I. Thermal Cyclization of (*Z*)-1,2,4-Heptatrien-6-yne

II. Studies Directed toward the Synthesis of Neocarzinostatin Chromophore

Thesis by

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In Partial Fulfillment of the Requirements

for the Degree of

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Listen for the sound of shattering glass.

Susan Katz Miller

Acknowledgment

First of all, I would like to thank my advisor, Prof. Andrew G. Myers, for teaching me my craft, so to speak, and for the support he has given me. I consider it a privilege to have been one of his first students.

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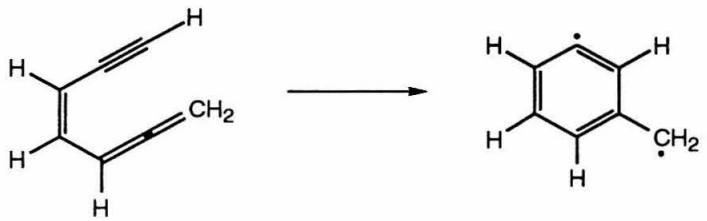
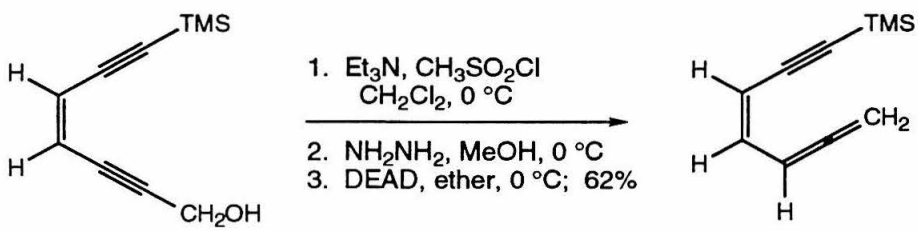
Lastly, I would like to thank the Eastman Kodak Company for my graduate fellowship. They have always treated me with kindness and generosity, and I am grateful.

Abstract

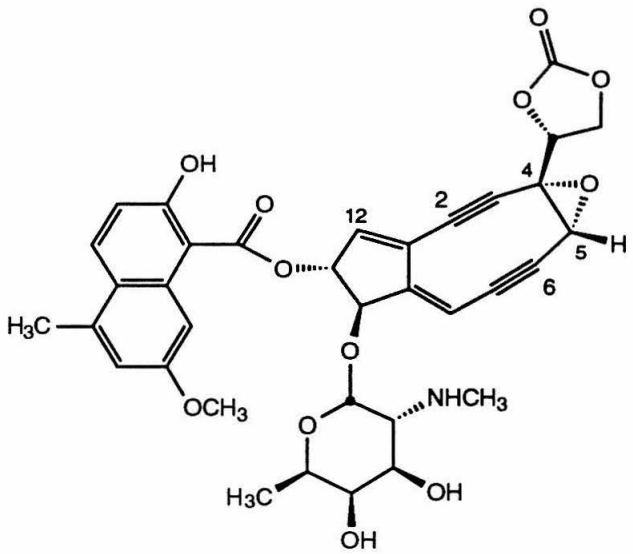
The possibility that the hydrocarbon (*Z*)-1,2,4-heptatrien-6-yne might undergo a thermal cyclization to the biradical α,3-dehydroluene was considered. A methodology



for the synthesis of (*Z*)-1,2,4-heptatrien-6-yne was developed wherein propargyl hydrazines, obtained from the corresponding propargyl alcohols, were oxidized to allenes with diethyl azodicarboxylate in good yields. The formation of products consistent with the intermediacy of the biradical α,3-dehydrotoluene is discussed.

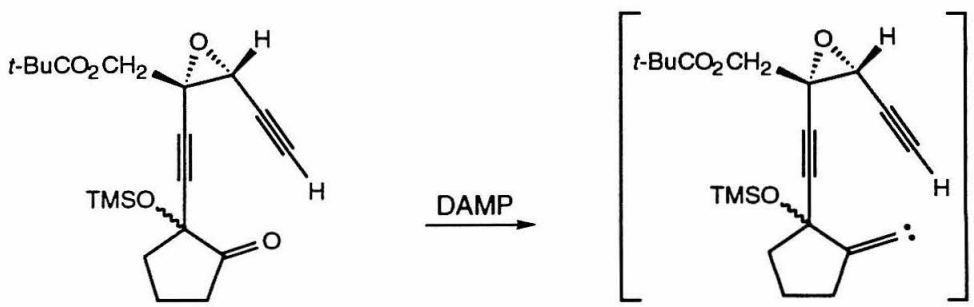


In studies directed toward the total synthesis of neocarzinostatin chromophore, the attempted formation of the cyclononadiyne core of the molecule via the intramolecular insertion of an alkylidene carbene into an acetylenic carbon-hydrogen bond was investigated. The alkylidene carbene was generated from the appropriately



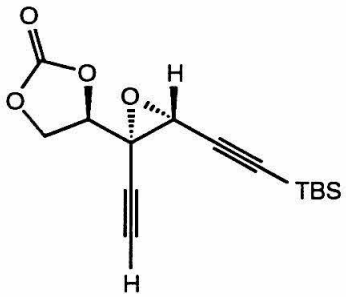
Neocarzinostatin Chromophore

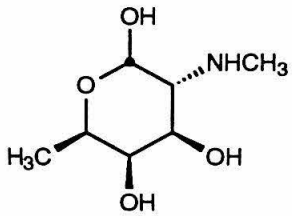
functionalized cyclopentanone precursor with the reagent dimethyl diazomethylphosphonate (DAMP). While the identification of the reaction products was consistent with the formation of the desired carbene, the formation of the desired insertion product was not observed. In conjunction with studies seeking to synthesize



neocarzinostatin chromophore via an intramolecular acetylide addition, the synthesis of an epoxy carbonate fragment to be used in the convergent synthesis of a suitable

cyclization precursor is described, as well as initial efforts concerning glycosylation with a suitably protected *N*-methyl D-fucosamine derivative.





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List of Abbreviations[1]

Å	angstrom
Ac	acetyl
AIBN	2,2'-azobisisobutyronitrile
Ar	aryl
Boc	benzyloxycarbonyl
Boc-ON	2-(*tert*-butoxycarbonyloxyimino)-2-phenylacetonitrile
Bpoc	2-(4-biphenylyl)propyloxycarbonyl
Bu	butyl
Bz	benzyl
°C	degree Celsius
cal	calorie
CAN	ceric ammonium nitrate
COSY	correlation spectroscopy
CSA	camphorsulfonic acid
DAMP	dimethyl diazomethylphosphonate
DBU	1,8-diazobicyclo[5.4.0]undec-7-ene
DCC	1,3-dicyclohexylcarbodiimide
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
Ddz	2-(3,5-dimethoxyphenyl)propyloxycarbonyl
DEAD	diethyl azodicarboxylate

[1] Abbreviations used in the compilation of spectral data are defined in the beginning of each experimental section.

dec	decomposition
DET	diethyl tartrate
DHP	dihydrofuran
DIBAL-H	diisobutylaluminum hydride
DIPHOS	1,2-bis(diphenylphosphino)ethane
DMAP	4-dimethylaminopyridine
DME	1,2-dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DMPM	3,4-dimethoxybenzyl
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

Im	imidazole
IR	infrared
J	coupling constant
k	rate constant
kcal	kilocalorie
L	liter
LDA	lithium diisopropylamide
lut	lutidine
m	meta
M	molar
MCPBA	*meta*-chloroperbenzoic acid
Me	methyl
mg	milligram
MHz	megahertz
min	minute
mL	milliliter
mM	millimolar
mmol	millimole
mol	mole
mp	melting point
μL	microliter
n	normal
N	normal (concentration)
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect
p	para

PCC	pyridinium chlorochromate
PDC	pyridinium dichromate
pH	hydrogen ion concentration
Ph	phenyl
Piv	pivaloyl
Poc	2-phenylpropyloxycarbonyl
Pr	propyl
PTFA	pyridinium trifluoroacetate
pyr	pyridine
R	rectus
R_f	retention factor
S	entropy
S	sinister
t	tertiary
TBAF	tetrabutylammonium fluoride
TBHP	*tert*-butyl hydroperoxide
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
Ts	*para*-toluenesulfonyl

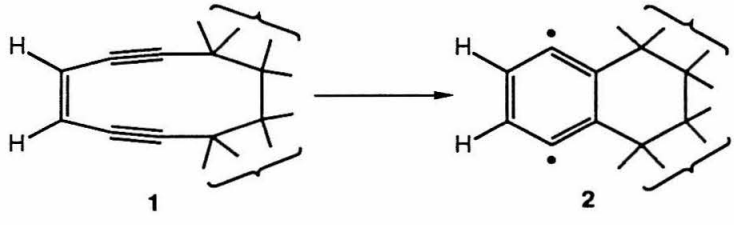
W	watt
w/v	weight-to-volume ratio
Z	zusammen

Chapter 1

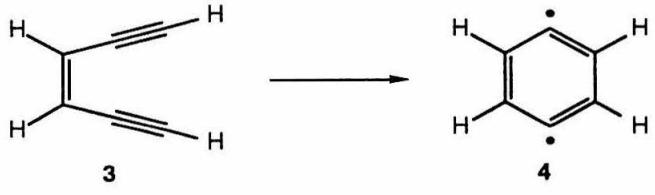
Thermal Generation of α,3-Dehydrotoluene from (*Z*)-1,2,4-Heptatrien-6-yne

Introduction[1]

Several lines of evidence now support the intermediacy of 1,4-biradicals as a common feature in the mechanism of action of the class of natural antitumor antibiotics comprising neocarzinostatin chromophore, calichemicin, esperamicin, and dynemicin (the enediyne antibiotics).[2] These biradical intermediates are proposed to arise by electrocyclization of highly unsaturated precursors, formed from the native antibiotic as the result of a prior chemical "activation" step. In the case of the natural products calichemicin, esperamicin, and dynemicin, the cyclization may be generally represented by the transformation of (*Z*)-enediyne **1** to the dehydrobenzene derivative **2**, and is recognized to be a cyclic version of the thermal rearrangement of (*Z*)-3-hexene-1,5-diyne (**3**) to 1,4-dehydrobenzene (**4**) studied extensively by Bergman and coworkers, now known as the Bergman reaction.[3]

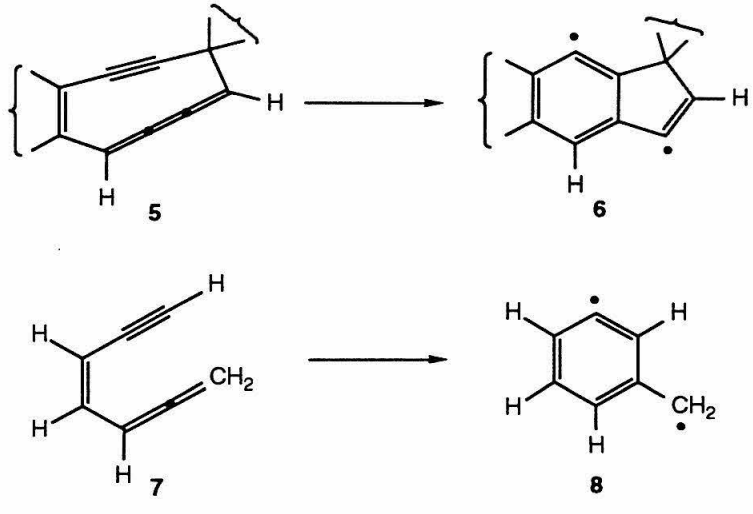


1 **2**



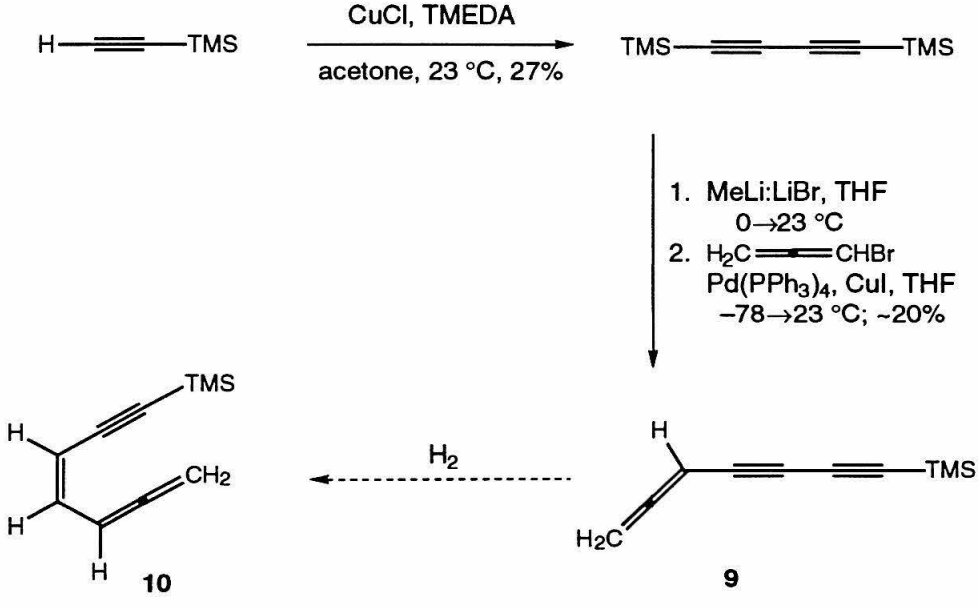
3 **4**

The proposed key step in the mechanism of action of the antitumor agent neocarzinostatin chromophore[2a-c] also involves the formation of a biradical, specifically the cyclization of the (*Z*)-cumulene-ene-yne **5** to the biradical **6**. In light of this transformation, the possibility that the hydrocarbon (*Z*)-1,2,4-heptatrien-6-yne (**7**) might undergo a similar transformation to the biradical α,3-dehydrotoluene (**8**) was considered.[1a,4] Though inspired by the transformation **5**→**6**, the rearrangement of **7** to **8** differs in that the ground-state structure of the biradical **8** is almost certain to be a σ,π-biradical, whereas **6** is constrained by geometry to be a σ,σ-biradical. The consequences of this difference in terms of reactivity, as well as methodology for the synthesis of (*Z*)-1,2,4-heptatrien-6-yne (**7**) and the formation of products consistent with the intermediacy of the biradical **8** are discussed in this chapter.



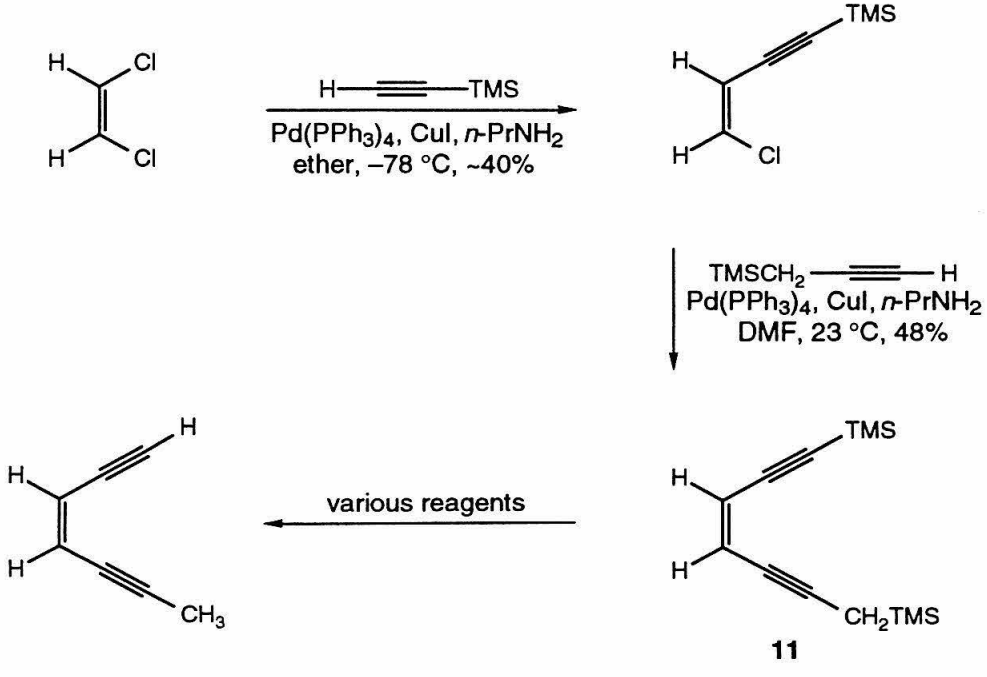
Synthesis of (*Z*)-1,2,4-Heptatrien-6-yne

The principal challenge in the synthesis of (*Z*)-1,2,4-heptatrien-6-yne (**7**) was the construction of the vinylallene with proper stereochemistry in a target molecule that is both thermally and chemically sensitive. Various strategies were examined. The first involved the use of an allenic subunit, 1-bromo-1,2-propadiene.[5] In this approach, 1,4-bis(trimethylsilyl)buta-1,3-diyne was synthesized from (trimethylsilyl)acetylene, cuprous chloride (0.10 equiv), and *N*,*N*,*N*',*N*'-tetramethylethylenediamine (0.03 equiv) in acetone at 23 °C (27%).[6] 1,4-Bis(trimethylsilyl)buta-1,3-diyne was then desilylated and lithiated with methyllithium complexed with lithium bromide (1.0 equiv) in tetrahydrofuran at 0→23 °C, and the resulting product was coupled to 1-bromo-1,2-propadiene with tetrakis(triphenylphosphine)palladium(0) (0.05 equiv) and cuprous iodide (1.05 equiv) in tetrahydrofuran at –78→23 °C to provide the allene-diyne **9** (~20% overall). With the aim of providing trimethylsilylated hydrocarbon **10**, allene-diyne **9** was subjected to selective hydrogenation conditions (hydrogen, palladium on activated carbon (5%, 0.05 wt equiv), triethylamine (0.12 equiv), tetrahydrofuran, 23 °C).[7] The hydrogenation,



however, did not proceed with the desired selectivity, providing a mixture of products instead.

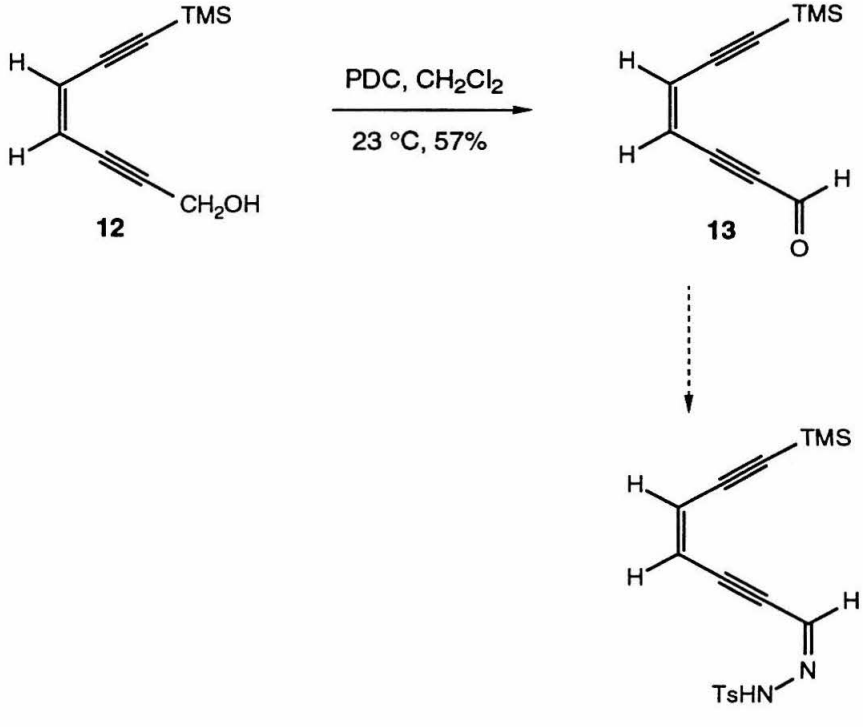
Another attempted synthesis involved the formation of the (*Z*)-enediyne **11**. (*Z*)-1,2-Dichloroethylene[8] (1.0 equiv) was coupled to (trimethylsilyl)acetylene (1.2 equiv) with tetrakis(triphenylphosphine)palladium(0) (0.05 equiv), cuprous iodide (0.15 equiv), and *n*-propylamine in ethyl ether at –78 °C (~40%).[9] A second coupling with 1-(trimethylsilyl)-2-propyne (1.5 equiv) (prepared from propargyl bromide (1.1 equiv), magnesium (1.0 equiv), and chlorotrimethylsilane (1.0 equiv) in ethyl ether at 0→23 °C (~60%))[10] under similar conditions (tetrakis(triphenylphosphine)palladium(0) (0.05 equiv), cuprous iodide (0.2 equiv), *n*-propylamine (2.0 equiv), *N*,*N*-dimethylformamide, 23 °C) furnished the (*Z*)-enediyne **11** (48%). In an effort to transform **11** to **7**, a wide range of desilylating reagents were examined: potassium hydroxide in various solvents (tetraethylene glycol, ethylene glycol, 1,3-propanediol, and 1,4-butanediol), ethanolamine, sulfuric acid, hydrochloric acid, perchloric acid, butyllithium, and

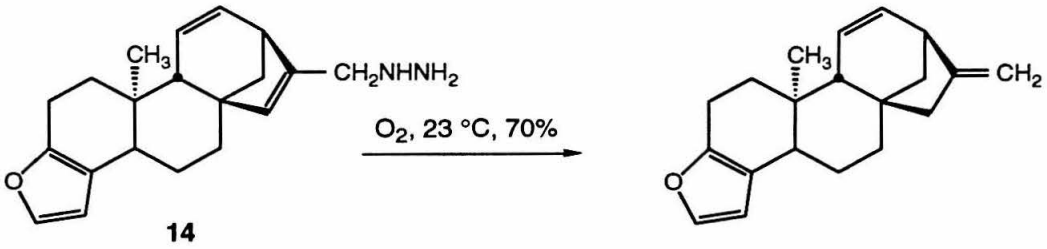


tetrabutylammonium fluoride. In these cases, desilylation of **11** with concomitant rearrangement of the propargyl group to provide hydrocarbon **7** was not detected. Potassium hydroxide, ethanolamine, and tetrabutylammonium fluoride resulted in the formation of (Z)-3-heptaen-1,5-diyne.

A third approach was the attempted synthesis of the tosyl hydrazone of the aldehyde **13**. The hydridic reduction of such a conjugated alkynyl tosyl hydrazone was anticipated to furnish the corresponding allene, **10**, presumably via the formation of a propargyl diazene intermediate with subsequent 1,5-sigmatropic rearrangement and extrusion of dinitrogen.[11] This approach proved unfeasible as the aldehyde, obtained from the corresponding alcohol (**12**, *vide infra*) by oxidation with pyridinium dichromate (14.0 equiv) in dichloromethane at 23 °C (57%),[12] was unstable.

While the desired propargyl diazene intermediate was not attainable via a tosyl hydrazone, its formation from a propargyl hydrazine derivative by oxidation was

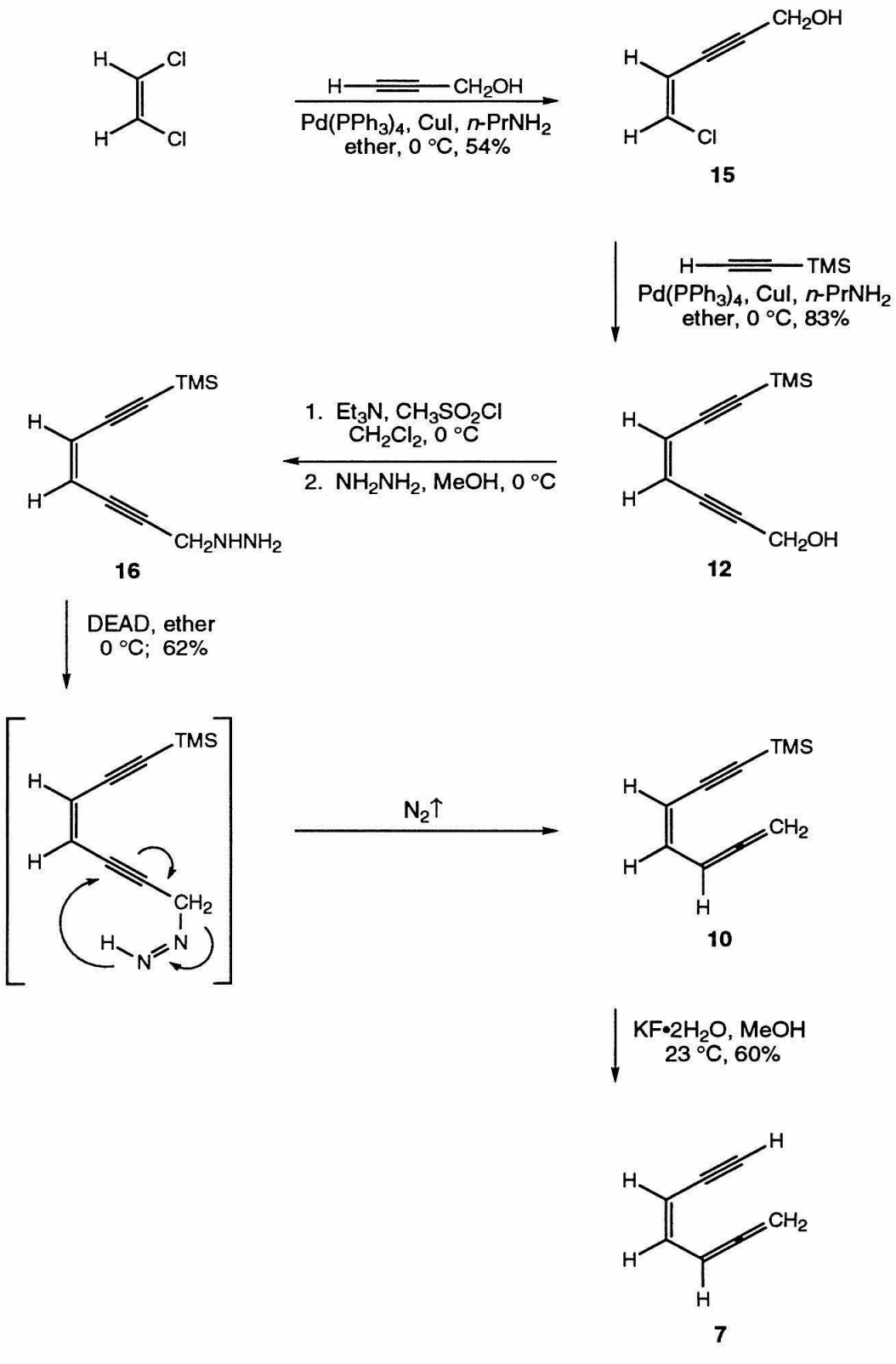




14

suggested by the synthesis of (±)-cafestol by Corey et al., in which the allylic hydrazine **14** was converted to the corresponding transposed olefin by stirring under an atmosphere of oxygen at 23 °C for 7 h (70%).[13] Presumably, this transformation involved the formation of an allylic diazene intermediate by oxidation and its subsequent sigmatropic rearrangement with loss of dinitrogen. In an analogous fashion, propargyl hydrazines, obtained from the corresponding propargyl alcohols, were oxidized with diethyl azodicarboxylate (DEAD) to afford allenes.[14] Specifically, this method allowed the transformation in the retrosynthetic sense of the target **10** into a more tractable precursor, the (*Z*)-enediyne **12**.[1a,15,16]

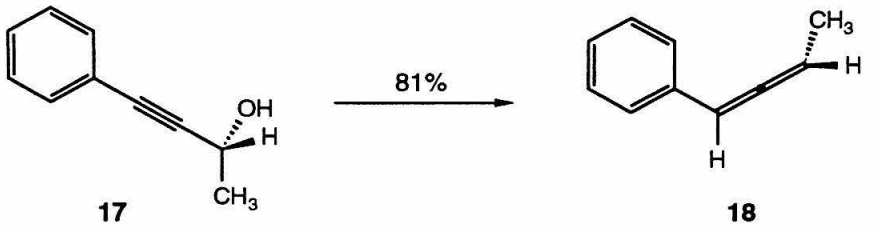
The (*Z*)-enediyne **12** was synthesized as follows. Propargyl alcohol and (*Z*)-1,2-dichloroethylene (1.1 equiv)[8] were coupled at 0 °C with tetrakis(triphenylphosphine)-palladium(0) (0.05 equiv) and cuprous iodide (0.20 equiv) in ethyl ether containing *n*-propylamine (4.0 equiv) to provide the (*Z*)-vinyl chloride **15** in 54% yield after chromatographic purification.[9] A second stereospecific coupling reaction with (trimethylsilyl)acetylene (1.4 equiv) under identical conditions gave the (*Z*)-enediyne **12** (83%). While the two coupling reactions could be run in sequence in a single flask, **12** was formed in greater yield when the intermediate (*Z*)-vinyl chloride **15** was isolated by flash column chromatography on silica gel. The indicated order of acetylene coupling was preferred for the lower volatility of (*Z*)-vinyl chloride **15**.


H
Cl
H
Cl
H—≡—CH2OH
Pd(PPh3)4, CuI, n-PrNH2
ether, 0 °C, 54%
CH2OH
H
H
Cl
15
H—≡—TMS
Pd(PPh3)4, CuI, n-PrNH2
ether, 0 °C, 83%
TMS
H
H
CH2OH
12
1. Et3N, CH3SO2Cl
CH2Cl2, 0 °C
2. NH2NH2, MeOH, 0 °C
TMS
H
H
CH2NHNH2
16
DEAD, ether
0 °C; 62%
TMS
H
H
CH2
H
N
N
N2↑
TMS
H
H
CH2
H
10
KF•2H2O, MeOH
23 °C, 60%
H
H
H
CH2
H
7

The conversion of (*Z*)-enediyne **12** to the allene **10** illustrates the new method. The hydroxyl group of **12** was activated with triethylamine (6.0 equiv) and methanesulfonyl chloride (3.0 equiv) in dichloromethane at 0 °C.[17] The direct addition of this reaction mixture to excess hydrazine (10 M, 100 equiv) in methanol at 0 °C afforded, after extractive isolation, the propargyl hydrazine **16**. The oxidation of crude **16** with diethyl azodicarboxylate (DEAD, 1.1 equiv) in ethyl ether at 0 °C furnished the allene **10** (62% from **12**, after chromatographic purification), presumably via the propargyl diazene intermediate.

Initial scouting experiments indicated that other methods of oxidation, in addition to the one employing DEAD, also converted the propargyl hydrazine **16** to the allene **10**. For example, vigorous stirring of **16** under an atmosphere of oxygen in benzene-d_6 at 23 °C for 140 h afforded **10** (~25% yield). The allene was also obtained by stirring a solution of the propargyl hydrazine and copper(II) chloride dihydrate in ethyl ether under an atmosphere of oxygen at 23 °C for 2 h (20%).[18] Iodine and potassium carbonate, oxygen and salcomine,[19] and oxygen with copper(II) sulfate-phenanthroline[20] furnished the desired allene as indicated by thin layer chromatography. Myers et al. found that 4-methyl-1,2,4-triazoline-3,5-dione (MTAD) was also an alternative.[15] Of these reagents, the most efficient and synthetically useful are DEAD and MTAD.

Myers and Finney studied the oxidation of propargyl hydrazines by ^{1}H NMR.[21] They have proposed that the reaction of (3-phenyl-2-propynyl)hydrazine with MTAD at –95 °C produces a 1:1 mixture of the corresponding (*E*)- and (*Z*)-diazenes. The *Z* isomer rearranges rapidly while, in accord with the presumed requirement for cis stereochemistry in the sigmatropic elimination, the *E* isomer persists, undergoing first-order decomposition at a higher temperature (–70 °C) to produce the same allenic product. This latter transformation presumably involves rate-limiting trans→cis isomerization of the diazene.



17 **18**

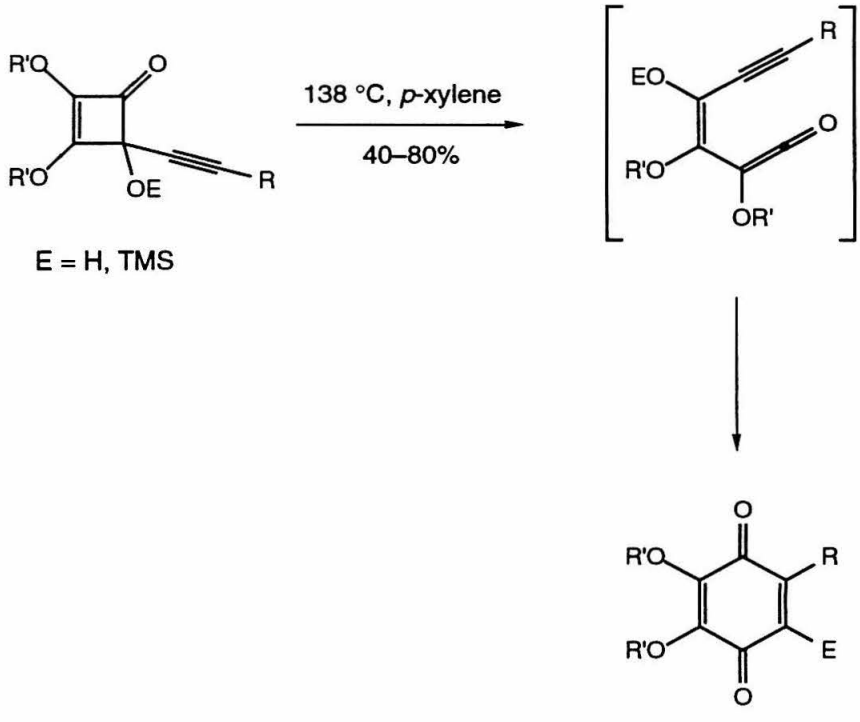
That this displacement-rearrangement sequence could be used to synthesize optically active allenes was demonstrated by Myers et al. with (*R*)-alcohol **17** (76 ± 2% ee), obtained by reduction of the corresponding ketone with (*R*)-Alpine-Borane®.[15] Application of the method furnished the (*S*)-allene **18** in 81% yield and 75 ± 2% ee, as shown by ^{1}H NMR analysis with the chiral shift reagent combination Ag(fod)-Yb(hfc)$_3$, demonstrating also that this sequence had proceeded with essentially complete stereospecificity.

With a successful route to allene **10**, the only transformation remaining in order to provide hydrocarbon **7** was desilylation. Various standard desilylation reagents, such as tetrabutylammonium fluoride,[22] potassium hydroxide, tetrabutylammonium chloride-potassium fluoride dihydrate, and silver nitrate-potassium cyanide,[23] were found to give the trans isomer of hydrocarbon **7** in addition to the desired cis. After additional experimentation, clean desilylation of allene **10** was achieved with potassium fluoride dihydrate (7.5 equiv) in methanol at 23 °C (ca. 60%). After extraction into pentane and preparative gas chromatography, the hydrocarbon **7** was obtained as a colorless, volatile liquid. Alternatively, solutions of **7** were prepared by direct extraction of the desilylation reaction mixture with an appropriate solvent (e.g., 1,4-cyclohexadiene) and were stored at −100 °C to avoid polymerization.

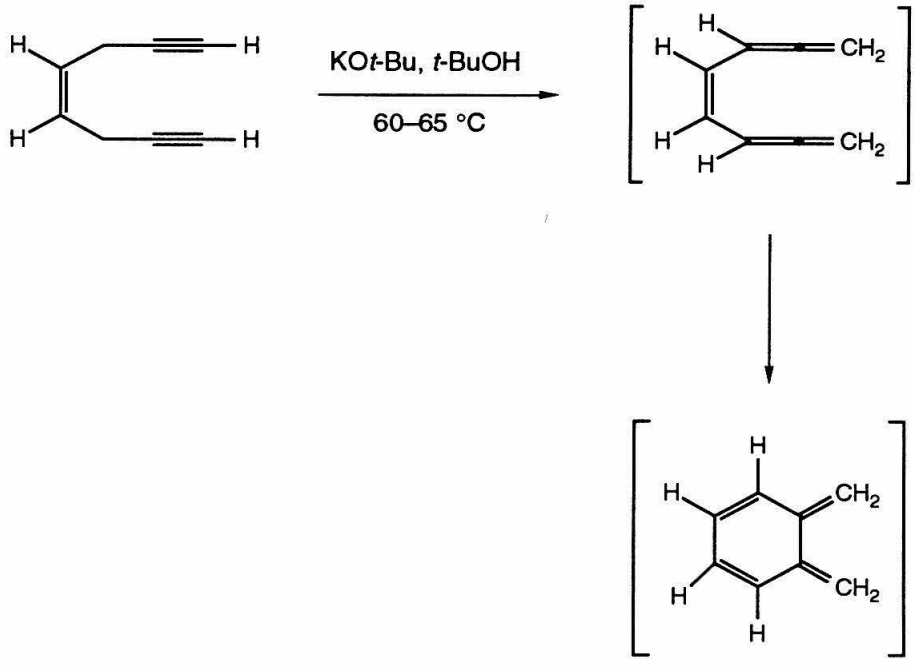
Rearrangement of (*Z*)-1,2,4-Heptatrien-6-yne (7)

Some precedent can be found for the desired transformation of **7** to **8**. For example, an isoelectronic rearrangement wherein the allene of **7** is replaced by a ketene was proposed by Moore et al. to occur in the thermolysis of 4-alkynyl-4-alkoxycyclobutenones to 1,4-benzoquinones (Scheme 1).[24] Cyclization reactions of bisallene precursors are also known. The dimerization of (*Z*)-4-octen-1,7-diyne observed by Ben-Efraim and Sondheimer is thought to involve its rearrangement to *o*-quinodimethane via a bisallene intermediate (Scheme 2).[25] Similarly, bisallenyl ether and thioether are believed to undergo cyclization to give the corresponding 3,4-dimethylenes (Scheme 3).[14b,26]

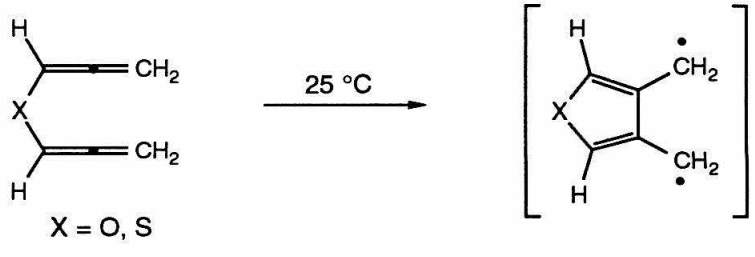
The thermolysis of **7** (0.003 M) in 1,4-cyclohexadiene resulted in the quantitative formation of toluene and 1,4-cyclohexadiene adducts **19** and **20** (60 and 40%, respectively; Table I, entry 3). The formation of these products is consistent with the



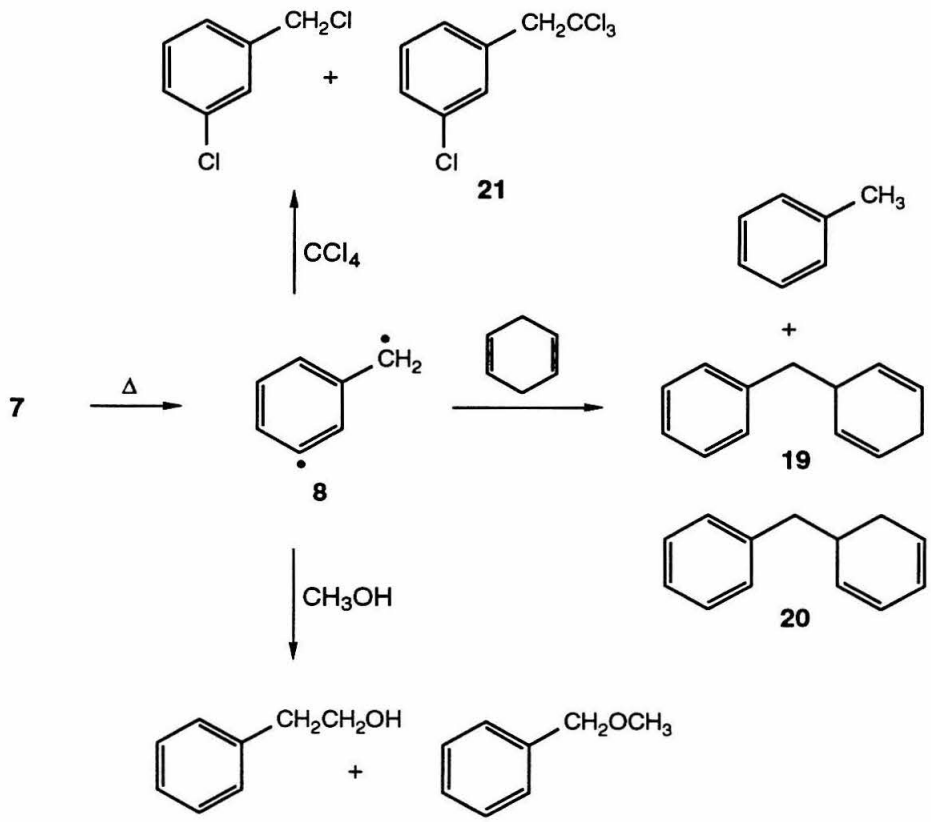
Scheme 1



Scheme 2



Scheme 3



intermediacy of the biradical **8**, α,3-dehydrotoluene. Products **19** and **20** can be thought to arise by hydrogen atom abstraction from 1,4-cyclohexadiene by the more reactive σ-radical of **8**, followed by recombination of the resulting pair of π-radicals. This is in keeping with the preferential carbon-carbon bond formation seen at the benzylic position (as opposed to the *m*-aryl position) in **19** and **20**. While these products can also be envisioned to result from a sequence involving addition of cyclohexadienyl to the allenic terminus of **7**, cycloaromatization, and hydrogen atom abstraction, the invariance of the ratio (**19** + **20**)/toluene with the concentration of **7** (Table I, entries 1–3) suggests that this pathway is at best a minor competitor with the simple recombination mechanism.

These thermolysis were performed in sealed reaction tubes at five temperatures, 39, 59, 77, 90, and 100 °C. The disappearance of starting material over time was

Table I. Product Distributions Obtained Upon Pyrolysis of **7** in Various Media at 100 °C.

Entry	Solvent	[7] (mM)	Products[a] Toluene	**19 + 20**	Bibenzyl	3-Chlorobenzyl chloride	**21**	Methyl benzyl ether	2-Phenyl ethanol
1	CHD[b] (0.4 M)–Benzene	9.0	16	10	-	-	-	-	-
2	CHD (4.0 M)–Benzene	4.5	34	15	-	-	-	-	-
3	CHD	3.0	60	40	-	-	-	-	-
4	CCl_4	8.0[c]	-	-	-	1	14	-	-
5	CCl_4	8.0	-	-	-	5	18	-	-
6	CCl_4	0.8	-	-	-	8	16	-	-
7	CH_3OH[d]	3.0	-	-	2	-	-	38	10
8	CH_3OH[e]	3.0	-	-	2	-	-	35	10
9	CH_3OH[f]	3.0	-	-	2	-	-	34	9
10	CD_3OH	3.0	-	-	-	-	-	70	-
11	CH_3OD	3.0	-	-	3	-	-	18	21

[a] Yields determined by GLC using *m*-xylene as an internal standard. [b] CHD = 1,4-Cyclohexadiene. [c] 10^{-2} M. [d] Reaction glassware not rinsed with 1,1,1,3,3,3-hexamethyldisilazane prior to pyrolysis. [e] Reaction glassware rinsed twice with 1,1,1,3,3,3-hexamethyldisilazane prior to pyrolysis. [f] Reaction glassware rinsed twice with glacial acetic acid prior to pyrolysis.

monitored relative to an internal standard, *m*-xylene (0.0015 M), by capillary gas chromatography (Table II) and when plotted, was found to follow clean first-order kinetic behavior (Figure 1). Rate constants were calculated from the slopes of these lines (Table III).[27] Eyring and Arrhenius plots provided the following activation parameters: $\Delta H^{\ddagger}$ = 21.8 ± 0.5[28] kcal/mol, $\Delta S^{\ddagger} = -11.6 \pm 1.5$ eu; E_a = 22.5 kcal/mol, log A = 10.7 (Figure 2). The values of $\Delta G^{\ddagger}$ corresponding to each reaction temperature were also calculated (Table IV).

It was found that the efficient formation of stable volatile products in these thermolysis experiments depended upon the presence of high concentrations of a good radical trapping agent. In pyrolyses with 1,4-cyclohexadiene in benzene, for example, the combined yield of **19**, **20**, and toluene increased with diminishing concentrations of **7** and with increasing concentrations of 1,4-cyclohexadiene (Table I, entries 1–3). The thermolysis of **7** under conditions (**7** (0.008 M), 1,4-cyclohexadiene (0.40 M)-benzene) that produced less than quantitative yields of volatile products (toluene, 20%) also exhibited first-order behavior (Table V), although with a shorter half-life than that of **7** thermolyzed under ideal conditions. The nonquantitative yield of products implies that **7** in this case was reacting via other processes, presumably giving oligomeric or highly unstable products, in addition to the desired cyclization.

Thermolysis of **7** in oxygen-free carbon tetrachloride afforded 3-chlorobenzyl chloride and the carbon tetrachloride adduct **21** in 15–24% combined yield, also supporting the intermediacy of α,3-dehydrotoluene (Table I, entries 4–6). The lower yield of volatile products in these experiments, as compared with 1,4-cyclohexadiene, presumably is due to the slower trapping of the 3-chlorobenzyl radical by carbon tetrachloride, allowing secondary reactions with **7** to compete more effectively. Correspondingly, the yield of 3-chlorobenzyl chloride was found to increase with decreasing concentrations of **7**. That the yield of **21** remained constant within

Table II. Thermal Cyclization of **7** (0.003 M) in 1,4-Cyclohexadiene.

T (°C)	time	**7** : *m*-xylene	ln (**7** : *m*-xylene)
39	0.00 h	2.09	0.73716
	20.03	1.09	0.086178
	40.00	0.58	-0.54473
	60.00	0.27	-1.3093
59	0.00 h	2.13	0.75612
	2.00	1.05	0.048790
	4.00	0.54	-0.61619
	6.00	0.20	-1.6094
77	0.00 min	2.19	0.78390
	20.15	1.26	0.23111
	40.03	0.67	-0.40048
	60.17	0.37	-0.99425
	80.28	0.21	-1.5606
90	0.00 min	2.12	0.75142
	7.00	1.13	0.12222
	14.12	0.56	-0.57982
	21.00	0.24	-1.42712
100	0.00 min	2.09	0.73716
	3.5	1.27	0.23902
	7.0	0.65	-0.43078
	10.5	0.24	-1.4271

Table III. Kinetic Parameters for the Thermal Cyclization of **7** (0.003 M) in 1,4-Cyclohexadiene.

T (°C)	k (s^{-1})	$t_{1/2}$
39	$9.40 \pm 1.50 \times 10^{-6}$	20.5 h
59	$1.08 \pm 0.24 \times 10^{-4}$	1.8 h
77	$4.92 \pm 0.01 \times 10^{-4}$	23.0 min
90	$1.72 \pm 0.52 \times 10^{-3}$	6.7 min
100	$3.40 \pm 1.20 \times 10^{-3}$	3.4 min

Table IV. Free Energies of Activation for the Thermal Cyclization of **7** (0.003 M) in 1,4-Cyclohexadiene.

T (°C)	$\Delta G^{\ddagger}$ (kcal/mol)
39	25.5
59	25.5
77	25.9
90	26.0
100	26.2

Table V. Kinetic Parameters for the Thermal Cyclization of **7** (0.008 M) in 1,4-Cyclohexadiene (0.4 M)-Benzene.

T (°C)	k (s^{-1})	$t_{1/2}$
50	4.04×10^{-5}	4.8 h
60	1.08×10^{-4}	1.8 h
77	6.23×10^{-4}	18.5 min
90	1.89×10^{-3}	6.1 min
100	4.70×10^{-3}	2.5 min

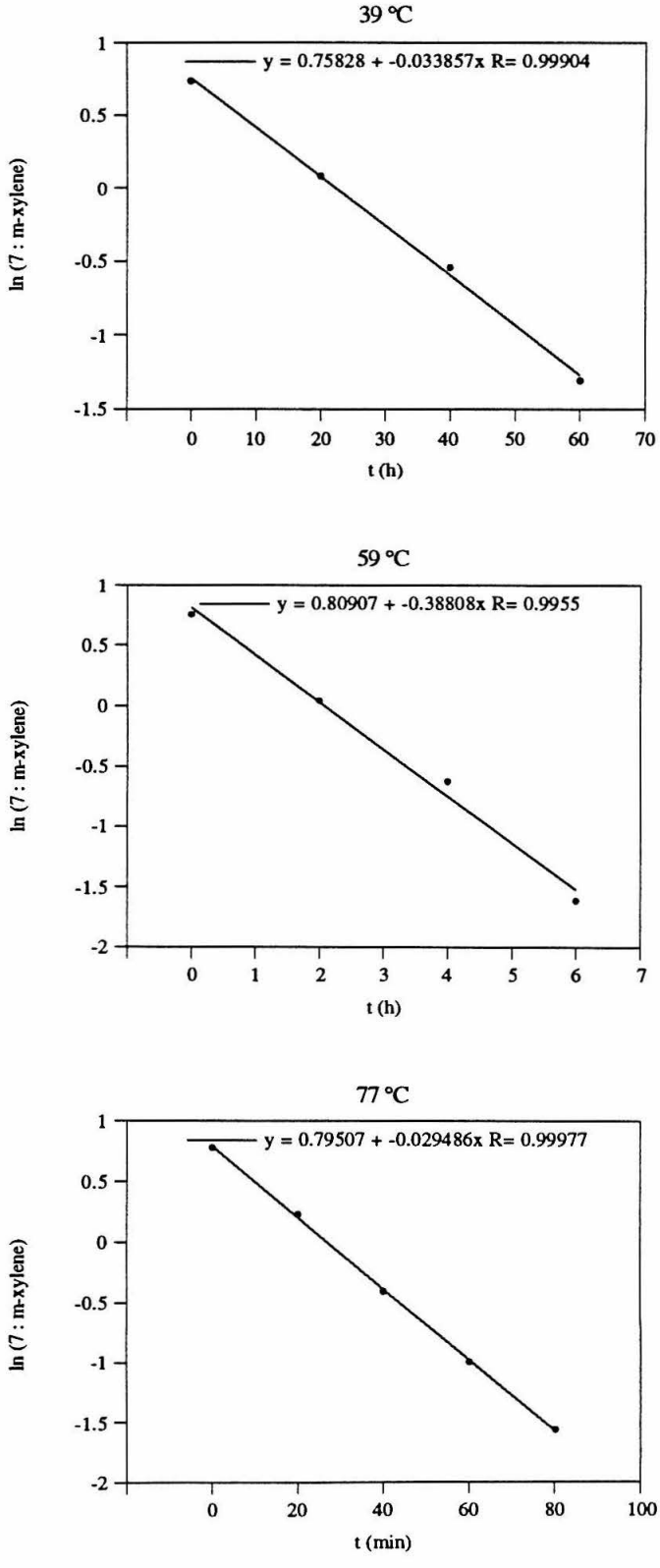


Figure 1. Thermal Cyclization of **7** (0.003 M) in 1,4-Cyclohexadiene.

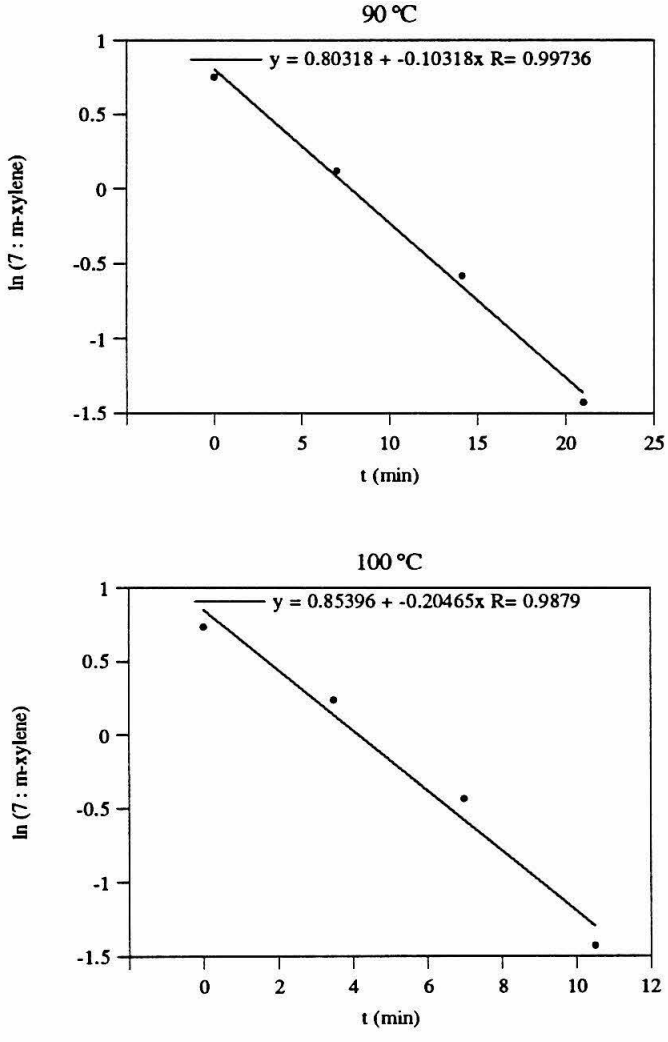


Figure 1. Thermal Cyclization of **7** (0.003 M) in 1,4-Cyclohexadiene (cont.).

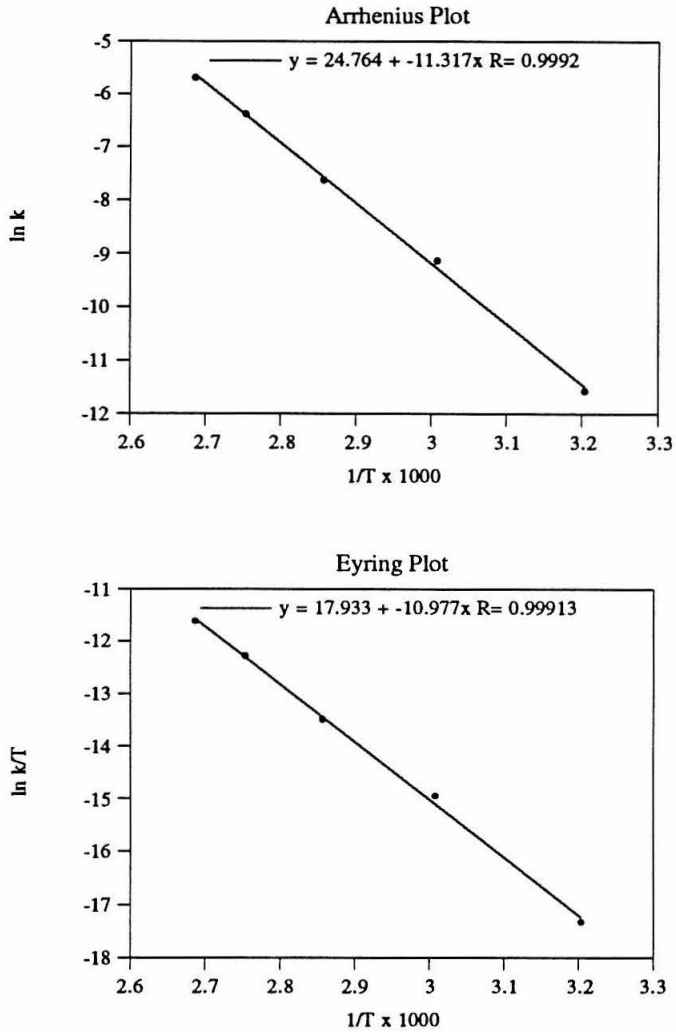
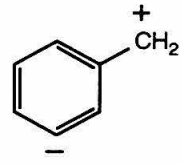


Figure 2. Arrhenius and Eyring Plots.



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experimental error suggests that **21** may be the product of a radical cage recombination mechanism.

Pyrolysis experiments conducted in methanol revealed dichotomous reactivity for the intermediate **8**. Heating **7** (0.003 M, 100 °C) in deoxygenated methanol afforded 2-phenylethanol (10%) and bibenzyl (2%), products anticipated from a biradical description of **8**, as well as methyl benzyl ether (38%), a product more consistent with the zwitterionic structure **22**. 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 7–9), discounting the formation of methyl benzyl ether by adventitious acid or base. Pyrolysis of **7** in CD_3OH (0.003 M, 100 °C) yielded methyl-d_3 benzyl ether (70%; Table I, entry 10). The kinetics of the decomposition of **7** in CD_3OH were first-order (Table VI, Figure 3) and indistinguishable, within experimental error, from those observed in pure 1,4-cyclohexadiene, where products anticipated from standard free radical reactions were 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). Pyrolysis in CH_3OD afforded methyl benzyl-d_1 ether (18%) and 2-phenylethanol (21%; Table I, entry 11).[29]

This observed near-doubling of the yield of methyl benzyl ether when methanol was replaced with CD_3OH is inconsistent with a pathway involving formation of a short-lived "polar" species that decays irreversibly to an intermediate with radical reactivity. Conversely, the results of the experiment in CH_3OD are inconsistent with a cascade involving the inverse order of reactive intermediates. These results suggest that these

Table VI. Thermal Cyclization of **7** (0.003 M) in Methanol-d_3 at 75 °C.

t (min)	**7** : *m*-xylene	ln (**7** : *m*-xylene)
0.00	0.88	-0.12783
20.00	0.57	-0.56212
40.05	0.36	-1.02165
60.12	0.22	-1.51413
80.00	0.13	-2.04022
100.32	0.08	-2.52573

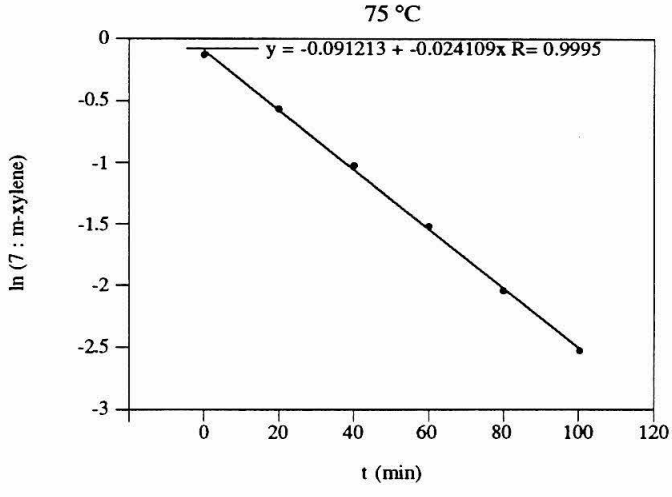


Figure 3. Thermal Cyclization of **7** (0.003 M) in Methanol-d_3 at 75°C.

products arose not from pathways involving slowly equilibrating or nonequilibrating intermediates (for example, ground-state and electronically-excited forms of **8**), but from a single reactive intermediate. Moreover, as the kinetics of decomposition of **7** in CD_3OH, where methyl-d_3 benzyl ether was formed essentially exclusively, were found to be indistinguishable from that in 1,4-cyclohexadiene, it is proposed that the two pathways, producing polar and free radical products, respectively, share a common rate-limiting step, the transformation of **7** to **8**.

This single reactive intermediate may perhaps be best described as a polar biradical, that is, some linear combination of limiting structures **8** and the zwitterion **22**.[30] Little et al. recently described a similar situation where a putative trimethylenemethane biradical intermediate was trapped in a polar fashion when the dielectric constant of the reaction solvent was sufficiently high.[31] The behavior of the intermediate was formulated as a linear combination of polar and biradical contributions, with the contribution of the polar form increasing in response to the polarity of the solvent. Implicit in this "polar biradical" description of the reactive intermediate of **7** is the fact that a singlet species is involved, consistent with the work of Squires et al. supporting a singlet ground state for **8**.[32] This polar reactivity differs from the known chemistry of the σ,σ-biradicals **2**, **4**, and **6**, which react exclusively by standard radical paths.[33] This may be due to the differing abilities of the electron-deficient benzylic and phenyl carbons to support a cation-like intermediate.

Other reactive intermediates may be proposed in the transformation of **7**, for example, the chiral closed-shell allene structure, methylene-2,3,5-cyclohexatriene. This is considered unlikely given the calculated energy of this species versus the planar, singlet biradical isomer[32] and the difficulty in reconciling the observed free radical and polar (orientation of methanol addition) products with this description.[34] A mechanism

involving rapid equilibration between species (for example, a singlet state and a low-lying triplet state) cannot, however, be ruled out by the experimental evidence presented.

The energetics of the rearrangement of **7** to **8** can be compared to that of the Bergman rearrangement (Figures 4 and 5). While the Bergman reaction is modestly endothermic ($\Delta H_r \sim 4 \pm 3$ kcal/mol),[3a,35] the formation of α,3-dehydrotoluene from **7** is strongly exothermic ($\Delta H_r \sim -15 \pm 3$ kcal/mol).[1,32] 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 **8**[32] and 11 ± 3 kcal/mol for **4**.[35] The greater exothermicity of the α,3-dehydrotoluene-forming reaction is due to the greater stability of a benzyl radical versus a phenyl radical. Consistent with the exothermicity of the reaction, Koga and Morokuma found an early transition state in a calculated reaction pathway.[36] The enthalpy of activation for the cyclization of **7** was determined to be some 10 kcal/mol lower than that for the cyclization of **3**, approximating that of certain strained cyclic (*Z*)-enediynes.[37] Koga and Morokuma attributed the higher enthalpy of activation for the cyclization of **3** to the greater repulsion between the in-plane π bonds of the transition state of **3**→**4**, where the π bonds are syn with respect to the partially formed carbon-carbon σ-bond.[36] In the transition state of **7**→**8**, the π bonds are anti, resulting in less repulsion between them. While the calculations of Koga and Morokuma indicated that the methylene group remains perpendicular to the phenyl ring in the transition state, discounting stabilization of the benzylic site by conjugation, this radical nevertheless occupies an orbital of greater p-character than the corresponding radical in **4** or **6**, which may lead to lower barriers to cyclization of (*Z*)-allene-ene-yne systems. The cyclization of **7** to **8** exhibits a rather large negative entropy of activation, while the entropy of activation for the Bergman reaction is assumed to be near-zero.[3a] This may be due, in part, to the loss of rotational freedom about the C3-C4 σ-bond in the transition state for cyclization of **7**.

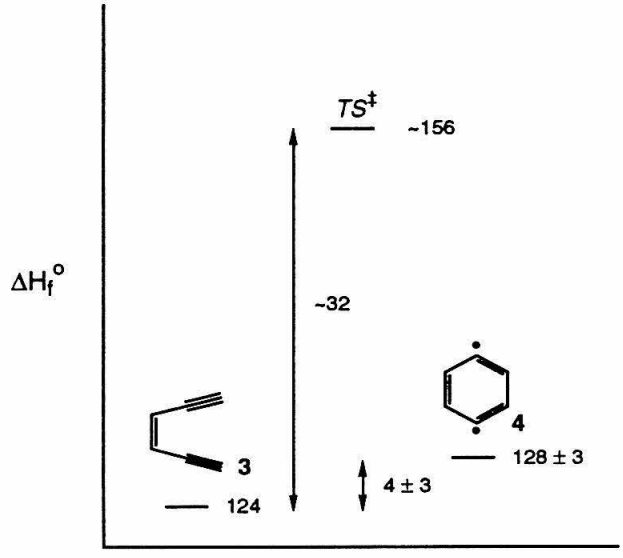


Figure 4. Energy Diagram for **3**→**4**.

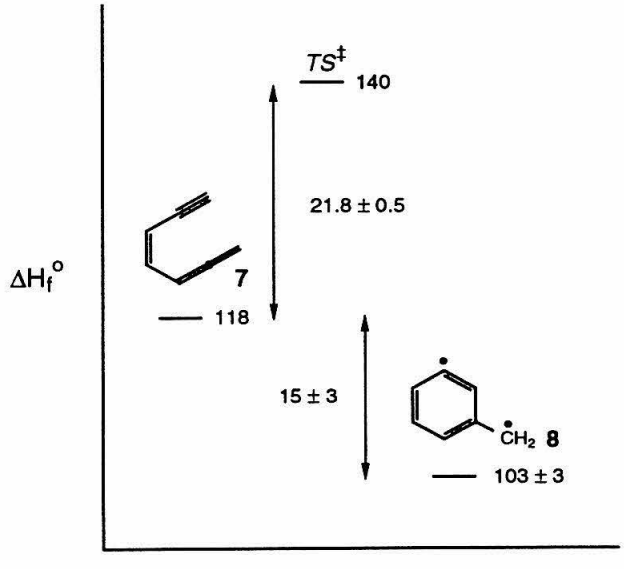
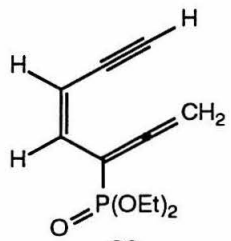


Figure 5. Energy Diagram for **7**→**8**.

Concurrent with and subsequent to this work, additional studies exploring the chemistry of allene-ene-ynes have appeared. Saito et al. synthesized the 3-diethyl phosphonate-substituted (*Z*)-1,2,4-heptatrien-6-yne, **23**, and provided evidence for its rearrangement to the corresponding α,3-dehydrotoluene biradical in the form of trapping studies.[38] A sulfur-containing allene-ene-yne, **24**, was generated by an intramolecular thiol addition reaction and was found to cyclize to the corresponding biradical by Myers and Dragovich.[39] Nicolaou et al. synthesized 1-diphenyl phosphine oxide analogs of **7** (**25**) and demonstrated their DNA-cleaving properties.[40] 1-Thia-3,8-diyn-5-ene (**26**) and its derivatives were observed by Tatsuta et al. to undergo aromatization and to exhibit some DNA-cleaving ability as well.[41] The mechanisms involved in these DNA-cleavage



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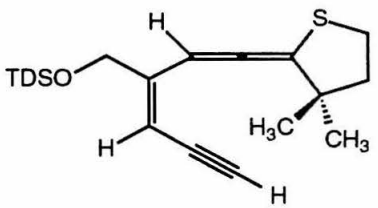

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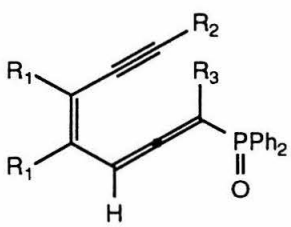

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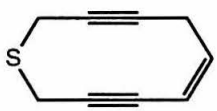

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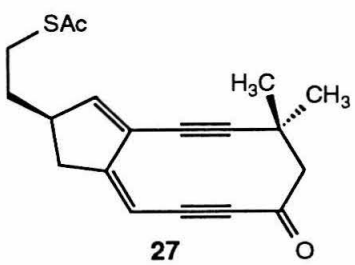
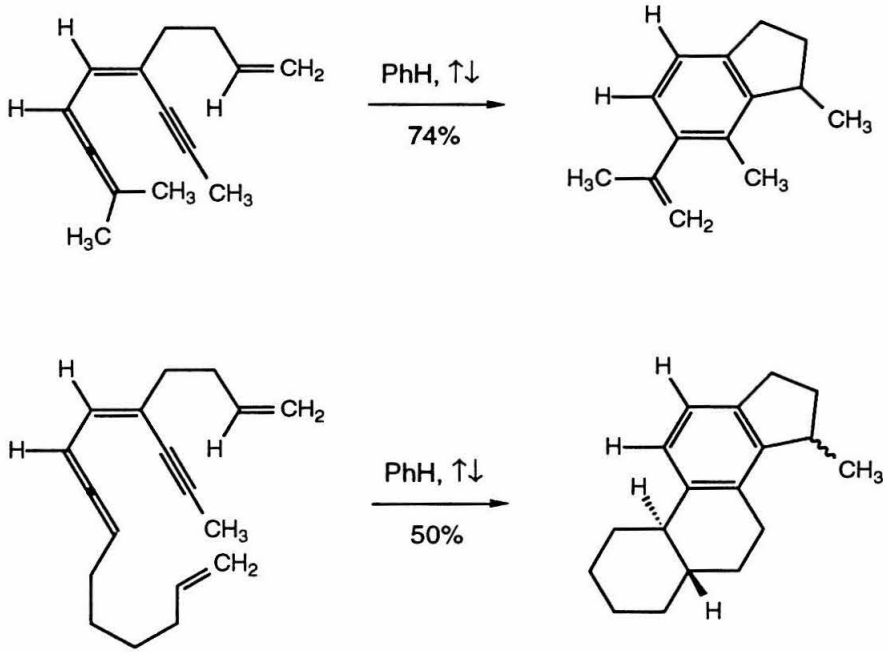


27

reactions have not been established. Hirama synthesized a ten-membered ring analog of neocarzinostatin chromophore (**27**) which formed an allene-ene-yne upon intramolecular thiol activation.[42] In a synthetic application, molecules were constructed by Wang et al. in which the biradical generated from an allene-ene-yne was trapped intramolecularly to afford an indane,[43] including one incorporated in a tetracyclic steroidal skeleton (Scheme 4).[44] These developments serve to confirm the results discussed in this chapter and demonstrate some of the applications of the rearrangement of allene-ene-ynes to α,3-dehydroalkylbenzene biradicals.[45]



Scheme 4

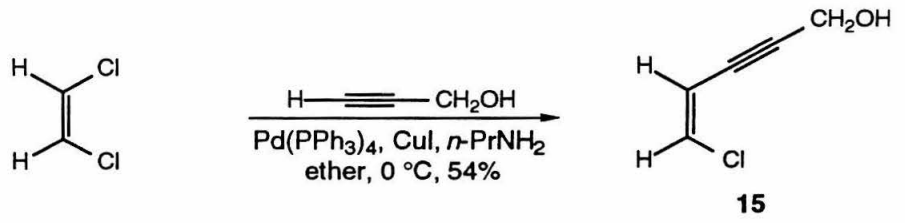
Experimental Section

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. 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 (three iterations). Organic solutions were concentrated by rotary evaporation at ~25 Torr (water aspirator). Flash column chromatography was performed as described by Still et al. employing 230-400 mesh silica gel.[46] 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).

