ketal and tautomerization. With this in mind, treatment of **91** with potassium hexamethyldisilazide (1.1 equiv), and trapping of the resultant anion with trimethylsilyl chloride produced 1,4,7- tris(trimethylsiloxy)isobenzofuran, as evidenced by the formation of the Diels-Alder adduct **102** upon addition of the quinone imine **79** and brief heating to reflux (61% yield, exo product, based on ^{1}H NMR integration against an internal standard, Scheme XXIV). Direct addition of this sensitive product to a solution of cuprous chloride and hydrogen fluoride-pyridine complex in pyridine under an oxygen atmosphere afforded dynemicin methyl ester (**103**) in 10-15% yield following purification by chromatography on Sephadex LH-20 (eluent 20% acetonitrile in methanol).[56] To the best of our knowledge, this trivial derivative of **1** has never been prepared from the natural product. Similarly, quinone imine **77** was transformed in two steps to synthetic dynemicin A (**1**), in 3-5% yield. Dynemicin A is only modestly stable under HPLC conditions, as

Scheme XXIV



79 R = CH3
77 R = Si(i-Pr)3
102 R = CH3
103 R = CH3
1 R = H

determined by the observation of identical decomposition products from both synthetic and authentic **1**, as well as a decrease in mass recovery versus time of elution of synthetic **1**. The method of choice for the purification of synthetic dynemicin A proved to be column chromatography on Sephadex LH-20, using a mixture of methanol and acetonitrile as eluent (ratio ca. 2:1, respectively).[57] Synthetic **1** was identical with an authentic sample of dynemicin A by spectroscopic comparison (^{1}H NMR, UV-visible), reverse-phase HPLC analysis (co-injection) in addition to TLC analysis (co-spotting), and circular dichroism. The latter establishes for the first time the absolute configuration of natural **1** as 2*S*, 3*S*, 4*S*, 7*R*, 8*R*.[58] Experimentation to improve the efficiency in the final step is an objective of current study. As a practical note, it is an unresolved issue at present what maximal efficiency may be anticipated from any transformation producing **1**, given the poor solubility properties of **1** and its apparent instability toward chromatography.

A key feature of the synthetic chemistry described herein is the fact that a wide variety of dynemicin analogs is now available for study by late-stage modification of the route. In preliminary studies, each of the synthetic anthraquinones **86**, **87**, **88** and **89** has shown DNA cleaving activity within a 193 base-pair restriction fragment in the presence of GSH or NADPH as activating agent (Figure 9).[59] Because dynemicn A (**1**) is a poorly selective DNA-cleaving agent, the subtle variance in sequence selectivity exhibited by **86-89** versus **1** may not be biologically significant. Of greater interest is the variation in cleavage efficiency observed with each analog and, in particular, with the activating agent. For example, whereas greater DNA cleavage is observed in the activation of **1** by NADPH than by GSH (cleavage efficiencies: 5.7 and 4.0%, respectively), the opposite is true with analog **86** (cleavage efficiencies: 3.5 and 7.2%, respectively, Figure 9). Reactivity differences such as these may well provide the basis for variations in biological activity and, perhaps, therapeutic potential, and underscore the need for the continued exploration of modified dynemicin structures.

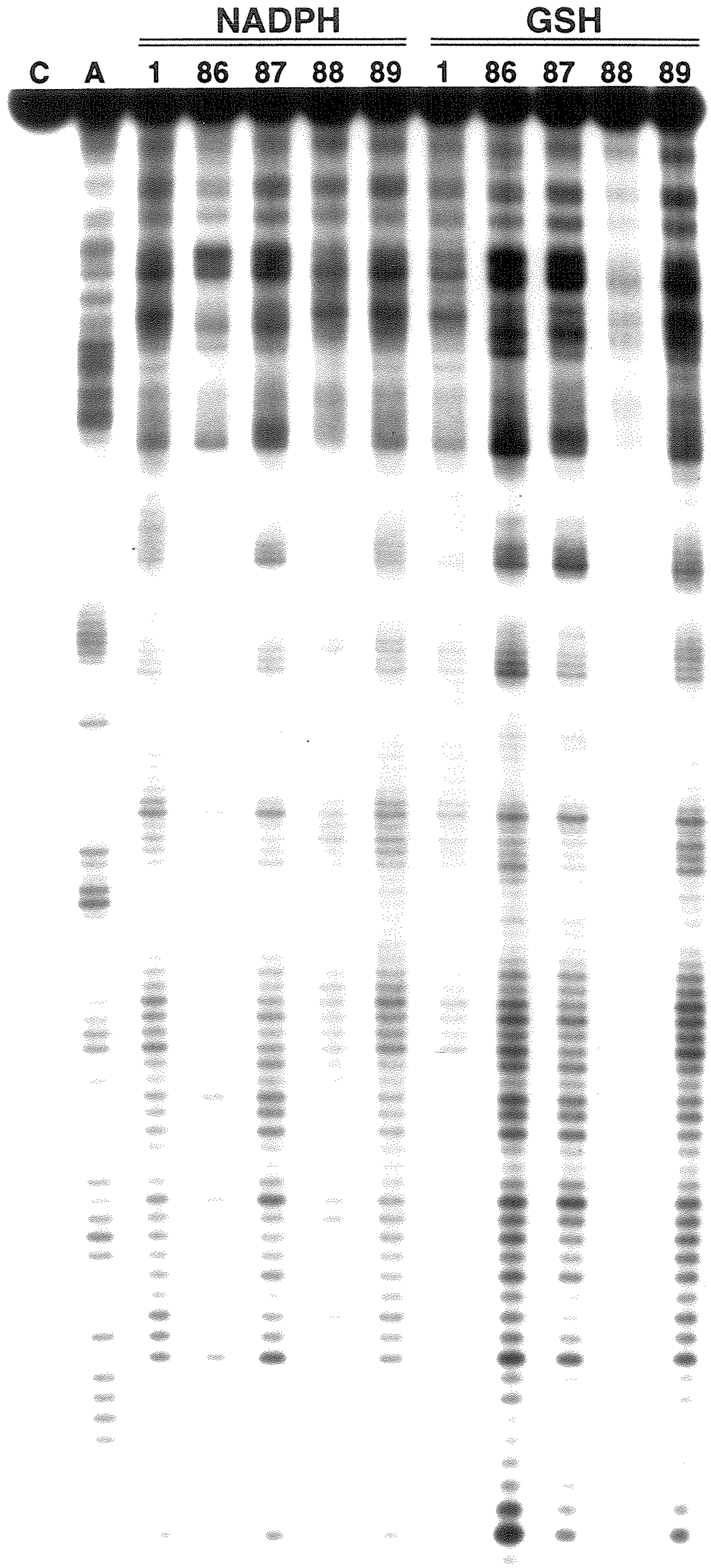

NADPH
GSH
C
A
1
86
87
88
89
1
86
87
88
89

Figure 9. DNA cleavage of a 3'-labeled 193 base-pair restriction fragment of pBR322 (Eco RI/Ssp I digests) from the reaction of Dynemicin A (**1**) and synthetic anthraquinones **86**, **87**, **88**, and **89** with NADPH and glutathione. Reactions were performed on a volume of 50 μL and contained calf thymus DNA (1.0 mM bp), 193 base-pair restriction fragment (~10^5 cpm), tris-HCl buffer (50 mM, pH 7.5), sodium chloride (50 mM), Dynemicin A (**1**) or synthetic anthraquinone (0.05 mM), and either NADPH (20 mM) or glutathione (20 mM). Reactions were incubated at 37 °C for 12 h. Lane **C**: 193 bp restriction fragment alone. Lane **A**: products from an adenine-specific cleavage reaction (Iverson, B. L.; Dervan, P. B. *Nucleic Acids Res.* **1987**, 15, 7823).

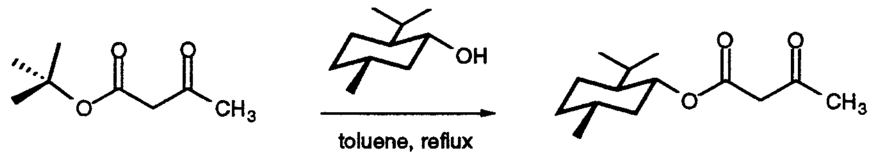
Experimental Section

General Procedure. All reactions were performed in flame-dried round bottom or modified Schlenk (Kjeldahl shape) flasks fitted with rubber septa under a positive pressure of argon, unless otherwise noted. Air- and moisture-sensitive liquids and solutions were transferred via syringe or stainless steel cannula. Where necessary (so noted), solutions were deoxygenated by alternate evacuation for 10-15 seconds and flushing with argon (≥ 5 iterations). Organic solutions were concentrated by rotary evaporation below 30 °C at ca. 25 Torr (water aspirator). Flash column chromatography was performed as described by Still et al.,[10] employing 230-400 mesh silica gel. Analytical and preparative thin layer chromatography were performed using glass plates pre-coated with 0.25 mm 230-400 mesh silica gel impregnated with a fluorescent indicator (254 nm). Thin-layer chromatography plates were visualized by exposure to ultraviolet light (noted as 'UV') and/or by immersion in an acidic staining solution (*p*-anisaldehyde unless otherwise noted) followed by heating on a hot-plate.

Materials. Commercial reagents and solvents were used as received with the following exceptions. Tetrahydrofuran and diethyl ether were distilled from sodium benzophenone ketyl. Methanol was distilled from magnesium turnings. Dichloromethane, chlorotrimethylsilane, *N,N*-diisopropylethylamine, triethylamine, hexamethyldisilazane, toluene, benzene, *t*-butanol and acetonitrile were distilled from calcium hydride. Dimethyl sulfoxide, *N,N*-dimethylformamide, and hexamethylphosphoramide were distilled from calcium hydride at reduced pressure and stored over 4Å molecular sieves. Anhydrous cerium(III) chloride was prepared from the heptahydrate by heating at 100 °C and 0.5 Torr for 12 h. Methanesulfonyl chloride was distilled from phosphorous pentoxide at atmospheric pressure. Trifluoromethanesulfonic anhydride and trimethylsilyl trifluoromethanesulfonate were stored in the glove-box in round bottom flasks fitted with polycarbonate or glass stoppers. Methyl trifluoromethanesulfonate was distilled at atmospheric pressure prior to use. Copper(I) iodide was purified by continuos extraction (24 h) with tetrahydrofuran in a Soxhlet apparatus. The molarity of *n*-butyllithium solutions was determined by titration using diphenylacetic acid as an indicator (average of three determinations).

Instrumentation. Infrared spectra were obtained using a Perkin-Elmer 1600 FT-IR spectrophotometer referenced to a polystyrene standard. Data are presented as follows: frequency of adsorption (cm^{-1}), intensity of adsorption (vs = very strong, s = strong, m = medium, w = weak, br = broad, sh = shoulder) and assignment (when appropriate). Proton magnetic resonance (^1H NMR) spectra were recorded with a JEOL JX-400 (400 MHz) or a GE QE-300-Plus (300 MHz) NMR spectrometer; chemical shifts are expressed in parts per million (δ scale) downfield from tetramethylsilane and are referenced to residual protium in the NMR solvent ($CHCl_3$: δ 7.26, C_6HD_5: δ 7.20, CD_2HOD: δ 3.30, $CD_3S(O)CD_2H$: δ 2.49). Data are presented as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet and/or multiple resonances, app = apparent), integration, coupling constant in Hertz (Hz), and assignment. High performance liquid chromatography (HPLC) was conducted with a Beckman HPLC system equipped with a Beckman Ultrasphere (C_{18}, 5 μm) reverse phase HPLC column and a Beckman 168 Programmable Photodiode Detector set at 250 and 540 nm. Circular dichroism spectra were obtained with a Jasco J-600 spectrophotometer using a solution cell with a path length of 1 cm. Optical rotations were determined with a Jasco DIP-181 digital polarimeter equipped with a sodium lamp source. High resolution mass spectra were obtained from the University of California, Riverside Mass Spectrometry Facility, or at the

Midwest Center for Mass Spectrometry at the University of Nebraska-Lincoln. X-ray crystallography was performed by Dr. Joseph Ziller at the University of California-Irvine. Melting points were recorded with a Büchi SMP-20 melting point apparatus and are uncorrected.

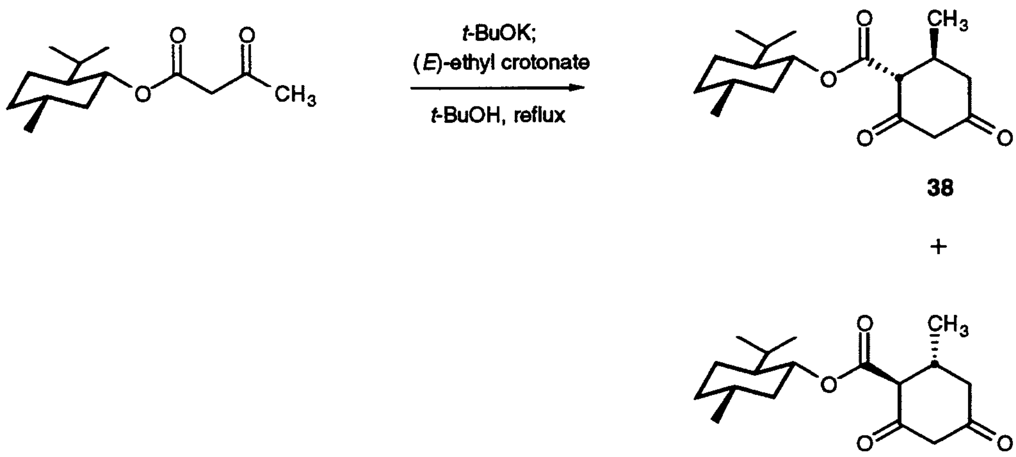


(1*R*, 3*R*, 4*S*)-*p*-Menth-3-yl Acetoacetate

A solution of (–)-menthol (23.0 g, 147 mmol, 1 equiv) and *t*-butyl acetoacetate (20.0 mL, 121 mmol, 0.819 equiv) in toluene (50 mL) was heated at reflux for 12 h, then was cooled to 23 °C. Volatiles were removed in vacuo and toluene (20 mL) and *t*-butyl acetoacetate (12.2 mL, 73.6 mmol, 0.500 equiv) were added to the residue. The resulting solution was heated at reflux for 12 h, then was cooled to 23 °C. The cooled reaction mixture was concentrated in vacuo, and the residue was purified by distillation under reduced pressure (bp 90 °C, 0.030 mmHg) to afford (1*R*, 3*R*, 4*S*)-*p*-menth-3-yl acetoacetate as a low-melting solid (33.3 g, 94%).

^1H NMR (300 MHz, $CDCl_3$) δ: 12.19 (s, 1H, enol OH), 4.95 (s, 1H, enol CH), 4.73 (td, 1H, *J* = 10.9, 4.4 Hz, menthyl CHO), 3.43 (s, 2H, -$COCH_2CO$-), 2.26 (s, 3H, $COCH_3$), 2.02 (m, 2H, menthyl CH_2), 1.87 (app td, 2H, *J* = 7.0, 2.9 Hz, menthyl CH_2), 1.68 (m, 2H, menthyl CH_2), 1.42 (m, 3H, menthyl CH), 0.91 (d, 3H, *J* = 4.8 Hz, menthyl CH_3), 0.89 (d, 3H, *J* = 5.4 Hz, menthyl CH_3), 0.76 (d, 3H, *J* = 7.0 Hz, menthyl CH_3).

FTIR (neat), cm^{-1}:	2948 (s), 2917 (m), 2856 (w), 1733 (s, C=O), 1713 (s, C=O), 1642 (w), 1449 (w), 1409 (w), 1358 (w), 1307 (w), 1241 (m), 1175 (w), 1145 (m).
TLC (40% EtOAc-hexanes), R_f:	(1*R*, 3*R*, 4*S*)-*p*-menth-3-yl acetoacetate: 0.66 *t*-butyl acetoacetate: 0.56 (magenta, anisaldehyde) (–)-menthol: 0.56 (blue, anisaldehyde)



(1*R*, 3*R*, 4*S*)-*p*-Menth-3-yl (1*R*, 2*S*)-2-Methyl-4,6-dioxocyclohexanecarboxylate (38)

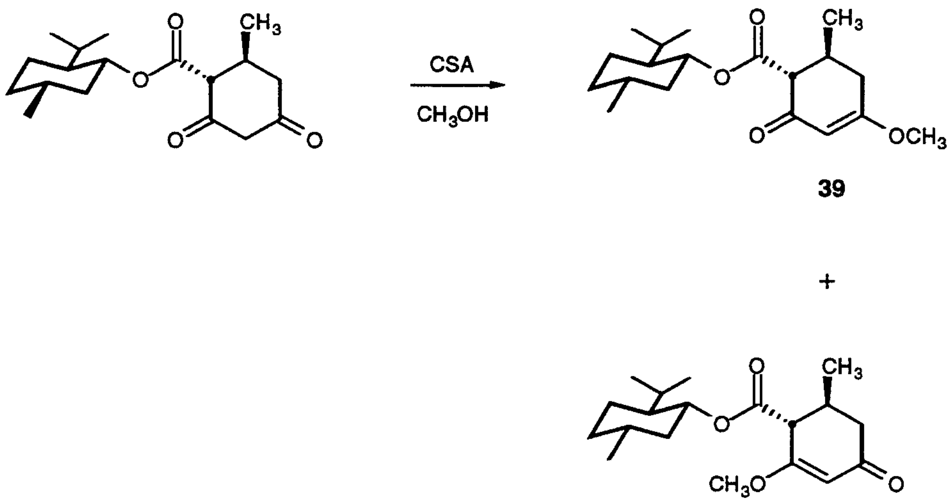
A 2-L, 3-N round bottom flask fitted with a reflux condenser, a mechanical stirrer, and a glass stopper was charged with *t*-butyl alcohol (300 mL) and potassium *t*-butoxide (68.7 g, 612 mmol, 1.04 equiv). The glass stopper was removed and, with efficient mechanical stirring, (1*R*, 3*R*, 4*S*)-*p*-menth-3-yl acetoacetate (150 g, 624 mmol, 1.06 equiv) was added rapidly to the yellow slurry. The open neck of the reaction flask was fitted with a 100-mL addition funnel containing (*E*)-ethyl crotonate (73.2 mL, 588 mmol, 1 equiv). The largely solid reaction mixture was heated to reflux with a heating mantle. At this point, (*E*)-ethyl crotonate was added to the refluxing, dark yellow slurry over 15 min via the addition funnel. The addition funnel was replaced with a glass stopper and heating at reflux was continued. Solids were observed to dissolve within 1 h after addition of (*E*)-ethyl crotonate; the product began to crystallize from solution after about 1.5 h. After a total reflux period of 2.5 h (from addition of (*E*)-ethyl crotonate), heating was discontinued and the reaction mixture was allowed to cool to 23 °C. The cooled reaction mixture was partitioned between aqueous sulfuric acid solution (5% v/v, 500 mL) and dichloromethane

(600 mL). The aqueous layer was separated and extracted further with two 600-mL portions of dichloromethane. The combined organic layers were dried over sodium sulfate and then were concentrated. The solid residue was dissolved in boiling benzene (ca. 600 mL) and the resulting solution was allowed to cool slowly to 23 °C whereupon (1*R*, 3*R*, 4*S*)-*p*-menth-3-yl (1*R*, 2*S*)-2-methyl-4,6-dioxocyclohexanecarboxylate (**38**) crystallized as a white powder (mp 180-181 °C, 64.5 g, 36%). To isolate the diastereomeric diketone product, (1*R*, 3*R*, 4*S*)-*p*-menth-3-yl (1*S*, 2*R*)-2-methyl-4,6-dioxocyclohexanecarboxylate (**3**), the mother liquors were concentrated and the solid residue was dissolved in boiling ethyl acetate (ca. 200 mL). Hexanes (50 mL) were added to the hot solution and the mixture was allowed to cool to 23 °C. Further cooling to –20 °C induced crystallization of diketone diastereomer **3** over a period of 12 h (mp 140-141 °C, 45 g, 25%).

^{1}H NMR (300 MHz, $CDCl_3$) δ:	4.79 (td, 1H, *J* = 10.9, 4.2 Hz, menthyl CHO), 3.63 (d, 1H, *J* = 17.2 Hz, $COCH_2CO$), 3.40 (d, 1H, *J* = 17.2 Hz, $COCH_2CO$), 3.30 (dd, 1H, *J* = 8.4, 0.9 Hz, COCHCO), 2.80 (ddd, 1H, *J* = 15.5, 4.4, 1.1 Hz, CH_2), 2.60 (m, 1H, $CHCH_3$), 2.39 (ddd, 1H, *J* = 15.5, 9.1, 1.1 Hz, CH_2), 2.05 (m, 2H, menthyl CH_2), 1.90 (td, 1H, *J* = 6.8, 2.6 Hz, menthyl CH), 1.70 (m, 2H, menthyl CH_2), 1.50 (m, 1H, menthyl CH), 1.40 (m, 1H, menthyl CH), 1.10 (d, 3H, *J* = 6.7 Hz, CH_3CH), 1.00 (m, 2H, menthyl CH_2), 0.92 (d, 3H, *J* = 5.7 Hz, menthyl CH_3), 0.90 (d, 3H, *J* = 6.8 Hz, menthyl CH_3), 0.78 (d, 3H, *J* = 6.9 Hz, menthyl CH_3).
FTIR (neat), cm^{-1}:	2936 (w), 1724 (s, C=O), 1608 (s, C=O), 1503 (m), 1458 (w), 1367 (w), 1312 (w), 1237 (m), 1186 (m).
HRMS (EI):	Calcd for $C_{18}H_{29}O_4$ $[MH]^+$: 309.2066 Found: 309.2081
$[\alpha]_D^{22}$ (CH_3OH):	+66.9°, C = 0.77

TLC (5% CH_3OH-CH_2Cl_2), R_f: **38**: 0.17

(1*R*, 3*R*, 4*S*)-*p*-menth-3-yl acetoacetate: 0.83

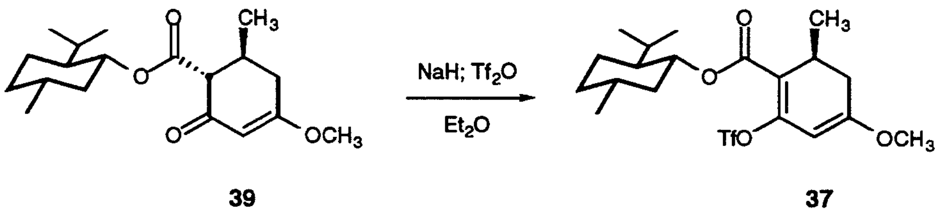


(1*R*, 3*R*, 4*S*)-*p*-Menth-3-yl (1*R*, 6*S*)-Methoxy-6-methyl-2-oxo-3-cyclohexene-1-carboxylate (39)

A solution of (1*R*, 3*R*, 4*S*)-*p*-menth-3-yl (1*R*, 2*S*)-2-methyl-4,6-dioxocyclohexanecarboxylate (**38**, 24.0 g, 77.8 mmol, 1 equiv) in methanol (300 mL) was treated with camphorsulfonic acid (ca. 800 mg, 3.9 mmol, 0.05 equiv) and the resulting solution was stirred at 23 °C for 12 h. The reaction mixture was neutralized by the addition of solid potassium carbonate (1.08 g, 7.81 mmol, 0.100 equiv) and the resulting suspension was filtered and the filtrate was concentrated. The residue was concentrated from toluene (2 x 15 mL) and then was purified by flash column chromatography (20% ethyl acetate in hexanes) to afford (1*R*, 3*R*, 4*S*)-*p*-menth-3-yl (1*R*, 6*S*)-4-methoxy-6-methyl-2-oxo-3-cyclohexene-1-carboxylate (**39**) as a white solid (mp 78-80 °C, 17.9 g, 71%). The regioisomeric enone, (1*R*, 3*R*, 4*S*)-*p*-menth-3-yl (1*R*, 6*S*)-2-methoxy-6-methyl-4-oxo-2-cyclohexene-1-carboxylate was isolated in separate fractions and was resubjected to the reaction conditions to establish the equilibrium mixture of enones, in which the desired product **39** is strongly favored.

^1H NMR (300 MHz, $CDCl_3$) δ:	5.38 (d, 1H, *J* = 1.3 Hz, C=CH), 4.76 (td, 1H, *J* = 10.9, 4.4 Hz, menthyl CHO), 3.70 (s, 3H, OCH_3), 2.98 (d, 1H, *J* = 11.3 Hz, COCHCO), 2.59 (m, 1H, $CHCH_3$), 2.48 (dd, 1H, *J* = 17.3, 4.8 Hz, CH_2), 2.21 (ddd, 1H, *J* = 17.3, 10.5, 1.4 Hz, CH_2), 2.05 (m, 3H, menthyl CH_2, menthyl CH), 1.70 (m, 2H, menthyl CH_2), 1.50 (m, 1H, menthyl CH), 1.40 (m, 1H, menthyl CH), 1.08 (d, 3H, *J* = 6.5 Hz, CH_3CH), 1.00 (m, 2H, menthyl CH_2), 0.91 (d, 3H, *J* = 1.9 Hz, menthyl CH_3), 0.89 (d, 3H, *J* = 2.5 Hz, menthyl CH_3), 0.79 (d, 3H, *J* = 9.8 Hz, menthyl CH_3).
FTIR (neat), cm^{-1}:	2947 (m), 2926 (w), 2865 (w), 1733 (s, C=O), 1657 (s, α,β unsaturated C=O), 1607 (vs, α,β unsaturated C=C), 1455 (w), 1379 (m), 1303 (w), 1227 (s), 1171 (m), 1141 (m), 1085 (w), 1004 (w).
HRMS (EI):	Calcd for $C_{19}H_{31}O_4$ $[MH]^+$: 323.2222 Found: 323.2228

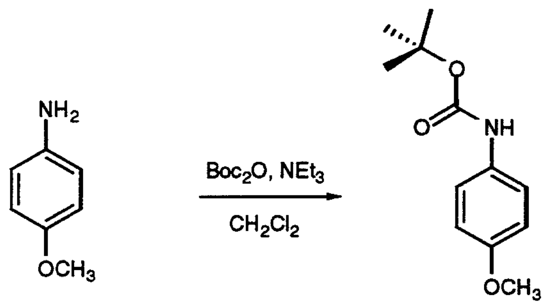
TLC (40% EtOAc-hexanes), R_f:	**39**: 0.49
	38: 0.11



(1*R*, 3*R*, 4*S*)-*p*-Menth-3-yl (*S*)-2-Hydroxy-4-methoxy-6-methyl-1,3-cyclohexadiene-1-carboxylate, Trifluoromethanesulfonate (37)

A solution of (1*R*, 3*R*, 4*S*)-*p*-menth-3-yl (1*R*, 6*S*)-4-methoxy-6-methyl-2-oxo-3-cyclohexene-1-carboxylate (**39**, 35.5 g, 110 mmol, 1 equiv) in diethyl ether (300 mL) was transferred by cannula over 15 min to a stirring suspension of sodium hydride (3.96 g, 165 mmol, 1.50 equiv) in diethyl ether (100 mL) at 0 °C. The slurry was allowed to warm to 23 °C over approximately 10 min, and was stirred at that temperature for 5 h. Excess sodium hydride was quenched by the addition of 10-μL aliquots of water to the suspension at 30-min intervals until such point as gas evolution was no longer evident. The reaction mixture was then cooled to –78 °C and trifluoromethanesulfonic anhydride (29.6 mL, 176 mmol, 1.60 equiv) was added by syringe over 10 min. Upon completion of the latter addition, the reaction mixture was placed in an ice bath and was stirred for 30 min. The product solution was partitioned between aqueous phosphate buffer solution (pH 7, 0.05 M in sodium hydrogen phosphate and 0.05 M in potassium dihydrogen phosphate, 400 mL) and diethyl ether (400 mL). The aqueous layer was separated and extracted further with diethyl ether (2 x 400 mL). The combined organic layers were dried over sodium sulfate, and then were concentrated. The residue was purified by flash column chromatography (10% ethyl acetate in hexanes) to afford (1*R*, 3*R*, 4*S*)-*p*-menth-3-yl (*S*)-2-hydroxy-4-methoxy-6-methyl-1,3-cyclohexadiene-1-carboxylate, trifluoromethanesulfonate (**37**) as a pale yellow oil (47.3 g, 95%). Due to its instability to storage, product **37** was typically carried directly on to the next step in the sequence.

^{1}H NMR (300 MHz, $CDCl_3$) δ:	4.88 (s, 1H, C=C**H**), 4.85 (td, 1H, *J* = 10.9, 4.3 Hz, menthyl C**H**O), 3.70 (s, 3H, OC**H**$_3$), 3.06 (m, 1H, CH_3C**H**), 2.81 (ddd, 1H, *J* = 17.1, 8.1, 2.2 Hz, C**H**$_2$), 2.06 (m, 3H, menthyl C**H**$_2$, C**H**$_2$), 1.95 (m, 1H, menthyl C**H**), 1.70 (m, 2H, menthyl C**H**$_2$), 1.50 (m, 1H, menthyl C**H**), 1.45 (m, 1H, menthyl C**H**), 1.01 (d, 3H, *J* = 7.0 Hz, CHC**H**$_3$), 1.00 (m, 2H, menthyl C**H**$_2$), 0.91 (d, 3H, *J* = 4.9 Hz, menthyl C**H**$_3$), 0.88 (d, 3H, *J* = 5.4 Hz, menthyl C**H**$_3$), 0.75 (d, 3H, *J* = 7.0 Hz, menthyl C**H**$_3$).
FTIR (neat), cm^{-1}:	2955 (m), 2925 (w), 2864 (w), 1693 (m, C=O), 1582 (s), 1425 (m), 1389 (w), 1253 (s), 1237 (m), 1207 (s), 1141 (m), 1111 (w), 1055 (w), 974 (m).
TLC (15% EtOAc-hexanes), R_f:	**37**: 0.49 **39**: 0.10



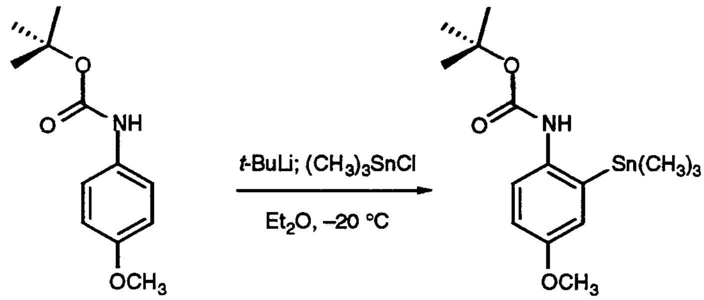
tert-Butyl 4-Methoxycarbanilate

Di-*t*-butyl dicarbonate (100 g, 458 mmol, 1.20 equiv) was added cautiously over 5 min to a solution of *p*-anisidine (47.0 g, 382 mmol, 1 equiv) and triethylamine (53.2 mL, 382 mmol, 1 equiv) in dichloromethane (600 mL) at 0 °C, producing a mild exotherm. After the exotherm had subsided, the reaction mixture was warmed to 23 °C and was stirred for 5 h at that temperature. The product solution was washed with saturated aqueous ammonium chloride solution (3 x 500 mL), was dried over sodium sulfate, and was then concentrated in vacuo. The crude product was dissolved in boiling ethyl acetate (800 mL) and hexanes (100 mL) was added to the hot solution. Slow cooling to 23 °C, and then to –20 °C, induced crystallization of *tert*-butyl 4-methoxycarbanilate over a period of 12 h. The crystalline product was collected by filtration (mp 93-94 °C, 72.3 g, 85%).

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.26 (d, 2H, J = 8.8 Hz, *o*-aryl), 6.83 (d, 2H, J = 9.0 Hz, *m*-aryl), 6.33 (br s, 1H, **NH**), 3.78 (s, 3H, OCH_3), 1.50 (s, 9H, $C(CH_3)_3$).

FTIR (neat), cm^{-1}: 3357 (m, NH), 2965 (w), 1694 (s, C=O), 1523 (s), 1458 (w), 1443 (w), 1408 (w), 1368 (w), 1242 (m), 1237 (m), 1152 (m), 1051 (w), 1021 (m).

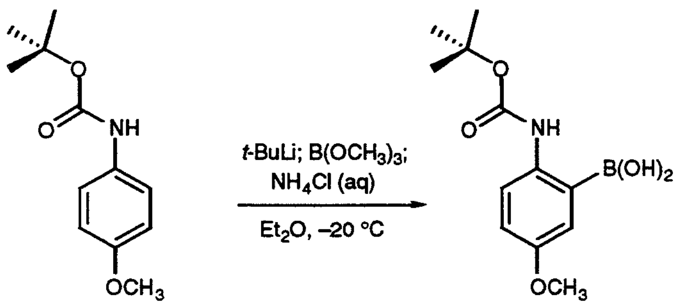
TLC (20% EtOAc-hexanes), R_f: *tert*-butyl 4-methoxycarbanilate: 0.32 (UV)
anisidine: 0.07 (UV)



***tert*-Butyl 4-Methoxy-2-(trimethylstannyl)carbanilate**

A solution of *t*-butyllithium in pentane (1.70 M, 148 mL, 251 mmol, 2.50 equiv) was added via cannula to a solution of *tert*-butyl 4-methoxycarbanilate (22.4 g, 100 mmol, 1 equiv) in diethyl ether (500 mL) at –20 °C, producing a cloudy yellow solution. After stirring at –20 °C for 5 h, the reaction mixture was cooled to –78 °C and a solution of trimethyltin chloride (50.0 g, 251 mmol, 2.50 equiv) in ether (50 mL) was added via cannula. After the addition, the reaction mixture was warmed to –20 °C and was stirred at that temperature for 30 min, then was stirred in an ice bath for 30 min. The product solution was partitioned between aqueous phosphate buffer solution (pH 7, 0.05 M in sodium hydrogen phosphate and 0.05 M in potassium dihydrogen phosphate, 600 mL) and diethyl ether (400 mL). The aqueous layer was separated and extracted further with diethyl ether (2 x 400 mL). The combined organic layers were dried over sodium sulfate and were concentrated. The product was purified by flash column chromatography (15% ethyl acetate in hexanes) to afford *tert*-butyl 4-methoxy-2-(trimethylstannyl)carbanilate as a yellow oil (33.3 g, 85%).

^{1}H NMR (400 MHz, $CDCl_3$) δ:	7.32 (d, 1H, *J* = 8.6 Hz, *o*-aryl), 6.95 (d, 1H, *J* = 3.0 Hz, *m*-aryl), 6.83 (dd, 1H, *J* = 8.6, 3.0 Hz, *m*-aryl), 6.13 (br s, 1H, NH), 3.79 (s, 3H, OCH_3), 1.49 (s, 9H, $C(CH_3)_3$), 0.32 (s, 9H, $Sn(CH_3)_3$).
FTIR (neat), cm^{-1}:	3324 (br, NH), 2977 (m), 2834 (w), 1702 (s, C=O), 1575 (m), 1481 (vs), 1391 (m), 1366 (m), 1244 (s), 1164 (s), 1060 (m), 1039 (m), 1023 (m), 770 (m).
HRMS (FAB):	Calcd for $C_{15}H_{25}O_3NSn$ $[M]^+$: 387.0856 Found: 387.0835
TLC (15% EtOAc-hexanes), R_f:	*tert*-butyl 4-methoxy-2-(trimethylstannyl)carbanilate: 0.33 (UV) *tert*-butyl 4-methoxycarbanilate: 0.26 (UV)

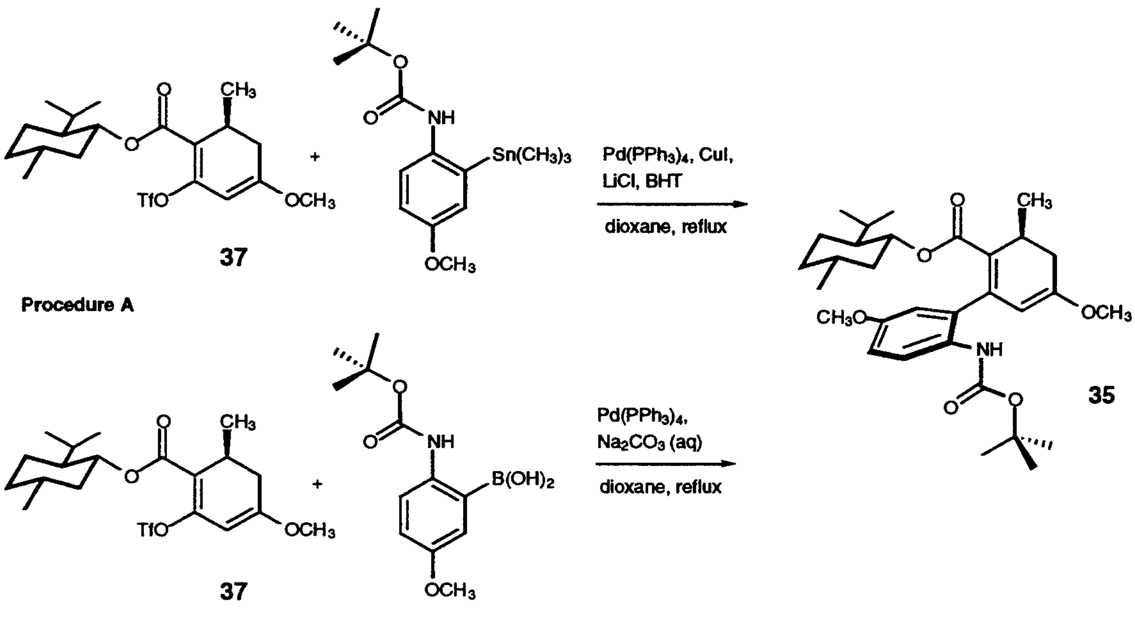


36

***tert*-Butyl 2-Borono-4-methoxycarbanilate (36)**

A solution of *t*-butyllithium in pentane (1.70 M, 200 mL, 340 mmol, 2.50 equiv) was added via cannula to a solution of *tert*-butyl 4-methoxycarbanilate (30.4 g, 136 mmol, 1 equiv) in ether (500 mL) at –20 °C, producing a cloudy yellow solution. After stirring at –20 °C for 5 h, trimethyl borate (46.3 mL, 408 mmol, 3.00 equiv) was added. The resulting viscous solution was swirled by hand for 5 min, then was allowed to warm to 23 °C and was held at that temperature for 12 h. The product solution was partitioned between saturated aqueous ammonium chloride solution (500 mL) and ethyl acetate (500 mL). The aqueous layer was separated and extracted further with ethyl acetate (2 x 500 mL). The combined organic layers were dried over sodium sulfate and were concentrated. The product was purified by flash column chromatography (2.5% methanol in dichloromethane initially, grading to 10% methanol in dichloromethane) to provide the *tert*-butyl 2-borono-4-methoxycarbanilate (**36**) as a yellow powder (19.9 g, 55%).

^{1}H NMR (400 MHz, C_6D_6, 70 °C) δ:	9.23 (br s, 1H, N**H**), 7.92 (d, 1H, *J* = 8.8 Hz, *o*-aryl), 7.78 (d, 1H, *J* = 2.9 Hz, *m*-aryl), 6.96 (dd, 1H, *J* = 8.8, 2.9 Hz, *m*-aryl), 3.48 (s, 3H, OC**H**$_3$), 1.38 (s, 9H, C(C**H**$_3$)$_3$).
FTIR (neat), cm^{-1}:	3328 (br s, NH), 2978 (s), 2834 (w), 2280 (w), 1723 (s, C=O), 1696 (s, C=O), 1592 (s), 1534 (s), 1482 (s), 1421 (s), 1365 (s), 1241 (vs), 1161 (vs), 1084 (m), 1041 (s), 879 (m), 814 (m), 759 (m), 706 (m).
TLC (10% MeOH-CH_2Cl_2), R_f:	**36**: 0.43 (UV) *tert*-butyl 4-methoxycarbanilate: 0.98 (UV)



37 36 37 35

2-[(*S*)-2-Carboxy-5-methoxy-3-methyl-1,5-cyclohexadien-1-yl]-4-methoxycarbanilic Acid, *N*-*tert*-Butyl (1*R*, 3*R*, 4 *S*)-*p*-Menth-3-yl Ester (35)

Procedure A:

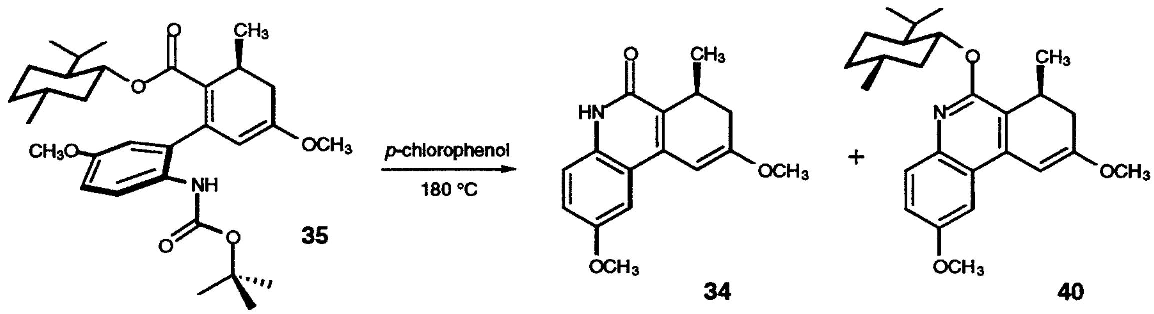
Tetrakistriphenylphosphinepalladium(0) (1.50 g, 1.30 mmol, 0.05 equiv) and copper(I) iodide (200 mg, 1.05 mmol, 0.04 equiv) were added sequentially to a deoxygenated solution of (1*R*, 3*R*, 4*S*)-*p*-menth-3-yl (*S*)-2-hydroxy-4-methoxy-6-methyl-1,3-cyclohexadiene-1-carboxylate, trifluoromethanesulfonate (**37**, 11.2 g, 24.6 mmol, 1 equiv), *tert*-butyl 4-methoxy-2-(trimethylstannyl)carbanilate (10.4 g, 26.8 mmol, 1.05 equiv), lithium chloride (3.40 g, 112 mmol, 4.40 equiv), and 2,6-di-*t*-butyl-4-methylphenol (100 mg, 450 μmol, 0.018 equiv) in dioxane (200 mL). The resulting solution was deoxygenated by alternately evacuating the reaction vessel and flushing with argon (5x). The deoxygenated reaction mixture was heated at reflux for 1 h, causing the solution to turn from yellow to black. After cooling to 23 °C, the product solution was filtered through a pad of Celite and the filtrate was concentrated in vacuo. The residue was dissolved in ethyl acetate (500 mL) and was washed sequentially with aqueous phosphate buffer solution (pH 7, 0.05 M in sodium hydrogen phosphate and 0.05 M in potassium dihydrogen phosphate, 2 x 300 mL) and saturated aqueous sodium chloride solution (300 mL). The organic layer was dried over sodium sulfate and was concentrated. The crude product was dissolved in boiling ethyl acetate (400 mL) and hexanes (100 mL) was added to the hot solution. Slow cooling to 23 °C induced crystallization of the product; further cooling to –20 °C produced additional crystals. The crystals were isolated by filtration. The mother liquor was concentrated and was purified by flash column chromatography (15% ethyl acetate-hexanes), followed by recrystallization (ethyl acetate-hexanes, as above). The combined yield of crystalline product **35** was 10.5 g (81%).

Procedure B:

Tetrakistriphenylphosphinepalladium(0) (2.78 g, 2.40 mmol, 0.0360 equiv) was added to a deoxygenated mixture of aqueous sodium carbonate solution (2.0 M, 48.5 mL, 97.0 mmol, 1.45 equiv) and a solution of (1*R*, 3*R*, 4*S*)-*p*-menth-3-yl (*S*)-2-hydroxy-4-methoxy-6-methyl-1,3-cyclohexadiene-1-carboxylate, trifluoromethanesulfonate (**37**, 30.4 g, 66.9 mmol, 1 equiv) and *tert*-butyl 2-borono-4-methoxycarbanilate (**36**, 19.9 g, 74.3 mmol, 1.11 equiv) in dioxane (220 mL). The reaction mixture was deoxygenated by alternately evacuating the reaction vessel and flushing with argon (5x) and then was heated at reflux for 45 min. The product mixture was cooled to 23 °C and was concentrated to half the original volume in vacuo. The concentrated product solution was partitioned between water (400 mL) and ethyl acetate (400 mL). The aqueous layer was separated and extracted further with ethyl acetate (2 x 400 mL). The combined organic layers were dried over sodium sulfate and were concentrated. The product was purified by chromatography on silica gel (10% ethyl acetate in hexanes initially, grading to 20% ethyl acetate in hexanes) and then by recrystallization [ethyl acetate (800 mL) and hexanes (150 mL)], affording product **35** after two crops of crystals (mp 141-142 °C, 31.9 g, 90%).

^{1}H NMR (300 MHz, $CDCl_3$) δ:	7.76 (br s, 1H, *o*-aryl), 6.81, 6.79 (m, 1H, *m*-aryl), 6.54, 6.48 (d, 1H, J = 2.9 Hz, *m*-aryl), 6.27, 6.19 (br s, 1H, NH), 4.89, 4.87 (d, 1H, J = 2.1 Hz, C=C**H**), 4.49 (m, 1H, menthyl C**H**O), 3.76, 3.75 (s, 3H, aryl OC**H**$_3$), 3.62 (s, 3H, enol OC**H**$_3$), 3.16, 2.98 (m, 1H, CH_3C**H**), 2.85, 2.80 (m, 1H, C**H**$_2$), 2.13, 2.07 (app d, 1H, J = 1.7 Hz, C**H**$_2$), 1.80 (m, 2H, menthyl C**H**$_2$), 1.75 (m, 3H, menthyl C**H**$_2$, menthyl C**H**), 1.65 (m, 1H, menthyl C**H**), 1.47, 1.46 (s, 9H, C(C**H**$_3$)$_4$), 1.35 (m, 1H, menthyl C**H**), 1.20 (m, 3H, CHC**H**$_3$), 0.85 (m, 2H, menthyl C**H**$_2$), 0.80 (m, 6H, menthyl C**H**$_3$), 0.65 (m, 3H, menthyl C**H**$_3$).
FTIR (neat), cm^{-1}:	2955 (m), 2925 (w), 2864 (w), 1693 (m, C=O), 1582 (s), 1425 (m), 1389 (w), 1253 (s), 1237 (m), 1207 (s), 1141 (m), 1111 (w), 1055 (w), 974 (m).

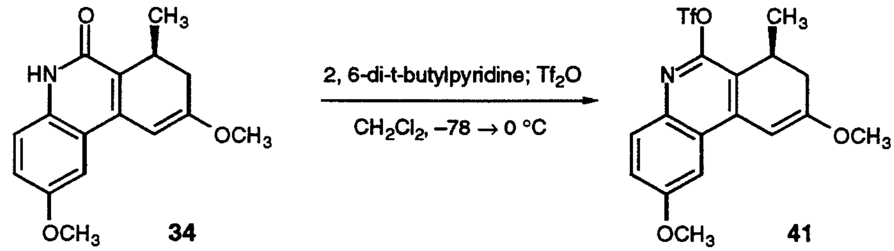
HRMS (EI):	Calcd for $C_{31}H_{46}NO_6$ $[MH]^+$: 528.3325 Found: 528.3308
$[\alpha]_D^{22}$ ($CHCl_3$):	+9.2 °, C = 1.50
TLC (15% EtOAc-hexanes), R_f:	**35**: 0.33 (green, anisaldehyde) **37**: 0.49 *tert*-butyl 4-methoxy-2-(trimethylstannyl)carbanilate: 0.33 (yellow, anisaldehyde) **36**: 0.01 (fluorescent by UV)



(*S*)-7,8-Dihydro-2,9-dimethoxy-7-methyl-6(5*H*)-phenanthridinone (34)

A deoxygenated, solid mixture of the coupling product **35** (23.5 g, 44.5 mmol) and *p*-chlorophenol (ca. 400 g) was heated at 180 °C for 30 min, whereupon all solids dissolved. The product solution was cooled to 23 °C and *p*-chlorophenol was removed by distillation under high vacuum. The residue was purified by flash column chromatography (dichloromethane initially, grading to 10% methanol in dichloromethane) to afford (*S*)-7,8-dihydro-2,9-dimethoxy-7-methyl-6(5*H*)-phenanthridinone (**34**) as a yellow solid (mp 153-157 °C, 10.2 g, 84%). The by-product (*S*)-7,8-dihydro-6-[(1*R*, 3*R*, 4*S*)-*p*-menth-3-yloxy]-2,9-dimethoxy-7-methylphenanthridine (**40**) was isolated in separate fractions and could be converted to the desired product **34** by resubjection to the reaction conditions (5 h, 98%).

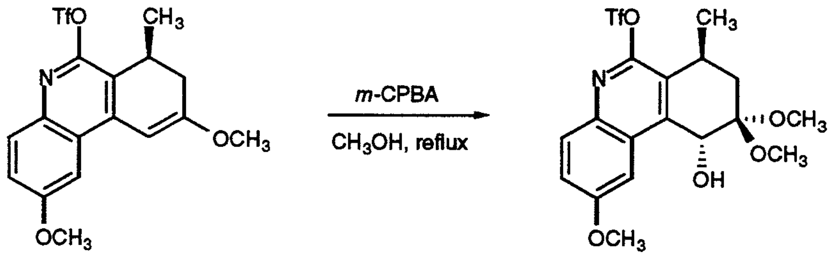
^1H NMR (300 MHz, $CDCl_3$) δ:	11.76 (br s, 1H, **NH**), 7.34 (d, 1H, *J* = 8.8 Hz, *o*-aryl), 7.17 (d, 1H, *J* = 2.6 Hz, *m*-aryl), 7.11 (dd, 1H, *J* = 8.8, 2.6 Hz, *m*-aryl), 5.86 (d, 1H, *J* = 2.1 Hz, C=C**H**), 3.88 (s, 3H, aryl OCH_3), 3.86 (s, 3H, enol OCH_3), 3.53 (p, 1H, *J* = 7.0 Hz, CH_3C**H**), 2.83 (ddd, 1H, *J* = 16.8, 8.2, 2.1 Hz, CH_2), 2.19 (d, 1H, *J* = 16.8 Hz, CH_2), 1.15 (d, 3H, *J* = 7.1 Hz, CHCH_3).
FTIR (CH_2Cl_2 sol'n cell), cm^{-1}:	3392 (w, NH), 2962 (w), 1655 (s, C=O), 1621 (s), 1586 (s), 1506 (m), 1464 (w), 1418 (w),1390 (w), 1365 (w), 1300 (w), 1274 (w), 1234 (w), 1199 (m),1101 (w), 1036 (w), 1017 (w).
HRMS (FAB):	Calcd for $C_{16}H_{18}NO_3$ $[MH]^+$: 272.1287 Found: 272.1293
$[\alpha]_D^{22}$ ($CHCl_3$):	–61.3°, C = 0.69
TLC, R_f:	**34:** 0.27 (EtOAc) **40**: 0.50 (15% EtOAc-hexanes) **35**: 0.33 (15% EtOAc-hexanes)



(*S*)-7,8-Dihydro-2,9-dimethoxy-7-methyl-6-phenanthridinol Trifluoromethanesulfonate (Ester) (41)

Trifluoromethanesulfonic anhydride (3.80 mL, 22.4 mmol, 1.10 equiv) was added via syringe to a suspension of (*S*)-7,8-dihydro-2,9-dimethoxy-7-methyl-6 (5*H*)-phenanthridinone (**34**, 5.52 g, 20.3 mmol, 1 equiv) and 2,6-di-*t*-butylpyridine (6.10 mL, 27.1 mmol, 1.33 equiv) in dichloromethane (400 mL) at –78 °C. The cold suspension was allowed to warm to 23 °C over 30 min and was stirred at that temperature for 15 min. Solids were observed to dissolve as the reaction proceeded. The reaction mixture was poured into aqueous phosphate buffer solution (pH 7, 0.05 M in sodium hydrogen phosphate and 0.05 M in potassium dihydrogen phosphate, 200 mL). The aqueous layer was separated and further extracted with two 200-mL portions of dichloromethane. The combined organic layers were dried over sodium sulfate and were concentrated in vacuo. The residue was purified by flash column chromatography (40% dichloromethane in hexanes) to provide (*S*)-7,8-dihydro-2,9-dimethoxy-7-methyl-6-phenanthridinol trifluoromethanesulfonate (ester) (**41**) as an off-white solid (mp 129.5-130.5 °C, 7.09 g, 86%).

^1H NMR (300 MHz, $CDCl_3$) δ:	7.84 (d, 1H, *J* = 7.2 Hz, *o*-aryl), 7.35 (dd, 1H, *J* = 7.2, 2.7 Hz, *m*-aryl), 7.20 (d, 1H, *J* = 2.7 Hz, *m*-aryl), 6.09 (d, 1H, *J* = 2.0 Hz, C=C**H**), 3.96 (s, 3H, aryl OC**H**$_3$), 3.91 (s, 3H, enol OC**H**$_3$), 3.38 (br p, 1H, *J* = 7.1 Hz, C**H**CH$_3$), 2.92 (ddd, 1H, *J* = 16.9, 7.7, 2.0 Hz, C**H**$_2$), 2.28 (d, 1H, *J* = 16.9 Hz, C**H**$_2$), 1.21 (d, 3H, *J* = 7.1 Hz, C**H**$_3$CH).
FTIR (neat), cm^{-1}:	2968 (m), 1622 (m), 1551 (m), 1514 (m), 1457 (w), 1413 (s), 1350 (m), 1224 (s), 1201 (s), 1136 (m).
HRMS (FAB):	Calcd for $C_{17}H_{16}NO_5SF_3$ $[M]^+$: 403.0701 Found: 403.0679
TLC, R_f:	**41**: 0.37 (40% CH_2Cl_2-hexanes) **34**: 0.27 (EtOAc)



41

42

(7*S*, 10*R*)-7,8,9,10-Tetrahydro-2,9,9-trimethoxy-7-methyl-6,10-phenanthridinediol 6-(Trifluoromethanesulfonate) (42)

A solution of (*S*)-7,8-dihydro-2,9-dimethoxy-7-methyl-6-phenanthridinol trifluoromethanesulfonate (ester) (**41**, 920 mg, 2.28 mmol, 1 equiv) and 55% *m*-chloroperoxybenzoic acid (810 mg, 2.58 mmol, 1.13 equiv) in methanol (30 mL) was heated at reflux for 80 min. After cooling to 23 °C, the reaction solution was partitioned between a 1:1 mixture of a saturated aqueous sodium bicarbonate solution and a saturated aqueous sodium thiosulfate solution (100 mL) and dichloromethane (100 mL). The aqueous layer was separated and extracted further with dichloromethane (2 x 100 mL). The combined organic layers were dried over sodium sulfate and were concentrated. The residue was purified by flash column chromatography (25% ethyl acetate in hexanes initially, grading to 60% ethyl acetate in hexanes) to afford separately (7*S*, 10*R*)-7,8,9,10-tetrahydro-2,9,9-trimethoxy-7-methyl-6,10-phenanthridinediol 6-(trifluoromethanesulfonate) (**42**) as a yellow foam (682 mg, 66%) as well as (7*S*, 10*S*)-7,8,9,10-tetrahydro-2,9,9-trimethoxy-7-methyl-6,10-phenanthridinediol 6-(trifluoromethanesulfonate) as a yellow foam (166 mg, 16%).

42, major epimer:

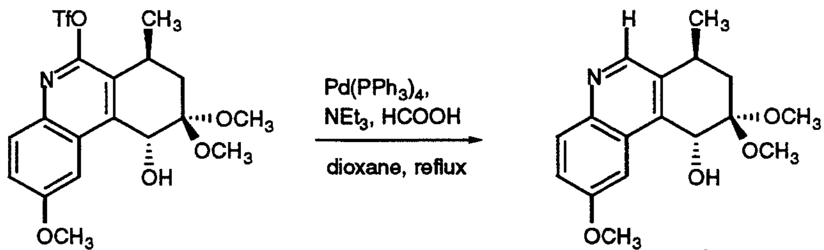
^{1}H NMR (400 MHz, $CDCl_3$) δ:	7.88 (d, 1H, *J* = 9.1 Hz, *o*-aryl), 7.45 (d, 1H, *J* = 3.0 Hz, *m*-aryl), 7.37 (dd, 1H, *J* = 9.1, 3.0 Hz, *m*-aryl), 5.19 (app t, 1H, *J* = 2.2 Hz, C**H**OH), 3.97 (s, 3H, aryl OC**H**$_3$), 3.49 (s, 3H, OC**H**$_3$), 3.35 (pd, 1H, *J* = 7.6, 2.0 Hz, C**H**CH_3), 3.30 (s, 3H, OC**H**$_3$), 2.71 (d, 1H, *J* = 2.4 Hz, O**H**), 2.25 (dd, 1H, *J* = 14.2, 7.6 Hz, C**H**$_2$), 2.07 (dt, 1H, *J* = 14.2, 2.0 Hz, C**H**$_2$), 1.47 (d, 3H, *J* = 7.6 Hz, C**H**$_3$CH).
FTIR (neat), cm^{-1}:	3460 (br, OH), 2947 (m), 1622 (m), 1513 (m), 1468 (m), 1416 (s), 1333 (m), 1228 (vs), 1132 (m).
HRMS (FAB):	Calcd for $C_{18}H_{21}NO_7SF_3$ $[MH]^+$: 452.0991 Found: 452.0984
TLC (40% EtOAc-hexanes), R_f:	**42**: 0.24 (UV) **41**: 0.47 (UV)

minor epimer:

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.88 (d, 1H, J = 9.1 Hz, *o*-aryl), 7.44 (d, 1H, J = 2.7 Hz, *m*-aryl), 7.36 (dd, 1H, J = 9.1 Hz, 2.7 Hz, *m*-aryl), 5.18 (app t, 1H, J = 2.0 Hz, C**H**OH), 3.98 (s, 3H, aryl OC**H**$_3$), 3.44 (s, 3H, OC**H**$_3$), 3.21 (br p, 1H, J = 7.1 Hz, CH_3C**H**), 3.21 (s, 3H, OC**H**$_3$), 2.70 (br d, 1H, J = 2.4 Hz, O**H**), 2.37 (ddd, 1H, J = 14.2, 7.2, 2.0 Hz, C**H**$_2$), 1.93 (dd, 1H, J = 14.2, 10.0 Hz, C**H**$_2$), 1.43 (d, 3H, J = 6.7 Hz, CHC**H**$_3$).

TLC (40% EtOAc-hexanes), R_f: minor epimer: 0.21 (UV)

41: 0.47 (UV)



42 43

(7*S*, 10*R*)-7,8,9,10-Tetrahydro-2,9,9-trimethoxy-7-methyl-10-phenanthridinol (43)

Tetrakistriphenylphosphinepalladium(0) (778 mg, 673 µmol, 0.0401 equiv) was added to a deoxygenated solution of (7*S*, 10*R*)-7,8,9,10-tetrahydro-2,9,9-trimethoxy-7-methyl-6,10-phenanthridinediol 6-(trifluoromethanesulfonate) (**42**, 7.60 g, 16.8 mmol, 1 equiv) and triethylamine (9.40 mL, 67.3 mmol, 4.00 equiv) in dioxane (300 mL) at 23 °C. The resulting solution was deoxygenated by alternately evacuating the reaction vessel and flushing with argon (5x). Formic acid (1.70 mL, 43.8 mmol, 2.63 equiv) was added slowly over 5 min via syringe and the resulting solution was heated at reflux for 20 min, then was allowed to cool to 23 °C. The reaction mixture was partitioned between saturated aqueous sodium chloride solution (300 mL) and ethyl acetate (300 mL). The aqueous layer was separated and extracted further with ethyl acetate (2 x 300 mL). The combined organic layers were dried over sodium sulfate and were concentrated in vacuo. The residue was purified by flash column chromatography (diethyl ether initially, grading to 20% ethyl acetate in diethyl ether) to provide (7*S*, 10*R*)-7,8,9,10-tetrahydro-2,9,9-trimethoxy-7-methyl-10-phenanthridinol (**43**) as a white foam (mp 135-136 °C, 4.94 g, 97%).

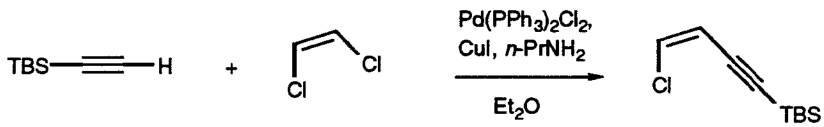
^1H NMR (400 MHz, C_6D_6) δ: 8.71 (s, 1H, N=CH), 8.31 (d, 1H, J = 9.0 Hz, o-aryl), 7.74 (d, 1H, J = 2.7 Hz, m-aryl), 7.30 (dd, 1H, J = 9.0, 2.7 Hz, m-aryl), 5.27 (br d, 1H, J = 5.7 Hz, CHOH), 3.50 (s, 3H, aryl OCH_3), 3.13 (s, 3H, OCH_3), 3.11 (s, 3H, OCH_3), 2.86 (br d, 1H, J = 5.7 Hz, OH), 2.82 (m, 1H, CH_3CH), 2.13 (dd, 1H, J = 14.2, 6.4 Hz, CH_2), 1.64 (ddd, 1H, J = 14.2, 4.7, 1.0 Hz, CH_2), 1.22 (d, 3H, J = 7.3 Hz, $CHCH_3$).

FTIR (neat), cm^{-1}: 3230 (br, OH), 2957 (m), 2834 (w), 1621 (m), 1510 (m), 1463 (m), 1437 (m), 1365 (w), 1276 (w), 1228 (s), 1174 (m), 1130 (m), 1071 (m).

HRMS (FAB): Calcd for $C_{17}H_{22}NO_4$ $[MH]^+$: 304.1549
Found: 304.1549

$[\alpha]_D^{22}$ ($CHCl_3$): +5.2°, C = 0.54

TLC (50% EtOAc-hexanes), R_f: **43**: 0.12 (UV)
42: 0.36 (UV)

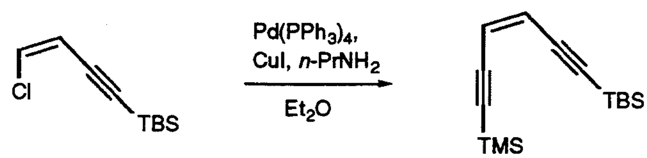


(Z)-1-Chloro-4-(*tert*-butyldimethylsilyl)-1-buten-3-yne

A solution of *tert*-butyldimethylsilylacetylene (14.5 g, 103 mmol, 1 equiv), *n*-propyl amine (42.5 mL, 517 mmol, 5.00 equiv), and (*Z*)-1,2-dichloroethene (32.5 mL, 413 mmol, 4.00 equiv) in diethyl ether (150 mL) was deoxygenated at –78 °C by alternately evacuating the reaction vessel and flushing with argon (8x). The deoxygenated solution was transferred to an ice bath and copper(I) iodide (2.95 g, 15.5 mmol, 0.15 equiv) was added. The mixture was cooled to –78 °C and was deoxygenated as above. In a similar fashion, bis(triphenylphosphine)palladium(II) chloride (3.64 g, 5.17 mmol, 0.05 equiv) was added at 0 °C and the reaction solution was deoxygenated at –78 °C. The deoxygenated reaction mixture was warmed to 23 °C and was stirred at that temperature for 3 h. The product solution was washed with a mixture of a 1:1 saturated aqueous potassium carbonate solution and a saturated aqueous ammonium chloride solution (3 x 150 mL), was dried over sodium sulfate, and was concentrated. The residue was purified by distillation under reduced pressure (bp 45-50 °C, 0.5 mmHg) to afford (*Z*)-1-chloro-4-(*tert*-butyldimethylsilyl)-1-buten-3-yne as a colorless oil (12.5 g, 60%).

^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.40 (d, 1H, J = 7.5 Hz, CHCl), 5.89 (d, 1H, J = 7.5 Hz, CHC≡C), 0.98 (s, 9H, $SiC(CH_3)_3$), 0.16 (s, 6H, $Si(CH_3)_2$).

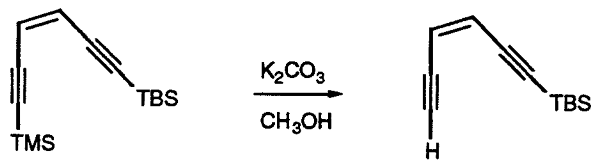
FTIR (neat), cm^{-1}:	2948 (s), 2917 (s), 2877 (m), 2846 (m), 2157 (w, C≡C), 1465 (m), 1246 (m), 1039 (m), 1003 (m), 830 (vs), 770 (s), 714 (m).
TLC (hexanes), R_f:	(*Z*)-1-chloro-4-(*tert*-butyldimethylsilyl)-1-buten-3-yne: 0.42



(Z)-1-(*tert*-Butyldimethylsilyl)-6-(trimethylsilyl)-3-hexen-1,5-diyne

Tetrakistriphenylphosphinepalladium(0) (4.75 g, 4.10 mmol, 0.048 equiv) was added to a solution of (Z)-1-chloro-4-(*tert*-butyldimethylsilyl)-1-buten-3-yne (17.2 g, 85.7 mmol, 1 equiv) in diethyl ether (160 mL) at –78 °C. The resulting suspension was deoxygenated by alternately evacuating the reaction vessel and flushing with argon (5x), then was warmed to 23 °C. In another flask, copper(I) iodide (2.45 g, 12.8 mmol, 0.15 equiv) was added to a solution of trimethylsilylacetylene (17.0 mL, 120 mmol, 1.40 equiv) and *n*-propyl amine (27.5 mL, 334 mmol, 3.90 equiv) in ether (100 mL) at –78 °C. The solution was deoxygenated (as above, 5x), then was stirred in an ice bath for 10 min causing the light green solution to turn reddish brown. The reddish brown solution was cooled to –78 °C and the palladium-containing suspension prepared above was added over 5 min via a wide-bore cannula. The mixture was deoxygenated (as above, 5x), then was stirred in an ice bath for 3 h and at 23 °C for 1 h. The reaction mixture was partitioned between saturated aqueous ammonium chloride solution (200 mL) and hexanes (300 mL). The aqueous layer was separated and extracted further with hexanes (2 x 300 mL). The combined organic layers were dried over sodium sulfate and were concentrated. The residue was filtered, then was purified by distillation under reduced pressure (bp 70-80 °C, 0.5 mmHg) to provide (Z)-1-(*tert*-butyldimethylsilyl)-6-(trimethylsilyl)-3-hexen-1,5-diyne as a light yellow oil (20.4 g, 90%).

^1H NMR (300 MHz, $CDCl_3$) δ:	5.85 (s, 2H, **H**C=C**H**), 0.98 (s, 9H, $(CH_3)_2SiC(C\mathbf{H}_3)_3$), 0.21 (s, 9H, $Si(C\mathbf{H}_3)_3$), 0.15 (s, 6H, $Si(C\mathbf{H}_3)_2$).
FTIR (neat), cm^{-1}:	2959 (s), 2919 (s), 2888 (w), 2858 (m), 2147 (w, C≡C), 1464 (w), 1256 (s), 1068 (s), 967 (m), 840 (vs), 769 (m).
TLC (hexanes), R_f:	(*Z*)-1-(*tert*-butyldimethylsilyl)-6-trimethylsilyl-3-hexen-1,5-diyne: 0.32 (*Z*)-1-chloro-4-(*tert*-butyldimethylsilyl)-1-buten-3-yne: 0.42

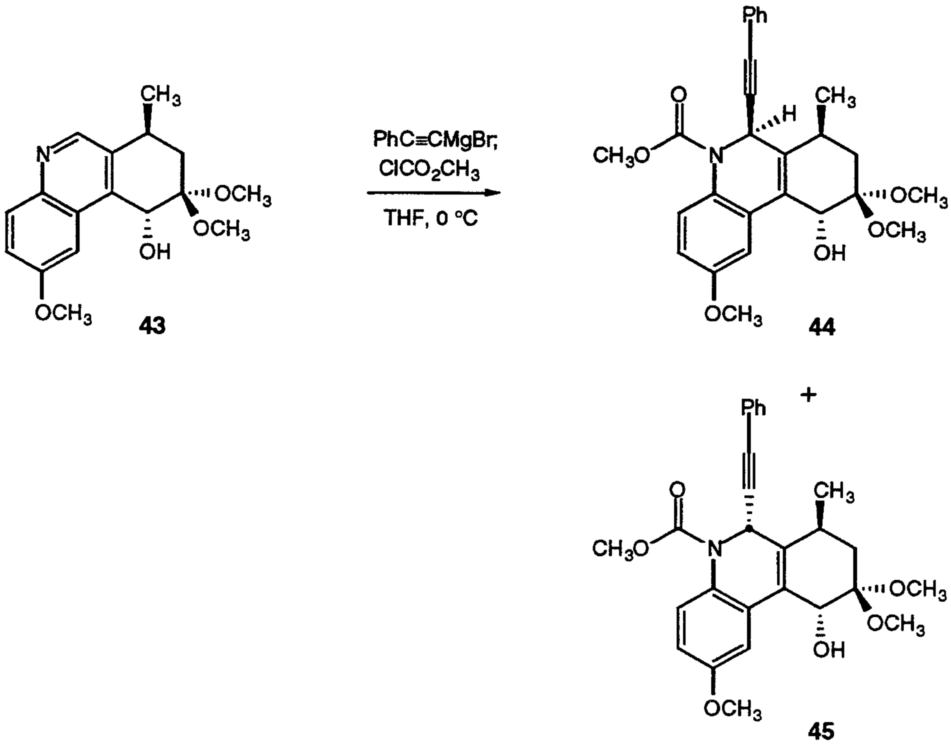


***tert*-Butyl[(Z)-3-hexene-1,5-diynyl]dimethylsilane**

Solid potassium carbonate (5.36 g, 38.9 mmol, 1.10 equiv) was added to a solution of (Z)-1-(*tert*-butyldimethylsilyl)-6-(trimethylsilyl)-3-hexen-1,5-diyne (9.26 g, 35.3 mmol, 1 equiv) in methanol (100 mL) at 23 °C and the resulting suspension was stirred at 23 °C for 1 h. The reaction mixture was partitioned between saturated aqueous sodium chloride solution (200 mL) and hexanes (200 mL). The aqueous layer was separated and extracted further with a 200-mL portion of hexanes. The combined organic layers were dried over sodium sulfate and were concentrated. The product was purified by flash column chromatography (hexanes) to furnish *tert*-butyl[(Z)-3-hexene-1,5-diynyl]dimethylsilane as a brown oil (6.35 g, 95%).

^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.93 (d, 1H, *J* = 11.2 Hz, SiC≡CC**H**=CH), 5.82 (dd, 1H, *J* = 11.2, 2.4 Hz, HC≡CC**H**=CH), 3.34 (d, 1H, *J* = 2.4 Hz, C≡C**H**), 0.97 (s, 9H, $SiC(CH_3)_3$), 0.15 (s, 6H, $Si(CH_3)_2$).

FTIR (neat), cm^{-1}:	3297 (m, C≡CH), 2942 (s), 2921 (s), 2879 (m), 2848 (s), 2150 (w, C≡C), 1464 (m), 1251 (s), 1047 (s), 917 (m), 834 (vs), 771 (s).
TLC (hexanes) R_f:	*tert*-butyl[(*Z*)-3-hexene-1,5-diynyl]dimethylsilane: 0.27 (*Z*)-1-(*tert*-butyldimethylsilyl)-6-trimethylsilyl-3-hexen-1,5-diyne: 0.32



Allylic Alcohols 44 and 45

Ethylmagnesium bromide (1.0 M, 0.330 mL, 0.330 mmol, 4.02 equiv) was added to a solution of phenylacetylene (40 μL, 0.36 mmol, 4.4 equiv) in tetrahydrofuran (1.5 mL) at 0 °C. The resulting reaction mixture was warmed to 23 °C and was stirred at that temperature for 30 min. The resulting acetylide solution was added via cannula to a solution of the quinoline **43** (25 mg, 0.082 mmol, 1 equiv) in tetrahydrofuran (1 mL) at –78 °C, and the resulting mixture was warmed to 0 °C for 10 min, then was cooled to –78 °C. Methyl chloroformate (20 μL, 0.26 mmol, 3.2 equiv) was added to the cold reaction mixture, and the resulting solution was warmed to 0 °C and was stirred at that temperature for 3 h. The product solution was partitioned between aqueous phosphate buffer solution (pH 7, 0.05 M in sodium hydrogen phosphate and 0.05 M in potassium dihydrogen phosphate, 50 mL) and ethyl acetate (30 mL). The aqueous layer was separated and extracted further with a 30-mL portion of ethyl acetate. The combined organic layers were dried over sodium sulfate and were concentrated. The residue was purified by flash column chromatography (50% ethyl acetate in hexanes initially, then 60% ethyl acetate in hexanes) to furnish separately alcohol **44** as a colorless oil (11 mg, 29%) as well as alcohol **45** as a colorless oil (1 mg, 3%).

Alcohol 44:

^{1}H NMR (400 MHz, $CDCl_3$), δ: (br, 1H, *o*-aryl), 7.25-7.14 (br m, 5H, $C_6\mathbf{H}_5$), 7.04 (d, 1H, J = 2.7 Hz, *m*-aryl), 6.82 (dd, 1H, J = 9.2, 2.7 Hz, *m*-aryl), 5.87 (br s, 1H, NC**H**), 4.80 (dd, 1H, J = 8.5, 1.7 Hz, C**H**OH), 3.84 (s, 3H, aryl $OC\mathbf{H}_3$), 3.81 (s, 3H, carbamate $OC\mathbf{H}_3$), 3.43 (s, 3H, OCH_3), 3.37 (s, 3H, OCH_3), 2.64 (m, 1H, C**H**CH_3), 2.38 (d, 1H, J = 8.5 Hz, OH), 2.18 (dd, 1H, J = 14.2, 5.7 Hz, $C\mathbf{H}_2$), 1.65 (dd, 1H, J = 14.2, 7.9 Hz, $C\mathbf{H}_2$), 1.37 (d, 3H, J = 7.2 Hz, CH_3CH).

FTIR (neat), cm^{-1}: (br OH), 2955 (m), 2836 (w), 1698 (vs, C=O), 1608 (w), 1574 (w), 1496 (s), 1441 (s), 1386 (m), 1333 (m), 1302 (s), 1214 (m), 1130 (m), 1085 (m), 1050 (s).

HRMS (FAB):	Calcd for $C_{27}H_{29}O_6N$ [M]$^+$: 463.1995 Found: 463.1983
TLC (40% EtOAc-hexane), R_f:	**44**: 0.14 **43** 0.04

Alcohol 45:

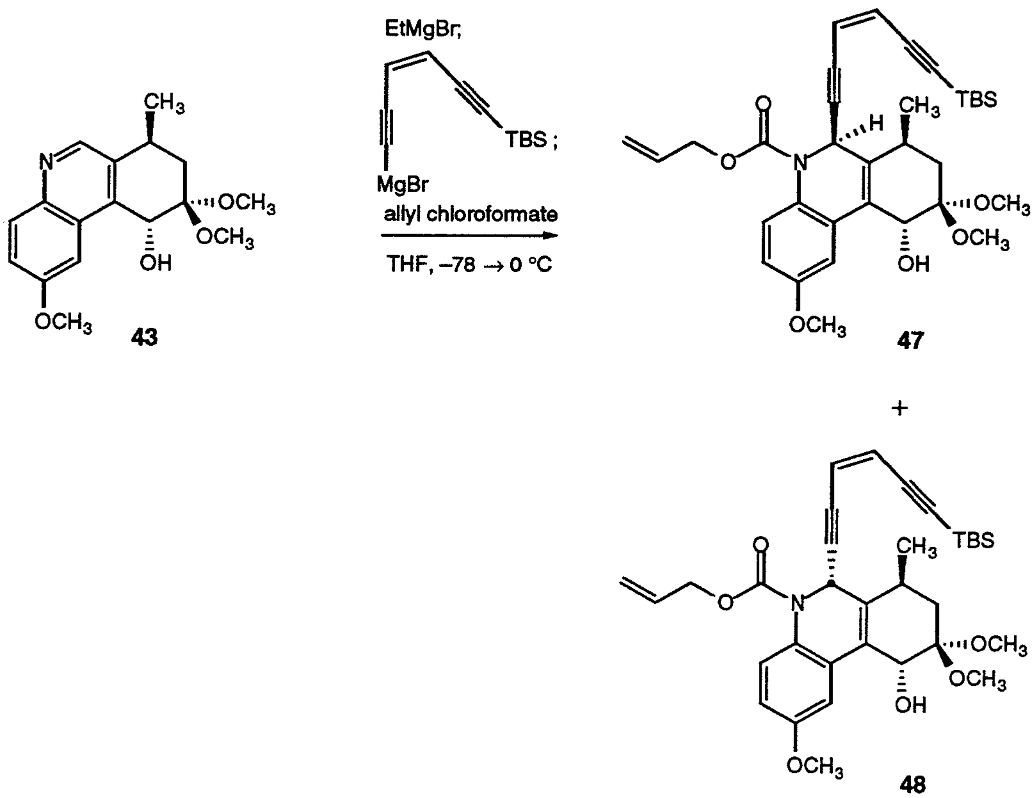
^{1}H NMR (400 MHz, $CDCl_3$), δ:	(br, 1H, *o*-aryl), 7.33 (d, 1H, *J* = 2.9 Hz, *m*-aryl), 7.25-7.18 (m, 5H, C_6H_5), 6.81 (dd, 1H, *J* = 8.9, 2.9 Hz, *m*-aryl), 6.12 (br s, 1H, NCH), 4.45 (br s, 1H, CHOH), 3.84 (s, 3H, aryl OCH_3), 3.82 (s, 3H, carbamate OCH_3), 3.39 (s, 3H, OCH_3), 3.21 (s, 3H, OCH_3), 2.80 (br p, *J* = 7.1 Hz, $CHCH_3$), 2.39 (d, 1H, *J* = 3.0 Hz, OH), 2.24 (dd, 1H, *J* = 14.2, 7.1 Hz, CH_2), 1.90 (br d, 1H, *J* = 14.2 Hz, CH_2), 1.37 (d, 3H, *J* = 7.1 Hz, CH_3CH).
FTIR (neat), cm^{-1}:	(br, OH), 2956 (m), 2836 (w), 1698 (vs, C=O), 1608 (w), 1574 (w), 1495 (s), 1443 (s), 1384 (m), 1329 (w), 1304 (m), 1288 (m), 1263 (m), 1217 (m), 1138 (m), 1091 (m), 1052 (s).

HRMS (FAB): Calcd for $C_{27}H_{29}O_6N$ $[M]^+$: 463.1995

Found: 463.2021

TLC (40% EtOAc-hexane), R_f: **45**: 0.23

43: 0.04



Allyl (6*S*, 7*S*, 10*R*)-6-[(*Z*)-6-(*tert*-butyldimethylsilyl)-3-hexene-1,5-diynyl]-7,8,9,10-tetrahydro-10-hydroxy-2,9,9-trimethoxy-7-methyl-5(6*H*)-phenanthridinecarboxylate (47) and Allyl (6*R*, 7*S*, 10*R*)-6-[(*Z*)-6-(*tert*-butyldimethylsilyl)-3-hexene-1,5-diynyl]-7,8,9,10-tetrahydro-10-hydroxy-2,9,9-trimethoxy-7-methyl-5(6*H*)-phenanthridinecarboxylate (48)

A solution of ethylmagnesium bromide in tetrahydrofuran (1.0 M, 3.0 mL, 3.0 mmol, 0.73 equiv) was added to a solution of (7*S*, 10*R*)-7,8,9,10-tetrahydro-2,9,9-trimethoxy-7-methyl-10-phenanthridinol (**43**, 1.25 g, 4.12 mmol, 1 equiv) in tetrahydrofuran (25 mL) at –78 °C. The mixture was stirred in an ice bath for 10 min, then was cooled to –78 °C. In a separate flask, a solution of ethylmagnesium bromide in tetrahydrofuran (1.0 M, 10.0 mL, 10.0 mmol, 2.43 equiv) was added to a solution of *tert*-butyl[(*Z*)-3-hexene-1,5-diynyl]dimethylsilane (2.50 g, 13.1 mmol, 3.19 equiv) in tetrahydrofuran (50 mL) at 0 °C, and the resulting mixture was stirred at that temperature for 10 min (gas evolution was observed over this period of time). The resulting solution was warmed to 23 °C, and after stirring at that temperature for 20 min, was heated briefly to reflux with a heat gun. After the mixture had cooled to 23 °C, it was transferred via cannula over 3 min to the cold solution (–78 °C) of magnesium alkoxide derived from the TBS quinoline. Allyl chloroformate (0.870 mL, 8.20 mmol, 1.99 equiv) was added, and the reaction mixture was warmed to 0 °C and was stirred at that temperature for 4 h. The product solution was partitioned between aqueous phosphate buffer solution (pH 7, 0.05 M in sodium hydrogen phosphate and 0.05 M in potassium dihydrogen phosphate, 100 mL) and ethyl acetate (80 mL). The aqueous layer was separated and extracted further with an 80-mL portion of ethyl acetate. The combined organic layers were dried over sodium sulfate and were concentrated. The residue was purified by flash column chromatography (20% ethyl acetate in hexanes initially, grading to 60% ethyl acetate in hexanes) to afford separately allyl (6*S*, 7*S*, 10*R*)-6-[(*Z*)-6-(*tert*-butyldimethylsilyl)-3-hexene-1,5-diynyl]-7,8,9,10-tetrahydro-10-hydroxy-2,9,9-trimethoxy-7-methyl-5(6*H*)-phenanthridinecarboxylate (**47**) as a light yellow oil (1.65 g, 69%) as well as (6*R*, 7*S*, 10*R*)-6-[(*Z*)-6-(*tert*-butyldimethylsilyl)-3-hexene-1,5-diynyl]-7,8,9,10-tetrahydro-10-hydroxy-2,9,9-trimethoxy-7-methyl-5(6*H*)-phenanthridinecarboxylate (**48**) as a light yellow oil (67 mg, 3%).

Alcohol 47:

^{1}H NMR (400 MHz, $CDCl_3$), δ: 7.41 (br s, 1H, *o*-aryl), 7.00 (d, 1H, *J* = 2.9 Hz, *m*-aryl), 6.79 (dd, 1H, *J* = 8.8 Hz, 2.9 Hz, *m*-aryl), 5.94 (br m, 2H, CH_2=C**H**, NC**H**), 5.71 (d, 1H, *J* = 11.2 Hz, SiC≡C-C**H**=CH), 5.62 (dd, 1H, *J* = 11.2, 1.9 Hz, CC≡CC**H**=CH), 5.32 (br d, 1H, *J* = 16.8 Hz, C**H**$_2$=CH), 5.23 (br d, 1H, *J* = 10.5 Hz, C**H**$_2$=CH), 4.77 (dd, 1H, *J* = 8.5, 1.9 Hz, C**H**OH), 4.75 (br dd, 1H, *J* = 13.9, 5.4 Hz, C**H**$_2$O), 4.62 (br m, 1H, C**H**$_2$O), 3.83 (s, 3H, aryl OC**H**$_3$), 3.43 (s, 3H, OC**H**$_3$), 3.35 (s, 3H, OC**H**$_3$), 2.59 (m, 1H, C**H**CH_3), 2.44 (br m, 1H, O**H**), 2.15 (dd, 1H, *J* = 14.4, 5.3 Hz, C**H**$_2$), 1.61 (dd, 1H, *J* = 14.4, 8.6 Hz, C**H**$_2$), 1.32 (d, 3H, *J* = 7.3 Hz, C**H**$_3$CH), 0.96 (s, 9H, C≡CSiC(C**H**$_3$)$_3$), 0.13 (s, 6H, C≡CSi(C**H**$_3$)$_2$).

FTIR (neat), cm^{-1}: 3476 (br, OH), 2953 (s), 2856 (w), 2245 (w, C≡C), 2140 (w, C≡C), 1698 (vs, C=O), 1650 (w), 1608 (w), 1577 (w), 1497 (s), 1462 (m), 1392 (s), 1325 (w), 1298 (s), 1283 (s), 1215 (m), 1137 (m), 1084 (m), 1050 (m), 1024 (m).

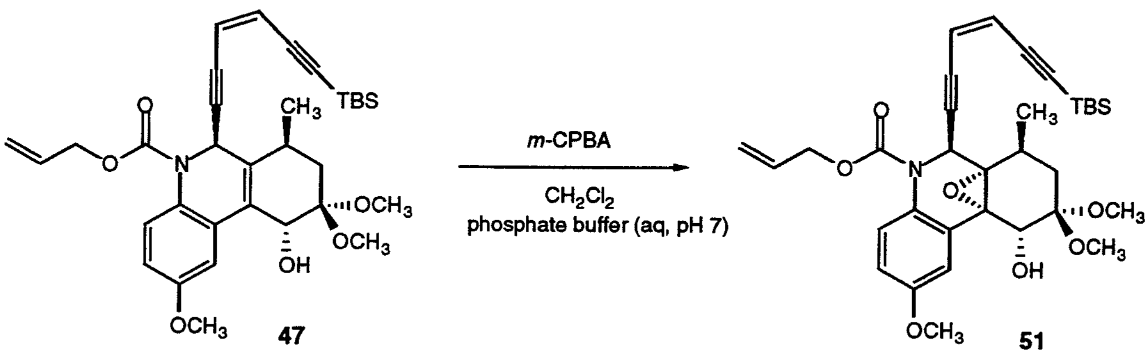
HRMS (FAB):	Calcd for $C_{33}H_{43}O_6NSiNa$ $[M+Na]^+$: 600.2757
	Found: 600.2738
TLC (40% EtOAc-hexanes), R_f:	**47**: 0.27
	43: 0.04

Allylic alcohol 48:

^1H NMR (400 MHz, $CDCl_3$), δ: 7.41 (br s, 1H, *o*-aryl), 7.27 (d, 1H, *J* = 2.9 Hz, *m*-aryl), 6.78 (dd, 1H, *J* = 8.8 Hz, 2.9 Hz, *m*-aryl), 6.11 (br s, 1H, NCH), 5.93 (br m, 1H, CH_2=**CH**), 5.72 (d, 1H, *J* = 11.2 Hz, SiC≡C-**CH**=CH), 5.63 (dd, 1H, *J* = 11.2, 2.0 Hz, CC≡CCH=**CH**), 5.30 (br d, 1H, *J* = 16.6 Hz, $\mathbf{CH_2}$=CH), 5.21 (br d, 1H, *J* = 10.5 Hz, $\mathbf{CH_2}$=CH), 4.75 (br dd, 1H, *J* = 13.9, 5.4 Hz, $\mathbf{CH_2}$O), 4.59 (br m, 1H, $\mathbf{CH_2}$O), 4.40 (br s, 1H, **CH**OH), 3.81 (s, 3H, aryl $\mathbf{OCH_3}$), 3.35 (s, 3H, $\mathbf{OCH_3}$), 3.18 (s, 3H, $\mathbf{OCH_3}$), 2.73 (br p, 1H, *J* = 7.3 Hz, **CH**CH_3), 2.42 (br s, 1H, **OH**), 2.08 (dd, 1H, *J* = 14.2, 7.3 Hz, $\mathbf{CH_2}$), 1.86 (br d, 1H, *J* = 14.2 Hz, $\mathbf{CH_2}$), 1.30 (d, 3H, *J* = 7.3 Hz, $\mathbf{CH_3}$CH), 0.96 (s, 9H, C≡CSiC($\mathbf{CH_3}$)$_3$), 0.13 (s, 6H, C≡CSi(CH_3)$_2$).

FTIR (neat), cm^{-1}: 3478 (br, OH), 2953 (s), 2857 (w), 2249 (w, C≡C), 2143 (w, C≡C), 1704 (vs, C=O), 1651 (w), 1608 (w), 1574 (w), 1496 (s), 1470 (m), 1393 (s), 1325 (w), 1300 (s), 1282 (s), 1215 (m), 1137 (m), 1084 (m), 1051 (m), 1024 (m).

TLC (40% EtOAc-hexanes), R_f:	**48**: 0.33
	43: 0.04

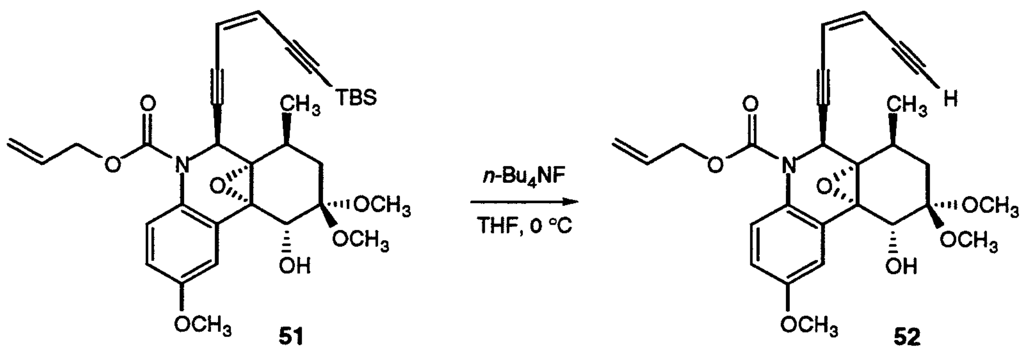


Allyl (6*S*, 6a*S*, 7*S*, 10*R*, 10a*S*)-6-[(*Z*)-6-(*tert*-butyldimethylsilyl)-3-hexene-1,5-diynyl]-7,8,0,10-tetrahydro-10-hydroxy-2,9,9-trimethoxy-7-methyl-6a,10a-epoxyphenanthridine-5(6*H*)-carboxylate (51)

m-Chloroperoxybenzoic acid (55%, 332 mg, 1.06 mmol, 1.20 equiv) was added to a biphasic solution of allyl (6*S*, 7*S*, 10*R*)-6-[(*Z*)-6-(*tert*-butyldimethylsilyl)-3-hexene-1,5-diynyl]-7,8,9,10-tetrahydro-10-hydroxy-2,9,9-trimethoxy-7-methyl-5(6*H*)-phenanthridinecarboxylate (**47**, 5.09 mg, 0.881 mmol, 1 equiv) in dichloromethane (25 mL) and aqueous phosphate buffer (pH 7, 0.05 M in sodium hydrogen phosphate and 0.05 M in potassium dihydrogen phosphate, 25 mL) at 0 °C. The reaction mixture was stirred vigorously at 0 °C for 6.5 h. A second portion of 55% *m*-chloroperoxybenzoic acid (343 mg, 1.09 mmol, 1.24 equiv) was added and the reaction mixture was stirred at 0 °C for another 3.5 h, then at 23 °C for 8 h. A final portion of 55% *m*-chloroperoxybenzoic acid (240 mg, 0.765 mmol, 0.868 equiv) was added at this point and the reaction mixture was stirred at 23 °C for 8 h. The product solution was poured into 1:1 mixture of a saturated aqueous sodium bicarbonate solution and saturated aqueous sodium thiosulfate solution (200 mL). The aqueous layer was separated and extracted further with dichloromethane (2 x 75 mL). The combined organic layers were dried over sodium sulfate and were concentrated. The residue was purified by flash column chromatography (40% ethyl acetate in hexanes) to provide allyl (6*S*, 6a*S*, 7*S*, 10*R*, 10a*S*)-6-[(*Z*)-6-(*tert*-butyldimethylsilyl)-3-hexene-1,5-diynyl]-7,8,0,10-tetrahydro-10-hydroxy-2,9,9-trimethoxy-7-methyl-6a,10a-epoxyphenanthridine-5(6*H*)-carboxylate (**51**) as a light yellow oil (370 mg, 71%).

^{1}H NMR (400 MHz, C_6D_6), δ: 7.58 (d, 1H, *J* = 2.9 Hz, *m*-aryl), 7.35 (br d, 1H, *J* = 8.8 Hz, *o*-aryl), 6.68 (dd, 1H, *J* = 8.8, 2.9 Hz, *m*-aryl), 6.44 (br s, 1H, NC**H**), 5.68 (m, 1H, CH_2=C**H**), 5.36 (d, 1H, *J* = 11.0 Hz, HC≡CCH=C**H**), 5.20 (dd, 1H, *J* = 11.0, 1.5 Hz, HC≡CC**H**=CH), 5.11 (br d, 1H, *J* = 17.1 Hz, C**H**$_2$=CH), 4.93 (br d, 1H, *J* = 10.5 Hz, C**H**$_2$=CH), 4.73 (d, 1H, *J* = 11.2 Hz, C**H**OH), 4.64 (br dd, 1H, *J* = 13.4, 5.1 Hz, C**H**$_2$O), 4.48 (br dd, 1H, *J* = 13.4 Hz, 5.1 Hz, C**H**$_2$O), 3.29 (s, 3H, OC**H**$_3$), 3.27 (s, 3H, OC**H**$_3$), 2.98 (s, 3H, OC**H**$_3$), 2.98 (br s, 1H, O**H**), 2.23 (m, 1H, C**H**CH$_3$), 1.91 (dd, 1H, *J* = 14.6, 4.2 Hz, C**H**$_2$), 1.56 (dd, 1H, *J* = 14.6, 11.2 Hz, C**H**$_2$), 1.37 (d, 3H, *J* = 7.6 Hz, C**H**$_3$), 1.14 (s, 9H, (C**H**$_3$)$_3$CSiC≡C), 0.24 (s, 6H, (C**H**$_3$)$_2$SiC≡C).

FTIR (neat), cm^{-1}:	3523 (br, OH), 2952 (s), 2857 (w), 2280 (w, C≡C), 2141 (w, C≡C), 1713 (vs, C=O), 1650 (w), 1614 (w), 1585 (w), 1505 (s), 1463 (s), 1390 (s), 1301 (vs), 1207 (m), 1161 (m), 1135 (m), 1085 (m), 1052 (m), 1026 (m).
HRMS (FAB):	Calcd for $C_{33}H_{43}O_7NSiNa$ $[M+Na]^+$: 616.2706 Found: 616.2688
TLC (40% EtOAc-hexanes), R_f:	**51**: 0.30 **47**: 0.27



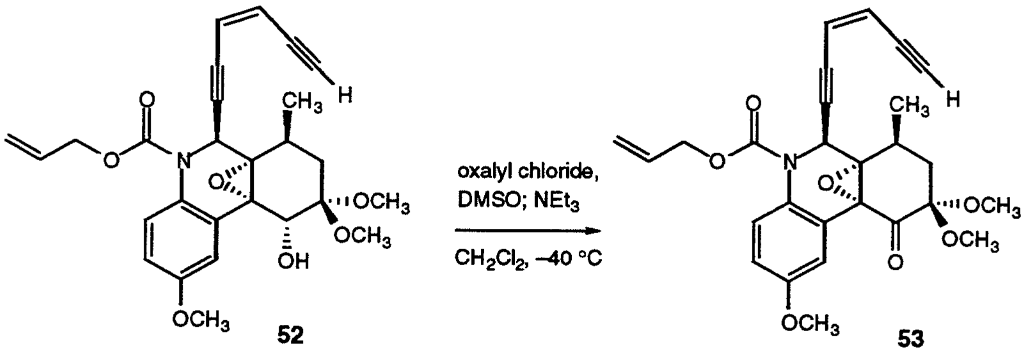
Allyl (6*S*, 6a*S*, 7*S*, 10*R*, 10a*S*)-6-[(*Z*)-3-Hexene-1,5-diynyl]-7,8,0,10-tetrahydro-2,10-dihydroxy-2,9,9-trimethoxy-7-methyl-6a,10a-epoxyphenanthridine-5(6*H*)-carboxylate (52)

A solution of tetrabutylammonium fluoride in tetrahydrofuran (3.0 M, 0.400 mL, 1.2 mmol, 1.0 equiv) was added to a solution of allyl (6*S*, 6a*S*, 7*S*, 10*R*, 10a*S*)-6-[(*Z*)-6-(*tert*-butyldimethylsilyl)-3-hexene-1,5-diynyl]-7,8,0,10-tetrahydro-10-hydroxy-2,9,9-trimethoxy-7-methyl-6a,10a-epoxyphenanthridine-5(6*H*)-carboxylate (**51**, 680 g, 1.14 mmol, 1 equiv) in tetrahydrofuran (25 mL) at 0 °C. After stirring at 0 °C for 5 min, the product solution was partitioned between aqueous phosphate buffer solution (pH 7, 0.05 M in sodium hydrogen phosphate and 0.05 M in potassium dihydrogen phosphate, 100 mL) and ethyl acetate (50 mL). The aqueous layer was separated and extracted further with ethyl acetate (2 x 50 mL). The combined organic layers were dried over sodium sulfate and were concentrated. The residue was purified by flash column chromatography (40% ethyl acetate in hexanes) to afford allyl (6*S*, 6a*S*, 7*S*, 10*R*, 10a*S*)-6-[(*Z*)-3-hexene-1,5-diynyl]-7,8,0,10-tetrahydro-2,10-dihydroxy-2,9,9-trimethoxy-7-methyl-6a,10a-epoxyphenanthridine-5(6*H*)-carboxylate (**52**) as a light yellow oil (491 mg, 89%).

^{1}H NMR (400 MHz, C_6D_6), δ: 7.59 (d, 1H, *J* = 2.9 Hz, *m*-aryl), 7.34 (br d, 1H, *J* = 8.8 Hz, *o*-aryl), 6.67 (dd, 1H, *J* = 8.8, 2.9 Hz, *m*-aryl), 6.42 (br s, 1H, NC**H**), 5.65 (m, 1H, CH_2=C**H**), 5.22 (dd, 1H, *J* = 11.2, 1.2 Hz, HC≡CCH=C**H**), 5.18 (dd, 1H, *J* = 11.2, 1.8 Hz, HC≡CC**H**=CH), 5.09 (br d, 1H, *J* = 17.3 Hz, C**H**$_2$=CH), 4.91 (br d, 1H, *J* = 10.3 Hz, C**H**$_2$=CH), 4.74 (d, 1H, *J* = 11.2 Hz, C**H**OH), 4.61 (ddt, 1H, *J* = 13.7, 5.4, 1.5 Hz, C**H**$_2$O), 4.48 (br dd, 1H, *J* = 13.7 Hz, 5.4 Hz, C**H**$_2$O), 3.28 (s, 3H, OC**H**$_3$), 3.27 (s, 3H, OC**H**$_3$), 3.00 (br s, 1H, O**H**), 2.97 (s, 3H, OC**H**$_3$), 2.93 (d, 1H, *J* = 2.0 Hz, **H**C≡C), 2.21 (m, 1H, C**H**CH$_3$), 1.88 (dd, 1H, *J* = 14.6, 4.2 Hz, C**H**$_2$), 1.64 (dd, 1H, *J* = 14.6, 11.7 Hz, C**H**$_2$), 1.30 (d, 3H, *J* = 7.3 Hz, C**H**$_3$).

FTIR (neat), cm^{-1}: 3480 (br, OH), 3282 (m, C≡CH), 2946 (m), 2836 (w), 2279 (w, C≡C), 2094 (w), 1706 (vs, C=O), 1649 (w), 1612 (w), 1585 (w), 1504 (s), 1460 (m), 1391 (s), 1301 (m), 1283 (m), 1238 (m), 1207 (w), 1159 (m), 1134 (m), 1084 (m), 1051 (m).

HRMS (FAB):	Calcd for $C_{27}H_{29}O_7NNa$ $[M+Na]^+$: 582.1841
	Found: 582.1847
TLC (40% hexanes-ethyl acetate), R_f:	**52**: 0.19
	51: 0.30



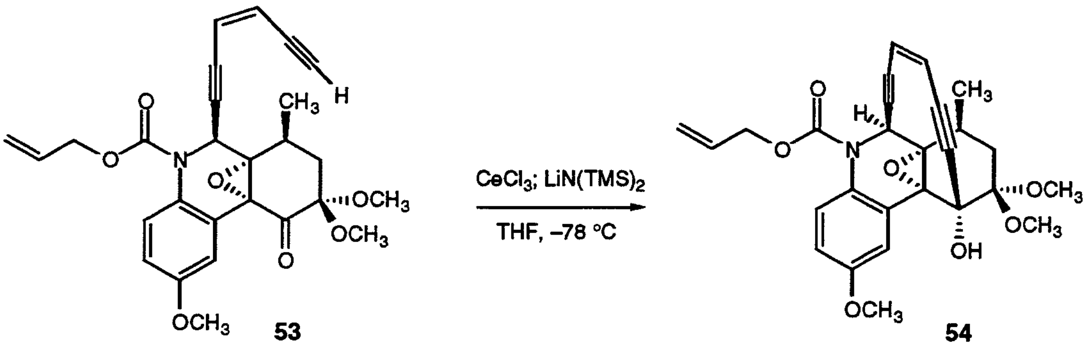
Allyl (6*S*, 6a*S*, 7*S*, 10a*R*)-6-[(*Z*)-3-hexene-1,5-diynyl]-7,8,9,10-tetrahydro-2,9,9-triimethoxy-7-methyl-10-oxo-6a,10a-epoxyphenanthridine-5(6*H*)-carboxylate (53)

Dimethyl sulfoxide (0.270 mL, 3.80 mmol, 6.93 equiv) was added to a solution of oxalyl chloride (0.240 mL, 2.75 mmol, 5.02 equiv) in dichloromethane (3 mL) at –78 °C. After stirring at –78 °C for 15 min, a solution of allyl (6*S*, 6a*S*, 7*S*, 10*R*, 10a*S*)-6-[(*Z*)-3-hexene-1,5-diynyl]-7,8,9,10-tetrahydro-10-hydroxy-2,9,9-trimethoxy-7-methyl-6a,10a-epoxyphenanthridine-5 (6*H*)-carboxylate (**52**, 263 mg, 0.548 mmol, 1 equiv) in dichloromethane (3.5 mL) was added via cannula to the cold reaction solution (–78 °C). The reaction mixture was warmed to –40 °C and was held at that temperature for 7 h. The reaction mixture was then cooled to –78 °C, triethylamine (1.4 mL, 10.0 mmol, 18.3 equiv) was added, and the resulting solution was warmed to 0 °C and stirred at that temperature for 10 min. The product solution was poured into aqueous phosphate buffer solution (pH 7, 0.05 M in sodium hydrogen phosphate and 0.05 M in potassium dihydrogen phosphate, 100 mL). The aqueous layer was separated and extracted further with ethyl acetate (2 x 70 mL). The combined organic layers were dried over sodium sulfate and were concentrated. The residue was purified by flash column chromatography

(30% ethyl acetate in hexanes) to afford allyl (6*S*, 6a*S*, 7*S*, 10a*R*)-6-[(*Z*)-3-hexene-1,5-diynyl]-7,8,9,10-tetrahydro-2,9,9-dimethoxy-7-methyl-10-oxo-6a,10a-epoxyphenanthridine-5(6*H*)-carboxylate (**53**) as a colorless oil (237 mg, 90%).

^{1}H NMR (400 MHz, $CDCl_3$), δ:	7.74 (d, 1H, *J* = 2.7 Hz, *m*-aryl), 7.23 (br d, 1H, *J* = 8.8 Hz, *o*-aryl), 6.87 (dd, 1H, *J* = 8.8, 2.7 Hz, *m*-aryl), 5.84 (m, 1H, CH_2=**CH**, NC**H**), 5.69 (br s, 2H, **HC=CH**), 5.22 (br d, 1H, *J* = 17.9 Hz, $\mathbf{CH_2}$=CH), 5.17 (br d, 1H, *J* = 10.7 Hz, $\mathbf{CH_2}$=CH), 4.68 (br dd, 1H, *J* = 12.5, 5.4 Hz, $\mathbf{CH_2}$O), 4.54 (br d, 1H, *J* = 12.5 Hz, $\mathbf{CH_2}$O), 3.81 (s, 3H, aryl $\mathbf{OCH_3}$), 3.30 (s, 6H, $\mathbf{OCH_3}$), 3.12 (d, 1H, *J* = 1.8 Hz, **HC**≡C), 2.77 (m, 1H, **CH**CH_3), 2.22 (dd, 1H, *J* = 14.2, 6.4 Hz, $\mathbf{CH_2}$), 1.99 (dd, 1H, *J* = 14.2, 3.4 Hz, $\mathbf{CH_2}$), 1.51 (d, 3H, *J* = 7.3 Hz, $\mathbf{CH_3}$).
FTIR (neat), cm^{-1}:	3287 (m, C≡CH), 2943 (m), 2837 (w), 2280 (w, C≡C), 2094 (w, C≡C), 1730 (sh, C=O), 1710 (vs, C=O), 1650 (w), 1613 (w), 1583 (w), 1504 (s), 1460 (m), 1392 (s), 1318 (w), 1299 (s), 1256 (m), 1217 (m), 1131 (m), 1083 (m), 1042 (m).

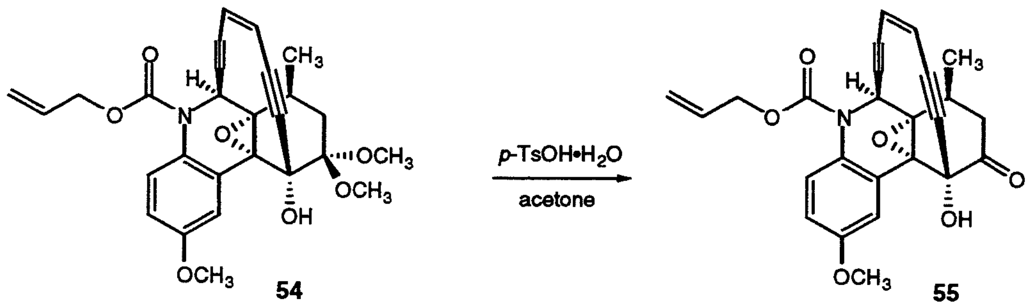
HRMS (FAB):	Calcd for $C_{27}H_{27}O_7NNa$ $[M+Na]^+$: 500.1686
	Found: 500.1676
TLC (40% EtOAc-hexanes), R_f:	**53**: 0.32
	52: 0.19



Allyl (6*S*, 6a*S*, 7*S*, 10*R*, 10a*S*, 14*Z*)-7,8,9,10-tetrahydro-10-hydroxy-2,9,9-trimethoxy-7-methyl-6a,10a-epoxy-6,10-[3]hexene[1,5]diynophenanthridine-5(6*H*)-carboxylate (54)

A suspension of cerium trichloride (520 mg, 2.11 mmol, 4.87 equiv) and allyl (6*S*, 6a*S*, 7*S*, 10a*R*)-6-[(*Z*)-3-hexene-1,5-diynyl]-7,8,9,10-tetrahydro-2,9,9-trimethoxy-7-methyl-10-oxo-6a,10a-epoxyphenanthridine-5(6*H*)-carboxylate (**53**, 207 mg, 0.433 mmol, 1 equiv) in tetrahydrofuran (5 mL) was stirred at 23 °C for 30 min. The suspension was then cooled to –78 °C and a solution of lithium hexamethyldisilylazide in tetrahydrofuran (0.46 M, 1.0 mL, 0.46 mmol, 1.1 equiv) was added, causing the white suspension to turn light brown, then brown, then dark grayish brown. The reaction flask was transferred to an ice bath and saturated aqueous ammonium chloride solution (100 mL) was added. The biphasic mixture was extracted with ethyl acetate (3 x 50 mL). The combined organic layers were dried over sodium sulfate and were concentrated. The residue was purified by flash column chromatography (7% ethyl acetate in dichloromethane) to afford allyl (6*S*, 6a*S*, 7*S*, 10*R*, 10a*S*, 14*Z*)-7,8,9,10-tetrahydro-10-hydroxy-2,9,9-trimethoxy-7-methyl-6a,10a-epoxy-6,10-[3]hexene[1,5]diynophenanthridine-5(6*H*)-carboxylate (**54**) as a colorless oil (150 mg, 72%).

^{1}H NMR (400 MHz, C_6D_6), δ:	8.65 (d, 1H, J = 2.9 Hz, *m*-aryl), 7.32 (br s, 1H, *o*-aryl), 6.72 (dd, 1H, J = 8.8, 2.9 Hz, *m*-aryl), 6.24 (br s, 1H, NC**H**), 5.65 (m, 1H, CH_2=C**H**), 5.13 (d, 1H, J = 10.0 Hz, HCC≡CCH=C**H**), 5.10 (br d, 1H, J = 16.3 Hz, C**H**$_2$=CH), 5.04 (dd, 1H, J = 10.0, 1.5 Hz, HCC≡CC**H**=CH), 4.91 (br d, 1H, J = 10.5 Hz, C**H**$_2$=CH), 4.55 (m, 2H, C**H**$_2$O), 3.48 (s, 1H, O**H**), 3.43 (s, 3H, OC**H**$_3$), 3.38 (s, 3H, OC**H**$_3$), 2.96 (s, 3H, OC**H**$_3$), 2.42 (m, 1H, C**H**CH_3), 2.18 (t, 1H, J = 13.9 Hz, C**H**$_2$), 1.88 (dd, 1H, J = 14.5, 5.7 Hz, C**H**$_2$), 1.20 (d, 3H, J = 7.3 Hz, C**H**$_3$CH).
FTIR (neat), cm^{-1}:	3448 (br, OH), 2943 (m), 2836 (w), 2278 (w, C≡C), 2197 (w, C≡C), 1704 (vs, C=O), 1648 (w), 1611 (w), 1582 (w), 1499 (s), 1458 (m), 1388 (s), 1319 (m), 1299 (m), 1273 (m), 1239 (w), 1204 (m), 1144 (m), 1109 (m), 1058 (m).
HRMS (FAB):	Calcd for $C_{27}H_{27}O_7NNa$ $[M+Na]^+$: 500.1686 Found: 500.1688
TLC (40% EtOAc-hexanes), R_f:	**54**: 0.28 **53**: 0.32

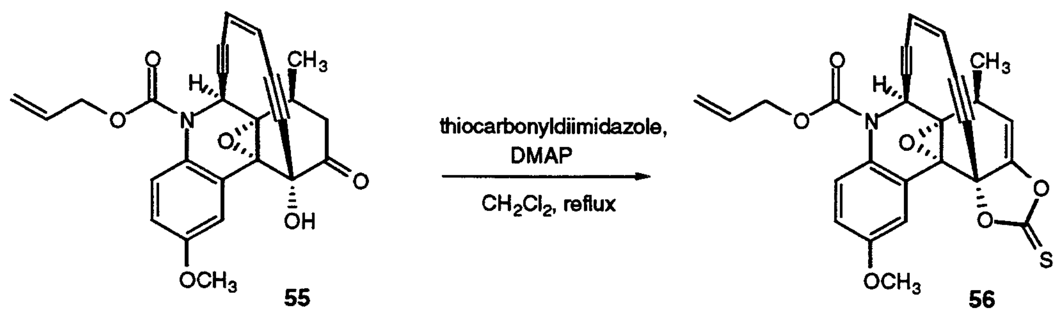


Allyl (6*S*, 6a*S*, 7*S*, 10*R*, 10a*S*, 14*Z*)-2-methoxy-7,8,9,10-tetrahydro-10-hydroxy-7-methyl-9-oxo-6a,10a-epoxy-6,10-[3]hexene[1,5]diynophenanthridine-5(6*H*)-carboxylate (55)

A solution of allyl (6*S*, 6a*S*, 7*S*, 10*R*, 10a*S*, 14*Z*)-7,8,9,10-tetrahydro-10-hydroxy-2,9,9-trimethoxy-7-methyl-6a,10a-epoxy-6,10[3]hexene[1,5]diynophenanthridine-5(6*H*)-carboxylate (**54**, 75 mg, 0.16 mmol, 1 equiv) in acetone (20 mL) was stirred with *p*-toluensulfonic acid monohydrate (48 mg, 0.25 mmol, 1.6 equiv) at 23 °C for 9 h. The reaction solution was partitioned between saturated aqueous sodium bicarbonate solution (100 mL) and ethyl acetate (50 mL). The aqueous layer was separated and extracted further with ethyl acetate (2 x 50 mL). The combined organic layers were dried over sodium sulfate and were concentrated. The residue was purified by flash column chromatography (30% ethyl acetate in hexanes) to afford allyl (6*S*, 6a*S*, 7*S*, 10*R*, 10a*S*, 14*Z*)-2-methoxy-7,8,9,10-tetrahydro-10-hydroxy-7-methyl-9-oxo-6a,10a-epoxy-6,10-[3]hexene[1,5]diynophenanthridine-5(6*H*)-carboxylate (**55**) as a colorless oil (49 mg, 72%).

^1H NMR (300 MHz, C_6D_6), δ:	8.58 (d, 1H, *J* = 2.9 Hz, *m*-aryl), 7.32 (br s, 1H, *o*-aryl), 6.71 (dd, 1H, *J* = 8.8, 2.9 Hz, *m*-aryl), 6.13 (br s, 1H, NC**H**), 5.63 (m, 1H, CH_2=C**H**), 5.09 (br d, 1H, *J* = 16.3 Hz, C**H**$_2$=CH), 5.09 (d, 1H, *J* = 10.1 Hz, HCC≡CCH=C**H**), 5.03 (dd, 1H, *J* = 10.1, 1.5 Hz, HCC≡CC**H**=CH), 4.94 (s, 1H, O**H**), 4.92 (br d, 1H, *J* = 10.5 Hz, C**H**$_2$=CH), 4.55 (ddt, 1H, *J* = 13.7, 5.3, 1.5 Hz, C**H**$_2$O), 4.47 (ddt, 1H, *J* = 13.7, 5.3, 1.5 Hz, C**H**$_2$O), 3.37 (s, 3H, OC**H**$_3$), 2.51 (m, 1H, C**H**CH_3), 2.41 (dd, 1H, *J* = 15.1, 6.8 Hz, C**H**$_2$), 2.34 (dd, 1H, *J* = 15.1, 8.8 Hz, C**H**$_2$), 1.02 (d, 3H, *J* = 7.2 Hz, C**H**$_3$CH).
FTIR (neat), cm^{-1}:	3416 (br, OH), 3090 (w), 3054 (w), 2951 (m), 2838 (w), 2275 (w, C≡C), 2182 (w, C≡C), 1732 (sh, C=O), 1704 (vs, C=O), 1650 (w), 1614 (w), 1583 (w), 1504 (s), 1462 (m), 1392 (s), 1320 (m), 1302 (m), 1273 (s), 1240 (m), 1209 (m), 1181 (m), 1142 (m), 1118 (m).
HRMS (FAB):	Calcd for $C_{25}H_{21}O_6NNa$ $[M+Na]^+$: 454.1267 Found: 454.1260

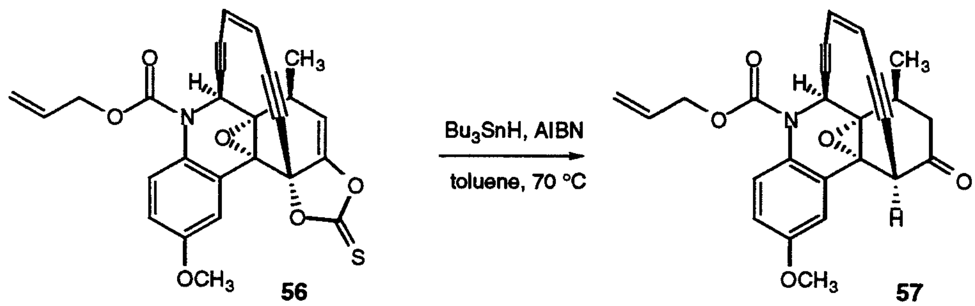
TLC (40% EtOAc-hexanes), R_f:	**55**: 0.36
	54: 0.28



Allyl (6*S*, 6a*S*, 7*S*, 10*S*, 10a*S*, 14*Z*)-2-methoxy-7,10-dihydro-9,10-dihydroxy-7-methyl-6a,10a-epoxy-6,10-[3]hexene[1,5]diynophenanthridine-5(6*H*)-carboxylate, Cyclic Thiocarbonate (56)

Thiocarbonyldiimidazole (109 mg, 0.612 mmol, 8.05 equiv) and 4-dimethylaminopyridine (35 mg, 0.286 mmol, 3.7 equiv) were added sequentially to a solution of allyl (6*S*, 6a*S*, 7*S*, 10*R*, 10a*S*, 14*Z*)-2-methoxy-7,8,9,10-tetrahydro-10-hydroxy-7-methyl-9-oxo-6a,10a-epoxy-6,10-[3]hexene[1,5]diynophenanthridine-5(6*H*)-carboxylate (**55**, 33 mg, 0.076 mmol, 1 equiv) in dichloromethane (2.5 mL) at 23 °C. The reaction mixture was heated to a gentle reflux for 6 h. The reaction mixture was cooled to 23 °C and volatiles were removed in vacuo. The residue was purified by flash column chromatography (dichloromethane initially, then 2% ethyl acetate in dichloromethane) to afford allyl (6*S*, 6a*S*, 7*S*, 10*S*, 10a*S*, 14*Z*)-2-methoxy-7,10-dihydro-9,10-dihydroxy-7-methyl-6a,10a-epoxy-6,10-[3]hexene[1,5]diynophenanthridine-5(6*H*)-carboxylate, cyclic thiocarbonate (**56**) as a colorless oil (33 mg, 92%).

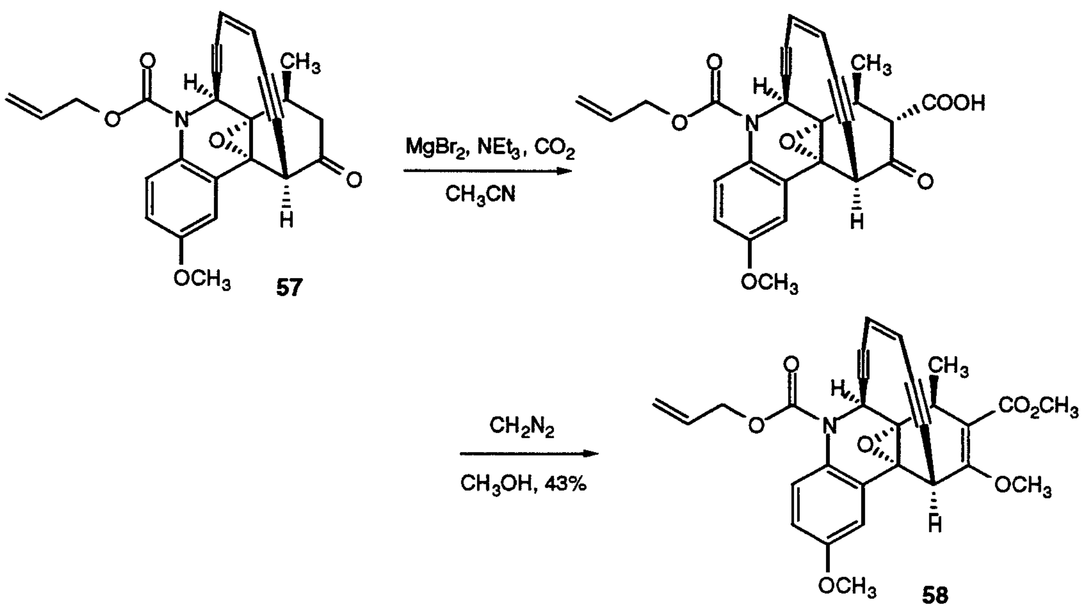
^{1}H NMR (400 MHz, C_6D_6), δ:	7.85 (d, 1H, *J* = 2.7 Hz, *m*-aryl), 7.26 (br s, 1H, *o*-aryl), 6.66 (dd, 1H, *J* = 8.8, 2.7 Hz, *m*-aryl), 6.06 (br s, 1H, NC**H**), 5.66 (m, 1H, CH_2=C**H**), 5.10 (br d, 1H, *J* = 17.3 Hz, **C**H_2=CH), 4.95 (dd, 1H, *J* = 10.0, 1.5 Hz, HCC≡CC**H**=CH), 4.95 (br d, 1H, *J* = 10.5 Hz, **C**H_2=CH), 4.91 (d, 1H, *J* = 10.0 Hz, HCC≡CCH=C**H**), 4.81 (d, 1H, *J* = 6.8 Hz, OC=C**H**), 4.52 (m, 2H, **C**H_2O), 3.25 (s, 3H, OCH_3), 2.72 (p, 1H, *J* = 7.3 Hz, CH_3C**H**), 0.93 (d, 3H, *J* = 7.3 Hz, CH_3).
FTIR (neat), cm^{-1}:	3082 (w), 3056 (w), 2956 (m), 2837 (w), 2280 (w, C≡C), 2195 (w, C≡C), 1722 (sh, C=S), 1714 (vs, C=O), 1651 (w), 1614 (w), 1584 (w), 1505 (s), 1455 (m), 1391 (s), 1340 (vs), 1224 (m), 1174 (m), 1155 (m), 1097 (s), 1056 (m), 1037 (m).
HRMS (FAB):	Calcd for $C_{26}H_{19}O_6NSNa$ $[M+Na]^+$: 496.0831 Found: 496.0824
TLC (40% EtOAc-hexanes), R_f:	**56**: 0.37 **55**: 0.36



Allyl (6*S*, 6a*S*, 7*S*, 10*S*, 10a*R*, 14*Z*)-2-methoxy-7,8,9,10-tetrahydro-7-methyl-9-oxo-6a,10a-epoxy-6,10-[3]hexene[1,5]diynophenanthridine-5(6*H*)-carboxylate (57)

Tributyltin hydride (16 μL, 0.059 mmol, 1.7 equiv) and azobis(isobutyronitrile) (5 mg, 30 μmol, 0.8 equiv) were added sequentially to a solution of allyl (6*S*, 6a*S*, 7*S*, 10*S*, 10a*S*, 14*Z*)-2-methoxy-7,10-dihydro-9,10-dihydroxy-7-methyl-6a,10a-epoxy-6,10-[3]hexene[1,5]diynophenanthridine-5(6*H*)-carboxylate, cyclic thiocarbonate (**56**, 17 mg, 0.036 mmol, 1 equiv) in toluene (2 mL). The resulting solution was heated at 70 °C for 10 min. The product solution was allowed to cool to 23 °C, and the volatiles were removed in vacuo. The residue was purified by flash column chromatography (2% ethyl acetate in dichloromethane) to furnish allyl (6*S*, 6a*S*, 7*S*, 10*S*, 10a*R*, 14*Z*)-2-methoxy-7,8,9,10-tetrahydro-7-methyl-9-oxo-6a,10a-epoxy-6,10-[3]hexene[1,5]diynophenanthridine-5(6*H*)-carboxylate (**57**) as a colorless oil (9 mg, 60%).

