Progress on the Synthesis of a Model System for the Neocarzinostatin Chromophore

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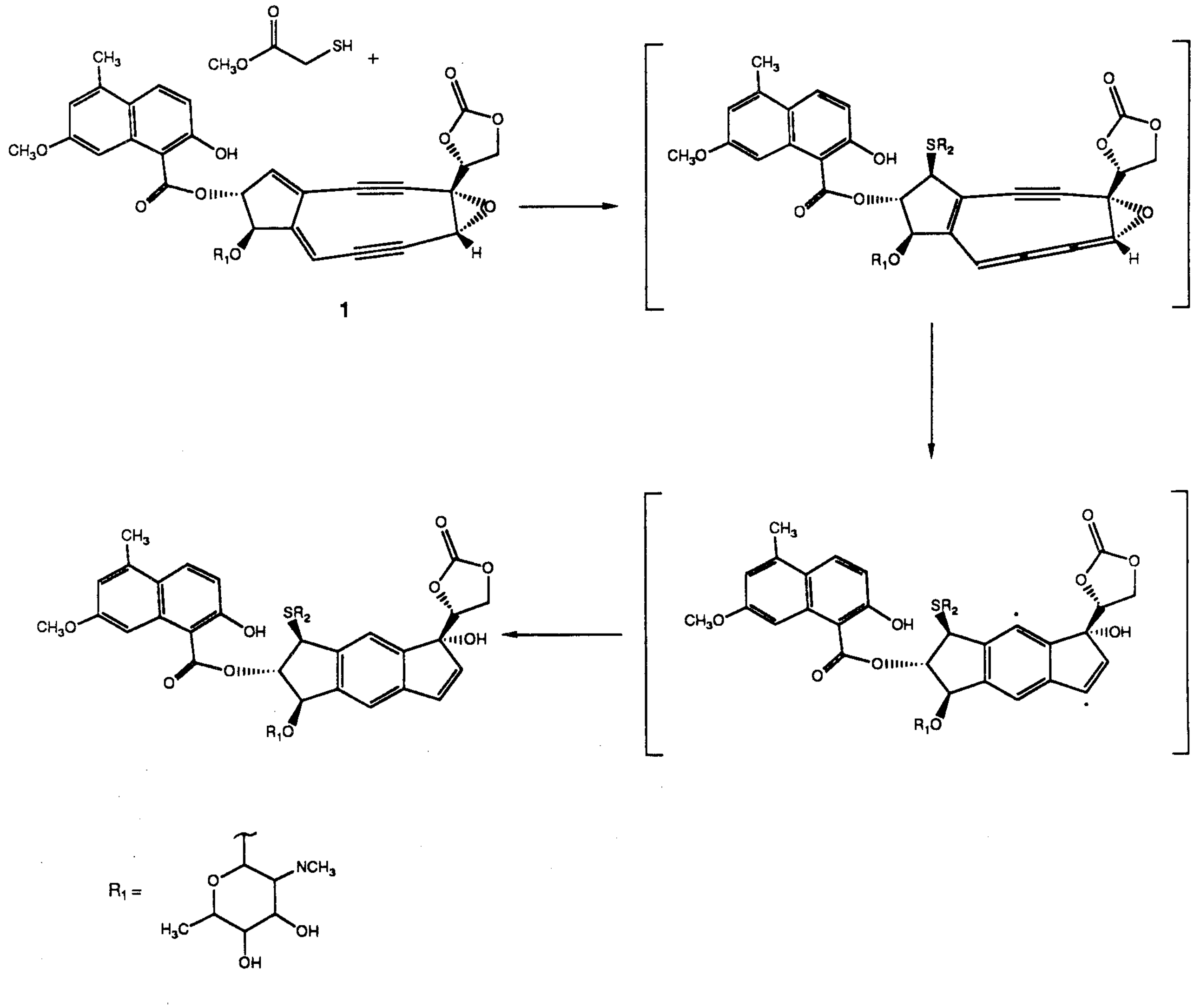
Introduction

The antitumor antibiotic neocarzinostatin (NCS)[1,2] is known to cleave DNA. This reaction is greatly stimulated by the addition of thiols, and, in the absence of DNA, preincubation with thiols rapidly inactivates the drug[1a]. NCS consists of two components, a protein of MW 10,700, and a very labile, methanol-extractable nonprotein component, chromophore **1**. The separated chromophore has been shown to be at least as active as NCS in inducing single-strand breaks in DNA and in inhibiting DNA synthesis; the protein component protects the chromophore and controls its release[3]. Both the isolated chromophore and NCS require thiols for optimal reactivity. The mechanism by which nucleophiles activate **1** toward DNA cleavage has been proposed[4,5] to proceed via a diradical species (Scheme I).

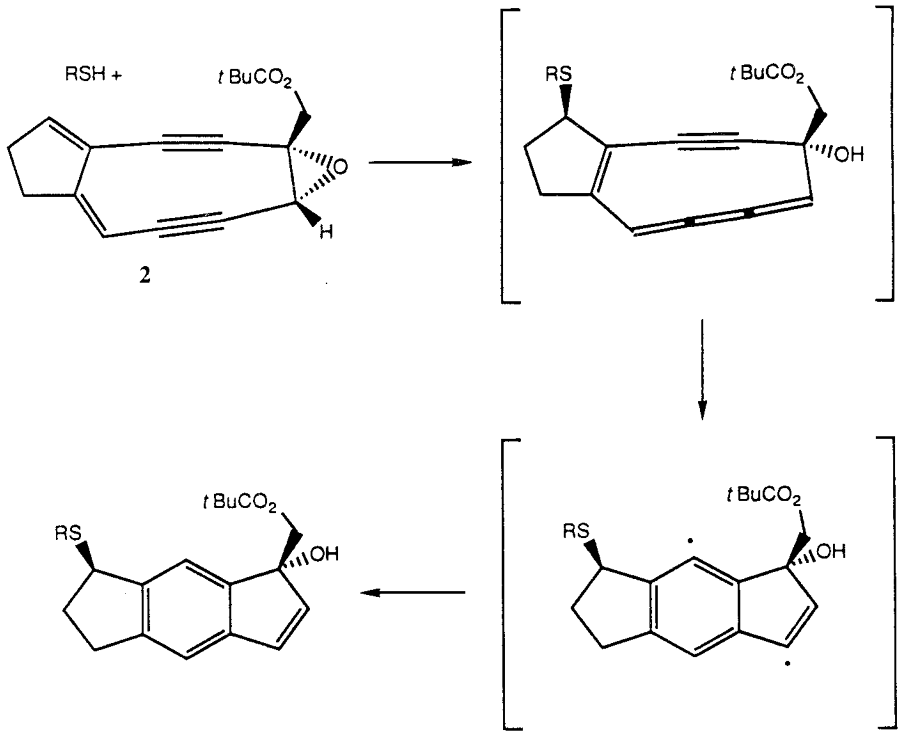
Scheme I



$R_2 = CH_2CO_2CH_3$

The focus of this research is the synthesis of the chromophore analog, **2**. This model system may react with thiols in an analogous manner to the natural product, as shown in scheme II.

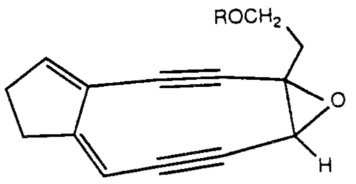
Scheme II



A successful synthesis of the core component would outline the strategy for the total synthesis of NCS chromophore. Finally, diyne **2** may be developed into new, non-diffusable DNA-cleaving reagents by tethering it to known DNA binders. Herein, progress on the synthesis of the NCS chromophore analog **2** will be reported.

Discussion

Compounds **3**, **4**, and **5** were investigated as possible precursors to the NCS chromophore model system, **2**. Each was prepared from multistep syntheses to be described in the following sections. Preliminary ring-closure studies were conducted on all systems.



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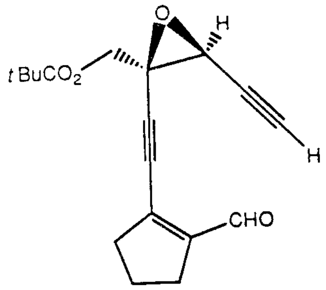

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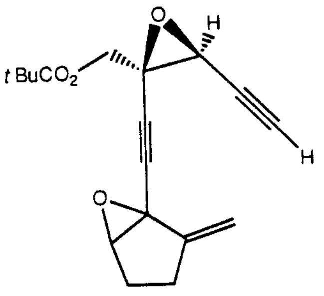

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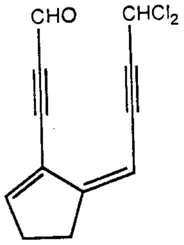
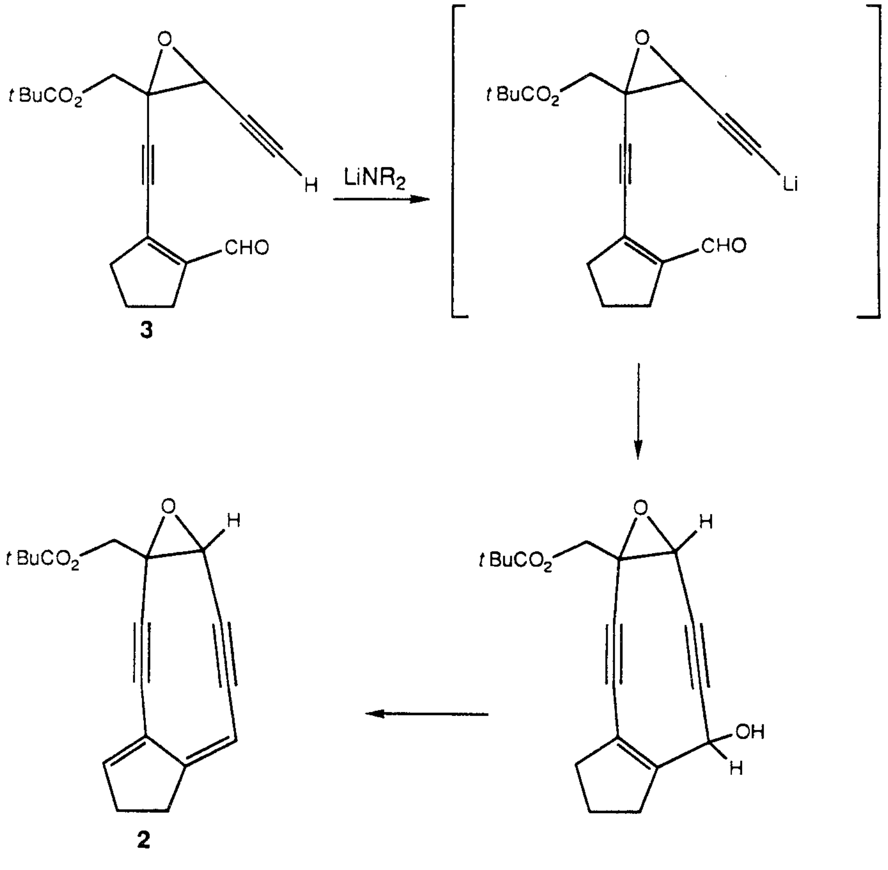


5

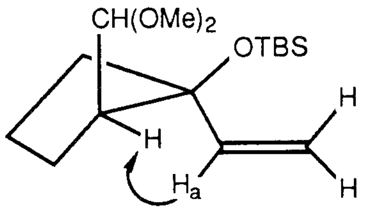
Aldehyde 3

Precursor **3** was designed to allow closure of the 9-membered ring by intramolecular addition of an acetylenic anion to an α,β-unsaturated aldehyde. Treatment with a hindered lithium base would metallate at the terminal acetylene position, as shown in Scheme III. The resulting alcohol could be eliminated to form the target compound, **2**.

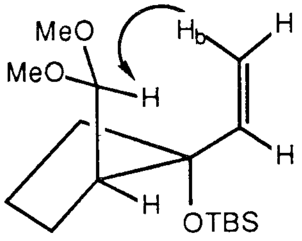
Scheme III



The synthesis of compound **3** is outlined in Scheme IV. Cyclopentanone was converted to the trimethylsilyl (TMS) enol ether, **6**, using TMSCl, NaI, and NEt_3 in CH_3CN[6]. This, on reaction with trimethylorthoformate and a catalytic amount of $TMSOSO_2CF_3$ (TMS triflate), gave the dimethyl acetal, **7**[7], which, on addition of lithium acetylide gave a 4:1 diastereomeric mixture of alcohols, **8**. The corresponding *t*-butyldimethylsilyl (TBS) ethers, **9**, were prepared with TBS triflate[9] and 2,6-lutidine. Although both stereocenters were eliminated later in the synthesis, separation of the isomers simplified analysis of the structures that followed. It was found most convenient to separate the diastereomers as TBS ethers by flash chromatography. The stereochemistry of the two ethers was determined by NOE difference studies. The acetylene group was selectively reduced to the olefin with H_2 over NEt_3-poisoned Pd(C); the arrows in the diagram below indicate the protons whose signals were enhanced on irradiation of protons a and b, respectively.



major

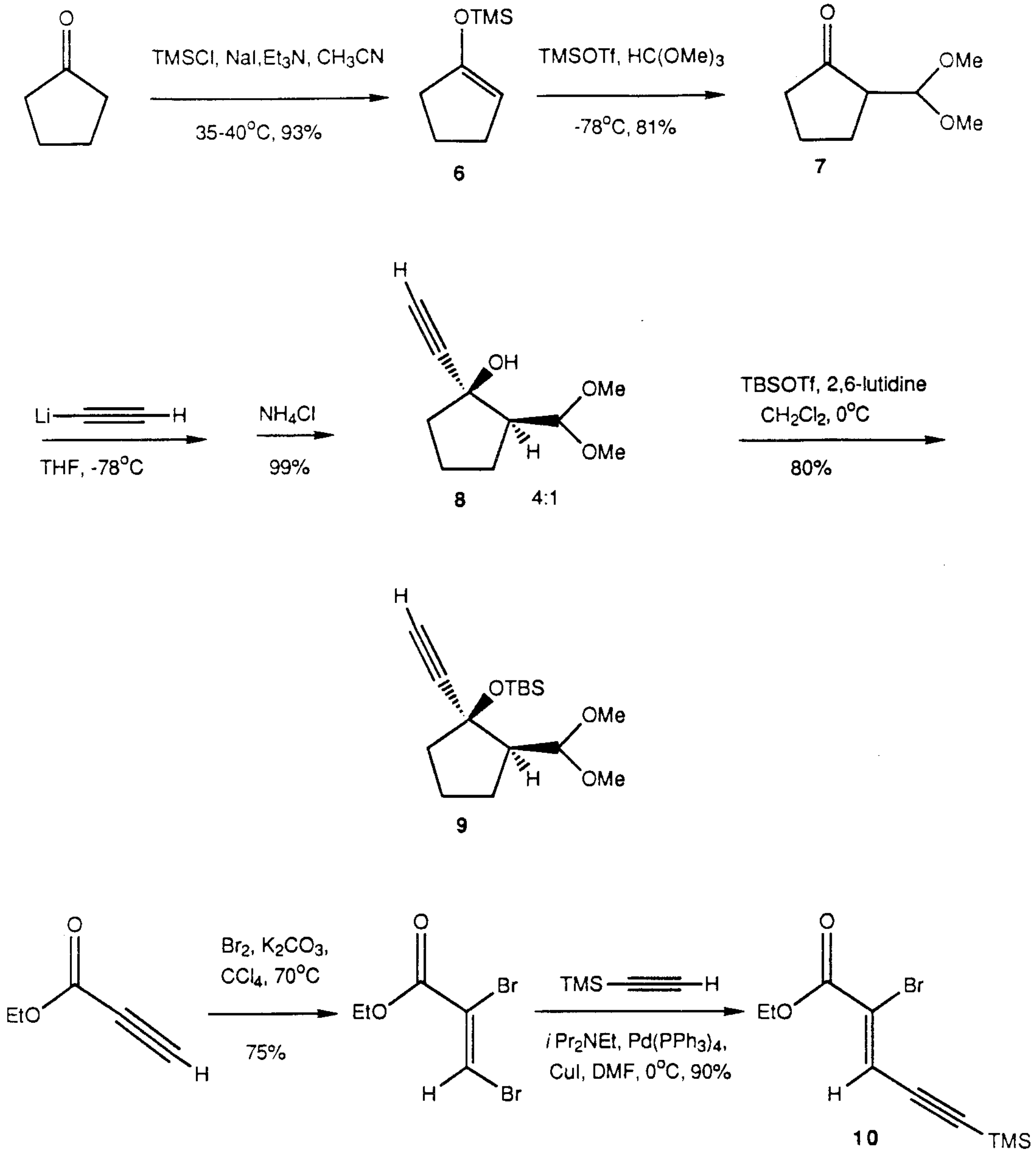


minor

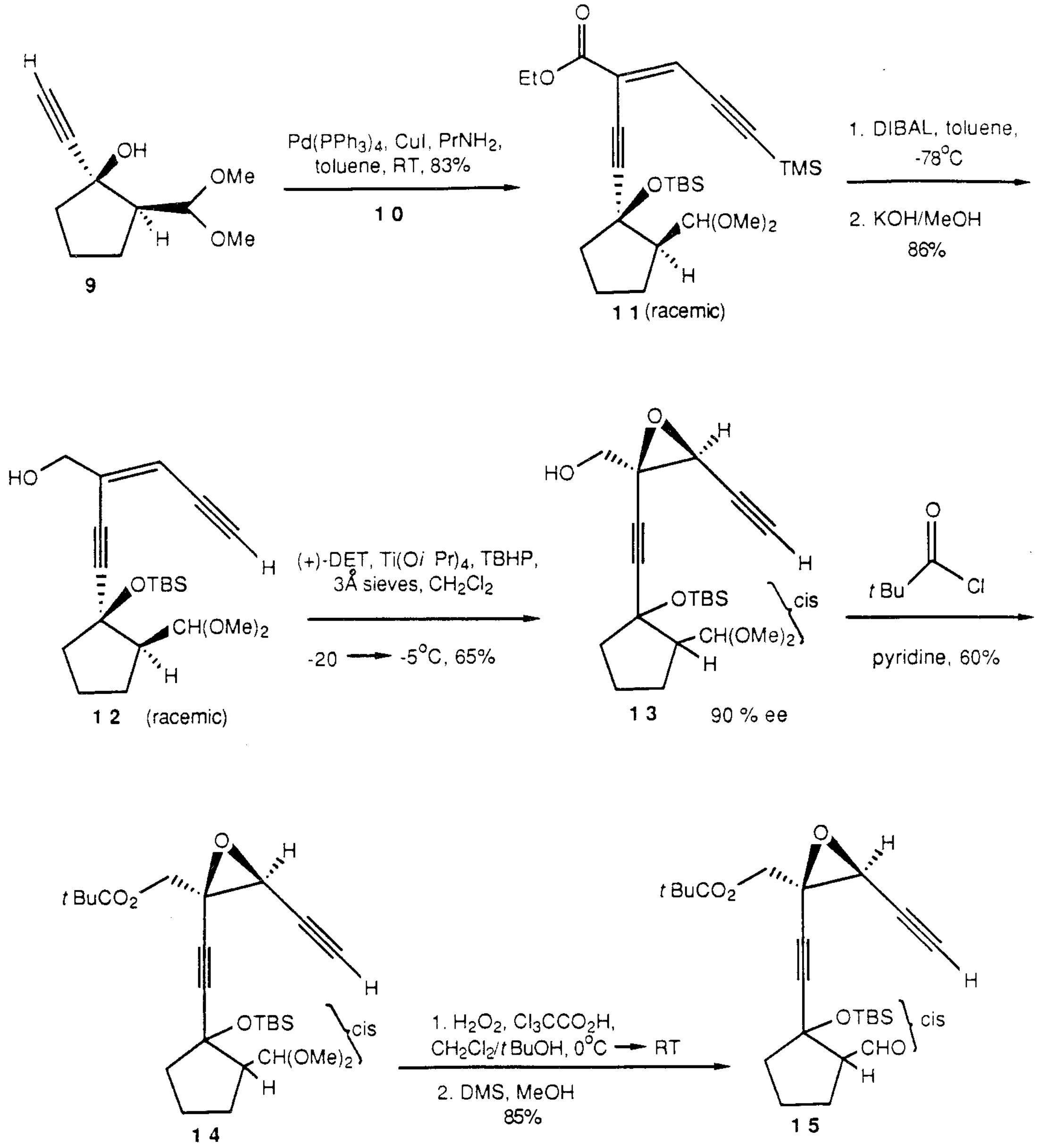
The second starting material, bromide **10**, was prepared by bromination of ethyl propiolate with Br_2 and K_2CO_3 in CCl_4, followed by Pd-catalyzed coupling with TMS acetylene[10].

Coupling of acetylide **9** and bromide **10** with CuI, $PrNH_2$, and a Pd catalyst under oxygen-free conditions lead to enediyne **11** in 85% yield. Diisobutyl aluminum (DIBAL) in toluene was used to reduce the carbonyl, and, in the same pot, the trimethylsilyl group was removed with methanolic KOH to provide alcohol **12**. A Sharpless oxidation was employed[11] to give a 95% crude yield of epoxide **13**; treatment

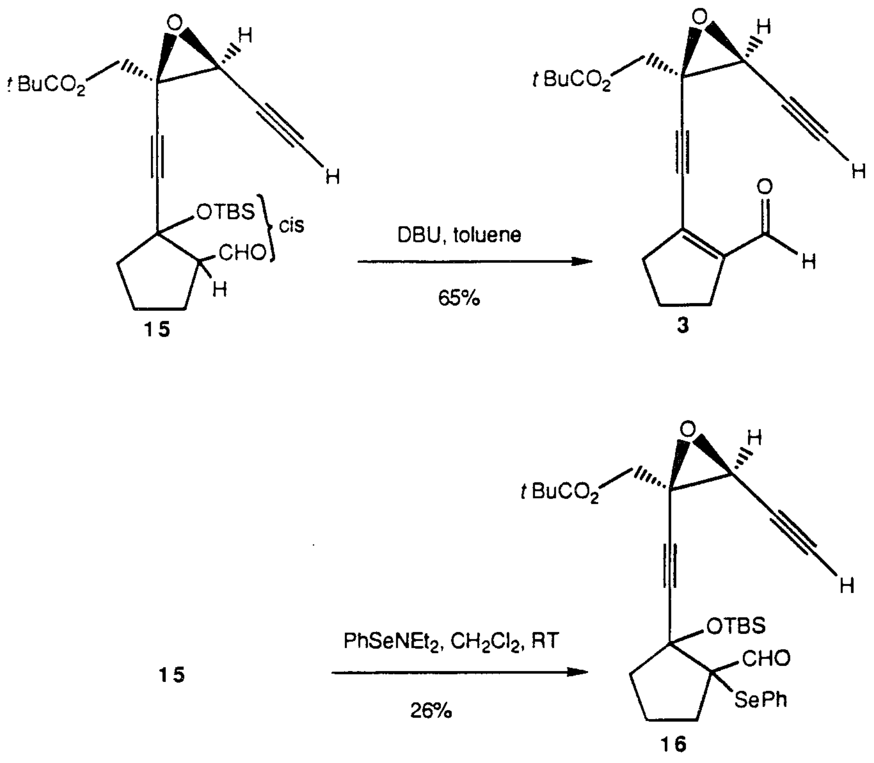
Scheme IV


O
TMSCl, NaI,Et3N, CH3CN
35-40°C, 93%
OTMS
6
TMSOTf, HC(OMe)3
-78°C, 81%
O
OMe
OMe
7
Li
H
THF, -78°C
NH4Cl
99%
H
OH
OMe
H
OMe
8
4:1
TBSOTf, 2,6-lutidine
CH2Cl2, 0°C
80%
H
OTBS
OMe
H
OMe
9
O
EtO
H
Br2, K2CO3,
CCl4, 70°C
75%
O
EtO
Br
H
Br
TMS
H
i Pr2NEt, Pd(PPh3)4,
CuI, DMF, 0°C, 90%
O
EtO
Br
H
10
TMS

Scheme IV (cont.)



Scheme IV (cont.)

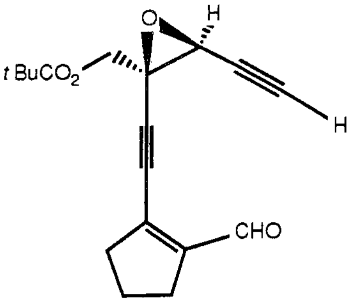


with trimethylacetylchloride in pyridine gave compound **14** in 60% yield from **12**.

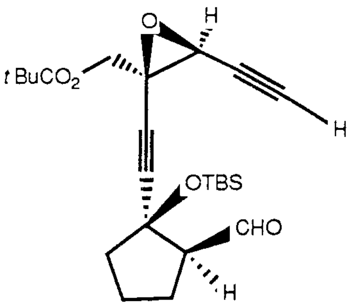
Attempts to hydrolize the dimethylacetal protecting group under conventional acidic conditions required high concentrations of acid and lengthy reaction times, resulting in poor yields. A much milder method was developed using H_2O_2 in CH_2Cl_2 / *t* BuOH and trichloroacetic acid to give a hydroperoxide (see Appendix); treatment with dimethyl sulfide (DMS) gave aldehyde **15** in 66-85% yield. Elimination to the final product, **3**, was accomplished with diazabicycloundecene (DBU) in toluene (65%).

Some preliminary cyclization attempts are shown in Table 1. Reaction of **15** with lithium tetramethylpiperidide (LiTMP) gave dimers or the elimination product **3**. In order to prevent enolization of the aldehyde, compound **16** was prepared in low yield from **15** with $PhSeNEt_3$[12]. Again, treatment with base resulted largely in elimination. Reaction of **3** with $LiN(TMS)_2$ resulted in formation of dimers, both acyclic and cyclic. Most recently, the epoxide of **3** has been opened and the resulting diol protected[13]; conditions for closure of this system are being investigated.

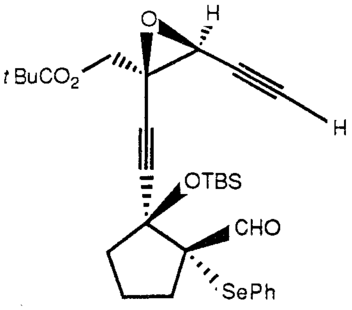
Table 1. Ring Closure Studies



3



15



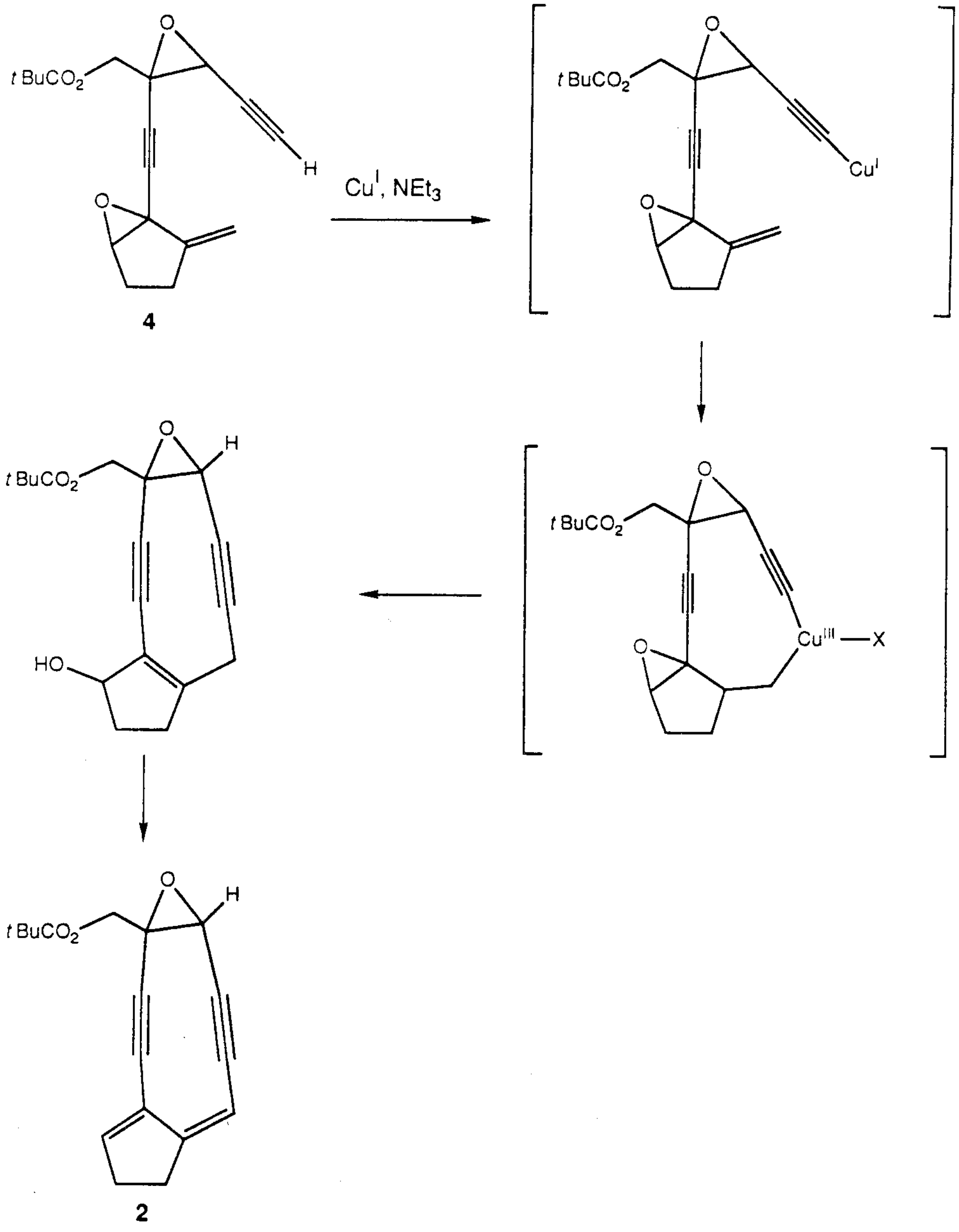
16

Substrate	Conditions	Results
15	LiTMP, $CeCl_3$, THF, -78°C base added to substrate	mixture of acyclic dimers
15	LiTMP, THF, -78°C substrate added to base	mostly **3**; unidentified side products
16	LiTMP, THF, -78°C substrate added to base	mostly **3**; some unreacted **16**
3	$LiN(TMS)_2$, THF, -78°C substrate added to base	cyclic and acyclic dimers

Bis-epoxide 4

The ring-closure strategy of compound **4** relies on intramolecular addition of a cuprous acetylide to a vinyl epoxide. Addition to the olefin would result in epoxide opening, as shown in Scheme V, possibly through a 10-membered intermediate with Cu^{III}, followed by reductive elimination. Elimination of the alcohol would provide the NCS chromophore model compound, **2**.

Scheme V



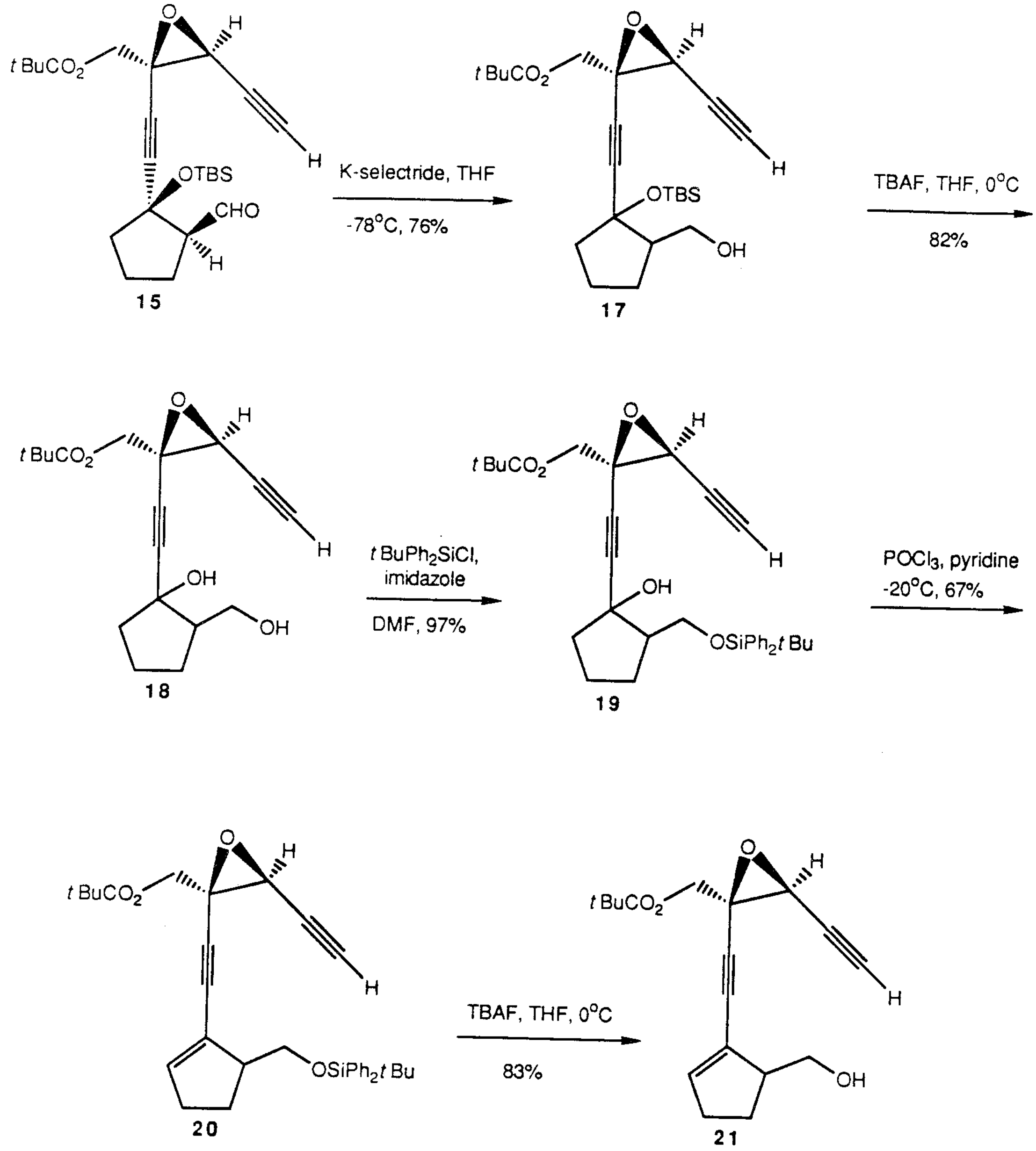
Precursor **4** was prepared from aldehyde **15** as shown in Scheme VI. The aldehyde was reduced with K-selectride to give of alcohol **16**, and the tertiary alcohol deprotected with fluoride to give diol **18** in 82% yield. The primary alcohol was converted to **19** in 97% yield by selective protection with *t*butyldiphenylsilyl chloride / imidazole. The tertiary alcohol was eliminated with $POCl_3$ in pyridine, providing a 67% yield of a 4:1 mixture of olefins of which **20** was the major isomer. After desilylation, the double bond was epoxidized with mCPBA to give a 63% yield of a mixture of the two *syn* epoxides, **22**. The alcohol was converted to **23** by treating the corresponding triflate (formed from Tf_2O / *i* Pr_2NEt) with PhSeH[14]. Elimination to the exo-methylene was accomplished by oxidation with mCPBA at -78°C, followed by treatment with DMS, and warming to room temperature, to give **4** in 40% yield from **22**.

Ring-closure studies of **4** are summarized in Table 2. Most conditions resulted in decomposition.

