To my parents on their birthdays in 1986

From my Blood Sweat and Tear

REACTIONS OF ORGANOCUPRATES WITH *a*-EPOXYALKYNES AND *a*-ALLENYL ESTERS

by

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ABSTRACT

Reaction of lithium dialkylcuprates with a variety of 4-alkynyl-2,3-epoxy-1-ols gave diastereoisomeric α,β-dihydroxyallenes. The reaction was previously shown by work in this laboratory to be highly stereoselective for anti S_N2' attack of the cuprate, and thus provided a route to α,β-hydroxyallenes of high diastereoisomeric purity. Systematic variation of the cuprate and epoxyalkyne structure allowed delineation of the regiochemistry of the reaction. The reaction was highly regioselective for S_N2' attack in 1-hydroxy-2,3-epoxy-4-alkynes substituted at position five with a hydrogen. In 1-hydroxy-2,3-epoxy-4-alkynes alkylated at C-5 both S_N2 and S_N2' attack were observed. Both S_N2 and S_N2' hydrogen transfer also occurred in reactions between cuprates and C-5 substituted epoxyalkynols.

Because of the easy access to diastereoisomerically pure α-hydroxyallenes provided by the cuprate-epoxyalkyne reaction, we studied the S_N2' reactions of the corresponding phosphate esters with cuprates. This reaction results in formation of 2-alkylated 1,3-dienes. Our investigation of this reaction showed it also to be anti selective.

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ABBREVIATION

Am	Amyl, Pentyl
Bu	n-Butyl
^{13}C NMR	Carbon-13 Nuclear Magnetic Resonance
(-)DET	(-)-Diethyl Tartarate
ee	Enantiomeric excess
Et	Ethyl
GC	Gas Chromatography
GC/CI	Gas Chromatography/Chemical Ionization
GC/MS	Gas Chromatography/Mass Spectrum
GLPC	Gas Liquid Pressure Chromatography
HMPA	Hexamethyl Phosphoramide
^{1}H NMR	Hydrogen Nuclear Magnetic Resonance
HRMS	High Resolution Mass Spectrum
IR	Infrared
J	Coupling Constant
M^{+}	Molecular ion
Me	Methyl
mCPBA	meta-Chloroperbenzoic Acid
NMR	Nuclear Magnetic Resonance
pyr	Pyridine
TLC	Thin Layer Chromatography
X_a	Mole Fraction of the Anti Conformation

PART A

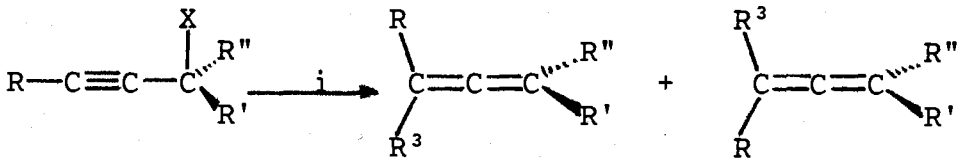
REACTIONS OF ORGANOCUPRATES WITH *a*-EPOXYALKYNOLS

SECTION I

INTRODUCTION

1. General

The discovery of natural allenes and the recognition that they were stable led to their becoming targets of the synthetic chemist. There are several methods to synthesize chiral allenes[1], the most effective of which is by coupling organometallics with chiral propargylic esters[2], ethers[3], tosylates[4] and halides[5]. The predominant stereochemical course of this reaction is without exception anti[6-8](Scheme 1).

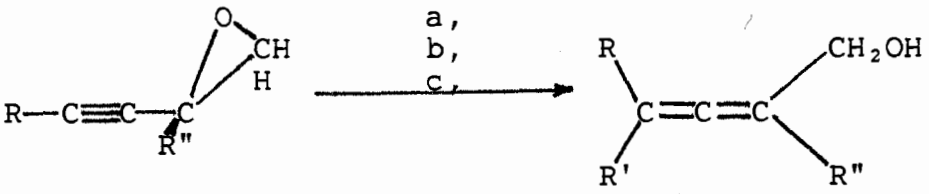


where i= $R^3{}_2CuM$

Scheme 1: Conversion of Propagylic Derivatives to Allenes.

Montellano[9], Suzuki[10], Vermeer[11] and Normant[12] reported the conversion of alkynyl-epoxides to hydroxy-allenes with lithium dialkylcuprates, trialkylboranes and magnesium bromide dialkylcuprates (Scheme 2). They did not, however,

investigate the stereochemistry of the coupling. This was probably because of the difficulty of synthesis of the required chiral epoxides.



a, R'R'CuLi
b, BR'_3, catalytic O_2
c, R'MgBr, catalytic amount CuI

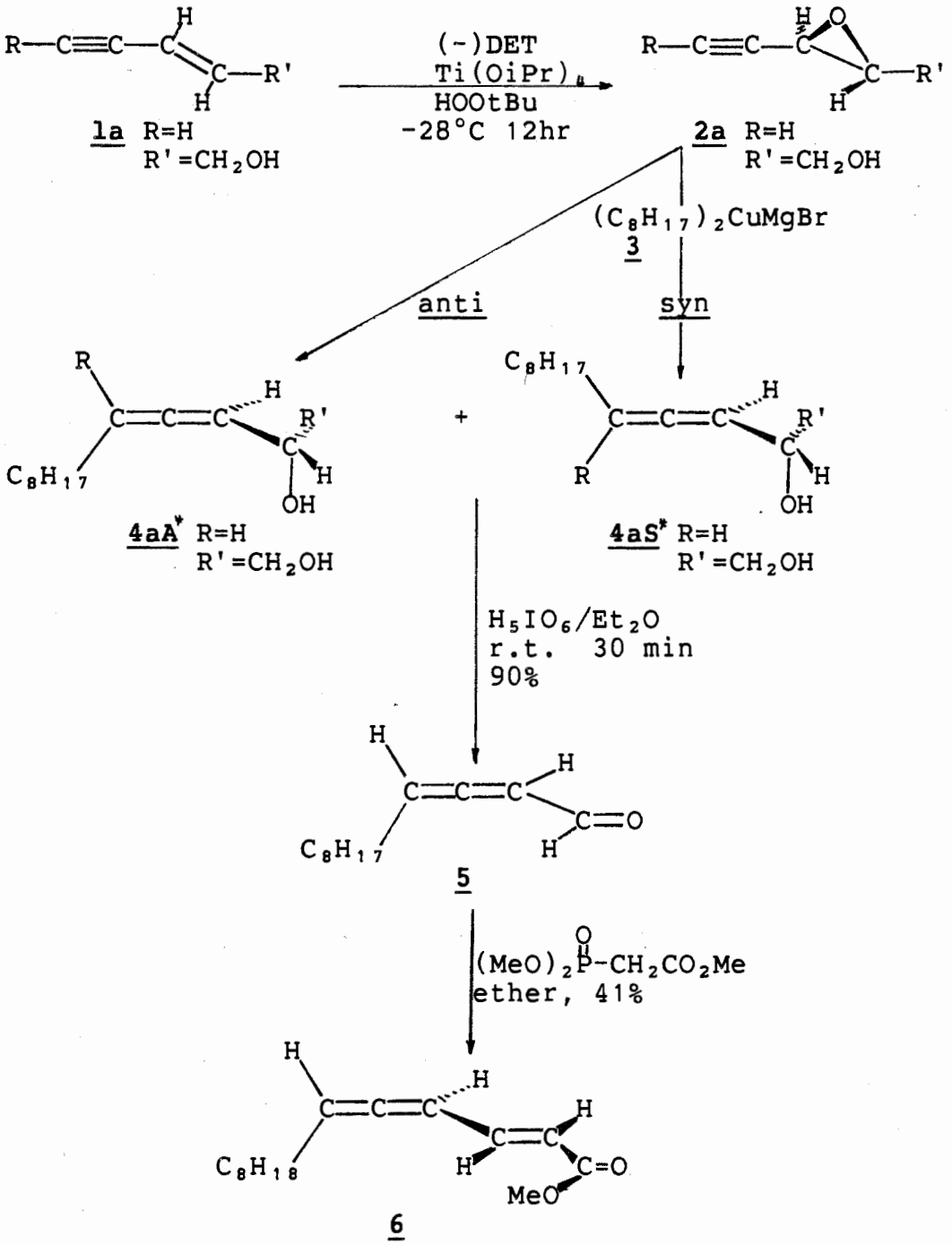
Scheme 2: Conversion of Epoxyalkynes to Allenes.