Commercial reagents and solvents were used as received with the following exceptions. Ethyl ether was distilled from sodium benzophenone ketyl. Dichloromethane, *n*-propylamine, and triethylamine were distilled from calcium hydride at 760 Torr. Tetrakis(triphenylphosphine)palladium(0) was prepared according to the literature procedure[47] and was stored in a nitrogen-filled glove box. Cuprous iodide was purified by continuous extraction (12 h) with tetrahydrofuran in a Soxhlet apparatus. Methanesulfonyl chloride was distilled from phosphorus pentoxide at 760 Torr. Hydrazine (anhydrous) and methanol were dried and were stored over 4 Å sieves.

Analytical gas-liquid chromatography (GLC) was carried out on a Hewlett Packard 5890A gas chromatograph with a splitless mode capillary injection system and a flame ionization detector using a flexible fused silica capillary column (25 m x 0.20 mm) wall-coated with phenylmethyl silicone (0.5 μm 5%). 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 absorbtion (cm^{-1}), intensity of absorbtion (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) 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). Data are presented 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 from the University of California, Riverside Mass Spectrometry Facility.



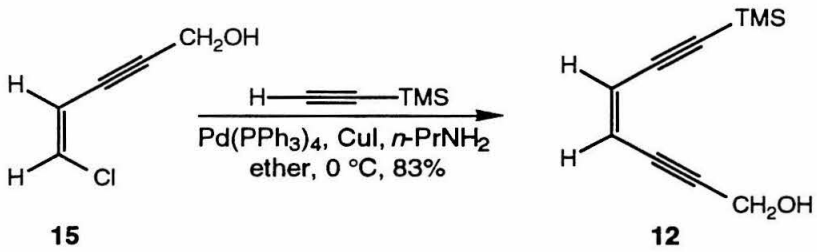
15

(Z)-Vinyl Chloride **15**

(Z)-1,2-Dichloroethylene (3.0 mL, 40.0 mmol, 1.1 equiv) was added to a suspension of tetrakis(triphenylphosphine)palladium(0) (2.10 g, 1.82 mmol, 0.05 equiv) in ethyl ether (45 mL) at –78°C. The resulting mixture was deoxygenated and was stirred at 0 °C for 30 min. In a separate flask, propargyl alcohol (2.12 mL, 36.4 mmol, 1.0 equiv) was added to a suspension of cuprous iodide (1.39 g, 7.30 mmol, 0.20 equiv) and *n*-propylamine (11.96 mL, 0.15 mol, 4.0 equiv) in ethyl ether (45 mL) at –78 °C. The resulting mixture was deoxygenated after each addition and was stirred at 23 °C until it became homogeneous. The resulting green solution was then cooled to 0 °C and was transferred via cannula to the palladium suspension at 0 °C. After the reaction mixture was stirred at 0 °C for 19 h, it was diluted with ethyl ether and was stirred in the air over saturated aqueous potassium carbonate and saturated aqueous ammonium chloride (120 mL each) for 40 min. The separated organic layer was washed with saturated aqueous sodium chloride, and then it was dried over sodium sulfate and was concentrated. The crude product was purified via flash chromatography (10→15% ethyl acetate in hexanes). The fractions were filtered through cotton with ethyl ether and were concentrated to give the (Z)-vinyl chloride **15** (2.26 g, 54%), which was stored in ethyl ether (3.0 mL).

R_f (20% ethyl acetate in hexanes):	0.30
IR (neat):	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)

^{1}H NMR (400 MHz, $CDCl_3$):	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)
HRMS:	calcd for C_5H_5ClO (M^+): 116.0029 found:116.0029



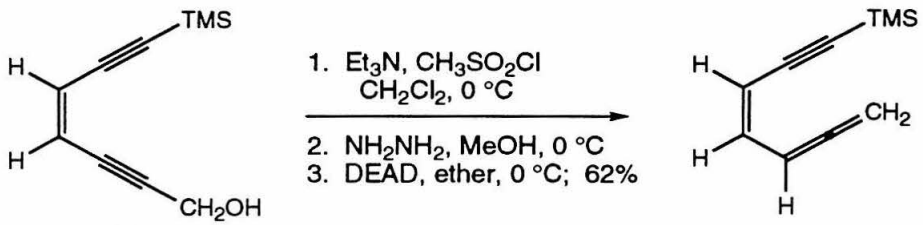
15 **12**

(*Z*)-Enediyne **12**

(*Z*)-Vinyl chloride **15** (2.26 g, 19.0 mmol, 1.0 equiv) was added to a suspension of tetrakis(triphenylphosphine)palladium(0) (1.13 g, 0.98 mmol, 0.05 equiv) in ethyl ether (45 mL) at –78 °C. The resulting mixture was deoxygenated and was stirred at 0 °C for 45 min. In a separate flask, *n*-propylamine (6.4 mL, 76.0 mmol, 4.0 equiv) was added to a suspension of cuprous iodide (0.74 g, 3.89 mmol, 0.20 equiv) and (trimethylsilyl)-acetylene (3.85 mL, 27.2 mmol, 1.4 equiv) in ethyl ether (40 mL) at –78 °C. The resulting suspension was deoxygenated at –78 °C after each addition and was stirred at 23 °C until it became homogeneous. The resulting green solution was cooled to 0 °C and was transferred via cannula to the palladium suspension at 0 °C. After the reaction mixture was stirred at 0 °C for 1 h, it was diluted with ethyl ether and was stirred over saturated aqueous potassium carbonate and saturated aqueous ammonium chloride (150 mL each) in the air for 45 min. The separated organic layer was partitioned between saturated aqueous sodium chloride (two portions) and ethyl ether. The combined organic layers were dried over sodium sulfate and were concentrated. The residue thus obtained was purified by flash chromatography (15 and 20% ethyl acetate in hexanes) to give the (*Z*)-enediyne **12** (2.87 g, 83%), which was stored in ethyl ether.

R_f (30% ethyl acetate in hexanes):	0.38
IR (neat):	3353 (br, OH), 3048 (m), 2960 (s), 2144 (s, C≡C), 1574 (w), 1251 (s), 1134 (s), 1027 (s), 843 (s), 759 (s)

^{1}H NMR (400 MHz, $CDCl_3$):	5.86 (s, 2 H, both C=C**H**), 4.47 (d, 2 H, J = 5.4 Hz, C**H**$_2$OH), 1.66 (t, 1 H, J = 5.4 Hz, CH$_2$O**H**), 0.22 (s, 9 H, Si(C**H**$_3$)$_3$)
HRMS:	calcd for $C_{10}H_{14}OSi$ (M^+): 178.0814
	found: 178.0809



12 **10**

Allene **10** (via Propargyl Hydrazine **16**)[48]

Methanesulfonyl chloride (61.0 μL, 0.79 mmol, 3.0 equiv) was added dropwise to a solution of (*Z*)-enediyne **12** (47.0 mg, 0.26 mmol, 1.0 equiv) and triethylamine (0.22 mL, 1.57 mmol, 6.0 equiv) in dichloromethane (2.0 mL) at 0 °C. The resulting mixture was stirred at 0 °C for 30 min and then was allowed to settle. The supernatant thus obtained was transferred via cannula to another flask, washing the residual solid with dichloromethane (5.0 mL). The resulting solution was concentrated to a volume of 2 mL. Methanol (2.0 mL) and hydrazine (0.85 mL, 26.21 mmol, 100.0 equiv) were added to this solution at 0 °C. The reaction mixture was stirred at 0 °C for 14 h, and then it was partitioned between 50% ethyl acetate in hexanes (2 x 25 mL) and saturated aqueous sodium chloride (25 mL). The combined organic layers were dried over sodium sulfate and were concentrated to give the crude propargyl hydrazine **16.**

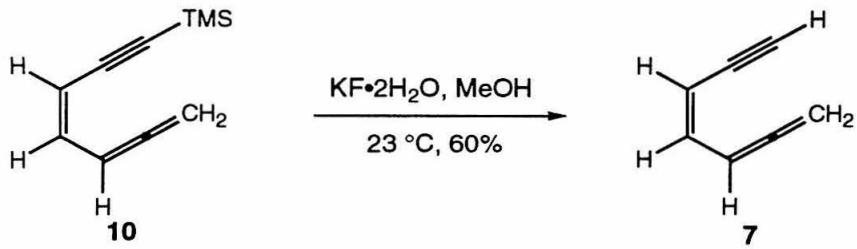
Diethyl azodicarboxylate (46.0 μL, 0.29 mmol, 1.1 equiv) was added slowly to a solution of the propargyl hydrazine **16** in ethyl ether (1.5 mL) at 0 °C, resulting in gas evolution. The reaction mixture was then purified directly by flash column chromatography (pentane). The fractions containing product were concentrated at –23 °C, providing the allene **10** (28.0 mg, 7:1 mixture with pentane, 62%).

Propargyl hydrazine **16**:

R_f(5% methanol in dichloromethane): 0.19

Allene **10**:

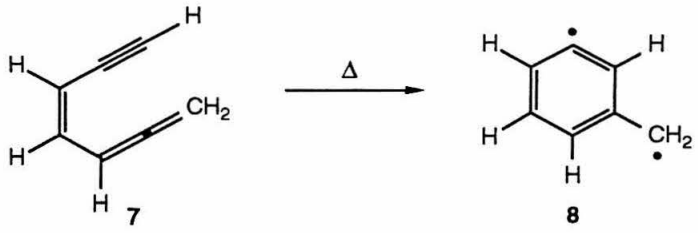
R_f (pentane):	0.55
IR (neat):	2960 (s), 2146 (s, C≡C), 1934 (s, C=C=C), 1710 (w, C=C=C), 1251 (s), 981 (s), 845 (s), 761 (s)
^{1}H NMR (400 MHz, C_6D_6):	6.74 (dt, 1 H, J = 10.99, 6.59 Hz, **H**C=C=CH_2), 6.13 (t, 1 H, J = 10.74 Hz, C≡CCH=C**H**), 5.27 (d, 1 H, J = 11.48 Hz, C≡CC**H**=CH), 4.63 (dm, 2 H, J = 6.59 Hz, CH=C=C**H**$_2$), 0.15 (s, 9 H, Si(C**H**$_3$)$_3$)
HRMS:	calcd for $C_{10}H_{14}Si$ (M^+): 162.0865 found: 162.0861



(Z)-1,2,4-Heptatrien-6-yne (**7**)

Potassium fluoride dihydrate (0.12 g, 1.24 mmol, 5.0 equiv) was added to a solution of allene **10** (40.0 mg, 0.25 mmol, 1.0 equiv) in methanol (2.0 mL) at 23 °C, and the resulting reaction mixture was stirred at 23 °C for 10 h. Additional potassium fluoride dihydrate (60.0 mg, 0.62 mmol, 2.5 equiv) was then added. The resulting mixture was stirred at 23 °C for another 13.5 h. It was then partitioned between benzene-d_6 (approx. 0.40 mL) and saturated aqueous sodium bicarbonate. The separated organic layer was washed with water (three portions) and was dried over sodium sulfate. ^{1}H NMR analysis with *m*-xylene (2.0 μL, 0.016 mmol) added as an internal standard indicated the formation of **7** (12.8 mg, 58%).

R_f (hexanes):	0.38
IR (C_6D_6 solution):	3291 (s, C≡CH), 2146 (w, C≡C), 1933 (s, C=C=C), 1604 (w), 787 (s)
^{1}H NMR (400 MHz, C_6D_6):	6.65 (dtd, 1 H, *J* = 11.0, 5.6, 1.0 Hz, **CH**=C=CH_2), 6.16 (td, 1 H, *J* = 11.0, 1.0 Hz, HC≡CCH=**CH**), 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)
HRMS:	calcd for C_7H_7 (MH^+): 91.0548 found: 91.0552



Pyrolysis Procedure

Pyrolyses of (*Z*)-1,2,4-heptatrien-6-yne (**7**) were conducted in medium-walled NMR tubes (Wilmad 503 PS, 9 in), sealed at reduced pressure (1–2 Torr). Tubes were washed twice with 1,1,1,3,3,3-hexamethyldisilazane or glacial acetic acid (as noted) and were dried *in vacuo* prior to use. Oxygen was removed prior to pyrolysis by three freeze-pump-thaw cycles. Pyrolysis samples containing allene **7** (0.8–80 mM) and *m*-xylene (1/2 concentration of **7**, internal reference) in the appropriate solvent were heated in boiling water (100 °C) or a large, thermostatted oil bath (39, 59, 77, and 90 °C). 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. During kinetic analyses, tubes were removed from the heating bath at appropriate time intervals and were immediately cooled to 0 °C, scored, and 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 **7**: 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: 7.9 min, methyl benzyl ether: 10.2 min, 2-phenylethanol: 12.6 min, bibenzyl: 21.8 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, **19** and **20**: 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.

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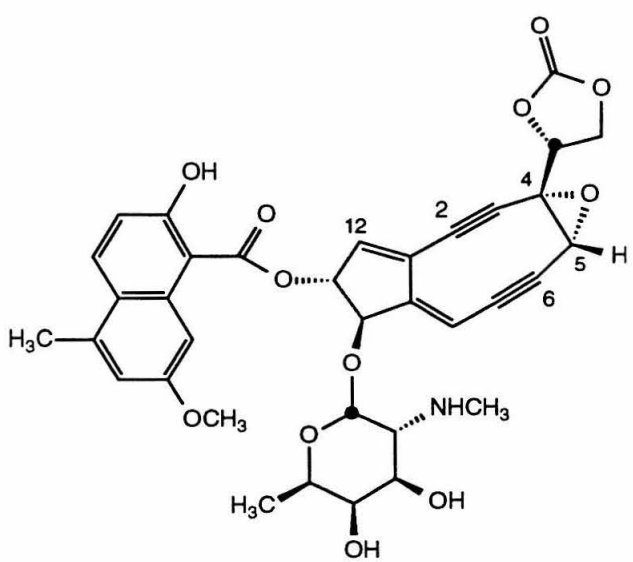
Chapter 2

Studies Directed toward an Enantioselective Synthesis of the Epoxy Diyne Core of Neocarzinostatin Chromophore

Introduction

The antitumor antibiotic neocarzinostatin was isolated from *Streptomyces carzinostaticus* var. F-41 in 1965 by Ishida et al.[1] It is composed of two parts. The first is a protein component of molecular weight 10,700.[2] The second is a UV-active component of molecular weight 659 known as neocarzinostatin chromophore (**1**), which is bound to the protein with high affinity ($K_d \cong 10^{-10}$).[3] Structure elucidation studies showed that the chromophore consists of ethylene carbonate, *N*-methyl D-fucosamine, and 2-hydroxy-7-methoxy-5-methyl-1-naphthoic acid subunits appended to an unusual epoxybicyclo[7.3.0]dodecadienediyne core.[4] The chromophore is responsible for the DNA-cleaving activity of neocarzinostatin, which is exhibited at predominantly

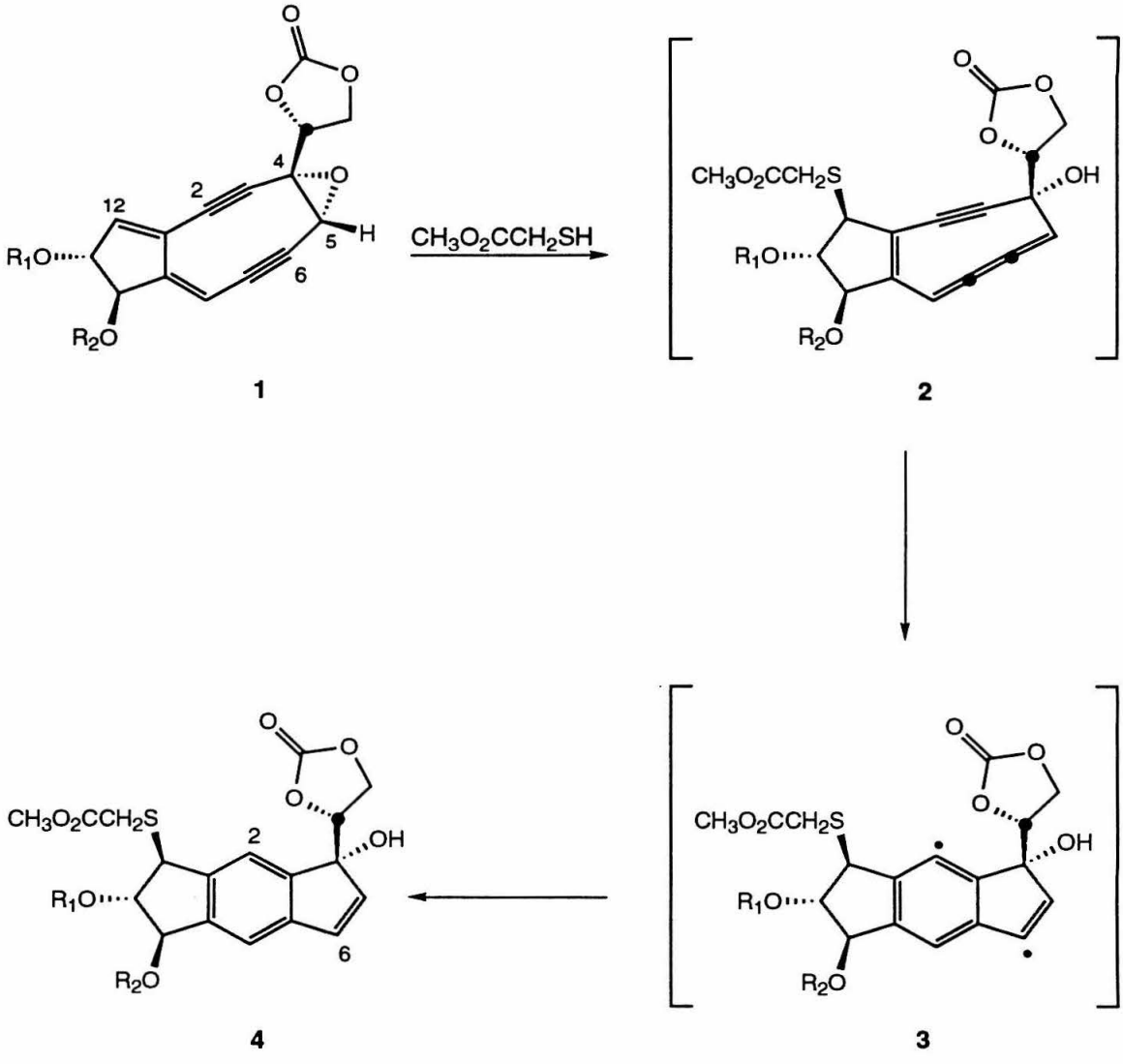


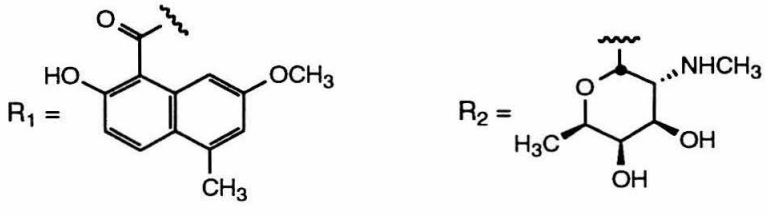
1

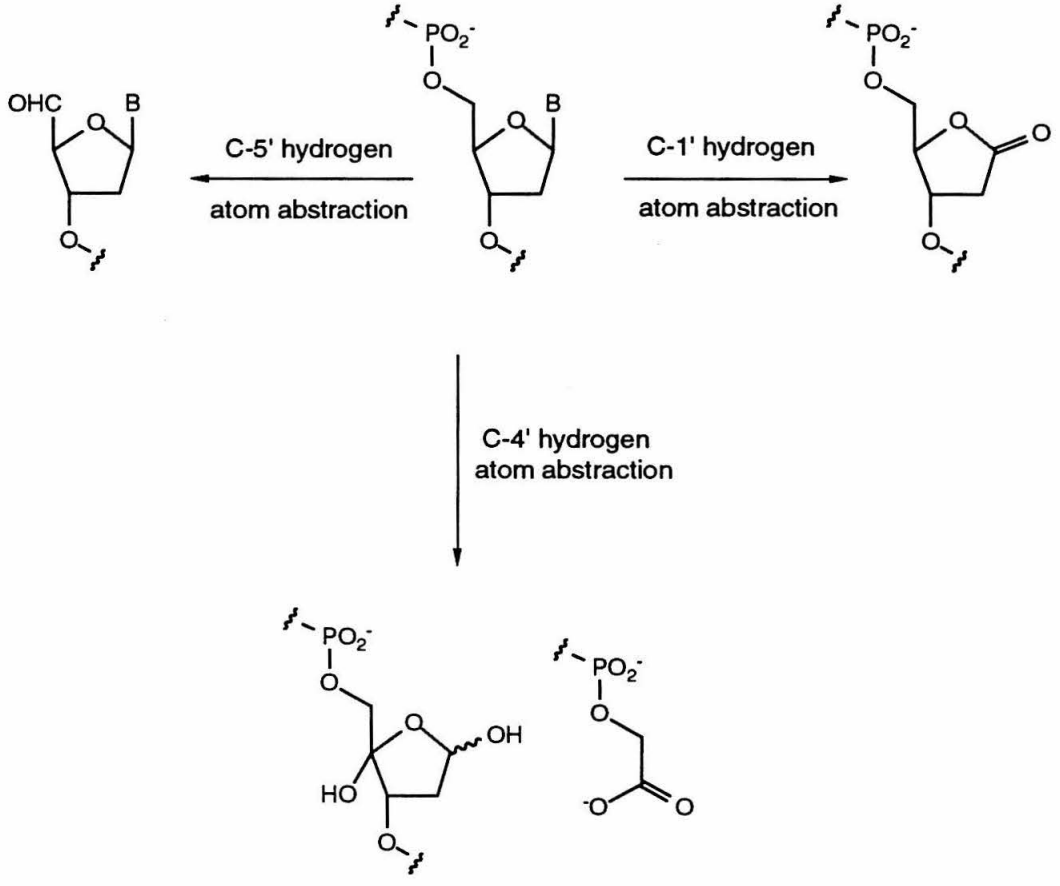
adenosine- and thymidine-rich sites, while the protein is found to prevent inactivation of the chromophore upon exposure to heat and basic conditions.[3a,5,6]

A mechanism of action for DNA-cleavage by neocarzinostatin chromophore has been proposed by Myers.[7] It involves activation of the drug by thiols, which accelerate the rate of DNA cleavage by at least 1,000 times.[8] Myers and Proteau, upon treating the chromophore with methyl thioglycolate, found that attack by the thiol at the C-12 position of the chromophore with concomitant rearrangement and epoxide opening generated the cumulene **2**.[9] The transformation of **2** to the indacene **4** was monitored by ^{1}H NMR and was found to have a half-life of ~0.5 s at 37 °C. Indacene **4** is believed to arise from the biradical **3**, the presence of which is supported by the deuterium incorporation seen at C-2 and C-6 of indacene **4** when the rearrangement was performed in deuterated solvents.

This biradical, **3**, is believed to initiate DNA cleavage by abstracting hydrogen atoms from the sugar backbone of DNA.[3a] Its abstraction of a hydrogen atom from a C-5' site of the sugar backbone under aerobic conditions results in single-strand lesions consisting of either 3'-phosphate and 5'-aldehyde ends or single-nucleoside gaps with phosphate at each end. Double-strand lesions, staggered toward the 3'-ends, are also seen, although approximately five times less often than single-strand lesions in vivo.[10] These result when an additional hydrogen atom is abstracted from the C-1' or C-4' site of a sugar two base pairs away on the complementary strand. A 2'-deoxyribonolactone results from hydrogen atom abstraction at the C-1' site, while a mixture of the 4'-hydroxylated strand and the 3'-phosphoglycolate results from abstraction at the C-4' site under aerobic conditions. Molecular modeling of the sequence AG<u>C</u>•GC<u>T</u> has suggested that it is C-6 of the biradical **3** which abstracts a hydrogen atom from the C-5' site of thymidine, while it is C-2 that abstracts a hydrogen atom from the C-1' site of cytidine.[11] When the C-5' position of the thymidine residue of the self-complementary oligomer


CH3O2CCH2SH
1
2
3
4


R1 =
R2 =
HO
OCH3
CH3
NHCH3
OH
H3C



GCAG<u>C</u>GC<u>T</u>GC was labeled with deuterium, it was seen that deuterium was incorporated only at the C-6 position of the biradical **3**, corroborating this model.[12] In addition, it has been proposed that the naphthoate is intercalated between the A:T and G:C base pairs and that the interaction of the positively charged amino sugar with the negatively charged phosphate backbone helps to position the biradical **3** in the minor groove of B-form DNA.[11] The amino sugar may participate also in thiol activation as an internal base.[13]

Synthetic Approaches to Neocarzinostatin Chromophore

Given this intriguing biological activity and unprecedented structure, neocarzinostatin chromophore has become the focus of much synthetic attention. Several considerations make it a challenging target. First of all, the molecule is highly unstable. It is extremely base sensitive ($t_{1/2}$ ~ 30 s, pH 8, 0 °C),[14] and exhibits a rather short half-life upon exposure to acid ($t_{1/2}$ ~ 25 min, 50% aqueous acetic acid containing 1% trifluoroacetic acid, 23 °C).[15] This behavior limits the reagents which may be employed, particularly toward the end of the synthesis. Secondly, the cyclononadiyne core of the chromophore is expected to be highly strained from studies of related structures (**5–10**). The (C-C≡C) angles of cyclic diacetylenes **5–7** were shown to be nonlinear by X-ray studies (Table I). Those of **8** have been proposed to be nonlinear based on calculations. Since the cyclononadiyne core is similar in structure to these compounds, its (C-C≡C) angles are likely to be nonlinear as well. This distortion contributes some amount of strain energy relative to a structure where the bond angles are 180°. Additional calculations have given some indication of what this strain energy might be. The strain energy of enediyne **9** has been estimated to be 15 kcal/mol[16] and that of the cyclononadienediyne carboskeleton **10** to be 26 kcal/mol.[17] Such strain energy is expected to increase the energy of activation in any cyclization reaction used to construct the cyclononadiyne core, making such a transformation more difficult. Lastly, the incorporation of the (C-4,C-5)-epoxide is another challenge to the successful synthesis of neocarzinostatin chromophore. This epoxide is considered central to the reactivity of the chromophore because epoxide opening occurs during thiol activation of the chromophore[7,9] and in the reaction of the chromophore with strong acids.[18] In the synthesis of the chromophore, the epoxide may be installed either before or after cyclization to the cyclononadiyne core. Installing it prior to cyclization limits the choice

Table I. (C-C≡C) Angles for **5–8.**

compound	(C-C≡C) angle
5[a]	159.3°
6[a]	171.1°
7[b]	155.3°, 156.4°
8[a]	160.0° (ethano)
	164.5° (propano)

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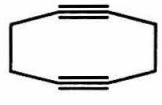

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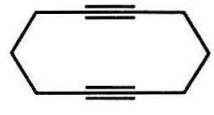

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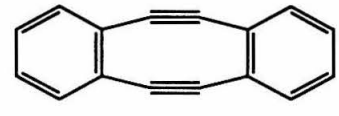
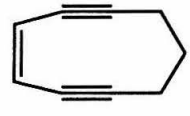
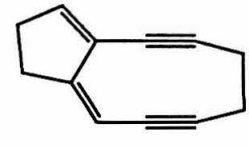


7

8



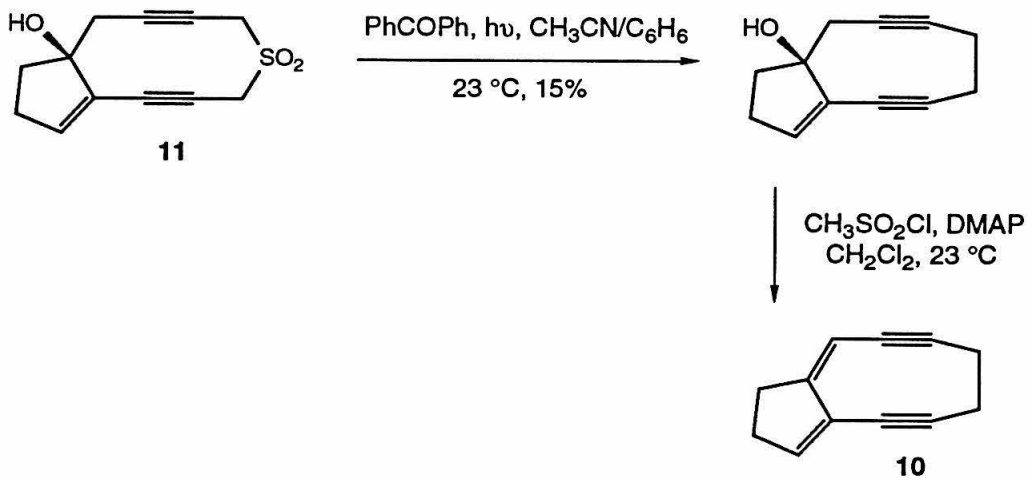
9

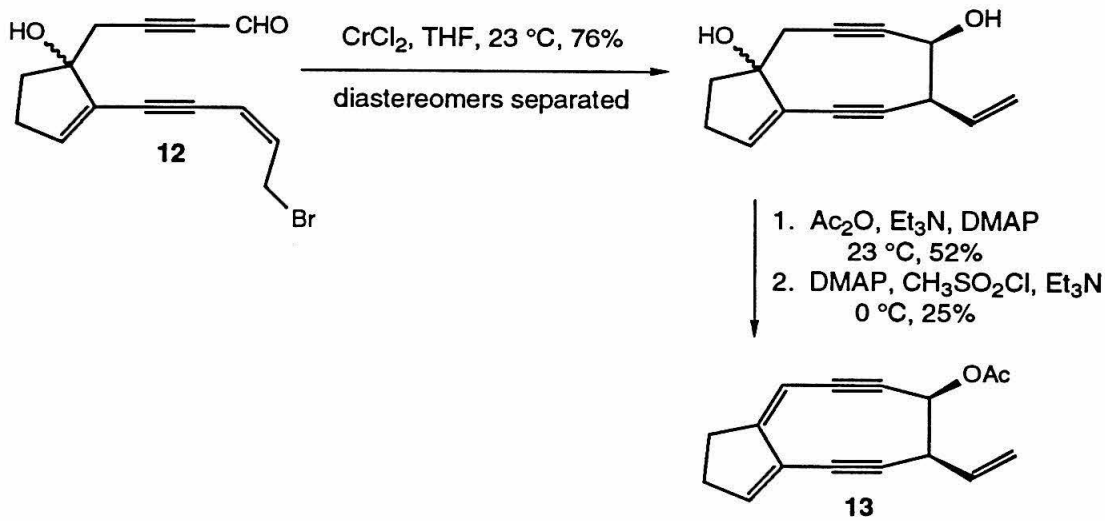


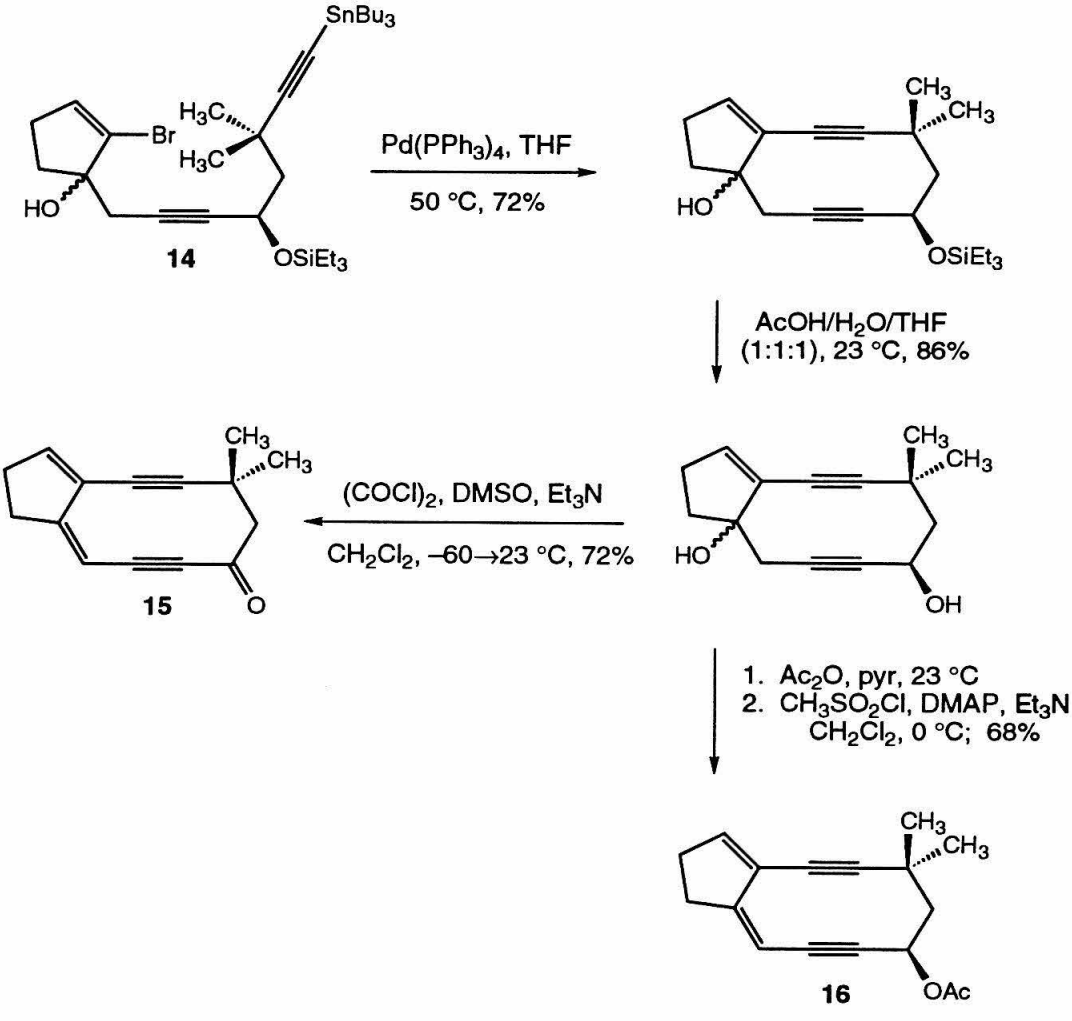
10

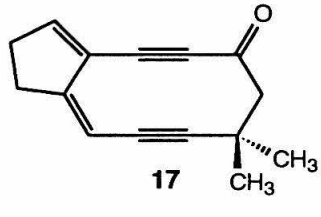
of cyclization methods. Conversely, epoxidizing after cyclization means that the instability of the cyclononadiyne system must be taken into account.

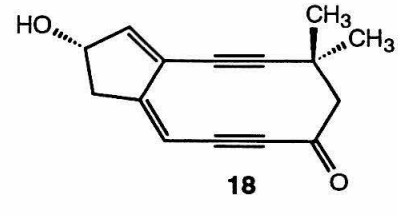
Several approaches to neocarzinostatin chromophore as well as to related molecules have appeared. As a first priority, researchers have examined various cyclization methods in an effort to obtain the cyclononadiyne core. None of the work, however, that has appeared constitutes a total synthesis of the target. Wender et al., for example, synthesized the carboskeleton of the chromophore (**10**) via a ring-contraction strategy.[19] Extrusion of sulfur dioxide from macrocycle **11** occurred upon photolysis. Subsequent dehydration of the resulting product with methanesulfonyl chloride and 4-dimethylaminopyridine provided **10**. This approach, however, does not address the incorporation of the epoxide or any other functionality. In view of this, Wender et al. synthesized the slightly more highly functionalized analog **13** using a chromium-mediated closure reaction.[20] Treatment of the bromo aldehyde **12** with chromium(II) chloride furnished the corresponding cyclononadiyne which, with acetylation and dehydration, was transformed to **13**. The epoxide again was not incorporated. Analogs **15** and **16** were synthesized by Hirama et al. via a palladium-mediated coupling reaction.[17] The vinyl bromide and alkynylstannyl groups of **14** were coupled intramolecularly with tetrakis(triphenylphosphine)palladium(0). Analog **15** was obtained by desilylation of the product followed by Swern oxidation. Alternatively, desilylation, acetylation, and dehydration yielded **16**. Analog **17** was synthesized following a similar strategy,[21] as was the more highly functionalized analog **18**.[22] Being ten-membered rings, these structures cannot be intended to demonstrate an approach to the total synthesis of the chromophore. Magnus et al. employed a boron-mediated aldol condensation reaction to synthesize the analog **21**.[23] The η^2-hexacarbonyldicobalt complex **19**, upon treatment with dibutylboron triflate, cyclized to **20**. The η^2-

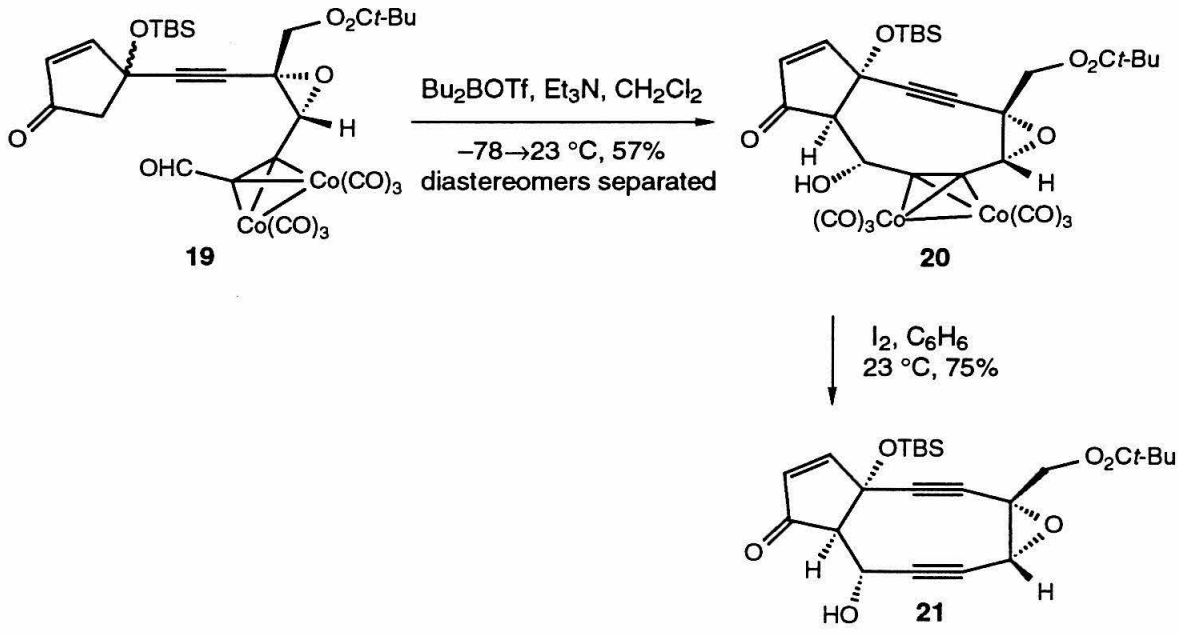

HO
SO2
11
PhCOPh, hυ, CH3CN/C6H6
23 °C, 15%
HO
CH3SO2Cl, DMAP
CH2Cl2, 23 °C
10


HO
CHO
12
Br
CrCl2, THF, 23 °C, 76%
diastereomers separated
HO
OH
1. Ac2O, Et3N, DMAP
23 °C, 52%
2. DMAP, CH3SO2Cl, Et3N
0 °C, 25%
OAc
13


SnBu3
H3C
Br
H3C
HO
14
OSiEt3
Pd(PPh3)4, THF
50 °C, 72%
CH3
CH3
HO
OSiEt3
AcOH/H2O/THF
(1:1:1), 23 °C, 86%
CH3
CH3
HO
OH
(COCl)2, DMSO, Et3N
CH2Cl2, –60→23 °C, 72%
CH3
CH3
15
O
1. Ac2O, pyr, 23 °C
2. CH3SO2Cl, DMAP, Et3N
CH2Cl2, 0 °C; 68%
CH3
CH3
16
OAc

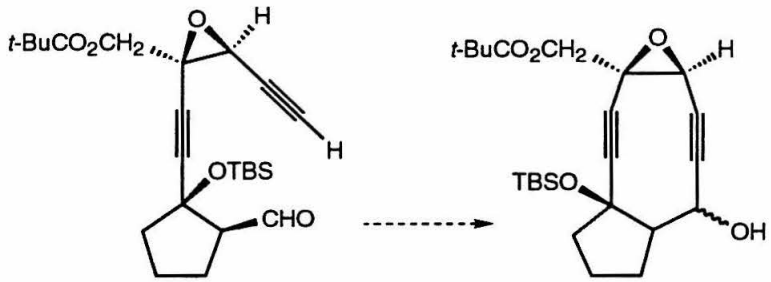

O
CH3
CH3
17


HO
CH3
CH3
18
O

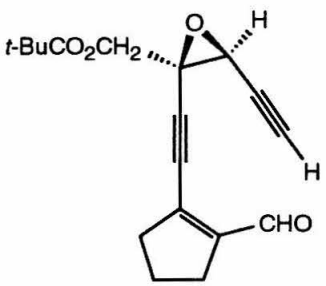


hexacarbonyldicobalt was removed by oxidation decomplexation with iodine, providing **21**.

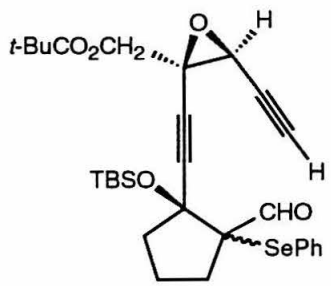
Myers and Fuhry examined the following compounds as possible precursors to be cyclized to the cyclononadiyne core of the chromophore: aldehyde **22**, epoxide **25**, and enediyne **26**.[24] With precursor **22**, an approach involving an intramolecular acetylide addition was investigated. Upon lithiation, compound **22** underwent either acyclic dimerization or elimination to provide α,β-unsaturated aldehyde **23**. Precursor **24**, obtained by selenesylation of **22**, also underwent elimination to give the aldehyde **23**. Compound **23**, when lithiated, dimerized. With epoxide **25**, an intramolecular cuprous acetylide addition to the vinyl epoxide was studied. Treatment of **25** with cuprous halides was found to result mainly in decomposition of **25**. With precursor **26**, ring closure initiated by the nucleophilic attack of cyanide ion was examined. Addition of potassium cyanide to **26** resulted in cyanohydrin formation at the aldehydic position. Based on this work, dienediyne **27** was examined as a possible cyclization precursor because the planar system perhaps had a conformation more suited for cyclization.[25] Its synthesis was not


t-BuCO2CH2
O
H
OTBS
CHO
H
TBSO
OH

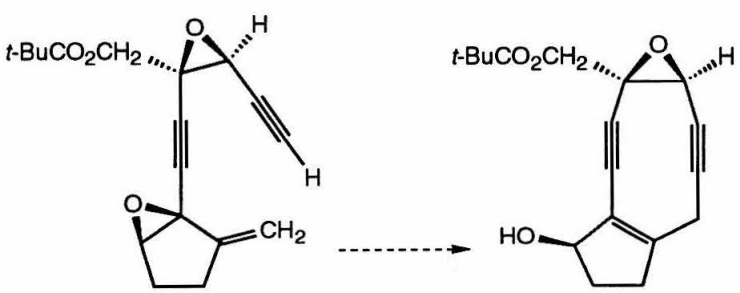
22


t-BuCO2CH2
O
H
H
CHO

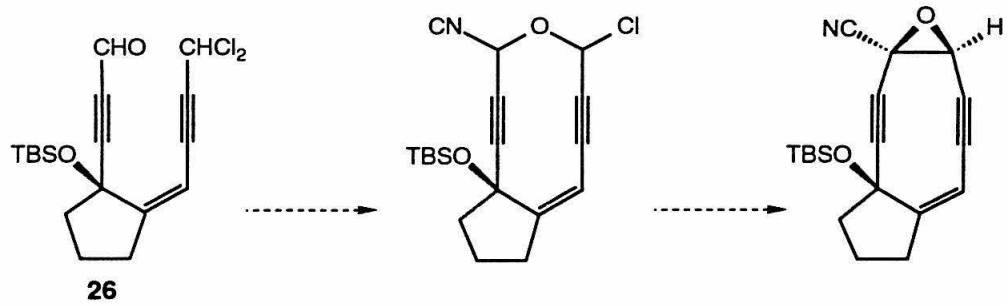
23


t-BuCO2CH2
O
H
H
TBSO
CHO
SePh

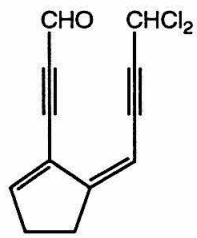
24


t-BuCO2CH2
O
H
H
O
CH2
HO

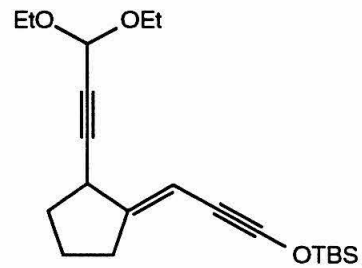
25



26



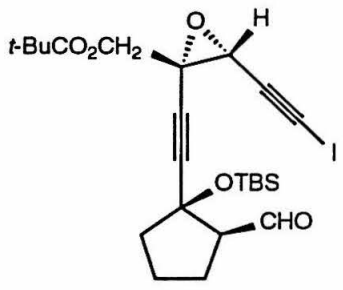
27



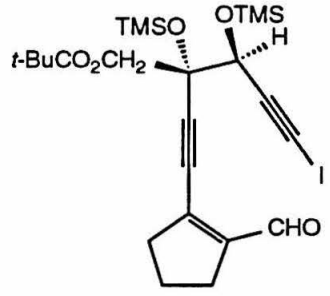
28

achieved as attempts at elimination of the tertiary hydroxyl group from an intermediate to **27** led to isomerization to the trans olefin **28**.

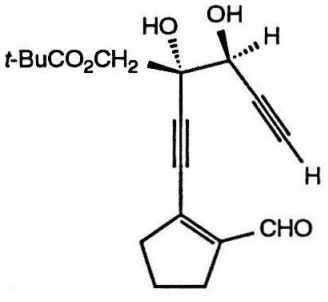
Myers and Proteau examined **29–33** as possible precursors to the cyclononadiyne core.[26] With iodo acetylenes **29** and **30**, intramolecular chromium acetylide additions catalyzed with nickel were considered. Treatment with chromium(II) chloride and nickel(II) acetylacetonate resulted in degradation of compound **29** and in reduction of the acetylenic iodide of compound **30**. Additional analogs, diol **31** and protected diols **32** and **33**, were studied but were not found to cyclize upon metalation.


t-BuCO2CH2
O
H
I
OTBS
CHO

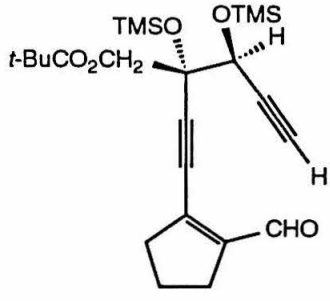
29


TMSO
OTMS
H
t-BuCO2CH2
I
CHO

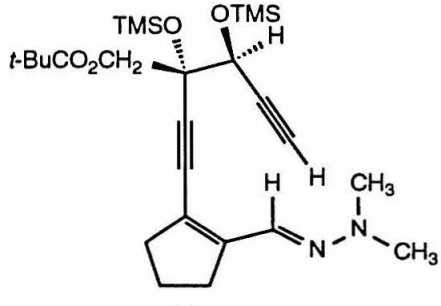
30


HO
OH
H
t-BuCO2CH2
H
CHO

31

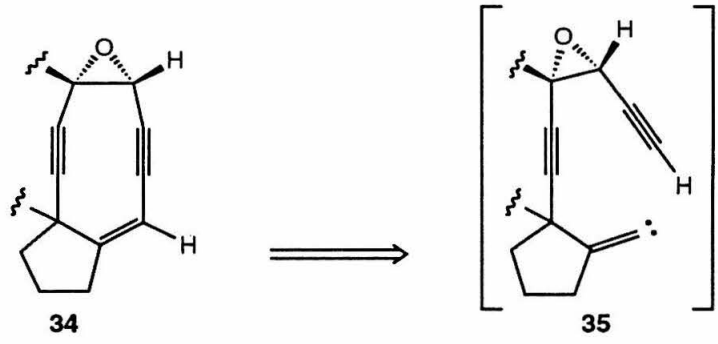

TMSO
OTMS
H
t-BuCO2CH2
H
CHO

32


TMSO
OTMS
H
t-BuCO2CH2
H
H
CH3
N
N
CH3

33

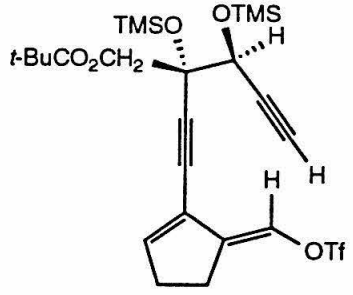
An Intramolecular Alkylidene Carbene Insertion Approach to Neocarzinostatin Chromophore



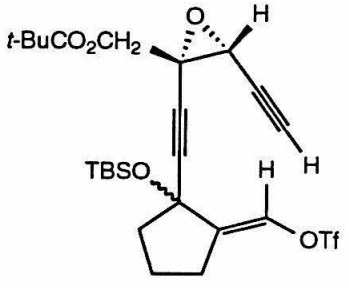
34 **35**

As seen above, various strategies were examined as a means of providing the cyclononadiyne core. An entirely different approach involves the generation of a cyclopentylidene carbene and its intramolecular insertion into an acetylenic carbon-hydrogen bond (**35**→**34**). Such an approach allows the synthesis of a cyclononadiyne core containing the epoxide as well as one of the double bonds of the chromophore. In addition, a high-energy intermediate, such as carbene **35**, may be able to overcome what is expected to be the high energy barrier to cyclization (*vide supra*). The insertion of a carbene such as **35** is initially estimated to be exothermic by approximately 60 kcal/mol because the acetylenic carbon-hydrogen bond, which has a bond energy of 125 kcal/mol,[27] is replaced with carbon-carbon and carbon-hydrogen bonds, which have bond energies of 81[28] and 103 kcal/mol,[27] respectively. The strain of the cyclononadiyne structure should decrease this exothermicity to some degree.

An alkylidene carbene can be generated from a variety of methods,[29] for example, by the α-elimination of an enol triflate with potassium *t*-butoxide as demonstrated by Stang.[30] In view of this, two enol triflates were synthesized in an effort to generate carbenes such as **35**. Enol triflate **36** was synthesized by Myers and Proteau.[26] Treatment of this compound with potassium *t*-butoxide resulted in its decomposition.



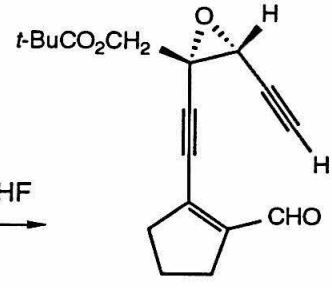
36



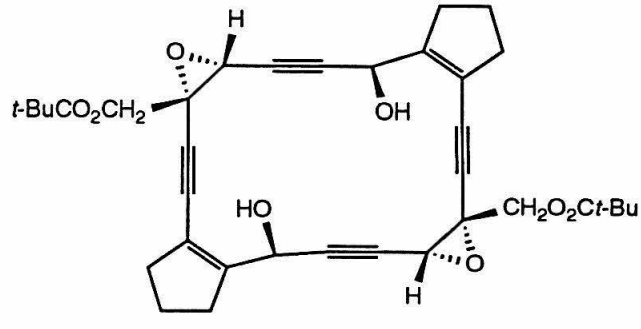
37

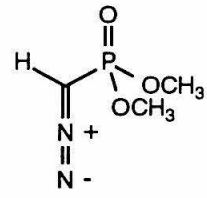
KO*t*-Bu, THF

–40 °C



~20%

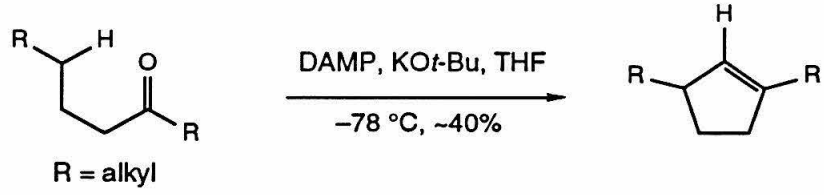


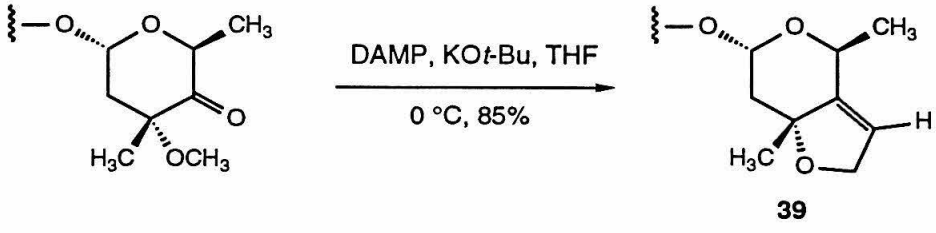


38

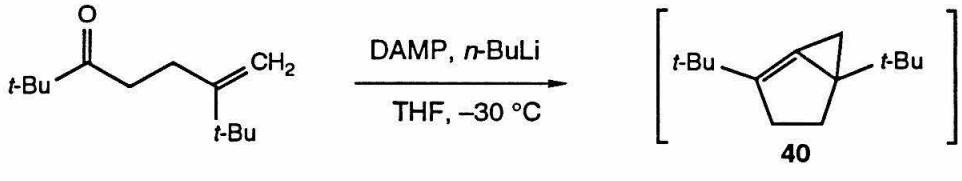
Another enol triflate, **37**, was constructed by Myers et al.[31] When it was treated with potassium *t*-butoxide, an α,β-unsaturated aldehyde was obtained, which formed cyclic dimers (20%). It was not shown in either case that the desired alkylidene carbene was generated.

Another method to generate an alkylidene carbene such as **35** was then considered, one which involves the reaction of a carbonyl with dimethyl diazomethylphosphonate (DAMP, **38**). Gilbert et al. showed that dimethyl diazomethylphosphonate transforms aldehydes and ketones to alkylidene carbenes with potassium *t*-butoxide.[32] A Wittig-type mechanism is presumed to be involved with loss of dinitrogen from an intermediate diazoethene. The (C=C=N) angle of a diazoethene has been proposed to be nonlinear based on calculations.[33] The carbene is produced initially free of complexation with solvent and in its singlet electronic state.[34] Precedent exists for the use of DAMP in intramolecular alkylidene carbene insertions. Gilbert et al. demonstrated that dialkyl ketones form cyclopentenes with DAMP and potassium *t*-butoxide at –78 °C in tetrahydrofuran (~40%).[35] These cyclopentenes appear to arise from insertion of the intermediate carbenes into γ-carbon-hydrogen bonds, with the following selectivity: tertiary > secondary (benzylic) > secondary > primary. Hauske et al. altered the cladinose moiety of erythromycin A to dihydrofuran **39** by reaction with DAMP and potassium *t*-butoxide at 0 °C in tetrahydrofuran (85%).[36] Salinaro and Berson generated the highly unstable bicyclo[3.1.0]hex-1-ene **40** with DAMP and butyllithium at –30 °C.[37]

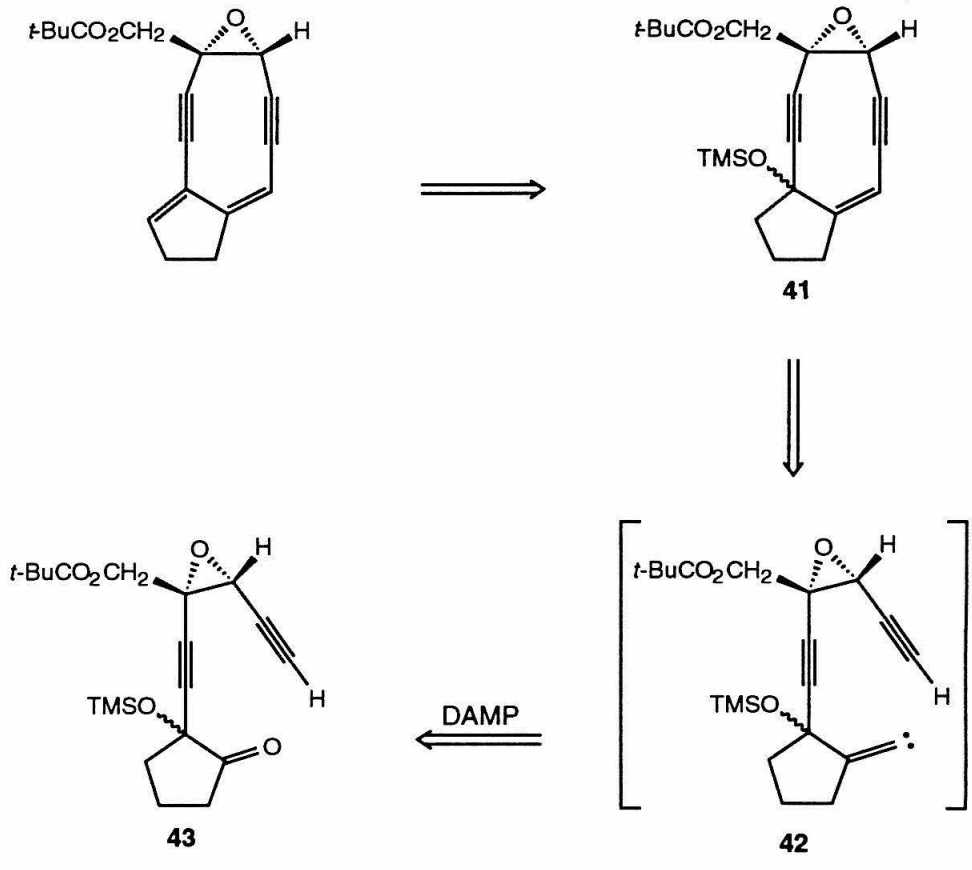

R
H
O
R
R = alkyl
DAMP, KO*t*-Bu, THF
–78 °C, ~40%
H
R
R


O
O
CH3
O
H3C
OCH3
DAMP, KO*t*-Bu, THF
0 °C, 85%
O
O
CH3
H
H3C
O

39

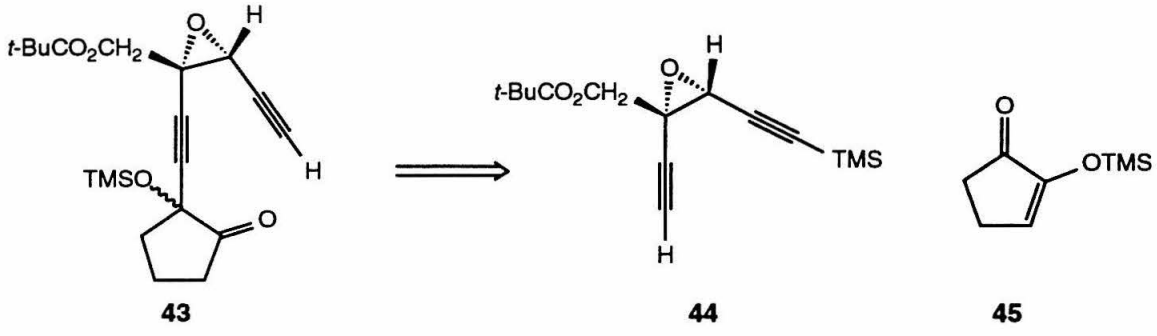

O
t-Bu
CH2
t-Bu
DAMP, *n*-BuLi
THF, –30 °C
t-Bu
t-Bu

40



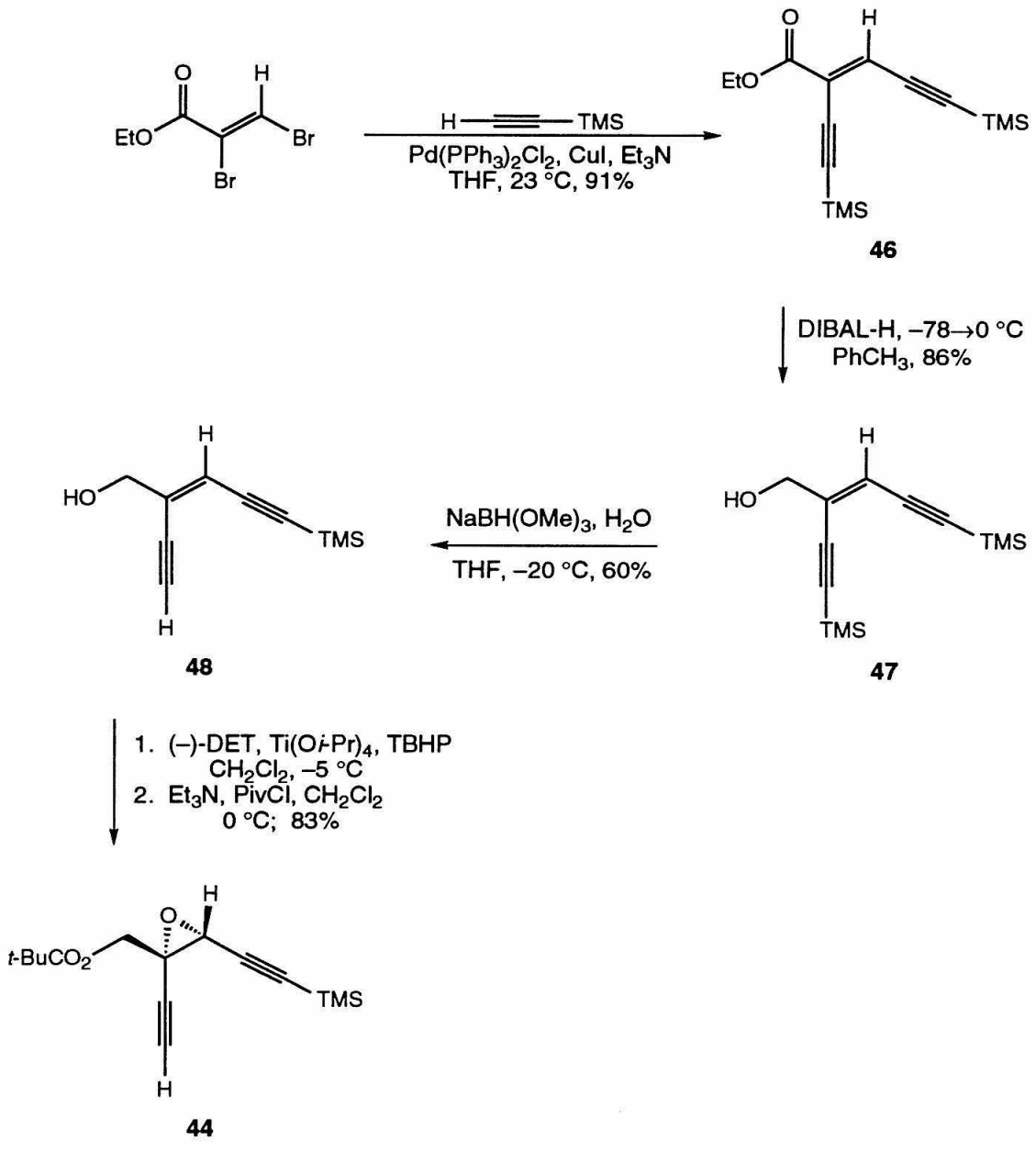
Ketone **43** was selected as the substrate for reaction with DAMP. It was designed with the ultimate goal of the total synthesis of neocarzinostatin chromophore in mind. It contains the (C-4,C-5)-epoxide crucial to neocarzinostatin chromophore activity. The pivalate-protected hydroxyl group provides a handle for the construction of the ethylene carbonate, while elimination of the tertiary hydroxyl group, after its deprotection, serves to complete the diene construction of the chromophore. As discussed in this chapter, ketone **43** was synthesized and was reacted with DAMP under various reaction conditions. While the identification of the reaction products was consistent with the formation of carbene **42**, the formation of the desired insertion product, **41**, was not observed.

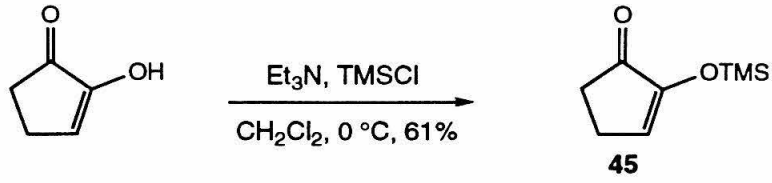
Synthesis of Ketone 43



Ketone **43** was synthesized from two fragments, epoxy diyne **44** and cyclopentenone **45**. Epoxy diyne **44** was synthesized as follows.[38] (*Z*)-Ethyl-2,3-dibromopropenoate[39] and (trimethylsilyl)acetylene (2.75 equiv) were coupled in the presence of bis(triphenylphosphine)palladium(II) chloride (0.063 equiv), cuprous iodide (0.25 equiv), and triethylamine (8.0 equiv) in tetrahydrofuran at 23 °C to afford the (*Z*)-enediyne **46** after flash column chromatography (91%). Reduction of **46** with diisobutylaluminum hydride (2.5 equiv) in toluene at –78→0 °C furnished the alcohol **47** (86%).

The acetylenic groups of **47** were differentiated by selective desilylation at –20 °C with a reagent prepared by limited exposure (5 min at –20°C) of sodium trimethoxyborohydride (1.25 equiv) to water (0.5 equiv) in tetrahydrofuran. Pure monodesilylated alcohol **48** (60%) and recovered starting material (20%) were obtained after flash column chromatography, as well as a small amount of the doubly desilylated product (< 20%). Under these reaction conditions, some silylation of the hydroxyl groups of the starting material and products were seen. An acidic work-up was employed to deprotect these compounds. Potassium fluoride dihydrate (3.0 equiv) in 2:3:15 methanol-*N*,*N*-dimethylformamide-tetrahydrofuran at –15 °C also differentially desilylated **47**,


EtO
Br
Br
H—≡—TMS
Pd(PPh3)2Cl2, CuI, Et3N
THF, 23 °C, 91%
TMS
TMS
46
DIBAL-H, –78→0 °C
PhCH3, 86%
HO
TMS
47
NaBH(OMe)3, H2O
THF, –20 °C, 60%
48
1. (–)-DET, Ti(Oi-Pr)4, TBHP
CH2Cl2, –5 °C
2. Et3N, PivCl, CH2Cl2
0 °C; 83%
t-BuCO2
TMS
44

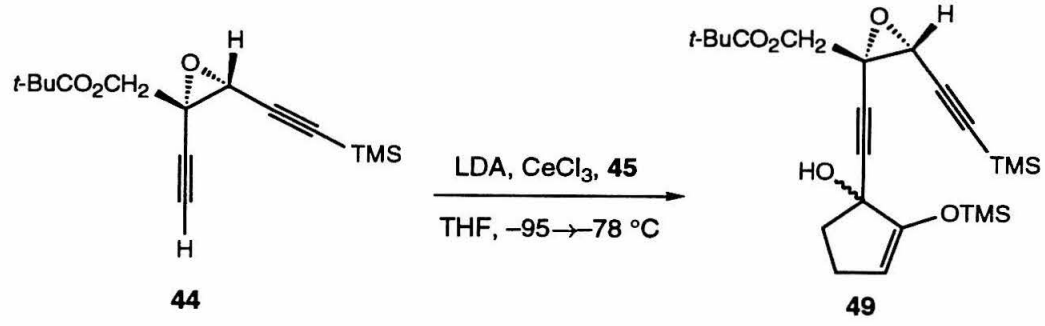


45

affording the desired product (28%) and recovered starting material (52%). The difference between the rates of desilylation of the two acetylenic trimethylsilyl groups seen was not as great as with sodium trimethoxyborohydride. Perhaps sodium trimethoxyborohydride complexes to some extent to the hydroxyl group of **47**, leading to a more selective removal of the proximal trimethylsilyl group.