^1H NMR (400 MHz, C_6D_6), δ:	7.31 (br s, 1H, *o*-aryl), 6.90 (d, 1H, *J* = 2.7 Hz, *m*-aryl), 6.60 (dd, 1H, *J* = 8.8, 2.7 Hz, *m*-aryl), 6.04 (br s, 1H, NC**H**), 5.67 (m, 1H, CH_2=C**H**), 5.11 (br d, 1H, *J* = 17.7 Hz, C**H**$_2$=CH), 5.05 (dd, 1H, *J* = 10.0, 1.5 Hz, CH=C**H**), 5.02 (dd, 1H, *J* = 10.0, 1.5 Hz, C**H**=CH), 4.95 (br d, 1H, *J* = 10.3 Hz, C**H**$_2$=CH), 4.54, (m, 2H, C**H**$_2$O), 4.13 (br s, 1H, C≡CC**H**), 3.20 (s, 3H, OC**H**$_3$), 2.62 (dd, 1H, *J* = 16.6, 8.1 Hz, C**H**$_2$), 2.53 (m, 1H, C**H**CH_3), 2.15 (dd, 1H, *J* = 16.6, 2.7 Hz, C**H**$_2$), 1.15 (d, 3H, *J* = 7.3 Hz, C**H**$_3$CH).
FTIR (neat), cm^{-1}:	3089 (w), 3054 (w), 2959 (m), 2838 (w), 2280 (w, C≡C), 2194 (w, C≡C), 1714 (vs, C=O), 1650 (w), 1614 (w), 1586 (w), 1505 (s), 1455 (m), 1392 (s), 1275 (vs), 1224 (w), 1207 (w), 1173 (m), 1137 (m), 1096 (m), 1063 (w), 1043 (m), 1023 (m).
HRMS (FAB):	Calcd for $C_{25}H_{21}O_5NNa$ $[M+Na]^+$: 438.1317 Found: 438.1315
TLC (40% EtOAc-hexanes), R_f:	**57**: 0.39 **56**: 0.37



57

58

Vinylogous Methyl Carbonate 58

Triethylamine (70 µL, 0.050 mmol, 12 equiv) was added to a solution of allyl (6*S*, 6a*S*, 7*S*, 10*S*, 10a*R*, 14*Z*)-2-methoxy-7,8,9,10-tetrahydro-7-methyl-9-oxo-6a,10a-epoxy-6,10-[3]hexene[1,5]diynophenanthridine-5(6*H*)-carboxylate (**57**, 18 mg, 43 µmol, 1 equiv) and magnesium bromide (44 mg, 240 µmol, 5.5 equiv) in acetonitrile (2 mL) at 23 °C under an atmosphere of carbon dioxide. After stirring for 15 min at 23 °C, the cloudy, light yellow mixture was diluted with water (15 mL) and acidified to pH 2 with an aqueous hydrochloric acid solution (1% v/v, ca. 5 mL). The resulting aqueous mixture was extracted with ethyl acetate (2 x 20 mL), and the combined organic layers were dried over sodium sulfate and were concentrated, leaving the carboxylic acid as a light yellow oil (18 mg). A solution of diazomethane in diethyl ether (ca. 0.3 M) was added to a solution of the unpurified carboxylic acid in anhydrous methanol at 23 °C until the reaction solution maintained a yellow color and gas evolution ceased. The reaction mixture was allowed to stir open to the atmosphere for 1 h (the product solution became colorless over this period of time). The product solution was concentrated, and the residue was purified by flash column chromatography (40% ethyl acetate in hexanes) to provide the vinylogous methyl carbonate **58** as a colorless oil (9 mg, 43%)

Carboxylic acid:

^{1}H NMR (400 MHz, C_6D_6), δ:	13.07 (s, 1H, C=CO**H**), 7.29 (br s, 1H, *o*-aryl), 6.95 (br s, 1H, *m*-aryl), 6.62 (dd, 1H, *J* = 8.8, 2.7 Hz, *m*-aryl), 6.10 (br s, 1H, NC**H**), 5.69 (m, 1H, CH_2=C**H**), 5.12 (br d, 1H, *J* = 17.0 Hz, C**H**$_2$=CH), 5.10 (dd, 1H, *J* = 11.2, 1.2 Hz, C≡CC**H**=C), 5.06 (dd, 1H, *J* = 11.2, 1.2 Hz, C≡CC**H**=C), 4.95 (br d, 1H, *J* = 9.8 Hz, C**H**$_2$=CH), 4.62 (m, 2H, C**H**$_2$O), 4.24 (br s, 1H, C≡CC**H**), 3.97 (br m, 1H, C**H**CH_3), 3.21 (s, 3H, OCH_3), 1.55 (br d, 3H, *J* = 7.3 Hz).
FTIR (neat), cm^{-1}:	3700-2370 (br m, COOH), 2959 (m), 2280 (w, C≡C), 2195 (w, C≡C), 1770-1560 (br vs, C=O), 1505 (s), 1454 (m), 1393 (s), 1300 (s), 1275 (s), 1229 (m), 1203 (m), 1101 (m), 1050 (m), 1019 (m).
TLC (ethyl acetate), R_f:	Carboxylic acid: 0.18

Vinylogous methyl carbonate 58:

^{1}H NMR (300 MHz, C_6D_6), δ: 7.37 (br s, 1H, *o*-aryl), 7.13 (d, 1H, *J* = 2.8 Hz, *m*-aryl), 6.59 (dd, 1H, *J* = 8.8, 2.8 Hz, *m*-aryl), 6.19 (br s, 1H, NC**H**), 5.68 (m, 1H, CH_2=C**H**), 5.12 (dd, 1H, *J* = 10.0, 1.6 Hz, C≡CC**H**=C), 5.12 (br d, 1H, *J* = 17.2 Hz, C**H**$_2$=CH), 5.06 (dd, 1H, *J* = 10.0, 1.6 Hz, C≡CC**H**=C), 4.94 (br d, 1H, *J* = 10.5 Hz, C**H**$_2$=CH), 4.55 (m, 2H, C**H**$_2$O), 4.09 (br s, 1H, C≡CC**H**), 3.98 (br q, 1H, *J* = 7.0 Hz, C**H**CH_3), 3.49 (s, 3H, OC**H**$_3$), 3.43 (s, 3H, OC**H**$_3$), 3.25 (s, 3H, OC**H**$_3$), 1.47 (br d, 3H, *J* = 7.2 Hz, C**H**$_3$CH).

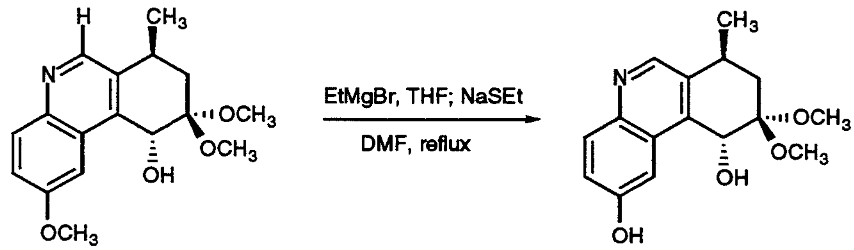
FTIR (neat), cm^{-1}: 2948 (s), 2839 (w), 2192 (w, C≡C), 1714 (vs, C=O), 1651 (m), 1622 (m), 1584 (m), 1505 (s), 1463 (m), 1385 (m), 1360 (m), 1319 (m), 1300 (m), 1275 (s), 1229 (m), 1208 (m), 1155 (s), 1097 (m), 1053 (m), 1037 (m), 1019 (m).

HRMS (FAB): Calcd for $C_{28}H_{25}O_7N$ [M]$^+$: 487.1631

Found: 487.1626

TLC (40% EtOAc-hexanes), R_f: **58**: 0.30

57: 0.39

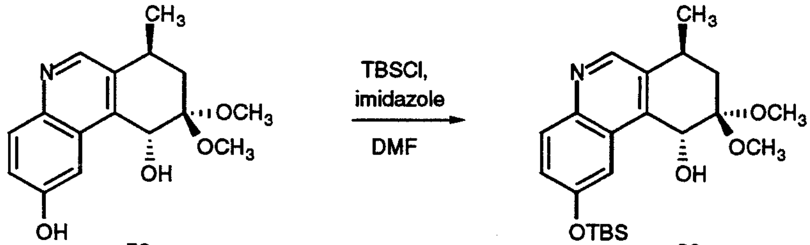


43 **59**

(7*S*, 10*R*)-7,8,9,10-Tetrahydro-9,9-dimethoxy-7-methyl-2,10-phenanthridinediol (59)

A solution of ethylmagnesium bromide in tetrahydrofuran (1.0 M, 8.90 mL, 8.90 mmol, 1.10 equiv) was added by syringe to a solution of (7*S*, 10*R*)-7,8,9,10-tetrahydro-2,9,9-trimethoxy-7-methyl-10-phenanthridinol (**43**, 2.46 g, 8.10 mmol, 1 equiv) in tetrahydrofuran (5 mL) at –78 °C. The reaction flask was transferred to an ice bath for 10 min, then was cooled to –78 °C. A 100-mL flame-dried Schlenk-type flask was charged with sodium hydride (1.17 g, 48.7 mmol, 6.00 equiv) and *N,N*-dimethylformamide (20 mL) was added slowly over 5 min. The resulting slurry was cooled to 0 °C and ethanethiol (1.80 mL, 24.3 mmol, 3.00 equiv) was added dropwise over 15 min by syringe, causing a vigorous exotherm. After the exotherm had subsided, the slurry was warmed to 23 °C and was stirred at that temperature for 10 min. The tetrahydrofuran solution of the magnesium alkoxide prepared above was added to the slurry via cannula over 5 min. Tetrahydrofuran was then removed in vacuo and the reaction mixture was heated at reflux for 1.5 h. The resulting thick brown slurry was cooled to 23 °C and was partitioned between saturated aqueous ammonium chloride solution (500 mL) and ethyl acetate (500 mL). The aqueous layer was separated and extracted further with ethyl acetate (500 mL) then 20% methanol in dichloromethane (500 mL). The aqueous layer was neutralized by the addition of aqueous hydrochloric acid solution (1% v/v, 400 mL) and was extracted with ethyl acetate (2 x 500 mL). The combined organic layers were dried over sodium sulfate and were concentrated in vacuo. The residue was purified by flash column chromatography (2.5% methanol in dichloromethane initially, grading to 5% methanol in dichloromethane) to afford (7*S*, 10*R*)-7,8,9,10-tetrahydro-9,9-dimethoxy-7-methyl-2,10-phenanthridinediol (**59**) as a yellow solid (1.66 g, 71%).

^1H NMR (300 MHz, $CDCl_3$) δ:	8.64 (s, 1H, N=CH), 7.95 (d, 1H, *J* = 9.1 Hz, *o*-aryl), 7.55 (d, 1H, *J* = 2.7 Hz, *m*-aryl), 7.25 (dd, 1H, *J* = 9.1, 2.7 Hz, *m*-aryl), 5.16 (m, 1H, CHOH), 3.44 (s, 3H, OCH_3), 3.30 (s, 3H, OCH_3), 3.25 (m, 1H, CH_3CH), 2.29 (dd, 1H, *J* = 14.2, 6.5 Hz, CH_2), 1.88 (m, 1H, CH_2), 1.46 (d, 3H, *J* = 7.3 Hz, $CHCH_3$).
FTIR (neat), cm^{-1}:	3200 (br, OH), 2933 (m), 1621 (m), 1506 (m), 1455 (m), 1435 (m), 1228 (m), 1130 (m), 1069 (m).
TLC (5% MeOH-CH_2Cl_2), R_f:	**59**: 0.39 (yellow by long-wave UV) **43**: 0.54 (UV)

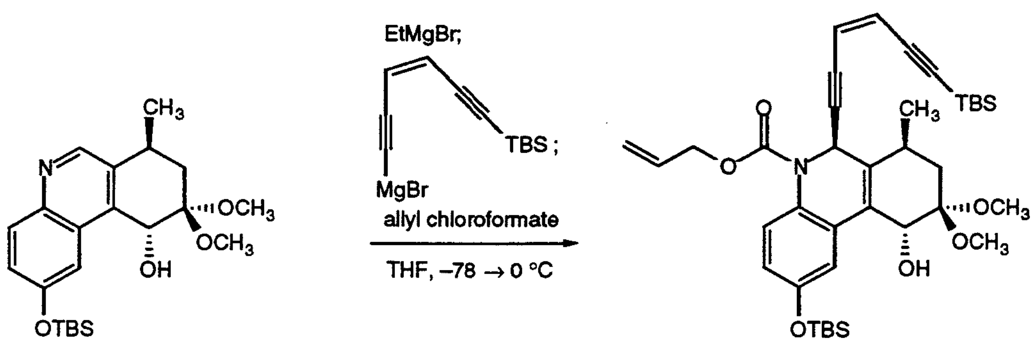


59 60

(7*S*, 10*R*)-2-(*tert*-Butyldimethylsiloxy)-7,8,9,10-tetrahydro-9,9-dimethoxy-7-methyl-10-phenanthridinol (60)

Imidazole (1.01 g, 14.8 mmol, 2.60 equiv) and *t*-butyldimethylsilyl chloride (1.11 g, 7.39 mmol, 1.30 equiv) were added sequentially to a solution of (7*S*, 10*R*)-7,8,9,10-tetrahydro-9,9-dimethoxy-7-methyl-2,10-phenanthridinediol (**59**, 1.64 g, 5.69 mmol, 1 equiv) in *N*,*N*-dimethylformamide (10 mL) at 23 °C. After stirring for 1 h at 23 °C, the reaction mixture was partitioned between water (100 mL) and ethyl acetate (100 mL). The aqueous layer was separated and extracted further with two 100-mL portions of ethyl acetate. The combined organic layers were dried over sodium sulfate and were concentrated. The residue was purified by flash column chromatography (30% ethyl acetate in hexanes) to afford (7*S*, 10*R*)-2-(*tert*-butyldimethylsiloxy)-7,8,9,10-tetrahydro-9,9-dimethoxy-7-methyl-10-phenanthridinol (**60**) as a light yellow foam (2.10 g, 91%).

^{1}H NMR (400 MHz, C_6D_6) δ:	8.74 (s, 1H, N=C**H**), 8.34 (d, 1H, *J* = 9.0 Hz, *o*-aryl), 8.03 (d, 1H, *J* = 2.7 Hz, *m*-aryl), 7.25 (dd, 1H, *J* = 9.0, 2.7 Hz, *m*-aryl), 5.22 (br d, 1H, *J* = 5.9 Hz, C**H**OH), 3.07 (s, 3H, OC**H**$_3$), 3.06 (s, 3H, OC**H**$_3$), 2.75 (m, 1H, CH_3C**H**), 2.70 (br d, 1H, *J* = 5.9 Hz, O**H**), 2.09 (dd, 1H, *J* = 14.2, 6.4 Hz, C**H**$_2$), 1.58 (ddd, 1H, *J* = 14.2, 5.1, 1.0 Hz, C**H**$_2$), 1.20 (d, 3H, *J* = 7.3 Hz, CHC**H**$_3$) 1.07 (s, 9H, (C**H**$_3$)$_3$CSi), 0.29 (s, 3H, (C**H**$_3$)$_2$Si), 0.26 (s, 3H, (C**H**$_3$)$_2$Si).
FTIR (neat), cm^{-1}:	3177 (br OH), 2961 (s), 2930 (s), 2857 (m), 1613 (s), 1504 (s), 1463 (m), 1427 (m), 1262 (s), 1225 (s), 1122 (s), 1071 (s).
HRMS (FAB):	Calcd for $C_{22}H_{34}NO_4Si$ $[MH]^+$: 404.2257 Found: 404.2242
TLC (40% hexanes-EtOAc), R_f:	**60**: 0.35 (UV) **59**: 0.08 (UV)



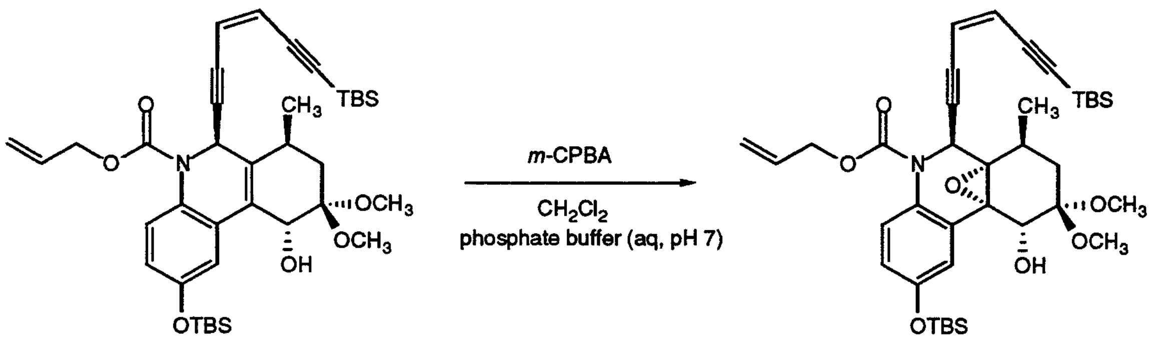
60 61

Allyl (6*S*, 7*S*, 10*R*)-2-(*tert*-Butyldimethylsiloxy)-6-[(*Z*)-6-(*tert*-butyldimethylsilyl)-3-hexene-1,5-diynyl]-7,8,9,10-tetrahydro-10-hydroxy-9,9-dimethoxy-7-methyl-5(6*H*)-phenanthridinecarboxylate (61)

A solution of ethylmagnesium bromide in tetrahydrofuran (1.0 M, 13.6 mL, 13.6 mmol, 0.901 equiv) was added to a solution of (7*S*, 10*R*)-2-(*tert*-butyldimethylsiloxy)-7,8,9,10-tetrahydro-9,9-dimethoxy-7-methyl-10-phenanthridinol (**60**, 6.10 g, 15.1 mmol, 1 equiv) in tetrahydrofuran (30 mL) at –78 °C. The mixture was stirred in an ice bath for 10 min, then was cooled to –78 °C. In a separate flask, a solution of ethylmagnesium bromide in tetrahydrofuran (1.0 M, 22.7 mL, 22.7 mmol, 1.50 equiv) was added to a solution of *tert*-butyl[(*Z*)-3-hexene-1,5-diynyl]dimethylsilane (5.75 g, 30.2 mmol, 2.00 equiv) in tetrahydrofuran (20 mL) at 0 °C. The resulting solution was warmed to 23 °C, then was heated briefly to reflux with a heat gun. After the mixture had cooled to 23 °C, it was transferred via cannula over 3 min to the cold solution (–78 °C) of magnesium alkoxide derived from the TBS quinoline. Allyl chloroformate (2.60 mL, 24.5 mmol, 1.62 equiv) was added, and the solution warmed to 0 °C and stirred at that temperature for 2 h. The reaction mixture was partitioned between aqueous phosphate buffer solution (pH 7, 0.05 M in sodium hydrogen phosphate and 0.05 M in potassium dihydrogen phosphate, 150 mL) and ethyl acetate (150 mL). The aqueous layer was separated and extracted further with ethyl acetate (2 x 150 mL). The combined organic layers were dried over sodium sulfate and were concentrated. The residue was purified by flash column chromatography (10% ethyl acetate in hexanes initially, grading to 20% ethyl acetate in hexanes) to afford allyl (6*S*, 7*S*, 10*R*)-2-(*tert*-butyldimethylsiloxy)-6-[(*Z*)-6-(*tert*-butyldimethylsilyl)-3-hexene-1,5-diynyl]-7,8,9,10-tetrahydro-10-hydroxy-9,9-dimethoxy-7-methyl-5(6*H*)-phenanthridinecarboxylate (**61**) as a light yellow foam (9.16 g, 89%).

^{1}H NMR (300 MHz, $CDCl_3$), δ: 7.36 (br s, 1H, *o*-aryl), 6.93 (d, 1H, J = 2.7 Hz, *m*-aryl), 6.70 (dd, 1H, J = 8.8, 2.6 Hz, *m*-aryl), 5.95 (m, 1H, CH_2=C**H**), 5.90 (br s, 1H, NC**H**), 5.71 (d, 1H, J = 11.1 Hz, SiC≡C-C**H**=CH), 5.61 (dd, 1H, J = 11.1, 1.9 Hz, CC≡C-CH=C**H**), 5.35 (br d, 1H, J = 17.5 Hz, C**H**$_2$=CH), 5.22 (br d, 1H, J = 10.5 Hz, C**H**$_2$=CH), 4.77 (br dd, 1H, J = 16.5, 5.4 Hz, C**H**$_2$O), 4.72 (dd, 1H, J = 8.5, 2.0 Hz, C**H**OH), 4.62 (br m, 1H, C**H**$_2$O), 3.43 (s, 3H, OC**H**$_3$), 3.34 (s, 3H, OC**H**$_3$), 2.59 (m, 1H, C**H**CH_3), 2.37 (br m, 1H, O**H**), 2.14 (dd, 1H, J = 14.2, 5.2 Hz, C**H**$_2$), 1.61 (dd, 1H, J = 14.3, 8.3 Hz, C**H**$_2$), 1.31 (d, 3H, J = 7.2 Hz, C**H**$_3$CH), 0.99 (s, 9H, OSiC(C**H**$_3$)$_3$), 0.96 (s, 9H, C≡CSiC(C**H**$_3$)$_3$), 0.22 (s, 3H, OSi(C**H**$_3$)$_2$), 0.21 (s, 3H, OSi(C**H**$_3$)$_2$), 0.14 (s, 6H, C≡CSi(C**H**$_3$)$_2$).

FTIR (neat), cm^{-1}:	3472 (br, OH), 2954 (s), 2932 (s), 2887 (m), 2858 (s), 2249 (w, C≡C), 2144 (w, C≡C), 1700 (vs, NC=O), 1648 (m), 1607 (m), 1574 (m), 1495 (s), 1471 (m), 1392 (m), 1362 (w), 1318 (m), 1284 (s), 1255 (s), 1209 (m), 1136 (m), 1084 (m), 1051 (m), 967 (m), 931 (m), 911 (m), 860 (m), 838 (s), 778 (m), 735 (m).
HRMS (FAB):	Calcd for $C_{38}H_{55}NO_6Si_2$ $[M]^+$: 677.3568 Found: 677.3575
TLC (20% EtOAc-hexanes), R_f:	**61**: 0.22 (UV) *tert*-butyl[(*Z*)-3-hexene-1,5-diynyl]dimethylsilane: 0.65 (UV)



Allyl (6*S*, 6a*S*, 7*S*, 10*R*, 10a*S*)-2-(*tert*-Butyldimethylsiloxy)-6-[(*Z*)-6-(*tert*-butyldimethylsilyl)-3-hexene-1,5-diynyl]-7,8,9,10-tetrahydro-10-hydroxy-9,9-dimethoxy-7-methyl-6a,10a-epoxyphenanthridine-5(6*H*)-carboxylate (62)

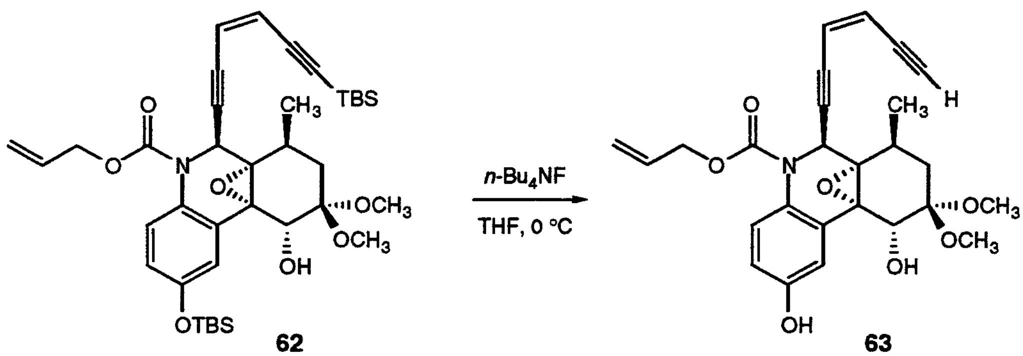
m-Chloroperoxybenzoic acid (55%, 1.04 g, 3.31 mmol, 2.08 equiv) was added to a biphasic solution of allyl (6*S*, 7*S*, 10*R*)-2-(*tert*-butyldimethylsiloxy)-6-[(*Z*)-6-(*tert*-butyldimethylsilyl)-3-hexene-1,5-diynyl]-7,8,9,10-tetrahydro-10-hydroxy-9,9-dimethoxy-7-methyl-5(6*H*)-phenanthridinecarboxylate (**61**, 1.08 g, 1.59 mmol, 1 equiv) in dichloromethane (50 mL) and aqueous phosphate buffer (pH 7, 0.05 M in sodium hydrogen phosphate and 0.05 M in potassium dihydrogen phosphate, 50 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 18 h. A second portion of 55% *m*-chloroperoxybenzoic acid (614 mg, 1.96 mmol, 1.23 equiv) was added and the reaction mixture was stirred at 0 °C for another 5 h. A final portion of 55% *m*-chloroperoxybenzoic acid (459 mg, 1.46 mmol, 0.918 equiv) was added at this point and the reaction mixture was stirred at 0 °C for 3.5 h. The product solution was poured into 1:1 mixture of a saturated aqueous sodium bicarbonate solution and saturated aqueous sodium thiosulfate solution (400 mL). The aqueous layer was separated and extracted further with dichloromethane (2 x 100 mL). The combined organic layers were dried over sodium sulfate and were concentrated. The residue was purified by flash column chromatography (20% ethyl acetate in hexanes) to provide allyl (6*S*, 6a*S*, 7*S*, 10*R*, 10a*S*)-2-(*tert*-butyldimethylsiloxy)-6-[(*Z*)-6-(*tert*-butyldimethylsilyl)-3-hexene-1,5-diynyl]-7,8,9,10-tetrahydro-10-hydroxy-9,9-dimethoxy-7-methyl-6a,10a-epoxyphenanthridine-5(6*H*)-carboxylate (**62**) as a yellow foam (967 mg, 88%).

^1H NMR (400 MHz, $CDCl_3$), δ: 7.23 (d, 1H, J = 2.7 Hz, *m*-aryl), 7.13 (br d, 1H, J = 8.6 Hz, *o*-aryl), 6.76 (dd, 1H, J = 8.6, 2.7 Hz, *m*-aryl), 5.87 (m, 1H, CH_2=C**H**), 5.83 (br s, 1H, NC**H**), 5.74 (d, 1H, J = 11.2 Hz, HC≡CCH=C**H**), 5.53 (br d, 1H, J = 11.2 Hz, HC≡CC**H**=CH), 5.21 (br d, 1H, J = 17.5 Hz, C**H**$_2$=CH), 5.14 (br d, 1H, J = 10.2 Hz, C**H**$_2$=CH), 4.68 (br dd, 1H, J = 13.6, 5.2 Hz, C**H**$_2$O), 4.64 (d, 1H, J = 11.0 Hz, C**H**OH), 4.50 (br dd, 1H, J = 13.6 Hz, 5.2 Hz, C**H**$_2$O), 3.41 (s, 3H, OC**H**$_3$), 3.28 (s, 3H, OC**H**$_3$), 2.92 (br d, 1H, J = 11.0 Hz, O**H**), 2.34 (m, 1H, C**H**CH_3), 1.96 (dd, 1H, J = 14.6, 4.4 Hz, C**H**$_2$), 1.50 (dd, 1H, J = 14.6, 11.0 Hz, C**H**$_2$), 1.46 (d, 3H, J = 7.6 Hz, C**H**$_3$), 0.99 (s, 9H, (C**H**$_3$)$_3$CSiO), 0.96 (s, 9H, (C**H**$_3$)$_3$CSiC≡C), 0.24 (s, 3H, (C**H**$_3$)$_2$SiO), 0.22 (s, 3H, (C**H**$_3$)$_2$SiO), 0.14 (s, 6H, (C**H**$_3$)$_2$SiC≡C).

FTIR (neat), cm^{-1}: 3554 (sh w, OH), 3475 (br, w, OH), 2953 (m), 2857 (w), 2255 (w, C≡C), 2140 (w, C≡C), 1712 (vs, NC=O,), 1648 (w), 1612 (w), 1580 (w), 1502 (s), 1463 (m), 1391 (s), 1280 (s), 1251 (s), 1203 (m), 1158 (m), 1135 (m), 1084 (m), 1053 (m), 994 (w), 969 (m), 922 (w), 899 (w), 862 (m), 838 (m), 810 (w), 778 (m), 736 (m), 678 (w).

HRMS (FAB): Calcd for $C_{38}H_{55}NO_7Si_2$ $[M]^+$: 693.3517
Found: 693.3487

TLC (20% EtOAc-hexanes), R_f: **62**: 0.23 (UV)
61: 0.22 (UV)



Allyl (6*S*, 6a*S*, 7*S*, 10*R*, 10a*S*)-6-[(*Z*)-3-Hexene-1,5-diynyl]-7,8,9,10-tetrahydro-2,10-dihydroxy-9,9-dimethoxy-7-methyl-6a,10a-epoxyphenanthridine-5(6*H*)-carboxylate (63)

A solution of tetrabutylammonium fluoride in tetrahydrofuran (1.0 M, 9.50 mL, 9.50 mmol, 2.00 equiv) was added to a solution of allyl (6*S*, 6a*S*, 7*S*, 10*R*, 10a*S*)-2-(*tert*-butyldimethylsiloxy)-6-[(*Z*)-6-(*tert*-butyldimethylsilyl)-3-hexene-1,5-diynyl]-7,8,9,10-tetrahydro-10-hydroxy-9,9-dimethoxy-7-methyl-6a,10a-epoxyphenanthridine-5(6*H*)-carboxylate (**62**, 3.30 g, 4.75 mmol, 1 equiv) in tetrahydrofuran (100 mL) at 0 °C. After stirring at 0 °C for 10 min, the product solution was partitioned between aqueous phosphate buffer solution (pH 7, 0.05 M in sodium hydrogen phosphate and 0.05 M in potassium dihydrogen phosphate, 150 mL) and dichloromethane (150 mL). The aqueous layer was separated and extracted further with dichloromethane (2 x 150 mL). The combined organic layers were dried over sodium sulfate and were concentrated. The residue was purified by flash column chromatography (60% ethyl acetate in hexanes) to afford allyl (6*S*, 6a*S*, 7*S*, 10*R*, 10a*S*)-6-[(*Z*)-3-hexene-1,5-diynyl]-7,8,9,10-tetrahydro-2,10-dihydroxy-9,9-dimethoxy-7-methyl-6a,10a-epoxyphenanthridine-5(6*H*)-carboxylate (**63**) as a yellow foam (2.21 g, 100%).

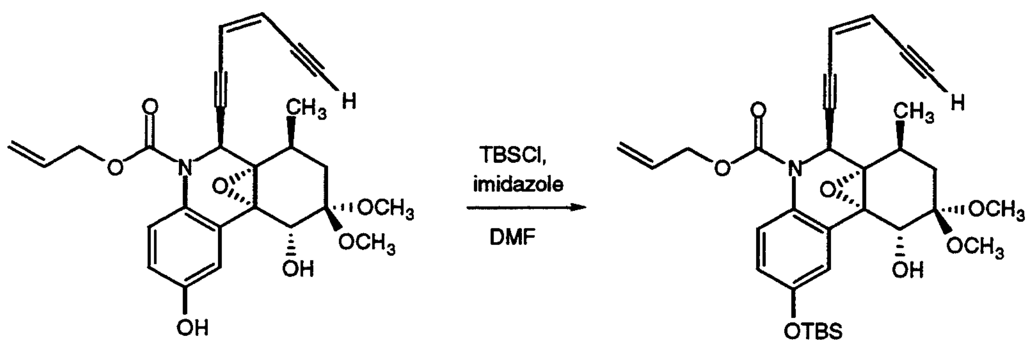
^{1}H NMR (400 MHz, $CDCl_3$), δ:	7.25 (d, 1H, *J* = 2.7 Hz, *m*-aryl), 7.16 (br d, 1H, *J* = 8.6 Hz, *o*-aryl), 6.77 (dd, 1H, *J* = 8.6, 2.7 Hz, *m*-aryl), 5.87 (s, 1H, aryl **OH**), 5.84 (m, 1H, CH_2=C**H**), 5.84 (br s, 1H, NC**H**), 5.68 (br s, 2H, C**H**=C**H**), 5.21 (br d, 1H, *J* = 17.1 Hz, C**H**$_2$=CH), 5.15 (br d, 1H, *J* = 10.5 Hz, C**H**$_2$=CH), 4.69 (br obscured, 1H, C**H**$_2$O), 4.69 (d, 1H, *J* = 11.0 Hz, C**H**OH), 4.52 (br dd, 1H, *J* = 13.7, 4.4 Hz, C**H**$_2$O), 3.38 (s, 3H, OC**H**$_3$), 3.25 (s, 3H, OC**H**$_3$), 3.18 (br d, 1H, *J* = 11.0 Hz, O**H**), 3.16 (d, 1H, *J* = 1.5 Hz, **H**C≡C), 2.32 (m, 1H, CH_3C**H**), 1.95 (dd, 1H, *J* = 14.5, 4.0 Hz, C**H**$_2$), 1.56 (dd, 1H, *J* = 14.5, 11.9 Hz, C**H**$_2$), 1.46 (d, 3H, *J* = 7.6 Hz, C**H**$_3$).
FTIR (neat), cm^{-1}:	3395 (br s, OH), 3297 (m, C≡CH), 2949 (m), 2838 (w), 2252 (w, C≡C), 2094 (w, C≡C), 1694 (vs, NC=O), 1651 (w), 1614 (w), 1591 (w), 1505 (s), 1462 (m), 1455 (m), 1393 (s), 1318 (s), 1298 (s), 1237 (m), 1202 (m), 1162 (m), 1136 (m), 1084 (m), 1052 (m), 995 (w), 958 (m), 914 (m), 868 (w), 810 (w) 736 (s).

HRMS (FAB): Calcd for $C_{26}H_{27}NO_7$ $[MH]^+$: 465.1788

Found: 465.1794

TLC (40% hexanes-ethyl acetate), R_f: **63**: 0.30 (UV)

62: 0.70 (UV)



63 64

Allyl (6*S*, 6a*S*, 7*S*, 10*R*, 10a*S*)-2-(*tert*-Butyldimethylsiloxy)-6-[(*Z*)-3-hexene-1,5-diynyl]-7,8,9,10-tetrahydro-10-hydroxy-9,9-dimethoxy-7-methyl-6a,10a-epoxyphenanthridine-5(6*H*)-carboxylate (64)

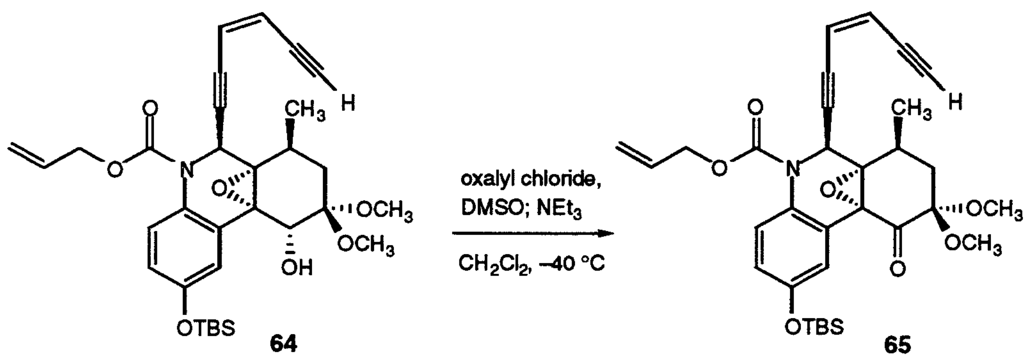
A solution of allyl (6*S*, 6a*S*, 7*S*, 10*R*, 10a*S*)-6-[(Z)-3-hexene-1,5-diynyl]-7,8,9,10-tetrahydro-2,10-dihydroxy-9,9-dimethoxy-7-methyl-6a,10a-epoxyphenanthridine-5(6*H*)-carboxylate (**63**, 6.10 g, 13.1 mmol, 1 equiv) in *N*,*N*-dimethylformamide (80 mL) at 23 °C was treated sequentially with imidazole (2.32 g, 34.1 mmol, 2.60 equiv) and *t*-butyldimethylsilylchloride (2.60 g, 17.0 mmol, 1.30 equiv). After stirring at 23 °C for 1 h, the reaction solution was partitioned between water (300 mL) and ethyl acetate (300 mL). The aqueous layer was separated and extracted further with two 300-mL portions of ethyl acetate. The combined organic layers were dried over sodium sulfate and were concentrated. The residue was purified by flash column chromatography (20% ethyl acetate in hexanes) to provide allyl (6*S*, 6a*S*, 7*S*, 10*R*, 10a*S*)-2-(*tert*-butyldimethylsiloxy)-6-[(*Z*)-3-hexene-1,5-diynyl]-7,8,9,10-tetrahydro-10-hydroxy-9,9-dimethoxy-7-methyl-6a,10a-epoxyphenanthridine-5(6*H*)-carboxylate (**64**) as a yellow foam (7.27 g, 96%).

^1H NMR (400 MHz, $CDCl_3$), δ: 7.24 (d, 1H, J = 2.7 Hz, *m*-aryl), 7.14 (br d, 1H, J = 8.6 Hz, *o*-aryl), 6.77 (dd, 1H, J = 8.6, 2.7 Hz, *m*-aryl), 5.87 (m, 1H, CH_2=C**H**), 5.83 (br s, 1H, NC**H**), 5.70 (dd, 1H, J = 10.0, 1.7 Hz, HC≡CC**H**=CH), 5.66 (br d, 1H, J = 10.0 Hz, HC≡CCH=C**H**), 5.21 (br d, 1H, J = 17.5 Hz, C**H**$_2$=CH), 5.15 (br d, 1H, J = 10.5 Hz, C**H**$_2$=CH), 4.68 (br dd, 1H, J = 13.4, 5.4 Hz, C**H**$_2$O), 4.64 (d, 1H, J = 10.7 Hz, C**H**OH), 4.50 (br d, 1H, J = 13.4 Hz, C**H**$_2$O), 3.42 (s, 3H, OC**H**$_3$), 3.27 (s, 3H, OC**H**$_3$), 3.16 (d, 1H, J = 1.7 Hz, **H**C≡C), 2.94 (br d, 1H, J = 10.7 Hz, O**H**), 2.34 (m, 1H, CH_3C**H**), 1.95 (dd, 1H, J = 14.5, 4.2 Hz, C**H**$_2$), 1.57 (dd, 1H, J = 14.5, 11.5 Hz, C**H**$_2$), 1.47 (d, 3H, J = 7.8 Hz, C**H**$_3$), 0.99 (s, 9H, (C**H**$_3$)$_3$CSi), 0.23 (s, 3H, (C**H**$_3$)$_2$Si), 0.22 (s, 3H, (C**H**$_3$)$_2$Si).

FTIR (neat), cm^{-1}: 3552 (sh w, OH), 3474 (br m, OH), 3298 (m, C≡CH), 2954 (m), 2858 (w), 2252 (w, C≡C), 2090 (w, C≡C), 1711 (vs, NC=O,), 1648 (w), 1611 (w), 1581 (w), 1504 (s), 1463 (m), 1391 (m), 1313 (s), 1280 (s), 1237 (w), 1203 (m), 1162 (m), 1132 (m), 1084 (m), 1052 (m), 994 (w), 969 (m), 922 (w), 899 (w), 862 (m), 840 (m) 782 (m), 735 (m), 625 (w).

HRMS (FAB): Calcd for $C_{32}H_{41}NO_7Si$ $[M]^+$: 579.2652
Found: 579.2633

TLC (20% EtOAc-hexanes), R_f: **64**: 0.25 (UV)
63: 0.05 (UV)

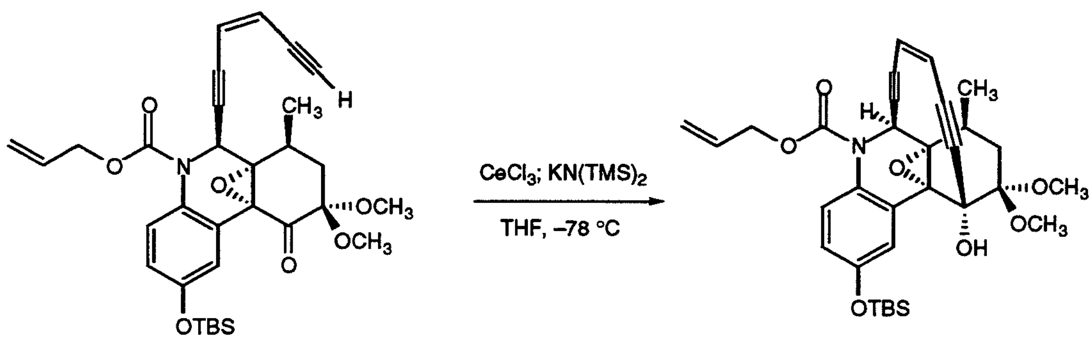


Allyl (6*S*, 6a*S*, 7*S*, 10a*R*)-2-(*tert*-Butyldimethylsiloxy)-6-[(*Z*)-3-hexene-1,5-diynyl]-7,8,9,10-tetrahydro-9,9-dimethoxy-7-methyl-10-oxo-6a,10a-epoxyphenanthridine-5(6*H*)-carboxylate (65)

Dimethyl sulfoxide (4.22 mL, 59.5 mmol, 15.0 equiv) was added to a solution of oxalyl chloride (3.46 mL, 39.7 mmol, 10.0 equiv) in dichloromethane (75 mL) at –78 °C. After stirring at –78 °C for 20 min, a solution of allyl (6*S*, 6a*S*, 7*S*, 10*R*, 10a*S*)-2-(*tert*-butyldimethylsiloxy)-6-[(*Z*)-3-hexene-1,5-diynyl]-7,8,9,10-tetrahydro-10-hydroxy-9,9-dimethoxy-7-methyl-6a,10a-epoxyphenanthridine-5(6*H*)-carboxylate (**64**, 2.30 g, 3.97 mmol, 1 equiv) in dichloromethane (75 mL) was added over 10 min via cannula to the cold reaction solution. The reaction mixture was warmed to –40 °C and was held at that temperature for 10 h. The reaction mixture was then cooled to –78 °C, triethylamine (16.6 mL, 119 mmol, 30.0 equiv) was added, and the resulting solution was stirred in an ice bath for 30 min. The product solution was poured into aqueous phosphate buffer solution (pH 7, 0.05 M in sodium hydrogen phosphate and 0.05 M in potassium dihydrogen phosphate, 150 mL). The aqueous layer was separated and extracted further with dichloromethane (2 x 150 mL). The combined organic layers were dried over sodium sulfate and were concentrated. The residue was purified by flash column chromatography (2% ethyl acetate in dichloromethane initially, grading to 5% ethyl acetate in dichloromethane) to afford allyl (6*S*, 6a*S*, 7*S*, 10a*R*)-2-(*tert*-butyldimethylsiloxy)-6-[(*Z*)-3-hexene-1,5-diynyl]-7,8,9,10-tetrahydro-9,9-dimethoxy-7-methyl-10-oxo-6a,10a-epoxyphenanthridine-5(6*H*)-carboxylate (**65**) as a light brown foam (2.10 g, 92%).

^{1}H NMR (400 MHz, $CDCl_3$), δ: 7.67 (d, 1H, *J* = 2.7 Hz, *m*-aryl), 7.18 (br d, 1H, *J* = 8.6 Hz, *o*-aryl), 6.81 (dd, 1H, *J* = 8.6, 2.7 Hz, *m*-aryl), 5.87 (m, 1H, CH_2=**CH**), 5.83 (br s, 1H, N**CH**), 5.71 (dd, 1H, *J* = 10.0, 1.5 Hz, HC≡C**CH**=CH), 5.67 (dd, 1H, *J* = 10.0, 1.7 Hz, HC≡CCH=**CH**), 5.22 (br d, 1H, *J* = 17.5 Hz, $\mathbf{CH_2}$=CH), 5.17 (br d, 1H, *J* = 10.5 Hz, $\mathbf{CH_2}$=CH), 4.69 (br dd, 1H, *J* = 13.4, 5.4 Hz, $\mathbf{CH_2}$O), 4.56 (br d, 1H, *J* = 13.4 Hz, $\mathbf{CH_2}$O), 3.30 (s, 3H, OCH_3), 3.29 (s, 3H, OCH_3), 3.15 (d, 1H, *J* = 1.5 Hz, **H**C≡C), 2.77 (m, 1H, CH_3**CH**), 2.21 (dd, 1H, *J* = 14.1, 6.2 Hz, $\mathbf{CH_2}$), 1.99 (dd, 1H, *J* = 14.1, 3.2 Hz, $\mathbf{CH_2}$), 1.52 (d, 3H, *J* = 7.3 Hz, $\mathbf{CH_3}$), 0.97 (s, 9H, $(CH_3)_3CSi$), 0.23 (s, 3H, $(CH_3)_2Si$), 0.23 (s, 3H, $(CH_3)_2Si$).

FTIR (neat), cm^{-1}:	3297 (m, C≡CH), 2954 (m), 2858 (w), 2094 (w, C≡C), 1713 (vs, NC=O, C=O), 1649 (w), 1610 (w), 1578 (w), 1495 (s), 1463 (m), 1391 (m), 1312 (s), 1278 (s), 1254 (m), 1215 (m), 1132 (m), 1082 (m), 1039 (m), 981 (m), 939 (m), 880 (s), 840 (m).
TLC (5% EtOAc-CH_2Cl_2), R_f:	**65**: 0.51 (UV) **64**: 0.16 (UV)



65 66

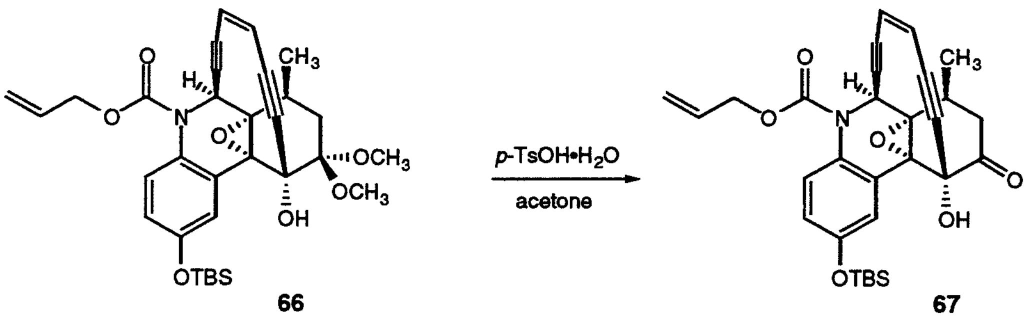
Allyl (6*S*, 6a*S*, 7*S*, 10*R*, 10a*S*, 14*Z*)-2-(*tert*-Butyldimethylsiloxy)-7,8,9,10-tetrahydro-10-hydroxy-9,9-dimethoxy-7-methyl-6a,10a-epoxy-6,10-[3]hexene[1,5]diynophenanthridine-5(6*H*)-carboxylate (66)

A suspension of cerium trichloride (1.70 g, 6.90 mmol, 4.93 equiv) and allyl (6*S*, 6a*S*, 7*S*, 10a*R*)-2-(*tert*-butyldimethylsiloxy)-6-[(*Z*)-3-hexene-1,5-diynyl]-7,8,9,10-tetrahydro-9,9-dimethoxy-7-methyl-10-oxo-6a,10a-epoxyphenanthridine-5(6*H*)-carboxylate (**65**, 810 mg, 1.40 mmol, 1 equiv) in tetrahydrofuran (30 mL) was stirred at 23 °C for 30 min. The suspension was then cooled to –78 °C and a solution of potassium hexamethyldisilylazide in toluene (0.5 M, 4.50 mL, 2.25 mmol, 1.61 equiv) was added dropwise over 5 min causing the yellow suspension to turn light brown, then brown, then dark grayish brown. The reaction flask was transferred to an ice bath and saturated aqueous ammonium chloride solution (150 mL) was added. The biphasic mixture was extracted with ethyl acetate (3 x 150 mL). The combined organic layers were dried over sodium sulfate and were concentrated. The residue was purified by flash column chromatography (25% ethyl acetate in hexanes) to afford allyl (6*S*, 6a*S*, 7*S*, 10*R*, 10a*S*, 14*Z*)-2-(*tert*-butyldimethylsiloxy)-7,8,9,10-tetrahydro-10-hydroxy-9,9-dimethoxy-7-

methyl-6a,10a-epoxy-6,10-[3]hexene[1,5]diynophenanthridine-5(6*H*)-carboxylate (**66**) as a pale yellow foam (761 mg, 94%).

^{1}H NMR (400 MHz, C_6D_6), δ: 8.57 (d, 1H, J = 2.7 Hz, *m*-aryl), 7.31 (br s, 1H, *o*-aryl), 6.83 (dd, 1H, J = 8.8, 2.7 Hz, *m*-aryl), 6.21 (br s, 1H, NC**H**), 5.62 (m, 1H, CH_2=C**H**), 5.17 (d, 1H, J = 10.0 Hz, HCC≡CCH=C**H**), 5.08 (br d, 1H, J = 17.5 Hz, C**H**$_2$=CH), 5.07 (dd, 1H, J = 10.0, 1.7 Hz, HCC≡CC**H**=CH), 4.90 (br d, 1H, J = 10.5 Hz, C**H**$_2$=CH), 4.55 (ddt, 1H, J = 13.7, 5.4, 1.5 Hz, C**H**$_2$O), 4.47 (br dd, 1H, J = 13.7, 5.4 Hz, C**H**$_2$O), 3.49 (s, 1H, O**H**), 3.35 (s, 3H, OC**H**$_3$), 2.95 (s, 3H, OC**H**$_3$), 2.40 (m, 1H, C**H**CH_3), 2.17 (t, 1H, J = 13.9 Hz, C**H**$_2$), 1.87 (dd, 1H, J = 14.7, 5.6 Hz, C**H**$_2$), 1.20 (d, 3H, J = 7.3 Hz, C**H**$_3$CH), 1.06 (s, 9H, (C**H**$_3$)$_3$CSi), 0.30 (s, 3H, (C**H**$_3$)$_2$Si), 0.30 (s, 3H, (C**H**$_3$)$_2$Si).

FTIR (neat), cm^{-1}:	3465 (br m, OH), 3089 (w), 3048 (w), 2943 (s), 2891 (m), 2858 (w), 2280 (w, C≡C), 2192 (w, C≡C), 1705 (vs, NC=O), 1651 (w), 1610 (w), 1581 (w), 1504 (s), 1463 (m), 1392 (m), 1313 (s), 1275 (vs), 1202 (m), 1145 (m), 1110 (m), 1083 (w), 1035 (w), 972 (m), 942 (w), 926 (w), 890 (m), 838 (m), 782 (m), 739 (w).
HRMS (FAB):	Calcd for $C_{32}H_{39}NO_7Si$ $[M]^+$: 577.2496 Found: 577.2527
$[\alpha]_D^{22}$ ($CHCl_3$):	+579.8°, C = 0.48
TLC (20% EtOAc-hexanes), R_f:	**66**: 0.14 (UV) **65**: 0.18 (UV)



Allyl (6*S*, 6a*S*, 7*S*, 10*R*, 10a*S*, 14*Z*)-2-(*tert*-Butyldimethylsiloxy)-7,8,9,10-tetrahydro-10-hydroxy-7-methyl-9-oxo-6a,10a-epoxy-6,10-[3]hexene[1,5]diynophenanthridine-5(6*H*)-carboxylate (67)

A solution of allyl (6*S*, 6a*S*, 7*S*, 10*R*, 10a*S*, 14*Z*)-2-(*tert*-butyldimethylsiloxy)-7,8,9,10-tetrahydro-10-hydroxy-9,9-dimethoxy-7-methyl-6a,10a-epoxy-6,10-[3]hexene[1,5]diynophenanthridine-5(6*H*)-carboxylate (**66**, 5.43 g, 9.40 mmol, 1 equiv) in acetone (300 mL) was stirred with *p*-toluensulfonic acid monohydrate (7.15 g, 37.6 mmol, 4.00 equiv) at 23 °C for 2 h. The reaction solution was partitioned between saturated aqueous sodium bicarbonate solution (300 mL) and ethyl acetate (300 mL). The aqueous layer was separated and extracted further with ethyl acetate (2 x 300 mL). The combined organic layers were dried over sodium sulfate and were concentrated. The residue was purified by flash column chromatography (25% ethyl acetate in hexanes) to afford allyl (6*S*, 6a*S*, 7*S*, 10*R*, 10a*S*, 14*Z*)-2-(*tert*-butyldimethylsiloxy)-7,8,9,10-tetrahydro-10-hydroxy-7-methyl-9-oxo-6a,10a-epoxy-6,10-[3]hexene[1,5]diynophenanthridine-5(6*H*)-carboxylate (**67**) as a pale yellow foam (4.03 g, 81%).

^1H NMR (400 MHz, C_6D_6), δ: 8.51 (d, 1H, J = 2.7 Hz, *m*-aryl), 7.30 (br s, 1H, *o*-aryl), 6.84 (dd, 1H, J = 8.8, 2.7 Hz, *m*-aryl), 6.09 (br s, 1H, NC**H**), 5.61 (m, 1H, CH_2=C**H**), 5.13 (d, 1H, J = 10.0 Hz, HCC≡CCH=C**H**), 5.07 (br d, 1H, J = 17.5 Hz, **C**$\mathbf{H_2}$=CH), 5.07 (br d, 1H, J = 10.0 Hz, HCC≡CC**H**=CH), 4.92 (s, 1H, O**H**), 4.91 (br d, 1H, J = 10.5 Hz, C$\mathbf{H_2}$=CH), 4.54 (dd, 1H, J = 13.7, 5.4 Hz, C$\mathbf{H_2}$O), 4.43 (br dd, 1H, J = 13.7, 5.4 Hz, C$\mathbf{H_2}$O), 2.49 (m, 1H, C**H**CH_3), 2.41 (dd, 1H, J = 15.2, 7.4 Hz, C$\mathbf{H_2}$), 2.34 (dd, 1H, J = 15.2, 8.6 Hz, C$\mathbf{H_2}$), 1.04 (s, 9H, (C$\mathbf{H_3}$)$_3$CSi), 1.03 (d, 3H, J = 7.3 Hz, C$\mathbf{H_3}$CH), 0.28 (s, 3H, (C$\mathbf{H_3}$)$_2$Si), 0.25 (s, 3H, (C$\mathbf{H_3}$)$_2$Si).

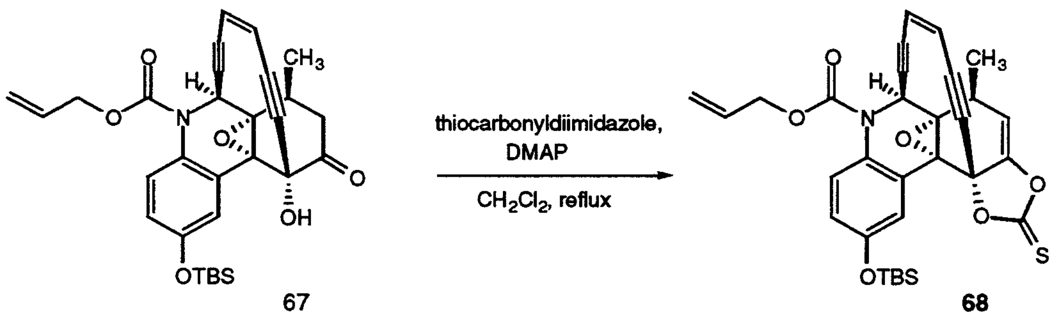
FTIR (neat), cm^{-1}: 3420 (br m, OH), 3085 (w), 3052 (w), 2952 (m), 2931 (m), 2889 (m), 2858 (w), 2280 (w, C≡C), 2187 (w, C≡C), 1714 (vs, NC=O, C=O), 1651 (w), 1611 (w), 1581 (w), 1503 (s), 1463 (m), 1392 (m), 1314 (s), 1274 (vs), 1209 (m), 1180 (w), 1138 (m), 1117 (m), 1084 (w), 1030 (w), 984 (m), 947 (w), 921 (w), 885 (w), 860 (m), 839 (m), 783 (m), 745 (m), 696 (w), 663 (w).

HRMS (FAB): Calcd for $C_{30}H_{33}NO_6Si$ $[M]^+$: 531.2077

Found: 531.2106

TLC (40% EtOAc-hexanes), R_f: **67**: 0.52 (UV)

66: 0.45 (UV)



Allyl (6*S*, 6a*S*, 7*S*, 10*S*, 10a*S*, 14*Z*)-2-(*tert*-Butyldimethylsiloxy)-7,10-dihydro-9,10-dihydroxy-7-methyl-6a,10a-epoxy-6,10-[3]hexene[1,5]diynophenanthridine-5(6*H*)-carboxylate, Cyclic Thiocarbonate (68)

Thiocarbonyldiimidazole (4.19 g, 23.5 mmol, 5.00 equiv) and 4-dimethylaminopyridine (862 mg, 7.05 mmol, 3.00 equiv) were added sequentially to a solution of allyl (6*S*, 6a*S*, 7*S*, 10*R*, 10a*S*, 14*Z*)-2-(*tert*-butyldimethylsiloxy)-7,8,9,10-tetrahydro-10-hydroxy-7-methyl-9-oxo-6a,10a-epoxy-6,10-[3]hexene[1,5]diynophenanthridine-5(6*H*)-carboxylate (**67**, 1.25 g, 2.35 mmol, 1 equiv) in dichloromethane (100 mL) at 23 °C. The reaction mixture was heated to a gentle reflux for 7 h. A second portion of thiocarbonyldiimidazole (838 mg, 4.70 mmol, 2.00 equiv) and 4-dimethylaminopyridine (287 mg, 2.35 mmol, 1 equiv) were added and the reaction mixture was heated to a gentle reflux for an additional 14 h. The reaction mixture was cooled to 23 °C and volatiles were removed in vacuo. The residue was purified by flash column chromatography (30% hexanes in dichloromethane) to afford allyl (6*S*, 6a*S*, 7*S*, 10*S*, 10a*S*, 14*Z*)-2-(*tert*-butyldimethylsiloxy)-7,10-dihydro-9,10-dihydroxy-7-methyl-6a,10a-epoxy-6,10-[3]hexene[1,5]diynophenanthridine-5(6*H*)-carboxylate, cyclic thiocarbonate (**68**) as an off-white foam (1.15 g, 85%).

^1H NMR (400 MHz, C_6D_6), δ: 7.97 (d, 1H, *J* = 2.7 Hz, *m*-aryl), 7.28 (br s, 1H, *o*-aryl), 6.82 (dd, 1H, *J* = 8.8, 2.7 Hz, *m*-aryl), 6.05 (br s, 1H, NC**H**), 5.63 (m, 1H, CH_2=C**H**), 5.08 (br d, 1H, *J* = 17.1 Hz, **C**$\mathbf{H_2}$=CH), 4.98 (dd, 1H, *J* = 10.0, 1.5 Hz, HCC≡CC**H**=CH), 4.94 (d, 1H, *J* = 10.0 Hz, HCC≡CCH=C**H**), 4.94 (br d, 1H, *J* = 10.7 Hz, **C**$\mathbf{H_2}$=CH), 4.79 (d, 1H, *J* = 6.6 Hz, OC=C**H**), 4.53 (br dd, 1H, *J* = 13.7, 5.4 Hz, **C**$\mathbf{H_2}$O), 4.47 (ddt, 1H, *J* = 13.7, 5.4, 1.5 Hz, **C**$\mathbf{H_2}$O), 2.70 (p, 1H, *J* = 7.3 Hz, CH_3C**H**), 1.02 (s, 9H, (**C**$\mathbf{H_3}$)$_3$CSi), 0.92 (d, 3H, *J* = 7.3 Hz, **C**$\mathbf{H_3}$), 0.29 (s, 3H, (**C**$\mathbf{H_3}$)$_2$Si), 0.24 (s, 3H, (**C**$\mathbf{H_3}$)$_2$Si).

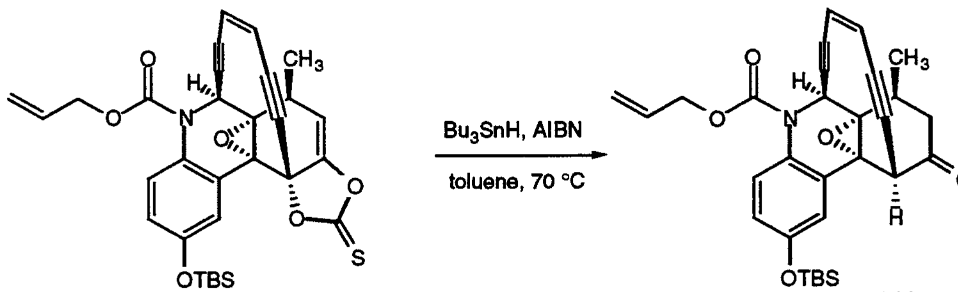
FTIR (neat), cm^{-1}: 3085 (w), 3056 (w), 2955 (m), 2931 (m), 2884 (m), 2858 (w), 2280 (w, C≡C), 2195 (w, C≡C), 1724 (sh, C=O), 1714 (vs, NC=O), 1651 (w), 1614 (w), 1582 (w), 1504 (s), 1455 (m), 1389 (s), 1346 (m), 1333 (m), 1303 (vs), 1275 (vs), 1232 (s), 1190 (m), 1174 (m), 1098 (m), 1050 (m), 1026 (w), 989 (m), 941 (m), 916 (w), 878 (m), 840 (m), 809 (w), 784 (w), 742 (w), 657 (w).

HRMS (FAB): Calcd for $C_{31}H_{31}NO_6SiS$ $[M]^+$: 573.1641

Found: 573.1660

TLC (dichloromethane), R_f: **68**: 0.44 (UV)

67: 0.24 (UV)



68 69

Allyl (6*S*, 6a*S*, 7*S*, 10*S*, 10a*R*, 14*Z*)-2-(*tert*-Butyldimethylsiloxy)-7,8,9,10-tetrahydro-7-methyl-9-oxo-6a,10a-epoxy-6,10-[3]hexene[1,5]diynophenanthridine-5(6*H*)-carboxylate (69)

Tributyltin hydride (722 µL, 2.68 mmol, 1.40 equiv) and azobis(isobutyronitrile) (75.0 mg, 457 µmol, 0.238 equiv) were added sequentially to a solution of allyl (6*S*, 6a*S*, 7*S*, 10*S*, 10a*S*, 14*Z*)-2-(*tert*-butyldimethylsiloxy)-7,10-dihydro-9,10-dihydroxy-7-methyl-6a,10a-epoxy-6,10-[3]hexene[1,5]diynophenanthridine-5(6*H*)-carboxylate, cyclic thiocarbonate (**68**, 1.10 g, 1.92 mmol, 1 equiv) in toluene (75 mL). The resulting pale yellow solution was deoxygenated by three consecutive freeze-pump-thaw cycles. The mixture was then heated at 70 °C for 30 min. The product solution was allowed to cool to 23 °C, and the volatiles were removed in vacuo. The residue was purified by flash column chromatography (dichloromethane initially, then 1% ethyl acetate in dichloromethane) to furnish allyl (6*S*, 6a*S*, 7*S*, 10*S*, 10a*R*, 14*Z*)-2-(*tert*-butyldimethylsiloxy)-7,8,9,10-tetrahydro-7-methyl-9-oxo-6a,10a-epoxy-6,10-[3]hexene[1,5]diynophenanthridine-5(6*H*)-carboxylate (**69**) as an off-white foam (957 mg, 97%).

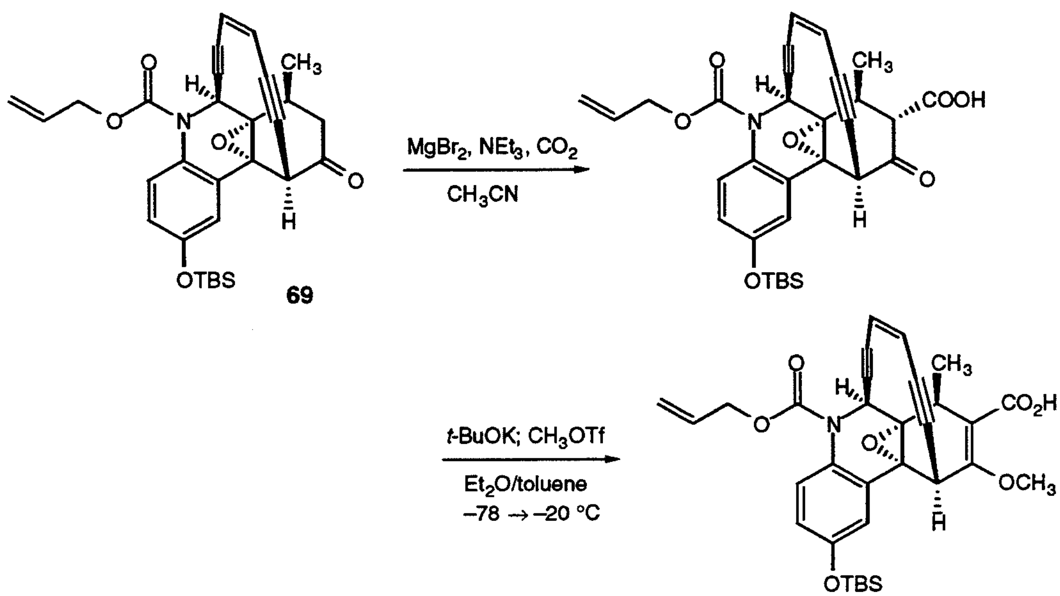
^1H NMR (400 MHz, C_6D_6), δ:	7.30 (br s, 1H, *o*-aryl), 7.00 (d, 1H, *J* = 2.7 Hz, *m*-aryl), 6.76 (dd, 1H, *J* = 8.8, 2.7 Hz, *m*-aryl), 6.01 (br s, 1H, NC**H**), 5.64 (m, 1H, CH_2=C**H**), 5.10 (br d, 1H, *J* = 16.8 Hz, C**H**$_2$=CH), 5.06 (dd, 1H, *J* = 10.0, 1.2 Hz, CH=C**H**), 5.03 (dd, 1H, *J* = 10.0, 1.2 Hz, C**H**=CH), 4.94 (br d, 1H, *J* = 10.2 Hz, C**H**$_2$=CH), 4.56, (ddt, 1H, *J* = 13.7, 5.4, 1.5 Hz, C**H**$_2$O), 4.48 (br dd, 1H, *J* = 13.7, 5.4 Hz, C**H**$_2$O), 4.13 (br s, 1H, C≡CC**H**), 2.61 (dd, 1H, *J* = 16.6, 8.1 Hz, C**H**$_2$), 2.52 (m, 1H, CH_3C**H**), 2.14 (dd, 1H, *J* = 16.6, 2.7 Hz, C**H**$_2$), 1.14 (d, 3H, *J* = 7.3 Hz, C**H**$_3$CH), 0.99 (s, 9H, (C**H**$_3$)$_3$CSi), 0.12 (s, 3H, (C**H**$_3$)$_2$Si), 0.10 (s, 3H, (C**H**$_3$)$_2$Si).
FTIR (neat), cm^{-1}:	3088 (w), 3058 (w), 2956 (m), 2931 (m), 2885 (w), 2858 (w), 2280 (w, C≡C), 2192 (w, C≡C), 1714 (vs, NC=O, C=O), 1650 (w), 1614 (w), 1580 (w), 1504 (s), 1463 (m), 1386 (s), 1313 (s), 1274 (s), 1222 (w), 1203 (w), 1136 (w) 1096 (w), 1027 (w), 986 (m), 943 (m), 895 (w), 840 (s), 782 (w), 742 (w), 668 (w).

HRMS (FAB): Calcd for $C_{30}H_{33}NO_5Si$ $[M]^+$: 515.2128

Found: 515.2119

TLC (dichloromethane), R_f: **69**: 0.21(UV)

68: 0.44 (UV)



69

70

Vinylogous Carbonic Acid 70

Triethylamine (405 μL, 2.91 mmol, 15.0 equiv) was added to a solution of allyl (6*S*, 6a*S*, 7*S*, 10*S*, 10a*R*, 14*Z*)-2-(*tert*-butyldimethylsiloxy)-7,8,9,10-tetrahydro-7-methyl-9-oxo-6a,10a-epoxy-6,10-[3]hexene[1,5]diynophenanthridine-5(6*H*)-carboxylate (**69**, 100 mg, 194 μmol, 1 equiv) and magnesium bromide (89.0 mg, 485 μmol, 2.50 equiv) in acetonitrile (4 mL) at 23 °C under an atmosphere of carbon dioxide. After stirring for 1 h at 23 °C, the reaction solution was concentrated in vacuo. The residue was partitioned between aqueous hydrochloric acid solution (1 N, 10 mL) and diethyl ether (10 mL). The aqueous layer was separated and was further extracted with diethyl ether (2 x 10 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (25 mL), were dried over sodium sulfate, and were concentrated to a volume of 1 mL. The concentrated ethereal solution was transferred via cannula to a suspension of potassium *t*-butoxide (87.0 mg, 776 μmol, 4.00 equiv) in ether (500 μL) at −78 °C. The transfer was quantitated with additional ether (1.5 mL). The reaction mixture was stirred at –78 °C for 2 min, then was transferred via cannula over 5 min to a solution of freshly distilled methyl trifluoromethanesulfonate (110.0 μL, 970 μmol, 5.00 equiv) in toluene (5 mL) at –20 °C. The transfer was quantitated with additional toluene (2 mL). The reaction mixture was stirred at –20 °C for 30 min. Excess methyl trifluoromethanesulfonate was quenched by the sequential addition of triethylamine (3 mL) and methanol (6 mL). The product solution was partitioned between aqueous hydrochloric acid solution (1 N, 25 mL) and dichloromethane (25 mL). The aqueous layer was separated and extracted further with dichloromethane (2 x 25 mL). The combined organic layers were dried over sodium sulfate and were concentrated. The product was purified by flash column chromatography (25% ethyl acetate in hexanes initially, then 50% ethyl acetate in hexanes) to afford the vinylogous carbonic acid **70** as a pale yellow foam (54 mg, 49%).

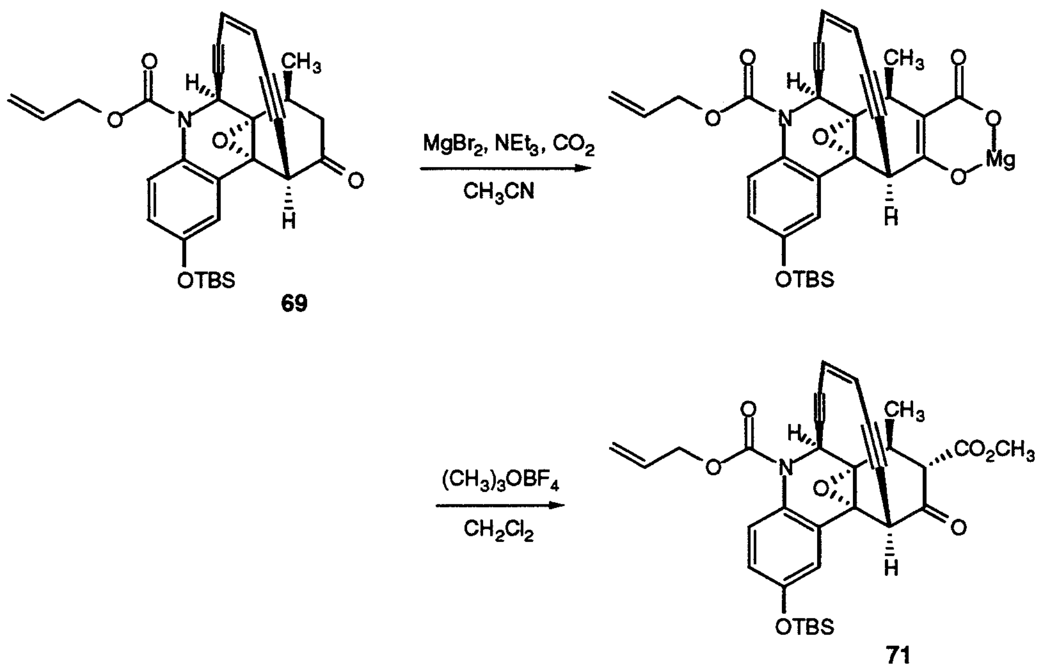
^{1}H NMR (300 MHz, C_6D_6) δ: 7.30 (br s, 1H, *o*-aryl), 7.06 (d, 1H J = 2.6 Hz, *m*-aryl), 6.73 (dd, 1H J = 8.7, 2.6 Hz, *m*-aryl), 6.06 (br s, 1H, NC**H**), 5.61 (m, 1H, CH_2=C**H**), 5.06 (br d, 1H, J = 16.3 Hz C**H**$_2$=CH), 5.03 (s, 2H, **H**C=C**H**), 4.89 (br d, 1H, J = 10.4 Hz, C**H**$_2$=CH), 4.52 (dd, 1H, J = 13.6, 5.3 Hz, C**H**$_2$O), 4.43 (dd, 1H, J = 13.4, 5.0 Hz, C**H**$_2$O), 4.10 (q, 1H, J = 7.1 Hz, CH_3C**H**), 3.88 (s, 1H, C≡CC**H**), 2.80 (s, 1H, OC**H**$_3$), 1.44 (d, 3H, J = 7.1 Hz, C**H**$_3$CH), 0.97 (s, 9H, OSiC(C**H**$_3$)$_3$), 0.12 (s, 3H, OSiC**H**$_3$), 0.11 (s, 3H, OSiC**H**$_3$).

FTIR (neat), cm^{-1}: 3274 (br, COOH), 2930 (m), 2857 (w), 1714 (s, C=O), 1646 (w), 1500 (s), 1462 (w), 1386 (s), 1313 (s), 1274 (s), 1205 (m), 1142 (m), 1096 (w), 1020 (w), 976 (w).

HRMS (FAB): Calcd for $C_{32}H_{35}NO_7Si$ $[M]^+$: 573.2183
Found: 573.2200

$[\alpha]_D^{22}$ ($CHCl_3$): +565.4°, C = 0.40

TLC, R_f: **70**: 0.61 (EtOAc)
69: 0.37 (20% EtOAc-hexanes)



β-Keto Methyl Ester 71

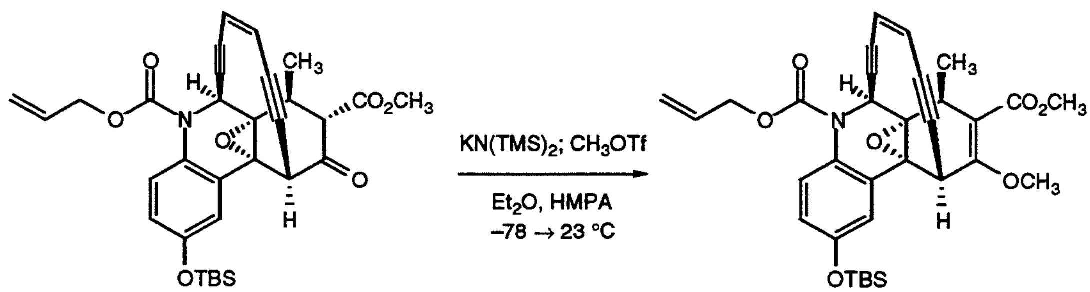
Triethylamine (203 μL, 1.45 mmol, 15.0 equiv) was added to a solution of allyl (6*S*, 6a*S*, 7*S*, 10*S*, 10a*R*, 14*Z*)-2-(*tert*-butyldimethylsiloxy)-7,8,9,10-tetrahydro-7-methyl-9-oxo-6a,10a-epoxy-6,10-[3]hexene[1,5]diynophenanthridine-5(6*H*)-carboxylate (**69**, 50.0 mg, 97.0 μmol, 1 equiv) and magnesium bromide (45.0 mg, 242 μmol, 2.50 equiv) in acetonitrile (2 mL) at 23 °C under an atmosphere of carbon dioxide. After stirring for 1 h at 23 °C, the reaction solution was concentrated in vacuo. The residue was dissolved in dichloromethane (5 mL) and was cooled to 0 °C. Trimethyloxonium tetrafluoroborate (717 mg, 4.58 mmol, 50.0 equiv) was added to the solution. The resulting suspension was warmed to 23 °C and was held at this temperature for 2.5 h. The product suspension was partitioned between saturated aqueous sodium bicarbonate solution (25 mL) and dichloromethane (15 mL). The aqueous layer was separated and extracted further with dichloromethane (2 x 15 mL). The combined organic layers were dried over sodium sulfate and were concentrated. The product was purified by flash column chromatography (15% ethyl acetate-hexanes) to provide the β-keto methyl ester **71** as a yellow oil (41 mg, 73%).

^{1}H NMR (300 MHz, C_6D_6) δ: 12.9 (s, 1H, C=COH), 7.29 (m, 1H, *o*-aryl), 7.05 (d, 1H J = 2.6 Hz, *m*-aryl), 6.73 (dd, 1H J = 8.7, 2.6 Hz, *m*-aryl), 6.11 (m, 1H, NC**H**), 5.59 (m, 1H, CH_2=C**H**), 5.08 (m, 1H, C**H**$_2$=CH), 5.05 (d, 1H, J = 1.3 Hz, C≡CC**H**=C), 5.04 (d, 1H, J = 1.3 Hz, C≡CCH=C)), 4.90 (m, 1H, C**H**$_2$=CH), 4.48 (m, 2H, C**H**$_2$O), 4.25 (s, 1H, C≡CC**H**), 3.66 (q, 1H, J = 7.1 Hz, CH_3C**H**), 3.15 (s, 1H, OC**H**$_3$), 1.34 (d, 3H, J = 7.1 Hz, C**H**$_3$CH), 0.95 (s, 9H, OSiC(C**H**$_3$)$_3$), 0.08 (s, 3H, OSi(C**H**$_3$)$_2$), 0.07 (s, 3H, OSi(C**H**$_3$)$_2$).

FTIR (neat), cm^{-1}: 3310 (w), 2955 (m), 2930 (m), 2857 (m), 2279 (w, C≡C), 2193 (w, C≡C), 1713 (s, NC=O, C=O), 1668 (s, C=C), 1625 (m), 1504 (s), 1441 (m), 1384 (m), 1313 (m), 1275 (s), 1232 (s), 1202 (m), 1139 (m), 1099 (w), 1079 (w), 1054 (w), 1026 (w), 999 (m).

TLC (20% EtOAc-hexanes), R_f: **71**: 0.40 (UV)

69: 0.37 (UV)



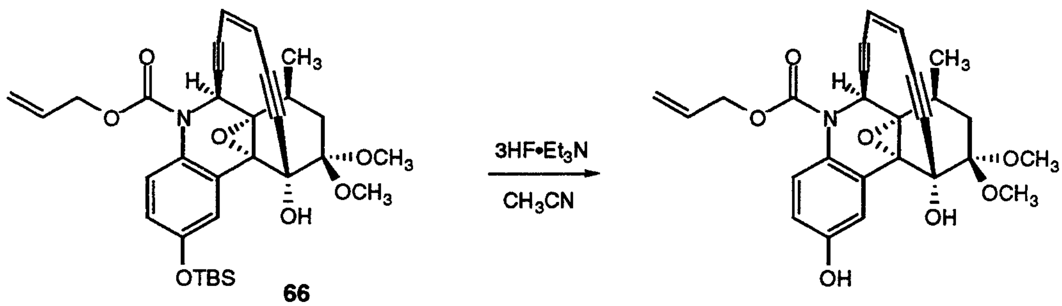
71 72

Vinylogous Methyl Carbonate 72

A solution of potassium hexamethyldisilylazide in toluene (0.5 M, 648 μL, 324 μmol, 3.00 equiv) was added to a solution of the β-keto methyl ester **71** (62.0 mg, 108 μmol, 1 equiv) in diethyl ether (5 mL) and hexamethylphosphoramide (25 μL) at −78 °C. After stirring the resulting solution at −78 °C for 5 min, methyl trifluoromethanesulfonate (37.0 μL, 324 μmol, 3.00 equiv) was added. The reaction mixture was then warmed to 23 °C and was held at this temperature for 1 h. The product solution was partitioned between saturated aqueous sodium bicarbonate solution (20 mL) and diethyl ether (15 mL). The aqueous layer was separated and further extracted with a 20-mL portion of diethyl ether. The combined organic layers were dried over sodium sulfate and were concentrated. The product was purified by flash column chromatography (20% ethyl acetate in hexanes) to furnish the vinylogous methyl carbonate **72** as a yellow foam (39 mg, 61%).

^1H NMR (400 MHz, C_6D_6), δ: 7.35 (br s, 1H, *o*-aryl), 7.16 (d, 1H, *J* = 2.4 Hz, *m*-aryl), 6.79 (dd, 1H, *J* = 8.5, 2.4 Hz, *m*-aryl), 6.18 (br s, 1H, NC**H**), 5.65 (m, 1H, CH_2=C**H**), 5.13 (dd, 1H, *J* = 10.0, 1.5 Hz, C≡CC**H**=C), 5.10 (br d, 1H, *J* = 16.5 Hz, C**H**$_2$=CH), 5.07 (dd, 1H, *J* = 10.0, 1.2 Hz, C≡CC**H**=C), 4.93 (br d, 1H, *J* = 10.5 Hz, C**H**$_2$=CH), 4.57 (br dd, 1H, *J* = 13.4, 5.6 Hz C**H**$_2$O), 4.49 (br dd, 1H, *J* = 13.4, 5.6 Hz, C**H**$_2$O), 4.11 (br s, 1H, C≡CC**H**), 3.97 (br q, 1H, *J* = 7.3 Hz, C**H**CH_3), 3.47 (s, 3H, OC**H**$_3$), 3.43 (s, 3H, OC**H**$_3$), 1.47 (br d, 3H, *J* = 7.3 Hz, C**H**$_3$CH), 1.01 (s, 9H, OSiC(C**H**$_3$)$_3$), 0.15 (s, 3H, OSi(C**H**$_3$)$_2$), 0.14 (s, 3H, OSi(C**H**$_3$)$_2$).

FTIR (neat), cm^{-1}:	3087 (w), 3056 (w), 2951 (m), 2932 (m), 2890 (w), 2857 (m), 2280 (w, C≡C), 2197 (w, C≡C), 1711 (vs, NC=O, C=O), 1649 (w), 1613 (w), 1582 (w), 1500 (m), 1458 (w), 1437 (w), 1387 (m), 1361 (m), 1313 (s), 1274 (s), 1225 (m), 1204 (m), 1141 (m), 1096 (w), 1046 (w), 1024 (w), 977 (w), 884 (m), 835 (m), 782 (m), 740 (w).
HRMS (FAB):	Calcd for $C_{33}H_{37}NO_7Si$ $[M]^+$: 587.2339 Found: 587.2332
TLC (20% EtOAc-hexanes), R_f:	**72**: 0.26 (UV) **71**: 0.40 (UV)



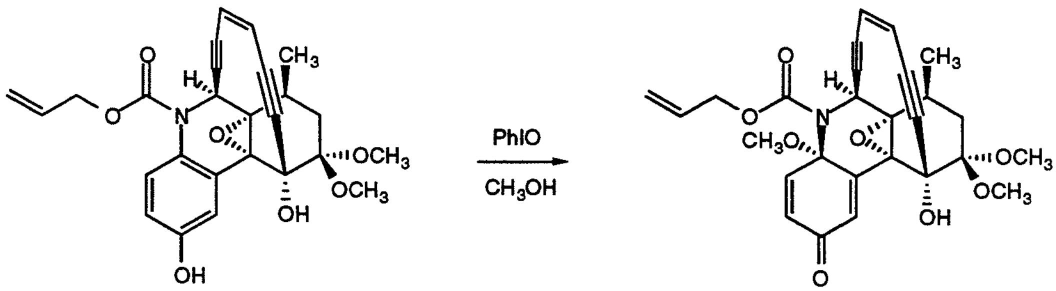
Allyl (6*S*, 6a*S*, 7*S*, 10*R*, 10a*S*, 14*Z*)-7,8,9,10-Tetrahydro-2,10-dihydroxy-9,9-dimethoxy-7-methyl-6a,10a-epoxy-6,10-[3]hexene[1,5]diynophenanthridine-5(6*H*)-carboxylate

Triethylamine trihydrofluoride (0.50 mL, 3.1 mmol, 4.5 equiv) was added to a solution of allyl (6*S*, 6a*S*, 7*S*, 10*R*, 10a*S*, 14*Z*)-2-(*tert*-butyldimethylsiloxy)-7,8,9,10-tetrahydro-10-hydroxy-9,9-dimethoxy-7-methyl-6a,10a-epoxy-6,10-[3]hexene[1,5]diynophenanthridine-5(6*H*)-carboxylate (**66**, 390 mg, 0.675 mmol, 1 equiv) in acetonitrile (10 mL) at 23 °C. The reaction mixture was stirred at 23 °C for 3 h, then was partitioned between saturated aqueous sodium bicarbonate solution (75 mL) and ethyl acetate (40 mL). The aqueous layer was separated and extracted further with a 40-mL portion of ethyl acetate. The combined organic layers were dried over sodium sulfate and were concentrated. The residue was purified by flash column chromatography (20% ethyl acetate in dichloromethane) to yield allyl (6*S*, 6a*S*, 7*S*, 10*R*, 10a*S*, 14*Z*)-7,8,9,10-tetrahydro-2,10-dihydroxy-9,9-dimethoxy-7-methyl-6a,10a-epoxy-6,10-[3]hexene[1,5]diynophenanthridine-5(6*H*)-carboxylate as a light yellow oil (313 mg, 100%).

^1H NMR (400 MHz, $CDCl_3$), δ:	8.01 (d, 1H, J = 2.9 Hz, m-aryl), 7.13 (br s, 1H, o-aryl), 6.75 (dd, 1H, J = 8.8, 2.9 Hz, m-aryl), 5.88 (m, 1H, CH_2=**CH**), 5.79 (d, 1H, J = 10.0, HCC≡CCH=C**H**), 5.72 (br s, 1H, NC**H**), 5.67 (dd, 1H, J = 10.0, 1.7 Hz, HCC≡CC**H**=CH), 5.25 (br d, 1H, J = 17.5 Hz, **CH_2**=CH), 5.18 (br d, 1H, J = 10.5 Hz, **CH_2**=CH), 4.99 (s, 1H, aryl **OH**), 4.69 (br dd, 1H, J = 13.2, 4.8 Hz, **CH_2**O), 4.56 (br, 1H, **CH_2**O), 3.60 (s, 1H, **OH**), 3.51 (s, 3H, O**CH_3**), 3.36 (s, 3H, O**CH_3**), 2.50 (m, 1H, **CH**CH_3), 2.07 (m, 2H, **CH_2**), 1.41 (d, 3H, J = 7.3 Hz, **CH_3**CH).
FTIR (neat), cm^{-1}:	3418 (br OH), 3090 (w), 2964 (m), 2838 (w), 2252 (w, C≡C), 2192 (w, C≡C), 1694 (vs, NC=O), 1614 (w), 1589 (w), 1505 (s), 1463 (m), 1393 (m), 1318 (s), 1278 (s), 1237 (m), 1200 (s), 1146 (m), 1110 (m), 1083 (m), 1060 (w), 1034 (w), 990 (w), 911 (m), 882 (m), 826 (w), 826 (w), 781 (w), 734 (s), 648 (w).
HRMS (FAB):	Calcd for $C_{26}H_{25}O_7N$ $[M]^+$: 463.1631 Found: 463.1636

TLC (40% ethyl acetate-hexanes), R_f: product phenol: 0.17 (UV)

66: 0.40 (UV)



Allyl (4a*S*, 6*S*, 6a*S*, 7*S*, 10*R*, 10a*S*, 14*Z*)-2,4a,7,8,9,10-Hexahydro-10-hydroxy-4a,9,9-trimethoxy-7-methyl-2-oxo-6a,10a-epoxy-6,10-[3]hexene[1,5]diynophenanthridine-5(6*H*)-carboxylate

Iodosobenzene (130 mg, 0.591 mmol, 1.14 equiv) was added to a solution of allyl (6*S*, 6a*S*, 7*S*, 10*R*, 10a*S*, 14*Z*)-7,8,9,10-tetrahydro-2,10-dihydroxy-9,9-dimethoxy-7-methyl-6a,10a-epoxy-6,10-[3]hexene[1,5]diynophenanthridine-5(6*H*)-carboxylate (240 mg, 0.518 mmol, 1 equiv) in dry methanol (30 mL) at 23 °C. The reaction mixture was stirred at 23 °C for 10 min. The product solution was then partitioned between 1:1 saturated aqueous sodium bicarbonate solution:saturated aqueous sodium thiosulfate solution (70 mL), saturated aqueous sodium chloride solution (50 mL), and ethyl acetate (50 mL). The aqueous layer was separated and extracted further with a 50-mL portion of ethyl acetate. The combined organic layers were dried over sodium sulfate and were concentrated. The residue was purified by flash column chromatography (40% hexanes in ethyl acetate) to give allyl (4a*S*, 6*S*, 6a*S*, 7*S*, 10*R*, 10a*S*, 14*Z*)-2,4a,7,8,9,10-hexahydro-10-hydroxy-4a,9,9-trimethoxy-7-methyl-2-oxo-6a,10a-epoxy-6,10-[3]hexene[1,5]diynophenanthridine-5(6*H*)-carboxylate as a light yellow oil (228 mg, 89%).

^1H NMR (400 MHz, $CDCl_3$), δ: 7.70 (br s, 1H, β-enone), 7.27 (d, 1H, J = 2.0 Hz, α-enone), 6.31 (dd, 1H, J = 10.2, 2.0 Hz, α-enone), 5.95 (m, 1H, CH_2=**CH**), 5.90 (d, 1H, J = 10.0, CHC≡CCH=**CH**), 5.81 (br s, 1H, N**CH**), 5.77 (dd, 1H, J = 10.0, 1.2 Hz, CHC≡C**CH**=CH), 5.36 (br d, 1H, J = 16.5 Hz, $\mathbf{CH_2}$=CH), 5.26 (dd, 1H, J = 10.5, 1.2 Hz, $\mathbf{CH_2}$=CH), 4.69 (br s, 2H, $\mathbf{CH_2}$O), 3.43 (s, 3H, $\mathbf{OCH_3}$), 3.37 (s, 3H, $\mathbf{OCH_3}$), 3.36 (s, 1H, **OH**), 3.10 (s, 3H, $\mathbf{OCH_3}$), 2.62 (m, 1H, $\mathbf{CH}CH_3$), 2.21 (dd, 1H, J = 14.6, 7.1 Hz, $\mathbf{CH_2}$), 1.96 (dd, 1H, J = 14.6, 11.2 Hz, $\mathbf{CH_2}$), 1.30 (d, 3H, J = 7.3 Hz, $\mathbf{CH_3}$CH).

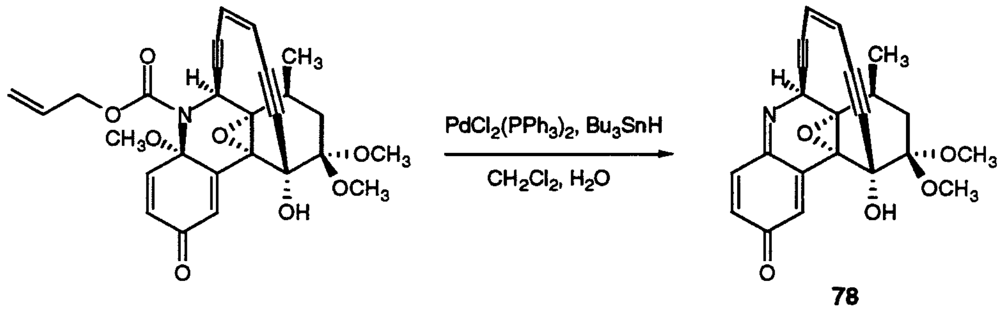
FTIR (neat), cm^{-1}: 3448 (br, OH), 3085 (w), 3054 (w), 2972 (m), 2941 (m), 2890 (sh), 2838 (w), 2249 (w, C≡C), 1701 (vs, NC=O), 1672 (s, C=O), 1633 (m), 1613 (w), 1460 (m), 1395 (s), 1309 (s), 1195 (m), 1149 (m), 1096 (m), 1056 (s), 1020 (w), 975 (w), 942 (w), 911 (w), 818 (w), 731 (s).

HRMS (FAB): Calcd for $C_{27}H_{28}O_8N$ $[MH]^+$: 494.1815

Found: 494.1832

TLC (40% hexanes-ethyl acetate), R_f: product enone: 0.28 (UV)

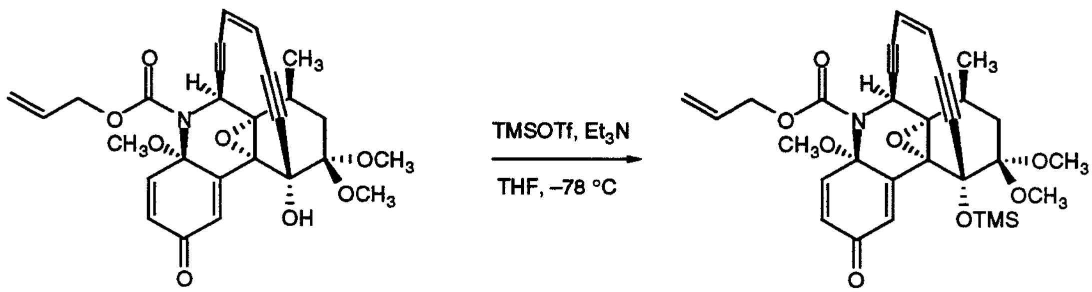
starting phenol: 0.38 (UV)



(6*S*, 6a*S*, 7*S*, 10*R*, 10a*S*, 14*Z*)-7,8,9,10-Tetrahydro-10-hydroxy-9,9-dimethoxy-7-methyl-6a,10a-epoxy-6,10-[3]hexene[1,5]-diynophenanthridin-2(6*H*)-one (78)

Tributyltin hydride (130 µL, 0.483 mmol, 1.04 equiv) was injected into a deoxygenated suspension of allyl (4a*S*, 6*S*, 6a*S*, 7*S*, 10*R*, 10a*S*, 14*Z*)-2,4a,7,8,9,10-hexahydro-10-hydroxy-4a,9,9-trimethoxy-7-methyl-2-oxo-6a,10a-epoxy-6,10-[3]hexene[1,5]diynophenanthridine-5(6*H*)-carboxylate (228 mg, 0.463 mmol, 1 equiv), bistriphenylphosphinepalladium(II) chloride (153 mg, 0.218 mmol, 0.471 equiv) and water (100 µL) in dichloromethane (20 mL) at 23 °C. The reaction mixture was stirred for 5 min at 23 °C, then was loaded directly onto a column of solvated (20% ethyl acetate in hexanes) flash-grade silica gel. Elution (20% ethyl acetate in hexanes initially, grading to 60% ethyl acetate in hexanes) provided (6*S*, 6a*S*, 7*S*, 10*R*, 10a*S*, 14*Z*)-7,8,9,10-tetrahydro-10-hydroxy-9,9-dimethoxy-7-methyl-6a,10a-epoxy-6,10-[3]hexene[1,5]-diynophenanthridin-2(6*H*)-one (**78**) as a yellow oil (143 mg, 82%).

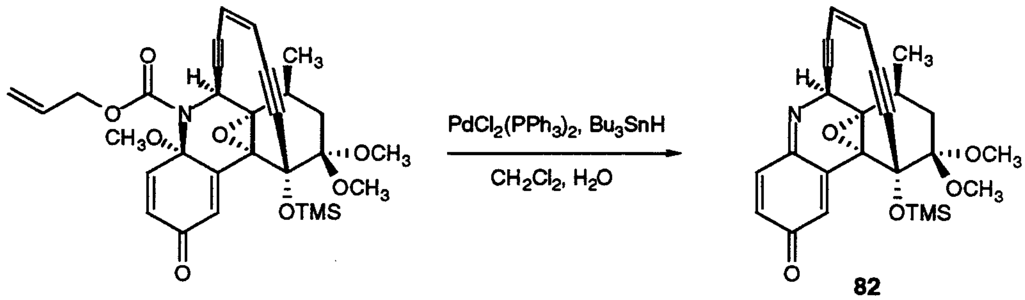
^{1}H NMR (400 MHz, C_6D_6), δ:	8.07 (d, 1H, J = 2.2 Hz, α-enone), 6.86 (d, 1H, J = 10.0 Hz, α-enone), 6.09 (dd, 1H, J = 10.0, 2.20 Hz, β-enone), 5.28 (d, 1H J = 1.2 Hz, NC**H**), 5.17 (dd, 1H, J = 10.0, 1.5 Hz, CHC≡CC**H**=CH), 5.14 (d, 1H, J = 10.0 Hz, CHC≡CCH=C**H**), 3.36 (s, 1H, O**H**), 3.32 (s, 3H, OC**H**$_3$), 2.91 (s, 3H, OC**H**$_3$), 2.22 (m, 1H, C**H**CH$_3$), 2.08 (t, 1H, J = 13.9, C**H**$_2$), 1.80 (dd, 1H, J = 14.5, 5.0 Hz, C**H**$_2$), 0.96 (d, 3H, J = 7.3 Hz, C**H**$_3$CH).
FTIR (neat), cm^{-1}:	3416 (br, OH), 3083 (w), 3051 (w), 2968 (m), 2946 (m), 2836 (w), 2280 (w, C≡C), 2187 (w, C≡C), 1646 (s, C=O), 1625 (m sh), 1590 (w), 1462 (m), 1384 (w), 1294 (w), 1264 (w), 1197 (w), 1153 (s), 1110 (s), 1055 (s), 998 (w), 904 (s), 813 (w), 735 (s).
TLC (40% hexanes-ethyl acetate), R_f:	**78**: 0.38 (UV, visibly light yellow) starting enone: 0.28 (UV)



Allyl (4a*S*, 6*S*, 6a*S*, 7*S*, 10*R*, 10a*S*, 14*Z*)-2,4a,7,8,9,10-Hexahydro-10-trimethylsiloxy-4a,9,9-trimethoxy-7-methyl-2-oxo-6a,10a-epoxy-6,10-[3]hexene[1,5]diynophenanthridine-5(6*H*)-carboxylate

Trimethylsilyl trifluoromethanesulfonate (240 µL, 1.22 mmol, 5.04 equiv) was added to a solution of allyl (4a*S*, 6*S*, 6a*S*, 7*S*, 10*R*, 10a*S*, 14*Z*)-2,4a,7,8,9,10-hexahydro-10-hydroxy-4a,9,9-trimethoxy-7-methyl-2-oxo-6a,10a-epoxy-6,10-[3]hexene[1,5]diyno-phenanthridine-5(6*H*)-carboxylate (119 mg, 0.242 mmol, 1 equiv) and triethylamine (340 µL, 2.44 mmol, 10.1 equiv) in tetrahydrofuran (5 mL) at –78 °C. The reaction mixture was transferred to an ice bath and was stirred for 10 min at 0 °C. The product solution was partitioned between saturated aqueous sodium bicarbonate solution (50 mL) and ethyl acetate (40 mL). The aqueous layer was separated and extracted further with ethyl acetate (40 mL). The combined organic layers were dried over sodium sulfate and were concentrated. The residue was purified by flash column chromatography (40% ethyl acetate in hexanes) to provide allyl (4a*S*, 6*S*, 6a*S*, 7*S*, 10*R*, 10a*S*, 14*Z*)-2,4a,7,8,9,10-hexahydro-10-trimethylsiloxy-4a,9,9-trimethoxy-7-methyl-2-oxo-6a,10a-epoxy-6,10-[3]hexene[1,5]diynophenanthridine-5(6*H*)-carboxylate as a light yellow oil (118 mg, 87%).

^1H NMR (400 MHz, $CDCl_3$), δ:	7.74 (br s, 1H, β-enone), 7.15 (d, 1H, J = 2.0 Hz, α-enone), 6.32 (dd, 1H, J = 10.5, 2.0 Hz, α-enone), 5.95 (m, 1H, CH_2=C**H**), 5.89 (d, 1H, J = 10.0, CHC≡CCH=C**H**), 5.81 (br s, 1H, NC**H**), 5.74 (dd, 1H, J = 10.0, 1.5 Hz, CHC≡CC**H**=CH), 5.36 (br d, 1H, J = 16.5 Hz, C**H**$_2$=CH), 5.26 (dd, 1H, J = 10.5, 1.2 Hz, C**H**$_2$=CH), 4.68 (br s, 2H, C**H**$_2$O), 3.39 (s, 3H, OC**H**$_3$), 3.35 (s, 3H, OC**H**$_3$), 3.12 (s, 3H, OC**H**$_3$), 2.67 (m, 1H, C**H**CH$_3$), 2.25 (dd, 1H, J = 14.2, 7.1 Hz, C**H**$_2$), 1.98 (dd, 1H, J = 14.2, 11.2 Hz, C**H**$_2$), 1.27 (d, 3H, J = 7.3 Hz, C**H**$_3$CH), 0.26 (s, 9H, Si(C**H**$_3$)$_3$.
FTIR (neat), cm^{-1}:	3054 (w), 2950 (s), 2827 (w), 2827 (w), 1706 (vs, NC=O), 1671 (s, C=O), 1636 (m), 1611 (w), 1495 (m), 1394 (s), 1308 (s), 1283 (m), 1252 (w), 1200 (m), 1154 (s), 1099 (m), 1060 (m), 973 (m), 885 (m), 846 (s).
TLC (40% ethyl acetate-hexanes), R_f:	TMS ether: 0.36 (UV) starting enone: 0.12 (UV)



82

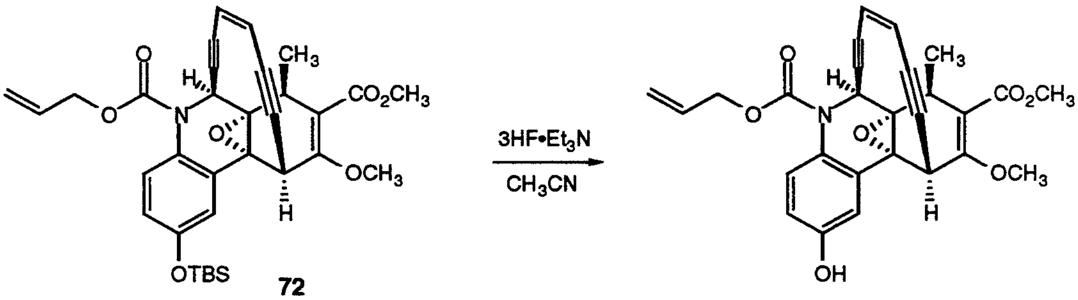
(6*S*, 6a*S*, 7*S*, 10*R*, 10a*R*, 14*Z*)-7,8,9,10-Tetrahydro-9,9-dimethoxy-7-methyl-10-(trimethylsiloxy)-6a,10a-epoxy-6,10-[3]hexene[1,5]diynophenanthridin-2(6*H*)-one (82)

Tributyltin hydride was injected in two portions (8.0 µL, 0.030 mmol, 0.67 equiv; 4.0 µL, 0.015 mmol, 0.33 equiv) with a 10 min interval between injections into a deoxygenated suspension of allyl (4a*S*, 6*S*, 6a*S*, 7*S*, 10*R*, 10a*S*, 14*Z*)-2,4a,7,8,9,10-hexahydro-10-trimethylsiloxy-4a,9,9-trimethoxy-7-methyl-2-oxo-6a,10a-epoxy-6,10-[3]hexene[1,5]diynophenanthridine-5(6*H*)-carboxylate (25 mg, 0.044 mmol, 1 equiv), bistriphenylphosphinepalladium(II) chloride (3.0 mg, 0.0043 mmol, 0.096 equiv) and water (150 µL) in dichloromethane (8 mL) at 23 °C. The reaction mixture was then stirred for 5 min at 23 °C. The product solution was concentrated in vacuo and the residue was purified by flash column chromatography (40% ethyl acetate in hexanes) to provide (6*S*, 6a*S*, 7*S*, 10*R*, 10a*R*, 14*Z*)-7,8,9,10-tetrahydro-9,9-dimethoxy-7-methyl-10-(trimethyl-siloxy)-6a,10a-epoxy-6,10-[3]hexene[1,5]diynophenanthridin-2(6*H*)-one (**82**) as a yellow oil (14 mg, 70%).

^1H NMR (400 MHz, C_6D_6), δ: 7.92 (d, 1H, J = 2.2 Hz, α-enone), 6.86 (d, 1H, J = 10.0 Hz, α-enone), 6.07 (dd, 1H, J = 10.0, 2.20 Hz, β-enone), 5.28 (d, 1H J = 1.5 Hz, NC**H**), 5.19 (d, 1H, J = 10.0 Hz, CHC≡CCH=C**H**), 5.16 (dd, 1H, J = 10.0, 1.5 Hz, CHC≡CC**H**=CH), 3.33 (s, 3H, OCH_3), 3.06 (s, 3H, OCH_3), 2.29 (m, 1H, $CHCH_3$), 2.10 (t, 1H, J = 13.7, CH_2), 1.85 (dd, 1H, J = 14.2, 5.4 Hz, CH_2), 0.96 (d, 3H, J = 7.3 Hz, CH_3CH), 0.42 (s, 9H, $Si(CH_3)_3$).

FTIR (neat), cm^{-1}: 3054 (w), 2960 (s), 2837 (w), 2279 (w, C≡C), 2189 (w, C≡C), 1649 (s, C=O), 1590 (w), 1459 (m), 1288 (m), 1252 (m), 1195 (m), 1164 (s), 1102 (s), 1061 (s), 999 (w), 978 (w), 906 (w), 890 (w), 865 (w), 844 (m), 746 (m).

TLC (40% ethyl acetate-hexanes), R_f: **82**: 0.38 (UV, visibly light yellow)
starting enone: 0.36 (UV)



72

5-Allyl Methyl (6*S*, 6a*S*, 7*S*, 10*R*, 10a*R*, 14*Z*)-7,10-Dihydro-2-hydroxy-9-methoxy-7-methyl-6a,10a-epoxy-6,10-[3]hexene[1,5]diynophenanthridine-5,8(6*H*)-dicarboxylate

Triethylamine trihydrofluoride (0.20 mL, 1.2 mmol, 10 equiv) was added to a solution of 5-allyl methyl (6*S*, 6a*S*, 7*S*, 10*R*, 10a*R*, 14*Z*)-2-(*tert*-butyldimethylsiloxy)-7,10-dihydro-9-methoxy-7-methyl-6a,10a-epoxy-6,10-[3]hexene[1,5]diynophenanthridine-5,8(6*H*)-dicarboxylate (**72**, 70 mg, 0.12 mmol, 1 equiv) in acetonitrile (8 mL) at 23 °C. The reaction mixture was stirred at 23 °C for 2 h, then was partitioned between saturated aqueous sodium bicarbonate solution (70 mL) and ethyl acetate (30 mL). The aqueous layer was separated and extracted further with ethyl acetate (30 mL). The combined organic layers were dried over sodium sulfate and were concentrated. The residue was purified by flash column chromatography (40% ethyl acetate in hexanes initially, then 60% ethyl acetate in hexanes) to afford 5-allyl methyl (6*S*, 6a*S*, 7*S*, 10*R*, 10a*R*, 14*Z*)-7,10-dihydro-2-hydroxy-9-methoxy-7-methyl-6a,10a-epoxy-6,10-[3]hexene[1,5]diynophenanthridine-5,8(6*H*)-dicarboxylate as a light yellow oil (56 mg, 100%).

^{1}H NMR (400 MHz, C_6D_6, 70 °C), δ: 7.32 (br d, 1H, J = 8.6 Hz, *o*-aryl), 6.83 (d, 1H, J = 2.7 Hz, *m*-aryl), 6.55 (dd, 1H, J = 8.8, 2.7 Hz, *m*-aryl), 5.92 (br s, 1H, NC**H**), 5.71 (m, 1H, CH_2=C**H**), 5.21 (dd, 1H, J = 10.0, 1.2 Hz, **CH**=CH), 5.14 (dd, 1H, J = 10.0, 1.2 Hz, CH=C**H**), 5.13 (d, 1H, J = 16.5 Hz, **CH$_2$**=CH), 4.97 (d, 1H, J = 10.5 Hz, **CH$_2$**=CH), 4.56 (br dd, 1H, J = 13.4, 5.6 Hz, **CH$_2$**O), 4.49 (br dd, 1H, J = 13.4, 5.6 Hz, **CH$_2$**O), 4.20 (s, 1H, C≡CC**H**), 3.93 (q, 1H, J = 7.3 Hz, **CH**CH$_3$), 3.64 (s, 3H, OC**H$_3$**), 3.51 (s, 3H, OC**H$_3$**), 1.49 (d, 3H, J = 7.3 Hz, **CH$_3$**CH).

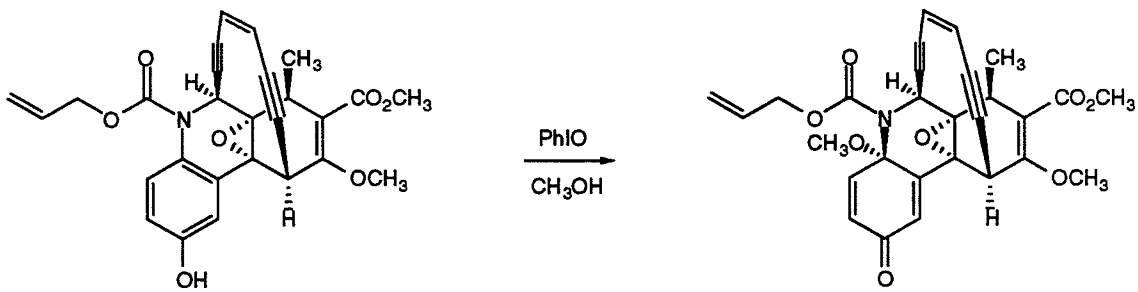
FTIR (neat), cm^{-1}: 3375 (br, OH), 3085 (w), 3044 (w), 2992 (m), 2941 (m), 2840 (w), 2280 (w, C≡C), 2195 (w, C≡C), 1763–1577 (br s, C=O, NC=O), 1505 (s), 1455 (m), 1393 (m), 1314 (s), 1273 (s), 1216 (s), 1154 (s), 1098 (w), 1079 (w), 1047 (m), 1022 (m), 917 (m), 847 (w), 812 (w), 784 (w), 761 (w), 742 (w).

HRMS (FAB): Calcd for $C_{27}H_{23}O_7N$ $[M]^+$: 473.1475

Found: 473.1467

TLC (40% ethyl acetate-hexanes), R_f: product phenol: 0.21 (UV)

72: 0.55 (UV)



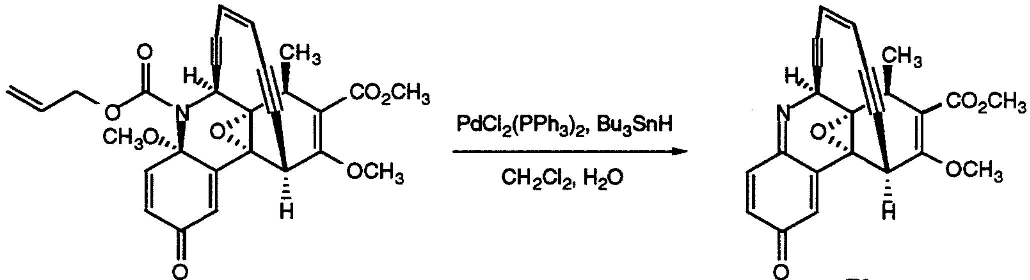
5-Allyl Methyl (4a*S*, 6*S*, 6a*S*, 7*S*, 10*R*, 10a*R*, 14*Z*)-2,4a,7,10-Tetrahydro-4a,9-dimethoxy-7-methyl-2-oxo-6a,10a-epoxy-6,10-[3]hexene[1,5]diynophenanthridine-5,8 (6*H*)-dicarboxylate

Iodosobenzene (63 mg, 0.29 mmol, 1.2 equiv) was added to a solution of 5-allyl methyl (6*S*, 6a*S*, 7*S*, 10*R*, 10a*R*, 14*Z*)-7,10-dihydro-2-hydroxy-9-methoxy-7-methyl-6a,10a-epoxy-6,10-[3]hexene[1,5]diynophenanthridine-5,8(6*H*)-dicarboxylate (115 mg, 0.243 mmol, 1 equiv) in dry methanol (10 mL) at 23 °C. The reaction mixture was stirred at 23 °C for 15 min. The product solution was then partitioned between 1:1 saturated aqueous sodium bicarbonate solution:saturated aqueous sodium thiosulfate solution (70 mL), saturated aqueous sodium chloride solution (25 mL), and ethyl acetate (25 mL). The aqueous layer was separated and extracted further with ethyl acetate (2 x 25 mL). The combined organic layers were dried over sodium sulfate and were concentrated. The residue was purified by flash column chromatography (10% hexanes in dichloromethane initially, then 20% ethyl acetate in dichloromethane) to give 5-allyl methyl (4a*S*, 6*S*, 6a*S*, 7*S*, 10*R*, 10a*R*, 14*Z*)-2,4a,7,10-tetrahydro-4a,9-dimethoxy-7-methyl-2-oxo-6a,10a-epoxy-6,10-[3]hexene[1,5]diynophenanthridine-5,8(6*H*)-dicarboxylate as a light yellow oil (97 mg, 80%).

^1H NMR (400 MHz, C_6D_6, 60 °C), δ:	7.51 (br s, 1H, β-enone), 6.71 (d, 1H, *J* = 2.0 Hz, α-enone), 6.20 (dd, 1H, *J* = 10.5, 2.0 Hz, α-enone), 5.98 (br s, 1H, NC**H**), 5.72 (m, 1H, CH_2=C**H**), 5.21 (dd, 1H, *J* = 10.0, 1.2 Hz, C**H**=CH), 5.18 (dd, 1H, *J* = 10.0, 1.2 Hz, CH=C**H**), 5.18 (dd, 1H, *J* = 17.1, 1.2 Hz, C**H**$_2$=CH), 5.00 (dd, 1H, *J* = 10.5, 1.2 Hz, C**H**$_2$=CH), 4.62 (br dd, 1H, *J* = 13.4, 5.6 Hz, C**H**$_2$O), 4.46 (br dd, 1H, *J* = 13.4, 5.6 Hz, C**H**$_2$O), 3.76 (q, 1H, *J* = 7.3 Hz, C**H**CH_3), 3.64 (s, 1H, C≡CC**H**), 3.46 (s, 3H, OC**H**$_3$), 3.46 (s, 3H, OC**H**$_3$), 2.99 (s, 3H, OC**H**$_3$), 1.35 (d, 3H, *J* = 7.3 Hz, C**H**$_3$CH).
FTIR (neat), cm^{-1}:	3088 (w), 3057 (w), 2984 (w), 2945 (w), 2840 (w), 2191 (w), 1710 (s, NC=O), 1673 (s, C=O), 1640 (m), 1614 (w), 1454 (m), 1434 (m), 1392 (s), 1309 (s), 1281 (s), 1209 (s), 1148 (s), 1099 (m), 1058 (m), 1014 (w), 931 (m).
HRMS (FAB):	Calcd for $C_{28}H_{26}O_8N$ $[MH]^+$: 504.1658 Found: 504.1646

TLC (20% ethyl acetate-CH_2Cl_2), R_f: product enone: 0.41 (UV)

starting phenol: 0.43 (UV)



Methyl (6*S*, 6a*S*, 7*S*, 10*R*, 10a*R*, 14*Z*)-2,6,7,10-Tetrahydro-9-methoxy-7-methyl-2-oxo-6a,10a-epoxy-6,10-[3]hexene[1,5]diynophenanthridine-8-carboxylate (79)

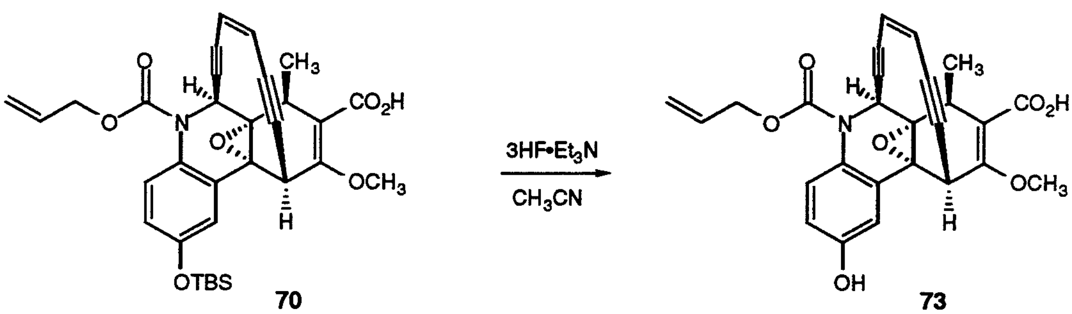
Tributyltin hydride (44 µL, 0.16 mmol, 1.1 equiv) was injected into a deoxygenated suspension of 5-allyl methyl (4a*S*, 6*S*, 6a*S*, 7*S*, 10*R*, 10a*R*, 14*Z*)-2,4a,7,10-tetrahydro-4a,9-dimethoxy-7-methyl-2-oxo-6a,10a-epoxy-6,10-[3]hexene[1,5]diynophenanthridine-5,8(6*H*)-dicarboxylate (76 mg, 0.15 mmol, 1 equiv), bistriphenylphosphinepalladium(II) chloride (60 mg, 0.85 mmol, 0.57 equiv) and water (50 µL) in dichloromethane (8 mL) at 23 °C. The reaction mixture was stirred for 15 min at 23 °C, then was loaded directly onto a column of solvated (20% ethyl acetate in hexanes) flash-grade silica gel. Elution (20% ethyl acetate in hexanes initially, then 40% ethyl acetate in hexanes) provided methyl (6*S*, 6a*S*, 7*S*, 10*R*, 10a*R*, 14*Z*)-2,6,7,10-tetrahydro-9-methoxy-7-methyl-2-oxo-6a,10a-epoxy-6,10-[3]hexene[1,5]diynophenanthridine-8-carboxylate (**79**) as a yellow oil (45 mg, 77%).

^{1}H NMR (400 MHz, C_6D_6), δ: 6.82 (d, 1H, J = 10.0 Hz, β-enone), 6.40 (d, 1H, J = 2.0 Hz, α-enone), 6.04 (dd, 1H, J = 10.0. 2.0 Hz, α-enone), 5.19 (dd, 1H J = 10.0, 1.5 Hz, **CH**=CH), 5.15 (dd, 1H, J = 10.0, 1.5 Hz, CH=**CH**), 5.04 (br s, 1H, NC**H**), 3.75 (q, 1H, J = 7.3 Hz, **CH**CH_3), 3.58 (br s, 1H, C≡CC**H**), 3.47 (s, 3H, OCH_3), 3.46 (s, 3H, OCH_3), 1.36 (d, 3H, J = 7.3 Hz, CH_3CH).

FTIR (neat), cm^{-1}: 3035 (w), 2948 (m), 1714 (s, C=O), 1651 (vs, C=O), 1593 (w), 1479 (w), 1435 (m), 1367 (m), 1293 (m), 1264 (m), 1213 (s), 1155 (m), 1115 (w), 1082 (w), 1037 (m), 987 (w), 909 (m), 844 (w), 817 (w), 789 (w), 741 (w), 681 (m).

HRMS (FAB): Calcd for $C_{23}H_{19}O_5N$ $[M+2H]^+$: 389.1263
Found: 389.1241

TLC (40% ethyl acetate-hexanes), R_f: **79**: 0.26 (UV, visibly light yellow)
starting enone: 0.16 (UV)

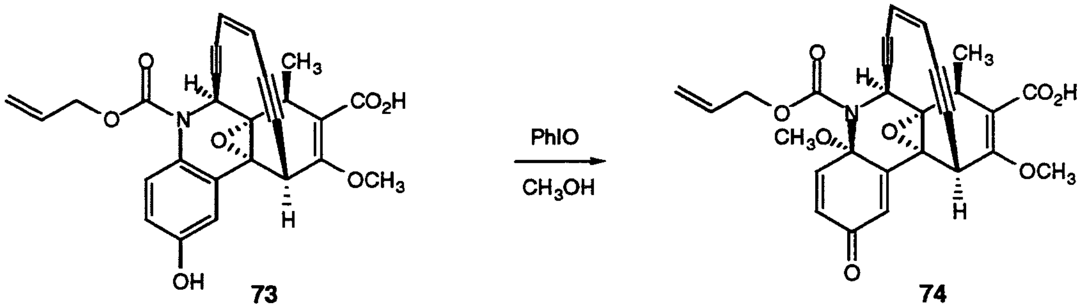


70 73

5-Allyl Hydrogen (6*S*, 6a*S*, 7*S*, 10*R*, 10a*R*, 14*Z*)-7,10-Dihydro-2-hydroxy-9-methoxy-7-methyl-6a,10a-epoxy-6,10-[3]hexene[1,5]diynophenanthridine-5,8(6*H*)-dicarboxylate (73)

Triethylamine trihydrofluoride (0.60 mL, 3.7 mmol, 8.3 equiv) was added to a solution of 5-allyl hydrogen (6*S*, 6a*S*, 7*S*, 10*R*, 10a*R*, 14*Z*)-2-(*tert*-butyldimethylsiloxy)-7,10-dihydro-9-methoxy-7-methyl-6a,10a-epoxy-6,10-[3]hexene[1,5]diynophenanthridine-5,8(6*H*)-dicarboxylate (**70**, 255 mg, 0.444 mmol, 1 equiv) in acetonitrile (30 mL). The reaction mixture was stirred at 23 °C for 1.5 h, then was partitioned between aqueous hrdrochloric acid solution (1% v/v, 100 mL) and ethyl acetate (70 mL). The aqueous layer was separated and extracted further with a 70-mL portion of ethyl acetate. The combined organic layers were dried over sodium sulfate and were concentrated. The residue was purified by flash column chromatography (50% hexanes in ethyl acetate initially, then 100% ethyl acetate, and finishing with 10% methanol in ethyl acetate) to provide 5-allyl hydrogen (6*S*, 6a*S*, 7*S*, 10*R*, 10a*R*, 14*Z*)-7,10-dihydro-2-hydroxy-9-methoxy-7-methyl-6a,10a-epoxy-6,10-[3]hexene[1,5]diynophenanthridine-5,8(6*H*)-dicarboxylate (**73**) as a viscous light yellow oil (165 mg, 81%).