In 1980 Sharpless[13] introduced a process that allowed facile synthesis of asymmetric epoxides from allylic alcohols. In this reaction chiral oxidation is induced by titanium tetraisopropoxide in combination with diethyl tartrate (as the chiral ligands) and tert-butylhydroperoxide. Epoxidation by this system occurs only on one face of the double bond of the allylic alcohol, and is related to the chirality of the tartrate.

2. Previous Work

Work on which this project is based was performed in our laboratory by Dr. E. Czyzewska. She found that the Sharpless asymmetric epoxidation[13] could be applied to conjugated

enynol, 1a[14], wherein the olefin was between the alkyne and the hydroxyl (Scheme 3). Using (-)diethyl tartrate as the chiral auxillary, chiral induction in these systems leads to epoxyalkynol (4-pentynyl-2,3-epoxy-1-ol, 2a) of ca. 95% ee[14]. Reaction of excess magnesium bromide dioctylcuprate, 3 with 2a gave trideca-3,4-dien-1,2-diols **4aA** and **4aS** in low diastereomeric excess unless the cuprate was stabilized by dimethyl sulfide[14](Scheme 3). The dihydroxyallene **4aA** and **4aS** mixture was oxidized with periodic acid in ether to dodeca-2,3-dien-1-al, 5, which was converted without prior purification to methyl tetradeca-2,4,5-trien-1-carboxylate, 6, with trimethylphosphonacetate. Since the absolute configuration and specific rotation of 6, the sex pheromone of the dried bean beetle, were known, the estimated enantiomeric excess of 6 was calculated to be 62% by comparison with the maximum reported specific rotation of 6. From this, the major diastereoisomer of 4a from the reaction of 2a with 3 was assigned to the product of anti attack[14](Scheme 3). Of particular significance to the present work was the observation by Czyzewska[14] that acetylated derivatives, 7aA and 7aS (Scheme 4), of diol mixture **4aA** and **4aS** were separated by capillary gas chromatography and differentiated by their 400 MHz proton nuclear magnetic resonance (^{1}H NMR) spectra. Thus the hydrogens on C-1 of each diastereoisomer of 7a were observable as quartets in benzene-D_6 (C_6D_6) solvent



Scheme 3: Establishment of anti Stereochemistry for Cuprate-Epoxyalkyne Reaction.

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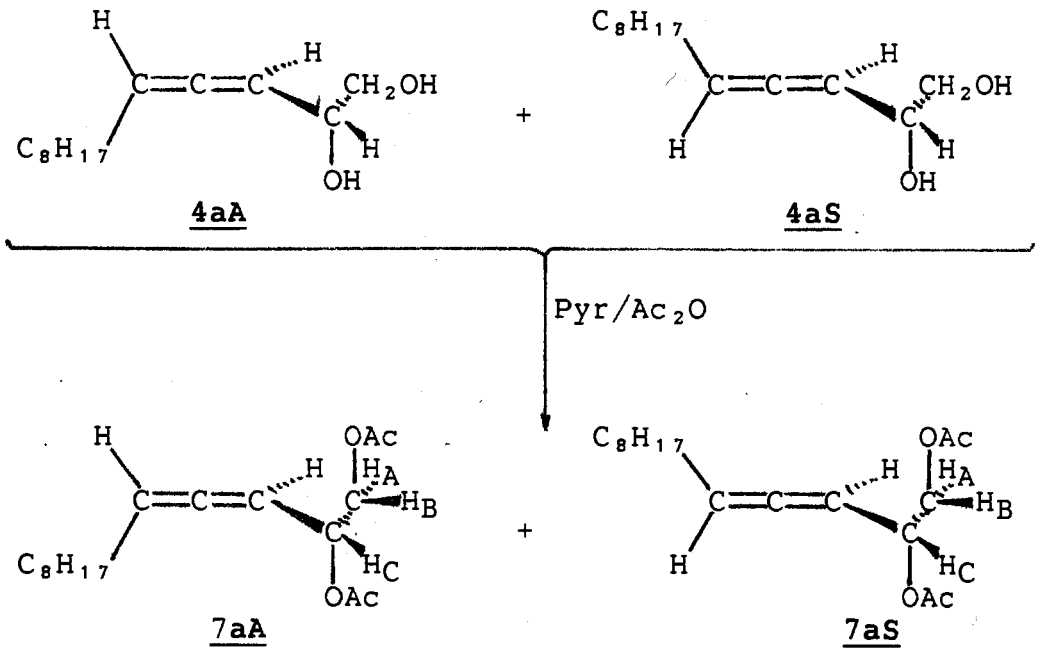
*The designation A or S signifies derivation of the product from anti S_N2' or syn S_N2' attack respectively.

(H_A(syn) = 4.17 ppm, H_A(anti) = 4.08 ppm, $^3J_{AC}$ = 7.5 Hz, $^2J_{AB}$ = 12 Hz; H_B(syn) = 5.23 ppm, H_B(anti) = 5.24 ppm, $^2J_{AB}$ = 12 Hz, $^3J_{BC}$ = 3.5 Hz)[14]. This differentiation allows assignment of composition to mixtures of *a*-hydroxyallene diastereoisomers.



Scheme 4: Acetylation of 3,4-Allenyl-1,2-diols.

It was shown in previous work by Dr. E. Czyzewska of this laboratory[14], the work of Cleasson[15], and the work of Vermeer[16] that lithium dialkylcuprates cause racemization of allenes. Dr. E. Czyzewska in our laboratory demonstrated that the addition of dimethyl sulfide decreased the racemization rate. In that work it was also shown that maintainance of a low temperature for the coupling of **2a** with lithium dialkylcuprate-dimethyl sulfide complexes was

necessary for high stereoselectivity[14].

The high stereoselectivity of the S_N2' reaction of conjugated epoxyalkynol, **2a**, with dialkylcuprates to give α-allenyl alcohol **4a** encouraged us to further study the stereochemistry and the regiochemistry of these coupling reactions. We felt that these reactions would lead to a general synthesis of α-hydroxyallenes wherein the relative stereochemistry of the allene and hydroxyl bearing carbon were known.