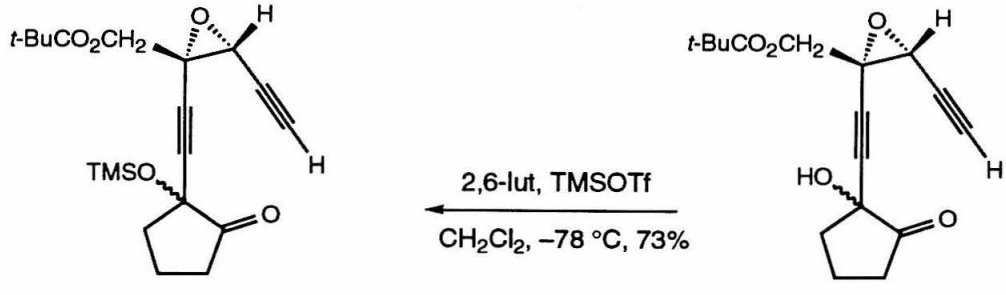
The epoxidation of the olefin of **48** was expected to be difficult as the double bond is deactivated by the electron-withdrawing acetylenic moieties. Myers and Fuhry[24] were able to epoxidize a similar enediyne with the Sharpless catalytic asymmetric epoxidation.[40] In this case as well, the Sharpless reaction proceeded in good yield and enantioselectivity. Epoxidation ((–)-diethyl D-tartrate (0.15 equiv), titanium(IV) isopropoxide (0.10 equiv), *tert*-butyl hydroperoxide (3.54 M in dichloromethane, 2.5 equiv), dichloromethane, –5 °C) followed by in situ esterification with triethylamine (3.4 equiv) and pivaloyl chloride (2.3 equiv) at 0 °C provided the (*R*,*R*)-epoxy diyne **44** (83% yield, 93% ee[41]).[42]

Cyclopentenone **45** was obtained from cyclopentane-1,2-dione[43] by silylation with triethylamine (2.5 equiv) and chlorotrimethylsilane (1.5 equiv) in dichloromethane at 0 °C (61%). The addition of the acetylide of **44**, prepared with lithium diisopropylamide (1.26 equiv) and cerium(III) chloride (1.3 equiv) in tetrahydrofuran at –95 °C,[44] to the cyclopentenone **45** (1.25 equiv) at–95→–78 °C in tetrahydrofuran furnished the adduct **49**. Acetylide addition was complicated by competing side reactions. Epoxide **44** was silylated at the acetylenic position or deprotonated at the epoxy position to provide the furan **51**. As adduct **49** was unstable, it was immediately

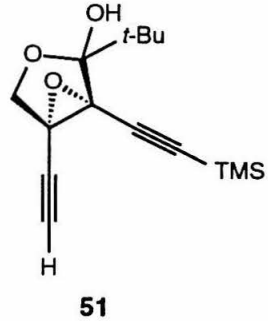


44 **49**

KF•2H2O, MeOH
0 °C; 41%



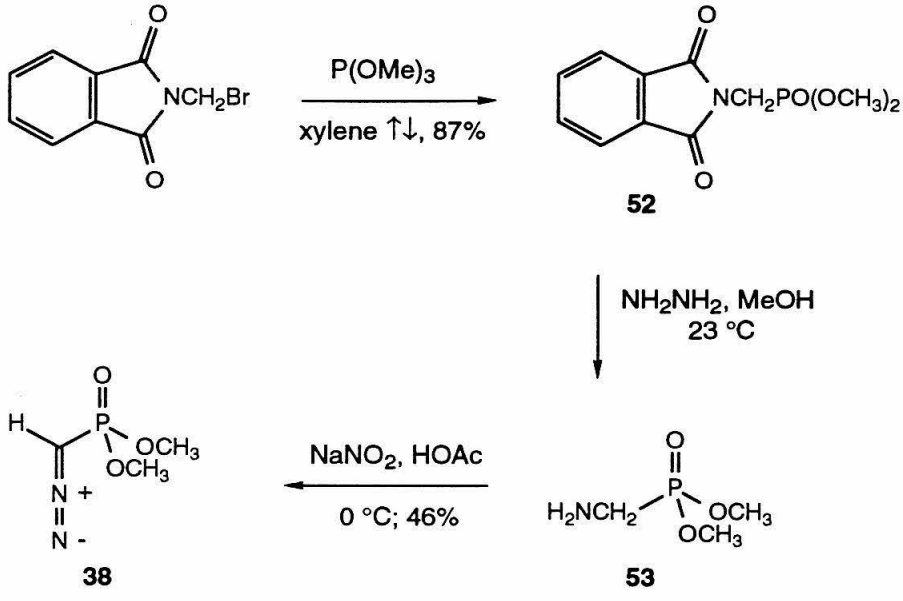
43 **50**



51

desilylated with potassium fluoride dihydrate (9.0 equiv) in methanol at 0 °C to the ketone **50** (41% from **44**, 1:1 diastereomeric ratio). Silylation of the tertiary hydroxyl group of **50** with 2,6-lutidine (15.0 equiv) and trimethylsilyl trifluoromethanesulfonate (1.5 equiv) in dichloromethane at –78 °C provided the desired ketone **43** (73%).

The Reaction of Ketone 43 with DAMP

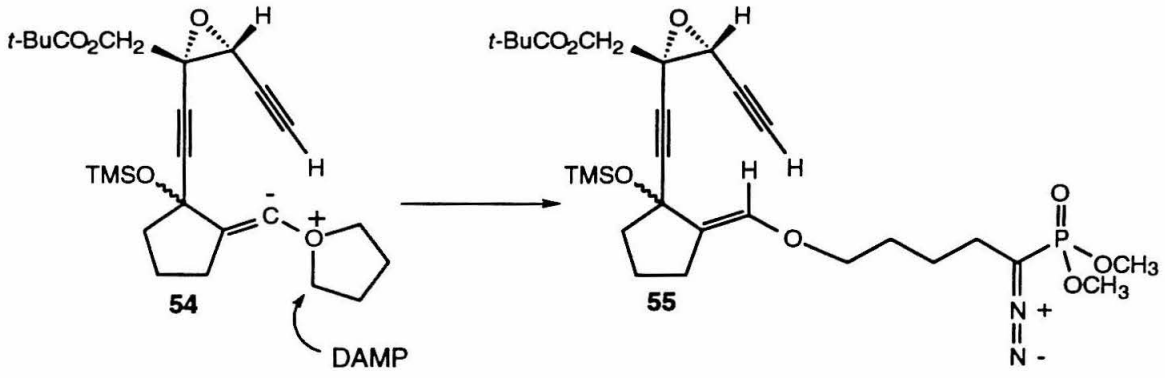


The Gilbert reagent, DAMP, was synthesized from bromomethylphthalimide according to the procedure of Seyferth et al.[45] The reaction of bromomethylphthalimide with trimethyl phosphite (1.1 equiv) in refluxing xylene resulted in dimethyl phthalimidomethylphosphonate (**52**, 87%). The addition of hydrazine (95%, 1.05 equiv) to a solution of **52** in methanol at 23 °C provided the dimethyl aminomethylphosphonate (**53**). Oxidation of **53** with sodium nitrite (1.5 equiv) and acetic acid (4.4 equiv) in water at 0 °C furnished DAMP (**38**, 46% from **52**, purified by distillation).

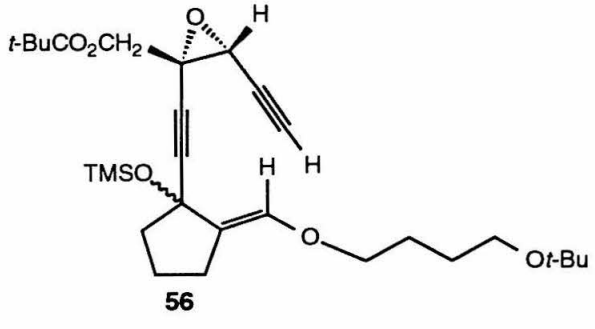
DAMP and ketone **43** were reacted under a variety of conditions. During the course of these studies, the reaction mixtures were partially concentrated with benzene-d_6 three or four times, permitting the ^{1}H NMR analysis of products without subjecting them to concentration, or flash column or preparative thin layer chromatography. This should have allowed for the observation of the unstable desired insertion product **41**. The reaction of ketone **43** with DAMP (3.3 equiv) and potassium *t*-butoxide (3.0 equiv) in tetrahydrofuran in –78 °C was found to provide the enol ether **55** (10%;[46] Table II, entry

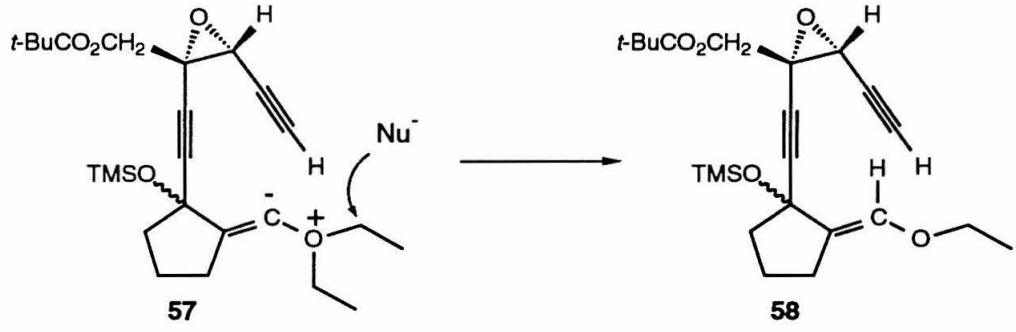
Table II. Reactions of Ketone **43** with Dimethyl Diazomethylphosphonate.

Entry	Reaction Conditions	Isolated Product (yield)
1	DAMP (3.3 equiv), KO*t*-Bu (3.0 equiv), THF, –78 °C	**55** (10%)
2	DAMP (2.0 equiv), KO*t*-Bu (2.0 equiv), THF, –78→23 °C	**56** (15%)
3	DAMP (2.0 equiv), KO*t*-Bu (3.9 equiv), THF, 0 °C	**55** (10%), **56** (10%)
4	DAMP (1.7 equiv), KO*t*-Bu (1.5 equiv), ethyl ether –78→23 °C	**58** (10%)
5	DAMP (1.7 equiv) $KN(TMS)_2$ (1.5 equiv) toluene, –78 °C	**59** (10%)
6	DAMP (8.0 equiv), LiCl (10.0 equiv), DBU (24.0 equiv) acetonitrile, 23 °C	**61** (15%), **62** (10%)



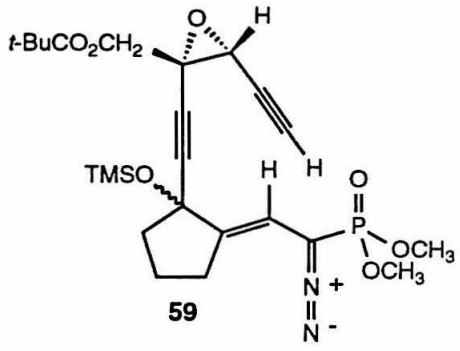
1) as the major product.[47] This enol ether may be thought to result from the complexation of tetrahydrofuran to the alkylidene carbene **42** to form the ylide **54** and the subsequent attack of DAMP at one of the α-carbons of tetrahydrofuran. Gilbert et al. discussed this phenomenon, indicating that ylides such as **54** arise from the thermal decomposition of the DAMP-generated diazoethenes followed by complexation with tetrahydrofuran, and may be trapped by attack of *t*-butanol at one of the α-carbons of tetrahydrofuran.[32c,f] Indeed, altering the reaction temperature to –78→23 °C (DAMP (2.0 equiv), potassium *t*-butoxide (2.0 equiv), THF; Table II, entry 2) furnished the enol ether **56** (15%), most likely resulting from the attack of potassium *t*-butoxide on ylide **54**. Performing the reaction at 0 °C (DAMP (2.0 equiv), potassium *t*-butoxide (3.9 equiv), THF; Table II, entry 3) allowed the isolation of both **55** and **56** (10% each).



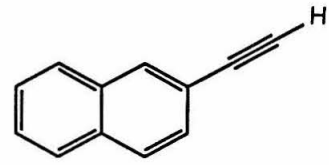


To prevent the formation of these tetrahydrofuran-trapped products, less coordinating solvents were used. Ketone **43** was reacted (DAMP (1.7 equiv), potassium *t*-butoxide (1.5 equiv), –78→23 °C) in ethyl ether (Table II, entry 4). The product isolated, the enol ether **58** (10%), still indicated solvent coordination, as it appears to result from the formation of ylide **57** and attack by a nucleophile at one of the α-carbons of ethyl ether. Performing the reaction in a non-coordinating solvent, toluene (DAMP (1.7 equiv), potassium bis(trimethylsilyl)amide (1.5 equiv), –78 °C; Table II, entry 5) allowed the isolation of the olefin **59** (10%), the product of the interaction of the intermediate carbene **42** with DAMP itself.

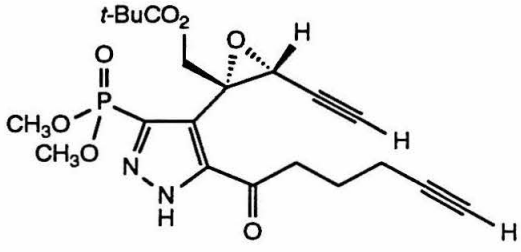
In a further modification of Gilbert's methodology, ketone **43** was reacted with DAMP using the Masamune and Roush variation of the Horner-Wadsworth-Emmons reaction, in which Wittig-type phosphonates are deprotonated in the presence of a lithium salt with an amine instead of with a stronger base.[48] These conditions allowed the use of a milder, bulkier base, the less reactive lithium-coordinated (versus potassium) anion of DAMP, and a higher reaction temperature. In order to demonstrate that DAMP was still effective under these conditions, 2-naphthaldehyde was transformed to 2-naphthacetylene (**60**, 92%) with lithium chloride (2.0 equiv), DAMP (2.0 equiv), and 1,8-diazobicyclo[5.4.0]undec-7-ene (1.8 equiv) in acetonitrile at 23 °C, presumably via an alkylidene carbene intermediate. When ketone **43** was subjected to similar reaction conditions (lithium chloride (10.0 equiv), DAMP (8.0 equiv), 1,8-diazobicyclo[5.4.0]-



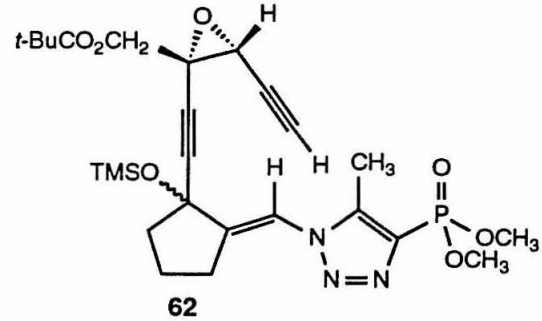
59



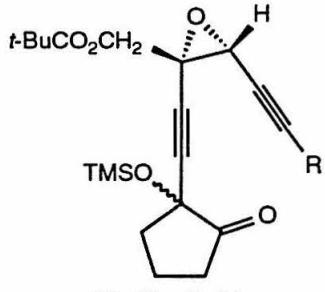
60



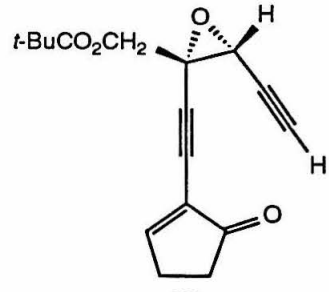
61



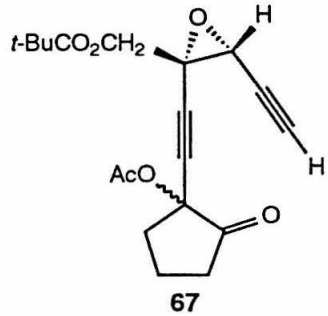
62



63 R = $SnMe_3$
64 R = TMS
65 R = I



66



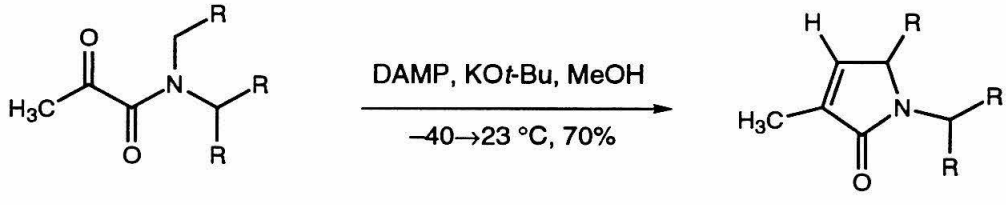
67

undec-7-ene (24.0 equiv), acetonitrile, 23 °C), the heterocycles **61** and **62** were obtained (15 and 10% each, respectively; Table II, entry 6). Both compounds reacted intermolecularly, incorporating DAMP. Compound **62** incorporated acetonitrile as well.

In an effort to make the intramolecular process more accessible, the carbon-hydrogen bond of ketone **43** was replaced with longer, more labile bonds. To this end, trimethylstannyl, trimethylsilyl, and iodo analogs (**63**, **64**, and **65**, respectively) were synthesized. The reaction of analog **63** under the modified, Masamune and Roush, conditions still produced the heterocycles **61** and **62** as the major products. The reaction of analog **64** under the Gilbert conditions in ethyl ether furnished the silylated analog of enol ether **58**, while the reaction under the modified conditions resulted in the heterocycles **61** and **62**. Analog **65** was also not seen to give the desired product under the modified conditions. Additional compounds where the putative trajectory of attack of the alkylidene carbene was altered by hybridization or substitution at the α-pentanone center, for example, alkene **66** and acetate **67**, were also not found to be effective under the modified conditions.

These studies showed that the intramolecular insertion of alkylidene carbene **42** is not a viable approach to neocarzinostatin chromophore under the investigated reaction conditions. While the carbene was generated, it reacted by pathways that were more accessible to it, in this case, intermolecular trapping by solvents and nucleophiles. Several factors may make the desired insertion more difficult than the known intramolecular insertions of DAMP-generated carbenes (*vide supra*). For example, the yields of products from 1,5-insertions in aliphatic systems were observed to be inversely related to the dissociation energy of the carbon-hydrogen bond undergoing insertion.[49] If this trend holds for all carbon-hydrogen bonds, the insertion into the stronger acetylenic hydrogen bond, while it is known,[50] should be more difficult than that into the aliphatic carbon-hydrogen bonds. In addition, as noted above, this insertion may have to

overcome substantial strain energy in order to be successful. While alkylidene carbene **42** was originally chosen for its reactivity, it does not seem to be able to overcome what may be a high energy barrier of cyclization. It may even simply be that the trajectory of attack necessary for insertion was inaccessible to alkylidene carbene **42**. Intramolecular insertions with DAMP-generated carbenes seem to be more favored over intermolecular processes also if the carbon-hydrogen bond undergoing insertion is adjacent to a heteroatom. The cyclization of Hauske et al. (*vide supra*) successfully occurred in the presence of tetrahydrofuran and in the presence of a large excess of allyl alcohol. In the reaction of pyruvamides with DAMP and potassium *t*-butoxide in methanol, intramolecular carbon-hydrogen insertion was observed by Gilbert and Blackburn with no methanol oxygen-hydrogen bond insertion.[51] They have proposed that orbital



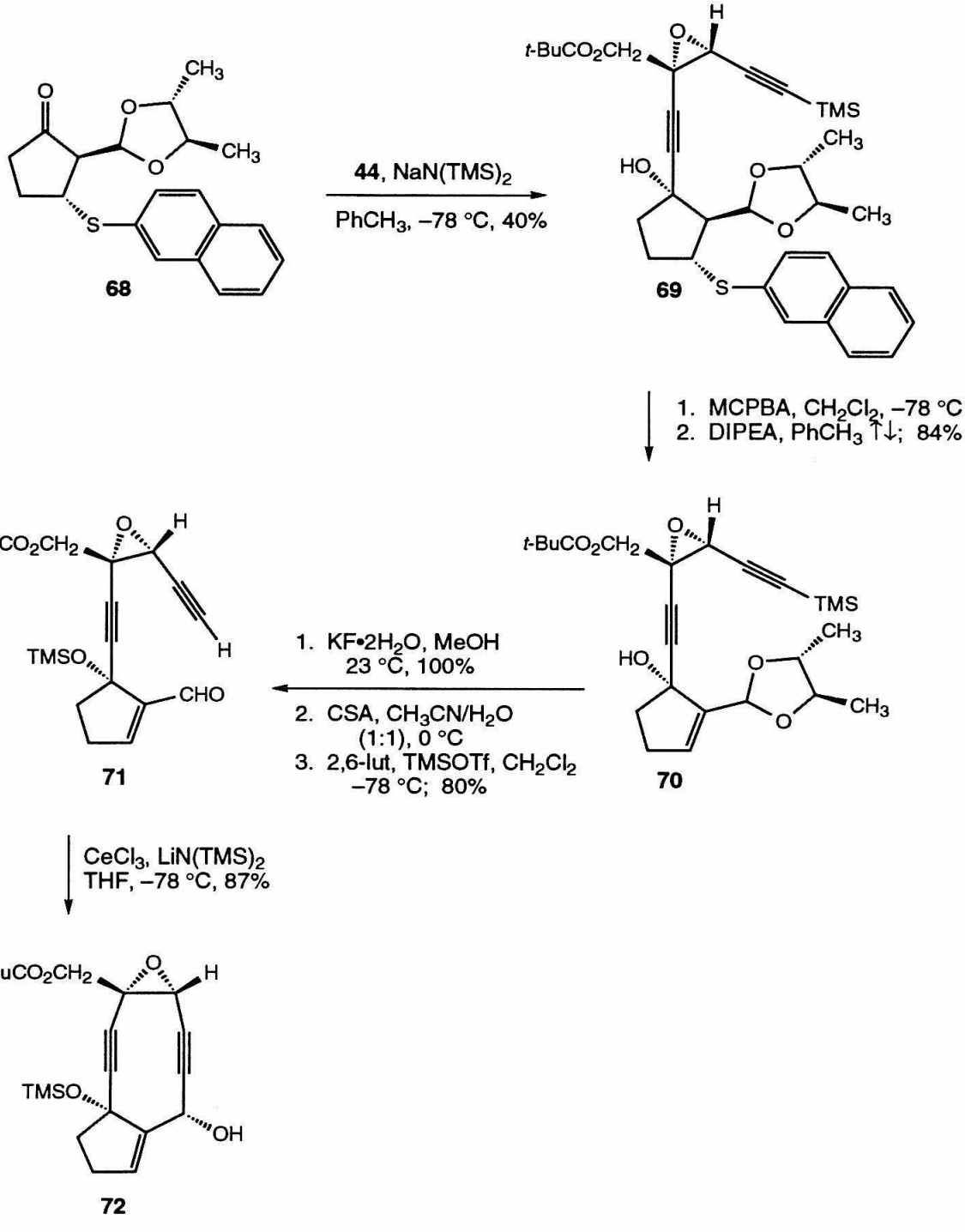
interactions between the non-bonding electrons of the heteroatom and the incoming carbon atom stabilize the transition state, making these insertions more favorable than intermolecular processes.

An Alternative Approach to Neocarzinostatin Chromophore

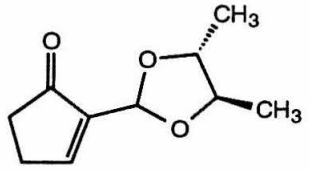
While the intramolecular insertion approach described above did not seem feasible, the cyclononadienediyne core **76** was synthesized with a different approach. The cyclization was accomplished by an intramolecular acetylide addition of substrate **71**.[52] Unlike in the studies of Fuhry and Proteau (*vide supra*), this substrate appeared more able to assume the conformation necessary for acetylide addition, presumably one allowing the acetylide to approach the aldehyde at the Dunitz angle.[53] Moreover, the acetylide addition was performed in the presence of cerium(III) chloride, which seemed to suitably mediate the reactivity of the acetylide.[44]

Metalation of epoxide **44** (1.15 equiv) with sodium bis(trimethylsilyl)amide (1.0 M in tetrahydrofuran, 1.05 equiv) in toluene at –78 °C followed by addition of ketone **68** provided the coupling product **69** (18:1 mixture of β-hydroxy epimers, separated by flash column chromatography, 40%). The absolute stereochemistry of ketone **68** was determined by X-ray cystallographic analysis of the corresponding anti oxime.[54] Sulfoxide formation (*meta*-chloroperbenzoic acid, dichloromethane, –78 °C) and elimination (diisopropylethylamine, toluene reflux) furnished exclusively the trisubstituted cyclopentene **70** (84%, from **69**). Desilylation of **70** occurred in quantitative yield upon exposure to potassium fluoride dihydrate in methanol at 23 °C. Acetal hydrolysis (0.05 M camphorsulfonic acid, 1:1 acetonitrile-water, 0 °C) and silylation of the tertiary hydroxyl group (2,6-lutidine (20.0 equiv), trimethylsilyl trifluoromethanesulfonate (8.0 equiv), dichloromethane, –78 °C) afforded the aldehyde **71** (80% overall). Cyclization was achieved by treating a slurry of **71** and anhydrous cerium(III) chloride (3.0 equiv) in tetrahydrofuran at –78 °C with excess lithium bis(trimethylsilyl)amide (25.0 equiv), providing the cyclononadiyne **72** (87%).[44]

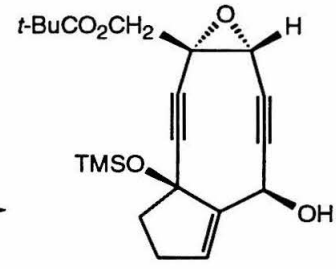
In a modification of this approach, metalation of epoxide **44** (1.0 equiv) with sodium bis(trimethylsilyl)amide (1.05 equiv, 1.0 M in tetrahydrofuran) in toluene at –78


68
44, NaN(TMS)2
PhCH3, –78 °C, 40%
69
1. MCPBA, CH2Cl2, –78 °C
2. DIPEA, PhCH3 ↑↓; 84%
70
1. KF•2H2O, MeOH
23 °C, 100%
2. CSA, CH3CN/H2O
(1:1), 0 °C
3. 2,6-lut, TMSOTf, CH2Cl2
–78 °C; 80%
71
CeCl3, LiN(TMS)2
THF, –78 °C, 87%
72

°C followed by addition of ketone **73** yielded a mixture of diastereomers (31%). Further manipulations as above and separation of the diastereomers after cyclization allowed the isolation of the cyclononadiyne **74**. Silylation with chlorotrimethylsilane and triethylamine followed by exposure to trifluoroacetic acid (0.2 M in dichloromethane, 5.0 equiv, 0 °C) provided the trifluoroacetate **75** (49%). Methanol and triethylamine in toluene at 0 °C hydrolyzed **75** to the corresponding alcohol, which was silylated at –78 °C with *tert*-butyldimethylsilyl trifluoromethanesulfonate-lutidine. Selective removal of the trimethylsilyl group with hydrogen fluoride-triethylamine in acetonitrile and elimination of the resulting hydroxyl group with methanesulfonic acid anhydride-pyridine afforded the epoxy dienediyne **76** (22%, from **75**). Current studies seek to apply this approach to the total synthesis of neocarzinostatin chromophore.[55]

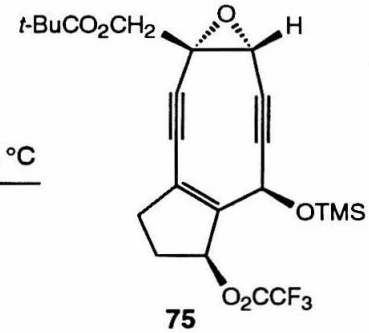


73



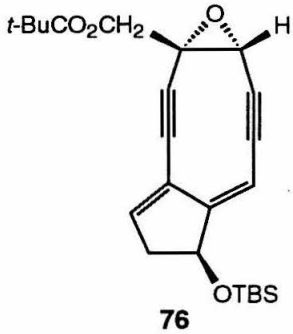
74

1. TMSCl, Et_3N
2. TFA, CH_2Cl_2, 0 °C; 49%



75

1. MeOH, Et_3N, 0 °C
2. TBSOTf, 2,6-lut, –78 °C
3. HF, Et_3N, CH_3CN
4. Ms_2O, pyr; 22%



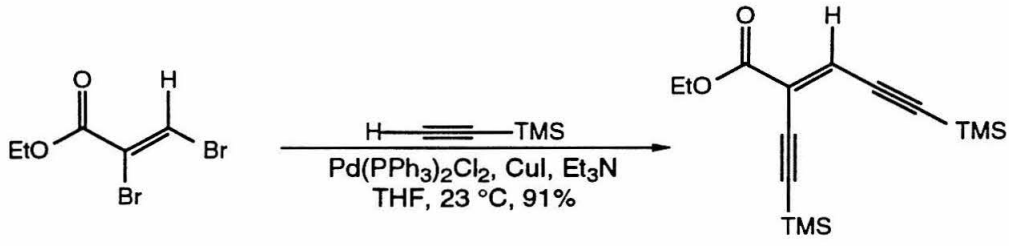
76

Experimental Section

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 (three iterations). Organic solutions were concentrated by rotary evaporation at ~25 Torr (water aspirator). Flash column chromatography was performed as described by Still et al. employing 230-400 mesh silica gel.[56] 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).

Commercial reagents and solvents were used as received with the following exceptions. (*Z*)-Ethyl-2,3-dibromopropenoate[39] and cyclopentane-1,2-dione[43] were prepared according to the literature procedure. Tetrahydrofuran was distilled from sodium benzophenone ketyl. Triethylamine, toluene, dichloromethane, and chlorotrimethylsilane were distilled from calcium hydride at 760 Torr. Cuprous iodide was purified by continuous extraction (12 h) with tetrahydrofuran in a Soxhlet apparatus. Solutions of *tert*-butyl hydroperoxide in dichloromethane were prepared and titrated according to the literature procedure.[40] Anhydrous cerium(III) chloride was prepared from the heptahydrate by heating at 100 °C and 1 Torr for 12 h. Solutions of lithium diisopropylamide in tetrahydrofuran (0.5 M) were prepared immediately prior to use by the addition of butyllithium (1.6 M in hexanes, 1.0 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. (–)-Diethyl D-tartrate, methanol, and 2,6-lutidine were dried and were stored over 3 Å sieves.

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 absorbtion (cm^{-1}), intensity of absorbtion (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) 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 7.24, C_6HD_5: δ 7.15). Data are presented 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 from the University of California, Riverside Mass Spectrometry Facility.[57]



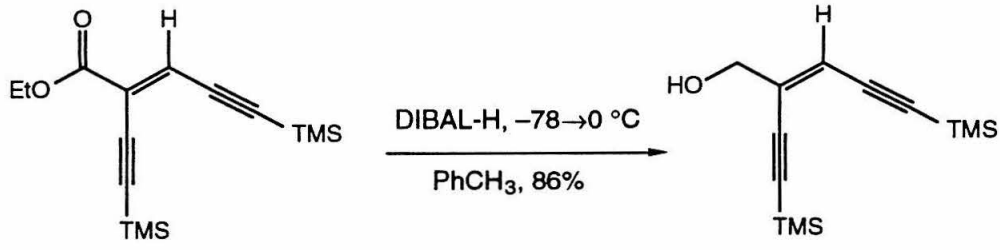
46

(Z)-Enediyne **46**

Bis(triphenylphosphine)palladium(II) chloride (4.29 g, 6.11 mmol, 0.063 equiv) and (Z)-ethyl-2,3-dibromopropenoate (25.0 g, 0.097 mol, 1.0 equiv) in tetrahydrofuran (200 mL) were deoxygenated and were stirred at 23 °C for 1 h. In a separate flask, deoxygenated triethylamine (108.0 mL, 0.77 mol, 8.0 equiv) and deoxygenated (trimethylsilyl)acetylene (38.0 mL, 0.27 mol, 2.75 equiv) were added to a deoxygenated suspension of cuprous iodide (4.61 g, 0.024 mol, 0.25 equiv) in tetrahydrofuran (250 mL) at 0 °C, deoxygenating after each addition. The mixture was stirred at 23°C for 15 min, and the resulting green solution was transferred portionwise via cannula to the palladium suspension at 0 °C. The combined mixtures were stirred at 23 °C for 7 h. The reaction mixture was diluted with 50% ethyl acetate in hexanes. The mixture was stirred over saturated aqueous ammonium chloride and saturated aqueous potassium carbonate (400 mL each) in the air at 23 °C for 30 min. The separated organic layer was washed with saturated aqueous sodium chloride, and then it was dried over sodium sulfate and was concentrated. The residue thus obtained was purified by flash column chromatography (3% and 5% ethyl acetate in hexanes) to provide the (Z)-enediyne **46** (25.67 g, 91%) as a brown oil.

R_f (15% toluene in hexanes): 0.14

IR (neat):	2963 (s), 2896 (m), 2147 (w, C≡C), 1719 (s, CO_2Et), 1562 (m), 1359 (m), 1247 (s), 1059 (s), 887 (m), 842 (s), 752 (s), 632 (s)
^1H NMR (400 MHz, $CDCl_3$):	6.91 (s, 1 H, C=C**H**), 4.22 (q, 2 H, J = 7.1 Hz, $CH_3C\mathbf{H}_2$), 1.29 (t, 3 H, J = 7.1 Hz, $\mathbf{CH}_3CH_2$), 0.23 (s, 9 H, $Si(C\mathbf{H}_3)_3$), 0.22 (s, 9 H, $Si(C\mathbf{H}_3)_3$)
HRMS:	calcd for $C_{15}H_{25}O_2Si_2$ (MH^+): 293.1393 found: 293.1393



46 **47**

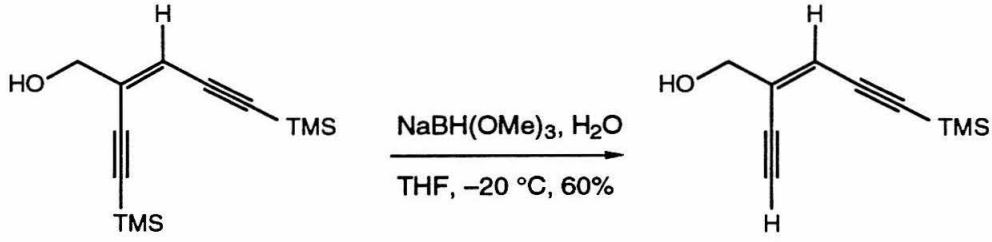
Alcohol **47**

Diisobutylaluminum hydride (1.0 M in toluene, 47.0 mL, 0.047 mol, 2.5 equiv) was added slowly to a deoxygenated solution of (*Z*)-enediyne **46** (5.52 g, 0.019 mol, 1.0 equiv, azeotropically dried with toluene) in toluene (120 mL) at –78 °C. The resulting reaction mixture was deoxygenated and was stirred at –78 °C for 1.25 h and at 0 °C for 1.75 h. The mixture was then stirred with 25% w/v aqueous tartaric acid (200 mL) at 23 °C until both the organic and aqueous phases were clear solutions. The separated organic layer was partitioned between saturated aqueous sodium chloride and ethyl acetate. The combined organic layers were dried over sodium sulfate and were concentrated. The resulting residue was purified by flash column chromatography (10% and 20% ethyl acetate in hexanes) to give the alcohol **47** (4.05 g, 86%).

R_f (20% ethyl acetate in hexanes):	0.28
IR (neat):	3361 (br, OH), 2956 (s), 2896 (m), 2184 (w, C≡C), 2132 (m, C≡C), 1247 (s), 1089 (m), 1052 (m), 880 (s), 842 (s), 752 (s), 700 (m)
^{1}H NMR (400 MHz, $CDCl_3$):	5.97 (t, 1 H, J = 1.6 Hz, C=C**H**), 4.15 (dd, 2 H, J = 6.5, 1.6 Hz, C**H**$_2$O), 1.81 (t, 1 H, J = 6.6 Hz, O**H**), 0.20 (s, 9 H, Si(C**H**$_3$)$_3$), 0.19 (s, 9 H, Si(C**H**$_3$)$_3$)

HRMS: calcd for $C_{13}H_{22}OSi_2$ (M^+): 250.1209

found: 250.1215



47 **48**

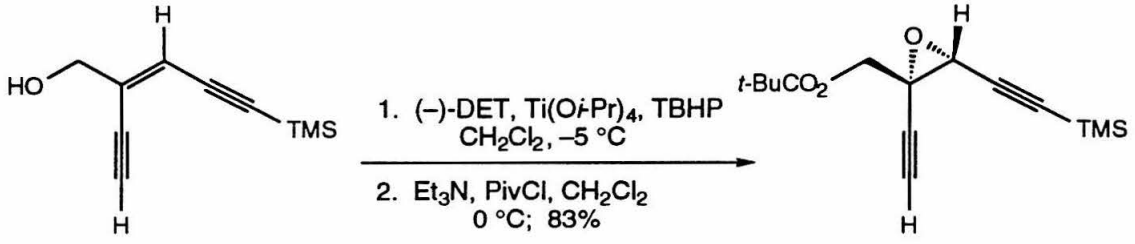
Monodesilylated Alcohol **48**

Sodium trimethoxyborohydride (1.6 g, 0.013 mol, 1.25 equiv) and water (90.0 μL, 5.0 mmol, 0.5 equiv) were stirred in tetrahydrofuran (75 mL) at –20 °C for 5 min. Alcohol **47** (2.5 g, 0.010 mol, 1.0 equiv) was added. After the reaction mixture was stirred at –20 °C for 12 h, it was quenched with saturated aqueous ammonium chloride and was acidified to pH 2 with 1 N hydrochloric acid. The mixture was partitioned between ethyl acetate (two portions) and 10% saturated aqueous sodium chloride (two portions). The combined organic layers were dried over sodium sulfate and were concentrated. The resulting residue was purified by flash column chromatography (8%, 10%, and 20% ethyl acetate in hexanes) to furnish the monodesilylated alcohol **48** (1.05 g, 60%, stored in benzene) and recovered alcohol **47** (0.49 g, 20%).

R_f (20% ethyl acetate in hexanes):	0.33
IR (neat):	3286 (s, C≡CH), 2956 (s), 2896 (s), 2866 (w), 2184 (w, C≡C), 2132 (m, C≡C), 2094 (w), 1247 (s), 1087 (m), 1044 (m), 1022 (m), 857 (s), 842 (m), 752 (m)
^{1}H NMR (400 MHz, $CDCl_3$):	6.03 (s, 1 H, C=C**H**), 4.18 (s, 2 H, **CH$_2$**O), 3.38 (s, 1 H, C≡C**H**), 1.68 (s, 1 H, **OH**), 0.19 (s, 9 H, Si(**CH$_3$**)$_3$)

HRMS: calcd for $C_{10}H_{14}OSi$ (M^+): 178.0814

found: 178.0817

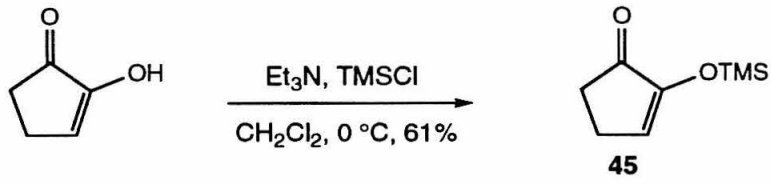


48 **44**

(*R*,*R*)-Epoxy Diyne **44**

Monodesilylated alcohol **48** (4.28 g, 0.024 mol, 1.0 equiv) and crushed 3 Å sieves (4.28 g, 1 wt equiv) were stirred in dichloromethane (130 mL) at –20 °C. In a separate flask, *tert*-butyl hydroperoxide (3.54 M in dichloromethane, 17.4 mL, 0.060 mol, 2.5 equiv) was added via a Teflon needle to a suspension of crushed 3 Å sieves (4.28 g, 1 wt equiv), (–)-diethyl D-tartrate (0.62 mL, 3.6 mmol, 0.15 equiv), and titanium(IV) isopropoxide (0.71 mL, 2.4 mmol, 0.10 equiv) in dichloromethane (220 mL) at –20 °C. The mixture was stirred at –20 °C for 50 min and was transferred via cannula to the substrate solution at –20 °C. The resulting mixture was stirred at –5 °C for 36 h, and was then recooled to –20 °C. Trimethyl phosphite (6.37 mL, 0.054 mol, 2.25 equiv) was added dropwise to the reaction mixture at –20 °C. The resulting mixture was stirred at –20 °C for 1 h. Triethylamine (11.4 mL, 0.082 mol, 3.4 equiv) and pivaloyl chloride (6.8 mL, 0.055 mol, 2.3 equiv) were added to the reaction mixture at –20 °C. The resulting mixture was stirred at 0 °C for 20 h, and then it was partitioned between 50% ethyl acetate in hexanes (200 mL) and 10% aqueous tartaric acid (200 mL). The resulting aqueous phase was extracted with ethyl acetate. After the combined organic layers were washed with 10% tartaric acid, saturated aqueous sodium bicarbonate, and saturated aqueous sodium chloride, they were dried over sodium sulfate and were concentrated. The resulting residue was purified by flash column chromatography (2% ethyl acetate in hexanes) to give the (*R*,*R*)-epoxy diyne **44** (5.57 g, 83%) as a yellow oil.

R_f (5% ethyl acetate in toluene):	0.50
IR (neat):	3279 (s, C≡CH), 2964 (s), 2904 (m), 2866 (m), 2184 (m, C≡C), 2124 (m, C≡C), 1734 (s, CO_2t-Bu), 1479 (s), 1277 (s), 1247 (s), 1142 (s), 850 (s)
^{1}H NMR (400 MHz, C_6D_6):	4.22 (d, 1 H, J = 12.45 Hz, CH_AH_BO), 3.78 (d, 1 H, J = 12.45 Hz, CH_AH_BO), 3.29 (s, 1 H, epoxy-H), 1.95 (s, 1 H, C≡CH), 1.05 (s, 9 H, $C(CH_3)_3$), 0.11 (s, 9 H, $Si(CH_3)_3$)
HRMS:	calcd for $C_{15}H_{23}O_3Si$ (MH^+): 279.1416 found: 279.1429

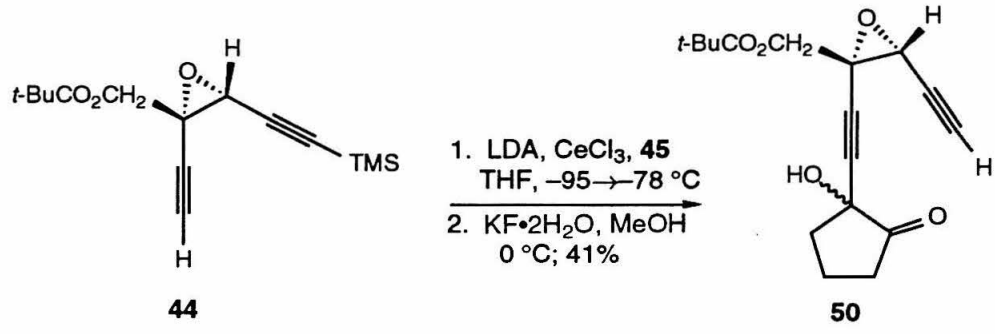


45

Cyclopentenone **45**

Triethylamine (5.33 mL, 0.038 mol, 2.5 equiv) and chlorotrimethylsilane (2.91 mL, 0.023 mol, 1.5 equiv) were added to a solution of cyclopentane-1,2-dione (1.5 g, 0.015 mol, 1.0 equiv, azeotropically dried with toluene) in dichloromethane (75 mL) at –78 °C. The resulting mixture was stirred at 0 °C for 3 h. The mixture was partitioned between hexanes and 5% saturated aqueous sodium bicarbonate (three portions). The organic layer was dried over sodium sulfate and was concentrated. The residue thus obtained was purified by distillation (Kugelrohr apparatus, 85 °C, 1–2 Torr), collecting the cyclopentenone **45** (1.58 g, 61%) as a yellow oil.

R_f (40% ethyl acetate in hexanes):	0.42 (product streaks)
IR (neat):	2959 (m), 1714 (s, C=O), 1627 (s, C=C), 1109 (s)
^{1}H NMR (400 MHz, $CDCl_3$):	6.85 (t, 1 H, J = 2.93 Hz, C=C**H**), 2.46 (m, 2 H, two of (C**H**$_2$)$_2$), 2.36 (m, 2 H, two of (C**H**$_2$)$_2$), 0.22 (s, 9 H, Si(C**H**$_3$)$_3$)
HRMS:	calcd for $C_8H_{15}O_2Si$ (MH^+): 171.0841 found: 171.0848



44 **50**

Ketone **50**

A suspension of cerium(III) chloride (0.26 g, 1.05 mmol, 1.3 equiv, flame-dried) in tetrahydrofuran (2.25 mL) was deoxygenated and was stirred at 23 °C for 2.25 h. In a separate flask, freshly prepared lithium diisopropylamide (0.5 M in tetrahydrofuran, 2.0 mL, 1.02 mmol, 1.26 equiv) was added dropwise to a deoxygenated solution of epoxy diyne **44** (0.225 g, 0.81 mmol, 1.0 equiv, azeotropically dried with toluene) in tetrahydrofuran (2.25 mL) at –95 °C, and the resulting reaction mixture was stirred at –95 °C for 15 min. The acetylide mixture was then transferred via a cannula jacketed with foil containing dry ice to the cerium suspension at –95 °C. The reaction mixture was stirred at –95 °C for 1 h. A solution of cyclopentenone **45** (0.172 g, 1.01 mmol, 1.25 equiv) in tetrahydrofuran (2.25 mL), dried with 3 Å sieves and deoxygenated at –78 °C, was added to the resulting suspension at –95 °C. The reaction mixture was stirred at –95 °C for 1 h and at –78 °C for 1.5 h. The mixture was quenched with saturated aqueous ammonium chloride and was diluted with ethyl acetate. The mixture was filtered through celite and was dried over sodium sulfate. The solution thus obtained was concentrated to give crude adduct **49**.

Potassium fluoride dihydrate (0.68 g, 7.3 mmol, 9.0 equiv) was added to a solution of adduct **49** in methanol (6.0 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 1.25 h. It was then diluted with 80% ethyl acetate in hexanes and was washed with saturated aqueous sodium bicarbonate and saturated aqueous sodium chloride. The separated organic layer was dried over sodium sulfate and was concentrated. The

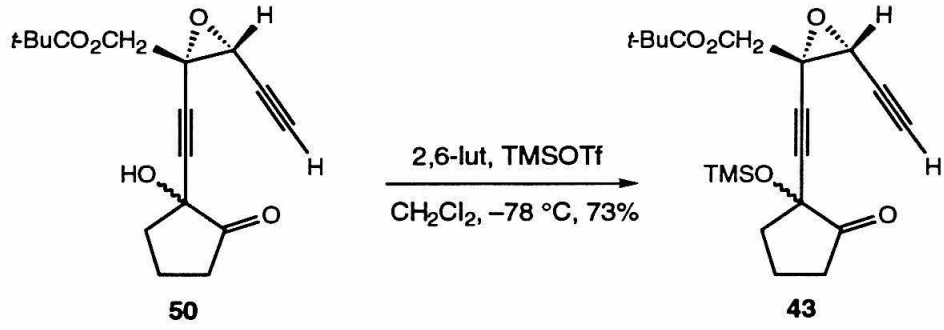
resulting residue was purified by flash column chromatography (25 and 30% ethyl acetate in hexanes) to provide the ketone **50** (0.102 g, 41%, 1:1 diastereomeric ratio).

Adduct **49**:

R_f (40% ethyl acetate in hexanes):	0.51

Ketone **50**:

R_f (20% ethyl acetate in hexanes):	0.17
IR (neat):	3430 (br, OH), 3273 (m, C≡CH), 2960 (s), 2127 (w, C≡C), 1731 (s, CO_2t-Bu)
^{1}H NMR (400 MHz, $CDCl_3$):	4.40 (d, J = 5.62 Hz, CH_AH_BO of first diastereomer), 4.37 (d, J = 5.61 Hz, CH_AH_BO of first diastereomer), 4.15 (d, J = 3.67 Hz, CH_AH_BO of second diastereomer), 4.12 (d, J = 3.42 Hz, CH_AH_BO of second diastereomer), 3.58 (s, 1 H, epoxy-**H**), 3.11 (s, **OH** of one diastereomer), 3.10 (s, **OH** of one diastereromer), 1.96–2.51 (m, 6 H, cyclopentyl-**H**), 2.491 (s, C≡C**H** of one diastereomer), 2.487 (s, C≡C**H** of one diastereomer), 1.21 (s, 9 H, $C(CH_3)_3$)
HRMS:	calcd for $C_{17}H_{21}O_5$ (MH^+): 305.1389 found: 305.1381



50 **43**

Ketone **43**

Trimethylsilyl trifluoromethanesulfonate (0.086 mL, 0.45 mmol, 1.5 equiv) was added to a solution of ketone **50** (0.090 g, 0.30 mmol, 1.0 equiv, azeotropically dried with toluene) and 2,6-lutidine (0.52 mL, 4.5 mmol, 15.0 equiv) in dichloromethane (3.0 mL) at –78 °C. The resulting reaction mixture was stirred at –78 °C for 45 min, and then it was quenched with methanol. The mixture was partitioned between 80% ethyl acetate in hexanes and saturated aqueous sodium chloride (three portions). The organic layer was dried over sodium sulfate and was concentrated. The resulting residue was purified by flash column chromatography (10% ethyl acetate in hexanes) to give the ketone **43** (80.6 mg, 73%, 1:1 diastereomeric ratio) as a yellow oil, which was stored frozen in benzene (3.5 mL).

R_f (40% ethyl acetate in hexanes):	0.64
IR (neat):	3266 (w, C≡CH), 2973 (m), 2130 (w, C≡C), 1765 (s, CO_2t-Bu), 1738 (s, CO_2t-Bu)
^{1}H NMR (400 MHz, $CDCl_3$):	4.27 (d, J = 12.21 Hz, one of CH_2O of one diastereomer), 4.20 (d, J = 12.21 Hz, one of CH_2O of one diastereomer), 3.80 (d, J = 12.21 Hz, one of CH_2O of one diastereomer), 3.75 (d, J = 12.20 Hz, one of

CH_2O of one diastereomer), 3.19 (s, 1 H, epoxy-**H**), 1.95 (s, C≡C**H** of one diastereomer), 1.91 (s, C≡C**H** of one diastereromer), 1.35–2.20 (m, 6 H, cyclopentyl-**H**), 1.14 (s, 9 H, $C(CH_3)_3$), 0.454 (s, one $Si(CH_3)_3$ of one diastereomer), 0.445 (s, one $Si(CH_3)_3$ of one diastereomer)

HRMS: calcd for $C_{20}H_{29}O_5Si$ (MH^+): 377.1784
found: 377.1786

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[46] The yields of the reactions of ketone **53** with DAMP should be considered estimates given the small scale on which the reactions were performed.

[47] The geometry of the double bonds in products **55**, **56**, **58**, **59**, **61**, and **62** was not vigorously determined.

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[57] Spectral and analytical data were compiled in part by Dr. Philip M. Harrington, California Institute of Technology (present address: American Cyanamid Company, Princeton, New Jersey).

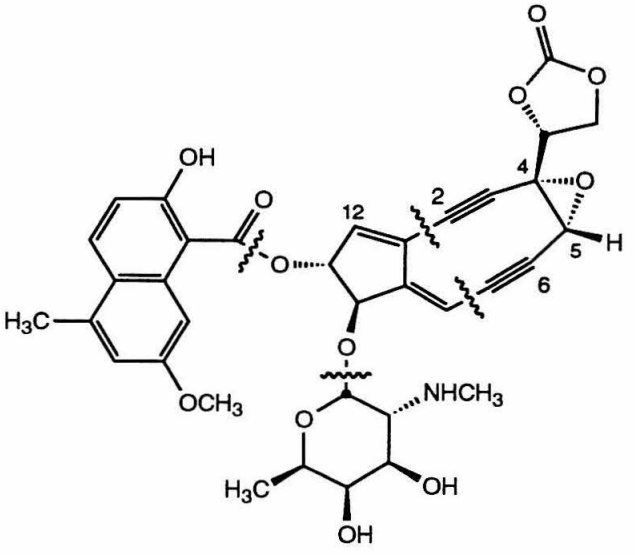
Chapter 3

Studies Directed toward the Total Synthesis of Neocarzinostatin Chromophore

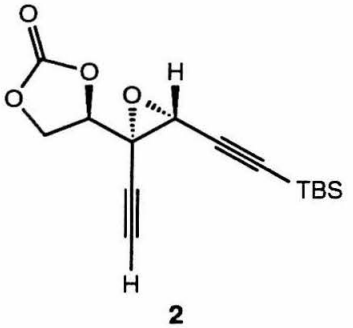
Introduction and Summary

As discussed in the previous chapter, the total synthesis of neocarzinostatin chromophore (**1**) has attracted much attention because of its unprecedented structure and biological activity. The initial synthetic efforts focused exclusively on the development of ring-closure strategies to form the cyclononadiyne core of the chromophore. With the development by Myers et al. of a successful cyclization strategy employing an intramolecular acetylide addition, attention has turned toward the implementation of this strategy in the total synthesis of the chromophore.[1]

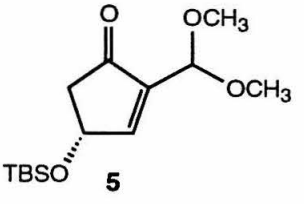
Retrosynthetically, neocarzinostatin chromophore (**1**) may be transformed into four fragments, the epoxy carbonate **2**, *N*-methyl D-fucosamine (**3**), 2-hydroxy-7-methoxy-5-methyl-1-napthoic acid (**4**), and the cyclopentenone **5**. The epoxy carbonate **2** was synthesized from (*R*)-2,3-*O*-isopropylidene-D-glyceraldehyde (**6**, Scheme 1).[2,3] Myers and Harrington developed a route to protected *N*-methyl D-fucosamine derivatives via the fucosamine derivative **18** (Scheme 2).[4] 2-Hydroxy-7-methoxy-5-methyl-1-napthoic acid (**4**) was synthesized by Myers and Subramanian (Scheme 3).[5,6] Cyclopentenone **5** was constructed by Myers and Xiang (Scheme 4).[7] Preliminary efforts by Myers and Xiang to assemble these fragments are detailed in Scheme 5.[7] The development of an enantioselective synthesis of the epoxy carbonate **2** and studies directed toward glycosylation with a suitably protected *N*-methyl D-fucosamine derivative are discussed in this chapter.



1



2



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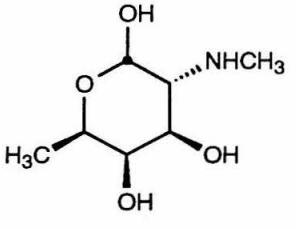
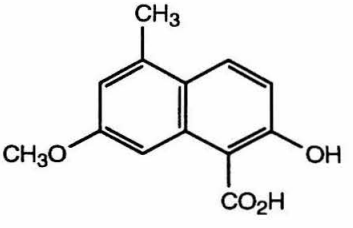
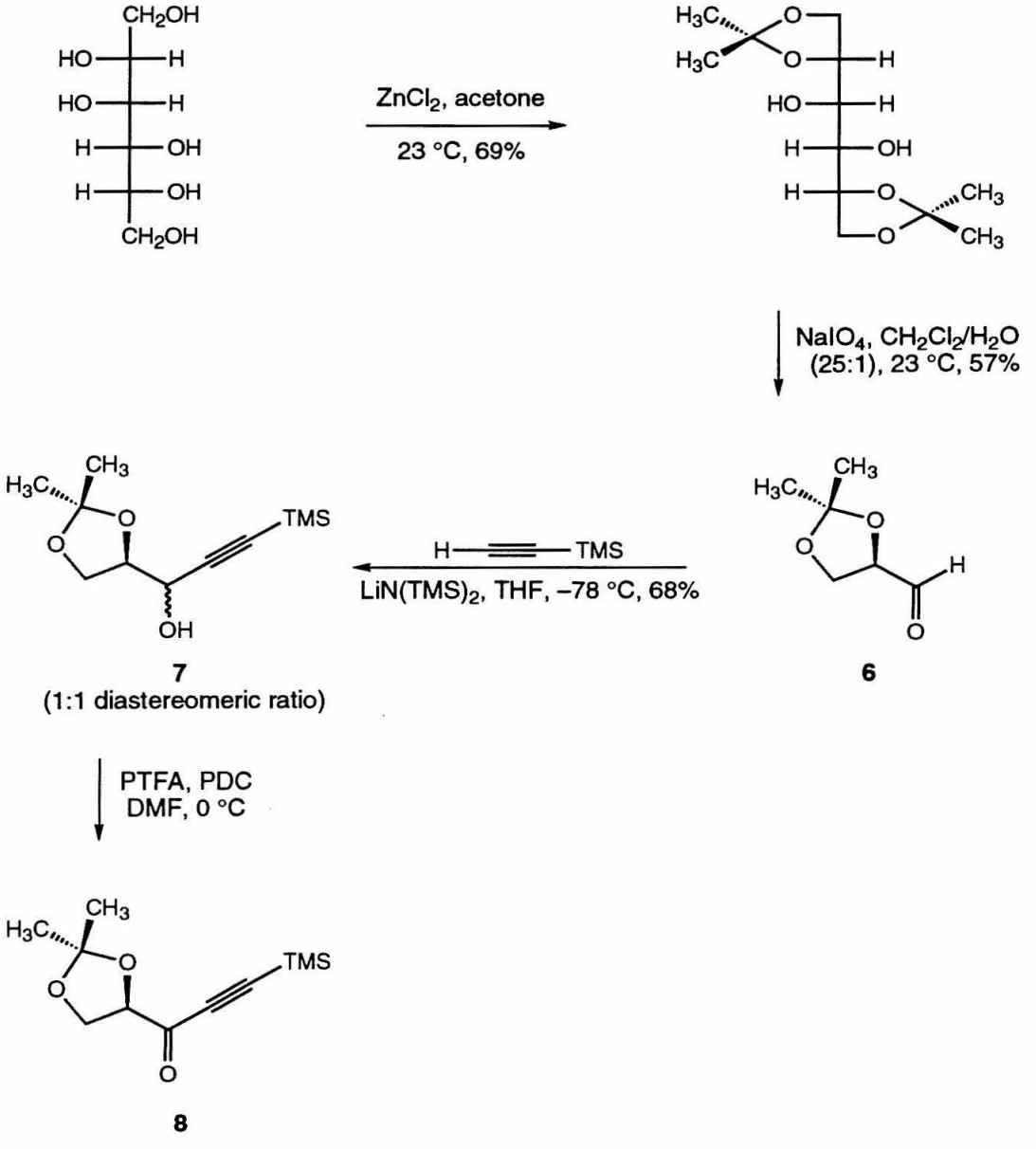


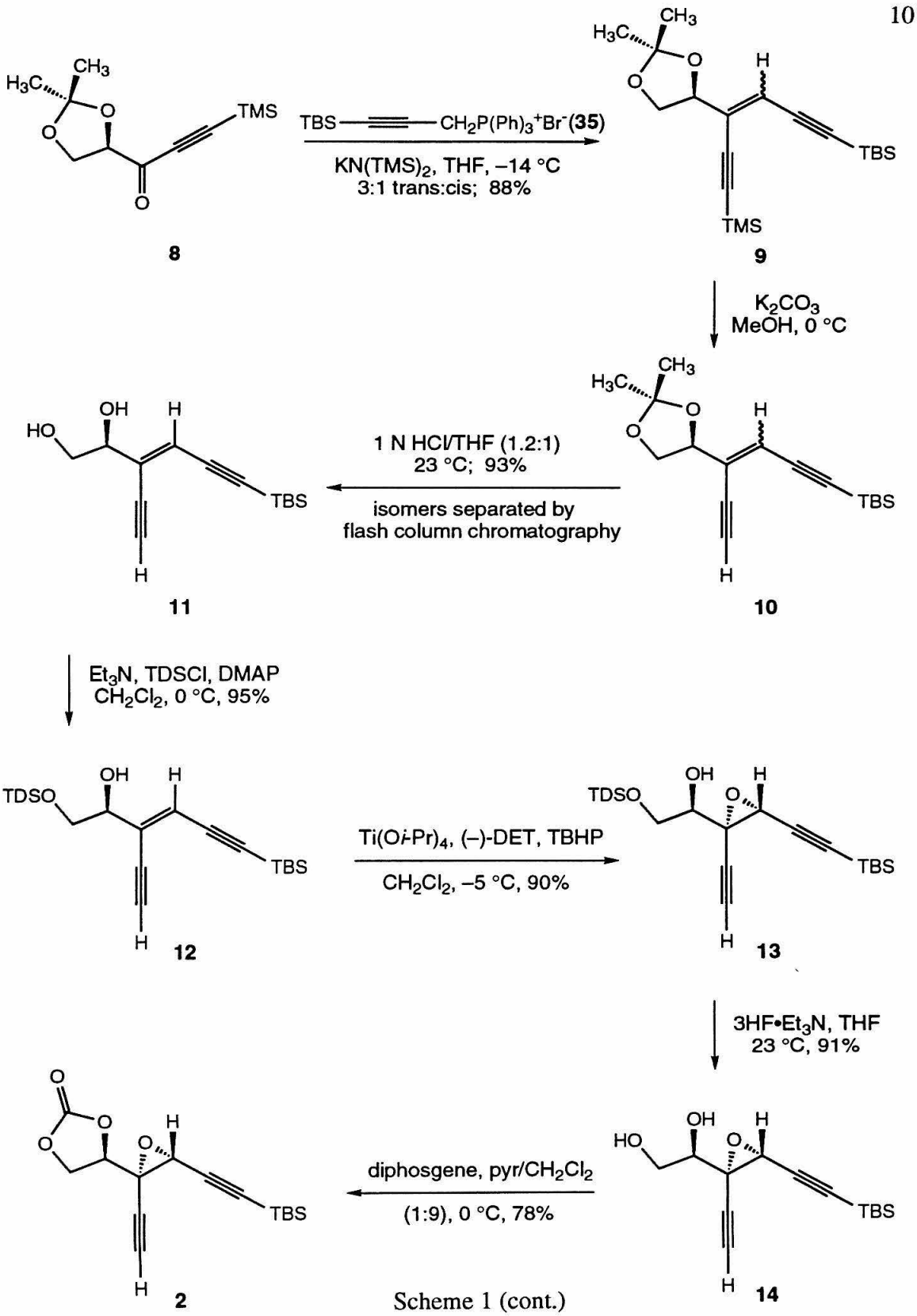
3



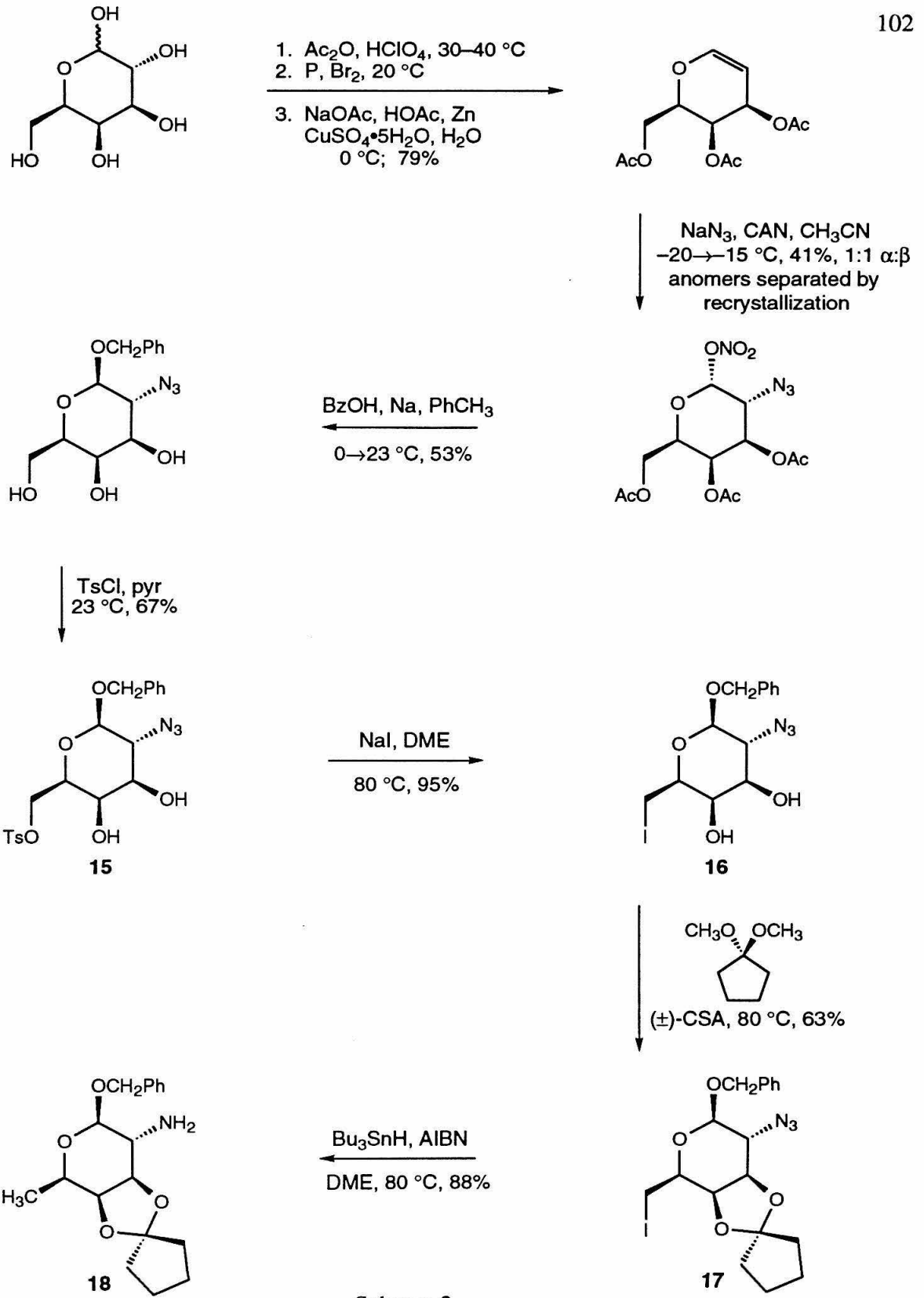
4


CH2OH
HO
H
HO
H
H
OH
H
OH
CH2OH
ZnCl2, acetone
23 °C, 69%
H3C
O
H3C
O
H
HO
H
H
OH
H
O
CH3
O
CH3
NaIO4, CH2Cl2/H2O
(25:1), 23 °C, 57%
CH3
H3C
O
O
H
O
6
H
TMS
LiN(TMS)2, THF, –78 °C, 68%
CH3
H3C
O
O
TMS
OH
7
(1:1 diastereomeric ratio)
PTFA, PDC
DMF, 0 °C
CH3
H3C
O
O
TMS
O
8

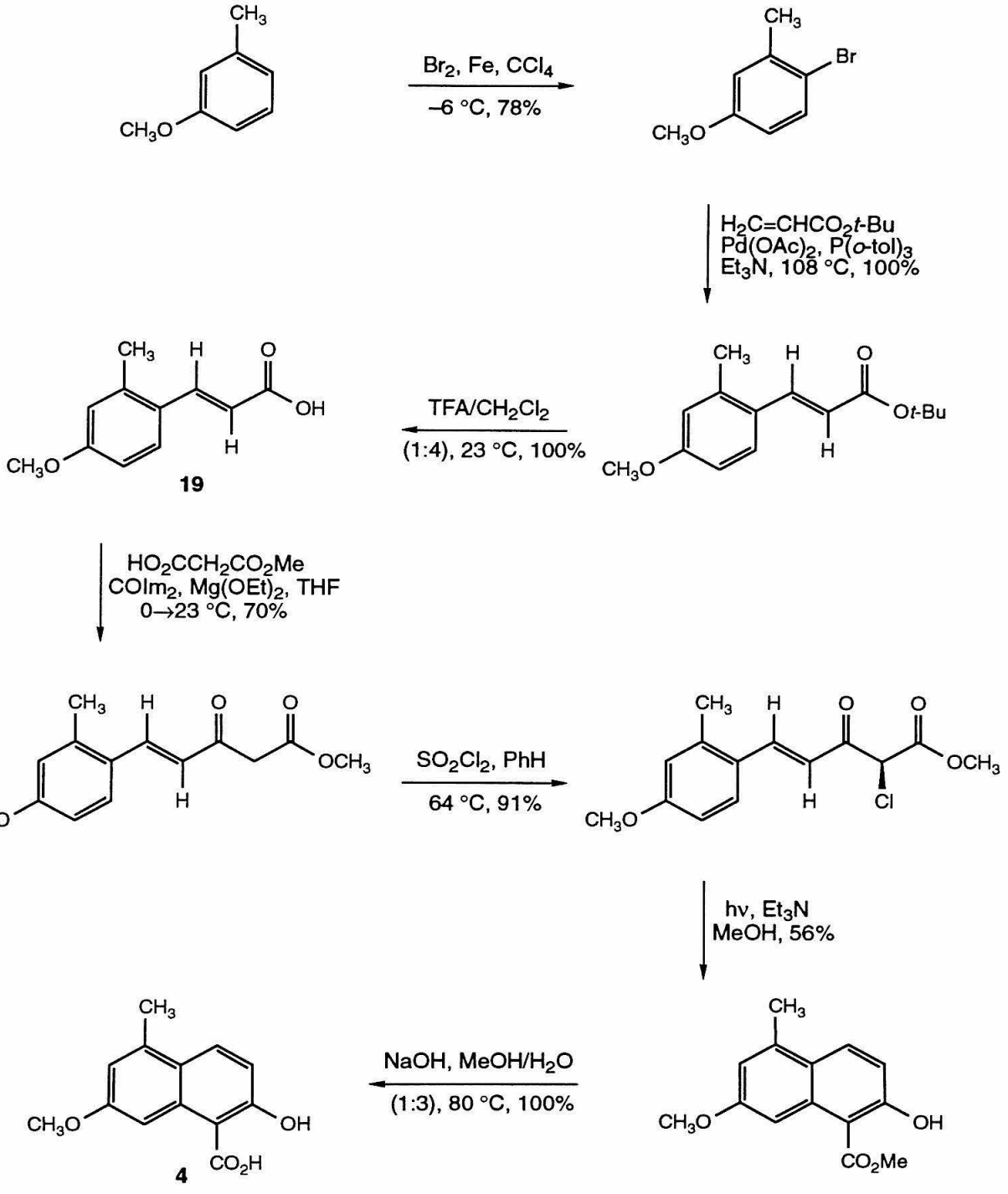
Scheme 1



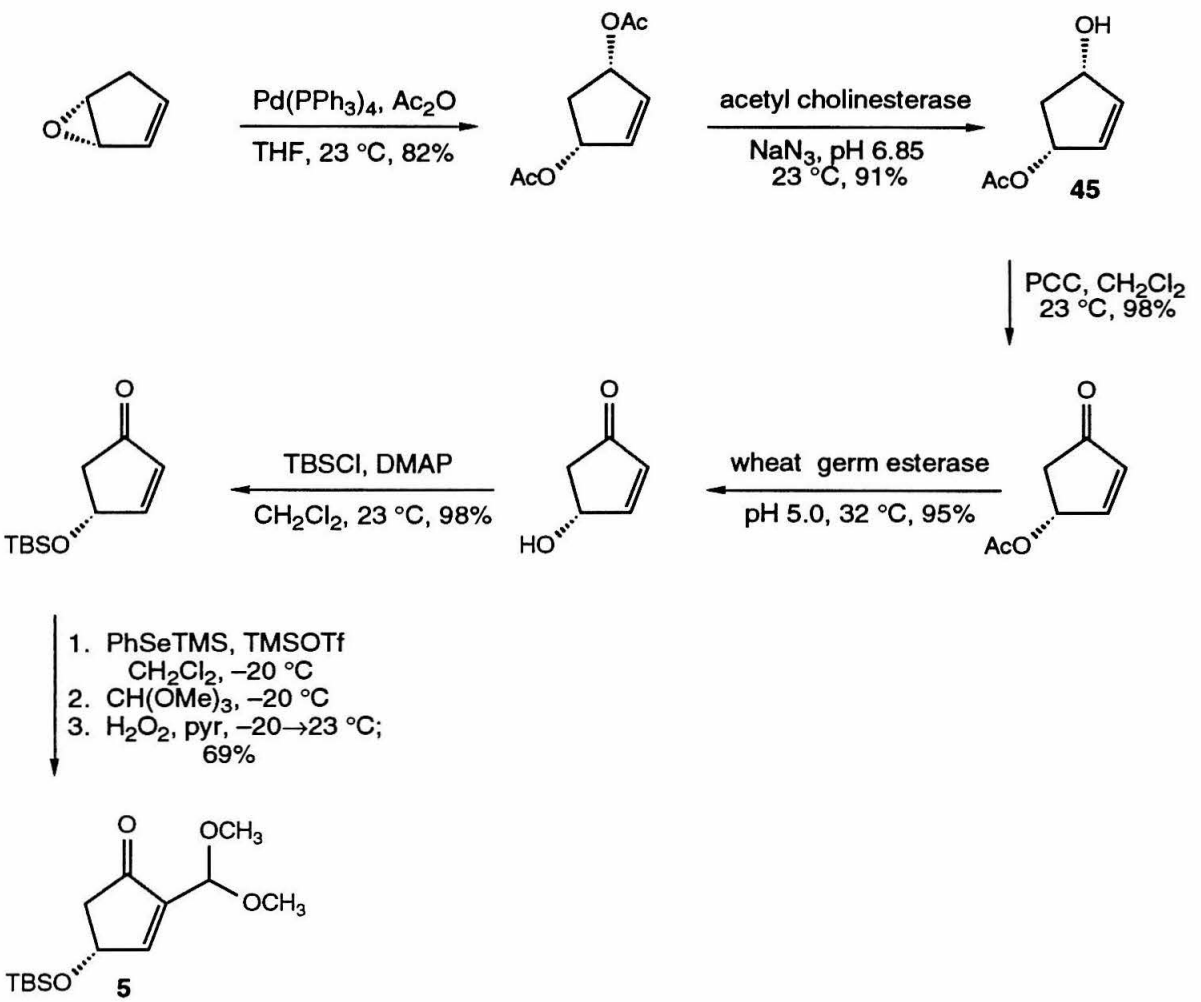
Scheme 1 (cont.)


