Synthesis and Study of Chemically Activated Biradical Precursors

Thesis by

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Generations come and go but it makes no difference. The sun rises and sets and hurries around to rise again. The wind blows south and north, here and there, twisting back and forth, getting nowhere. The rivers run into the sea but the sea is never full, and the water returns again to the rivers, and flows again to the sea...

Everything is unutterably weary and tiresome. No matter how much we see, we are never satisfied; no matter how much we hear, we are not content. So I saw that there is nothing better for men than that they should be happy in their work, for that is what they are here for, and no one can bring them back to life to enjoy what will be in the future, so let them enjoy it now.

–Ecclesiastes–

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Abstract

The design, synthesis and study of molecules which produce 1,4-biradical intermediates upon thermal or chemical activation is described. The preparation and cyclization behavior of (*Z*)-1,2,4-heptatrien-6-yne and compounds that contain the (*Z*)-allene-ene-yne functional group or that form it in a serial reaction sequence are discussed. Evidence is presented that supports the thermal transformation of the (*Z*)-allene-ene-yne functional group to an α,3-dehydrotoluene intermediate that is best described as a singlet σ,π-biradical with substantial polar character. The partitioning between polar and free radical reaction pathways in these systems is shown to be influenced by biradical substitution and by the reaction medium in which the intermediate is generated. These results are discussed with reference to electrocyclization reactions occurring within the enediyne family of natural antitumor agents.

The design, synthesis and reactivity of a system that produces a strained (*Z*)-enediyne moiety via the reductive activation of an anthraquinone-diacetylene conjugate in water with a flavin-based enzymatic system is described. The (*Z*)-enediyne thus produced is shown to undergo thermal rearrangement to form a naphthofuran product via a 1,4-dehydrobenzene biradical intermediate.

The preparation of a molecule which forms a substituted 1,6-didehydro[10]-annulene intermediate by nucleophilic addition of thiol is described. This intermediate is not observed, but rearranges to form two isomeric 1,5-dehydronaphthalene biradicals as evidenced by the isolation of the corresponding aromatized products.

Table of Contents

Index of Figures, Schemes, and Tables

List of Abbreviations

Å	angstrom
Ac	acetyl
Bu	butyl
°C	degree Celsius
cal	calorie
CAN	ceric ammonium nitrate
CSA	camphorsulfonic acid
Cy	cyclopropyl
DBU	1,8-diazobicyclo[5.4.0]undec-7-ene
DCC	1,3-dicyclohexylcarbodiimide
DEAD	diethyl azodicarboxylate
dec	decomposition
DIBAL	diisobutylaluminum hydride
DMAP	4-dimethylaminopyridine
DME	dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DMSO	dimethyl sulfoxide
DNA	deoxyribonucleic acid
E	entgegen
ee	enantiomeric excess
equiv	equivalent
Et	ethyl
eu	entropy unit

FT	Fourier transform
g	gram
G	free energy (Gibbs)
GLC	gas-liquid chromatography
h	hour
H	enthalpy
hν	light
HRMS	high resolution mass spectroscopy
Hz	Hertz
i	iso
IR	infrared
J	coupling constant
k	rate constant
kcal	kilocalorie
L	liter
LDA	lithium diisopropylamide
m	meta
M	molar
m-CPBA	*meta*-chloroperbenzoic acid
Me	methyl
mg	milligram
MHz	megahertz
min	minute
mL	milliliter
mM	millimolar
mmol	millimole

mol	mole
mp	melting point
Ms	methanesulfonyl
μL	microliter
n	normal
N	normal (concentration)
NMR	nuclear magnetic resonance
nOe	nuclear Overhauser effect
p	para
PCC	pyridinium chlorochromate
pH	hydrogen ion concentration
Ph	phenyl
Piv	pivaloyl
Pr	propyl
R	rectus
R_f	retention factor
S	entropy
S	sinister
t	tertiary
TBAF	tetrabutylammonium fluoride
TBS	*tert*-butyldimethylsilyl
TDS	*tert*-butyldiphenylsilyl
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
THP	tetrahydropyranyl

TMEDA	*N*,*N*,*N*',*N*'-tetramethylethylenediamine
TMS	trimethysilyl
tol	tolyl
w/v	weight-to-volume ratio
Z	zusammen

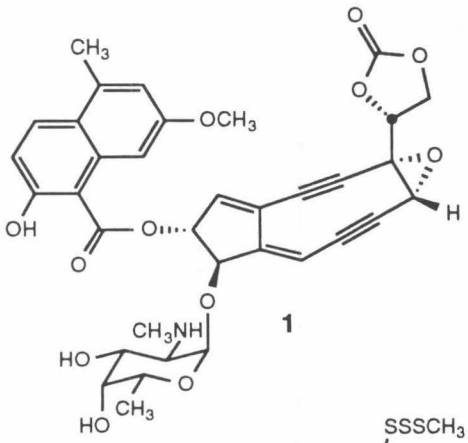
Introduction

The Enediyne Antibiotics

Several lines of evidence now support the intermediacy of 1,4-biradicals as a common feature in the mechanism of action of the extremely potent natural antitumor antibiotics neocarzinostatin chromophore (**1**), calichemicin γ_1^I (**2**), esperamicin A_1 (**3**), and dynemicin A (**4**) (collectively known as the enediyne antibiotics).[1-6] These biradical intermediates are proposed to arise by electrocyclization of highly unsaturated precursors formed from the native antibiotics as the result of a prior chemical "activation" step, and have been shown to abstract hydrogen atoms from the deoxyribose backbone of double stranded DNA.[7-9] In the presence of oxygen, this abstraction process results in DNA cleavage, and is believed to underlie the remarkable antitumor properties exhibited by this class of antibiotics.[10]

In vitro experiments conducted with the above natural products reveal that several unique chemical activation mechanisms serve to initiate biradical formation. For example, addition of an external thiol nucleophile to neocarzinostatin chromophore (**1**) produces the (*Z*)-cumulene-ene-yne intermediate **5** which subsequently cyclizes to biradical **6** (Scheme I).[11] The trapping of **6** with hydrogen atom sources, including DNA, produces the aromatic product **7**. Since the reactive (*Z*)-cumulene-ene-yne moiety is not present in the native antibiotic, thiol addition (chemical activation) necessarily precedes biradical formation in the above scheme.

An alternative method of chemical activation is observed with calichemicin (**2**) and (presumably) esperamicin (**3**). In this case, attack of an external thiol nucleophile on the trisulfide moiety of the antibiotic produces either a thiolate anion, which forms saturated ketone **8** via rapid conjugate addition to the adjacent α,β-unsaturated carbonyl, or the corresponding mixed disulfide which is transformed to **8** more slowly (Scheme II).[3a,3b,4a,4b,12] The strained (*Z*)-enediyne moiety present in **8** *then rapidly* cyclizes to 1,4-biradical **9** in a reaction recognized as a cyclic version of a hydrocarbon thermal



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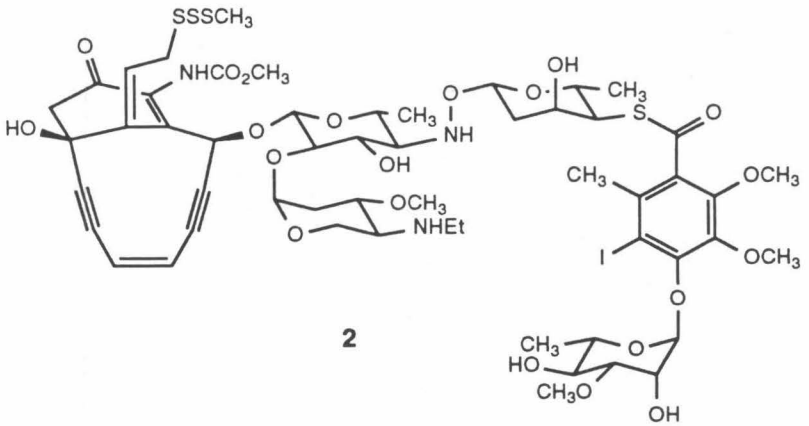

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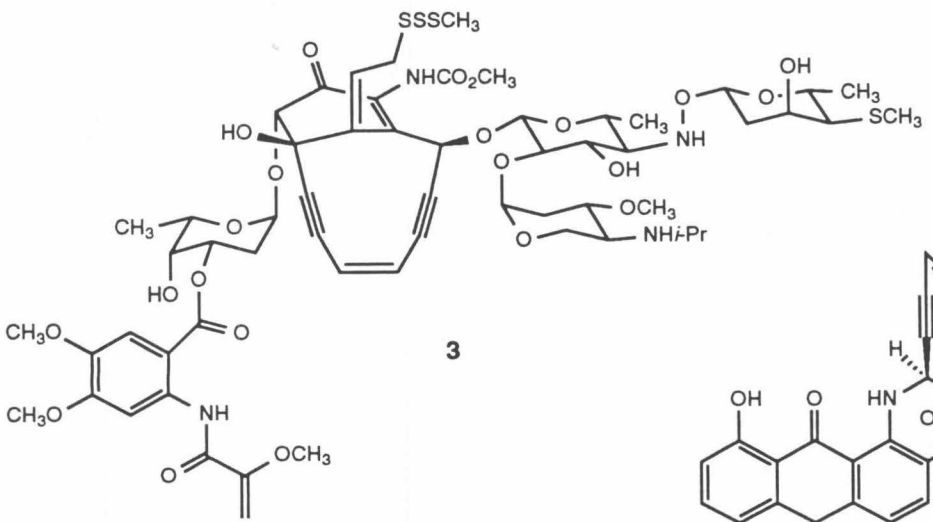

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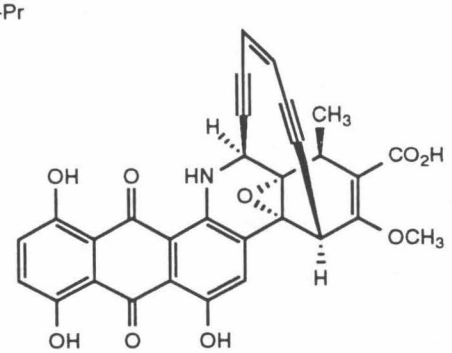

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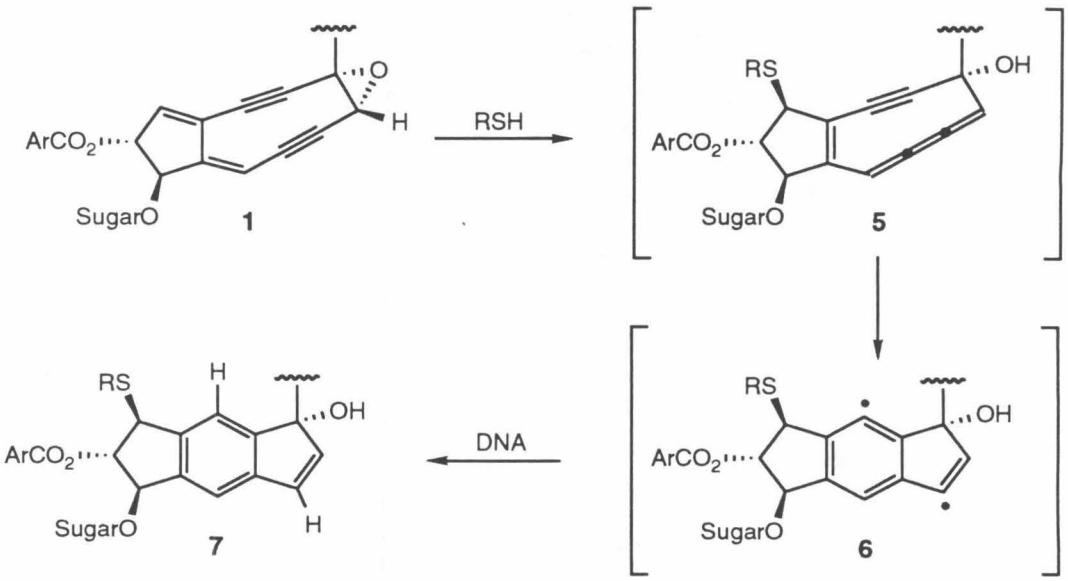
Scheme I

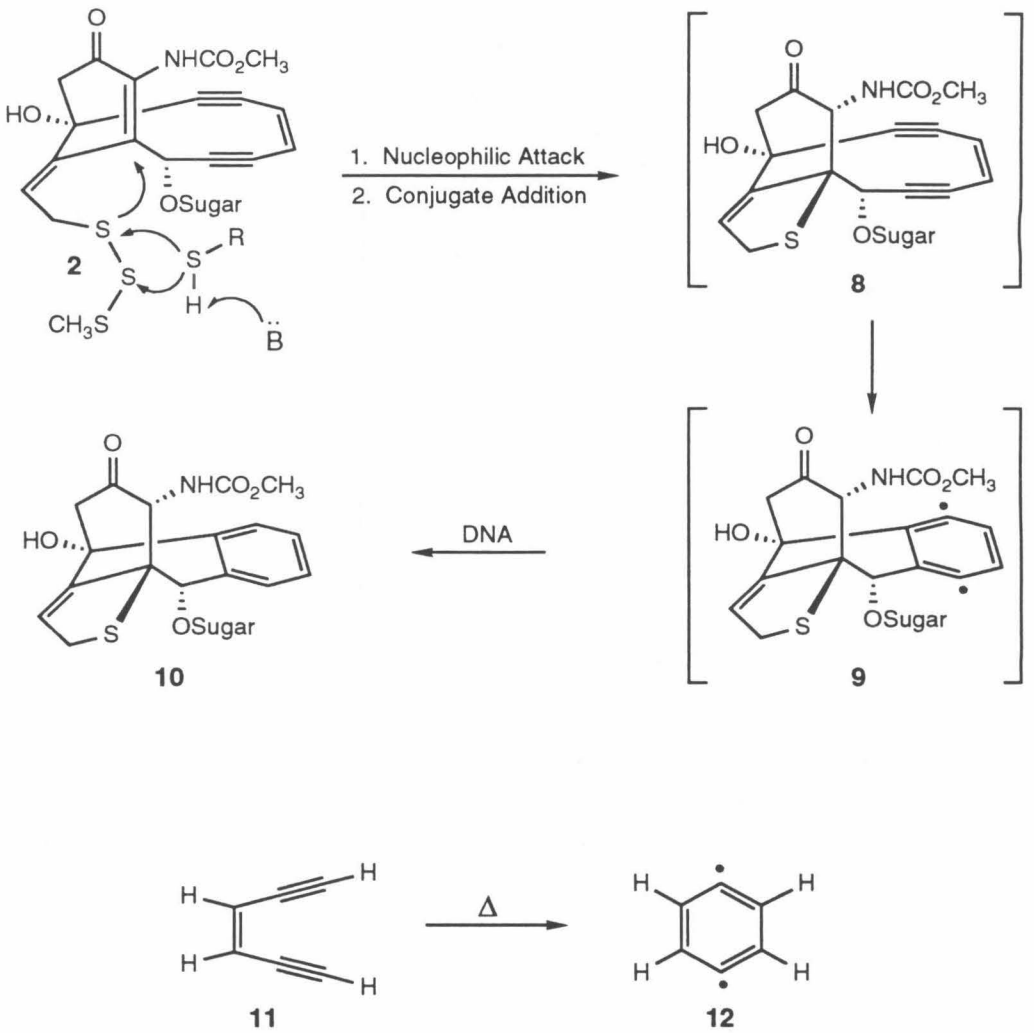


rearrangement studied extensively by Bergman and co-workers (**11**→**12**, the Bergman reaction).[13] As with neocarzinostatin above, trapping of the intermediate biradical (**9**) with hydrogen atom sources produces an aromatic product (**10**). Importantly, biradical formation does not readily occur in the native antibiotic (**2**) due to strain imparted by the α,β-unsaturated carbonyl group. Chemical activation and subsequent intramolecular thiol addition are therefore required to remove this inhibiting functionality.

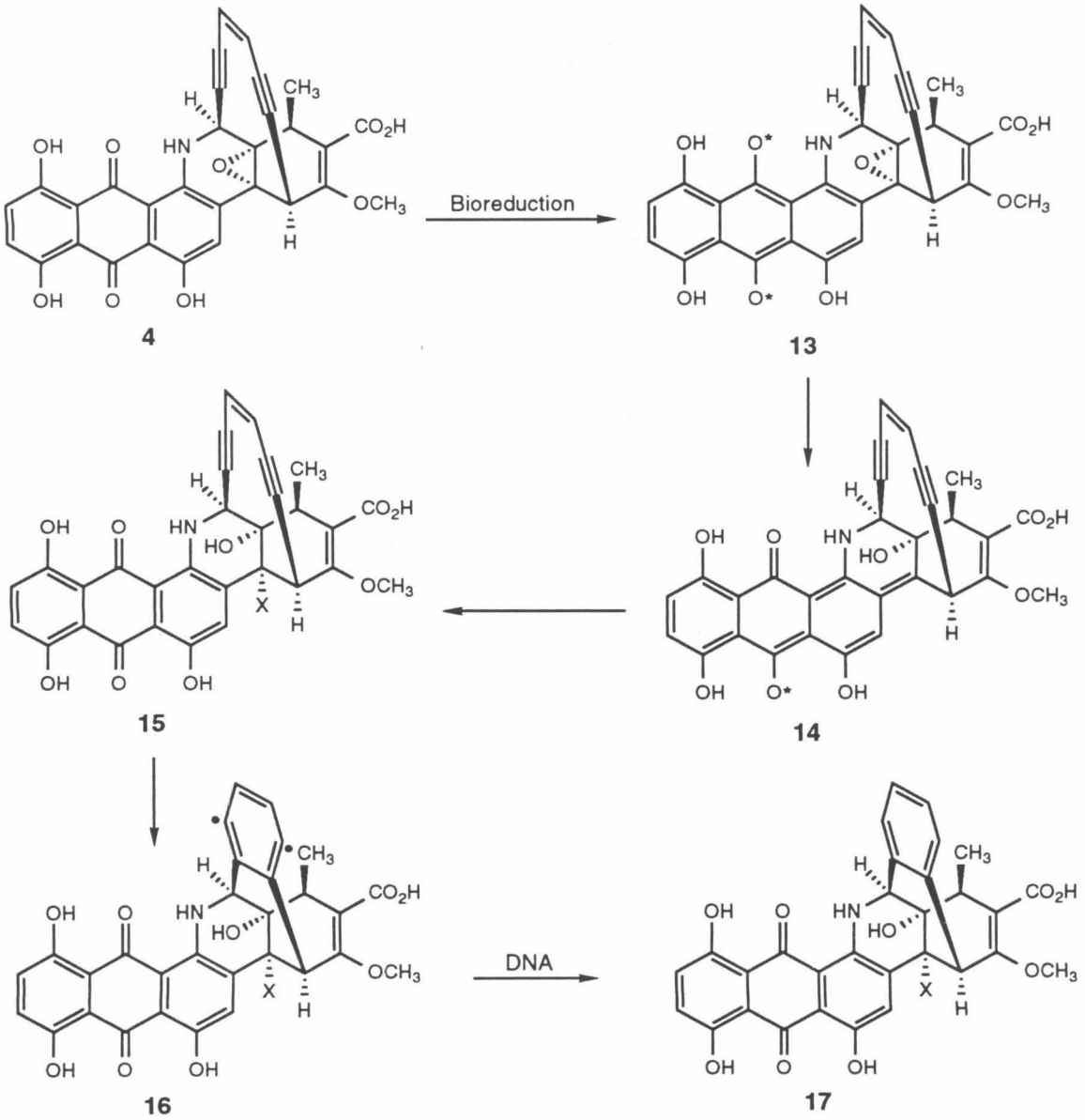
Dynemicin (**4**) is proposed to undergo yet another form of chemical activation prior to biradical formation.[14] In analogy to the calichemicin activation event described above, reduction of the anthraquinone nucleus and subsequent formation of quinone methide **14** remove a structural feature that impedes the cyclization of the strained (*Z*)-enediyne to biradical **16** (e.g., the epoxide moiety, Scheme III, asterisks are used to accommodate either semiquinone or hydroquinone intermediates). The addition of two hydrogen atoms, possibly from DNA, to **16** then produces compound **17**.

The above examples illustrate how each of the enediyne antibiotics undergoes a

Scheme II


O
NHCO2CH3
HO
OSugar
S
R
S
S
H
CH3S
B
2
1. Nucleophilic Attack
2. Conjugate Addition
8
9
DNA
10
H
H
H
H
11
Δ
12

Scheme III



4 **13** **14** **15** **16** **17**

unique chemical activation event prior to biradical formation. In the case of calicheamicin/esperamicin and dynemicin, the activation step removes a structural feature that impedes cyclization, while in the case of neocarzinostatin chromophore chemical activation creates the functionality necessary for cyclization.

Thesis Research

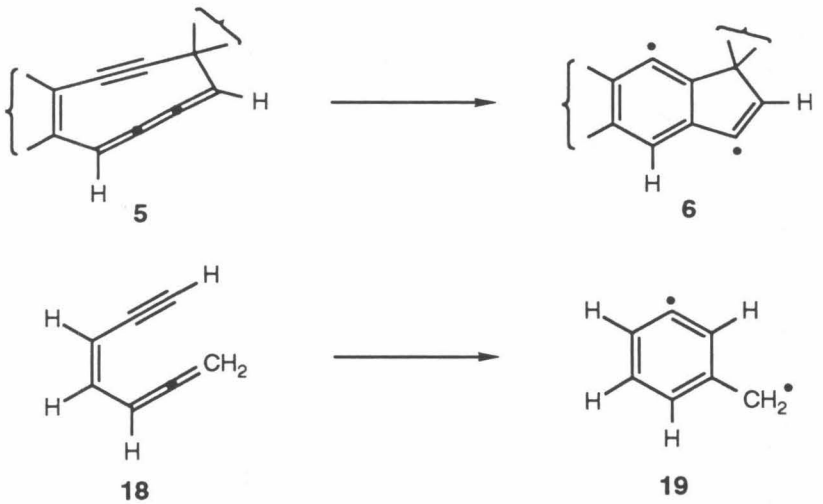
Because of their novel structures, unique mechanism of action, and favorable antitumor properties, much effort has been exerted by organic chemists to synthesize each member of enediyne antibiotic class.[15-19] However, the structural complexity of these molecules complicates their large-scale preparation by multi-step synthetic methods. The purpose of the following research is the utilization of synthetic organic chemistry to construct relatively simple molecules which mimic the mode of action of the enediyne antibiotics.[20-22] Thus, this work details the design, preparation and study of several synthetic compounds which produce 1,4-biradical intermediates upon thermal or chemical activation. The research is divided into three parts. Chapter 1 describes the preparation and cyclization behavior of (*Z*)-1,2,4-heptatrien-6-yne and several other compounds that contain the (*Z*)-allene-ene-yne functional group, or that form it in a serial reaction sequence. Chapter 2 details the design, preparation and reactivity of a system that produces a strained (*Z*)-enediyne moiety via anthraquinone reductive activation. Finally, chapter 3 describes the design and synthesis of a molecule which undergoes a chemical activation event to produce substituted 1,5-dehydronaphthalene biradicals via an electrocyclization that is not (as yet) precedented by the action of a natural product.

Chapter 1

Studies on the Thermal Generation and Reactivity of a Class of (σ,π)-1,4-Biradicals

Background

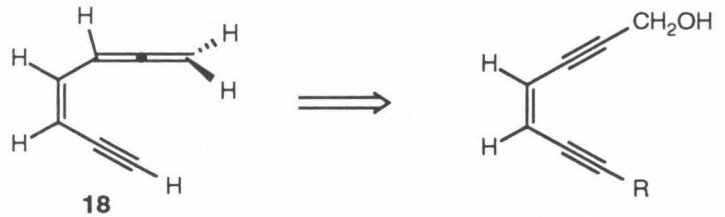
The cyclization of the (*Z*)-cumulene-ene-yne **5** to form the biradical **6** is proposed as a key step in the mechanism of action of the antitumor agent neocarzinostatin.[11] The fact that this reaction lacked precedent in known hydrocarbon thermal rearrangements led to the evaluation of the related rearrangement of the acyclic hydrocarbon **18** to the biradical **19**.[23] Though inspired by the transformation of **5** to **6**, the latter proposal differs significantly in that the ground state structure of the product (**19**) is almost certain to be that of a σ,π-biradical, whereas **6** is constrained by geometry to be a σ,σ-biradical. As discussed below, this distinction has important consequences in terms of thermochemistry and reactivity.



Synthesis of (*Z*)-1,2,4-Heptatrien-6-yne (18)

The principal challenge in the development of a synthetic route to the hydrocarbon **18** was to construct the vinylallene with proper stereochemistry in a target molecule that is both thermally and chemically sensitive. Towards this end, a method for the synthesis of allenes from propargylic alcohols was devised which transforms, in the

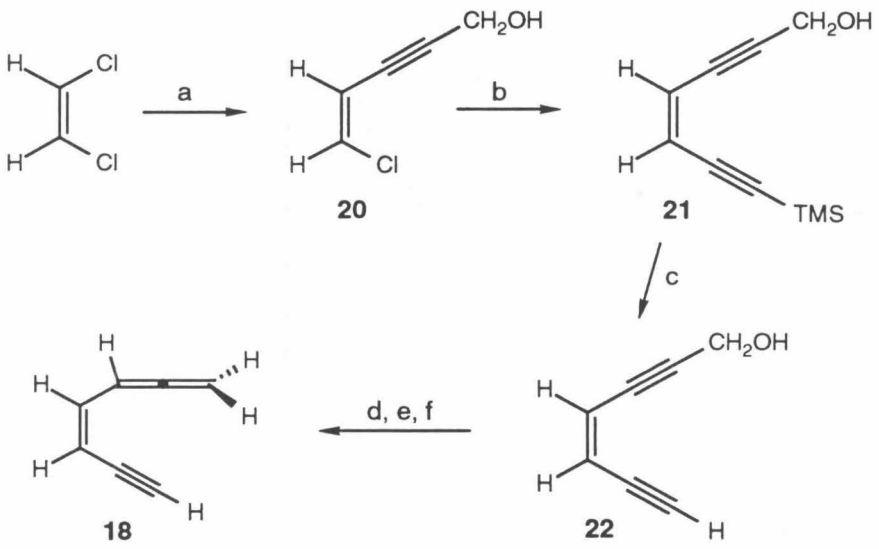
retrosynthetic sense, the target **18** into a more tractable precursor, (*Z*)-enediyne **22**.[23,24] The stereospecific synthesis of this enediyne in protected form (**21**, TMS = $Si(CH_3)_3$)



21 R = TMS
22 R = H

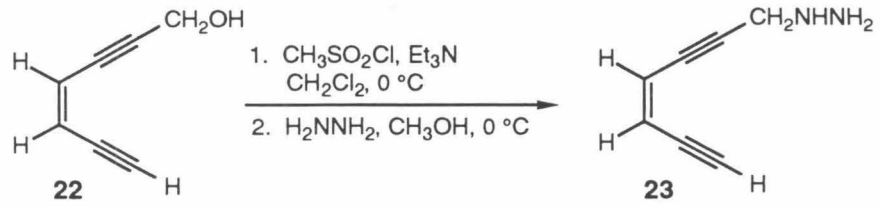
was readily achieved from (*Z*)-1,2-dichloroethylene, following the precedent of Kende and Smith,[25] by sequential coupling reactions with propargyl alcohol and (trimethylsilyl)acetylene, respectively (Scheme IV).[26] Although the two coupling reactions could be run in sequence in a single flask, **21** was formed in greater yield and was more readily purified when the intermediate (*Z*)-vinyl chloride (**20**) was isolated by flash column chromatography on silica gel. The indicated order of acetylene coupling was preferred for the greater ease of purification of the vinyl chloride **20**. Thus, reaction of propargyl alcohol (1 equiv) with (*Z*)-1,2-dichloroethylene (5 equiv), bis-(triphenylphosphine)palladium(II) chloride (0.05 equiv), and cuprous iodide (0.15 equiv) in ethyl ether containing *n*-propylamine (5 equiv) at 23 °C for 6 h afforded, after extractive isolation and flash column chromatography, the (*Z*)-vinyl chloride **20** in 78% yield.[25,26] Subsequent coupling of **20** with (trimethylsilyl)acetylene (1.4 equiv) under similar conditions, albeit employing tetrakis(triphenylphosphine)palladium(0) (0.05 equiv) as the palladium catalyst, provided the (*Z*)-enediyne **21** (83%).[26] Desilylation of **21** with potassium fluoride in methanol at 0 °C afforded **22** in 96% yield. Although this deprotection could be deferred to a later stage of the synthesis, the sequence described here minimized the number of volatile intermediates and ultimately facilitated the purification of **18**.

Scheme IV

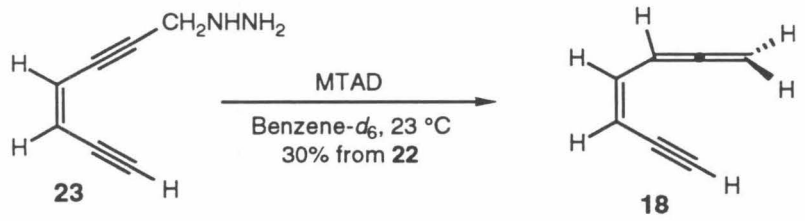


Reagents and conditions (TMS = $Si(CH_3)_3$): (a) 0.20 equiv $HC{\equiv}CCH_2OH$, 1.0 equiv $CH_3(CH_2)_2NH_2$, 0.030 equiv CuI, 0.010 equiv $Pd(PPh_3)_2Cl_2$, Et_2O, 0→23 °C, 6 h, 78%; (b) 1.4 equiv $HC{\equiv}CSi(CH_3)_3$, 4.0 equiv $CH_3(CH_2)_2NH_2$, 0.20 equiv CuI, 0.05 equiv $Pd(PPh_3)_4$, Et_2O, 0 °C, 1 h, 83%; (c) 2.0 equiv $KF{\bullet}2H_2O$, CH_3OH, 0 °C, 2.5 h, 96%; (d) 3.0 equiv CH_3SO_2Cl, 5.0 equiv Et_3N, CH_2Cl_2, 0 °C, 20 min; (e) 14.3 equiv H_2NNH_2, CH_3OH, 0 °C, 2 h; (f) 1.3 equiv MTAD, benzene-d_6, 23 °C, 20 min, 30% from **22**.

The transformation of the propargyl alcohol **22** to the allene **18** was initiated by hydroxyl activation with methanesulfonyl chloride (3.0 equiv) and triethylamine (5.0 equiv) in dichloromethane at 0 °C.[27] Following extractive isolation, the crude methanesulfonate ester (~0.3 M in CH_2Cl_2) was treated with a large excess of anhydrous hydrazine in methanol (14.3 equiv, 15 M) at 0 °C for 2 h to form the monoalkyl hydrazine **23**. Use of lesser quantities of hydrazine led to competitive dialkylation, as



anticipated given the greater nucleophilicity of alkyl hydrazines versus hydrazine itself.[28] A simple aqueous extraction procedure served to separate **23** from excess hydrazine. Treatment of crude **23** with a slight excess of diethyl azodicarboxylate (DEAD) or 4-methyl-1,2,4-triazoline-3,5-dione (MTAD) under anaerobic conditions at 23 °C then

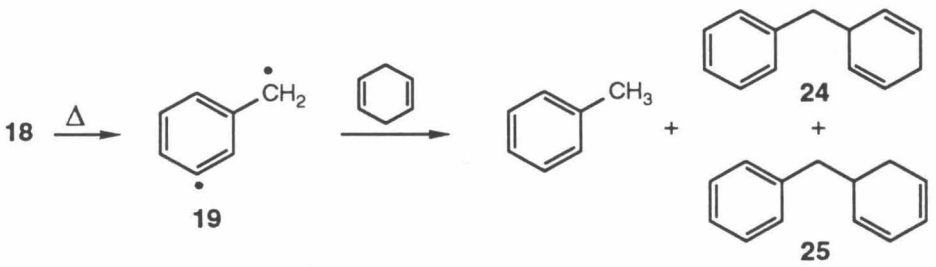


afforded the allene **18**.[23,24] Mechanistic studies suggest that the latter reaction produces a mixture of (*E*)- and (*Z*)-diazenes; sigmatropic elimination of dinitrogen from the (*Z*)-diazene forms **18** directly while the (*E*)-isomer must first undergo rate-limiting *E*→*Z* isomerization.[29] Though several procedures were found effective for the purification of **18**, including preparative gas chromatography, the most straightforward entailed the use of benzene-d_6 as solvent in the hydrazine oxidation step, the washing of the crude

product solution with several portions of water, and separation and purification of the hydrocarbon layer by passage through a short column of silica gel. In this manner, solutions of the allene **18** in benzene-d_6 were obtained in >90% purity and ~30% yield (determined by addition of *m*-xylene as an internal standard and ^{1}H NMR analysis). Allene **18** is exceedingly volatile and must be stored anaerobically to avoid decomposition. Although the yield of **18** by this isolation method was modest, the simplicity of the procedure and purity of the product obtained recommend it above other methods of purification proceeding in higher yield.

A Surprisingly Facile Cyclization Reaction Forming α,3-Dehydrotoluene

Thermolysis of **18** in various solvents afforded products consistent with the intermediacy of the biradical **19**, "α,3-dehydrotoluene." For example, heating solutions of **18** in deoxygenated 1,4-cyclohexadiene formed toluene and the 1,4-cyclohexadiene

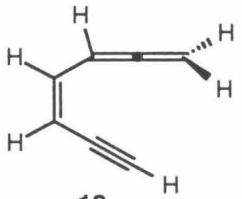


adducts **24** and **25** as the only detectable volatile products (Table I, entry 1).[23] Preferential carbon-carbon bond formation at the benzylic position (as opposed to the *m*-aryl position) in **24** and **25** is consistent with a scheme in which the more reactive σ-radical of **8** reacts initially by hydrogen atom abstraction from 1,4-cyclohexadiene, followed by recombination of the resulting pair of π-radicals (Scheme V). Products **24** and **25** can also be envisioned to arise by a sequence involving addition of cyclohexadienyl to the allenic terminus of **18**, cycloaromatization, and hydrogen atom

Table 1. Product Distributions Obtained Upon Pyrolysis of **18** in Various Media at 100 °C.

Entry	Solvent	[**18**] (mM)	Products[a] Toluene	**24 + 25**	Bibenzyl	Methyl benzyl ether	2-Phenyl ethanol
1	CHD[b]	3.0	60	40	-	-	-
2	CH_3OH	3.0	-	-	2	38	10
3	CH_3OH[c]	3.0	-	-	2	35	10
4	CH_3OH[d]	3.0	-	-	2	34	9
5	CD_3OH	3.0	-	-	-	70	-
6	CH_3OD	3.0	-	-	3	18	21
7	CHD (0.2 M)–CH_3OH	3.0	19	9	1	25	1
8	CHD (1.0 M)–CH_3OH	3.0	32	19	-	12	-
9	H_2O (5.6 M)–CH_3OH	3.0	-	-	1	47[e]	7
10	CF_3CH_2OH (1.4 M)–CH_3OH	3.0	-	-	1	51[f]	7

[a] Yields determined by GLC using *m*-xylene as an internal standard. [b] CHD=1,4-Cyclohexadiene. [c] Reaction glassware rinsed twice with 1,1,1,3,3,3-hexamethyldisilazane prior to pyrolysis. [d] Reaction glassware rinsed twice with glacial acetic acid prior to pyrolysis. [e] Benzyl alcohol also obtained in 6% yield. [f] 1,1,1-Trifluoroethyl benzyl ether also obtained in 3% yield.



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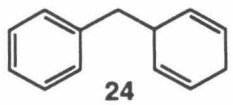

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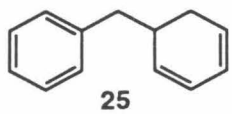

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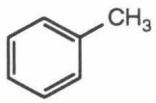
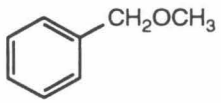
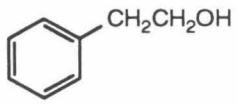
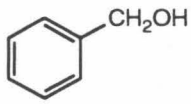
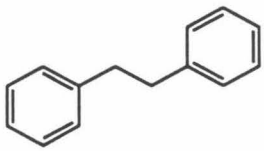
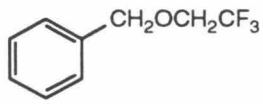


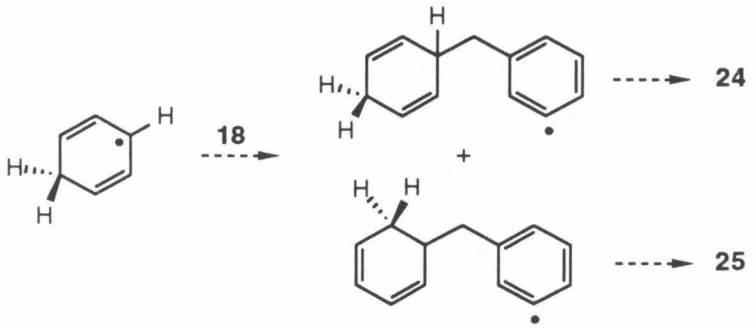






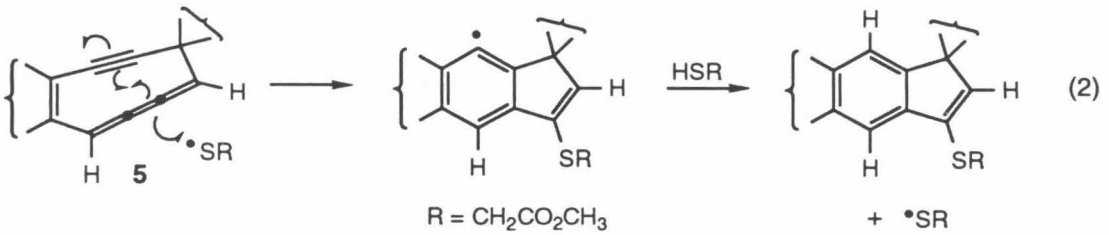






(1)

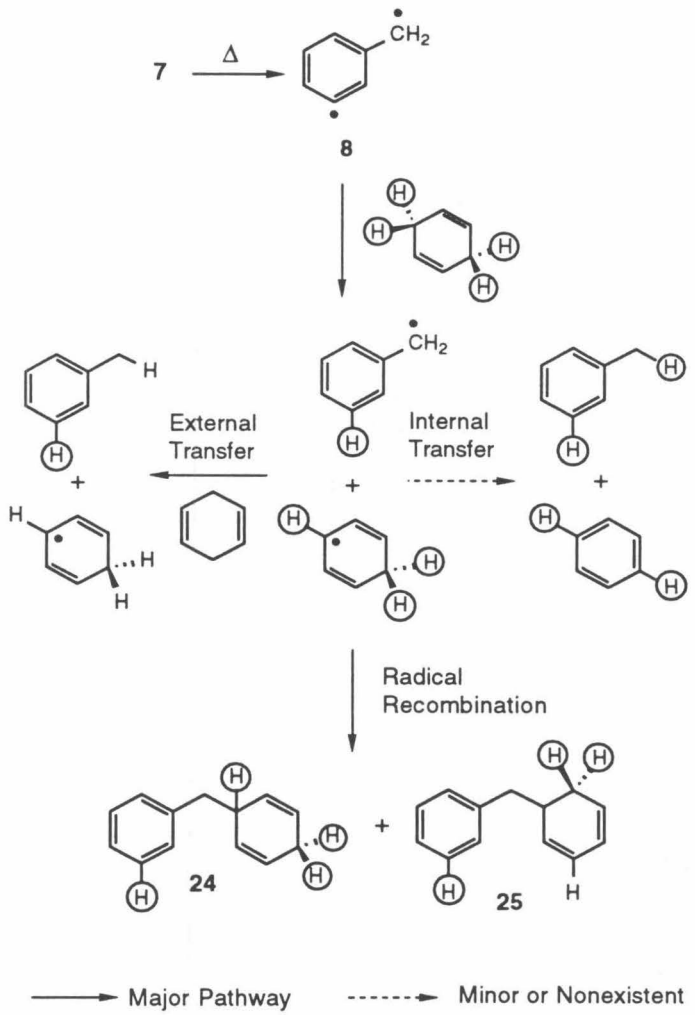
abstraction (eq 1). Although precedent for such a radical chain aromatization exists (e.g., eq 2),[11b] the invariance of the ratio (**24** + **25**)/toluene with the concentration of **18** suggests that, in the present case, this pathway is at best a minor competitor with the simple recombination mechanism.[23]



(2)

Further support for this contention was obtained from thermolysis experiments of **18** conducted in a mixture of 3,3,6,6-tetradeuterio-1,4-cyclohexadiene and unlabeled 1,4-cyclohexadiene (2:1, respectively, weighted to offset the isotope effect, 0.003 M **18**, 100 °C, 30 min, Scheme V). Under these conditions, the 1,4-cyclohexadiene addition products **24** and **25** were obtained as a 1:1 mixture in 55% yield.[30] The increased yield of radical recombination products **24** and **25** versus toluene reflects the primary isotope effect in hydrogen atom transfer to the benzyl radical. Mass spectroscopic analysis of **24** and **25** showed that these products contained primarily four (d_4) or zero (d_0) deuterium atoms (36 and 55%, respectively, 91 ± 9% total) with ≤7% of crossover products (d_1, d_3, average of two runs).[31] This result demonstrates that **24** and **25** arise primarily by radical

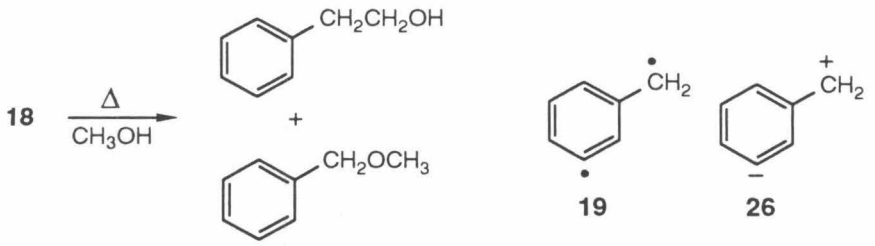
Scheme V



cage recombination and not to any significant extent by a mechanism such as shown in eq 1. In contrast, toluene produced in the above experiment was shown by mass spectroscopy to arise primarily by external hydrogen atom transfer (d_1:d_2 ~6:1, average of two runs, Scheme V).[30]

Dichotomous Reactivity – Polar Chemistry of α,3-Dehydrotoluene

Pyrolysis experiments conducted in protic media revealed an unanticipated complexity in the reactivity of the hypothesized intermediate **19**. For example, heating **18** (0.003 M, 100 °C) in deoxygenated methanol formed in addition to 2-phenylethanol (10%) and bibenzyl (2%), products anticipated from a biradical description of **19**, methyl benzyl ether (38%)–a product more consistent with the zwitterionic structure **26**.[23] This

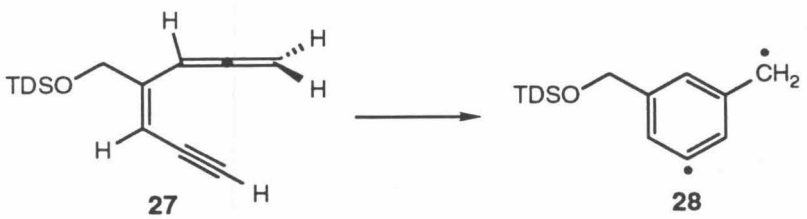


product distribution was reproducible and was shown in control experiments to be insensitive to acidic or basic pretreatment of the glass reaction surface (Table I, entries 2-4), discounting the formation of methyl benzyl ether by adventitious acid or base. Mechanistic studies presented below support the notion that products from both polar and free radical reaction pathways arise from a single reactive intermediate or, indistinguishable by our experiments, a pair of rapidly equilibrating species, rather than from discreet pathways involving slowly- or non-equilibrating intermediates, e.g., ground state and electronically-excited forms of **19**. The latter cascade-type mechanisms are rendered less likely by the following observations. Heating **18** in CD_3OH (0.003 M, 100 °C) formed methyl-d_3 benzyl ether as the only detectable product, in 70% yield (Table I, entry 5).[23] A pathway involving formation of a short-lived "polar" species that decays irreversibly to an intermediate with radical reactivity is clearly inconsistent with the observed near-doubling of the yield of methyl benzyl ether. Conversely, pyrolysis of **18** in CH_3OD afforded methyl benzyl-d_1 ether (18%) and 2-phenylethanol (21%) (Table I,

entry 6), a distribution inconsistent with a cascade involving the inverse order of reactive intermediates, i.e., a short-lived biradical and ground state polar species. Importantly, the kinetics of decomposition of **18** in CD_3OH, where methyl-d_3 benzyl ether is formed essentially exclusively, are first-order and are indistinguishable, within experimental error, from those observed in pure 1,4-cyclohexadiene, where products anticipated from standard free radical reactions are formed ($k = 4.0 \pm 0.2 \times 10^{-4}$ and $3.8 \pm 0.2 \times 10^{-4}$ s^{-1}, respectively, at 75 °C).[23] This result strongly suggests that the two pathways, producing polar and free-radical products, respectively, share a common rate-limiting step, proposed here to be the cyclization of **18** to **19**. It is further proposed that **19** partitions irreversibly in the next step, bond formation at the *m*-aryl position, in a manner predictable given the relevant homolytic bond strengths and acidity constants of the pyrolysis medium. In support of this proposal, it was found that addition of 1,4-cyclohexadiene to pyrolysis solutions of **18** in methanol led to the formation of toluene, bibenzyl, and **24** and **25**, with a corresponding diminution in the production of methyl benzyl ether (Table I, entries 7 and 8).[23] Similarly, increasing the acidity of the medium, by addition of water or trifluoroethanol, shifted the product distribution in favor of polar addition products (Table I, entries 9 and 10).

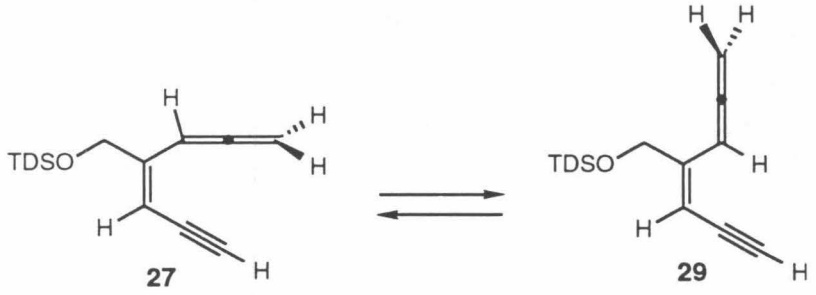
Simple Substitution and Further Reactivity Studies

Substrate **27** (TDS = *t*-Bu(Ph)$_2$Si) probes the effect of simple substitution upon the "parent" cyclization reaction of **18** to **19** and provides important background



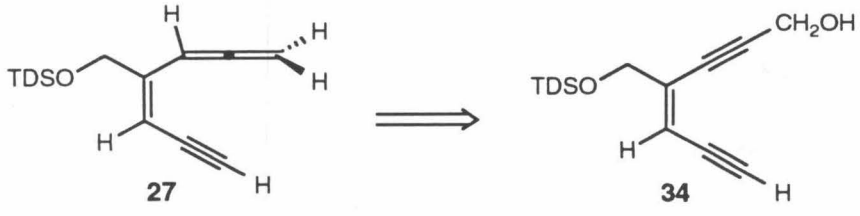
27 **28**

information for studies of more elaborate substrates described later in this work.[23c] "Meta"-substitution of the (*Z*)-1,2,4-heptatrien-6-yne framework, as exemplified by substrate **27**, was anticipated to have little impact upon the rate of cyclization to biradical **28**, barring an influence on the population of rotamers **27** and **29**. The latter is reminiscent of the effect of butadiene 2-substitution in the Diels-Alder reaction.

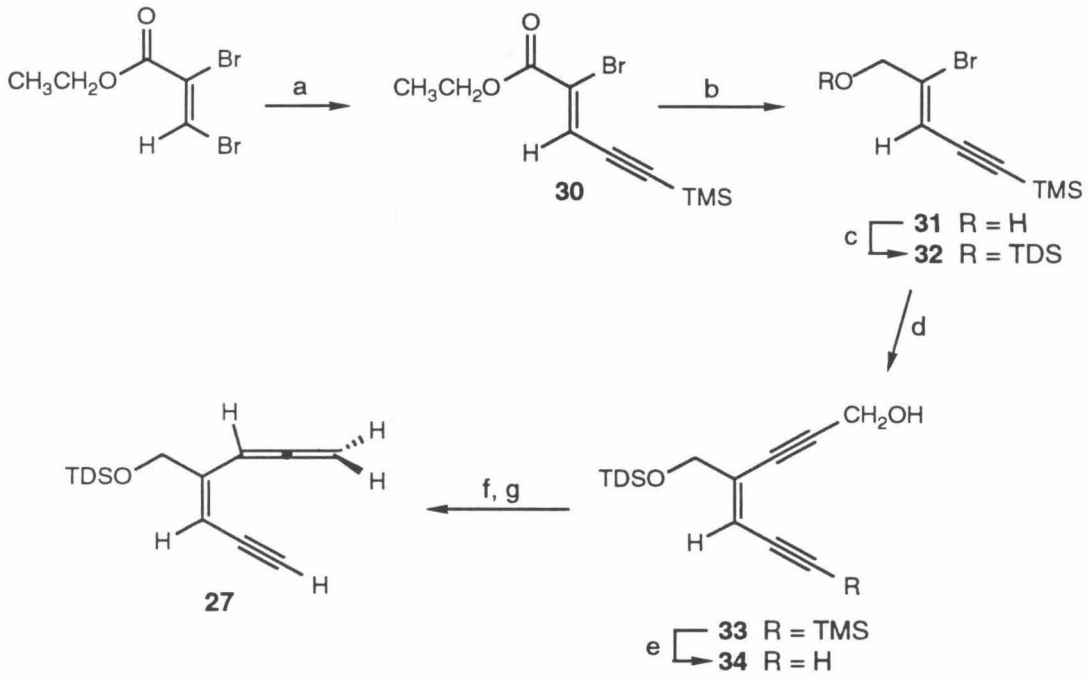


The *tert*-butyldiphenylsilyloxymethyl group ($TDSOCH_2$) was chosen for the dual purpose of examining its effect as a substituent and for its potential as a site for the attachment of auxiliary groups, e.g., DNA-binding moieties (vide infra).

In order to employ the synthetic strategy used to prepare allene **18** in the synthesis of **27**, the trisubstituted enediyne **34** was required.[23,24] The preparation of this substrate on multigram scale was based on the development of a high-yield, β-selective coupling reaction of (*Z*)-ethyl 2,3-dibromopropenoate[32] with (trimethylsilyl)acetylene to form (*Z*)-bromoenyne **30** (Scheme VI).[33] Ester reduction with diisobutylaluminum hydride in toluene at -78 °C and protection of the resulting alcohol **31** with *tert*-butyldiphenylsilyl chloride, triethylamine, and a catalytic quantity of 4-dimethyl-

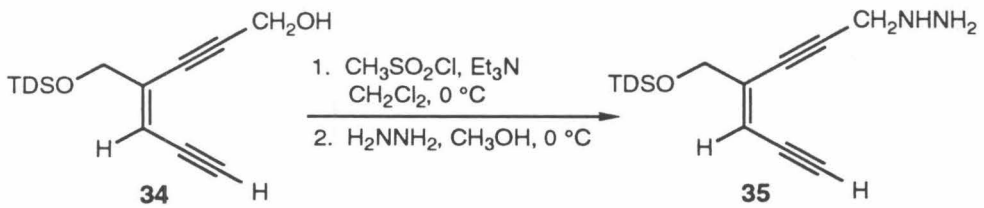


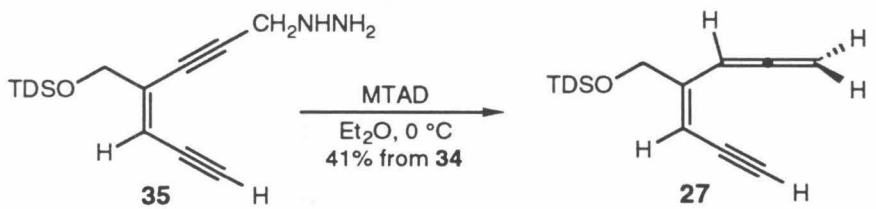
Scheme VI



Reagents and conditions (TMS = $Si(CH_3)_3$, TDS = $SiPh_2t$-Bu): (a) 1.7 equiv $HC{\equiv}CSi(CH_3)_3$, 1.7 equiv $EtN(i\text{-}Pr)_2$, 0.20 equiv CuI, 0.05 equiv $Pd(PPh_3)_4$, DMF, 0 °C, 10 h, 86%; (b) 2.3 equiv DIBAL, toluene, -78→0 °C, 30 min, 94%; (c) 1.2 equiv *t*-$BuPh_2SiCl$, 5.0 equiv Et_3N, 0.27 equiv DMAP, CH_2Cl_2, 0→23 °C, 3.5 h, 95%; (d) 2.0 equiv $HC{\equiv}CCH_2OH$, 4.0 equiv $CH_3(CH_2)_2NH_2$, 0.15 equiv CuI, 0.05 $Pd(PPh_3)_2Cl_2$, THF, 0→23 °C, 14 h, 86%; (e) 0.1 M NaOH, CH_3OH, 0 °C, 45 min, 95%; (f) 3.0 equiv CH_3SO_2Cl, 5.0 equiv Et_3N, CH_2Cl_2, 0 °C, 15 min; 30 equiv H_2NNH_2, CH_3OH, 0 °C, 12 h; (g) 1.2 equiv MTAD, Et_2O, 0 °C, 15 min, 41% from **34.**

aminopyridine furnished (Z)-bromoenyne **32** in 89% yield. Coupling of **32** and propargyl alcohol (2 equiv) in the presence of *n*-propylamine (4 equiv), cuprous iodide (0.15 equiv), and bis(triphenylphosphine)palladium(II) chloride (0.05 equiv) produced the enediyne **33** (86%), which was subsequently deprotected under basic conditions to provide **34** in 95% yield.[26] Enediyne **34** was submitted to a sequence of steps similar to those outlined for the synthesis of allene **18** to provide the target allene **27**.[23,24] Thus, treatment of **34** with methanesulfonyl chloride (3.0 equiv) and triethylamine (5.0 equiv) in dichloromethane at 0 °C provided the crude methanesulfonate ester,[27] which was subsequently exposed to a large excess of anhydrous hydrazine in methanol (30 equiv, 15 M) at 0 °C for 12 h to

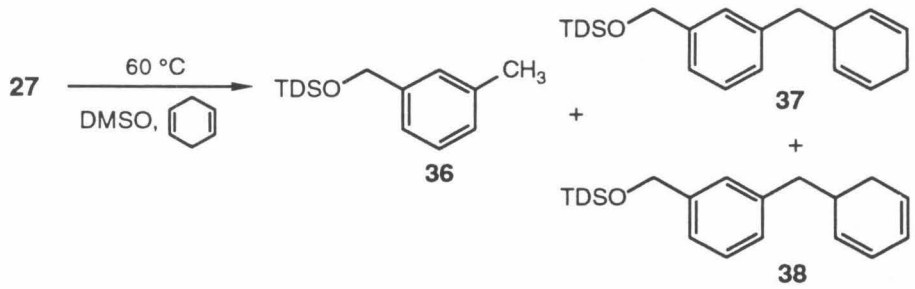




form the monoalkyl hydrazine **35**. After separation of the crude product from excess hydrazine by an aqueous extraction, **35** was oxidized with a slight excess (1.2 equiv) of 4-methyl-1,2,4-triazoline-3,5-dione (MTAD) under anaerobic conditions at 0 °C to afford, after purification by flash column chromatography, **27** in 41% yield from **34**.[24] Allene **27** exists as a non-volatile oil which can be stored anaerobically (concentrated or in solution) for several days without noticeable decomposition.

Heating **27** (0.01 M, 60 °C) in deoxygenated dimethyl sulfoxide (DMSO)

containing 1,4-cyclohexadiene (4.0 M) afforded 3-tolyl *tert*-butyldiphenylsilyl ether **36** (50%), 1,4-cyclohexadiene addition products **37** and **38** (40%), and the bibenzyl derivative **39** (1%) (Table II, entry 1). The kinetics of cyclization of **27** (0.01 M in dimethyl sulfoxide-d_6, 4.0 M 1,4-cyclohexadiene, determined by ^{1}H NMR analysis at 60 °C) are first order (see experimental section) and are indistinguishable from those of **18** in 1,4-cyclohexadiene at the same temperature (k =1.09 ± 0.01 x 10^{-4} and 1.08 ± 0.24



x 10^{-4} s^{-1}, respectively). Thermolysis of **27** at 60 °C in oxygen-free methanol (CH_3OH, CH_3OD, and CD_3OH) essentially replicated the distribution of polar (**40**) and free radical (**39** and **41**) addition products observed with **18** in the same solvents (Table II, entries 2-4), whereas heating **27** in 4.0 M methanol in dimethyl sulfoxide formed only products of free radical addition, **39** and **41** (Table II, entry 5). The low yield of products in the latter experiment is consistent with the poorer ability of methanol to function as an effective radical trap versus, e.g., 1,4-cyclohexadiene. The decreased polar reactivity of **28** in methanol-dimethyl sulfoxide mixtures versus neat methanol is presumably due to strong hydrogen-bonding and decreased acidity of the methanolic hydroxyl group in the former medium. Heating solutions of **27** in deoxygenated 20% aqueous tetrahydrofuran

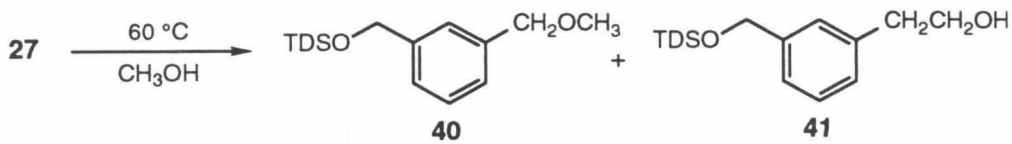
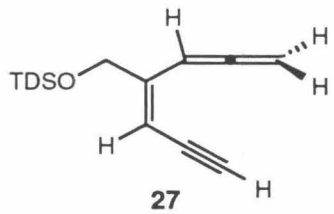


Table II. Thermal Cyclization of **27** in Various Media.[a]

Entry	Medium	Products[b]					
		36	**37 + 38**	**39**	**40**	**41**	**42**
1	1,4-Cyclohexadiene (4.0 M)–DMSO	50	40	1	-	-	-
2	CH_3OH	-	-	1	39	7	-
3	CH_3OD	-	-	1	19	12	-
4	CD_3OH	-	-	-	52	-	-
5	CH_3OH (4.0 M)–DMSO	-	-	1	-	10	-
6	H_2O (11.0 M)–THF	6	-	1	-	-	23

[a] 0.01 M, 60 °C. [b] Yields determined by ^1H NMR analysis of crude reaction mixtures using (*Z*)-1,2-dichloroethylene as an internal standard.



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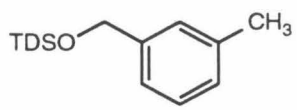

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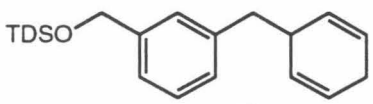

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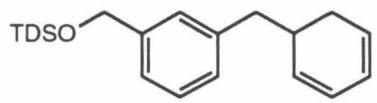

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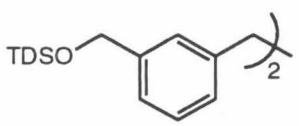

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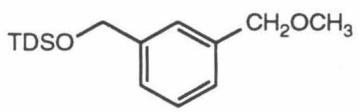

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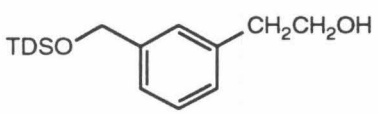

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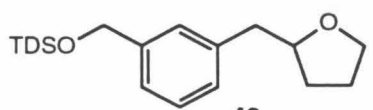
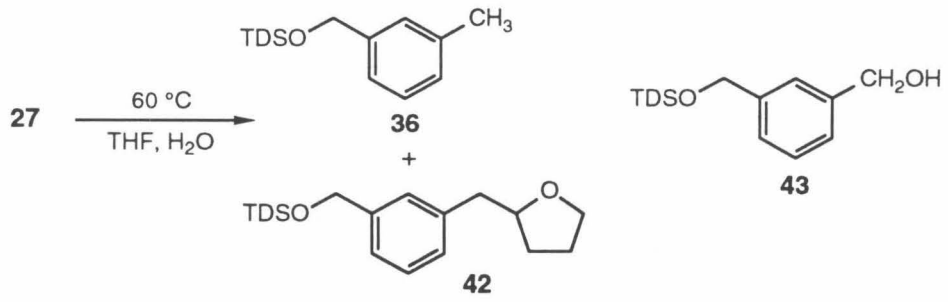


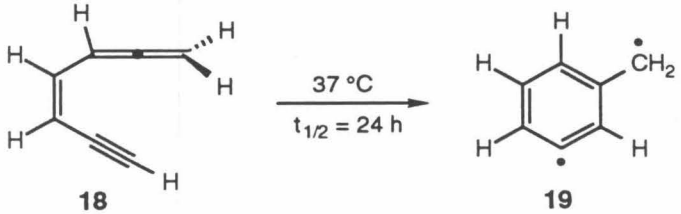
42

at 60 °C (Table II, entry 6) afforded the tetrahydrofuran adduct **42** as the major product (23%), as well as lesser amounts of free-radical products **36** and **39** (6 and 1%, respectively), with <1% of benzyl alcohol **43**, the product of polar addition of water. The latter observation is significant in that it demonstrates the ability of biradicals such as **28** to undergo hydrogen atom transfer reactions, in lieu of polar trapping, in the presence of water.



Chemical Activation in Biradical Formation-Design, Dynamics, and Reactivity

From activation parameters derived above, the half-life for the formation of α,3-dehydrotoluene (**19**) from (*Z*)-1,2,4-heptatrien-6-yne (**18**) can be calculated to be ~24 h at 37 °C. Thus, it is clear that the (*Z*)-allene-ene-yne functional group offers the potential for biradical formation under exceedingly mild conditions. Since model studies described elsewhere suggest that proper substitution of **18**, particularly at the "benzylic" carbon, can accelerate biradical formation,[23c] and given that biradical formation at or

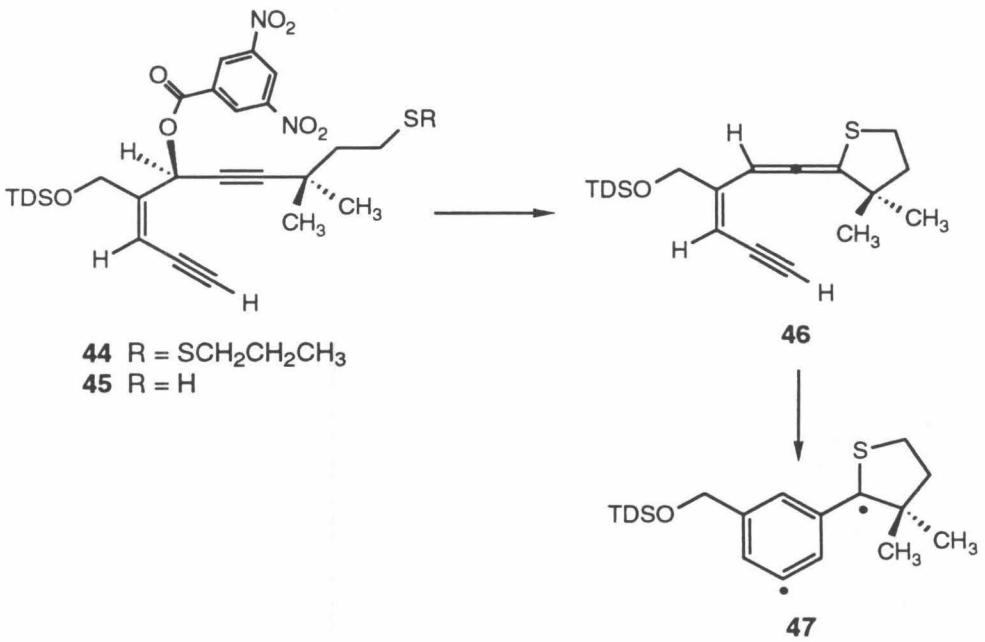


below physiological temperatures is a defining feature of the enediyne antitumor antibiotics, it is logical to ask whether the cyclization of substrates such as **18** could form the basis for the design of nonnatural antibiotics.

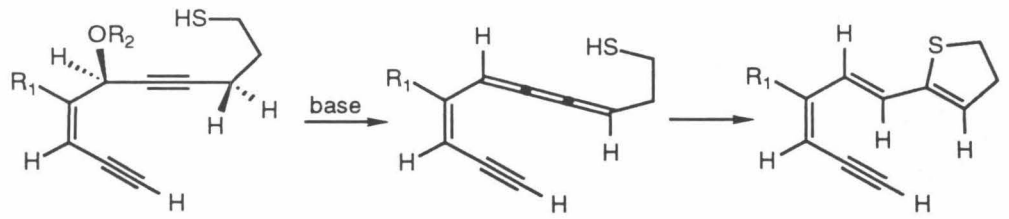
As described in the introduction to this work, a further defining feature of the enediyne antibiotics is the requirement for chemical "activation" prior to biradical formation (cf. Schemes I, II, and III). In the case of calichemicin and dynemicin the activation step removes a structural feature that impedes cyclization, while in the case of neocarzinostatin chromophore chemical activation creates the functionality necessary for cyclization. In our initial efforts to design a chemically activated substrate for α,3-dehydrotoluene formation, we have chosen to adopt the latter strategy.[23c,34]

Scheme VII depicts such a substrate (**44**, TDS = *t*-Bu(Ph)$_2$Si) and the sequence of chemical steps proposed to form the (*Z*)-1,2,4-heptatrien-6-yne subunit (**44**→**45**→**46**) and, subsequently, the biradical **47**.[23c,34] The allene is generated by disulfide bond

Scheme VII



cleavage and intramolecular S_N' cyclization, a sequence inspired by chemical activation steps occurring in the natural enediyne antibiotics described above, though differing somewhat in detail. Preliminary studies established a requirement for the presence of the *gem*-dimethyl group; substrates bearing a proton at this position apparently undergo preferential 1,4-elimination to form a cumulene intermediate (eq 3). The *tert*-butyldiphenylsilyloxymethyl substituent ($TDSOCH_2$), as modeled in allene **27**, provides a potential site for further structural elaboration (e.g., attachment of a DNA-binding

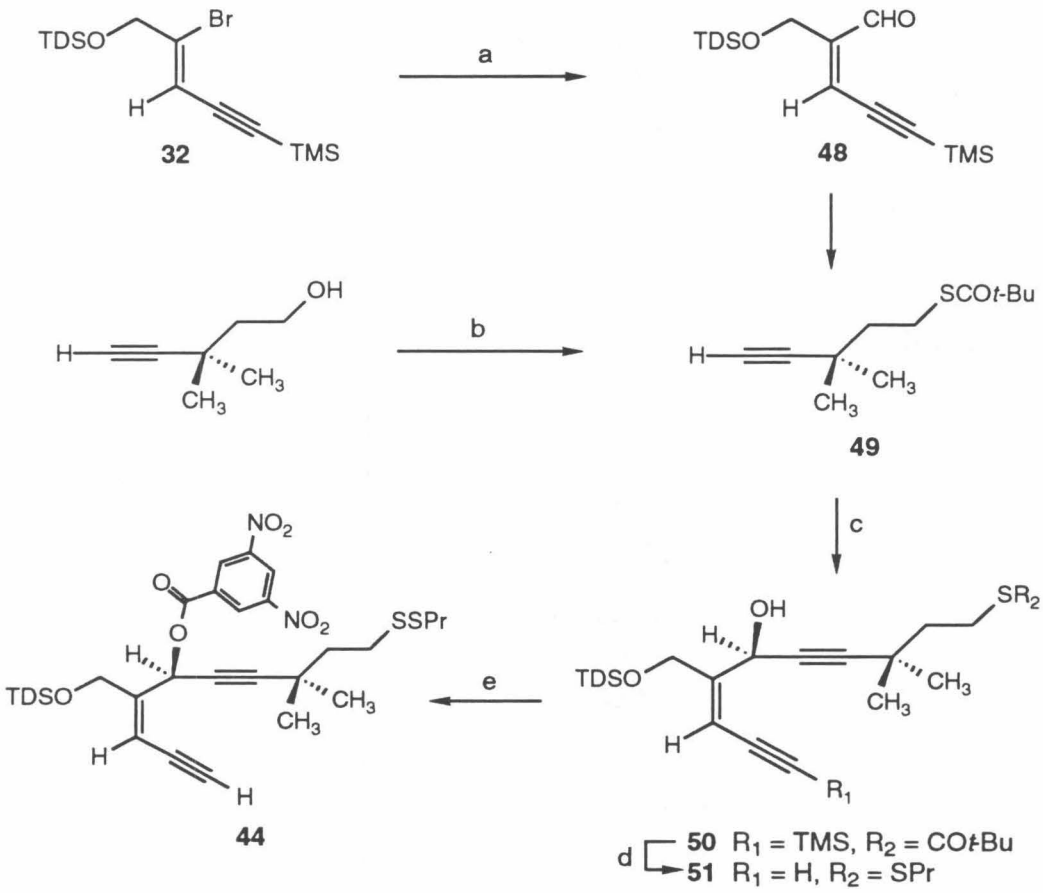


(3)

group) while the sulfur and alkyl substituents on the allene terminus (of **46**) were anticipated to accelerate biradical formation.[23c]

The target substrate **44** was synthesized by the convergent route shown in Scheme VIII.[34] Slow addition of (*Z*)-bromoenyne **32** to a solution of *tert*-butyllithium (2.5 equiv, 0.14 M) in tetrahydrofuran-ethyl ether-pentane[35] (4:1:1) at -120 °C led to its smooth transformation to the corresponding vinyllithium reagent, which was trapped at -120 °C with *N,N*-dimethylformamide (2.5 equiv) to produce the aldehyde **48** in 71% yield after aqueous workup and flash column chromatography. The use of very low temperatures in the halogen-metal exchange reaction was necessary to avoid elimination of the silyloxy group from the vinyllithium intermediate. Addition of methanesulfonyl chloride (1.2 equiv) to a solution of the known alcohol 3,3-dimethyl-4-pentyn-1-ol[36] (0.28 M) and triethylamine (1.3 equiv) in dichloromethane at 0 °C formed the corresponding methanesulfonate ester[27] which, after extractive isolation, was subjected to nucleophilic displacement with thiopivalic acid (6 equiv)-triethylamine (10 equiv) in tetrahydrofuran

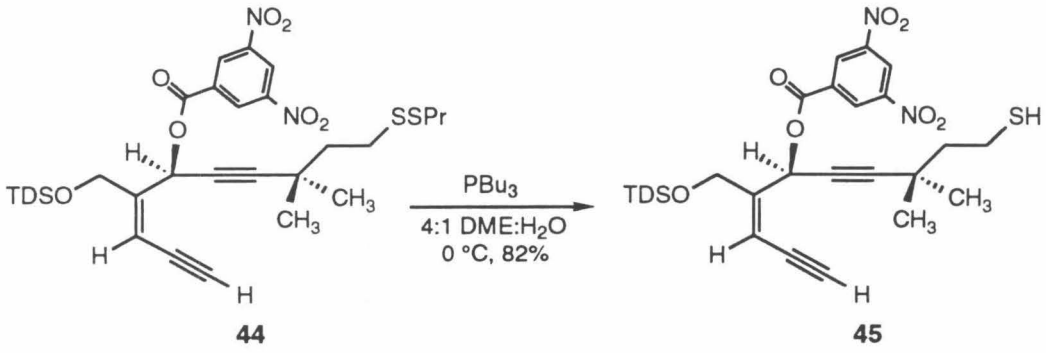
Scheme VIII



Reagents and conditions (TMS = $Si(CH_3)_3$, TDS = $SiPh_2t$-Bu): (a) 2.5 equiv *t*-BuLi, 2.5 equiv DMF, 4:1:1 THF:Et_2O:pentane, -120→-40 °C, 3 h, 71%; (b) 1.2 equiv CH_3SO_2Cl, 1.3 equiv Et_3N, CH_2Cl_2, 0 °C, 5 min; 10.0 equiv Et_3N, 6.0 equiv HSCO*t*-Bu, THF, 0→60 °C, 6 h, 85%; (c) 1.5 equiv LDA, 1.5 equiv **49**, 1.6 equiv $CeCl_3$, then 1 equiv **48**, THF, -78 °C, 1 h, 90%; (d) 0.1 M NaOH, 4:1:1 THF:CH_3OH:propyl disulfide, 0 °C, 4 h, 70%; (e) 10.0 equiv 3,5-dinitrobenzoic acid, 10.0 equiv $CH_3CH_2N{=}C{=}N(CH_2)_3N(CH_3)_2{\bullet}HCl$, 5.0 equiv DMAP, CH_2Cl_2, 0 °C, 30 min, 90%.

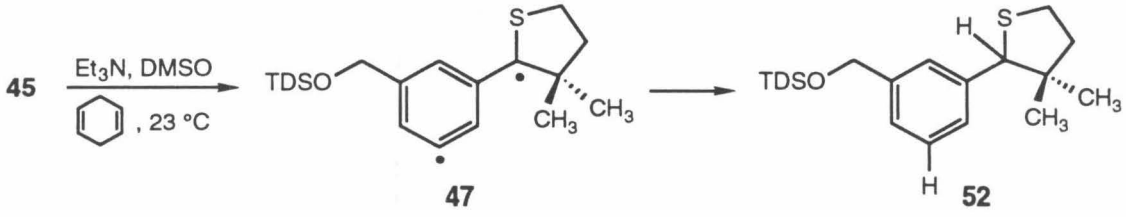
at 60 °C for 6 h to provide the thiol ester **49** in 85% yield. The pivaloyl thiol-protecting group is notable for its stability to the conditions of alkyne metalation, as demonstrated in the convergent step. Lithiation of **49** (1.2 equiv, 1.5 equiv lithium diisopropylamide (LDA), tetrahydrofuran, -78 °C, 10 min) and subsequent addition of anhydrous cerium(III) chloride (1.6 equiv, -78 °C, 30 min incubation)[37] and the aldehyde **48** (1 equiv) afforded the coupling product **50** in 90% yield. Although there are no enolizable protons in **48** or lithiated **49**, the acetylide addition proceeded in moderately higher yield (90 vs. 75%) when cerium(III) chloride was present in the reaction mixture. Treatment of coupling product **50** with sodium hydroxide (0.1 M) in tetrahydrofuran-methanol-propyl disulfide (4:1:1) at 0 °C led to rapid removal of the trimethylsilyl group (<20 min) and, more slowly, cleavage of the thiol ester (~4 h for completion) to form, after trapping the liberated thiol with propyl disulfide, the mixed disulfide **51** in 70% yield. The hydroxyl group of **51** was activated toward displacement by treatment with 3,5-dinitrobenzoic acid (10 equiv), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (10 equiv), and 4-dimethylaminopyridine (5 equiv) in dichloromethane at 0 °C for 30 min, affording the dinitrobenzoate **44** in 90% yield after purification by flash column chromatography. The 3,5-dinitrobenzoate ester represents a near optimum balance between chemical stability and reactivity toward displacement in this system. Accordingly, the corresponding methanesulfonate ester and chloride were too reactive to manipulate conveniently, while the acetate or benzoate esters proved to be too stable for subsequent facile displacement.

Disulfide cleavage occurred under neutral conditions when **44** was treated with tributylphosphine (10 equiv) in 1,2-dimethoxyethane-water (4:1) at 0 °C, affording the thiol **45** in 82% yield.[38] Thiol **45** is stable to neutral or slightly acidic conditions and can be purified by chromatography on silica gel, but undergoes rapid cyclization in the



44 **45**

presence of base. Thus, addition of triethylamine (5.0 equiv) to a deoxygenated solution of thiol **45** (0.01 M) in dimethyl sulfoxide (DMSO) containing 1,4-cyclohexadiene (1.0 M) at 23 °C formed the tetrahydrothiophene derivative **52**, the product of addition of two hydrogen atoms to the putative biradical **47**, in 75% yield (Table III, entry 1). Omission of 1,4-cyclohexadiene from the reaction medium led to an intractable product mixture suggesting that **46**, like **18**, was unstable to the free radical products of its cyclization, but apparently not to cyclohexadienyl. The trapping sites were labeled by using 1,4-cyclohexadiene-d_8 (96% deuterium content at the allylic positions) in the cyclization



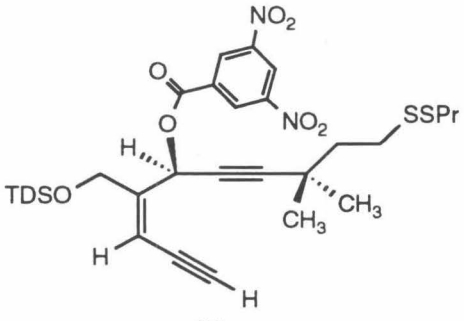
47 **52**

reaction (Table III, entry 2). It was necessary to remove the *tert*-butyldiphenylsilyl group in **52** (tetrabutylammonium fluoride, tetrahydrofuran, 23 °C) in order to resolve the newly-formed aromatic signals in the ^{1}H NMR spectrum; analysis of the resulting alcohol **53** showed the incorporation of deuterium at C5 (60%) and C1' (90%). The source of residual protium at C5, the more reactive site in the biradical, is not known with certainty. As experiments described below rule out the thiol S-H bond as the source of protium

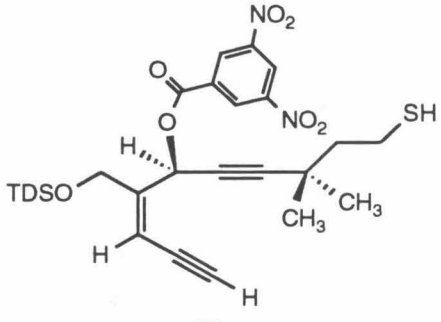
Table III. Reaction of Thiol **45** and Disulfide **44** in Various Media.[a]

Entry	Substrate	Medium	Products[b]			
			52	**54**	**55**	**58**
1	**45**	1,4-Cyclohexadiene (4.0 M)–DMSO	75	-	-	-
2	**45**	1,4-Cyclohexadiene (d_8) (4.0 M)–DMSO	45	-	-	-
3	**44**	*p*-Methoxythiophenol (0.02 M)–DMSO	22	75		-
4	**45**	CH_3OH (4.0 M)–DMSO	33	-	33	-
5	**45**	H_2O (11.0 M)–THF	-	-	-	40

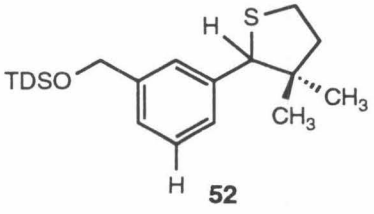
[a] 0.01 M, 23 °C. [b] Yields determined by ^1H NMR analysis of crude reaction mixtures using (*Z*)-1,2-dichloroethylene as an internal standard.



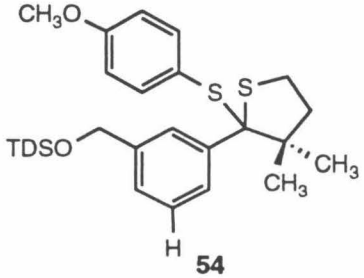
44



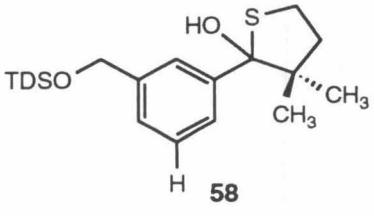
45



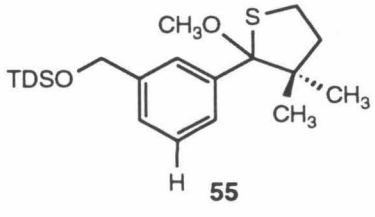
52



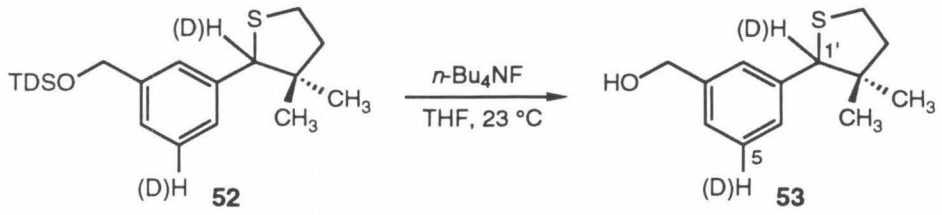
54



58

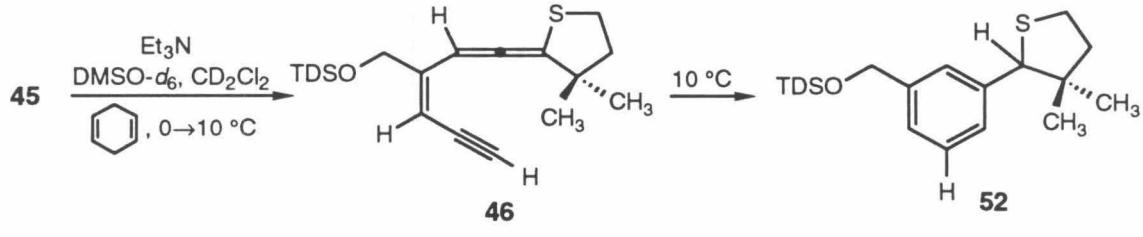


55

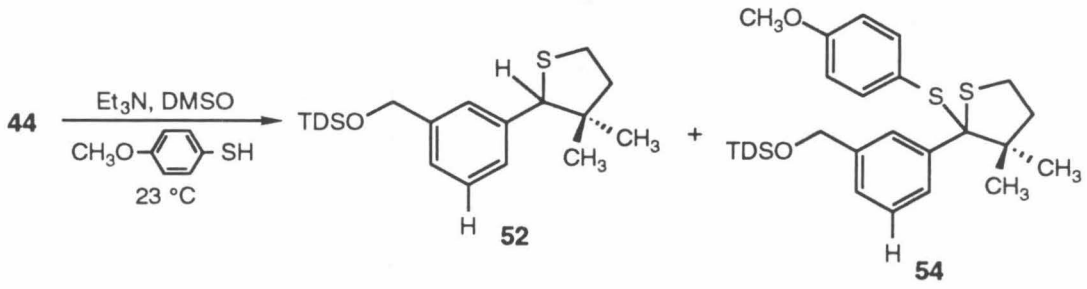


(cyclization of **45** to **46** is more rapid than **46** to **47**), the only possible sources appear to be 3,5-dinitrobenzoic acid, triethylamine, or dimethyl sulfoxide.[39] Though less than quantitative, the incorporation of deuterium at the indicated sites in **52** support the intermediacy of the biradical **47** in the transformation **45**→**52**.

Due to a favorable ordering of rate constants, it was possible to observe the intermediate allene **46** by ^{1}H NMR spectroscopy and to follow its transformation to **52**. Addition of triethylamine (2.2 equiv) to a solution of **45** (0.02 M) and 1,4-cyclohexadiene (0.26 M) in deoxygenated DMSO-d_6:CD_2Cl_2 (2.3:1; CD_2Cl_2 was required to prevent freezing of the sample) at 0 °C caused rapid reaction of **45** (<30 min at 10 °C) to form an intermediate displaying signals consistent with structure **46**. This intermediate was



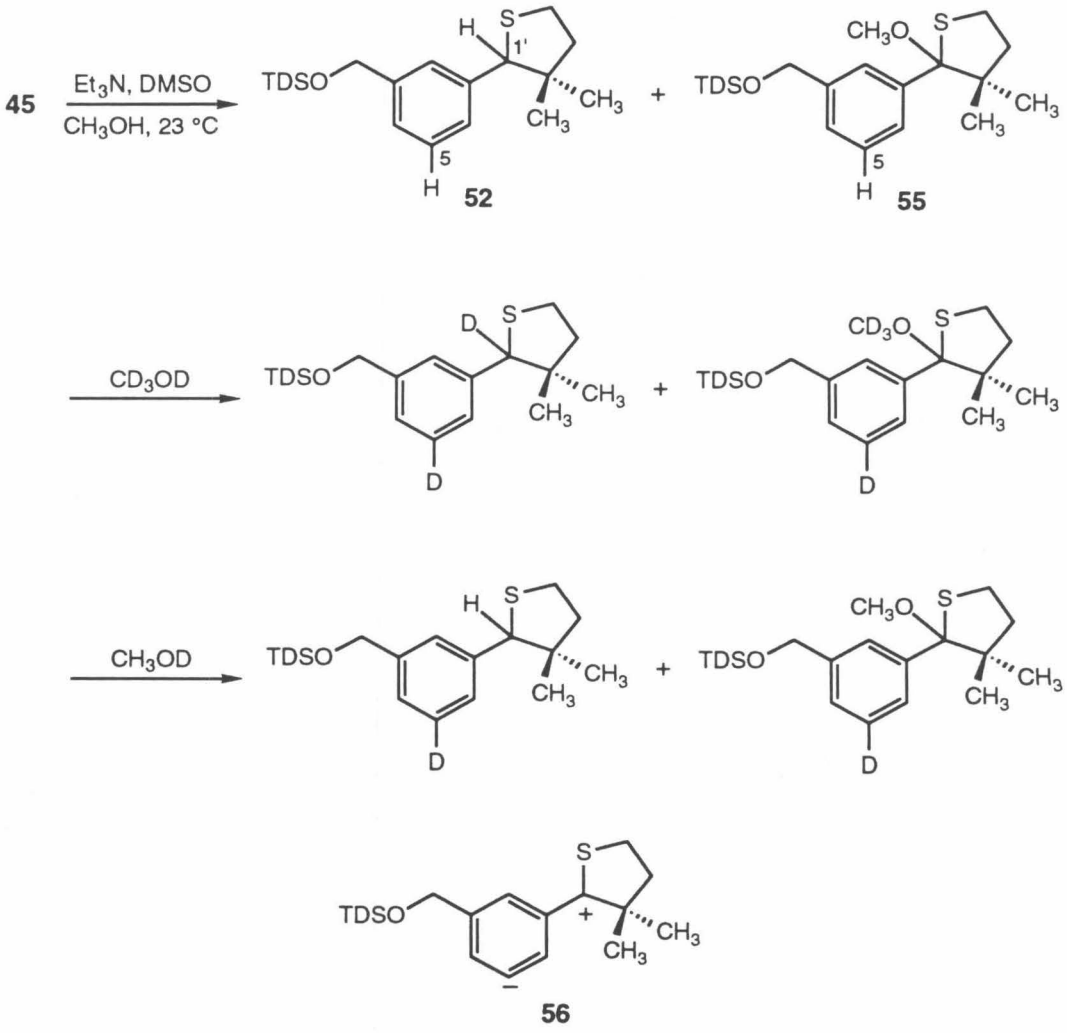
observed to undergo first-order transformation to **52** in a slower step ($k = 3.6 \pm 0.5 \times 10^{-4}$ s^{-1} at 10 °C, two determinations; see experimental section). The entire cascade (**44**→**45**→**46**→**47**→**52**) could be brought about by treating the disulfide **44** (0.01 M) with triethylamine (5 equiv) and 4-methoxythiophenol (3 equiv) in oxygen-free dimethyl sulfoxide, producing tetrahydrothiophene derivative **52** and the thiophenol adduct **54** in excellent combined yield (Table III, entry 3). This reaction was considerably slower than



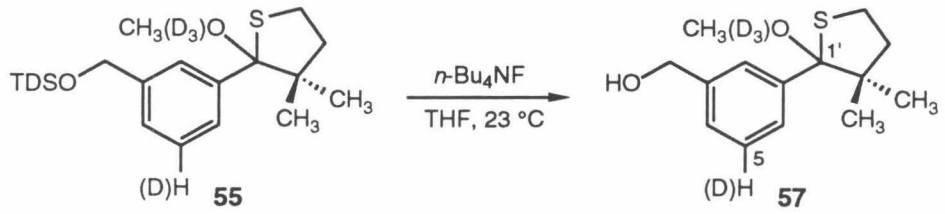
the cyclization of the free thiol (**45**), requiring 30 min at 23 °C for completion, and exhibited a rather large solvent dependence, slowing markedly in less polar media ($t_{1/2}$ = 6 h in 1.5:1 dimethyl sulfoxide-tetrahydrofuran). Control experiments with the non-activated disulfide **51** showed that the rate of simple disulfide cleavage in this substrate followed closely the rate of formation of **52** from **44** in a given solvent, demonstrating that the rate-determining step in the latter reaction was likely disulfide cleavage.

Further trapping studies showed that the biradical **47** displays enhanced polar reactivity as compared with the biradicals **19** and **28**. Attempts to cyclize the thiol **45** in neat methanol using triethylamine (5 equiv) led to transesterification of the 3,5-dinitrobenzoate ester. This complication was avoided by treatment of **45** (0.01 M) with triethylamine (5 equiv) in deoxygenated dimethyl sulfoxide containing methanol (4.0 M) at 23 °C; cyclization produced equal amounts of tetrahydrothiophene derivative **52** and the methyl ether **55** in good yield (Table III, entry 4, Scheme IX). Cursory consideration of these products suggests that both polar and free radical reaction pathways operate in this system. However, further experiments showed that this was not the case, and implicated instead the exclusive operation of a polar reaction pathway (see resonance form **56**). Cyclization of thiol **45** (0.01 M) with triethylamine (5 equiv) in dimethyl sulfoxide containing CD_3OD (4.0 M) demonstrated that both of the newly added hydrogen atoms in **52** were derived from methanol (>95% *incorporation* of

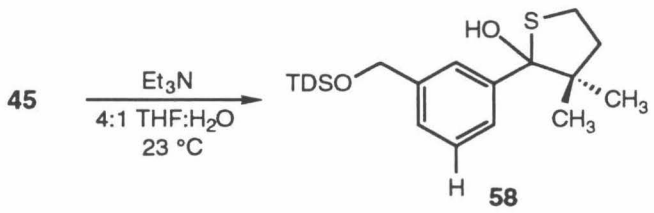
Scheme IX



deuterium at the C5 and C1' positions, as determined by ^{1}H NMR analysis of alcohol **53**) (Scheme IX). Methyl ether **55** formed in the latter experiment also showed >95% incorporation of deuterium at C5, as determined by ^{1}H NMR analysis of the corresponding alcohol **57**. Use of CH_3OD led to exclusive incorporation of deuterium at the C5 positions (>95%) of **52** and **55** with <5% incorporation at the C1' position of **52** (Scheme IX). These experiments support a scheme whereby **52** and **55** are formed by



initial proton transfer from the hydroxyl group of methanol to C5 of biradical **47**, with partitioning of the resultant ion pair by a (net) hydride transfer to form **52** (and presumably formaldehyde), or by simple recombination to form **55**. When compared with data from substrate **18** and **27**, these results show that the biradical **47** exhibits a greater propensity to react as a polar species than intermediates **19** or **28**. In further support of this conclusion, it was found that treatment of thiol **45** with triethylamine (5 equiv) in deoxygenated 20% aqueous tetrahydrofuran provided hemithioketal **58** as the only isolable product (Table III, entry 5, cf. Table II, entry 6).

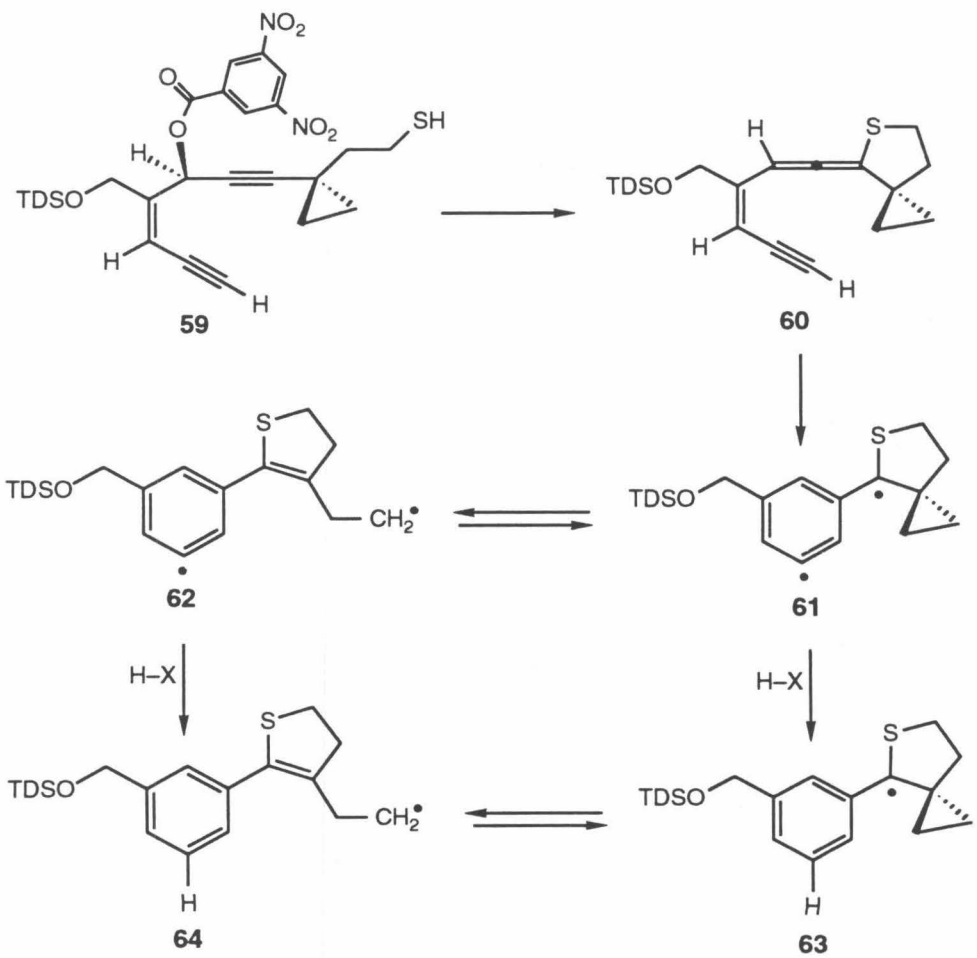


A More Reactive Biradical-Another Step in the Cascade

The trapping studies described above confirm the expectation that the benzylic radical is less reactive than the phenyl radical within α,3-dehydroalkylbenzene biradicals. This difference in reactivity presents a concern with regard to the use of such a species to mimic biradicals generated from the enediyne antibiotics in the damage of double-stranded DNA. The latter biradicals have been shown to induce double stranded lesions, as a subset of total DNA damage products, via the direct abstraction of hydrogen atoms

from the ribose backbone of DNA by both radical sites.[7-9] It is questionable whether a benzylic radical is sufficiently reactive to abstract a ribose-bound hydrogen atom at a rate rapid with respect to alternative trapping pathways (e.g., reaction with molecular oxygen). To address this issue, and to further probe the radical reactivity of α,3-dehydrotoluene intermediates, the cyclopropane-containing thiol **59** was prepared. As outlined in Scheme X, thioallene formation and cyclization of the resultant (*Z*)-allene-ene-yne **60** were anticipated to form the biradical **61**. This cyclopropylcarbinyl radical was expected to enter into dynamic equilibrium with the corresponding homoallylic

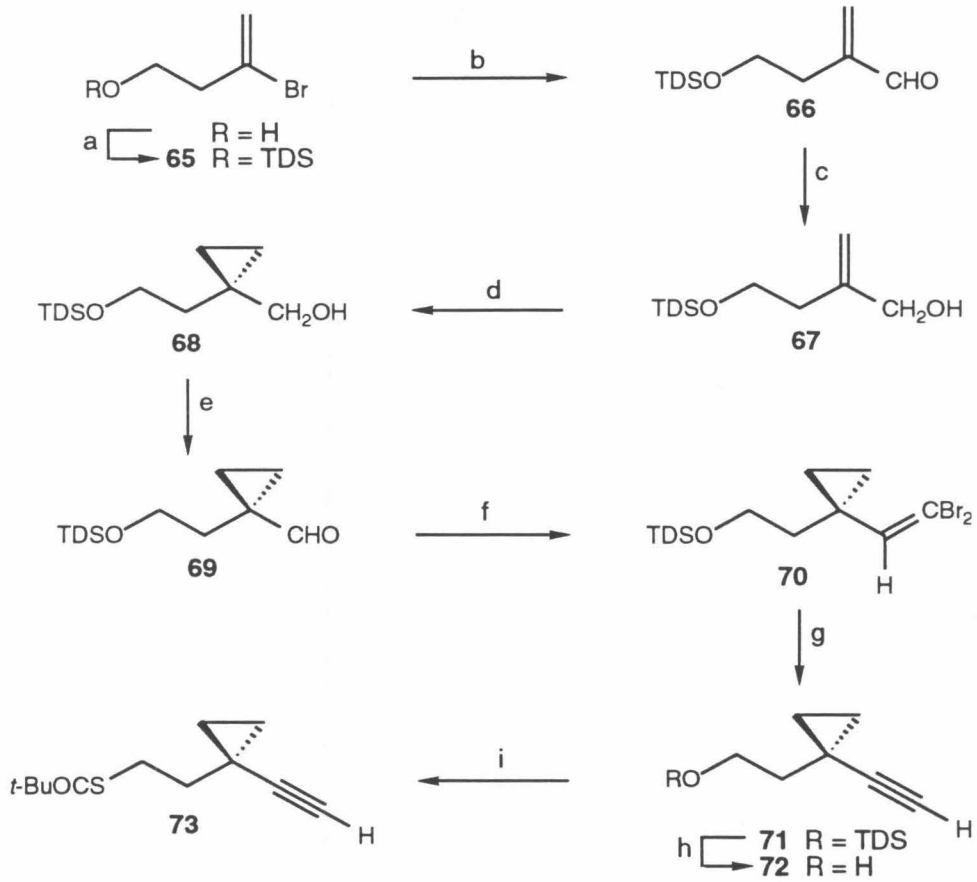
Scheme X



radical, either directly or, more likely, subsequent to hydrogen atom transfer to the phenyl radical (**61** → **62** and **63** → **64**, respectively).[40] Through this ring-opening process, a second highly reactive radical site is generated.

The synthesis of cyclopropane thiol **59** parallels that of thiol **45** (Scheme VIII), employing instead the alkyne **73** for coupling with the aldehyde **48**. Alkyne **73** was synthesized in 8 steps (Scheme XI) from 3-bromo-3-butene-1-ol *tert*-butyldiphenylsilyl ether **65**, obtained by treatment of the known bromo alcohol[41] with *tert*-butyldiphenylsilyl chloride (1.2 equiv), triethylamine (5.0 equiv), and 4-dimethylaminopyridine (0.62 equiv) in dichloromethane at 23 °C (95%). Addition of a solution of **65** in tetrahydrofuran-ethyl ether-pentane[35] (4:1:1) to a solution of *tert*-butyllithium in the same solvent mixture at -120 °C, followed by the addition of a solution of *N,N*-dimethylformamide (2.5 equiv, 0.15 M) in tetrahydrofuran afforded the aldehyde **66** in 91% yield following aqueous workup and flash column chromatography. Reduction of **66** with sodium borohydride (1.0 equiv) in ethanol proceeded cleanly at 0 °C to provide the allylic alcohol **67** (88%). Cyclopropanation of this product with diethyl zinc (5.0 equiv) and diiodomethane (10.0 equiv) in diethyl ether at 23 °C afforded the alcohol **68** in 68% yield after purification by flash column chromatography.[42] Swern oxidation of **68** (oxalyl chloride (1.1 equiv), dimethyl sulfoxide (2.2 equiv), triethylamine (5.0 equiv), dichloromethane, -78→0 °C) provided cyclopropane carboxaldehyde **69** in 87% yield.[43] Transformation of this aldehyde to the alkyne **71** was accomplished by the two-step homologation procedure of Corey and Fuchs.[44] Thus, addition of **69** to a suspension of triphenylphosphine (2.0 equiv), carbon tetrabromide (2.0 equiv), and zinc dust (2.0 equiv) in dichloromethane at 23 °C provided the corresponding 1,1-dibromo olefin **70** following workup and flash column chromatography. Subsequent treatment of a solution of **70** in tetrahydrofuran at -78 °C with *n*-butyllithium (2.2 equiv) afforded the alkyne **71** in 91% yield after an aqueous quench and flash column chromatography.

Scheme XI



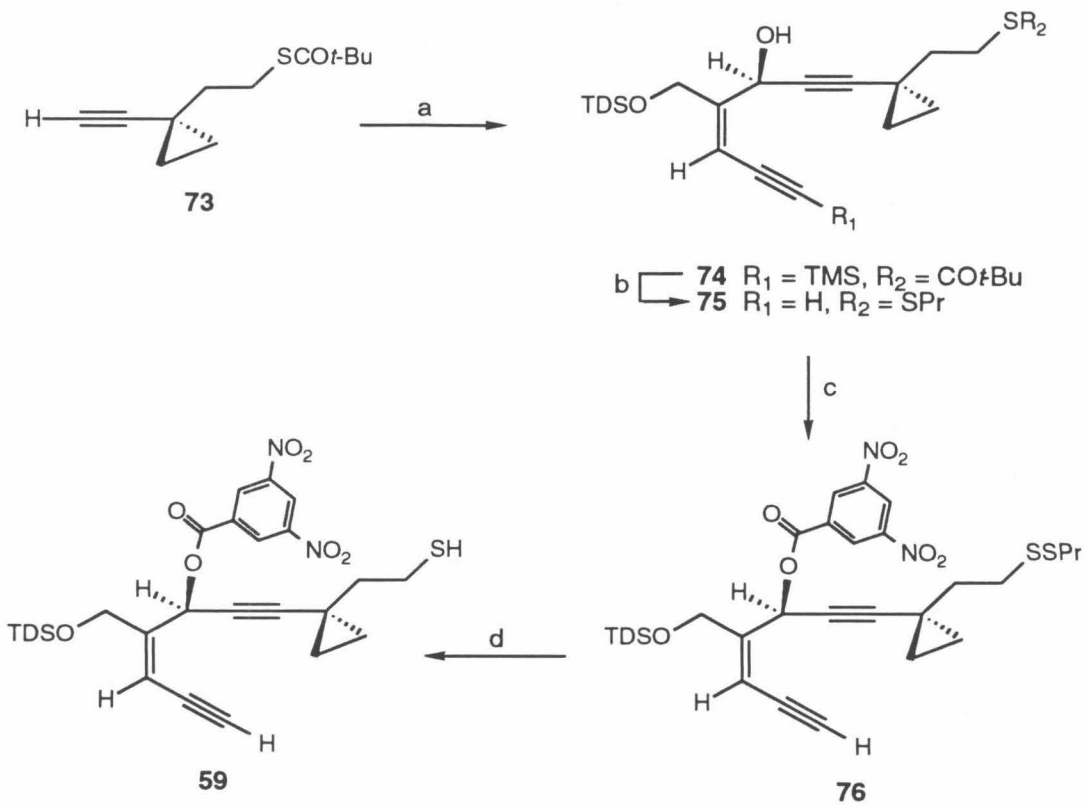
Reagents and conditions (TMS = $Si(CH_3)_3$, TDS = $SiPh_2t$-Bu): (a) 1.2 equiv *t*-$BuPh_2SiCl$, 5.0 equiv Et_3N, 0.62 equiv DMAP, CH_2Cl_2, 0→23 °C, 2 h, 93%; (b) 2.5 equiv *t*-BuLi, 2.5 equiv DMF, 4:1:1 THF:Et_2O:pentane, -120 °C, 3 h, 91%; (c) 1.0 equiv $NaBH_4$, EtOH, 0 °C, 1 h, 88%; (d) 5.0 equiv Et_2Zn, 10.0 equiv CH_2I_2, Et_2O, 0→23 °C, 4 h, 68%; (e) 1.1 equiv $(COCl)_2$, 2.2 equiv DMSO, 5.0 Et_3N, CH_2Cl_2, -78→0 °C, 87%; (f) 2.0 equiv Zn dust, 2.0 equiv PPh_3, 2.0 equiv CBr_4 (precomplexed for 24 h at 23 °C), CH_2Cl_2, then introduced **69**, 23 °C, 5 h; (g) 2.2 equiv *n*-BuLi, THF, -78 °C, 3 h, 91% from **69**; (h) 3.0 equiv *n*-Bu_4NF, THF, 0 °C, 24 h, 86%; (i) 1.2 equiv CH_3SO_2Cl, 1.3 equiv Et_3N, CH_2Cl_2, 0 °C, 15 min; 10.0 equiv Et_3N, 5.0 equiv HSCO*t*-Bu, THF, 0→50 °C, 6 h, 85% from **72**.

Exposure of **71** to a solution of tetrabutylammonium fluoride (3.0 equiv) in tetrahydrofuran at 23 °C cleanly removed the silyl protecting group to give the alcohol **72** in 86% yield. Addition of methanesulfonyl chloride (1.2 equiv) and triethylamine (1.3 equiv) to a solution of **72** in dichloromethane at 0 °C provided the corresponding methanesulfonate ester[27] which, without purification, was treated with thiopivalic acid (5.0 equiv) and triethylamine (10.0 equiv) in tetrahydrofuran at 50 °C, affording the thiol ester **73** in 90% yield from **72** after flash column chromatography. The remaining steps of the synthesis of **59** were virtually identical to those described for the preparation of the thiol **45**.

Accordingly, lithiation of **73** (1.2 equiv, 1.5 equiv LDA, THF, -78 °C, 10 min) and subsequent addition of anhydrous cerium(III) chloride (1.6 equiv, -78 °C, 30 min incubation)[37] and the aldehyde **48** (1 equiv) afforded the coupled product **74** in 63% yield (Scheme XII). Treatment of **74** with sodium hydroxide (0.1 M) in tetrahydrofuran-methanol-propyl disulfide (4:1:1) at 0 °C led to rapid removal of the trimethylsilyl group (<20 min) and, more slowly, cleavage of the thiol ester (~4 h for completion) to form, after trapping the liberated thiol with propyl disulfide, the mixed disulfide **75** in 64% yield. As with disulfide **51**, the hydroxyl group of **75** was activated toward displacement by treatment with 3,5-dinitrobenzoic acid (10 equiv), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (10 equiv), and 4-dimethylaminopyridine (5 equiv) in dichloromethane at 0 °C for 30 min, affording the cyclopropane dinitrobenzoate **76** in 82% yield after purification by flash column chromatography. Treatment of **76** with tributylphosphine (10 equiv) in 1,2-dimethoxyethane-water (4:1) at 0 °C afforded the target cyclopropane thiol **59** in 68% yield.[38] As observed with thiol **45**, **59** is stable to neutral or acidic conditions and can be purified by flash column chromatography.

Cyclopropane thiol **59** (0.01 M) cyclized rapidly at 23 °C upon treatment with triethylamine (5 equiv) in deoxygenated dimethyl sulfoxide (DMSO) containing 1,4-

Scheme XII



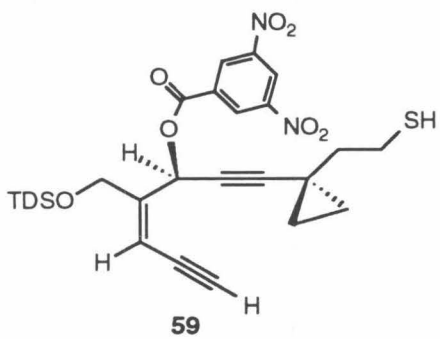
(a) 1.3 equiv LDA, 1.4 equiv $CeCl_3$, THF, -78 °C, 30 min, then 0.91 equiv **48**, -78 °C, 40 min, 63%; (b) 0.1 M NaOH, 4:1:1 THF:CH_3OH:propyl disulfide, 0 °C, 4 h, 64%; (c) 10.0 equiv 3,5-dinitrobenzoic acid, 10.0 equiv $CH_3CH_2N{=}C{=}N(CH_2)_3N(CH_3)_2{\bullet}HCl$, 5.0 equiv DMAP, CH_2Cl_2, 0 °C, 30 min, 82%; (d) 10.0 equiv PBu_3, 4:1 DME:H_2O, 0 °C, 30 min, 68%.

cyclohexadiene (4.0 M) to form products consistent with the intermediacy of the biradical **61**, i.e., the spirocyclopropyltetrahydrothiophene derivative **77** (28%) and the cyclopropane ring-opened product **78** (21%) (Table IV, entry 1). The ratio of these products was highly dependent upon the concentration of 1,4-cyclohexadiene in the medium. For example, use of four-fold less 1,4-cyclohexadiene (1.0 M) resulted in a sharp reduction in the yield of ring-opened product **78** (5%) with a corresponding

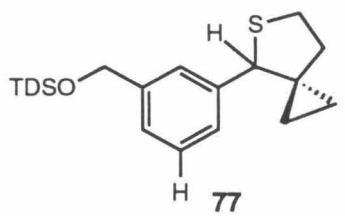
Table IV. Cyclization of Cyclopropane Thiol **59** (0.01 M) in Various Media.

Entry	Solvent	Products[a]			77 : 78
		77	**78**	**81**	
1	DMSO–1,4-Cyclohexadiene (4.0 M)	28	21	-	1.33 : 1
2	DMSO–1,4-Cyclohexadiene (1.0 M)	50	5	-	10.0 : 1
3	DMSO–CH_3OH (4.0 M)	13	-	67	na

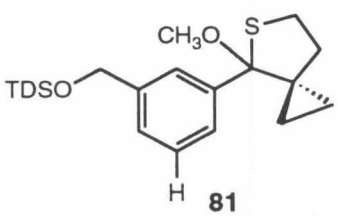
[a] Yields determined by ^1H NMR analysis of crude reaction mixtures using (*Z*)-1,2-dichloroethylene as standard.



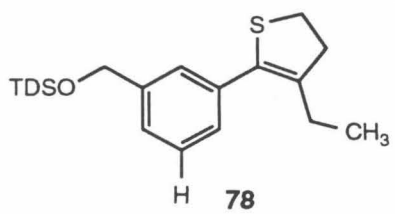
59



77

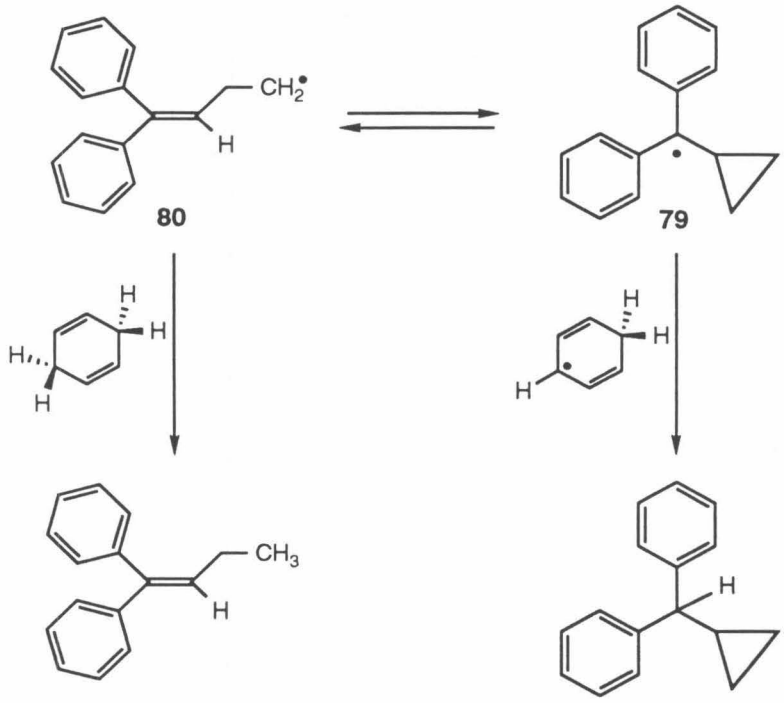


81



78

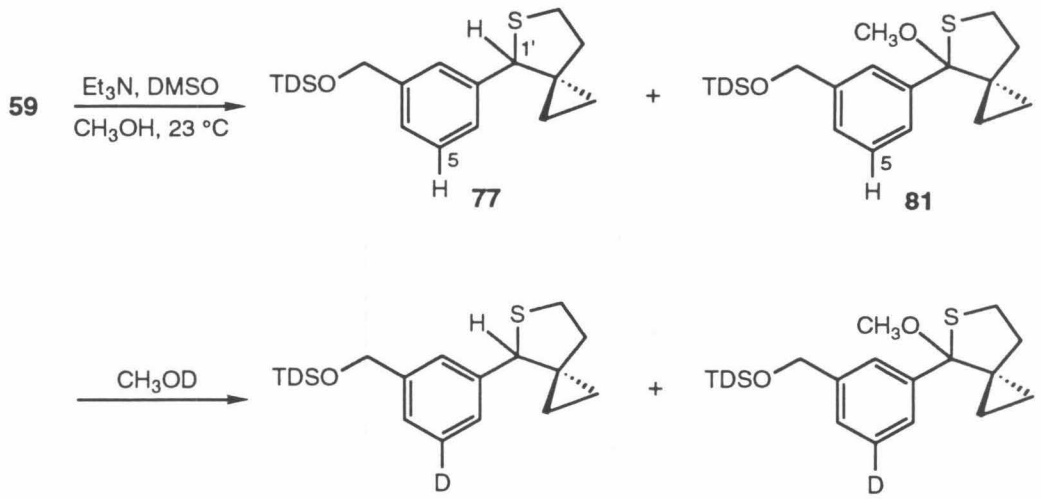
Scheme XIII



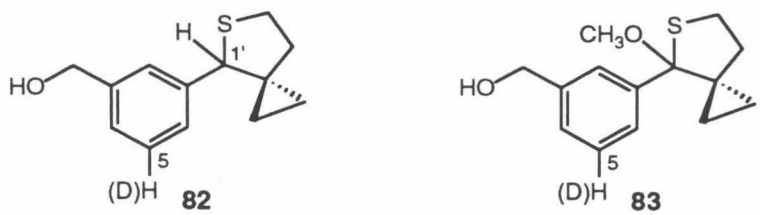
increase in the yield of spiro product **77** (50%) (Table IV, entry 2). These results closely parallel the observations of Roberts et al. in their study of the trapping of the stabilized cyclopropylcarbinyl radical **79** with 1,4-cyclohexadiene.[45] These authors present data to support the reasonable hypothesis that the benzyl radical **79** and its ring-opened isomer **80** enter into a dynamic equilibrium; only the latter is capable of direct hydrogen atom abstraction from 1,4-cyclohexadiene, while the former is quenched exclusively with cyclohexadienyl (Scheme XIII).[45]

Under conditions where the dimethyl-substituted thiol **45** reacts solely to form products described by a polar reaction mechanism (4.0 M methanol in dimethyl sulfoxide, 0.05 M triethylamine, 23 °C), cyclopropane-substituted analog **59** was found to react analogously, producing the spirotetrahydrothiophene derivatives **81** (67%) and **77**

Scheme XIV



(13%) (Scheme XIV; Table IV, entry 3). As with thiol **45**, trapping studies of **59** with CH_3OD established that a polar mechanism operates in this case as well. Thus, cyclization of thiol **59** (0.01 M) with triethylamine (5 equiv) in dimethyl sulfoxide containing CH_3OD (4.0 M) led to exclusive incorporation of deuterium at the C5 positions (>95%) of **77** and **81** with <5% incorporation at the C1' position of **77** (determined by ^1H NMR analysis of the corresponding alcohols **82** and **83**) (Scheme XIV). In contrast to the radical reaction pathway, polar trapping of **61** did not lead to cyclopropane ring-opened products.



Discussion of α,3-Dehydrotoluene Thermochemistry[23c]

(*Z*)-1,2,4-Hepatrien-6-yne (**18**) undergoes a mild thermal cyclization to form the biradical α,3-dehydrotoluene (**19**). It is instructive to compare the energetics of this process with the more familiar Bergman reaction (**11**→**12**) (Figures 1 and 2).[13] Through the innovative contributions of Squires and co-workers, the enthalpics of both reactions are now known;[46] kinetic measurements of Jones and Bergman,[13a] and Myers and Kuo,[23a] complete the energy diagrams of Figures 1 and 2. It can be seen that while the Bergman reaction is modestly endothermic, formation of α,3-dehydrotoluene from **18** is strongly exothermic (ΔH_r ~ -15 ± 3 kcal/mol). As reported in the work of Squires et al., the interaction of the two radical centers is stabilizing in each 1,4-biradical, worth 6 ± 3 kcal/mol in the case of **19** and 11 ± 3 kcal/mol for **12**.[46] The greater exothermicity of the α,3-dehydrotoluene-forming reaction is easily traced to the greater stability of a benzyl radical versus a phenyl radical. Given these thermodynamic data, it is perhaps not surprising that the barrier to cyclization of **18** is considerably lower than that of **11**. As demonstrated in this work, this barrier can be further reduced by appropriate substitution of the allenic terminus of **18** (and thus the benzylic site of **19**). In a calculated reaction pathway from **18** to **19**, Koga and Morokuma find an early transition state, as expected given the exothermicity of the reaction, with no evidence of twisting of the incipient benzyl radical toward conjugation with the phenyl ring.[47] This radical nevertheless occupies an orbital of greater p-character than the corresponding radical in cyclizations of **11**, a fact which may lead to a lower barrier to cyclizations of (*Z*)-allene-ene-yne systems. It is also true that the cyclizations of **18** lack the repulsive interactions between the two in-plane p-orbitals not involved in bonding, a feature which likely contributes to the enthalpy of activation of (*Z*)-enediyne cyclizations.[47] Regardless of the origin of the effect, it is clear that the (*Z*)-allene-ene-yne functional group *cyclizes rapidly* in the

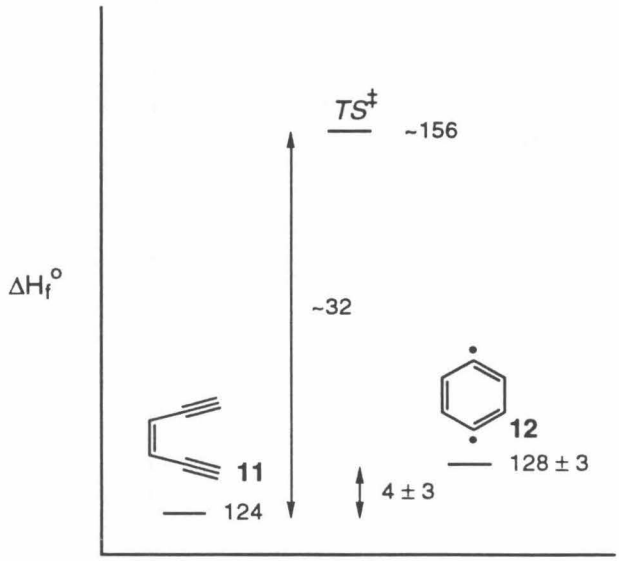


Figure 1. Enthalpy diagram for cyclization of (*Z*)-hex-3-ene-1,5-diyne (**11**). $\Delta H_f°$ (**11**): Calculated using revised group additivities (Benson, S. W.; Garland, L. J. *J. Phys. Chem.* **1991**, *95*, 4915). See also: Lias, S. G.; Bartmess, J. E.; Liebman, J. F.; Holmes J. L.; Levin, R. D.; Mallard, W. G. *J. Phys Chem. Ref. Data* **1988**, *17*, Suppl. 1. $\Delta H^‡$: ref 13a. $\Delta H_f°$ (**12**): ref 46a.

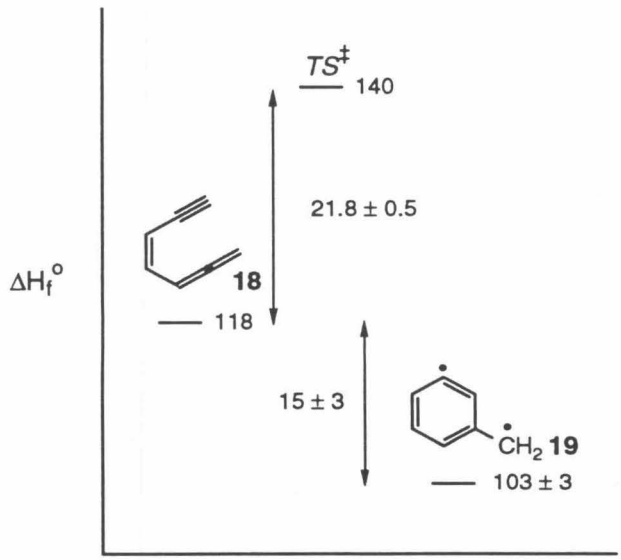
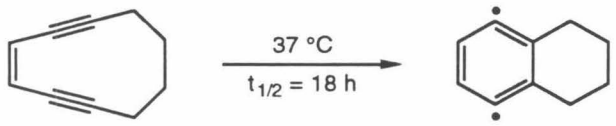


Figure 2. Enthalpy diagram for cyclization of (*Z*)-1,2,4-heptatrien-6-yne (**18**). $\Delta H_f°$ (**18**): ref 23a. Revision of this number downward by 1-2 kcal/mol may be warranted: Benson, S. W.; Garland, L. J. *J. Phys. Chem.* **1991**, *95*, 4915. $\Delta H^‡$: ref 23a. $\Delta H_f°$ (**19**): ref 46b.

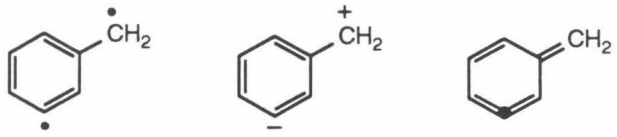
absence of additional ground-state destabilization, as required for the cyclization of (Z)-enediynes at comparable rates (e.g., eq 4).[21e]



(4)

Conclusions

Dichotomous (polar and free radical) reactivity is observed when **18** is pyrolyzed in the presence of polar reactants. Mechanistic studies suggest that both radical and polar products arise from a common intermediate or, if arising by a dynamic process, that this process must be rapid on the timescale of the trapping reactions. In the former case, the data support a description of the common intermediate as a polar biradical, that is, some linear combination of limiting structures **19** and **26**.[48] Little et al. have recently proposed and discussed in detail a similar description for a trimethylenemethane biradical intermediate.[49] Implicit in the "polar biradical" description is the fact that singlet species

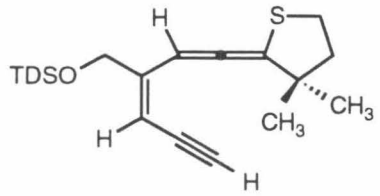


19 **26** **84**

are involved, consistent with the work of Squires et al. supporting a singlet ground state for **19**.[46b] In light of the latter results and in consideration of the experimental evidence presented in this work, the involvement of a single reactive intermediate **19**, best described as a polar, singlet biradical, is favored to account for all products observed. A mechanism involving rapid equilibration between species (e.g., a singlet state and a low-lying triplet state) cannot, however, be ruled out. A third possibility involving the intermediacy of a chiral closed-shell allene structure (methylene-2,3,5-cyclohexatriene,

84) is considered to be unlikely given the calculated energy of this species versus the planar, singlet biradical isomer[46b] and given the difficulty in reconciling the observed free radical and polar (orientation of methanol addition) products in terms of a species of this description.[50] The polar reactivity of **19** represents a departure from the known chemistry of the σ,σ-biradicals derived from (*Z*)-enediyne **11** and the enediyne antibiotics (introduction) which react exclusively by standard radical reaction paths.[51] Here again, the discriminating feature may well be the differential stabilities of the electron deficient benzyl and phenyl carbons, in this instance with reference to the corresponding cations.

In light of this discussion of thermochemistry and reactivity, it is worthwhile to briefly consider the possibility that an α,3-dehydroalkylbenzene biradical might function as a DNA-damaging agent, perhaps forming the basis for the design of a nonnatural antitumor agent, in analogy to the enediyne antitumor antibiotics (cf., introduction). In this regard, several factors must be considered. First, will the cyclization reaction that forms a biradical such as **19** be sufficiently rapid? To answer this question, it must be known what are optimum, or even adequate, rates of cyclization in a physiological system. Beyond certain obvious limitations defined by the biological system in question (e.g., the half-life for cell division), an optimum cyclization rate has yet to be determined. Given the high reactivity of the (*Z*)-allene-ene-yne functional group, one critical requirement is that the cyclization be rapid with respect to competing, nonproductive reactions. Even by these minimal criteria, the rate of the parent cyclization (**18**→**19**) would appear to be slow ($t_{1/2}$ at 37 °C ~ 1 day). As demonstrated in this work, appropriate substitution of the allenic terminus dramatically accelerates the cyclization reaction. For example, the (*Z*)-allene-ene-yne **46** is found to cyclize with a half-life of ~1 h at 10 °C. Unfortunately, this example illustrates a further consideration with these systems in that the product biradical (**47**) favors a polar trapping mechanism in polar media. It remains to be established whether it is possible to accelerate cyclization by



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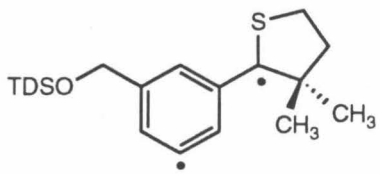

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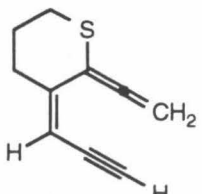
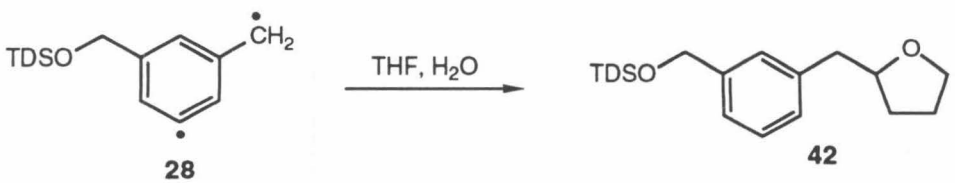


85

substitution of the allenic terminus without enhancing polar reactivity. As suggested above, an alternative strategy for rate acceleration in (Z)-allene-ene-yne cyclizations might exploit entropic factors. For example, by constraining the allene group in the proper orientation for cyclization (as in compound **85**), rate enhancements of perhaps more than one order of magnitude might be obtained.[52,53]

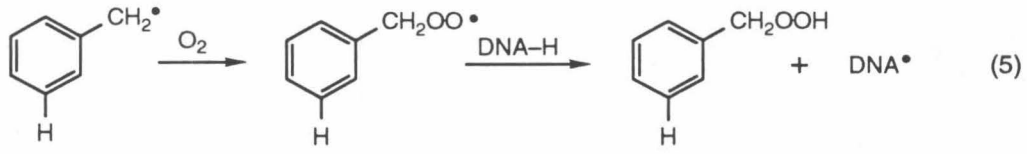
As illustrated with biradical **47**, and discussed in detail above, a second major issue in this system concerns the dichotomous (polar vs. free-radical) reactivity of these σ,π-biradicals. This feature necessarily introduces a mechanistic ambiguity into any DNA cleavage chemistry induced by biradicals such as **47**. However, in simple systems such as **28**, there is little doubt that radical reactions will predominate, even in the presence of water. For example, the major product from trapping of **28** in 20% aqueous tetrahydrofuran is the adduct **42**.



28 **42**

Finally, a third consideration is the stability of the benzylic site within α,3-dehydroalkylbenzene biradicals, given a radical reaction pathway. The enediyne antibiotics have been shown to produce double stranded lesions in B-form DNA wherein both radical sites within the biradical intermediate directly abstract hydrogen atoms from

the ribose backbone.[7-9] It has been suggested that these lesions are the most lethal products of DNA damage in the case of neocarzinostatin chromophore.[7g] The stability of the benzylic site raises a concern as to whether the σ,π-biradicals described herein could participate directly in such a reaction. An indirect pathway with a similar outcome might involve a peroxyl intermediate, as illustrated in eq 5. The notion of using a secondary rearrangement to transform the benzyl radical into a more reactive species has been demonstrated above with cyclopropane thiol **59** and represents one strategy to mimic the more reactive biradicals of the enediyne antibiotics.