Table 2. Ring Closure Studies of **4**

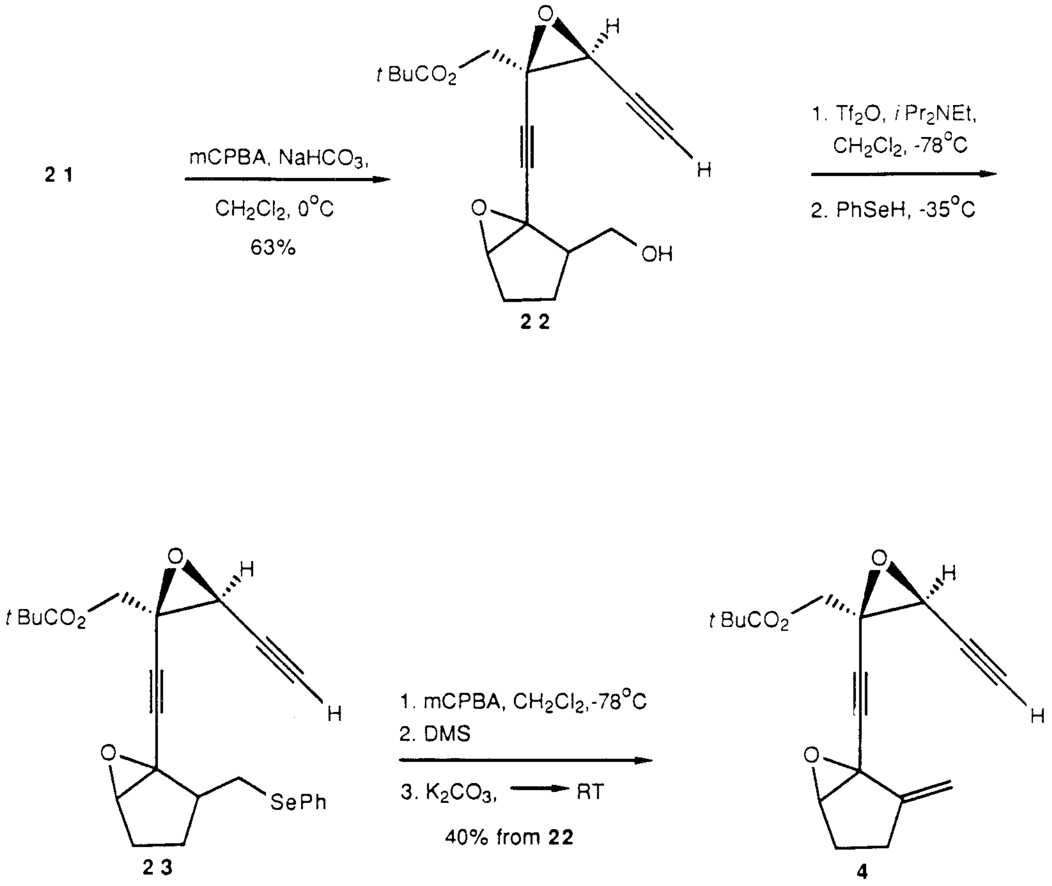
Conditions	Results
CuCl, NEt_3, THF, RT	mostly starting material
CuCl, $PrNH_2$, toluene, RT	decomposition
CuI, NEt_3/$NEt_3 \cdot$ HCl, DMF, THF	decomposition
CuCl, $PrNH_2$, $H_2NOH \cdot HCl$, EtOH, RT	decomposition

Scheme VI



t BuCO2
OTBS
CHO
15
K-selectride, THF
-78°C, 76%
17
OH
TBAF, THF, 0°C
82%
18
t BuPh2SiCl, imidazole
DMF, 97%
19
OSiPh2t Bu
POCl3, pyridine
-20°C, 67%
20
TBAF, THF, 0°C
83%
21

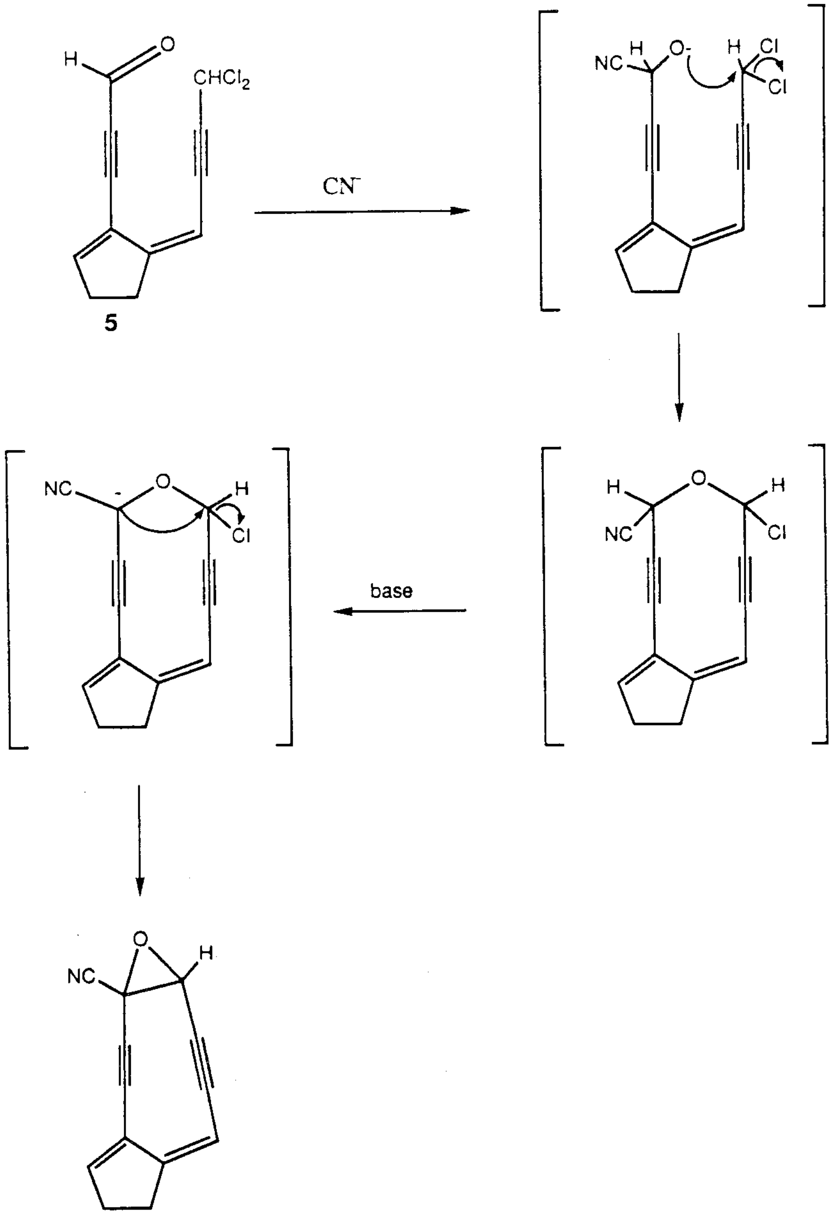
Scheme VI (cont.)



Aldehyde dichloride 5

The most recently-studied system involves formation of the epoxide of **2** during the ring-closure step. Unlike compounds **3** and **4**, the double bond of **5** holds the reactive ends of the molecule together in an unambiguous way. The planned strategy was to cyclize **5** through nucleophilic attack at the aldehyde functionality, forming an alkoxide anion which, through loss of Cl^-, should close to form a 10-membered heterocycle (Scheme VII). Subsequent deprotonation at the acidic site should kinetically favor epoxide formation, displacing the second chlorine anion. As in the preceding systems, elimination of the protected alcohol would give the precursor to the final product, **2**.

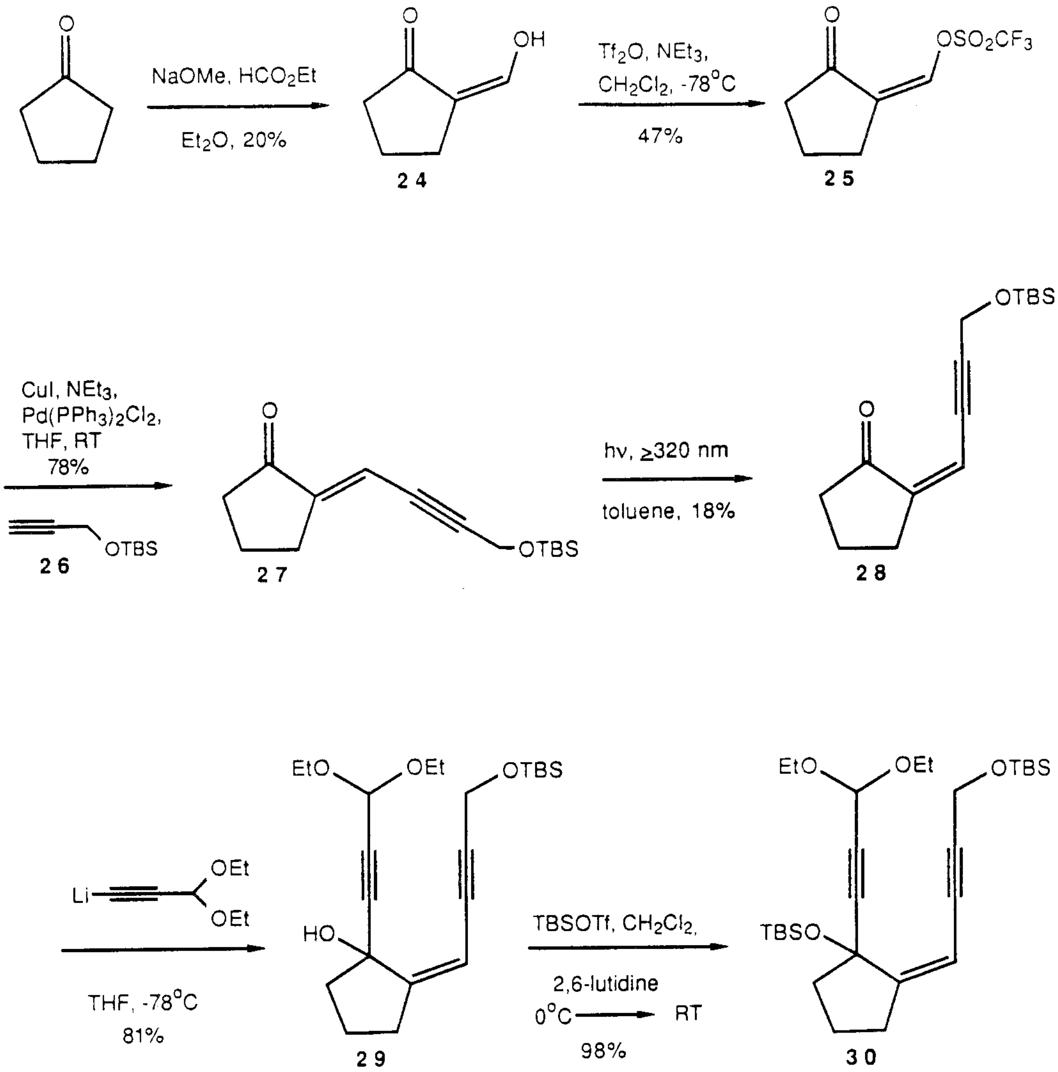
Scheme VII



Aldehyde dichloride **5** was prepared as outlined in Scheme VIII. Cyclopentanone was α-alkylated[15] (NaOMe, HCO_2Et, Et_2O, 20%) to give ketoaldehyde **24** ; treatment with triflic anhydride / triethylamine resulted in a clean conversion to enol triflate, **25**. Protected propargyl alcohol, **26**, (prepared from propargyl alcohol and TBSCl / NEt_3 in 83% yield) was coupled with **25** ($Pd(PPh_3)_2Cl_2$, CuI, NEt_3, THF, RT, 78%) to give enone **27**, with the geometry shown. Photoisomerization gave a poor yield (18%) of enone **28** ; the geometry was confirmed through NOE experiments. Addition of propiolaldehyde diethylacetal anion to the ketone gave alcohol **29** in good yield (81%). Protection of the tertiary alcohol (TBSOTf, 2,6-lutidine, CH_2Cl_2, 0^oC RT, 98%), followed by selective deprotection (1 eq TBAF, THF, 0^oC, 87%), revealed primary alcohol, **31**. Oxidation under standard Swern conditions (oxalyl chloride, DMSO, NEt_3, CH_2Cl_2, -78^oC, 75%) to aldehyde **32** was followed by treatment with PCl_5 / di*t*butylmethylpyridine[16] which, after workup with saturated aqueous ammonium chloride, provided aldehyde dichloride **5** (87%).

Preliminary cyclization studies of **5** are summarized in Table 3[17]. Continued research will involve elimination of the protected tertiary alcohol to give a planar system. Ring-closure experiments on this system will be conducted in due course.

Scheme VIII


O
NaOMe, HCO$_2$Et
Et$_2$O, 20%
O
OH
24
Tf$_2$O, NEt$_3$,
CH$_2$Cl$_2$, -78°C
47%
O
OSO$_2$CF$_3$
25
CuI, NEt$_3$,
Pd(PPh$_3$)$_2$Cl$_2$,
THF, RT
78%
OTBS
26
O
OTBS
27
hν, ≥320 nm
toluene, 18%
OTBS
O
28
Li
OEt
OEt
THF, -78°C
81%
EtO
OEt
OTBS
HO
29
TBSOTf, CH$_2$Cl$_2$,
2,6-lutidine
0°C → RT
98%
EtO
OEt
OTBS
TBSO
30

Scheme VIII (cont.)

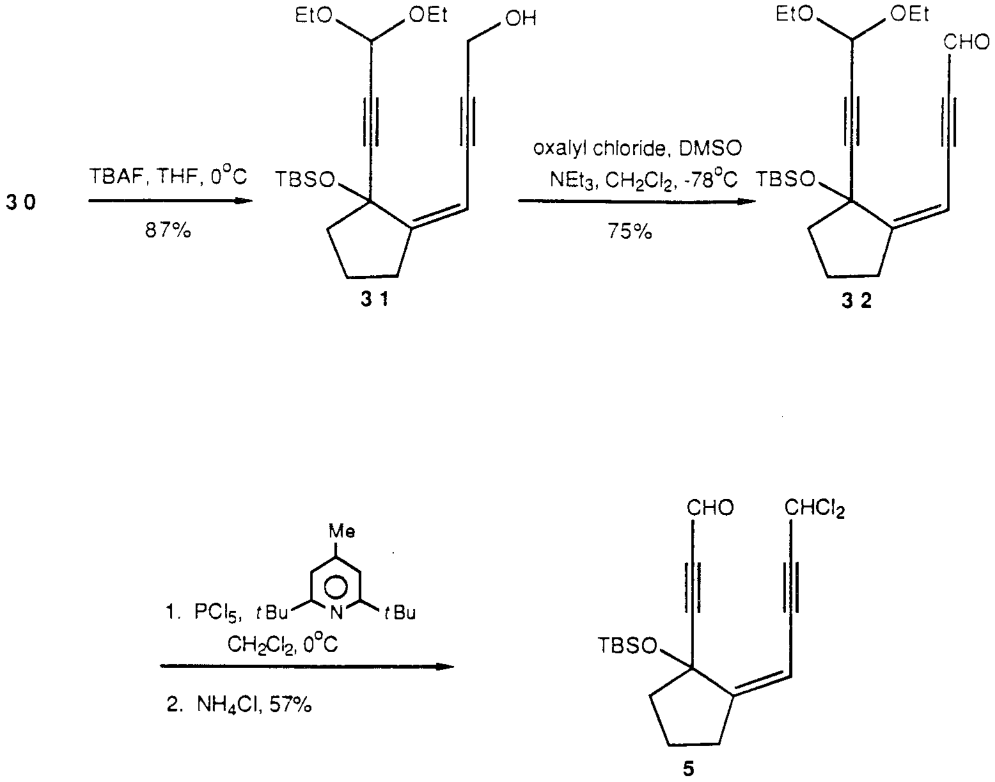
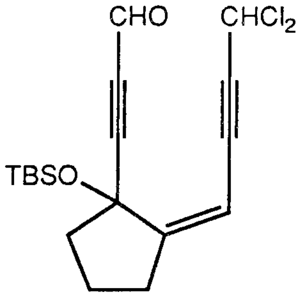
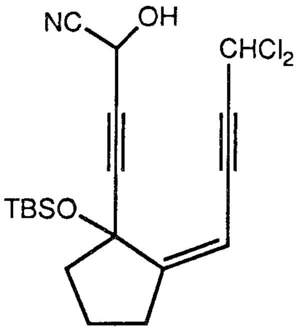


Table 3. Ring Closure Studies of **5**

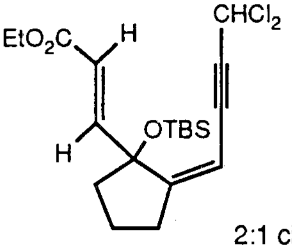


5



33

substrate	conditions	results
5	KCN, HOAc, THF, 0°C	cyanohydrins **33**
33	pyridine, CH_2Cl_2	no reaction
5	KCN, DMF, 0°C	mostly starting material + uncharacterized mixture of products
5	KCN, EtOH / H_2O, 0°C	ethyl ester, **34**, below



2:1 cis:trans

34

References and Notes

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10) Bromide **10** was prepared by Dr. Mian M. Alauddin.

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12) Jefson, M.; Meinwald, J. *Tetrahedron Lett.* **1981**, *22*, 3561.

13) Diol formation and subsequent ring- closure studies are being conducted by Philip J. Proteau.

14) *Org. Synth. Coll. Vol. III* p. 771.

15) Michael R. Lewis, 1987, I-13.

16) Dr. Paul Kamer, 1988, I-199.

17) Cyanohydrin **33** was prepared from aldehyde dichloride **5** by treatment with an excess of KCN in THF / acetic acid at room temperature.

18) Coulson, D.R. *Inorg. Synth. Vol. 13*, p. 121.

Experimental

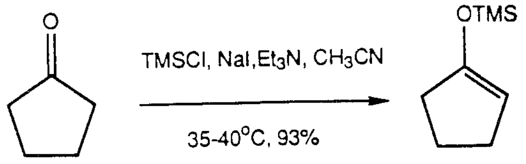
All solvents used in the following reactions were distilled under moisture- and oxygen-free conditions. Dichloromethane and acetonitrile were distilled over CaH_2. Toluene was distilled over sodium, and tetrahydrofuran (THF), over sodium and benzophenone. Ethyl acetate and hexanes used for extractions and chromatography were purchased from J. T. Baker (HPLC grade) and used without drying.

Amines distilled from CaH_2 included triethylamine, 2,6-lutidine, propylamine, pyridine, diisopropylethylamine, and 2,6-di*t*butyl-4-methylpyridine. Other reagents distilled from CaH_2 were diazabicycloundecene (DBU), dimethylsulfoxide (DMSO), and trimethylsilyl chloride (TMSCl). Dimethylformamide (DMF) was distilled from BaO, and imidazole and oxalyl chloride were distilled directly.

Triflic anhydride (Tf_2O) was prepared from distillation of triflic acid from P_2O_5. Reagents prepared according to literature procedures included *t*butyldimethylsilyltriflate (TBSOTf)[9], $PhSeNEt_2$[12], PhSeH[14], and $Pd(PPh_3)_4$[18].

Sodium iodide was dried at 120°C / .6 mm Hg for 12 h before use. The remaining reagents were purchased and used without further purification, including trichloroacetic acid (Mallinkrodt), methanol (Fisher), *meta*-chloroperbenzoic acid (mCPBA, Fluka), phosphorus pentoxide (EM), and the following reagents from Aldrich: *t*butyl alcohol, dimethyl sulfide (DMS), K-selectride (potassium tri-*sec*-butylborohydride), tetrabutylammonium fluoride (TBAF), *t*butyldiphenylsilylchloride, phosphorus oxychloride, bis(triphenylphosphine) palladium(II)chloride, propiolaldehyde diethylacetal, trimethylsilyltriflate (TMSOTf), trimethylorthoformate, copper(II)iodide, diisobutylaluminum hydride (DIBAL), (+)-diethyl tartrate (DET), titanium(IV) isopropoxide, *t*butylhydroperoxide (TBHP), and trimethylacetyl chloride.

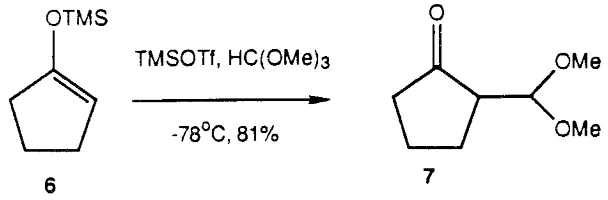
Glassware was dried in a 100°C oven for at least 6 h or flame-dried before use. An argon atmosphere was standard for all procedures. IR spectra were obtained on a Perkin-Elmer 1600 FTIR instrument, all as neat films. A JEOL 400MHz or a Bruker 500MHz spectrometer was used for ^1H NMR spectra. An Oriel 1000-watt arc lamp was used for photochemistry in the synthesis of **5**.



6

Cyclopentanone (22.2 ml, .251 mol, 1 eq) and NEt_3 (40.0 ml, .287 mol, 1.14 eq) were placed in a three-neck flask and treated with TMSCl (34.1 ml, .269 mol, 1.07 eq). A solution of NaI (35.1 g, .234 mol, .93 eq) in CH_3CN (270 ml) was introduced over 1.5 h through an addition funnel. After 1 h, the reaction was complete by IR. The mixture was poured carefully into 500 ml pentane / 15 ml NEt_3 / 500 ml brine / ice, extracted once, dried over Na_2SO_4, and concentrated. The crude product was used directly in the following reaction.

IR: 3080, 2970, 2860, 1643, 1350, 1250, 1195, 1040, 970, 930, 900, 870, 850.



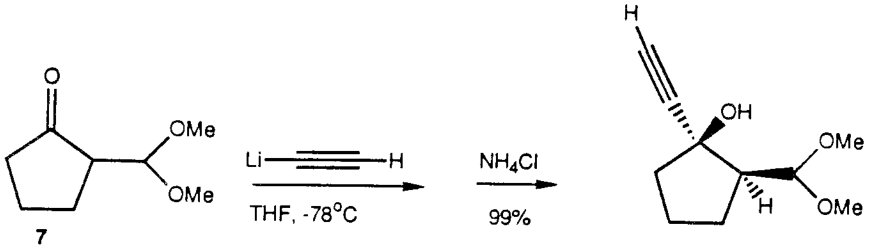
A solution of **6** (40.6 g crude, .26 mol, 1 eq) and $HC(OMe)_3$ (34.2 ml, .313 mol, 1.2 eq) in 270 ml CH_2Cl_2 at -78 °C was treated with TMS-triflate (9.0 ml, .046 mol, 0.18 eq). The reaction was quenched with NEt_3 (2.0 ml, .014 mol, .06 eq) and allowed to warm to room temperature. A small amount of anhydrous K_2CO_3 was added and the mixture was filtered and concentrated. The product was distilled at 0.6 mm Hg, and the fraction at 63-69°C was collected to give 31.93 g **7**(82%).

FTIR: 2965, 2834, 1741, 1452, 1357, 1069, 968.

^{1}HNMR (90 MHz, $CDCl_3$): 4.53 (d, J=1Hz, 1H, C<u>H</u>$(OMe)_2$); 3.34 (s, 6H, OMe);
2.58-1.59 (m, 7H).

TLC (20% EtOAc / hexanes): product: .21

MS(EI): 158, 127, 97, 84, 75, 67, 57, 49, 43.



7

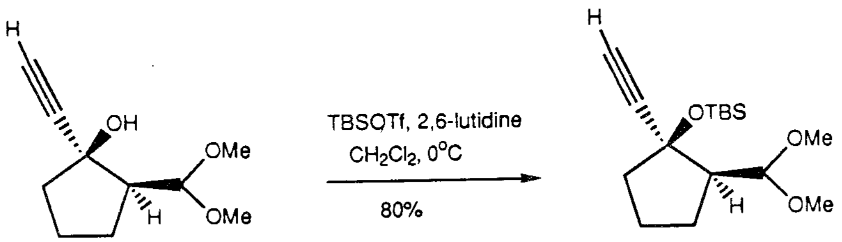
8 4:1

Deoxygenated THF (250 ml) was cooled to -78°C. Approximately 2L acetylene (purified by passing through first a -78°C trap, then concentrated sulfuric acid, and finally a KOH tower) was bubbled through, then BuLi (50.5 ml, 110.5 mmol, 1.9 eq, cooled to -78°C) in 5 ml THF was added by cannula below the level of the liquid. Ketone **7** (9.0438 g, 57.17 mmol, 1.0 eq) was added dropwise by syringe, and the mixture stirred for 3 h. Saturated NH_4Cl solution was added (45 ml), and the mixture allowed to warm to room temperature. Dilution with 50% EtOAc / hexanes followed, and the separated organic layer washed several times with water. The combined washings were extracted again, and the organic portions were dried over sodium sulfate and concentrated under vacuum; the ratio of isomers was 4:1 by NMR. The product was purified by flash chromatography (40% EtOAc / hexanes), collecting both isomers of **8** together in near quantitative yield.

FTIR: 3595-3385, 3315-3215, 2095.

^{1}HNMR (400MHz, $CDCl_3$): 4.62 (d, J=3Hz, 1H, $C\underline{H}(OMe)_2$); 3.71 (s, 1H, OH); 3.48 (s, 3H, OCH_3); 3.30 (s, 3H, OCH_3); 2.51 (s, 1H, acetylene-H); 2.18 (m, 2H); 1.88 (m, 2H); 1.73 (m, 2H); 1.55 (m, 1H).

TLC (20% EtOAc / hexanes): SM: .21
product: .19



8 4:1 **9**

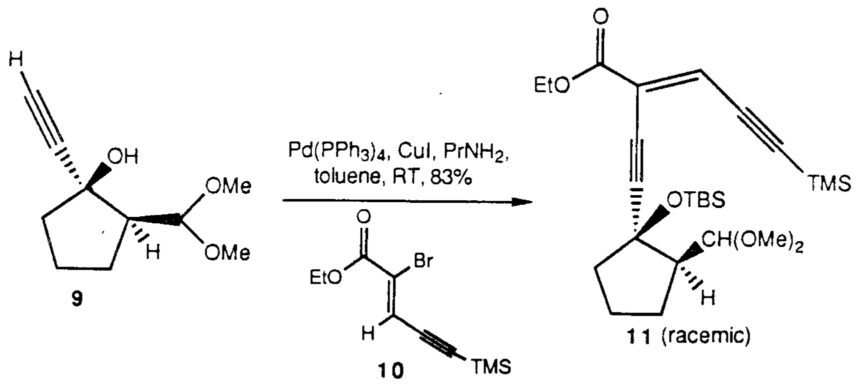
A solution of alcohol **8** (3.030 g, 16.45 mmol, 1.0 eq) in 15 ml CH_2Cl_2 at 0°C was treated with 2,6-lutidine (4.2 ml, 20.20 mmol, 1.23 eq) and TBS-triflate (5.60 ml, 24.36 mmol, 1.48 eq). After 1 h, the reaction was quenched with methanol, diluted in 1 :1 EtOAc / hexanes, washed twice with water, dried over Na_2SO_4, and concentrated under vacuum. The product was purified by flash chromatography (50% to 75% EtOAc / hexanes), collecting 2.400 g of the major isomer of **9** and 1.549 g of a mixture of both isomers (80% yield).

FTIR: 3310, 2090, 1250.

^{1}HNMR (400MHz, $CDCl_3$): major: 4.50 (d, J=6Hz, 1H, $C\underline{H}(OMe)_2$); 3.33 (s, 3H, OCH_3); 3.32 (s, 3H, OCH_3); 2.54 (s, 1H, acetylene-H); .26 (m, 1H); 1.98 (m, 2H); 1.83 (m, 2H); 1.64 (m, 2H); 0.84 (s, 9H, Si-*t* Bu); 0.17 (s, 3H, Si-CH_3); 0.15 (s, 3H, Si-CH_3).

minor: 4.52 (d, J=6Hz, 1H, $C\underline{H}(OMe)_2$); 3.40 (s, 3H, OCH_3); 3.29 (s, 3H, OCH_3); 2.51 (s, 1H, acetylene-H); 2.30 (m, 1H); 1.99 (m, 2H); 1.78 (m, 2H); 1.68 (m, 2H); 0.88 (s, 9H, Si-*t* Bu); 0.21 (s, 3H, Si-CH_3); 0.20 (s, 3H, Si-CH_3).

TLC (10% EtOAc / hexanes):
SM: .11
major: .42
minor: .38



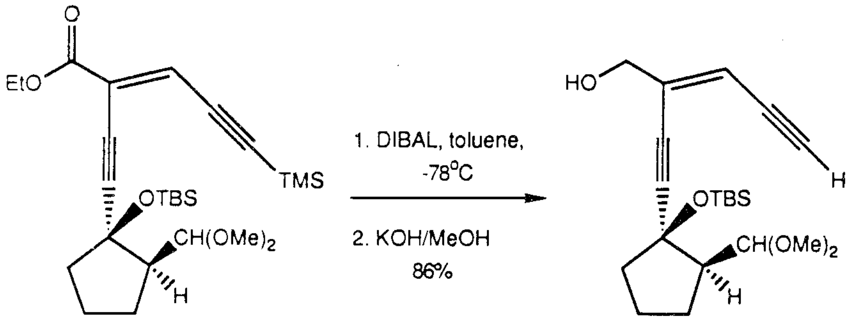
A solution of acetylide **9** (7.5602 g, 25.13 mmol, 1 eq) and propylamine (3.10 ml, 37.71 mmol, 1.50 eq) in 10 ml toluene was prepared in a dry Schlenk flask. Bromide **10** (8.3451 g, 30.32 mmol, 1.21 eq) was stirred with the Pd catalyst (1.4492 g, 1.25 mmol, 0.05 eq, protected from light) in 20 ml toluene for 45 min, then transferred by cannula to the acetylide solution. After heating to 60°C for 1 h, the mixture was poured into 150 ml saturated NH_4Cl / 60 ml 5% $NaHCO_3$ and stirred for 1 h. Dilution in 1:1 EtOAc / hexanes followed; the aqueous layer was separated and extracted twice. The combined organic layers were washed with saturated NH_4Cl, then H_2O, dried over sodium sulfate, and concentrated under vacuum. The product was purified by flash chromatography (3% EtOAc / hexanes) to give the desired compound in 83% yield (10.2351 g, 20.77 mmol).

FTIR: 1735, 1575, 1255.

^{1}HNMR (500MHz, $CDCl_3$): 6.96 (s, 1H, vinyl-H); 4.62 (d, J=7.4Hz, 1H, $C\underline{H}(OMe)_2$); 4.27 (m, 1H, $CH_3C\underline{H_2}$); 3.35 (s, 3H, OCH_3); 3.34 (s, 3H, OCH_3); 2.36 (m, 1H, $C\underline{H}CH(OMe)_2$); 2.11 (m, 1H); 1.93 (dt, J=7.9, 12.9Hz, 1H); 1.84 (m, 1H); 1.72 (m, 3H); 1.32 (t, J=7.9Hz, 3H, $C\underline{H_3}CH_2$); 0.87 (s, 9H, Si-*t* Bu); 0.22 (s, 15H, Si-CH_3).

TLC(7% EtOAc / hexanes): RBr: .34
acetylide: .30
product: .24

MS(DCI): 448, 262, 240, 225, 183, 169, 73.



11 (racemic) **12** (racemic)

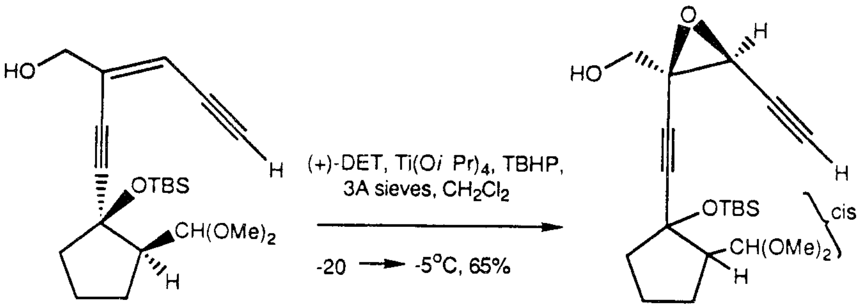
A solution of **11** (2.3522 g, 4.773 mmol, 1 eq) in 16 ml toluene at -78°C was treated with DIBAL (10.0 ml, 10.0 mmol, 2.1 eq) and warmed to 0°C. After reduction of the ester was complete (10 min), freshly prepared 3N KOH / MeOH (30.0 ml, 90.0 mmol, 18.8 eq) was cooled to 0°C and added by cannula. After 30 min, the reaction mixture was poured into 5:1 H_2O / brine, stirred for 10 min, extracted with 1:1 EtOAc / hexanes, dried (Na_2SO_4), and concentrated. Purification on a short flash column (20% EtOAc / hexanes) gave 1.5490 g allylic alcohol **12** (4.09 mmol, 86% yield).

FTIR: 3436, 3309, 2929, 1598, 1251.

^{1}HNMR (400MHZ, C_6D_6): 5.72 (dd, J=1.8, 4.0Hz, 1H, vinyl-H); 4.76 (d, J=6.8Hz, 1H, $C\underline{H}(OMe)_2$); 3.83 (br s, 2H, $C\underline{H}_2OH$); 3.28 (s, 3H, OCH_3); 3.21 (s, 3H, OCH_3); 2.92 (d, J=2.4Hz, 1H, acetylene-H); 2.50 (dd, J=7.1, 8.7Hz, 1H, $C\underline{H}CH(OMe)_2$); 2.15-2.10 (m, 1H); 1.96-1.62 (m, 5H); 1.03 (s, 9H, Si-*t* Bu); 0.38 (s, 3H, Si-CH_3); 0.31 (s, 3H, Si-CH_3).

TLC (10% EtOAc / hexanes):

SM: .76
intermediate: .15
product: .47



12 (racemic)

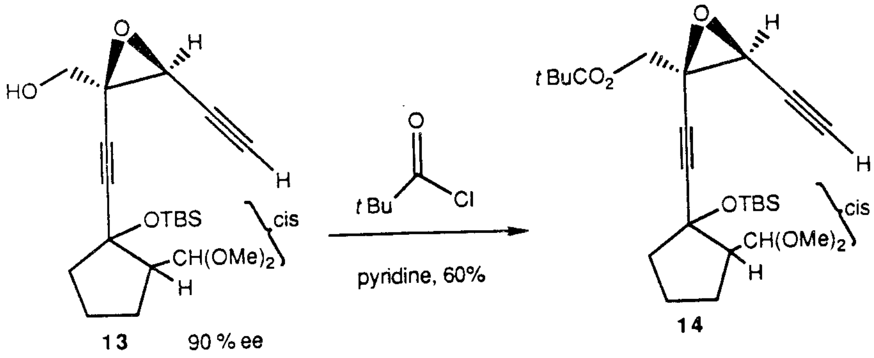
13

The catalyst was prepared by adding (+)-DET (3.0 ml, 17.53 mmol), Ti(O*i* Pr)$_3$ (4.8 ml, 16.13 mmol), and TBHP (37.08 mmol) to a dry flask at -20°C containing 30 ml CH_2Cl_2 and 0.2 g 3A molecular sieves. After 30 min, a solution of alcohol **12** (1.549 g, 4.09 mmol) in 18 ml CH_2Cl_2 at -20°C was introduced by cannula to the catalyst; the reaction mixture was warmed to -5°C. After 24 h, the mixture was warmed to 0°C, added to 300 ml of a solution of $FeSO_4$ (99 g) and tartaric acid (30 g), and stirred for 10 min. The organic layer was separated; the aqueous layer was extracted twice with 100-ml portions of ether. The combined organic layers were then cooled to 0°C and treated with 30% NaOH in brine (30 ml). After stirring for 1 h, the mixture was diluted in H_2O; the aqueous layer was separated and extracted with ether. The combined organic layers were dried and concentrated to give 1.5286 g crude product (3.87 mmol, 95% yield).

FTIR: 3411, 3310, 2930, 1252.

^{1}HNMR (200MHz, C_6D_6): 4.76 (t, J=6Hz, 1H, $C\underline{H}(OMe)_2$); 3.56 (m, 2H, $C\underline{H}_2OH$); 3.41 (2s, 1H, epoxy-H); 3.34 (2s, 3H, OCH_3); 3.28 (2s, H, OCH_3); 2.51 (m, 1H, $C\underline{H}CH(OMe)_2$); 2.12 (m, 1H); 2.40 (2s, 1H, acetylene-H); 1.90 (m, 5H); 1.10 (2s, 9H, Si-*t* Bu); 0.44 (2s, 3H, Si-CH_3); 0.36 (2s, 3H, Si-CH_3).

TLC (20% EtOAc / hexanes; 4 elutions): SM: .62
product: .52, .48



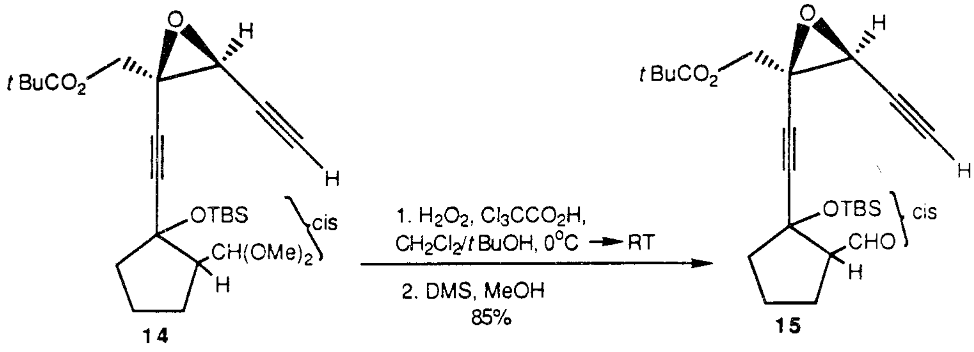
A solution of alcohol **13** (6.3637 g, 16.13 mmol, 1 eq) in 20 ml pyridine was treated with trimethylacetyl chloride (5.0 ml, 40.60 mmol, 2.52 eq) at room temperature. After 20 min, during which a light brown precipitate formed, the reaction mixture was diluted in 1:1 EtOAc / hexanes, washed 3 times with H_2O, dried over Na_2SO_4, and concentrated. The product was purified by flash chromatography (10% EtOAc / hexanes), giving 4.635 g **14** as a yellow oil (60% yield from alcohol **12**).

FTIR: 3311, 2957, 2129, 1742, 1251.

^{1}HNMR (500MHz, C_6D_6): 4.74 (2d, J=6.7Hz, 1H, C<u>H</u>(OMe)$_2$); 4.33 (2d, J=12.3Hz, 1H, OCH_2); 3.92 (2d, J=12.3Hz, 1H, OCH_2); 3.30, 3.29 (2s, 3H, OCH_3); 3.28, 3.26 (2d, J=9.0Hz, 1H, epoxy-H); 3.25, 3.23 (2s, 3H, OCH_3); 2.43 (dd, J=6.9, 8.7Hz, 1H, C<u>H</u>CH(OMe)$_2$); 2.10 (m, 1H); 1.98 (s, 1H, acetylene-H); 1.92-1.80 (m, 3H); 1.72-1.55 (m, 2H); 1.08 (s, 9H, CO-*t* Bu); 1.00 (s, 9H, Si-*t* Bu); 0.38 (2s, 3H, Si-CH_3); 0.30 (2s, 3H, Si-CH_3).

TLC(20% EtOAc / hexanes): SM: .17
product: .45

MS (DCI): 447, 387, 361, 345, 315, 175.