^1H NMR (400 MHz, C_6D_6), δ:	7.88 (br s, 1H, *o*-aryl), 6.82 (br d, *J* = 8.3 Hz, *m*-aryl), 6.67 (br s, 1H, *m*-aryl), 5.62 (m, 1H, CH_2=CH), 5.53 (br s, 1H, NCH), 5.12 (dd, 1H, *J* = 17.2, 1.2 Hz, CH_2=CH), 5.00 (br s, 2H, CH=CH) 4.99 (dd, 1H, *J* = 10.5, 1.2 Hz, CH_2=CH), 4.85 (br s, 1H, C≡CCH), 4.49 (br dd, 1H, *J* = 13.2, 5.4 Hz, CH_2O), 4.20 (br dd, 1H, *J* = 13.2, 5.4 Hz, CH_2O), 4.04 (br q, 1H, *J* = 7.3 Hz, $CHCH_3$), 3.62 (s, 3H, OCH_3), 1.45 (d, 3H, *J* = 7.3 Hz, CH_3CH).
FTIR (neat), cm^{-1}:	3690-2400 (br m, COOH), 3344 (m, OH), 2930 (m), 2858 (w, C≡C), 1710 (vs, C=O), 1675 (sh), 1588 (w), 1505 (m), 1455 (m), 1393 (s), 1278 (s), 1226 (m), 1205 (m), 1149 (w), 1040 (w), 1021 (m), 933 (m), 847 (w), 737 (m).
HRMS (FAB):	Calcd for $C_{26}H_{21}O_7N$ $[M]^+$: 459.1318 Found: 459.1325
TLC (ethyl acetate), R_f:	**73**: 0.31 (UV) **70**: 0.39 (UV)



5-Allyl Hydrogen (4a*S*, 6*S*, 6a*S*, 7*S*, 10*R*, 10a*R*, 14*Z*)-2,4a,7,10-Tetrahydro-4a,9-dimethoxy-7-methyl-2-oxo-6a,10a-epoxy-6,10-[3]hexene[1,5]diynophenanthridine-5,8(6*H*)-dicarboxylate (74)

Iodosobenzene (40 mg, 0.18 mmol, 1.1 equiv) was added to a solution of 5-allyl hydrogen (6*S*, 6a*S*, 7*S*, 10*R*, 10a*R*, 14*Z*)-7,10-dihydro-2-hydroxy-9-methoxy-7-methyl-6a,10a-epoxy-6,10-[3]hexene[1,5]diynophenanthridine-5,8(6*H*)-dicarboxylate (**73**, 75 mg, 0.16 mmol, 1 equiv) in dry methanol (8 mL) at 23 °C. The reaction mixture was stirred at 23 °C for 10 min. The product solution was concentrated to half the original volume and the concentrate was partitioned between 1:1:1 saturated aqueous sodium bicarbonate solution:saturated aqueous sodium thiosulfate solution:saturated aqueous sodium chloride solution (60 mL) and ethyl acetate (30 mL). The aqueous layer was separated and extracted further with ethyl acetate (30 mL), then was acidified with aqueous hydrochloric acid solution (1% v/v, 30 mL). The acidified aqueous layer was extracted with ethyl acetate (2 x 40 mL). The combined organic layers were dried over sodium sulfate and were concentrated. The residue was purified by flash column chromatography (50% hexanes in ethyl acetate initially, grading to 100% ethyl acetate, and finishing with 10% methanol in ethyl acetate) to give 5-allyl hydrogen (4a*S*, 6*S*, 6a*S*, 7*S*, 10*R*, 10a*R*, 14*Z*)-2,4a,7,10-tetrahydro-4a,9-dimethoxy-7-methyl-2-oxo-6a,10a-epoxy-6,10-

[3]hexene-[1,5]diynophenanthridine-5,8(6*H*)-dicarboxylate (**74**) as a viscous light yellow oil, which solidified to afford an off-white solid when concentrated from benzene (71 mg, 89%).

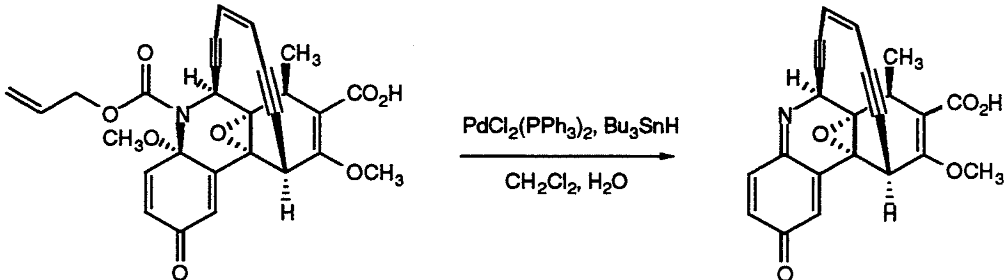
^{1}H NMR (400 MHz, C_6D_6, 60 °C) δ:	9.67 (br s, 1H, CO**OH**), 7.55 (br s, 1H, β-enone), 6.66 (d, 1H, *J* = 2.0 Hz, α-enone), 6.19 (dd, 1H, *J* = 10.5, 2.0 Hz, α-enone), 5.93 (br s, 1H, NC**H**), 5.71 (m, 1H, CH_2=C**H**), 5.16 (dd, 1H, *J* = 17.5, 1.2 Hz, C**H**$_2$=CH), 5.17 (d, 1H, *J* = 10.5 Hz, C**H**=CH), 5.12 (d, 1H, *J* = 10.5 Hz, CH=C**H**), 5.00 (dd, 1H, *J* = 10.2, 1.2 Hz, C**H**$_2$=CH), 4.60 (br dd, 1H, *J* = 13.2, 5.6 Hz, C**H**$_2$O), 4.44 (br dd, 1H, *J* = 13.2, 5.6 Hz, C**H**$_2$O), 3.94 (q, 1H, *J* = 7.3 Hz, C**H**CH_3), 3.46 (s, 1H, C≡CC**H**), 3.02 (s, 3H, OC**H**$_3$), 2.89 (s, 3H, OC**H**$_3$), 1.36 (d, 3H, *J* = 7.3 Hz, C**H**$_3$CH).
FTIR (neat), cm^{-1}:	3282 (br m, COOH), 3064 (m), 2941 (m), 1711 (vs, C=O, NC=O), 1670 (s, C=O), 1639 (m), 1613)w), 1453 (m), 1390 (s), 1308 (s), 1200 (m), 1150 (s), 1097 (w), 1056 (m), 1014 (m), 932 (m), 818 (w), 736 (m).

HRMS (FAB): Calcd for $C_{27}H_{24}O_8N$ $[MH]^+$: 490.1502

Found: 490.1511

TLC (ethyl acetate), R_f: **74**: 0.21 (UV)

73: 0.31 (UV)

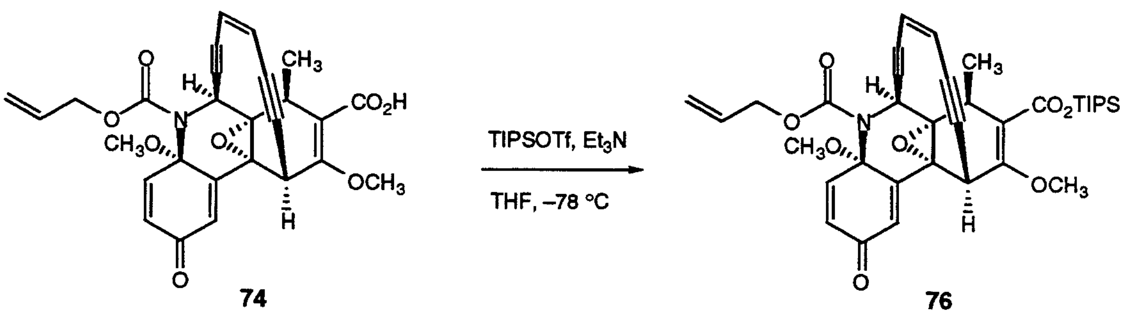


74 75

(6*S*, 6a*S*, 7*S*, 10*R*, 10a*R*, 14*Z*)-2,6,7,10-Tetrahydro-9-methoxy-7-methyl-2-oxo-6a,10a-epoxy-6,10-[3]hexene[1,5]diynophenanthridine-8-carboxylic acid (75)

Tributyltin hydride (18 μL, 0.067 mmol, 0.99 equiv) was injected into a deoxygenated suspension of 5-allyl hydrogen (4a*S*, 6*S*, 6a*S*, 7*S*, 10*R*, 10a*R*, 14*Z*)-2,4a,7,10-tetrahydro-4a,9-dimethoxy-7-methyl-2-oxo-6a,10a-epoxy-6,10-[3]hexene[1,5]diynophenanthridine-5,8(6*H*)-dicarboxylate (**74**, 76 mg, 0.15 mmol, 1 equiv), bistriphenylphosphinepalladium(II) chloride (25 mg, 0.36 mmol, 0.53 equiv) and water (20 μL) in dichloromethane (5 mL) at 23 °C. The reaction mixture was stirred for 15 min at 23 °C, then was concentrated in vacuo. The residue was purified by flash column chromatography (40% ethyl acetate in hexanes initially, grading to 100% ethyl acetate, and finishing with 10% methanol in ethyl acetate) to afford separately (6*S*, 6a*S*, 7*S*, 10*R*, 10a*R*, 14*Z*)-2,6,7,10-tetrahydro-9-methoxy-7-methyl-2-oxo-6a,10a-epoxy-6,10-[3]hexene[1,5]diynophenanthridine-8-carboxylic acid (**75**, ca. 75% purity) as a viscous yellow oil (7 mg, corrected yield: 21%) as well as recovered starting material (10 mg, 30%).

^1H NMR (400 MHz, C_6D_6), δ:	10.45 (br s, 1H, COO**H**), 6.83 (d, 1H, *J* = 10.0 Hz, β-enone), 6.45 (br s, 1H, α-enone), 6.05 (br d, 1H, *J* = 10.0, α-enone), 5.19 (br d, 1H *J* = 10.0, C**H**=CH), 5.12 (br d, 1H, *J* = 10.0 CH=C**H**), 5.00 (br s, 1H, NC**H**), 3.90 (br q, 1H, *J* = 7.3 Hz, C**H**CH_3), 3.47 (br s, 1H, C≡CC**H**), 2.90 (s, 3H, OC**H**$_3$), 1.40 (d, 3H, *J* = 7.3 Hz, CH_3CH).
TLC (ethyl acetate), R_f:	**75**: 0.29 (UV, visibly light yellow) **74**: 0.21 (UV)

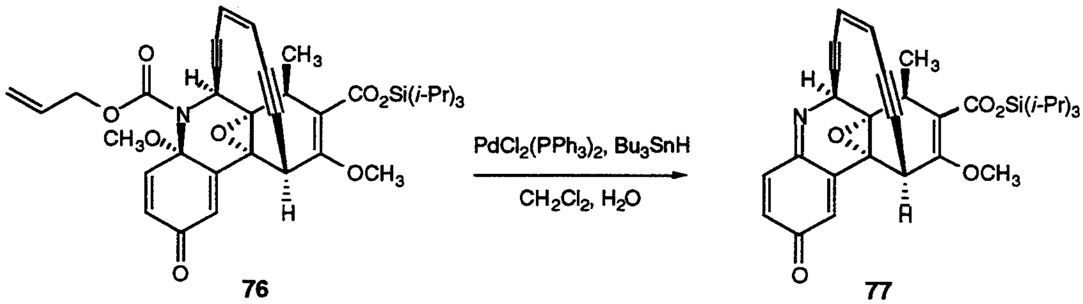


5-Allyl Triisopropylsilyl (4a*S*, 6*S*, 6a*S*, 7*S*, 10*R*, 10a*R*, 14*Z*)-2,4a,7,10-Tetrahydro-4a,9-dimethoxy-7-methyl-2-oxo-6a,10a-epoxy-6,10-[3]hexene[1,5]diynophenan-thridine-5,8(6*H*)-dicarboxylate (76)

Triisopropylsilyl trifluoromethanesulfonate (50 µL, 0.19 mmol, 2.3 equiv) was added to a solution of 5-allyl hydrogen (4a*S*, 6*S*, 6a*S*, 7*S*, 10*R*, 10a*R*, 14*Z*)-2,4a,7,10-tetrahydro-4a,9-dimethoxy-7-methyl-2-oxo-6a,10a-epoxy-6,10-[3]hexene[1,5]diynophenanthridine-5,8(6*H*)-dicarboxylate (**74**, 40 mg, 0.082 mmol, 1 equiv) and triethylamine (60 µL, 0.43 mmol, 5.3 equiv) in tetrahydrofuran (5 mL) at –78 °C. The reaction mixture was transferred to an ice bath and was stirred for 10 min at 0 °C. The product solution was partioned between saturated aqueous sodium bicarbonate solution and ethyl acetate (20 mL). The aqueous layer was separated and extracted further with ethyl acetate (20 mL). The combined organic layers were dried over sodium sulfate and were concentrated. The residue was purified by flash column chromatography (30% ethyl acetate in hexanes) to provide 5-allyl triisopropylsilyl (4a*S*, 6*S*, 6a*S*, 7*S*, 10*R*, 10a*R*, 14*Z*)-2,4a,7,10-tetrahydro-4a,9-dimethoxy-7-methyl-2-oxo-6a,10a-epoxy-6,10-[3]hexene[1,5]diynophenanthridine-5,8(6*H*)-dicarboxylate (**76**) as a colorless oil (45 mg, 85%).

^1H NMR (400 MHz, C_6D_6, 60 °C), δ:	7.54 (br s, 1H, β-enone), 6.72 (d, 1H, *J* = 2.0 Hz, α-enone), 6.21 (dd, 1H, *J* = 10.5, 2.0 Hz, α-enone), 6.01 (br s, 1H, NCH), 5.69 (m, 1H, CH_2=**CH**), 5.21 (dd, 1H, *J* = 10.0, 1.2 Hz, **CH**=CH), 5.18 (dd, 1H, *J* = 10.0, 1.2 Hz, CH=**CH**), 5.15 (dd, 1H, *J* = 17.3, 1.5 Hz, **CH**$_2$=CH), 4.98 (dd, 1H, *J* = 10.5, 1.5 Hz, **CH**$_2$=CH), 4.57 (br dd, 1H, *J* = 13.4, 5.6 Hz, **CH**$_2$O), 4.41 (br dd, 1H, *J* = 13.4, 5.6 Hz, **CH**$_2$O), 3.97 (q, 1H, *J* = 7.3 Hz, **CH**CH_3), 3.65 (s, 1H, C≡C**CH**), 3.49 (s, 3H, O**CH**$_3$), 2.99 (s, 3H, O**CH**$_3$), 1.46 (d, 3H, *J* = 7.3 Hz, **CH**$_3$CH), 1.37 (m, 3H, Si**CH**$(CH_3)_2$), 1.17 (app dd, 18H, *J* = 7.4, 1.1 Hz, SiCH(**CH**$_3$)$_2$.
FTIR (neat), cm^{-1}:	2944(s), 2867 (w), 1700 (vs, NC=O, C=O), 1671 (vs, C=O), 1636 (m), 1615 (w), 1458 (m), 1388 (s), 1306 (s), 1278 (s), 1206 (m), 1148 (m), 1099 (w), 1059 (m), 1018 (m), 934 (m), 883 (m), 752 (m), 711 (m), 679 (m).
HRMS (FAB):	Calcd for $C_{36}H_{44}O_8NSi$ $[MH]^+$: 646.2836 Found: 646.2805

TLC (40% ethyl acetate-hexanes), R_f: **76**: 0.45 (UV)

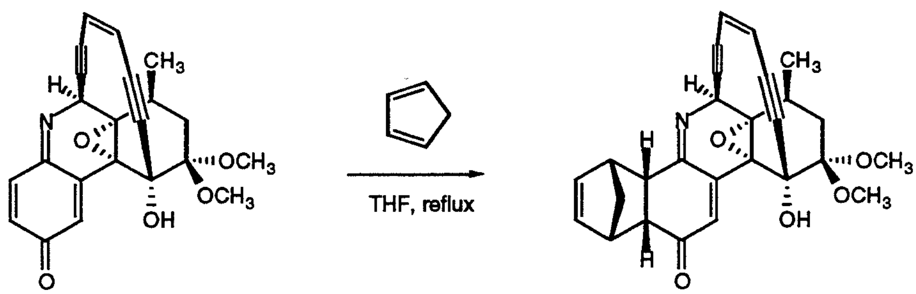


76 77

Triisopropylsilyl (6*S*, 6a*S*, 7*S*, 10*R*, 10a*R*, 14*Z*)-2,6,7,10-Tetrahydro-9-methoxy-7-methyl-2-oxo-6a,10a-epoxy-6,10-[3]hexene[1,5]diynophenanthridine-8-carboxylate (77)

Tributyltin hydride (18.0 µL, 0.0669 mmol, 0.983 equiv) was injected into a deoxygenated suspension of 5-allyl triisopropylsilyl (4a*S*, 6*S*, 6a*S*, 7*S*, 10*R*, 10a*R*, 14*Z*)-2,4a,7,10-tetrahydro-4a,9-dimethoxy-7-methyl-2-oxo-6a,10a-epoxy-6,10-[3]hexene[1,5]diynophenanthridine-5,8(6*H*)-dicarboxylate (**76**, 44.0 mg, 0.0681 mmol, 1 equiv), bistriphenylphosphinepalladium(II) chloride (20.0 mg, 0.0285 mmol, 0.418 equiv) and water (50 µL) in dichloromethane (5 mL) at 23 °C. The reaction mixture was stirred for 20 min at 23 °C, then was loaded directly onto a column of solvated (20% ethyl acetate in hexanes) flash-grade silica gel. Elution (20% ethyl acetate in hexanes initially, then 40% ethyl acetate in hexanes) provided separately triisopropylsilyl (6*S*, 6a*S*, 7*S*, 10*R*, 10a*R*, 14*Z*)-2,6,7,10-tetrahydro-9-methoxy-7-methyl-2-oxo-6a,10a-epoxy-6,10-[3]hexene[1,5]diynophenanthridine-8-carboxylate (**77**, 90% purity) as a yellow partially solidified oil (24.3 mg, corrected yield: 61%) as well as the enone **76** (6.0 mg, 14%). The desired product **77** can be further purified by flash column chromatography (1% ethyl acetate in dichloromethane) to furnish pure **77** as a yellow half-solidified oil.

^1H NMR (400 MHz, C_6D_6), δ:	6.81 (d, 1H, J = 10.0 Hz, β-enone), 6.44 (d, 1H, J = 2.0 Hz, α-enone), 6.04 (dd, 1H, J = 10.0. 2.0 Hz, α-enone), 5.19 (dd, 1H J = 10.0, 1.5 Hz, **CH**=CH), 5.14 (dd, 1H, J = 10.0, 1.5 Hz, CH=**CH**), 5.04 (d, 1H, N**CH**), 3.91 (q, 1H, J = 7.3 Hz, **CH**CH_3), 3.61 (br s, 1H, C≡C**CH**), 3.50 (s, 3H, OCH_3), 1.36 (d, 3H, J = 7.3 Hz, CH_3CH), 1.40 (m, 3H, Si**CH**$(CH_3)_2$), 1.19 (d, 18H, SiCH$(CH_3)_2$.
FTIR (neat), cm^{-1}:	2944 (m), 2867 (w), 2280 (vw, C≡C), 2193 (vw, C≡C), 1652 (vs, C=O), 1593 (w), 1463 (m), 1370 (m), 1298 (m), 1260 (w), 1218 (m), 1157 (m), 1116 (w), 1049 (w), 1027 (w), 904 (m), 883 (m), 742 (m), 680 (m).
HRMS (FAB):	Calcd for $C_{31}H_{38}O_5NSi$ $[M+3H]^+$: 532.2519 Found: 532.2528
$[\alpha]_D^{20}$ (benzene):	+1,149°, C = 0.500
TLC (20% ethyl acetate-hexanes), R_f:	**77**: 0.23 (UV, visibly light yellow) **76**: 0.13 (UV)



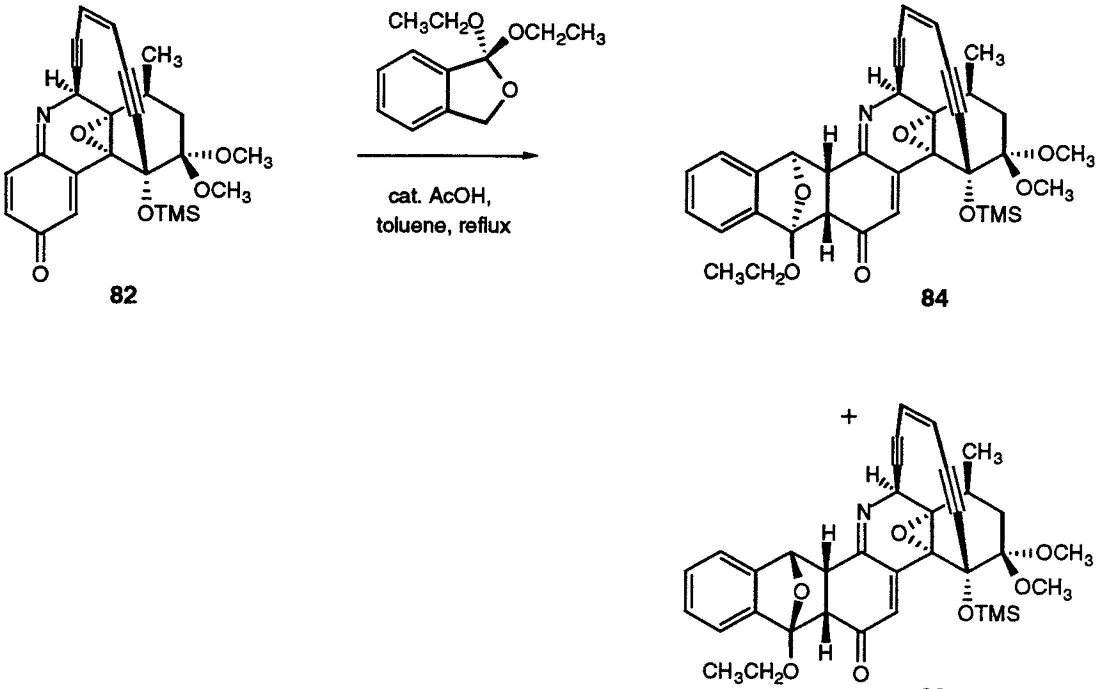
78 81

(1*S*, 4*R*, 4a*S*, 6*S*, 6a*S*, 7*S*, 10*R*, 10a*S*, 12a*R*, 16*Z*)-1,4,4a,6,7,8,9,10-Octahydro-10-hydroxy-9,9-dimethoxy-7-methyl-6a,10a-epoxy-6,10-[3]hexene[1,5]diyno-1,4-methanobenzo[*c*]phenanthridin-12(12a*H*)-one (81)

A solution of (6*S*, 6a*S*, 7*S*, 10*R*, 10a*S*, 14*Z*)-7,8,9,10-tetrahydro-10-hydroxy-9,9-dimethoxy-7-methyl-6a,10a-epoxy-6,10-[3]hexene[1,5]-diynophenanthridin-2(6*H*)-one (**78**, 2.0 mg, 0.0053 mmol, 1 equiv) and cyclopentadiene (200 µL, 3.0 mmol, 570 equiv) in tetrahydrofuran (1.5 mL) was heated at reflux for 45 min. The product solution was cooled to 23 °C, then was concentrated in vacuo. The residue was purified by flash column chromatography (50% ethyl acetate in hexanes initially, then 60% ethyl acetate in hexanes) to provide (1*S*, 4*R*, 4a*S*, 6*S*, 6a*S*, 7*S*, 10*R*, 10a*S*, 12a*R*, 16*Z*)-1,4,4a,6,7,8,9,10-octahydro-10-hydroxy-9,9-dimethoxy-7-methyl-6a,10a-epoxy-6,10-[3]hexene[1,5]diyno-1,4-methanobenzo[*c*]phenanthridin-12(12a*H*)-one (**81**) as a colorless oil (2.0 mg, 90%).

^1H NMR (400 MHz, C_6D_6), δ:	7.63 (s, 1H, α-enone), 6.32 (dd, 1H, *J* = 5.6, 2.9 Hz, HCC**H**=CHCH), 5.93 (dd, 1H, *J* = 5.6, 2.7 Hz, HCCH=C**H**CH), 5.26 (dd, 1H, *J* = 10.0, 2.0 Hz, CHC≡CC**H**=CH), 5.18 (d, 1H, *J* = 10.0 Hz, CHC≡CCH=C**H**), 5.10 (d, 1H *J* = 2.0 Hz, NC**H**), 3.32 (s, 3H, OCH_3), 3.30 (m, 1H, $\mathbf{CH}CH_2CH$), 3.27 (s, 1H, O**H**), 3.27 (dd, 1H, *J* = 8.0, 4.2 Hz, **C**HC=O), 3.23 (m, 1H, $CHCH_2C\mathbf{H}$), 2.90 (s, 3H, $OC\mathbf{H}_3$), 2.65 (dd, 1H, *J* = 8.0, 4.2 Hz, **C**HC=N), 2.18 (m, 1H, $\mathbf{CH}CH_3$), 2.07 (t, 1H, *J* = 13.8, $(CH_3O)_2CC\mathbf{H}_2$), 1.80 (dd, 1H, *J* = 14.2, 5.2 Hz, $(CH_3O)_2CC\mathbf{H}_2$), 1.14 (br d, 1H, *J* = 8.5 Hz, $CHC\mathbf{H}_2CH$), 0.97 (d, 3H, *J* = 7.1 Hz, $C\mathbf{H}_3CH$), 0.85 (br d, 1H, *J* = 8.5 Hz, $CHC\mathbf{H}_2CH$).
FTIR (neat), cm^{-1}:	3600-3100 (br, OH), 3060 (w), 2977 (m), 2946 (m), 2840 (w), 2282 (w, C≡C), 2187 (w, C≡C), 1660 (s, C=O), 1652 (sh), 1626 (w), 1601 (m), 1462 (m), 1360 (m), 1339 (m), 1297 (w), 1260 (m), 1197 (m), 1153 (s), 1114 (m), 1093 (w), 1058 (s), 981 (m), 900 (m), 805 (m), 737 (s).

HRMS (FAB):	Calcd for $C_{27}H_{26}O_5N$ $[MH]^+$: 444.1811
	Found: 444.1826
TLC (40% hexanes-ethyl acetate), R_f:	**81**: 0.26 (UV)
	78: 0.38 (UV, visibly light yellow)



Diels-Alder Adducts 84 and 83

A deoxygenated solution of (6*S*, 6a*S*, 7*S*, 10*R*, 10a*R*, 14*Z*)-7,8,9,10-tetrahydro-9,9-dimethoxy-7-methyl-10-(trimethylsiloxy)-6a,10a-epoxy-6,10-[3]hexene[1,5]diynophenan-thridin-2(6*H*)-one (**82**, 5.0 mg, 0.011 mmol, 1 equiv), 1,1-diethoxyphthalan (50 mg, 0.24 mmol, 22 equiv) and glacial acetic acid (1.0 μL, 0.017 mmol, 1.6 equiv) in toluene (2 mL) was heated at reflux for 20 min. Heating was discontinued and glacial acetic acid (1.0 μL, 0.017 mmol, 1.6 equiv) was added to the warm reaction mixture. The reaction mixture was heated at reflux for 15 min, then was cooled to 23 °C and was concentrated in vacuo. The residue was purified twice by flash column chromatography (first column: 10% ethyl acetate in dichloromethane; second column: 40% ethyl acetate in hexanes) to provide separately (1*S*, 4*R*, 4a*S*, 6a*R*, 7*S*, 12*R*, 12a*S*, 14*S*, 14a*S*, 18*Z*)-7-ethoxy-1,2,3,4,7,12,12a,14-octahydro-3,3-dimethoxy-1-

methyl-4-trimethylsiloxy-4a,14a:7,12-diepoxy-4,14-[3]hexene[1,5]diynonaphtho[2,3-*c*]phenanthridin-6(6a*H*)-one (**84**) as a colorless oil (2.0 mg, 30%) as well as (1*S*, 4*R*, 4a*S*, 6a*R*, 7*R*, 12*S*, 12a*S*, 14*S*, 14a*S*, 18*Z*)-7-ethoxy-1,2,3,4,7,12,12a,14-octahydro-3,3-dimethoxy-1-methyl-4-trimethylsiloxy-4a,14a:7,12-diepoxy-4,14-[3]hexene[1,5]diynonaphtho[2,3-*c*]phenanthridin-6(6a*H*)-one (**83**) as colorless oil (2.0 mg, 30%).

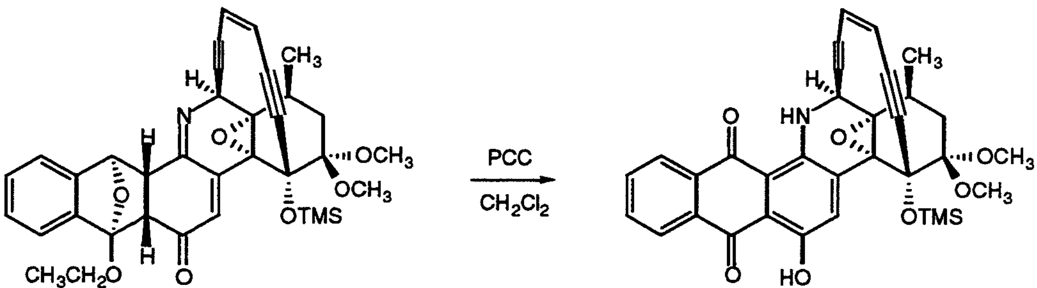
84:

^{1}H NMR (400 MHz, C_6D_6), δ: 7.83 (s, 1H, α-enone), 6.97 (br d, 1H, *J* = 6.8 Hz, aryl), 6.89 (td, 1H, *J* = 6.8, 1.2 Hz, aryl), 6.86 (td, 1H, *J* = 6.8, 1.2 Hz, aryl), 6.73 (br d, 1H, *J* = 6.8 Hz, aryl), 5.44 (s, 1H, OCH), 5.23 (br s, 2H, **CH**=**CH**), 5.17 (br s, 1H, N**CH**), 3.82 (q, 2H, *J* = 7.1 Hz, CH_2CH_3), 3.50 (s, 3H, OCH_3), 3.07 (d, 1H, *J* = 7.8 Hz, **CH**), 3.06 (s, 3H, OCH_3), 2.75 (d, 1H, *J* = 7.8 Hz, **CH**), 2.27 (m, 1H, $CHCH_3$), 2.19 (t, 1H, *J* = 13.7, $\mathbf{CH_2}$), 1.92 (dd, 1H, *J* = 14.7, 4.8 Hz, $\mathbf{CH_2}$), 1.24 (t, 3H, *J* = 7.1 Hz, $CH_2\mathbf{CH_3}$), 1.00 (d, 3H, *J* = 6.8 Hz, CH_3CH), 0.54 (s, 9H, $Si(CH_3)_3$).

FTIR (neat), cm^{-1}:	3083 (w), 3072 (w), 3030 (w), 2977 (m), 2946 (m), 2904 (m), 2831 (w), 1678 (s, C=O), 1632 (w), 1605 (m), 1479 (m), 1462 (m), 1369 (w), 1341 (m), 1325 (m), 1293 (s), 1251 (s), 1203 (m), 1166 (s), 1126 (m), 1102 (m), 1064 (s), 984 (m), 939 (m), 875 (m), 845 (s), 766 (m), 751 (w), 737 (m), 679 (s).
TLC (10% ethyl acetate-CH_2Cl_2), R_f:	**84**: 0.32 (UV)
	82: 0.34 (UV, visibly light yellow)
(40% ethyl acetate-hexanes), R_f:	**84**: 0.24 (UV)
	82: 0.38 (UV, visibly light yellow)

83:

^1H NMR (400 MHz, C_6D_6), δ:	7.44 (br d, 1H, J = 6.3 Hz, aryl), 7.31 (br d, 1H, J = 6.8 Hz, aryl), 7.10 (td, 1H, J = 6.8, 1.2 Hz, aryl), 7.05 (td, 1H, J = 6.8, 1.2 Hz, aryl), 6.70 (s, 1H, α-enone), 5.42 (d, 1H, J = 5.4 Hz, OCH), 5.20 (br s, 2H, CH=CH), 5.09 (br s, 1H, NCH), 4.01 (m, 1H, CH_2CH_3), 3.91 (m, 2H, CH_2CH_3 and CH), 3.32 (s, 3H, OCH_3), 3.10 (d, 1H, J = 9.6 Hz, CH), 2.97 (s, 3H, OCH_3), 2.75 (d, 1H, J = 7.8 Hz, CH), 2.58 (m, 1H, $CHCH_3$), 1.82 (d, 2H, J = 9.7 Hz, CH_2), 1.26 (t, 3H, J = 6.8 Hz, CH_2CH_3), 0.98 (d, 3H, J = 7.1 Hz, CH_3CH), 0.41 (s, 9H, $Si(CH_3)_3$).
FTIR (neat), cm^{-1}:	3083 (w), 3030 (w), 2947 (s), 2840 (w), 1667 (s, C=O), 1631 (w), 1604 (m), 1479 (m), 1462 (m), 1371 (w), 1352 (w), 1312 (s), 1252 (s), 1142 (s), 1116 (m), 1069 (s), 1001 (m), 916 (w), 867 (m), 843 (s), 761 (s), 646 (s).
TLC (10% ethyl acetate-CH_2Cl_2), R_f:	**83**: 0.12 (UV)
	82: 0.34 (UV, visibly light yellow)
(40% ethyl acetate-hexanes), R_f:	**83**: 0.24 (UV)
	82: 0.38 (UV, visibly light yellow)



84 85

(1*S*, 4*R*, 4a*S*, 14*S*, 14a*S*, 18*Z*)-1,2,3,4,7,13,14-Hexahydro-6-hydroxy-3,3-dimethoxy-1-methyl-4-trimethylsiloxy-4a,14a-epoxy-4,14-[3]hexene[1,5]diynonaphtho[2,3-*c*]phenanthridine-7,12-dione (85)

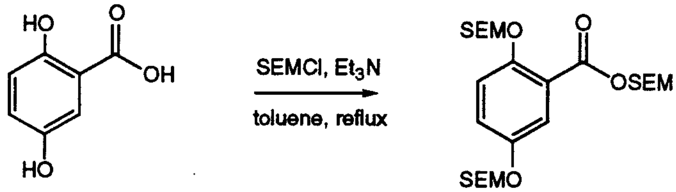
Pyridinium chlorochromate (4 mg, 0.02 mmol, 11 equiv) was added to a solution of (1*S*, 4*R*, 4a*S*, 6a*R*, 7*S*, 12*R*, 12a*S*, 14*S*, 14a*S*, 18*Z*)-7-ethoxy-1,2,3,4,7,12,12a,14-octahydro-3,3-dimethoxy-1-methyl-4-trimethylsiloxy-4a,14a:7,12-diepoxy-4,14-[3]hexene[1,5]diynonaphtho[2,3-*c*]phenanthridin-6(6a*H*)-one (**84**, 1.0 mg, 0.0016 mmol, 1 equiv) in dichloromethane (0.5 mL) at 23 °C. The reaction mixture was stirred for 10 min, then was loaded directly onto a column of solvated (20% ethyl acetate in hexanes) flash grade silica gel. Elution (20% ethyl acetate in hexanes) provided (1*S*, 4*R*, 4a*S*, 14*S*, 14a*S*, 18*Z*)-1,2,3,4,7,13,14-hexahydro-6-hydroxy-3,3-dimethoxy-1-methyl-4-trimethylsiloxy-4a,14a-epoxy-4,14-[3]hexene[1,5]diynonaphtho[2,3-*c*]phenanthridine-7,12-dione (**85**) as a red oil (300 µg, 30%).

^{1}H NMR (400 MHz, C_6D_6), δ: 13.77 (s, 1H, **OH**), 10.51 (br d, 1H, *J* = 4.0 Hz, **NH**), 9.09 (s, 1H, aryl), 8.36 (br d, 1H, *J* = 7.6 Hz, aryl), 8.14 (br d, 1H, *J* = 7.6 Hz, aryl), 7.15 (t, 1H, *J* = 7.6 Hz, aryl), 7.07 (t, *J* = 7.6 Hz, aryl), 5.21 (d, 1H, *J* = 10.0 Hz, C**H**=CH), 5.16 (br d, 1H, *J* = 10.0 Hz, CH=C**H**), 3.86 (dd, 1H, *J* = 4.0, 1.2 Hz, NC**H**), 3.49 (s, 3H, OCH_3), 3.07 (s, 3H, OCH_3), 2.28 (m, 1H, $CHCH_3$), 2.23 (t, 1H, *J* = 13.1 Hz, CH_2), 1.90 (dd, 1H, *J* = 13.6, 4.8 Hz, CH_2), 0.98 (d, 3H, *J* = 6.8 Hz, CH_3CH), 0.52 (s, 9H, $(CH_3)_3Si$).

FTIR (neat), cm^{-1}: 3245 (w), 2957 (m), 2278 (w, C≡C), 1651 (w), 1622 (m), 1589 (m), 1569 (w), 1489 (m), 1462 (w), 1355 (m), 1250 (s), 1200 (m), 1167 (m), 1120 (m), 1057 (m), 875 (m), 843 (m).

HRMS (FAB): Calcd for $C_{33}H_{32}O_7NSi$ $[MH]^+$: 582.1948
Found: 582.1979

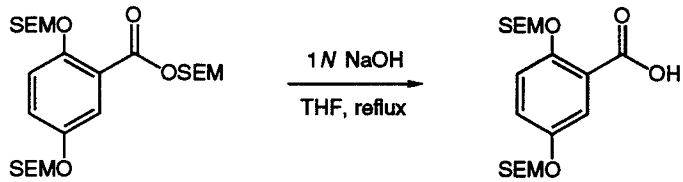
TLC (40% ethyl acetate-hexanes), R_f: **85**: 0.45 (visibly red)
84: 0.24 (UV)



2-(Trimethylsilyl)ethoxymethyl 2,5-Bis[[2-(trimethylsilyl)ethoxy] methoxy]benzoate

2-(Trimethylsilyl)ethoxymethyl chloride (13.0 mL, 73.5 mmol, 5.07 equiv) was added over 5 min to a suspension of 2,5-dihydroxybenzoic acid (2.23 g, 14.5 mmol, 1 equiv) and triethylamine (12.0 mL, 86.1 mmol, 5.94 equiv) in toluene (70 mL) at 23 °C. The ensuing reaction was sufficiently exothermic to bring the suspension to a gentle reflux over a period of 30 min. After 1 h, external heating was applied and the suspension was heated at reflux for 16 hours, then was cooled to 23 °C. The product was partitioned between half-saturated aqueous sodium chloride solution (200 mL) and dichloromethane (100 mL). The aqueous layer was separated and extracted further with dichloromethane (2 x 100 mL). The combined organic layers were dried over sodium sulfate and were concentrated. The residue was purified by flash column chromatography (10% ethyl acetate in hexanes) to provide 2-(trimethylsilyl)ethoxymethyl 2,5-bis[[2-(trimethylsilyl)-ethoxy]methoxy]benzoate as a colorless oil (7.18 g, 91%).

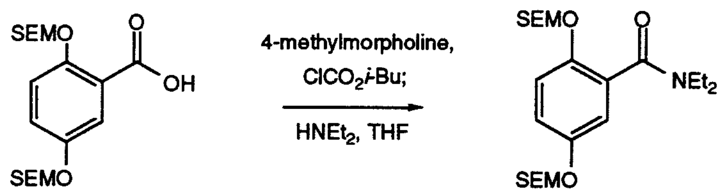
^1H NMR (300 MHz, $CDCl_3$), δ:	7.48 (d, 1H, J = 2.8 Hz, aryl), 7.17 (d, 1H J = 8.8 Hz, aryl), 7.13 (dd, 1H, J = 8.8, 2.8 Hz, aryl), 5.49 (s, 2H, OCH_2O), 5.22 (s, 2H, OCH_2O), 5.18 (s, 2H, OCH_2O), 3.84–3.71 (m, 3H, $(CH_3)_3SiCH_2CH_2O$), 3.65–3.57 (m, 1H, $(CH_3)_3SiCH_2CH_2O$), 1.03–0.90 (m, 4H, $(CH_3)_3SiCH_2CH_2O$), 0.02 (s, 9H, $(CH_3)_3Si$), –0.01 (s, 9H, $(CH_3)_3Si$).
FTIR (neat), cm^{-1}:	2953 (s), 2896 (s), 1732 (s, C=O), 1620 (w), 1583 (w), 1495 (s), 1420 (m), 1381 (w), 1250 (s), 1204 (s), 1153 (m), 1095 (m), 1003 (s), 940 (m), 860 (s), 840 (s), 760 (m), 700 (m).
TLC (10% ethyl acetate-hexanes), R_f:	product SEM ester: 0.16 (UV, CAM)



2,5-Bis[[2-(trimethylsilyl)ethoxy]methoxy]benzoic Acid

A biphasic solution of 2-(trimethylsilyl)ethoxymethyl 2,5-bis[[2-(trimethylsilyl)-ethoxy]methoxy]benzoate (7.18 g, 13.2 mmol, 1 equiv) in tetrahydrofuran (80 mL) and 1.0 N aqueous sodium hydroxide solution (80 mL, 80 mmol, 6.1 equiv) was heated at reflux for 24 h. The product solution was cooled to 23 °C, then was diluted with aqueous hydrochloric acid solution (1% v/v, 300 mL). The aqueous layer was further acidified to pH 1 by the addition of concentrated aqueous hydrochloric acid solution. The acidified aqueous phase was extracted with dichloromethane (2 x 300 mL). The combined organic layers were dried over sodium sulfate and were concentrated. The residue was purified by flash column chromatography (40% ethyl acetate in hexanes initially, grading to 100% ethyl acetate) to provide 2,5-bis[[2-(trimethylsilyl)ethoxy]methoxy]benzoic acid as a colorless oil (5.44, 100%). Because of the propensity of the ortho SEM ether to migrate to the carboxylic acid, the purified product was used immediately in the next step in the sequence.

^1H NMR (300 MHz, $CDCl_3$), δ:	7.82 (d, 1H, *J* = 2.8 Hz, aryl), 7.23 (m, 2H, aryl), 5.40 (s, 2H, OCH_2O), 5.20 (s, 2H, OCH_2O), 3.83–3.61 (m, 4H, $(CH_3)_3SiCH_2CH_2O$), 0.99–0.91 (m, 4H, $(CH_3)_3SiCH_2CH_2O$), 0.01 (s, 9H, $(CH_3)_3Si$), –0.01 (s, 9H, $(CH_3)_3Si$).
FTIR (neat), cm^{-1}:	3700–2500 (br), 3272 (br m), 3072 (br m), 2953 (s), 2896 (m), 1742 (s, C=O), 1698 (s, C=O), 1613 (w), 1583 (w), 1495 (s), 1433 (m), 1408 (m), 1381 (w), 1250 (s), 1204 (s), 1153 (m), 1095 (s), 1003 (vs), 939 (w), 919 (w), 858 (s), 836 (s), 758 (w), 694 (w).
TLC (40% ethyl acetate-hexanes), R_f:	product acid: 0.17 (UV, CAM) starting SEM ester: 0.70 (UV, CAM)



2,5-Bis[[2-(trimethylsilyl)ethoxy]methoxy]benzoic Acid *N*,*N*-Diethylamide

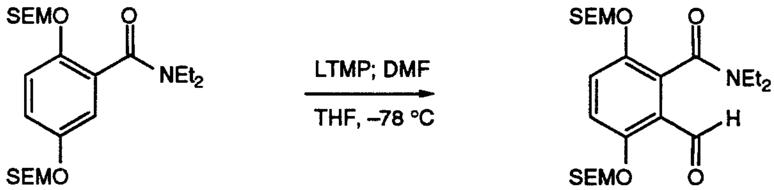
Isobutyl chloroformate (8.0 mL, 62 mmol, 3.7 equiv) was added to a solution of 4-methylmorpholine (7.0 mL, 64 mmol, 3.9 equiv) and 2,5-bis[[2-(trimethylsilyl)ethoxy]-methoxy]benzoic acid (6.85 g, 16.5 mmol, 1 equiv) in tetrahydrofuran (150 mL) at 0 °C, producing a white precipitate. The reaction mixture was swirled manually at 0 °C for 20 min. Diethylamine (20.0 mL, 193 mmol, 11.7 equiv) was added to the suspension, and the mixture was swirled manually at 0 °C for 5 min, producing a solid mass. Additional tetrahydrofuran (100 mL) was added to the mass, followed by diethylamine (10.0 mL, 96.7 mmol, 5.58 equiv). The resultant suspension was swirled manually as it was allowed to warm to 23 °C. The product suspension was partitioned between half-saturated aqueous sodium chloride solution (200 mL) and ethyl acetate (200 mL). The aqueous layer was separated and extracted further with a 200-mL portion of ethyl acetate. The combined organic layers were dried over sodium sulfate and were concentrated. The residue was purified by flash column chromatography (20% ethyl acetate in hexanes initially, then 40% ethyl acetate in hexanes) to give 2,5-bis[[2-(trimethylsilyl)ethoxy]methoxy]benzoic acid *N*,*N*-diethylamide as a light yellow oil (5.89 g, 76%).

^1H NMR (300 MHz, $CDCl_3$), δ: 7.09 (d, 1H, *J* = 8.8 Hz, aryl), 6.97 (dd, 1H, *J* = 8.8, 2.8 Hz, aryl), 6.89 (d, 1H, *J* = 2.8 Hz, aryl), 5.15 (br m, 4H, OCH_2O), 3.73 (m, 4H, $(CH_3)_3SiCH_2CH_2O$), 3.62 (m, 1H, CH_2CH_3), 3.51 (m, 1H, CH_2CH_3), 3.18 (br q, 2H, *J* = 7.2 Hz, CH_2CH_3), 1.23 (t, 3H, *J* = 7.2 Hz, CH_2CH_3), 1.06 (t, 3H, *J* = 7.2 Hz, CH_2CH_3), 0.95 (m, 4H, $(CH_3)_3SiCH_2CH_2O$), 0.00 (s, 18H, $CH_3)_3Si$).

FTIR (neat), cm^{-1}: 2953 (s), 2896 (m), 1639 (vs, NC=O), 1495 (s), 1440 (m), 1380 (m), 1291 (m), 1249 (s), 1207 (s), 1173 (w), 1149 (m), 1092 (s), 998 (vs), 920 (m), 860 (s), 836 (s), 757 (m), 694 (m).

HRMS (CI): Calcd for $C_{23}H_{44}O_5NSi_2$ $[MH]^+$: 470.2758
Found: 470.2735

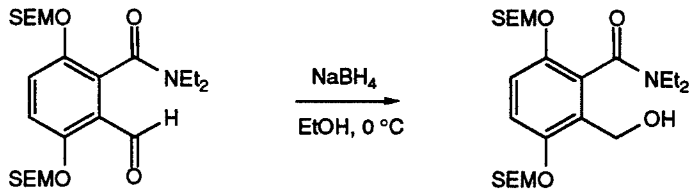
TLC (40% ethyl acetate-hexanes), R_f: product amide: 0.43 (UV, CAM)
starting acid: 0.17 (UV, CAM)



2-Formyl-3,6-bis[[2-(trimethylsilyl)ethoxy]methoxy]benzoic Acid *N,N*-Diethylamide

A solution of 2,5-bis[[2-(trimethylsilyl)ethoxy]methoxy]benzoic acid *N,N*-diethylamide (1.50 g, 3.19 mmol, 1 equiv) in tetrahydrofuran (5 mL) at 23 °C was transferred via cannula to a solution of lithium 2,2,6,6-tetramethylpiperidide in tetrahydrofuran (0.329 M, 13.6 mL, 4.48 mmol, 1.40 equiv) at –78 °C. The reaction mixture was stirred at –78 °C for 2 h. *N,N*-Dimethylformamide (1.50 mL, 19.4 mmol, 6.07 equiv) was added, and the reaction mixture was transferred to an ice bath. After 10 min, the ice bath was removed, and the reaction mixture was allowed to warm to 23 °C and was stirred at that temperature for 1 h. The product solution was partitioned between aqueous phosphate buffer solution (pH 7, 0.05 M in sodium hydrogen phosphate and 0.05 M in potassium dihydrogen phosphate, 100 mL) and ethyl acetate (100 mL). The aqueous layer was separated and extracted further with a 100-mL portion of ethyl acetate. The combined organic layers were dried over sodium sulfate and were concentrated. The residue was purified by flash column chromatography (30% ethyl acetate in hexanes intially, then 40% ethyl acetate in hexanes) to provide separately 2-formyl-3,6-bis[[2-(trimethylsilyl)ethoxy]methoxy]benzoic acid *N,N*-diethylamide as a colorless oil (1.072 g, 67%) as well as recovered 2,5-bis[[2-(trimethylsilyl)ethoxy]methoxy]benzoic acid (0.305 g, 20%).

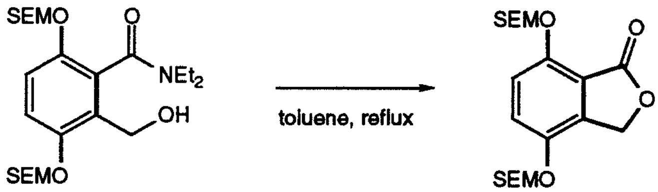
^1H NMR (300 MHz, $CDCl_3$), δ:	10.42 (s, 1H, **CHO**), 7.38 (d, 1H, *J* = 9.2 Hz, aryl), 7.19 (d, 1H, *J* = 9.2 Hz, aryl), 5.28 (m, 2H, OCH_2O), 5.13 (m, 2H, OCH_2O), 3.87–3.62 (m, 5H, $(CH_3)_3SiCH_2CH_2O$ and CH_2CH_3), 3.53 (m, 1H, CH_2CH_3), 3.08 (q, 2H, *J* = 7.2 Hz, CH_2CH_3), 1.30 (t, 3H, *J* = 7.2 Hz, CH_2CH_3), 1.02 (t, 3H, *J* = 7.2 Hz, CH_2CH_3), 0.99–0.91 (m, 4H, $(CH_3)_3SiCH_2CH_2O$), 0.00 (s, 9H, $(CH_3)_3Si$), –0.01 (s, 9H, $(CH_3)_3Si$).
FTIR (neat), cm^{-1}:	2954 (s), 2891 (m), 1693 (s, C=O), 1644 (vs, NC=O), 1587 (m), 1473 (s), 1395 (m), 1250 (s), 1189 (m), 1151 (m), 1098 (s), 1027 (s), 992 (m), 944 (m), 912 (w), 862 (m), 836 (s), 760 (m), 693 (w).
HRMS (FAB):	Calcd for $C_{24}H_{44}O_6NSi_2$ $[MH]^+$: 498.2707 Found: 498.2721
TLC (40% ethyl acetate-hexanes), R_f:	product aldehyde: 0.22 (UV, CAM) starting amide: 0.43 (UV, CAM)



2-(Hydroxymethyl)-3,6-bis[[2-(trimethylsilyl)ethoxy]methoxy]benzoic Acid *N,N*-Diethylamide

Sodium borohydride (272 mg, 7.19 mmol, 4.99 equiv) was added to a solution of 2-formyl-3,6-bis[[2-(trimethylsilyl)ethoxy]methoxy]benzoic acid *N,N* diethylamide (718 mg, 1.44 mmol, 1 equiv) in absolute ethanol (15 mL) at 0 °C. The reaction mixture was stirred for 3 h at 0 °C, then was partitioned between half-saturated aqueous sodium chloride solution (100 mL) and ethyl acetate (70 mL). The aqueous layer was separated and extracted further with ethyl acetate (2 x 70 mL). The combined organic layers were dried over sodium sulfate and were concentrated. The residue was purified by flash column chromatography (50% ethyl acetate in hexanes) to provide 2-(hydroxymethyl)-3,6-bis[[2-(trimethylsilyl)ethoxy]methoxy]benzoic acid *N,N* diethylamide as a colorless oil (660 mg, 92%).

^1H NMR (300 MHz, $CDCl_3$), δ:	7.09 (d, 1H, *J* = 9.1 Hz, aryl), 7.05 (d, 1H, *J* = 9.1 Hz, aryl), 5.21 (m, 2H, OCH_2O), 5.13 (m, 2H, OCH_2O), 4.61 (d, 1H, *J* = 12.1 Hz, CH_2OH), 4.44 (d, 1H, *J* = 12.1 Hz, CH_2OH), 3.79–3.66 (m, 4H, $(CH_3)_3SiCH_2CH_2O$), 3.59 (q, 2H, *J* = 7.1 Hz, CH_2CH_3), 3.20 (m, 2H, CH_2CH_3), 2.90 (br s, 1H, OH), 1.26 (t, 3H, *J* = 7.1 Hz, CH_2CH_3), 1.06 (t, 3H, *J* = 7.1 Hz, CH_2CH_3), 0.98–0.91 (m, 4H, $(CH_3)_3SiCH_2CH_2O$), –0.01 (s, 18H, $(CH_3)_3Si$).
FTIR (neat), cm^{-1}:	3445 (br, OH), 2953 (s), 2897 (m), 1615 (vs, NC=O), 1480 (vs), 1423 (m), 1380 (w), 1288 (m), 1248 (s), 1147 (m), 1098 (s), 1036 (vs), 1008 (s), 940 (m), 858 (s), 836 (s), 757 (m), 694 (m).
HRMS (CI):	Calcd for $C_{24}H_{46}O_6NSi_2$ $[MH]^+$: 500.2864 Found: 500.2837
TLC (40% ethyl acetate-hexanes), R_f:	product alcohol: 0.15 (CAM) starting aldehyde: 0.22 (UV, CAM)



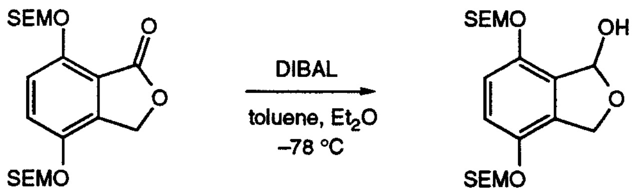
90

4,7-Bis[[2-(trimethylsilyl)ethoxyl]methoxy]phthalide (90)

A suspension of 2-(hydroxymethyl)-3,6-bis[[2-(trimethylsilyl)ethoxy]methoxy]-benzoic acid *N,N* diethylamide (695 mg, 1.39 mmol, 1 equiv) and potassium carbonate (10 mg, 0.07 mmol, 0.05 equiv) in 1,3,5-trimethylbenzene (30 mL) was heated at reflux for 80 min. The reaction mixture was cooled to 23 °C, then was concentrated in vacuo. The residue was purified by flash column chromatography (30% ethyl acetate in hexanes) to provide 4,7-bis[[2-(trimethylsilyl)ethoxyl]methoxy]phthalide (**90**) as a white solid (mp 80.0-81.5 °C, 481 mg, 81%).

^{1}H NMR (300 MHz, $CDCl_3$), δ: 7.31 (d, 1H, *J* = 8.9 Hz, aryl), 7.16 (d, 1H, *j* = 8.9 Hz, aryl), 5.35 (s, 2H, Ar**CH**$_2$O), 5.22 (s, 2H, O**CH**$_2$O), 5.20 (s, 2H, O**CH**$_2$O), 3.84–3.72 (m, 4H, $(CH_3)_3SiCH_2$**CH**$_2$O), 0.98–0.91(m, 4H, $(CH_3)_3Si$**CH**$_2$$CH_2O$), 0.00 (s, 9H, (**CH**$_3$)$_3$Si), –0.01 (s, 9H, (**CH**$_3$)$_3$Si).

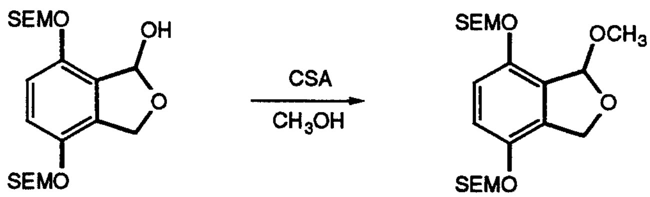
FTIR (neat), cm^{-1}:	3094 (w), 2954 (m), 2900 (m), 1765 (vs, C=O), 1608 (w), 1503 (s), 1462 (w), 1410 (w), 1364 (w), 1305 (m), 1254 (s), 1231 (w), 1187 (m), 1156 (w), 1093 (m), 1008 (s), 986 (s), 942 (s), 890 (w), 862 (m), 834 (s), 766 (m), 692 (m).
HRMS (CI):	Calcd for $C_{20}H_{38}O_6NSi_2$ $[MNH_4]^+$: 444.2238 Found: 444.2213
TLC (40% ethyl acetate-hexanes), R_f:	**90**: 0.53 (UV, CAM) starting alcohol: 0.15 (CAM



1-Hydroxy-4,7-bis[[2-(trimethylsilyl)ethoxy]methoxy]phthalan

A solution of diisobutylaluminum hydride in toluene (1.0 M, 290 µL, 0.290 mmol, 1.18 equiv) and diethyl ether (2 mL) were added sequentially to a solution of 4,7-bis[[2-(trimethylsilyl)ethoxyl]methoxy]phthalide (105 mg, 0.246 mmol, 1 equiv) in toluene (2 mL) at –78 °C. The resulting solution was stirred at –78 °C for 1 h. The cold bath was removed and diethyl ether (2 mL) and saturated sodium chloride solution (5 mL) were added sequentially to the resulting cold product solution. The biphasic mixture was allowed to warm to 23 °C, then was partitioned between saturated sodium chloride solution (100 mL) and ethyl acetate (70 mL). The aqueous layer was separated and extracted further with ethyl acetate (70 mL). The combined organic layers were dried over sodium sulfate then were concentrated to provide 1-hydroxy-4,7-bis[[2-(trimethylsilyl)ethoxy]methoxy]phthalan as a colorless oil (97 mg, 92%).

^1H NMR (300 MHz, C_6D_6), δ:	7.11 (m, 2H, aryl), 6.77 (dd, 1H, *J* = 7.7, 2.2 Hz, C**H**OH), 5.39 (dd, 1H, *J* = 12.7, 2.2 Hz, ArC**H**$_2$O), 5.16 (d, 1H, *J* = 12.7 Hz, ArC**H**$_2$O), 5.07 (app q, 2H, *J* = 6.8 Hz, OC**H**$_2$O), 4.94 (m, 2H, OC**H**$_2$O), 3.75 (app t, 2H, *J* = 7.9 Hz, $(CH_3)_3SiCH_2CH_2O$), 3.65 (app t, 2H, *J* = 7.9 Hz, $(CH_3)_3SiCH_2CH_2O$), 2.71 (d, 1H, *J* = 7.7 Hz, O**H**), 0.98–0.86 (m, 4H, $(CH_3)_3SiCH_2CH_2O$), –0.02 (s, 9H, $(CH_3)_3Si$), –0.03 (s, 9H, $(CH_3)_3Si$).
TLC (40% ethyl acetate-hexanes), R_f:	product lactol: 0.45 (CAM) **90**: 0.53 (UV, CAM)



92

1-Methoxy-4,7-bis[[2-(trimethylsilyl)ethoxy]methoxy]phthalan (92)

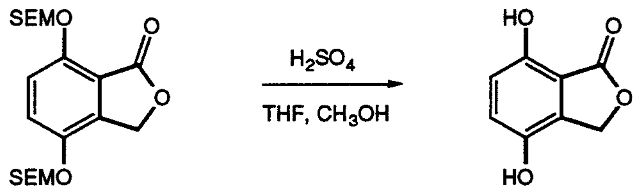
10-Camphorsulfonic acid (ca. 2 mg, 0.009 mmol, 0.04 equiv) was added to a solution of 1-hydroxy-4,7-bis[[2-(trimethylsilyl)ethoxy]methoxy]phthalan (97 mg, 0.226 mmol, 1 equiv) in anhydrous methanol (15 mL) at 23 °C, and the resulting solution was stirred for 10 min. The product solution was concentrated to 5 mL then was partitioned between saturated sodium chloride solution (75 mL) and ethyl acetate (50 mL). The aqueous layer was separated and extracted further with ethyl acetate (50 mL). The combined organic layers were dried over sodium sulfate and were concentrated. The residue was purified by flash column chromatography (20% ethyl acetate in hexanes) to furnish 1-methoxy-4,7-bis[[2-(trimethylsilyl)ethoxy]methoxy]phthalan (**92**) as a colorless oil (84 mg, 84%).

^1H NMR (300 MHz, C_6D_6), δ: 7.13 (m, 2H, aryl), 6.58 (d, 1H, *J* = 2.2 Hz, $CHOCH_3$), 5.41 (dd, 1H, *J* = 12.9, 2.2 Hz, $ArCH_2O$), 5.23 (d, 1H, *J* = 12.9 Hz, $ArCH_2O$), 5.12 (d, 1H, *J* = 6.8 Hz, OCH_2O), 5.05 (d, 1H, *J* = 6.8 Hz, OCH_2O), 4.91 (m, 2H, OCH_2O), 3.74 (app t, 2H, *J* = 7.9 Hz, $(CH_3)_3SiCH_2CH_2O$), 3.64 (app t, 2H, *j* = 7.9 Hz, $(CH_3)_3SiCH_2CH_2O$), 3.45 (s, 3H, OCH_3), 2.71 (d, 1H, *J* = 7.7 Hz, OH), 0.97–0.85 (m, 4H, $(CH_3)_3SiCH_2CH_2O$), –0.03 (s, 9H, $(CH_3)_3Si$), –0.04 (s, 9H, $(CH_3)_3Si$).

FTIR (neat), cm^{-1}: 2952 (s), 2891 (m), 1497 (s), 1410 (w), 1377 (m), 1307 (m), 1248 (s), 1190 (m), 1151 (m), 1101 (s), 1057 (m), 1003 (vs), 962 (m), 917 (m), 858 (m), 836 (s), 757 (w), 693 (w).

TLC (20% ethyl acetate-hexanes), R_f: **92**: 0.39 (CAM)

starting lactol: 0.15 (CAM)

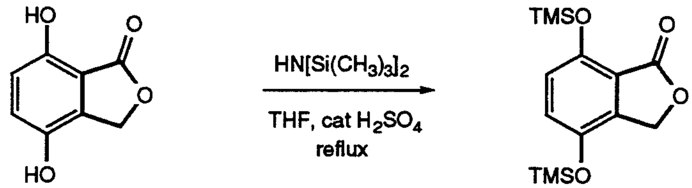


90

4,7-Dihydroxyphthalide

A solution of concentrated sulfuric acid (4.0 mL, 75 mmol, 15 equiv) in methanol (50 mL) at 23 °C was added to a solution of 4,7-bis[[2-(trimethylsilyl)ethoxyl]methoxy]phthalide (**90**, 2.148 g, 5.034 mmol, 1 equiv) in tetrahydrofuran (50 mL) at 23 °C. The reaction mixture was stirred for 2.0 h at 23 °C. The product solution was partitioned carefully between saturated aqueous sodium bicarbonate solution (200 mL), saturated aqueous sodium chloride solution (150 mL), and ethyl acetate (100 mL). The aqueous layer was separated and extracted further with ethyl acetate (2 x 100 mL). The combined organic layers were dried over sodium sulfate and were concentrated affording 4,7-dihydroxyphthalide as an off-white solid (mp >220 °C, 821 mg, 98%).

^{1}H NMR (300 MHz, CD_3OD), δ:	6.93 (d, 1H, J = 8.7 Hz, aryl), 6.72 (d, 1H, J = 8.7 Hz, aryl), 5.20 (s, 2H, CH_2O).
HRMS (EI):	Calcd for $C_8H_6O_4$ $[M]^+$: 166.0266 Found:166.0264
TLC (40% ethyl acetate-hexane), R_f:	4,7-dihydroxyphthalide: 0.14 (UV, CAM) **90**: 0.53 (UV, CAM)

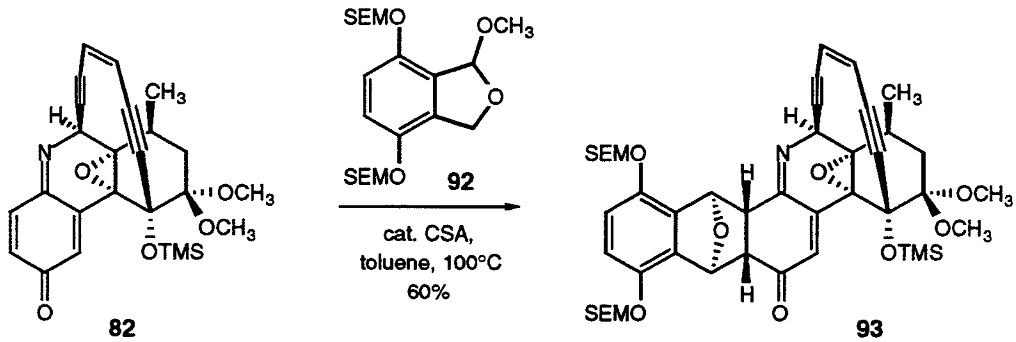


91

4,7-Bis(trimethylsiloxy)phthalide (91)

A suspension of 4,7-dihydroxyphthalide (46 mg, 0.28 mmol, 1 equiv), hexamethyldisilazane (1.0 mL, 4.7 mmol, 17 equiv) and concentrated sulfuric acid (1.0 µL, 19 µmol, 68 µequiv) in tetrahydrofuran (2 mL) was heated at reflux for 30 min. The reaction mixture was cooled to 23 °C and was concentrated in vacuo affording 4,7-bis(trimethylsiloxy)phthalide (**91**) as a moisture-sensitive, colorless oil (86 mg, 100%).

^{1}H NMR (400 MHz, C_6D_6), δ:	6.69 (d, 1H, J = 8.6 Hz, aryl), 6.63 (d, 1H, J = 8.6 Hz, aryl), 4.64 (s, 2H, CH_2O), 0.35 (s, 9H, $(CH_3)_3Si$), 0.07 (s, 9H, $(CH_3)_3Si$).



Diels-Alder Adduct 93

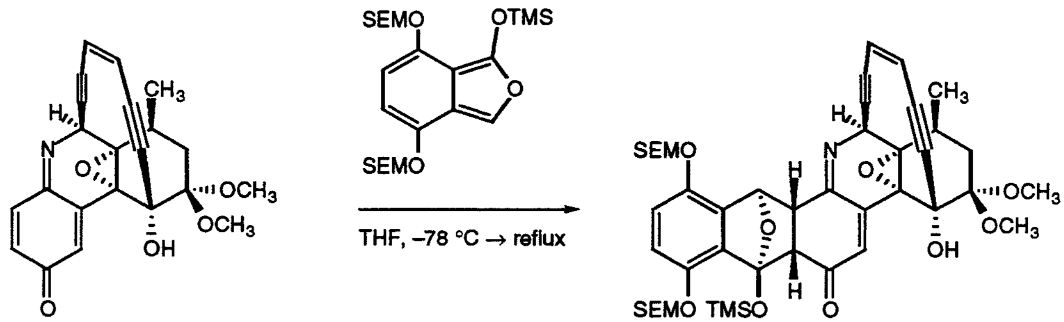
10-Camphorsulfonic acid (1 mg, 0.004 mmol, 0.2 equiv) was added to a solution of 1-methoxy-4,7-bis[[2-(trimethylsilyl)ethoxy]methoxy]phthalan (**92**, 29 mg, 0.066 mmol, 3.3 equiv) and (6*S*, 6a*S*, 7*S*, 10*R*, 10a*R*, 14*Z*)-7,8,9,10-tetrahydro-9,9-dimethoxy-7-methyl-10-(trimethylsiloxy)-6a,10a-epoxy-6,10-[3]hexene[1,5]diynophenanthridin-2(6*H*)-one (**82**, 9 mg, 0.02 mmol, 1 equiv) in toluene (1 mL). The reaction flask was immersed in an oil bath preheated to 100 °C, and the reaction mixture was stirred at that temperature for 15 min. The product solution was allowed to cool to 23 °C, then loaded directly onto a column of solvated (20% ethyl acetate in hexanes) flash grade silica gel. Elution (20% ethyl acetate in hexanes) provided the exo Diels-Alder adduct **93** as a colorless oil (10 mg, 60%).

^1H NMR (400 MHz, C_6D_6), δ:	7.79 (s, 1H, α-enone), 6.99 (d, 1H, J = 8.8 Hz, aryl), 6.95 (d, 1H, J = 8.8 Hz, aryl), 6.13 (s, 1H, OCH), 6.09 (s, 1H, OCH), 5.20 (br s, 2H, CH=CH), 5.17 (br s, 1H, NCH), 4.98 (br s, 2H, OCH_2O), 4.97 (d, 1H, J = 7.1 Hz, OCH_2O), 4.92 (d, 1H, J = 7.1 Hz, OCH_2O), 3.75-3.67 (m, 4H, $(CH_3)_3SiCH_2CH_2O$), 3.48 (s, 3H, OCH_3), 3.25 (d, 1H, J = 7.6 Hz, CHC=O), 3.00 (s, 3H, OCH_3), 2.76 (d, 1H, J = 7.6 Hz, CHC=N), 2.22 (m, 1H, $CHCH_3$), 2.17 (t, 1H, J = 13.3, CH_2), 1.91 (dd, 1H, J = 13.3, 4.0 Hz, CH_2), 1.01 (d, 3H, J = 6.8 Hz, CH_3CH), 0.97–0.89 (m, 4H, $CH_3)_3SiCH_2CH_2O$), 0.45 (s, 9H, $OSi(CH_3)_3$), 0.00 (s, 9H, $(CH_3)_3SiCH_2CH_2O$), -0.01 (s, 9H, $(CH_3)_3SiCH_2CH_2O$).
FTIR (neat), cm^{-1}:	2952 (s), 2897 (m), 2280 (w, C≡C), 1668 (s, C=O), 1627 (w), 1604 (m), 1496 (s), 1460 (w), 1410 (w), 1381 (w), 1295 (m), 1249 (s), 1202 (w), 1166 (m), 1127 (w), 1101 (m), 1058 (m), 983 (s), 940 (w), 904 (w),855 (w sh), 837 (s), 764 (m), 693 (w), 662 (w).

TLC (40% ethyl acetate-hexanes), R_f: **93**: 0.49 (UV)

82: 0.36 (UV, visibly light yellow)

92: 0.65 (CAM)

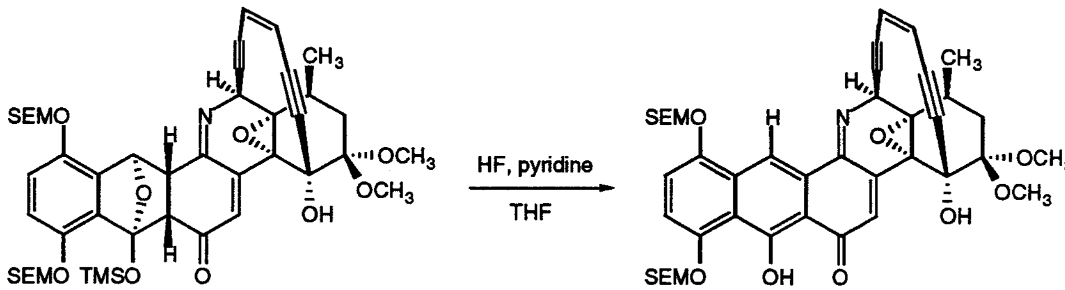


78 **95**

(1*S*, 4*R*, 4a*S*, 6a*R*, 7*R*, 12*R*, 12a*S*, 14*S*, 14a*S*, 18*Z*)-1,2,3,4,7,12,12a,14-Octahydro-4-hydroxy-3,3-dimethoxy-1-methyl-7-(trimethylsiloxy)-8,11-bis[[2-(trimethylsilyl)ethoxy]methoxy]-4a,14a:7,12-diepoxy-4,14-[3]hexene[1,5]diynonaphtho[2,3-*c*]phenanthridin-6(6a*H*)-one (95)

A solution of lithium hexamethyldisilazide in tetrahydrofuran (0.090 M, 1.09 mL, 0.098 mmol, 3.7 equiv) at –78 °C was transferred via cannula over 5 s to a solution of 4,7-bis[[2-(trimethylsilyl)ethoxyl]methoxy]phthalide (**90**, 31 mg, 0.073 mmol, 2.7 equiv) in tetrahydrofuran (0.5 mL) at –78 °C, and the resulting bright yellow reaction solution was stirred for 15 min at –78 °C. Chlorotrimethylsilane was added in two portions (12 µl, 0.095 mmol, 3.6 equiv; 12 µl, 0.095 mmol, 3.6 equiv) to the cold reaction mixture with an interval of 5 min between additions. The reaction mixture became colorless upon the final addition of chlorotrimethylsilane. A solution of (6*S*, 6a*S*, 7*S*, 10*R*, 10a*S*, 14*Z*)-7,8,9,10-tetrahydro-10-hydroxy-9,9-dimethoxy-7-methyl-6a,10a-epoxy-6,10-[3]hexene[1,5]-diynophenanthridin-2 (6*H*)-one (**78**, 10.0 mg, 0.026 mmol, 1 equiv) in tetrahydrofuran (1 mL) at 23 °C was transferred over 5 s via cannula to the cold reaction mixture. The cooling bath was removed and the reaction mixture was heated to reflux within 2 min using a heat gun. When the reaction mixture began to boil, heating was discontinued and the flask was allowed to cool to 23 °C. The product solution was partitioned between saturated aqueous sodium bicarbonate solution (5 mL) and ethyl acetate (5 mL). The aqueous layer was separated and extracted further with ethyl acetate (2 x 5 mL). The combined organic layers were dried over sodium sulfate and were concentrated. The residue was purified by flash column chromatography (20% ethyl acetate in hexanes initially, then 40% ethyl acetate in hexanes) to provide (1*S*, 4*R*, 4a*S*, 6a*R*, 7*R*, 12*R*, 12a*S*, 14*S*, 14a*S*, 18*Z*)-1,2,3,4,7,12,12a,14-octahydro-4-hydroxy-3,3-dimethoxy-1-methyl-7-(trimethylsiloxy)-8,11-bis[[2-(trimethylsilyl)ethoxy]methoxy]-4a,14a:7,12-diepoxy-4,14-[3]hexene[1,5]diynonaphtho[2,3-*c*]phenanthridin-6(6a*H*)-one (**95**) as a light yellow oil (7.8 mg, 34%).

^{1}H NMR (400 MHz, C_6D_6), δ:	7.88 (s, 1H, α-enone), 6.99 (br s, 2H, aryl), 5.91 (s, 1H, OC**H**), 5.22 (dd, 1H, *J* = 10.0 1.7 Hz, CHC≡CC**H**=CH), 5.21 (d, 1H, *J* = 6.8 Hz, OC**H**$_2$O), 5.16 (d, 1H, *J* = 10.0 Hz, CHC≡CCH=C**H**), 5.09 (d, 1H *J* = 1.2 Hz, NC**H**), 5.06 (d, 1H, *J* = 6.8 Hz, OC**H**$_2$O), 4.94 (br s, 2H, OC**H**$_2$O), 3.90 (t, 2H, *J* = 8.2 Hz, $(CH_3)_3SiCH_2$C**H**$_2$O), 3.69 (d, 1H, *J* = 7.6 Hz, $(CH_3)_3SiCH_2$C**H**$_2$O), 3.66 (d, 1H, *J* = 7.6 Hz, $(CH_3)_3SiCH_2$C**H**$_2$O), 3.41 (s, 1H, O**H**), 3.34 (s, 3H, OC**H**$_3$), 3.32 (d, 1H, *J* = 7.6 Hz, C**H**C=O), 3.08 (d, 1H, *J* = 7.8 Hz, C**H**C=N), 2.93 (s, 3H, OC**H**$_3$), 2.23 (m, 1H, C**H**CH$_3$), 2.10 (dd, 1H, *J* = 14.6, 11.5 Hz, C**H**$_2$), 1.86 (dd, 1H, *J* = 14.6, 5.4 Hz, C**H**$_2$), 1.01 (d, 3H, *J* = 7.3 Hz, C**H**$_3$CH), 0.99–0.86 (m, 4H, $(CH_3)_3Si$C**H**$_2$CH$_2$O), 0.37 (s, 9H, OSi(C**H**$_3$)$_3$), 0.07 (s, 9H, (C**H**$_3$)$_3SiCH_2CH_2O$), –0.03 (s, 9H, (C**H**$_3$)$_3SiCH_2CH_2O$).
TLC (40% ethyl acetate-hexanes), R_f:	**95**: 0.44 (UV) **78**: 0.18 (UV, visibly light yellow)

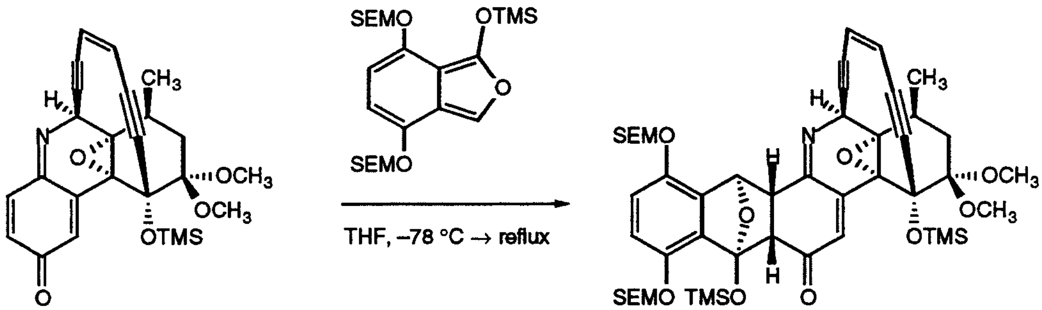


95 96

(1*S*, 4*R*, 4a*S*, 14*S*, 14a*S*, 18*Z*)-1,2,3,4,-Tetrahydro-4-7-dihydroxy-3,3-dimethoxy-1-methyl-8,11-bis[[2-(trimethylsilyl)ethoxy]methoxy]-4a,14a-epoxy-4,14-[3]hexene[1,5]diynonaphtho[2,3-*c*]phenanthridin-6(14*H*)-one (96)

A solution of hydrogen fluoride-pyridine in tetrahydrofuran at 0 °C was prepared by the addition of 70% hydrogen fluoride in pyridine (1.0 mL) to a solution of pyridine (4.0 mL) in tetrahydrofuran (10.0 mL) at 0°C. A 500-μL aliquot of this solution was added to a solution of (1*S*, 4*R*, 4a*S*, 6a*R*, 7*R*, 12*R*, 12a*S*, 14*S*, 14a*S*, 18*Z*)-1,2,3,4,7,12,12a,14-octahydro-4-hydroxy-3,3-dimethoxy-1-methyl-7-(trimethylsiloxy)-8,11-bis[[2-(trimethylsilyl)ethoxy]methoxy]-4a,14a:7,12-diepoxy-4,14-[3]hexene[1,5]diynonaphtho[2,3-*c*]phenanthridin-6(6a*H*)-one (**95**, 7.0 mg, 0.0080 mmol, 1 equiv) in tetrahydrofuran (3 mL) at 23 °C. The reaction mixture was stirred for 45 min at 23 °C, then was partitioned between saturated aqueous sodium bicarbonate solution (30 mL) and ethyl acetate (10 mL). The organic layer was dried over sodium sulfate and was concentrated. The residue was purified by flash column chromatography (30% ethyl acetate in hexanes) to afford (1*S*, 4*R*, 4a*S*, 14*S*, 14a*S*, 18*Z*)-1,2,3,4,-tetrahydro-4-7-dihydroxy-3,3-dimethoxy-1-methyl-8,11-bis[[2-(trimethylsilyl)ethoxy]methoxy]-4a,14aepoxy-4,14-[3]hexene[1,5]diynonaphtho[2,3-*c*]phenanthridin-6(14*H*)-one (**96**) as a red oil (2.3 mg, 37%).

^{1}H NMR (400 MHz, C_6D_6), δ:	15.18 (s, 1H, **OH**), 9.21 (s, 1H, CC**H**C), 8.18 (s, 1H, α-enone), 7.29 (d, 1H, *J* = 8.7 Hz, aryl), 7.19 (d, 1H, *J* = 8.7 Hz, aryl), 5.35 (d, 1H, *J* = 1.2 Hz, NC**H**), 5.25 (dd, 1H, *J* = 10.0, 1.2 Hz, CHC≡CC**H**=CH), 5.21 (d, 1H, *J* = 10.0 Hz, CHC≡CCH=C**H**), 5.16 (br s, 2H, OC**H**$_2$O), 5.12 (d, 1H, *J* = 6.8 Hz, OC**H**$_2$O), 5.10 (d, 1H, *J* = 6.8 Hz, OC**H**$_2$O), 3.97 (t, 2H, *J* = 7.9 Hz, $(CH_3)_3SiCH_2$**C**H_2O), 3.75 (t, 2H, *J* = 8.1 Hz, $(CH_3)_3SiCH_2$**C**H_2O), 3.38 (s, 3H, OC**H**$_3$), 2.94 (s, 3H, OC**H**$_3$), 2.30 (m, 1H, C**H**CH_3), 2.15 (t, 1H, *J* = 13.7, C**H**$_2$), 1.85 (dd, 1H, *J* = 14.1, 5.4 Hz, C**H**$_2$), 1.05 (d, 3H, *J* = 7.3 Hz, C**H**$_3$CH), 1.00–0.96 (m, 4H, $(CH_3)_3Si$C**H**$_2CH_2O$), 0.02 (s, 9H, (C**H**$_3$)$_3SiCH_2CH_2O$), –0.01 (s, 9H, (C**H**$_3$)$_3SiCH_2CH_2O$).
TLC (40% ethyl acetate-hexanes), R_f:	**96**: 0.47 (visibly red) **95**: 0.44 (UV)



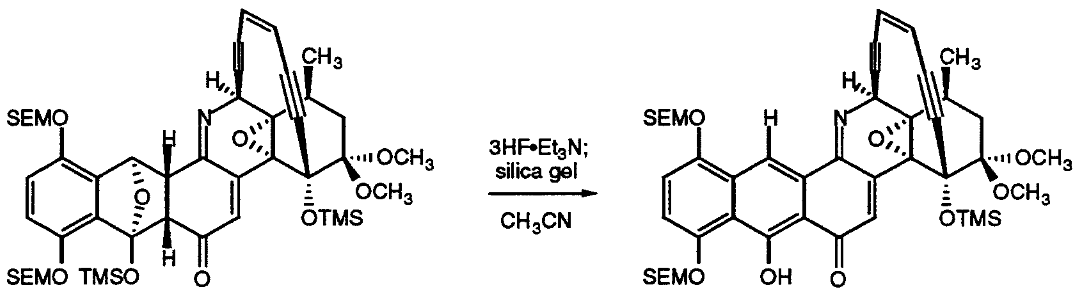
82 98

(1*S*, 4*R*, 4a*S*, 6a*R*, 7*R*, 12*R*, 12a*S*, 14*S*, 14a*S*, 18*Z*)-1,2,3,4,7,12,12a,14-Octahydro-3,3-dimethoxy-1-methyl-4,7-bis(trimethylsiloxy)-8,11-bis[[2-(trimethylsilyl)ethoxy]methoxy]-4a,14a:7,12-diepoxy-4,14-[3]hexene[1,5]diynonaphtho[2,3-*c*]phenanthridin-6(6a*H*)-one (98)

A solution of lithium hexamethyldisilazide in tetrahydrofuran (0.077 M, 1.08 mL, 0.084 mmol, 4.9 equiv) at –78 °C was transferred via cannula over 5 s to a solution of 4,7-bis[[2-(trimethylsilyl)ethoxyl]methoxy]phthalide (**90**, 32 mg, 0.075 mmol, 4.3 equiv) in tetrahydrofuran (0.5 mL) at –78 °C, and the resulting bright yellow solution was stirred for 20 min at –78 °C. Chlorotrimethylsilane (30 µL, 0.24 mmol, 14 equiv) was added to the cold reaction mixture. The reaction solution became colorless after 10 min at –78 °C. A solution of (6*S*, 6a*S*, 7*S*, 10*R*, 10a*R*, 14*Z*)-7,8,9,10-tetrahydro-9,9-dimethoxy-7-methyl-10-(trimethylsiloxy)-6a,10a-epoxy-6,10-[3]hexene[1,5]diynophenanthridin-2(6*H*)-one (**82**, 7.8 mg, 0.017 mmol, 1 equiv) in tetrahydrofuran (1 mL) at 23 °C was transferred via cannula over 5 s to the cold reaction mixture. The cooling bath was removed, and the reaction mixture was heated to reflux within 2 min using a heat gun. The reaction mixture was held at reflux for 10 min, then was allowed to cool to 23 °C. The product solution was partitioned between saturated aqueous sodium bicarbonate solution (20 mL) and ethyl acetate (20 mL). The aqueous layer was separated and extracted further with ethyl acetate (20 mL). The combined organic layers were dried over sodium sulfate and were concentrated. The residue was purified by flash column chromatography (20% ethyl acetate in hexanes initially, then 40% ethyl acetate in hexanes) to provide (1*S*, 4*R*, 4a*S*, 6a*R*, 7*R*, 12*R*, 12a*S*, 14*S*, 14a*S*, 18*Z*)-1,2,3,4,7,12,12a,14-octahydro-3,3-dimethoxy-1-methyl-4,7-bis(trimethylsiloxy)-8,11-bis[[2-(trimethylsilyl)ethoxy]methoxy]-4a,14a:7,12-diepoxy-4,14-[3]hexene[1,5]diynonaphtho[2,3-*c*]phenanthridin-6(6a*H*)-one (**98**) as a light yellow oil (5.2 mg, 32%).

^1H NMR (400 MHz, C_6D_6), δ: 7.80 (2, 1H, α-enone), 6.99 (d, 1H, *J* = 8.8 Hz, aryl), 6.95 (d, 1H, *J* = 8.8 Hz, aryl), 5.89 (s, 1H, OC**H**), 5.22 (d, 1H, *J* = 10.0 Hz, CHC≡CCH=C**H**), 5.19 (dd, 1H, *J* = 10.0, 1.2 Hz, CHC≡CC**H**=CH), 5.16 (d, 1H, *J* = 7.1 Hz, OC**H**$_2$O), 5.08 (d, 1H *J* = 1.2 Hz, NC**H**), 5.01 (d, 1H, *J* = 7.1 Hz, OC**H**$_2$O), 4.97 (d, 1H, *J* = 6.8 Hz, OC**H**$_2$O), 4.95 (d, 1H, *J* = 6.8 Hz, OC**H**$_2$O), 3.87 (m, 2H, $(CH_3)_3SiCH_2$C**H**$_2$O), 3.70 (m, 2H, $(CH_3)_3SiCH_2$C**H**$_2$O), 3.30 (s, 3H, OC**H**$_3$), 3.24 (d, 1H, *J* = 7.6 Hz, C**H**C=O), 3.12 (s, 3H, OC**H**$_3$), 2.98 (d, 1H, *J* = 7.8 Hz, C**H**C=N), 2.37 (m, 1H, C**H**CH_3), 2.12 (t, 1H, *J* = 13.6, C**H**$_2$), 1.88 (dd, 1H, *J* = 14.0, 5.5 Hz, C**H**$_2$), 1.03 (d, 3H, *J* = 7.3 Hz, C**H**$_3$CH), 1.03–0.88 (m, 4H, $CH_3)_3Si$C**H**$_2$C**H**$_2$O), 0.56 (s, 9H, OSi(C**H**$_3$)$_3$), 0.41 (s, 9H, OSi(C**H**$_3$)$_3$), 0.05 (s, 9H, $(CH_3)_3SiCH_2CH_2O$), -0.01 (s, 9H, (C**H**$_3$)$_3SiCH_2CH_2O$).

FTIR (neat), cm^{-1}:	2955 (s), 2898 (m), 1674 (s, C=O), 1605 (m), 1496 (s), 1416 (m), 1296 (m), 1250 (s), 1203 (w), 1168 (w), 1152 (w), 1102 (m), 1063 (w), 1002 (s), 839 (s), 756 (m), 693 (w).
TLC (40% ethyl acetate-hexanes), R_f:	**98**: 0.52 (UV)
	82: 0.38 (UV, visibly light yellow)



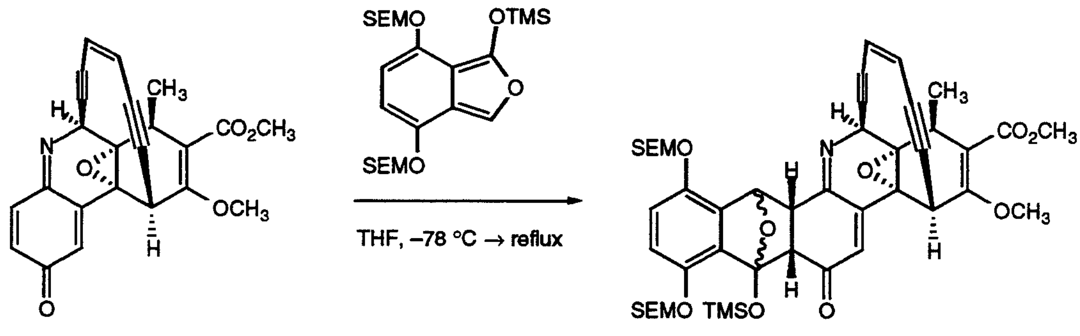
98 100

(1*S*, 4*R*, 4a*S*, 14*S*, 14a*S*, 18*Z*)-1,2,3,4,-Tetrahydro-4-(trimethylsiloxy)-7-hydroxy-3,3-dimethoxy-1-methyl-8,11-bis[[2-(trimethylsilyl)ethoxy]methoxy]-4a,14a-epoxy-4,14-[3]hexene[1,5]diynonaphtho[2,3-*c*]phenanthridin-6(14*H*)-one (100)

Triethylamine trihydrofluoride (10 µL, 0.061 mmol, 23 equiv) was added to a solution of (1*S*, 4*R*, 4a*S*, 6a*R*, 7*R*, 12*R*, 12a*S*, 14*S*, 14a*S*, 18*Z*)-1,2,3,4,7,12,12a,14-octahydro-4,7-bis(trimethylsiloxy)-3,3-dimethoxy-1-methyl-8,11-bis[[2-(trimethylsilyl)ethoxy]methoxy]-4a,14a:7,12-diepoxy-4,14-[3]hexene[1,5]diynonaphtho[2,3-*c*]phenan-thridin-6(6a*H*)-one (**98**, 2.5 mg, 0.0026 mmol, 1 equiv) in acetonitrile (1.5 mL) at 23 °C, and the reaction solution was stirred for 1 h at 23 °C. The yellow product solution was partitioned between saturated aqueous sodium bicarbonate solution (20 mL) and ethyl acetate (20 mL). The aqueous layer was separated and extracted further with ethyl acetate (20 mL). The combined organic layers were dried over sodium sulfate and were concentrated. Silica gel (100 mg) was added to a solution of the residue in benzene (1.0 mL) at 23 °C, and the slurry was stirred for 1 h at 23 °C. During this time, the yellow slurry darkened to a red color. The slurry was concentrated and the residue was purified by flash column chromatography (10% ethyl acetate in hexanes initially, then 20% ethyl acetate in hexanes) to provide (1*S*, 4*R*, 4a*S*, 14*S*, 14a*S*, 18*Z*)-1,2,3,4,-tetrahydro-4-(trimethylsiloxy)-7-hydroxy-3,3-dimethoxy-1-methyl-8,11-bis[[2-(trimethylsilyl)ethoxy]methoxy]-4a,14a-epoxy-4,14-[3]hexene[1,5]diynonaphtho[2,3-*c*]phenanthridin-6(14*H*)-one (**100**) as a red oil (1.0 mg, 44%).

^{1}H NMR (400 MHz, C_6D_6), δ: 15.17 (s, 1H, **OH**), 9.15 (s, 1H, CC**H**C), 8.08 (s, 1H, α-enone), 7.29 (d, 1H, *J* = 8.7 Hz, aryl), 7.20 (d, 1H, *J* = 8.7 Hz, aryl), 5.35 (br s, 1H, NC**H**), 5.30 (d, 1H, *J* = 6.6 Hz, OCH_2O), 5.27 (d, 1H, *J* = 6.6 Hz, OCH_2O), 5.26 (d, 1H, *J* = 10.0 Hz, CHC≡CCH=C**H**), 5.23 (dd, 1H, *J* = 10.0, 1.2 Hz, CHC≡CC**H**=CH), 5.09 (d, 1H, *J* = 7.1 Hz, OCH_2O), 5.07 (d, 1H, *J* = 7.1 Hz, OCH_2O), 3.94 (t, 2H, *J* = 7.9 Hz, $(CH_3)_3SiCH_2CH_2O$), 3.74 (t, 2H, *J* = 8.1 Hz, $(CH_3)_3SiCH_2CH_2O$), 3.38 (s, 3H, OCH_3), 3.08 (s, 3H, OCH_3), 2.35 (m, 1H, $CHCH_3$), 2.18 (t, 1H, *J* = 13.7, CH_2), 1.90 (dd, 1H, *J* = 14.1, 5.4 Hz, CH_2), 1.04 (d, 3H, *J* = 7.3 Hz, CH_3CH), 1.02 (t, 2H, *J* = 8.1 Hz, $(CH_3)_3SiCH_2CH_2O$), 0.94 (t, 2H, *J* = 8.1 Hz, $(CH_3)_3SiCH_2CH_2O$), 0.43 (s, 9H, $OSi(CH_3)_3$), 0.02 (s, 9H, $(CH_3)_3SiCH_2CH_2O$), –0.02 (s, 9H, $(CH_3)_3SiCH_2CH_2O$).

FTIR (neat), cm^{-1}:	2953 (s), 2897 (m), 1636 (m), 1615 (m), 1600 (s), 1500 (m), 1456 (m), 1381 (m), 1327 (w), 1253 (s), 1201 (w), 1171 (m), 1150 (m), 1101 (m), 1062 (s), 1012 (m), 964 (w), 891 (w), 838 (s), 755 (w).
HRMS (FAB):	Calcd for $C_{45}H_{60}O_{10}NSi_3$ $[MH]^+$: 856.8506 Found: 858.8504
TLC (40% ethyl acetate-hexanes), R_f:	**100**: 0.57 (visibly red) **98**: 0.52 (UV)



Diels-Alder Adducts 97

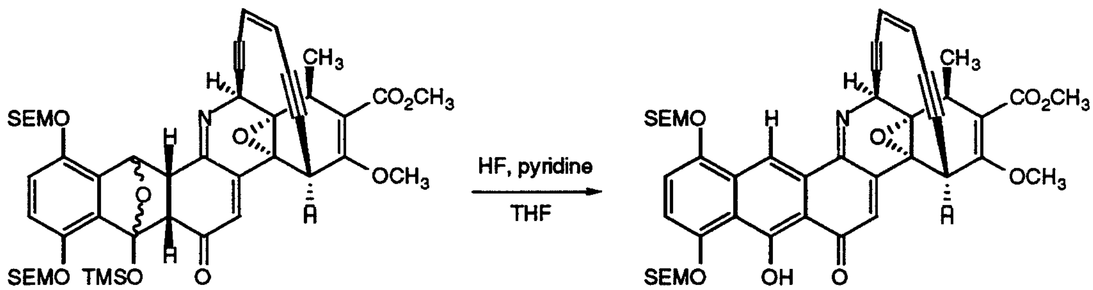
A solution of lithium hexamethyldisilazide in tetrahydrofuran (0.059 M, 1.1 mL, 0.063 mmol, 4.9 equiv) at –78 °C was transferred via cannula over 5 s to a solution of 4,7-bis[[2-(trimethylsilyl)ethoxyl]methoxy]phthalide (**90**, 22 mg, 0.052 mmol, 4.0 equiv) in tetrahydrofuran (0.5 mL) at –78 °C, and the resulting bright yellow solution was stirred for 20 min at –78 °C. Chlorotrimethylsilane was added in two portions (9 μL, 0.071 mmol, 5.5 equiv; 9 μL, 0.071 mmol, 5.5 equiv) to the cold reaction mixture with an interval of 5 min between additions. The reaction mixture became colorless upon the final addition of chlorotrimethylsilane. A solution of methyl (6*S*, 6a*S*, 7*S*, 10*R*, 10a*R*, 14*Z*)-2,6,7,10-tetrahydro-9-methoxy-7-methyl-2-oxo-6a, 10a-epoxy-6, 10-[3]hexene [1,5] diynophenanthridine-8-carboxylate (**79**, 5.0 mg, 0.013 mmol, 1 equiv) in tetrahydrofuran (1 mL) at 23 °C was transferred over 5 s via cannula to the cold reaction mixture. The cooling bath was removed and the reaction mixture was heated to reflux within 2 min using a heat gun. When the reaction began to boil, heating was discontinued and the flask was allowed to cool to 23 °C. The product solution was partitioned between saturated aqueous sodium bicarbonate solution (10 mL) and ethyl acetate (10 mL). The aqueous layer was separated and extracted further with ethyl acetate (2 x 10 mL). The combined organic layers were dried over sodium sulfate and were concentrated. The residue was purified by flash column chromatography (30% ethyl acetate in hexanes initially, then 40% ethyl acetate in hexanes) to provide together methyl (1*S*, 4*R*, 4a*R*, 6a*R*, 7*R*, 12*R*, 12a*S*, 14*S*, 14a*S*, 18*Z*)-1,4,6,6a,7,12,12a,14-octahydro-3-methoxy-1-methyl-6-oxo-7-(trimethylsiloxy)-8,11-bis[[2-(trimethylsilyl)ethoxy]methoxy]-4a,14a:7,12-diepoxy-4,14-[3]hexene[1,5]diynonaphtho[2,3,*c*]phenanthridine-2-carboxylate and methyl (1*S*, 4*R*, 4a*R*, 6a*R*, 7*S*, 12*S*, 12a*S*, 14*S*, 14a*S*, 18*Z*)-1,4,6,6a,7,12,12a,14-octahydro-3-methoxy-1-methyl-6-oxo-7-(trimethylsiloxy)-8,11-bis[[2-(trimethylsilyl)ethoxy]methoxy]-4a,14a:7,12-diepoxy-4,14-[3]hexene[1,5]diynonaphtho[2,3,*c*]phenanthridine-2-carboxylate (**97**, 2:1 ratio, respectively) as a light yellow oil (3.4 mg, 30%).

Exo adduct 97:

^{1}H NMR (400 MHz, C_6D_6), δ: 6.99 (d, 1H, J = 8.8 Hz, aryl), 6.95 (d, 1H, J = 8.8 Hz, aryl), 5.91 (s, 1H, OCH), 5.26 (dd, 1H, J = 10.0 1.7 Hz, CHC≡CCH=CH), 5.22 (d, 1H, J = 10.0 Hz, CHC≡CCH=C**H**), 5.19 (d, 1H, J = 6.8 Hz, OC**H**$_2$O), 5.04 (d, 1H, J = 6.8 Hz, OC**H**$_2$O), 4.99 (br s, 1H, NCH), 4.95 (br s, 2H, OC**H**$_2$O), 3.95–3.55 (m, 5H, $(CH_3)_3SiCH_2$**C****H**$_2$O and C**H**CH_3), 3.43 (s, 3H, OC**H**$_3$), 3.42 (s, 3H, OC**H**$_3$), 3.27 (d, 1H, J = 7.6 Hz, C**H**C=O), 3.03 (d, 1H, J = 7.8 Hz, C**H**C=N), 1.40 (d, 3H, J = 7.3 Hz, C**H**$_3$CH), 1.06–0.85 (m, 4H, $(CH_3)_3SiC$**H**$_2$C**H**$_2$O), 0.30 (s, 9H, OSi(C**H**$_3$)$_3$), 0.07 (s, 9H, (C**H**$_3$)$_3SiCH_2CH_2O$), –0.03 (s, 9H, $(CH_3)_3SiCH_2CH_2O$).

TLC (40% ethyl acetate-hexanes), R_f: **97**: 0.44 (UV)

79: 0.26 (UV, visibly light yellow)



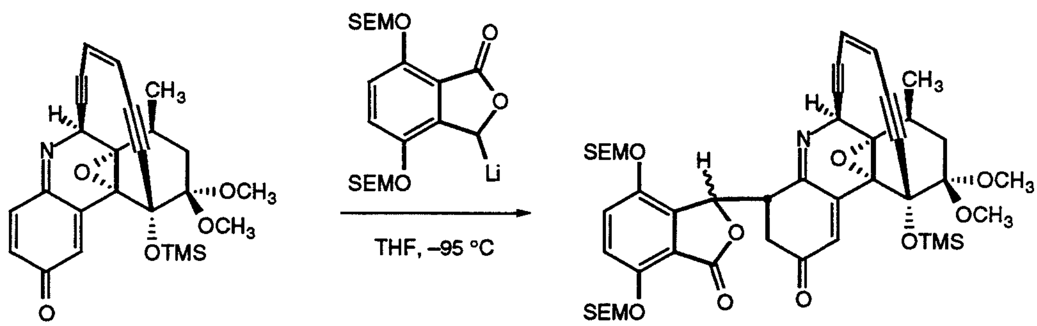
97 99

Methyl (1*S*, 4*R*, 4a*R*, 14*S*, 14a*S*, 18*Z*)-1,4,6,14-Tetrahydro-7-hydroxy-3-methoxy-1-methyl-6-oxo-8,11-bis[[(2-trimethylsilyl)ethoxy]methoxy]-4a,14a-epoxy-4,14-[3]hexene[1,5] diynonaphtho [2,3,*c*]phenanthridine-2-carboxylate (99)

A solution of hydrogen fluoride-pyridine in tetrahydrofuran at 0 °C was prepared by the addition of 70% hydrogen fluoride in pyridine (1.0 mL) to a solution of pyridine (4.0 mL) in tetrahydrofuran (10.0 mL) at 0°C. A 700-µL aliquot of this solution was added to a solution of the Diels-Alder adducts **97** (3.0 mg, 0.0034 mmol, 1 equiv) in tetrahydrofuran (2 mL) at 23 °C. The reaction mixture was stirred for 2h at 23 °C, then was partitioned between saturated aqueous sodium bicarbonate solution (30 mL) and ethyl acetate (20 mL). The aqueous layer was separated and extracted further with ethyl aceate (20 mL). The combined organic layers were dried over sodium sulfate and were concentrated. The residue was purified by flash column chromatography (20% ethyl acetate in hexanes initially, then 40% ethyl acetate in hexanes) to afford methyl (1*S*, 4*R*, 4a*R*, 14*S*, 14a*S*, 18*Z*)-1,4,6,14-tetrahydro-7-hydroxy-3-methoxy-1-methyl-6-oxo-8,11-bis[[(2-trimethylsilyl)ethoxy]methoxy]-4a,14a-epoxy-4,14-[3]hexene[1,5]diynonaphtho[2,3,*c*]phenanthridine-2-carboxylate (**99**) as a red oil (0.90 mg, 33%).

^1H NMR (400 MHz, C_6D_6), δ:	15.18 (s, 1H, OH), 9.25 (s, 1H, OH), 7.33 (d, 1H, J = 8.6 Hz, aryl), 7.25 (d, 1H, J = 8.6 Hz, aryl), 6.55 (s, 1H, α-enone), 5.33 (br s, 2H, OCH_2O), 5.27 (br d, 1H, J = 10.0 Hz, CH=CH), 5.24 (d, 1H, J = 1.5 Hz, NCH), 5.22 (br d, 1H, J = 10.0 Hz, CH=CH), 5.11 (d, 1H, J = 7.0 Hz, OCH_2O), 5.07 (d, 1H, J = 7.0 Hz, OCH_2O), 3.97 (m, 2H, $(CH_3)_3SiCH_2CH_2O$), 3.79 (q, 1H, J = 7.0 Hz, $CHCH_3$), 3.73 (t, 2H, J = 8.0 Hz, $(CH_3)_3SiCH_2CH_2O$), 3.65 (br s, 1H, C≡CCH), 3.51 (s, 3H, OCH_3), 3.46 (s, 3H, OCH_3), 1.40 (d, 3H, J = 7.0 Hz, CH_3CH), 1.04 (t, 2H, J = 8.0 Hz, $(CH_3)_3SiCH_2CH_2O$), 0.94 (t, 2H, J = 8.0 Hz, $(CH_3)_3SiCH_2CH_2O$), 0.02 (s, 9H, $(CH_3)_3SiCH_2CH_2O$), –0.02 (s, 9H, $(CH_3)_3SiCH_2CH_2O$).
FTIR (neat), cm^{-1}:	3054 (w), 2952 (m), 2900 (m), 1775 (m), 1714 (s), 1642 (m, C=O), 1601 (s), 1499 (s), 1455 (m), 1376 (s), 1250 (vs), 1207 (w), 1152 (m), 1100 (m), 1056 (s), 1022 (m), 859 (s), 836 (s), 693 (w).

HRMS (FAB):	Calcd for $C_{43}H_{50}O_{10}NSi_2$ $[MH]^+$: 796.2944
	Found: 796.2936
TLC (40% ethyl acetate-hexanes), R_f:	**99**: 0.44 (visibly red)
	97: 0.44 (UV)



82

Addition Product 101 and Diastereomer

A solution of lithium hexamethyldisilazide in tetrahydrofuran (0.023 M, 1.5 mL, 0.035 mmol, 2.9 equiv) was added to a solution of 4,7-bis[[2-(trimethylsilyl)ethoxyl]methoxy]phthalide (**90**, 15 mg, 0.035 mmol, 2.9 equiv) in tetrahydrofuran (1 mL) at –95 °C (ethanol-liquid N_2). The resulting bright yellow solution was stirred for 10 min at –95 °C, then a solution of (6*S*, 6a*S*, 7*S*, 10*R*, 10a*R*, 14*Z*)-7,8,9,10-tetrahydro-9,9-dimethoxy-7-methyl-10-(trimethylsiloxy)-6a,10a-epoxy-6,10-[3]hexene[1,5]diynophenanthridin-2 (6*H*)-one (**82**, 5.5 mg, 0.0122 mmol, 1 equiv) in tetrahydrofuran (2 mL) was added via cannula within 10 s, causing the reaction mixture to turn first orange then yellow. The cold bath was removed and the reaction solution was allowed to warm to 23 °C, then was stirred at that temperature for 2 h, causing the product solution to darken over this time. The product solution was partitioned between aqueous phosphate buffer solution (pH 7, 0.05 M in sodium hydrogen phosphate and 0.05 M in potassium dihydrogen phosphate, 20 mL) and ethyl acetate (10 mL). The aqueous layer was separated then was extracted further with ethyl acetate (2 x 10 mL). The combined organic layers were dried over sodium sulfate and then were concentrated. The residue was purified by flash column chromatography to provide separately the addition product diastereomer A as a colorless oil (3.0 mg, 28%) and the diastereomer B (**101**) as a colorless oil (3.8 mg, 36%).

Diastereomer A:

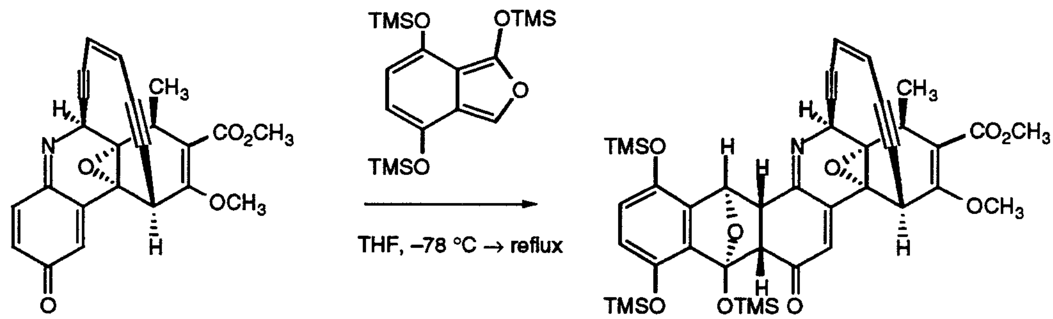
^{1}H NMR (400 MHz, C_6D_6), δ: 7.61 (s, 1H, α-enone), 7.08 (d, 1H, *J* = 8.8 Hz, aryl), 7.05 (d, 1H, *J* = 8.8 Hz, aryl), 6.67 (br s, 1H,, **CHO**), 5.24 (dd, 1H, *J* = 10.0, 1.5 Hz, HCC≡C**CH**=CH), 5.21 (d, 1H, *J* = 1.5 Hz, N**CH**), 5.19 (d, 1H, *J* = 10.0 Hz, HCC≡CCH=**CH**), 5.16 (br s, 2H, O**CH**$_2$O), 4.66 (d, 1H, *J* = 7.1 Hz, O**CH**$_2$O), 4.58 (d, 1H, *J* = 7.1 Hz, O**CH**$_2$O), 4.28 (br dd, 1H, *J* = 13.4, 5.4 Hz, **CH**C=N), 3.78 (m, 2H, $(CH_3)_3SiCH_2$**CH**$_2$O), 3.50 (m, 2H, $(CH_3)_3SiCH_2$**CH**$_2$O), 3.29 (s, 3H, O**CH**$_3$), 3.08 (s, 3H, O**CH**$_3$), 2.59 (dd, 1H, *J* = 16.6, 13.4 Hz, **CH**$_2$C=O), 2.33 (m, 1H, **CH**CH$_3$), 2.29 (dd, 1H , *J* = 16.6, 5.0 Hz, **CH**$_2$C=O), 2.09 (t, 1H, *J* = 13.1, **CH**$_2$C(OCH$_3$)$_2$), 1.87 (dd, 1H, *J* = 14.2, 5.6 Hz, **CH**$_2$C(OCH$_3$)$_2$), 1.00 (d, 3H, *J* = 7.3 Hz, **CH**$_3$CH), 0.92 (m, 2H, CH$_3$)$_3$Si**CH**$_2$CH$_2$O), 0.85 (m, 2H, CH$_3$)$_3$Si**CH**$_2$CH$_2$O), 0.45 (s, 9H, OSi(**CH**$_3$)$_3$), –0.01 (s, 9H, (**CH**$_3$)$_3$SiCH$_2$CH$_2$O), –0.04 (s, 9H, (**CH**$_3$)$_3$SiCH$_2$CH$_2$O).

FTIR (neat), cm^{-1}:	2953 (s), 2275 (w, C≡C), 1770 (vs, phthalide C=O), 1682 (s, C=O), 1648 (w), 1604 (m), 1499 (s), 1456 (w), 1434 (w), 1298 (m), 1251 (vs), 1203 (w), 1160 (m), 1104 (s), 1064 (m), 1006 (vs), 935 (m), 838 (vs), 756 (m), 693 (m).
TLC (40% EtOAc in hexanes), R_f:	A: 0.40 (UV) starting quinone imine: 0.38 (UV, visibly light yellow)

Diastereomer B (101):

^{1}H NMR (400 MHz, C_6D_6), δ: 7.86 (s, 1H, α-enone), 7.09 (d, 1H, J = 9.0 Hz, aryl), 7.02 (d, 1H, J = 9.0 Hz, aryl), 5.67 (d, 1H, J = 1.2 Hz, **CH**O), 5.27 (dd, 1H, J = 10.0, 1.5 Hz, HCC≡CC**H**=CH), 5.23 (d, 1H, J = 10.0 Hz, HCC≡CCH=C**H**), 5.15 (d, 1H, J = 1.5 Hz, NC**H**), 5.13 (d, 1H, J = 7.1 Hz, OC**H**$_2$O), 5.10 (d, 1H, J = 7.1 Hz, OC**H**$_2$O), 4.80 (br s, 2H, OC**H**$_2$O), 4.12 (td, 1H, J = 4.4, 1.2 Hz, C**H** C=N), 3.76 (m, 2H, $(CH_3)_3SiCH_2CH_2O$), 3.59 (m, 2H, $(CH_3)_3SiCH_2CH_2O$), 3.46 (s, 3H, OC**H**$_3$), 3.05 (s, 3H, OC**H**$_3$), 2.26 (m, 1H, C**H**CH$_3$), 2.21 (m, 2H, C**H**$_2$C=O), 2.17 (t, 1H, J = 13.4, C**H**$_2$C(OCH$_3$)$_2$), 1.90 (dd, 1H, J = 14.2, 4.9 Hz, C**H**$_2$C(OCH$_3$)$_2$), 0.99 (d, 3H, J = 7.1 Hz, C**H**$_3$CH), 0.97–0.85 (m, 4H, $CH_3)_3SiCH_2CH_2O$), 0.67 (s, 9H, $OSi(CH_3)_3$), –0.01 (s, 9H, $(CH_3)_3SiCH_2CH_2O$), –0.02 (s, 9H, $(CH_3)_3SiCH_2CH_2O$).

FTIR (neat), cm^{-1}:	2952 (s), 2897 (m), 2274 (w, C≡C), 1780 (vs, phthalide C=O), 1682 (s, C=O), 1631 (w), 1603 (m), 1499 (s), 1462 (w), 1411 (m), 1380 (w), 1250 (vs), 1201 (m), 1166 (m), 1103 (m), 1063 (w), 1007 (vs), 937 (m), 839 (vs), 756 (m), 690 (w).
TLC (40% EtOAc in hexanes), R_f:	**B**: 0.29 (UV) starting quinone imine: 0.38 (UV, visibly light yellow)



79

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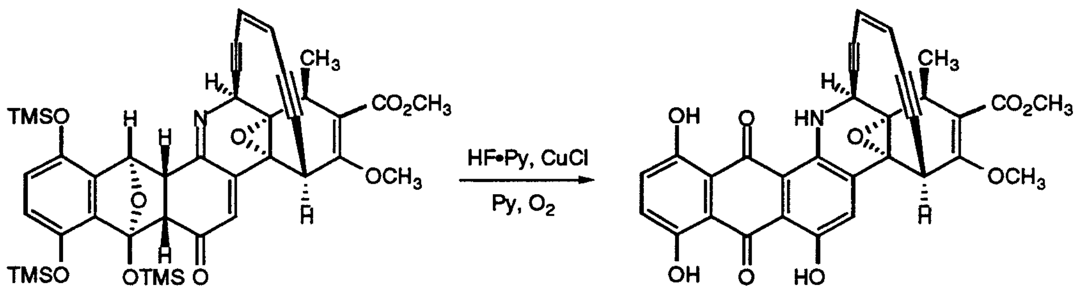
Methyl (1*S*, 4*R*, 4a*R*, 6a*R*, 7*R*, 12*R*, 12a*S*, 14*S*, 14a*S*, 18*Z*)-1,4,6,6a,7,12,12a,14-Octahydro-3-methoxy-1-methyl-6-oxo-7,8,11-tris(trimethylsiloxy)-4a,14a:7,12-diepoxy-4,14-[3]hexene[1,5]diynonaphtho[2,3,*c*]phenanthridine-2-carboxylate (102)

A solution of potassium bis(trimethylsilyl)amide (0.5 M, 400 μL, 0.200 mmol, 6.46 equiv) was added to a solution of 4,7-bis(trimethylsiloxy)phthalide (**91**, 60 mg, 0.19 mmol, 6.2 equiv) in tetrahydrofuran (2.5 mL) at –78 °C, and the resulting bright yellow solution was stirred for 25 min at –78 °C. During this time, the reaction mixture darkened to yellow-brown. Chlorotrimethylsilane (75 μL, 0.59 mmol, 19 equiv) was added, and the reaction mixture was stirred at –78 °C for 5 min. The addition of chlorotrimethylsilane caused the reaction mixture to become bright yellow. After 5 min at –78 °C, the viscous reaction mixture was warmed to –50 °C and was swirled manually until the reaction mixture became colorless. At this point, the reaction solution was cooled to –78 °C. A solution of methyl (6*S*, 6a*S*, 7*S*, 10*R*, 10a*R*, 14*Z*)-2,6,7,10-tetrahydro-9-methoxy-7-methyl-2-oxo-6a,10a-epoxy-6,10-[3]hexene[1,5]diynophenanthridine-8-carboxylate (**79**, 12 mg, 0.031 mmol, 1 equiv) in tetrahydrofuran (1.0 mL) at 23 °C was transferred via cannula over 5 s to the cold reaction mixture. The cooling bath was removed and the reaction solution was heated to reflux within 2 min using a heat gun. When the reaction mixture began to boil, heating was discontinued and the flask was allowed to cool to 23 °C. The reaction solution was concentrated to afford a light yellow residue. Analysis of the residue by ^{1}H NMR spectroscopy using dichloromethane as an internal standard indicated that the methyl (1*S*, 4*R*, 4a*R*, 6a*R*, 7*R*, 12*R*, 12a*S*, 14*S*, 14a*S*, 18*Z*)-1,4,6,6a,7,12,12a,14-octahydro-3-methoxy-1-methyl-6-oxo-7,8,11-tris(trimethylsiloxy)-4a,14a:7,12-diepoxy-4,14-[3]hexene[1,5]diynonaphtho[2,3,*c*]phenanthridine-2-carboxylate (**102**) had been formed in 61% yield.

^{1}H NMR (400 MHz, C_6D_6), δ:	unobscured protons: 6.80 (s, 1H, α-enone), 5.69 (s, 1H, OC**H**), 5.30 (dd, 1H *J* = 10.0, 1.5 Hz, C**H**=CH), 5.25 (dd, 1H, *J* = 10.0, 1.5 Hz, CH=C**H**), 4.90 (br s, 1H, NC**H**), 3.86 (br s, 1H,C≡CC**H**), 3.65 (q, 1H, *J* = 7.3 Hz, C**H**CH$_3$), 3.46 (s, 3H, OC**H**$_3$), 3.46 (s, 3H, OC**H**$_3$), 3.21 (d, 1H, *J* = 7.6 Hz, C**H**), 2.89 (d, 1H, *J* = 7.6 Hz, C**H**), 1.36 (d, 3H, *J* = 7.3 Hz, C**H**$_3$CH).



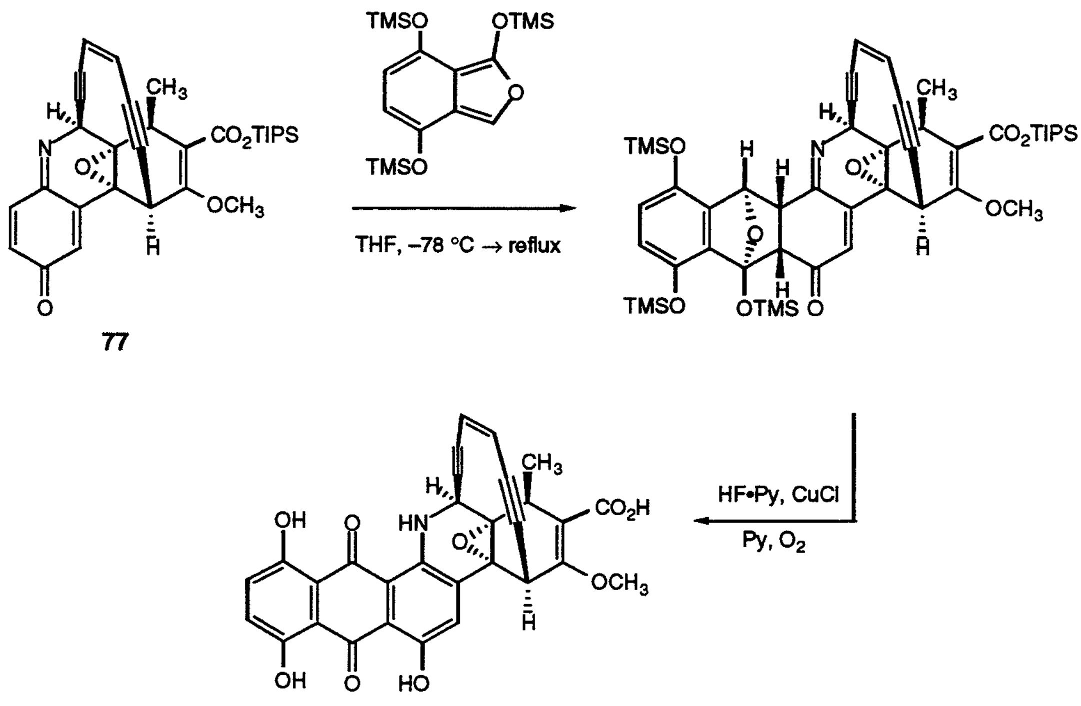
102 103

Methyl (1*S*, 4*R*, 4a*R*, 14*S*, 14a*S*, 18*Z*)-1,4,7,12,13,14-Hexahydro-3,8,11-trihydroxy-3-methoxy-1-methyl-7,12-dioxo-4a,14a-epoxy-4,14-[3]hexene[1,5]diynonaphtho[2,3,*c*]phenanthridine-2-carboxylate (103, Dynemicin A Methyl Ester)

A solution of hydrogen fluoride-pyridine in tetrahydrofuran at 0 °C was prepared by the addition of 70% hydrogen fluoride in pyridine (1.0 mL) to a solution of pyridine (3.5 mL) in tetrahydrofuran (10 mL) at 0 °C. A 350-µl aliquot of this solution was added to a yellow-brown suspension of unpurified methyl (1*S*, 4*R*, 4a*R*, 6a*R*, 7*R*, 12*R*, 12a*S*, 14*S*, 14a*S*, 18*Z*)-1,4,6,6a,7,12,12a,14-octahydro-3-methoxy-1-methyl-6-oxo-7,8,11-tris(trimethylsiloxy)-4a,14a:7,12-diepoxy-4,14-[3]hexene[1,5]diynonaphtho[2,3,*c*]phenanthridine-2-carboxylate (**102**, 0.0051 mmol, 1 equiv) and copper (I) chloride (22.2 mg, 0.224 mmol, 44.3 equiv) in pyridine (2.5 mL) at 23 °C under an atmosphere of oxygen. The resulting dark brown reaction mixture was stirred for 45 min at 23 °C. The product suspension was partitioned between ethyl acetate (20 mL) and saturated aqueous sodium bicarbonate solution (30 mL). The aqueous layer was separated and further extracted with ethyl acetate (20 mL). The combined organic layers were washed with five 15-mL portions of saturated aqueous sodium bicarbonate solution. The organic layer was dried over sodium sulfate and was concentrated. Analysis of the blue residue by ^{1}H NMR spectroscopy using dichloromethane as an internal standard indicated that methyl (1*S*, 4*R*, 4a*R*, 14*S*, 14a*S*, 18*Z*)-1,4,7,12,13,14-hexahydro-3,8,11-trihydroxy-3-methoxy-1-methyl-7,12-dioxo-4a,14a-epoxy-4,14-[3]hexene[1,5]diynonaphtho[2,3,*c*]phenanthridine-2-carboxylate (**103**, dynemicin A methyl ester) had formed in 13% yield. Purification of the crude product mixture by column chromatography on Sephadex LH-20 (28 cm by 1 cm, 20% acetonitrile in methanol) provided pure dynemicin A methyl ester as a brick-red solid (350 μg, 12%, or 8% over two steps including a 61% yield for the Diels-Alder cycloaddition reaction).

^{1}H NMR (400 MHz, C_6D_6), δ: 13.49 (s, 1H, **OH**), 12.89 (s, 1H, **OH**), 12.47 (s, 1H, **OH**), 9,84 (d, 1H, *J* = 4.2 Hz, **NH**), 7.38 (s, 1H, aryl), 6.96 (d, 1H, *J* = 9.2 Hz, aryl), 6.86 (d, 1H, *J* = 9.2 Hz, aryl), 5.22 (dd, 1H, *J* = 10.0, 1.2 Hz, **CH**=CH), 5.19 (dd, 1H, *J* = 10.0, 1.2 Hz, CH=**CH**), 3.91 (br s, 1H, C≡C**CH**) 3.81 (q, 1H, *J* = 7.3 Hz, **CH**CH_3), 3.63 (br d, 1H, NC**H**), 3.51 (s, 3H, OCH_3), 3.50 (s, 3H, OCH_3), 1.44 (d, 3H, *J* = 7.3 Hz, CH_3CH).