(5)

The preceding considerations follow rationally from the background studies described above. Clearly, however, the nature of the detailed interaction of double stranded DNA with α,3-dehydroalkylbenzene biradicals must await experimental determination.[54]

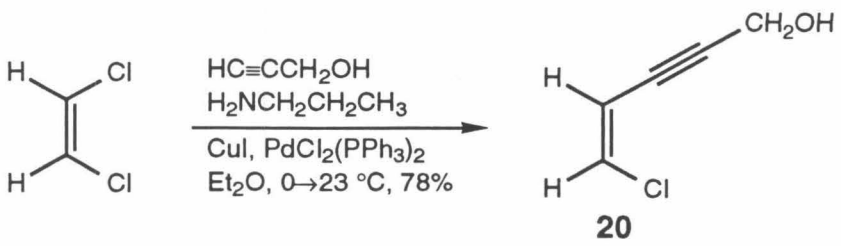
Experimental Section

General Procedures. 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/argon-flush cycles (≥ five iterations). Organic solutions were concentrated by rotary evaporation at ~25 Torr (water aspirator). Flash column chromatography was performed as described by Still et al.[55] 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). Electrochemical experiments were performed using a Princeton Applied Research (PAR) model 173 potentiostat/galvinostat equipped with a PAR model 179 digital coulometer.

Materials. Commercial reagents and solvents were used as received with the following exceptions. Ethyl ether and tetrahydrofuran (THF) were distilled from sodium benzophenone ketyl. Pentane, dichloromethane, tributylphosphine, *N,N*-diisopropylethylamine, diisopropylamine, *n*-propylamine and triethylamine were distilled from calcium hydride at 760 Torr. Dimethyl sulfoxide (DMSO) was distilled from calcium sulfate at 40 Torr and stored over 4Å molecular sieves. *N,N*-Dimethylformamide (DMF) was either distilled from calcium sulfate at 40 Torr or was purchased from Aldrich Chemical Company (HPLC grade, < 0.03% water content) and was stored over 4Å molecular sieves. Anhydrous cerium(III) chloride was prepared from the heptahydrate by heating at 100 °C and 1 Torr for 12 h. 3,5-Dinitrobenzoic acid was recrystallized from water. Methanesulfonyl chloride was distilled from phosphorous pentoxide at 760 Torr. Oxalyl chloride was distilled at 760 Torr immediately prior to use. Cuprous iodide was purified by continuous extraction (12 h) with tetrahydrofuran in a Soxhlet apparatus.[56]

Tetrakis(triphenylphosphine)palladium(0)[57] and trifluoroethyl benzyl ether[58] were prepared according to literature procedures. Cyclohexadiene adducts **24** and **25** were prepared as an inseparable mixture by reaction of cyclohexadienyl anion[59] with benzyl bromide. 3,3,6,6-Tetradeuterio-1,4-cyclohexadiene was purchased from MSD Isotopes Inc.[60] The molarity of *n*-butyllithium solutions was determined by titration using diphenylacetic acid as an indicator (average of three determinations).[61] Solutions of lithium diisopropylamide in tetrahydrofuran (0.2-0.4 M) were prepared immediately prior to use by the addition of *n*-butyllithium (1.6 M in hexanes, 1 equiv) to a solution of diisopropylamine (1.1 equiv) in tetrahydrofuran at -78 °C with brief warming of the resultant mixture (5-min immersion of the reaction flask in an ice bath) and then cooling to -78 °C.

Instrumentation. Infrared (IR) spectra were obtained using a Perkin-Elmer 1600 FT-IR spectrophotometer referenced to a polystyrene standard. Data are presented as follows: frequency of absorption (cm^{-1}), intensity of absorption (s = strong, m = medium, w = weak, br = broad) and assignment (when appropriate). Proton nuclear magnetic resonance (^1H NMR) spectra were recorded with a JEOL JX-400 (400 MHz) or a Bruker AM-500 (500 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 7.15, $CHDCl_2$: δ 5.29). Data are represented as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), integration, coupling constant in Hertz (Hz), and assignment. High resolution mass spectra were obtained at the University of California, Riverside Mass Spectrometry Facility.



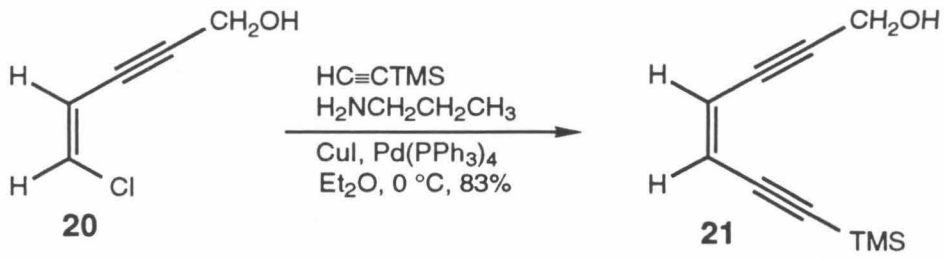
20

(*Z*)-Vinyl Chloride **20**.

Cuprous iodide (0.62 g, 3.26 mmol, 0.15 equiv) and bis(triphenylphosphine)-palladium(II) chloride (0.76 g, 1.08 mmol, 0.05 equiv) were added sequentially to an ice-cooled, deoxygenated solution of (*Z*)-1,2-dichloroethylene (8.41 mL, 107 mmol, 5.0 equiv), propargyl alcohol (1.21 g, 21.7 mmol, 1 equiv), and *n*-propylamine (8.90 mL, 108 mmol, 5.0 equiv) in ethyl ether (25 mL) and the resulting brown suspension was thoroughly degassed. After stirring at 23 °C for 6 h, the reaction mixture was partitioned between an aqueous solution comprised of equal parts of saturated aqueous ammonium chloride and saturated aqueous potassium carbonate solutions (100 mL) and ethyl ether (3 x 100 mL). The combined organic layers were dried over sodium sulfate and were concentrated. Purification of the residue by flash column chromatography (20% ethyl acetate in hexanes) afforded (*Z*)-vinyl chloride **20** (1.91 g, 78%) as a brown oil.

^{1}H NMR (400 MHz, $CDCl_3$), δ: 6.40 (d, 1 H, J = 7.3 Hz, C≡CCH=C**H**), 5.91 (dt, 1 H, J = 7.3, 2.0 Hz, C≡CC**H**=CH), 4.46 (d, 2 H, J = 2.0 Hz, C**H**$_2$OH).

FTIR (neat), cm^{-1}:	3346 (br, OH), 3087 (m), 2917 (m), 2865 (m), 2209 (w, C≡C), 1592 (s), 1331 (s), 1126 (s), 1015 (s), 849 (s), 725 (s).
MS (EI), m/z (%base):	116 (53), 99 (10), 87 (9), 81 (100), 73 (19), 63 (19).
HRMS (EI):	Calcd for $C_5H_5ClO(M^+)$: 116.0029 Found: 116.0029
TLC (20% EtOAc in Hexanes), R_f:	(*Z*)-Vinyl Chloride **20**: 0.30 (UV)

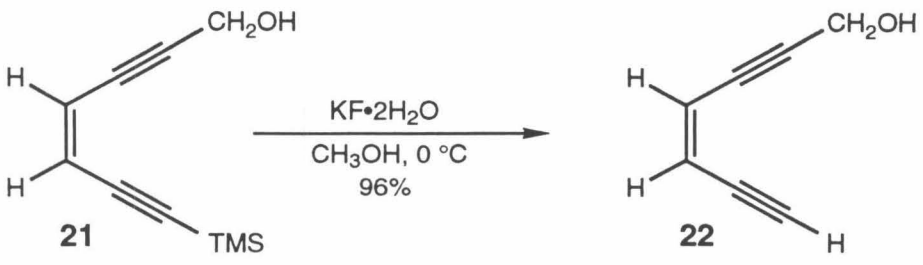


(Z)-Enediyne **21**.

A deoxygenated suspension of tetrakis(triphenylphosphine)palladium(0) (1.13 g, 0.98 mmol, 0.05 equiv) and (Z)-vinyl chloride **20** (2.26 g, 19.0 mmol, 1 equiv) in ethyl ether (45 mL) at 23 °C was transferred via wide-bore cannula to an ice-cooled, deoxygenated solution of cuprous iodide (0.74 g, 3.9 mmol, 0.20 equiv), (trimethylsilyl)acetylene (3.85 mL, 27.2 mmol, 1.4 equiv), and *n*-propylamine (6.4 mL, 76.0 mmol, 4.0 equiv) in ethyl ether (40 mL). The resulting brown suspension was thoroughly deoxygenated and was stirred at 0 °C for 1 h. The reaction mixture was poured into an aqueous solution comprised of equal parts of saturated aqueous ammonium chloride and saturated aqueous potassium carbonate solutions (100 mL) and the resulting biphasic solution was stirred under air at 23 °C for 45 min. The organic phase was separated, and the aqueous layer was extracted with ethyl ether (3 x 75 mL). The combined organic layers were dried over sodium sulfate and were concentrated. The residue was purified by flash column chromatography (5% ethyl acetate in hexanes) to give (Z)-enediyne **21** (2.87 g, 83%) as a brown oil.

^{1}H NMR (400 MHz, $CDCl_3$), δ: 5.86 (s, 2 H, both C=C**H**), 4.47 (d, 2 H, J = 5.4 Hz, CH_2OH), 1.66 (t, 1 H, J = 5.4 Hz, CH_2OH), 0.22 (s, 9 H, $Si(CH_3)_3$).

FTIR (neat), cm^{-1}:	3353 (br, OH), 3048 (m), 2960 (s), 2144 (s, C≡C), 1574 (w), 1251(s), 1134 (s), 1027 (s), 843 (s), 759 (s).
MS (EI), m/z (%base):	178 (65), 163 (100), 145 (48), 137 (48), 75 (58).
HRMS (EI):	Calcd for $C_{10}H_{14}OSi$ (M^+): 178.0814 Found: 178.0809
TLC (20% EtOAc in Hexanes), R_f:	(*Z*)-Vinyl Chloride **20**: 0.29 (UV) (*Z*)-Enediyne **21**: 0.40 (UV)



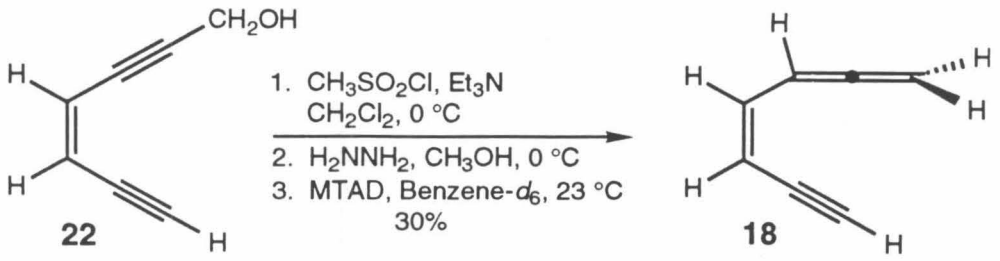
Propargyl Alcohol **22**.

Potassium fluoride dihydrate (0.26 g, 2.76 mmol, 2.0 equiv) was added to an ice-cooled solution of (*Z*)-enediyne **21** (0.248 g, 1.39 mmol, 1 equiv) in methanol (5.0 mL). After stirring at 0 °C for 2.5 h, the reaction mixture was partitioned between brine (100 mL) and ethyl acetate (4 x 75 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 give propargyl alcohol **22** (0.142 g, 96%) as a pale yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$), δ: 5.95 (dm, 1 H, J = 11.1 Hz, HC=C**H**C≡CCH_2OH), 5.83 (dd, 1 H, J = 11.1, 2.3 Hz, **H**C=CHC≡CCH_2OH), 4.48 (d, 2 H, J = 2.0 Hz, C**H**$_2$OH), 3.36 (d, 1 H, J = 2.3 Hz, C≡C**H**), 1.76 (s, 1 H, CH_2O**H**).

FTIR (neat), cm^{-1}: 3327 (br, OH), 3287 (s, C≡CH), 2922 (m), 2209 (w, C≡C), 2097 (w), 1574 (w), 1391 (m), 1130 (s), 1015 (s), 751 (s).

MS (EI), m/z (%base):	106 (80), 89 (11), 78 (100), 74 (26), 63 (49), 51 (92).
HRMS (EI):	Calcd for C_7H_6O (M^+): 106.0419 Found: 106.0419
TLC (30% EtOAc in Hexanes), R_f:	(*Z*)-Enediyne **21**: 0.59 (UV) Propargyl Alcohol **22**: 0.39 (UV)



(*Z*)-1,2,4-Heptatrien-6-yne (**18**).

Methanesulfonyl chloride (0.26 mL, 3.31 mmol, 3.0 equiv) was added dropwise over 15 min to an ice-cooled solution of propargyl alcohol **22** (0.12 g, 1.10 mmol, 1 equiv) and triethylamine (0.78 mL, 5.56 mmol, 5.0 equiv) in dichloromethane (5.0 mL). The resulting yellow suspension was stirred at 0 °C for 20 min, then was partitioned between brine (100 mL) and ethyl acetate (3 x 75 mL). The combined organic layers were dried over sodium sulfate and were concentrated. The brown residue was dissolved in dichloromethane (4 mL) and was treated with a solution of anhydrous hydrazine (0.50 mL, 15.6 mmol, 14.3 equiv) in methanol (0.50 mL) at 0 °C. After stirring at 0 °C for 2 h, the reaction mixture was partitioned between water (100 mL) and a 9:1 mixture of dichloromethane and methanol (3 x 100 mL). The combined organic layers were dried over sodium sulfate and were concentrated to provide the crude hydrazine **23** which was diluted with deoxygenated benzene-d_6 (2.0 mL). The resulting suspension was treated with a deoxygenated solution of 4-methyl-1,2,4-triazoline-3,5-dione (0.162 g, 1.43 mmol, 1.3 equiv) in benzene-d_6 (5.0 mL, dropwise addition via cannula over 10 min). After stirring at 23 °C for 10 min, the reaction mixture was washed with water (5 x 10 mL) and was dried over sodium sulfate. The crude solution of (*Z*)-1,2,4-heptatrien-6-yne in benzene-d_6 was purified by passage through a short column of flash-grade silica gel (2

cm x 1 cm, eluting with 5 mL benzene-d_6). The yield of **18** was determined to be 30% by addition of 0.25 mmol *m*-xylene to the chromatographed solution and ^{1}H NMR analysis.

^{1}H NMR (400 MHz, C_6D_6), δ:	6.65 (dtd, 1 H, J = 11.0, 5.6, 1.0 Hz, C**H**=C=CH_2), 6.16 (td, 1 H, J = 11.0, 1.0 Hz, HC≡CCH=C**H**), 5.14-5.19 (m, 1 H, HC≡CC**H**=CH), 4.64-4.67 (dm, 2 H, J = 5.6 Hz, CH=C=C**H**$_2$), 2.89 (dd, 1 H, J = 1.7, 0.7 Hz, **H**C≡CCH=CH).
FTIR (C_6D_6 solution), cm^{-1}:	3291 (s, C≡CH), 2146 (w, C≡C), 1933 (s, C=C=C), 1604 (w), 787 (s).
HRMS (EI):	Calcd for C_7H_7 (MH^+): 91.0548 Found: 91.0552
TLC (Hexanes), R_f:	(*Z*)-1,2,4-heptatrien-6-yne **18**: 0.38 (UV)

General Pyrolysis Procedure (Allene **18**).

Pyrolyses of (*Z*)-1,2,4-heptatrien-6-yne (**18**) were conducted in medium-walled NMR tubes (Wilmad 503 PS, 9 in, used as received), sealed at reduced pressure (ca. 0.015 Torr). Oxygen was removed prior to pyrolysis by three freeze-pump-thaw cycles. Pyrolysis samples containing allene **18** (3.0 mM) and *m*-xylene (1/2 concentration of **18**, internal reference) in an appropriate solvent were heated in boiling water (100 °C) for 30 min. In each case, samples were placed in a beaker fully submerged in the bath, and were not allowed to contact the sides of the heating apparatus. After completion of each reaction, sample tubes were cooled to 0 °C, scored, opened, and their contents analyzed by GLC; GC Parameters #1: Initial Temperature: 45 °C, Initial Time: 14.0 min, Rate: 50 °C/min, Final Temperature: 70 °C, Injector Temperature: 90 °C, Detector Temperature: 110 °C, Head Pressure: 65 kPa; Retention Times: toluene: 9.6 min, allene **18**: 12.3 min, *m*-xylene: 16.9 min; GC Parameters #2: Initial Temperature: 40 °C, Initial Time: 1.00 min, Rate: 10 °C/min, Final Temperature: 175 °C, Injector Temperature: 225 °C, Detector Temperature: 250 °C, Head Pressure: 65 kPa; Retention Times: *m*-xylene: 7.7 min, methyl benzyl ether: 10.0 min, 1,1,1-trifluoroethyl benzyl ether: 10.3 min, benzyl alcohol: 10.8 min, 2-phenylethanol: 12.3 min, bibenzyl: 21.3 min; GC Parameters #3: Initial Temperature: 70 °C, Initial Time: 10.0 min, Rate: 20 °C/min, Final Temperature: 200 °C, Injector Temperature: 119 °C, Detector Temperature: 154 °C, Head Pressure: 65 kPa; Retention Times: *m*-xylene: 8.8 min, **24** and **25**: 19.0 and 19.3 min. Product yields were determined by integration of the corresponding GLC signals and comparison to *m*-xylene with appropriate response factor corrections.

Crossover Experiments (Allene **18**).

Pyrolyses of **18** were conducted as described in the general procedure above in a mixture of 3,3,6,6-tetradeuterio-1,4-cyclohexadiene and unlabeled 1,4-cyclohexadiene (2:1 respectively). The crude reaction mixtures were analyzed by gas chromatography/mass spectroscopy (GCMS), and the amount of deuterium present in the pyrolysis products was calculated as follows.

A. Cyclohexadiene Adducts **24** and **25**. The raw data were corrected for natural abundance ^{13}C interference, and the ratio of products was calculated from the corrected data. An example of this correction is given in Table V below (note that ^{13}C correction is 1.1% • C, where C = # of carbon atoms in the molecule in question, and is thus 1.1% • 13 = 14.3% of the n-1 peak for this analysis).

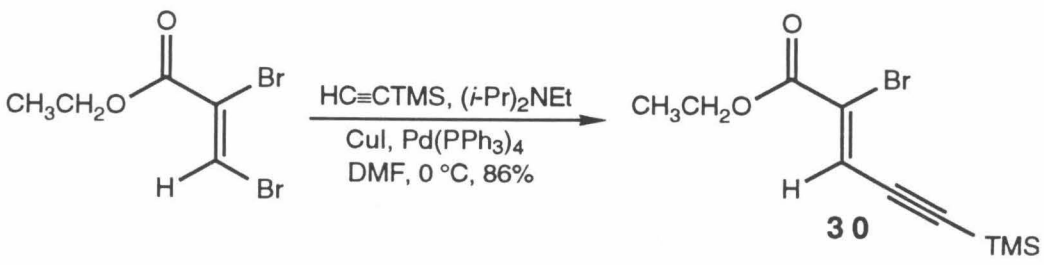
Table V. Example of ^{13}C Correction Applied to Mass Spectrometry Data.

Assignment	m/z	Raw Data	^{13}C Corrected Data	% of Product
n-1 for d_0	170	–	–	–
d_0	171	100	100	57
d_1	172	18	3.7	2
$d2$	173	3	–	–
d_3	174	8	7.6	4
d_4	175	65	64	37

Thus, the bulk of this product mixture contains d_0 and d_4 (non-crossover) products. The deuterium incorporation determined for both **24** and **25** in two separate experiments were averaged to compute the final values.

B. Toluene. Since the commercial 3,3,6,6-tetradeuterio-1,4-cyclohexadiene was found to contain a toluene (d_0) impurity, the isotopic analysis of the toluene pyrolysis products proved to be more difficult than that applied to the cyclohexadiene adducts. The true abundances of d_1 and d_2 species (m/z = 94 and 95 respectively) were calculated

using a ^{13}C correction similar to that described above (although now using 7.7% *of the* n-1 peak) and the ratio of crossover to non-crossover products was calculated using these values alone (i.e., not using the d_0 peak). As before, the data obtained from two separate experiments were averaged to produce the final value.

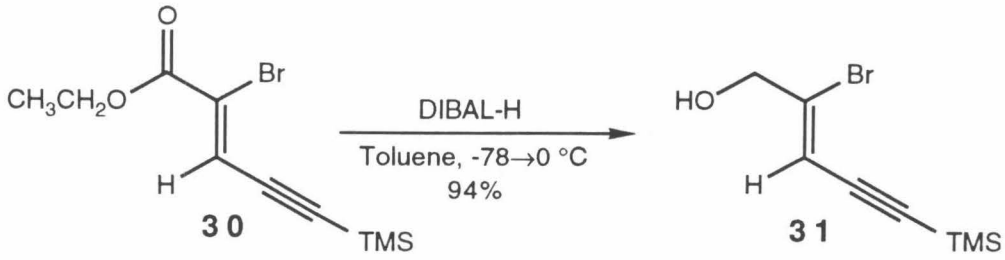


(*Z*)-Bromoenyne **30**.

Cuprous iodide (1.48 g, 7.76 mmol, 0.20 equiv) and tetrakis-(triphenylphosphine)palladium(0) (2.24 g, 1.94 mmol, 0.05 equiv) were added sequentially to a deoxygenated, ice-cooled solution of (*Z*)-ethyl 2,3-dibromopropenoate[32] (10.0 g, 38.8 mmol, 1 equiv), (trimethylsilyl)acetylene (9.32 mL, 66.0 mmol, 1.7 equiv), and *N,N*-diisopropylethylamine (11.5 mL, 66.0 mmol, 1.7 equiv) in *N,N*-dimethylformamide (60 mL). The resulting brown solution was thoroughly degassed and was stirred at 0 °C for 10 h. The reaction mixture was partitioned between an aqueous solution comprised of equal parts of saturated aqueous ammonium chloride and saturated aqueous potassium carbonate solutions (50 mL) and a 1:1 mixture of ethyl acetate and hexanes (3 x 100 mL). The combined organic layers were dried over sodium sulfate and were concentrated. The brown residue was purified by flash column chromatography (5% ethyl acetate in hexanes) to give (*Z*)-bromoenyne **30** (9.19 g, 86%) as a brown oil.

^{1}H NMR (400 MHz, $CDCl_3$), δ: 7.29 (s, 1 H, C=C**H**), 4.30 (q, 2 H, J = 7.1 Hz, CH_3CH_2O), 1.34 (t, 3 H, J = 7.1 Hz, CH_3CH_2O), 0.25 (s, 9 H, $Si(CH_3)_3$).

FTIR (neat), cm^{-1}:	2962 (m), 2901 (w), 2131 (w, C≡C), 1732 (s, C=O), 1717 (s), 1584 (m), 1446 (w), 1367 (m), 1253 (s), 1083 (s), 1044 (m), 846 (s), 760 (m).
MS (EI), m/z (%base):	274 (12), 259 (100), 233 (13), 195 (22), 179 (24), 167 (26), 139 (33), 107 (51).
HRMS (EI):	Calcd for $C_{10}H_{15}BrO_2Si$ (M^+): 274.0025 Found: 274.0024
Elemental Analysis:	Calcd for $C_{10}H_{15}BrO_2Si$: C, 43.64, H, 5.49 Found: C, 43.74, H, 5.26
TLC (5% EtOAc in Hexanes), R_f:	(*Z*)-Ethyl 2,3-Dibromopropenoate: 0.32 (UV) (*Z*)-Bromoenyne **30**: 0.42 (UV)



Alcohol **31.**

Diisobutylaluminumhydride (75.0 mL, 1.0 M solution in hexanes, 75.0 mmol, 2.27 equiv) was transferred via cannula over 15 min to a solution of (*Z*)-bromoenyne **30** (9.10 g, 33.1 mmol, 1 equiv) in toluene (100 mL) at -78 °C. The reaction mixture was stirred at -78 °C for 30 min, then was maintained at 0 °C for 30 min. After quenching with water (75 mL) at 0 °C, the cloudy mixture was stirred with tartaric acid (2 g) at 23 °C for 20 min and the resulting biphasic solution was extracted with a 1:1 mixture of ethyl acetate and hexanes (3 x 100 mL). The combined organic layers were dried over sodium sulfate and were concentrated. The residue was purified by flash column chromatography (gradient elution: ethyl acetate in hexanes, 5→30%) to give alcohol **31** (7.23 g, 94%) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$), δ: 6.31 (s, 1 H, C=C**H**), 4.31 (d, 2 H, *J* = 5.4 Hz, HOC**H**$_2$), 2.57 (t, 1 H, *J* = 6.5 Hz, **H**OCH$_2$), 0.23 (s, 9 H, Si(C**H**$_3$)$_3$).

FTIR (neat), cm^{-1}: 3333 (br, OH), 2960 (m), 2900 (m), 2140 (m, C≡C), 1409 (w), 1250 (s), 1082 (m), 1011 (m), 843 (s), 760 (m).

MS (EI), m/z (%base): 232 (25), 217 (100), 153 (79), 139 (67), 75 (19).

HRMS (EI): Calcd for $C_8H_{13}BrOSi$ (M^+): 231.9919

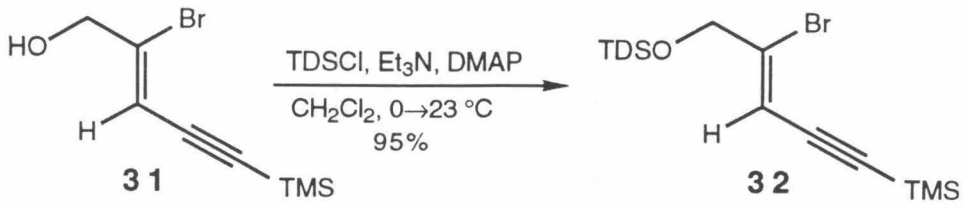
Found: 231.9923

Elemental Analysis: Calcd for $C_8H_{13}BrOSi$: C, 41.21, H, 5.62

Found: C, 41.03, H, 5.58

TLC (10% EtOAc in Hexanes), R_f: (Z)-Bromoenyne **30**: 0.50 (UV)

Alcohol **31**: 0.12 (UV)



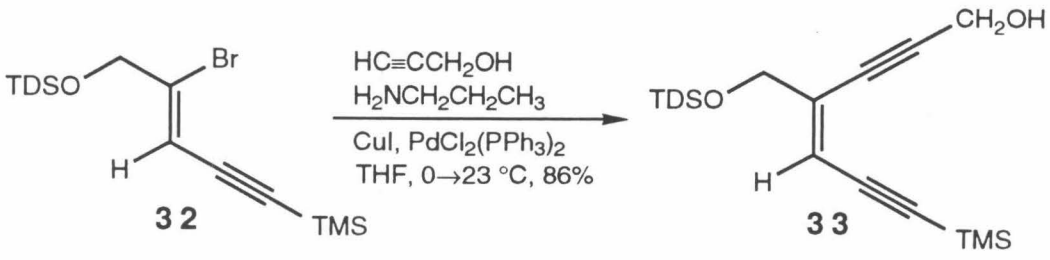
(*Z*)-Bromoenyne **32**.

tert-Butyldiphenylsilyl chloride (4.68 mL, 18.0 mmol, 1.2 equiv) was added to a solution of alcohol **31** (3.50 g, 15.0 mmol, 1 equiv) and triethylamine (10.5 mL, 75.3 mmol, 5.0 equiv) in dichloromethane (100 mL) at 0 °C. After warming to 23 °C, 4-dimethylaminopyridine (0.5 g, 4.09 mmol, 0.27 equiv) was added, and the solution stirred at 23 °C for 3.5 h. The reaction mixture was partitioned between water (100 mL) and a 1:1 mixture of ethyl acetate and hexanes (3 x 150 mL). The combined organic layers were dried over sodium sulfate and were concentrated. The residue was purified by flash column chromatography (5% ethyl acetate in hexanes) to give (*Z*)-bromoenyne **32** (6.73 g, 95%) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$), δ: 7.64-7.67 (m, 4 H, **Ph**Si), 7.38-7.48 (m, 6 H, **Ph**Si), 6.57 (t, 1 H, J = 2.0 Hz, C=C**H**), 4.33 (d, 2 H, J = 2.0 Hz, SiOC**H**$_2$), 1.08 (s, 9 H, SiC(C**H**$_3$)$_3$), 0.25 (s, 9 H, Si(C**H**$_3$)$_3$).

FTIR (neat), cm^{-1}: 3072 (m), 2959 (s), 2858 (m), 2144 (m, C≡C), 1472 (m), 1428 (m), 1250 (s), 1114 (s), 1091 (s), 1034 (m), 843 (s), 760 (m).

MS (EI), m/z (%base):	471 (89), 415 (34), 313 (53), 268 (61), 196 (55).
HRMS (EI):	Calcd for $C_{24}H_{32}BrOSi_2$ (MH^+): 471.1175 Found: 471.1180
Elemental Analysis:	Calcd for $C_{24}H_{31}BrOSi_2$: C, 61.13, H, 6.63 Found: C, 61.47, H, 6.73
TLC (20% EtOAc in Hexanes), R_f:	Alcohol **31**: 0.24 (UV) (*Z*)-Bromoenyne **32**: 0.62 (UV)

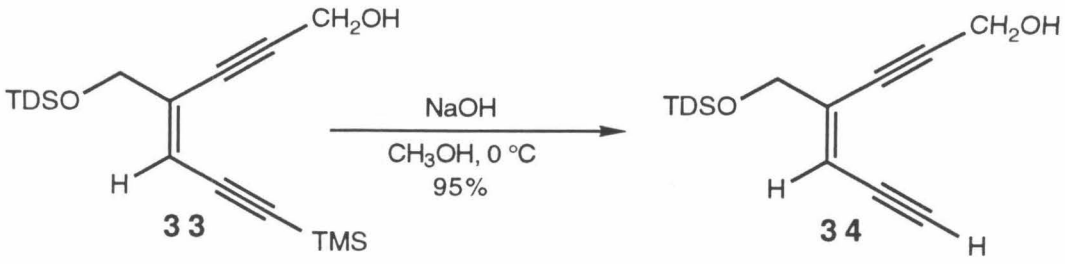


Enediyne **33**.

Cuprous iodide (0.082 g, 0.43 mmol, 0.15 equiv) and bis(triphenylphosphine)palladium(II) chloride (0.10 g, 0.14 mmol, 0.05 equiv) were added sequentially to an ice-cooled solution of (*Z*)-bromoenyne **32** (1.35 g, 2.86 mmol, 1 equiv), propargyl alcohol (0.33 mL, 5.72 mmol, 2.0 equiv), and *n*-propylamine (0.94 mL, 11.4 mmol, 4.0 equiv) in tetrahydrofuran (40 mL), and the resulting brown suspension was thoroughly degassed. After stirring at 23 °C for 14 h, the reaction mixture was partitioned between an aqueous solution comprised of equal parts of saturated aqueous ammonium chloride and saturated aqueous potassium carbonate solutions (50 mL) and a 1:1 mixture of ethyl acetate and hexanes (3 x 75 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 afford enediyne **33** (1.10 g, 86%) as a pale yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$), δ: 7.63-7.65 (m, 4 H, **Ph**Si), 7.37-7.46 (m, 6 H, **Ph**Si), 6.28 (t, 1 H, J = 2.2 Hz, C=C**H**), 4.41 (s, 2 H, SiOC**H**$_2$), 4.22 (d, 2 H, J = 2.2 Hz, C≡CC**H**$_2$OH), 1.06 (s, 9 H, SiC(C**H**$_3$)$_3$), 0.23 (s, 9 H, Si(C**H**$_3$)$_3$).

FTIR (neat), cm^{-1}:	3348 (br, OH), 3071 (w), 2958 (m), 2138 (m, C≡C), 1590 (w), 1428 (m), 1250 (m), 1112 (s), 846 (s), 703 (s).
MS (CI/NH_3), m/z (%base):	447 (16), 429 (16), 389 (41), 371 (26), 251 (96), 191 (53).
HRMS (CI/NH_3):	Calcd for $C_{27}H_{35}O_2Si_2$ (MH^+): 447.2176 Found: 447.2182
TLC (20% EtOAc in Hexanes), R_f:	(*Z*)-Bromoenyne **32**: 0.64 (UV) Enediyne **33**: 0.23 (UV)



Propargyl Alcohol **34.**

Sodium hydroxide (50% aqueous, 0.5 mL) was added via pipette to an ice-cooled solution of enediyne **33** (1.10 g, 2.46 mmol) in methanol (30 mL). The colorless solution was stirred at 0 °C for 45 min, then was partitioned between water (100 mL) and a 1:1 mixture of ethyl acetate and hexanes (3 x 75 mL). The combined organic layers were dried over sodium sulfate and were concentrated. The residue was purified by flash column chromatography (20% hexanes in toluene) to give propargyl alcohol **34** (0.89 g, 95%) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$), δ: 7.64-7.66 (m, 4 H, **Ph**Si), 7.37-7.47 (m, 6 H, **Ph**Si), 6.24 (dd, 1 H, J = 4.4, 2.2 Hz, C=C**H**), 4.41 (s, 2 H, SiOC**H**$_2$), 4.24 (d, 2 H, J = 4.4 Hz, C≡CC**H**$_2$OH), 3.32 (d, 1 H, J = 2.2 Hz, C≡C**H**), 1.07 (s, 9 H, SiC(C**H**$_3$)$_3$).

FTIR (neat), cm^{-1}: 3369 (br, OH), 3287 (m, C≡CH), 3071 (w), 2931 (m), 2857 (m), 1428 (m), 1112 (s), 824 (m), 704 (s).

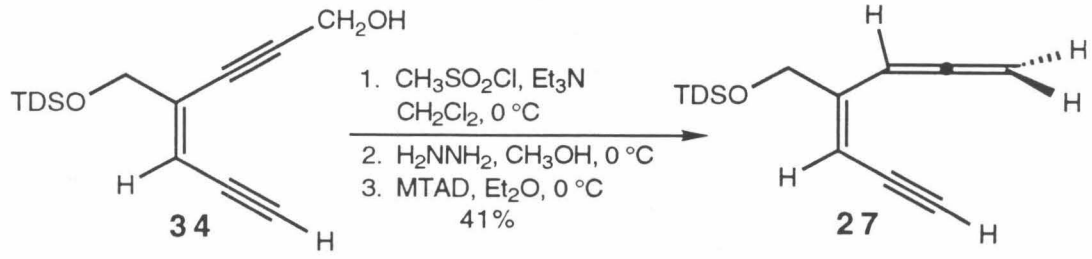
MS (CI/NH_3), m/z (%base): 392 (71), 302 (13), 275 (23), 274 (100), 216 (53).

HRMS (CI/NH_3): Calcd for $C_{24}H_{30}NO_2Si$ (MNH_4^+): 392.2046

Found: 392.2059

TLC (20% EtOAc in Hexanes), R_f: Enediyne **33**: 0.23 (UV)

Propargyl Alcohol **34**: 0.13 (UV)



Allene **27**.

Methanesulfonyl chloride (0.10 mL, 1.33 mmol, 3.0 equiv) was added dropwise over 15 min to an ice-cooled solution of propargyl alcohol **34** (0.17 g, 0.44 mmol, 1 equiv) and triethylamine (0.31 mL, 2.22 mmol, 5.0 equiv) in dichloromethane (10 mL). The resulting yellow suspension was stirred for 20 min at 0 °C, then anhydrous hydrazine (0.42 mL, 13.3 mmol, 30 equiv) in methanol (2 mL) was added dropwise via syringe over 2 min. The reaction mixture was stirred at 0 °C for 12 h, then was partitioned between water (100 mL) and ethyl acetate (3 x 100 mL). The combined organic layers were dried over sodium sulfate and were concentrated to provide the crude hydrazine (**35**). The crude hydrazine was diluted with deoxygenated ethyl ether (10 mL) at 0 °C and the resulting suspension was treated with a deoxygenated solution of 4-methyl-1,2,4-triazoline-3,5-dione (0.060 g, 0.531 mmol, 1.2 equiv) in ethyl ether (20 mL, dropwise addition over 20 min). After stirring at 0 °C for 5 min, the reaction mixture was partitioned between water (100 mL) and pentane (3 x 75 mL). The combined organic layers were dried over sodium sulfate and were concentrated at 23 °C. The residue was purified by flash column chromatography (hexanes) to give allene **27** (0.065 g, 41%) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$), δ:	7.66-7.68 (m, 4 H, **Ph**Si), 7.38-7.46 (m, 6 H, **Ph**Si), 6.51 (t, 1 H, J = 6.8 Hz, **H**C=C=CH_2), 5.93 (s, 1 H, C=C**H**), 4.88 (d, 2 H, J = 6.8 Hz, HC=C=C**H**$_2$), 4.32 (s, 2 H, SiOC**H**$_2$), 3.31 (s, 1 H, C≡C**H**), 1.07 (s, 9 H, SiC(C**H**$_3$)$_3$).
FTIR (neat), cm^{-1}:	3297 (m, C≡CH), 3070 (w), 2931 (m), 2857 (m), 1934 (m, C=C=C), 1427 (m), 1112 (s), 828 (m), 703 (s).
MS (CI/NH_3), m/z (%base):	359 (98), 318 (15), 301 (12), 274 (43), 216 (100).
HRMS (CI/NH_3):	Calcd for $C_{24}H_{27}OSi$ (MH^+): 359.1831 Found: 359.1848
TLC (10% EtOAc in Hexanes), R_f:	Propargyl Alcohol **34**: 0.04 (UV) Allene **27**: 0.53 (UV)

Kinetic Experiments (Allene **27**).

A solution of **27** (0.002 M) in deoxygenated dimethyl sulfoxide-d_6 containing 1,4-cyclohexadiene (0.26 M) and *m*-xylene (0.0074 M, internal standard) was placed in an NMR tube which was then sealed with a Teflon vacuum adapter. The sample was deoxygenated (three freeze-pump-thaw cycles) and placed in the probe of an NMR spectrometer (400 MHz). The probe was heated to 60 °C, and the disappearance of **27** was monitored by ^{1}H NMR over 4 h by integration of its olefinic signals (corrected by integration of the *m*-xylene peak). The collected data (Table VI) were in agreement with first order reaction kinetics (Figure 3) with $k = 1.09 \pm 0.01 \times 10^{-4}$ s^{-1}. The combined yield of cyclized products at the end of the experiment (16 h) was determined to be 69% by integration of the corresponding benzylic signals and comparison to the *m*-xylene standard.

Table VI. Kinetic Data Obtained for Cyclization of **27** in 1,4-Cyclohexadiene (4.0 M)–DMSO-d_6 at 60 °C.

Data Point	Time (h)	-ln [**27**]	Data Point	Time (h)	-ln [**27**]
1	0	4.73	6	2.0	5.42
2	0.25	4.84	7	2.5	5.56
3	0.58	4.95	8	3.0	5.95
4	1.0	5.03	9	3.5	6.11
5	1.5	5.31	10	4.0	6.28

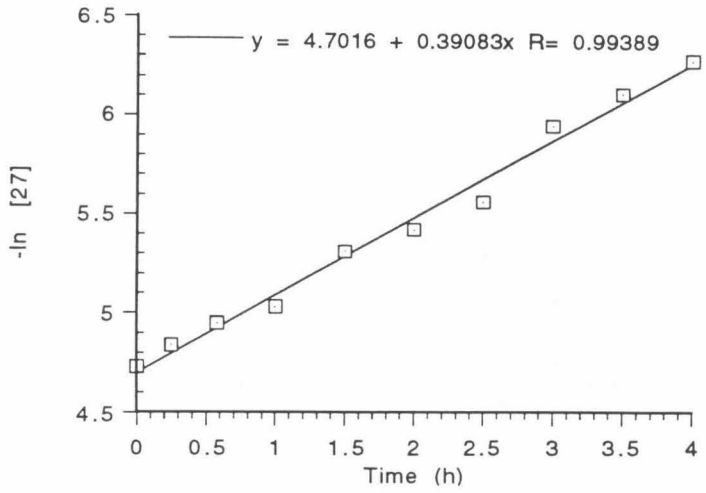
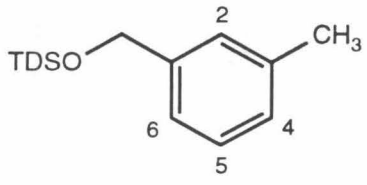


Figure 3. Plot of Kinetic Data Obtained for Cyclization of **27** in 1,4-Cyclohexadiene (4.0 M)–DMSO-d_6 at 60 °C.

General Pyrolysis Procedure (Allene **27**).

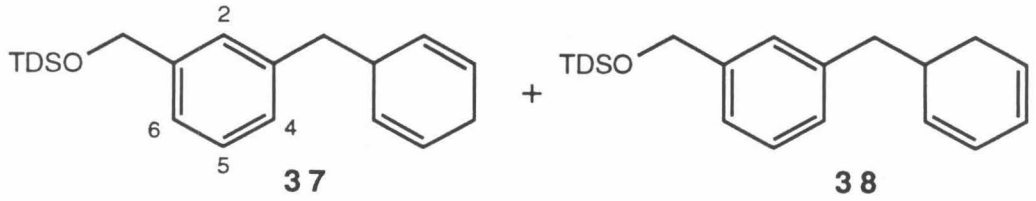
Solutions of **27** (3.0-5.0 mg, 0.01 M) in a deoxygenated solvent (methanol, 4.0 M methanol in dimethyl sulfoxide, 4.0 M 1,4-cyclohexadiene in dimethyl sulfoxide or a 4:1 mixture of tetrahydrofuran and water) were stirred at 60 °C for 18 h, then each reaction mixture was partitioned between water (50 mL) and a 1:1 mixture of ethyl acetate and hexanes (3 x 50 mL). The combined organic layers were dried over sodium sulfate and were concentrated. The residue was purified by preparative thin-layer chromatography (3-5% ethyl acetate in hexanes). Product yields were determined prior to chromatography by addition of (*Z*)-1,2-dichloroethylene as an internal standard and ^{1}H NMR analysis.



36

3-Tolyl *tert*-Butyldiphenylsilyl Ether **36.**

^{1}H NMR (500 MHz, $CDCl_3$), δ:	7.69-7.71 (m, 4 H, **Ph**Si), 7.36-7.44 (m, 7 H, **Ph**Si and **Ar**-2), 7.06-7.24 (m, 3 H, **Ar**-4, **Ar**-5, and **Ar**-6), 4.74 (s, 2 H, SiO**CH**$_2$), 2.34 (s, 3 H, **CH**$_3$), 1.09 (s, 9 H, SiC(**CH**$_3$)$_3$).
FTIR (neat), cm^{-1}:	3070 (w), 2932 (m), 2858 (m), 1590 (w), 1428 (m), 1157 (m), 1111 (s), 1079 (s), 824 (m), 703 (s).
MS (EI), m/z (%base):	359 (12), 303 (49), 273 (13), 225 (21), 199 (24), 179 (22), 135 (38), 105 (100).
HRMS (EI):	Calcd for $C_{24}H_{27}OSi$ (M–H$^+$): 359.1831 Found: 359.1838
TLC (5% EtOAc in Hexanes), R_f:	3-Tolyl *tert*-Butyldiphenylsilyl Ether **36**: 0.70 (UV)



37 **38**

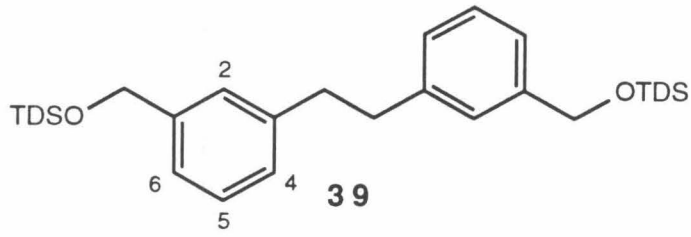
1,4-Cyclohexadiene Addition Products **37** and **38.**

^{1}H NMR (500 MHz, $CDCl_3$), δ: 7.69-7.70 (m, **Ph**Si in both), 7.36-7.44 (m, **Ph**Si, **Ar**-2, **Ar**-4, **Ar**-5, and/or **Ar**-6 in both), 7.04-7.25 (m, **Ph**Si, **Ar**-2, **Ar**-4, **Ar**-5, and/or **Ar**-6 in both), 5.89-5.91 (m, C=C**H**), 5.69-5.76 (m, C=C**H**), 5.60-5.63 (m, C=C**H**), 4.76 (s, SiO**C**$\mathbf{H_2}$ in both), 2.69-2.71 (m, **C**$\mathbf{H_2}$ in either), 2.67 (d, J = 7.5 Hz, **C**$\mathbf{H_2}$CH in **37**), 2.55-2.64 (m, CH_2**C**H in **37**), 1.97-2.04 (m, **C**$\mathbf{H_2}$ in either), 1.09 (s, SiC(**C**$\mathbf{H_3}$)$_3$ in both).

FTIR (neat), cm^{-1}: 3026 (w), 2930 (m), 2857 (m), 1590 (w), 1428 (m), 1156 (m), 1110 (s), 1081 (s), 702 (s).

MS (EI), m/z (%base): 437 (12), 381 (16), 359 (10), 303 (53), 225 (26), 199 (60), 181 (59), 135 (100).

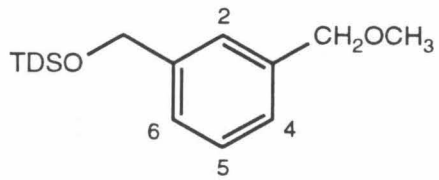
HRMS (EI):	Calcd for $C_{30}H_{33}OSi$ (MH^+): 437.2301
	Found: 437.2323
TLC (Hexanes), R_f:	1,4-Cyclohexadiene Addition Products **37** and **38**:
	0.33 (UV)



39

Bibenzyl Derivative **39**.

^{1}H NMR (400 MHz, $CDCl_3$), δ:	7.68-7.71 (m, 8 H, **Ph**Si), 7.35-7.44 (m, 14 H, **Ph**Si and **Ar**-2), 7.17-7.23 (m, 6 H, **Ar**-4, **Ar**-5, and **Ar**-6), 4.76 (s, 4 H, SiOC**H**$_2$), 2.89 (s, 4 H, C**H**$_2$), 1.09 (s, 18 H, SiC(C**H**$_3$)$_3$).
FTIR (neat), cm^{-1}:	2927 (m), 2857 (m), 1468 (w), 1429 (m), 1109 (s), 822 (m), 701 (s).
MS (EI), m/z (%base):	718 (7), 307 (21), 285 (53), 199 (43), 179 (19), 154 (92), 135 (100).
HRMS (EI):	Calcd for $C_{48}H_{54}O_2Si_2$ (M^+): 718.3662 Found: 718.3654
TLC (5% EtOAc in Hexanes), R_f:	Bibenzyl Derivative **39**: 0.40 (UV)



40

Methyl Ether **40.**

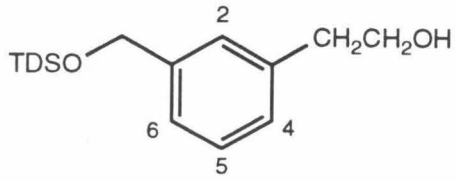
^{1}H NMR (400 MHz, $CDCl_3$), δ: 7.69-7.71 (m, 4 H, **Ph**Si), 7.38-7.43 (m, 7 H, **Ph**Si and **Ar**-2), 7.24-7.36 (m, 3 H, **Ar**-4, **Ar**-5, and **Ar**-6), 4.78 (s, 2 H, $SiOC\mathbf{H}_2$), 4.45 (s, 2 H, $C\mathbf{H}_2OCH_3$), 3.38 (s, 3 H, $CH_2OC\mathbf{H}_3$), 1.10 (s, 9 H, $SiC(C\mathbf{H}_3)_3$).

FTIR (neat), cm^{-1}: 2931 (m), 2857 (m), 1428 (m), 1156 (m), 1109 (s), 823 (m), 702 (s).

MS (EI), m/z (%base): 389 (28), 359 (20), 333 (13), 303 (33), 255 (13), 197 (40), 181 (92), 135 (100).

HRMS (EI): Calcd for $C_{25}H_{29}O_2Si$ ($M-H^+$): 389.1937
Found: 389.1931

TLC (5% EtOAc in Hexanes), R_f: Methyl Ether **40**: 0.33 (UV)



41

Alcohol **41.**

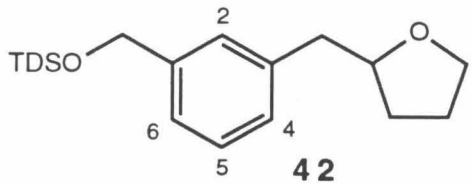
^{1}H NMR (400 MHz, $CDCl_3$), δ: 7.68-7.70 (m, 4 H, **Ph**Si), 7.35-7.42 (m, 7 H, **Ph**Si and **Ar**-2), 7.11-7.29 (m, 3 H, **Ar**-4, **Ar**-5, and **Ar**-6), 4.76 (s, 2 H, $SiOC\mathbf{H}_2$), 3.85 (t, 2 H, J = 6.6 Hz, $CH_2C\mathbf{H}_2OH$), 2.86 (t, 2 H, J = 6.6 Hz, $\mathbf{CH}_2CH_2OH$), 1.09 (s, 9 H, $SiC(C\mathbf{H}_3)_3$).

FTIR (neat), cm^{-1}: 3349 (br, OH), 3072 (w), 2933 (m), 2854 (m), 1428 (m), 1110 (s), 701 (s).

MS (CI/NH_3), m/z (%base): 408 (100), 350 (13), 212 (48), 196 (16), 195 (47).

HRMS (CI/NH_3): Calcd for $C_{25}H_{34}NO_2Si$ (MNH_4^+): 408.2359
Found: 408.2342

TLC (10% EtOAc in Hexanes), R_f: Alcohol **41**: 0.07 (UV)



42

Tetrahydrofuran Adduct **42.**

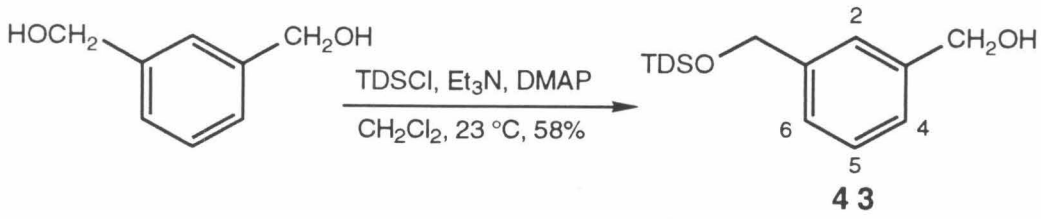
^{1}H NMR (500 MHz, $CDCl_3$), δ: 7.68-7.70 (m, 4 H, **Ph**Si), 7.36-7.44 (m, 7 H, **Ph**Si and **Ar**-2), 7.11-7.27 (m, 3 H, **Ar**-4, **Ar**-5, and **Ar**-6), 4.76 (s, 2 H, SiOC**H**$_2$), 4.03-4.08 (m, 1 H, one of C**H**OC**H**$_2$), 3.87-3.91 (m, 1 H, one of C**H**OC**H**$_2$), 3.71-3.76 (m, 1 H, one of C**H**OC**H**$_2$), 2.93 (dd, 1 H, J = 13.5, 6.8 Hz, C**H**$_A$H$_B$CH), 2.72 (dd, 1 H, J = 13.5, 6.8 Hz, CH$_A$**H**$_B$CH), 1.82-1.92 (m, 4 H, CHC**H**$_2$C**H**$_2$), 1.09 (s, 9 H, SiC(C**H**$_3$)$_3$).

FTIR (neat), cm^{-1}: 2931 (m), 2857 (m), 1428 (m), 1156 (w), 1110 (s), 823 (m), 741 (m), 702 (s).

MS (CI/NH_3), m/z (%base): 448 (100), 373 (14), 353 (15), 295 (12), 235 (61), 216 (16), 196 (29), 175 (36), 157 (48).

HRMS (CI/NH_3): Calcd for $C_{28}H_{38}NO_2Si$ (MNH_4^+): 448.2672
Found: 448.2661

TLC (5% EtOAc in Hexanes), R_f: Tetrahydrofuran Adduct **42**: 0.18 (UV)



43

Benzyl Alcohol **43**.

tert-Butyldiphenylsilyl chloride (0.48 mL, 1.9 mmol, 1.0 equiv) was added to a solution of 1,3-benzenedimethanol (0.26 g, 1.9 mmol, 1 equiv), triethylamine (0.78 mL, 5.6 mmol, 3.0 equiv), and 4-dimethylaminopyridine (0.02 g, 0.16 mmol, 0.10 equiv) in dichloromethane (12 mL) at 23 °C. After stirring at 23 °C for 2 h, the reaction mixture was partitioned between water (100 mL) and a 1:1 mixture of ethyl acetate and hexanes (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 give benzyl alcohol **43** (0.41 g, 58%) as a colorless oil.

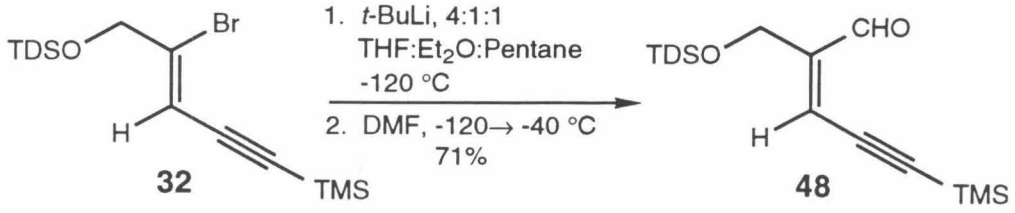
^{1}H NMR (400 MHz, $CDCl_3$), δ: 7.68-7.70 (m, 4 H, **Ph**Si), 7.26-7.43 (m, 10 H, **Ph**Si, **Ar**-2, **Ar**-4, **Ar**-5, and **Ar**-6), 4.78 (s, 2 H, SiOC**H**$_2$), 4.68 (s, 2 H, C**H**$_2$OH), 1.10 (s, 9 H, SiC(C**H**$_3$)$_3$).

FTIR (neat), cm^{-1}: 3333 (br, OH), 3071 (m), 2931 (m), 2857 (m), 1472 (m), 1428 (s), 1112 (s), 824 (s), 740 (s).

MS (EI), m/z (%base): 375 (17), 359 (22), 319 (14), 307 (15), 301 (16), 289 (29), 241 (16), 181 (27), 121 (100).

HRMS (EI): Calcd for $C_{24}H_{27}O_2Si$ ($M-H^+$): 375.1780
Found: 375.1764

TLC (30% EtOAc in Hexanes), R_f: 1,3-Benzenedimethanol: 0.15 (UV)
Benzyl Alcohol **43**: 0.42 (UV)



Aldehyde **48.**

A solution of (*Z*)-bromoenyne **32** (2.50 g, 5.3 mmol, 1 equiv) in a mixture of tetrahydrofuran, ethyl ether, and pentane (4:1:1, respectively, 10.3 mL) was added dropwise via cannula over 20 min to a solution of *tert*-butyllithium (7.80 mL, 1.70 M solution in pentane, 13.3 mmol, 2.5 equiv) in a mixture of tetrahydrofuran, ethyl ether, and pentane (4:1:1, respectively, 37.5 mL) at -120 °C. Upon completion of the addition, a solution of *N,N*-dimethylformamide (1.03 mL, 13.3 mmol, 2.5 equiv) in tetrahydrofuran (3.0 mL) was added via cannula to the orange reaction mixture, and the resulting yellow solution was allowed to warm to -40 °C over 3 h. After quenching with water (5 mL) at -40 °C, the product was partitioned between brine (100 mL) and a 1:1 mixture of ethyl acetate and hexanes (3 x 100 mL). The combined organic layers were dried over sodium sulfate and were concentrated. The residue was purified by flash column chromatography (gradient elution: toluene in hexanes, 10→50%) to give aldehyde **48** (1.58 g, 71%) as a pale yellow oil.

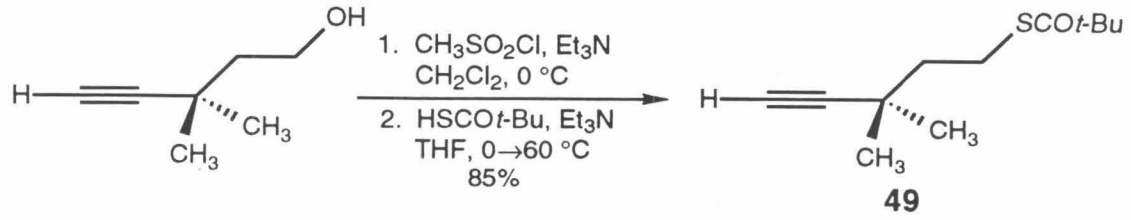
^{1}H NMR (400 MHz, $CDCl_3$), δ: 10.20 (s, 1 H, C**H**O), 7.61-7.63 (m, 4 H, **Ph**Si), 7.35-7.44 (m, 6 H, **Ph**Si), 6.99 (t, 1 H, *J* = 2.4 Hz, C=C**H**), 4.45 (d, 2 H, *J* = 2.4 Hz, SiOC$\mathbf{H}_2$), 1.08 (s, 9 H, SiC(C$\mathbf{H}_3$)$_3$), 0.25 (s, 9 H, Si(C$\mathbf{H}_3$)$_3$).

FTIR (neat), cm^{-1}: 2959 (m), 2858 (m), 2130 (w), 1684 (s, C=O), 1472 (m), 1430 (m), 1303 (m), 1251 (m), 1192 (m), 1113 (s), 845 (s), 761 (m), 740 (m).

MS (CI/NH_3), m/z (%base): 421 (6), 363 (40), 343 (100), 216 (11), 196 (12).

HRMS (CI/NH_3): Calcd for $C_{25}H_{33}O_2Si_2$ (MH^+): 421.2019
Found: 421.2011

TLC (10% EtOAc in Hexanes), R_f: (*Z*)-Bromoenyne **32**: 0.61 (UV)
Aldehyde **48**: 0.55 (UV)



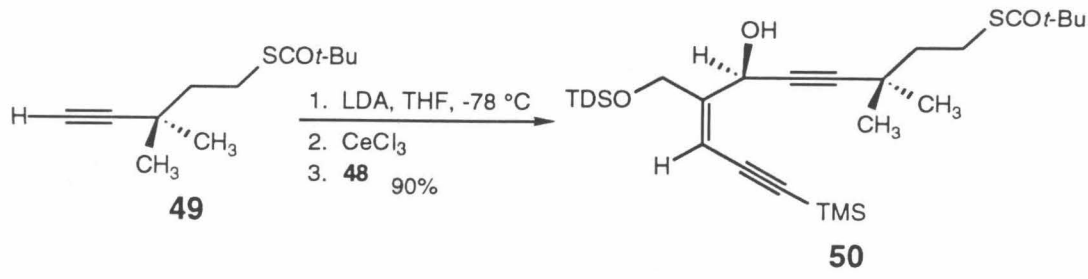
49

Thiol Ester **49.**

Methanesulfonyl chloride (0.39 mL, 5.1 mmol, 1.2 equiv) was added dropwise over 15 min to an ice-cooled solution of 3,3-dimethyl-4-pentyn-1-ol[36] (0.47 g, 4.2 mmol, 1 equiv) and triethylamine (0.77 mL, 5.5 mmol, 1.3 equiv) in dichloromethane (15 mL). The resulting yellow suspension was stirred at 0 °C for 5 min, then was partitioned between brine (40 mL) and a 1:1 mixture of ethyl acetate and hexanes (3 x 75 mL). The combined organic layers were dried over sodium sulfate and were concentrated. The remaining yellow oil was dissolved in tetrahydrofuran (6 mL) and the resulting solution was cooled to 0 °C. Triethylamine (5.9 mL, 42.2 mmol, 10.0 equiv) and thiopivalic acid (3.2 mL, 25.4 mmol, 6.0 equiv) were added sequentially at 0 °C; the mixture was heated at 60 °C for 6 h. After cooling to 23 °C, the reaction mixture was partitioned between water (30 mL) and a 1:1 mixture of ethyl acetate and hexanes (3 x 75 mL). The combined organic layers were dried over sodium sulfate and were concentrated. The residue was purified by flash column chromatography (5% ethyl acetate in hexanes) to give thiol ester **49** (0.72 g, 85%) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$), δ: 2.94-2.98 (m, 2 H, $SCH_2CH_2C(CH_3)_2$), 2.15 (s, 1 H, C≡C**H**), 1.61-1.66 (m, 2 H, $SCH_2CH_2C(CH_3)_2$), 1.26 (s, 6 H, $SCH_2CH_2C(CH_3)_2$), 1.23 (s, 9 H, $C(CH_3)_3$).

FTIR (neat), cm^{-1}:	3299 (m, C≡CH), 2972 (s), 2948 (m), 2870 (m), 2109 (w), 1680 (s, C=O), 1479 (m), 1365 (m), 1246 (w), 1037 (m), 953 (s), 810 (m).
MS (CI/CH_4), m/z (%base):	213 (20), 155 (65), 129 (10), 113 (6), 95 (11), 85 (28), 57 (100).
HRMS (CI/CH_4):	Calcd for $C_{12}H_{21}OS$ (MH^+): 213.1313 Found: 213.1301
TLC (20% EtOAc in Hexanes), R_f:	3,3-Dimethyl-4-pentyn-1-ol: 0.12 Thiol Ester **49**: 0.62

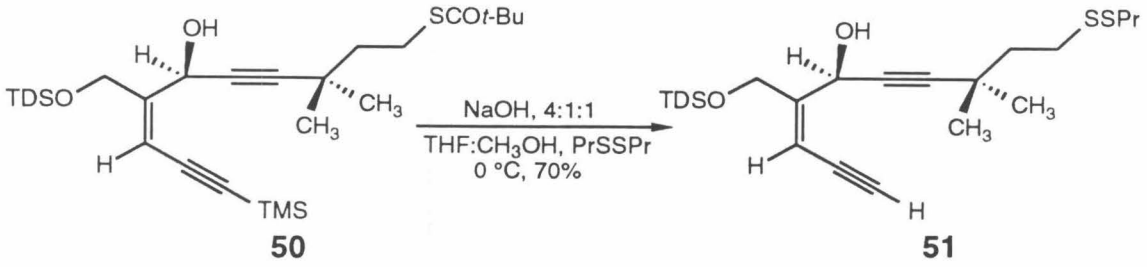


Alcohol **50**.

A solution of lithium diisopropylamide in tetrahydrofuran (0.50 M, 10 mL, 1.5 equiv) was added via cannula to a solution of thiol ester **49** (0.86 g, 4.04 mmol, 1.2 equiv) in tetrahydrofuran (40 mL) at -78 °C. After stirring at -78 °C for 10 min, anhydrous cerium(III) chloride (1.33 g, 5.40 mmol, 1.6 equiv) was added to the reaction mixture, and the resulting orange suspension stirred at -78 °C for 30 min. A solution of aldehyde **48** (1.41 g, 3.36 mmol, 1 equiv) in tetrahydrofuran (10 mL) was then added via cannula over 2 min, and the reaction mixture was stirred at -78 °C for 30 min. After quenching with water (3 mL) at -78 °C, sodium tartrate (0.5 g) was added and the crude mixture was partitioned between water (400 mL) and a 1:1 mixture of ethyl acetate and hexanes (3 x 100 mL). The combined organic layers were dried over sodium sulfate and were concentrated. Purification of the residue by flash column chromatography (gradient elution: ethyl acetate in hexanes, 5→10%) provided alcohol **50** (1.92 g, 90%) as a pale yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$), δ: 7.64-7.68 (m, 4 H, **Ph**Si), 7.39-7.41 (m, 6 H, **Ph**Si), 5.85 (s, 1 H, C=C**H**), 5.56 (d, 1 H, J = 5.9 Hz, C**H**OH), 4.59 (dd, 1 H, J = 15.4, 2.0 Hz,

	$SiOCH_AH_B$), 4.36 (dd, 1 H, J = 15.4, 2.0 Hz, $SiOCH_AH_B$), 2.99 (d, 1 H, J = 6.4 Hz, CHOH), 2.80-2.84 (m, 2 H, $SCH_2CH_2C(CH_3)_2$), 1.52-1.57 (m, 2 H, $SCH_2CH_2C(CH_3)_2$), 1.20 (s, 9 H, $C(CH_3)_3$), 1.14 (s, 3 H, one of $SCH_2CH_2C(CH_3)_2$), 1.13 (s, 3 H, one of $SCH_2CH_2C(CH_3)_2$), 1.06 (s, 9 H, $SiC(CH_3)_3$), 0.22 (s, 9 H, $Si(CH_3)_3$).
FTIR (neat), cm^{-1}:	3506 (br, OH), 2965 (s), 2934 (m), 2859 (m), 2132 (w), 1679 (s, C=O), 1472 (m), 1364 (w), 1250 (m), 1110 (s), 952 (m), 846 (s), 704 (m).
MS (CI/NH_3), m/z (%base):	633 (9), 615 (100), 559 (27), 531 (12), 473 (6), 377 (8), 343 (12), 268 (23), 196 (23).
HRMS (CI/NH_3):	Calcd for $C_{37}H_{53}O_3SSi_2$ (MH^+): 633.3254 Found: 633.3236
TLC (10% EtOAc in Hexanes), R_f:	Aldehyde **48**: 0.56 (UV) Alcohol **50**: 0.24 (UV)



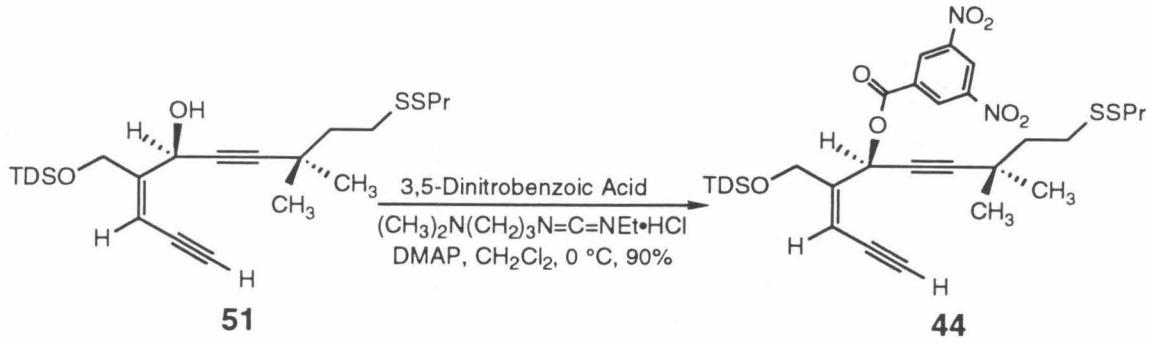
50 **51**

Disulfide **51.**

Sodium hydroxide (50% aqueous, 0.5 mL) was added via pipette to an ice-cooled solution of alcohol **50** (0.60 g, 0.97 mmol) in a mixture of tetrahydrofuran, methanol, and propyl disulfide (4:1:1, respectively, 18 mL). The yellow reaction mixture was stirred at 0 °C for 4 h, then was partitioned between water (30 mL) and a 1:1 mixture of ethyl acetate and hexanes (3 x 70 mL). The combined organic layers were dried over sodium sulfate and were concentrated. The residue was purified by flash column chromatography (20% hexanes in toluene) to give disulfide **51** (0.37 g, 70%) as a pale yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$), δ: 7.65-7.69 (m, 4 H, **Ph**Si), 7.40-7.42 (m, 6 H, **Ph**Si), 5.78 (s, 1 H, C=C**H**), 5.57 (s, 1 H, C**H**OH), 4.59 (d, 1 H, J = 15.1 Hz, $SiOCH_AH_B$), 4.36 (d, 1 H, J = 15.1 Hz, $SiOCH_AH_B$), 3.22 (s, 1 H, C≡C**H**), 2.66-2.70 (m, 2 H, $SSCH_2CH_2C(CH_3)_2$), 2.62 (t, 2 H, J = 7.21 Hz, $SSCH_2CH_2CH_3$), 1.65-1.74 (m, 4 H, $SSCH_2CH_2C(CH_3)_2$ and $SSCH_2CH_2CH_3$), 1.13 (s, 6 H, $SSCH_2CH_2C(CH_3)_2$), 1.08 (s, 9 H, $SiC(CH_3)_3$), 0.97 (t, 3 H, J = 7.33 Hz, $SSCH_2CH_2CH_3$).

FTIR (neat), cm^{-1}:	3428 (br, OH), 3289 (m, C≡CH), 3070 (w), 2961 (s), 2930 (s), 2857 (m), 2235 (w), 1427 (s), 1363 (m), 1249 (w), 1158 (m), 1112 (s), 1060 (m), 822 (m), 740 (s).
MS (CI/NH_3), m/z (%base):	551 (14), 533 (54), 476 (22), 458 (43), 418 (30), 397 (14), 295 (24), 216 (55), 199 (79).
HRMS (CI/NH_3):	Calcd for $C_{32}H_{43}O_2S_2Si$ (MH^+): 551.2474 Found: 551.2457
Elemental Analysis:	Calcd for $C_{32}H_{42}O_2S_2Si$: C, 69.77, H, 7.68 Found: C, 69.85, H, 7.52
TLC (Toluene), R_f:	Alcohol **50**: 0.35 (UV) Disulfide **51**: 0.30 (UV)



Dinitrobenzoate **44.**

3,5-Dinitrobenzoic acid (2.86 g, 13.5 mmol, 10.0 equiv), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (2.58 g, 13.5 mmol, 10.0 equiv), and 4-dimethylaminopyridine (0.822 g, 6.73 mmol, 5.0 equiv) were added sequentially to a solution of disulfide **51** (0.742 g, 1.35 mmol, 1 equiv) in dichloromethane (100 mL) at 0 °C. The resulting yellow suspension was stirred at 0 °C for 30 min, then was partitioned between water (200 mL) and a 1:1 mixture of ethyl acetate and hexanes (3 x 100 mL). The combined organic layers were dried over sodium sulfate and were concentrated. Purification of the residue by flash column chromatography (10% ethyl acetate in hexanes) afforded dinitrobenzoate **44** (0.903 g, 90%) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$), δ: 9.20 (t, 1 H, J = 2.1 Hz, $Ph(NO_2)_2\mathbf{H}_p$), 9.02 (d, 2 H, J = 2.1 Hz, $Ph(NO_2)_2\mathbf{H}_o$), 7.64-7.70 (m, 4 H, **Ph**Si), 7.35-7.43 (m, 6 H, **Ph**Si), 6.79 (s, 1 H, C=CC**H**(OR)C≡C), 6.19 (d, 1 H, J = 2.2 Hz, C=C**H**), 4.63 (d, 1 H, J = 16.7 Hz, $SiOC\mathbf{H}_AH_B$),

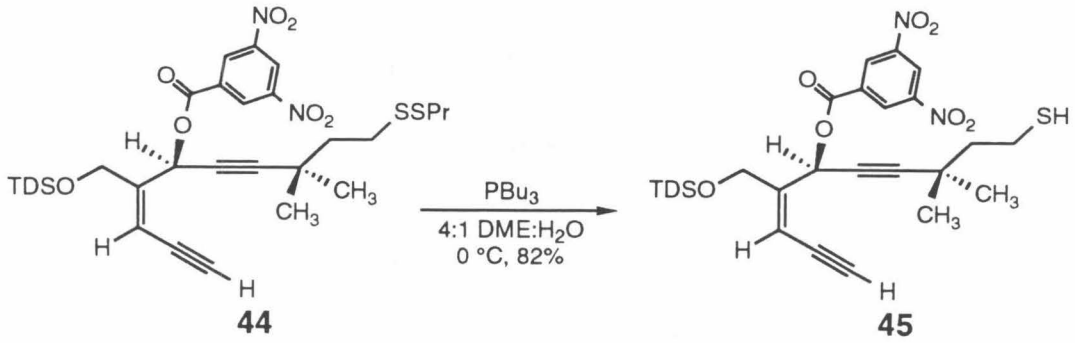
4.51 (d, 1 H, J = 16.7 Hz, $SiOCH_AH_B$), 3.35 (d, 1 H, J = 2.4 Hz, C≡C**H**), 2.59-2.65 (m, 4 H, $SSCH_2CH_2C(CH_3)_2$ and $SSCH_2CH_2CH_3$), 1.62-1.72 (m, 4 H, $SSCH_2CH_2C(CH_3)_2$ and $SSCH_2CH_2CH_3$), 1.10 (s, 3 H, one of $SSCH_2CH_2C(CH_3)_2$), 1.09 (s, 12 H, $SiC(CH_3)_3$ and one of $SSCH_2CH_2C(CH_3)_2$), 0.96 (t, 3 H, J = 7.3 Hz, $SSCH_2CH_2CH_3$).

FTIR (neat), cm^{-1}: 3286 (w, C≡CH), 3101 (w), 2961 (m), 2930 (m), 2857 (m), 1738 (m, C=O), 1547 (s, NO_2), 1428 (w), 1344 (s, NO_2), 1264 (m), 1156 (m), 1113 (s), 922 (m).

MS (EI), m/z (%base): 745 (6), 305 (31), 211 (100), 168 (25), 153 (56), 151 (29).

HRMS (EI): Calcd for $C_{39}H_{44}N_2O_7S_2Si$ (M^+): 744.2359
Found: 744.2377

TLC (10% EtOAc in Hexanes), R_f: Disulfide **51**: 0.15 (UV)
Dinitrobenzoate **44**: 0.31 (UV)



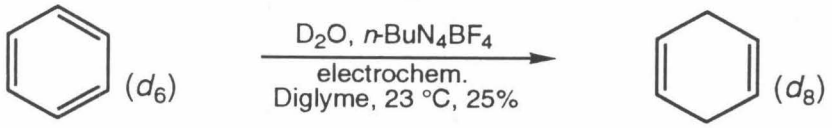
44 **45**

Thiol **45.**

Tributylphosphine (0.119 mL, 0.478 mmol, 10 equiv) was added to an ice-cooled solution of disulfide **44** (0.360 g, 0.48 mmol, 1 equiv) in a 4:1 mixture of 1,2-dimethoxyethane and water (5 mL). The resulting purple solution was stirred at 0 °C for 30 min, then was partitioned between water (75 mL) and a 1:1 mixture of ethyl acetate and hexanes (3 x 50 mL). The combined organic layers were dried over sodium sulfate and were concentrated. The residue was purified by flash column chromatography (5% ethyl acetate in hexanes) to give thiol **45** (0.262 g, 82%) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$), δ: 9.21 (t, 1 H, J = 2.2 Hz, $Ph(NO_2)_2\mathbf{H}_p$), 9.02 (d, 2 H, J = 2.2 Hz, $Ph(NO_2)_2\mathbf{H}_o$), 7.65-7.70 (m, 4 H, **Ph**Si), 7.36-7.42 (m, 6 H, **Ph**Si), 6.79 (s, 1 H, C=CC**H**(OR)C≡C), 6.19 (d, 1 H, J = 2.3 Hz, C=C**H**), 4.61 (d, 1 H, J = 16.6 Hz, $SiOC\mathbf{H}_AH_B$), 4.50 (d, 1 H, J = 16.6 Hz, $SiOCH_A\mathbf{H}_B$), 3.35 (d, 1 H, J = 2.3 Hz, C≡C**H**), 2.43-2.49 (m, 2 H, $HSC\mathbf{H}_2CH_2C(CH_3)_2$), 1.60-1.64 (m, 2 H,

	$HSCH_2C\mathbf{H}_2C(CH_3)_2$), 1.29 (t, 1 H, J = 7.7 Hz, $\mathbf{H}SCH_2CH_2C(CH_3)_2$), 1.09 (s, 9 H, $SiC(C\mathbf{H}_3)_3$), 1.08 (s, 3 H, one of $HSCH_2CH_2C(C\mathbf{H}_3)_2$), 1.07 (s, 3 H, one of $HSCH_2CH_2C(C\mathbf{H}_3)_2$).
FTIR (neat), cm^{-1}:	3286 (w, C≡CH), 2964 (w), 2851 (w), 1737 (m, C=O), 1547 (s, NO_2), 1344 (s, NO_2), 1265 (m), 1156 (m), 1113 (m), 702 (m).
MS (EI), m/z (%base):	459 (4), 199 (25), 197 (46), 135 (100).
HRMS (EI):	Calcd for $C_{36}H_{37}N_2O_7SSi$ ($M-H^+$): 669.2098 Found: 669.2115
TLC (Toluene), R_f:	Dinitrobenzoate **44**: 0.68 (UV) Thiol **45**: 0.60 (UV)



1,4-Cyclohexadiene-d_8.

The apparatus depicted in Figure 4 was assembled and was filled with a solution of deuterium oxide (99.8 % deuterated, 4.4 M) and tetrabutylammonium tetrafluoroborate (0.05 M) in 2-methoxyethyl ether (diglyme, 150 mL). The apparatus was separated into two compartments (anode: Pt electrode, cathode: mercury pool) via a crucible (alundum, Fisher AN889, medium) suspended with string in the reaction solution. Benzene-d_6 (99.6% deuterated, 8.7 mL, 98.0 mmol) was added to the cathode compartment and was subjected to electrochemical reduction (0.90 A constant current, -1.56 V versus Ag wire reference) with magnetic stirring at 23 °C.[62] During the reduction, the reaction apparatus was isolated from the atmosphere (rubber stopper) and was continuously purged with a slow stream of argon. Additional portions of deuterium oxide (2.0 mL) were added to the anode (Pt electrode) compartment at 4 h intervals. Upon completion of the reduction (as indicated by GCMS analysis of a reaction mixture aliquot, 36,180 total coulombs passed, 12 h), the reaction mixture was partitioned between water (100 mL) and pentane (3 x 50 mL). The organic layers were dried over sodium sulfate and were concentrated at 0 °C to ~ 10 mL volume. The remaining liquid was distilled twice at 760 Torr to provide 1,4-cyclohexadiene-d_8 (bp = 81-85 °C, 1.94 g, 25%, 96% deuterium incorporation at the allylic positions as determined by ^{1}H NMR analysis). Drs. James Toth and David Blauch are gratefully acknowledged for their assistance with this procedure.

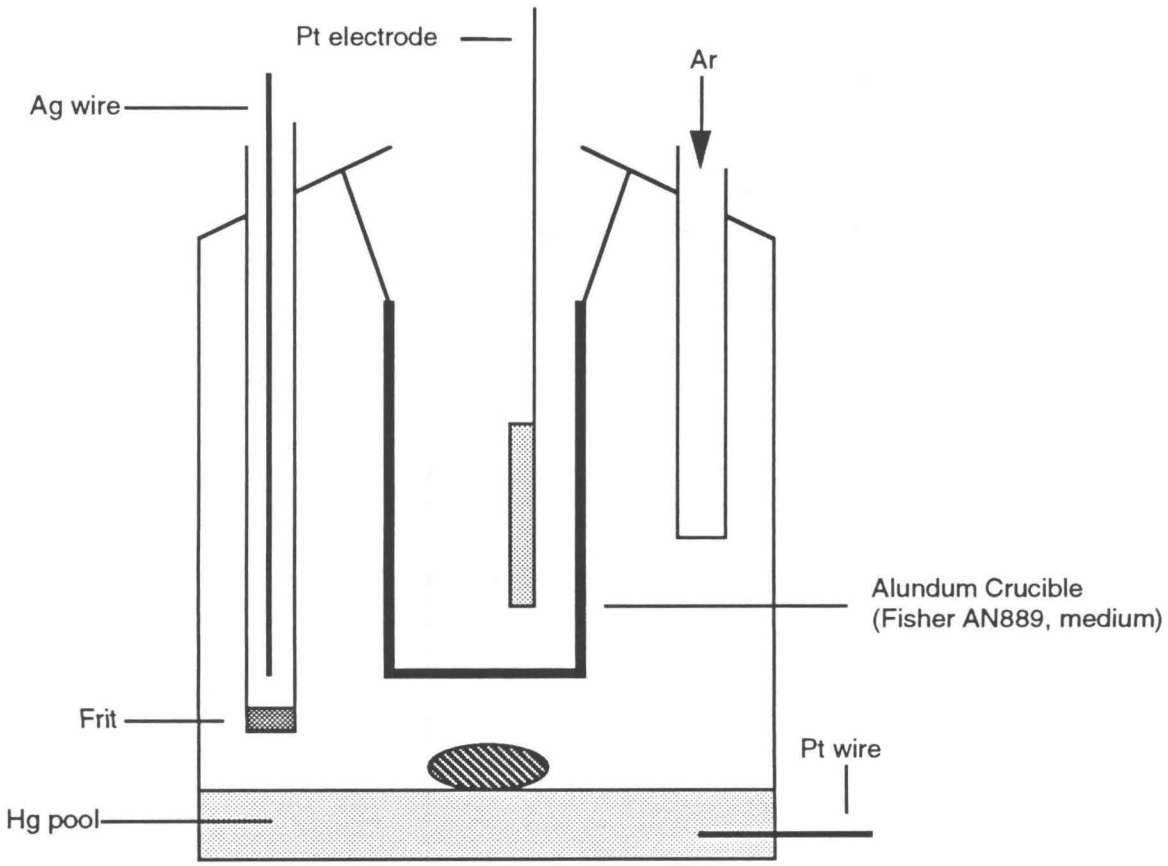


Figure 4. Diagram of electrochemical cell used in preparation of 1,4-cyclohexadiene-d_8.

Allene **46** and Kinetic Experiments.

Triethylamine (0.005 mL, 0.036 mmol, 2.2 equiv) was added to a deoxygenated solution of thiol **45** (0.011 g, 0.017 mmol, 1 equiv), 1,4-cyclohexadiene (0.016 mL, 0.17 mmol), and (*Z*)-1,2-dichloroethylene (0.072 mmol, internal standard) in a mixture of

dimethyl sulfoxide-d_6 and dichloromethane-d_2 (2.3:1, respectively, 0.66 mL) contained in a septum-capped NMR tube at 0 °C. After rapid mixing, the tube was transferred without temperature increase to the probe of a high-field NMR spectrometer (400 MHz) that was maintained at 0 °C. The probe was warmed to 10 °C, and within 30 min, spectroscopic examination revealed the conversion (>95%) of thiol **45** to allene **46**. Selected ^{1}H NMR spectral data for **45** and **46**: C=C**H** (**45**) 6.12 (d, J = 2.2 Hz), (**46**) 5.90 (d, J = 1.5 Hz); CH_2OTDS (**45**) 4.60 (AB, J = 21.9 Hz), (**46**) 4.21 (AB, J = 19.8 Hz); ArCO_2C**H** → C=C=C**H** (**45**) 6.72 (s), (**46**) 6.62 (s).

After the conversion of **45** to **46** was essentially complete, the disappearance of **46** was monitored over 1.5 h by integration of its olefinic signals (corrected by integration of the (*Z*)-1,2-dichloroethylene peak). The collected data (Table VII) were in agreement with first order reaction kinetics (Figure 5) with $k = 3.6 \pm 0.5 \times 10^{-4}$ s^{-1} at 10 °C. The yield of cyclized products at the conclusion of the experiment (3 h) was determined to be 67% by integration of the appropriate benzylic signals and comparison to the internal standard.

Table VII. Kinetic Data for Cyclization of **46** in DMSO-d_6:CD_2Cl_2 (2.3:1) at 10 °C.

Data Point	Time (min)	-ln [**46**]	Data Point	Time (min)	-ln [**46**]
1	0	4.30	8	45	5.24
2	5	4.37	9	50	5.35
3	11	4.52	10	55	5.43
4	20	4.75	11	60	5.53
5	25	4.81	12	68	5.72
6	30	4.93	13	74	5.90
7	40	5.10	14	86	6.19

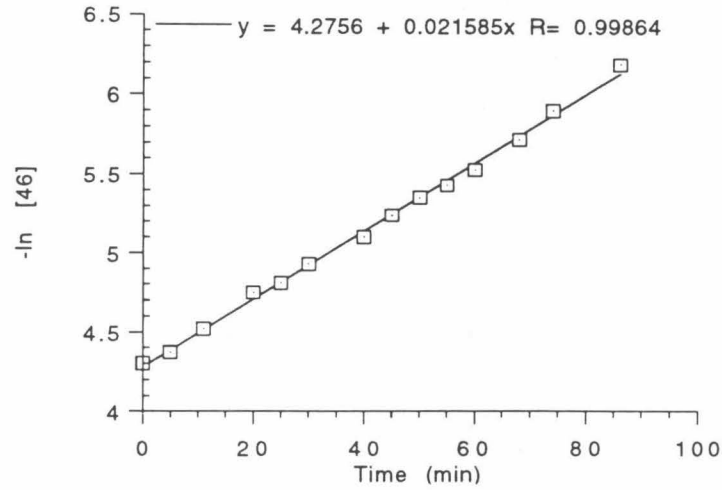
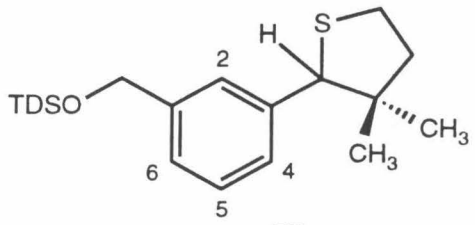


Figure 5. Plot of Kinetic Data Obtained for Cyclization of **46** in DMSO-d_6:CD_2Cl_2 (2.3:1) at 10 °C.

General Cyclization Procedure (Dinitrobenzoate **44** and Thiol **45**).

Triethylamine (5 equiv) was added to a deoxygenated solution of dinitrobenzoate **44** or thiol **45** (each 0.01 M) and trapping agent (1,4-cyclohexadiene, 1,4-cyclohexadiene-d_8 or methanol, each 4.0 M) in dimethyl sulfoxide at 23 °C. 4-Methoxythiophenol (3 equiv) was included in the reaction mixture when dinitrobenzoate **44** was used as a substrate. After stirring at 23 °C for 10 h, each reaction mixture was partitioned between water (50 mL) and a 1:1 mixture of ethyl acetate and hexanes (3 x 50 mL). The combined organic layers were dried over sodium sulfate and were concentrated. The residue was purified by preparative thin-layer chromatography (3-5% ethyl acetate in hexanes, 2 elutions). Product yields were determined prior to chromatography by addition of (Z)-1,2-dichloroethylene to the crude reaction mixtures as an internal standard and ^1H NMR analysis.



52

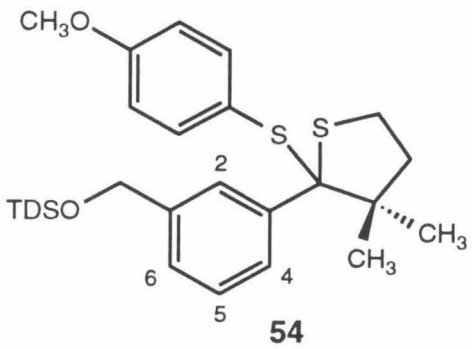
Tetrahydrothiophene Derivative **52.**

^{1}H NMR (500 MHz, CD_2Cl_2), δ: 7.69-7.71 (m, 4 H, **Ph**Si), 7.36-7.45 (m, 7 H, **Ph**Si and **Ar**-2), 7.22-7.30 (m, 3 H, **Ar**-4, **Ar**-5, and **Ar**-6), 4.78 (s, 2 H, $SiOCH_2$), 4.17 (s, 1 H, $SCHC(CH_3)_2$), 3.02-3.07 (m, 1 H, one of SCH_2CH_2), 2.81-2.92 (m, 1 H, one of SCH_2CH_2), 1.99-2.04 (m, 1 H, one of SCH_2CH_2), 1.87-1.93 (m, 1 H, one of SCH_2CH_2), 1.09 (s, 9 H, $SiC(CH_3)_3$), 1.08 (s, 3 H, one of $C(CH_3)_2$), 0.74 (s, 3 H, one of $C(CH_3)_2$).

FTIR (neat), cm^{-1}: 3070 (w), 2959 (m), 2856 (m), 1472 (w), 1427 (m), 1364 (w), 1155 (w), 1113 (s), 1079 (m), 998 (w), 740 (m), 701 (s).

MS (EI), m/z (%base): 433 (4), 403 (16), 357 (6), 325 (100), 307 (17), 291 (12), 247 (27).

HRMS (EI):	Calcd for $C_{29}H_{36}OSSi$ (MH^+): 460.2256
	Found: 460.2243
TLC (5% EtOAc in Hexanes), R_f:	Tetrahydrothiophene Derivative **52**: 0.57 (UV)



54

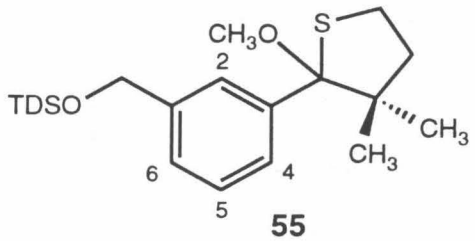
Thiophenol Adduct **54**.

^{1}H NMR (500 MHz, $CDCl_3$), δ: 7.69-7.71 (m, 4 H, **Ph**Si), 7.40-7.42 (m, 1 H, **Ar**-2), 7.34-7.38 (m, 6 H, **Ph**Si), 7.17-7.21 (m, 3 H, **Ar**-4, **Ar**-5, and **Ar**-6), 7.06-7.08 (m, 2 H, *p*-$CH_3OPh\mathbf{H}_o$), 6.63-6.64 (m, 2 H, *p*-$CH_3OPh\mathbf{H}_m$), 4.76 (d, 2 H, J = 1.7 Hz, $SiOC\mathbf{H}_2$), 3.70 (s, 3 H, *p*-$C\mathbf{H}_3OPh$), 2.99-3.04 (m, 2 H, $SC\mathbf{H}_2CH_2$), 2.70-2.77 (m, 1 H, one of $SCH_2C\mathbf{H}_2$), 2.00-2.06 (m, 1 H, one of $SCH_2C\mathbf{H}_2$), 1.45 (s, 3 H, one of $C(C\mathbf{H}_3)_2$), 1.09 (s, 9 H, $SiC(C\mathbf{H}_3)_3$), 0.79 (s, 3 H, one of $C(C\mathbf{H}_3)_2$).

FTIR (neat), cm^{-1}: 3057 (w), 2959 (m), 2927 (m), 1591 (m), 1492 (s), 1288 (m), 1246 (s), 1109 (s), 824 (m), 702 (s).

MS (EI), m/z (%base): 597 (2), 541 (2), 459 (100), 373 (3), 323 (2), 204 (9).

HRMS (EI):	Calcd for $C_{36}H_{41}O_2S_2Si$ ($M-H^+$): 597.2317
	Found: 597.2343
TLC (5% EtOAc in Hexanes), R_f:	Thiophenol Adduct **54**: 0.57 (UV)



55

Methyl Ether **55**.

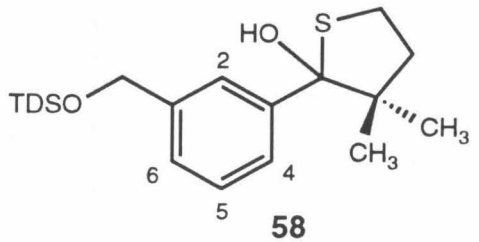
^{1}H NMR (500 MHz, $CDCl_3$), δ: 7.69-7.71 (m, 4 H, **Ph**Si), 7.22-7.44 (m, 10 H, **Ph**Si, **Ar**-2, **Ar**-4, **Ar**-5, and **Ar**-6), 4.79 (s, 2 H, $SiOC\mathbf{H}_2$), 3.16 (s, 3 H, $C\mathbf{H}_3O$), 2.95-3.05 (m, 1 H, one of $SC\mathbf{H}_2CH_2$), 2.82-2.90 (m, 1 H, one of $SC\mathbf{H}_2CH_2$), 2.42-2.50 (m, 1 H, one of $SCH_2C\mathbf{H}_2$), 1.84-1.96 (m, 1 H, one of $SCH_2C\mathbf{H}_2$), 1.10 (s, 9 H, $SiC(C\mathbf{H}_3)_3$), 1.04 (s, 3 H, one of $C(C\mathbf{H}_3)_2$), 0.71 (s, 3 H, one of $C(C\mathbf{H}_3)_2$).

FTIR (neat), cm^{-1}: 3071 (w), 2959 (s), 2856 (s), 1472 (m), 1428 (s), 1112 (s), 1078 (s), 825 (m), 701 (s).

MS (EI), m/z (%base): 489 (13), 459 (100), 433 (20), 285 (10).

HRMS (EI): Calcd for $C_{30}H_{37}O_2SSi$ ($M-H^+$): 489.2284
Found: 489.2278

TLC (5% EtOAc in Hexanes), R_f: Methyl Ether **55**: 0.42 (UV)



58

Hemithioketal **58.**

^{1}H NMR (500 MHz, CD_2Cl_2), δ: 7.69-7.75 (m, 5 H, **Ph**Si and **Ar**-2), 7.60-7.66 (m, 1 H, **Ar**-4 or **Ar**-6), 7.36-7.46 (m, 6 H, **Ph**Si), 7.27-7.29 (m, 2 H, **Ar**-5 and one of **Ar**-4 or **Ar**-6), 4.80 (s, 2 H, $SiOCH_2$), 3.09-3.14 (m, 1 H, one of SCH_2CH_2), 3.00-3.04 (m, 1 H, one of SCH_2CH_2), 2.47-2.54 (m, 1 H, one of SCH_2CH_2), 2.42 (s, 1 H, **OH**), 1.99-2.03 (m, 1 H, one of SCH_2CH_2), 1.09 (s, 9 H, $SiC(CH_3)_3$), 1.02 (s, 3 H, one of $C(CH_3)_2$), 0.78 (s, 3 H, one of $C(CH_3)_2$).

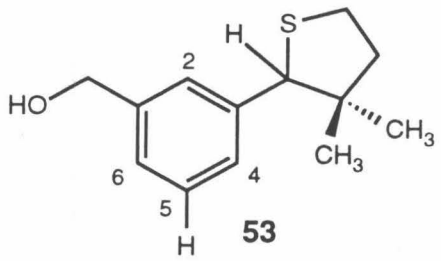
FTIR (neat), cm^{-1}: 3484 (br, OH), 3065 (w), 2925 (m), 2855 (m), 1474 (m), 1427 (m), 1113 (s), 1078 (m), 822 (m), 700 (s).

MS (EI), m/z (%base): 459 (100), 443 (23), 419 (31), 399 (5), 373 (4), 281 (13), 199 (24).

HRMS (EI):	Calcd for $C_{29}H_{35}O_2SSi$ ($M-H^+$): 475.2127
	Found: 475.2130
TLC (20% EtOAc in Hexanes), R_f:	Hemithioketal **58**: 0.49 (UV)

General Desilylation Procedure.

Tetrabutylammonium fluoride (2.0 mL, 1.0 M in tetrahydrofuran) was added to a solution of silyl ether (0.5-1.0 mg) in tetrahydrofuran (2 mL) at 23 °C. After stirring at 23 °C for 30 min, each reaction mixture was partitioned between water (25 mL) and a 1:1 mixture of ethyl acetate and hexanes (3 x 25 mL). The combined organic layers were dried over sodium sulfate and were concentrated. The residue was purified by preparative thin-layer chromatography (20% ethyl acetate in hexanes). Using the above procedure, alcohols **53** and **57** were prepared from tetrahydrothiophene derivative **52** and methyl ether **55** respectively.



53

Alcohol **53.**

^{1}H NMR (500 MHz, CD_2Cl_2), δ: 7.40 (s, 1 H, **Ar**-2), 7.33 (d, 1 H, J = 7.4 Hz, **Ar**-4 or **Ar**-6), 7.28 (t, 1 H, J = 7.4 Hz, **Ar**-5), 7.24 (d, 1 H, J = 7.4 Hz, **Ar**-4 or **Ar**-6), 4.69 (d, 2 H, J = 5.6 Hz, HOC**H**$_2$), 4.19 (s, 1 H, SC**H**C(CH$_3$)$_2$), 3.04-3.10 (m, 1 H, one of SC**H**$_2$CH$_2$), 2.89-2.94 (m, 1 H, one of SC**H**$_2$CH$_2$), 2.00-2.05 (m, 1 H, one of SCH$_2$C**H**$_2$), 1.88-1.96 (m, 1 H, one of SCH$_2$C**H**$_2$), 1.60 (t, 1 H, J = 5.6 Hz, O**H**), 1.09 (s, 3 H, one of C(C**H**$_3$)$_2$), 0.76 (s, 3 H, one of C(C**H**$_3$)$_2$).

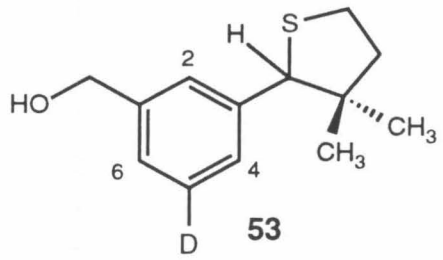
FTIR (neat), cm^{-1}: 3326 (br, OH), 2954 (s), 2921 (s), 2862 (m), 1452 (m), 1359 (m), 1021 (m), 790 (m).

MS (EI), m/z (%base): 222 (100), 207 (37), 191 (43), 166 (45), 148 (34), 135 (87), 121 (17).

HRMS (EI): Calcd for $C_{13}H_{18}OS$ (M^+): 222.1078
Found: 222.1072

TLC (20% EtOAc in Hexanes), R_f: Tetrahydrothiophene Derivative **52**: 0.61 (UV)

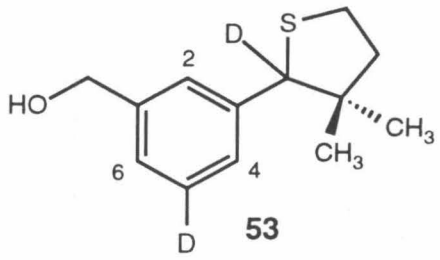
Alcohol **53**: 0.18 (UV)



53

Alcohol **53** (d_1).

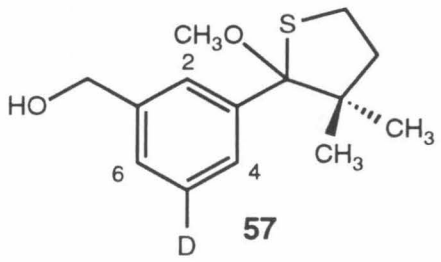
^{1}H NMR (500 MHz, CD_2Cl_2), δ: 7.39 (s, 1 H, **Ar**-2), 7.32 (s, 1 H, **Ar**-4 or **Ar**-6), 7.24 (s, 1 H, **Ar**-4 or **Ar**-6), 4.65 (d, 2 H, J = 5.8 Hz, HOC**H**$_2$), 4.18 (s, 1 H, SC**H**C(CH$_3$)$_2$), 3.03-3.09 (m, 1 H, one of SC**H**$_2$CH$_2$), 2.88-2.92 (m, 1 H, one of SC**H**$_2$CH$_2$), 2.00-2.04 (m, 1 H, one of SCH$_2$C**H**$_2$), 1.88-1.94 (m, 1 H, one of SCH$_2$C**H**$_2$), 1.73 (t, 1 H, J = 5.8 Hz, O**H**), 1.08 (s, 3 H, one of C(C**H**$_3$)$_2$), 0.74 (s, 3 H, one of C(C**H**$_3$)$_2$).



53

Alcohol **53** (d_2).

^{1}H NMR (500 MHz, CD_2Cl_2), δ: 7.40 (s, 1 H, **Ar**-2), 7.32 (s, 1 H, **Ar**-4 or **Ar**-6), 7.24 (s, 1 H, **Ar**-4 or **Ar**-6), 4.65 (d, 2 H, J = 5.8 Hz, HOC**H**$_2$), 3.03-3.09 (m, 1 H, one of SC**H**$_2$CH$_2$), 2.87-2.92 (m, 1 H, one of SC**H**$_2$CH$_2$), 2.00-2.04 (m, 1 H, one of SCH$_2$C**H**$_2$), 1.88-1.94 (m, 1 H, one of SCH$_2$C**H**$_2$), 1.74 (t, 1 H, J = 5.8 Hz, O**H**), 1.08 (s, 3 H, one of C(C**H**$_3$)$_2$), 0.74 (s, 3 H, one of C(C**H**$_3$)$_2$).



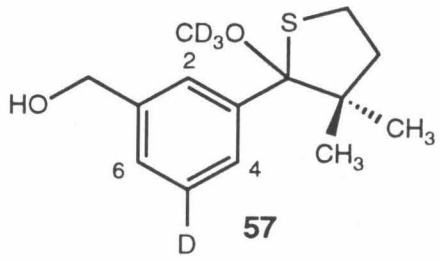
57

Alcohol **57** (d_1).

^{1}H NMR (500 MHz, CD_2Cl_2), δ: 7.58 (s, 1 H, **Ar**-2), 7.51 (s, 1 H, **Ar**-4 or **Ar**-6), 7.29 (s, 1 H, **Ar**-4 or **Ar**-6), 4.67 (d, 2 H, J = 5.8 Hz, HOC**H**$_2$), 3.14 (s, 3 H, C**H**$_3$O), 2.99-3.05 (m, 1 H, one of SC**H**$_2$CH$_2$), 2.81-2.85 (m, 1 H, one of SC**H**$_2$CH$_2$), 2.40-2.46 (m, 1 H, one of SCH$_2$C**H**$_2$), 1.90-2.04 (m, 1 H, one of SCH$_2$C**H**$_2$), 1.75 (t, 1 H, J = 5.8 Hz, O**H**), 1.04 (s, 3 H, one of C(C**H**$_3$)$_2$), 0.69 (s, 3 H, one of C(C**H**$_3$)$_2$).

FTIR (neat), cm^{-1}: 3374 (br, OH), 2933 (m), 1426 (m), 1149 (w), 1077 (s), 822 (m), 790 (m), 708 (m).

TLC (20% EtOAc in Hexanes), R_f: Methyl Ether **55**: 0.59 (UV)
Alcohol **57** (d_1): 0.16 (UV)



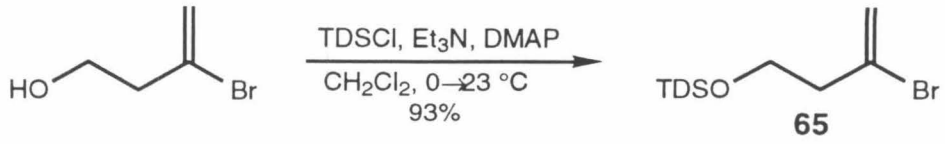
57

Alcohol **57** (d_4).

^{1}H NMR (500 MHz, CD_2Cl_2), δ: 7.58 (s, 1 H, **Ar**-2), 7.51 (s, 1 H, **Ar**-4 or **Ar**-6), 7.29 (s, 1 H, **Ar**-4 or **Ar**-6), 4.67 (d, 2 H, J = 5.8 Hz, HOC**H**$_2$), 2.99-3.05 (m, 1 H, one of SC**H**$_2$CH$_2$), 2.81-2.85 (m, 1 H, one of SC**H**$_2$CH$_2$), 2.40-2.46 (m, 1 H, one of SCH$_2$C**H**$_2$), 1.90-1.94 (m, 1 H, one of SCH$_2$C**H**$_2$), 1.76 (t, 1 H, J = 5.8 Hz, O**H**), 1.04 (s, 3 H, one of C(C**H**$_3$)$_2$), 0.69 (s, 3 H, one of C(C**H**$_3$)$_2$).

MS (CI/NH_3), m/z (%base): 256 (11), 199 (4), 186 (10), 169 (15), 152 (10), 136 (4).

HRMS (CI/NH_3): Calcd for $C_{14}H_{16}D_4O_2S$ (M^+): 256.1435
Found: 256.1426



65

3-Bromo-3-butene-1-ol *tert*-Butyldiphenylsilyl Ether **65.**

tert-Butyldiphenylsilyl chloride (2.07 mL, 7.96 mmol, 1.2 equiv) was added to a solution of 3-bromo-3-butene-1-ol[41] (1.00 g, 6.62 mmol, 1 equiv) and triethylamine (4.61 mL, 33.1 mmol, 5.0 equiv) in dichloromethane (75 mL) at 0 °C. The reaction mixture was allowed to attain 23 °C whereupon 4-dimethylaminopyridine (0.5 g, 4.09 mmol, 0.62 equiv) was added. After stirring at 23 °C for 2 h, the product solution was partitioned between water (100 mL) and a 1:1 mixture of ethyl acetate and hexanes (3 x 100 mL). The combined organic layers were dried over sodium sulfate and were concentrated. The residue was purified by flash column chromatography (5% ethyl acetate in hexanes) to afford 3-bromo-3-butene-1-ol *tert*-butyldiphenylsilyl ether **65** (2.50 g, 93%) as a yellow oil.

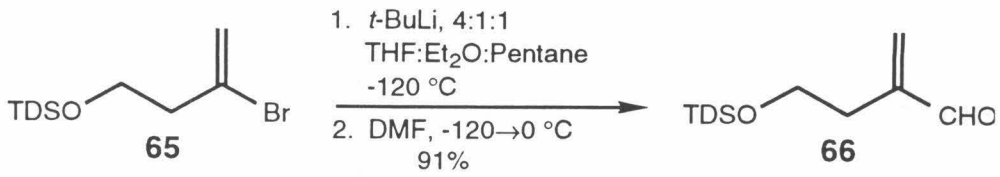
^{1}H NMR (400 MHz, $CDCl_3$), δ: 7.70-7.72 (m, 4 H, **Ph**Si), 7.40-7.46 (m, 6 H, **Ph**Si), 5.68 (s, 1 H, one of C=C**H**$_2$), 5.51 (s, 1 H, one of C=C**H**$_2$), 3.87 (t, 2 H, J = 6.1 Hz, SiOC**H**$_2$CH$_2$), 2.67 (t, 2 H, J = 6.1 Hz, SiOCH$_2$C**H**$_2$), 1.09 (s, 9 H, SiC(C**H**$_3$)$_3$).

FTIR (neat), cm^{-1}: 3070 (w), 2931 (m), 2857 (m), 1630 (m), 1428 (m), 1112 (s), 888 (w), 701 (s), 622 (m).

MS (CI/CH_4), m/z (%base): 389 (2), 331 (61), 313 (28), 293 (32), 273 (44), 269 (98), 251 (72), 239 (45), 199 (100).

HRMS (CI/CH_4): Calcd for $C_{20}H_{24}BrOSi$ ($M-H^+$): 387.0780
Found: 387.0757

TLC (20% EtOAc in Hexanes), R_f: 3-Bromo-3-butene-1-ol: 0.19 (UV)
3-Bromo-3-butene-1-ol *tert*-Butyldiphenylsilyl Ether **65**: 0.67 (UV)

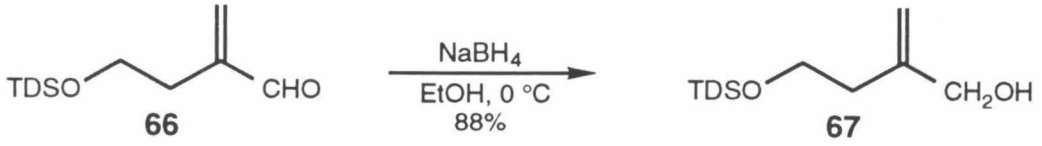


Aldehyde **66.**

A solution of *tert*-butyldiphenylsilyl ether **65** (2.67 g, 6.86 mmol, 1 equiv) in a mixture of tetrahydrofuran, ethyl ether, and pentane (4:1:1, respectively, 9.0 mL) was added dropwise via cannula over 5 min to a solution of *tert*-butyllithium (9.74 mL, 1.76 M solution in pentane, 17.1 mmol, 2.5 equiv) in a mixture of tetrahydrofuran, ethyl ether, and pentane (4:1:1, respectively, 60 mL) at -120 °C. After stirring at -120 °C for 5 min, a solution of *N,N*-dimethylformamide (1.33 mL, 17.1 mmol, 2.5 equiv) in tetrahydrofuran (4.0 mL) was added dropwise via cannula over 7 min to the orange reaction mixture. The resulting yellow solution was warmed to 0 °C over 3 h, then was quenched with water (5 mL). The product was partitioned between water (150 mL) and a 1:1 mixture of ethyl acetate and hexanes (3 x 100 mL). The combined organic layers were dried over sodium sulfate and were concentrated. Purification of the residue by flash column chromatography (gradient elution: ethyl acetate in hexanes, 3→20%) afforded aldehyde **66** (2.11 g, 91%) as a pale yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$), δ: 9.49 (s, 1 H, **CH**O), 7.63-7.66 (m, 4 H, **Ph**Si), 7.37-7.43 (m, 6 H, **Ph**Si), 6.36 (s, 1 H, one of C=C**H**$_2$), 6.05 (s, 1 H, one of C=C**H**$_2$), 3.78 (t, 2 H, J = 6.5 Hz, SiOC**H**$_2$CH$_2$), 2.52 (t, 2 H, J = 6.5 Hz, SiOCH$_2$C**H**$_2$), 1.04 (s, 9 H, SiC(C**H**$_3$)$_3$).

FTIR (neat), cm^{-1}:	3070 (w), 2958 (m), 2857 (m), 1961 (s, C=O), 1472 (m), 1112 (s), 823 (m), 738 (m), 702 (s), 613 (m).
MS (CI/CH_4), m/z (%base):	339 (5), 281 (75), 261 (41), 219 (21), 199 (22), 83 (100).
HRMS (CI/CH_4):	Calcd for $C_{21}H_{27}O_2Si$ (MH^+): 339.1780 Found: 339.1765
TLC (5% EtOAc in Hexanes), R_f:	3-Bromo-3-butene-1-ol *tert*-Butyldiphenylsilyl Ether **65**: 0.55 (UV) Aldehyde **66**: 0.20 (UV)



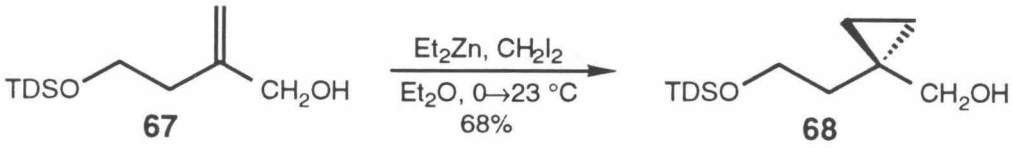
Allylic Alcohol **67.**

Sodium borohydride (powder, 0.235 g, 6.22 mmol, 1.0 equiv) was added in small portions over 10 min to an ice-cooled solution of aldehyde **66** (2.11 g, 6.22 mmol, 1 equiv) in absolute ethanol (50 mL). After stirring at 0 °C for 1 h, saturated aqueous ammonium chloride solution (20 mL) was added, and the crude reaction mixture was partitioned between water (150 mL) and a 1:1 mixture of ethyl acetate and hexanes (3 x 100 mL). The combined organic layers were dried over sodium sulfate and were concentrated. The residue was purified by flash column chromatography (gradient elution: ethyl acetate in hexanes, 10→40%) to give allylic alcohol **67** (1.87 g, 88%) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$), δ: 7.67-7.68 (m, 4 H, **Ph**Si), 7.38-7.44 (m, 6 H, **Ph**Si), 5.07 (s, 1 H, one of C=C**H**$_2$), 4.89 (s, 1 H, one of C=C**H**$_2$), 4.08 (d, 2 H, J = 5.9 Hz, C**H**$_2$OH), 3.77 (t, 2 H, J = 6.2 Hz, SiOC**H**$_2$CH$_2$), 2.35 (t, 2 H, J = 6.2 Hz, SiOCH$_2$C**H**$_2$), 2.30 (t, 1 H, J = 6.1 Hz, CH$_2$O**H**), 1.06 (s, 9 H, SiC(C**H**$_3$)$_3$).

FTIR (neat), cm^{-1}: 3348 (br, OH), 3070 (w), 2930 (m), 2857 (m), 1427 (m), 1111 (s), 823 (m), 738 (m), 702 (s).

MS (CI/CH_4), m/z (%base):	341 (10), 323 (44), 283 (65), 269 (38), 253 (45), 239 (53), 205 (64), 199 (100), 165 (44), 139 (48).
HRMS (CI/CH_4):	Calcd for $C_{21}H_{29}O_2Si$ (MH^+): 341.1937 Found: 341.1917
TLC (20% EtOAc in Hexanes), R_f:	Aldehyde **66**: 0.48 (UV) Allylic Alcohol **67**: 0.25 (UV)



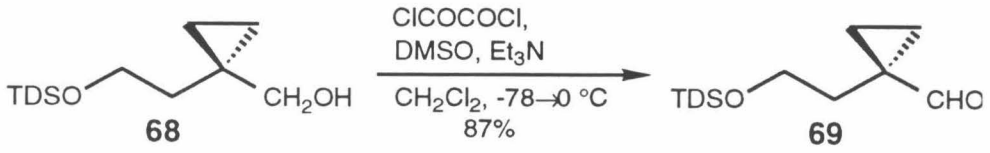
Alcohol **68.**

Diethylzinc (26.5 mL, 1.0 M solution in hexanes, 26.5 mmol, 5.0 equiv) was added via cannula over 5 min to a solution of allylic alcohol **67** (1.80 g, 5.29 mmol, 1 equiv) in ethyl ether (40.0 mL) at 0 °C. Diiodomethane (4.26 mL, 52.9 mmol, 10.0 equiv) was added via syringe over 2 min, and the pale orange reaction solution was stirred at 23 °C for 4 h, during which time a white precipitate formed. After quenching with water (5 mL), the reaction mixture was partitioned between brine (150 mL) and a 1:1 mixture of ethyl acetate and hexanes (3 x 100 mL). The combined organic layers were dried over sodium sulfate and were concentrated. Purification of the residue by flash column chromatography (gradient elution: ethyl acetate in hexanes, 5→40%) afforded alcohol **68** (1.29 g, 68%) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$), δ: 7.67-7.71 (m, 4 H, **Ph**Si), 7.39-7.45 (m, 6 H, **Ph**Si), 3.78 (t, 2 H, *J* = 5.37 Hz, SiOC**H**$_2$CH$_2$), 3.44 (s, 2 H, C**H**$_2$OH), 1.60 (t, 2 H, *J* = 5.37 Hz, SiOCH$_2$C**H**$_2$), 1.07 (s, 9 H, SiC(C**H**$_3$)$_3$), 0.49 (t, 2 H, *J* = 5.0 Hz, two of **Cy**), 0.34 (t, 2 H, *J* = 5.0 Hz, two of **Cy**).

FTIR (neat), cm^{-1}: 3383 (br, OH), 3071 (w), 2999 (w), 2931 (m), 1472 (m), 1112 (s), 823 (m), 701 (s), 688 (m).

MS (CI/CH_4), m/z (%base):	355 (3), 337 (30), 297 (21), 269 (64), 229 (65), 199 (97), 167 (44), 139 (32), 81 (100), 57 (37).
HRMS (CI/CH_4):	Calcd for $C_{22}H_{31}O_2Si$ (MH^+): 355.2093 Found: 355.2086
TLC (10% EtOAc in Toluene), R_f:	Allylic Alcohol **67**: 0.46 (UV) Alcohol **68**: 0.46 (identical) (UV)

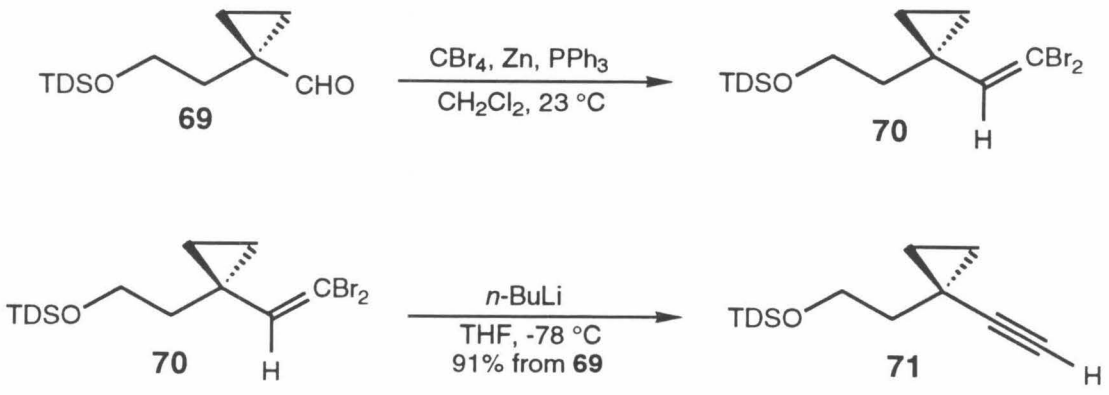


Cyclopropane Carboxaldehyde **69.**

Dimethyl sulfoxide (0.541 mL, 7.62 mmol, 2.2 equiv) was added over 2 min to a solution of oxalyl chloride (0.330 mL, 3.81 mmol, 1.1 equiv) in dichloromethane (15 mL) at -78 °C. The resulting clear solution was allowed to stir at -78 °C for 5 min before addition of a solution of alcohol **68** (1.23 g, 3.46 mmol, 1 equiv) in dichloromethane (15 mL, via cannula over 3 min). After 15 min, triethylamine (2.41 mL, 17.3 mmol, 5.0 equiv) was added to the reaction mixture and the resulting solution was warmed to 0 °C and was stirred at that temperature for 30 min. The reaction was quenched at 0 °C with water (5 mL), and the product was partitioned between water (150 mL) and a 1:1 mixture of ethyl acetate and hexanes (3 x 100 mL). The combined organic layers were dried over sodium sulfate and were concentrated. The residue was purified by flash column chromatography (gradient elution: ethyl acetate in hexanes, 5→20%) to give cyclopropane carboxaldehyde **69** (1.06 g, 87%) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$), δ: 8.85 (s, 1 H, C**H**O), 7.64-7.66 (m, 4 H, **Ph**Si), 7.36-7.43 (m, 6 H, **Ph**Si), 3.76 (t, 2 H, J = 6.5 Hz, $SiOC\mathbf{H}_2CH_2$), 1.89 (t, 2 H, J = 6.5 Hz, $SiOCH_2C\mathbf{H}_2$), 1.13 (dd, 2 H, J = 7.2, 4.5 Hz, two of **Cy**), 1.04 (s, 9 H, $SiC(\mathbf{CH}_3)_3$), 0.96 (dd, 2 H, J = 7.2, 4.5 Hz, two of **Cy**).

FTIR (neat), cm^{-1}:	3068 (w), 2997 (w), 2930 (m), 1710 (s, C=O), 1427 (m), 1110 (s), 903 (m), 739 (m), 702 (s).
MS (CI/CH_4), m/z (%base):	351 (6), 295 (56), 275 (24), 247 (13), 199 (23), 97 (100).
HRMS (CI/CH_4):	Calcd for $C_{22}H_{27}O_2Si$ ($M-H^+$): 351.1780 Found: 351.1783
TLC (20% EtOAc in Hexanes), R_f:	Alcohol **68**: 0.20 (UV) Cyclopropane Carboxaldehyde **69**: 0.40 (UV)



Alkyne **71**.

Zinc dust (1.09 g, 16.7 mmol, 2.0 equiv), triphenylphosphine (4.38 g, 16.7 mmol, 2.0 equiv), and carbon tetrabromide (5.53 g, 16.7 mmol, 2.0 equiv) were combined at 23 °C in dichloromethane (80 mL) and the resulting olive suspension was stirred at 23 °C for 24 h. A solution of cyclopropane carboxaldehyde **69** (2.94 g, 8.34 mmol, 1 equiv) in dichloromethane (10 mL) was added via cannula to the then-purple suspension, and the mixture was stirred at 23 °C for 5 h. Pentane (150 mL) was added, producing a white precipitate, and the reaction mixture was filtered through a coarse frit. The cloudy filtrate was solubilized with dichloromethane (~10 mL), was reprecipitated with pentane (~50 mL) and was filtered a second time. After a third iteration of the above cycle, the filtrate was dried over sodium sulfate and was concentrated. The residue was purified by flash column chromatography (10% dichloromethane in hexanes) to give 1,1-dibromo olefin **70** as a colorless oil (5.62 g).

n-Butyllithium (13.8 mL, 1.6 M solution in hexanes, 22.0 mmol, 2.2 equiv) was added over 5 min to a solution of **70** (5.62 g, 8.34 mmol, 1 equiv) in tetrahydrofuran (100 mL) at -78 °C. After stirring at -78 °C for 3 h, the reaction mixture was quenched at -78 °C with saturated aqueous ammonium chloride solution (10 mL) and was partitioned

between water (150 mL) and a 1:1 mixture of ethyl acetate and hexanes (3 x *100 mL).* The combined organic layers were dried over sodium sulfate and were concentrated. Purification of the residue by flash chromatography (gradient elution: toluene in hexane, 5→10%) provided alkyne **71** (2.65 g, 91%) as a colorless oil.

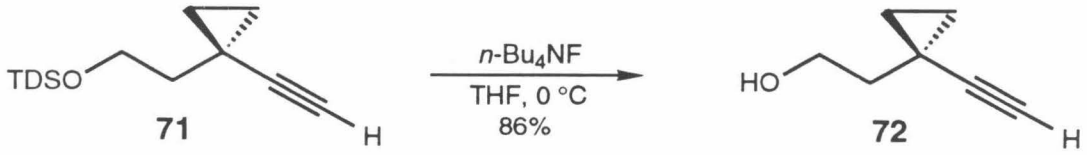
^{1}H NMR (400 MHz, $CDCl_3$), δ: 7.68-7.71 (m, 4 H, **Ph**Si), 7.36-7.42 (m, 6 H, **Ph**Si), 3.90 (t, 2 H, *J* = 6.8 Hz, $SiOC\mathbf{H}_2CH_2$), 1.78 (s, 1 H, C≡C**H**), 1.63 (t, 2 H, *J* = 6.8 Hz, $SiOCH_2C\mathbf{H}_2$), 1.05 (s, 9 H, $SiC(C\mathbf{H}_3)_3$), 0.87 (dd, 2 H, *J* = 6.7, 4.3 Hz, two of **Cy**), 0.62 (dd, 2 H, *J* = 6.7, 4.3 Hz, two of **Cy**).

FTIR (neat), cm^{-1}: 3310 (w, C≡CH), 3071 (w), 3015 (w), 2930 (m), 2112 (w), 1473 (m), 1427 (m), 1112 (s), 701 (s).

MS (CI/CH_4), m/z (%base): 349 (5), 291 (93), 263 (100), 239 (36), 213 (56), 183 (36), 135 (33).

HRMS (CI/CH_4): Calcd for $C_{23}H_{29}OSi$ (MH^+): 349.1988
Found: 349.1986

TLC (20% EtOAc in Hexanes), R_f: Cyclopropane Carboxaldehyde **69**: 0.40 (UV)
Alkyne **71**: 0.51 (UV)



Alcohol **72.**

Tetrabutylammonium fluoride (22.8 mL, 1.0 M solution in tetrahydrofuran, 22.8 mmol, 3.0 equiv) was added via syringe to an ice-cooled solution of alkyne **71** (2.65 g, 7.60 mmol, 1 equiv) in tetrahydrofuran (125 mL). After stirring at 0 °C for 24 h, saturated aqueous ammonium chloride solution (10 mL) was added and the mixture was partitioned between water (200 mL) and a 1:1 mixture of ethyl acetate and hexanes (3 x 150 mL). The combined organic layers were dried over sodium sulfate and were concentrated. The residue was purified by flash column chromatography (gradient elution: ethyl acetate in hexanes, 20→30%) to give alcohol **72** (0.72 g, 86%) as a pale yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$), δ: 3.88-3.91 (m, 2 H, $HOC\mathbf{H}_2CH_2$), 1.91 (s, 1 H, C≡C**H**), 1.72-1.73 (m, 1 H, O**H**), 1.63 (t, 2 H, J = 6.2 Hz, $HOCH_2C\mathbf{H}_2$), 0.95 (dd, 2 H, J = 6.5, 4.3 Hz, two of **Cy**), 0.67 (dd, 2 H, J = 6.5, 4.3 Hz, two of **Cy**).

FTIR (neat), cm^{-1}: 3352 (br, OH), 3297 (s, C≡CH), 3090 (w), 3009 (w), 2942 (m), 2882 (m), 2111 (m), 1426 (m), 1057 (s), 1026 (s).

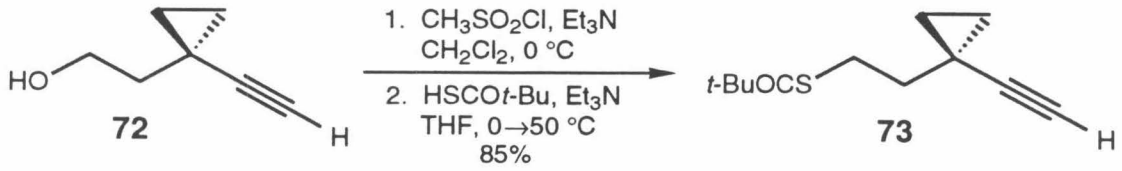
MS (EI), m/z (%base): 110 (21), 95 (36), 91 (100), 79 (84), 65 (23).

HRMS (EI): Calcd for $C_7H_{10}O$ (M^+): 110.0732

Found: 110.0733

TLC (30% EtOAc in Hexanes), R_f: Alkyne **71**: 0.77 (UV)

Alcohol **72**: 0.38

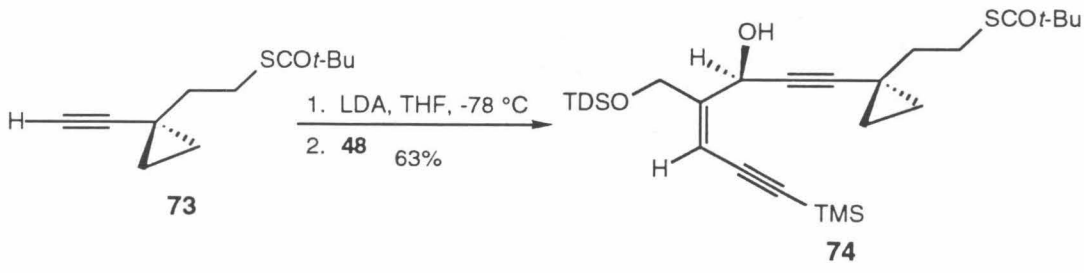


Thiol Ester **73.**

Methanesulfonyl chloride (0.61 mL, 7.85 mmol, 1.2 equiv) was added dropwise via syringe over 15 min to an ice-cooled solution of alcohol **72** (0.72 g, 6.54 mmol, 1 equiv) and triethylamine (1.19 mL, 8.50 mmol, 1.3 equiv) in dichloromethane (100 mL). The resulting yellow suspension was stirred at 0 °C for 5 min, then was partitioned between brine (150 mL) and a 1:1 mixture of ethyl acetate and hexanes (3 x 100 mL). The combined organic layers were dried over sodium sulfate and were concentrated. The remaining yellow oil was dissolved in tetrahydrofuran (15 mL) and the resulting solution was cooled to 0 °C. Triethylamine (9.12 mL, 65.4 mmol, 10.0 equiv) and thiopivalic acid (4.16 mL, 32.7 mmol, 5.0 equiv) were added sequentially at 0 °C; the mixture was heated at 50 °C for 3 h. After cooling to 23 °C, the reaction mixture was partitioned between water (100 mL) and a 1:1 mixture of ethyl acetate and hexanes (3 x 100 mL). The combined organic layers were dried over sodium sulfate and were concentrated. The residue was purified by flash column chromatography (3% ethyl acetate in hexanes) to give thiol ester **73** (1.27 g, 90%) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$), δ: 3.03-3.07 (m, 2 H, SCH_2CH_2), 1.89 (s, 1 H, C≡C**H**), 1.55-1.60 (m, 2 H, SCH_2CH_2), 1.22 (s, 9 H, $C(CH_3)_3$), 0.93 (dd, 2 H, *J* = 6.6, 4.4 Hz, two of **Cy**), 0.67 (dd, 2 H, *J* = 6.6, 4.4 Hz, two of **Cy**).