A solution of epoxide **14** (0.2089 g, 0.436 mmol, 1 eq) in 5 ml CH_2Cl_2 / 3 ml *t* BuOH at 0°C was treated with 85% H_2O_2 (1.0 ml, 35.16 mmol, 81.0 eq, 8.1%) and trichloroacetic acid (0.054 g, 0.33 mmol, 0.76 eq). The homogeneous solution was warmed to room temperature and stirred for 24 h. The mixture was then poured into 10% brine / ice and diluted in a minimum volume of 1:1 EtOAc / hexanes. The organic layer was separated and washed sequentially with brine, 1M $Na_2S_2O_3$, and saturated $NaHCO_3$. After drying over Na_2SO_4, it was transferred to a larger flask, treated with 3 ml DMS in 15 ml MeOH, and stirred for 1 h. The solution was concentrated, dissolved in 1:1 EtOAc / hexanes, and washed twice with water. The organic layer was dried and concentrated; purification was by flash chromatography, pretreating the column first with 3% NEt_3 / hexanes, then eluting with 10% EtOAc / hexanes, to give 0.1246 g aldehyde **15** (0.299 mmol, 66% yield).

FTIR: 3314, 2960, 2743, 1739, 1726, 1251.

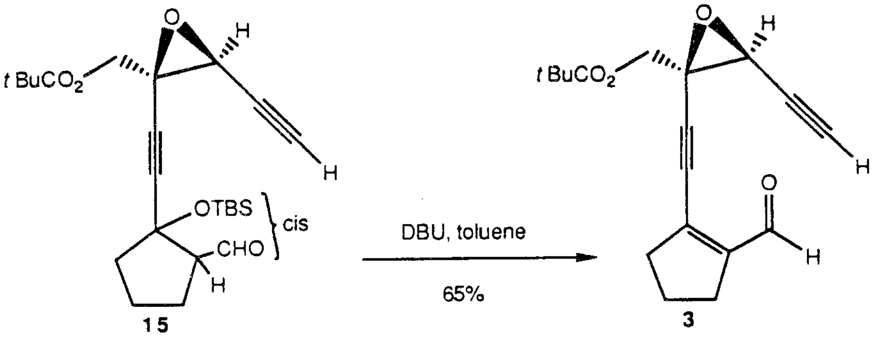
^{1}HNMR (400MHz, C_6D_6): 9.96 (2d, J=1.7, 2.1Hz, 1H, aldehyde-H); 4.21 (2d, J=12.3Hz, 1H, OCH_2); 3.78 (2d, J=12.31Hz, 1H, OCH_2); 3.17 (2d, J=1.7Hz, 1H, epoxy-H); 2.58 (m, 1H, C$\underline{H}$CHO); 2.00 (2d, J=1.7Hz, 1H, acetylene-H); 1.79 (m, 2H); 1.57 (m, 4H); 1.09 (2s, 9H, CO-*t* Bu); 0.94 (2s, 9H, Si-*t* Bu); 0.28 (2s, 3H, Si-CH_3); 0.22 (2s, 3H, Si-CH_3).

TLC(20% EtOAc / hexanes): SM: .45
peroxides: .37, .33

TLC(20% EtOAc / hexanes): SM: .45
peroxides: .37, .33
product: .48

MS(DCI): 433, 391, 375, 347, 289, 273, 245, 215, 187, 159, 85, 75, 57.

Exact mass: calculated: 433.2410281
found: 433.2390000
Δ= 4.7 ppm



A solution of aldehyde **15** (0.084 g, 0.19 mmol, 1 eq) in 3 ml toluene at 0°C was treated with DBU (150µl, 1.00 mmol, 5.3 eq) and warmed to room temperature. After 1.5 h, the mixture was diluted in 1:1 EtOAc / hexanes, washed first with 1:1 saturated citric acid / water, then with water, dried over Na_2SO_4, and concentrated under vacuum. The crude product was run through a small flash silica gel column (20% EtOAc / hexanes) to give 0.0373 g pure **3** (65% yield).

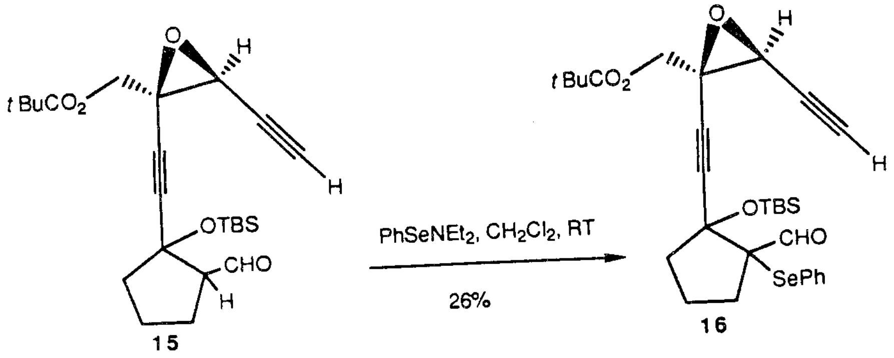
FTIR: 3266, 2973, 2727, 2129, 1739, 1674.

^{1}HNMR (400MHz, C_6D_6): 10.32 (s, 1H, aldehyde-H); 4.24 (d, J=11.7Hz, 1H, OCH_2); 3.73 (d, J=11.7Hz, 1H, OCH_2); 3.23 (2s, 1H, epoxy-H); 2.32 (t, J=7.5Hz, 2H); 2.18 (t, J=7.5Hz, 2H); 1.89 (2s, 1H, acetylene-H); 1.29 (p, J=7.5Hz, 2H); 1.09 (s, 9H, *t* Bu).

TLC (20% EtOAc / hexanes):
SM: .48
product: .32

MS(DCI): 301, 275, 261, 248, 217, 199, 162, 135, 115, 103, 85, 57.

Exact mass:
calculated: 301.1439844
found: 301.1445000
Δ= 1.7 ppm

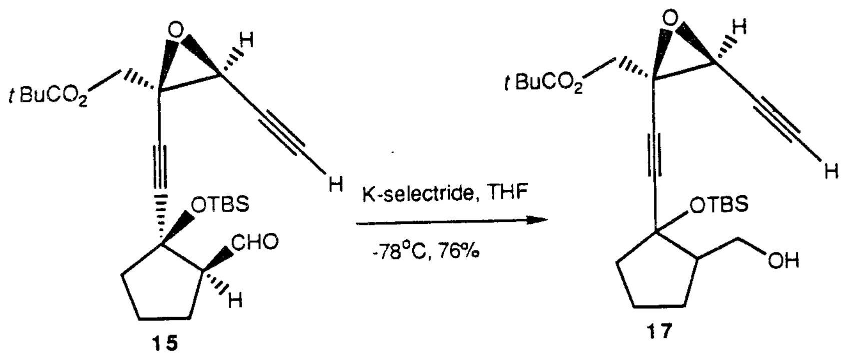


PhSeNH$_2$ (approx. 50 eq) was added to a solution of aldehyde **15** (0.021 g, 0.046 mmol) in 0.2 ml CH$_2$Cl$_2$ at room temperature. After 5 h, the solvent was removed under vacuum and the residue purified by prep-TLC (10% EtOAc / hexanes) to give 0.007 g of **16** (0.012 mmol, 26% yield).

FTIR: 3306, 3057, 2956, 2722, 1742, 1705, 1251.

^{1}HNMR (500MHz, C$_6$D$_6$): 10.07 (2s, 1H, aldehyde-H); 7.54 (m, 1H, *p*-ArH); 7.14-6.90 (m, 4H, *o, m* -ArH); 4.24, 4.17 (2d, J=12.3Hz, 1H, OCH$_2$); 3.83, 3.80 (2d, J=12.3Hz, 1H, OCH$_2$); 3.22, 3.18 (2s, 1H, epoxy-H); 2.50 (m, 2H); 2.12, 2.07 (2s, 1H, acetylene-H); 1.76 (m, 2H); 1.63 (m, 2H); 1.15, 1.14 (2s, 9H, CO*t* Bu); 1.10, 1.09 (2s, 9H, Si-*t* Bu); 0.42, 0.40 (2s, 3H, Si-CH$_3$); 0.30, 0.27 (2s, 3H, Si-CH$_3$).

TLC (10% EtOAc / hexanes; 2 elutions): SM: .40
product: .33

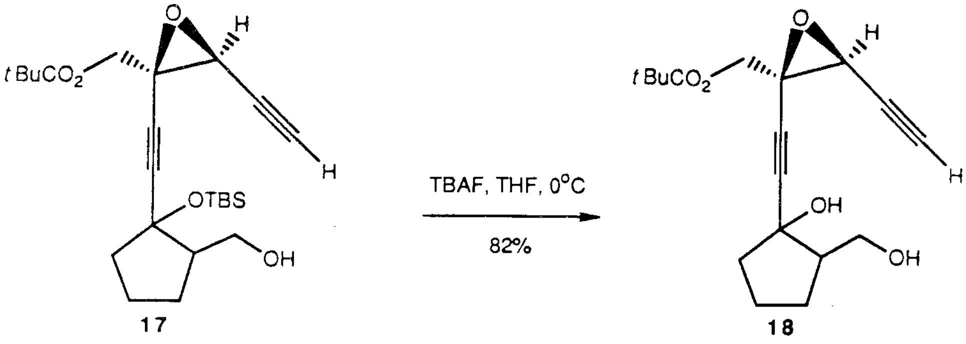


A solution of aldehyde **15** (0.1749 g, 0.404 mmol, 1 eq) in 5 ml THF was cooled to -78°C and treated with a 1-M solution of K-selectride (0.400 mmol, 1 eq). After 10 min, the reaction was quenched with 1 ml of saturated $NaHCO_3$ solution and allowed to warm to room temperature. The mixture was poured into brine and diluted with 1:1 EtOAc / hexanes ; the aqueous layer was separated and extracted with EtOAc. The combined organic layers were dried over Na_2SO_4 and concentrated. Purification by flash chromatography (20% EtOAc / hexanes) gave 0.1338 g of alcohol **17** (0.308 mmol, 76%).

FTIR: 3312, 2958, 2858, 1738, 1463, 1281, 1251, 1143, 1045, 839, 778.

^{1}HMNR (400MHz, C_6D_6): 4.28, 4.23 (2d, J=12.2Hz, 1H, *t* $BuCO_2C\underline{H}_2$); 3.96-3.93 (m, 1H, $C\underline{H}_2OH$); 3.81 (d, J=12.2Hz, 1H, *t* $BuCO_2C\underline{H}_2$); 3.80 (d, J=12.2Hz, 1H, *t* $BuCO_2C\underline{H}_2$); 3.19 (t, J=0.7Hz, 1H, epoxy-H); 2.20-2.05 (m, 1H, $C\underline{H}CH_2OH$); 1.98 (2d, J=0.7Hz, acetylene-H); 1.87-1.72 (m, 1H); 1.72-1.48 (m, 4H); 1.42-1.28 (m, 1H); 1.10 (2s, 9H, *t* $BuCO_2$); 0.96 (s, 9H, Si-*t* Bu); 0.32 (s, 3H, Si-CH_3); 0.21 (s, 3H, Si-CH_3).

TLC (20% EtOAc / hexanes): SM: .43
product: .21

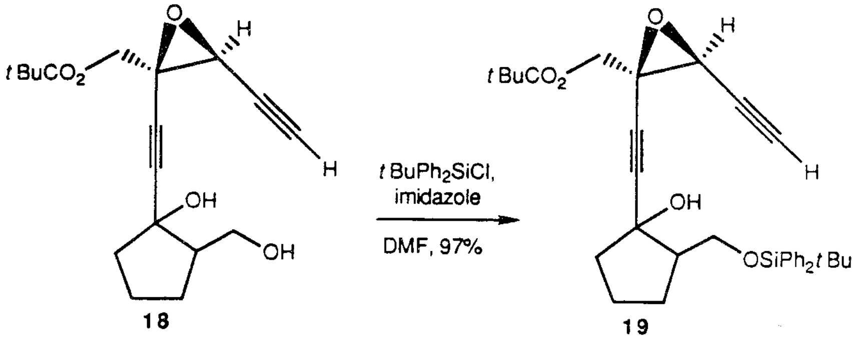


Alcohol **17** (0.0667 g, 0.153 mmol, 1 eq) in 2 ml deoxygenated THF at 0°C was treated with 1-M TBAF (0.920 mmol, 6.0 eq). After 40 min, the mixture was partitioned between 1:1 EtOAc / hexanes and brine. The organic layer was separated, dried over Na_2SO_4, and concentrated under vacuum. Diol **18** was purified by flash chromatography (40% EtOAc / hexanes) to give 0.0425 g (0.125 mmol, 82% yield).

FTIR: 3285, 2966, 1732, 1481, 1282, 1143, 1033.

^{1}HNMR (400MHz, C_6D_6): 4.34, 4.25 (2d, J=12.2Hz, 1H, *t* BuCO$_2$C$\underline{H}_2$); 3.86-3.77 (m, 1H, C$\underline{H}_2$OH); 3.80 (d, J=12.4Hz, 1H, *t* BuCO$_2$C$\underline{H}_2$); 3.68 (d, J=12.2Hz, 1H, *t* BuCO$_2$C$\underline{H}_2$); 3.58-3.50 (m, 1H, C$\underline{H}_2$OH); 3.20, 3.16 (2d, J=1.6Hz, 1H, epoxy-H); 2.13-2.07 (m, 2H); 1.94 (2d, J=1.7Hz, 1H, acetylene-H); 1.93-1.87 (m, 1H); 1.64-1.47 (m, 4H); 1.09 (2s, 9H, *t*-Bu).

TLC (60% EtOAc / hexanes): SM: .72
product: .34

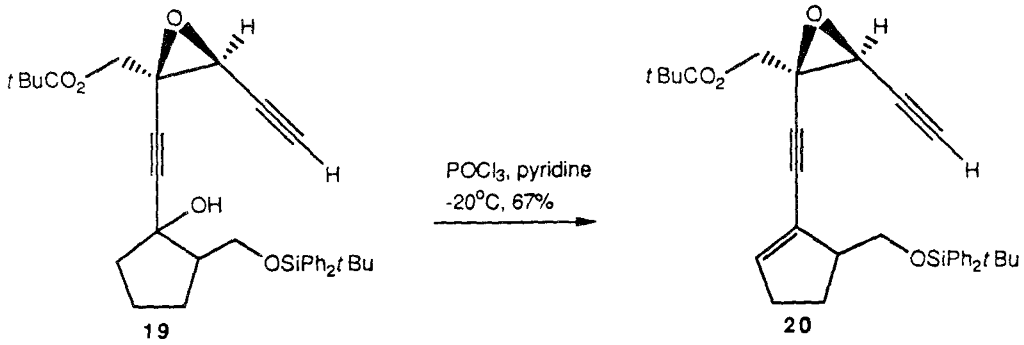


A solution of diol **18** (0.0415 g, 0.122 mmol, 1 eq) and imidazole (0.3555 g, 5.22 mmol, 42.8 eq) in DMF (3 ml) at room temperature was treated with *t*BuPh$_2$SiCl (0.160 ml, 0.615 mmol, 5.10 eq) and allowed to stir for 1h. The mixture was poured into 75 ml water and extracted 4 times with 50-ml portions of hexanes. The combined organic layers were dried (Na$_2$SO$_4$) and concentrated; the residue was purified by flash chromatography (20% EtOAc / NEt$_3$ / hexanes) to give 0.0684 g alcohol **19** (0.118 mmol, 97% yield).

FTIR: 3431, 3319, 3071, 2931, 1740, 1472, 1428, 1391, 1362, 1262, 1113, 938, 822, 738.

^{1}HNMR (400MHz, C$_6$D$_6$): 7.18 (s, 10H, Si-Ph$_2$); 4.28, 4.25 (2d, J=12Hz, 1H, *t*BuCO$_2$C$\underline{H_2}$); 4.15-4.08 (m, 1H, C$\underline{H_2}$OH); 3.83-3.71 (m, 2H, *t*BuCO$_2$C$\underline{H_2}$ + C$\underline{H_2}$OH); 3.62 (br s , 1H, OH); 3.22 (br s, 1H, epoxy-H); 2.28-2.60 (m, 3H); 2.04-1.88 (m, 2H); 1.68 (2s, 18H, Si-*t*Bu + *t*BuCO$_2$).

TLC (40% EtOAc / hexanes):	SM: .13
	product: .60

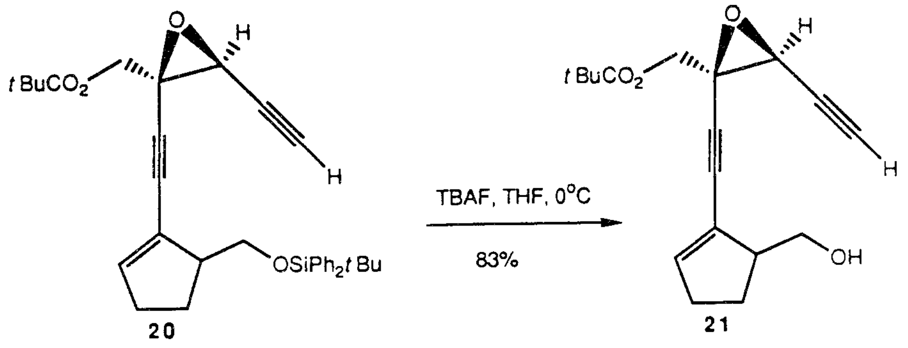


A solution of alcohol **19** (0.1341 g, 0.231 mmol, 1 eq) in 5 ml dry pyridine at -20°C was treated with $OPCl_3$ (0.50 ml, 5.36 mmol, 23.0 eq). The mixture was allowed to stir overnight, while slowly warming to 0°C. The reaction was quenched carefully with water, poured into 1:1 water / brine (50 ml), and extracted twice with 100-ml portions of EtOAc / hexanes. The combined organic layers were washed again with water / brine, dried over Na_2SO_4, and concentrated. Purification by flash chromatography (15% EtOAc / hexanes) gave 0.0866 g (0.154 mmol, 67% yield) of a 4.5:1 mixture of elimination products, of which the major isomer was **20**.

FTIR: 3283, 3072, 2931, 2858, 2224, 2130, 1959, 1889, 1823, 1739, 1721, 1590, 1473, 1428, 1282, 1149, 1113, 998, 823, 741, 702, 608.

^{1}HNMR (400MHz, C_6D_6): 7.15 (s, 10H, Si-Ph_2); 6.08 (d, J=3Hz, 1H, vinyl-H); 4.34, 4.29 (2d, J=13Hz, 1H, *t* $BuCO_2C\underline{H}_2$); 3.96-3.80 (m, 1H, $C\underline{H}_2OSiR_3$); 3.87-3.74 (m, 2H, *t* $BuCO_2C\underline{H}_2$ + $C\underline{H}_2SiR_3$); 3.31 (br s, 1H, epoxy-H); 2.40-2.32 (m, 1H); 2.28-2.17 (m, 1H); 2.10-2.01 (m, 1H); 1.93-1.84 (m, 1H); 1.75 (2 br s, 1H, acetylene-H); 1.18 (s, 9H, *t* $BuCO_2$); 1.06 (s, 9H, Si-*t* Bu).

TLC (20% EtOAc / hexanes):	SM: .21
	product: .46

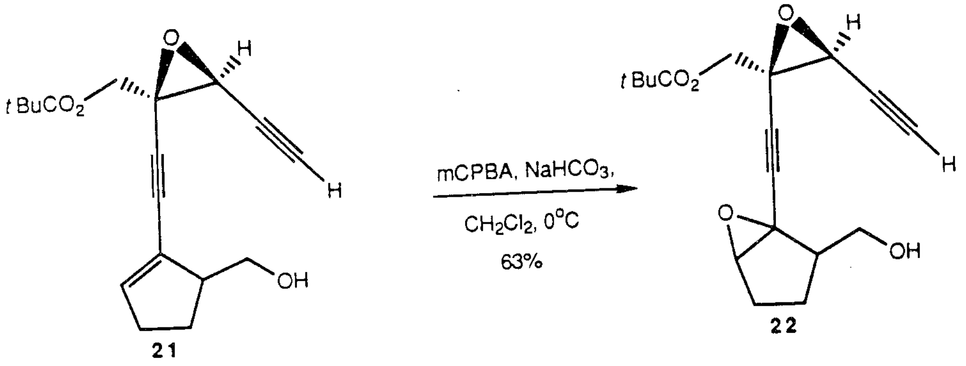


Silyl ether **20** (0.1111 g, 0.198 mmol, 1eq) in 3 ml deoxygenated THF at -10°C was treated with a 1-M solution of TBAF (1.00 mmol, 5.05 eq). The reaction was warmed to -5°C and allowed to stir overnight. The mixture was diluted in 1:1 EtOAc / hexanes, washed twice with brine, dried over Na_2SO_4, and concentrated. Purification by flash chromatography (20% EtOAc / hexanes) afforded alcohol **21** in 83% yield (0.0494 g, 0.163 mmol).

FTIR: 3286, 2960, 2224, 2128, 1739, 1481, 1400, 1282, 1143, 1035.

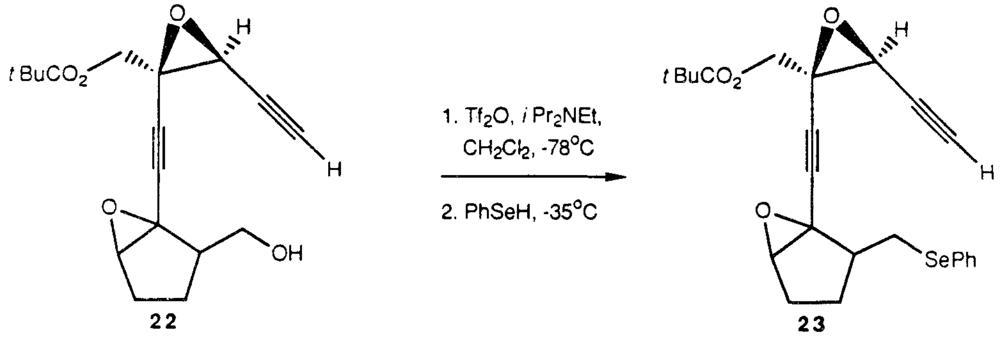
^{1}HNMR (400MHz, C_6D_6): 6.01 (d, J=2.7Hz, 1H, vinyl-H); 4.34, 4.28 (2d, J=12.0Hz, 1H. *t* $\text{BuCO}_2\text{C}\underline{\text{H}}_2$); 4.19 (s, 1H, OH); 3.84, 3.76 (2d, J=12.2Hz, 1H,*t* $\text{BuCO}_2\text{C}\underline{\text{H}}_2$); 3.61-3.57 (m, 2H, $\text{C}\underline{\text{H}}_2\text{OH}$); 3.25, 3.23 (2d, J=1.6Hz, epoxy-H); 2.06-1.96 (m, 1H); 2.10 (d, J=1.7Hz, 1H, acetylene-H); 1.70-1.64 (m, 1H); 1.60-1.52 (m, 1H); 1.45-1.41 (m, 1H); 1.35-1.31 (m, 1H); 1.10 (s, 9H, *t* Bu).

TLC (40% EtOAc / hexanes): SM: .70
product: .35



Alcohol **21** (0.0623 g, 0.206 mmol, 1 eq) in 4 ml CH_2Cl_2 with 0.5 ml saturated aqueous $NaHCO_3$ at 0°C was treated with mCPBA (0.2572 g, 1.490 mmol, 7.2 eq) and stirred vigorously for 2 h. Saturated K_2CO_3 was added (2 ml), followed by 2M $Na_2S_2O_3$ (2 ml), and the mixture was diluted in 1:1 EtOAc / hexanes. After washing with 5% NaOH, the organic layer was dried over Na_2SO_4 and concentrated. The crude product was purified by flash chromatography (25% EtOAc / 5% NEt_3 / hexanes) to give 0.0411 g epoxide **22** (0.129 mmol, 63% yield).

^{1}HNMR (400MHz, C_6D_6):	4.27, 4.21 (2d, J=12.4Hz, 1H, t BuCO$_2$C$\underline{H}_2$); 3.90-3.82 (m, 1H, C$\underline{H}_2$OH); 3.74, 3.63 (2d, J=12.2Hz, 1H, t BuCO$_2$C$\underline{H}_2$); 3.68-3.59 (m, 1H, C$\underline{H}_2$OH); 3.31, 3.27 (2s, 1H, ring epoxy-H); 3.16, 3.14 (2d, J=1.6Hz, 1H, diyne epoxy-H); 2.12-2.05 (m, 1H, C$\underline{H}$CH$_2$OH); 1.50-1.42 (m, 2H); 1.26-1.18 (m, 2H); 1.10 (s, 9H, t Bu).
TLC (40% EtOAc / hexanes):	SM: .28 product: .18



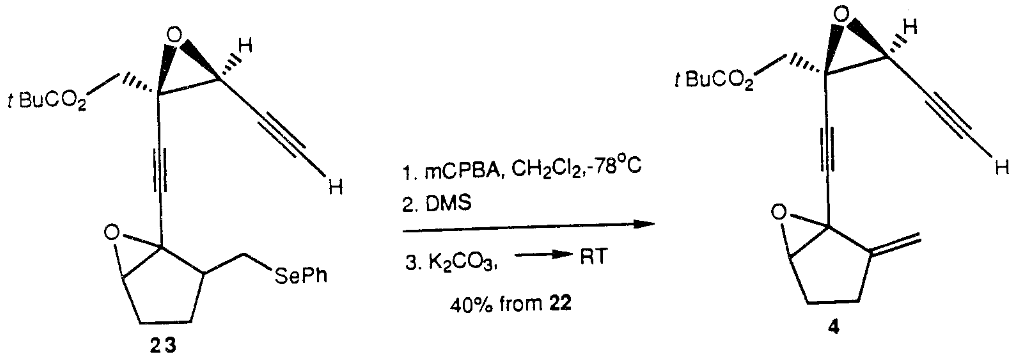
A solution of alcohol **22** (0.021 g, 0.066 mmol, 1 eq) and i Pr$_2$NEt (0.140 ml, 0.804 mmol, 12.18 eq) in 1 ml CH$_2$Cl$_2$ at -78°C was treated with triflic anhydride (0.030 ml, 0.18 mmol, 2.69 eq). After conversion to the triflate was complete (10 min), PhSeH (0.034 ml, 0.32 mmol, 4.8 eq) was introduced and the reaction mixture was warmed to -35°C for 5 h. The reaction was quenched with I$_2$, diluted in 1:1 EtOAc / hexanes, washed twice with water, dried (Na$_2$SO$_4$), and concentrated. The product was filtered through a short plug of silica gel (20% EtOAc / 5% NEt$_3$ / hexanes), and used crude for the elimination reaction.

FTIR: 3283, 2960, 2928, 2253, 2129, 1738, 1579, 1479, 1282, 1143, 1073, 1022, 890, 801, 738.

^{1}HNMR (400MHz, C$_6$D$_6$): 7.48-7.42 (m, 2H, Ar-H); 7.02-6.91 (m, 3H, Ar-H); 4.24 (dd, J=12.2, 10.5Hz, 1H, t BuCO$_2$C$\underline{H}_2$); 3.75, (dd, J=12.2, 4.9Hz, 1H, t BuCO$_2$C$\underline{H}_2$); 3.66-3.56 (m, 1H, C$\underline{H}_2$SePh); 3.33, 3.29 (2s, 1H, ring epoxy-H); 3.20, 3.19 (2d, J=1.7Hz, diyne epoxy-H); 2.87-2.79 (m, 1H, C$\underline{H}_2$SePh); 2.26-2.18 (m, 1H); 1.89 (br s, 1H, acetylene-H); 1.58-1.52 (m, 2H); 1.49-1.42 (m, 2H); 1.08 (s, 9H, t Bu).

TLC (40% EtOAc / hexanes): SM: .05
triflate: .18

(60% EtOAc / hexanes): triflate: .23
product: .36



23

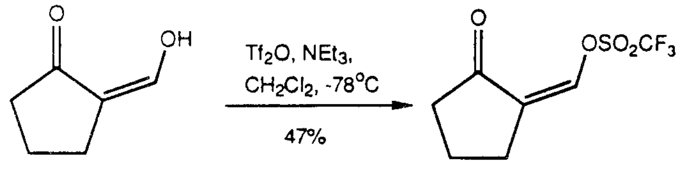
4

Crude epoxide **23** in 6 ml CH_2Cl_2 / 1 ml saturated $NaHCO_3$ at -78°C was treated with mCPBA (0.3199 g, 1.854 mmol, 14.05 eq vs. **22**). Oxidation was complete after 3h; the reaction was quenched with 1 ml DMS and allowed to stir for 1.25 h. A large excess of solid K_2CO_3 was added, and the mixture slowly warmed to room temperature overnight. The mixture was partitioned between saturated K_2CO_3 and 1:1 EtOAc / hexanes; the organic layer was washed sequentially with water, 5% NaOH, and saturated $NaHCO_3$, dried over Na_2SO_4, and concentrated. Purification by flash chromatography (10% EtOAc / 5% NEt_3 / hexanes) gave 0.0080 g **4** (0.027 mmol, 40% yield from **22**).

FTIR: 3286, 2924, 2256, 2130, 1736, 1275, 1129.

^{1}HNMR (400MHz, C_6D_6): 5.75 (dd, J=19.4, 2.3Hz, 1H, vinyl-H); 5.01 (br s, 1H, vinyl-H); 4.28 (dd, J=7.1, 12.2Hz, 1H, *t* $BuCO_2C\underline{H_2}$); 3.72 (dd, J=6.0, 12.3Hz, 1H, *t* $BuCO_2C\underline{H_2}$); 3.65, 3.56 (2d, J=1.3Hz, 1H, ring epoxy-H); 3.20, 3.17 (2d, J=1.7Hz, 1H, diyne epoxy-H); 2.04-1.80 (m, 1H); 1.82-1.73 (m, 1H); 1.64 (br s, 1H, acetylene-H); 1.52-1.41 (m, 2H); 1.08 (s, 9H, *t* Bu).

TLC (20% EtOAc / hexanes):
SM: .36
product: .35



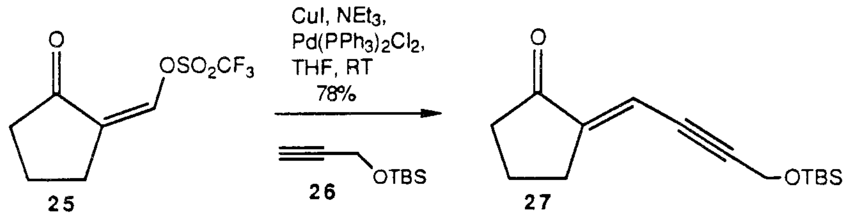
24

25

A solution of ketoaldehyde **24** (1.0039 g, 8.95 mmol, 1 eq) and NEt_3 (2.4 ml, 17.22 mmol, 1.92 eq) in 30 ml CH_2Cl_2 at -78°C was treated with triflic anhydride (2.9 ml, 17.24 mmol, 1.93 eq). After 30 min, the reaction was quenched with water, extracted twice with 100-ml portions of diethyl ether, dried over Na_2SO_4 , and concentrated to about 5 ml. The crude product was purified by flash chromatography (20% EtOAc / hexanes) to give 1.0276 g enol triflate **25** (4.208 mmol, 47%).

^{1}HNMR (400MHz, $CDCl_3$): 7.41 (m, 1H, vinyl-H); 2.60 (m, 2H); 2.34 (m, 2H); 1.94 (m, 2H).

TLC (20% EtOAc / hexanes): SM: .13
product: .37

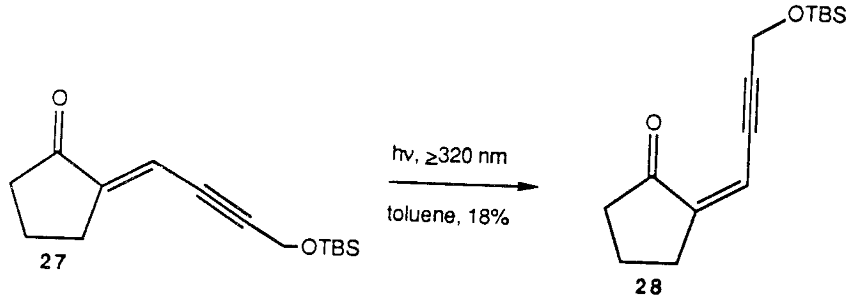


A solution of triflate **25** (1.0276 g, 4.208 mmol, 1 eq) and $Pd(PPh_3)_2Cl_2$ (0.1205 g, 0.125 mmol, 0.03 eq) in 6 ml THF was added to a stirred solution of acetylide **26** (0.9316 g, 5.469 mmol, 1.30 eq), NEt_3 (1.8 ml, 12.914 mmol, 3.07 eq), and CuI (0.0607 g, 0.319 mmol, 0.075 eq) in 6 ml THF. After 1 h, the reaction mixture was poured into saturated NH_4Cl solution, extracted twice with 1:1 EtOAc / hexanes, dried over Na_2SO_4, and concentrated. Purification by flash chromatography (10% EtOAc / hexanes) gave 0.8730 g enone **27** (3.30 mmol, 78% yield).

FTIR: 2956, 2858, 2210, 1718, 1618, 1254, 1157, 1086, 837.

^{1}HNMR (400MHz, $CDCl_3$): 6.38 (m, 1H, vinyl-H); 4.50 (d, J=1Hz, 2H, $C\underline{H_2}OTBS$); 2.76 (td, J=7.3, 2.7Hz, 2H); 2.37 (t, J=7.8Hz, 2H); 1.95 (p, J=7.6Hz, 2H); 0.90 (s, 9H, Si-*t* Bu); 0.12 (s, 6H, Si-CH_3).

TLC (20% EtOAc / hexanes): SM: .32
product: .45



27 **28**

Enone **27** (1.0153 g) in 12 ml toluene was irradiated through a 320-nm filter for 45 min with stirring. The solvent was removed, and the isomers separated by flash chromatography (10% EtOAc / hexanes) to give 0.1808 g of *cis* -enone **28** (18%), and 0.7485 g of recovered **27** (74%).

FTIR: 2957, 2857, 1996, 1721, 1613, 1258, 1161, 1083, 837, 779.

^{1}HNMR (400MHz, CDCl$_3$): 5.88 (m, 1H, vinyl-H); 4.55 (d, J=1Hz, 2H); 2.72 (m, 2H); 2.37 (t, J=7.7Hz, 2H); 1.93 (p, J=7.6Hz, 2H); 0.91 (s, 9H, Si-*t* Bu); 0.14 (s, 6H. Si-CH$_3$).

TLC (20% EtOAc / hexanes): SM: .39
product: .29

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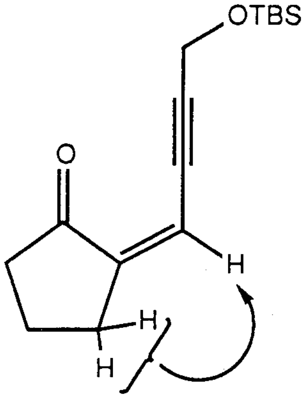
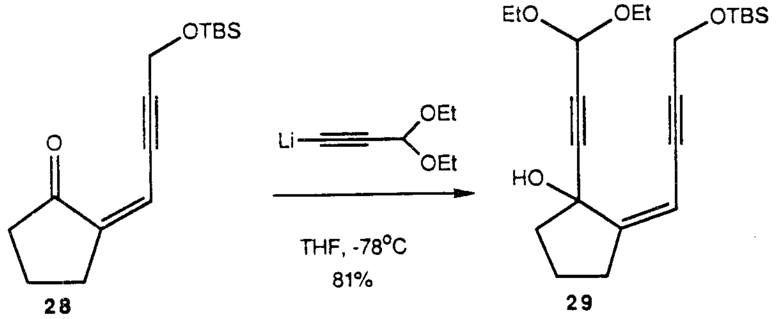


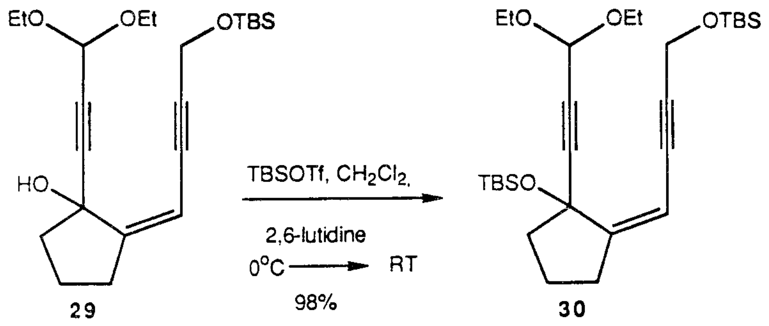


A solution of enone **28** (0.1534 g, 0.580 mmol, 1 eq) in 6 ml THF at -78°C was treated with $(EtO)_2HCC_2Li$ (prepared from $(EtO)_2HCC_2H$ (0.420 ml, 2.93 mmol, 5.05 eq) and *n* BuLi (2.0 ml, 2.94 mmol, 5.06 eq) in 6 ml THF at -78°C). After 30 min, the reaction was quenched cold with saturated NH_4Cl solution, extracted with 1:1 EtOAc / hexanes, dried (Na_2SO_4), and concentrated. Alcohol **29** was purified by flash chromatography (15% EtOAc / hexanes) to give 0.1850 g (0.471 mmol, 81%).

FTIR: 3543, 2930, 2858, 2210, 1473, 1255, 1081, 1055, 837, 778.

^{1}HNMR (500MHz, $CDCl_3$): 5.57 (m, 1H, vinyl-H); 5.30 (s, 1H, $C\underline{H}(OEt)_2$); 4.48 (d, J=1.8Hz, 2H, $C\underline{H_2}OTBS$); 3.76-3.70 (m, 2H, $OC\underline{H_2}CH_3$); 3.61-3.55 (m, 2H, $OC\underline{H_2}CH_3$); 3.48 (s, 1H, OH); 2.55-2.52 (m, 2H); 2.24-2.21 (m, 1H); 2.10-2.04 (m, 1H); 1.81-1.72 (m, 2H); 1.22 (t, J=7.1Hz, 6H, $OCH_2C\underline{H_3}$); 0.91 (s, 9H, Si-*t* Bu); 0.12 (2s, 6H, Si-CH_3).