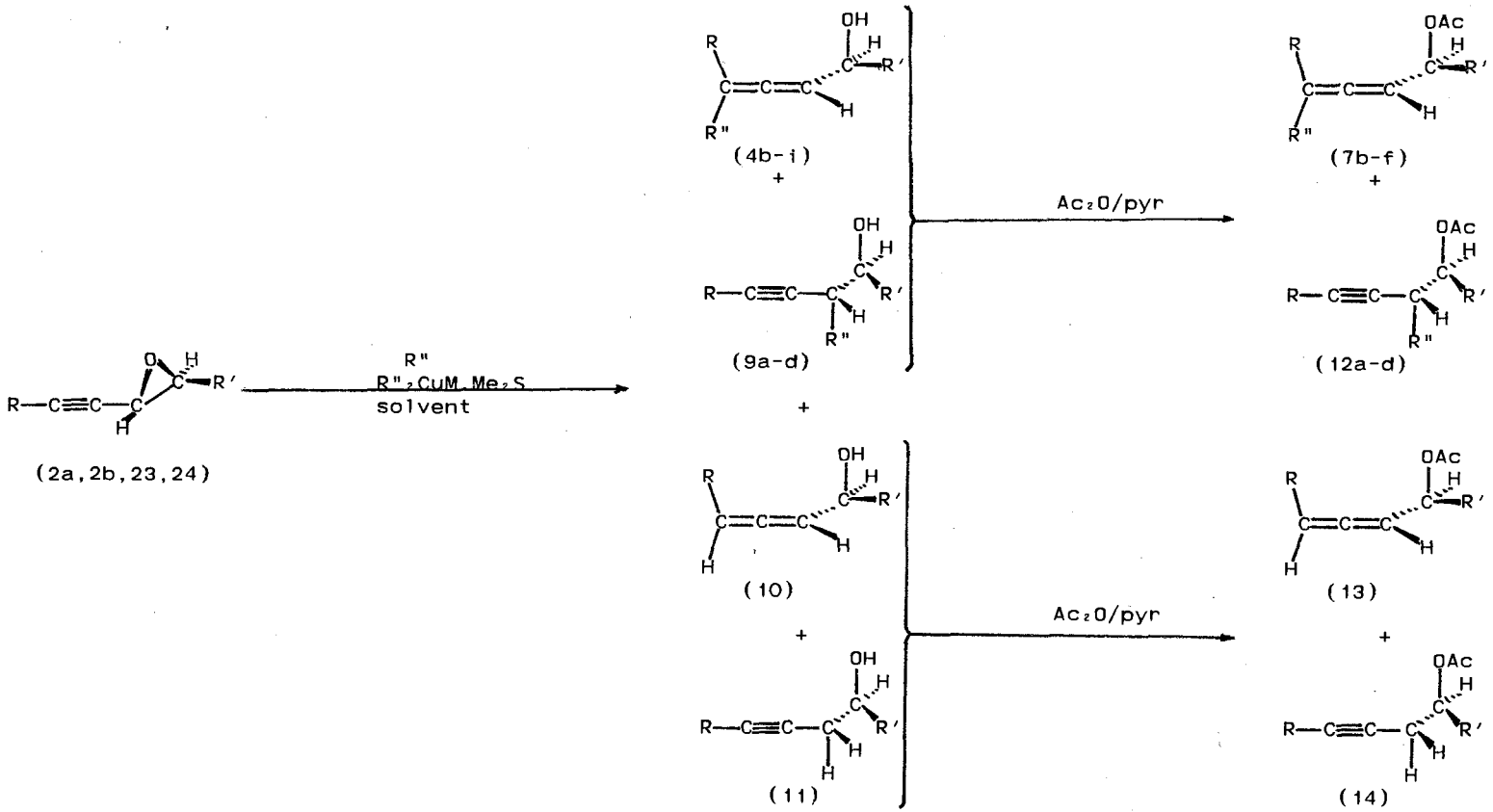
SECTION II

RESULTS AND DISCUSSION

1. Effect of Alkynyl Substituent on the Reaction of Organocuprates with Epoxyalkynols

The reaction of epoxyalkynols, **2a** and **2b**, with lithium dibutylcuprate-dimethyl sulfide, **8a**, in the presence of dimethyl sulfide was studied (Scheme 5, Table 1). We found that the alkynyl substituents, R, affected the regiochemistry of the reaction. Epoxyalkynol **2a**, wherein R was H, gave only alkylated allene **4b** (Table 1, entry a). The ^{1}H NMR spectrum of **4b** revealed two resonances at 5.22 ppm and 5.36 ppm which were assigned to the two allenyl hydrogens. These resonances were in the region expected for this compound based on comparison of the ^{1}H NMR of **4b** with that of **4a**.

Substituted epoxyalkynol, **2b**, wherein R was pentyl, coupled with cuprate **8a** to give a mixture of four products (Scheme 5). They were identified as alkylated allene product, **4c**, alkylated alkyne product, **9a**, non-alkylated allene product, **10**, and non-alkylated alkyne product, **11** (Table 1, entries b to e). Acetylation of the reaction mixture gave **7b**, **12a**, **13** and **14** respectively (Scheme 5).



where:

2a: R=H R′=CH_2OH

2b: R=nAm R′=CH_2OH
23: R=nAm R′=$CH_2OSi(Me)_2Bu$
24, R=H R′=nAm

8a : $Bu_2CuLi.Me_2S$
8b : $Me_2CuLi.Me_2S$
21a: $iPr_2CuMgBr.Me_2S$
21b: $Et_2CuMgBr.Me_2S$
21c: $Me_2CuMgBr.Me_2S$
21d: $Bu_2CuMgBr.Me_2S$
22a: $nBu_2CuCNLi_2$
22b: $Me_2CuCNLi_2$
25 : $Me_2Cuhexynyl.Me_2S$

4b: R=H R′=CH_2OH R"=Bu
4c, 9a: R=nAm R′=CH_2OH R"=nBu
4e, 9b: R=nAm R′CH_2OH R"=iPr
4f, 9c: R=nAm R′=CH_2OH R"=Et
4d, 9d: R=nAm R′=CH_2OH R"=Me
4g: R=H R′=nAm R"=iPr
4h: R=H R′=nAm R"=Me
4i: R=H R"=nBu R′=nBu
10, 11: R=nAm R′=CH_2OH R"=H

7c: R=H R′=CH_2OAc R"=nBu
7b, 12a: R=nAm R′=CH_2OAc R"=nBu
7d, 12b: R=nAm R′=CH_2OAc R"=iPr
7e, 12c: R=nAm R′=CH_2OAc R"=Et
7f, 12d: R=nAm R′=CH_2OAc R"=Me
13, 14: R=nAm R′=CH_2OAc R"=H

where: in this Scheme and the remaining text, structure 10 is differentiated from 4a and 4b for clarity of presentation.

Scheme 5: Conversion of α-Epoxyalkynes to Alkynes and Allenes with Organocuprates.

Table 1 Coupling of Organocuprates with Epoxyalkynes 2a, 2b, 23 and 24 Using Normal Addition Method

	Epoxyalkynes R	R′	R"M	Copper(I)	Sol[1]	T[6](C)	Yield of 4+9[2](4/9)[3]	A/S of 4	Yield of 10+11[2](10/11)[3]	A/S of 10	Conversion[3]
a,	H	CH_2OH	n-BuLi	$CuBrMe_2S$	E/D	-60	53(100:0)				
b,	n-pentyl	CH_2OH	n-BuLi	"	"	-65	32(91:9)	>99/1	3[3]		35
c,	"	"	"	"	"	-50	26.5[4](88:12)		8.5[4](61:39)		
d,	"	"	"	"	"	-18	58(93:7)	>99/1	13(60:40)	52/48	90
e,	"	"	"	"	"	20	62(93:7)	>99/1	9.5(55:45)	59/41	94
f,	"	"	4n-BuLi	2	"	-70	86[3](95:5)				86[3]
g,	"	"	MeLi	"	E/D	22	21.5(95/5)	60/40	1.5(39:61)		97
h,	"	"	MeMgBr	"	"	20	12.6(96:4)	43/57			100
i,	"	"	EtMgBr	"	"	22	31(94/6)	49/51			100
j,	"	"	i-PrMgBr	"	E/D	-70	48.5(96:4)				96
k,	"	"	"	"	"	20	53(95:5)	>99/1			100
l,	"	"	MeMgBr	"	"[5]	20(.45hr)	31(95/5)	80/20			100
m,	"	"	n-BuLi	CuCN	E	20	60(93/7)	>99/1			100
n,	"	$CH_2OSi(Me)_2t$-Bu	"	$CuBrMe_2S$	E/D	-30	18.5[4](90:10)	>99/1	42.5[4](70:30)	40/60	100
o,	H	n-pentyl	i-PrMgBr	"	"	25	67(90:10)				100
p,	H	n-pentyl	MeMgBr	"	"	14	33.5(31.5/2).	mess			100

[1]E/D; Represents three portions of anhydrous diethyl ether to two portions of dimethyl sulfide; E; Represents anhydrous diethyl ether only. [2]Isolated yield by flash column chromatography. [3]Determined by GC and/or ^1H NMR with about +/- 10%. [4]Isolated by means of prep. TLC. [5]20% dry HMPA was present. [6]The starting material 2b was added to the dialkylcuprate.dimethyl sulfide at -70°C and warmed quickly to the temperature indicated.