FTIR (neat), cm^{-1}:	3269 (br w), 2915 (w), 2844 (w), 1692 (m, C=O), 1643 (w), 1584 (vs), 1471 (s), 1435 (m), 1396 (m), 1364 (m), 1288 (m sh), 1274 (vs), 1187 (m sh), 1171 (s), 1145 (w sh), 1101 (w), 1066 (w), 1040 (w), 1025 (w), 969 (w), 934 (w), 919 (w), 853 (w), 782 (m).
HRMS (FAB):	Calcd for $C_{31}H_{22}O_9N$ $[MH]^+$: 552.1295 Found: 552.1294
TLC (40% ethyl acetate-hexanes), R_f:	**103**: 0.33 (visibly blue)
(10% ethyl acetate-CH_2Cl_2), R_f:	**103**: 0.56 (visibly blue)



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1

Dynemicin A (1)

A solution of potassium bis(trimethylsilyl)amide (0.5 M, 310 μL, 0.155 mmol, 19.0 equiv) was added to a solution of 4,7-bis(trimethylsiloxy)phthalide (**91**, 44 mg, 0.14 mmol, 17 equiv) in tetrahydrofuran (2.5 mL) at –78 °C, and the resulting bright yellow solution was stirred for 25 min at –78 °C. During this time, the reaction mixture darkened to yellow-brown. Chlorotrimethylsilane (100 μL, 0.79 mmol, 97 equiv) was added, and the reaction mixture was stirred at –78 °C for 5 min. The addition of chlorotrimethylsilane caused the reaction mixture to become bright yellow. After 5 min at –78 °C, the viscous reaction mixture was warmed to –50 °C and was swirled manually until the reaction mixture became colorless. At this point, the reaction solution was cooled to –78 °C. A solution of triisopropylsilyl (6*S*, 6a*S*, 7*S*, 10*R*, 10a*R*, 14*Z*)-2,6,7,10-tetrahydro-9-methoxy-7-methyl-

2-oxo-6a,10a-epoxy-6,10-[3]hexene[1,5]diynophenanthridine-8-carboxylate (**77**, 4.3 mg, 0.0082 mmol, 1 equiv) in tetrahydrofuran (1.0 mL) at 23 °C was transferred via cannula over 5 s to the cold reaction mixture. The cooling bath was removed and the reaction solution was heated to reflux within 2 min using a heat gun. When the reaction mixture began to boil, heating was discontinued and the flask was allowed to cool to 23 °C. The reaction solution was concentrated to near dryness and the light yellow residue was immediately dissolved in pyridine (1.0 mL) and added quickly, quantitated with a pyridine rinse (0.5 mL), to a green suspension of copper (I) chloride (22.3 mg, 0.225 mmol, 27.6 equiv) in pyridine (1.0 mL) at 23 °C which had been placed under an atmosphere of oxygen for 20 min prior to addition of the residue solution. A solution of hydrogen fluoride-pyridine in tetrahydrofuran (450 μL) at 0 °C, prepared by the addition of 70% hydrogen fluoride in pyridine (1.0 mL) to a solution of pyridine (4.0 mL) in tetrahydrofuran (10 mL) at 0 °C, was immediately added to the resulting dark brown reaction mixture, causing it to turn black within 5 min and form precipitate. The reaction suspension was stirred at 23 °C for a total of 30 min under an atmosphere of oxygen. The product suspension then was partitioned between ethyl acetate (50 mL) and water (80 mL). The aqueous layer was separated and extracted further with ethyl acetate (50 mL). The combined organic layers were washed with eight 40-mL portions of water, then three 40-mL portions of saturated sodium chloride solution. The organic layer was dried over sodium sulfate and was concentrated. The residue was purified by reverse phase HLPC (70% aqueous ammonium acetate solution (10 mM, pH 6.0) in acetonitrile initially, grading to 100% acetonitrile over 1 h) provided dynemicin A (**1**) as a brick-red solid (160 μg, 4%, as calculated from the UV-visible spectrum of the product using the estimated extinction coefficient ε = 10,000 at 568 nm).[60]

Repetition of this experimental procedure on a 6-mg scale (based on the starting quinone imine **77**) and purification of the crude product mixture by column chromatography on Sephadex LH-20 (46 cm by 2 cm, 30% acetonitrile in methanol) and subsequent trituration of the concentrated violet fractions with cold methanol provided pure dynemicin A. After five experiments were identically conducted on this scale, the purified dynemicin A from each was pooled to give ca. 1 mg of **1** as a brick-red solid. The average yield of **1** over the five experiments was 3%.

^{1}H NMR (400 MHz, C_6D_6), δ: 13.45 (br s, 1H, O**H**), 12.91 (br s, 1H, O**H**), 12.43 (br s, 1H, O**H**), 9.77 (d, 1H, *J* = 4.8 Hz, N**H**), 7.35 (s, 1H, aryl), 6.95 (d, 1H, *J* = 9.2 Hz, aryl), 6.85 (d, 1H, *J* = 9.2 Hz, aryl), 5.22 (dd, 1H, *J* = 10.0, 1.5 Hz, C**H**=CH), 5.14 (dd, 1H, *J* = 10.0, 1.5 Hz, CH=C**H**), 3.94 (q, 1H, *J* = 7.3 Hz, CH_3C**H**), 3.70 (d, 1H, *J* = 1.5 Hz, C≡CC**H**), 3.53 (dd, 1H, *J* = 4.8, 1.5 Hz, NC**H**), 2.87 (s, 3H, OC**H**$_3$), 1.47 (d, 3H, *J* = 7.3 Hz, C**H**$_3$).

^{1}H NMR (400 MHz, DMSO), δ: 13.13 (s, 1H, O**H**), 12.73 (s, 1H, O**H**), 12.14 (s, 1H, O**H**), 9.85 (br s, 1H, N**H**), 8.04 (s, 1H, aryl), 7.37 (br m, 2H, aryl), 6.09 (br d, 1H, *J* = 10.0 Hz, C**H**=CH), 6.05 (br d, 1H, *J* = 10.0 Hz, CH=C**H**), 5.07 (br m, 1H, NC**H**), 4.89 (br s, 1H, C≡CC**H**), 3.81 (s, 3H, OC**H**$_3$), 3.57 (m, 1H, CH_3C**H**), 1.26 (d, 3H, *J* = 7.0 Hz, C**H**$_3$).

FTIR (neat), cm^{-1}:	3686-2730 (br, m), 3405 (br, m), 3285 (m), 2924 (w), 2854 (w), 1750-1500 (br, m), 1642 (m), 1585 (vs), 1471 (s), 1395 (s), 1295 (sh), 1274 (s), 1189 (s), 1169 (s), 1144 (m), 1099 (w), 1034 (m), 969 (w), 923 (w), 783 (w).
TLC (ethyl acetate), R_f:	**1**: 0.37 (blue, visible)
(30% MEK-*p*-xylene), R_f:	**1**: 0.21 (blue, visible)

References and Notes

(1) Isolation and structural characterization of dynemicins: (a) Konishi, M.; Ohkuma, H; Matsumoto, K; Tsuno, T.; Kamei, H.; Miyaki, T.; Oki, T.; Kawaguchi, H.; VanDuyne, G. D.; Clardy, J. *J. Antibiot.* **1989**, *42*, 1449. (b) Konishi, M.; Ohkuma, H.; Tsuno, T.; Oki, T.; VanDuyne, G. D.; Clardy, J. *J. Am. Chem. Soc.* **1990**, *112*, 3715. (c) Shiomi, K.; Iinuma, H.; Naganawa, H.; Hamada, M.; Hattori, S.; Nakamura, H.; Takeuchi, T.; Iitaka, Y. *J. Antibiot.* **1990**, *43*, 1000. (d) Konishi, M.; Ohkuma, H.; Matsumoto, K.; Saitoh, K.; Miyaki, T.; Oki, T.; Kawaguchi, H. *J. Antibiot.* **1991**, *44*, 1300. (e) Miyoshi-Saitoh, M.; Morisaki, N.; Tokiwa, Y.; Iwasaki, S.; Konishi, M.; Saitoh, K.; Oki, T. *J. Antibiot.* **1991**, *44*, 1037.

(2) For a review of the anthracycline antibiotics, see: (a) *Anthracycline Antibiotics*; El Khadem, H. S., Ed.; Academic: New York, 1982. (b) *Recent Aspects in Anthracyclinone Chemistry (Tetrahedron Symposia-in-Print)*; Kelly, T. R., Ed.;*Tetrahedron* **1980**, *40*, 4537. (c) *Anthracycline and Anthracenedione-Based Anticancer Agents*; Lown, J. W., Ed.; Elsevier: Amsterdam, 1988. (d) Fisher, J. F.; Aristoff, P. A. *Prog. Drug. Res.* **1988**, *32*, 411.

(3) For a review of the enediyne antibiotics, see: Nicolaou, K. C.; Dai, W.-M. *Angew. Chem., Int. Ed. Engl.* **1991**, 30, 1387.

(4) (a) Sugiura, Y.; Shiraki, T.; Konishi, M.; Oki, T.; *Proc. Nat. Acad. Sci. USA* **1990**, *87*, 3831. (b) Semmelhack, M. F.; Gallagher, J.; Cohen, D. *Tetrahedron Lett.* **1990**, *31*, 1521. (c) Sugiura, Y.; Arakawa, T.; Vesugi, M.; Shiraki, T.; Ohkuma, H.; Konishi, M. *Biochemistry* **1991**, *30*, 2989. (d) Snyder, J. P.; Tipsword, G. E. *J. Am. Chem. Soc.* **1990**, *112*, 4040.

(5) For experimental studies, see: Sugiura, Y.; Shiraki, T.; Konishi, M.; Oki, T.; *Proc. Nat. Acad. Sci. USA* **1990**, *87*, 3831. For computational studies, see: (a) Langley,

D. R.; Doyle, T. W.; Beveridge, D. L. *J. Am. Chem. Soc.* **1991**, *113*, 4395. (b) Wender, P. A.; Kelly, R. C.; Beckham, S.; Miller, B. L. *Proc. Natl. Acad. Sci. USA* **1991**, *88*, 8835. (c) Cardozo, M. G.; Hopfinger, A. J. *Mol. Pharmacol.* **1991**, *40*, 1023.

(6) (a) Sugiura, Y.; Shiraki, T.; Konishi, M.; Oki, T.; *Proc. Nat. Acad. Sci. USA* **1990**, *87*, 3831. (b) Shiraki, T.; Sugiura, Y. *Biochemistry* **1990**, *29*, 9795. (c) Shiraki, T.; Uesugi, M.; Sugiura, Y. *Biochem. Biophys. Res. Commun.* **1992**, *188*, 584. (d) Ichikawa, A; Kuboya, T.; Aoyama, T.; Sugiura, Y. *Biochemistry* **1992**, *31*, 6784. (e) Kusakabe, T.; Maekawa, K.; Ichikawa, A; Uesugi, M.; Sugiura, Y. *Biochemistry* **1993**, *32*, 11669.

(7) Antitumor and antibiotic activity of dynemicins: (a) Konishi, M.; Ohkuma, H; Matsumoto, K; Tsuno, T.; Kamei, H.; Miyaki, T.; Oki, T.; Kawaguchi, H.; VanDuyne, G. D.; Clardy, J. *J. Antibiot.* **1989**, *42*, 1449. (b) Konishi, M.; Ohkuma, H.; Tsuno, T.; Oki, T.; VanDuyne, G. D.; Clardy, J. *J. Am. Chem. Soc.* **1990**, *112*, 3715. (c) Shiomi, K.; Iinuma, H.; Naganawa, H.; Hamada, M.; Hattori, S.; Nakamura, H.; Takeuchi, T.; Iitaka, Y. *J. Antibiot.* **1990**, *43*, 1000. (d) Kamei, H.; Nishiyama, Y.; Takahashi, A.; Obi, Y.; Oki, T. *J. Antibiot.* **1991**, *44*, 1306. (e) Miyoshi-Saitoh, M.; Morisaki, N.; Tokiwa, Y.; Iwasaki, S.; Konishi, M.; Saitoh, K.; Oki, T. *J. Antibiot.* **1991**, *44*, 1037.

(8) For efforts directed toward the synthesis of dynemicin A, see: (a) Porco, J. A., Jr.; Schoenen, F. J.; Stout, T. J.; Clardy, J.; Schreiber, S. L. *J. Am. Chem. Soc.* **1990**, *112*, 7410. (b) Chikashita, H.; Porco, J. A., Jr.; Stout, T. J.; Clardy, J.; Schreiber, S. L. *J. Org. Chem.* **1991**, *56*, 1692. (c) Wood, J. L.; Porco, J. A., Jr.; Taunton, J.; Lee, A. Y.; Clardy, J.; Schreiber, S. L. *J. Am. Chem. Soc.* **1992**, *114*, 5898. (d) Taunton, J.; Wood, J. L.; Schreiber, S. L. *J. Am. Chem. Soc.* **1993**, *115*, 10378. (e) Yoon, T.; Shair, M. D.; Danishefsky, S. J.; Shulte, G. K. *J. Org. Chem.* **1994**, *59*, 3752. (f) Shair, M. D.; Yoon, T.; Danishefsky, S. J. *J. Org. Chem.* **1994**, *59*, 3755. (g) Yoon, T.; Shair, M. D.; Danishefsky, S. J. *Tetrahedron Lett.* **1994**, *35*, 6259. (h) Nicolaou, K. C.; Gross, J. L.; Kerr, M. A.; Lemus, R. H.; Ikeda, K.; Ohe, K. *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 781. For related model systems, see: (i) Nicolaou, K. C.; Hwang, C.-K.; Smith, A. L.; Wendeborn, S. V. *J. Am. Chem. Soc.* **1990**, *112*, 7416. (j) Nishikawa, T.; Isobe, M.; Goto, T. *Synlett* **1991**, 393. (k) Magnus, P.; Fortt, S. M. *J.*

Chem. Soc., Chem. Commun. **1991**, 544. (l) Nishikawa, T.; Ino, A.; Isobe, M.; Goto, T. *Chem. Lett.* **1991**, 1271. (m) Wender, P. A.; Zercher, C. K. *J. Am. Chem. Soc.* **1991**, *113*, 2311. (n) Nicolaou, K. C.; Smith, A. L.; Wendeborn, S. V.; Hwang, C.-K. *J. Am. Chem. Soc.* **1991**, *113*, 3106.

(9) Prepared in the following way: A solution of 3-butene-2-one (3.33 mL, 40.0 mmol, 1 equiv) in dichloromethane (15 mL) over 12 h to a solution of triisopropylsilyl trifluoromethanesulfonate (12.9 mL, 48.0 mmol, 1.2 equiv) and *N*,*N*-diisopropylethylamine (10.4 mL, 60.0 mmol, 1.5 equiv) in dichloromethane (100 mL) at 23 °C. After the addition was completed, the resulting mixture was allowed to stir for 6 h. Sodium bicarbonate was added (500 mg) and the volatiles were removed in vacuo. Hexane (150 mL) was added to the residue, and the solids were removed by vacuum filtration (water aspirator). The filtrate was concentrated, and the residue was purified by vacuum distillation, furnishing 2-(triisopropylsilyl)-1,3-butadiene as a colorless oil (bp 43-45 °C, 0.09 mm Hg, 8.22 g, 91%). For the preparation of related trialkylsiloxy enol ethers employing trialkylsilyl triflates, see: (a) Emde, H.; Götz, A.; Kofmann, K.; Simchen, G. *Liebigs Ann. Chem.* **1981**, 1643. (b) Corey, E. J.; Cho, H.; Rücker, C.; Hua, D. H. *Tetrahedron Lett.* **1981**, *22*, 3455. (c) Mander, L. N.; Sethi, S. P. *Tetrahedron Lett.* **1984**, *25*, 5953.

(10) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

(11) (a) Solodar, W. E.; Simon, M. S. *J. Org. Chem.* **1962**, *27*, 689. (b) Krapcho, A. P.; Getahun, Z. *Synth. Commun.* **1985**, *15*, 907, and references therein.

(12) Valkanas, G.; Hopff, H. *J. Org. Chem.* **1962**, *27*, 3680.

(13) Krapcho, A. P.; Getahun, Z. *Synth. Commun.* **1985**, *15*, 907. For an alternative synthesis, see: Bentov, M.; Lévy, A.; Bergmann, E. D. *Bull. Soc. Chim. Fr.* **1970**, 1550.

(14) (a) Sutherland, J. K.; Towers, P. *J. Chem. Soc., Chem. Commun.* **1981**, 740. (b) Sutherland, J. K.; Ashcroft, A. E. *J. Chem. Soc., Chem. Commun.* **1981**, 1075. (c)

Cava, M. P.; Ahmed, Z. *Tetrahedron Lett.* **1981**, *22*, 5239. (d) Cava, M. P.; Murphy, R. A. *Tetrahedron Lett.* **1984**, *25*, 803. (e) Krohn, K.; Baltus, W. *Synthesis*, **1986**, 942.

(15) Evans, D. A.; Chapman, K. T.; Bisaha, J. *J. Am. Chem. Soc.* **1988**, *110*, 1238.

(16) DeGraw, J. I.; Goodman, L.; Baker, B. R. *J. Org. Chem.* **1961**, *26*, 1156.

(17) Kukkola, P. unpublished results. For related methodology, see: (a) Evans, D. A.; Chapman, K. T.; Bisaha, J. *J. Am. Chem. Soc.* **1988**, *110*, 1238. (b) Narasaka, K.; Iwasawa, N.; Inoue, M.; Yamada, T.; Nakashima, M.; Sugimori, J. *J. Am. Chem. Soc.* **1989**, *111*, 5340.

(18) Damon, R. E.; Coppola, G. M. *Tetrahedron Lett.* **1990**, *31*, 2849.

(19) Fukuyama, T; Lin, S.-C.; Li, L. *J. Am. Chem. Soc.* **1990**, *112*, 7050.

(20) (a) Adachi, T.; Yamada, Y.; Inoue, I.; Saneyoshi, M. *Synthesis* **1977**, 45. For the use of propane-1,3-dithiol as a reducing agent, see: (b) Bayley, H.; Strandring, D. N.; Knowles, J. R. *Tetrahedron Lett.* **1978**, 3633.

(21) For related transformations, see: (a) Krapcho, A. P.; Getahun, Z. *Synth. Commun.* **1985**, *15*, 907. (b) Bentov, M.; Lévy, A.; Bergmann, E. D. *Bull. Soc. Chim. Fr.* **1970**, 1550.

(22) Dragovich, P. S. Ph.D. Thesis, California Institute of Technology, 1993.

(23) Witzeman, J. S. *Tetrahedron Lett.* **1990**, *31*, 1401.

(24) For related transformations, see: (a) Smith, C. R. *J. Org. Chem.* **1960**, *25*, 588. (b) von Schilling, R.; Vorländer, D. *Ann.* **1899**, *308*, 184.

(25) Extensive experimentation by Norma J. Tom with alkyl acetoacetates derived by transesterification of *tert*-butyl acetoacetate with various commercially available alcohols of enantiomeric purity led to this result. Of the alkyl acetoacetates studied, only (–)-menthol

acetoacetate provided diastereomeric diketones which were separable by selective recrystallization.

(26) For ortho-lithiation of *N*-(*tert*-butoxycarbonyl)aniline, see: (a) Muchowski, J. M.; Venuti, M. C. *J. Org. Chem.* **1980**, *45*, 4798. (b) Stanetty, P.; Koller, H.; Mihovilovic, M. *J. Org. Chem.* **1992**, *57*, 6833.

(27) (a) Miyaura, N.; Yanagi, T.; Suzuki, A. *Synth. Commun.* **1981**, *11*, 513. See also: (b) Alo, B. I.; Kandil, A.; Patil, P. A.; Sharp, M. J.; Siddiqui, M. A.; Snieckus, V.; Josephy, P. D. *J. Org. Chem.* **1991**, *56*, 3763. (c) Yasuda, N.; Xavier, L.; Rieger, D. L.; Li, Y.; DeCamp, A. E.; Dolling, U.-H. *Tetrahedron Lett.* **1993**, *34*, 3211.

(28) (a) Scott, W. J.; Crisp, G. T.; Stille, J. K. *J. Am. Chem. Soc.* **1984**, *106*, 4630. For the use of a Cu(I) salt as a co-catalyst, see: (b) Liebeskind, L. S.; Fengl, R. W. *J. Org. Chem.* **1990**, *55*, 5359. (c) Gómez-Bengoa, E.; Echavarren, A. M. *J. Org. Chem.* **1991**, *56*, 3497.

(29) For examples of thermal deprotection of *t*-butyl carbamates, see: (a) Rawal, V. H.; Jones, R. J.; Cava, M. P. *J. Org. Chem.* **1987**, *52*, 19. (b) Wasserman, H. H.; Berger, G. D.; Cho, K. R. *Tetrahedron Lett.* **1982**, *23*, 465.

(30) Cacchi, S.; Ciattini, P. G.; Morera, E.; Ortar, G. *Tetrahedron Lett.* **1986**, *27*, 5541.

(31) Yamaguchi, R.; Nakazono, Y.; Kawanisi, M. *Tetrahedron Lett.* **1983**, *24*, 1801.

(32) Computer modeling was performed on a Silicon Graphics Personal Iris workstation using the MM2 force field contained in the Macromodel 3.5a software package provided by W. Clark Still, Columbia University.

(33) (a) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, 4467. (b) Ratovelomana, V.; Linstrumelle, G. *Synth. Commun.* **1981**, *11*, 917. (c) Stephens, R. D.; Castro, C. E. *J. Org. Chem.* **1963**, *28*, 3313.

(34) (a) Danishefsky, S. J.; Mantlo, N. B.; Yamashita, D. S.; Schulte, G. *J. Am. Chem. Soc.* **1988,** *110*, 6890. (b) Kende, A. S.; Smith, C. A. *Tetrahedron Lett.* **1988,** *29*, 4217. (c) Tius, M. A.; Cullingham, J. M. *Tetrahedron Lett.* **1989,** *29*, 3749.

(35) Mancuso, A. J.; Swern, D. *Synthesis* **1981,** 165.

(36) For the use of $CeCl_3$, see: (a) Myers, A. G.; Harrington, P. M.; Kuo, E. Y. *J. Am. Chem. Soc.* **1991,** *113*, 694. For a similar cyclization in dynemicin model studies, see: (b) Nicolaou, K. C.; Hwang, C.-K.; Smith, A. L.; Wendeborn, S. V. *J. Am. Chem. Soc.* **1990,** *112*, 7416.

(37) (a) Barton, D. H. R.; McCombie, S. W. *J. Chem. Soc., Perkin Trans. 1* **1975,** 1574. See also: (b) Nicolaou, K. C.; Hwang, C.-K.; Smith, A. L.; Wendeborn, S. V. *J. Am. Chem. Soc.* **1990,** *112*, 7416.

(38) (a) Matsumura, N.; Yagyu, Y.; Imoto, E. *Nippon Kaguku Kaishi* **1977**, 1344. (b) Tirpak, R. E.; Olsen, R. S.; Rathke, M. W. *J. Org. Chem.* **1985,** *50*, 4877.

(39) Wood, J. L.; Porco, J. A., Jr.; Taunton, J.; Lee, A. Y.; Clardy, J.; Schreiber, S. L. *J. Am. Chem. Soc.* **1992,** *114*, 5898.

(40) Feutrill, G. I.; Mirrington, R. N. *Tetrahedron Lett.* **1970,** 1327.

(41) Corey, E. J.; Venkateswarlu, A. *J. Am. Chem. Soc.* **1972,** *94*, 6190.

(42) For related transformations, see: (a) Barret, R.; Daudon, M. *Tetrahedron Lett.* **1991,** *32*, 2133. (b) Swenton, J. S.; Benke, B. R.; Clark, W. M.; Chen, C.-P.; Martin, K. V. *J. Org. Chem.* **1990,** *55*, 2027, and references therein.

(43) (a) Guibe, F.; Dangles, O.; Balavoine, G. *Tetrahedron Lett.* **1986,** *27*, 2365. For leading references on the chemistry of quinone imines, see: (a) Finley, K. T.; Tong, L. K. J. *The Chemistry of the Carbon-Nitrogen Double Bond*; Patai, S., Ed.; Interscience: New York, 1990; pp. 663-729. (b) Swenton, J. S.; Shih, C.; Chen, C.-P.; Chou, C.-T. *J.*

Org. Chem. **1990**, *55*, 2019. (c) Swenton, J. S.; Benke, B. R.; Clark, W. M.; Chen, C.-P.; Martin, K. V. *J. Org. Chem.* **1990**, *55*, 2027.

(44) Quinone imine **80** was prepared by Scott B. Cohen.

(45) (a) Sugiura, Y.; Shiraki, T.; Konishi, M.; Oki, T.; *Proc. Nat. Acad. Sci. USA* **1990**, *87*, 3831. (b) Sugiura, Y.; Arakawa, T.; Vesugi, M.; Shiraki, T.; Ohkuma, H.; Konishi, M. *Biochemistry* **1991**, *30*, 2989.

(46) DNA cleaving studies with compound **81** were conducted by Scott B. Cohen.

(47) (a) Kende, A. S.; Curran, D. P.; Tsay, Y-g.; Mills, J. E. *Tetrahedron Lett.* **1977**, 3537. (b) Mehendale, A. R.; Gupta, M.; Nagarajan, G. *Indian J. Chem.* **1987**, *26B*, 205.

(48) (a) Meerwein, H. *Org. Synth.* **1966**, *46*, 113. (b) Contreras, L.; Slemon, C. E.; MacLean, D. B. *Tetrahedron Lett.* **1978**, 4237.

(49) Anthraquinones **86-89** were prepared by Scott. B. Cohen.

(50) (a) Iwao, M.; Inoue, H.; Kuraishi, T. *Chem. Lett.* **1984**, 1263. (b) Bloomer, J. L.; Lankin, M. E. *Tetrahedron Lett.* **1992**, *33*, 2769.

(51) Shih, T. L.; Wyvratt, M. J.; Mrozik, H. *J. Org. Chem.* **1987**, *52*, 2029.

(52) Barker, S. A.; Settine, R. L. *Org. Prep. Proced. Int.* **1979**, *11*, 87.

(53) (a) Keay, B. A.; Plaumann, H. P.; Rajapaksa, D.; Rodrigo, R. *Can. J. Chem.* **1983**, *61*, 1987. (b) Naito, K.; Rickborn, B. *J. Org. Chem.* **1980**, *45*, 4061. (c) Moss, R. J.; Rickborn, B. *J. Org. Chem.* **1984**, *49*, 3694.

(54) Trost, B. M.; Cadwell, C. G.; Murayama, E.; Heissler, D. *J. Org. Chem.* **1983**, *48*, 3252.

(55) (a) Waller, C. W.; Hutchings, B. L.; Broschard, R. W.; Goldman, A. A.; Stein, W. J.; Wolf, C. F.; Williams, J. H. *J. Am. Chem. Soc.* **1952**, *74*, 4981. (b) Stephens, C. R.; Conover, L. H.; Pasternack, R.; Hochstein, F. A.; Moreland, W. T.; Regna, P. P.; Pilgrim, F. J.; Brunings, K. J.; Woodward, R. B. *J. Am. Chem. Soc.*, **1954**, *76*, 3568.

(56) For oxidation of hydroquinones to benzoquinones using molecular oxygen and a copper salt catalyst, see: (a) Karpov, V. V.; Khidekel, M. L. *Zh. Org. Khim.* **1967**, *3*, 1669. (b) Orlando, C. M., Jr. *J. Org. Chem.* **1968**, *33*, 2516. (c) Radel, R. J.; Sullivan, J. M.; Hatfield, J. D. *Ind. Eng. Chem. Prod. Res. Dev.* **1982**, *21*, 566.

(57) (a) Konishi, M.; Ohkuma, H; Matsumoto, K; Tsuno, T.; Kamei, H.; Miyaki, T.; Oki, T.; Kawaguchi, H.; VanDuyne, G. D.; Clardy, J. *J. Antibiot.* **1989**, *42*, 1449. (b) Konishi, M.; Ohkuma, H.; Matsumoto, K.; Saitoh, K.; Miyaki, T.; Oki, T.; Kawaguchi, H. *J. Antibiot.* **1991**, *44*, 1300.

(58) This numbering convention is of that found in reference 1; it is not the convention used by Chemical Abstracts.

(59) DNA cleaving studies with compounds **86-89** and **1** were conducted by Scott B. Cohen.

(60) For reported extinction coefficients, see reference 1.

Appendix 1

Alternative Approaches to Anthraquinone Synthesis

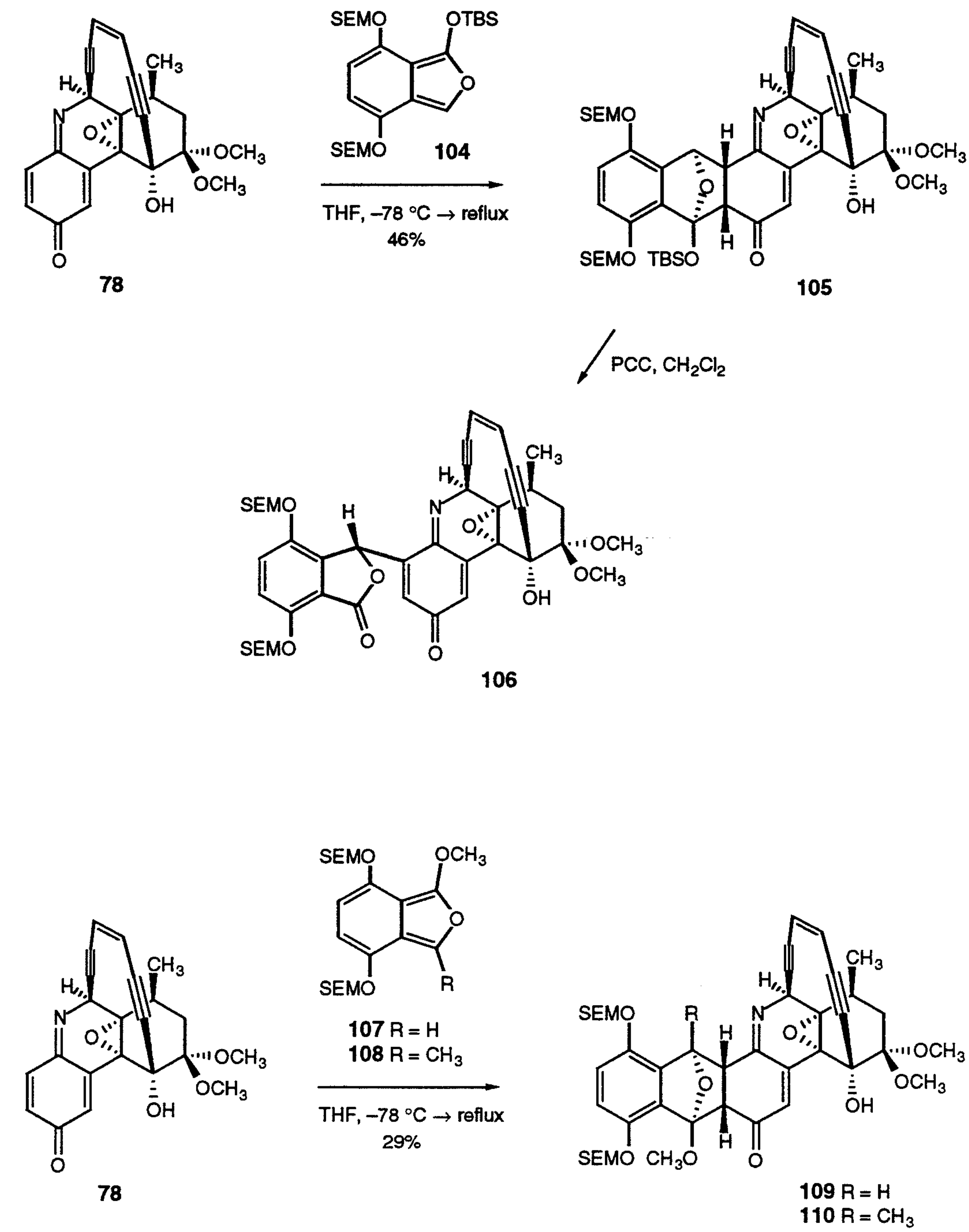
Isobenzofurans

Isobenzofuran **104** was prepared by the deprotonation of phthalide **90** (5.7 equiv) with potassium hexamethyldisilazide (6.1 equiv) in THF at –78 °C, and subsequent trapping of the resultant anion with *tert*-butyldimethylsilyltrifluoromethane sulfonate (TBSOTf, 6.6 equiv, Scheme IA). Warming of this cold solution of isobenzofuran **104** in the presence of the quinone imine **78** (1 equiv) produced the Diels-Alder adduct **105** in 46% yield. This acid-sensitive product failed to produce an anthraquinone upon treatment with excess PCC in dichloromethane, but afforded in high yield the phthalide **106**.

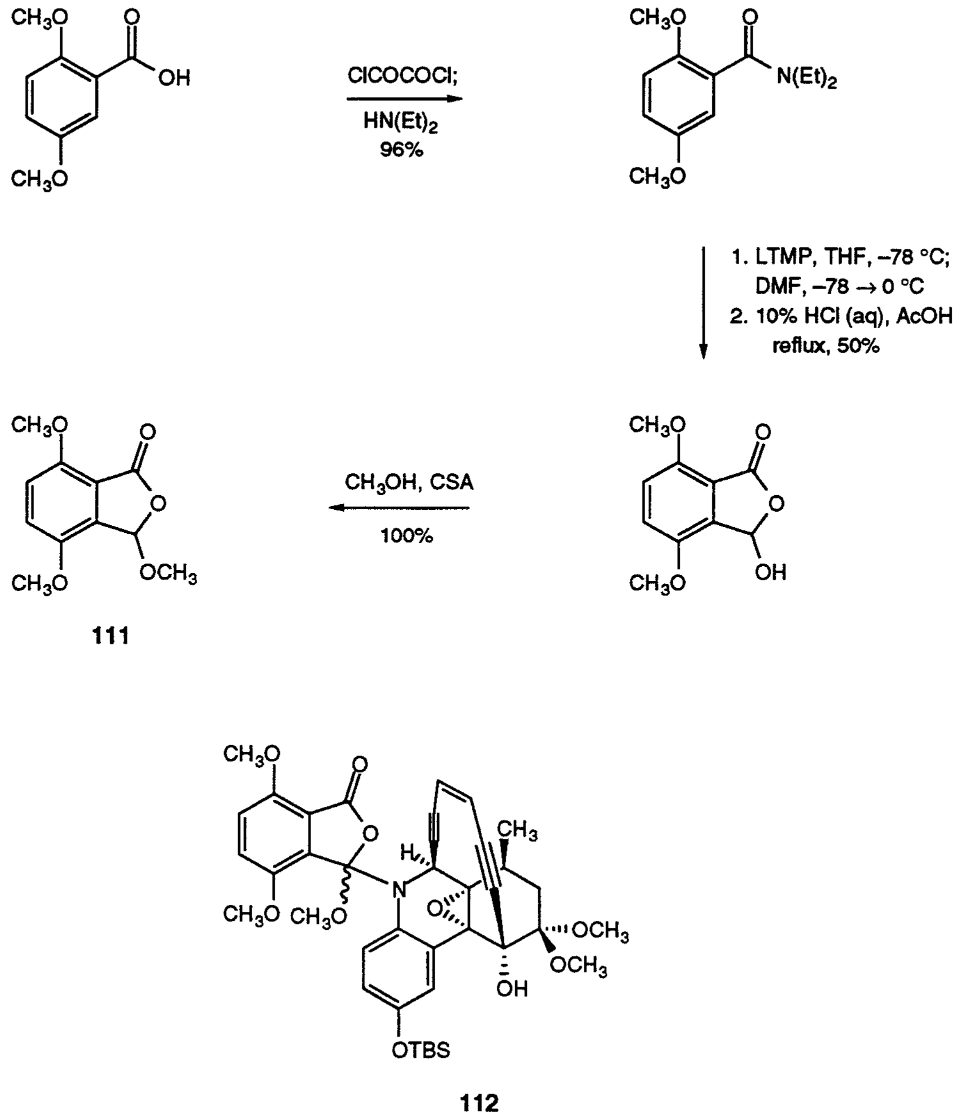
After extensive experimentation, the following procedure was developed for the preparation of isobenzofuran **107**: Treatment of phthalide **90** (4.9 equiv) with potassium hexamethyldisilazide (5.9 equiv) in the presence of 18-crown-6 (5.3 equiv) in a mixture of THF and HMPA (10:1, respectively) at –78 °C, followed by the addition of methyl trifluoromethylsulfonate (6.7 equiv) provided the isobenzofuran **107** as well as isobenzofuran **108**, as evidenced by the formation of Diels-Alder adducts **109** and **110** (ratio ca. 3:1, respectively, 29% yield) upon warming with quinone imine **78** (1 equiv). The addition of PCC or PDC to a solution of adduct **109** in dichloromethane failed to bring about the conversion of the latter to an anthraquinone, furnishing instead the phthalide **106**.

The preparation of an isobenzofuran derived from the methoxyphthalide **111** (Scheme IIA) was also investigated. Treatment of phthalide **111** with LTMP (5.3 equiv) in the presence of 18-crown-6 (6.3 equiv) in a mixture of THF and HMPA (15:1,

Scheme IA

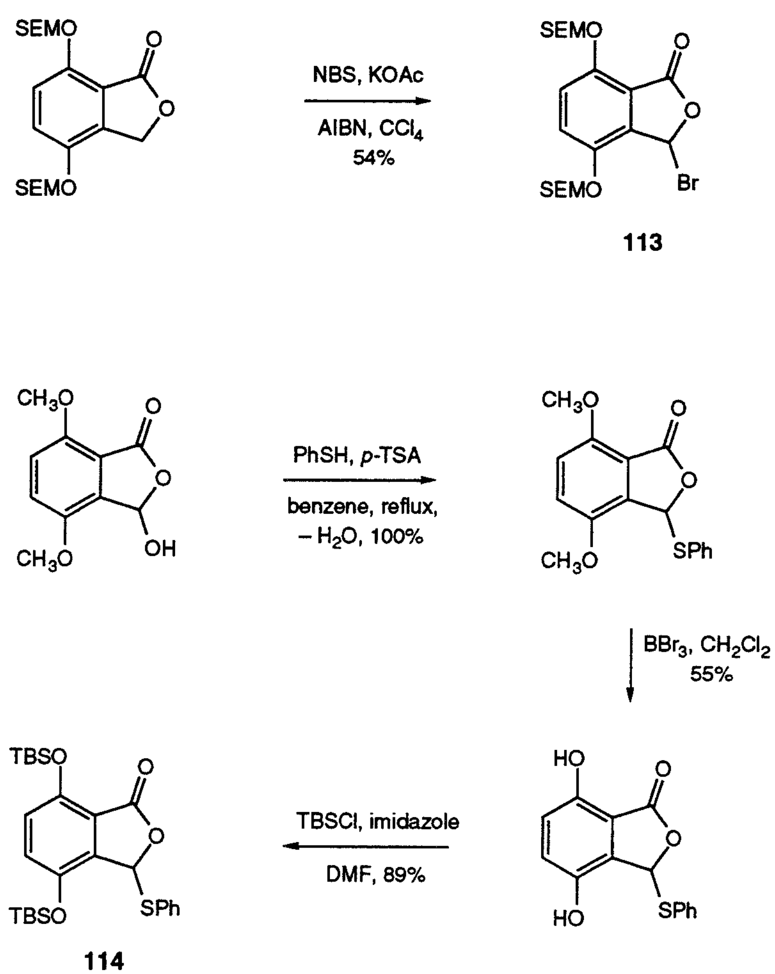

SEMO
OTBS
SEMO
104
THF, –78 °C → reflux
46%
78
105
PCC, CH2Cl2
106
SEMO
OCH3
SEMO
R
107 R = H
108 R = CH3
THF, –78 °C → reflux
29%
78
109 R = H
110 R = CH3

Scheme IIA


CH3O
O
OH
ClCOCOCl;
HN(Et)2
96%
N(Et)2
1. LTMP, THF, –78 °C;
DMF, –78 → 0 °C
2. 10% HCl (aq), AcOH
reflux, 50%
CH3OH, CSA
100%
OCH3
OH
111
H
N
CH3
OTBS
112

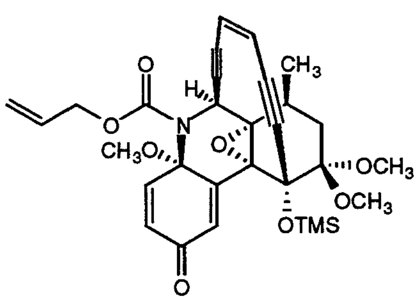
respectively) at –78 °C, followed by the sequential addition of TBSOTf (6.4 equiv) and quinone imine **78** provided the phthalide **112** in low yield. Variations in the base, additives, and silylating (or alkylating) agent failed to produce Diels-Alder adducts; rather these measures led invariably to the decomposition of the quinone imine component. Similar studies with bromophthalide **113** and sulfide **114** (prepared by the method outlined in Scheme IIIA) were also unsuccessful.[1]

Scheme IIIA

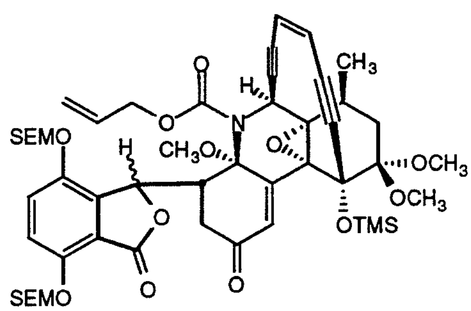


Cyano- and Sulfonylphthalides

A related method for the synthesis of naphthols, naphthoquinones, and anthraquinones was investigated, involving the addition of the anion of a cyano- or sulfonylphthalide to an enone.[2] Treatment of the quinone imine **78** with the lithium or potassium anion of cyanophthalide **115**[3] (8.1 equiv, *n*-butyllithium or potassium hexamethylsiliazide, THF, –78 °C, Scheme IVA) furnished, unexpectedly, the phthalide **116** in quantitative yield. Addition of the lithium or potassium anion of either cyanophthalide **115** or sulfonylphthalide **118**[4] to a solution of the protected quinone imine **117** failed under a large set of conditions to form an anthraquinone, or even a product resulting from a conjugate addition reaction. In contrast, addition of the lithium anion of **90** (3.4 equiv, lithium hexamethyldisilazide, THF, –78 °C) to a solution of the enone **117** in THF at –95 °C provided in 96% yield the phthalide **119** as a single diastereomer. All efforts directed toward Dieckman closure of this product were unsuccessful.[5]



117

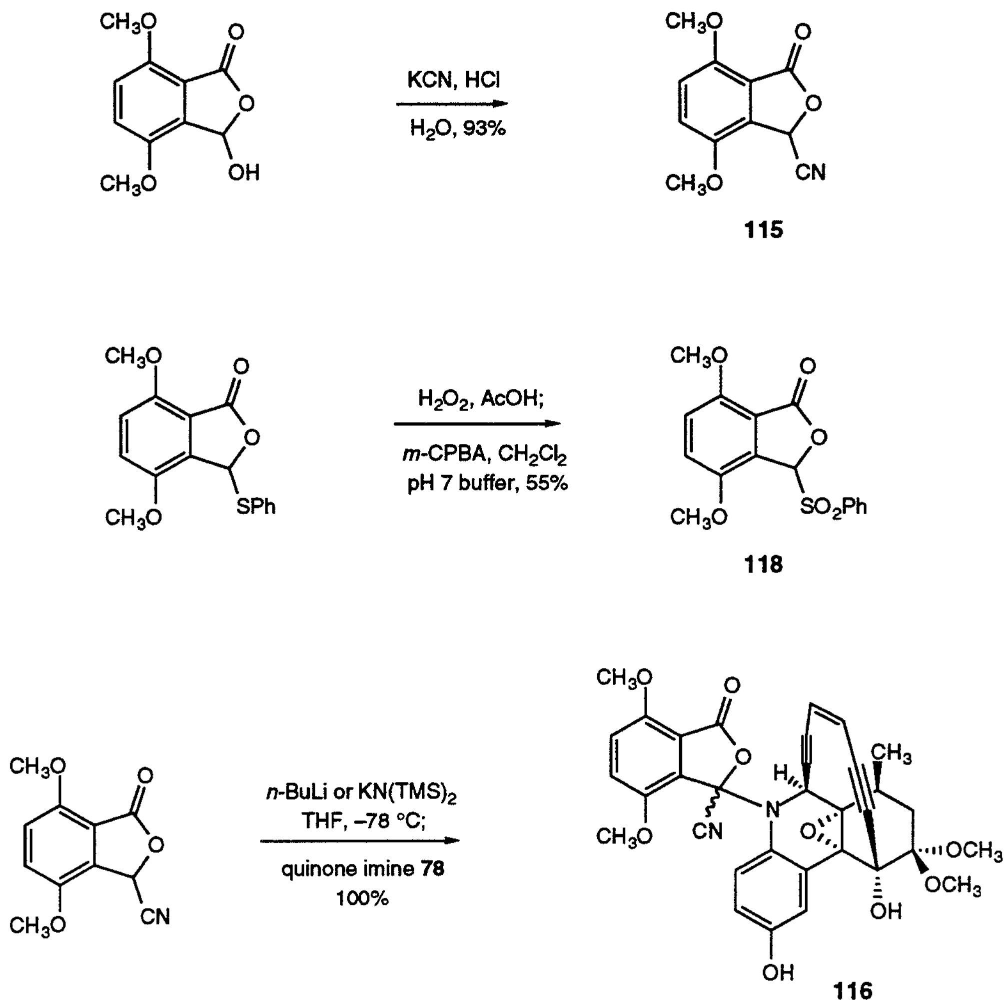


119

A Sultine as a Diene Precursor

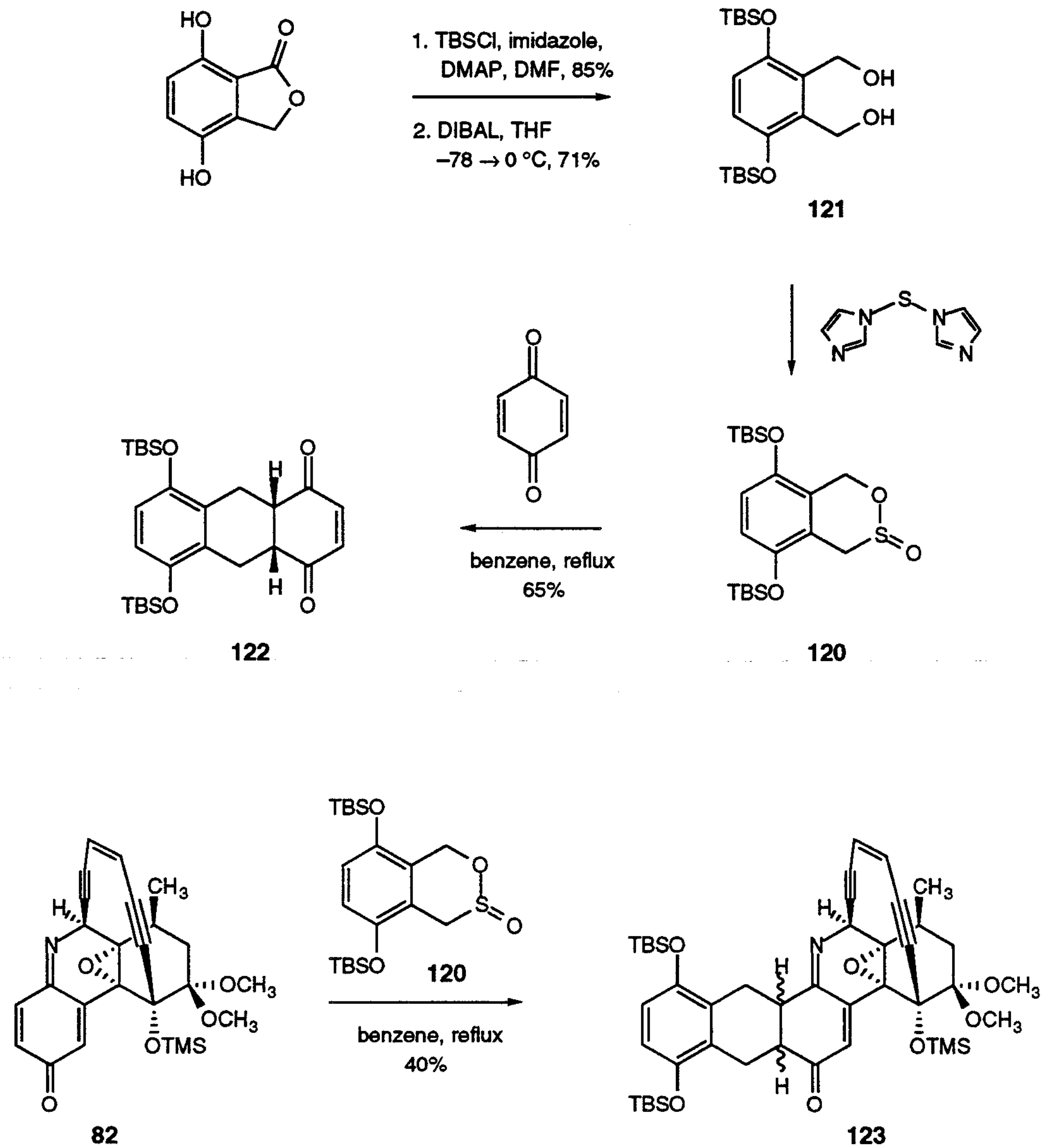
In addition to isobenzofurans, other dienes were investigated as a means to construct the anthraquinone of **1**. One approach employed the sultine **120** as a diene precursor.[6] Sultine **120** was prepared beginning with the reduction of 4,7-bis(*t*-butyldimethylsiloxy)phthalide with excess DIBAL in THF, providing the diol **121** as a

Scheme IVA

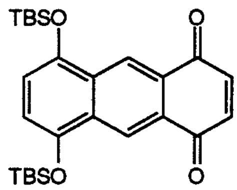


colorless oil (71%, Scheme VA). Diol **121** was converted to the sultine **120** in quantitative yield (as monitored by ^{1}H NMR) by the treatment of the former with *N,N'*-thiobisimidazole (1.1 equiv, prepared by the dropwise addition of 1 equiv of sulfur dichloride over 2 h to 2 equiv of 1-(trimethylsilyl)imidazole in carbon tetrachloride at 23 °C)[7] in carbon tetrachloride for 17 h at 23 °C. Adduct **122** was formed in 65% yield by heating a solution of the sultine **120** (1 equiv) and benzoquinone (3.6 equiv) in benzene at reflux for 3 h. Similarly, heating a solution of sultine **120** (6.6 equiv) with quinone imine

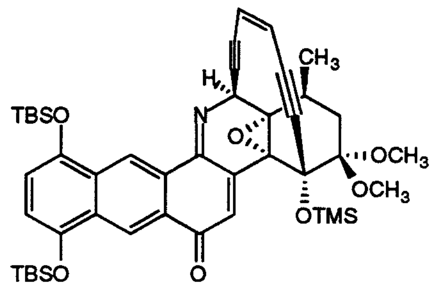
Scheme VA



82 (1 equiv) in benzene at reflux afforded a 2:1 mixture of Diels-Alder adducts **123** in 40% yield. Treatment of adduct **122** or adducts **123** with excess triethylamine in acetonitrile under air furnished naphthalene **124** and **125**, respectively, in quantitative yield. As with the related naphthalenols of Chapter 2 (**96**, **99** and **100**), a large series of oxidants failed to bring about the conversion of **124** and **125** to anthraquinones.



124

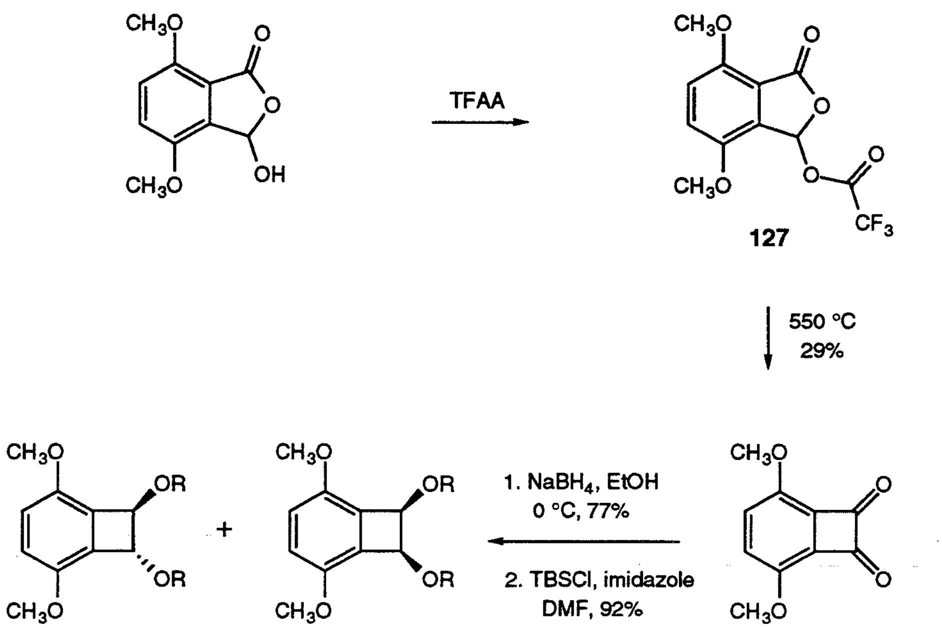


125

A Benzocyclobutene as a Diene Precursor

Benzocyclobutene **126** was prepared beginning with the thermolysis of the trifluoroacetate **127** (conducted by the vacuum sublimation of the latter through a tube furnace set to 550 °C), providing 4,7-dimethoxybenzocyclobutenedione (**128**) as a light-sensitive yellow solid in 29% yield (Scheme VIA).[8] Reduction of **128** with sodium borohydride in ethanol at 0 °C furnished separately in equal amounts the cis and trans diols **129** and **130**, respectively, following chromatography on silica gel (77% yield). Silylation of **129** and **130** (TBSCl, imidazole, DMAP) furnished cis and trans TBS ethers **131** and **126**, respectively, in 92% yield. The configuration of the ethers was determined by heating each separately with benzoquinone (1.5 equiv) in toluene at reflux: TBS ether **126** produced the adduct **132** in 72% yield after 5 h, while TBS ether **131** failed to form a cycloaddition product after 22 h. From these results, the ether **126** was assigned as the trans ether, as only this isomer would be thermally allowed to generate the highly reactive diene **133**. It is interesting to note that trans diol **130** produced only a small amount of naphthalene **134** (the product resulting from the dehydration of the Diels-Alder adduct) when heated with benzoquinone (1.5 equiv) in toluene at reflux, and the trans acetate **135** failed to produce Diels-Alder adducts under the same conditions. Naphthalene **134** was formed in quantitative yield from adduct **132** by treatment of the latter with triethylamine or silica gel. All attempts to oxidize adduct **132** or naphthalene **134** to an anthraquinone were

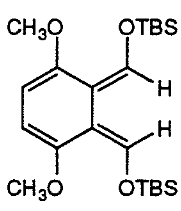
Scheme VIA



128

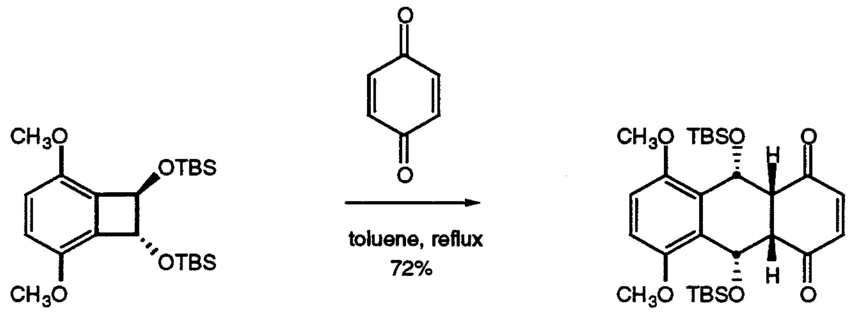
130 R = H
126 R = TBS
135 R = Ac

129 R = H
131 R = TBS

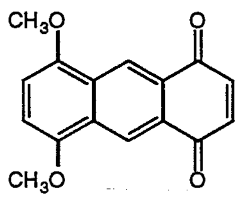


133

unsuccessful. Heating TBS ether **126** with quinone imine **79** in toluene at reflux for 1 h failed to produce a Diels-Alder adduct.



126 **132**



134

References and Notes for Appendix 1

(1) It is undetermined whether isobenzofurans were actually generated from phthalides **111, 113**, and **114** by the deprotonation/silylation procedure, for a cycloaddition adduct was never isolated or observed. The problem may reside in the stability of the phthalide anion and/or the stability of the resulting isobenzofuran.

(2) (a) Broom, N. J. P.; Sammes, P. G. *J. Chem. Soc., Chem. Commun.* **1978**, 162. (b) Kraus, G. A.; Sugimoto, H. *Tetrahedron Lett.* **1978**, 2263. (c) Broom, N. J. P.; Sammes, P. G. *J. Chem. Soc., Perkin Trans. 1* **1981**, 465. (d) Hauser, F. M.; Rhee, R. *J. Org. Chem.* **1980**, *45*, 3061. (e) Dolson, M. G.; Chenard, B. L.; Swenton, J. S. *J. Am. Chem. Soc.* **1981**, *103*, 5263. (f) Chenard, B. L.; Dolson, M. G.; Sercel, A. D.; Swenton, J. S. *J. Org. Chem.* **1984**, *49*, 318. (g) Hauser, F. M.; Prasanna, S. *J. Am. Chem. Soc.* **1981**, *103*, 6378. (h) Hauser, F. M.; Mal, D. *J. Am. Chem. Soc.* **1984**, *106*, 1098. (i) Hauser, F. M.; Hewawasam, P; Baghdanov, V. M. *J. Org. Chem.* **1988**, *53*, 224. (j) Hauser, F. M.; Caringal, Y. *J. Org. Chem.* **1990**, *55*, 555.

(3) Freskos, J. N.; Morrow, G. W.; Swenton, J. S. *J. Org. Chem.* **1985**, *50*, 805.

(4) Hauser, F. M.; Mal, D. *J. Am. Chem. Soc.* **1984**, *106*, 1098.

(5) The reason may be that Dieckman closure is thermodynamically unfavorable (discussed further in Chapter 2 of this thesis).

(6) (a) Jung, F.; Molin, M.; Van Den Elzen, R.; Durst, T. *J. Am. Chem. Soc.* **1974**, *96*, 935. (b) Askari, S.; Lee, S.; Perkins, R. R.; Schieffer, J. R. *Can. J. Chem.* **1985**, *63*, 3526. (c) Durst, T.; Charlton, J. L.; Mount, D. B. *Can. J. Chem.* **1986**, *64*, 246. (d) Hoey, M. D.; Dittmer, D. C. *J. Org. Chem.* **1991**, *56*, 1947.

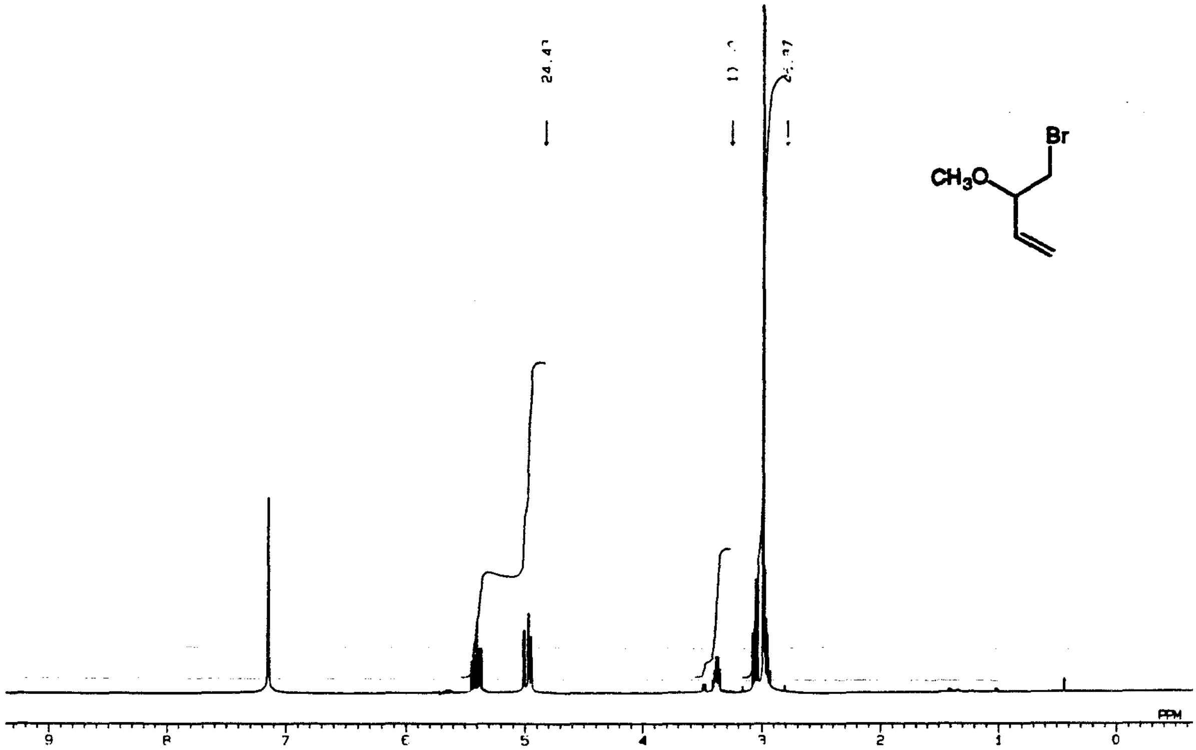
(7) Harpp, D. N.; Steliou, K.; Chan, T. H. *J. Am. Chem. Soc.* **1978**, *78*, 1222.

(8) Krohn, K.; Rieger, H.; Broser, E.; Schiess, P.; Chen, S.; Strubin, T. *Liebigs Ann. Chem.* **1988**, 943.

Appendix 2

Catalog of Spectra

(Chapter 1)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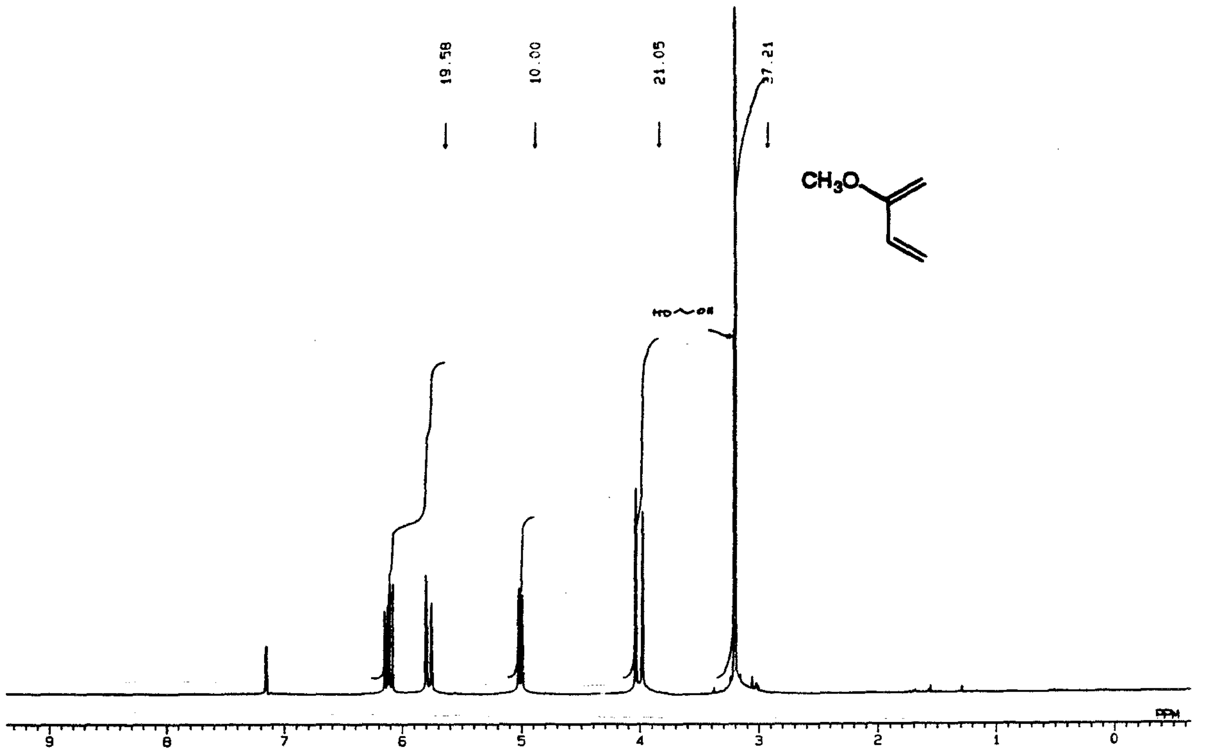
PPM
9
8
7
6
5
4
3
2
1
0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37.21
CH_3O
HO~OH
PPM
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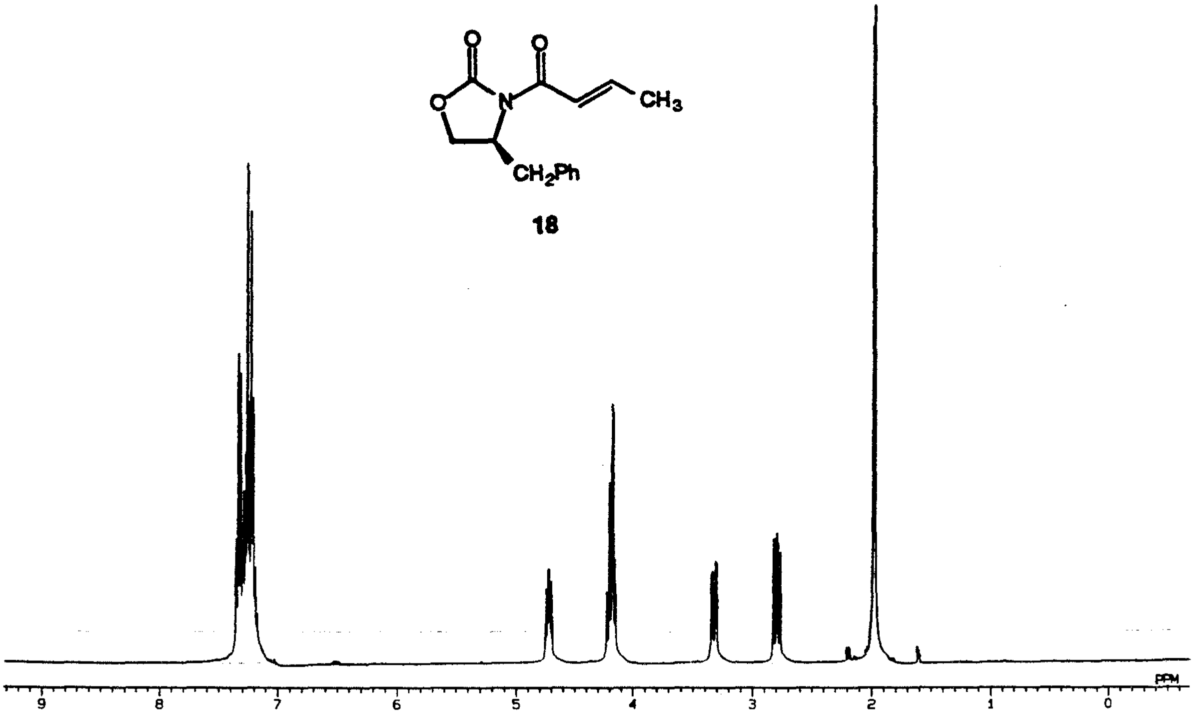
8
7
6
5
4
3
2
1
0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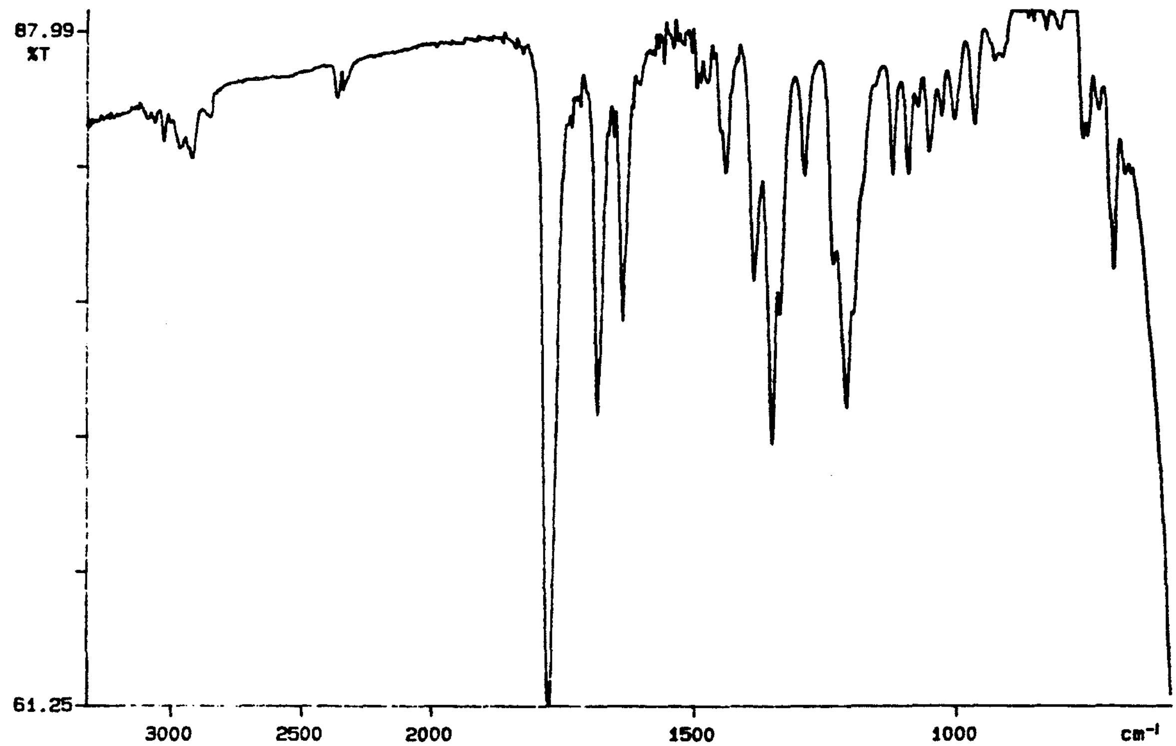
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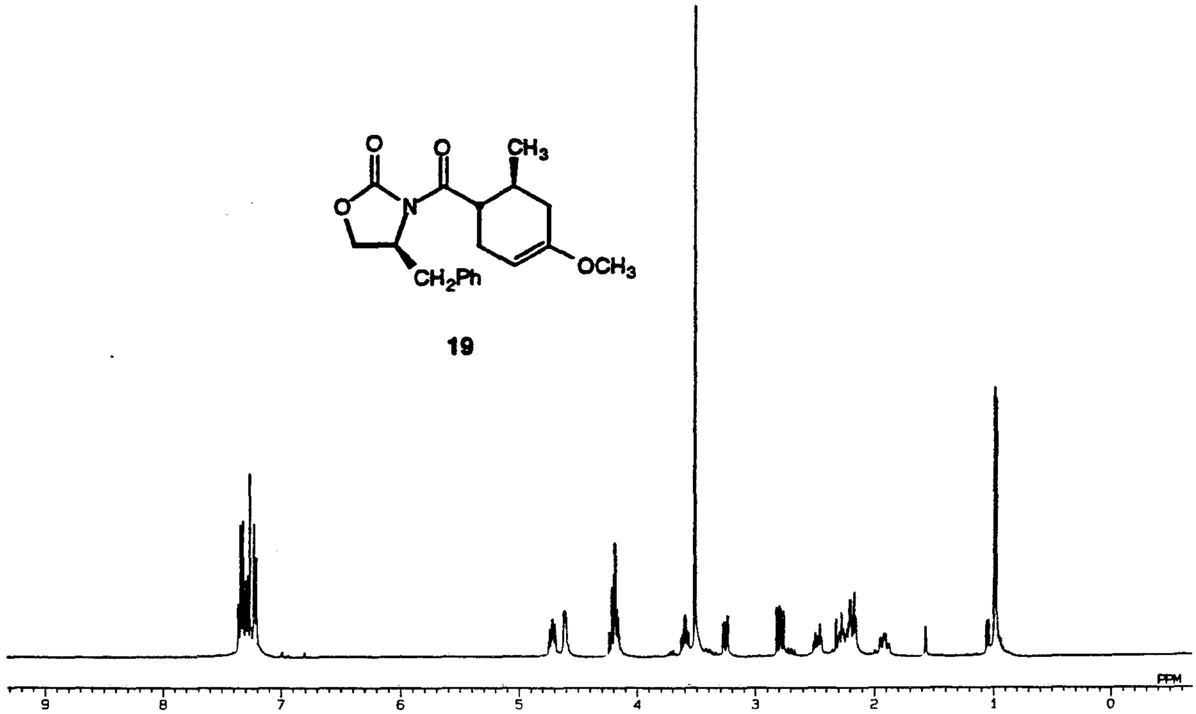
3000
2500
2000
1500
1000
cm-1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8
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5
4
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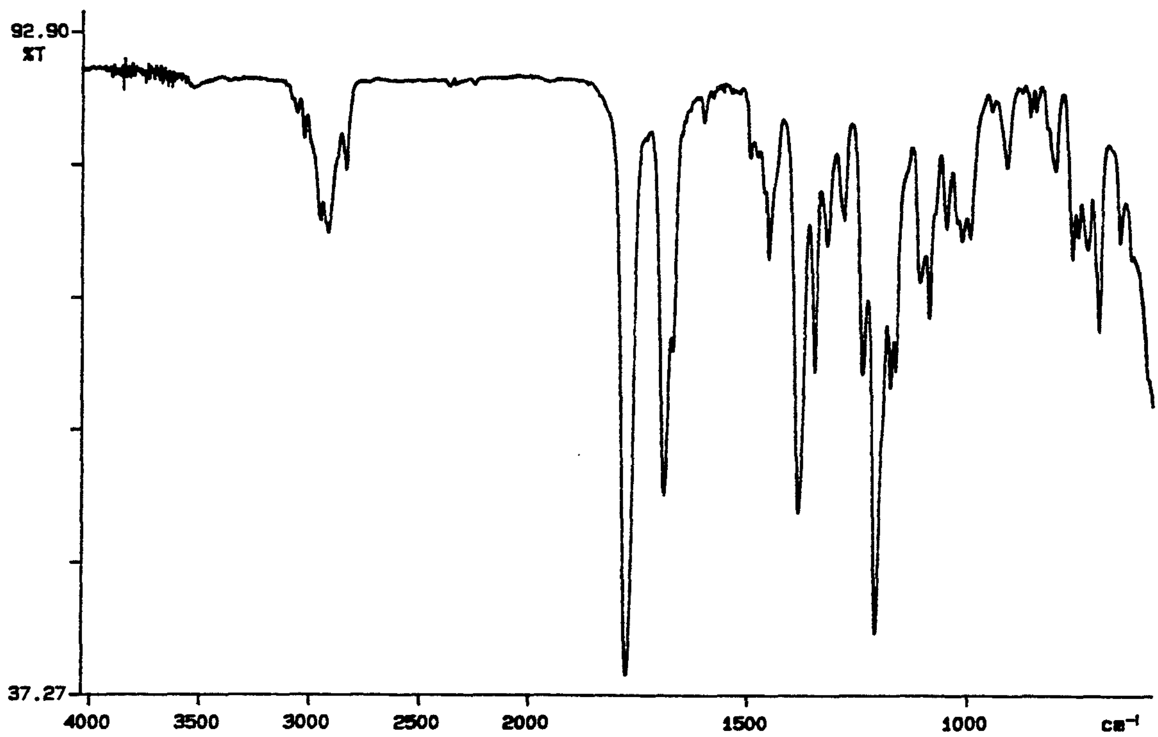
2
1
0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3500
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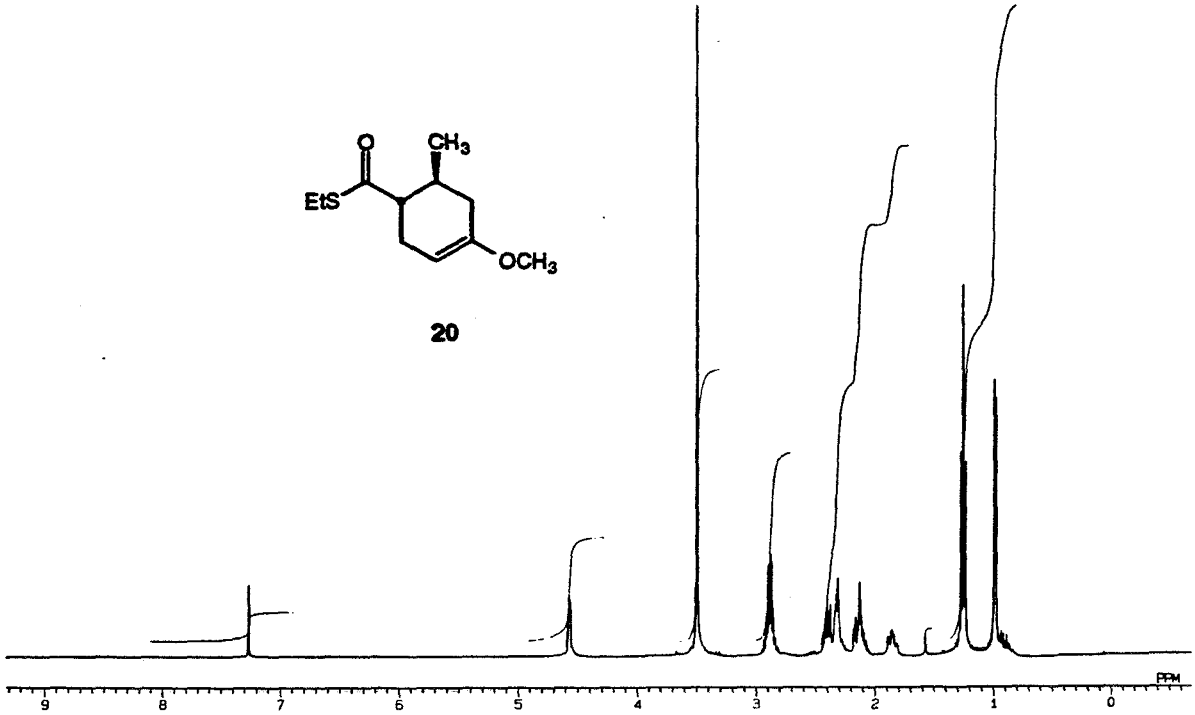
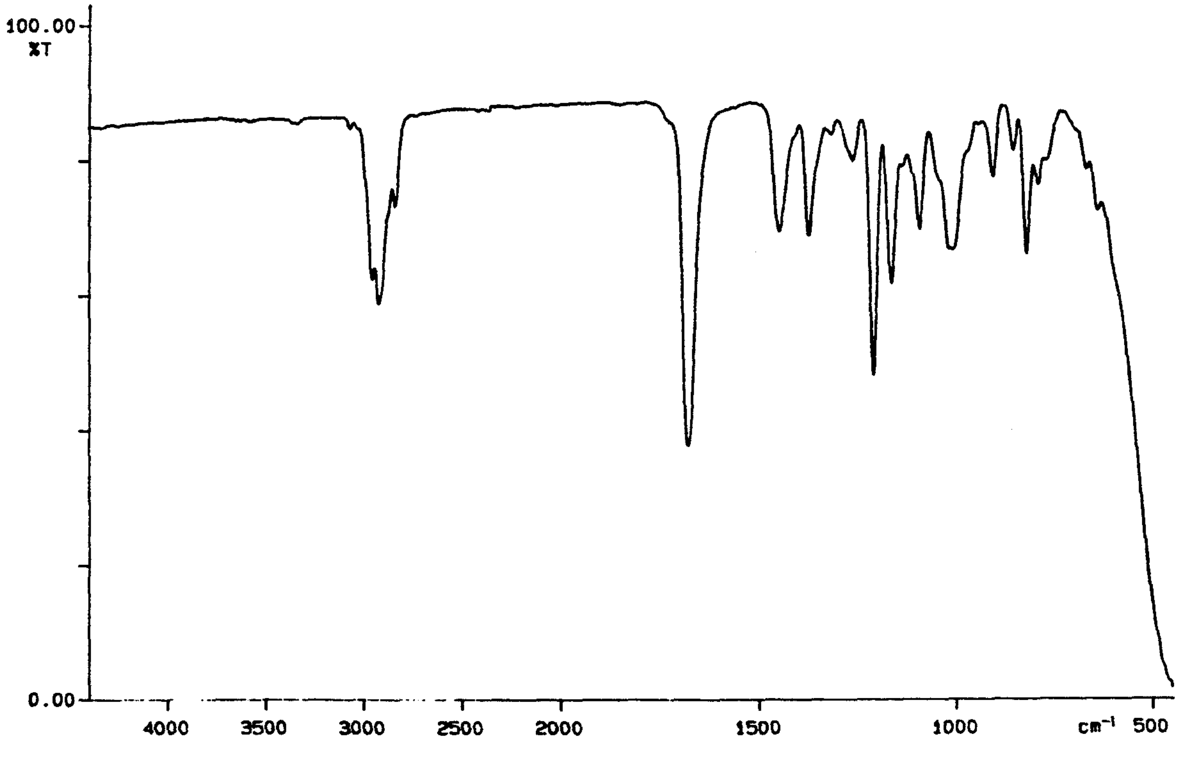
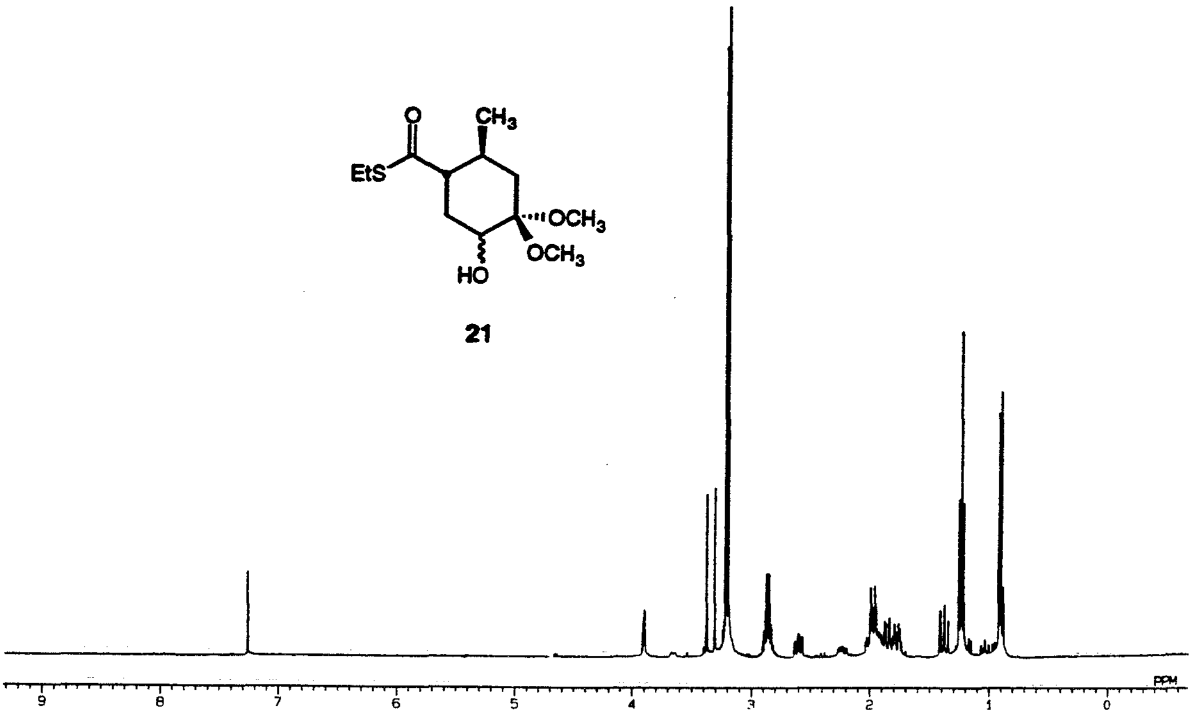
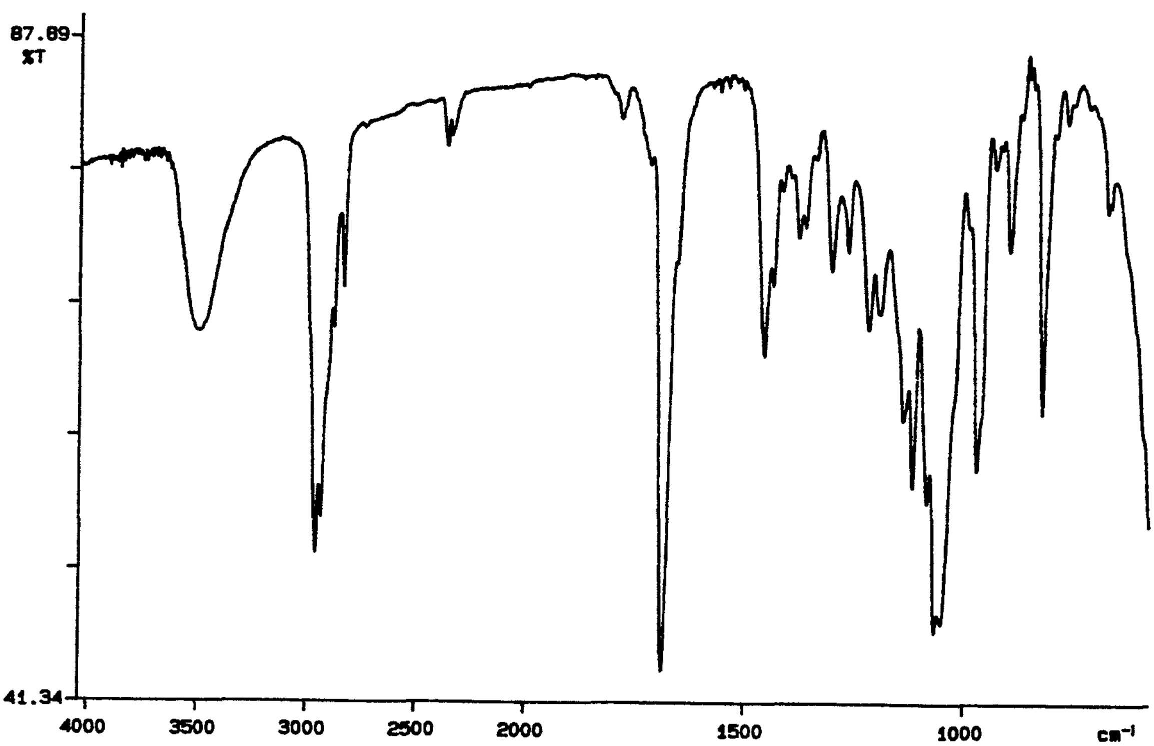
1500
1000
cm-1


O
CH3
EtS
OCH3
20
9
8
7
6
5
4
3
2
1
0
PPM

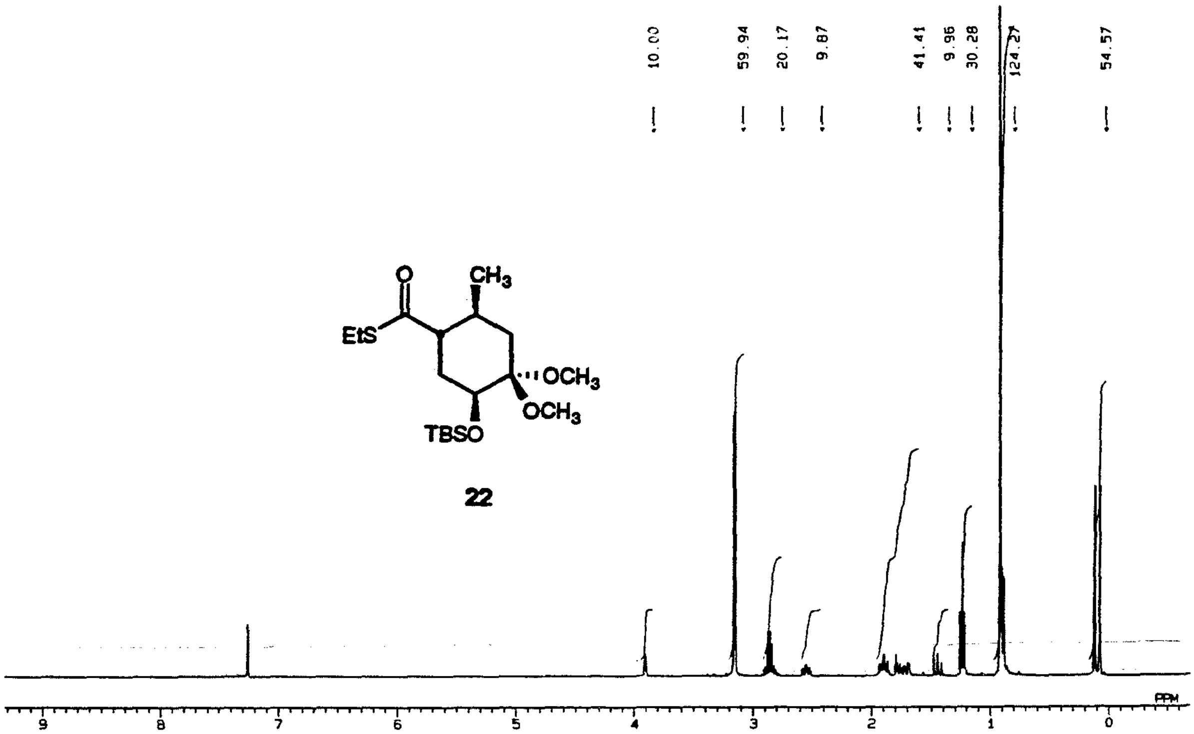

100.00
%T
0.00
4000
3500
3000
2500
2000
1500
1000
cm-1
500



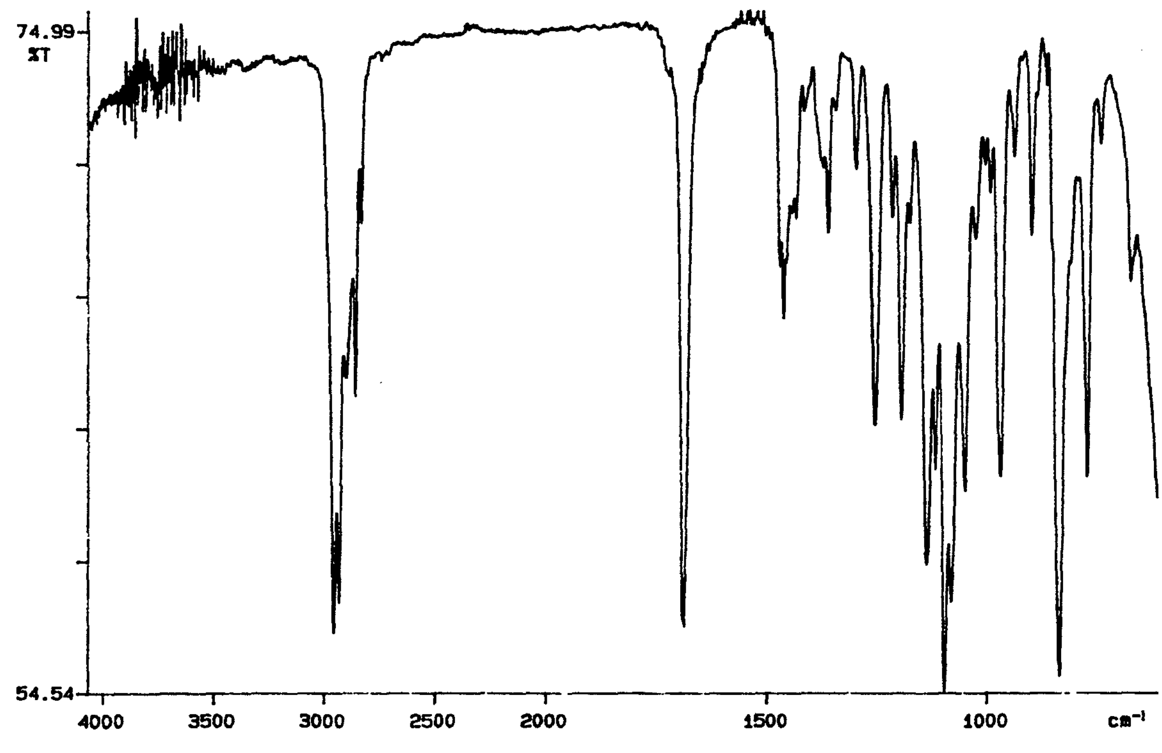
EtS
O
CH3
OCH3
OCH3
HO
21
PPM
9
8
7
6
5
4
3
2
1
0

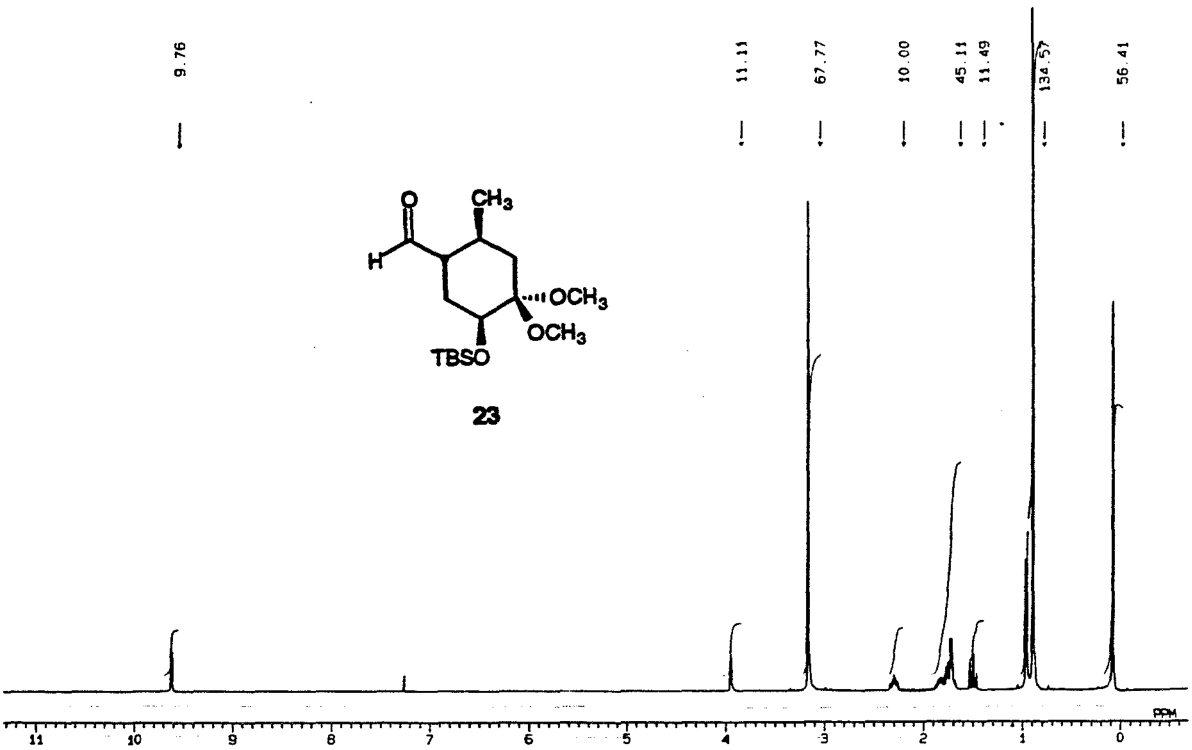


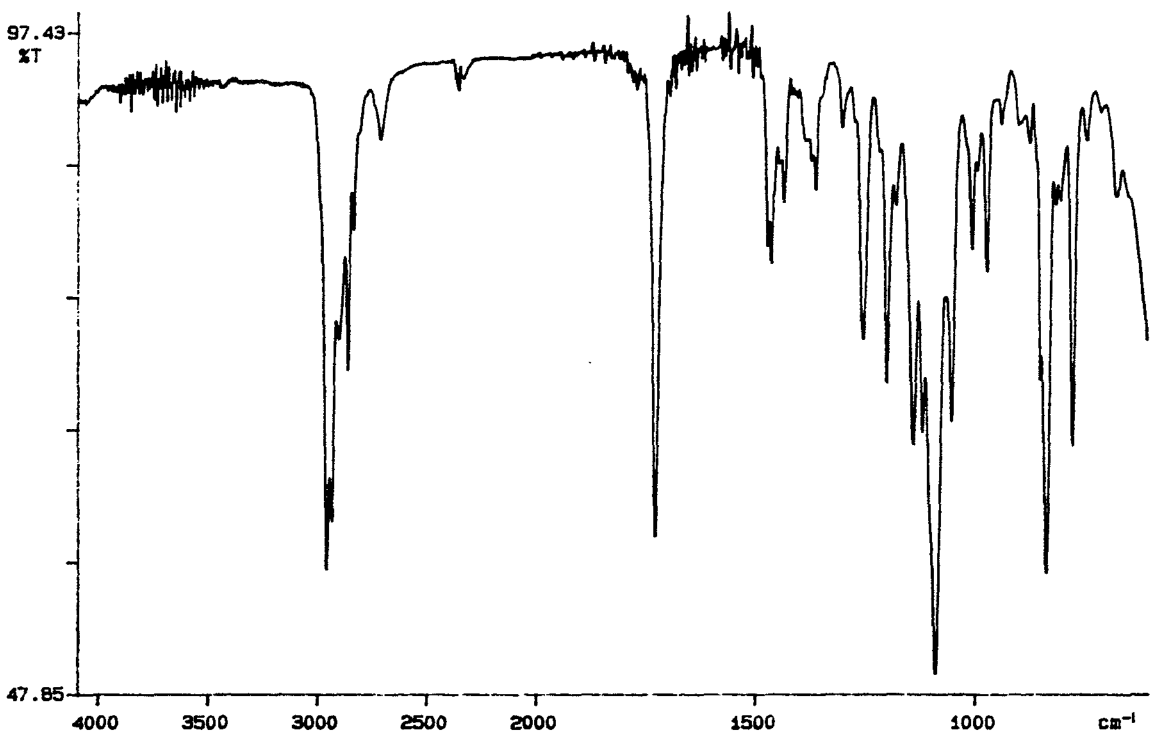
87.89
%T
41.34
4000
3500
3000
2500
2000
1500
1000
cm-1

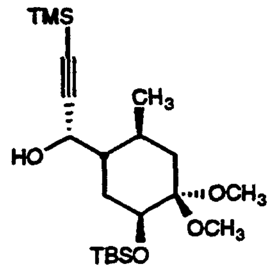

10.00
59.94
20.17
9.87
41.41
9.96
30.28
124.27
54.57
O
CH3
EtS
OCH3
OCH3
TBSO
9
8
7
6
5
4
3
2
1
0
PPM

22

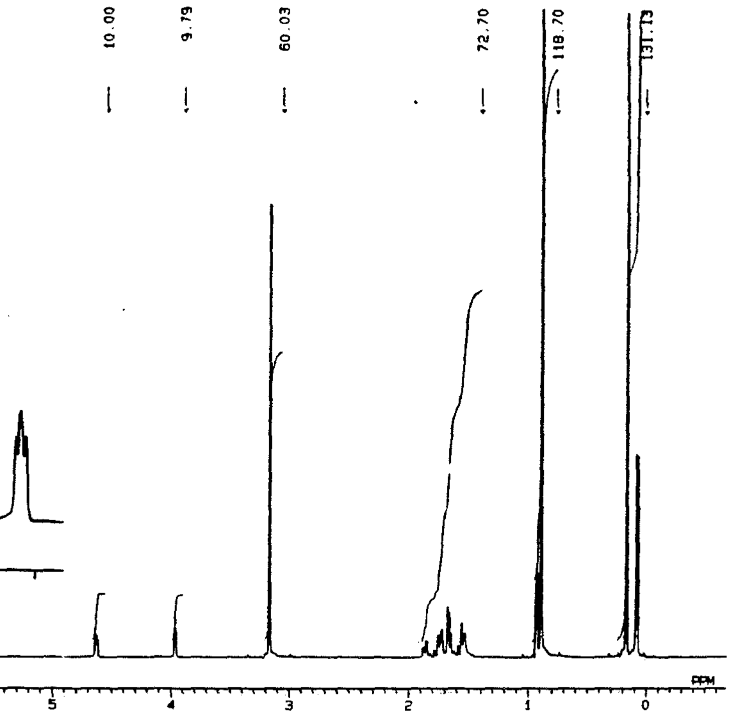

74.99
%T
54.54
4000
3500
3000
2500
2000
1500
1000
cm-1

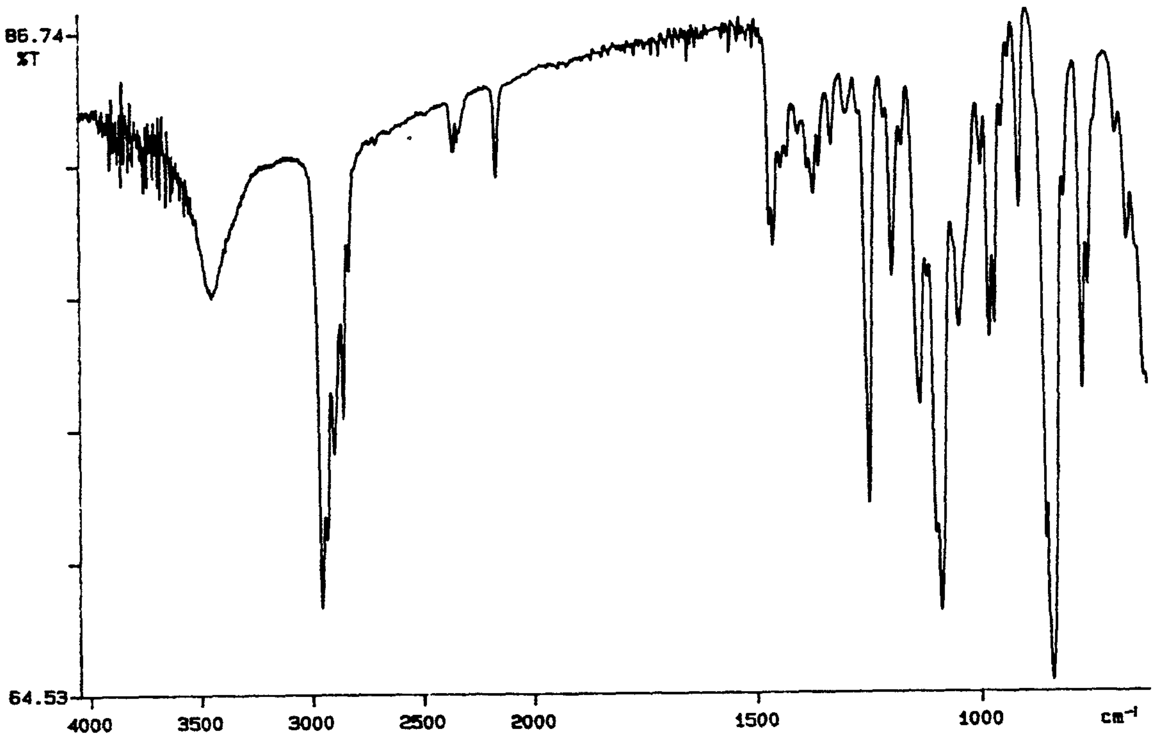

9.76
11.11
67.77
10.00
45.11
11.49
134.57
56.41
PPM
11
10
9
8
7
6
5
4
3
2
1
0
O
H
CH3
OCH3
OCH3
TBSO
23

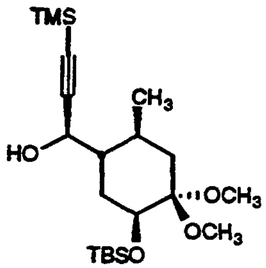

97.43
%T
47.85
4000
3500
3000
2500
2000
1500
1000
cm-1


TMS
CH3
HO
OCH3
OCH3
TBSO

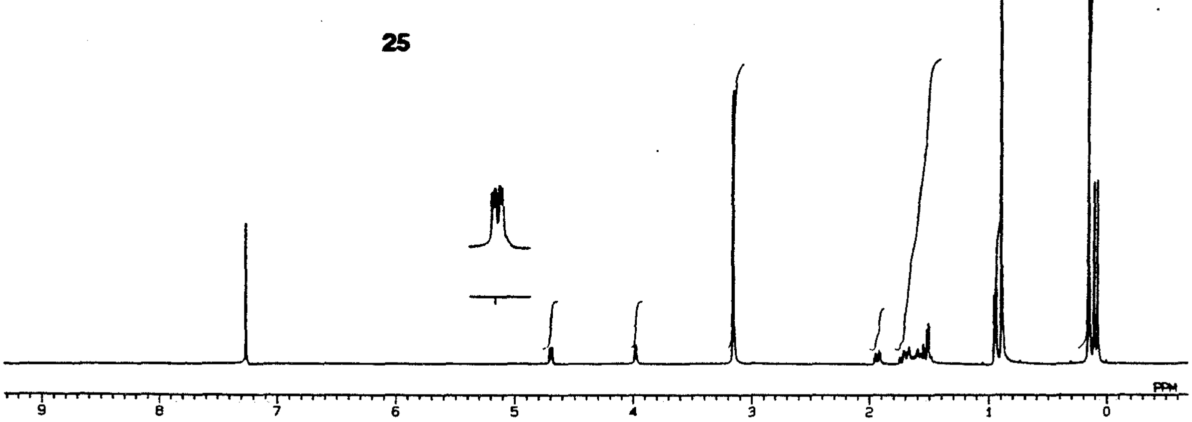
24

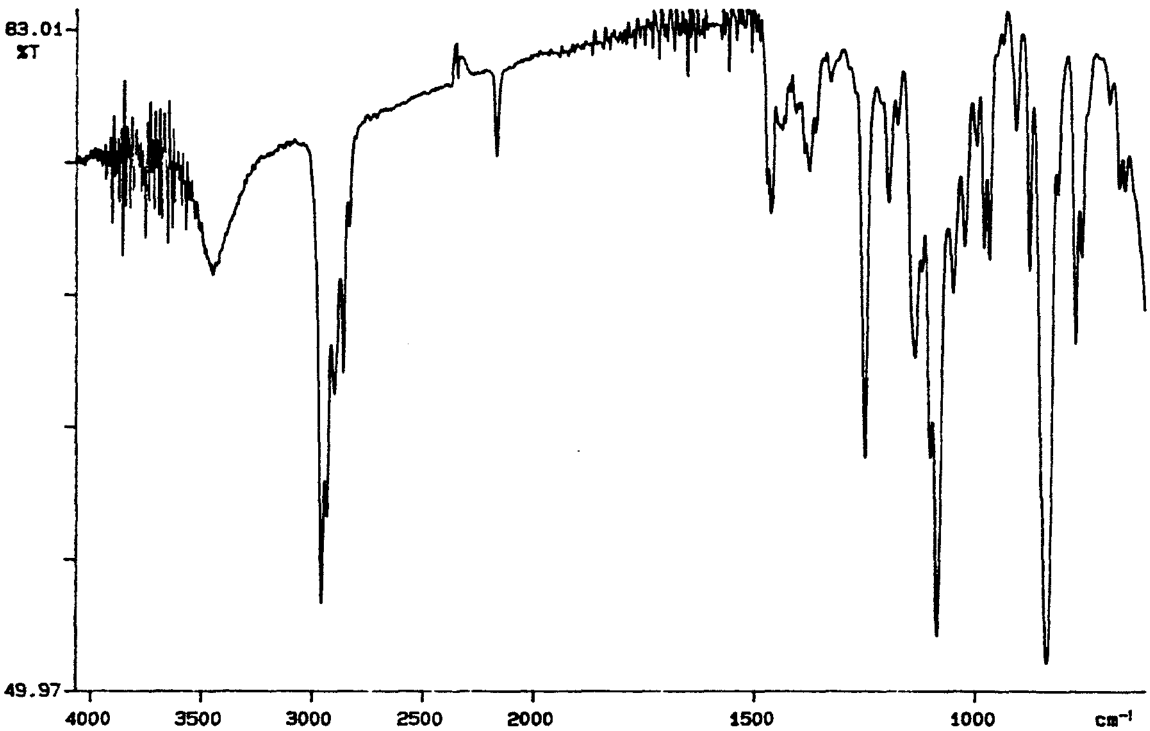

10.00
9.79
60.03
72.70
118.70
131.13
PPM
9
8
7
6
5
4
3
2
1
0


86.74
%T
64.53
4000
3500
3000
2500
2000
1500
1000
cm-1


TMS
CH3
HO
OCH3
OCH3
TBSO

25


10.00
9.98
60.10
8.42
60.96
119.37
133.47
PPM
9
8
7
6
5
4
3
2
1
0


83.01
%T
49.97
4000
3500
3000
2500
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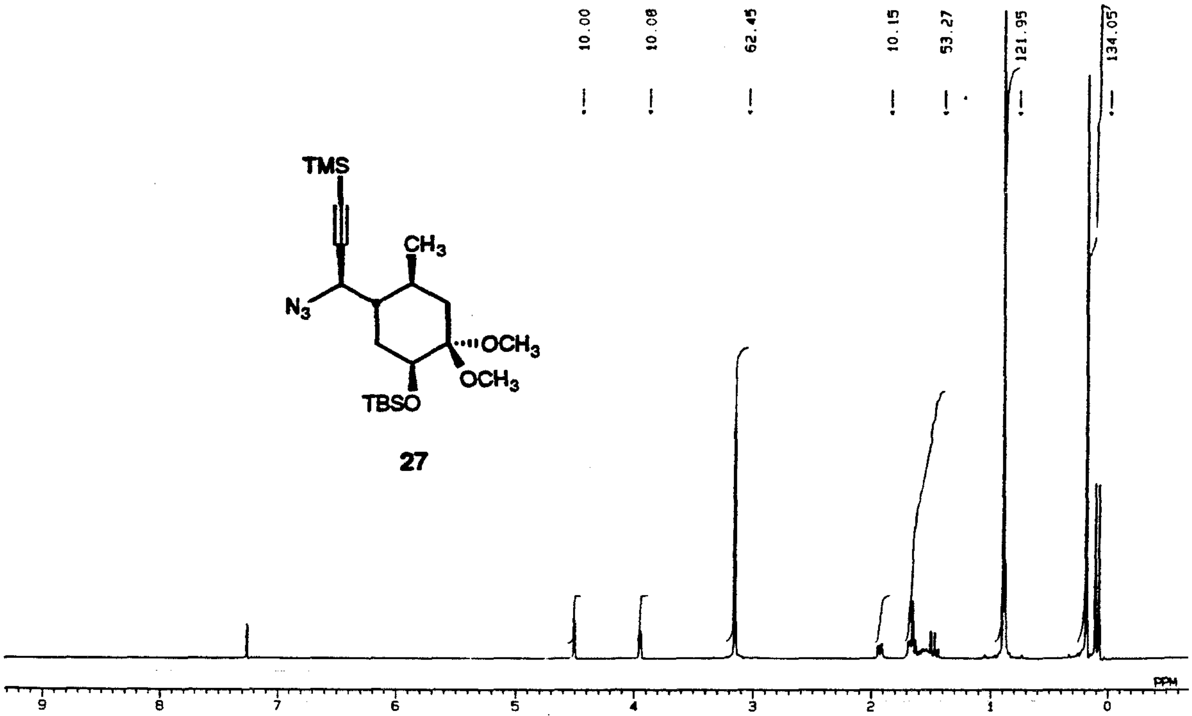
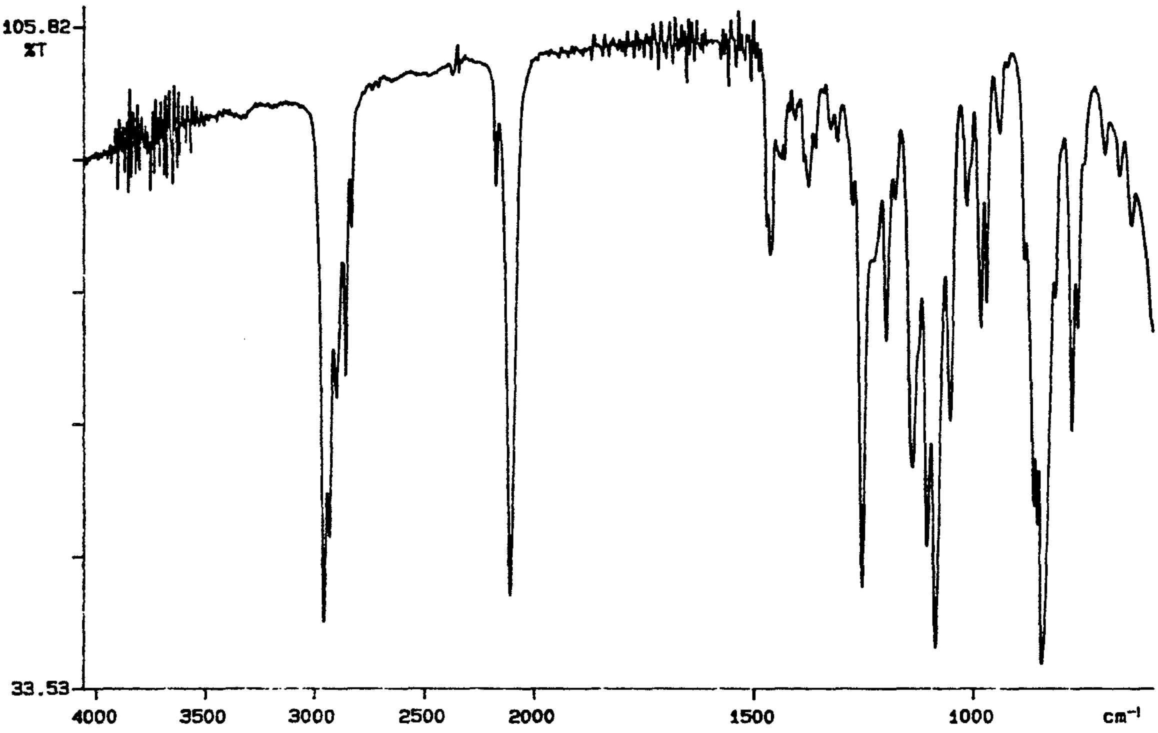
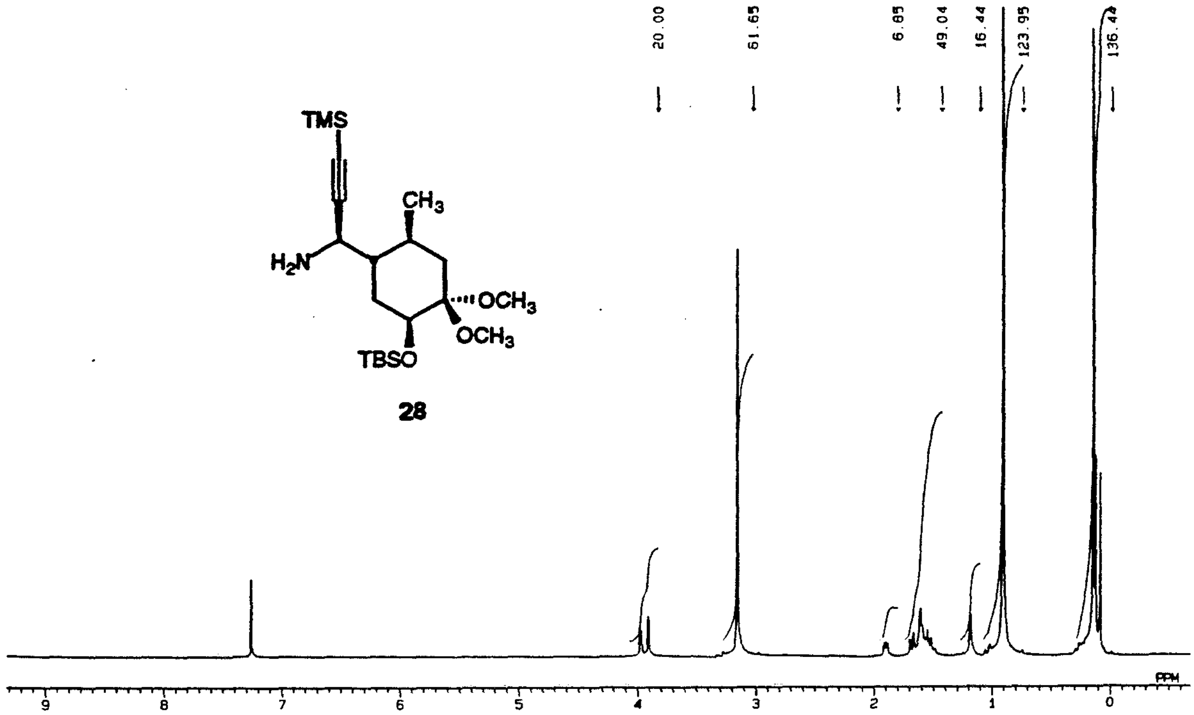
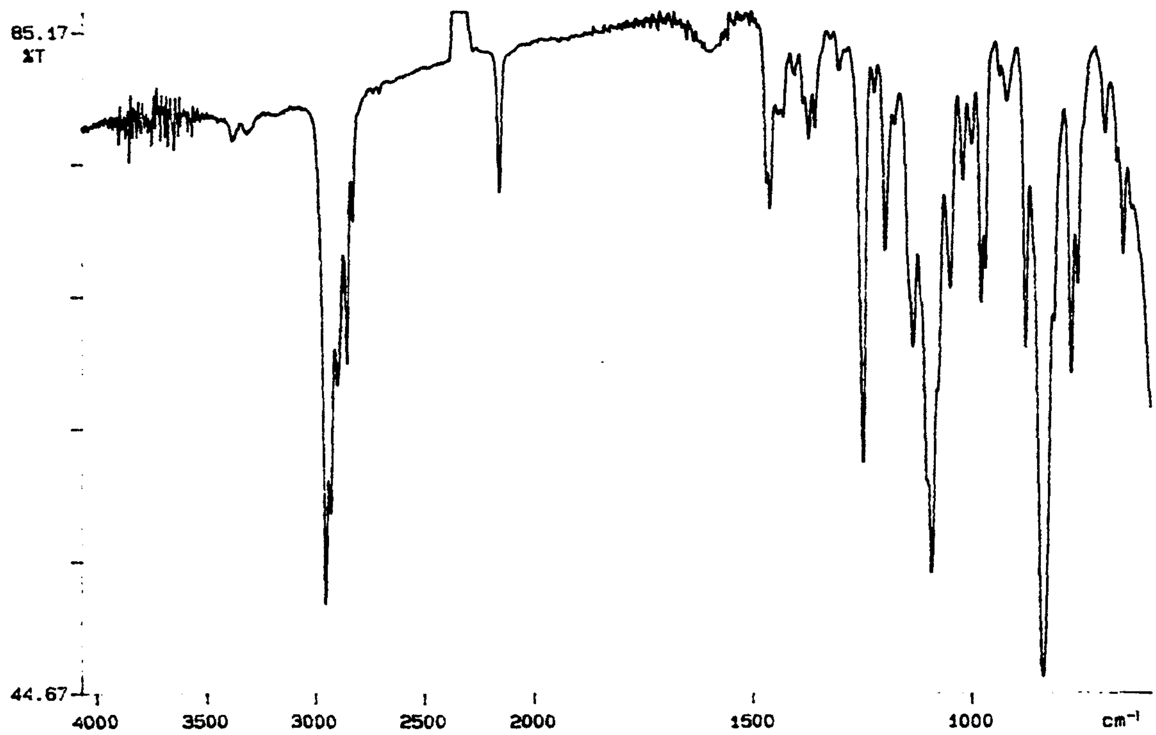
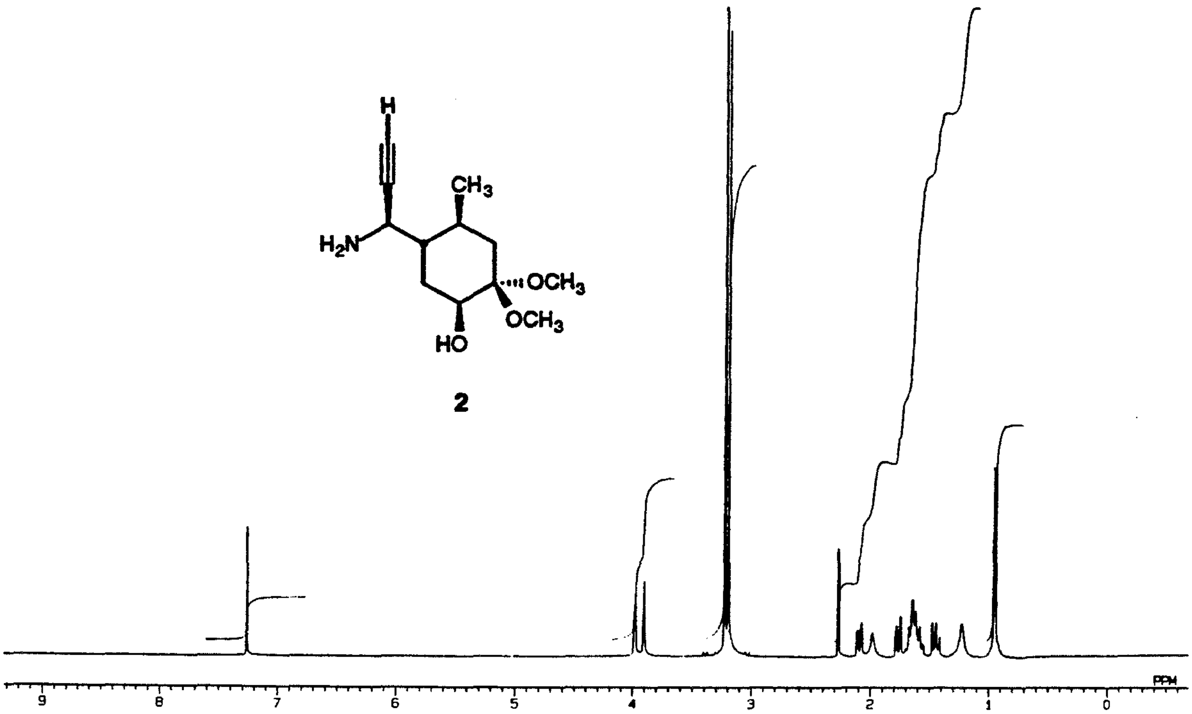
1500
1000
cm-1

