Structural and Mechanistic Study of Monoalkyl Diazenes. Synthesis, Characterization, and Reactivity of 1,6-Didehydro[10]annulene

Dissertation by

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You work that you may keep pace with the earth and the soul of the earth. For to be idle is to become a stranger to the seasons, and to step out of life's procession, which marches in majesty and proud submission towards the infinite.

...(If) you cannot work with love, but only with distaste, it is better you should leave your work and sit at the gate of the temple and take alms of those who work with joy. For if you bake bread with indifference, you bake a bitter bread that feeds only half a man's hunger. And if you grudge the crushing of the grapes, your grudge distills a poison in the wine. And if you sing though as angels, if you love not the singing, you muffle man's ears to the voices of the day and the voices of the night.

– Kahlil Gibran

Acknowledgments

I would like to thank Andy Myers for his guidance and patience over the last five years. He has provided me with an opportunity to work independently on a number of exciting projects, and if I had to do it over, I would do the same research for the same advisor.

Of course, I would have been at a loss without my family and friends (all of whom presumably know who they are). It has been a long road, and I can't imagine having made it without them to lean on, early and often.

I would also like to thank the past and present members of the Myers group for their companionship, both intellectual and personal. They have been an exceptional group of people to work with, and I will certainly miss them.

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Last, but certainly not least, I am indebted to my undergraduate research advisor, Steve Zimmerman. He remains a source of encouragement and guidance, and it is unlikely that I would be here without him.

Abstract

Methodology for the preparation of allenes from propargylic hydrazine precursors under mild conditions is described. Oxidation of the propargylic hydrazines, which can be readily prepared from propargylic alcohols, with either of two azo oxidants, diethyl azodicarboxylate (DEAD) or 4-methyl 1,2-triazoline-3,5-dione (MTAD), effects conversion to the allenes, presumably via sigmatropic rearrangement of a monoalkyl diazene intermediate. This rearrangement is demonstrated to proceed with essentially complete stereospecificity. The application of this methodology to the preparation of other allenes, including two that are notable for their reactivity and thermal instability, is also described.

The structural and mechanistic study of a monoalkyl diazene intermediate in the oxidative transformation of propargylic hydrazines to allenes is described. The use of long-range heteronuclear NMR coupling constants for assigning monoalkyl diazene stereochemistry (*E* vs *Z*) is also discussed. Evidence is presented that all known monoalkyl diazenes are the *E* isomers, and the erroneous assignment of stereochemistry in the previous report of the preparation of *(Z)*-phenyldiazene is discussed.

The synthesis, characterization, and reactivity of 1,6-didehydro[10]annulene are described. This molecule has been recognized as an interesting synthetic target for over 40 years and represents the intersection of two sets of extensively studied molecules: non-benzenoid aromatic compounds and molecules containing sterically compressed π-systems. The formation of 1,5-dehydronaphthalene from 1,6-didehydro[10]annulene is believed to be the prototype for cycloaromatizations that produce 1,4-dehydroaromatic species with the radical centers disposed *anti* about the newly formed single bond. The aromaticity of this annulene and the facility of its cycloaromatization are also analyzed.

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List of Abbreviations

$[\alpha]_D^{21}$	optical rotation at 589 nanometers and 21 degrees Celsius
Å	angstrom
Ac	acetyl
aq	aqueous
Ar	aryl
Bu	butyl
C	grams per 100 milliliters of solution
°C	degrees Celsius
C_6D_6	hexadeuteriobenzene
CI	chemical ionization
cm	centimeters
CSA	camphorsulfonic acid
δ	chemical shift in parts per million
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DEAD	diethyl azodicarboxylate
DHP	dihydropyran
dimsyl	dimethyl sulfoxyl
dm	decimeter
DMAP	4-dimethylaminopyridine
DMF	*N,N*-dimethylformamide
DMSO	dimethyl sulfoxide
DNA	deoxyribonucleic acid
ε	extinction coefficient at a specified wavelength

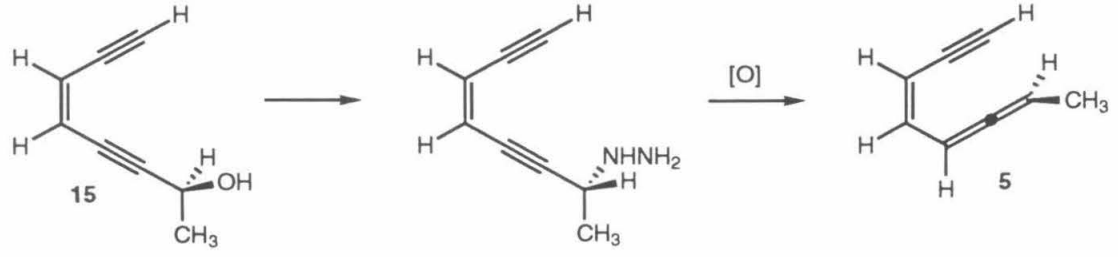
E	entgegen
ee	enantiomeric excess
EI	electron impact
Et	ethyl
equiv	equivalent
FAB	fast atom bombardment
FT	Fourier transform
fod	6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedione
4 Å MS	4 angstrom molecular sieves
g	gram
G	Gibbs free energy
H	enthalpy
hfc	3-(heptafluoropropylhydroxymethylene)-(–)-camphor
HMDS	hexamethyldisilazide
HMPA	hexamethylphosphoramide
HRMS	high resolution mass spectrometry
Hz	hertz
i	iso
IR	infrared
J	coupling constant
k	rate constant
kcal	kilocalories
L	liter
LAH	lithium aluminum hydride
λ_{max}	frequency of absorbance maximum

m	meta
μ	micron
M	molar
Me	methyl
mesylate	methanesulfonate
MHz	megahertz
min	minutes
ml	milliliter
mm	millimeter
mm Hg	pressure in millimeters of mercury
mmol	mmol
MS	mass spectrometry
Ms	methane sulfonate
MTAD	4-methyl-1,2-triazoline-3,5-dione
mTorr	millitorr
NIS	N-iodosuccinimide
nm	nanometers
NMR	nuclear magnetic resonance
o	ortho
o.d.	outer diameter
PCC	pyridinium chlorochromate
Ph	phenyl
ppm	parts per million
Pr	propyl
p	para
pH	hydrogen ion concentration (log scale)
R_f	retention factor

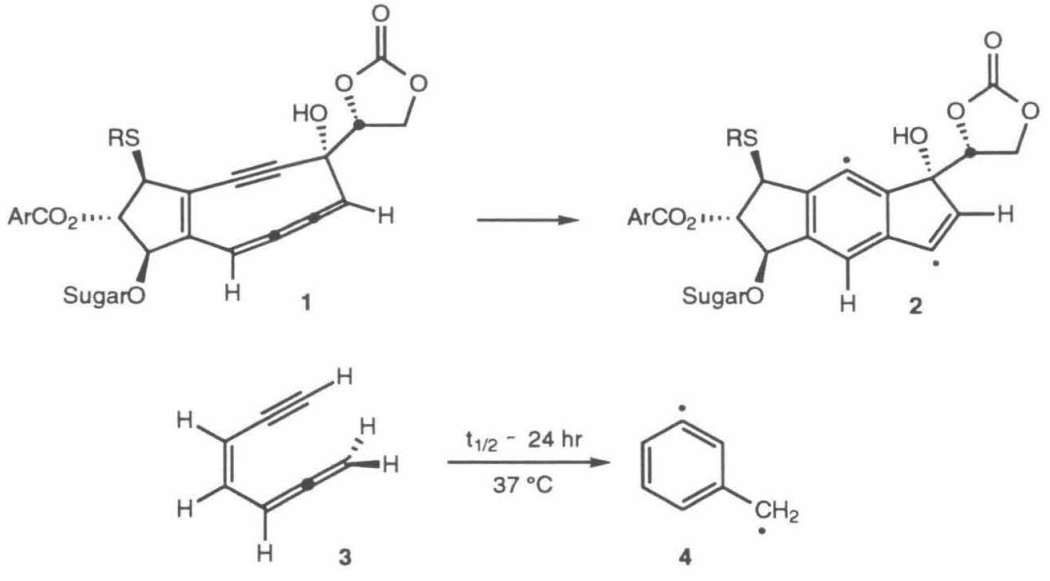
s	seconds
t	tertiary
TBAF	tetrabutylammonium fluoride
TBS	*tert*-butyldimethylsilyl
Tf	trifluoromethane sulfonate
THF	tetrahydrofuran
THF-d_8	octadeuteriotetrahydrofuran
THP	tetrahydropyran
3 Å MS	3 angstrom molecular sieves
TMS	trimethylsilyl
TLC	thin layer chromatography
tosylate	*p*-toluenesulfonate
triflate	trifluoromethane sulfonate
Ts	*p*-toluenesulfonate
UV	ultraviolet
v/v	volume-to-volume ratio
W	watt
w/v	weight-to-volume ratio
w/w	weight-to-weight ratio
xs	excess
Z	zusammen

Summary

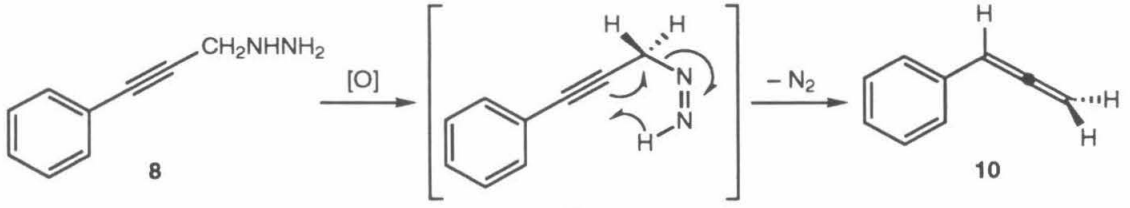
The research described in this thesis comprises three projects, which are presented in separate chapters. The first chapter describes methodology for the preparation of allenes from propargylic hydrazines, which can be readily prepared from propargylic alcohol precursors, under mild conditions (e.g., **15** → **5**). Oxidation of the propargylic hydrazines with either of two azo oxidants, diethyl azodicarboxylate (DEAD) or 4-methyl 1,2-triazoline-3,5-dione (MTAD), effects conversion to the corresponding allenes, presumably



via sigmatropic rearrangement of a monoalkyl diazene intermediate. This rearrangement is demonstrated to proceed with essentially complete stereospecificity. The synthesis of two thermally unstable allenes that undergo a cycloaromatization reaction (**3** → **4**) analogous to that of neocarzinostatin (**1** → **2**) are also described.

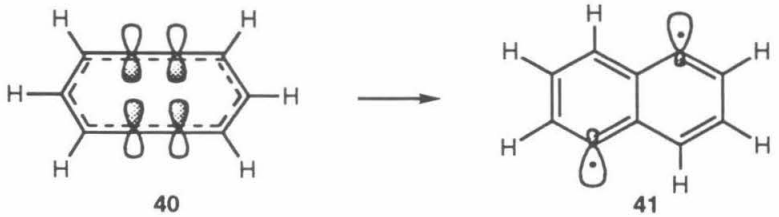


The second chapter reports the structural and mechanistic study of a monoalkyl diazene intermediate in the oxidative transformation of propargylic hydrazines to allenes (**8** → **10**). The use of long-range heteronuclear NMR coupling constants for assigning monoalkyl diazene stereochemistry (*E* vs *Z*) is also discussed. Evidence is presented that all known monoalkyl diazenes are the *E* isomers, and the erroneous assignment of stereochemistry in the previous report of the preparation of *(Z)*-phenyldiazene is discussed.



8 *(Z)*-**9** **10**

The third chapter describes the synthesis, characterization, and reactivity of 1,6-didehydro[10]annulene (**40**). This molecule has been recognized as an interesting synthetic target for over 40 years and represents the intersection of two sets of extensively studied molecules: non-benzenoid aromatic compounds and molecules containing sterically compressed π-systems. The formation of 1,5-dehydronaphthalene from **40** (**40** → **41**) is believed to be the prototype for cycloaromatizations that produce 1,4-dehydroaromatic species with the radical centers disposed *anti* about the newly formed single bond. The aromaticity of this annulene and the facility of its cycloaromatization are also analyzed.



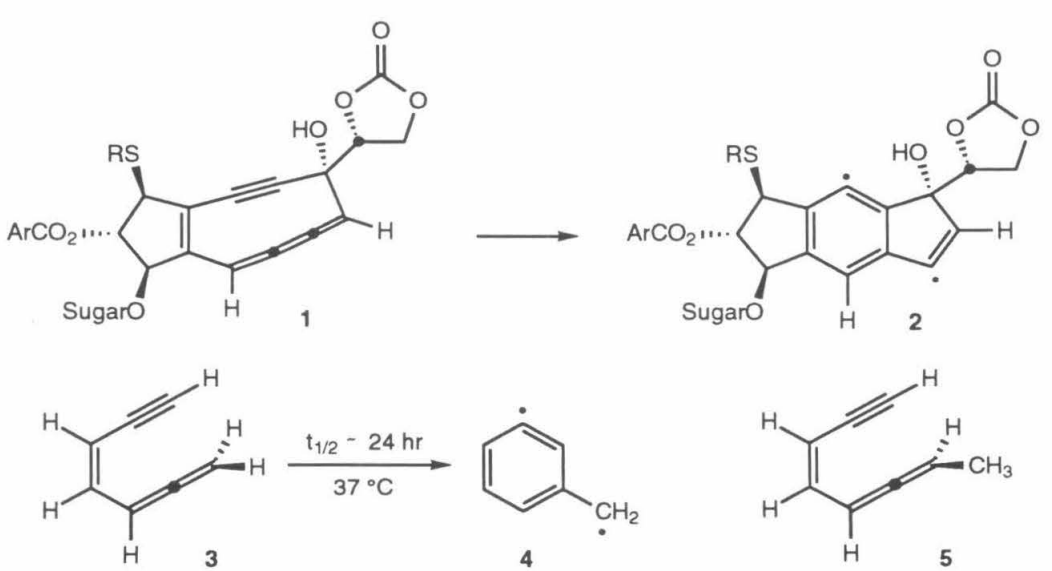
40 **41**

Chapter 1

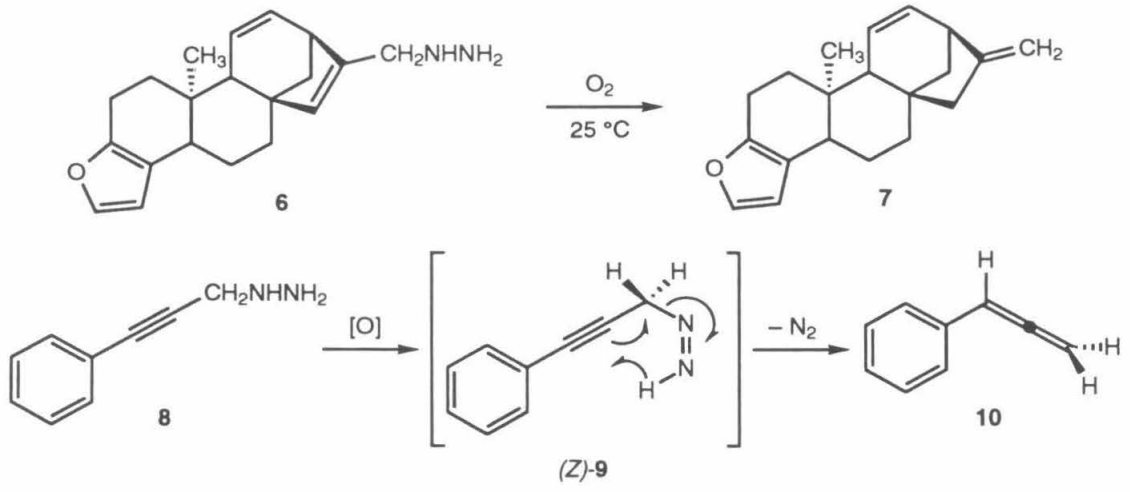
Allene Synthesis from 2-Alkyn-1-ols

Background and Introduction

An essential step in the cleavage of DNA by the antibiotic neocarzinostatin (**1**) is the cycloaromatization of a cumulene intermediate to a 1,4-(σ,σ)-biradical with the radical centers disposed *anti* about the newly-formed single bond (**1** → **2**).[1] This discovery has led to the intensive study of hydrocarbons that display similar reactivity, in an effort to characterize the fundamental properties of such unsaturated systems. Two of the simplest hydrocarbons studied in this context, the allenes *(Z)*-1,2,4-heptatrien-6-yne (**3**) and *(Z)*-3,5,6-octatrien-1-yne (**5**), undergo cycloaromatization to the corresponding (σ, π)-dehydroaromatic biradicals at low temperatures (**3** → **4**).[2] A central challenge in the preparation of these compounds was the requirement for conditions compatible with the high reactivity and low thermal stability of **3** and **5**. Commonly employed methods for the preparation of allenes, such as base-catalyzed isomerization of alkynes or S_N2' displacement of propargylic electrophiles, involve strongly basic conditions and were judged unlikely to be satisfactory for the preparation of **3** and **5**.[3] Described herein are the development of a general method for the preparation of allenes from propargylic alcohols under mild conditions and the application of this methodology to the synthesis of several allenes, including **3** and **5**.



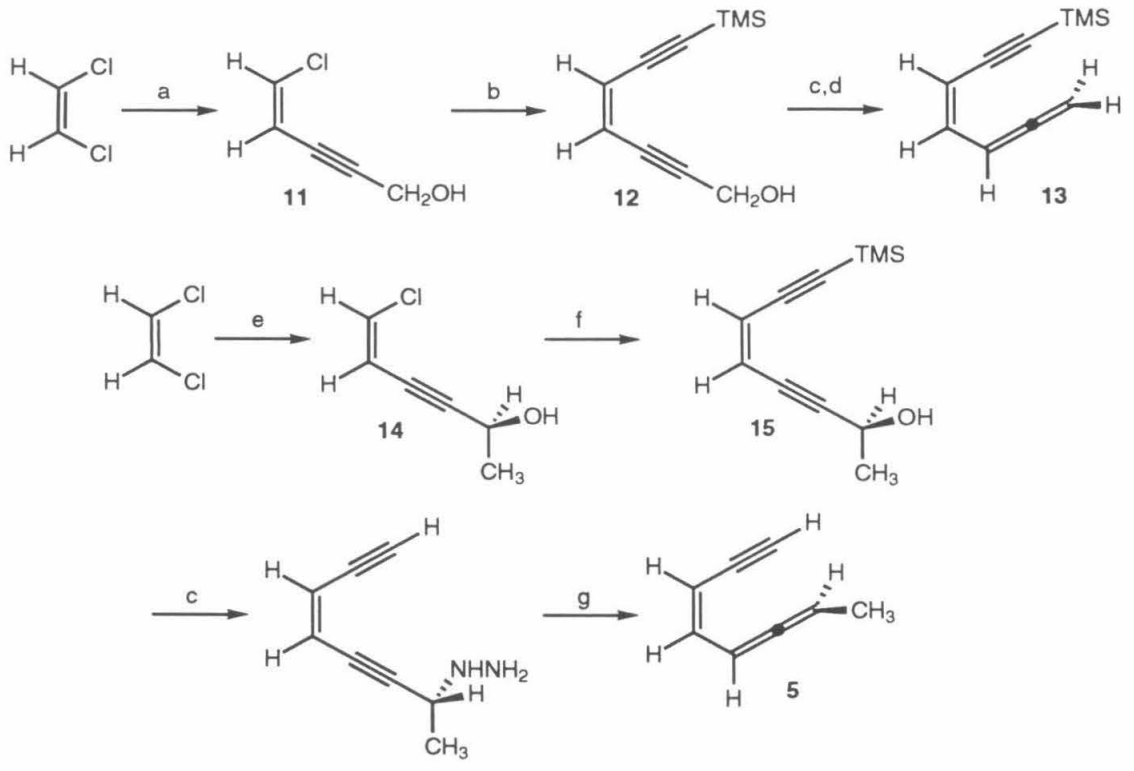
The formation of allenes and transposed alkenes upon hydridic reduction of conjugated alkynyl and alkenyl tosyl hydrazones, respectively, has been rationalized as arising via [3,3]-sigmatropic rearrangement of a propargylic or allylic diazene intermediate with extrusion of dinitrogen.[4] An allylic transposition sequence involving the air-oxidation of an allylic hydrazine has recently been exploited in the preparation of a precursor to (±)-cafestol, and presumably also proceeds through an allylic diazene intermediate (**6** → **7**).[5] We have found that while propargylic hydrazines undergo similar air-oxidation to form allenes (e.g., **8** → **10**), this reaction is much more rapid and efficient when diethyl azodicarboxylate (DEAD) or 4-methyl-1,2,4-triazoline-3,5-dione (MTAD) is used as the oxidant.[6,7]



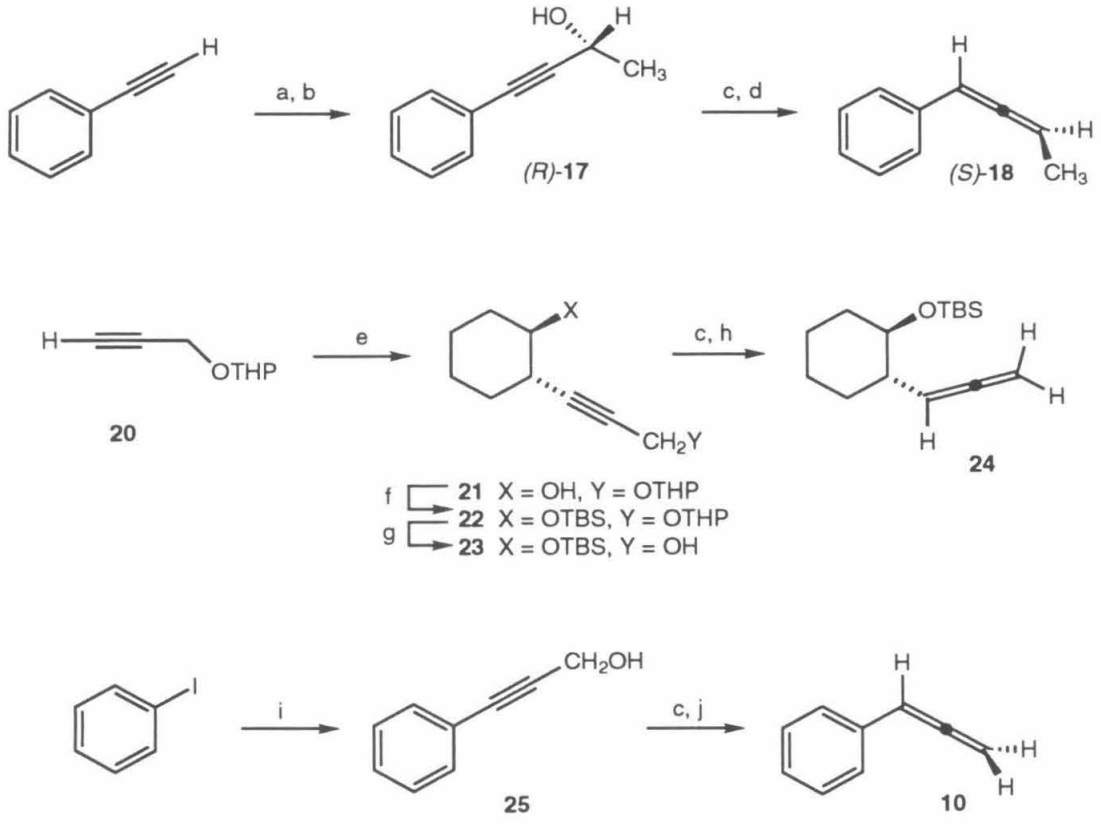
Synthesis of Allenes

The transformation of acetylenic alcohol **15** to allene **5** is representative of the synthetic method (Scheme 1). Conversion of **15** to the corresponding methanesulfonate ester,[8] followed by displacement of the methanesulfonate by dry hydrazine in methanol at 0 °C afforded, after extractive isolation, the desilylated propargylic hydrazine. A survey of several oxidants revealed the commercially available azo compounds DEAD and MTAD as superior reagents in terms of rapidity and efficiency in effecting oxidative

rearrangement. Thus, treatment of a solution of the propargylic hydrazine prepared from **15** in tetrahydrofuran at 0 °C with MTAD (1.2 equiv) resulted in the spontaneous evolution of dinitrogen with concomitant formation of **5**. The allene **5** could be isolated in 46% yield (from **15**) after purification by flash column chromatography.[9] A similar sequence of events allowed the conversion of the alcohol **12** to the allene **13** (63%).



Scheme 1. Reagents and Conditions: (a) $HC{\equiv}CCH_2OH$ (0.20 equiv), $PrNH_2$ (1.00 equiv), CuI (0.03 equiv), $Pd(PPh_3)_2Cl_2$ (0.01 equiv), THF, 23 °C, 82%;[10] (b) $TMSC{\equiv}CH$ (1.40 equiv), $PrNH_2$ (4.00 equiv), CuI (0.20 equiv), $Pd(PPh_3)_4$ (0.05 equiv), Et_2O, 23 °C, 83%; (c) i CH_3SO_2Cl (1.10 equiv), NEt_3 (1.3 equiv), CH_2Cl_2, 0 °C ii xs N_2H_4, CH_3OH, 0 °C; (d) DEAD (1.10 equiv), Et_2O, 0 °C, 62%; (e) $HC{\equiv}CCH(CH_3)OH$ (0.20 equiv), $PrNH_2$ (1.00 equiv), CuI (0.03 equiv), $Pd(PPh_3)_2Cl_2$ (0.01 equiv), THF, 23 °C, 86%; (f) $TMSC{\equiv}CH$ (1.50 equiv), $PrNH_2$ (5.00 equiv), CuI (0.15 equiv), $Pd(PPh_3)_2Cl_2$ (0.05 equiv), THF, 23 °C, 81%; (g) MTAD (1.20 equiv), THF, 0 °C, 46%.



Scheme 2. Reagents and Conditions: (a) i BuLi (1.01 equiv), THF, –78 °C ii BF_3•OEt_2 (1.15 equiv) iii Ac_2O (1.50 equiv), 40%; (b) *(R)*-Alpine Borane® (1.00 equiv), THF, 23 °C, 89%; (c) i CH_3SO_2Cl (1.10 equiv), NEt_3 (1.3 equiv), CH_2Cl_2, 0 °C ii xs N_2H_4 , CH_3OH, 0 °C; (d) DEAD (1.10 equiv), Et_2O, 0 °C, 81%; (e) i BuLi (1.00 equiv), THF, –78 °C ii BF_3•OEt_2 (1.07 equiv) iii cyclohexene oxide (0.66 equiv), 82%;[11] (f) TBSCl (2.50 equiv), NEt_3 (3.00 equiv), DMAP (0.05 equiv), CH_2Cl_2, 23 °C, 85%; (g) CCl_3CO_2H (1.66 equiv), H_2O_2 (75.0 equiv), 1:1 CH_2Cl_2:*t*-BuOH, 23 °C, 74%;[12] (h) MTAD (1.20 equiv), THF, 0 °C, 70%; (i) $HC{\equiv}CCH_2OH$ (1.10 equiv), $PrNH_2$ (5.00 equiv), CuI (0.15 equiv), $Pd(PPh_3)_2Cl_2$ (0.05 equiv), THF, 23 °C, 89%; (j) MTAD (1.00 equiv), THF, –78 °C, 75%.

The successful preparation of the substituted allene **5** suggested that this method would be applicable to the synthesis of optically active allenes. This was demonstrated with the *(R)*-alcohol **17** (76 ± 2% ee),[13] obtained by reduction of the corresponding ketone (**16**) with *(R)*-Alpine Borane® (Scheme 2).[14] Conversion of **17** to the corresponding hydrazine, followed by oxidation with DEAD provided *(S)*-3-methyl phenylallene (**18**) ($[\alpha]_D^{21} = -176°$) in 81% yield.[15] ^{1}H NMR analysis of *(S)*-**18** in the presence of the chiral shift reagent combination Ag(fod)-Yb(hfc)$_3$ indicated the product to be of 75 ± 2% ee,[16] demonstrating that the overall transformation of the alcohol **17** to the allene **18** had proceeded with essentially complete stereospecificity. The generality of this method is further illustrated by the syntheses of the allene **23** (70%) and the allene **10** (75%).

Conclusions

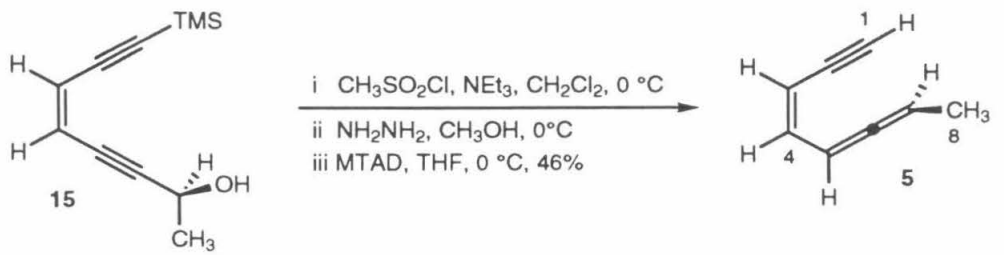
The oxidation of propargylic hydrazines by DEAD or MTAD has been demonstrated to be an efficient and general method for the stereospecific preparation of allenes under mild conditions. Of the two commercially available oxidants, DEAD is the less expensive; however, the use of this oxidant typically leads to the formation of a small amount (≤ 5%) of the carboethoxy transfer product. MTAD, which is a somewhat more efficient oxidant than DEAD and effects the oxidation of hydrazines at lower temperature, is the preferred oxidant in most cases. A structural and mechanistic study of a monoalkyl diazene intermediate in the transformation of **8** to **10** is described in the following chapter.

Experimental Section

General Procedures. All reactions were performed in flame-dried round-bottom or modified Schlenk (Kjeldahl shape) flasks fitted with rubber septa under a positive pressure of argon, unless otherwise noted. Air- and moisture-sensitive liquids and solutions were transferred via syringe or stainless steel cannula. Where necessary (so noted), reaction mixtures were degassed by evacuating for 10-15 seconds and flushing with argon (≥ 5 iterations). Organic solutions were concentrated by rotary evaporation at ≈ 25 Torr (water aspirator) at or slightly above ambient temperature, unless otherwise noted. Flash column chromatography was performed as described by Still *et al.*,[17] employing 230-400 mesh silica gel. Analytical and preparative thin-layer chromatography were performed using glass plates pre-coated with 0.25 mm 230-400 mesh silica gel impregnated with a fluorescent indicator (254 nm). Thin-layer chromatography plates were visualized by exposure to ultraviolet light (noted as 'UV') and/or by exposure to an acidic solution of *p*-anisaldehyde in ethanol followed by heating on a hot-plate (noted as 'anisaldehyde').

Materials. Commercially available reagents were used as received, with the following exceptions. Ethyl ether and tetrahydrofuran were distilled from sodium benzophenone ketyl. Benzene and toluene were distilled from sodium metal. Methylene chloride, triethylamine, and propylamine were distilled from calcium hydride. Methanol was distilled from magnesium turnings and was stored over 4 Å molecular sieves. *N,N*-Dimethylformamide and hexamethylphosphoramide were distilled from calcium sulfate at reduced pressure and were stored over 4 Å molecular sieves. Methanesulfonyl chloride was distilled from phosphorus pentoxide at atmospheric pressure. Copper(I) iodide was purified by continuos extraction (24 hours) with tetrahydrofuran in a Soxhlet apparatus. The molarity of butyllithium solutions was determined by titration using diphenylacetic acid as an indicator (average of three determinations).[18]

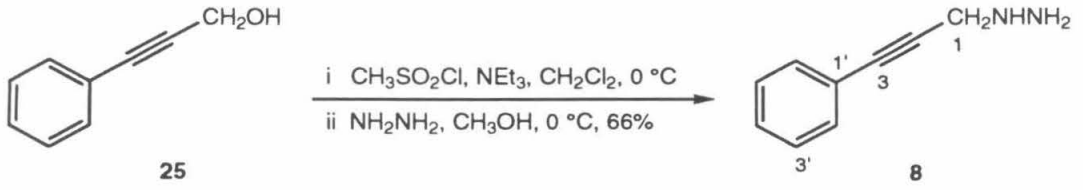
Instrumentation. Infrared spectra were obtained using a Perkin-Elmer 1600 FT-IR spectrophotometer referenced to a polystyrene standard. Data are presented as follows: frequency of absorption (cm^{-1}), intensity of absorption (s = strong, m = medium, w = weak, br = broad). ^{1}H NMR and ^{13}C NMR spectra were obtained on a JEOL GX-400 (9.40 Tesla) spectrometer; chemical shifts are expressed in parts per million. ^{1}H NMR chemical shifts are referenced to the signal for residual hydrogen in the NMR solvent ($CHCl_3$: δ 7.26, C_6D_5H: δ 7.15, $CHDCl_2$: δ 5.32, THF-d_7: δ 1.73, 3.58). Data are presented as follows: chemical shift, multiplicity, (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), integration, coupling constant in Hertz, and assignment (where possible). ^{13}C NMR chemical shifts are referenced to the carbon signal for the solvent ($CDCl_3$: δ 77.0, C_6D_6: δ 128.0, CD_2Cl_2: δ 53.8, THF-d_8: δ 25.3, 67.4). Data are presented as follows: chemical shift, and assignment (where possible). Optical rotation data were acquired on a Jasco DIP-181 Optical Polarimeter. Mass spectrometry was performed at the University of California at Riverside, Riverside Mass Spectrometry Facility, or at the Midwest Center for Mass Spectrometry at the University of Nebraska–Lincoln (with partial support by the National Science Foundation, Biology Division; Grant No. DIR9017262).



Allene **5**.

Methanesulfonyl chloride (0.280 ml, 3.65 mmol, 3.00 equiv) was added dropwise to a solution of triethylamine (0.850 ml, 6.09 mmol, 5.00 equiv) and the enediyne **15** (0.233 g, 1.22 mmol, 1 equiv) in methylene chloride (5 ml) at 0 °C. After stirring for 20 minutes, hydrazine (5.90 ml, 183 mmol, 150 equiv, 50% v/v in methanol, precooled to 0 °C) was added via cannula and the reaction mixture was stirred at 0 °C for 23 hours. The reaction mixture was poured into saturated aqueous sodium bicarbonate (30 ml) and the aqueous phase was washed with 10% methanol-methylene chloride (2x40 ml). The combined organic fractions were washed with water (5 ml), were dried, and were concentrated. A solution of 4-methyl triazolinedione (0.166 g, 1.46 mmol, 1.20 equiv) in tetrahydrofuran (10 ml) was added to a solution of the crude hydrazine in tetrahydrofuran (10 ml) at 0 °C. After the subsequent gas evolution had subsided, the reaction mixture was poured into half-saturated aqueous sodium bicarbonate (10 ml), and the aqueous phase was washed with pentane (25 ml). The organic phase was dried over sodium sulfate and was concentrated to ≈ 4 ml. Purification by flash column chromatography (100% pentane) followed by concentration of the desired fractions at –23 °C under reduced pressure (≈ 200 mm Hg) provided a mixture of pentane and the allene **5** (0.115 g, 2:3 **5**:pentane by ^{1}H NMR analysis; 0.054 g **5**, 46%).

^1H *NMR (400 MHz, $CDCl_3$)*, δ:	6.62 (ddq, 1H, *J* = 10.3, 6.4, 3.2 Hz, H5), 6.18 (dd, 1H, *J* = 10.5, 10.3 Hz, H4), 5.15 (dd, 1H, *J* = 10.5, 2.4 Hz, H3), 5.07 (qd, 1H, *J* = 7.1, 6.4 Hz, H7), 2.86 (d, 1H, *J* = 2.4 Hz, H1), 1.37 (dd, 3H, *J* = 7.1, 3.2 Hz, H8).
HRMS (EI):	Calcd for $C_{10}H_{15}O_2$ (M^+): 105.0705. Found: 105.0705.
TLC (100% Hexanes), R_f:	0.50 (UV).



25 8

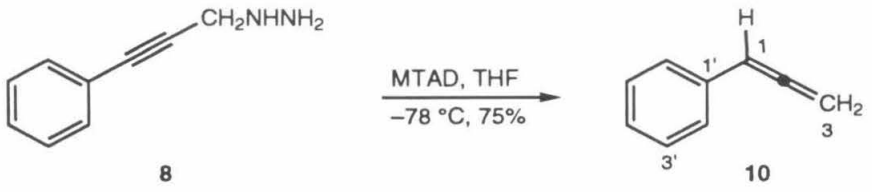
Hydrazine **8**.

Methanesulfonyl chloride (1.08 ml, 13.6 mmol, 1.10 equiv) was added dropwise over 2 minutes to a solution of the alcohol **25** (1.64 g, 12.9 mmol, 1.00 equiv) and triethylamine (2.25 ml, 16.11 mmol, 1.3 equiv) in methylene chloride (20 ml) at 0 °C. After 10 minutes, hydrazine (11.00 ml, 372 mmol, 30.0 equiv, 50% v/v in methanol, precooled to 0 °C) was added, and stirring was continued for 12 hours. The opaque yellow solution was poured into saturated ammonium chloride (50 ml), and the aqueous phase was extracted with 10% methanol-methylene chloride (4x30 ml). The combined organic fractions were washed with water (1x20 ml), were dried over sodium sulfate, and were concentrated to provide crude **8** (1.77 g, 98%) as a yellow oil. Purification by bulb-to-bulb distillation at reduced pressure (22 mTorr) afforded pure **8** (1.19 g, 66%) as a colorless oil.

^{1}H NMR (400 MHz, C_6D_6), δ: 7.55-7.65 (m, 2H), 7.10-7.20 (m, 3H), 3.53 (s, 2H, H1), 3.07 (br s, 3H, hydrazine NH).

^{13}C NMR (100 MHz, C_6D_6), δ: 137.3 (C3'), 128.9 (C2'), 128.6 (C4'), 124.2 (C1'), 88.0 (C3), 84.4 (C2), 45.5 (C1).

FTIR (neat), cm^{-1}:	3386 (w, br), 3242 (w, br), 3056 (w), 2985 (w), 2935 (w), 2910 (w), 2845 (w), 1490 (m), 758 (s), 692 (s).
MS (EI), m/z (%base):	146 (25), 145 (50), 116 (25), 115 (100).
HRMS (EI):	Calcd for $C_9H_{10}N_2$ (M^+): 146.0832. Found: 146.0844.
TLC (50% EtOAc in Hexanes), R_f:	0.10

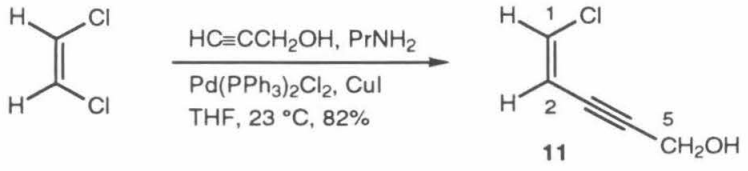


8 10

Phenylallene, **10**.

4-Methyl triazolinedione (0.010 g, 0.09 mmol, 1.00 equiv) was added to a solution of hydrazine **8** (0.012 g, 0.09 mmol, 1 equiv) in tetrahydrofuran (1 ml) at –78 °C, and gas evolution ensued. After stirring for 5 minutes, the reaction was diluted with pentane (5 ml), was warmed to 23 °C, and was extracted with saturated aqueous ammonium chloride (5 ml). The organic phase was dried over sodium sulfate, was partially concentrated, and was purified by flash column chromatography (100% pentane) to provide allene **8** (0.008 g, 75%) as a volatile colorless oil.

^{1}H NMR (400 MHz, THF-d_8), δ:	6.95-7.25 (m, 5H), 6.03 (t, 1H, J = 6.8 Hz, H1), 4.84 (d, 2H, J = 6.8 Hz, H3).
^{13}C NMR (100 MHz, THF-d_8), δ:	210.6 (C2), 134.8 (C1'), 129.2 (C4'), 127.5, 127.4 (C2', C3'), 94.4 (C1), 88.9 (C3).
FTIR (neat), cm^{-1}:	3081 (m), 3061 (m), 3031 (m), 2979 (w), 1942 (s), 1494 (s), 1458 (s), 853 (s), 761 (s), 694 (s).
MS (EI), m/z (%base):	116 (80), 115 (100), 89 (12), 63 (11), 42 (10).
TLC (100% Hexanes), R_f:	0.55 (UV).



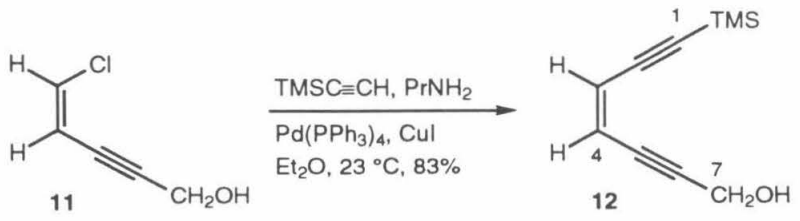
11

Enyne **11**.

Copper(I) iodide (2.55 g, 13.4 mmol, 0.15 equiv) was added to a degassed solution of propylamine (29.00 ml, 356 mmol, 4.00 equiv) and propargyl alcohol (5.00 g, 89.0 mmol, 1 equiv) in tetrahydrofuran (30 ml) at –78 °C, and the resulting suspension was degassed and was warmed to 0 °C. A degassed suspension of bis(triphenylphosphine)palladium(II) chloride (3.12 g, 4.50 mmol, 0.05 equiv) and dichloroethylene (13.70 ml, 178 mmol, 2.00 equiv) in tetrahydrofuran (20 ml) was added via cannula to the acetylide solution, and the reaction mixture was allowed to warm to 23 °C. After stirring for 14 hours, a solution comprising equal parts saturated aqueous potassium carbonate and saturated aqueous ammonium chloride (100 ml) was added, and the biphasic mixture was stirred vigorously for 45 minutes. The phases were separated, and the aqueous phase was washed with methylene chloride (100 ml). The combined organic fractions were dried over sodium sulfate and were concentrated. Purification of the residue by flash column chromatography (15% ethyl acetate-hexanes) provided the enyne **11** (8.52 g, 82%) as a light yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$), δ: 6.40 (d, 1H, J = 7.3 Hz, H1), 5.91 (dt, 1H, J = 7.3, 2.0 Hz, H2), 4.46 (d, 2H, J = 2.0 Hz, H5).

FTIR (neat), cm^{-1}:	3346 (m, br), 3087 (m), 2917 (m), 2865 (m), 2209 (w), 1592 (s), 1331 (s), 1126 (s), 1015 (s), 849 (s), 725 (s).
TLC (20% Ethyl Acetate-Hexanes), R_f:	0.30 (UV, anisaldehyde).



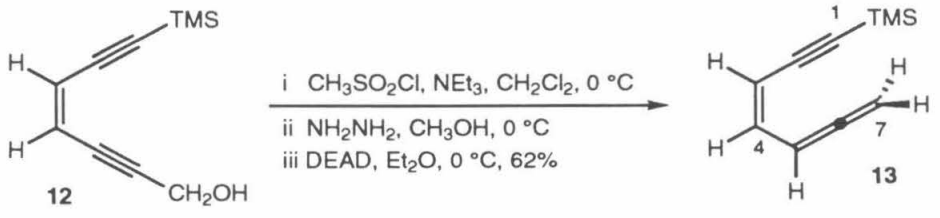
Enediyne **12.**

Copper(I) iodide (0.740 g, 3.89 mmol, 0.20 equiv) was added to a degassed solution of propylamine (6.40 ml, 74.0 mmol, 4.00 equiv) and trimethylsilylacetylene (3.85 ml, 27.2 mmol, 1.40 equiv) in diethyl ether (45 ml) at –78 °C, and the resulting suspension was degassed and was warmed to 0 °C. A degassed solution of tetrakis-(triphenylphosphine)palladium(0) (1.13 g, 0.98 mmol, 0.05 equiv) and the enyne **11** (2.26 g, 19.0 mmol, 1 equiv) was added via cannula to the acetylide solution, and the reaction mixture was allowed to warm to 23 °C. After stirring for 1 hour, a solution comprising equal parts saturated aqueous potassium carbonate and saturated aqueous ammonium chloride (150 ml) was added, and the biphasic mixture was stirred vigorously for 45 minutes. The phases were separated, and the aqueous phase was washed with diethyl ether (100 ml). The combined organic fractions were dried over sodium sulfate and were concentrated. Purification of the residue by flash column chromatography (15% ethyl acetate-hexanes) provided the enediyne **12** (2.87 g, 83%) as a light yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$), δ: 5.86 (s, 2H, H3, H4), 4.47 (d, 2H, J = 5.4 Hz, H7), 1.66 (t, 1H, J = 5.4 Hz, alcohol OH), 0.22 (s, 9H, $Si(CH_3)_3$).

FTIR (neat), cm^{-1}: 3353 (m, br), 3048 (m), 2960 (s), 2144 (s), 1574 (w), 1331 (s), 1251 (s), 1134 (s), 1027 (s), 843 (s), 759 (s).

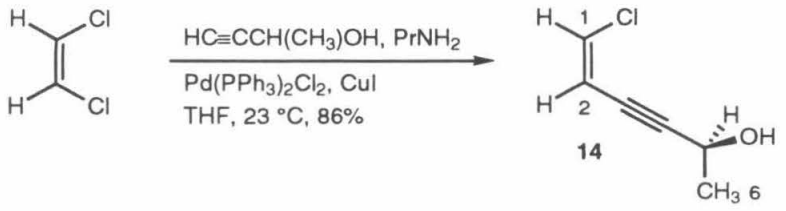
TLC (20% Ethyl Acetate-Hexanes), R_f: 0.38 (UV, anisaldehyde).



Allene **13**.

Methanesulfonyl chloride (0.061 ml, 0.79 mmol, 3.00 equiv) was added dropwise to a solution of triethylamine (0.365 ml, 2.62 mmol, 10.0 equiv) and the enediyne **12** (0.47g, 0.26 mmol, 1 equiv) in methylene chloride (2 ml). After stirring for 20 minutes, a cold (0 °C) solution of hydrazine (0.847 ml, 26.2 mmol, 100 equiv) in methanol (2 ml) was added via cannula, and the mixture was stirred at 0 °C for 14 hours. The reaction mixture was poured into saturated aqueous sodium chloride (25 ml), the aqueous phase was washed with 50% ethyl acetate-hexanes (2x25 ml), and the combined organic fractions were washed with water (5 ml), were dried over sodium sulfate, and were concentrated. Diethyl azodicarboxylate (0.046 ml, 0.29 mmol, 1.10 equiv) was added to a solution of the crude hydrazine in diethyl ether (2 ml) at 0 °C, and the reaction mixture was stirred under gas evolution had subsided. The crude reaction mixture was chromatographed directly (100% pentane), and the desired fractions were concentrated under reduced pressure (≈ 200 mm Hg) at –23 °C to afford a mixture of the allene **13** and pentane (0.028 g, 7:1 **13**:pentane by ^{1}H NMR analysis; 0.023 g **13**, 62%).

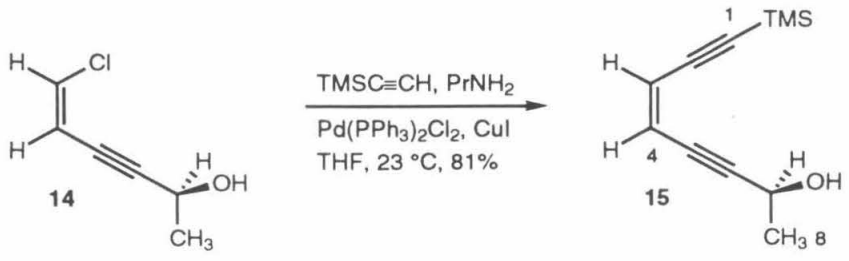
^1H *NMR (400 MHz, $CDCl_3$)*, δ:	6.74 (dt, 1H, J = 11.0, 6.6 Hz, H5), 6.13 (dd, 1H, J = 11.5, 11.0 Hz, H4), 5.27 (d, 1H, J = 11.5 Hz, H3), 4.63 (d, 2H, J = 6.6 Hz, H7), 0.15 (s, 9H, $Si(CH_3)_3$).
FTIR (neat), cm^{-1}:	2960 (s), 2146 (s), 1934 (s), 1710 (w), 1251 (s), 981 (s), 845 (s), 761 (s).
TLC (100% Hexanes), R_f:	0.55 (UV).



Enyne **14**.

Copper(I) iodide (0.827 g, 4.34 mmol, 0.15 equiv) was added to a degassed solution of propylamine (12.00 ml, 145 mmol, 5.00 equiv) and 3-butyn-2-ol (2.00 g, 29.0 mmol, 1 equiv) in diethyl ether (25 ml) at –78 °C, and the resulting suspension was degassed and was warmed to 0 °C. A degassed suspension of dichloroethylene (11.18 ml, 145 mmol, 5.00 equiv) and bis(triphenylphosphine)palladium(II) chloride (1.020 g, 1.45 mmol, 0.05 equiv) was added via cannula to the acetylide solution, and the reaction mixture was warmed to 23 °C. After 13 hours, saturated aqueous sodium bicarbonate (20 ml) and saturated aqueous ammonium chloride (10 ml) were added, and the mixture was stirred vigorously for 45 minutes. The phases were separated, the aqueous phase was washed with 30% ethyl acetate-hexanes (2x30 ml), and the combined organic fractions were dried over sodium sulfate and were concentrated. The residue was dissolved in diethyl ether (20 ml), and the solution was filtered to remove the insoluble palladium salts. Concentration of the solution and purification of the residue by flash column chromatography (100% methylene chloride) provided the enyne **14** (3.24 g, 86%) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$), δ:	6.35 (d, 1H, J = 7.7 Hz, H1), 5.85 (dd, 1H, J = 7.7, 1.7 Hz, H2), 4.68 (qd, 1H, J = 6.8, 1.7, H5), 2.65 (br s, 1H, alcohol OH), 1.47 (d, 3H, J = 6.8 Hz, H6).
^{13}C NMR (100 MHz, $CDCl_3$), δ:	128.6 (C1), 111.5 (C2), 99.3 (C3), 77.7 (C4), 58.7 (C5), 24.0 (C6).
FTIR (neat), cm^{-1}:	3354 (s, br), 3086 (w), 3028 (w), 2984 (m), 2933 (w), 2901 (w), 1632 (w), 1590 (m), 1329 (s), 1145 (s), 1078 (s), 725 (s).
MS (EI), m/z (%base):	130 (14), 117 (29), 115 (100), 95 (58), 87 (34).
HRMS (EI):	Calcd for C_6H_7ClO (M^+): 130.0174. Found: 130.0185.
TLC (15% Ethyl Acetate-Hexanes), R_f:	0.35 (UV, anisaldehyde).

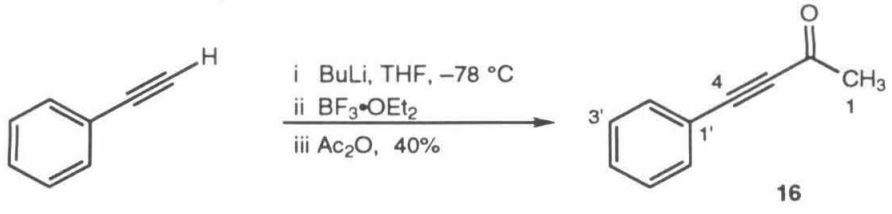


Enediyne **15**.

Copper(I) iodide (0.309 g, 1.62 mmol, 0.15 equiv) was added to a degassed solution of propylamine (4.43 ml, 54.0 mmol, 5.00 equiv) and the enyne **14** (1.40 g, 10.8 mmol, 1 equiv) in tetrahydrofuran (10 ml) at –78 °C, and the resulting suspension was degassed and was warmed to 23 °C. A degassed suspension of bis(triphenylphosphine)-palladium(II) chloride (0.379 g, 0.54 mmol, 0.05 equiv) and trimethylsilylacetylene (2.30 ml, 16.2 mmol, 1.50 equiv) in tetrahydrofuran (10 ml) was added via cannula to the acetylide solution, and the reaction mixture was stirred at 23 °C for 2 hours. A solution comprising equal parts saturated aqueous potassium carbonate and saturated aqueous ammonium chloride (60 ml) was added, and the biphasic mixture was stirred vigorously for 30 minutes. The phases were separated, the aqueous phase was washed with 30% ethyl acetate-hexanes (3x40 ml), and the combined organic fractions were dried over sodium sulfate and were concentrated. Purification of the residue by flash column chromatography (15% ethyl acetate-hexanes) provided the enediyne **15** (1.66 g, 81%) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$), δ: 5.83 (s, 2H, H3, H4), 4.68 (q, 1H, J = 6.6 Hz, H7), 1.78 (br s, 1H, alcohol OH), 1.48 (d, 3H, J = 6.6 Hz, H8), 0.20 (s, 9H, $Si(CH_3)_3$).