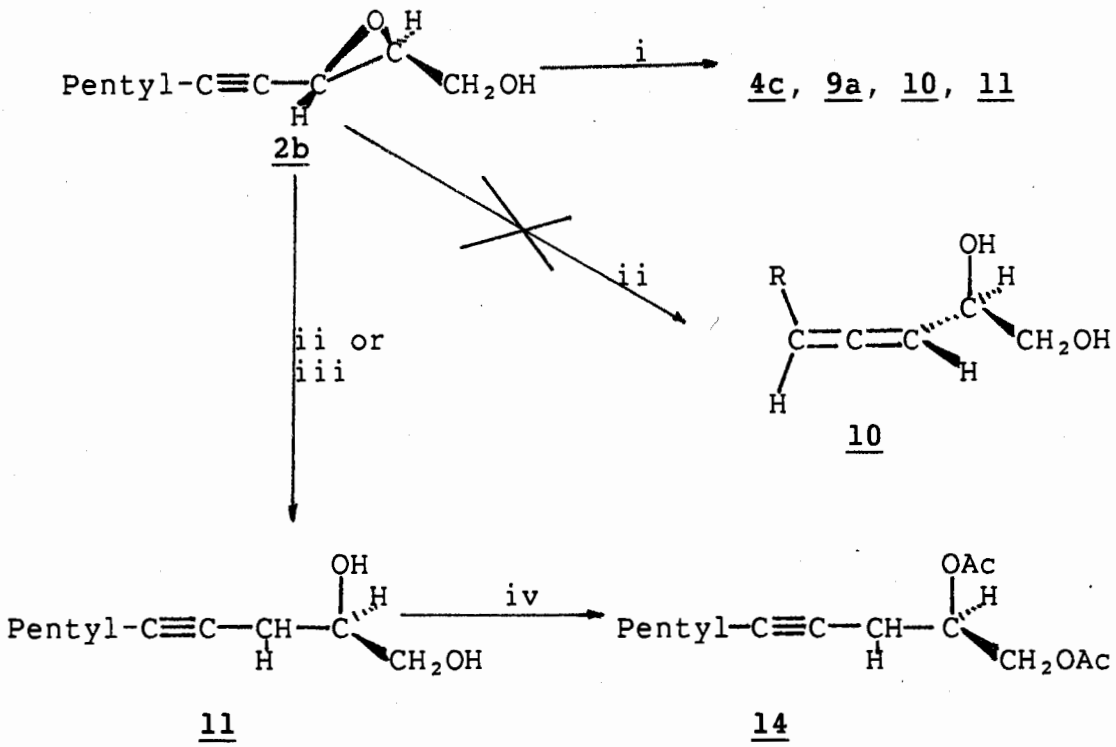
Table 2 Reaction of Epoxyalkynol 2b with Selected Organocuprate and Organolithium Reagents

	Epoxyalkynes R	R′	R"M	Copper(I)	Sol[1]	T[6](C)	Yield of 4+9[2](4/9)[3]	A/S of 4	Yield of 10+11[2](10/11)[3]	A/S of 10	Conversion[3]
q,	n-pentyl	CH_2OH	n-BuLi	$CuBrMe_2S$	E	-70(3hr)	26(43:57)	80/20	14(60:40)	52/48	81
r,	"	"	"	CuBr	E	-30	17.5(50:50)	90/10	23(71:29)		100
s,	"	"	"	"	E	2	mess				
t,	"	"	n-BuLi/ LiAlH4	$CuBrMe_2S$	E/D	20	messy				31
u,	"	"	n-BuLi/ LiAlH4	$CuBrMe_2S$[4]	E/D	20			52(0:100)		100
v,	"	"	LiAlH4	nil	THF	20			45.5(0/100)		100
w,	"	"	n-BuLi	nil	THF	-35	27(100/0)				100

[1]E/D; Represents three portions of anhydrous diethyl ether to two portions of dimethyl sulfide; E; Represents anhydrous diethyl ether only. [2]Isolated yield by flash column chromatography. [3]Determined by GC and/or ^1H NMR with about +/- 10%. [4]1 eq. of nBuLi and 1 eq. of LiAlH4 were first react with CuBr.Me_2S to form nBuCuH complex to which 2b was added. [6]The starting material, 2b, was added to the dialkylcuprate.dimethyl sulfide at -70°C and warmed quickly to the temperature indicated.

Diols 4c and 9a were easily separated from diols 10 and 11 by flash chromatography[17]. However, it was not possible to separate diol 4c, from diol 9a nor 10 from 11. Furthermore, it was not possible to separate 7b from 12a nor 13 from 14. Mixtures of 12a and 7a, and of 14 and 13 clearly revealed ^{1}H NMR signals due to 12a and 14 as determined by comparison with the ^{1}H NMR spectra of 12a and 14 produced by independent methods.

Initial attempts to prepare 13 by other methods were unsuccessful. Crabbe's method (Scheme 6) of adding lithium tetrahydridoaluminate to inhibit the transfer of alkyl group from the copper to the allenic carbon[18] was used. The reaction gave a mixture of four products which were identified as above (*i.e.* 4c, 9a, 10 and 11) by gas chromatography (GLPC) and ^{1}H NMR spectral analysis (Table 2, entry t). Furthermore, the reaction of the copper (I) hydride[19] with 2b gave alkyne, 11 (Scheme 6, Table 2, entry u). Allene 10 was finally identified by comparison of its ^{1}H NMR, infrared (IR), and mass spectrum (MS) with the relevant spectra of the product 4b of reaction of epoxyalkynol 2a with lithium dibutylcuprate 8a. After acetylation of 4b and 10 to give diacetates 7c and 13, the only difference between the ^{1}H NMR spectra of allenes 7c and 13 was that 13 had resonances for an extra two hydrogens in the multiplet at 1.32 ppm. The remainder of the two spectra were

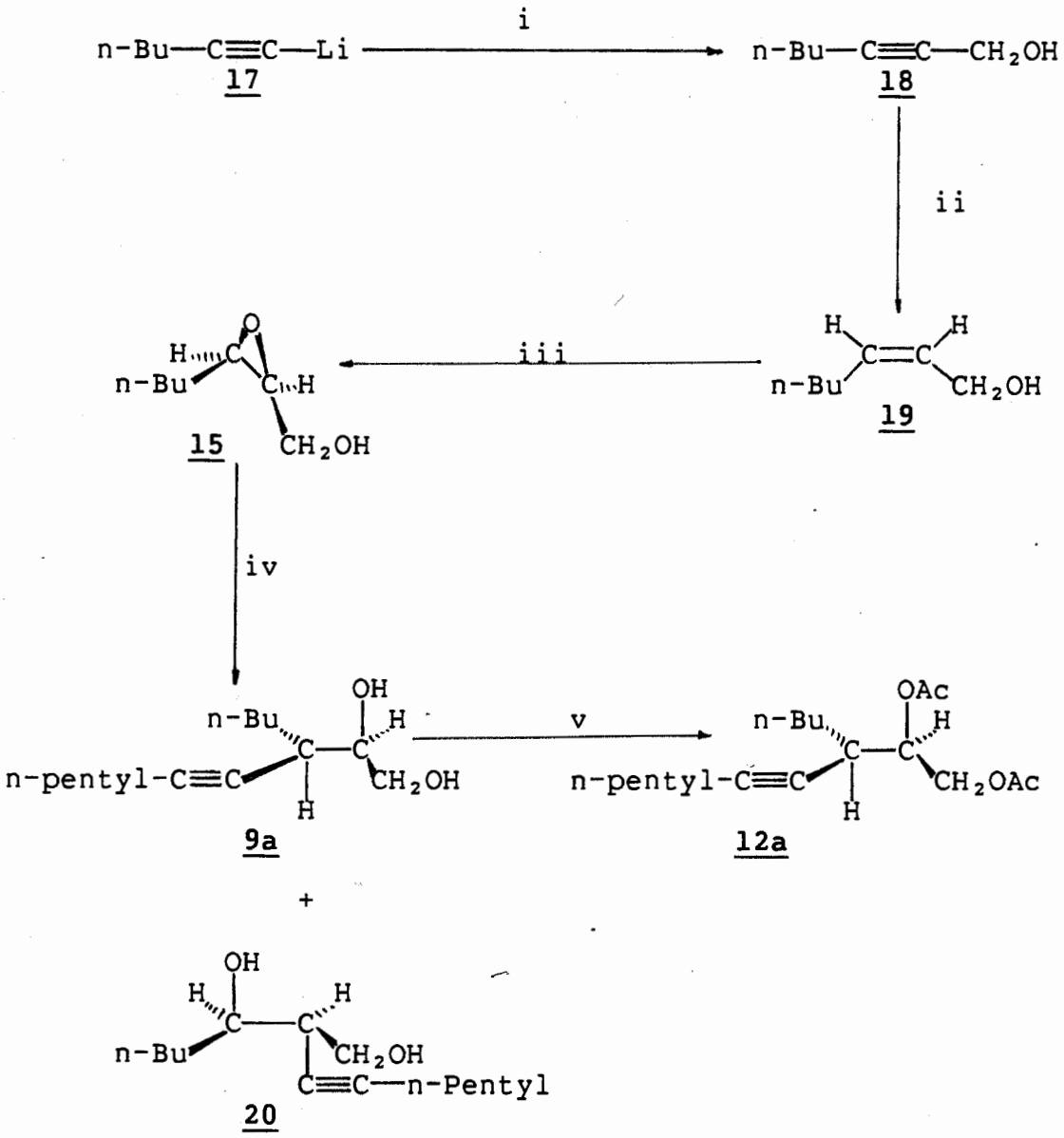


where: i, n-$Bu_2CuLi.Me_2S$, $LiAlH_4$
ii, n-BuCuH
iii, $LiAlH_4$/THF
iv, AcOAc/Pyr

Scheme 6: Independent Synthesis of Alkynyl Diacetate **14**.

superimposable. The mass spectrum of **13** exhibited an extra fourteen mass units in the molecular ion peak.