1. Ac_2O, $HClO_4$, 30–40 °C
2. P, Br_2, 20 °C
3. NaOAc, HOAc, Zn
$CuSO_4 \cdot 5H_2O$, H_2O
0 °C; 79%
NaN_3, CAN, CH_3CN
–20→–15 °C, 41%, 1:1 α:β
anomers separated by
recrystallization
BzOH, Na, $PhCH_3$
0→23 °C, 53%
TsCl, pyr
23 °C, 67%
NaI, DME
80 °C, 95%
(±)-CSA, 80 °C, 63%
Bu_3SnH, AIBN
DME, 80 °C, 88%
15
16
17
18

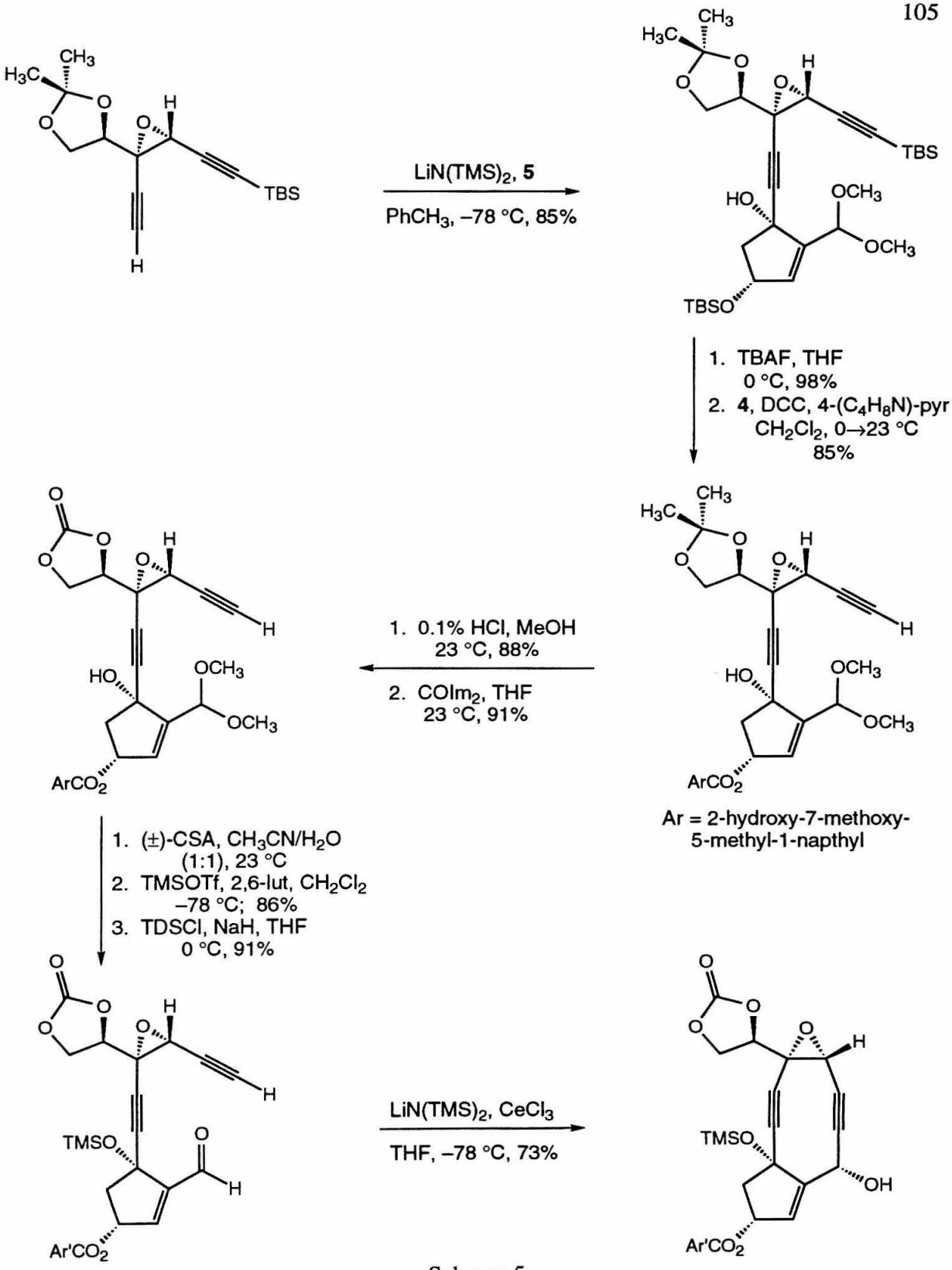
Scheme 2


CH3
CH3O
Br2, Fe, CCl4
–6 °C, 78%
Br
H2C=CHCO2t-Bu
Pd(OAc)2, P(o-tol)3
Et3N, 108 °C, 100%
Ot-Bu
TFA/CH2Cl2
(1:4), 23 °C, 100%
OH
19
HO2CCH2CO2Me
COIm2, Mg(OEt)2, THF
0→23 °C, 70%
OCH3
SO2Cl2, PhH
64 °C, 91%
Cl
hv, Et3N
MeOH, 56%
CO2Me
NaOH, MeOH/H2O
(1:3), 80 °C, 100%
CO2H
4

Scheme 3


Pd(PPh3)4, Ac2O
THF, 23 °C, 82%
OAc
AcO
acetyl cholinesterase
NaN3, pH 6.85
23 °C, 91%
OH
AcO
45
PCC, CH2Cl2
23 °C, 98%
O
AcO
wheat germ esterase
pH 5.0, 32 °C, 95%
O
HO
TBSCl, DMAP
CH2Cl2, 23 °C, 98%
O
TBSO
1. PhSeTMS, TMSOTf
CH2Cl2, –20 °C
2. CH(OMe)3, –20 °C
3. H2O2, pyr, –20→23 °C;
69%
O
OCH3
OCH3
TBSO
5

Scheme 4


LiN(TMS)2, 5
PhCH3, –78 °C, 85%
1. TBAF, THF
0 °C, 98%
2. 4, DCC, 4-(C4H8N)-pyr
CH2Cl2, 0→23 °C
85%
1. 0.1% HCl, MeOH
23 °C, 88%
2. COIm2, THF
23 °C, 91%
1. (±)-CSA, CH3CN/H2O
(1:1), 23 °C
2. TMSOTf, 2,6-lut, CH2Cl2
–78 °C; 86%
3. TDSCl, NaH, THF
0 °C, 91%
LiN(TMS)2, CeCl3
THF, –78 °C, 73%
Ar = 2-hydroxy-7-methoxy-
5-methyl-1-napthyl
Ar' = 2-tert-butyldiphenylsilyloxy-
7-methoxy-5-methyl-1-napthyl

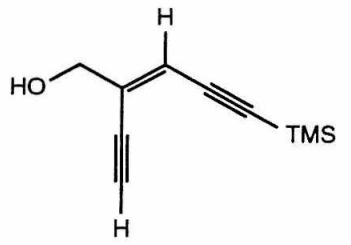
Scheme 5

Synthesis of the Epoxy Carbonate 2

Epoxy carbonate **2** was designed with a number of characteristics in mind. It contains an epoxide and a carbonate so that installation of these moieties need not take place after ring closure to the unstable cyclononadiyne core. Its two acetylenic groups are differentiated, allowing for the selective elaboration of each group.

Initially, the synthesis of the epoxy carbonate **2** from the aldehyde **22** by the diastereoselective addition of a hydroxymethyl anion equivalent was attempted. The aldehyde **22** was readily available from the allylic alcohol **20**, which had been prepared in prior synthetic studies directed toward the cyclononadiyne core of neocarzinostatin chromophore.[8] The hydroxymethyl anion equivalent, 3,4-dimethoxybenzyloxymethyltributyltin (**23**), was chosen on the basis of work by Still, in which it was shown that α-alkoxymethylstannanes undergo transmetalation with butyllithium and that the resulting organolithium reagents add to ketones in excellent yields.[9,10] The 3,4-dimethoxybenzyl (DMPM) protective group was chosen because it was known to be base-stable and was thought to be removable without harm to the desired product.[11]

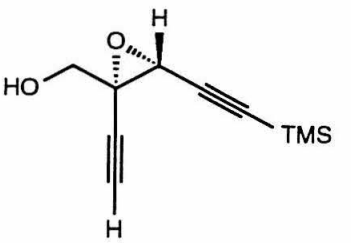
Epoxidation of the allylic alcohol **20** by the Sharpless procedure ((–)-diethyl D-tartrate (0.30 equiv), titanium(IV) isopropoxide (0.25 equiv), *tert*-butyl hydroperoxide (2.5 equiv), dichloromethane, –5 °C) provided the epoxide **21** (72%).[12] Oxidation of **21** with sulfur trioxide pyridine complex (3.3 equiv) and triethylamine (12.5 equiv) in dimethyl sulfoxide at 23 °C furnished the epoxide **22** (77%).[13] 3,4-Dimethoxybenzyloxymethyltributyltin (**23**) was synthesized in a manner similar to that of benzyloxymethyltributyltin by Still.[9] Thus, tributylstannylmethyl iodide, obtained from iodomethylzinc iodide (1.5 equiv) and tributyltin chloride (1.0 equiv) in tetrahydrofuran at 23 °C,[14] was added to 3,4-dimethoxybenzyl alcohol (1.3 equiv) and sodium hydride (1.5 equiv) in tetrahydrofuran at 23 °C to provide the organostannane **23** (59%). The addition of aldehyde **22** to the organolithium reagent obtained from organostannane **23**



20

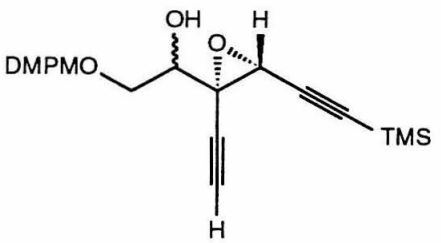
(–)-DET, $Ti(O\textit{i}\text{-}Pr)_4$, TBHP

CH_2Cl_2, –5 °C, 72%



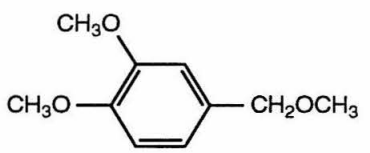
21

SO_3•pyr, Et_3N
DMSO, 23 °C, 77%



6% (2:1 diastereomeric ratio)

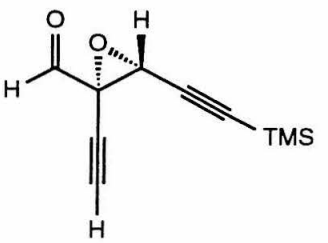
+



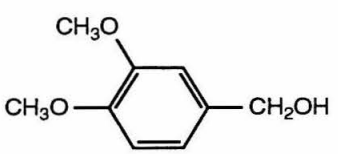
60%

$DMPMOCH_2SnBu_3$ (**23**)

n-BuLi, THF, –78 °C

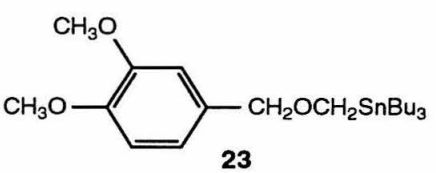


22



$SnBu_3CH_2I$, NaH

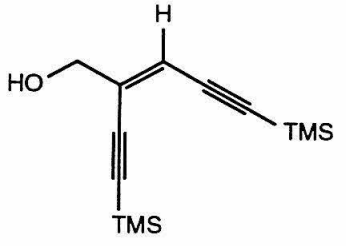
THF, 23 °C, 59%



23

(1.25 equiv) and butyllithium (1.2 equiv) in tetrahydrofuran at –78 °C resulted in a low yield of the desired mono-protected diol (6%, 1:2 diastereomeric ratio) accompanied by a large amount of 3,4-dimethoxybenzyl methyl ether (60%). As a control experiment, benzaldehyde was added to a mixture of the organostannane **23** (1.25 equiv) and butyllithium (1.2 equiv) in tetrahydrofuran at –78 °C, providing styrene glycol in 90% yield. Thus, it appeared that while **23** did undergo transmetalation, it reacted preferentially as a base in the presence of substrate **22**.

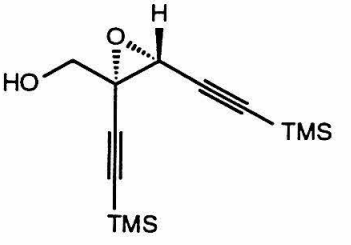
In light of these results, the bis-silylated aldehyde **26** was prepared. The allylic alcohol **24**, also an intermediate in prior synthetic studies directed toward the cyclononadiyne core of neocarzinostatin chromophore,[8] upon epoxidation with (–)-diethyl D-tartrate (0.06 equiv), titanium(IV) isopropoxide (0.05 equiv), and *tert*-butyl hydroperoxide (2.0 equiv) at –5 °C in dichloromethane (78% yield, 88% ee) afforded the epoxide **25**.[15,16] Oxidation of **25** to the aldehyde **26** was accomplished with oxalyl chloride (1.8 equiv), dimethyl sulfoxide (2.25 equiv), and triethylamine (4.5 equiv) in dichloromethane at –78→0 °C (82%).[17] The subsequent hydroxymethylation of the aldehyde **26** with the organolithium reagent obtained from organostannane **23** and butyllithium was low yielding. The use of boron trifluoride etherate was found to improve these yields. For example, the addition of aldehyde **26** to a suspension of organostannane **23** (1.6 equiv), butyllithium (1.5 equiv), and boron trifluoride etherate (2.0 equiv) in tetrahydrofuran at –78 °C provided the alcohols **27** in 54% yield (1:1 diastereomeric ratio) as well as 3,4-dimethoxybenzyl methyl ether (46%). The diastereomers **27** were deprotected in a two-step procedure. 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (1.0 equiv) was first added to a solution of **27** in 3:1 dichloromethane-water at 0 °C. The resulting mixture of diastereomeric benzylic ketals was purified by extractive isolation and was hydrolyzed to the diols with 14:6:1 glacial acetic acid-tetrahydrofuran-water at 23 °C (70%, from **27**).[11a]



24

(–)-DET, $Ti(O\textit{i}\text{-}Pr)_4$, TBHP

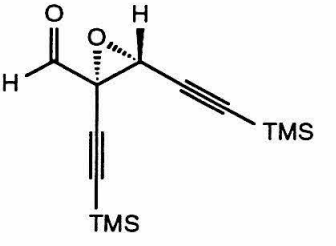
CH_2Cl_2, –5 °C, 78%



25

$(COCl)_2$, DMSO, Et_3N

CH_2Cl_2, –78→0 °C, 82%

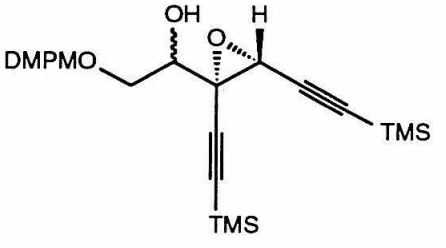


26

$DMPMOCH_2SnBu_3$ (**23**)

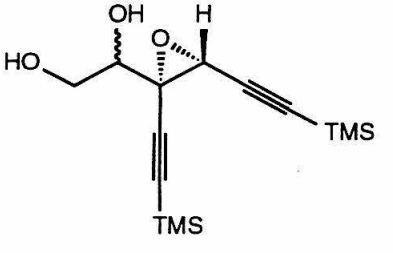
$BF_3{\bullet}OEt_2$, *n*-BuLi

THF, –78 °C



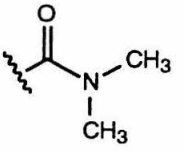
27, 54% (1:1 diastereomeric ratio)
(3,4-dimethoxybenzyl methyl ether, 46%)

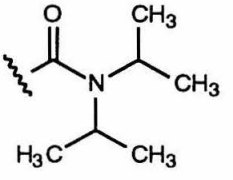
1. DDQ, CH_2Cl_2/H_2O (3:1), 0 °C
2. HOAc/THF/H_2O (14:6:1)
   23 °C; 70%



$SnBu_3CH_2OP$:

28. P = TBS

29. P = 

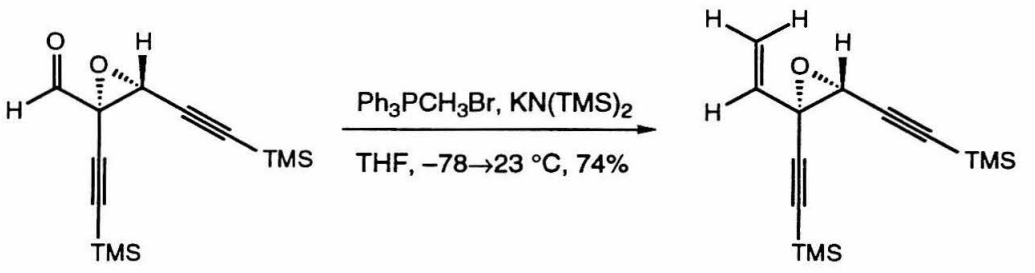
30. P = 

In an effort to improve the yields and diastereoselectivities of the hydroxymethylation of aldehyde **26**, the corresponding *tert*-butyldimethylsilyl ether, dimethyl carbamate, and diisopropyl carbamate hydroxymethyl anion equivalents were prepared (**28–30**). The latter two had the potential for intramolecular carbonate formation. Each was synthesized from (tributylstannyl)methanol, obtained from tributyltin hydride, lithium diisopropylamide (1.2 equiv), and paraformaldehyde (1.2 equiv) in tetrahydrofuran at 23 °C (78%).[18] The reaction of (tributylstannyl)methanol with *tert*-butyldimethylsilyl chloride (1.2 equiv) and imidazole (2.5 equiv) in *N*,*N*-dimethylformamide at 23 °C provided the silyl ether **28** (92%).[19] The addition of aldehyde **26** to a suspension of organostannane **28** (1.4 equiv), butyllithium (1.2 equiv), and boron trifluoride etherate (2.0 equiv) in tetrahydrofuran at –78 °C resulted in the recovery of **26** (72%) with no apparent hydroxymethylation. The addition of benzaldehyde (1.1 equiv) to a suspension of organostannane **28** and butyllithium (1.1 equiv) in tetrahydrofuran at –78 °C provided the desired addition product in low yield as well (14%), suggesting that the transmetalation of **28** with butyllithium is poor.

Compound **29** was synthesized from (tributylstannyl)methanol and dimethylcarbamyl chloride (2.2 equiv) in pyridine at 23→90 °C (32%, based on tributyltin hydride).[20] The addition of benzaldehyde to the organolithium species resulting from the transmetalation of **29** (1.2 equiv) with butyllithium (1.1 equiv) in tetrahydrofuran at –78 °C provided several products. Compound **30** was similarly synthesized from (tributylstannyl)methanol and diisopropylcarbamyl chloride[21] (1.3 equiv) in pyridine at 75 °C (40%, based on tributyltin hydride).[20] The organolithium reagent obtained from compound **30** (1.3 equiv) and butyllithium (1.1 equiv) was found to hydroxymethylate benzaldehyde in tetrahydrofuran at –78 °C in good yield (86%), but not the more sensitive substrate, aldehyde **26** (similar conditions, 25%).

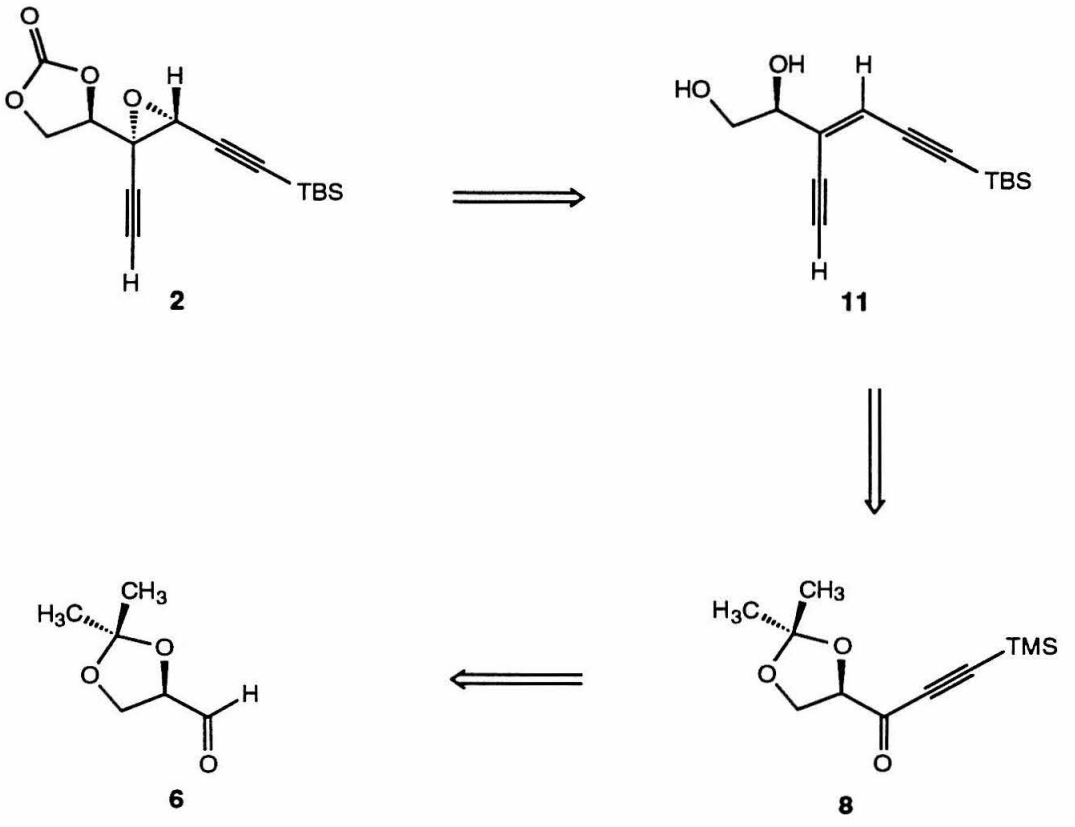
As is evident, the hydroxymethylation of substrates such as **26** was characterized by a number of problems. The addition of the hydroxymethyl anion equivalents proved to be low yielding. Secondly, the diastereoselective excesses of the hydroxymethylations need to be improved. Epoxy alcohols such as **27** might be obtained in diastereomerically pure form by oxidation followed by stereospecific reduction with, for example, zinc borohydride.[22] However, it remains to be seen how compounds such as **27** are to be selectively desilylated. Subjecting the diastereomers **27** to sodium trimethoxyborohydride (5.0 equiv) and water (2.5 equiv) in tetrahydrofuran at –20→23 °C, conditions which previous work had indicated were successful for the selective removal of the internal trimethylsilyl group in a related substrate,[8] gave no reaction.

As an alternative approach, the aldehyde **26** was converted to the corresponding olefin with the ylide prepared from methyltriphenylphosphonium bromide (1.3 equiv) and sodium bis(trimethylsilyl)amide (1.1 equiv) in tetrahydrofuran at –78→23 °C (74%). Attempted osmylation of this olefin (osmium tetroxide (0.08 equiv), 4-methylmorpholine *N*-oxide (1.05 equiv), 1:1 tetrahydrofuran-water, 23 °C)[23] was not found to provide any of the desired diol.



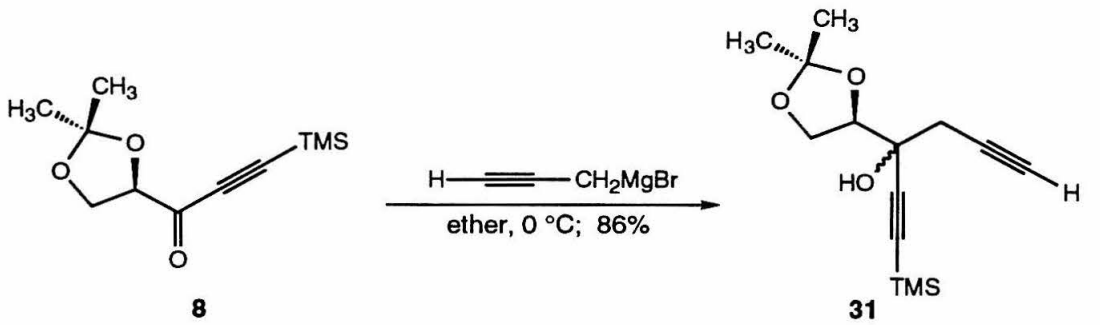
26

Given the difficulties encountered in constructing the diol from **22** or **26**, approaches to the epoxy carbonate **2** utilizing a substrate from the chiral pool were investigated. The chiral starting material chosen was (*R*)-2,3-*O*-isopropylidene-D-glyceraldehyde (**6**).[3] Retrosynthetically, epoxy carbonate **2** was transformed sequentially to the olefin **11**, the propargyl ketone **8**, and (*R*)-2,3-*O*-isopropylidene-D-glyceraldehyde (**6**). According to published procedures, (*R*)-2,3-*O*-isopropylidene-D-glyceraldehyde (**6**) was synthesized from D-mannitol in two steps (Scheme 1). Thus, protection of D-mannitol as its 1,2:5,6-di-*O*-isopropylidene derivative was accomplished with zinc chloride (2.1 equiv) in acetone at 23 °C (69%).[24] Oxidative cleavage of the resulting diol bisacetonide with sodium periodate (2.5 equiv) in 25:1 dichloromethane-water at 23 °C provided (*R*)-2,3-*O*-isopropylidene-D-glyceraldehyde (**6**, 57%).[3a] The addition of (*R*)-2,3-*O*-isopropylidene-D-glyceraldehyde (**6**) to (trimethylsilyl)acetylene (1.2 equiv) and lithium bis(trimethylsilyl)amide (1.0 M in THF, 1.1 equiv) in tetrahydrofuran at –78 °C furnished the propargyl alcohols **7** (68%, 1:1 diastereomeric ratio).[25] Oxidation of alcohols **7** with pyridinium trifluoroacetate (0.40 equiv) and pyridinium dichromate (2.6 equiv) in *N*,*N*-dimethylformamide at 0 °C afforded the propargyl ketone **8**.[26] As **8** was unstable toward flash column chromatography and could not be concentrated without decomposition, it was used in crude form and in solution following

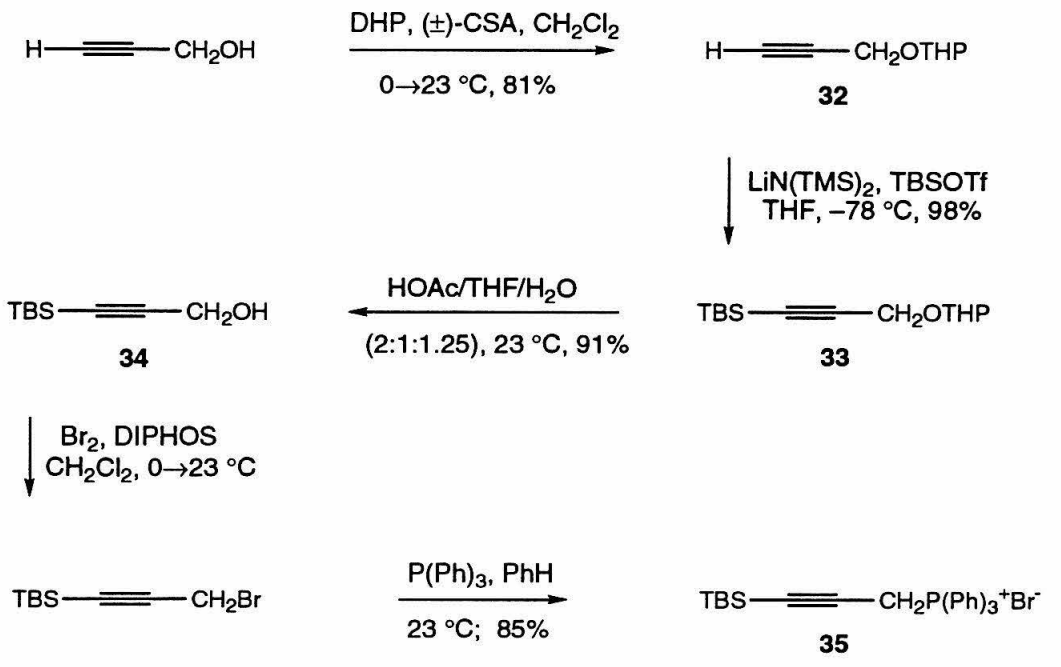


a simple extraction procedure. Neither manganese(IV) oxide[27] nor the Swern oxidation[17] produced the propargyl ketone **8** cleanly.

Initial efforts to construct a (*Z*)-enediyne from **8** involved the elimination of the tertiary hydroxyl group of **31**, which was obtained from **8** by addition of propargyl magnesium bromide (1.0 equiv) in ethyl ether at 0 °C (86%, from **7**).[28] Various elimination procedures were examined but none displayed both adequate yield and stereoselectivity. For example, treatment of **31** with trifluoromethanesulfonic anhydride (5.0 equiv) and diisopropylethylamine (8.0 equiv) in dichloromethane at –78→0 °C provided a 1:1 mixture of the cis and trans enediynes in 69% yield.



Propargyl ketone **8** was efficiently converted to a (*Z*)-enediyne with the Wittig reagent derived from (3-*tert*-butyldimethylsilylprop-2-ynyl)triphenylphosphonium bromide (**35**), which was synthesized in a manner similar to that of the corresponding trimethylsilyl phosphonium salt.[29] The use of the *tert*-butyldimethylsilyl group allows the two acetylenic groups to be differentiated. Phosphonium salt **35** was synthesized as follows. Treatment of propargyl alcohol with dihydropyran (1.1 equiv) in the presence of (±)-camphorsulfonic acid (0.001 equiv) in dichloromethane at 0→23 °C provided the tetrahydropyranyl ether **32** (81%). Conversion of **32** to the silylated tetrahydropyranyl ether, **33**, was accomplished with lithium bis(trimethylsilyl)amide (1.0 M in THF, 1.1 equiv) and *tert*-butyldimethylsilyl trifluoromethanesulfonate[30] (1.2 equiv) in tetrahydrofuran at –78 °C (98%). Ether **33** was hydrolyzed to afford 3-*tert*-butyldimethylsilyl propargyl alcohol (**34**) by exposure to 2:1:1.25 glacial acetic acid-tetrahydrofuran-water at 23 °C (91%).[31] Alcohol **34** was transformed to the phosphonium salt **35** in a two-step procedure. The alcohol was first added to bromine (2.5 equiv) and 1,2-bis(diphenylphosphino)ethane (1.25 equiv) in dichloromethane at 0→23 °C, and the resulting volatile propargyl bromide intermediate was isolated following trituration of the reaction by-products with 2:1:0.5 pentane-ethyl ether-dichloromethane and removal of the solvents by distillation.[32] Addition of triphenylphosphine (1.3 equiv) to a solution of the propargyl bromide intermediate in



benzene at 23 °C afforded the phosphonium salt **35**, which was isolated by vacuum filtration (85%, from **34**).[29b]

Studies on the olefination of **8** with phosphonium salt **35** indicated that the cis/trans ratio of product olefins **9**[33] depended upon the base used, in line with ample precedent (Table I).[34] Performing the reaction with butyllithium and lithium bromide at –78→–14 °C resulted in a trans to cis ratio of 0.3 (Table I, entry 1). Omitting the lithium bromide improved the ratio to 0.5 (Table I, entry 2), while replacing the lithium base with sodium bis(trimethylsilyl)amide further raised it to 2.0 (Table 1, entry 3). The use of potassium bis(trimethylsilyl)amide provided an optimum ratio, while altering the experimental procedure (–14 °C, dropwise addition of **8**) improved the yield. Specifically, the reaction of propargyl ketone **8** with phosphonium salt **35** (1.15 equiv) and potassium bis(trimethylsilyl)amide (0.5 M in toluene, 1.1 equiv) in tetrahydrofuran at

Table I. The Formation of Olefins **9** from Propargyl Ketone **8** and Propynyl Wittig Salt **35**.

Entry	Reaction Conditions	Ratio of Trans **9** to Cis **9**
1	**8**, **35** (1.5 equiv), *n*-BuLi (1.5 equiv), LiBr (18.0 equiv), THF, –78→–14 °C[35]	0.30
2	**8**, **35** (1.5 equiv), *n*-BuLi (1.5 equiv) THF, –78→–14 °C, 66% (from **7**)	0.50
3	**8**, **35** (1.5 equiv), $NaN(TMS)_2$ (1.5 equiv) toluene, –78→–14 °C[35]	2.0
4	**8**, **35** (1.15 equiv), $KN(TMS)_2$ (1.1 equiv) THF, –14 °C, 88% (from **7**)	3.0

–14 °C resulted in the formation of the olefins **9** in 88% yield (from **7**) and a trans to cis ratio of 3.0.

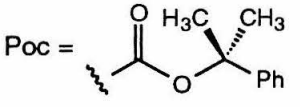
Because the trans and cis isomers of **9** were difficult to separate by flash column chromatography, the isolation of the desired trans olefin was deferred to later in the synthesis. The trimethylsilyl group was removed selectively by the treatment of the olefins **9** with potassium carbonate (1.0 equiv) in methanol at 0 °C, providing the olefins **10**, which were purified by extractive isolation.[36] Hydrolysis of **10** (1 N hydrochloric acid-tetrahydrofuran (1.2:1), 23 °C)[37] furnished the corresponding diols (93%, from **9**), at which point the trans (**11**) and cis olefins were separated by flash column chromatography. The cis olefin could be isomerized to a 1:1 mixture of cis and trans isomers by photolysis (450 W medium pressure Ace Hanovia mercury arc lamp, quartz reaction vessel, hexanes, 23 °C), allowing for the recycling of material.

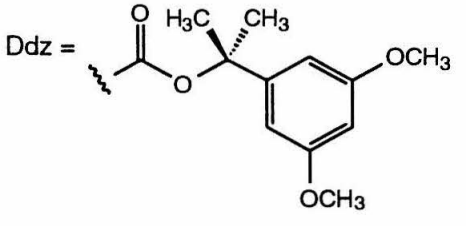
Attempted Sharpless epoxidation[12] of diol **11** to provide the desired erythro epoxide proved to be ineffective. No reaction was seen with either catalytic or stoichiometric[38] (–)-diethyl D-tartrate-titanium(IV) isopropoxide-*tert*-butyl hydroperoxide or with stoichiometric (–)-diisopropyl D-tartrate-titanium(IV) isopropoxide-*tert*-butyl hydroperoxide, while under the same conditions, epoxidations with stoichiometric (+)-diethyl L-tartrate and (+)-diisopropyl L-tartrate did afford the threo epoxide[39] in quantitative and 70% yields, respectively. This is an exception to the usual kinetic resolution behavior seen with the Sharpless procedure, and may be attributed to the diol functionality, as recently documented by others.[40] Thus, diol **11** was transformed to the allylic alcohol **12** by selective silylation with triethylamine (7.5 equiv), *tert*-butylchlorodiphenylsilane (2.5 equiv), and 4-dimethylaminopyridine (1.0 equiv) at 0 °C in dichloromethane (95%).[41] Stoichiometric Sharpless epoxidation[38] then proceeded with (–)-diethyl D-tartrate (1.25 equiv), titanium(IV) isopropoxide (1.2 equiv), and *tert*-butyl hydroperoxide (2.5 equiv) in dichloromethane at –5 °C to furnish the epoxide **13**

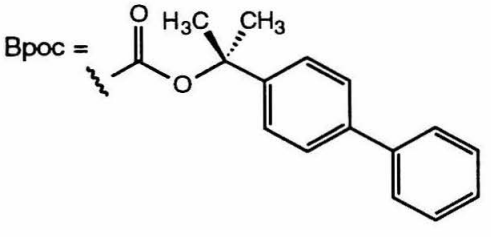
(90%).[42] The diastereoselective excess of this reaction appeared to be quite high (≥ 95%) as the threo diastereomer could not be observed by ^{1}H NMR analysis. Epoxide **13** was selectively desilylated with triethylamine trihydrofluoride (3.0 equiv) in tetrahydrofuran at 23 °C to provide the diol **14** (91%). Treatment of **14** with diphosgene (5.5 equiv) in 1:9 pyridine-dichloromethane at 0 °C completed the synthesis of the epoxy carbonate **2** (78%).

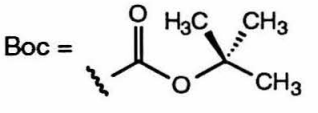
Glycosylation Studies with *N*-Methyl D-Fucosamine (3) Derivatives

As part of studies directed toward the total synthesis of neocarzinostatin chromophore (**1**), glycosylation reactions with *N*-methyl D-fucosamine (**3**) derivatives were examined. The choice of protecting group for the amino group of the sugar is critical given the instability of the chromophore. The chromophore is exceedingly sensitive to base and also decomposes under certain acidic conditions.[43] The half-life for the decomposition of **1** at 23 °C was found to be 47 h in neat glacial acetic acid, 5 h in 50% aqueous acetic acid, and 25 min in 50% aqueous acetic acid containing 1% trifluoroacetic acid.[44] Therefore, as deprotection of the amino group is to be deferred until after assemblage of the chromophore, the protecting group chosen must be rather acid-labile. Moreover, the protecting group chosen must be compatible with the sequence of steps necessary for glycosylation. Four protecting groups were examined: 2-phenylpropyloxycarbonyl (Poc), 2-(4-biphenylyl)propyloxycarbonyl (Bpoc), 2-(3,5-dimethoxyphenyl)propyloxycarbonyl (Ddz), and benzyloxycarbonyl (Boc).[45] All four are acid-labile, and show decreasing lability toward acid in the following order: Bpoc > Ddz > Poc > Boc.[46]



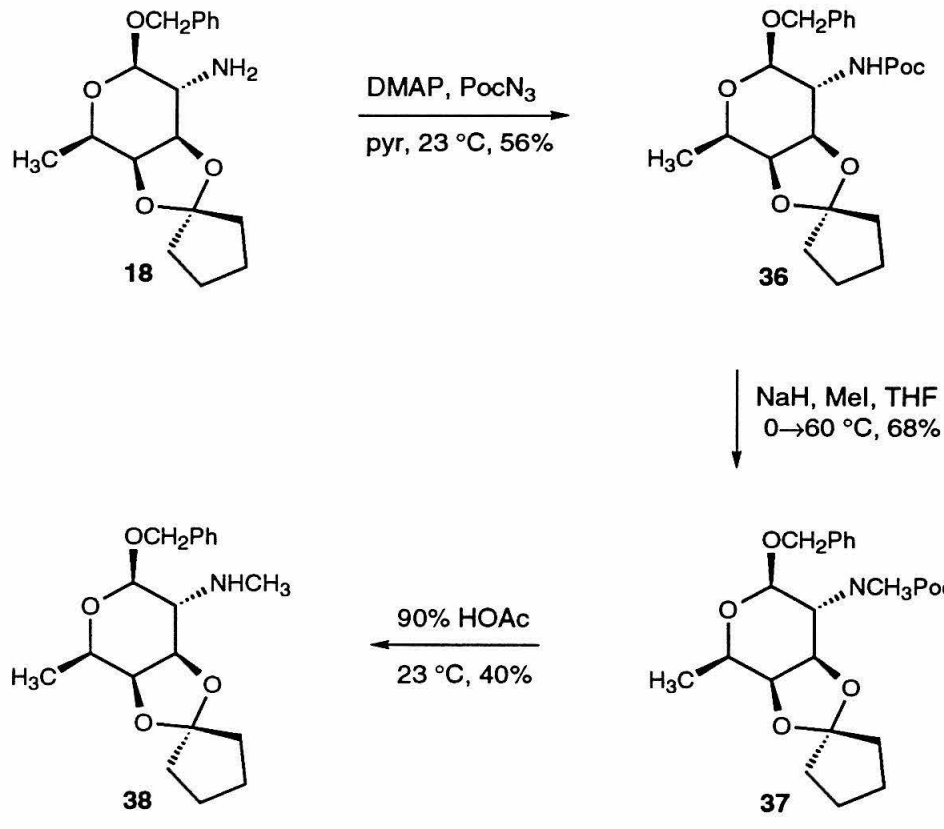


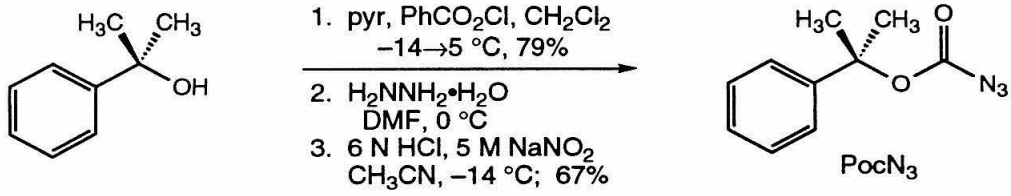




The synthesis of these protected *N*-methyl D-fucosamines centered on fucosamine derivative **18**, which was synthesized from D-galactose according to the procedure of Myers and Harrington (Scheme 2).[44,47,48] Treatment of D-galactose with acetic anhydride (7.5 equiv) and perchloric acid (60%, 0.07 equiv) at 30→40 °C, followed by red phosphorus (1.8 equiv) and bromine (2.0 equiv) at 20 °C, and sodium acetate (5.3 equiv), zinc dust (6.0 equiv), and copper(II) sulfate pentahydrate (0.16 equiv) in 30% aqueous acetic acid at 0 °C, provided 3,4,6-tri-*O*-acetal-D-galactal in 79% yield.[49] Azidonitration of this galactal was accomplished with the procedure of Lemieux and Ratcliffe employing sodium azide (1.5 equiv) and ceric ammonium nitrate (3.0 equiv) in acetonitrile at −20→−15 °C, affording 3,4,6-tri-*O*-acetyl-2-azido-2-deoxy-D-galactopyranosyl nitrate (1:1 mixture of α- and β-anomers obtained in 41% yield, α-anomer obtained by recrystallization with ethyl ether).[50] The addition of the α-anomer of this product to a suspension of sodium benzyloxide (1.5 equiv) in toluene at 0→23 °C afforded benzyl 2-azido-2-deoxy-β-D-galactopyranoside (53%), as demonstrated by Sinay et al.[51] Selective tosylation of this galactopyranoside with *p*-toluenesulfonyl chloride (1.1 equiv) in pyridine at 23 °C furnished the tosylate **15** in 67% yield, which was transformed to the iodide **16** with sodium iodide (10.0 equiv) in 1,2-dimethoxyethane at 80 °C (95%).[47b] Treatment of **16** with cyclopentanone dimethyl ketal[52] in the presence of (±)-camphorsulfonic acid (0.1 equiv) at 80 °C afforded the iodo ketal **17** (63%). Fucosamine derivative **18** was obtained by the reaction of **17** with tributyltin hydride (5.0 equiv) and 2,2'-azobisisobutyronitrile (0.1 equiv) in 1,2-dimethoxyethane at 80 °C (88%).

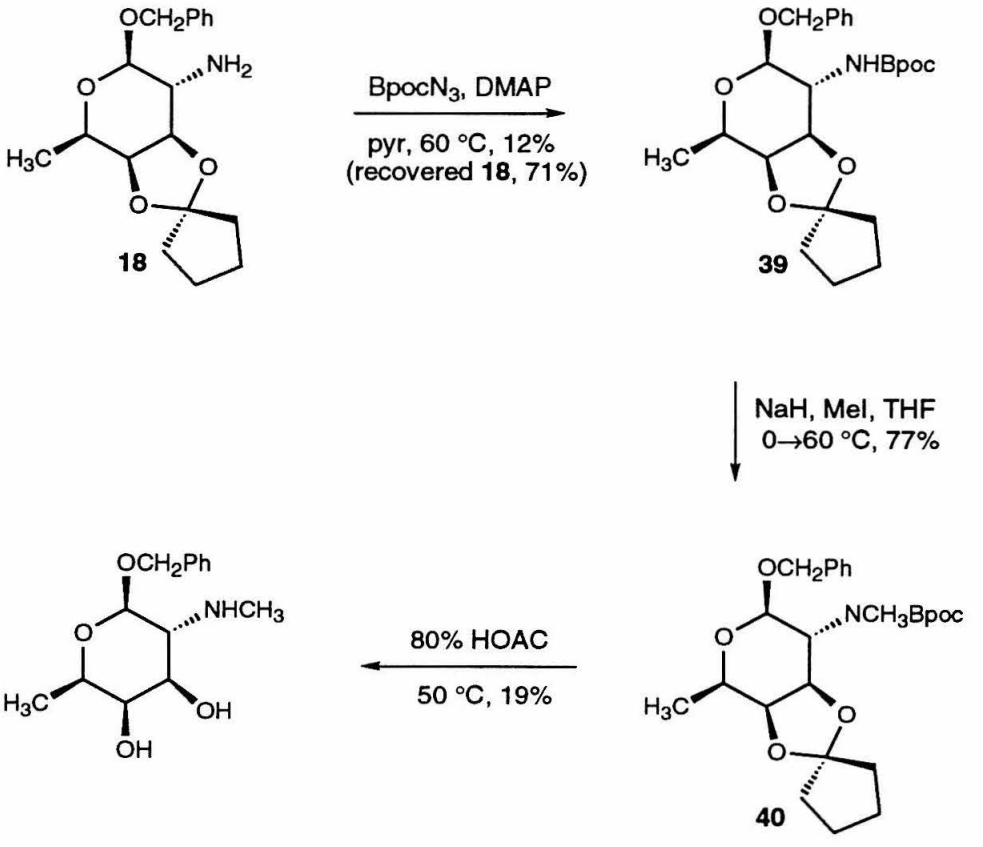
Fucosamine derivative **18** was first protected as its Poc-derivative. Reaction of **18** with 4-dimethylaminopyridine (1.0 equiv) and Poc azide (30.0 equiv) in pyridine at 23 °C provided the Poc-protected amino sugar **36** (56%). Poc azide was synthesized in a manner analogous to the synthesis of Bpoc azide developed by Sieber and Iselin.[53] 2-Phenyl-2-propanol and phenyl chloroformate (1.2 equiv) were condensed in the presence


OCH2Ph
NH2
H3C
O
O
O
18
DMAP, PocN3
pyr, 23 °C, 56%
OCH2Ph
NHPoc
H3C
O
O
O
36
NaH, MeI, THF
0→60 °C, 68%
OCH2Ph
NCH3Poc
H3C
O
O
O
37
90% HOAc
23 °C, 40%
OCH2Ph
NHCH3
H3C
O
O
O
38


H3C
CH3
OH
1. pyr, PhCO2Cl, CH2Cl2
−14→5 °C, 79%
2. H2NNH2•H2O
DMF, 0 °C
3. 6 N HCl, 5 M NaNO2
CH3CN, −14 °C; 67%
H3C
CH3
O
O
N3
PocN3

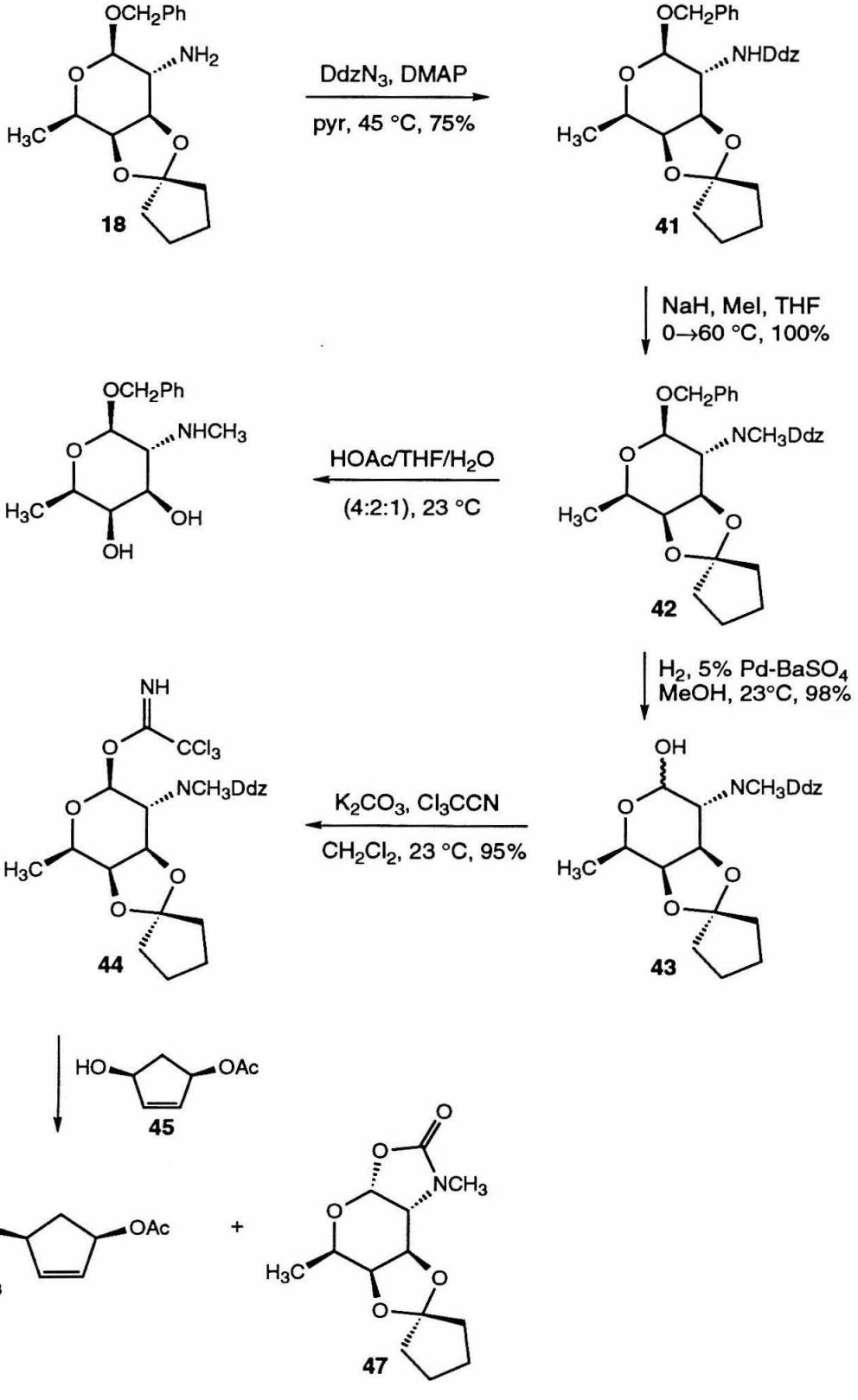
of pyridine (1.5 equiv) in dichloromethane at –14→5 °C (79%). Treatment of the carbonate thus obtained with hydrazine hydrate (5.0 equiv) in *N,N*-dimethylformamide at 0 °C, followed by extractive isolation and oxidation of the resulting hydrazine with sodium nitrite (5 M, 1.3 equiv)-hydrochloric acid (6 N, 2.6 equiv) in acetonitrile at –14 °C furnished Poc azide (purified by flash column chromatography,[54] 67%). Poc-protected amino sugar **36** was methylated with sodium hydride (10.0 equiv) and iodomethane (40.0 equiv) in tetrahydrofuran at 0→60 °C, providing the Poc-protected *N*-methyl D-fucosamine derivative **37** (68%). The deprotection of **37** was studied. For example, in a small-scale experiment, it was found that the exposure of **37** to 90% aqueous acetic acid at 23 °C for 20 h removed the Poc group but not the cyclopentylidene group, allowing the isolation of **38** in 40% yield.

A similar study was carried out with Bpoc as the protecting group. Fucosamine derivative **18** was protected with Bpoc azide[53,55] (3.0 equiv) and 4-dimethylamino-pyridine (1.1 equiv) in pyridine at 60 °C to give the Bpoc-protected amino sugar **39** (12%; recovered starting material: 71%). The transformation of **18** to **39** was not improved by initial variations in the base, solvent, or reaction temperature. The low yield of this reaction may be due to the steric requirements of the Bpoc group, as cyclohexylamine was protected as its Bpoc derivative under similar, but milder conditions (Bpoc azide (5.0 equiv), pyridine, 23 °C) in quantitative yield. Methylation of **39** (sodium hydride (10.0 equiv), iodomethane (40.0 equiv), tetrahydrofuran, 0→60 °C) furnished the Bpoc-protected *N*-methyl D-fucosamine derivative **40** (77%). The deprotection of **40** with 80% aqueous acetic acid at 50 °C was not a clean reaction, but did provide some of the amino diol (19%). The exposure of **40** to 4:2:1 acetic acid-tetrahydrofuran-water at 23 °C also furnished the amino diol (as indicated by thin layer chromatography). When manipulations were begun to activate the C-1 position of **40** for



glycosylation, it was found that conditions which removed the benzyl group (hydrogen, 5% palladium on carbon, ethanol, 23 °C) appeared to remove the Bpoc group as well.[56]

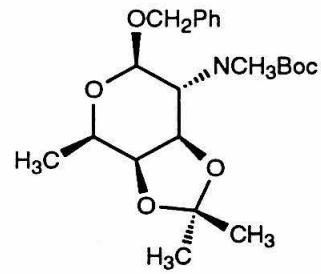
Fucosamine derivative **18** was next converted to the Ddz-protected amino sugar **41**, because the Ddz group was reported to be stable to certain hydrogenation conditions.[57] The Ddz-protected amino sugar **41** was synthesized from fucosamine derivative **18**, Ddz azide (3.0 equiv), obtained in the same manner as Poc and Bpoc azide,[58] and 4-dimethylaminopyridine (1.0 equiv) in pyridine at 45 °C (75%). Methylation of **41** with sodium hydride (8.0 equiv) and iodomethane (30.0 equiv) in tetrahydrofuran at 0→60 °C furnished the Ddz-protected *N*-methyl D-fucosamine **42** (quantitative). Deprotection of **42** with 4:2:1 acetic acid-tetrahydrofuran-water at 23 °C provided the amino diol (as indicated by thin layer chromatography). The treatment of **42**


OCH2Ph
NH2
H3C
O
18
DdzN3, DMAP
pyr, 45 °C, 75%
OCH2Ph
NHDdz
41
NaH, MeI, THF
0→60 °C, 100%
OCH2Ph
NCH3Ddz
42
HOAc/THF/H2O
(4:2:1), 23 °C
OCH2Ph
NHCH3
OH
H2, 5% Pd-BaSO4
MeOH, 23°C, 98%
OH
NCH3Ddz
43
K2CO3, Cl3CCN
CH2Cl2, 23 °C, 95%
NH
CCl3
NCH3Ddz
44
HO
OAc
45
OCH3
CH3O
OAc
H3C
CH3
46
+
O
NCH3
47

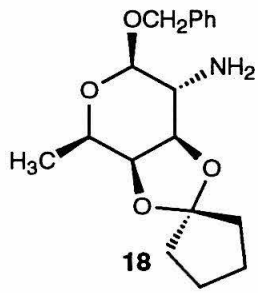
with hydrogen and palladium on barium sulfate (5%, 3.0 wt equiv) in methanol at 23 °C efficiently removed the benzyl group to furnish the alcohol **43** without affecting the Ddz group (98%). Formation of the imidate **44**, presumably the β-anomer as shown by ample precedent,[59] with potassium carbonate (0.75 equiv) and trichloroacetonitrile (31.0 equiv) in dichloromethane at 23 °C proceeded in 95% yield. Efforts to confirm the stereochemistry of the C-1 position of **44** by variable-temperature ^{1}H NMR (–60, 50, 80, and 100 °C) did not provide spectra with the necessary resolution.

Studies of the glycosylation of model compound 1(*R*)-acetoxy-2-cyclopenten-4(*S*)-ol (**45**, Scheme 4) with imidate **44** were problematic. For example, the reaction of **44** and **45** in the presence of trifluoromethanesulfonic acid (0.27 equiv) in toluene at –20 °C produced compound **46** (46%), the result of Ddz-group fragmentation. In the presence of trimethylsilyl trifluoromethanesulfonate (0.30 equiv) in dichloromethane at –20 °C,[60] the reaction of **44** and **45** (2.0 equiv) provided a new product as well, the cyclic carbamate **47** (46%). Cyclic carbamate **47** can be thought to result from rapid intramolecular displacement of the imidate by neighboring-group participation of the Ddz group, followed by fragmentation of the acid-labile Ddz group, which makes the displacement irreversible. Not unexpectedly, neither the variation of solvent nor the use of a large excess of cyclopentenol (20.0 equiv) corrected these problems.

Earlier studies by Myers and Harrington had indicated that the Boc group was compatible with the glycosylation reaction.[44] The reaction of imidate **48**, cyclopentenol **45** (2.0 equiv), and trimethylsilyl trifluoromethanesulfonate (0.1 equiv) at –20→23 °C in dichloromethane furnished the corresponding glycosylation product (63%, 3:1 α:β ratio). Accordingly, the Boc derivative **50** was prepared. Fucosamine derivative **18** was transformed to the Boc-protected amino sugar **49** with triethylamine (20.0 equiv) and Boc-ON (5.0 equiv) in 1:1 acetone-water at 23 °C (85%).[61] Methylation of **49** (sodium hydride (10.0 equiv), iodomethane (40.0 equiv), tetrahydrofuran, 0→60 °C) provided the



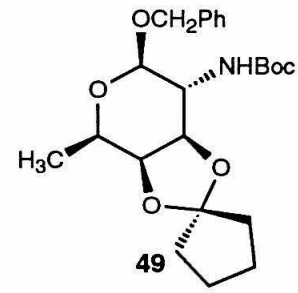
48



18

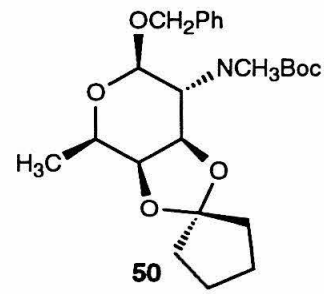
Et_3N, Boc-ON

acetone/H_2O (1:1)
23 °C, 85%



49

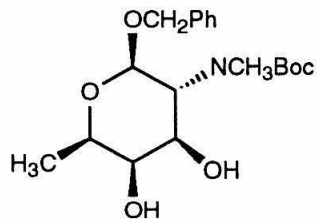
NaH, MeI, THF
0→60 °C, 88%



50

HOAc/THF/H_2O

(4:2:1), 23 °C, 90%



Boc-protected *N*-methyl D-fucosamine derivative **50** in 88% yield. Exposure of **50**, however, to 4:2:1 acetic acid-tetrahydrofuran-water at 23 °C for 94 h failed to remove the Boc group, providing the corresponding diol in 90% yield. It is unlikely that neocarzinostatin chromophore would withstand the more vigorous acid hydrolysis conditions that appear to be necessary to remove this Boc group (*vide supra*).

Of the four protecting groups studied, Poc, Bpoc, Ddz, and Boc, the most promising is Ddz. Not only is it removable under conditions to which neocarzinostatin chromophore should be stable, but also it is compatible with the reactions necessary for construction of the imidate, as evidenced by the excellent yields. However, glycosylation conditions which do not lead to fragmentation of the Ddz group must be found. As an alternative strategy, neocarzinostatin chromophore might be constructed by the nucleophilic attack of the sugar **43** on a suitably activated chromophore substrate.[62]

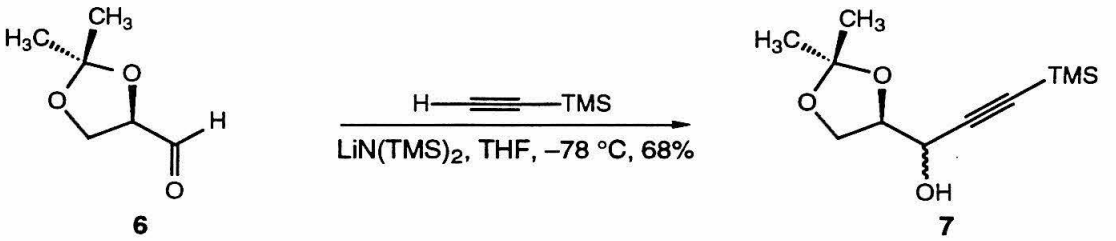
Experimental Section

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 (three iterations). Organic solutions were concentrated by rotary evaporation at ~25 Torr (water aspirator). Flash column chromatography was performed as described by Still et al. employing 230–400 mesh silica gel.[63] 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).

Commercial reagents and solvents were used as received with the following exceptions. Tetrahydrofuran and 1,2-dimethoxyethane were distilled from sodium benzophenone ketyl. (Trimethylsilyl)acetylene, methanol, and trichloroacetonitrile were dried and were stored over 3 Å sieves. *N*,*N*-Dimethylformamide was distilled from calcium sulfate at 20 Torr. Triethylamine, dichloromethane, pyridine, benzene, and acetonitrile were distilled from calcium hydride at 760 Torr. *tert*-Butyldimethylsilyl trifluoromethanesulfonate,[30] *tert*-butyl hydroperoxide in dichloromethane,[12] cyclopentanone dimethylketal,[52] Bpoc azide,[55] pH 7 phosphate buffer,[64] and Ddz azide[58] were prepared according to the literature procedure.

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 absorbtion (cm^{-1}), intensity of absorbtion (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 GE QE-300-Plus (300 MHz) NMR spectrometer; chemical shifts are expressed in parts per

million (δ scale) downfield from tetramethylsilane and are referenced to residual protium in the NMR solvent ($CHCl_3$: δ 7.26 (7.24 where noted), C_6HD_5: δ 7.15). Data are presented 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 from the University of California, Riverside Mass Spectrometry Facility.



6 7

Propargyl Alcohols **7**

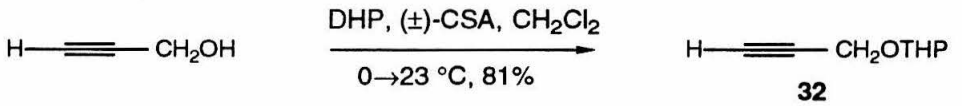
Lithium bis(trimethylsilyl)amide (1.0 M in THF, 85.0 mL, 0.085 mol, 1.1 equiv) was added slowly to a solution of (trimethylsilyl)acetylene (13.0 mL, 0.092 mol, 1.2 equiv) in tetrahydrofuran (380 mL) at –78 °C. After the reaction mixture was stirred at –78 °C for 5 min, a solution of (*R*)-2,3-*O*-isopropylidene-D-glyceraldehyde (**6**, 10.0 g, 0.077 mol, 1.0 equiv) in tetrahydrofuran (50 mL), dried with 3 Å sieves, was added. After the resulting reaction mixture was stirred at –78 °C for 1.5 h, it was quenched at –78 °C with saturated aqueous ammonium chloride (40 mL). The mixture was stirred at 23 °C and was partitioned between ethyl acetate (two portions) and saturated aqueous sodium chloride. The combined organic layers were dried over sodium sulfate and were concentrated. The resulting residue was purified by flash column chromatography (20% ethyl acetate in hexanes), furnishing the propargyl alcohols **7** (11.94 g, 68%, 1:1 diastereomeric ratio) as a pale yellow oil, which was stored in benzene.