FTIR (neat), cm^{-1}:	3293 (m, C≡CH), 2969 (s), 2933 (m), 2112 (w, C≡C), 1679 (s, C=O), 1477 (m), 1036 (m), 953 (s), 807 (m).
MS (CI/NH_3), m/z (%base):	211(4), 153 (100), 125 (14), 91 (13), 85 (34), 57 (96).
HRMS (CI/NH_3):	Calcd for $C_{12}H_{19}OS$ (MH^+): 211.1157 Found: 211.1161
TLC (5% EtOAc in Hexanes), R_f:	Alcohol **72**: 0.10 Thiol Ester **73**: 0.47



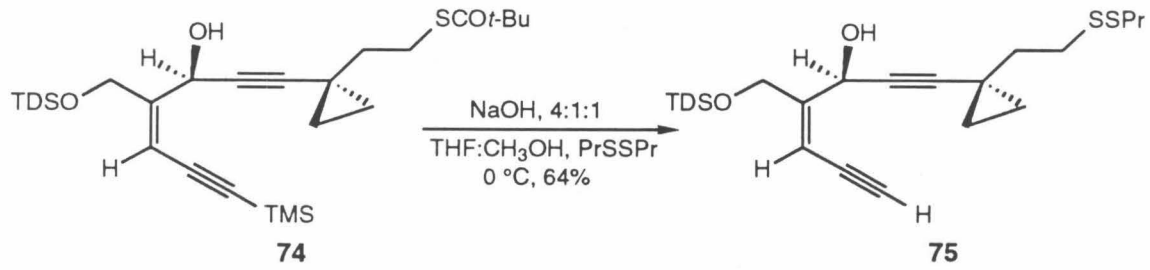
73 74

Cyclopropane Alcohol **74.**

A solution of lithium diisopropylamide in tetrahydrofuran (1.0 M, 3.0 mL, 1.4 equiv) was added via cannula to a solution of thiol ester **73** (0.43 g, 2.18 mmol, 1.1 equiv) in tetrahydrofuran (20 mL) at -78 °C. After stirring at -78 °C for 10 min, anhydrous cerium(III) chloride (0.82 g, 3.31 mmol, 1.6 equiv) was added, and the resulting orange suspension was stirred at -78 °C for 30 min. A solution of aldehyde **48** (0.87 g, 2.07 mmol, 1 equiv) in tetrahydrofuran (8 mL) was then added via cannula over 2 min, and the reaction mixture was maintained at -78 °C for 40 min. The reaction was quenched with water (3 mL) at -78 °C, and sodium tartrate (0.5 g) was added. The reaction mixture was partitioned between water (200 mL) and a 1:1 mixture of ethyl acetate and hexanes (3 x 100 mL) and the combined organic layers were dried over sodium sulfate and were concentrated. The residue was purified by flash column chromatography (gradient elution: ethyl acetate in hexanes, 3→10%) to give cyclopropane alcohol **74** (0.82 g, 63%) as a pale yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$), δ: 7.64-7.69 (m, 4 H, **Ph**Si), 7.37-7.44 (m, 6 H, **Ph**Si), 5.81 (s, 1 H, C=C**H**), 5.53 (d, 1 H, J = 6.6 Hz, C**H**OH), 4.58 (dd, 1 H, J = 15.1, 2.0 Hz,

	$SiOCH_AH_B$), 4.32 (dd, 1 H, J = 15.1, 1.7 Hz, $SiOCH_AH_B$), 2.90-2.94 (m, 2 H, SCH_2CH_2Cy), 1.47-1.51 (m, 2 H, SCH_2CH_2Cy), 1.20 (s, 9 H, $C(CH_3)_3$), 1.06 (s, 9 H, $SiC(CH_3)_3$), 0.81 (m, 2 H, two of **Cy**), 0.63 (m, 2 H, two of **Cy**), 0.22 (s, 9 H, $Si(CH_3)_3$).
FTIR (neat), cm^{-1}:	3497 (br, OH), 3078 (w), 2964 (m), 2133 (w), 1677 (s, C=O), 1428 (m), 1250 (m), 1111 (s), 955 (m), 853 (s), 703 (s).
MS (EI), m/z (%base):	629 (3), 613 (6), 273 (12), 199 (54).
HRMS (EI):	Calcd for $C_{37}H_{49}O_3SSi_2$ ($M-H^+$): 629.2941 Found: 629.2906
TLC (10% EtOAc in Hexanes), R_f:	Aldehyde **48**: 0.59 Cyclopropane Alcohol **74**: 0.23



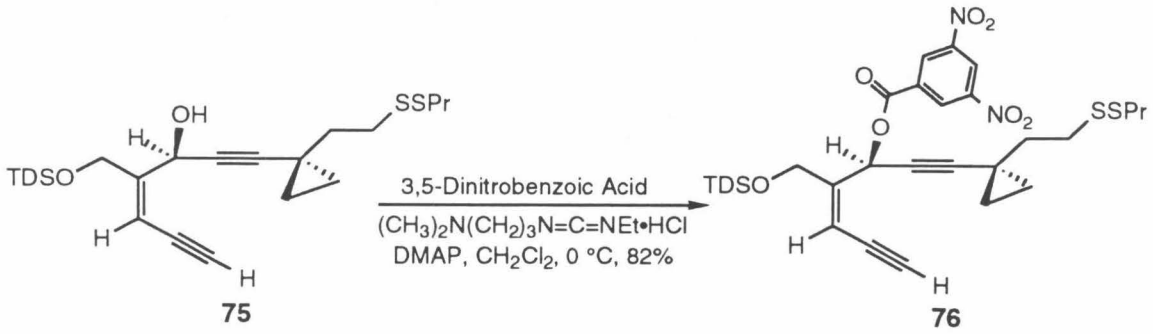
74 **75**

Cyclopropane Disulfide **75**.

Sodium hydroxide (50% aqueous, 0.5 mL) was added via pipette to an ice-cooled solution of cyclopropane alcohol **74** (1.20 g, 1.90 mmol) in a mixture of tetrahydrofuran, methanol and propyl disulfide (4:1:1, respectively, 18 mL). The yellow reaction mixture was stirred at 0 °C for 4 h, then was partitioned between water (100 mL), and a 1:1 mixture of ethyl acetate and hexanes (3 x 75 mL). The combined organic layers were dried over sodium sulfate and were concentrated. Purification of the residue by flash column chromatography (gradient elution: toluene in hexanes, 60→90%) provided cyclopropane disulfide **75** (0.66 g, 64%) as a pale yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$), δ: 7.66-7.74 (m, 4 H, **Ph**Si), 7.38-7.46 (m, 6 H, **Ph**Si), 5.77 (d, 1 H, J = 2.0 Hz, C=C**H**), 5.57 (d, 1 H, J = 6.1 Hz, C**H**OH), 4.60 (d, 1 H, J = 15.1 Hz, $SiOCH_AH_B$), 4.34 (d, 1 H, J = 15.1 Hz, $SiOCH_AH_B$), 3.23 (d, 1 H, J = 2.4 Hz, C≡C**H**), 2.77-2.82 (m, 2 H, $SSCH_2CH_2Cy$), 2.63 (t, 2 H, J = 7.3 Hz, $SSCH_2CH_2CH_3$), 1.65-1.72 (m, 4 H, $SSCH_2CH_2Cy$ and $SSCH_2CH_2CH_3$), 1.09 (s, 9 H,

	$SiC(CH_3)_3$), 0.98 (t, 3 H, J = 7.3 Hz, $SSCH_2CH_2CH_3$), 0.82-0.84 (m, 2 H, two of **Cy**), 0.62-0.63 (m, 2 H, two of **Cy**).
FTIR (neat), cm^{-1}:	3444 (br, OH), 3287 (m, C≡CH), 3071 (w), 2960 (s), 2237 (m), 1472 (m), 1428 (s), 1113 (s), 823 (s), 702 (s).
MS (EI), m/z (%base):	548 (17), 473 (47), 416 (56), 395 (65), 291 (31), 217 (35), 199 (100).
HRMS (EI):	Calcd for $C_{32}H_{40}O_2S_2Si$ (M^+): 548.2239 Found: 548.2228
TLC (10% EtOAc in Hexanes), R_f:	Cyclopropane Alcohol **74**: 0.27 Cyclopropane Disulfide **75**: 0.16



Cyclopropane Dinitrobenzoate **76.**

3,5-Dinitrobenzoic acid (0.19 g, 0.89 mmol, 10.0 equiv), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.171 g, 0.89 mmol, 10.0 equiv), and 4-dimethylaminopyridine (0.054 g, 0.44 mmol, 5.0 equiv) were added sequentially to a solution of cyclopropane disulfide **75** (0.049 g, 0.089 mmol, 1 equiv) in dichloromethane (5 mL) at 0 °C. The resulting yellow suspension was stirred at 0 °C for 30 min, then was partitioned between water (20 mL) and a 1:1 mixture of ethyl acetate and hexanes (3 x 50 mL). The combined organic layers were dried over sodium sulfate and were concentrated. The residue was purified by flash column chromatography (3% ethyl acetate in hexanes) to give cyclopropane dinitrobenzoate **76** (0.054 g, 82%) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$), δ: 9.20 (t, 1 H, J = 2.2 Hz, Ph$(NO_2)_2\mathbf{H}_p$), 9.01 (d, 2 H, J = 2.2 Hz, Ph$(NO_2)_2\mathbf{H}_o$), 7.64-7.70 (m, 4 H, **Ph**Si), 7.35-7.45 (m, 6 H, **Ph**Si), 6.78 (s, 1 H, C=CC**H**(OR)Cy), 6.18 (d, 1 H, J = 2.2 Hz,

C=C**H**), 4.60 (d, 1 H, J = 17.6 Hz, SiOC$\mathbf{H}_A$H$_B$), 4.48 (d, 1 H, J = 17.6 Hz, SiOCH$_A$**H**$_B$), 3.36 (d, 1 H, J = 1.7 Hz, C≡C**H**), 2.72 (t, 2 H, J = 7.8 Hz, SSC**H**$_2$CH$_2$Cy), 2.60 (t, 2 H, J = 7.2 Hz, SSC**H**$_2$CH$_2$CH$_3$), 1.62-1.69 (m, 4 H, SSCH$_2$C**H**$_2$Cy and SSCH$_2$C**H**$_2$CH$_3$), 1.08 (s, 9 H, SiC(C**H**$_3$)$_3$), 0.96 (t, 3 H, J = 7.3 Hz, SSCH$_2$CH$_2$C**H**$_3$), 0.79-0.81 (m, 2 H, two of **Cy**), 0.62-0.63 (m, 2 H, two of **Cy**).

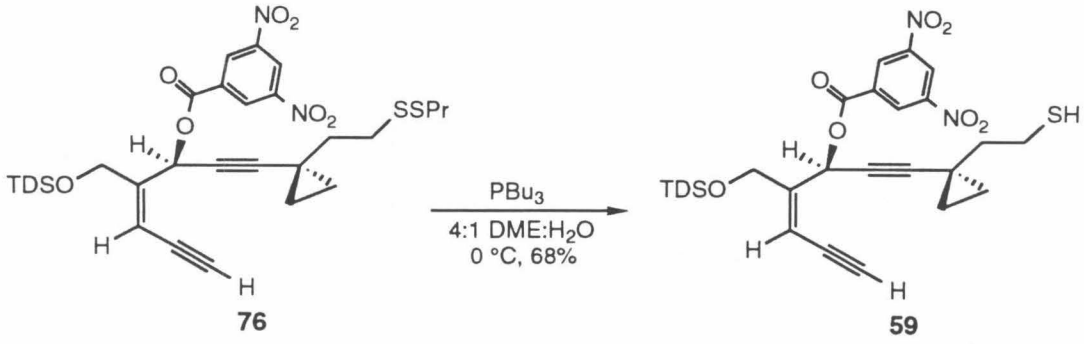
FTIR (neat), cm^{-1}: 3289 (m), 3072 (w), 2959 (m), 2241 (m), 1738 (s, C=O), 1629 (m), 1547 (s, NO_2), 1428 (m), 1344 (s, NO_2), 1266 (s), 1113 (m), 703 (m).

MS (EI), m/z (%base): 456 (1), 393 (16), 212 (12), 199 (100), 69 (22).

HRMS (EI): Calcd for $C_{39}H_{42}N_2O_7S_2Si$ (M^+): 742.2203
Found: 742.2246

Elemental Analysis: Calcd for $C_{39}H_{42}N_2O_7S_2Si$: C, 63.05, H, 5.70, N, 3.77
Found: C, 63.20, H, 5.91, N, 3.63

TLC (10% EtOAc in Hexanes), R_f: Cyclopropane Disulfide **75**: 0.13
Cyclopropane Dinitrobenzoate **76**: 0.25



Cyclopropane Thiol **59**.

Tributylphosphine (0.167 mL, 0.67 mmol, 10.0 equiv) was added via syringe to a deoxygenated, ice-cooled solution of cyclopropane dinitrobenzoate **76** (0.050 g, 0.67 mmol, 1 equiv) in a 4:1 mixture of 1,2-dimethoxyethane and water (5 mL). The resulting purple solution was stirred at 0 °C for 30 min, then was partitioned between water (50 mL) and a 1:1 mixture of ethyl acetate and hexanes (3 x 50 mL). The combined organic layers were dried over sodium sulfate and were concentrated. The residue was purified by flash column chromatography (5% ethyl acetate in hexanes) to give cyclopropane thiol **59** (0.031 g, 68%) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$), δ: 9.20 (t, 1 H, J = 2.2 Hz, $Ph(NO_2)_2\mathbf{H}_p$), 9.02 (d, 2 H, J = 2.2 Hz, $Ph(NO_2)_2\mathbf{H}_o$), 7.64-7.70 (m, 4 H, **Ph**Si), 7.34-7.45 (m, 6 H, **Ph**Si), 6.78 (s, 1 H, C=CC**H**(OR)Cy), 6.18 (d, 1 H, J = 2.2 Hz, C=C**H**), 4.59 (d, 1 H, J = 16.7 Hz, $SiOC\mathbf{H}_AH_B$), 4.48 (d, 1 H, J = 16.7 Hz, $SiOCH_A\mathbf{H}_B$), 3.36 (d, 1 H, J = 2.2 Hz, C≡C**H**), 2.54-2.60 (m, 2 H,

HSC**H**$_2$CH$_2$Cy), 1.52-1.57 (m, 2 H, HSCH$_2$C**H**$_2$Cy), 1.33 (t, 1 H, J = 7.9 Hz, S**H**), 1.08 (s, 9 H, SiC(C**H**$_3$)$_3$), 0.79-0.81 (m, 2 H, two of **Cy**), 0.62-0.63 (m, 2 H, two of **Cy**).

FTIR (neat), cm^{-1}: 3289 (w, C≡CH), 3097 (w), 2931 (m), 2236 (w), 1739 (m), 1547 (s, NO_2), 1428 (m), 1344 (s, NO_2), 1265 (m), 1157 (m), 1113 (m), 703 (m).

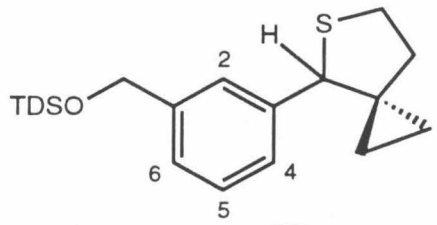
MS (EI), m/z (%base): 669 (2), 255 (34), 211 (100), 195 (33), 167 (90).

HRMS (EI): Calcd for $C_{36}H_{37}N_2O_7SSi$ (MH^-): 669.2091
Found: 669.2073

TLC (Toluene), R_f: Cyclopropane Dinitrobenzoate **76**: 0.61
Cyclopropane Thiol **59**: 0.56

General Cyclization Procedure (Cyclopropane Thiol **59**).

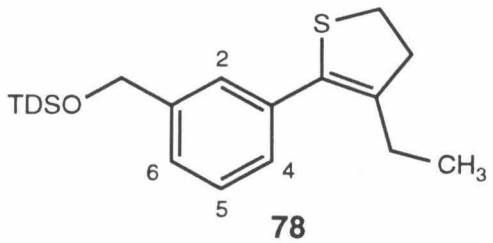
Triethylamine (5 equiv) was added to a deoxygenated solution of cyclopropane thiol **59** (0.010 M) and trapping agent (1,4-cyclohexadiene or methanol, each 4.0 M) in dimethyl sulfoxide at 23 °C. After stirring at 23 °C for 10 h, each reaction mixture was partitioned between water (50 mL) and a 1:1 mixture of ethyl acetate and hexanes (3 x 50 mL). The combined organic layers were dried over sodium sulfate and were concentrated. The residue was purified by preparative thin-layer chromatography (3-5% ethyl acetate in hexanes, 2 elutions). Product yields were determined prior to chromatography by addition of (*Z*)-1,2-dichloroethylene as an internal standard and ^{1}H NMR analysis.



77

Spirocyclopropyltetrahydrothiophene Derivative **77.**

^{1}H NMR (400 MHz, $CDCl_3$), δ:	7.69-7.70 (m, 4 H, **Ph**Si), 7.35-7.68 (m, 10 H, **Ph**Si, **Ar**-2, **Ar**-4, **Ar**-5, and **Ar**-6), 4.77 (s, 2 H, $SiOCH_2$), 4.15 (s, 1 H, SCHCy), 3.02-3.15 (m, 2 H, SCH_2CH_2), 2.15-2.21 (m, 1 H, one of SCH_2CH_2), 1.86-1.93 (m, 1 H, one of SCH_2CH_2), 1.09 (s, 9 H, $SiC(CH_3)_3$), 0.58-0.64 (m, 1 H, one of **Cy**), 0.41-0.52 (m, 3 H, three of **Cy**).
FTIR (neat), cm^{-1}:	3070 (w), 3000 (w), 2928 (m), 1427 (m), 1110 (s), 1073 (m), 859 (m), 740 (m), 701 (s).
MS (EI), m/z (%base):	458 (4), 433 (100), 401 (18), 325 (15), 285 (28), 203 (18).
HRMS (EI):	Calcd for $C_{29}H_{34}OSSi$ (M^+): 458.2100 Found: 458.2106
TLC (3% EtOAc in Hexanes), R_f:	Spirocyclopropyltetrahydrothiophene Derivative **77**: 0.70 (UV)



78

Ring-Opened Sulfide **78.**

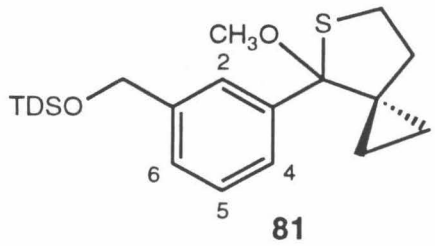
^{1}H NMR (400 MHz, $CDCl_3$), δ: 7.68-7.71 (m, 4 H, **Ph**Si), 7.24-7.43 (m, 10 H, **Ph**Si, **Ar**-2, **Ar**-4, **Ar**-5, and **Ar**-6), 4.76 (s, 2 H, $SiOC\mathbf{H}_2$), 3.23 (t, 2 H, J = 8.6 Hz, $SC\mathbf{H}_2CH_2$), 2.96 (t, 2 H, J = 8.6 Hz, $SCH_2C\mathbf{H}_2$), 2.22 (q, 2 H, J = 7.6 Hz, $C\mathbf{H}_2CH_3$), 1.09 (s, 9 H, $SiC(C\mathbf{H}_3)_3$), 1.03 (t, 3 H, J = 7.6 Hz, $CH_2C\mathbf{H}_3$).

FTIR (neat), cm^{-1}: 3067 (w), 2964 (m), 2933 (m), 1426 (m), 1108 (s), 1077 (m), 821 (m), 703 (s).

MS (EI), m/z (%base): 458 (52), 401 (53), 371 (14), 323 (100), 279 (6), 199 (22).

HRMS (EI): Calcd for $C_{29}H_{34}OSSi$ (M^+): 458.2100
Found: 458.2101

TLC (3% EtOAc in Hexanes), R_f: Ring-Opened Sulfide **78**: 0.77 (UV)



81

Spirocyclopropyltetrahydrothiophene Derivative **81.**

^{1}H NMR (400 MHz, $CDCl_3$), δ: 7.68-7.70 (m, 4 H, **Ph**Si), 7.57 (s, 1 H, **Ar**-2), 7.35-7.43 (m, 9 H, **Ph**Si, **Ar**-4, **Ar**-5, and **Ar**-6), 4.77 (s, 2 H, $SiOC\mathbf{H}_2$), 3.26 (s, 3 H, $C\mathbf{H}_3O$), 3.16-3.23 (m, 1 H, one of $SC\mathbf{H}_2CH_2$), 2.97-3.01 (m, 1 H, one of $SC\mathbf{H}_2CH_2$), 2.76-2.84 (m, 1 H, one of $SCH_2C\mathbf{H}_2$), 1.67-1.71 (m, 1 H, one of $SCH_2C\mathbf{H}_2$), 1.10 (s, 9 H, $SiC(C\mathbf{H}_3)_3$), 0.60-0.69 (m, 2 H, two of **Cy**), 0.19-0.24 (m, 1 H, one of **Cy**), –0.12 to –0.17 (m, 1 H, one of **Cy**).

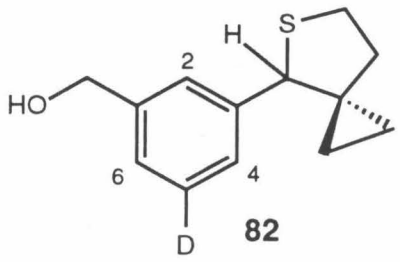
FTIR (neat), cm^{-1}: 3071 (w), 2999 (m), 2930 (m), 2857 (m), 1428 (m), 1112 (s), 1076 (s), 824 (m), 701 (s).

MS (EI), m/z (%base): 488 (10), 457 (22), 401 (18), 323 (100), 289 (6), 199 (27).

HRMS (EI):	Calcd for $C_{30}H_{36}O_2SSi$ (M^+): 488.2210
	Found: 488.2235
TLC (5% EtOAc in Hexanes), R_f:	Spirocyclopropyltetrahydrothiophene Derivative **81**: 0.41 (UV)

General Desilylation Procedure.

Tetrabutylammonium fluoride (2.0 mL, 1.0 M in tetrahydrofuran) was added to a solution of silyl ether (0.5-1.0 mg) in tetrahydrofuran (2 mL) at 23 °C. After stirring at 23 °C for 30 min, each reaction mixture was partitioned between water (25 mL) and a 1:1 mixture of ethyl acetate and hexanes (3 x 25 mL). The combined organic layers were dried over sodium sulfate and were concentrated. The residue was purified by preparative thin-layer chromatography (20% ethyl acetate in hexanes). Using the above procedure, alcohols **82** and **83** were prepared from spirotetrahydrothiophene derivatives **77** and **81**, respectively.



82

Cyclopropane Alcohol **82** (d_1).

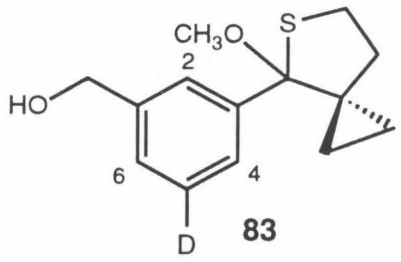
^{1}H NMR (500 MHz, CD_2Cl_2), δ: 7.55 (s, 1 H, **Ar**-2), 7.45 (s, 1 H, **Ar**-4 or **Ar**-6), 7.27 (s, 1 H, **Ar**-4 or **Ar**-6), 4.67 (d, 2 H, J = 5.8 Hz, HOC**H**$_2$), 4.15 (s, 1 H, SC**H**Cy, 3.17-3.23 (m, 1 H, one of SC**H**$_2$CH$_2$), 2.96-3.00 (m, 1 H, one of SC**H**$_2$CH$_2$), 2.72-2.78 (m, 1 H, one of SCH$_2$C**H**$_2$), 1.75 (t, 1 H, J = 5.8 Hz, O**H**), 1.67-1.72 (m, 1 H, one of SCH$_2$C**H**$_2$), 0.56-0.64 (m, 2 H, two of **Cy**), 0.21-0.25 (m, 1 H, one of **Cy**), –0.17 to –0.21 (m, 1 H, one of **Cy**).

FTIR (neat), cm^{-1}: 3360 (br, OH), 3079 (w), 2931 (m), 1428 (m), 1153 (w), 1020 (m), 860 (s), 677 (m).

MS (EI), m/z (%base): 220 (10), 189 (32), 167 (16), 135 (25).

HRMS (EI): Calcd for $C_{13}H_{15}DOS$ (M^+): 220.1032
Found: 220.1055

TLC (20% EtOAc in Hexanes), R_f: Cyclopropane Alcohol **82** (d_1): 0.17 (UV)



83

Cyclopropane Alcohol **83** (d_1).

^{1}H NMR (500 MHz, CD_2Cl_2), δ: 7.55 (s, 1 H, **Ar**-2), 7.45 (s, 1 H, **Ar**-4 or **Ar**-6), 7.27 (s, 1 H, **Ar**-4 or **Ar**-6), 4.66 (d, 2 H, J = 5.7 Hz, HOC**H**$_2$), 3.17-3.23 (m, 1 H, one of SC**H**$_2$CH$_2$), 3.22 (s, 3 H, OC**H**$_3$), 2.96-3.00 (m, 1 H, one of SC**H**$_2$CH$_2$), 2.72-2.78 (m, 1 H, one of SCH$_2$C**H**$_2$), 1.75 (t, 1 H, J = 5.8 Hz, **OH**), 1.67-1.72 (m, 1 H, one of SCH$_2$C**H**$_2$), 0.56-0.64 (m, 2 H, two of **Cy**), 0.21-0.25 (m, 1 H, one of **Cy**), –0.17 to –0.21 (m, 1 H, one of **Cy**).

FTIR (neat), cm^{-1}: 3369 (br, OH), 3079 (w), 2931 (m), 1426 (m), 1151 (w), 1075 (s), 1020 (m), 888 (s), 677 (m).

MS (EI), m/z (%base): 253 (10), 222 (100), 219 (91), 203 (8), 189 (9), 173 (8), 143 (11).

HRMS (EI):	Calcd for $C_{14}H_{17}DO_2S$ (M^+): 253.1327
	Found: 253.1320
TLC (20% EtOAc in Hexanes), R_f:	Cyclopropane Alcohol **83** (d_1): 0.20 (UV)

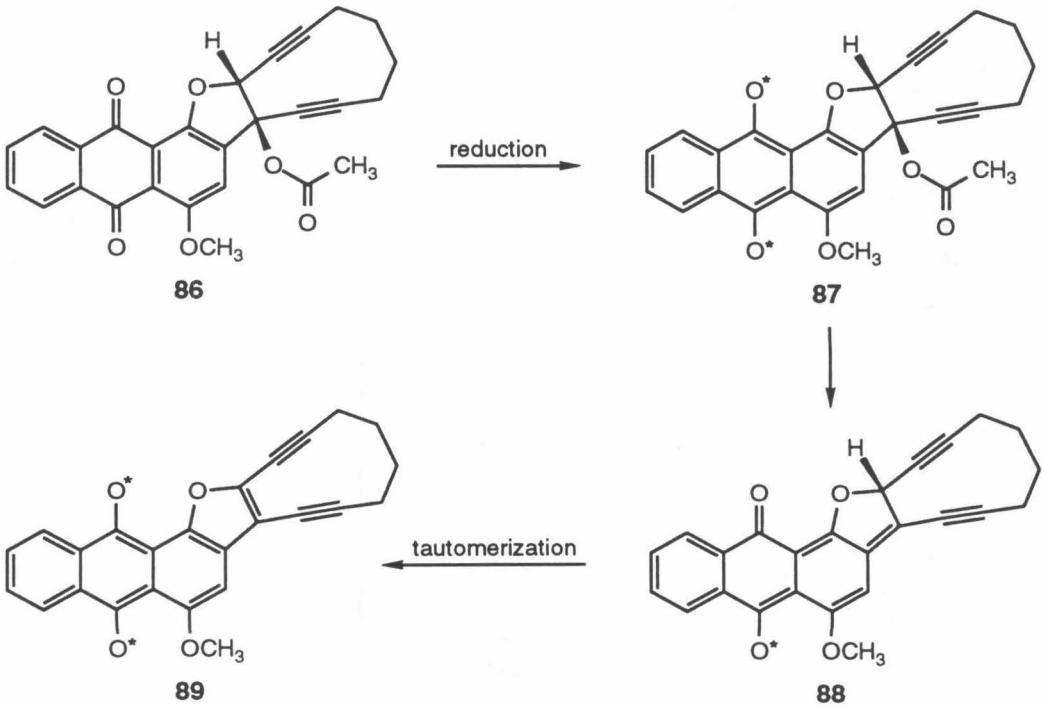
Chapter 2

Design and Synthesis of a System for Enediyne Formation by Anthraquinone Reductive Activation

Background

In vitro experiments conducted with the natural antitumor agents calichemicin, esperamicin and dynemicin support, as a common mechanistic feature, the cyclization of a carbocyclic (*Z*)-enediyne to form a highly reactive 1,4-dehydrobenzene intermediate (Bergman cyclization) (cf. introduction).[12-14] In each case, a chemical activation step leads to a structural change within the antibiotic that accelerates Bergman cyclization. In an alternative strategy for formation of a 1,4-dehydrobenzene intermediate by reductive activation, the anthraquinone-cyclic diacetylene conjugate **86** was conceived as a masked (*Z*)-enediyne. This compound was envisioned to enter the reaction cascade outlined in Scheme XV upon reduction of the anthraquinone ring (asterisks are used to accommodate the possible involvement of either semiquinone or hydroquinone intermediates). Central to this plan is the notion that spontaneous aromatization of **86** would be slow due to strain

Scheme XV

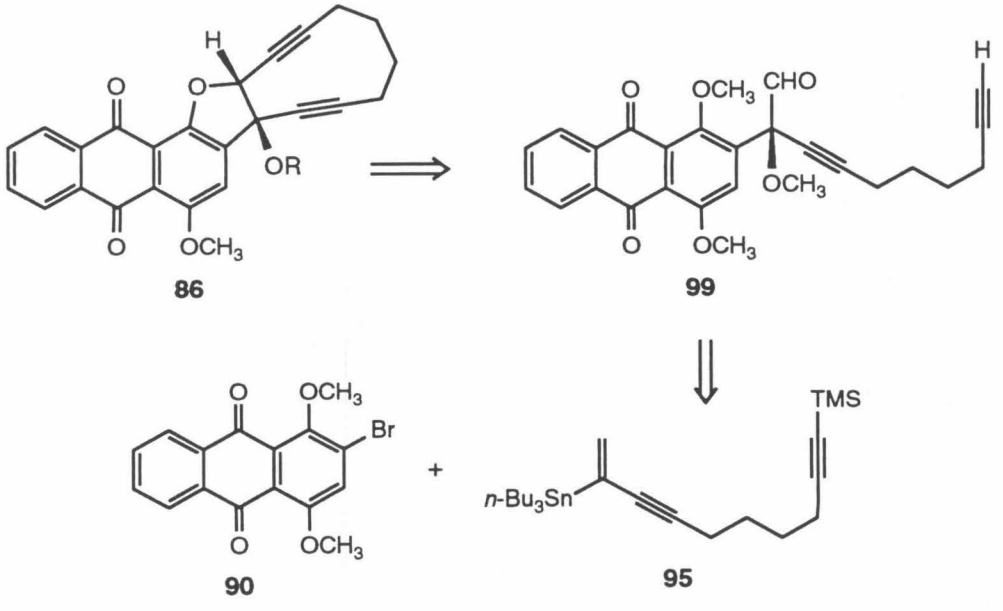


considerations. Reductive elimination (**87**→**88**) and tautomerization (**88**→**89**), steps related to the proposed initial events in the activation of dynemicin,[14] adriamicin,[63] and mitomycin C,[64] then provide a pathway for generation of the strained (Z)-enediyne **89**.

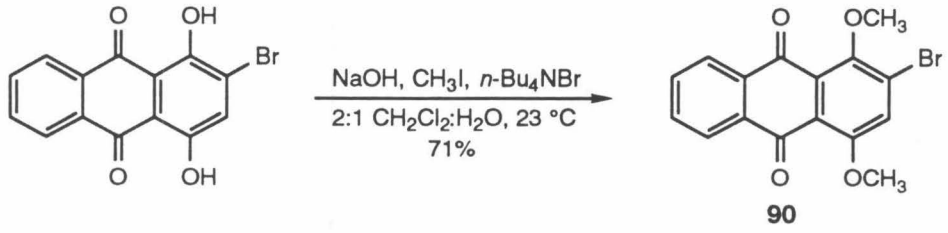
Initial Studies-Derivitization of Anthraquinones via Palladium-Mediated Couplings

The primary challenge in the synthesis of diyne **86** was to devise a scheme for the construction of the strained cyclodecadiyne ring that was compatible with the highly reactive anthraquinone functional group. Toward this end, the strained ring was envisioned to be formed intramolecularly by metalation of acetylene-aldehyde **99**. This substrate would, in turn, be derived from the vinylstannane **95** and the bromo-anthraquinone **90** via a palladium-mediated coupling reaction.[65] The feasibility of such a coupling reaction was therefore examined.

Treatment of 2-bromo-1,4-dihydroxyanthraquinone[66] with sodium hydroxide (4 equiv) and a large excess of iodomethane (80 equiv) under phase transfer conditions (4.0

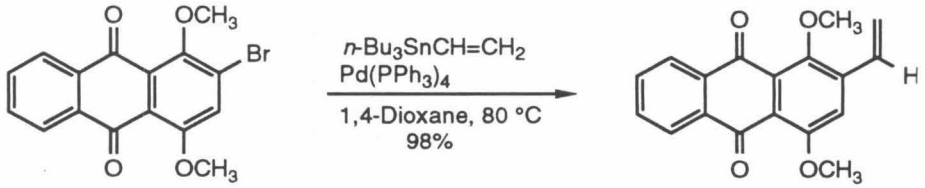


equiv *n*-Bu_4NBr, 2:1 dichloromethane-water, 23 °C, 2 days) provided 2-bromo-1,4-dimethoxyanthraquinone (**90**) in 71% yield after purification by flash column



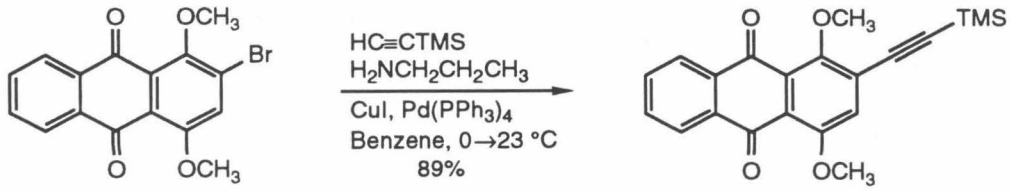
90

chromatography.[67] This compound was shown to undergo a variety of palladium-mediated transformations to provide the corresponding coupled products in good yields. For example, reaction of **90** with vinyltributyltin (1.1 equiv) and tetrakis(triphenylphosphine)palladium(0) (0.05 equiv) in deoxygenated 1,4-dioxane at 80 °C for 12 h



90 **91**

afforded the vinyl anthraquinone **91** in 98% yield following silica gel chromatography. In another application, anaerobic treatment of **90** with (trimethylsilyl)acetylene (2.0 equiv), *n*-propylamine (5.0 equiv), cuprous iodide (0.15 equiv) and tetrakis(triphenylphosphine)palladium(0) (0.05 equiv) in benzene at 23 °C for 2 h provided the coupled acetylene product (**92**) in 89% yield. The above examples demonstrated the use of



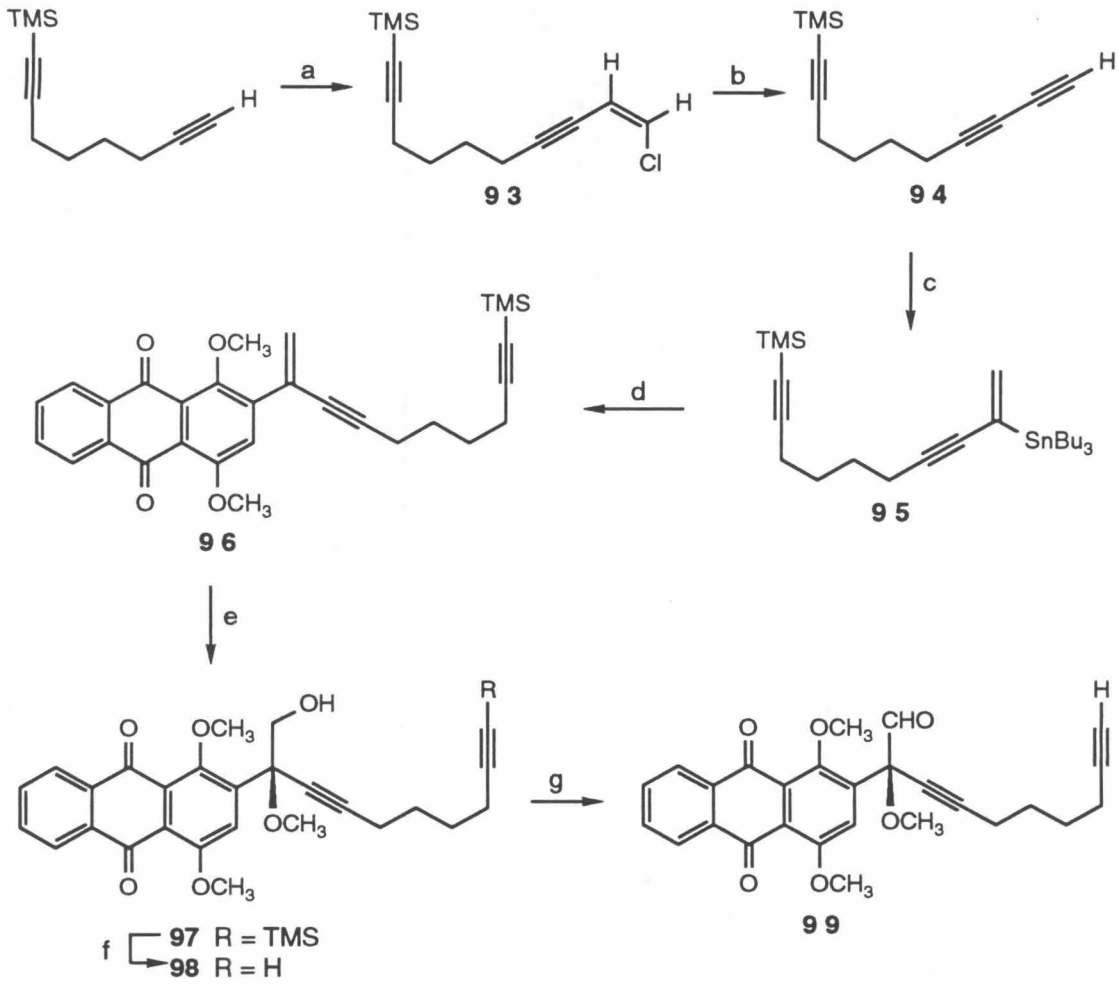
90 **92**

palladium-catalyzed transformations to functionalize the anthraquinone ring, and supported the coupling of **90** and **95** as a viable synthetic step in the preparation of **99**.

The synthesis of the aldehyde **99** is illustrated in Scheme XVI. Conversion of 1-(trimethylsilyl)-1,7-octadiyne[68] to the triyne **94** was accomplished by a modification of the method originally developed by Kende and Smith.[25a,69] Thus, reaction of 1-(trimethylsilyl)-1,7-octadiyne[68] with (*Z*)-1,2-dichloroethylene (2.0 equiv), *n*-propylamine (5.0 equiv), cuprous iodide (0.15 equiv) and tetrakis(triphenylphosphine)palladium(0) (0.05 equiv) in deoxygenated benzene at 23 °C provided the (*Z*)-vinyl chloride **93** in 82% yield.[25a] Treatment of a solution of **93** in tetrahydrofuran with *n*-butyllithium (1.95 equiv) at -78 °C and subsequent warming to -20 °C afforded triyne **94** in 73% yield following purification by flash column chromatography.[25a] Slightly less than a stoichiometric amount of *n*-butyllithium was utilized in the transformation of **93** to **94** due to the apparent sensitivity of the product acetylene toward excess organolithium reagent. Triyne **94** was treated with tributyltin hydride (1.2 equiv) in tetrahydrofuran in the presence of a catalytic amount of bis(triphenylphosphine)palladium(II) chloride (0.02 equiv) at 23 °C to produce, after silica gel chromatography, the vinylstannane **95** in 55% yield.[70]

Heating 2-bromo-1,4-dimethoxyanthraquinone (**90**, 1 equiv), vinylstannane **95** (1.2 equiv), and tetrakis(triphenylphosphine)palladium(0) (0.05 equiv) in deoxygenated 1,4-dioxane at 90 °C for 18 h afforded the coupled product (anthraquinone **96**) in 51% yield. The olefin present in **96** was transformed to the corresponding epoxide by treatment with dimethyldioxirane[71] (1.2 equiv) in dichloromethane at 0 °C. Interestingly, a similar (but lower yielding) epoxidation reaction occurred when solutions of **96** were exposed to the air for several days. The intermediate epoxide produced by oxidation of **96** was not isolated, but was instead subjected to methanolysis under mildly acidic conditions (3:1 methanol-dichloromethane, 0.20 M HCl, 0 °C) to provide the alcohol **97**

Scheme XVI



Reagents and conditions (TMS = $Si(CH_3)_3$): (a) 2.0 equiv (Z)-1,2-dichloroethylene, 5.0 equiv *n*-$PrNH_2$, 0.15 equiv CuI, 0.05 equiv $Pd(PPh_3)_4$, Benzene, 23 °C, 5 h, 82%; (b) 1.95 equiv *n*-BuLi, THF, -78→-20 °C, 2 h, 73%; (c) 1.2 equiv *n*-Bu_3SnH, 0.02 equiv $PdCl_2(PPh_3)_2$, THF, 23 °C, 10 min, 55%; (d) 1.0 equiv **90**, 1.2 equiv **95**, 0.05 equiv $Pd(PPh_3)_4$, 1,4-Dioxane, 90 °C, 18 h, 51%; (e) 1.2 equiv dimethyldioxirane, CH_2Cl_2, 0 °C, 20 min; 0.20 M. HCl, 3:1 CH_3OH:CH_2Cl_2, 0 °C, 2 h, 53% from **96**; (f) 2.0 equiv KF•$2H_2O$, CH_3CN, 23 °C, 4 days, 60%; (g) 2.2 equiv $(COCl)_2$, 4.4 equiv DMSO, 10.0 equiv Et_3N, CH_2Cl_2, -78→0 °C, 81%.

in 53% overall yield from **96** following purification by flash column chromatography. Removal of the trimethylsilyl protecting group present in **97** proceeded slowly ($KF•2H_2O$, CH_3CN, 23 °C, 4 days), but eventually provided the acetylene **98** in 60% yield. Acetylene **97** proved to be sensitive toward other fluoride sources and toward strongly basic conditions, preventing the application of potentially more rapid deprotection methods (e.g., $KF•2H_2O$ in CH_3OH, *n*-Bu_4NF, NaOH, $Et_3N•3HF$, HF•pyridine). Swern oxidation of **98** (oxalyl chloride (2.2 equiv), dimethyl sulfoxide (4.4 equiv), triethylamine (10.0 equiv), dichloromethane, -78→0 °C) proceeded cleanly to provide the desired cyclodecadiyne precursor (aldehyde **99**) in 81% yield following purification on silica gel.[43]

All attempts to convert **99** to the cyclized compound **100** met with failure. Aldehyde **99** was treated with a variety of bases: lithium bis(trimethylsilyl)amide, both in the presence and absence of cerium(III) chloride,[37] potassium bis(trimethylsilyl)amide, lithium tetramethylpiperidide,[72] and *tert*-butyllithium, in several solvents

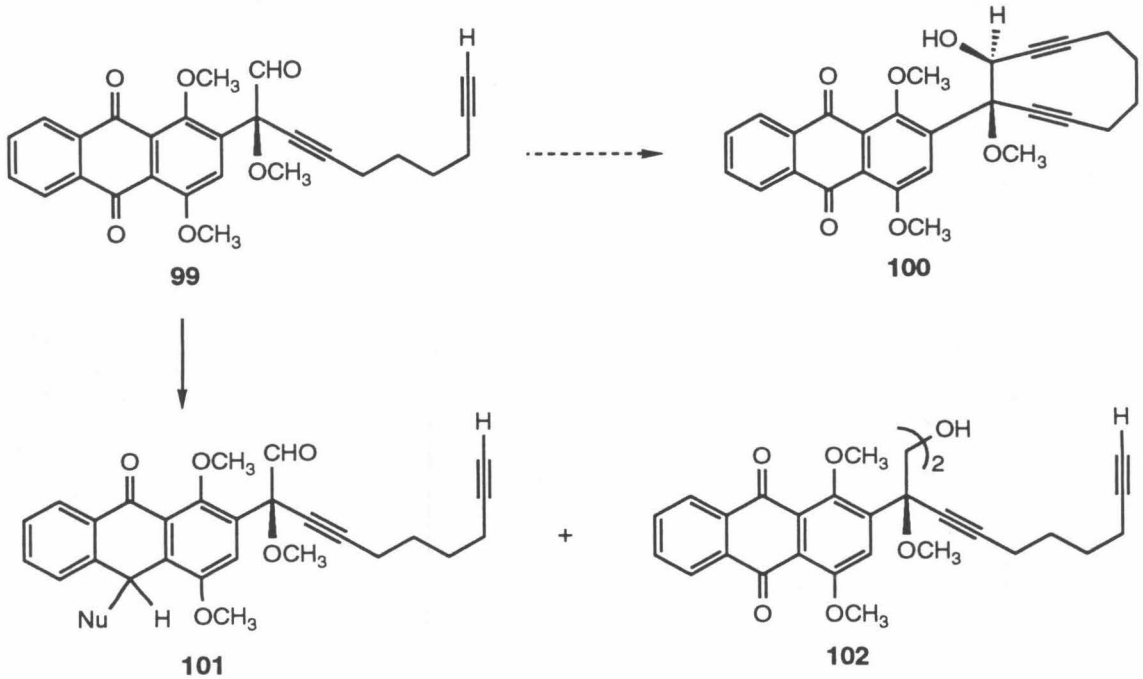


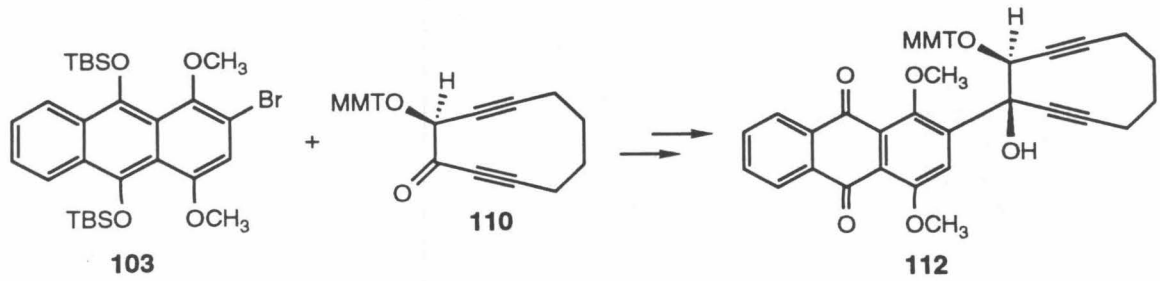
Table VIII. Attempts to Cyclize **99**.

Entry	Base[a]	Solvent[b]	T (°C)	Entry	Base[a]	Solvent[b]	T (°C)
1	$LiN(TMS)_2$	THF	-78	4	LTMP	THF	-78
2	$LiN(TMS)_2 + CeCl_3$	THF	-78	5	*t*-BuLi	THF	-78
3	$KN(TMS)_2$	Toluene	-78				

[a] TMS = $Si(CH_3)_3$, LTMP = lithium tetramethylpiperadide, [b] THF = tetrahydrofuran.

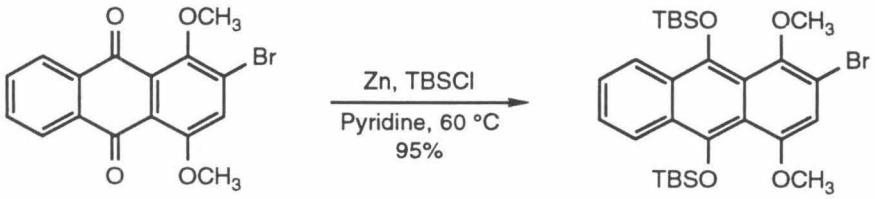
(tetrahydrofuran and toluene) at low temperature (Table VIII). These experiments afforded no isolable quantities of the desired product (**100**), but instead produced compounds which apparently arose from either nucleophilic addition to the anthraquinone ring (**101**, site of addition unknown) or reductive dimerization of the aldehyde moiety (**102**).

Clearly, alternate methods, in addition to those described above, could be applied to potentially produce the cyclized product.[73] However, the number of linear synthetic steps that follow the palladium-catalyzed coupling (Scheme XVI) complicate the preparation of large quantities of the cyclization precursor **99**. This fact, along with the apparent high reactivity of the anthraquinone ring, led to the abandonment of the above synthetic route as a means to prepare diyne **86** in favor of a more convergent approach in which the preformed cyclodecadiynone **110** was coupled with the anthraquinone precursor **103** to form **112**.[74] The feasibility of this approach was demonstrated by the following model studies.



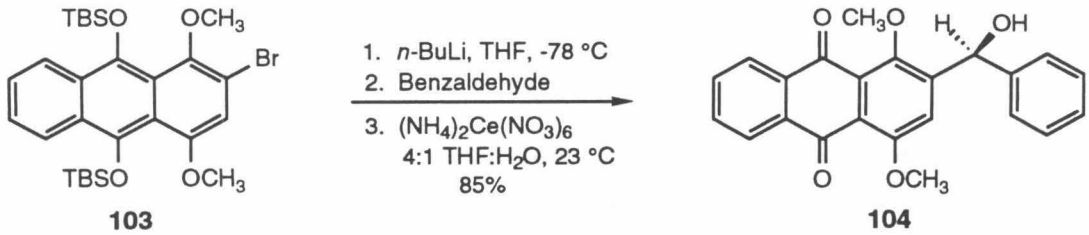
Development of a Nucleophilic Anthraquinone Synthon

Anthracene derivative **103** was prepared by treatment of 2-bromo-1,4-dimethoxy anthraquinone (**90**) with zinc dust (2.2 equiv) and *tert*-butyldimethylsilyl chloride (2.2 equiv) in deoxygenated pyridine at 60 °C (95% yield). This compound is a yellow solid and can be readily purified by flash column chromatography. Subjection of **103** to

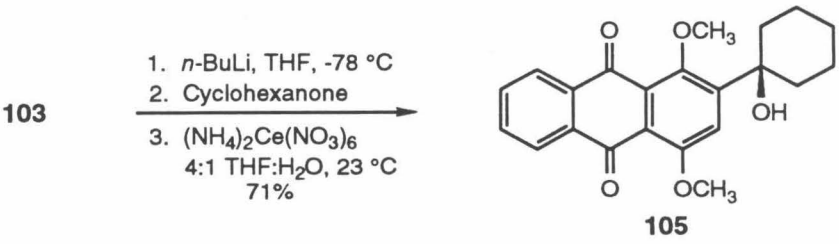


90 **103**

conditions of metal-halogen exchange (1.0 equiv *n*-butyllithium, tetrahydrofuran, -78 °C, 20 min) and addition of benzaldehyde (1.0 equiv) afforded the corresponding addition product which was subsequently oxidized with ceric ammonium nitrate (~ 2.0 equiv) in 20% aqueous tetrahydrofuran at 23 °C to provide, after flash column chromatography, the anthraquinone **104** in 85% overall yield from **103**. Similar trapping of the metalated



103 **104**

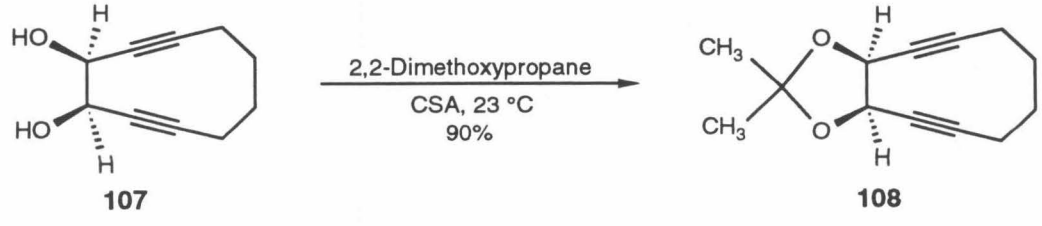


105

intermediate derived from **103** with cyclohexanone provided, after cerium-mediated oxidation, the anthraquinone **105** in 71% yield. The success of the above coupling reactions demonstrated that **103** could function as a nucleophilic anthraquinone synthon and suggested its use in the preparation of **86**.

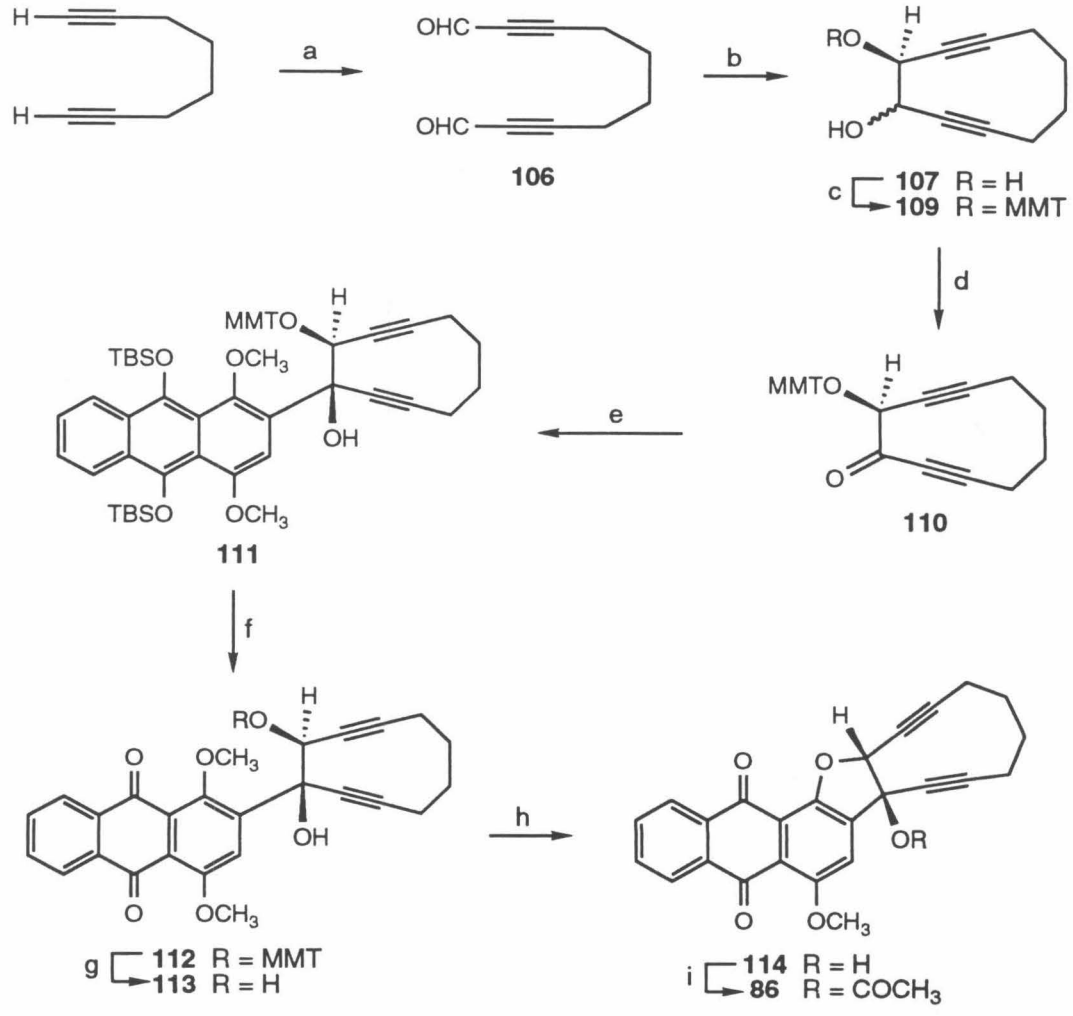
Synthesis and Reactivity of Cyclodecadiyne-Anthraquinone Conjugates

The synthesis of cyclodecadiyne-anthraquinone conjugate **86** is depicted in Scheme XVII.[75] Metalation of 1,7-octadiyne with *n*-butyllithium (2.0 equiv) in tetrahydrofuran at 0 °C followed by the addition of *N,N*-dimethylformamide (DMF, 5.0 equiv), also at 0 °C and warming to 23 °C for 15 h afforded the dialdehyde **106** in 70% yield after flash column chromatography. In an unusual application of the Pedersen pinacolic coupling procedure, dialdehyde **106** (2.0 M in dichloromethane) was added by syringe pump over 3 h to a solution of $[V_2Cl_3(THF)_6]_2[Zn_2Cl_6]$ (1.2 equiv, 0.2 M) and DMF (6.0 equiv) in dichloromethane at 23 °C to provide the diol **107** as a 4:1 mixture of cis and trans isomers in 36% yield.[76-78] The major diol isomer produced in the above experiment was assigned as cis by its conversion to the corresponding acetonide **108** (2,2-dimethoxypropane, catalytic camphorsulfonic acid, 23 °C, 90%). Treatment of a diastereomeric mixture of diols **107** (4:1 cis:trans) with methoxytrityl chloride (2.5 equiv) in dichloromethane containing triethylamine (3.0 equiv) and 4-dimethylaminopyridine (0.08 equiv) afforded monomethoxytrityl (MMT) ether **109** as a 9:1 mixture of cis and trans isomers in 78% yield after flash column chromatography. The alteration of the diastereomer ratio observed



107 **108**

Scheme XVII

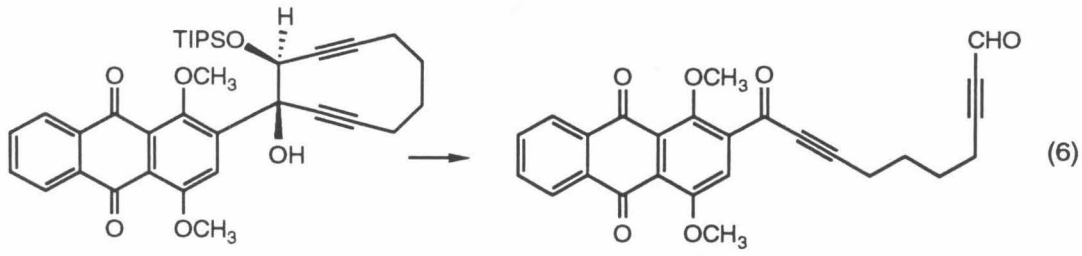


Reagents and conditions (MMT = *p*-$CH_3OPhC(Ph)_2$, TBS = *t*-$Bu(CH_3)_2Si$): (a) 2.0 equiv *n*-BuLi, 5.0 equiv DMF, THF, 0→23 °C, 15 h, 70%; (b) 1.2 equiv $[V_2Cl_3(THF)_6]_2[Zn_2Cl_6]$, 6.0 equiv DMF, CH_2Cl_2, 23 °C, 4 h, 36%; (c) 2.5 equiv MMTCl, 3.0 equiv Et_3N, 0.08 equiv DMAP, CH_2Cl_2, 23 °C, 8 h, 78%; (d) 2.5 equiv Dess-Martin periodinane, CH_2Cl_2, 23 °C, 12 h; (e) 1.0 equiv **103**, 1.0 equiv *n*-BuLi, then 1.0 equiv crude **110**, THF, -78 °C; (f) 2.0 equiv $(NH_4)_2Ce(NO_3)_6$, 4:1 THF:H_2O, 23 °C, 20 min, 36% from **109**; (g) 0.10 M. HCl, 9:1 CH_3CN:H_2O, 0 °C, 1 h, 71%; (h) 3.0 equiv $O(COCF_3)_2$, 5.0 equiv 2,6-lutidine, CH_2Cl_2, -78 °C, 45 min, 82%; (i) 5.0 equiv $O(COCH_3)_2$, 5.0 equiv Et_3N, 0.82 equiv DMAP, CH_2Cl_2, 23 °C, 91%.

in the above experiment is presumably due to the more facile conversion of the trans **109** isomer to the corresponding bis-monomethoxytrityl ether. Subsequent oxidation of diastereomers **109** with the Dess-Martin periodinane (2.5 equiv, dichloromethane, 23 °C) formed the acetylenic ketone **110** in >90% yield and >90% purity.[79] Due to the sensitivity of this product toward silica gel, the following coupling reaction was performed using crude material.

Metalation of anthracene **103** (1.0 equiv, 1.0 equiv *n*-butyllithium, tetrahydrofuran, -78 °C, 20 min) and addition of crude acetylenic ketone **110** (1.0 equiv) afforded the corresponding 1,2-addition product **111**. This alcohol was isolated by extraction and was oxidized without purification employing ceric ammonium nitrate (2.0 equiv) in 20% aqueous tetrahydrofuran at 23 °C providing, after flash column chromatography, the anthraquinone **112** in 36% overall yield from **109**. The stereochemistry of this product was tentatively assigned as shown, on the basis of the presumption that aryllithium attack on **110** occurs opposite the bulky MMT group. The lower yield observed in this coupling reaction, as compared to the preparation of anthraquinones **104** and **105** above, is presumably due to competitive enolization of acetylenic ketone **110**. Attempts to circumvent this problem by forming the corresponding organocerium reagent[37] led to destruction of the anthracene moiety.

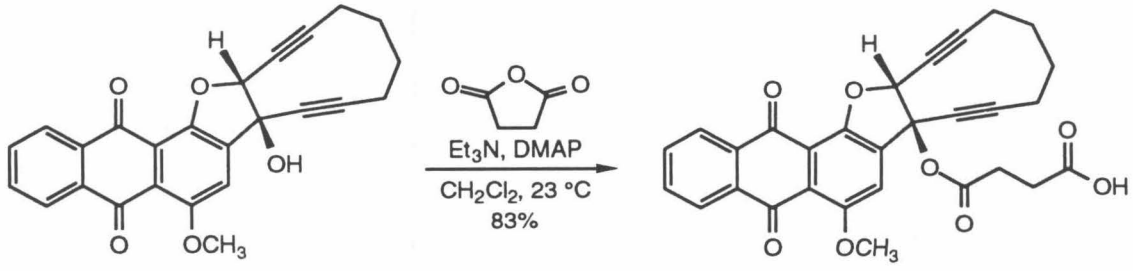
The methoxytrityl protecting group of **112** was removed by treatment with 0.1 M hydrochloric acid in aqueous acetonitrile (9:1 CH_3CN-H_2O) at 0 °C to produce the diol **113** in 71% yield. The MMT group is utilized in the synthesis since previous experiments had demonstrated that the use of related silyl ether protecting groups led to opening of the cyclodecadiyne ring during deprotection (e.g., eq. 6, TIPS = $(i\text{-Pr})_3Si$). The dimethoxytrityl (DMT) ether was unsuitable as it proved to be unstable toward the Dess-Martin oxidation conditions.[80] Treatment of **113** with trifluoromethanesulfonic anhydride (3.0 equiv) and 2,6-lutidine (5.0 equiv) in dichloromethane at -78 °C formed the cyclic



(6)

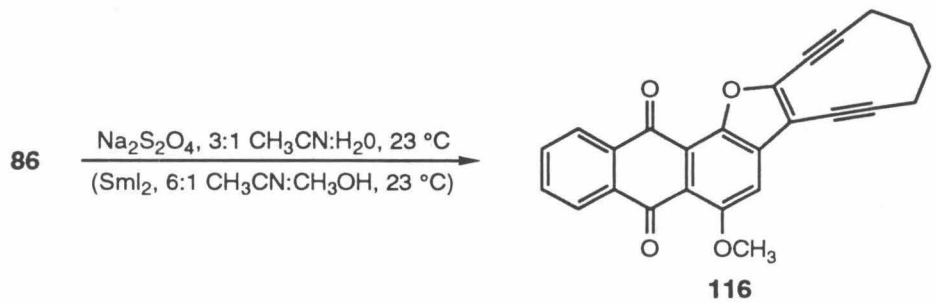
ether **114** in 82% yield after purification on silica gel. This product is believed to arise by intramolecular displacement of the secondary trifluoromethanesulfonic acid ester by methoxyl, followed by nucleophilic demethylation of the resulting oxonium ion by 2,6-lutidine or the trifluoromethanesulfonate anion.[81] Conversion of **114** to diyne **86** was accomplished by treatment with acetic anhydride (5.0 equiv), triethylamine (5.0 equiv) and catalytic 4-dimethylaminopyridine (0.82 equiv) in dichloromethane at 23 °C (91% yield). Diyne **86** is a yellow powder and is stable to routine handling and purification procedures (e.g., silica gel chromatography). The succinate half-ester **115** was prepared by the treatment of **114** with succinic anhydride (10.0 equiv), triethylamine (10.0 equiv) and 4-dimethylaminopyridine (0.25 equiv) in dichloromethane at 23 °C (83% yield). Diyne **115** is also stable to routine handling and purification protocols as well as to basic (pH = 8.0) aqueous buffer solutions, in which the molecule is soluble.

Diynes **86** and **115** were readily converted to (*Z*)-enediyne **116** when subjected to reductive reaction conditions. Thus, anaerobic treatment of **86** with sodium dithionite



114 **115**

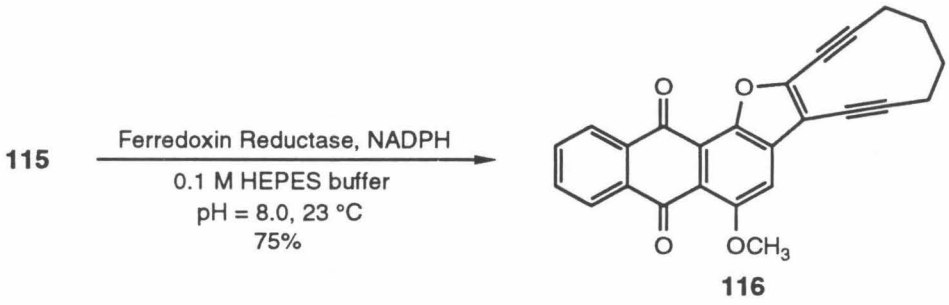
(sodium hydrosulfite, 3.0 equiv) in 25% aqueous acetonitrile at 23 °C rapidly provided the (*Z*)-enediyne **116** (presumably via air-oxidation during workup of a semiquinone or hydroquinone intermediate, cf. Scheme XV) along with several other unidentifiable products. The yields of **116** obtained under these conditions were low and varied



116

considerably from experiment to experiment (15-30%), suggesting that the product **116** might be unstable to the reaction conditions.[82] In contrast, treatment of **86** with samarium diiodide (3.0 equiv) in a deoxygenated mixture of acetonitrile and methanol (6:1, respectively) at 23 °C formed **116** in greater yield (65%). Control experiments established that enediyne formation did not occur to any appreciable extent in the absence of a reducing agent; a solution of diyne **86** in either aqueous acetonitrile or acetonitrile-methanol was stable for at least several days under anaerobic conditions.

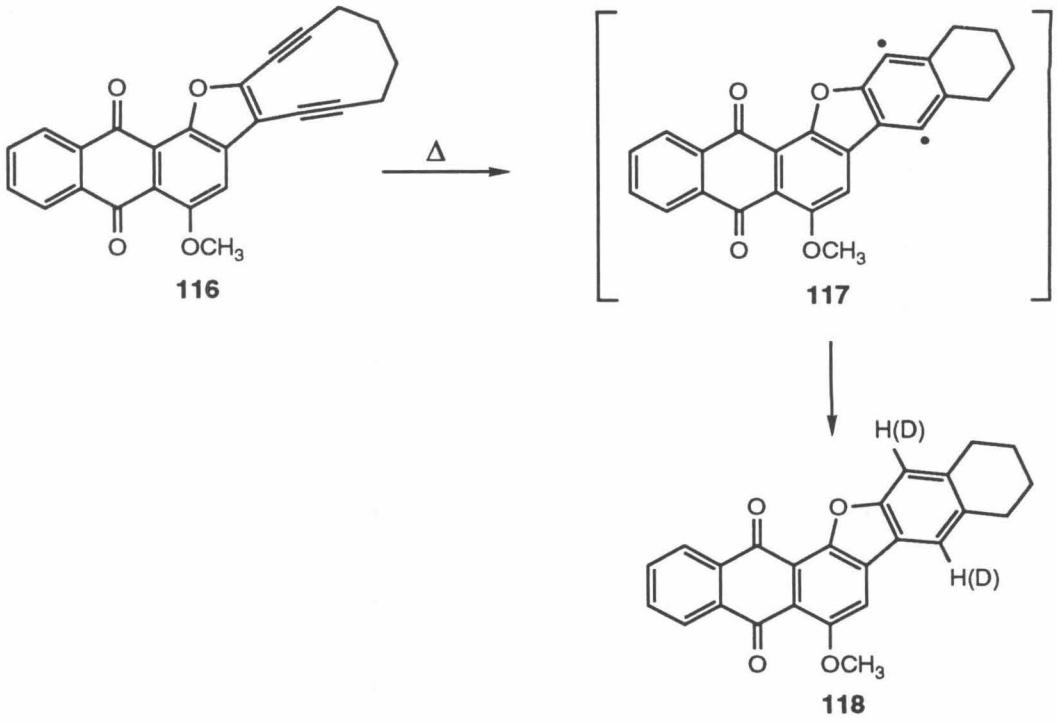
Diyne **115** was also shown to undergo reductive activation, albeit in aqueous media. Anaerobic treatment of **115** with ferredoxin reductase and NADPH, (0.1 M aqueous HEPES buffer, pH = 8.0, 23 °C, 45 min) provided **116** as the only isolable product in 75% yield following workup and flash column chromatography.[83] Control experiments showed that ferredoxin reductase was the primary reductant; enediyne formation was slow in its absence and did not occur when both ferredoxin reductase and NADPH were omitted. NADPH alone induced clean formation of **116** from **115**, albeit more slowly than the enzyme-mediated reaction.



116

As anticipated in light of ample precedent, (*Z*)-enediyne **116** cyclized slowly in tetrahydrofuran at 37 °C ($t_{1/2}$ ~ 2 days) to form, in the presence of 1,4-cyclohexadiene, the aromatized product **118** in moderate yields (35%, Scheme XVIII).[84] Conducting the rearrangement at higher temperatures (tetrahydrofuran, 2.0 M 1,4-cyclohexadiene, 70 °C, 24 h) increased the yield of **118** to 75%. Monitoring of this rearrangement by ^{1}H NMR

Scheme XVIII



116 117 118

spectroscopy at elevated temperature (dimethyl sulfoxide-d_6, 0.20 M 1,4-cyclohexadiene, 1,4-di-*tert*-butyl benzene internal standard, 80 °C) established that **116** underwent first order transformation to **118** with a half life of ~ 25 min ($k = 2.66 \pm 0.08 \times 10^{-2}$ min^{-1}, 80 °C, see experimental section). Deuterium was incorporated quantitatively at the newly formed aromatic positions of **118** when the cyclization was conducted in tetrahydrofuran-d_8 (60 °C, 36 h, 50% yield), consistent with the intermediacy of 1,4-dehydrobenzene derivative **117** in the transformation of **116** to **118** (Scheme XVIII).

Conclusions

The potential of producing a reactive (*Z*)-enediyne by reductive activation of a stable diyne precursor has been demonstrated by preparing and studying the cyclodecadiyne-anthraquinone conjugates **86** and **115**. These compounds undergo reductive activation in organic and aqueous media respectively to produce (*Z*)-enediyne **116** which subsequently rearranges to 1,4-dehydrobenzene intermediate **117** at physiological temperature. The efficacy of the enzyme-mediated activation of **115** is significant in that flavin-based enzymatic reductants have been implicated as potential in vivo activation factors for the clinically important quinone-containing antitumor agents adriamycin, mitomycin, and daunomycin.[63,64,83] Efforts to increase the rate of enediyne cyclization by introducing additional strain in these systems are currently in progress.[85]

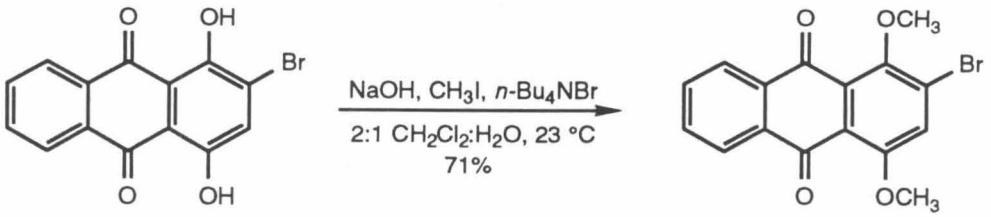
Experimental Section

General Procedures. 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), organic solutions were deoxygenated by alternate evacuation/argon-flush cycles (≥ five iterations). Aqueous solutions were deoxygenated by bubbling argon through them for a minimum of 15 min. Organic solutions were concentrated by rotary evaporation at ~25 Torr (water aspirator). Flash column chromatography was performed as described by Still et al.[32] employing 230-400 mesh silica gel. Analytical thin-layer chromatography was performed using glass plates pre-coated with 0.25 mm 230-400 mesh silica gel impregnated with a fluorescent indicator (254 nm).

Materials. Commercial reagents and solvents were used as received with the following exceptions. Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl. Dichloromethane, benzene, *n*-propylamine, and triethylamine were distilled from calcium hydride at 760 Torr. Dimethyl sulfoxide (DMSO) was distilled from calcium sulfate at 40 Torr and stored over 4Å molecular sieves. *N,N*-Dimethylformamide (DMF) was purchased from Aldrich Chemical Company (HPLC grade, < 0.03% water content) and stored over 4Å molecular sieves. Pyridine was dried over potassium hydroxide prior to use. Oxalyl chloride was distilled at 760 Torr prior to use. Cuprous iodide was purified by continuous extraction (12 h) with tetrahydrofuran in a Soxhlet apparatus.[56] Dimethyldioxirane was prepared as a dilute (~ 0.05 M) solution in acetone according to the literature procedure.[71] The Dess-Martin periodinane (~ 8 g lots) was prepared according to the literature procedure.[79] Trichlorotris(tetrahydrofuran)vanadium(III)[86] ($VCl_3(THF)_3$), tetrakis(triphenylphosphine)palladium(0)[57] and trifluoromethanesulfonic anhydride[87] were prepared according to the literature procedures. The molarity of *n*-butyllithium solutions

was determined by titration using diphenylacetic acid as an indicator (average of three determinations).[61]

Instrumentation. Infrared (IR) spectra were obtained using a Perkin-Elmer 1600 FT-IR spectrophotometer referenced to a polystyrene standard. Data are presented as follows: frequency of absorption (cm^{-1}), intensity of absorption (s = strong, m = medium, w = weak, br = broad) and assignment (when appropriate). Proton nuclear magnetic resonance (^1H NMR) spectra were recorded with a JEOL JX-400 (400 MHz) or a Bruker AM-500 (500 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 7.15, $CHDCl_2$: δ 5.29). Data are represented as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), integration, coupling constant in Hertz (Hz), and assignment. High resolution mass spectra were obtained at the University of California, Riverside Mass Spectrometry Facility.



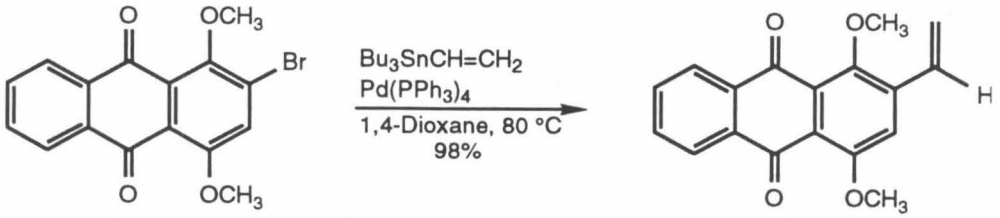
90

2-Bromo-1,4-Dimethoxyanthraquinone (**90**).

Tetrabutylammonium bromide (8.20 g, 25.4 mmol, 4.0 equiv), sodium hydroxide (1.02 g, 25.5 mmol, 4.0 equiv), and iodomethane (31.7 mL, 509 mmol, 80 equiv) were added sequentially to a vigorously stirred suspension of 2-bromo-1,4-dihydroxyanthraquinone[66] (2.03 g, 6.36 mmol, 1 equiv) in a 2:1 mixture of dichloromethane and water (150 mL) at 23 °C. The resulting purple reaction mixture was stirred at 23 °C for 2 days, then was partitioned between water (100 mL) and 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 (20% ethyl acetate in hexanes) to give 2-bromo-1,4-dimethoxyanthraquinone (**90**) (1.60 g, 71%) as yellow solid (mp 157-158 °C).

^{1}H NMR (400 MHz, C_6D_6), δ: 8.09-8.15 (m, 2 H, both CHC**H**CC=O), 7.04-7.09 (m, 2 H, both C**H**CHCC=O), 7.02 (s, 1 H, C**H**COCH$_3$), 3.95 (s, 3 H, one of OC**H**$_3$), 3.15 (s, 3 H, one of OC**H**$_3$).

FTIR (neat), cm^{-1}:	2941 (w), 1673 (s, C=O), 1542 (m), 1312 (s), 1252 (s), 1041 (m), 981 (m), 723 (m).
MS (CI/NH_3), m/z (%base):	346 (94), 317 (43), 196 (24), 181 (34), 168 (30).
HRMS (CI/NH_3):	Calcd for $C_{16}H_{11}BrO_4$ (M^+): 345.9841 Found: 345.9858
TLC (20% EtOAc in Hexanes), R_f:	2-Bromo-1,4-Dihydroxyanthraquinone: 0.51 (UV) 2-Bromo-1,4-Dimethoxyanthraquinone (**90**): 0.20 (UV)



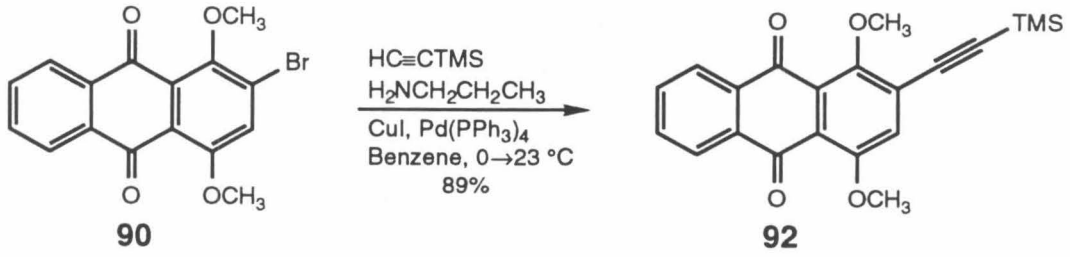
90 **91**

Vinyl Anthraquinone **91.**

A deoxygenated solution of 2-bromo-1,4-dimethoxyanthraquinone (**90**, 0.361 g, 1.04 mmol, 1 equiv), vinyltributyltin (0.334 g, 1.05 mmol, 1.1 equiv), tetrakis-(triphenylphosphine)palladium(0) (0.060 g, 0.052 mmol, 0.05 equiv), and a few crystals 2,6-di-*tert*-butyl-4-methyl-phenol in 1,4-dioxane was stirred at 80 °C for 12 h. After cooling to 23 °C, the reaction mixture was partitioned between water (100 mL) and a 1:1 mixture of ethyl acetate and hexanes (2 x 100 mL). The organic layers were dried over sodium sulfate and were concentrated. Purification of the residue by flash column chromatography (30% ethyl acetate in hexanes) afforded vinyl anthraquinone **91** (0.30 g, 98%) as a yellow solid (mp = 134-135 °C).

^{1}H NMR (500 MHz, $CDCl_3$), δ: 8.15-8.18 (m, 2 H, both CHC**H**CC=O), 7.69-7.74 (m, 2 H, both C**H**CHCC=O), 7.45 (s, 1 H, C**H**COCH$_3$), 7.17 (dd, 1 H, J = 17.7, 11.2 Hz, C**H**=CH$_2$), 5.94 (d, 1 H, J = 17.7 Hz, one of CH=C**H**$_2$), 5.56 (d, 1 H, J = 11.2 Hz, one of CH=C**H**$_2$), 4.05 (s, 3 H, one of OC**H**$_3$), 3.89 (s, 3 H, one of OC**H**$_3$).

FTIR (neat), cm^{-1}:	2957 (w), 2925 (w), 1664 (s, C=O), 1585 (m), 1458 (m), 1395 (m), 1332 (s), 1252 (s), 1037 (s), 979 (m), 724 (m).
TLC (30% EtOAc in Hexanes), R_f:	2-Bromo-1,4-Dimethoxyanthraquinone (**90**): 0.30 (UV) Vinyl Anthraquinone **91**: 0.42 (UV)



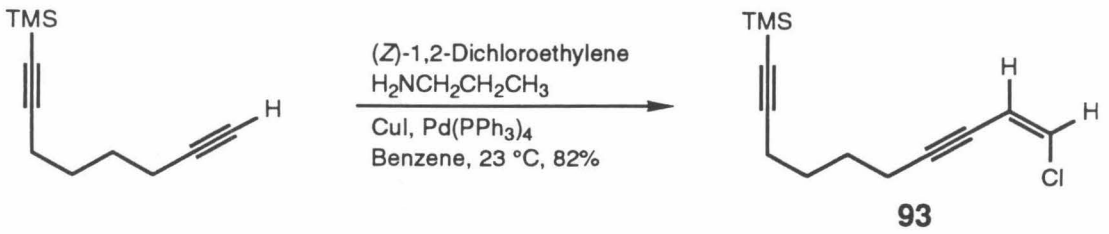
90 **92**

Acetylene **92.**

Cuprous iodide (0.057 g, 0.30 mmol, 0.15 equiv) and tetrakis-(triphenylphosphine)palladium(0) (0.12 g, 0.10 mmol, 0.05 equiv) were added sequentially to a deoxygenated, ice-cooled solution of 2-bromo-1,4-dimethoxy-anthraquinone (**90**) (0.697 g, 2.01 mmol, 1 equiv), (trimethylsilyl)acetylene (0.567 mL, 4.01 mmol, 2.0 equiv), and *n*-propylamine (0.825 mL, 10.0 mmol, 5.0 equiv) in benzene (60 mL). The resulting yellow solution was thoroughly degassed and was stirred at 23 °C for 2 h. The reaction mixture was partitioned between water (150 mL) and a 1:1 mixture of ethyl acetate and hexanes (2 x 100 mL). The combined organic layers were dried over sodium sulfate and were concentrated. The brown residue was purified by flash column chromatography (gradient elution: ethyl acetate in hexanes, 10→30%) to give acetylene **92** (0.65 g, 89%) as a yellow solid (mp 159-160 °C).

^{1}H NMR (500 MHz, $CDCl_3$), δ: 8.13-8.16 (m, 2 H, both CHC**H**CC=O), 7.69-7.74 (m, 2 H, both C**H**CHCC=O), 7.34 (s, 1 H, C**H**COCH$_3$), 4.04 (s, 3 H, one of OC**H**$_3$), 4.01 (s, 3 H, one of OC**H**$_3$), 0.30 (s, 9 H, Si(C**H**$_3$)$_3$).

FTIR (neat), cm^{-1}:	2959 (m), 2157 (w, C≡C), 1672 (s, C=O), 1578 (m), 1461 (m), 1325 (s), 1249 (s), 1043 (m), 983 (m), 851 (s).
MS (FAB), m/z (%base):	365 (100), 364 (40).
HRMS (FAB):	Calcd for $C_{21}H_{21}O_4Si$ (MH^+): 365.1209 Found: 365.1200
TLC (30% EtOAc in Hexanes), R_f:	2-Bromo-1,4-Dimethoxyanthraquinone (**90**): 0.30 (UV) Acetylene **92**: 0.42 (UV)



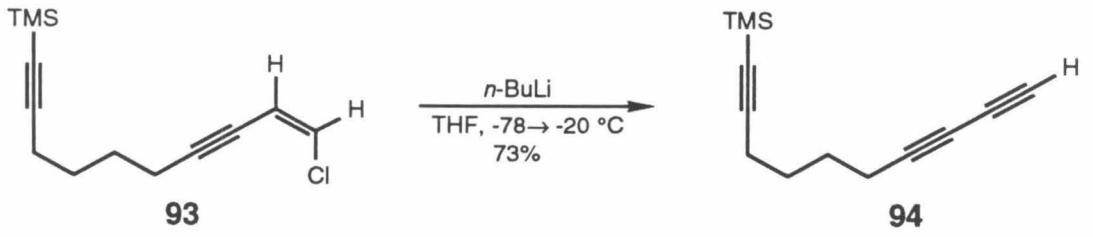
93

(Z)-Vinyl Chloride **93** .

Cuprous iodide (0.30 g, 1.56 mmol, 0.15 equiv) and tetrakis(triphenylphosphine)-palladium(0) (0.60 g, 0.52 mmol, 0.05 equiv) were added sequentially to a deoxygenated solution of (*Z*)-1,2-dichloroethylene (1.57 mL, 20.8 mmol, 2.0 equiv), 1-(trimethylsilyl)-1,7-octadiyne[68] (1.86 g, 10.4 mmol, 1 equiv), and *n*-propylamine (4.29 mL, 52.2 mmol, 5.0 equiv) in benzene (40 mL) at 23 °C and the resulting yellow suspension was thoroughly degassed. After stirring at 23 °C for 5 h, the reaction mixture was partitioned between a solution comprised of equal parts of saturated aqueous ammonium chloride and saturated aqueous potassium carbonate solutions (100 mL) and hexanes (2 x 100 mL). The combined organic layers were dried over sodium sulfate and were concentrated. Purification of the residue by flash column chromatography (hexanes) afforded (*Z*)-vinyl chloride **93** (2.04 g, 82%) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$), δ: 6.29 (d, 1 H, *J* = 7.3 Hz, CH=C(Cl)**H**), 5.84 (dt, 1 H, *J* = 7.3, 2.0 Hz, C**H**=C(Cl)H), 2.39-2.45 (m, 2 H, $CH_2CH_2C{\equiv}CC{=}C$), 2.23-2.26 (m, 2 H, $CH_2CH_2C{\equiv}CSi$), 1.57-1.68 (m, 4 H, $CH_2CH_2C{\equiv}CC{=}C$ and $CH_2CH_2C{\equiv}CSi$), 0.14 (s, 9 H, $Si(CH_3)_3$).

FTIR (neat), cm^{-1}:	3084 (w), 2952 (s), 2268 (w, C≡C), 2216 (m, C≡C), 2174 (s), 1250 (s), 843 (s).
MS (CI/NH_3), m/z (%base):	239 (100), 223 (14), 203 (7), 145 (17), 90 (80).
HRMS (CI/NH_3):	Calcd for $C_{13}H_{20}ClSi$ (MH^+): 239.1023 Found: 239.1031
TLC (Hexanes), R_f:	1-(Trimethylsilyl)-1,7-Octadiyne: 0.23 (UV) (*Z*)-Vinyl Chloride **93**: 0.27 (UV)



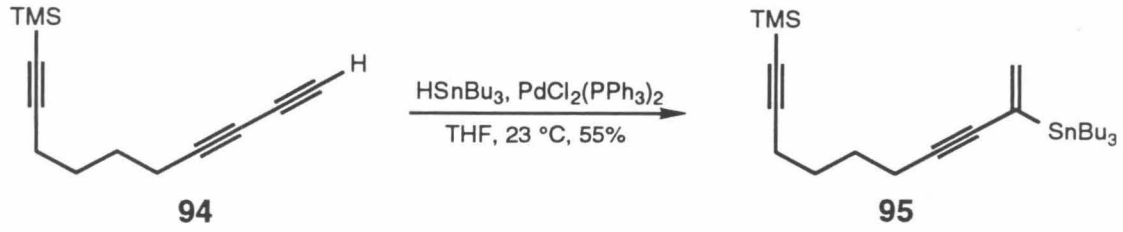
Triyne **94.**

n-Butyllithium (8.11 mL of a 1.6 M solution in hexanes, 13.0 mmol, 1.95 equiv) was added over 3 min to a solution of (*Z*)-vinyl chloride **93** (1.59 g, 6.66 mmol, 1 equiv) in tetrahydrofuran (60 mL) at -78 °C. The resulting yellow solution was stirred at -78 °C for 2 h, then was maintained at -20 °C for an additional 2 h. The reaction mixture was quenched at -20 °C with water (20 mL) and was partitioned between water (100 mL) and ether (2 x 150 mL). The combined organic layers were dried over sodium sulfate and were concentrated. The residue was purified by flash column chromatography (hexanes) to give triyne **94** (0.99 g, 73%) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$), δ: 2.30 (t, 2 H, *J* = 5.8 Hz, $CH_2CH_2C{\equiv}CC{\equiv}C$), 2.25 (t, 2 H, *J* = 6.6 Hz, $CH_2CH_2C{\equiv}CSi$), 1.97 (s, 1 H, C≡CH), 1.61-1.66 (m, 4 H, $CH_2CH_2C{\equiv}CC{\equiv}C$ and $CH_2CH_2C{\equiv}CSi$), 0.14 (s, 9 H, $Si(CH_3)_3$).

FTIR (neat), cm^{-1}: 3305 (m, C≡CH), 2953 (m), 2226 (w, C≡C), 2174 (m, C≡C), 1427 (w), 1328 (w), 1250 (m), 843 (s), 760 (m).

MS (CI/NH_3), m/z (%base):	203 (91), 187 (14), 159 (4), 90 (100), 73 (24).
HRMS (CI/NH_3):	Calcd for $C_{13}H_{19}Si$ (MH^+): 203.1256 Found: 203.1268
TLC (Hexanes), R_f:	(*Z*)-Vinyl Chloride **93**: 0.17 (UV) Triyne **94**: 0.31 (UV)



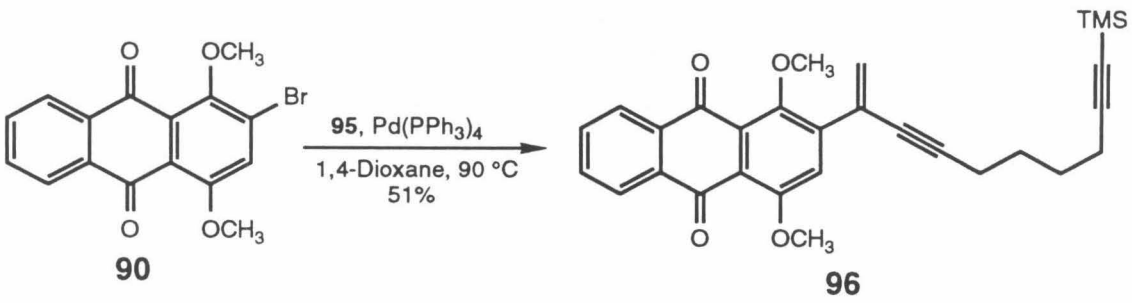
94 **95**

Vinylstannane **95.**

Tributyltin hydride (1.57 mL, 5.84 mmol, 1.2 equiv) was added over 2 min to a deoxygenated solution of triyne **94** (0.985 g, 4.87 mmol, 1 equiv) and bis-(triphenylphosphine)palladium(II) chloride (0.068 g, 0.097 mmol, 0.02 equiv) in tetrahydrofuran (100 mL) at 23 °C. The reaction mixture was stirred at 23 °C for 10 min, then was concentrated under reduced pressure. The resulting brown residue was purified by flash column chromatography (hexanes) to give vinylstannane **95** (1.33 g, 55% yield) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$), δ: 6.14 (d, 1 H, J = 3.4 Hz, one of C=C**H**$_2$), 5.46 (d, 1 H, J = 3.4 Hz, one of C=C**H**$_2$), 2.38 (t, 2 H, J = 6.1 Hz, $CH_2CH_2C{\equiv}CC{=}C$), 2.25 (t, 2 H, J = 6.3 Hz, $CH_2CH_2C{\equiv}CSi$), 1.61-1.66 (m, 4 H, $CH_2CH_2C{\equiv}CC{=}C$ and $CH_2CH_2C{\equiv}CSi$), 1.47-1.59 (m, 6 H, $SnCH_2CH_2$), 1.29-1.36 (m, 6 H, $SnCH_2CH_2$), 0.93-1.05 (m, 6 H, CH_2CH_3), 0.90 (t, 9 H, J = 7.3 Hz, CH_2CH_3), 0.14 (s, 9 H, $Si(CH_3)_3$).

FTIR (neat), cm^{-1}:	2956 (s), 2927 (s), 2175 (m, C≡C), 1461 (m), 1249 (m), 843 (s).
TLC (Hexanes), R_f:	Triyne **94**: 0.35 (UV) Vinylstannane **95**: 0.46 (UV)



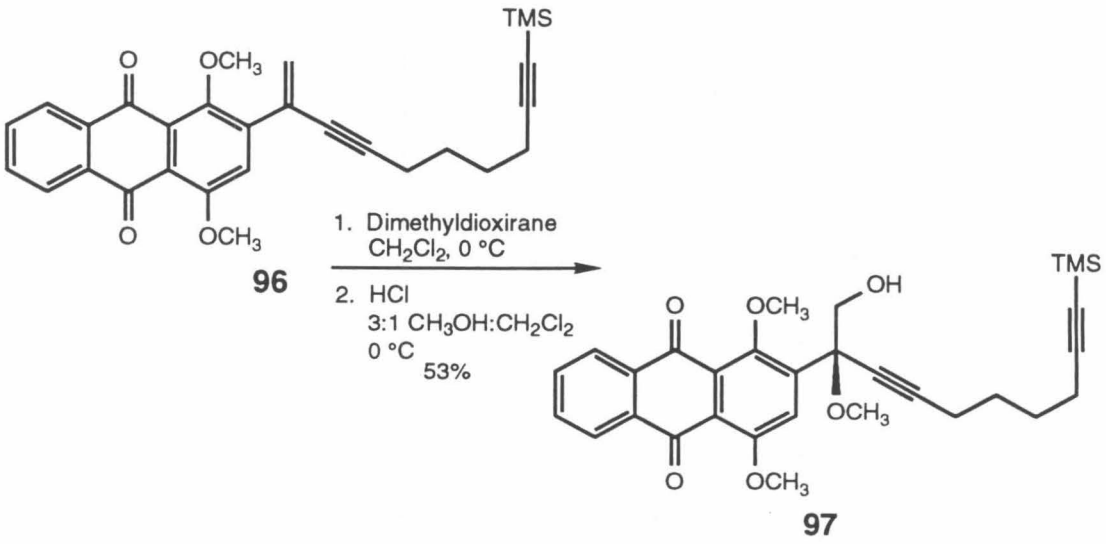
90 **96**

Anthraquinone **96.**

Tetrakis(triphenylphosphine)palladium(0) (0.041 g, 0.0354 mmol, 0.05 equiv) was added to a solution of 2-bromo-1,4-dimethoxyanthraquinone (**90**) (0.207 g, 0.596 mmol, 1 equiv), vinylstannane **95** (0.353 g, 0.715 mmol, 1.2 equiv), and a few crystals of 2,6-di-*tert*-butyl-4-methylphenol in 1,4-dioxane (5.0 mL) at 23 °C. The resulting orange/brown solution was thoroughly deoxygenated and was maintained at 90 °C for 18 h. After cooling to 23 °C, the reaction mixture was partitioned between water (100 mL) and a 1:1 mixture of ethyl acetate and hexanes (2 x 100 mL). The combined organic layers were dried over sodium sulfate and were concentrated. The residue was purified by flash column chromatography (15% ethyl acetate in hexanes) to give anthraquinone **96** (0.143 g, 51%) as an orange oil.

^{1}H NMR (500 MHz, $CDCl_3$), δ: 8.14-8.18 (m, 2 H, both CHC**H**CC=O), 7.69-7.74 (m, 2 H, both C**H**CHCC=O), 7.48 (s, 1 H, C**H**COCH$_3$), 6.07 (d, 1 H, J = 1.5 Hz, one of C=C**H**$_2$), 5.92 (d, 1 H, J = 1.5 Hz, one of C=C**H**$_2$), 4.03 (s, 3 H, one of OC**H**$_3$), 3.87 (s, 3 H, one of

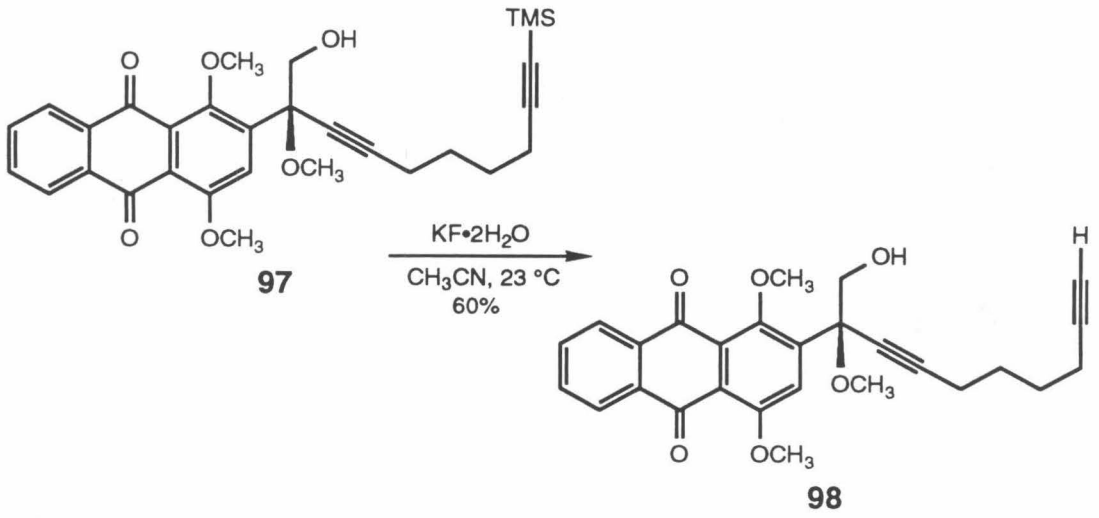
	OCH_3), 2.42 (t, 2 H, J = 6.5 Hz, $CH_2CH_2C{\equiv}C$-C=C), 2.27 (t, 2 H, J = 6.7 Hz, $CH_2CH_2C{\equiv}CSi$), 1.65-1.71 (m, 4 H, $CH_2CH_2C{\equiv}CC{=}C$ and CH_2-$CH_2C{\equiv}CSi$), 0.14 (s, 9 H, $Si(CH_3)_3$).
FTIR (neat), cm^{-1}:	2938 (m), 2218 (w, C≡C), 2173 (m, C≡C), 1673 (s, C=O), 1580 (m), 1315 (m), 1244 (s), 1044 (m), 843 (s).
MS (FAB), m/z (%base):	471 (90), 455 (31), 383 (19), 303 (19).
HRMS (FAB):	Calcd for $C_{29}H_{31}O_4Si$ (MH^+): 471.1992 Found: 471.1990
TLC (30% EtOAc in Hexanes), R_f:	2-Bromo-1,4-Dimethoxyanthraquinone (**90**): 0.29 (UV) Anthraquinone **96**: 0.56 (UV)



Alcohol **97.**

Dimethyldioxirane[71] (7.30 mL of a 0.05 M solution in acetone, 0.365 mmol, 1.2 equiv) was added via pipette to an ice-cooled solution of anthraquinone **96** (0.143 g, 0.304 mmol, 1 equiv) in dichloromethane (5.0 mL). The reaction mixture was stirred at 0 °C for 20 min, then was partitioned between water (50 mL) and a 1:1 mixture of ethyl acetate and hexanes (2 x 75 mL). The combined organic layers were dried over sodium sulfate and were concentrated. The residue was exposed to hydrochloric acid (0.20 M) in a 3:1 mixture of methanol and dichloromethane (12 mL) at 0 °C for 2 h, then was partitioned between water (50 mL) and a 1:1 mixture of ethyl acetate and hexanes (2 x 75 mL). The combined organic layers were dried over sodium sulfate and were concentrated. Purification of the residue by flash column chromatography (15% ethyl acetate in hexanes) afforded alcohol **97** (0.084 g, 53% yield) as a yellow/orange oil.

^{1}H NMR (500 MHz, C_6D_6), δ:	8.13-8.18 (m, 2 H, both CHCHCC=O), 7.65 (s, 1 H, $CHCOCH_3$), 7.05-7.10 (m, 2 H, both CHCHCC=O), 4.30 (dd, 1 H, J = 11.2, 7.1 Hz, CH_AH_BOH), 4.22 (dd, 1 H, J = 11.2, 6.6 Hz, CH_AH_BOH), 3.90 (s, 3 H, one of OCH_3), 3.55 (s, 3 H, one of OCH_3), 3.34 (s, 3 H, one of OCH_3), 2.11 (t, 1 H, J = 7.0 Hz, OH), 2.01-2.03 (m, 2 H, $CC{\equiv}CCH_2CH_2$), 1.95-1.97 (m, 2 H, CH_2CH_2-C≡CSi), 1.39-1.44 (m, 4 H, $CC{\equiv}CCH_2CH_2$ and $CH_2CH_2C{\equiv}CSi$), 0.19 (s, 9 H, $Si(CH_3)_3$).
FTIR (neat), cm^{-1}:	3476 (br, OH), 2945 (m), 2237 (w, C≡C), 2173 (m, C≡C), 1670 (s, C=O), 1461 (m), 1327 (m), 1244 (s), 1043 (m), 843 (m).
MS (FAB), m/z (%base):	519 (69), 487 (66), 469 (18), 425 (11).
HRMS (FAB):	Calcd for $C_{30}H_{35}O_6Si$ (MH^+): 519.2203 Found: 519.2183
TLC (20% EtOAc in Hexanes), R_f:	Anthraquinone **96**: 0.35 (UV) Alcohol **97**: 0.12 (UV)



Acetylene **98.**

Potassium fluoride dihydrate was added to a solution of alcohol **97** (0.035 g, 0.0674 mmol) in acetonitrile at 23 °C until saturation occurred. The resulting suspension was stirred at 23 °C for 4 days, then was partitioned between water (120 mL) and a 1:1 mixture of ethyl acetate and hexanes (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 acetylene **98** (0.018 g, 60% yield) as a yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$), δ: 8.16-8.19 (m, 2 H, both CHC**H**CC=O), 7.71-7.76 (m, 3 H, both C**H**CHCC=O and C**H**COCH$_3$), 4.14 (dd, 1 H, J = 11.4, 7.4 Hz, C**H**$_A$H$_B$OH), 4.04 (dd, 1 H, J = 11.4, 6.5 Hz, CH$_A$**H**$_B$OH), 4.04 (s, 3 H, one of OC**H**$_3$), 3.92 (s, 3 H, one of OC**H**$_3$), 3.48 (s, 3 H, one of OC**H**$_3$), 2.42 (t, 2 H, J = 6.8

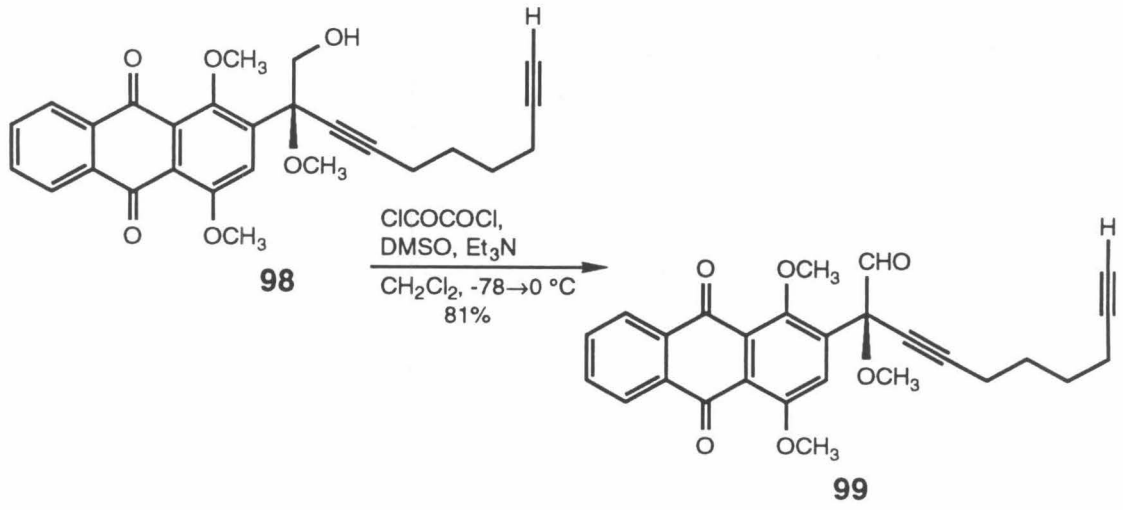
Hz, CC≡CC**H**$_2$CH$_2$), 2.24 (td, 2 H, J = 6.7, 2.7 Hz, CH$_2$C**H**$_2$C≡CH), 2.13 (t, 1 H, J = 7.0 Hz, **OH**), 1.95 (t, 1 H, J = 2.7 Hz, C≡C**H**), 1.65-1.77 (m, 4 H, CC≡CCH$_2$C**H**$_2$ and C**H**$_2$CH$_2$C≡CH).

FTIR (neat), cm^{-1}: 3473 (b, OH), 3289 (b, C≡CH), 2941 (m), 2244 (w, C≡C), 1669 (s, C=O), 1461 (m), 1327 (s), 1240 (s), 1043 (s), 729 (m).

MS (FAB), m/z (%base): 447 (45), 415 (24), 383 (13).

HRMS (FAB): Calcd for $C_{27}H_{27}O_6$ (MH^+): 447.1808
Found: 447.1805

TLC (50% EtOAc in Hexanes), R_f: Alcohol **97**: 0.38 (UV)
Acetylene **98**: 0.29 (UV)



Aldehyde **99**.

Dimethyl sulfoxide (0.020 mL, 0.260 mmol, 4.4 equiv) was added over 2 min to a solution of oxalyl chloride (0.012 mL, 0.133 mmol, 2.2 equiv) in dichloromethane (3 mL) at -78 °C. The resulting clear solution was stirred at -78 °C for 5 min, then a solution of acetylene **98** (0.027 g, 0.061 mmol, 1 equiv) in dichloromethane (2 mL) was added over 1 min. After 15 min, triethylamine (0.84 mL, 0.602 mmol, 10.0 equiv) was added to the reaction mixture and the resulting solution was warmed to 0 °C and was stirred at that temperature for 30 min. The reaction was quenched at 0 °C with water (5 mL), and the product was partitioned between water (100 mL) and a 1:1 mixture of ethyl acetate and hexanes (2 x 75 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 give aldehyde **99** (0.022 g, 81%) as a yellow oil.

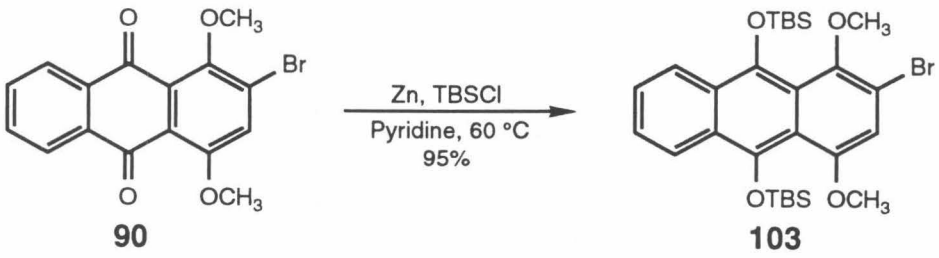
^{1}H NMR (500 MHz, C_6D_6), δ: 9.68 (s, 1 H, **CH**O), 8.10-8.17 (m, 2 H, both CHC**H**CC=O), 7.75 (s, 1 H, **CH**COCH$_3$), 7.03-7.08 (m, 2 H, both **CH**CHCC=O), 3.88 (s, 3 H, one of OC**H**$_3$), 3.54 (s, 3 H, one of OC**H**$_3$), 3.29 (s, 3 H, one of OC**H**$_3$), 1.88-1.90 (m, 2 H, CC≡CC**H**$_2$CH$_2$), 1.81-1.84 (m, 2 H, CH$_2$C**H**$_2$-C≡CH), 1.70 (t, 1 H, J = 2.7 Hz, C≡C**H**), 1.30-1.34 (m, 4 H, CC≡CCH$_2$C**H**$_2$ and C**H**$_2$CH$_2$-C≡CH).

FTIR (neat), cm^{-1}: 3282 (w, C≡CH), 2943 (m), 2235 (w, C≡C), 1741 (m, HC=O), 1672 (s, C=O), 1592 (m), 1462 (m), 1390 (m), 1326 (s), 1261 (s), 1040 (m).

MS (FAB), m/z (%base): 445 (9), 416 (12), 220 (10).

HRMS (FAB): Calcd for $C_{27}H_{25}O_6$ (MH^+): 445.1651
Found: 445.1662

TLC (30% EtOAc in Hexanes), R_f: Acetylene **98**: 0.08 (UV)
Aldehyde **99**: 0.30 (UV)



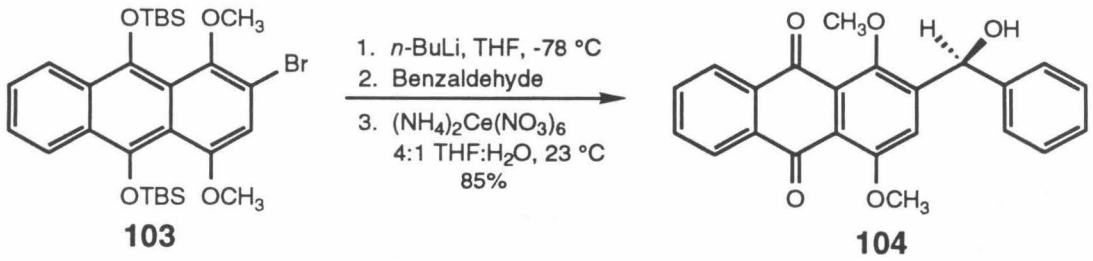
90 **103**

Anthracene **103**.

Zinc powder (0.261 g, 3.52 mmol, 2.2 equiv) and *tert*-butyldimethylsilyl chloride (0.530 g, 3.52 mmol, 2.2 equiv) were added sequentially to a solution of 2-bromo-1,4-dimethoxyanthraquinone (**90**) (0.555 g, 1.60 mmol, 1 equiv) in pyridine (10 mL) at 23 °C. The resulting orange suspension was deoxygenated and was stirred at 60 °C for 2 h. After cooling to 23 °C, the reaction mixture was diluted with 1:1 mixture of ethyl acetate and hexanes (150 mL) and was washed with dilute hydrochloric acid (0.1 M, 3 x 150 mL). The organic layer was dried over sodium sulfate and was concentrated. The residue was purified by flash column chromatography (5% ethyl acetate in hexanes) to provide anthracene **103** (0.893 g, 97% yield) as a yellow powder (mp 129-130 °C).

^{1}H NMR (400 MHz, C_6D_6), δ: 8.51-8.58 (m, 2 H, both CHC**H**CCOSi), 7.32-7.39 (m, 2 H, both C**H**CHCCOSi), 6.66 (s, 1 H, C**H**COCH$_3$), 3.65 (s, 3 H, one of OC**H**$_3$), 3.31 (s, 3 H, one of OC**H**$_3$), 1.19 (s, 9 H, one of SiC(C**H**$_3$)$_3$), 1.16 (s, 9 H, one of SiC(C**H**$_3$)$_3$), 0.10 (s, 6 H, one of Si(C**H**$_3$)$_2$), -0.01 (s, 6 H, one of Si(C**H**$_3$)$_2$).

FTIR (neat), cm^{-1}:	2931 (m), 1593 (m), 1382 (s), 1257 (m), 1039 (s), 902 (m), 841 (m), 779 (m).
MS (EI), m/z (%base):	576 (32), 504 (34), 432 (92).
HRMS (EI):	Calcd for $C_{28}H_{41}BrO_4Si_2$ (M^+): 576.1727 Found: 576.1747
TLC (5% EtOAc in Hexanes), R_f:	2-Bromo-1,4-dimethoxyanthraquinone (**90**): 0.04 (UV) Anthracene **103**: 0.74 (UV)

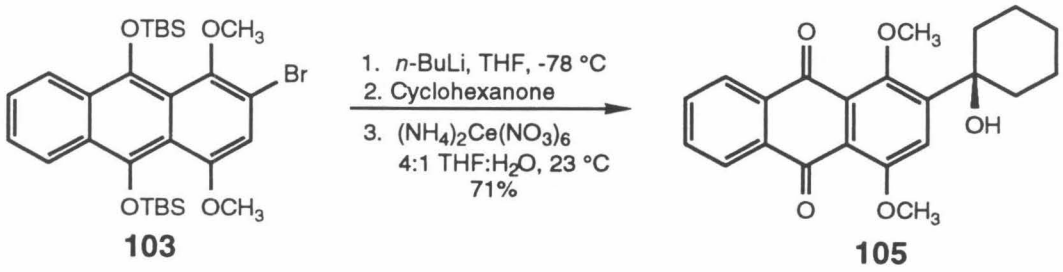


103 **104**

Anthraquinone **104.**

n-Butyllithium (0.221 mL of a 1.6 M solution in hexanes, 0.354 mmol, 1.0 equiv) was added over 1 min to a solution of anthracene **103** (0.204 g, 0.353 mmol, 1 equiv) in tetrahydrofuran at -78 °C. The resulting orange solution was stirred at -78 °C for 20 min, then benzaldehyde (0.036 mL, 0.354 mmol, 1.0 equiv) was added and the yellow reaction mixture was maintained at -78 °C for 20 min, then was partitioned between water (100 mL) and a 1:1 mixture of ethyl acetate and hexanes (2 x 75 mL). The combined organic layers were dried over sodium sulfate and were concentrated. The residue was dissolved in a 4:1 mixture of tetrahydrofuran and water (20 mL) at 23 °C and ceric ammonium nitrate (CAN) was added to the resulting solution in small portions until tlc analysis indicated completion of the reaction (~0.50 g CAN, 20 min). The reaction mixture was partitioned between water (100 mL) and a 1:1 mixture of ethyl acetate and hexanes (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 anthraquinone **104** (0.112 g, 85% yield) as a yellow powder (mp 79-80 °C).

^{1}H NMR (400 MHz, $CDCl_3$), δ:	8.12-8.17 (m, 2 H, both CHC**H**CC=O), 7.70-7.74 (m, 2 H, both C**H**CHCC=O), 7.66 (s, 1 H, C**H**COCH$_3$), 7.26-7.41 (m, 5 H, C$_6$**H**$_5$), 6.21 (s, 1 H, C**H**OH), 4.03 (s, 3 H, one of OC**H**$_3$), 3.56 (s, 3 H, one of OC**H**$_3$).
FTIR (neat), cm^{-1}:	3456 (br, OH), 2940 (w), 1667 (s, C=O), 1591 (m), 1462 (m), 1243 (s), 1041 (s), 728 (s).
MS (EI), m/z (%base):	374 (74), 359 (58), 281 (49), 225 (14), 117 (30), 105 (100).
HRMS (EI):	Calcd for $C_{23}H_{18}O_5$ (M^+): 374.1154 Found: 374.1142
TLC (50% EtOAc in Hexanes), R_f:	Anthraquinone **104**: 0.32 (UV)

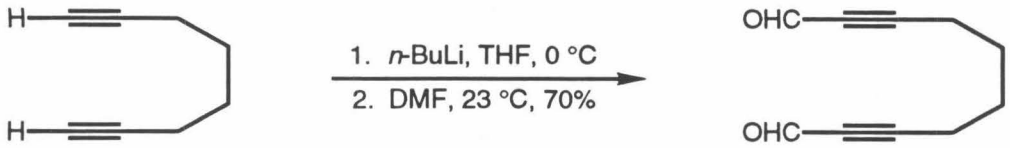


103 **105**

Anthraquinone **105.**

n-Butyllithium (0.162 mL of a 1.6 M solution in hexanes, 0.260 mmol, 1.0 equiv) was added over 1 min to a solution of anthracene **103** (0.150 g, 0.260 mmol, 1 equiv) in tetrahydrofuran at -78 °C. The resulting orange solution was stirred at -78 °C for 20 min, then cyclohexanone (0.027 mL, 0.261 mmol, 1.0 equiv) was added and the yellow reaction mixture was maintained at -78 °C for 15 min, then was partitioned between water (50 mL) and a 1:1 mixture of ethyl acetate and hexanes (2 x 50 mL). The combined organic layers were dried over sodium sulfate and were concentrated. The residue was dissolved in a 4:1 mixture of tetrahydrofuran and water (10 mL) at 23 °C and ceric ammonium nitrate (CAN) was added to the resulting solution in small portions until tlc analysis indicated completion of the reaction (~0.50 g CAN, 20 min). The reaction mixture was partitioned between water (50 mL) and a 1:1 mixture of ethyl acetate and hexanes (2 x 50 mL). The combined organic layers were dried over sodium sulfate and were concentrated. The residue was purified by flash column chromatography (gradient elution: ethyl acetate in hexanes, 30→40%) to provide anthraquinone **105** (0.068 g, 71% yield) as a yellow powder (mp 162-163 °C).

^{1}H NMR (400 MHz, $CDCl_3$), δ:	8.17-8.20 (m, 2 H, both CHC**H**CC=O), 7.72-7.76 (m, 2 H, both C**H**CHCC=O), 7.55 (s, 1 H, C**H**COCH$_3$), 4.03 (s, 3 H, one of OC**H**$_3$), 3.93 (s, 3 H, one of OC**H**$_3$), 3.44 (s, 1 H, O**H**), 1.99-2.06 (m, 3 H, three of (C**H**$_2$)$_5$), 1.77-1.92 (m, 5 H, five of (C**H**$_2$)$_5$), 1.66-1.69 (m, 1 H, one of (C**H**$_2$)$_5$), 1.24-1.36 (m, 1 H, one of (C**H**$_2$)$_5$).
FTIR (neat), cm^{-1}:	3480 (br, OH), 2932 (m), 2151 (w), 1668 (s, C=O), 1462 (m), 1328 (s), 1237 (s), 1041 (m), 729 (s).
MS (EI), m/z (%base):	366 (82), 351 (39), 335 (33), 232 (100), 281 (29).
HRMS (EI):	Calcd for $C_{22}H_{22}O_5$ (M^+): 366.1467 Found: 366.1457
TLC (50% EtOAc in Hexanes), R_f:	Anthraquinone **105**: 0.38 (UV)



106

Dialdehyde **106.**

n-Butyllithium (38.1 mL of a 1.6 M solution in hexanes, 61.0 mmol, 2.0 equiv) was added over 10 min to an ice-cooled solution of 1,7-octadiyne (3.24 g, 30.5 mmol, 1 equiv) in tetrahydrofuran (300 mL), producing a white precipitate. The mixture was stirred for 5 min at 0 °C, then *N,N*-dimethylformamide (11.8 mL, 152 mmol, 5.0 equiv) was added and the milky suspension was maintained at 23 °C for 15 h. The reaction mixture was quenched with aqueous citric acid (1.0 M, 10 mL) at 23 °C, then was partitioned between aqueous citric acid (1.0 M, 150 mL) and dichloromethane (3 x 100 mL). The combined organic layers were dried over sodium sulfate and were concentrated. Purification of the residue by flash column chromatography (15% ethyl acetate in hexanes) afforded dialdehyde **106** (3.45 g, 70% yield) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$), δ: 9.17 (s, 2 H, C**H**O), 2.45-2.48 (m, 4 H, C≡CC**H**$_2$CH$_2$), 1.72-1.78 (m, 4 H, C≡CCH$_2$C**H**$_2$).

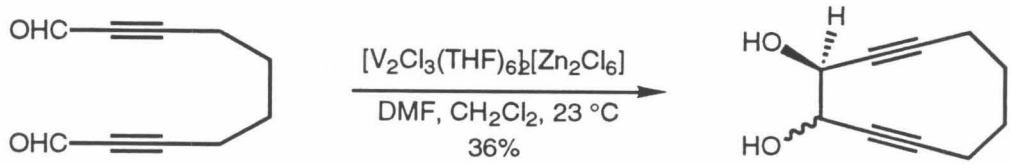
FTIR (neat), cm^{-1}: 3305 (w), 2946 (m), 2277 (m, C≡C), 2201 (s, C≡C), 1677 (s, C=O), 1390 (m), 1135 (s), 824 (m).

MS (EI), m/z (%base): 161 (40), 133 (46), 115 (20), 105 (100), 91 (70).

HRMS (EI): Calcd for $C_{10}H_9O_2$ $(M-H)^+$: 161.0603

Found: 161.0608

TLC (50% EtOAc in Hexanes), R_f: Dialdehyde **106**: 0.71 (UV)



106 **107**

Diol **107.**

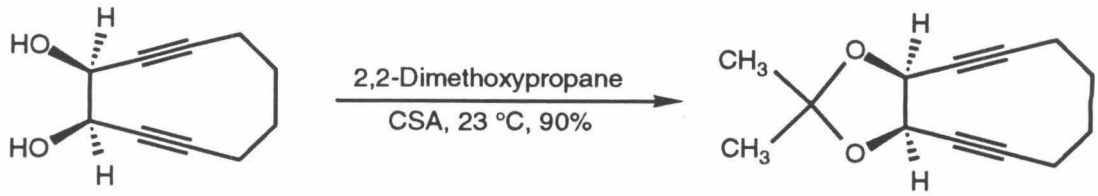
Degassed dichloromethane (200 mL) was added via cannula over 15 min to a mixture of trichlorotris(tetrahydrofuran)vanadium(III) $[VCl_3(THF)_3]$[86] (11.2 g, 30.0 mmol, 2.3 equiv) and zinc powder (1.20 g, 18.4 mmol, 1.4 equiv) at 23 °C. The resulting brown suspension was stirred for 30 min at 23 °C to provide a green solution to which *N,N*-dimethylformamide (6.07 mL, 78.4 mmol, 6.0 equiv) was added. The reaction mixture was stirred for 5 min at 23 °C, then a solution of dialdehyde **106** (2.12 g, 13.1 mmol, 1 equiv) in dichloromethane (3 mL) was added via syringe pump over 3 h. The brown mixture was stirred for an additional 2 h at 23 °C, 10% aqueous potassium/sodium tartrate (200 mL) was added, and the mixture was stirred vigorously in the atmosphere until a blue aqueous phase and brown organic phase were produced (~2 h at 23 °C). The layers were separated, and the aqueous phase was extracted with dichloromethane (3 x 150 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 give diol **107** (4:1 mixture of cis and trans isomers, respectively, 0.771 g, 36% yield) as an off-white solid (mp of mixture 103-104 °C).

Diol **107** (cis isomer).

^{1}H NMR (500 MHz, $CDCl_3$), δ:	4.44 (s, 2 H, C**H**OH), 2.53 (s, br, 2 H, O**H**), 2.20 (s, br, 4 H, C≡CC**H**$_2$CH$_2$), 1.75-1.76 (m, 4 H, C≡CCH$_2$C**H**$_2$).
FTIR (neat), cm^{-1}:	3555 (br, OH), 2940 (m), 2276 (w, C≡C), 2220 (m, C≡C), 1387 (m), 1268 (m), 1134 (m), 1052 (s).
MS (EI), m/z (%base):	164 (18), 136 (100), 121 (14), 108 (20), 93 (21), 79 (27).
HRMS (EI):	Calcd for $C_{10}H_{12}O_2$ (M^+): 164.0837 Found: 164.0840
TLC (50% EtOAc in Hexanes), R_f:	Dialdehyde **106**: 0.71 (UV) Diol **107**: 0.49

Diol **107** (trans isomer).

^{1}H NMR (500 MHz, $CDCl_3$), δ:	4.40 (s, 2 H, C**H**OH), 2.53 (s, br, 2 H, O**H**), 2.20 (s, br, 4 H, C≡CC**H**$_2$CH$_2$), 1.75-1.76 (m, 4 H, C≡CCH$_2$C**H**$_2$).



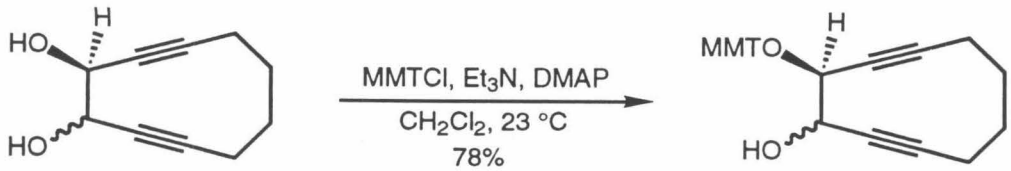
107 **108**

Acetonide **108.**

(±)-Camphorsulfonic acid (0.015 g, 0.065 mmol, 0.32 equiv), was added to a solution of diol **107** (cis isomer, 0.033 g, 0.201 mmol, 1 equiv) in 2,2-dimethoxypropane (4 mL) at 23 °C. The mixture was stirred for 45 min at 23 °C, then partitioned between a saturated aqueous solution of sodium bicarbonate (100 mL) and a 1:1 mixture of ethyl acetate and hexanes (2 x 75 mL). The combined organic layers were dried over sodium sulfate and were concentrated. The residue was purified by flash column chromatography (5% ethyl acetate in hexanes) to give cis-acetonide **108** (0.037 g, 90% yield) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$), δ: 4.87 (s, 2 H, C**H**OC$(CH_3)_2$), 2.16-2.28 (m, 4 H, C≡CC**H**$_2$C**H**$_2$), 1.66-1.81 (m, 4 H, C≡CC**H**$_2$C**H**$_2$), 1.57 (s, 3 H, one of C$(CH_3)_2$), 1.32 (s, 3 H, one of C$(CH_3)_2$).

FTIR (neat), cm^{-1}:	2988 (m), 2935 (s), 2235 (w, C≡C), 1449 (m), 1378 (m), 1233 (s), 1163 (s), 1034 (s), 865 (m).
MS (EI), m/z (%base):	204 (23), 189 (37), 161 (24), 147 (27), 117 (100), 91 (71).
HRMS (EI):	Calcd for $C_{13}H_{16}O_2$ (M^+): 204.1150 Found: 204.1157
TLC (50% EtOAc in Hexanes), R_f:	Diol **107**: 0.45 Acetonide **108**: 0.84



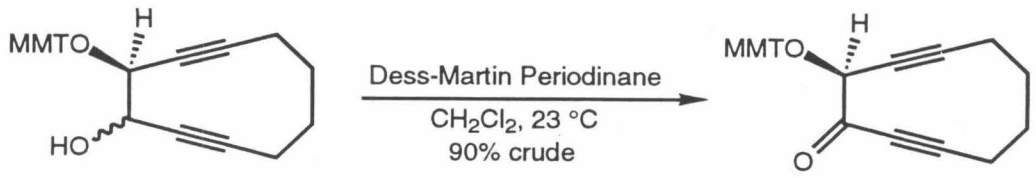
107 **109**

Monomethoxytrityl Ether **109.**

4-Methoxytriphenylmethyl chloride (1.64 g, 5.31 mmol, 2.5 equiv) was added to a solution of diol **107** (4:1 mixture of cis and trans isomers, respectively, 0.348 g, 2.12 mmol, 1 equiv) and triethylamine (0.886 mL, 0.164 mmol, 3.0 equiv) in dichloromethane (8.0 mL) at 23 °C. 4-Dimethylaminopyridine (0.020 g, 4.09 mmol, 0.077 equiv) was added, and the solution stirred at 23 °C for 8 h. The reaction mixture was partitioned between water (100 mL) and a 1:1 mixture of ethyl acetate and hexanes (2 x 75 mL). The combined organic layers were dried over sodium sulfate and were concentrated. The residue was purified by flash column chromatography (15% ethyl acetate in hexanes) to give monomethoxytrityl ether **109** (9:1 mixture of cis and trans isomers, respectively, 0.723 g, 78%) as a white foam.

^{1}H NMR (500 MHz, C_6D_6), δ: 7.74-7.76 (m, 2 H, two of Ar**H**), 7.67-7.69 (m, 2 H, two of Ar**H**), 7.49-7.52 (m, 2 H, two of Ar**H**), 7.09-7.16 (m, 4 H, four of Ar**H**), 7.00-7.05 (m, 2 H, two of Ar**H**), 6.68-6.71 (m, 2 H, two of Ar**H**), 4.59-4.61 (m, 1 H, C**H**OH), 3.56-3.59 (m, 1 H,

	$CHOC(Ar)_3$), 3.26 (s, 3 H, OCH_3), 2.80 (d, 1 H, J = 5.0 Hz, OH), 1.98-2.03 (m, 1 H, one of $C{\equiv}CCH_2CH_2$), 1.77-1.91 (m, 3 H, three of $C{\equiv}CCH_2CH_2$), 1.29-1.47 (m, 4 H, $C{\equiv}CCH_2CH_2$).
FTIR (neat), cm^{-1}:	3546 (br, OH), 2934 (m), 2272 (w, C≡C), 2224 (w, C≡C), 1607 (m), 1510 (s), 1447 (m), 1252 (s), 1036 (s), 787 (s).
MS (CI/NH_3), m/z (%base):	437 (2), 273 (100), 254 (5).
HRMS (CI/NH_3):	Calcd for $C_{30}H_{29}O_3$ (MH^+): 437.2117 Found: 437.2115
TLC (30% EtOAc in Hexanes), R_f:	Diol **107**: 0.12 Monomethoxytrityl Ether **109**: 0.44 (UV)

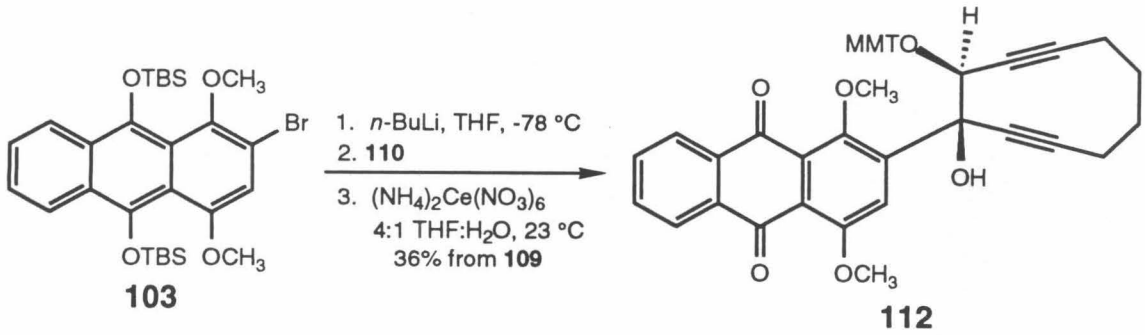


109 **110**

Ketone **110**.