TLC (5% EtOAc / hexanes): SM: .34
product: .25

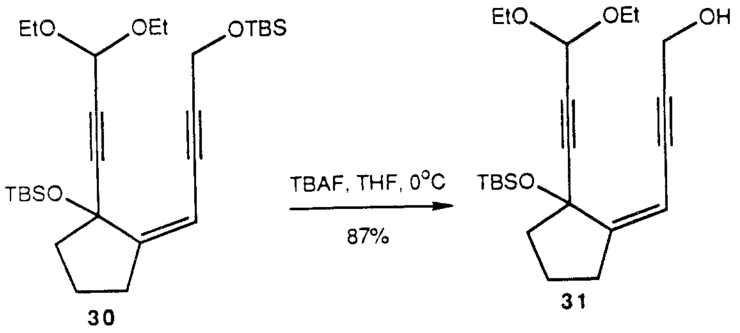


A solution of alcohol **29** (0.1850 g, 0.471 mmol, 1 eq) and 2,6-lutidine (1.10 ml, 9.44 mmol, 20.0 eq) in 8 ml CH_2Cl_2 at 0°C was treated with TBSOTf (0.75 ml, 3.26 mmol, 6.92 eq) and warmed to room temperature. After 1.5 h, the reaction was quenched with 5 ml MeOH, diluted in 1:1 EtOAc / hexanes, washed with water, dried over Na_2SO_4, and concentrated. Purification by flash chromatography (10% EtOAc / hexanes) gave 0.2348 g of **30** (0.463 mmol, 98% yield).

FTIR: 2956, 2929, 2886, 2857, 2211, 1599, 1472, 1360, 1252, 1167, 1122, 1080, 1056, 1006, 838, 778.

^{1}HNMR (400MHz, $CDCl_3$): 5.56 (t, J=2.2Hz, 1H, vinyl-H); 5.30 (s, 1H, C$\underline{H}$(OEt)$_2$); 4.46 (d, J=2.2Hz, 2H, C$\underline{H}_2$OTBS); 3.76-3.69 (m, 2H, OC$\underline{H}_2$CH$_3$); 3.60-3.55 (m, 2H, OC$\underline{H}_2$CH$_3$); 2.50-2.42 (m, 2H); 2.09-2.01 (m, 2H); 1.75-1.67 (m, 2H); 1.21 (t, J=7.1Hz, 6H, OCH$_2$C$\underline{H}_3$); 0.90 (s, 9H, Si-*t* Bu); 0.87 (s, 9H, Si-*t* Bu); 0.22 (s, 3H, Si-CH$_3$); 0.19 (s, 3H, Si-CH$_3$); 0.11 (s, 6H, Si-CH$_3$).

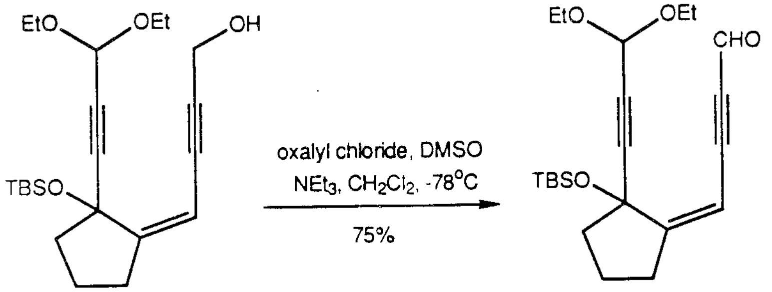
TLC (20% EtOAc / hexanes): SM: .35
product: .54



A 10-ml solution of **30** (0.2348 g, 0.463 mmol, 1 eq) in THF at 0°C was deoxygenated and treated with 1- M TBAF (0.46 ml, 0.46 mmol, 1.0 eq). The reaction was quenched after 10 min with brine, extracted twice with 1:1 EtOAc / hexanes, dried over Na_2SO_4, and concentrated. The crude product was purified by flash chromatography (10% EtOAc / hexanes) to give 0.1584 g alcohol **31** (0.403 mmol, 87% yield).

^{1}HNMR (400MHz, $CDCl_3$): 5.54 (m, 1H, vinyl-H); 5.35 (s, 1H, C$\underline{H}$(OEt)$_2$); 4.43-4.29 (m, 2H, C$\underline{H}_2$OH); 3.82-3.71 (m, 2H, OC$\underline{H}_2$CH$_3$); 3.65-3.56 (m, 2H, OC$\underline{H}_2$CH$_3$); 3.09 (t, J=8Hz, 1H, OH); 2.60-2.51 (m, 1H); 2.44-2.33 (m, 1H); 2.14-2.07 (m, 1H); 2.03-1.95 (m, 1H); 1.87-1.76 (m, 1H); 1.73-1.64(m, 1H); 1.25 (m, 6H, OCH$_2$C$\underline{H}_3$); 0.86 (s, 9H, Si-*t* Bu); 0.25 (s, 3H, Si-CH$_3$); 0.22 (s, 3H, Si-CH$_3$).

TLC (20% EtOAc / hexanes): SM: .72
product: .26



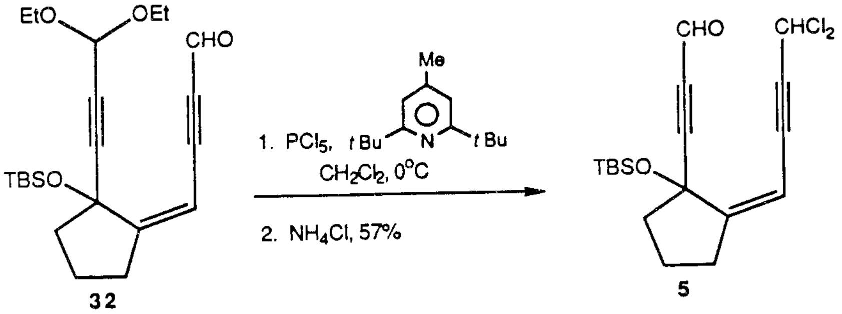
31 **32**

DMSO (0.150 ml, 2.11 mmol, 73 eq) was added to a solution of oxalyl chloride (0.10 ml, 1.15 mmol, 40 eq) in 2 ml CH_2Cl_2 at -78°C, causing gas evolution for 1 sec. Alcohol **31** (0.0115 g, 0.029 mmol, 1 eq) in 1 ml CH_2Cl_2 was introduced; the mixture was stirred for 15 min, then treated with NEt_3 (0.5 ml, 3.59 mmol, 124 eq). After 15 min, the reaction was warmed to 0°C, stirred for 10 min, then partitioned between brine and 1:1 EtOAc / hexanes. The organic layer was separated, dried over Na_2SO_4, and concentrated. The residue was run through a short flash column (20% EtOAc / hexanes) to give 0.0085 g aldehyde **32** (0.022 mmol, 75% yield).

FTIR: 2955, 2856, 2177, 1661, 1630, 1472, 1251, 1169, 1020, 1054, 1013, 839, 779.

^{1}HNMR (400MHz, $CDCl_3$): 9.38 (s, 1H, aldehyde-H); 5.69 (br s, 1H, vinyl-H); 5.31 (s, 1H, $C\underline{H}(OEt)_2$); 3.74-3.68 (m, 2H, $OC\underline{H_2}CH_3$); 3.60-3.55 (m, 2H, $OC\underline{H_2}CH_3$); 2.60-2.53 (m, 2H); 2.23-2.05 (m, 2H); 1.82-1.74 (m, 2H); 1.22 (m, 6H, $OCH_2C\underline{H_3}$); 0.86 (s, 9H, Si-*t* Bu); 0.27 (s, 3H, Si-CH_3); 0.22 (s, 3H, Si-CH_3).

TLC (20% EtOAc / hexanes): SM: .42
product: .47

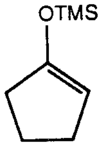


A solution of aldehyde **32** (0.0992 g, 0.254 mmol, 1 eq, dried with toluene) and di*t*butylmethylpyridine (1.60 ml, 6.93 mmol, 27.27 eq) in 16 ml CH_2Cl_2 at 0°C was treated with PCl_5 (0.260 g, 1.248 mmol, 4.91 eq) in 4 ml CH_2Cl_2. The reaction was quenched cold after 10 min with saturated aqueous NH_4Cl and extracted with 1:1 EtOAc / hexanes. The organic layer was separated, washed with water, dried (Na_2SO_4), and concentrated. Purification by flash chromatography (100% hexanes to 10% EtOAc / hexanes) afforded aldehyde dichloride **5** in 87% yield (0.0821 g, 0.221 mmol).

FTIR: 2956, 2857, 2216, 1674-1668, 1472, 1253, 1084, 839, 779, 722.

^{1}HNMR (500MHz, $CDCl_3$): 9.28 (s, 1H, aldehyde-H); 6.43 (d, J=1.8Hz, 1H, $CHCl_2$); 5.69 (m, 1H, vinyl-H); 2.67-2.60 (m, 1H); 2.53-2.44 (m, 1H); 2.17-2.10 (m, 2H); 1.92-1.73 (m, 2H); 0.88 (s, 9H, Si-*t* Bu); 0.29 (s, 3H, Si-CH_3); 0.23 (s, 3H, Si-CH_3).

TLC (10% EtOAc / hexanes): SM: .31
product: .40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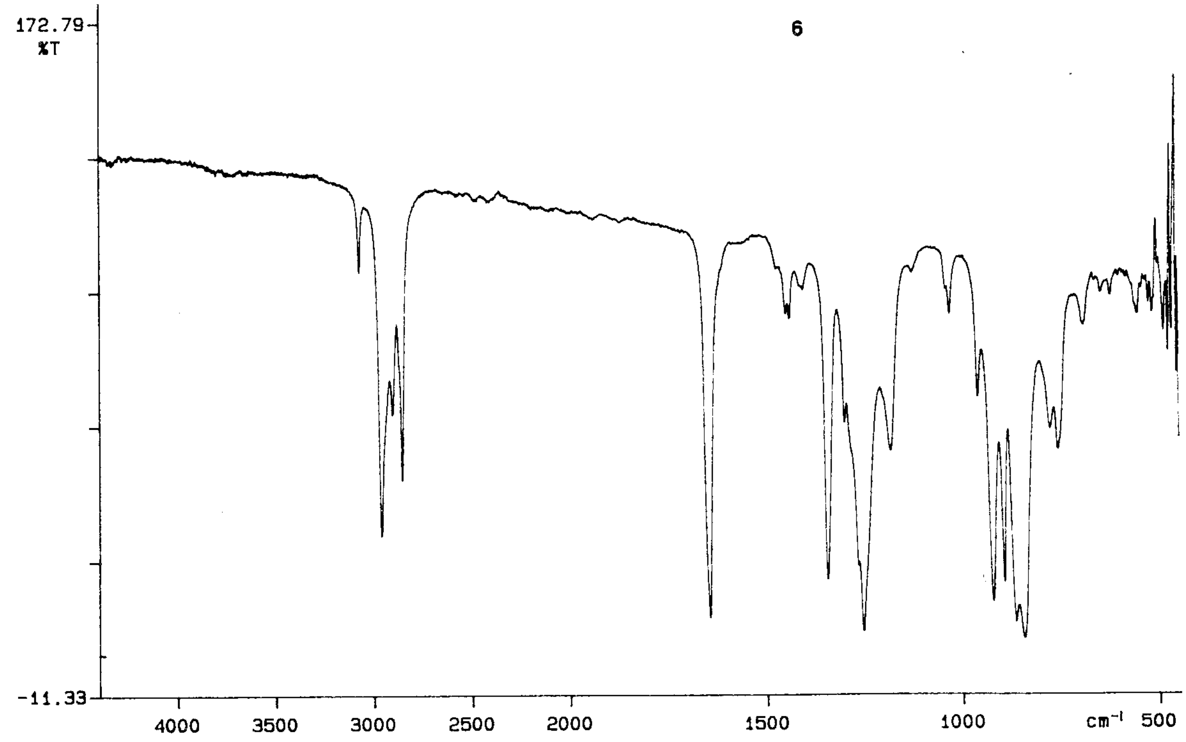
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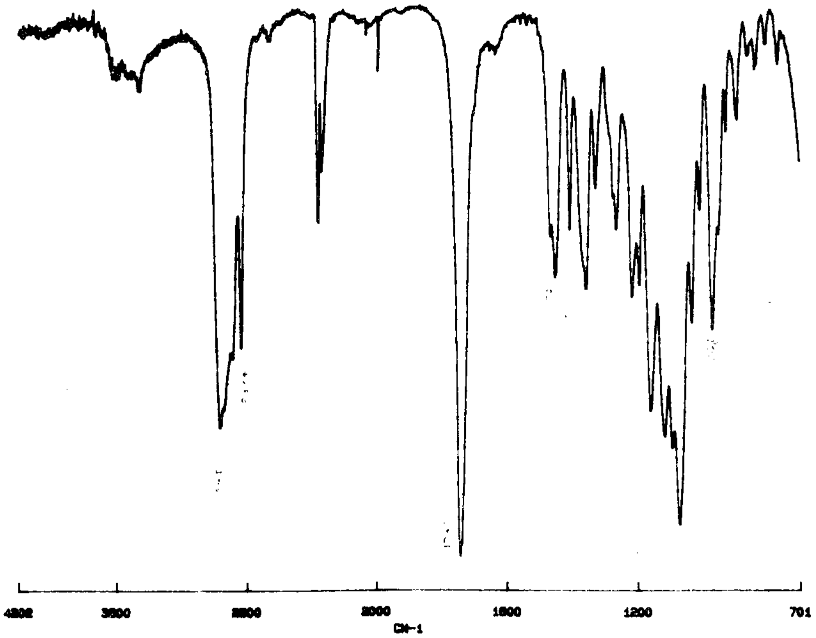
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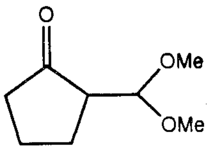
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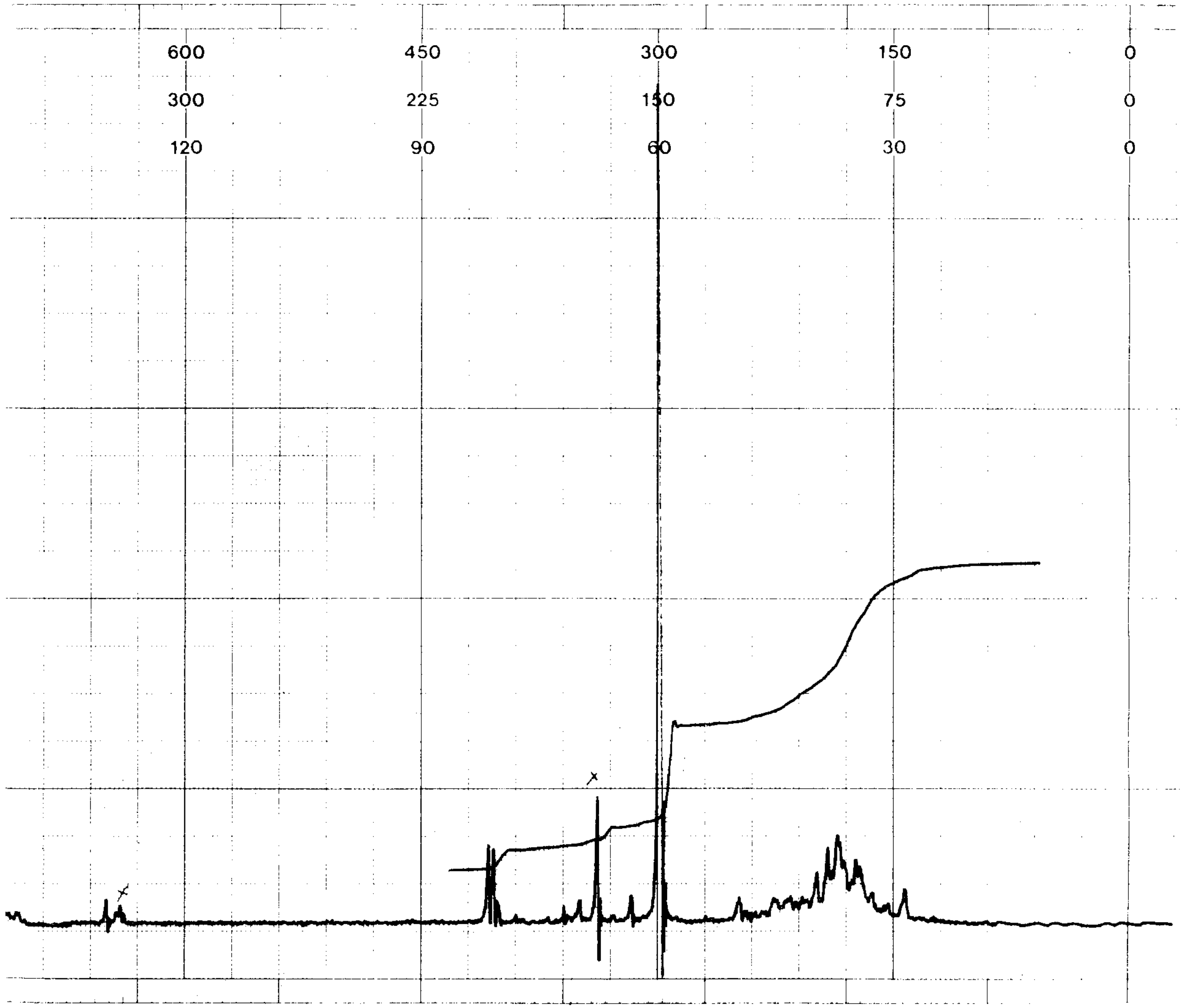
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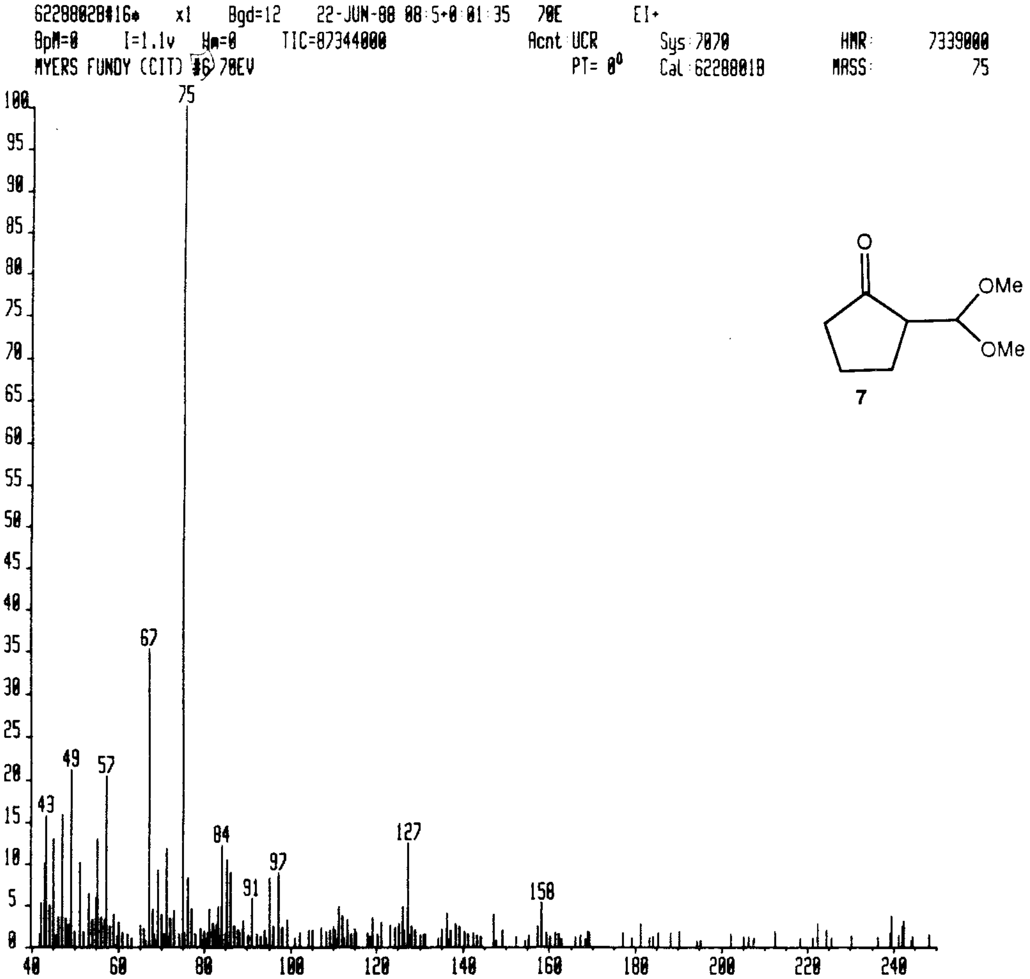

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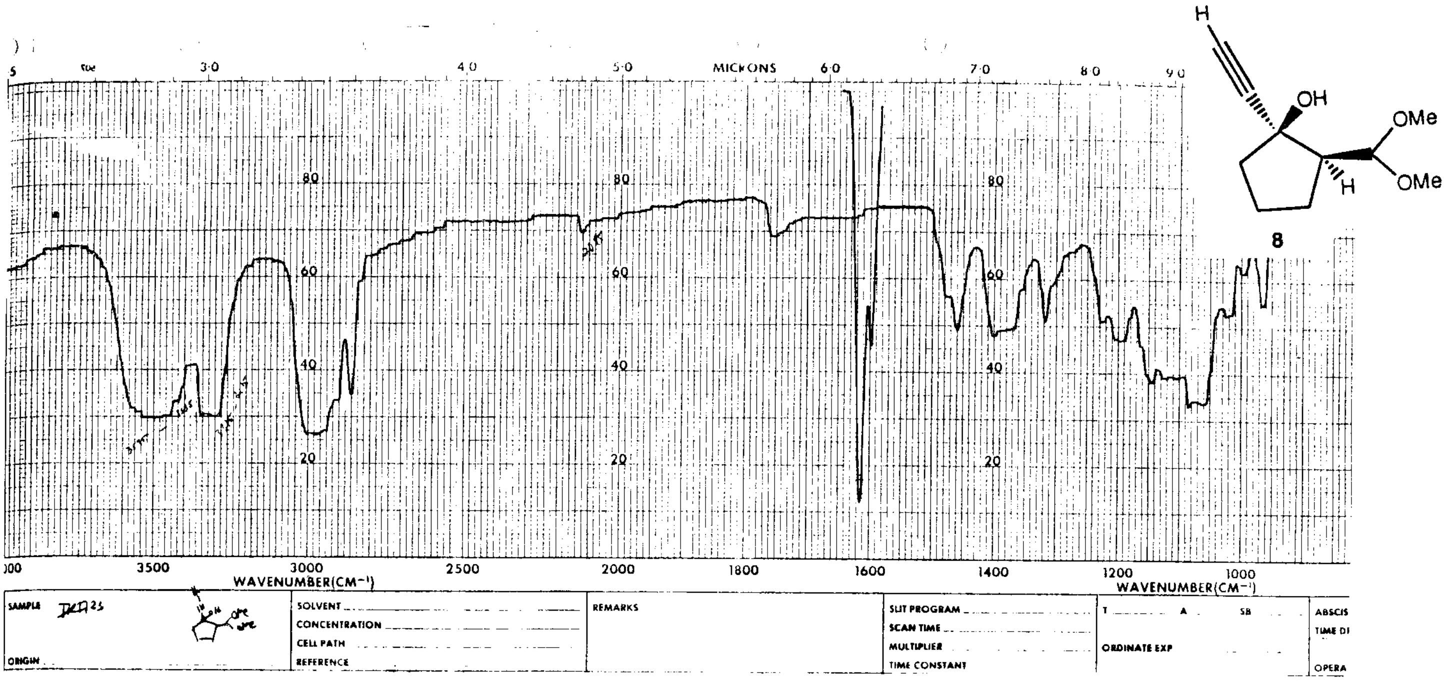

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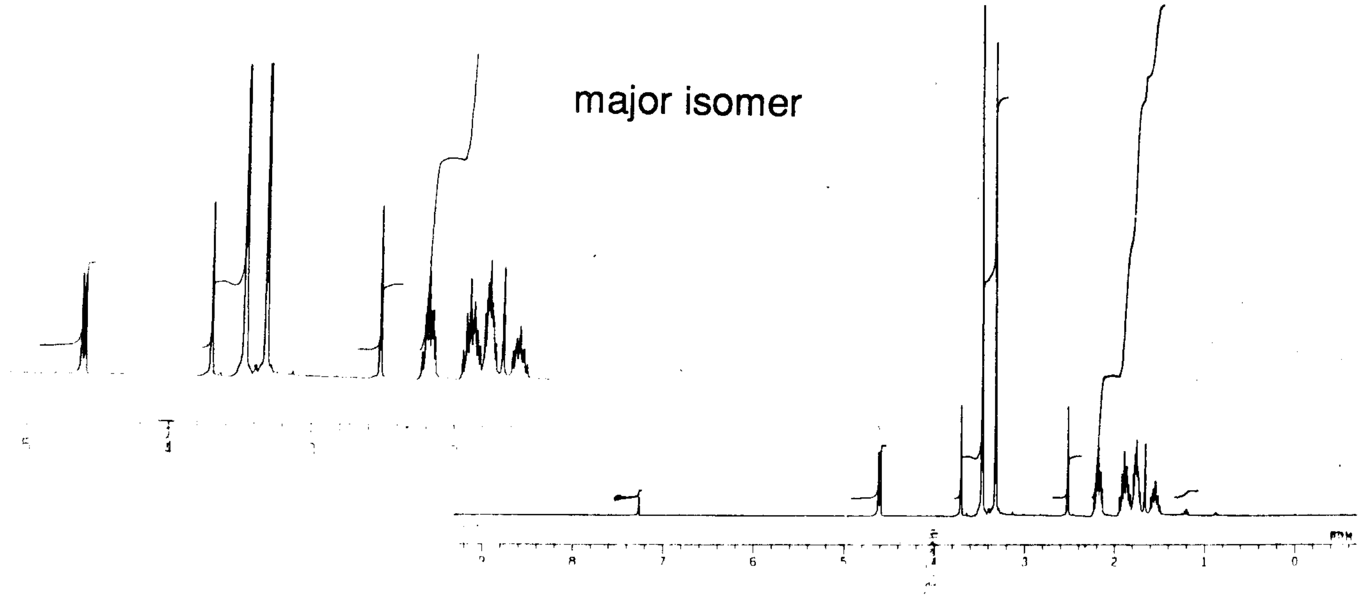
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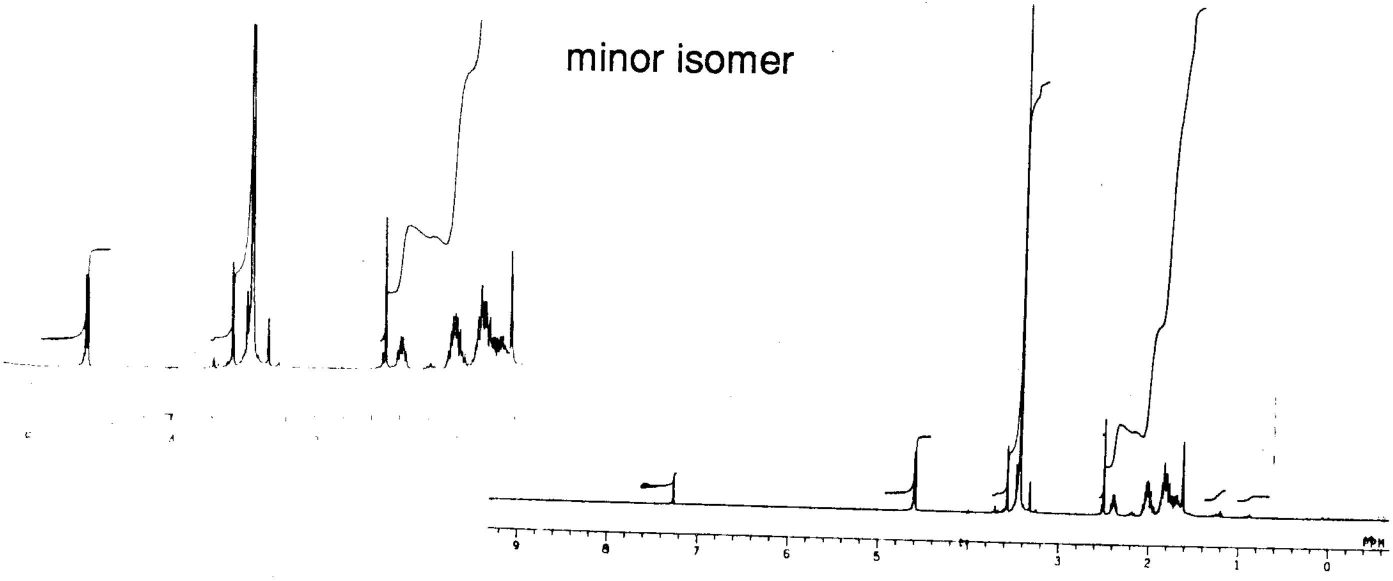
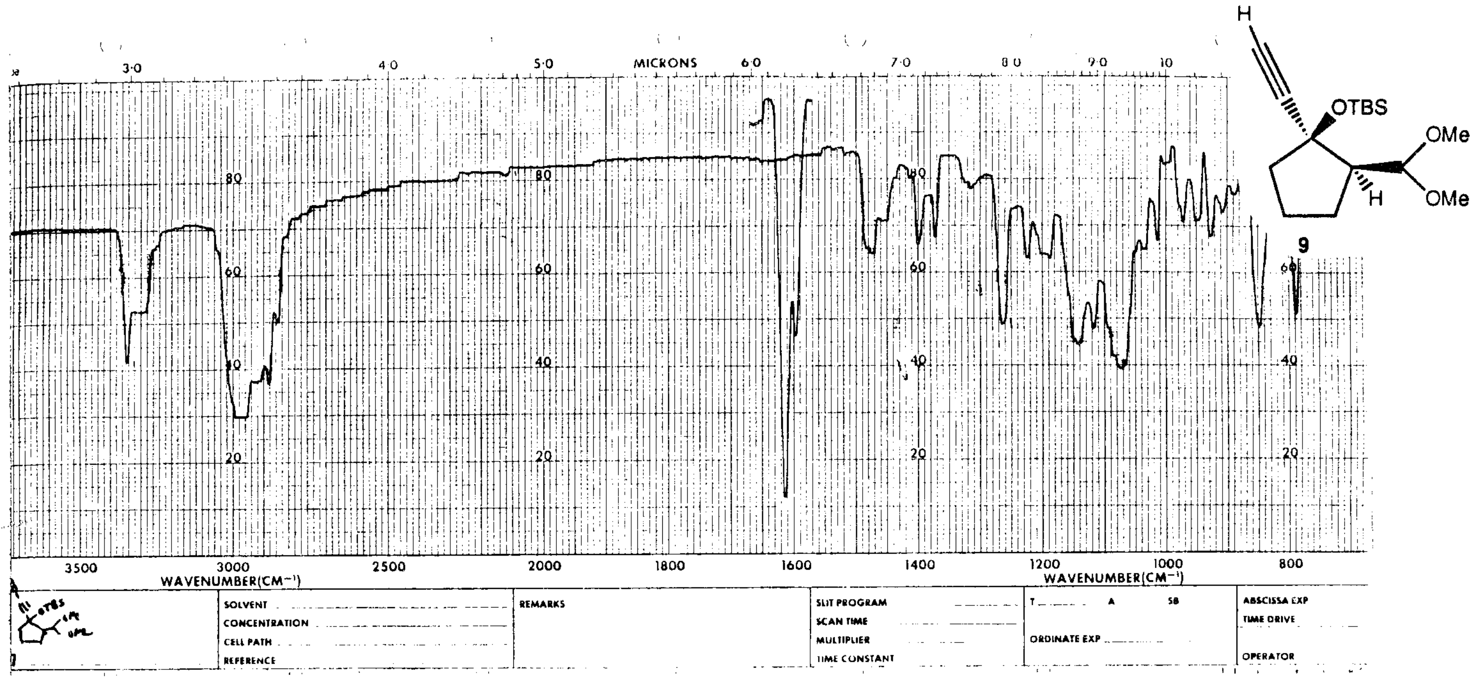
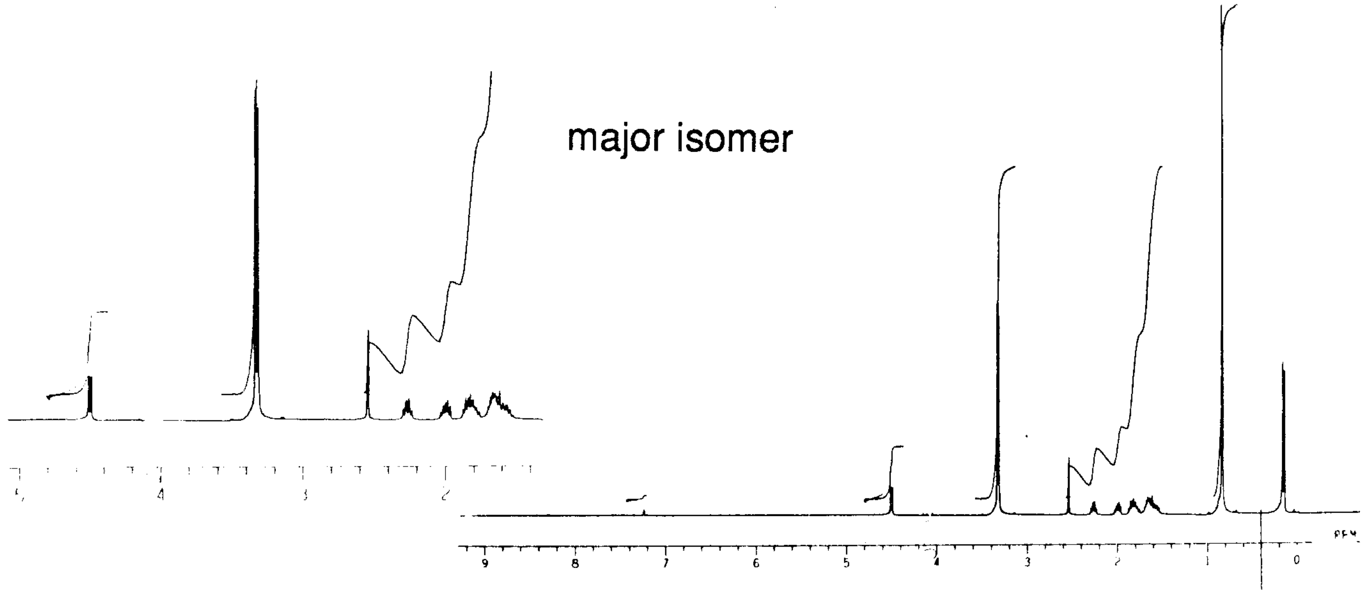