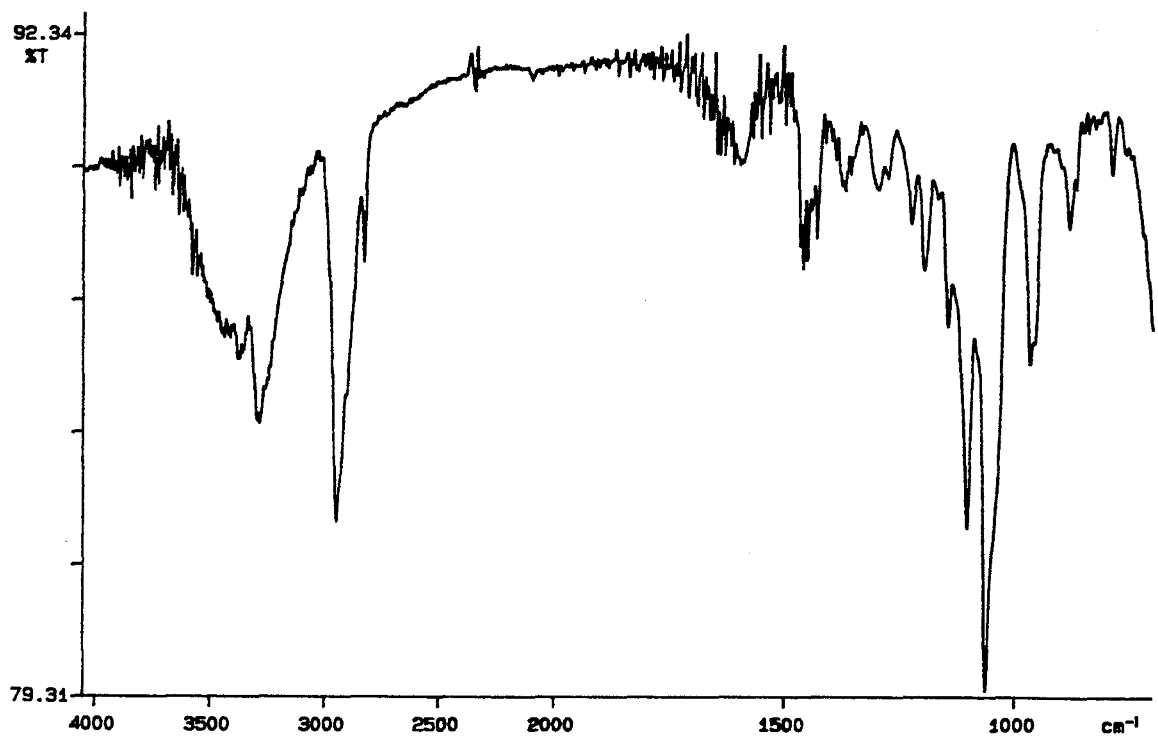

TMS
CH3
N3
OCH3
OCH3
TBSO
27
10.00
10.08
62.45
10.15
53.27
121.95
134.05
PPM
9
8
7
6
5
4
3
2
1
0

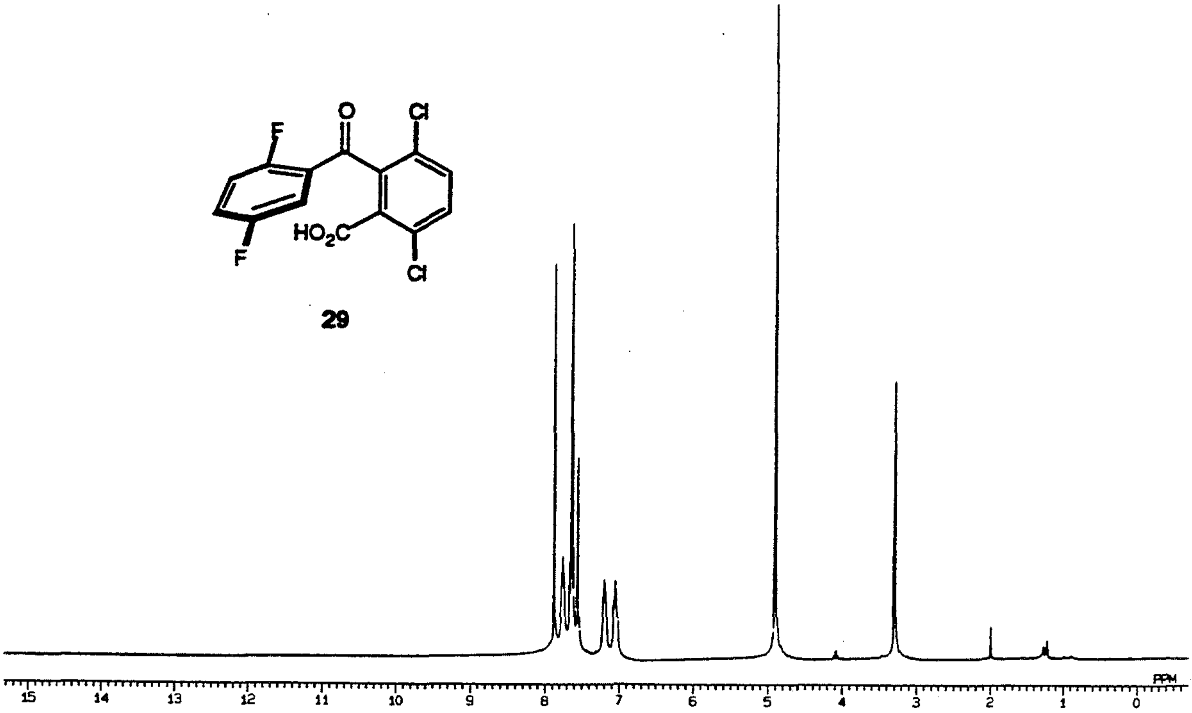

105.82
%T
33.53
4000
3500
3000
2500
2000
1500
1000
cm⁻¹

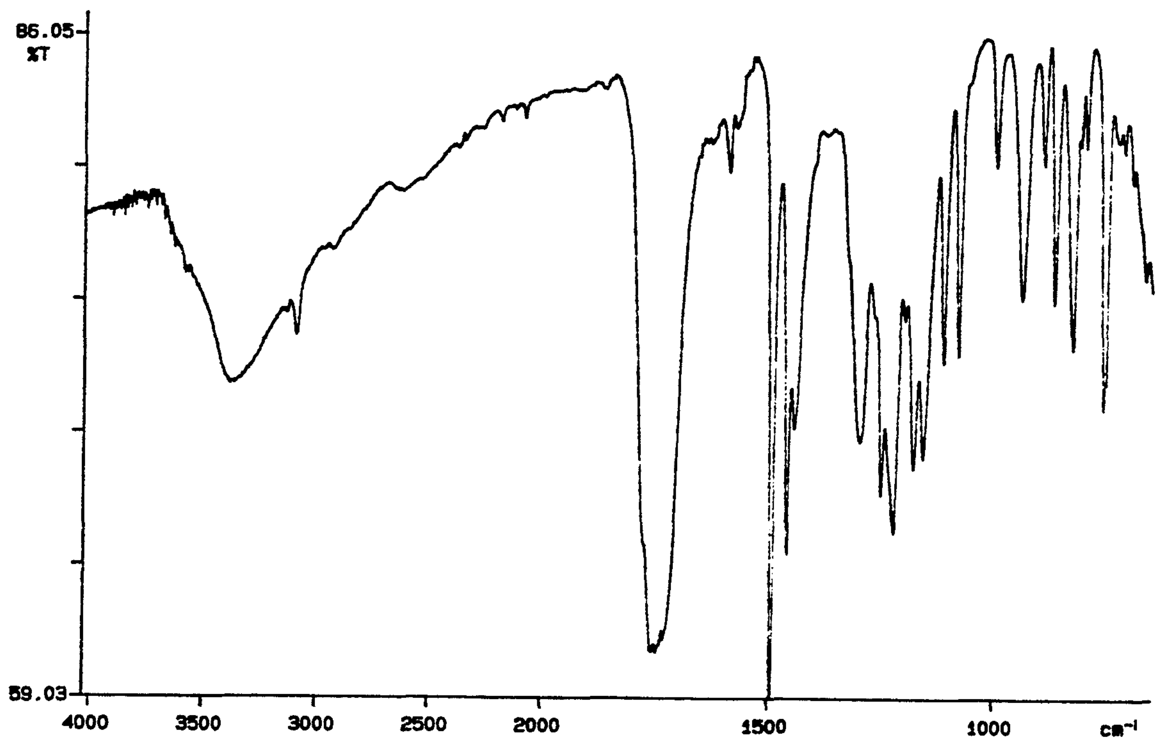

TMS
CH3
H2N
OCH3
OCH3
TBSO
28
20.00
61.65
6.85
49.04
16.44
123.95
136.44
PPM
9
8
7
6
5
4
3
2
1
0

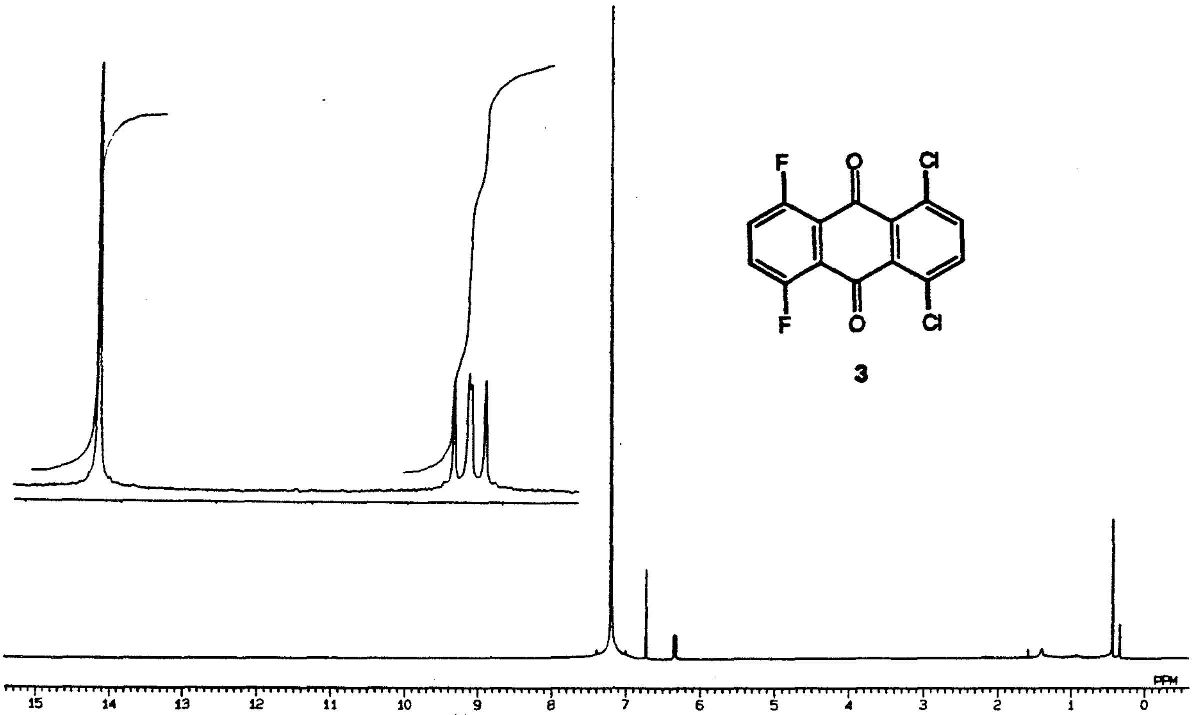

85.17
%T
44.67
4000
3500
3000
2500
2000
1500
1000
cm-1


H
CH3
H2N
OCH3
OCH3
HO
2
9
8
7
6
5
4
3
2
1
0
PPM

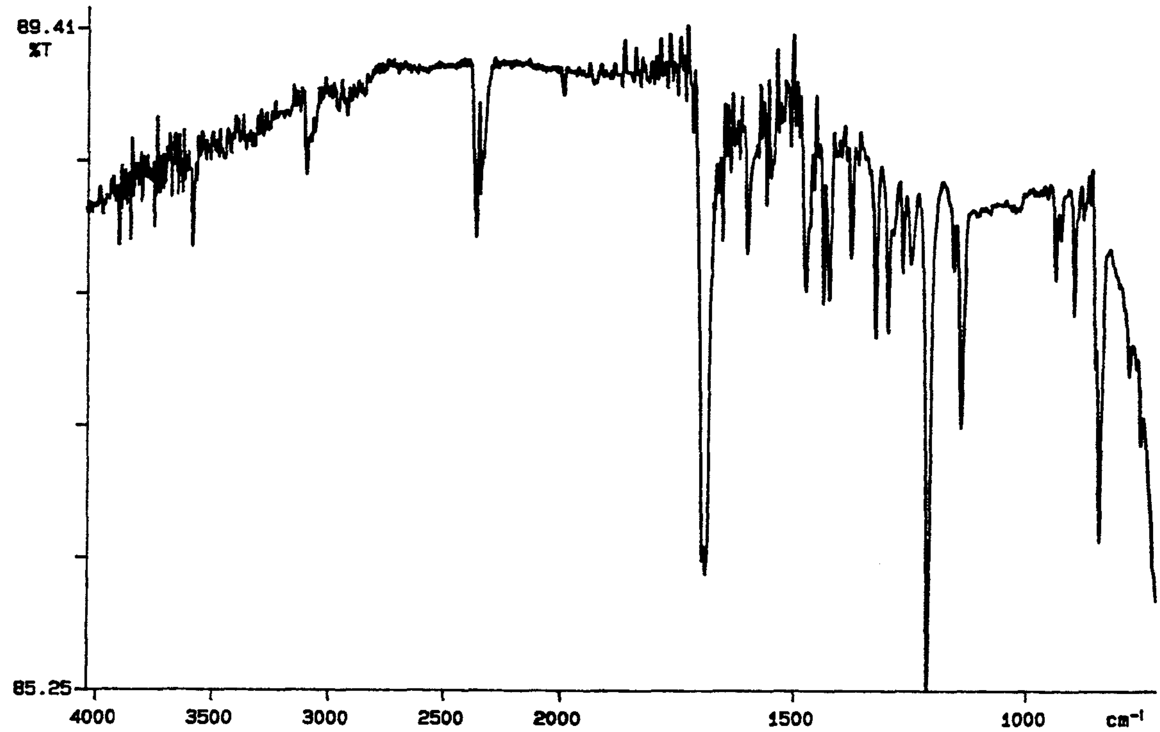

92.34
%T
79.31
4000
3500
3000
2500
2000
1500
1000
cm-1

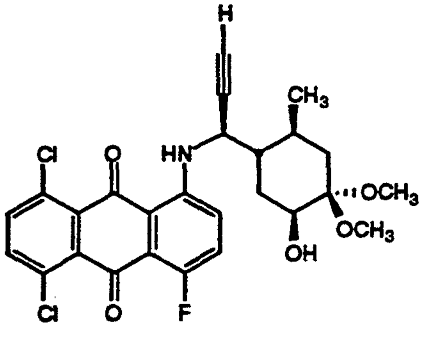

O
Cl
F
HO2C
F
Cl
29
PPM
15
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0


86.05
%T
59.03
4000
3500
3000
2500
2000
1500
1000
cm⁻¹

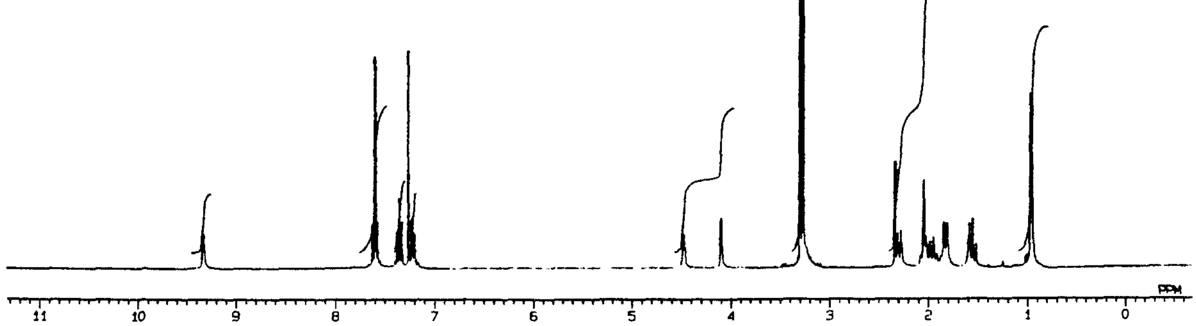

PPM
15
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
F
O
Cl
F
O
Cl

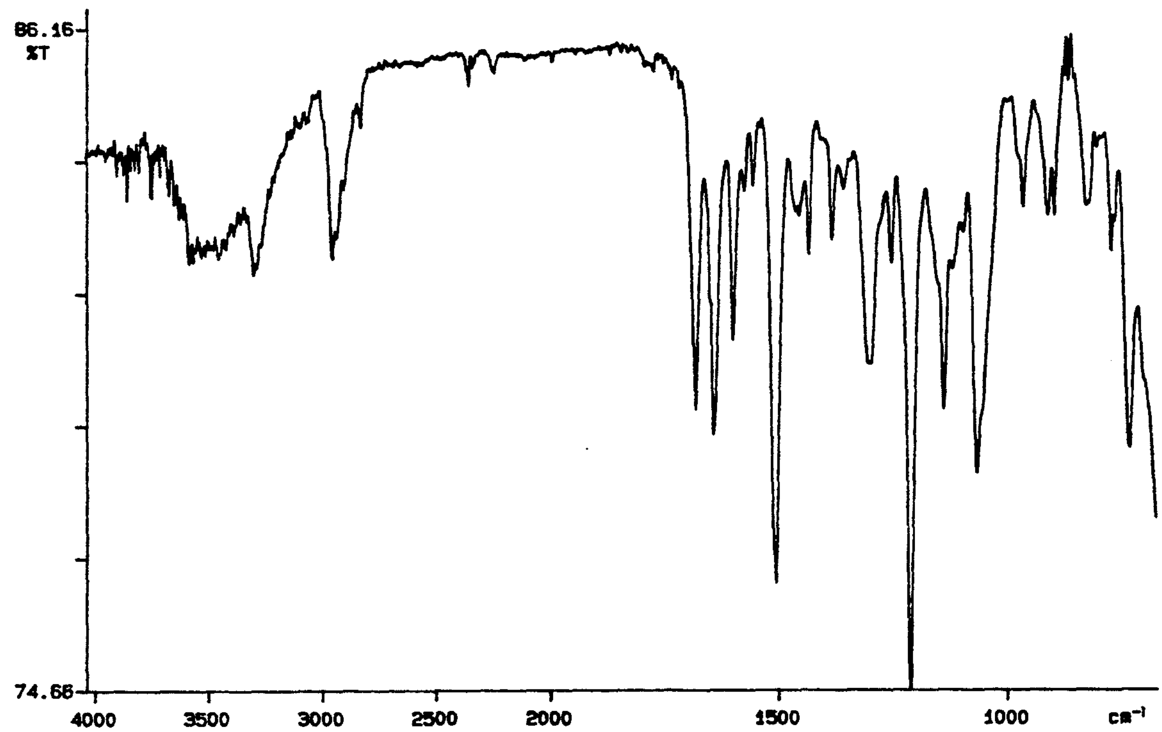
3

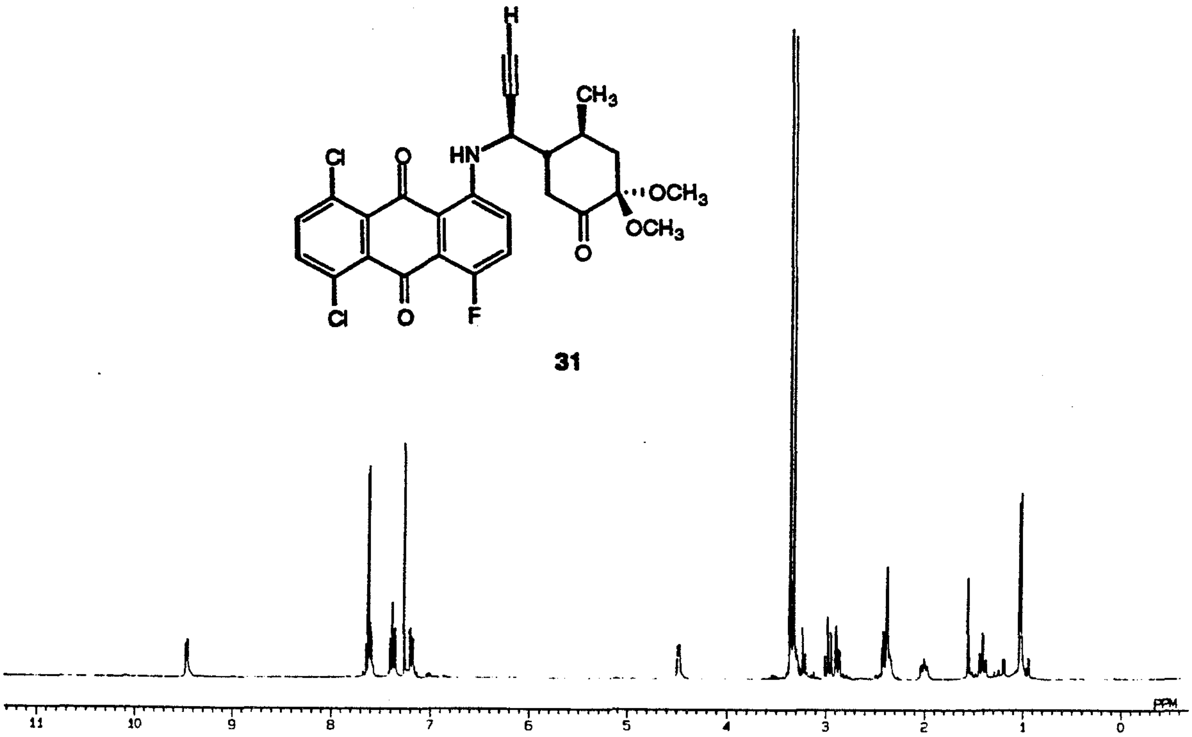

89.41
%T
85.25
4000
3500
3000
2500
2000
1500
1000
cm⁻¹

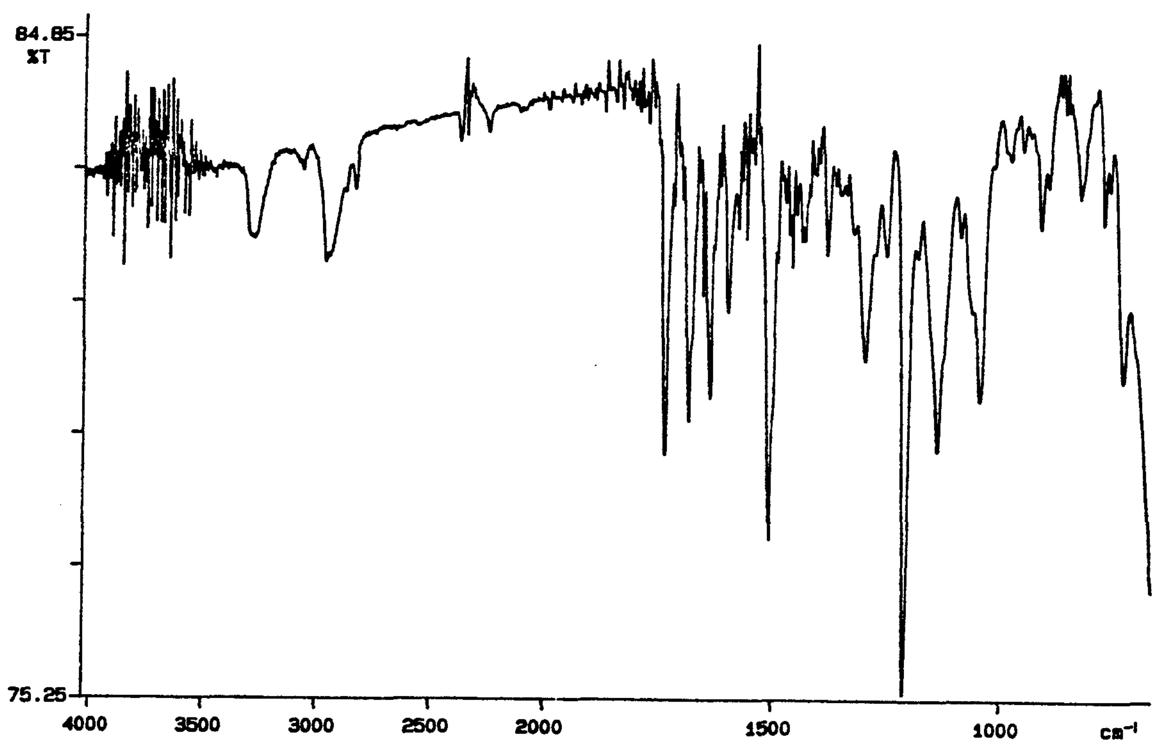

H
CH3
Cl
O
HN
OCH3
OCH3
OH
Cl
O
F

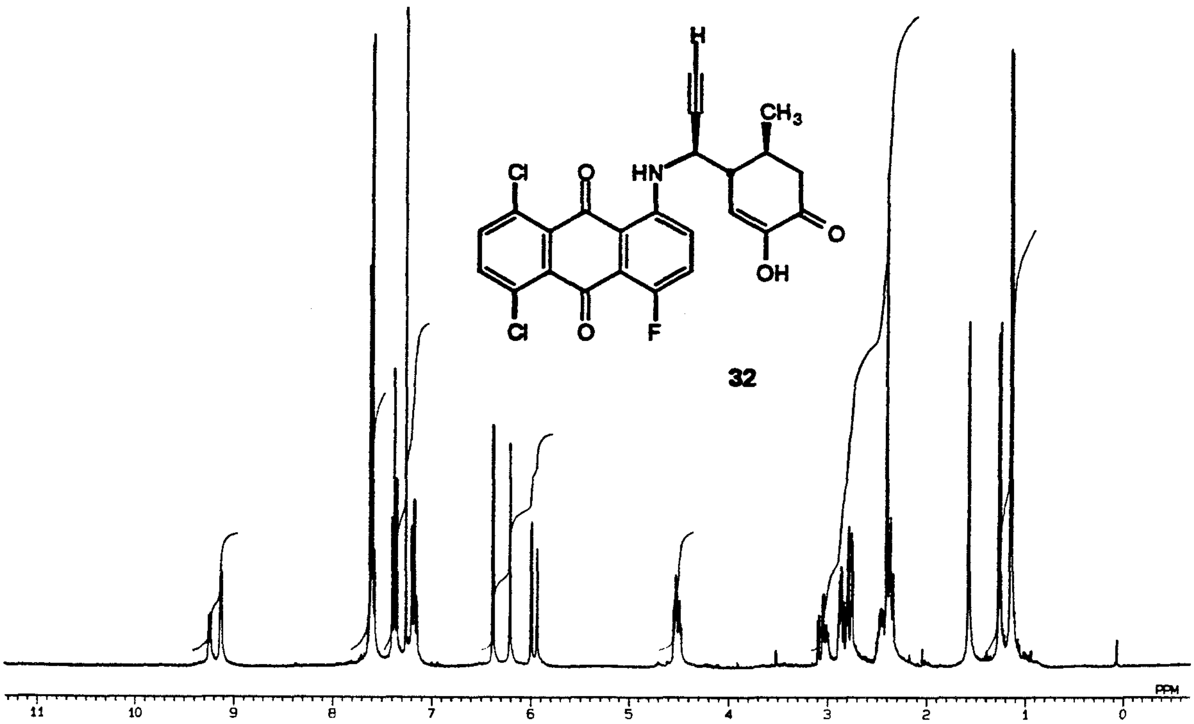
30

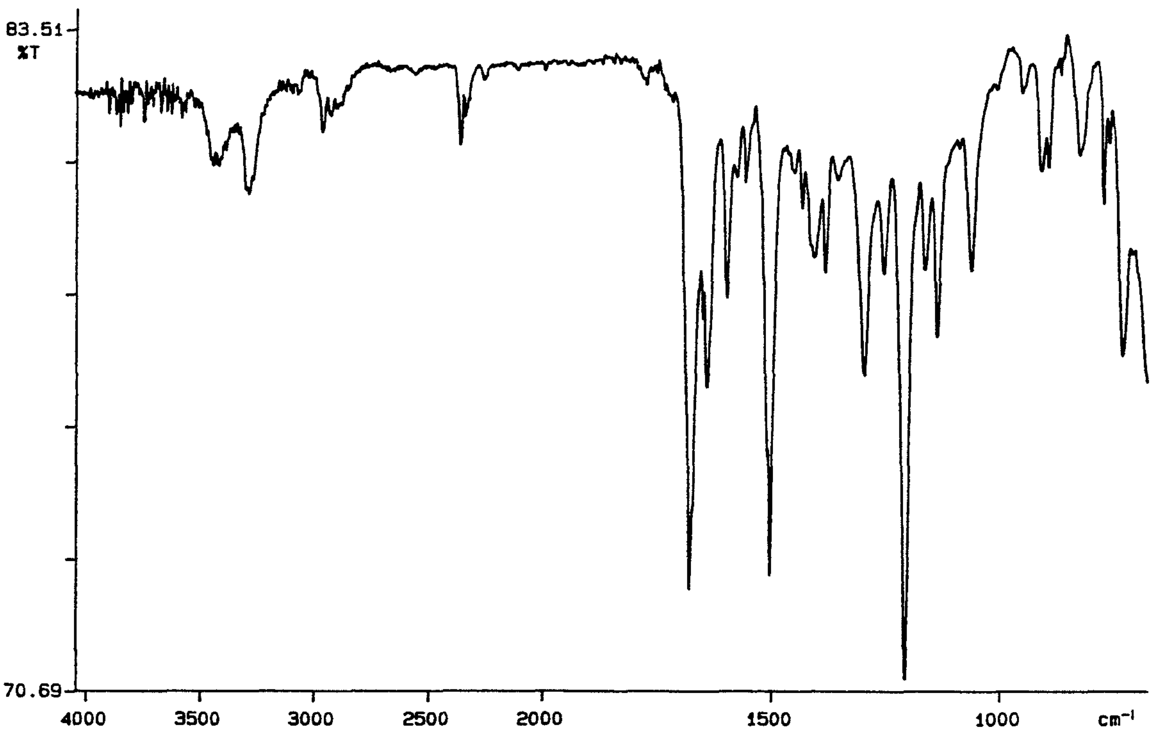

PPM
11 10 9 8 7 6 5 4 3 2 1 0

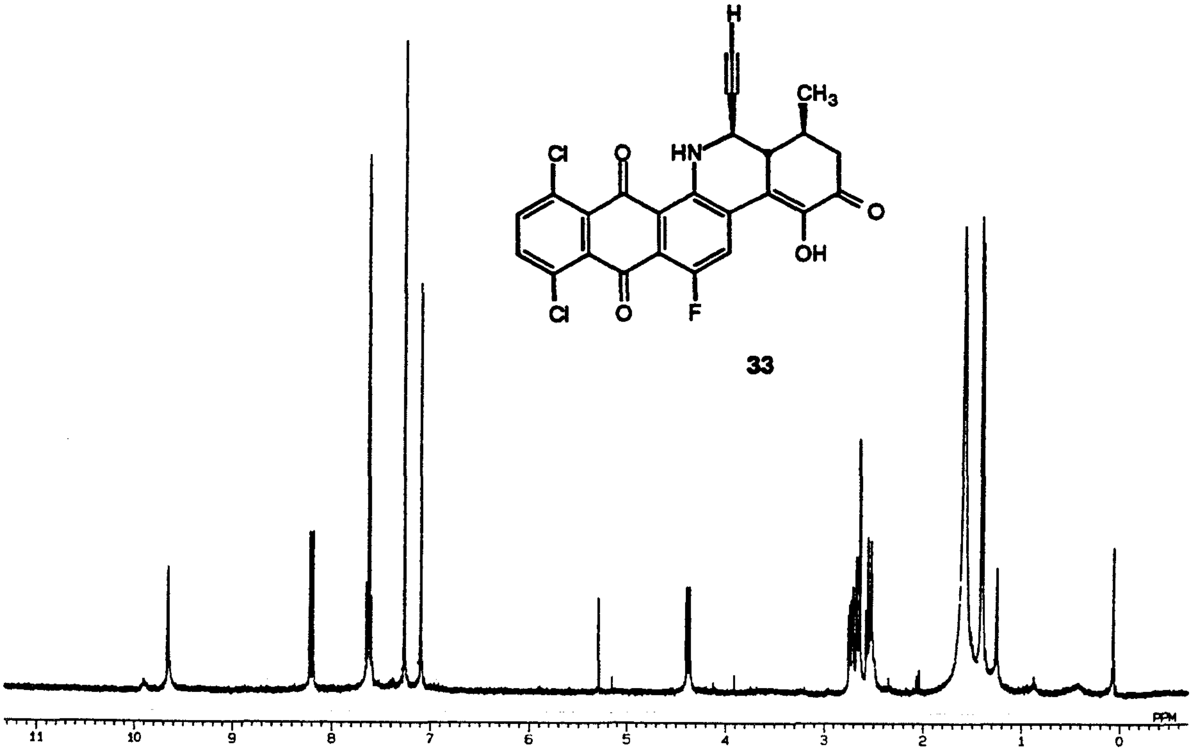

86.16
%T
74.66
4000 3500 3000 2500 2000 1500 1000 cm-1


H
CH_3
Cl
O
HN
OCH_3
OCH_3
O
Cl
O
F
31
PPM
11
10
9
8
7
6
5
4
3
2
1
0

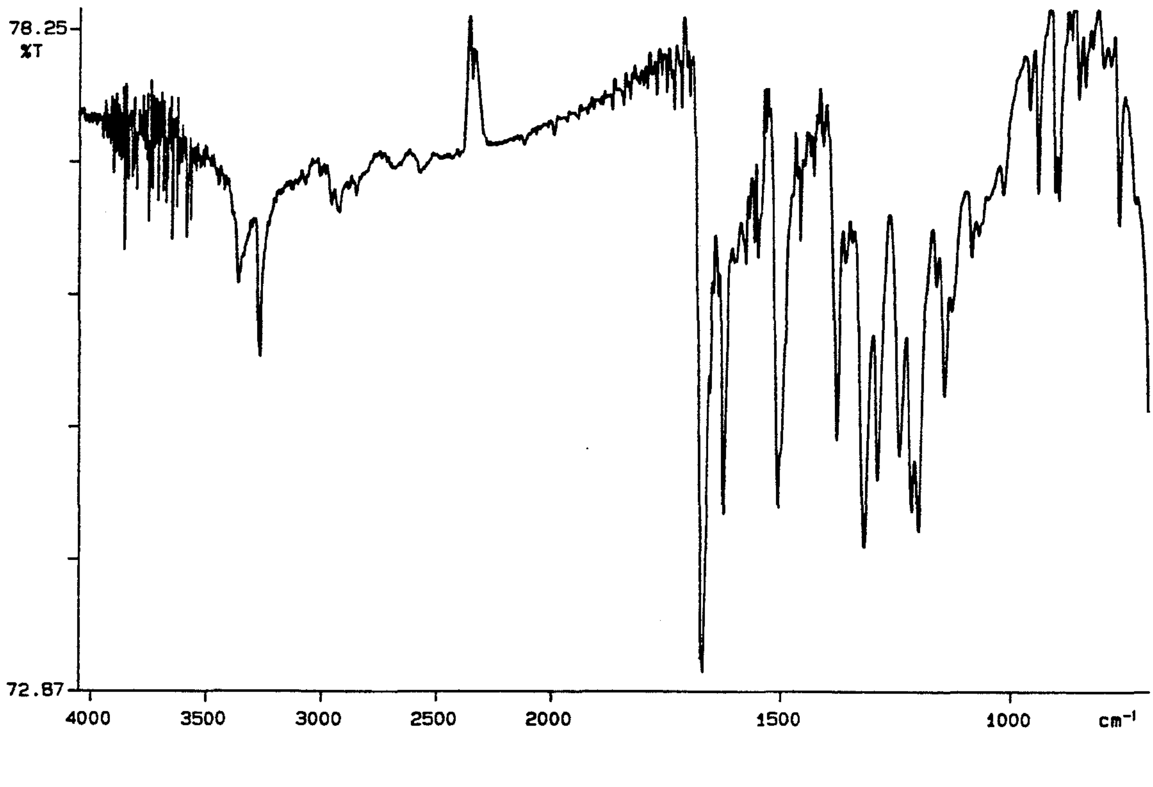

84.85
%T
75.25
4000
3500
3000
2500
2000
1500
1000
cm⁻¹


H
CH3
HN
Cl
O
OH
F
32
PPM
11 10 9 8 7 6 5 4 3 2 1 0


83.51
%T
70.69
4000 3500 3000 2500 2000 1500 1000 cm⁻¹


H
CH3
Cl
O
HN
O
OH
Cl
O
F
PPM
11
10
9
8
7
6
5
4
3
2
1
0

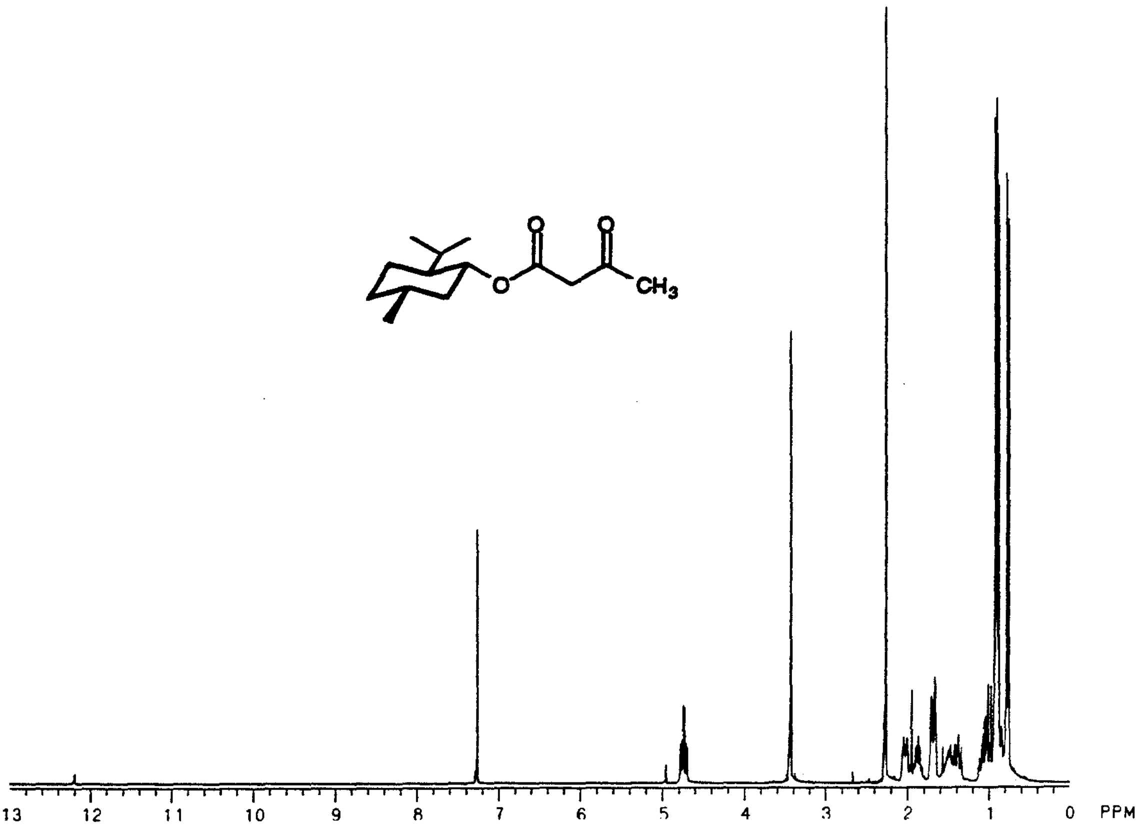
33

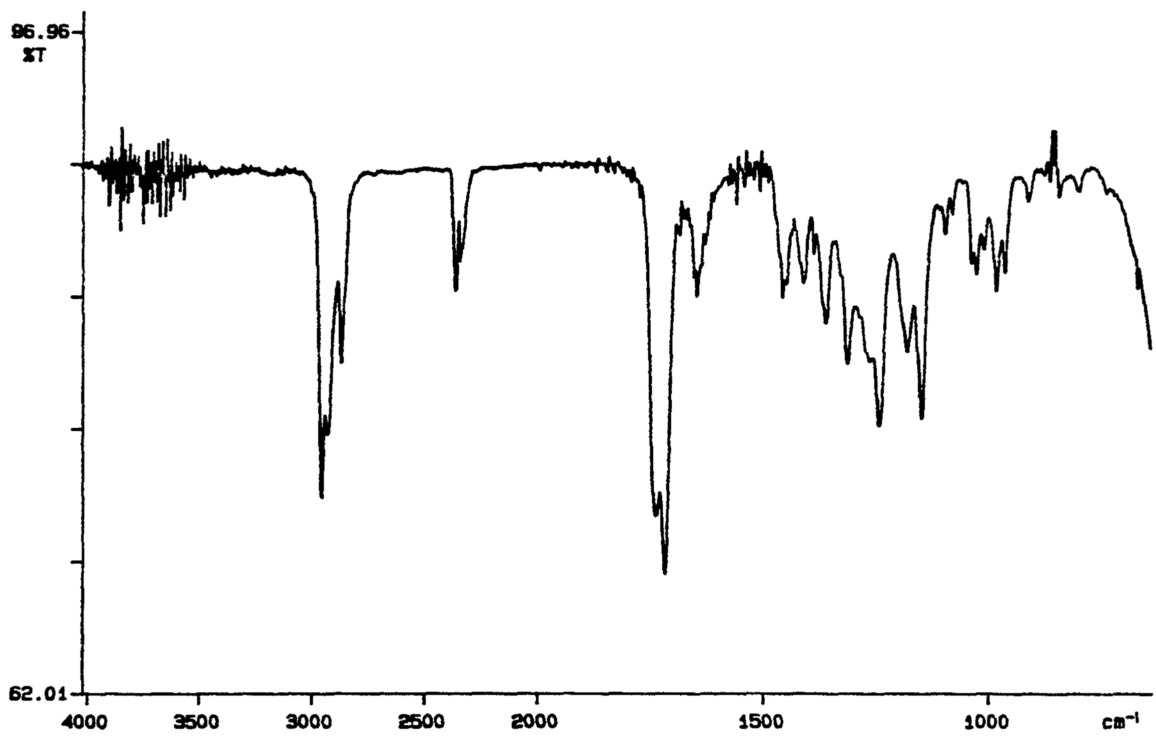

78.25
%T
72.87
4000
3500
3000
2500
2000
1500
1000
cm-1

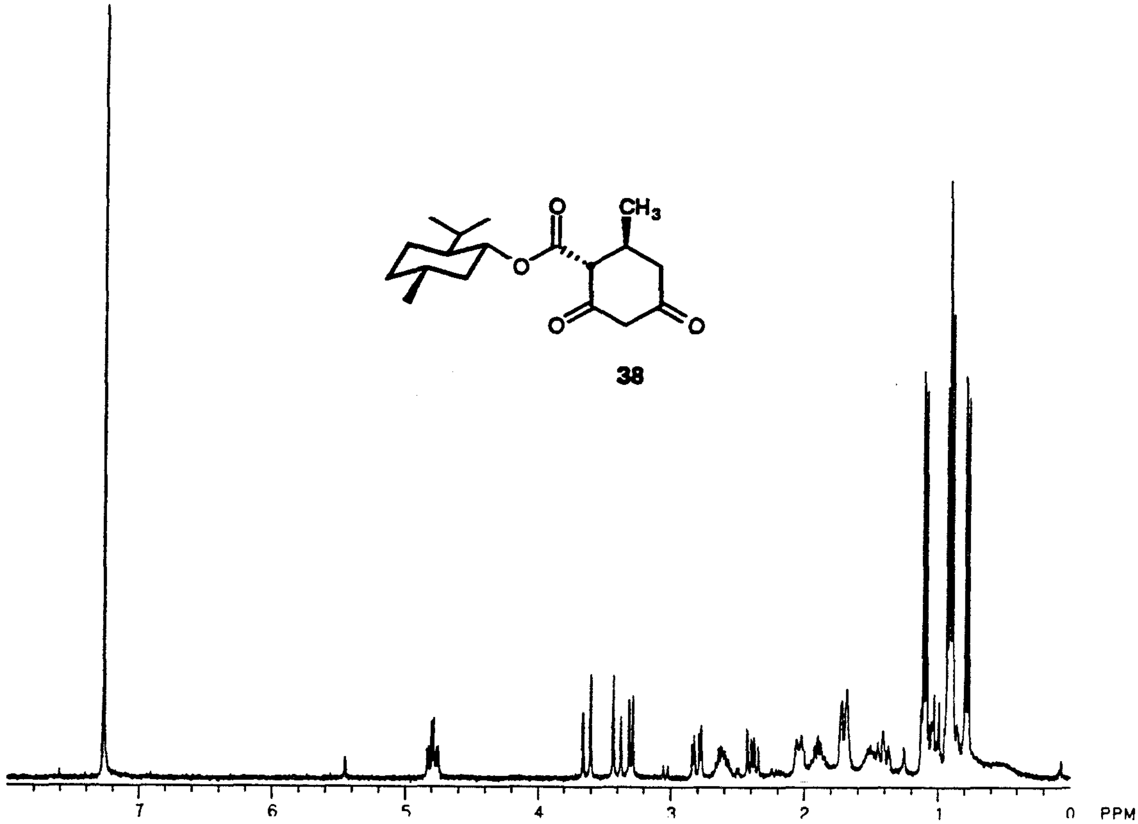
Appendix 3

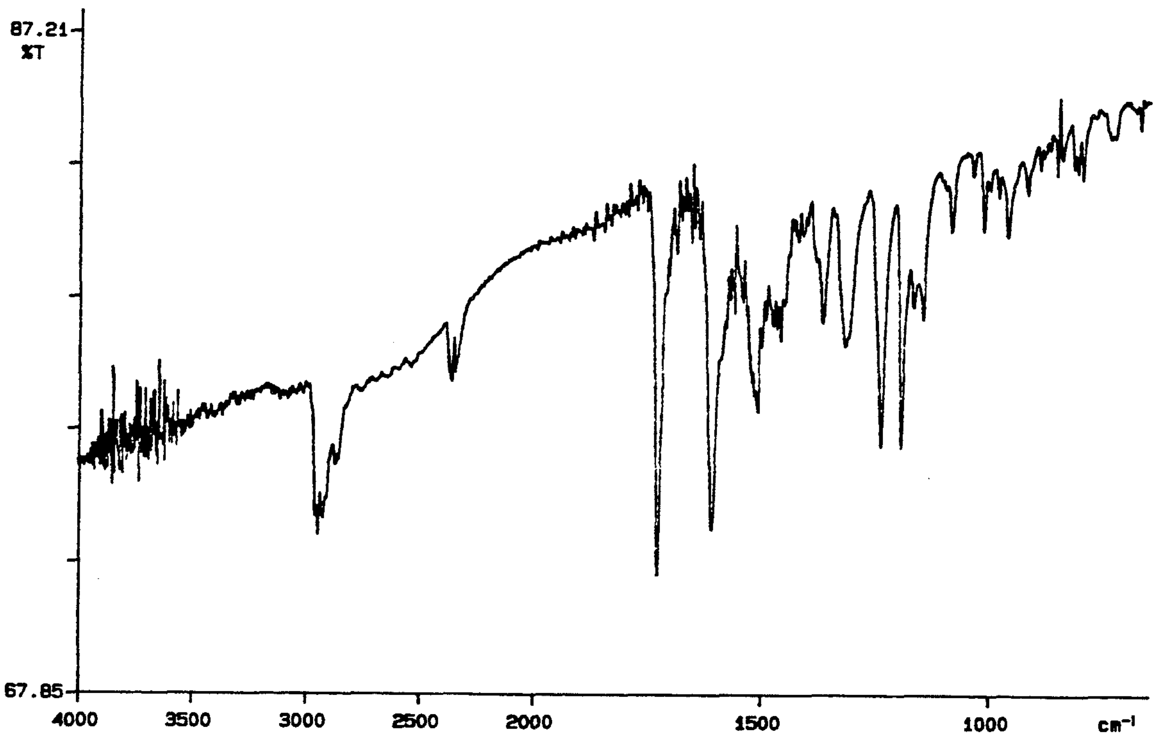
Catalog of Spectra

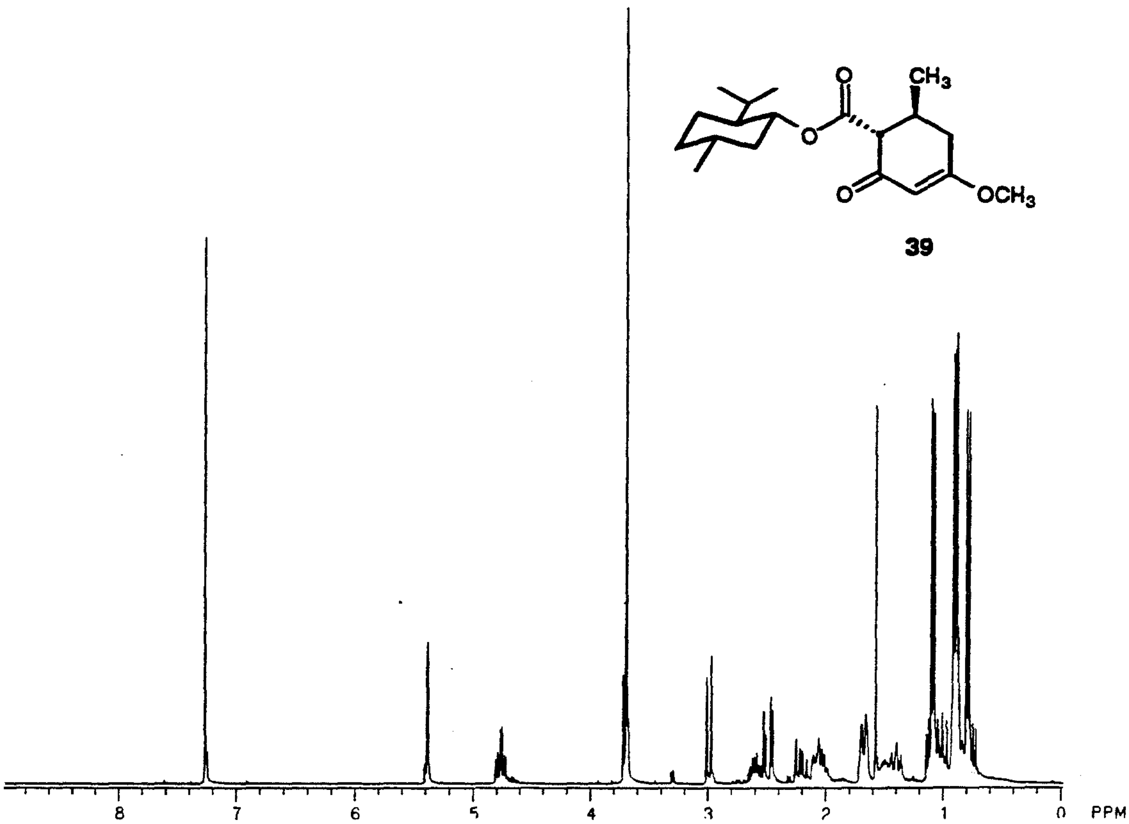
(Chapter 2)