A solution of monomethoxytrityl ether **109** (9:1 mixture of cis and trans isomers, respectively, 0.800 g, 1.84 mmol, 1 equiv) in dichloromethane (8.0 mL) was added over 5 min to a solution of the Dess-Martin periodinane[79] (1.74 g, 4.59 mmol, 2.5 equiv) in dichloromethane (15 mL) at 23 °C. The pale yellow solution was stirred at 23 °C for 12 h, then was concentrated to ~4 mL volume and was diluted with hexanes (50 mL). The resulting beige precipitate was removed by vacuum filtration through a fine frit and was washed with a 9:1 mixture of hexanes and toluene (3 x 15 mL). The combined filtrate and washings were concentrated to afford crude ketone **110** (~90% yield) as a yellow oil which ^{1}H NMR analysis showed to be >90% pure. Since ketone **110** decomposed when concentrated on silica gel (both untreated and triethylamine-washed), subsequent coupling reactions were carried out using the above crude material.

^{1}H NMR (500 MHz, C_6D_6), δ:	7.93-7.97 (m, 4 H, four of Ar**H**), 7.75-7.78 (m, 2 H, two of Ar**H**), 7.29-7.33 (m, 4 H, four of Ar**H**), 7.18-7.23 (m, 2 H, two of Ar**H**), 6.86-6.89 (m, 2 H, two of Ar**H**), 4.94 (dd, 1 H, J = 3.4, 1.9 Hz, C**H**OC(Ar)$_3$), 3.46 (s, 3 H, OC**H**$_3$), 1.71-1.88 (m, 4 H, C≡CC**H**$_2$C**H**$_2$), 1.19-1.37 (m, 4 H, C≡CCH$_2$C**H**$_2$).
FTIR (neat), cm^{-1}:	2934 (m), 2204 (w, C≡C), 1694 (s, C=O), 1668 (m), 1510 (s), 1447 (m), 1252 (s), 1181 (s), 1035 (m), 704 (s).
MS (CI/NH$_3$), m/z (%base):	435 (70), 407 (28), 273 (100), 253 (16), 197 (19).
HRMS (CI/NH$_3$):	Calcd for $C_{30}H_{27}O_3$ (MH^+): 435.1960 Found: 435.1957
TLC (30% EtOAc in Hexanes), R_f:	Monomethoxytrityl Ether **109**: 0.43 (UV) Ketone **110**: 0.50 (UV)



103 **112**

Anthraquinone **112.**

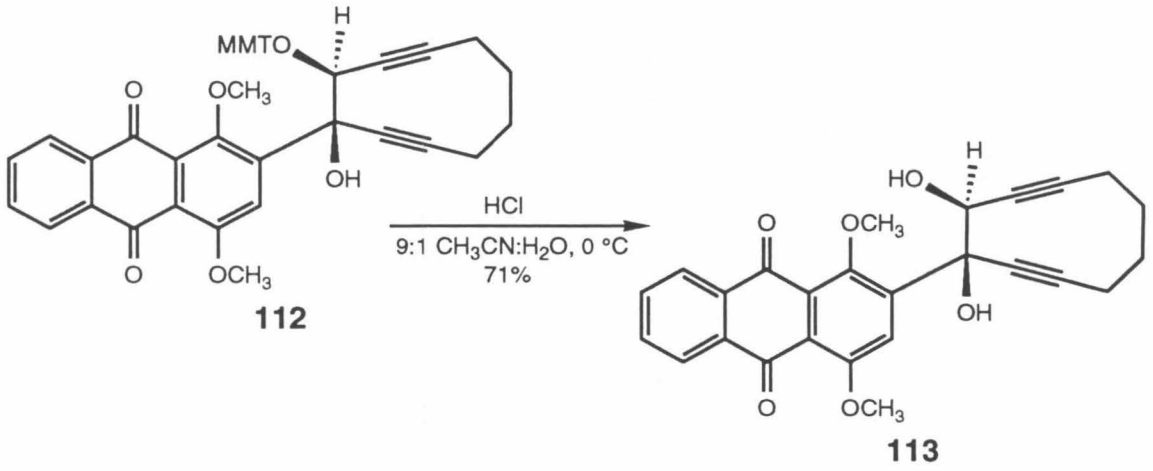
n-Butyllithium (1.15 mL of a 1.6 M solution in hexanes, 1.84 mmol, 1.0 equiv) was added over 1 min to a solution of anthracene **103** (1.06 g, 1.83 mmol, 1 equiv) in tetrahydrofuran at -78 °C. The resulting orange solution was stirred at -78 °C for 20 min, then a solution of crude ketone **110** (1.84 mmol, 1.0 equiv) in tetrahydrofuran (4.0 mL) was added. The yellow reaction mixture was maintained for 1 h at -78 °C, then was partitioned between water (100 mL) and a 1:1 mixture of ethyl acetate and hexanes (3 x 100 mL). The combined organic layers were dried over sodium sulfate and were concentrated. Purification of the residue by flash column chromatography (gradient elution: ethyl acetate in hexanes, 5→10%) provided the coupled anthracene product (**111**) as a yellow oil.

The purified anthracene product was dissolved in a 4:1 mixture of tetrahydrofuran and water (25 mL) at 23 °C and ceric ammonium nitrate (CAN) was added in small portions until tlc analysis indicated completion of the reaction (~0.50 g CAN, 20 min). The reaction mixture was partitioned between water (100 mL) and a 1:1 mixture of ethyl acetate and hexanes (2 x 100 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 anthraquinone **112** (0.469 g,

36% yield from **109**) as a yellow foam. Due to the instability of the methoxytrityl ether moiety present in anthraquinone **112**, the above material was immediately deprotected.

^{1}H NMR (400 MHz, $CDCl_3$), δ: 8.17-8.21 (m, 2 H, both CHC**H**CC=O), 7.72-7.74 (m, 2 H, both C**H**CHCC=O), 7.71 (s, 1 H, C**H**COCH$_3$), 7.40-7.42 (m, 2 H, two of Ar**H**), 7.28-7.29 (m, 2 H, two of Ar**H**), 7.06-7.18 (m, 8 H, eight of Ar**H**), 6.56-6.58 (m, 2 H, two of Ar**H**), 4.92 (s, 1 H, C**H**OC(Ar)$_3$), 4.29 (s, 1 H, O**H**), 4.00 (s, 3 H, one of OC**H**$_3$), 3.72 (s, 3 H, one of OC**H**$_3$), 3.59 (s, 3 H, one of OC**H**$_3$), 2.20-2.21 (m, 4 H, C≡CC**H**$_2$CH$_2$), 2.03-2.09 (m, 1 H, one of C≡CCH$_2$C**H**$_2$), 1.65-1.86 (m, 3 H, three of C≡CCH$_2$C**H**$_2$).

FTIR (neat), cm^{-1}: 3466 (w, OH), 2937 (m), 2279 (w, C≡C), 2226 (w, C≡C), 1669 (s, C=O), 1593 (m), 1461 (m), 1328 (s), 1257 (s), 1179 (m), 1040 (s).



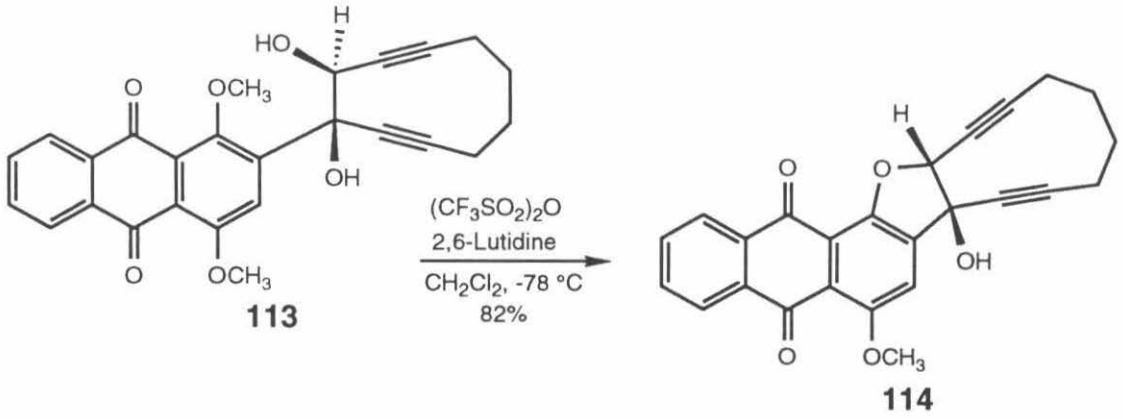
112 **113**

Diol **113.**

Hydrochloric acid (12 M, 1.0 mL) was added dropwise to an ice-cooled solution of anthraquinone **112** (0.469 g, 0.667 mmol) in a 9:1 mixture of acetonitrile and water (*15* mL). The mixture was stirred at 0 °C for 1 h, then was partitioned between water (100 mL) and ethyl acetate (2 x 100 mL). The combined organic layers were dried over sodium sulfate and were concentrated. Purification of the residue by flash column chromatography (20% ethyl acetate in dichloromethane) afforded diol **113** (0.203 g, 71% yield) as a yellow solid (mp 135-136 °C).

^{1}H NMR (500 MHz, $CDCl_3$), δ: 8.15-8.17 (m, 2 H, both CHC**H**CC=O), 7.81 (s, 1 H, C**H**COCH$_3$), 7.70-7.75 (m, 2 H, both C**H**CHCC=O), 5.15 (s, 1 H, C**H**OH), 4.03 (s, 3 H, one of O**CH$_3$**), 3.98 (s, 3 H, one of O**CH$_3$**), 2.19-2.36 (m, 4 H, C≡CC**H$_2$**CH$_2$), 1.86-1.96 (m, 2 H, two of C≡CCH$_2$C**H$_2$**), 1.72-1.80 (m, 2 H, two of C≡CCH$_2$C**H$_2$**).

FTIR (CH_2Cl_2 solution), cm^{-1}:	3686 (m, OH), 3597 (m, OH), 2943 (m), 2222 (w, C≡C), 1671 (s, C=O), 1596 (m), 1324 (m), 1241 (s), 1041 (s), 768 (s).
MS (CI/NH_3), m/z (%base):	431 (100), 415 (14), 401 (14), 253 (48).
HRMS (CI/NH_3):	Calcd for $C_{26}H_{23}O_6$ (MH^+): 431.1495 Found: 431.1473
TLC (50% EtOAc in Hexanes), R_f:	Diol **113**: 0.20 (UV)

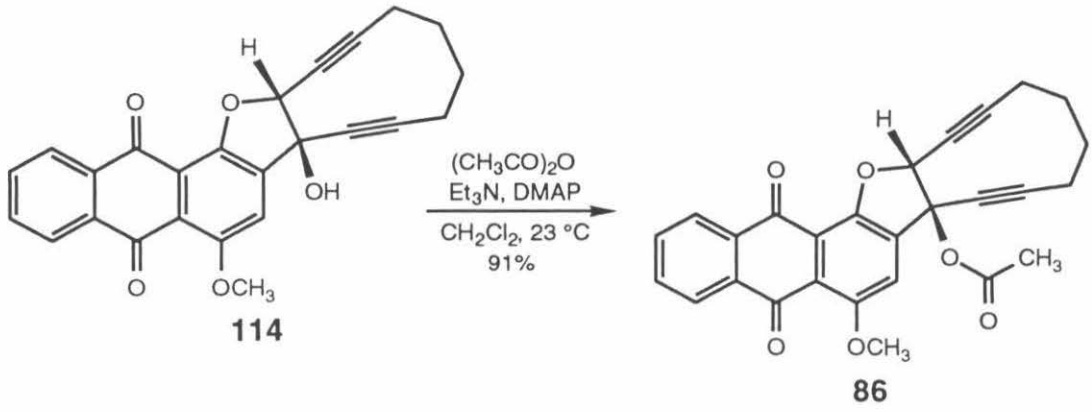


Alcohol **114.**

Trifluoromethanesulfonic anhydride (0.035 mL, 0.208 mmol, 3.0 equiv) was added to a solution of diol **113** (0.030 g, 0.070 mmol, 1 equiv) and 2,6-lutidine (0.041 mL, 0.352 mmol, 5.0 equiv) in dichloromethane (9 mL) at - 78 °C. The reaction mixture was stirred for 45 min at -78 °C, then was partitioned between water (100 mL) and ethyl acetate (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 dichloromethane) to give alcohol **114** (0.023 g, 82% yield) as a yellow solid (mp 124 °C dec).

^{1}H NMR (500 MHz, $CDCl_3$), δ: 8.09-8.18 (m, 2 H, both CHC**H**CC=O), 7.68-7.74 (m, 2 H, both C**H**CHCC=O), 7.44 (s, 1 H, C**H**COCH$_3$), 5.52 (t, 1 H, J = 2.2 Hz, C**H**C≡C), 3.96 (s, 3 H, OC**H**$_3$), 2.20-2.34 (m, 4 H, C≡CC**H**$_2$CH$_2$), 1.65-1.80 (m, 4 H, C≡CCH$_2$C**H**$_2$).

FTIR (neat), cm^{-1}:	3402 (br, OH), 2938 (m), 2242 (m, C≡C), 1667 (s, C=O), 1579 (s), 1411 (s), 1257 (s), 937 (m), 730 (s).
MS (CI/NH_3), m/z (%base):	399 (58), 385 (59), 255 (71), 241 (49), 227 (11).
HRMS (CI/NH_3):	Calcd for $C_{25}H_{19}O_5$ (MH^+): 399.1232 Found: 399.1248
TLC (20% EtOAc in Hexanes), R_f:	Diol **113**: 0.10 (UV) Alcohol **114**: 0.22 (UV)

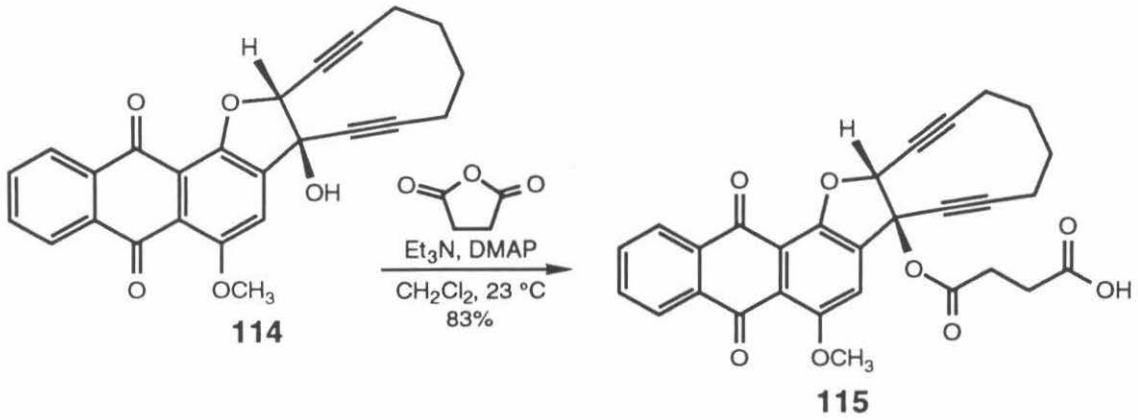


Diyne **86.**

Acetic anhydride (0.024 mL, 0.254 mmol, 5.0 equiv) was added to a solution of alcohol **114** (0.020 g, 0.0501 mmol, 1 equiv) and triethylamine (0.035 mL, 0.251 mmol, 5.0 equiv) in dichloromethane (2 mL) at 23 °C. 4-Dimethylaminopyridine (0.005 g, 0.041 mmol, 0.82 equiv) was then added, and the solution was stirred at 23 °C for 15 min. The reaction mixture was partitioned between water (75 mL) and a 1:1 mixture of ethyl acetate and hexanes (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 give diyne **86** (0.020 g, 91%) as a yellow powder (mp 124 °C dec).

^{1}H NMR (500 MHz, $CDCl_3$), δ: 8.20-8.23 (m, 2 H, both CHC**H**CC=O), 7.81 (s, 1 H, C**H**COCH$_3$), 7.71-7.76 (m, 2 H, both C**H**CHCC=O), 5.76 (t, 1 H, J = 2.4 Hz, C**H**C≡C), 4.07 (s, 3 H, OC**H**$_3$), 2.37-2.42 (m, 1 H, one of

	$C{\equiv}CC\mathbf{H}_2CH_2$), 2.23-2.30 (m, 3 H, three of $C{\equiv}CC\mathbf{H}_2CH_2$), 2.06 (s, 3 H, $C(O)C\mathbf{H}_3$), 1.81-1.86 (m, 2 H, two of $C{\equiv}CCH_2C\mathbf{H}_2$), 1.59-1.73 (m, 2 H, two of $C{\equiv}CCH_2C\mathbf{H}_2$).
FTIR (neat), cm^{-1}:	2936 (m), 2247 (m, C≡C), 1748 (s, $C(O)CH_3$), 1670 (s, C=O), 1581 (m), 1412 (m), 1257 (s), 1222 (s), 1017 (m), 730 (s).
MS (FAB), m/z (%base):	441 (16), 398 (7), 381 (10).
HRMS (FAB):	Calcd for $C_{27}H_{21}O_6$ (MH^+): 441.1338 Found: 441.1346
TLC (30% EtOAc in Hexanes), R_f:	Alcohol **114**: 0.35 (UV) Diyne **86**: 0.43 (UV)



Diyne **115.**

Succinic anhydride (0.145 g, 1.45 mmol, 20 equiv) was added to a solution of alcohol **114** (0.029 g, 0.073 mmol, 1 equiv) and triethylamine (0.202 mL, 1.45 mmol, 20 equiv) in dichloromethane (4 mL) at 23 °C. 4-Dimethylaminopyridine (0.010 g, 0.082 mmol, 1.12 equiv) was then added, and the solution stirred at 23 °C for 1.5 h. The reaction mixture was partitioned between dilute hydrochloric acid (1.0 M, 75 mL) and ethyl acetate (2 x 50 mL). The combined organic layers were dried over sodium sulfate and were concentrated. Purification of the residue by flash column chromatography (50% ethyl acetate in dichloromethane) afforded diyne **115** (0.030 g, 83%) as a yellow/orange powder (mp 115 °C dec).

^{1}H NMR (500 MHz, CD_2Cl_2), δ: 8.15-8.17 (m, 2 H, both CHC**H**CC=O), 7.72-7.77 (m, 3 H, both C**H**CHCC=O and C**H**COCH$_3$), 5.73 (t, 1 H, J = 2.3 Hz, C**H**C≡C), 4.00 (s, 3 H, OC**H**$_3$), 2.54-2.65 (m, 4 H, C(O)C**H**$_2$C**H**$_2$C(O)), 2.35-2.40 (m, 1 H, one of C≡CC**H**$_2$CH$_2$), 2.24-2.30 (m, 3 H,

three of $C{\equiv}CC\mathbf{H}_2CH_2$), 1.79-1.86 (m, 2 H, two of $C{\equiv}CCH_2C\mathbf{H}_2$), 1.59-1.73 (m, 2 H, two of $C{\equiv}CCH_2C\mathbf{H}_2$).

FTIR (neat), cm^{-1}: 3265 (br, COOH), 2938 (m), 2240 (w, C≡C), 1745 (s, $C(O)CH_2$), 1669 (s, C=O), 1580 (m), 1412 (s), 1257 (s), 1221 (s), 1151 (S), 957 (m), 710 (m).

MS (FAB), m/z (%base): 499 (4), 447 (7), 419 (4).

HRMS (FAB): Calcd for $C_{29}H_{23}O_8$ (MH^+): 449.1393
Found: 449.1396

TLC (50% EtOAc in CH_2Cl_2), R_f: Alcohol **114**: 0.55 (UV)
Diyne **115**: 0.24 (UV)

General Reductive Activation Procedures for Diynes **86** and **115.**

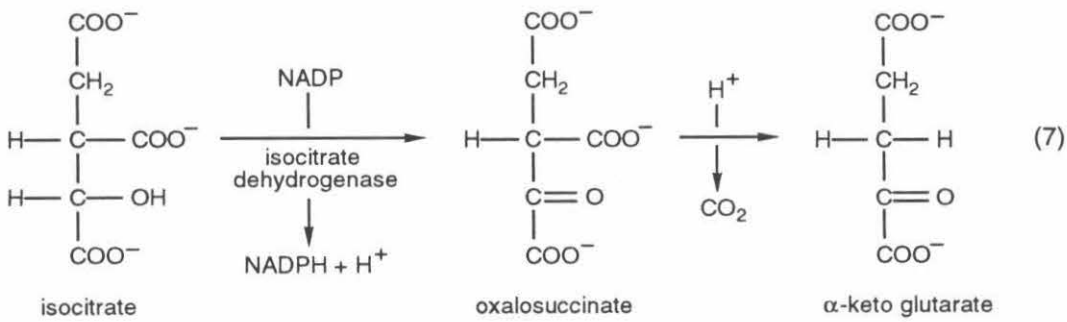
A. A solution of sodium dithionite (0.055 mL of a 0.29 M solution in deoxygenated water, 0.16 mmol, 3.0 equiv) in a deoxygenated mixture of acetonitrile and water (6:1 respectively, 4.0 mL) was added to a deoxygenated solution of diyne **86** (0.0023 g, 0.0052 mmol, 1 equiv) in the same solvent at 23 °C. The resulting orange solution was stirred for 5 min at 23 °C, then it was partitioned between water (75 mL) and ethyl acetate (2 x 75 mL). The 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 (*Z*)-enediyne **116** (15% yield determined by addition of (*Z*)-1,2-dichloroethylene and ^{1}H NMR analysis) as an orange solid (mp = 120 °C dec).

B. Samarium diiodide (0.30 mL of a 0.10 M solution in tetrahydrofuran, 0.030 mmol, 3.0 equiv) was added over 10 sec to a deoxygenated solution of diyne **86** (0.0042 g, 0.0095 mmol, 1 equiv) in a mixture of acetonitrile and methanol (6:1, respectively, 7.0 mL) at 23 °C. The resulting orange solution was stirred for exactly 1.5 min at 23 °C, then it was purged with a stream of air for 30 sec. The red solution was diluted with ethyl acetate (10 mL), and the mixture was partitioned between water (75 mL) and ethyl acetate (2 x 75 mL). The organic layers were dried over sodium sulfate and were concentrated. Purification of the residue by flash column chromatography (30% ethyl acetate in hexanes) afforded (*Z*)-enediyne **116** (0.0023 g, 64%) as an orange solid.

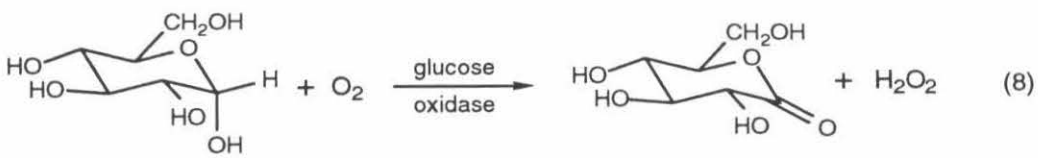
C. Ferredoxin Reductase (E.C. 1.18.1.2, 0.50 mL of a solution of 0.575 units in 10 mL HEPES buffer, 0.029 units) was added to a solution of diyne **115** (0.0042 g, 0.0084 mmol, 0.28 mM) in deoxygenated HEPES buffer (0.10 M, pH = 8.0, Na counterion, 30 mL) containing glucose (0.129 g, 24 mM), manganese(II) sulfate (0.0022 g, 0.61 mM), NADPH (0.012 g, 0.53 mM), isocitrate (0.077 g, 10 mM), glucose oxidase (E.C. 1.1.3.4, 200 units), isocitrate dehydrogenase (E.C. 1.1.1.42, 6.5 units) and catalase

(E.C. 1.11.1.6, 300,000 units) at 23 °C. The reaction mixture was stirred at 23 °C for 45 min, then it was partitioned between water (75 mL) and ethyl acetate (3 x 75 mL). The organic layers were dried over sodium sulfate and were concentrated. The residue was purified by flash column chromatography to provide (*Z*)-enediyne **116** (0.0023 g, 74%) as an orange solid.

Note: the large number of enzymes and reagents utilized in this reaction accomplish three functions. (1) Reduction of **115** (ferredoxin reductase, NADPH), (2) regeneration of NADPH (isocitrate dehydrogenase, isocitrate, eq 7), and (3) deoxygenation of the reaction medium (glucose oxidase, catalase, glucose, eqs 8 and 9). For other reductions which utilize this enzymatic system, see reference 83.

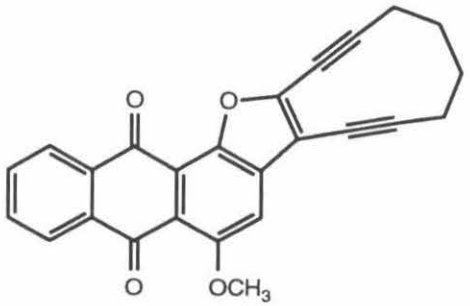


(7)



(8)

(9)



116

(Z)-Enediyne **116**.

^{1}H NMR (500 MHz, CD_2Cl_2), δ:	8.19-8.21 (m, 2 H, both CHC**H**CC=O), 7.73-7.80 (m, 2 H, both C**H**CHCC=O), 7.39 (s, 1 H, C**H**COCH$_3$), 4.04 (s, 3 H, OC**H**$_3$), 2.62-2.64 (m, 2 H, two of C≡CC**H**$_2$CH$_2$), 2.52-2.54 (m, 2 H, two of C≡CC**H**$_2$CH$_2$), 2.03-2.12 (m, 4 H, C≡CCH$_2$C**H**$_2$).
FTIR (CH_2Cl_2 solution), cm^{-1}:	2933 (w), 2194 (w, C≡C), 1671 (s, C=O), 1606 (s), 1393 (m), 1270 (s), 1253 (s), 1120 (m), 840 (w).
MS (FAB), m/z (%base):	381 (10).
HRMS (FAB):	Calcd for $C_{25}H_{17}O_4$ (MH^+): 381.1127 Found: 381.1106
TLC (50% EtOAc in Hexanes), R_f:	(Z)-Enediyne **116**: 0.53 (UV)

Kinetic Experiments ((Z)-Enediyne **116**).

A deoxygenated solution of (*Z*)-enediyne **116** (0.001 g, 0.0026 mmol), 1,4-cyclohexadiene (0.01 mL, 0.106 mmol, 0.20 M), and 1,4-di-*tert*-butylbenzene (0.0005 g, 0.0026 mmol, internal standard) in dimethyl sulfoxide-d_6 (0.50 mL) was heated to 80 °C in the probe of an NMR spectrometer (400 MHz). The disappearance of **116** was monitored by ^{1}H NMR spectroscopy by integration of an aromatic signal (corrected by comparison to the internal standard). The data thus obtained (Table IX) were in agreement with first order reaction kinetics (Figure 6) with $k = 2.66 \pm 0.08 \times 10^{-2}$ min^{-1}.

Table IX. Kinetic Data for Cyclization of (Z)-Enediyne **116** (0.005 M) in DMSO-d_6 at 80 °C.

Data Point	Time (min)	-ln [**116**]
1	30	4.92
2	45	5.28
3	60	5.72

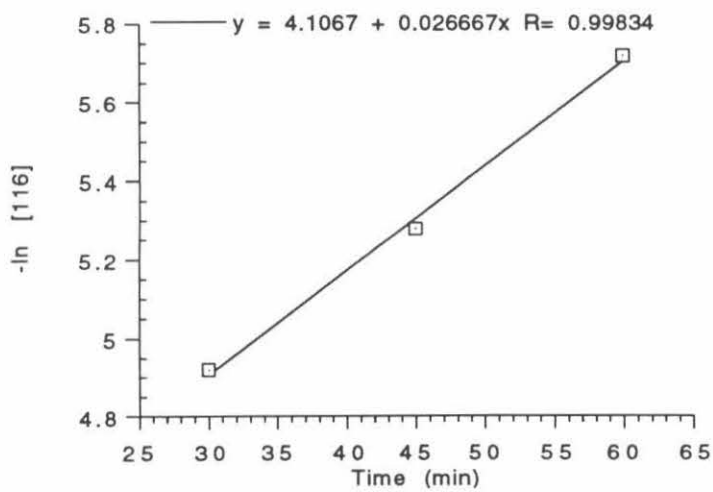
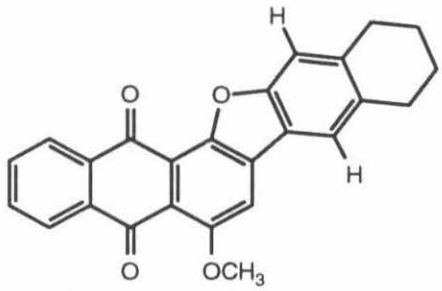


Figure 6. Plot of Kinetic Data for Cyclization of (Z)-Enediyne **116** (0.005 M) in DMSO-d_6 at 80 °C.

Pyrolysis of (Z)-Enediyne **116.**

A deoxygenated solution of **116** (0.0083 g, 0.0218 mmol, 0.0022 M) in tetrahydrofuran containing 1,4-cyclohexadiene (2.0 M) was stirred at 70 °C for 24 h. The reaction mixture was then partitioned between water (50 mL) and a 1:1 mixture of ethyl acetate and hexanes (3 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 the cyclized product **118** (0.0061 g, 75%) as a yellow film.



118

Cyclized Product **118.**

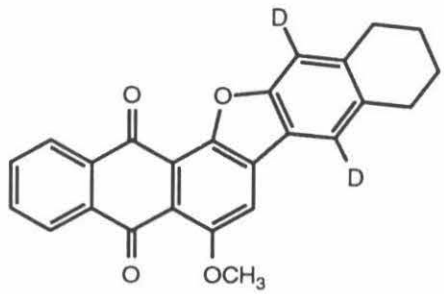
^{1}H NMR (500 MHz, CD_2Cl_2), δ: 8.21-8.24 (m, 2 H, both CHC**H**CC=O), 7.82 (s, 1 H, C**H**COCH$_3$), 7.74-7.81 (m, 2 H, both C**H**CHCC=O), 7.71 (s, 1 H, one of Ar**H**), 7.43 (s, 1 H, one of Ar**H**), 4.11 (s, 3 H, OC**H**$_3$), 2.95-2.99 (m, 4 H, ArC**H**$_2$CH$_2$), 1.86-1.89 (m, 4 H, ArCH$_2$C**H**$_2$).

FTIR (neat), cm^{-1}: 2934 (m), 1669 (s, C=O), 1639 (m), 1454 (m), 1418 (m), 1357 (w), 1261 (s), 1107 (w), 1013 (w).

MS (FAB), m/z (%base): 383 (7).

HRMS (FAB): Calcd for $C_{25}H_{19}O_4$ (MH^+): 383.1283
Found: 383.1280

TLC (50% EtOAc in Hexanes), R_f: (*Z*)-Enediyne **116**: 0.53 (UV)
Cyclized Product **118**: 0.54 (UV)



118

Cyclized Product **118** (d_2).

^{1}H NMR (500 MHz, CD_2Cl_2), δ: 8.21-8.24 (m, 2 H, both CHC**H**CC=O), 7.82 (s, 1 H, C**H**COCH$_3$), 7.74-7.81 (m, 2 H, both C**H**CHCC=O), 4.11 (s, 3 H, OC**H**$_3$), 2.95-2.99 (m, 4 H, ArC**H**$_2$CH$_2$), 1.86-1.89 (m, 4 H, ArCH$_2$C**H**$_2$).

MS (FAB), m/z (%base): 385 (5).

HRMS (FAB): Calcd for $C_{24}{}^{13}CH_{16}D_2O_4$ (MH^+): 385.1364
Found: 385.1345

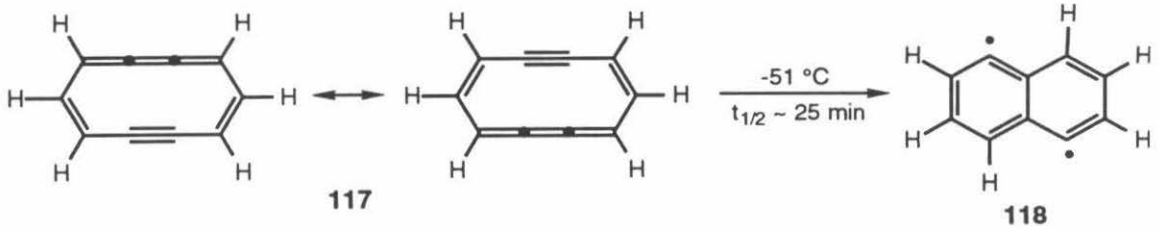
Chapter 3

Design, Synthesis and Reactivity of a 1,6-Didehydro[10]annulene Precursor

Background

The preceding chapters of this work describe the design, synthesis and study of several molecules which form biradical intermediates upon thermal or chemical activation (chapters 1 and 2). In each case, the inspiration for design of these biradical precursors has been electrocyclization reactions utilized by members of the enediyne family of antibiotics (e.g., **5→6** and **11→12**, cf. introduction). Recently, a fundamentally

new electrocyclization reaction not, as yet, precedented by the action of a natural product has been discovered and studied. Thus, the aromatic hydrocarbon 1,6-didehydro[10]-annulene (**117**) was observed to undergo first-order transformation to the biradical 1,5-dehydronaphthalene (**118**) at low temperature ($k = 4.6 \pm 0.9 \times 10^{-4}$ s^{-1} at -51 °C).[88,89] The half-life for cyclization of **117** at -51 °C is ~25 min, making this the most rapid biradical-forming reaction reported to date.[90] The facility of the above transformation

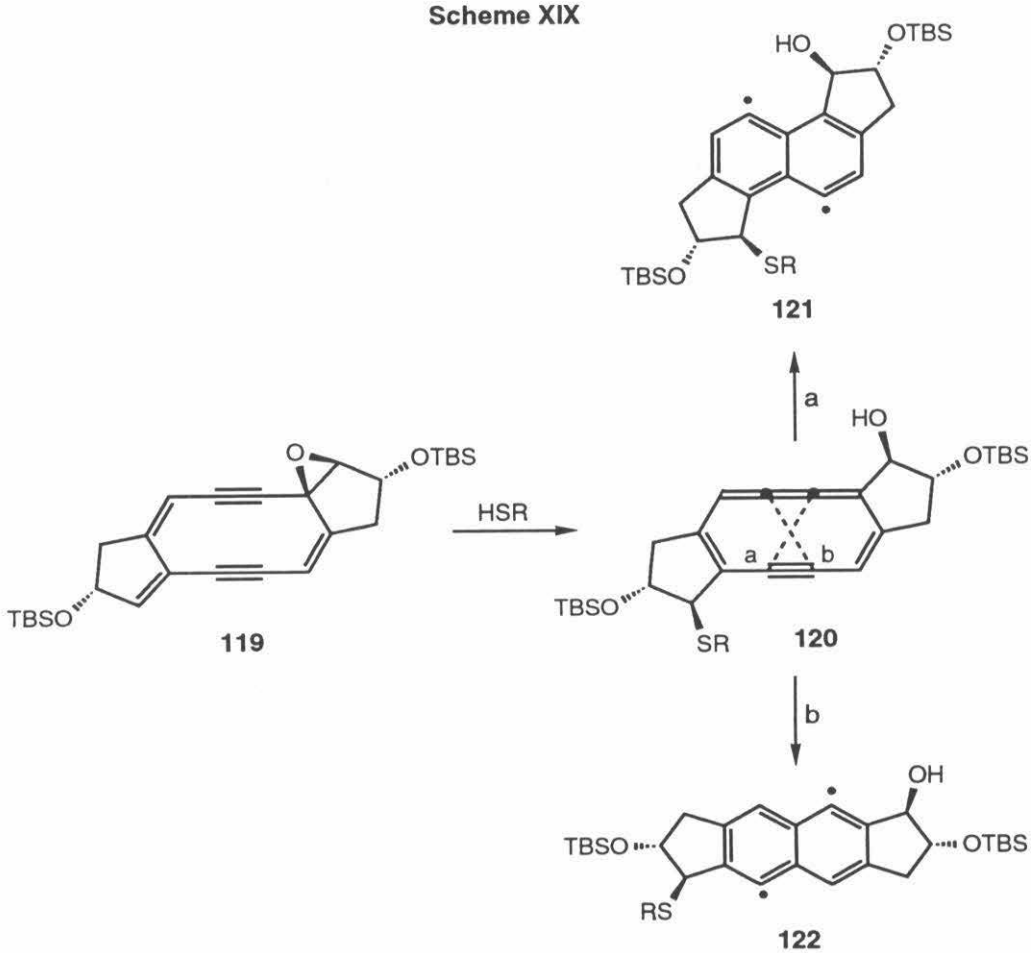


suggests that 1,6-didehydro[10]annulenes possessing DNA binding properties may function as novel antitumor agents analogous to the enediyne antibiotics (cf. introduction). Since the thermal instability of the 1,6-didehydro[10]annulene functional group precludes the routine isolation and handling of molecules which contain it, the design and preparation of a suitable precursor to this reactive moiety was undertaken.

Synthesis and Reactivity of a 1,6-Didehydro[10]annulene Precursor

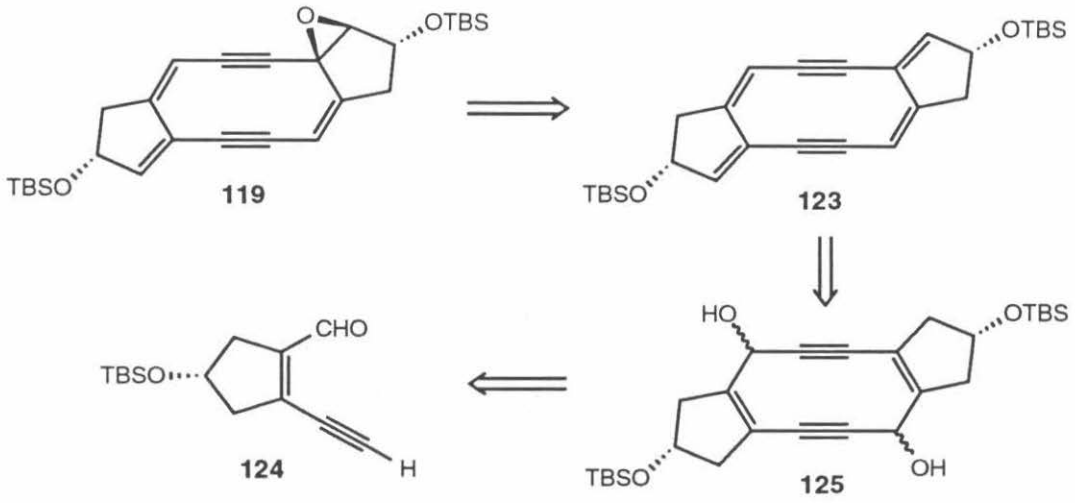
Epoxide **119** was conceived as a stable precursor to the 1,6-didehydro-[10]-annulene nucleus and, in analogy to neocarzinostatin chromophore, was envisioned

Scheme XIX

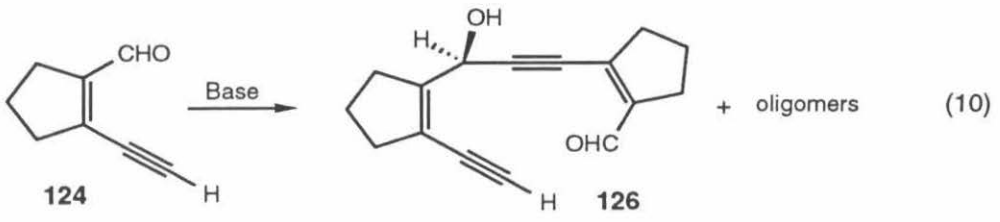


to enter the reaction cascade outlined in Scheme XIX upon treatment with an appropriate thiol nucleophile (cf. Scheme I). Unlike the rearrangement of **117** to **118**, which produces a single biradical intermediate, cyclization of the 1,6-didehydro[10]annulene **120** may produce two distinct 1,5-dehydronaphthalene biradicals (**121** and **122**, pathways a and b, respectively, Scheme XIX).

Initial retrosynthetic analysis suggested silyl ether **123** as a potential precursor of epoxide **119**. This compound, in turn, was envisioned to be prepared by dimerization of

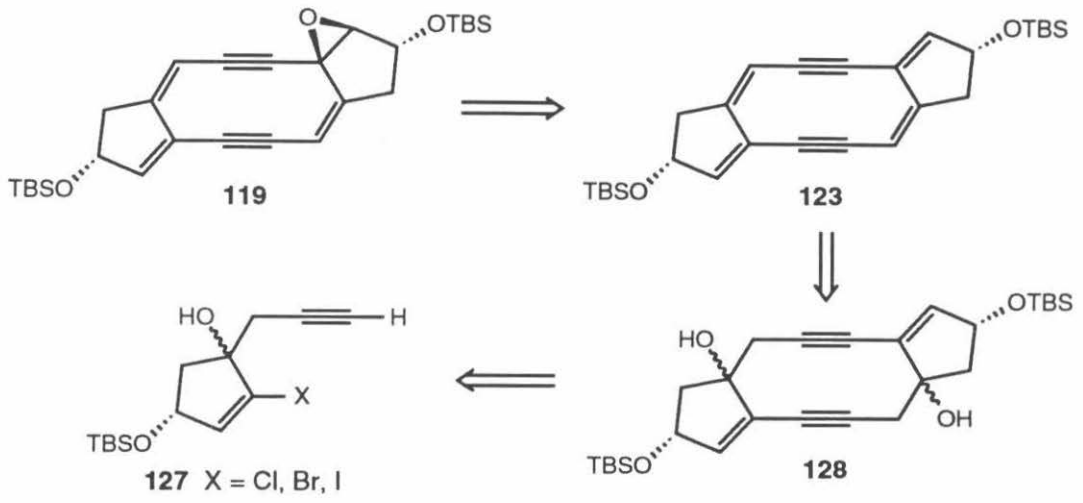


acetylene-aldehyde **124** followed by elimination of the resulting diol **125**. In the event, however, attempted base-induced cyclization of **124** produced the uncyclized dimer **126** along with several other acyclic oligomers (trimers, tetramers, eq 10). The reluctance of **126** to undergo base-induced ring closure is presumably due to the inability of the intermediate acetylide to achieve proper trajectory for attack on the conjugated aldehyde

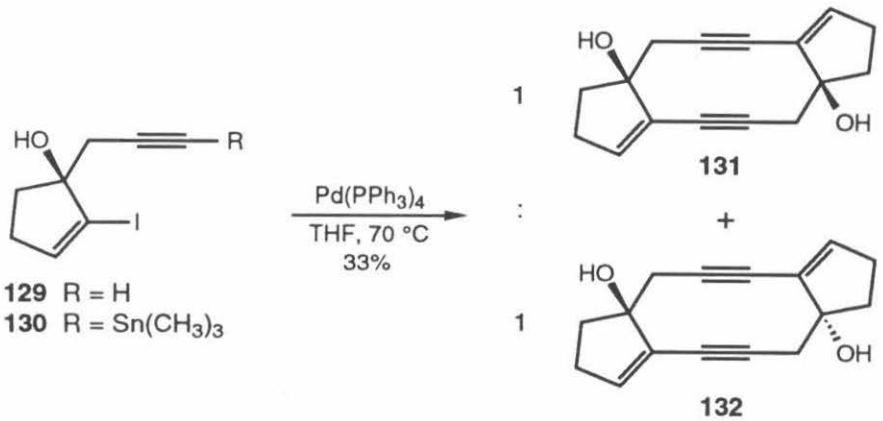


lying in the plane of cyclopentene ring.[91]

In light of the above failure, the initial approach to silyl ether **123** was abandoned in favor of a route in which the ten-membered ring was formed by the palladium-



mediated dimerization of a suitable monomer (**127**→**128**). The feasibility of such an approach was demonstrated by the following model studies. Treatment of allenylmagnesium bromide[92] (3.0 equiv) with 2-iodo-2-cyclopenten-1-one[93] (1 equiv) in ethyl ether at 23 °C produced alcohol **129** in 88% yield. Previous experiments had revealed that attempted dimerization of a related molecule (**127**, X = Br) using copper/palladium-catalyzed coupling conditions[26] (5.0 equiv $(i\text{-Pr})_2NH$, 0.30 equiv CuI, 0.10 equiv $Pd(PPh_3)_4$, tetrahydrofuran, 23 °C) led only to the formation of acetylene dimers, in accordance with literature precedent.[94] Alcohol **129** was therefore converted to trimethylstannane **130** by treatment with an excess of (diethylamino)trimethylstannane[95] (3.0 equiv, neat) followed by an aqueous workup. Heating **130** at 70 °C for 13 h in deoxygenated tetrahydrofuran in the presence of tetrakis(triphenylphosphine)-palladium(0) (0.20 equiv) produced the diastereomeric alcohols **131** and **132** (stereochemistry undetermined) in moderate combined yield (1:1, respectively, 33%).

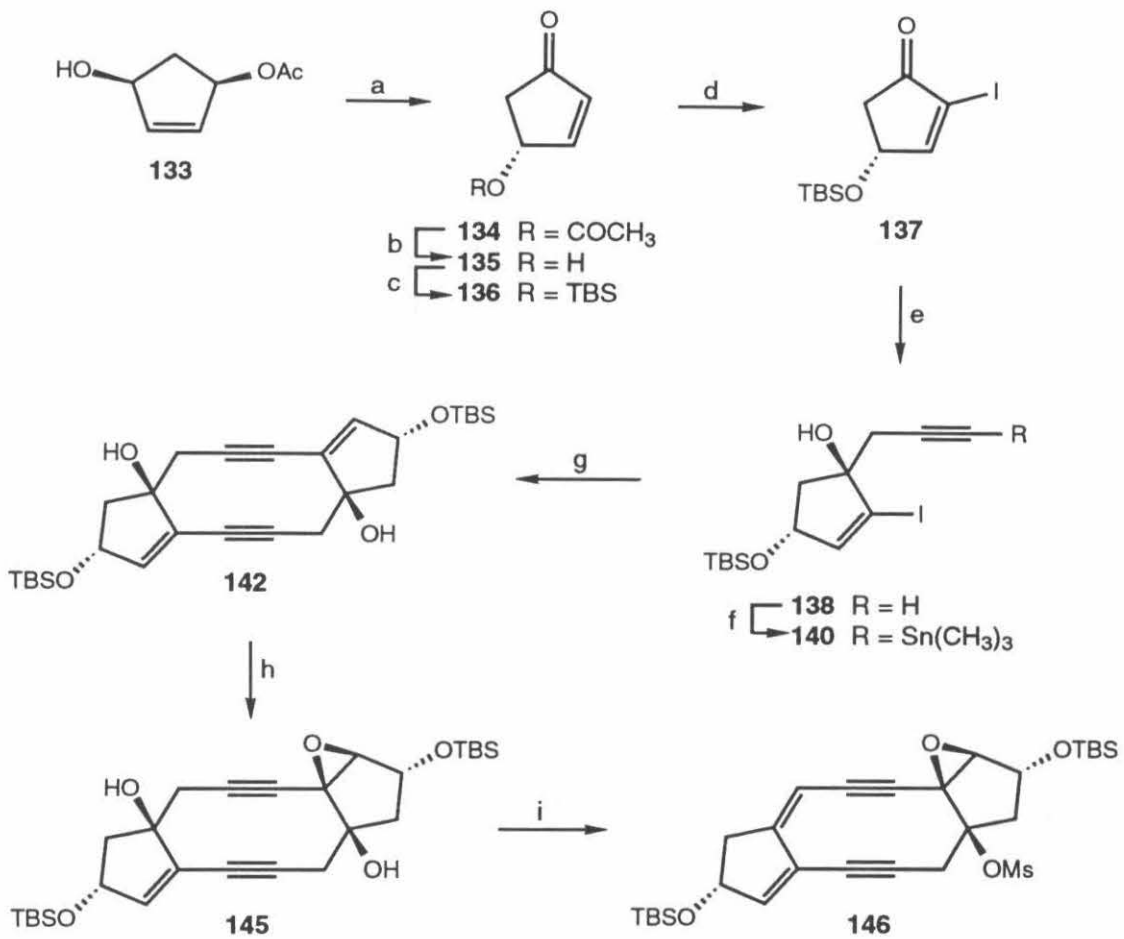


129 R = H
130 R = $Sn(CH_3)_3$

Further examination of the above reaction revealed that neither the trimethylsilyl ether nor the vinyl bromide corresponding to **130** produced dimerized products when subjected to similar reaction conditions. The success of the above palladium-mediated dimerization demonstrated the ability of such couplings to produce the desired ten-membered ring products and suggested a similar approach for the construction of silyl ether **123**.

The preparation of an immediate precursor to silyl ether **123** (diol **142**) and to epoxide **119** (mesylate **146**) is depicted in Scheme XX. Oxidation of optically pure 3(*R*)-acetoxy-5(*S*)-hydroxycyclopent-1-ene[96] (96.5% ee as determined by ^{1}H NMR analysis of the corresponding Mosher ester)[97] with pyridinium chlorochromate (1.7 equiv) in dichloromethane at 23 °C produced ketone **134** in 88% yield. This compound racemized easily under basic conditions and was therefore converted to alcohol **135** by enzymatic hydrolysis (wheat germ lipase, 0.06 M HOAc/NaOAc buffer, pH = 5.0, 32 °C, 2.5 days) at mildly acidic pH. Treatment of crude alcohol **135** with triethylamine (2.0 equiv), *tert*-butyldimethylsilyl chloride (1.5 equiv), and a catalytic amount of 4-dimethyl-aminopyridine (0.16 equiv) in dichloromethane at 23 °C afforded, after silica gel chromatography, silyl ether **136** in 72% overall yield from **134**. Conversion of **136** to iodide **137** was accomplished by a modification of the method originally developed by

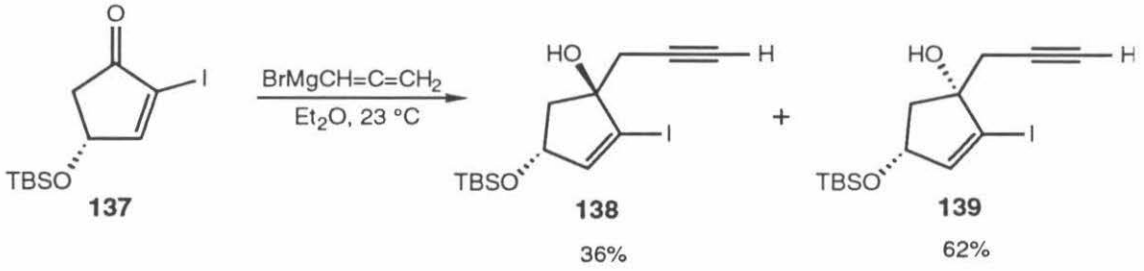
Scheme XX



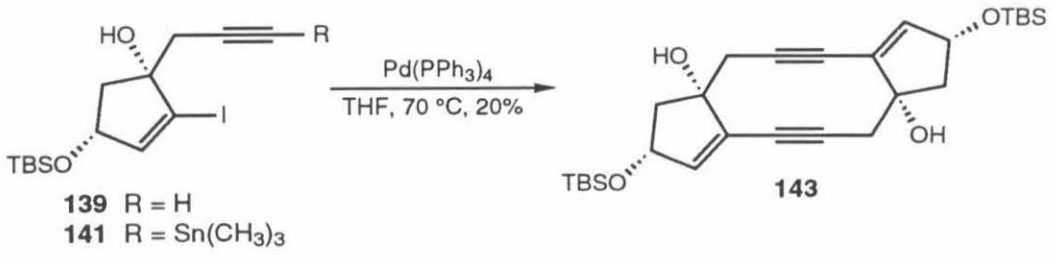
Reagents and conditions (TBS = *t*-Bu$(CH_3)_2$Si, Ac = $COCH_3$, Ms = SO_2CH_3). (a) 1.7 equiv PCC, CH_2Cl_2, 23 °C, 3 h, 88%; (b) wheat germ lipase, 0.06 M HOAc/NaOAc buffer, pH = 5.00, 32 °C, 2.5 days; (c) 2.0 equiv Et_3N, 1.5 equiv TBSCl, 0.16 equiv DMAP, CH_2Cl_2, 23 °C, 6 h, 72% from **134**; (d) 1.7 equiv I_2, 1:1 CH_2Cl_2-pyridine, 0→23 °C, 2 h, 93%; (e) 4.0 equiv $BrMgCH{=}C{=}CH_2$, Et_2O, 23 °C, 15 min, 36%; (f) 3.0 equiv $Et_2N{\bullet}Sn(CH_3)_3$, neat, 23 °C, 3.5 h; H_2O, 95% crude; (g) 0.20 equiv $Pd(PPh_3)_4$, benzene, 70 °C, 12 h, 34%; (h) 1.0 equiv dimethyldioxirane, CH_2Cl_2, 0 °C, 30 min, 41%; (i) 20 equiv DMAP, 10 equiv Ms_2O, CH_2Cl_2, 23 °C, 7 h, 70%.

Johnson and co-workers.[98] Thus, slow addition of a solution of iodine (1.7 equiv) in a mixture of dichloromethane and pyridine (1:1, respectively) to an ice-cooled solution of **136** in the same solvent, followed by stirring at 23 °C for 2 h, provided iodide **137** in 93% yield after workup and flash column chromatography.

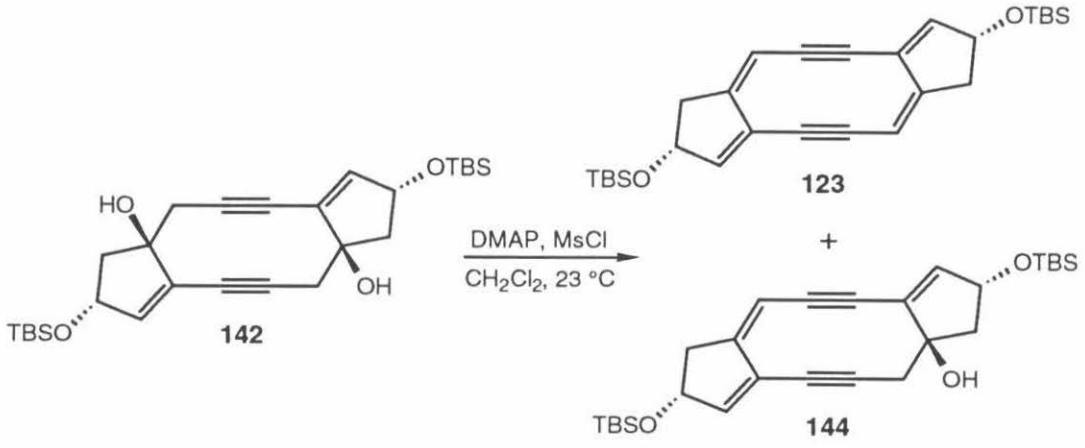
Addition of a solution of **137** in ethyl ether to an excess of allenylmagnesium bromide[92] (4.0 equiv) in the same solvent at 23 °C afforded the diastereomeric alcohols **138** and **139** in excellent combined yield following separation by silica gel chromatography (36% and 62%, respectively). The stereochemistry of the major isomer



produced in this reaction (**139**) was established by X-ray crystallography (see Appendix 1). Treatment of the minor product (**138**) with (diethylamino)trimethylstannane[95] (3.0 equiv, neat) provided, after an aqueous workup, trimethylstannane **140** (95% crude yield) which was dimerized by heating in deoxygenated benzene at 70 °C for 12 h in the presence of tetrakis(triphenylphosphine)palladium(0) (0.20 equiv) to provide diol **142** in 34% yield. The trimethylstannyl-acetylene derived from the major iodo-alcohol isomer (**139→141**) also dimerized when subjected to similar reaction conditions to afford diol



143, albeit in only 20% yield. Attempted conversion of diol **142** to silyl ether **123** by treatment with 4-dimethylaminopyridine (10.0 equiv) and methanesulfonyl chloride (5.0 equiv) in dichloromethane at 0 °C produced only alcohol **144** in 22% yield.[99] This result



suggested that silyl ether **123** was unstable to either the above reaction conditions or to the isolation techniques employed in the experiment (aerobic, aqueous workup and silica gel chromatography). The validity of the latter supposition was verified by the following experiment. Addition of methanesulfonyl chloride (2.5 equiv) to a deoxygenated solution of 4-dimethylaminopyridine (5.0 equiv) and diol **142** in dichloromethane-d_2 at 23 °C produced, as determined by ^{1}H NMR monitoring over 30 min at 23 °C, alcohol **144** and a compound which exhibited signals consistent with **123** (2:1, respectively, Figure 7). Addition of air (0.25 mL volume, syringe injection) to the above mixture resulted in the disappearance of the signals corresponding to **123** (Figure 7), demonstrating that this molecule undergoes rapid decomposition under aerobic conditions and discouraging its use in the preparation of epoxide **119**.

Accordingly, treatment of a solution of diol **142** in dichloromethane at 0 °C with dimethyldioxirane[71] (~1.0 equiv) afforded epoxide **145** in 41% yield following purification by flash column chromatography. Epoxidation of **142** with *m*-CPBA (1.0

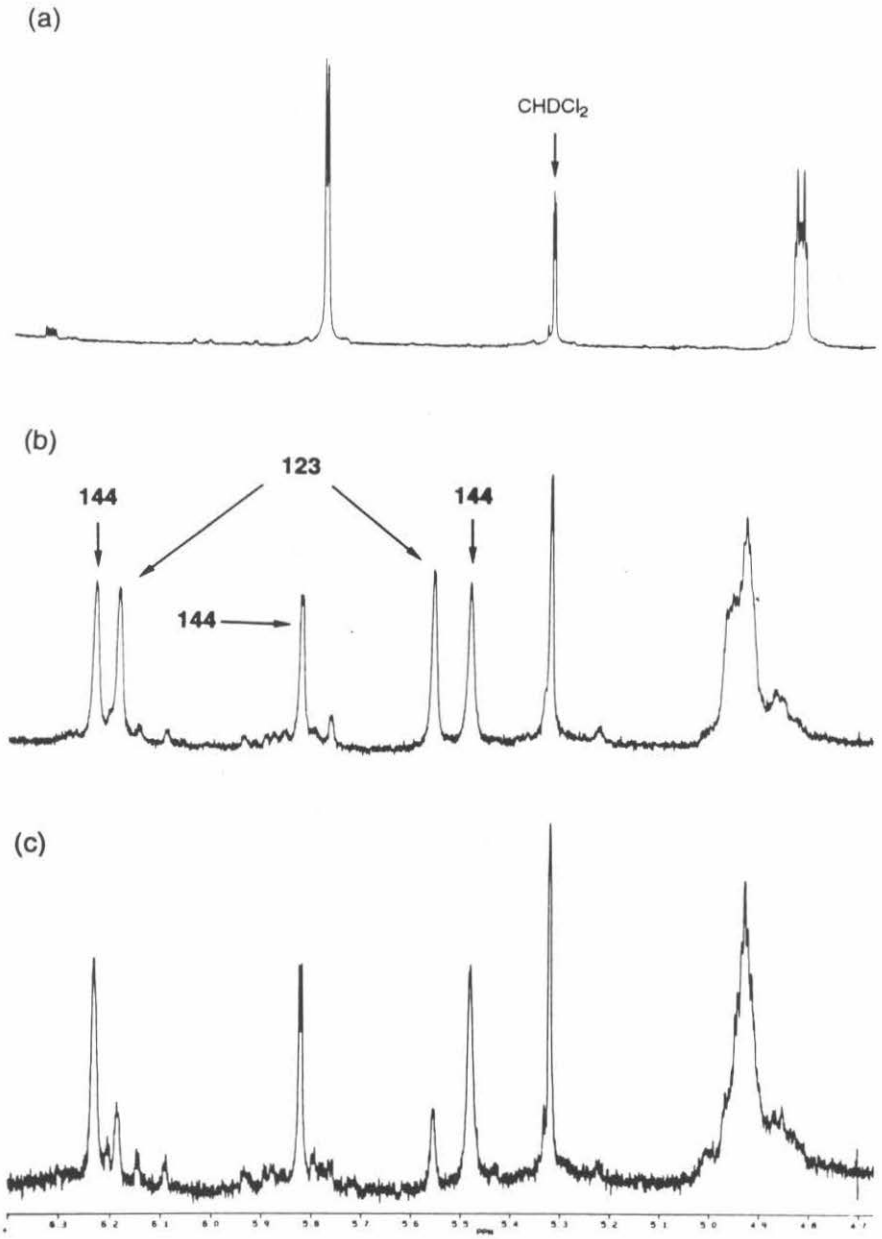
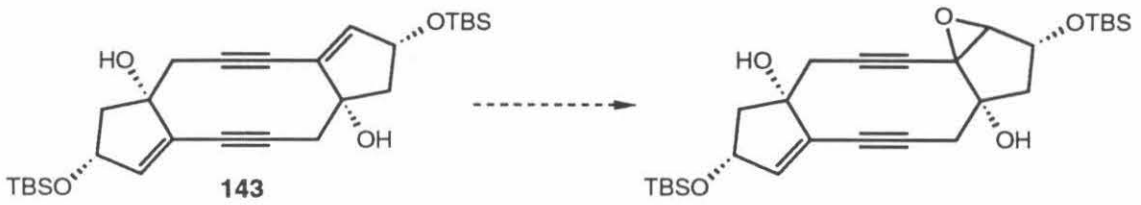
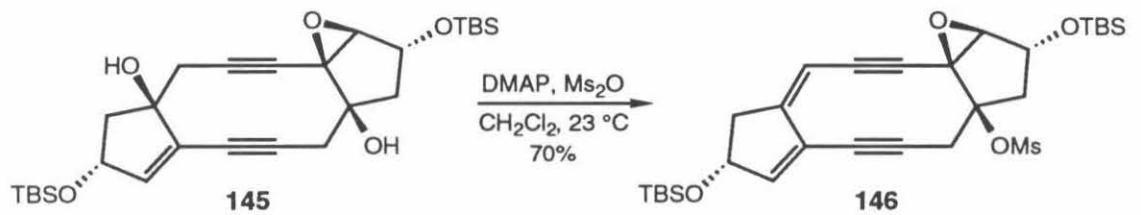


Figure 7. ^{1}H NMR (500 MHz) monitoring of conversion of diol **142** to silyl ether **123** and alcohol **144**. (a) Spectrum of diol **142** in deoxygenated CD_2Cl_2 at 23 °C. (b) Spectrum 30 min after sequential addition of 4-dimethylaminopyridine (5.0 equiv) and methanesulfonyl chloride (2.5 equiv) showing conversion of diol **142** to silyl ether **123** and alcohol **144** (1:2, respectively). (c) Spectrum taken immediately following addition of 0.25 mL air to NMR sample showing decomposition of silyl ether **123**.

equiv) in dichloromethane at 0 °C produced the identical epoxide, albeit in lower yield (~20%). The epoxide stereochemistry was assigned as shown based on the assumption that *m*-CPBA-mediated epoxidation proceeded with direction from the hydroxyl group. Interestingly, subjection of the diastereomeric diol (**143**) to identical reaction conditions



produced very little (if any) of the corresponding epoxide. Treatment of epoxide **145** with 4-dimethylaminopyridine (20 equiv) and methanesulfonic anhydride (10 equiv) in dichloromethane at 23 °C for 7 h afforded mesylate **146** (Ms = SO_2CH_3) in 70% yield. This compound could be purified by silica gel chromatography, but decomposed slowly under aerobic conditions in the absence of a radical inhibitor.



All attempts to convert mesylate **146** to epoxide **119** were unsuccessful. A variety of elimination conditions were applied (Table X) employing both thin layer chromatography and ^{1}H NMR monitoring of reaction progress. In each case, either no reaction after several hours of monitoring or consumption of mesylate **146** without formation of identifiable products was observed. These results suggested that **119** could be formed from **146**, but was unstable toward the reaction conditions used to create it. The possibility of utilizing mesylate **146** as a precursor to the 1,6-didehydro[10]annulene

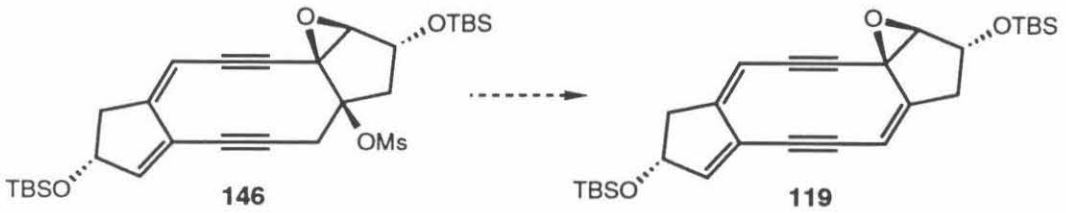


Table X. Conditions for Attempted Transformation of Mesylate **146** to Epoxide **119**.

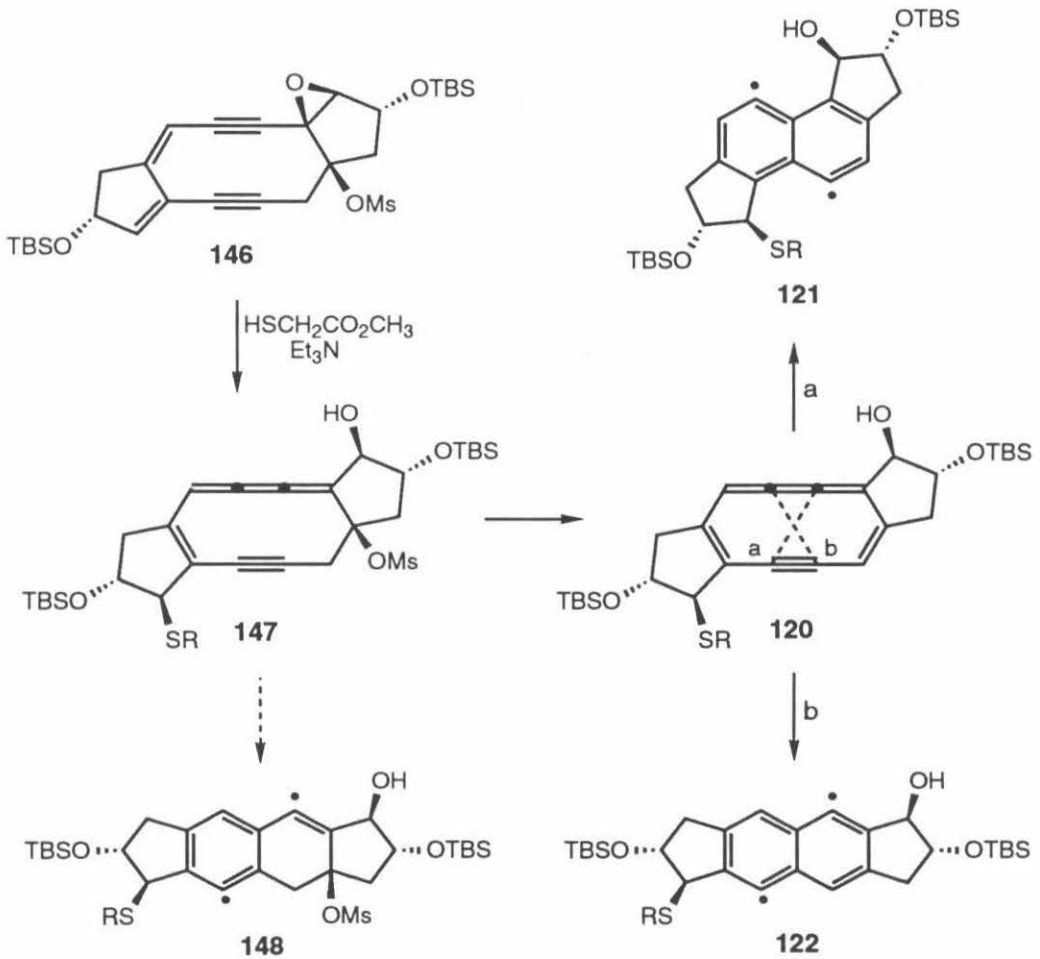
Entry	Base[a]	Solvent[b]	Temp (°C)	Result[c]
1	Et_3N	CH_2Cl_2	23	NR
2	DBU	Benzene	23	dec.
3	Et_3N	CF_3CH_2OH	23	NR
4	Proton Sponge	Benzene	23	NR
5	Dabco	Benzene	23	NR
6	$LiN[Si(CH_3)_3]_2$	THF	-78	NR
7	1,1,2,3,3-Pentaisopropyl-guanidine[d]	Benzene	23	NR

[a] Et_3N = triethylamine, DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, Dabco = 1,4-diazabicyclo[2.2.2]octane. [b] CH_2Cl_2 = dichloromethane, THF = tetrahydrofuran. [c] NR = no reaction, dec. = decomposition of **146** without product formation. [d] See: Barton, D. H. R.; Elliott, J. D.; Géro, S. D. *J. Chem. Soc., Chem. Commun.* **1981** 1136 and Barton, D. H. R.; Elliott, J. D.; Géro, S. D. *J. Chem. Soc., Perkin Trans. I* **1982**, 2085.

functional group was therefore assessed.

Ideally, **146** could, upon treatment with a thiol nucleophile, enter into the reaction cascade depicted in Scheme XXI in which formation of 1,6-didehydro[10]annulene **120** by loss of methanesulfonic acid from intermediate **147** was envisioned to be more rapid than electrocyclization of the (*Z*)-cumulene-ene-yne moiety (forming biradical **148**, cf. introduction). In the event, exposure of mesylate **146** (0.0017 M) to methyl thioglycolate

Scheme XXI

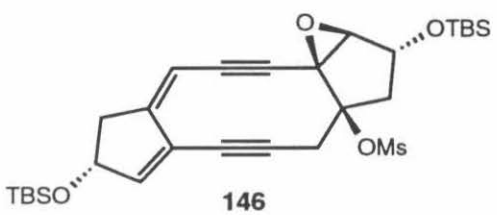


(10.0 equiv) and triethylamine (10.0 equiv) in a deoxygenated mixture of acetonitrile and tetrahydrofuran (1:1, respectively) containing 1,4-cyclohexadiene (1.0 M) for 12 h at 23 °C produced the isomeric naphthalenes **149** and **150** along with the disulfide **151** in good combined yield (Table XI, entry 1). The relative stereochemistry of these naphthalene products was assigned based on coupling constant analysis and the presumption that thiol addition occurred opposite the bulky *tert*-butyldimethylsilyl group. Conducting the reaction in a mixture of dimethyl sulfoxide and tetrahydrofuran (4:1, respectively)

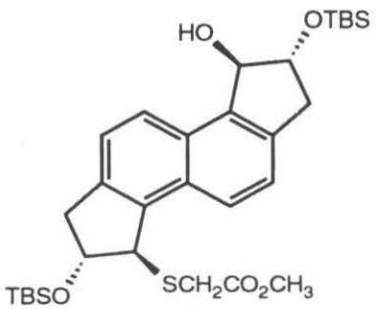
Table XI. Reaction of Mesylate **146** in Various Media.[a]

Entry	Solvent[b]	[$HSCH_2CO_2CH_3$] (M)	[Et_3N] (M)	Products[c]		
				149	**150**	**151**
1	1:1 CH_3CN-THF	0.017	0.017	27	8	36
2	4:1 DMSO-THF	0.017	0.017	65	20	<5
3	4:1 DMSO-THF[d]	0.017	0.017	25	10	<1
4	1:1 CH_3CN-THF	-	0.017	-	-	-
5	4:1 DMSO-THF	-	0.017	-	-	-
6	1:1 CH_3CN-THF	0.017	-	-	-	-
7	4:1 DMSO-THF	0.017	-	<5	<5	<5
8	THF	0.017	0.017	-	-	-

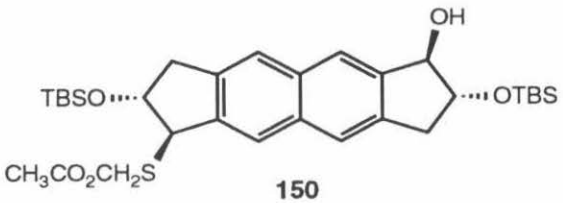
[a] 0.0017 M, 23 °C. [b] Also included 1.0 M 1,4-cyclohexadiene. [c] Yields determined by ^1H NMR analysis of crude reaction mixtures using benzene as an internal standard. [d] Included 0.90 M 1,4-cyclohexadiene-d_8.



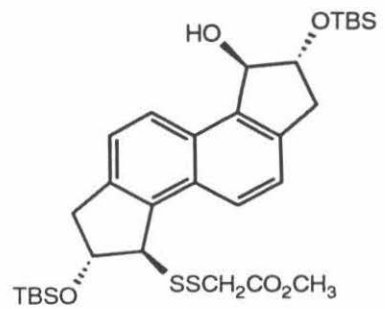
146



149

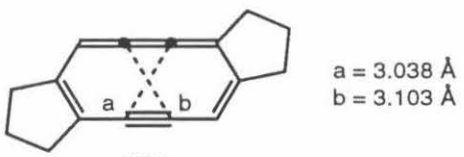


150



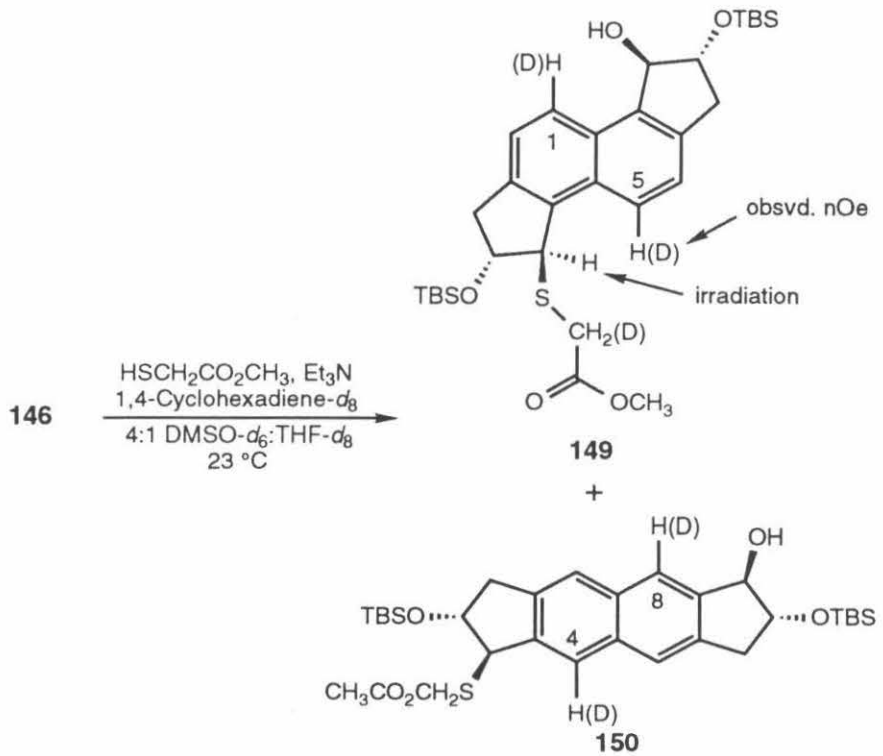
151

afforded naphthalenes **149** and **150** in good yield (Table XI, entry 2) and only a trace of **151** (<5%). The mechanism for formation of **151** is not known with certainty, but may involve internal hydrogen atom abstraction from the methyl thioglycolate sidechain of **121** (R = $CH_2CO_2CH_3$) by the adjacent naphthalene radical (see below). The formation of unequal amounts of isomeric naphthalenes in the above experiments (**149** + **151** versus **150**) was attributed to structural changes induced in the 1,6-didehydro[10]annulene system by the appended five-membered rings. Accordingly, a shorter distance between the atoms involved in the biradical-forming reaction leading to the major naphthalene isomer was observed in the computer-minimized structure of model compound **152** (pathway a, d = 3.038 versus pathway b, d = 3.103 Å).[100]



152

Treatment of **146** with methyl thioglycolate (10.0 equiv) and triethylamine (10.0 equiv) in the presence of 1,4-cyclohexadiene-d_8 (0.90 M) in deoxygenated 4:1 dimethyl sulfoxide-d_6:tetrahydrofuran-d_8 at 23 °C afforded naphthalenes **149** and **150** in moderate combined yield (Table XI entry 3).[101,102] Under these conditions, deuterium was incorporated at the C1 and C5 positions of **149** (identified by nOe experiments conducted with non-deuterated **149**, 39% and 10%, respectively) and the C4 and C8 positions of **150** (27% and 36%, respectively). In addition, substantial deuterium incorporation was observed in the methyl thioglycolate sidechain of **149** (60%), suggesting that internal hydrogen atom abstraction occurred during trapping of the intermediate naphthalene biradical. The incorporation of deuterium in the above experiments supported the intermediacy of biradicals **121** and **122** in the formation of naphthalenes **149** and **150**,



respectively.

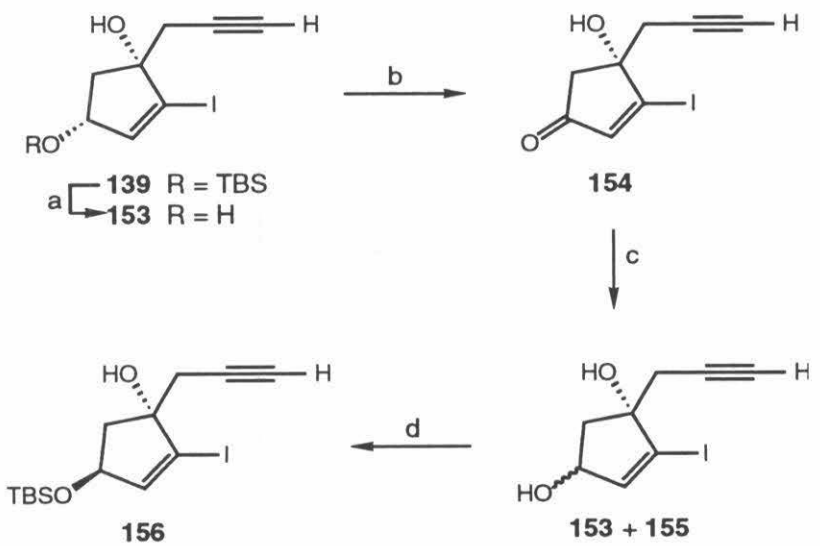
Control experiments conducted in several solvent mixtures established the presence of a thiol as a requirement for the production of naphthalene products. Thus, solutions of mesylate **146** (0.0017 M) in either deoxygenated acetonitrile-tetrahydrofuran (1:1) or deoxygenated dimethyl sulfoxide-tetrahydrofuran (4:1) containing 1,4-cyclohexadiene (1.0 M) and triethylamine (10 equiv) were stable in the absence of methyl thioglycolate for at least 12 h at 23 °C (Table XI, entries 4 and 5). The presence of the amine base was also determined to be critical for rapid naphthalene formation. No reaction of **146** (0.0017 M) was observed in deoxygenated acetonitrile-tetrahydrofuran (1:1) containing 1,4-cyclohexadiene (1.0 M) and methyl thioglycolate (10 equiv) after 12 h at 23 °C. Similarly, only traces of aromatized products were isolated when **146** (0.0017 M) was treated with methyl thioglycolate (10 equiv) in deoxygenated dimethyl sulfoxide-

tetrahydrofuran (4:1) containing 1,4-cyclohexadiene (1.0 M) for 12 h at 23 °C (Table XI, entries 6 and 7). Attempted cyclization of **146** in deoxygenated tetrahydrofuran at 23 °C led only to recovery of the starting material after 18 h, establishing the requirement for a polar reaction solvent (Table XI, entry 8).

Isomerization of Alcohol 139

The conversion of alcohol **139** to alcohol **156** is illustrated in Scheme XXII. This isomerization enables **139** to be utilized in the preparation of a 1,6-didehydro[10]-annulene precursor, i.e., the enantiomer of mesylate **146**. Removal of the silyl protecting group present in alcohol **139** was accomplished by treatment with tetrabutylammonium

Scheme XXII



Reagents and conditions (TBS = *t*-Bu$(CH_3)_2$Si): (a) 2.0 equiv *n*-Bu_4NF, THF, 23 °C, 45 min, 98%; (b) 1.5 equiv PCC, CH_2Cl_2, 23 °C, 1 h, 88%; (c) 1.1 equiv $NaBH_4$, CH_3OH, 0 °C, 15 min, 91%; (d) 1.1 equiv Et_3N, 1.1 equiv TBSCl, 0.13 equiv DMAP, CH_2Cl_2, 23 °C, 30 h, 85%.

fluoride (2.0 equiv) in tetrahydrofuran at 23 °C to afford diol **153** in 98% yield. Oxidation of **153** with pyridinium chlorochromate (1.5 equiv) in dichloromethane at 23 °C produced ketone **154** (88%) which was subsequently treated with a variety of reducing agents in an attempt to produce diol **155** (Table XII). The optimal conditions discovered involved reduction of **154** with sodium borohydride (1.1 equiv) in methanol at 0 °C and provided alcohols **155** and **153** as an inseparable mixture (5:1, respectively, 91% yield). Treatment of the above mixture of alcohols **155** and **153** with triethylamine (1.1 equiv), *tert*-butyldimethylsilyl chloride (1.1 equiv) and 4-dimethylaminopyridine (0.13 equiv) in dichloromethane at 23 °C for 30 h provided, after purification by flash column chromatography, pure alcohol **156** in 85% yield. Thus, **139** was efficiently converted to the isomeric alcohol **156** in four steps in 67% overall yield.

Table XII. Reduction of Ketone **154** under Various Conditions.

Entry	Conditions	**155:153**[a]
1	$CeCl_3 \cdot 7H_2O$-$NaBH_4$, CH_3OH, -78 °C	1:15
2	$CeCl_3 \cdot 7H_2O$-$NaBH_4$, CH_3OH, 23 °C	1:10
3	$NaBH(OAc)_3$, EtOAc, 0→23 °C	*b*
4	$NaBH(OAc)_3$, HOAc, 23 °C	*b*
5	$Zn(BH_4)_2$	*b*
6	1.1 equiv DIBAL, THF, 0 °C	3:1
7	2.2 equiv DIBAL, THF, 0 °C	2:1
8	$NaBH_4$, CH_3OH, 0 °C	5:1

[a] Determined by ^1H NMR analysis of crude reduction products. [b] Multiple products other than **153** and **155** were produced under these conditions.

Conclusions

The potential for a synthetic molecule to function as a 1,6-didehydro[10]annulene precursor has been demonstrated by the preparation and study of mesylate **146**. When treated with methyl thioglycolate and triethylamine in deoxygenated polar solvents at ambient temperature, this compound enters into a reaction cascade which culminates with the formation of two distinct 1,5-naphthalene biradicals via a novel electrocyclization reaction. The interaction of molecules such as **146** with nucleic acids must await their combination with appropriate DNA binding moieties.

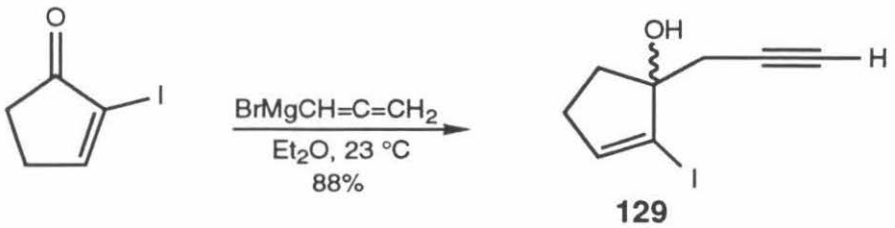
Experimental Section

General Procedures. 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/argon-flush cycles (≥ five iterations). Organic solutions were concentrated by rotary evaporation at ~25 Torr (water aspirator). Flash column chromatography was performed as described by Still et al.[55] employing 230-400 mesh silica gel. Analytical thin-layer chromatography was performed using glass plates pre-coated with 0.25 mm 230-400 mesh silica gel impregnated with a fluorescent indicator (254 nm).

Materials. Commercial reagents and solvents were used as received with the following exceptions. Ethyl ether and tetrahydrofuran (THF) were distilled from sodium benzophenone ketyl. Dichloromethane, benzene, and triethylamine were distilled from calcium hydride at 760 Torr. Dimethyl sulfoxide (DMSO) was distilled from calcium sulfate at 40 Torr and stored over 4Å molecular sieves. Methanesulfonyl chloride was distilled from phosphorous pentoxide at 760 Torr. Cuprous iodide was purified by continuous extraction (12 h) with tetrahydrofuran in a Soxhlet apparatus.[56] Tetrakis-(triphenylphosphine)palladium(0),[57] dimethyldioxirane,[71] and (diethylamino)trimethyl-stannane[95] were prepared according to literature procedures.

Instrumentation. Infrared (IR) spectra were obtained using a Perkin-Elmer 1600 FT-IR spectrophotometer referenced to a polystyrene standard. Data are presented as follows: frequency of absorption (cm^{-1}), intensity of absorption (s = strong, m = medium, w = weak, br = broad) and assignment (when appropriate). Proton nuclear magnetic resonance (^1H NMR) spectra were recorded with a JEOL JX-400 (400 MHz) or a Bruker AM-500 (500 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 7.15, $CHDCl_2$: δ 5.29). Data are represented as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), integration, coupling constant in Hertz (Hz), and assignment. High resolution mass spectra were obtained at the University of California, Riverside Mass Spectrometry Facility and at the Midwest Center for Mass Spectrometry, University of Nebraska-Lincoln (partially supported by the National Science Foundation, Biology Division; Grant No. DIR9017262).



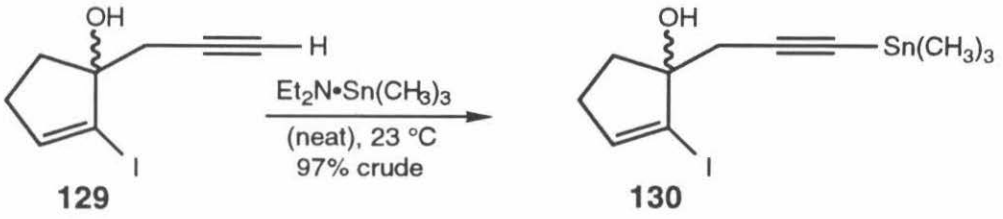
129

Alcohol **129**.

A solution of allenylmagnesium bromide[92] (16.4 mmol, 3.0 equiv) was prepared by sequential addition of propargyl bromide (1.83 mL of an 80 wt. % solution in toluene, 16.4 mmol, 3.0 equiv) and mercury(II) chloride (0.20 g, 0.74 mmol, 0.14 equiv) to a suspension of magnesium turnings (0.40 g, 16.4 mmol, 3.0 equiv) in ethyl ether (50 mL) at 23 °C. The resulting mixture was allowed to reflux gently for a brief time (5-15 min), then was stirred at 23 °C for 1 h. An additional portion of ethyl ether (20 mL) was added to the reaction mixture followed by a solution of 2-iodo-2-cyclopenten-1-one[93] (1.14 g, 5.48 mmol, 1 equiv) in ethyl ether (20 mL, dropwise addition over 5 min). The resulting suspension was maintained at 23 °C for 15 min, then was quenched (CAUTIOUSLY) with hydrochloric acid (1.0 M, 10 mL) and was partitioned between hydrochloric acid (1.0 M, 150 mL) and a 1:1 mixture of ethyl acetate and hexanes (2 x 200 mL). The combined organic layers were dried over sodium sulfate and were concentrated. The residue was purified by flash column chromatography (gradient elution: ethyl acetate in hexanes, 5→10%) to provide alcohol **129** (1.20 g, 88%) as a white solid (mp = 37-39 °C).

^{1}H NMR (500 MHz, $CDCl_3$), δ: 6.31 (t, 1 H, *J* = 2.6 Hz, C**H**=C), 2.59 (dd, 1 H, *J* = 16.6, 2.7 Hz, one of C$\mathbf{H}_2$C≡C), 2.35-2.53 (m, 4 H,

	both $CH_2CH=C$, one of CH_2COH, and one of $CH_2C\equiv C$), 2.09 (s, 1 H, OH), 2.01-2.07 (m, 1 H, one of CH_2COH), 2.00 (t, 1 H, J = 2.6 Hz, $C\equiv CH$).
FTIR (neat), cm^{-1}:	3397 (br, OH), 3293 (s, C≡CH), 2936 (m), 2846 (m), 2117 (w, C≡C), 1605 (w), 1422 (m), 1061 (s), 947 (m), 635 (s).
MS (EI), m/z (%base):	209 (100), 82 (63), 63 (10), 53 (7).
HRMS (EI):	Calcd for C_8H_9IO (M^+): 247.9698 Found: 247.9704
TLC (50% EtOAc in Hexanes), R_f:	2-Iodo-2-cyclopentenone: 0.65 (UV) Alcohol **129**: 0.76 (faint UV)

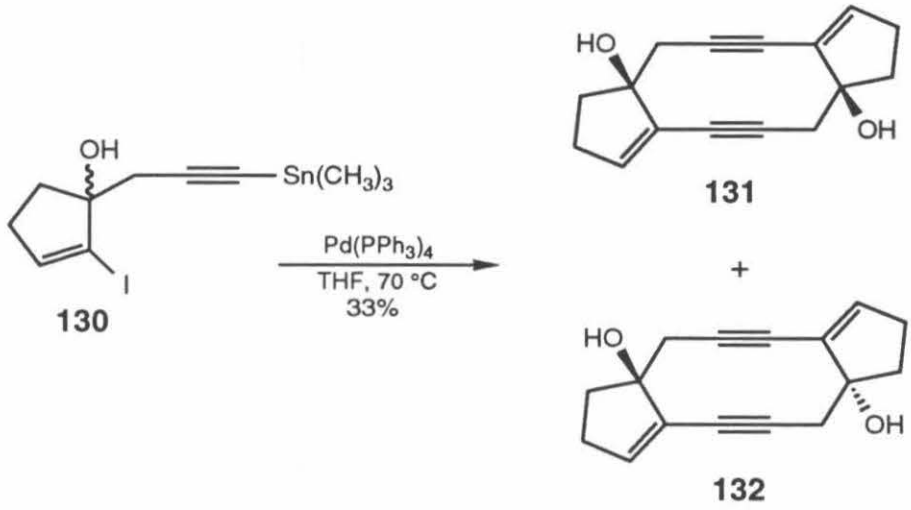


Trimethylstannane **130**.

(Diethylamino)trimethylstannane[95] (1.09 mL, 4.62 mmol assuming d = 1.0, 3.0 equiv) was added to alcohol **129** (neat, 0.383 g, 1.54 mmol, 1 equiv) at 23 °C over 1 min. The resulting yellow solution was stirred for 2 h at 23 °C, then the volatiles were removed under reduced pressure (2 Torr). The remaining orange oil was partitioned between a 1:1 mixture of ethyl acetate and hexanes (150 mL) and water (3 x 75 mL). The organic layer was dried over sodium sulfate and was concentrated to provide crude trimethylstannane **130** (0.611 g, 97% crude yield) as an off-white solid (mp not determined).

^{1}H NMR (500 MHz, C_6D_6), δ: 5.85 (t, 1 H, *J* = 2.5 Hz, C**H**=C), 2.59 (d, 1 H, *J* = 16.6, Hz, one of C**H**$_2$C≡C), 2.47 (d, 1 H, *J* = 16.6, Hz, one of C**H**$_2$C≡C), 2.27-2.32 (m, 1 H, one of C**H**$_2$CH=C), 1.92-1.96 (m, 2 H, one of C**H**$_2$CH=C and one of C**H**$_2$COH), 1.73-1.78 (m, 1 H, one of C**H**$_2$COH), 1.71 (s, 1 H, C≡C**H**), 0.11 (s, 9 H, Sn(C**H**$_3$)$_3$).

FTIR (neat), cm^{-1}: 3418 (br, OH), 2981 (m), 2917 (m), 2847 (w), 2154 (m, C≡C), 1607 (w), 1422 (m), 1163 (m), 1063 (s), 1005 (m), 961 (m), 778 (s).



Diols **131** and **132.**

Tetrakis(triphenylphosphine)palladium(0) (0.344 g, 0.298 mmol, 0.20 equiv) was added to a solution of crude trimethylstannane **130** (0.611 g, 1.49 mmol, 1 equiv) in deoxygenated tetrahydrofuran (100 mL) at 70 °C. The resulting orange solution was stirred at 70 °C for 13 h, then was cooled to 23 °C and was partitioned between water (150 mL) and a 1:1 mixture of ethyl acetate and hexanes (3 x 150 mL). The combined organic layers were dried over sodium sulfate and were concentrated. Purification of the residue by flash column chromatography (gradient elution: ethyl acetate in toluene, 0→30%) afforded diols **131** and **132** (stereochemistry undetermined, high R_f, 0.030 g, 17%, mp = 175 °C; low R_f, 0.029 g, 16%, mp = 150 °C, dec) as white solids.

Diol **131** or **132** (High R_f).

^{1}H NMR (500 MHz, $CDCl_3$), δ: 6.00 (t, 2 H, J = 2.7 Hz, C**H**=C), 2.97 (s, 2 H, O**H**), 2.78 (d, 2 H, J = 17.0 Hz, two of C**H**$_2$C≡C),

	2.73 (d, 2 H, J = 17.0 Hz, two of $CH_2C{\equiv}C$), 2.46-2.53 (m, 2 H, two of $CH_2CH{=}C$), 2.31-2.39 (m, 2 H, two of $CH_2CH{=}C$), 2.08-2.14 (m, 2 H, two of CH_2COH), 1.90-1.95 (m, 2 H, two of CH_2COH).
FTIR (neat), cm^{-1}:	3460 (br, OH), 2937 (w), 2850 (m), 2211 (w, C≡C), 1654 (w), 1412 (m), 1354 (m), 1264 (m), 1071 (s).
MS (EI), m/z (%base):	222 (50), 207 (7), 179 (41), 165 (44), 153 (10), 141 (3).
HRMS (EI):	Calcd for $C_{16}H_{14}O$ ($M\text{-}H_2O^+$): 222.1045 Found: 222.1042
TLC (50% EtOAc in Hexanes), R_f:	Alcohol **129**: 0.79 (faint UV) Diol **131** or **132** (High R_f): 0.50 (UV)

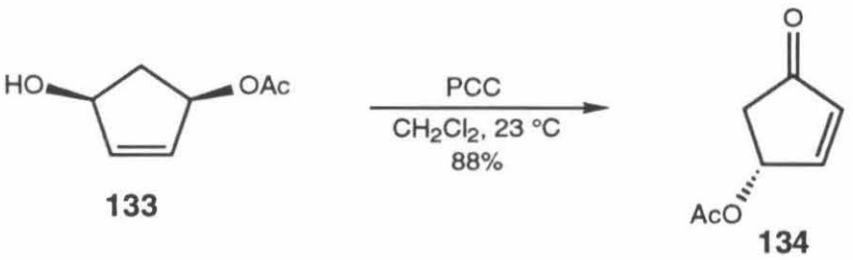
Diol **131** or **132** (Low R_f).

^{1}H NMR (500 MHz, $CDCl_3$), δ: 5.93 (t, 2 H, J = 2.7 Hz, C**H**=C), 3.22 (s, 2 H, O**H**), 2.80 (d, 2 H, J = 17.3 Hz, two of C**H**$_2$C≡C), 2.69 (d, 2 H, J = 17.3 Hz, two of C**H**$_2$C≡C), 2.46-2.53 (m, 2 H, two of C**H**$_2$CH=C), 2.30-2.37 (m, 2 H, two of C**H**$_2$CH=C), 2.06-2.12 (m, 2 H, two of C**H**$_2$COH), 1.90-1.95 (m, 2 H, two of C**H**$_2$COH).

FTIR (neat), cm^{-1}: 3154 (br, OH), 2926 (m), 2896 (m), 2215 (w, C≡C), 1620 (w), 1410 (m), 1322 (m), 1170 (m), 1072 (s), 843 (s).

TLC (50% EtOAc in Hexanes), R_f: Alcohol **129**: 0.79 (faint UV)

Diol **131** of **132** (Low R_f): 0.34 (UV)



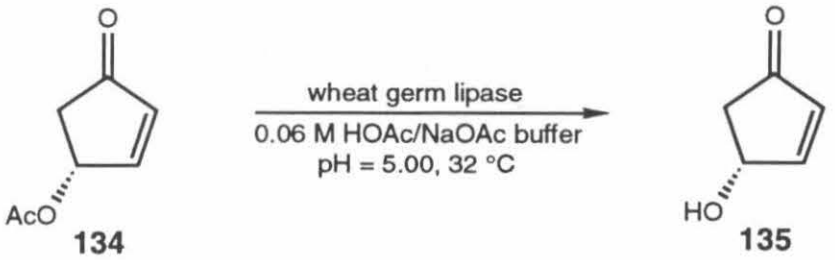
133 **134**

Ketone **134.**

Pyridinium chlorochromate (12.6 g, 58.5 mmol, 1.7 equiv) was added in six portions to a solution of 3(*R*)-acetoxy-5(*S*)-hydroxycyclopent-1-ene[96] (**133**, 96.5% ee, 4.91 g, 34.5 mmol, 1 equiv) in dichloromethane (200 mL) at 23 °C. The brown reaction mixture was stirred for 3 h at 23 °C, then was concentrated to ~ 30 mL volume. The resulting brown tar was passed through a short column of silica gel, eluting with ethyl acetate. The fractions containing the product were concentrated and the residue was purified by flash column chromatography (30% ethyl acetate in hexanes) to provide ketone **134** (4.25 g, 88%) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$), δ: 7.56 (ddd, 1 H, *J* = 5.7, 2.4, 0.7 Hz, C**H**=CHC=O), 6.33 (dd, 1 H, *J* = 5.7, 1.1 Hz, CH=C**H**C=O), 5.84-5.86 (m, 1 H, AcOC**H**), 2.82 (dd, 1 H, *J* = 19.0, 6.4 Hz, one of C$\mathbf{H}_2$C=O), 2.32 (dd, 1 H, *J* = 19.0, 2.2 Hz, one of C$\mathbf{H}_2$C=O), 2.09 (s, 3 H, $\mathbf{CH}_3$).

FTIR (neat), cm^{-1}:	3081 (w), 2941 (w), 1728 (s, both C=O), 1373 (m), 1240 (s), 1184 (m), 1102 (m), 1033 (s), 795 (m).
MS (EI), m/z (%base):	140 (17), 112 (25), 98 (81), 80 (33), 70 (30).
HRMS (EI):	Calcd for $C_7H_8O_3$ (M^+): 140.0473 Found: 140.0472
TLC (50% EtOAc in Hexanes), R_f:	3(*R*)-acetoxy-5(*S*)-hydroxycyclopent-1-ene: 0.30 Ketone **134**: 0.52 (faint UV)



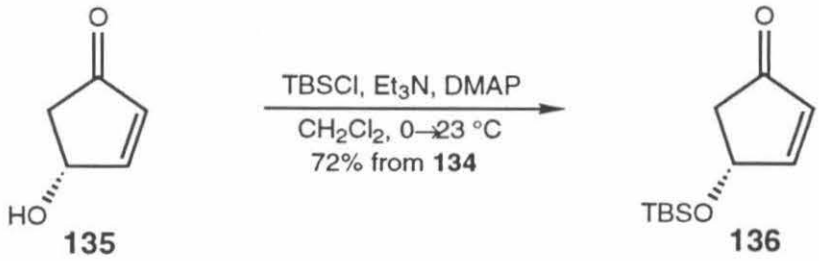
Alcohol **135.**

Ketone **134** (7.04 g, 50.2 mmol) was added to a suspension of wheat germ lipase (E.C. 3.1.1.3, Type I, 2.90 g lyophilized powder) in an acetate buffer (NaOAc/HOAc, 0.06 M, pH = 5.00, 250 mL) at 32 °C. The brown reaction mixture was stirred at 32 °C for 2.5 days, then was vacuum-filtered through coarse filter paper. The filtrate was saturated with ammonium sulfate and was exhaustively extracted with ethyl acetate (6 x 200 mL). The combined organic layers were dried over sodium sulfate and were concentrated to provide crude alcohol **135** (brown oil) which was used without further purification.

^{1}H NMR (500 MHz, $CDCl_3$), δ: 7.57 (dd, 1 H, *J* = 5.7, 2.2 Hz, C**H**=CHC=O), 6.23 (dd, 1 H, *J* = 5.7, 1.1 Hz, CH=C**H**C=O), 5.05-5.06 (m, 1 H, HOC**H**), 2.78 (dd, 1 H, *J* = 18.5, 6.1 Hz, one of C**H**$_2$C=O), 2.28 (dd, 1 H, *J* = 18.5, 2.1 Hz, one of C**H**$_2$C=O).

FTIR (neat), cm^{-1}: 3392 (br, OH), 2925 (w), 1713 (s, C=O), 1587 (w), 1405 (w), 1343 (m), 1192 (m), 1105 (s), 1046 (s), 948 (w), 798 (m).

MS (EI), m/z (%base):	98 (52), 81 (9), 70 (100), 55 (83).
HRMS (EI):	Calcd for $C_5H_6O_2$ (M^+): 98.0368 Found: 98.0369
TLC (50% EtOAc in Hexanes), R_f:	Ketone **134**: 0.56 (faint UV) Alcohol **135**: 0.12 (faint UV)

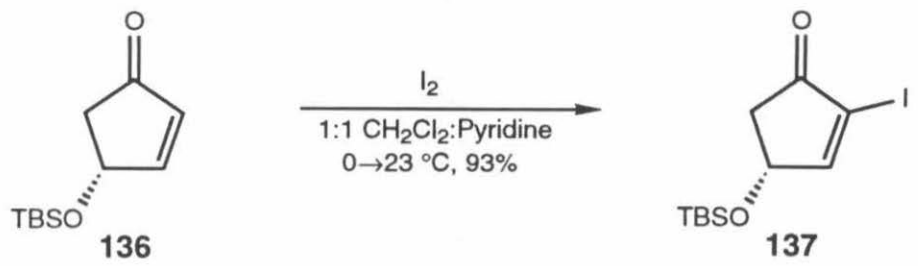


Silyl Ether **136.**

Triethylamine (14.0 mL, 100 mmol, 2.0 equiv), *tert*-butyldimethylsilyl chloride (11.3 g, 75.0 mmol, 1.5 equiv), and 4-dimethylaminopyridine (1.0 g, 8.0 mmol, 0.16 equiv) were added sequentially to an ice-cooled solution of crude alcohol **135** (~ 50 mmol, prepared in preceding experimental) in dichloromethane (110 mL). The resulting pale yellow solution was warmed to 23 °C and stirred for 6 h, then was partitioned between water (150 mL) and a 1:1 mixture of ethyl acetate and hexanes (2 x 200 mL). The combined organic layers were dried over sodium sulfate and were concentrated. The resulting oil was placed in a flask fitted with a short-path distillation apparatus and was heated under reduced pressure (2 Torr) until the distillation of a clear liquid (bp 35-40 °C, silyl impurity) was complete. The liquid remaining in the distillation pot was chromatographed on silica gel (20% ethyl acetate in hexanes) to afford silyl ether **136** (7.66 g, 72% from ketone **134**) as a colorless oil which solidified when stored at -20 °C.

^{1}H NMR (500 MHz, $CDCl_3$), δ: 7.45 (dd, 1 H, *J* = 5.6, 2.3 Hz, C**H**=CHC=O), 6.18 (dd, 1 H, *J* = 5.6, 1.2 Hz, CH=C**H**C=O), 4.97-5.00 (m, 1 H, SiOC**H**), 2.70 (dd, 1 H, *J* = 18.2, 6.0 Hz, one of C**H**$_2$C=O), 2.24 (dd, 1 H, *J* = 18.2, 2.3 Hz,

	one of $CH_2C=O$), 0.91 (s, 9 H, $SiC(CH_3)_3$), 0.13 (s, 3 H, one of $Si(CH_3)_2$), 0.12 (s, 3 H, one of $Si(CH_3)_2$).
FTIR (neat), cm^{-1}:	2955 (s), 2932 (s), 2858 (s), 1722 (s, C=O), 1471 (m), 1357 (m), 1256 (m), 1110 (s), 1072 (s), 901 (s), 836 (s), 779 (s).
MS (EI), m/z (%base):	212 (0.1), 197 (2), 155 (100), 125 (4), 111 (9), 81 (53).
HRMS (EI):	Calcd for $C_{11}H_{20}O_2Si$ (M^+): 212.1233 Found: 212.1228
TLC (50% EtOAc in Hexanes), R_f:	Alcohol **135**: 0.15 (faint UV) Silyl Ether **136**: 0.86 (UV)

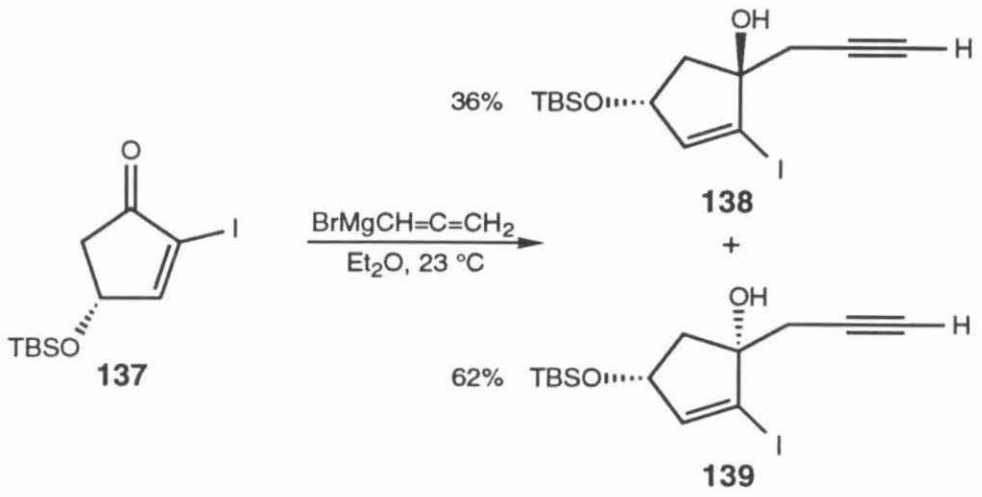


Iodide **137.**

A solution of iodine (3.92 g, 15.4 mmol, 1.7 equiv) in a 1:1 mixture of pyridine and dichloromethane (50 mL) was added dropwise via addition funnel over 45 min to an ice-cooled solution of silyl ether **136** (1.93 g, 9.09 mmol 1 equiv) in the same solvent mixture (50 mL). Upon completion of the addition, the reaction mixture was warmed to 23 °C and was maintained at that temperature for 2 h. Ethyl ether (150 mL) was added and the combined mixture was washed sequentially with a saturated solution of sodium thiosulfate (1 x 150 mL), dilute hydrochloric acid (1.0 M, 3 x 150 mL) and water (1 x 150 mL), then was dried over sodium sulfate and was concentrated. The residue was purified by flash column chromatography (5% ethyl acetate in hexanes) to afford iodide **137** (2.86, 93%) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$), δ: 7.79 (d, 1 H, J = 2.7 Hz, C**H**=CI), 4.95 (dt, 1 H, J = 6.1, 2.3 Hz, SiOC**H**), 2.86 (dd, 1 H, J = 18.2, 6.1 Hz, one of CH_2C=O), 2.34 (dd, 1 H, J = 18.2, 2.1 Hz, one of CH_2C=O), 0.90 (s, 9 H, SiC(CH_3)$_3$), 0.13 (s, 3 H, one of Si(CH_3)$_2$), 0.12 (s, 3 H, one of Si(CH_3)$_2$).

FTIR (neat), cm^{-1}:	2953 (m), 2930 (m), 2857 (m), 1727 (s, C=O), 1579 (m), 1470 (m), 1257 (m), 1088 (s), 905 (s), 834 (s), 780 (m).
MS (CI/NH_3), m/z (%base):	356 (100), 339 (4), 281 (27), 230 (3), 91 (4), 75 (5).
HRMS (CI/NH_3):	Calcd for $C_{11}H_{23}INO_2Si$ (MNH_4^+): 356.0543 Found: 356.0528
TLC (20% EtOAc in Hexanes), R_f:	Silyl Ether **136**: 0.55 (UV) Iodide **137**: 0.70 (UV)



Alcohols **138** and **139**.

A solution of allenylmagnesium bromide[92] (15.0 mmol, 4.0 equiv) was prepared by sequential addition of propargyl bromide (1.69 mL of an 80 wt. % solution in toluene, 15.0 mmol, 4.0 equiv) and mercury(II) chloride (0.20 g, 0.74 mmol, 0.20 equiv) to a suspension of magnesium turnings (0.37 g, 15.0 mmol, 4.0 equiv) in ethyl ether (30 mL) at 23 °C. The resulting mixture was allowed to reflux gently for a brief time (5-15 min), then was stirred at 23 °C for 1 h. An additional portion of ethyl ether (20 mL) was added to the reaction mixture followed by a solution of iodide **137** (1.28 g, 3.78 mmol, 1 equiv) in ethyl ether (10 mL, dropwise addition over 5 min). The resulting suspension was maintained at 23 °C for 15 min, then was quenched (CAUTIOUSLY) with hydrochloric acid (1.0 M, 10 mL) and was partitioned between hydrochloric acid (1.0 M, 150 mL) and a 1:1 mixture of ethyl acetate and hexanes (2 x 150 mL). The combined organic layers were dried over sodium sulfate and were concentrated. The residue was purified by careful flash column chromatography (gradient elution: ethyl acetate in hexanes, 5→10%) to provide the diastereomeric alcohols **138** (low R_f, clear oil, 0.51 g, 36%) and **139** (high R_f, white solid, mp = 57-61 °C, 0.89 g, 62%) in 98% combined yield. The

stereochemistry of alcohol **139** was determined by X-ray analysis of a crystal obtained by maintaining a saturated solution of **139** in hexanes in a sealed vial at -20 °C for 5 days (see Appendix 1).

Alcohol **138** (Low *Rf*).

^{1}H NMR (500 MHz, $CDCl_3$), δ: 6.29 (d, 1 H, J = 2.4 Hz, C**H**=CI), 4.86-4.88 (m, 1 H, SiOC**H**), 2.69 (dd, 1 H, J = 16.6, 2.6 Hz, $CH_AH_BC{\equiv}C$), 2.50 (dd, 1 H, J = 16.6, 2.6 Hz, $CH_AH_BC{\equiv}C$), 2.36 (dd, 1 H, J = 11.9, 6.8 Hz, one of $CH_2C(OH)$), 2.18 (s, 1 H, O**H**), 2.16 (dd, 1 H, J = 11.9, 3.5 Hz, one of $CH_2C(OH)$), 2.08 (t, 1 H, J = 2.6 Hz, C≡C**H**), 0.88 (s, 9 H, $SiC(CH_3)_3$), 0.08 (s, 3 H, one of $Si(CH_3)_2$), 0.07 (s, 3 H, one of $Si(CH_3)_2$).

FTIR (neat), cm^{-1}: 3381 (br, OH), 3311 (m, C≡CH), 2931 (s), 2857 (s), 2119 (w, C≡C), 1604 (m), 1470 (m), 1360 (m), 1255 (s), 1082 (s), 907 (s), 835 (s), 777 (s).

MS (CI/NH_3), m/z (%base): 396 (13), 361 (16), 321 (20), 264 (100), 247 (16), 235 (16), 194 (10).

HRMS (CI/NH_3): Calcd for $C_{14}H_{27}INO_2Si$ (MNH_4^+): 396.0856
Found: 396.0851

TLC (20% EtOAc in Hexanes), R_f: Silyl Ether **137**: 0.67 (UV)
Alcohol **138** (Low R_f): 0.44

Alcohol **139** (High R_f).

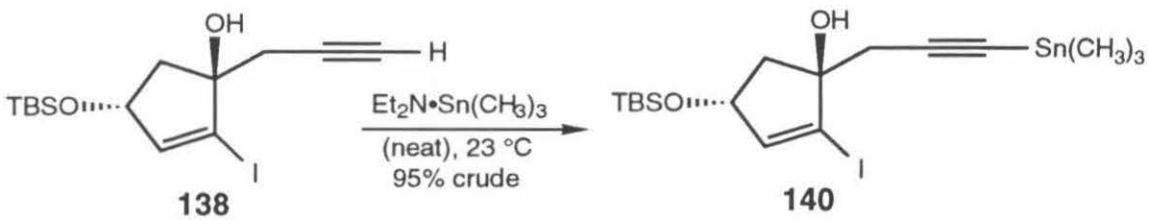
^{1}H NMR (500 MHz, $CDCl_3$), δ: 6.30 (d, 1 H, J = 2.2 Hz, C**H**=CI), 4.68-4.71 (m, 1 H, SiOC**H**), 2.81 (dd, 1 H, J = 13.6, 7.0 Hz, one of C$\mathbf{H}_2$C(OH)), 2.53 (dd, 1 H, J = 16.6, 2.7 Hz, C$\mathbf{H}_A$H$_B$C≡C), 2.40 (dd, 1 H, J = 16.6, 2.7 Hz, CH$_A$**H**$_B$C≡C), 2.25 (s, 1 H, O**H**), 1.99 (t, 1 H, J = 2.7 Hz, C≡C**H**), 1.89 (dd, 1 H, J = 13.6, 4.2 Hz, one of C$\mathbf{H}_2$C(OH)), 0.89 (s, 9 H, SiC(C$\mathbf{H}_3$)$_3$), 0.09 (s, 6 H, both Si(C$\mathbf{H}_3$)$_2$).

FTIR (neat), cm^{-1}: 3440 (br, OH), 3310 (m, C≡CH), 2953 (m), 2931 (m), 2857 (m), 2122 (w, C≡C), 1604 (m), 1468 (m), 1358 (m), 1255 (s), 1081 (s), 908 (s), 836 (s), 777 (s).

MS (CI/NH_3), m/z (%base): 396 (13), 361 (16), 321 (20), 264 (100), 247 (16), 235 (16), 194 (10).

HRMS (CI/NH_3): Calcd for $C_{14}H_{27}INO_2Si$ (MNH_4^+): 396.0856
Found: 396.0851

TLC (20% EtOAc in Hexanes), R_f: Iodide **137**: 0.67 (UV)
Alcohol **139** (High R_f): 0.54

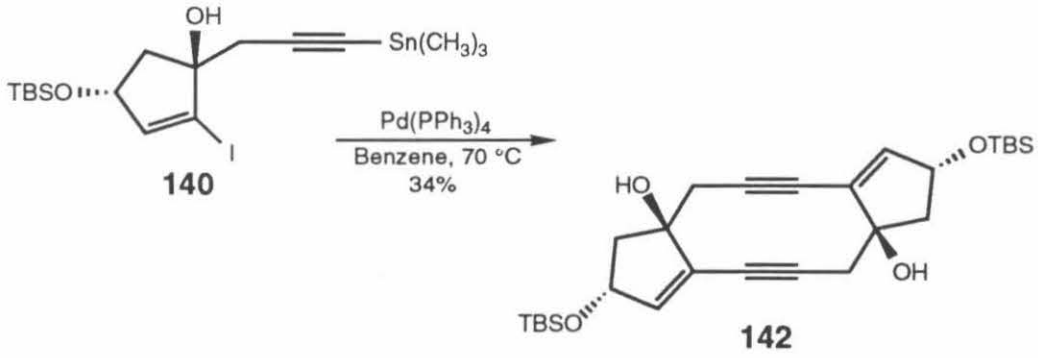


Trimethylstannane **140.**

(Diethylamino)trimethylstannane[95] (0.797 mL, 3.38 mmol assuming d = 1.0, 3.0 equiv) was added to alcohol **138** (neat, 0.43 g, 1.13 mmol, 1 equiv) at 23 °C over 1 min. The resulting yellow solution was stirred for 3.5 h at 23 °C, then the volatiles were removed under reduced pressure (2 Torr). The remaining orange oil was partitioned between a 1:1 mixture of ethyl acetate and hexanes (150 mL) and water (3 x 100 mL). The organic layer was dried over sodium sulfate and was concentrated to provide crude trimethylstannane **140** as an off-white solid (0.58 g, 95% crude yield).

^{1}H NMR (500 MHz, C_6D_6), δ: 6.08 (d, 1 H, J = 2.3 Hz, C**H**=CI), 4.56-4.58 (m, 1 H, SiOC**H**), 2.74 (d, 1 H, J = 16.7 Hz, C$\mathbf{H}_A$H$_B$C≡C), 2.61 (d, 1 H, J = 16.7 Hz, CH$_A$**H**$_B$C≡C), 2.34 (dd, 1 H, J = 13.3, 3.7 Hz, one of C**H**$_2$C(OH)), 2.27 (dd, 1 H, J = 13.3, 6.7 Hz, one of C**H**$_2$C(OH)), 0.88 (s, 9 H, SiC(C**H**$_3$)$_3$), 0.18 (s, 9 H, Sn(C**H**$_3$)$_3$), -0.06 (s, 3 H, one of Si(C**H**$_3$)$_2$), -0.08 (s, 3 H, one of Si(C**H**$_3$)$_2$).

FTIR (neat), cm^{-1}: 3330 (w, OH), 2929 (s), 2857 (s), 2155 (m, C≡C), 1605 (m), 1470 (m), 1359 (m), 1256 (s), 1081 (s), 909 (s), 835 (s), 776 (s).

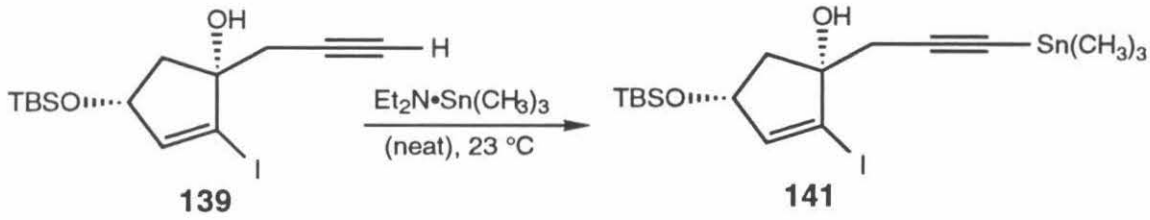


Diol **142**.

Tetrakis(triphenylphosphine)palladium(0) (0.400 g, 0.346 mmol, 0.20 equiv) was added to a solution of crude trimethylstannane **140** (0.936 g, 1.73 mmol, 1 equiv) in deoxygenated benzene (350 mL) at 70 °C. The resulting orange solution was stirred at 70 °C for 12 h, then was cooled to 23 °C and was partitioned between water (150 mL) and a 1:1 mixture of ethyl acetate and hexanes (3 x 150 mL). The combined organic layers were dried over sodium sulfate and were concentrated. Purification of the residue by flash column chromatography (gradient elution 0→10% ethyl acetate in toluene) afforded diol **142** (0.150 g, 34%) as a brown oil.

^{1}H NMR (500 MHz, $CDCl_3$), δ: 5.83 (d, 2 H, J = 2.5 Hz, C**H**=C), 4.86-4.88 (m, 2 H, SiOC**H**), 2.93 (d, 2 H, J = 17.5 Hz, C$\mathbf{H}_A$H$_B$C≡C), 2.84 (d, 2 H, J = 17.5 Hz, CH$_A$**H**$_B$C≡C), 2.32 (dd, 2 H, J = 13.8, 6.7 Hz, two of C**H**$_2$C(OH)), 1.76 (dd, 2 H, J = 13.8, 2.4 Hz, two of C**H**$_2$C(OH)), 0.87 (s, 18 H, SiC(C**H**$_3$)$_3$), 0.05 (s, 6 H, two of Si(C**H**$_3$)$_2$), 0.05 (s, 6 H, two of Si(C**H**$_3$)$_2$).

FTIR (neat), cm^{-1}:	3330 (br, OH), 2932 (s), 2858 (s), 2223 (w, C≡C), 1624 (w), 1469 (m), 1359 (s), 1255 (s), 1093 (s), 910 (s), 837 (s), 777 (s).
MS (CI/NH_3), m/z (%base):	518 (17), 402 (7), 311 (6), 279 (10), 254 (14), 237 (10).
HRMS (CI/NH_3):	Calcd for $C_{28}H_{48}NO_4Si_2$ (MNH_4^+): 518.3122 Found: 518.3114
TLC (20% EtOAc in Hexanes), R_f:	Alcohol **138** (Low R_f): 0.44 Diol **142**: 0.20 (UV)

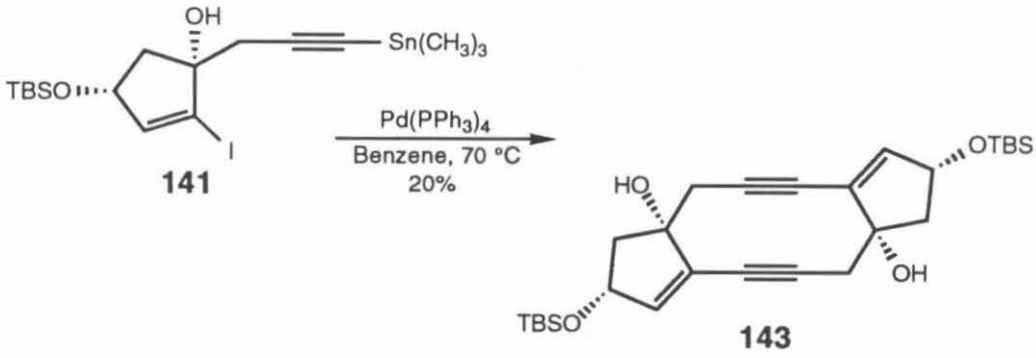


Trimethylstannane **141.**

(Diethylamino)trimethylstannane[95] (0.56 mL, 2.39 mmol assuming d = 1.0, 3.0 equiv) was added to alcohol **139** (neat, 0.30 g, 0.80 mmol, 1 equiv) at 23 °C over 1 min. The resulting yellow solution was stirred for 2 h at 23 °C, then the volatiles were removed under reduced pressure (2 Torr). The remaining orange oil was partitioned between a 1:1 mixture of ethyl acetate and hexanes (150 mL) and water (3 x 75 mL). The organic layer was dried over sodium sulfate and was concentrated to provide crude trimethylstannane **141** as an off-white solid (yield not determined).

^{1}H NMR (500 MHz, C_6D_6), δ: 6.20 (d, 1 H, *J* = 2.1 Hz, C**H**=CI), 4.68-4.71 (m, 1 H, SiOC**H**), 2.82 (dd, 1 H, *J* = 13.2, 7.2 Hz, one of C$\mathbf{H}_2$C(OH)), 2.54 (d, 1 H, *J* = 16.4 Hz, C$\mathbf{H}_A$H$_B$C≡C), 2.50 (d, 1 H, *J* = 16.4 Hz, CH$_A$**H**$_B$C≡C), 2.25 (s, 1 H, O**H**), 1.87 (dd, 1 H, *J* = 13.2, 4.9 Hz, one of C**H**$_2$C(OH)), 0.91 (s, 9 H, SiC(C**H**$_3$)$_3$), 0.12 (s, 9 H, Sn(C**H**$_3$)$_3$), 0.02 (s, 3 H, one of Si(C**H**$_3$)$_2$), 0.02 (s, 3 H, one of Si(C**H**$_3$)$_2$).

FTIR (neat), cm^{-1}: 3423 (br, OH), 2930 (s), 2857 (m), 2156 (m, C≡C), 1608 (w), 1347 (m), 1256 (s), 1068 (s), 1035 (s), 921 (m), 832 (s), 777 (s).

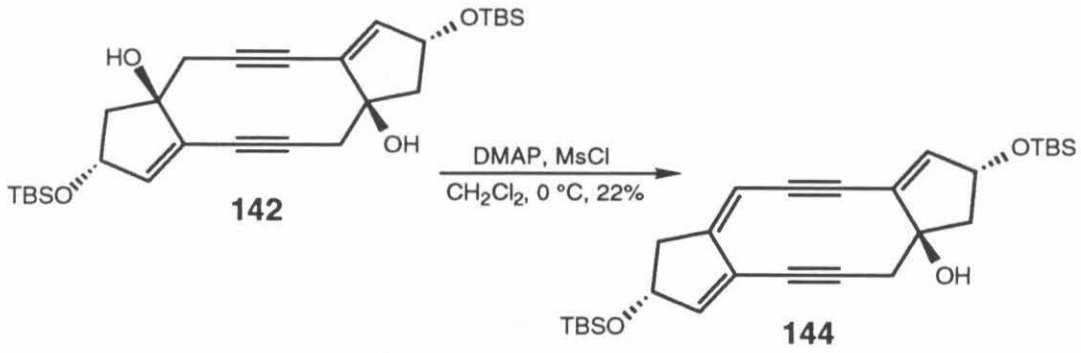


Diol **143.**

Tetrakis(triphenylphosphine)palladium(0) (0.035 g, 0.030 mmol, 0.20 equiv) was added to a solution of crude trimethylstannane **141** (0.083 g, 0.153 mmol, 1 equiv) in deoxygenated benzene (40 mL) at 70 °C. The resulting orange solution was stirred at 70 °C for 12 h, then was cooled to 23 °C and was partitioned between water (100 mL) and a 1:1 mixture of ethyl acetate and hexanes (2 x 100 mL). The combined organic layers were dried over sodium sulfate and were concentrated. Purification of the residue by flash column chromatography (10% ethyl acetate in hexanes) afforded diol **143** (0.010 g, 20%) as a brown oil.

^{1}H NMR (500 MHz, $CDCl_3$), δ: 5.79 (d, 2 H, J = 1.9 Hz, C**H**=C), 4.70-4.72 (m, 2 H, SiOC**H**), 2.85 (d, 2 H, J = 17.3 Hz, C$\mathbf{H}_A$H$_B$C≡C), 2.49 (d, 2 H, J = 17.3 Hz, CH$_A$**H**$_B$C≡C), 2.35 (dd, 2 H, J = 13.6, 6.9 Hz, two of C$\mathbf{H}_2$C(OH)), 1.97 (dd, 2 H, J = 13.6, 5.5 Hz, two of C$\mathbf{H}_2$C(OH)), 0.88 (s, 18 H, SiC(C$\mathbf{H}_3$)$_3$), 0.07 (s, 6 H, two of Si(C$\mathbf{H}_3$)$_2$), 0.06 (s, 6 H, two of Si(C$\mathbf{H}_3$)$_2$).

FTIR (neat), cm^{-1}:	3391 (br, OH), 2930 (s), 2857 (s), 2223 (w, C≡C), 1628 (w), 1469 (m), 1359 (m), 1254 (m), 1115 (s), 1082 (s), 919 (m), 835 (s), 777 (m).
MS (CI/NH_3), m/z (%base):	518 (17), 402 (7), 311 (6), 279 (10), 254 (14), 237 (10).
HRMS (CI/NH_3):	Calcd for $C_{28}H_{48}NO_4Si_2$ (MNH_4^+): 518.3122 Found: 518.3114
TLC (20% EtOAc in Hexanes), R_f:	Alcohol **139** (High R_f): 0.54 Diol **143**: 0.34 (UV)



Alcohol **144.**

4-Dimethylaminopyridine (0.044 g, 0.360 mmol, 10.0 equiv) and methanesulfonyl chloride (0.014 mL, 0.181 mmol, 5.0 equiv) were added sequentially to an ice-cooled solution of diol **142** (0.018 g, 0.036 mmol, 1 equiv) in dichloromethane (7.0 mL). The resulting suspension was stirred for 20 min at 0 °C, then was partitioned between water (100 mL) and a 1:1 mixture of ethyl acetate and hexanes (2 x 75 mL). The combined organic layers were dried over sodium sulfate and were concentrated. The residue was purified by flash column chromatography (5% ethyl acetate in hexanes) to provide alcohol **144** (0.0038 g 22%) as a clear film.