^{13}C *NMR (100 MHz, $CDCl_3$)*, δ:	120.0, 199.9 (C3, C4), 103.1 (C2), 101.8 (C5), 99.2 (C3), 81.3 (C6), 58.8 (C7), 24.3 (C8), -0.2 ($Si(CH_3)_3$).
FTIR (neat), cm^{-1}:	3360 (m, br), 3046 (w), 2961 (m), 2899 (m), 2358 (w), 2213 (m), 1950 (w), 1881 (w), 1251 (s), 1150 (s), 1029 (s), 850 (s), 760 (s).
MS (EI), m/z (%base):	192 (28), 177 (39), 159 (43), 84 (35).
HRMS (EI):	Calcd for $C_{11}H_{16}OSi$ (M^+): 192.0974. Found: 192.0970.
TLC (20% Ethyl Acetate-Hexanes), R_f:	0.40 (UV, anisaldehyde).



16

Ketone **16.**

Butyllithium (2.50 M, 8.92 ml, 22.3 mmol, 1.01 equiv) was added dropwise to a solution of phenylacetylene (2.48 ml, 22.1 mmol, 1 equiv) in tetrahydrofuran (20 ml) at –78 °C. After stirring for 30 minutes, boron trifluoride etherate (3.12 ml, 25.4 mmol, 1.15 equiv) was added, and stirring was continued for 30 minutes. Acetic anhydride (3.12 ml, 33.1 mmol, 1.50 equiv) was added rapidly and the reaction mixture was allowed to stir for 1 hour at –78 °C. The reaction mixture was partitioned between half-saturated aqueous ammonium chloride (40 ml) and ethyl acetate (20 ml), and the organic phase was washed with water (10 ml), was dried over sodium sulfate, and was concentrated. Purification of the residue by flash column chromatography provided the ketone **16** (1.28 g, 40%) as a light orange oil.

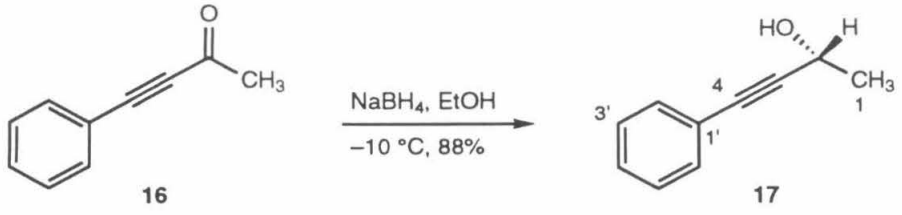
^{1}H NMR (400 MHz, $CDCl_3$), δ: 7.54 (d, 2H, J = 7.3 Hz, H2'), 7.43 (t, 1H, J = 7.6 Hz, H4'), 7.36 (t, 2H, J = 7.5 Hz, H3'), 2.43 (s, 3H, H1).

^{13}C NMR (100 MHz, $CDCl_3$), δ: 184.5 (C2), 133.0 (C2'), 130.7 (C4'), 128.6 (C3'), 119.9 (C1'), 90.2 (C3), 88.2 (C4), 32.7 (C1).

FTIR (neat), cm^{-1}: 3064 (w), 2201 (m), 1670 (s), 1489 (s), 1359 (s), 1279 (s), 1156 (s), 977 (s), 757 (s), 689 (s).

TLC (5% Ethyl Acetate-

Hexanes), R_f: 0.20 (UV, anisaldehyde).



16 17

Alcohol **17.**

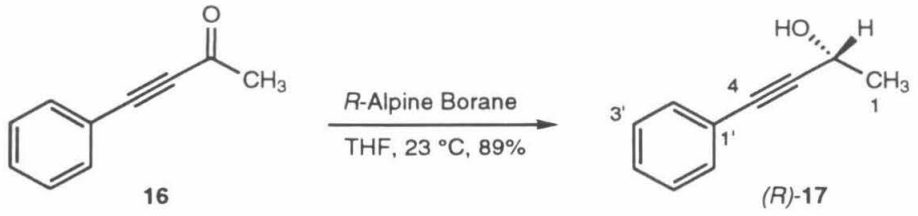
Sodium borohydride (0.180 g, 4.70 mmol, 5.00 equiv) was added in one portion to a solution of the ketone **16** in ethanol (5 ml) at –10 °C. After stirring for 3 hours, excess sodium borohydride was quenched by the slow addition of acetone (10 ml), and the reaction mixture was poured into saturated aqueous ammonium chloride (10 ml). The aqueous phase was washed with 50% ethyl acetate-hexanes (3x10 ml), and the combined organic fractions were dried over sodium sulfate and were concentrated. Purification of the residue by flash column chromatography (15% ethyl acetate-hexanes) produced the alcohol **17** (0.121 g, 88%) as a light yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$), δ: 7.35-7.45 (m, 2H), 7.20-7.35 (m, 3H), 4.75 (q, 1H, J = 6.5 Hz, H2), 2.77 (br s, 1H, alcohol OH), 1.54 (d, 3H, J = 6.5 H, H1).

^{13}C NMR (100 MHz, $CDCl_3$), δ: 131.5 (C2'), 128.2 (C4'), 128.1 (C3'), 122.5 (C1'), 91.0 (C3), 83.8 (C4), 58.6 (C2), 24.3 (C1).

FTIR (neat), cm^{-1}: 3288 (s), 2218 (m).

TLC (10% Ethyl Acetate-Hexanes), R_f: 0.10 (UV, anisaldehyde).



R-Alcohol **17**.

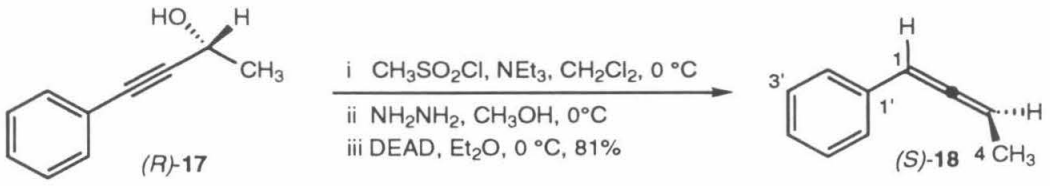
A solution of *(R)*-Alpine Borane® in tetrahydrofuran (0.50 M, 7.60 ml, 3.79 mmol, 1.00 equiv) was added to the ketone **16** at 23 °C, and the solution was stirred at 23 °C for 36 hours. Excess borane was quenched by the addition of acetaldehyde (0.5 ml), and stirring was continued for 1 hour. The reaction mixture was concentrated at reduced pressure, and the residue was purified by flash column chromatography (75% methylene chloride-hexanes) to provide the *(R)*-**17** (0.494 g, 89%) as a light yellow oil. The alcohol was determined to be of 78% ee by ^{1}H NMR analysis of the corresponding *(R)*-(α-methoxy-α-trifluoromethyl)phenylacetate, **19**.

^{1}H NMR (400 MHz, $CDCl_3$), δ: 7.35-7.45 (m, 2H), 7.20-7.35 (m, 3H), 4.75 (q, 1H, *J* = 6.5 Hz, H2), 2.77 (br s, 1H, alcohol OH), 1.54 (d, 3H, *J* = 6.5 H, H1).

^{13}C NMR (100 MHz, $CDCl_3$), δ: 131.5 (C2'), 128.2 (C4'), 128.1 (C3'), 122.5 (C1'), 91.0 (C3), 83.8 (C4), 58.6 (C2), 24.3 (C1).

FTIR (neat), cm^{-1}: 3288 (s), 2218 (m).

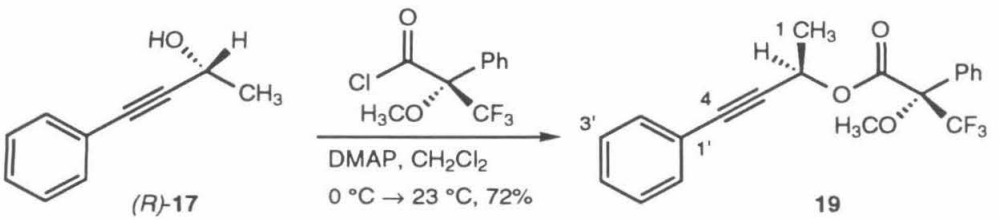
TLC (10% Ethyl Acetate-Hexanes), R_f: 0.10 (UV, anisaldehyde).



(S)-3-Methyl Phenylallene, **18**.

Methanesulfonyl chloride (0.714 ml, 9.22 mmol, 1.10 equiv) was added dropwise over 2 minutes to a solution of triethylamine (1.75 ml, 12.6 mmol, 1.50 equiv) and *(R)*-**17** (1.2225 g, 8.38 mmol, 1 equiv, 78% ee) in methylene chloride (15 ml) at 0 °C. After 15 minutes, hydrazine (14.93 ml, 50.3 mmol, 60.0 equiv, 50% v/v in methanol, precooled to 0 °C) was added via cannula over 5 minutes. After stirring for 12 hours, the reaction mixture was partition between half-saturated ammonium chloride (60 ml) and 5% methanol-methylene chloride (60 ml), and the aqueous phase was washed with 5% methanol-methylene chloride (1x25 ml). The combined organic fractions were washed with water (5 ml), were dried, and were concentrated. The residue was dissolved in diethyl ether (20 ml), was cooled to 0 °C, and diethyl azodicarboxylate (1.53 mmol, 9.22 mmol, 1.10 equiv) was added dropwise over 2 minutes. After gas evolution had subsided, the reaction mixture was partitioned between pentane (10 ml) and saturated aqueous sodium chloride (15 ml). The organic phase was dried over sodium sulfate and was concentrated to ≈ 5 ml under reduced pressure. Purification by flash column chromatography (100% pentane) afforded provided *(S)*-**18** (0.887 g, 81%) as a volatile colorless liquid. ^{1}H NMR analysis of a solution of **18** (1 equiv) in deuteriochloroform in the presence of the shift reagents Yb(hfc)$_3$ (1.50 equiv) and Ag(fod) (2.00 equiv) indicated an enantiomeric excess of 75 ± 2%. Racemic **18** could be prepared from racemic **17** under conditions identical to those employed for *(S)*-**18**.

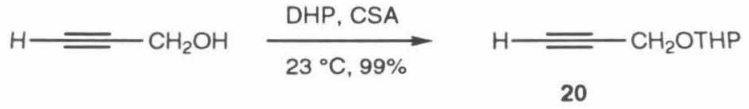
^{1}H NMR (400 MHz, $CDCl_3$), δ:	7.25-7.30 (m, 3H), 7.15-7.20 (m, 2H), 6.09 (dq, 1H, J = 6.3, 3.2 Hz, H1), 5.54 (qd, 1H, J = 7.3, 6.3 Hz, H3), 1.78 (dd, 3H, J = 7.3, 3.2 Hz, H4).
$[\alpha]_D^{21}$ (C = 1.21, acetone):	–176° ml/g•dm
FTIR (neat), cm^{-1}:	2357 (w), 1948 (w), 1723 (s), 1453 (m), 1267 (m).
TLC (100% Hexanes), R_f:	0.60 (UV, anisaldehyde).



Ester **19**.

Oxalyl chloride (0.890 ml, 10.2 mmol, 30.0 equiv) was added dropwise to a solution of *(R)*-(α-methoxy-α-trifluoromethyl)phenylacetic acid (0.478 g, 2.04 mmol, 6.00 equiv) and *N,N*-dimethylformamide (0.030 ml) in benzene (3 ml) at 0 °C. After stirring for 45 minutes at 0 °C, the reaction mixture was cooled to –14 °C and was concentrated under reduced pressure. The residue was dissolved in methylene chloride (4 ml) and the solution was transferred away from the remaining insoluble material via cannula. This solution was added to a solution of 4-dimethylaminopyridine (0.291 g, 2.38 mmol, 7.00 equiv) and *(R)*-**17** (0.050 g, 0.34 mmol, 1 equiv) in methylene chloride (4 ml) at 0 °C. The reaction mixture was allowed to warm to 23 °C and was stirred for 3 hours. Excess acyl chloride was quenched by the addition of saturated aqueous ammonium chloride (10 ml), the aqueous phase was washed with methylene chloride (5 ml), and the combined organic fractions were dried over sodium sulfate and were concentrated. Purification of the residue by flash column chromatography (100% methylene chloride) provided the ester **19** (0.089 g, 72%) as a colorless oil. ^{1}H NMR analysis of **19** indicated an enantiomeric excess of 76 ± 2%. Samples of **19** racemic at C2 could be prepared from racemic **17** under the conditions identical to those employed for **19**.

^{1}H NMR (400 MHz, $CDCl_3$), δ:	Racemic at C2; 7.20-7.65 (m, 10 H), 5.91 (q, 1H, J = 6.7 Hz, H2), 5.88 (q, 1H, J = 6.7 Hz, H2), 3.62 (s, 3H, OCH_3), 3.60 (s, 3H, OCH_3), 1.67 (d, 3H, J = 6.7 Hz, H1), 1.61 (d, 3H, J = 6.7 Hz, H1).
FTIR (neat), cm^{-1}:	2924 (s), 2851 (s), 2359 (w), 2234 (s), 1752 (s), 1169 (s).
MS (EI), m/z (%base):	362 (2), 190 (11), 189 (100), 129 (80), 128 (32), 127 (17), 105 (32).
HRMS (EI):	Calcd for $C_{20}H_{17}F_3O_3(M^+)$: 362.1110. Found: 362.1130.
TLC (10% Ethyl Acetate-Hexanes), R_f:	0.42 (UV, anisaldehyde).



20

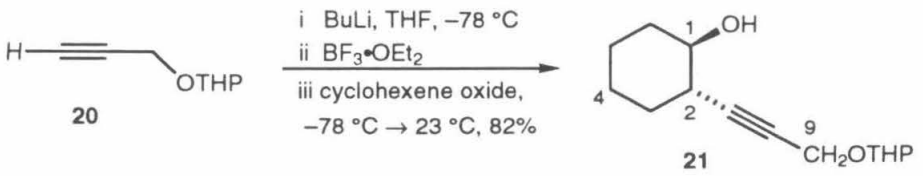
Ether **20.**

Camphorsulfonic acid (0.008 g, 0.03 mmol, 0.01 equiv) was added to a mixture of dihydropyran (2.90 g, 34.4 mmol, 1.00 equiv) and propargyl alcohol (2.00 g, 34.4 mmol, 1 equiv) at 0 °C, and the reaction mixture was allowed to warm to 23 °C. After stirring for 6 hours, the crude reaction mixture was purified by flash column chromatography (10% ethyl acetate-hexanes), providing the tetrahydropyranyl ether **20** (4.85 g, 99%) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$), δ: 4.79 (t, 1H, J = 3.4 Hz, THP), 4.27 (dd, 1H, J = 15.6, 2.5 Hz, H1), 4.20 (dd, 1H, J = 15.6, 2.5 Hz, H1), 3.75-3.85 (m, 1H), 3.40-3.50 (m, 1H), 2.40 (t, 1H, J = 2.5 Hz, H3), 1.40-1.85 (m, 6H).

FTIR (neat), cm^{-1}: 3292 (s), 2944 (s), 2871 (s), 2117 (w), 1441 (m), 1202, (m), 1120 (s), 1029 (s), 902 (m).

TLC (20% Ethyl Acetate-Hexanes), R_f: 0.55 (anisaldehyde).

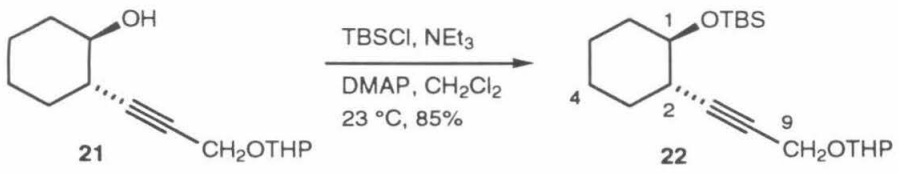


Cyclohexanol **21**.

Butyllithium (2.50 M, 3.00 ml, 7.50 mmol, 1.50 equiv) was added dropwise to a solution of the tetrahydropyranyl ether **20** (1.05 g, 7.50 mmol, 1.50 equiv) in tetrahydrofuran (10 ml) at –78 °C. The solution was stirred for 15 minutes, and boron trifluoride etherate (1.00 ml, 8.10 mmol, 1.60 equiv) was added over 2 minutes. After stirring the heterogenous reaction mixture for 15 minutes, a solution of cyclohexene oxide (0.34 ml, 5.00 mmol, 1 equiv) in tetrahydrofuran (5 ml) was added over 5 minutes and stirring was continued at –78 °C for 45 minutes. Excess acetylide was quenched by the addition of saturated aqueous ammonium chloride (5 ml) and the reaction mixture was allowed to warm to 23 °C. The mixture was partitioned between water (15 ml) and ethyl acetate (15 ml), the aqueous phase was washed with ethyl acetate (3x15 ml), and the combined organic fractions were dried over sodium sulfate and were concentrated. Purification of the residue by flash column chromatography (20% ethyl acetate-hexanes) afforded the cyclohexanol **21** (0.97 g, 82%) as a light yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$), δ: 4.80 (t, 1H, J = 3.3 Hz, THP), 4.30 (d, 1H, J = 15.4 Hz, H9), 4.26 (d, 1H, J = 15.4 Hz, H9), 3.85-3.95 (m, 1H), 3.30-3.55 (m, 2H), 2.45 (br s, alcohol OH), 2.25-2.35 (m, 1H), 1.05-2.10 (m, 14H).

^{13}C NMR (*100 MHz*, $CDCl_3$), δ:	97.0, 87.5 (C7), 78.2 (C8), 73.4, 62.0, 54.7 (C9), 39.0, 33.0, 30.9, 25.3, 24.8, 24.2, 19.1.
FTIR (neat), cm^{-1}:	3430 (m, br), 2936 (s), 2859 (s), 2232 (s), 1450 (m), 1118 (s).
MS (FAB), m/z (%base):	239 (13), 120 (9), 107 (17), 91 (16), 85 (100).
HRMS (FAB):	Calcd for $C_{14}H_{23}O_3$ (M^+): 239.1659. Found: 239.1647.
TLC (20% Ethyl Acetate-Hexanes), R_f:	0.10 (anisaldehyde).

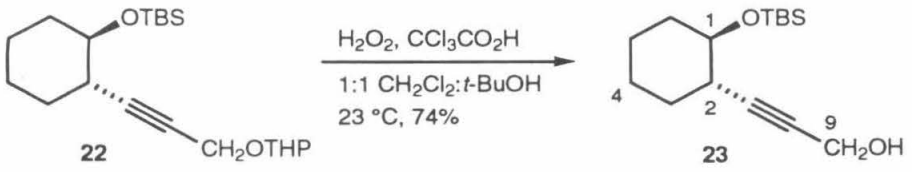


Ether **22**.

A powdered mixture of *tert*-butyldimethylsilyl chloride (0.582 g, 4.20 mmol, 2.50 equiv) and 4-dimethylaminopyridine (0.010 g, 0.08 mmol, 0.05 equiv) was added to a solution of triethylamine (0.700 ml, 5.04 mmol, 3.00 equiv) and the cyclohexanol **21** (0.400 g, 1.68 mmol, 1 equiv) in methylene chloride (5 ml) at 0 °C, and the reaction mixture was allowed to warm to 23 °C. After stirring for 23 hours, the mixture was poured into half-saturated aqueous ammonium chloride (5 ml) and methylene chloride (5 ml), and the aqueous phase was washed with methylene chloride (2x5 ml). The combined organic fractions were dried over sodium sulfate and were concentrated. Purification of the residue by flash column chromatography (2% ethyl acetate-hexanes) provided the ether **22** (0.486 g, 85%) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$), δ: 4.78 (d, 2H, = 3.2 Hz, THP), 4.27 (d, 1H, J = 15.1 Hz, H9), 4.19 (d, 1H, J = 15.1 Hz, H9), 3.85-3.95 (m, 1H), 3.45-4.60 (m, 2H), 2.25-2.35 (m, 1H), 1.15-2.00 (m, 14H), 0.86 (s, 9H, $Si(CH_3)_2$-$C(CH_3)_3$), 0.06 (s, 3H), 0.04 (s, 3H, $Si(CH_3)_2$-$C(CH_3)_3$).

^{13}C *NMR (100 MHz, $CDCl_3$)*, δ:	96.6, 89.1 (C7), 72.9 (C8), 61.9, 54.7 (C9), 37.6, 33.9, 30.3, 29.9, 25.8 ($Si(CH_3)_2C(\mathbf{C}H_3)_3$), 25.4, 24.0, 23.1, 19.1, 18.1, -4.6, -4.7 ($Si(\mathbf{C}H_3)_2$-$C(CH_3)_3$).
FTIR (neat), cm^{-1}:	3454 (m, br), 2929 (s), 2857 (m), 1101 (m), 1024 (m), 837 (m).
MS (FAB), m/z (%base):	351 (20), 295 (56), 269 (57), 251 (100), 211 (48), 195 (40), 159 (89), 119 (98).
HRMS (FAB):	Calcd for $C_{20}H_{35}O_3Si$ (M^+): 251.2336. Found: 251.2355.
TLC (20% Ethyl Acetate-Hexanes), R_f:	0.54 (anisaldehyde).

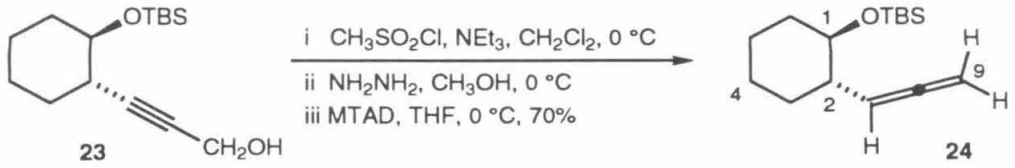


Alcohol **23**.

Hydrogen peroxide (70% w/w, 2.385 ml, 69.0 mmol, 75.0 equiv) was added to a solution of the ether **22** (0.315 g, 0.92 mmol, 1 equiv) in 1:1 methylene chloride:*tert*-butanol (5 ml) at 0 °C. Trichloroacetic acid (0.251 g, 1.54 mmol, 1.66 equiv) was added, and the solution was allowed to warm to 23 °C. After stirring for 12 hours, the reaction mixture was poured into saturated aqueous sodium chloride (15 ml) and the aqueous phase was washed with 50% ethyl acetate-hexanes (3x20 ml). Dimethyl sulfide (15 ml) was added to the organic combined organic fractions, and the solution was stirred for 12 hours, was dried over sodium sulfate, and was concentrated. Purification of the residue by flash column chromatography (10% ethyl acetate-hexanes) afforded the alcohol **23** (0.186 g, 74%) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$), δ: 4.78 (d, 2H, J = 3.2 Hz, H9), 3.45-3.60 (m, 1H, H1), 2.25-2.35 (m, 1H, H2), 1.75-2.00 (m, 2H), 1.50-1.70 (m, 3H), 1.10-1.45 (m, 3H), 0.86 (s, 9H, $Si(CH_3)_2C(C\mathbf{H}_3)_3$), 0.06 (s, 3H), 0.03 (s, 3H, $Si(C\mathbf{H}_3)_2C(CH_3)_3$).

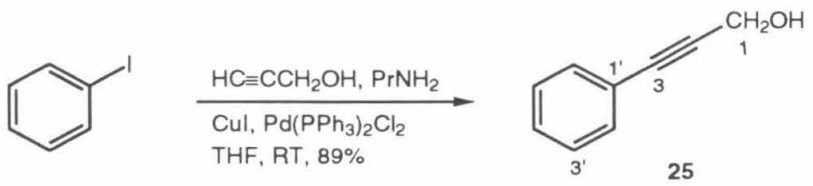
^{13}C NMR (*100* MHz, $CDCl_3$), δ:	89.1 (C7), 79.4 (C8), 73.0, 51.4 (C9), 37.7, 34.0, 30.0, 25.8 ($Si(CH_3)_2C(\mathbf{C}H_3)_3$), 24.0, 23.2, 18.1, -4.5, -4.7 ($Si(\mathbf{C}H_3)_2C(CH_3)_3$).
FTIR (neat), cm^{-1}:	3344 (m, br), 2933 (s), 2856 (s), 2233 (w), 1256 (s), 1100 (s), 839 (s), 778 (s).
MS (FAB), m/z (%base):	269 (100), 251 (32), 211 (93), 154 (90), 137 (89), 119 (71).
HRMS (FAB):	Calcd for $C_{15}H_{28}O_2Si$ (M^+): 269.1940. Found: 269.1937.
TLC (20% Ethyl Acetate-Hexanes), R_f:	0.35 (anisaldehyde).



Cyclohexyl Allene **24.**

Methanesulfonyl chloride (0.345 ml, 4.47 mmol, 3.00 equiv) was added dropwise over 2 minutes to a solution of triethylamine (1.04 ml, 7.45 mmol, 5.00 equiv) and the alcohol **23** (0.400 g, 1.49 mmol, 1 equiv) in methylene chloride (10 ml) at 0 °C. After stirring for 15 minutes, hydrazine (6.62 ml, 223 mmol, 150 equiv, 50% v/v in methanol, precooled to 0 °C) was added via cannula over 5 minutes and the cloudy solution was stirred for 8 hours. The reaction mixture was partitioned between saturated aqueous ammonium chloride (15 ml) and 5% methanol-methylene chloride (15 ml) and the aqueous phase was washed with 5% methanol-methylene chloride (2x5 ml). The combined organic fractions were washed with water (5 ml), were dried over sodium sulfate, and were concentrated. A solution of 4-methyl triazolinedione in tetrahydrofuran (0.44 M) was added dropwise to a solution of the the crude hydrazine in tetrahydrofuran (15 ml) at 0 °C until gas evolution had ceased and the pale pink color indicative of excess 4-methyl triazolinedione persisted. The reaction mixture was poured into saturated aqueous ammonium chloride (15 ml) and the aqueous phase was washed with hexanes (3x10 ml). The combined organic fraction were dried over sodium sulfate and were concentrated. Purification of the residue by flash column chromatography (100% hexanes) afforded the cyclohexyl allene **24** (0.248 g, 70%) as a slightly volatile colorless oil.

^1H NMR (*400 MHz*, $CDCl_3$), δ:	5.26 (dt, 1H, *J* = 6.5, 6.8 Hz, H7), 4.68 (dd, 1H, *J* = 6.8, 2.8 Hz, H7), 3.24 (ddd, 1H, *J* = 9.8, 9.2, 3.9 Hz, H1), 2.22-2.42 (m, 2H), 1.55-2.00 (m, 5H), 1.10-1.35 (m, 3H), 0.87 (s, 9H, $Si(CH_3)_2C(C\mathbf{H})_3$), 0.38 (s, 3H, $Si(C\mathbf{H}_3)_2C(CH)_3$), 0.31 (s, 3H, $Si(C\mathbf{H}_3)_2C(CH)_3$).
^{13}C NMR (100 MHz, $CDCl_3$), δ:	208.1 (C8), 93.4 (C7), 75.4, 75.2 (C9), 44.5 (C1), 35.8 (C2), 30.2 (C6), 25.9 ($Si(CH_3)_2C(\mathbf{C}H)_3$), 25.1, 24.6, 18.1 (C3, C4, C5), -4.1, -4.6 ($Si(\mathbf{C}H_3)_2C(CH)_3$).
FTIR (neat), cm^{-1}:	2935 (s), 2856 (s), 2353 (w), 2346 (w), 1957 (w), 1255 (m), 1096 (s), 835 (s), 773 (s)
MS (EI), m/z (%base):	252 (1), 197 (5), 196 (20), 195 (100), 194 (8), 127 (5), 119 (5), 75 (32).
HRMS (EI):	Calcd for $C_{15}H_{28}OSi$ (M^+): 252.1905. Found: 252.1909.
TLC (100% Hexanes), R_f:	0.20 (anisaldehyde).



25

Alcohol **25.**

Copper(I) iodide (0.56 g, 2.94 mmol, 0.15 equiv) was added to a degassed solution of propargyl alcohol (1.21 g, 21.6 mmol, 1.10 equiv) and propylamine (6.45 ml, 78.4 mmol, 4.00 equiv) in tetrahydrofuran (5 ml) at –78 °C, the suspension was degassed, and the mixture was warmed to 23 °C. A suspension of iodobenzene (4.00 g, 19.6 mmol, 1 equiv) and bis(triphenylphosphine)palladium(II) chloride (0.69 g, 0.98 mmol, 0.05 equiv) in tetrahydrofuran (10 ml) was degassed at –78 °C, was warmed to 23 °C, and was added via cannula to the acetylene solution. After stirring for 12 hours, the reaction mixture was poured into a solution comprising equal parts saturated aqueous ammonium chloride and saturated aqueous potassium carbonate (100 ml), and the biphasic solution was stirred for 30 minutes. The aqueous phase was extracted with 20% ethyl acetate-hexanes (3x50 ml), and the combined organic fractions were dried over sodium sulfate and were concentrated. Purification of the residue by flash column chromatography afforded the alcohol **25** (2.31 g, 89%) as a colorless oil.

^{1}H NMR (400 MHz, C_6D_6), δ: 7.30-7.40 (m, 2H), 7.15-7.25 (m, 3H), 4.43 (s, 2H, H1), 2.57 (br s, 1H, alcohol OH).

^{13}C NMR (100 MHz, C_6D_6), δ: 131.7 (C3'), 128.5 (C4'), 128.3 (C2'), 122.5 (C1'), 87.2 (C3), 85.7 (C2), 51.6 (C1).

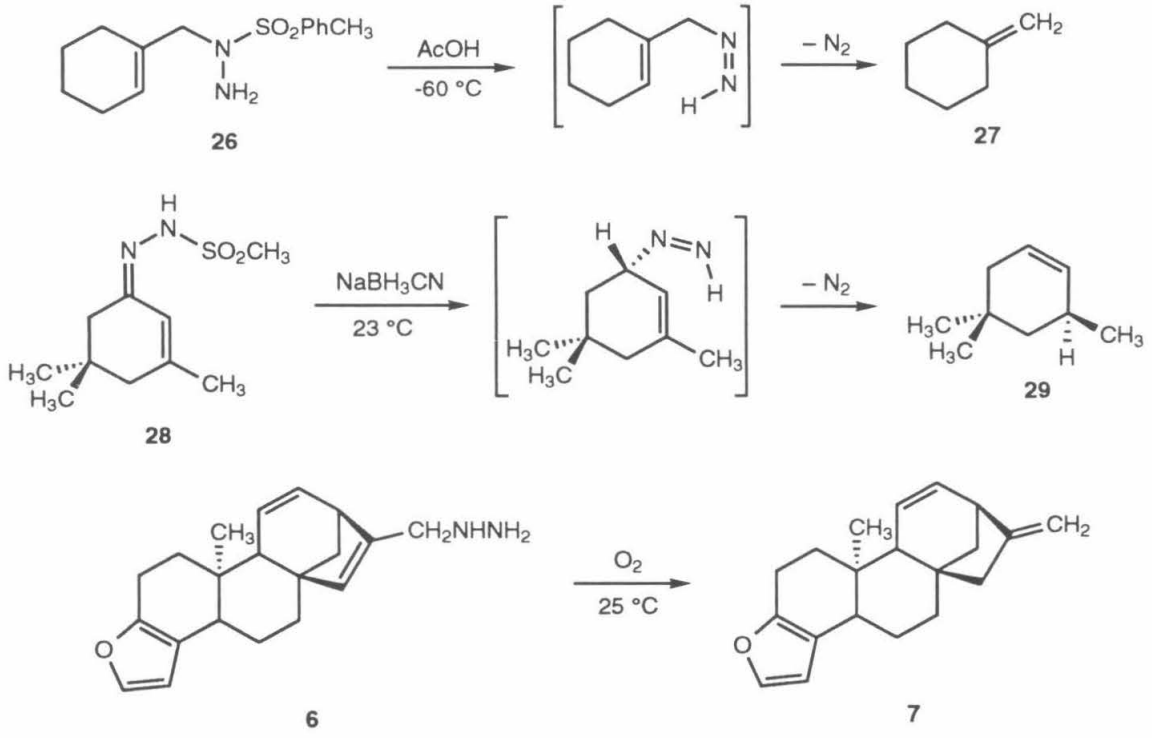
FTIR (neat), cm^{-1}:	3316 (s, br), 3060 (w), 2921 (w), 2839 (w), 2237 (w), 1489 (s), 1020 (s), 755 (s), 690 (s).
MS (EI), m/z (%base):	132 (68), 131 (100), 115 (24), 104 (24), 103 (39).
HRMS (EI):	Calcd for C_9H_8O (M^+): 132.0570. Found: 132.0575.
TLC (15% Ethyl Acetate-Hexanes), R_f:	0.15 (UV, anisaldehyde).

Chapter 2

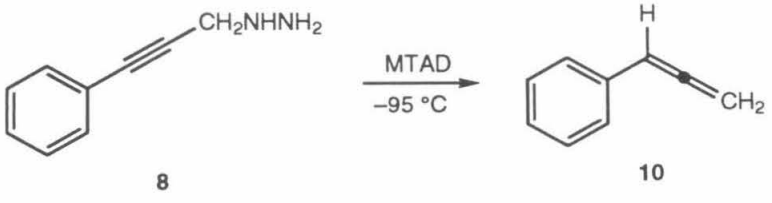
Structural and Mechanistic Studies of Monoalkyl Diazenes

Background and Introduction

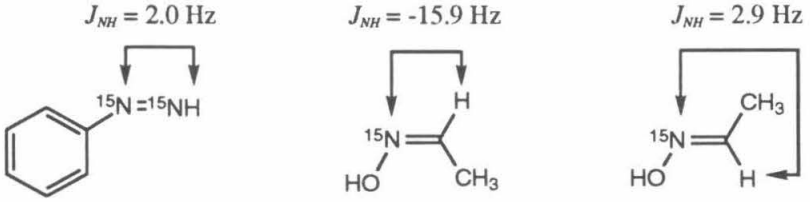
Allylic and propargylic monoalkyl diazenes are presumed to be intermediates in numerous organic transformations.[19,20] [3,3]-Sigmatropic extrusion of dinitrogen from these species has been invoked to explain alkene migration during acid treatment of tosylhydrazines (**26** → **27**)[19b] or during the reduction of α,β-unsaturated tosylhydrazones



(**28** → **29**).[19d,e] Rearrangement of an allylic diazene generated by air-oxidation of the corresponding allylic hydrazine has been exploited in the synthesis of a precursor to (±)-cafestol (**6** → **7**).[19f] A new method for hydrazine oxidation, the low temperature reaction with 4-methyl triazolinedione (MTAD), has recently been employed in the preparation of allenes under mild conditions (e.g., **8** → **10**).[20]



In contrast to allylic and propargylic diazenes, alkyl and aryl monoalkyl diazenes have been studied extensively. They have been characterized by UV and ^{1}H NMR spectroscopy, and are known to undergo bimolecular decomposition to produce dinitrogen and the corresponding hydrocarbon.[21] In analogy to *(E)*-diimide, which is calculated to be 5-7 kcal/mol more stable than *(Z)*-diimide,[22] and *(E)*-dialkyl diazenes, which are typically more stable than the *Z* isomers by 10-15 kcal/mol,[19h] it has generally been assumed that the *E* configuration of monoalkyl diazenes is more stable than the *Z* configuration. With one exception, all monoalkyl diazenes prepared in solution have been presumed to be the *E* isomers, as they were generated under conditions where proton transfer is rapid and the thermodynamically favored isomer should predominate. In addition, the long-wavelength UV spectral characteristics for those monoalkyl diazenes which have been characterized are quite similar to those for *(E)*-dialkyl diazenes and distinct from those for *(Z)*-dialkyl diazenes. In the only reported preparation of a *(Z)*-monoalkyl diazene [*(Z)*-phenyldiazene, *(Z)*-**31**],[23] the stereochemical determination was based on the ^{1}H NMR spectroscopic measurement of the two-bond coupling constant between the diazenyl proton and an ^{15}N label, employing the *(E)*- and *(Z)*-acetaldehyde oximes as stereochemical references.[24] In no case have both isomers of a monoalkyl diazene been observed simultaneously, and these stereochemical assignments cannot therefore be regarded as certain.[25]



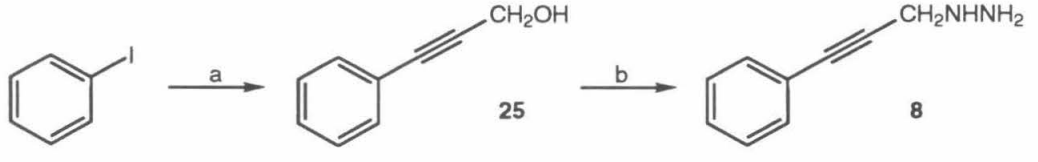
[$^{15}N_2$]-**31**

Despite the number of processes thought to involve unsaturated diazenes, they have not been characterized, and fundamental questions concerning their stereochemistry (*E* vs *Z*) and physical properties remain. The oxidation of hydrazines by MTAD has provided a convenient method for the generation of discrete monoalkyl diazenes under carefully

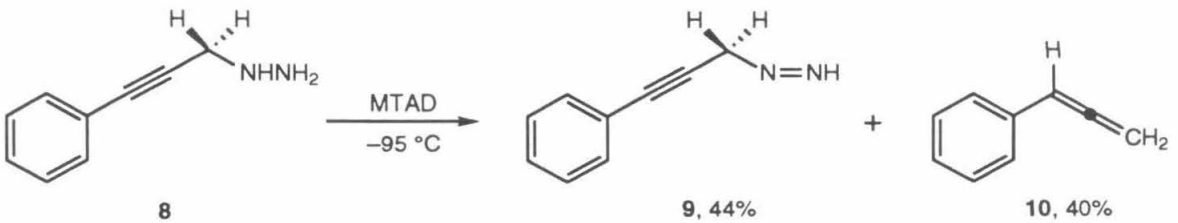
controlled conditions. With the goals of characterizing and exploring the reactivity of the intermediate diazene(s), we undertook a low-temperature ^{1}H NMR investigation of the oxidative transformation of the propargylic hydrazine **8** to phenylallene (**10**).

Preparation and Characterization of Monoalkyl Diazenes

(3-Phenyl-2-propynyl)hydrazine (**8**, Scheme 3) was selected as the first substrate for study because of its synthetic accessibility and the simplicity of the ^{1}H NMR spectrum of the oxidation product, phenylallene (**10**). A solution of **8** in tetrahydrofuran-d_8 was degassed and frozen in an NMR tube. Solid MTAD was added, and the NMR tube was sealed under vacuum. The sample was thawed, was gently agitated at –100 °C, and was loaded into the probe of a 400 MHz NMR spectrometer, precooled to –95 °C. The three products that were cleanly and reproducibly formed under these conditions are: 4-methyl urazole (85%), phenylallene **10** (44%), and the propargylic diazene **9** (40%, Figure 1). The latter compound was identified by the diagnostic monoalkyl diazene resonance (N=N**H**) at δ 15.9 ppm[26] and the readily observable coupling between the diazenyl proton and the propargylic methylene protons (J = 2.4 Hz). These products were stable at –95 °C, and their relative proportions did not vary appreciably between experiments. The same product distribution was observed when a frozen sample of the reaction mixture was thawed in the NMR probe at –105 °C, suggesting that the formation of multiple products was not a result of warming during the transfer of the sample. Upon warming to –75 °C, **9**



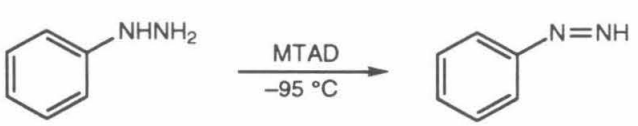
Scheme 3. Reagents and conditions: (a) $HC{\equiv}CCH_2OH$ (1.10 equiv), $CH_3(CH_2)_2NH_2$ (4.00 equiv), CuI (0.15 equiv), $Pd(PPh_3)_2Cl_2$ (0.05 equiv), THF, 89%; (b) i CH_3SO_2Cl (1.10 equiv), NEt_3 (1.20 equiv), 0 °C, CH_2Cl_2[8] ii xs N_2H_4, CH_3OH, 0 °C, 66%.



8 **9**, 44% **10**, 40%

underwent smooth first-order decomposition ($k = (8 \pm 2) \times 10^{-5}$ s^{-1}, $t_{1/2} \approx 2.5$ h) with concomitant formation of **10** ($k = (7 \pm 4) \times 10^{-5}$ s^{-1}). While the reaction was invariably first-order in **9**, the rate of reaction was reproducible only when great care was taken to exclude oxygen.

Adopting the hypothesis that *Z* stereochemistry is required of the diazene in the transition state for sigmatropic rearrangement, there are two plausible interpretations of these data. The first is that two distinct mechanistic pathways are operative under the reaction conditions, one that produces **10** directly from **8** and one that produces either *(E)*- or *(Z)*-**9**, which rearranges to form **10**. The alternative interpretation is that the oxidation initially produces an approximately equal mixture of *(E)*- and *(Z)*-**9**. The *Z* isomer so formed rearranges too rapidly to be detected, and the *E* isomer persists, undergoing thermal or base-catalyzed isomerization to the reactive *Z* isomer. Distinguishing between these two mechanisms required a method for assigning the stereochemistry of the diazene **9**.



30 **31**, 43%

As *(Z)*-phenyldiazene [*(Z)*-**31**] presumably cannot undergo sigmatropic rearrangement, it was hoped that the reaction of phenylhydrazine (**30**) with MTAD would provide insight into the immediate stereochemical outcome of the oxidation. When a sample of phenylhydrazine was oxidized under the conditions employed for the oxidation of **8**, a signal for the diazenyl proton of phenyldiazene (δ 16.1 ppm) was observed in the

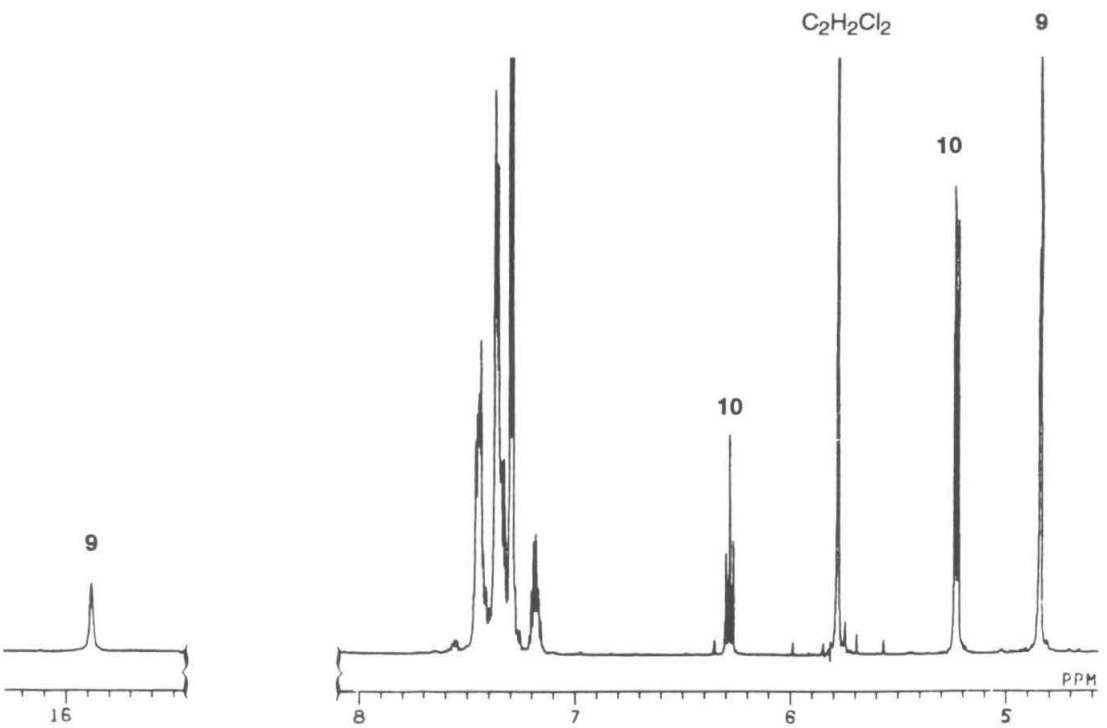


Figure 1. Oxidation of **8** by MTAD (^{1}H NMR, THF-d_8, –95 °C).

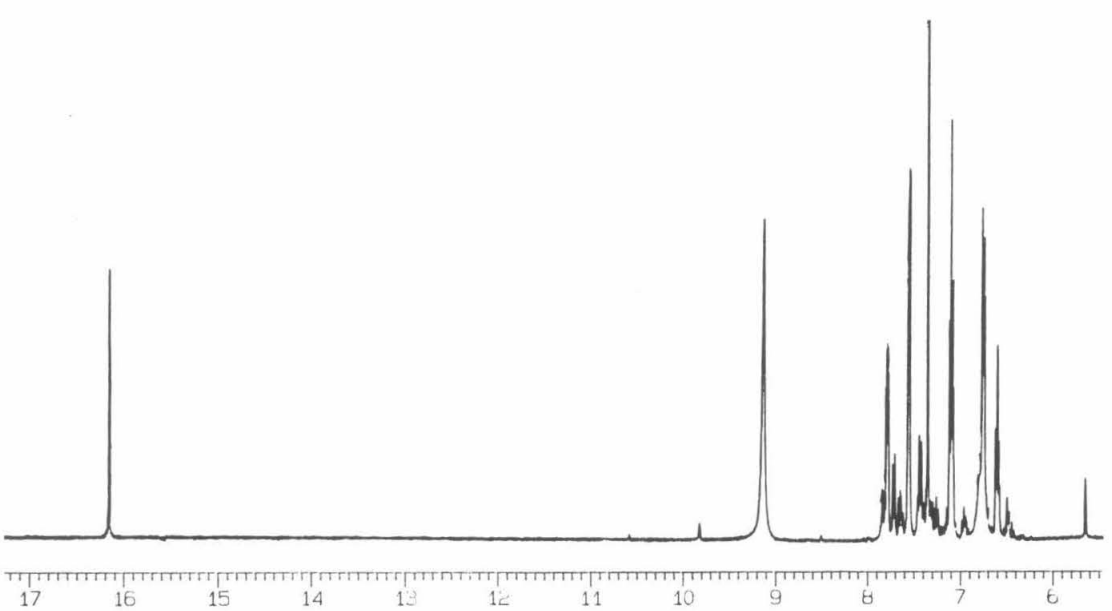
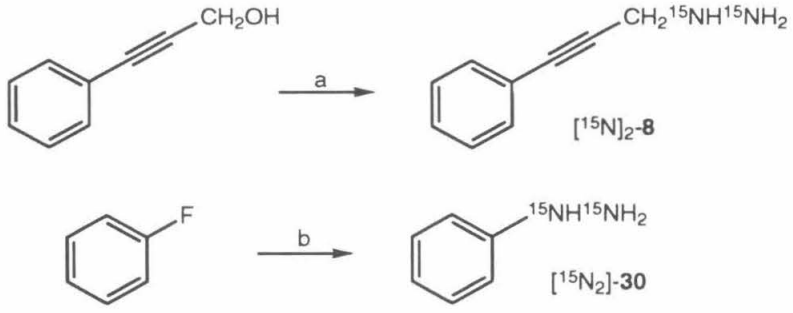


Figure 2. Oxidation of **30** by MTAD (^{1}H NMR, THF-d_8, –95 °C).

^{1}H NMR spectrum of the reaction mixture (Figure 2). However, phenyldiazene accounted for only 43% of the material formed; the balance of the material could not be identified on the basis of the ^{1}H NMR spectrum alone. While the generation of phenyldiazene did not clarify the issue of diazene stereochemistry, it expanded the scope of this oxidation and provided an additional substrate for stereochemical analysis.



Scheme 4. Reagents and Conditions: (a) i CH_3SO_2Cl (1.10 equiv), NEt_3 (1.20 equiv), 0 °C, CH_2Cl_2 ii $^{15}N_2H_4$•H_2SO_4 (10.0 equiv), CH_3ONa (20.0 equiv), CH_3OH, 0 °C, 43%; (b) $^{15}N_2H_4$•H_2SO_4 (0.10 equiv), KH (0.40 equiv), THF, 0 °C, 42%.

In view of the apparently successful use of the two-bond ^{15}N-^{1}H coupling constant to assign the stereochemistry of *(Z)*-**31**,[23] it was anticipated that similar measurements would elucidate the stereochemistry of **9** and **31**. After preparation of the labelled precursors, [$^{15}N_2$]-**8** and [$^{15}N_2$]-**30** (Scheme 4), these hydrazines were oxidized to the corresponding diazenes in analogy to the unlabelled compounds. In both cases, the ^{15}N-^{1}H coupling constants were virtually identical to those reported for *(Z)*-**31** (Table I), suggesting *Z* stereochemistry for both **9** and **31**. However, this method of stereochemical assignment presumed a strong correlation of oximes and diazenes, and the obvious structural differences between these classes of molecules made their direct comparison questionable. Further, the reported UV spectroscopic data for *(Z)*-**31** were inconsistent with *Z* stereochemistry, and the development of an alternative method to rigorously establish monoalkyl diazene stereochemistry was undertaken.

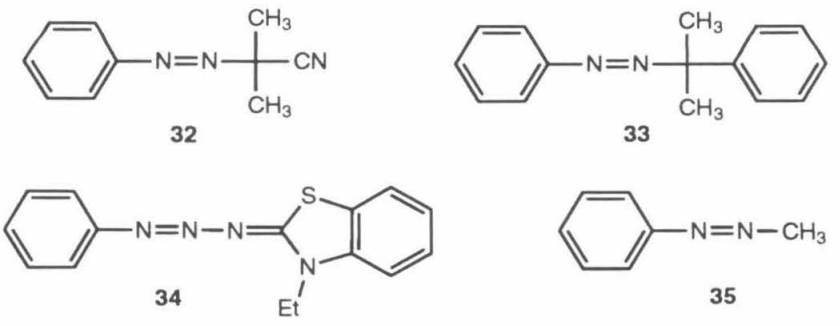
Table I. ^{15}N-^{1}H Coupling Constants for **9** and **31**.

Compound	$\lvert^{1}J_{NH}\rvert$ (Hz)	$\lvert^{2}J_{NH}\rvert$ (Hz)	δ (NN**H**) (ppm)
9[a]	50.8	2.0	15.9
31[a]	51.6	2.0	16.1
(Z)-**31**[b]	49.4	2.0	15.5

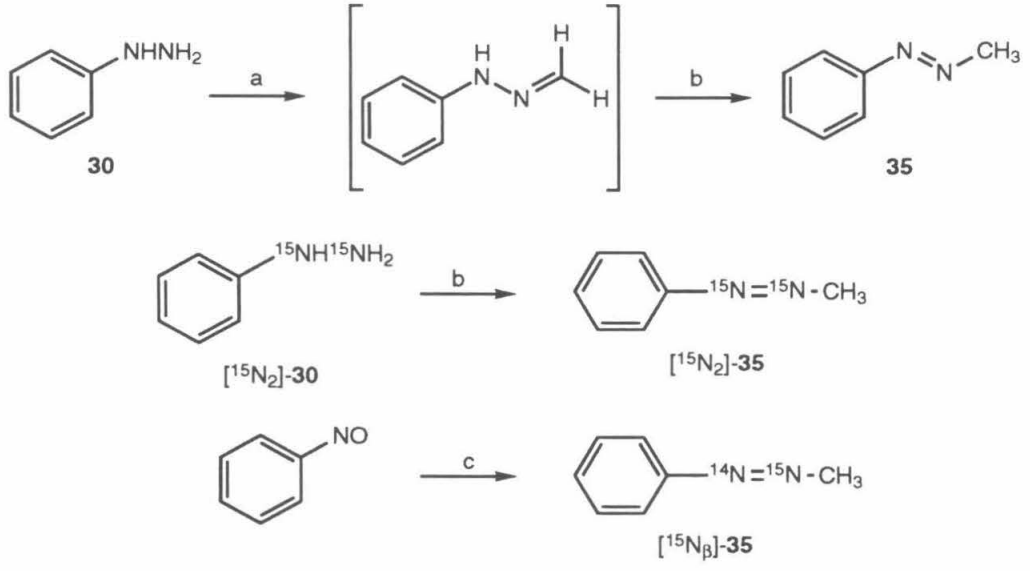
[a] NMR Solvent: THF-d_8. [b] NMR Solvent: CD_2Cl_2, data from reference 23.