minor isomer

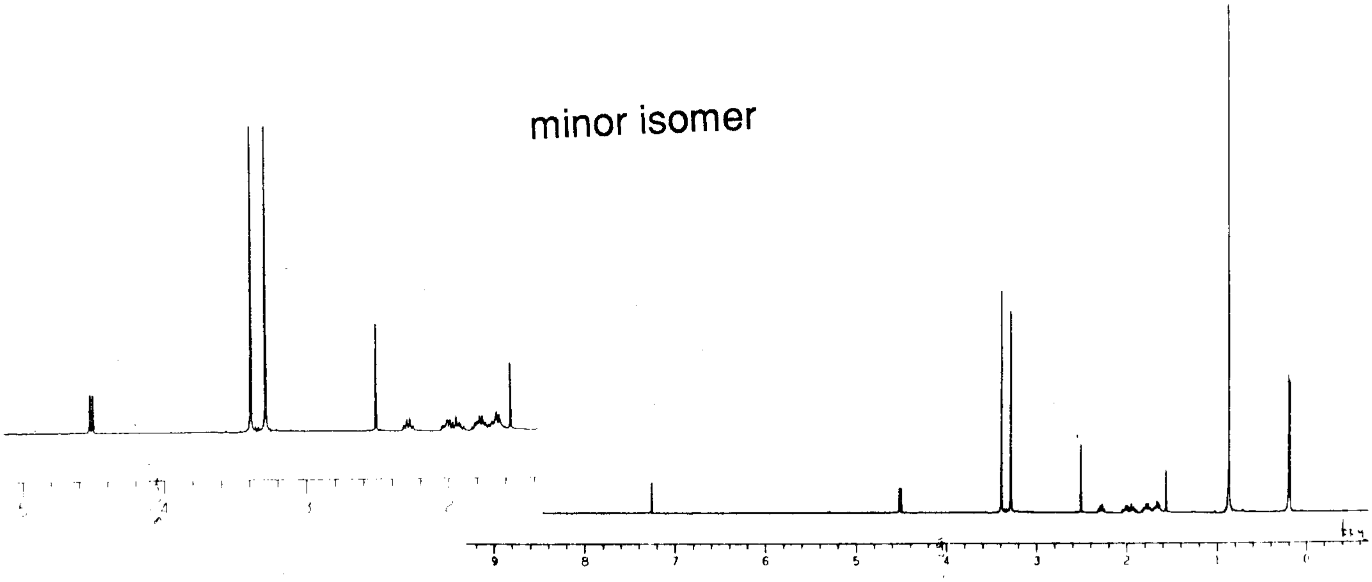


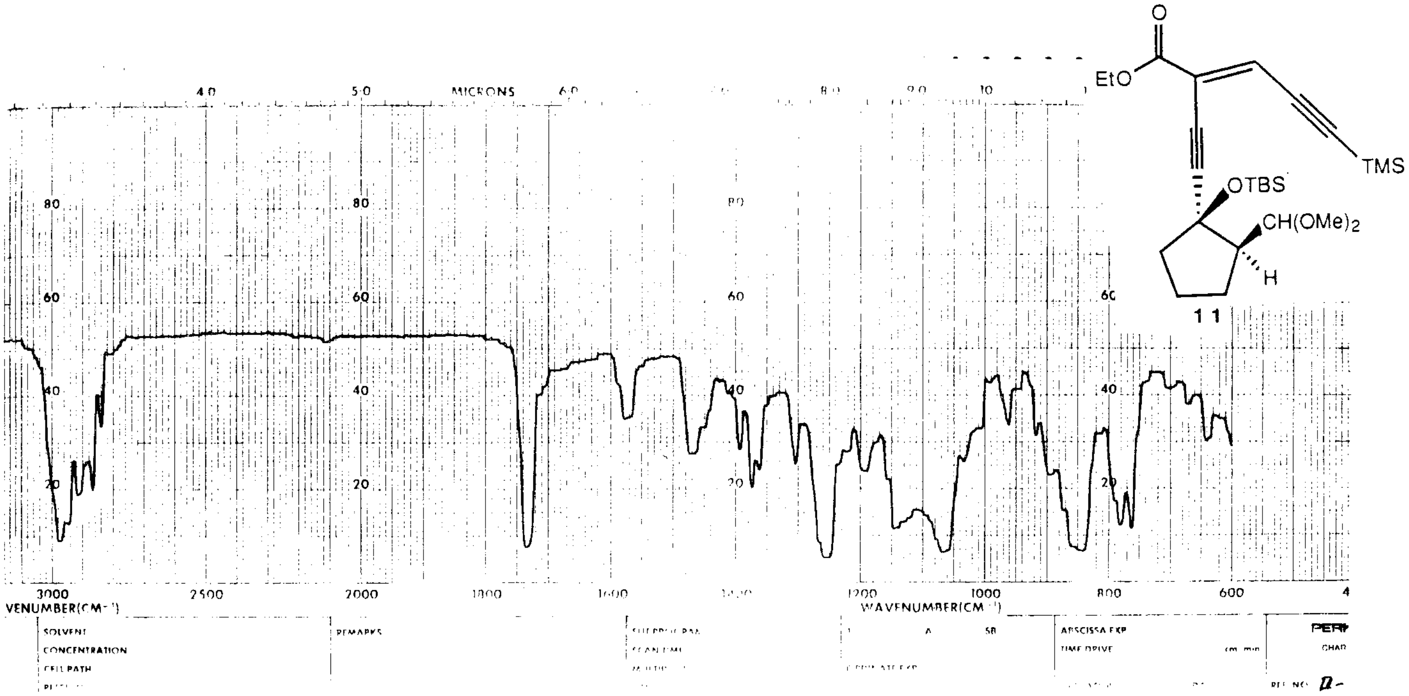
9

major isomer



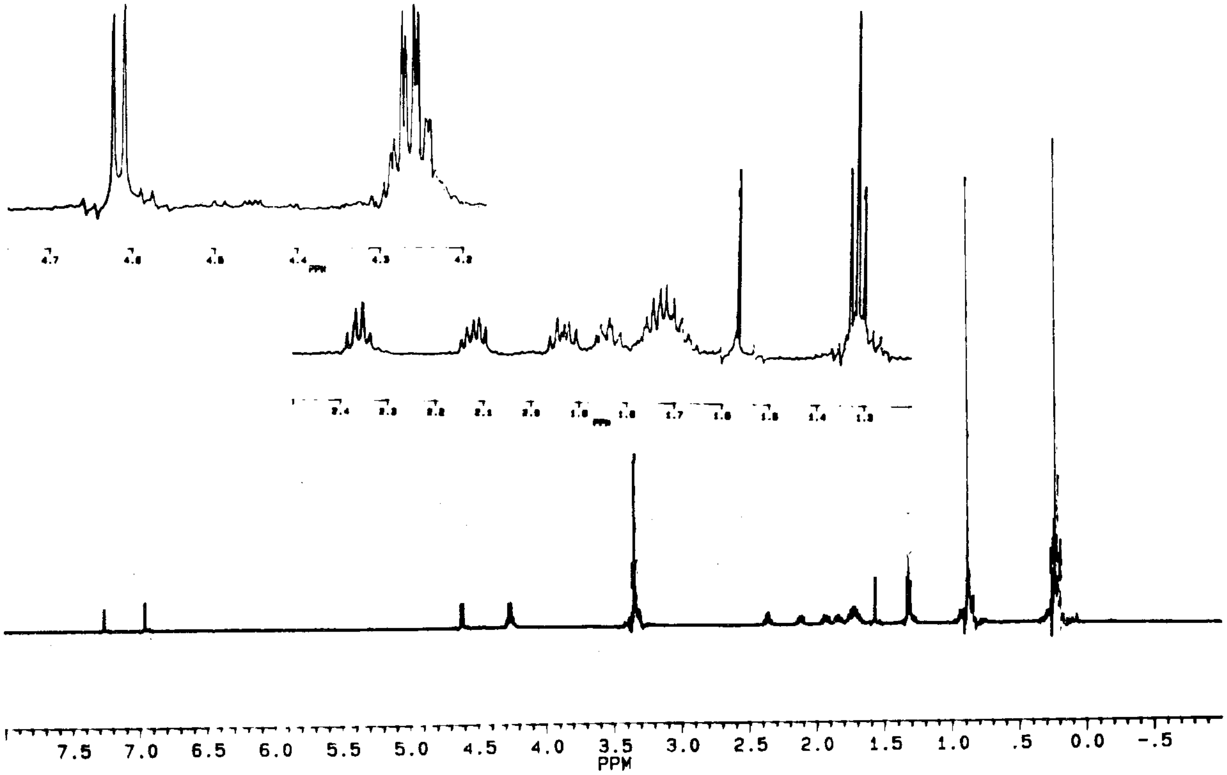
minor isomer



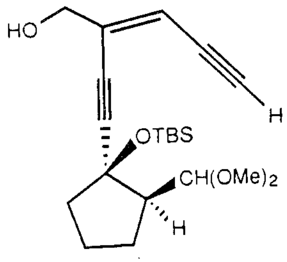


O
EtO
TMS
OTBS
CH(OMe)2
H
MICRONS
4.0
5.0
6.0
8.0
9.0
10
80
60
40
20
3000
2500
2000
1800
1600
1200
1000
800
600
WAVENUMBER(CM⁻¹)
SOLVENT
CONCENTRATION
CELL PATH
REMARKS
ABSCISSA EXP
TIME DRIVE
REF. NO.

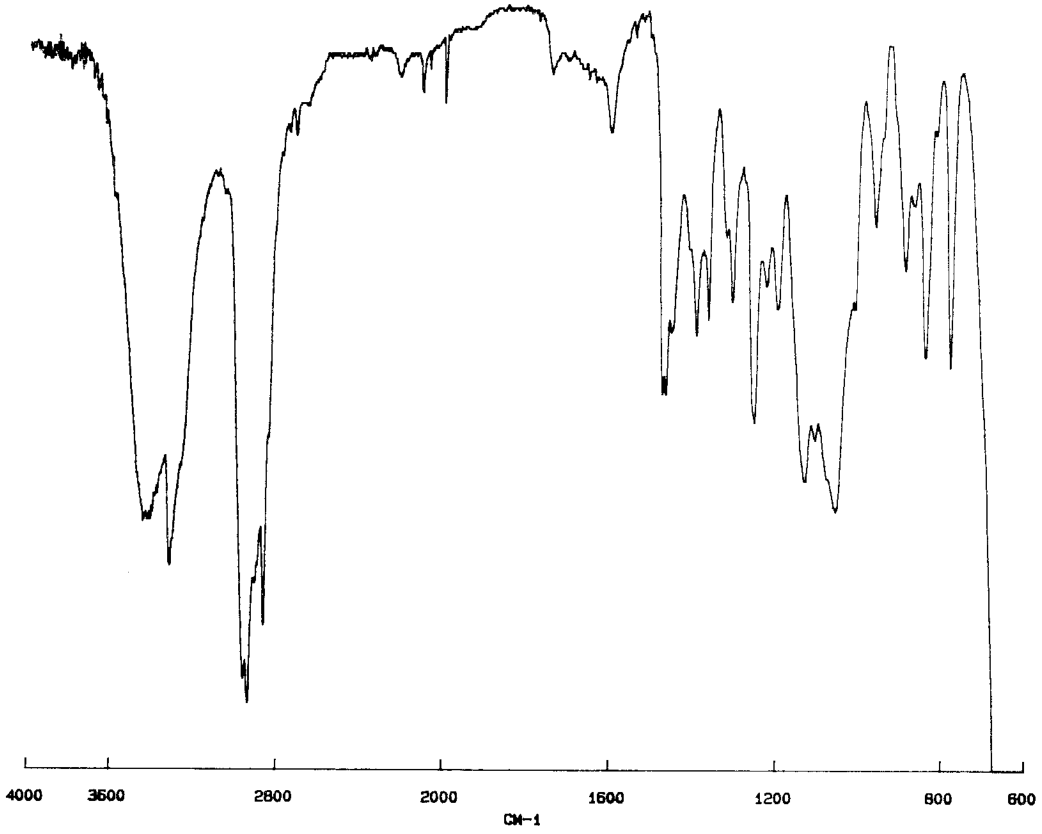
11



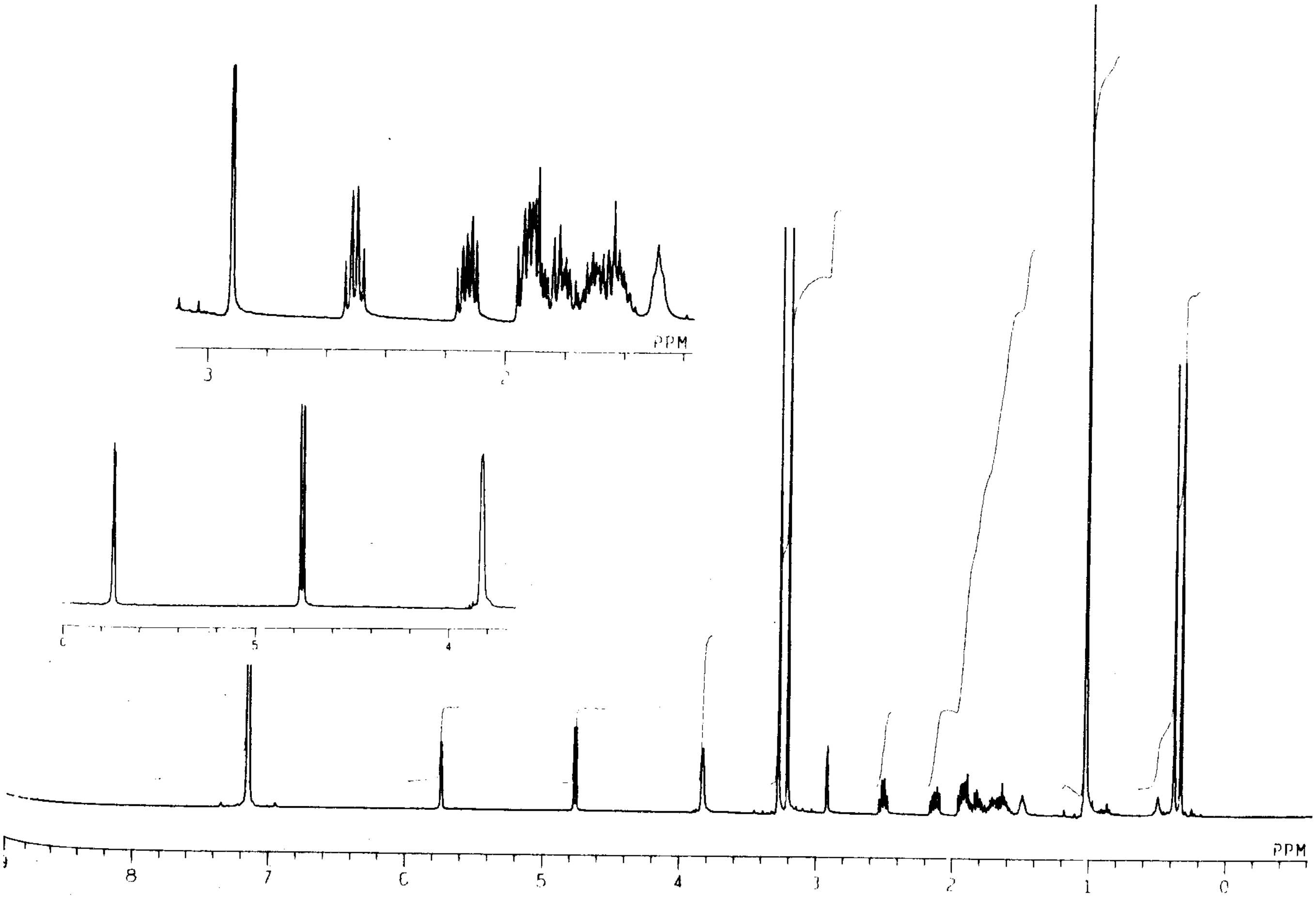
4.7
4.6
4.5
4.4
4.3
4.2
PPM
2.4
2.3
2.2
2.1
2.0
1.9
1.8
1.7
1.6
1.5
1.4
1.3
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
.5
0.0
-.5
PPM

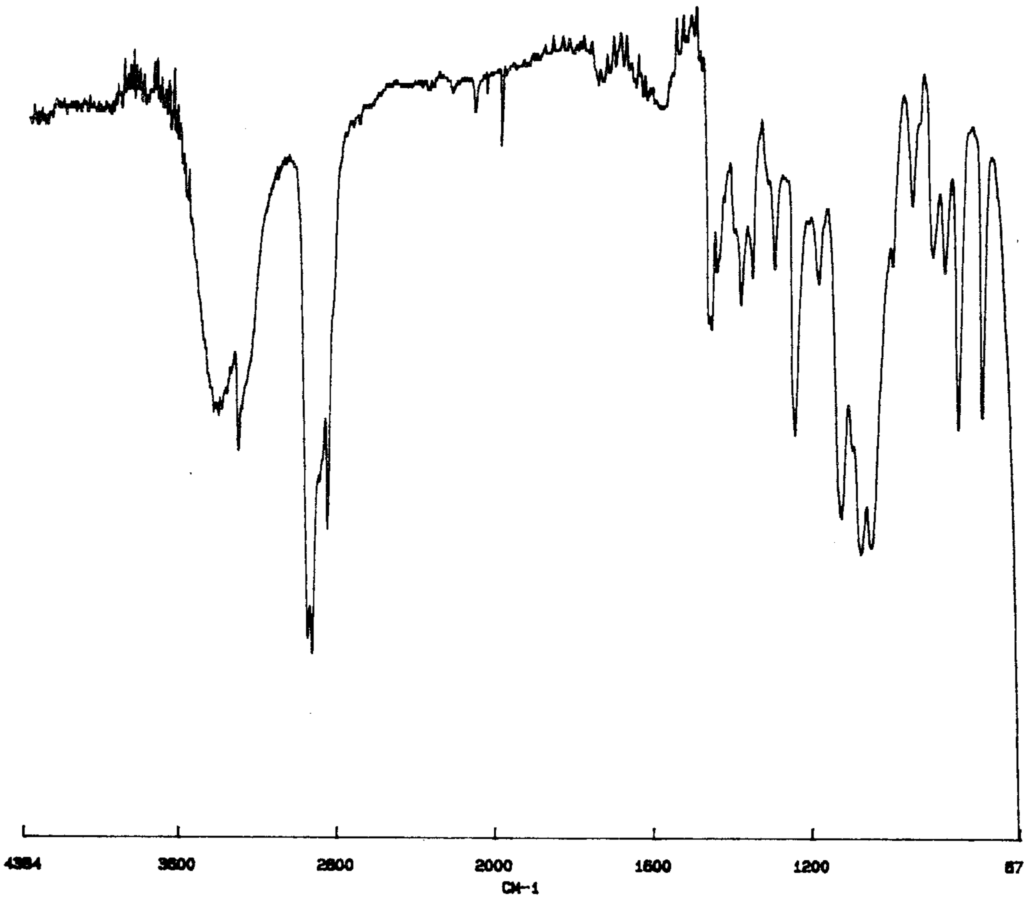


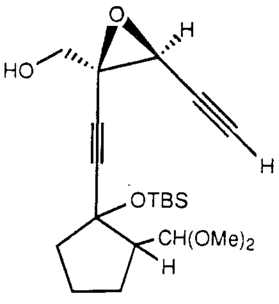
12



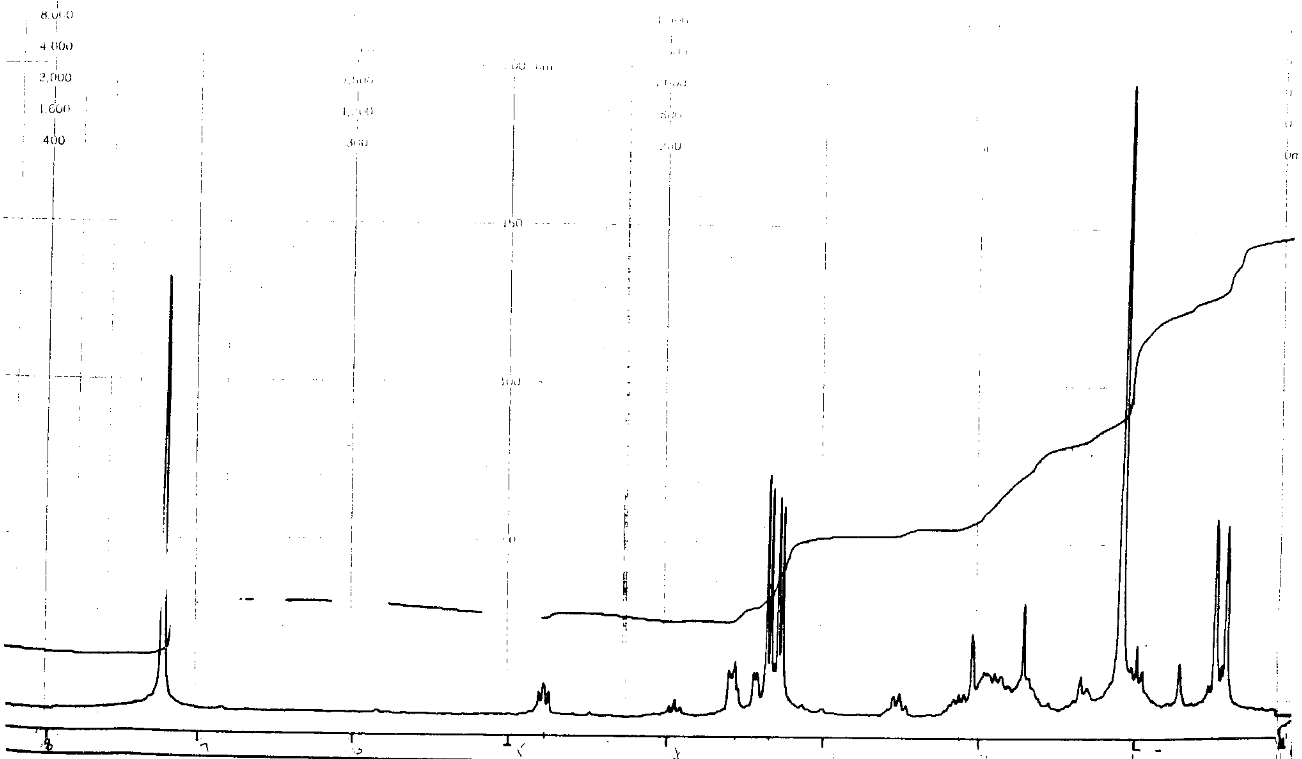
6/21/88
Neat

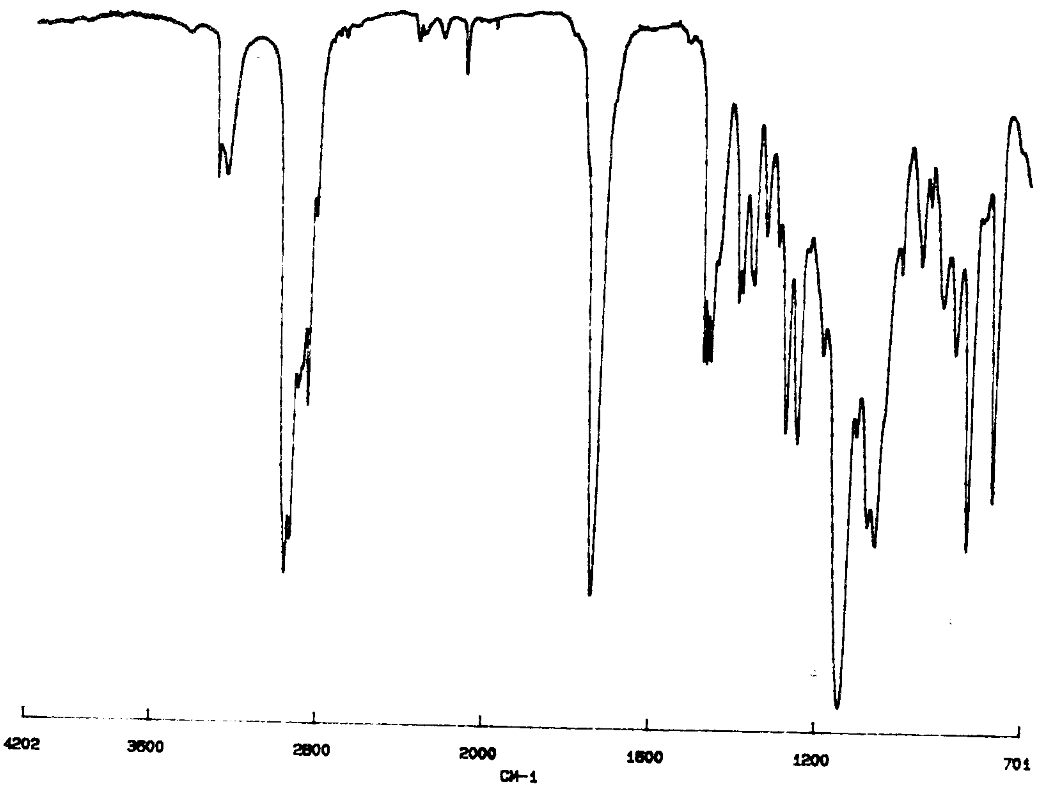


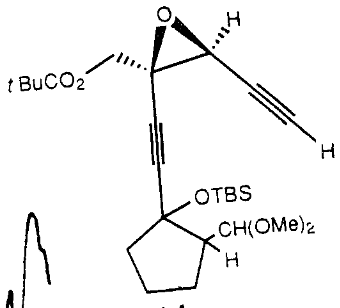

4384
3600
2800
2000
1600
1200
874
CM-1


O
H
HO
H
OTBS
CH(OMe)2
H

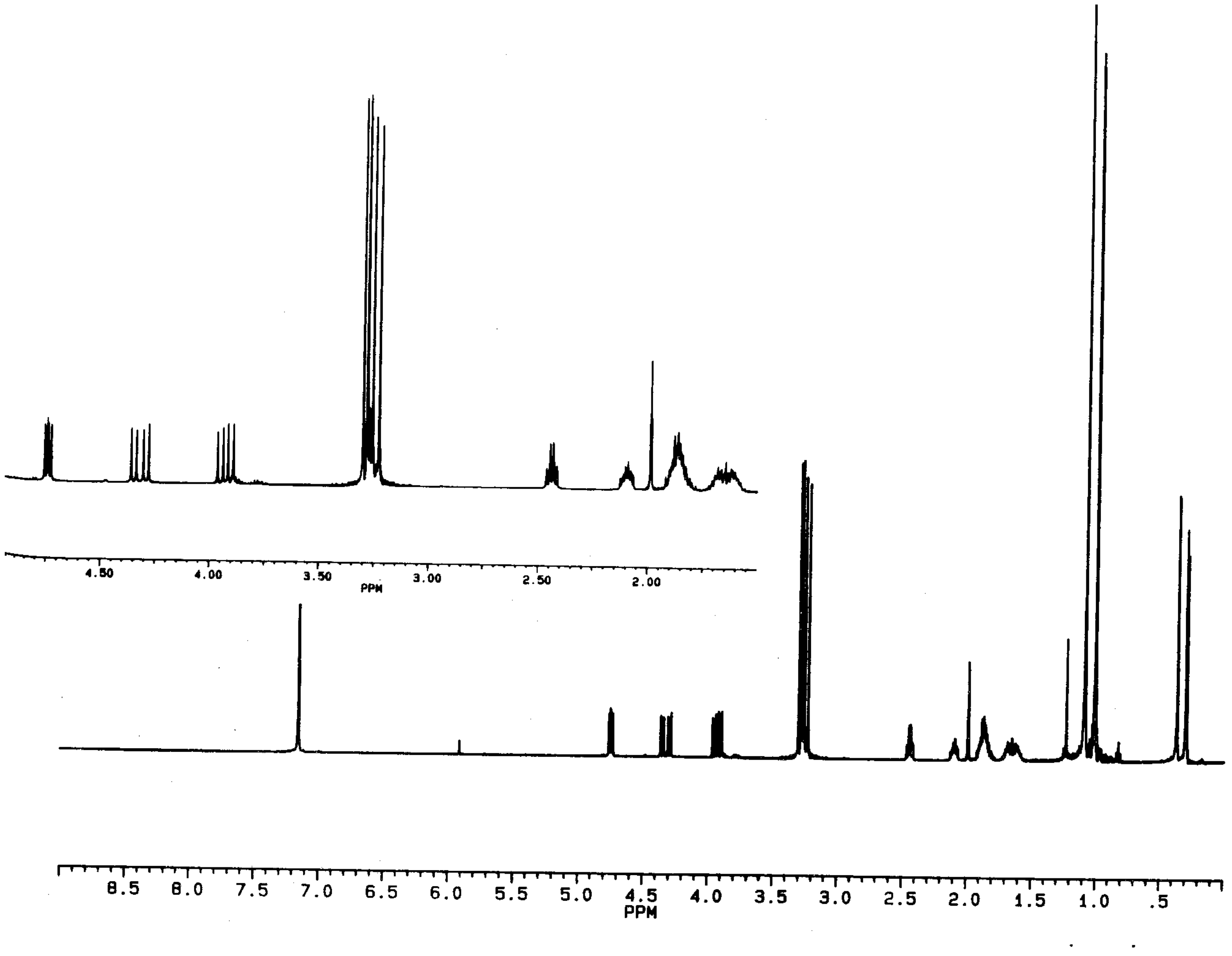
1 3

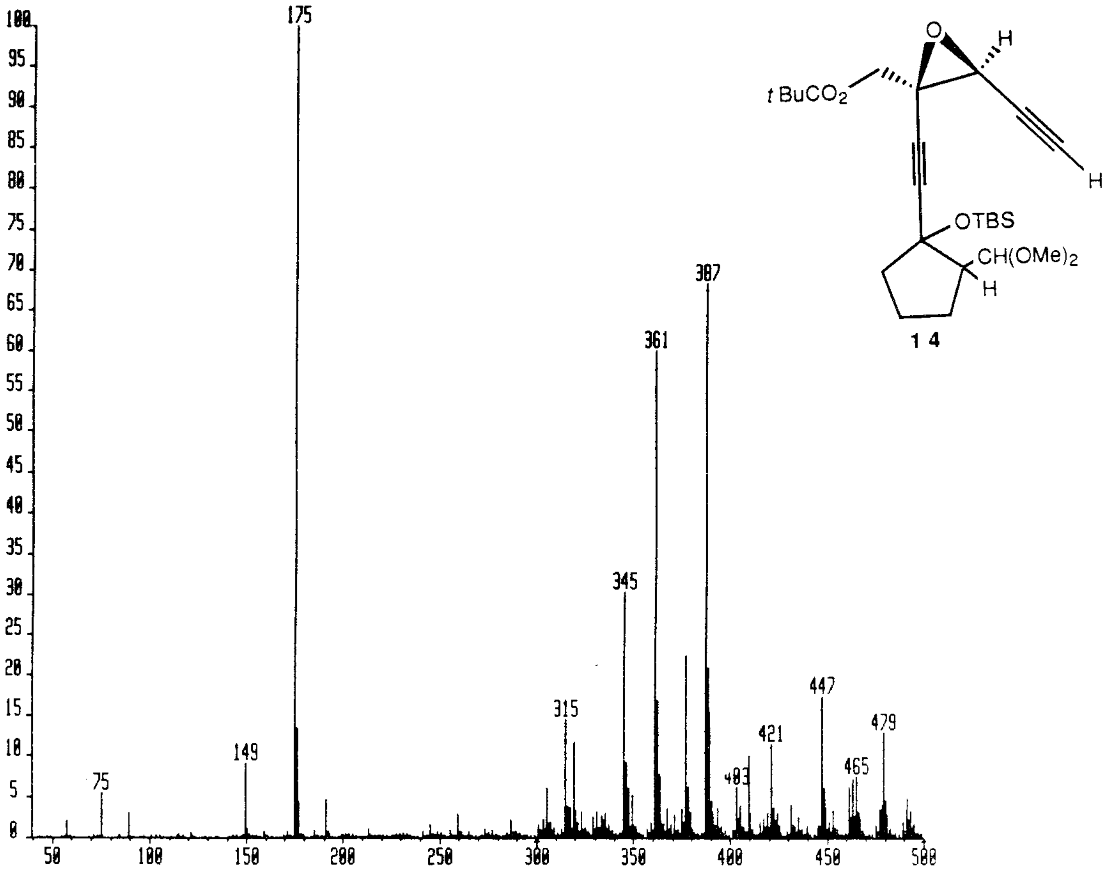

8.000
4.000
2,000
1,600
400


4202
3600
2800
2000
1600
1200
701
CM-1

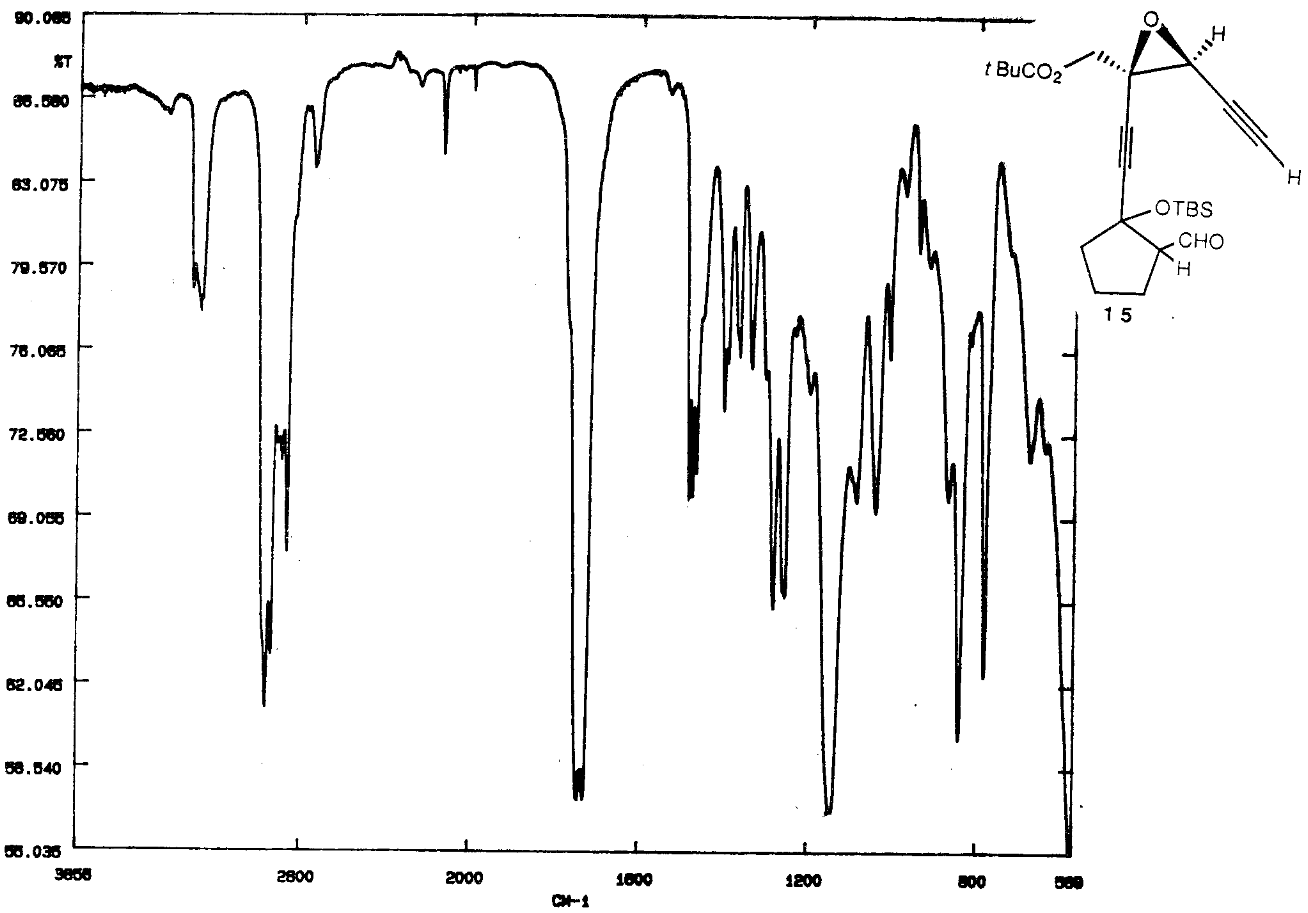

O
H
tBuCO2
H
OTBS
CH(OMe)2
H

1 4

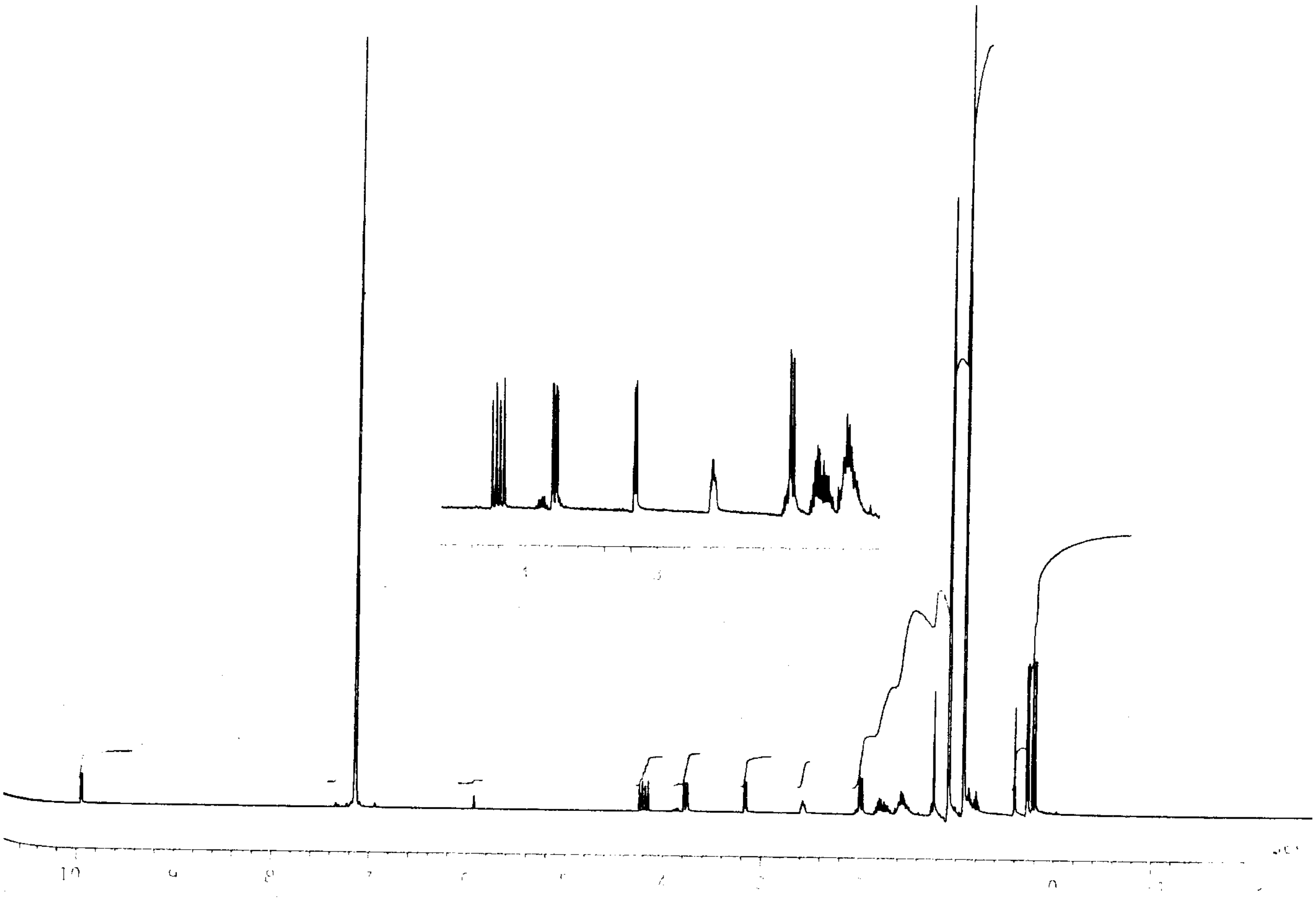

4.50
4.00
3.50
3.00
2.50
2.00
PPM
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
.5
PPM