Alkyne **11** was prepared independently from **2b** by reaction with lithium tetrahydridoaluminate (Scheme 6), and was acetylated to give **14**. GLPC and ^1H NMR spectral comparison revealed **14** produced in this manner was identical to that produced from the reaction of **2b** with organocuprate reagent **8a**.



where i, paraformaldehyde
ii, P2-Ni/EtOH
iii, m-CPBA/CH_2Cl_2
iv, $(Et)_2AlC{\equiv}C$-nPentyl, **16**
v, Ac_2O/Pyr

Scheme 7: Independent Synthesis of Alkynyl Diacetate **12a**.

Substituted alkyne **9a** was synthesized independently (Scheme 7) by reaction of (Z)-2,3-epoxyheptan-1-ol, **15**, with diethyl 1-heptynylaluminum[20], **16**. The epoxy alcohol **15** was prepared by reaction of 1-hexynyllithium, **17** with paraformaldehyde to give 2-heptyn-1-ol, **18**, which was hydrogenated with P-2 nickel in ethanol to give **19**. Epoxidation of **19** with m-chloroperbenzoic acid in dichloromethane (CH_2Cl_2) gave the desired product **15**. The reaction of **15** and organometallic reagent, **16**, gave a mixture of two products of which **9a** was the minor component and **20** was the major component. Comparison by GC/MS, GLPC, and ^1H NMR of the diacetoxy derivative, **12a**, derived from **15** with that produced from **2b**, revealed the two were identical.

Increasing the size of the substituent R on the epoxyalkynol (*eg* from H, **2a**, to pentyl, **2b**) not only decreases the regioselectivity of the coupling with organocuprate **8a**, but also lowers the rate of the reaction. When one equivalent of **8a** was reacted at -60°C with an equivalent of **2a**, all epoxyalkynol **2a** was converted to substituted diol **4b**. Using the same reagent to substrate ratio only half of **2b** was consumed at -65°C (Table 1, compare entries a and c) during the same time. The epoxyalkynol **2b** required two equivalents of organocuprate **8a** in order to achieve 86% conversion at -70°C (Table 1, entry f). Alternatively, **2b** completely reacted with one equivalent

of **8a** if a higher temperature was used (Table 1, entries d and e).

2. Effect of Organocuprate Structure on Product Distribution

Various lithium dialkylcuprate-dimethyl sulfide, **8**, magnesium bromide dialkylcuprate-dimethyl sulfide, **21**, and lithium dialkylcyanocuprate, **22**, reagents were coupled with epoxyalkynol **2b** (Scheme 5, Table 1). In these reactions, all **2b** was consumed at ambient temperature. The yields and proportions of the products were found to be affected by the size of the cuprate alkyl group, R", and by the type of organocuprate. When the alkyl group on the organocuprate **8** was changed from n-butyl, **8a**, to methyl, **8b**, the yield of allenic-diol decreased from 62% (**4c**) to 21.5% (**4d**) (Table 1, entries e and g). This is probably due to the known sluggish reactions of methylcuprates compared to their higher alkyl analogs.

In the case of the reaction of epoxyalkynol **2b** with magnesium bromide diisopropylcuprate-dimethyl sulfide reagent, **21a**, only allene **4e** and alkyne **9b** could be detected (Scheme 5, Table 1, compare entries j and k). No **10** or **11** were observed. More interestingly, this reaction could be completed at -70°C with no decrease in yield of **4e** compared to the reaction at 20°C (Scheme 5, Table 1, entries j and

k). Similar to its reaction with **8a**, epoxyalkynol, **2b**, gave decreased yields of **4f** (31%) and **4d** (12%) with magnesium bromide diethyl and dimethylcuprate-dimethyl sulfide reagents, **21b** and **21c**, respectively (Table 1, entries i and h).

The minor products of the reactions of **2b** with **21a** to **21c** were alkylated alkynes **9b**, **9c** and **9d**. These alkynes were identified by analysis of the ^{1}H NMR spectra of the corresponding diacetoxy derivatives, **12b**, **12c** and **12d** respectively. The ^{1}H NMR spectra in chloroform-D ($CDCl_3$) of the diacetoxy derivatives of **12b**, **12c** and **12d** all revealed signals attributable to the two hydrogens on C-6 (2.16 ppm), a resonance due to a single hydrogen associated with C-2 (5.1 ppm) and a resonance due to two methylene hydrogens associated with C-1 as two sets of quartets (4.17 ppm and 4.39 ppm). In these spectra, resonances due to the hydrogen on C-3 (near 2.5 ppm) were also present.

Epoxyalkynol **2b** was added to lithium dibutylcyanocuprate, **22a**, in anhydrous ether at -70°C, and the temperature slowly raised to room temperature for one hour rather than applying a temperature jump by immersion of the flask in warm water (method A). After acetylation, a 60% yield of a mixture of diacetate **7b** (93%) and diacetate **12a** (7%) was obtained (Table 1, entry m). No non-alkylated products, **13** and **14**, were detectable.

Thus, organometallics 8, 21 and 22, all gave comparable yields of alkylated products 4a-4f and 9a-9d. The last two organometallic reagents did not give any non-alkylated product 10 and 11, and the yield of alkylated product did not increase with organocuprate complexes 21 and 22. This suggested that the reactions of 2b with 8, 21 and 22 might involve similar intermediates. Some intermediates could then be converted to non-alkylated allene 10 and non-alkylated alkyne 11 when organocuprate 8 was the reagent, but not if organocuprates 21 or 22 were the reagents.

3. Effect of 1-Hydroxyl Protection and C-1 Substitution on Product Distribution

Hydroxyl protection affects the coupling of epoxyalkynol, 2b, with organocuprate reagents 8a and 22a (Scheme 5). The hydroxyl group of the epoxyalkynol 2b was derivatized as a t-butyldimethyl siloxy ether to give 23. This derivative gave a larger proportion of the allene 10 and alkyne 11 upon coupling with 8a compared to the reaction of 2b and with 8a (Table 1, compare entries e and n).

Reaction of epoxyalkyne, 24, with 21a and 21c gave alkylated allene 4g and 4h respectively with moderate yield (Scheme 5, Table 1, entries o and p). Analysis of the complete reaction mixture (Table 1, entries o, p and a)