Generation and characterization of the other isomers of **9** and **31** would have been of great assistance in determining the diazene stereochemistry. *(Z)*-Dialkyl diazenes undergo thermal isomerization to the *E* isomers, and the isomerization of both *(E)*- and *(Z)*-dialkyl diazenes can be readily achieved photochemically.[19h] However, all attempts to isomerize **9** by low-temperature irradiation with a medium pressure mercury-arc lamp or by wavelength-specific irradiation with a xenon-arc lamp produced no observable change in the ^{1}H NMR spectrum. Similar irradiation of samples of **31** resulted only in the disappearance of **31** and the formation of benzene. If **9** and **31** were, in fact, *(Z)*-diazenes, it was expected that they would have undergone isomerization to the corresponding *E* isomers, which are presumably more stable. The fact that these diazenes did not undergo isomerization cast further doubt on the validity of the *Z* stereochemical assignments derived from the two-bond ^{15}N-^{1}H coupling constants.

In the absence of direct comparison between the two isomers of **9** or **31**, measurement of heteronuclear coupling constants appeared to be a potential solution to the problem of assigning the stereochemistry of monoalkyl diazenes. The ^{15}N–^{15}N coupling constants in **32** and **33** are known to vary with the stereochemistry of the diazene; for both compounds, $^{1}J_{NN}$ = 17.0 Hz for the *E* isomer while $^{1}J_{NN}$ = 21.0 Hz for the *Z* isomer.[27] It has also been observed that the relative magnitudes of long-range ^{15}N-^{13}C coupling constants in triazene **34** depend on the configuration the diazene bond.[28]



While the putative *(Z)*-**31** provided a reference for the $^{2}J_{NH}$ values of labelled **9** and **31**, no such reference was available for both ^{15}N-^{15}N and ^{15}N-^{13}C coupling constants. It was decided to carry out preliminary studies on a simple dialkyl diazene, for which both isomers could be readily obtained. Methyl phenyldiazene, **35**, was selected in the hope that, in labelled form, it would provide representative ^{15}N-^{13}C coupling constants for both alkyl and aryl carbon centers, in addition to ^{15}N-^{15}N coupling constants.



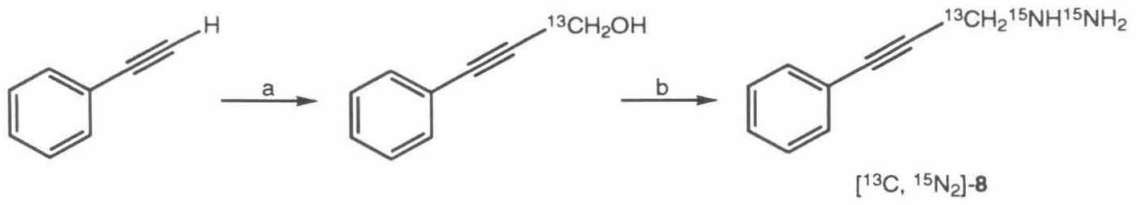
Scheme 5. Reagents and conditions: (a) CH_2O (1.00 equiv, 37% aq.), Et_2O, 0 °C; (b) 4% KOH/$HOCH_2CH_2OH$, 85 °C, 27%; (c) $CH_3{}^{15}NH_2$•HCl (1.00 equiv), KOH (1.00 equiv), Et_2O, 50%.

(E)-Methyl phenyldiazene, *(E)*-**35**, was prepared by the base-catalyzed isomerization of the formaldehyde phenylhydrazone (Scheme 5).[29] After distillation, **35** could be isomerized in solution by Pyrex-filtered irradiation with a medium-pressure mercury-arc lamp. The mixture of *E* and *Z* isomers so obtained could be readily separated by chromatography. The individual isomers were characterized by ^{1}H, and ^{13}C NMR spectroscopy, and by measurement of their UV absorption spectra. To facilitate ^{15}N NMR spectroscopy, labelled phenyl methyldiazene, *(E)*-[$^{15}N_2$]-**35** was prepared from [$^{15}N_2$]-phenylhydrazine and formaldehyde. To allow definitive assignment of chemical shifts and coupling constants, the singly labelled compound, *(E)*-[$^{15}N_\beta$]-**35**, was prepared from nitrosobenzene and ^{15}N-methylamine hydrochloride.[30] Photochemical isomerization resulted in partial conversion to the corresponding *Z* isomers, which were characterized by ^{1}H, ^{13}C, and ^{15}N NMR spectroscopy. The measured values of $^{1}J_{NN}$, $^{1}J_{NC}$, and $^{2}J_{NC}$ for [$^{15}N_2$]-**35** and [$^{15}N_\beta$]-**35**, combined with similar measurements for **32**, **33**, and **34**, reveal a clear correlation between the magnitude of these coupling constants and diazene geometry (Table II).

Table II. Heteronuclear Coupling Constants for **32** - **35**.

Compound	$\lvert^{1}J_{NN}\rvert$ (Hz)	$\lvert^{1}J_{NC}\rvert$[a] (Hz)	$\lvert^{2}J_{NC}\rvert$[a] (Hz)
(E)-**32**	17.0		
(E)-**33**	17.0		
(E)-**34**		0.0	6.0
(E)-**35**	16.1	4.2	8.0
		2.8[b]	4.9[b]
(Z)-**32**	21.0		
(Z)-**33**	21.0		
(Z)-**34**		7.7	2.7
(Z)-**35**	21.0	10.5	3.9
		11.2[b]	3.5[b]

[a] Coupling to aromatic carbon. [b] Coupling to methyl carbon.



Scheme 6. Reagents and conditions: (a) i BuLi (1.00 equiv), THF, –78 C ii $(^{13}CH_2O)_n$ (1.00 equiv), –78 °C → 0 °C, 75%. (b) i CH_3SO_2Cl (1.10 equiv), NEt_3 (1.20 equiv), 0 °C, CH_2Cl_2 ii $^{15}N_2H_4 \bullet H_2SO_4$ (10.0 equiv), CH_3ONa (20.0 equiv), CH_3OH, 0 °C, 41%.

With these data in hand, a new labelled precursor to diazene **9** was prepared. As **9** was most easily prepared at low concentration, triply labelled **8** ([^{13}C, $^{15}N_2$]-**8**) was synthesized to facilitate ^{13}C and ^{15}N NMR spectroscopy (Scheme 6). This hydrazine was oxidized to [^{13}C, $^{15}N_2$]-**9** under conditions identical to those employed for the unlabelled compound. The observed value of $^1J_{NN}$ = 17.2 Hz for both monoalkyl diazenes strongly suggests *E* stereochemistry (Table III). More compelling in the case of **9** is the variation in the one- and two-bond ^{15}N-^{13}C coupling constants. The observation that the one-bond coupling is smaller than the two-bond coupling is inconsistent with *Z* stereochemistry. The complexity of the product mixture prevented the identification of the long-range couplings for **31**. However, the ^1H chemical shifts and one- and two-bond ^{15}N-^1H coupling constants for the diazenyl protons of **9** and **31** are virtually identical, as are the values of $^1J_{NN}$. Taking into account that these diazenes are produced under identical conditions, **9**

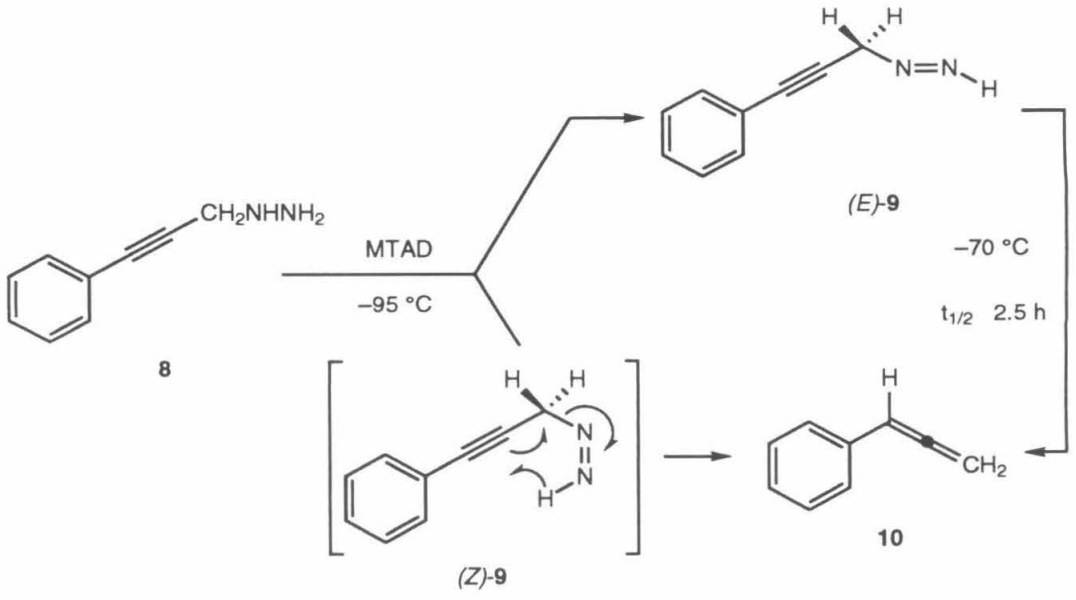
Table III. Heteronuclear Coupling Constants for **9** and **31**.

Compound	$\lvert^1J_{NN}\rvert$ (Hz)	$\lvert^1J_{NC}\rvert$ (Hz)	$\lvert^2J_{NC}\rvert$ (Hz)
9	17.2	5.4	8.1
31	17.2		

and **31** are likely of the same stereochemistry. The available NMR data for **31** prepared by oxidation with MTAD and for the putative *(Z)*-**31** are virtually identical; it appears that earlier reports describing the preparation of *(Z)*-monoalkyl diazenes are in error.[23]

While the stereochemical assignment for **9** and **31** cannot be made conclusively in the absence of the other isomers, two circumstantial arguments also support the assignment of *E* stereochemistry. It is reasonable to assume that *(E)*-monoalkyl diazenes are more stable than *(Z)*-monoalkyl diazenes, in analogy to calculations for diimide and experimental data for dialkyl diazenes. If a persistent *(Z)*-diazene were formed by low-temperature MTAD oxidation of hydrazines, it should be possible to induce thermal or photochemical isomerization to the corresponding *E* isomer. Neither **9** nor **31** prepared by oxidation with MTAD could be isomerized photochemically, and warming samples of **31** led only to decomposition. Further, the observation that oxidation of 2-methyl-1-phenylhydrazine with MTAD produces an equal mixture of *(Z)*- and *(E)*-methyl phenyldiazenes argues strongly for an oxidation that partitions between *(E)*-and *(Z)*-diazenes.[31]

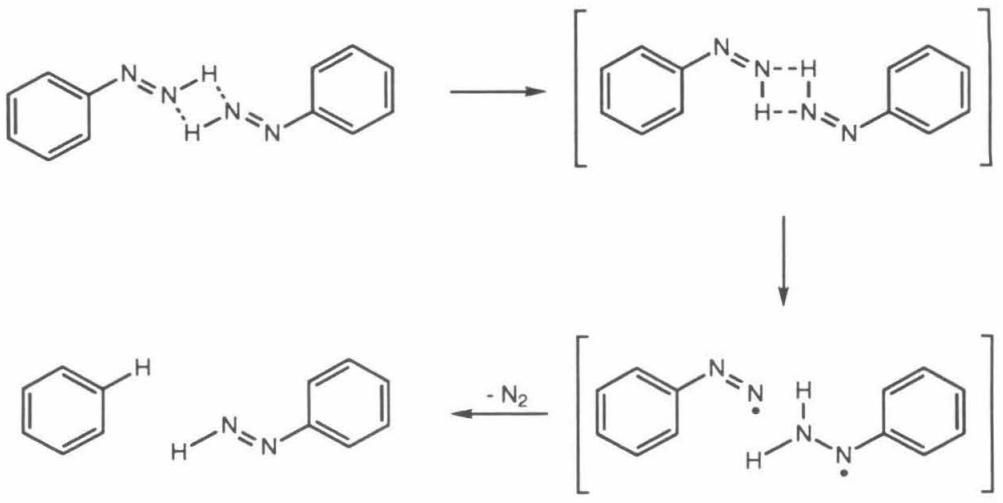
The assignment of *E* stereochemistry to the intermediate diazene **9** leads to the following mechanistic interpretation of allene formation from **8**. Low-temperature oxidation of **8** with MTAD rapidly produces **9**, as an approximately equal mixture of *E* and *Z* isomers (Scheme 7). The *Z* isomer undergoes facile sigmatropic rearrangement to form **10**, while the stable *E* isomer persists at low temperature. On warming to –71 °C, *(E)*-**9** undergoes base-catalyzed isomerization to *(Z)*-**9**, which rearranges to **10** too rapidly to be detected. 4-Methyl urazole increases the rate of disappearance of **9**, entering into the rate equation with order ≈ 1, and may function as a catalyst for $E \rightarrow Z$ isomerization.[32] Given the modest yield of *(E)*-**31** produced on oxidation of phenylhydrazine, it is tempting to speculate that *(Z)*-**31** was also formed, but is extremely unstable, even at –95 °C.



Scheme 7.

Conclusions

The rapidity of the sigmatropic rearrangement of *(Z)*-**9** places a limit of ≤ 12 kcal/mol for the free energy of reaction ($\Delta G^{\neq}$) at –95 °C. Considering that this reaction is estimated to be exothermic by at least 60 kcal/mol[33] and that the conformational changes in the ground state structure required for reaction are likely small, the facility of this transformation is not entirely unexpected. The instability of *(Z)*-**31** is less readily understood, save to say that it is consistent with the previously observed behavior of phenyldiazene. In earlier work, it was shown that phenyldiazene undergoes bimolecular decomposition, forming benzene as the predominant product.[23] It was hypothesized that the rate-limiting step in decomposition of *(Z)*-monoalkyl diazenes is a bimolecular cage *E* → *Z* isomerization (Scheme 8). This was thought to be followed by excitation of one molecule of the *(Z)*-diazene to a thermally accessible triplet biradical. This biradical was then to abstract a hydrogen atom from the other diazene in the solvent-cage pair, after which rapid bimolecular decomposition would produce one equivalent each of benzene, nitrogen, and the *(E)* diazene.



Scheme 8.

When prepared directly by MTAD oxidation at –95 °C, *(Z)*-**31**, if formed, decomposes so rapidly that it cannot be detected. Analysis of the ^{15}N NMR spectrum of the [$^{15}N_2$]-phenylhydrazine oxidation reaction indicates that three major species are produced in addition to *(E)*-**31** and benzene, at least two of which derive from coupling of two or more molecules of phenyldiazene. While this data is consistent with bimolecular decomposition for *(Z)*-**31**, the triplet state postulated to be involved in this decomposition has been estimated to be ≈ 18 kcal/mol above the ground-state singlet.[23] As a process with energetic barrier of this magnitude is clearly ruled out by the rapidity of reaction, these data suggests that a mechanism for decomposition other than thermal triplet-state excitation must be invoked to explain the extraordinary reactivity of *(Z)*-**31** in particular and *(Z)*-monoalkyl diazenes in general.

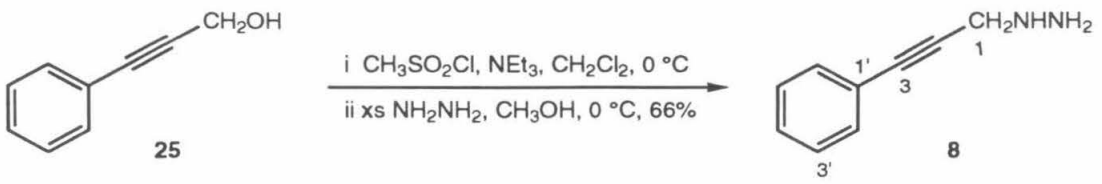
Experimental Section

General Procedures. All reactions were performed in flame-dried round-bottom or modified Schlenk (Kjeldahl shape) flasks fitted with rubber septa under a positive pressure of argon, unless otherwise noted. Air- and moisture-sensitive liquids and solutions were transferred via syringe or stainless steel cannula. Where necessary (so noted), reaction mixtures were degassed by evacuating for 10-15 seconds and flushing with argon (≥ 5 iterations). Organic solutions were concentrated by rotary evaporation at ≈ 25 Torr (water aspirator) at or slightly above ambient temperature, unless otherwise noted. Flash column chromatography was performed as described by Still *et al.*,[17] employing 230-400 mesh silica gel. Analytical and preparative thin-layer chromatography were performed using glass plates pre-coated with 0.25 mm 230-400 mesh silica gel impregnated with a fluorescent indicator (254 nm). Thin-layer chromatography plates were visualized by exposure to ultraviolet light (noted as 'UV') and/or by exposure to an acidic solution of *p*-anisaldehyde in ethanol followed by heating on a hot-plate (noted as 'anisaldehyde'). NMR tubes for sealed tube experiments were fabricated by attaching a 3"x5 mm o.d. medium-wall borosilicate extension, equipped with a female 14/20 joint, to a standard 7"x5 mm o.d. NMR tube. The NMR tubes so prepared were pretreated by soaking with *aqua regia*, rinsing thoroughly with filtered (4 μ) distilled water, soaking with hexamethyldisilazane, rinsing thoroughly with filtered distilled water, and drying under vacuum. Sealed NMR samples were prepared by flame-sealing an evacuated sample, degassed by freeze-pump-thaw to an overpressure of ≤ 10 mTorr, under vacuum. Photochemical isomerizations were carried out with a Pyrex-filtered 450 W medium-pressure mercury-vapor lamp.

Materials. Commercially available reagents were used as received, with the following exceptions. Ethyl ether and tetrahydrofuran were distilled from sodium benzophenone ketyl. Benzene was distilled from sodium metal. Methylene chloride, acetonitrile, triethylamine, and propylamine were distilled from calcium hydride. Methanol

Dimethylformamide and ethylene glycol were distilled from calcium sulfate at reduced pressure and were stored over 4 Å molecular sieves. Methanesulfonyl chloride was distilled from phosphorus pentoxide at atmospheric pressure. Copper(I) iodide was purified by continuos extraction (24 hours) with tetrahydrofuran in a Soxhlet apparatus. The molarity of butyllithium solutions was determined by titration using diphenylacetic acid as an indicator (average of three determinations).[18]

Instrumentation. Infrared spectra were obtained using a Perkin-Elmer 1600 FT-IR spectrophotometer referenced to a polystyrene standard. Data are presented as follows: frequency of absorption (cm^{-1}), intensity of absorption (s = strong, m = medium, w = weak, br = broad). ^{1}H NMR, ^{13}C NMR, and ^{15}N NMR spectra were obtained on a JEOL GX-400 (9.40 Tesla) spectrometer; chemical shifts are expressed in parts per million. ^{1}H NMR chemical shifts are referenced to the signal for residual hydrogen in the NMR solvent ($CHCl_3$: δ 7.26, C_6D_5H: δ 7.15, $CHDCl_2$: δ 5.32, THF-d_7: δ 1.73, 3.58). Data are presented as follows: chemical shift, multiplicity, (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), integration, coupling constant in Hertz, and assignment (where possible). ^{13}C NMR chemical shifts are referenced to the carbon signal for the solvent ($CDCl_3$: δ 77.0, C_6D_6: δ 128.0, CD_2Cl_2: δ 53.8, THF-d_8: δ 25.3, 67.4). ^{15}N NMR chemical shifts are referenced to nitric acid (δ –270) as an external standard. Data are presented as follows: chemical shift, and assignment (where possible). Mass spectrometry was performed at the University of California at Riverside, Riverside Mass Spectrometry Facility, or at the Midwest Center for Mass Spectrometry at the University of Nebraska–Lincoln (with partial support by the National Science Foundation, Biology Division; Grant No. DIR9017262). Ultraviolet absorption spectra were measured on a Hewlett-Packard 8452A Diode Array Spectrophotometer.



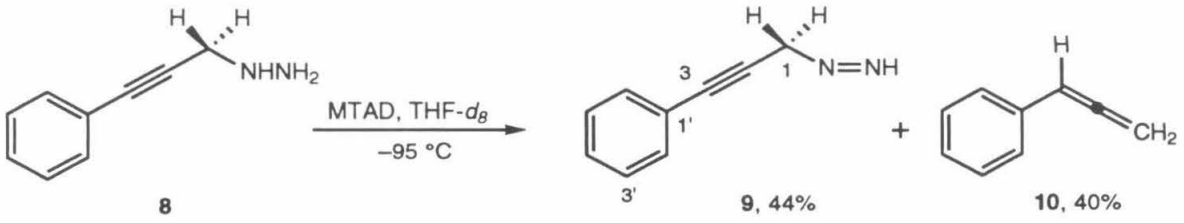
(3-Phenyl-2-propynyl)hydrazine, **8**.

Methanesulfonyl chloride (1.08 ml, 13.6 mmol, 1.10 equiv) was added dropwise over 2 minutes to a solution of the alcohol **25** (1.64 g, 12.9 mmol, 1 equiv) and triethylamine (2.25 ml, 16.1 mmol, 1.30 equiv) in methylene chloride (20 ml) at 0 °C. After 10 minutes, hydrazine (11.00 ml, 372 mmol, 30.0 equiv, 50% v/v in CH_3OH) was added, and stirring was continued for 12 hours. The opaque yellow solution was poured into saturated aqueous ammonium chloride (50 ml), and the aqueous phase was extracted with 10% methanol-methylene chloride (4x30 ml). The combined organic fractions were washed with water (1x20 ml), were dried over sodium sulfate, and were concentrated to provide crude **8** (1.77 g, 98%) as a yellow oil. Purification of the crude oil by bulb-to-bulb distillation at reduced pressure (22 mTorr) afforded pure **8** (1.19 g, 66%) as a colorless oil.

^{1}H NMR (400 MHz, C_6D_6), δ: 7.55-7.65 (m, 2H), 7.10-7.20 (m, 3H), 3.53 (s, 2H, H1), 3.07 (br s, 3H, hydrazine NH).

^{13}C NMR (100 MHz, C_6D_6), δ: 137.3 (C3'), 128.9 (C2'), 128.6 (C4'), 124.2 (C1'), 88.0 (C3), 84.4 (C2), 45.5 (C1).

FTIR (neat), cm^{-1}:	3386 (w, br), 3242 (w, br), 3056 (w), 2985 (w), 2935 (w), 2910 (w), 2845 (w), 1490 (m), 758 (s), 692 (s).
MS (EI), m/z (%base):	146 (25), 145 (50), 116 (25), 115 (100).
HRMS (EI):	Calcd for $C_9H_{10}N_2$ (M^+): 146.0832. Found: 146.0844.
TLC (50% Ethyl Acetate-Hexanes), R_f:	0.10 (UV, anisaldehyde).



(3-Phenyl-2-propynyl)diazene, **9**.

A solution of (3-phenyl-2-propynyl)hydrazine (**8**) in tetrahydrofuran-d_8 (0.20 M, 0.140 ml, 0.027 mmol, 1 equiv) was frozen in an NMR tube and the sample was thoroughly degassed on a high-vacuum line. The frozen sample was momentarily detached from the vacuum line and vinylidene chloride (0.001 ml) and 4-methyl triazolinedione (0.003 g, 0.027 mmol, 1.00 equiv) were quickly added. The sample was agitated to settle the reagents onto the frozen solution, and the NMR tube was reattached to the vacuum line and was sealed under vacuum. The sample was thawed at –105 °C (pentane-liquid nitrogen) and gently agitated to mix the thawing solution. The sample was then loaded into the probe of a 400 MHz NMR, precooled to –110 °C (T ≤ –85 °C during sample loading). ^{1}H NMR analysis of the reaction mixture indicated formation of the allene **10** (40%), the propargyl diazene **9** (44%), and 4-methyl urazole (85%). ^{13}C NMR spectra were obtained at –100 °C. On warming to –71 °C, **9** underwent smooth first-order decomposition (k = (8 ± 2) × 10^{-5} s^{-1}, $t_{1/2}$ = 2.4 h, Figure 3), with concomitant appearance of allene **10** (k = (7 ± 4) × 10^{-5} s^{-1}). Kinetic data were measured by integration against the vinylidene chloride reference. Warming the sample to 23 °C and recooling to –71 °C effected complete conversion of **9** to **10** (85% yield by integration).

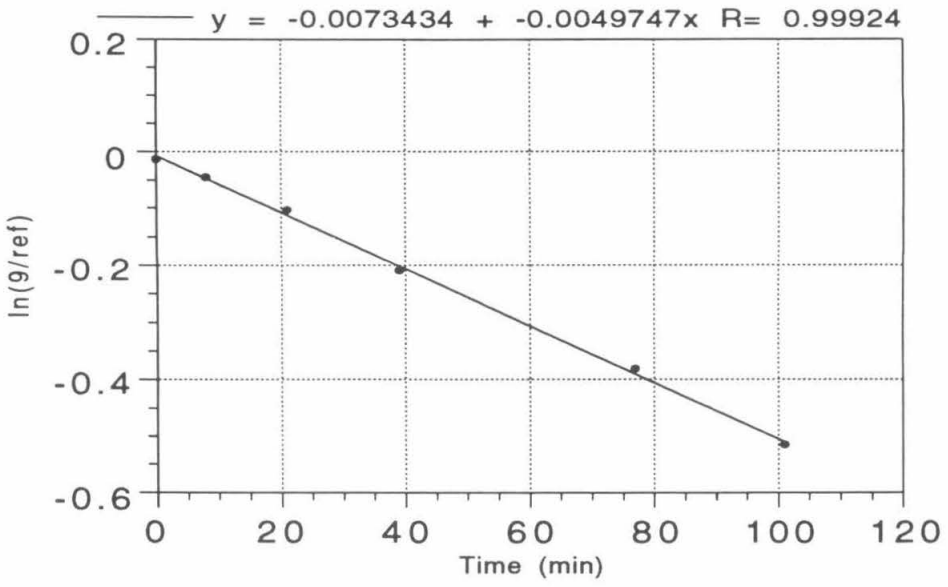
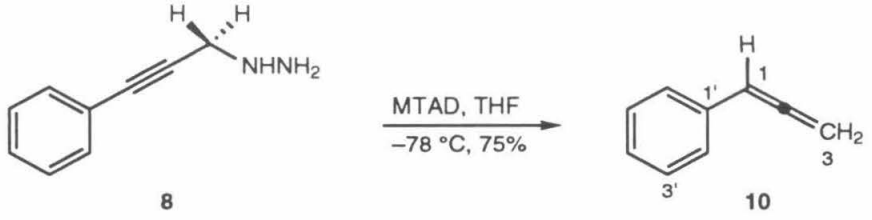


Figure 3. Disappearance of **9** at –71 °C in Tetrahydrofuran-d_8.

^{1}H NMR (400 MHz, THF-d_8), δ: 15.90 (ddd, 1H, $^4J_{HH}$ = 2.4 Hz, N=N**H**), 7.20-7.50 (m, 5H), 4.85 (d, 2H, $^4J_{HH}$ = 2.4 Hz, H1).

^{13}C NMR (100 MHz, THF-d_8), δ: 157.5 (C4'), 132.4, 132.2 (C2', C3'), 124.2 (C1'), 87.2 (C3), 83.8 (C2), 58.5 (C1).



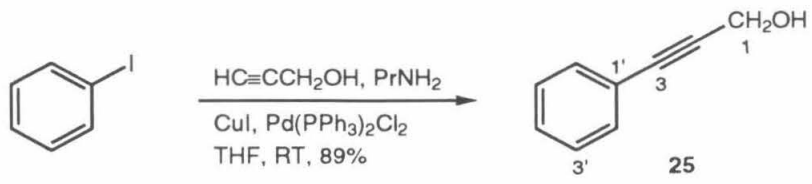
8 10

Phenylallene, **10**.

4-Methyl triazolinedione (0.010 g, 0.09 mmol, 1.00 equiv) was added to a solution of hydrazine **8** (0.012 g, 0.09 mmol, 1 equiv) in tetrahydrofuran (1 ml) at –78 °C, and gas evolution ensued. After stirring for 5 minutes, the reaction was diluted with pentane (5 ml), was warmed to 23 °C, and was extracted with saturated aqueous ammonium chloride (5 ml). The organic phase was dried over sodium sulfate, was partially concentrated, and was purified by flash column chromatography (100% pentane) to provide allene **10** (0.008 g, 75%) as a colorless oil.

^{1}H NMR (400 MHz, THF-d_8), δ:	6.95-7.25 (m, 5H), 6.03 (t, 1H, J = 6.8 Hz, H1), 4.84 (d, 2H, J = 6.8 Hz, H3).
^{13}C NMR (100 MHz, THF-d_8), δ:	210.6 (C2), 134.8 (C1'), 129.2 (C4'), 127.5, 127.4 (C2', C3'), 94.4 (C1), 88.9 (C3).
FTIR (neat), cm^{-1}:	3081 (m), 3061 (m), 3031 (m), 2979 (w), 1942 (s), 1494 (s), 1458 (s), 853 (s), 761 (s), 694 (s).
MS (EI), m/z (%base):	116 (80), 115 (100), 89 (12), 63 (11), 42 (10).

TLC (100% Hexanes), R_f: 0.55 (UV).



25

3-Phenyl-2-propynol, **25.**

Copper(I) iodide (0.56 g, 2.94 mmol, 0.15 equiv) was added to a degassed solution of propargyl alcohol (1.21 g, 21.6 mmol, 1.10 equiv) and propylamine (6.45 ml, 78.4 mmol, 4.00 equiv) in tetrahydrofuran (5 ml) at –78 °C. The suspension was degassed, and the mixture was warmed to 23 °C. A suspension of iodobenzene (4.00 g, 19.6 mmol, 1 equiv) and bis(triphenylphosphine)palladium(II) chloride (0.69 g, 0.98 mmol, 0.05 equiv) in tetrahydrofuran (10 ml) was degassed at –78 °C, was warmed to 23 °C, and was added via cannula to the acetylene solution. After stirring for 12 hours, the dark brown reaction was poured into a solution comprising equal parts saturated aqueous ammonium chloride and saturated aqueous potassium carbonate (100 ml) and was allowed to stir for 30 minutes. The aqueous phase was extracted with 20% ethyl acetate-hexanes (3x50 ml) and the combined organic fractions were dried over sodium sulfate and were concentrated. Purification of the residue by flash column chromatography afforded **25** (2.31 g, 89%) as a colorless oil.

^{1}H NMR (400 MHz, C_6D_6), δ: 7.30-7.40 (m, 2H), 7.15-7.25 (m, 3H), 4.43 (s, 2H, H1), 2.57 (br s, 1H, alcohol OH).

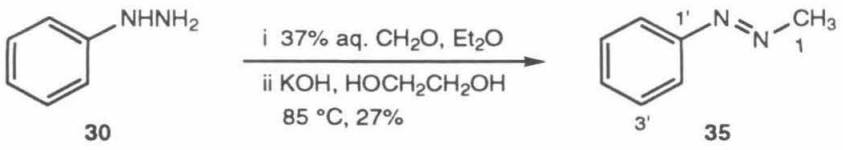
^{13}C NMR (100 MHz, C_6D_6), δ: 131.7 (C3'), 128.5 (C4'), 128.3 (C2'), 122.5 (C1'), 87.2 (C3), 85.7 (C2), 51.6 (C1).

FTIR (neat), cm^{-1}: 3316 (s, br), 3060 (w), 2921 (w), 2839 (w), 2237 (w), 1489 (s), 1020 (s), 755 (s), 690 (s).

MS (EI), m/z (%base): 132 (68), 131 (100), 115 (24), 104 (24), 103 (39).

HRMS (EI): Calcd for C_9H_8O (M^+): 132.0570.
Found: 132.0575.

TLC (15% Ethyl Acetate-Hexanes), R_f: 0.15 (UV, anisaldehyde).



30 35

Methyl Phenyldiazene, **35**.

Formalin (3.80 ml, 46.2 mmol, 1.00 equiv, 37% aq.) was added over 5 minutes to a solution of phenylhydrazine (4.55 ml, 46.2 mmol, 1 equiv) in diethyl ether (10 ml) at 0 °C. After stirring for 30 min, the reaction was partitioned between water (5 ml) and diethyl ether (5 ml). The aqueous phase was washed with diethyl ether (2x5 ml) and the combined organic extracts were dried over sodium sulfate and were concentrated to ≈ 1 ml. Potassium hydroxide in ethylene glycol (4% w/v, 10 ml) was added, and the solution was gradually warmed to 85 °C under reduced pressure (10 mm Hg). Slow distillation from the reaction mixture afforded *(E)*-**35** as a bright yellow liquid (1.51 g, 27%). Irradiation of a solution of *(E)*-**35** in tetrahydrofuran-d_8 with a medium-pressure mercury-arc lamp effected partial isomerization to the *Z* isomer (≈ 3:1 *E*:*Z* at the photostationary state). The two isomers could be separated by chromatography (80% methylene chloride-hexanes). The *Z* isomer underwent thermal reversion to the *E* isomer at 23 °C, but could be stored for prolonged periods at –100 °C.

^{1}H NMR (400 MHz, THF-d_8), δ: *(E)*: 7.60-7.70 (m, 2H), 7.35-7.50 (m, 3H), 3.97 (s, 3H, H1).

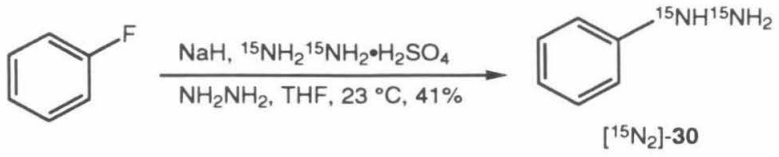
(Z): 7.42 (dd, 2H, *J* = 5.5, 4.5 Hz, H3'), 7.22 (t, 1H, *J* = 4.5 Hz, H4'), 6.75 (d, 2H, *J* = 5.5 Hz, H2'), 3.59 (s, 3H, H1).

^{13}C NMR (100 MHz, THF-d_8), δ: *(E)*: 153.1 (C1'), 131.1 (C4'), 129.7 (C2'), 122.9 (C3'), 57.3 (C1).

(Z): 155.1 (C1'), 129.9 (C2'), 127.1 (C4'), 118.2 (C3'), 52.1 (C1).

FTIR (neat), cm^{-1}: *(E)*: 3066 (w), 2973 (w), 2911 (m), 1531 (m), 1479 (m), 1429 (m), 764 (s), 689 (s).

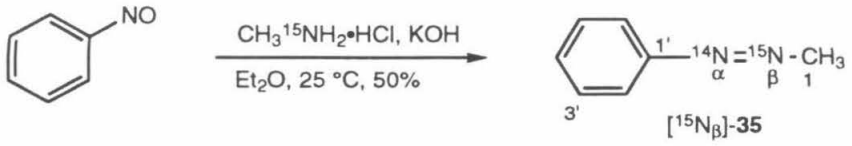
TLC (100% CH_2Cl_2), R_f: 0.55 (UV).



$[^{15}N_2]$-**30**

$[^{15}N_2]$-Phenylhydrazine, $[^{15}N_2]$-**30**.

$[^{15}N_2]$-Hydrazine sulfate (0.287 g, 2.17 mmol, 0.20 equiv) was added to a suspension of sodium hydride (0.376 g, 15.2 mmol, 1.40 equiv) in tetrahydrofuran (40 ml) at 0 °C. After stirring for 5 minutes, hydrazine (0.275 ml, 8.67 mmol, 0.80 equiv) was added over 2 minutes. The mixture was allowed to warm to 23 °C over 8 hours, and fluorobenzene (10.20 ml, 108 mmol, 10.0 equiv) was added over 1 minute. After stirring for 36 hours, the reaction was poured into saturated aqueous ammonium chloride (40 ml), and the aqueous phase was extracted with 2.5% methanol-methylene chloride (2x25 ml). The combined organic fractions were dried over sodium sulfate and were concentrated to afford $[^{15}N_2]$-**30** (0.388 g, 41%) as a pale yellow liquid. The isolated hydrazine was identical to unlabelled phenylhydrazine by thin-layer chromatography and by ^1H NMR spectroscopy.



[$^{15}N_\beta$]-Methyl Phenyldiazene, **35**.

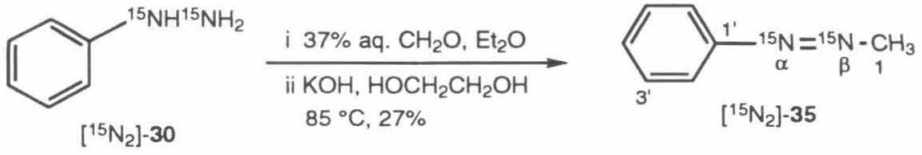
Potassium hydroxide (0.189 g, 3.37 mmol, 0.98 equiv) was added to a solution of $CH_3{}^{15}NH_2$•HCl (0.232 g, 3.44 mmol, 1 equiv) in water (0.75 ml). The solution was diluted with diethyl ether (20 ml), and nitrosobenzene (0.361 g, 3.37 mmol, 0.98 equiv) was added. After stirring the green biphasic reaction for 36 hours, the phases were separated and the organic phase was dried and was concentrated. Bulb-to-bulb distillation at reduced pressure (50 mTorr) provided [$^{15}N_\beta$]-**35** as a bright yellow liquid (0.190 g, 51%). Photochemical isomerization was performed in analogy to unlabelled **35**; the individual isomers were not separated. Assignments of chemical shifts and heteronuclear coupling constants were made on the basis of NMR data obtained prior to and subsequent to isomerization. ^{13}C NMR data (100 MHz) were obtained in tetrahydrofuran-d_8 at –60 °C. ^{15}N NMR data (40.5 MHz) were obtained in tetrahydrofuran-d_8 at ambient temperature. Heteronuclear coupling constants for [$^{15}N_\beta$]-**35** are presented in Table IV. ^{15}N NMR data are presented in Table V.

Table IV. Heteronuclear Coupling Constants.

	(E)-**35**	*(Z)*-**35**
Carbon	$\lvert J_{NC}\rvert$ (N_β) (Hz)	$\lvert J_{NC}\rvert$ (N_β) (Hz)
C1	4.2	11.2
C1'	4.9	3.9
C2'	0.0	0.0
C3'	4.4	1.9
C4'	0.0	0.0

Table V. ^{15}N NMR Data.

Compound	δ N_β (ppm)	$\lvert {}^2J_{NH}\rvert$ (Hz)
(E)-**35**	119.2	4.3
(Z)-**35**	123.2	3.7



[$^{15}N_2$]-**30** [$^{15}N_2$]-**35**

[$^{15}N_2$]-Methyl Phenyldiazene, [$^{15}N_2$]-**35**.

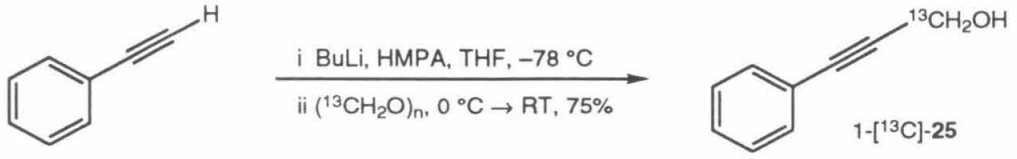
[$^{15}N_2$]-**35** was prepared in analogy to unlabelled **35**, employing labelled phenylhydrazine ([$^{15}N_2$]-**30**) as the starting material. Photochemical isomerization was performed in analogy to unlabelled **35**; the individual isomers were not separated. Assignments of chemical shifts and heteronuclear coupling constants were made on the basis of NMR data obtained prior to and subsequent to isomerization, and by comparison to data obtained for [β-^{15}N]-**35**. ^{13}C NMR data (100 MHz) were obtained in tetrahydrofuran-d_8 at –60 °C. ^{15}N NMR data (40.5 MHz) were obtained in tetrahydrofuran-d_8 at ambient temperature. The heteronuclear coupling constants for *(E)*- and *(Z)*-[$^{15}N_2$]-**35** are presented in Table VI. ^{15}N NMR data are presented in Table VII.

Table VI. Heteronuclear Coupling Constants.

	(E)-**35**		*(Z)*-**35**	
Carbon	$\lvert J_{NC}\rvert$ (N_α) (Hz)	$\lvert J_{NC}\rvert$ (N_β) (Hz)	$\lvert J_{NC}\rvert$ (N_α) (Hz)	$\lvert J_{NC}\rvert$ (N_β) (Hz)
C1	8.0	4.2	3.5	11.2
C1'	2.8	4.9	10.5	3.9
C2'	1.7	0.0	0.0	0.0
C3'	1.9	4.4	1.9	1.9
C4'	0.0	0.0	0.0	0.0

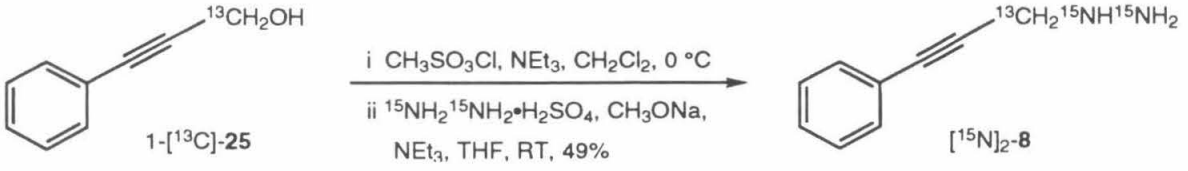
Table VII. ^{15}N NMR Data.

Compound	$\lvert J_{NN}\rvert$ (Hz)	δ N_α (ppm)	δ N_β (ppm)	$\lvert ^2J_{NH}\rvert$ (Hz)
(E)-**35**	16.1	118.4	119.2	4.3
(Z)-**35**	21.0	109.2	123.2	3.7



1-[^{13}C]-3-Phenyl-2-propynol, 1-[^{13}C]-**25**.

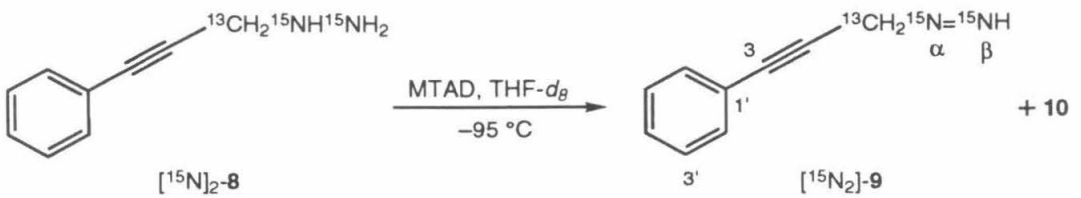
Butyllithium (1.59M, 11.13 ml, 17.8 mmol, 1.10 equiv) was added dropwise to a solution of phenylacetylene (1.60 g, 17.8 mmol, 1.10 equiv) in tetrahydrofuran (10 ml) at –78 °C. Hexamethylphosphoramide (3.08 ml, 17.8 mmol, 1.10 equiv) was added, and the solution was stirred for 2.5 hours. After warming to 0°C, [^{13}C]-paraformaldehyde (0.50 g, 16.1 mmol, 1 equiv) was added, was warmed to 23 °C, and the reaction was stirred for 5 hours. The reaction mixture was poured into water (20 ml), the organic phase was washed with water (1x5 ml), and the combined aqueous fractions were washed with diethyl ether (3x15 ml). The combined organic fractions were dried over sodium sulfate and were concentrated. Purification of the residue by flash column chromatography (22.5% ethyl acetate-hexanes) afforded 1-[^{13}C]-**25** (1.46 g, 75%) as an orange oil. The physical properties of this alcohol were identical to those of the unlabelled compound, save for the relative intensity of the signals in the ^{13}C NMR spectrum and the observable one-bond ^{13}C-^{1}H coupling in the ^{1}H NMR spectrum ($^{1}J_{CH}$ = 146.2 Hz).



1-[^{13}C]-**25** [^{15}N]$_2$-**8**

[$^{15}N_2$]-1-[^{13}C]-(3-Phenyl-propynyl)hydrazine, [$^{15}N_2$]-**8**.

Sodium methoxide (0.405 g, 7.59 mmol, 40.0 equiv) was added to a solution of [$^{15}N_2$]-hydrazine sulfate (0.500 g, 3.78 mmol, 20.0 equiv) in methanol (2 ml) and the mixture was stirred for 2 hours. Methanesulfonyl chloride (0.016 ml, 0.21 mmol, 1.10 equiv) was added over 2 minutes to a solution of 1-[^{13}C]-**25** (0.025 g, 0.19 mmol, 1 equiv) and triethylamine (0.034 ml, 0.25 mmol, 1.30 equiv) in methylene chloride (1 ml) at 0 °C. The hydrazine solution was cooled to 0 °C and added via cannula to the methanesulfonate ester solution. After stirring for 9.5 hours, the reaction was poured into water (10 ml) and the aqueous phase was extracted with 2.5% methanol-methylene chloride (3x5 ml). The combined organic extracts were dried over sodium sulfate and were concentrated. After purification by bulb-to-bulb distillation at reduced pressure (50 mTorr), [$^{15}N_2$]-**8** was obtained as a yellow oil (0.018g, 63%). The labelled hydrazine was identical to unlabelled material in all respects save intensities of signals in the ^{13}C NMR spectrum and the heteronuclear coupling constants apparent in the ^{13}C NMR spectra.



[$^{15}N_2$]-(3-Phenyl-2-propynyl)diazene, [$^{15}N_2$]-**9**.

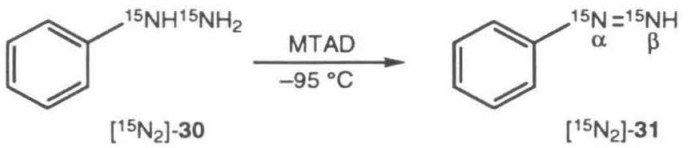
[$^{15}N_2$]-**9** was prepared in analogy to unlabelled **9**, employing [$^{15}N_2$]-1-[^{13}C]-(3-phenyl-2-propynyl)hydrazine ([$^{15}N_2$]-**8**) as the starting material. ^{13}C NMR data (100 MHz) and ^{15}N NMR data (40.5 MHz) were obtained in tetrahydrofuran-d_8 at −100 °C. The heteronuclear coupling constants are presented in Table VIII. ^{15}N NMR data are presented in Table IX.

Table VIII. Heteronuclear Coupling Constants.

Carbon	$\lvert J_{NC}\rvert$ (N_α) (Hz)	$\lvert J_{NC}\rvert$ (N_β) (Hz)
C1	5.4	8.1

Table IX. ^{15}N NMR Data.

$\lvert J_{NN}\rvert$ (Hz)	δ N_α (ppm)	δ N_β (ppm)	$\lvert {}^1J_{NH}\rvert$ (Hz)	$\lvert {}^2J_{NH}\rvert$ (Hz)
17.2	154.0	128.4	50.8	2.0



[$^{15}N_2$]-**30** [$^{15}N_2$]-**31**

[$^{15}N_2$]-Phenyldiazene, [$^{15}N_2$]-**31**.

[$^{15}N_2$]-**31** was prepared in analogy to unlabelled **9**, employing [$^{15}N_2$]-phenylhydrazine ([$^{15}N_2$]-**30**) as the starting material. ^{15}N NMR data (40.5 MHz) were obtained in tetrahydrofuran-d_8 at –100 °C. ^{15}N NMR data are presented in Table X.

Table X. ^{15}N NMR Data.

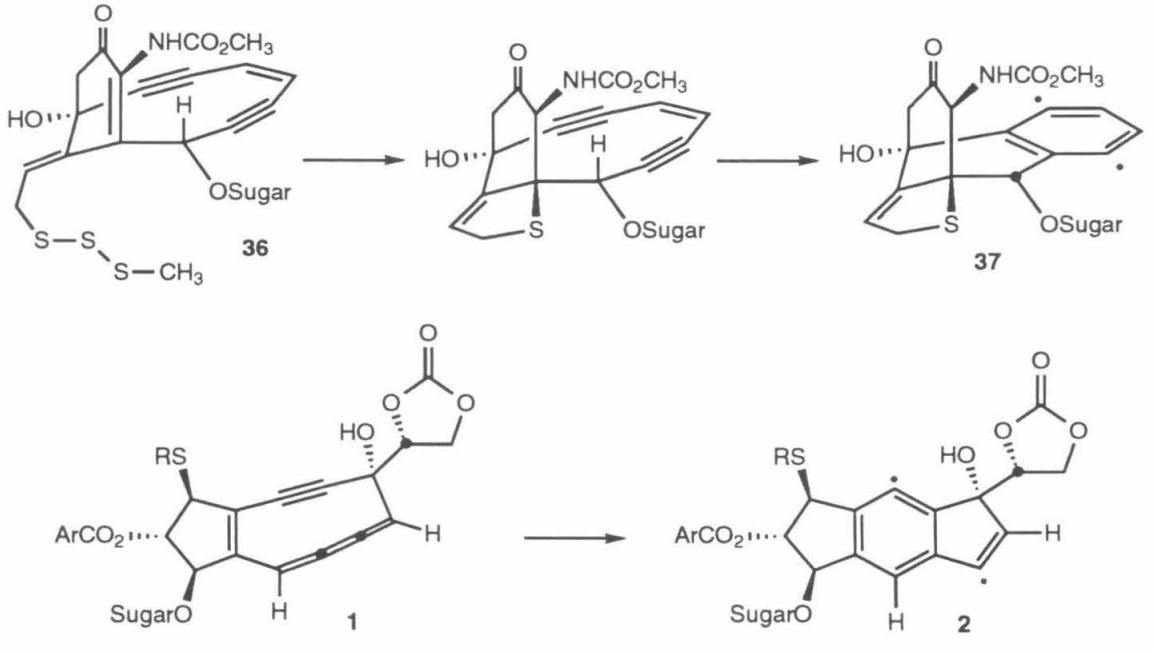
$\lvert J_{NN}\rvert$ (Hz)	δ N_α (ppm)	δ N_β (ppm)	$\lvert {}^1J_{NH}\rvert$ (Hz)	$\lvert {}^2J_{NH}\rvert$ (Hz)
17.2	150.0	124.4	51.6	2.0

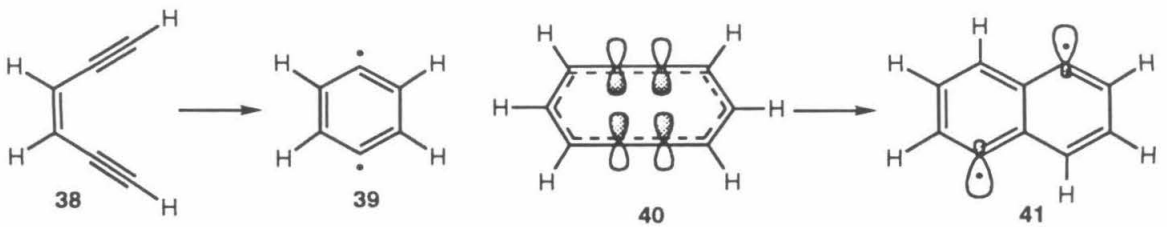
Chapter 3

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

Background and Introduction

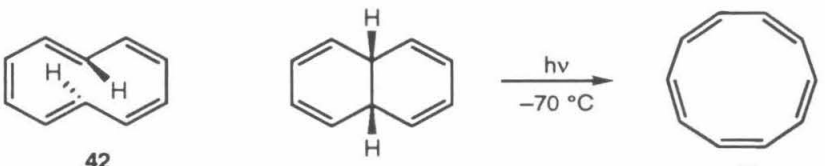
Calicheamicin (**36**) is a representative member of the enediyne class of antibiotics.[34] These natural products share as a common mode of action the cyclization of a strained enediyne to form a biradical intermediate (e.g., **37**), which is responsible for their DNA-damaging activity. Neocarzinostatin effects DNA cleavage after the similar but distinct cycloaromatization reaction of a cumulene intermediate (**1** → **2**) to form a dehydroaromatic biradical in which the radical centers are disposed *anti* about the newly formed bond.[1] While the prototypical enediyne cyclization, the formation of 1,4-dehydrobenzene **39** from hex-3-ene-1,5-diyne **38**,[35] was thoroughly studied long before the discovery of the enediyne antibiotics, no such parent rearrangement is known for neocarzinostatin. 1,5-Dehydronaphthalene (**41**) is arguably the simplest aromatic biradical with radical centers *anti* relative to the central sigma bond, and it was in view of the potential transformation of **40** to **41** that we undertook the preparation 1,6-didehydro[10]annulene, **40**.[36]





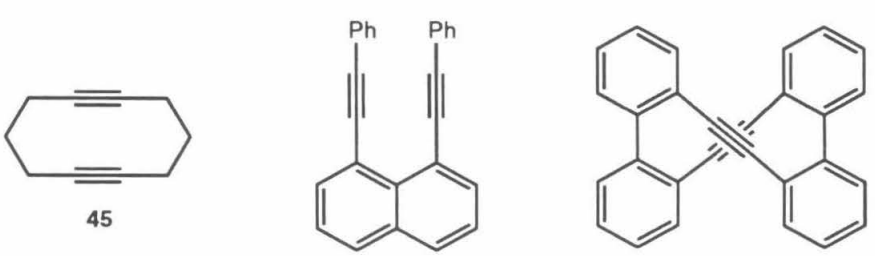
Annulene **40** has been recognized as an interesting synthetic target for more than 40 years.[37] It represents the intersection of two sets of intensely studied cyclic compounds: non-benzenoid "aromatic" molecules[38] and compounds which possess sterically compressed π-systems.[39] In spite of this prolonged interest, prior to this work neither the parent hydrocarbon nor any derivative thereof had been successfully prepared.[40]

Cyclically conjugated molecules with (4n+2) π electrons are, by Hückel's definition, aromatic. This is essentially an empirical observation drawn from the study of benzene and its congeners. In addition to possessing (4n+2) π electrons in a conjugated system, benzenoid aromatics consist entirely of rigid, planar six-membered rings, and Hückel's rule may thus represent a necessary but not a sufficient condition for aromaticity. In order to rigorously determine the prerequisites for aromaticity, extensive effort has been devoted to varying all structural parameters associated with benzenoid compounds. Interest in conjugated species with ring sizes greater than six atoms has led to the preparation of 14, 18, and 24 π electron systems. These annulenes possess many of the spectroscopic properties of benzenoid aromatics, but in general their planarity, rigidity, and chemical stability vary inversely with ring size. Monocyclic 10 π electron species have proven more elusive, although they might be expected to bear a closer resemblance to benzene than the larger annulenes. One of the simplest of these 10 π electron compounds, cyclopentadecaene **42**, is anticipated to deviate substantially from planarity, as a result of a



42 43 44

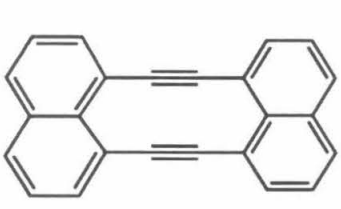
transannular steric interaction between the two hydrogen atoms pointing into the ring. In an attempt to circumvent this potential problem, all-*cis* cyclopentadecaene (**44**) has been prepared by the low-temperature photochemical isomerization of *cis*-9,10-dihydronaphthalene (**43**).[41] This cyclopentadecaene undergoes ready thermal reversion to **43**, and even at low temperatures it is non-planar and non-conjugated. While a planar, conjugated conformation for **44** would clearly require severe bond angle deformation, this is not the case for the annulene **40**, and **40** has long been postulated to be aromatic. It should be noted that **40** is potentially a strained molecule, due to repulsion between the in-plane π-bonds.