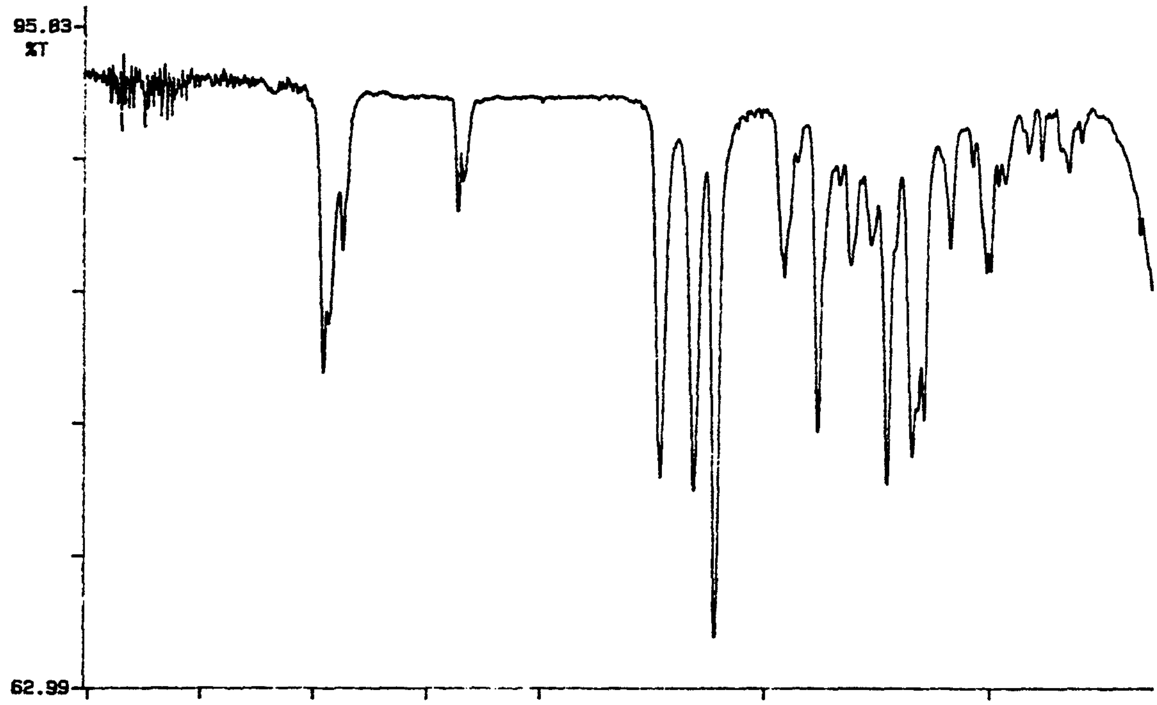

O
O
O
CH3
13
12
11
10
9
8
7
6
5
4
3
2
1
0
PPM

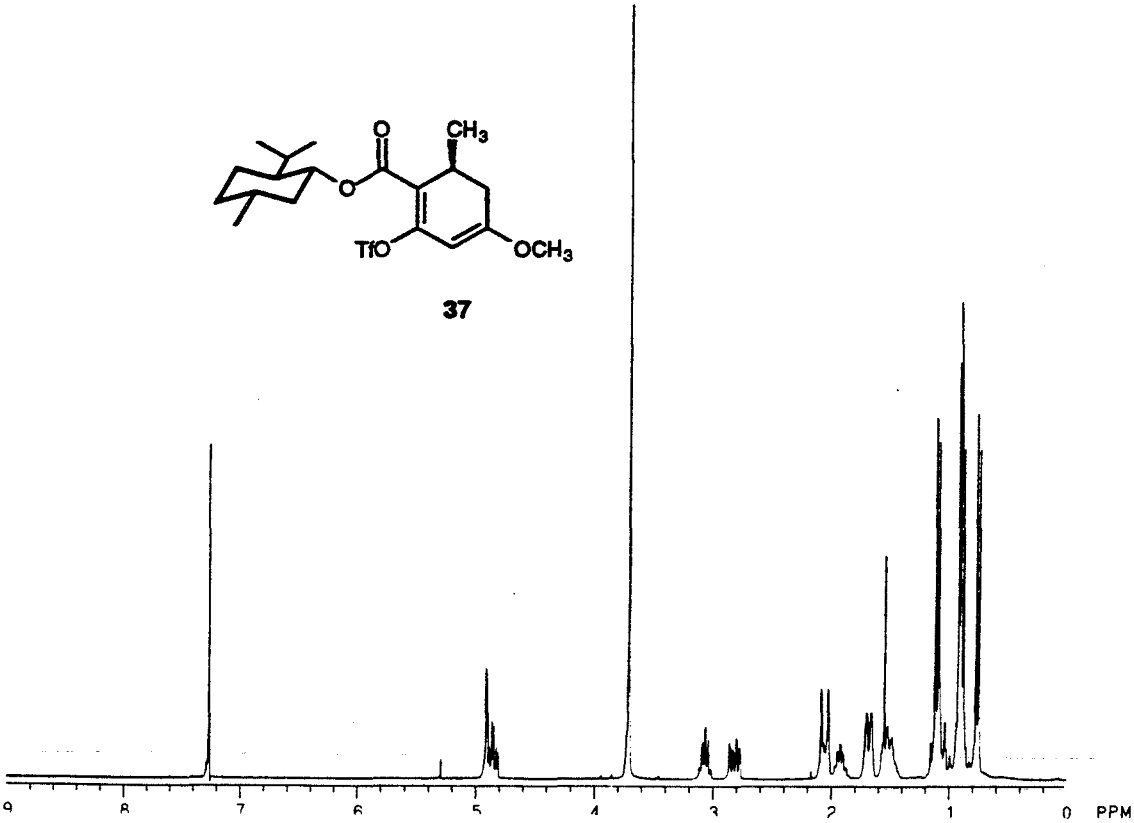

96.96
%T
62.01
4000
3500
3000
2500
2000
1500
1000
cm⁻¹

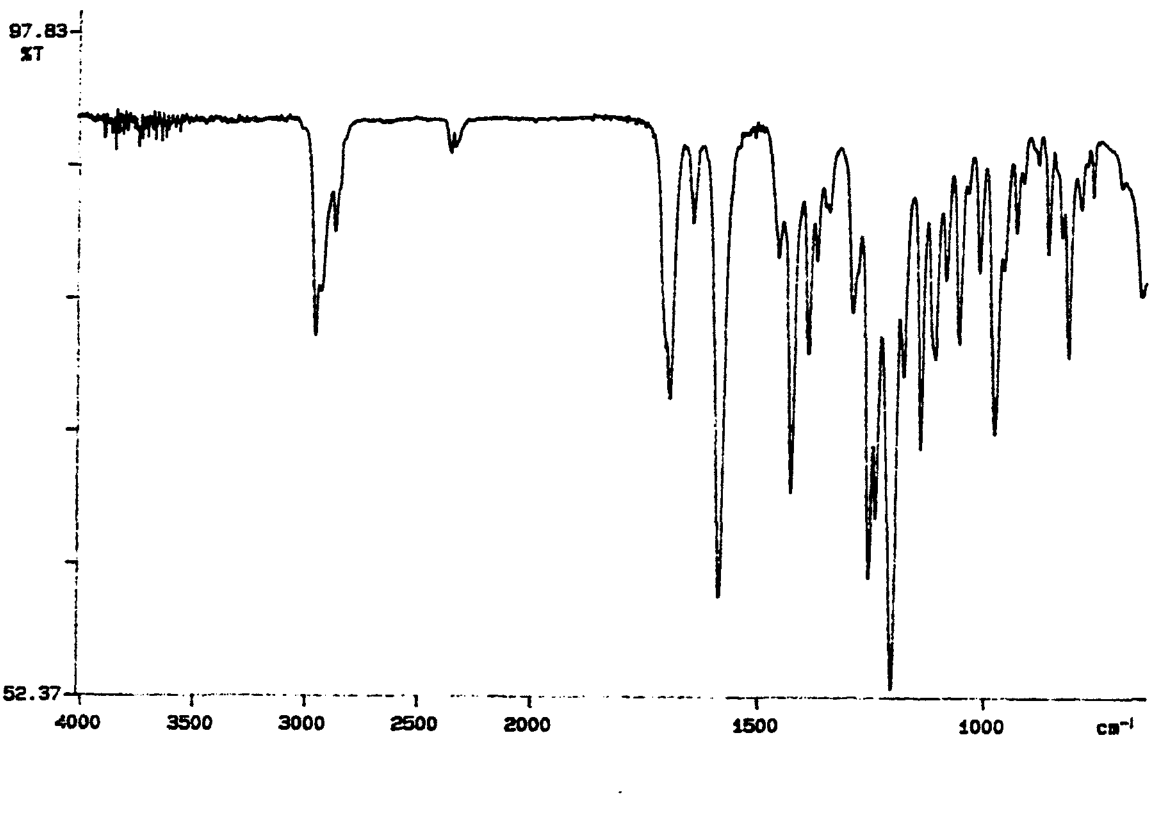

CH3
O
O
O
O
38
7
6
5
4
3
2
1
0
PPM

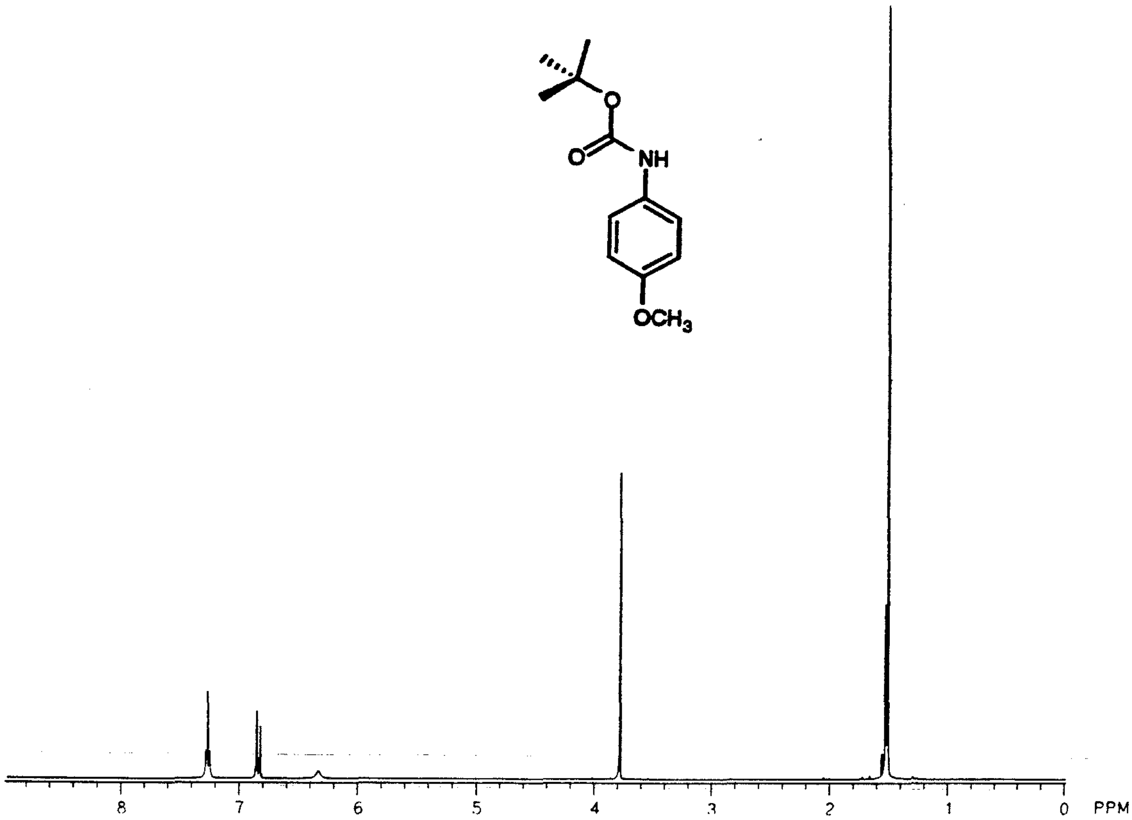

87.21
%T
67.85
4000
3500
3000
2500
2000
1500
1000
cm-1

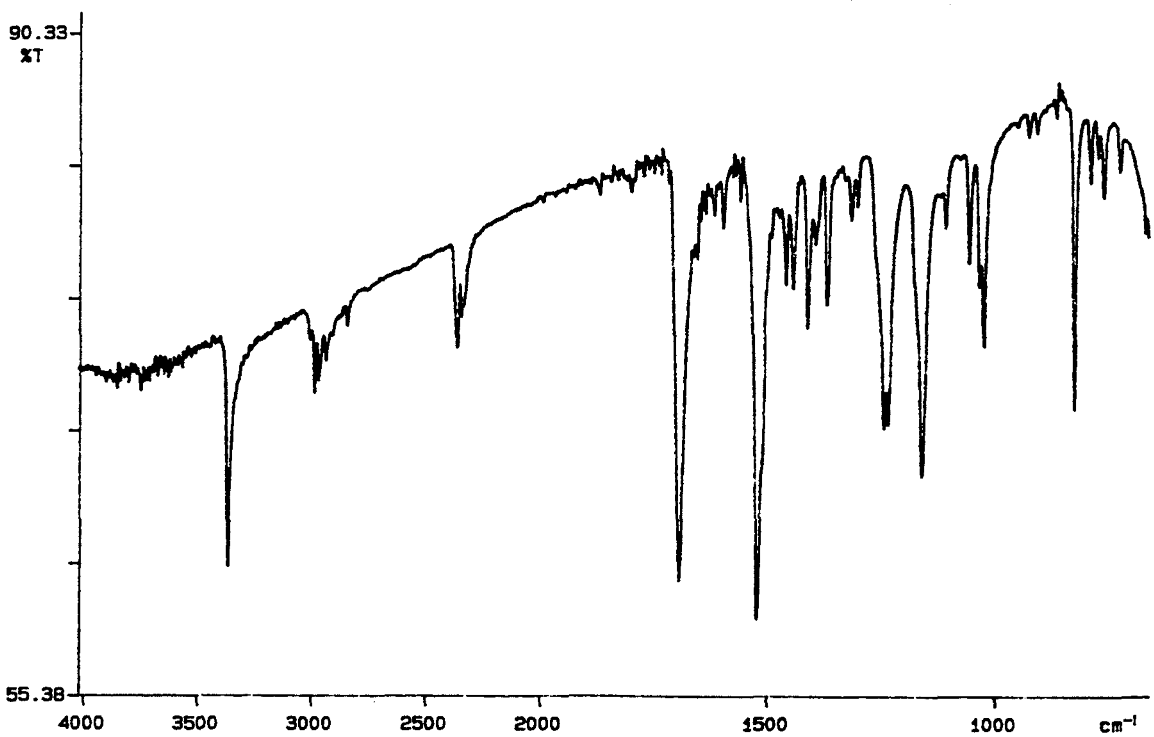

O
CH3
O
O
OCH3
39
8
7
6
5
4
3
2
1
0
PPM

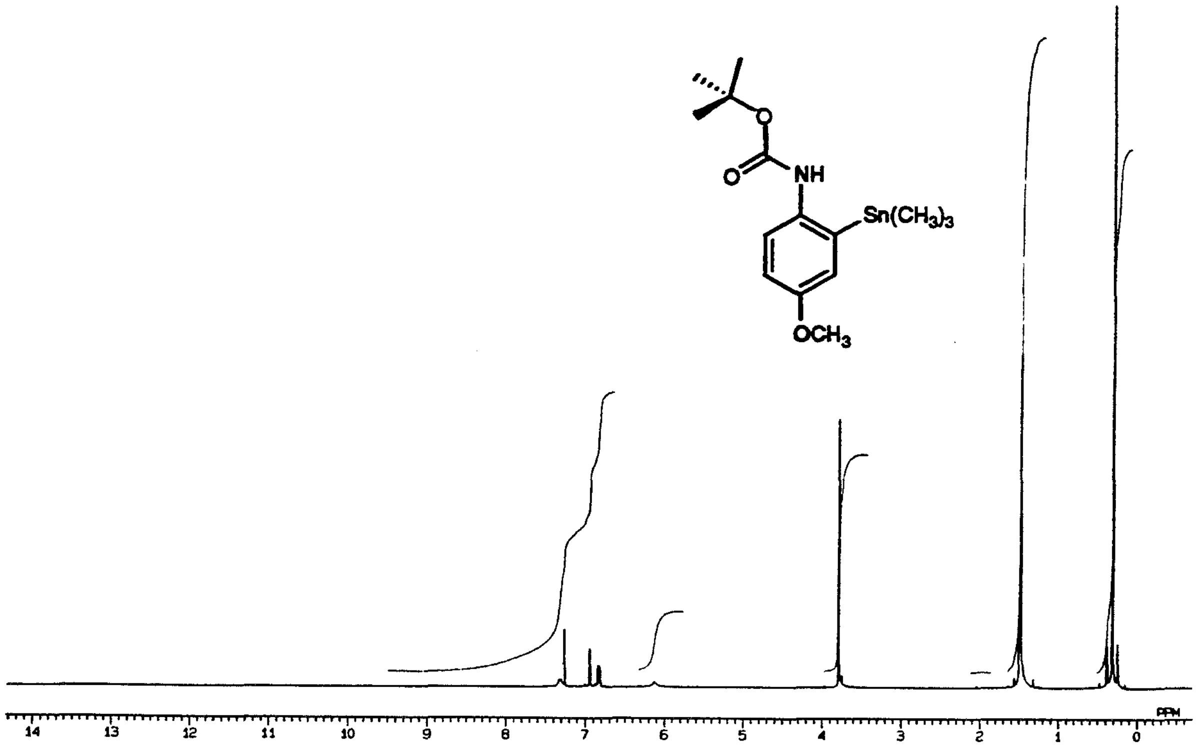

95.83
%T
62.99
4000
3500
3000
2500
2000
1500
1000
cm⁻¹

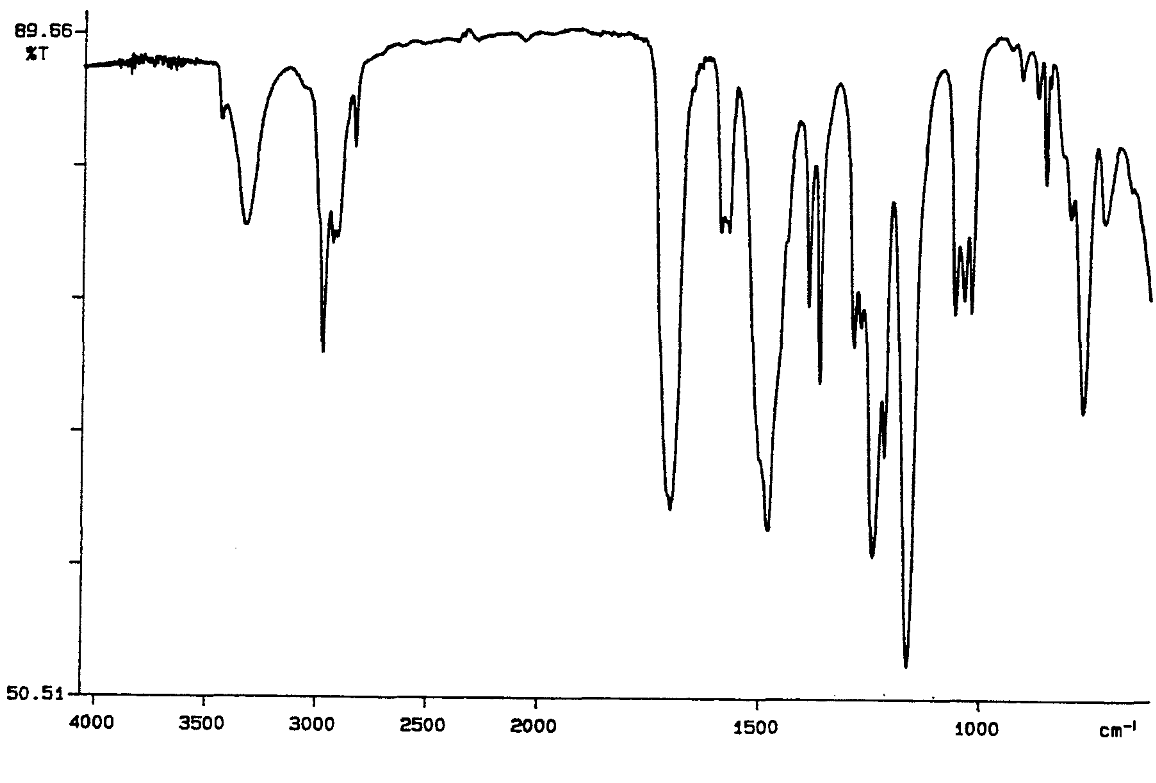

O
CH3
TfO
OCH3
37
9
8
7
6
5
4
3
2
1
0
PPM

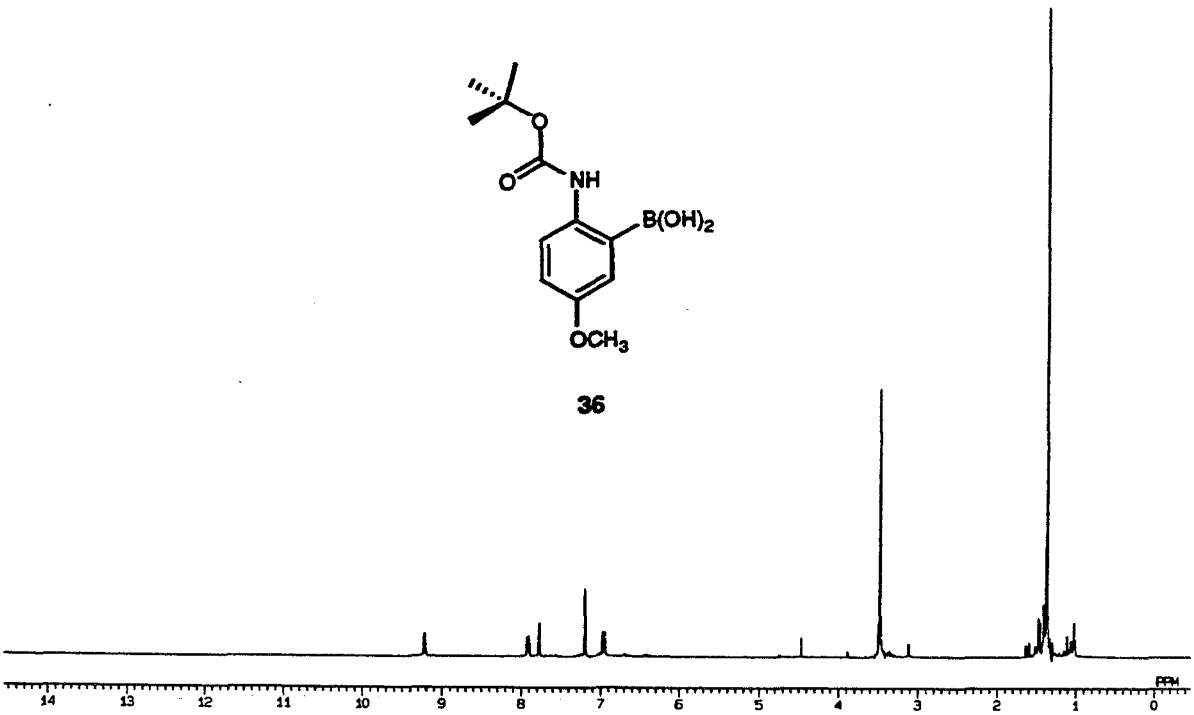

97.83
%T
52.37
4000
3500
3000
2500
2000
1500
1000
cm-1


O
NH
O
OCH3
8
7
6
5
4
3
2
1
0
PPM

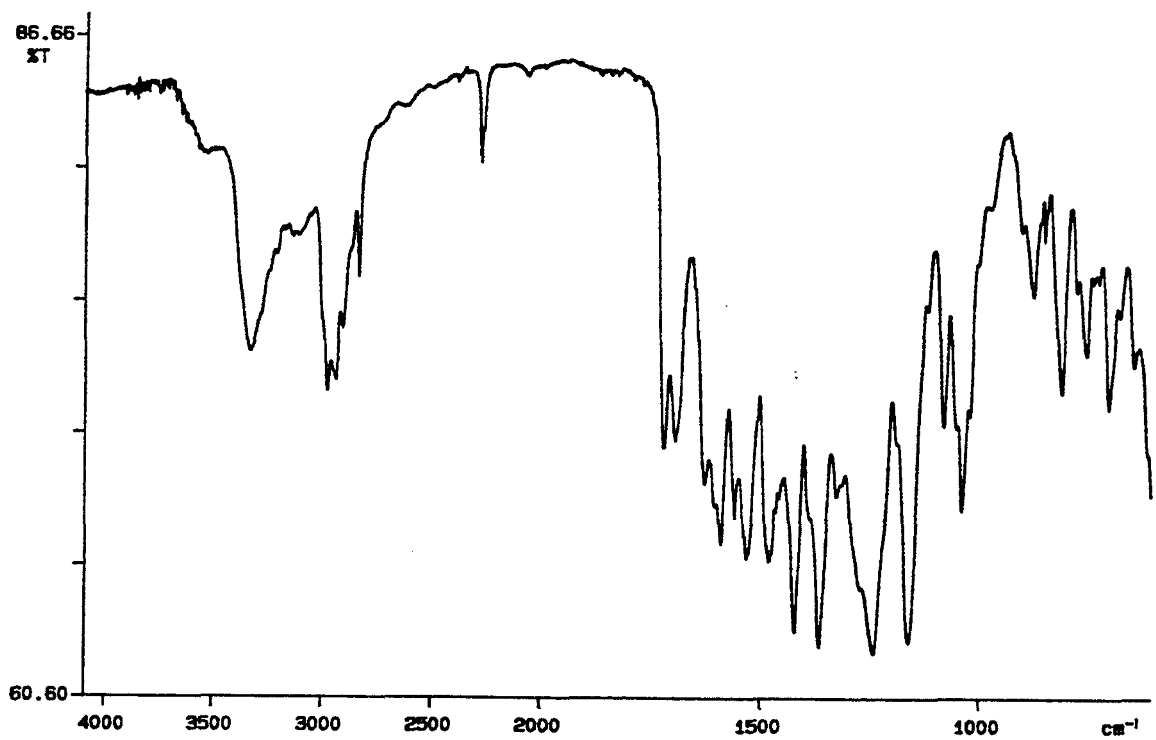

90.33
%T
55.38
4000
3500
3000
2500
2000
1500
1000
cm-1

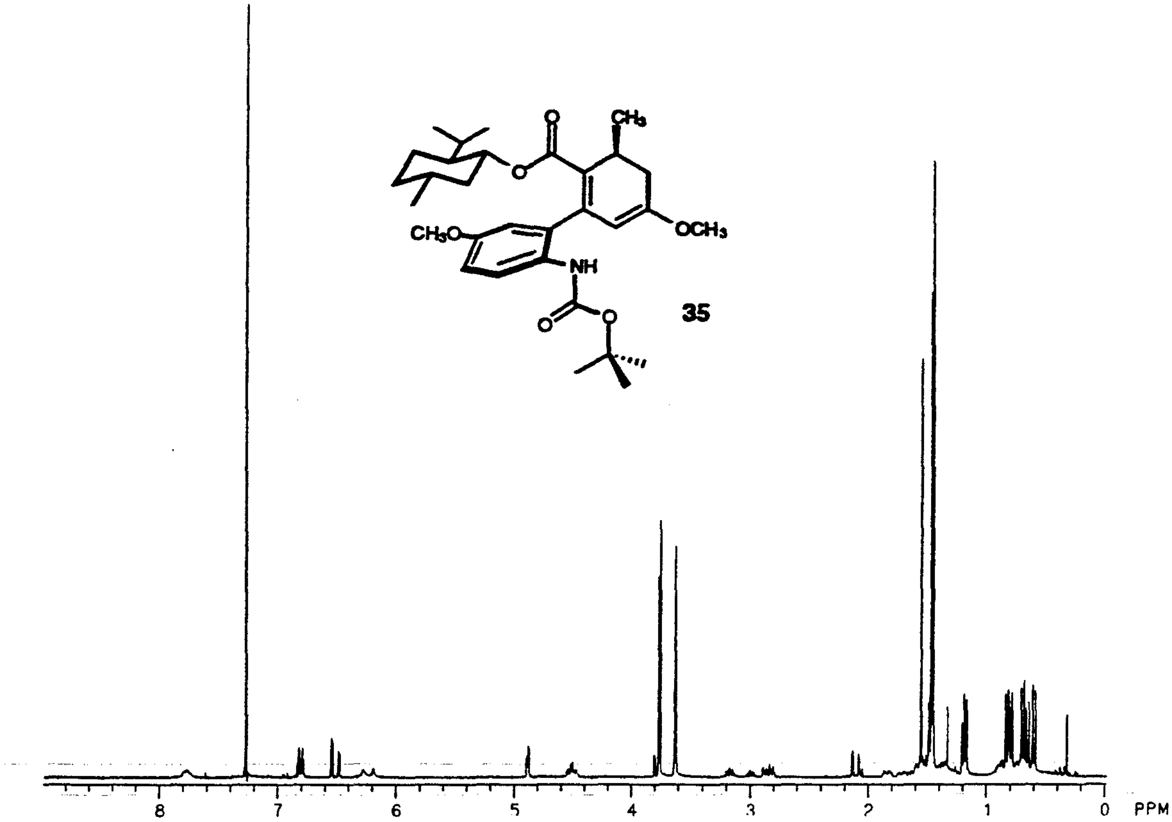

NH
O
Sn(CH3)3
OCH3
PPM
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0

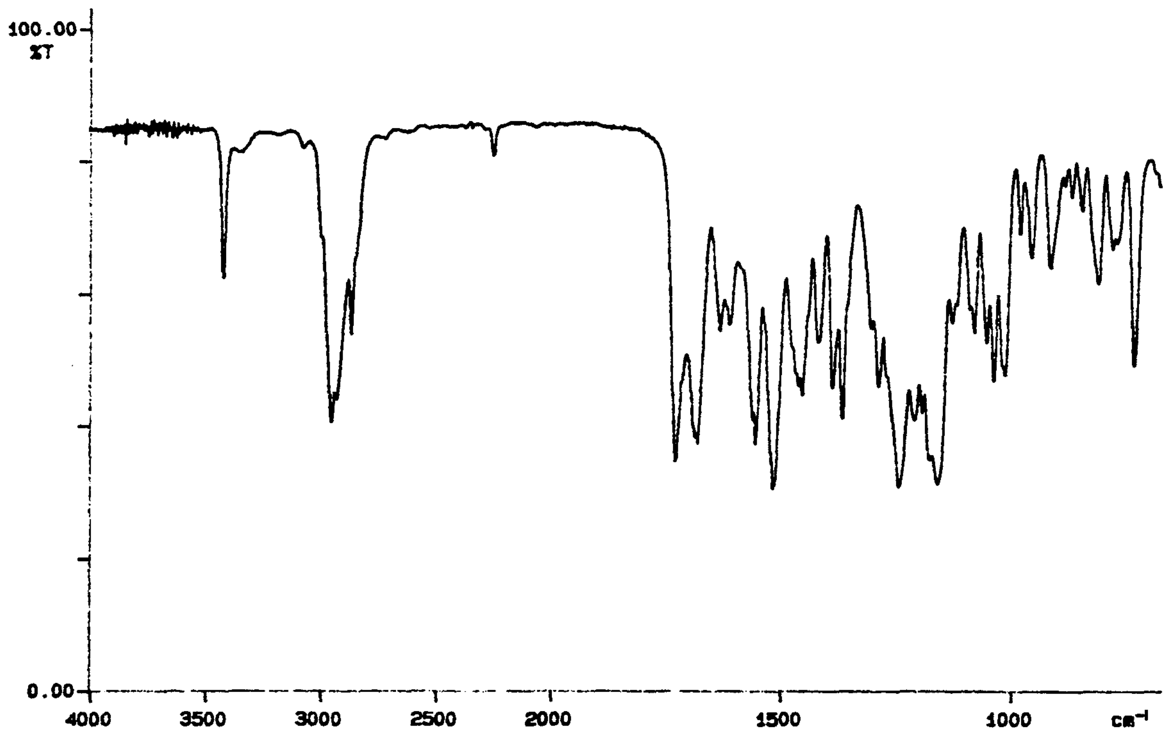

89.66
%T
50.51
4000
3500
3000
2500
2000
1500
1000
cm-1

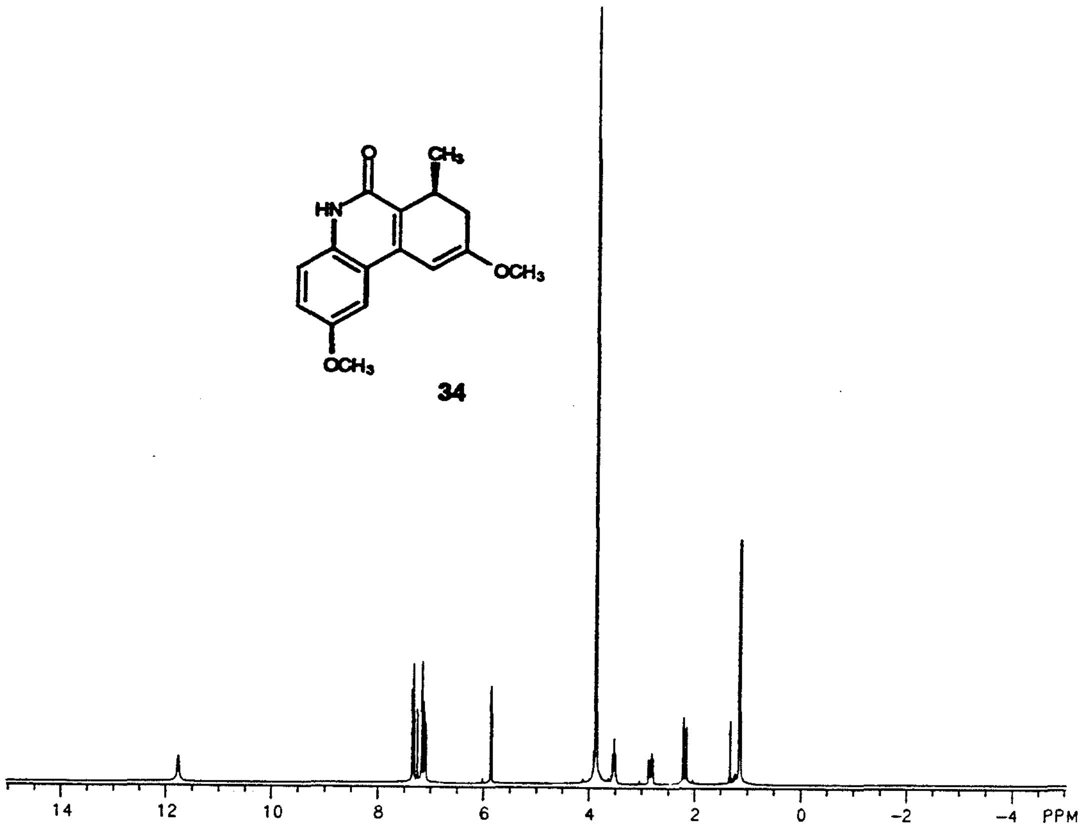

NH
B(OH)2
O
O
OCH3
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
PPM

36

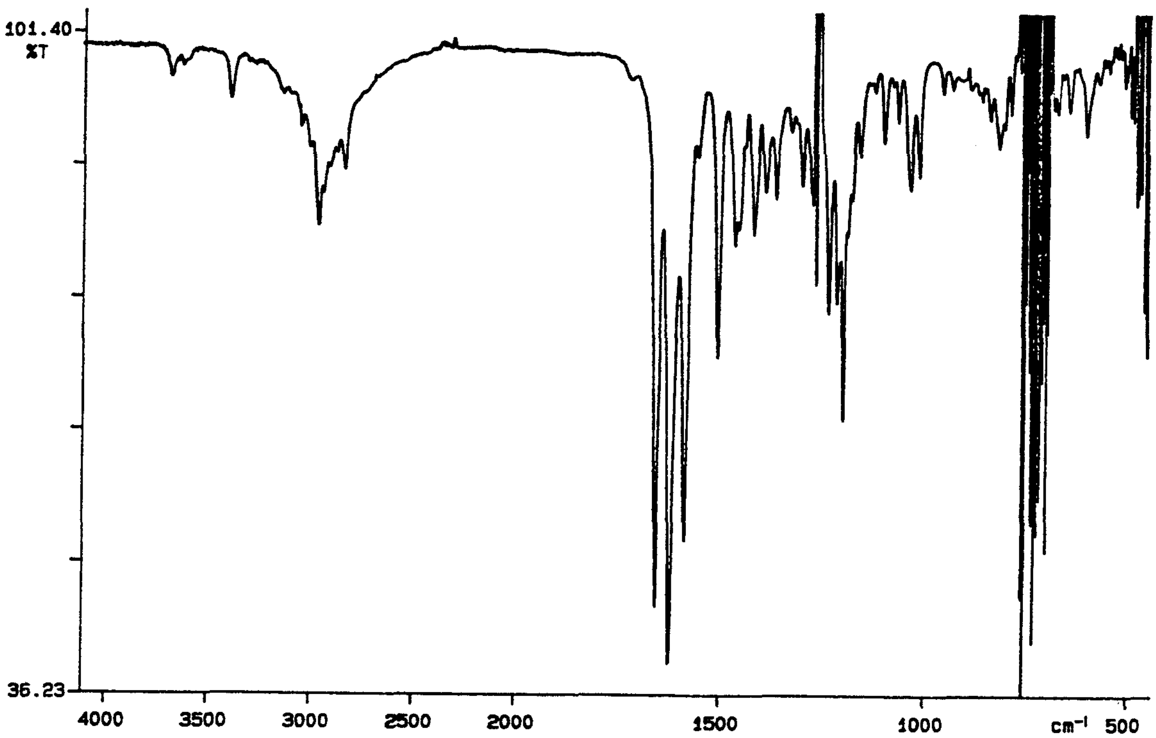

86.66
%T
60.60
4000
3500
3000
2500
2000
1500
1000
cm-1

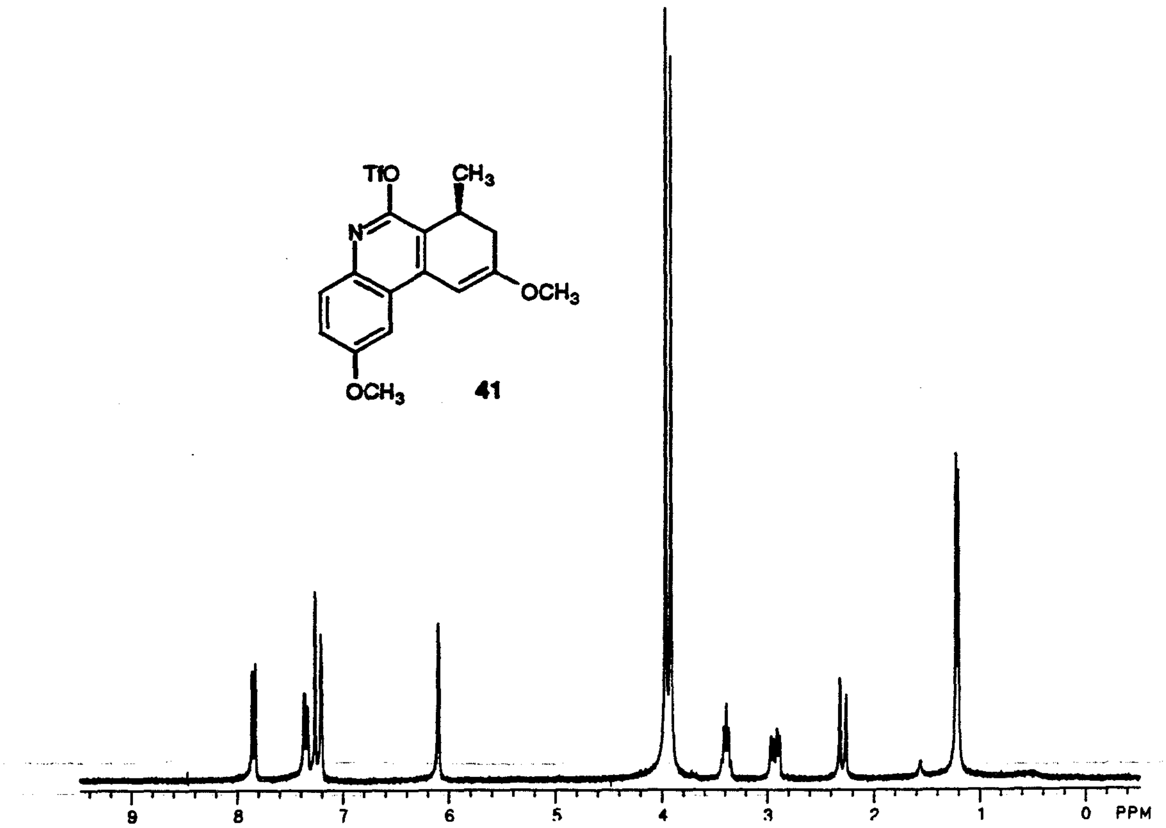

CH3
OCH3
CH3O
NH
35
8
7
6
5
4
3
2
1
0
PPM

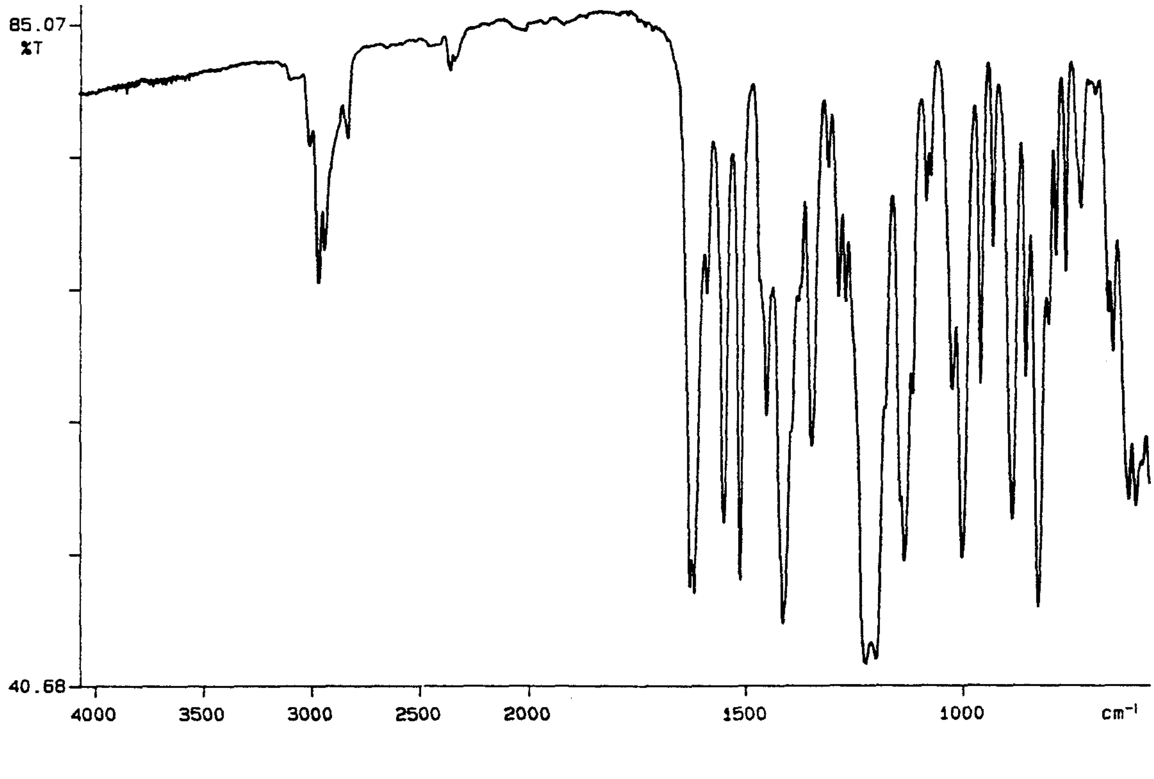

100.00
%T
0.00
4000
3500
3000
2500
2000
1500
1000
cm⁻¹

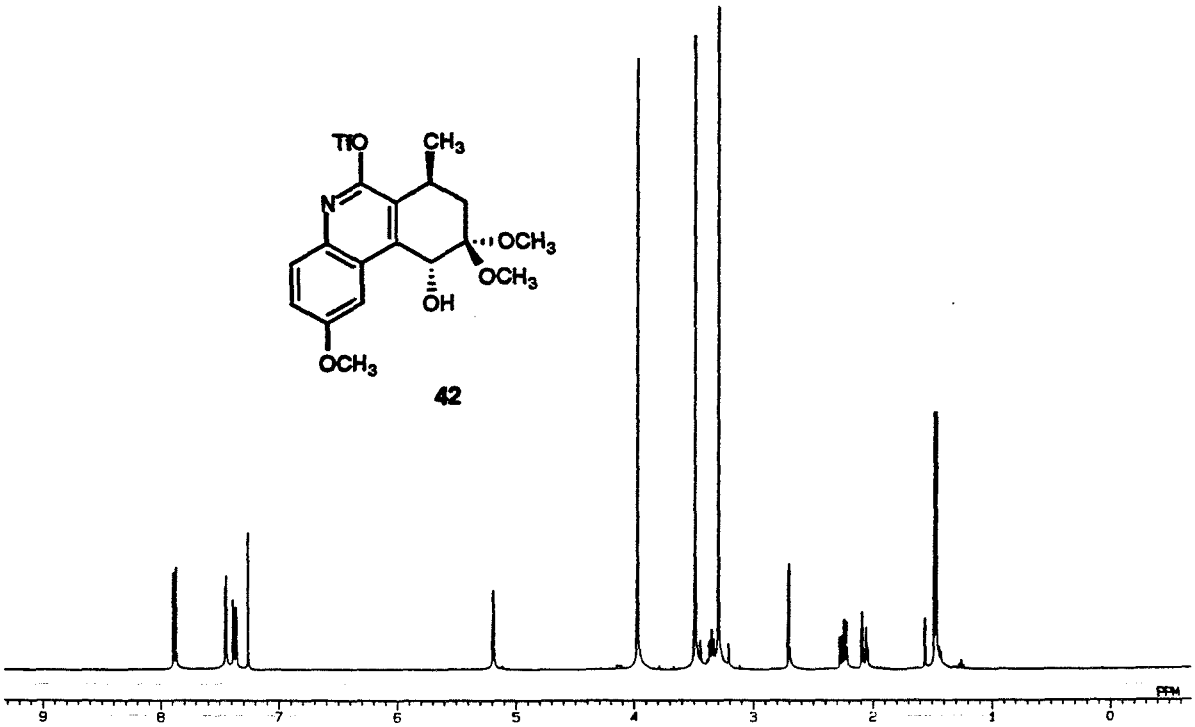

O
CH3
HN
OCH3
OCH3
14
12
10
8
6
4
2
0
-2
-4
PPM

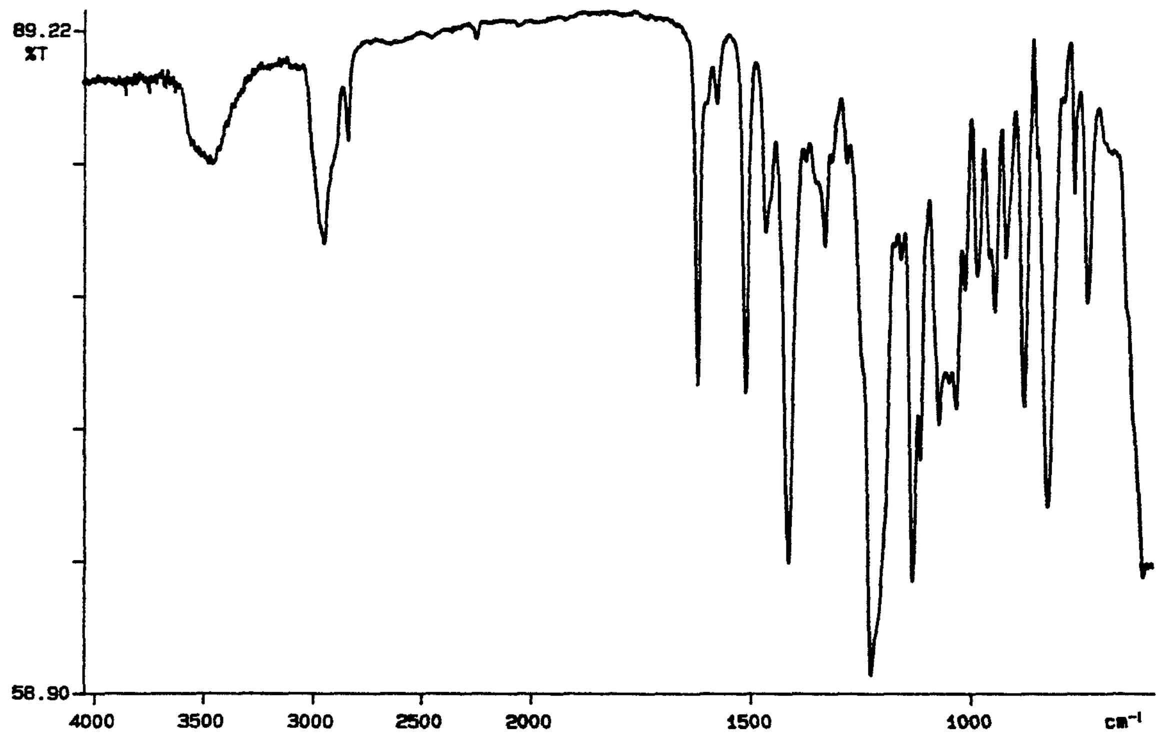
34

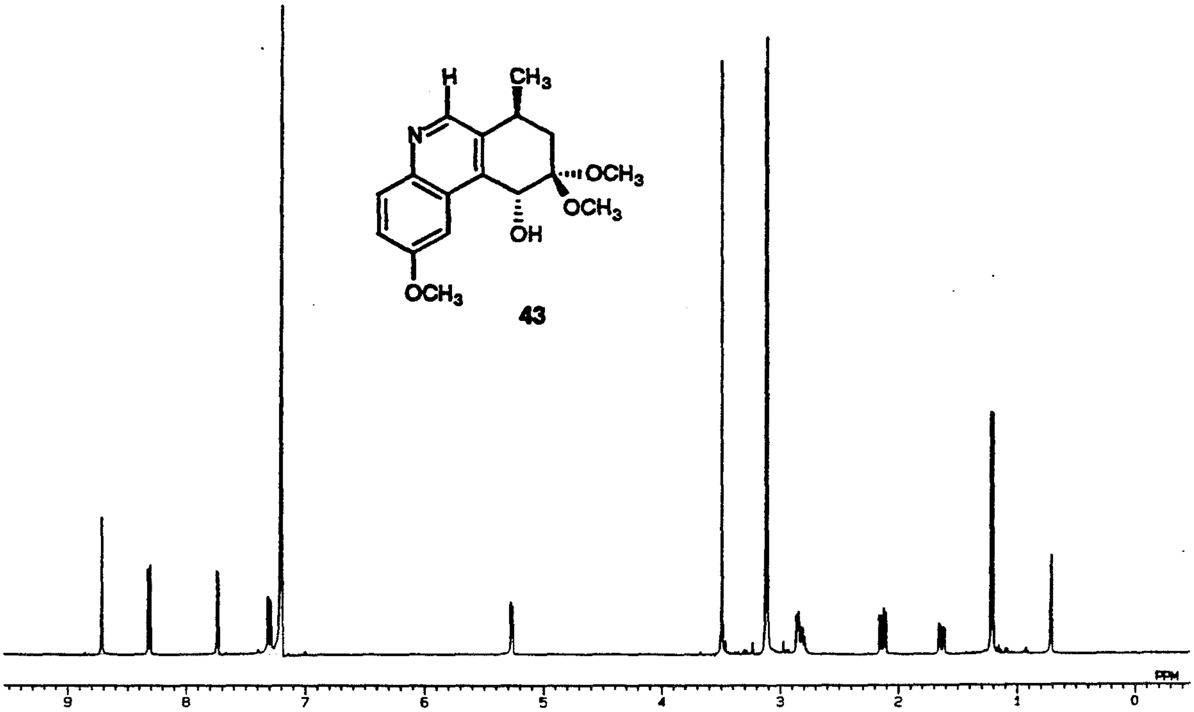

101.40
%T
36.23
4000
3500
3000
2500
2000
1500
1000
cm-1
500

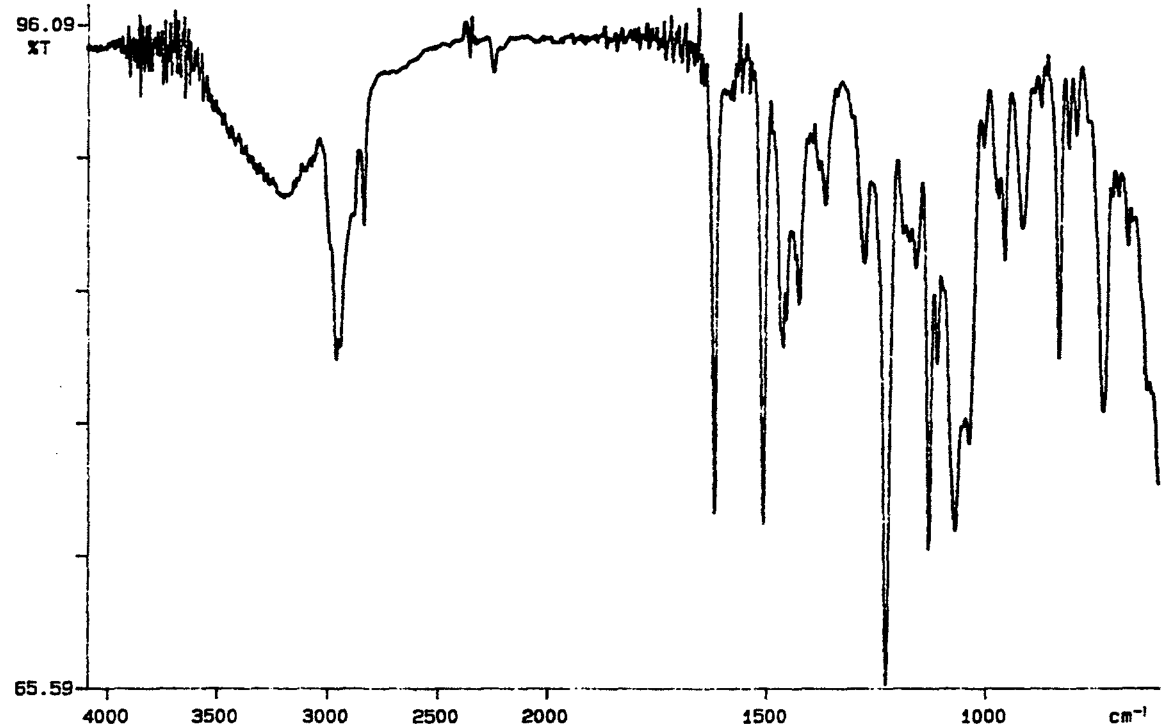

41
9
8
7
6
5
4
3
2
1
0
PPM

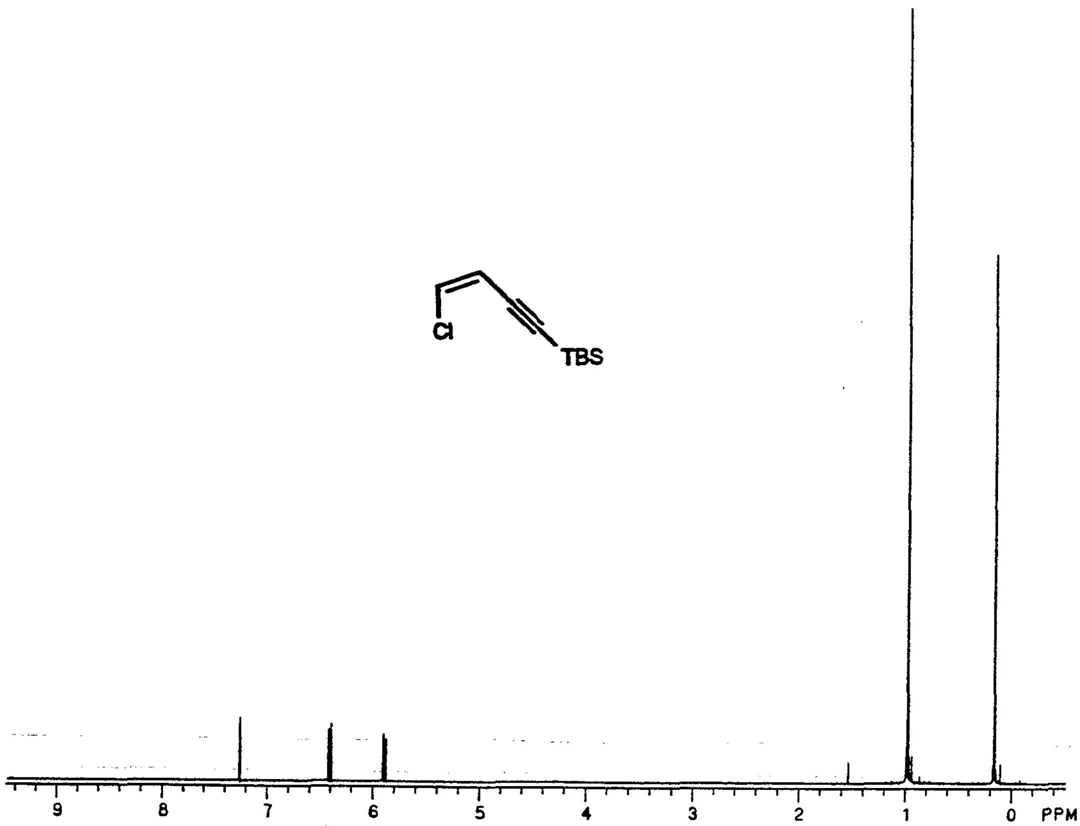

85.07
%T
40.68
4000
3500
3000
2500
2000
1500
1000
cm⁻¹

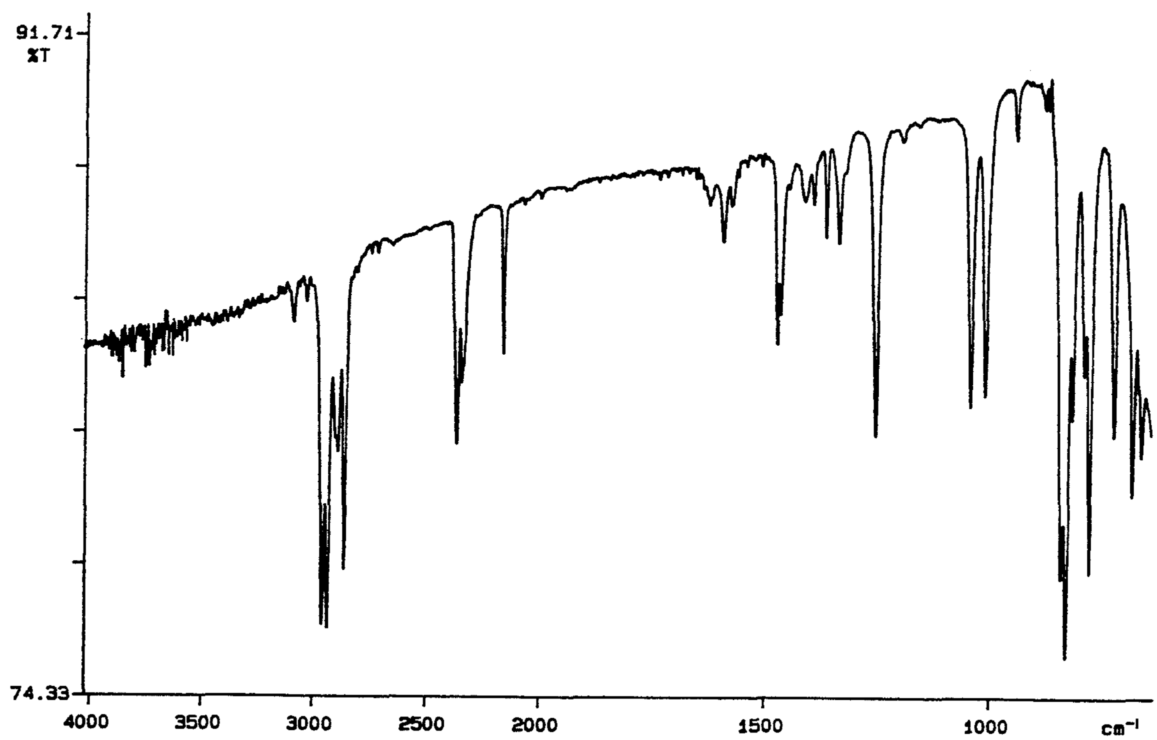

TfO
CH3
N
OCH3
OCH3
OH
OCH3
42
PPM
9
8
7
6
5
4
3
2
1
0

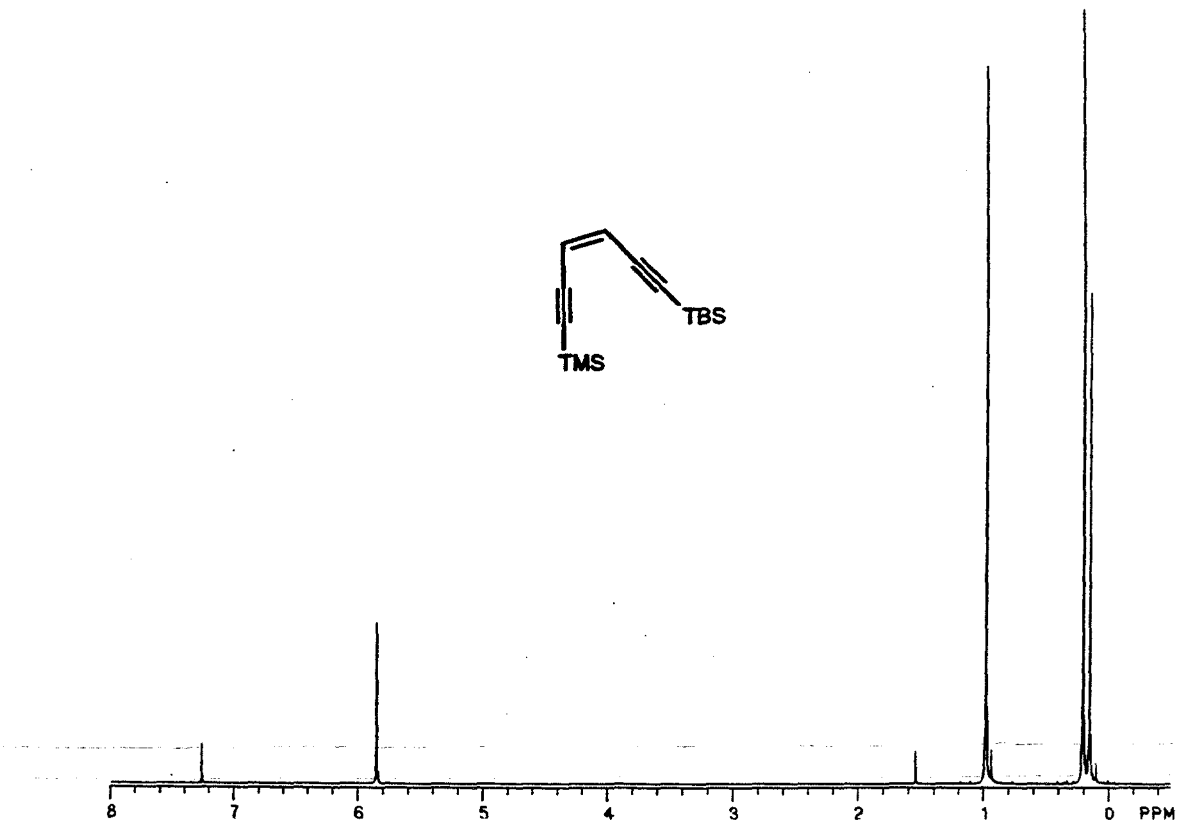

89.22
%T
58.90
4000
3500
3000
2500
2000
1500
1000
cm-1

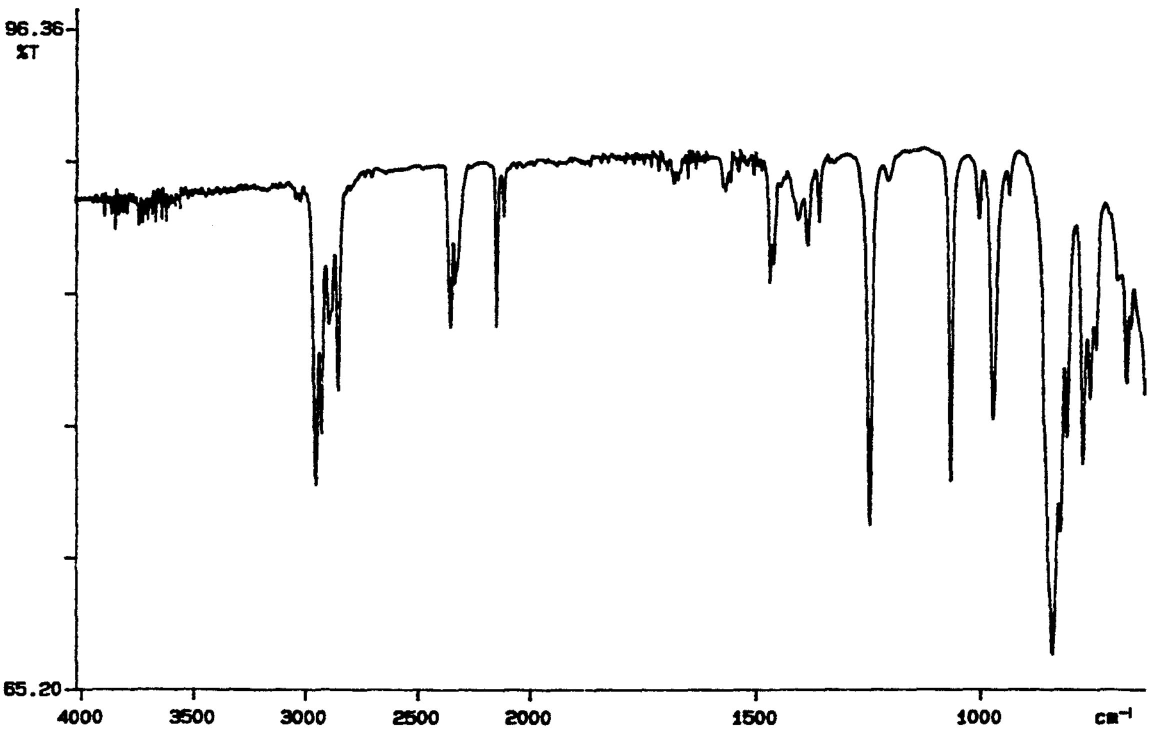

H
CH3
N
OCH3
OCH3
OH
OCH3
43
9
8
7
6
5
4
3
2
1
0
PPM

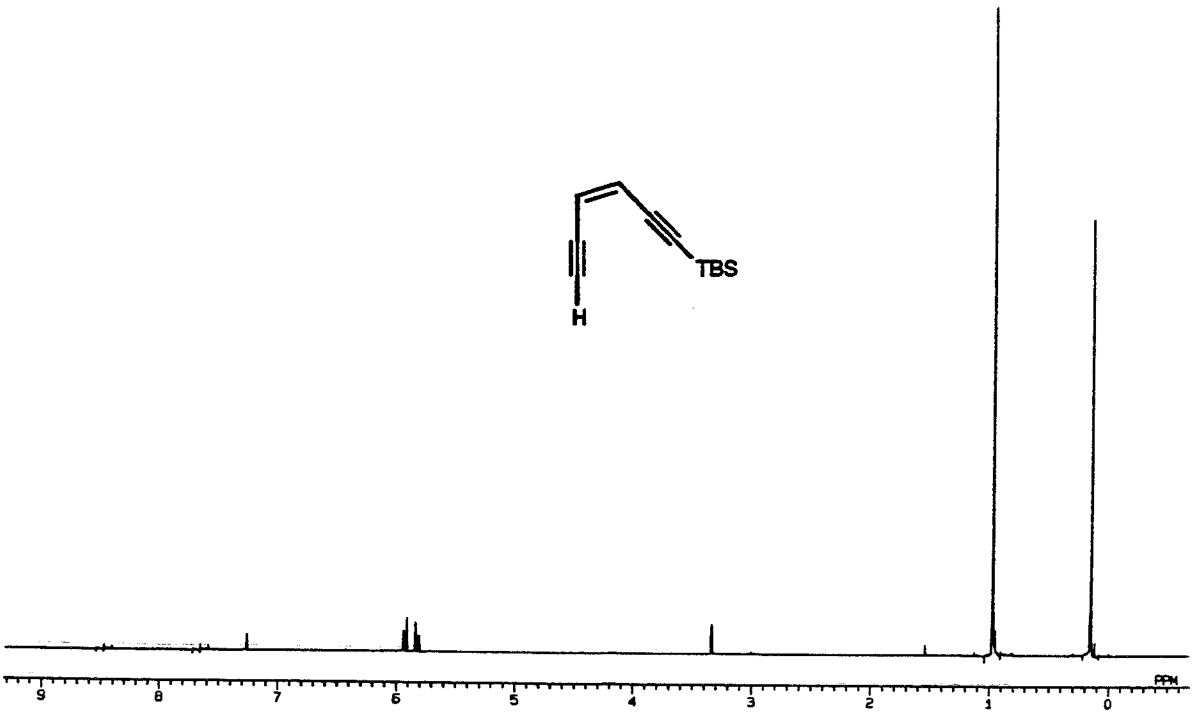

96.09
%T
65.59
4000
3500
3000
2500
2000
1500
1000
cm-1

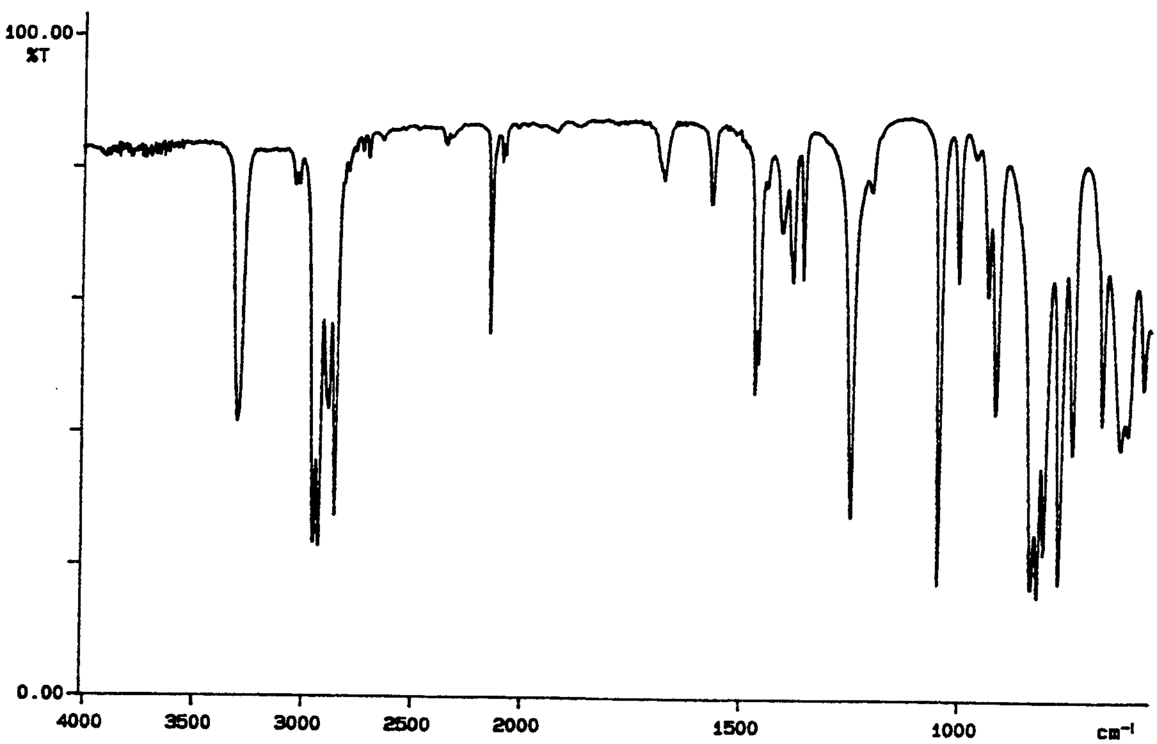

Cl
TBS
9
8
7
6
5
4
3
2
1
0
PPM

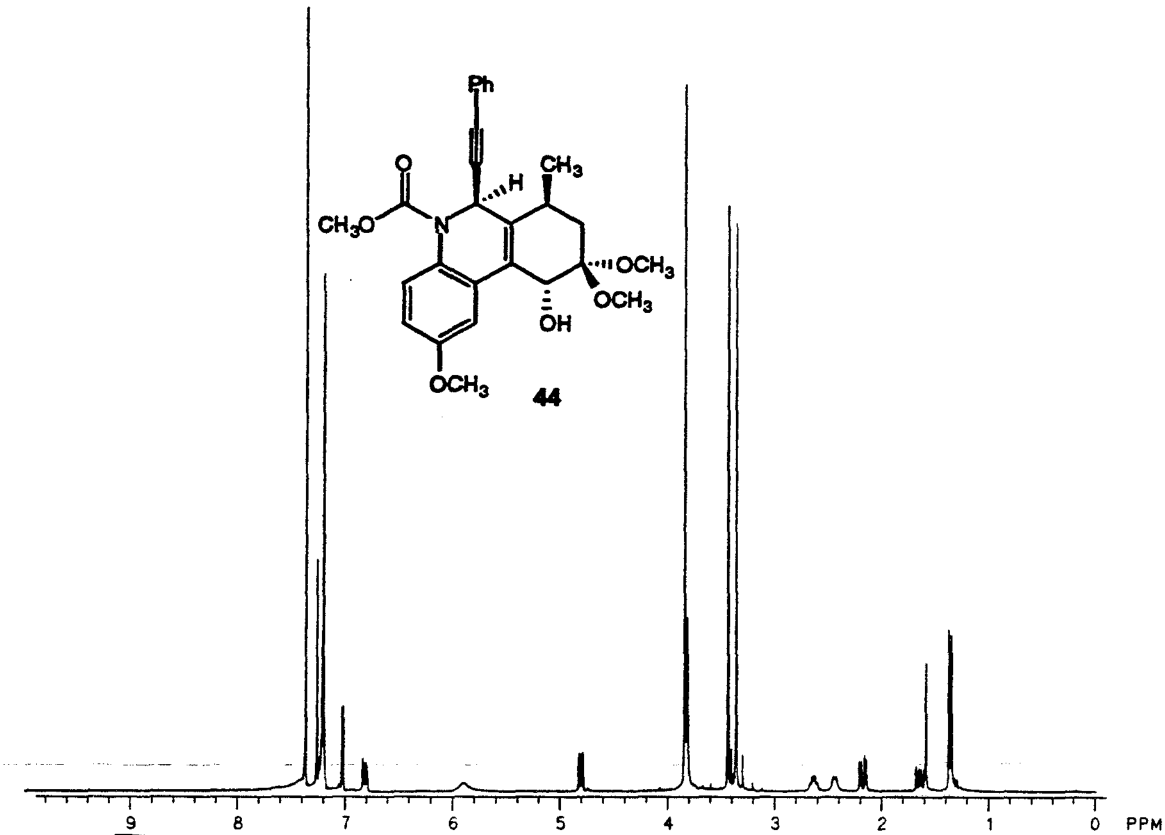

91.71
%T
74.33
4000
3500
3000
2500
2000
1500
1000
cm⁻¹

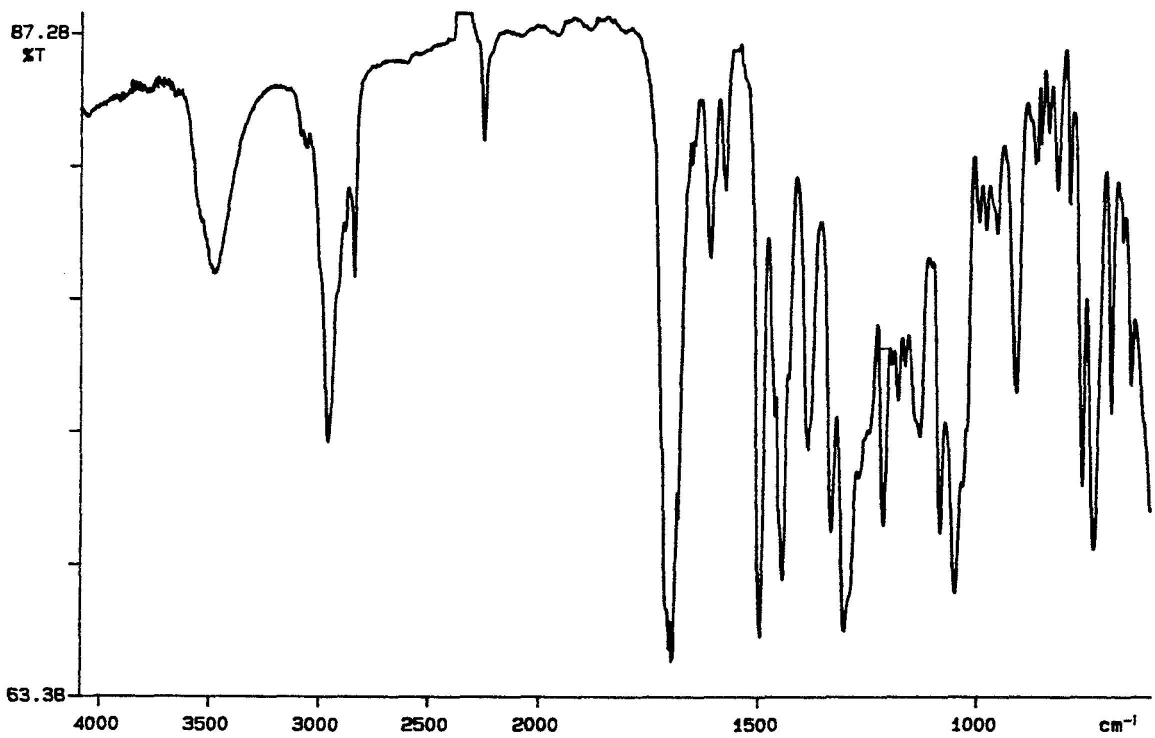

TBS
TMS
8
7
6
5
4
3
2
1
0
PPM

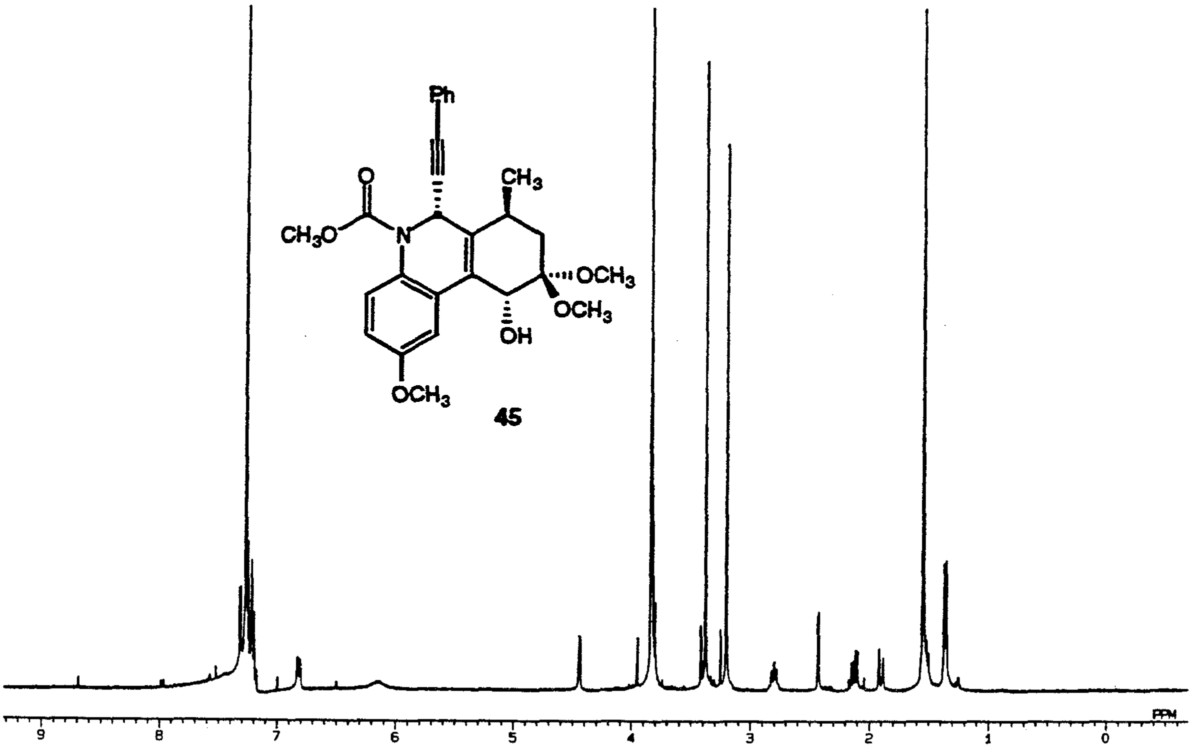

96.36
%T
65.20
4000
3500
3000
2500
2000
1500
1000
cm⁻¹

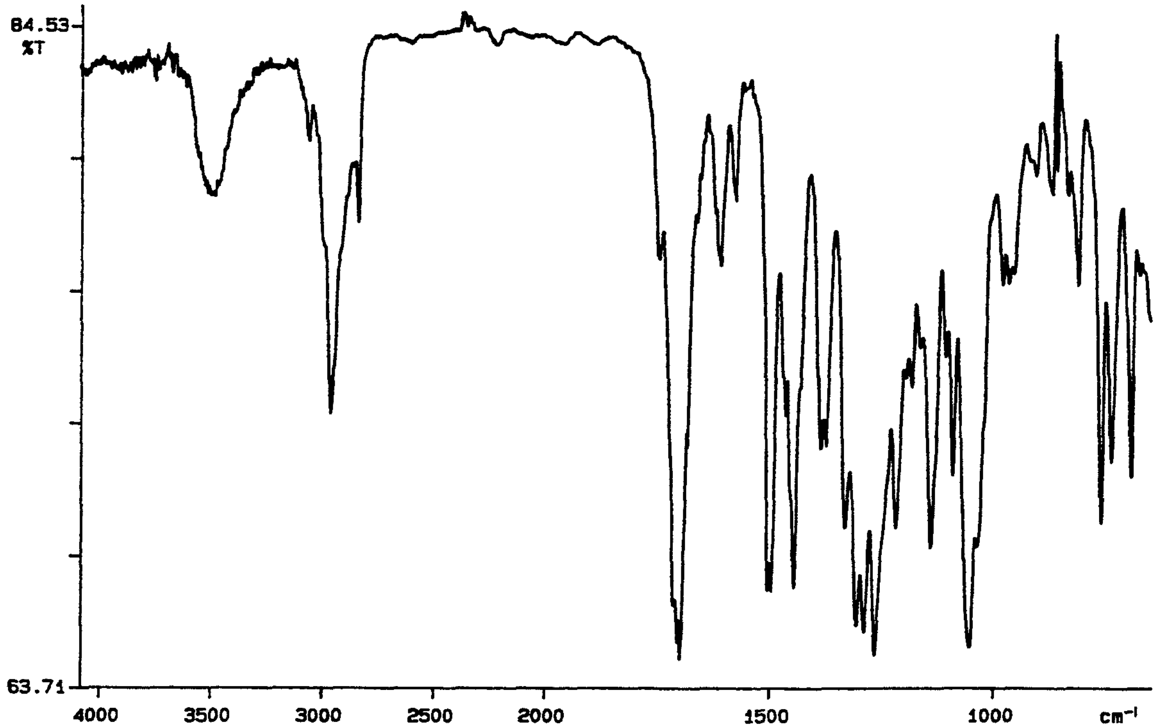

TBS
H
9
8
7
6
5
4
3
2
1
0
PPM

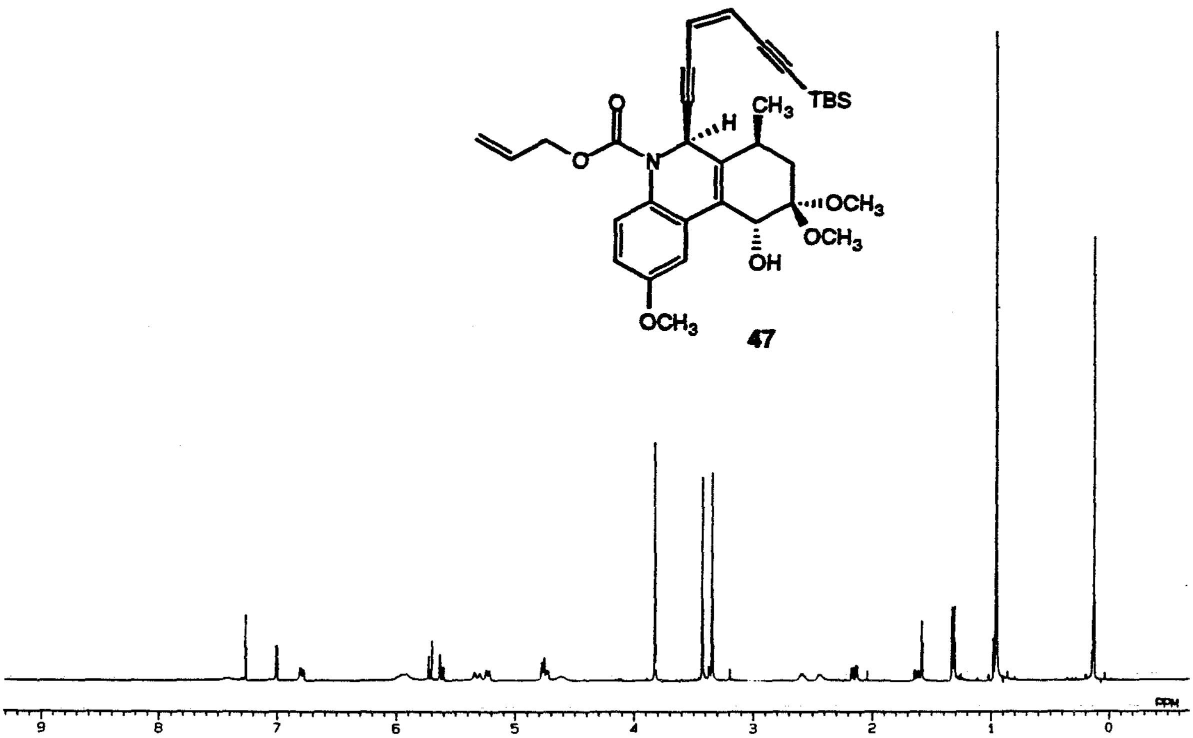

100.00
%T
0.00
4000
3500
3000
2500
2000
1500
1000
cm⁻¹

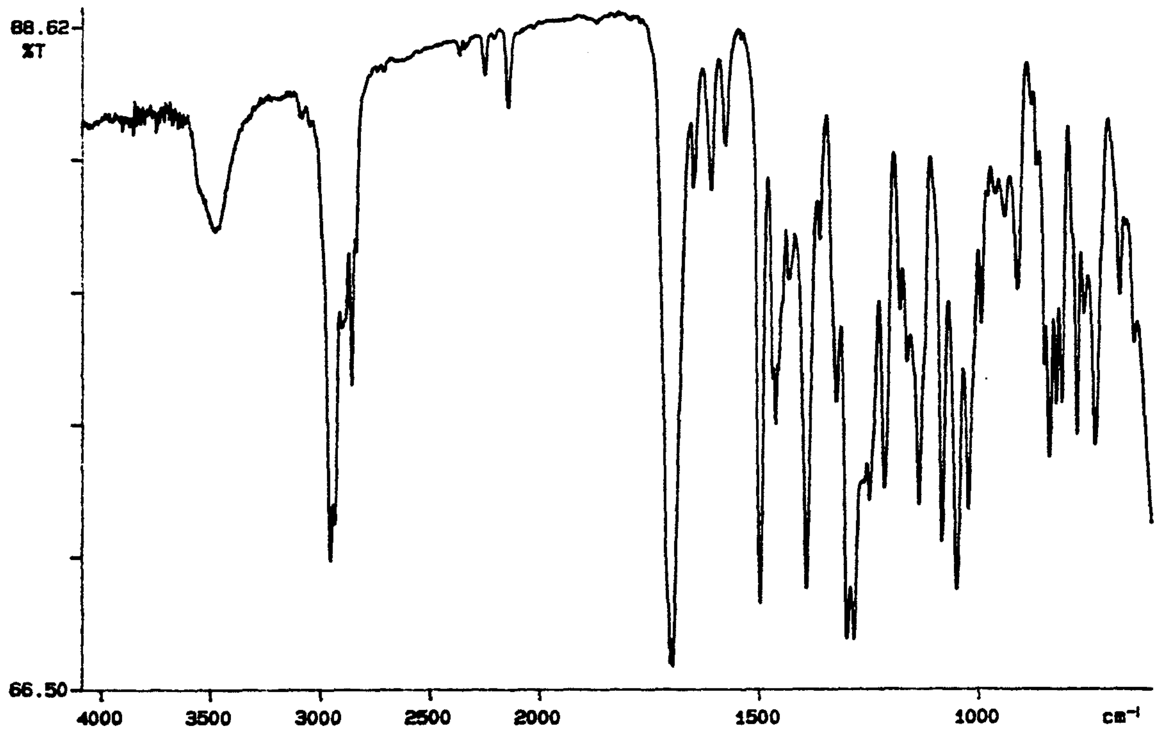

Ph
CH3
H
CH3O
N
OCH3
OCH3
OH
OCH3
44
9
8
7
6
5
4
3
2
1
0
PPM

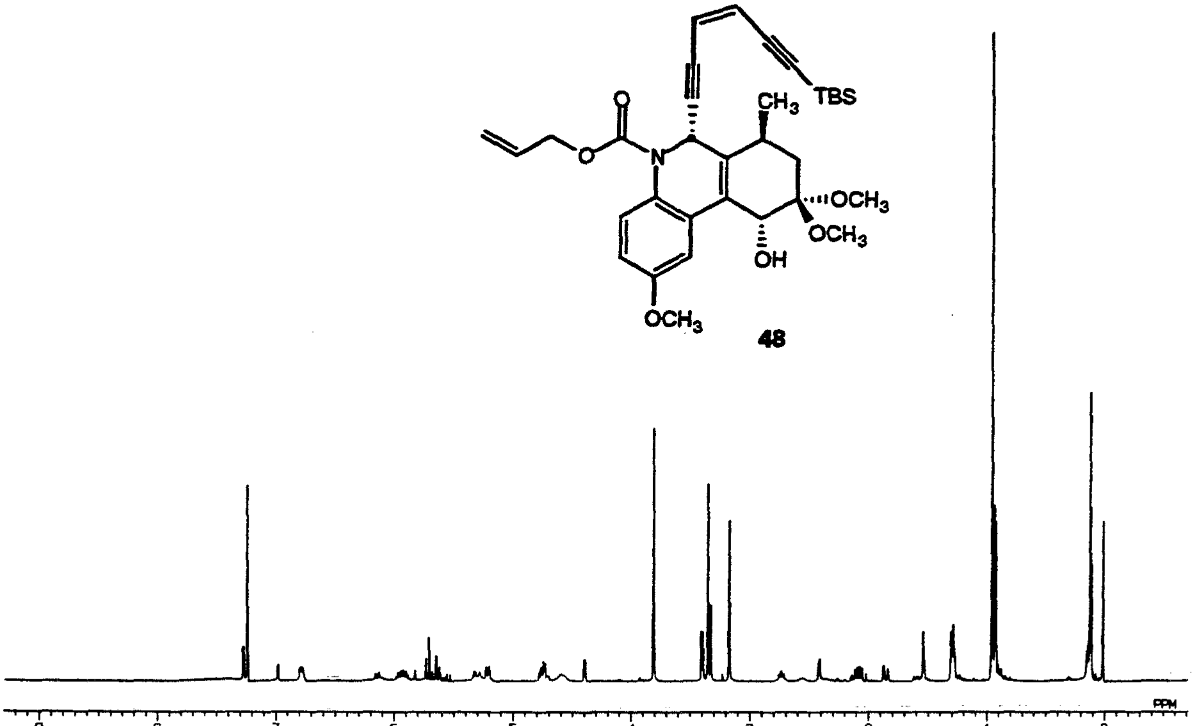

87.28
%T
63.38
4000
3500
3000
2500
2000
1500
1000
cm⁻¹


Ph
CH3
CH3O
O
N
OCH3
OCH3
OH
OCH3
45
PPM
9
8
7
6
5
4
3
2
1
0

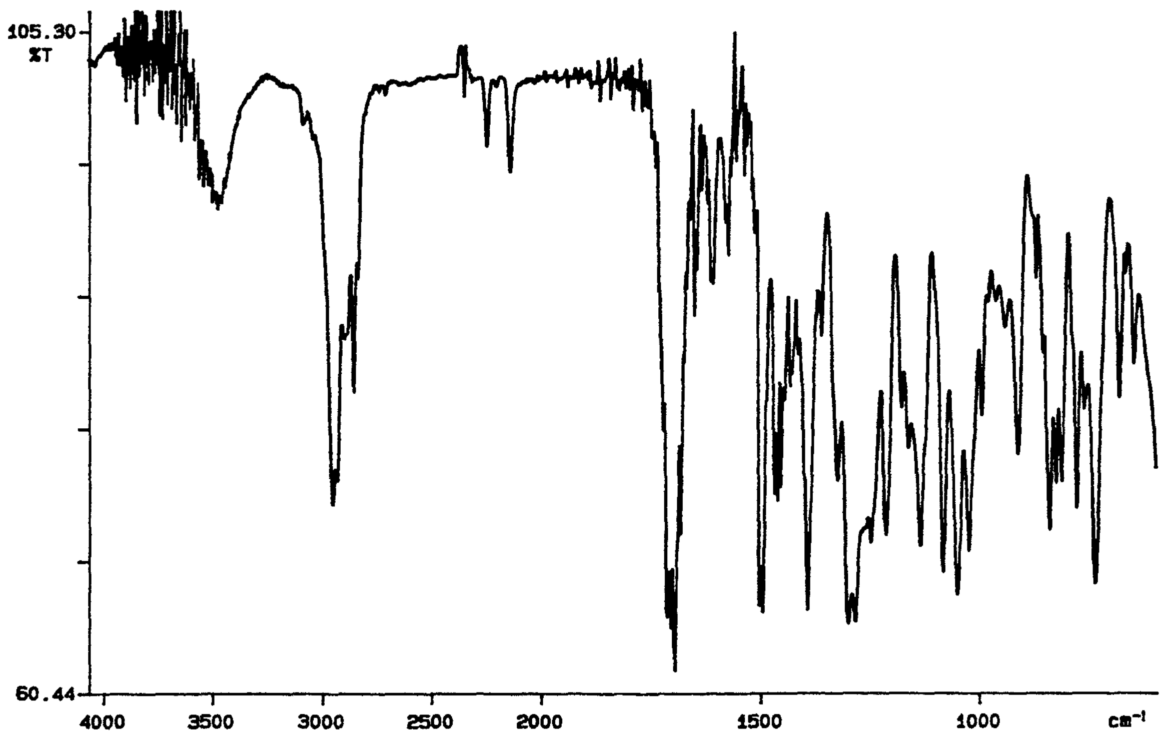

84.53
%T
63.71
4000
3500
3000
2500
2000
1500
1000
cm-1


CH3
TBS
H
O
N
O
OCH3
OCH3
OH
OCH3
47
9
8
7
6
5
4
3
2
1
0
PPM

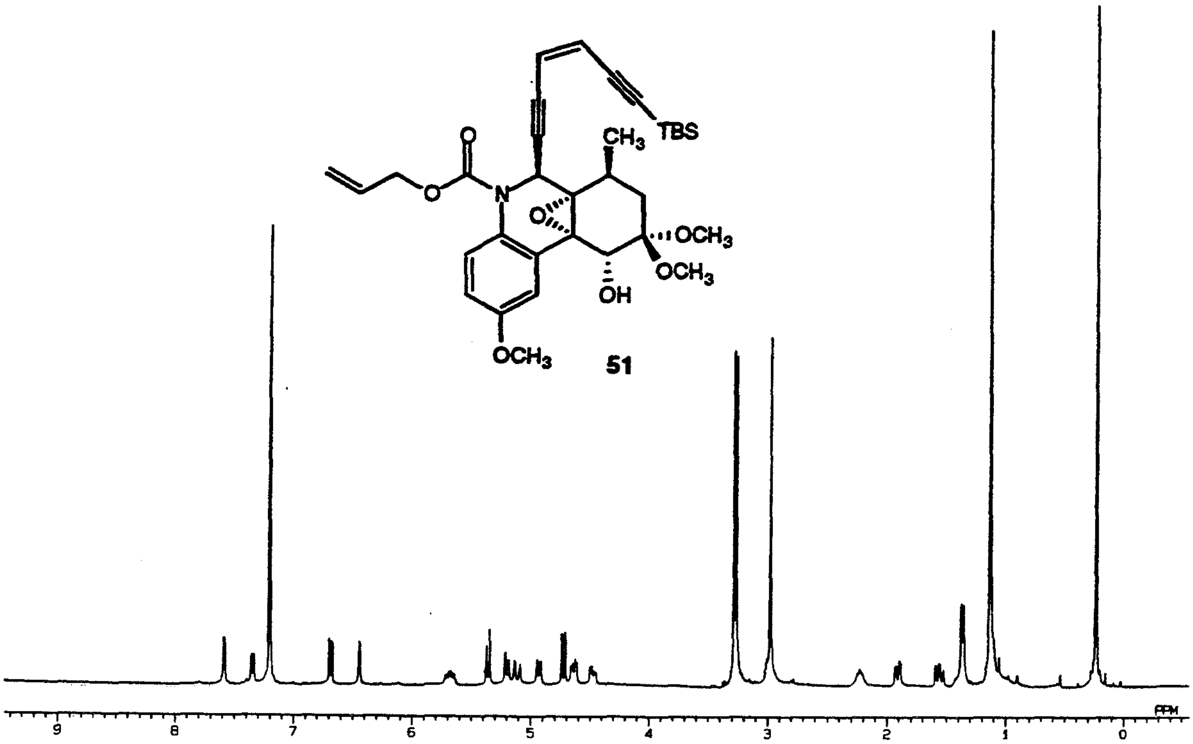

88.62
%T
66.50
4000
3500
3000
2500
2000
1500
1000
cm-1



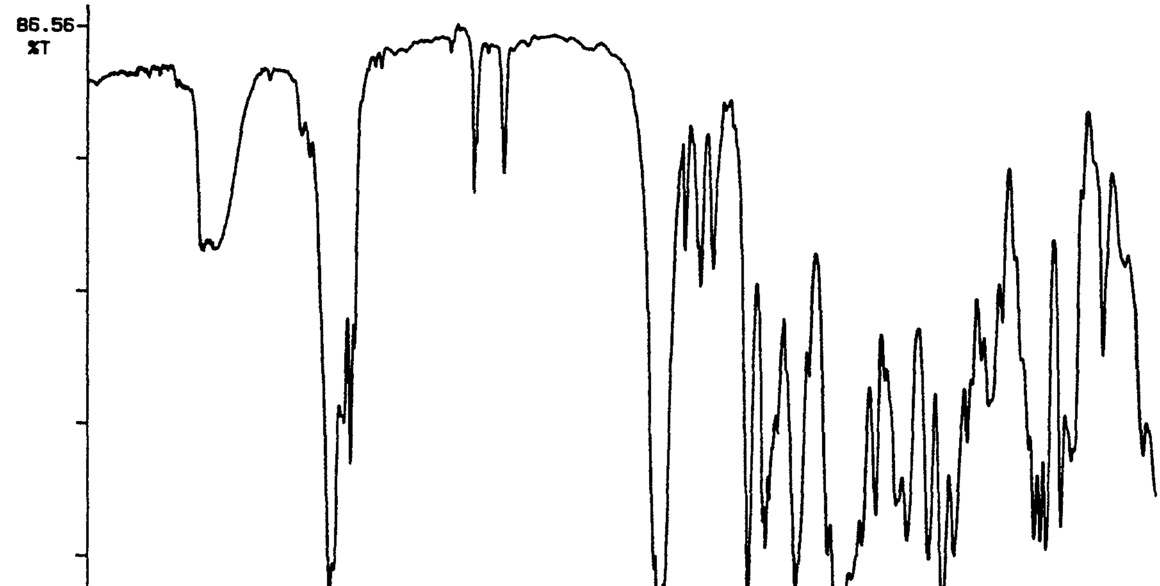
TBS
CH₃
N
O
O
OCH₃
OCH₃
OH
OCH₃
48
PPM
9
8
7
6
5
4
3
2
1
0



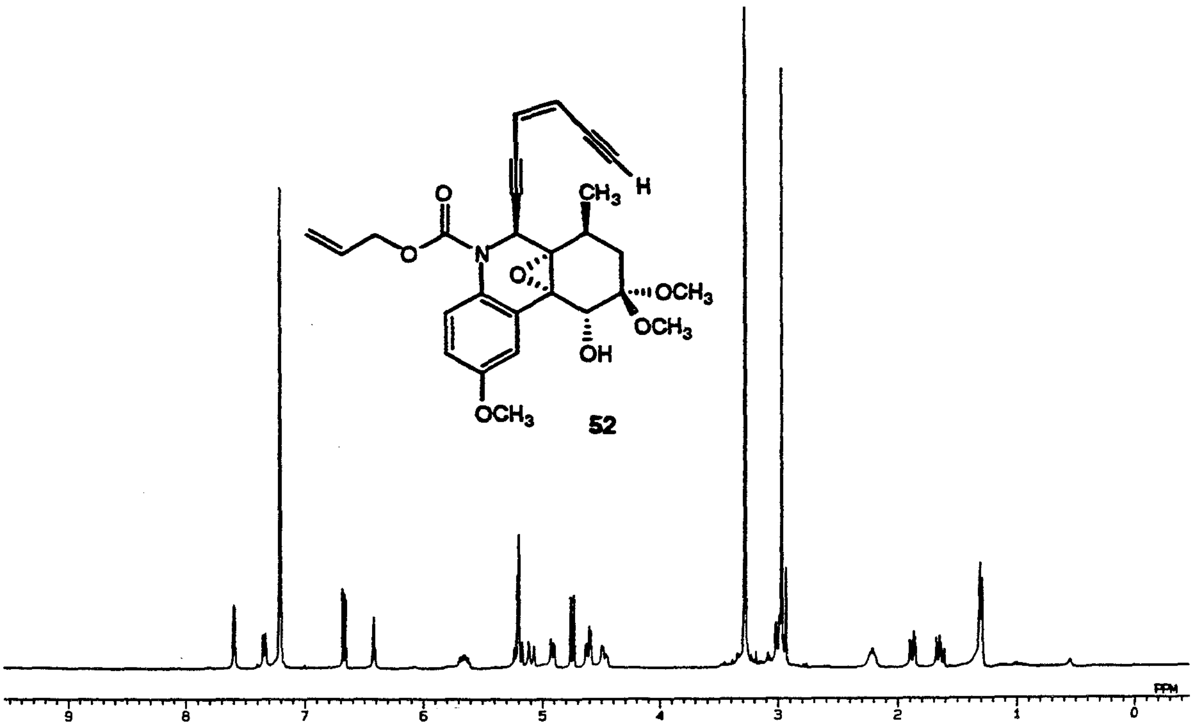
105.30
%T
60.44
4000
3500
3000
2500
2000
1500
1000
cm⁻¹

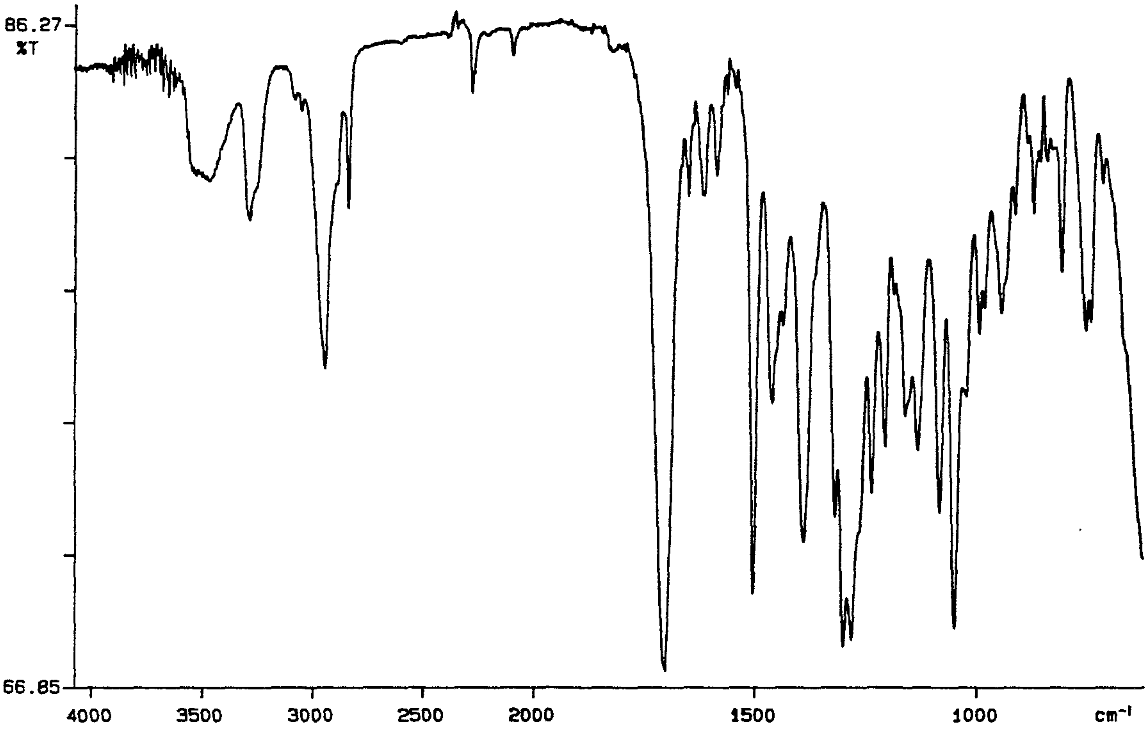


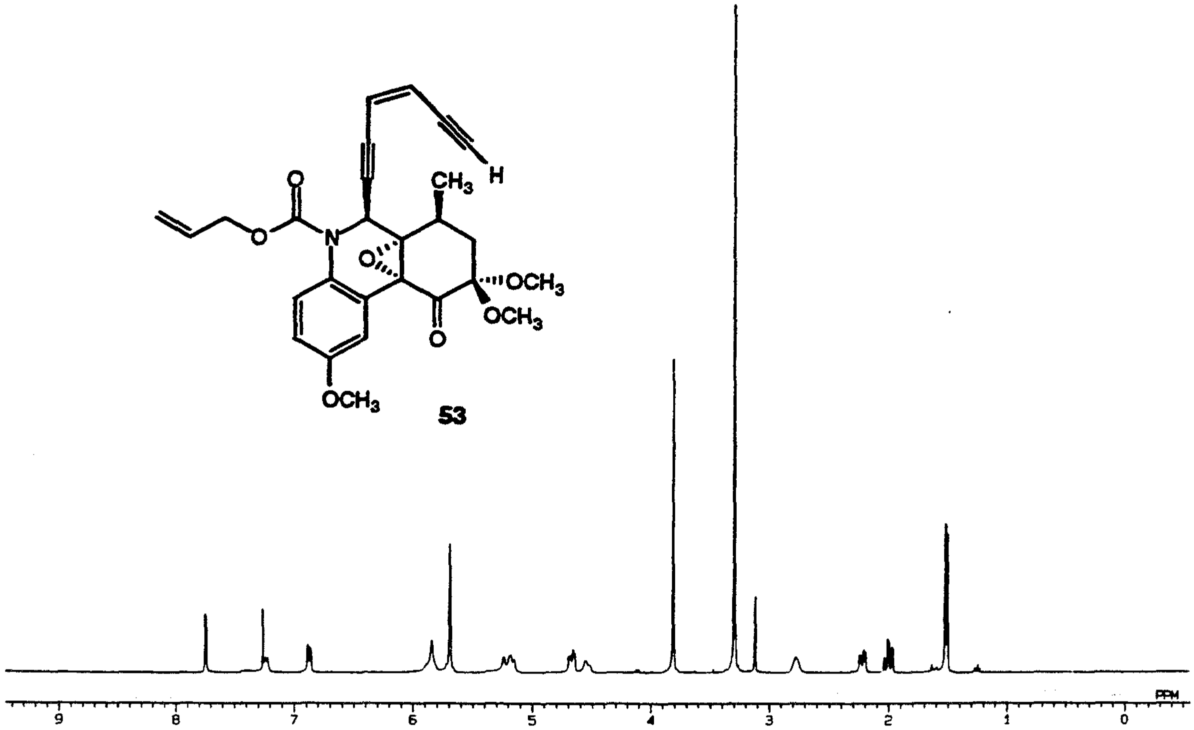
CH$_3$
TBS
O
N
O
OCH$_3$
OCH$_3$
OH
OCH$_3$
51
9
8
7
6
5
4
3
2
1
0
PPM

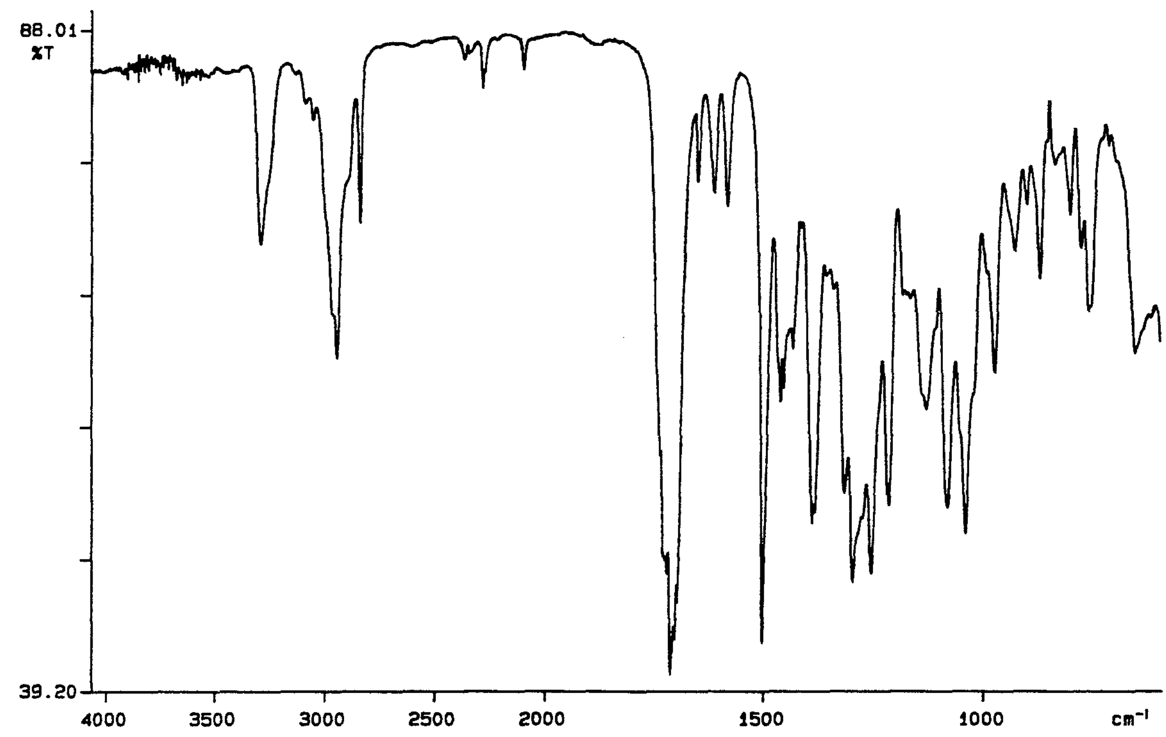


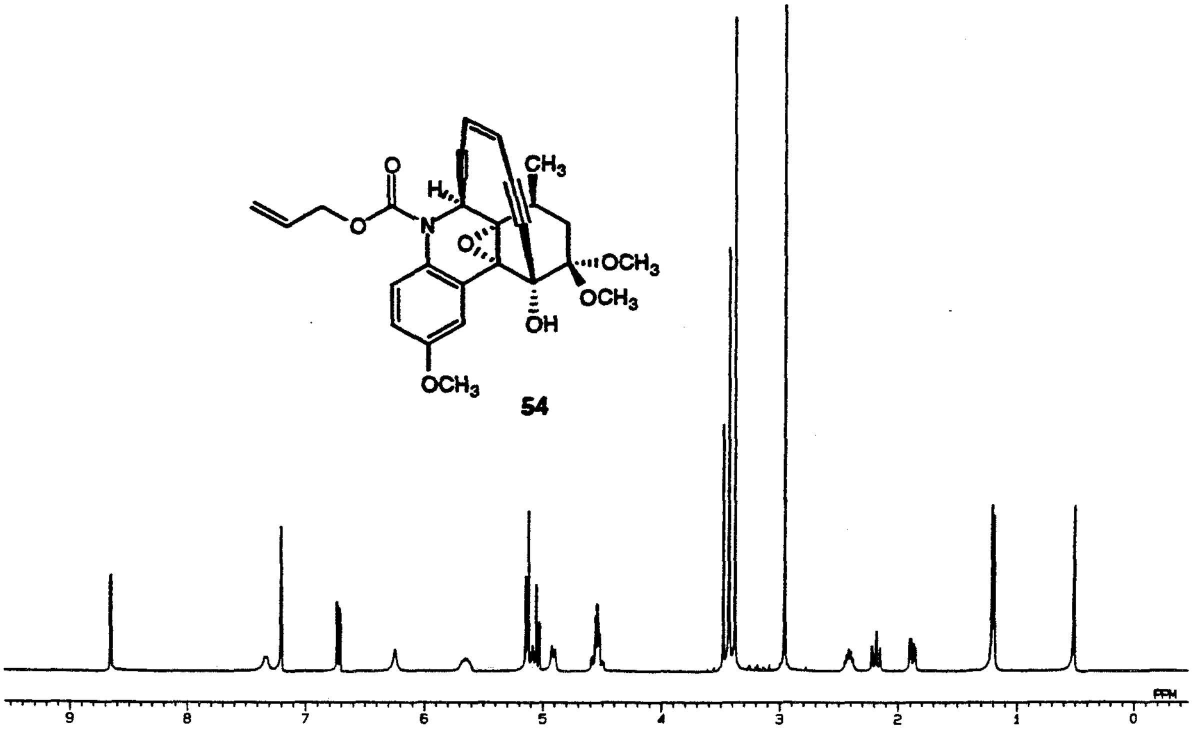
86.56
%T
28.70
4000
3500
3000
2500
2000
1500
1000
cm^{-1}

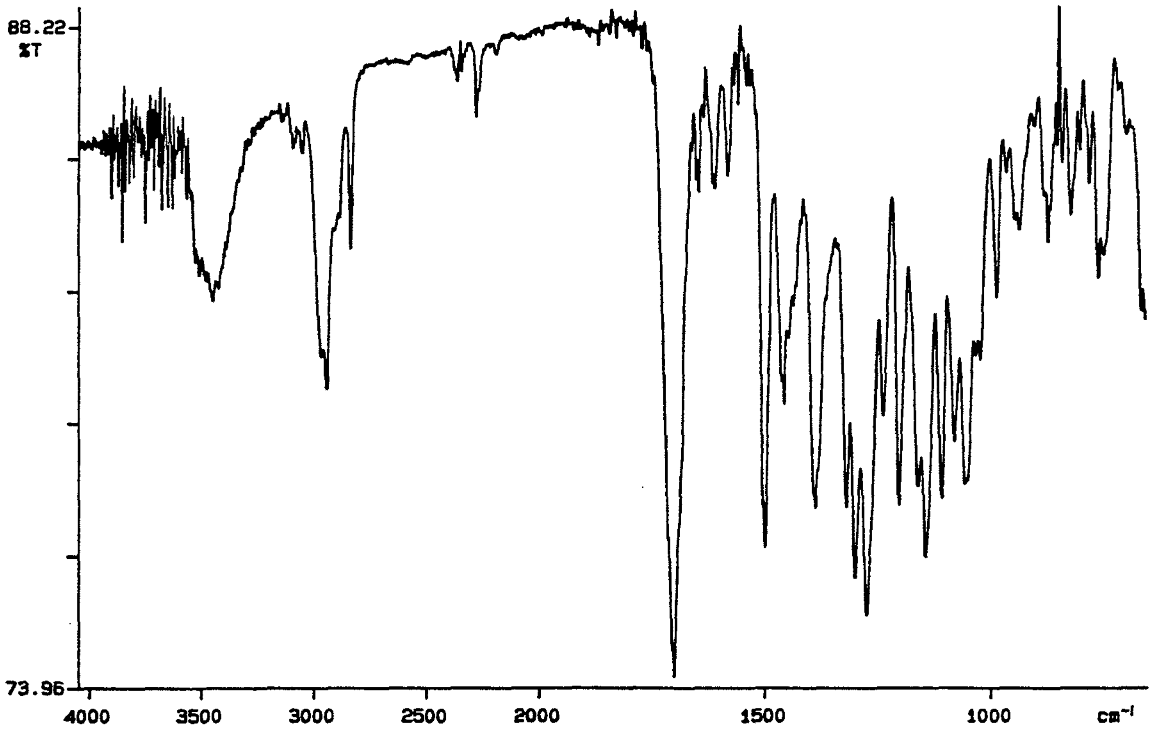

O
O
N
O
CH3
H
OCH3
OCH3
OH
OCH3
52
PPM
9
8
7
6
5
4
3
2
1
0

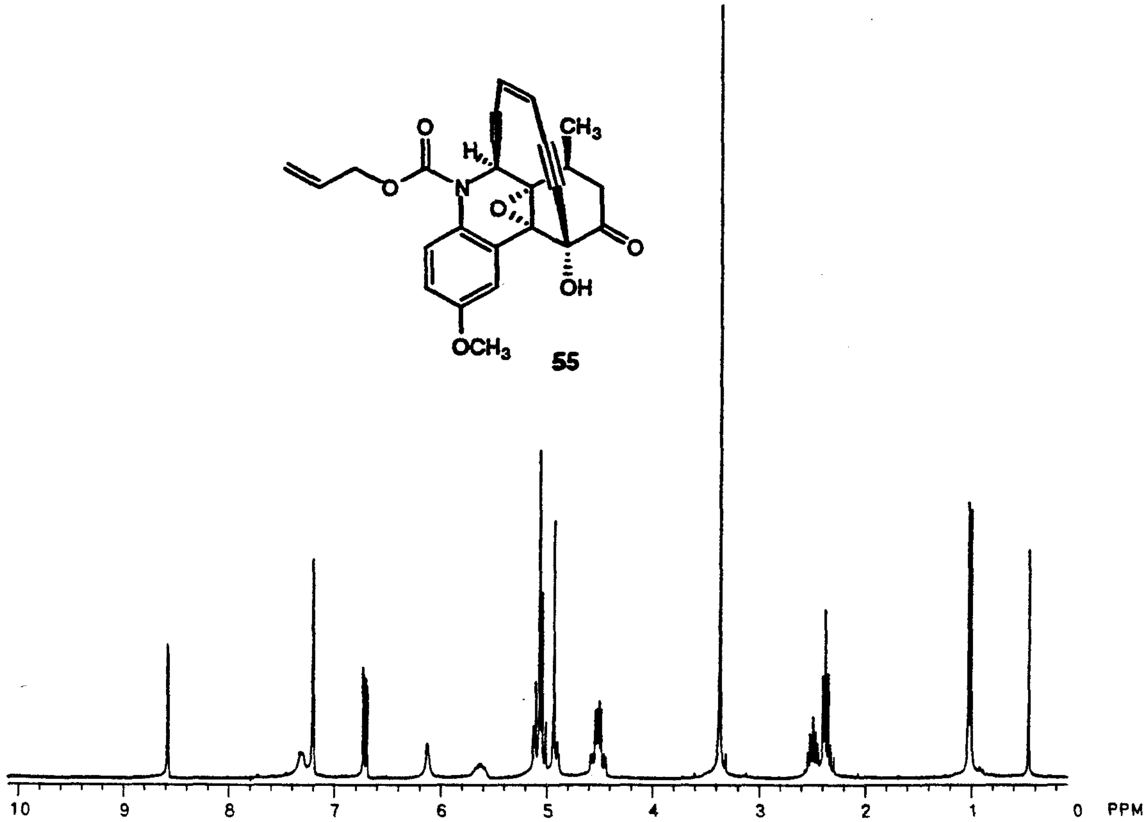

86.27
%T
66.85
4000
3500
3000
2500
2000
1500
1000
cm-1


H
CH3
O
N
OCH3
OCH3
O
OCH3
53
PPM
9
8
7
6
5
4
3
2
1
0

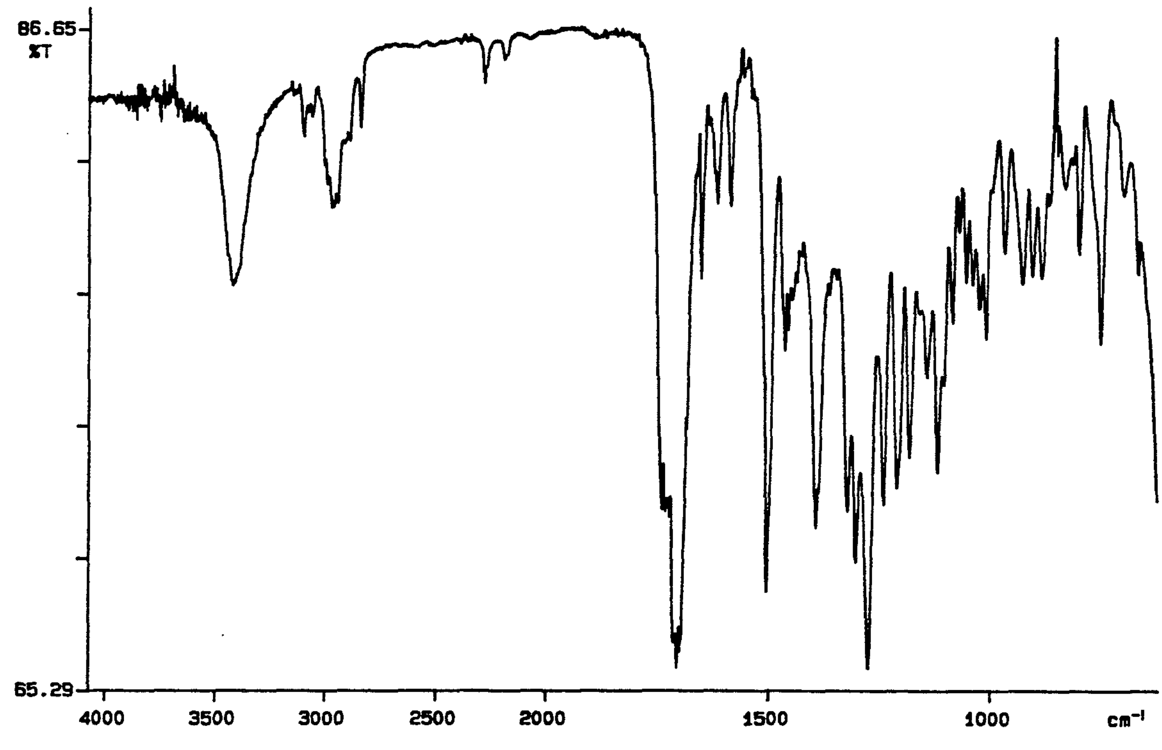

88.01
%T
39.20
4000
3500
3000
2500
2000
1500
1000
cm-1

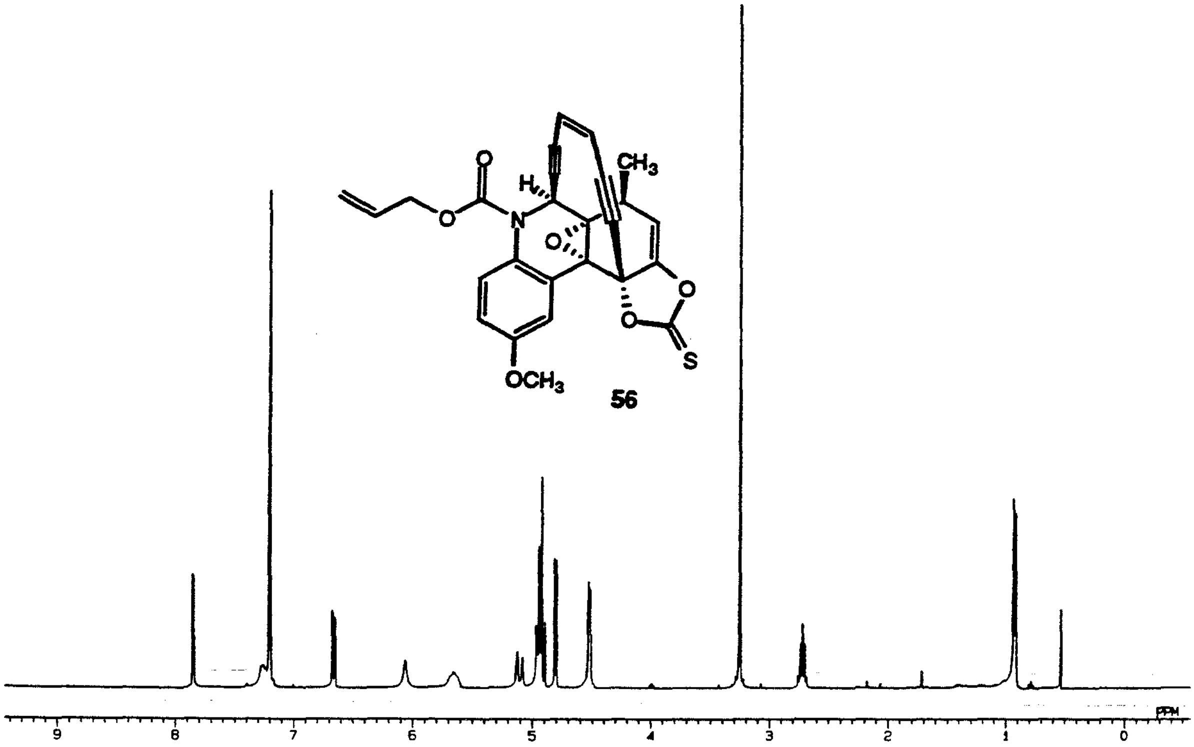

O
H
N
O
CH3
OCH3
OCH3
OH
OCH3
54
PPM
9
8
7
6
5
4
3
2
1
0


88.22
%T
73.96
4000
3500
3000
2500
2000
1500
1000
cm-1

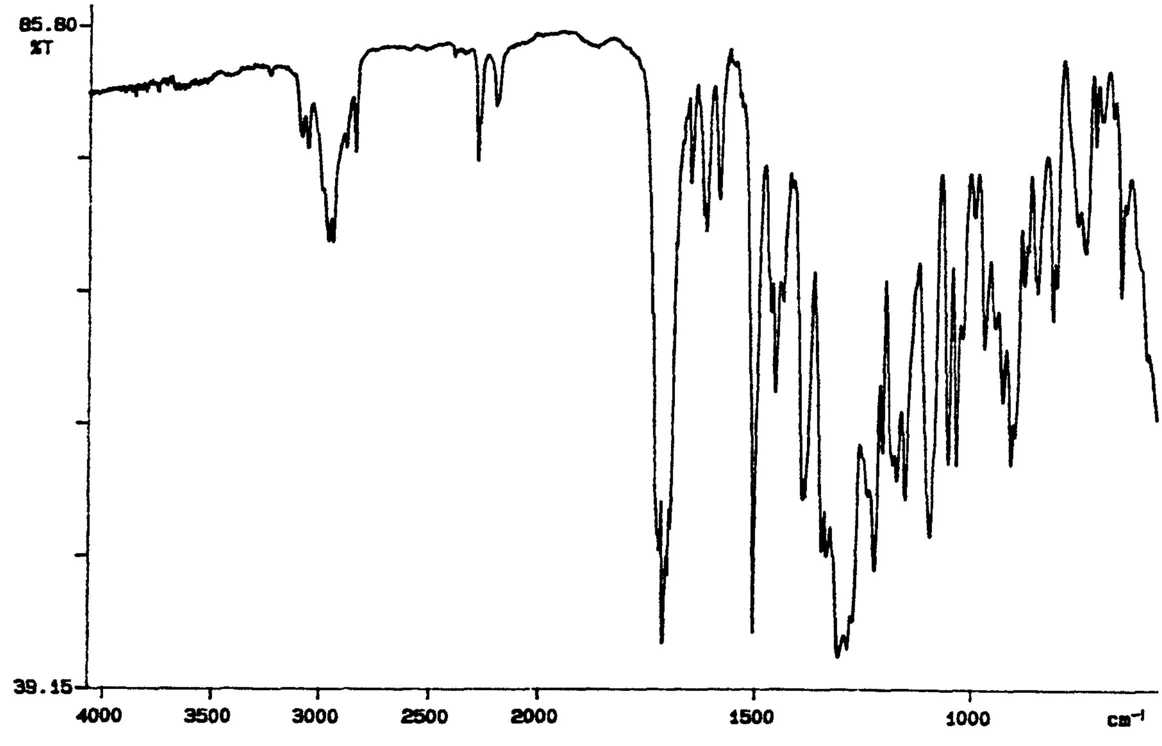

O
H
N
O
O
CH3
O
OH
OCH3
10
9
8
7
6
5
4
3
2
1
0
PPM

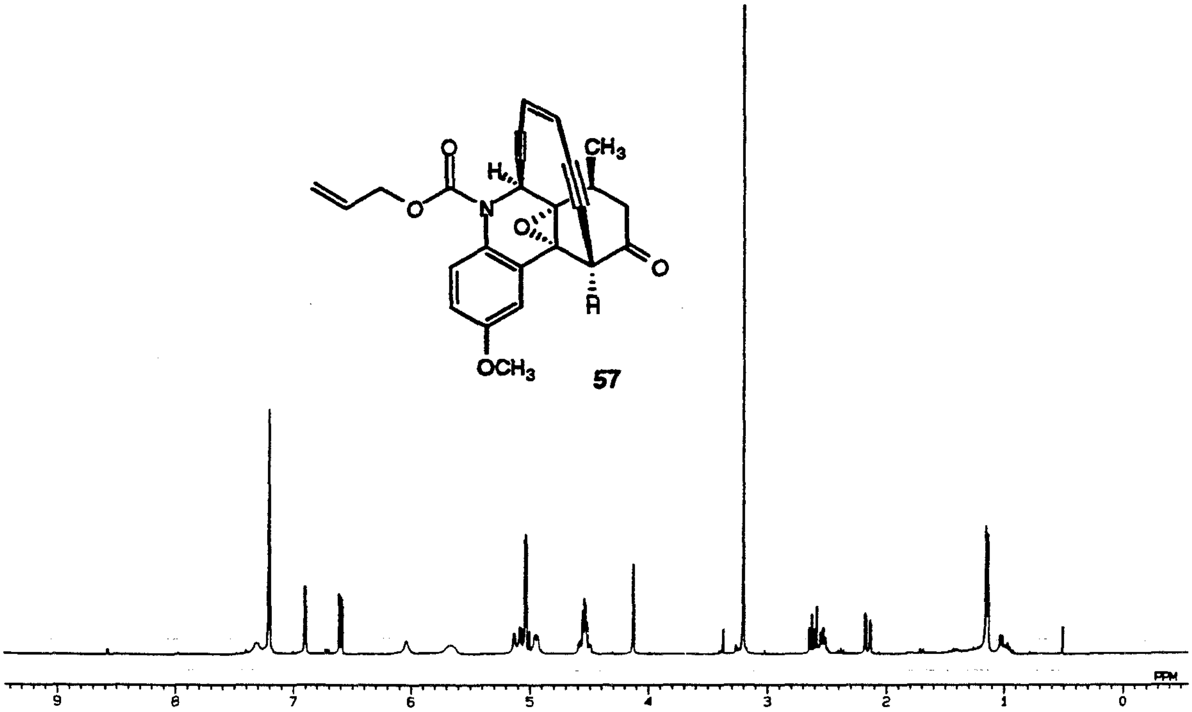
55


86.65
%T
65.29
4000
3500
3000
2500
2000
1500
1000
cm-1

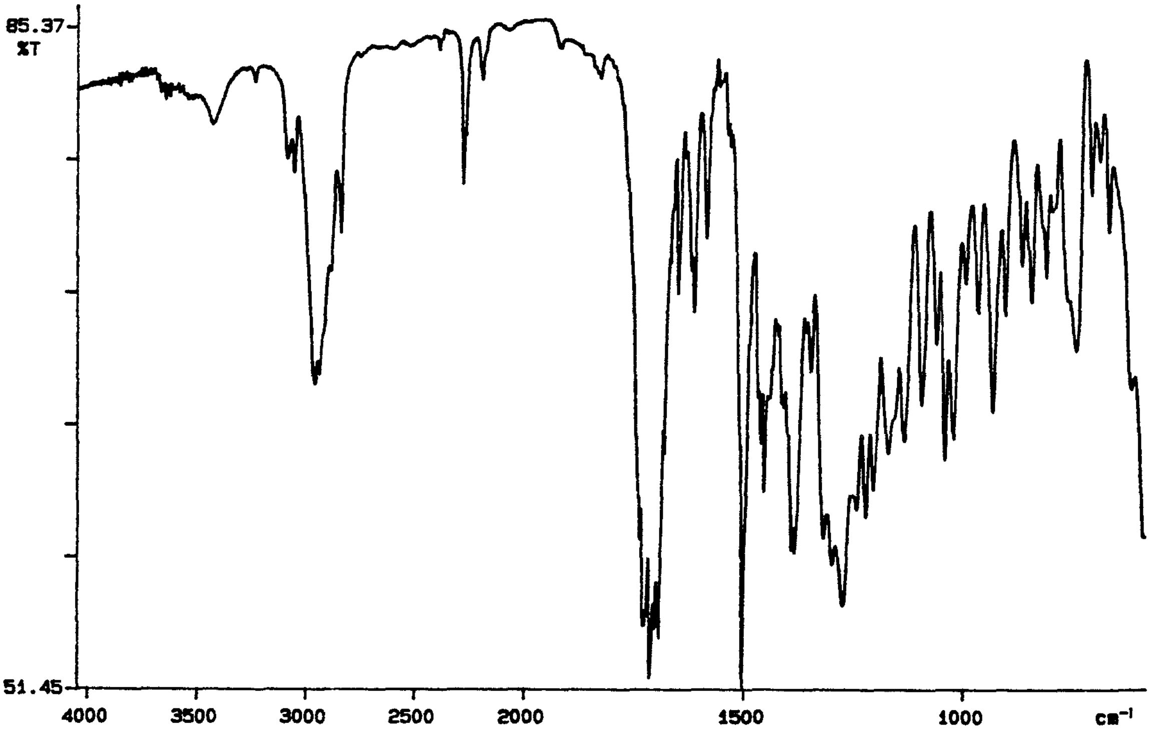

CH3
H
N
O
O
O
O
S
OCH3
9
8
7
6
5
4
3
2
1
0
PPM

56

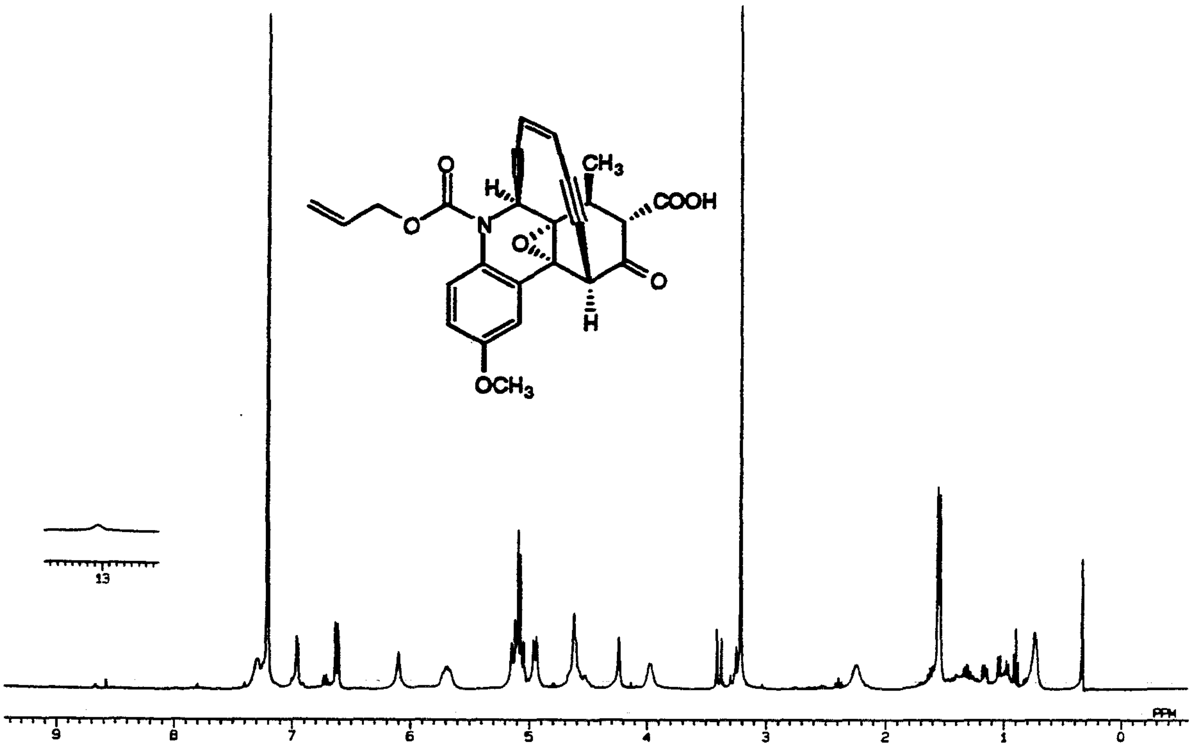

85.80
%T
39.15
4000
3500
3000
2500
2000
1500
1000
cm-1

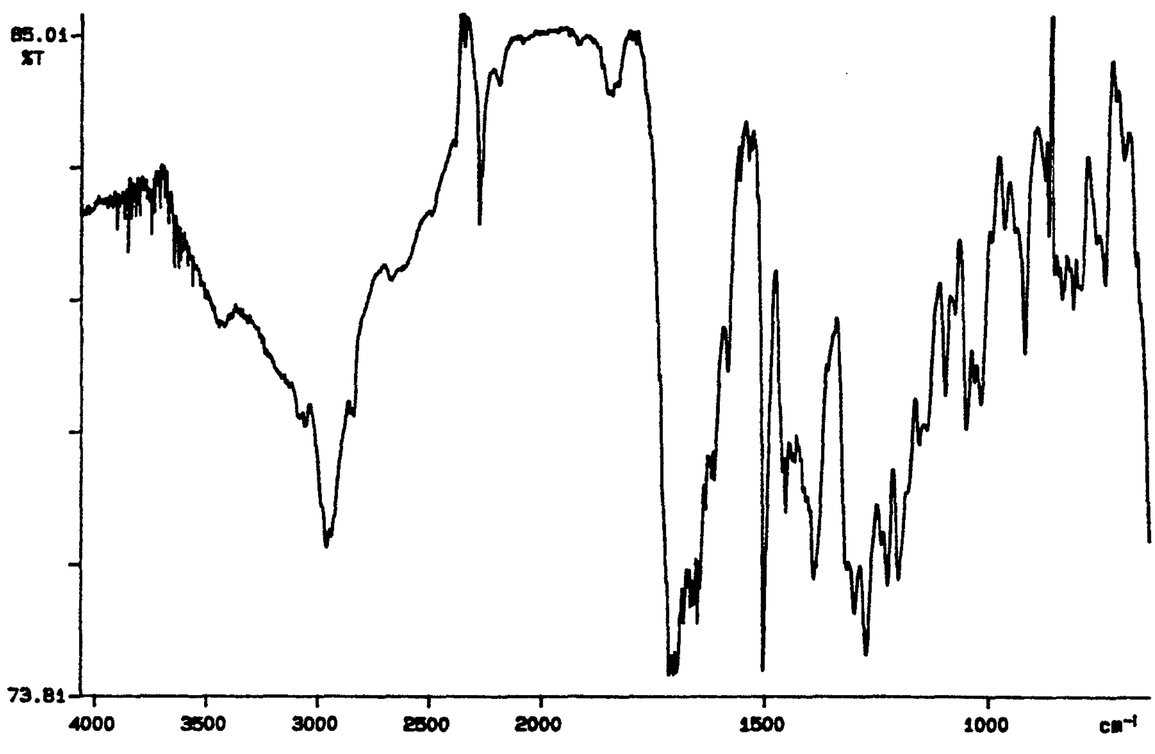


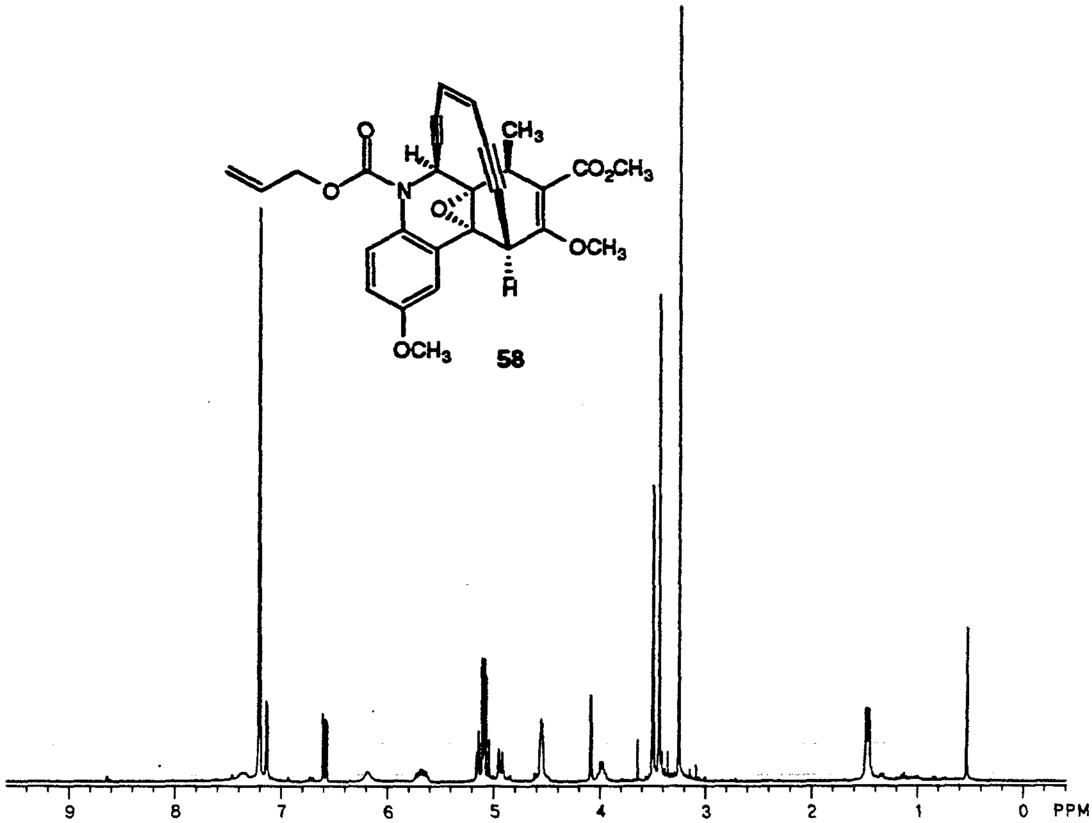
CH3
H
N
O
O
O
O
H
OCH3
57
9
8
7
6
5
4
3
2
1
0
PPM



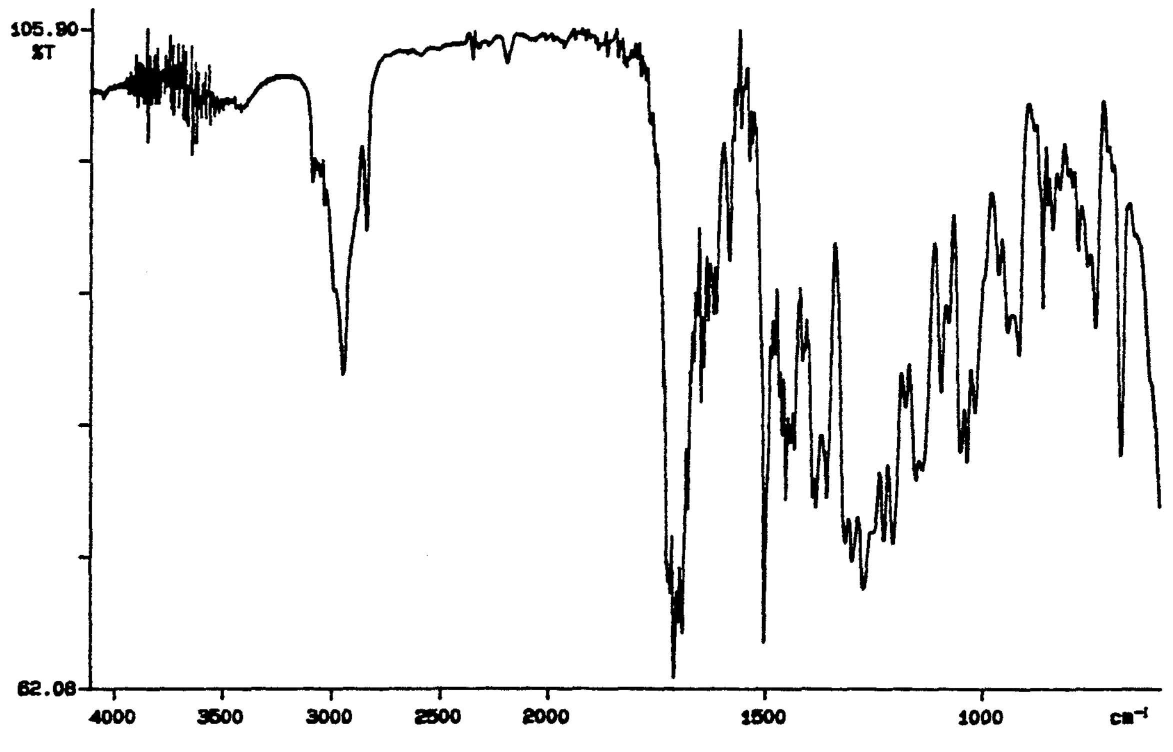
85.37
%T
51.45
4000
3500
3000
2500
2000
1500
1000
cm-1

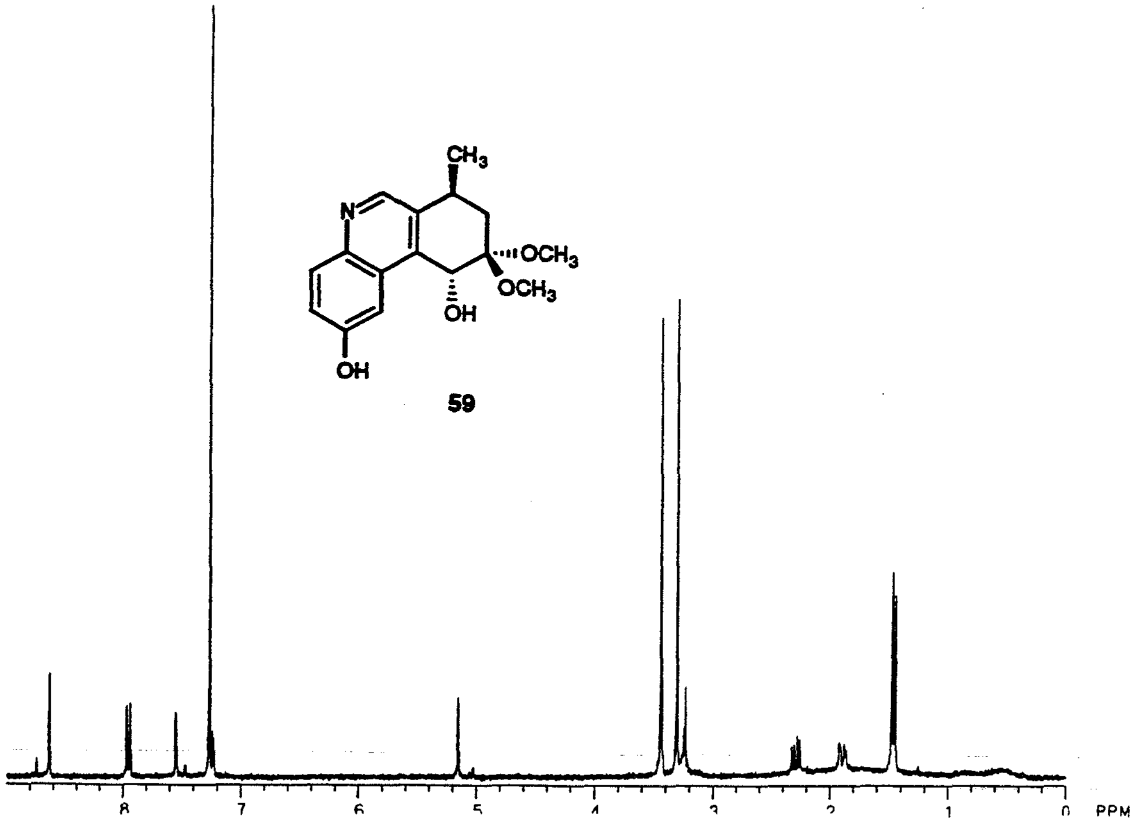

CH3
COOH
N
OCH3
13
PPM
9
8
7
6
5
4
3
2
1
0

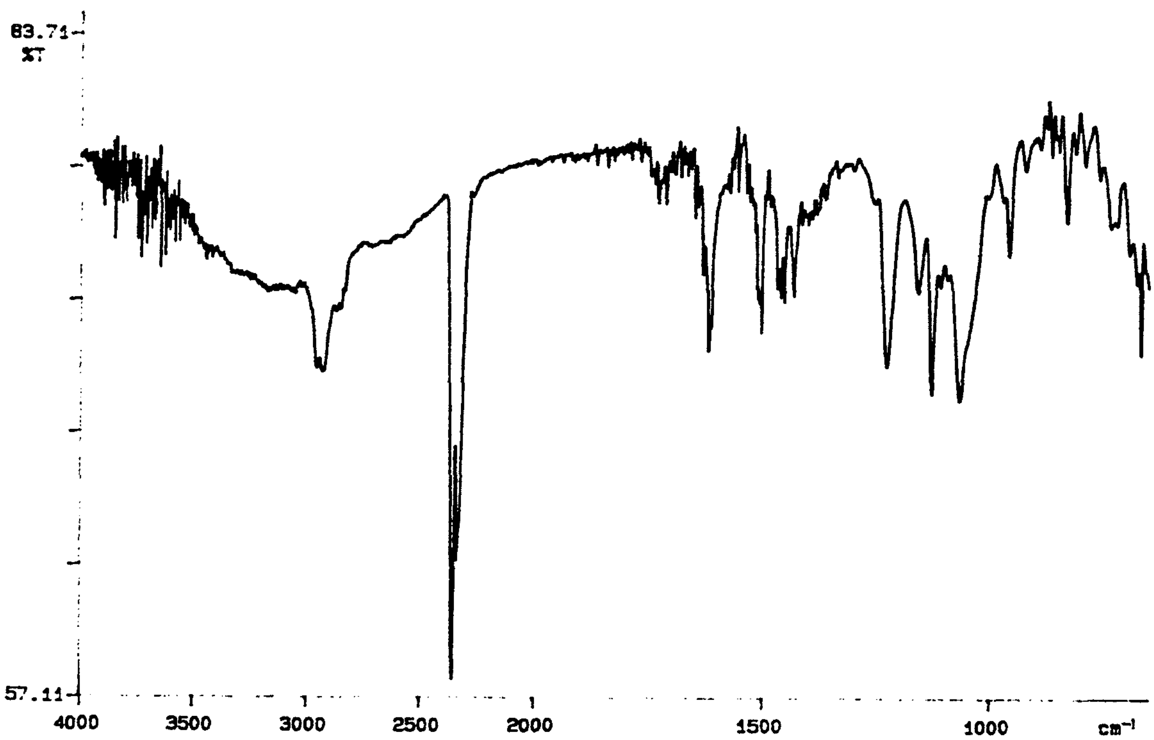

85.01
%T
73.81
4000
3500
3000
2500
2000
1500
1000
cm-1

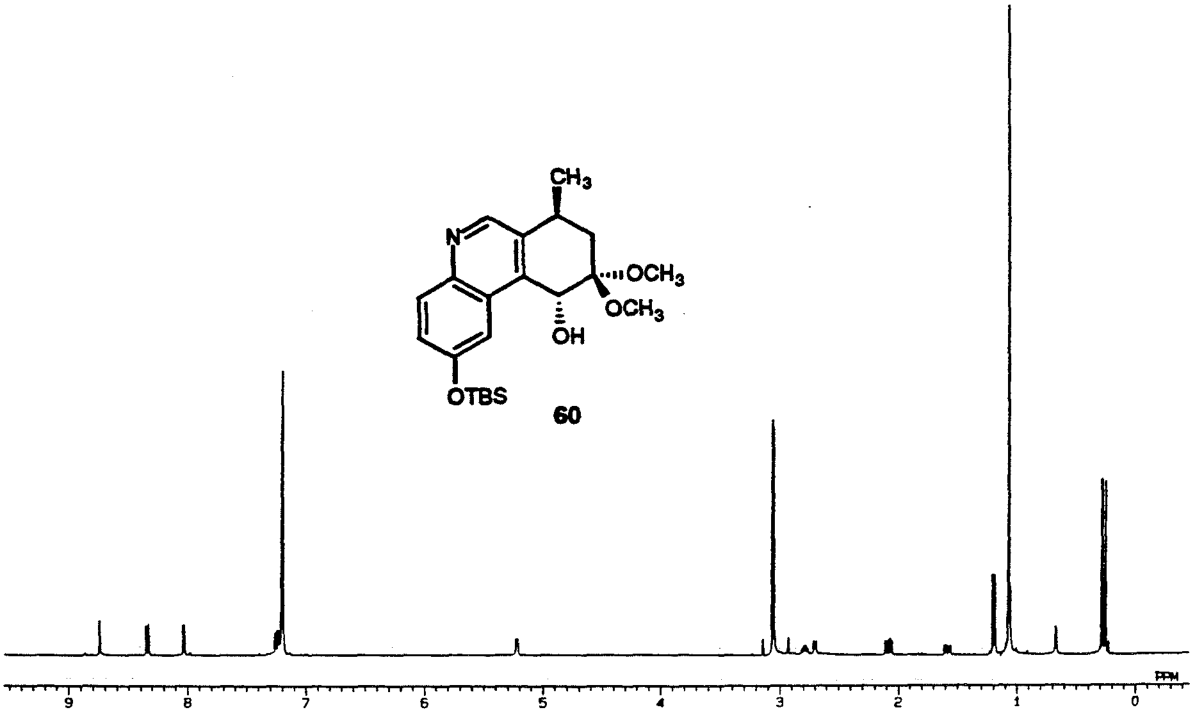

CO2CH3
CH3
OCH3
OCH3
9 8 7 6 5 4 3 2 1 0 PPM

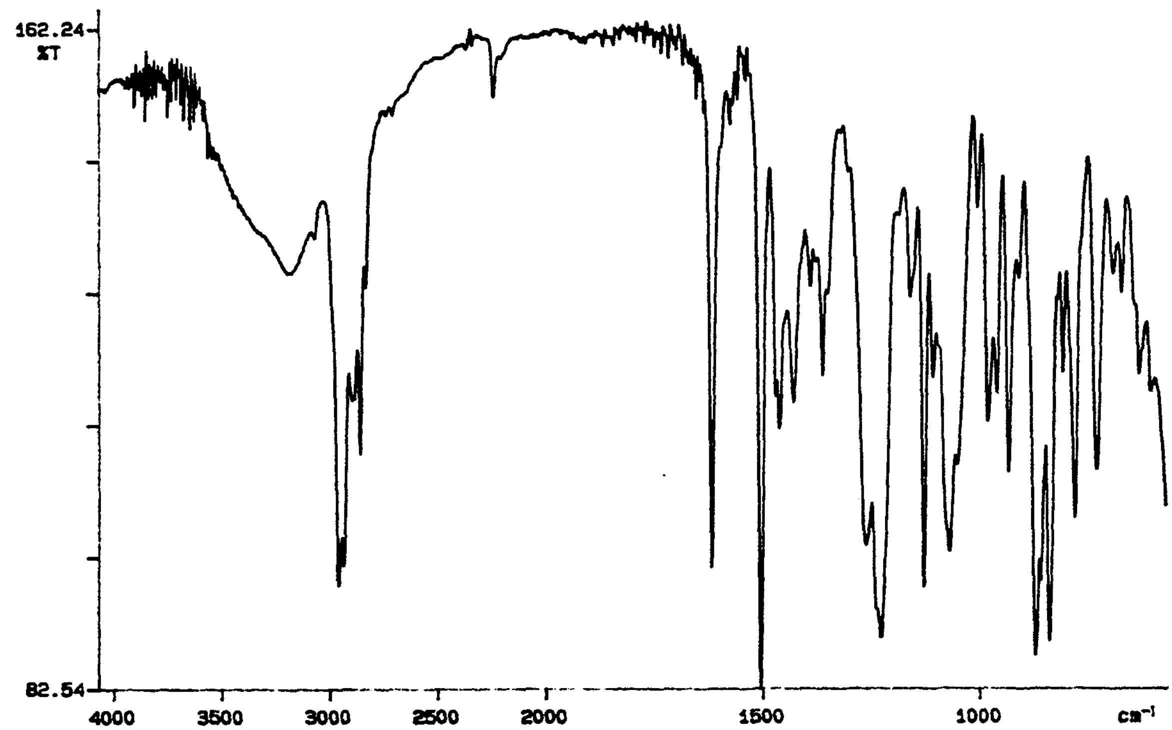
58

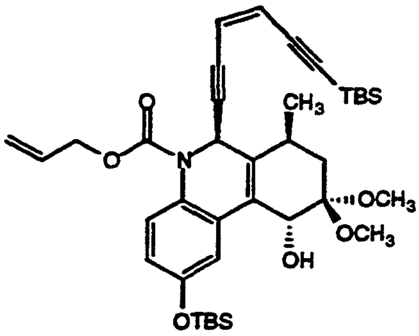

105.90
%T
62.08
4000 3500 3000 2500 2000 1500 1000 cm-1


CH3
N
OCH3
OCH3
OH
OH
59
8
7
6
5
4
3
2
1
0
PPM


83.71
%T
57.11
4000
3500
3000
2500
2000
1500
1000
cm-1

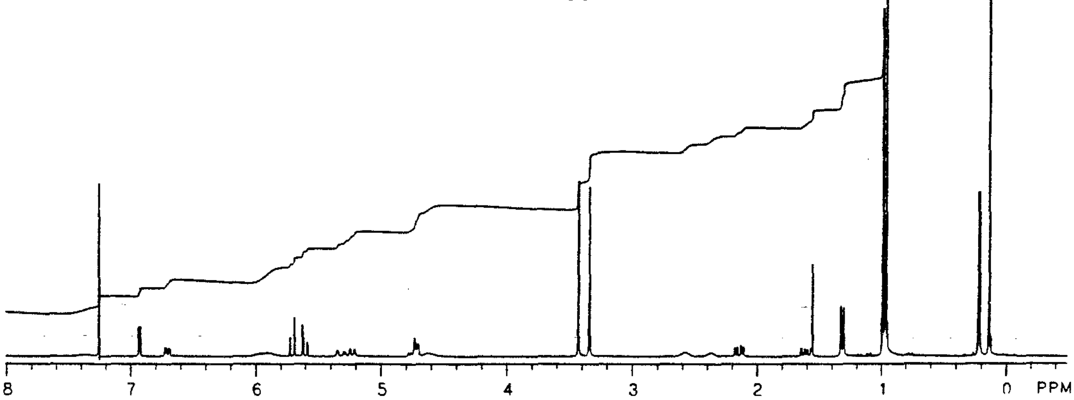

CH3
N
OCH3
OCH3
OH
OTBS
60
PPM
9
8
7
6
5
4
3
2
1
0


162.24
%T
82.54
4000
3500
3000
2500
2000
1500
1000
cm-1

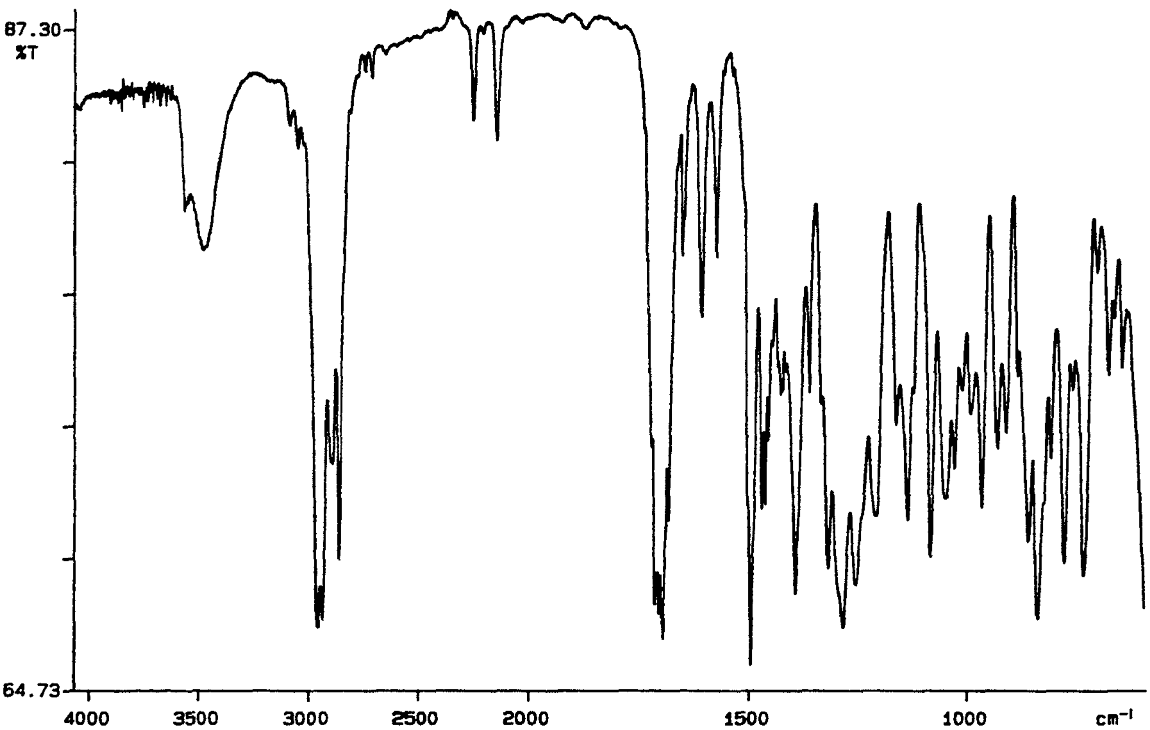


CH3
TBS
N
O
OCH3
OCH3
OH
OTBS

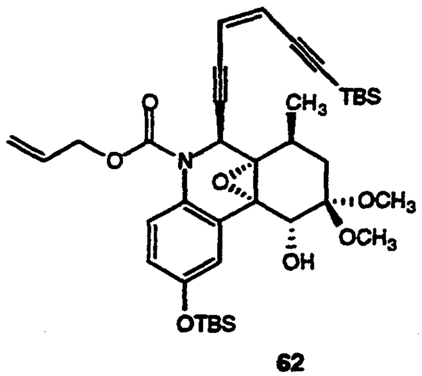
61



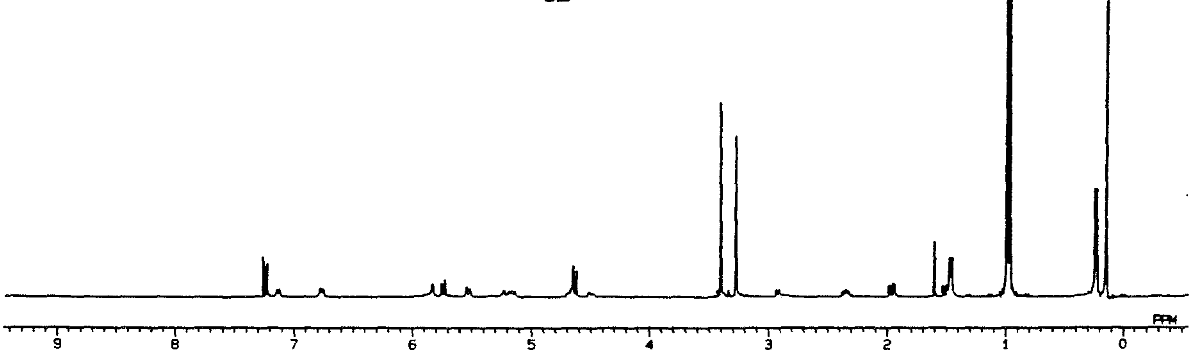
8
7
6
5
4
3
2
1
0
PPM

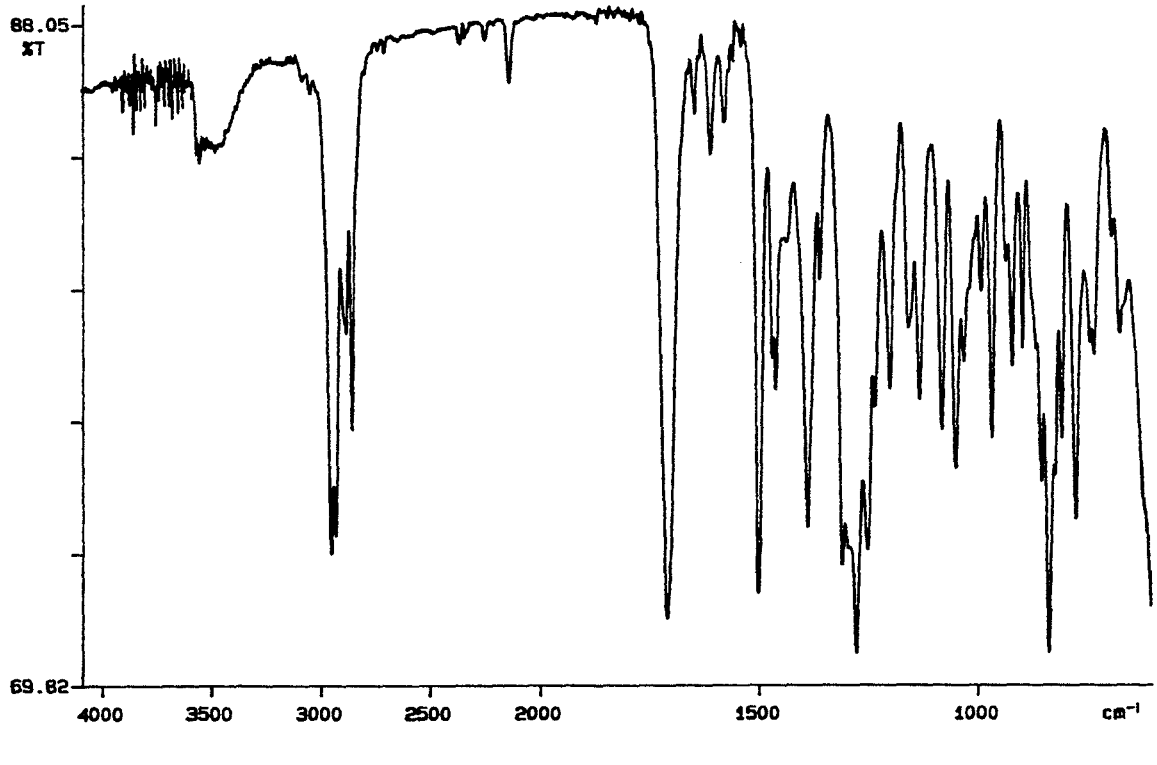


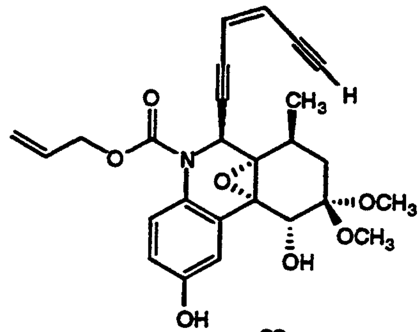
87.30
%T
64.73
4000
3500
3000
2500
2000
1500
1000
cm-1


TBS
CH$_3$
N
O
OCH$_3$
OCH$_3$
OH
OTBS

62

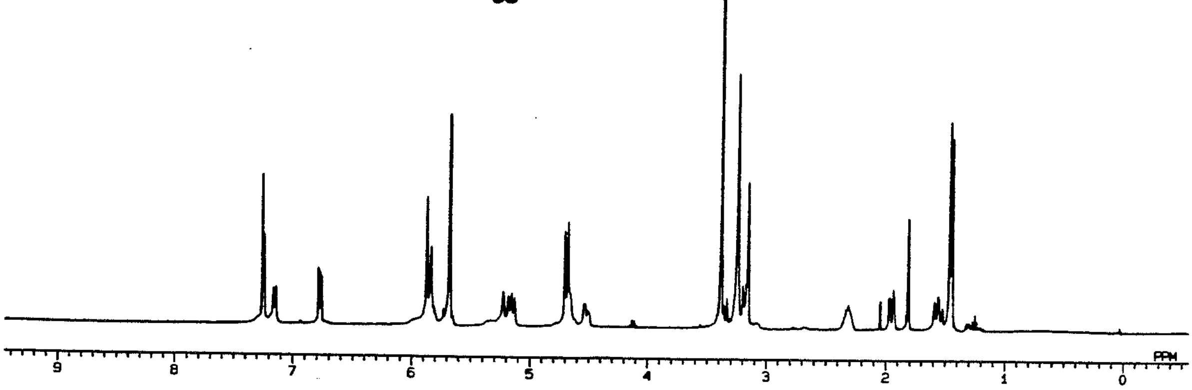

PPM
9
8
7
6
5
4
3
2
1
0


88.05
%T
69.82
4000
3500
3000
2500
2000
1500
1000
cm^{-1}

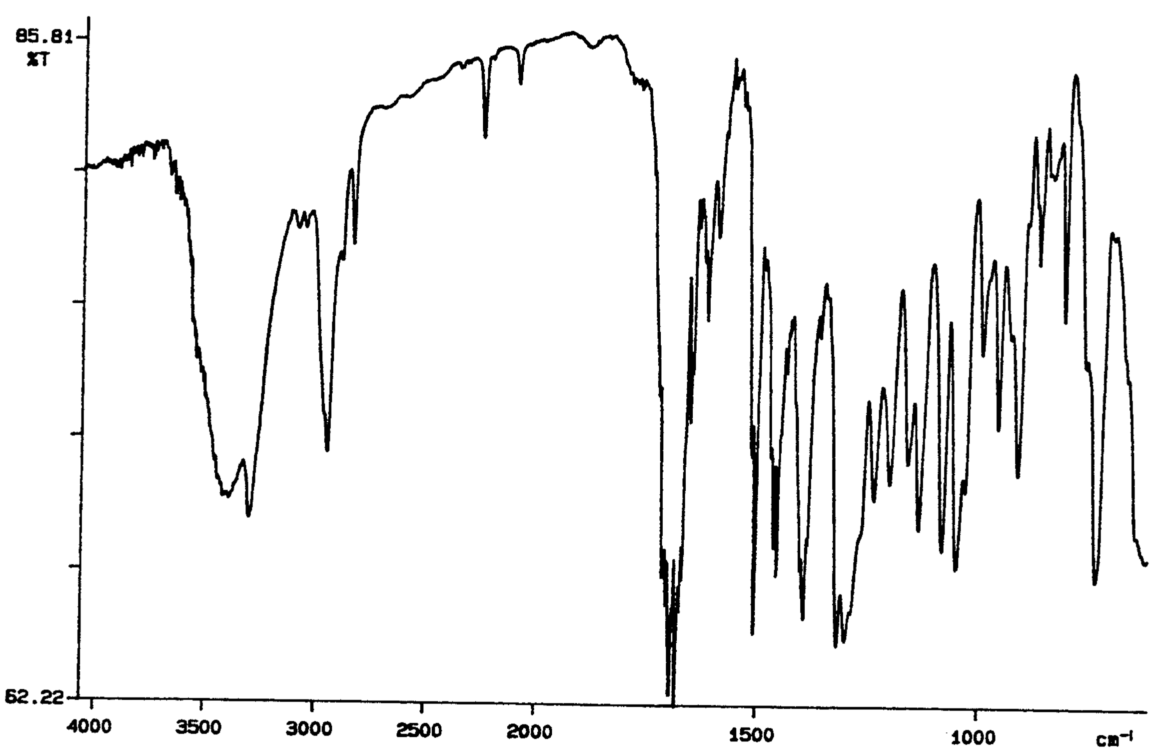


CH3
H
O
O
N
O
OCH3
OCH3
OH
OH

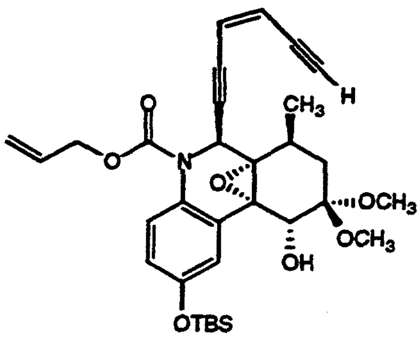
63



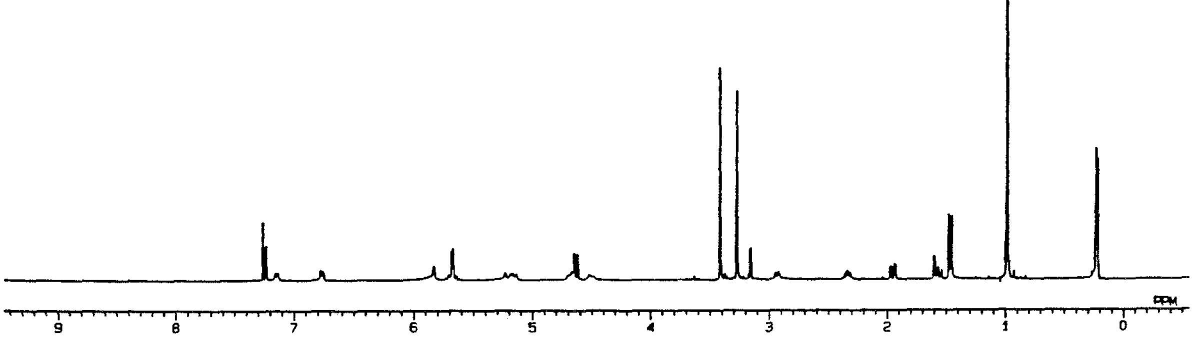
9
8
7
6
5
4
3
2
1
0
PPM

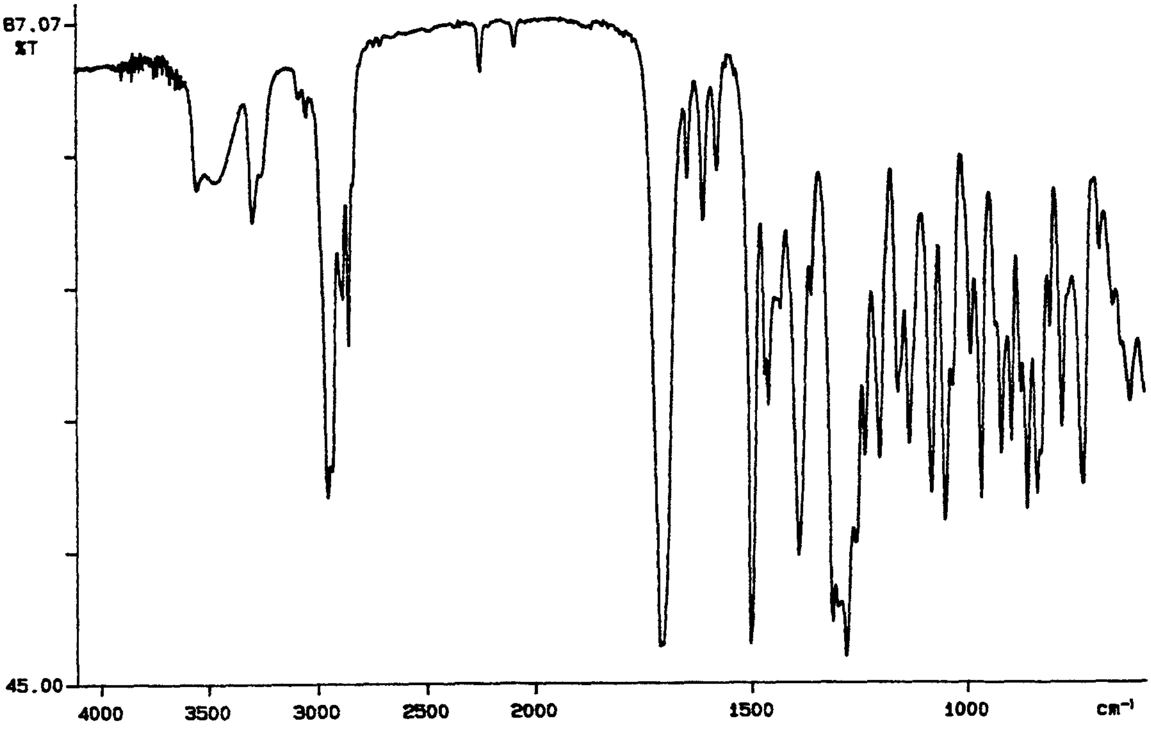


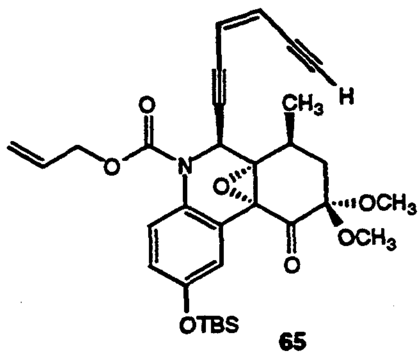
85.81
%T
62.22
4000
3500
3000
2500
2000
1500
1000
cm-1


O
N
O
CH3
H
OCH3
OCH3
OH
OTBS

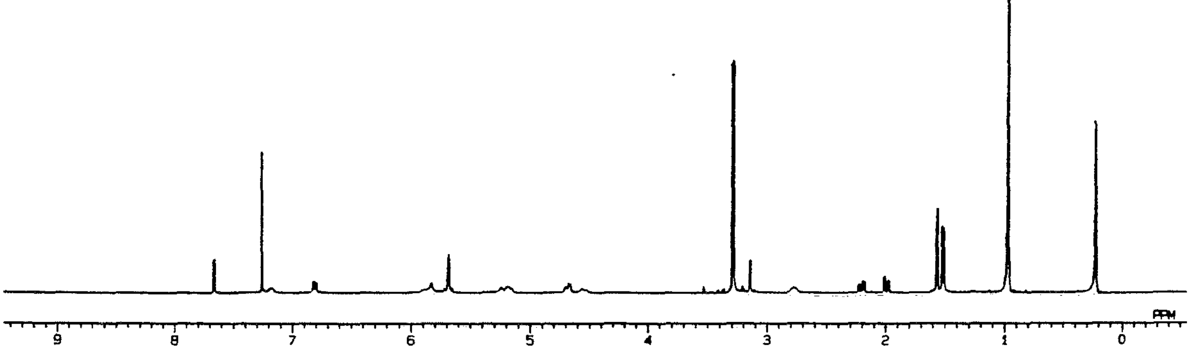
64

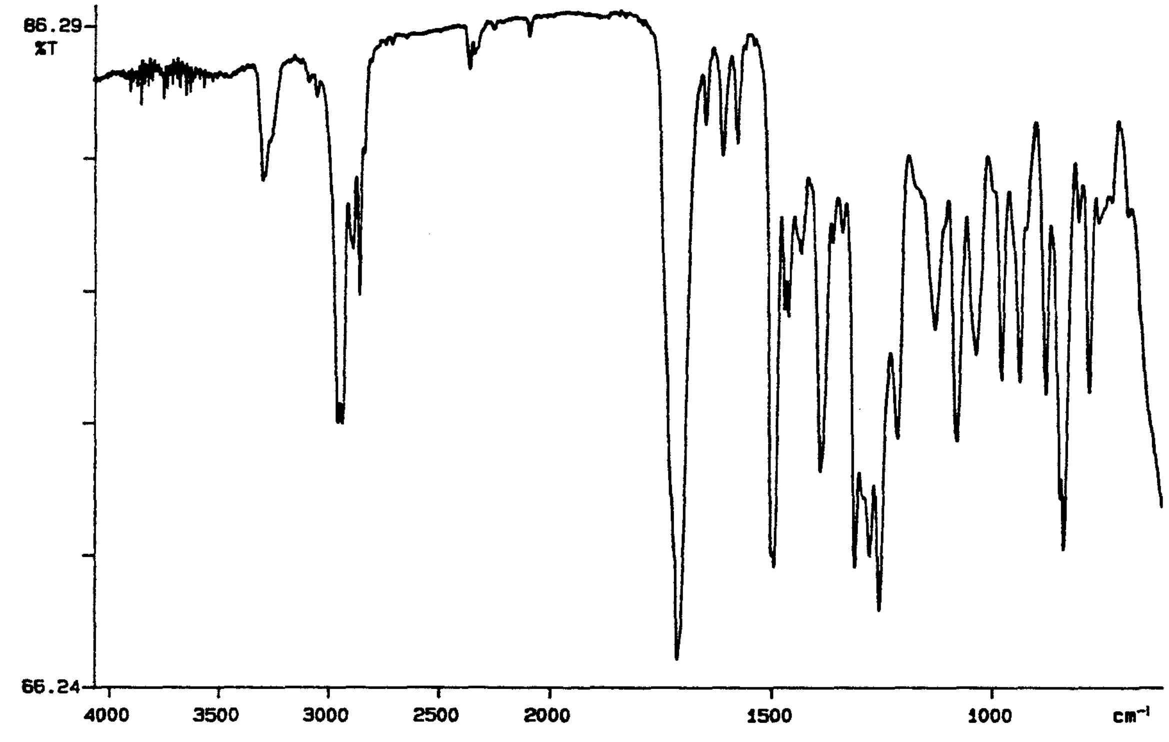

9
8
7
6
5
4
3
2
1
0
PPM

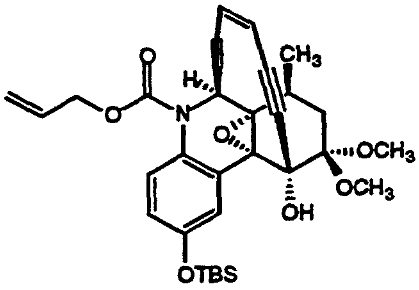

87.07
%T
45.00
4000
3500
3000
2500
2000
1500
1000
cm⁻¹


CH3
H
O
N
O
OCH3
OCH3
O
OTBS

65

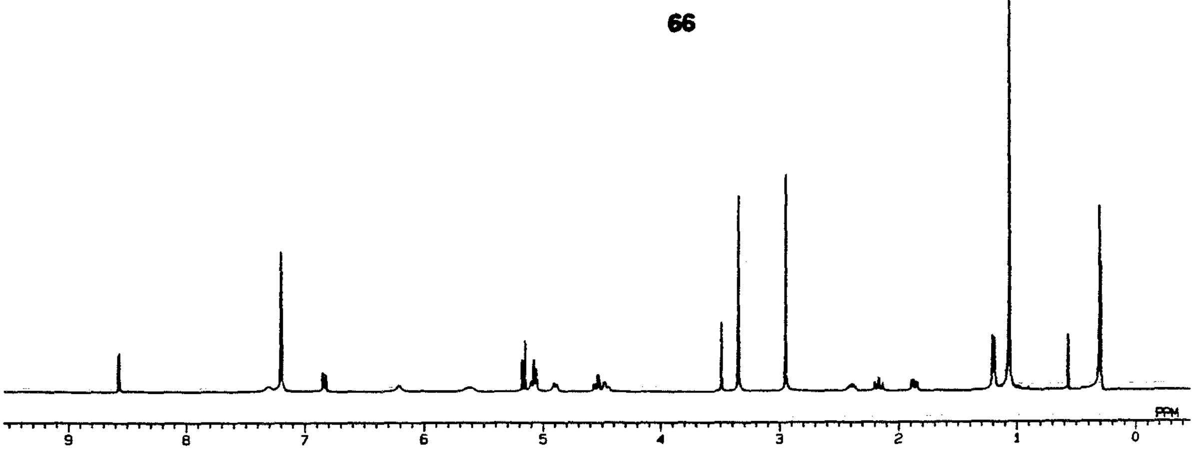

PPM
9
8
7
6
5
4
3
2
1
0


86.29
%T
66.24
4000
3500
3000
2500
2000
1500
1000
cm-1

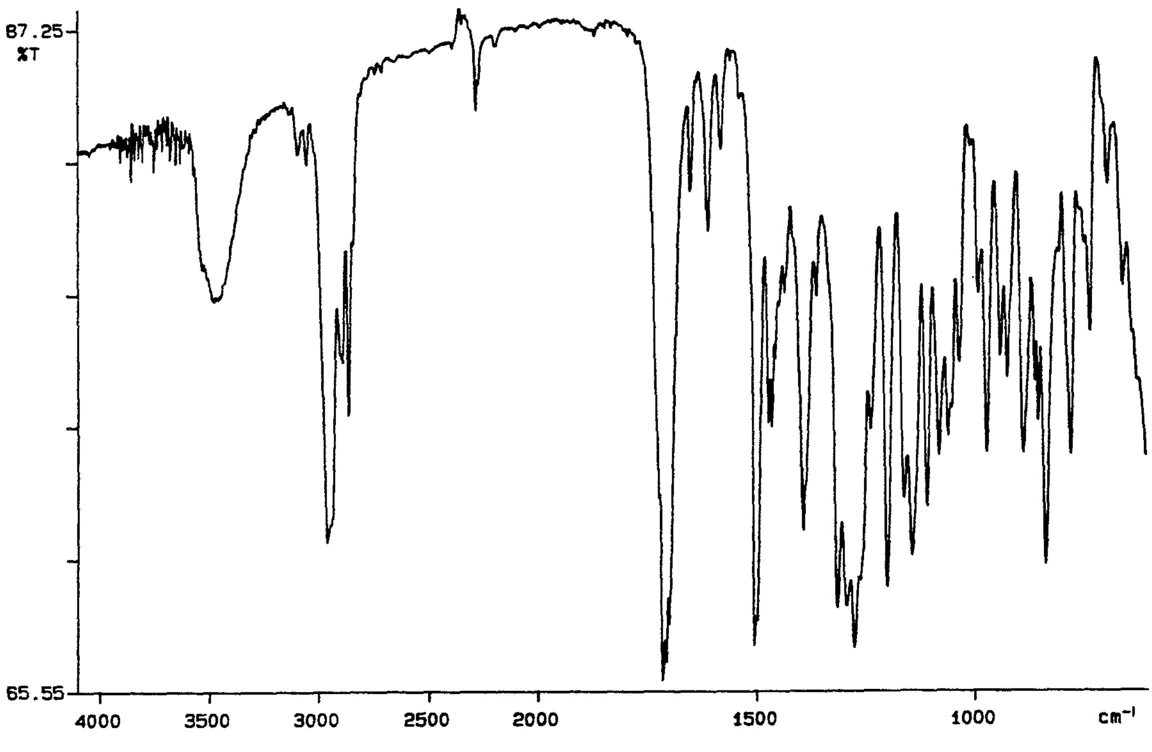


H
CH3
O
N
O
O
OCH3
OCH3
OH
OTBS

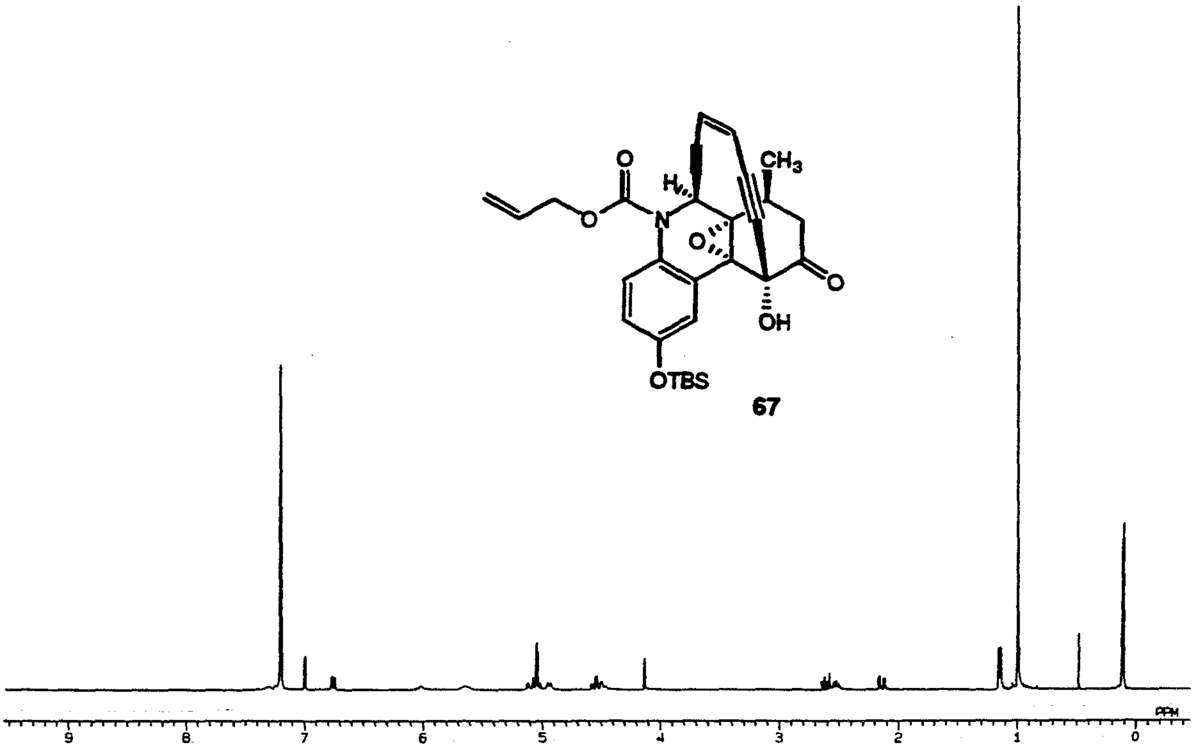
66



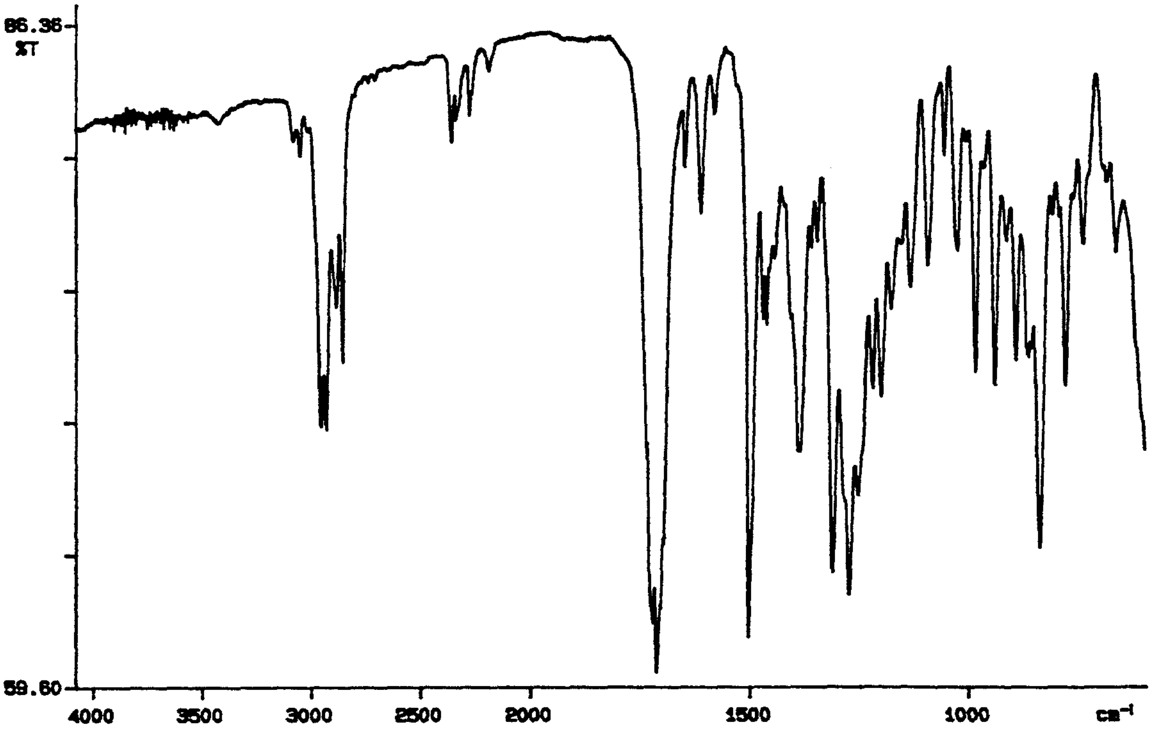
PPM
9
8
7
6
5
4
3
2
1
0



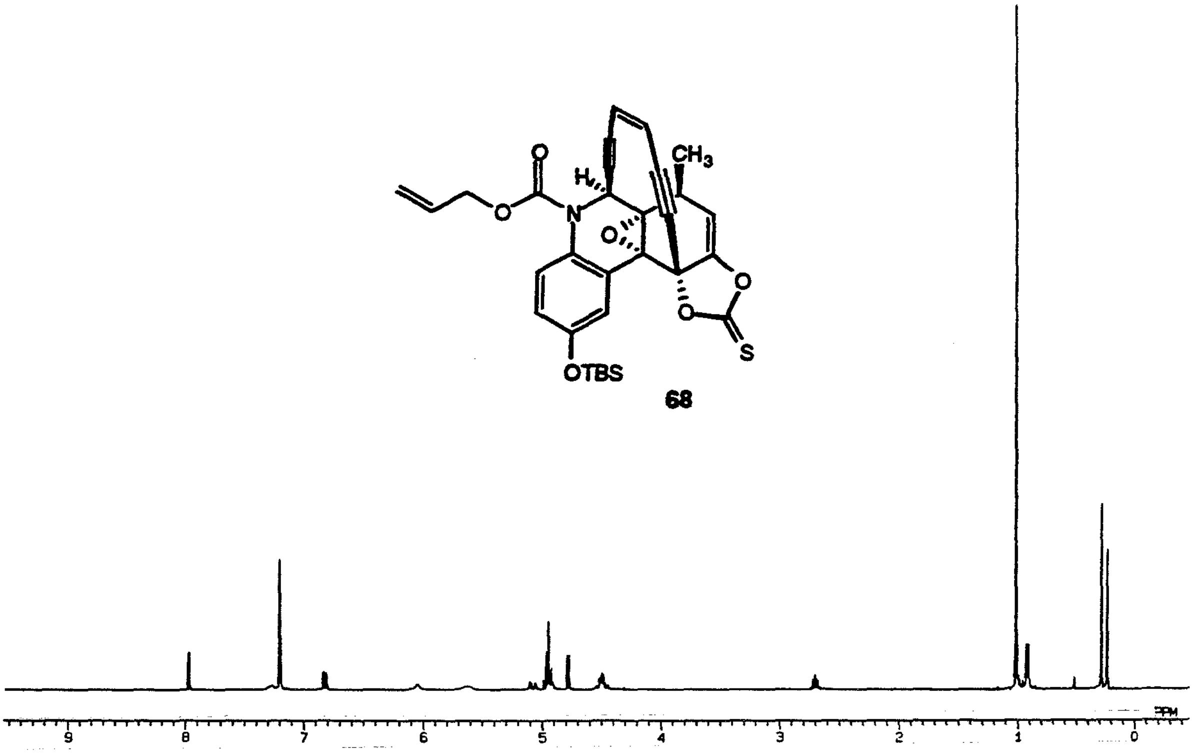
87.25
%T
65.55
4000
3500
3000
2500
2000
1500
1000
cm⁻¹