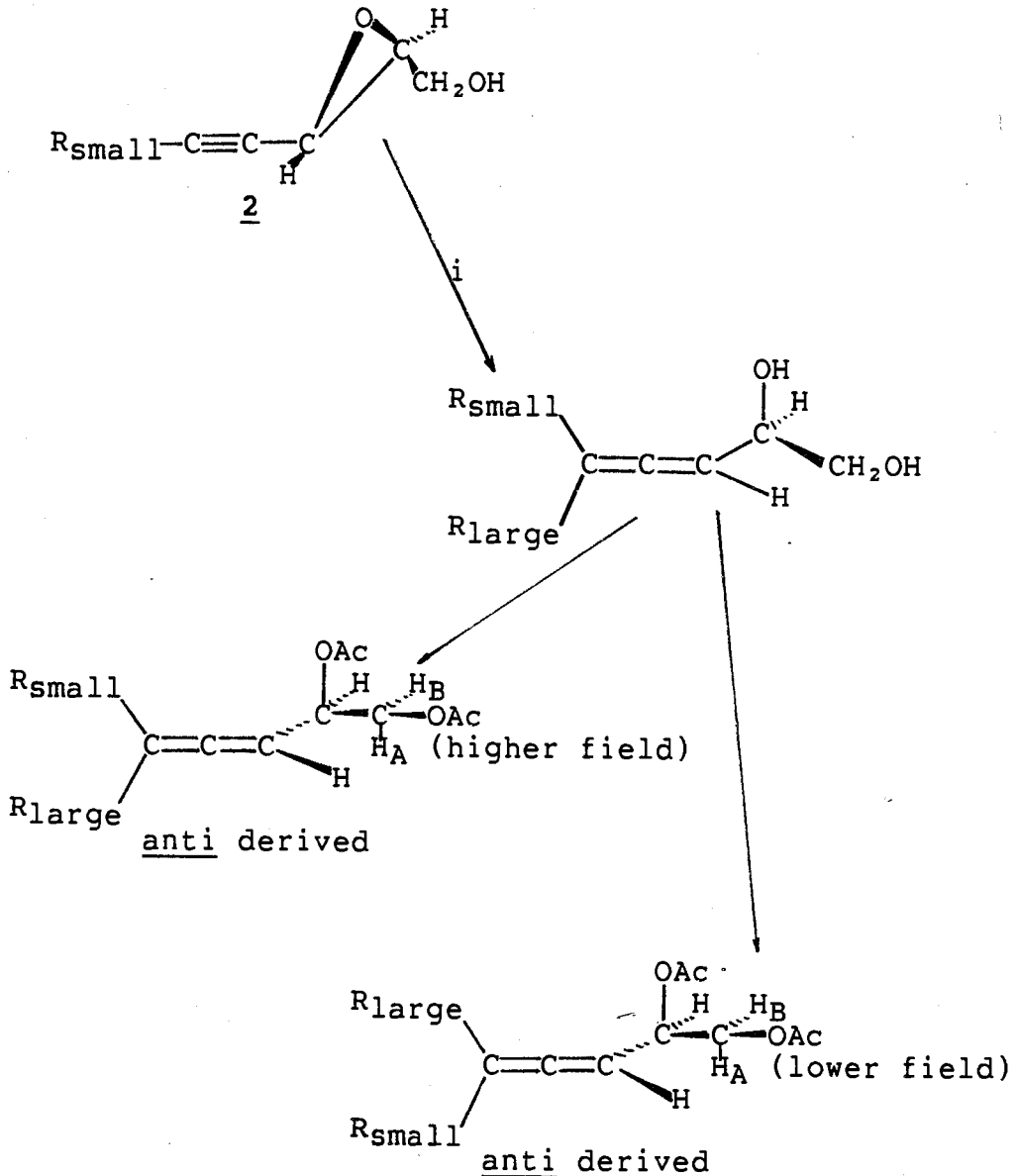
suggested that the absence of the alcohol did not significantly affect the reaction of epoxyalkynes with organocuprate reagent 21.

4. The Stereochemistry of the Coupling Reaction

It has been reported that organocuprate 3 couples with epoxyalkynol 2a in an anti Sn2' manner[14]. The stereochemistry of organocuprate coupling with substituted epoxyalkynols such as 2b would also be expected to be anti.

As previously shown[14] the ^1H NMR resonances of one diastereotopic hydrogen, H_A, on C-1 of each diastereoisomeric 1,2-diacetoxy-3,4-diene was exhibited as a quartet in benzene-D_6 (Scheme 8). The chemical shift of H_A in the product of anti S_N2' attack was at 4.08 ppm, but that due to H_A in the product of syn S_N2' attack was at 4.17 ppm[14]. We found that the signals due to the A hydrogens on C-1 of the 1,2-diacetoxy-3,4-dienic diastereoisomers were also separated in chloroform-D (Table 3). Detailed NMR information is presented in the Experimental section.

Since the signal for H_A of the product derived from anti S_N2' reaction of 3 ($R_{large} = C_8H_{17}$) with 2a ($R_{small} = H$) was at higher field than the corresponding signal in the diastereoisomeric allenic diol derived from syn attack, we expected that substituted allenic diols with similar



where: i, $R_{large}{}_2CuM$
ii, Ac_2O/Pyr

Scheme 8: Syn vs Anti Stereochemistry in the Reaction of Organocuprates with *a*-Epoxyalkynols.

Table 3: Chemical Shifts of the H_A on C-1 in *a*-Allenyl-diacetates (See Scheme 8)

	R'=CH_2OH			Chemical Shit Of δH_A		
R"CuM	R	R"	Product	major	minor	Major Attack
1, 8a	H	$n-C_4H_9$	7c	4.122	4.129	A
2, 8b	$n-C_5H_{11}$	CH_3	7d	4.115	4.102	A
3, 21c	$n-C_5H_{11}$	CH_3	7f	4.102	4.115	S
4, 21b	$n-C_5H_{11}$	C_2H_5	7e	4.098	4.105	S
5, 21a	$n-C_5H_{11}$	$i-C_3H_7$	7d	4.093		A
6, 8a	$n-C_5H_{11}$	$n-C_4H_9$	7b	4.098		A
7, BuLi[1]	$n-C_5H_{11}$	$n-C_4H_9$	7b	4.098	4.083	S

[1]n-Butyllithium only

diastereoisomeric relationships would exhibit a comparable shift for the resonances due to H_A (Scheme 8). It is on the basis of this assumption that syn and anti attack ratios are estimated in Table 3.

For most reactions wherein the size of the substituents on C-5 of the allenic diols, **4**, were dramatically different in size, the mixture of two acetylated diastereoisomers was easy to be differentiated by GLPC and ^1H NMR. In the case of reaction of **2b** with **8a**, however, the C-5 substituents of the allenic diol product, **4c**, were n-butyl and n-pentyl. This product, after acetylation, gave a single peak by GLPC and exhibited an ^1H NMR spectrum (Figure 1, ^1H NMR of diacetate) consistent with it being a single diastereoisomer. Because the C-5 groups in **4c** are of similar size, it is possible