45 46 47

The possibility of transannular electronic interaction is, in fact, another intriguing aspect of **40**. The study of compressed, non-aromatic π systems has focused largely on molecules that enforce the spatial proximity of acetylenes, either by incorporating them into a ring, as in **45**, or attaching them to a rigid framework, as in **46** or **47**.[42] These molecules are of interest not only in terms of their electronic properties but also because of their potential transannular cyclization to form cyclobutadienes, tetrahedranes, and biradicals such as **41**. The work of Sondheimer *et al.*[43] and Staab *et al.*,[44] directed

towards the synthesis of **48**, is relevant to the formation of biradicals from compressed π systems. Although **48** does not formally represent a derivative of **40**, it is noteworthy that all attempts to prepare **48** resulted instead in the formation of the hydrocarbon zethrene (**49**). This observation led the Sondheimer and Staab groups to propose that **49** is derived from the biradical **50**, which in turn is proposed to arise from cyclization of transient **48**. While **48** was never observed, and while the vigorous reaction conditions employed allow for alternative interpretation of this result, this work represents the only clear precedent for the putative cycloaromatization of **40** to **41**.



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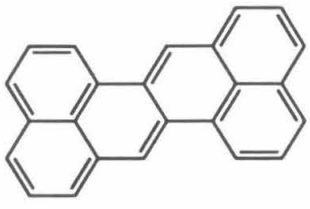

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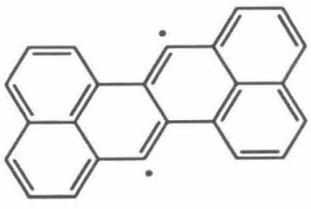

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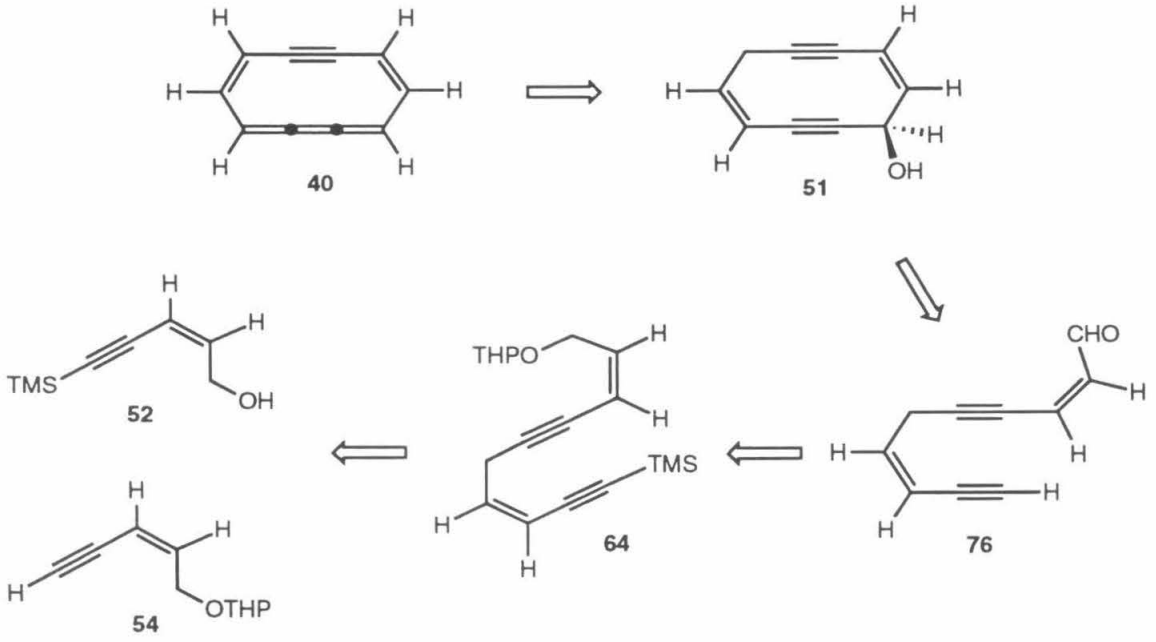
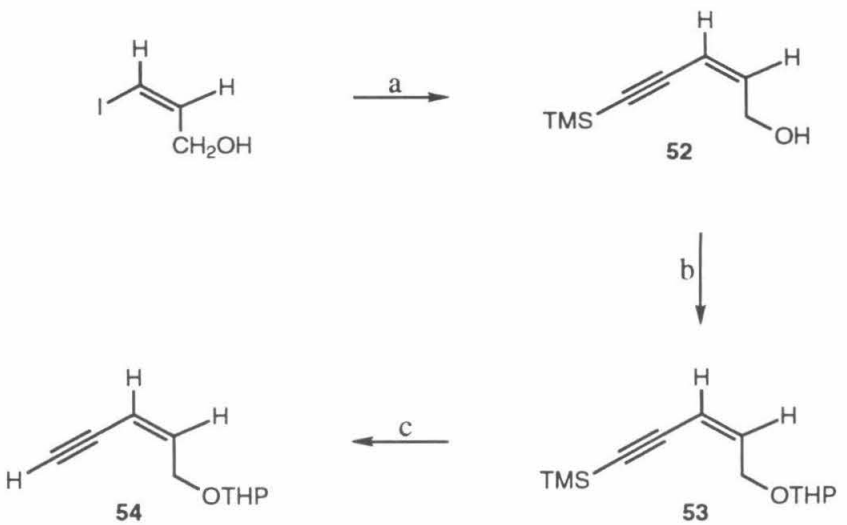
Synthesis of a Precursor to 1,6-Didehydro[10]annulene

Retrosynthetic analysis of **40** suggested alcohol **51** as an immediate precursor, on the assumption that it would undergo ready dehydration to form **40** (Scheme 9). Alcohol **51** was anticipated to derive from the base-induced cyclization of the aldehyde **77**, which, in turn, might be obtained from the dienediyne **64**. The initial synthetic route to **64** was designed to maximize convergence, exploiting the latent symmetry of the molecule by preparing it from two similar halves. Thus, **64** was envisioned to arise from the coupling of terminal acetylene **54** and allylic electrophile derived from alcohol **52**. Both of these enyne precursors were to be prepared from *(Z)*-iodopropenol.



Scheme 9. Retrosynthesis of 1,6-Didehydro[10]annulene, **40**.

(Z)-iodopropenol was effectively prepared by either of two known methods. In the first instance, *(Z)*-methyl iodoacrylate (prepared from propiolic acid in two steps) was reduced with lithium aluminum hydride (0.75 equiv, Et_2O, –78 °C) to provide the *(Z)*-iodopropenol in 58% yield.[45] Alternatively, direct reduction of propargyl alcohol with lithium aluminum hydride (1.00 equiv) and sodium methoxide (2.00 equiv) in refluxing tetrahydrofuran followed by reaction with iodine (3.00 equiv) at –78 °C produced a mixture of isomeric iodoalkenes, which could be purified to afford *(Z)*-iodopropenol in 66% yield.[46] While the separation of these isomers typically required repeated chromatography, this method was preferred because it was more amenable to large-scale execution and it did not involve *(Z)*-methyl iodoacrylate, which is a potent lachrymator.

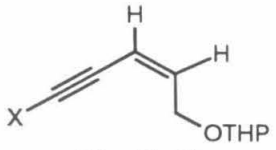


Scheme 10. Reagents and conditions: (a) TMSC≡CH (1.20 equiv), NEt_3 (7.50 equiv), CuI (0.20 equiv), $Pd(PPh_3)_2Cl_2$ (0.05 equiv), Et_2O, 23 °C, 73%; (b) DHP (1.20 equiv), CSA (0.04 equiv), CH_2Cl_2, 23 °C, 82%; (c) xs NaOH (50% w/w aq.), CH_3OH, 0 °C, 80%.

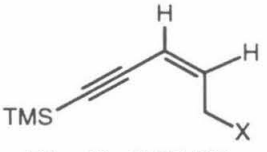
Submission of this alcohol and a slight excess of trimethylsilylacetylene to palladium/copper coupling conditions (7.50 equiv NEt_3, 0.20 equiv CuI, 0.05 equiv $Pd(PPh_3)_2Cl_2$, Et_2O, 23 °C)[10] afforded, after aqueous workup and chromatographic purification, enyne **52** in 73% yield (Scheme 10). Ether **53** was produced in 82% yield by the treatment of a solution of **52** in methylene chloride with dihydropyran and a catalytic quantity of camphorsulfonic acid at 23 °C. Deprotection of the silylacetylene with excess sodium hydroxide in methanol at 0 °C afforded **54** in 80% purified yield, after purification by chromatography.

Direct addition of a solution of lithium acetylide **55** in tetrahydrofuran to a solution of trifluoromethanesulfonate ester **57** (prepared by the method of Vedejs *et al.*)[47] in the same solvent at –78 °C produced the desired unsaturated product, **64**. Yields for this

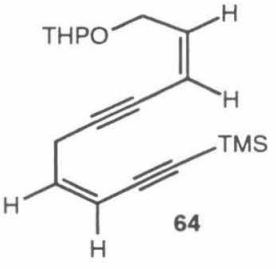
procedure were both highly variable and quite low (4-30%), and alternative coupling methods were thus explored. Initial efforts focused on variation of the electrophilic partner, in view of the high reactivity and thus possible instability of the trifluoromethanesulfonate ester **57**. However, treatment of **55** or the corresponding Grignard reagent with methanesulfonate ester **58** or bromide **59** failed to produce any of the desired product. Attempted couplings of the lithium acetylide with **60**, **62**, **61**, or **63** were also entirely without success.



54 X = H
55 X = Li
56 X = Cu



57 X = OSO_2CF_3
58 X = OSO_2CH_3
59 X = Br



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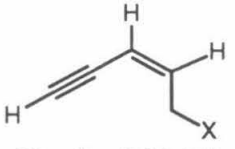
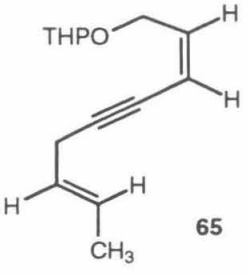
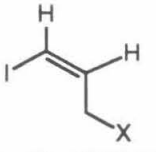


60 X = OSO_2CH_3
61 X = Br



65

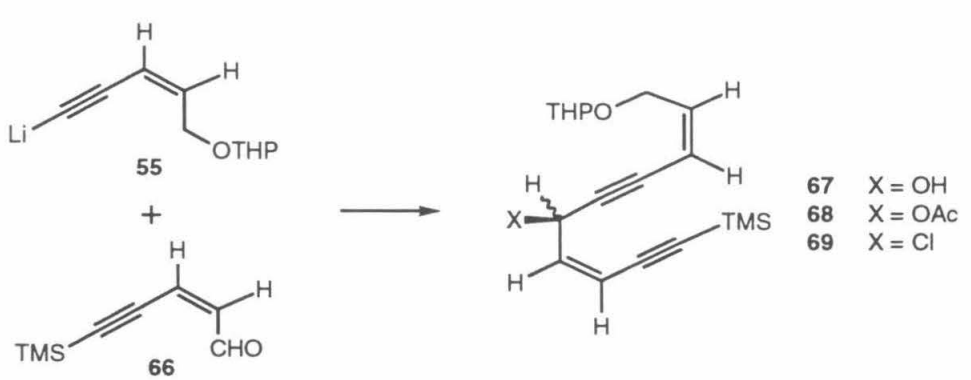


62 X = OSO_2CH_3
63 X = Br

Many methods for the copper-mediated reaction of acetylenes with alkyl, allylic, and propargylic electrophiles are known, and a number of these procedures were next explored. The use of copper(I) cyanide, a convenient and comparatively air-stable copper(I) source, in catalytic or stoichiometric amounts[48a-c] failed to effect the coupling of the lithium acetylide **55** with methanesulfonate esters **58**, **60**, or **62**; similar results were observed for coupling with bromides **61** and **63**. Copper(I) cyanide was observed to

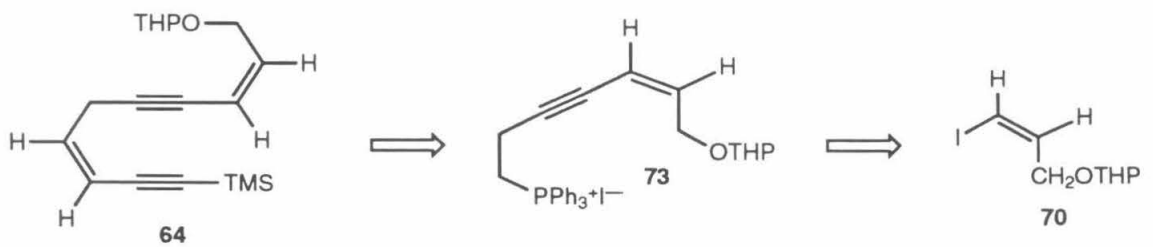
catalyze the reaction of **55** with the bromide **59**, but the yields for this reaction were not reproducible. The use of catalytic or stoichiometric copper(I) iodide as an alternative copper(I) source did not alter the outcome. Also ineffective were treatment of the free acetylene with diazabicycloundecene in the presence of catalytic or stoichiometric copper(I)[48d-f] and treatment with potassium carbonate and catalytic copper(I) under phase-transfer conditions.[48g,h] Likewise, attempted couplings of the pre-formed copper(I) acetylide **56** with **58** or **59** were without success.[48i,j] In contrast, it was observed that **55** reacted smoothly with *(E)*-bromo-2-butene in the presence of stoichiometric copper(I) cyanide to produce the adduct **65** (77% yield). Thus it appeared that some property of either the *(Z)* allylic electrophiles **57–63** or of *(Z)* allylic electrophiles in general make them poor substrates for these reactions, and that a different synthetic approach was in order.

The use of an unsaturated aldehyde as the electrophile was a potential solution to the coupling problem. While the immediate product of this addition would be a secondary alcohol, deoxygenation might then provide the desired hydrocarbon. The reaction of **55** (generated with 1.00 equiv butyllithium in tetrahydrofuran at –78 °C) with the aldehyde **66** (prepared in 61% yield by oxidation of the alcohol **52** with the Dess-Martin periodinane[49] in methylene chloride) in tetrahydrofuran at 23 °C provided the adduct **67** in 58% yield after purification (Scheme 11). Subsequent acetylation to form **68** proceeded in moderate



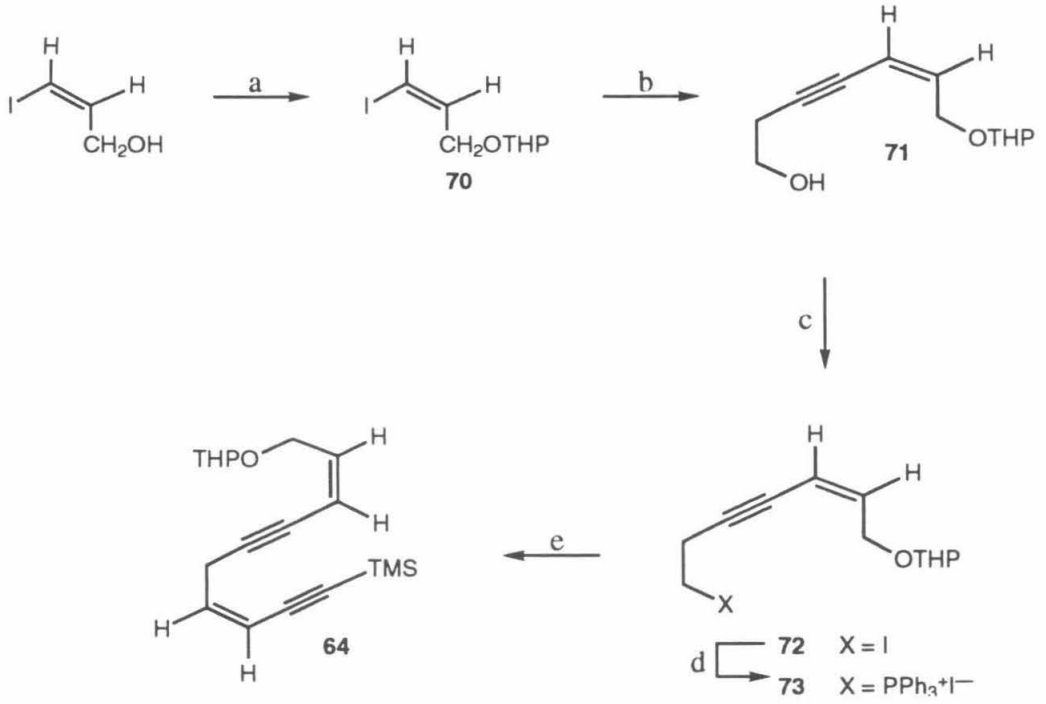
Scheme 11.

yield (3.00 equiv AcCl, 3.10 equiv DMAP, CH_2Cl_2, 23 °C, 40%). Attempted reduction of this acetate with samarium(II) iodide in tetrahydrofuran[50] led only to the recovery of starting material, in low yield. Efforts to prepare the toluenesulfonate or methanesulfonate esters resulted in decomposition of the starting material in the former case and decomposition accompanied by formation of small amounts of the chloride **69** in the latter. Treatment of **69** with lithium triethylborohydride in tetrahydrofuran[51] led to consumption of starting material but did not afford any isolable products, and deoxygenation was abandoned as a preparative method.



Scheme 12. Linear Retrosynthesis of Annulene **40**.

The successful approach to the preparation of **64** proved to be a linear one. Aldehyde **76** remained the penultimate target, but the precursor dienediyne **64** was now envisioned to derive from Wittig coupling of 1-trimethylsilylpropynal and the ylide derived from phosphonium iodide **73** (Scheme 12). The phosphonium iodide would in turn be obtained by modification of the alcohol prepared from the coupling of vinyl iodide **70** and a terminal acetylene, 3-butynol. The *(Z)* vinyl iodide **70** was obtained in 92% yield from treatment of *(Z)*-iodopropenol with dihydropyran (1.20 equiv) and camphorsulfonic acid (0.04 equiv) in methylene chloride (Scheme 13). The reaction of **70** with 3-butynol (1.20 equiv) in the presence of triethylamine (5.00 equiv), copper(I) iodide (0.15 equiv), and bis(triphenylphosphine)palladium(II) chloride (0.05 equiv) in tetrahydrofuran at 23 °C



Scheme 13. Reagents and conditions: (a) DHP (1.20 equiv), CSA (0.04 equiv), CH_2Cl_2, 23 °C, 92%; (b) $HC{\equiv}CCH_2CH_2OH$ (1.20 equiv), NEt_3 (5.00 equiv), CuI (0.20 equiv), $Pd(PPh_3)_2Cl_2$ (0.05 equiv), THF, 23 °C, 79%; (c) i CH_3SO_2Cl (1.05 equiv), NEt_3 (1.10 equiv), CH_2Cl_2, 0 °C ii LiI (2.50 equiv), THF, 55 °C, 76%; (d) PPh_3 (1.01 equiv), CH_3CN, 80 °C, 89%; (e) i BuLi (0.98 equiv), THF, –78 °C ii $TMSC{\equiv}CCHO$ (1.00 equiv), THF, 73%, 4:1 *Z*:*E*.

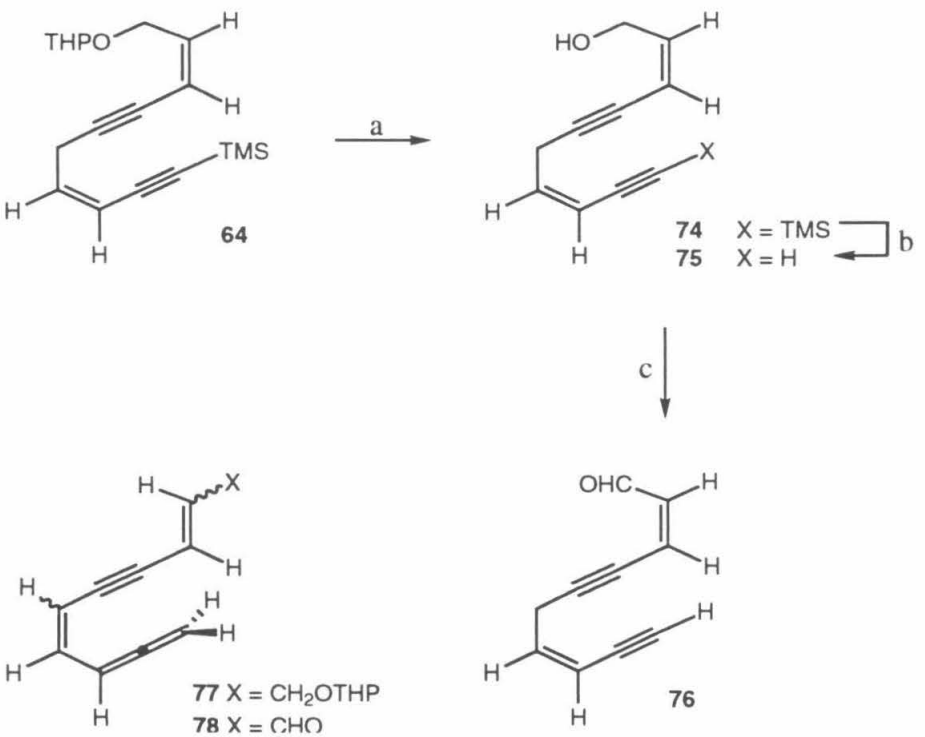
afforded enyne **71** in 79% yield. Eneyne **71** was converted to the corresponding methanesulfonate ester by addition of methanesulfonyl chloride (1.10 equiv) to a solution of **71** and triethylamine (1.20 equiv) in methylene chloride at 0 °C.[8] Displacement of the methanesulfonate by iodide (2.50 equiv LiI, THF, 55°C) produced **72** in 76% yield. The phosphonium iodide **73** was then prepared by heating a solution of **72** in acetonitrile with triphenylphosphine (1.02 equiv) at 80 °C (89% yield, after precipitation). 1-Trimethylsilyl-propynal was prepared from propargyl alcohol in four steps. Propargyl alcohol was treated

sequentially with butyllithium (2.00 equiv) and chlorotrimethylsilane (2.00 equiv) in tetrahydrofuran at –78 °C. Hydrolysis of the crude silylation product with aqueous citric acid (20% w/v) afforded 1-trimethylsilyl-2-propynol in 89% yield after purification by chromatography. Oxidation of 1-trimethylsilyl-2-propynol with pyridinium dichromate (1.20 equiv) and acetic acid (1.75 equiv) in methylene chloride[52] at 0 °C then produced 1-trimethylsilylpropynal in 43% yield after distillation.

Determination of appropriate conditions for the Wittig coupling reaction required extensive experimentation. After unsuccessfully employing a variety of bases for ylide generation, including both sodium and potassium hexamethyldisilazide, sodium amide, potassium hydride, dimsyl sodium, potassium *tert*-butoxide, and triethylamine, butyllithium proved to be the optimal reagent. Exposure of a solution of **73** (1.02 equiv) in tetrahydrofuran at –78 °C to butyllithium (1.00 equiv) for 20 minutes followed by rapid addition of a solution of 1-trimethylsilylpropynal in tetrahydrofuran provided, after 2.5 hours at –78 °C, dienediyne **64** in 71% yield as a 4:1 mixture of *Z*:*E* isomers at the newly-formed bond. These two isomers could be separated by careful chromatography on silica gel, producing pure **64** in 28% overall yield from *(Z)*-iodopropenol.

Dienediyne **64** proved to be unstable to the conditions normally employed to remove the terminal trimethylsilyl group: treatment of **64** with sodium hydroxide, or even with the mild reagent, potassium fluoride dihydrate, invariably produced appreciable quantities of the isomerization product, allene **77** (Scheme 14). While preliminary studies with acidic fluoride sources (HF-pyridine and triethylamine trihydrofluoride) were promising, concomitant partial loss of the tetrahydropyranyl group proved problematic, and it was decided to effect ether hydrolysis first. Thus, after treatment of **64** with trichloroacetic acid (5.00 equiv) in aqueous acetonitrile (6.5:1 acetonitrile:water) at 23 °C, alcohol **74** could be obtained in 88% yield. Subsequent removal of the trimethylsilyl group was carried out by heating a solution of **74** in methanol with an equal volume of

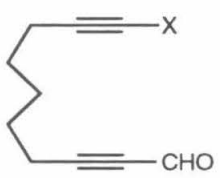
triethylamine trihydrofluoride at 55 °C in sealed a polyethylene vial, and afforded the alkyne **75** in 97% yield. While the outcome of these deprotections was observed to depend strongly on the purity of the starting materials, both could be routinely executed in high yield following careful purification of the precursor.



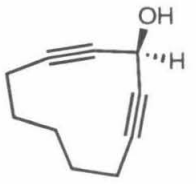
Scheme 14. Reagents and conditions: (a) CCl_3CO_2H (5.00 equiv), 6.5:1 CH_3CN:H_2O, 88%; (b) 1:1 CH_3OH:Et_3N•3HF, 55 °C, 97%; (c) Dess-Martin periodinane (2.50 equiv), CH_2Cl_2, 23 °C, 90%.

Oxidation of the alcohol **75** was quickly achieved with the Dess-Martin periodinane (2.50 equiv) in methylene chloride, producing **76** in 90% yield. Although a wide array of bases were employed (butyllithium, lithium diisopropylamide, lithium, potassium, and sodium hexamethyldisilazide, lithium tetramethylpiperidide), all attempts to cyclize this aldehyde to the alcohol **51** under basic conditions met with failure. With the exception of

treatment with potassium hexamethyldisilazide, which gave no observable reaction, the addition of base invariably led to the immediate formation of a bright red color accompanied by extensive decomposition of the starting material. In some cases it was possible to isolate small quantities of the isomerized allenic product **78**.

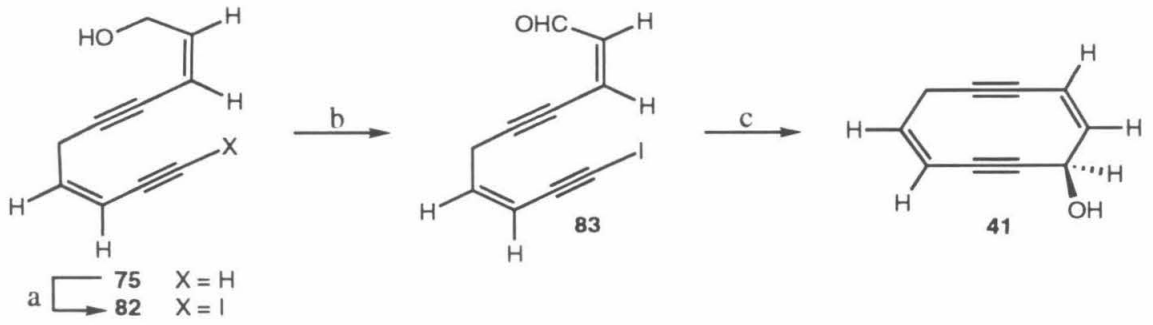


79 X = H
80 X = I



81

In a previous study, similar difficulty had been encountered in the preparation of the cyclodiynol **81**.[31] All attempts to convert the acetylenic aldehyde **79** to **81** under basic conditions resulted primarily in decomposition or oligomer formation. However, treatment of a dilute solution of the iodoacetylenic aldehyde **80** (0.002 M) in deoxygenated tetrahydrofuran with chromium(II) chloride (2.50 equiv) doped with 0.01% nickel(II) chloride[53] formed the desired intramolecular addition product in 32% yield, along with reduced starting material and oligomeric species. It was thus conjectured that a similar approach might allow the preparation of the alcohol **51**. Electrophilic iodination of alkyne **76** proceeded smoothly (1.02 equiv NIS, 0.20 equiv $AgNO_3$, acetone, 23 °C, 81%)[54] to form iodoacetylene **82** (Scheme 15), as did subsequent oxidation of **82** to the unstable aldehyde **83** (2.50 equiv Dess-Martin periodinane, CH_2Cl_2, 23 °C, 85%). Submission of this aldehyde to the conditions described above (2.50 equiv $CrCl_2$/0.01% $NiCl_2$, THF, 23 °C) resulted in formation of the desired alcohol **51** in 15-25% yield, along with reduced starting material, isomerized starting material, and decomposition products that were not identified.



Scheme 15. Reagents and conditions: (a) (1.02 equiv) NIS, (0.20 equiv) $AgNO_3$, acetone, 23 °C, 81%; (b) Dess-Martin periodinane (2.50 equiv), CH_2Cl_2, 23 °C, 85%; (c) $CrCl_2$ (2.50 equiv, 0.01% w/w $NiCl_2$), THF, 0 °C, 40%.

Several modifications allowed for an improvement in this yield. Preliminary experimentation suggested that the alcohol **51** was not entirely stable to the reaction conditions, as prolonged reaction times resulted in decreased yields and the slow addition of the aldehyde to a solution of the metal halides gave no product whatsoever. In addition, the aldehyde **83** had been observed to be sensitive to light and air (and likely to trace acid or base as well), and underwent ready isomerization and polymerization on standing at room temperature; **83** decomposed more slowly when stored cold (–20 °C) in frozen benzene under an inert atmosphere. In the optimized procedure, the metal halides were added to a solution of **83** (0.003 M) in deoxygenated tetrahydrofuran in a dry box and the reaction was carefully sealed against contamination by air. The reaction mixture was then removed from the dry box, and was allowed to stir in the dark at 0 °C for 2.5 hours. After aqueous workup and column chromatography, **51** could be isolated in 40% yield. The alcohol **51** proved extremely unstable, but could be concentrated for short periods of time in the presence of a free-radical inhibitor such as 3-*tert*-butyl-4-hydroxy-5-methyphenyl sulfide. With the preparation of **51** complete, its conversion to 1,6-didehydro[10]annulene was undertaken.

Synthesis and Characterization of 1,6-Didehydro[10]annulene

Initial studies were directed at the formation of **40** from **51** via the corresponding methanesulfonate ester. Toward this end, a solution of **51**, methanesulfonic anhydride (1.20 equiv), and triethylamine (2.40 equiv) in deoxygenated tetrahydrofuran-d_8 in an NMR tube was prepared and sealed at –78 °C. Initial low-temperature (–80 °C) ^{1}H NMR spectra indicated only starting materials to be present. Warming the sample to –40 °C in the probe of the spectrometer led to slow disappearance of **51** and concomitant formation of 1,5-dideuterionaphthalene ($t_{1/2} \approx 1.5$ hours). Signals attributable to the presumed intermediate methanesulfonate ester or to **40** were not observed, suggesting that, under these conditions, formation of the methanesulfonate ester is rate-determining and that both the elimination reaction that forms **40** and the subsequent cyclization of **40** to 1,5-dehydronaphthalene **41** are rapid at –40 °C.

In contrast, variable-temperature ^{1}H NMR analysis at –90 °C of a sample of **51**, trifluoromethanesulfonic anhydride, and triethylamine showed complete and clean conversion to a product assigned as 1,6-didehydro[10]annulene. ^{1}H and ^{13}C NMR data (Figures 4, 5) are consistent with static or time-averaged D_{2h} symmetry at –90 °C. The proton-decoupled ^{13}C NMR spectrum (methylene chloride-d_2, –90 °C) contains singlets at δ 137.1, δ 125.1, and δ 107.5. These chemical shifts may be approximated by averaging the anticipated values for the chemical shifts of the corresponding carbon centers in the two canonical resonance structures of **40**. The ^{1}H NMR spectrum (2:1 tetrahydrofuran-d_8:methylene chloride-d_2, –75 °C) comprises a doublet (δ 7.81, J = 8.3 Hz) and a triplet (δ

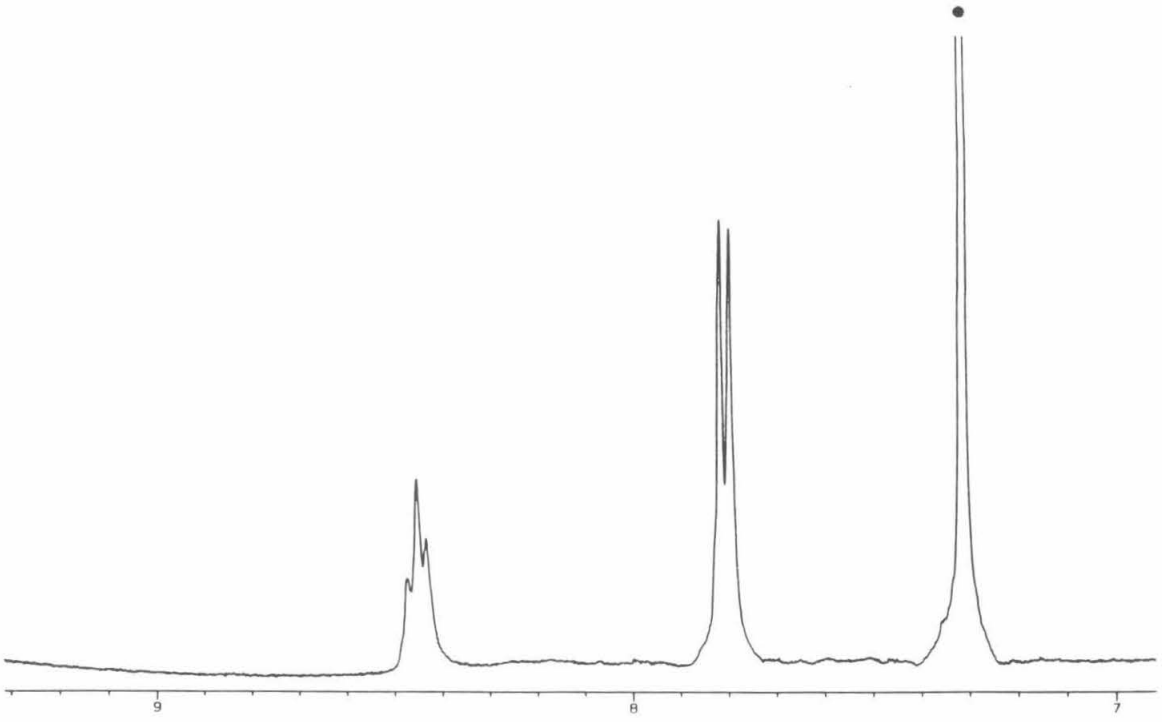


Figure 4. ^{1}H NMR Spectrum of **40** (2:1 THF-d_8:CD_2Cl_2, –75 °C; • denotes benzene).

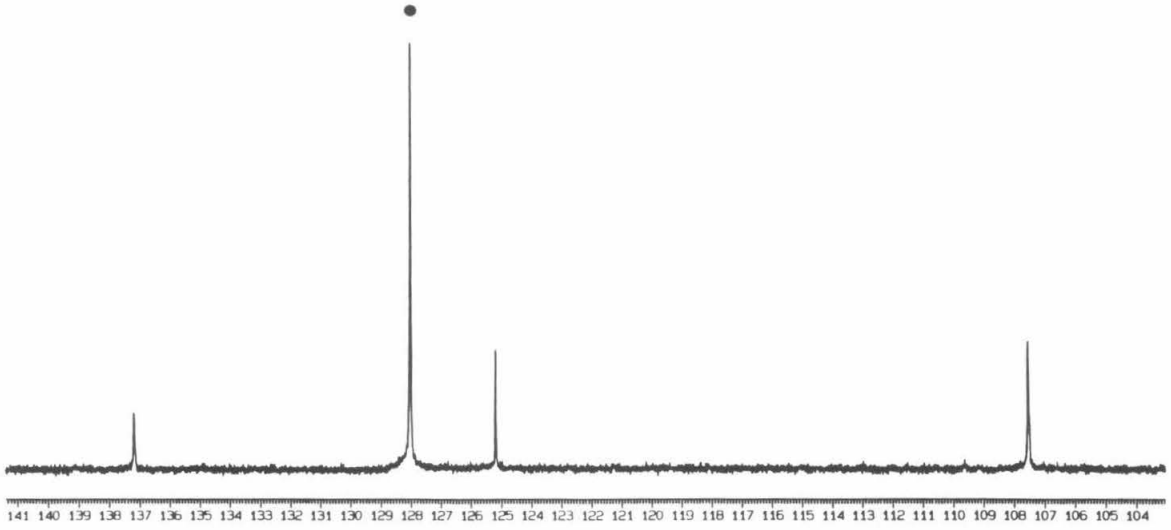


Figure 5. ^{13}C NMR Spectrum of **40** (CD_2Cl_2, –90 °C; • denotes benzene).

8.45, J = 8.3 Hz) in a 2:1 ratio by integration; these chemical shifts are clearly indicative of a strong diamagnetic ring current. In conjunction with the $^1J_{HH}$ (J = 8.3 Hz) and $^1J_{CH}$ ($J_{C1\text{-}H1}$ = 164 Hz, $J_{C2\text{-}H2}$ = 158 Hz) values, which are typical of aromatic compounds, these data support the notion that **40** is an aromatic compound, at least in a spectroscopic sense.[55]

While samples of **40** were stable at –90 °C for extended periods of time, on warming to higher temperatures, rapid cyclization ensued, forming naphthalene in 50-85% yield varying with the medium. Incorporation of deuterium was observed at C1 and C5 of the newly-formed naphthalene,[56] supporting the intermediacy of the biradical **41**. Kinetic analysis was carried out at –51 °C in methylene chloride-d_2 in the presence of 1,4-cyclohexadiene (0.6 M). The reaction was reproducibly first order in annulene (k = (4.6 ± 0.9) × 10^{-4} s^{-1}, $\Delta G^{\neq}$ = 16.3 ± 0.1 kcal/mol, –51±1 °C) and formed naphthalene in 85% yield. The rate of reaction was strongly temperature dependent, prohibiting practical kinetic measurement over a broad temperature range.

Discussion

With a half life of approximately 25 minutes at –51 °C, the rearrangement of **40** to **41** is the fastest cycloaromatization reaction reported to date. The next most rapid cyclization is that of **1**, the neocarzinostatin cumulene intermediate ($t_{1/2}$ ≈ 2 hours at –38 °C, $\Delta G^{\neq}$ = 18.0 ± 0.1 kcal/mol). Assuming the entropy of activation to be negligible, the free energies may be compared directly, indicating a 1.7 kcal/mol lower activation barrier for the cyclization of **40** than for **1**. The results of calculations performed to determine the transannular separation of the reacting centers in **40** and in **84**, a hydrocarbon analog of **1**, are presented in Table XI. Calculated heats of formation for **40** and **84**, as well as the products of their respective cycloaromatization reactions, **41** and **85**, are shown in Table XII. These calculations suggest the reacting centers in **1** are closer than the reacting centers in **40**, and that the cycloaromatization reaction of **1** is more exothermic than the

cycloaromatization reaction of **40**. Nonetheless, the cycloaromatization reaction of **40** is faster than that of **3**. It is intriguing to note that the conjugation of **40** is not disrupted during transformation to **41**, and that to the extent that **40** is stabilized by aromaticity, the transition state should enjoy at least an equal degree of aromatic stabilization. While aromaticity is now most often associated with distinct spectral characteristics rather than any property embodying chemical stability, the facility of the cycloaromatization of **40** may represent a clear manifestation of aromatic stabilization in a non-benzenoid system.

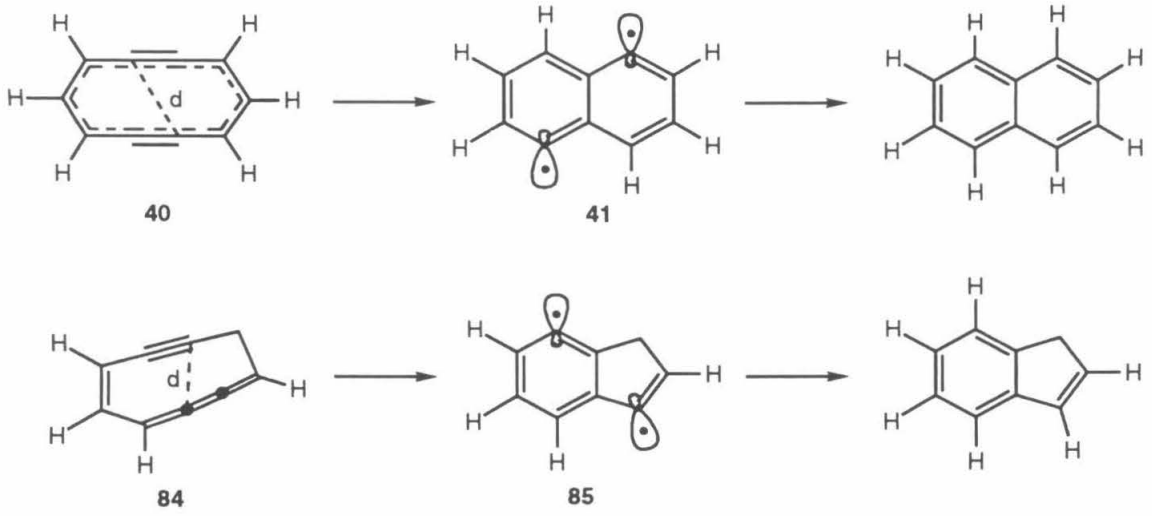


Table XI. Transannular Distances.

Compound	d[a]	d[b]
40	3.02	3.02
84	2.94	2.96

Table XII. Heats of Formation.

Compound	ΔH_f [c]	ΔH_f [d]
40	166	151
41	142	147
84[e]	169	150
85[e]	141	141

[a] In Å, from minimized geometries calculated using the MM2(90) program.[57] [b] In Å, from minimized geometries calculated using the AM1 Molecular Modeling program.[58] [c] In kcal/mol, calculated using Benson Additivities.[59] [d] In kcal/mol, calculated using the AM1 Molecular Modeling program. [e] Based on the value of ΔH_f for the corresponding hydrocarbon and standard bond dissociation energies.[60]

Conclusions

It seems reasonable and useful to separate cycloaromatization reactions into two categories: those leading to a σ,σ-biradical in which the radical centers have a syn disposition about the newly formed bond, and those leading to radical centers with an anti disposition. The Bergman reaction (**38** → **39**, $k = 2.9 \times 10^{-4}$ s^{-1}, $\Delta G^{\neq} \approx 32$ kcal/mol, $t_{1/2} \approx 40$ min, 145 °C) may be considered prototypical of the former class of reaction, while the cyclization of 1,6-didehydro[10]annulene, **40**, perhaps best illustrates the latter class. While rigorous comparisons are not possible, it would appear that cycloaromatizations leading to *anti*-biradicals are the more rapid class of reaction. On the basis of ab initio calculations, it has been suggested that in-plane π-π repulsions may account for this difference in rate.[61] This repulsion would be most pronounced in Bergman-type cyclizations, where bond formation requires the temporary compression of the in-plane non-bonding π-orbitals, and least pronounced in annulene-type cyclizations, where such repulsion is actually relieved during bond formation.

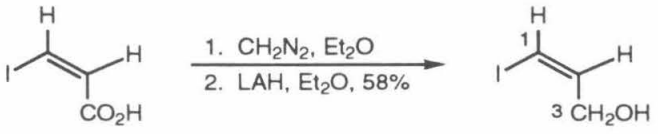
Experimental Section

General Procedures. All reactions were performed in flame-dried round-bottom or modified Schlenk (Kjeldahl shape) flasks fitted with rubber septa under a positive pressure of argon, unless otherwise noted. Air- and moisture-sensitive liquids and solutions were transferred via syringe or stainless steel cannula. Where necessary (so noted), reaction mixtures were degassed by evacuating for 10-15 seconds and flushing with argon ($\geq$ 5 iterations). Organic solutions were concentrated by rotary evaporation at $\approx$ 25 Torr (water aspirator) at or slightly above ambient temperature, unless otherwise noted. Flash column chromatography was performed as described by Still *et al.*,[17] employing 230-400 mesh silica gel. Analytical and preparative thin-layer chromatography were performed using glass plates pre-coated with 0.25 mm 230-400 mesh silica gel impregnated with a fluorescent indicator (254 nm). Thin-layer chromatography plates were visualized by exposure to ultraviolet light (noted as 'UV') and/or by exposure to an acidic solution of *p*-anisaldehyde in ethanol followed by heating on a hot-plate (noted as 'anisaldehyde'). NMR tubes for sealed tube experiments were standard 7"x5 mm o.d. Young-valve NMR tubes purchased from Wilmad. The NMR tubes were pretreated by soaking with *aqua regia*, rinsing thoroughly with filtered (4 μ) distilled water, soaking with hexamethyldisilazane, rinsing thoroughly with filtered distilled water, and drying under vacuum. Tetrahydrofuran for use in chromium(II)-mediated reactions was degassed in a Schlenk pot on a high vacuum line to an overpressure of $\leq$ 10 mTorr by freeze-pump-thaw.

Materials. Commercially available reagents were used as received, with the following exceptions. Ethyl ether and tetrahydrofuran were distilled from sodium benzophenone ketyl. Benzene was distilled from sodium metal. Methylene chloride, acetonitrile, triethylamine, propylamine, and trimethylsilyl chloride were distilled from calcium hydride. Methanol was distilled from magnesium turnings and was stored over 4 Å molecular sieves. Acetic acid was distilled from chromium trioxide at reduced pressure

and was stored over 4 Å molecular sieves. Methanesulfonyl chloride was distilled from phosphorus pentoxide at atmospheric pressure. Copper(I) iodide was purified by continuous extraction (24 hours) with tetrahydrofuran in a Soxhlet apparatus. The molarity of butyllithium solutions was determined by titration using diphenylacetic acid as an indicator (average of three determinations).[18]

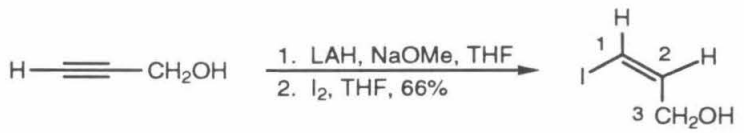
Instrumentation. Infrared spectra were obtained using a Perkin-Elmer 1600 FT-IR spectrophotometer referenced to a polystyrene standard. Data are presented as follows: frequency of absorption (cm^{-1}), intensity of absorption (s = strong, m = medium, w = weak, br = broad). Proton nuclear magnetic resonance (^1H NMR) and carbon nuclear magnetic resonance (^{13}C NMR) spectra were obtained on a JEOL GX-400 (9.40 Tesla) spectrometer; chemical shifts are expressed in parts per million. ^1H NMR chemical shifts are referenced to the signal for residual hydrogen in the NMR solvent ($CHCl_3$: δ 7.26, C_6D_5H: δ 7.15, $CHDCl_2$: δ 5.32, THF-d_7: δ 1.73, 3.58). Data are presented as follows: chemical shift, multiplicity, (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), integration, coupling constant in Hertz, and assignment (where possible). ^{13}C NMR chemical shifts are referenced to the carbon signal for the solvent ($CDCl_3$: δ 77.0, C_6D_6: δ 128.0, CD_2Cl_2: δ 53.8, THF-d_8: δ 25.3, 67.4). Data are presented as follows: chemical shift, assignment (where possible). Mass spectrometry was performed at the University of California at Riverside, Riverside Mass Spectrometry Facility, or at the Midwest Center for Mass Spectrometry at the University of Nebraska–Lincoln (with partial support by the National Science Foundation, Biology Division; Grant No. DIR9017262). Ultraviolet absorption spectra were measured on a Hewlett-Packard 8452A Diode Array Spectrophotometer.



(Z)-Iodopropenol.

A solution of *(Z)*-iodoacrylic acid (40.00 g, 202 mmol, 1 equiv) in diethyl ether (200 ml) was treated with an excess of ethereal diazomethane in an open erlenmeyer flask and until such time as gas evolution ceased and the persistent yellow color of the diazomethane faded. The crude *(Z)*-methyl iodoacrylate solution (*Caution: Lachrymator, Irritant*) was dried over sodium sulfate and was concentrated. The residue was dissolved in diethyl ether (150 ml), and the resulting solution was added dropwise over 1 hour to a suspension of lithium aluminum hydride (5.75 g, 152 mmol, 0.75 equiv) in diethyl ether (150 ml) at –78 °C. After 1 hour, the gray slurry was warmed to 23 °C and excess lithium aluminum hydride was quenched by addition of water (25 ml, *Caution: Exothermic*) and cold (0 °C) aqueous sulfuric acid (20% v/v, 100 ml). The mixture was stirred for 15 minutes and the phases were separated. The aqueous phase was extracted with diethyl ether (5x100 ml) and the combined organic fractions were washed sequentially with saturated aqueous sodium thiosulfate (2x50ml) and saturated aqueous sodium chloride (50 ml). The organic phase was then dried over sodium sulfate, was concentrated, and the residue was purified by flash column chromatography (20% ethyl acetate-hexanes) to provide *(Z)*-iodopropenol (21.41 g, 58%) as a light yellow liquid.

^{1}H NMR (400 MHz, $CDCl_3$), δ:	6.42 (dt, 1H, J = 7.6, 5.5 Hz, H2), 6.29 (d, 1H, J = 7.6 Hz, H1), 4.15 (d, 2H, J = 5.5 Hz, H3), 3.48 (br s, 1H, alcohol OH).
FTIR (neat), cm^{-1}:	3350 (m), 2990 (m), 2963 (w), 1610 (w), 1300 (m), 1060 (m), 1025 (m).
TLC (20% Ethyl Acetate-Hexanes), R_f:	0.15 (UV, anisaldehyde).



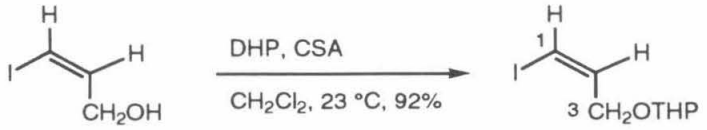
(Z)-Iodopropenol.

A mixture of sodium methoxide (17.02 g, 299 mmol, 2.20 equiv) and lithium aluminum hydride (5.98 g, 150 mmol, 1.10 equiv) was added slowly via powder addition funnel to tetrahydrofuran (500 ml, *Caution: Exothermic*) at –78 °C. The addition funnel was replaced with a septum and propargyl alcohol (8.00 ml, 136 mmol, 1 equiv) was added dropwise over 10 minutes. After stirring for 1 hour, the reaction was warmed to 23 °C over 4.5 hours, was heated to reflux for 4 hours, and was allowed to cool to 23 °C overnight. The gray slurry was cooled to –78 °C, iodine (103.60 g, 408 mmol, 3.00 equiv) was added in 5 portions over 5 minutes, and the mixture was stirred for 45 minutes. After warming the heterogeneous brown reaction mixture to 23 °C and stirring for 1 hour, the mixture was partitioned between saturated aqueous potassium carbonate (200 ml), saturated aqueous potassium sodium tartrate (100 ml), water (100 ml), and 20% ethyl acetate-hexanes (200 ml). The aqueous phase was extracted with 20% ethyl acetate-hexanes (4x200 ml), and the combined organic layers were washed with saturated aqueous sodium thiosulfate (200 ml), were dried over sodium sulfate, and were concentrated. Two flash column chromatographic purifications (15% ethyl acetate-hexanes) provided *(Z)*-iodopropenol (16.59 g, 66%) as a yellow liquid.