R_f (40% ethyl acetate in hexanes):	0.51
IR (neat):	3444 (br, OH), 2988 (s), 2175 (m, C≡C), 1372 (s), 1252 (s), 1069 (s), 866 (s)
^{1}H NMR (400 MHz, $CDCl_3$):	3.86–4.48 (m, 4 H, **CH**O), 2.69 (d, J = 4.40 Hz, **OH** of one diastereomer), 2.55 (d, J = 5.13 Hz, **OH** of one diastereomer), 1.45 (s, C(**CH**$_3$) of one diastereomer), 1.43 (s, C(**CH**$_3$) of one diastereomer), 1.36 (s, two

C(CH_3) of the diastereomers), 0.15 (s, 9 H, Si(CH_3)$_3$)

HRMS: calcd for $C_{11}H_{21}O_3Si$ (MH^+): 229.1260

found: 229.1257

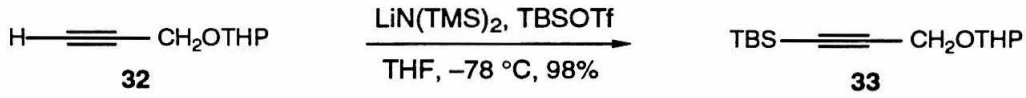


32

Tetrahydropyranyl Ether **32**

A solution of dihydropyran (17.2 mL, 0.19 mol, 1.1 equiv) in dichloromethane (50 mL) was added slowly over 10 min to a solution of propargyl alcohol (10.0 mL, 0.17 mol, 1.0 equiv) in dichloromethane (250 mL) at 0 °C. (±)-Camphorsulfonic acid (40.0 mg, 1.7 mmol, 0.001 equiv) was then added at 0 °C. The resulting mixture was stirred at 0 °C for 40 min and at 23 °C for 3.5 h. The reaction mixture was quenched with saturated aqueous sodium bicarbonate and was partitioned between water and dichloromethane. The combined organic layers were dried over sodium sulfate and were concentrated. The resulting residue was purified by fractional distillation (head temperature 85–90 °C, 25 Torr) to give the tetrahydropyranyl ether **32** (19.43 g, 81%) as a colorless oil.

R_f (40% ethyl acetate in hexanes):	0.64
IR (neat):	3293 (m, C≡CH), 2945 (s), 2872 (m), 2118 (w, C≡C), 1121 (s), 1030 (s)
^{1}H NMR (400 MHz, $CDCl_3$):	4.80 (s, 1 H, OC**H**O), 4.27 (d, 1 H, J = 15.62 Hz, C≡CC**H**$_A$H$_B$), 4.23 (d, 1 H, J = 15.62 Hz, C≡CCH$_A$**H**$_B$), 3.81 (m, 1 H, $CH_2CH_AH_BO$), 3.52 (m, 1 H, $CH_2CH_AH_BO$), 2.40 (d, 1 H, J = 1.46 Hz, C≡C**H**), 1.52–1.82 (m, 6 H, (C**H**$_2$)$_3$)
HRMS:	calcd for $C_8H_{11}O_2$ ($M-H^+$): 139.0759 found: 139.0766

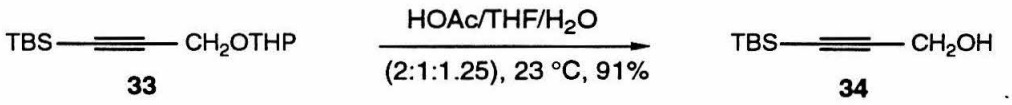


32 **33**

Silylated Tetrahydropyranyl Ether **33**

Lithium bis(trimethylsilyl)amide (1.0 M in THF, 21.9 mL, 0.022 mol, 1.1 equiv) was added slowly to a deoxygenated suspension of tetrahydropyranyl ether **32** (2.75 mL, 0.020 mol, 1.0 equiv) and 3 Å sieves in tetrahydrofuran (170 mL) at –78 °C. After the reaction mixture was stirred at –78 °C for 10 min, *tert*-butyldimethylsilyl trifluoromethanesulfonate (5.48 mL, 0.024 mol, 1.2 equiv) was slowly introduced. After the reaction mixture was stirred at –78 °C for an additional 1.5 h, it was quenched at –78 °C with saturated aqueous ammonium chloride (15 mL). The mixture was diluted with ethyl acetate (50 mL) and was washed with water and saturated aqueous sodium chloride. The organic layer was dried over sodium sulfate and was concentrated. The crude product thus obtained was purified by flash column chromatography (2.5% ethyl acetate in hexanes) to provide the silylated tetrahydropyranyl ether **33** (4.95 g, 98%) as a pale yellow oil.

R_f (20% ethyl acetate in hexanes):	0.55
IR (neat):	2953 (s), 2857 (s), 2176 (m, C≡C), 1030 (s)
^{1}H NMR (400 MHz, $CDCl_3$):	4.83 (s, 1 H, OC**H**O), 4.26 (s, 2 H, C≡CC**H**$_2$), 3.82 (m, 1 H, CH$_2$C**H**$_A$H$_B$O), 3.52 (m, 1 H, CH$_2$CH$_A$**H**$_B$O), 1.52–1.80 (m, 6 H, (C**H**$_2$)$_3$), 0.92 (s, 9 H, SiC(C**H**$_3$)$_3$), 0.09 (s, 6 H, Si(C**H**$_3$)$_2$)
HRMS:	calcd for $C_{14}H_{27}O_2Si$ (MH^+): 255.1780 found: 255.1766

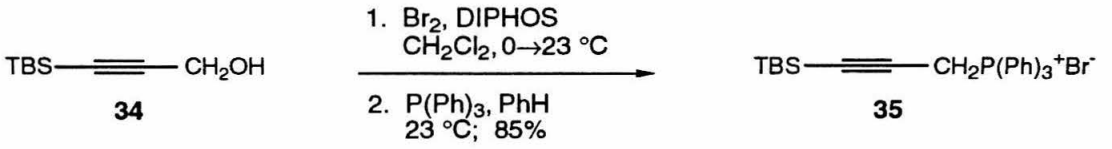


33 **34**

3-*tert*-Butyldimethylsilyl Propargyl Alcohol (**34**)

Silylated tetrahydropyranyl ether **33** (13.58 g, 0.053 mol, 1.0 equiv) in 4:2:1 glacial acetic acid-tetrahydrofuran-water (700 mL) was stirred at 23 °C. After the reaction mixture was stirred at 23 °C for 29 h, water (150 mL) was added. After the reaction mixture was stirred at 23 °C for an additional 14 h, it was diluted with ethyl acetate and was neutralized with solid and saturated aqueous sodium bicarbonate. The separated organic phase was washed twice with saturated aqueous sodium bicarbonate, and then it was dried over sodium sulfate and was concentrated. The resulting residue was purified by flash column chromatography (10 and 20% ethyl acetate in hexanes) to provide 3-*tert*-butyldimethylsilyl propargyl alcohol (**34**, 8.23 g, 91%) as a white solid: mp 36 °C (uncorrected).

R_f (20% ethyl acetate in hexanes):	0.26
IR (neat):	3286 (br, OH), 2931 (s), 2849 (s), 2179 (m, C≡C), 1471 (s), 1361 (m), 1251 (s), 1043 (s), 982 (s), 824 (s)
^{1}H NMR (400 MHz, $CDCl_3$):	4.28 (d, 2 H, J = 6.34 Hz, CH_2OH), 1.54 (t, 1 H, J = 6.35 Hz, CH_2OH), 0.94 (s, 9 H, $SiC(CH_3)_3$), 0.11 (s, 6 H, $Si(CH_3)_2$)
HRMS:	calcd for $C_9H_{18}OSi$ (M^+): 170.1127 found: 170.1126



Phosphonium Salt **35**

A solution of bromine (5.13 mL, 0.10 mol, 2.5 equiv) in dichloromethane (50 mL) was added dropwise over 20 min to a solution of 1,2-bis(diphenylphosphino)ethane (19.82 g, 0.050 mol, 1.25 equiv) in dichloromethane (215 mL) at 0 °C. After the reaction mixture was stirred at 0 °C for 15 min, a solution of 3-*tert*-butyldimethylsilyl propargyl alcohol (**34**, 6.78 g, 0.040 mol, 1.0 equiv) in dichloromethane (50 mL), dried with 3 Å sieves, was introduced at 0 °C. The transfer was quantitated with dichloromethane (15 mL). The reaction mixture was placed at 23 °C and was stirred at 23 °C for 2.75 h, and then it was poured into 2:1 pentane-ethyl ether (1.8 L). The resulting suspension was filtered through a pad of silica gel, which was washed with several portions (100 mL each) of 2:1 pentane-ethyl ether. The combined eluents were concentrated by fractional distillation at 760 Torr until the head temperature reached 40 °C, when a pale yellow solution (approx. 25 mL in volume) of 3-*tert*-butyldimethylsilyl propargyl bromide remained.

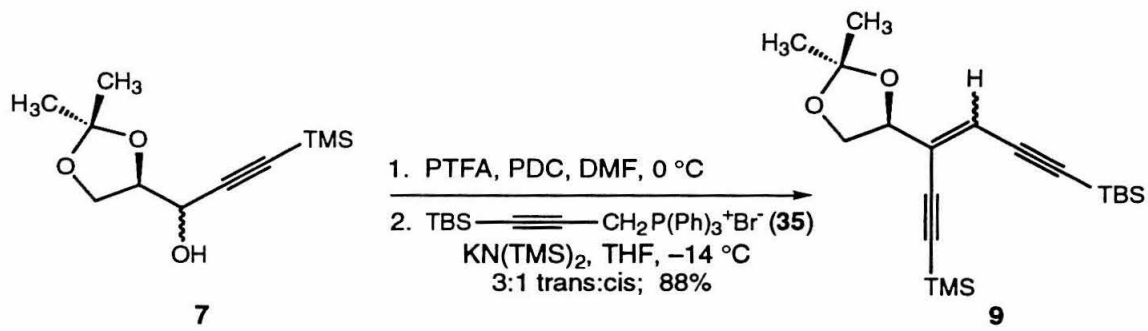
Triphenylphosphine (13.6 g, 0.052 mol, 1.3 equiv) was added to this solution of 3-*tert*-butyldimethylsilyl propargyl bromide in benzene (70 mL) at 23 °C. The resulting solution was stirred protected from light at 23 °C for 22.5 h. The suspension thus obtained was vacuum filtered. The collected solid was washed with cold benzene and was dried over Drierite and phosphorus pentoxide at 1–2 Torr for 20 h. The phosphonium salt **35** (16.7 g, 85% from **34**) was obtained as a fine white powder (mp 210 °C (dec, uncorrected)) and was stored away from light.

3-*tert*-Butyldimethylsilyl Propargyl Bromide:

R_f (20% ethyl acetate in hexanes):	0.74

Phosphonium Salt **35**:

IR (neat):	3355 (br), 2929 (s), 2816 (s), 2178 (m, C≡C), 1439 (s), 1250 (m), 1114 (s), 919 (s)
^{1}H NMR (400 MHz, $CDCl_3$):	7.66–7.91 (m, 15 H, P**Ph**$_3$), 5.16 (d, 2 H, J = 15.38 Hz, C≡CC**H**$_2$), 0.66 (s, 9 H, SiC(C**H**$_3$)$_3$), –0.09 (s, 6 H, Si(C**H**$_3$)$_2$)
HRMS:	calcd for $C_{27}H_{32}PSi$ (M^+): 415.2011 found: 415.2021



7 9

Olefins **9**

Pyridinium trifluoroacetate (1.01 g, 5.2 mmol, 0.40 equiv) and pyridinium dichromate (8.65 g, 0.023 mol, 1.75 equiv) were added to a suspension of propargyl alcohols **7** (3.0 g, 0.013 mol, 1.0 equiv, azeotropically dried with toluene three times) and crushed 3 Å sieves in *N*,*N*-dimethylformamide (60 mL) at 0 °C. The reaction mixture was deoxygenated and was stirred at 0 °C for 20 h. Additional pyridinium dichromate (2.5 g, 6.6 mmol, 0.51 equiv) was introduced and the reaction mixture was again deoxygenated. After the reaction mixture was stirred at 0 °C for another 18.5 h, additional pyridinium dichromate (1.5 g, 4.0 mmol, 0.31 equiv) was added, and the resulting reaction mixture was deoxygenated. After the reaction mixture was stirred at 0 °C for an additional 23 h, it was partitioned between ethyl ether (3 x 200mL) and water (600 mL). The combined organic layers were thoroughly mixed with magnesium sulfate[26] and the mixture was filtered. The resulting solution of the propargyl ketone **8** was partially concentrated with tetrahydrofuran a few times (to a final volume of ~100 mL), and the solution thus obtained was dried with 3 Å sieves.

Potassium bis(trimethylsilyl)amide (0.5 M in toluene, 29.0 mL, 0.014 mol, 1.1 equiv) was added to a deoxygenated suspension of phosphonium salt **35** (7.49 g, 0.015 mol, 1.15 equiv) in tetrahydrofuran (150 mL) at –78 °C. The reaction mixture was placed at –40 °C and was stirred at –40 °C for 35 min, and then it was placed at –14 °C. The solution of propargyl ketone **8** was added dropwise over 30 min (transfer quantitated with

2 x 10 mL THF) at –14 °C. After the reaction mixture was stirred at –14 °C for 2 h, it was quenched at –14 °C with saturated aqueous ammonium chloride (25 mL). The mixture was stirred at 23 °C for 15 min and, subsequently, it was diluted with hexanes and was washed with water and saturated aqueous sodium chloride. The combined aqueous layers were extracted with hexanes. The combined organic layers were dried over sodium sulfate and were concentrated. The resulting residue was purified by flash column chromatography (2% ethyl acetate in hexanes) to furnish the olefins **9** (4.2 g, 88% from **7**, 3:1 ratio of trans to cis olefins; trans olefin is a solid, cis a yellow oil) as a yellow solid.

Propargyl Ketone **8**:

R_f (40% ethyl acetate in hexanes):	0.66

(*Z*)-Enediyne **9** (trans olefin):

mp (uncorrected):	31–32 °C
R_f (20% ethyl acetate in hexanes):	0.64
IR (neat):	2956 (s), 2858 (m), 2147 (m, C≡C), 1251 (s), 1070 (s), 841 (s)
^{1}H NMR (400 MHz, $CDCl_3$):	6.06 (s, 1 H, C=C**H**), 4.53 (dd, 1 H, J = 6.83, 6.59 Hz, one of CH_AH_BCH), 4.17 (dd, 1 H, J = 8.30, 6.59 Hz, one of CH_AH_BCH), 3.91 (dd, 1 H, J = 8.30, 7.08 Hz, one of CH_AH_BCH), 1.45 (s, 3 H, $C(CH_3)$), 1.40 (s, 3 H, $C(CH_3)$), 0.97 (s, 9 H, $SiC(CH_3)_3$), 0.20 (s, 9 H, $Si(CH_3)_3$), 0.14 (s, 6 H, $Si(CH_3)_2$)

HRMS: calcd for $C_{20}H_{34}O_2Si$ (M^+): 362.2097
found: 362.2107

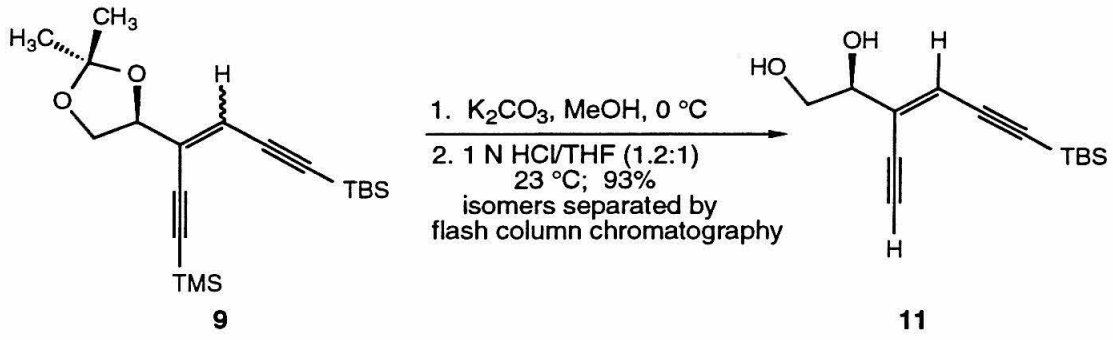
(*E*)-Enediyne **9** (cis olefin):

R_f (20% ethyl acetate in hexanes): 0.70

IR (neat): 2958 (s), 2849 (s), 2145 (m, C≡C), 1472 (m), 1372 (m), 1251 (m), 1066 (m), 863 (m)

^1H NMR (400 MHz, $CDCl_3$): 5.99 (s, 1 H, C=C**H**), 5.14 (dd, 1 H, J = 8.06, 6.34 Hz, one of CH_AH_BCH), 4.15 (dd, 1 H, J = 8.06, 6.35 Hz, one of CH_AH_BCH), 3.84 (dd, 1 H, J = 8.06, 8.05 Hz, one of CH_AH_BCH), 1.47 (s, 3 H, C(CH_3)), 1.41 (s, 3 H, C(CH_3)), 0.93 (s, 9 H, SiC(CH_3)$_3$), 0.18 (s, 9 H, Si(CH_3)$_3$), 0.12 (s, 6 H, Si(CH_3)$_2$)

HRMS: calcd for $C_{20}H_{35}O_2NSi_2$ (MH^+): 363.2176
found: 363.2177



9 **11**

Diol **11**

Potassium carbonate (3.31 g, 0.024 mol, 1.0 equiv) was added to a solution of the olefins **9** (8.68 g, 0.024 mol, 1.0 equiv) in methanol (300 mL) at 0 °C and the resulting mixture was stirred at 0 °C for 40 min. The reaction mixture was diluted with pentane and was washed twice with water and twice with saturated aqueous sodium chloride. The combined aqueous layers were extracted with pentane. The combined organic layers were dried over sodium sulfate and were concentrated to give the crude olefins **10**.

The crude olefins **10** were stirred in 1:1 1 N hydrochloric acid-tetrahydrofuran (1.2 L) at 23 °C for 16.5 h. Additional 1 N hydrochloric acid (100 mL) was then added. After the reaction mixture was stirred at 23 °C for another 2 h, it was neutralized with sodium bicarbonate (~70 g), and the resulting suspension was dissolved with a small amount of water. The mixture was partitioned between ethyl acetate (three portions) and saturated aqueous sodium bicarbonate. The combined organic layers were dried over sodium sulfate and were concentrated. Purification of the resulting residue with flash column chromatography (30 and 40% ethyl acetate in hexanes) provided the diol **11** as a yellow solid (mp 54 °C (uncorrected)) and its cis isomer (5.57 g total, 93% from **9**).

Olefins **10**:

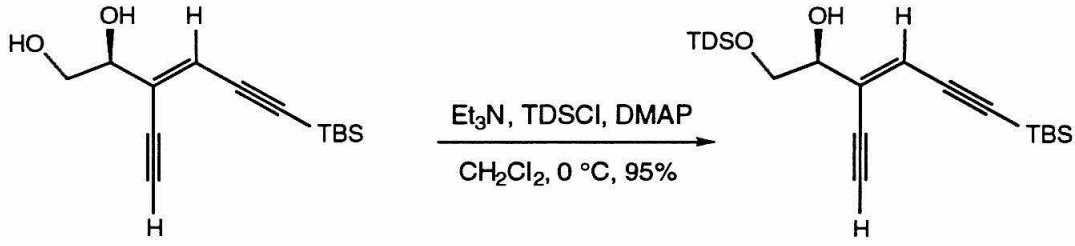
R_f (20% ethyl acetate in hexanes): cis olefin 0.72, trans olefin 0.61

Cis isomer of diol **11**:

R_f (40% ethyl acetate in hexanes):	0.30

Diol **11**:

R_f (40% ethyl acetate in hexanes):	0.25
IR (neat):	3300 (br, OH), 2930 (s), 2858 (s), 2136 (w, C≡C), 1472 (w), 1251 (m), 1082 (m), 826 (m)
^{1}H NMR (400 MHz, $CDCl_3$):	6.17 (s, 1 H, C=C**H**), 4.30 (m, 1 H, one of CH_AH_BCH), 3.82 (m, 1 H, one of CH_AH_BCH), 3.71 (m, 1 H, one of CH_AH_BCH), 3.44 (s, 1 H, C≡C**H**), 0.96 (s, 9 H, $SiC(CH_3)_3$), 0.14 (s, 6 H, $Si(CH_3)_2$)
HRMS:	calcd for $C_{14}H_{23}SiO_2$ (MH^+): 251.1467 found: 251.1466



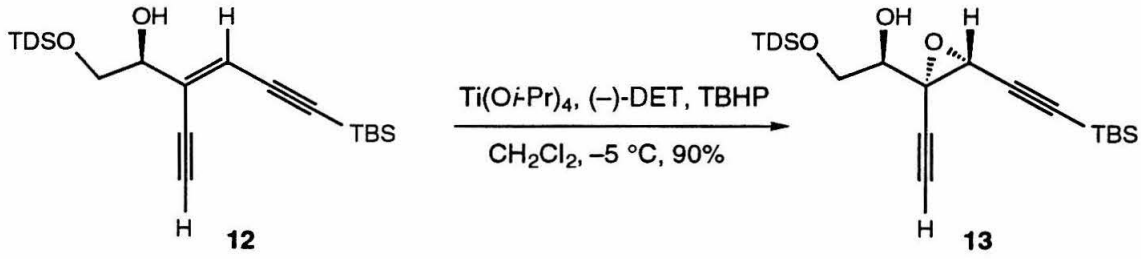
11 **12**

Allylic Alcohol **12**

Triethylamine (5.01 mL, 0.036 mol, 7.5 equiv), *tert*-butylchlorodiphenylsilane (3.12 mL, 0.012 mol, 2.5 equiv), and 4-dimethylaminopyridine (0.59 g, 4.79 mmol, 1.0 equiv) were added to a solution of diol **11** (1.2 g, 4.79 mmol, 1.0 equiv, azeotropically dried twice with toluene) in dichloromethane (30 mL) at 0 °C. After the reaction mixture was stirred at 0 °C for 50 min, it was quenched with methanol (10 mL, dried with 3 Å sieves). The mixture was stirred at 23 °C for 10 min and was washed twice with water. The organic layer was dried over sodium sulfate and was concentrated. The resulting residue was purified by flash column chromatography (5% ethyl acetate in hexanes) to give the allylic alcohol **12** (2.22 g, 95%) as a yellow oil.

R_f (40% ethyl acetate in hexanes):	0.68
IR (neat):	3564 (br, OH), 3300 (w, C≡CH), 3072 (w, Ar-H, C=CH), 2930 (s), 2858 (s), 2136 (w, C≡C), 1471 (m), 1428 (m), 1250 (m), 1113 (s), 824 (s), 702 (s)
^{1}H NMR (400 MHz, $CDCl_3$):	7.26–7.74 (m, 10 H, Si**Ph**$_2$), 6.17 (s, 1 H, C=C**H**), 4.30 (m, 1 H, C**H**OH), 3.90 (dd, 1 H, J = 10.25, 3.67 Hz, C**H**$_A$H$_B$O), 3.73 (dd, 1 H, J = 10.25, 6.60 Hz, CH$_A$**H**$_B$O), 3.31 (s, 1 H, C≡C**H**), 2.84 (s, 1 H, O**H**), 1.09 (s, 9 H,

	$SiC(CH_3)_3$), 0.99 (s, 9 H, $SiC(CH_3)_3$), 0.17 (s, 6 H, $Si(CH_3)_2$)
HRMS:	calcd for $C_{30}H_{41}O_2Si_2$ (MH^+): 489.2645
	found: 489.2653

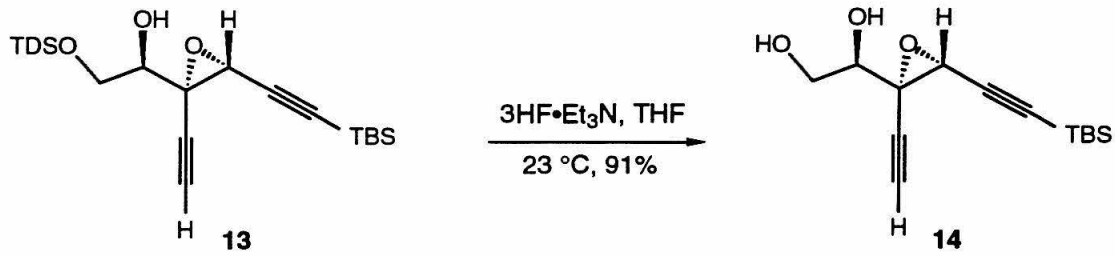


Epoxide **13**

Titanium(IV) isopropoxide (0.34 mL, 1.16 mmol, 1.2 equiv), (–)-diethyl D-tartrate (0.21 mL, 1.21 mmol, 1.25 equiv), and crushed 3 Å sieves in dichloromethane (11 mL) were stirred at –20 °C for 10 min. A solution of allylic alcohol **12** (0.47 g, 0.97 mmol, 1.0 equiv, azeotropically dried with toluene three times) in dichloromethane (4.0 mL) was introduced at –20 °C. The transfer was quantitated with dichloromethane (2 x 2.0 mL). After the reaction mixture was stirred at –20 °C for 25 min, *tert*-butyl hydroperoxide (4.07 M in dichloromethane, 0.60 mL, 2.42 mmol, 2.5 equiv) was added with a Teflon needle at –20 °C. The reaction mixture was then stirred at –5 °C for 18.5 h, and was quenched with 10% aqueous tartaric acid (20 mL). The mixture was stirred vigorously at 23 °C for 1.5 h. The resulting clear organic phase was separated, and the aqueous phase was extracted with dichloromethane. After the combined organic layers were washed with water, they were dried over sodium sulfate and were concentrated. The resulting residue was subjected to purification by flash column chromatography (8% ethyl acetate in hexanes), providing the epoxide **13** (0.44 g, 90%) as a yellow oil which was stored frozen in benzene.

R_f (20% ethyl acetate in hexanes):	0.36
IR (neat):	3483 (br, OH), 3310 (m, C≡CH), 3071 (m, Ar-H), 2931 (s), 2858 (s), 2186 (w, C≡C),

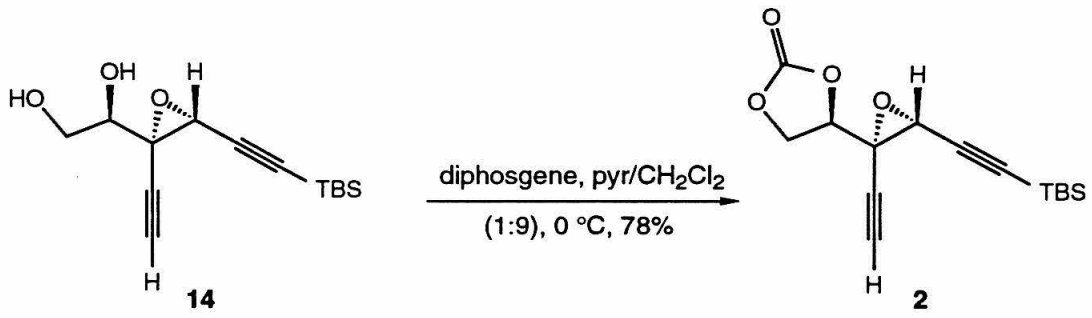
	2126 (w, C≡C), 1471 (s), 1428 (s), 1251 (s), 1114 (s), 1080 (s), 825 (s)
^{1}H NMR (400 MHz, $CDCl_3$):	7.38–7.73 (m, 10 H, Si**Ph**$_2$), 3.89–3.99 (m, 3 H, C**H**$_A$**H**$_B$C**H**), 3.83 (s, 1 H, epoxy-H), 2.46 (s, 1 H, C≡C**H**), 2.34 (d, 1 H, J = 3.66 Hz, O**H**), 1.07 (s, 9 H, SiC(C**H**$_3$)$_3$), 0.94 (s, 9 H, SiC(C**H**$_3$)$_3$), 0.13 (s, 6 H, Si(C**H**$_3$)$_2$)
HRMS:	calcd for $C_{30}H_{41}O_3Si_2$ (MH^+): 505.2594 found: 505.2581



Diol **14**

Triethylamine trihydrofluoride (1.82 mL, 0.011 mol, 3.0 equiv) was added to a solution of epoxide **13** (1.88 g, 3.70 mmol, 1.0 equiv) in tetrahydrofuran (70 mL) at 23 °C. The resulting reaction mixture was stirred at 23 °C for 27 h, and then it was quenched with saturated aqueous sodium bicarbonate. The mixture was partitioned between 50% ethyl acetate in hexanes and saturated aqueous sodium chloride. The organic layer was dried over sodium sulfate and was concentrated. The resulting crude product was purified by flash column chromatography (40% ethyl acetate in hexanes). The diol **14** (0.90 g, 91%) was isolated as a pale yellow solid: mp 78 °C (uncorrected).

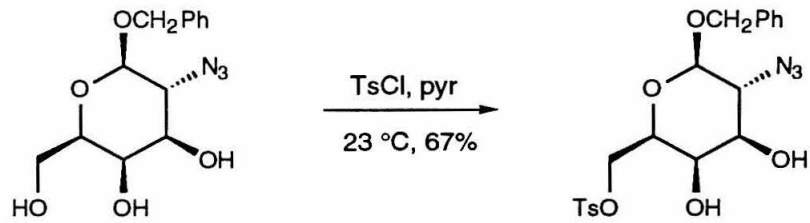
R_f (40% ethyl acetate in hexanes):	0.19
IR (neat):	3401 (br, OH), 3295 (s, C≡CH), 2943 (s), 2919 (s), 2849 (s), 2179 (w, C≡C), 2120 (w, C≡C), 1467 (m), 1249 (s), 1108 (s), 826 (s)
^{1}H NMR (400 MHz, $CDCl_3$):	3.93 (m, 2 H, two of CH_AH_BCH), 3.76 (m, 1 H, one of CH_AH_BCH), 3.70 (s, 1 H, epoxy-H), 2.53 (s, 1 H, C≡CH), 0.93 (s, 9 H, $SiC(CH_3)_3$), 0.12 (s, 6 H, $Si(CH_3)_2$)
HRMS:	calcd for $C_{14}H_{23}SiO_3$ (MH^+): 267.1416 found: 267.1427



Epoxy Carbonate **2**

Pyridine (0.5 mL, 6.1 mmol, 80.0 equiv) and diphosgene (50.0 μL, 0.41 mmol, 5.5 equiv) were added to a solution of diol **14** (20.0 mg, 0.075 mmol, 1.0 equiv) in dichloromethane (4.5 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 15 min, and then it was washed with water and saturated aqueous sodium bicarbonate. The organic layer was dried over sodium sulfate and was concentrated. The residue thus obtained was purified by flash column chromatography (20% ethyl acetate in hexanes) to provide the epoxy carbonate **2** (17.2 mg, 78%) as a white solid: mp 76 °C (uncorrected).

R_f (40% ethyl acetate in hexanes):	0.49
IR (neat):	3286 (m, C≡CH), 2931 (s), 2859 (s), 2129 (w, C≡C), 2179 (w, C≡C), 1822 (s, CO_2), 1384 (s), 1162 (s), 1088 (s), 841 (s)
^{1}H NMR (400 MHz, $CDCl_3$):	4.64 (m, 2 H, two of CH_AH_BCH), 4.38 (dd, 1 H, J = 7.81, 5.85 Hz, one of CH_AH_BCH), 3.63 (s, 1 H, epoxy-H), 2.61 (s, 1 H, C≡CH), 0.94 (s, 9 H, $SiC(CH_3)_3$), 0.14 (s, 6 H, $Si(CH_3)_2$)
HRMS:	calcd for $C_{15}H_{21}O_4Si$ (MH^+): 293.1209 found: 293.1207



15

Tosylate **15**

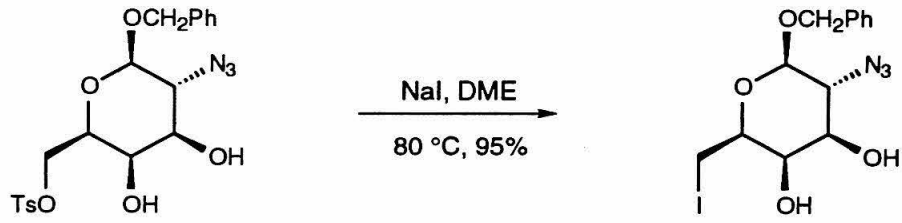
p-Toluenesulfonyl chloride (0.40 g, 2.1 mmol, 1.1 equiv) was added to a solution of benzyl 2-azido-2-deoxy-β-D-galactopyranoside (0.57 g, 1.9 mmol, 1.0 equiv) in pyridine (12 mL) at 23 °C. After the reaction mixture was stirred at 23 °C for 7.5 h, it was partitioned between ethyl acetate (four portions) and saturated aqueous citric acid (two portions). The combined organic layers were dried over sodium sulfate and were concentrated. The resulting residue was purified by flash column chromatography (50% ethyl acetate in hexanes, compound loaded onto column with ethyl acetate) to give the tosylate **15** (0.58 g, 67%) as a yellow oil.

R_f (ethyl acetate):	0.67
IR (neat):	3333 (br, OH), 2920 (m), 2117 (s, N_3), 1599 (m), 1455 (m), 1360 (s), 1190 (m), 1174 (s), 1094 (m), 989 (s), 843 (m)
^{1}H NMR (400 MHz, $CDCl_3$):	7.81 (d, 2 H, J = 8.30 Hz, Ar-**H**), 7.30–7.37 (m, 7 H, Ar-**H**), 4.86 (d, 1 H, J = 11.97 Hz, PhC**H**$_A$H$_B$), 4.62 (d, 1 H, J = 11.72 Hz, PhCH$_A$**H**$_B$), 4.29 (d, 1 H, J = 8.05 Hz, (C-1)-**H**), 4.27 (dd, 1 H, J = 10.5, 5.61 Hz, **CH**$_A$H$_B$OTs), 4.21 (dd, 1 H, J = 10.49, 6.59 Hz, CH$_A$**H**$_B$OTs), 3.89 (s, 1 H, (C-4)-**H**),

3.67 (t, 1 H, J = 6.35 Hz, (C-5)-**H**), 3.57 (dd, 1 H, J = 10.26, 8.06 Hz, (C-2)-**H**), 3.41 (d, 1 H, J = 10.01 Hz, (C-3)-**H**), 2.99 (s, 1 H, **OH**), 2.88 (s, 1 H, **OH**), 2.43 (s, 3 H, Ar-$\mathbf{CH_3}$)

HRMS: calcd for $C_{20}H_{24}O_7N_3S$ (MH^+): 450.1335

found: 450.1357



15 **16**

Iodide **16**

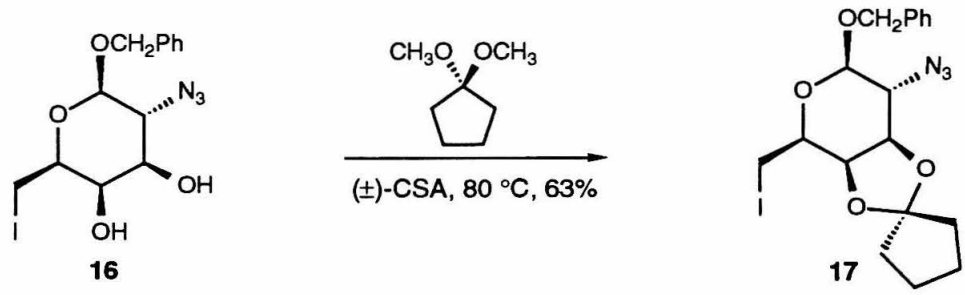
Sodium iodide (8.6 g, 0.057 mol, 10.0 equiv) was added to a solution of tosylate **15** (2.57 g, 5.72 mmol, 1.0 equiv, azeotropically dried with benzene) in 1,2-dimethoxyethane (40 mL) at 23 °C. The resulting reaction mixture was heated to 80 °C and was stirred at 80 °C for 22 h. The reaction mixture was then allowed to cool to 23 °C and was partitioned between ethyl acetate (three portions) and saturated aqueous sodium chloride. The combined organic layers were dried over sodium sulfate and were concentrated. The resulting crude material was purified by flash column chromatography (40% ethyl acetate in hexanes) to provide the iodide **16** (2.21 g, 95%) as a white solid: mp 90–95 °C (uncorrected).

R_f (50% ethyl acetate in hexanes):	0.25
IR (neat):	3287 (br, OH), 2914 (m), 2875 (m), 2109 (s, N_3), 1463 (m), 1366 (m), 1259 (m), 1116 (s), 1042 (s), 736 (s)
^{1}H NMR (400 MHz, $CDCl_3$, δ 7.24):	7.31–7.41 (m, 5 H, Ph**H**), 4.95 (d, 1 H, J = 11.96 Hz, PhC**H**$_A$H$_B$), 4.72 (d, 1 H, J = 11.96 Hz, PhCH$_A$**H**$_B$), 4.31 (d, 1 H, J = 8.05 Hz, (C-1)-**H**), 4.05 (d, 1 H, J = 3.18 Hz, (C-4)-**H**), 3.56 (dd, 1 H, J = 10.01, 8.06 Hz, (C-2)-**H**), 3.56 (m, 1 H, J = 5.86, 3.66 Hz, (C-

5)-**H**), 3.37–3.42 (m, 3 H, J = 10.26, 6.84, 3.67, 3.18 Hz, (C-3)-**H**, CH_2I), 2.64 (s, 1 H, **OH**), 2.43 (s, 1 H, **OH**)

HRMS: calcd for $C_{13}H_{20}O_4N_4I$ (MNH_4^+): 423.0529

found: 423.0549



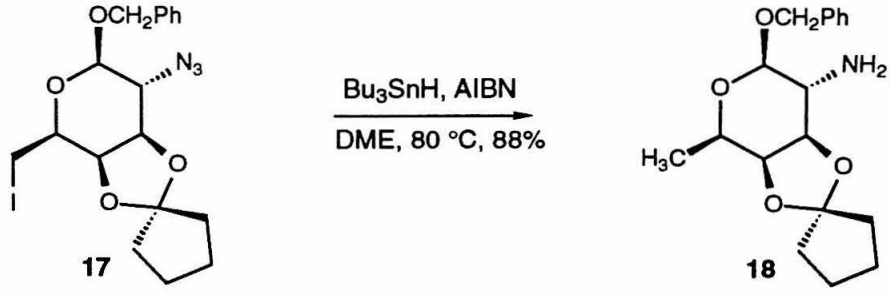
Iodo Ketal **17**

(±)-Camphorsulfonic acid (30.0 mg, 0.13 mmol, 0.1 equiv) was added to a solution of iodide **16** (0.52 g, 1.28 mmol, 1.0 equiv, azeotropically dried twice with benzene) in cyclopentanone dimethyl ketal (2.0 mL) at 23 °C. The resulting reaction mixture was heated to 80 °C and was stirred at 80 °C for 22 h. It was then allowed to cool to 23 °C and was concentrated at 1–2 Torr. The resulting residue was directly purified by flash column chromatography (5% ethyl acetate in hexanes) to furnish the iodo ketal **17** (0.38 g, 63%) as a colorless oil.

R_f (50% ethyl acetate in hexanes):	0.83
IR (neat):	3031 (w, Ar-H), 2961 (m), 2874 (m), 2113 (s, N_3), 1454 (w), 1333 (m), 1103 (m), 1044 (m), 970 (m), 698 (m)
^{1}H NMR (400 MHz, $CDCl_3$, δ 7.24):	7.30–7.41 (m, 5 H, Ph**H**), 4.96 (d, 1 H, J = 11.97 Hz, PhC**H**$_A$H$_B$), 4.73 (d, 1 H, J = 11.96 Hz, PhCH$_A$**H**$_B$), 4.23 (d, 1 H, J = 8.54 Hz, (C-1)-**H**), 4.06 (dd, 1 H, J = 5.13, 1.96 Hz, (C-4)-**H**), 3.80–3.86 (m, 2 H, J = 8.05, 7.32, 2.93 Hz, (C-2)-**H**, (C-5)-**H**), 3.39–3.43 (m, 3 H, J = 8.05, 7.33, 2.93, 2.19 Hz, (C-3)-

H, CH_2I), 1.94 (m, 2 H, two of $(CH_2)_4$), 1.60–1.70 (m, 6 H, six of $(CH_2)_4$)

HRMS: calcd for $C_{18}H_{23}N_3O_4I$ (MH^+): 472.0733
found: 472.0736



Fucosamine Derivative **18**

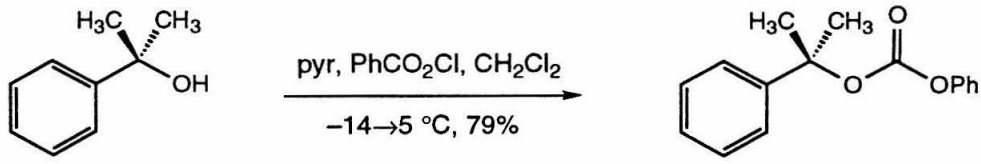
Tributyltin hydride (1.1 mL, 4.05 mmol, 5.0 equiv) and 2,2'-azobisisobutyronitrile (13.0 mg, 0.081 mmol, 0.1 equiv) were added to a solution of iodo ketal **17** (0.38 g, 0.81 mmol, 1.0 equiv, azeotropically dried with benzene) in 1,2-dimethoxyethane (6.0 mL) at 23 °C. After the resulting reaction mixture was deoxygenated, it was heated to 80 °C and was stirred at 80 °C for 18 h. The mixture was then allowed to cool to 23 °C and was quenched with a small amount of water. The mixture was partitioned between ethyl acetate (three portions) and water (separation eased with a small amount of saturated aqueous sodium chloride). The combined organic layers were dried over sodium sulfate and were concentrated. The resulting residue was purified by flash column chromatography (50% ethyl acetate in hexanes and ethyl acetate) to afford the fucosamine derivative **18** (0.23 g, 88%). The yellow oil was stored frozen in benzene.

R_f (ethyl acetate):	0.16
IR (neat):	3383 (w, NH_2), 2938 (m), 2872 (m), 1455 (m), 1378 (m), 1332 (m), 1104 (s), 1071 (s), 1043 (s), 986 (m), 699 (m)
^{1}H NMR (400 MHz, $CDCl_3$, δ 7.24):	7.26–7.33 (m, 5 H, Ph**H**), 4.90 (d, 1 H, J = 11.72 Hz, PhC$\mathbf{H}_A\mathbf{H}_B$), 4.54 (d, 1 H, J = 11.72 Hz, PhC$H_A\mathbf{H}_B$), 4.14 (d, 1 H, J = 8.54 Hz, (C-1)-**H**), 3.80–3.84 (m, 2 H, J = 8.06,

5.13 Hz, (C-3)-**H**, (C-5)-**H**), 3.75 (dd, 1 H, *J* = 5.13, 2.20 Hz, (C-4)-**H**), 2.85 (dd, 1 H, *J* = 8.30, 8.30 Hz, (C-2)-**H**), 1.88 (m, 2 H, two of (C**H**$_2$)$_4$), 1.65 (m, 6 H, six of (C**H**$_2$)$_4$), 1.41 (d, 3 H, *J* = 6.59 Hz, (C-5)-C**H**$_3$)

HRMS: calcd for $C_{18}H_{26}NO_4$ (MH^+): 320.1862

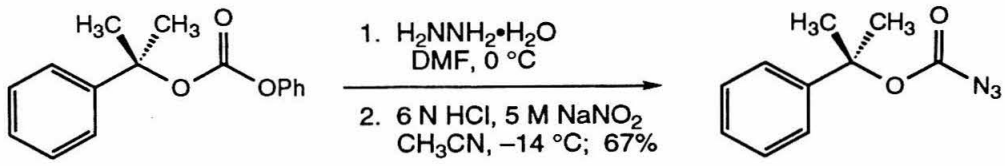
found: 320.1849



2-Phenyl-2-propyl Phenyl Carbonate

Pyridine (11.0 mL, 0.14 mol, 1.5 equiv) was added to a solution of 2-phenyl-2-propanol (12.1 g, 0.092 mol, 1.0 equiv) in dichloromethane (75 mL) at 23 °C. The resulting reaction mixture was cooled to –14 °C. A solution of phenyl chloroformate (13.8 mL, 0.11 mol, 1.2 equiv) in dichloromethane (50 mL), dried with 3 Å sieves, was added dropwise over 20 min at –14 °C. The resulting suspension was placed at 5 °C and was stirred at 5 °C for 18 h. The mixture was then vacuum filtered, and the filter cake was washed with cold dichloromethane. The filtrate was washed with 0.1 M sodium bisulfate (2 x 250 mL) and ice water (3 x 150 mL). The separated organic phase was dried over magnesium sulfate and was concentrated. The residue thus obtained was purified by flash column chromatography (5% ethyl acetate in hexanes), providing 2-phenyl-2-propyl phenyl carbonate (18.2 g, 79%) as a white solid: mp 35 °C (uncorrected).

R_f (20% ethyl acetate in hexanes):	0.50
IR (neat):	2984 (w), 1764 (s, CO_2), 1496 (m), 1256 (s), 1212 (s), 1134 (s)
^{1}H NMR (300 MHz, $CDCl_3$):	7.11–7.47 (m, 10 H, Ar-**H**), 1.91 (s, 6 H, $C(CH_3)_2$)
HRMS:	calcd for $C_{16}H_{20}O_3N_1$ (MNH_4^+): 274.1443 found: 274.1431

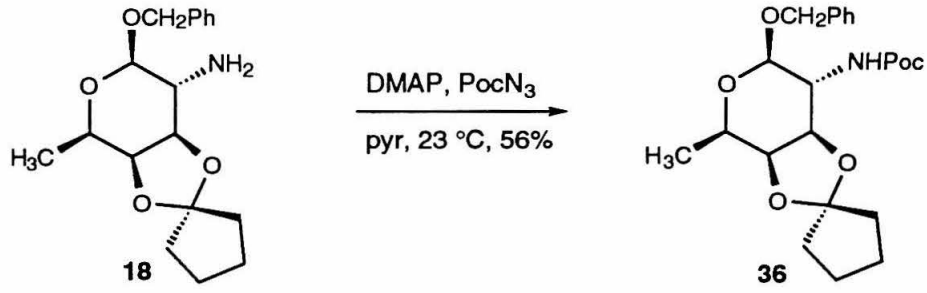


Poc Azide

Hydrazine hydrate (0.50 mL, 10.5 mmol, 5.0 equiv) was added to a solution of 2-phenyl-2-propyl phenyl carbonate (0.53 g, 2.1 mmol, 1.0 equiv) in *N*,*N*-dimethylformamide (1.5 mL) at 0 °C. The resulting solution was stirred at 0 °C for 9.5 h, and then was partitioned between water and 10% methanol in dichloromethane (three portions). The combined organic layers were dried over sodium sulfate and were concentrated, providing the corresponding crude hydrazine product.

5 M Sodium nitrite (0.6 mL, 2.73 mmol, 1.3 equiv) was added dropwise to a mixture of the crude hydrazine product and 1:2 6 N hydrochloric acid-acetonitrile (3.0 mL, 5.46 mmol, 2.6 equiv) in acetonitrile (5.0 mL) at –14 °C. After the reaction mixture was stirred at –14 °C for 0.5 h, it was neutralized with 2 M sodium carbonate (approx. 2 mL). The mixture was partitioned between ice water (10 mL) and ethyl ether (three portions). The combined organic layers were dried over sodium sulfate and were concentrated. The residue thus obtained was purified by flash column chromatography (2.5% ethyl acetate in hexanes),[54] affording Poc azide (0.28 g, 67%) as a yellow oil.

R_f (20% ethyl acetate in hexanes):	0.37
IR (neat):	2985 (m), 2183 (s, N_3), 2130 (s, N_3), 1732 (s, CO_2), 1240 (s), 1132 (s), 699 (s)
^{1}H NMR (300 MHz, $CDCl_3$):	7.32–7.43 (m, 5 H, Ar-**H**), 1.85 (s, 6 H, $C(CH_3)_2$)
HRMS:	calcd for $C_{10}H_{11}N_3O_2$ (M^+): 205.0851 found: 205.0845



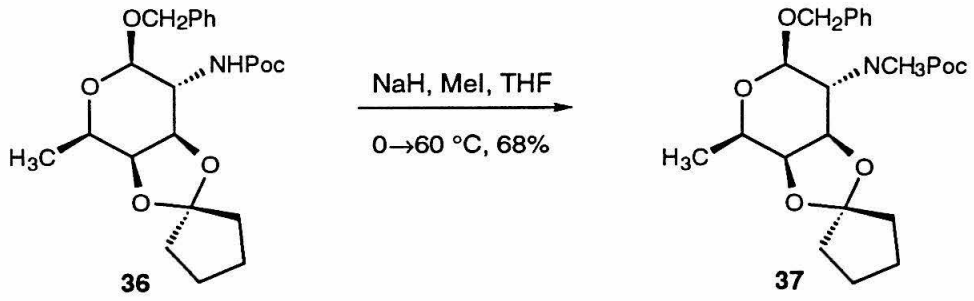
Poc-protected Amino Sugar **36**

4-Dimethylaminopyridine (4.0 mg, 0.031 mmol, 1.0 equiv) and Poc azide (70.0 μL, 0.42 mmol, 14.0 equiv) were added to a solution of fucosamine derivative **18** (10.0 mg, 0.031 mmol, 1.0 equiv, azeotropically dried with benzene) in pyridine (0.20 mL) at 23 °C. After 20 h, additional Poc azide (50.0 μL, 0.30 mmol, 10.0 equiv) was added, and after 8 h, Poc azide (30.0 μL, 0.18 mmol, 6.0 equiv) was added again. The reaction mixture was stirred at 23 °C for another 14.5 h, and then it was concentrated at 1–2 Torr. The residue thus obtained was partitioned between ethyl acetate and saturated aqueous sodium chloride. The organic layer was dried over sodium sulfate and was concentrated. The crude product was purified by flash column chromatography (30% ethyl acetate in hexanes), providing the Poc-protected amino sugar **36** (8.4 mgs, 56%) as a white solid: mp 115 °C (uncorrected).

R_f (40% ethyl acetate in hexanes):	0.33
IR (neat):	3340 (m, NH), 2978 (m), 2872 (s), 1698 (s, NCO_2), 1532 (m), 1143 (s), 1110 (s), 1070 (s)
^{1}H NMR (300 MHz, $CDCl_3$):	7.21–7.42 (m, 10 H, Ar-**H**), 4.88 (d, 1 H, J = 11.25 Hz, PhC**H**$_A$H$_B$), 4.52 (d, 1 H, J = 11.25 Hz, PhCH$_A$**H**$_B$), 3.82 (d, 1 H, J = 6.12 Hz, (C-5)-**H**), 1.40–1.98 (m, 8 H, (**CH**$_2$)$_4$),

1.78 (s, 3 H, C(CH_3)), 1.71 (s, 3 H, C(CH_3)), 1.41 (d, 3 H, J = 6.42 Hz, (C-5)-CH_3) (Coupling between peaks at 4.88 and 4.52 and between 3.82 and 1.41 confirmed by COSY experiment.)

HRMS: calcd for $C_{28}H_{35}NO_6Na$ (MNa^+): 504.2362
found: 504.2393



Poc-protected *N*-Methyl D-Fucosamine Derivative **37**

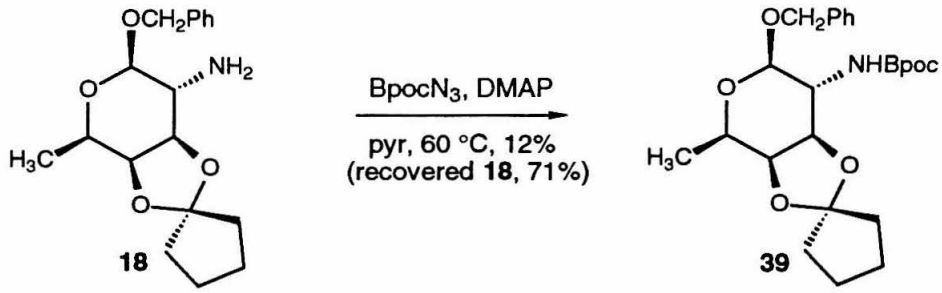
A solution of Poc-protected amino sugar **36** (0.119 g, 0.25 mmol, 1.0 equiv, azeotropically dried with benzene) in tetrahydrofuran (4.0 mL), dried with crushed 3 Å sieves, was added to sodium hydride (60.0 mg, 2.5 mmol, 10.0 equiv) at 0 °C. After the reaction mixture was stirred at 0 °C for 0.5 h, iodomethane (0.62 mL, 0.010 mol, 40.0 equiv) was added to the resulting suspension at 0 °C. The reaction mixture was heated to 60 °C and was stirred at 60 °C for 2.5 h. It was then allowed to cool and was quenched carefully with water. The mixture was partitioned between ethyl ether (two portions) and water. The combined organic layers were dried over sodium sulfate and were concentrated. The residue thus obtained was purified by flash column chromatography (20% ethyl acetate in hexanes) to provide the Poc-protected *N*-methyl D-fucosamine derivative **37** (83.0 mg, 68%) as a colorless oil which was stored frozen in benzene.

R_f (40% ethyl acetate in hexanes):	0.49
IR (neat):	3201 (w, NH), 2934 (m), 1698 (s, NCO_2), 1138 (s), 1109 (s), 1067 (s)
^{1}H NMR (300 MHz, $CDCl_3$):	7.17–7.45 (m, 10 H, Ar-**H**), 4.99 (d, J = 12.09 Hz, one of Ph**CH**$_2$ of one rotamer), 4.86 (d, J = 11.91 Hz, one of Ph**CH**$_2$ of one rotamer), 4.64 (d, J = 12.01 Hz, one of Ph**CH**$_2$ of one rotamer), 4.46 (d, J = 12.19

Hz, one of $PhCH_2$ of one rotamer), 3.82 (m, 3 H, sugar-H), 3.20 (s, 3 H, $N(CH_3)$), 1.28–2.09 (m, 8 H, $(CH_2)_4$), 1.83 (s, 3 H, $C(CH_3)$), 1.71 (s, 3 H, $C(CH_3)$), 1.39 (d, 3 H, J = 6.45 Hz, (C-5)-CH_3)

HRMS: calcd for $C_{29}H_{37}NO_6Na$ (MNa^+): 518.2519

found: 518.2516



Bpoc-protected Amino Sugar **39**

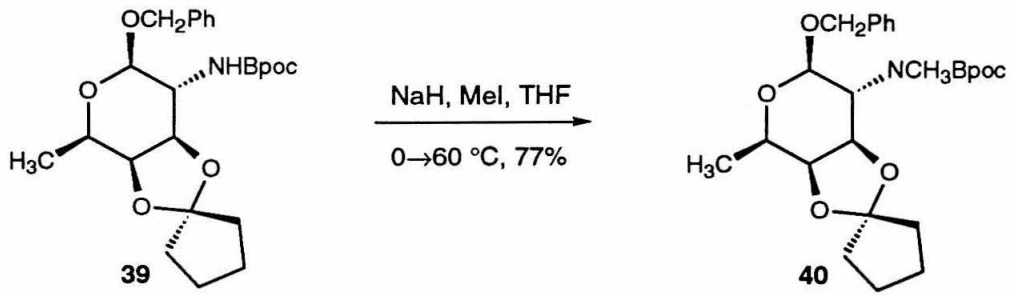
Bpoc azide (1.2 g, 4.14 mmol, 3.0 equiv) and 4-dimethylaminopyridine (0.19 g, 1.52 mmol, 1.1 equiv) were added to a solution of fucosamine derivative **18** (0.44 g, 1.38 mmol, 1.0 equiv, azeotropically dried with benzene) in pyridine (1.5 mL) at 23 °C. The reaction mixture was then heated to 60 °C and was stirred at 60 °C for 5.5 h. (**Caution**: Though this transformation was performed a number of times without incident, appropriate precautions should be exercised as acyl azides are potentially explosive. The reaction mixture, therefore, was heated behind a blast shield.) The reaction mixture was concentrated at 1–2 Torr and was partitioned between ethyl acetate and pH 7 phosphate buffer. The organic layer was dried over sodium sulfate and was concentrated. The resulting residue was purified by flash column chromatography (gradient elution: 25% ethyl acetate in hexanes→ethyl acetate). The Bpoc-protected amino sugar **39** (94.0 mgs, 12%), a yellow oil, and recovered amino sugar **18** (0.314 g, 71%) were isolated and each was stored frozen in benzene.

R_f (40% ethyl acetate in hexanes):	0.44
IR (neat):	3331 (w, NH), 2966 (m), 2872 (m), 1713 (s, NCO_2), 1487 (m), 1362 (m), 1103 (s)
^{1}H NMR (300 MHz, C_6D_6):	7.20–7.53 (m, 14 H, Ar-**H**), 4.86 (d, 1 H, J = 12.07 Hz, PhC**H**$_A$CH$_B$), 4.45 (d, 1 H, J = 12.07 Hz, PhCH$_A$C**H**$_B$), 3.36 (d, 1 H, J =

4.98 Hz, sugar-**H**), 1.50–2.00 (m, 8 H, $(CH_2)_4$), 1.74 (s, 3 H, $C(CH_3)$), 1.69 (s, 3 H, $C(CH_3)$), 1.31 (d, 3 H, J = 6.23 Hz, (C-5)-CH_3)

HRMS: calcd for $C_{34}H_{38}NO_6$ ($M-H^+$): 556.2699

found: 556.2693



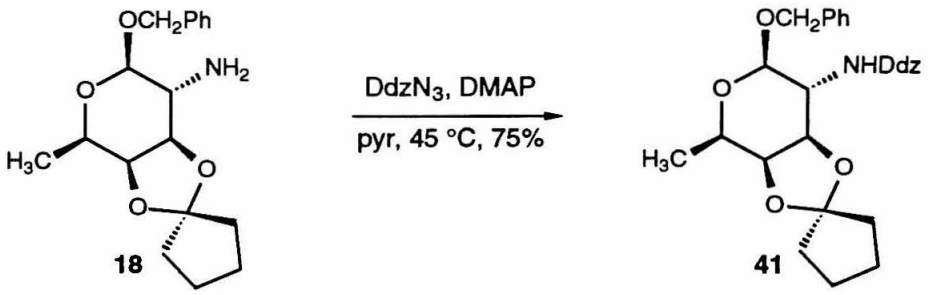
Bpoc-protected *N*-Methyl D-Fucosamine Derivative **40**

A solution of Bpoc-protected amino sugar **39** (94.0 mg, 0.16 mmol, 1.0 equiv) in tetrahydrofuran (4.0 mL), dried with 3 Å sieves, was added to sodium hydride (40.0 mg, 1.6 mmol, 10.0 equiv) at 0 °C. After the reaction mixture was stirred at 0 °C for 1 h, iodomethane (0.42 mL, 6.4 mmol, 40.0 equiv) was added to the resulting suspension at 0 °C. The reaction mixture was heated to 60 °C and was stirred at 60 °C for 2.3 h. Gas evolution was seen. The reaction mixture was then cooled to 0 °C and was quenched with a few drops of pH 7 phosphate buffer. The mixture was partitioned between pH 7 phosphate buffer and ethyl ether (two portions). The combined organic layers were dried over sodium sulfate and were concentrated. The resulting residue was purified by flash column chromatography (20% ethyl acetate in hexanes) to give the Bpoc-protected *N*-methyl D-fucosamine derivative **40** (74.0 mgs, 77%), a colorless oil which was stored frozen in benzene.

R_f (40% ethyl acetate in hexanes):	0.48
IR (neat):	2964 (s), 2861 (s), 1713 (s, NCO_2), 1690 (s), 1487 (s), 1455 (s), 1385 (s), 1115 (s), 849 (s), 698 (s)
^{1}H NMR (300 MHz, C_6D_6):	7.03–7.50 (m, 14 H, Ar-**H**), 4.86 (d, 1 H, J = 11.91 Hz, PhC**H**$_A$H$_B$), 4.46 (d, 1 H, J = 12.12 Hz, PhCH$_A$**H**$_B$), 3.39 (d, 1 H, J = 5.65

Hz, sugar-**H**), 3.12 (s, 3 H, N(C**H**$_3$)), 1.28–1.96 (m, 8 H, (C**H**$_2$)$_4$), 1.76 (s, 3 H, C(C**H**$_3$)), 1.69 (s, 3 H, C(C**H**$_3$)), 1.40 (d, J = 6.55 Hz, (C-5)-C**H**$_3$ of one rotamer), 1.29 (d, J = 6.47 Hz, (C-5)-C**H**$_3$ of one rotamer)

HRMS: calcd for $C_{35}H_{40}NO_6$ ($M-H^+$): 570.2856
found: 570.2834



Ddz-protected Amino Sugar **41**

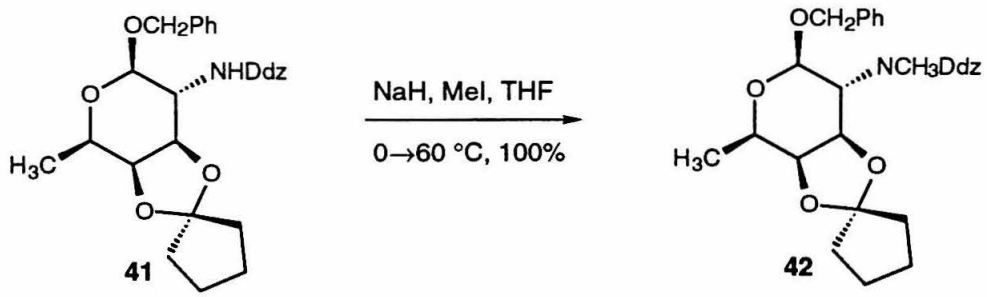
Ddz azide (90.0 μL, 0.48 mmol, 3.0 equiv) and 4-dimethylaminopyridine (20.0 mg, 0.16 mmol, 1.0 equiv) were added to a solution of fucosamine derivative **18** (50.0 mg, 0.16 mmol, 1.0 equiv, azeotropically dried with benzene) in pyridine (0.25 mL) at 23 °C. The reaction mixture was heated to 45 °C and was stirred at 45 °C for 24 h. (**Caution**: Though this transformation was performed a number of times without incident, appropriate precautions should be exercised as acyl azides are potentially explosive. The reaction, therefore, was heated behind a blast shield.) The reaction mixture was concentrated at 1–2 Torr and was purified directly by flash column chromatography (20 and 30% ethyl acetate in hexanes). The Ddz-protected amino sugar **41** (64.0 mg, 75%) was obtained as a white solid: mp 120 °C (uncorrected).

R_f (40% ethyl acetate in hexanes):	0.33
IR (neat):	3356 (m, NH), 2939 (s), 2861 (m), 1731 (s, NCO_2), 1708 (s, NCO_2), 1600 (s), 1520 (s), 1455 (s), 1156 (s), 1086 (s)
^{1}H NMR (300 MHz, C_6D_6):	6.39–7.36 (m, 8 H, Ar-**H**), 4.85 (d, 1 H, J = 11.98 Hz, PhC**H**$_A$H$_B$), 4.75 (s, 1 H, sugar-**H**), 4.52 (d, 1 H, J = 11.62 Hz, PhCH$_A$**H**$_B$), 3.37 (s, 6 H, Ar-(O**CH**$_3$)$_2$), 1.31–1.94 (m, 8

H, (CH_2)$_4$), 1.72 (s, 3 H, C(CH_3)), 1.68 (s, 3 H, C(CH_3)), 1.32 (s, 3 H, (C-5)-CH_3)

HRMS: calcd for $C_{30}H_{39}NO_8$ (M^+): 541.2676

found: 541.2688



Ddz-protected *N*-Methyl D-Fucosamine Derivative **42**

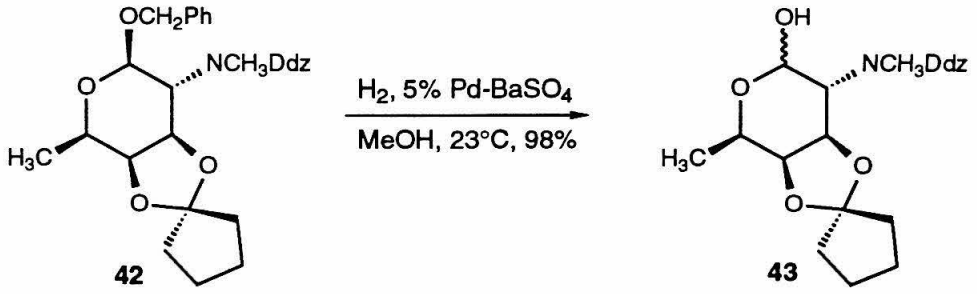
A solution of Ddz-protected amino sugar **41** (0.65 g, 1.2 mmol, 1.0 equiv) in tetrahydrofuran (30 mL), dried with 3 Å sieves, was added to sodium hydride (0.23 g, 9.6 mmol, 8.0 equiv) at 0 °C. After the reaction mixture was stirred at 0 °C for 1 h, iodomethane (2.24 mL, 0.036 mol, 30.0 equiv) was added to the resulting suspension at 0 °C. The reaction mixture was heated to 60 °C and was stirred at 60 °C for 2.5 h. It was then cooled to 0 °C and was carefully quenched with pH 7 buffer. The mixture was partitioned between pH 7 buffer and ethyl acetate (two portions). The combined organic layers were dried over sodium sulfate and were concentrated. The crude product was purified by flash column chromatography (20% ethyl acetate in hexanes) to give the Ddz-protected *N*-methyl D-fucosamine derivative **42** (0.67 g, 100%) as a colorless oil which was stored frozen in benzene.

R_f (40% ethyl acetate in hexanes):	0.38
IR (neat):	2939 (s), 2872 (s), 1708 (s, NCO_2), 1694 (s), 1600 (s), 1456 (s), 1156 (s), 1068 (s), 698 (s)
^{1}H NMR (300 MHz, C_6D_6):	6.40–7.34 (m, 8 H, Ar-**H**), 4.84 (d, 1 H, J = 11.65 Hz, PhC**H**$_A$H$_B$), 4.55 (d, 1 H, J = 11.98 Hz, PhCH$_A$**H**$_B$), 3.34 (s, 6 H, Ar-(OC**H**$_3$)$_2$), 3.06 (s, 3 H, N(C**H**$_3$)), 1.24–2.04 (m, 8 H, (C**H**$_2$)$_4$), 1.74 (s, 3 H, C(C**H**$_3$)),

1.71 (s, 3 H, C(CH_3)), 1.29 (d, 3 H, J = 6.44 Hz, (C-5)-CH_3)

HRMS: calcd for $C_{31}H_{41}NO_8$ (M^+): 555.2832

found: 555.2827



Alcohol **43**

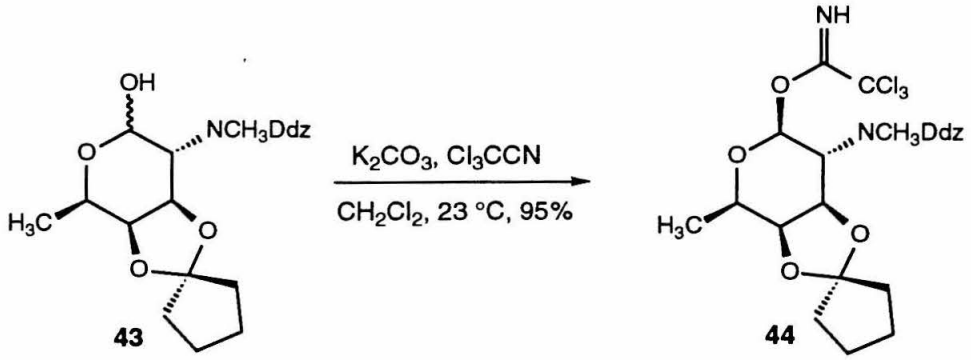
5% Palladium on barium sulfate (0.18 g, 3.0 wt equiv) was added to a solution of Ddz-protected *N*-methyl D-fucosamine derivative **42** (60.0 mg, 0.11 mmol, 1.0 equiv, azeotropically dried with benzene) in methanol (0.75 mL) at 23 °C. Hydrogen was bubbled through the resulting suspension for 2.5 h. The reaction mixture was then purged with Argon and was filtered through celite. The filtrate was concentrated. The resulting residue was purified by flash column chromatography (50% ethyl acetate in hexanes). The alcohol **43** (49.0 mg, 98%) was isolated as a colorless oil.