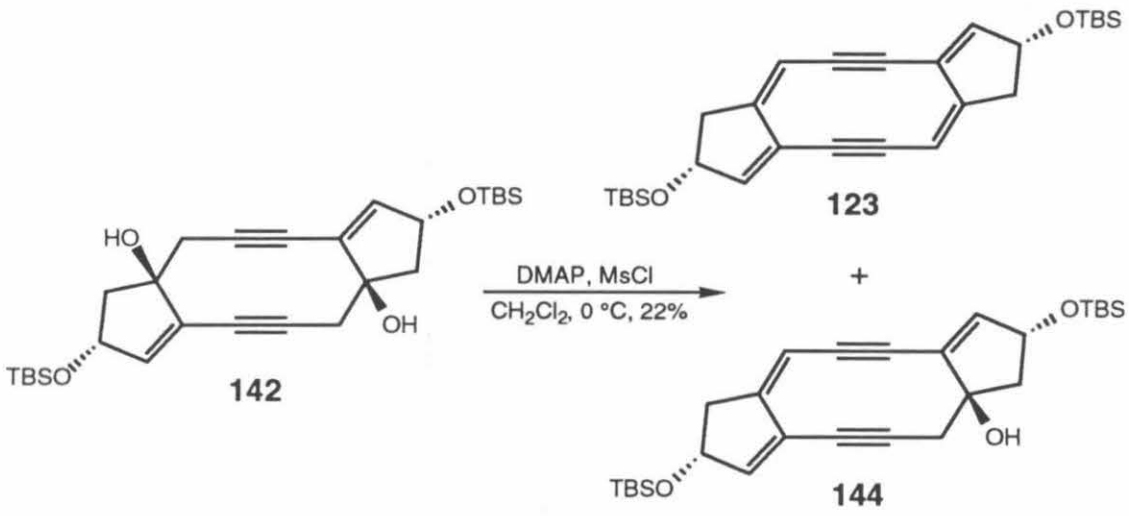
^{1}H NMR (500 MHz, CD_2Cl_2), δ: 6.26 (s, 1 H, SiOCHC**H**=CC=CH), 5.83 (d, 1 H, *J* = 2.5 Hz, C**H**=CCOH), 5.49 (d, 1 H, *J* = 1.5 Hz, SiOCHCH=CC=C**H**), 4.92-4.95 (m, 2 H, both SiOC**H**), 2.98 (ddd, 1 H, *J* = 17.4, 6.6, 1.7 Hz, one of SiOCHC$\mathbf{H}_2$), 2.93 (d, 1 H, *J* = 17.3 Hz, C$\mathbf{H}_A$H$_B$C≡C), 2.83 (d, 1 H, *J* = 17.3 Hz, CH$_A$**H**$_B$C≡C), 2.46 (dt, 1 H, *J* = 17.4, 2.5 Hz, one

of SiOCHC**H**$_2$), 2.39 (dd, 1 H, J = 13.9, 6.9 Hz, one of SiOCHC**H**$_2$), 1.70 (dd, 1 H, J = 13.9, 3.3 Hz, one of SiOCHC**H**$_2$), 0.88 (s, 9 H, SiC(C**H**$_3$)$_3$), 0.08 (s, 3 H, one of Si(C**H**$_3$)$_2$), 0.07 (s, 3 H, one of Si(C**H**$_3$)$_2$).

FTIR (neat), cm^{-1}: 3433 (br, OH), 2931 (s), 2857 (s), 2221 (w, C≡C), 2180 (w, C≡C), 1471 (m), 1359 (m), 1255 (s), 1087 (s), 911 (m), 836 (s), 777 (s).

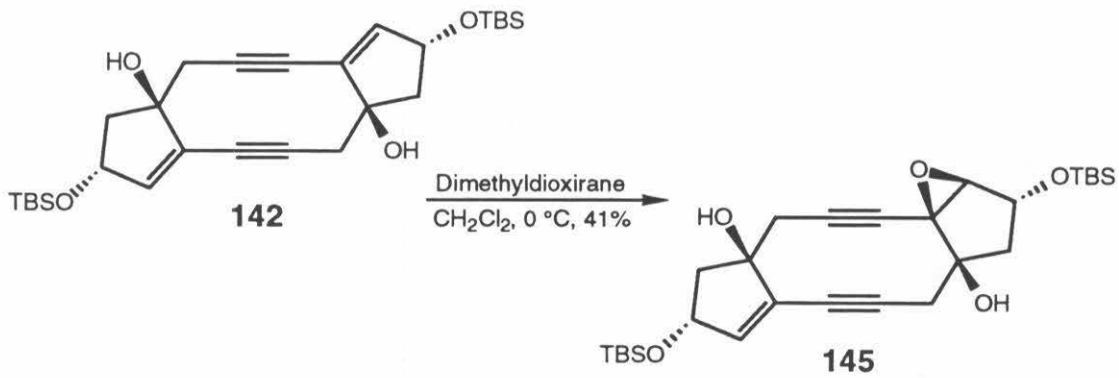
TLC (20% EtOAc in Hexanes), R_f: Diol **142**: 0.17 (UV)

Alcohol **144**: 0.62 (UV)



Silyl Ether **123** and Alcohol **144** (NMR Experiment).

Methanesulfonyl chloride (0.0019 mL, 0.025 mmol, 2.5 equiv) was added to a deoxygenated solution of diol **142** (0.005 g, 0.010 mmol, 1 equiv) and 4-dimethylaminopyridine (0.006 g, 0.049 mmol, 5.0 equiv) in dichloromethane-d_2 (1.0 mL) at 23 °C in an NMR tube. The mixture was shaken vigorously and examined by ^{1}H NMR spectroscopy (500 MHz) which showed, within 30 min at 23 °C, conversion of diol **142** to silyl ether **123** and alcohol **144** (1:2, respectively, see Figure 7). Selected ^{1}H NMR spectral data for **123** and **144**: SiOCHC**H**=CC=CH (**123**) 6.19 (s), SiOCHCH=CC=C**H** (**123**) 5.56 (s), SiOCHC**H**=CC=CH (**144**) 6.23 (s), C**H**=CC(OH) (**144**) 5.82 (s), SiOCHCH=CC=C**H** (**144**) 5.48 (s). Addition of 0.25 mL air (syringe injection) to the above reaction mixture resulted in the disappearance of the ^{1}H NMR signals corresponding to **123** within 5 min.

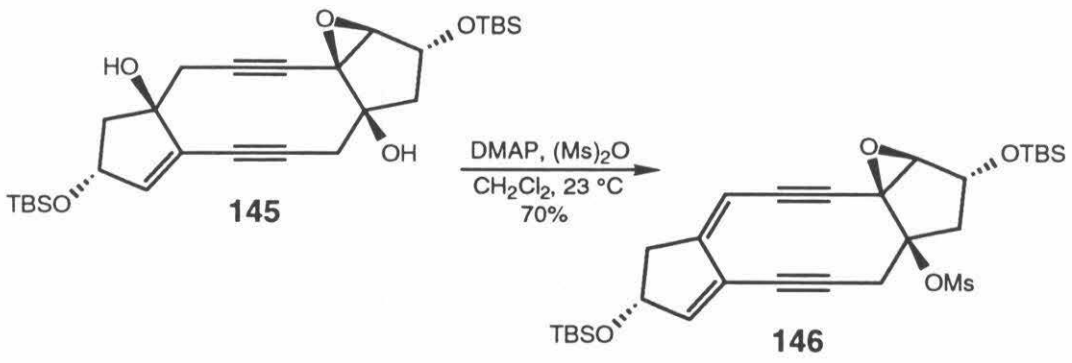


Epoxide **145.**

Dimethydioxirane[71] (~ 0.05 M solution in acetone) was added via pipette in small portions (~ 0.5 mL) to an ice-cooled solution of diol **142** (0.027 g, 0.055 mmol) in dichloromethane (5.0 mL) until analysis by thin layer chromatography indicated the starting material was half consumed. The yellow solution was then concentrated and the residue was purified by flash column chromatography (30% ethyl acetate in hexanes) to afford epoxide **145** (0.0115 g, 41%) as a yellow film.

^{1}H NMR (500 MHz, C_6D_6), δ: 5.83 (d, 1 H, J = 2.3 Hz, C**H**=C), 4.79-4.82 (m, 1 H, SiOC**H**CH=C), 3.95 (dd, 1 H, J = 5.3, 0.8 Hz, SiOC**H**CH), 3.53 (s, 1 H, SiOCHC**H**), 3.28 (d, 1 H, J = 17.9 Hz, one of C$\mathbf{H}_A$H$_B$C≡C), 2.70 (d, 1 H, J = 17.9 Hz, one of CH$_A$**H**$_B$C≡C), 2.63 (d, 1 H, J = 17.1 Hz, one of C$\mathbf{H}_A$H$_B$C≡C), 2.57 (d, 1 H, J = 17.1 Hz, one of CH$_A$**H**$_B$C≡C), 2.43 (dd, 1 H, J = 13.7, 6.8 Hz, one of SiOCHC**H**$_2$), 1.85 (dd, 1 H, J = 13.9, 5.5 Hz, one of SiOCHC**H**$_2$), 1.57 (dd, 1 H,

	J = 13.7, 3.5 Hz, one of SiOCHC**H**$_2$), 1.30 (d, 1 H, J = 13.9 Hz, one of SiOCHC**H**$_2$), 0.88 (s, 9 H, one of SiC(C**H**$_3$)$_3$), 0.77 (s, 9 H, one of SiC(C**H**$_3$)$_3$), -0.05 (s, 3 H, one of Si(C**H**$_3$)$_2$), -0.05 (s, 3 H, one of Si(C**H**$_3$)$_2$), -0.18 (s, 3 H, one of Si(C**H**$_3$)$_2$), -0.20 (s, 3 H, one of Si(C**H**$_3$)$_2$).
FTIR (neat), cm^{-1}:	3387 (br, OH), 2931 (s), 2857 (s), 2282 (w, C≡C), 2242 (w, C≡C), 2221 (w, C≡C), 1468 (m), 1359 (m), 1256 (s), 1122 (s), 1093 (s), 1008 (m), 910 (s), 836 (s), 777 (s).
MS (FAB), m/z (%base):	515 (37), 499 (100), 386 (28), 309 (26), 253 (25), 231 (21).
HRMS (FAB):	Calcd for $C_{28}H_{43}O_5Si_2$ (M-H$^+$): 515.2649 Found: 515.2651
TLC (30% EtOAc in Hexanes), R_f:	Diol **142**: 0.36 (UV) Epoxide **145**: 0.22 (UV)

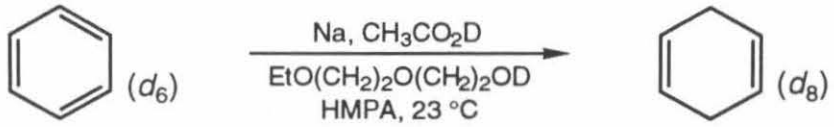


Mesylate **146.**

4-Dimethylaminopyridine (0.057 g, 0.465 mmol 20 equiv) and methanesulfonic anhydride (0.40 g, 0.230 mmol, 10 equiv) were added sequentially to a solution of epoxide **145** (0.012 g, 0.023 mmol, 1 equiv) in dichloromethane (6.0 mL) at 23 °C. The resulting yellow suspension was stirred at 23 °C for 7 h, then was partitioned between water (100 mL) and a 1:1 mixture of ethyl acetate and hexanes (2 x 100 mL). The combined organic layers were dried over sodium sulfate and were concentrated. Purification of the residue by flash column chromatography afforded mesylate **146** (0.0090 g, 70%) as a colorless film.

^{1}H NMR (500 MHz, C_6D_6), δ: 6.11 (s, 1 H, SiOCHC**H**=CC=CH), 5.10 (s, 1 H, SiOCHCH=CC=C**H**), 4.51-4.52 (m, 1 H, SiOC**H**CH=C), 3.92 (d, 1 H, *J* = 5.8 Hz, SiOC**H**CH), 3.78 (d, 1 H, *J* = 18.4 Hz, $CH_AH_BC{\equiv}C$), 3.52 (s, 1 H, SiOCHC**H**), 3.42 (d, 1 H, *J* = 18.4 Hz, $CH_A\mathbf{H}_BC{\equiv}C$), 2.75 (dd, 1 H, *J* = 14.2, 5.5 Hz, one of SiOCHC$\mathbf{H}_2$), 2.46 (s, 3 H, SO_2CH_3), 2.42 (ddd, 1 H, *J* = 17.2, 6.6, 1.6 Hz,

	one of $SiOCHCH_2$), 2.21 (dt, 1 H, J = 17.2, 2.6 Hz, one of $SiOCHCH_2$), 2.01 (d, 1 H, J = 14.2 Hz, one of $SiOCHCH_2$), 0.88 (s, 9 H, one of $SiC(CH_3)_3$), 0.73 (s, 9 H, one of $SiC(CH_3)_3$), -0.05 (s, 3 H, one of $Si(CH_3)_2$), -0.06 (s, 3 H, one of $Si(CH_3)_2$), -0.23 (s, 3 H, one of $Si(CH_3)_2$), -0.24 (s, 3 H, one of $Si(CH_3)_2$).
FTIR (neat), cm^{-1}:	2931 (s), 2857 (s), 2217 (w, C≡C), 1466 (m), 1353 (s), 1256 (m), 1176 (s), 1083 (m), 905 (s), 836 (s), 779 (m).
MS (FAB), m/z (%base):	575 (26), 481 (84), 386 (35), 371 (22), 219 (29).
HRMS (FAB):	Calcd for $C_{29}H_{43}O_6SSi_2$ ($M-H^+$): 575.2319 Found: 575.2318
TLC (30% EtOAc in Hexanes), R_f:	Epoxide **145**: 0.26 (UV) Mesylate **146**: 0.65 (UV)

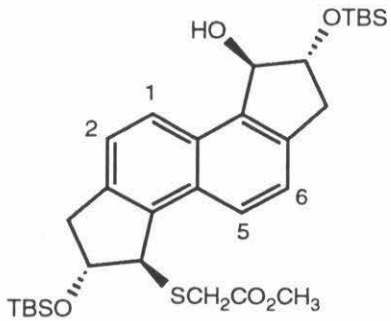


1,4-Cyclohexadiene-d_8.

Freshly cut sodium metal (6.23 g, 0.271 mol, 2.5 equiv) was added in small pieces to a solution of benzene-d_6 (99.6% D, 9.6 mL, 0.108 mol, 1 equiv) in hexamethylphosphoric triamide (HMPA, 100 mL) at 23 °C and the resulting suspension was stirred at 23 °C until a deep blue color appeared (~ 30 min). A mixture of 2-(2-ethoxyethoxy)-ethan(ol-*d*) (36.4 mL, 0.271 mol, 2.5 equiv) and acetic acid-*d* (18.7 mL, 0.324 mol, 3.0 equiv) was then added very slowly via addition funnel (typically over 4-8 h) until the blue color no longer persisted in the reaction mixture (see reference 102). Excess sodium metal was then removed from the reaction flask and the remainder of the 2-(2-ethoxyethoxy)-ethan(ol-*d*) and acetic acid mixture was added over 30 min. The resulting suspension was clarified by addition of deuterium oxide (25 mL) and the contents of the reaction flask were distilled at 760 Torr. The fraction boiling between 75-80 °C was dried over sodium sulfate and was filtered to provide a mixture of 1,4-cyclohexadiene-d_8 and 1,3-cyclohexadiene-d_8 (1:5, respectively, ~ 4.0 mL) slightly contaminated with benzene-d_6 and several unidentifiable hydrocarbons.

General Cyclization Procedure (Mesylate **146**).

Methyl thioglycolate (10.0 equiv) and triethylamine (10.0 equiv) were added sequentially to a deoxygenated (three cycles freeze-pump-thaw) solution of mesylate **146** (0.0017 M) in a mixture of either acetonitrile-tetrahydrofuran (1:1, respectively) or dimethyl sulfoxide-tetrahydrofuran (4:1, respectively) containing 1,4-cyclohexadiene (1.0 M) at 23 °C. The reaction mixture was stirred overnight (12-18 h) at 23 °C then was partitioned between water (100 mL) and a 1:1 mixture of ethyl acetate and hexanes (2 x 100 mL). The combined organic layers were dried over sodium sulfate and were concentrated. The residue was purified by preparative thin layer chromatography (15% ethyl acetate in hexanes, 2 elutions) to provide naphthalenes **149**, **150** and **151**. Product yields were determined prior to chromatography by addition of benzene as an internal standard and ^{1}H NMR analysis.

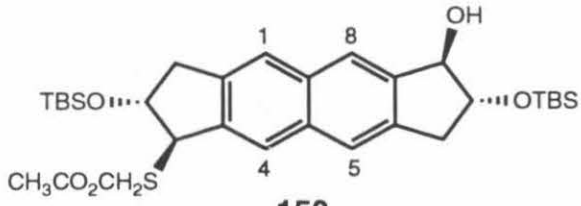


149

Naphthalene **149**.

^{1}H NMR (500 MHz, CD_2Cl_2), δ: 8.20 (d, 1 H, *J* = 8.4 Hz, **Ar**-1), 8.05 (d, 1 H, *J* = 8.4 Hz, **Ar**-5), 7.44 (d, 1 H, *J* = 8.4 Hz, **Ar**-2), 7.42 (d, 1 H, *J* = 8.4 Hz, **Ar**-6), 5.41-5.42 (m, 1 H, SiOCHC**H**OH), 4.76 (d, 1 H, *J* = 4.9 Hz, SiOC**H**CHS), 4.71 (s, 1 H, SiOCHC**H**S), 4.52-4.55 (m, 1 H, SiOC**H**CHOH), 3.73 (s, 3 H, OC**H**$_3$), 3.57 (dd, 1 H, *J* = 16.8, 5.0 Hz, one of SiOCHC**H**$_2$), 3.45 (dd, 1 H, *J* = 16.8, 6.6 Hz, one of SiOCHC**H**$_2$), 3.37 (d, 1 H, *J* = 15.3 Hz, SC**H**$_A$H$_B$C=O), 3.22 (d, 1 H, *J* = 15.3 Hz, SCH$_A$**H**$_B$C=O), 2.94 (d, 1 H, *J* = 16.7 Hz, one of SiOCHC**H**$_2$), 2.88 (dd, 1 H, *J* = 16.1, 4.6 Hz, one of SiOCHC**H**$_2$), 0.93 (s, 9 H, one of SiC(C**H**$_3$)$_3$), 0.85 (s, 9 H, one of SiC(C**H**$_3$)$_3$), 0.18 (s, 3 H, one of Si(C**H**$_3$)$_2$), 0.17 (s, 3 H, one of Si(C**H**$_3$)$_2$), 0.13 (s, 3 H, one of Si(C**H**$_3$)$_2$), 0.13 (s, 3 H, one of Si(C**H**$_3$)$_2$).

FTIR (neat), cm^{-1}:	3422 (br, OH), 2930 (s), 2856 (s), 1739 (s, C=O), 1465 (m), 1362 (m), 1255 (s), 1072 (s), 835 (s).
MS (FAB), m/z (%base):	587 (10), 571 (23), 531 (13), 483 (34).
HRMS (FAB):	Calcd for $C_{31}H_{47}O_5SSi_2$ ($M-H^+$): 587.2683 Found: 587.2706
TLC (5% EtOAc in Toluene), R_f:	Mesylate **146**: 0.53 (UV) Naphthalene **149**: 0.35 (UV)

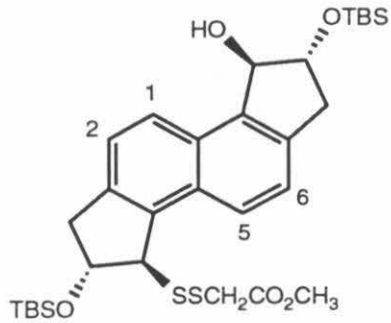


150

Naphthalene **150.**

^{1}H NMR (500 MHz, CD_2Cl_2), δ: 7.74 (s, 1 H, **Ar**-1), 7.71 (s, 1 H, **Ar**-4), 7.64 (s, 1 H, **Ar**-5 or **Ar**-8), 7.58 (s, 1 H, **Ar**-5 or **Ar**-8), 5.00-5.05 (m, 1 H, SiOCHC**H**OH), 4.55-4.59 (m, 1 H, SiOC**H**CHS), 4.36 (d, 1 H, *J* = 4.3 Hz, SiOCHC**H**S), 4.30-4.34 (m, 1 H, SiOC**H**CHOH), 3.70 (s, 3 H, OC$\mathbf{H}_3$), 3.42 (d, 1 H, *J* = 15.3 Hz, SC$\mathbf{H}_A$H$_B$C=O), 3.38-3.42 (m, 1 H, one of SiOCHC$\mathbf{H}_2$), 3.32 (d, 1 H, *J* = 15.3 Hz, SCH$_A$$\mathbf{H}_B$C=O), 3.27 (dd, 1 H, *J* = 16.2, 7.0 Hz, one of SiOCHC$\mathbf{H}_2$), 2.85-2.97 (m, 2 H, two of SiOCHC$\mathbf{H}_2$), 0.95 (s, 9 H, one of SiC(C$\mathbf{H}_3$)$_3$), 0.90 (s, 9 H, one of SiC(C$\mathbf{H}_3$)$_3$), 0.17 (s, 3 H, one of Si(C$\mathbf{H}_3$)$_2$), 0.16 (s, 3 H, one of Si(C$\mathbf{H}_3$)$_2$), 0.16 (s, 3 H, one of Si(C$\mathbf{H}_3$)$_2$), 0.15 (s, 3 H, one of Si(C$\mathbf{H}_3$)$_2$).

FTIR (neat), cm^{-1}:	3394 (br, OH), 2930 (s), 2853 (m), 1739 (s, C=O), 1464 (m), 1359 (m), 1255 (s), 1071 (s), 835 (s).
MS (FAB), m/z (%base):	587 (7), 571 (21), 531 (15), 483 (100).
HRMS (FAB):	Calcd for $C_{31}H_{47}O_5SSi_2$ ($M-H^+$): 587.2683 Found: 587.2655
TLC (5% EtOAc in Toluene), R_f:	Mesylate **146**: 0.53 (UV) Naphthalene **150**: 0.42 (UV)

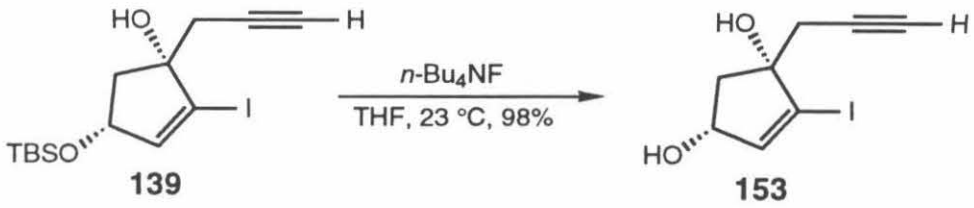


151

Disulfide **151**.

^{1}H NMR (500 MHz, CD_2Cl_2), δ: 8.22 (d, 1 H, *J* = 8.5 Hz, **Ar**-1), 8.03 (d, 1 H, *J* = 8.5 Hz, **Ar**-5), 7.46 (d, 1 H, *J* = 8.5 Hz, **Ar**-2), 7.44 (d, 1 H, *J* = 8.5 Hz, **Ar**-6), 5.41-5.43 (m, 1 H, SiOCHC**H**OH), 4.84 (d, 1 H, *J* = 4.9 Hz, SiOC**H**CHS), 4.83 (s, 1 H, SiOCHC**H**S), 4.52-4.55 (m, 1 H, SiOC**H**CHOH), 3.74 (s, 3 H, OC**H**$_3$), 3.60 (dd, 1 H, *J* = 16.7, 5.0 Hz, one of SiOCHC**H**$_2$), 3.45 (dd, 1 H, *J* = 16.1, 6.7 Hz, one of SiOCHC**H**$_2$), 3.40 (d, 1 H, *J* = 14.4 Hz, SC**H**$_A$H$_B$C=O), 3.36 (d, 1 H, *J* = 14.4 Hz, SCH$_A$**H**$_B$C=O), 2.94 (d, 1 H, *J* = 16.8 Hz, one of SiOCHC**H**$_2$), 2.88 (dd, 1 H, *J* = 16.1, 4.5 Hz, one of SiOCHC**H**$_2$), 2.06 (d 1 H, *J* = 7.1 Hz, O**H**), 0.93 (s, 9 H, one of SiC(C**H**$_3$)$_3$), 0.87 (s, 9 H, one of SiC(C**H**$_3$)$_3$), 0.18 (s, 3 H, one of Si(C**H**$_3$)$_2$), 0.18 (s, 3 H, one of Si(C**H**$_3$)$_2$), 0.17 (s, 3 H, one of Si(C**H**$_3$)$_2$), 0.17 (s, 3 H, one of Si(C**H**$_3$)$_2$).

FTIR (neat), cm^{-1}:	3395 (br, OH), 2930 (s), 2850 (s), 1737 (s, C=O), 1464 (m), 1255 (s), 1072 (s), 835 (s).
MS (FAB), m/z (%base):	619 (4), 603 (5), 571 (7), 483 (100).
HRMS (FAB):	Calcd for $C_{31}H_{47}O_5S_2Si_2$ ($M-H^+$): 619.2404 Found: 619.2409
TLC (5% EtOAc in Toluene), R_f:	Mesylate **146**: 0.53 (UV) Disulfide **151**: 0.42 (UV)

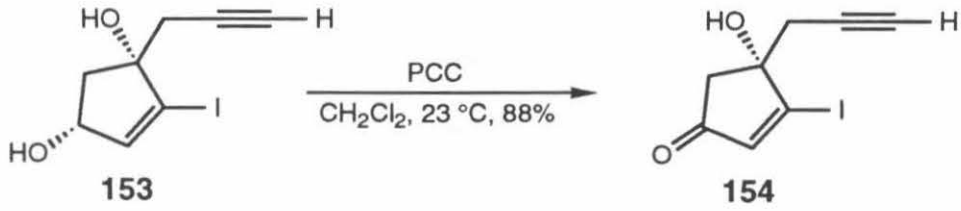


Diol **153**.

A solution of tetrabutylammonium fluoride (9.51 mL of a 1.0 M solution in tetrahydrofuran, 9.51 mmol, 2.0 equiv) was added to a solution of alcohol **139** (1.80 g, 4.76 mmol, 1 equiv) in tetrahydrofuran (50 mL) at 23 °C. The resulting orange solution was stirred at 23 °C for 45 min, then was partitioned between water (150 mL) and ethyl acetate (4 x 150 mL, emulsions were dispersed by addition of a small amount of hexanes). The combined organic layers were dried over sodium sulfate and were concentrated. Purification of the residue by flash column chromatography (50% ethyl acetate in hexanes) afforded diol **153** (1.25 g, 98%) as a white solid (mp = 120 °C).

^{1}H NMR (500 MHz, $CDCl_3$), δ: 6.42 (d, 1 H, J = 2.3 Hz, C**H**=CI), 4.69-4.73 (m, 1 H, SiOC**H**), 2.88 (dd, 1 H, J = 14.0, 7.2 Hz, one of C$\mathbf{H}_2$C(OH)), 2.57 (dd, 1 H, J = 16.6, 2.7 Hz, C$\mathbf{H}_A$H$_B$C≡C), 2.41 (dd, 1 H, J = 16.6, 2.6 Hz, CH$_A$**H**$_B$C≡C), 2.36 (s, 1 H, O**H**), 2.01 (td, 1 H, J = 2.7, 0.5 Hz, C≡C**H**), 1.89-1.93 (m, 1 H, one of C$\mathbf{H}_2$C(OH)).

FTIR (neat), cm^{-1}:	3274 (br, s, OH and C≡CH), 2896 (w), 1602 (w), 1438 (w), 1323 (m), 1077 (m), 1014 (m), 907 (w).
MS (CI/NH_3), m/z (%base):	264 (100), 247 (20), 225 (64), 197 (14).
HRMS (CI/NH_3):	Calcd for $C_8H_{11}INO$ (MNH_4^+): 263.9885 Found: 263.9875
TLC (50% EtOAc in Hexanes), R_f:	Alcohol **139** (High R_f): 0.77 Diol **153**: 0.23



153 **154**

Ketone **154**.

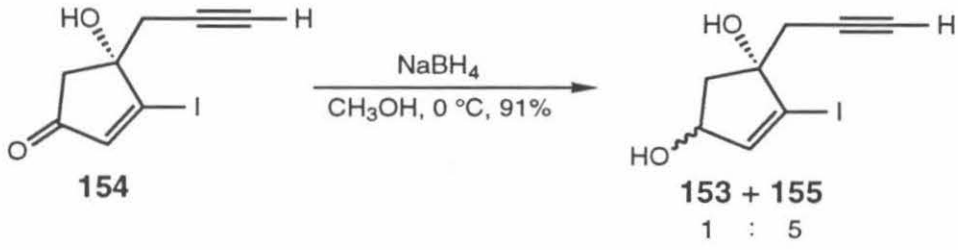
Pyridinium chlorochromate (0.96 g, 0.446 mmol, 1.5 equiv) was added in three portions to a solution of alcohol **153** (0.78 g, 0.295 mmol, 1 equiv) in dichloromethane (10.0 mL) at 23 °C. The brown reaction mixture was stirred for 1 h at 23 °C, then was loaded onto a column of silica gel and was purified by flash column chromatography (30% ethyl acetate in hexanes) to provide ketone **154** (0.68 g, 88%) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$), δ: 6.72 (s, 1 H, C**H**=CI), 2.99 (d, 1 H, J = 18.2 Hz, $CH_AH_BC{\equiv}C$), 2.71 (dd, 1 H, J = 16.6, 2.7 Hz, one of $CH_2C(OH)$), 2.65 (d, 1 H, J = 18.2 Hz, $CH_AH_BC{\equiv}C$), 2.55-2.58 (m, 1 H, one of $CH_2C(OH)$), 2.07 (t, 1 H, J = 2.6 Hz, C≡C**H**).

FTIR (neat), cm^{-1}: 3385 (br, OH), 3293 (s, C≡CH), 2121 (w, C≡C), 1714 (s, C=O), 1686 (s), 1568 (s), 1401 (m), 1243 (s), 1180 (m), 1051 (m).

MS (EI), m/z (%base): 262 (6), 223 (100), 195 (17).

HRMS (EI):	Calcd for $C_8H_7IO_2$ (M^+): 261.9491
	Found: 261.9493
TLC (50% EtOAc in Hexanes), R_f:	Diol **153**: 0.30
	Ketone **154**: 0.54 (UV)



154 **153 + 155**
1 : 5

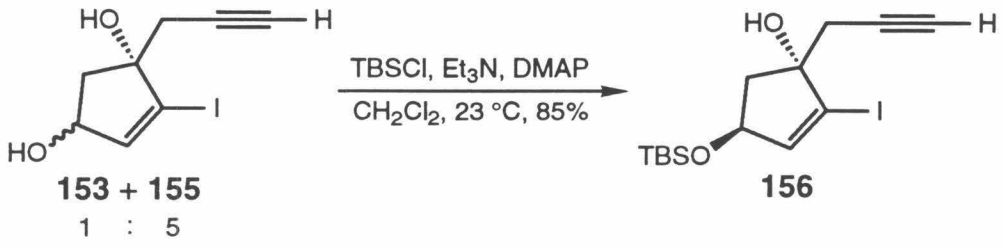
Diol **155** + Diol **153.**

Sodium borohydride (0.116 g, 3.07 mmol, 1.1 equiv) was added in small portions to an ice-cooled solution of ketone **154** (0.73 g, 2.79 mmol, 1 equiv) in methanol (10.0 mL). The resulting solution was stirred at 0 °C for 15 min, then was partitioned between water (100 mL) and ethyl acetate (4 x 100 mL). The combined organic layers were dried over sodium sulfate and were concentrated. Purification of the residue by flash column chromatography (50% ethyl acetate in hexanes) afforded an inseparable mixture of diols **153** and **155** (0.669 g, 91%, 1:5, respectively).

Diol **155.**

^{1}H NMR (500 MHz, $CDCl_3$), δ: 6.42 (d, 1 H, J = 2.7 Hz, C**H**=CI), 4.77-4.81 (m, 1 H, SiOC**H**), 2.62 (dd, 1 H, J = 16.6, 2.6 Hz, $CH_AH_BC{\equiv}C$), 2.57 (dd, 1 H, J = 16.6, 2.7 Hz, $CH_AH_BC{\equiv}C$), 2.46 (dd, 1 H, J = 14.7, 7.5 Hz, one of $CH_2C(OH)$), 2.21 (dd, 1 H, J = 14.7, 2.0 Hz, one of $CH_2C(OH)$), 2.18 (s, 1 H, one of O**H**), 2.14-2.16 (m, 2 H, one of O**H** and C≡C**H**).

FTIR (neat), cm^{-1}:	3344 (br, OH), 3291 (s, C≡CH), 2937 (w), 2125 (w, C≡C), 1605 (m), 1420 (m), 1317 (m), 1077 (s), 1045 (s), 858 (m).
MS (CI/NH_3), m/z (%base):	264 (100), 247 (20), 225 (64), 197 (14).
HRMS (CI/NH_3):	Calcd for $C_8H_{11}INO$ (MNH_4^+): 263.9885 Found: 263.9875
TLC (50% EtOAc in Hexanes), R_f:	Ketone **154**: 0.54 (UV) Diol **155**: 0.30



153 + 155
1 : 5

156

Alcohol **156.**

Triethylamine (0.383 mL, 2.75 mmol, 1.1 equiv), *tert*-butyldimethylsilyl chloride (0.414 g, 2.75 mmol, 1.1 equiv), and 4-dimethylaminopyridine (0.040 g, 0.33 mmol, 0.13 equiv) were added sequentially to a solution of crude alcohols **153** and **155** (1:5, respectively, 0.659 g, 2.50 mmol, 1 equiv) in dichloromethane (10.0 mL) at 23 °C. The resulting pale yellow solution was stirred for 30 h at 23 °C, then was partitioned between water (100 mL) and a 1:1 mixture of ethyl acetate and hexanes (3 x 100 mL). The combined organic layers were dried over sodium sulfate and were concentrated. The residue was purified by careful flash column chromatography (gradient elution: ethyl acetate in hexanes, 5→10%) to afford pure alcohol **156** (0.804 g, 85%) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$), δ: 6.29 (d, 1 H, J = 2.4 Hz, C**H**=CI), 4.86-4.88 (m, 1 H, SiOC**H**), 2.69 (dd, 1 H, J = 16.6, 2.6 Hz, $CH_AH_BC{\equiv}C$), 2.50 (dd, 1 H, J = 16.6, 2.6 Hz, $CH_AH_BC{\equiv}C$), 2.36 (dd, 1 H, J = 11.9, 6.8 Hz, one of $CH_2C(OH)$), 2.18 (s, 1 H, O**H**), 2.16 (dd, 1 H, J = 11.9, 3.5 Hz, one of $CH_2C(OH)$), 2.08 (t, 1 H, J = 2.6 Hz, C≡C**H**), 0.88 (s, 9 H, $SiC(CH_3)_3$), 0.08 (s, 3 H, one of $Si(CH_3)_2$), 0.07 (s, 3 H, one of $Si(CH_3)_2$).

FTIR (neat), cm^{-1}:	3381 (br, OH), 3311 (m, C≡CH), 2931 (s), 2857 (s), 2119 (w, C≡C), 1604 (m), 1470 (m), 1360 (m), 1255 (s), 1082 (s), 907 (s), 835 (s), 777 (s).
MS (CI/NH_3), m/z (%base):	396 (13), 361 (16), 321 (20), 264 (100), 247 (16), 235 (16), 194 (10).
HRMS (CI/NH_3):	Calcd for $C_{14}H_{27}INO_2Si$ (MNH_4^+): 396.0856 Found: 396.0851
TLC (20% EtOAc in Hexanes), R_f:	Diols **153** and **155**: 0.10 Alcohol **156**: 0.44

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101. The 1,4-cyclohexadiene-d_8 used in this experiment was contaminated with 1,3-cyclohexadiene-d_8 (1:5, respectively). The indicated concentration of cyclohexadiene refers to the 1,4 isomer.

102. Prepared by reduction of benzene-d_6 (99.6% D) with sodium in HMPA. See experimental section and: (a) reference 20. (b) Whitesides, G. M.; Ehmann, W. J. *J. Am. Chem. Soc.* **1969**, *91*, 3800. (c) Whitesides, G. M.; Ehmann, W. J. *J. Org. Chem.* **1970**, *35*, 3565.

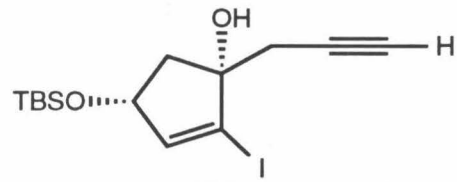
Appendix 1

X-ray Data Collection, Refinement, and Structure Determination for Alcohol 139

This analysis was performed by Dr. Joseph Ziller at the University of *California*, Irvine (UCI). A colorless crystal of approximate dimensions 0.30 x 0.40 x 0.46 mm was oil-mounted on a glass fiber and transferred to the Siemens P3 diffractometer (equipped with a locally modified LT-2 low temperature system). The determination of Laue symmetry, crystal class, unit cell parameters and the crystal's orientation matrix were carried out by previously described methods similar to those of Churchill.[1] Intensity data were collected at 163 K using a θ-2θ scan technique with Mo Kα radiation under the conditions listed in Table A-1. All 2282 data were corrected for absorption and for Lorentz and polarization effects and were placed on approximately absolute scale. The diffraction symmetry was *mmm* with systematic absences $h00$ for h = 2n+1; $0k0$ for k = 2n+1 and $00l$ for l = 2n+1. The space group is therefore uniquely defined as the non-centrosymmetric orthorhombic $P2_12_12_1$ (D_2^4; No. 19).

All crystallographic calculations were carried out using either the UCI modified version of the UCLA Crystallographic Computing Package[2] or the SHELXTL PLUS Program set.[3] The analytical scattering factors for neutral atoms were used throughout the analysis;[4a] both the real ($\Delta f'$) and imaginary ($i\Delta f''$) components of anomalous dispersion[4b] were included. The quantity minimized during least-squares analysis was $\sum w(|F_o| - |F_c|)^2$ where $w^{-1} = \sigma^2(|F_o|) + 0.0001(|F_o|)^2$.

The structure was solved by direct methods (SHELXTL PLUS) and refined by full-matrix least squares techniques. Hydrogen atoms were included using a riding model with d(C-H) = 0.96Å, d(O-H) = 0.85Å and U(iso) = 0.05Å^2. Refinement of positional and thermal parameters led to convergence with R_F = 1.8%; R_{wF} = 2.1% and GOF = 1.39 for 165 variables refined against those 2196 data with $|F_o| > 3.0\sigma(|F_o|)$. The absolute structure was determined by refinement of the Rogers' η-parameter[5] (η = 1.07(4)). A final difference-Fourier synthesis yielded ρ(max) = 0.34 eÅ^{-3}.



139

Table A-1. Experimental Data for the X-ray Diffraction Study of Alcohol **139**.

Formula: $C_{16}H_{23}O_2SiI$	Fw: 378.3
Temperature (K): 163	Crystal System: Orthorhombic
Space Group: $P2_12_12_1$ (D_2^4; No. 19)	Z = 4
a = 7.5227(10) Å	V = 1713.6(4) Å^3
b = 15.046(2) Å	D_{calcd}, g/cm^3 = 1.466
c = 15.139(2) Å	Diffractometer: Siemens P3 (R3m/V System)
Radiation: Mo Kα (λ = 0.710730 Å)	Monochrometer: Highly oriented graphite
Data Collected: $+h$, $+k$, $+l$	Scan Type: θ-2θ
Scan Width: 1.2° plus Kα-separation	Scan Speed: 3.0 deg min^{-1} (in ω)
2θ Range: 4.0 to 55.0°	μ(Mo Kα), mm^{-1} = 1.91
Absorbtion Correction:	Reflections Collected: 2282
Semi-empirical (φ-scan method)	Reflections with ($\|F_o\| > 3.0\sigma(\|F_o\|)$): 2196
No. of Variables: 165	R_F = 1.8%
Goodness of Fit: 1.39	R_{wF} = 2.1%

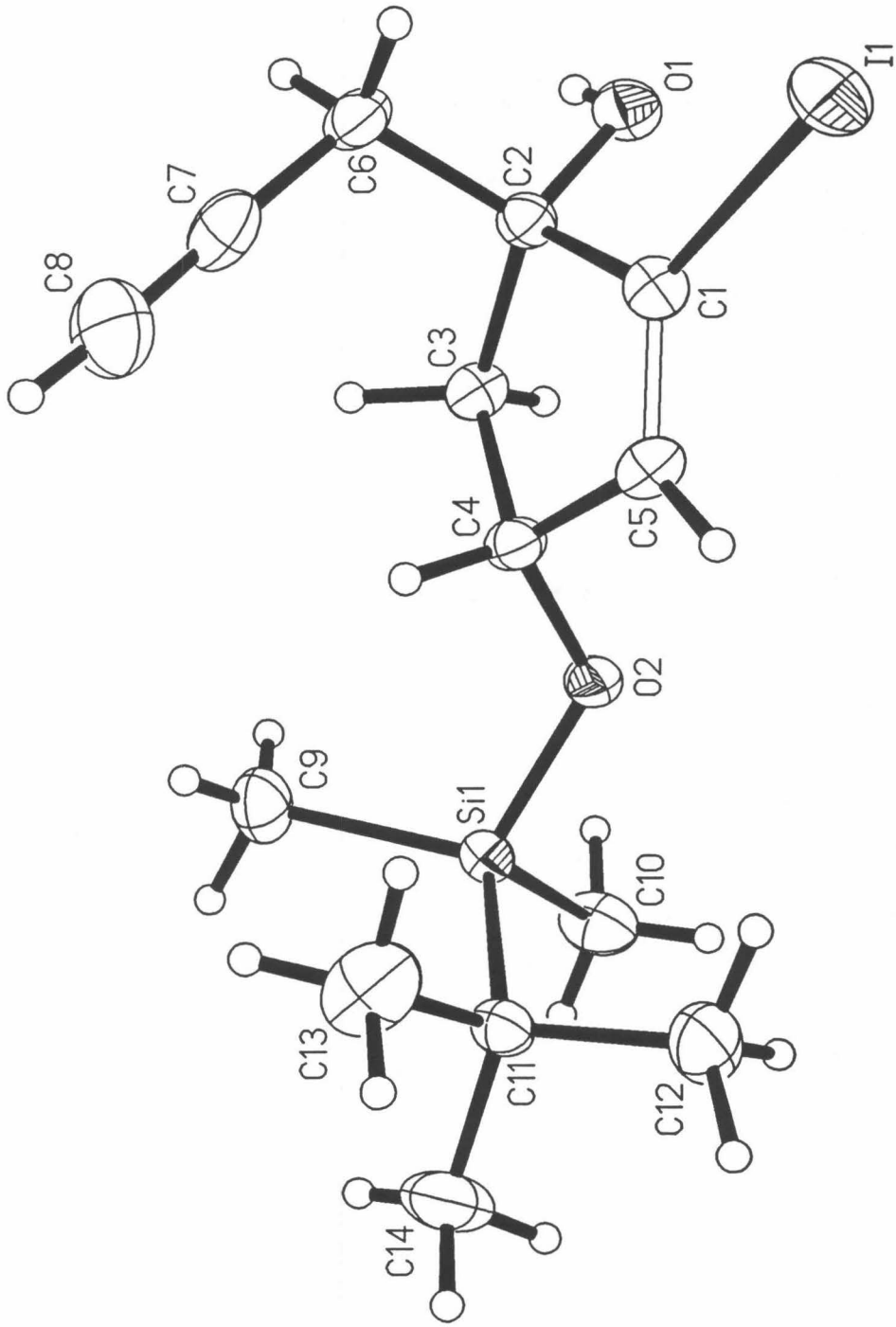


Figure 8. ORTEP plot of alcohol **139**. Thermal ellipsoids are drawn at the 50% probability level.

Table A-2. Atomic Coordinates ($x10^4$) and Equivalent Isotropic Displacement Coefficients ($Å^2 \times 10^4$).[a]

	x	y	z	U(eq)
C(1)	7058(3)	2583(2)	3531(2)	206(7)
C(2)	5302(3)	2320(2)	3929(2)	199(7)
C(3)	5067(3)	3050(2)	4633(2)	222(7)
C(4)	6297(3)	3821(2)	4373(2)	208(7)
C(5)	7608(3)	3385(2)	3759(2)	213(7)
C(6)	3787(4)	2310(2)	3242(2)	267(8)
C(7)	3388(4)	3183(2)	2864(2)	331(8)
C(8)	3070(5)	3895(2)	2582(2)	484(11)
C(9)	4240(4)	5391(2)	5457(2)	334(9)
C(10)	7455(5)	5182(2)	6682(2)	329(9)
C(11)	7923(4)	6073(2)	4860(2)	229(7)
C(12)	9862(4)	5787(2)	4762(3)	417(11)
C(13)	7110(5)	6212(3)	3946(2)	443(11)
C(14)	7858(5)	6965(2)	5359(3)	422(10)
O(1)	5498(3)	1457(1)	4293(1)	249(5)
O(2)	7166(2)	4199(1)	5132(1)	218(5)
Si(1)	6679(1)	5212(1)	5518(1)	187(2)
I(1)	8360(1)	1749(1)	2643(1)	312(1)

[a]Equivalent isotropic U defined as one third of the trace of the orthogonalized U_{ij} tensor.

Table A-3. Interatomic Distances (Å) with Esd's.

C(1)-C(2)	1.505(4)	C(1)-C(5)	1.322(4)
C(1)-I(1)	2.084(3)	C(2)-C(3)	1.541(4)
C(2)-C(6)	1.543(4)	C(2)-O(1)	1.418(3)
C(3)-C(4)	1.535(4)	C(4)-C(5)	1.505(4)
C(4)-O(2)	1.439(3)	C(6)-C(7)	1.464(4)
C(7)-C(8)	1.177(5)	C(9)-Si(1)	1.857(3)
C(10)-Si(1)	1.856(3)	C(11)-C(12)	1.529(4)
C(11)-C(13)	1.527(4)	C(11)-C(14)	1.541(4)
C(11)-Si(1)	1.884(3)	O(2)-Si(1)	1.672(2)

Table A-4. Interatomic Angles (Deg.) with Esd's.

C(2)-C(1)-C(5)	114.2(2)	C(2)-C(1)-I(1)	120.9(2
C(5)-C(1)-I(1)	124.8(2)	C(1)-C(2)-C(3)	101.0(2)
C(1)-C(2)-C(6)	112.4(2)	C(3)-C(2)-C(6)	112.9(2)
C(1)-C(2)-O(1)	108.0(2)	C(3)-C(2)-O(1)	113.3(2)
C(6)-C(2)-O(1)	109.1(2)	C(2)-C(3)-C(4)	107.0(2)
C(3)-C(4)-C(5)	103.0(2)	C(3)-C(4)-O(2)	111.6(2)
C(5)-C(4)-O(2)	111.6(2)	C(1)-C(5)-C(4)	110.7(2)
C(2)-C(6)-C(7)	114.0(2)	C(6)-C(7)-C(8)	178.2(3)
C(12)-C(11)-C(13)	109.4(3)	C(12)-C(11)-C(14)	108.8(2)
C(13)-C(11)-C(14)	108.2(3)	C(12)-C(11)-Si(1)	109.4(2)
C(13)-C(11)-Si(1)	112.0(2)	C(14)-C(11)-Si(1)	109.0(2)
C(4)-O(2)-Si(1)	122.7(2)	C(9)-Si(1)-C(10)	111.2(2)
C(9)-Si(1)-C(11)	111.3(1)	C(10)-Si(1)-C(11)	111.2(1)
C(9)-Si(1)-O(2)	109.3(1)	C(10)-Si(1)-O(2)	104.0(1)
C(11)-Si(1)-O(2)	109.5(1)		

Table A-5. Anisotropic Displacement Coefficients ($Å^2 \times 10^4$).

	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
C(1)	237(14)	224(12)	155(11)	7(10)	5(10)	4(10)
C(2)	213(12)	178(11)	205(11)	-11(10)	-5(11)	19(10)
C(3)	210(12)	253(13)	203(12)	-27(11)	13(11)	-17(9)
C(4)	222(14)	194(11)	207(12)	-27(10)	-38(10)	-5(10)
C(5)	218(12)	245(13)	177(11)	-55(11)	-9(10)	40(10)
C(6)	252(14)	285(14)	263(13)	-36(11)	-76(11)	-18(11)
C(7)	292(13)	417(16)	283(13)	-31(16)	-111(12)	22(12)
C(8)	507(21)	447(18)	499(20)	49(16)	-169(19)	111(16)
C(9)	235(14)	353(16)	414(17)	55(13)	48(13)	44(14)
C(10)	485(18)	293(15)	211(13)	-10(15)	-35(13)	-25(12)
C(11)	237(13)	182(12)	268(13)	-2(10)	8(11)	20(10)
C(12)	266(15)	348(16)	637(22)	12(15)	124(17)	102(16)
C(13)	473(21)	545(21)	310(16)	-133(17)	-58(15)	168(15)
C(14)	477(19)	214(14)	574(21)	-50(13)	82(17)	-35(13)
O(1)	253(10)	202(9)	292(10)	-36(8)	27(9)	37(8)
O(2)	236(9)	186(8)	233(9)	8(8)	-60(8)	-25(7)
Si(1)	202(3)	175(3)	185(3)	13(3)	5(3)	-3(2)
I(1)	354(1)	321(1)	261(1)	46(1)	64(1)	-48(1)

The anisotropic displacement exponent takes the form:

$-2\pi^2(h^2a^{*2}U_{11} + ... + 2hka^*b^*U_{12})$

Table A-6. H-Atom Coordinates ($x10^4$) and Isotropic Displacement Coefficients ($Å^2 \times 10^4$).

	x	y	z	U
H(3A)	3869	3266	4697	500
H(3B)	5704	2825	5202	500
H(4A)	5651	4252	4034	500
H(5A)	8643	3703	3566	500
H(6A)	2662	2114	3467	500
H(6B)	4156	1974	2734	500
H(8A)	2731	4466	2362	500
H(9A)	3687	4939	5806	500
H(9B)	3925	5918	5779	500
H(9C)	3693	5487	4893	500
H(1O)	4438	1350	4464	500
H(10A)	6877	4698	6985	500
H(10B)	8678	5018	6753	500
H(10C)	7339	5743	6975	500
H(12A)	10283	5649	5345	500
H(12B)	10596	6235	4492	500
H(12C)	10020	5258	4416	500
H(13A)	7143	5690	3581	500
H(13B)	7766	6664	3638	500
H(13C)	5853	6309	3931	500
H(14A)	8452	7442	5054	500
H(14B)	6705	7123	5561	500
H(14C)	8630	6933	5870	500

References (Appendix 1).

1. Churchill, M. R.; Lashewycz, R. A.; Rotella, F. J. *Inorg. Chem.* **1977**, *16*, 265.

2. UCLA Crystallographic Computing Package, University of California, Los Angeles, 1981, C. Strouse, personal communication.

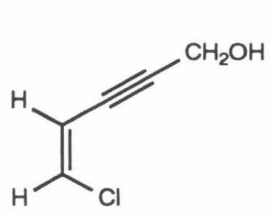
3. SHELXTL PLUS Program set; Siemens Analytical X-ray Instruments, Inc.; Madison, WI, 1990.

4. International Tables for X-ray Crystallography; Kynoch Press: Birmingham, England, 1974; (a) pp 99-101; (b) pp 149-150.

5. Rogers, D. *Acta. Cryst.* **1981**, *A37*, 734.

Appendix 2

Catalog of Spectra (Chapter 1)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Cl

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6
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4
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2
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0
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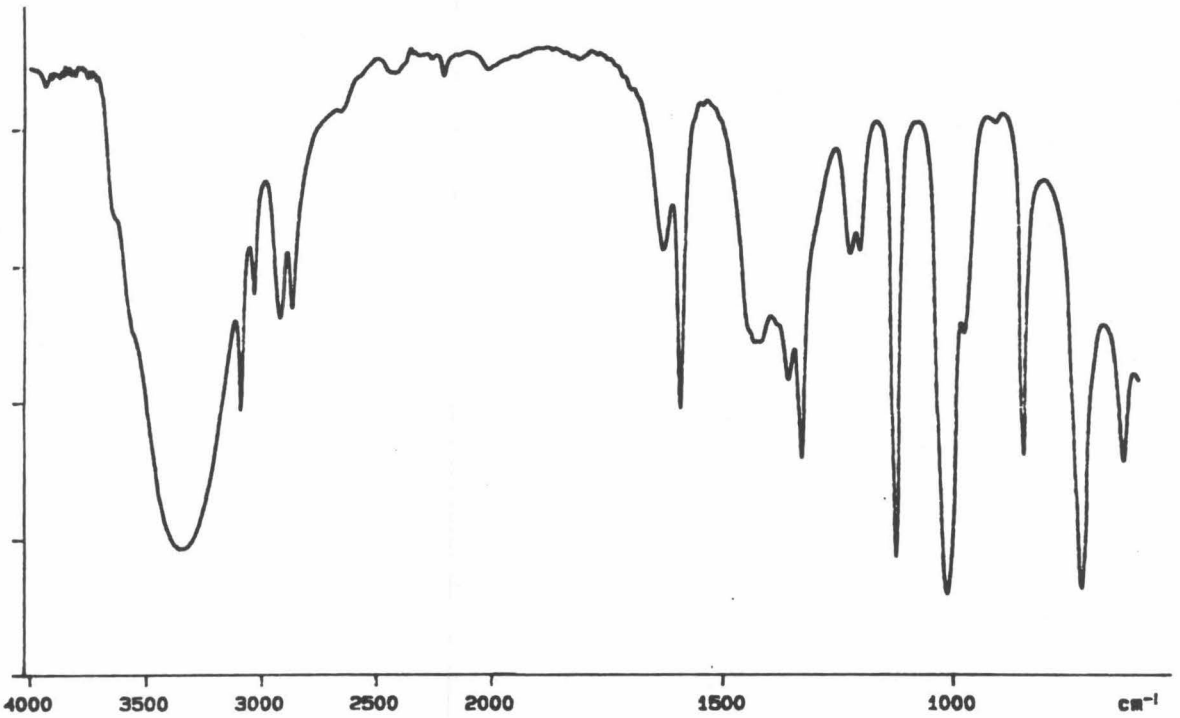
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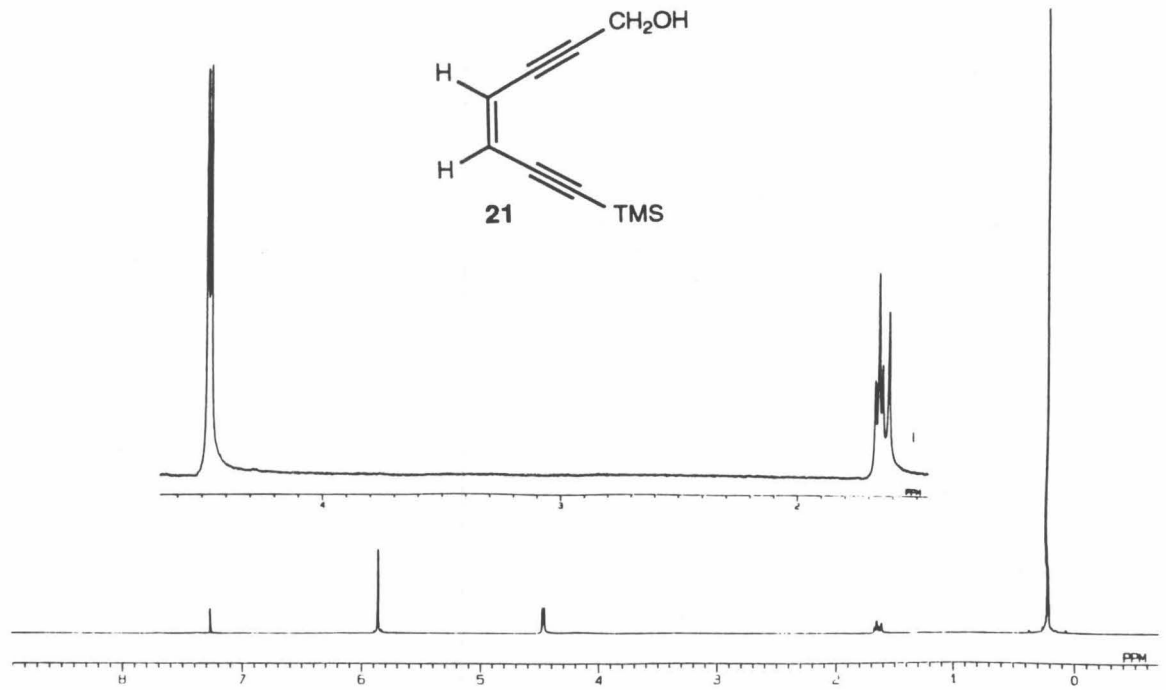
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PPM
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1
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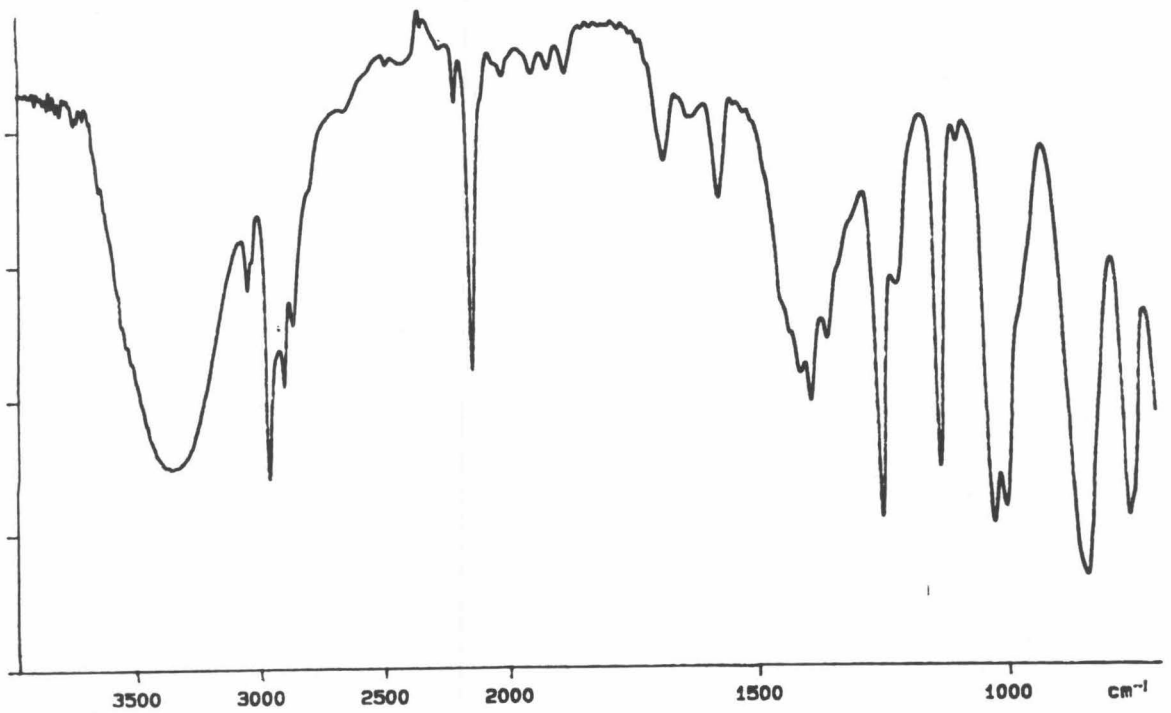
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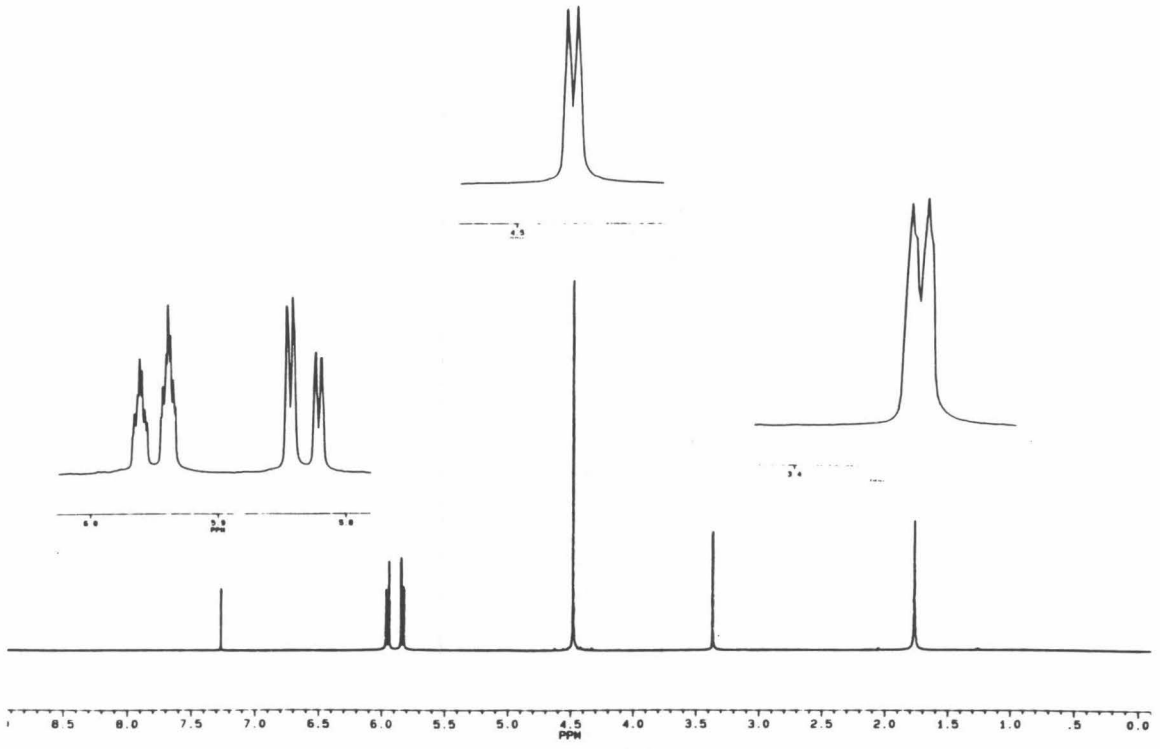
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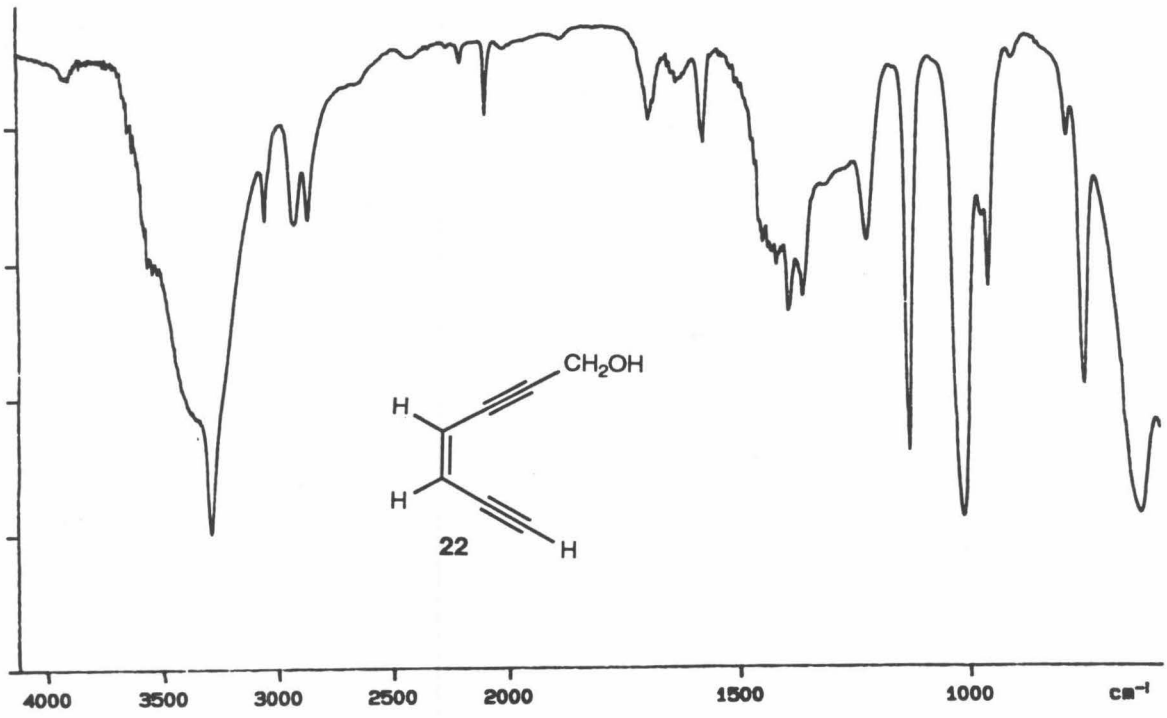
0.0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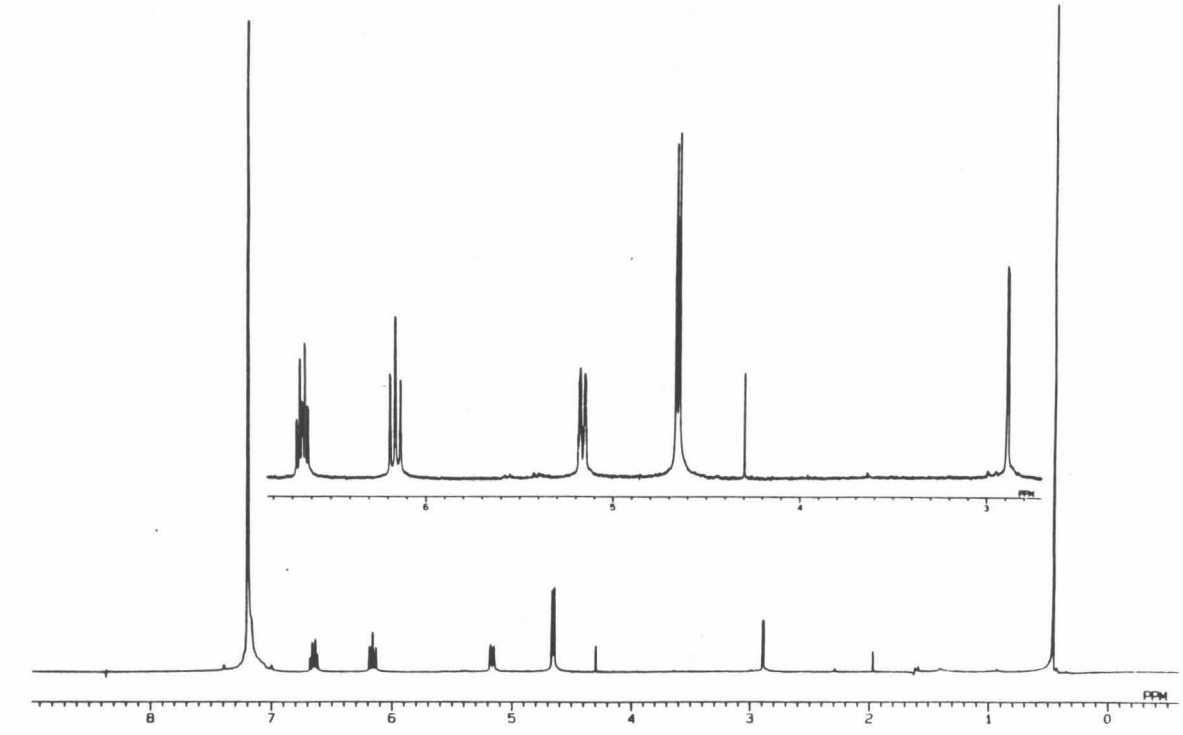
H
H
4000
3500
3000
2500
2000
1500
1000
cm⁻¹

22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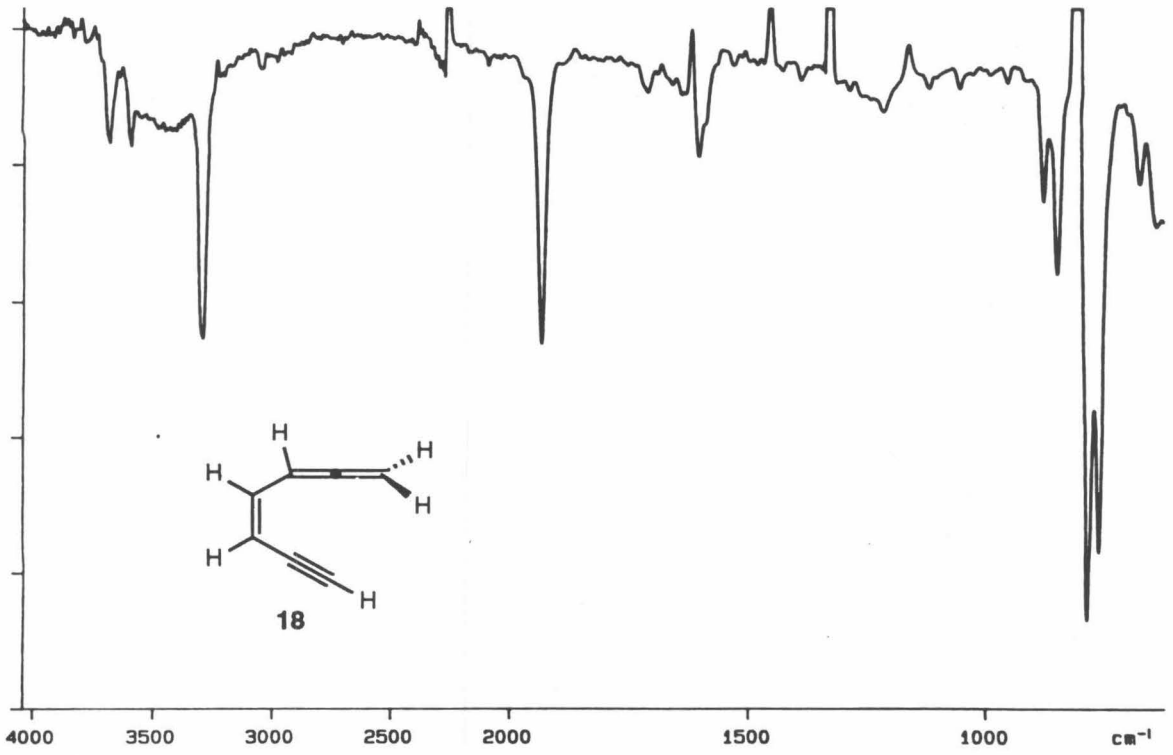
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H
H
H
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18
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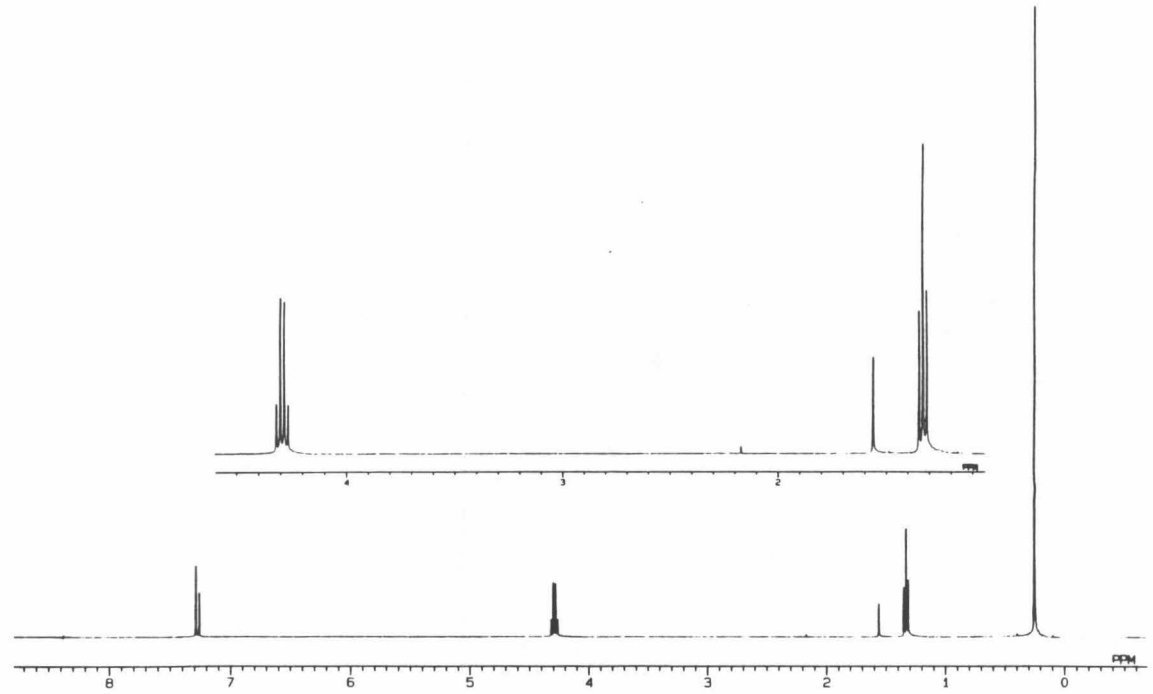
1500
1000
cm⁻¹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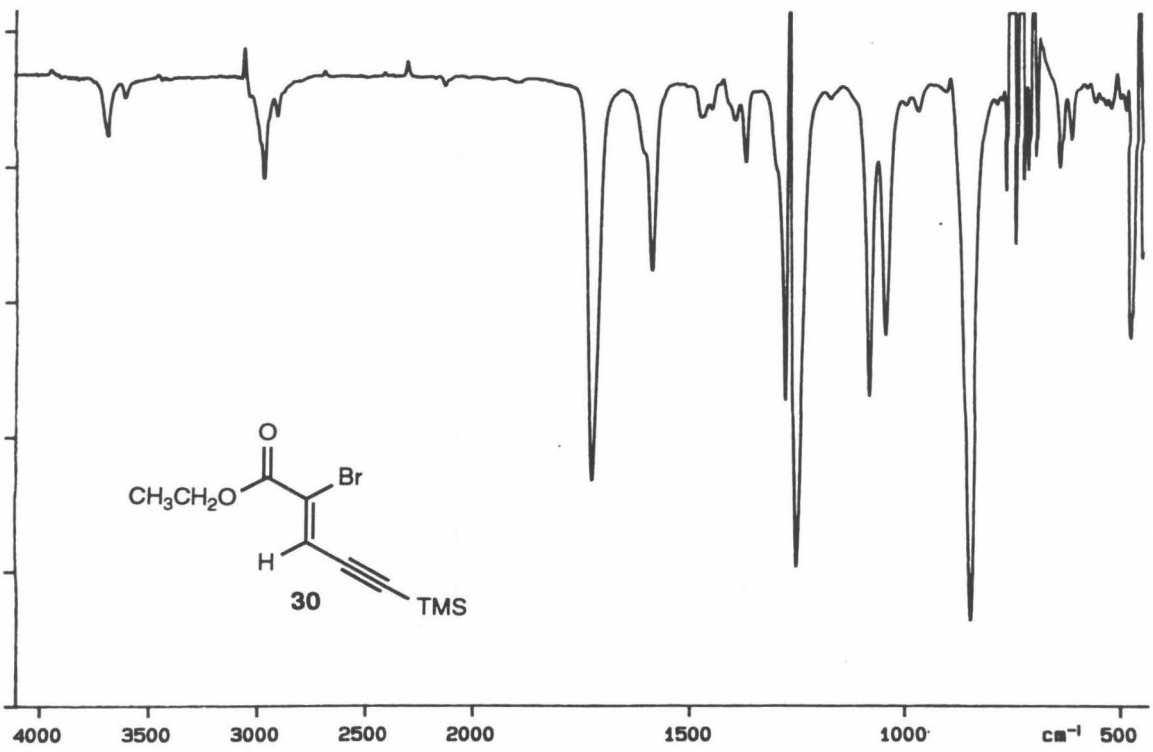
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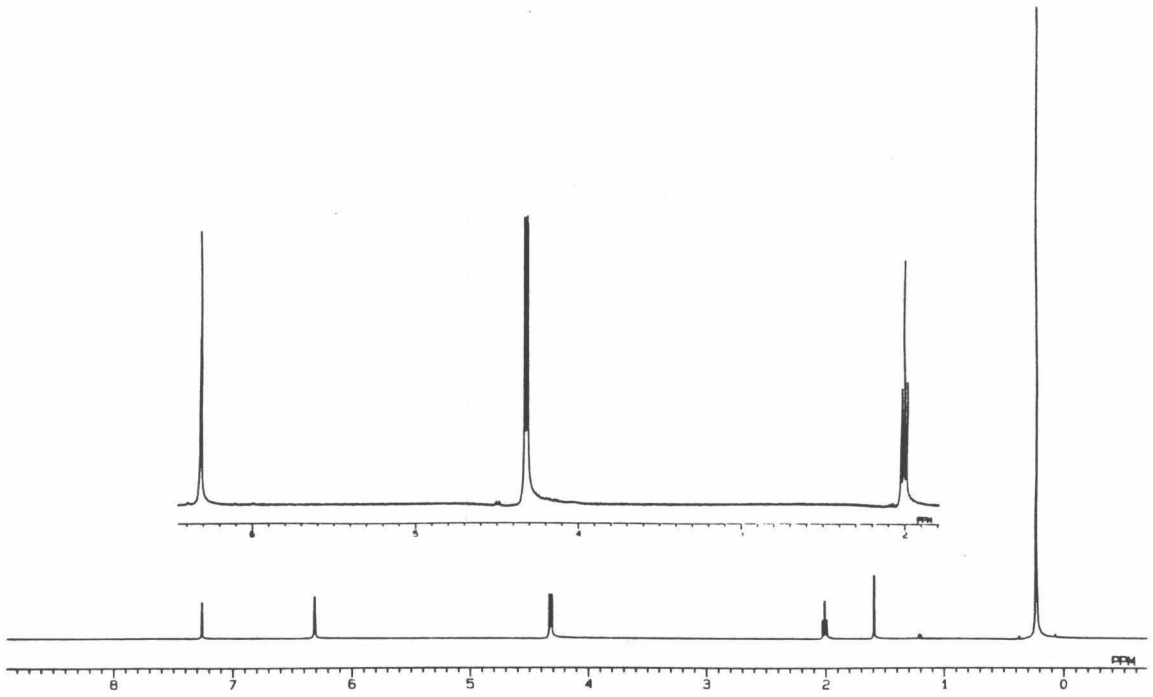
1500
1000
cm-1
500

30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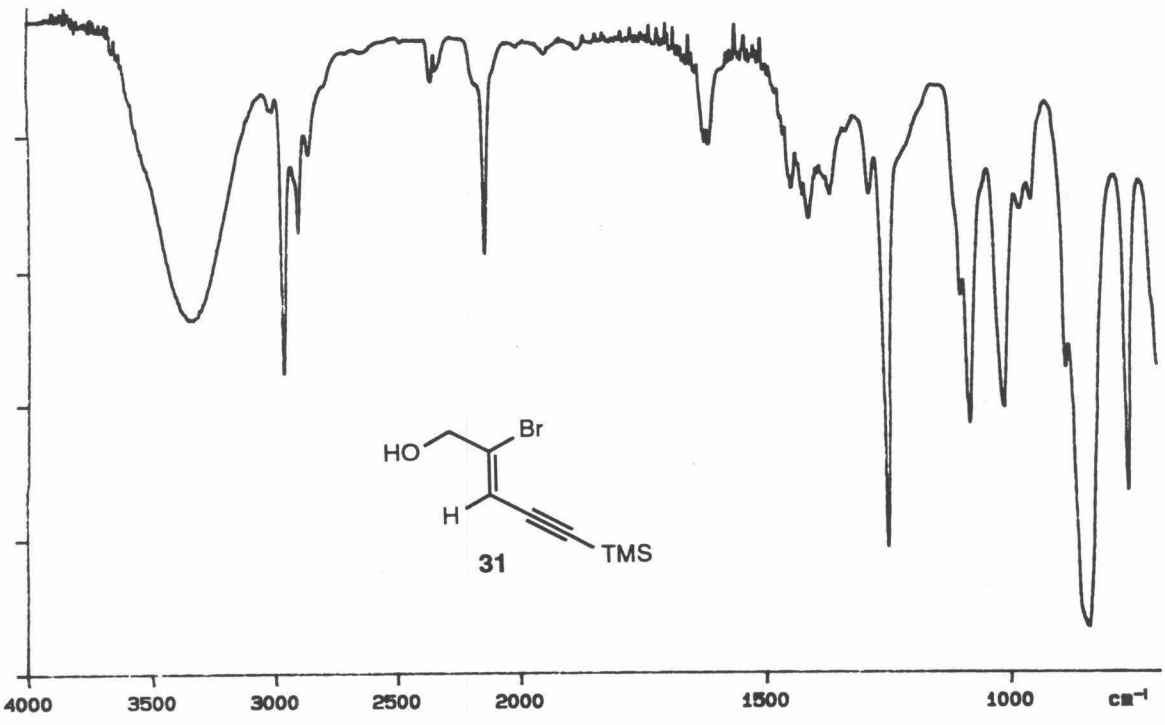
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Br
H
TMS
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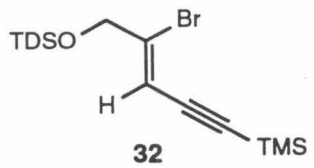
3500
3000
2500
2000
1500
1000
cm⁻¹

31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Br
H
TMS

32

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6
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4
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2
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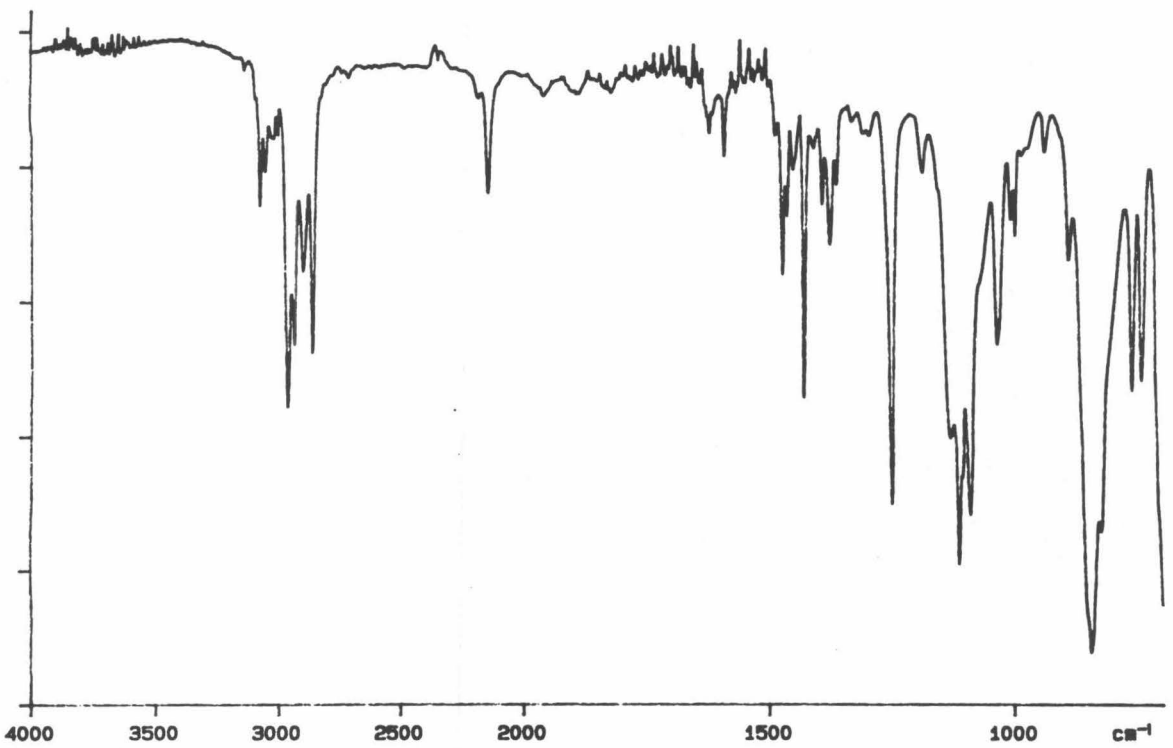
0
PPM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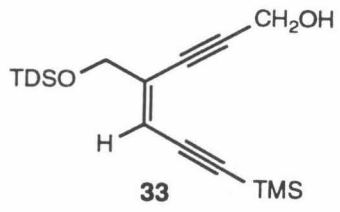
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TMS

33

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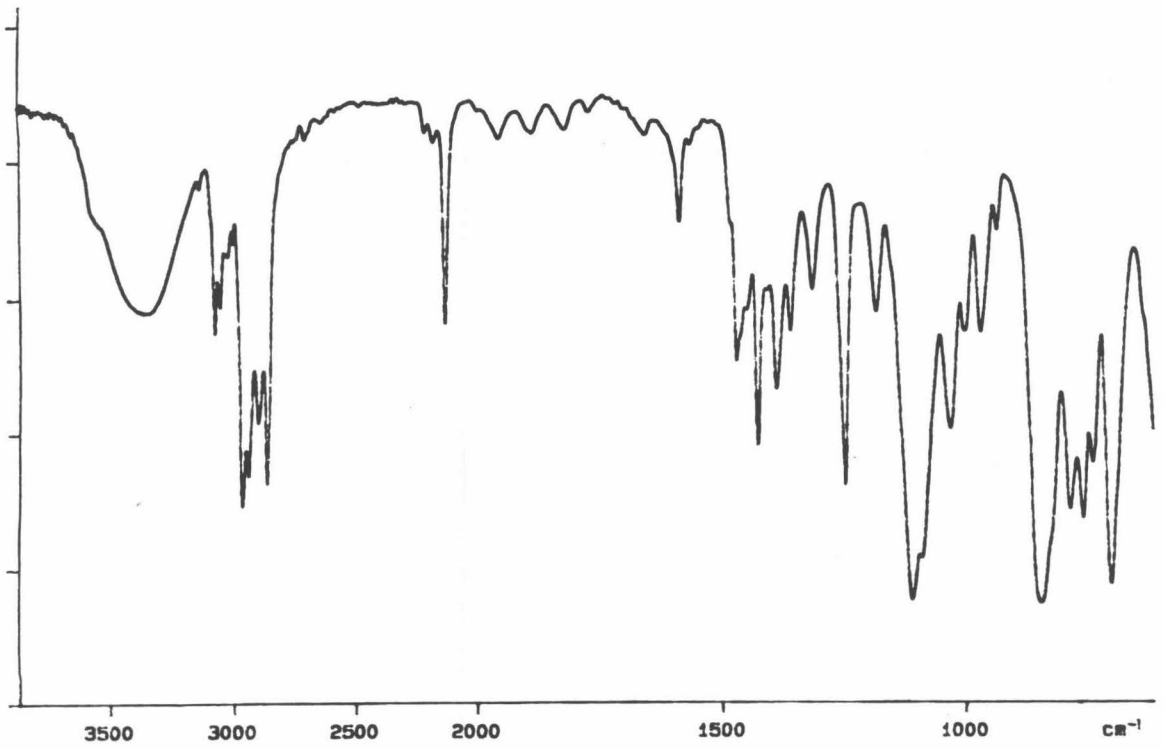
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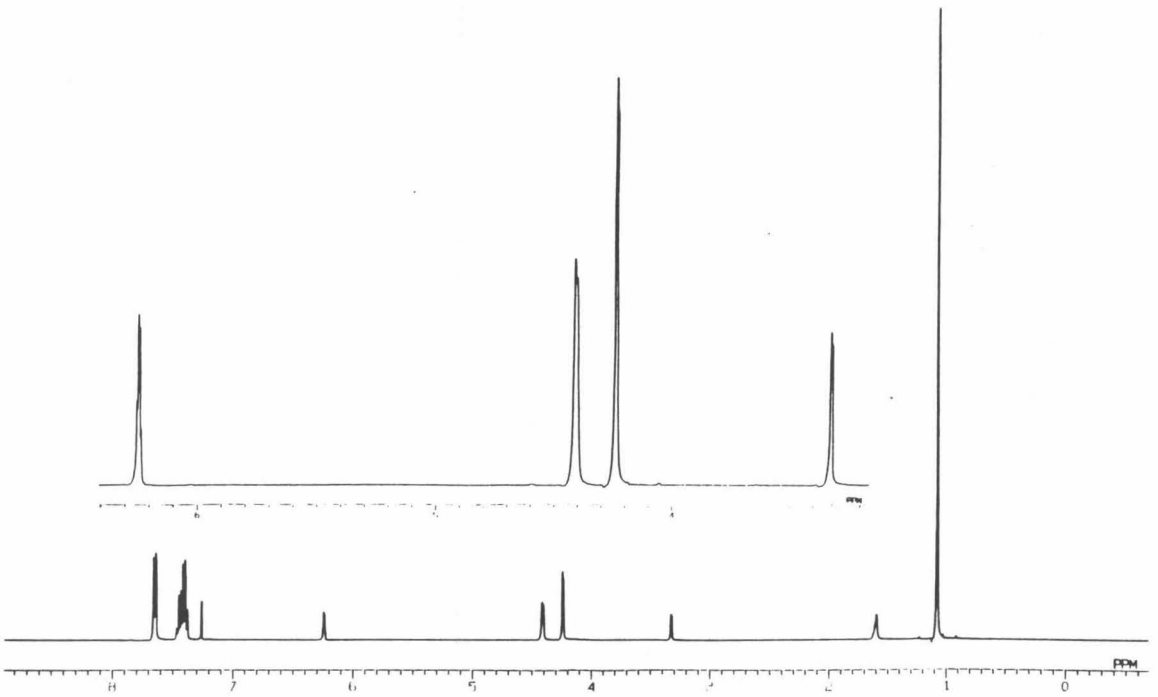
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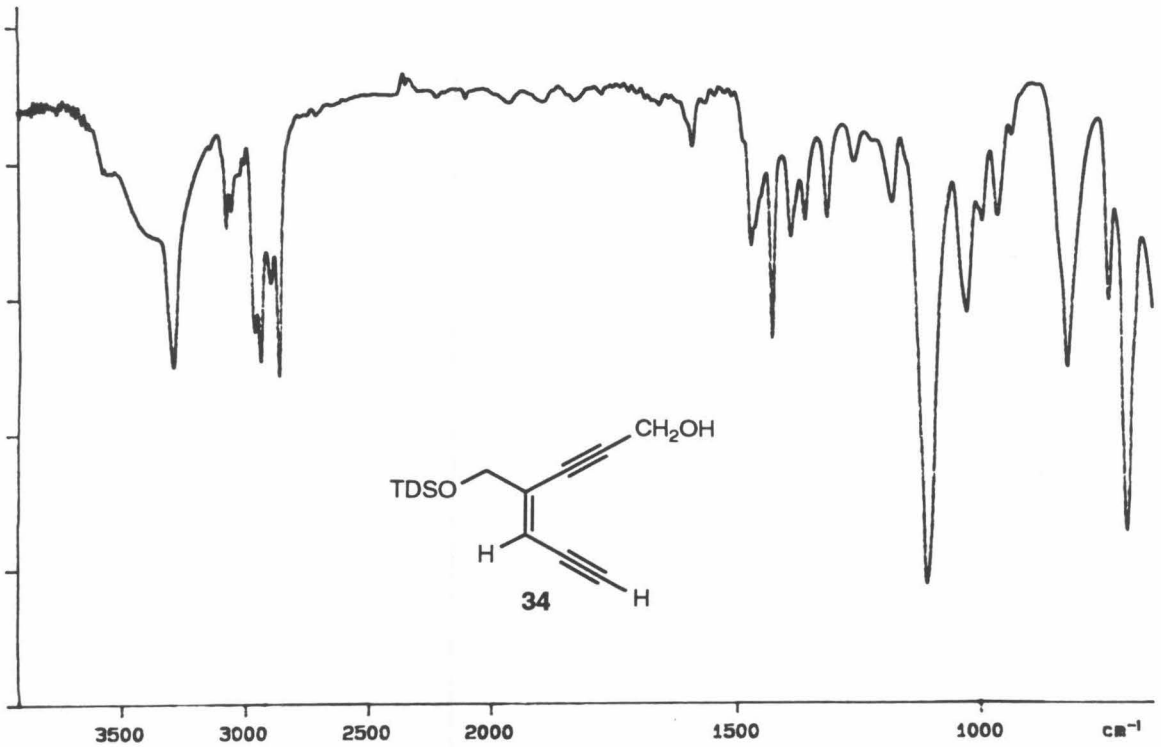
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H
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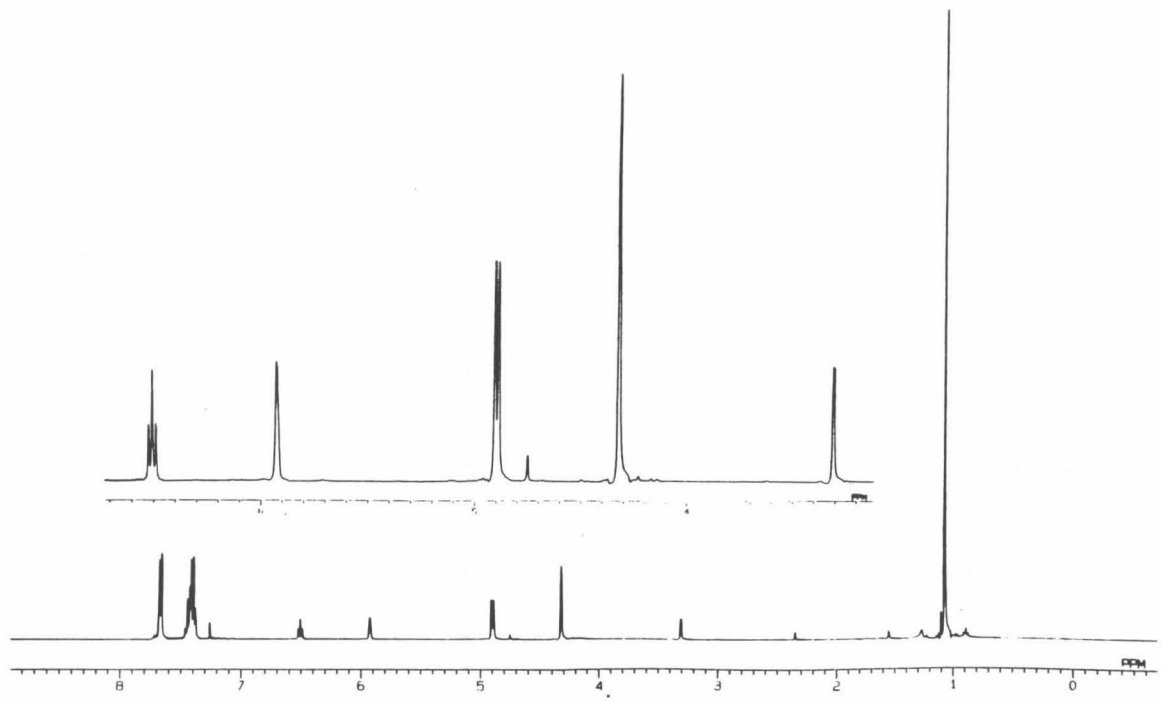
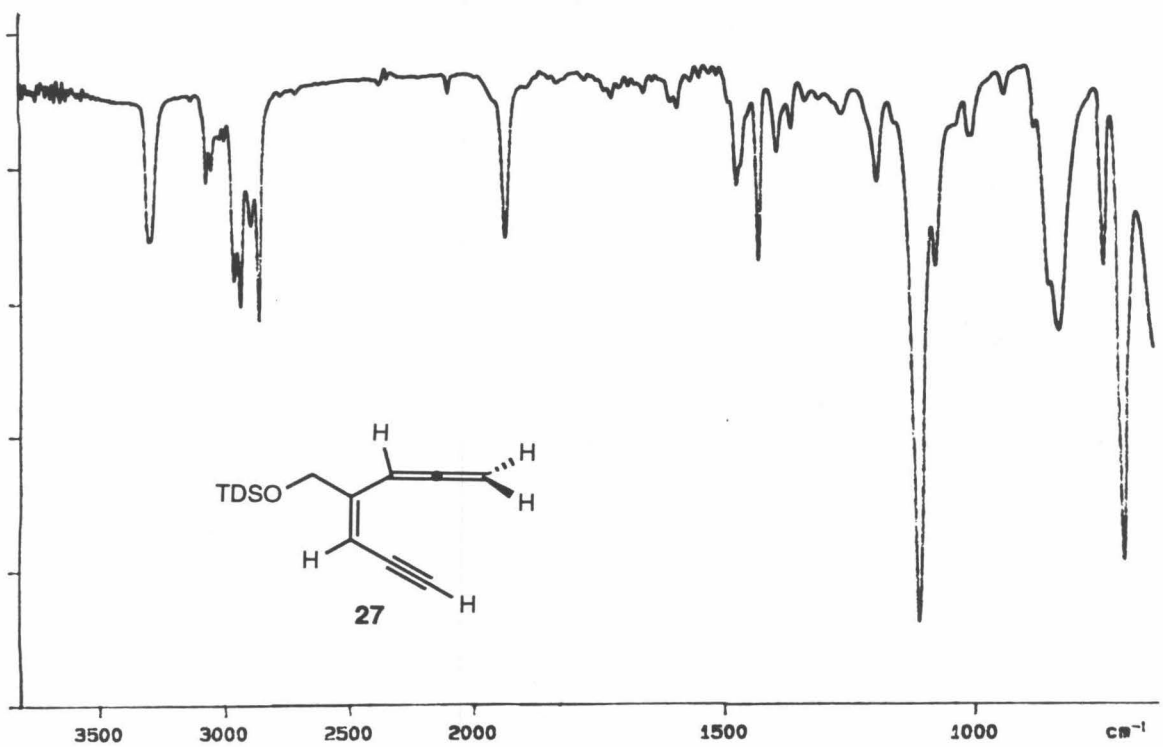
1500
1000
cm-1

34





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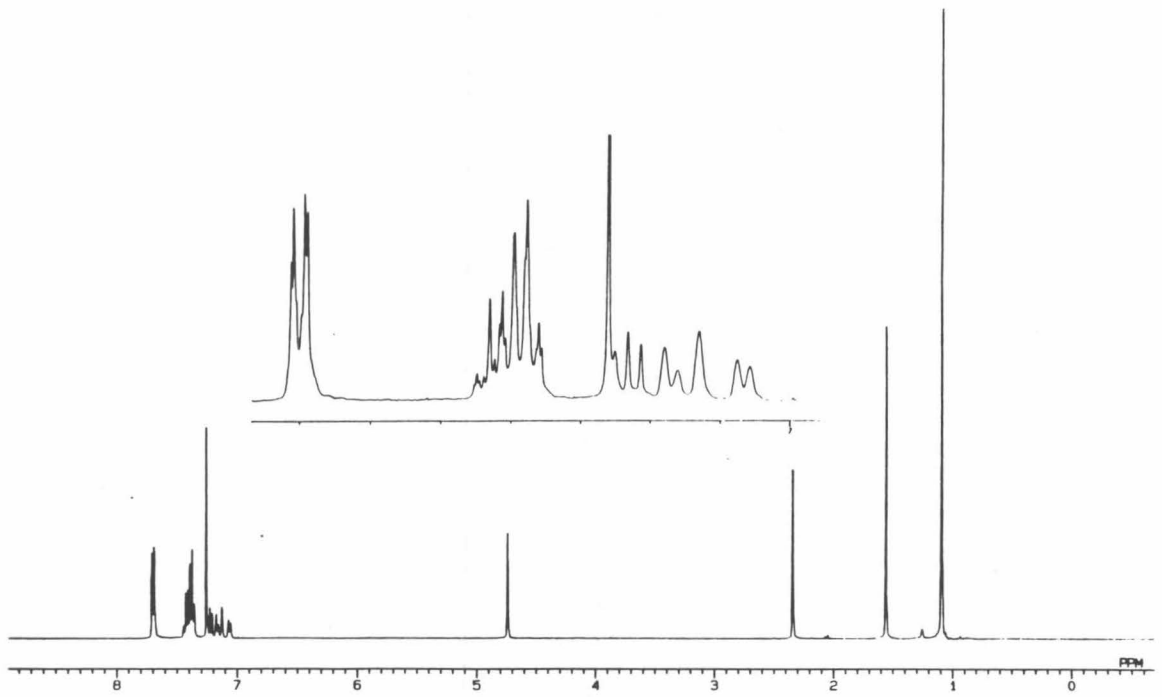
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6
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4
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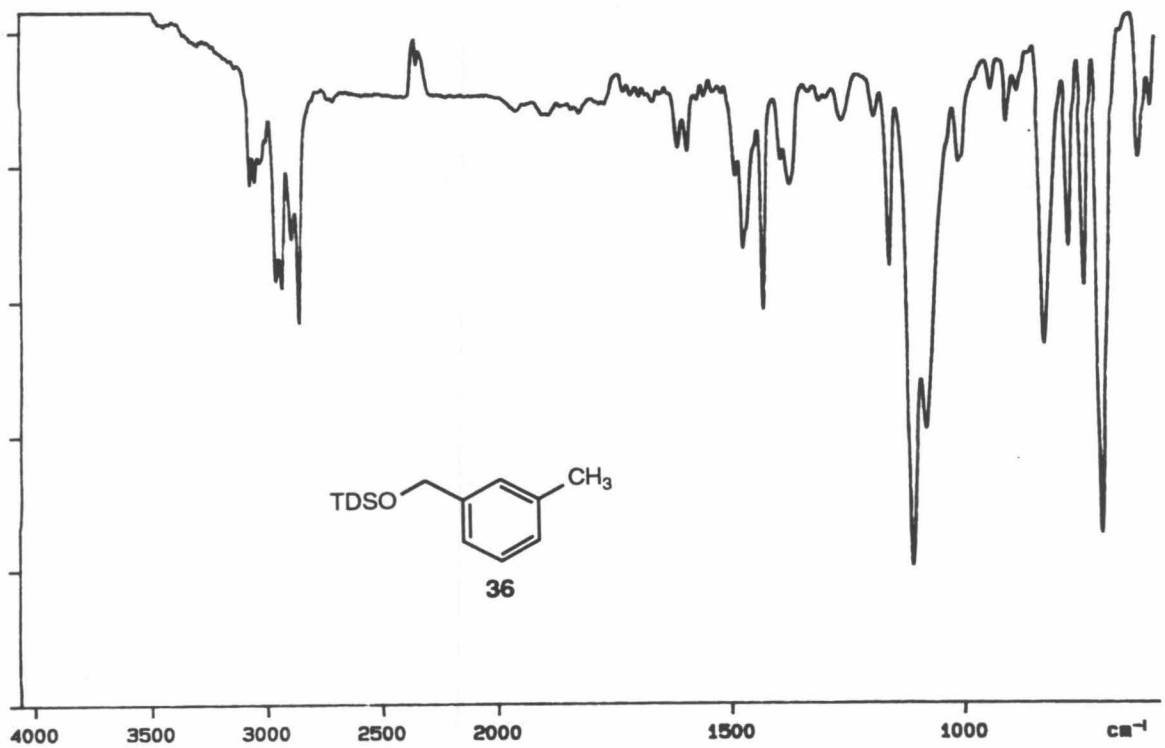
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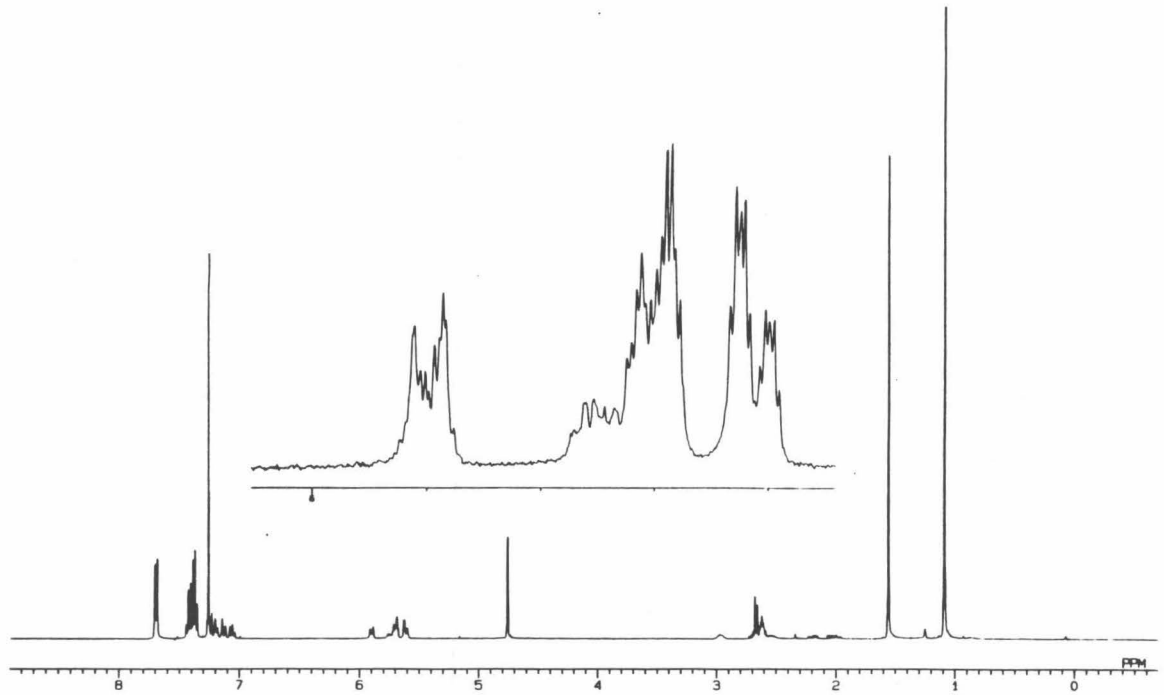
cm-1

36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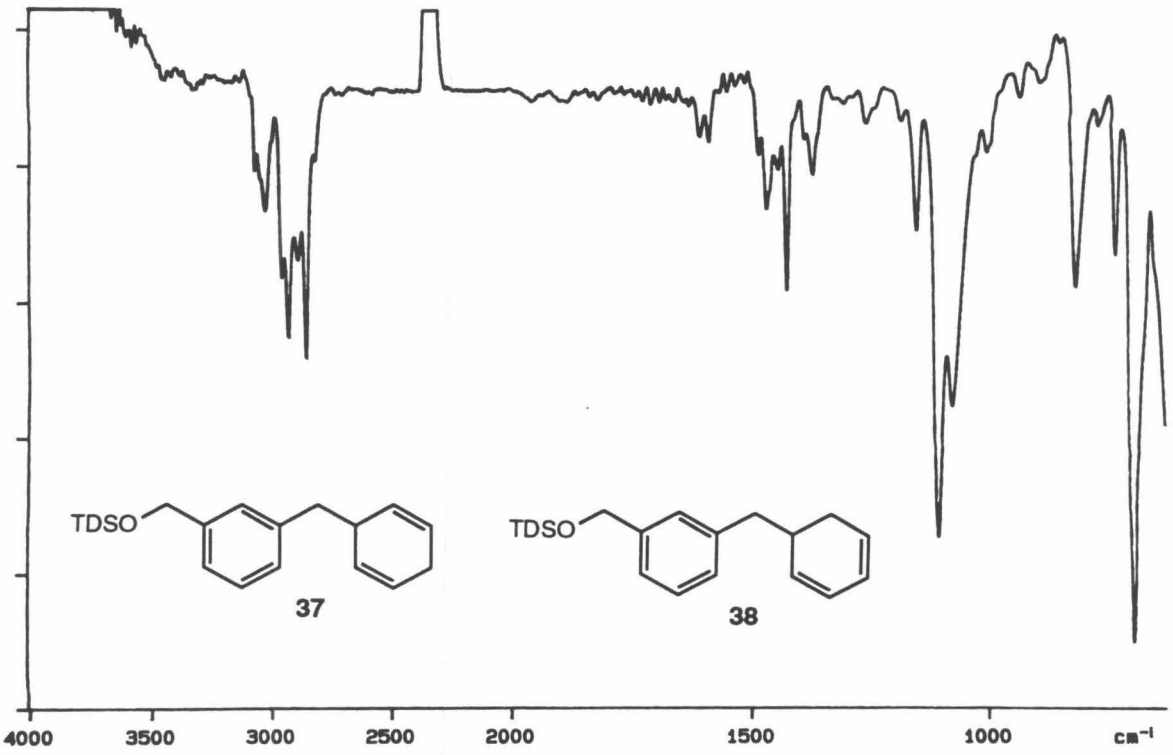
TDSO
37
TDSO
38
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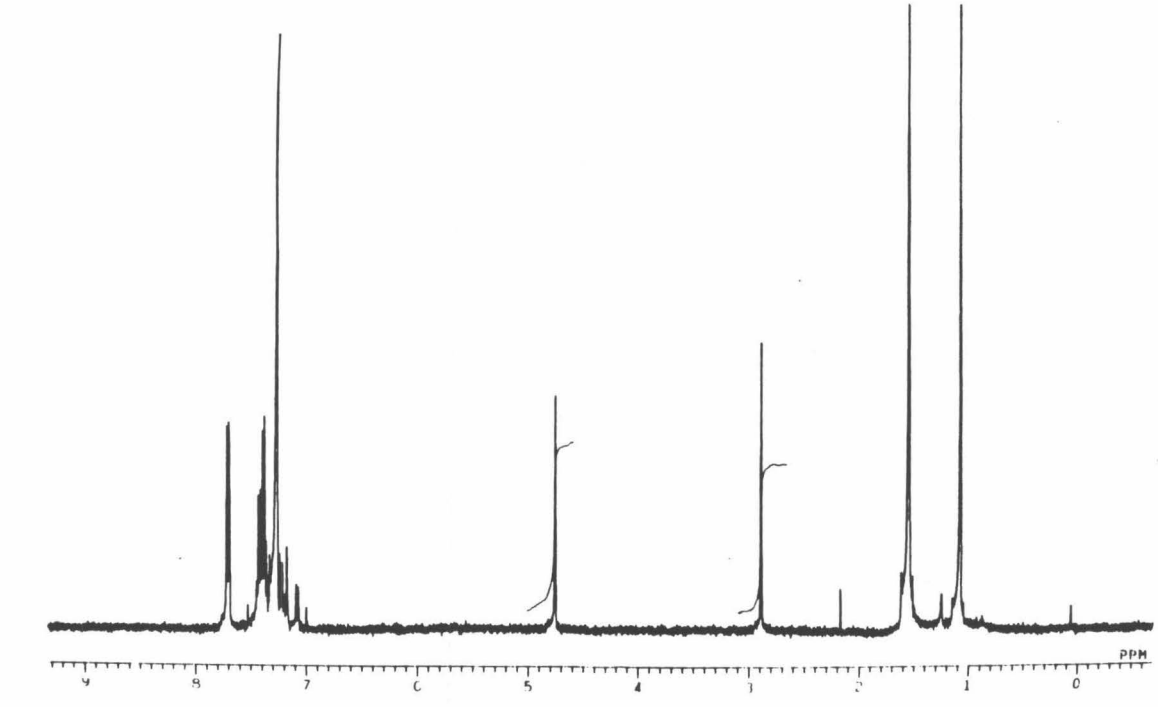
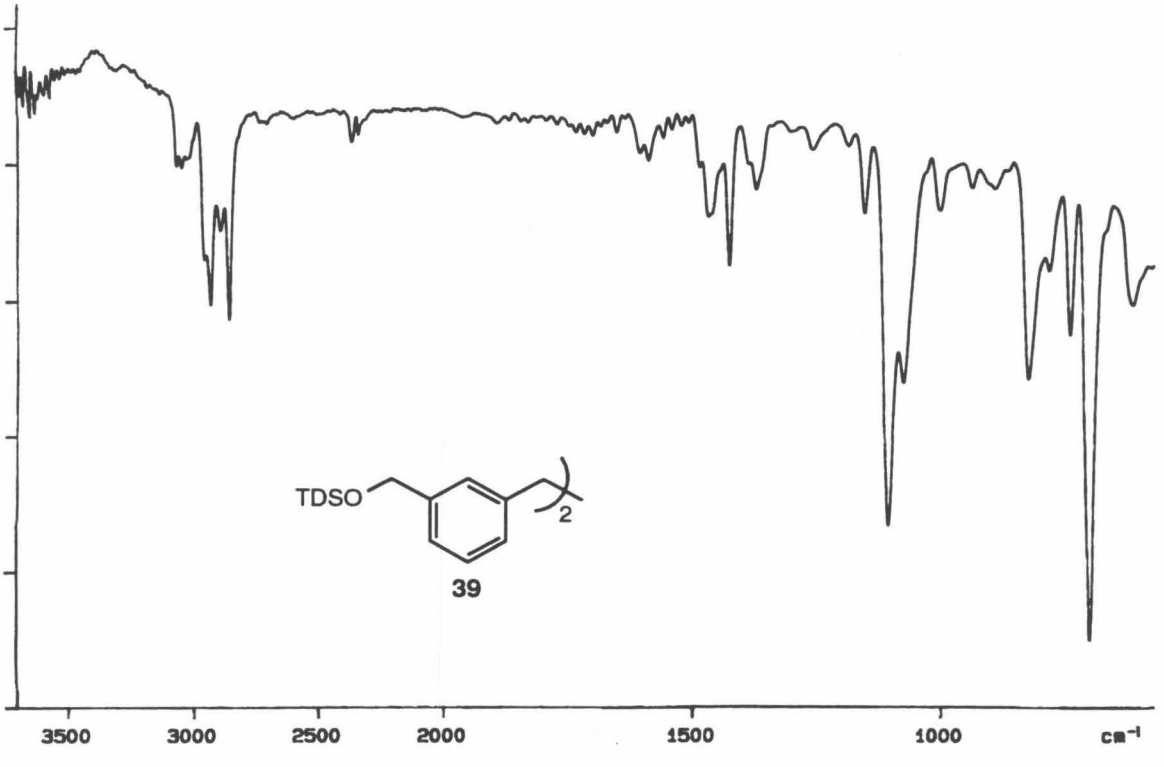
3000
2500
2000
1500
1000
cm⁻¹





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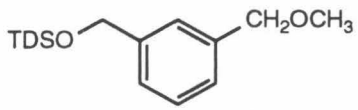

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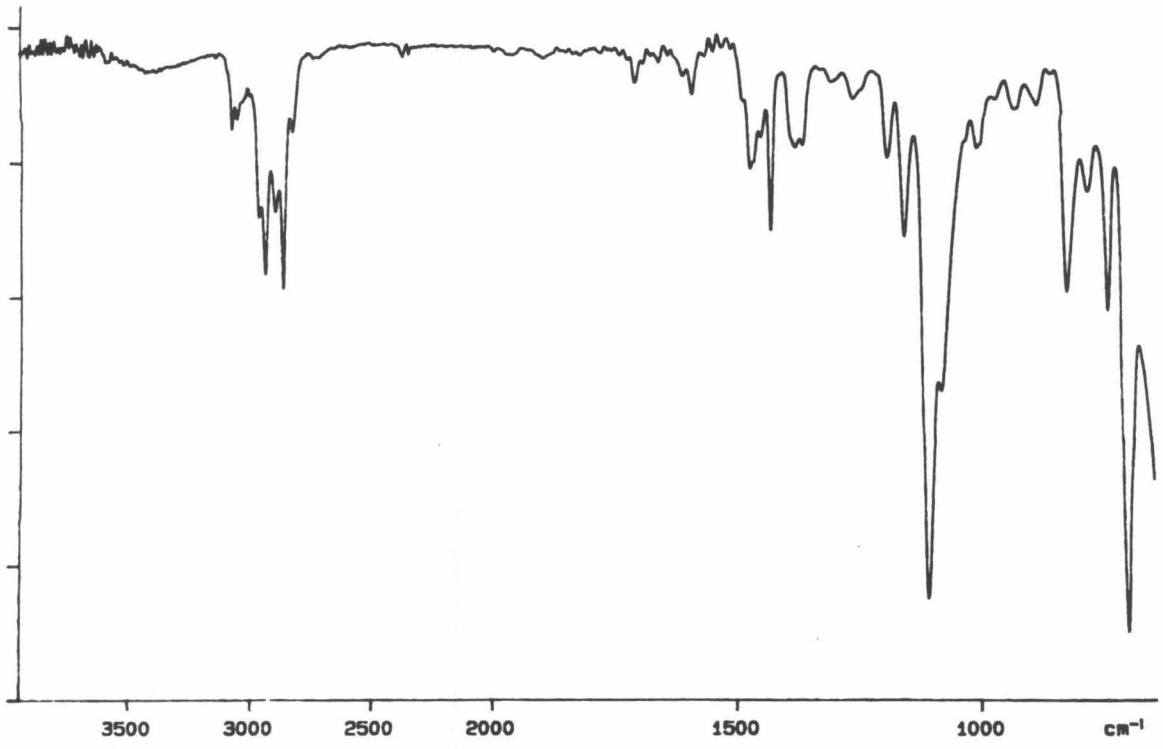

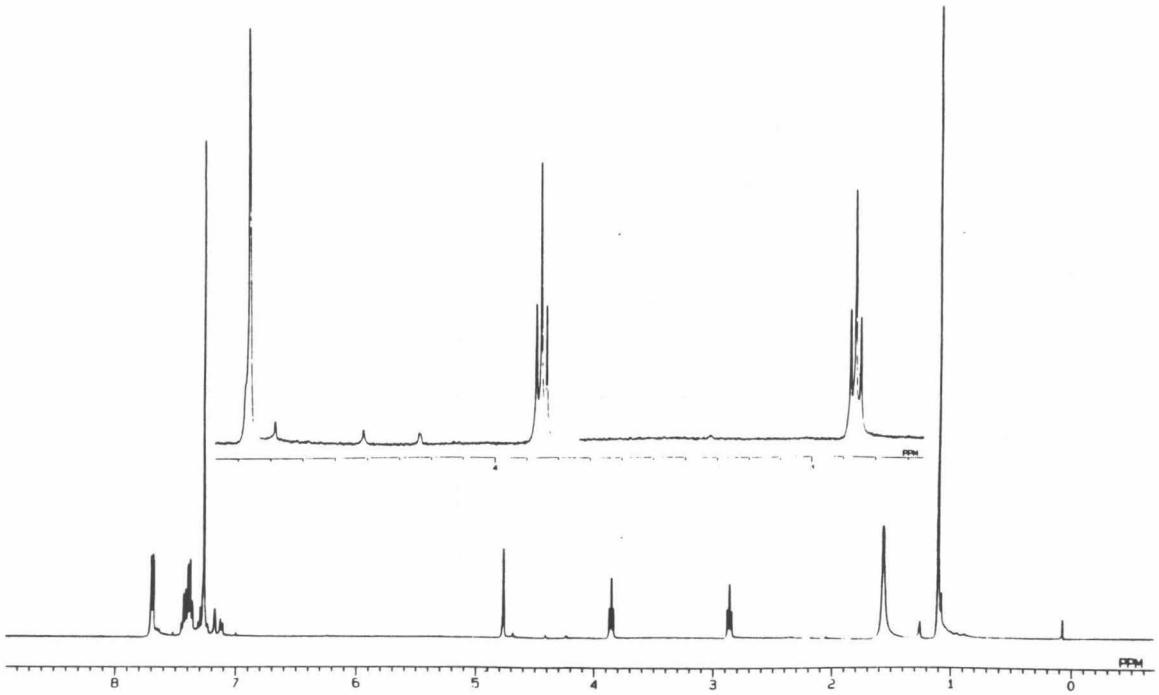
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4
3
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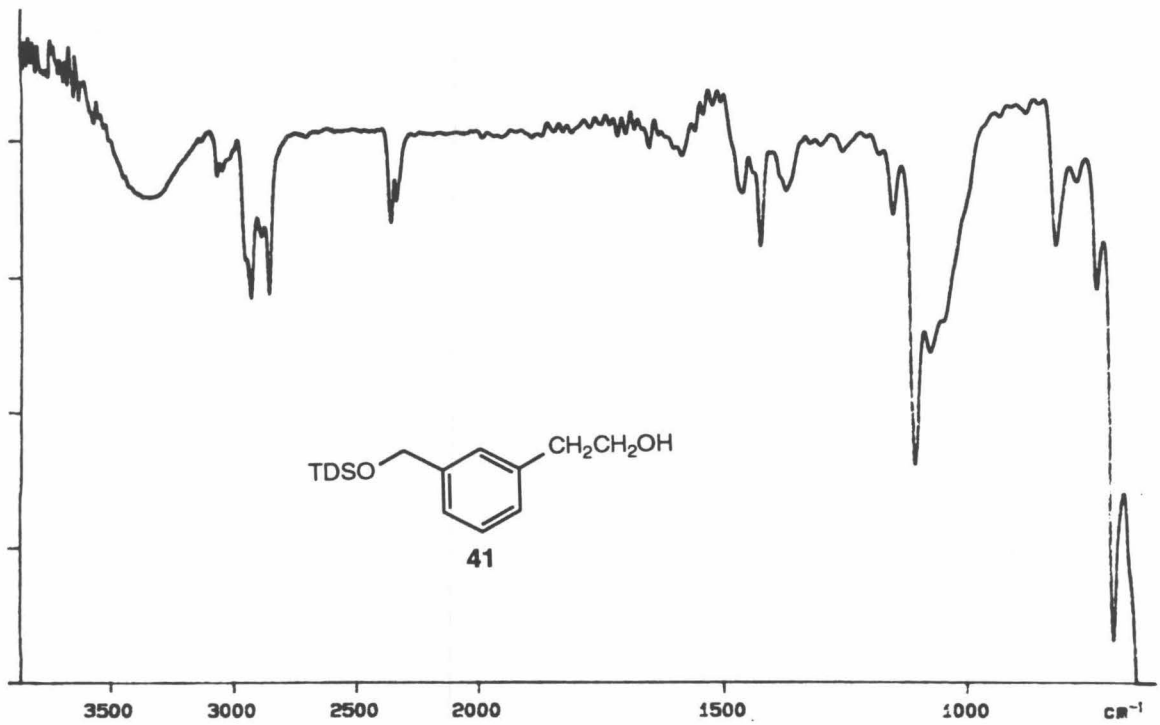
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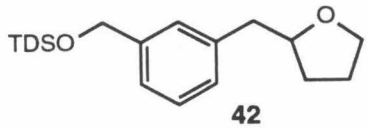
CH2CH2OH
3500
3000
2500
2000
1500
1000
cm-1

41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O

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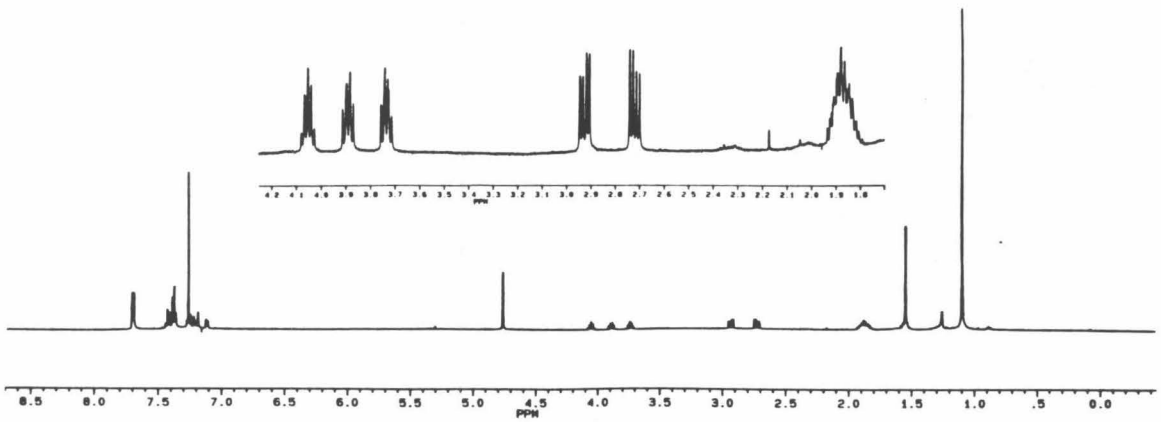
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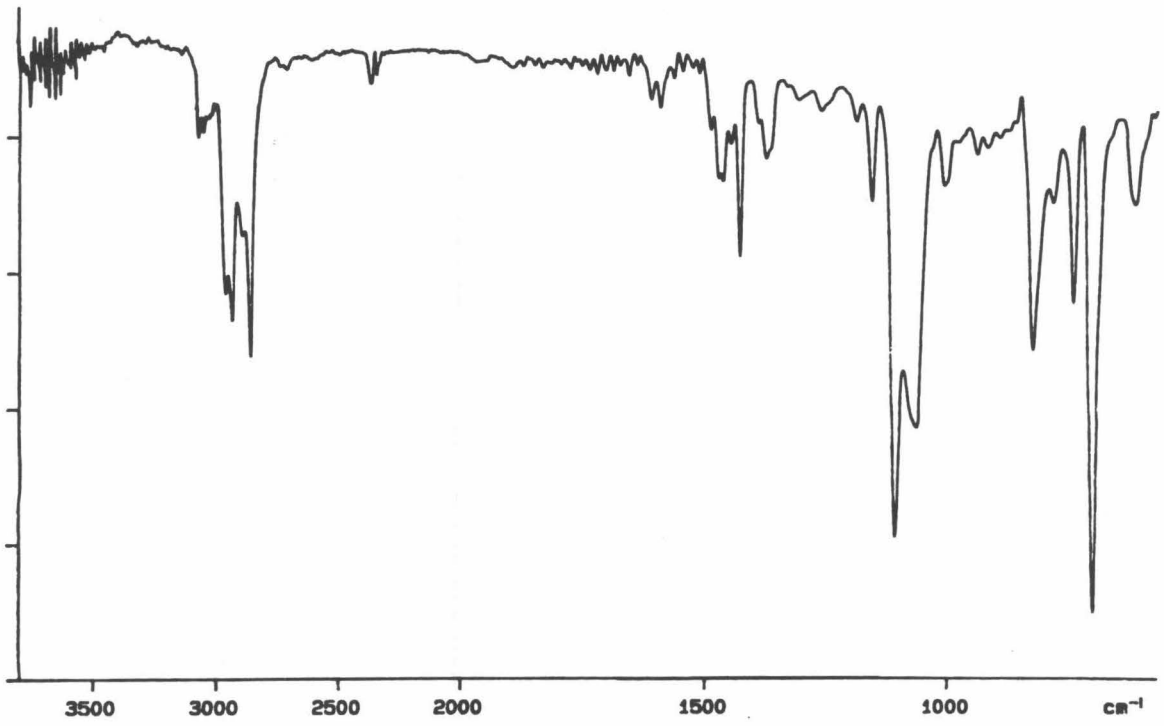
PPM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2000
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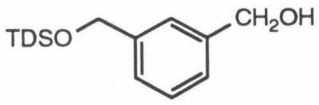
cm⁻¹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CH2OH