^{1}H NMR (400 MHz, $CDCl_3$), δ: 6.42 (dt, 1H, J = 7.6, 5.5 Hz, H2), 6.29 (d, 1H, J = 7.6 Hz, H1), 4.15 (d, 2H, J = 5.5 Hz, H3), 3.48 (br s, 1H, alcohol OH).

FTIR (neat), cm^{-1}: 3350 (m), 2990 (m), 2963 (w), 1610 (w), 1300 (m), 1060 (m), 1025 (m).

TLC (20% Ethyl Acetate-Hexanes), R_f: 0.15 (UV, anisaldehyde).



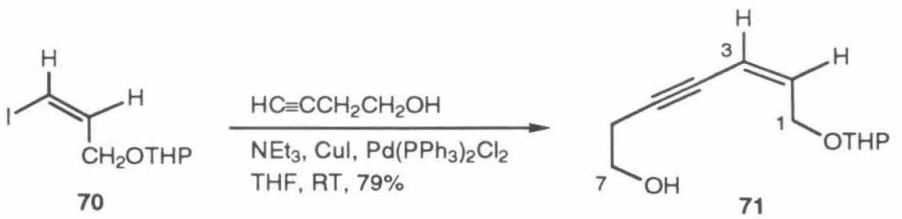
70

Ether **70.**

Camphorsulfonic acid (0.075 g, 0.32 mmol, 0.04 equiv) was added to a solution of dihydropyran (0.810 ml, 8.87 mmol, 1.20 equiv) and *(Z)*-iodopropenol (1.36 g, 7.39 mmol, 1 equiv) in methylene chloride (15 ml) in an open flask. The reaction flask was capped with a septum and the solution was allowed to stir at 23 °C for 50 minutes. The dark green solution was then poured into half-saturated aqueous sodium bicarbonate (30 ml), and the aqueous phase was extracted with 10% ethyl acetate-hexanes (3x50 ml). The combined organic extracts were dried over sodium sulfate and were concentrated. Flash column chromatography of the residue (10% ethyl acetate-hexanes) afforded the tetrahydropyranyl ether **70** (1.82 g, 92%) as a colorless oil.

^{1}H NMR (400 MHz, C_6D_6), δ: 6.29 (ddd, 1H, *J* = 7.8, 5.9, 4.9 Hz, H2), 5.95 (d, 1H, *J* = 7.8 Hz, H1), 4.54 (t, 1H, *J* = 3.4 Hz, THP), 4.37 (dd, 1H, *J* = 13.7, 4.9 Hz, H3), 4.09 (dd, 1H, *J* = 13.7, 5.9 Hz, H3), 3.75 (dt, 1H, *J* = 8.3, 2.9 Hz, THP), 3.33-3.42 (m, 1H, THP), 1.65-1.80 (m, 1H, THP), 1.45-1.65 (m, 2H, THP), 1.20-1.42 (m, 3H, THP).

^{13}C NMR (100 MHz, C_6D_6), δ:	139.0 (C2), 98.3 (THP acetal), 82.1 (C1), 70.2 (C3), 61.6, 30.7, 25.7, 19.4 (THP).
FTIR (neat), cm^{-1}:	3068 (w), 2940 (s, br), 2870 (s), 2849 (s), 1454 (m), 1440 (m), 1345 (m, br), 1279 (s, br), 1201 (s), 1120 (s, br), 1028 (s, br), 963 (m, br), 905 (s), 870 (m), 816 (m).
MS (EI), m/z (%base):	167 (77), 101 (50), 85 (100), 67 (32).
HRMS (EI):	Calcd for $C_8H_{13}IO_2$ (M^+): 267.9960. Found: 267.9948.
Elemental Analysis:	Calcd for $C_8H_{13}IO_2$: C, 35.84; H, 4.89. Found: C, 35.82; H, 4.90.
TLC (20% Ethyl Acetate-Hexanes), R_f:	0.51 (UV, anisaldehyde).



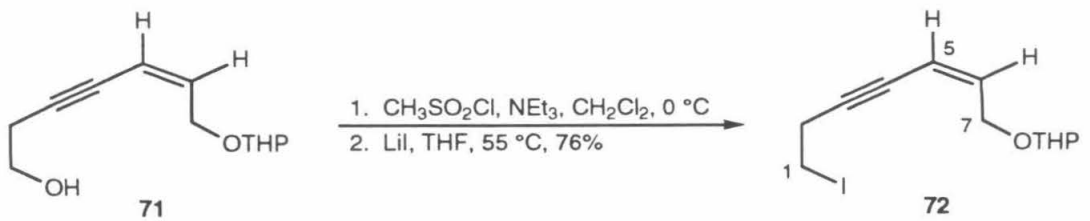
Eneyne **71**.

Copper(I) iodide (0.194 g, 0.15 mmol 0.15 equiv) was added to a degassed solution of 3-butynol (0.644 g, 8.15 mmol, 1.20 equiv) and triethylamine (4.73 ml, 33.95 mmol, 5.00 equiv) in tetrahydrofuran (30 ml) at –78 °C, the suspension was degassed and was allowed to warm to 23 °C. A suspension of bis(triphenylphosphine)palladium(II) dichloride (0.243 g, 0.34 mmol, 0.05 equiv) and the tetrahydropyranyl ether **70** (1.820 g, 6.79 mmol, 1 equiv) in tetrahydrofuran (25 ml) was degassed at –78 °C and the mixture was added via cannula to the cloudy white acetylide solution, resulting in the immediate darkening of the reaction mixture. After 2.5 hours, an aqueous solution (50 ml) comprising equal parts saturated aqueous ammonium chloride and saturated aqueous potassium carbonate was added and the biphasic mixture was stirred vigorously for 30 minutes. 20% Ethyl acetate-hexanes (100ml) was added, the phases were separated, and the aqueous phase was washed with 20% ethyl acetate-hexanes (2x50 ml). The combined organic fractions were dried over sodium sulfate and were concentrated. Flash column chromatography of the residue (40% ethyl acetate-hexanes) afforded the eneyne **71** (1.130 g, 79%) as a yellow oil.

^{1}H NMR (400 MHz, C_6D_6), δ:	5.96 (ddd, 1H, *J* = 10.7, 7.6, 6.1 Hz, H2), 5.57 (d, 1H, *J* = 10.7 Hz, H3), 4.73 (t, 1H, *J* = 3.3 Hz, THP), 4.45-4.60 (m, 2H, H1), 3.83 (td, 1H, *J* = 10.6, 2.6 Hz, THP), 3.43-3.52 (m, 3H, H7, THP), 2.46 (br s, 1H, alcohol OH), 2.29 (td, 2H, *J* = 6.0, 2.0 Hz, THP), 1.70-1.84 (m, 1H, THP), 1.52-1.62 (m, 2H, THP), 1.20-1.45 (m, 3H, THP).
^{13}C NMR (100 MHz, C_6D_6), δ:	138.6 (C2), 112.7 (C3), 97.0 (THP acetal), 93.6 (C5), 78.5 (C4), 64.2, 62.5 (C1, C7), 62.1, 30.7, 25.8 (THP), 24.5 (C6), 19.2 (THP).
FTIR (neat), cm^{-1}:	3400 (w, br), 2942 (m), 2872 (m), 1132 (m), 1117 (m), 1024 (s).
MS (EI), m/z (%base):	125 (2), 109 (3), 101 (7), 85 (100), 69 (10), 67 (12), 57 (16), 56 (12), 55 (24).
HRMS (EI):	Calcd for $C_{12}H_{18}O_3$ (M^+): 210.1255. Found: 210.1265.
Elemental Analysis:	Calcd for $C_{12}H_{18}O_3$: C, 68.54; H, 8.63. Found: C, 68.42; H, 8.63.

TLC (40% Ethyl Acetate-

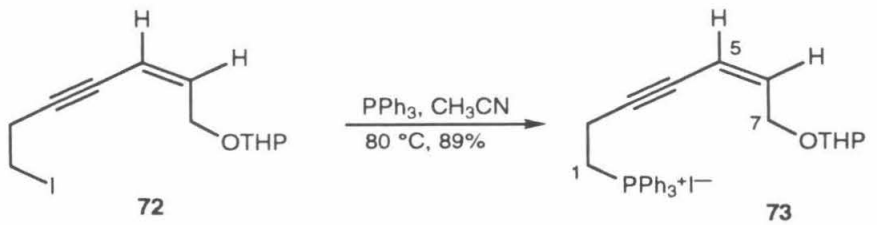
Hexanes), R_f: 0.24 (UV, anisaldehyde).



Iodide **72.**

Methanesulfonyl chloride (2.13 ml, 27.0 mmol, 1.05 equiv) was added dropwise over 10 minutes to a solution of triethylamine (3.94 ml, 28.3 mmol, 1.10 equiv) and the alcohol **71** (5.41 g, 25.7 mmol, 1.00 equiv) in methylene chloride (50 ml) at 0 °C. After 30 minutes, excess methanesulfonyl chloride was quenched by the addition of aqueous citric acid (20% w/w, 100 ml) and 20% ethyl acetate-hexanes (100 ml). The aqueous phase was extracted with 20% ethyl acetate-hexanes (2x100 ml), and, after addition of benzene (50 ml), the combined organic fractions were dried over sodium sulfate and were concentrated. The resultant brown oil was dissolved in tetrahydrofuran (100 ml), was added via cannula to lithium iodide (8.61 g, 64.3 mmol, 2.50 equiv), and the resulting red solution was heated at 55 °C for 5 hours. After cooling to 23 °C, hexanes (150 ml) were added and the crude reaction was allowed to stand at –20 °C for several hours. The supernatant was decanted and the residual solids were washed with 20% ethyl acetate-hexanes (2x50 ml). The combined organic fractions were concentrated and were purified by flash column chromatography (10% ethyl acetate-hexanes), providing the iodide **72** (6.30 g, 76%) as an orange oil.

^{1}H NMR (400 MHz, C_6D_6), δ:	6.02 (ddd, 1H, *J* = 10.9, 6.5, 5.6 Hz, H6), 5.43 (d, 1H, *J* = 10.9 Hz, H5), 4.60-4.75 (m, 2H, THP, H7), 4.45 (dd, 1H, *J* = 13.4, 6.5 Hz, H7), 3.70-3.85 (m, 1H, THP), 3.30-3.40 (m, 1H, THP), 2.61 (t, 2H, *J* = 7.0 Hz, H2), 2.33 (t, 2H, *J* = 7.0 Hz, H1), 1.50-1.80 (m, 3H, THP), 1.15-1.40 (m, 3H, THP).
^{13}C NMR (100 MHz, C_6D_6), δ:	140.2 (C6), 110.8 (C5), 98.4 (THP acetal), 94.5 (C3), 28.7 (C4), 65.5 (C7), 61.7, 30.9, 25.8 (THP), 24.7 (C2), 19.5 (THP), 1.4 (C1).
FTIR (neat), cm^{-1}:	3029.7 (w), 2940.4 (s), 2869.5 (m), 2849.1 (m), 2218.6 (w), 1132.8 (s), 1118.3 (s), 1029.4 (s), 905.6 (m), 869.1 (m), 815.2 (m).
MS (EI), m/z (%base):	219 (47), 92 (33), 91 (89), 85 (57).
HRMS (EI):	Calcd for $C_{12}H_{17}IO_2$ (M^+): 320.0273. Found: 320.0267.
TLC (20% Ethyl Acetate-Hexanes), R_f:	0.63 (UV, anisaldehyde).



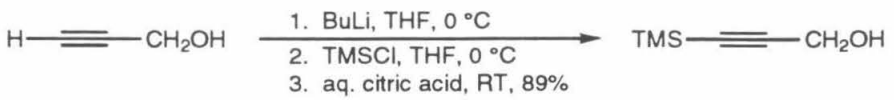
Triphenylphosphonium Iodide **73.**

A solution of the iodide **72** (6.30 g, 19.7 mmol, 1 equiv) and triphenylphosphine (5.16 g, 19.6 mmol, 0.99 equiv) in acetonitrile (100 ml) was heated at 80 °C for 13 hours. Upon cooling to 23 °C, the reaction was concentrated under reduced pressure. The resultant red oil was allowed to stand overnight with diethyl ether (100 ml) at –20 °C. The ethereal layer was then decanted, and the frozen oil was dissolved in methylene chloride (30 ml) and diethyl ether (20 ml). After allowing the solution to stand at –20 °C for several hours, the supernatant was decanted and the solid orange residue was rinsed with 50% ethyl acetate-hexanes (20 ml). Prolonged drying of the residue in the dark under reduced pressure produced the triphenylphosphonium iodide **73** (10.16 g, 89%) as a brittle orange foam.

^{1}H NMR (400 MHz, C_6D_6), δ: 7.65-7.95 (m, 18H, PPh_3), 5.92 (ddd, 1H, J = 11.0, 7.0, 4.1 Hz, H6), 5.21 (d, 1H, J = 11.0 Hz, H5), 4.55 (t, 1H, J = 2.5 Hz, THP), 4.19 (dd, 1H, J = 12.8, 4.1 Hz, H7), 4.03 (dd, 1H, J = 7.0, 12.8, H7), 3.70-3.90 (m, 3H, 2 x H2, THP), 3.35-3.45 (m, 2H, THP), 2.95 (dt, 2H, $^2J_{H\text{-}P}$ = 19.1 Hz, J = 6.8 Hz), 1.45-1.85 (m, 6H, THP).

^{13}C NMR (100 MHz, C_6D_6), δ: 140.2 (C6), 135.42, 134, 130.5 (PPh_3), 110.0 (C5), 98.5 (THP acetal), 91.6 (C3), 80.4 (C4), 65.0 (C7), 62.3 (THP), 30.8, 25.6 (THP), 22.8 (C7, $J_{C\text{-}P}$ = 42 Hz), 19.6 (THP), 14.1 (C6).

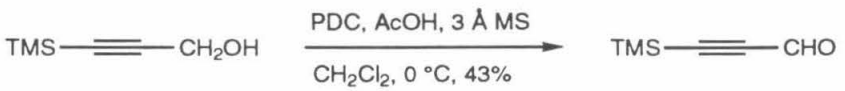
MS (FAB), m/z (%base): 455 (100), 369 (15), 262 (43).



Trimethylsilylpropyn-3-ol

Butyllithium (2.5 M, 136.00 ml, 340 mmol, 2.00 equiv) was added via cannula over 10 minutes to a solution of propargyl alcohol (10.00 ml, 170 mmol, 1 equiv) in tetrahydrofuran (500 ml) at 0 °C. After 30 minutes, chlorotrimethylsilane (43.17 ml, 340 mmol, 2.00 equiv) was added to the thick white slurry in two portions. The reaction quickly became clear and colorless, and after 25 minutes it was warmed to 23 °C. The reaction was quenched by addition of aqueous citric acid (20% w/w, 100 ml) and was stirred vigorously for 5.5 hours. The phases of the mixture were then separated, and the aqueous phase was extracted with 20% ethyl acetate-hexanes (1x100 ml). The organic extracts were dried over sodium sulfate and were concentrated. Purification of the residue by flash column chromatography (15% ethyl acetate-hexanes) afforded trimethylsilylpropyn-3-ol (19.45 g, 89%) as a colorless liquid.

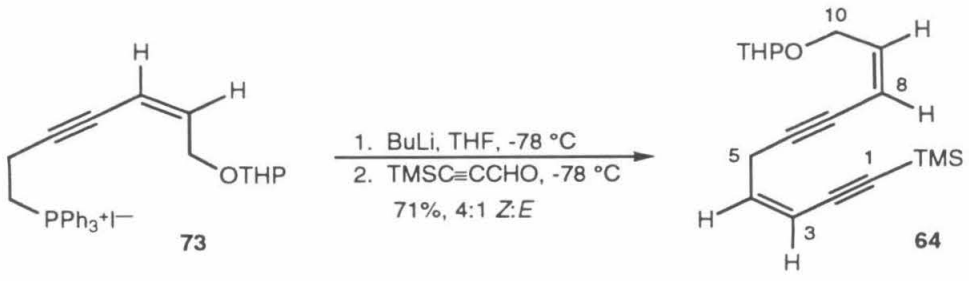
^{1}H NMR (400 MHz, $CDCl_3$), δ:	3.55 (s, 2H, H3), 1.34 (br s, 1H, alcohol OH), 0.22 (s, 9H, $Si(CH_3)_3$).
FTIR (neat), cm^{-1}:	3450 (w), 2959 (m), 2900 (m), 2185 (w), 856 (m).
TLC (20% Ethyl Acetate-Hexanes), R_f:	0.36 (UV, anisaldehyde).



1-Trimethylsilylpropynal.

3 Å molecular sieves (142g, 1/8" pellets) were flame dried under vacuum in a three-neck round bottom flask, were cooled to 23 °C, and were covered with methylene chloride (350 ml). The flask was then equipped with a mechanical stirring apparatus and placed under a constant slow stream of argon. Pyridinium dichromate (85.47 g, 222 mmol, 1.25 equiv) and acetic acid (17.80 ml, 311 mmol, 1.75 equiv) were added with gentle stirring, and the mixture was cooled to 0 °C. A solution of trimethylsilylpropyn-3-ol (22.80 g, 178 mmol, 1 equiv) in methylene chloride (100 ml) was added via cannula over 5 minutes, and the ice bath was removed. After 3 hours, the reaction mixture was vacuum-filtered through a large pad of silica (500 ml) in a coarse fritted funnel. The silica was rinsed with 10% ethyl acetate-hexanes (100 ml) and benzene (100 ml), and the combined filtrates were concentrated to approximately 100 ml. Benzene (250 ml) was added and the solution was concentrated to 14.66 g (1.86:1.00 benzene:aldehyde by ^{1}H NMR analysis; 9.57 g aldehyde, 43 %), which was diluted to 50.00 ml with tetrahydrofuran to provide a stock solution (1.51 M) of trimethylsilylpropynal.

^{1}H NMR (400 MHz, CD_2Cl_2), δ:	9.17 (s, 1H, H3), 0.24 (s, 9H, $Si(CH_3)_3$).
FTIR (neat), cm^{-1}:	2916 (m), 2123 (w), 1663 (s).
TLC (20% Ethyl Acetate-Hexanes), R_f:	0.80 (UV).



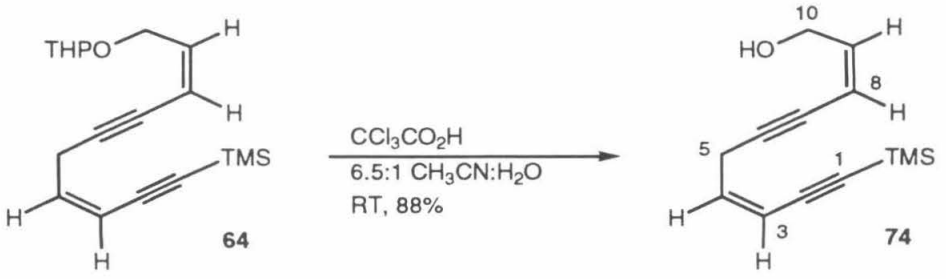
Dienediyne **64**.

Butyllithium (1.21 M, 5.16 ml, 6.25 mmol, 1 equiv) was added dropwise over 3 minutes to a solution of the phosphonium iodide **73** (3.71 g, 6.37 mmol, 1.02 equiv; concentrated from 1:1 benzene:methylene chloride) in tetrahydrofuran (150 ml) at –78 °C. The initially yellow solution turned an opaque reddish-brown, then became clear red in color after 20 minutes. After 35 minutes, a solution of trimethylsilylpropynal in tetrahydrofuran (1.51 M, 4.21 ml, 6.37 mmol, 1.02 equiv) was added, causing the color to fade to a light reddish orange. After 2.5 hours, the reaction was quenched by the addition of 20% ethyl acetate-hexanes (100 ml) and aqueous pH 7.0 phosphate buffer (0.05M, 75 ml). The mixture was warmed to 23 °C and was partitioned between water (25 ml) and 20% ethyl acetate-hexanes (100 ml). The aqueous phase was washed with 20% ethyl acetate-hexanes (1x100 ml), and the combined organic extracts were dried over sodium sulfate and were concentrated. Flash column chromatography (4% ethyl acetate-hexanes) of the soluble portion of the residue produced the dienediyne **64** (1.37 g, 71%) as a mixture of isomers (4:1 *Z:E* by ^{1}H NMR analysis) at the newly formed double bond. The two isomers could be separated after careful purification twice by flash column chromatography (2% ethyl acetate-hexanes).

^{1}H NMR (400 MHz, C_6D_6), δ:	6.02 (ddd, 1H, *J* = 10.7, 6.4, 6.1 Hz, H9), 5.72 (dt, 1H, *J* = 10.7, 7.0 Hz, H4), 5.51 (d, 1H, *J* = 10.7 Hz, H8), 5.42 (d, 1H, *J* = 10.7, H3), 4.65 (d of d, 1H, *J* = 12.9, 6.4 Hz, H10), 4.63 (t, 1H, *J* = 3.4 Hz, THP), 4.42 (dd, 1H, *J* = 12.9, 6.1 Hz, H10), 3.82 (dt, 1H, *J* = 10.3, 2.8 Hz, THP), 3.35-3.40 (m, 1H, THP), 3.36 (d, 2H, *J* = 7.0, H5), 1.65-1.80 (m, 1H, THP), 1.45-1.60 (m, 2H, THP), 1.15-1.40 (m, 3H, THP), 0.17 (s, 9H, TMS).
^{13}C NMR (100 MHz, C_6D_6), δ:	139.6 (C9), 138.7 (C4), 111.1 (C8), 101.3 (C3), 100.9, 98.2 (C1, C2), 98.2 (THP acetal), 92.7 (C6), 77.7 (C7), 65.4 (C10), 61.5, 30.9, 25.8 (THP), 21.2 (C10), 19.4 (THP), -0.10 (TMS).
FTIR (neat), cm^{-1}:	2956 (m), 2872 (w), 2152 (w), 1250 (m), 1119 (m), 1031 (m), 847 (s).
MS (EI), m/z (%base):	229 (7), 85 (100), 73 (27).
HRMS (EI):	Calcd for $C_{18}H_{26}O_2Si$ (M^+): 302.1710. Found: 302.1671.

Elemental Analysis: Calcd for $C_{18}H_{26}O_2Si$: C, 71.47; H, 8.66.
Found: C, 71.87; H, 8.77.

TLC (20% Ethyl Acetate-Hexanes), R_f: *(Z, Z)*: 0.50 (UV, anisaldehyde).
(E, Z): 0.47 (UV, anisaldehyde).

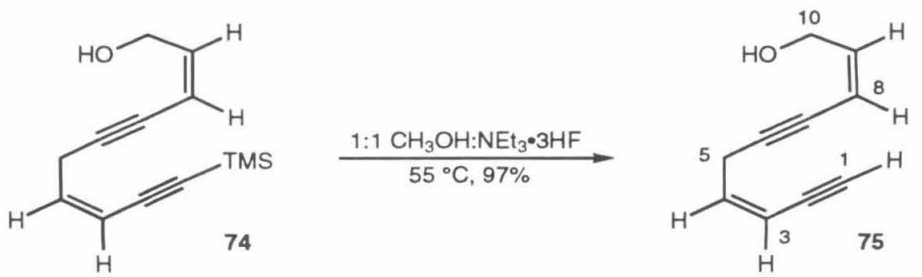


Alcohol **74.**

Trichloroacetic acid (1.76 g, 10.8 mmol, 5.00 equiv) was added to a cloudy solution of the dienediyne **64** (0.650 g, 2.15 mmol, 1 equiv) in 6.5:1 acetonitrile:water (75 ml). After 4 hours at 23 °C, the clear yellow reaction mixture was carefully partitioned between saturated aqueous sodium bicarbonate (50 ml) and 20% ethyl acetate-hexanes (50 ml). The aqueous phase was extracted with 20% ethyl acetate-hexanes (2x100 ml), and the combined organic fractions were dried over sodium sulfate and were concentrated. Flash column chromatography of the residue (20% ethyl acetate-hexanes) provided the alcohol **74** (0.415 g, 88%) as a light yellow oil.

^{1}H NMR (400 MHz, C_6D_6), δ: 5.88 (dt, 1H, *J* = 11.0, 6.3 Hz), 5.74 (dt, 1H, *J* = 10.5, 7.1 Hz, H4), 5.45 (d, 1H, *J* = 10.5 Hz, H3), 5.42 (d, 1H, *J* = 11.0 Hz, H8), 4.31 (d, 2H, *J* = 6.3 Hz, H10), 3.35 (d, 2H, *J* = 7.1 Hz), 2.49 (br s, 1H, alcohol OH), 0.17 (s, 9H, TMS).

^{13}C NMR (100 MHz, C_6D_6), δ:	141.9 (C9), 138.6 (C4), 111.2 (C8), 110.2 (C3), 101.2, 101.0 (C1, C2), 92.6 (C6), 77.6 (C7), 60.8 (C10), 21.1 (C5), -0.10 (TMS).
FTIR (neat), cm^{-1}:	3316.2 (m, br), 3030.0 (w), 2958.1 (m), 2897.5 (w), 2216.3 (w), 2151.2 (m), 1249.6 (s), 841.2 (s).
MS (EI), m/z (%base):	204 (2), 203 (8), 185 (5), 159 (7), 75 (88), 73 (100).
HRMS (EI):	Calcd for $C_{13}H_{18}OSi$ (M^+): 218.1127. Found: 218.1124.
TLC (30% Ethyl Acetate-Hexanes), R_f:	0.45 (UV, anisaldehyde).

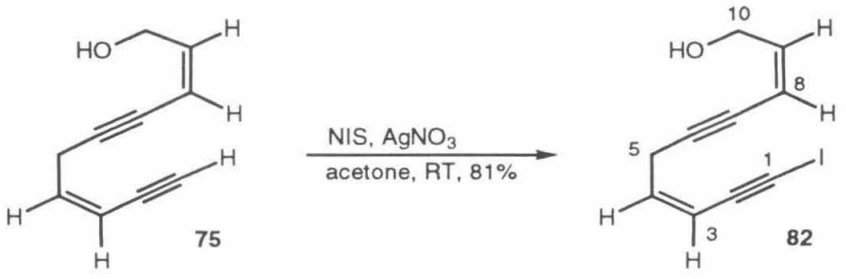


Acetylene **75**.

A solution of the alcohol **74** (0.410 g, 1.88 mmol, 1.00 equiv) in 1:1 methanol: triethylamine trihydrofluoride (10 ml) was heated at 55 °C for 3 hours in a tightly-capped polyethylene centrifuge tube. After cooling to 23 °C, the reaction was diluted with 20% ethyl acetate-hexanes (40 ml) and was poured slowly into half-saturated aqueous sodium bicarbonate (50 ml). After gas evolution had ceased, the aqueous phase was extracted with 20% ethyl acetate-hexanes (2x50 ml). The combined organic fractions were dried over sodium sulfate and were concentrated. Flash column chromatography of the residue (20% ethyl acetate-hexanes) afforded the acetylene **75** (0.267 g, 97%) as a pale yellow oil.

^{1}H NMR (400 MHz, C_6D_6), δ: 5.84 (dt, 1H, *J* = 11.0, 6.1 Hz, H2), 5.70 (dt, 1h, *J* = 10.5, 7.1 Hz, H7), 5.43 (d, 1H, *J* = 10.7, H3), 5.29 (d, 1H, *J* = 10.5 Hz, H8), 4.29 (d, 2H, *J* = 6.1 Hz, H1), 3.26 (d, 2H, *J* = 7.1 Hz, H6), 2.81 (s, 1H, H10), 1.78 (br s, 1H, alcohol OH).

^{13}C NMR (100 MHz, C_6D_6), δ:	142.0 (C2), 139.2 (C7), 110.2 (C3), 110.1 (C8), 92.5 (C5), 83.7 (C10), 79.3 (C4), 77.6 (C9), 60.9 (C1), 20.9 (C6).
FTIR (neat), cm^{-1}:	3294 (s), 3033 (w), 2915 (w), 2873 (w), 2216 (w), 2098 (w), 1416 (w), 1288 (m), 1013 (s), 618 (s).
MS (EI), m/z (%base):	127 (28), 115 (100), 102 (31).
HRMS (EI):	Calcd for $C_{10}H_{10}O$ (M^+): 146.0731. Found: 146.0725.
Elemental Analysis:	Calcd for $C_{10}H_{10}O$: C, 92.26; H, 7.74. Found: C, 92.22; H, 7.80.
TLC (30% Ethyl Acetate-Hexanes), R_f:	0.38 (UV, anisaldehyde).

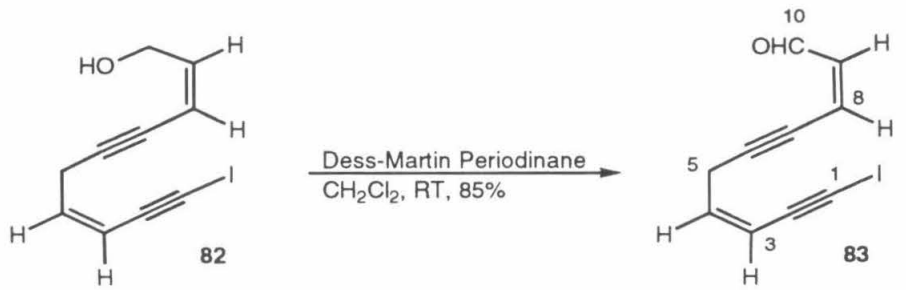


Iodoacetylene **82**.

N-Iodosuccinimide (0.512 g, 2.16 mmol, 1.02 equiv) was added to a solution of the acetylene **75** (0.310 g, 2.12 mmol, 1 equiv) and 2-methyl-2-butene (0.5 ml) in acetone (25 ml) in a foil-wrapped flask at 0 °C. Silver nitrate (0.036 g, 0.21 mmol, 0.10 equiv) was added to the suspension, and the reaction was warmed to 23 °C. After 3 hours, the reaction was partitioned between 20% ethyl acetate-hexanes (50 ml) and water (50 ml). The aqueous phase was washed with 20% ethyl acetate-hexanes (2x50 ml) and the combined organic fractions were dried over sodium sulfate and were concentrated. Flash column chromatography of the residue (20% ethyl acetate-hexanes) provided the iodoacetylene **82** (0.470 g, 81%) as a red oil.

^{1}H NMR (400 MHz, C_6D_6), δ: 5.75 (dt, 1h, J = 11.0, 6.1 Hz, H9), 5.51 (dt, 1H, J = 10.5, 6.9 Hz, H4), 5.35 (d, 1H, J = 11.0 Hz, H8), 5.30 (d, 1H, J = 10.5 Hz, H3), 4.20 (d, 2H, J = 6.1 Hz, H10), 3.13 (d, 2H, J = 6.9 Hz, H5).

^{13}C NMR (100 MHz, C_6D_6), δ:	141.9 (C9), 139.7 (C4), 111.2 (C8), 110.1 (C3), 92.5, 90.3, 77.6 (C1, C2, C6, C7), 61.0 (C10), 20.9 (C5).
FTIR (neat), cm^{-1}:	3314 s (br), 3031 (w), 2926 (w), 2870 (w), 1287 (m), 1012 (m).
MS (EI), m/z (%base):	145 (11), 128 (100), 127 (32), 115 (54), 102 (12), 91 (20), 81 (27).
HRMS (EI):	Calcd for $C_{10}H_9OI$ (M^+): 271.9699. Found: 271.9708.
TLC (30% Ethyl Acetate-Hexanes), R_f:	0.38 (UV, anisaldehyde).

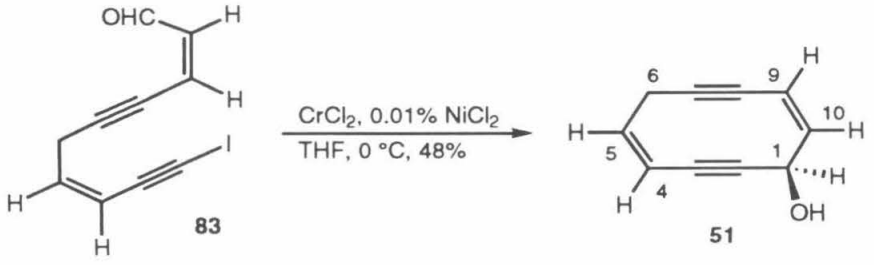


Aldehyde **83**.

A solution of the iodoacetylene **82** (0.175 g, 0.64 mmol, 1 equiv, concentrated from benzene) in methylene chloride was added to a suspension of the Dess-Martin periodinane (0.677 g, 1.60 mmol, 2.50 equiv) in methylene chloride (5 ml) at 23 °C. After 1.5 hours, the reaction was partitioned between half-saturated aqueous potassium carbonate (25 ml) and 20% ethyl acetate-hexanes (25 ml). The aqueous phase was extracted with 20% ethyl acetate-hexanes (2x25 ml), and the combined organic extracts were dried over sodium sulfate. Flash column chromatography (10% ethyl acetate-hexanes) immediately after concentration of the organic fractions provided the aldehyde **83** (0.148 g, 85%) as an air- and light-sensitive orange oil which was prone to polymerization on standing.

^{1}H NMR (400 MHz, C_6D_6), δ: δ 10.12 (d, 1H, J = 7.0 Hz, H10), 5.85 (m, 2H, H4, H9), 5.30 (m, 2H, H3, H8), 2.99 (d, 2H, J = 5.8 Hz, H5).

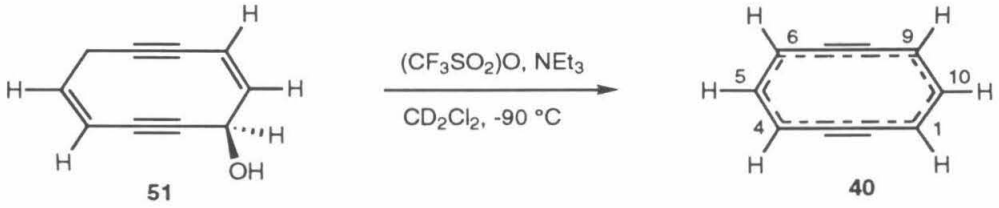
^{13}C NMR (100 MHz, C_6D_6), δ:	190.7 (C10), 138.1, 138.0, 115.3, 115.0 (C3, C4, C8, C9), 99.0, 90.0, 76.4, 76.3 (C1, C2, C6, C7), 20.8 (C5).
FTIR (neat), cm^{-1}:	2839 (w), 1682 (s), 1582 (m), 1351 (m), 1287 (m), 1211 (m), 1140 (m), 1072 (m), 768 (m), 729 (m).
MS (EI), m/z (%base):	230 (18), 116 (10), 115(100).
HRMS (EI):	Calcd for $C_{10}H_7OI$ (M^+): 269.9528. Found: 269.9535.
TLC (20% Ethyl Acetate-Hexanes), R_f:	0.43 (UV, anisaldehyde).



Alcohol **51.**

Chromium(II) chloride (0.113g, 0.92 mmol, 2.50 equiv) doped with nickel(II) chloride (0.01% w/w) was added to a solution of the aldehyde **83** (0.099 g, 0.37 mmol, 1 equiv) in deoxygenated tetrahydrofuran in a dry box. After vigorous swirling to suspend the metal halides, a fresh septum was added and the reaction was removed from the dry box. Immediately thereafter, the green solution was cooled to 0 °C, the septum was wrapped in parafilm, an inverted septum was placed over the first septum, and the inverted septum was wrapped with parafilm. After 3 hours, the brown reaction was partitioned between half-saturated aqueous ammonium chloride (50 ml) and 20% ethyl acetate (100 ml). The aqueous phase was rinsed with 20% ethyl acetate (2x100 ml) and was dried over sodium sulfate. After concentrating it to approximately 1 ml, the crude mixture was subjected to flash column chromatography (20% ethyl acetate-hexanes). The product-containing fractions were combined with di-(3-*tert*-butyl-4-hydroxy-5-methyl)-phenyl sulfide (0.005 g) and were concentrated to afford the alcohol **51** (0.021 g after subtraction of sulfide, 40%) as an air- and light-sensitive brown oil which was prone to rapid polymerization on standing.

^{1}H NMR (400 MHz, C_6D_6), δ:	5.58 (dd, 1H, J = 11.9, 4.2 Hz, H10), 5.40 (m, 2H), 5.13 (dt, J = 11.8, 4.2 Hz), 4.92 (br s, 1H, H1), 2.79 (m, 2H, H6).
^{13}C NMR (100 MHz, C_6D_6), δ:	138.6, 135.4, 128.5, 110.8 (C2, C3, C7, C8), 94.3, 93.9, 84.3, 82.4 (C3, C4, C9, C10), 61.5 (C1), 22.8 (C6).
FTIR (neat), cm^{-1}:	3390 m (br), 3021 (w), 2874 (w), 1165 (m), 995 (m), 848 (m), 715 (m).
MS (EI), m/z (%base):	63 (3), 57 (1), 52 (18), 51 (17).
HRMS (EI):	Calcd for $C_{10}H_8O$ (M^+): 144.0575. Found: 144.0570.
TLC (20% Ethyl Acetate-Hexanes), R_f:	0.22 (UV, anisaldehyde).



Preparation and Kinetics Measurements for Annulene **40**.

A solution of trifluoromethanesulfonic anhydride in methylene chloride-d_2 (0.100 ml, 19% v/v, 0.111 mmol, 2.00 equiv) was transferred to a Young-valve NMR tube in a dry box. The tube was removed from the dry box, was cooled to –94 °C (pentane-liquid nitrogen), and triethylamine (0.023 ml, 0.167 mmol, 3.00 equiv) and 1,4-cyclohexadiene (0.026 ml, 0.278 mmol, 5.0 equiv) were added under a stream of dry argon. After addition of a solution of freshly purified **51** (0.008 g, 0.056 mmol, 1 equiv) in methylene chloride-d_2 (0.350 ml) in like fashion, the sample was degassed by freeze-pump-thaw (3x, thaw temperature –94 °C) and was stored frozen in liquid nitrogen.

The sample was thawed at –94 °C and was loaded into the probe of a 400 MHz NMR (precooled to –110 °C), maintaining the probe temperature below –95 °C during loading. After obtaining preliminary spectra between –90 °C and –75 °C, the probe temperature was increased to – 51 °C, and the disappearance of starting material, accompanied by concomitant appearance of naphthalene, was followed over several hours. The disappearance of annulene was reproducibly first order ($k = (4.6 \pm 0.9) \times 10^{-4}$ s^{-1}, Figure 6), as was the appearance of product. Careful integration after approximately four half-lives indicated the yield of naphthalene to be ≥ 85%.

{^{1}H}-^{1}H and selective {^{1}H}-^{13}C experiments performed in the absence of 1,4-cyclohexadiene confirmed the assigned structure and allowed definitive assignment of the carbon signals. The UV spectrum was obtained by preparing a dilute (6.0×10^{-4} M)

solution of the annulene in methylene chloride-d_2 by the procedure described above. The Young-valve NMR tube was placed in a quartz finger Dewar containing pentane-liquid nitrogen slush (-95 °C), and the UV spectrum was obtained; the slightly opaque nature of the cold bath, accompanied by diffraction from and absorbance by the borosilicate NMR tube prevented reliable absorbance measurement below 260nm.

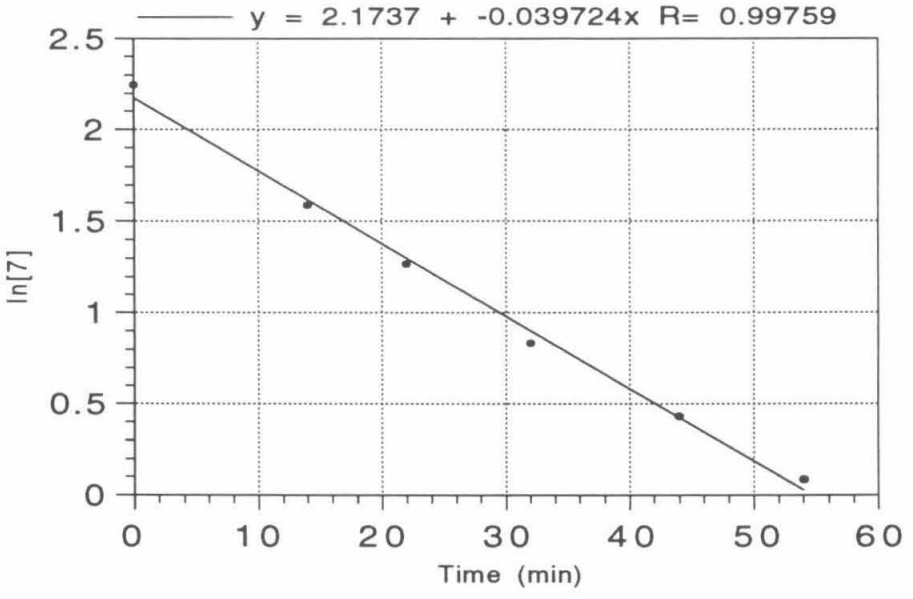


Figure 6. Decay of the Annulene **40** at –51 °C.

^{1}H NMR (400 MHz, 2:1 THF-d_8: CD_2Cl_2, –75 °C), δ:	8.45 (t, 2H, J = 8.3 Hz, H5, H10), 7.81 (d, 4H, J = 8.3 Hz, H1, H4, H6, H9).
^{13}C NMR (100 MHz, CD_2Cl_2, –90 °C), δ:	137.1 ($^1J_{CH}$ = 158 Hz, C5, C10), 125.1 (C2, C3, C7, C8), 107.5 ($^1J_{CH}$ = 164 Hz, C1, C4, C6, C9).
UV/Vis (THF, –90 °C), λ_{max} (ε):	308 nm (2481), 302 nm (shoulder, 1678).

Footnotes and References

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56. 1,5-Dideuterionaphthalene isolated by chromatographic purification of an NMR sample was spectroscopically identical to authentic material. Authentic material could be prepared by the reduction of 1,5-bis(trifluoromethylsulfoxy)-naphthalene[47] with bis(triphenylphosphine)palladium(II) dichloride (0.02 equiv),

triethylamine (3.00 equiv), and formic acid-d_2 (2.00 equiv) in terahydrofuran at 60 °C (Cacchi, S.; Ciattini, P. G.; Morera, E.; Ortar, G. *Tetrahedron Lett.* **1986**, *27*, 5541).

57. MacroModel V3.5X; Mohamadi, F.; Richards, N. G. J.; Guida, W. C.; Liskamp, R.; Caufield, C.; Chang, G.; Hendrickson, T.; Still, W. C. *H. Comput. Chem.* **1990**, *11*, 440.

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59. Calculated using revised group additivities: Benson, S. J.; Garland, L. J. *J. Phys. Chem.* **1991**, *95*, 4915.

60. The heats of formation of the biradical species were calculated by subtraction of the bond dissociation energy of molecular hydrogen (104 kcal/mol, Herzberg, G. *J. Mol. Spectrosc.* **1970**, *33*, 147) from the sum of ΔH_f for the hydrocarbon and the relevant bond dissociation energies (110 and 100 kcal/mol, Squires, R. R.; Paulino, J. A.; Wenthold, P. G. *J. Am. Chem. Soc.* **1991**, *113*, 7414).

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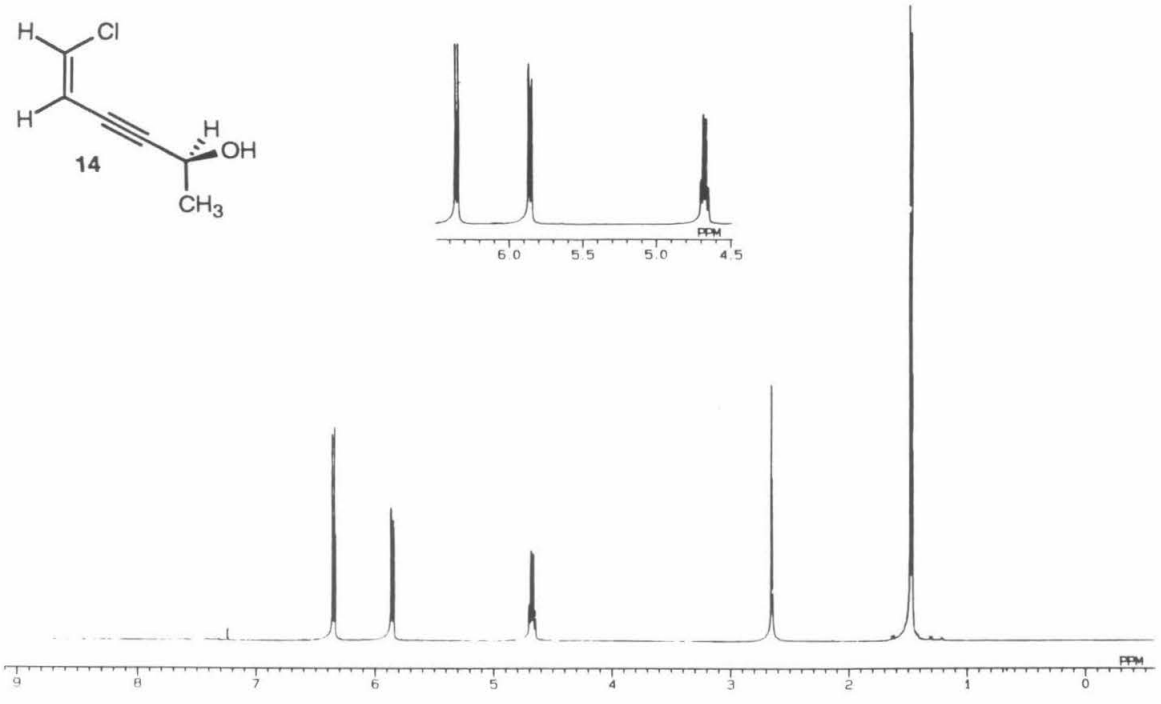
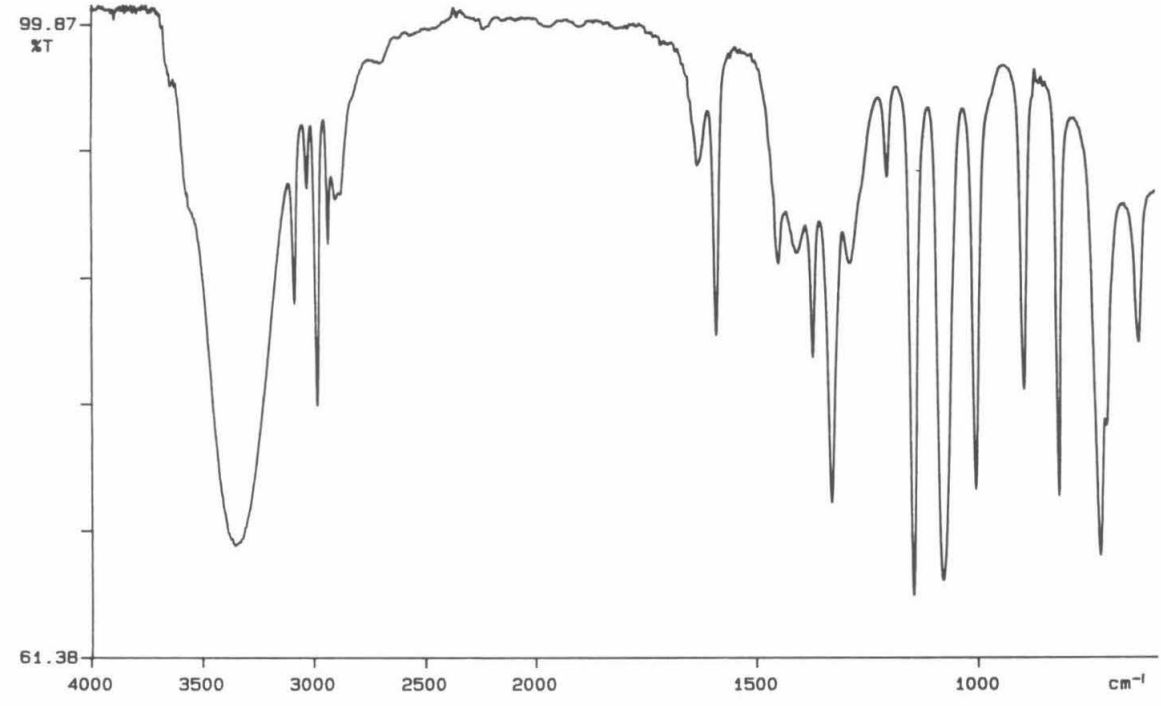
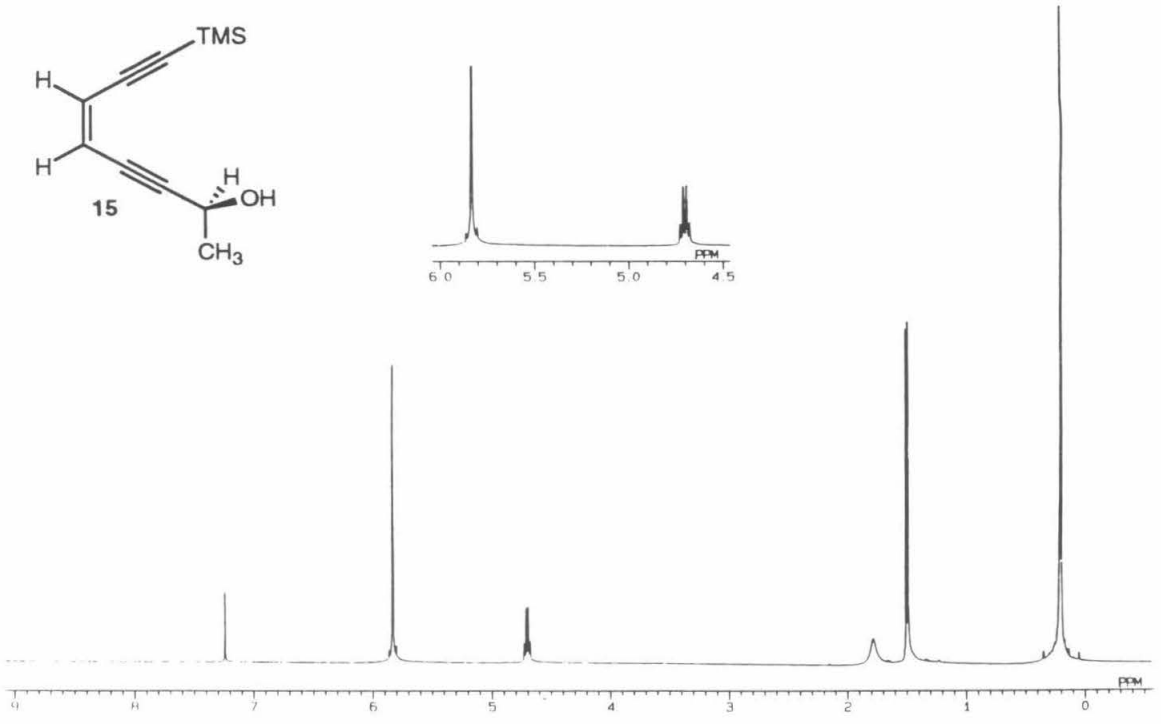
Appendices