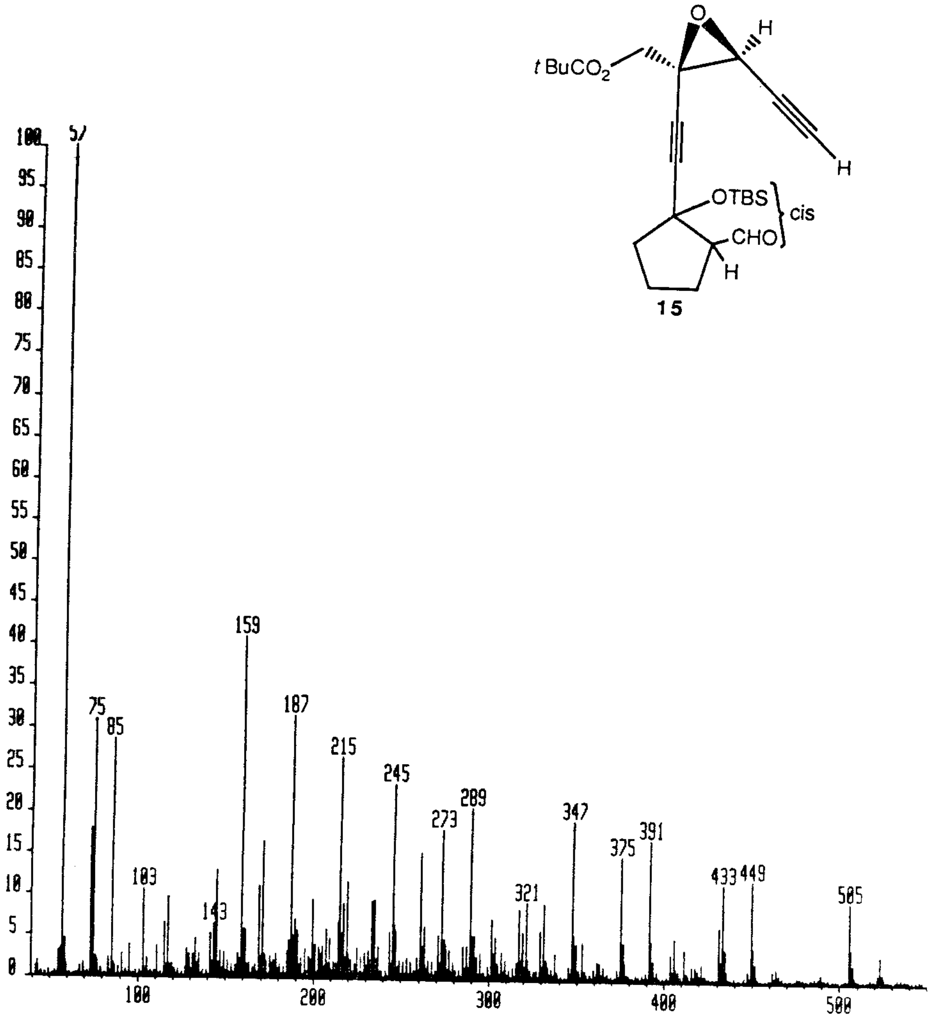

175
387
361
345
315
149
75
447
479
421
465
403
100
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
10
5
0
50
100
150
200
250
300
350
400
450
500
O
H
t BuCO$_2$
H
OTBS
CH(OMe)$_2$
H

14


90.066
%T
86.560
83.075
79.570
76.065
72.560
69.055
65.550
62.045
58.540
55.035
3656
2800
2000
1600
1200
800
569
CM-1
tBuCO$_2$
O
H
H
OTBS
CHO
H

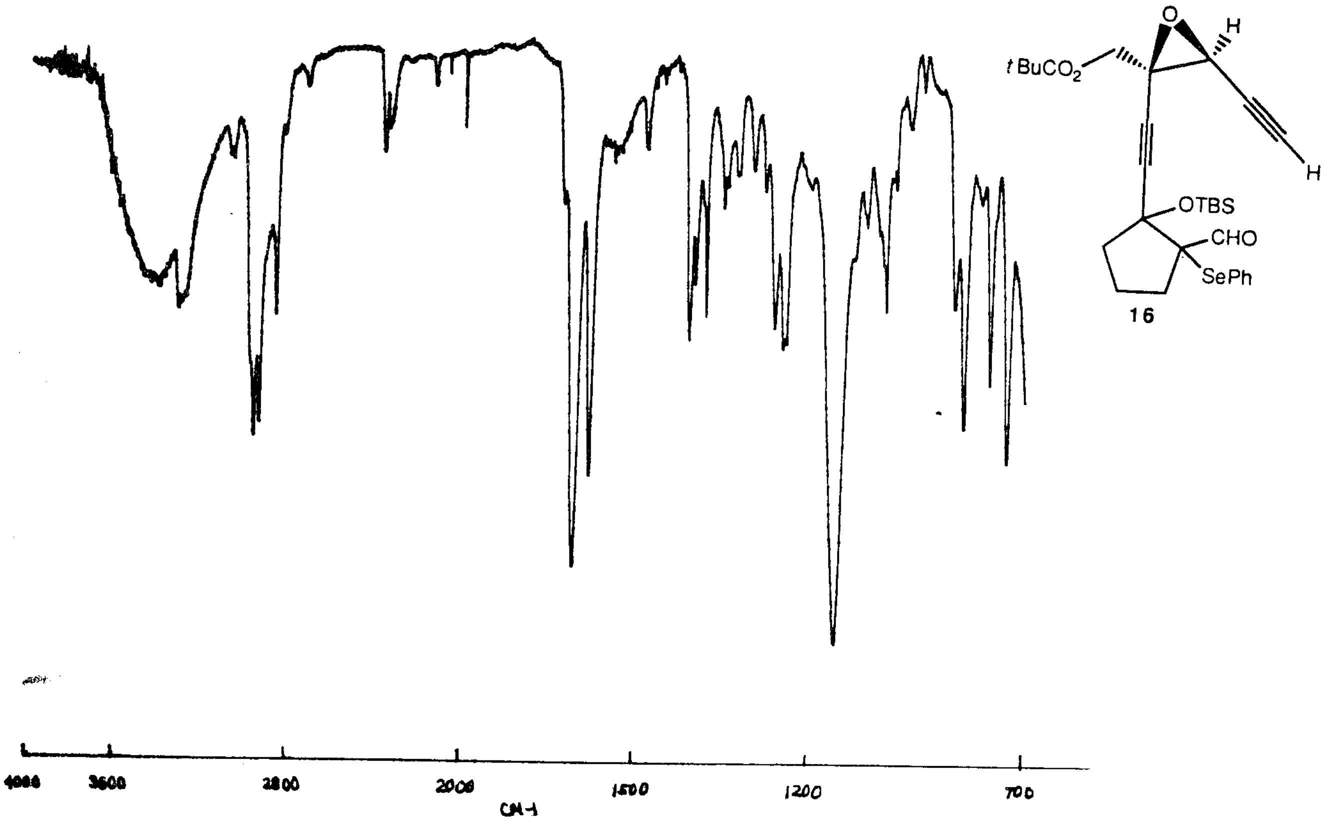
15



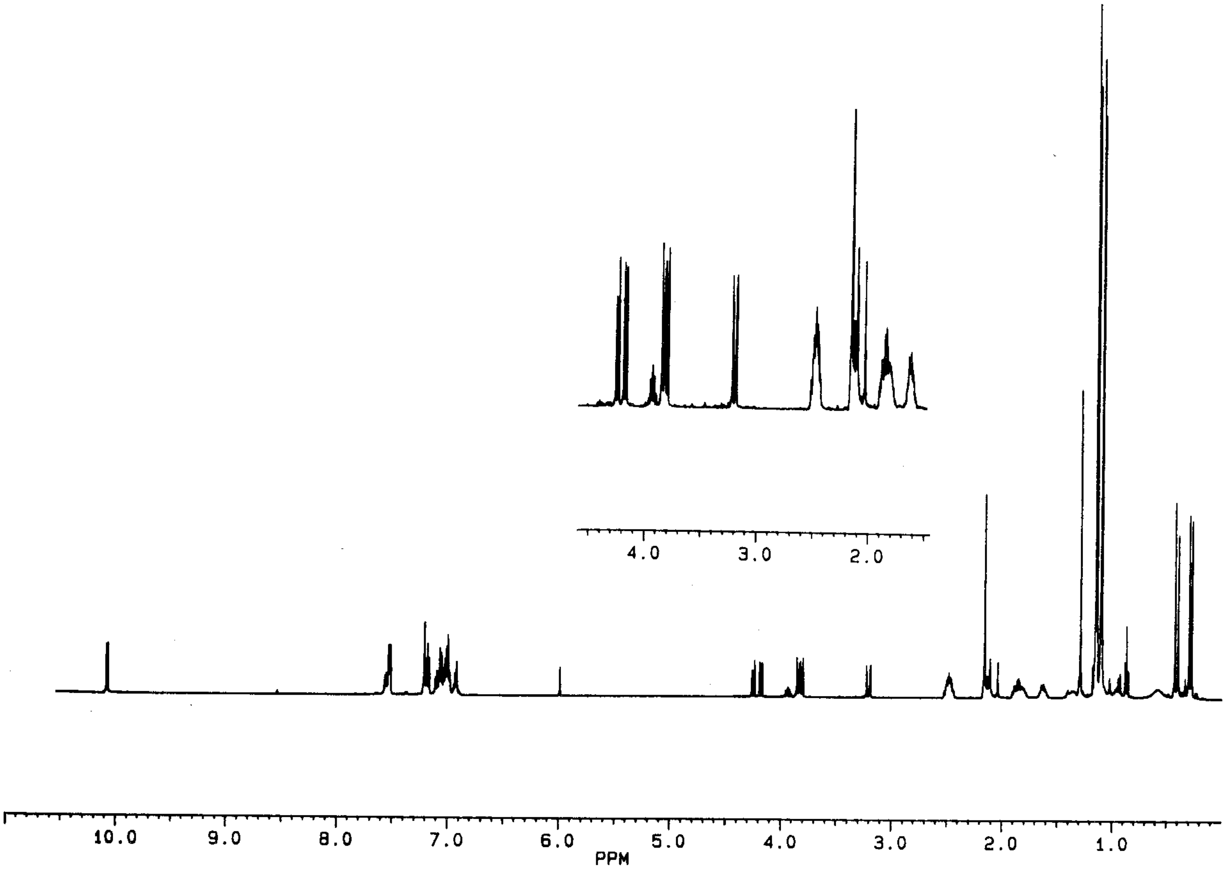

tBuCO2
O
H
H
OTBS
cis
CHO
H

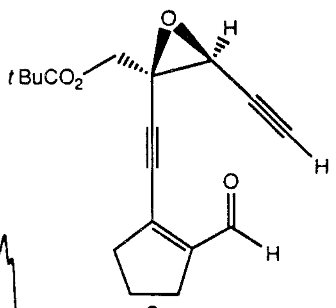
15

100
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
10
5
0
57
75
85
103
143
159
187
215
245
273
289
321
347
375
391
433
449
505
100
200
300
400
500


tBuCO2
O
H
H
OTBS
CHO
SePh
4000
3600
2800
2000
1500
1200
700
CM-1

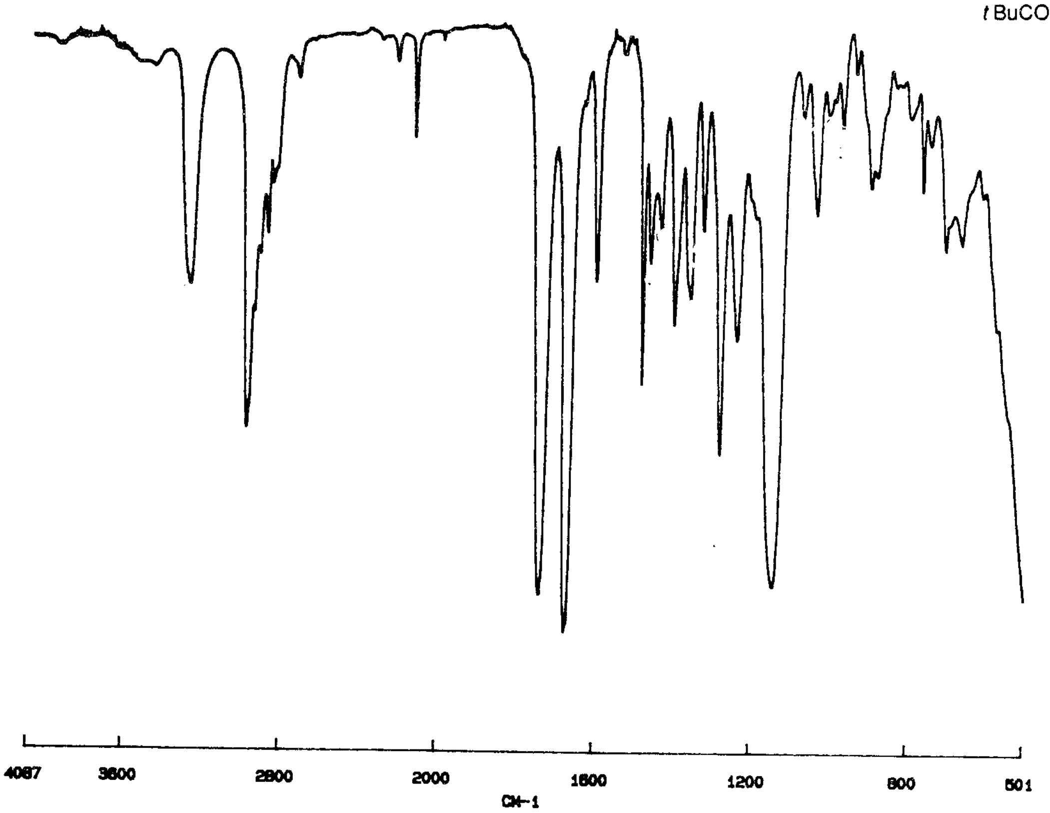
16


4.0
3.0
2.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
PPM

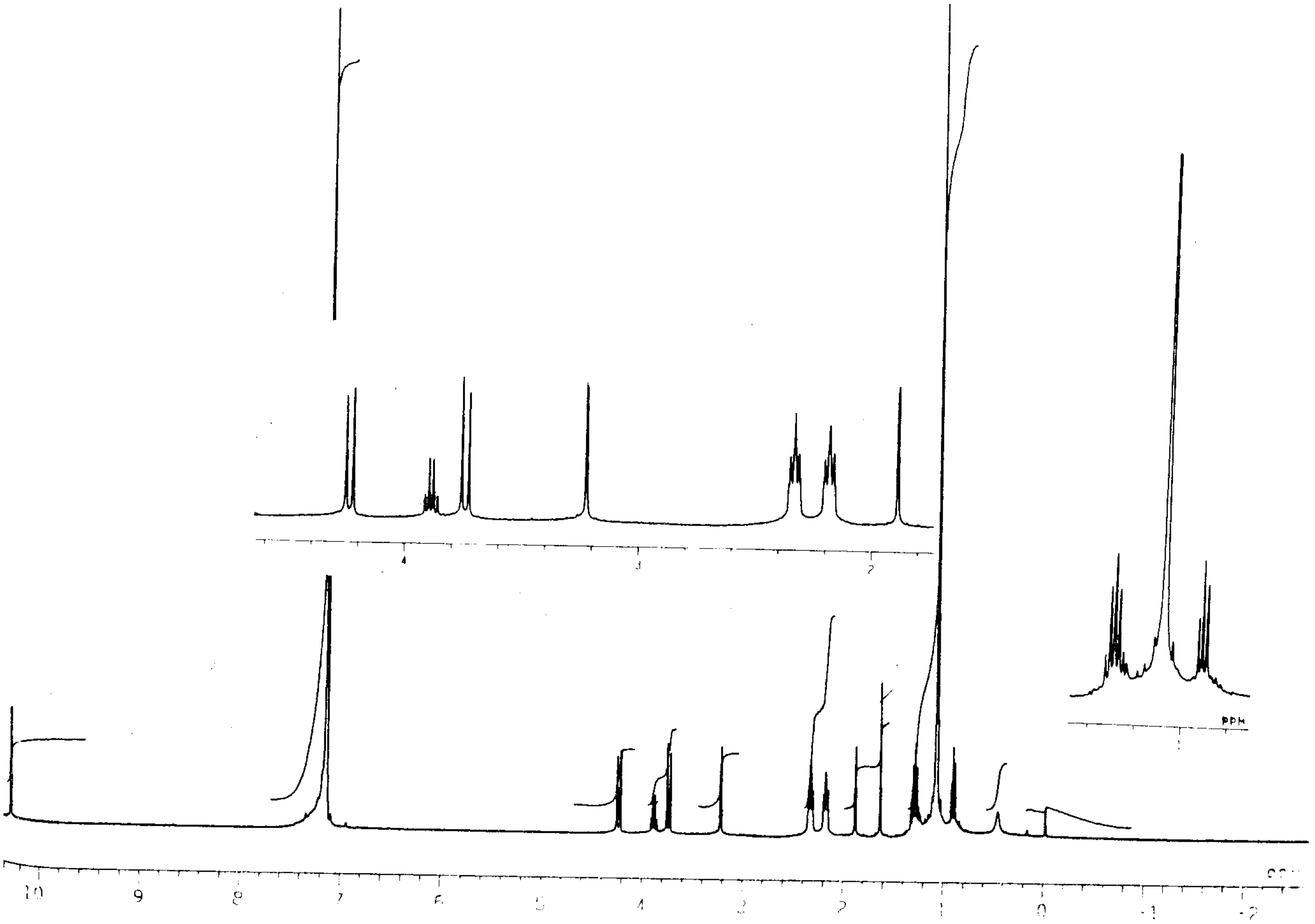


t BuCO$_2$
O
H
H
O
H

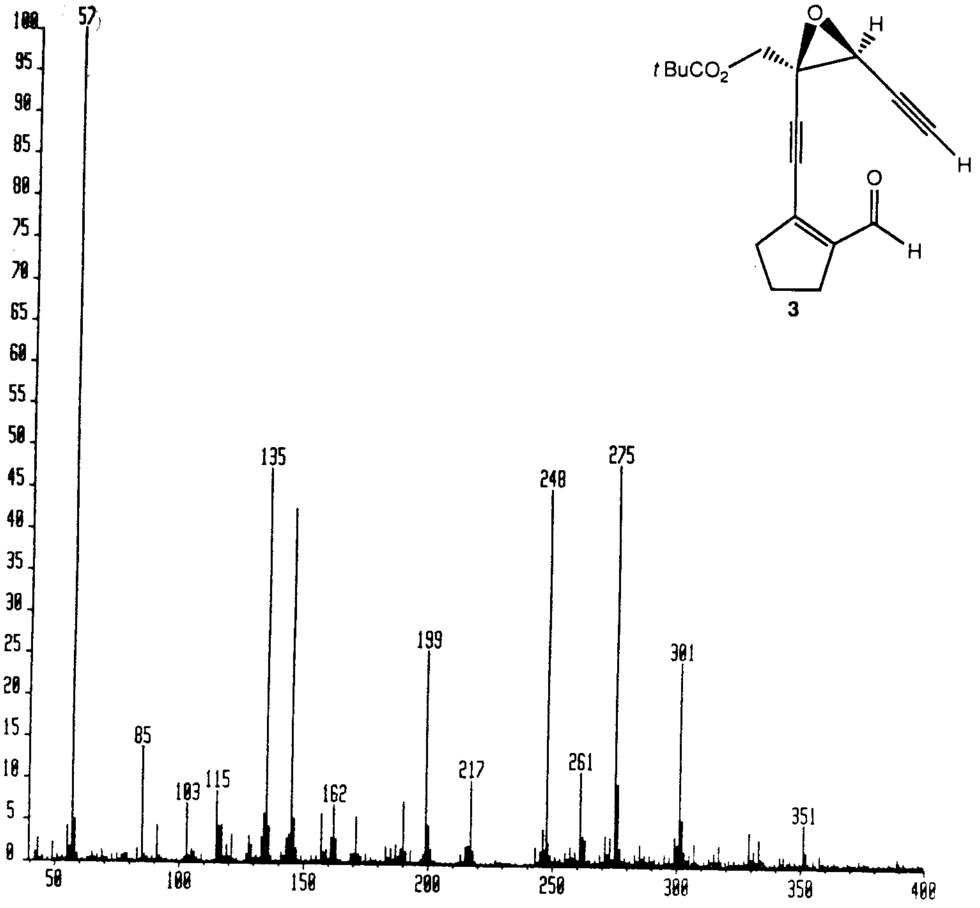
3



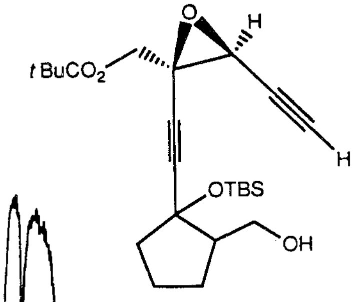
4087
3600
2800
2000
1600
1200
800
501
CM-1



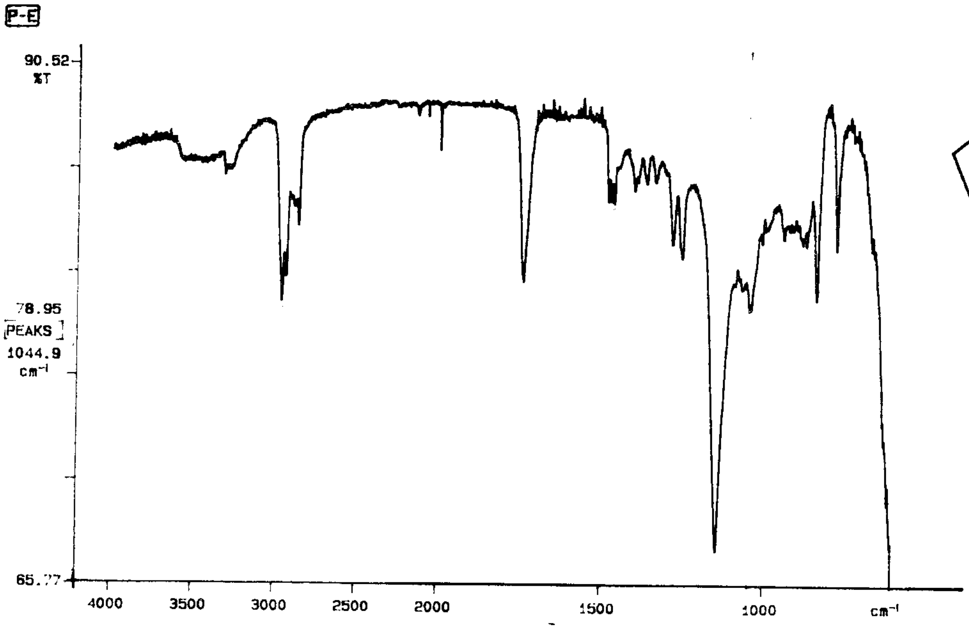
4
3
2
PPM
10
9
8
7
6
5
4
3
2
1
0
-1
-2

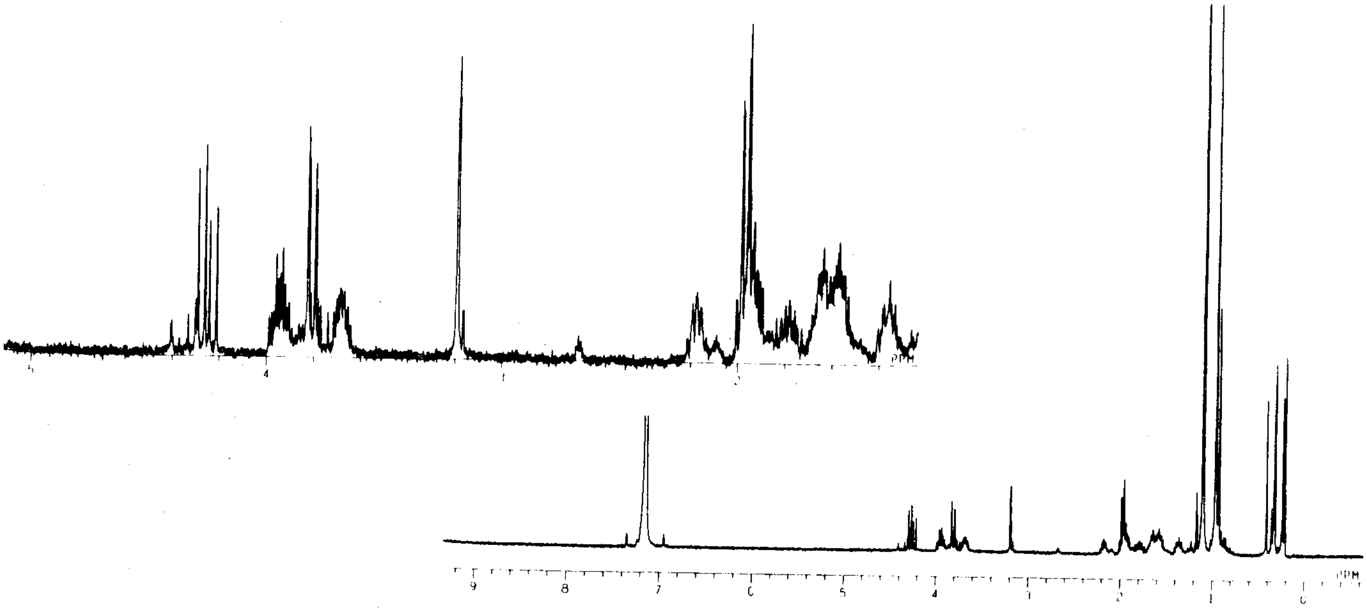

100
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
10
5
0
57
85
103
115
135
162
199
217
248
261
275
301
351
50
100
150
200
250
300
350
400
tBuCO2
O
H
H
O
H

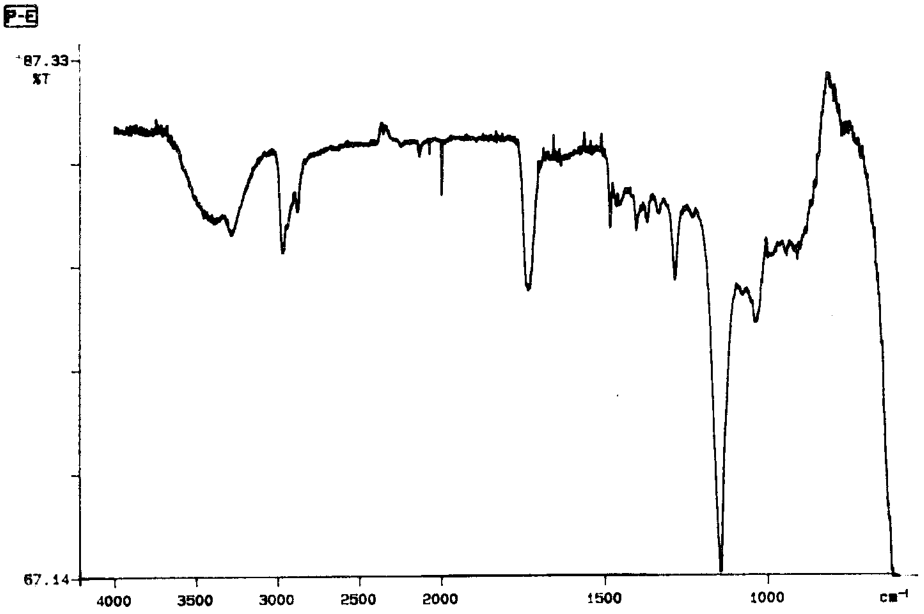
3

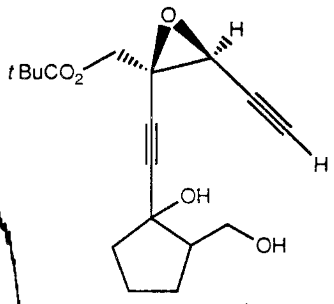

O
H
tBuCO2
H
OTBS
OH

17

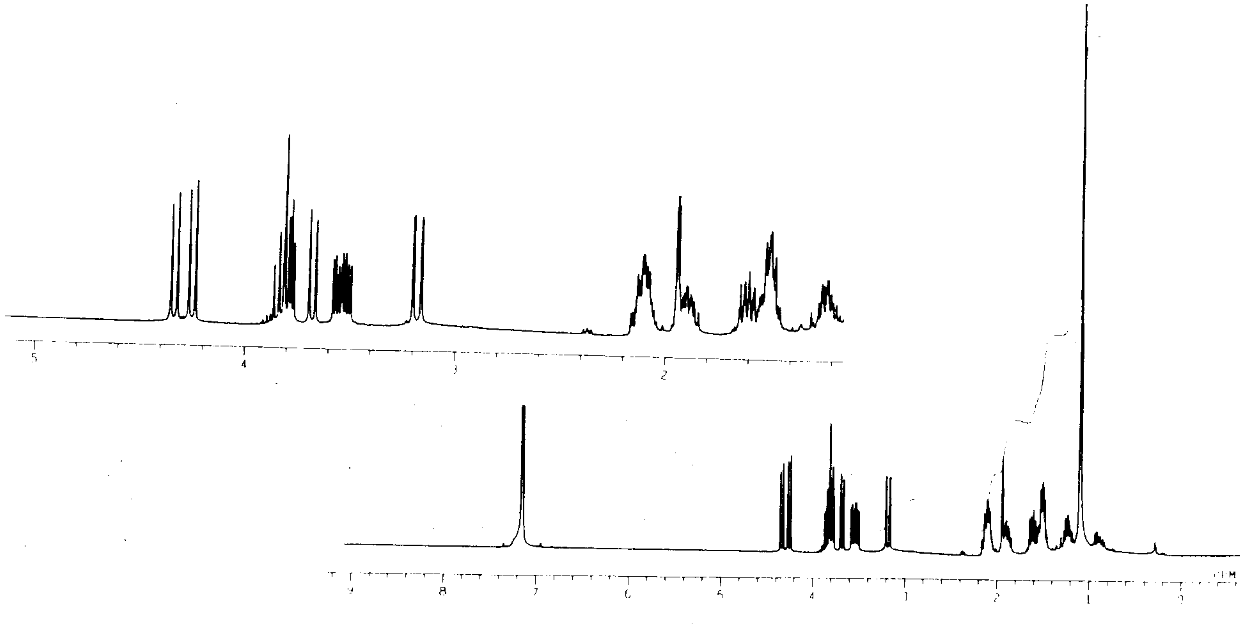

P-E
90.52
%T
78.95
PEAKS
1044.9
cm-1
65.77
4000
3500
3000
2500
2000
1500
1000
cm-1