43

PPM
8
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6
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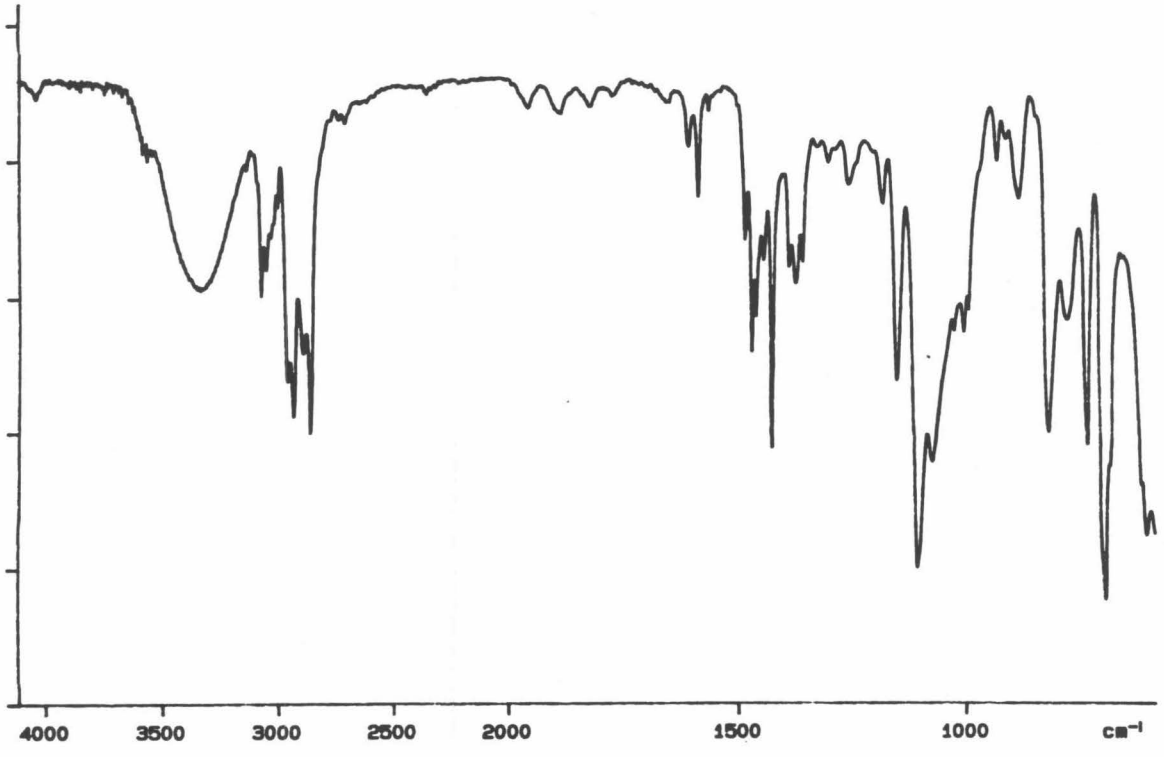
4
3
2
1
0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2500
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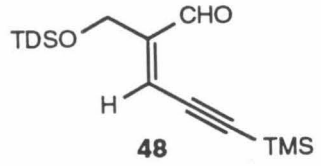
cm⁻¹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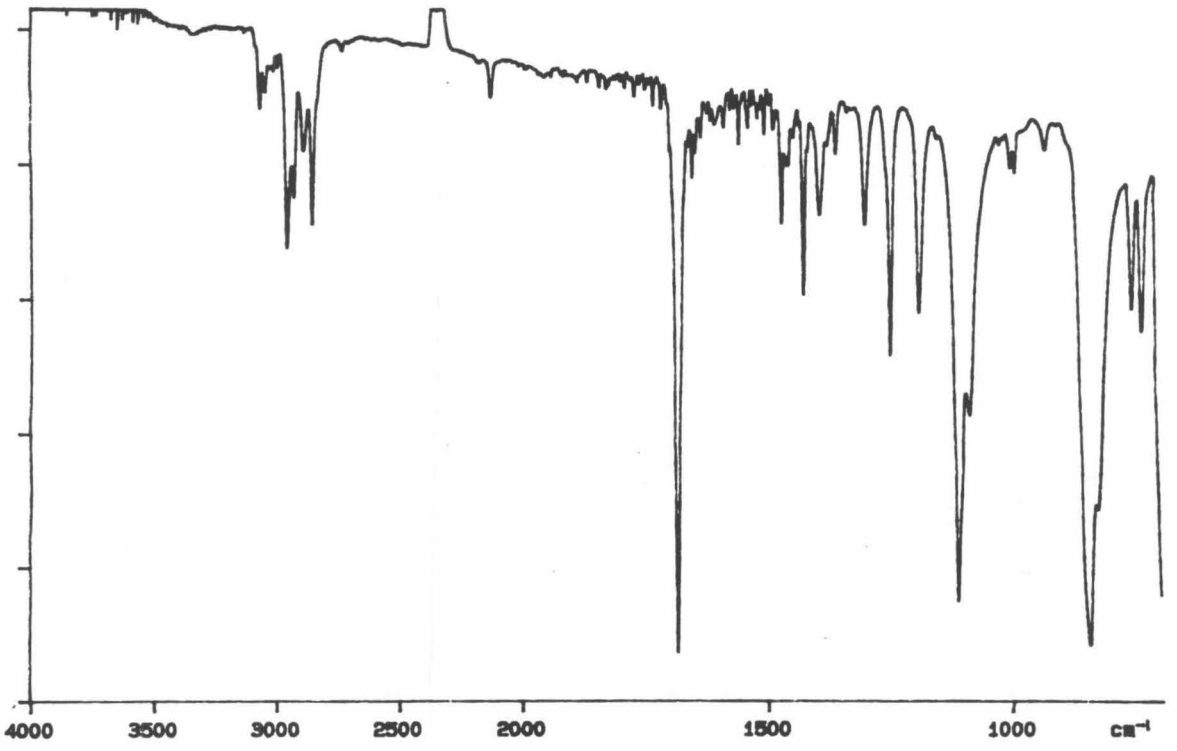
CHO
H
TMS

48

10
9
8
7
6
5
4
3
2
1
0
-1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1500
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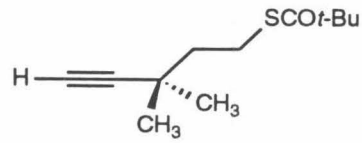
cm⁻¹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CH3

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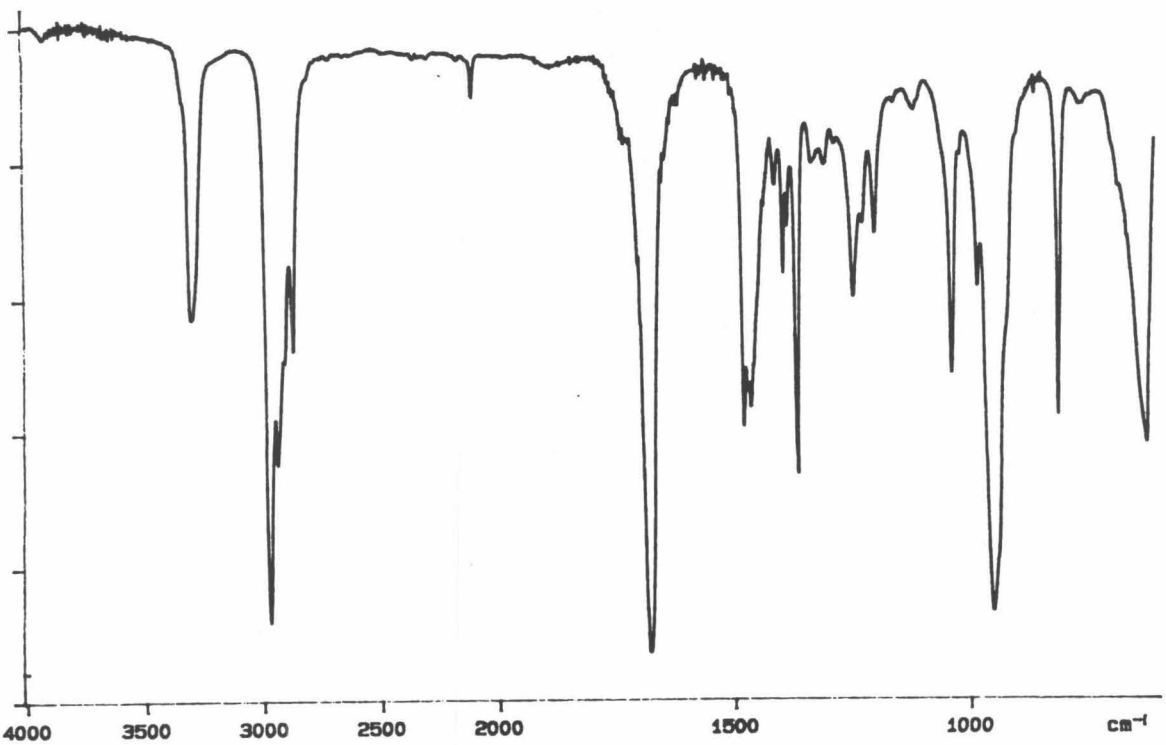
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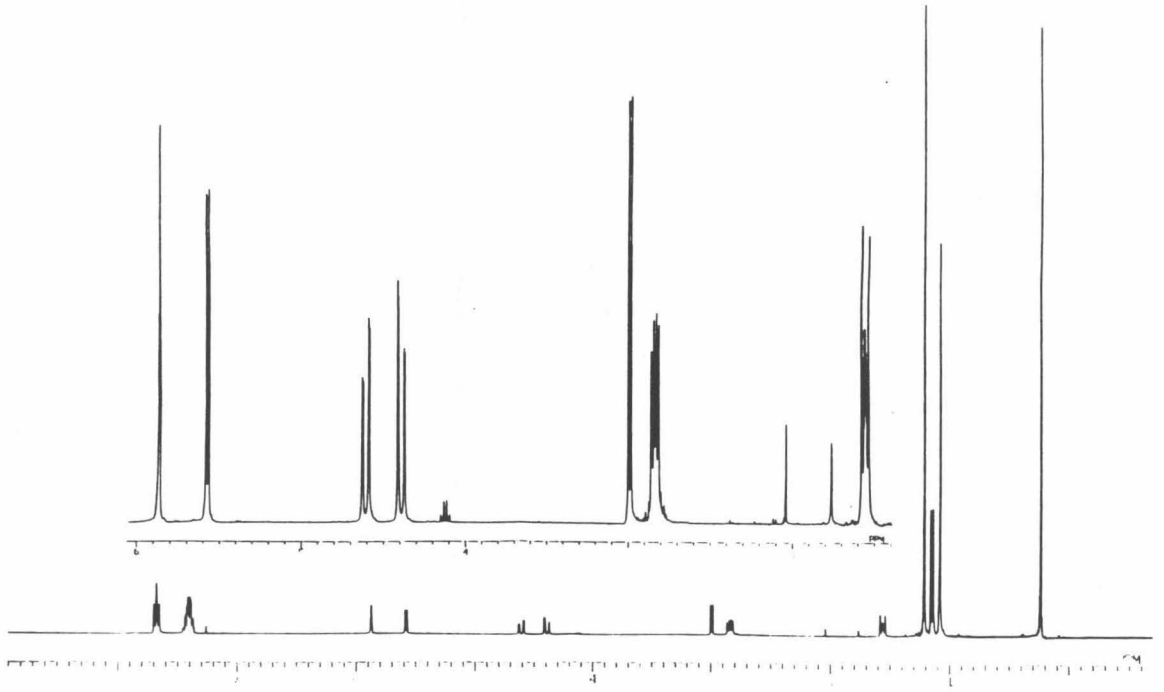
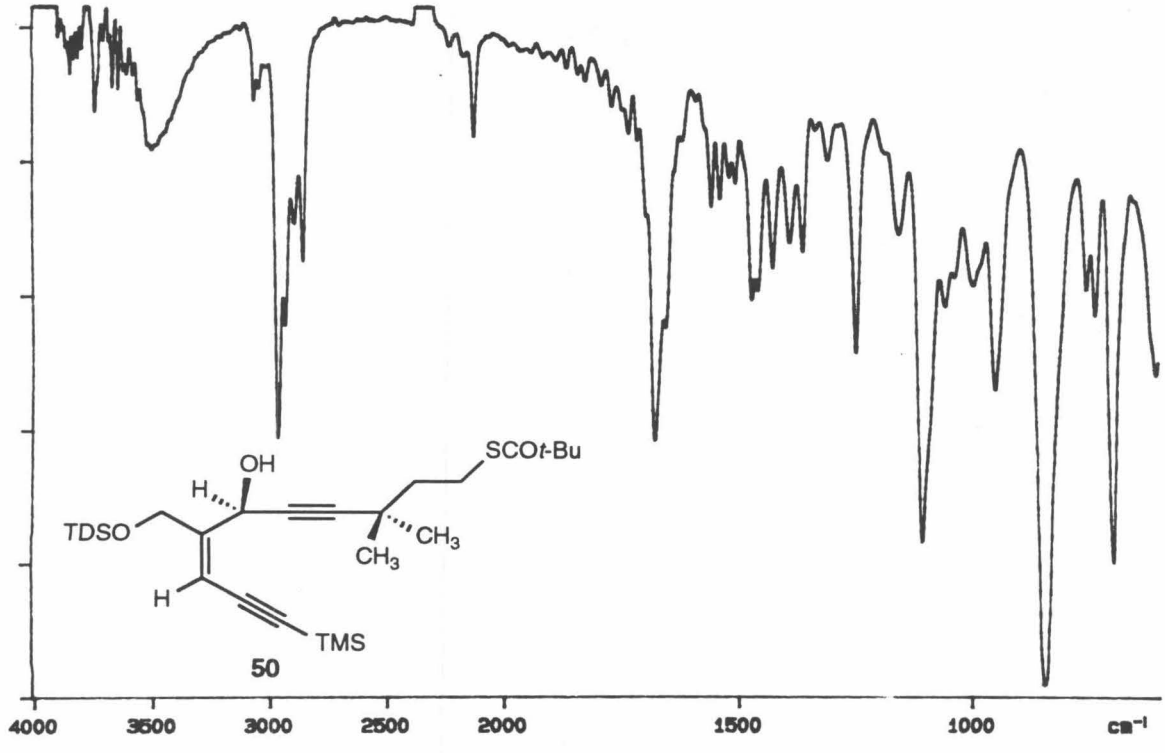
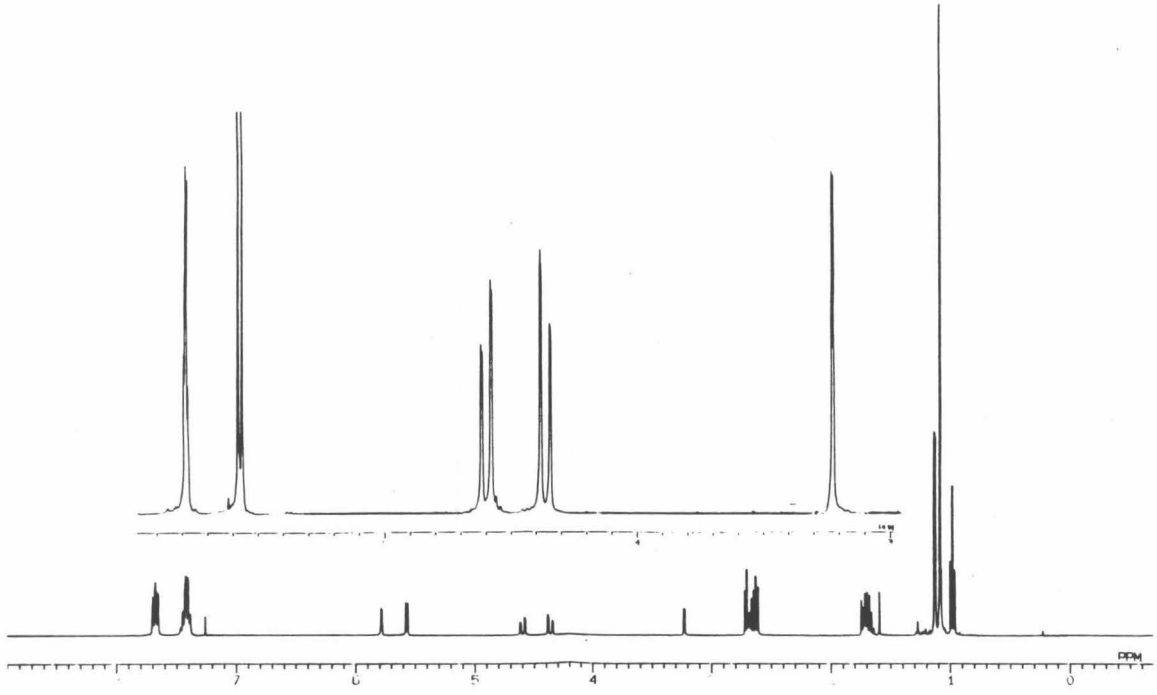
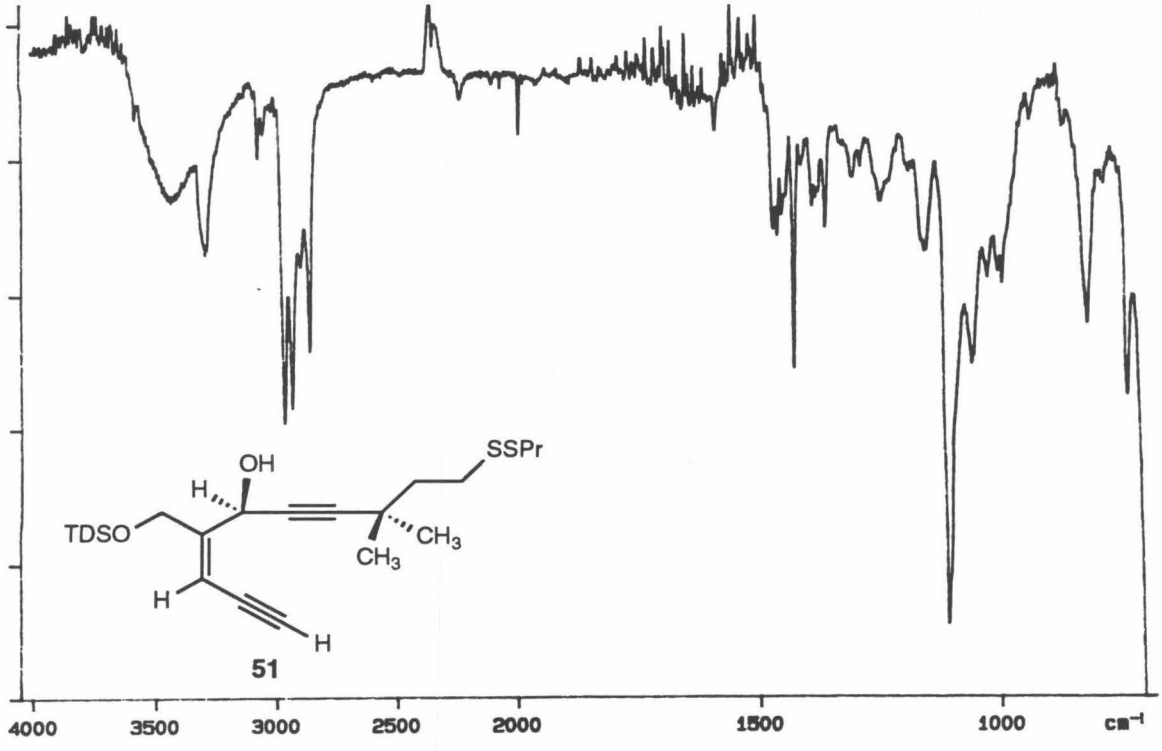
cm⁻¹

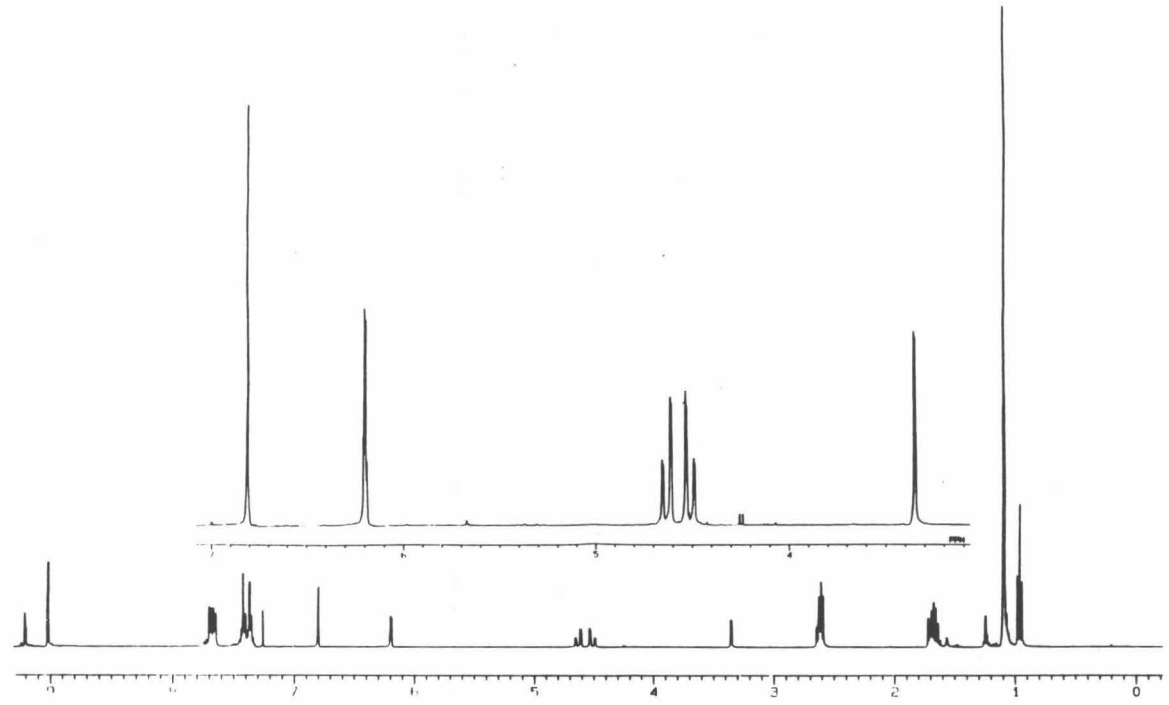


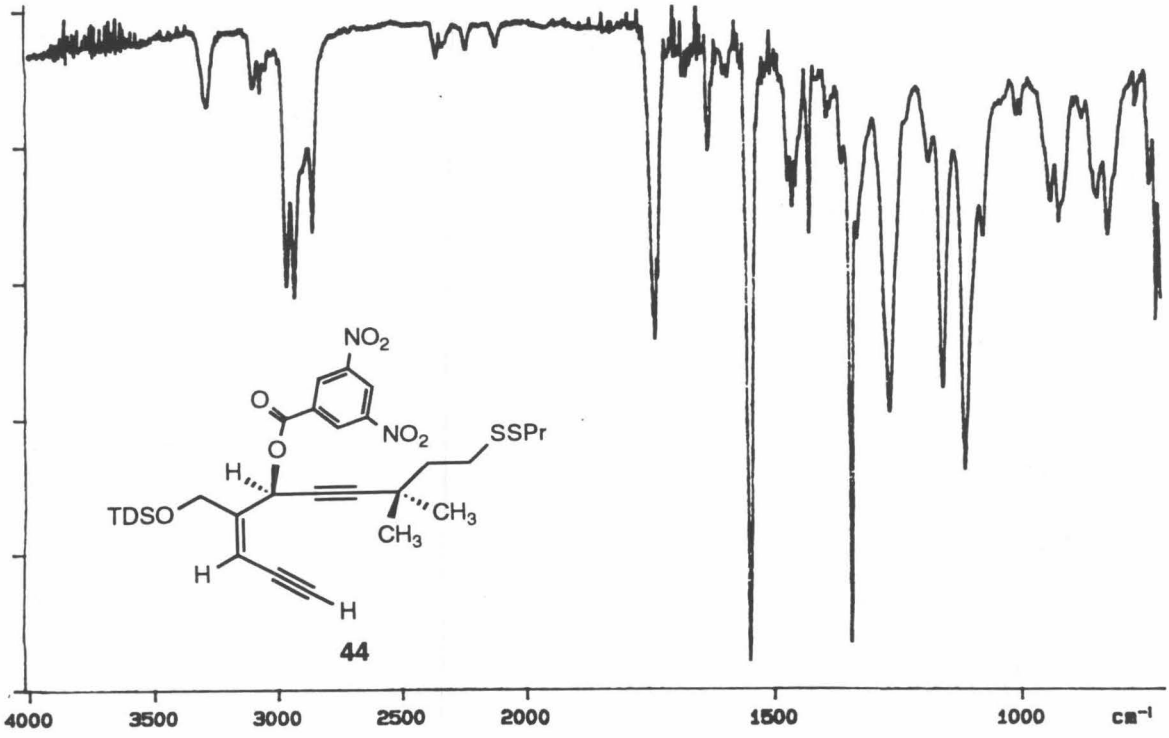

OH
H
SCOt-Bu
TDSO
CH3
CH3
H
TMS
50
4000
3500
3000
2500
2000
1500
1000
cm-1


PPM
7
6
5
4
1
0

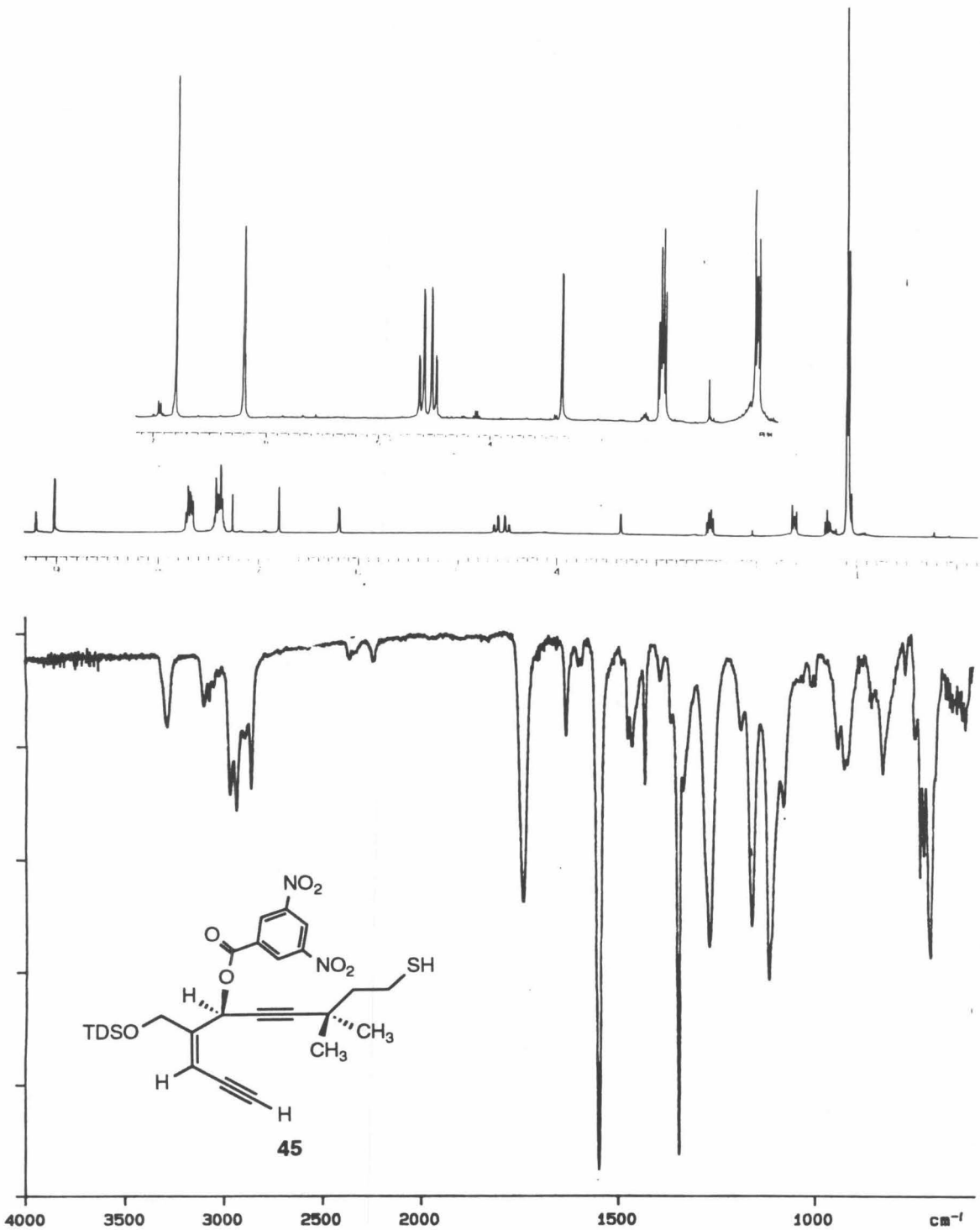

OH
H
SSPr
TDSO
CH3
CH3
H
H
4000
3500
3000
2500
2000
1500
1000
cm-1

51

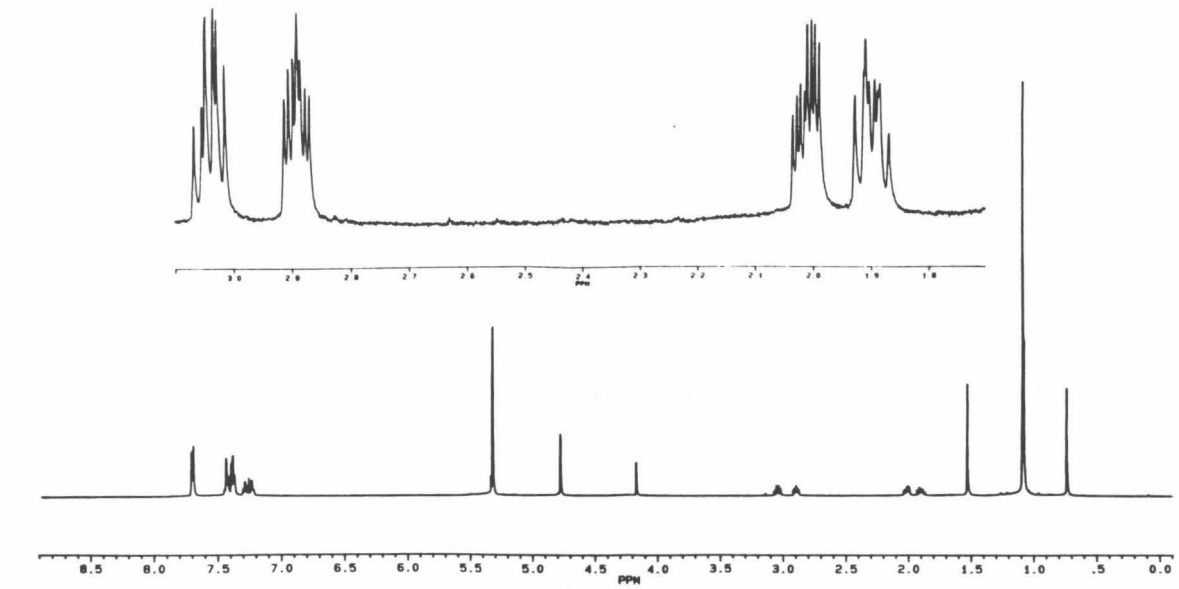


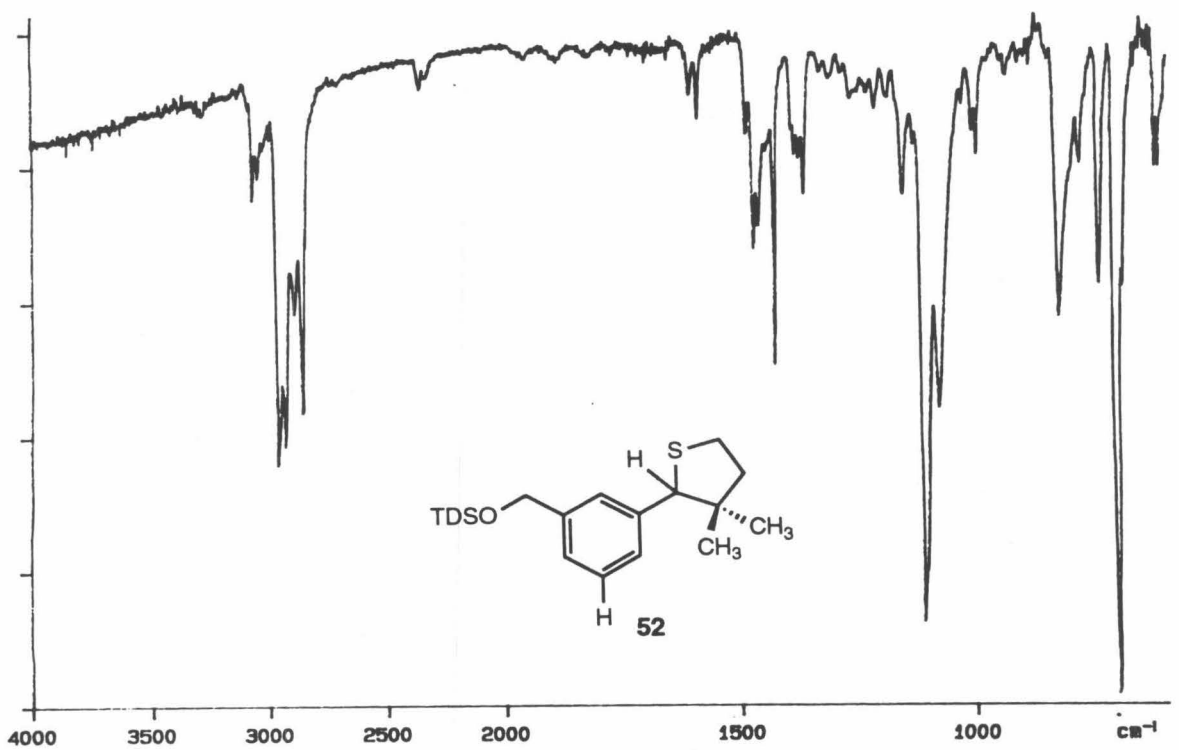

NO2
O
NO2
SSPr
O
H
TDSO
CH3
CH3
H
H
4000
3500
3000
2500
2000
1500
1000
cm-1

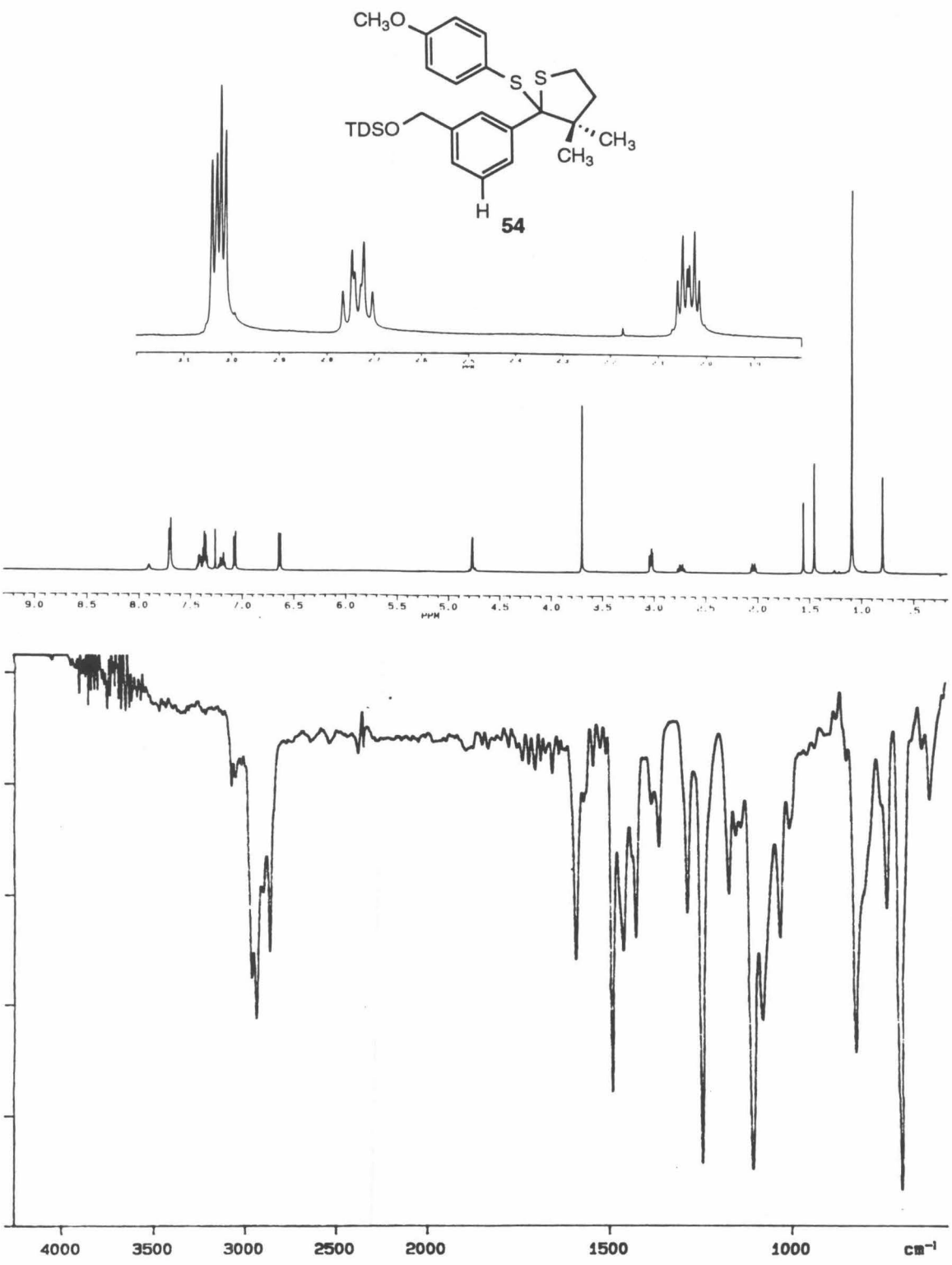
44

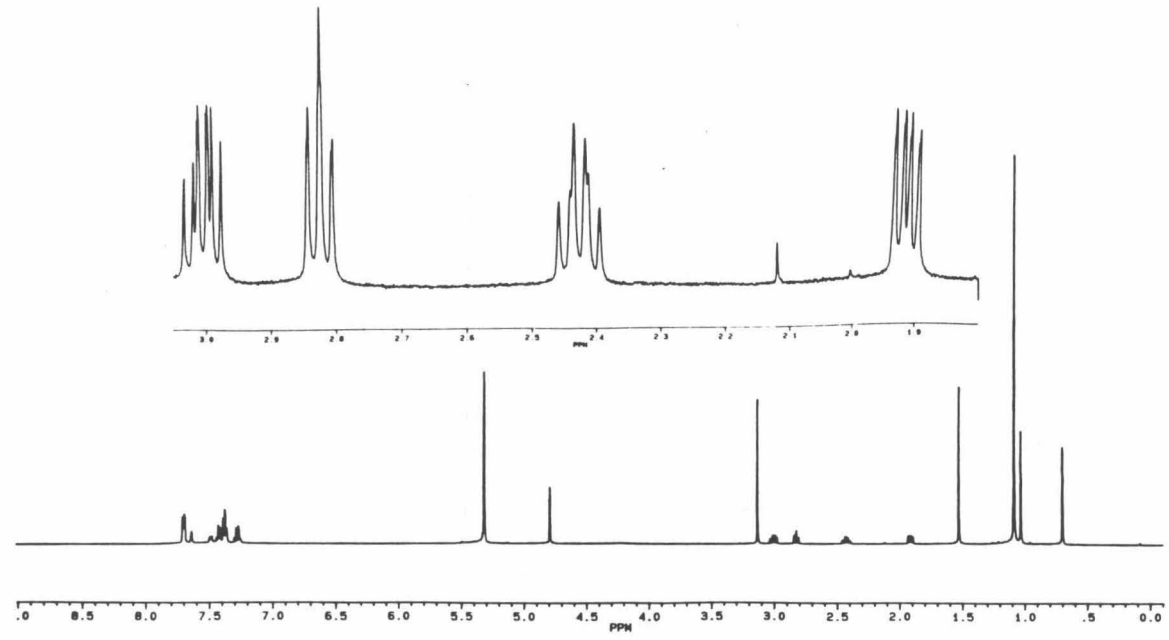

NO2
O
NO2
SH
O
H
TDSO
CH3
CH3
H
H
4000
3500
3000
2500
2000
1500
1000
cm-1

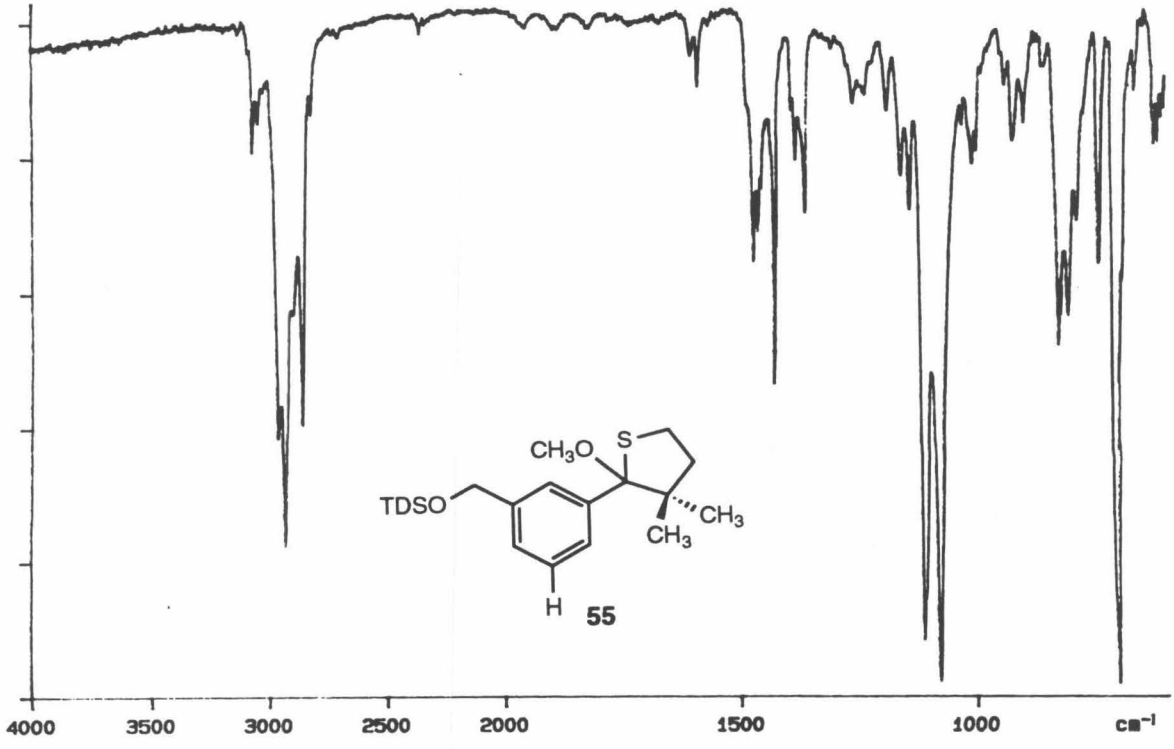
45


8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
.5
0.0
PPM

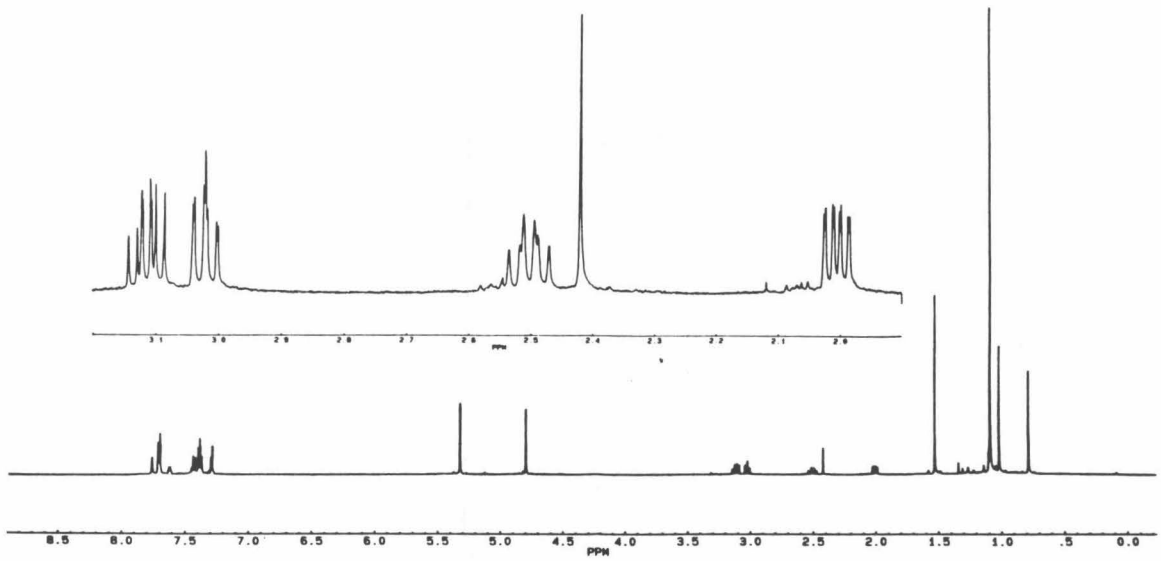

H
S
TDSO
CH3
CH3
H
52
4000
3500
3000
2500
2000
1500
1000
cm-1

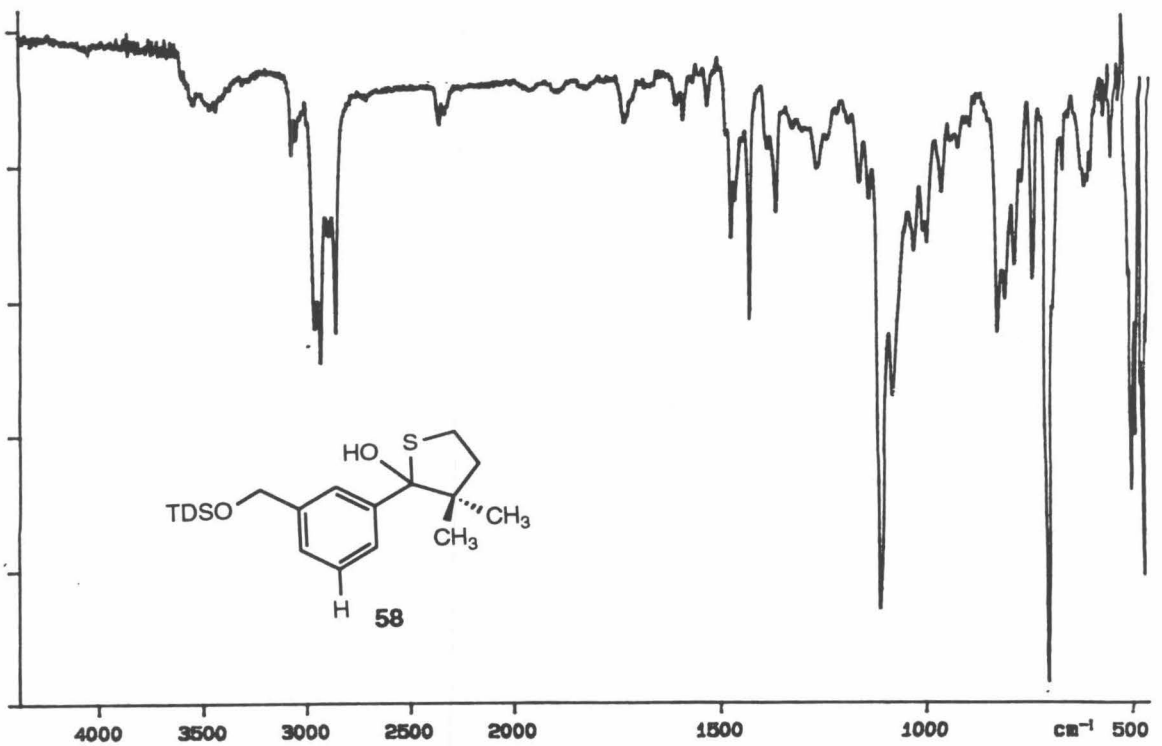

CH3O
S
S
TDSO
CH3
CH3
H
54
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
.5
PPM
4000
3500
3000
2500
2000
1500
1000
cm-1


PPM

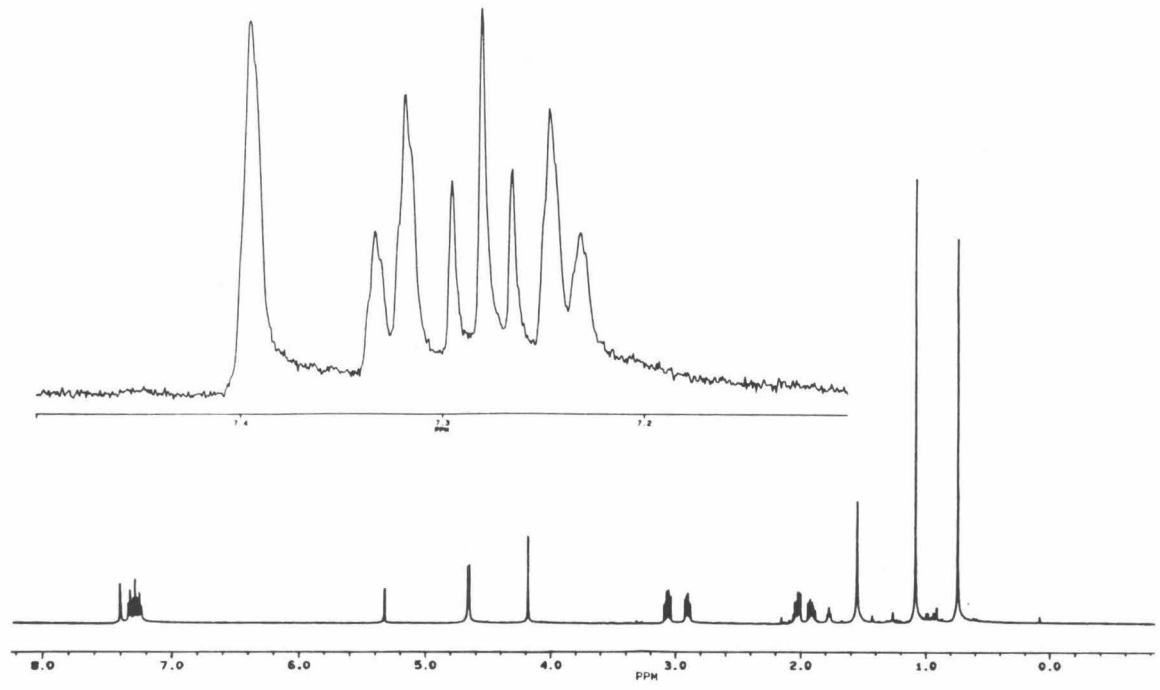

CH3O
S
TDSO
CH3
CH3
H
4000
3500
3000
2500
2000
1500
1000
cm-1

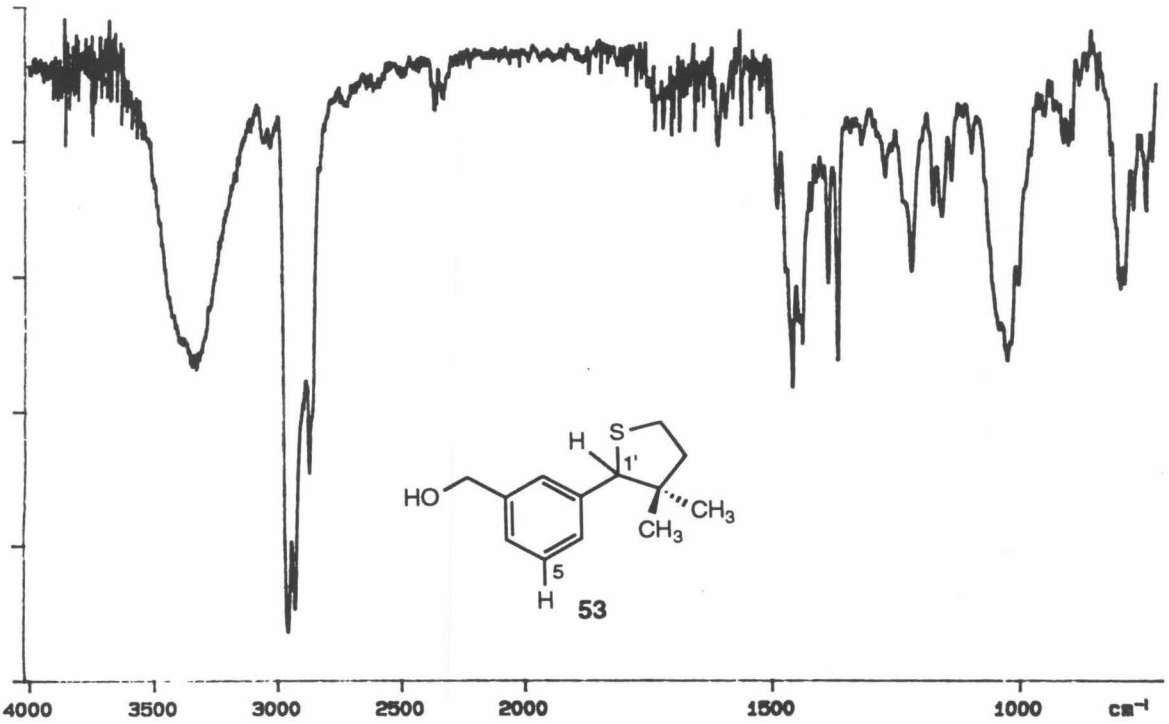
55


8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
PPM
4.0
3.5
3.0
2.5
2.0
1.5
1.0
.5
0.0

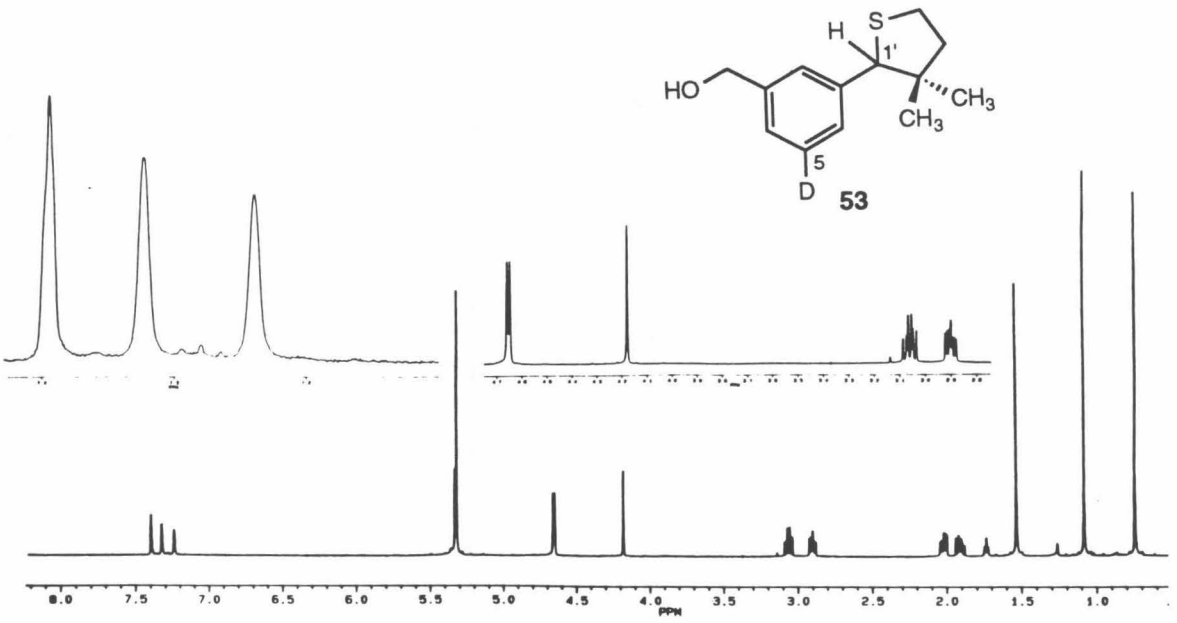

HO
S
TDSO
CH3
CH3
H
4000
3500
3000
2500
2000
1500
1000
cm-1
500

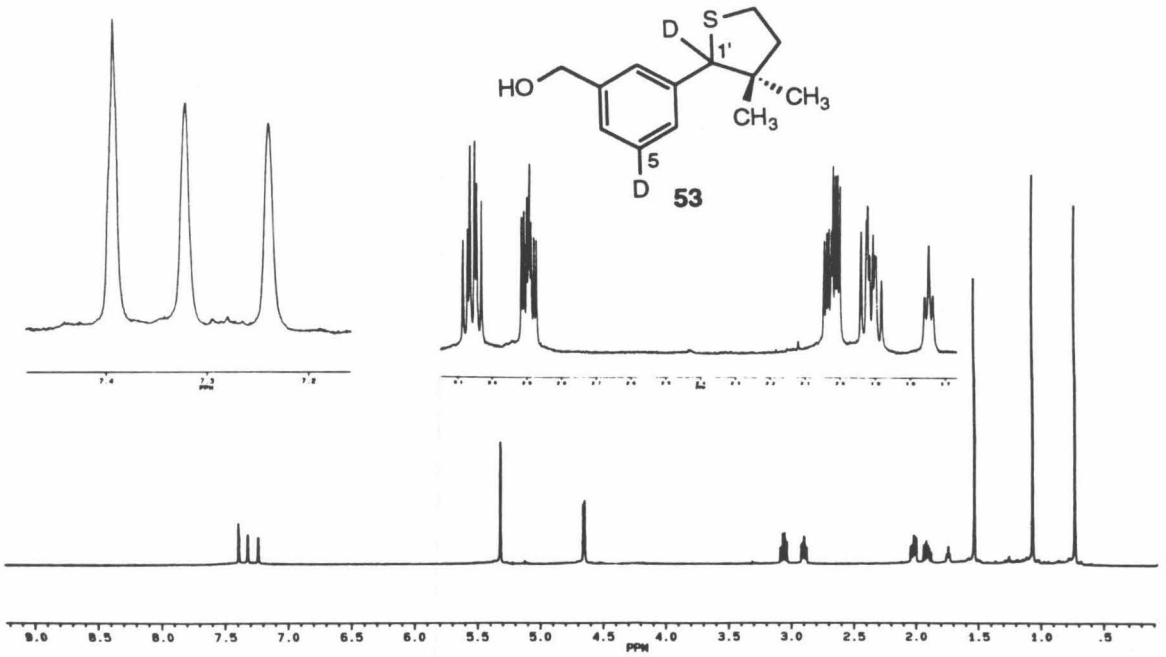
58

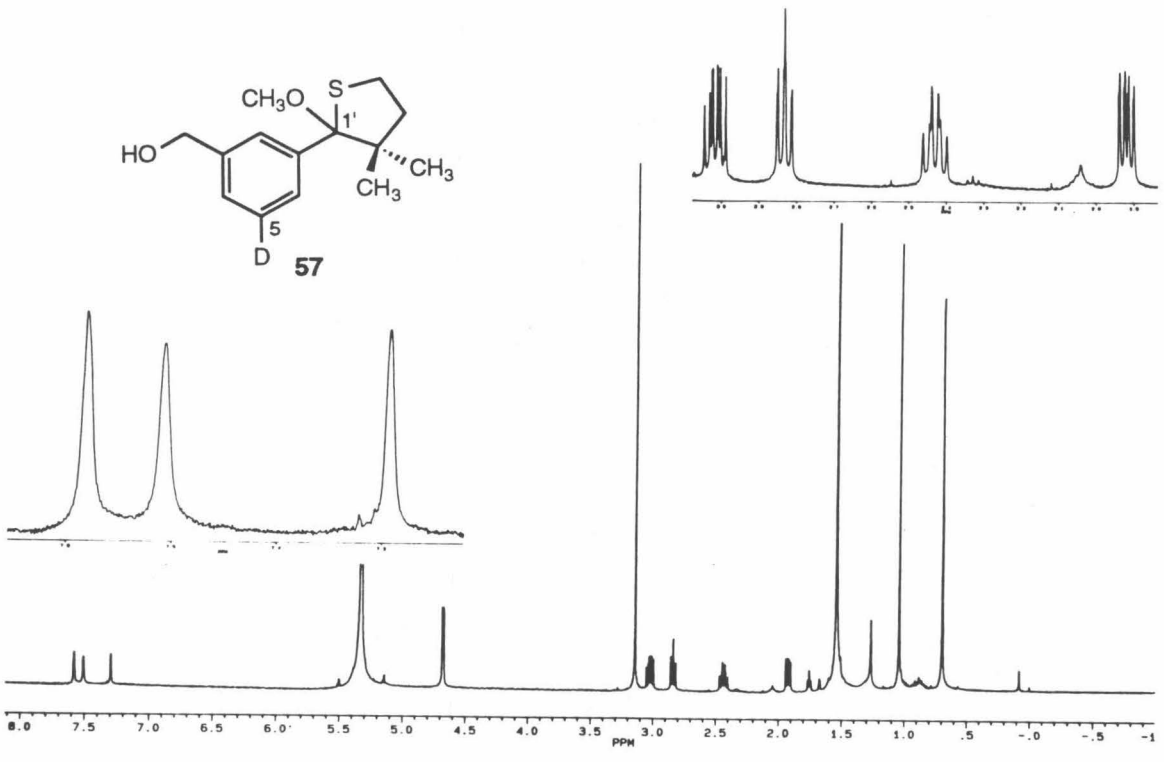

8.0
7.0
6.0
5.0
4.0
PPM
3.0
2.0
1.0
0.0

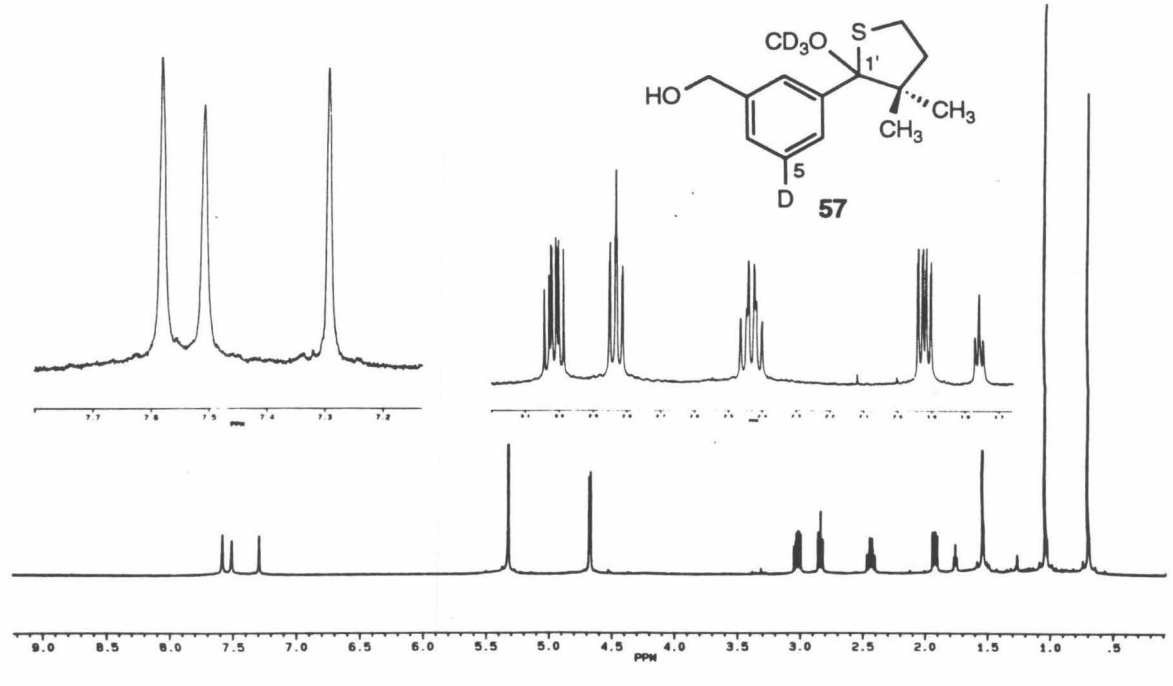

HO
H
S
1'
CH3
CH3
5
H
4000
3500
3000
2500
2000
1500
1000
cm-1

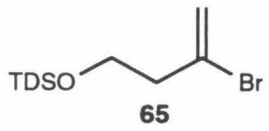
53


H
S
1'
HO
CH3
CH3
5
D
53
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
PPM

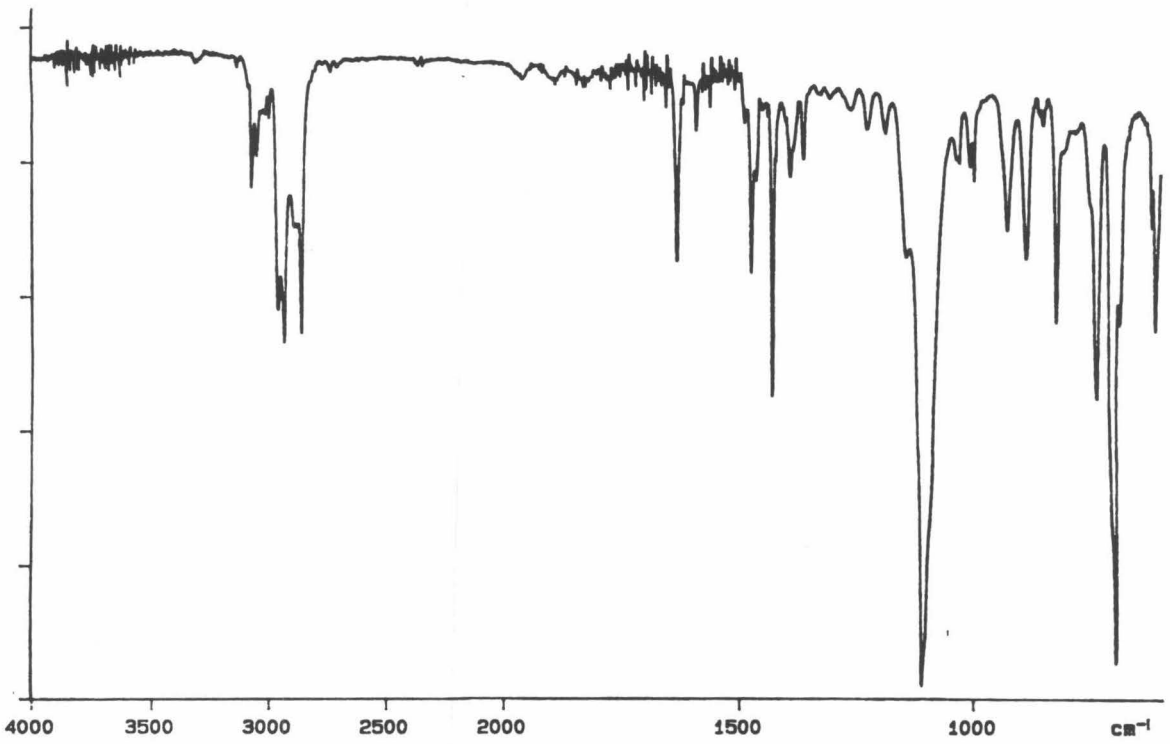

D
S
1'
HO
CH3
CH3
5
D
53
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
.5
PPM

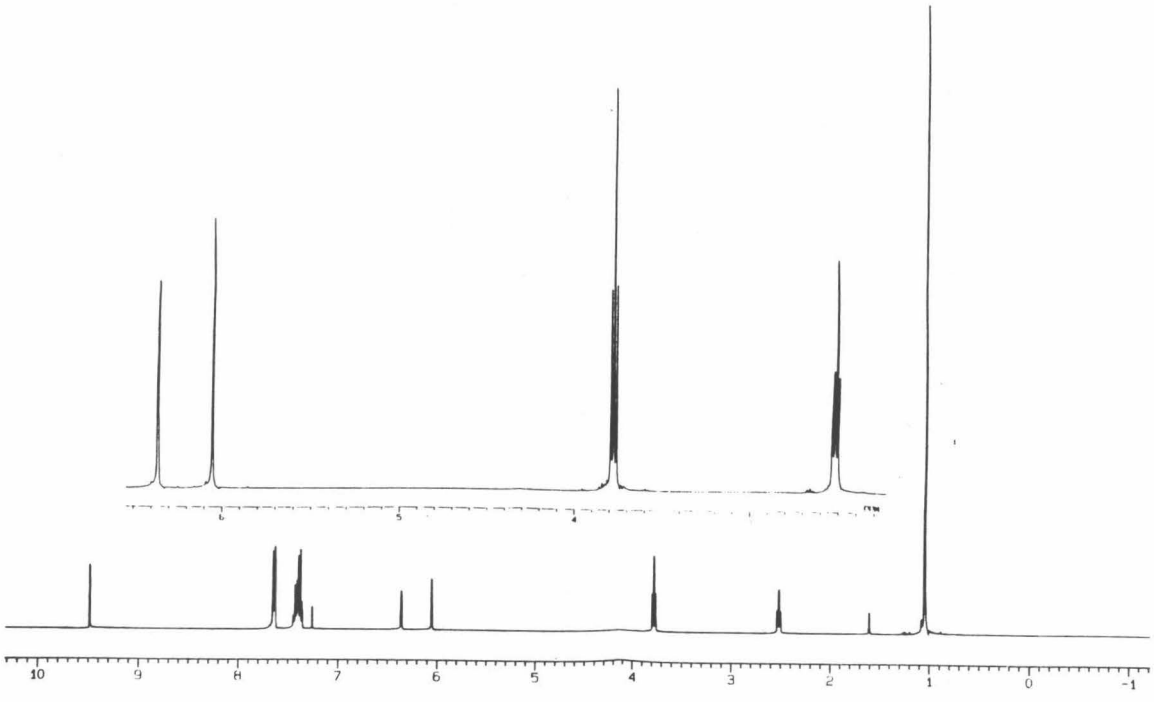

CH3O
S
1'
HO
CH3
CH3
5
D
57
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
.5
-.0
-.5
-1
PPM

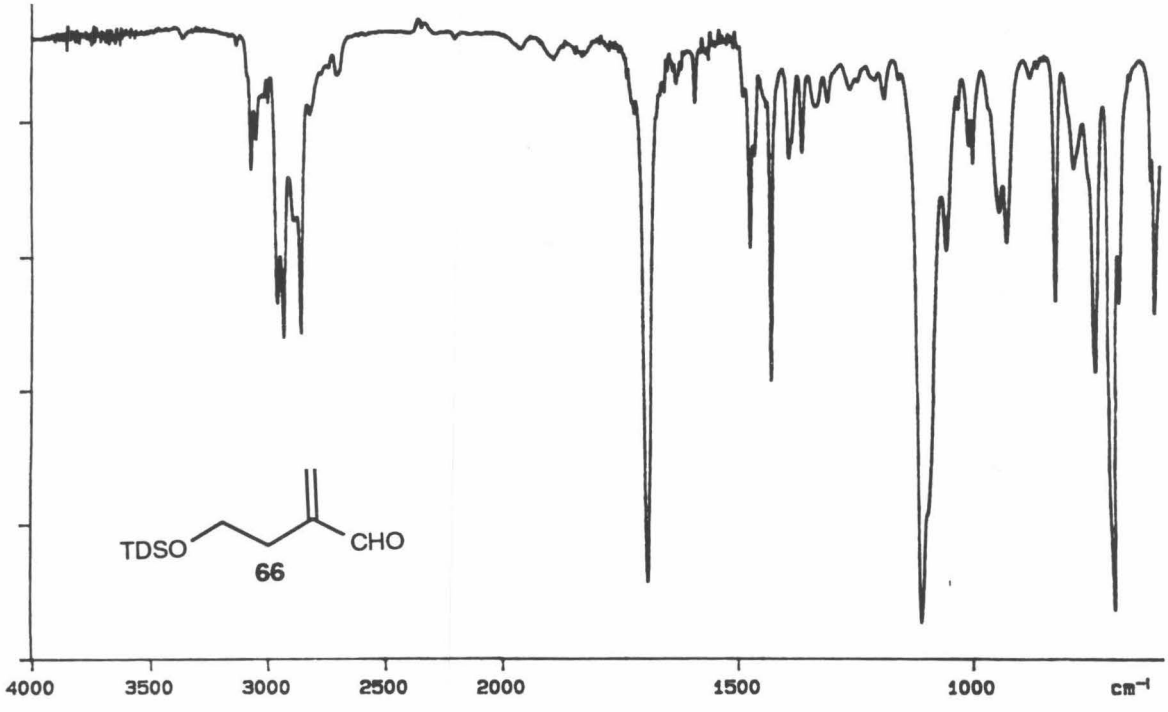

CD3O
S
1'
HO
CH3
CH3
5
D
57
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
.5
PPM

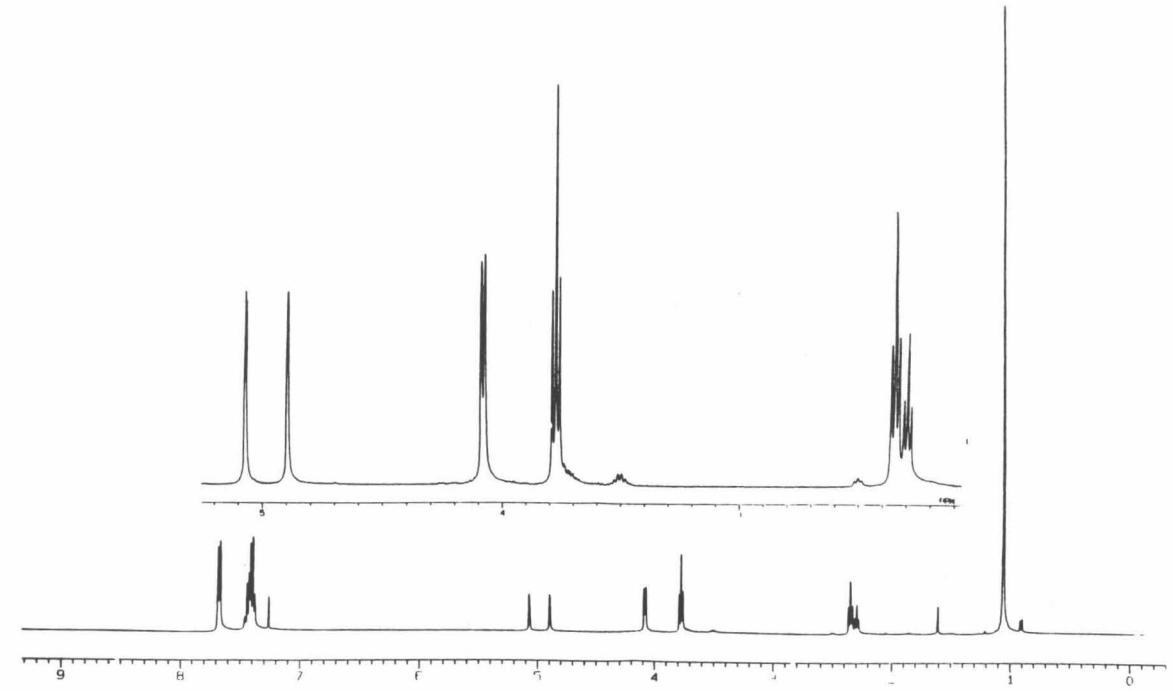


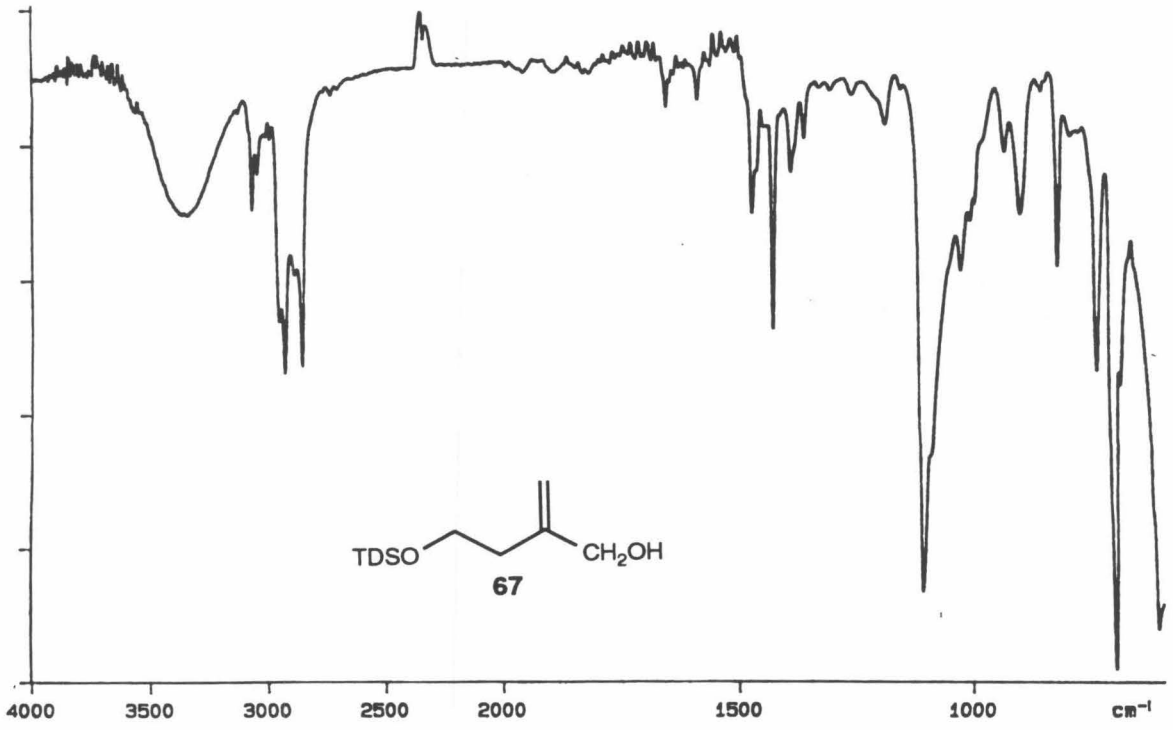
65

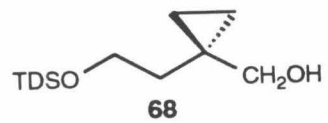



10
9
8
7
6
5
4
3
2
1
0
-1


TDSO
CHO
66
4000
3500
3000
2500
2000
1500
1000
cm⁻¹

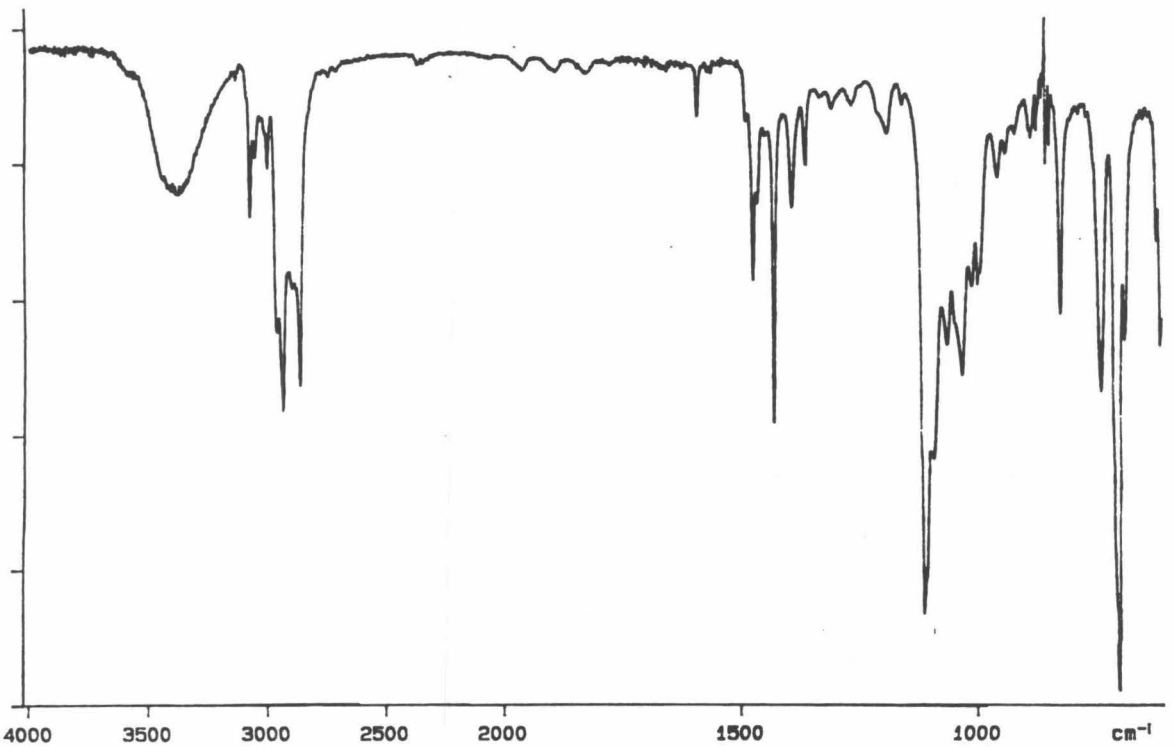


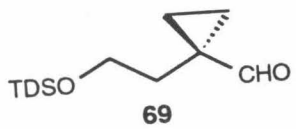

TDSO
CH2OH
67
4000
3500
3000
2500
2000
1500
1000
cm-1


TDSO
CH2OH

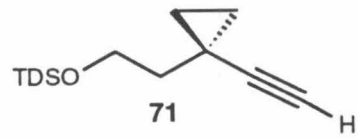
68

8
7
6
5
4
3
2
1
0
PPM

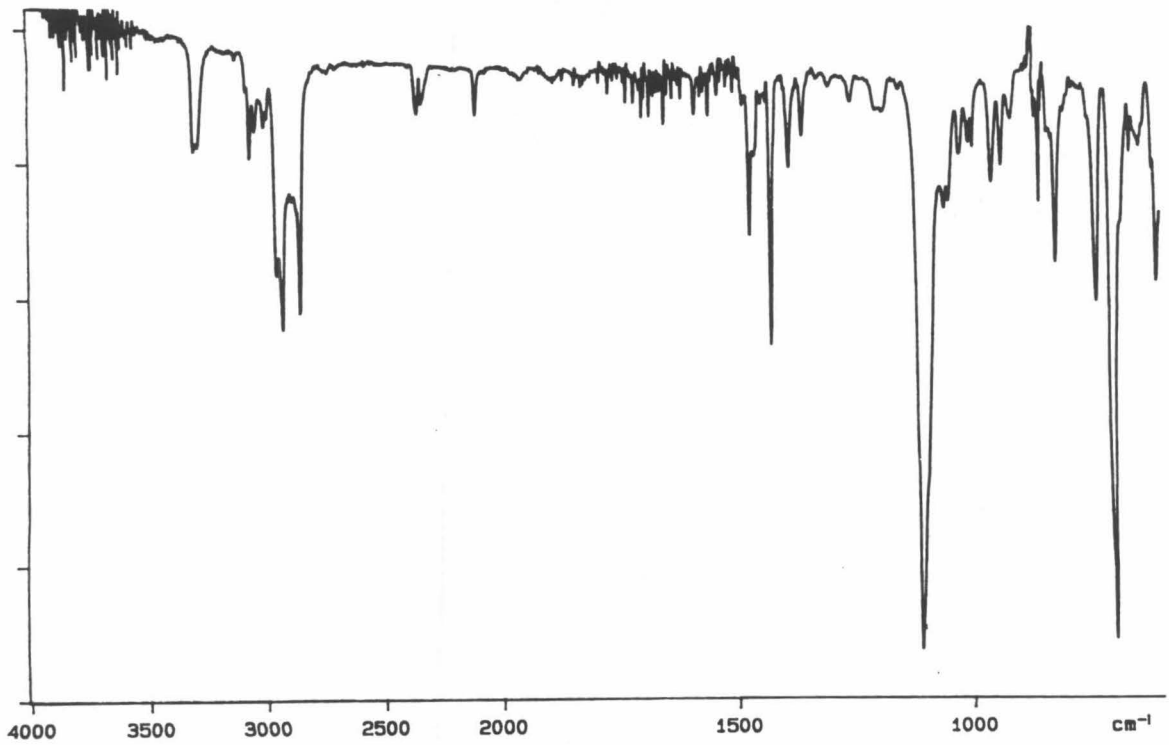

4000
3500
3000
2500
2000
1500
1000
cm-1

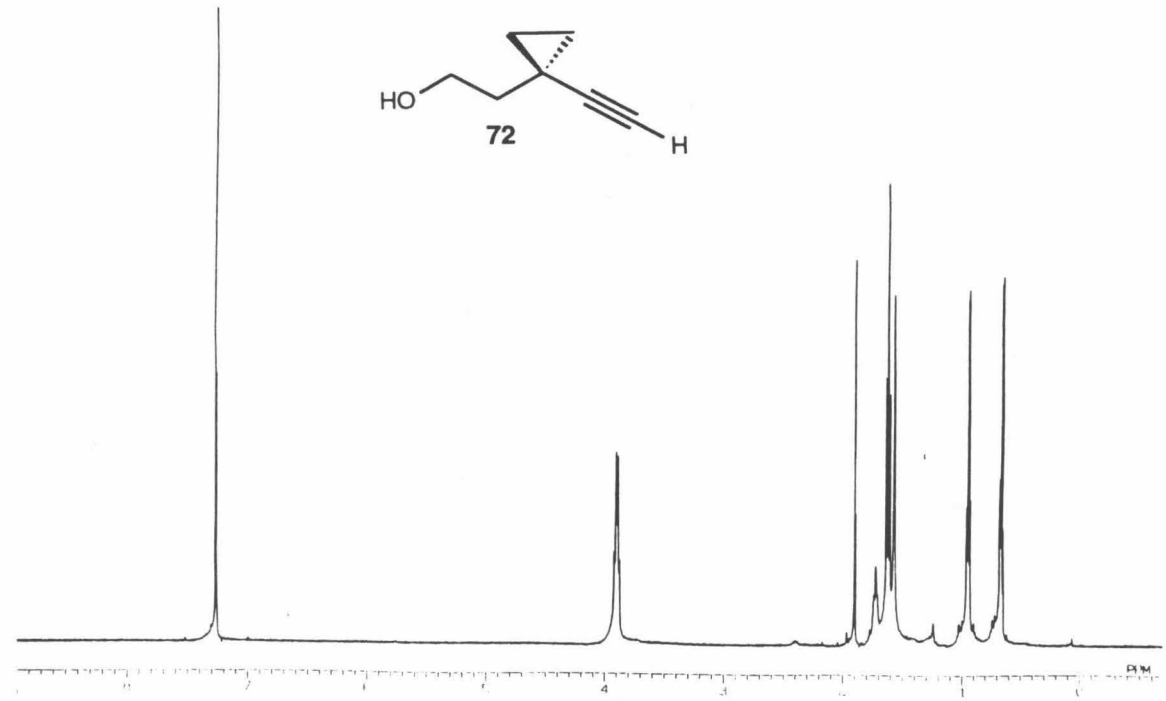


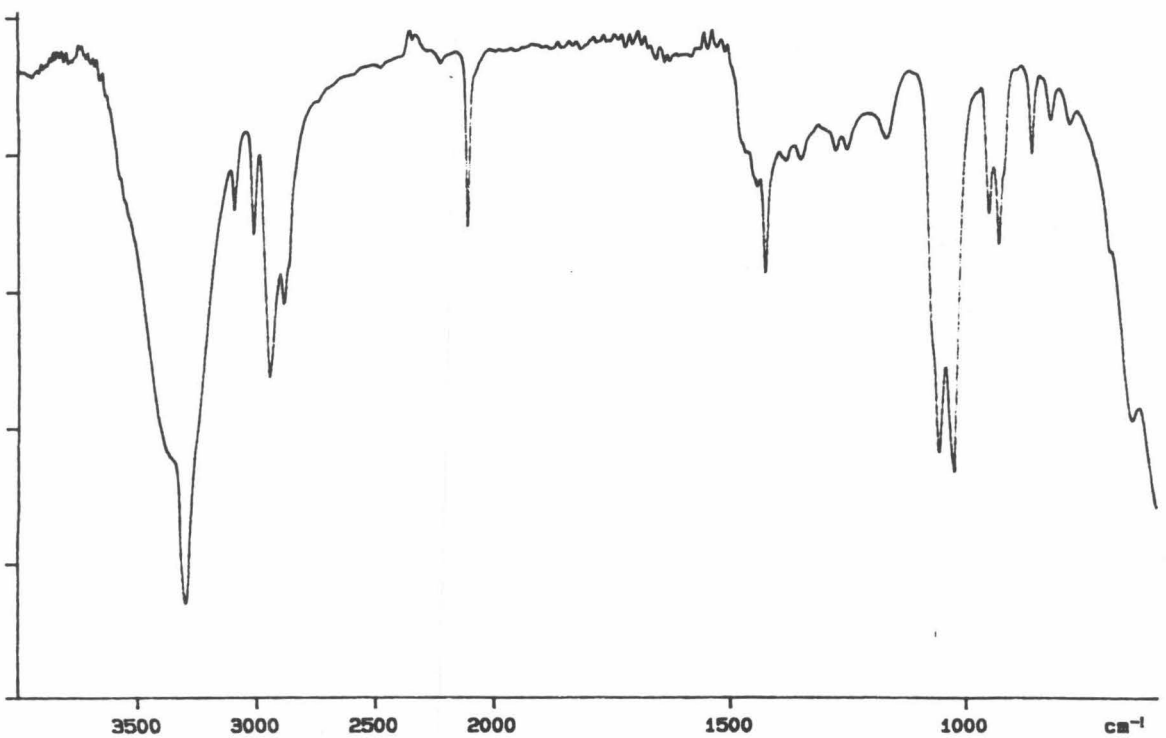
69

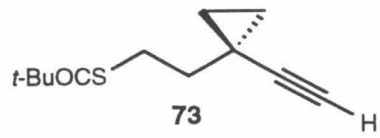


71

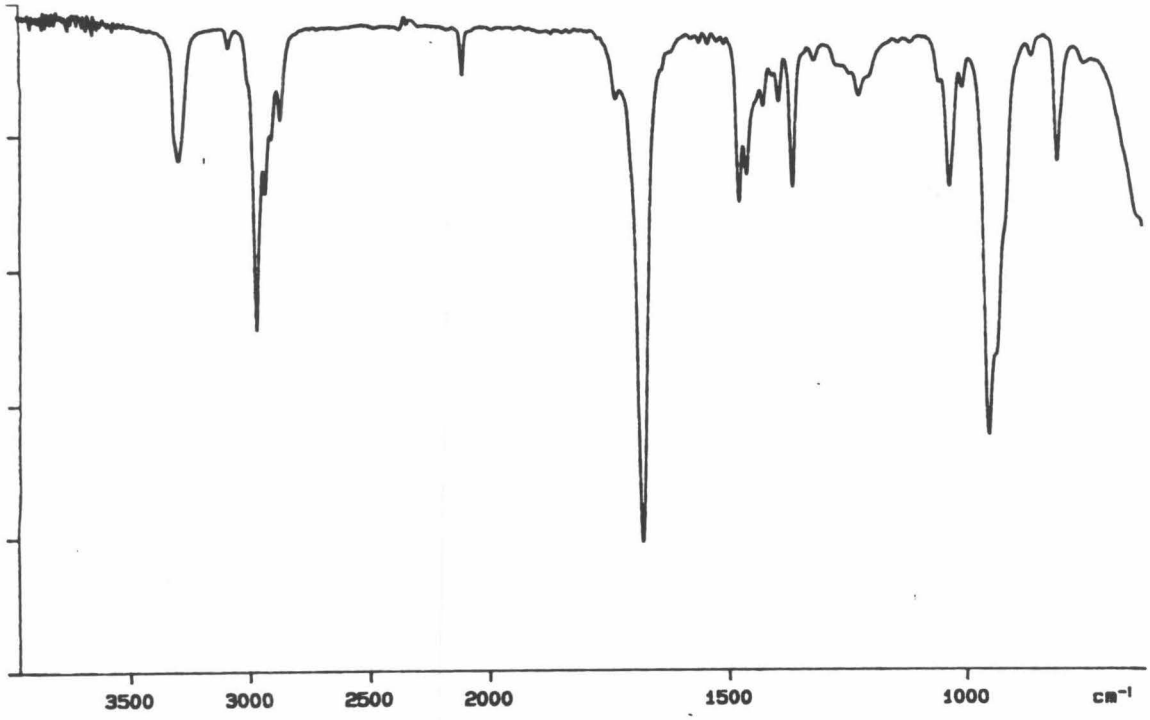


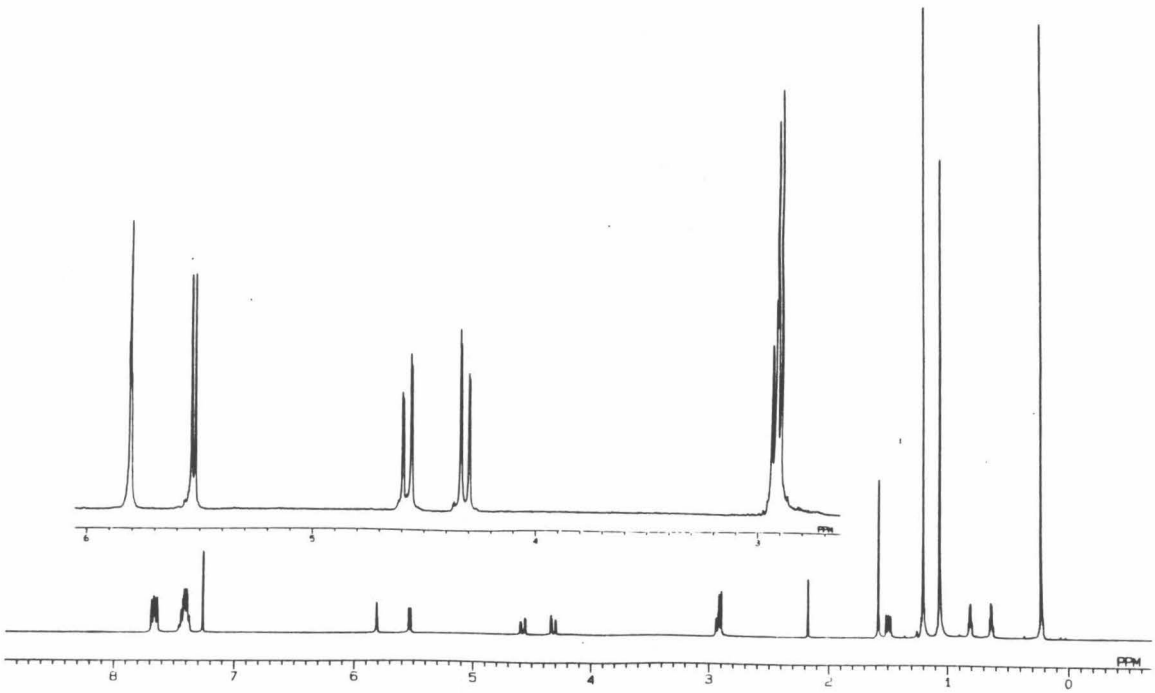

HO
H
72
PPM

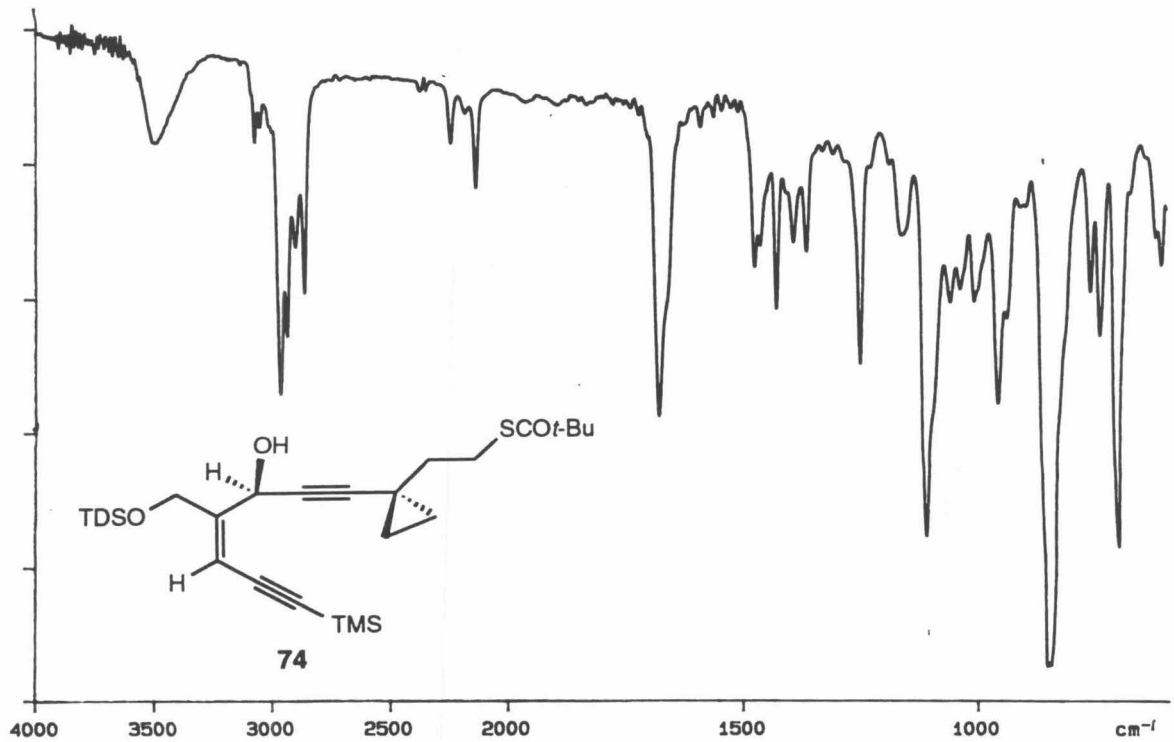

3500
3000
2500
2000
1500
1000
cm⁻¹

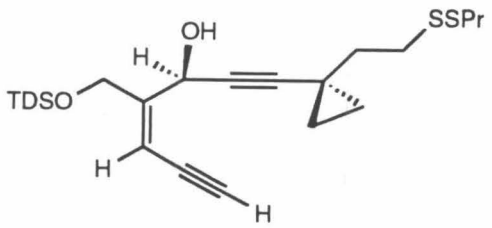


73

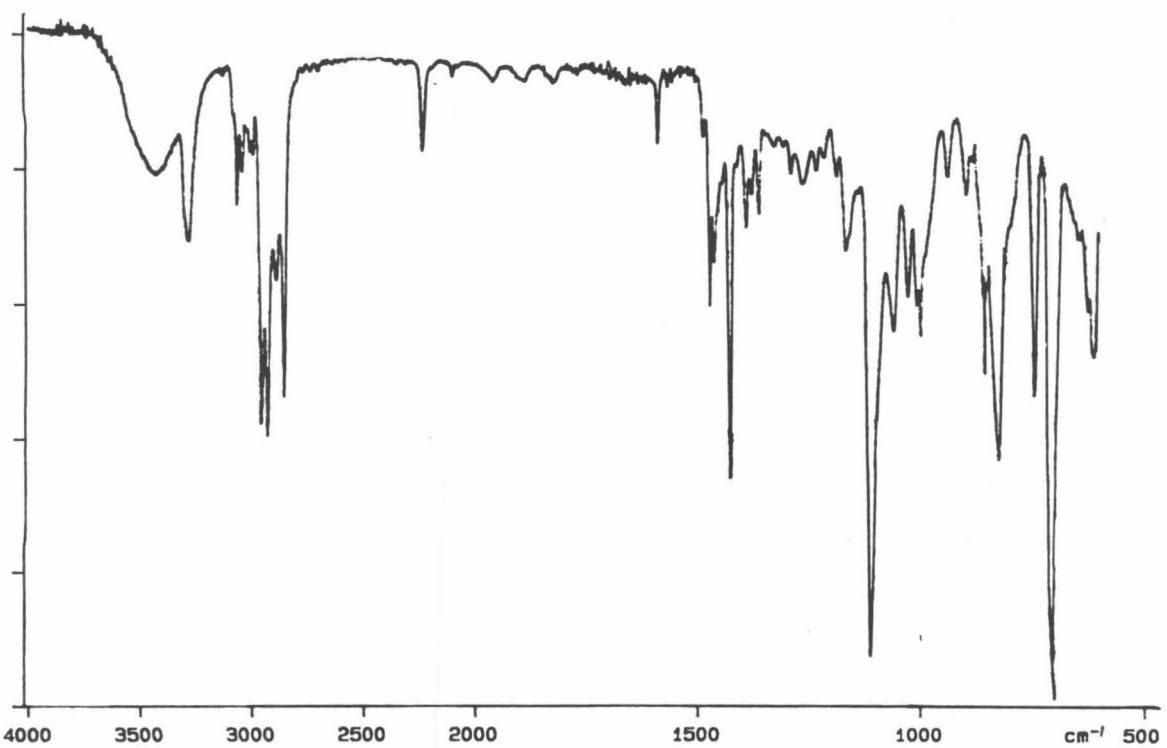


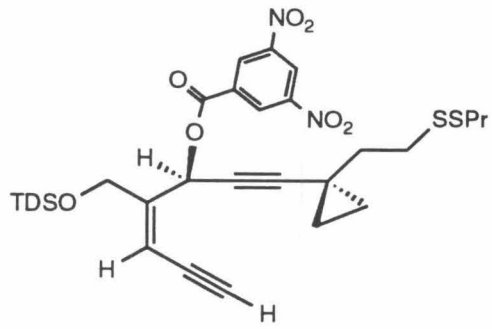

PPM
8
7
6
5
4
3
2
1
0


OH
H
SCOt-Bu
TDSO
H
TMS
74
4000
3500
3000
2500
2000
1500
1000
cm⁻¹



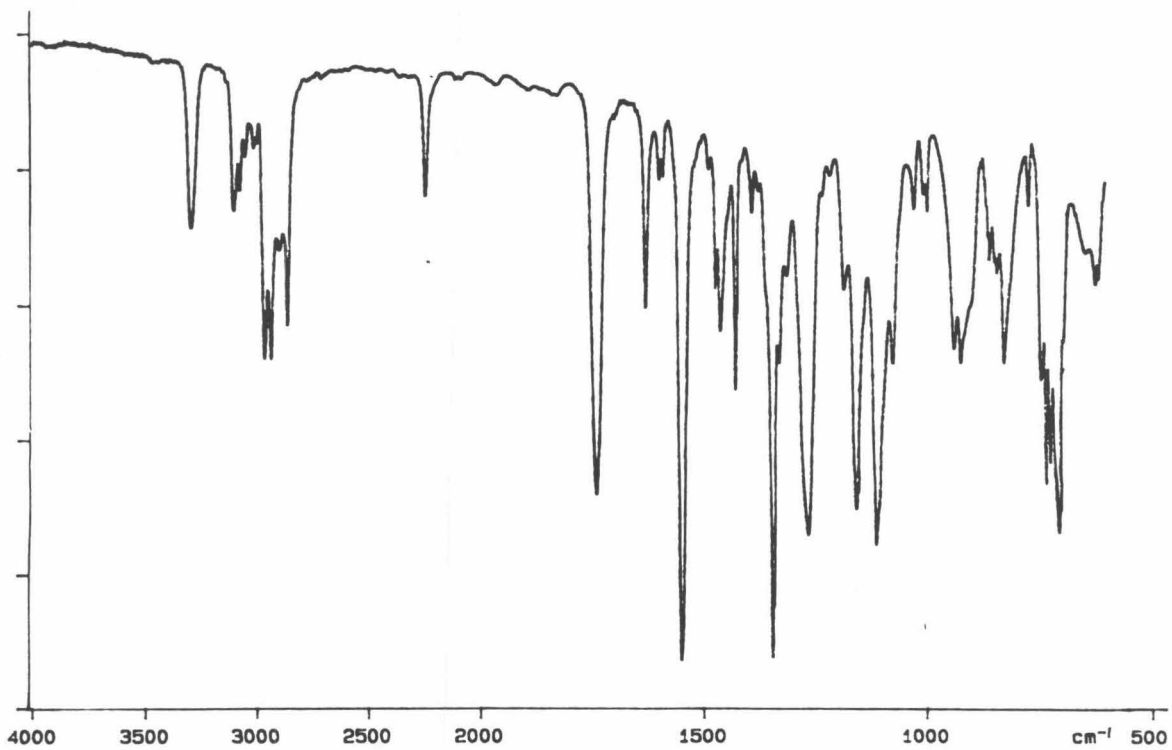
75

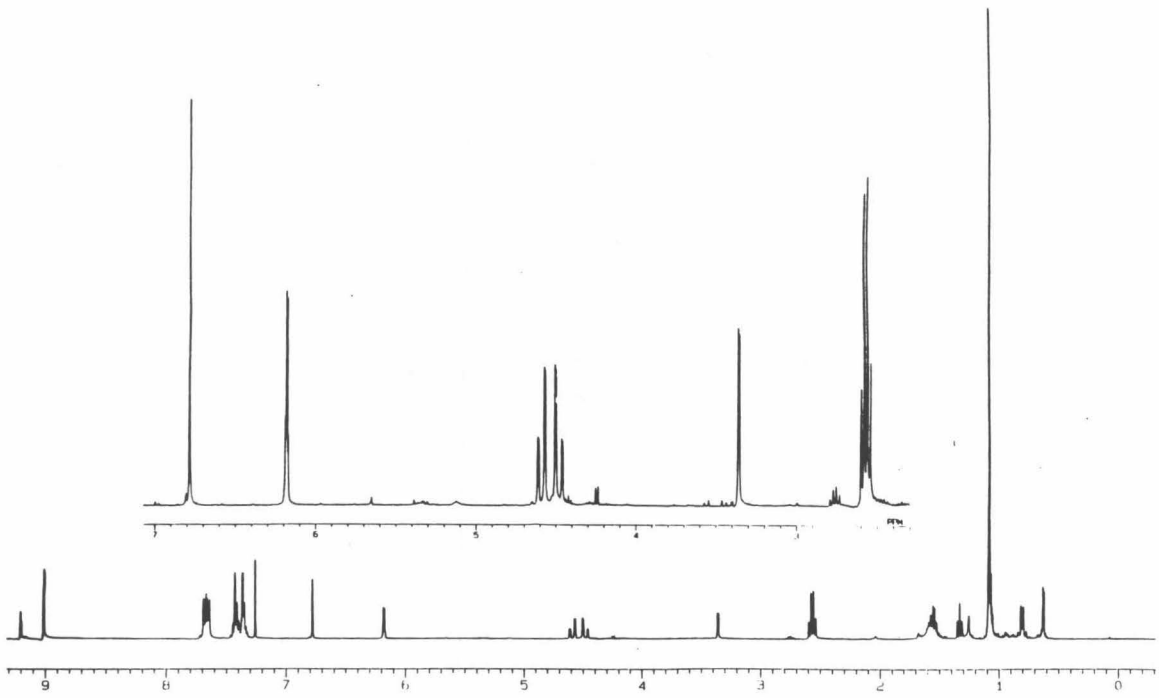


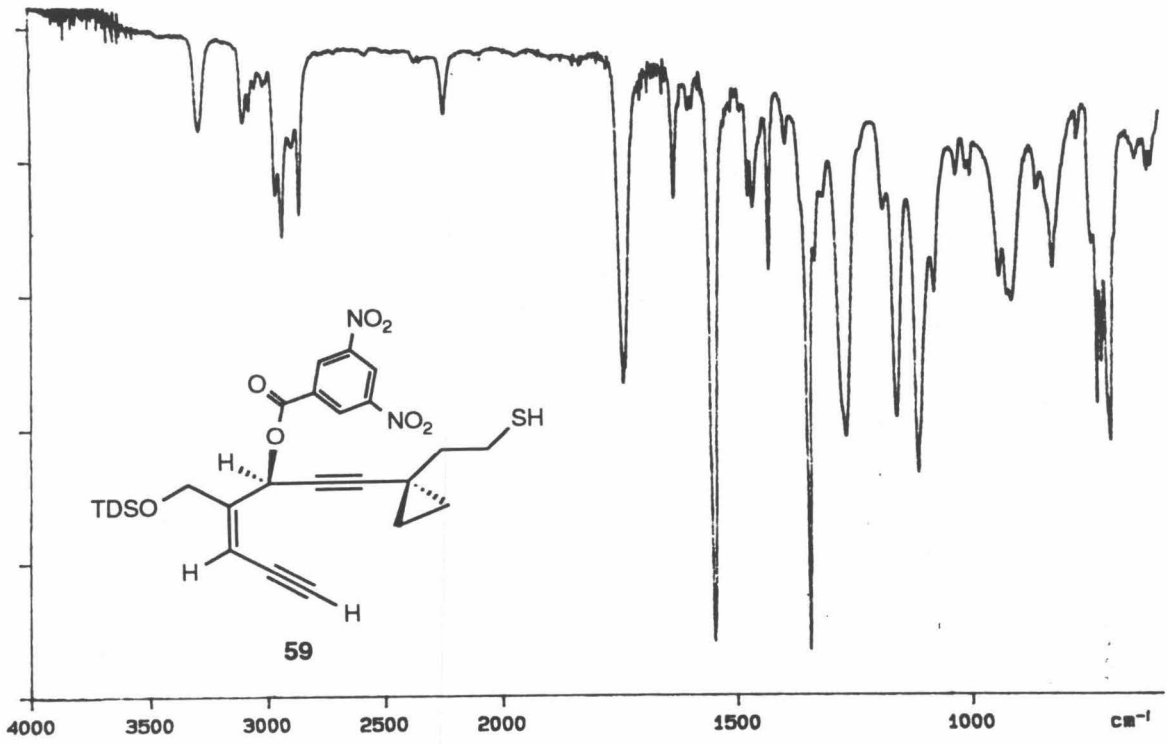

NO2
O
NO2
SSPr
O
H
TDSO
H
H

76

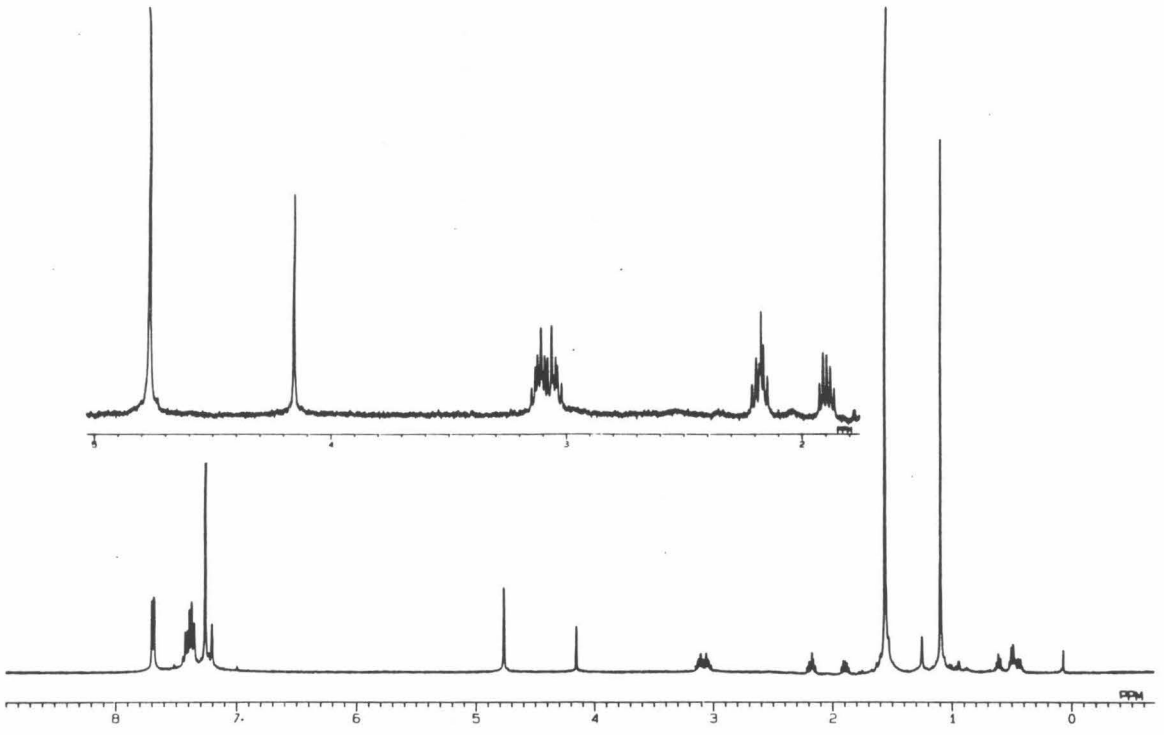
9
8
7
6
5
4
3
2
1

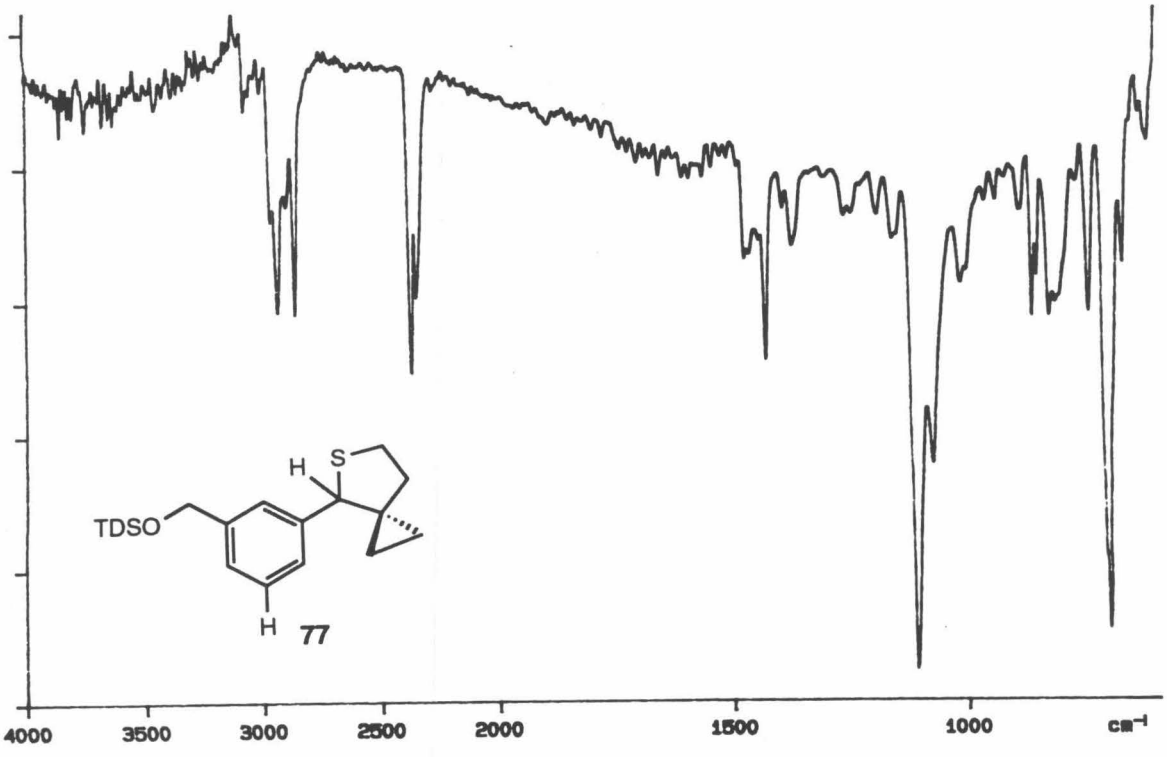

4000
3500
3000
2500
2000
1500
1000
cm-1
500

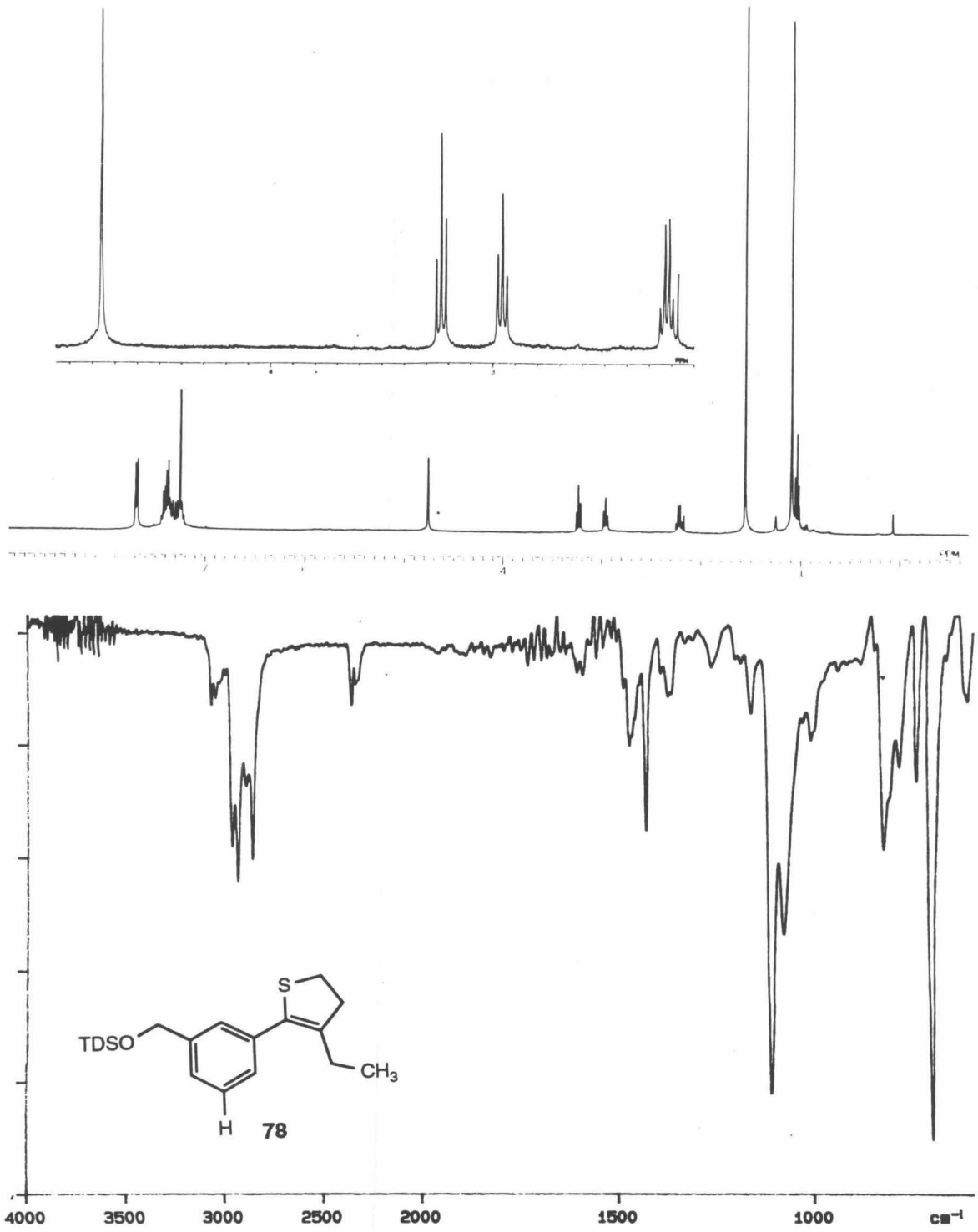

9
8
7
6
5
4
3
2
1
0

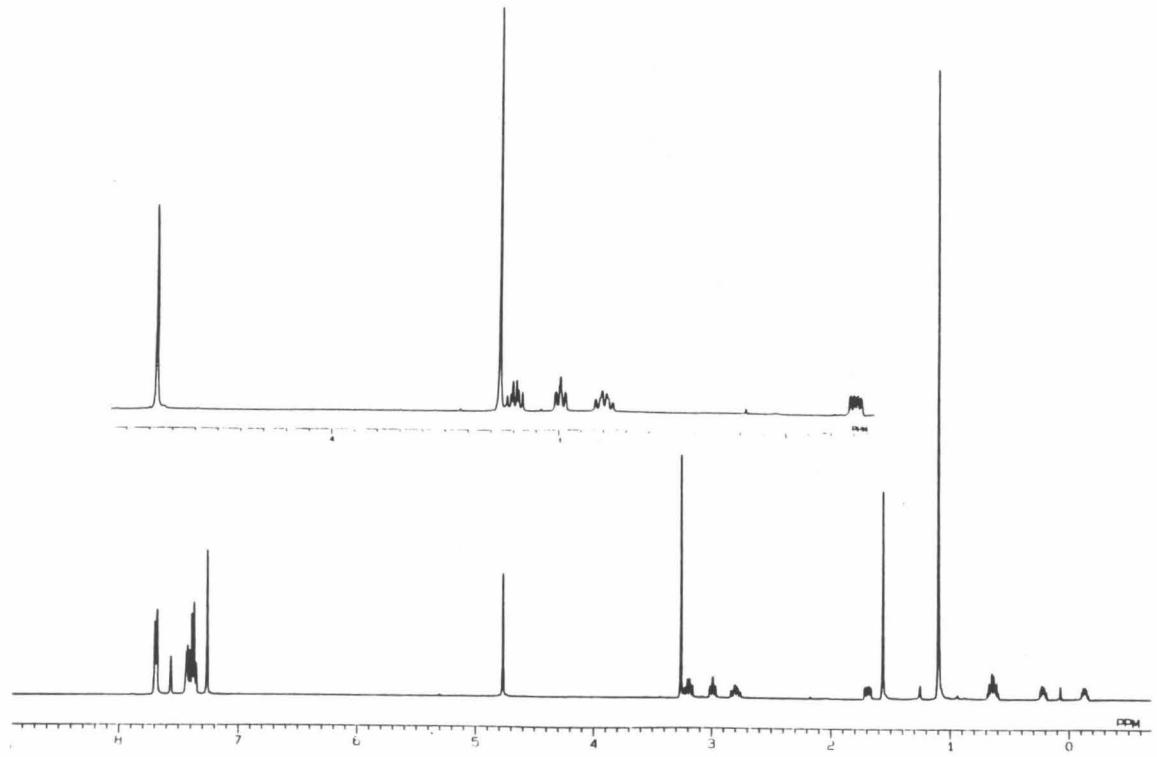

NO2
O
NO2
SH
O
H
TDSO
H
H
4000
3500
3000
2500
2000
1500
1000
cm-1

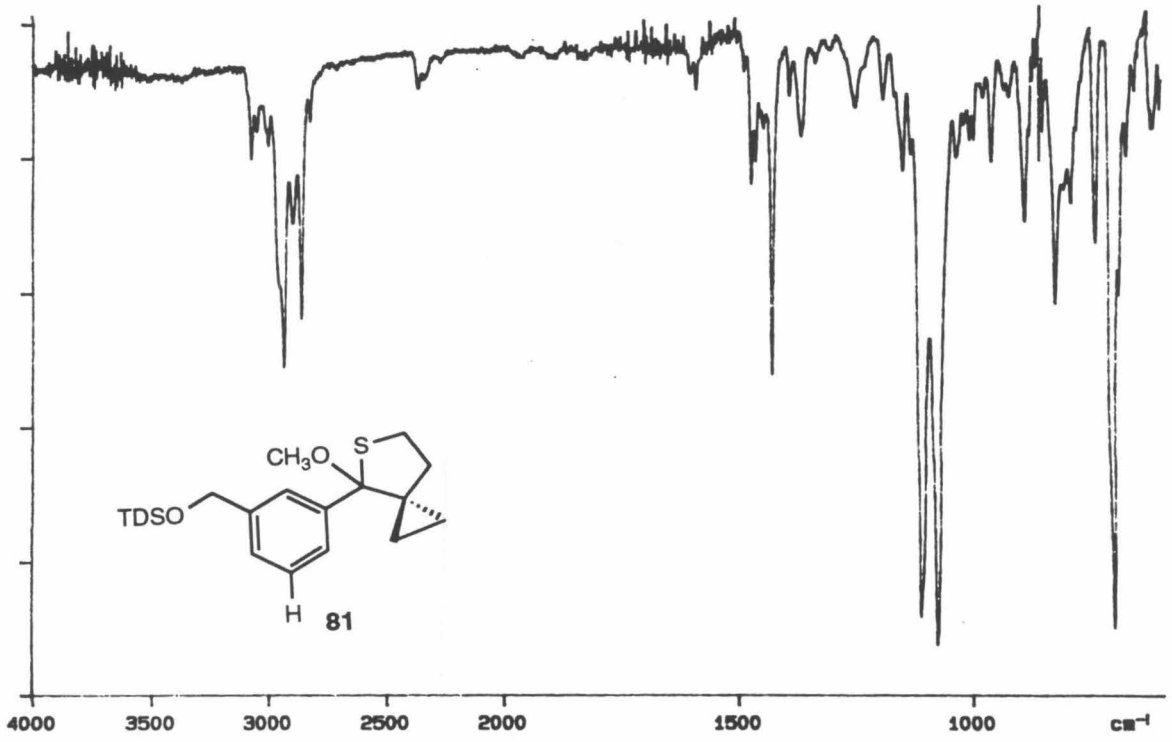
59

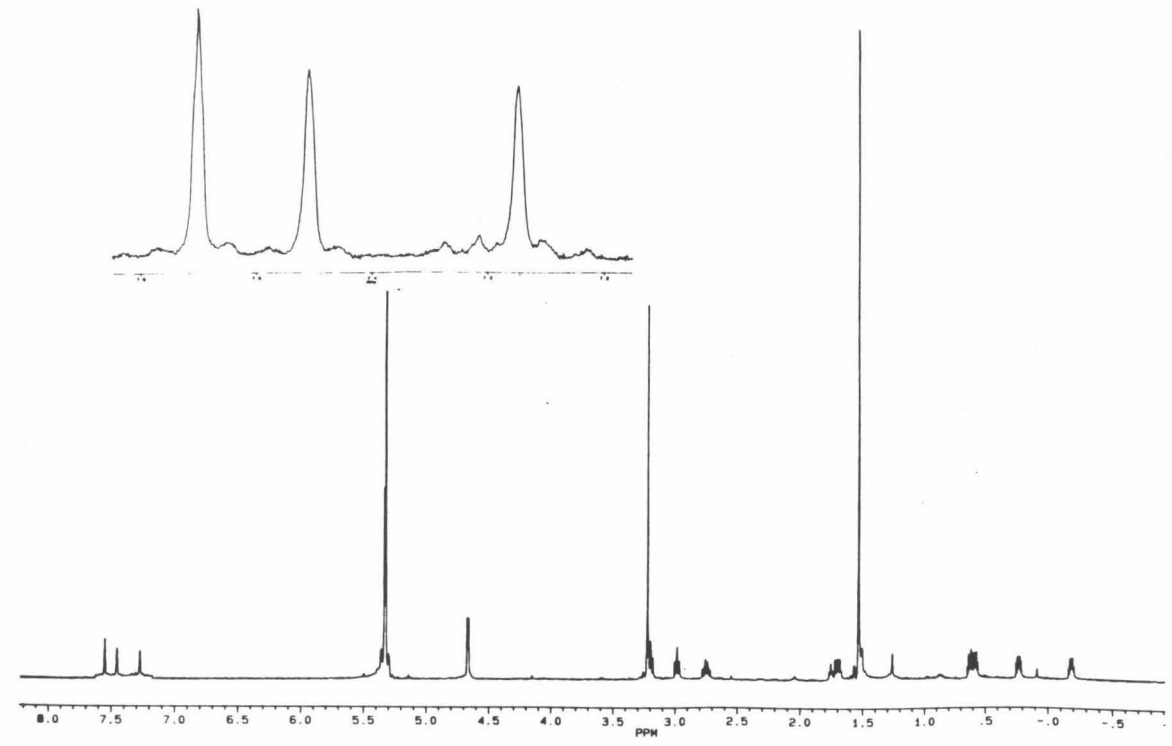

PPM
8
7
6
5
4
3
2
1
0

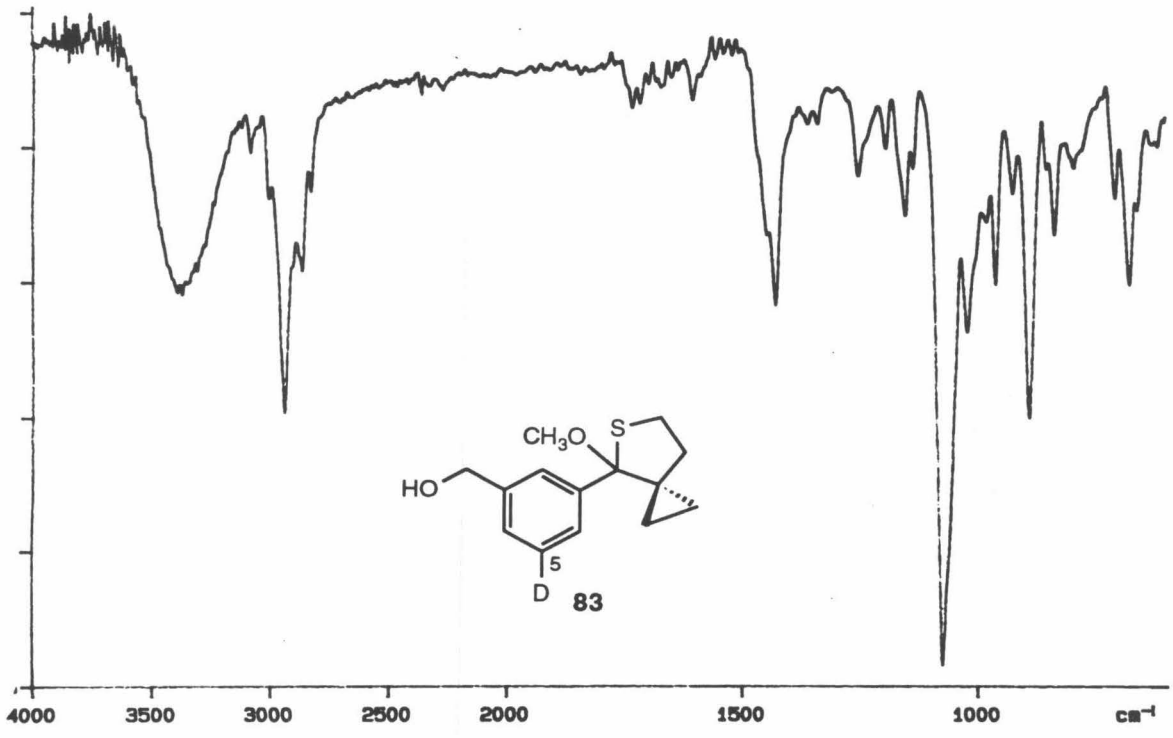

H
S
TDSO
H
77
4000
3500
3000
2500
2000
1500
1000
cm⁻¹


S
TDSO
CH3
H
78
4000
3500
3000
2500
2000
1500
1000
cm-1


H
7
6
5
4
3
2
1
0
PPM


CH3O
S
TDSO
H
81
4000
3500
3000
2500
2000
1500
1000
cm-1

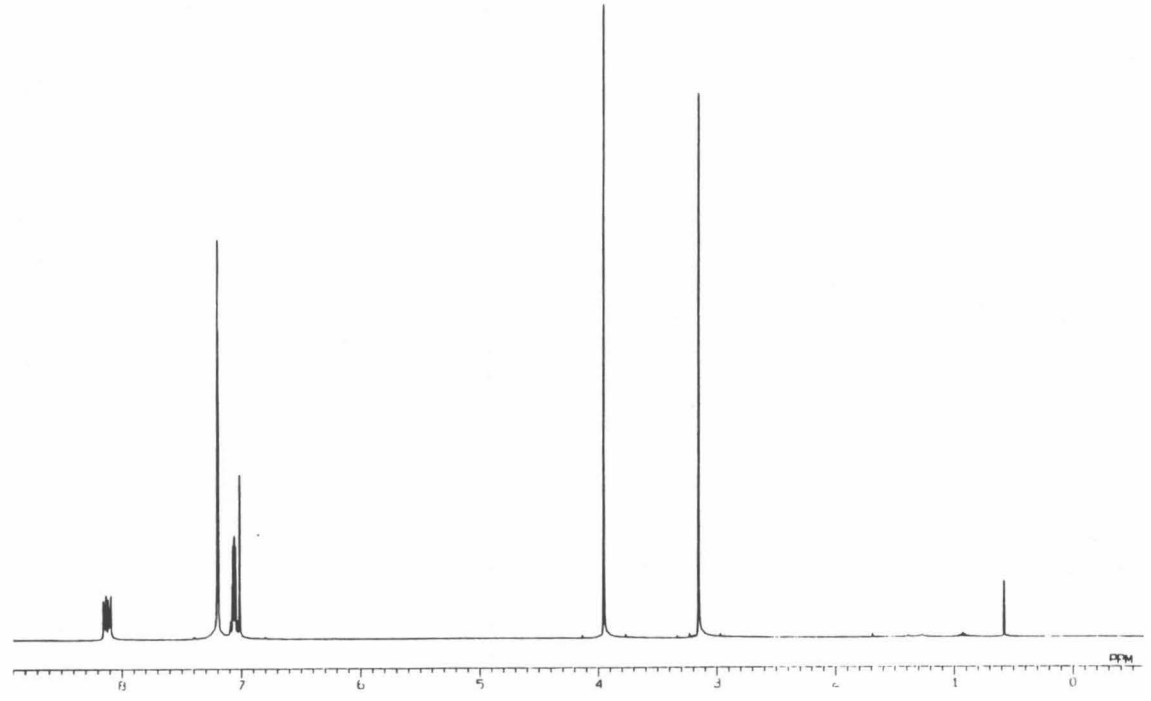

8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
PPM
3.0
2.5
2.0
1.5
1.0
.5
-.0
-.5