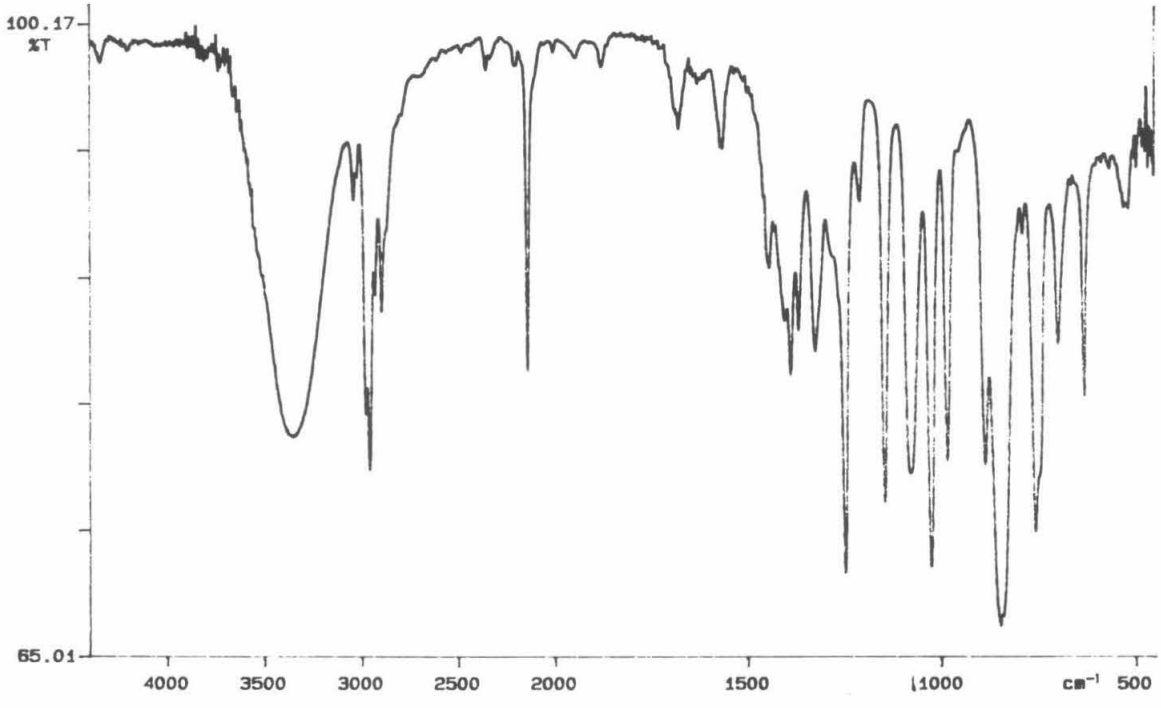
Appendix 1

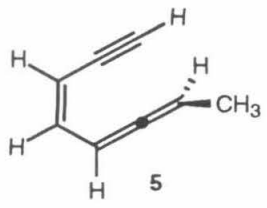
Catalog of Spectra (Chapter 1)


H
Cl
H
H
OH
CH3
14
6.0
5.5
5.0
4.5
PPM
9
8
7
6
5
4
3
2
1
0
PPM

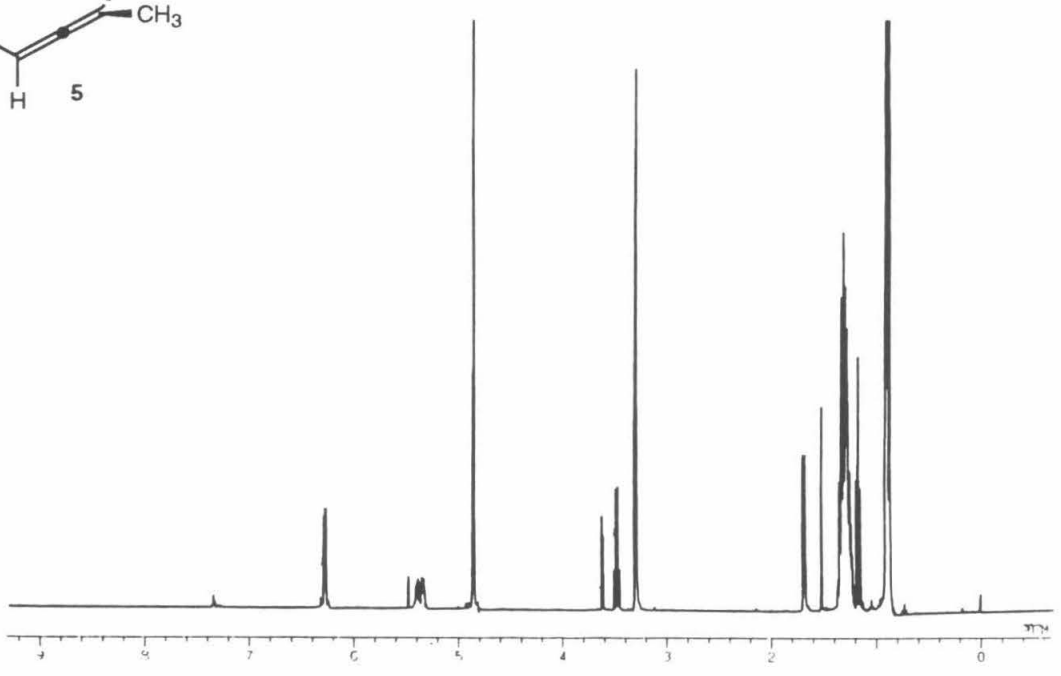

99.87
%T
61.38
4000
3500
3000
2500
2000
1500
1000
cm-1

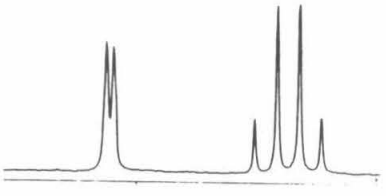

TMS
H
H
H
OH
CH3
15
PPM
6.0
5.5
5.0
4.5
PPM
9
8
7
6
5
4
3
2
1
0

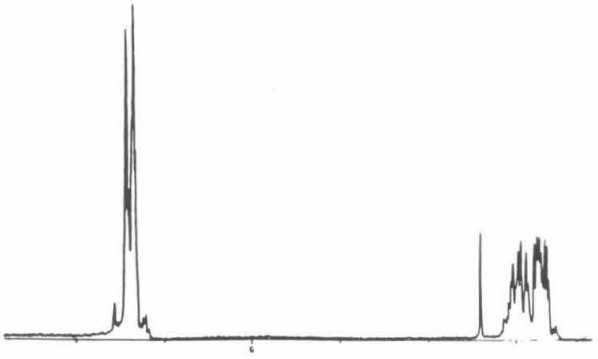

100.17
%T
65.01
4000
3500
3000
2500
2000
1500
1000
cm-1
500

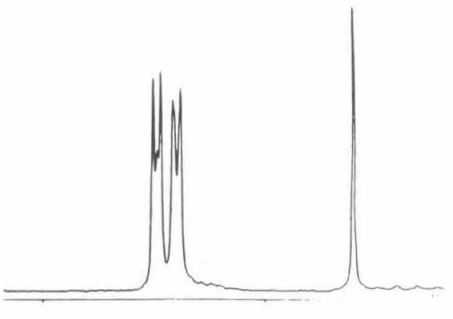


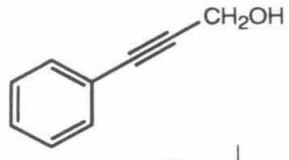
5



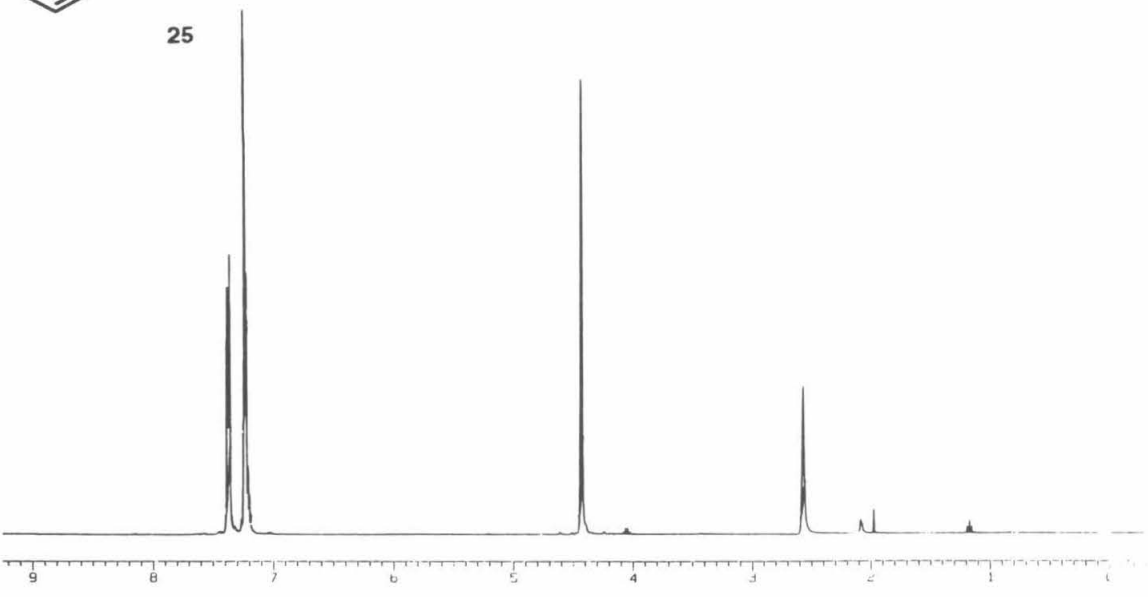


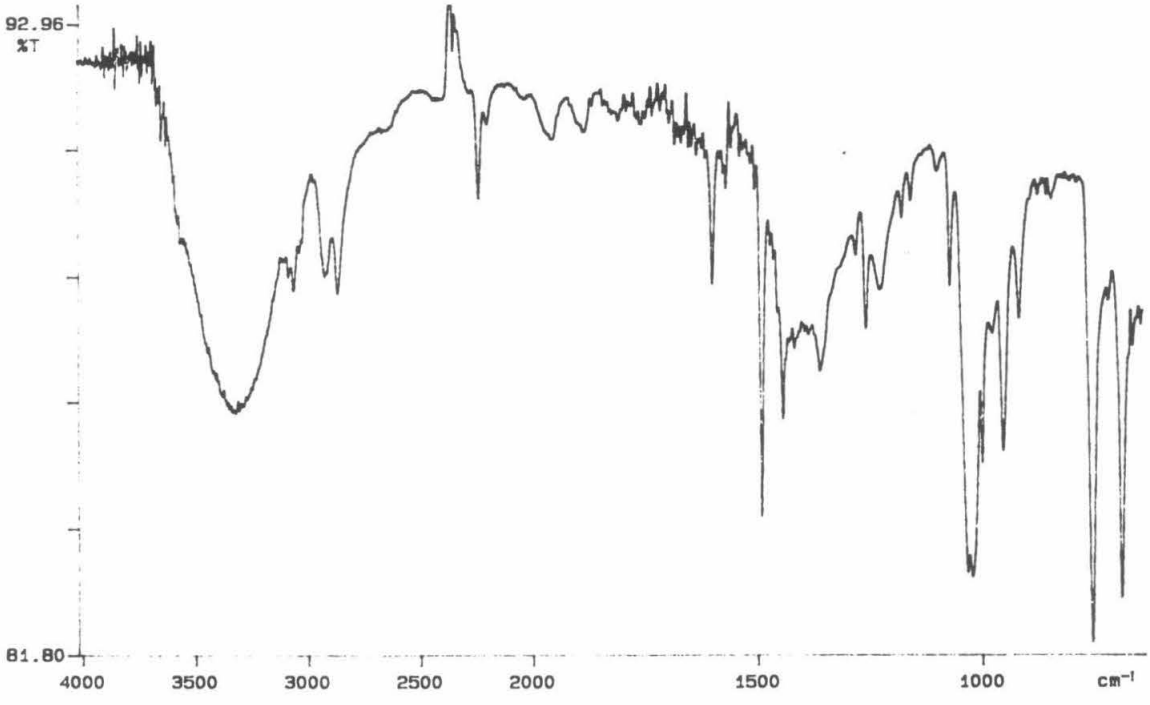


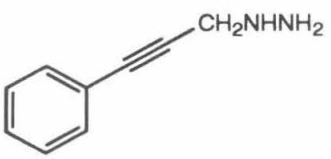



CH2OH

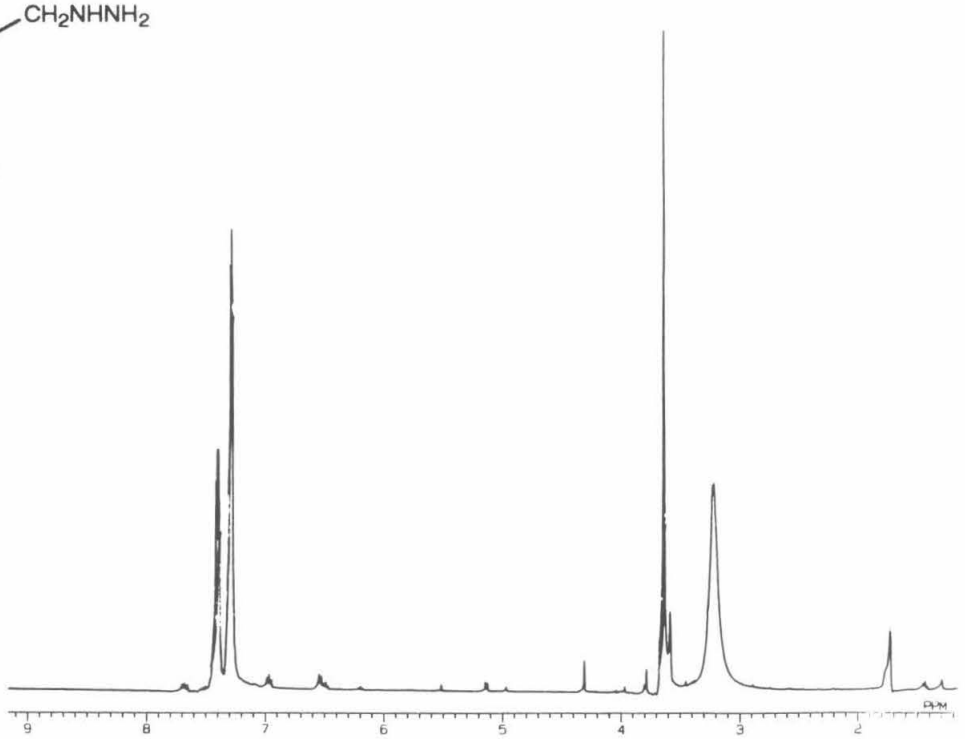
25

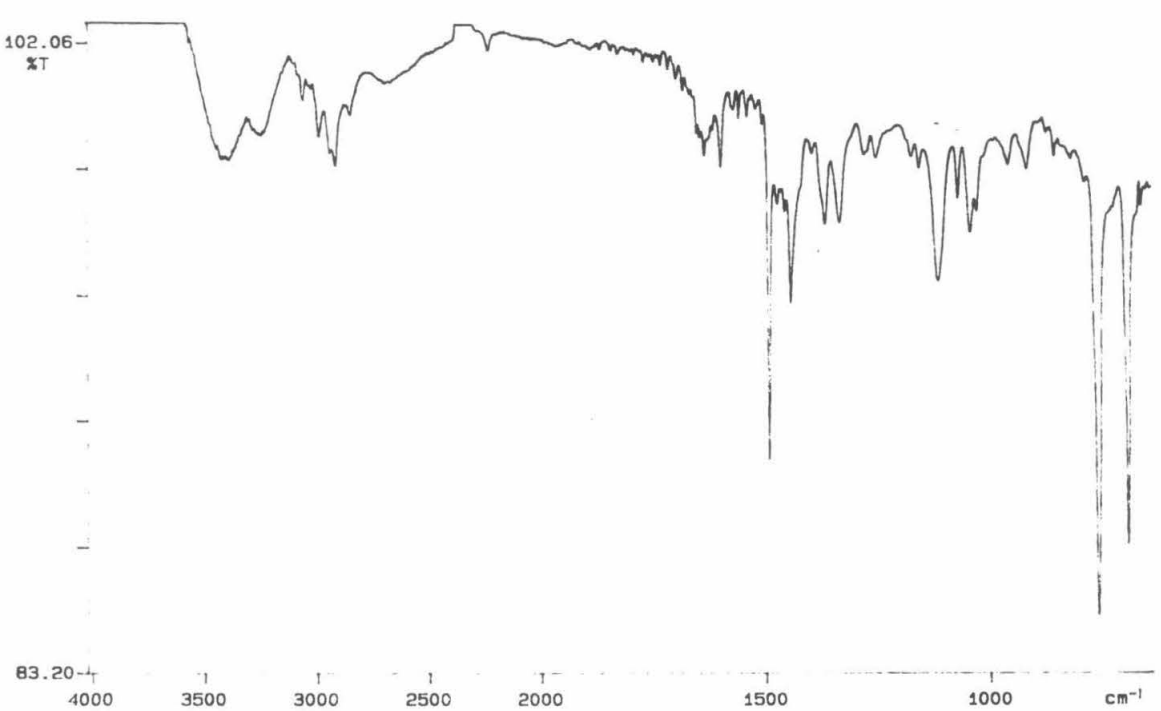

9
8
7
6
5
4
3
2
1
0

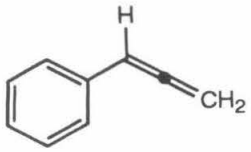

92.96
%T
81.80
4000
3500
3000
2500
2000
1500
1000
cm-1


CH2NHNH2

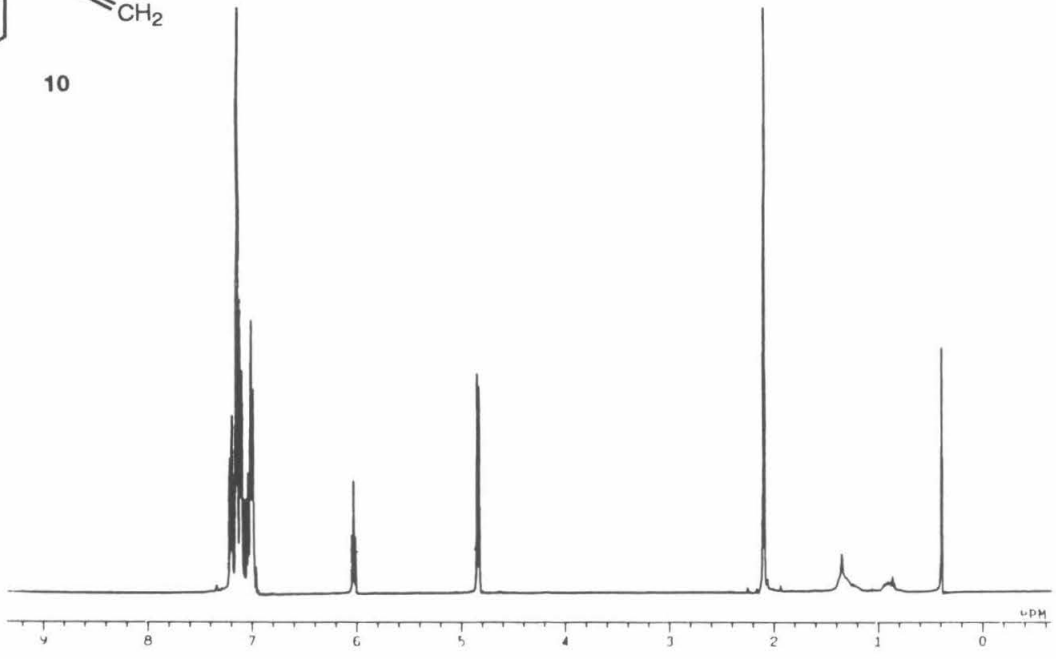
8

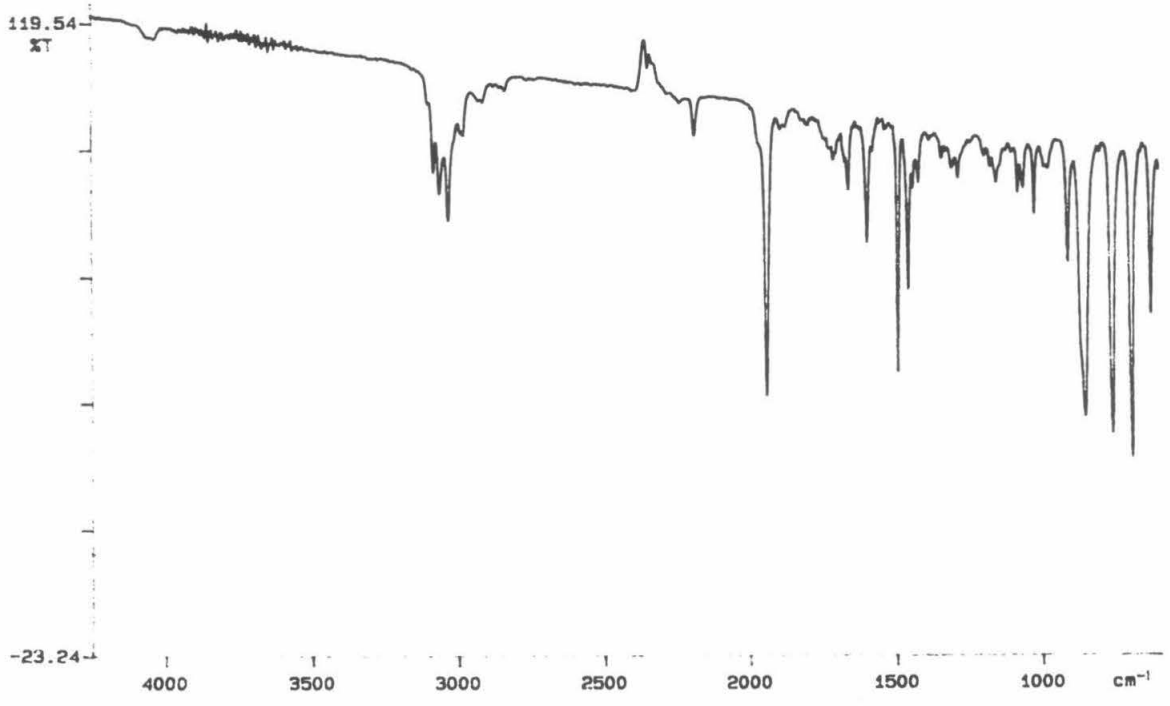

9
8
7
6
5
4
3
2
PPM

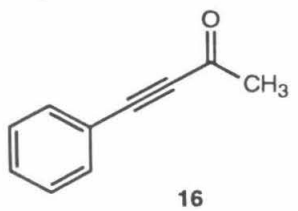

102.06
%T
83.20
4000
3500
3000
2500
2000
1500
1000
cm-1


H
CH2

10

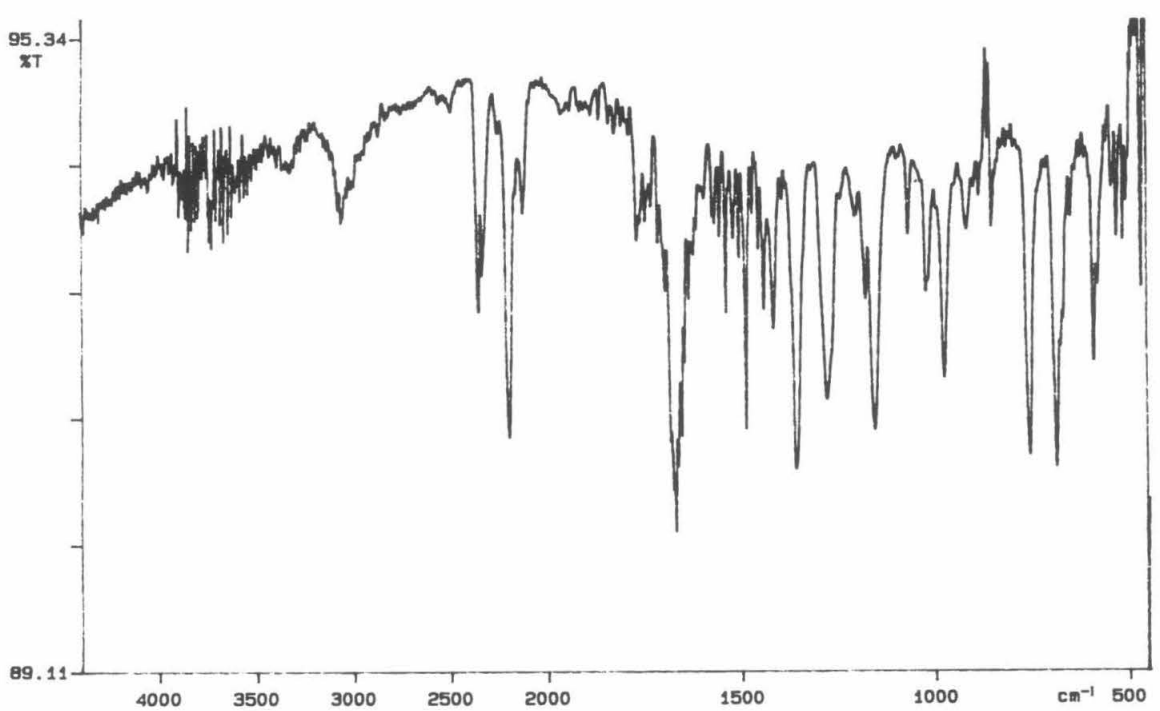

ppm
9
8
7
6
5
4
3
2
1
0

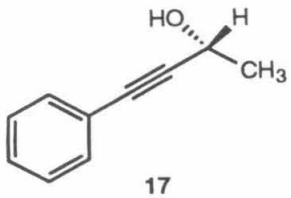

119.54
%T
-23.24
4000
3500
3000
2500
2000
1500
1000
cm-1


O
CH3

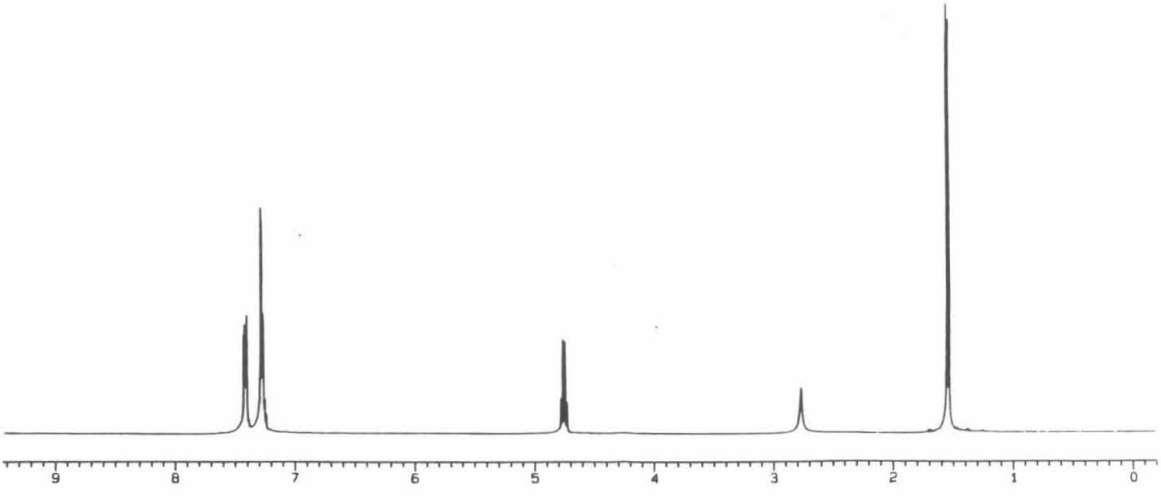
16

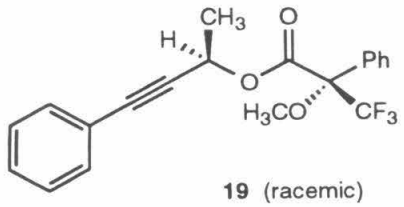
9
8
7
6
5
4
3
2
1
0


95.34
%T
89.11
4000
3500
3000
2500
2000
1500
1000
cm-1
500



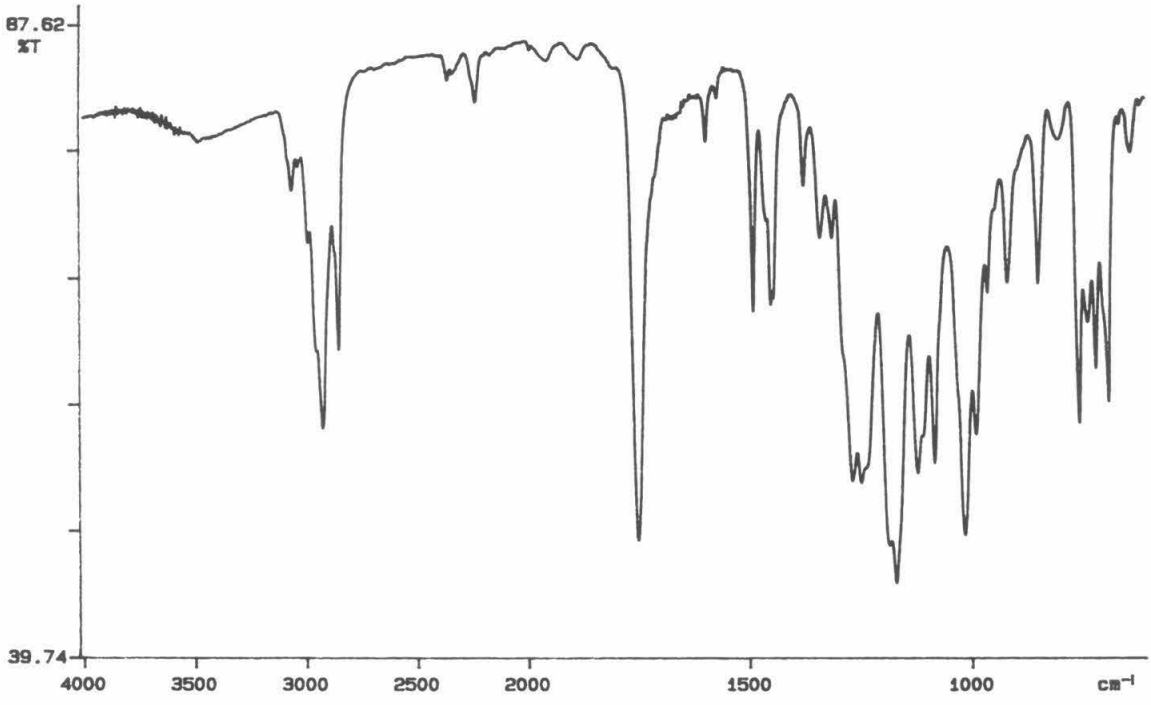
17




CH3
O
H
Ph
O
H3CO
CF3

19 (racemic)

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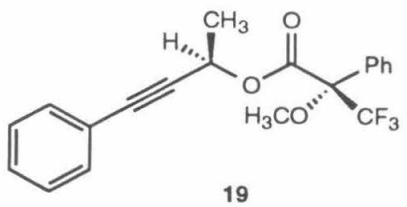
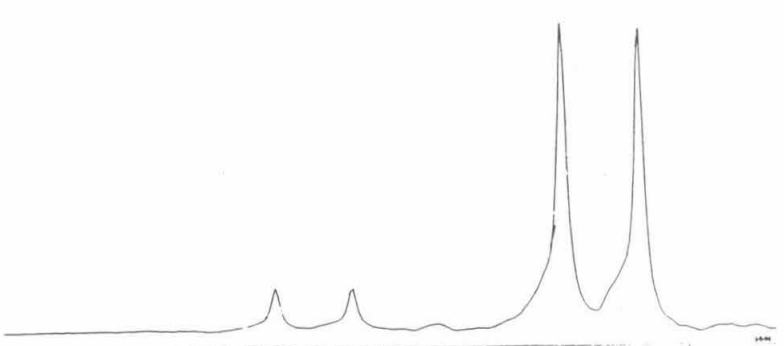
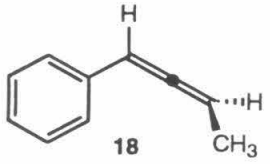
3500
3000
2500
2000
1500
1000
cm-1

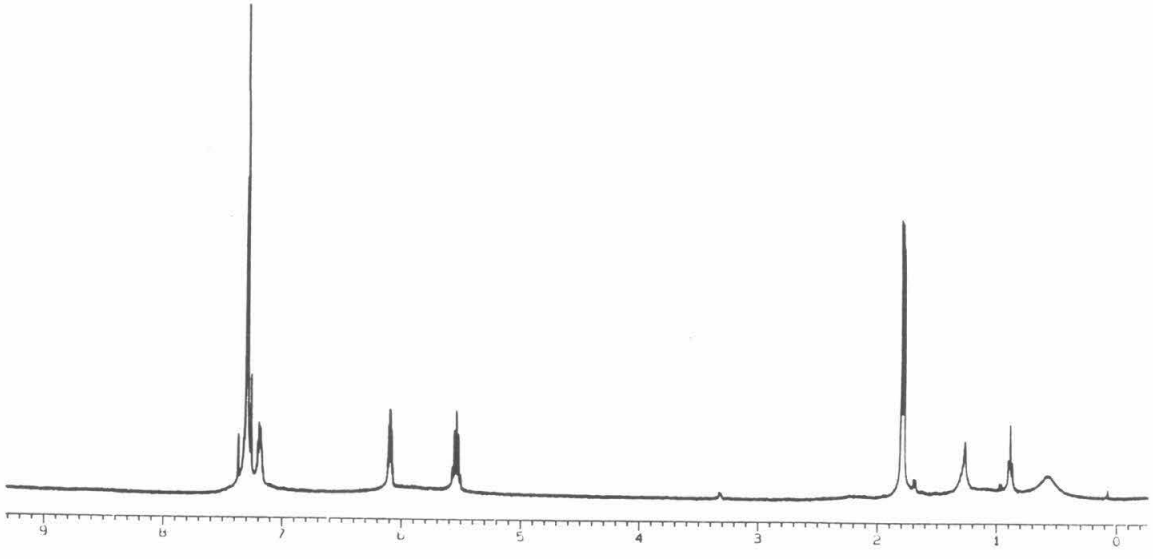


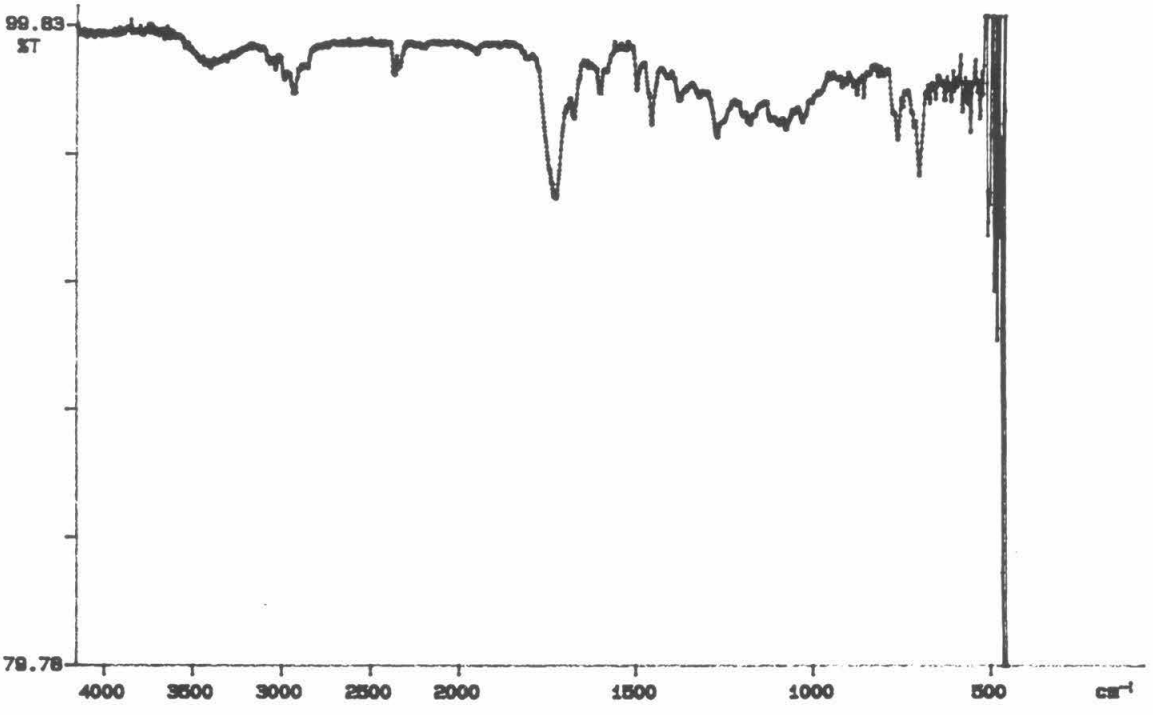
19




H
H
CH3

18


9
8
7
6
5
4
3
2
1
0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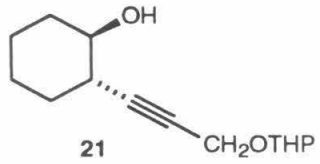
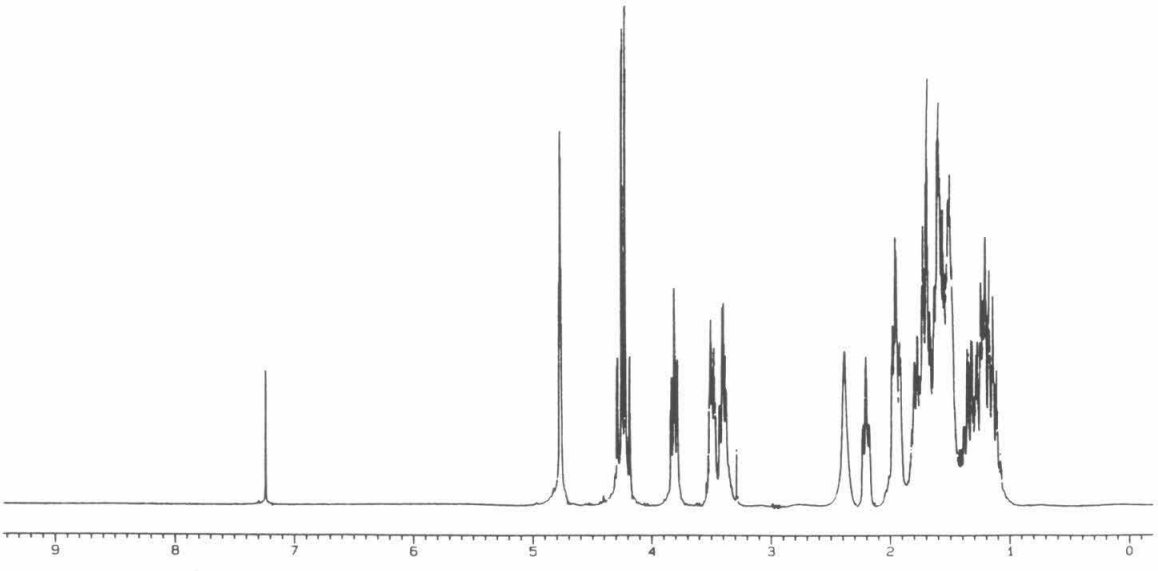
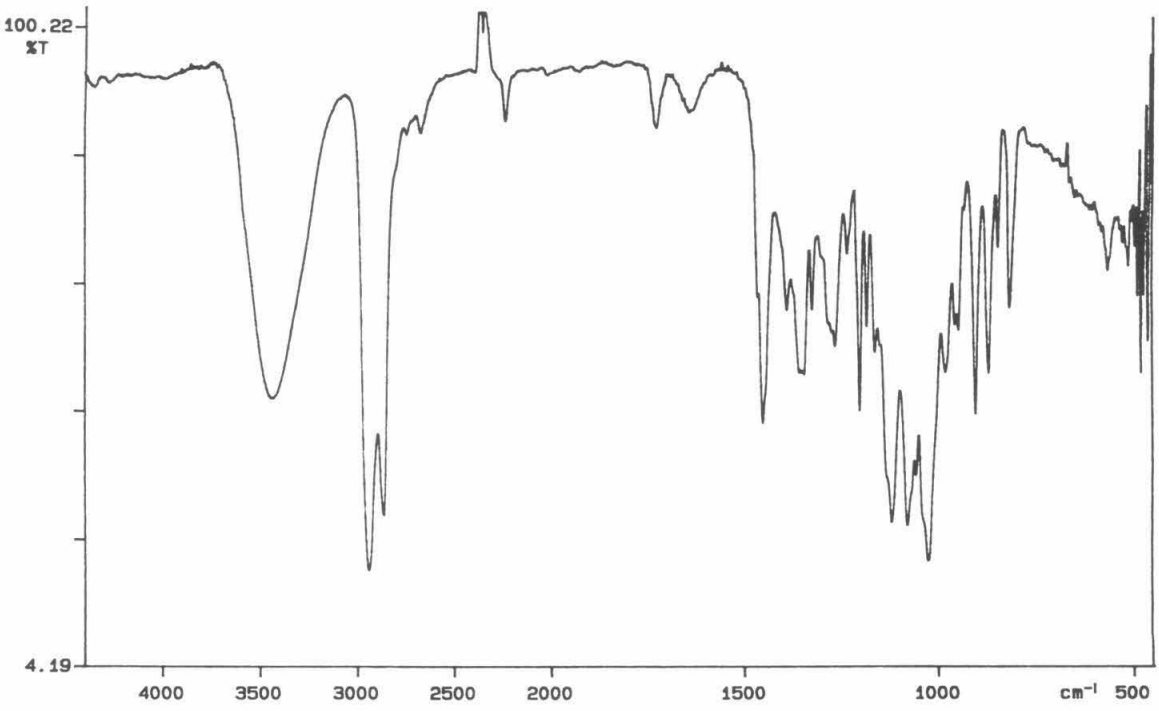
%T
79.78
4000
3500
3000
2500
2000
1500
1000
500
cm-1


OH
CH2OTHP

21


9
8
7
6
5
4
3
2
1
0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4.19
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2500
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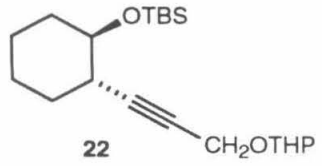
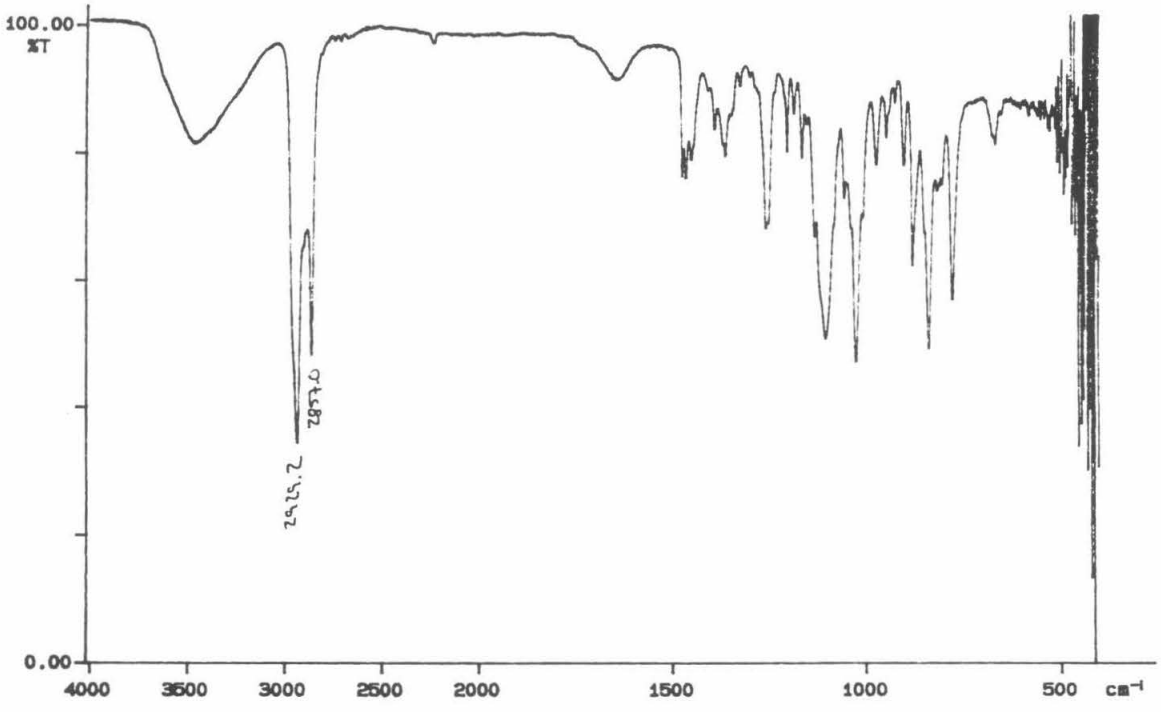
1500
1000
cm-1
500


OTBS
CH2OTHP

22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2857.0
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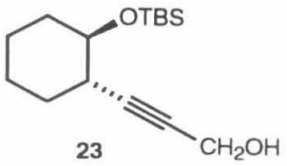
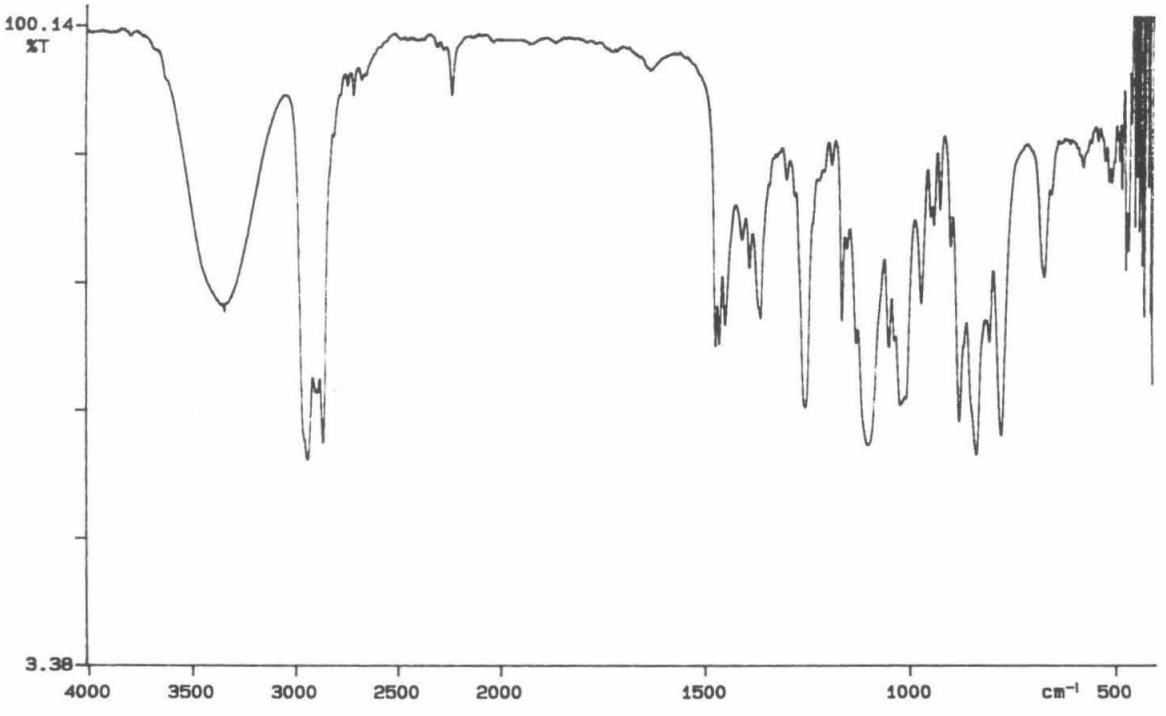
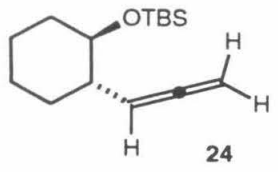
3500
3000
2500
2000
1500
1000
500
cm-1


OTBS
CH2OH

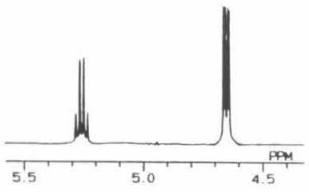
23

9
8
7
6
5
4
3
2
1
0

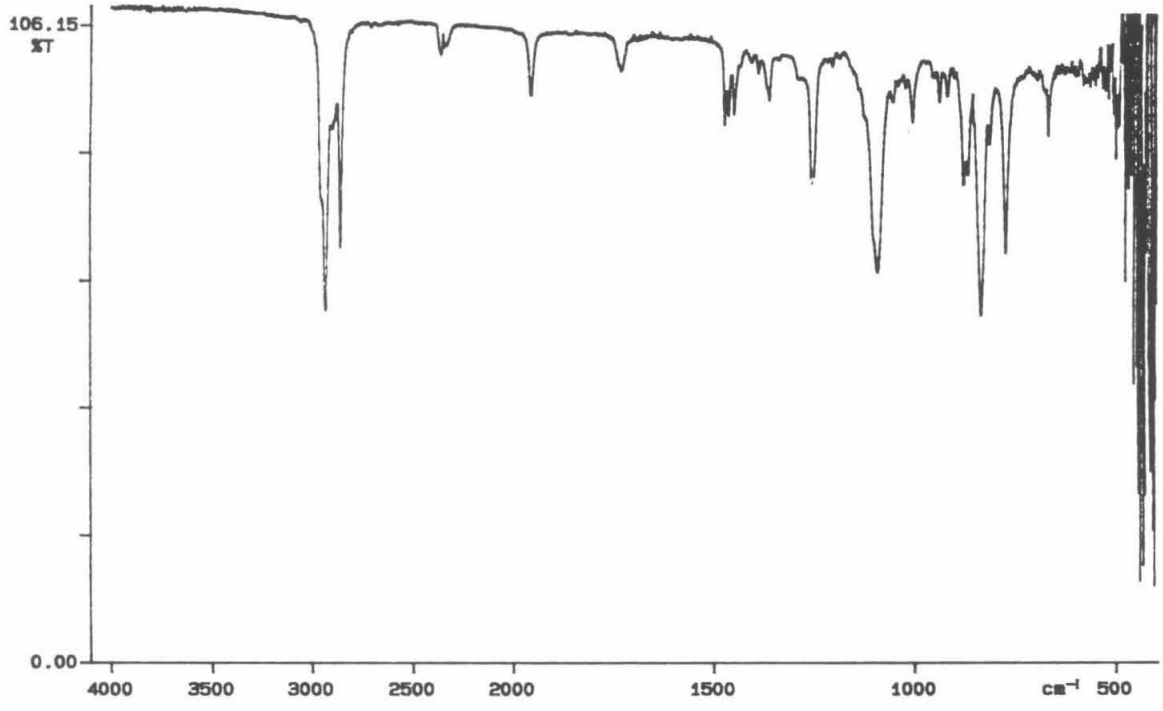

100.14
%T
3.38
4000
3500
3000
2500
2000
1500
1000
cm-1
500


OTBS
H
H
H

24

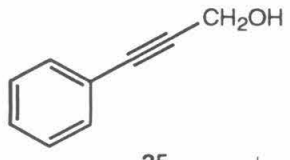

5.5
5.0
4.5
PPM

9
8
7
6
5
4
3
2
1
0

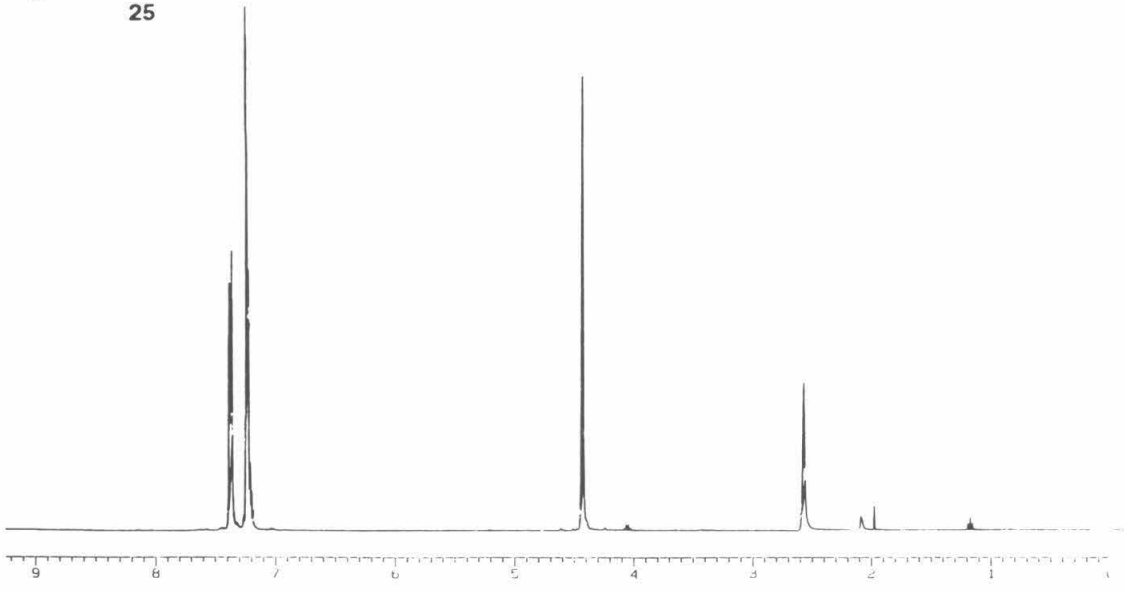

106.15
%T
0.00
4000
3500
3000
2500
2000
1500
1000
cm⁻¹
500

Appendix 2

Catalog of Spectra (Chapter 2)