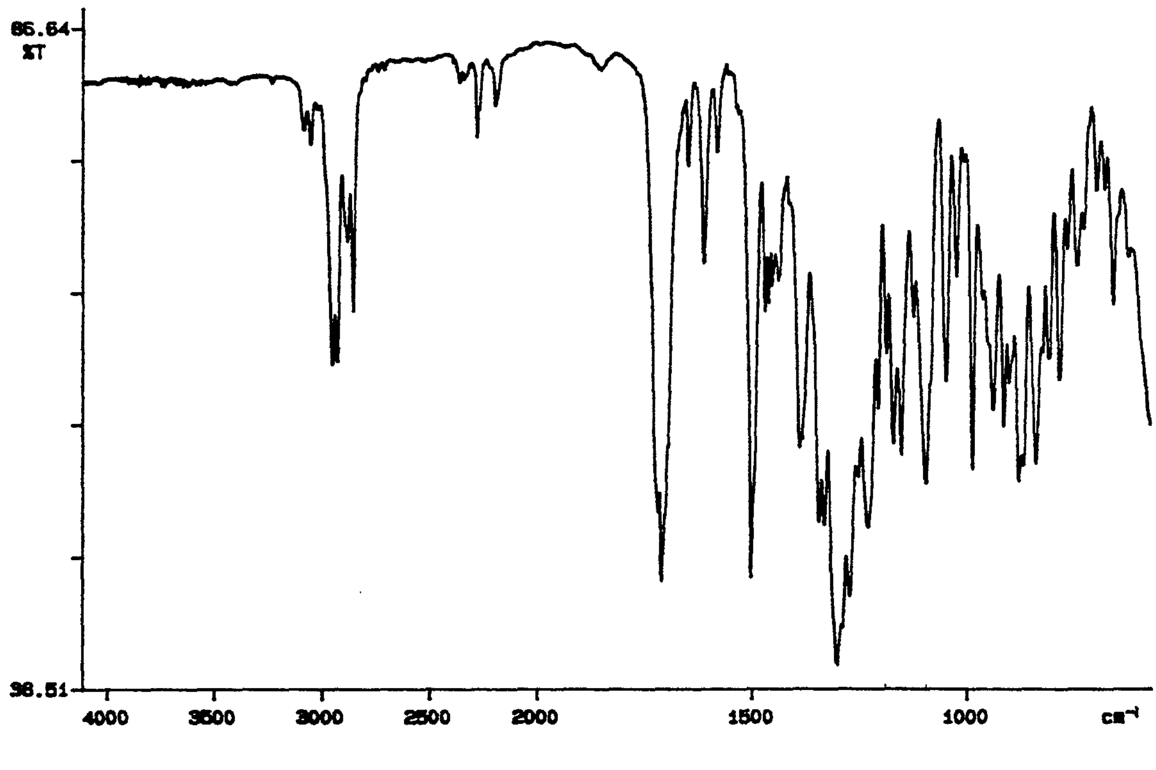


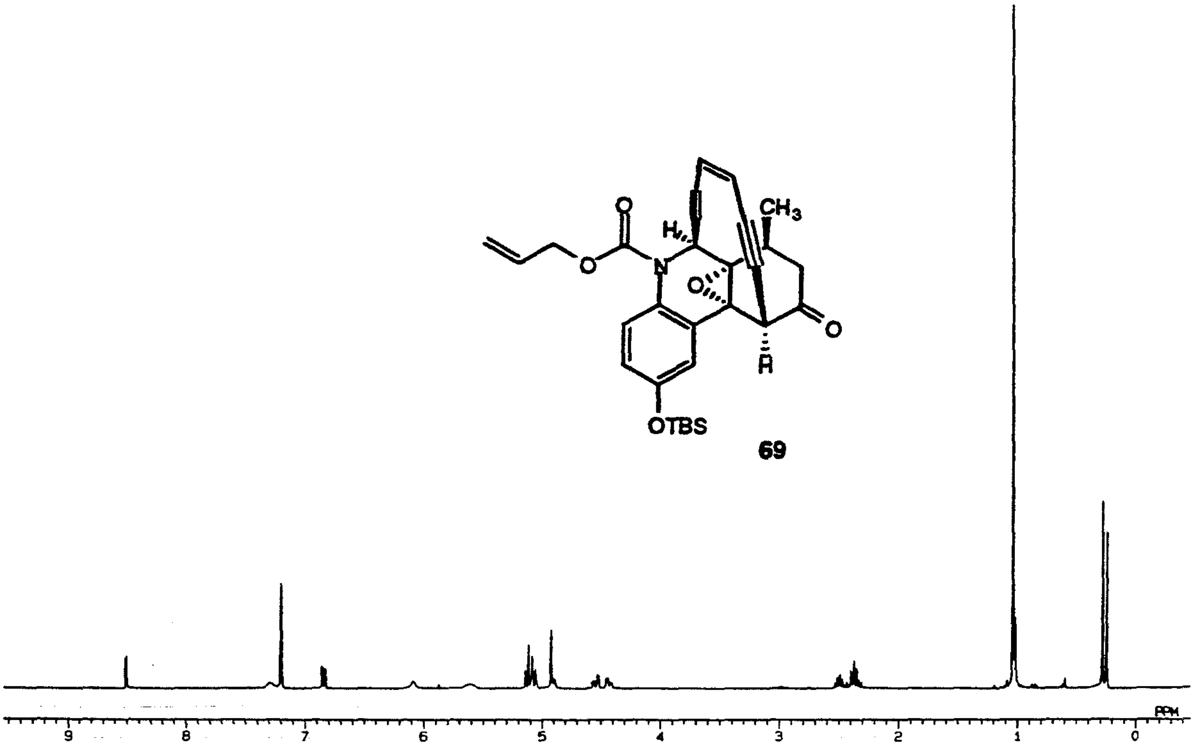
O
H
CH3
N
O
O
OH
OTBS
67
PPM
9
8
7
6
5
4
3
2
1
0



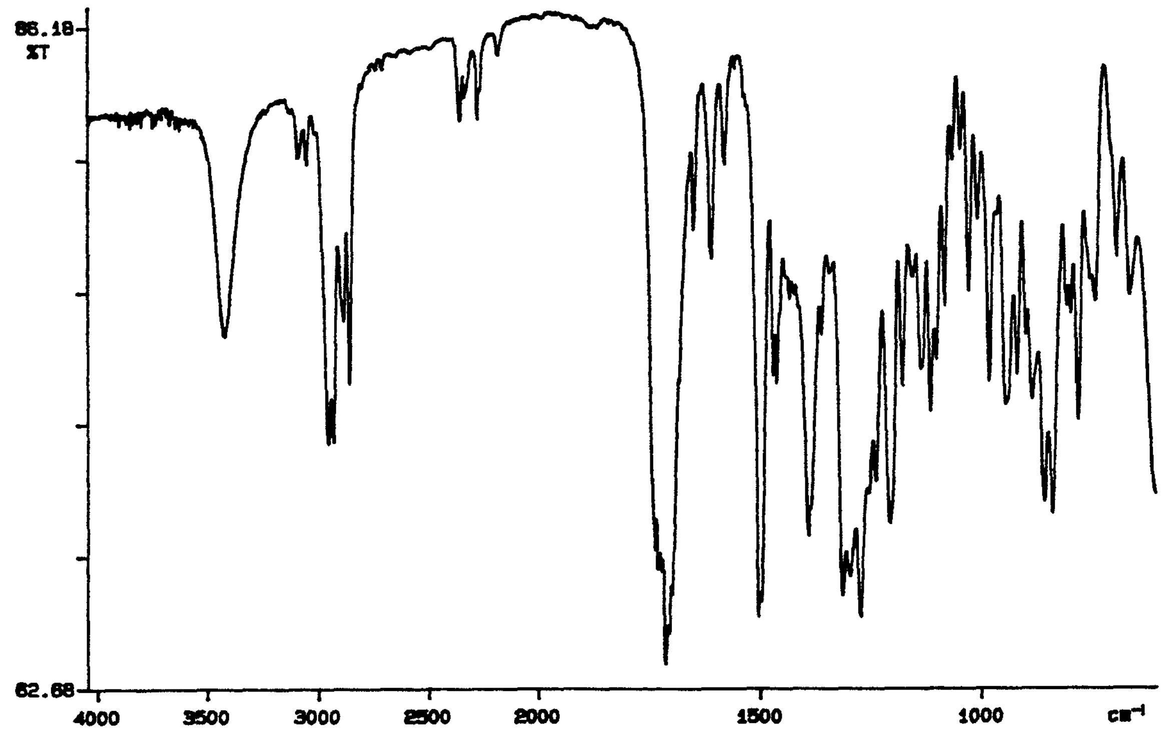
86.36
%T
59.60
4000
3500
3000
2500
2000
1500
1000
cm-1


CH3
H
N
O
O
O
O
O
S
OTBS
68
PPM
9
8
7
6
5
4
3
2
1
0

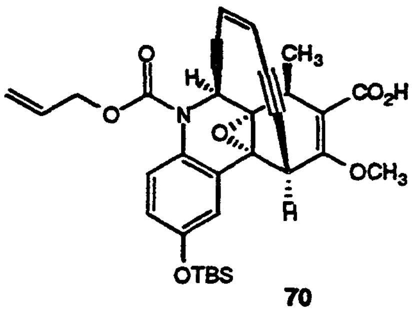

86.64
%T
38.51
4000
3500
3000
2500
2000
1500
1000
cm-1



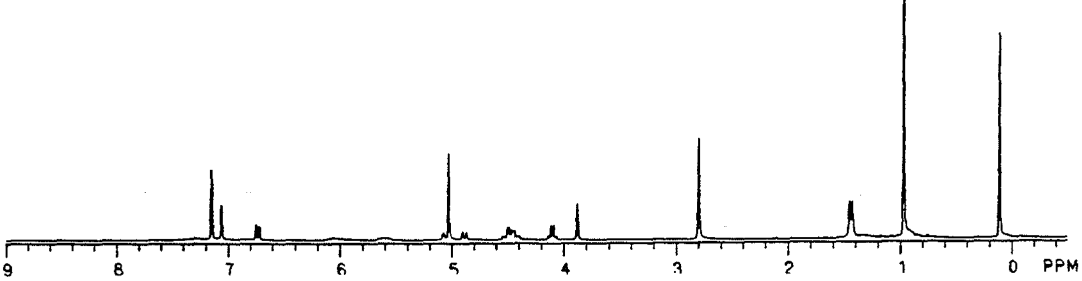
CH3
H
N
O
O
O
O
H
OTBS
69
9
8
7
6
5
4
3
2
1
0
PPM

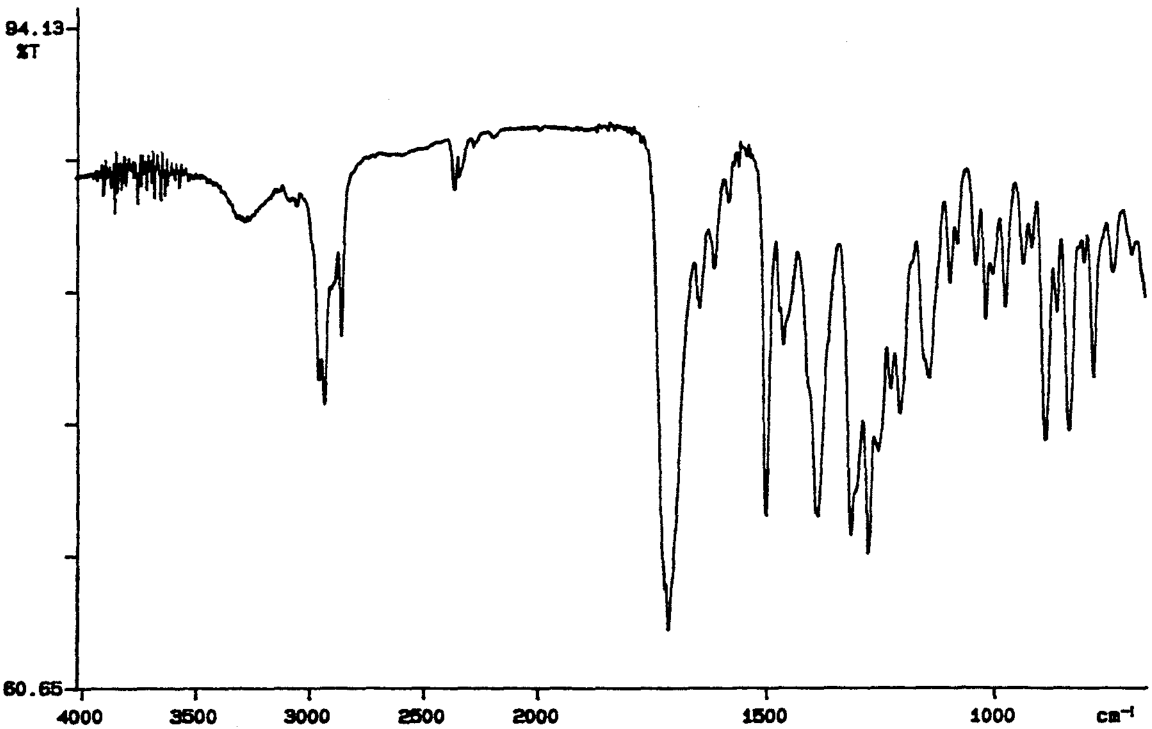


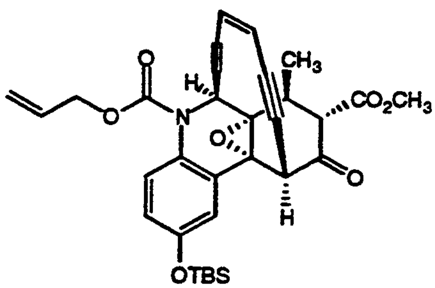
86.18
%T
62.68
4000
3500
3000
2500
2000
1500
1000
cm-1


CH3
H
CO2H
O
N
O
OCH3
H
OTBS

70

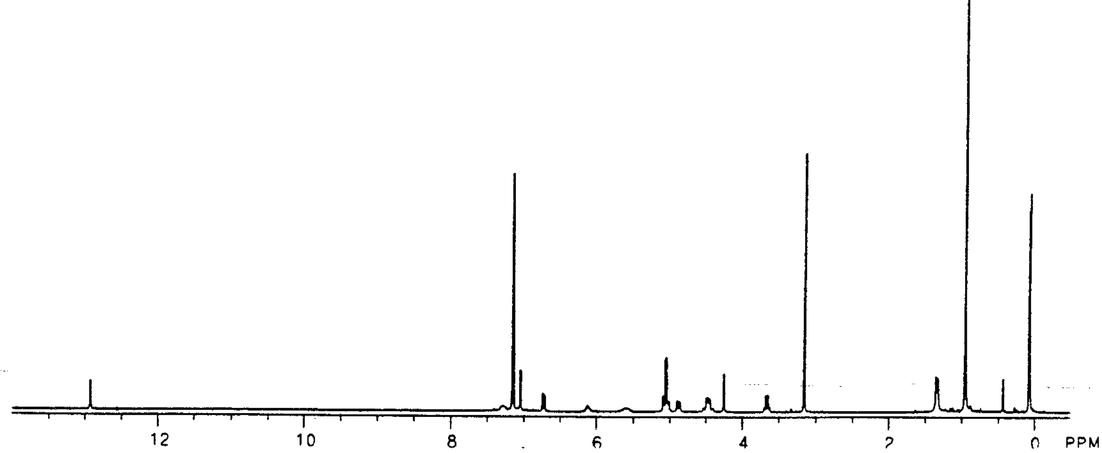

9
8
7
6
5
4
3
2
1
0
PPM


94.13
%T
60.65
4000
3500
3000
2500
2000
1500
1000
cm-1

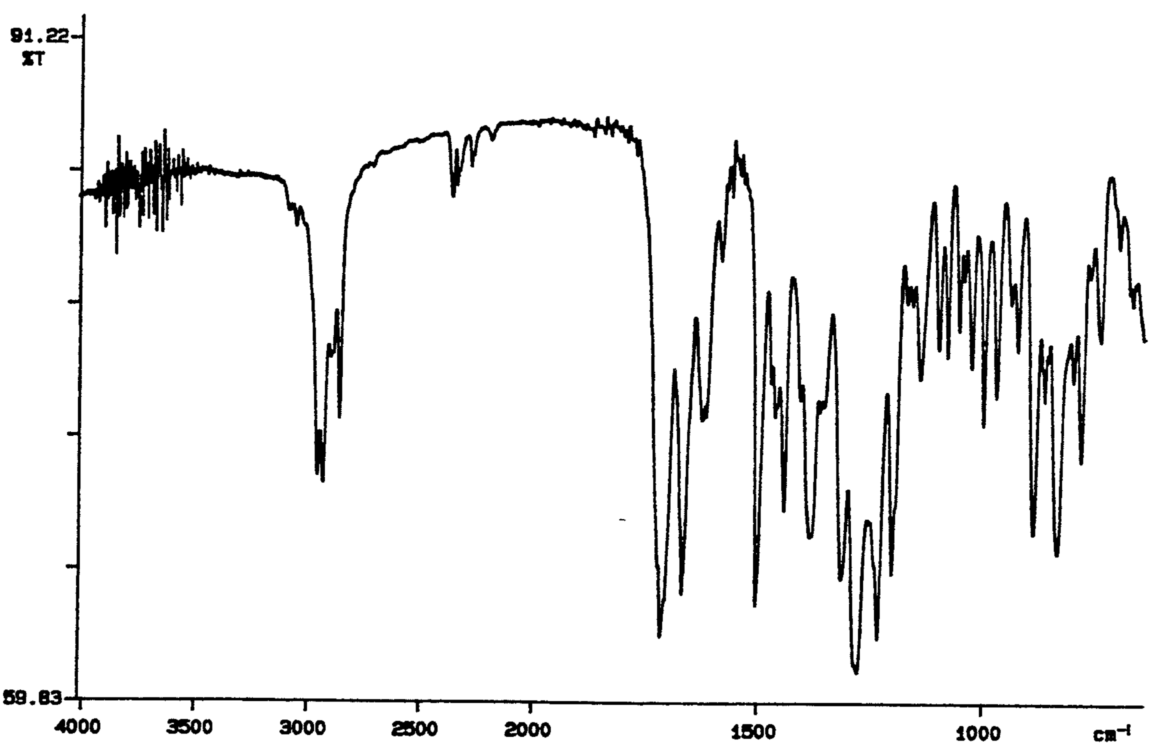


CH3
CO2CH3
H
N
O
OTBS

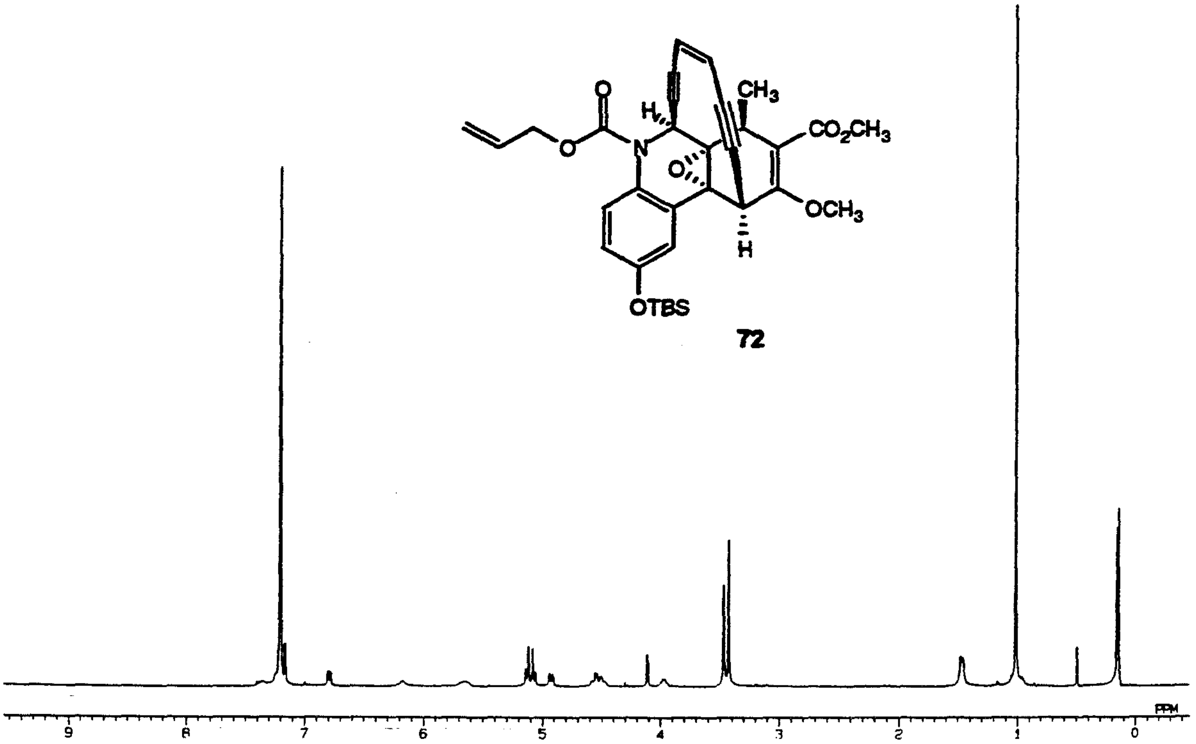
71



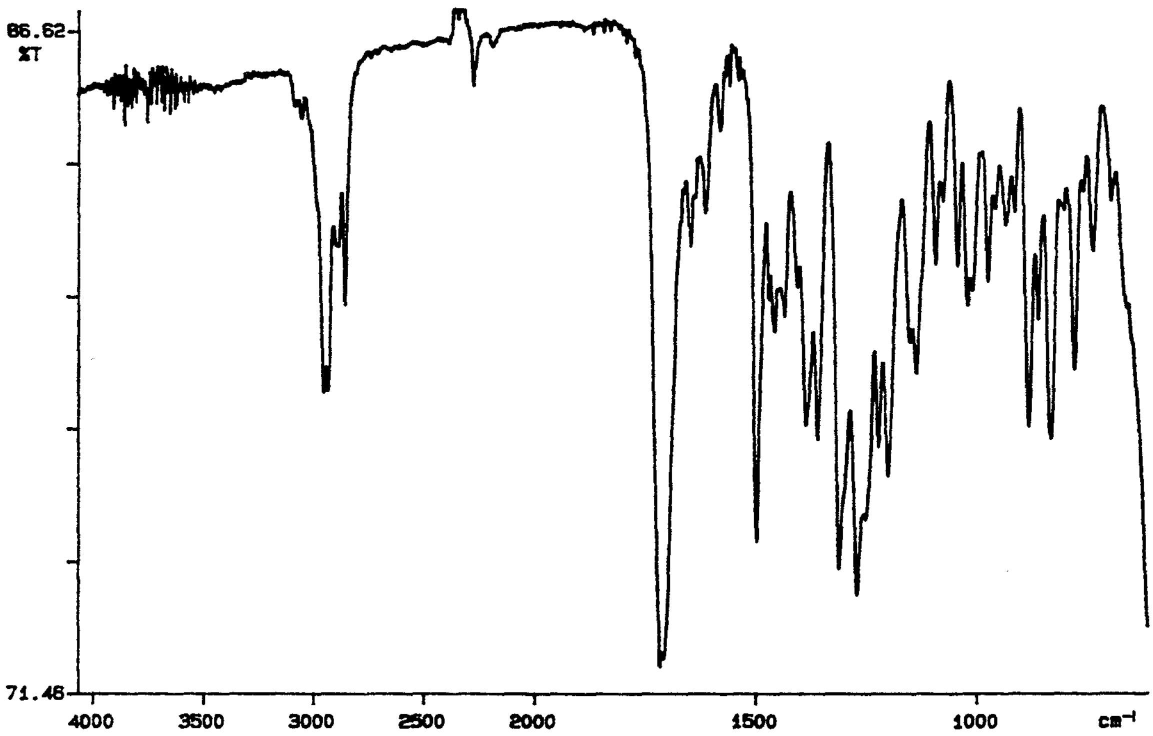
12
10
8
6
4
2
0
PPM



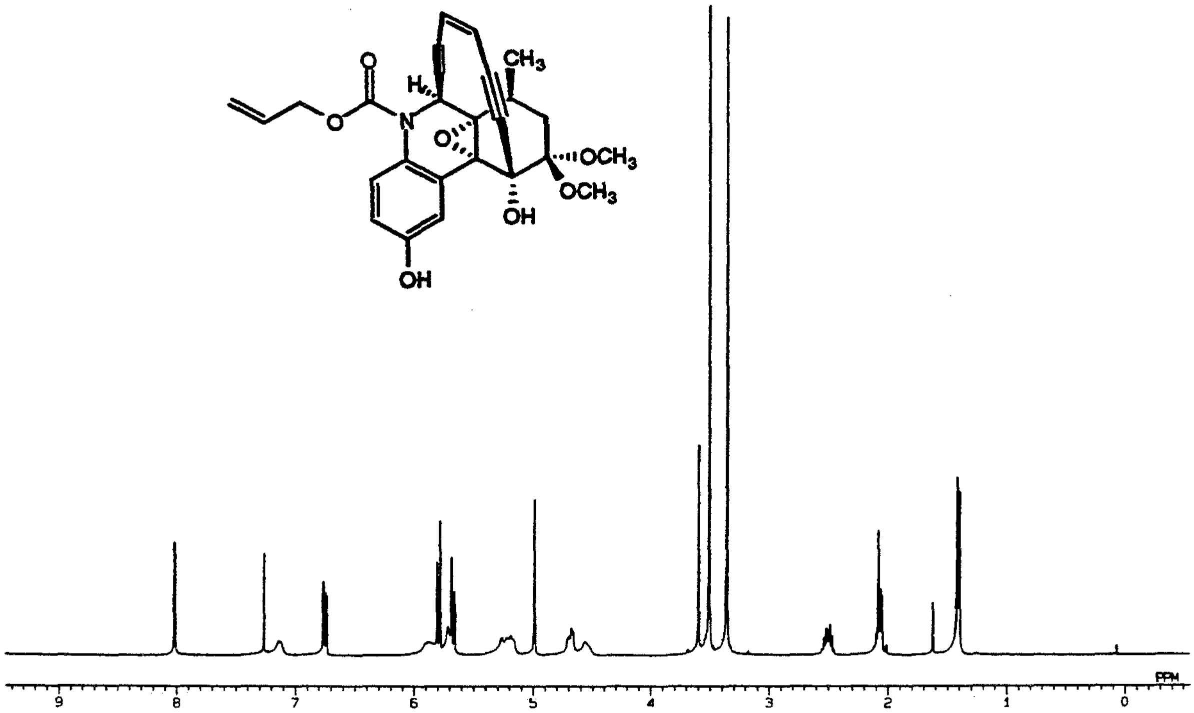
91.22
%T
59.83
4000
3500
3000
2500
2000
1500
1000
cm-1



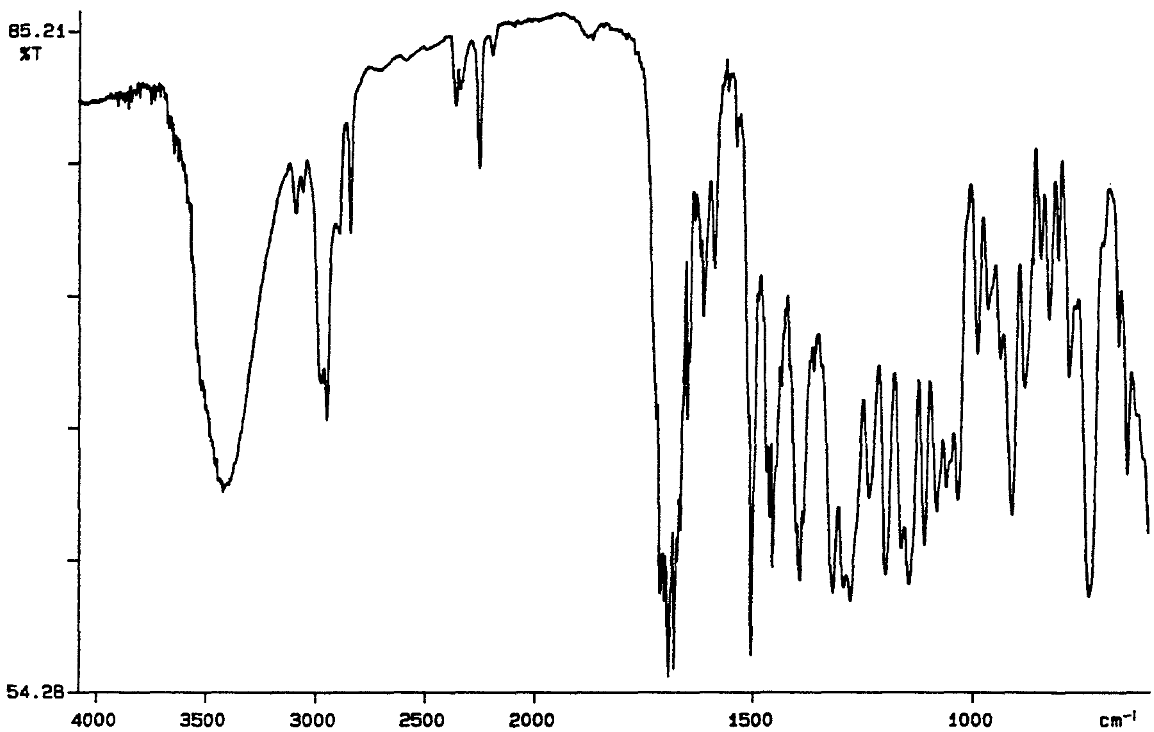
O
H
N
O
CH3
CO2CH3
OCH3
H
OTBS
72
PPM
9
8
7
6
5
4
3
2
1
0



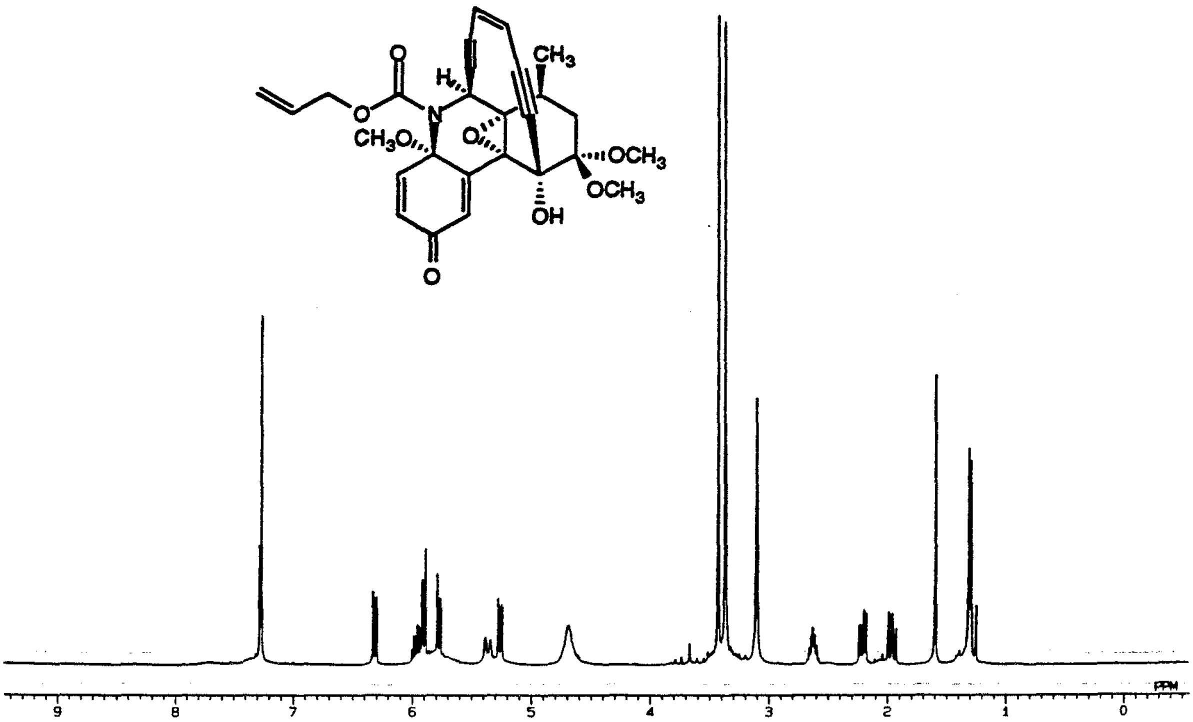
86.62
%T
71.46
4000
3500
3000
2500
2000
1500
1000
cm-1

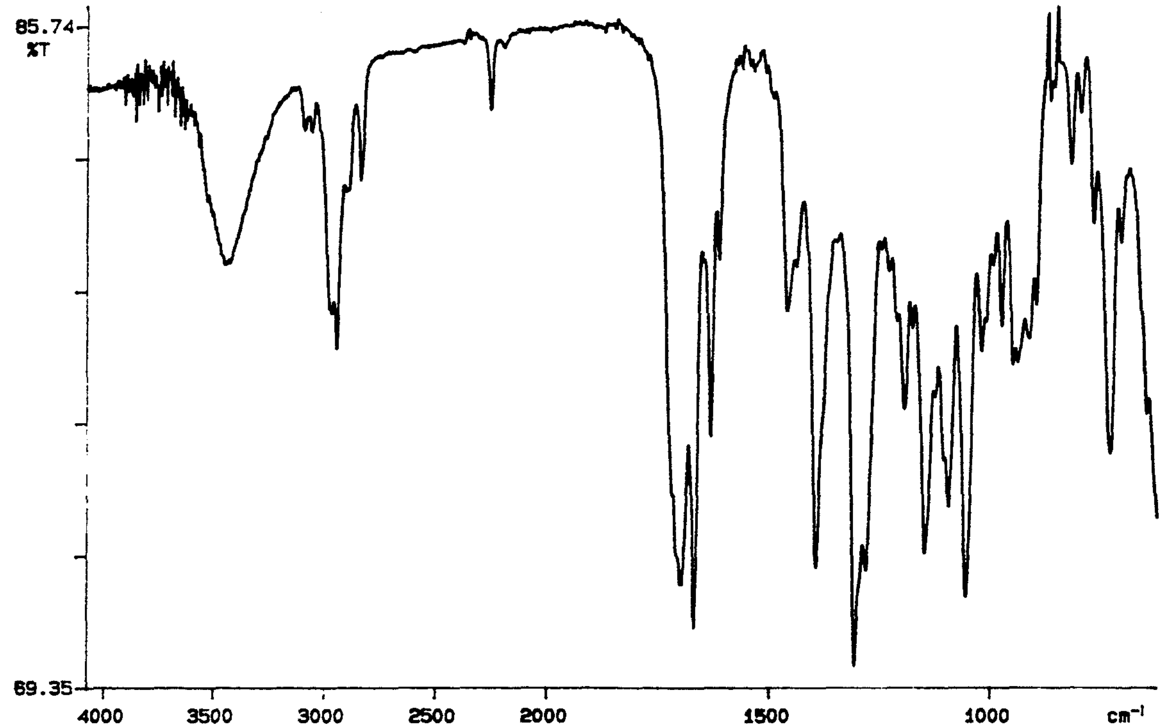


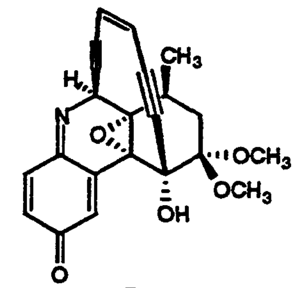
CH3
H
N
O
O
O
OCH3
OCH3
OH
OH
PPM
9
8
7
6
5
4
3
2
1
0



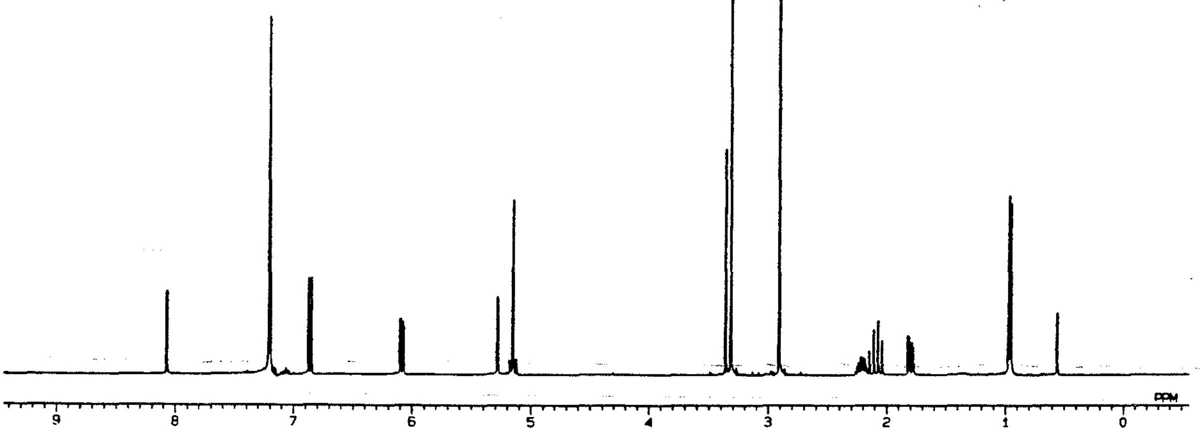
85.21
%T
54.28
4000
3500
3000
2500
2000
1500
1000
cm-1

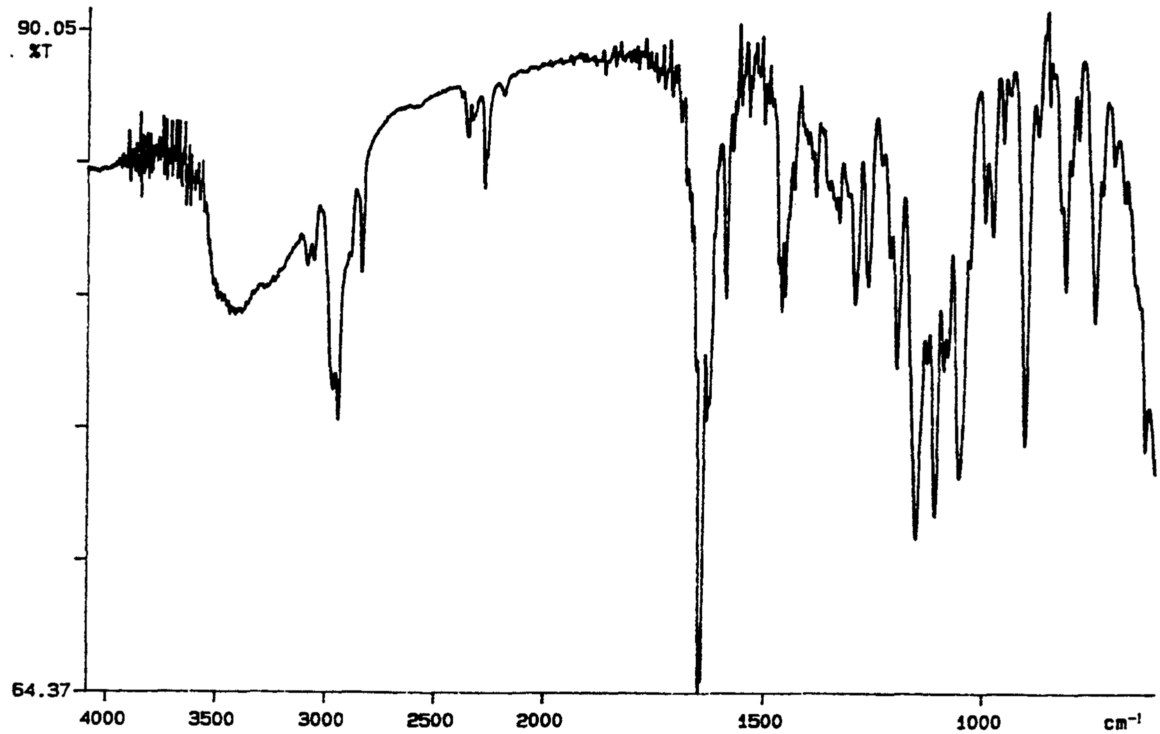

CH3
H
O
N
CH3O
O
OCH3
OCH3
OH
O
9
8
7
6
5
4
3
2
1
0
PPM

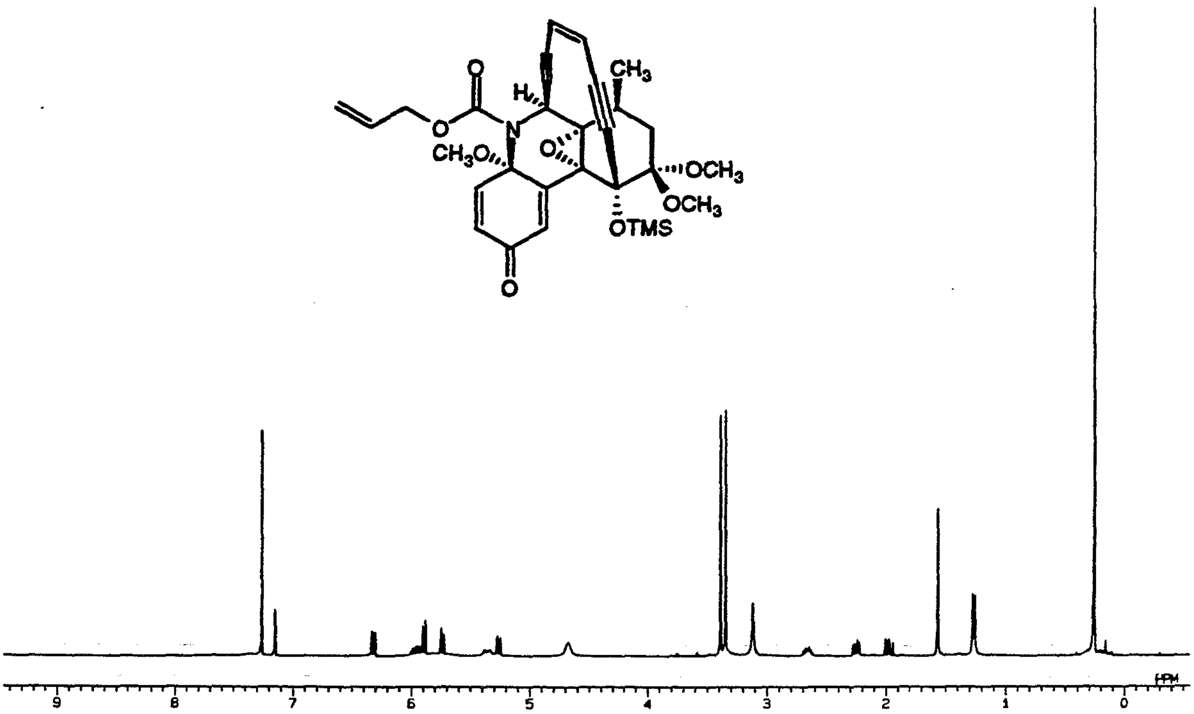

85.74
%T
69.35
4000
3500
3000
2500
2000
1500
1000
cm-1


CH3
H
N
O
OCH3
OCH3
OH
O

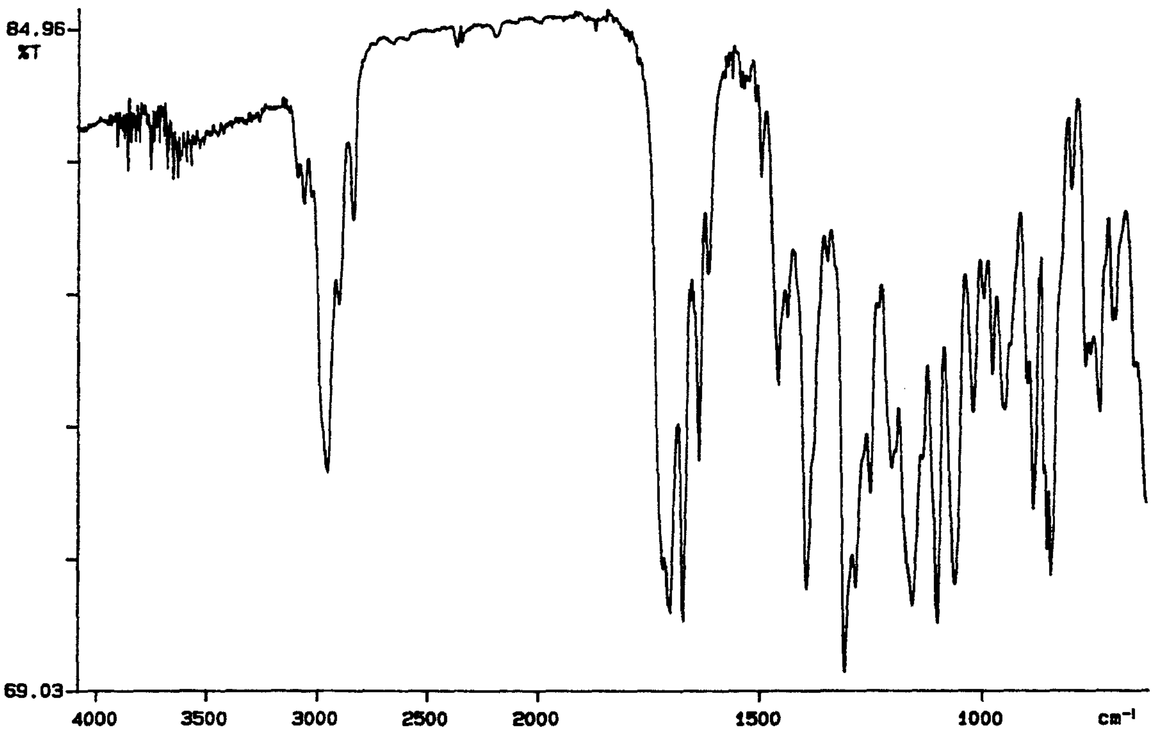
78


9
8
7
6
5
4
3
2
1
0
PPM

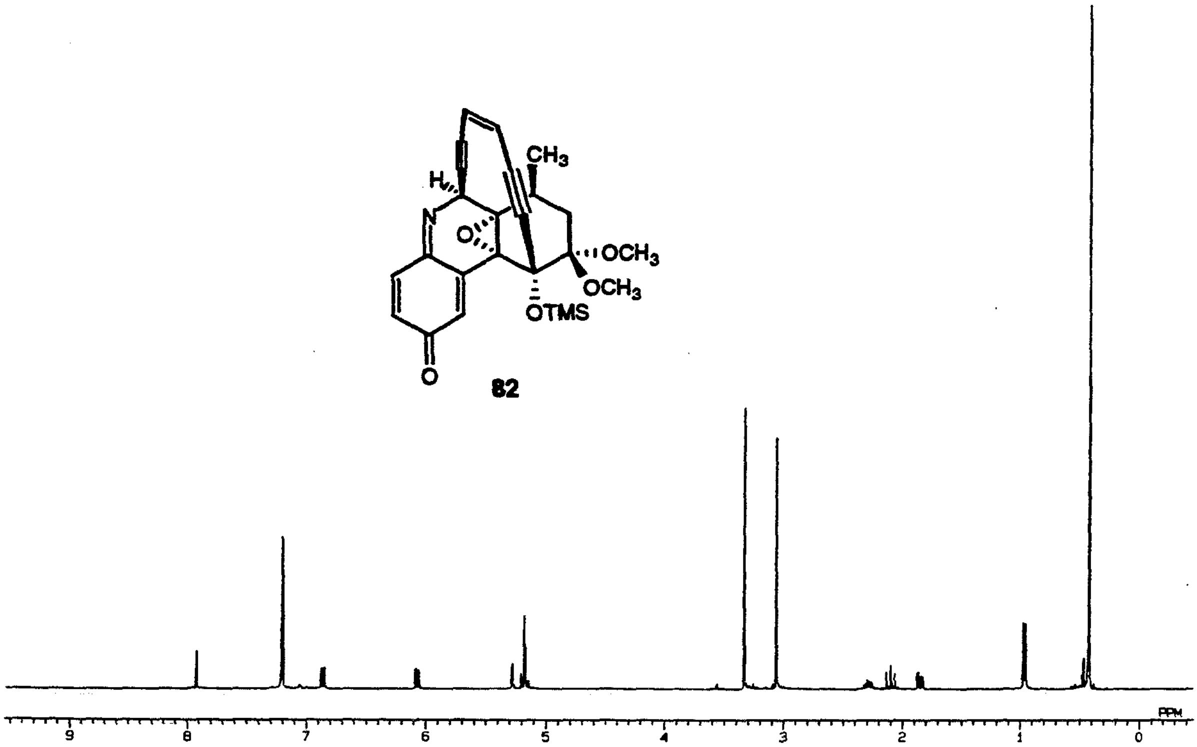

90.05
%T
64.37
4000
3500
3000
2500
2000
1500
1000
cm-1

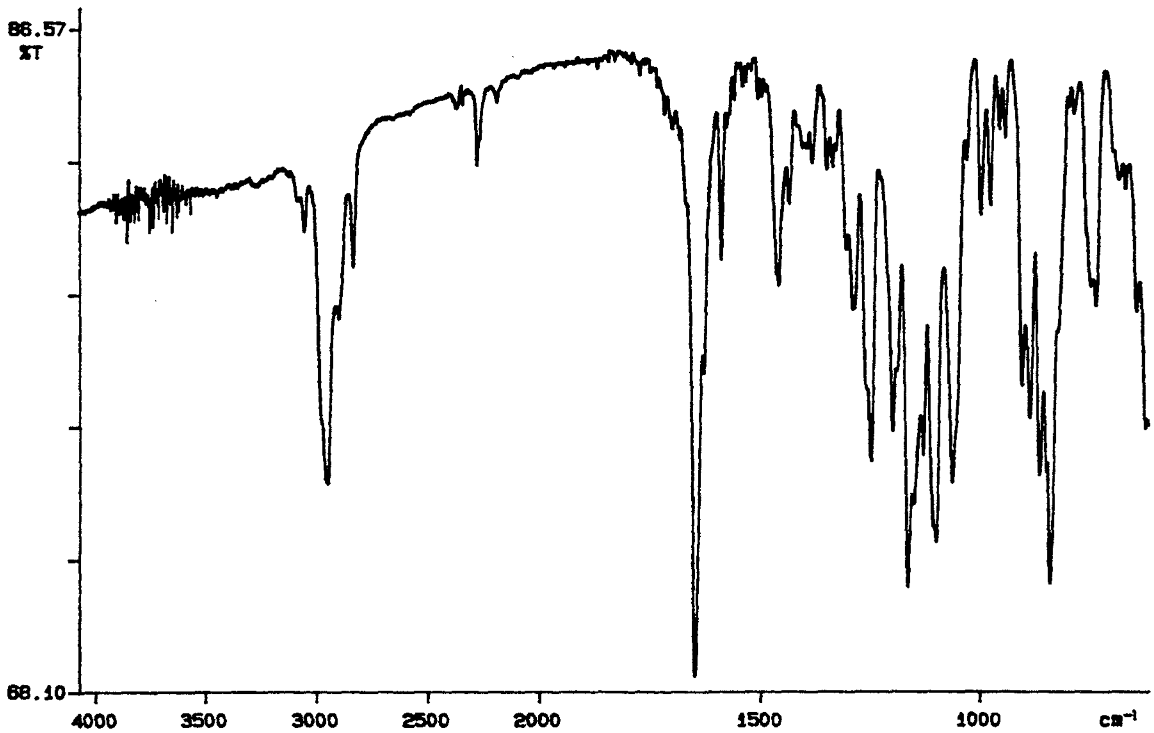


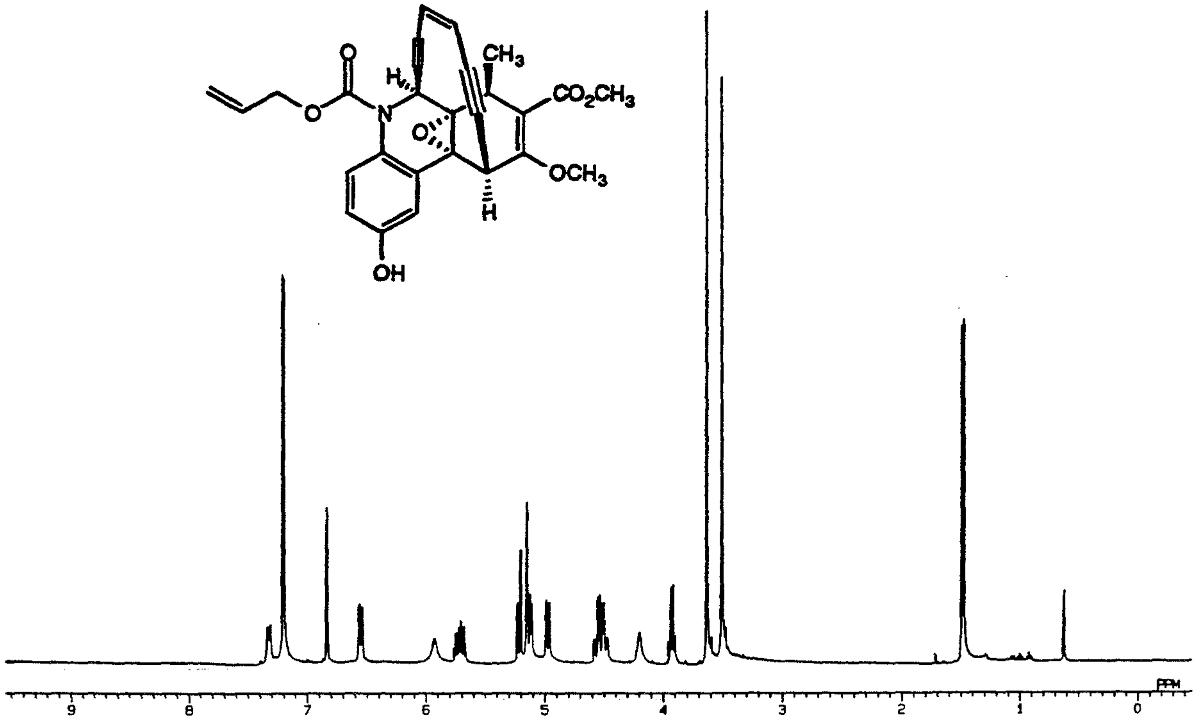
O
H
N
O
CH3O
O
CH3
OCH3
OCH3
OTMS
O
9
8
7
6
5
4
3
2
1
0
PPM

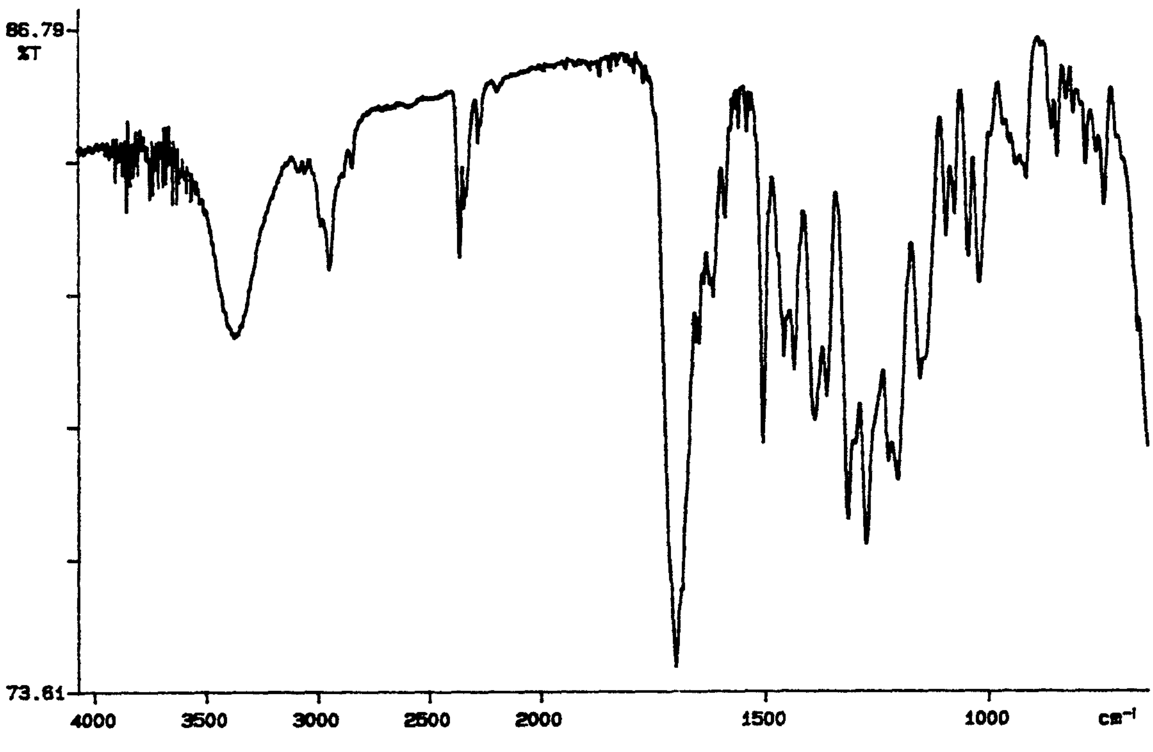


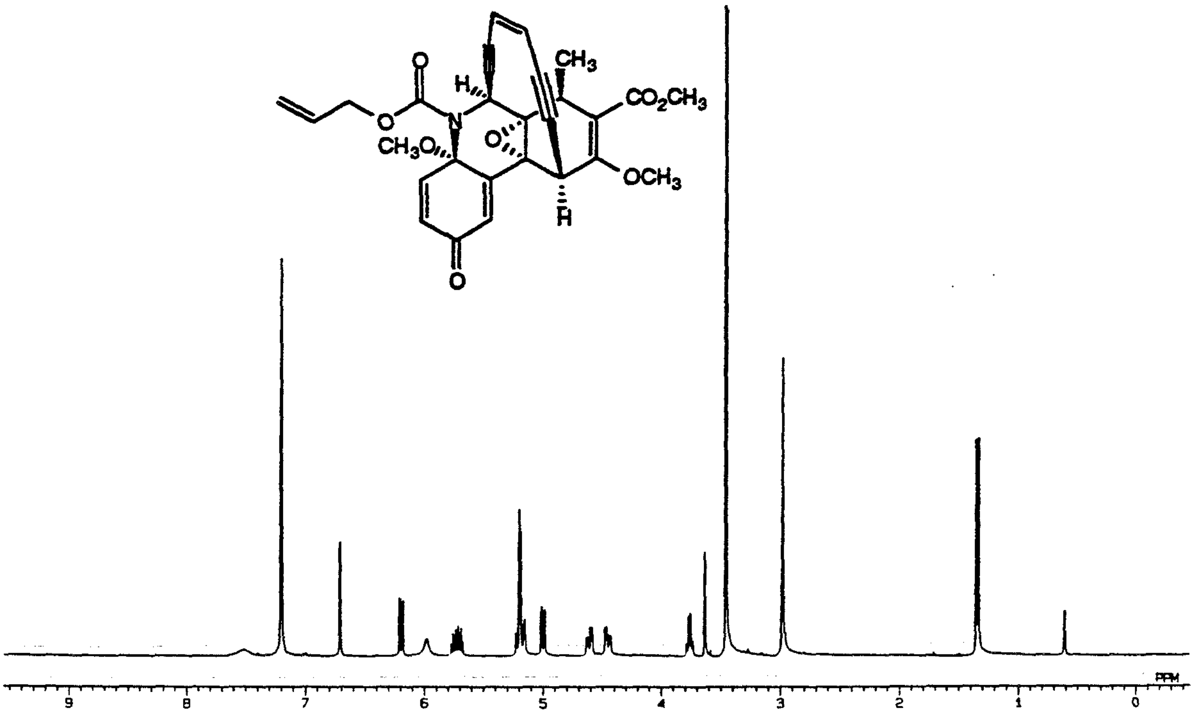
84.96
%T
69.03
4000
3500
3000
2500
2000
1500
1000
cm-1

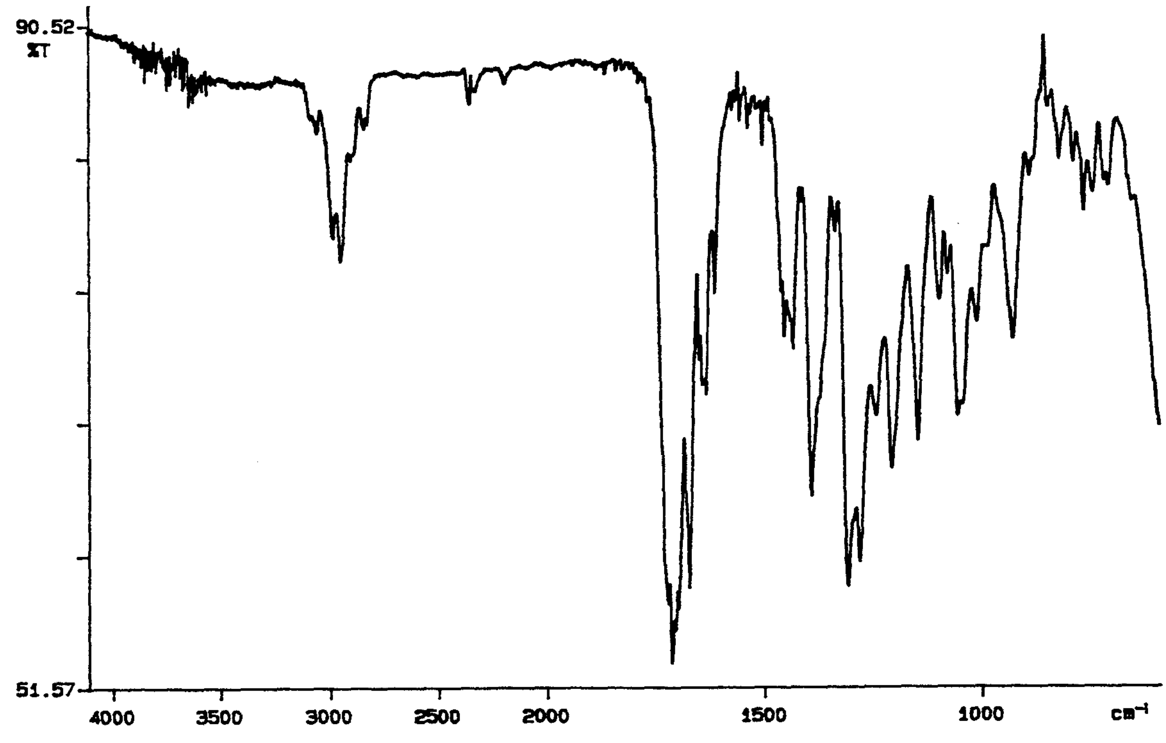

CH3
H
N
O
OCH3
OCH3
OTMS
O
82
PPM
9
8
7
6
5
4
3
2
1
0

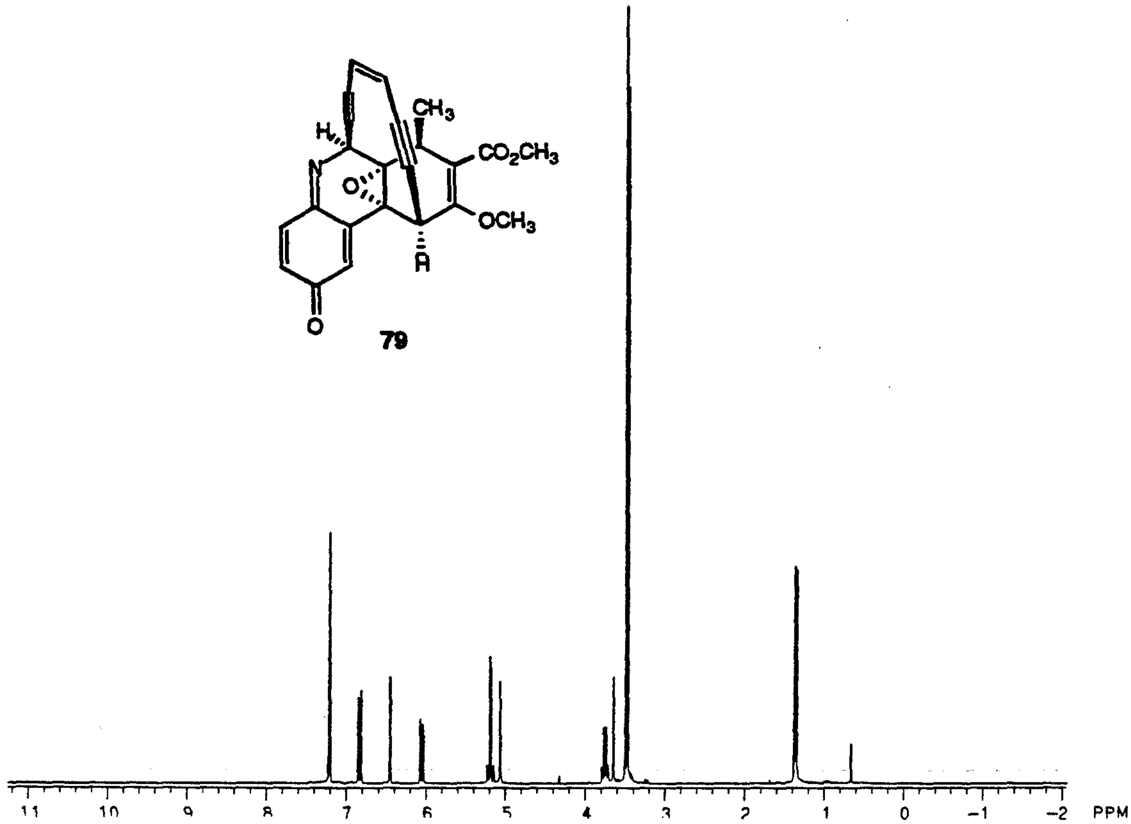

86.57
%T
68.10
4000
3500
3000
2500
2000
1500
1000
cm⁻¹

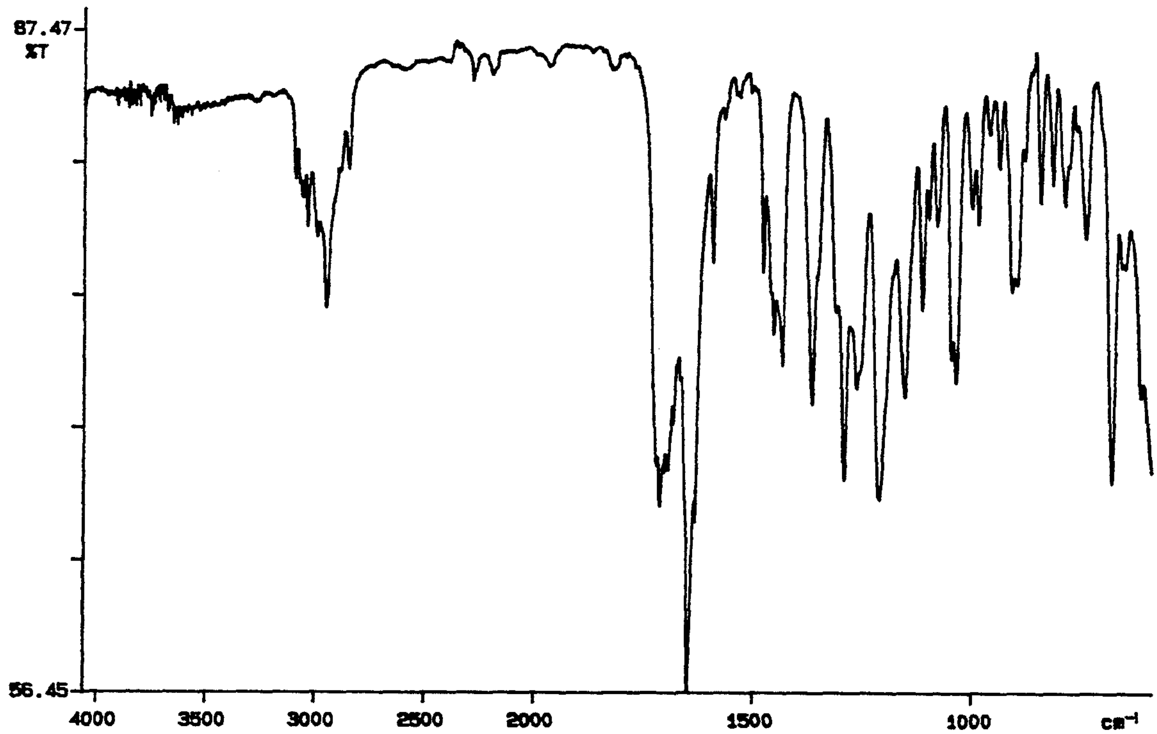

CH3
CO2CH3
OCH3
OH
PPM
9
8
7
6
5
4
3
2
1
0

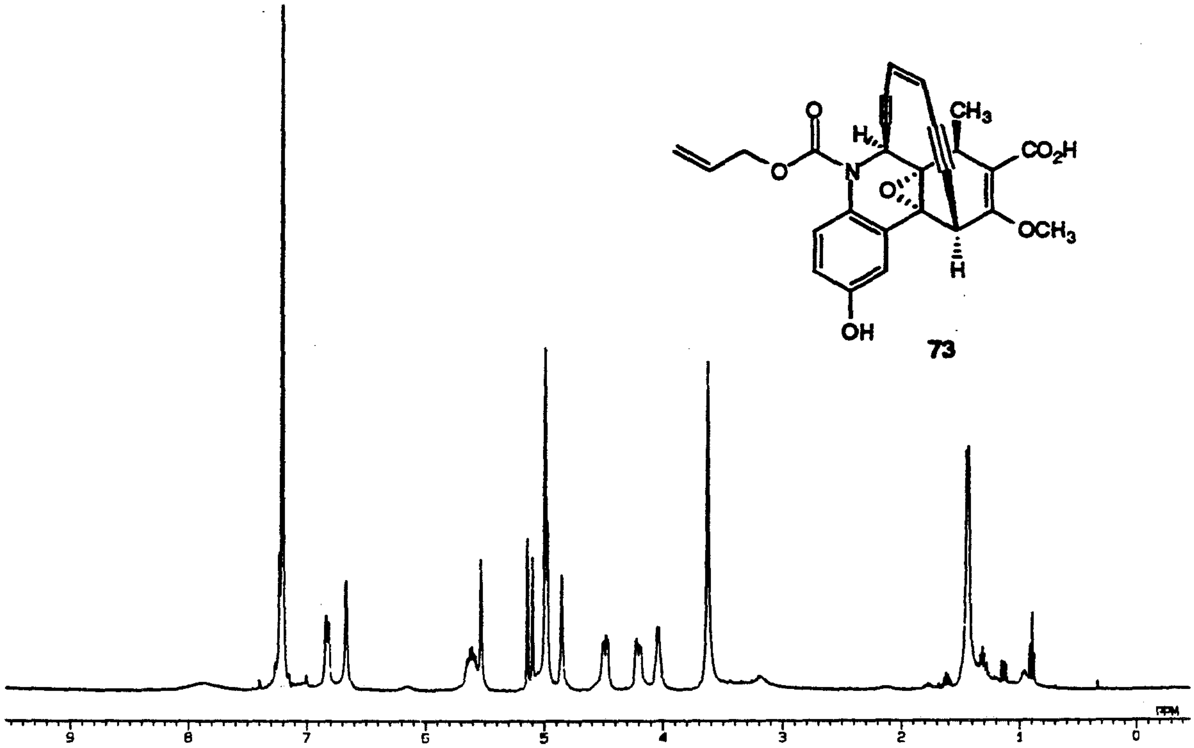

86.79
%T
73.61
4000
3500
3000
2500
2000
1500
1000
cm-1

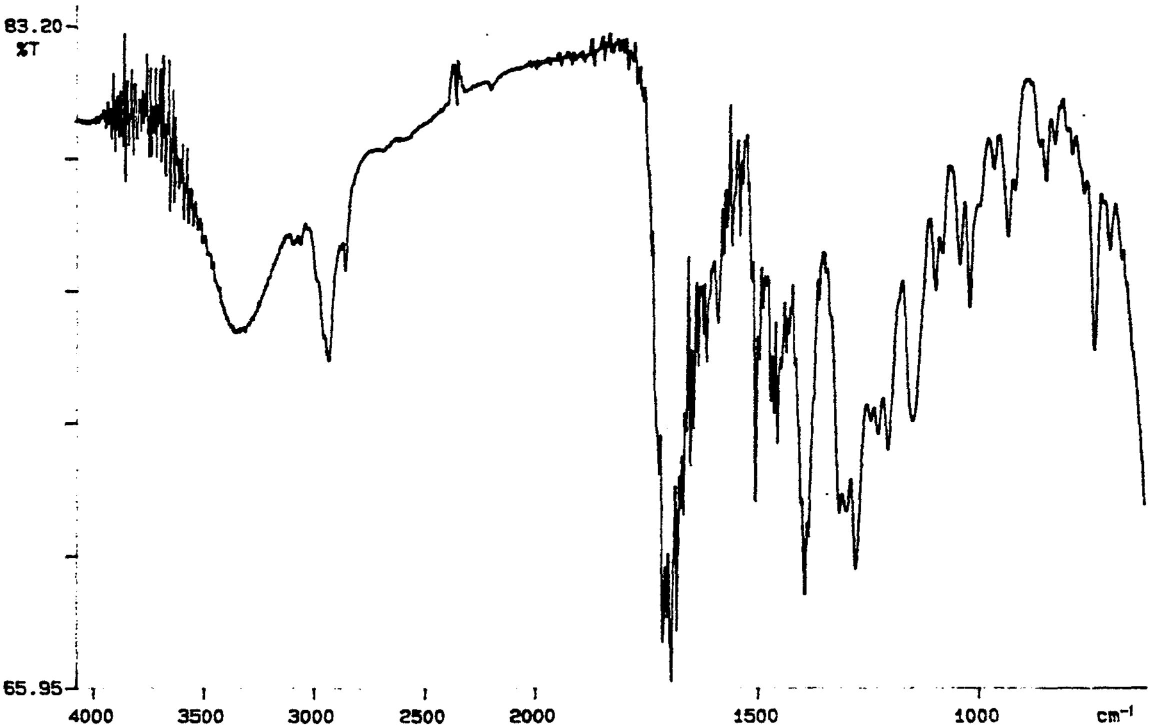

CH3
CO2CH3
OCH3
CH3O
H
N
O
PPM
9
8
7
6
5
4
3
2
1
0

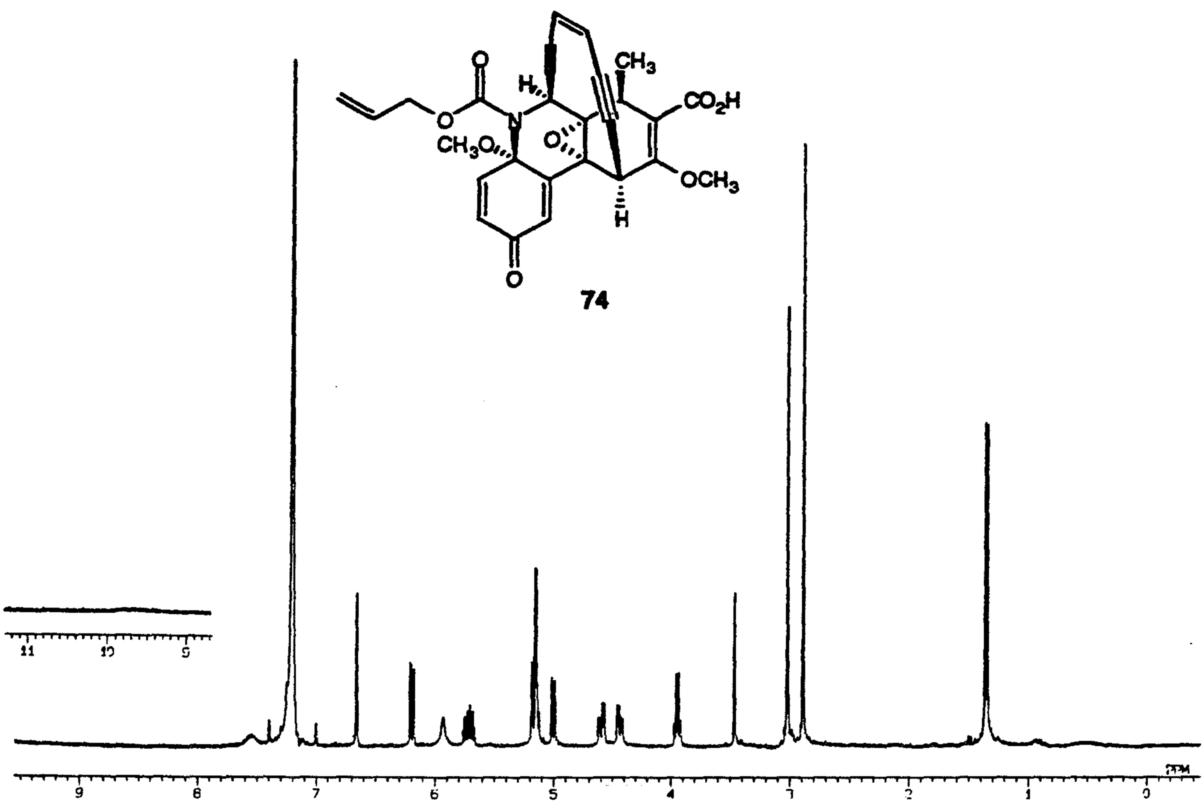

90.52
%T
51.57
4000
3500
3000
2500
2000
1500
1000
cm-1

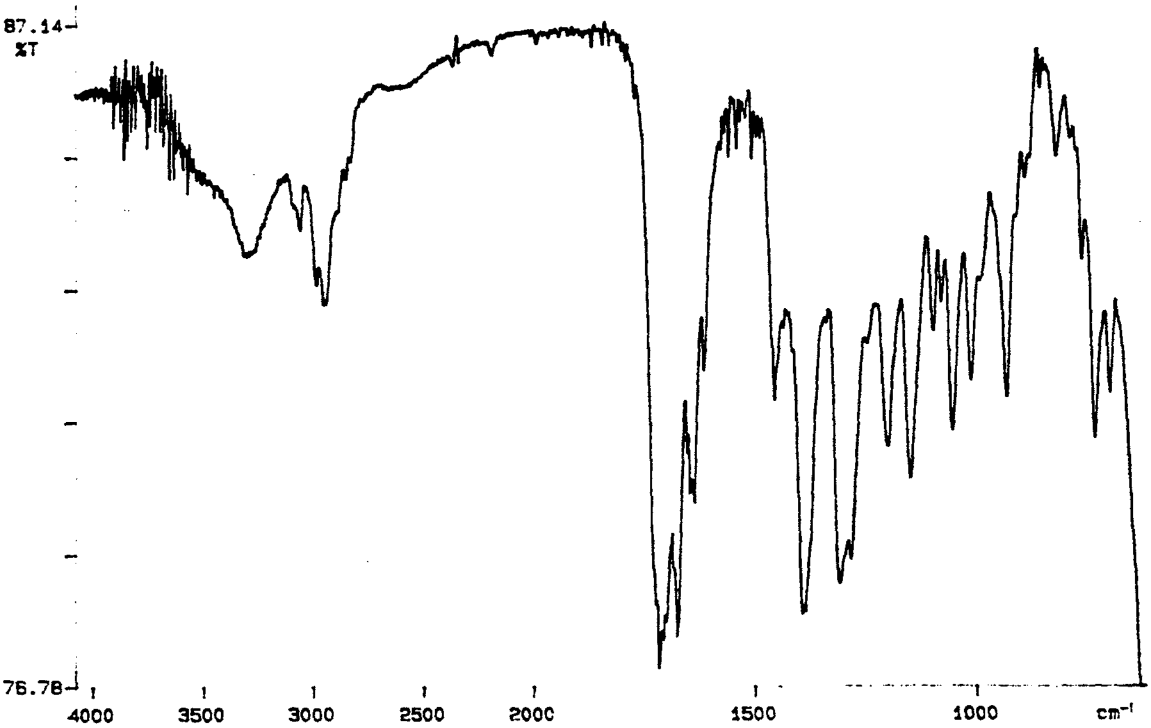

H
N
O
CH3
CO2CH3
OCH3
H
O
79
11
10
9
8
7
6
5
4
3
2
1
0
−1
−2
PPM

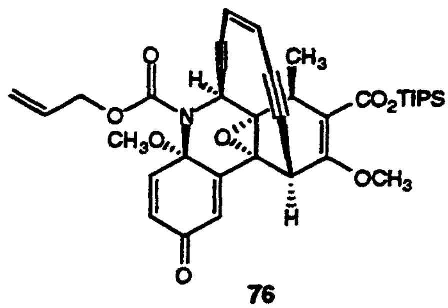

87.47
%T
56.45
4000
3500
3000
2500
2000
1500
1000
cm-1


O
H
N
O
CH3
CO2H
OCH3
H
OH
73
PPM
9
8
7
6
5
4
3
2
1
0


83.20
%T
65.95
4000
3500
3000
2500
2000
1500
1000
cm-1

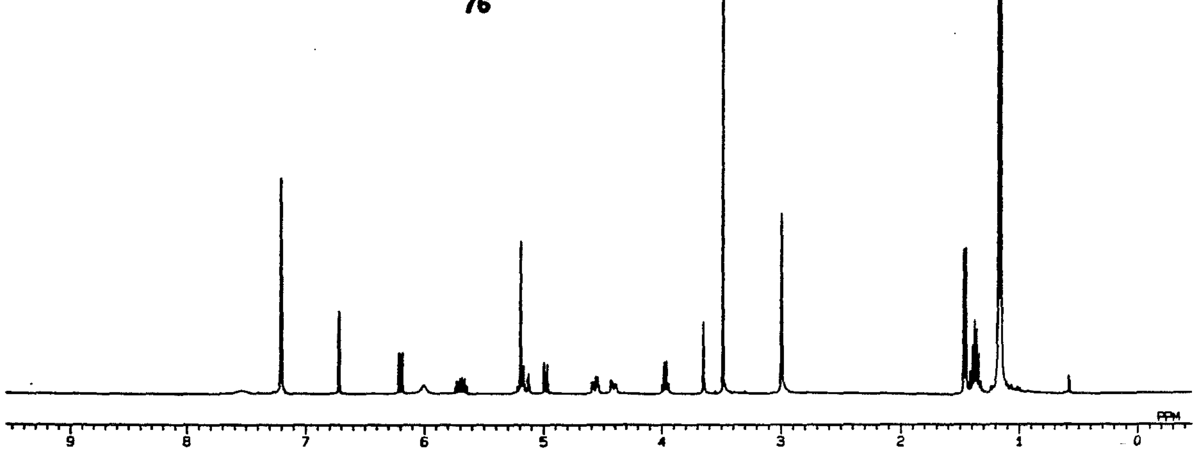

CH3
CO2H
H
N
O
CH3O
OCH3
H
O
74
11
10
9
9
8
7
6
5
4
3
2
1
0
PPM


87.14
%T
76.78
4000
3500
3000
2500
2000
1500
1000
cm-1

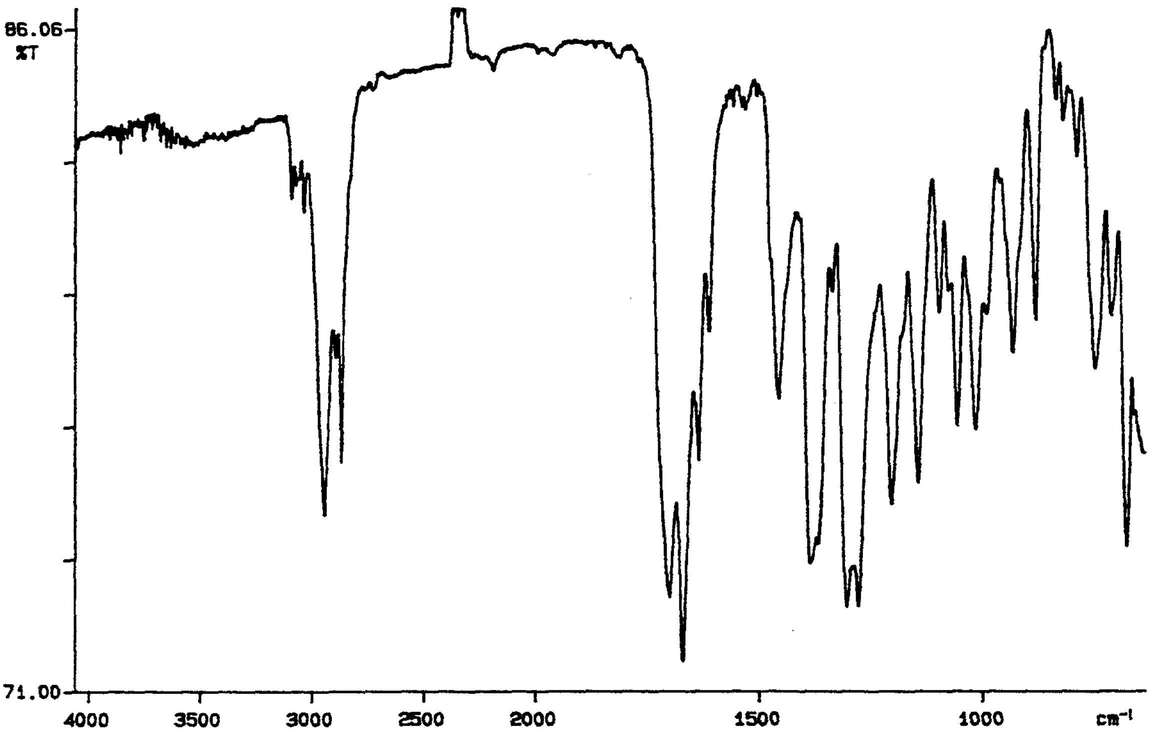


CH3
CO2TIPS
H
N
O
CH3O
OCH3
H
O

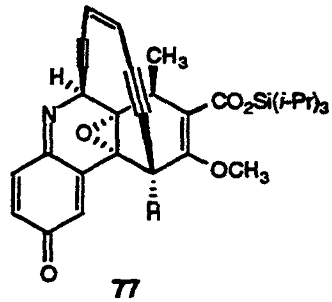
76



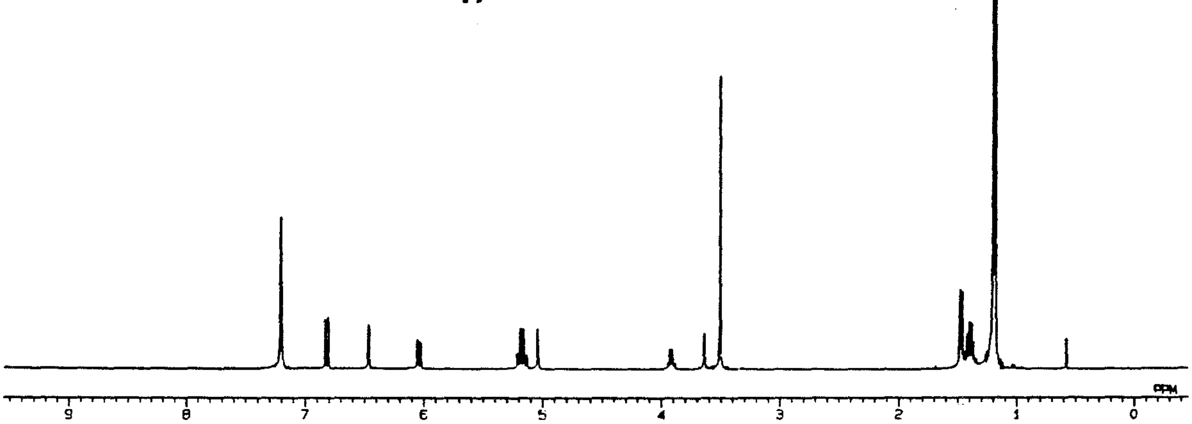
PPM
9
8
7
6
5
4
3
2
1
0

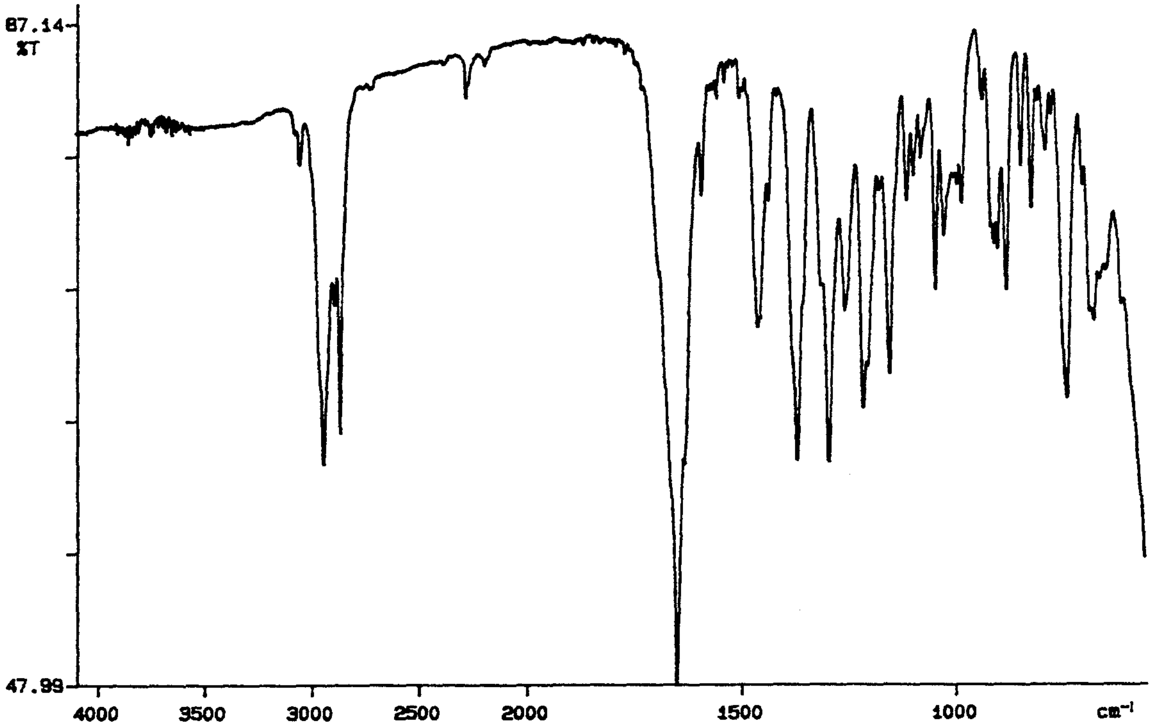


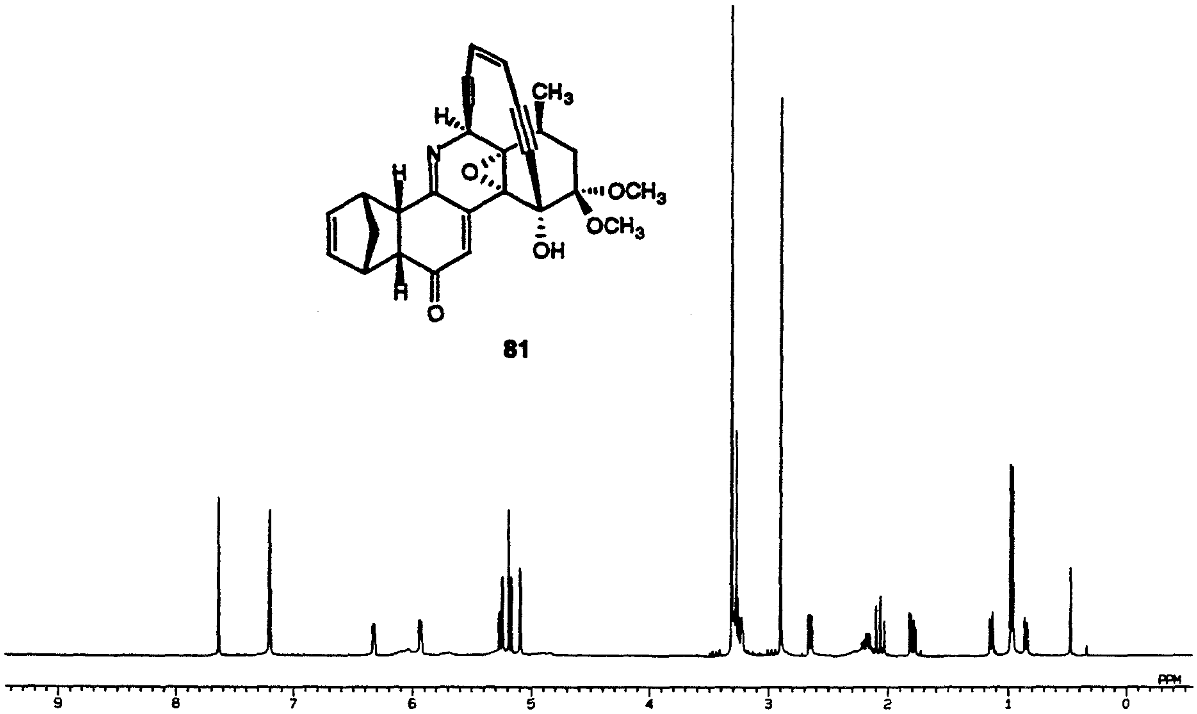
86.06
%T
71.00
4000
3500
3000
2500
2000
1500
1000
cm-1


CH3
H
N
O
CO2Si(i-Pr)3
OCH3
H
O

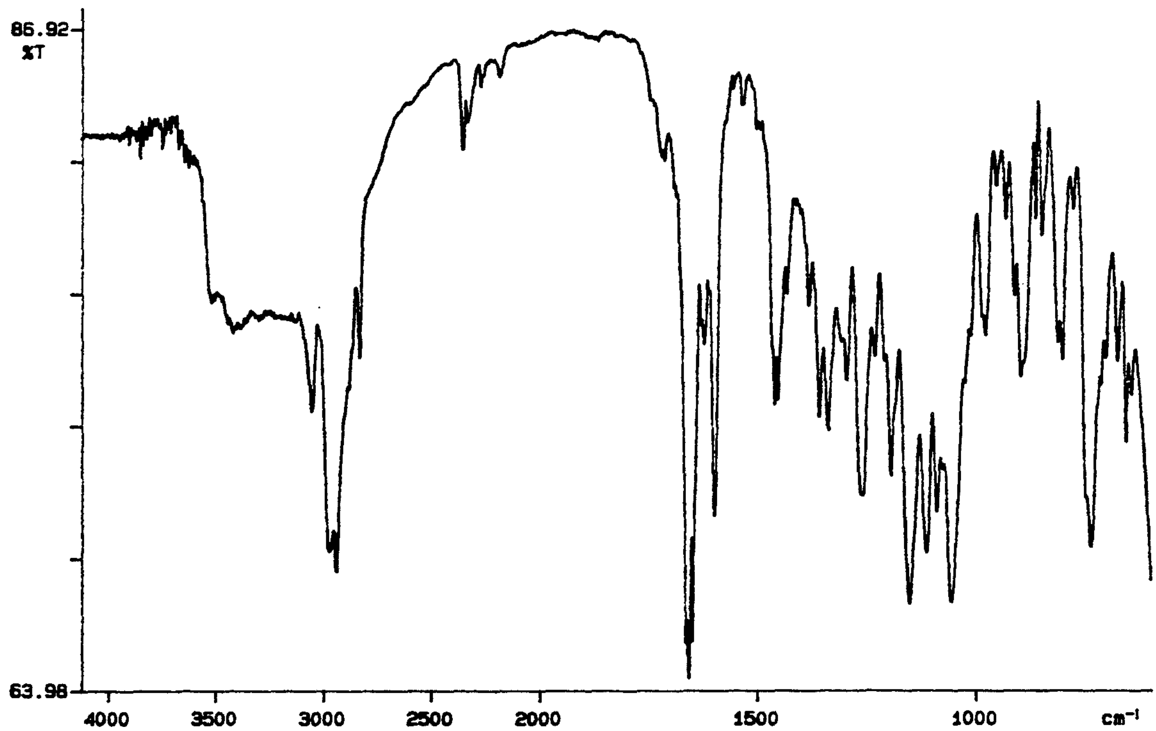
77


PPM
9
8
7
6
5
4
3
2
1
0

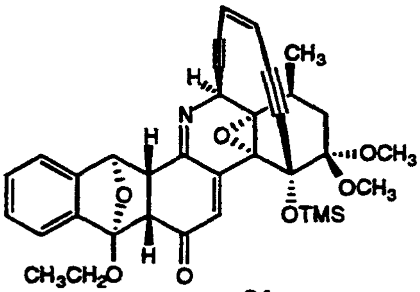

87.14
%T
47.99
4000
3500
3000
2500
2000
1500
1000
cm-1



CH3
H
N
O
H
OCH3
OCH3
OH
H
O
81
PPM
9
8
7
6
5
4
3
2
1
0

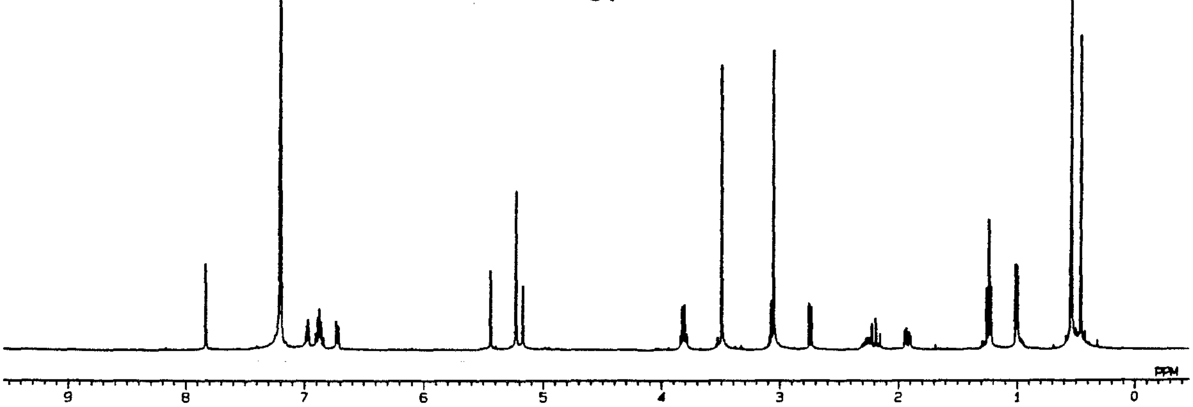


86.92
%T
63.98
4000
3500
3000
2500
2000
1500
1000
cm-1

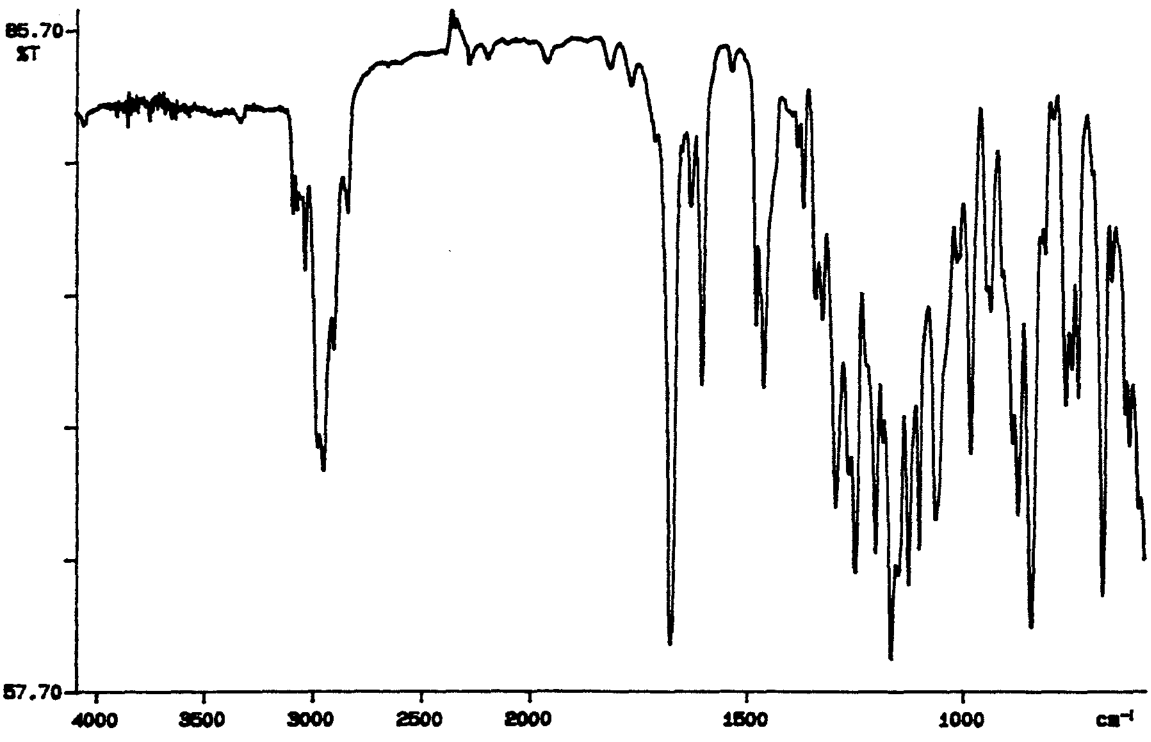


CH3
H
N
O
OCH3
OCH3
OTMS
H
H
CH3CH2O
O

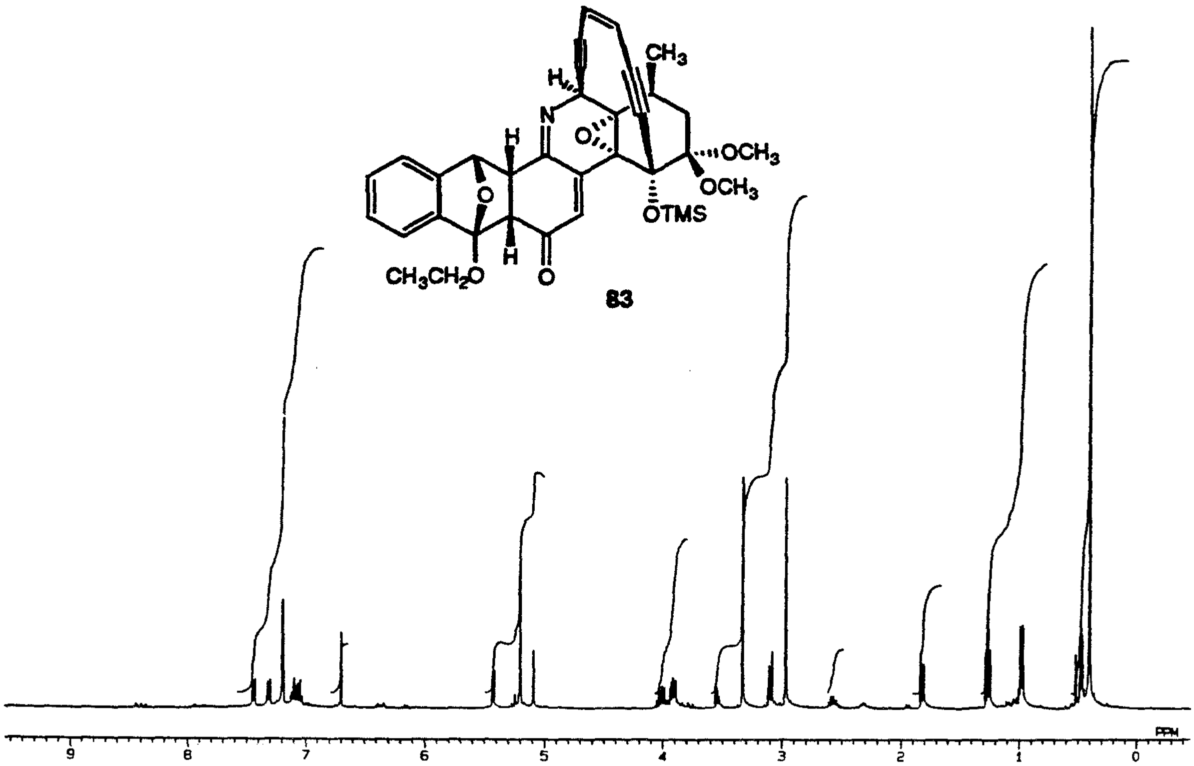
84

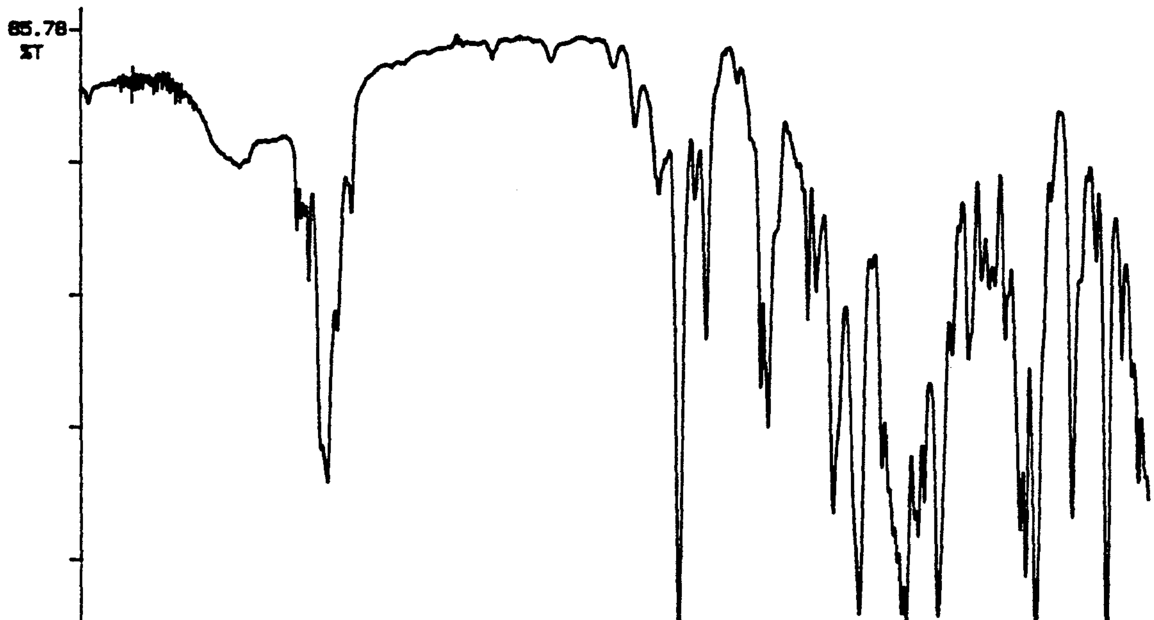


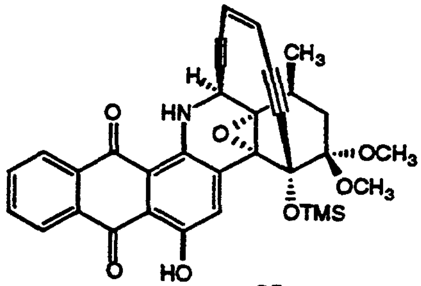
PPM
9
8
7
6
5
4
3
2
1
0



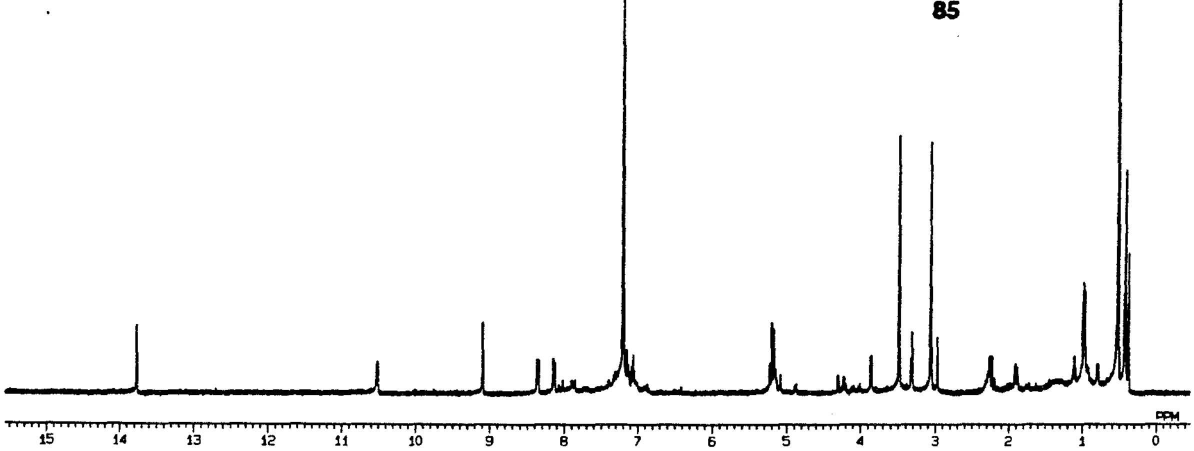
85.70
%T
57.70
4000
3500
3000
2500
2000
1500
1000
cm-1