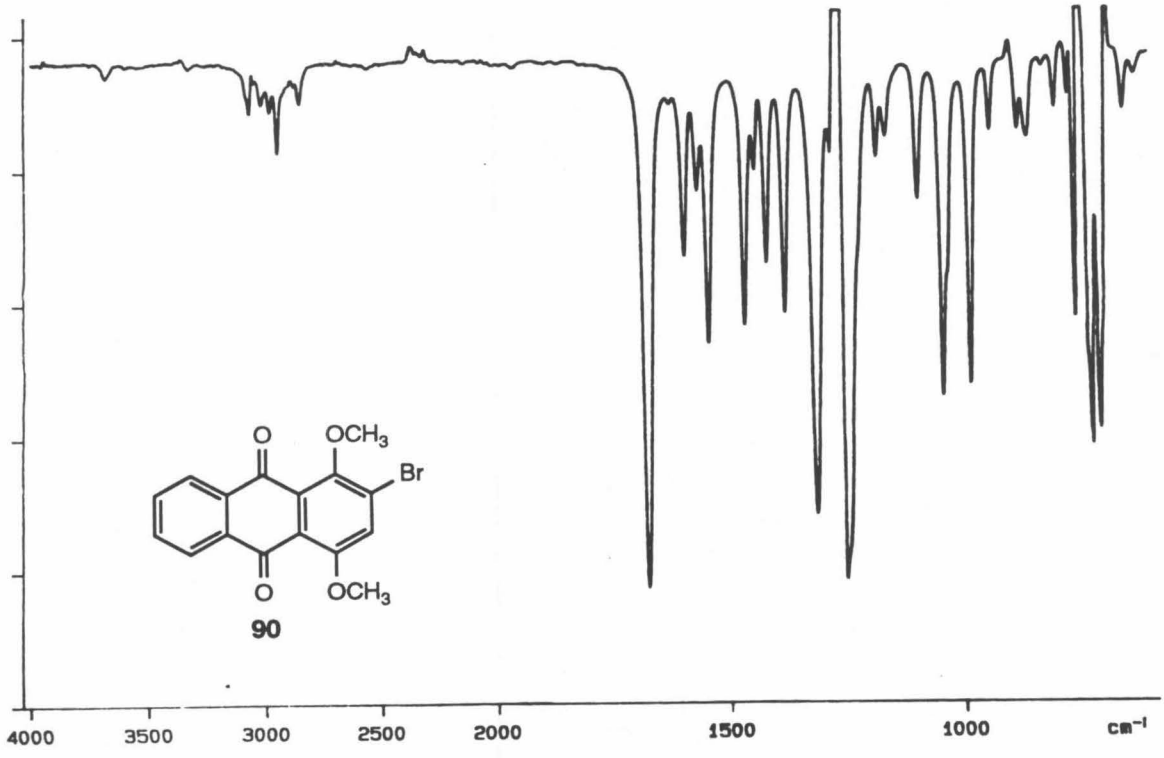

CH3O
S
HO
5
D
4000
3500
3000
2500
2000
1500
1000
cm-1

83

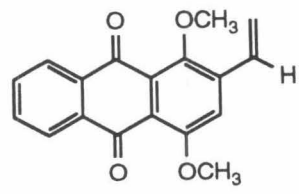
Appendix 3

Catalog of Spectra (Chapter 2)


PPM
8
7
6
5
4
3
2
1
0

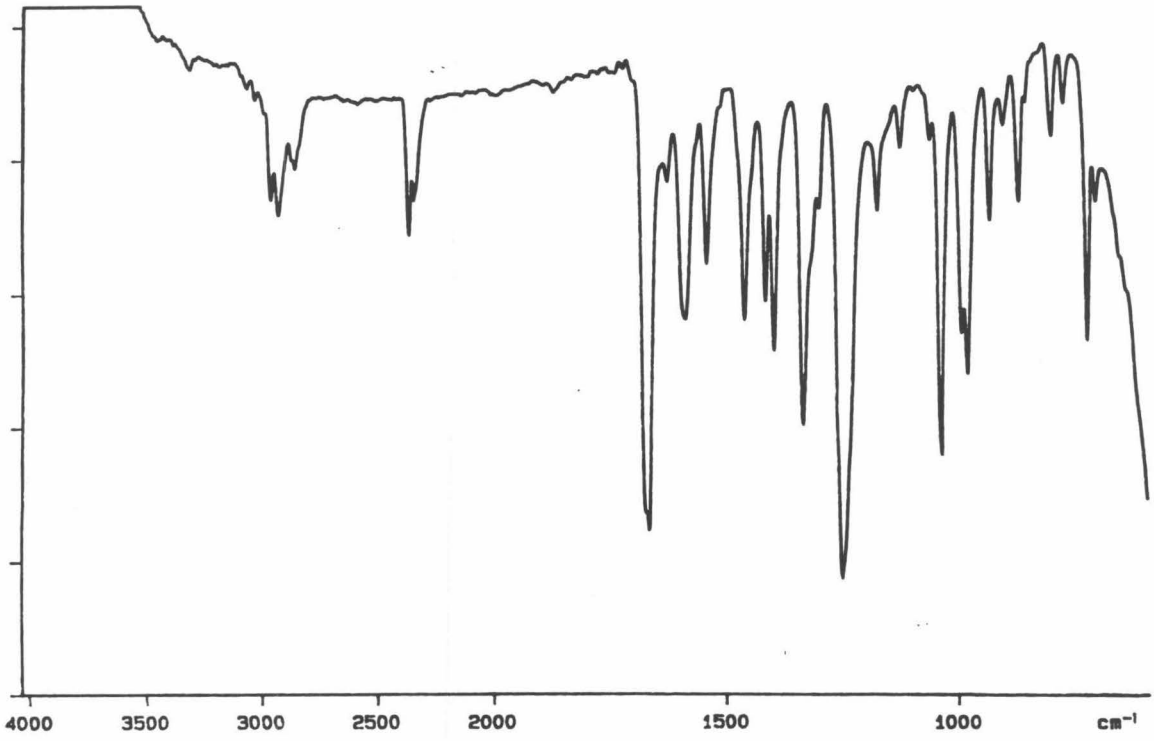

O
OCH3
Br
O
OCH3
4000
3500
3000
2500
2000
1500
1000
cm-1

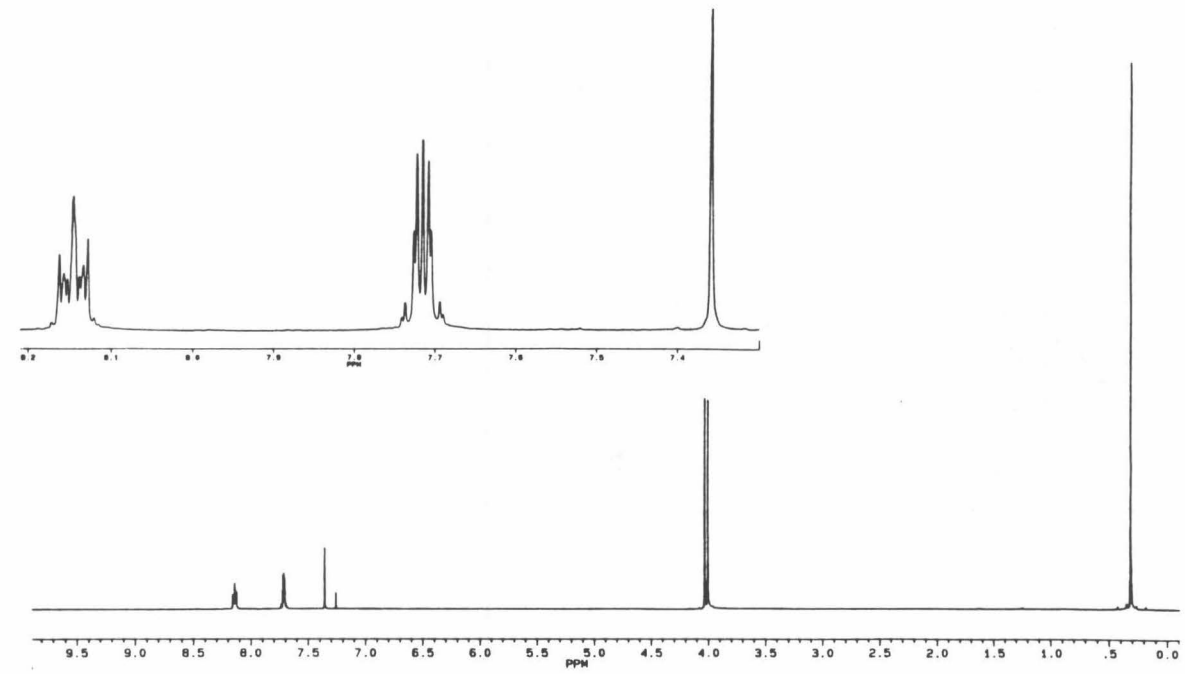
90

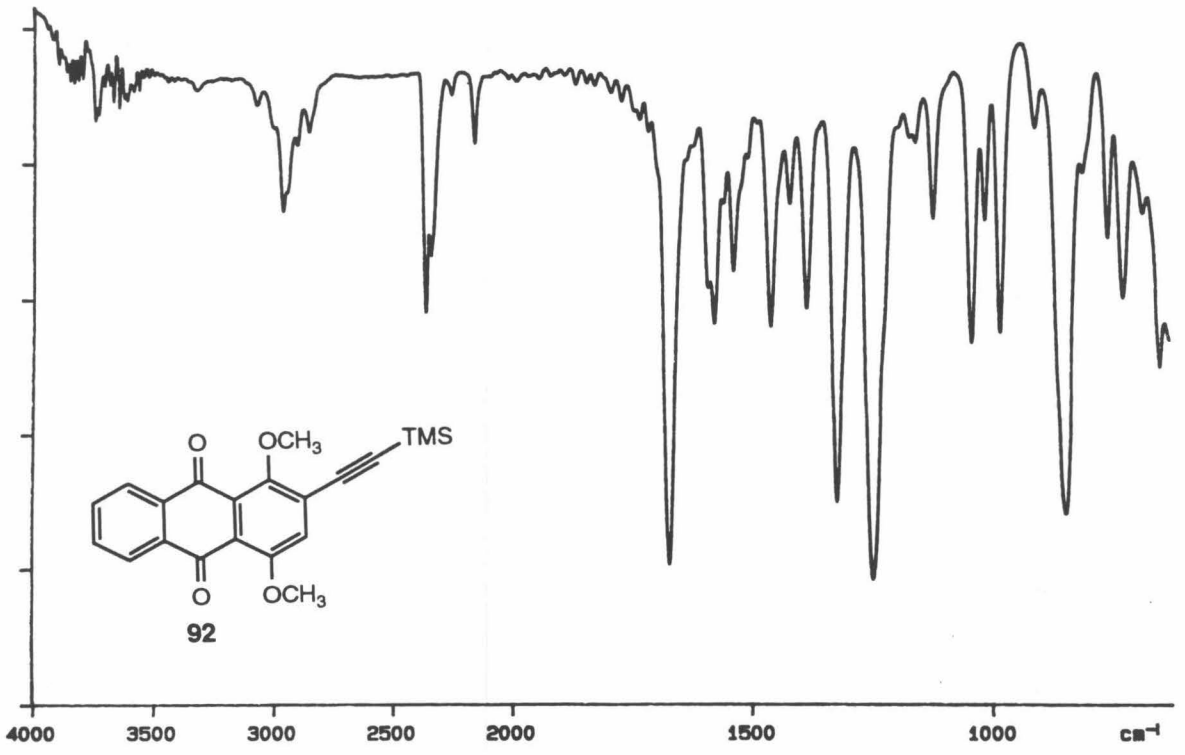

O
OCH3
H
O
OCH3

91

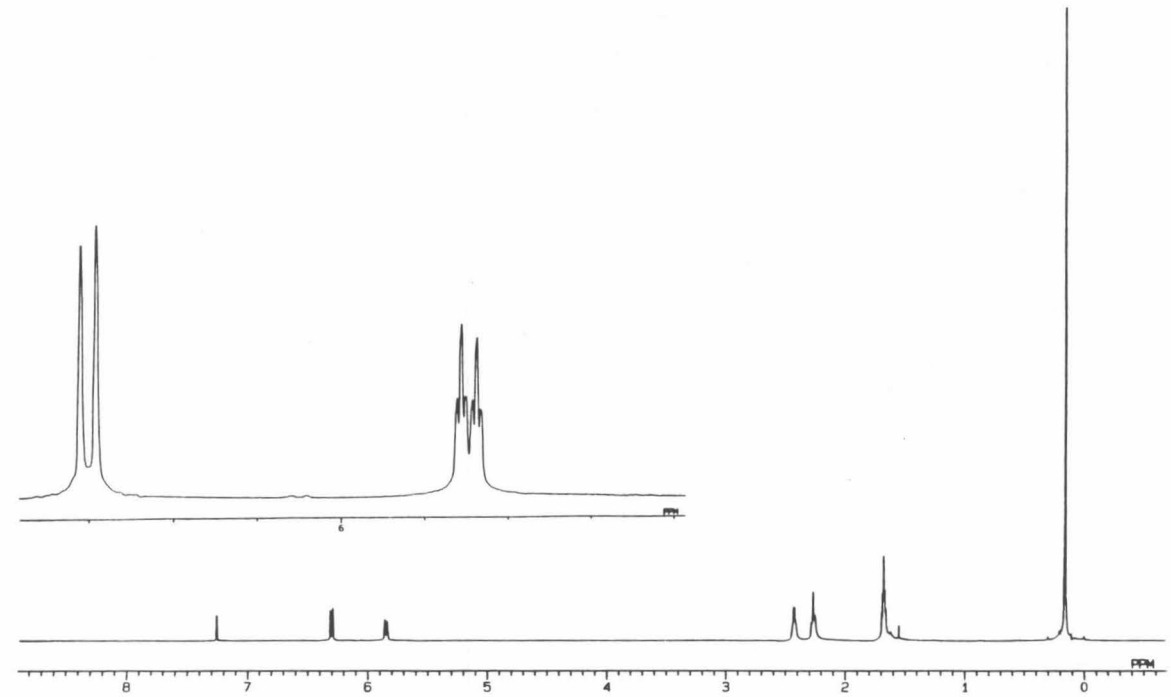
8.5
8.0
7.5
7.0
6.5
6.0
PPM
5.5
5.0
4.5
4.0
3.5
3.0
2.5

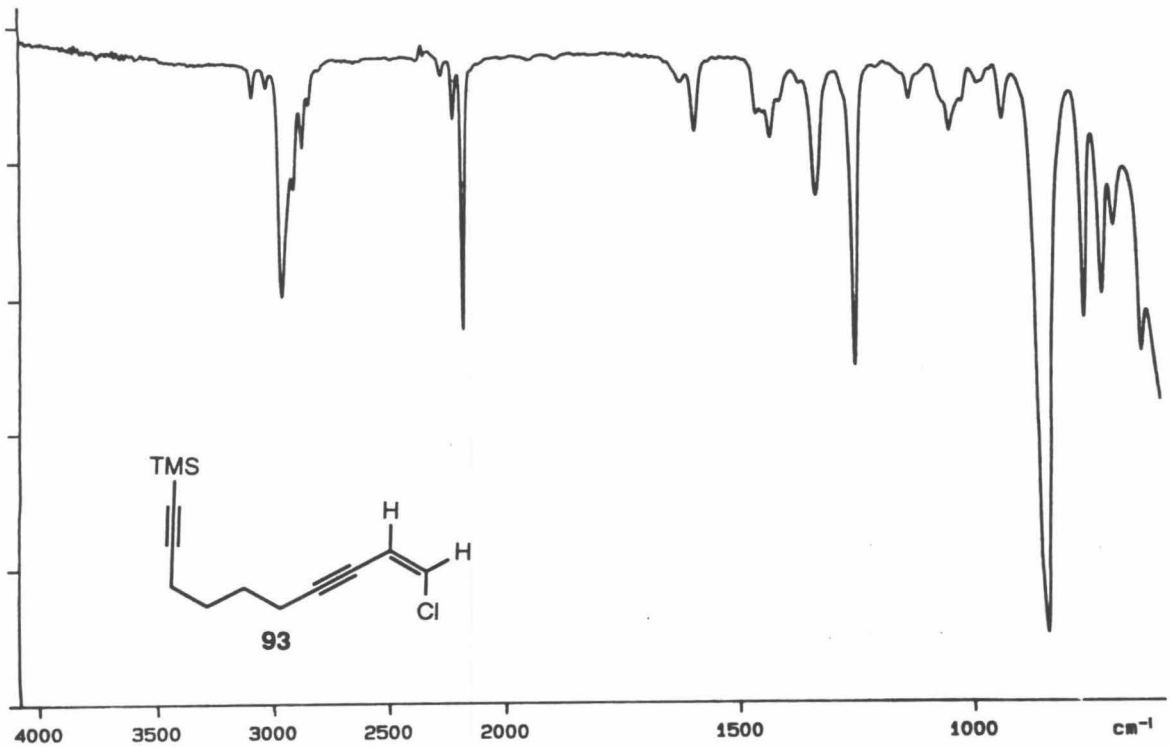

4000
3500
3000
2500
2000
1500
1000
cm-1


9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 .5 0.0
PPM

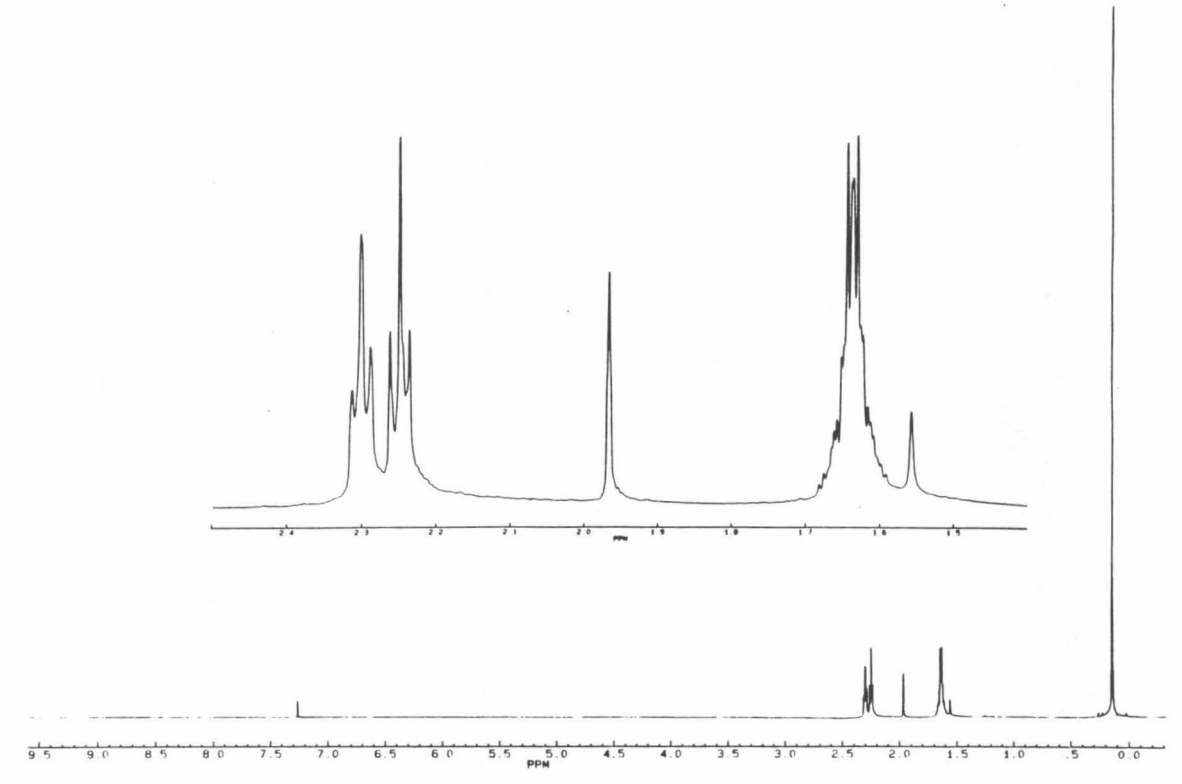

O
OCH3
TMS
O
OCH3
4000
3500
3000
2500
2000
1500
1000
cm-1

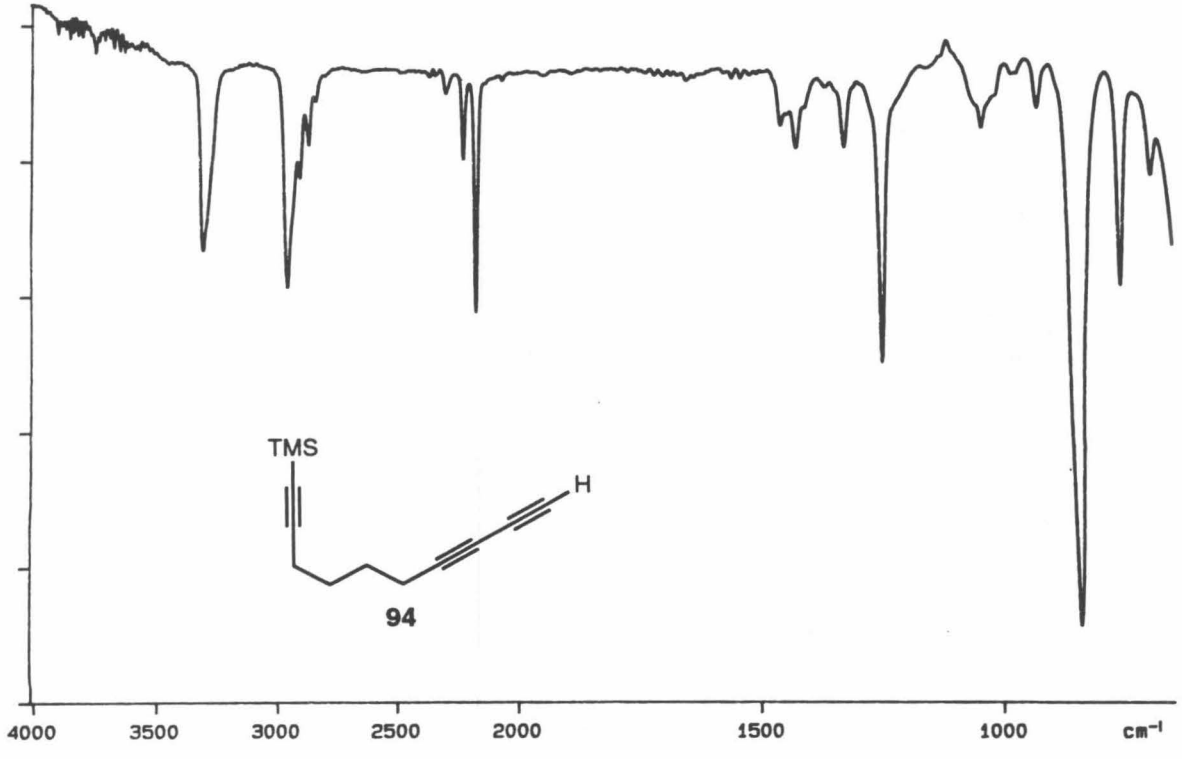
92

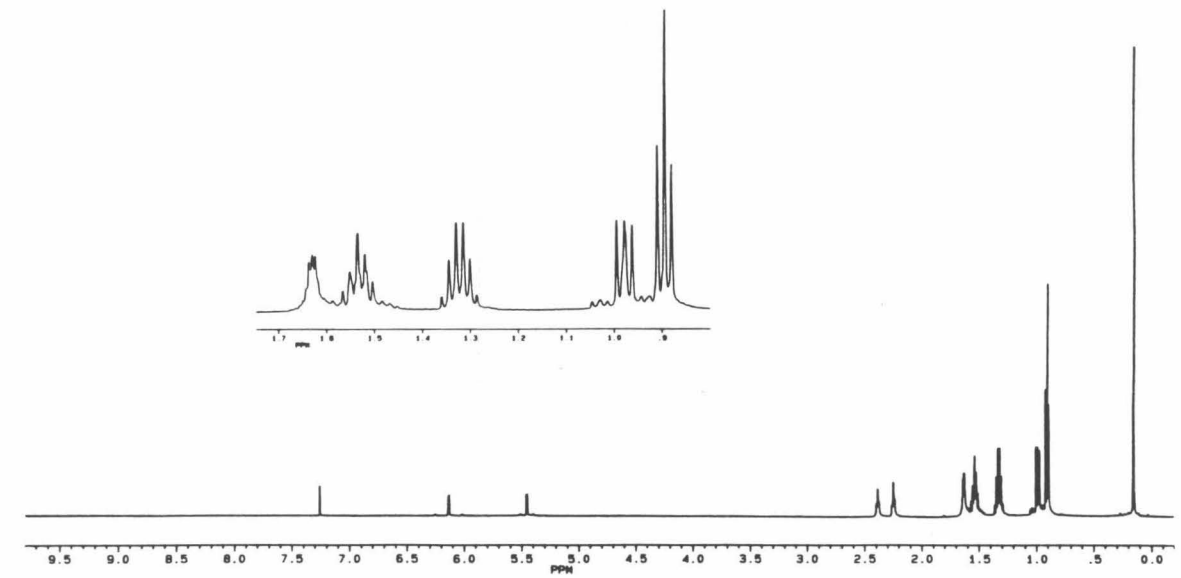

PPM
8
7
6
5
4
3
2
1
0

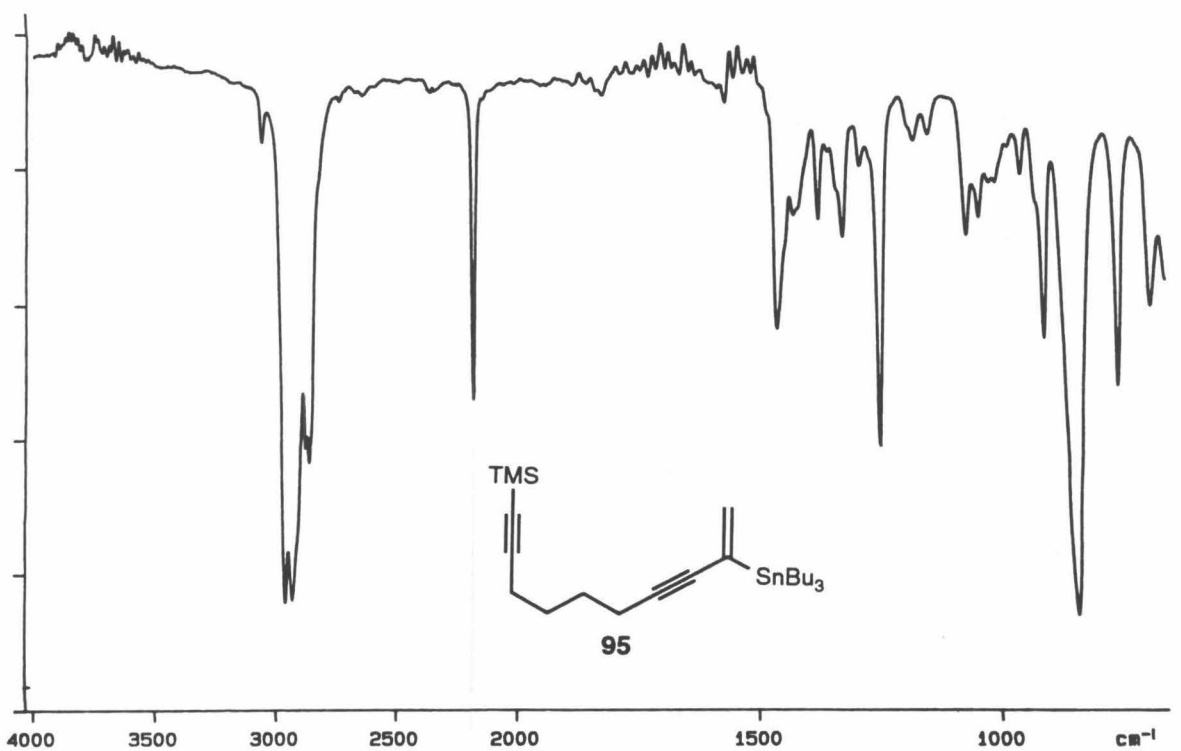

TMS
H
H
Cl
4000
3500
3000
2500
2000
1500
1000
cm⁻¹

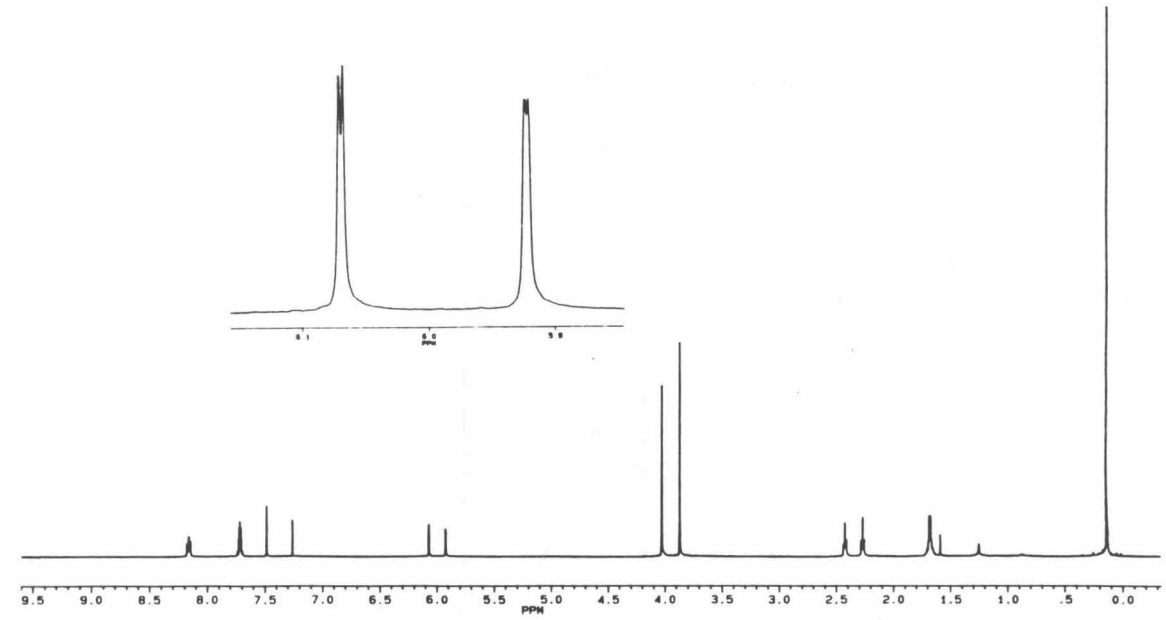
93

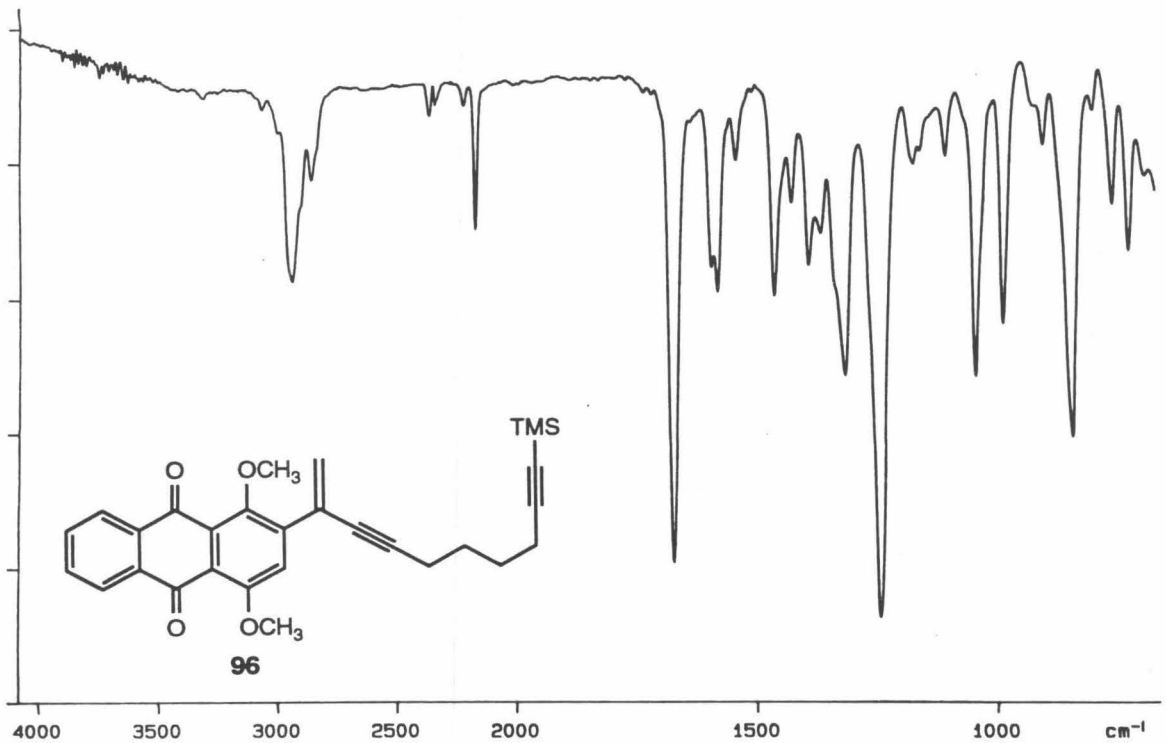

9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 .5 0.0
PPM


TMS
H
94
4000
3500
3000
2500
2000
1500
1000
cm⁻¹

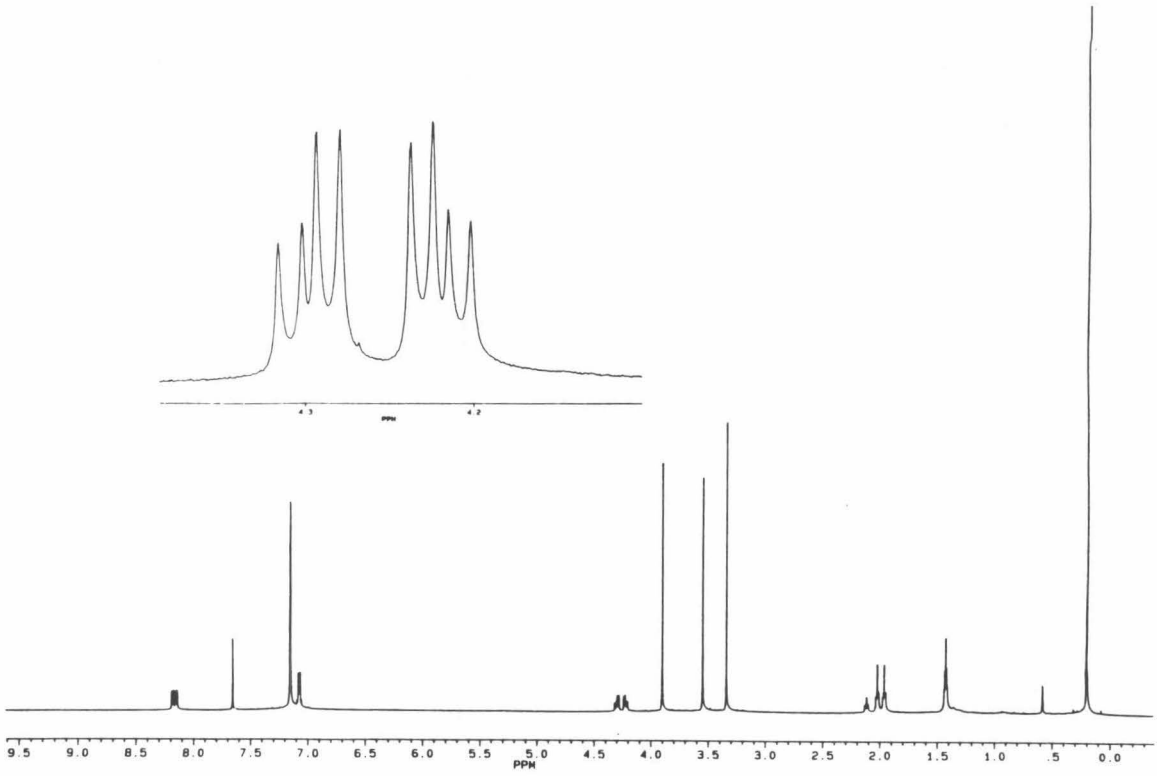

9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
.5
0.0
PPM

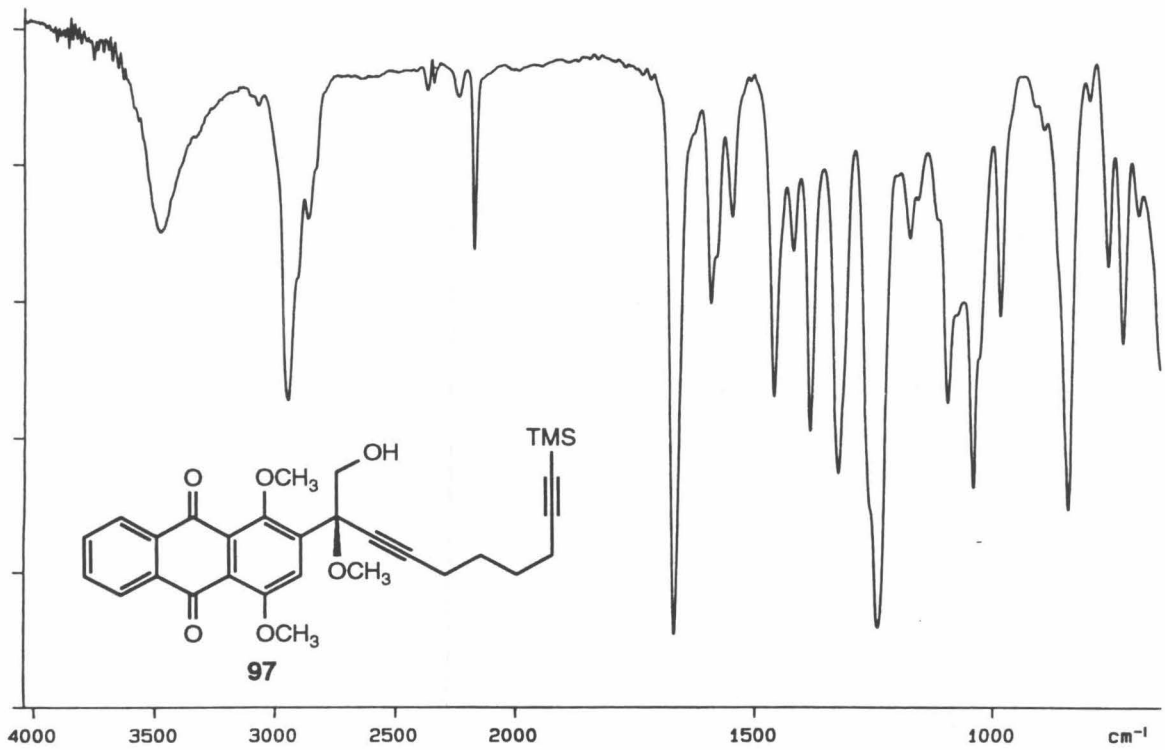

TMS
SnBu3
95
4000
3500
3000
2500
2000
1500
1000
cm-1


9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 .5 0.0
PPM

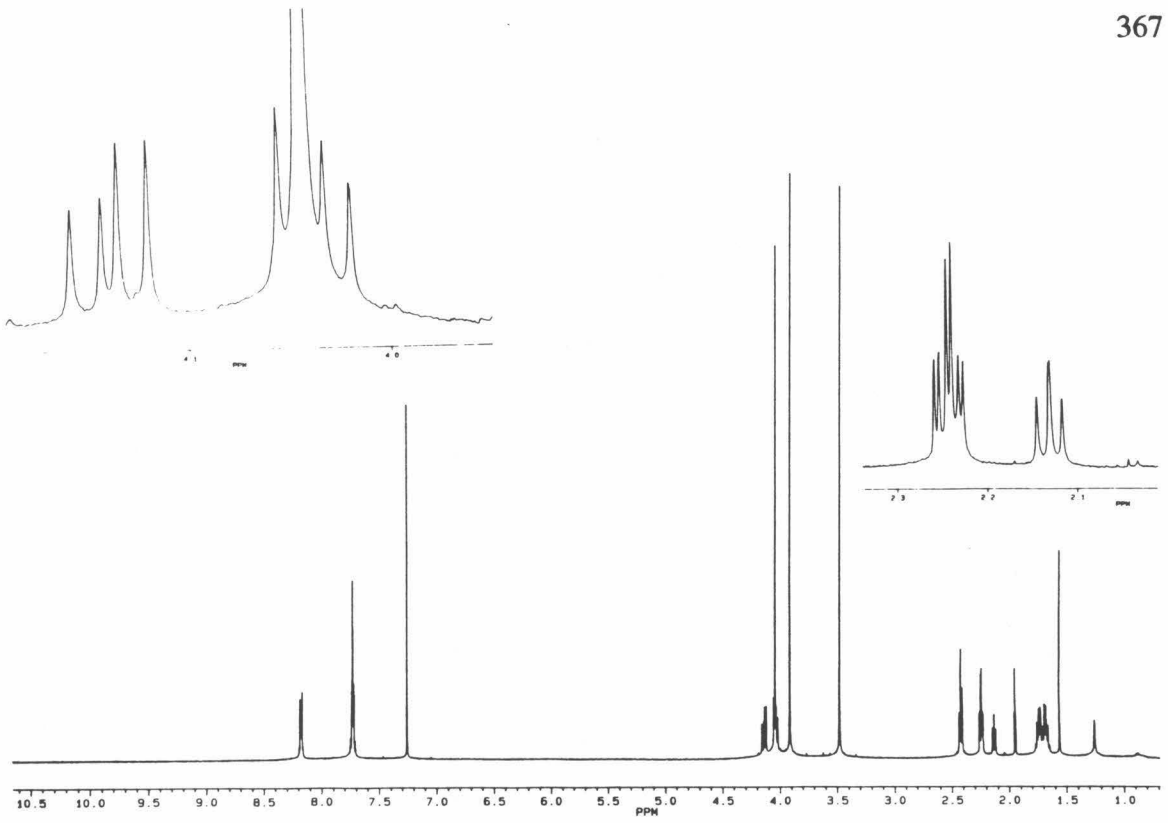

TMS
O
OCH3
O
OCH3
4000 3500 3000 2500 2000 1500 1000 cm-1

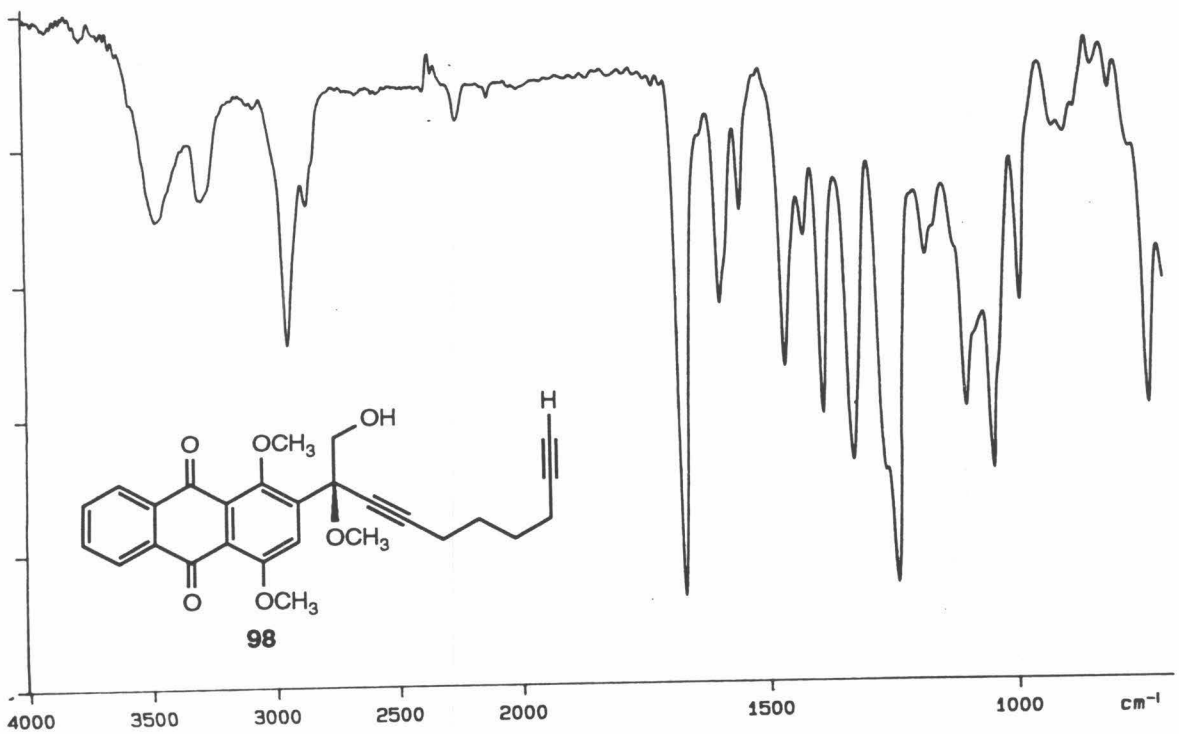
96


9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 .5 0.0
PPM

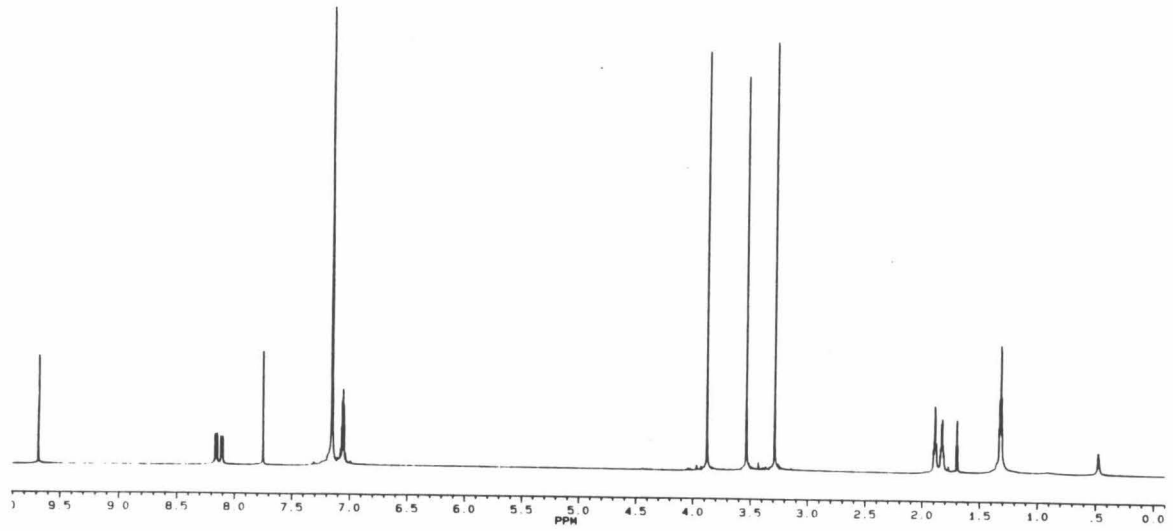

TMS
OH
O
OCH3
OCH3
O
OCH3
4000 3500 3000 2500 2000 1500 1000 cm-1

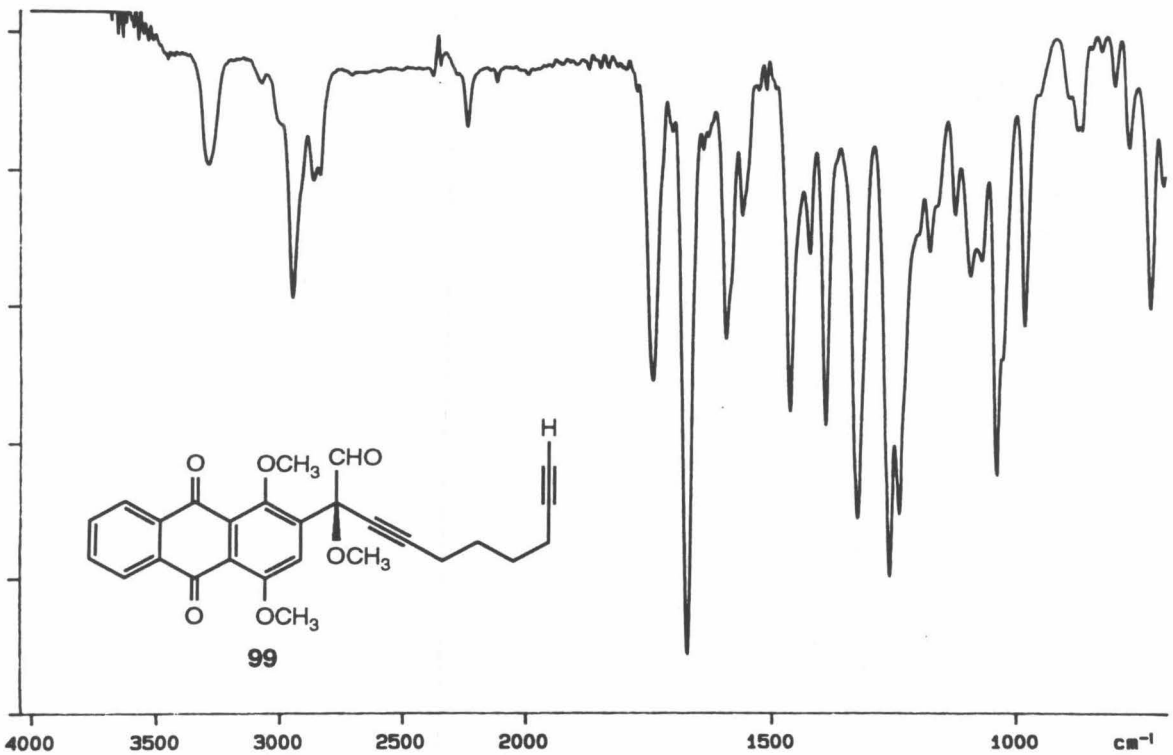
97


10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0
PPM

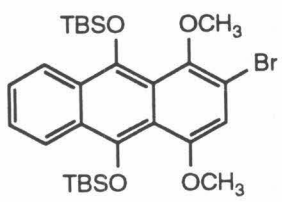

OH
H
O
OCH3
OCH3
O
OCH3
4000 3500 3000 2500 2000 1500 1000 cm-1

98


9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
PPM
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
.5
0.0

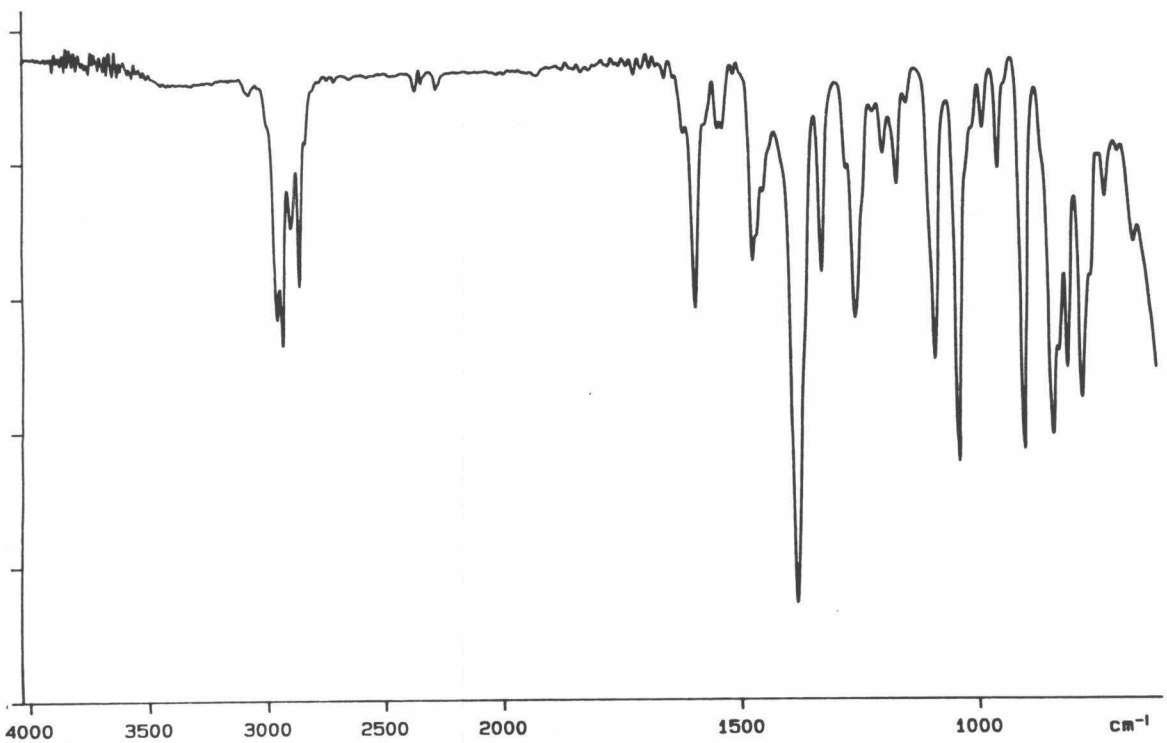

O
OCH3
CHO
H
OCH3
O
OCH3
4000
3500
3000
2500
2000
1500
1000
cm-1

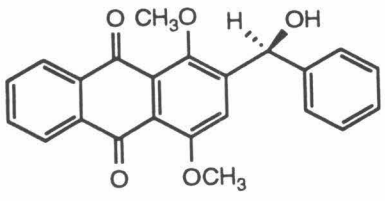
99


TBSO
OCH3
Br
TBSO
OCH3

103

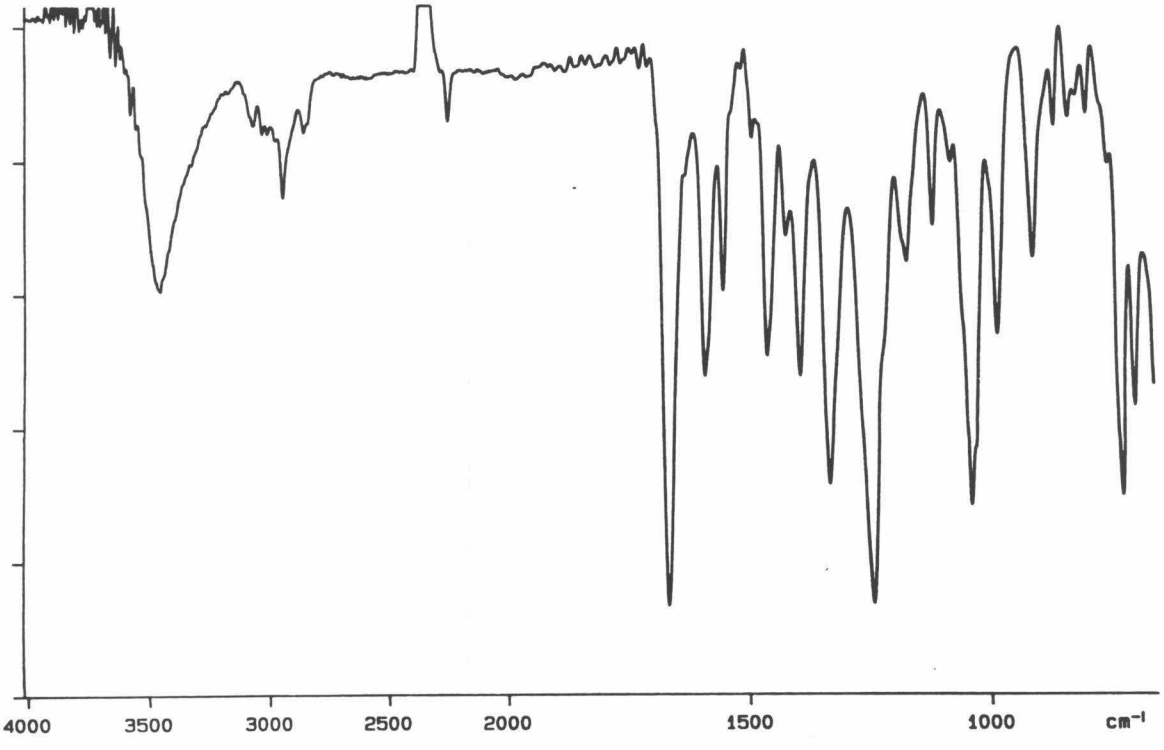
PPM
8
7
6
5
4
1
0

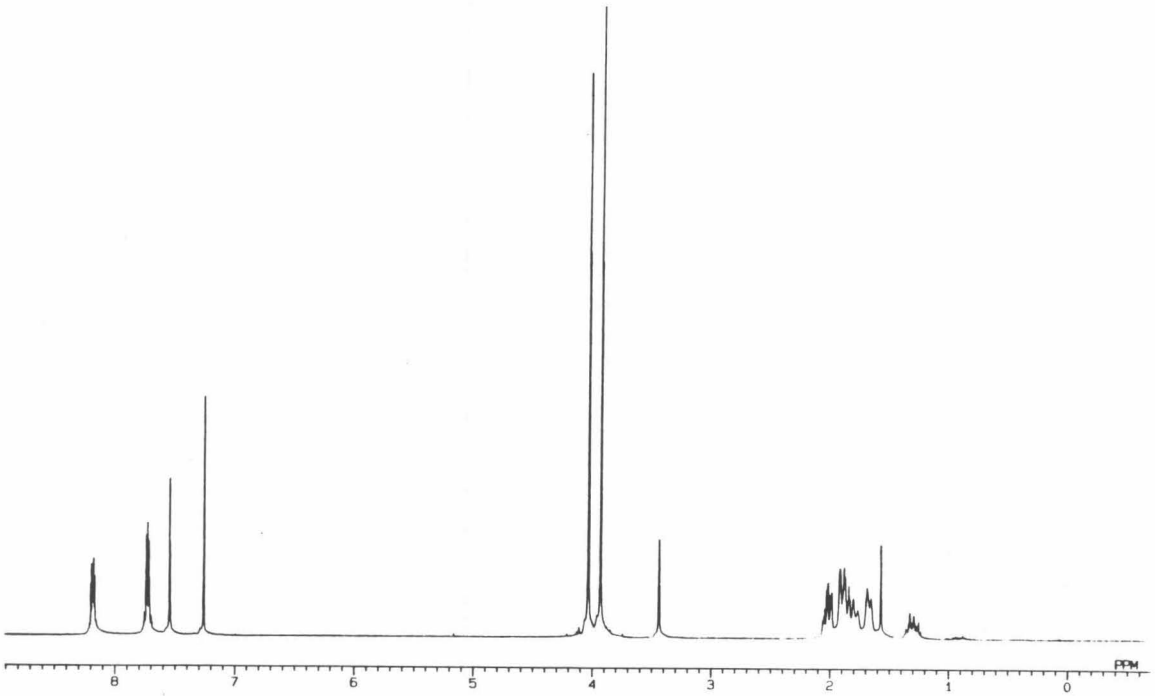

4000
3500
3000
2500
2000
1500
1000
cm-1

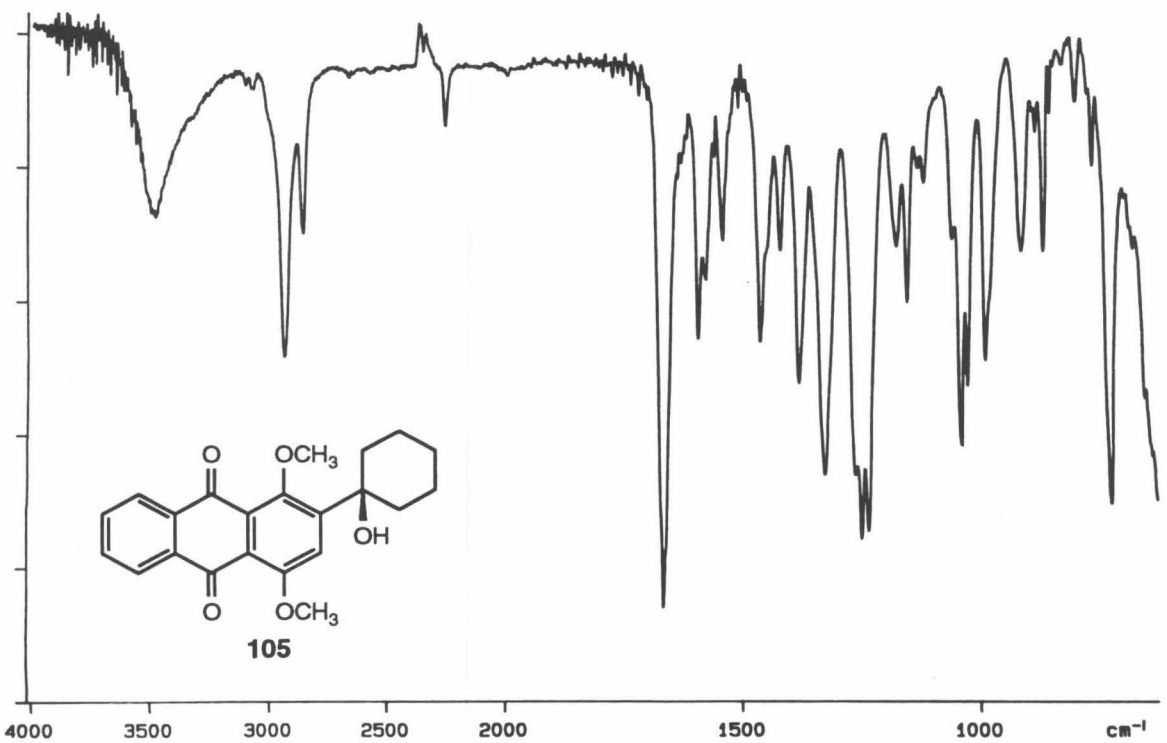

O
CH3O
H
OH
O
OCH3

104

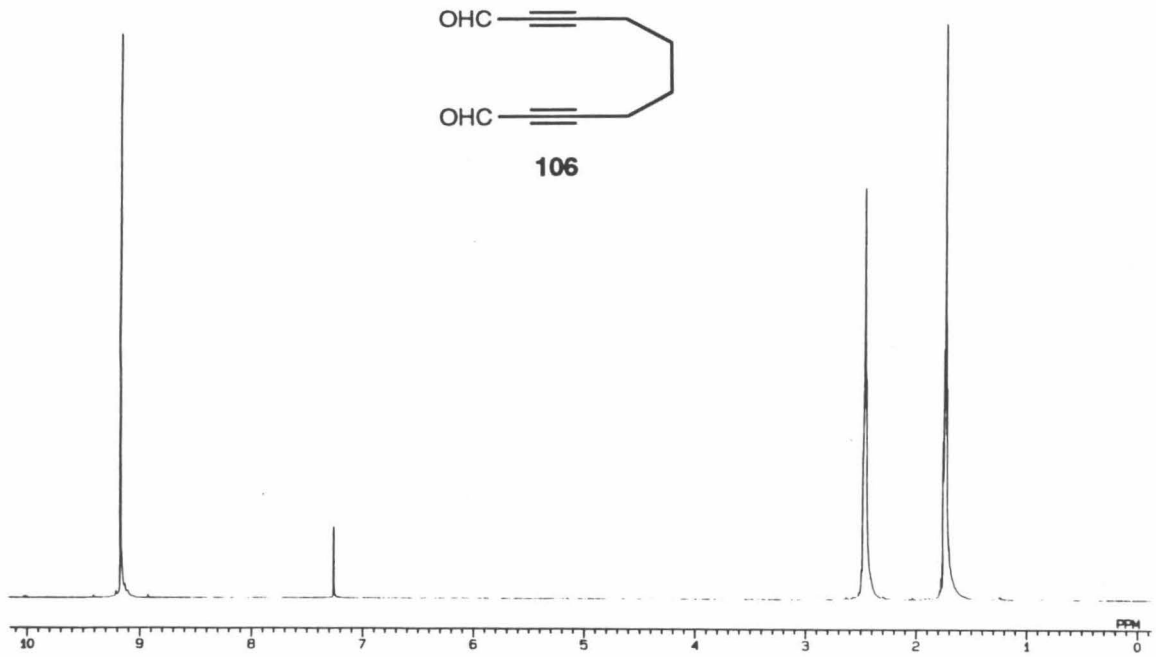
8
7
6
5
4
3
2
1
PPM

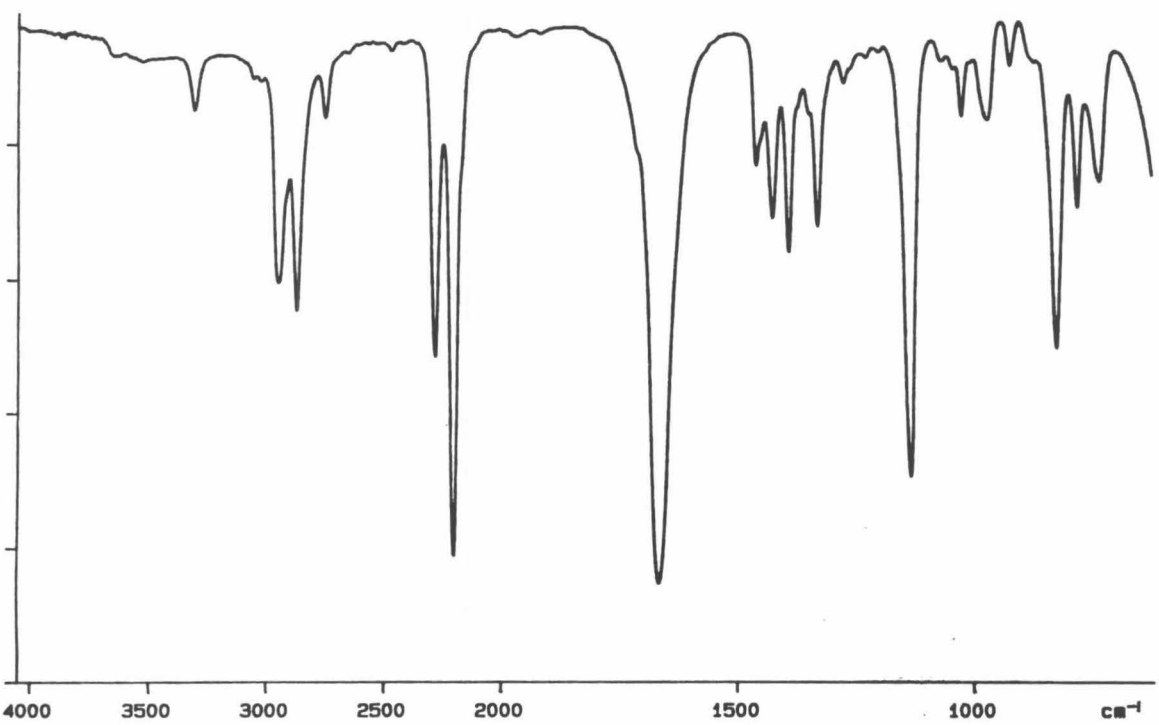

4000
3500
3000
2500
2000
1500
1000
cm-1

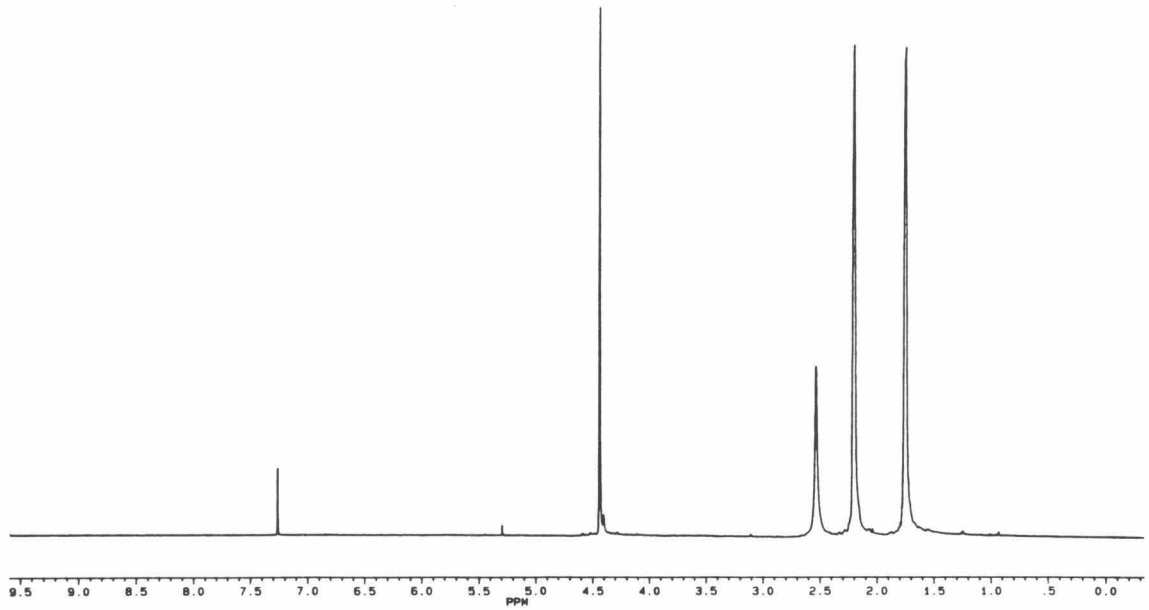

8
7
6
5
4
3
2
1
0
PPM

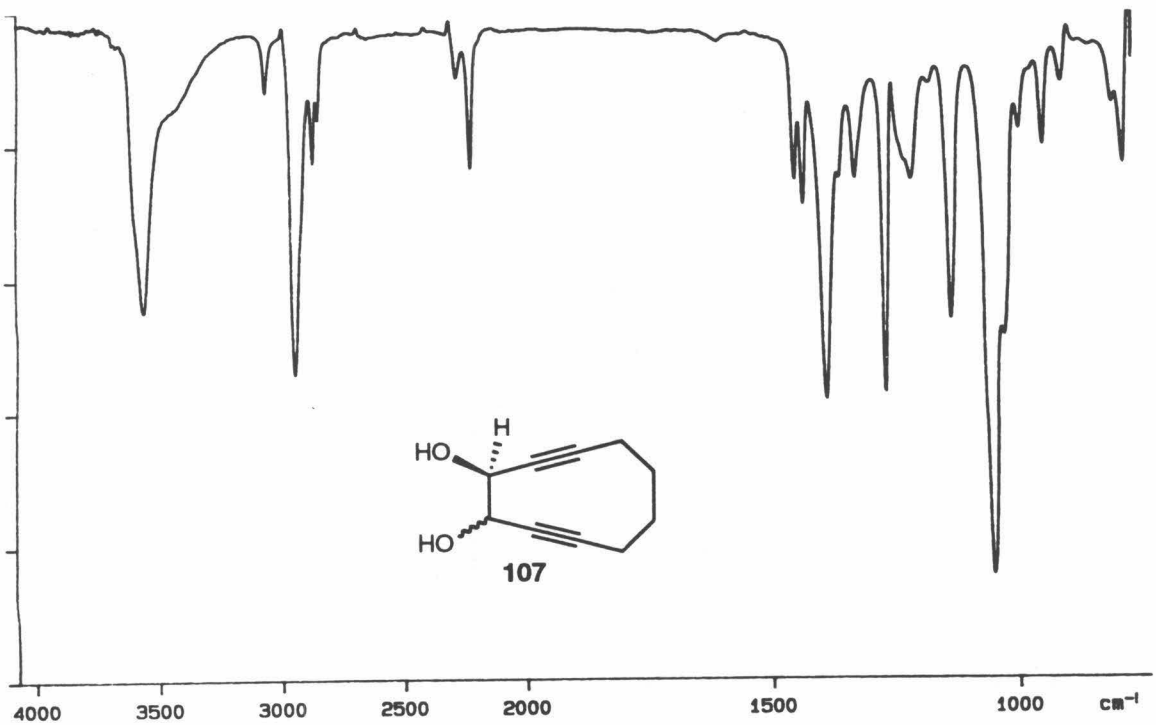

O
OCH3
OH
O
OCH3
4000
3500
3000
2500
2000
1500
1000
cm-1

105

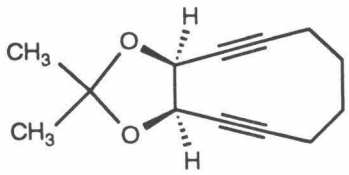

OHC
OHC
106
10
9
8
7
6
5
4
3
2
1
0
PPM


4000
3500
3000
2500
2000
1500
1000
cm⁻¹

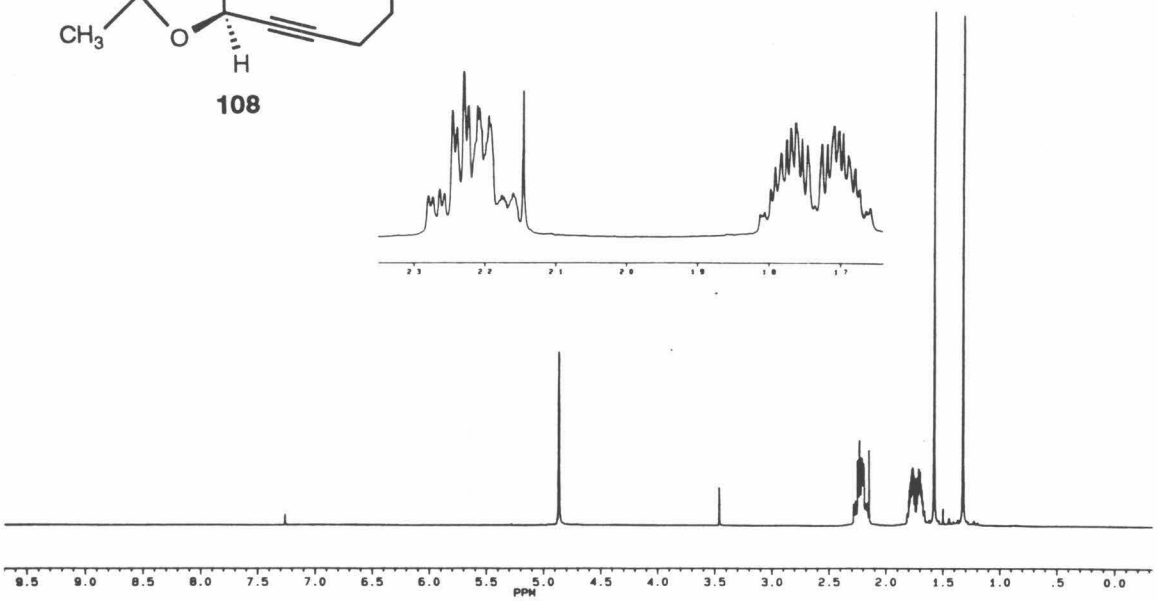

9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
.5
0.0
PPM

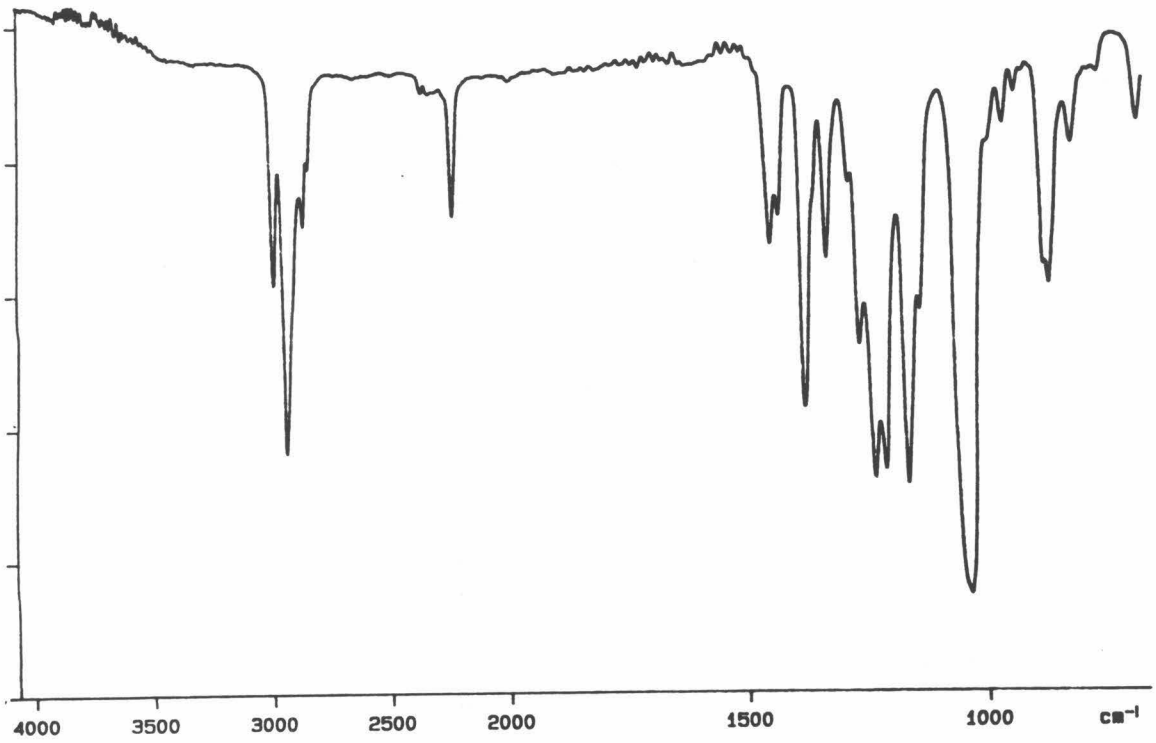

HO
H
HO
4000
3500
3000
2500
2000
1500
1000
cm⁻¹

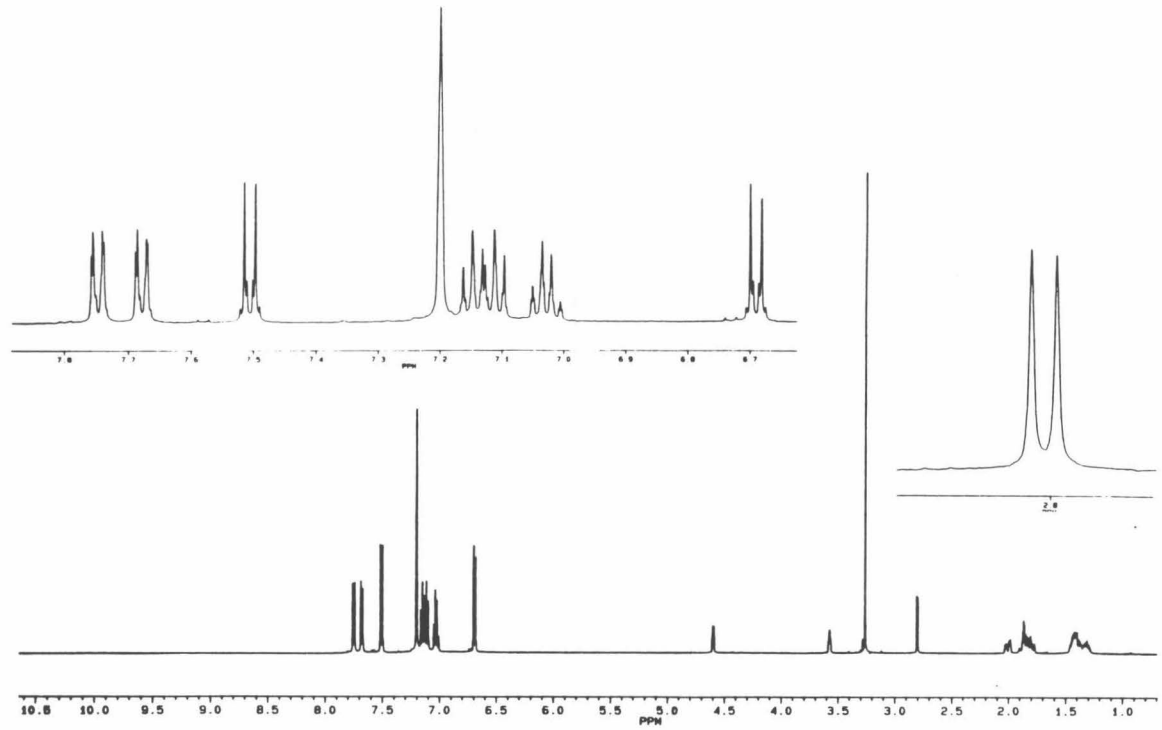
107

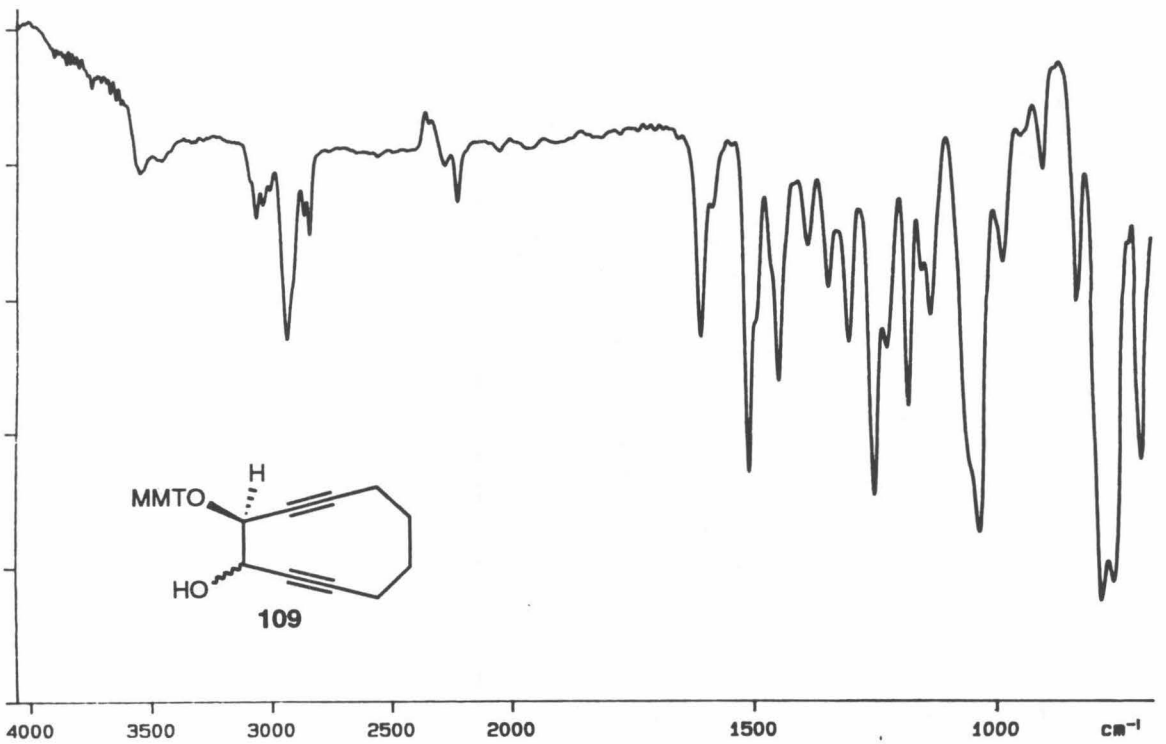

H
O
CH3
CH3
O
H

108

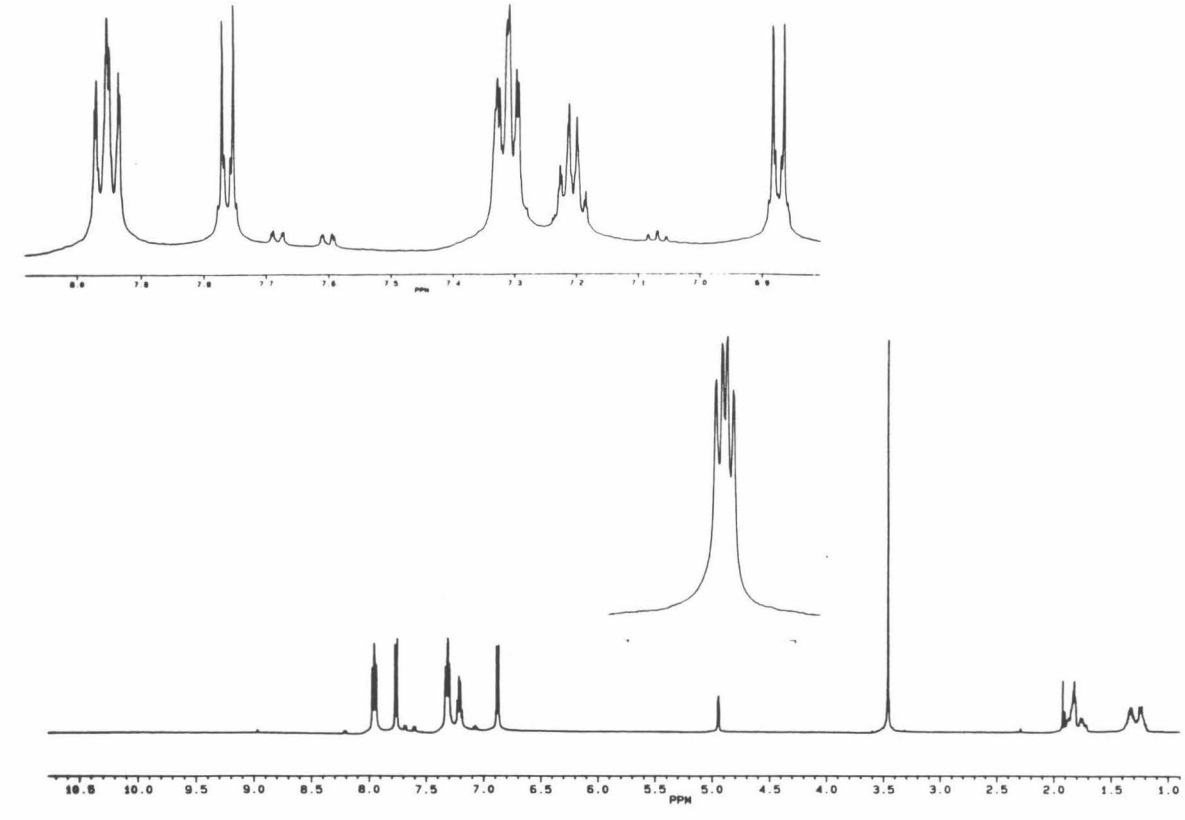

9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 .5 0.0
PPM


4000
3500
3000
2500
2000
1500
1000
cm-1


10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0
PPM


MMTO
H
HO
4000 3500 3000 2500 2000 1500 1000 cm⁻¹

109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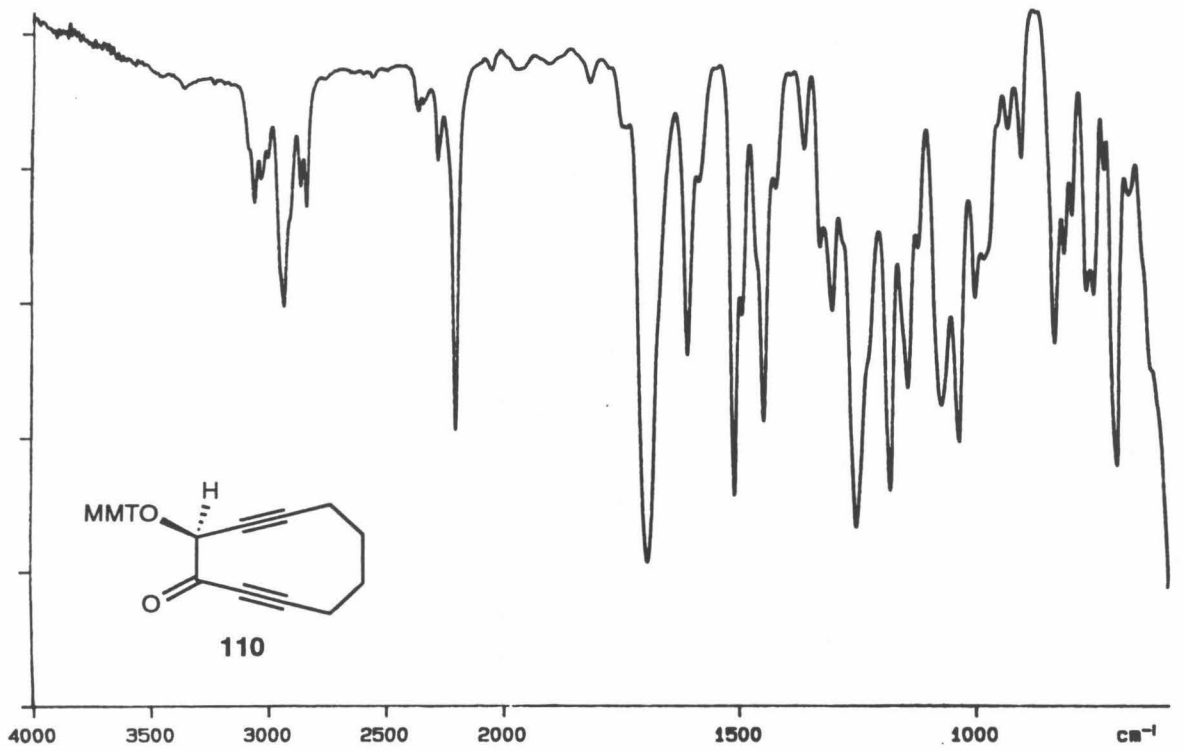
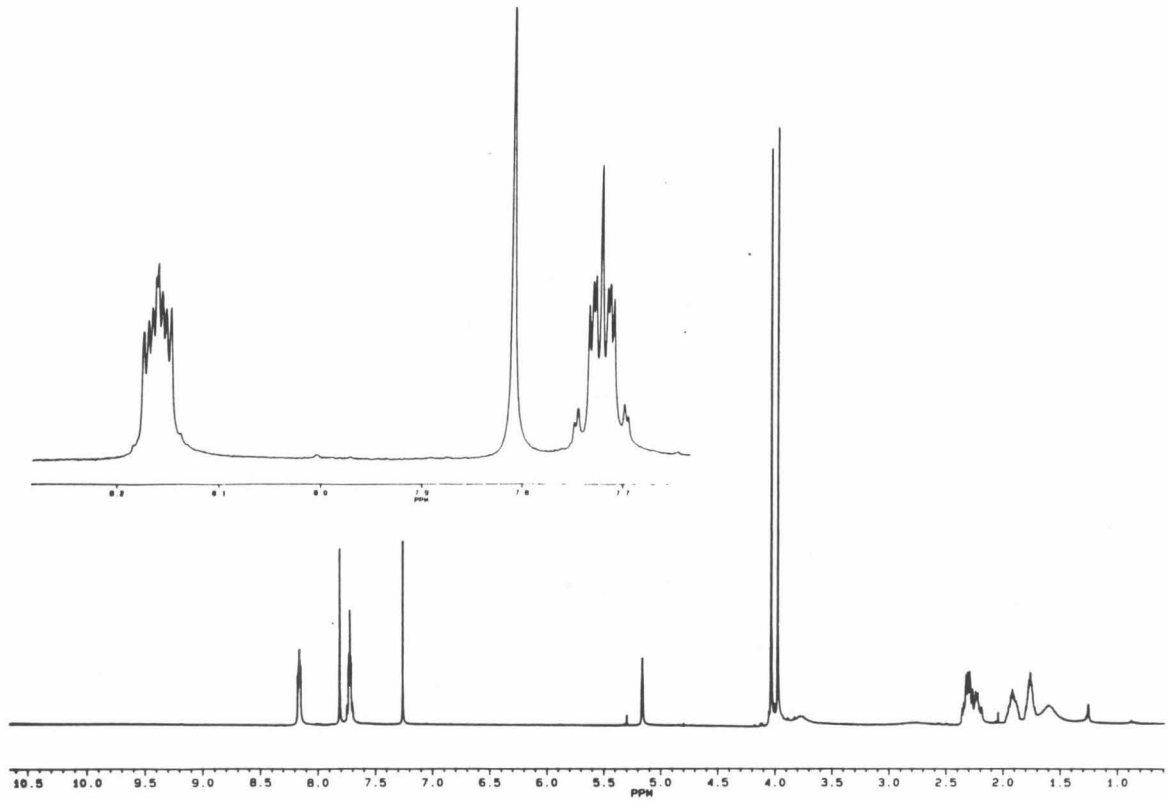
PPM


MMTO
H
O
4000 3500 3000 2500 2000 1500 1000 cm⁻¹

110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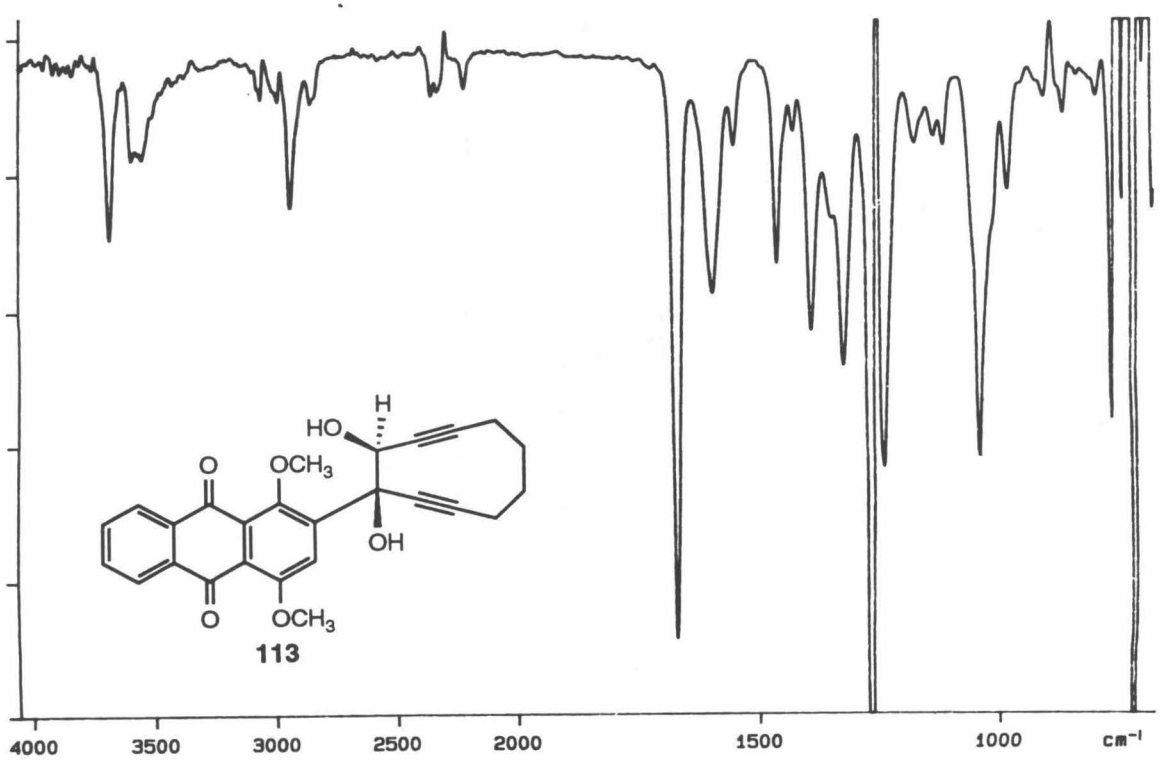
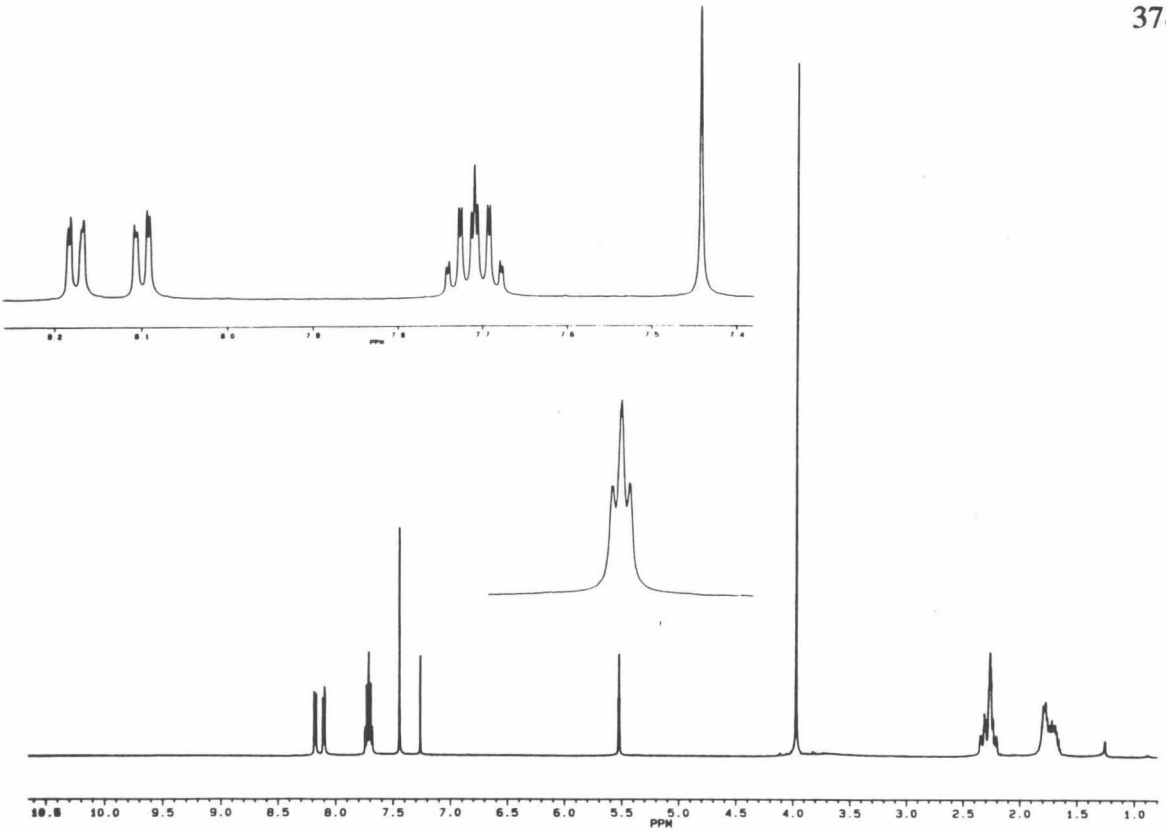
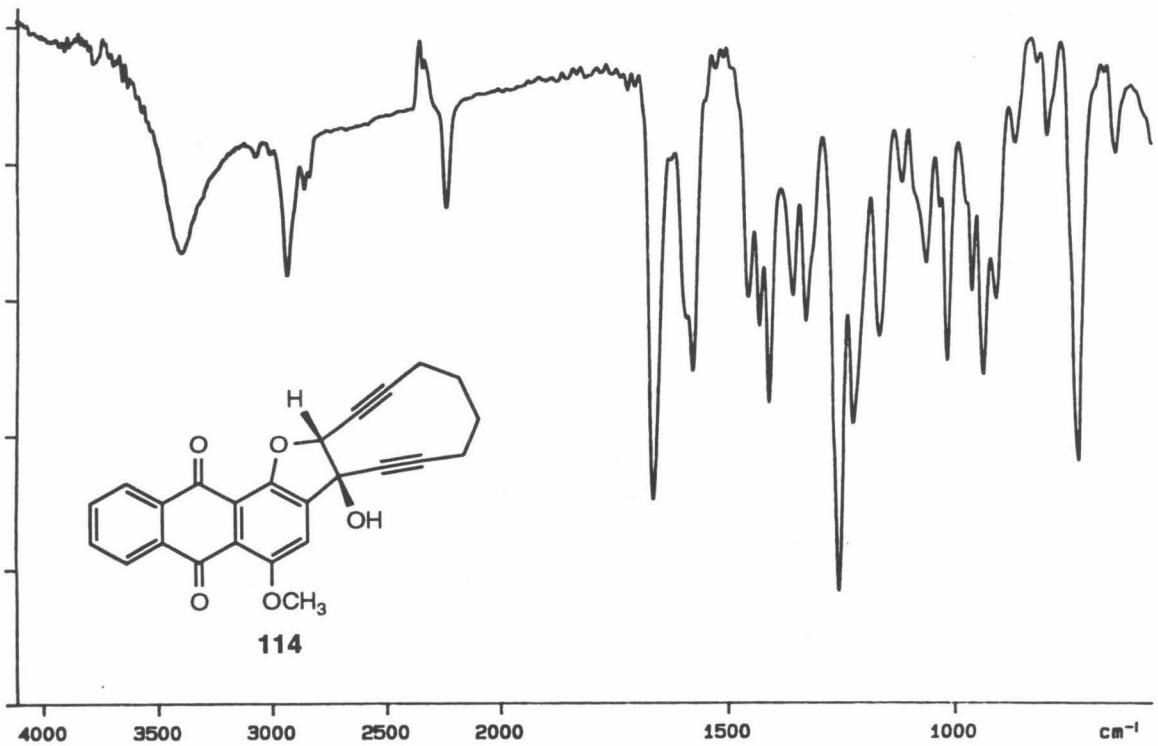
PPM

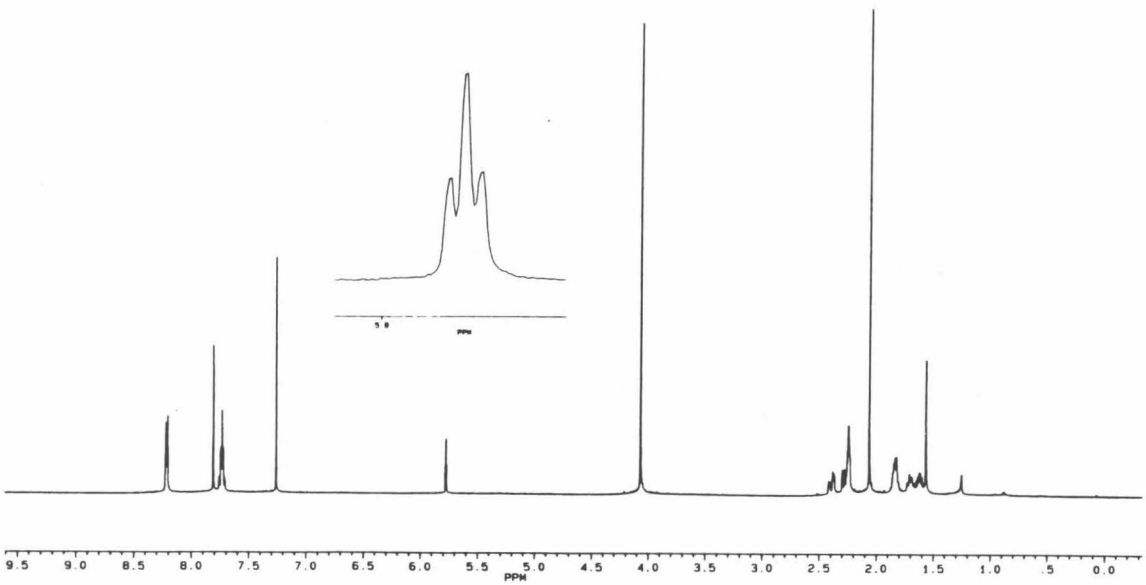

H
HO
O
OCH3
OH
O
OCH3
4000 3500 3000 2500 2000 1500 1000 cm-1

113


10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0
PPM


H
O
O
OH
O
OCH3
4000 3500 3000 2500 2000 1500 1000 cm-1

114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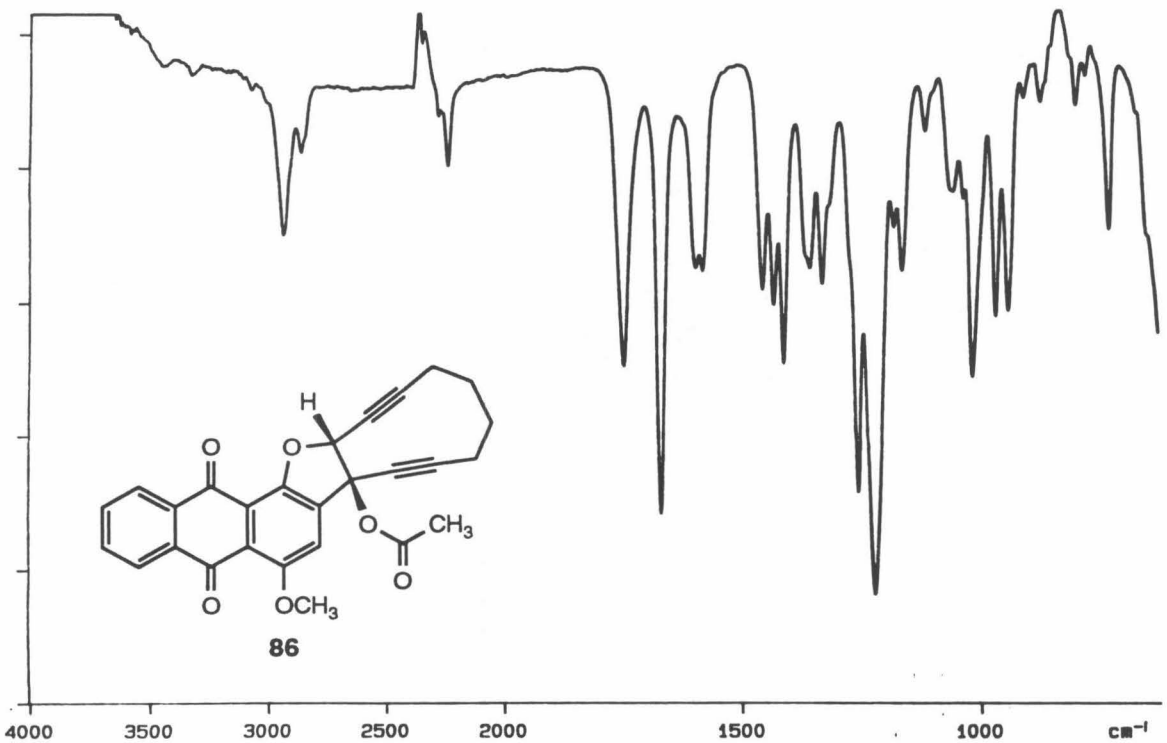
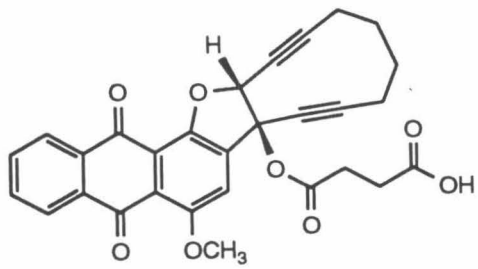
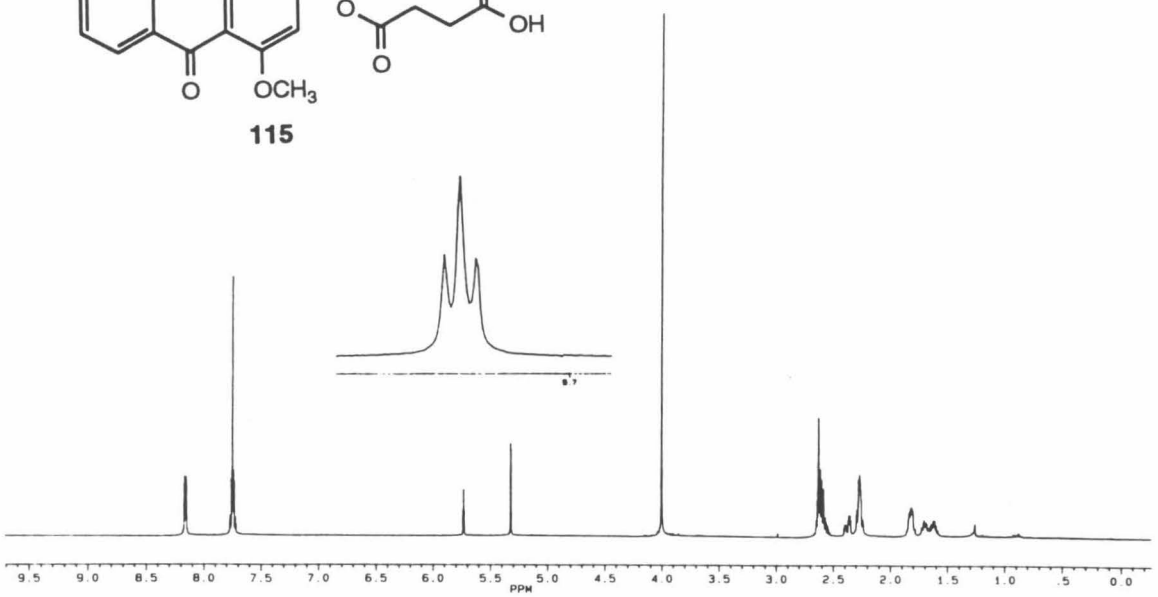
PPM

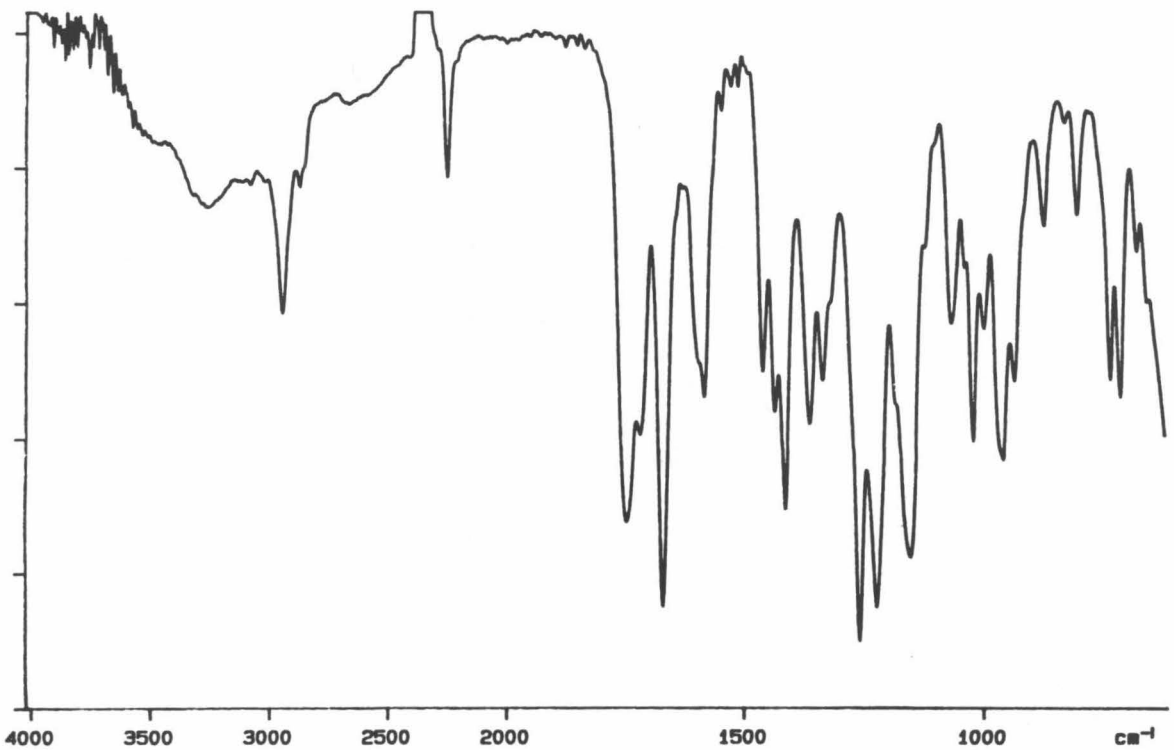

H
O
O
O
O
CH3
O
OCH3
4000 3500 3000 2500 2000 1500 1000 cm-1

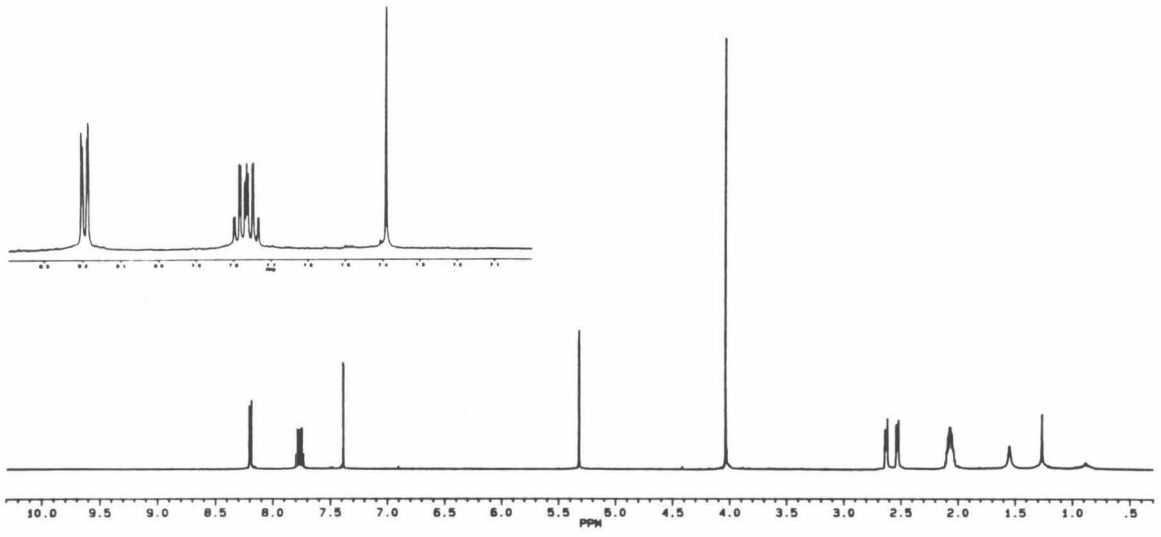
86

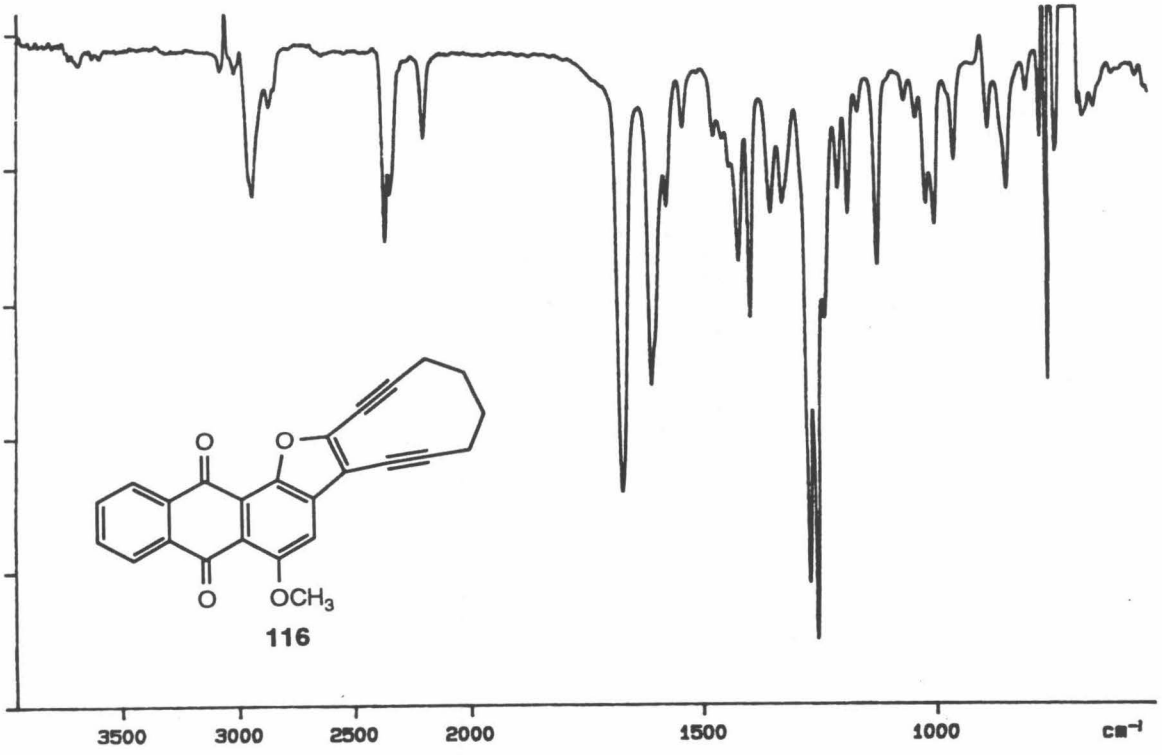

H
O
O
O
O
O
OH
O
O
OCH3

115

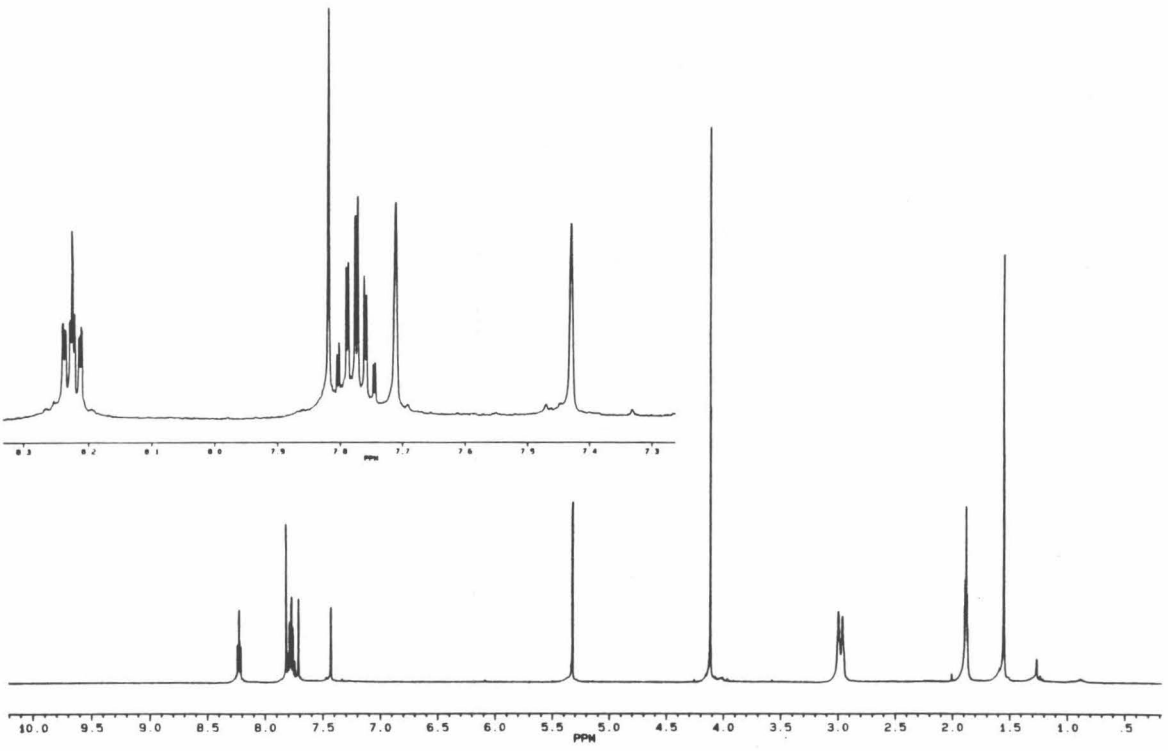

9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
.5
0.0
PPM

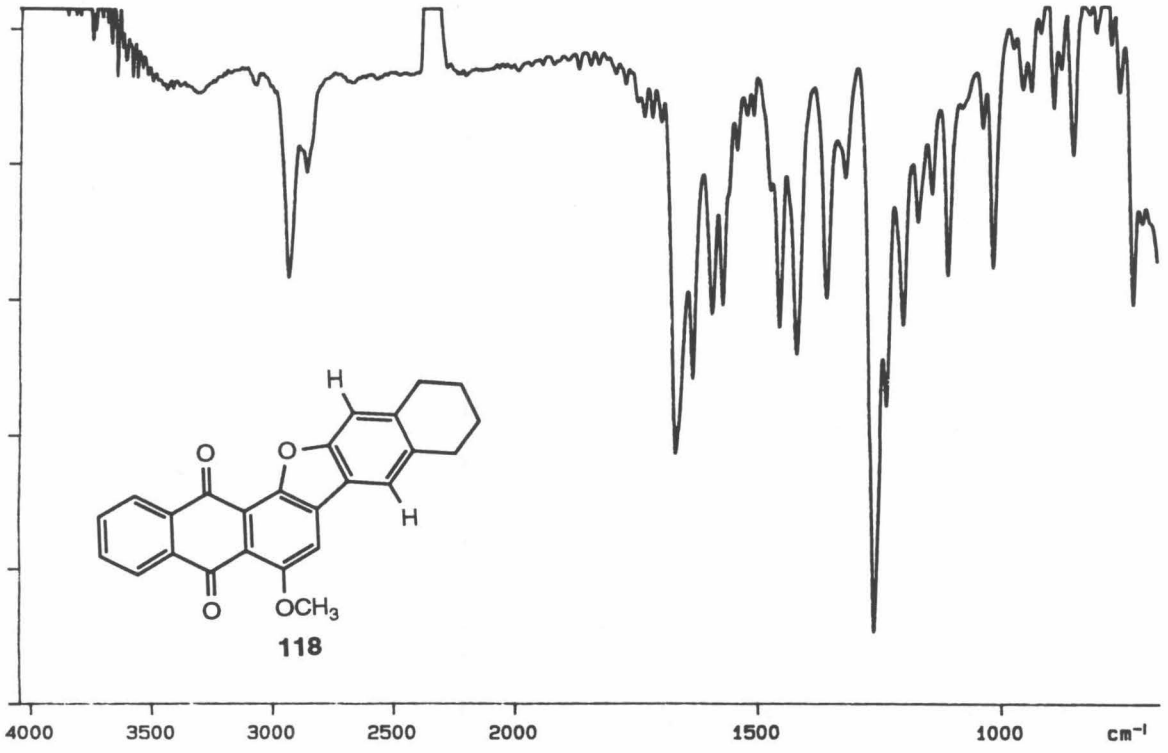

4000
3500
3000
2500
2000
1500
1000
cm-1


10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
.5
PPM

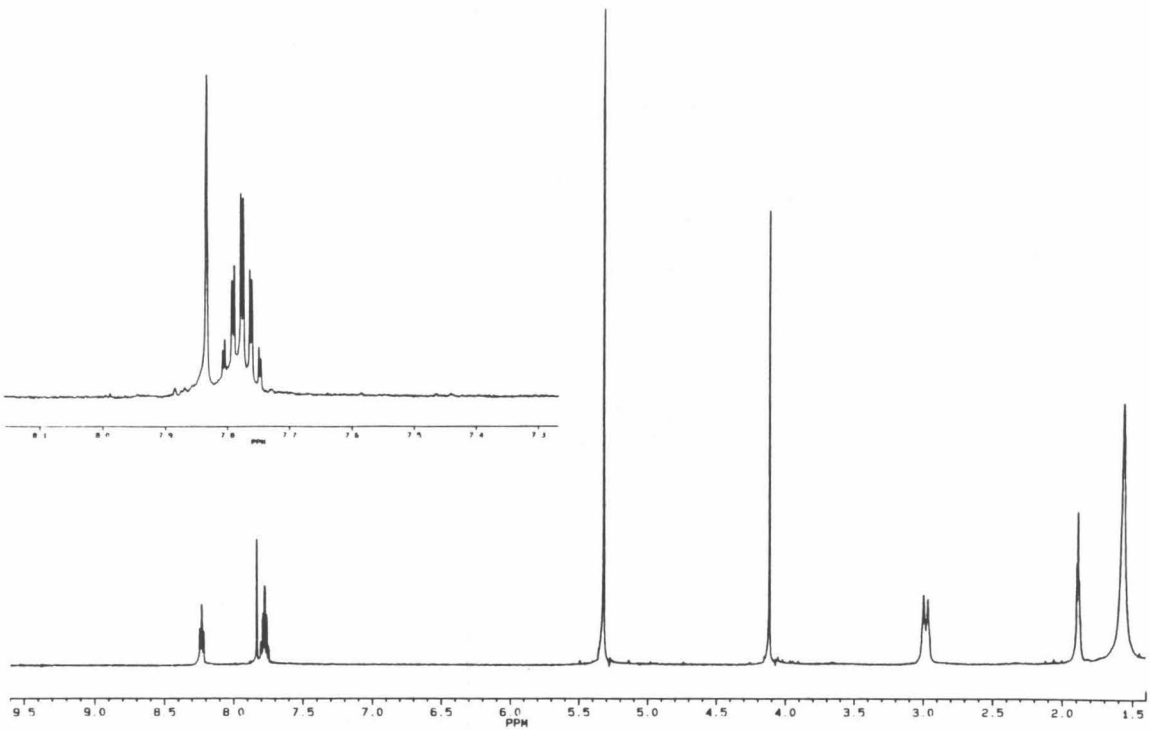

O
O
O
OCH3
3500
3000
2500
2000
1500
1000
cm-1

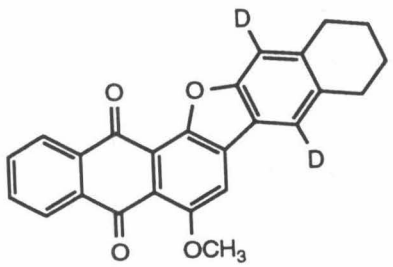
116


10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 .5
PPM


H
O
O
H
O
OCH3
4000 3500 3000 2500 2000 1500 1000 cm-1

118

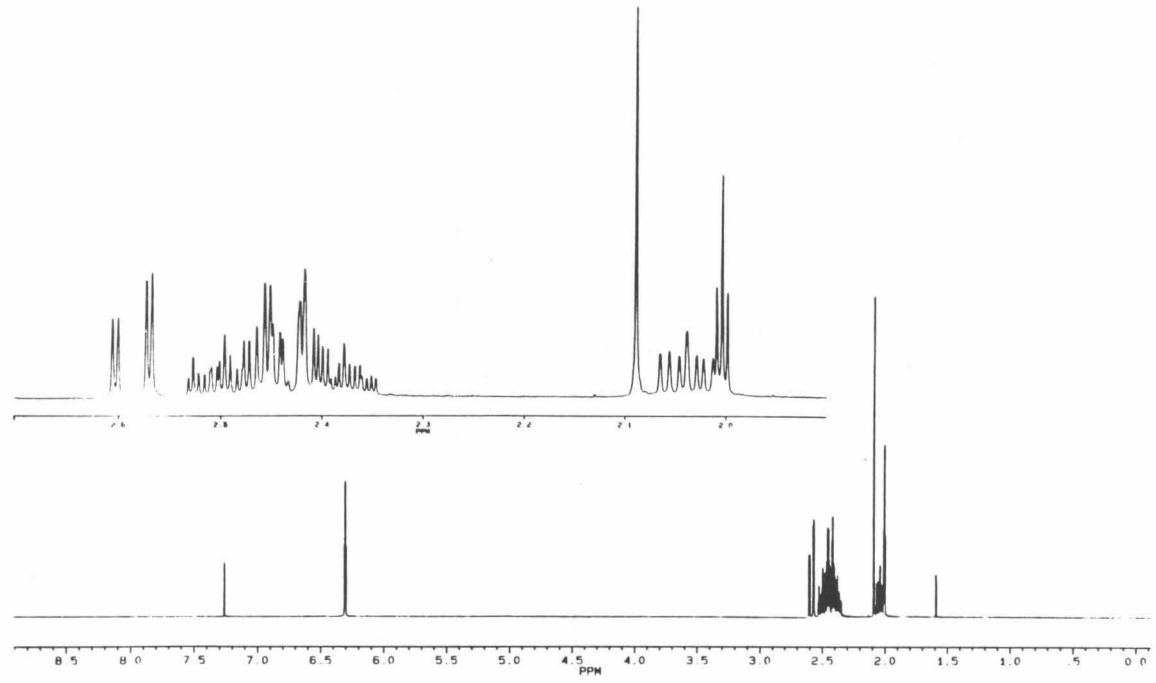


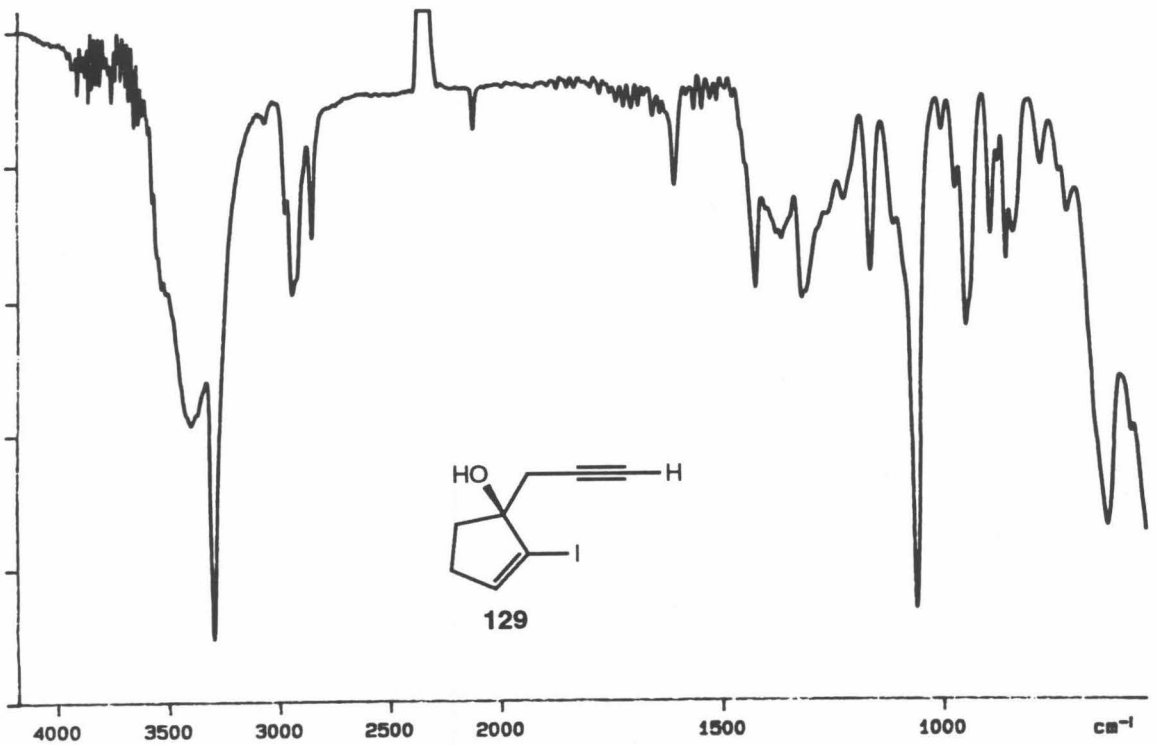


118

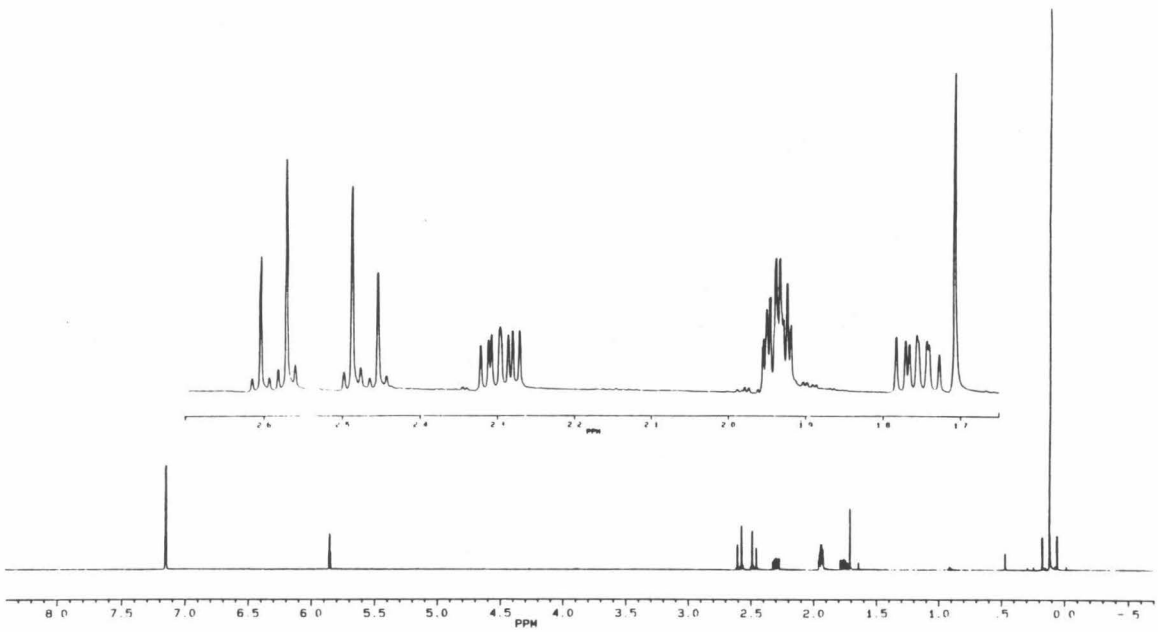
Appendix 4

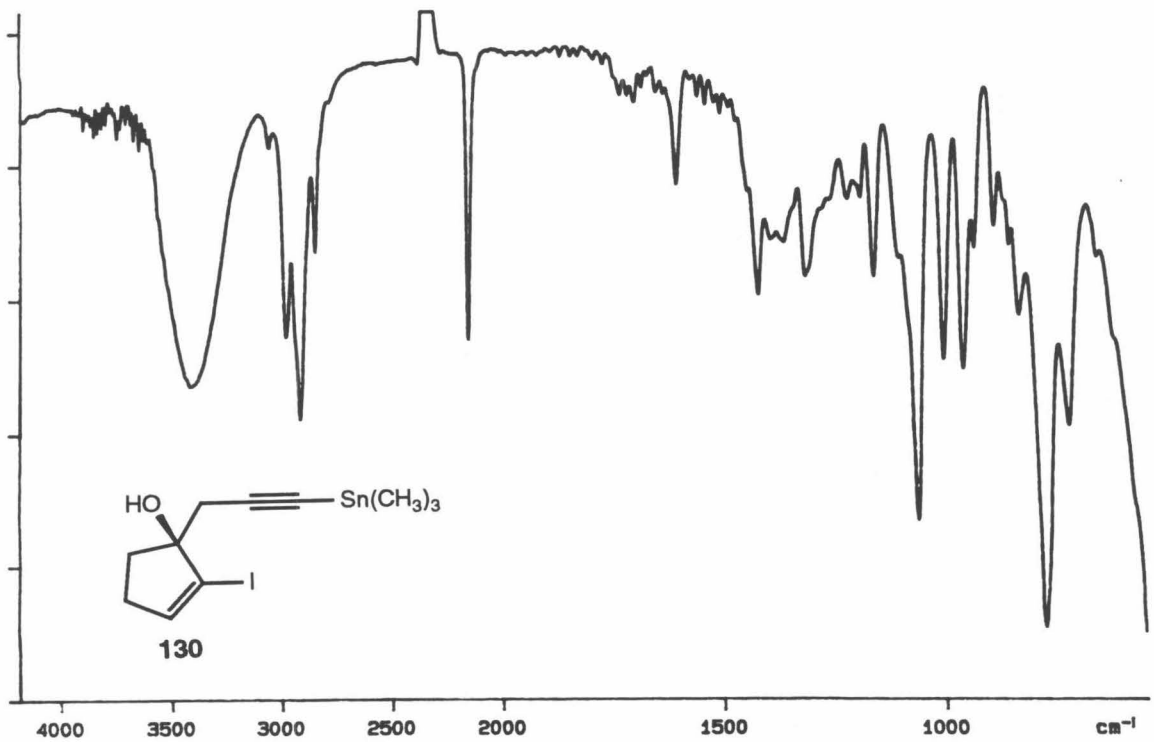
Catalog of Spectra (Chapter 3)