CH2OH

25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4
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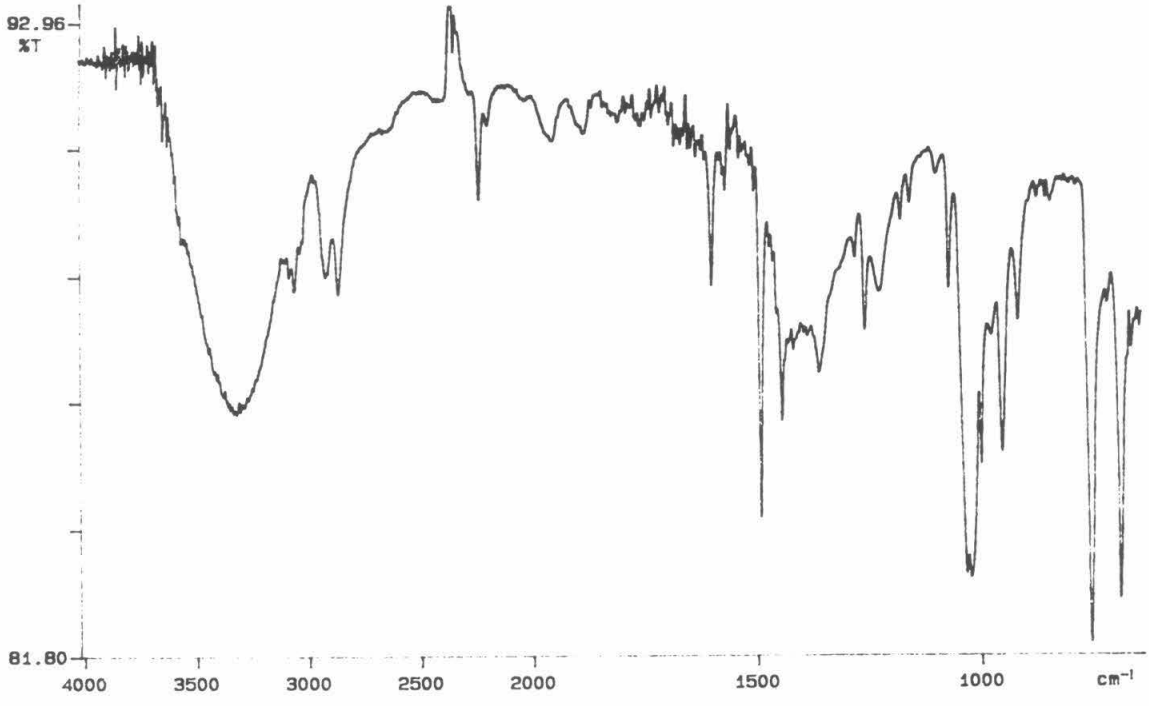
2
1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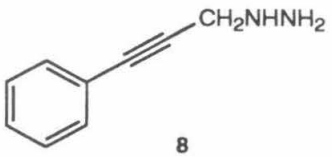
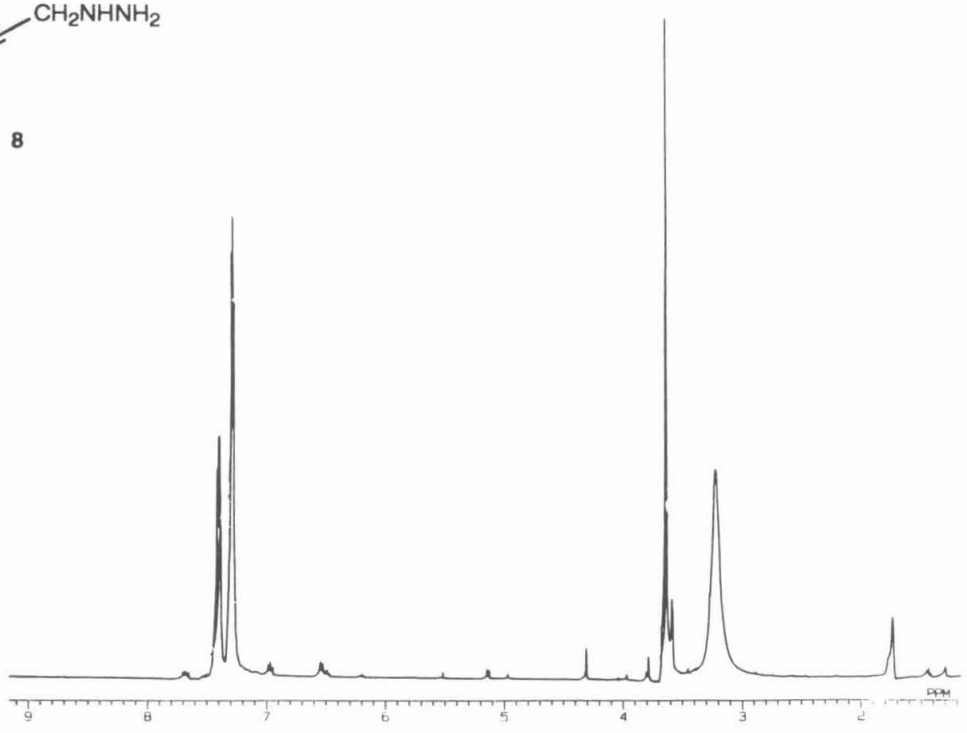
%T
81.80
4000
3500
3000
2500
2000
1500
1000
cm-1


CH2NHNH2

8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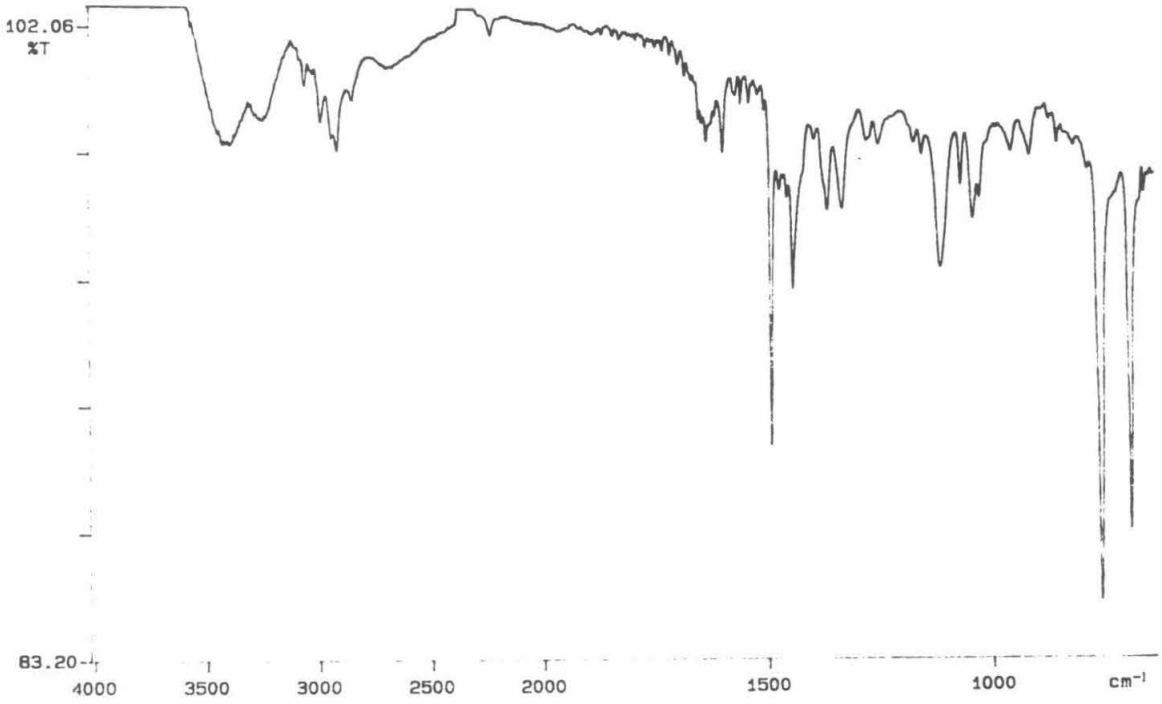
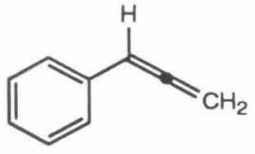
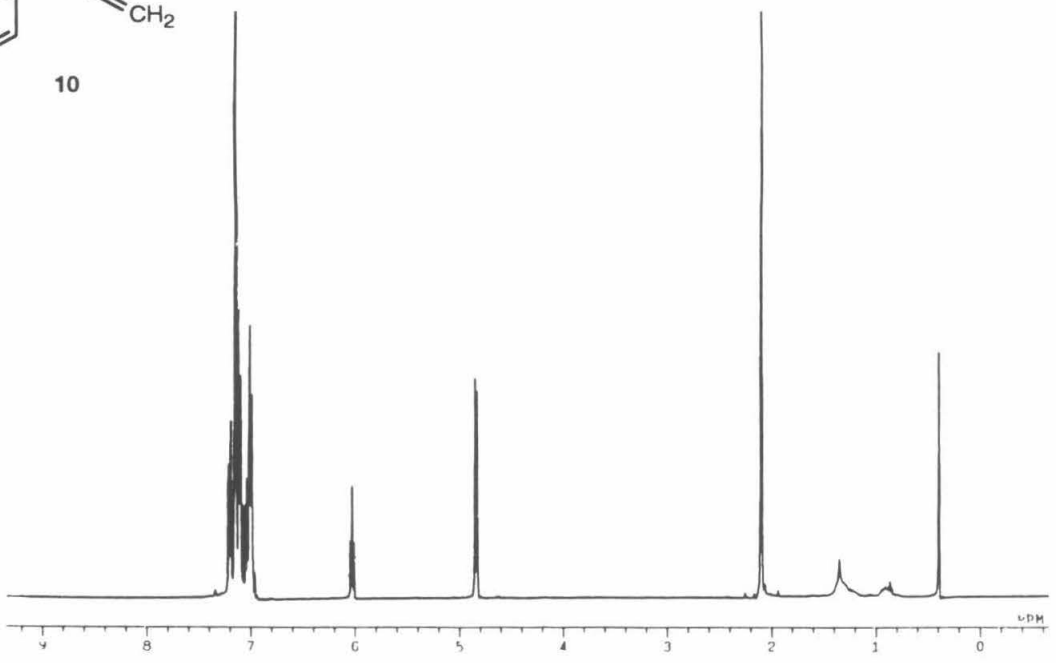
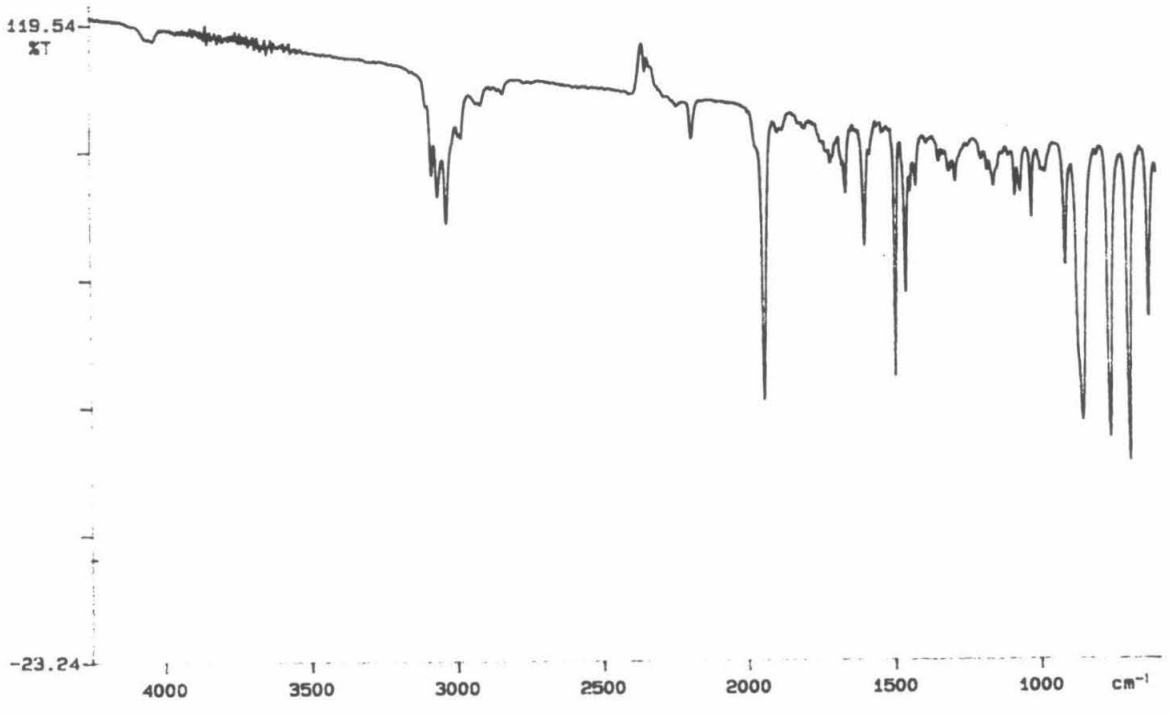
8
7
6
5
4
3
2
PPM


102.06
%T
83.20
4000
3500
3000
2500
2000
1500
1000
cm-1


H
CH2

10


ppm
9
8
7
6
5
4
3
2
1
0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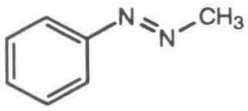
%T
-23.24
4000
3500
3000
2500
2000
1500
1000
cm-1



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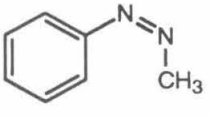

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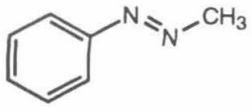
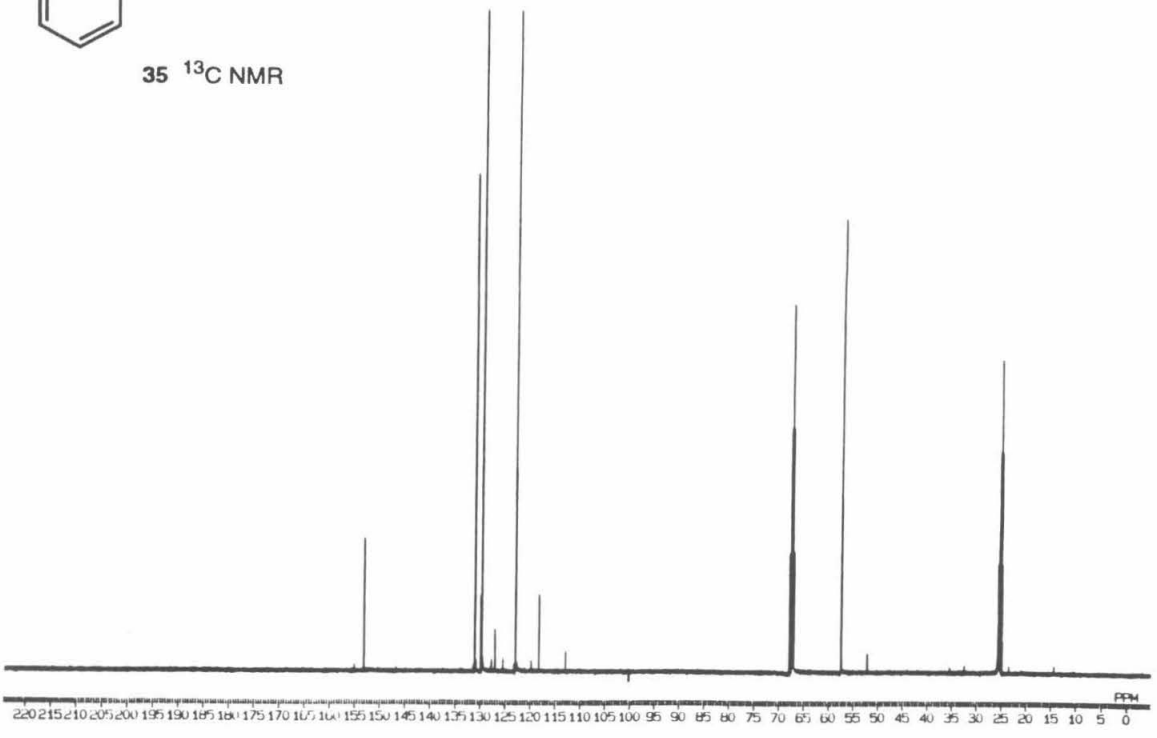
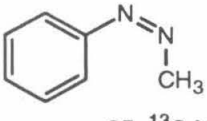
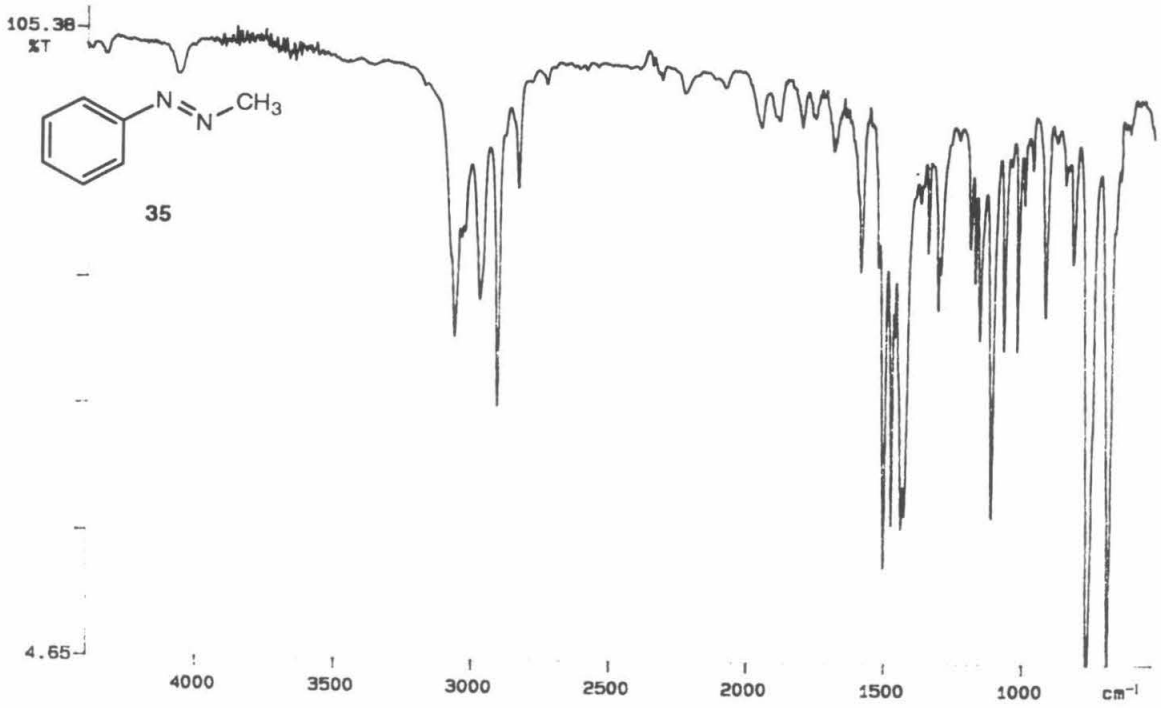


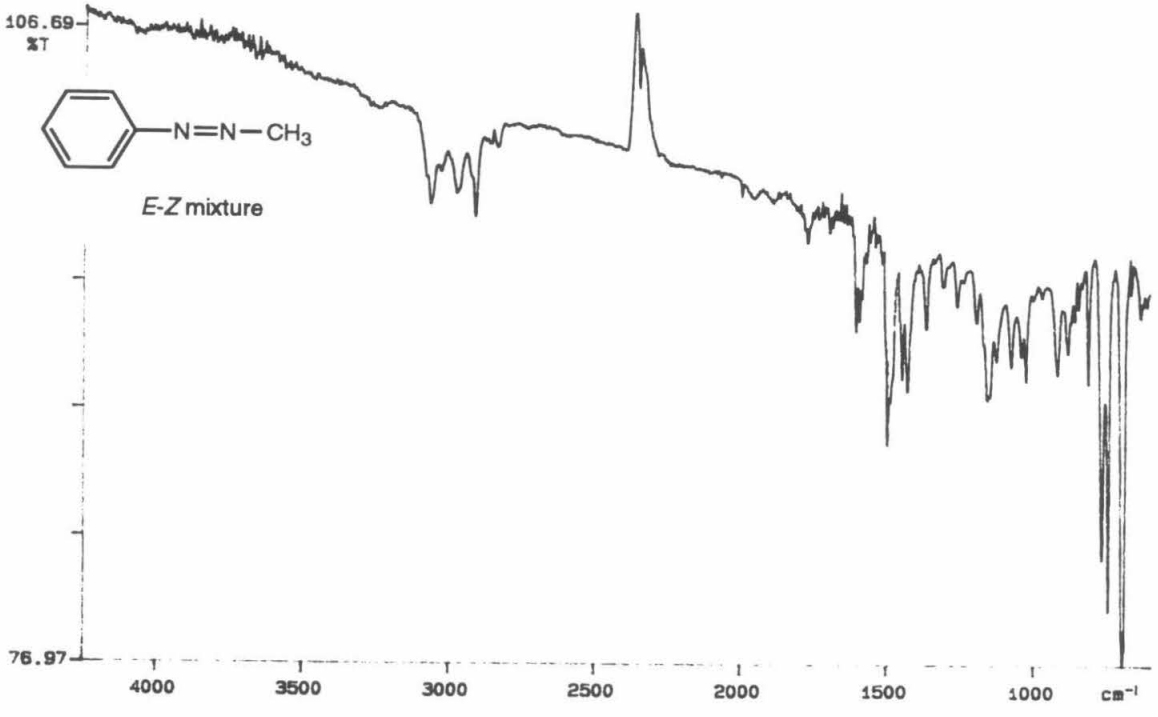
35 ^{13}C NMR

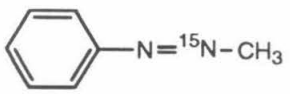




35 ^{13}C NMR

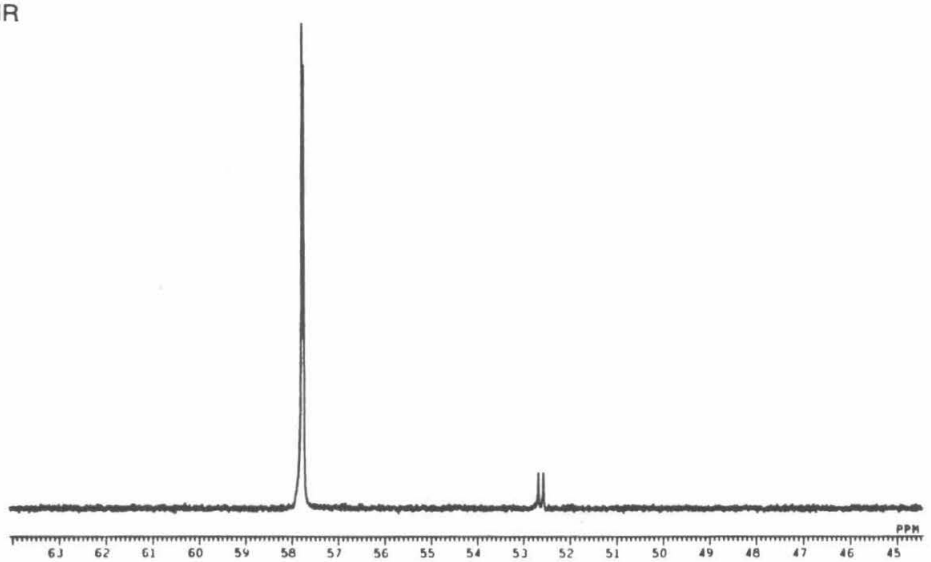

105.38
%T
N=N
CH3
35
4.65
4000
3500
3000
2500
2000
1500
1000
cm-1

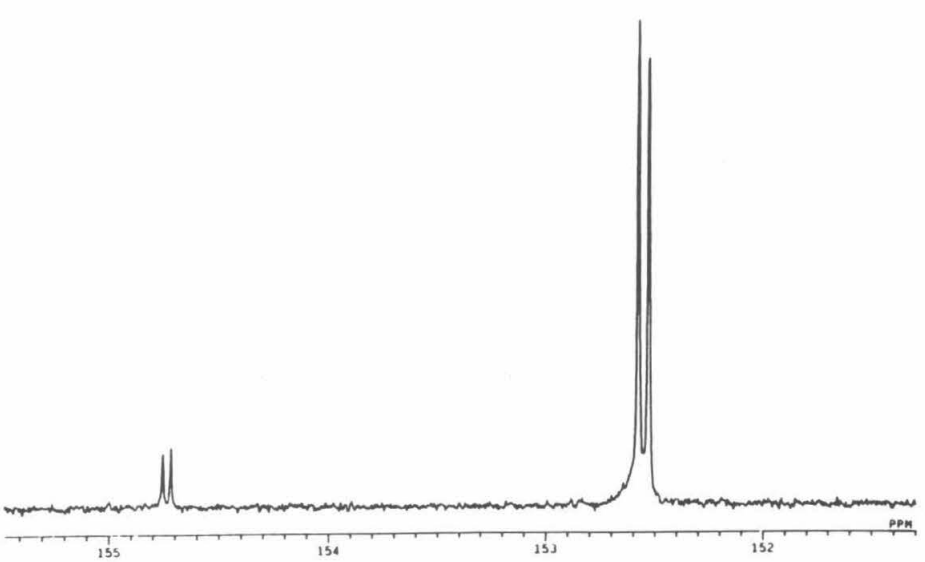

106.69
%T
N=N—CH3
E-Z mixture
76.97
4000
3500
3000
2500
2000
1500
1000
cm-1

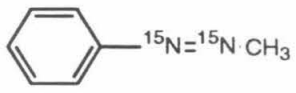


E-Z mixture

^{13}C NMR

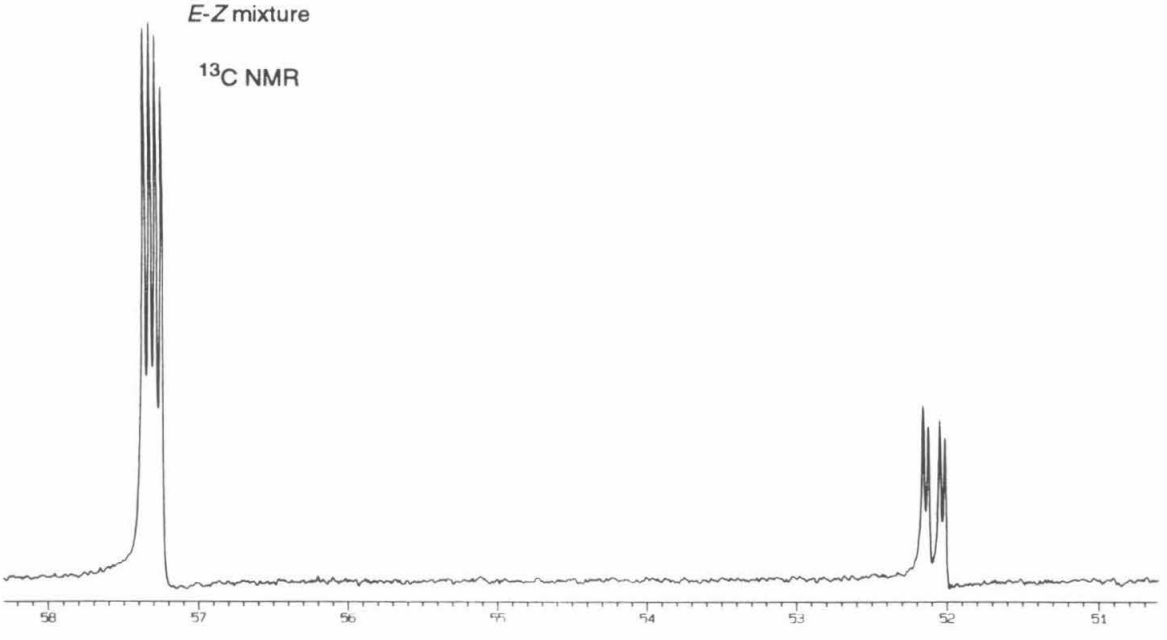


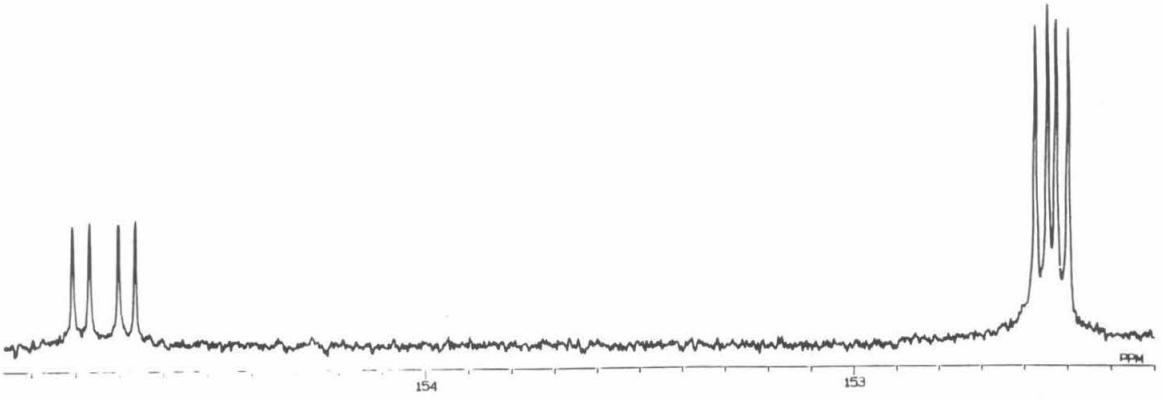


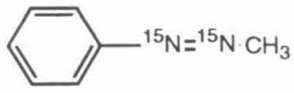


E-Z mixture

^{13}C NMR

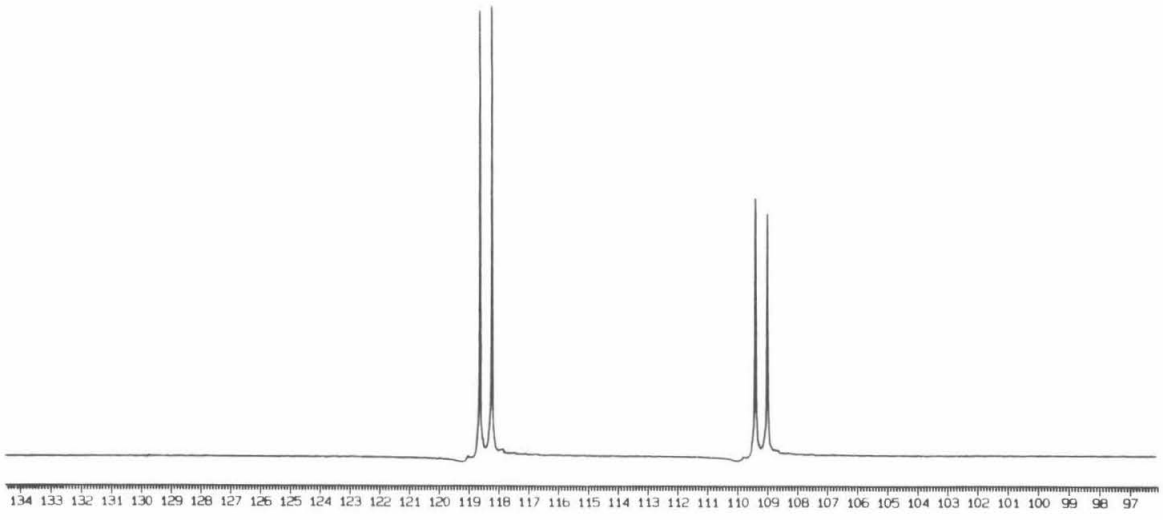


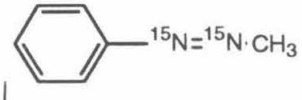




(E)-**35**

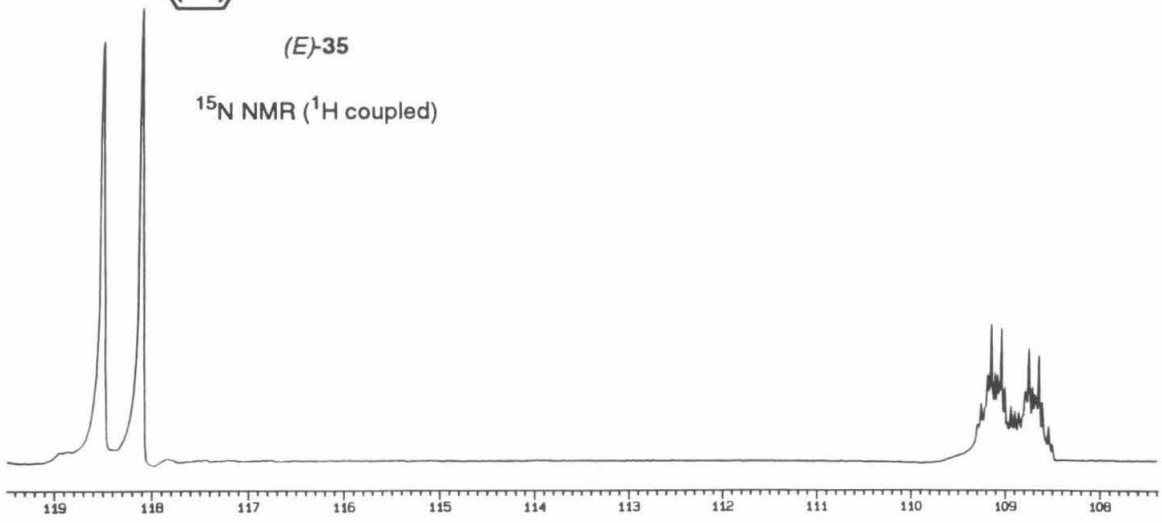
^{15}N NMR

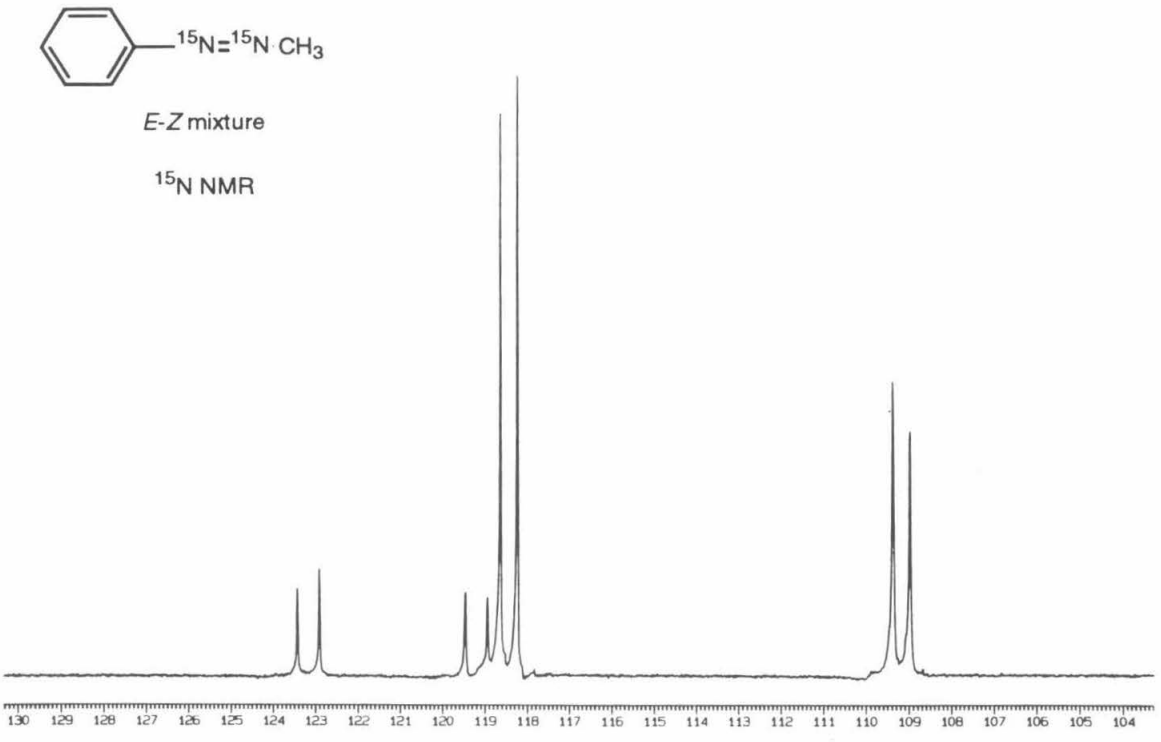


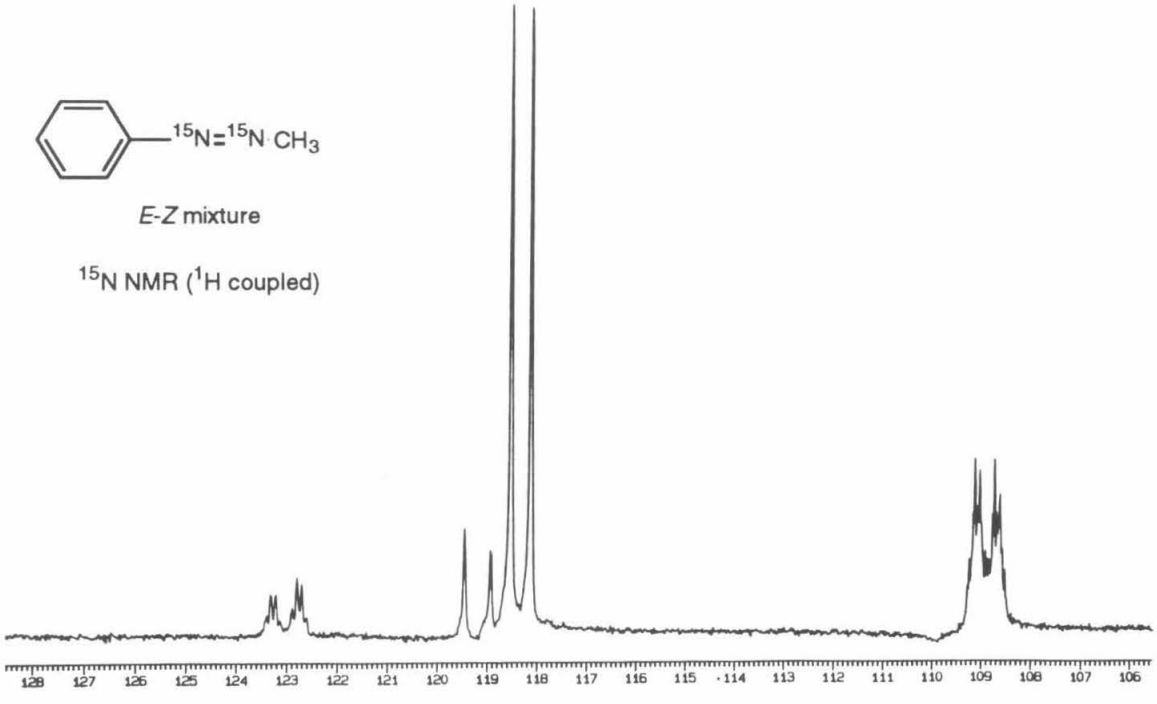


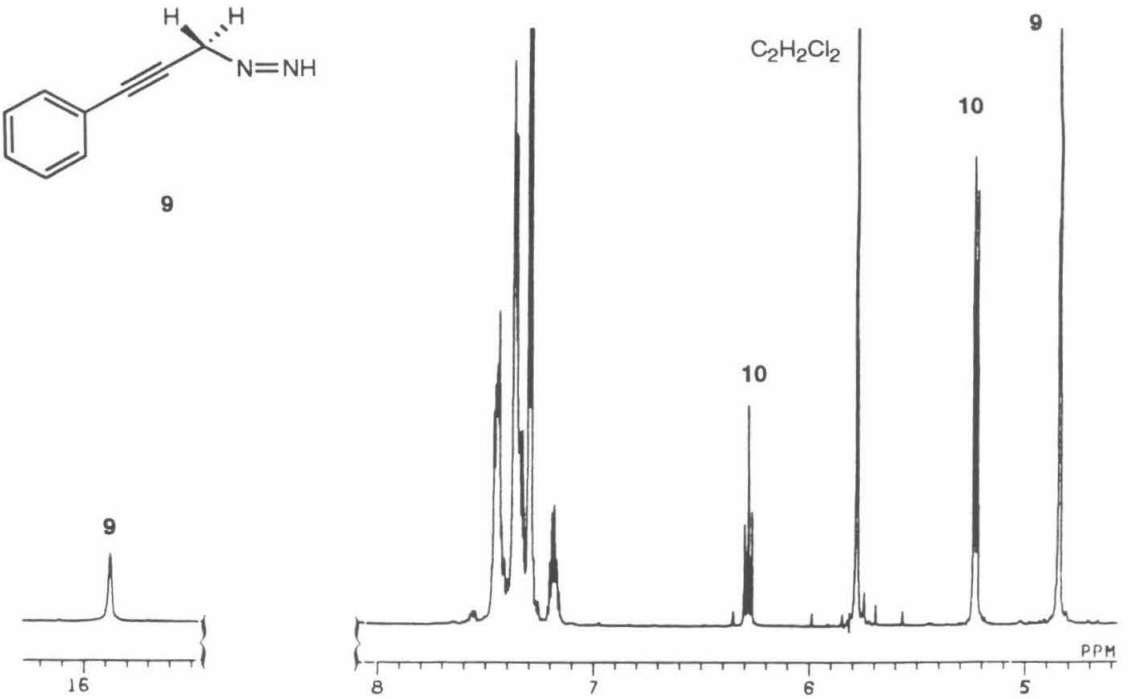
(E)-**35**

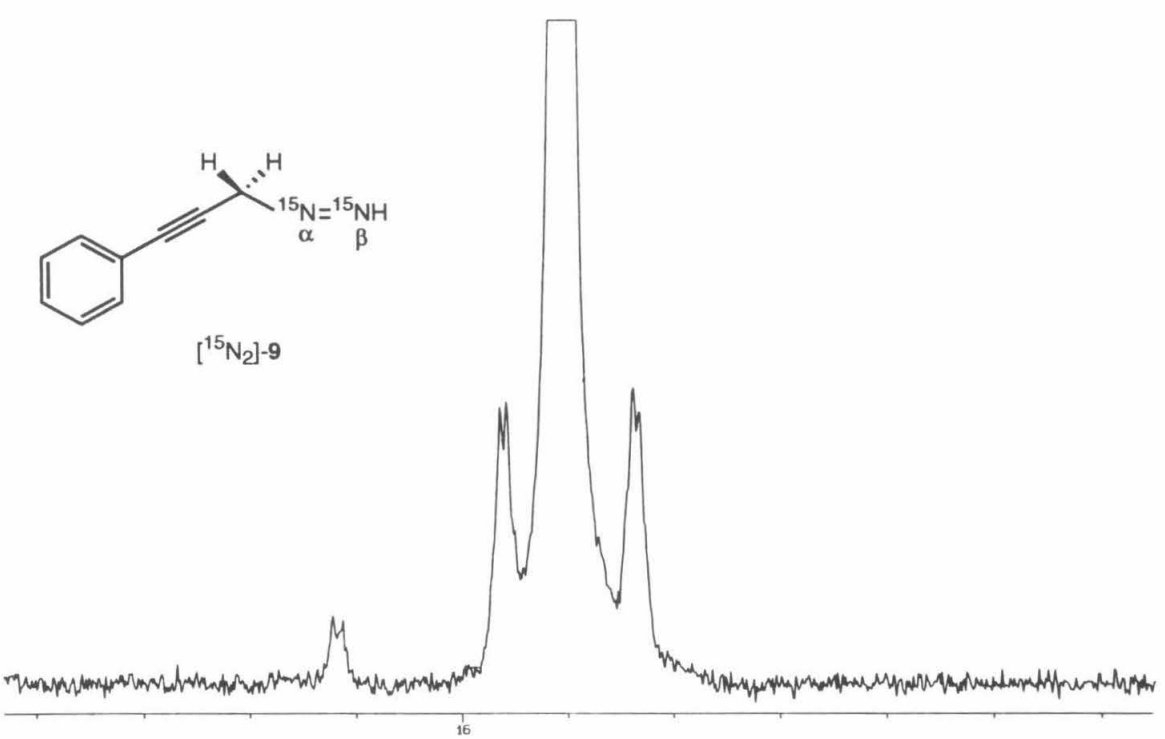
^{15}N NMR (^{1}H coupled)

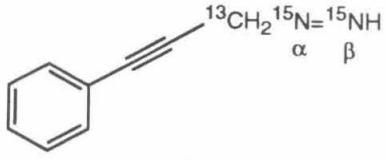



$^{15}N=^{15}N\cdot CH_3$
E-Z mixture
^{15}N NMR
130 129 128 127 126 125 124 123 122 121 120 119 118 117 116 115 114 113 112 111 110 109 108 107 106 105 104


$^{15}N=^{15}N\cdot CH_3$
E-Z mixture
^{15}N NMR (^{1}H coupled)
128 127 126 125 124 123 122 121 120 119 118 117 116 115 114 113 112 111 110 109 108 107 106

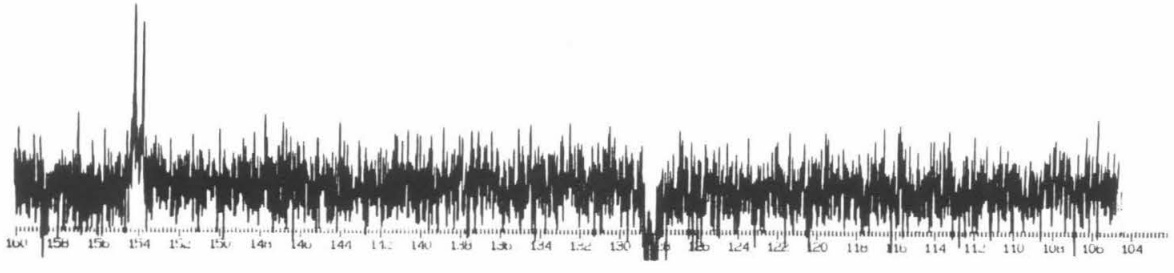

H
H
N=NH
9
9
16
C2H2Cl2
9
10
10
8
7
6
5
PPM

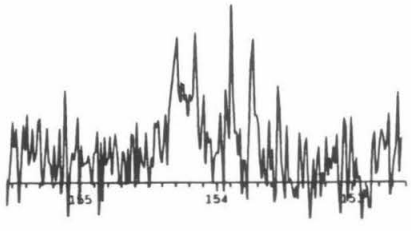

H
H
15N=15NH
α
β
[15N2]-9
16

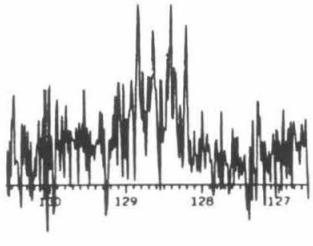


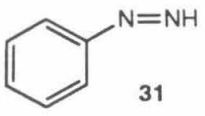
$[^{15}N_2]$-**9**

^{15}N NMR

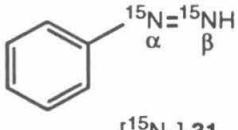




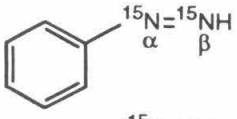




31

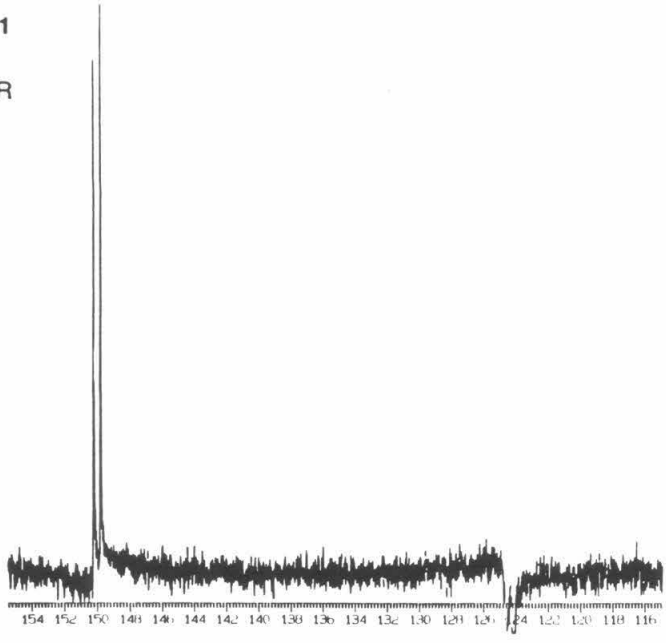


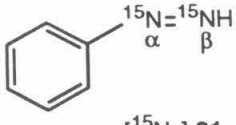
$[^{15}N_2]$-**31**



[$^{15}N_2$]-**31**

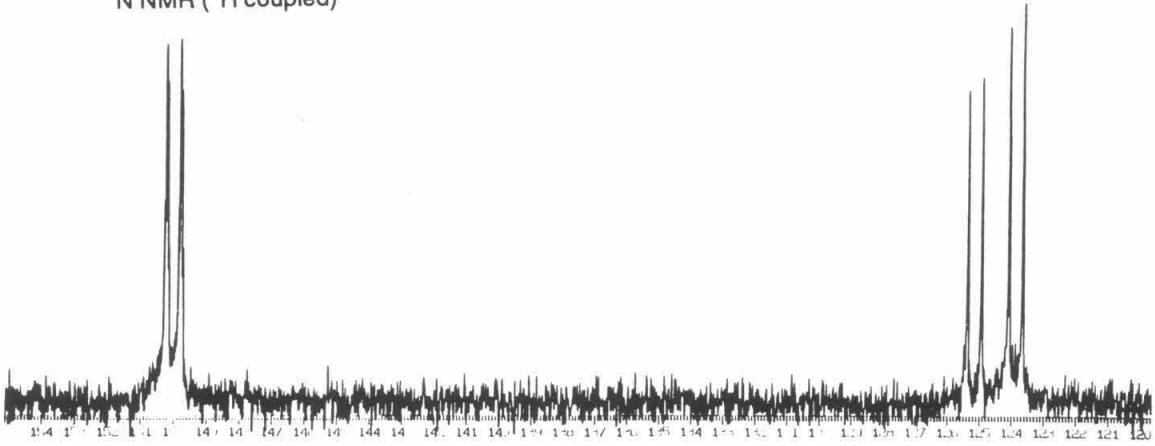
^{15}N NMR





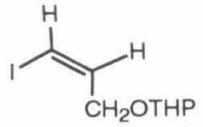
[$^{15}N_2$]-**31**

^{15}N NMR (^{1}H coupled)