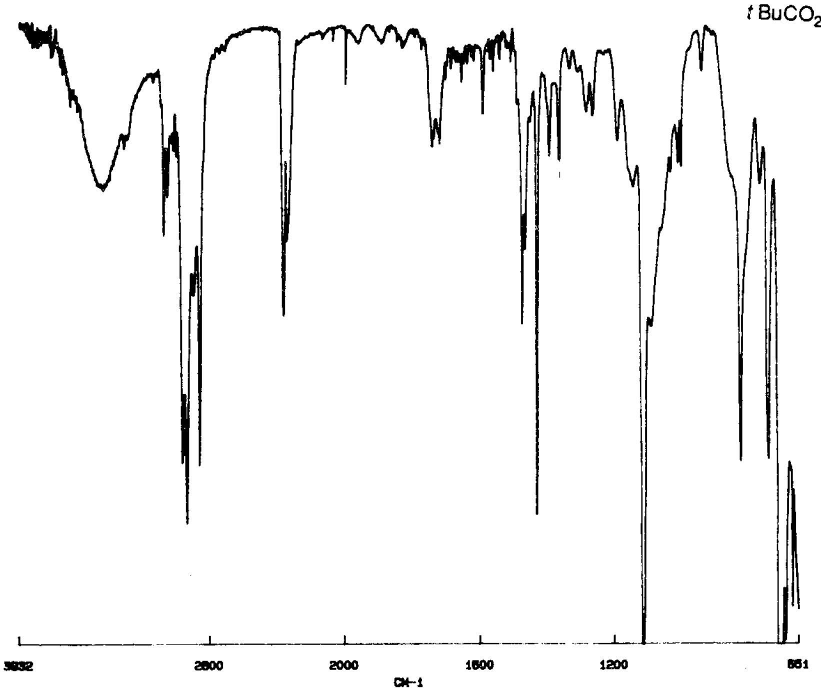

4
3
2
PPM
9
8
7
6
5
4
3
2
1
0
PPM

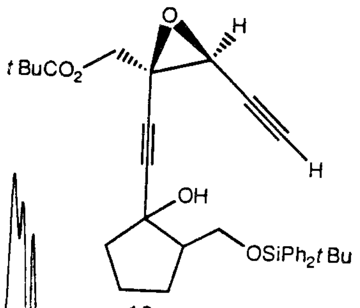

P-E
87.33
%T
67.14
4000
3500
3000
2500
2000
1500
1000
cm⁻¹


tBuCO2
O
H
H
OH
OH

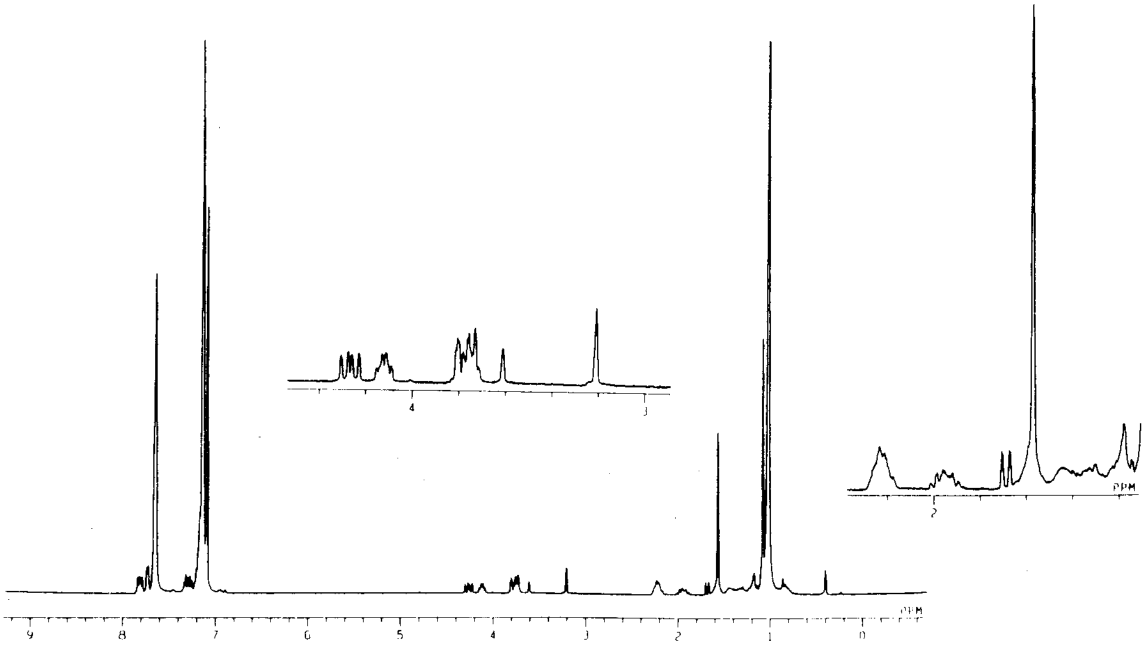
18

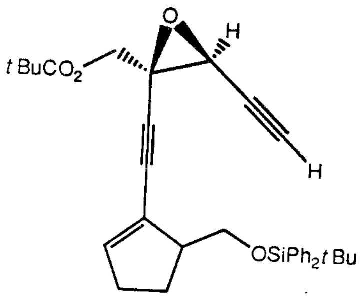

5
4
3
2
9
8
7
6
5
4
3
2
1
0
PPM


3832
2800
2000
1600
1200
851
CM-1

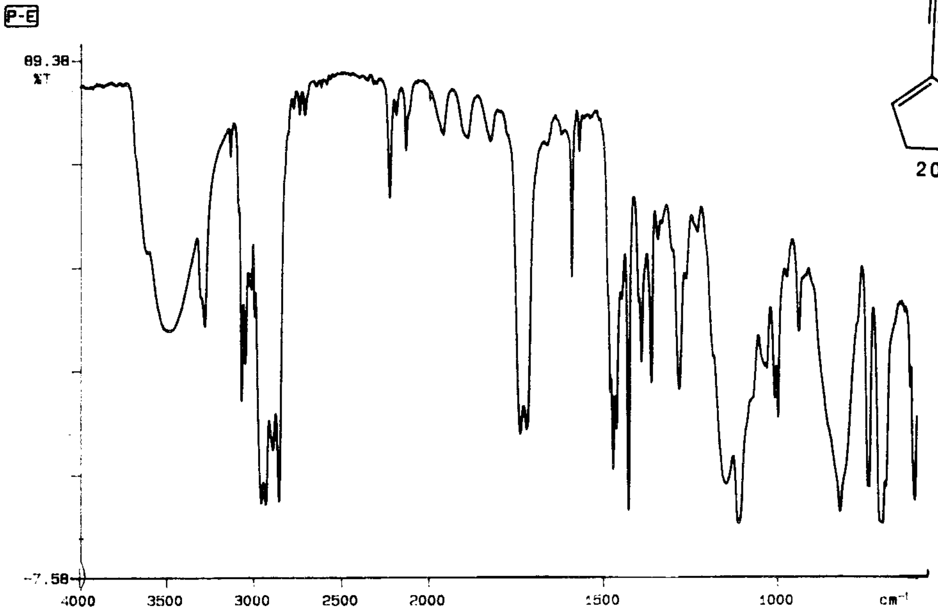

O
H
t BuCO2
H
OH
OSiPh2*t* Bu

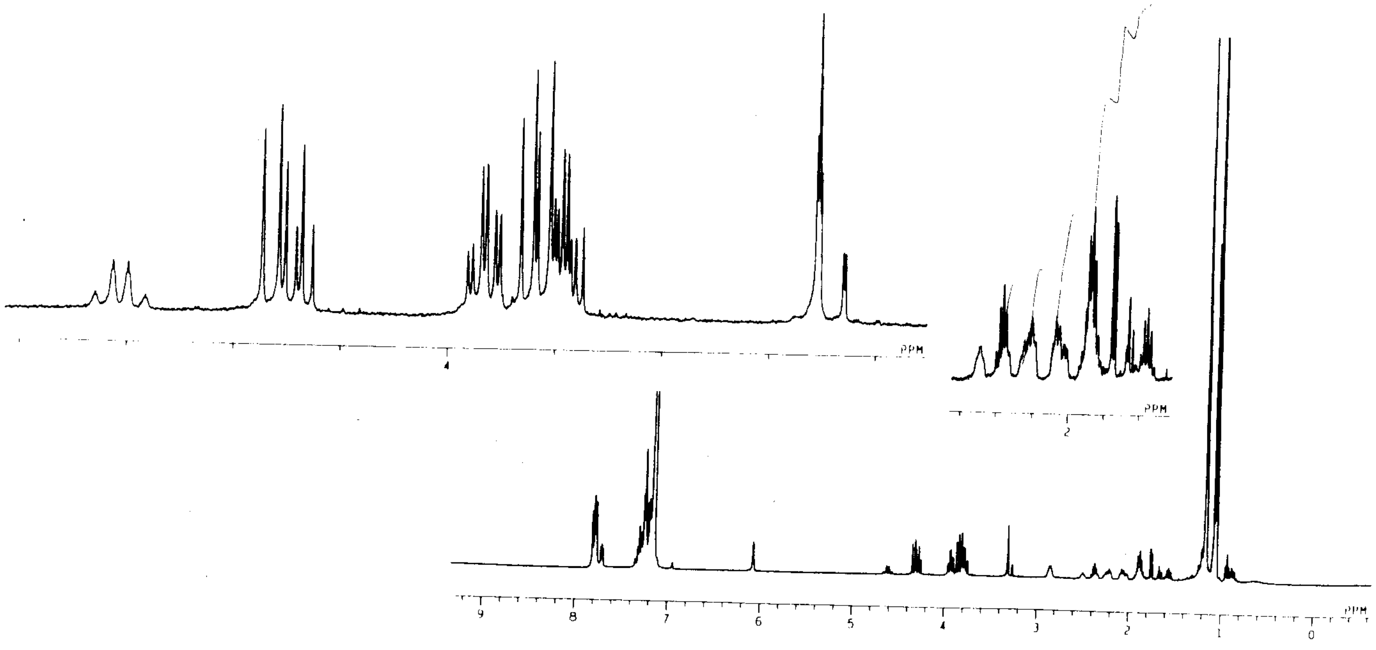
19

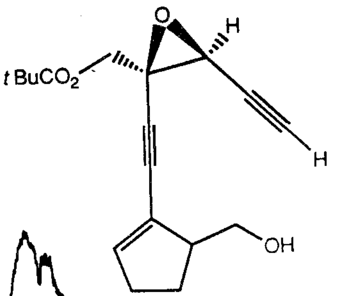

4
3
2
PPM
9
8
7
6
5
4
3
2
1
0
PPM


O
H
tBuCO2
H
OSiPh2tBu

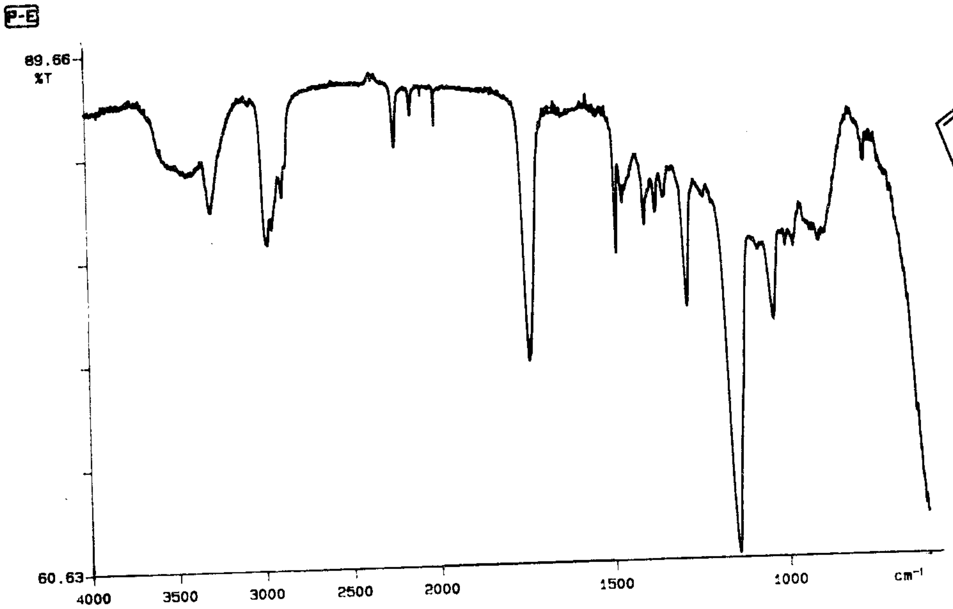
20

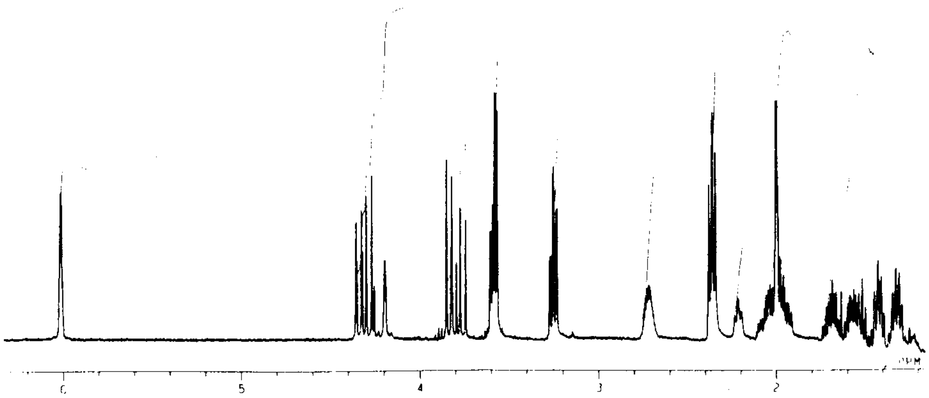

P-E
89.38
%T
-7.58
4000
3500
3000
2500
2000
1500
1000
cm-1

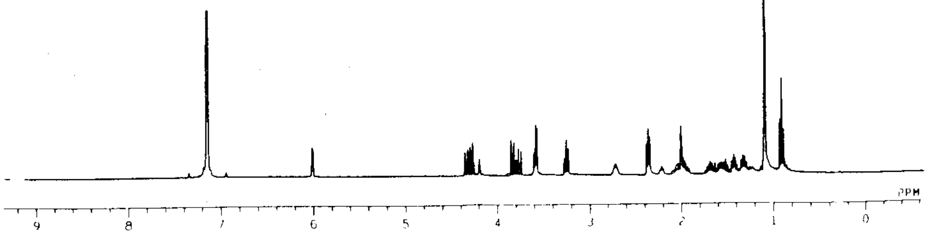

PPM
4
PPM
2
9
8
7
6
5
4
3
2
1
0
PPM

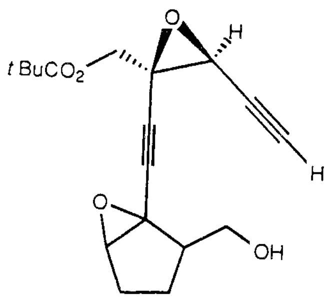

O
H
tBuCO2
H
OH

21

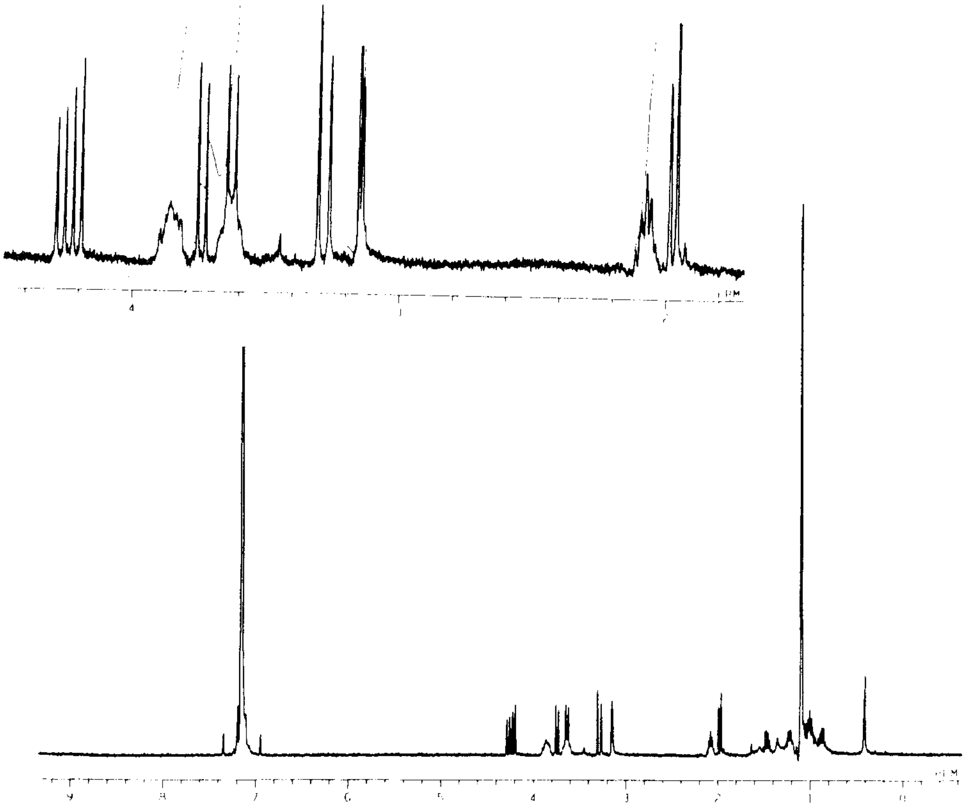

P-E
89.66
%T
60.63
4000
3500
3000
2500
2000
1500
1000
cm-1

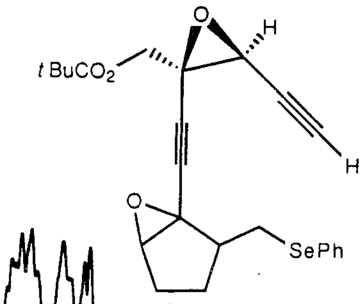

PPM
6
5
4
3
2


PPM
9
8
7
6
5
4
3
2
1
0

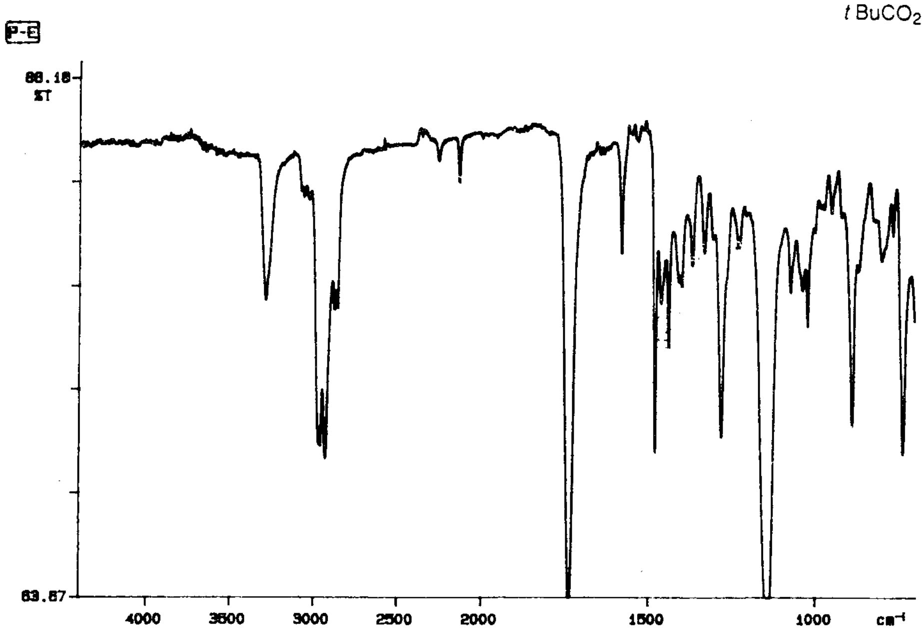


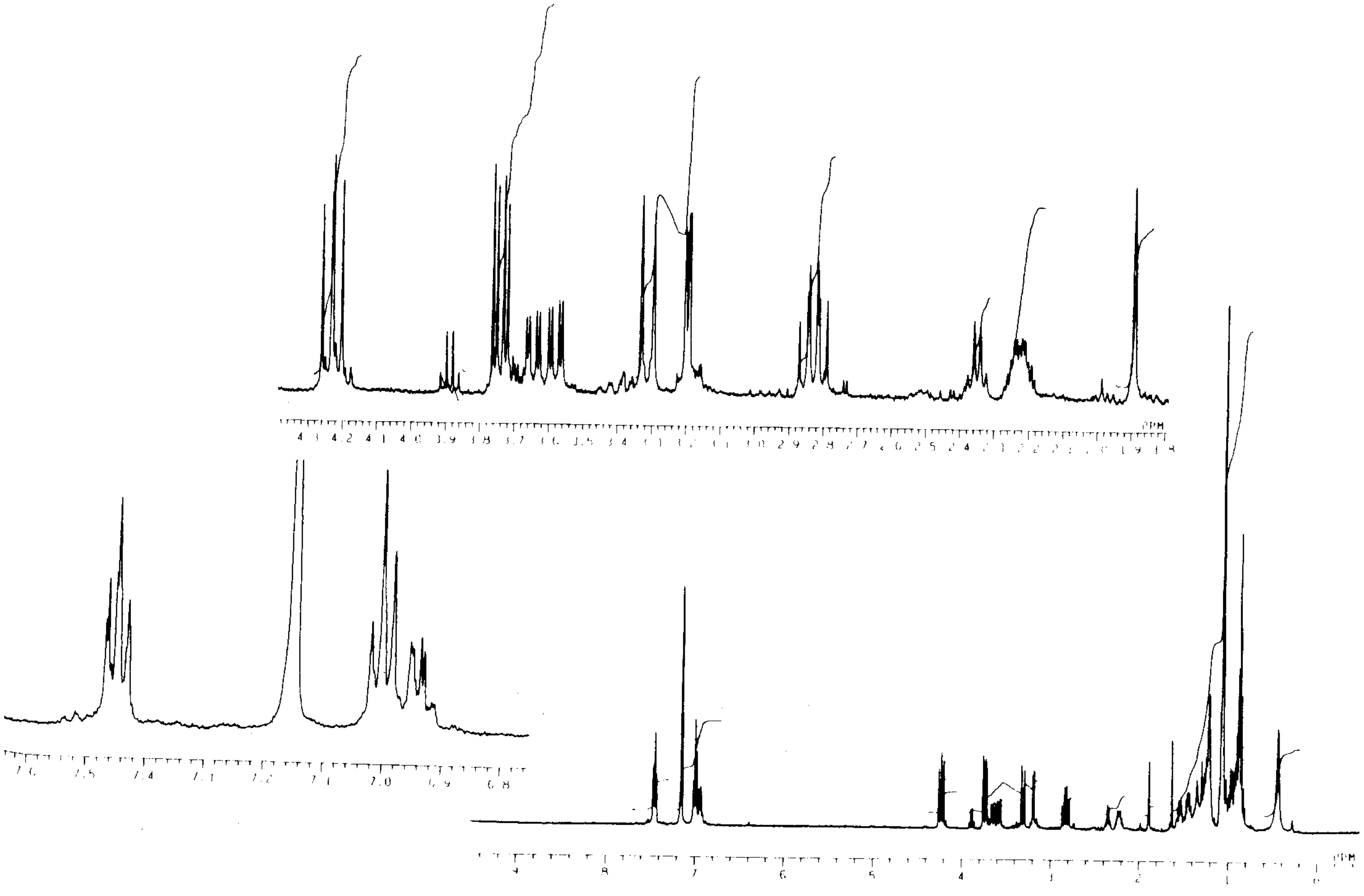
2 2

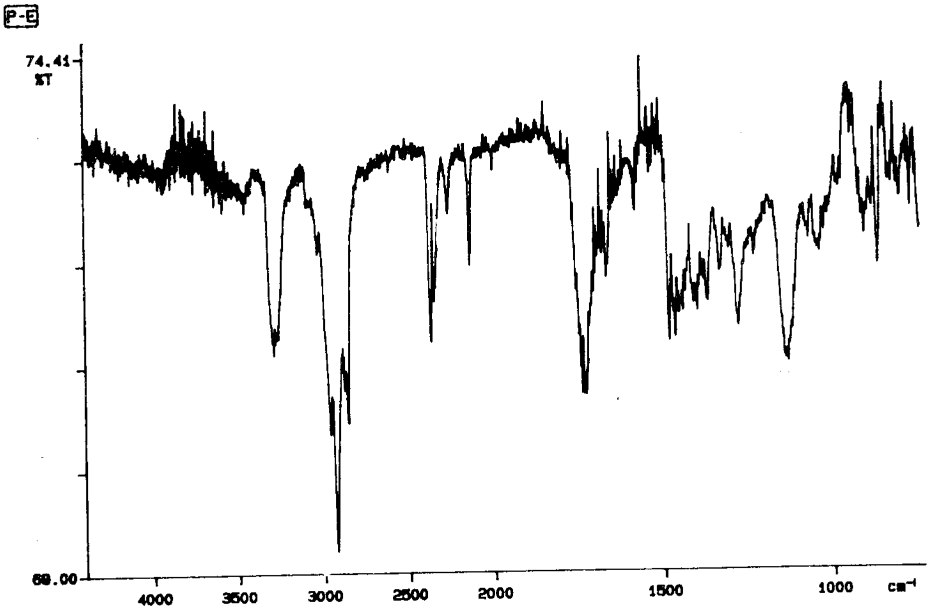


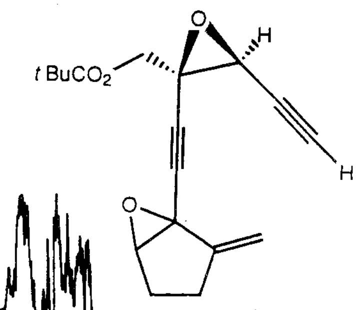

O
H
t BuCO$_2$
H
O
SePh

2 3

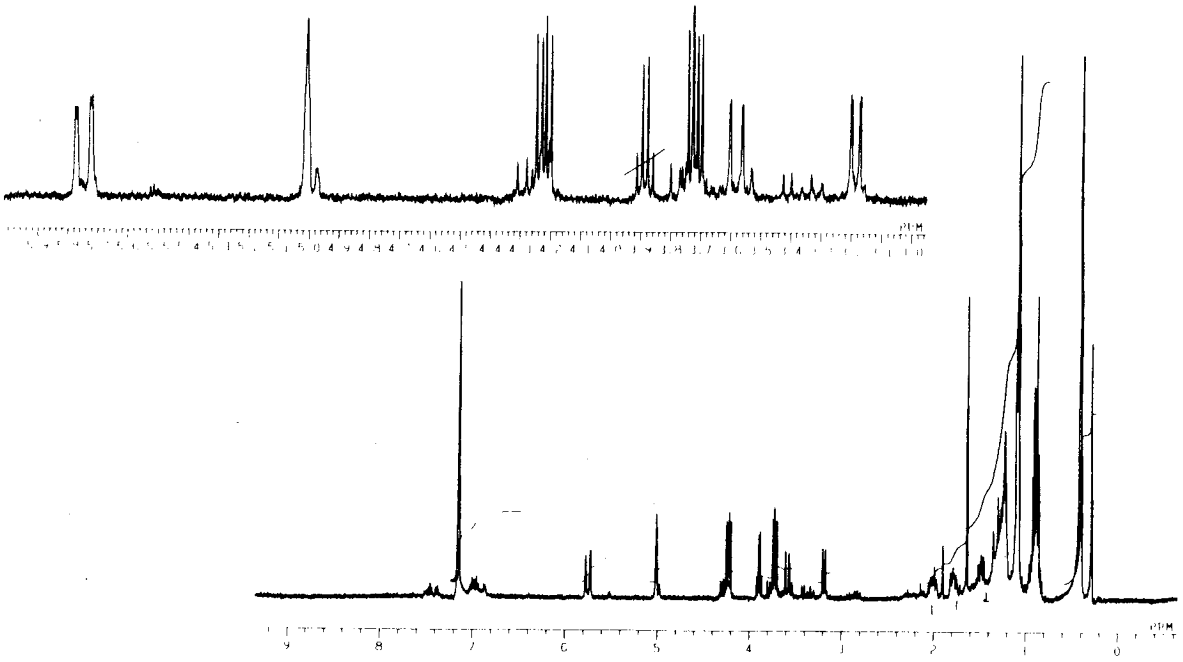

P-E
88.18
%T
83.87
4000
3500
3000
2500
2000
1500
1000
cm⁻¹

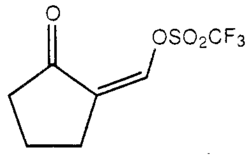

PPM
4.3
4.2
4.1
4.0
3.9
3.8
3.7
3.6
3.5
3.4
2.9
2.8
2.6
2.5
2.4
1.9
1.8
7.6
7.5
7.4
7.1
7.0
6.9
6.8
9
8
7
6
5
4
3
2
1
0
PPM


P-E
74.41
%T
69.00
4000
3500
3000
2500
2000
1500
1000
cm⁻¹

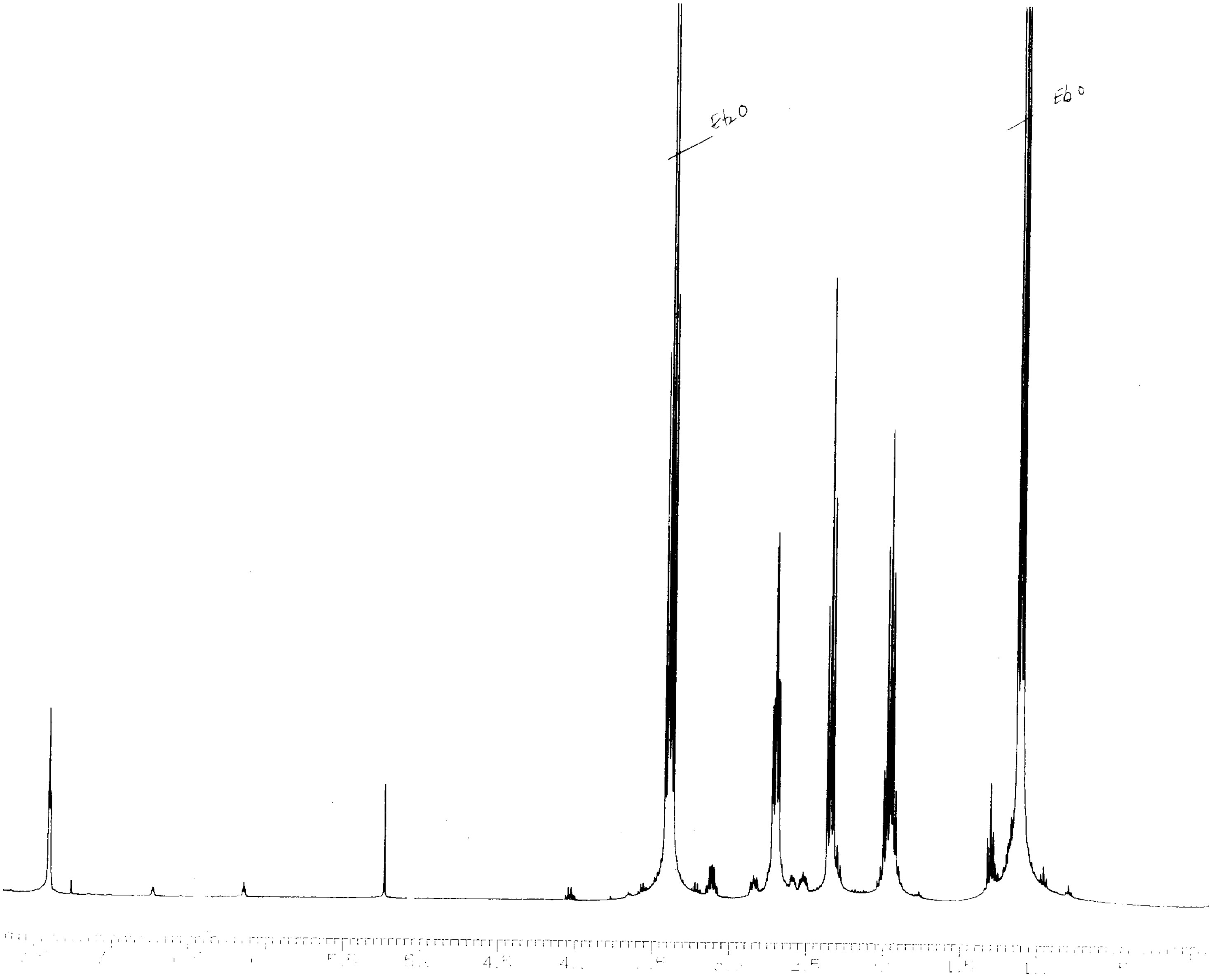

tBuCO2
O
H
H
O

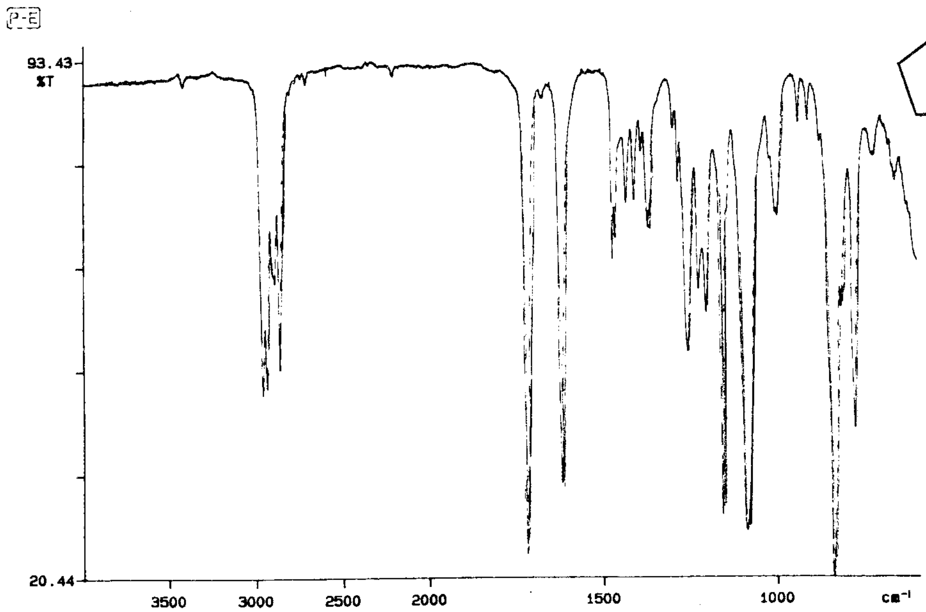
4

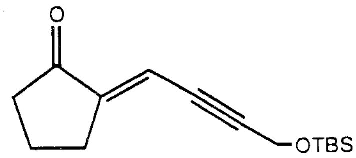

PPM
9
8
7
6
5
4
3
2
1
0



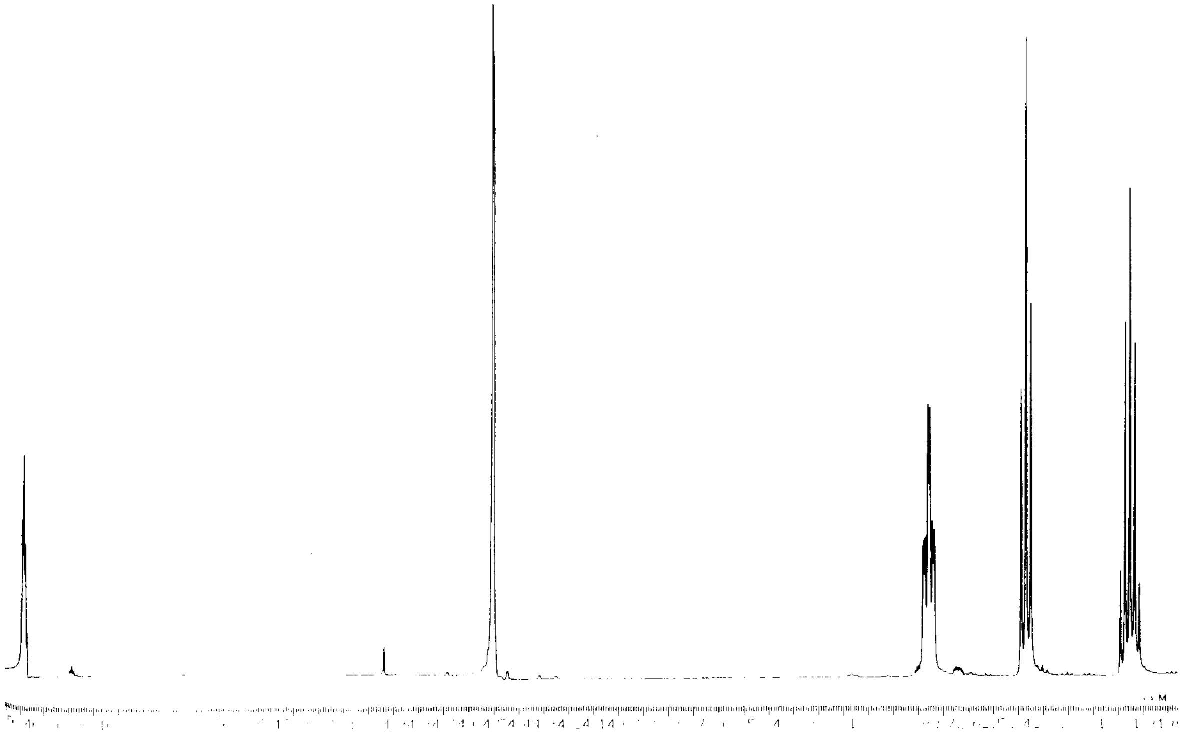
25

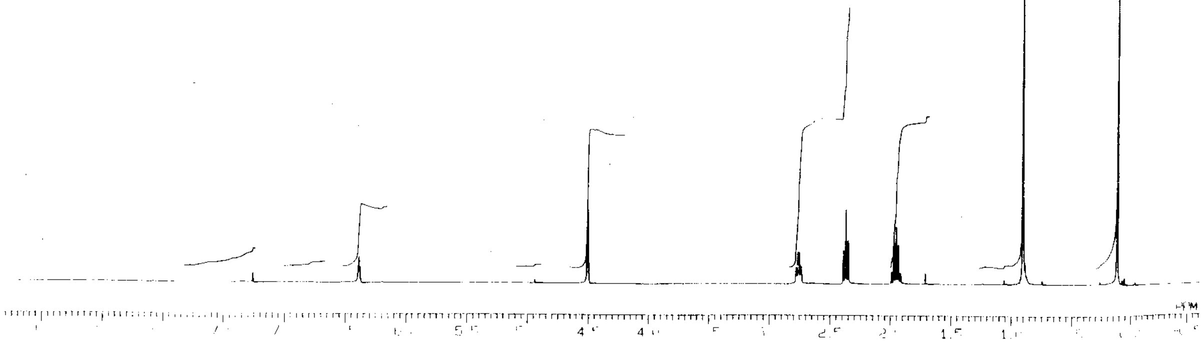



P-E
93.43
%T
20.44
3500
3000
2500
2000
1500
1000
cm⁻¹


O
OTBS

27


PPM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7
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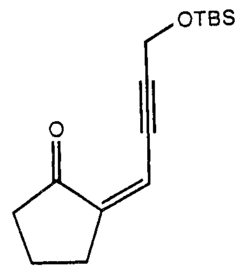
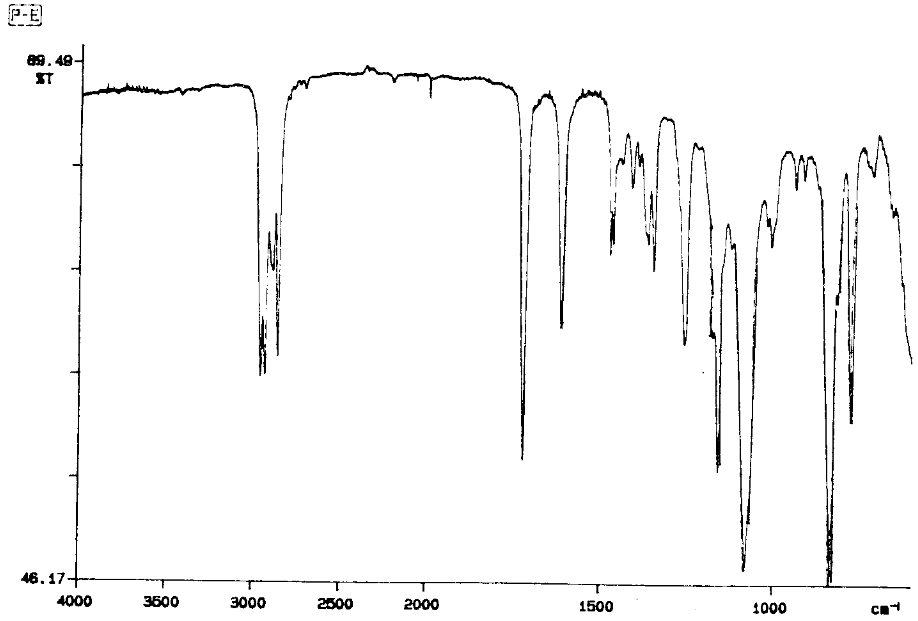
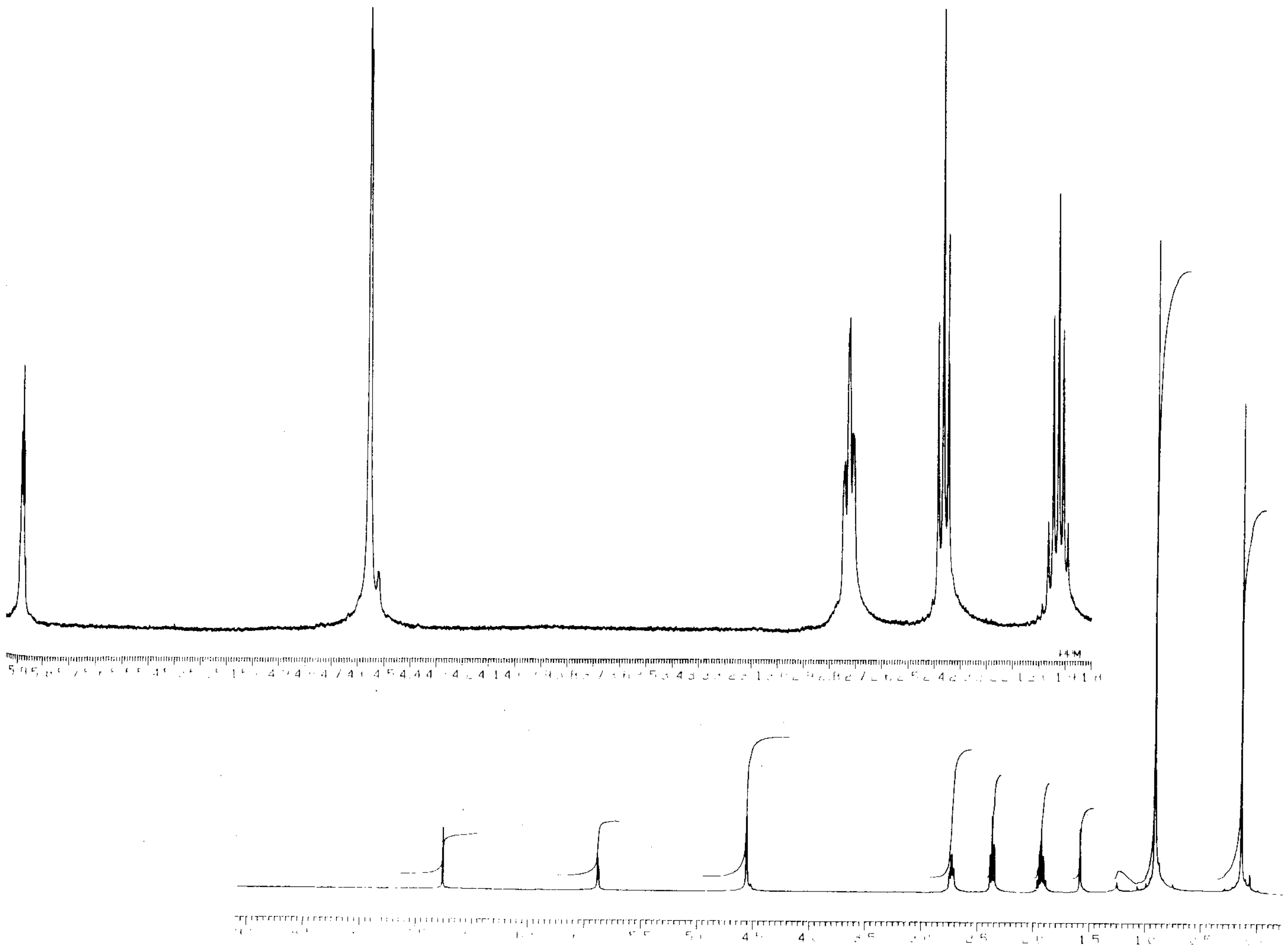
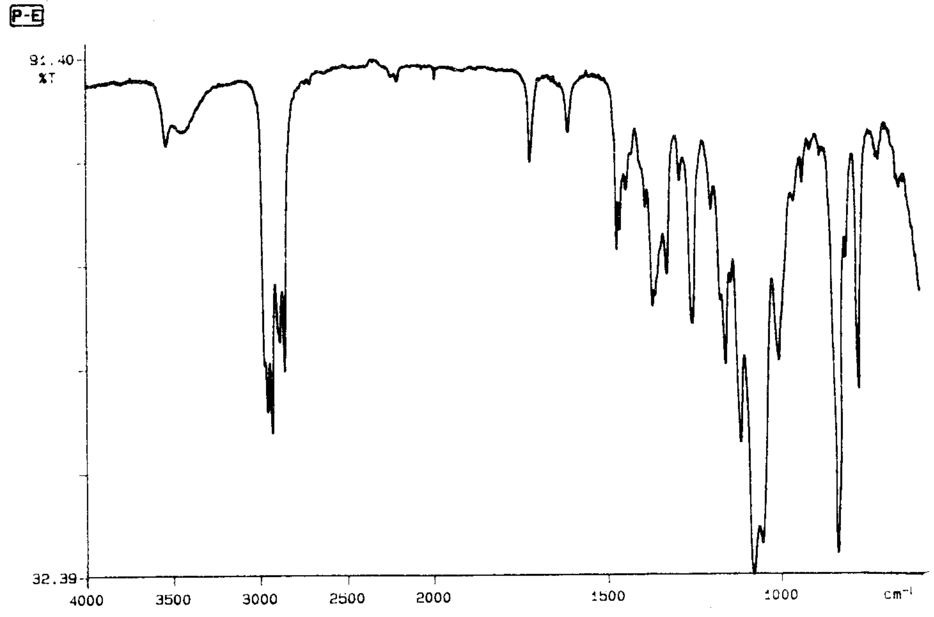
4.0
2.5
2.0
1.5
1.0