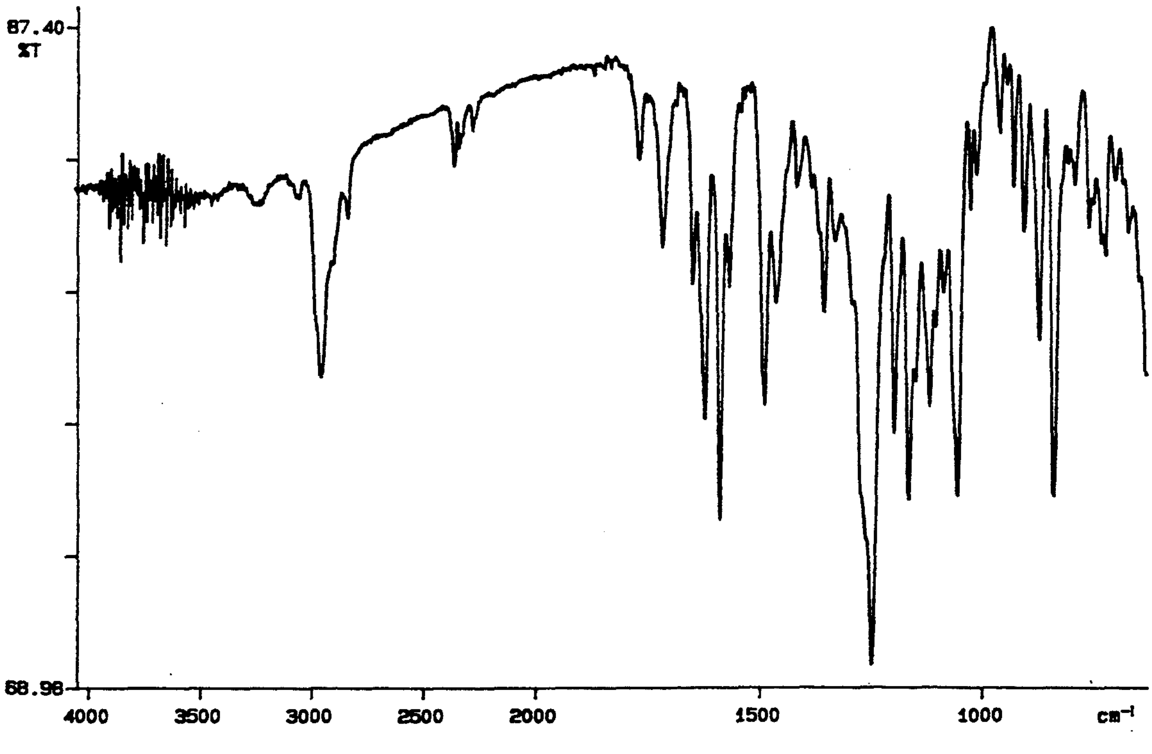

CH3
H
N
H
O
OCH3
OCH3
OTMS
O
H
CH3CH2O
O
83
9
8
7
6
5
4
3
2
1
0
PPM

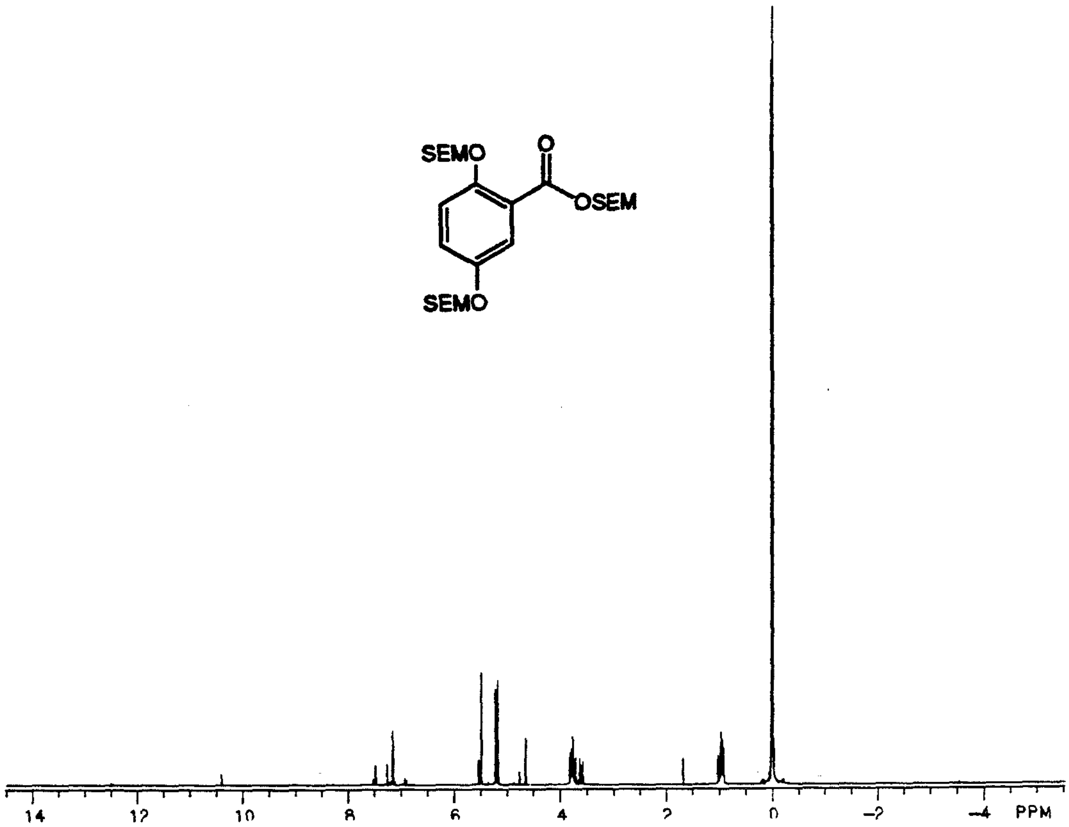

85.78
%T
51.77
4000
3500
3000
2500
2000
1500
1000
cm-1

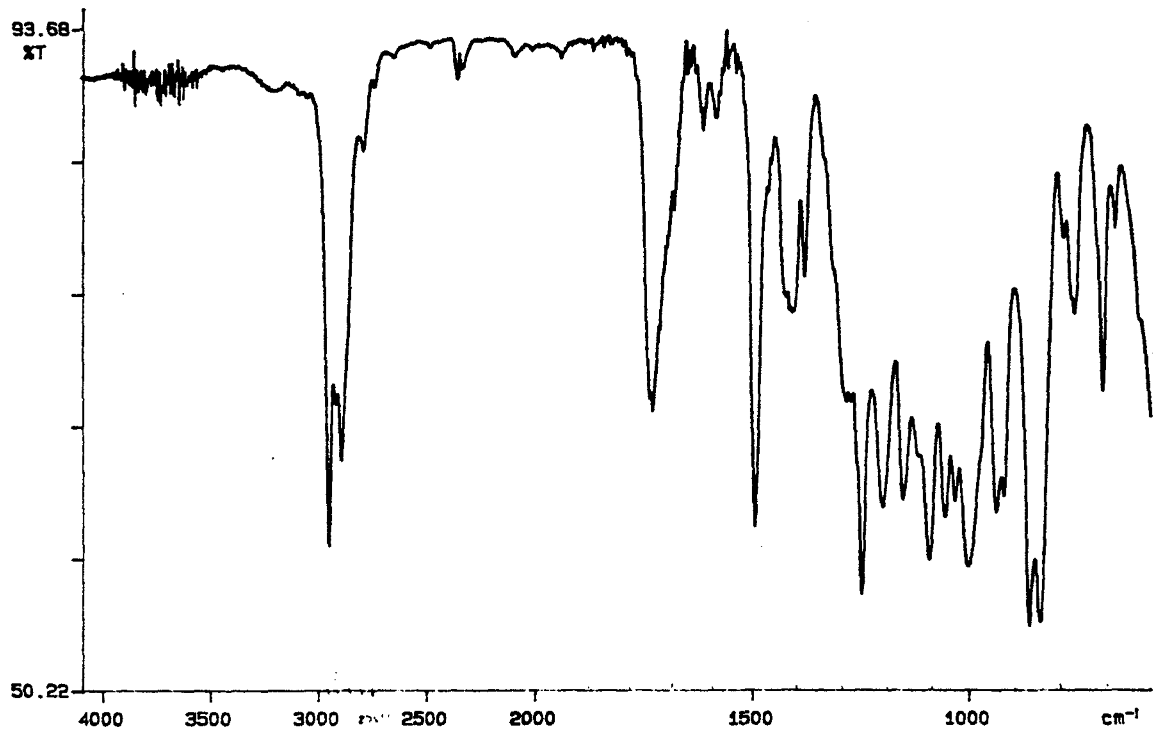

CH3
H
HN
O
O
O
OCH3
OCH3
OTMS
O
HO

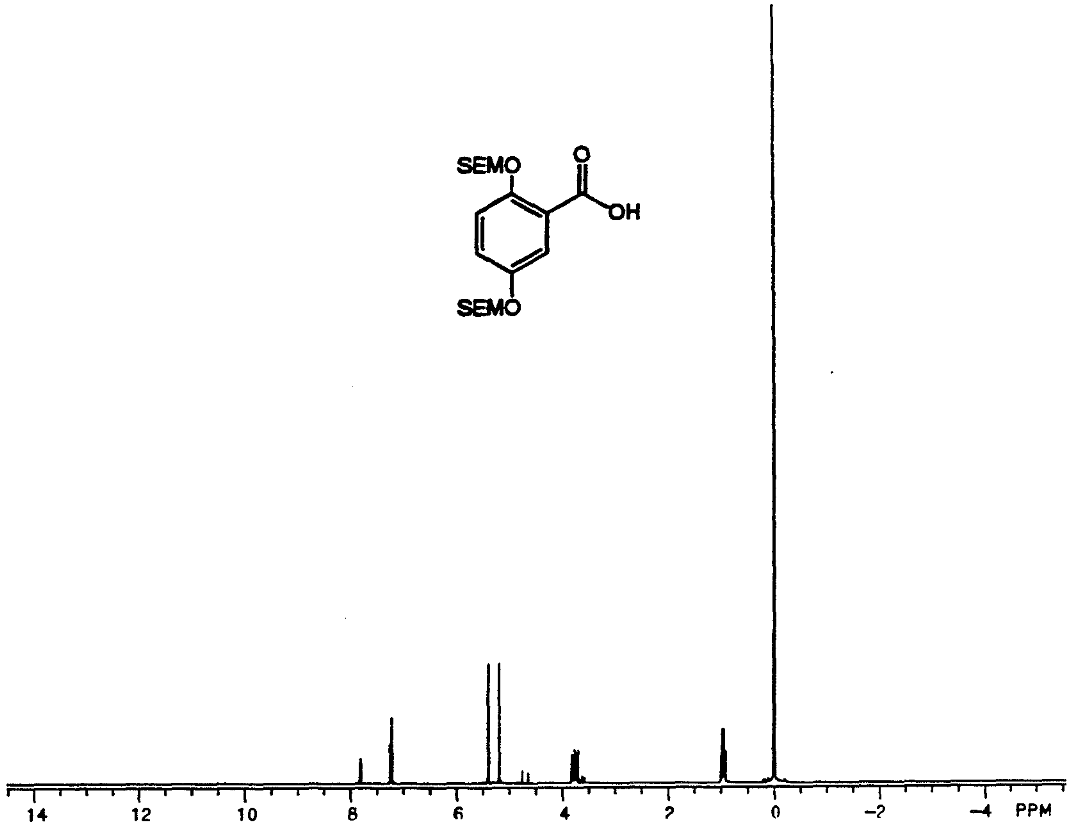
85

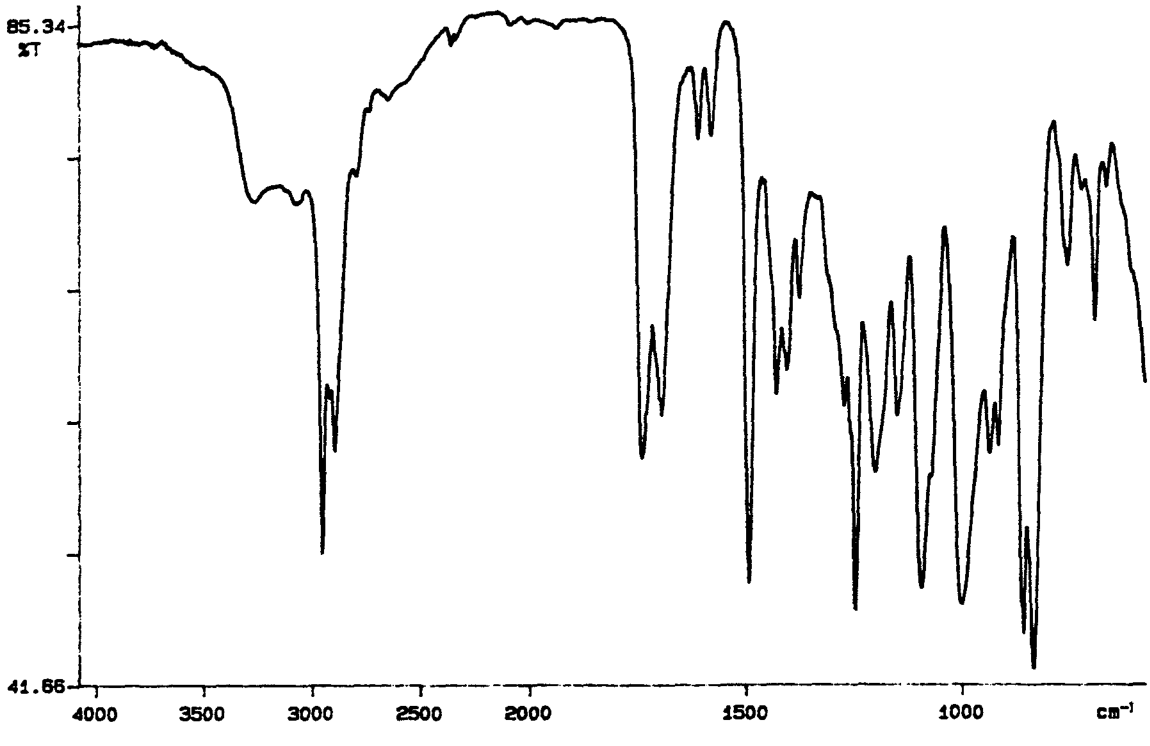

PPM
15
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0

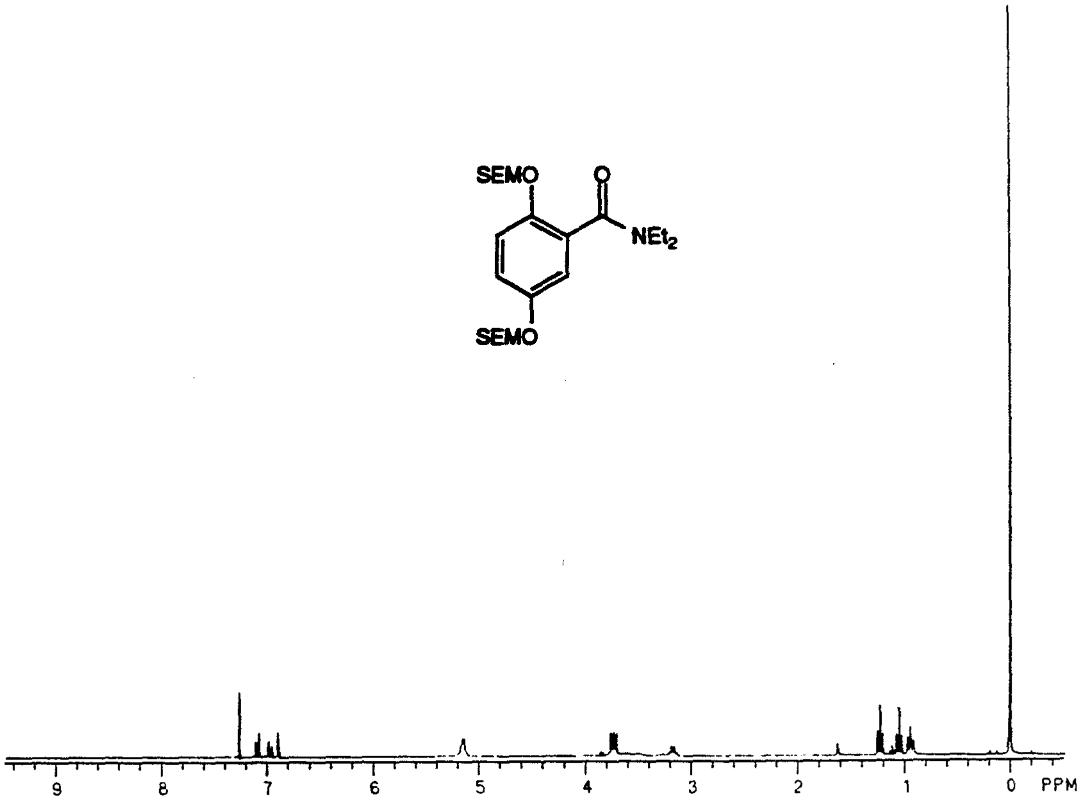

87.40
%T
68.98
4000
3500
3000
2500
2000
1500
1000
cm-1

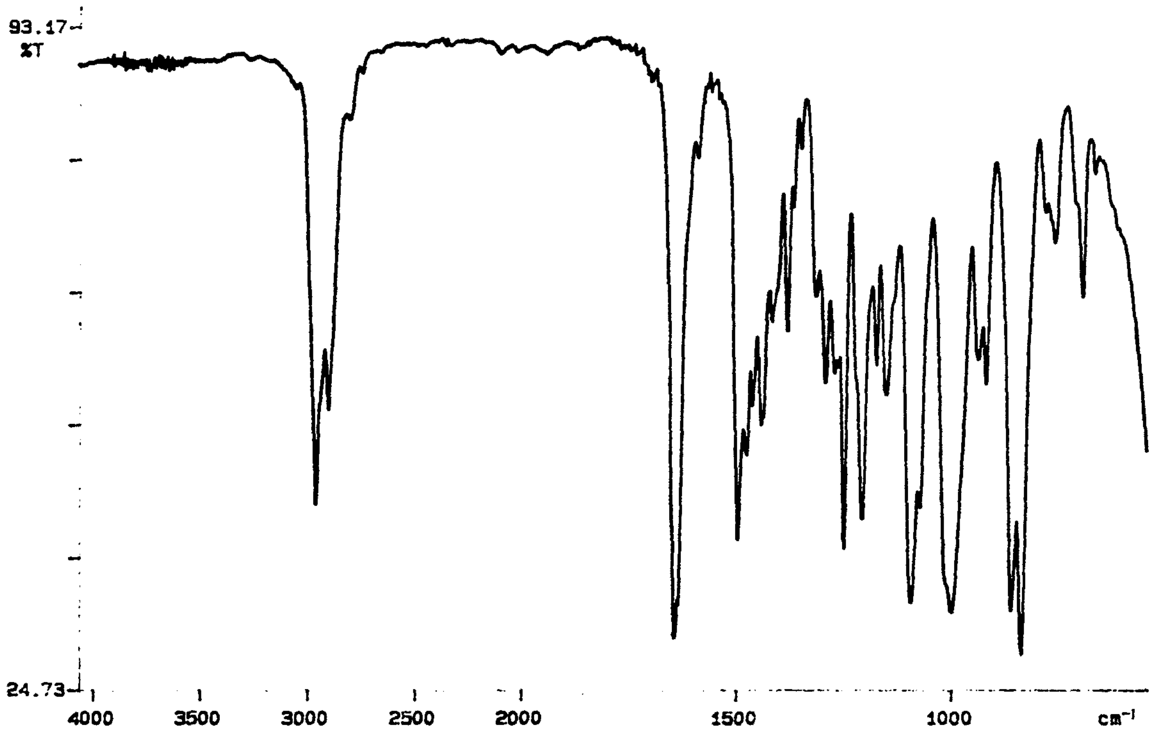

SEMO
O
OSEM
SEMO
14
12
10
8
6
4
2
0
-2
-4
PPM

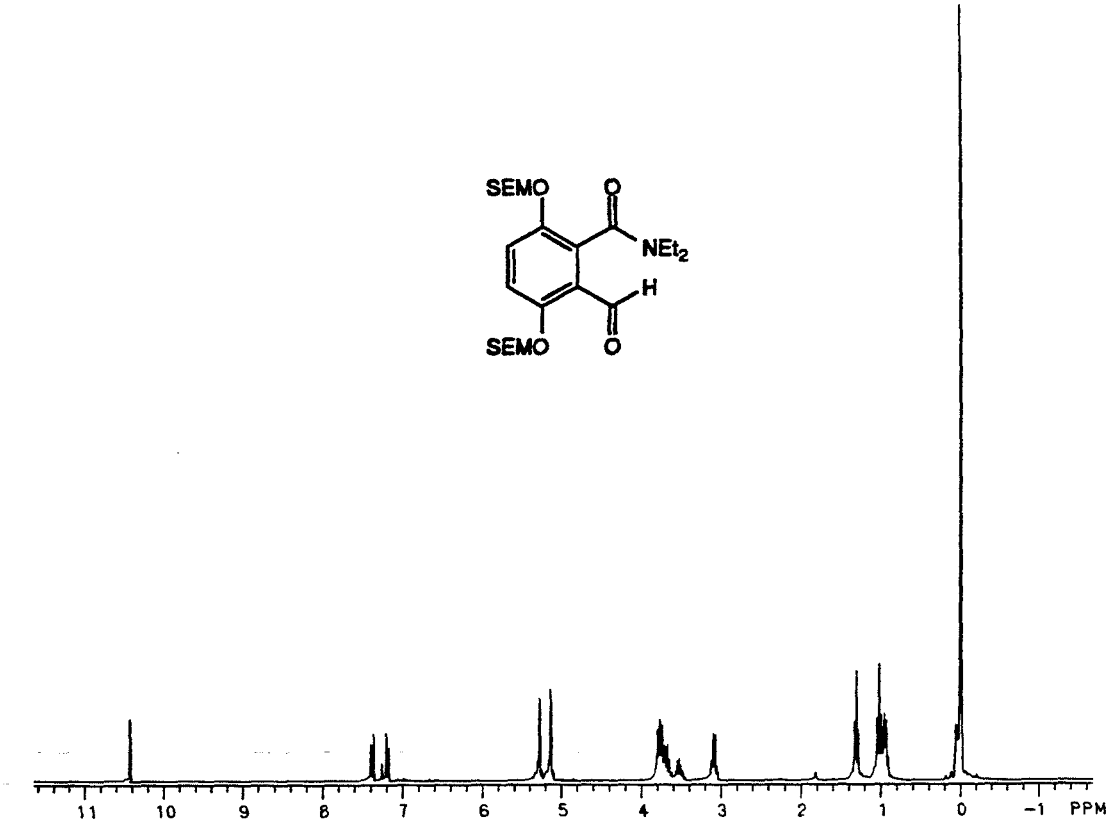

93.68
%T
50.22
4000
3500
3000
2500
2000
1500
1000
cm-1

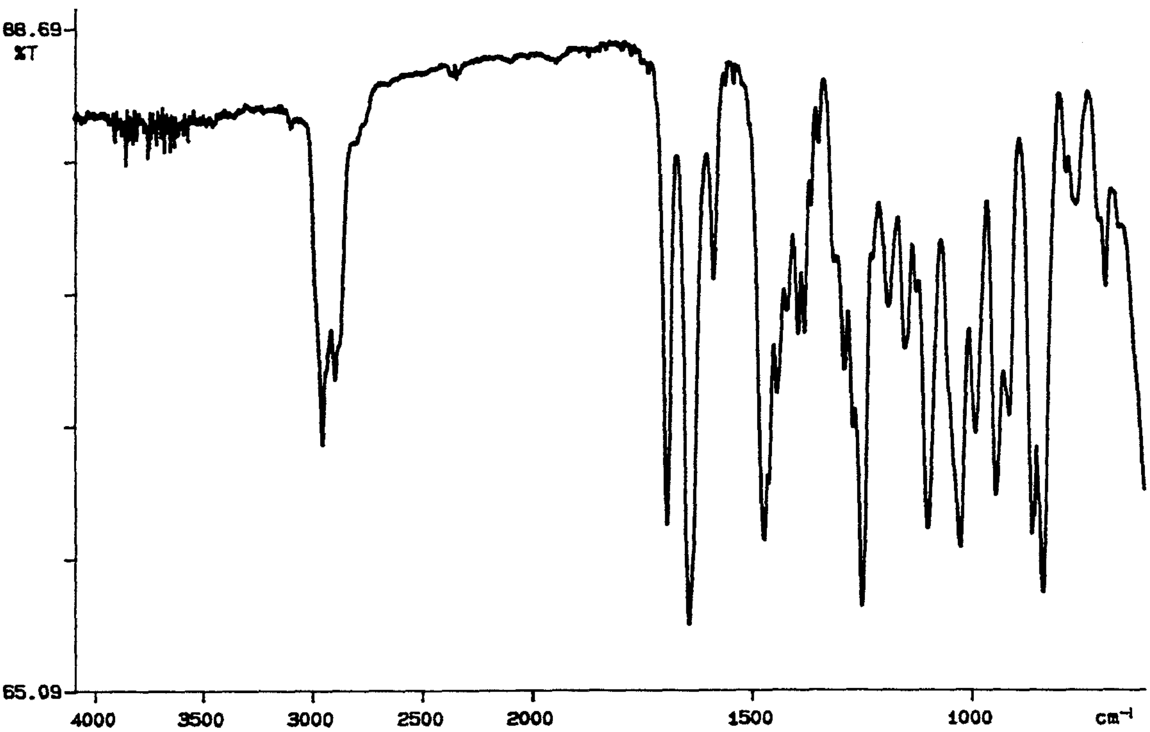

SEMO
O
OH
SEMO
14
12
10
8
6
4
2
0
-2
-4
PPM

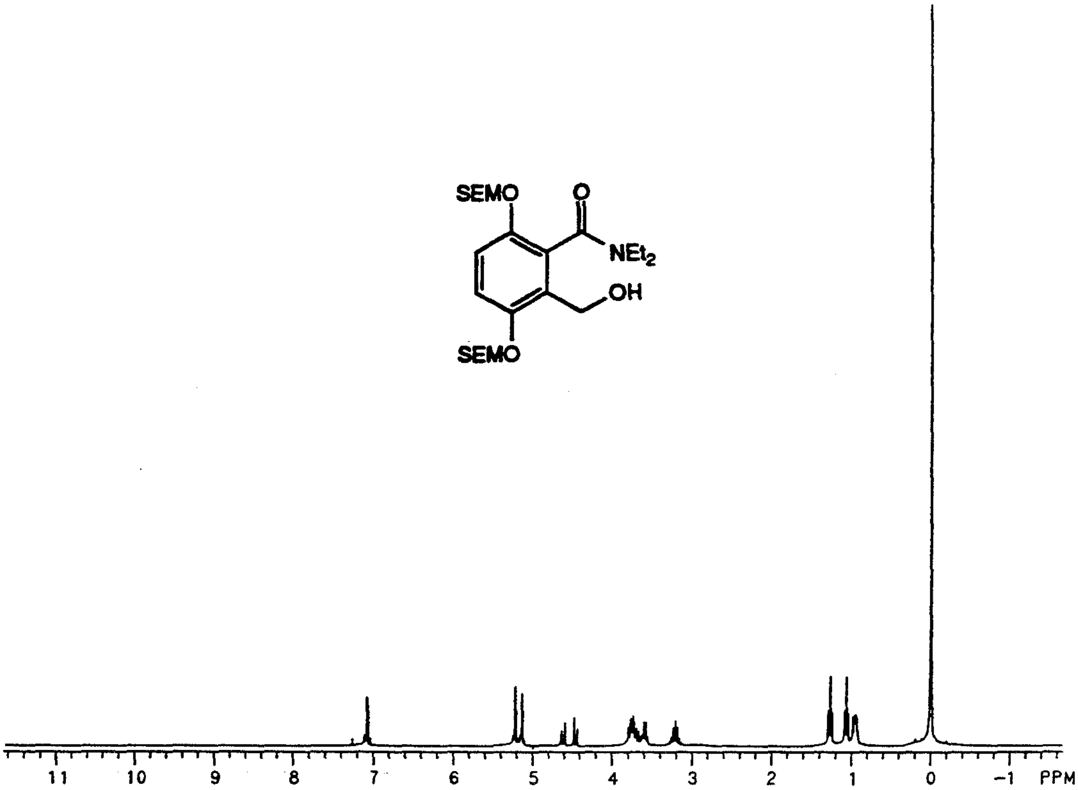

85.34
%T
41.66
4000
3500
3000
2500
2000
1500
1000
cm⁻¹

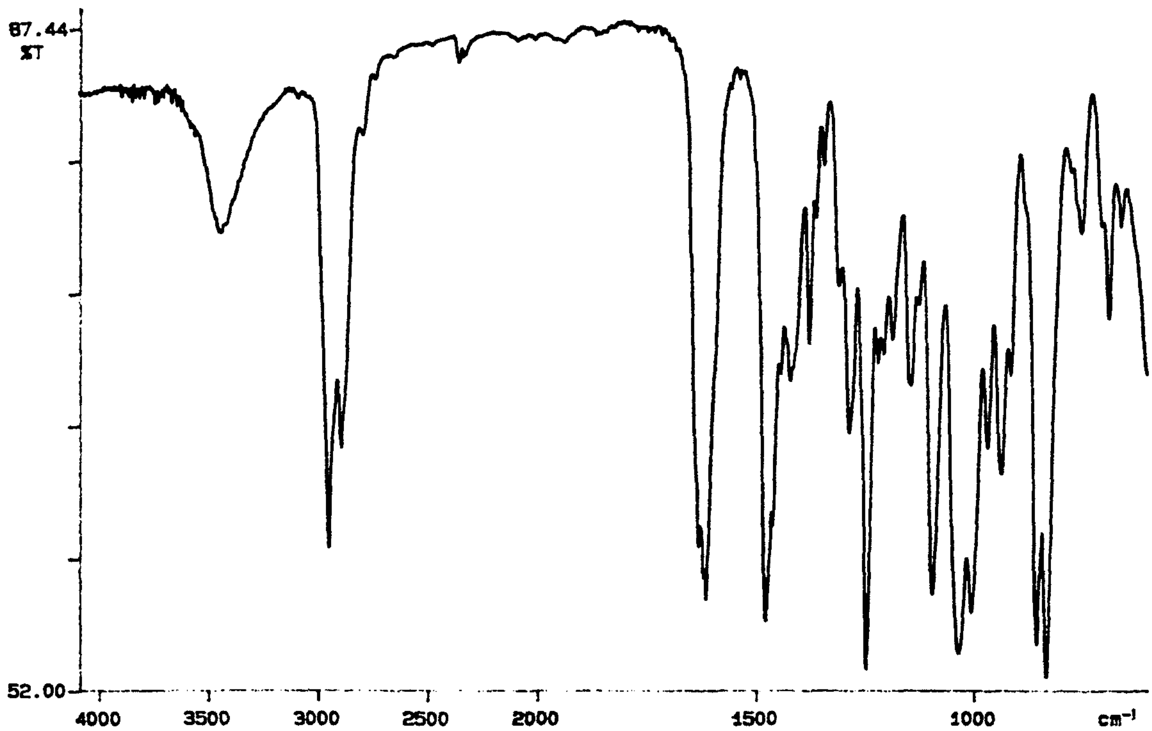

SEMO
O
NEt2
SEMO
9
8
7
6
5
4
3
2
1
0
PPM

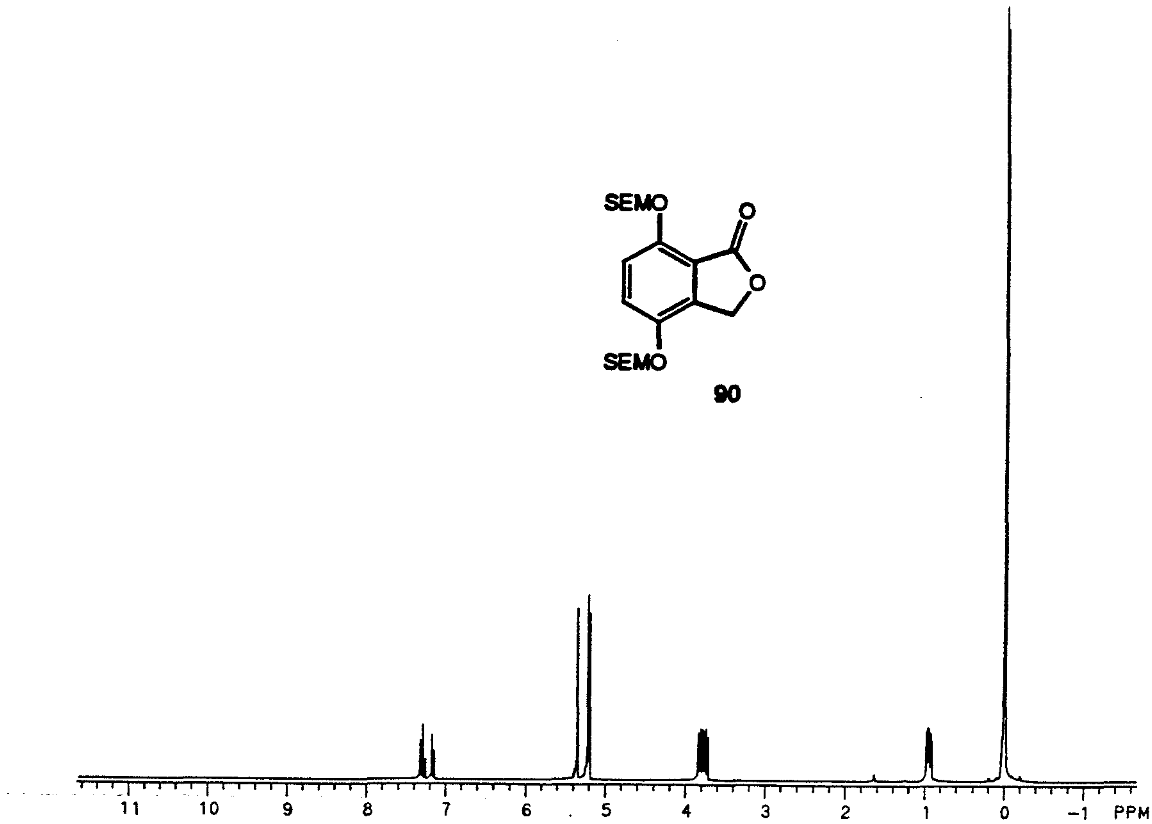

93.17
%T
24.73
4000
3500
3000
2500
2000
1500
1000
cm-1

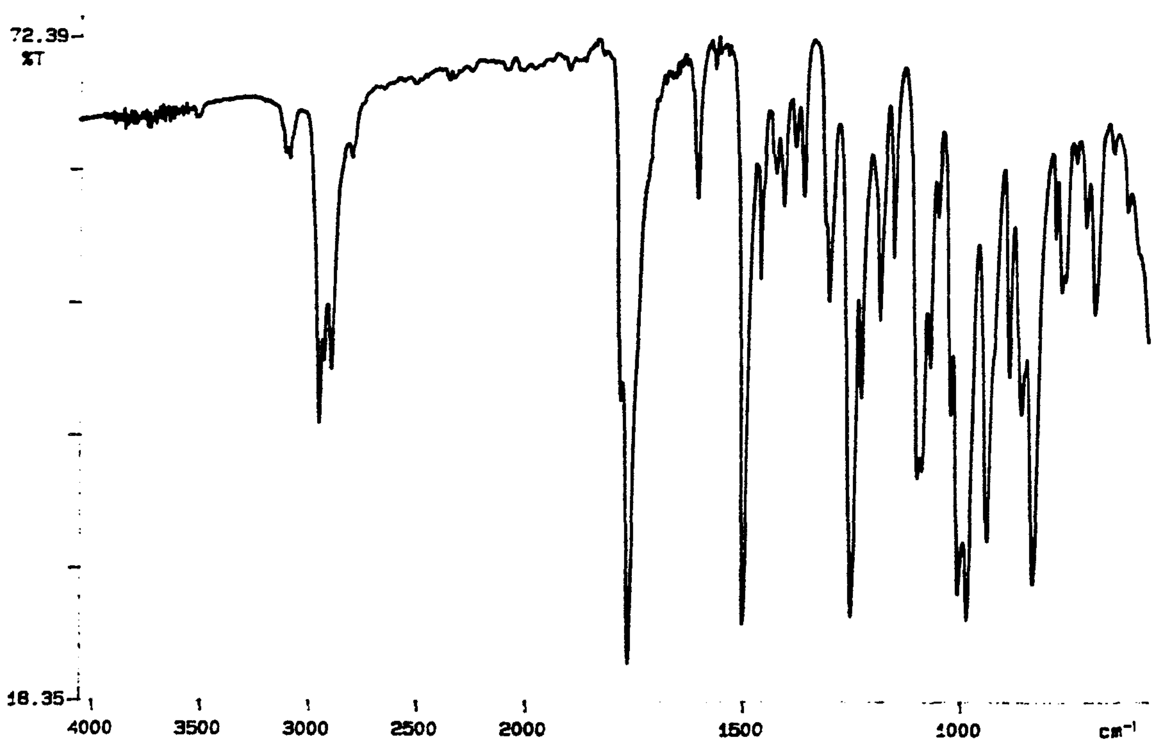

SEMO
O
NEt$_2$
H
SEMO
O
11
10
9
8
7
6
5
4
3
2
1
0
-1
PPM

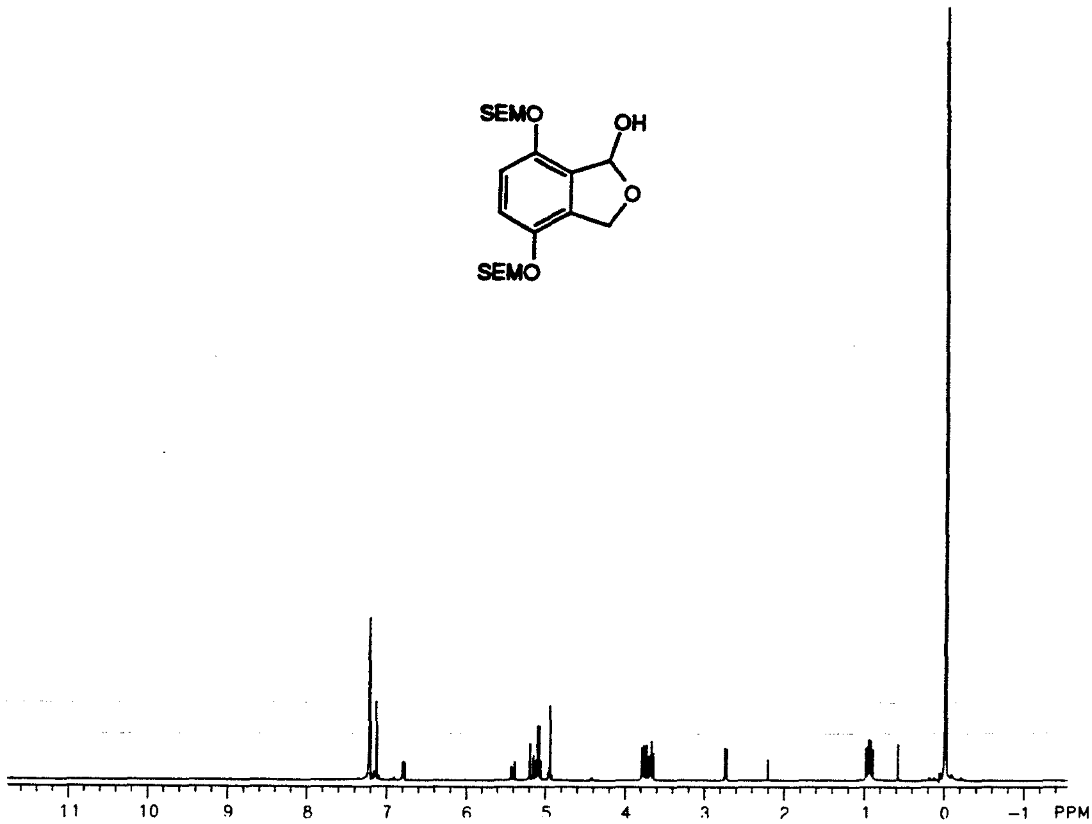

88.69
%T
65.09
4000
3500
3000
2500
2000
1500
1000
cm-1

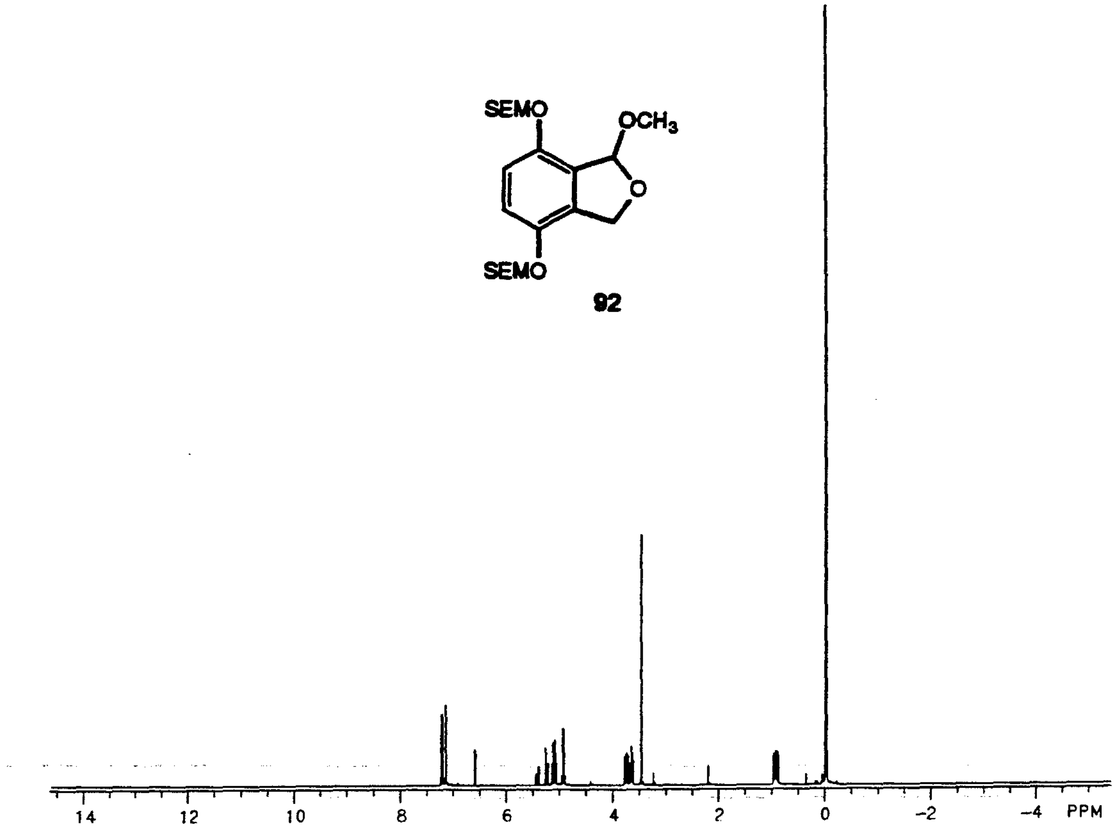

SEMO
O
NEt2
OH
SEMO
11
10
9
8
7
6
5
4
3
2
1
0
-1
PPM

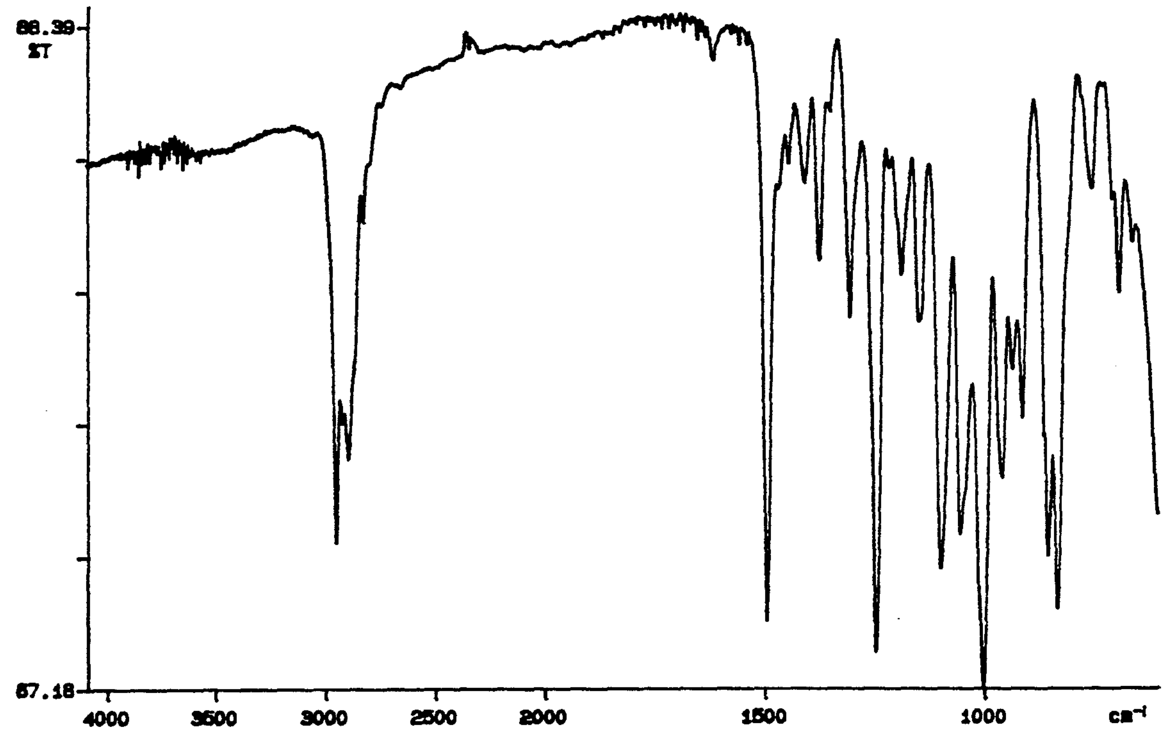

87.44
%T
52.00
4000
3500
3000
2500
2000
1500
1000
cm-1

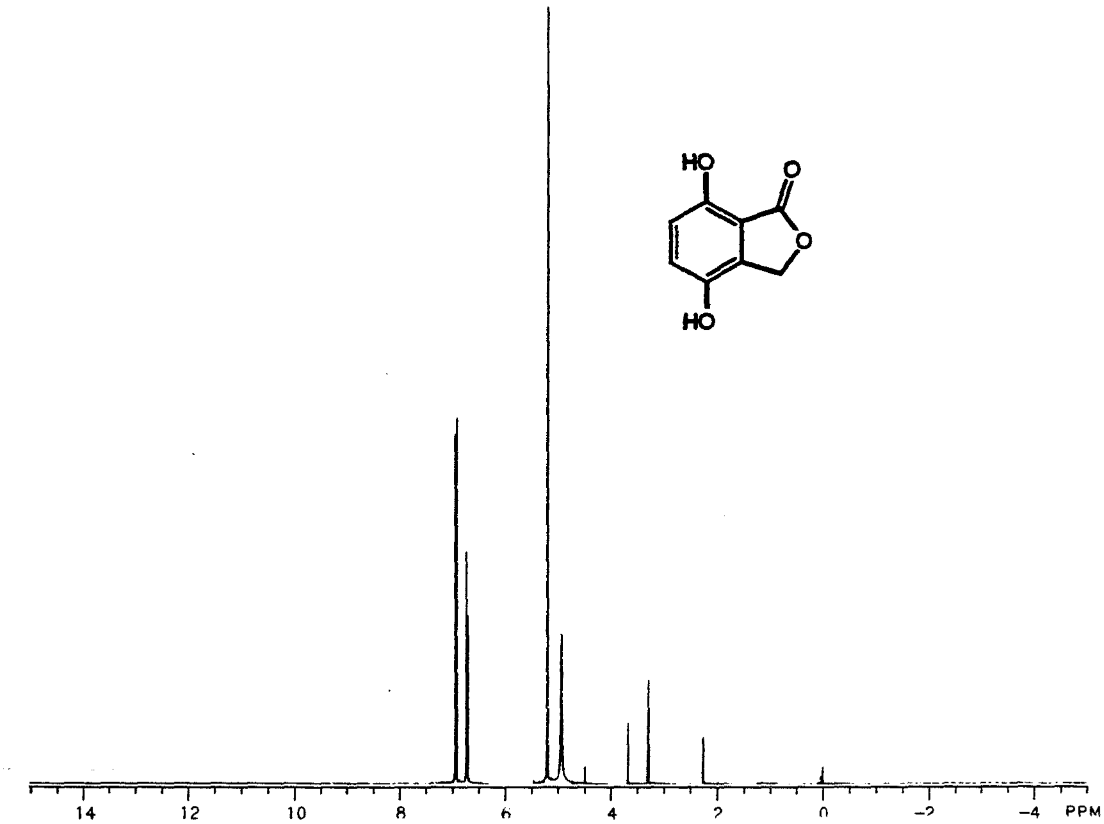

SEMO
O
O
SEMO
90
11
10
9
8
7
6
5
4
3
2
1
0
-1
PPM

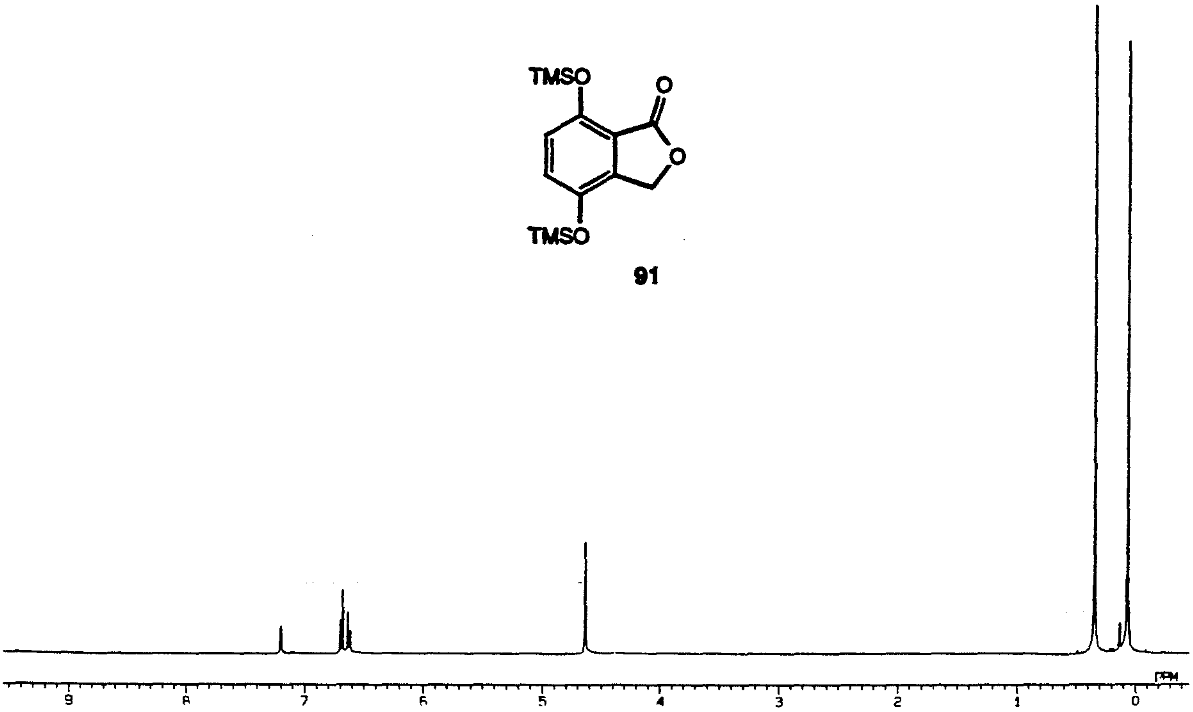

72.39
%T
18.35
4000
3500
3000
2500
2000
1500
1000
cm⁻¹

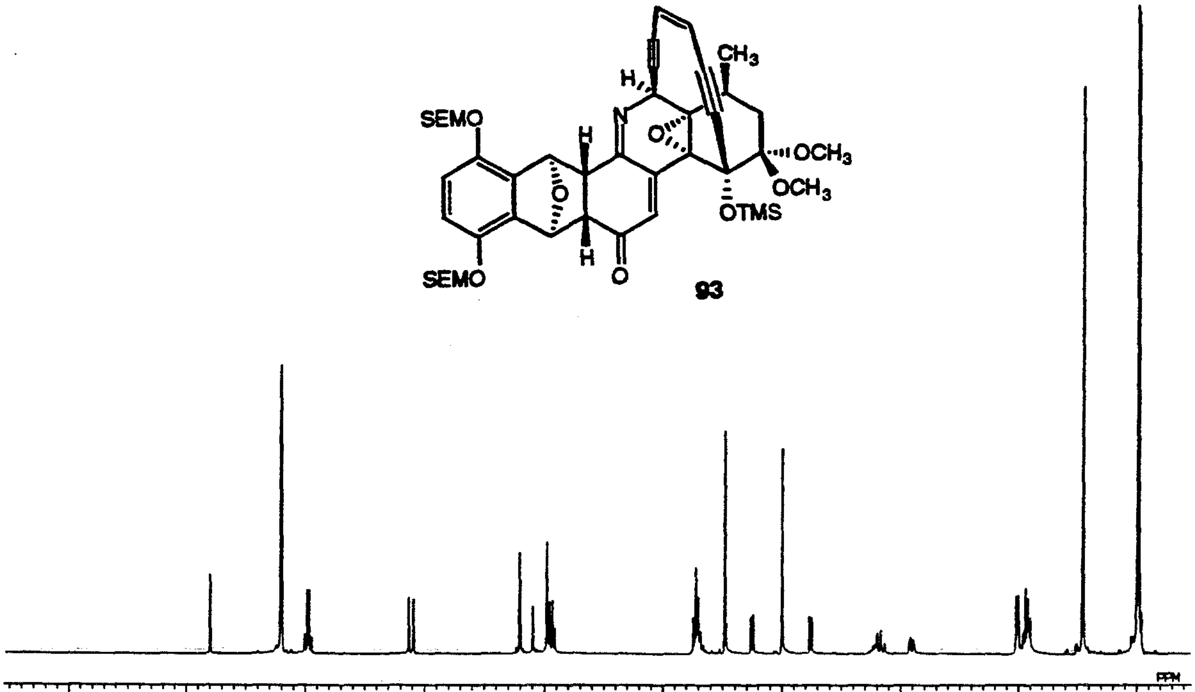

SEMO
OH
O
SEMO
11
10
9
8
7
6
5
4
3
2
1
0
-1
PPM

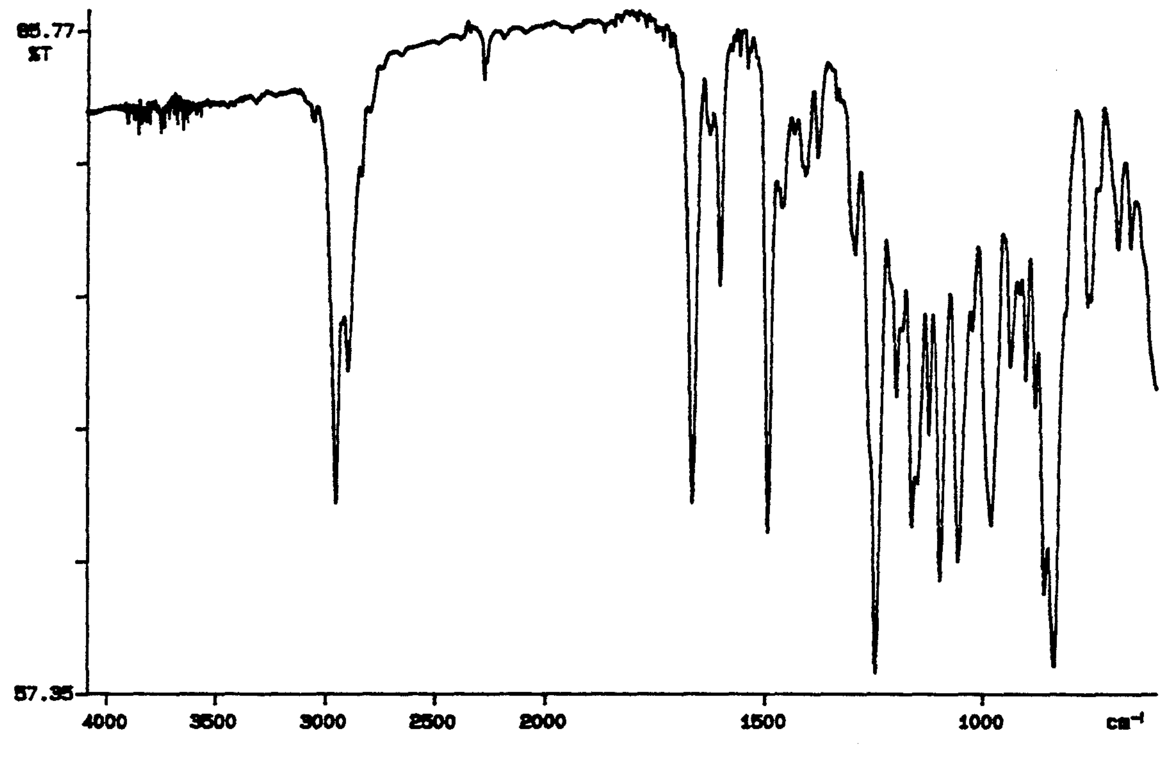

SEMO
OCH3
O
SEMO
92
14
12
10
8
6
4
2
0
-2
-4
PPM

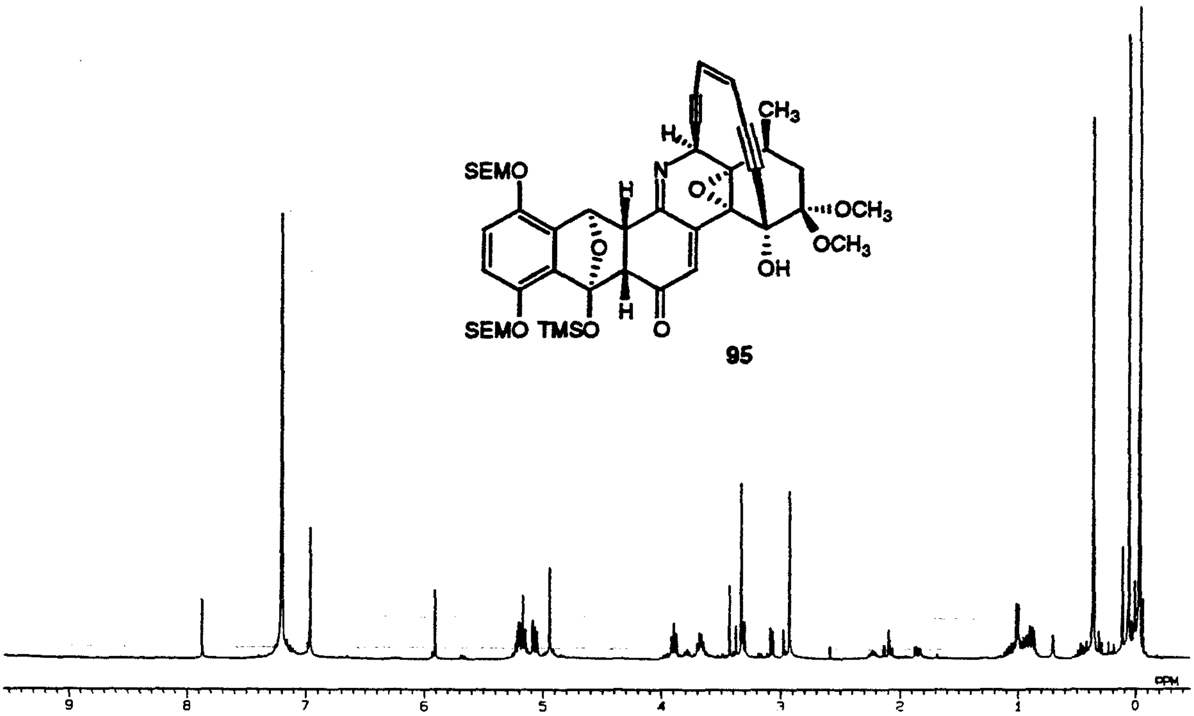

88.39
%T
57.18
4000
3500
3000
2500
2000
1500
1000
cm⁻¹

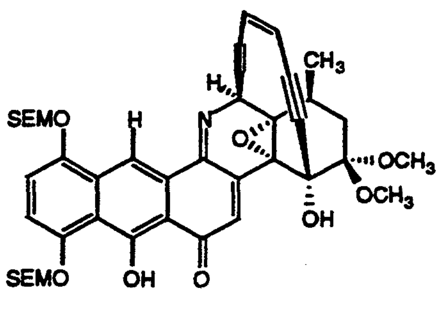

HO
O
O
HO
14
12
10
8
6
4
2
0
−2
−4
PPM


TMSO
O
O
TMSO
91
PPM
9
8
7
6
5
4
3
2
1
0

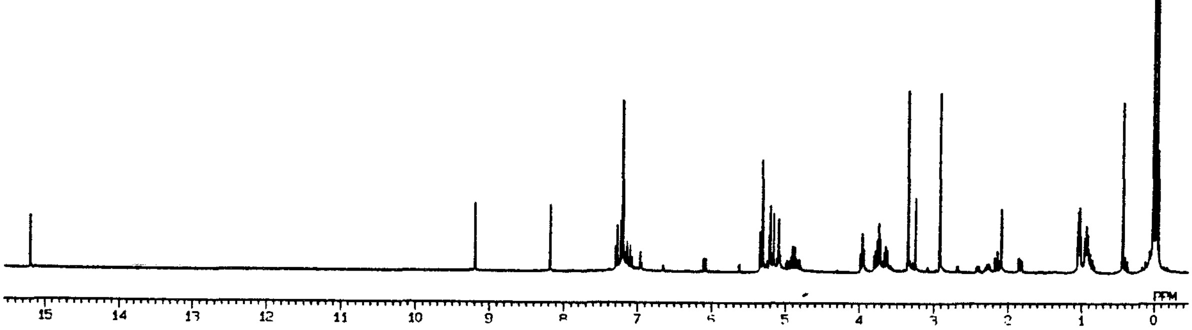

SEMO
SEMO
OTMS
OCH3
OCH3
CH3
93
PPM
9
8
7
6
5
4
3
2
1
0

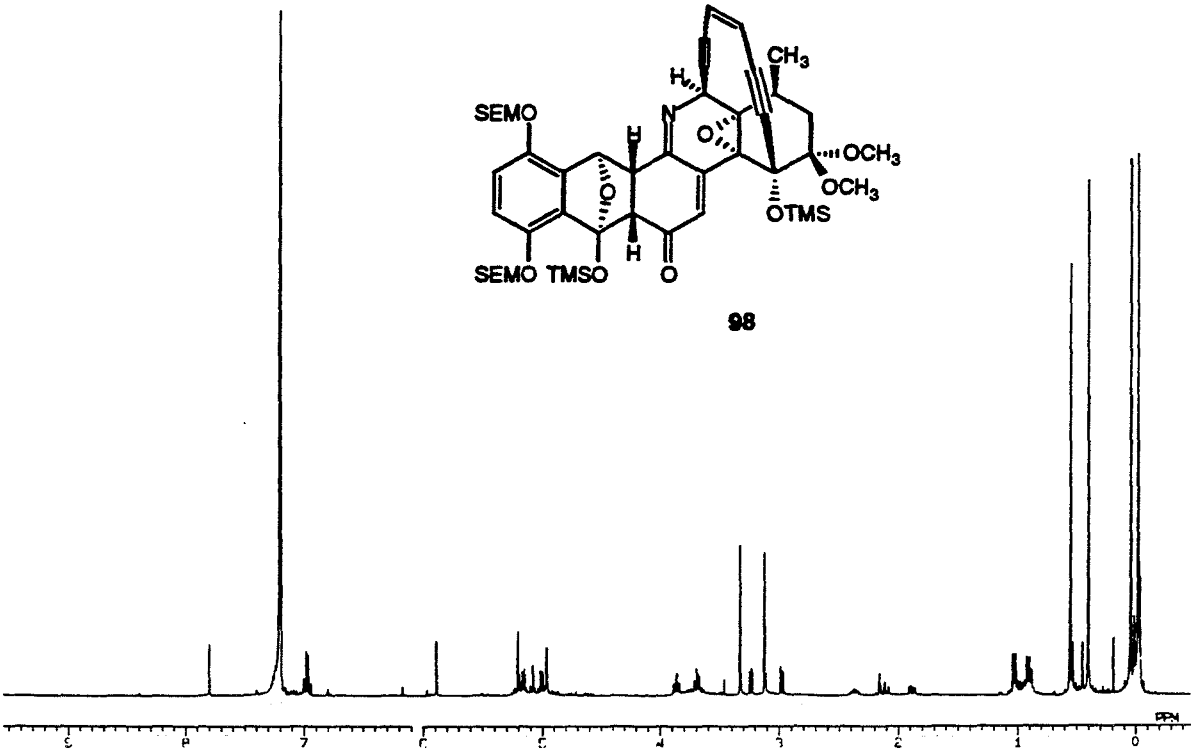

85.77
%T
57.35
4000
3500
3000
2500
2000
1500
1000
cm-1


SEMO
SEMO TMSO
H
H
N
O
H
CH3
OCH3
OCH3
OH
O
95
9
8
7
6
5
4
3
2
1
0
PPM

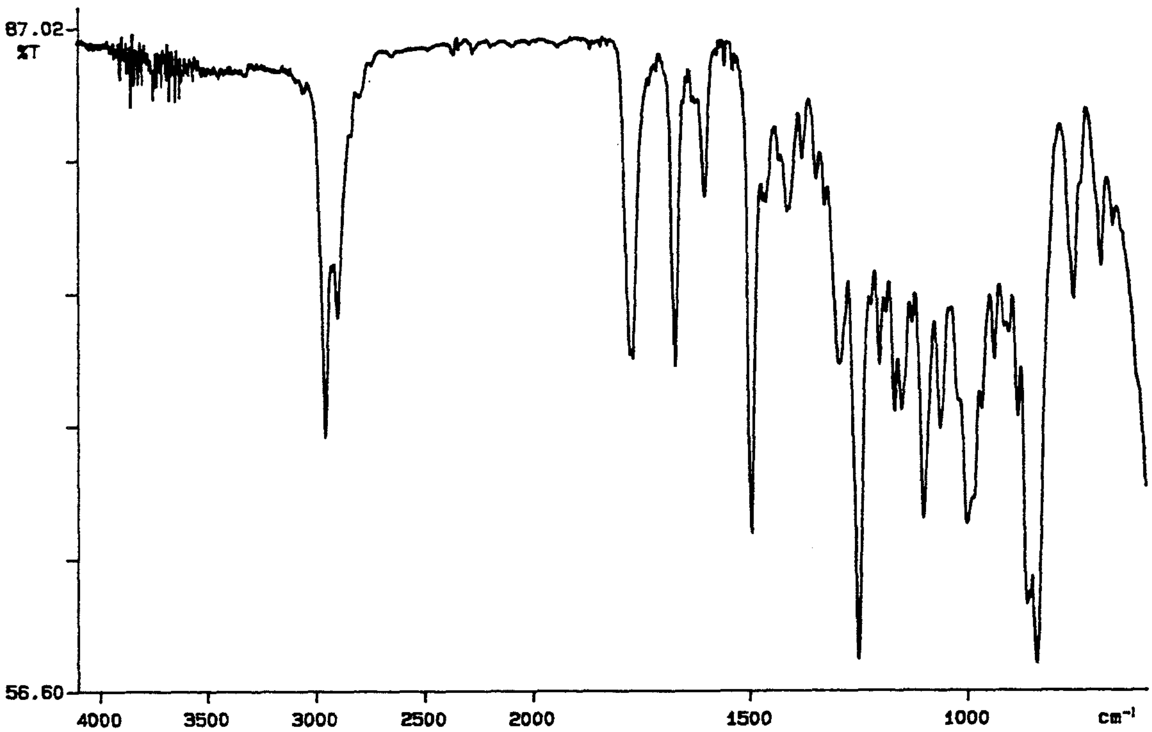

SEMO
H
N
H
CH3
O
OCH3
OCH3
OH
SEMO
OH
O

96

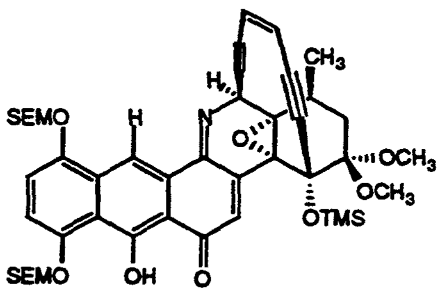

15
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
PPM



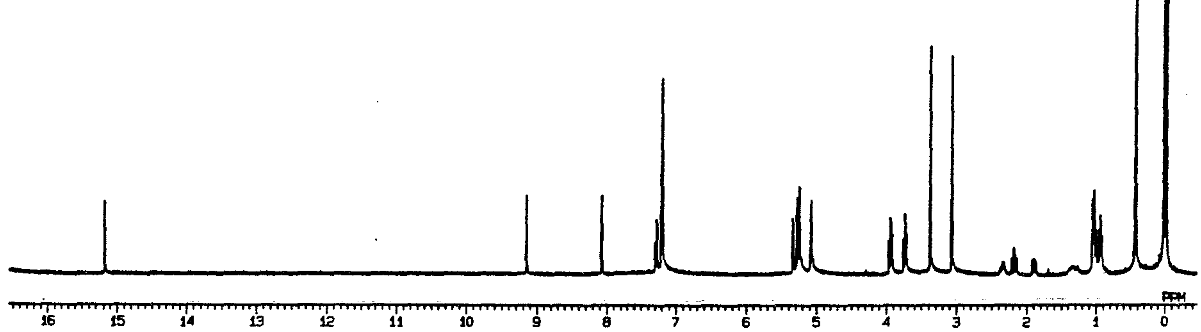
SEMO
SEMO
TMSO
OTMS
OCH3
OCH3
CH3
98
7
5
4
3
2
1
0
PPM

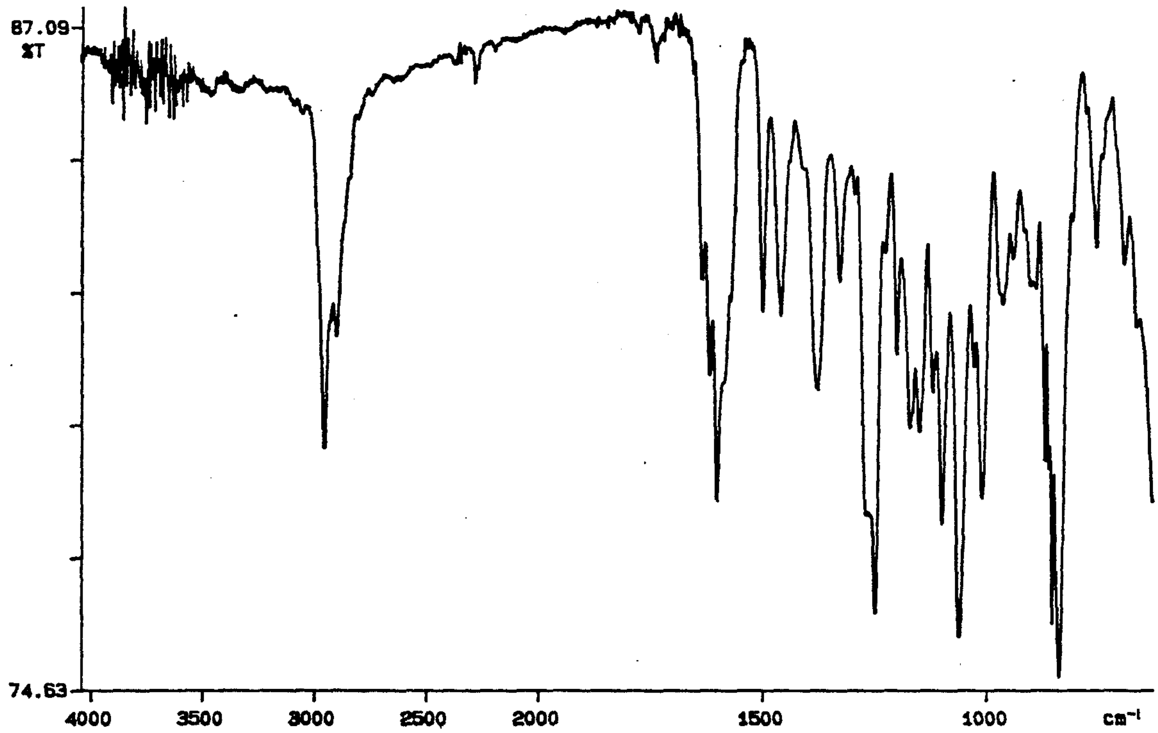


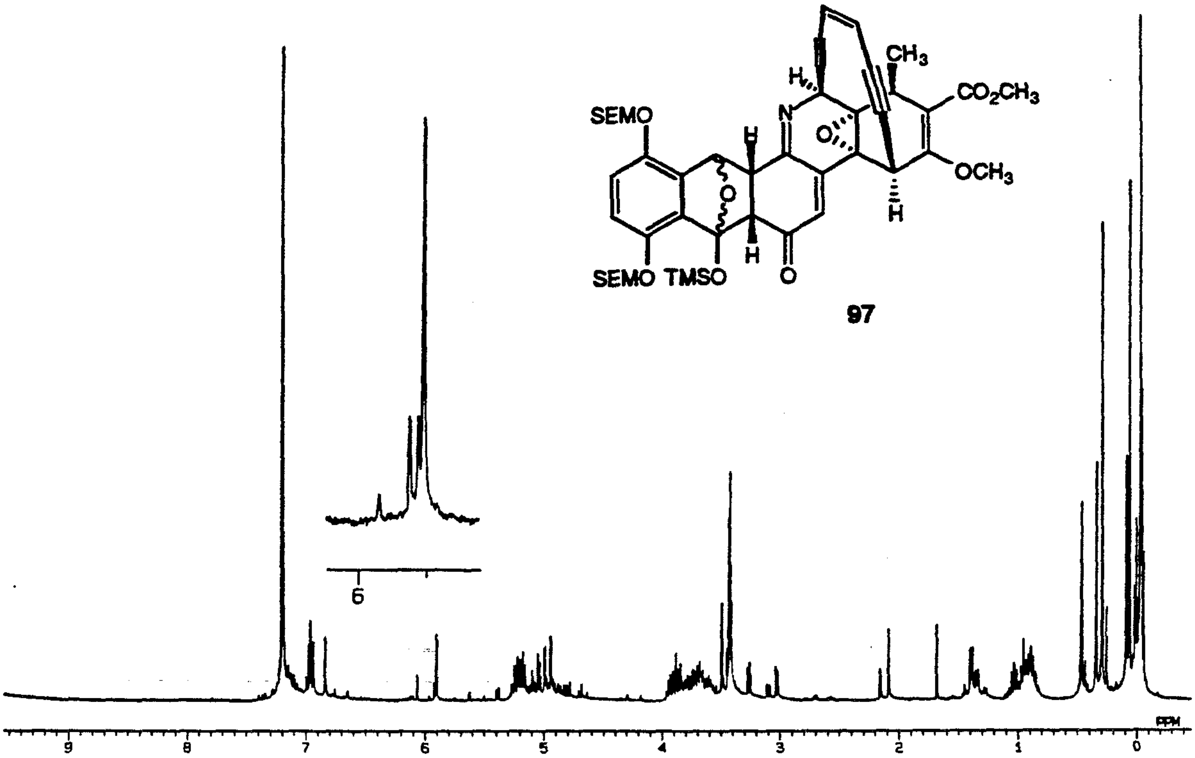
87.02
%T
56.60
4000
3500
3000
2500
2000
1500
1000
cm-1

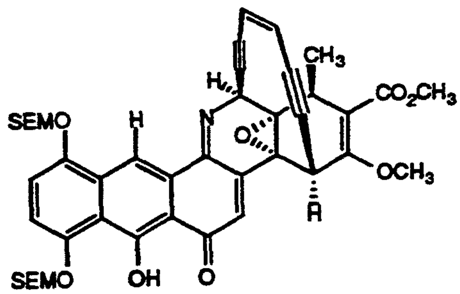

SEMO
H
N
H
CH3
O
OCH3
OCH3
OTMS
SEMO
OH
O

100

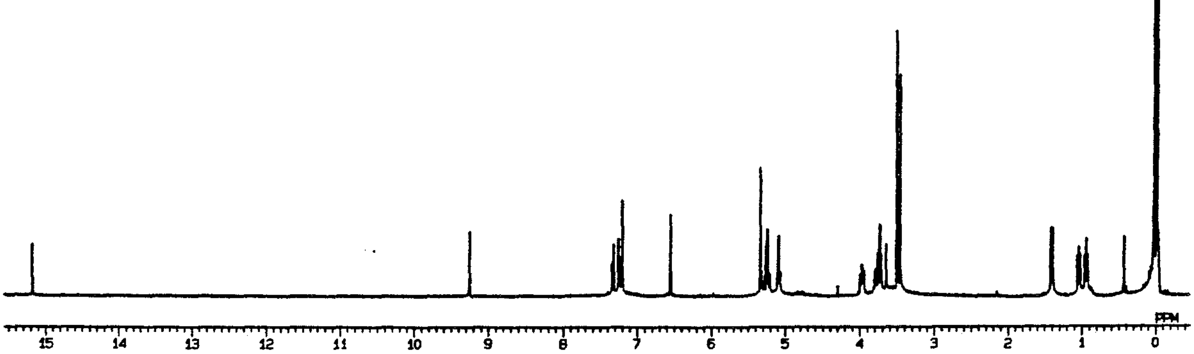

PPM
16
15
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0

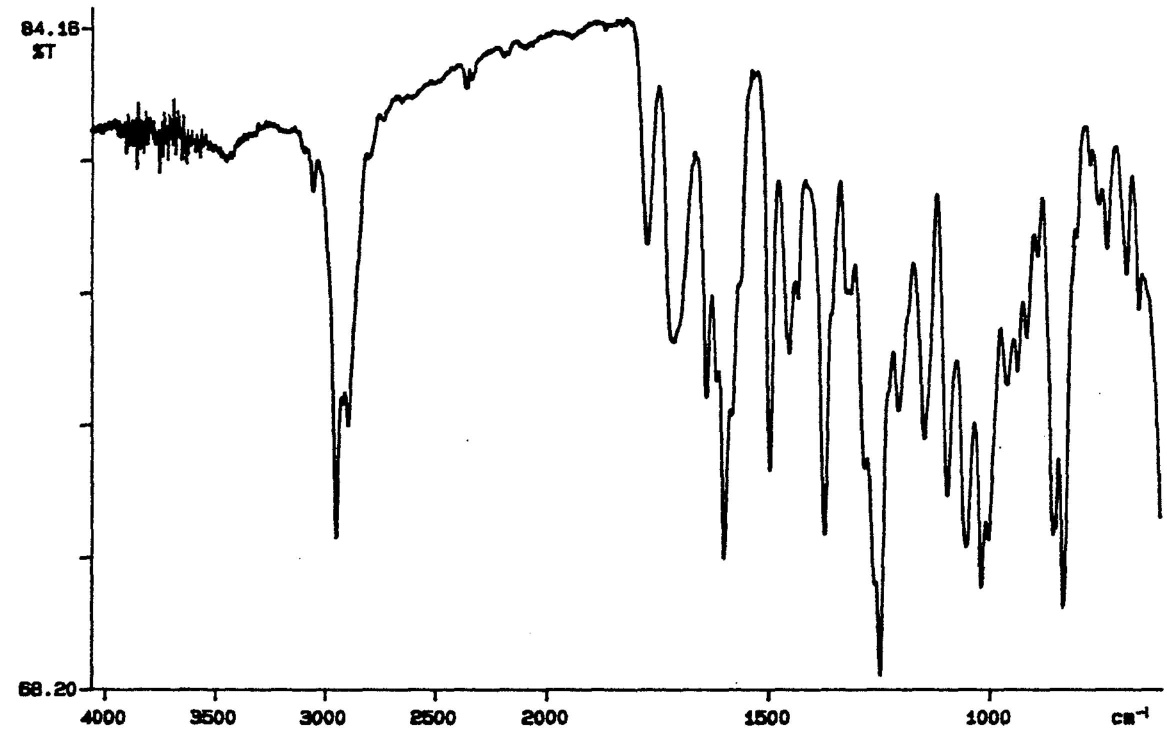

87.09
%T
74.63
4000
3500
3000
2500
2000
1500
1000
cm⁻¹

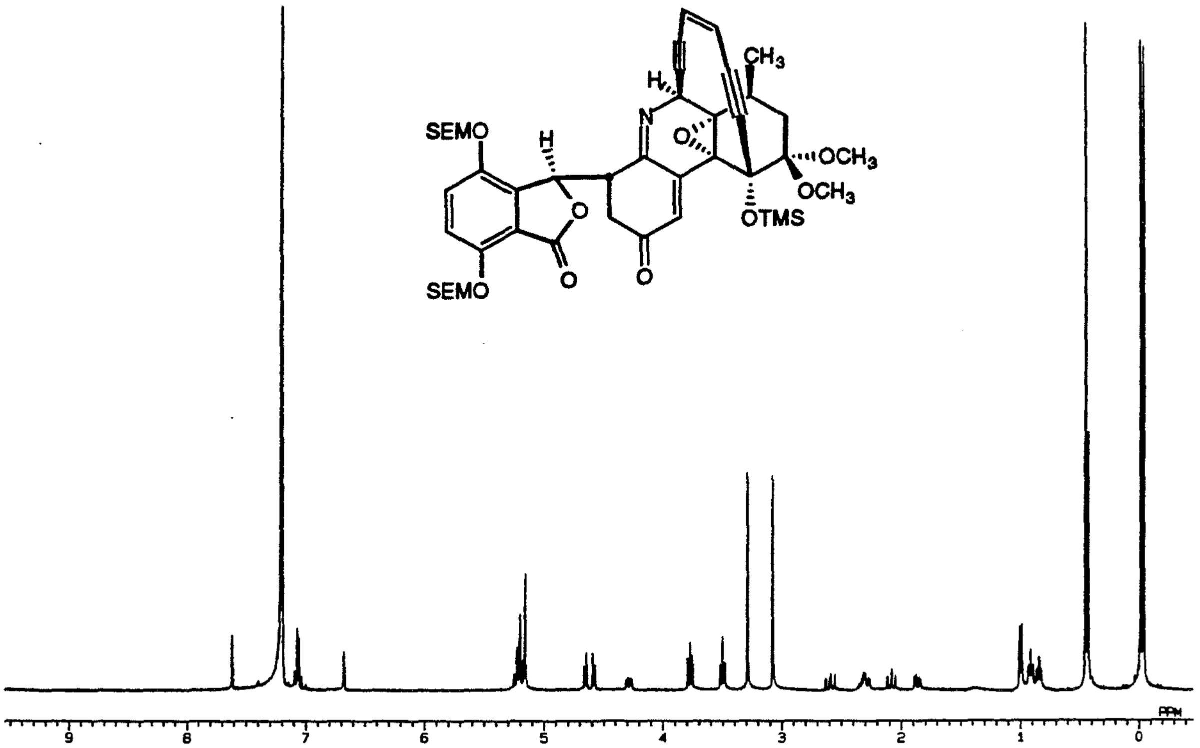

SEMO
SEMO TMSO
CH3
CO2CH3
OCH3
97
6
9 8 7 6 5 4 3 2 1 0
PPM

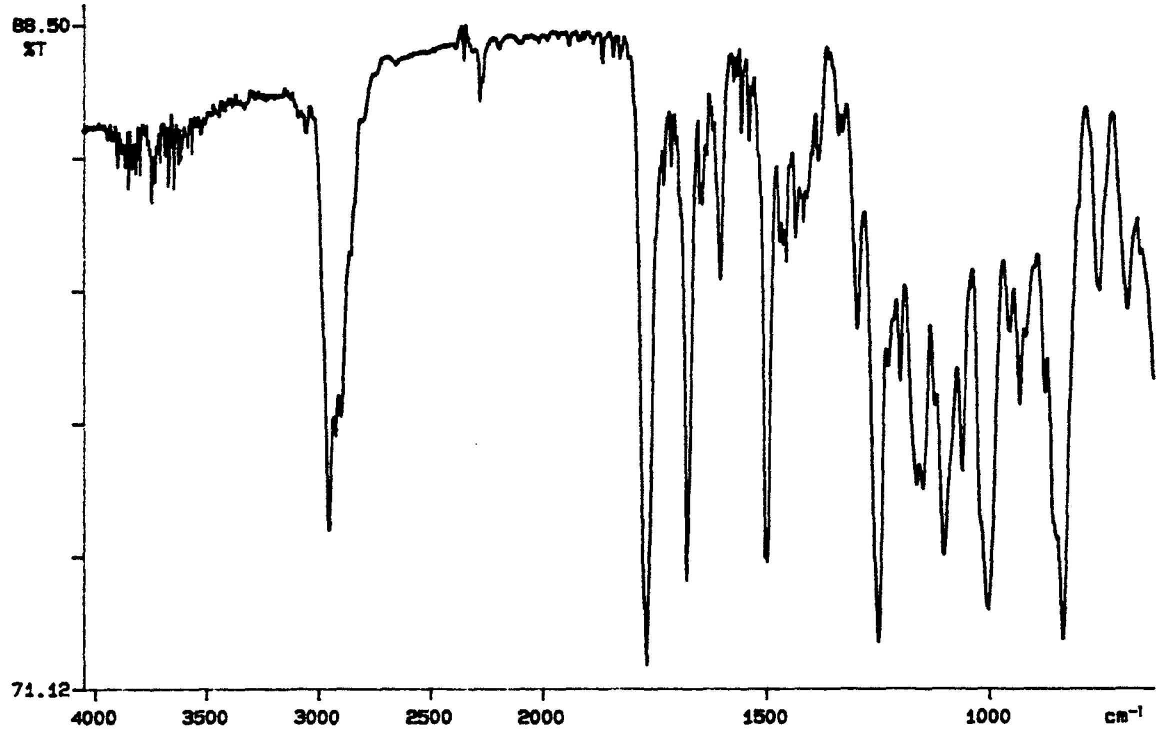

SEMO
H
N
H
CH3
CO2CH3
O
OCH3
H
SEMO
OH
O

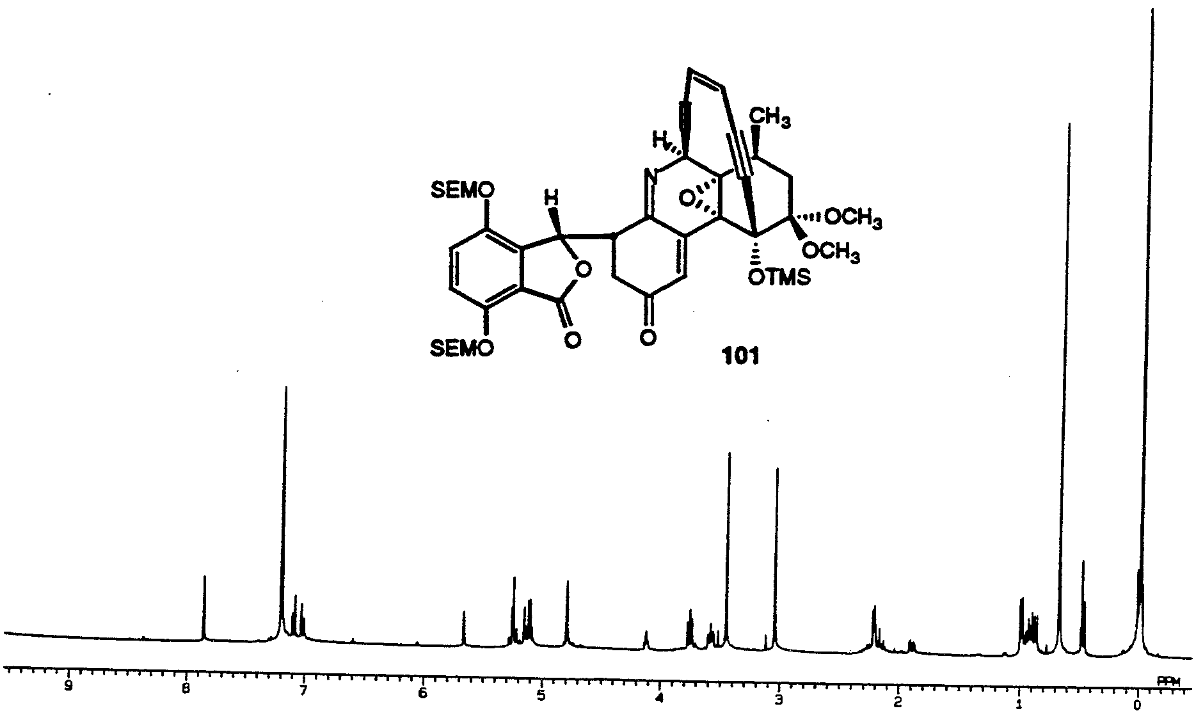
99

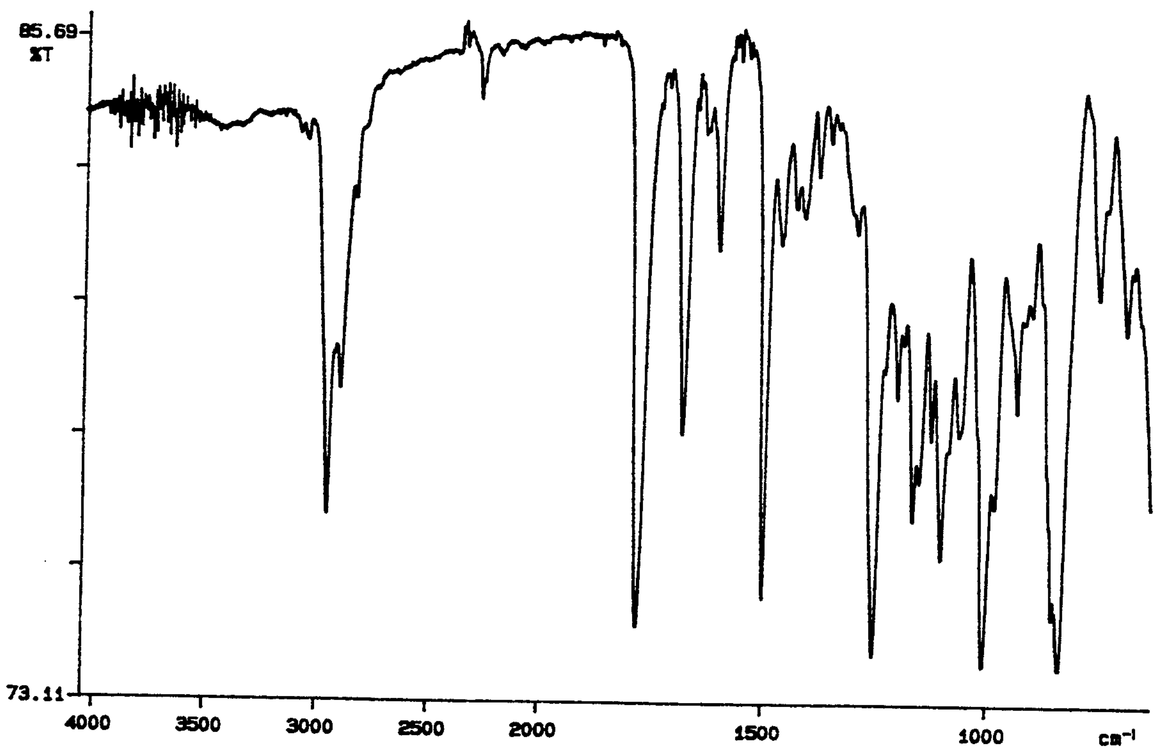

PPM
15
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0

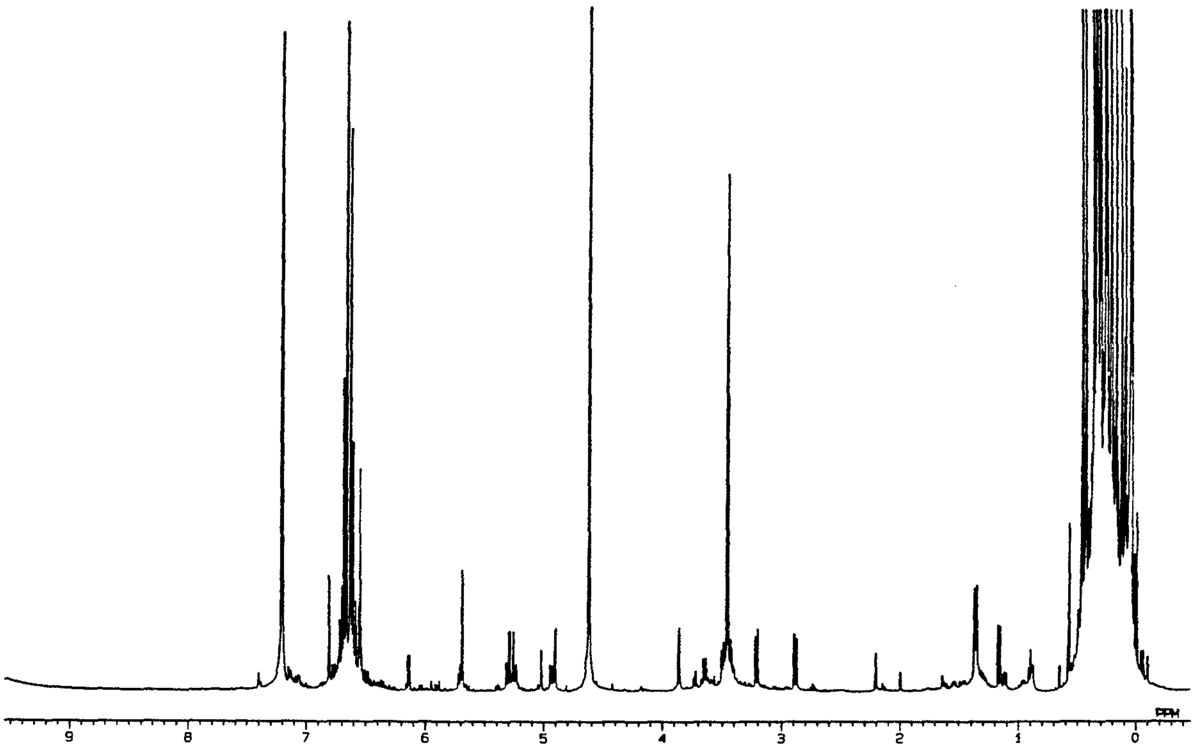

84.16
%T
68.20
4000
3500
3000
2500
2000
1500
1000
cm-1

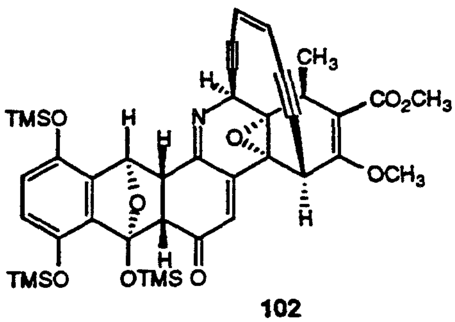

SEMO
H
O
SEMO
O
O
N
H
O
CH3
OCH3
OCH3
OTMS
PPM
9
8
7
6
5
4
3
2
1
0


88.50
%T
71.12
4000
3500
3000
2500
2000
1500
1000
cm-1

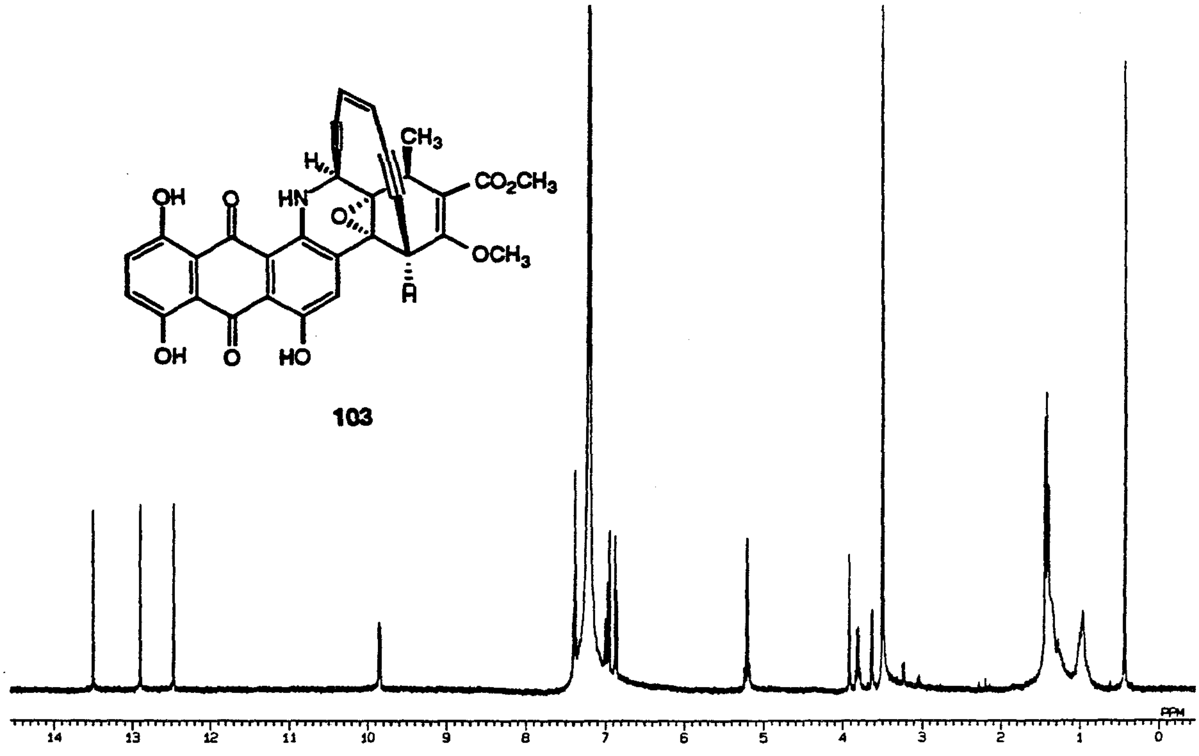

SEMO
SEMO
H
H
N
O
O
O
O
O
CH3
OCH3
OCH3
OTMS
101
9
8
7
6
5
4
3
2
1
0
PPM


85.69
%T
73.11
4000
3500
3000
2500
2000
1500
1000
cm-1

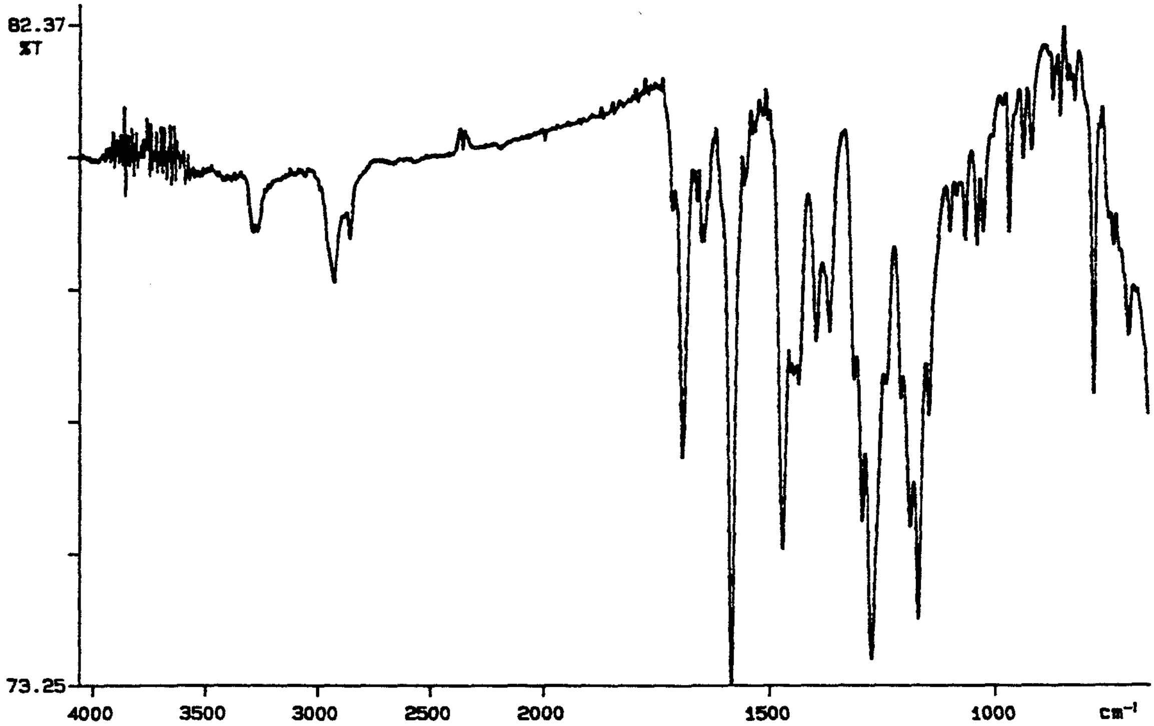




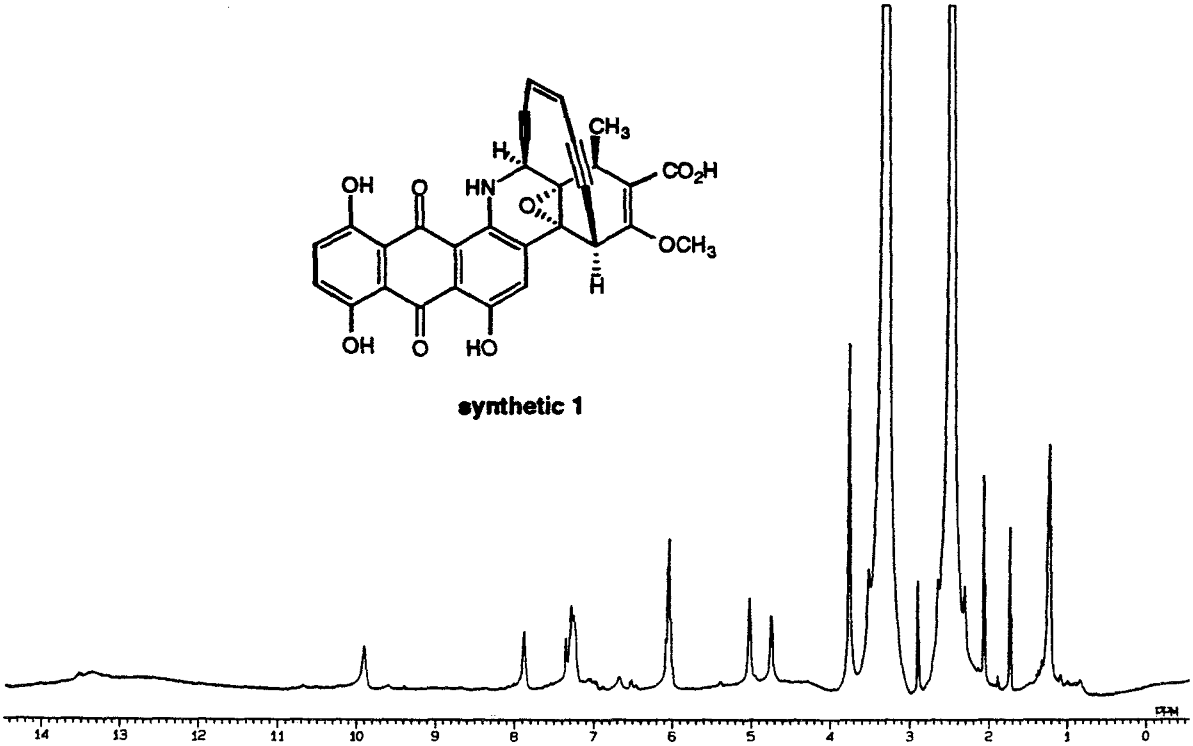
102

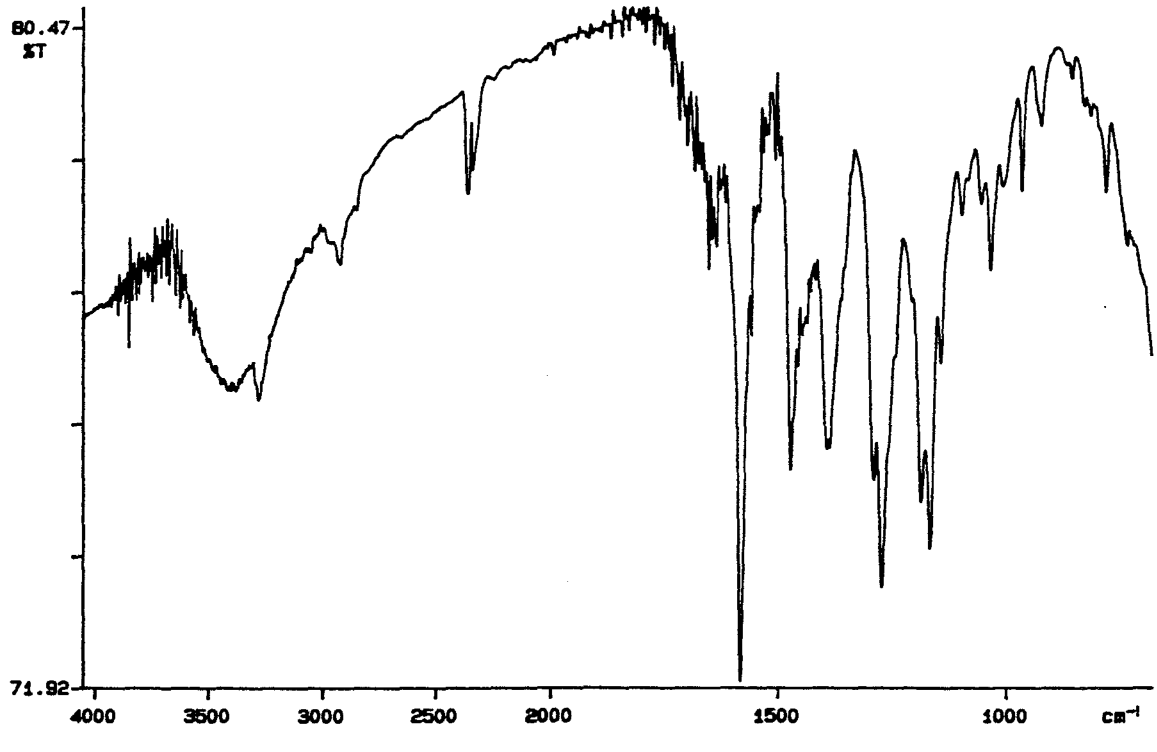


OH
O
HN
H
CH3
CO2CH3
OCH3
OH
O
HO
H
103
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
PPM

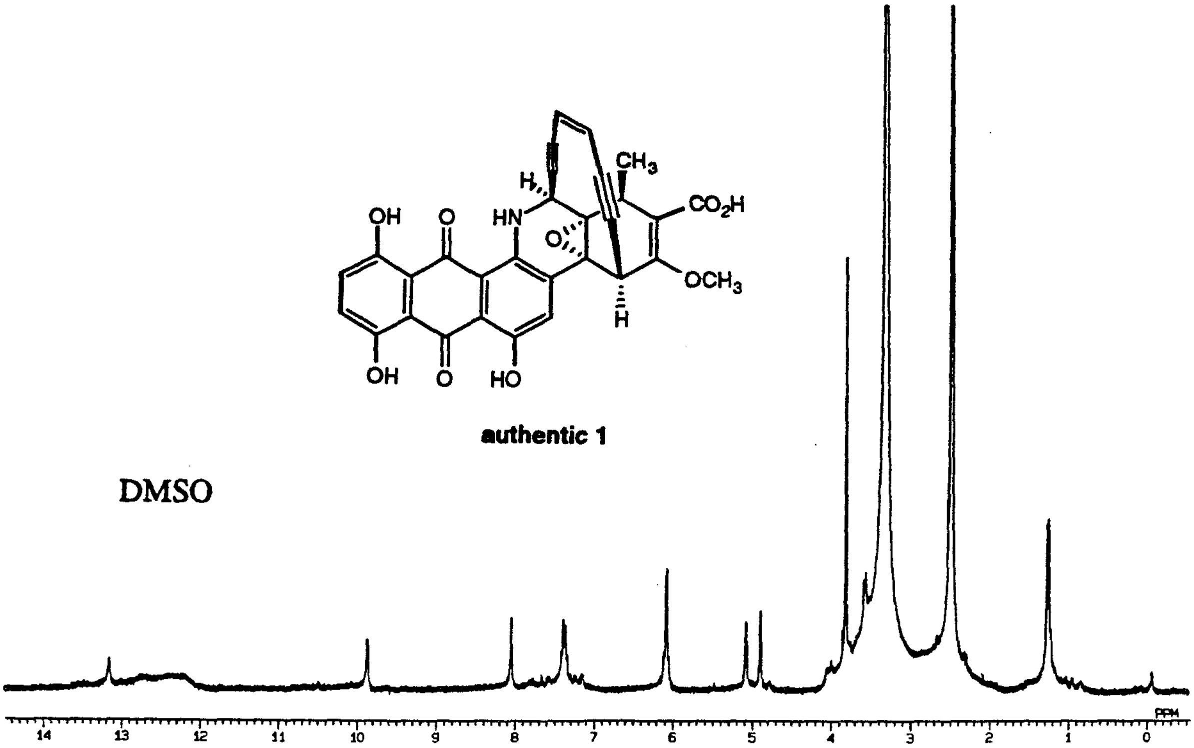


82.37
%T
73.25
4000
3500
3000
2500
2000
1500
1000
cm-1

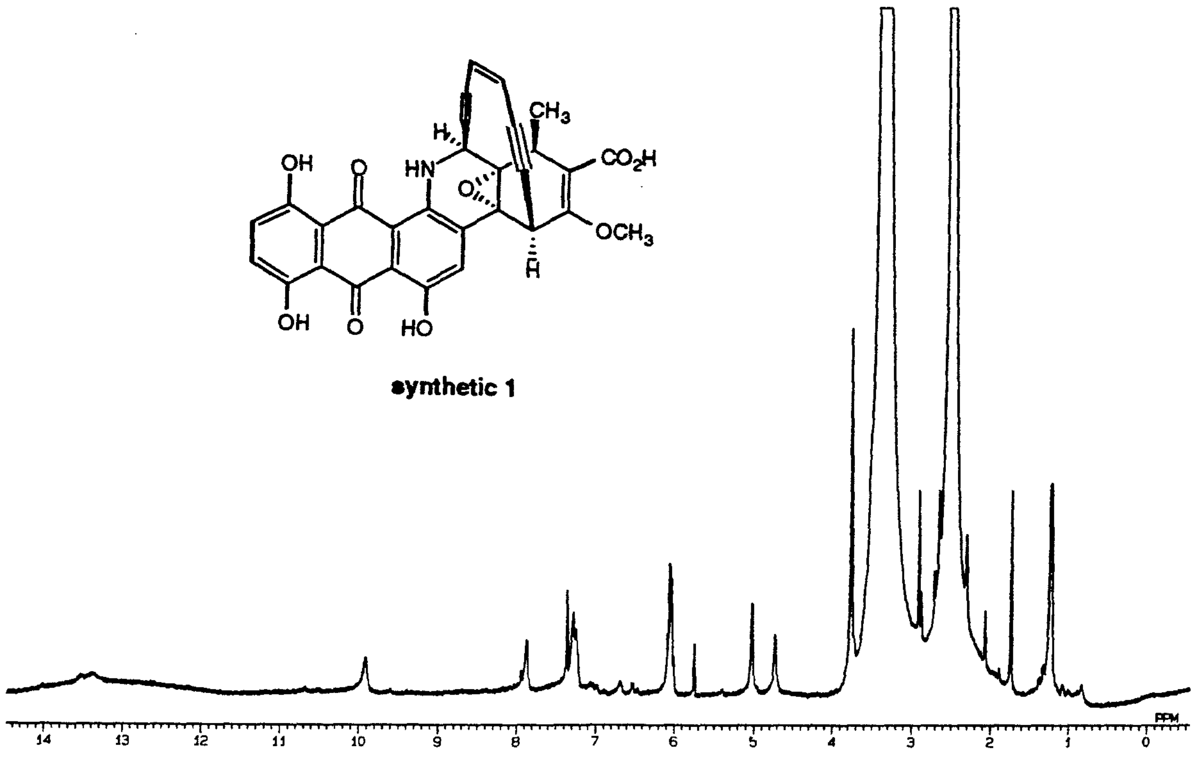

CH3
H
CO2H
OH
O
HN
O
OCH3
H
OH
O
HO
synthetic 1
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
PPM


80.47
%T
71.92
4000
3500
3000
2500
2000
1500
1000
cm-1

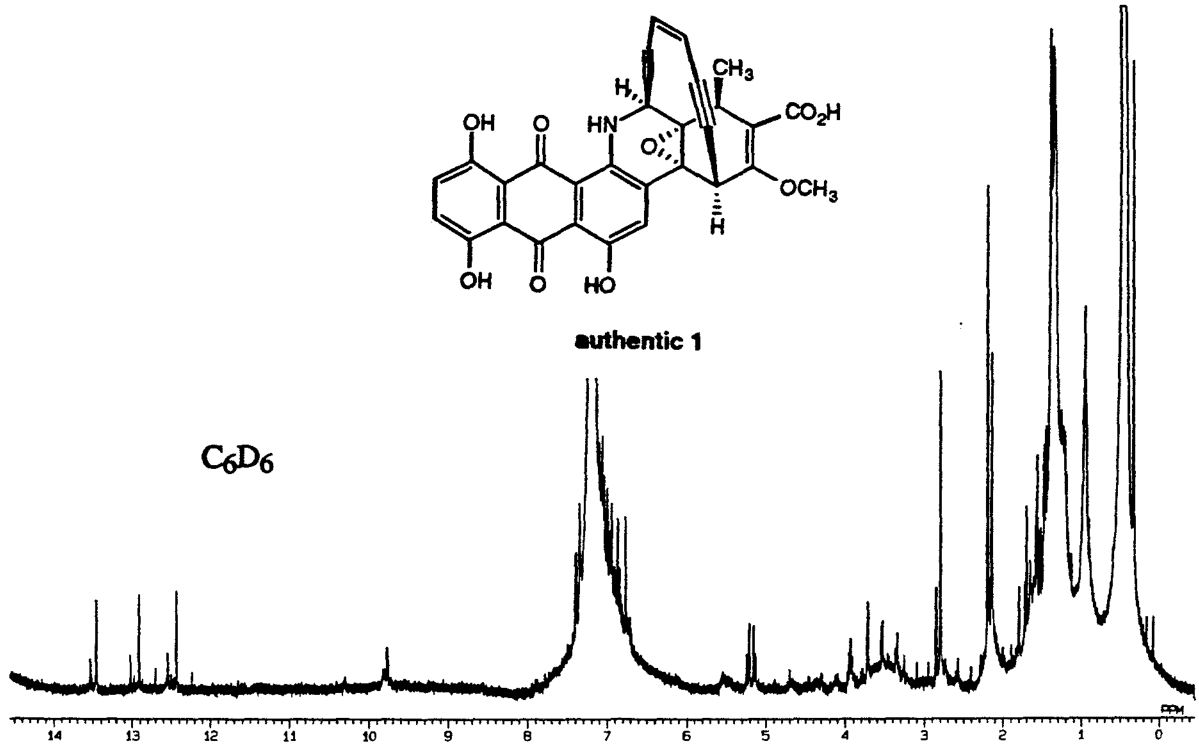
DMSO



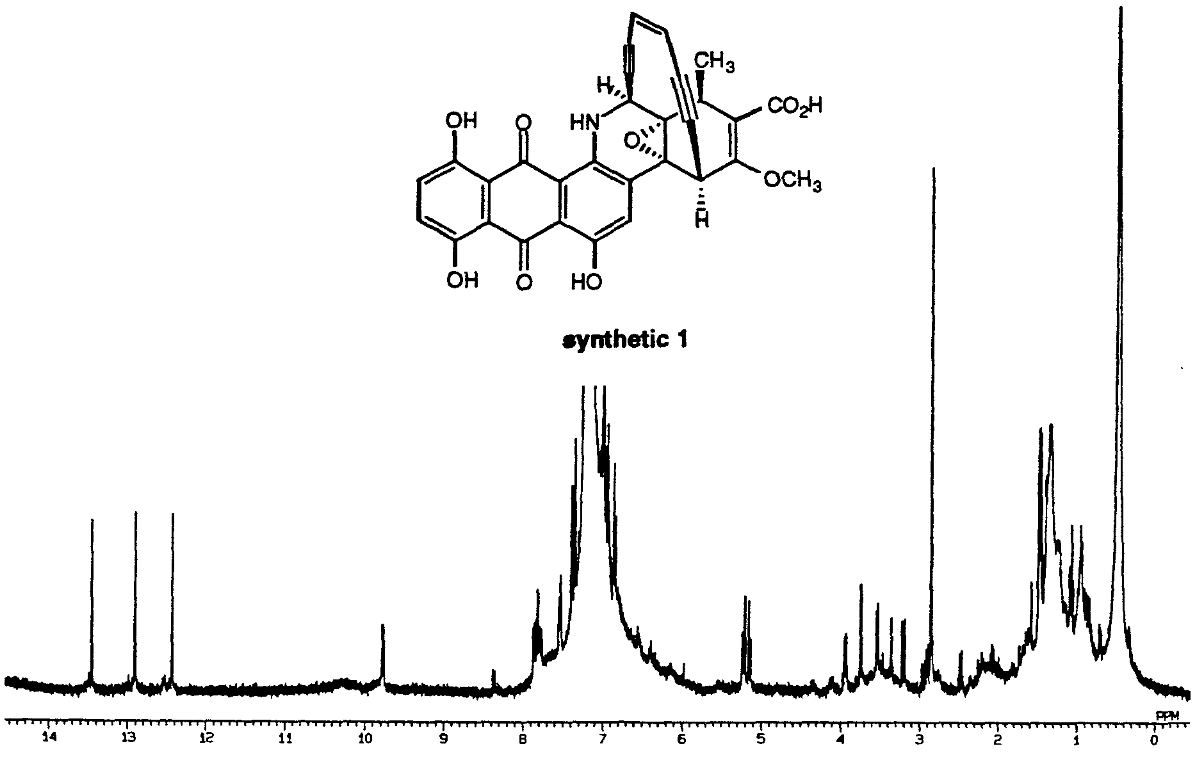
authentic 1



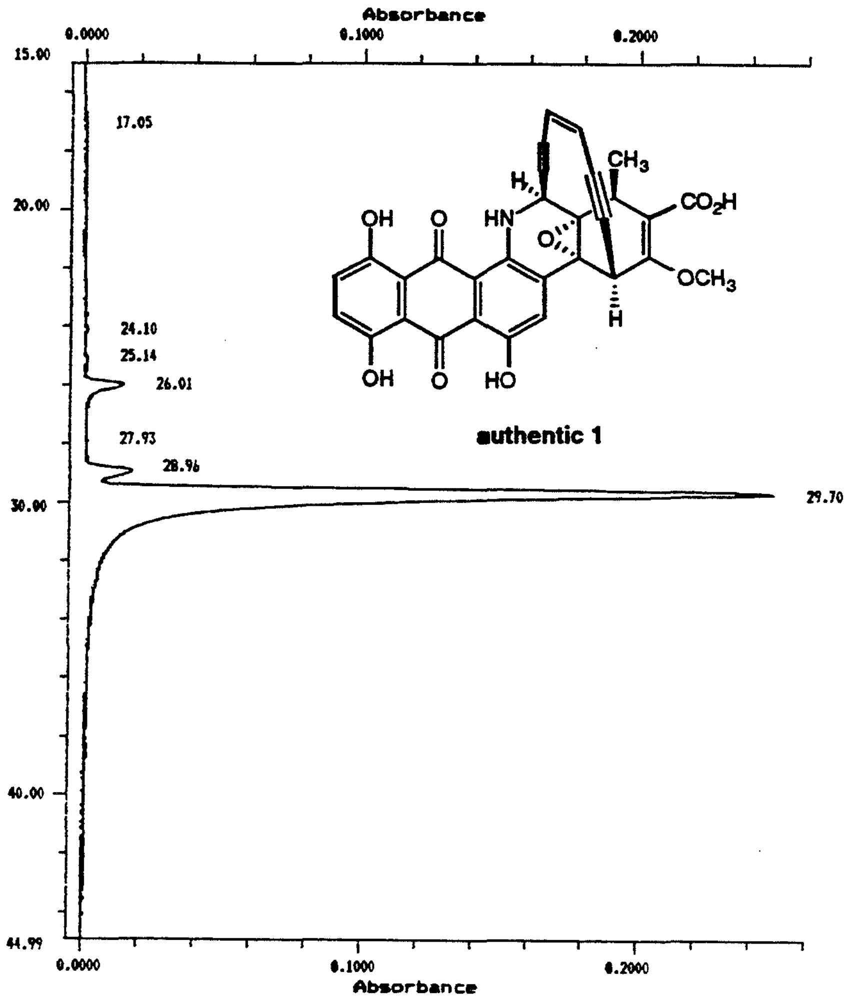
synthetic 1



authentic 1

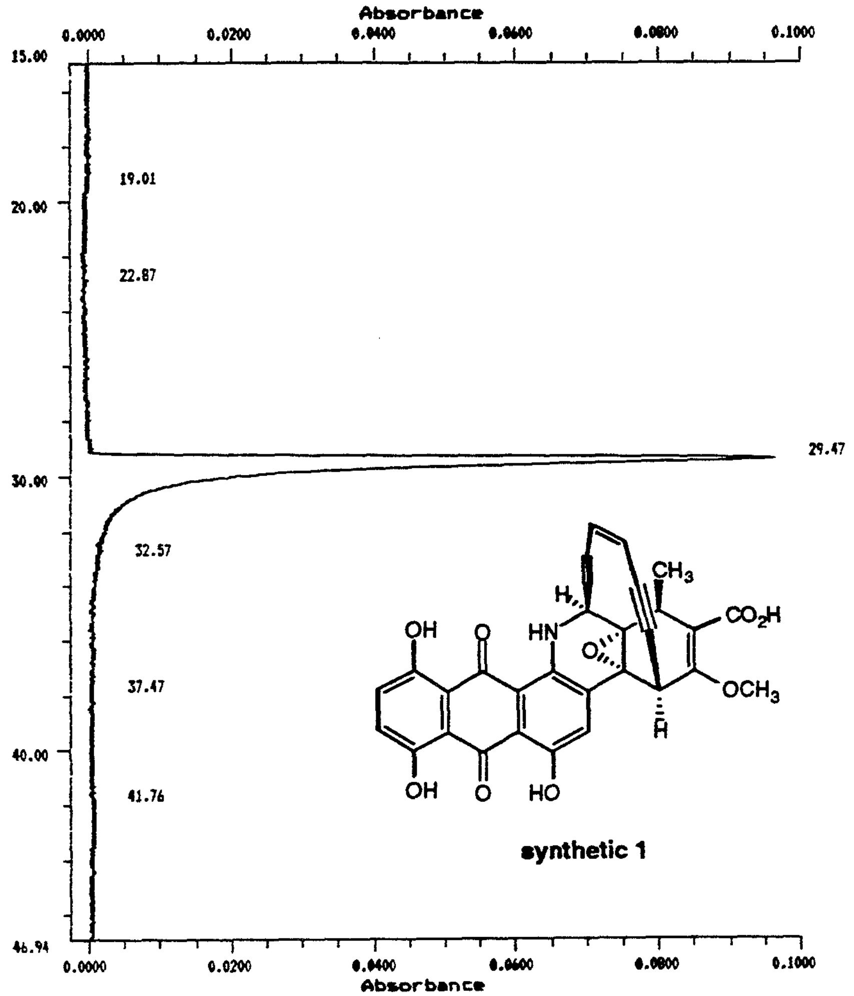


synthetic 1



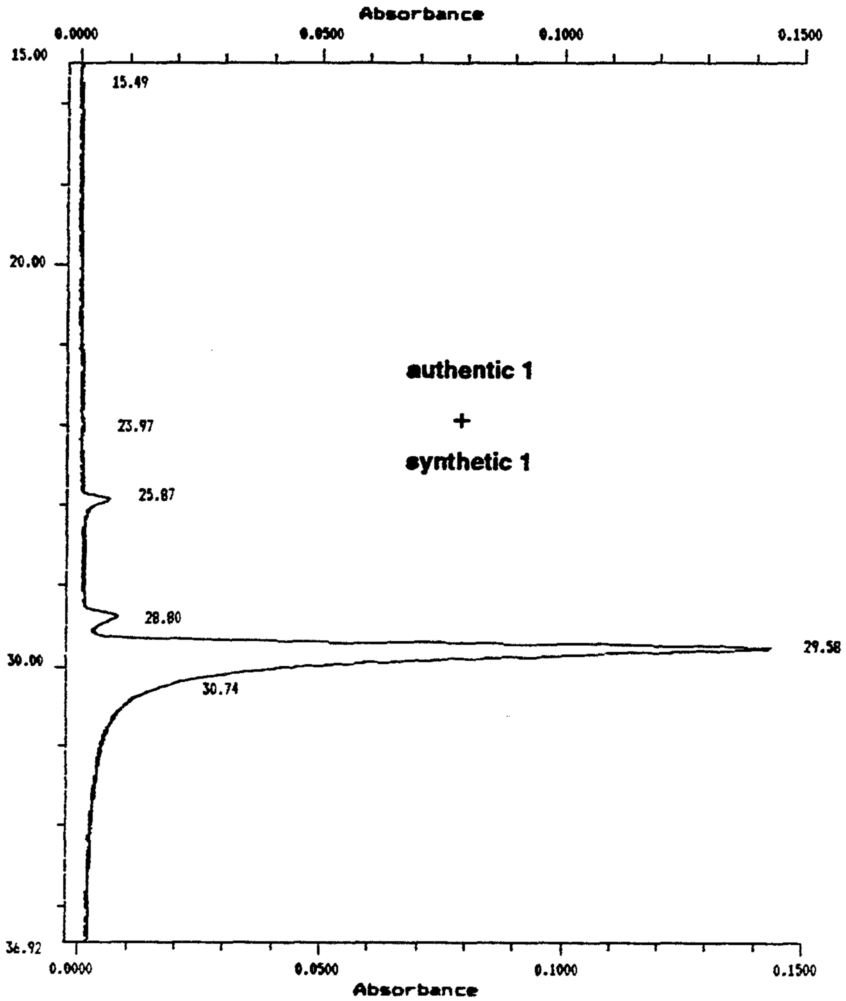
Authentic Dynemicin A from Japan
BECKMAN ODS C18, 4.6 MM X 250 MM
10 mM NH4OAC, pH 6 and CH3CN
20% CH3CN to 100% CH3CN, t = 40 minutes

Retention Time	Peak Area	Area Percent
5.799	0.12907	0.009
6.569	805.39661	53.460
7.077	149.81616	9.945
7.208	58.21168	3.864
8.026	2.63435	0.175
16.573	0.21512	0.014
20.017	0.12631	0.008
20.469	0.00600	0.001
21.192	0.30331	0.020
22.678	18.98108	1.260
23.121	1.70524	0.113
24.080	0.69226	0.046
25.133	1.02806	0.068
25.997	26.57245	1.764
27.604	0.38943	0.026
28.962	14.53533	0.965
29.701	425.77927	28.262
	1506.52172	100.000



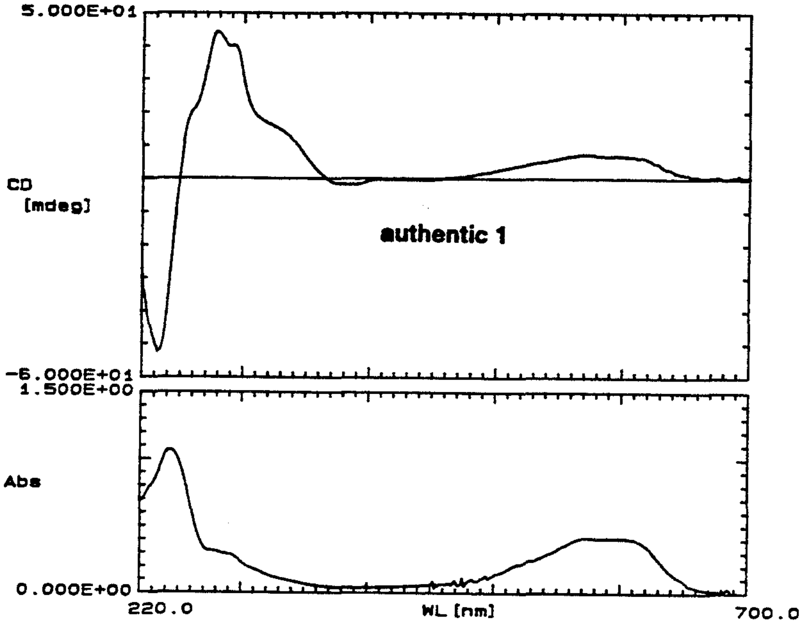
Synthetic Dynemicin A after HPLC purification
BECKMAN ODS C18, 4.6 MM X 250 MM
10 mM NH4OAC, pH 6 and CH3CN
20% CH3CN to 100% CH3CN, t = 40 minutes

Retention Time	Peak Area	Area Percent
6.389	0.02568	0.050
7.491	0.03722	0.072
7.771	0.11002	0.214
12.155	0.01306	0.026
19.010	0.01176	0.022
22.867	0.01486	0.029
29.466	51.15615	99.461
32.570	0.02433	0.047
37.474	0.01722	0.033
41.757	0.02343	0.046
	51.43372	100.000

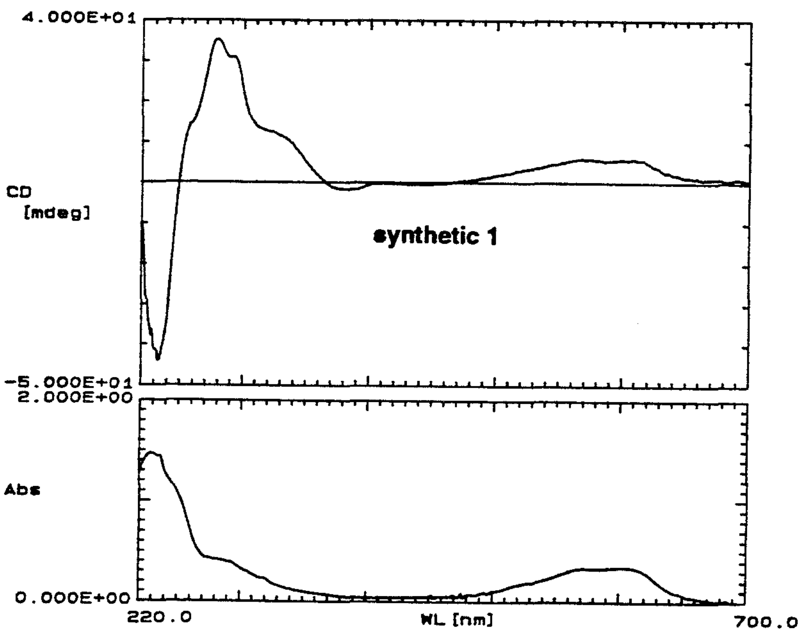


Co-injection: Authentic Dynemicin A w/ purified synthetic
BECKMAN ODS C18, 4.6 MM X 250 MM
10 mM NH4OAC, pH 6 and CH3CN
20% CH3CN to 100% CH3CN, t = 40 minutes

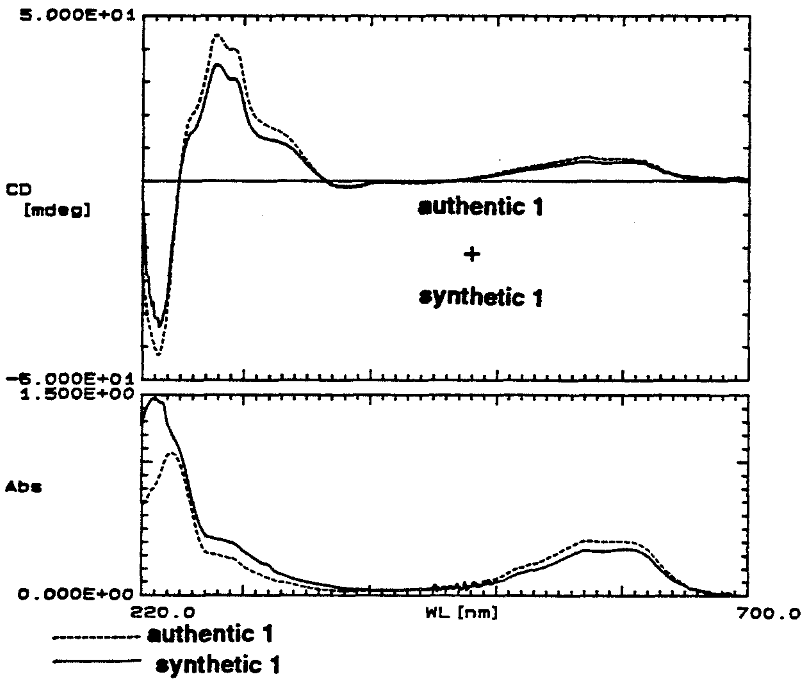
Retention Time	Peak Area	Area Percent
6.020	0.25528	0.271
6.104	2.01581	2.144
6.481	6.47121	6.880
6.580	6.94958	7.389
15.491	0.01769	0.019
23.971	0.01298	0.013
25.866	1.25497	1.335
28.801	1.95061	2.074
29.578	72.05327	76.607
30.737	1.09724	1.167
30.896	1.97630	2.101
	94.05495	100.000



Conditions of Memory 3
File :
Date : 8-10-94
Data : CD
Scan : WL
Band width :
1.0 nm
Sensitivity :
50 mdeg
Time const. :
1 sec
Wavelength range :
700.0 - 220.0nm
Step resolution :
1.0 nm/data
Scan speed :
50nm/min
Accumulation : 6



Conditions of Memory 2
File :
Date : 8-10-94
Data : CD
Scan : WL
Band width :
1.0 nm
Sensitivity :
50 mdeg
Time const. :
1 sec
Wavelength range :
700.0 - 220.0nm
Step resolution :
1.0 nm/data
Scan speed :
50nm/min
Accumulation : 6



Conditions of Memory 3
File :
Date : 8-10-94
Data : CD
Scan : WL
Band width :
1.0 nm
Sensitivity :
50 mdeg
Time const. :
1 sec
Wavelength range :
700.0 - 220.0nm
Step resolution :
1.0 nm/data
Scan speed :
50nm/min
Accumulation : 6