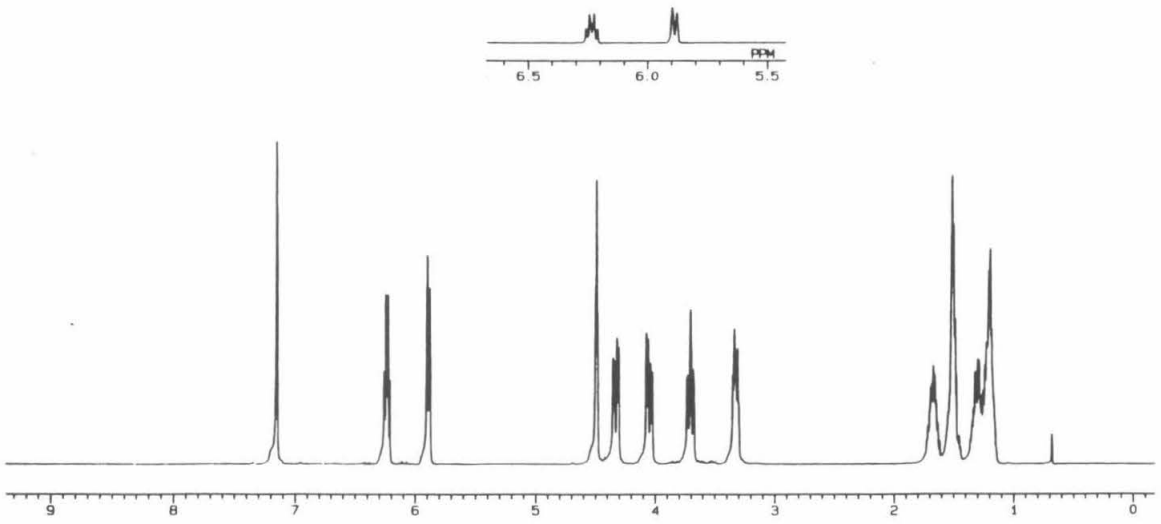


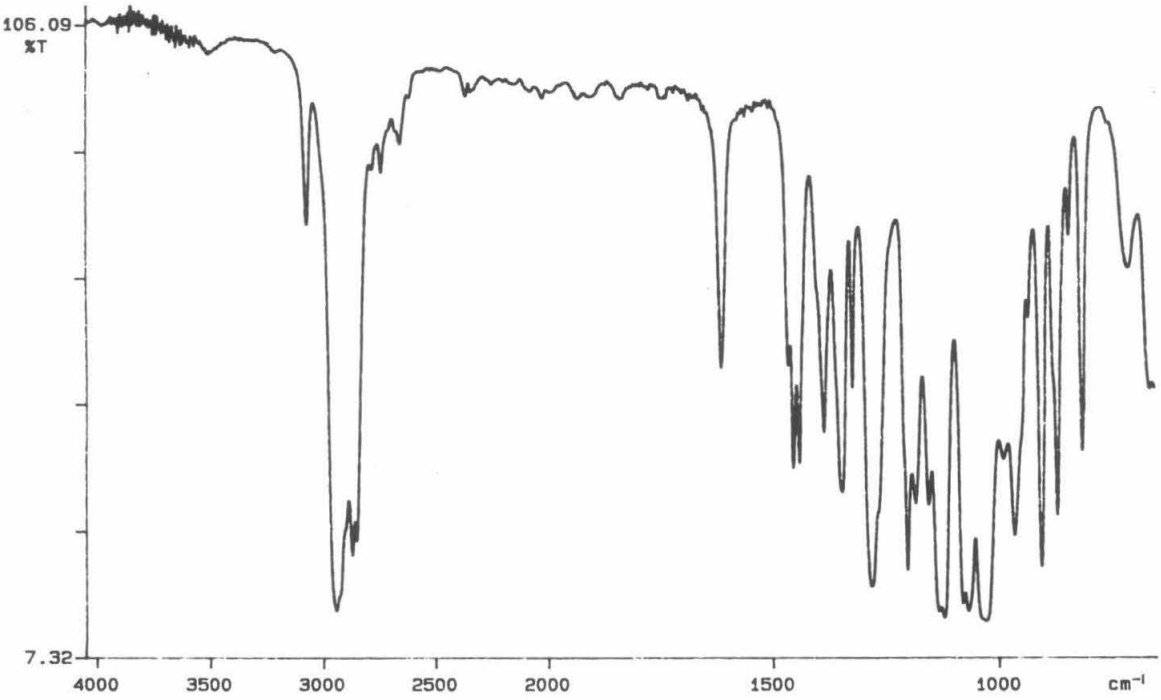
Appendix 3

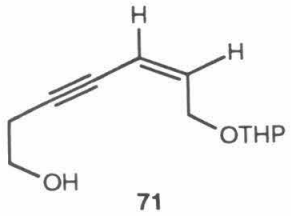
Catalog of Spectra (Chapter 3)


H
H
I
CH2OTHP

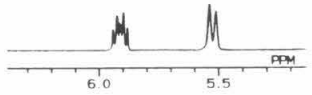
70

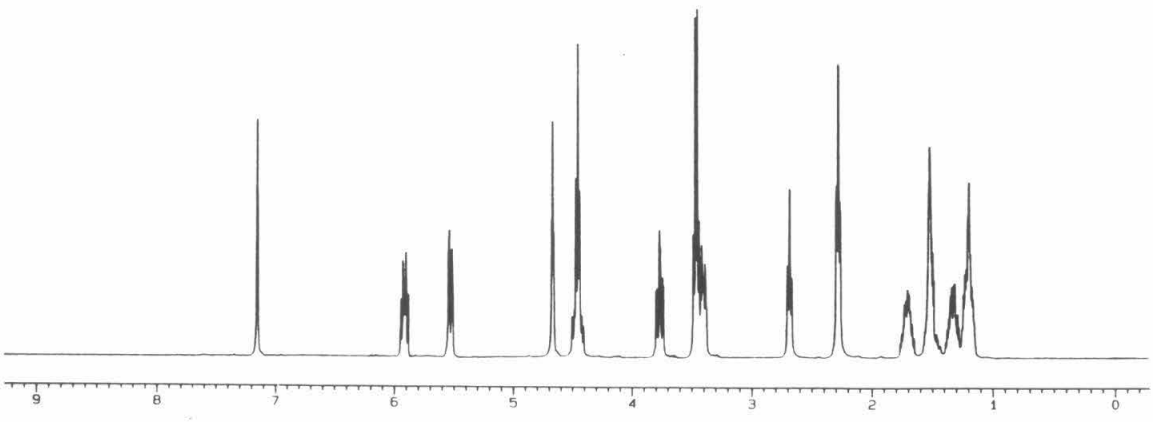

PPM
6.5
6.0
5.5
9
8
7
6
5
4
3
2
1
0

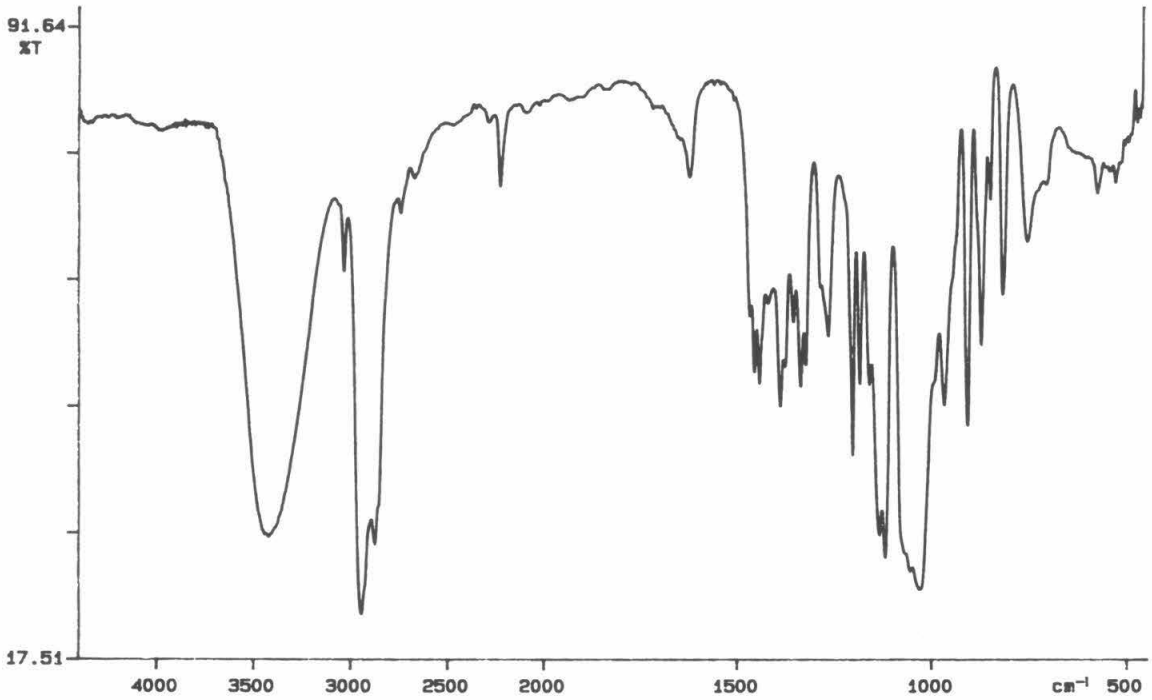

106.09
%T
7.32
4000
3500
3000
2500
2000
1500
1000
cm-1

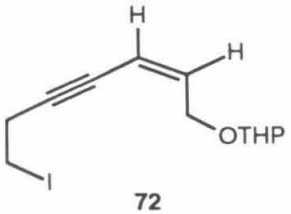

H
H
OTHP
OH

71


PPM
6.0
5.5

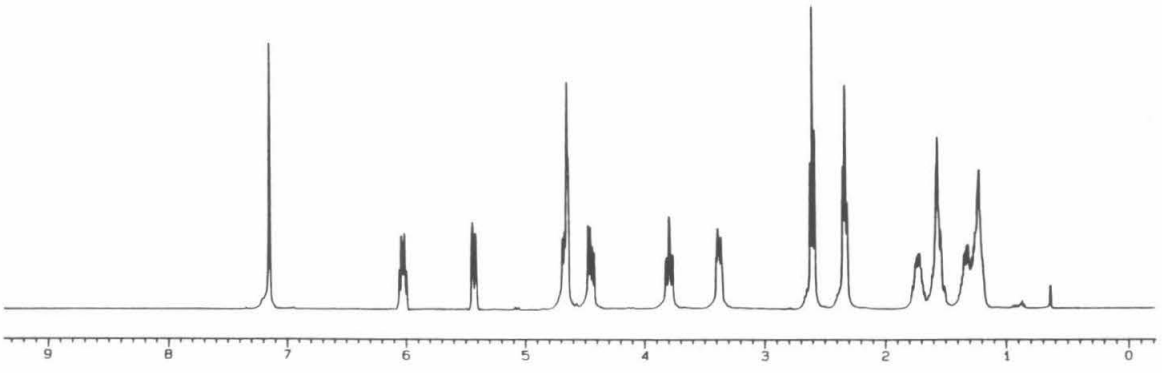

9
8
7
6
5
4
3
2
1
0

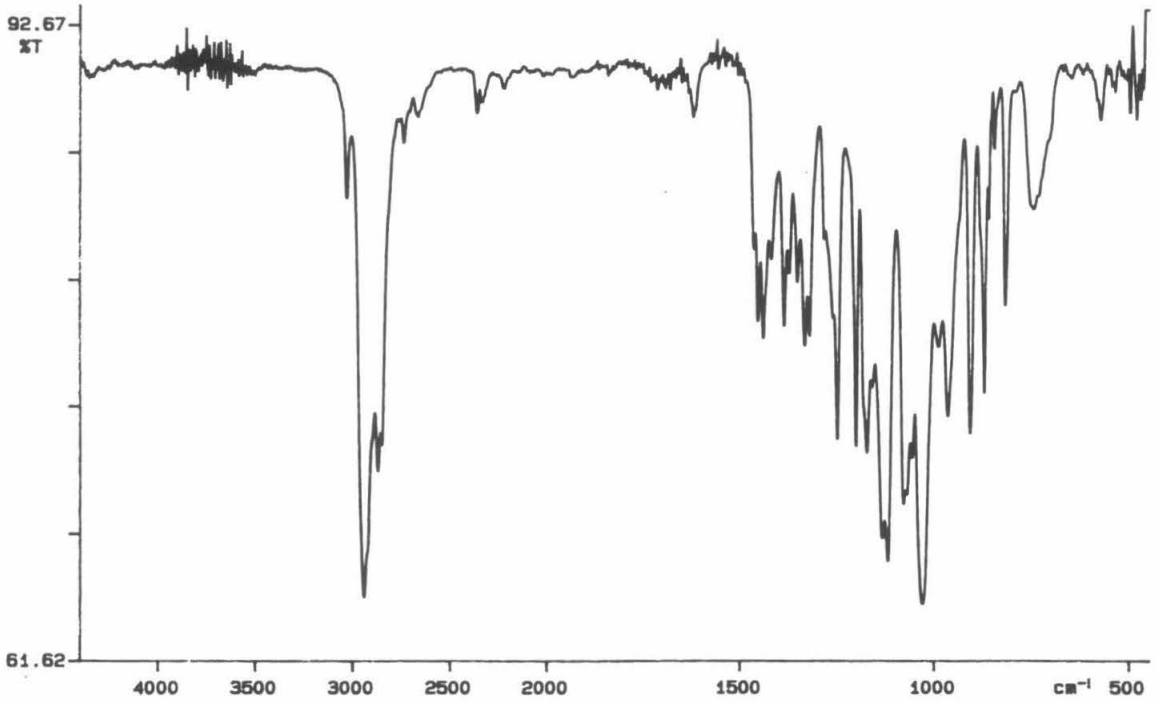

91.64
%T
17.51
4000
3500
3000
2500
2000
1500
1000
cm⁻¹
500

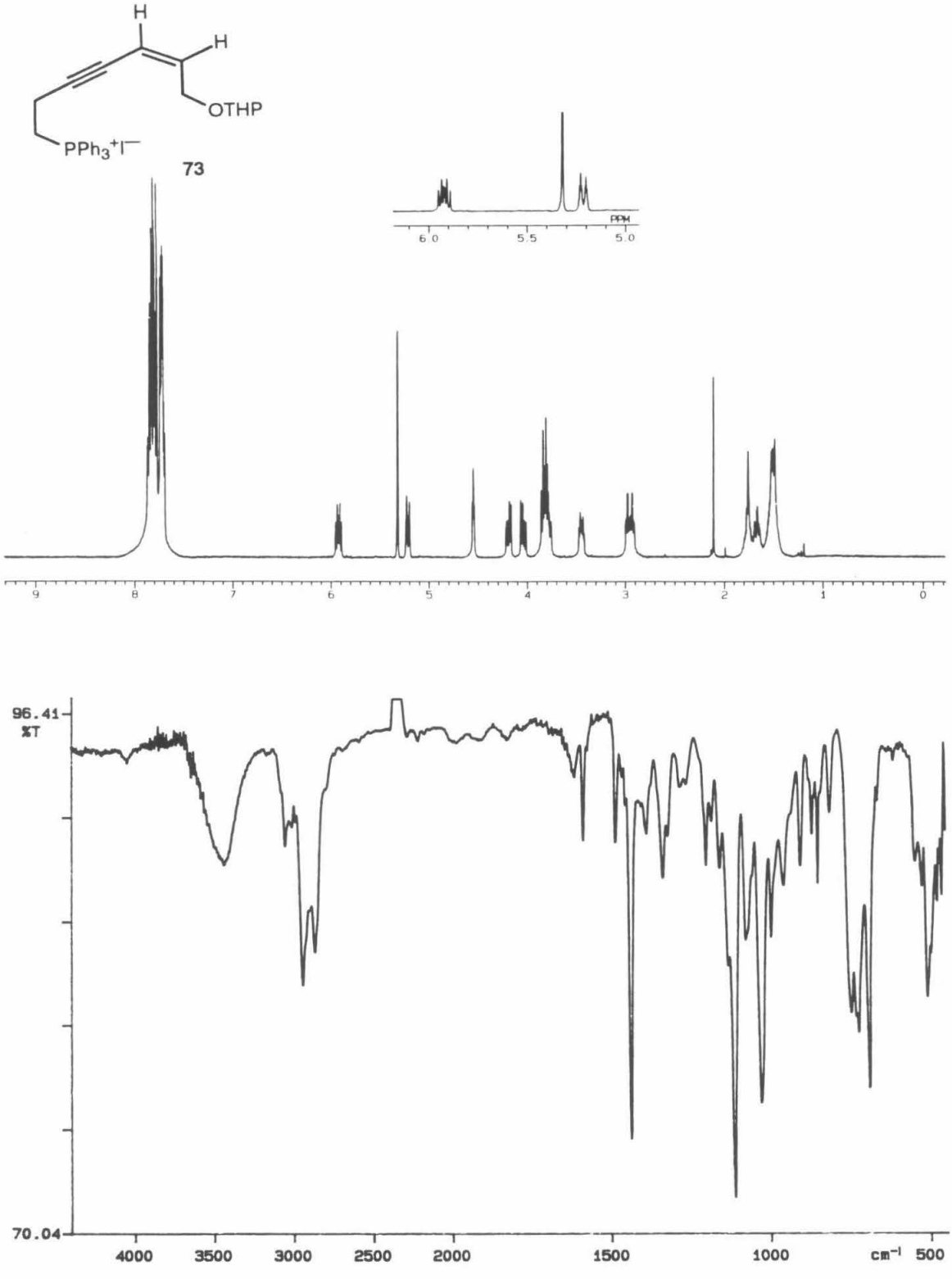

H
H
OTHP
I

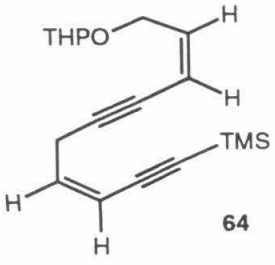
72


PPM
6.0
5.5

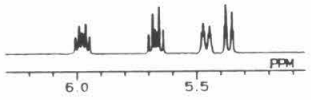

9
8
7
6
5
4
3
2
1
0


92.67
%T
61.62
4000
3500
3000
2500
2000
1500
1000
cm⁻¹
500

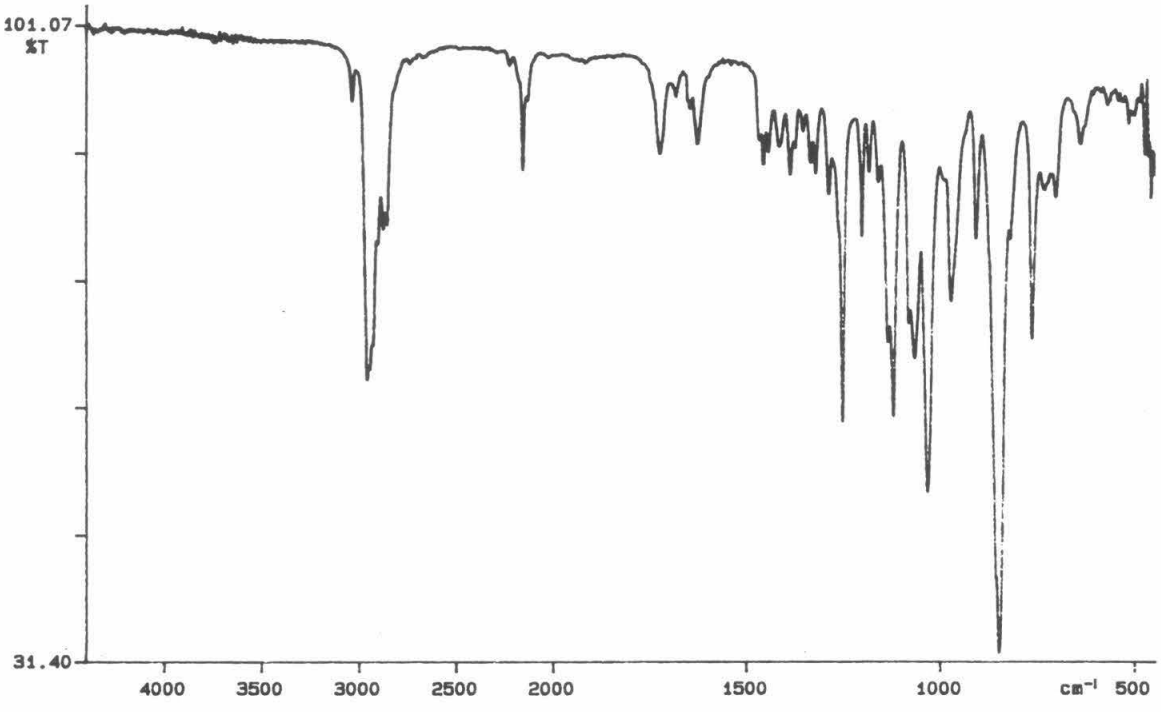

H
H
OTHP
PPh3+I−
73
6.0
5.5
5.0
PPM
9
8
7
6
5
4
3
2
1
0
96.41
%T
70.04
4000
3500
3000
2500
2000
1500
1000
cm-1
500

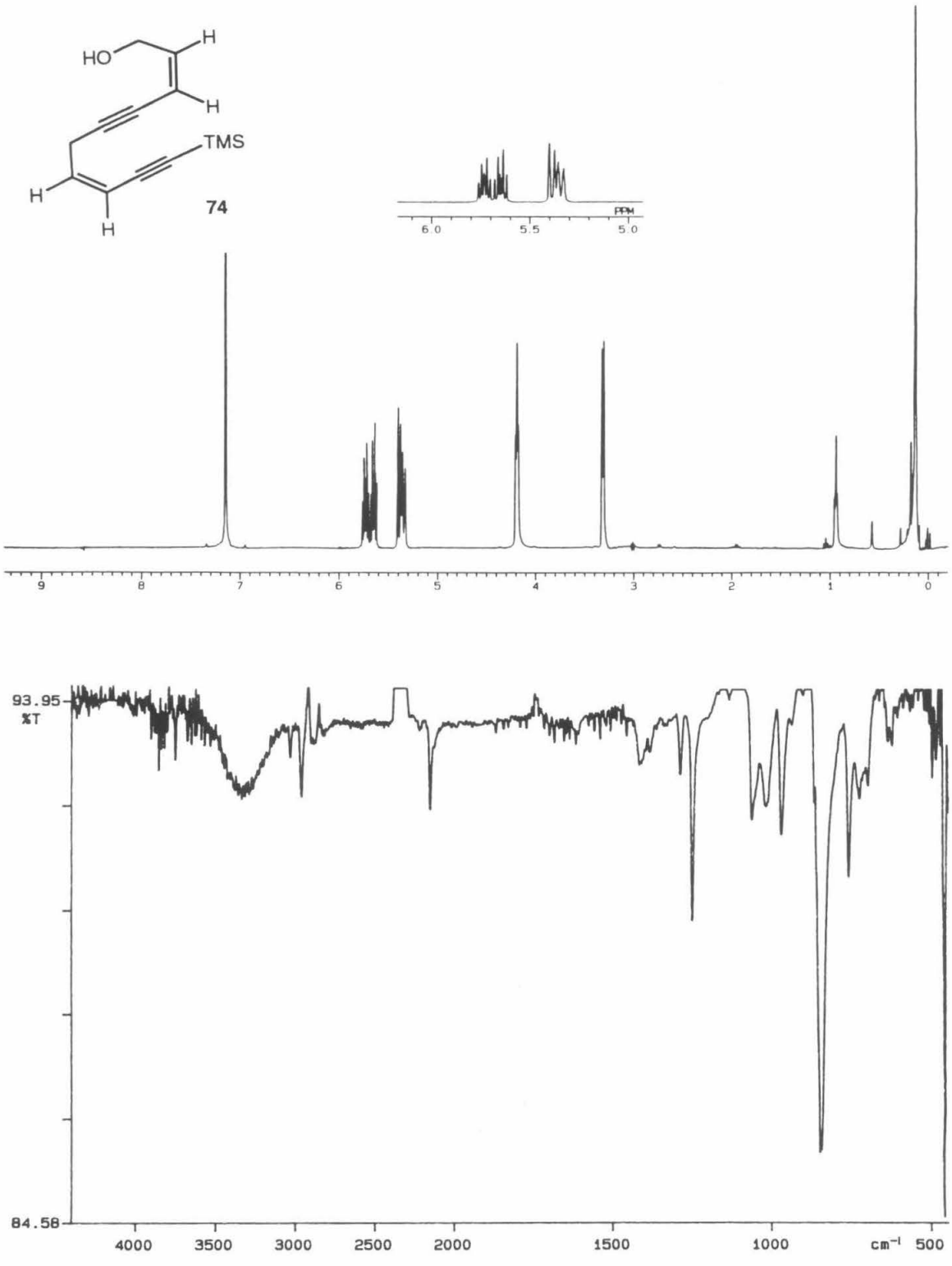

THPO
H
H
TMS
H
H

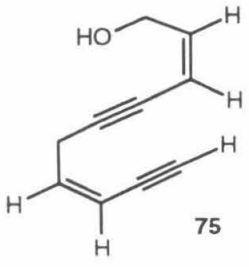
64


PPM
6.0
5.5

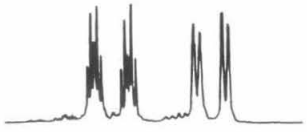
9
8
7
6
5
4
3
2
1
0

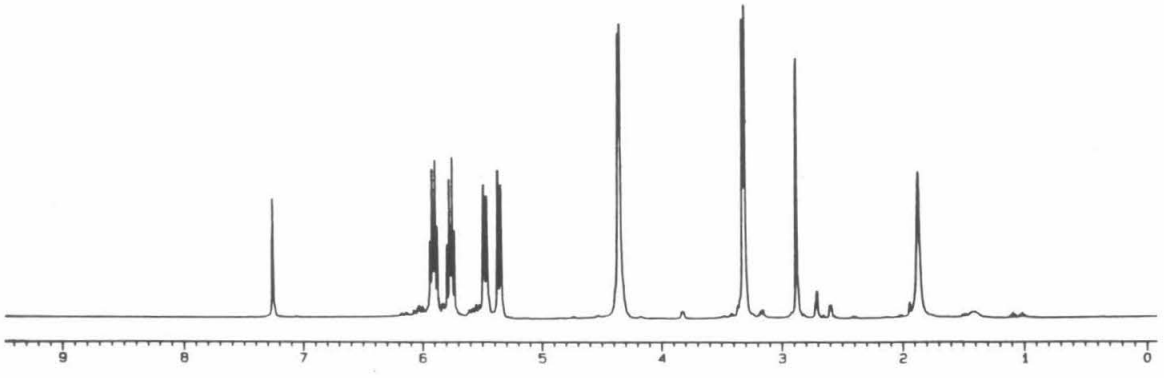

101.07
%T
31.40
4000
3500
3000
2500
2000
1500
1000
cm-1
500

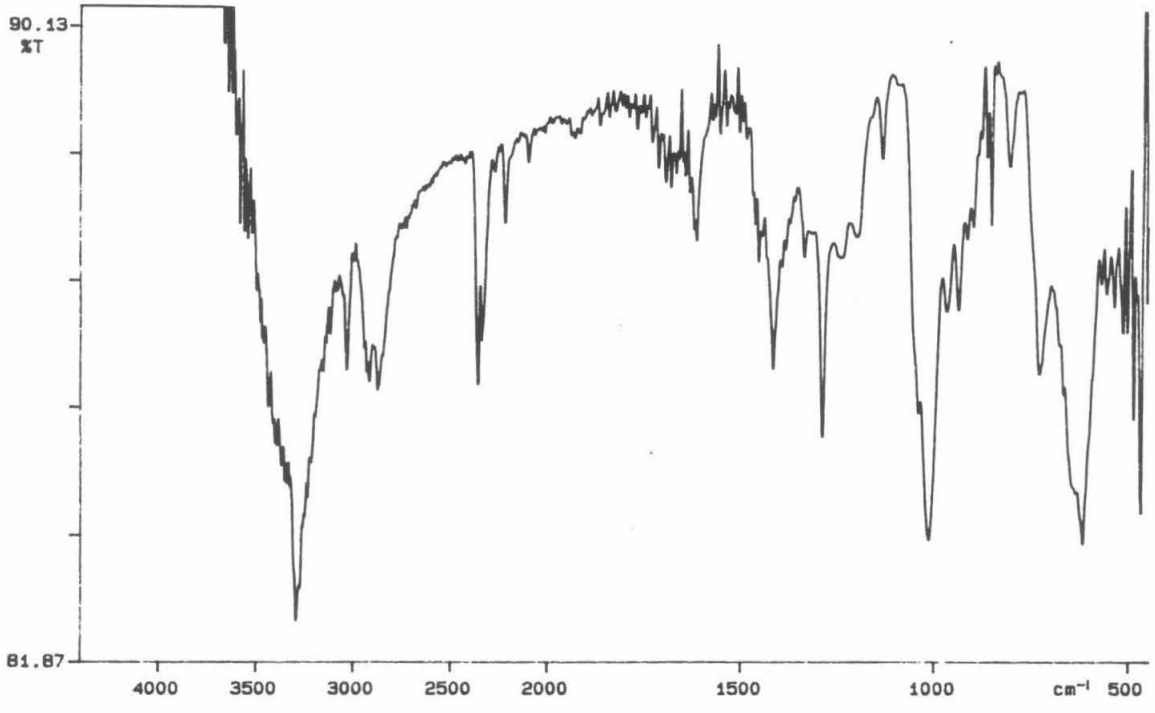

HO
H
H
TMS
H
H
74
6.0
5.5
5.0
PPM
9
8
7
6
5
4
3
2
1
0
93.95
%T
84.58
4000
3500
3000
2500
2000
1500
1000
cm⁻¹
500

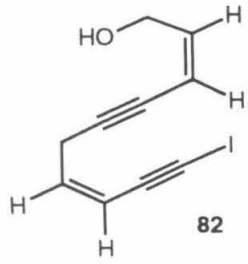

HO
H
H
H
H
H

75

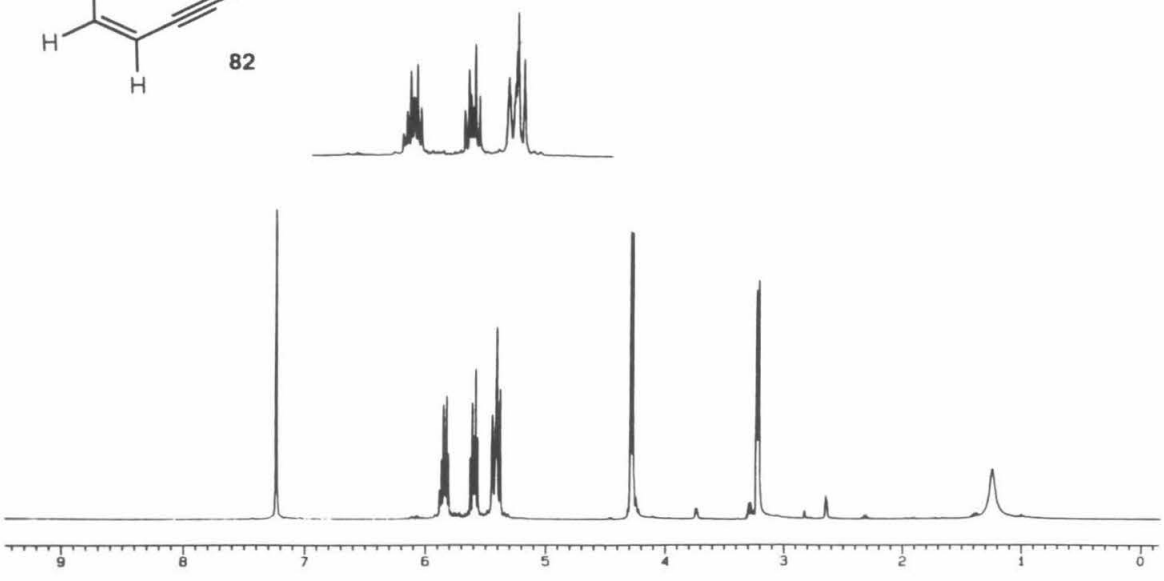


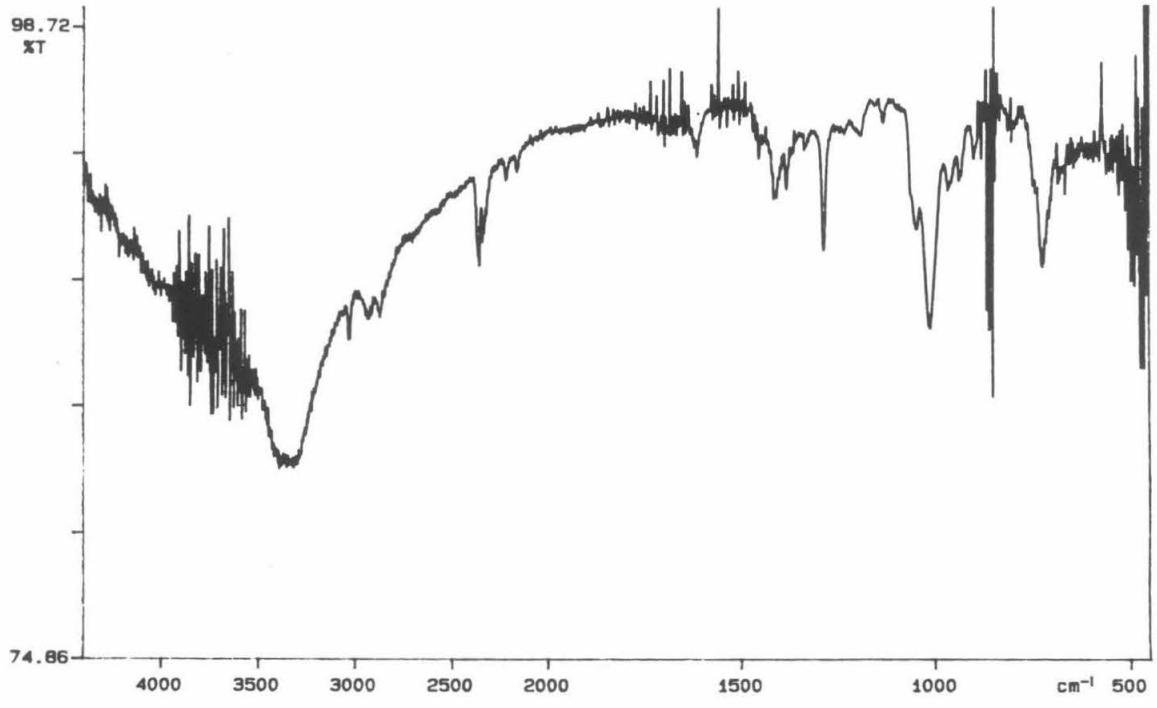

9
8
7
6
5
4
3
2
1
0

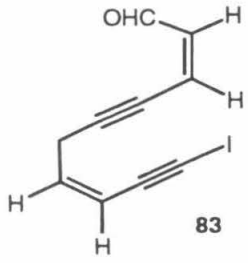

90.13
%T
81.87
4000
3500
3000
2500
2000
1500
1000
cm⁻¹
500


HO
H
H
I
H
H

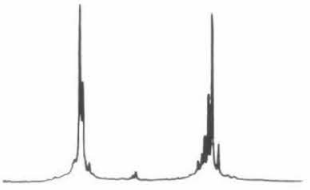
82

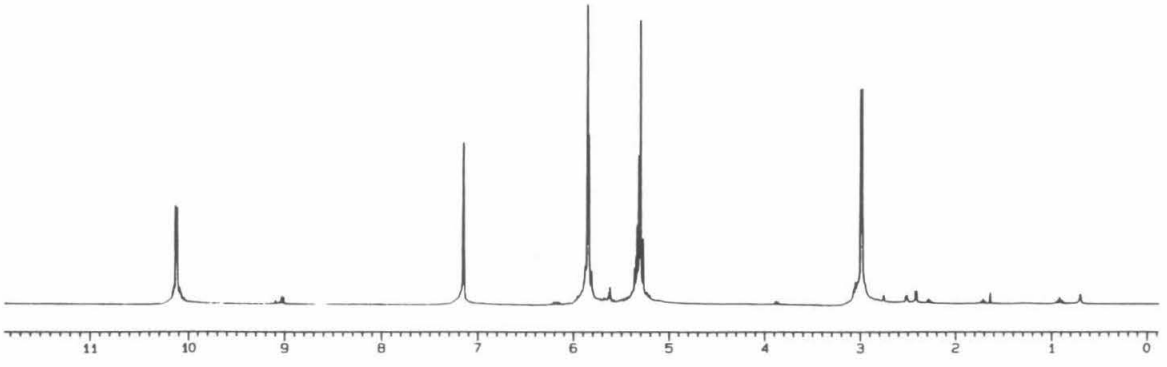

9
8
7
6
5
4
3
2
1
0

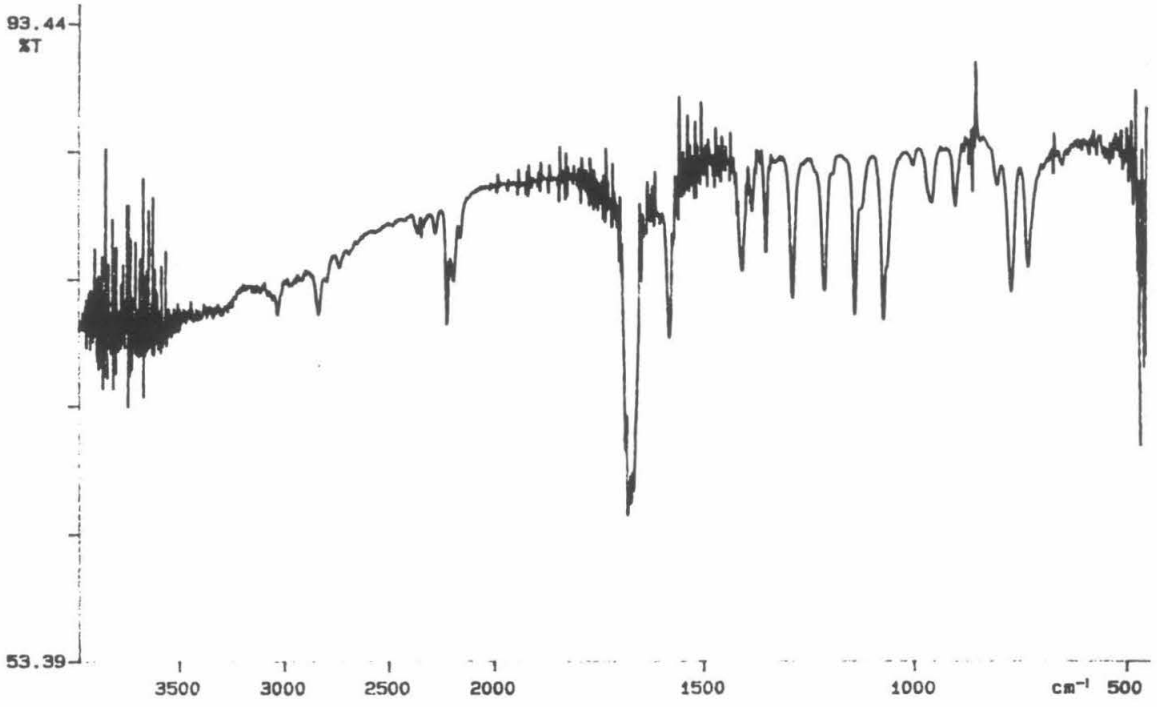

98.72
%T
74.86
4000
3500
3000
2500
2000
1500
1000
cm-1
500

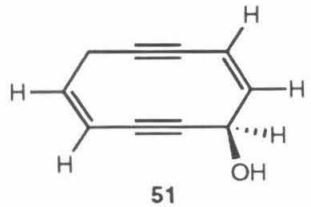

OHC
H
H
I
H
H

83

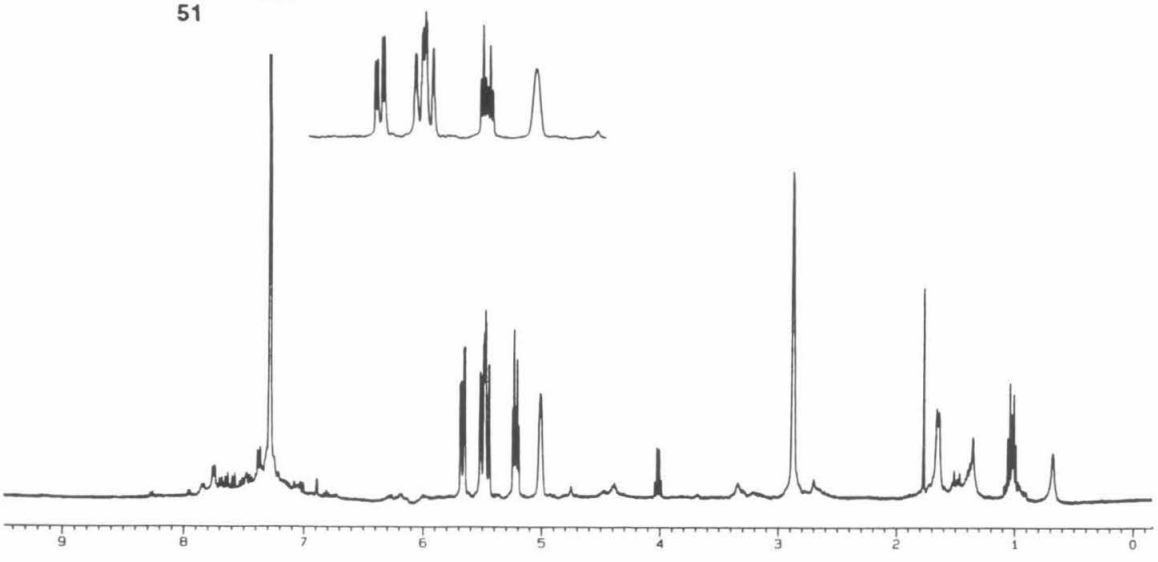


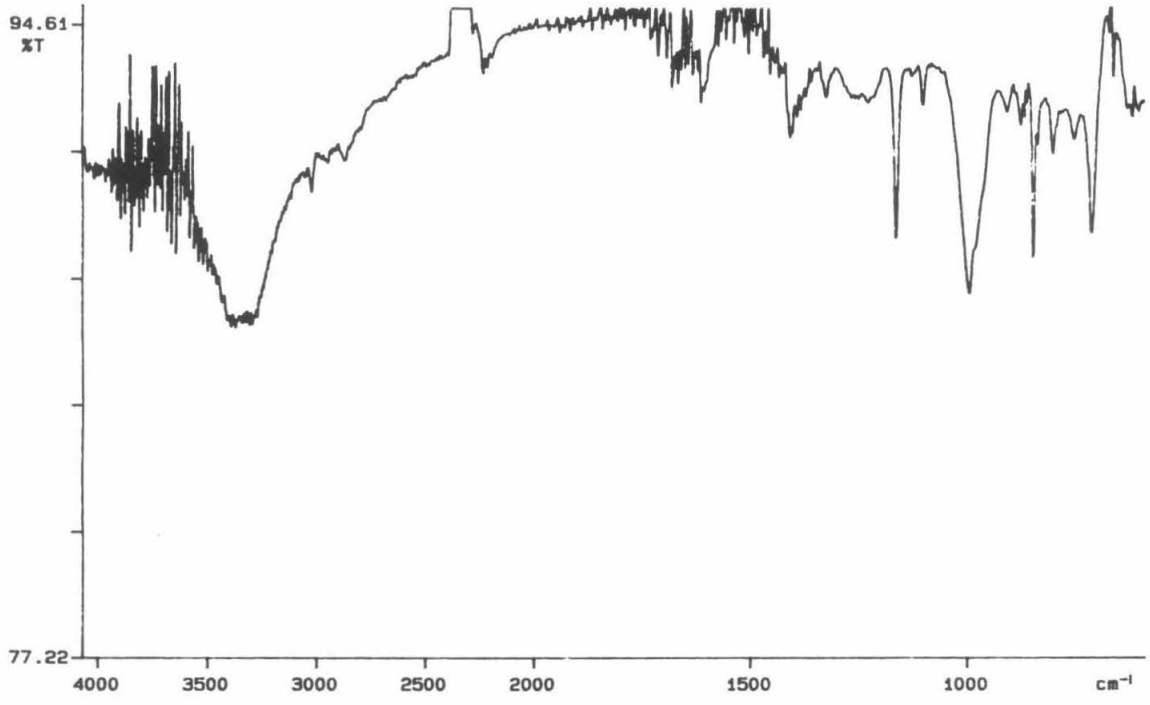

11
10
9
8
7
6
5
4
3
2
1
0

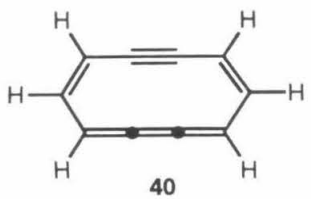

93.44
%T
53.39
3500
3000
2500
2000
1500
1000
cm⁻¹
500


H
H
H
H
H
OH

51


9
8
7
6
5
4
3
2
1
0


94.61
%T
77.22
4000
3500
3000
2500
2000
1500
1000
cm⁻¹



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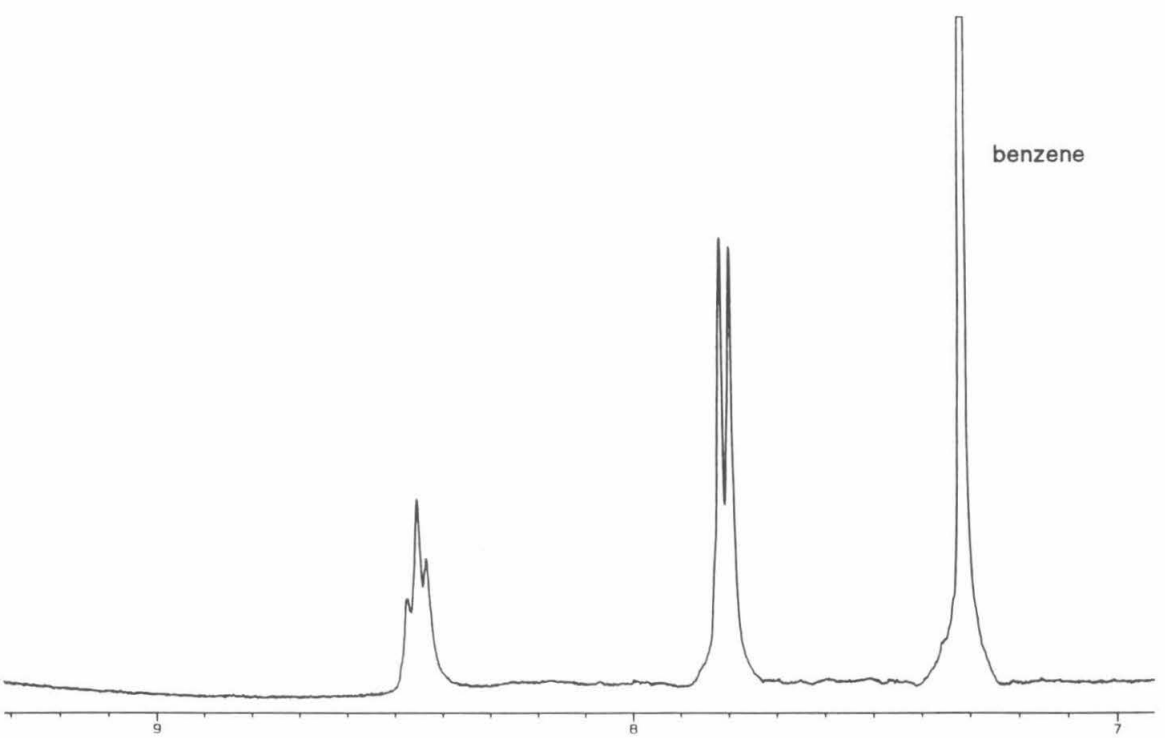
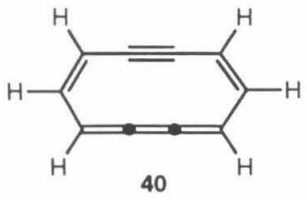
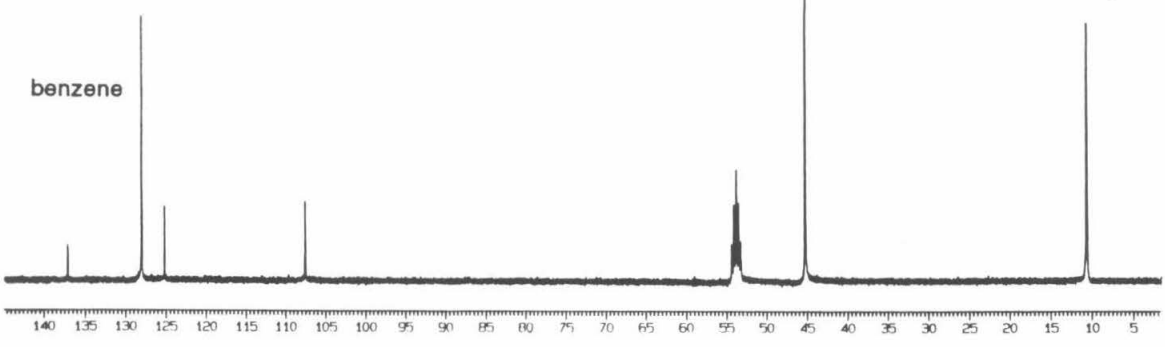
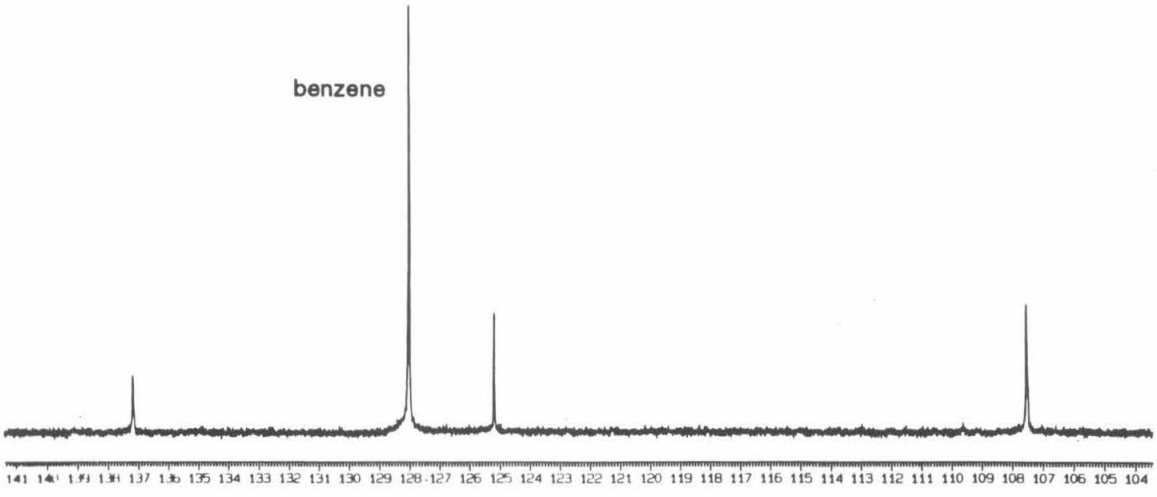


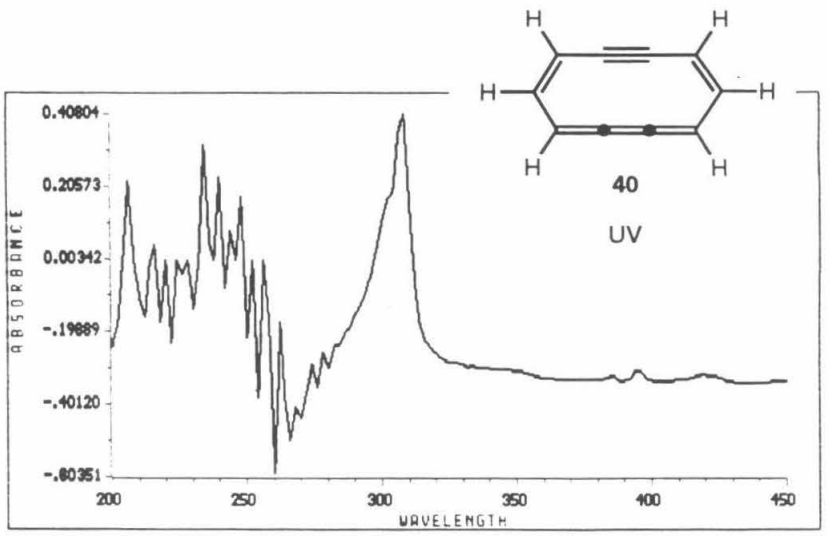

H
H
H
H
H
H

40

^{13}C NMR

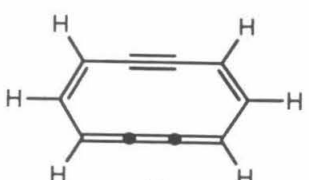

NEt3
NEt3
benzene
140 135 130 125 120 115 110 105 100 95 90 85 80 75 70 65 60 55 50 45 40 35 30 25 20 15 10 5


benzene
141 140 139 138 137 136 135 134 133 132 131 130 129 128 127 126 125 124 123 122 121 120 119 118 117 116 115 114 113 112 111 110 109 108 107 106 105 104



40

UV



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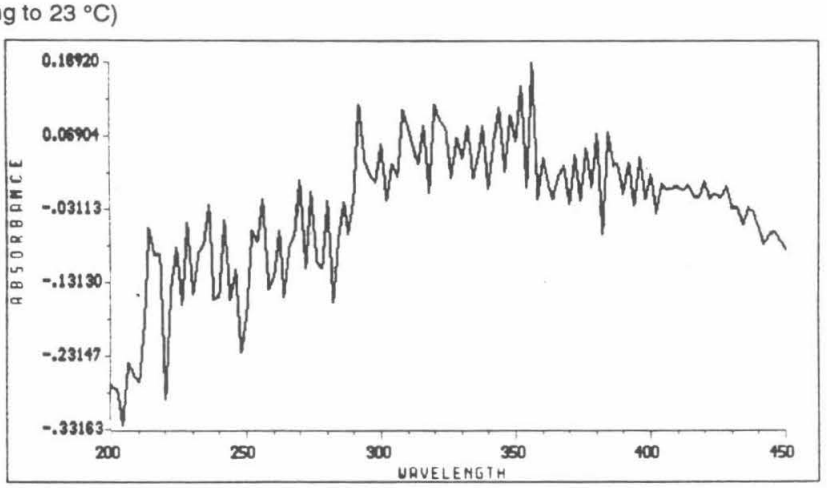
UV (after warming to 23 °C)



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