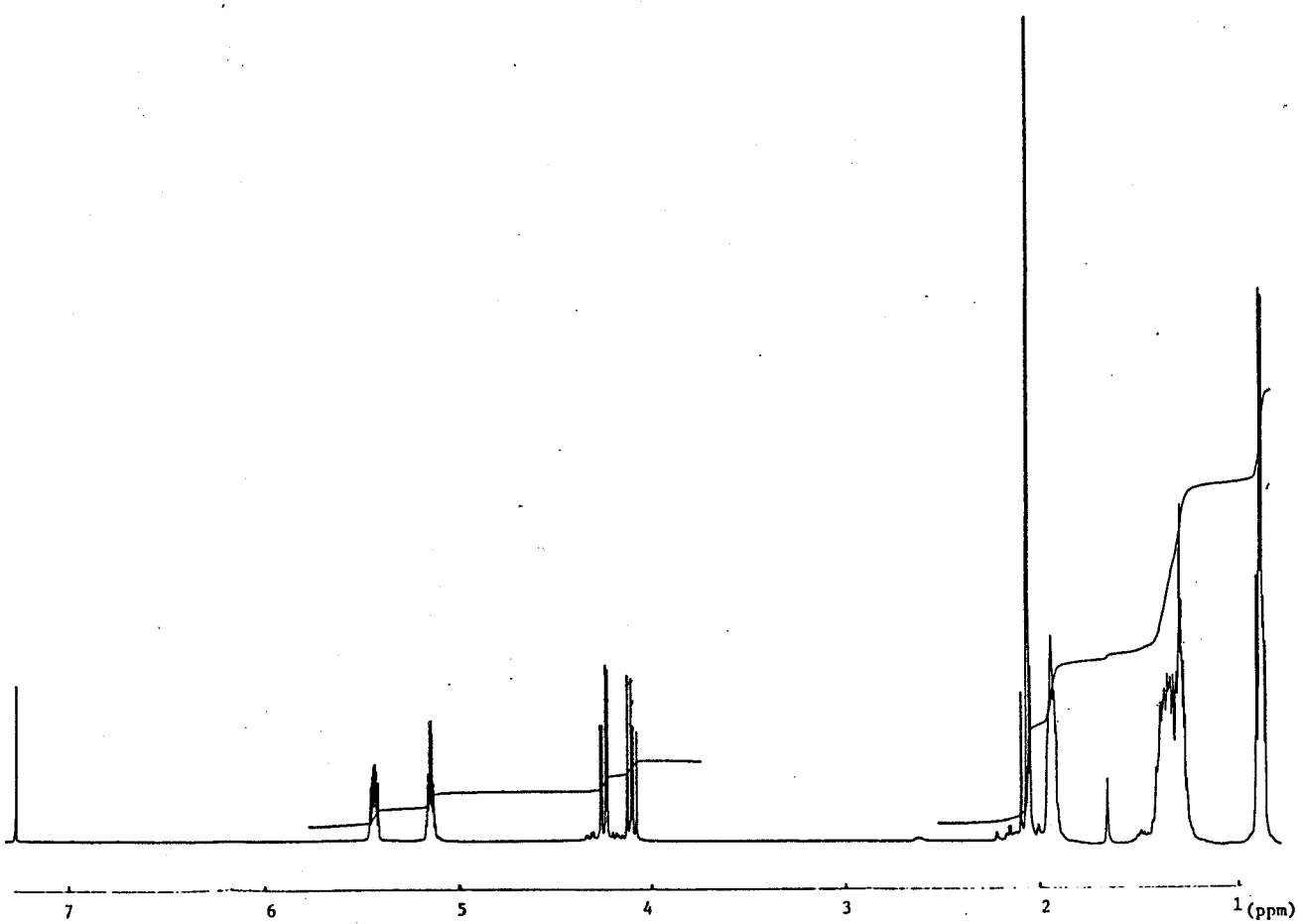


Figure 1: 400 MHz HMR Spectrum of
5-n-Butyl-3,4-decadien-1,2-diacetates, 7b,
Derived from Reaction of 2b with 8a

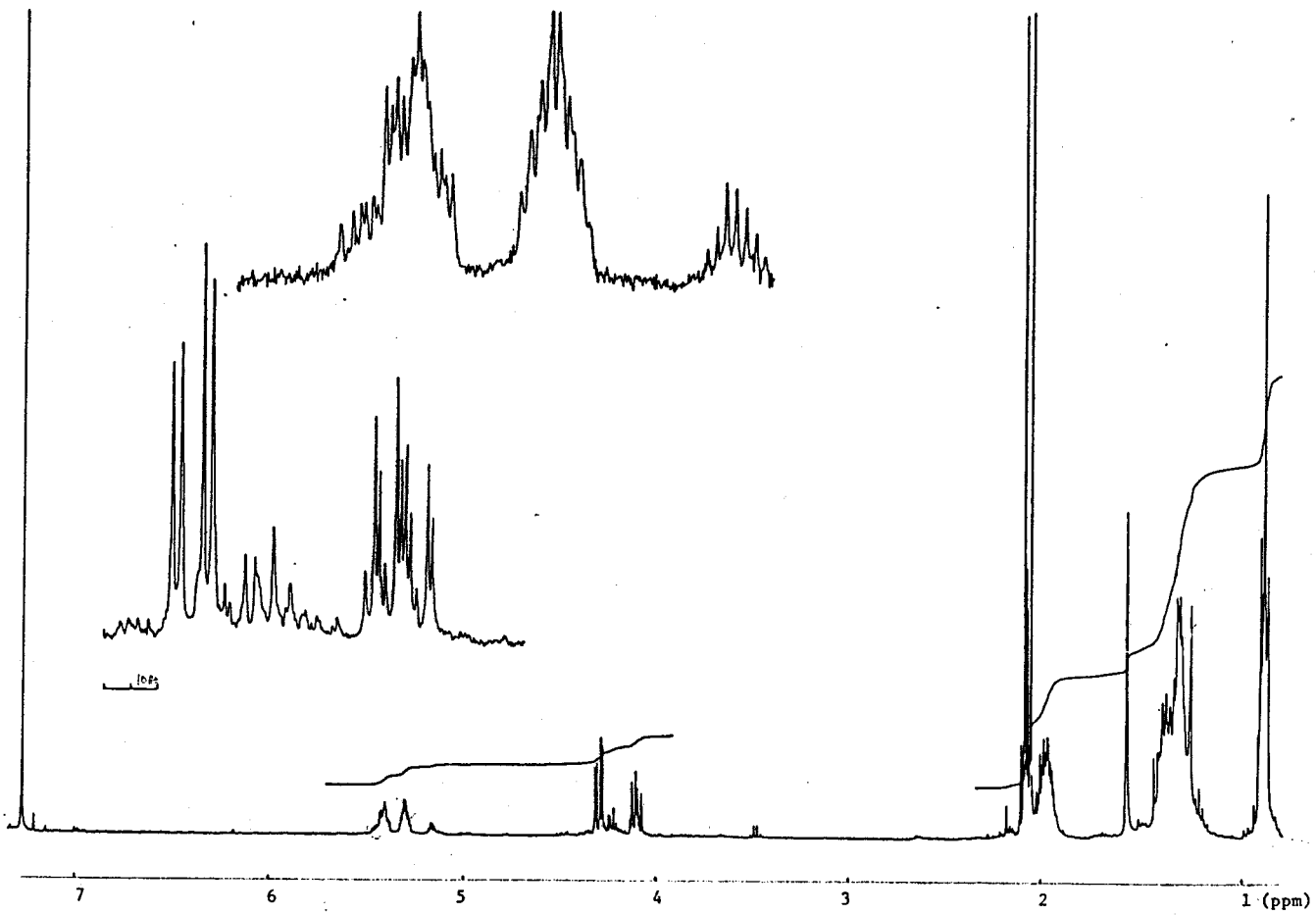
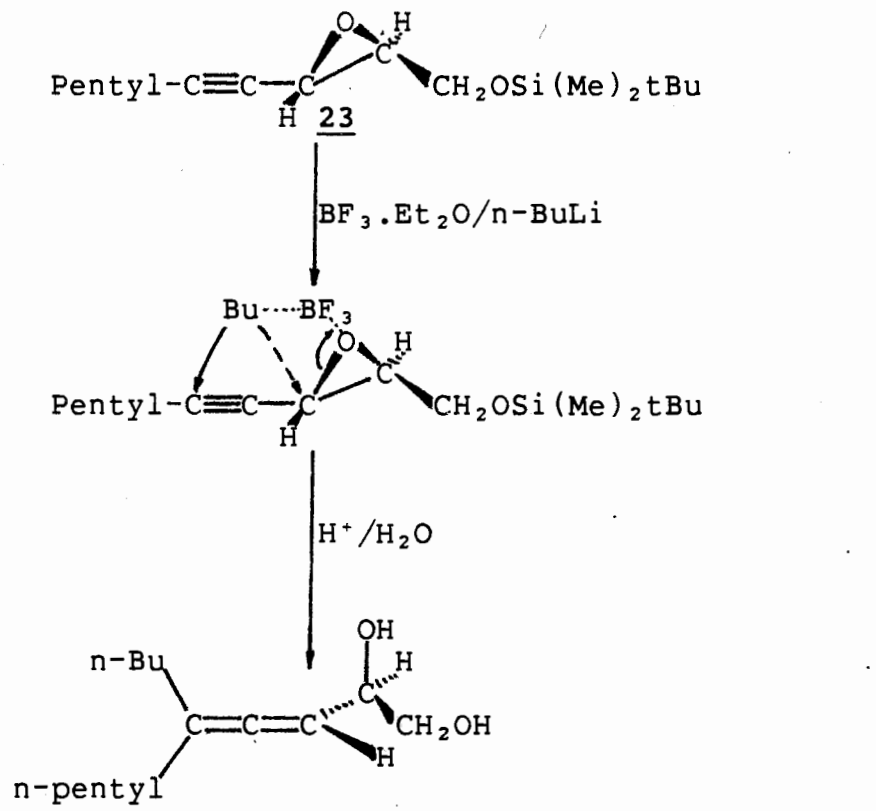


Figure 2: 400 MHz HMR Spectrum of Diastereoisomeric Mixture of 5-n-Butyl-3,4-decadien-1,2-diacetates Derived from Reaction of 2b with n-Butyllithium



Scheme 9: Independent Synthesis of **4cS**.