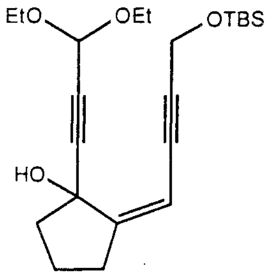


2 8

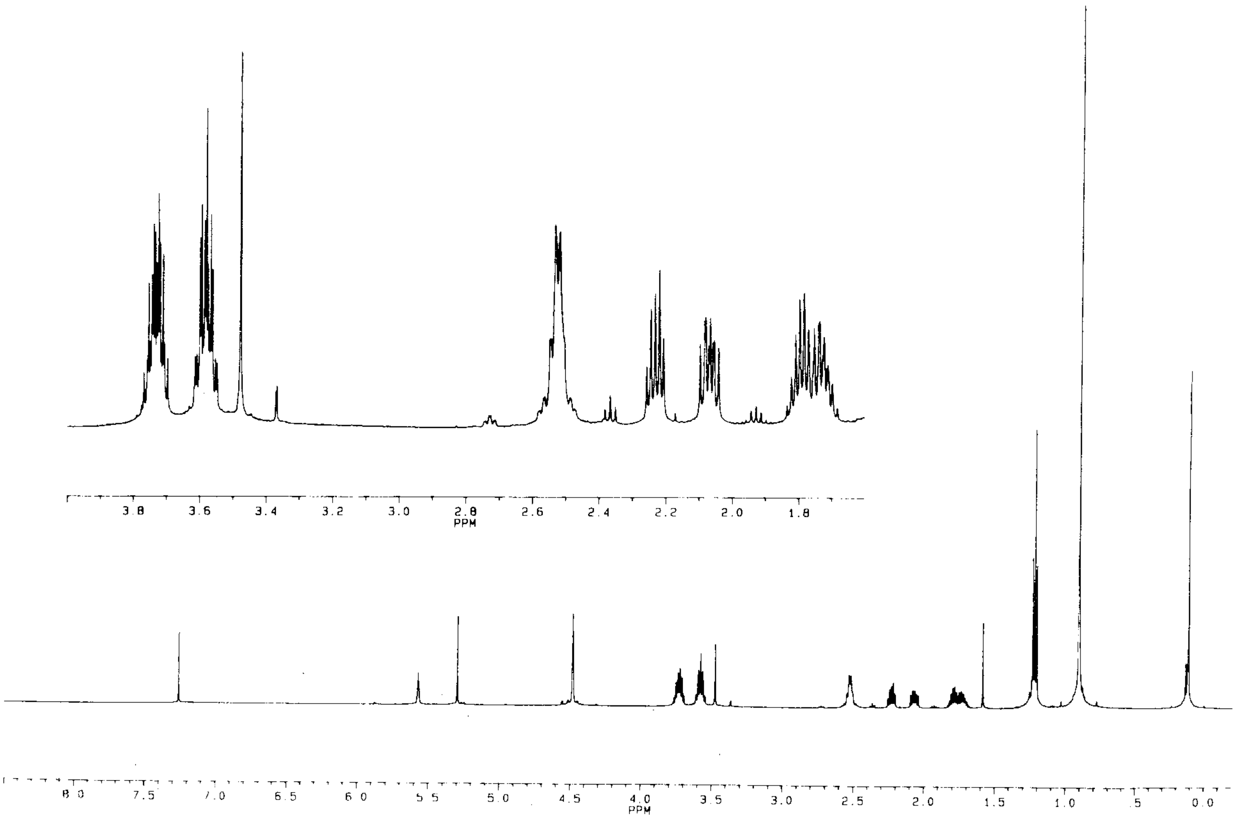


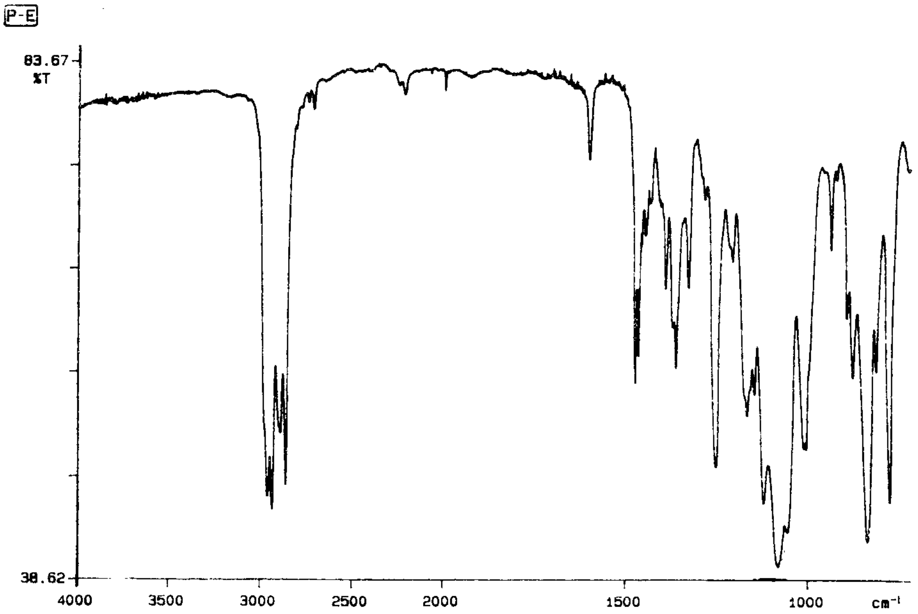


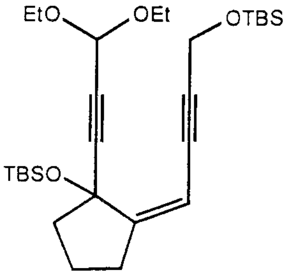

P-E
91.40
%T
32.39
4000
3500
3000
2500
2000
1500
1000
cm⁻¹


EtO
OEt
OTBS
HO

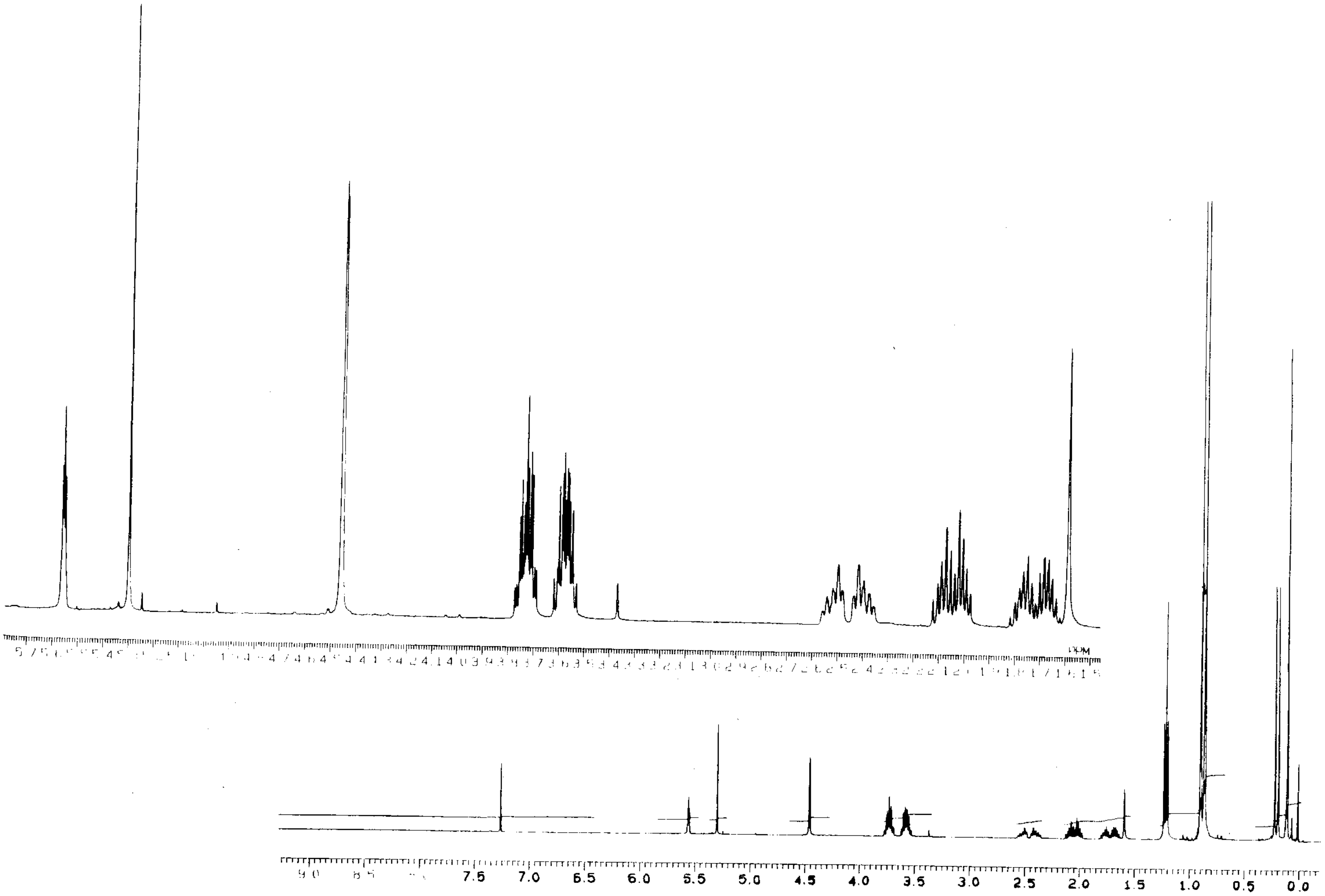
2 9


3.8
3.6
3.4
3.2
3.0
2.8
PPM
2.6
2.4
2.2
2.0
1.8
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
PPM
3.5
3.0
2.5
2.0
1.5
1.0
.5
0.0


P-E
83.67
%T
38.62
4000
3500
3000
2500
2000
1500
1000
cm⁻¹


EtO
OEt
OTBS
TBSO

3 0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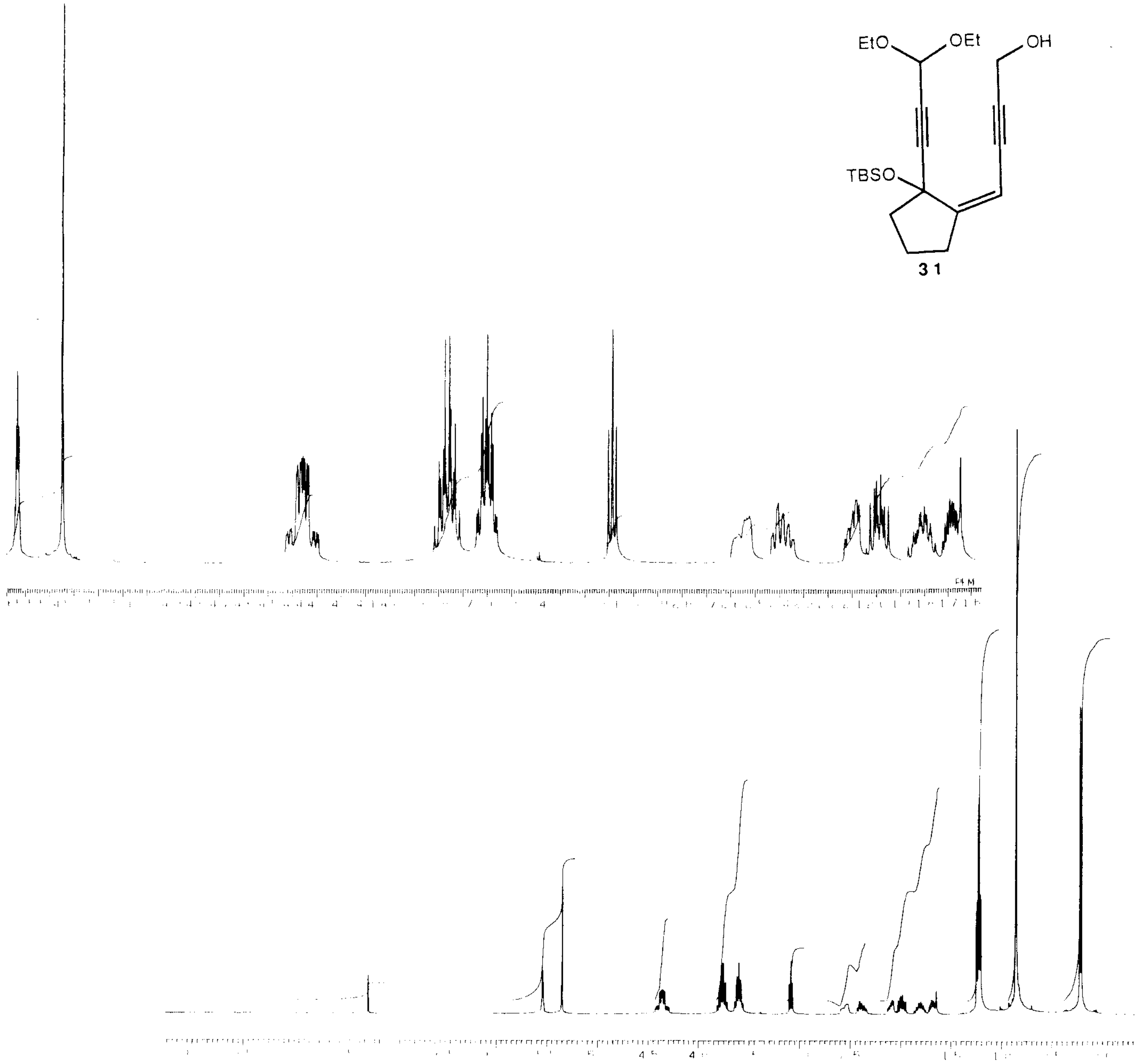
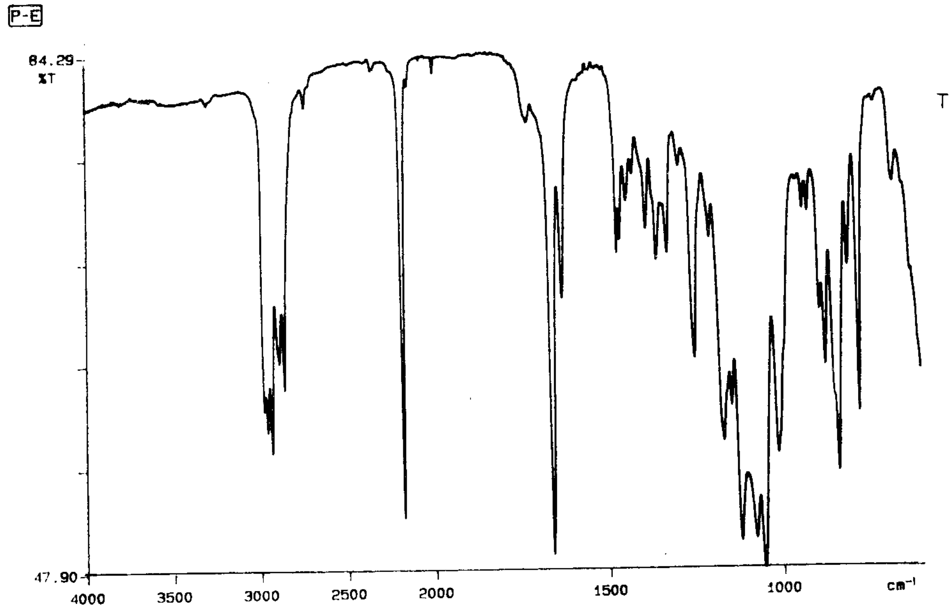
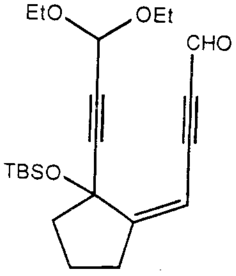
9.0
8.5
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

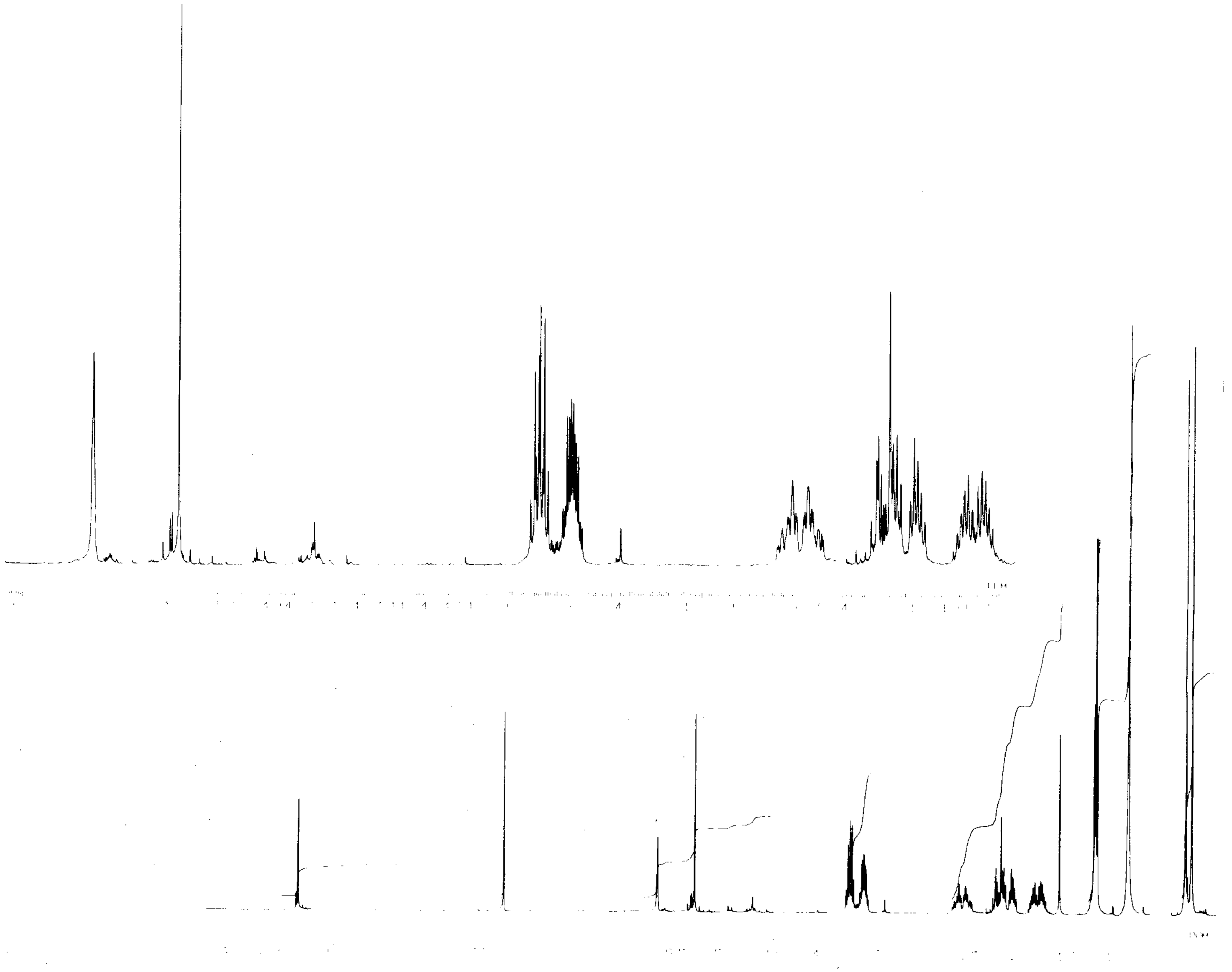


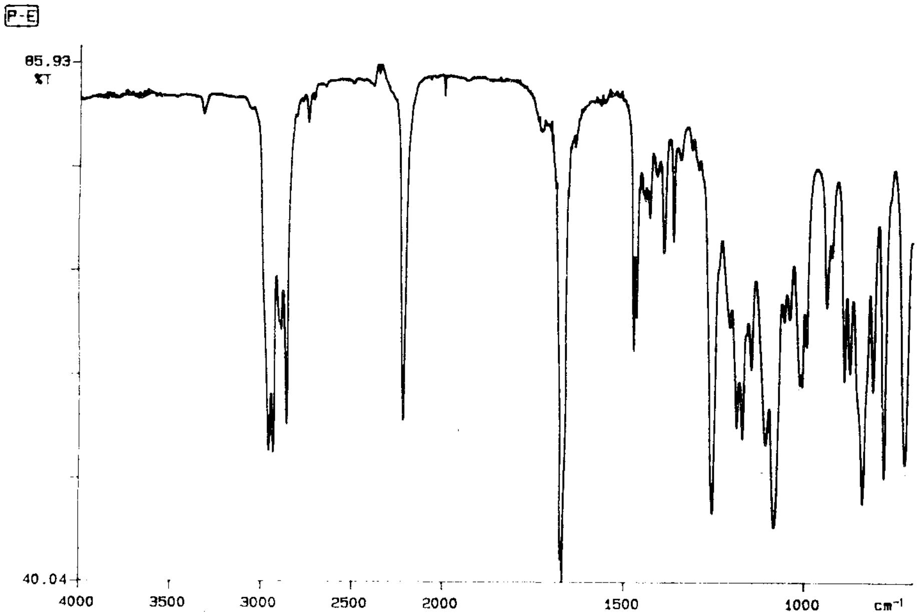
31

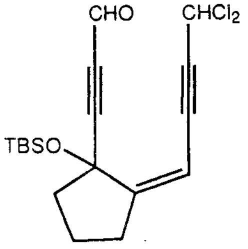

P-E
84.29
%T
47.90
4000
3500
3000
2500
2000
1500
1000
cm⁻¹


EtO
OEt
CHO
TBSO

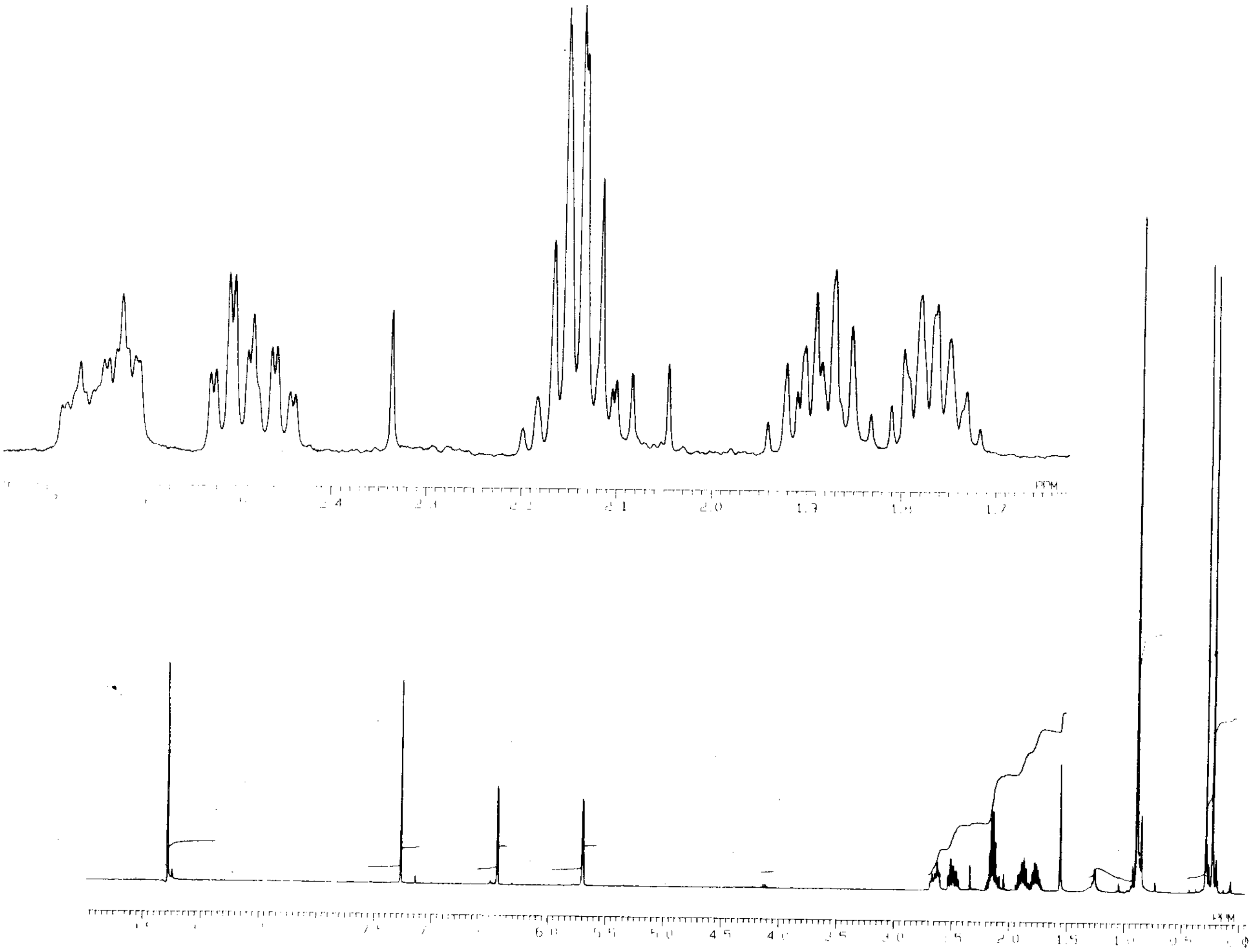
3 2




P-E
85.93
%T
40.04
4000
3500
3000
2500
2000
1500
1000
cm⁻¹


CHO
CHCl2
TBSO

5


2.4
2.3
2.2
2.1
2.0
1.9
1.8
1.7
PPM
7.5
7
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
PPM

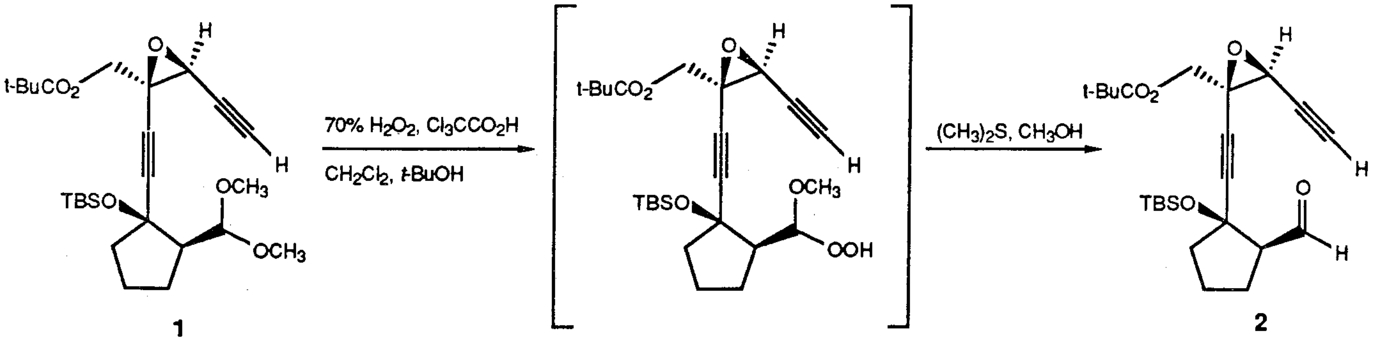
Appendix

MILD CONDITIONS FOR THE REMOVAL OF ACID-LABILE PROTECTIVE GROUPS†

Andrew G. Myers,* Mary Ann M. Fundy and Peter A. Lindstrom, Jr.
Contribution No. 7819 from the Arnold and Mabel Beckman Laboratories of Chemical Synthesis
California Institute of Technology, Pasadena, California 91125

Summary: Hydrogen peroxide-trichloroacetic acid is an effective reagent combination for the mild cleavage of acid-labile protective groups.

In the course of research directed towards a synthesis of neocarzinostatin chromophore and related compounds, we required a means to transform the dimethyl acetal **1** into the aldehyde **2**.[1] An extensive survey of aqueous acid-cosolvent combinations failed to reveal conditions which would effect hydrolysis of the dimethyl acetal group of **1** without competitive opening of the epoxide ring. The ability of hydrogen peroxide to enter into acetal exchange reactions has long been recognized, though reported reaction conditions (acetal and hydrogen peroxide, neat, 70 °C, 15 h)[2] have perhaps dissuaded wider exploration of the method. We find that **1** is cleanly transformed into the mixed hydroperoxy methyl acetal (stereochemistry not determined) upon treatment with 70% hydrogen peroxide (caution--see below)-trichloroacetic acid in 1:1 *t*-butyl alcohol-dichloromethane at 0-23 °C. This hydroperoxide was stable to isolation and could be purified by flash column chromatography, but for convenience and safety was typically directly reduced by treatment with methanolic dimethyl sulfide solution,[3] providing the aldehyde **2** in 80% (overall) yield after chromatographic purification. The presence of water in the



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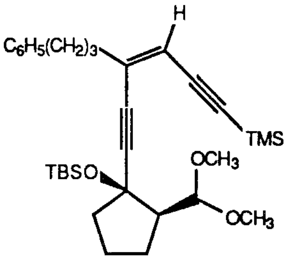
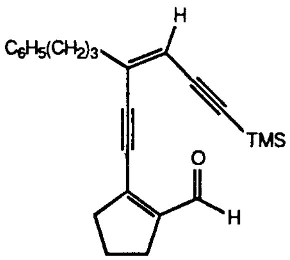
† Dedicated to the memory of our friend and colleague, Peter A. Lindstrom, Jr.

reaction mixture is markedly deleterious; use of 90% hydrogen peroxide leads to faster reaction with a slight increase in yield whereas reaction with 30% hydrogen peroxide is prohibitively slow and epoxide-ring-opening is observed. The substantial hazard in working with the former reagent and its removal from the commercial market have led us to develop our procedure around the commercially available (FMC), and safer, 70% solution. A particular advantage of this sequence are the mild conditions of final deprotection;[3] neither aldehyde epimerization nor elimination of the β-silyloxy group are observed. By contrast, subjection of the acetal **3** to acidic hydrolysis conditions (1 M *p*-toluenesulfonic acid, 3:1 THF:H_2O, 23 °C, 3 days) produces competitively the α,β-unsaturated aldehyde **4**. It should be noted that this alternative preparation of hydroperoxy alkyl acetals provides access to a number of useful oxidative transformations as well.[4]

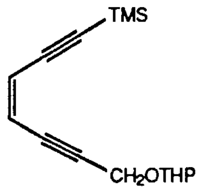
We have also found that the tetrahydropyranyl group of **5** (9 h, 80%)[1] and the trityl group of **6** (24 h, 85%)[5] are smoothly removed under similar reaction conditions, suggesting potential for wider application of the method in the removal of acid-labile protective groups and indicating that complications arising from free-radical or peracid impurities are, at best, minor.



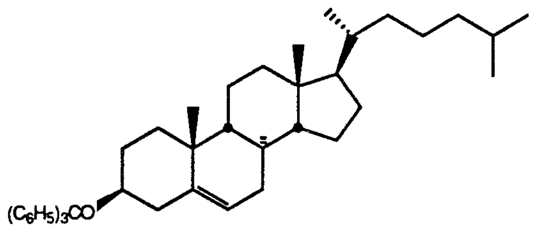
3



4



5



6

Extreme caution should be exercised in handling mixtures of organic materials and high-strength hydrogen peroxide.[6] Explosions have resulted upon distillation of hydrogen-peroxide-treated tetrahydropyranyl ethers.[7] For this reason we have made it a practice not to concentrate organic solutions which have been in contact with hydrogen peroxide without first treating with dimethyl sulfide-methanol and then only after obtaining a negative indication with EM Quant® Peroxide Test Paper.[7] All manipulations with high-strength hydrogen peroxide solution should be carried out behind a good safety shield. Employing these and other safety precautions, described in greater detail in the experimental procedure which follows, we have never experienced a mishap in the laboratory.

The superior nucleophilicity of hydrogen peroxide (relative to water)[8] is evident in the smooth transacetalization of **1** under conditions too weakly acidic for reaction with water. A more subtle distinction is the difference in relative rates of attack exhibited by these two nucleophiles towards the epoxide and acetal groups of **1**.[9] With care in execution, we feel that the procedure described herein provides a useful addition to existing methods for the removal of acid-labile protective groups.[10]

Experimental

All manipulations with hydrogen peroxide and peroxide-treated solutions are carried out behind a sturdy blast shield.

A 50-mL round-bottom flask was charged with dimethyl acetal **1** (327 mg, 0.683 mmol), anhydrous *t*-butyl alcohol-dichloromethane solution (1:1, 15 mL) and a teflon-coated magnetic stir bar which had been carefully cleaned to remove adhering metal contaminants. The mixture was cooled in an ice bath and 70% hydrogen peroxide solution (FMC, 2.80 mL) was administered slowly from a 5-mL glass syringe fitted with a polyethylene needle (gloves should be worn as hydrogen peroxide causes severe chemical burns). A solution of trichloroacetic acid in anhydrous dichloromethane (3 M, 0.36 mL, 1.6 equiv) was added and the ice bath was removed. After stirring at 23 °C for 35 h, the clear, homogeneous solution was carefully poured into ice-cold brine (100 mL). The organic layer was brought to 60 mL volume by the addition of 1:1 ethyl acetate:hexanes and the layers were separated (this and all subsequent aqueous layers were treated with 2 M aqueous sodium thiosulfate solution prior to disposal). The organic layer was washed again with ice-cold brine (100 mL), then slowly added to an ice-cold mixture of 1 M aqueous sodium bicarbonate solution and 2 M aqueous sodium thiosulfate solution (1:1, 100 mL). After separation, the organic layer was washed with saturated aqueous sodium bicarbonate solution (50 mL) and then treated with methanolic dimethyl sulfide solution (5:1 methanol:dimethyl sulfide, 24 mL). The progress of hydroperoxide reduction was conveniently monitored by thin-layer chromatography (R_f values 0.45, 0.35 and 0.48, respectively, for **1**, the hydroperoxy methyl acetal and **2**, 20% ethyl acetate-hexanes) and was judged complete after 45 min. Peroxide analysis at this point with EM Quant® Peroxide Test Paper was negative. The solution was concentrated and the product purified by flash column chromatography (87:10:3 hexanes:ethyl acetate:triethylamine) to provide the aldehyde **2** as a colorless oil (236 mg, 80%).

Acknowledgement

Generous financial assistance from the National Institutes of Health (CA-47148-01) and Merck & Co., Inc., a Dreyfus New Faculty Award (to AGM) and a Summer Undergraduate Research Fellowship (to PAL) are gratefully acknowledged.

References

(1) Our synthetic materials, here designated as **1** and **2**, are composed of a 1:1 mixture of diastereomers, *cis* about the cyclopentane ring with *S,S* epoxide stereochemistry. Preparation of compounds **1**, **3** and **5** will be described elsewhere.

(2) Rieche, A.; Bischoff, C. *Chem. Ber.* **1961**, *94*, 2722.

(3) Pappas, J.J.; Keaveney, W.P.; Gancher, E.; Berger, M. *Tetrahedron Lett.* **1966**, 4273.

(4) Schreiber, S.L.; Liew, W-F. *Tetrahedron Lett.* **1983**, 2363.

(5) Blickenstaff, R.T. *J. Am. Chem. Soc.* **1960**, *82*, 3673.

(6) Shanley, E.S.; Perrin, J.R. *Jet Propul.* **1958**, *28*, 382; available within FMC Technical Bulletin 46.

(7) Meyers, A.I.; Schwartzman, S.; Olson, G.L.; Cheung, H-C. *Tetrahedron Lett.* **1976**, 2417.

(8) Hiatt, R. In *Organic Peroxides*; Swern, D. Ed.; Wiley: New York, 1971; Vol. 2, Chapter I.

(9) For interesting examples of relative rate differences in base-catalyzed reactions of hydrogen peroxide and water, see: Evans, D.A.; Britton, T.C.; and Ellman, J.A. *Tetrahedron Lett.* **1987**, *28*, 6141.

(10) The α-effect nucleophile semicarbazide has recently been used for acetonide removal in an advanced intermediate in the total synthesis of Forskolin: Corey, E.J.; Jardine, P.D.S.; Rohloff, J.C. *J. Am. Chem. Soc.* **1988**, *110*, 3672.