8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
PPM
4.0
3.5
3.0
2.5
2.0
1.5
1.0
.5
0.0

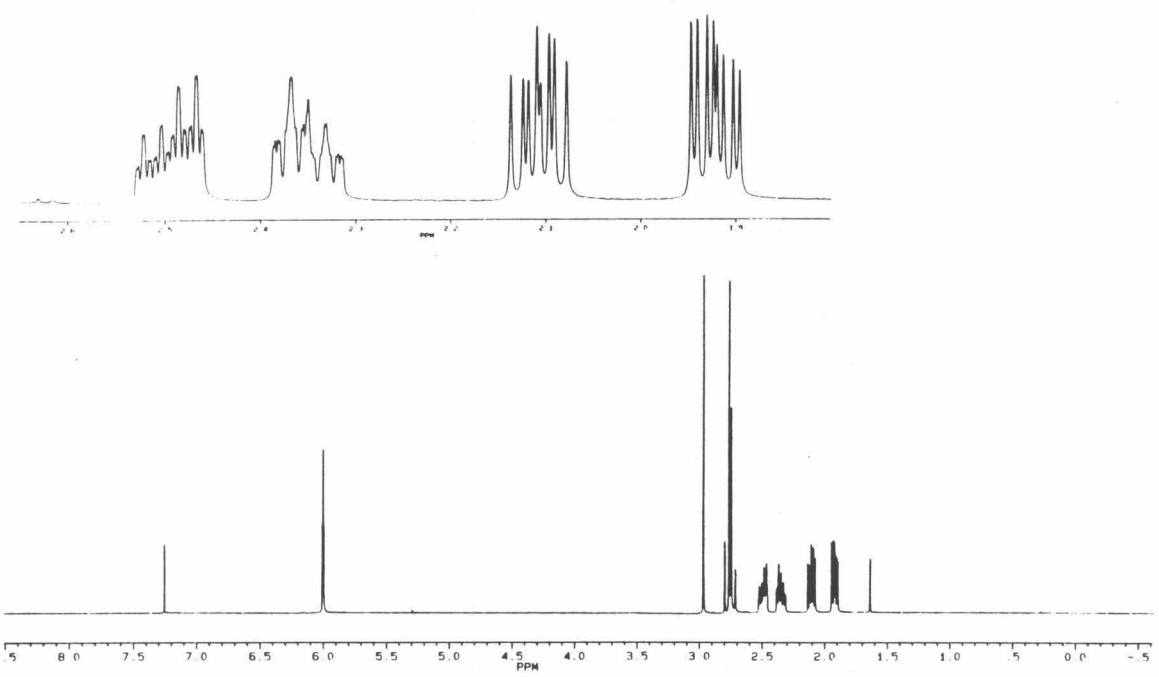

HO
H
I
4000
3500
3000
2500
2000
1500
1000
cm⁻¹

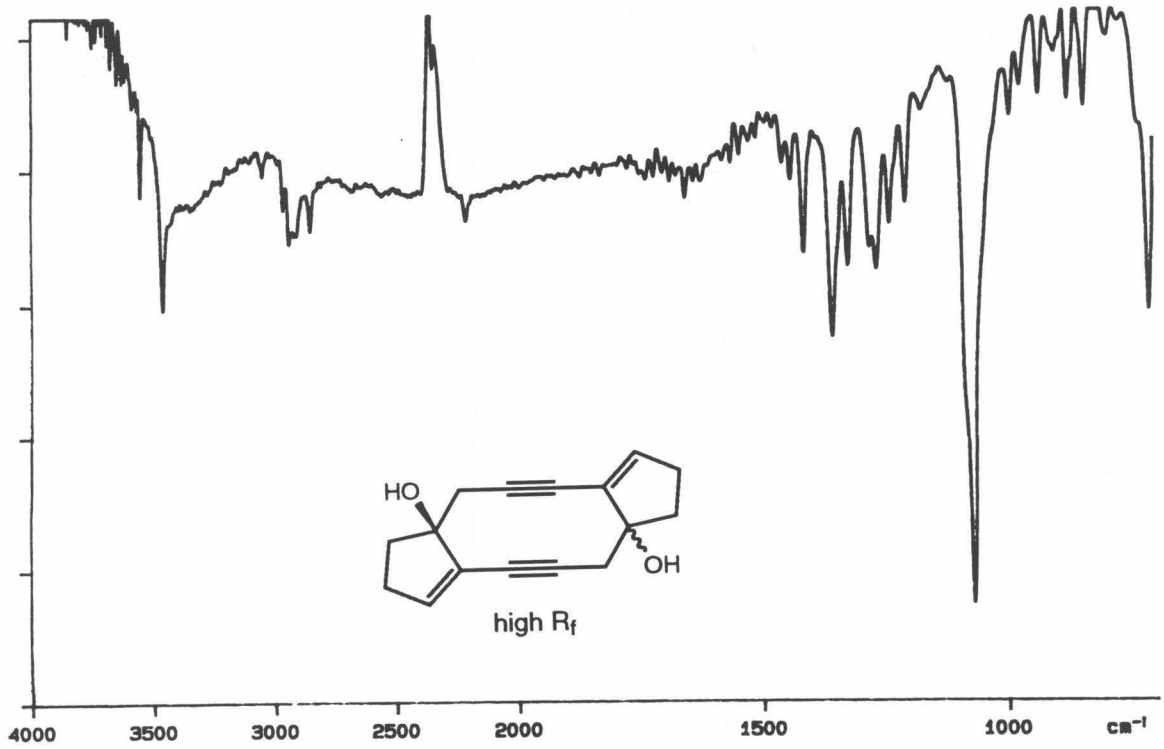
129

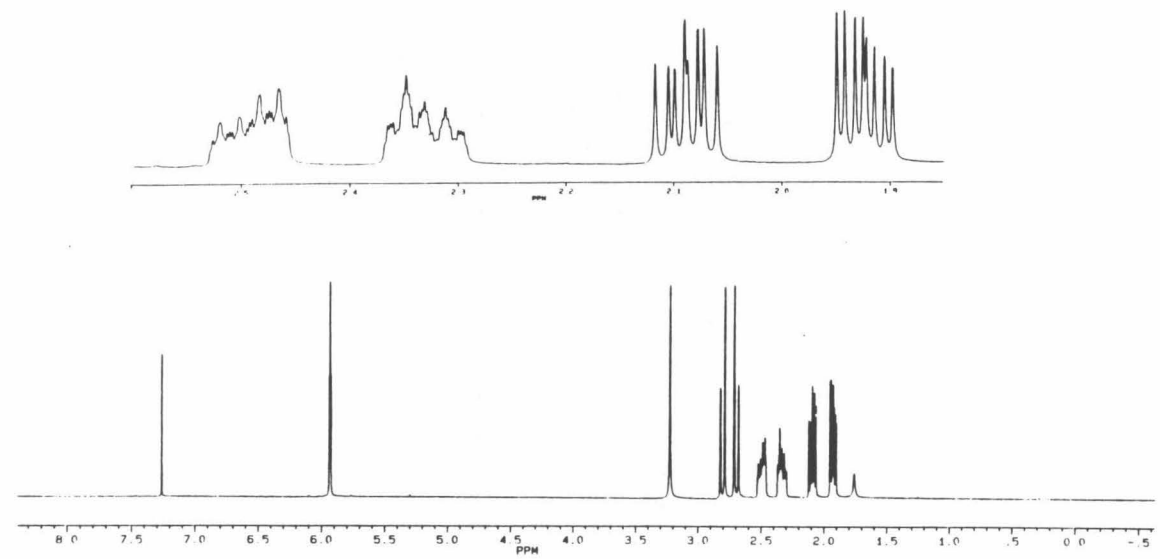

8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
PPM
4.0
3.5
3.0
2.5
2.0
1.5
1.0
.5
0.0
-.5

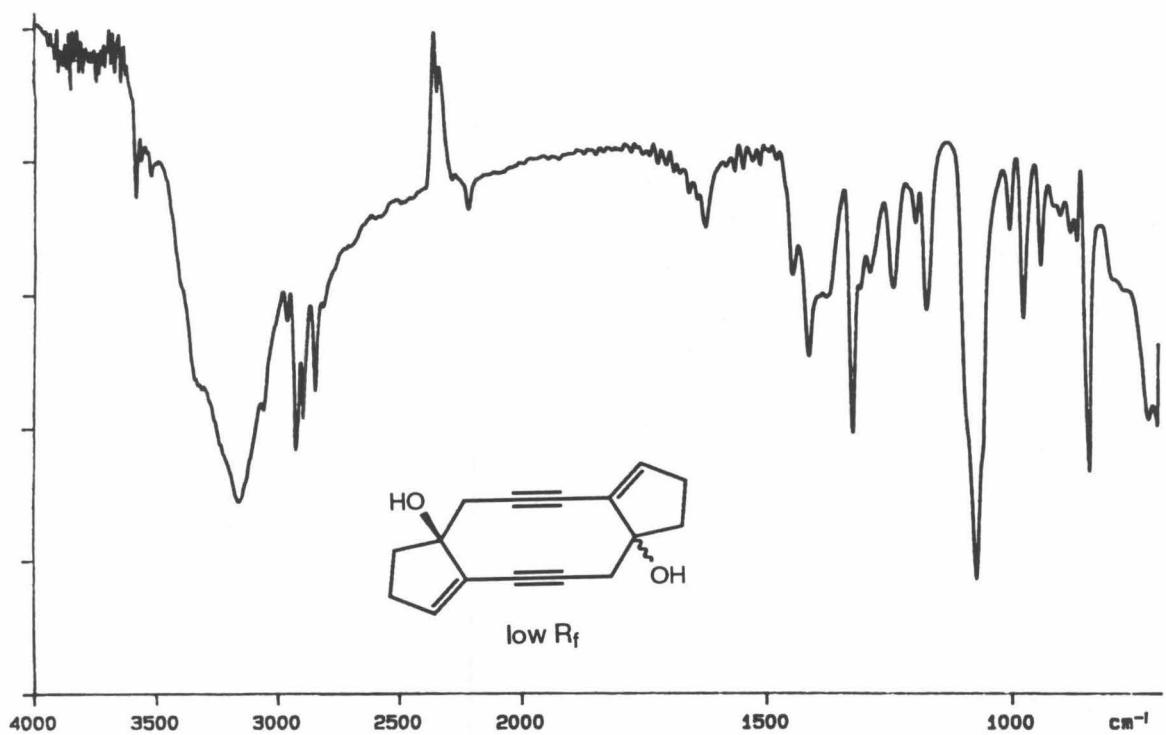

HO
Sn(CH3)3
I
4000
3500
3000
2500
2000
1500
1000
cm-1

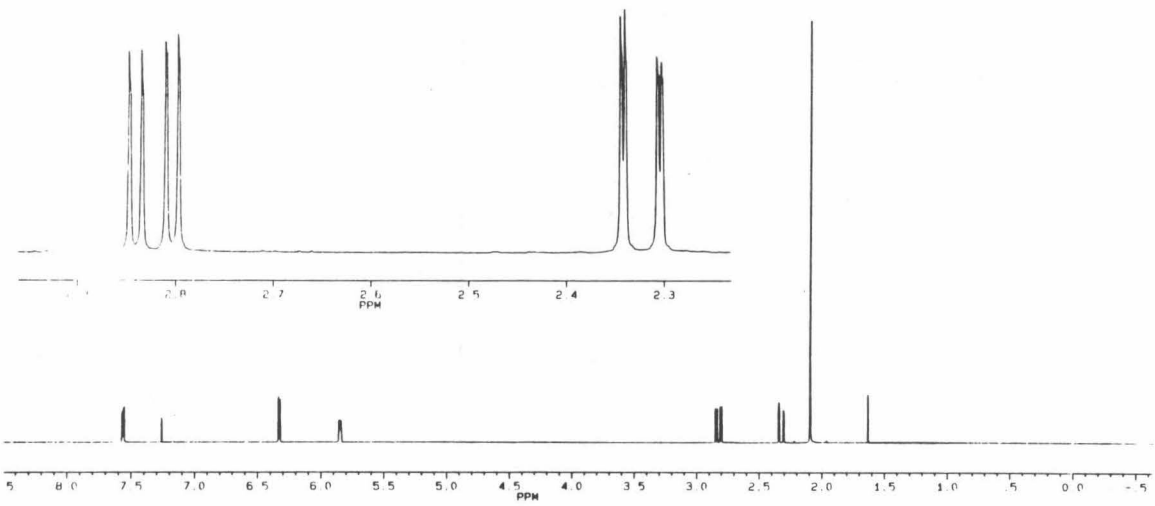
130

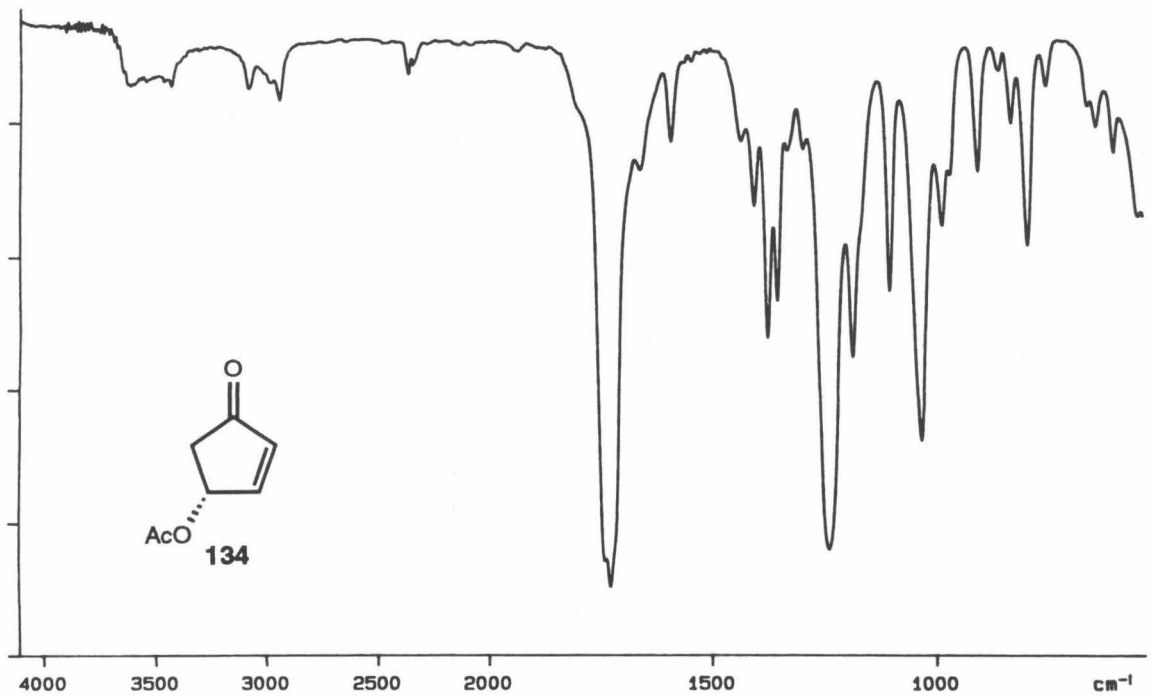

PPM

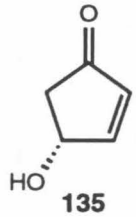

HO
OH
high R_f
4000
3500
3000
2500
2000
1500
1000
cm⁻¹


8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
PPM
4.0
3.5
3.0
2.5
2.0
1.5
1.0
.5
0.0
-.5

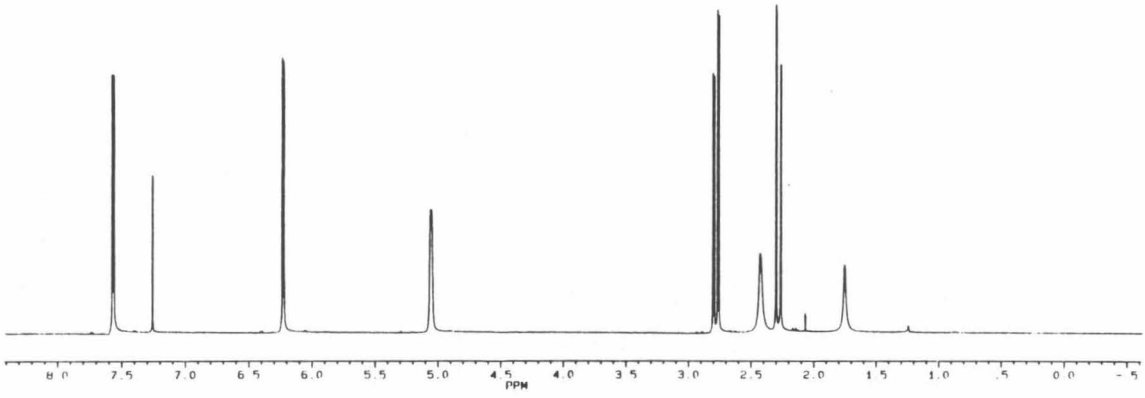

HO
OH
low R_f
4000
3500
3000
2500
2000
1500
1000
cm⁻¹

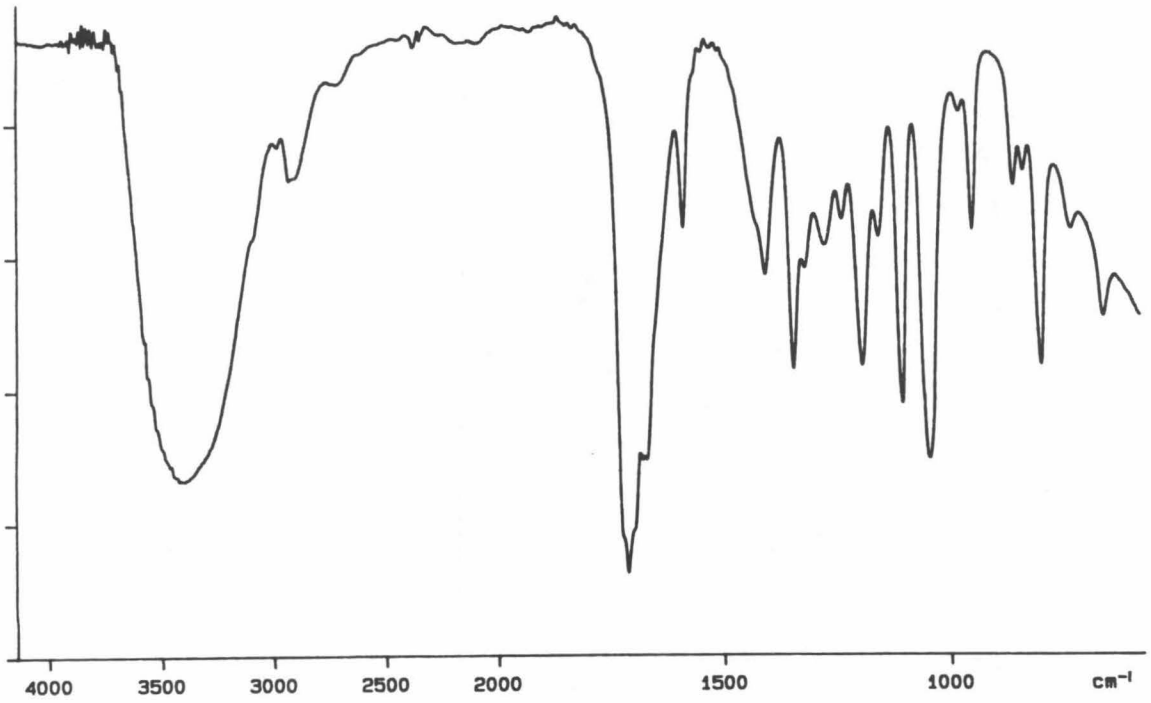

2.8
2.7
2.6
PPM
2.5
2.4
2.3
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
PPM
4.0
3.5
3.0
2.5
2.0
1.5
1.0
.5
0.0

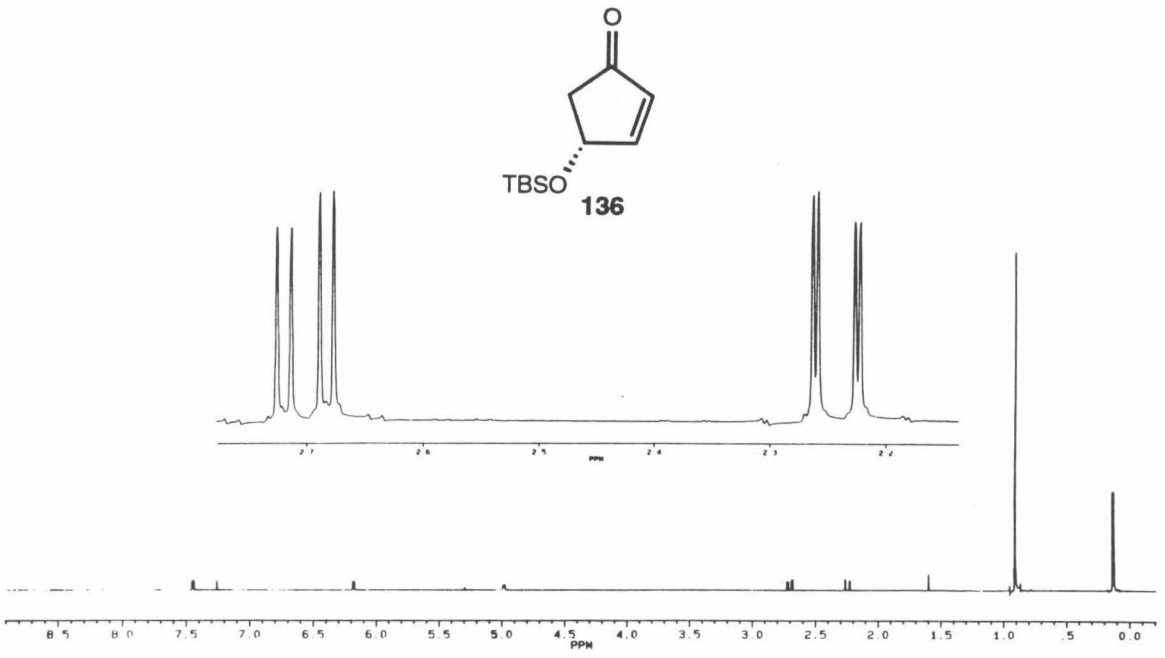

O
AcO
134
4000
3500
3000
2500
2000
1500
1000
cm⁻¹


O
HO

135

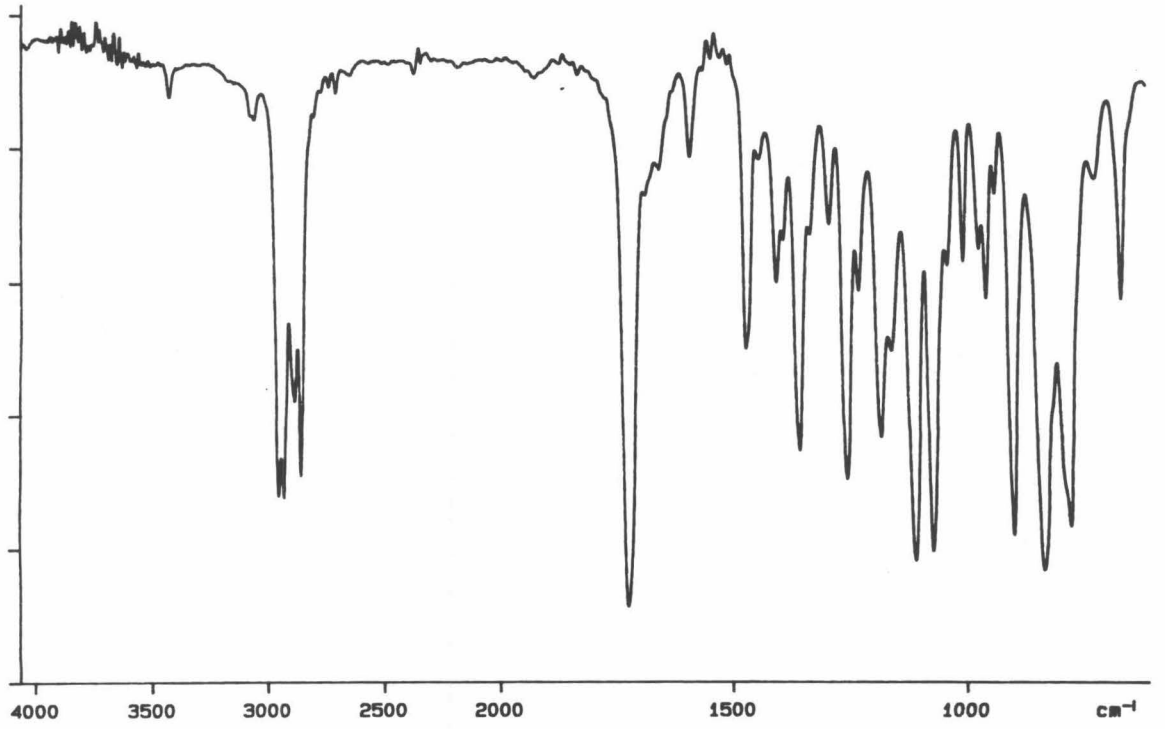

8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
PPM
4.0
3.5
3.0
2.5
2.0
1.5
1.0
.5
0.0
-.5

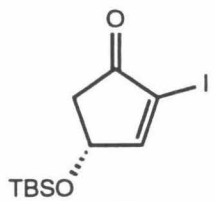

4000
3500
3000
2500
2000
1500
1000
cm⁻¹


O
TBSO

136

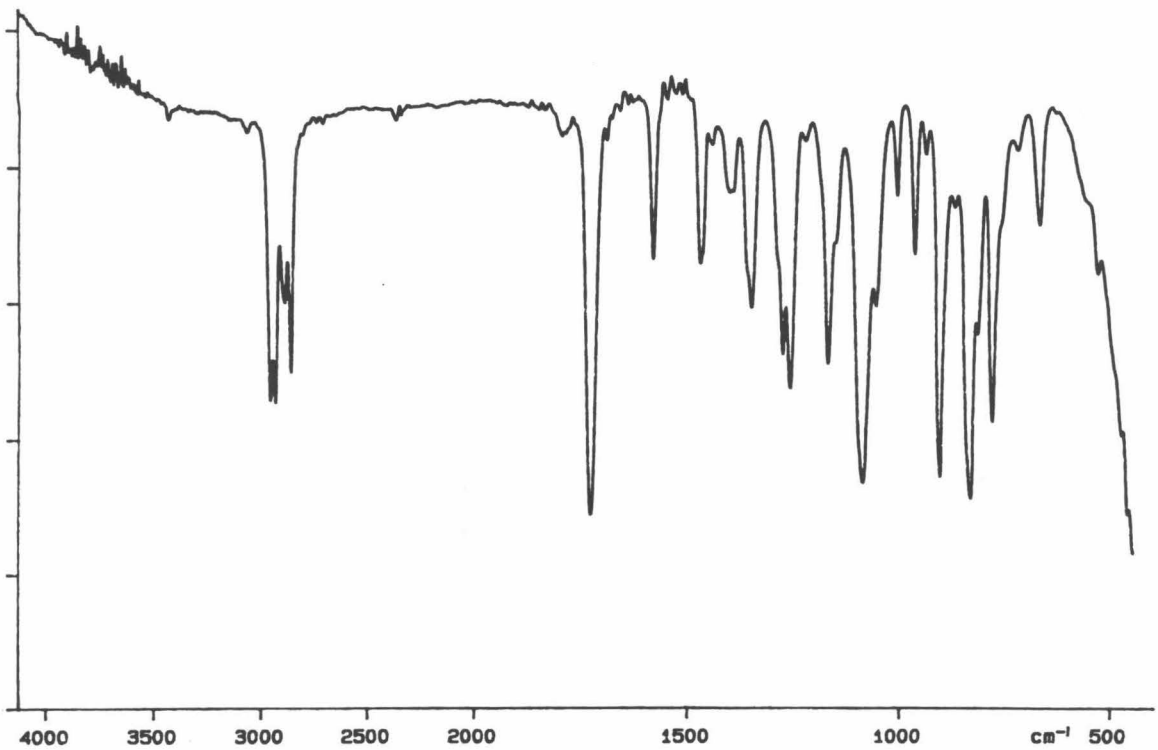
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
PPM
4.0
3.5
3.0
2.5
2.0
1.5
1.0
.5
0.0

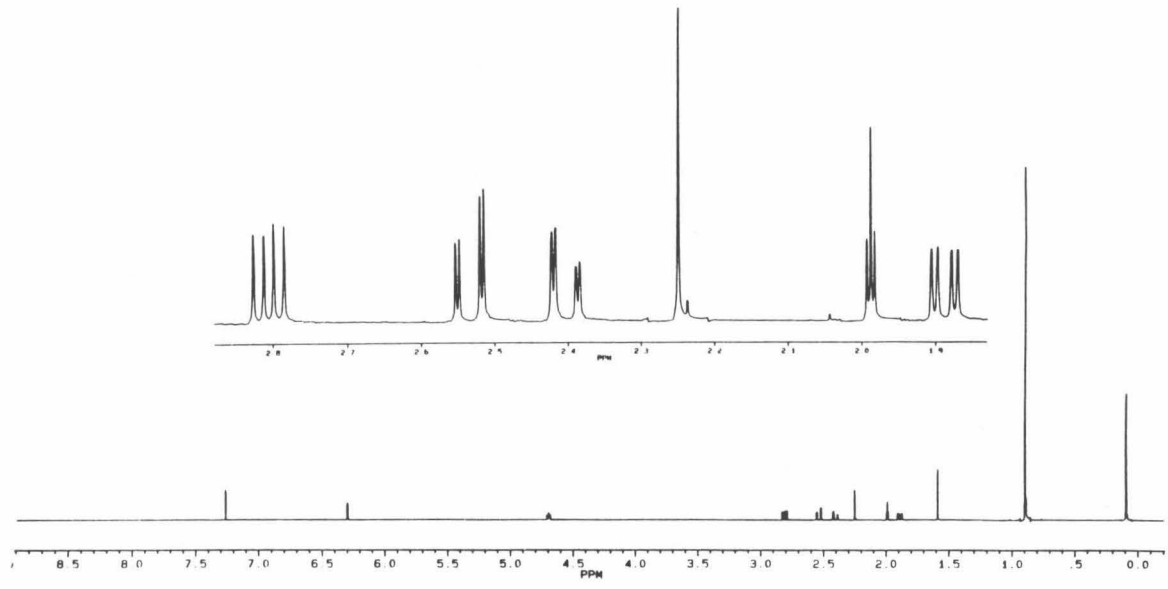

4000
3500
3000
2500
2000
1500
1000
cm⁻¹

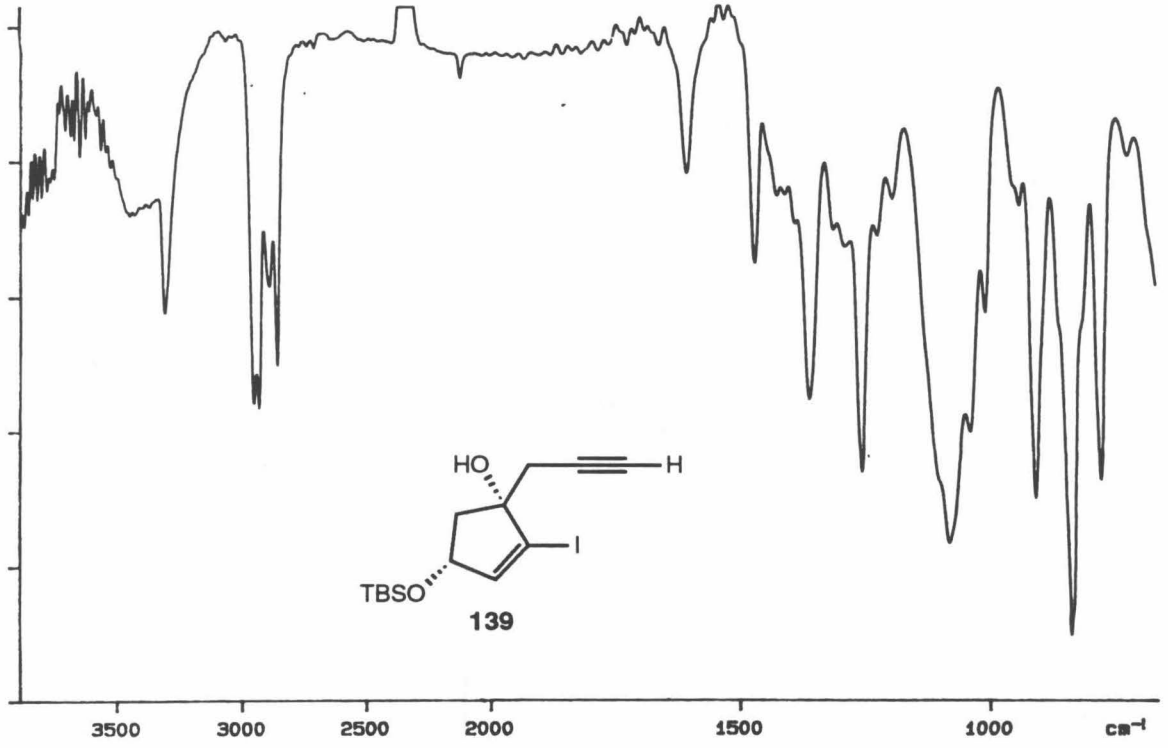

O
I
TBSO

137

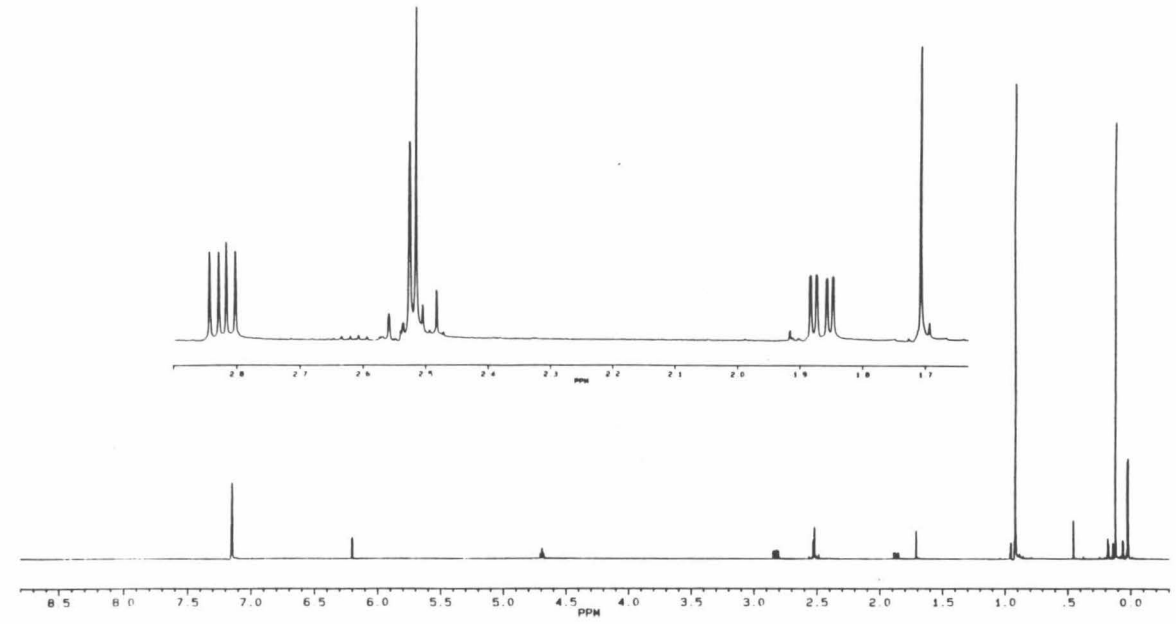
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
PPM
4.0
3.5
3.0
2.5
2.0
1.5
1.0
.5
0.0

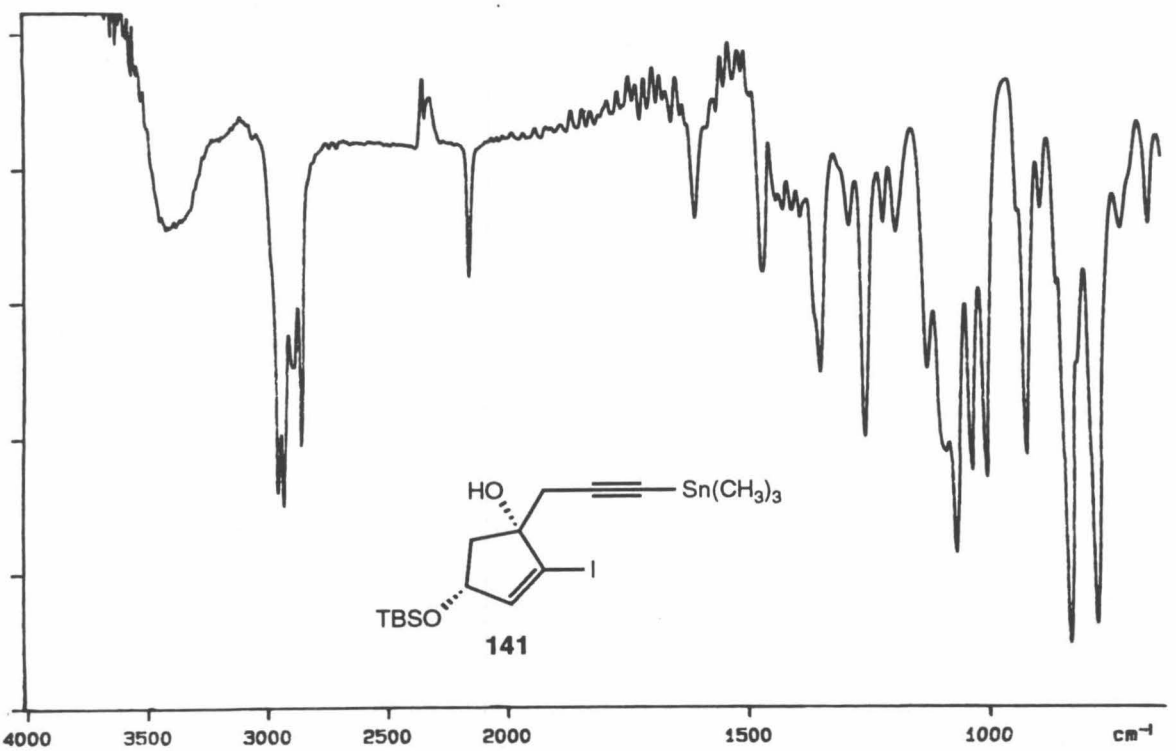

4000
3500
3000
2500
2000
1500
1000
cm⁻¹
500


8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
.5
0.0
PPM

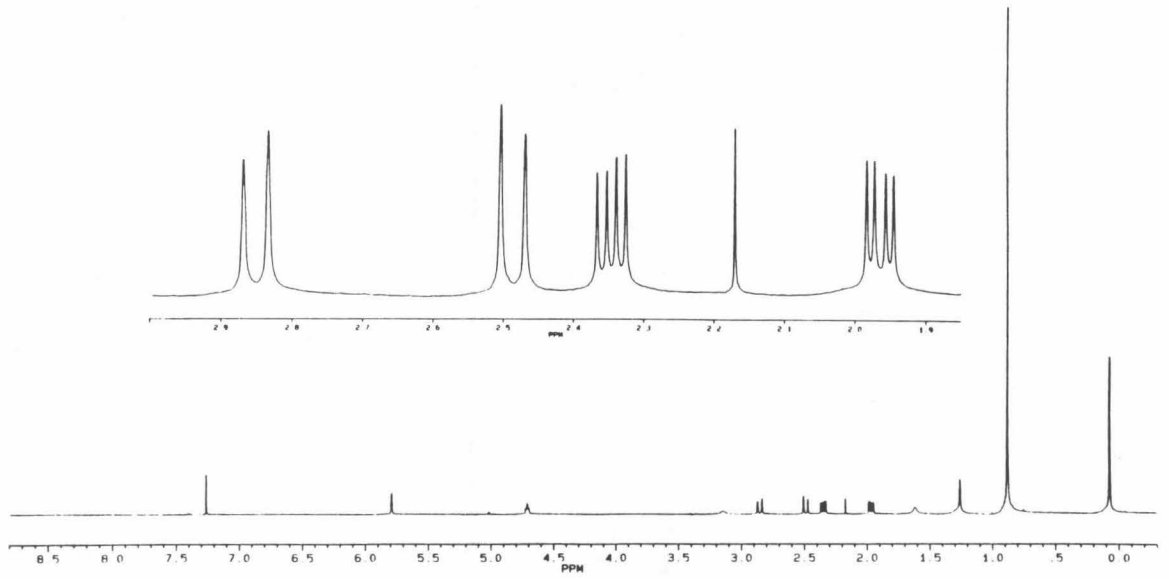

HO
H
I
TBSO
3500
3000
2500
2000
1500
1000
cm⁻¹

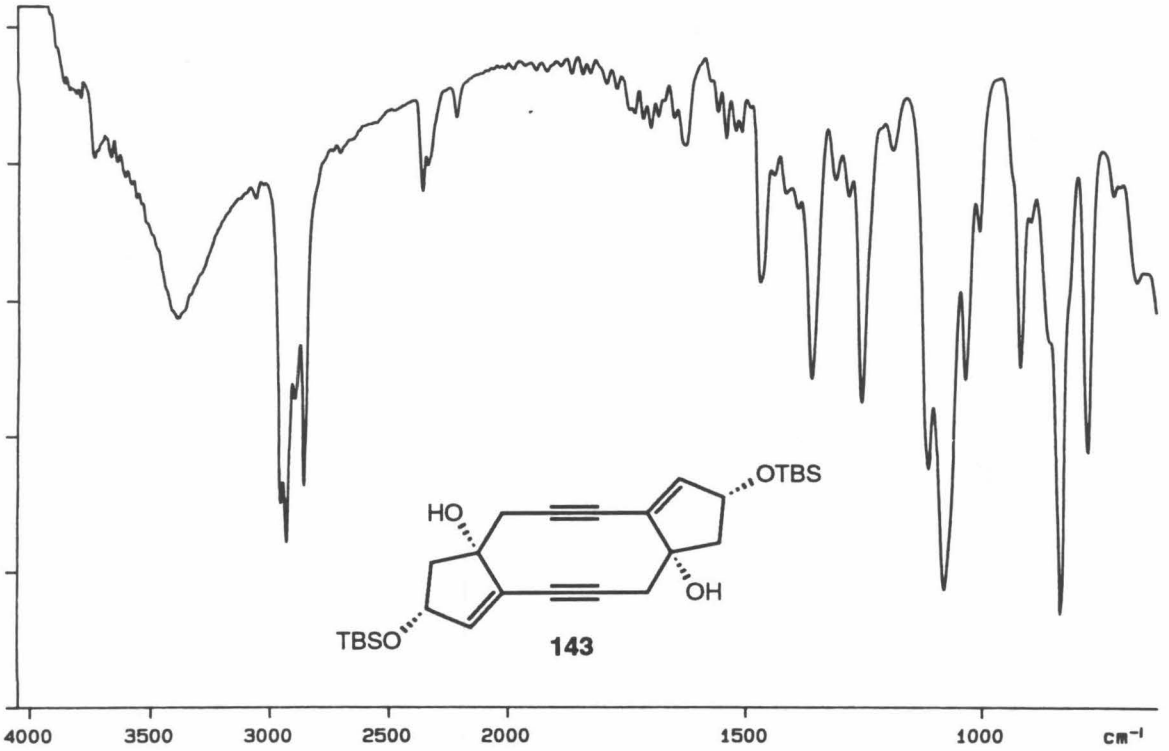
139


8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
PPM
4.0
3.5
3.0
2.5
2.0
1.5
1.0
.5
0.0


HO
Sn(CH3)3
I
TBSO
4000
3500
3000
2500
2000
1500
1000
cm-1

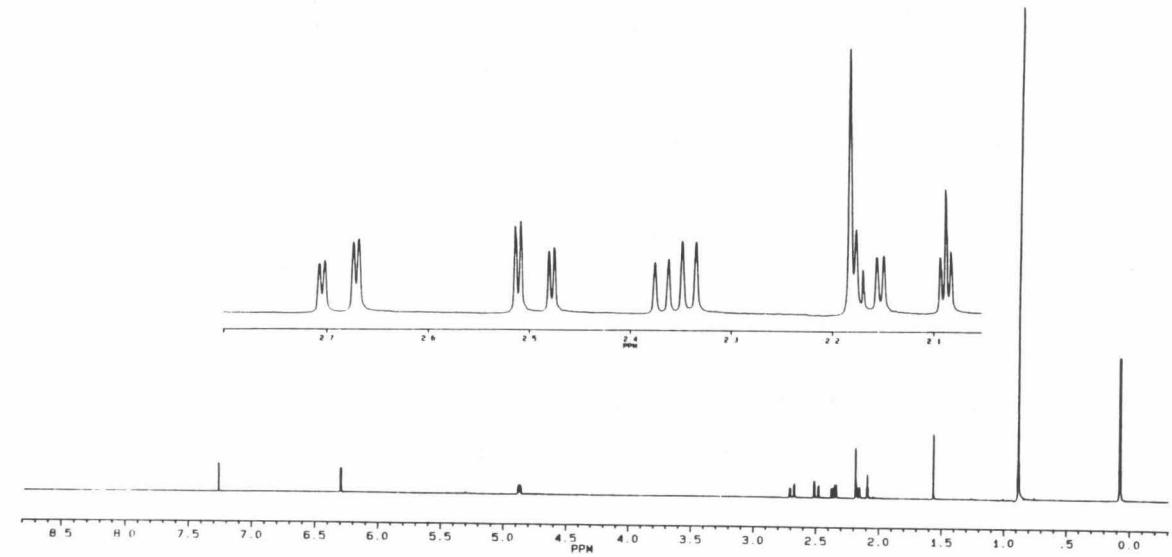
141

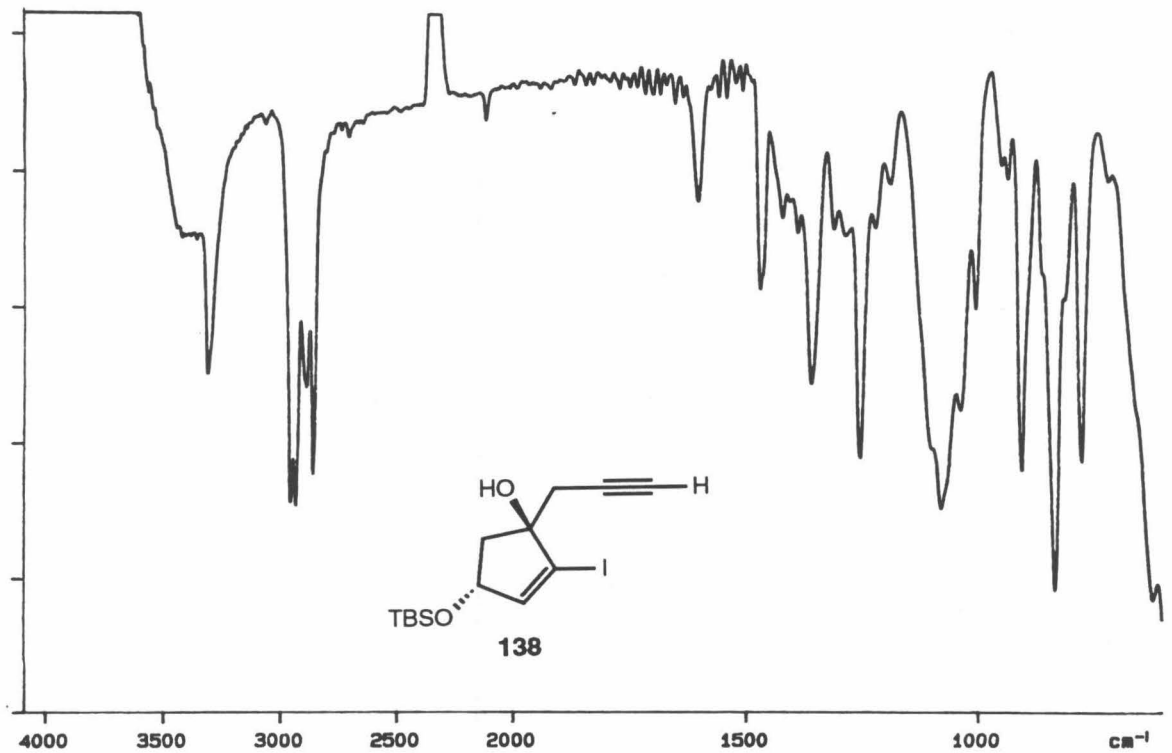

8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
.5
0.0
PPM


4000
3500
3000
2500
2000
1500
1000
cm⁻¹

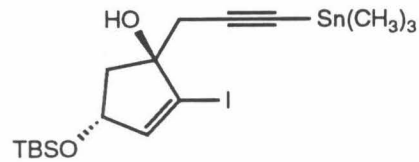
HO
OTBS
OH
TBSO

143

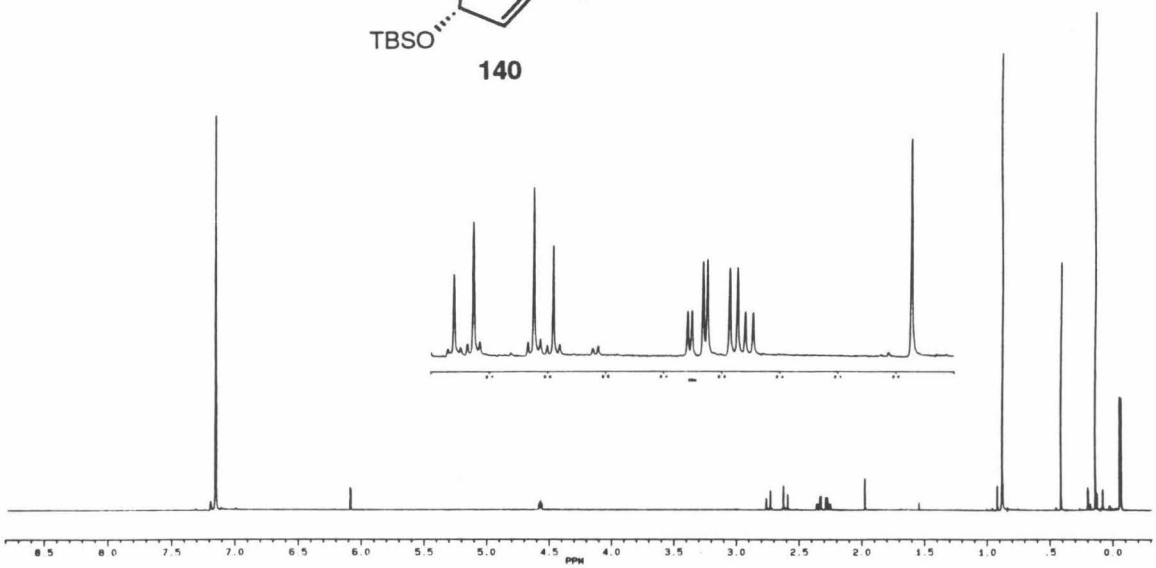

8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
PPM
4.0
3.5
3.0
2.5
2.0
1.5
1.0
.5
0.0

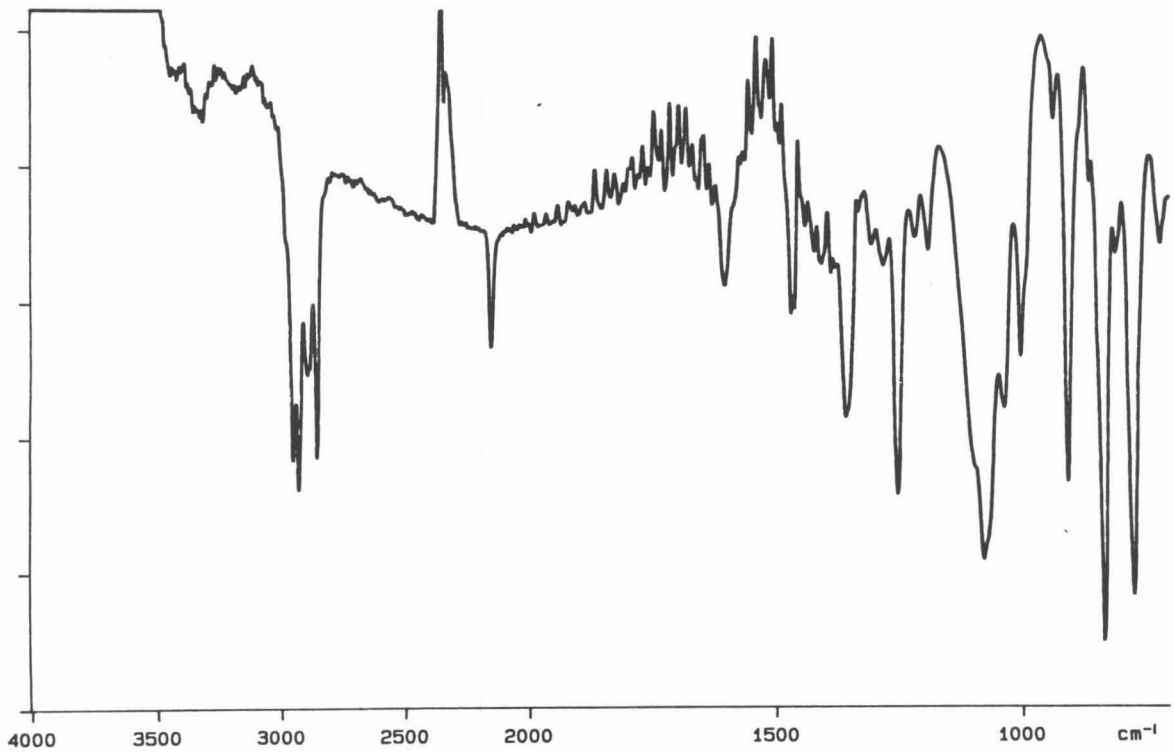

HO
H
I
TBSO
4000
3500
3000
2500
2000
1500
1000
cm⁻¹

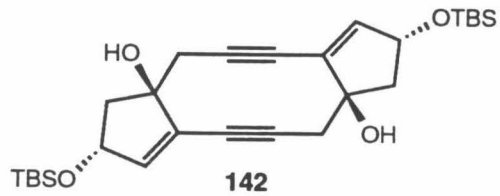
138


HO
Sn(CH3)3
I
TBSO

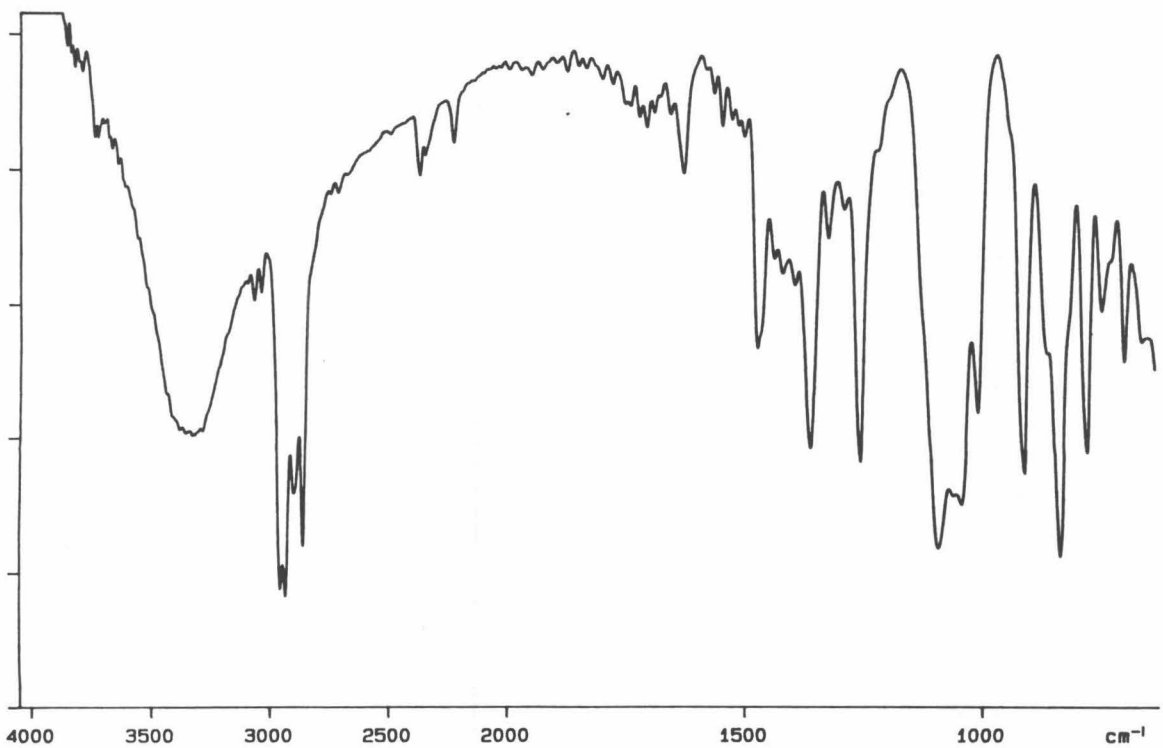
140

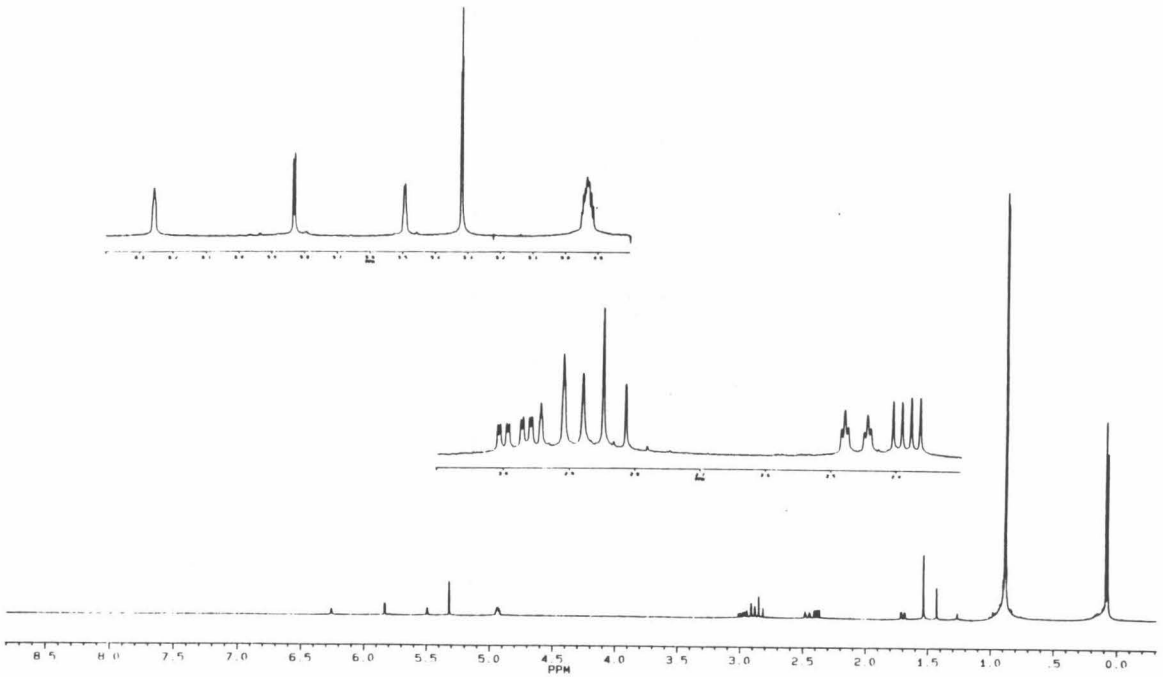

8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
PPM
4.0
3.5
3.0
2.5
2.0
1.5
1.0
.5
0.0

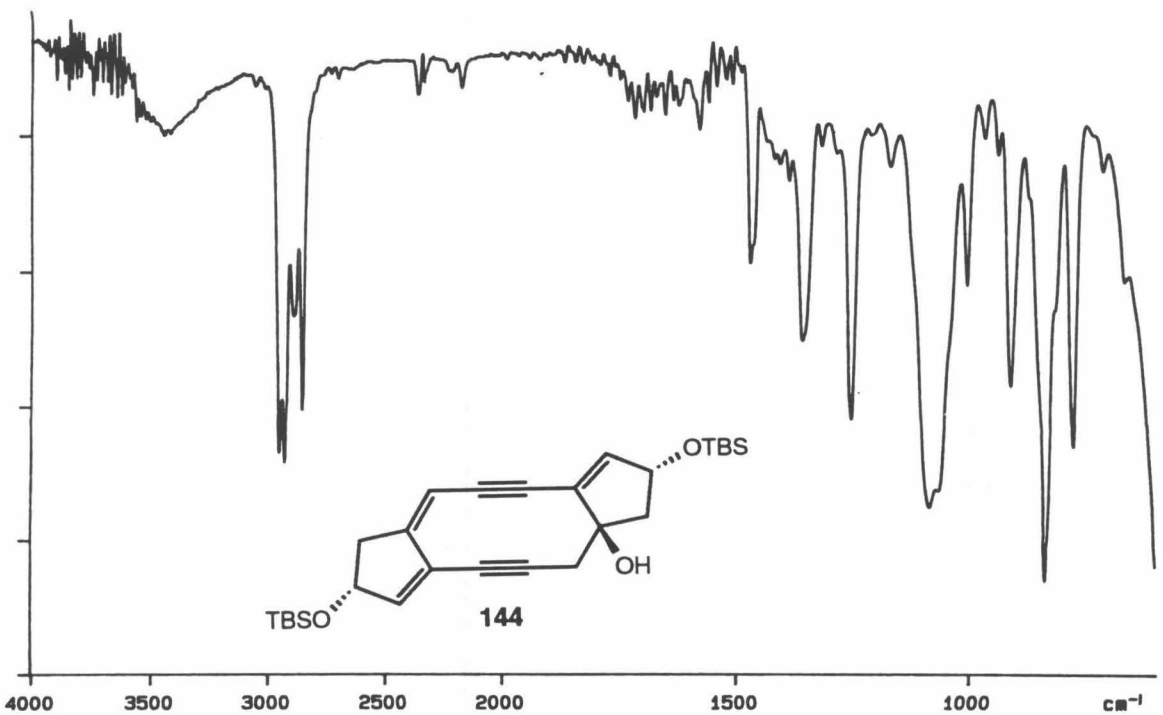

4000
3500
3000
2500
2000
1500
1000
cm-1

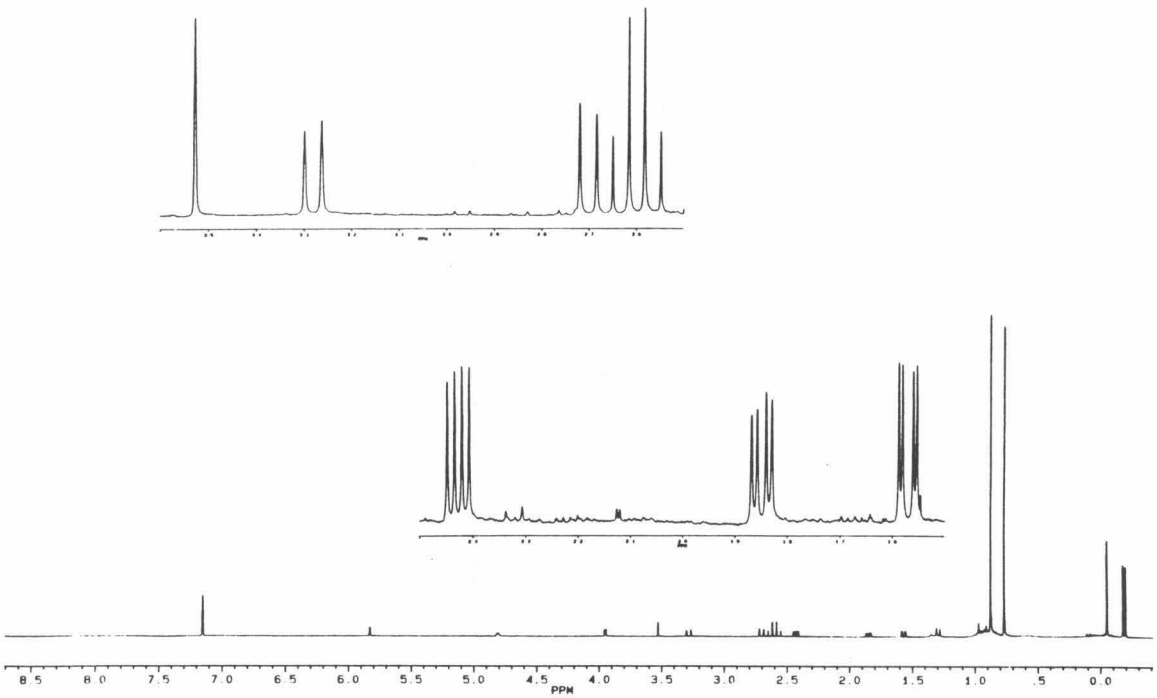


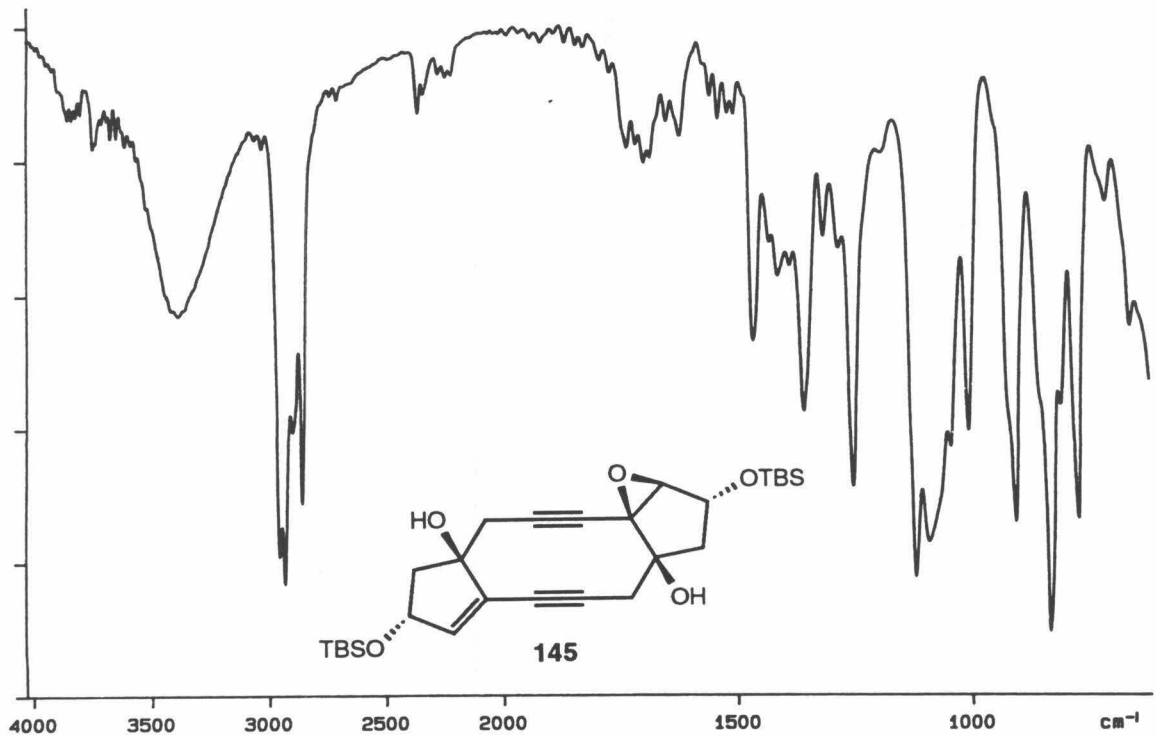
142

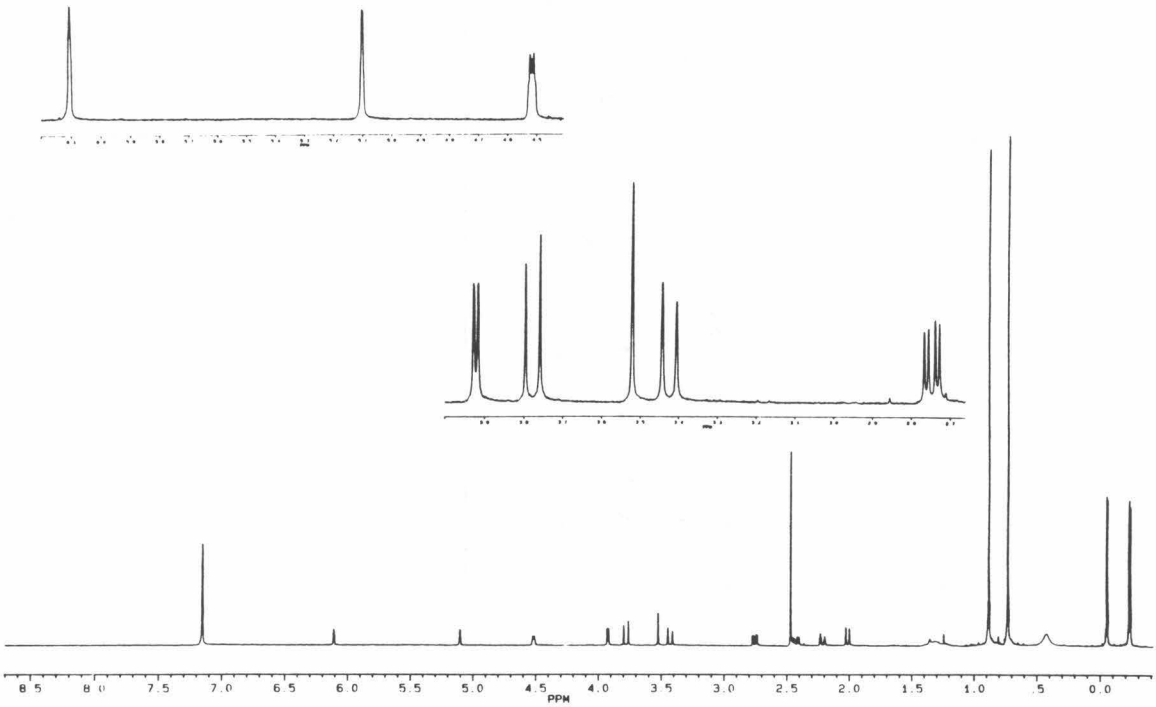


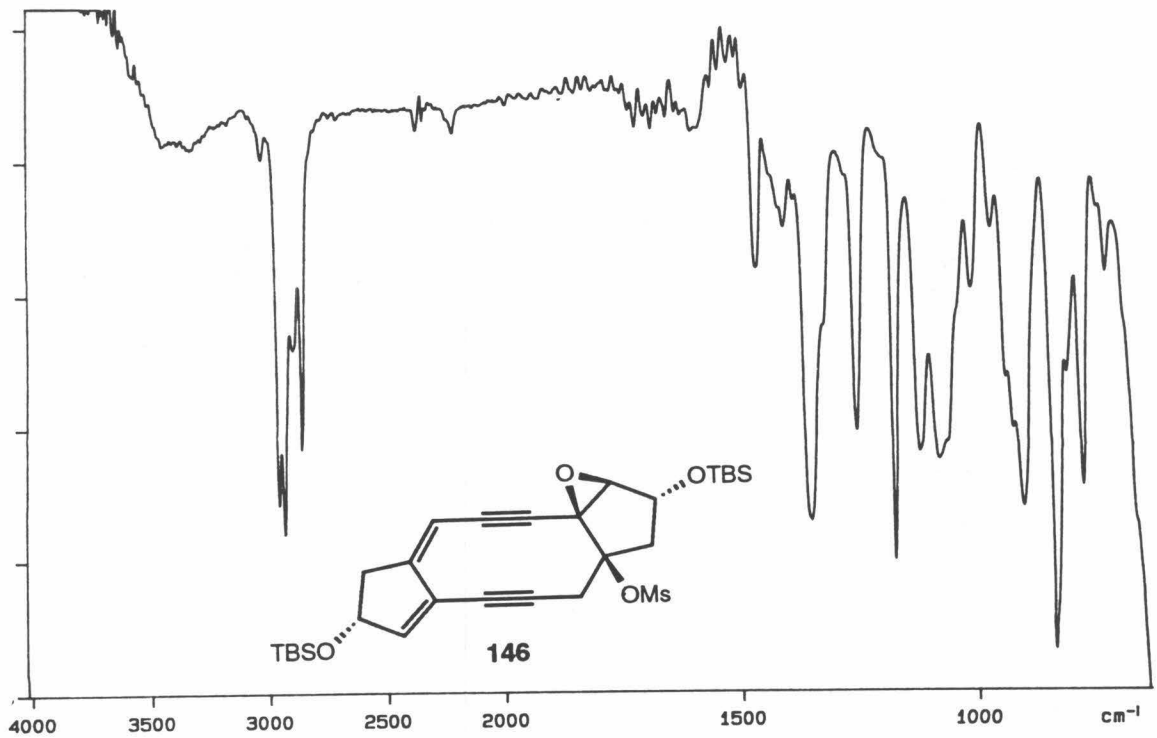

8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
PPM
4.0
3.5
3.0
2.5
2.0
1.5
1.0
.5
0.0

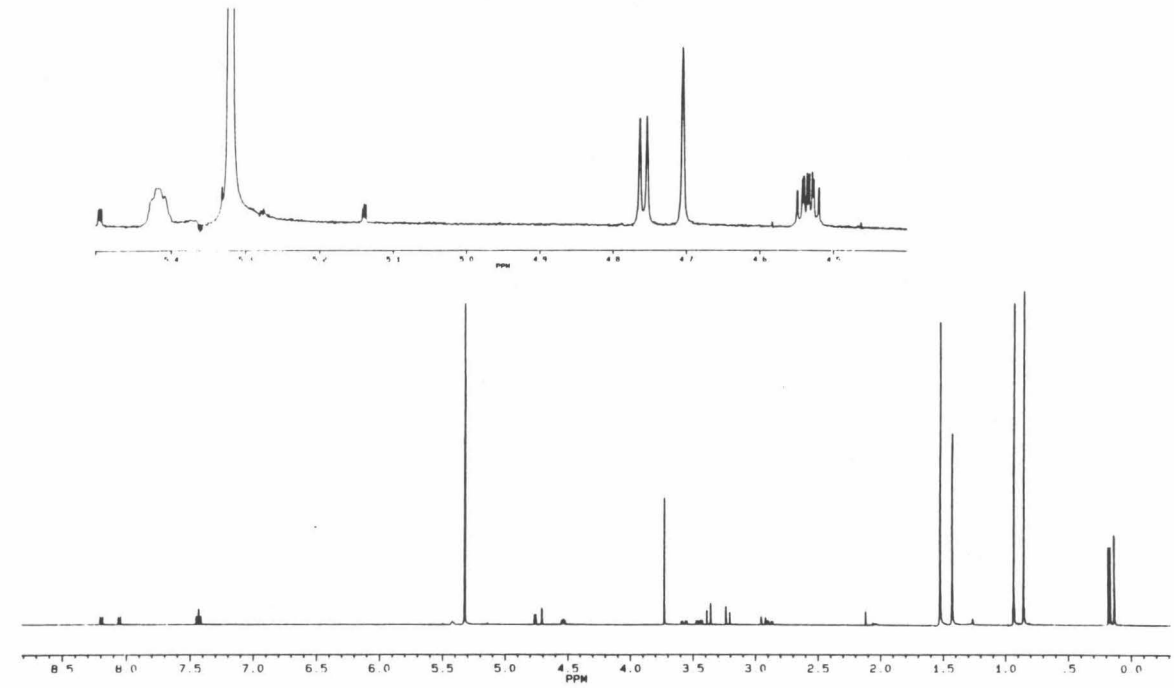

OTBS
OH
TBSO
144
4000
3500
3000
2500
2000
1500
1000
cm⁻¹

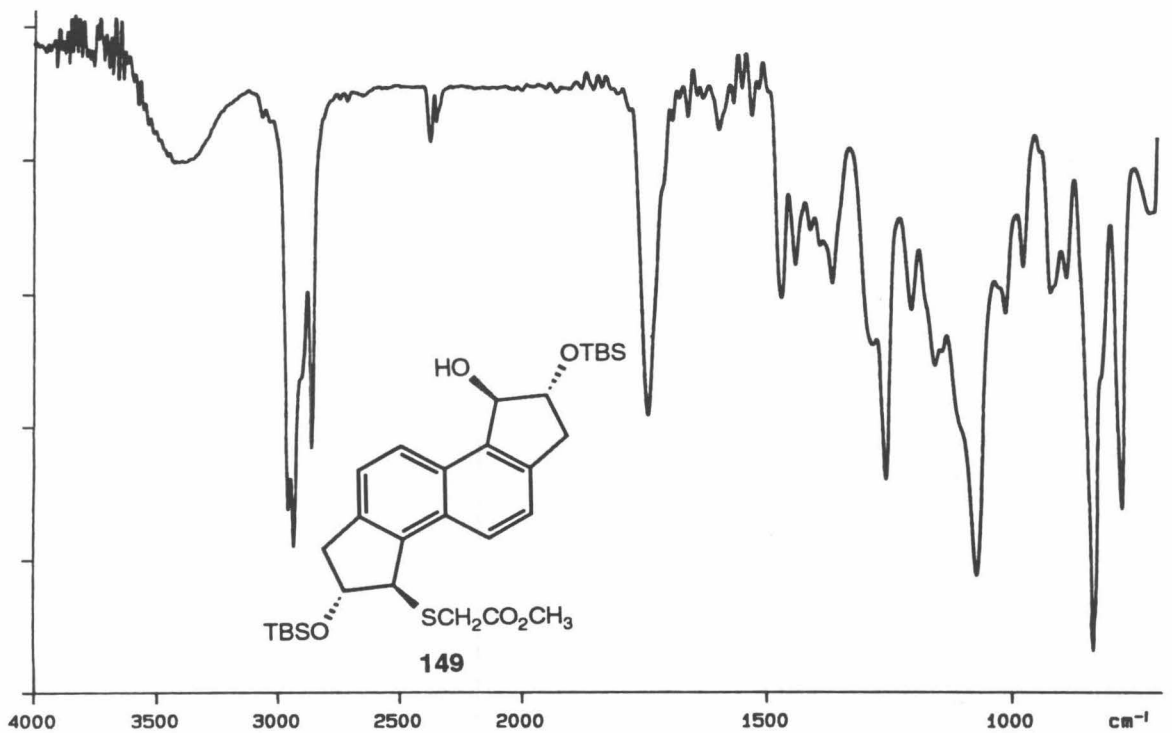

8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
PPM
4.0
3.5
3.0
2.5
2.0
1.5
1.0
.5
0.0

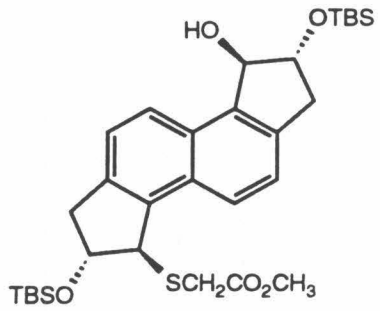

O
OTBS
HO
OH
TBSO
145
4000
3500
3000
2500
2000
1500
1000
cm⁻¹


8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
PPM
4.0
3.5
3.0
2.5
2.0
1.5
1.0
.5
0.0

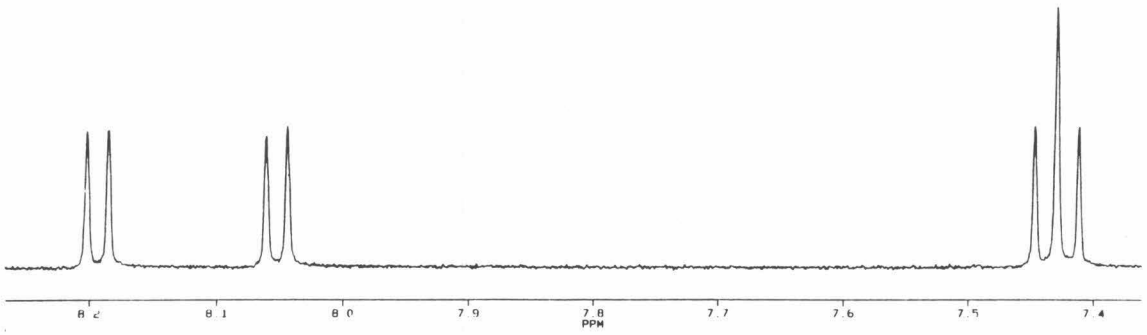

O
OTBS
OMs
TBSO
146
4000
3500
3000
2500
2000
1500
1000
cm⁻¹

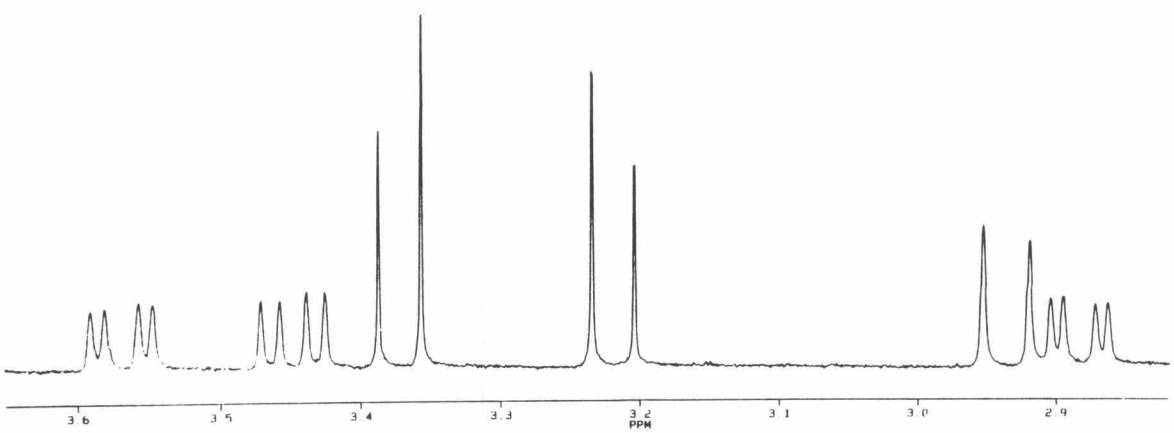

8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
PPM
4.0
3.5
3.0
2.5
2.0
1.5
1.0
.5
0.0

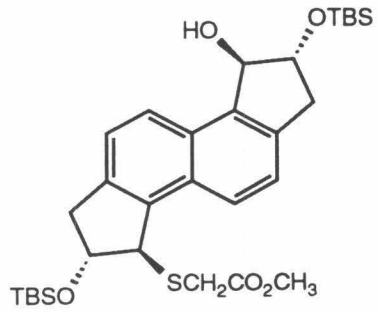

HO
OTBS
TBSO
SCH2CO2CH3
149
4000
3500
3000
2500
2000
1500
1000
cm-1


HO
OTBS
TBSO
SCH2CO2CH3

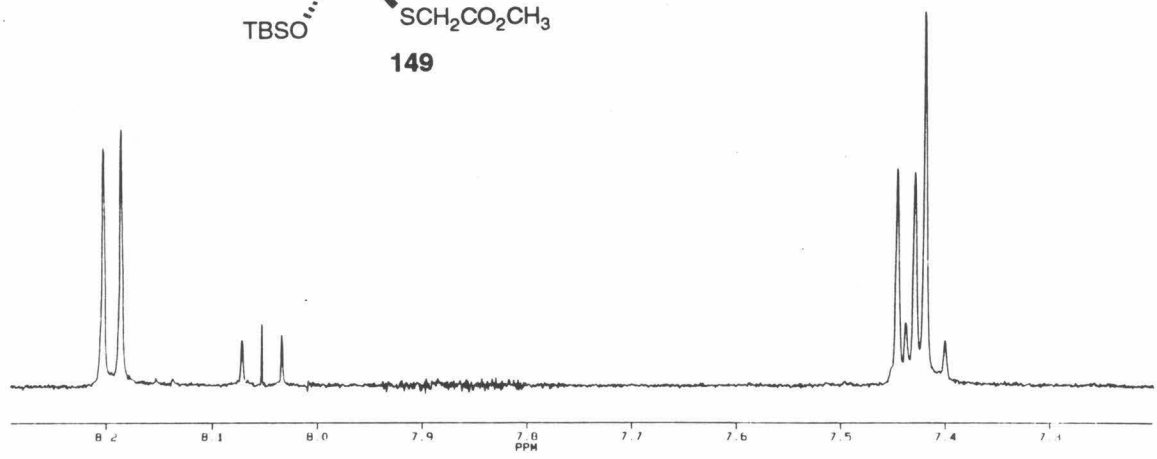
149

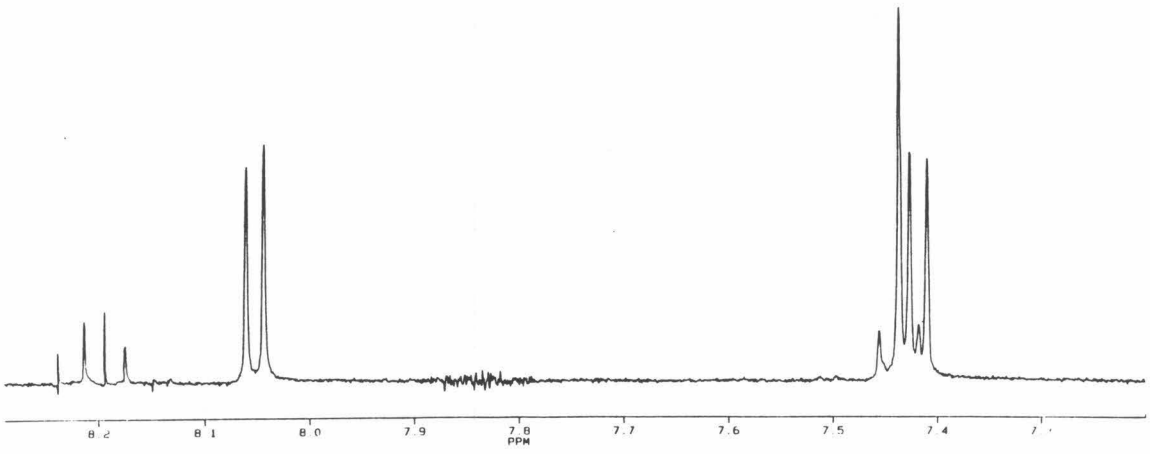

8.2
8.1
8.0
7.9
7.8
7.7
7.6
7.5
7.4
PPM

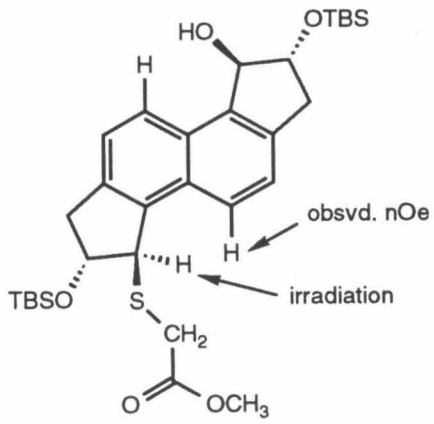

3.6
3.5
3.4
3.3
3.2
3.1
3.0
2.9
PPM


HO
OTBS
TBSO
SCH2CO2CH3

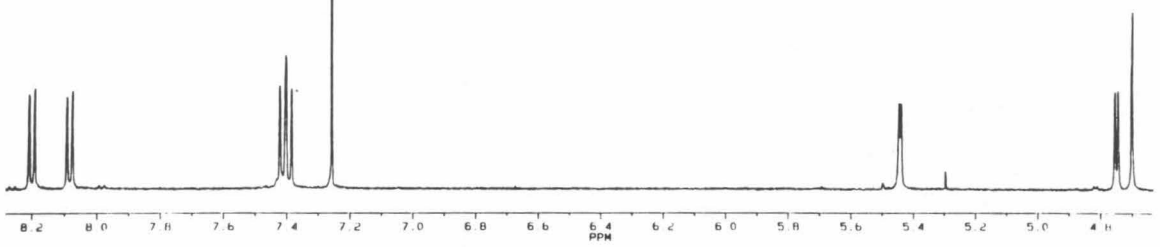
149

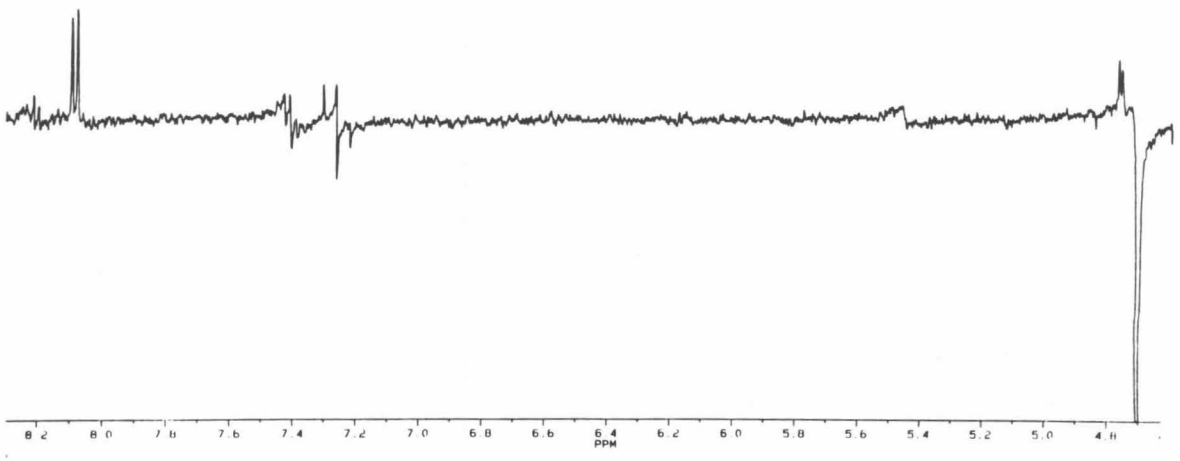

8.2
8.1
8.0
7.9
7.8
PPM
7.7
7.6
7.5
7.4

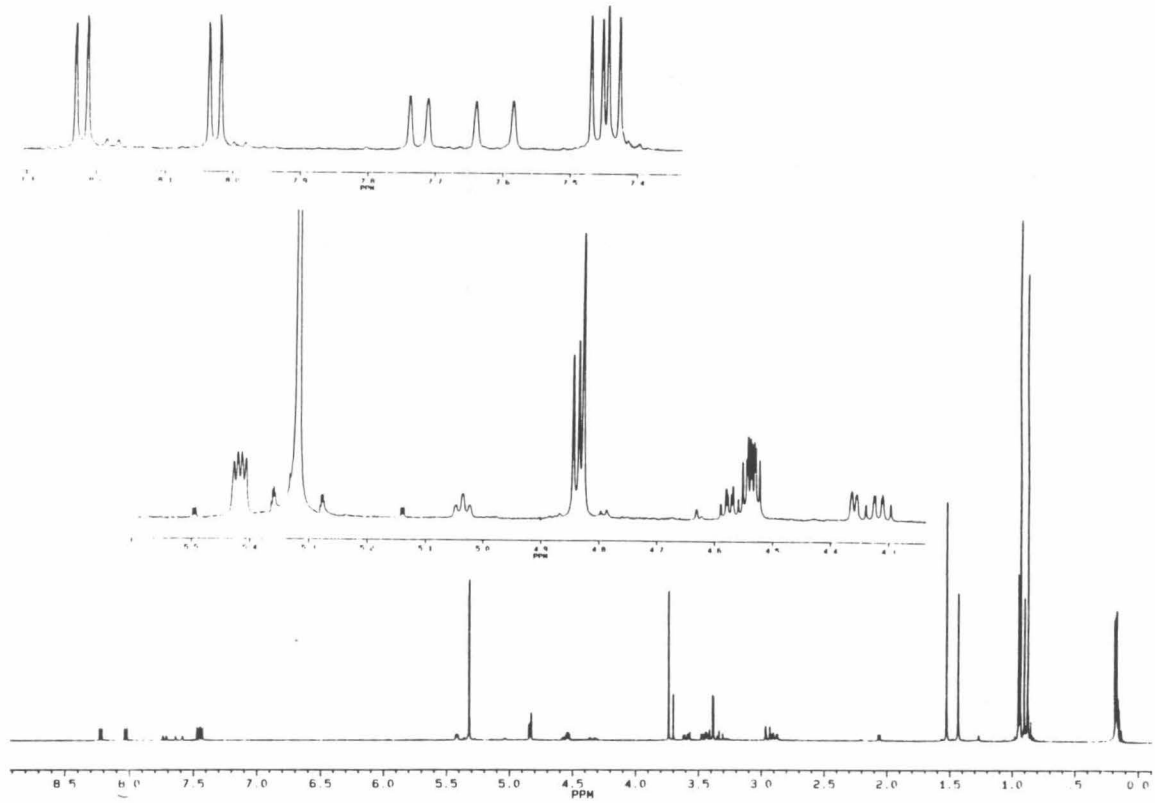

8.2
8.1
8.0
7.9
7.8
PPM
7.7
7.6
7.5
7.4

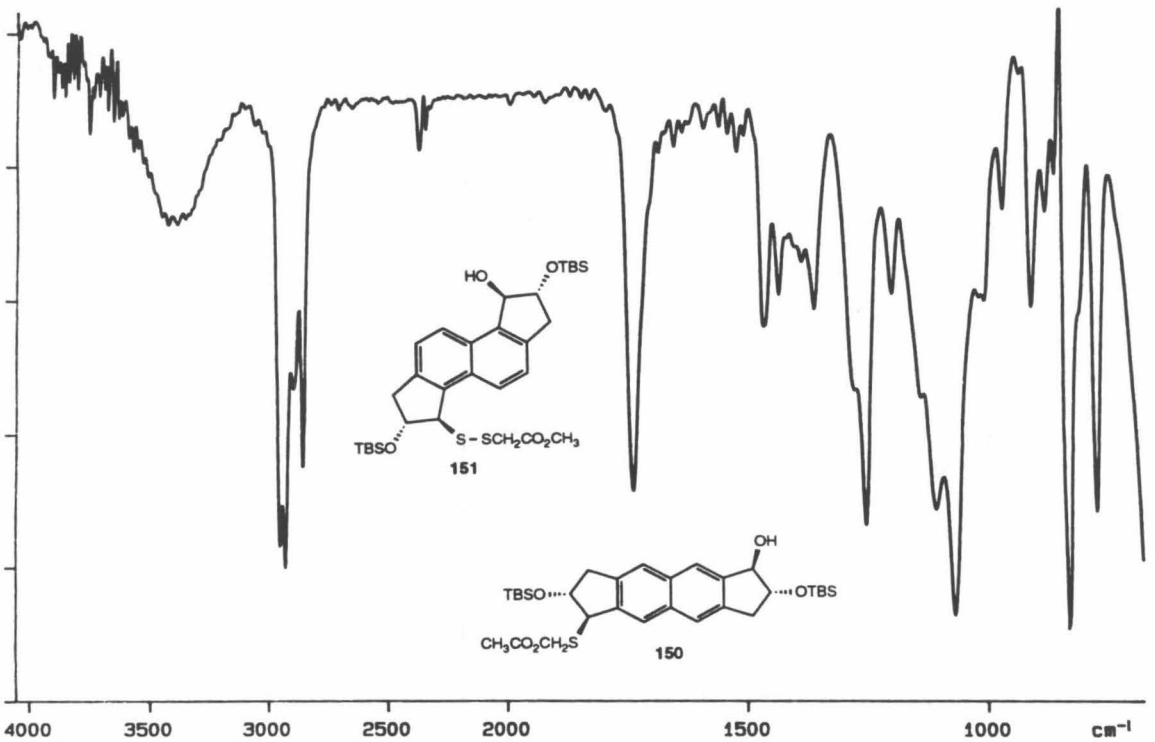

HO
OTBS
H
obsvd. nOe
H
H
irradiation
TBSO
S
CH2
O
OCH3

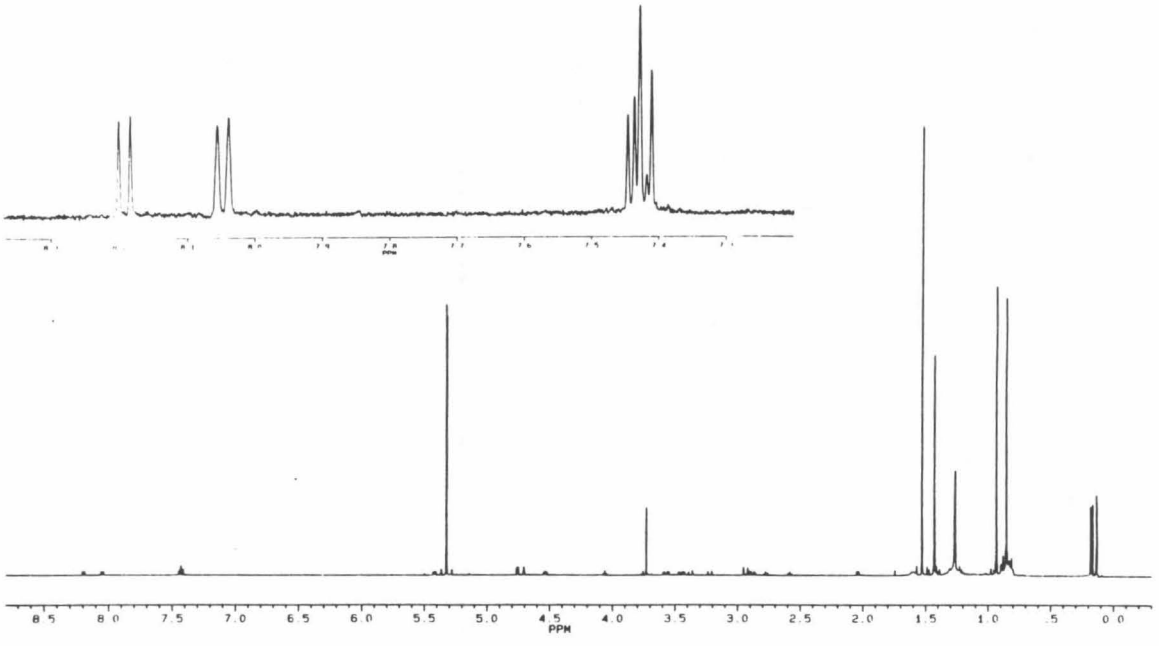
149

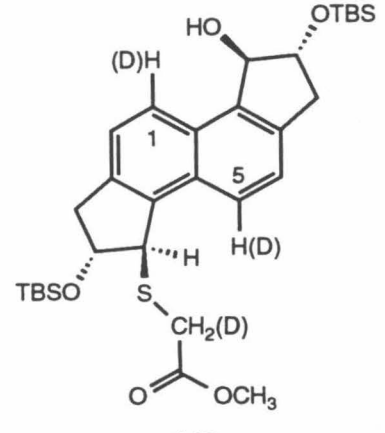

8.2
8.0
7.8
7.6
7.4
7.2
7.0
6.8
6.6
6.4
PPM
6.2
6.0
5.8
5.6
5.4
5.2
5.0
4.8


8.2
8.0
7.8
7.6
7.4
7.2
7.0
6.8
6.6
6.4
PPM
6.2
6.0
5.8
5.6
5.4
5.2
5.0
4.8

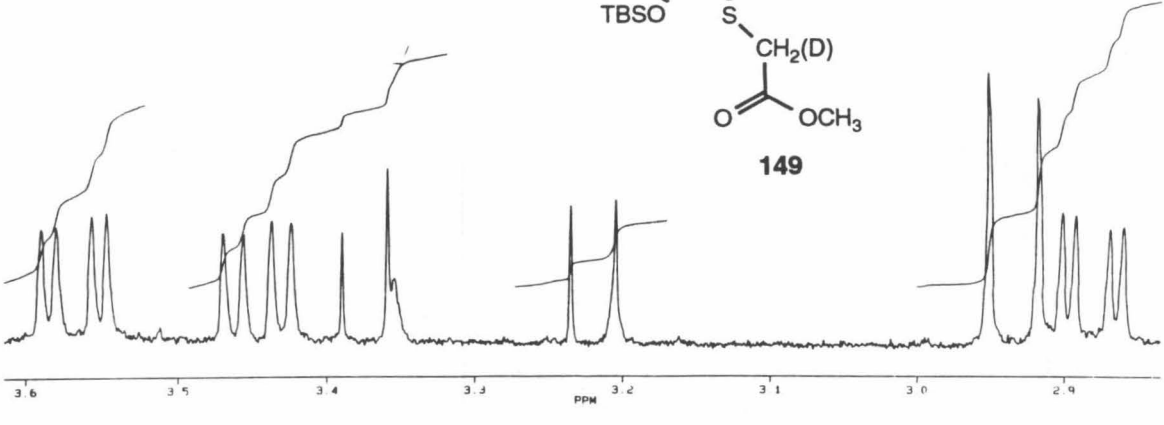

8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
PPM
4.0
3.5
3.0
2.5
2.0
1.5
1.0
.5
0.0

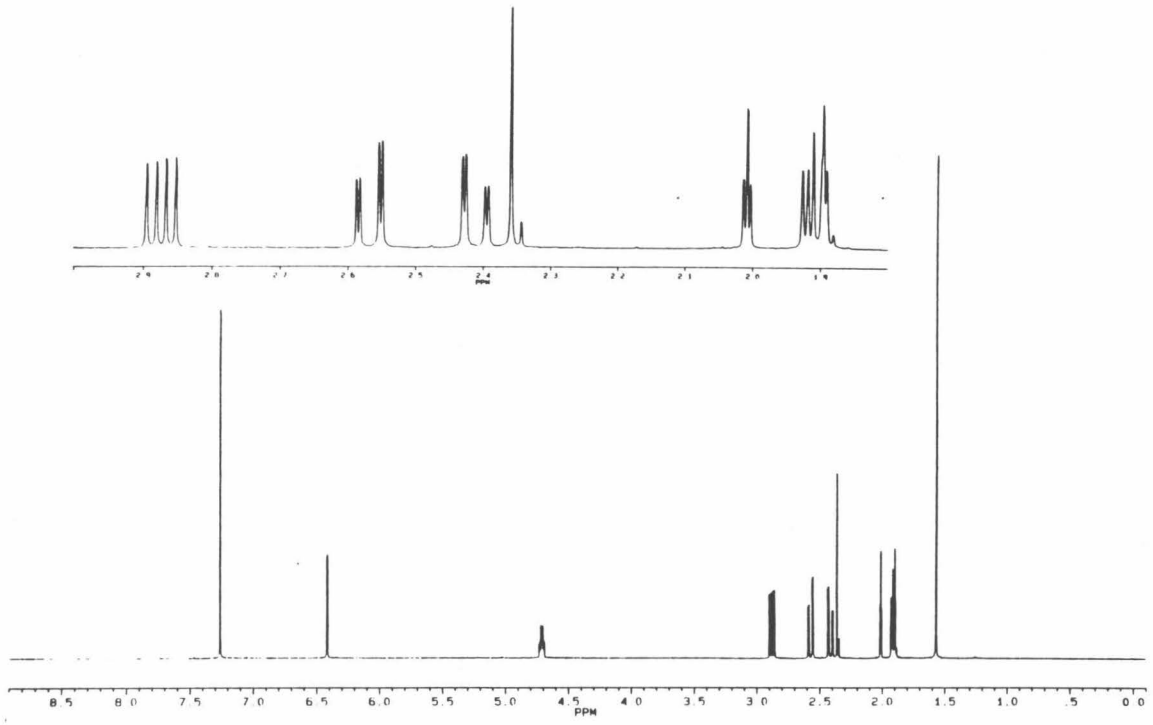

HO
OTBS
TBSO
S - SCH2CO2CH3
151
OH
TBSO
OTBS
CH3CO2CH2S
150
4000
3500
3000
2500
2000
1500
1000
cm-1

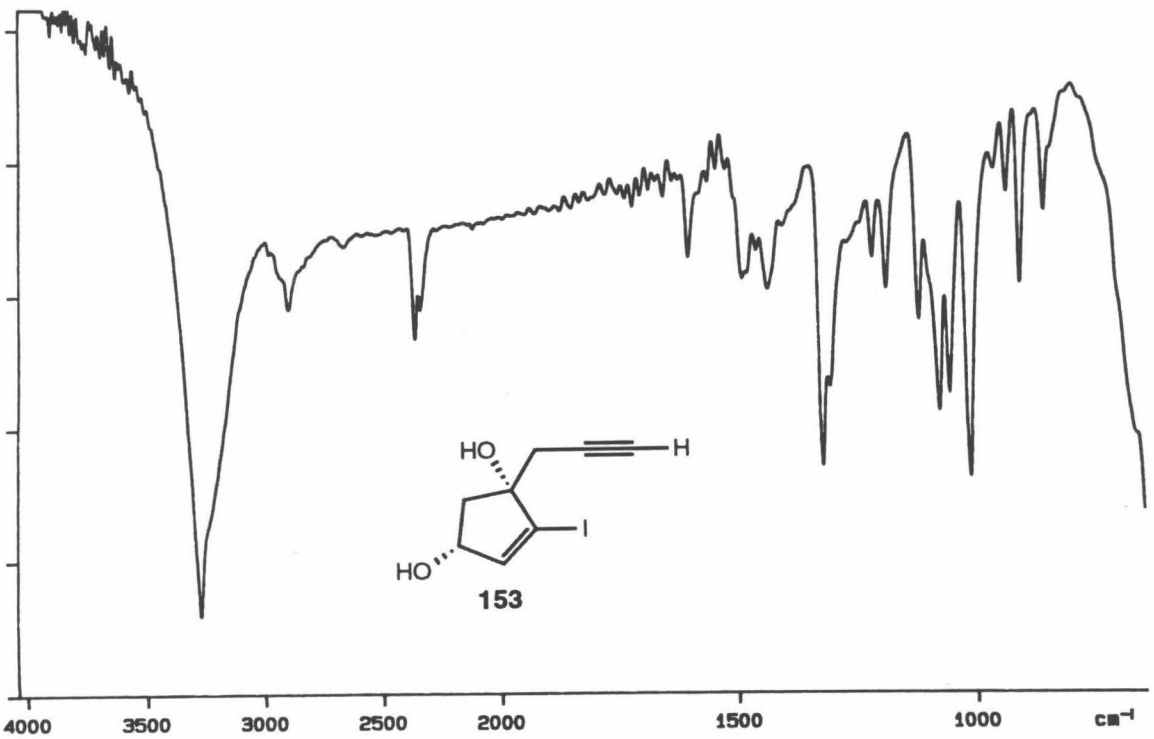

8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
.5
0.0
PPM


HO
OTBS
(D)H
1
5
H(D)
H
TBSO
S
CH2(D)
O
OCH3

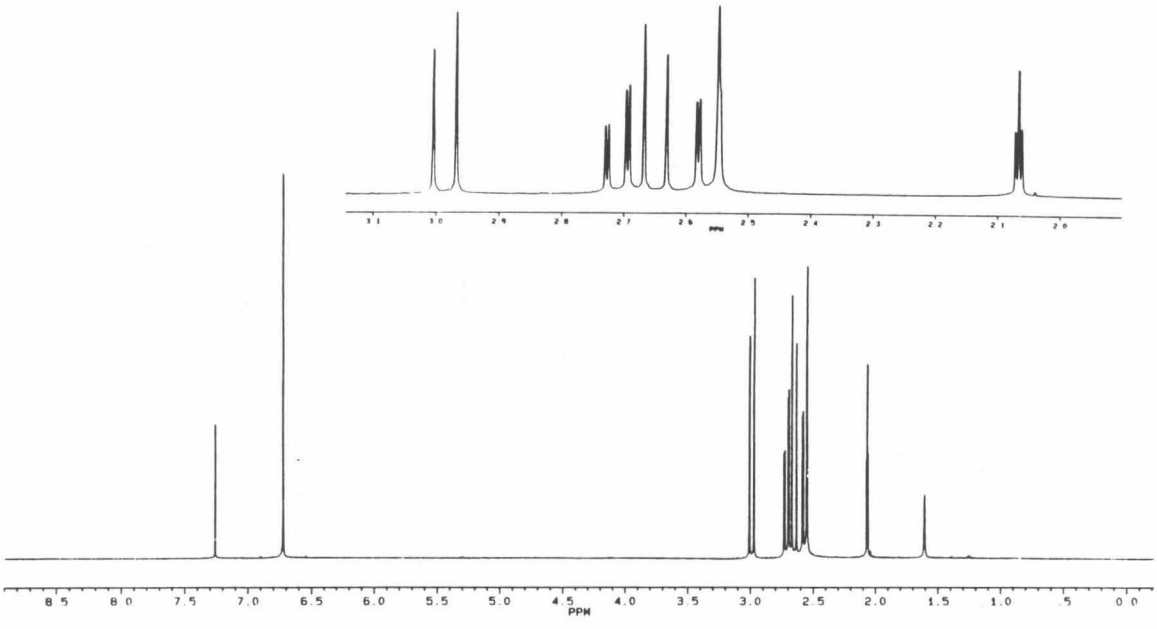
149

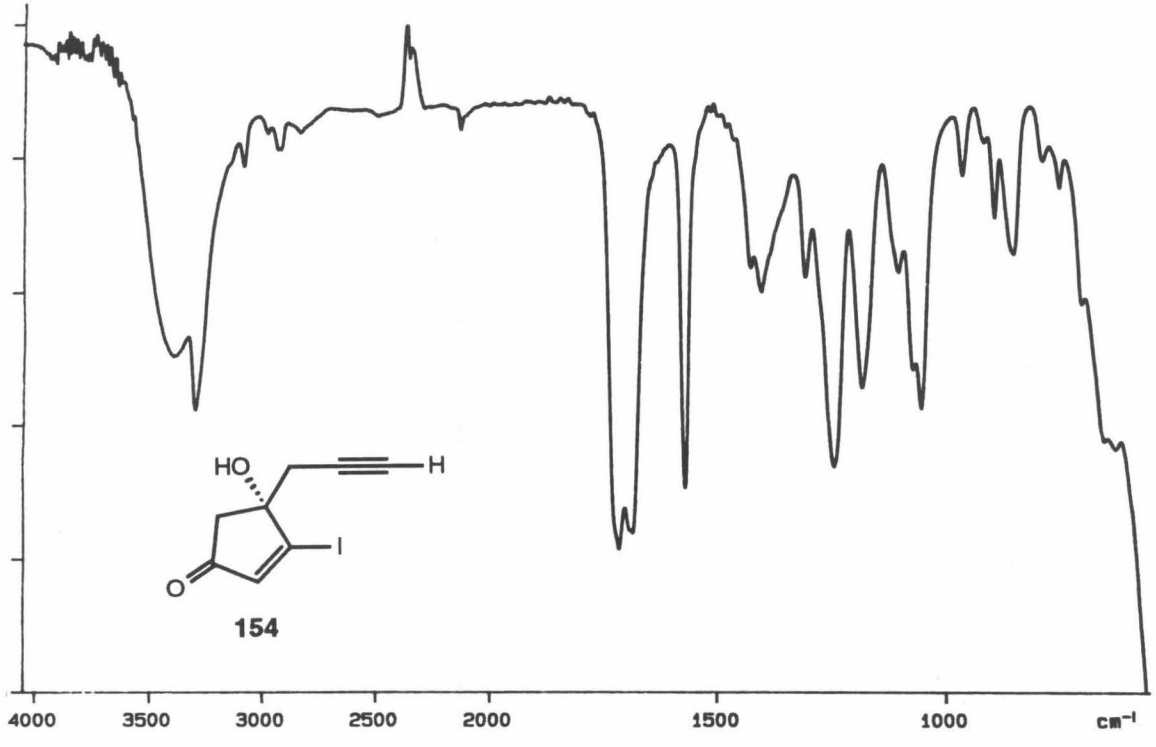

3.6
3.5
3.4
3.3
3.2
3.1
3.0
2.9
PPM


8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
PPM
4.0
3.5
3.0
2.5
2.0
1.5
1.0
.5
0.0

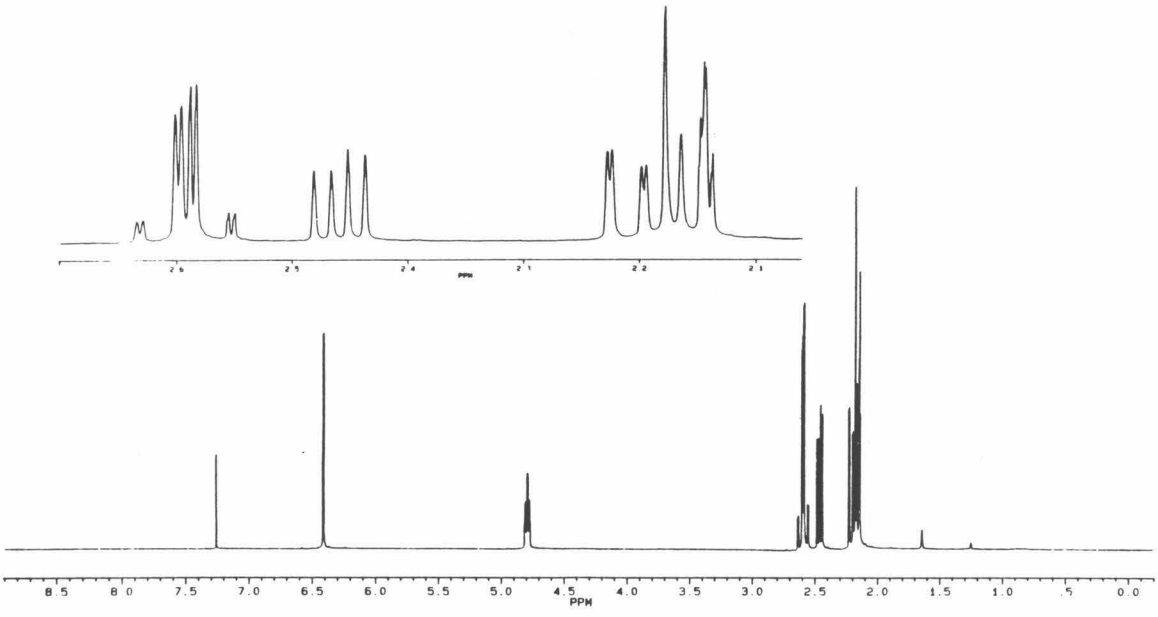

HO
H
I
HO
4000
3500
3000
2500
2000
1500
1000
cm⁻¹

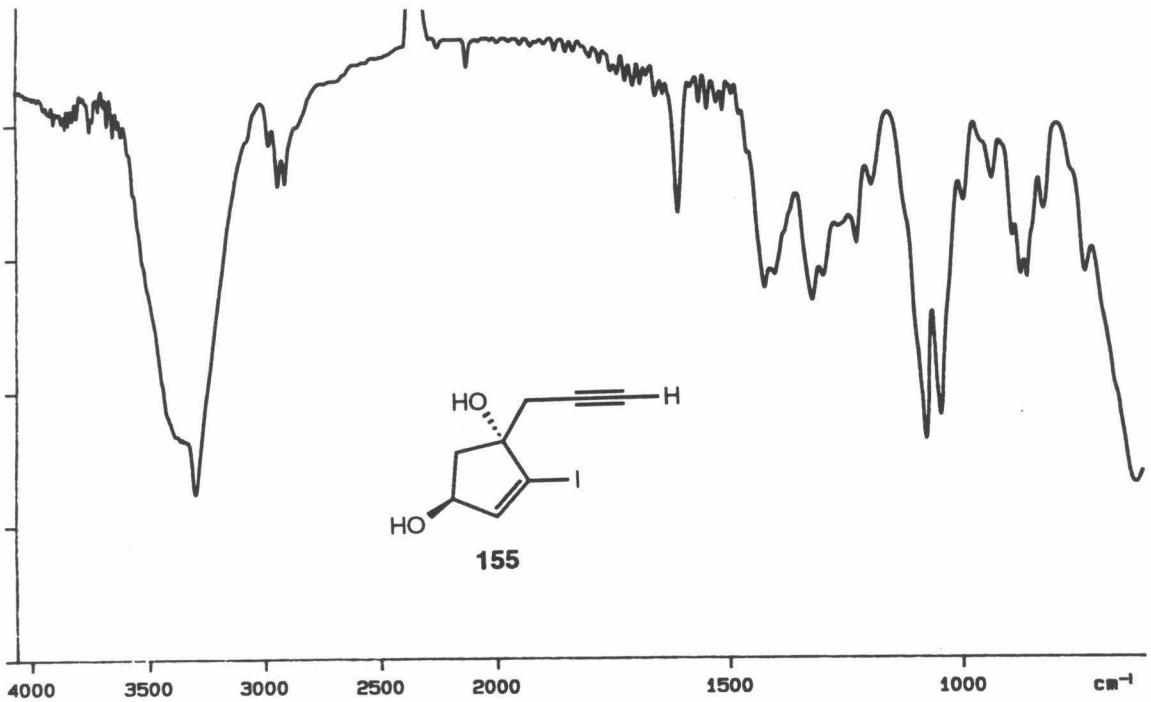
153


8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 .5 0.0
PPM


HO
H
I
O
4000
3500
3000
2500
2000
1500
1000
cm⁻¹

154


8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
.5
0.0
PPM


HO
H
I
HO
4000
3500
3000
2500
2000
1500
1000
cm⁻¹

155

Index of Products

Index of Products (cont'd.)

Product	Experimental	Spectra
103	186	369
104	188	370
105	190	371
106	192	372
107	194	373
108	196	374
109	198	375
110	200	376
112	202	-
113	204	377
114	206	378
115	210	380
116	214	381
118	217	382
118(d_2)	218	383
123	265	228
129	240	385
130	242	386
131	243	387-388
132	243	387-388
134	246	389
135	248	390
136	250	391
137	252	392
138	254	396
139	254	393
140	257	397
141	260	394
142	258	398
143	261	395

Product	Experimental	Spectra
144	263	399
145	266	400
146	268	401
149	272	402
150	274	406
151	276	406
153	278	408
154	280	409
155	282	410
156	284	396