R_f (40% ethyl acetate in hexanes):	0.09
IR (neat):	3422 (br, OH), 2937 (s), 1684 (s, NCO_2), 1598 (s), 1425 (s), 1330 (s), 1155 (s), 1068 (s), 983 (s), 846 (s), 697 (s)
^{1}H NMR (300 MHz, C_6D_6):	6.80 (d, J = 1.95 Hz, Ar-**H** of one rotamer), 6.74 (d, J = 1.14 Hz, Ar-**H** of one rotamer), 6.67 (d, J = 2.15 Hz, Ar-**H** of one rotamer), 6.64 (d, J = 1.99 Hz, Ar-**H** of one rotamer), 6.43 (t, J = 2.13 Hz, Ar-**H** of one rotamer), 3.44 (d, 1 H, J = 5.03 Hz, sugar-**H**), 3.39 (s, 3 H, Ar-(OCH_3)), 3.37 (s, 3 H, Ar-(OCH_3)), 2.96 (s, N(CH_3) of one rotamer), 2.92 (s,

N(CH_3) of one rotamer), 1.24–1.98 (m, 8 H, (CH_2)$_4$), 1.70 (s, 3 H, C(CH_3)), 1.69 (s, 3 H, C(CH_3)), 1.34 (d, J = 6.37 Hz, (C-5)-CH_3 of one rotamer), 1.28 (d, J = 6.47 Hz, (C-5)-CH_3 of one rotamer)

HRMS: calcd for $C_{24}H_{35}NO_8$ (M^+): 465.2363

found: 465.2348



Imidate **44**

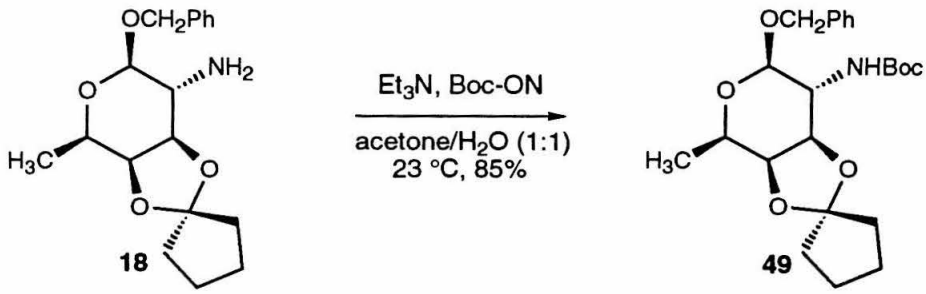
Potassium carbonate (7.0 mg, 0.048 mmol, 0.75 equiv, ground with mortar and pestle) and trichloroacetonitrile (0.20 mL, 2.0 mmol, 31.0 equiv) were added to a solution of alcohol **43** (30.0 mg, 0.064 mmol, 1.0 equiv, azeotroped with benzene) in dichloromethane (0.80 mL) at 23 °C. The reaction mixture was stirred at 23 °C for 5 h, and then it was concentrated at 1–2 Torr. The resulting residue was filtered through celite, washing the pad with ethyl acetate. The filtrate was concentrated. The residue thus obtained was purified by flash column chromatography (20% ethyl acetate in hexanes containing 2% triethylamine), providing imidate **44** (37.0 mg, 95%) as a colorless oil.

R_f (40% ethyl acetate in hexanes):	0.29
IR (neat):	2955 (m), 1690 (s, NCO_2, OCN), 1600 (s), 1455 (s), 1290 (s), 1149 (s), 1055 (s), 791 (s)
^{1}H NMR (300 MHz, C_6D_6):	8.58 (s, 1 H, C=NH), 6.82 (s, 1 H, Ar-**H**), 6.66 (d, 1 H, J = 2.13 Hz, Ar-**H**), 6.40 (d, 1 H, J = 2.13 Hz, Ar-**H**), 3.63 (d, 1 H, J = 6.11 Hz, (C-5)-**H**), 3.36 (s, 6 H, Ar-(O**C**H$_3$)$_2$), 3.06 (s, 3 H, N(**C**H$_3$)), 1.24–1.97 (m, 8 H, (**C**H$_2$)$_4$), 1.74 (s, 3 H, C(**C**H$_3$)), 1.64 (s, 3 H,

C(CH_3)), 1.25 (d, 3 H, J = 6.45 Hz, (C-5)-CH_3) (Coupling between peaks at 6.66 and 6.40, 6.66 and 1.74, 3.63 and 1.25 confirmed by COSY experiment).

HRMS: calcd for $C_{26}H_{35}N_2O_8Cl_3$ (M^+): 608.1459

found: 608.1456



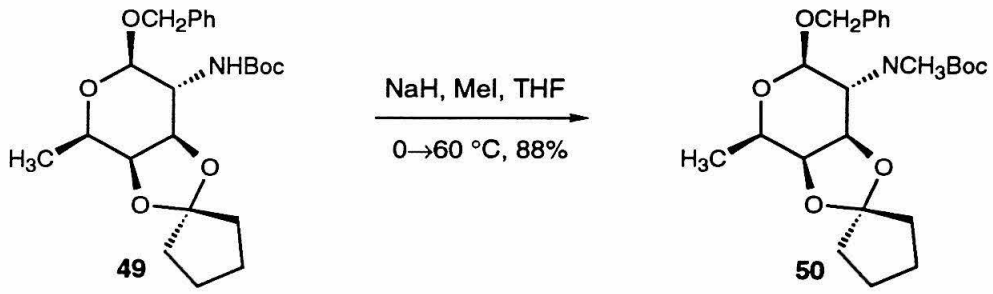
Boc-protected Amino Sugar **49**

Triethylamine (0.44 mL, 3.14 mmol, 20.0 equiv) and Boc-ON (0.19 g, 0.79 mmol, 5.0 equiv) were added to a solution of fucosamine derivative **18** (50.0 mg, 0.16 mmol, 1.0 equiv, azeotroped with benzene) in 1:1 acetone-water (1.5 mL) at 23 °C. The reaction mixture was stirred at 23 °C for 23 h and then it was partitioned between water and ethyl acetate (two portions). The combined organic layers were dried over sodium sulfate and were concentrated. The resulting residue was purified by flash column chromatography (10 and 20% ethyl acetate in hexanes) to give the Boc-protected amino sugar **49** (56.0 mg, 85%) as a white solid: mp 150 °C (uncorrected).

R_f (ethyl acetate):	0.71
IR (neat):	3320 (m, NH), 2972 (m), 2869 (m), 1694 (s, NCO_2), 1682 (s, NCO_2), 1538 (s), 1175 (m), 1119 (m), 1066 (m)
^{1}H NMR (300 MHz, $CDCl_3$):	7.29–7.37 (m, 5 H, Ar-**H**), 4.92 (d, 1 H, J = 11.83 Hz, Ph$\mathbf{H_A}\mathbf{H_B}$), 4.60 (d, 1 H, J = 11.90 Hz, Ph$\mathbf{H_A}\mathbf{H_B}$), 3.88 (m, 2 H, sugar-**H**), 1.98 (m, 2 H, two of $(\mathbf{CH_2})_4$), 1.73 (m, 6 H, six of $(\mathbf{CH_2})_4$), 1.45 (d, 3 H, J = 6.52 Hz, (C-5)-$\mathbf{CH_3}$), 1.43 (s, 9 H, $C(\mathbf{CH_3})_3$)

HRMS: calcd for $C_{23}H_{34}NO_6$ (MH^+): 420.2386

found: 420.2372



Boc-protected *N*-Methyl D-Fucosamine Derivative **50**

A solution of Boc-protected amino sugar **49** (25.0 mg, 0.060 mmol, 1.0 equiv, azeotroped with benzene) in tetrahydrofuran (3.0 mL) was added to sodium hydride (14.0 mg, 0.60 mmol, 10.0 equiv) at 0 °C. After the reaction mixture was stirred at 0 °C for 45 min, iodomethane (0.15 mL, 2.40 mmol, 40.0 equiv) was added to the resulting suspension at 0 °C. The reaction mixture was heated to 60 °C and was stirred at 60 °C for 1.5 h. The reaction was then cooled to 0 °C and was quenched with a few drops of pH 7 phosphate buffer. The mixture was partitioned between water and ethyl acetate (two portions). The combined organic layers were dried over sodium sulfate and were concentrated. The crude product was purified by flash column chromatography (10% ethyl acetate in hexanes). The Boc-protected *N*-methyl D-fucosamine derivative **50** (23.0 mg, 88%) was obtained as a colorless oil and was stored frozen in benzene.

R_f (40% ethyl acetate in hexanes):	0.54
IR (neat):	2974 (s), 2874 (s), 1694 (s, NCO_2), 1456 (m), 1386 (m), 1367 (s), 1151 (s), 1111 (s), 1069 (s), 735 (m), 698 (m)
^{1}H NMR (300 MHz, $CDCl_3$):	7.28–7.34 (m, 5 H, Ar-**H**), 4.89 (d, 1 H, J = 12.08 Hz, PhC**H**$_A$H$_B$), 4.59 (d, 1 H, J = 12.10 Hz, PhCH$_A$**H**$_B$), 3.87 (m, 2 H, sugar-**H**), 2.99 (s, 3 H, N(C**H**$_3$)), 2.06 (m, 2 H, two

of $(CH_2)_4$), 1.73 (m, 6 H, six of $(CH_2)_4$), 1.44 (s, 9 H, $C(CH_3)_3$), 1.43 (d, 3 H, J = 5.29 Hz, (C-5)-CH_3)

HRMS: calcd for $C_{24}H_{36}NO_6$ (MH^+): 434.2543

found: 434.2520

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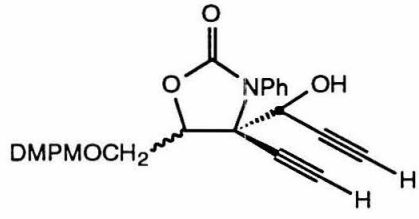
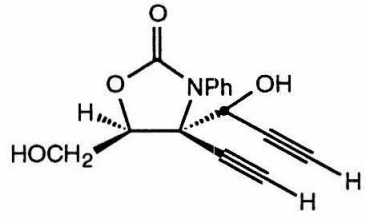
[39] This stereochemistry was determined by ^{1}H NMR NOE studies of both diastereomers of the following compound:



[40] Takano, S.; Iwabuchi, Y.; Ogasawara, K. *J. Am. Chem. Soc.* **1991**, *113*, 2786.

[41] Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 2nd ed.; John Wiley and Sons: New York, 1991; p 83.

[42] That epoxide **13** was the erythro diastereomer was confirmed by ^{1}H NMR NOE studies of the following derivative:



[43] (a) Povirk, L. F.; Goldberg, I. H. *Biochemistry* **1980**, *19*, 4773. (b) Ishida, N.; Miyazaki, K.; Kumagai, K.; Rikimaru, M. *J. Antibiotics, Ser. A* **1965**, *18*, 68.

[44] Myers, A. G.; Harrington, P. M., California Institute of Technology, unpublished results (present address of PMH: American Cyanamid Company, Princeton, New Jersey).

[45] *The Peptides*; Gross, E.; Meienhofer, J., Eds.; Academic: New York, 1981; Chapter 1.

[46] *The Peptides*; Gross, E.; Meienhofer, J., Eds.; Academic: New York, 1981; pp 212–213.

[47] For a synthesis of *N*-methyl D-fucosamine, see: (a) Edo, K.; Akiyama, Y.; Saito, K.; Mizugaki, M. *J. Antibiotics* **1986**, *39*, 1615. For a synthesis of D-fucosamine, see: (b) Zehavi, U.; Sharon, N. *J. Org. Chem.* **1964**, *29*, 3654.

[48] The following yields are those of EYK.

[49] (a) Roth, W.; Pigman, W. In *Methods in Carbohydrate Chemistry*; Whistler, R. L.; Wolfrom, M. L., Eds.; Academic: New York, 1963; Vol. 2, pp 405–408. (b) Rosenthal, A.; Read, D. *ibid.*, pp 457–462.

[50] Lemieux, R. U.; Ratcliffe, R. M. *Can. J. Chem.* **1979**, *57*, 1244.

[51] Catelani, G.; Marra, A.; Paquet, F.; Sinay, P. *Carbohydr. Res.* **1986**, *155*, 131.

[52] (a) Lorette, N. B.; Howard, W. L. *J. Org. Chem.* **1960**, *25*, 521. (b) Tsunoda, T.; Suzuki, M.; Noyori, R. *Tetrahedron Lett.* **1980**, *21*, 1357.

[53] Sieber, P.; Iselin, B. *Helv. Chim. Acta* **1968**, *51*, 622.

[54] The purification of Poc azide by flash column chromatography was carried out numerous times. Once, however, it appeared to decompose on the column, as gas evolution was seen.

[55] Kemp, D. S.; Fotouhi, N.; Boyd, J. G.; Carey, R. I.; Ashton, C.; Hoare, J. *Int. J. Peptide Protein Res.* **1988**, *31*, 359.

[56] *The Peptides*; Gross, E.; Meienhofer, J., Eds.; Academic: New York, 1981; p 36.

[57] König, W.; Kernebeck, K. *Leibigs. Ann. Chem.* **1979**, 227.

[58] Birr, C.; Lochinger, W.; Stahnke, G.; Lang, P. *Liebigs Ann. Chem.* **1972**, *763*, 162.

[59] (a) Schmidt, R. R.; Michel, J. *Tetrahedron Lett.* **1984**, *25*, 821. (b) Schmidt, R. R. *Pure Appl. Chem.* **1989**, *61*, 1257.

[60] Ogawa, T.; Beppu, K.; Nakabayashi, S. *Carbohydr. Res.* **1981**, *93*, C6.

[61] Itoh, M.; Hagiwara, D.; Kamiya, T. *Tetrahedron Lett.* **1975**, *49*, 4393.

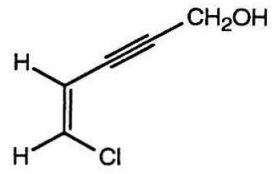
[62] Schmidt, R. R.; Reichrath, M. *Angew. Chem. Int. Ed. Engl.* **1979**, *18*, 466. See also: ref 59b.

[63] Still, D. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

[64] Gordon, A. J.; Ford, R. A. *The Chemist's Companion*; John Wiley and Sons: New York, 1972; p 72.

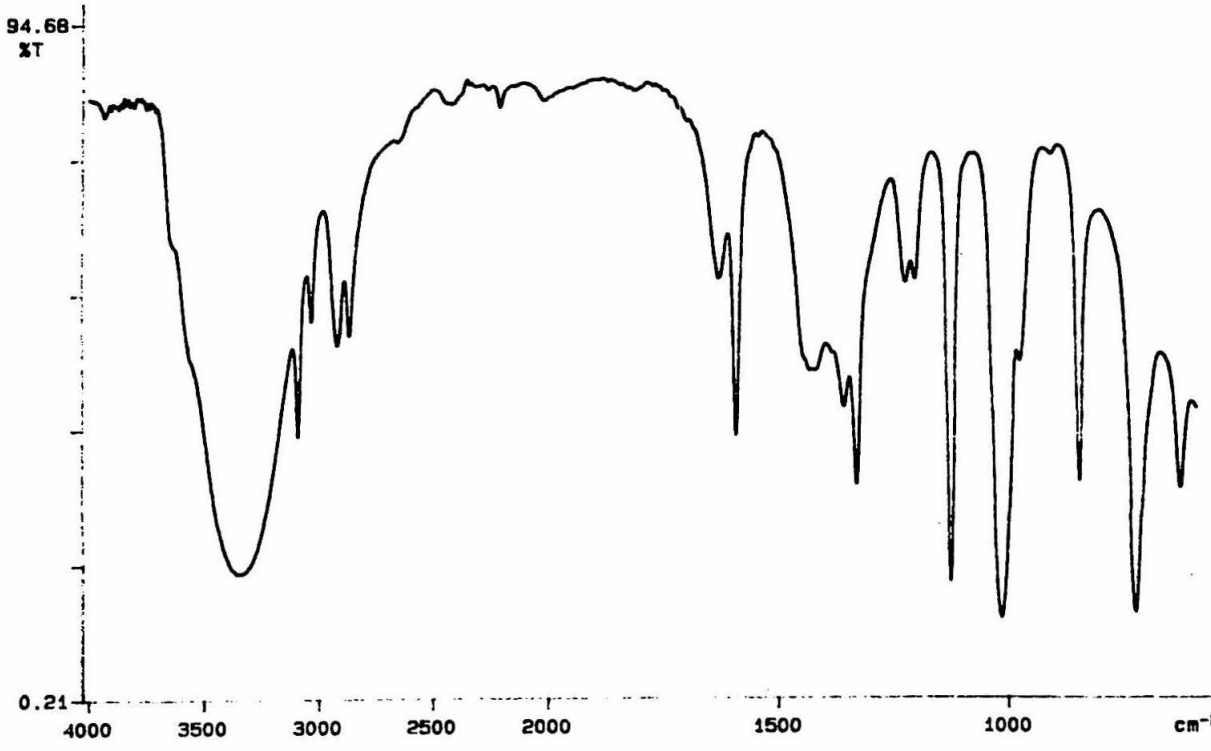
Appendix

Spectral Catalog


CH2OH
H
H
Cl

15

9
8
7
6
5
4
3
2
1
0
PPM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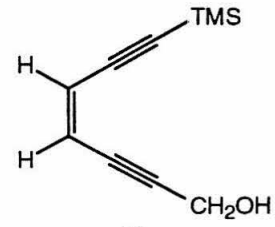
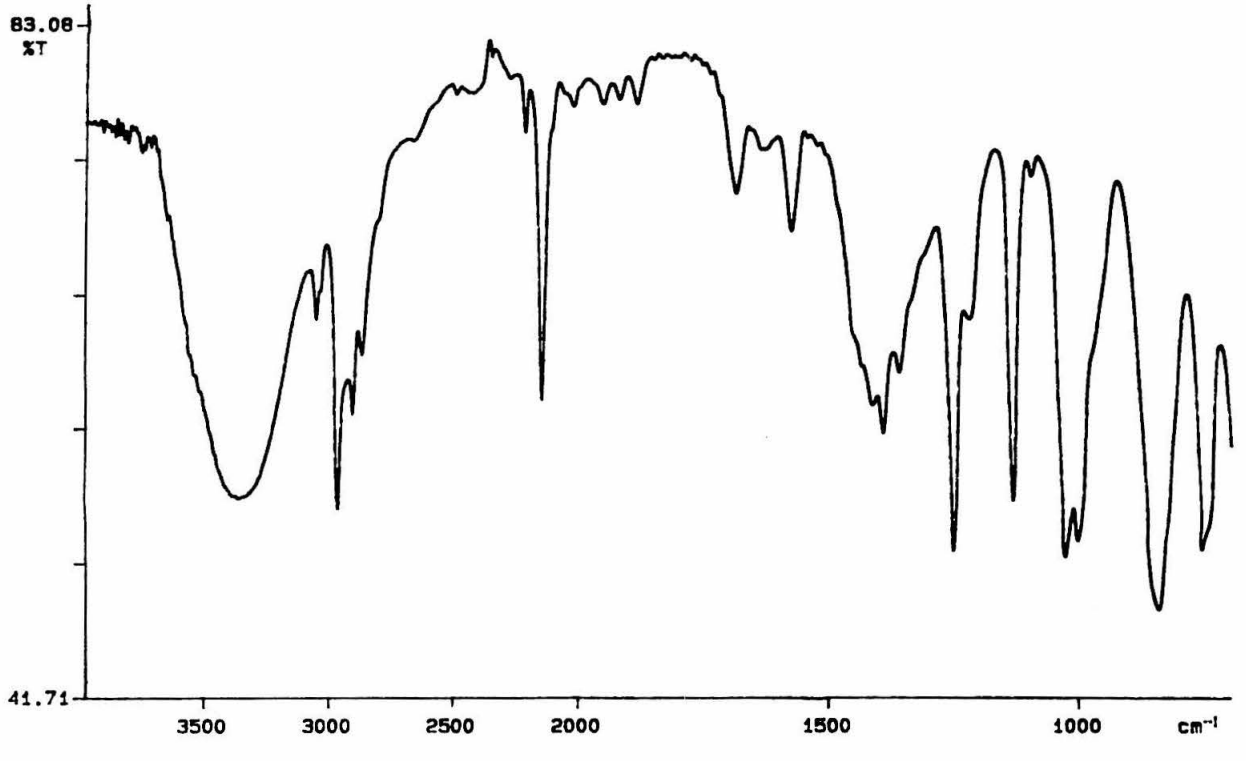
%T
0.21
4000
3500
3000
2500
2000
1500
1000
cm-1


TMS
H
H
CH2OH

12

9
8
7
6
5
4
3
2
1
0
PPM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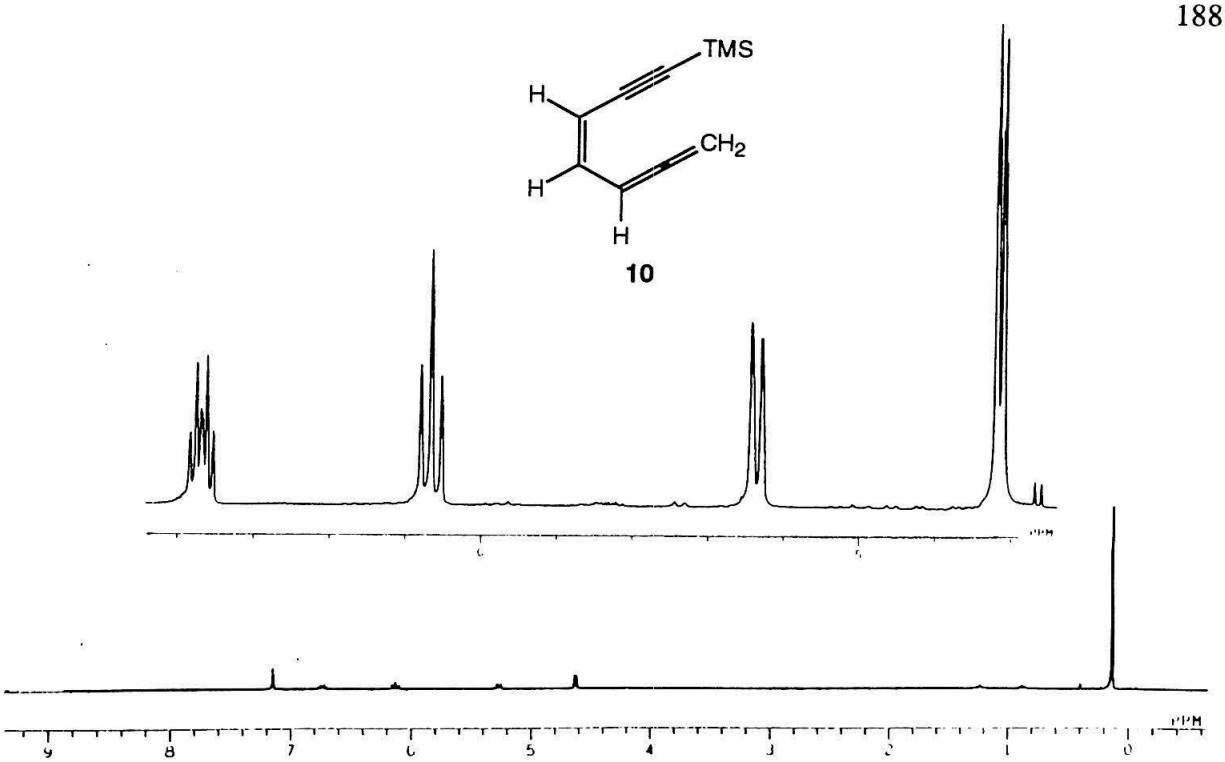
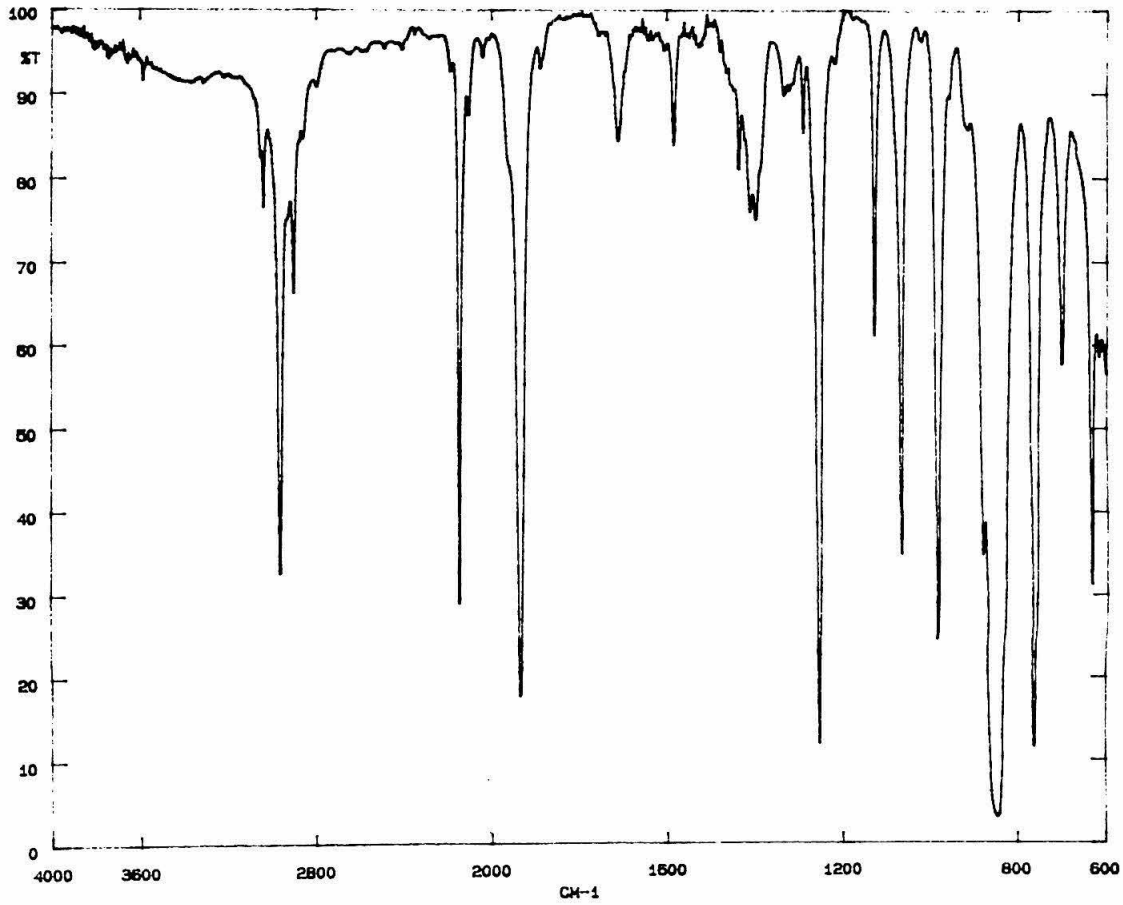
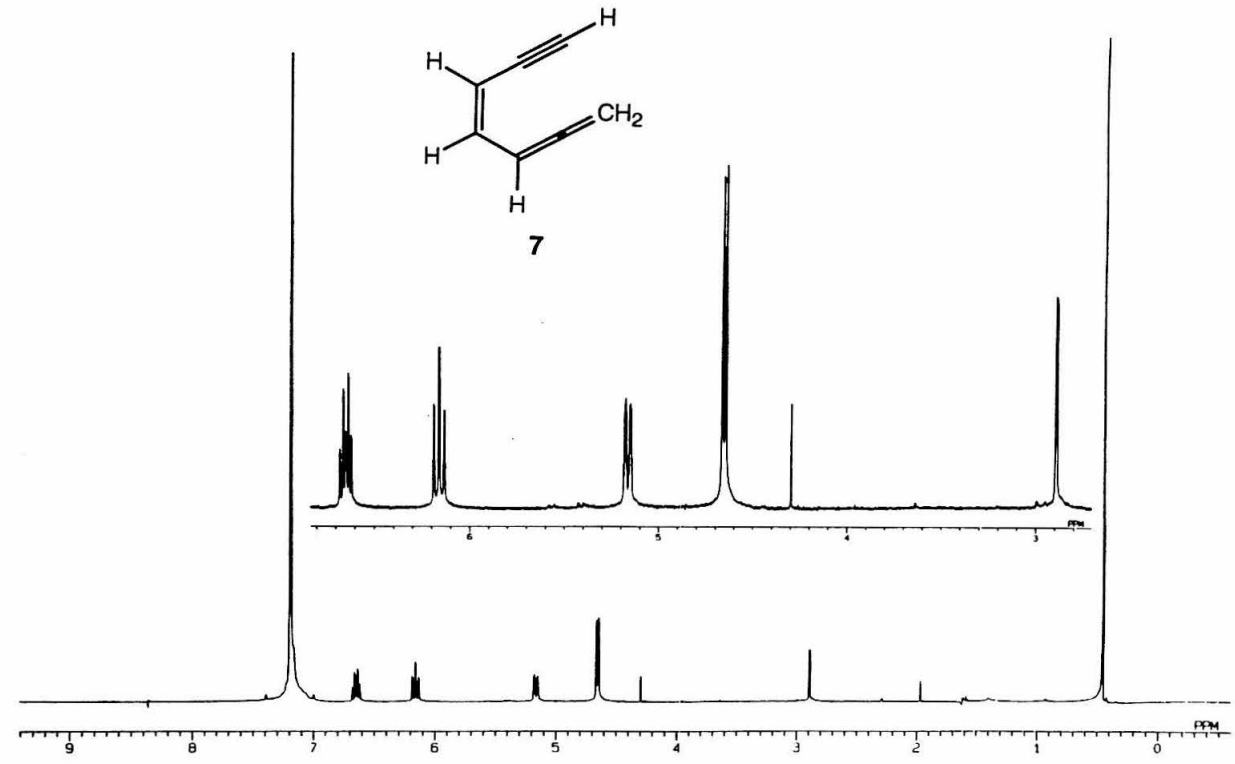
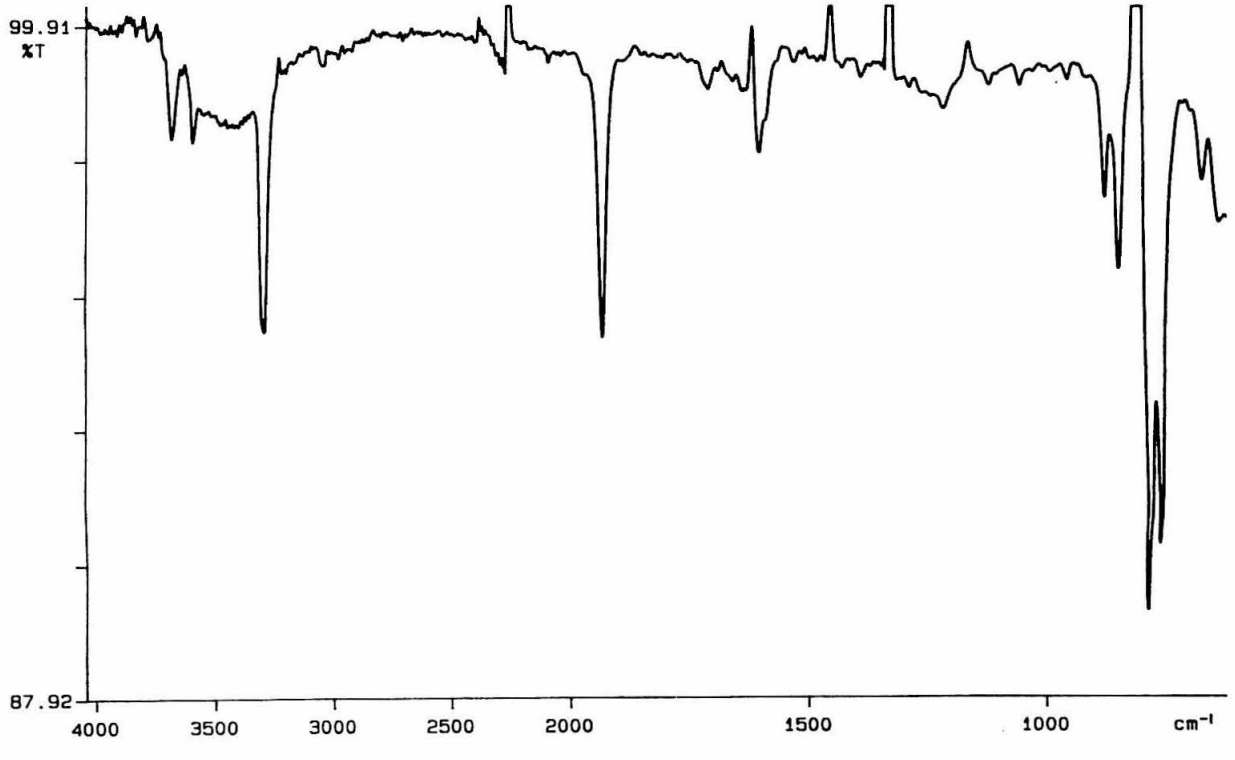
%T
41.71
3500
3000
2500
2000
1500
1000
cm-1


TMS
H
H
H
CH2
10
PPM
9
8
7
6
5
4
3
2
1
0


100
%T
90
80
70
60
50
40
30
20
10
0
4000
3600
2800
2000
1500
1200
800
600
CM-1


H
H
CH2
H
H
9
8
7
6
5
4
3
2
1
0
PPM

7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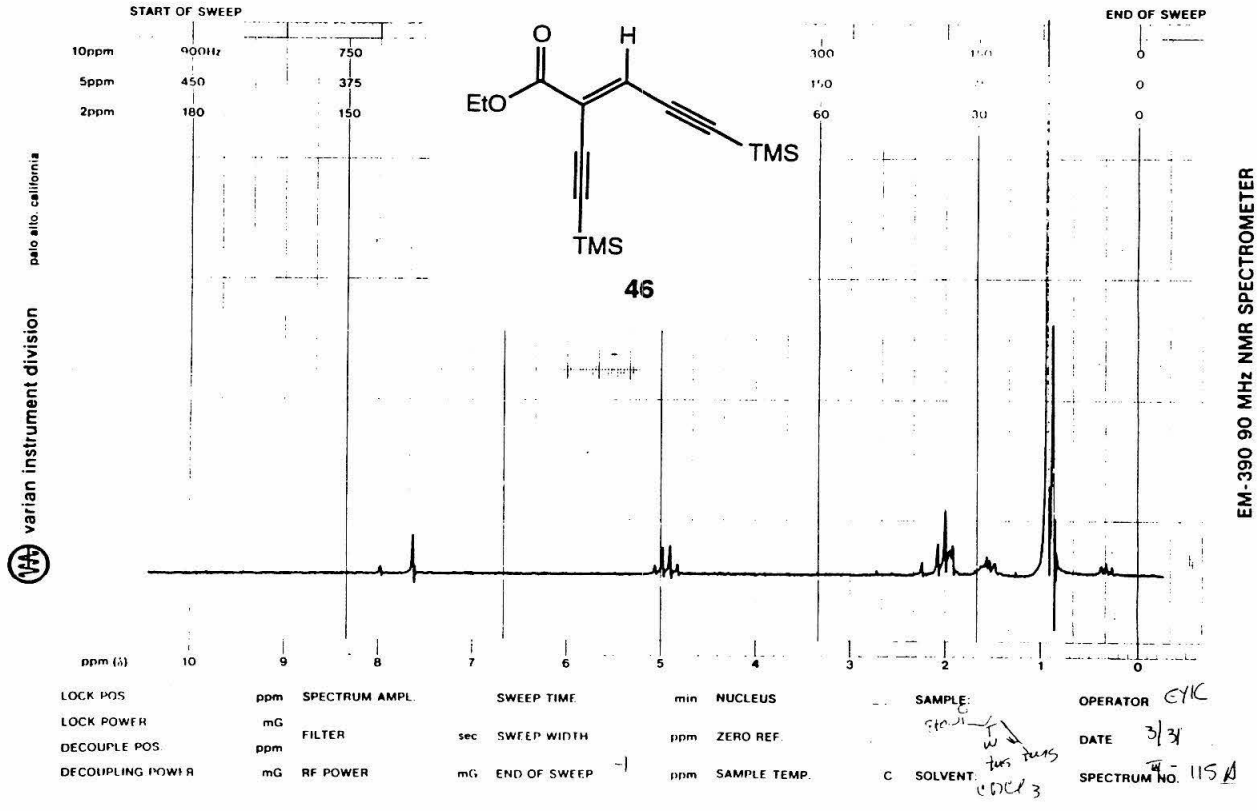
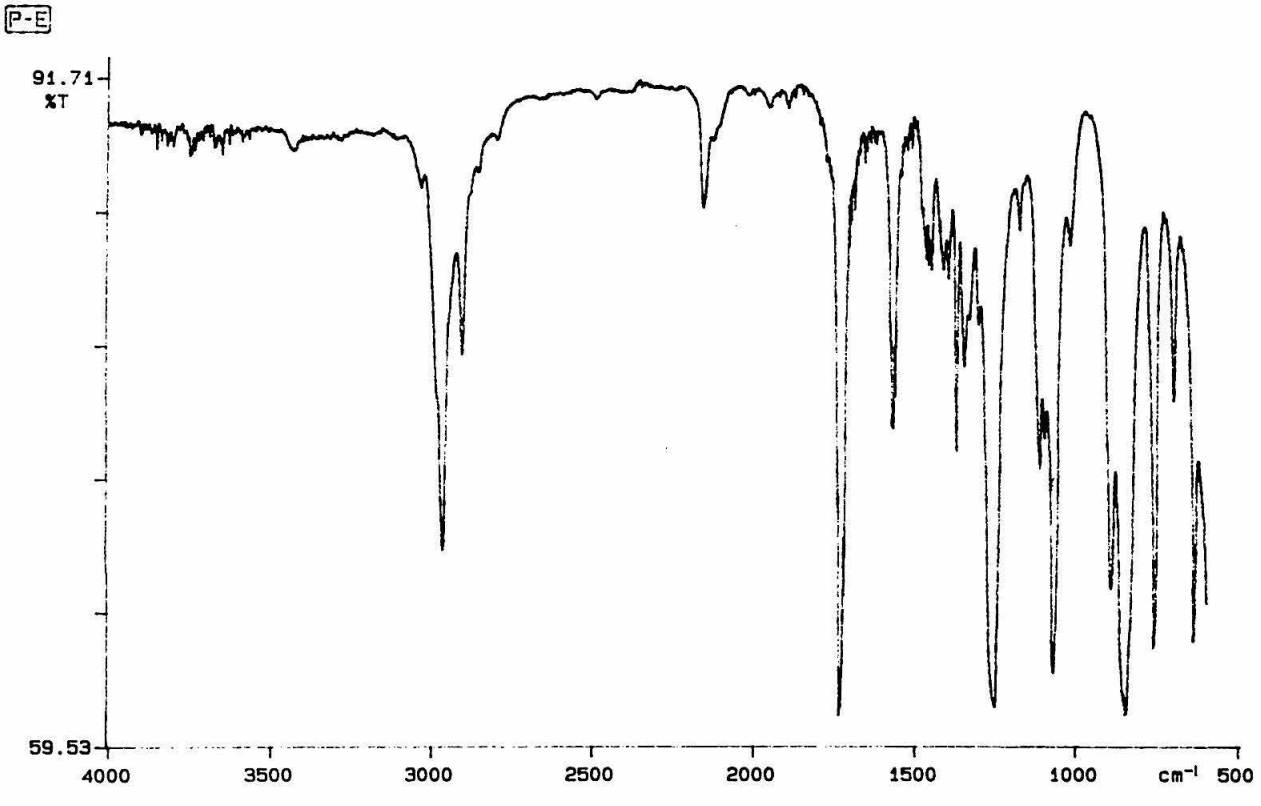
%T
87.92
4000
3500
3000
2500
2000
1500
1000
cm-1


START OF SWEEP
END OF SWEEP
10ppm
5ppm
2ppm
900Hz
450
180
750
375
150
300
60
O
H
EtO
TMS
TMS
46
varian instrument division
palo alto, california
EM-390 90 MHz NMR SPECTROMETER
ppm (δ)
10
9
8
7
6
5
4
3
2
1
0
LOCK POS
LOCK POWER
DECOUPLE POS.
DECOUPLING POWER
ppm
mG
ppm
mG
SPECTRUM AMPL.
FILTER
RF POWER
SWEEP TIME
SWEEP WIDTH
END OF SWEEP
min
sec
mG
ppm
ppm
C
NUCLEUS
ZERO REF.
SAMPLE TEMP.
SAMPLE:
SOLVENT:
CDCl3
OPERATOR
DATE
SPECTRUM NO.
EYC
3/31
115


P-E
91.71
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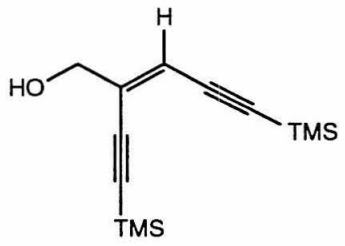
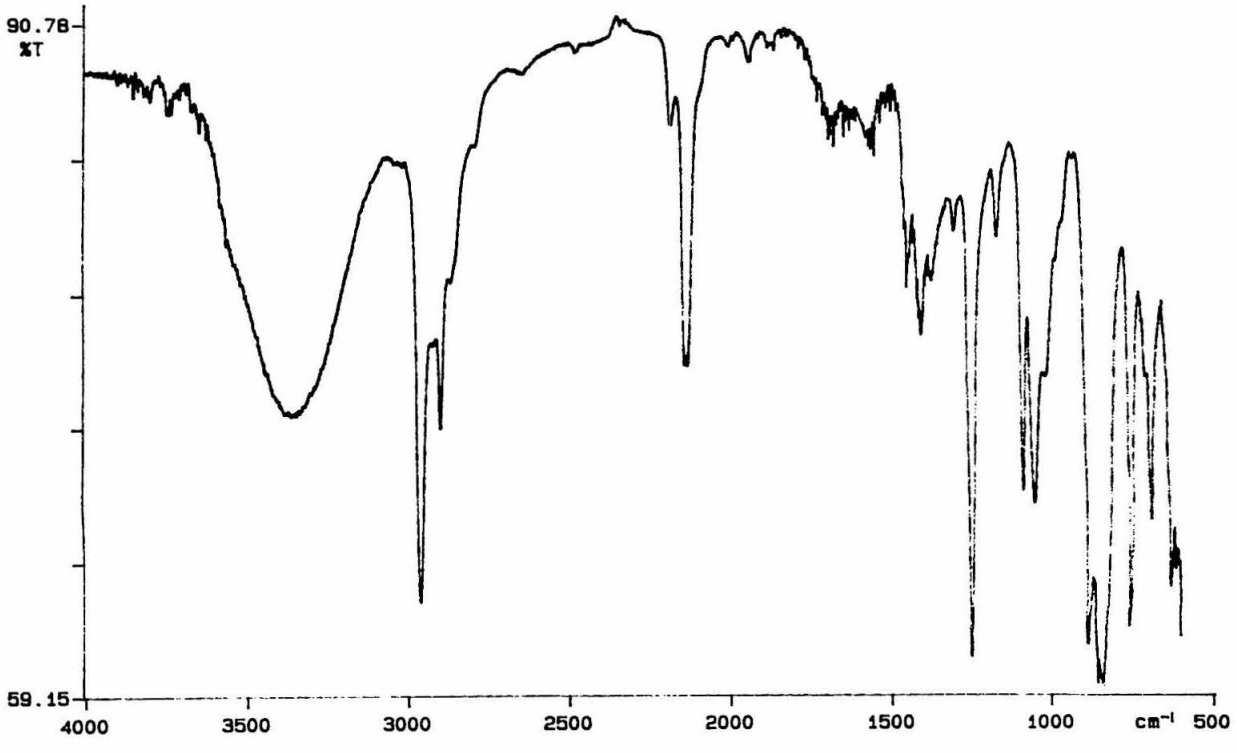
59.53
4000
3500
3000
2500
2000
1500
1000
cm⁻¹
500


H
HO
TMS
TMS

47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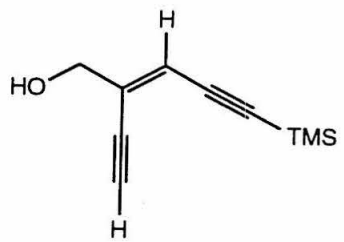
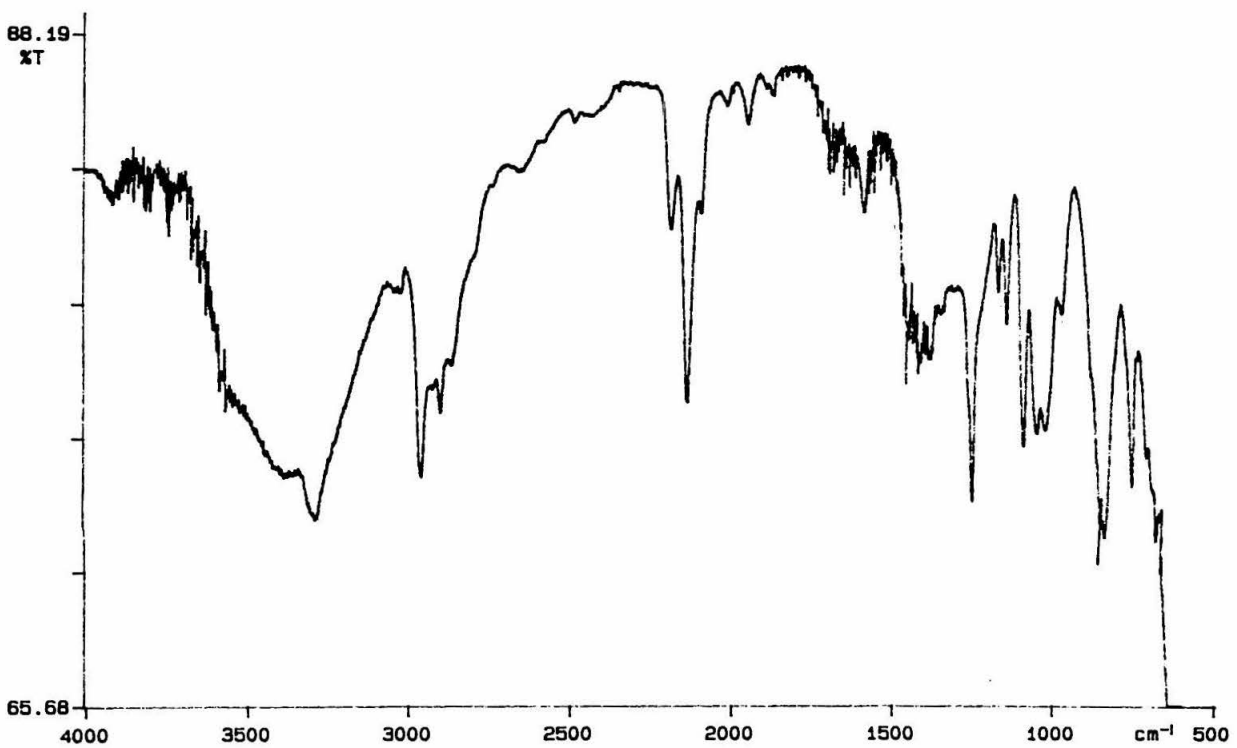
4000
3500
3000
2500
2000
1500
1000
cm⁻¹
500


H
HO
TMS
H

48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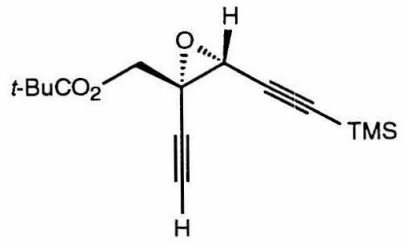
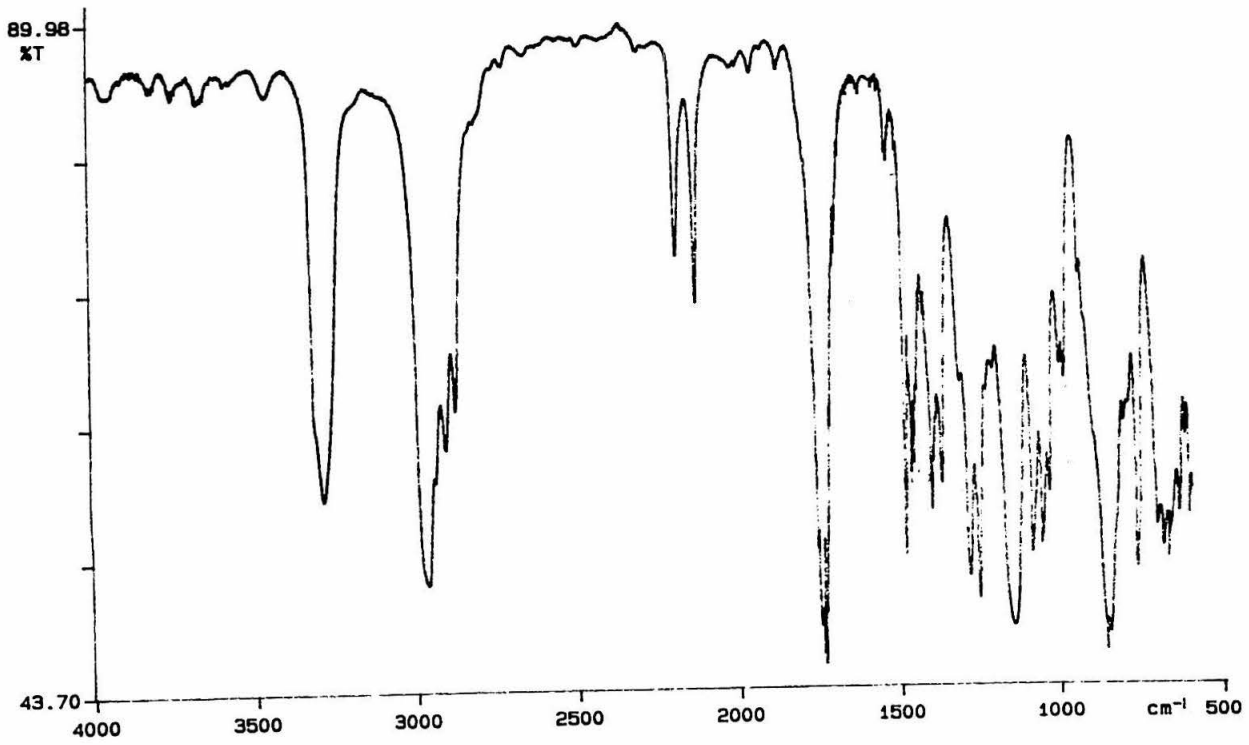
65.68
4000
3500
3000
2500
2000
1500
1000
cm⁻¹
500


H
O
t-BuCO2
TMS
H

44

PPM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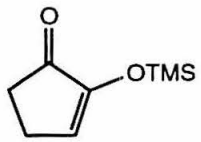
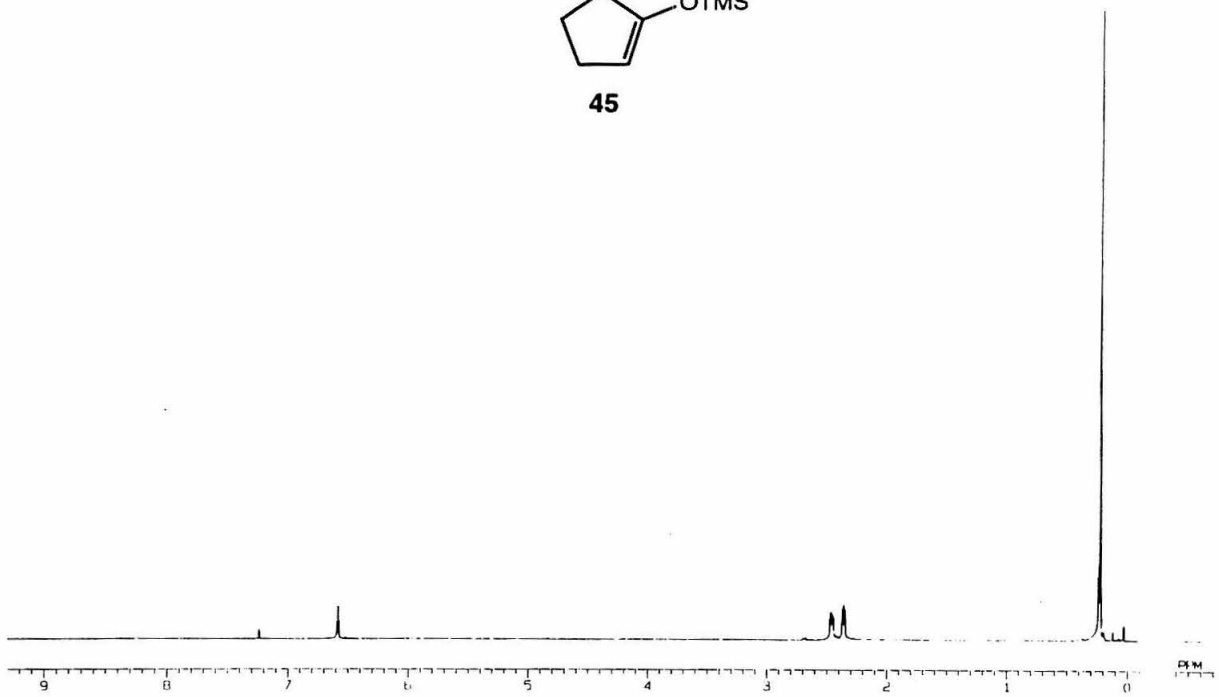
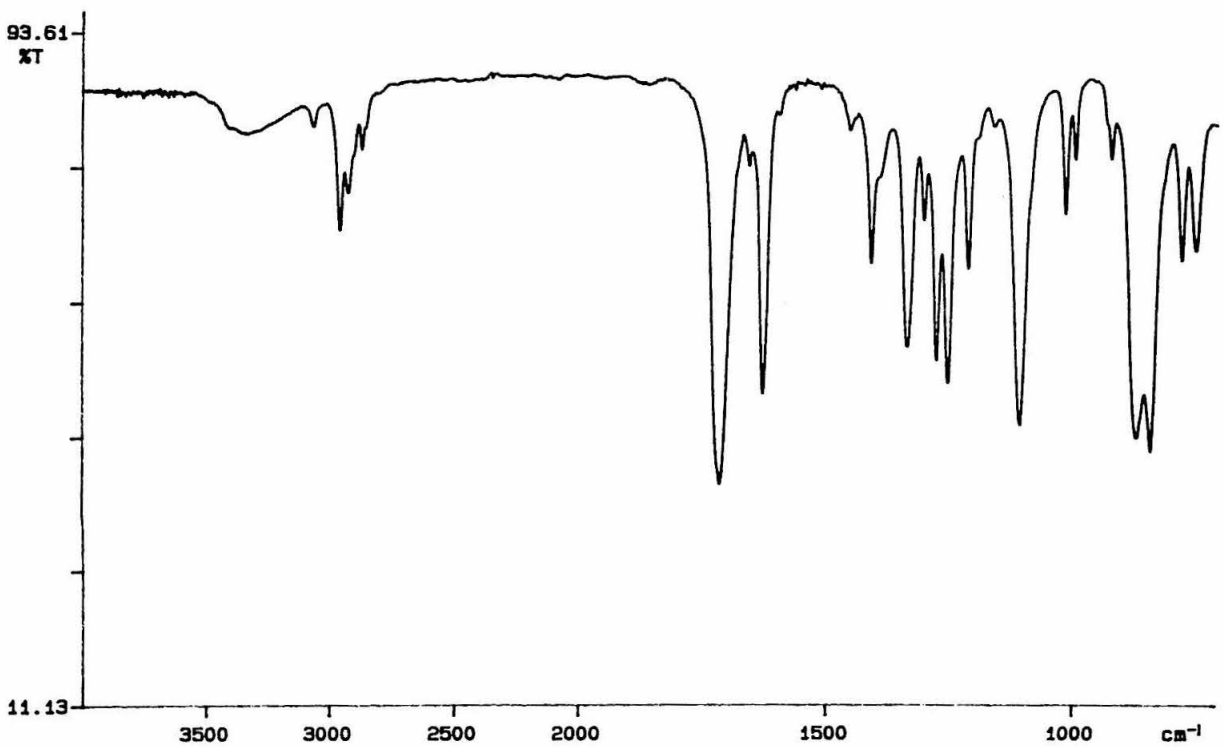
3000
2500
2000
1500
1000
cm-1
500


O
OTMS

45


9
8
7
6
5
4
3
2
1
0
PPM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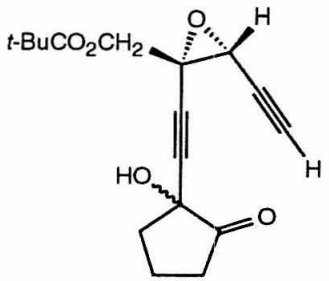
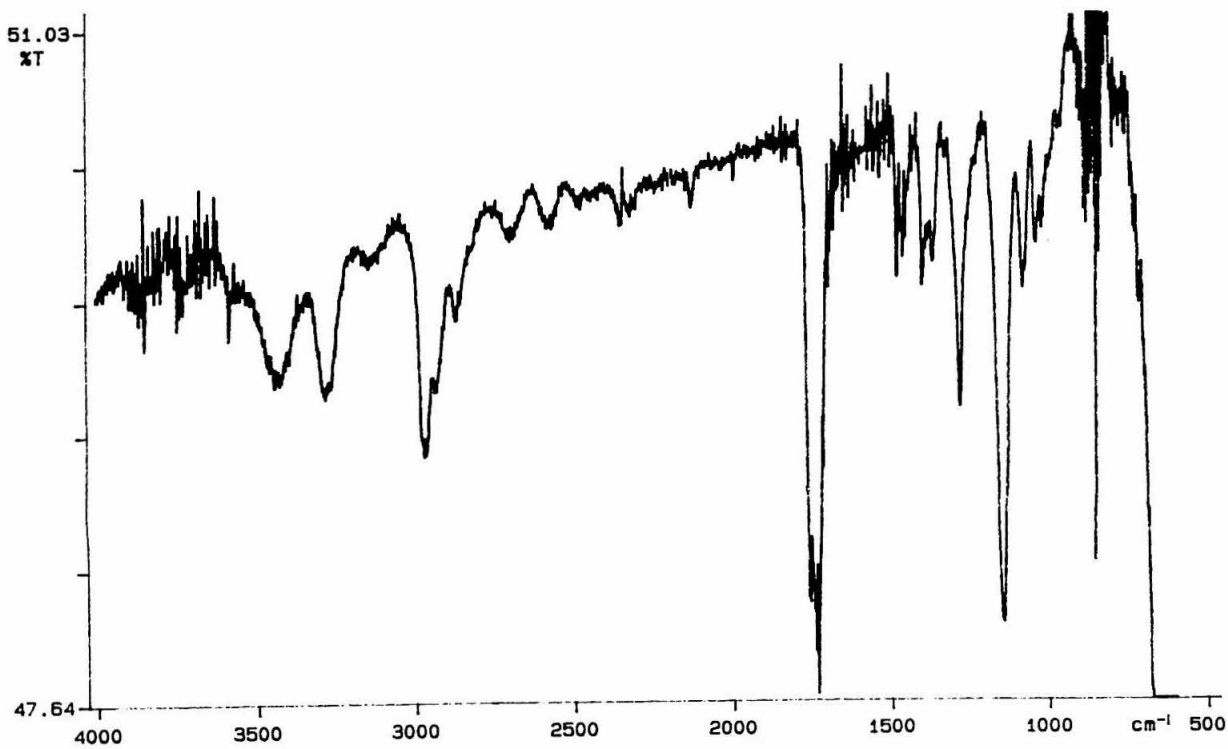
11.13
3500
3000
2500
2000
1500
1000
cm⁻¹


t-BuCO2CH2
O
H
HO
H
O

50

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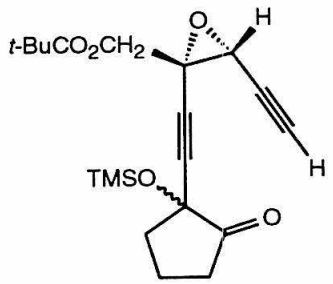
1500
1000
cm-1
500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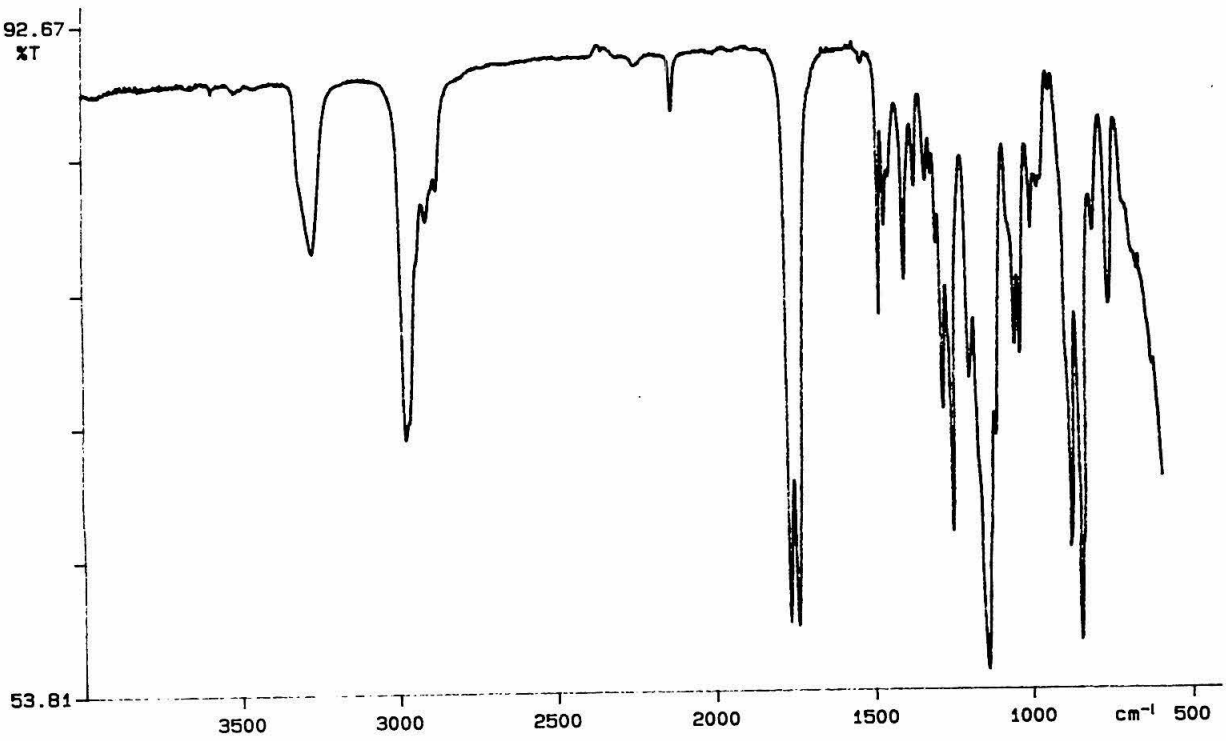
O
H
TMSO
H
O

43

PPM
9
8
7
6
5
4
3
2
1
0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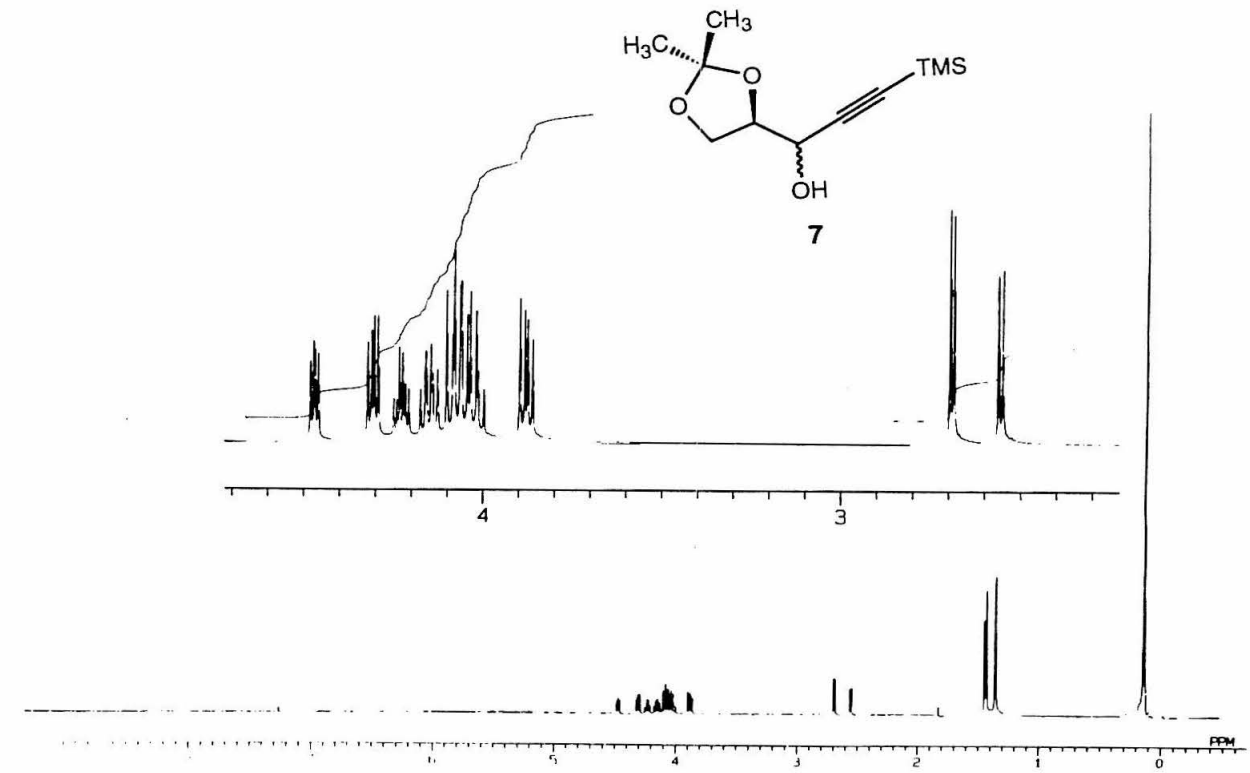
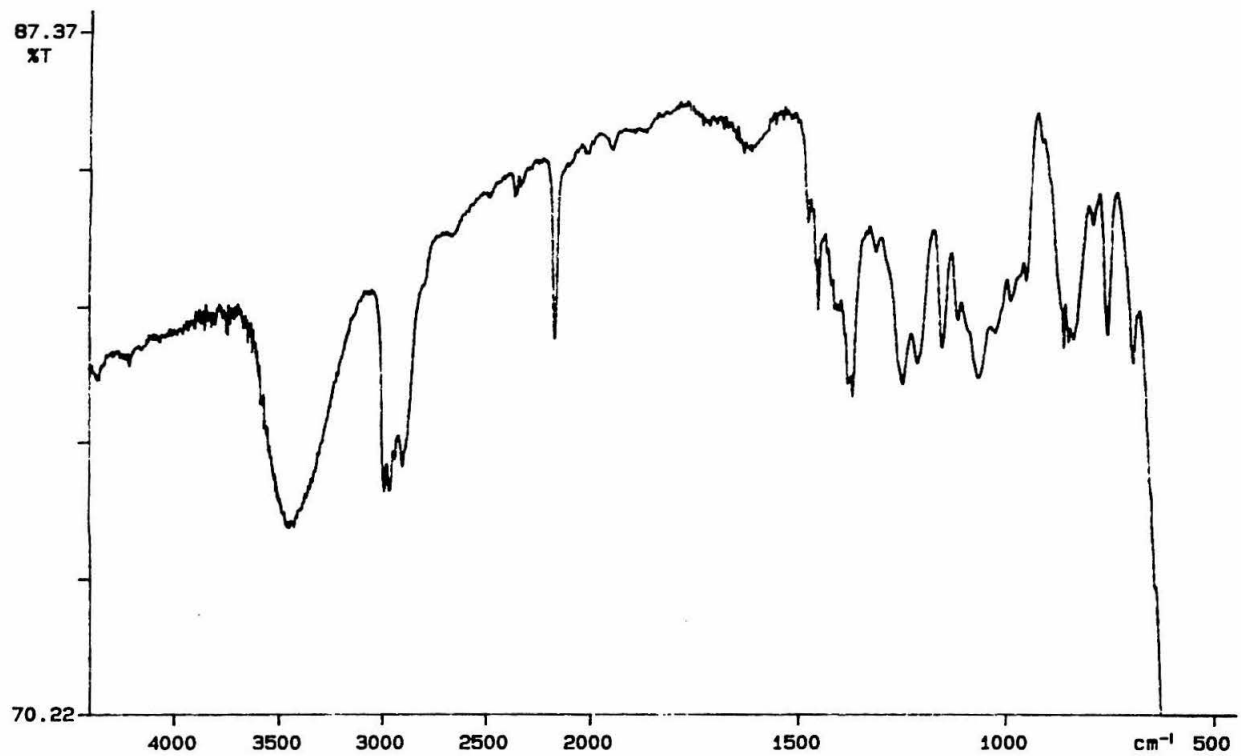
53.81
3500
3000
2500
2000
1500
1000
cm-1
500


CH3
H3C
O
O
TMS
OH
4
3
PPM

7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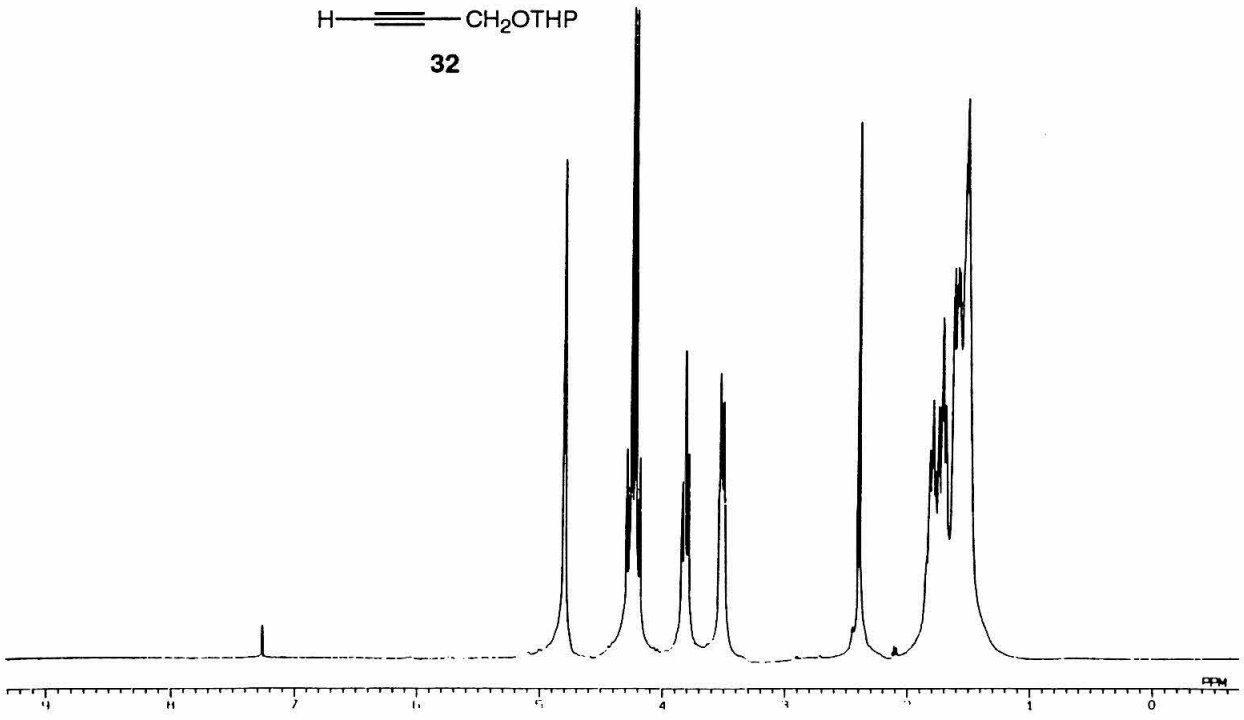
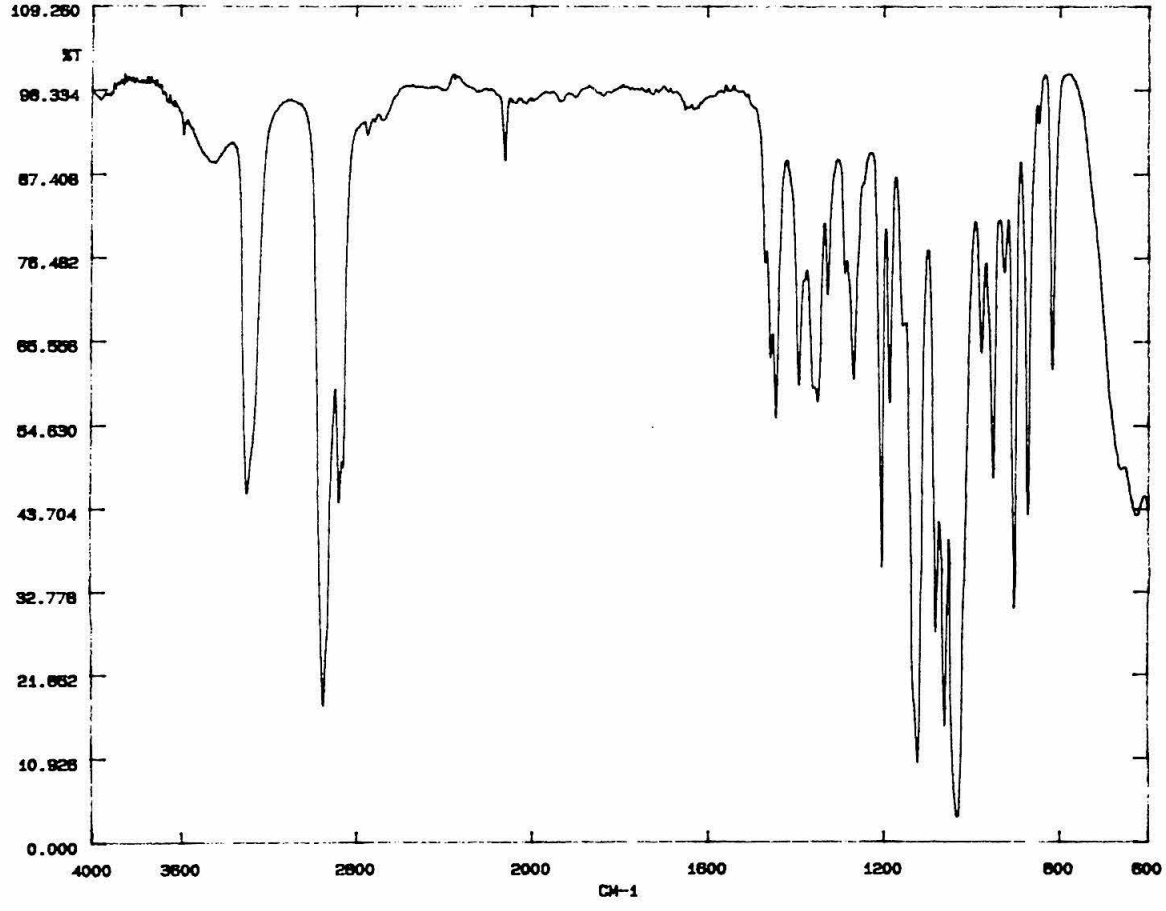
1500
1000
cm-1
500


H—≡—CH2OTHP
32
PPM


109.260
%T
98.334
87.408
76.482
65.556
54.630
43.704
32.778
21.852
10.926
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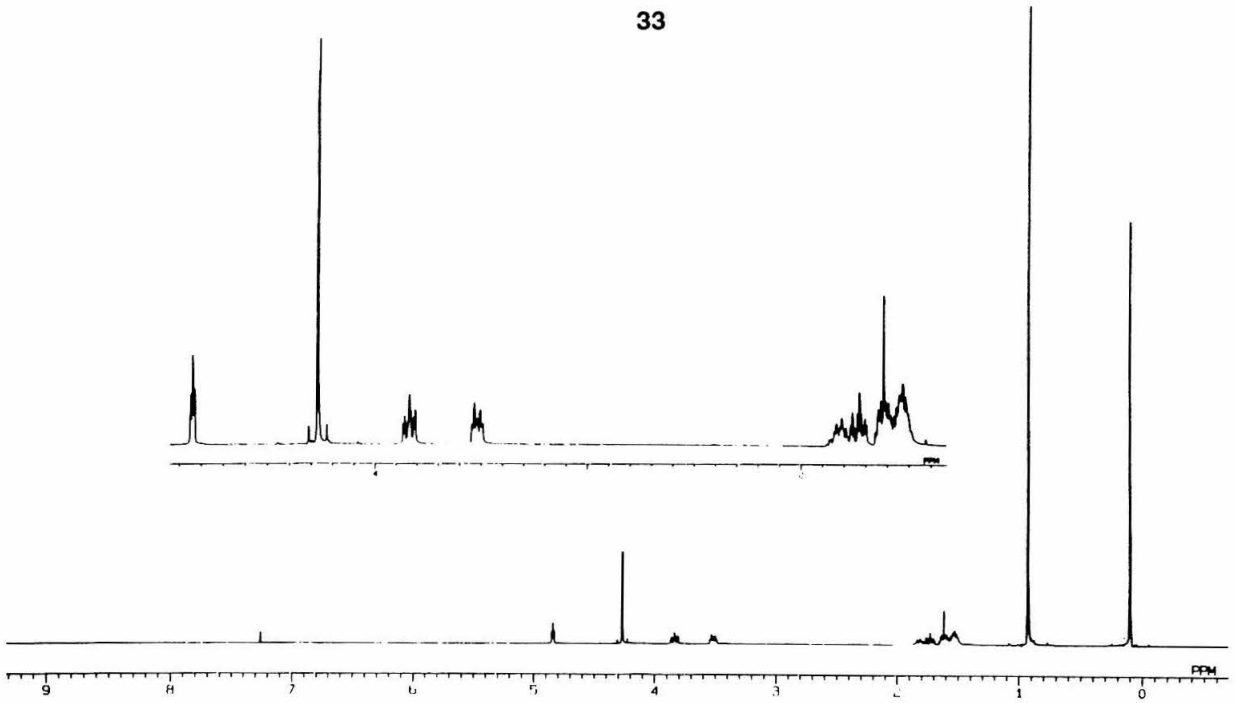
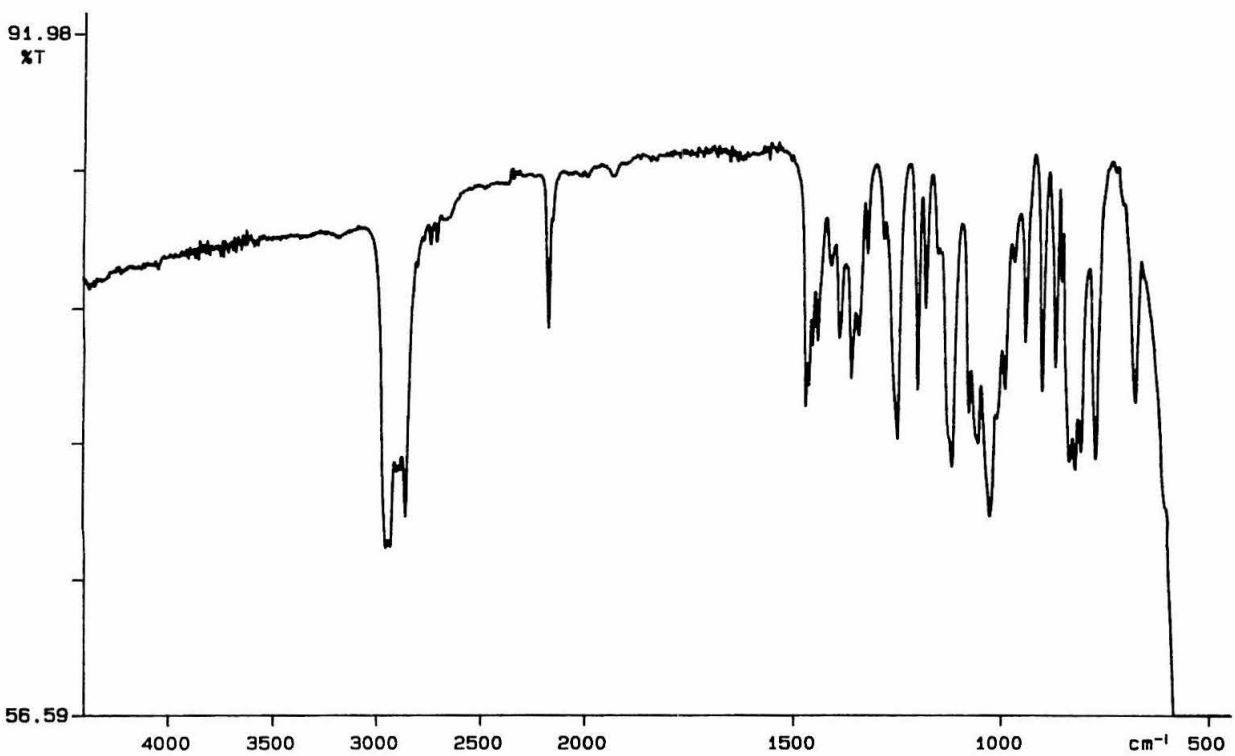
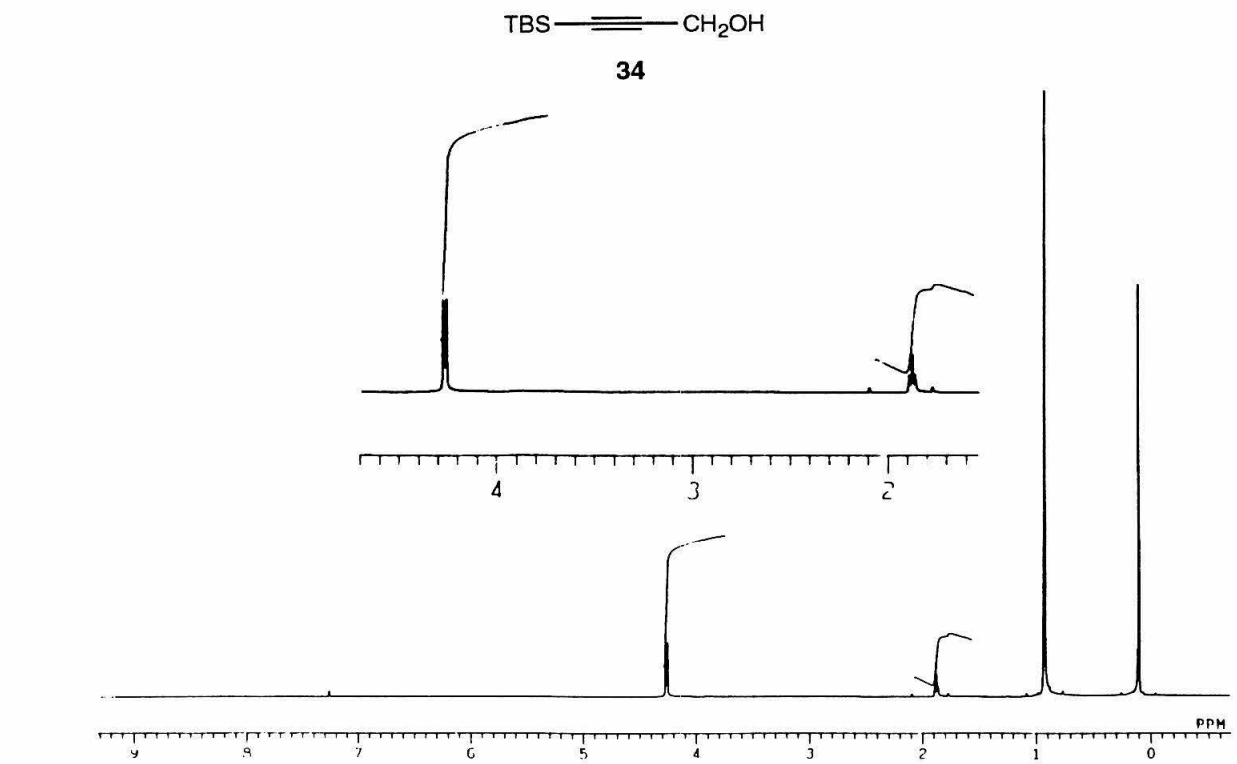
4000
3600
2800
2000
1600
1200
800
600
CM-1

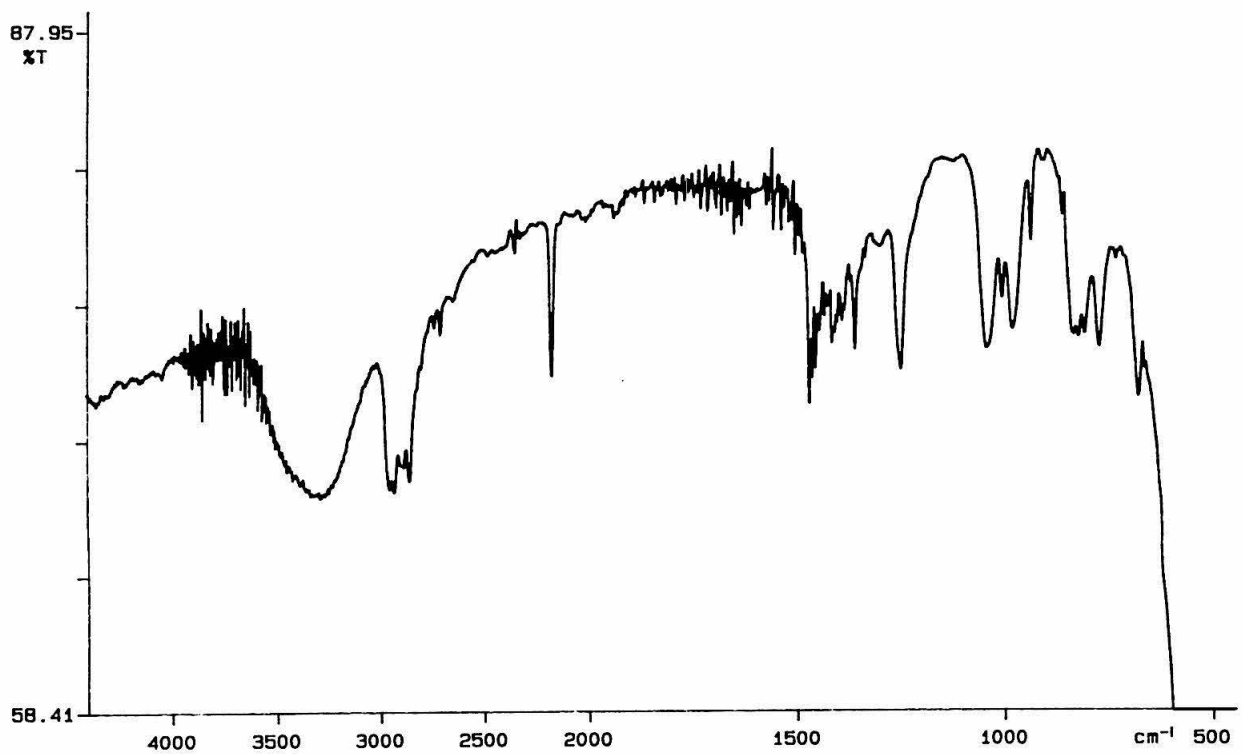
TBS—≡—CH_2OTHP

33






TBS
CH2OH
34
PPM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%T
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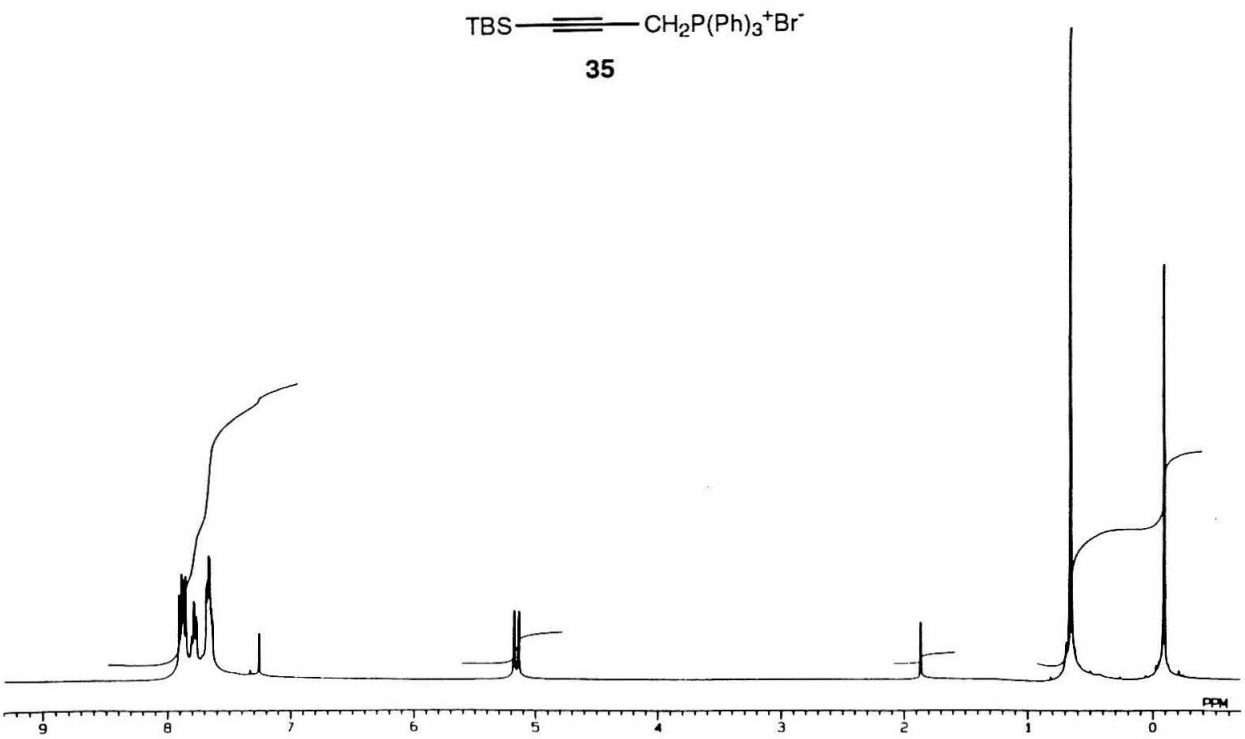
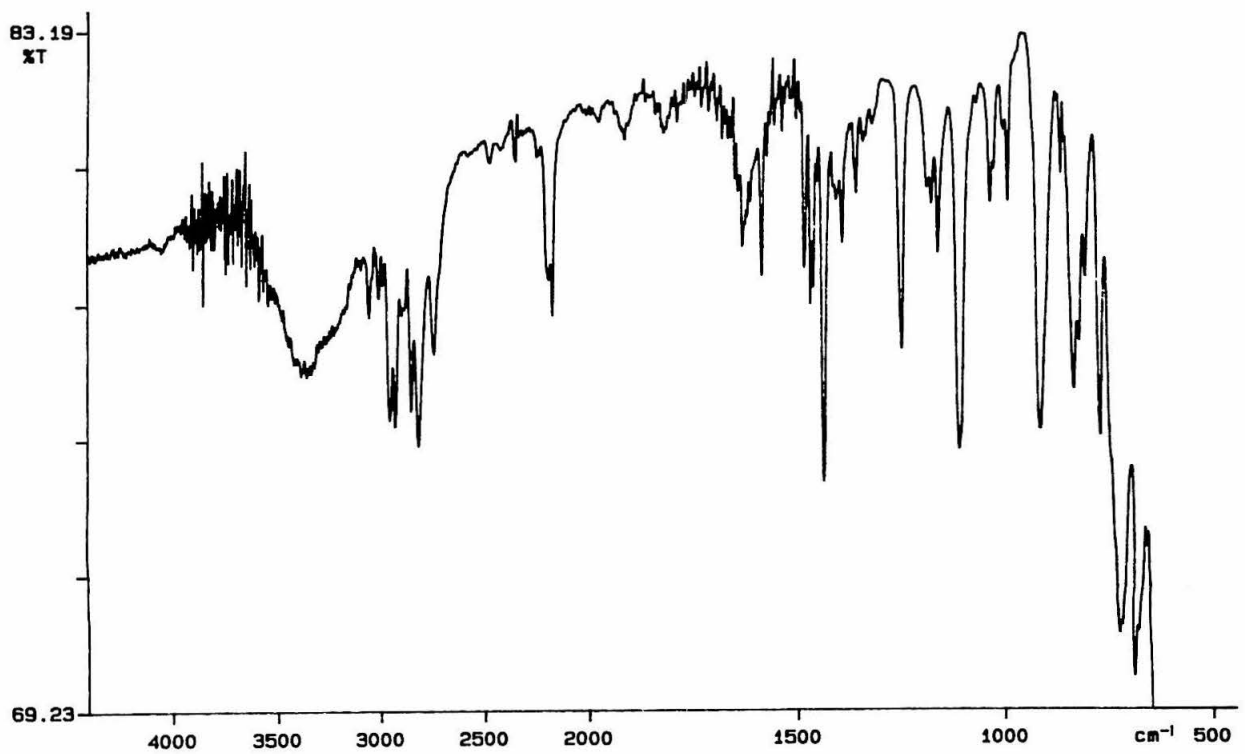
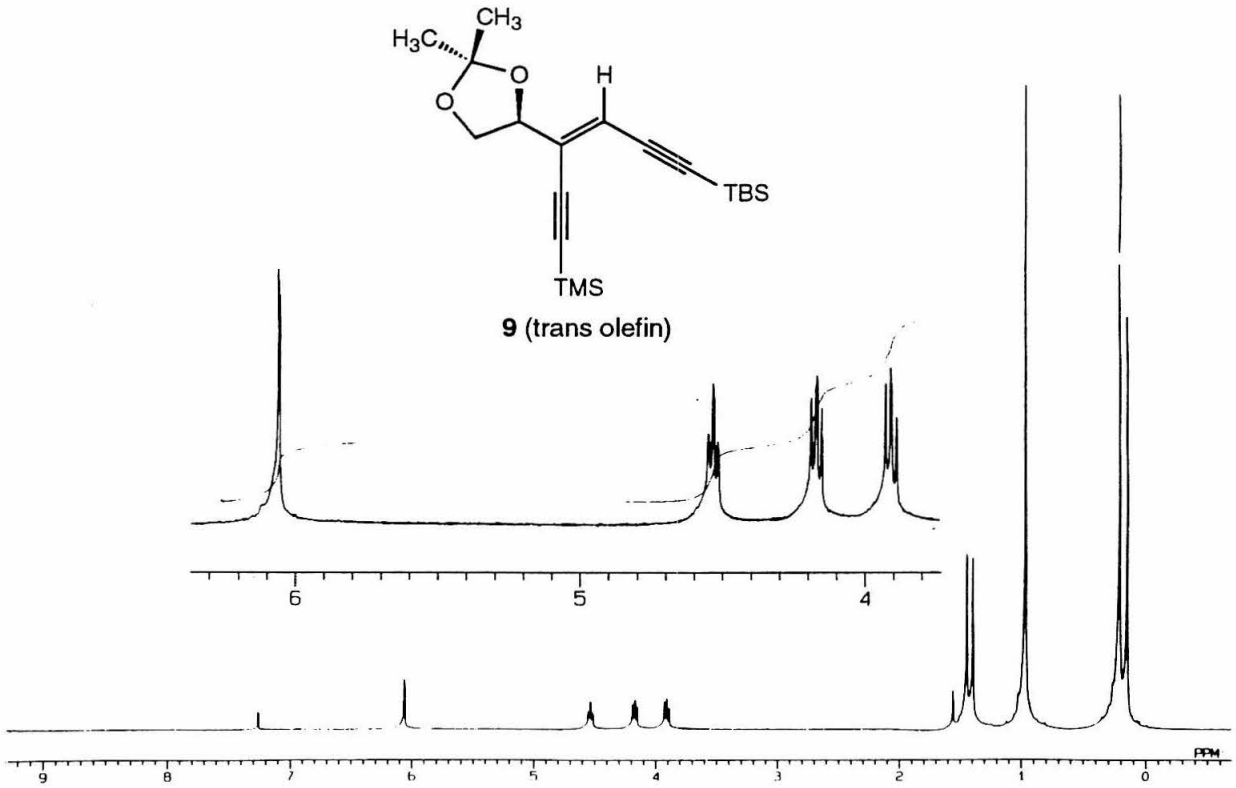
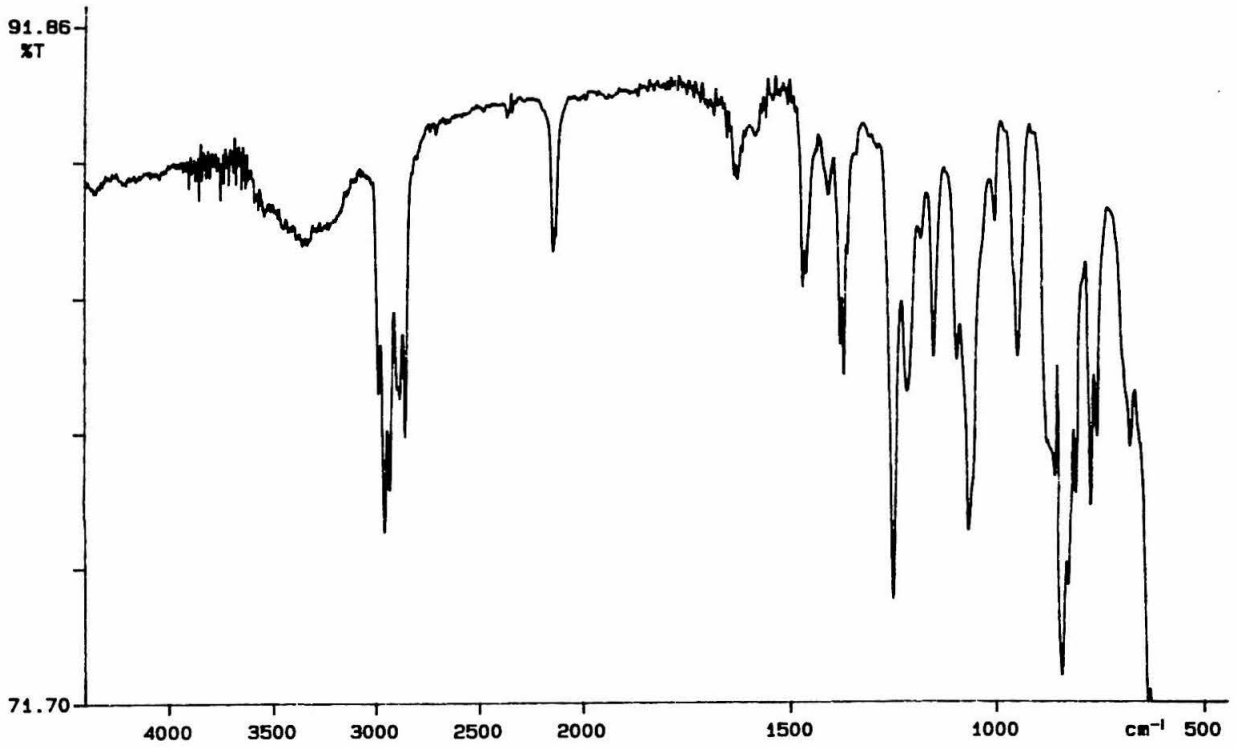
2000
1500
1000
cm-1
500

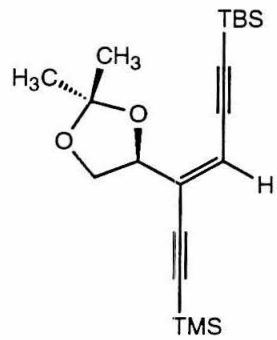

TBS
CH2P(Ph)3+Br-
35
9
8
7
6
5
4
3
2
1
0
PPM


83.19
%T
69.23
4000
3500
3000
2500
2000
1500
1000
cm-1
500



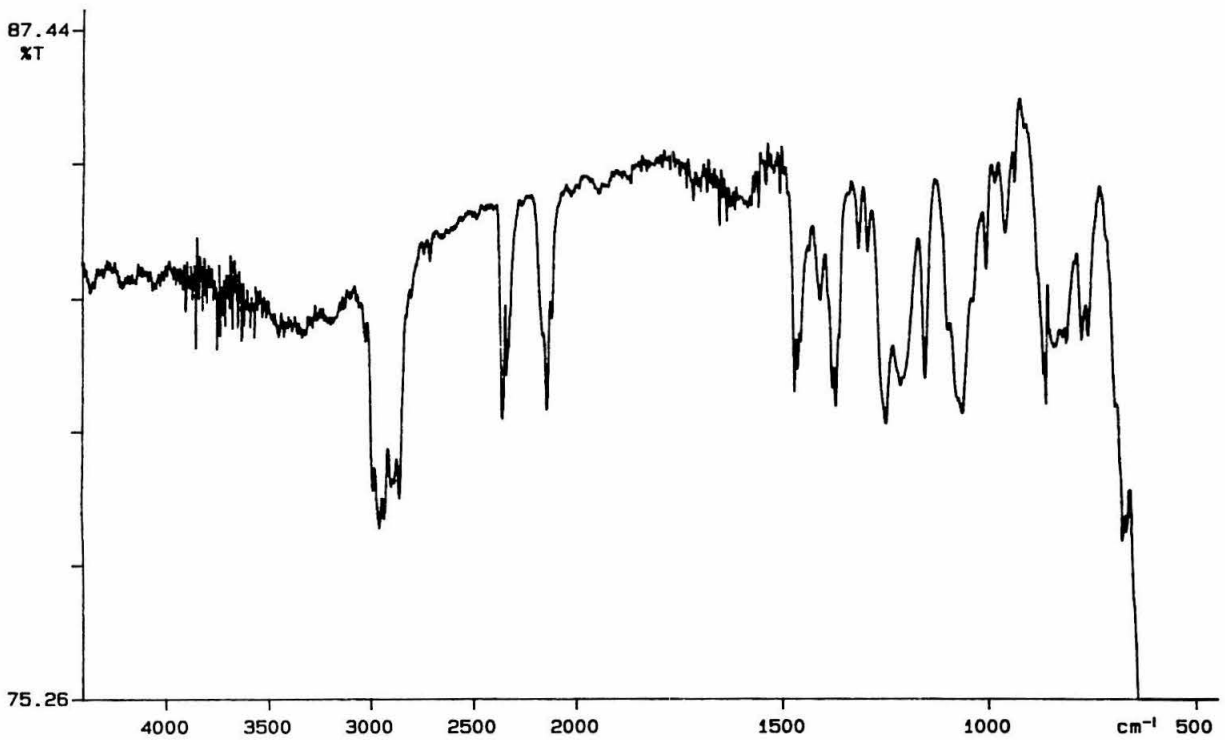
9 (trans olefin)

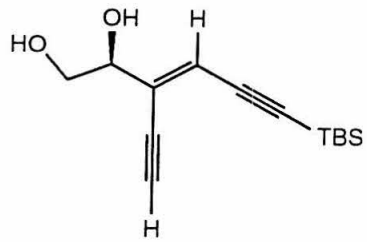



TBS
CH3
H3C
O
O
H
TMS

9 (cis olefin)

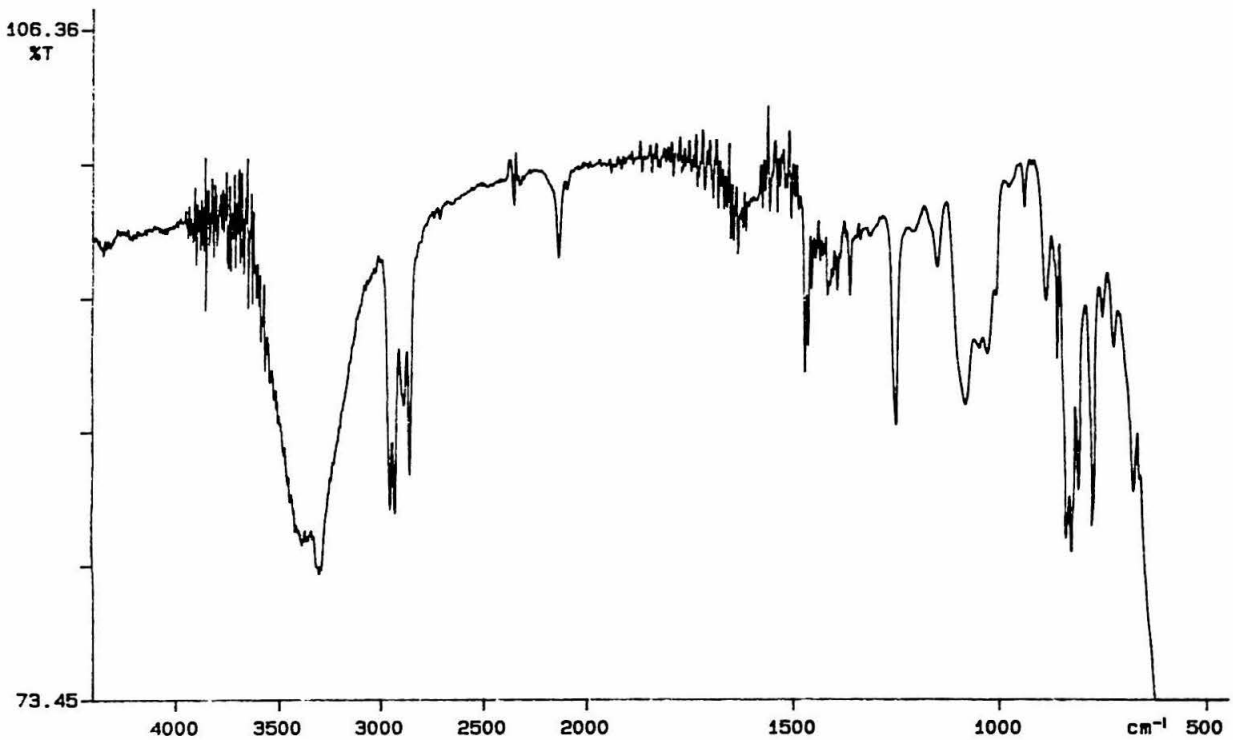
PPM

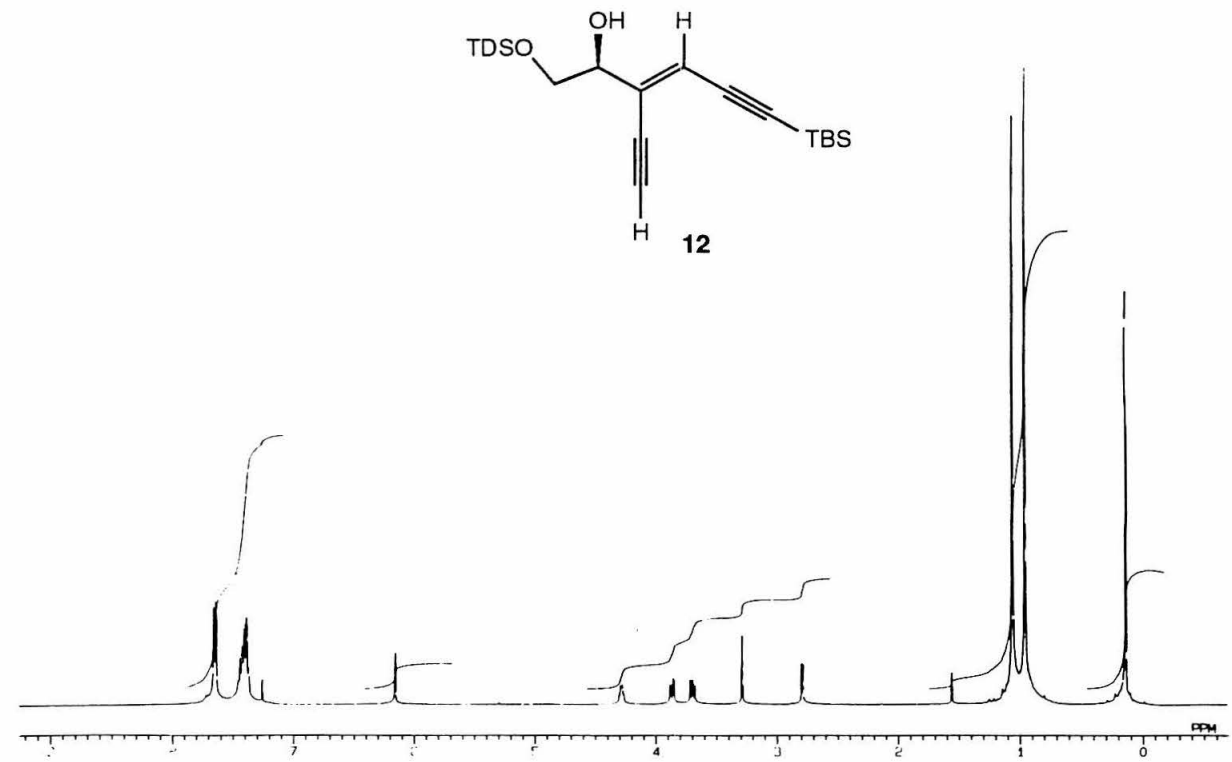

87.44
%T
75.26
4000
3500
3000
2500
2000
1500
1000
cm-1
500

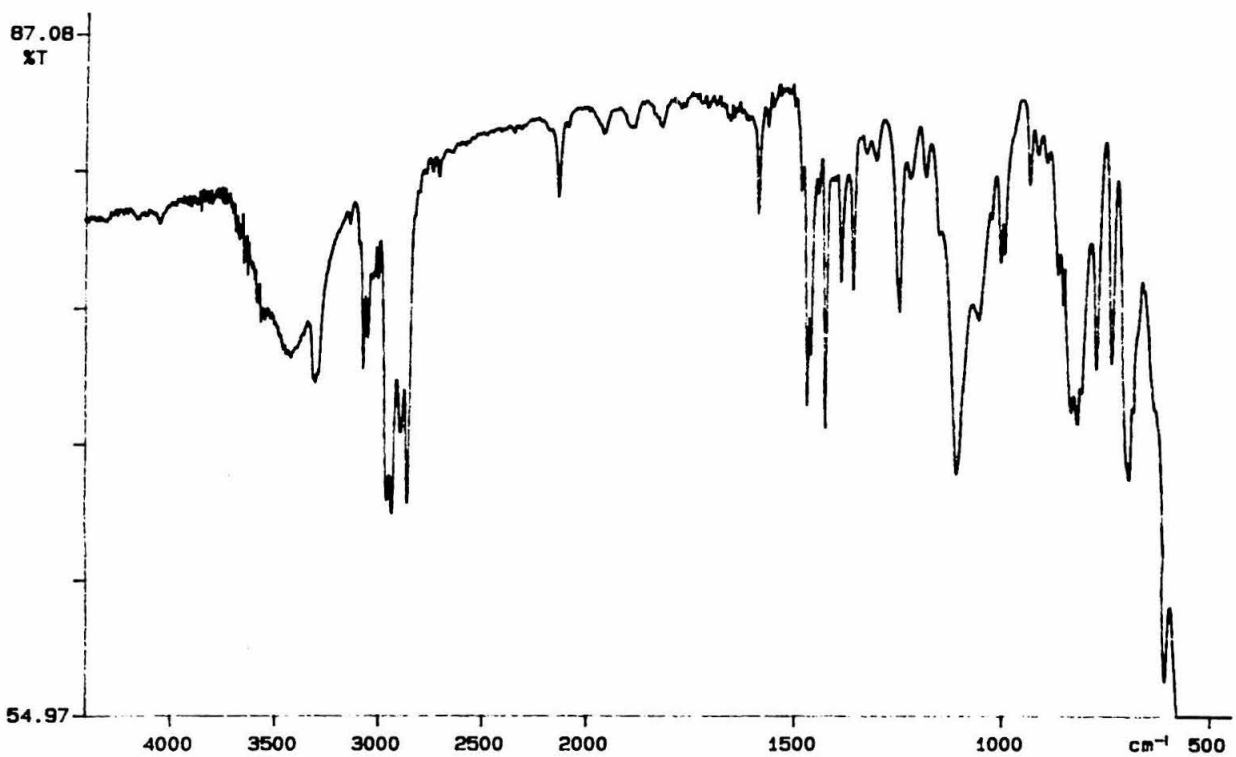

OH
H
HO
TBS
H

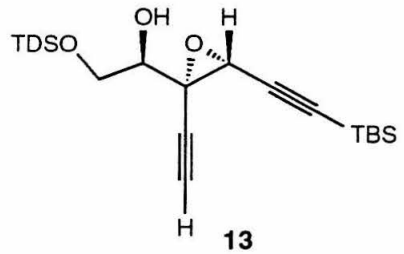
11

9
8
7
6
5
4
3
2
1
0
PPM

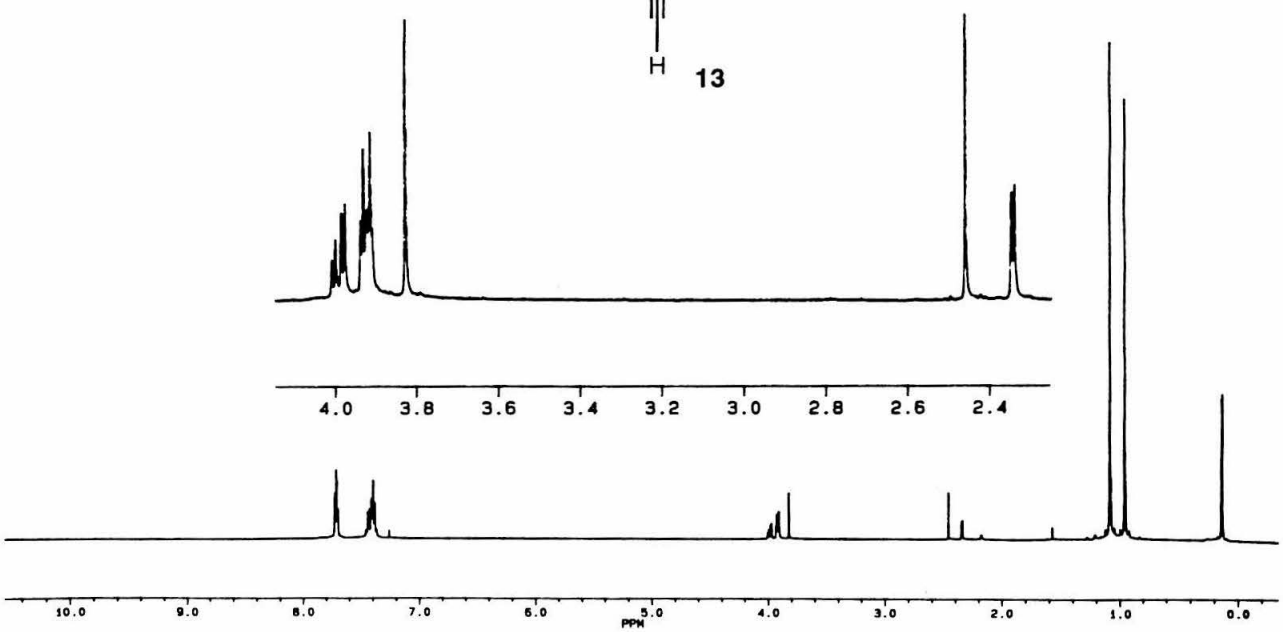

106.36
%T
73.45
4000
3500
3000
2500
2000
1500
1000
cm-1
500

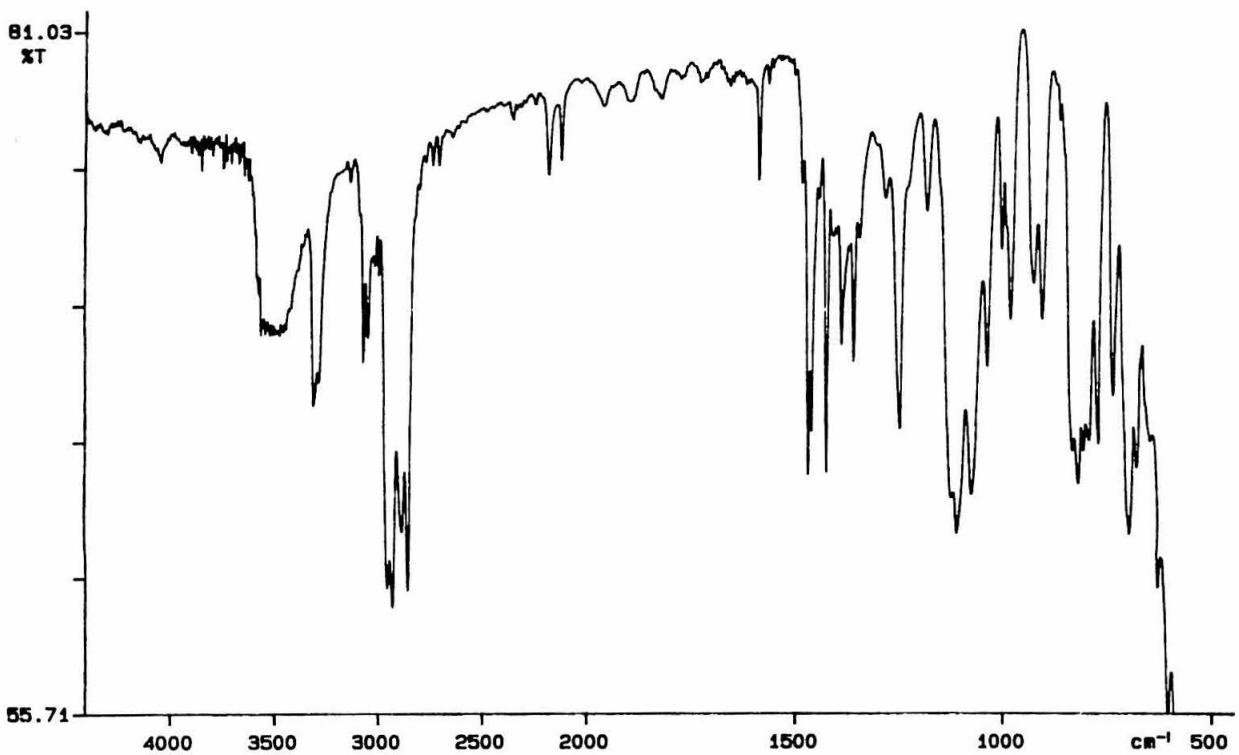

OH
H
TDSO
TBS
H
12
PPM

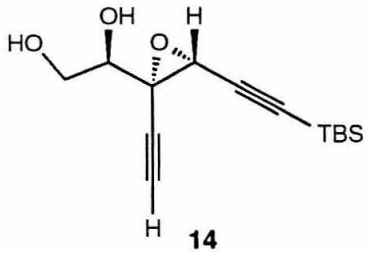

87.08
%T
54.97
4000
3500
3000
2500
2000
1500
1000
cm⁻¹
500


OH
H
TDSO
O
TBS
H

13

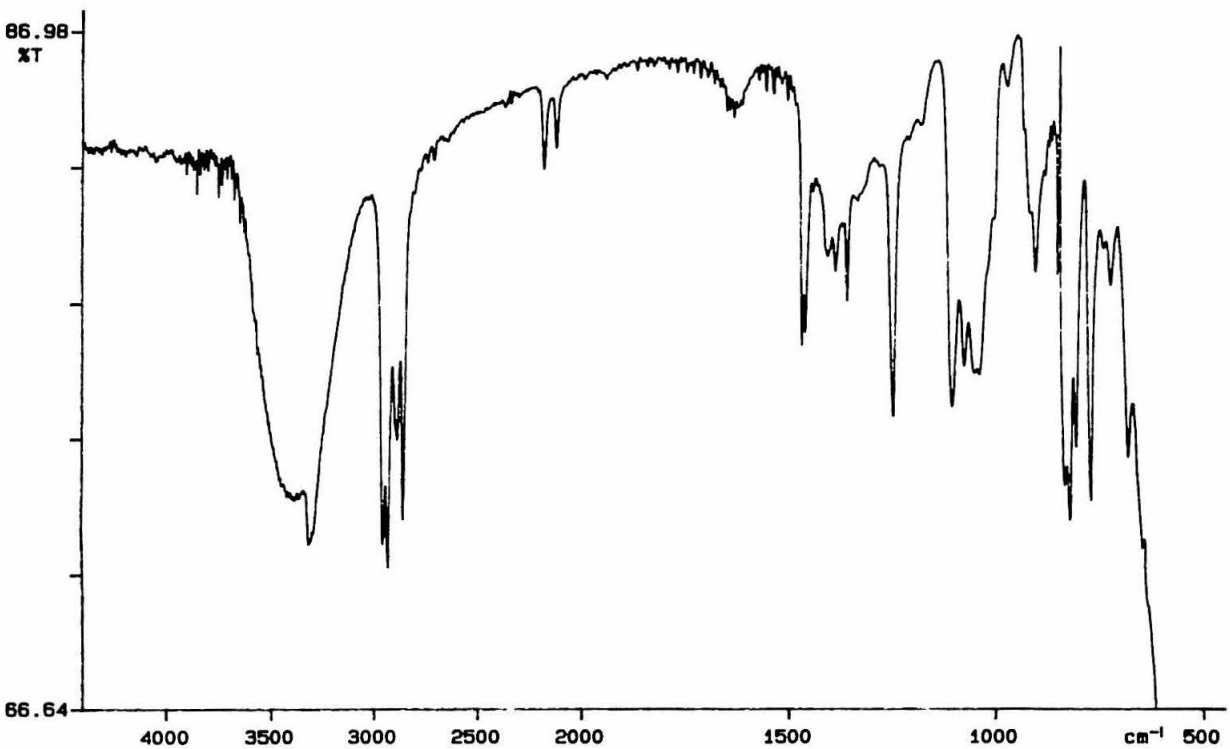

4.0
3.8
3.6
3.4
3.2
3.0
2.8
2.6
2.4
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
PPM

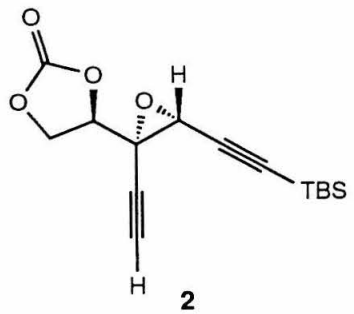

81.03
%T
55.71
4000
3500
3000
2500
2000
1500
1000
cm⁻¹
500


HO
OH
O
H
TBS
H

14

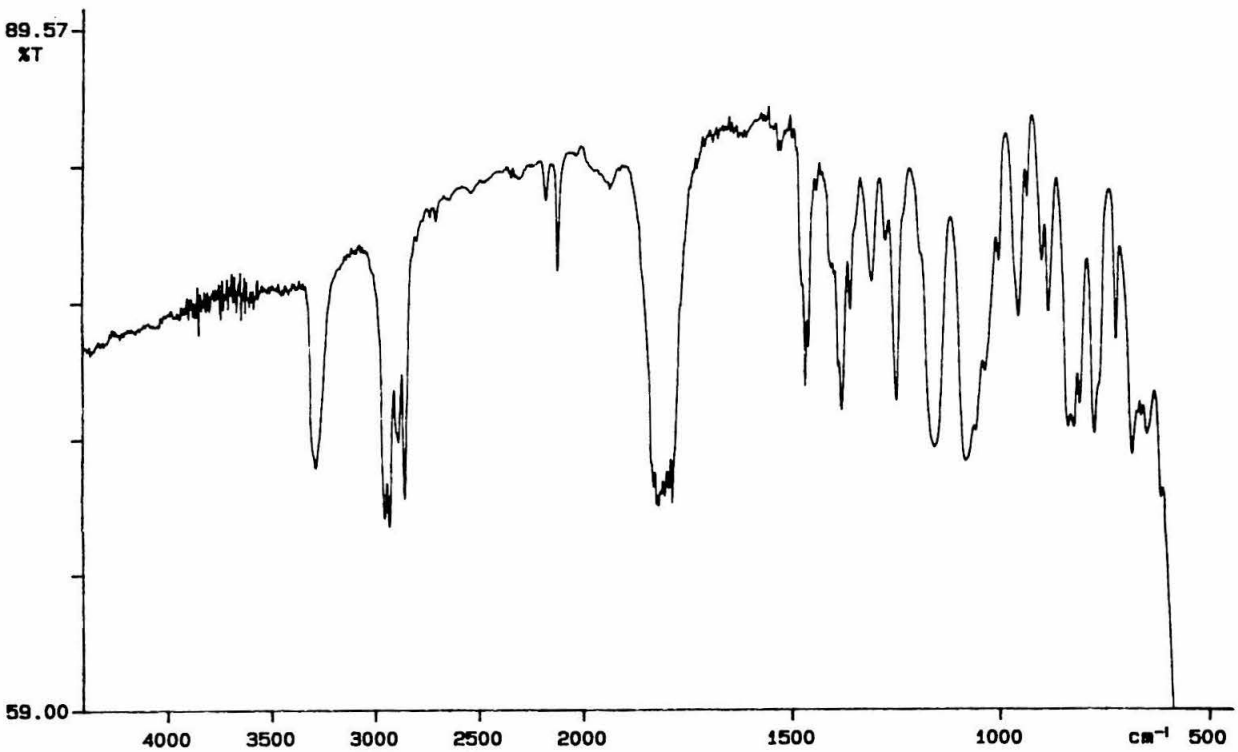
4
3
2
9
8
7
6
5
4
3
2
1
0
PPM

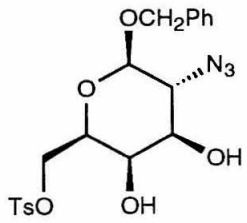

86.98
%T
86.64
4000
3500
3000
2500
2000
1500
1000
cm⁻¹
500


O
O
O
H
O
TBS
H

2

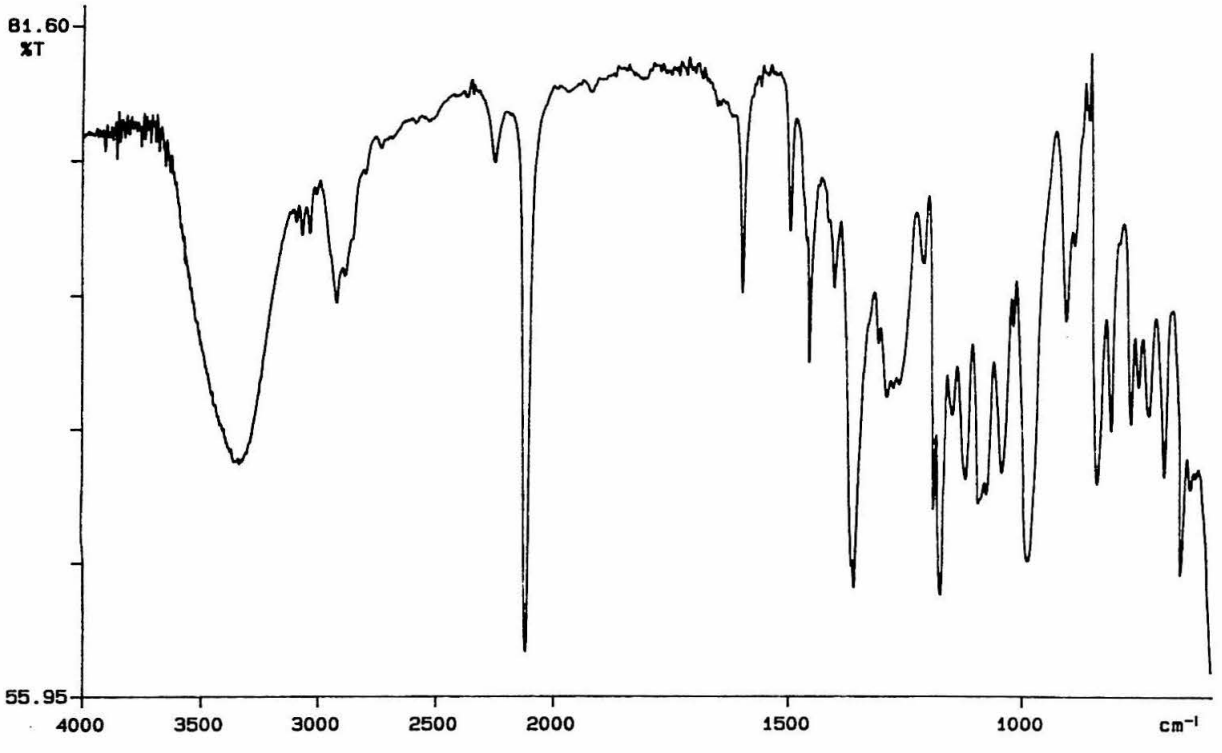
4
9
8
7
6
5
4
3
2
1
0
PPM


89.57
%T
59.00
4000
3500
3000
2500
2000
1500
1000
cm⁻¹
500


OCH2Ph
N3
O
OH
TsO
OH

15

PPM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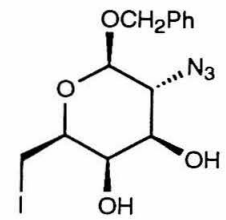
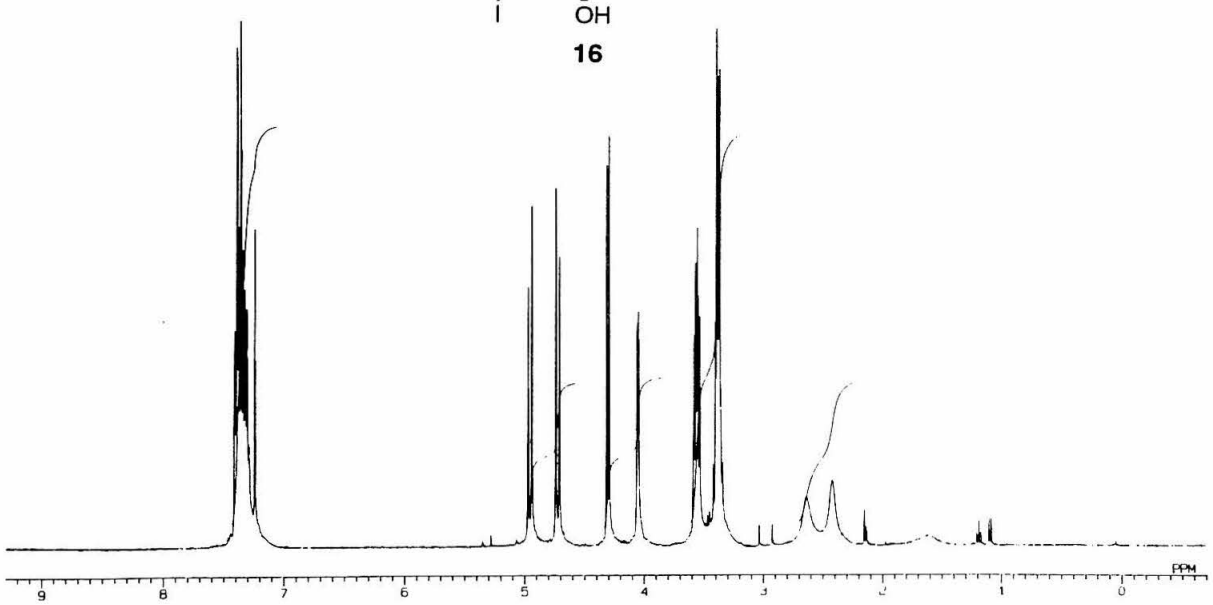
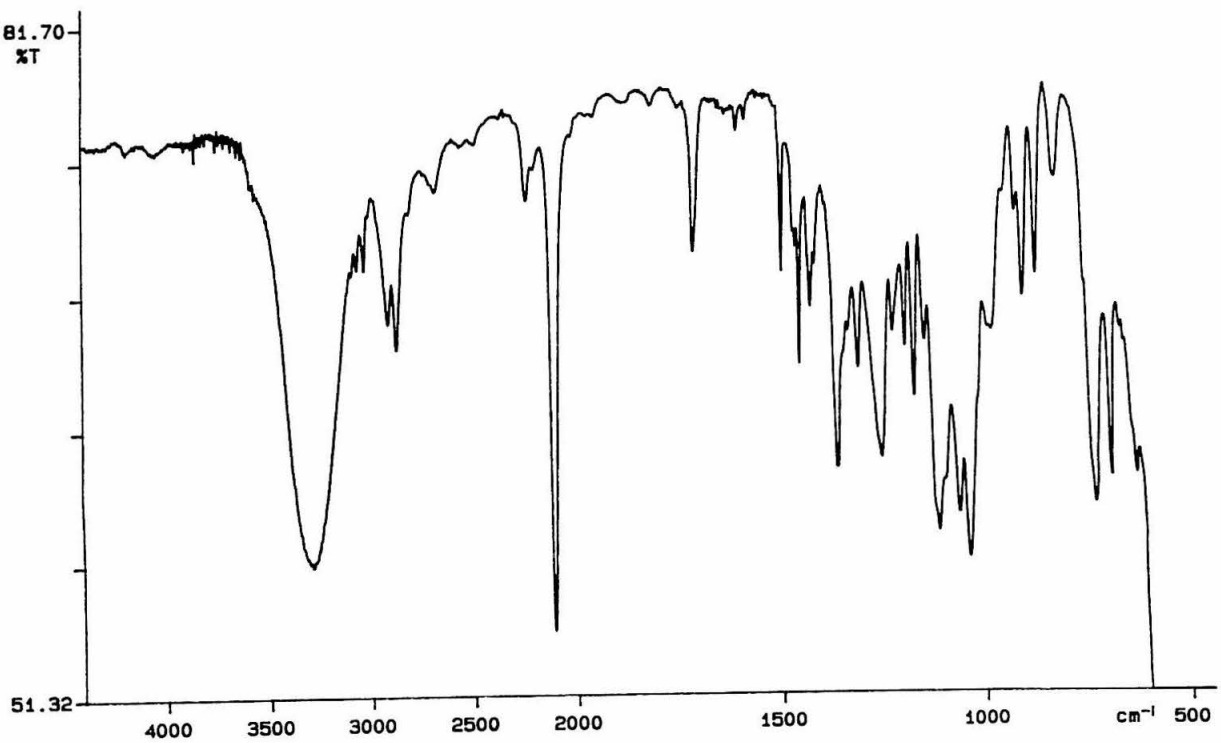
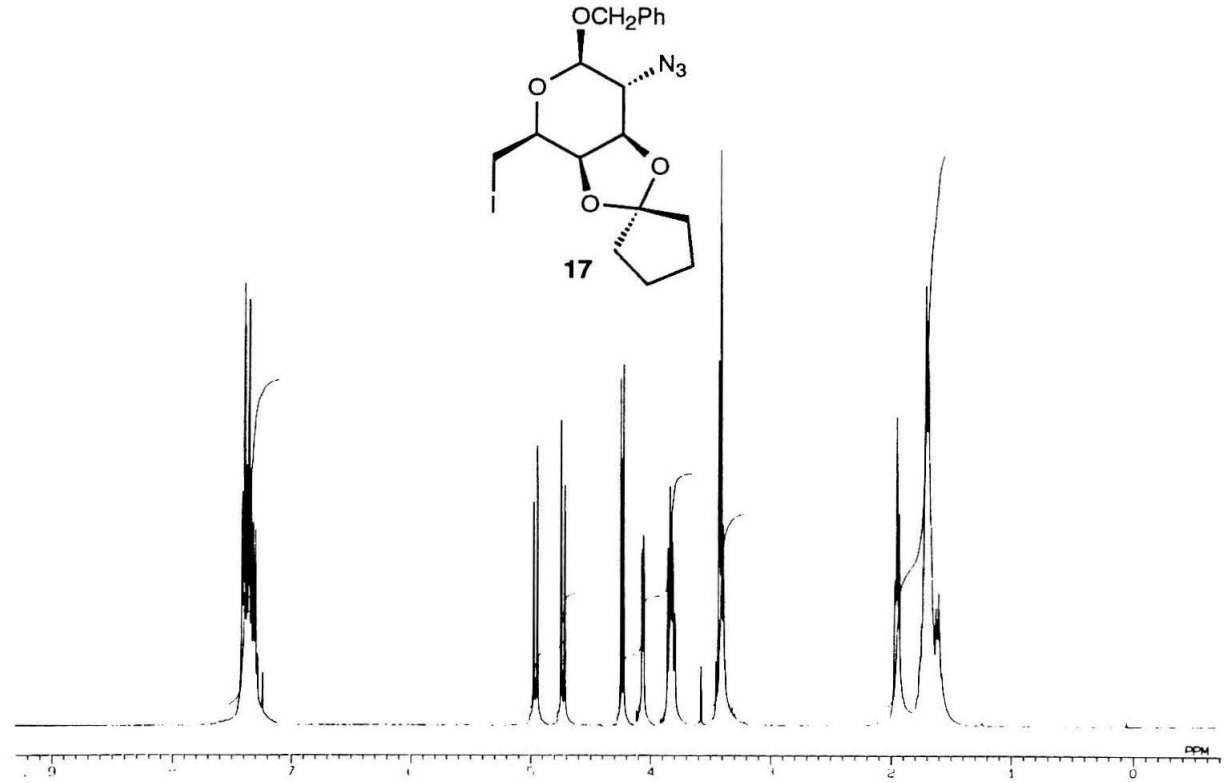
%T
55.95
4000
3500
3000
2500
2000
1500
1000
cm-1

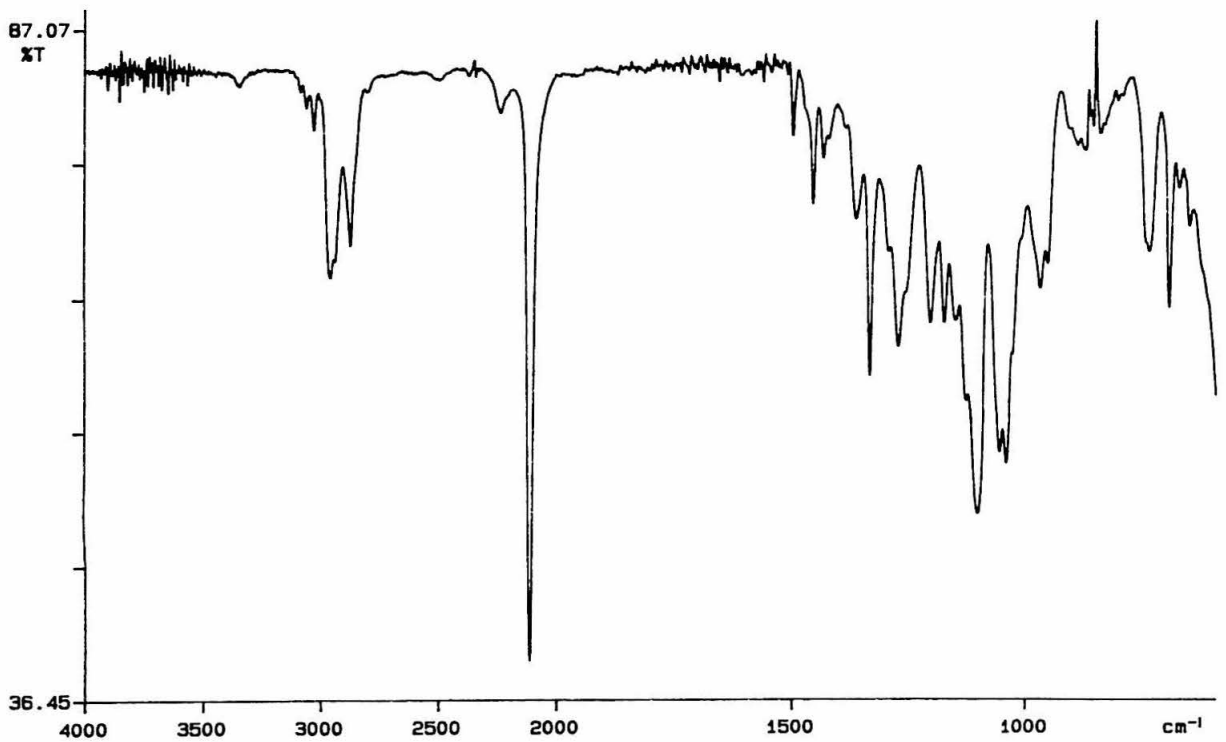

OCH2Ph
N3
O
OH
OH

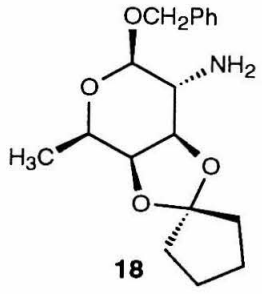
16


9
8
7
6
5
4
3
2
1
0
PPM

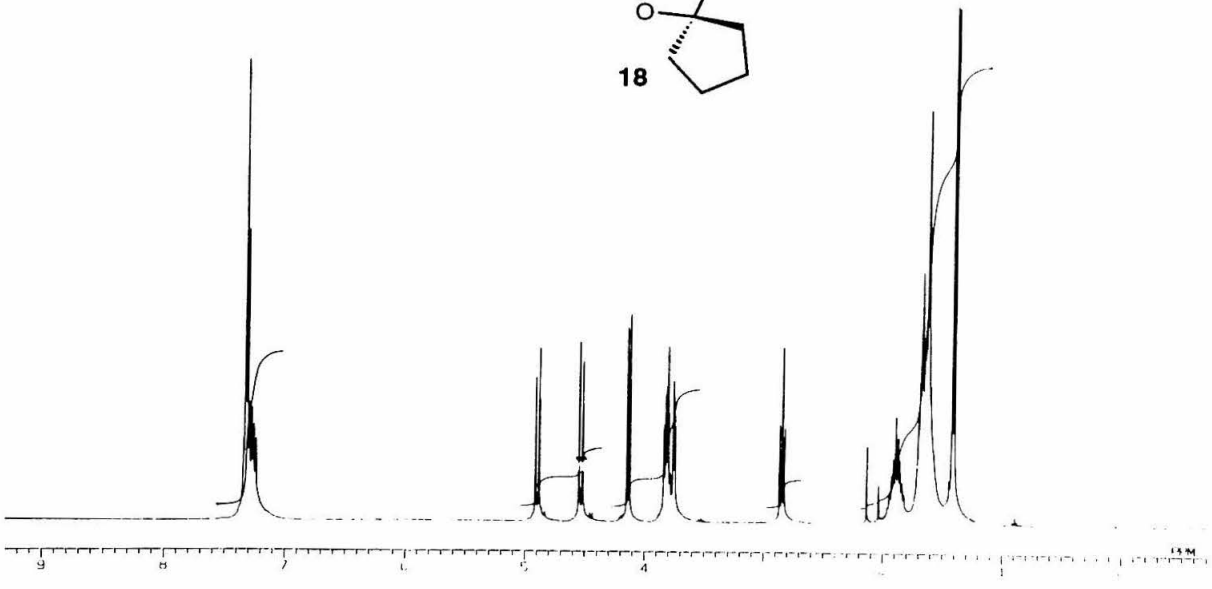

81.70
%T
51.32
4000
3500
3000
2500
2000
1500
1000
cm-1
500

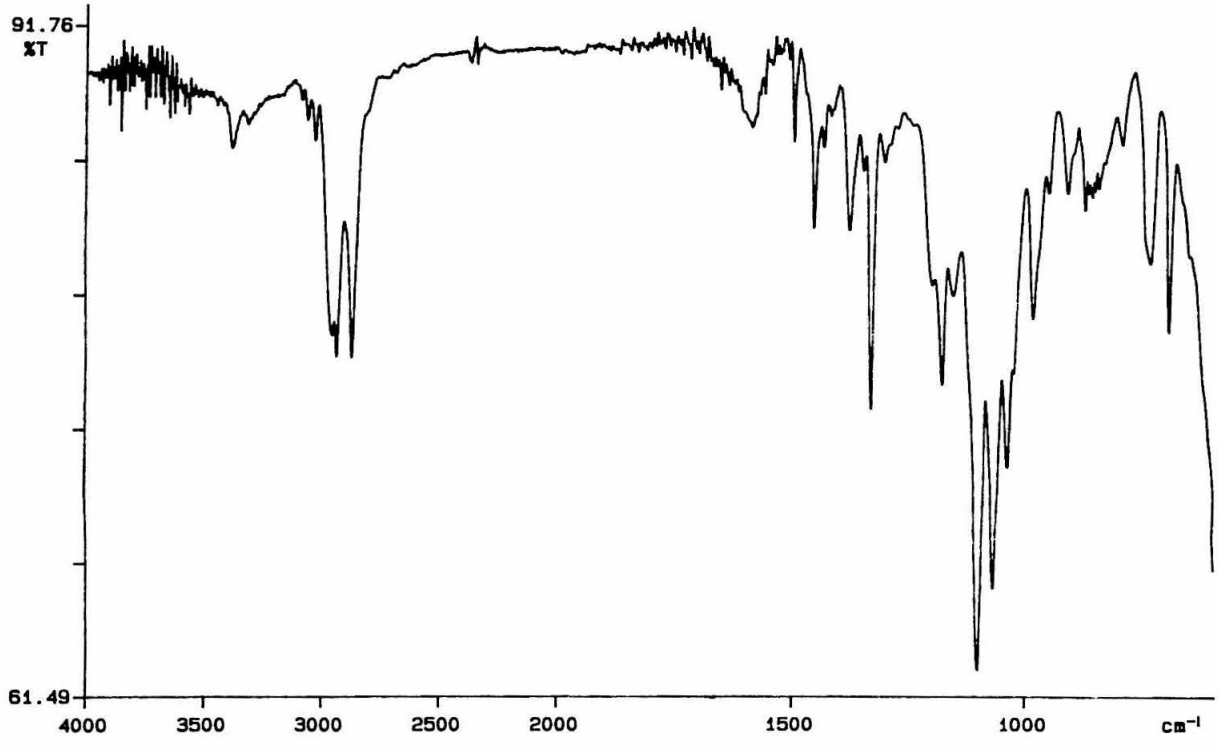

OCH2Ph
N3
O
O
O
I
17
PPM

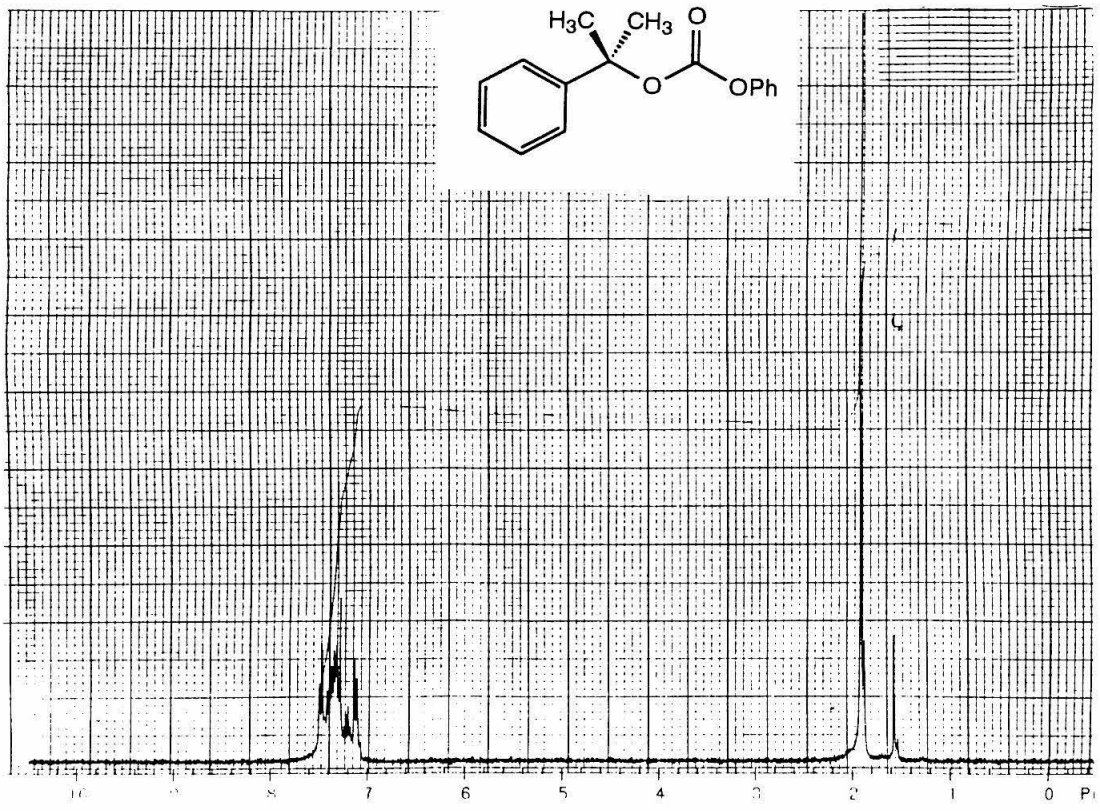

87.07
%T
36.45
4000
3500
3000
2500
2000
1500
1000
cm-1

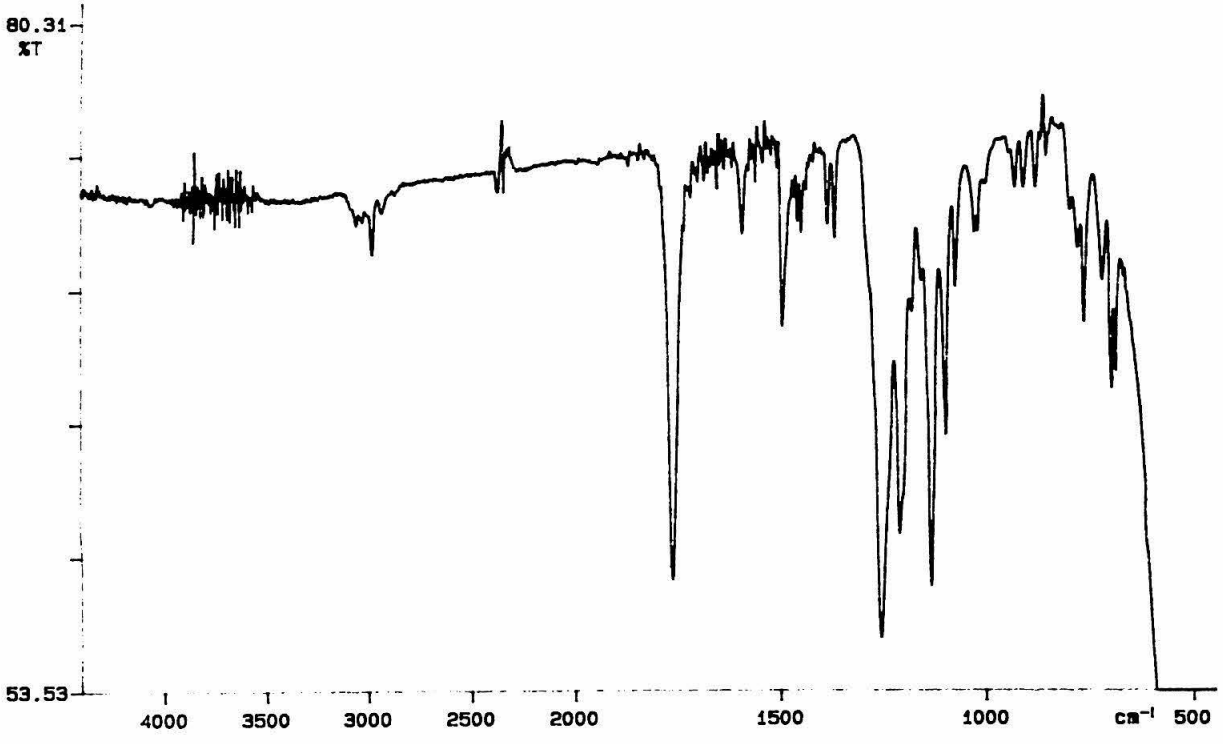

OCH2Ph
NH2
O
H3C
O
O

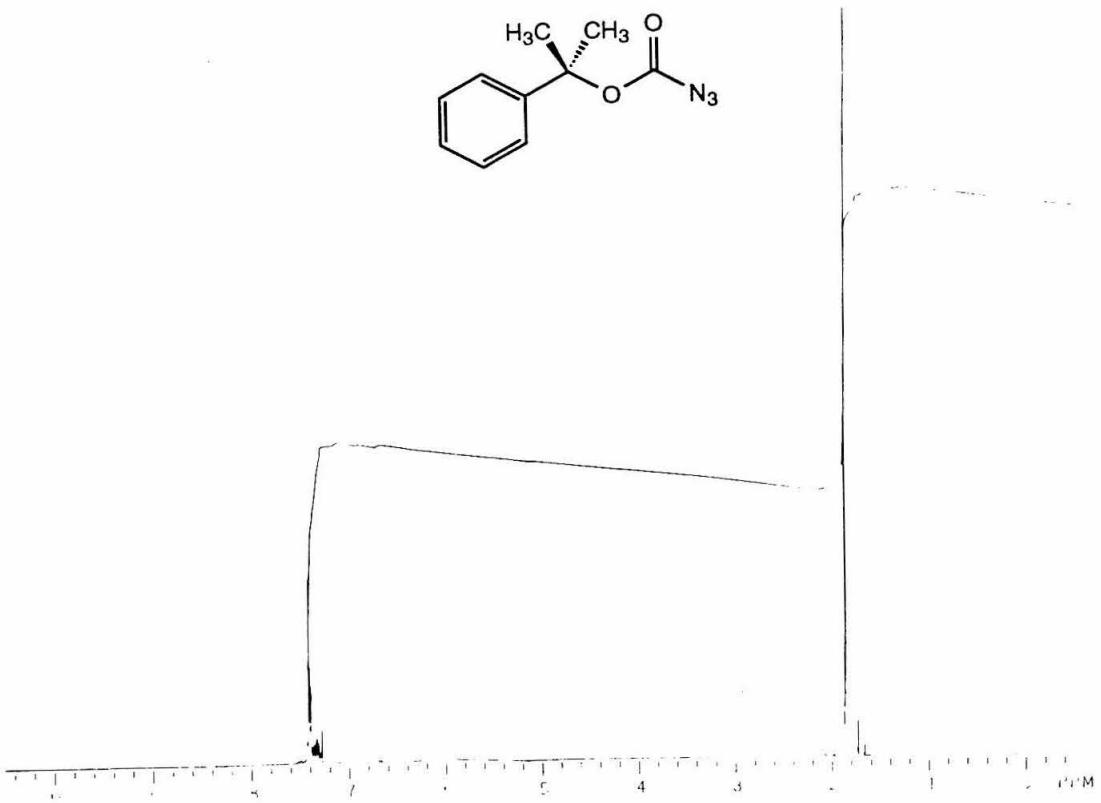
18

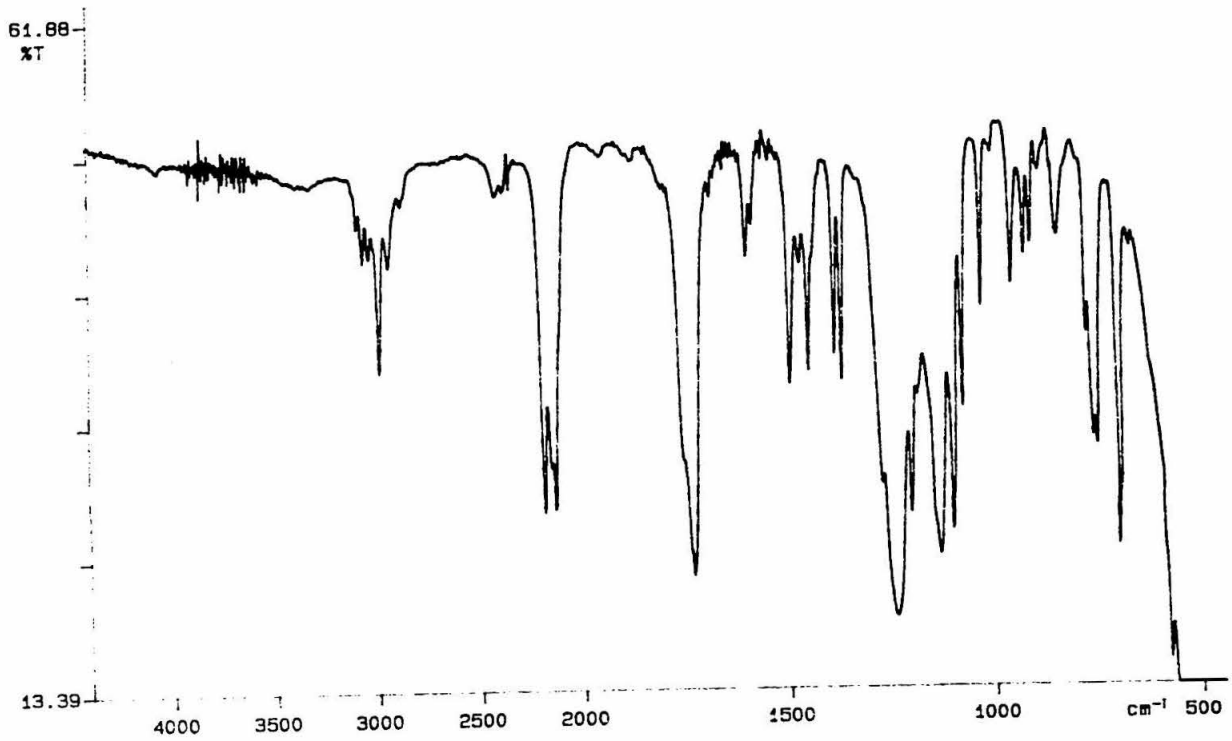


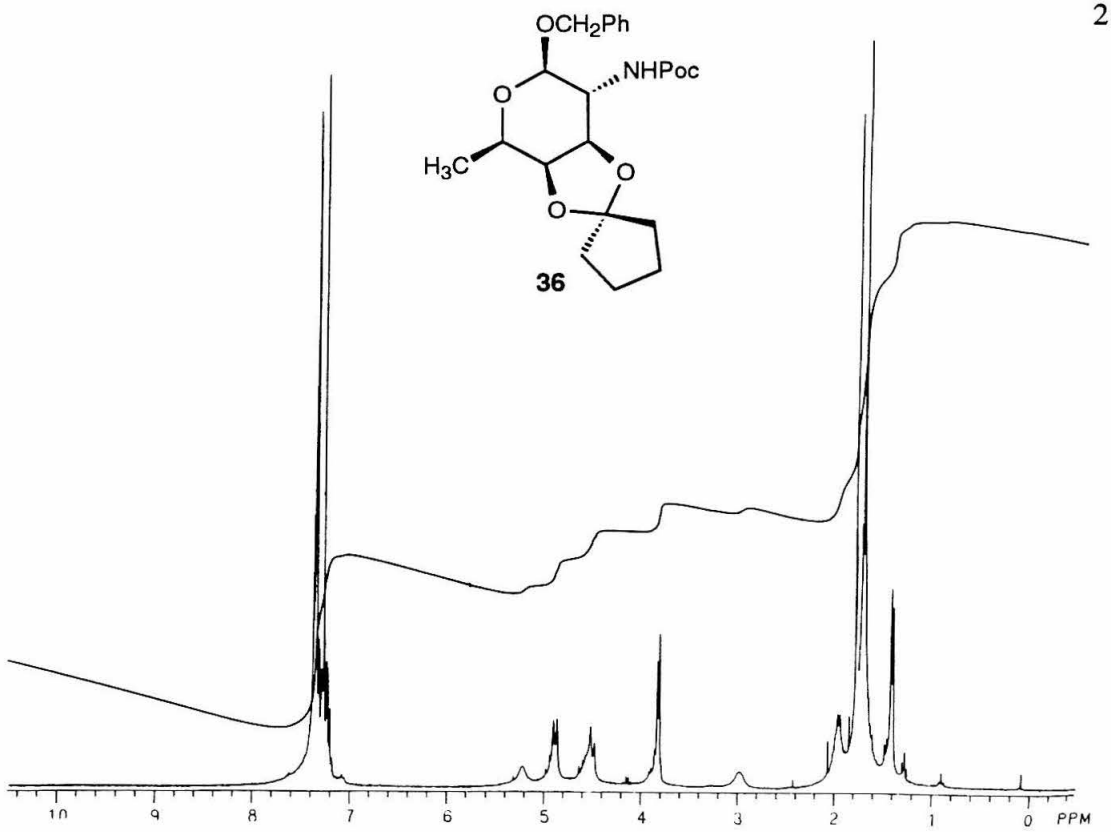

91.76
%T
61.49
4000
3500
3000
2500
2000
1500
1000
cm-1

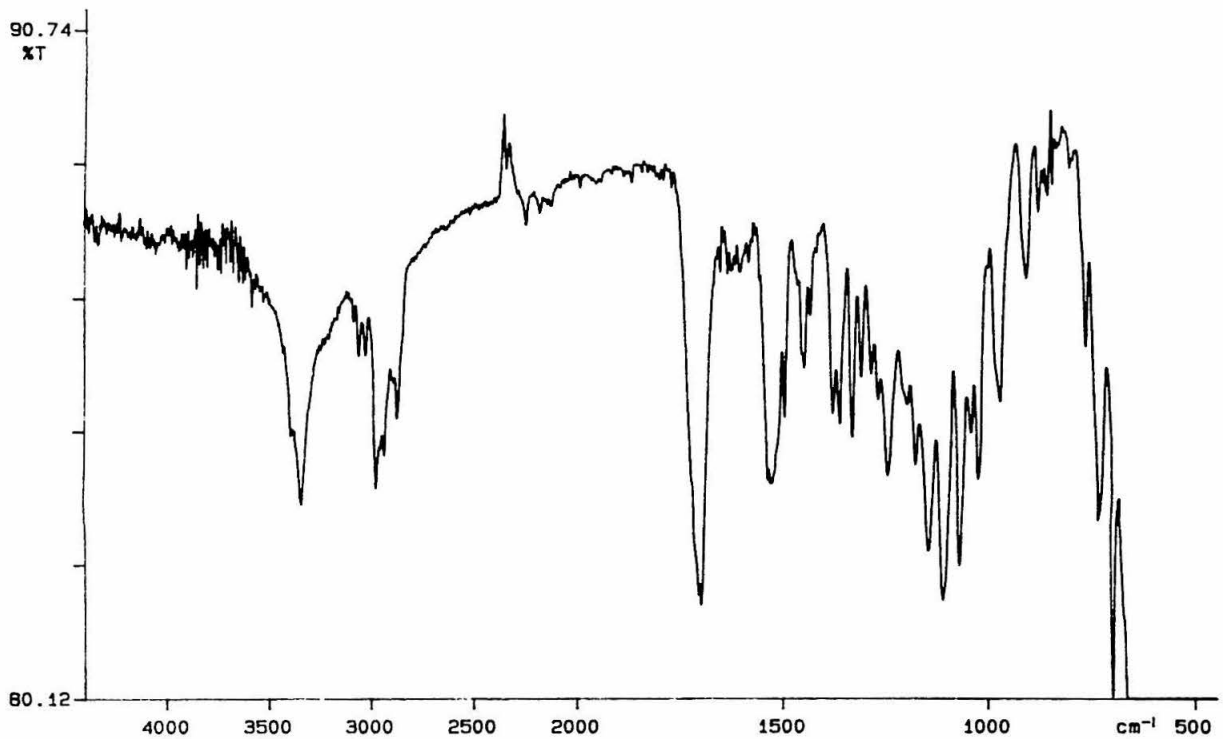

H3C
CH3
O
O
OPh
10
8
7
6
5
4
3
2
1
0

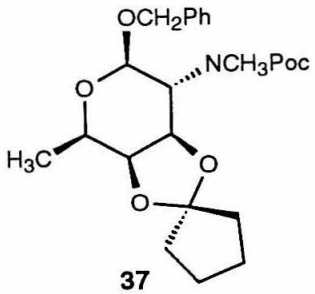

80.31
%T
53.53
4000
3500
3000
2500
2000
1500
1000
cm-1
500


H3C
CH3
O
O
N3
PPM

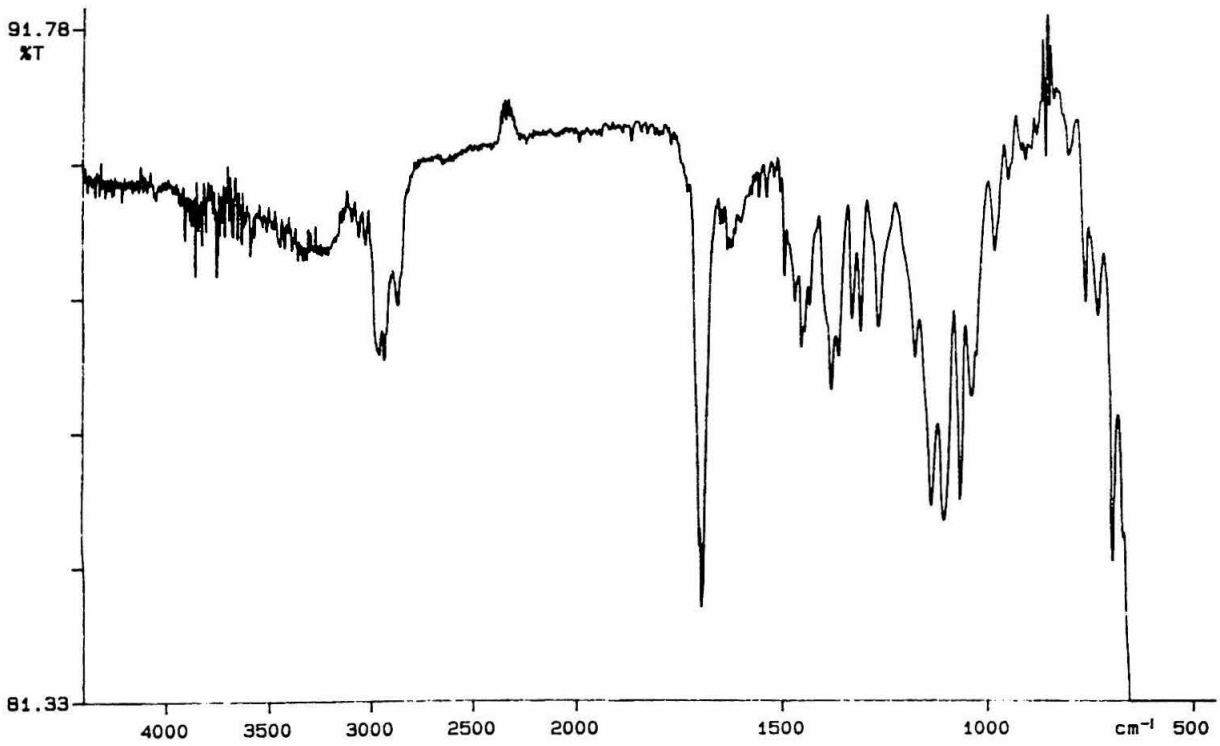

61.88
%T
13.39
4000
3500
3000
2500
2000
1500
1000
cm-1
500

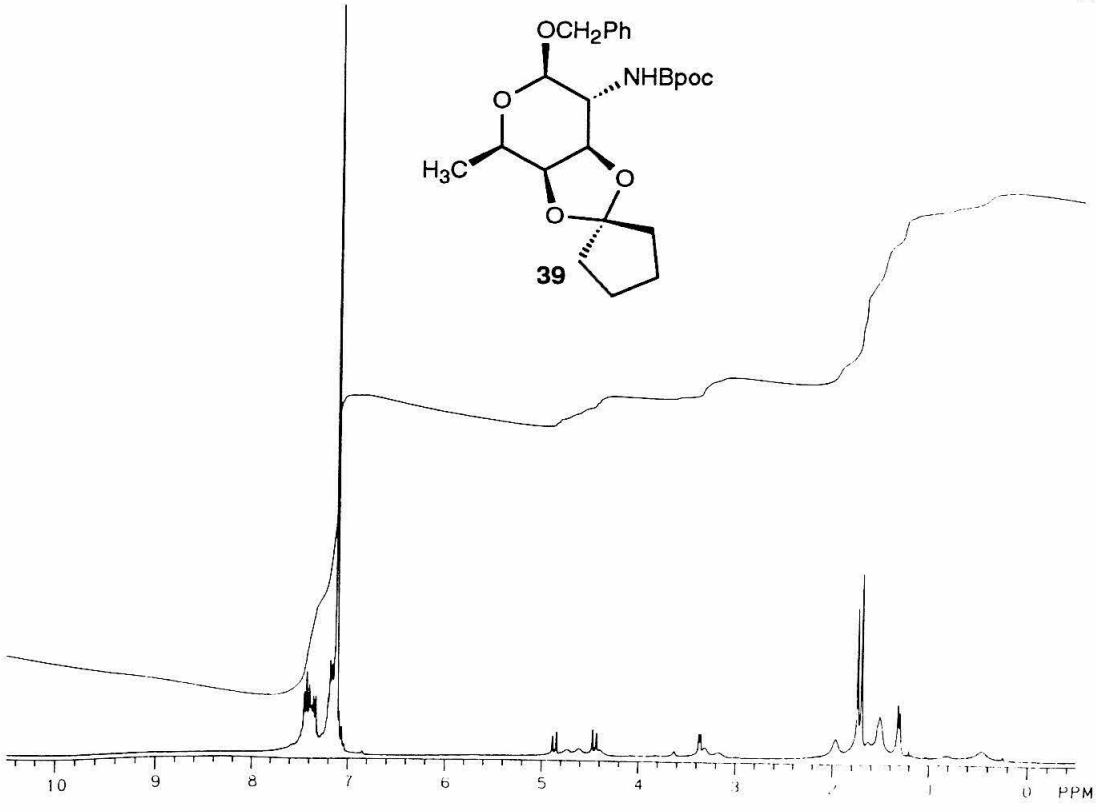

OCH2Ph
NHPoc
O
H3C
O
O
36
10
9
8
7
6
5
4
3
2
1
0
PPM

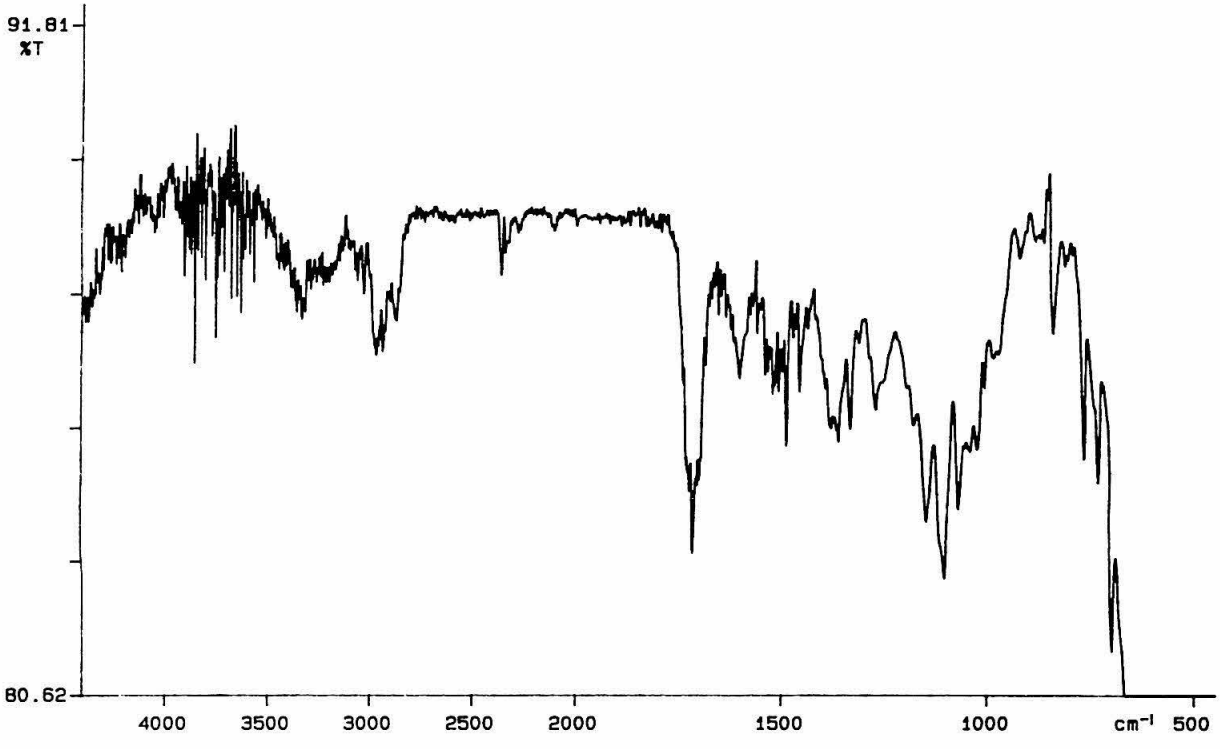

90.74
%T
80.12
4000
3500
3000
2500
2000
1500
1000
cm-1
500

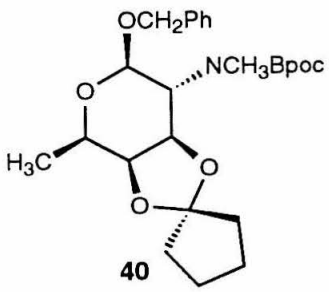

OCH2Ph
NCH3Poc
O
H3C
O
O

37

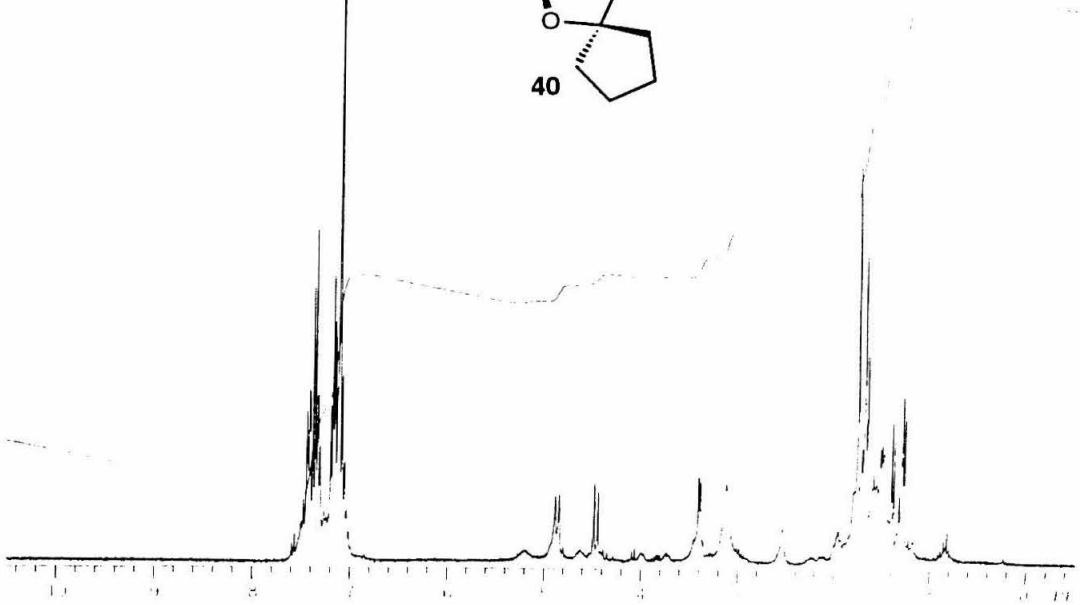

91.78
%T
81.33
4000
3500
3000
2500
2000
1500
1000
cm-1
500

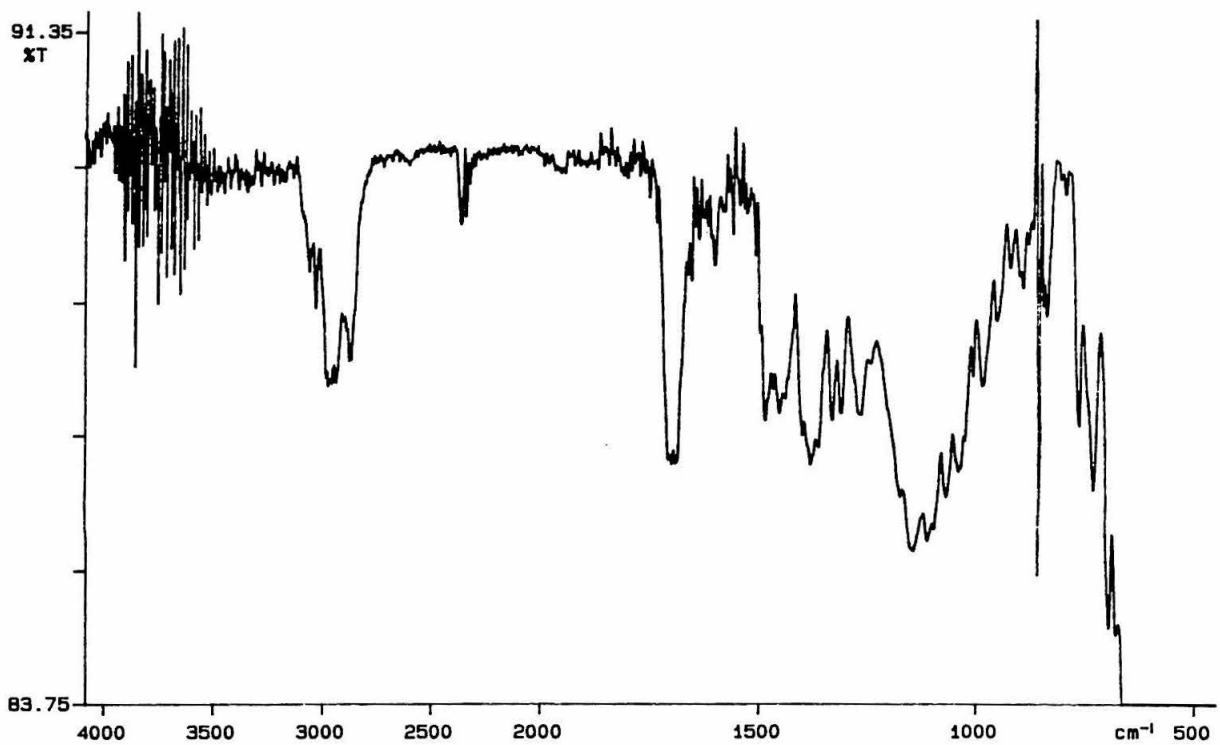

OCH2Ph
NHBpoc
O
H3C
O
O
39
10
9
8
7
6
5
4
3
2
1
0
PPM

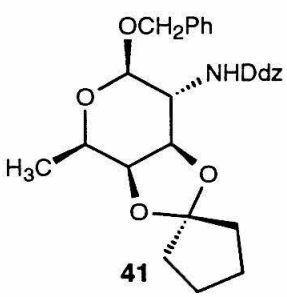

91.81
%T
80.62
4000
3500
3000
2500
2000
1500
1000
cm-1
500


OCH2Ph
NCH3Bpoc
O
H3C
O
O

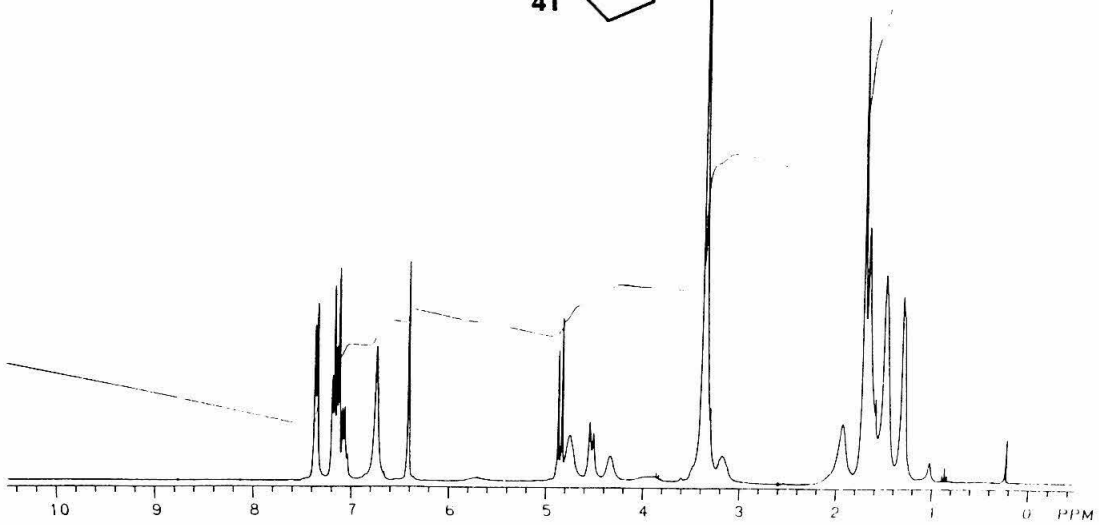
40

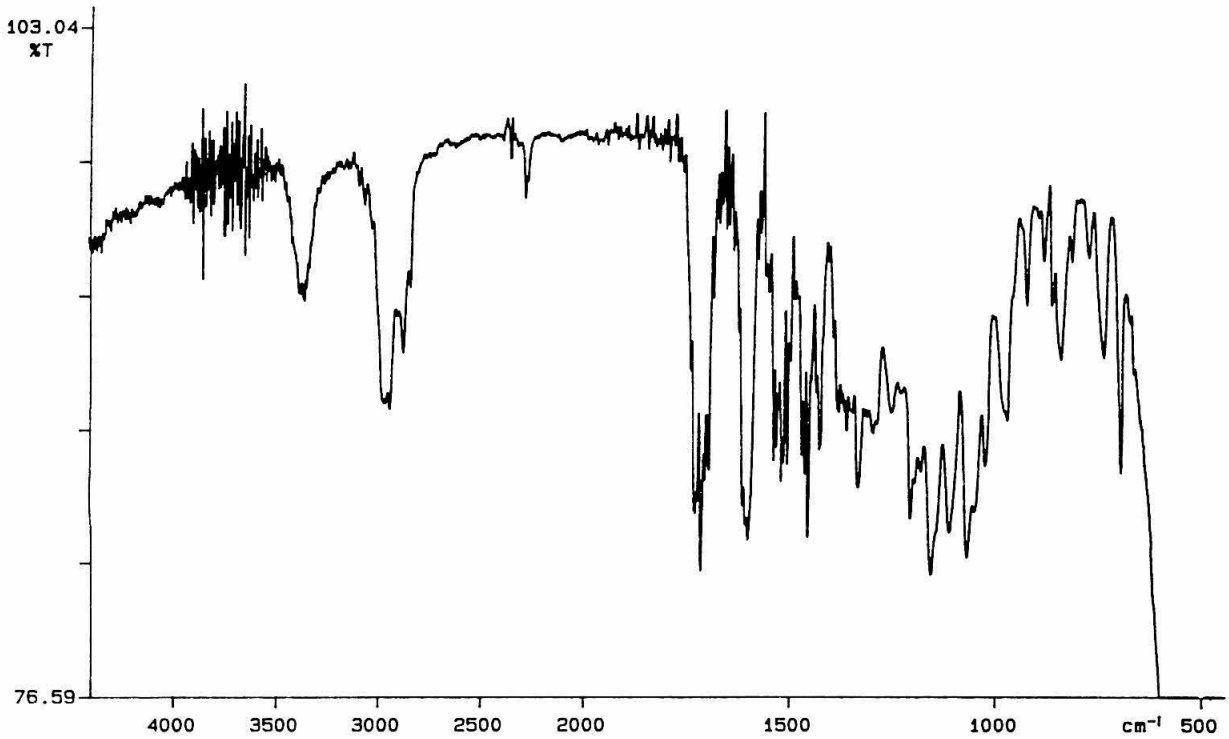


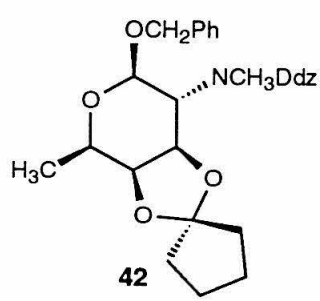

91.35
%T
83.75
4000
3500
3000
2500
2000
1500
1000
cm-1
500


OCH2Ph
NHDdz
O
H3C
O
O

41

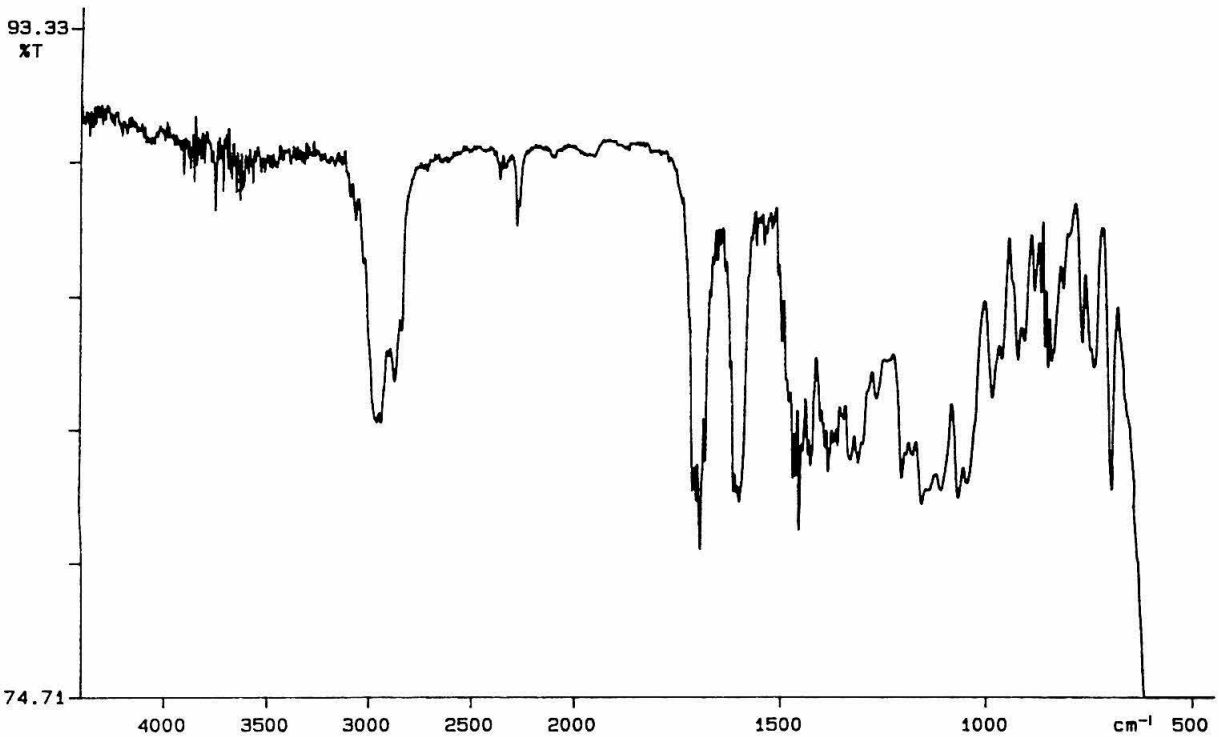

10
9
8
7
6
5
4
3
2
1
0
PPM

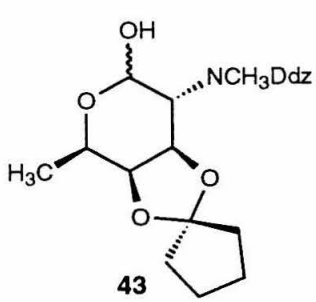

103.04
%T
76.59
4000
3500
3000
2500
2000
1500
1000
cm-1
500


OCH2Ph
NCH3Ddz
H3C
O
O
O

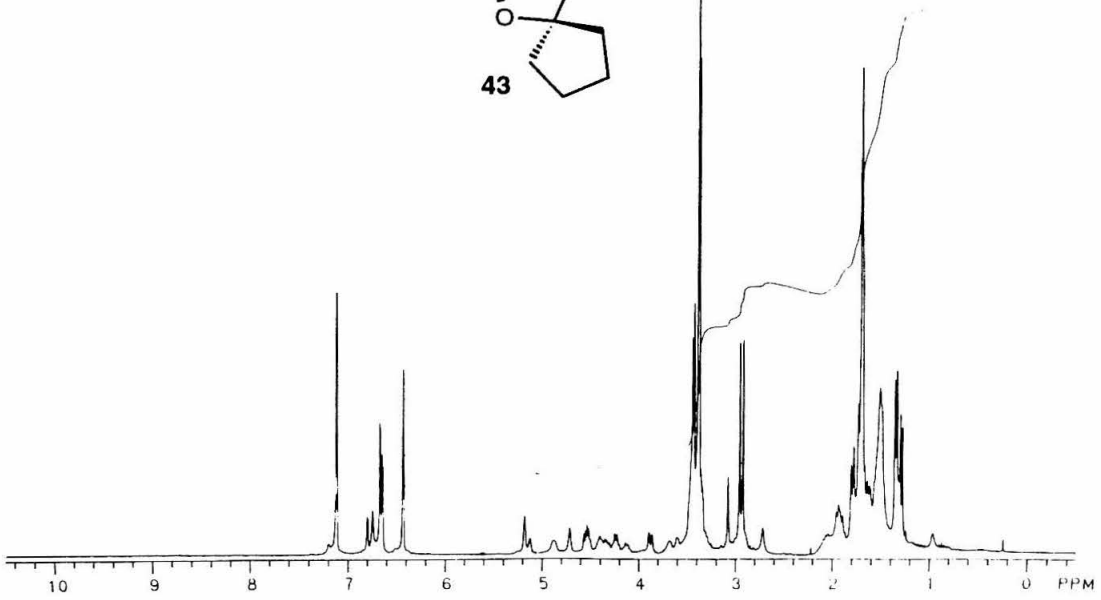
42

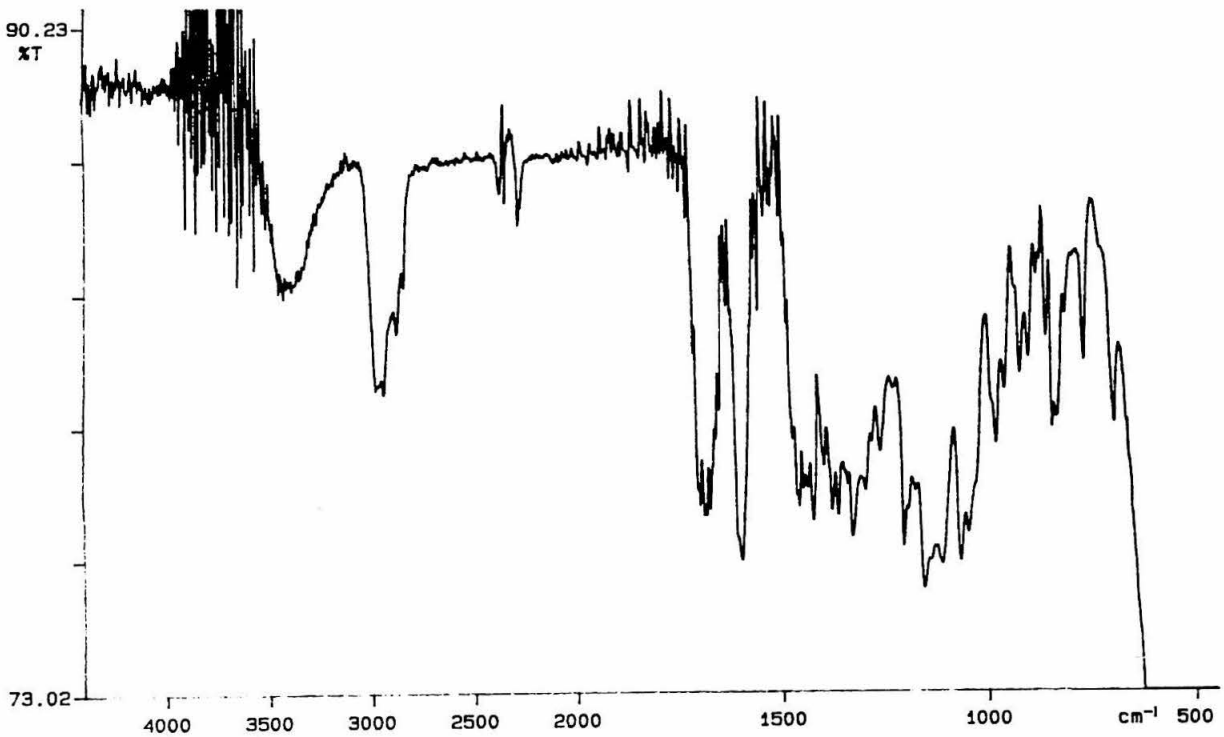
10
9
8
7
6
5
4
PPM

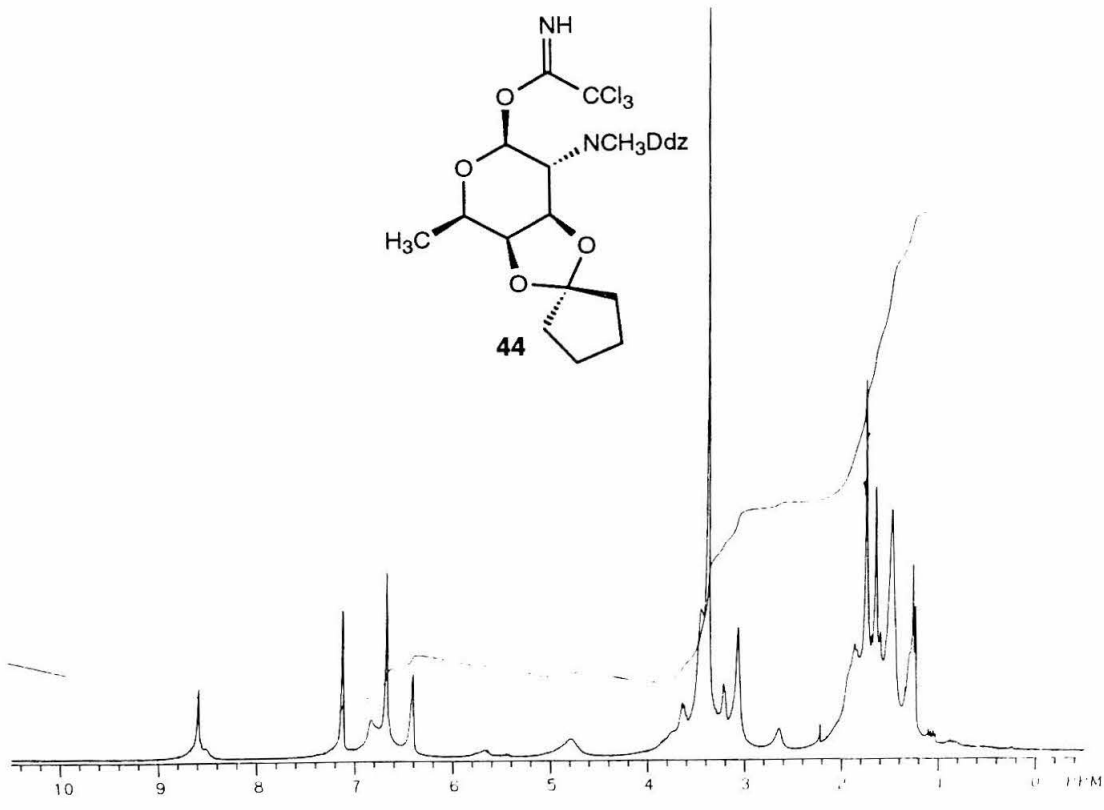

93.33
%T
74.71
4000
3500
3000
2500
2000
1500
1000
cm-1
500


OH
NCH3Ddz
O
H3C
O
O

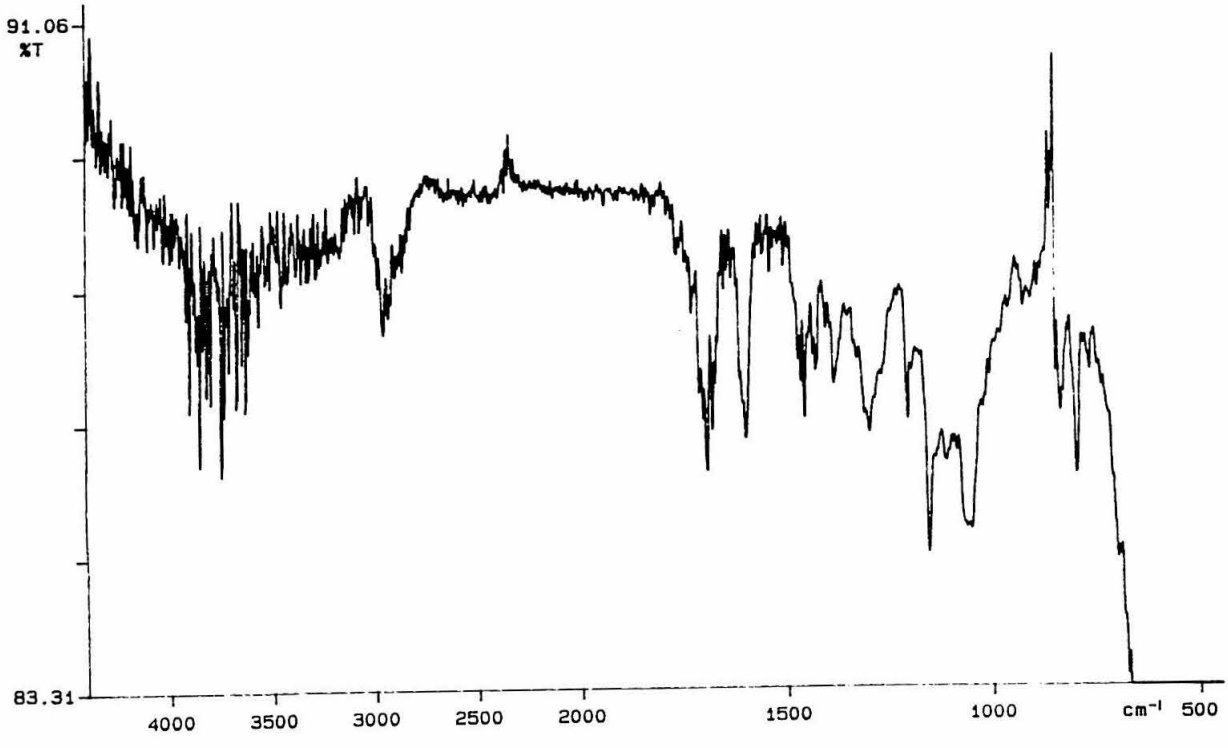
43


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


90.23
%T
73.02
4000
3500
3000
2500
2000
1500
1000
cm-1
500


NH
O
CCl3
NCH3Ddz
O
H3C
O
O
10
9
8
7
6
5
4
3
2
1
0
PPM

44


91.06
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83.31
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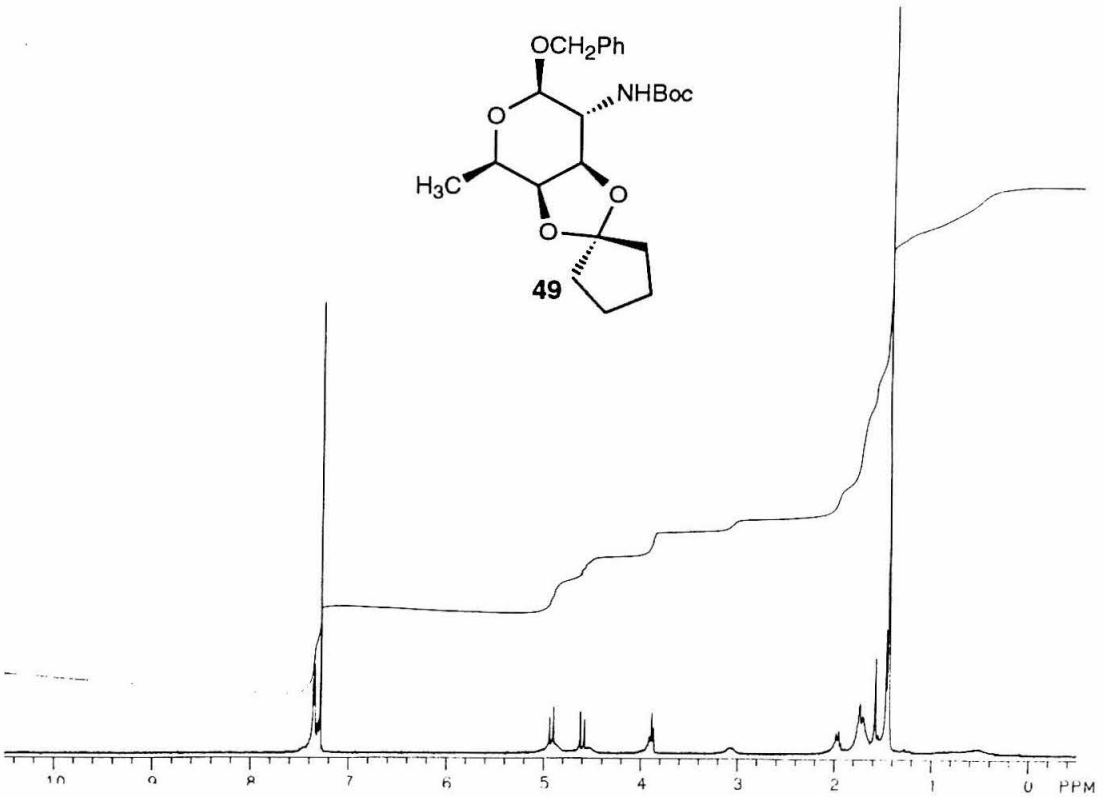
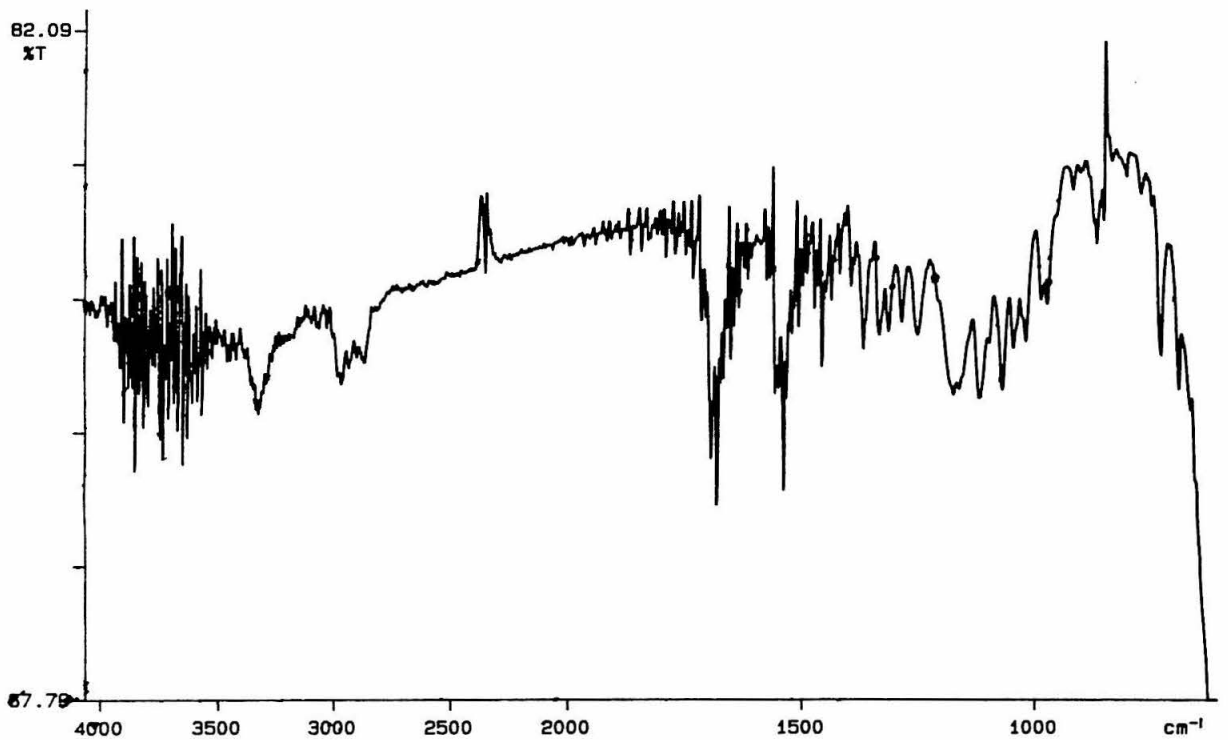
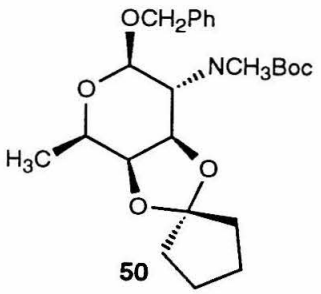
3500
3000
2500
2000
1500
1000
cm-1
500

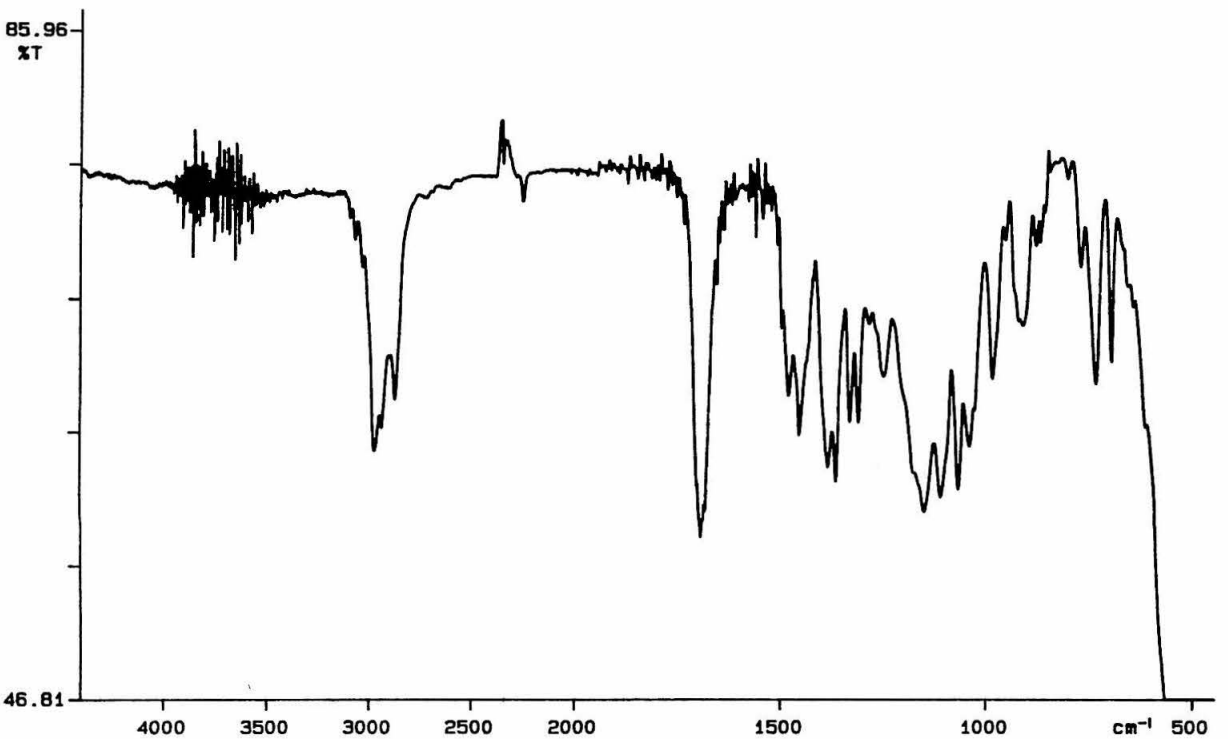

OCH2Ph
NHBoc
H3C
O
O
O
49
10
9
8
7
6
5
4
3
2
1
0
PPM


82.09
%T
67.79
4000
3500
3000
2500
2000
1500
1000
cm-1


OCH2Ph
NCH3Boc
H3C
O
O
O

50

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


85.96
%T
46.81
4000
3500
3000
2500
2000
1500
1000
cm-1
500