that differentiation of diastereoisomers by GLPC or ^{1}H NMR might not be achieved (Scheme 8). To determine if diastereoisomers of **4c** were separable, we undertook generation of this diol by a route expected to provide a diastereoisomeric mixture. We reacted **2b** with n-butyllithium at -25°C. This reaction gave a diol mixture which, after acetylation (Figure 2), revealed two diastereoisomers of **4c** by both ^{1}H NMR and GLPC. The minor diastereoisomer of **4c** from the reaction of n-butyllithium with **2b** was identical by

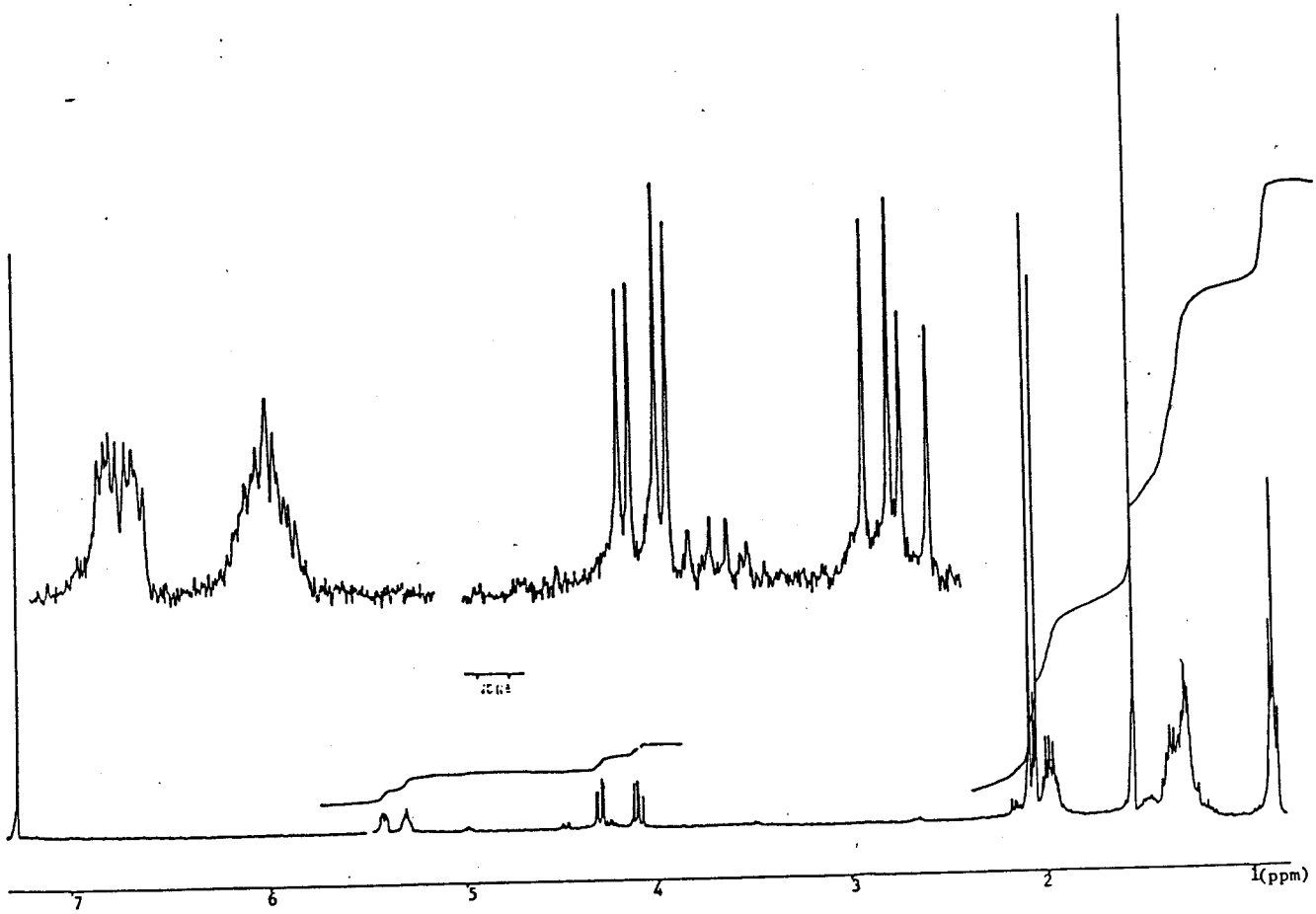
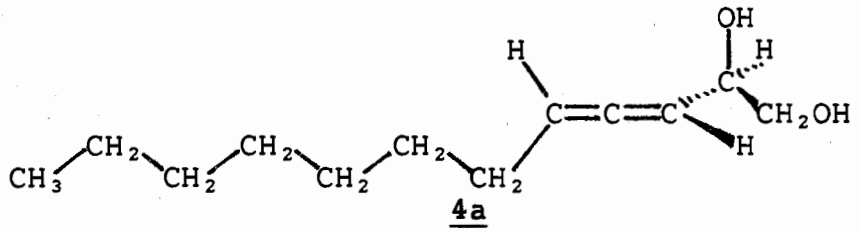


Figure 3: 400 MHz HMR Spectrum of 5-n-Butyl-3,4-decadien-1,2-diacetates, **7b**, Derived from Reaction of **2b** with n-Butyllithium Boron Trifluroide Etherate

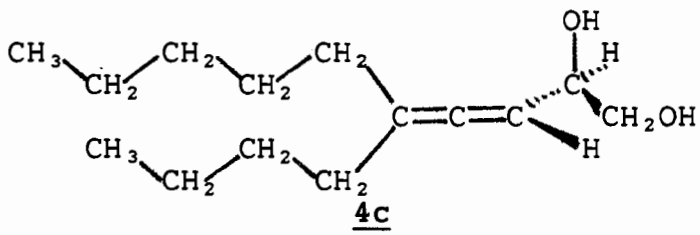
GLPC co-injection with the diastereoisomer produced from reaction of **2b** with **8a**. The major diastereoisomer of **4c** from the reaction of **2b** with n-butyllithium was identical by GLPC co-injection with the diastereoisomer from reaction of **23** with n-butyllithium.BF_3 etherate[22] (Figure 3 is of diacetate, Scheme 9). In related reactions, Lewis acids have been reported to cleave epoxides with retention of configuration[23]. We therefore, suspected that S_N2' cleavage of **23** by n-butyllithium.BF_3 etherate would proceed by *syn* attack. By this analysis, both n-butyllithium and n-butyllithium.BF_3 etherate react with **23** to give predominantly **4cS**; whereas, **8a** reacts with **2b** to give **4cA**.

Non-alkylated allenes, **10**, (Scheme 5) were shown by both GLPC and ^1H NMR spectral analyses to be an approximate 1:1 mixture of two compounds. These are assumed from their spectra to be diastereoisomers.

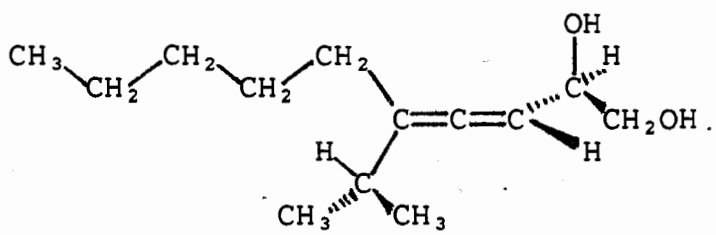
We suspected the formation of alkylated alkyne **9a** from **2b** resulted from S_N2 attack involving inversion of configuration at C-3 of **2b**. To generate this product independently, we reacted (*Z*)-epoxyalcohol **15** and organometallic reagent, **16**[20] (Scheme 7). The identity of the diacetoxy derivatives of **9a** from the two sources confirmed **12a** was derived from **2b** by S_N2 attack with inversion at C-3.



4a



4c



4e

Figure 4: 5-Alkylated-3,4-allenyl-1,2-diols.

In order to further demonstrate that **4cA** resulted from anti reaction of **2b** with **8a** and **4cS** resulted from syn attack of **2b**, we reacted the epoxyalkynol **2b** with organocuprate **21a**. Since the alkyl, R", transferred from the cuprate was more bulky than n-pentyl, R, at the carbon attached to the allene (Figure 4) the ^{1}H NMR signal of H_A(anti) in the diacetate derivative of **4e** (Figure 5) should be upfield of H_A(syn)[14] if the reaction proceed via anti attack.

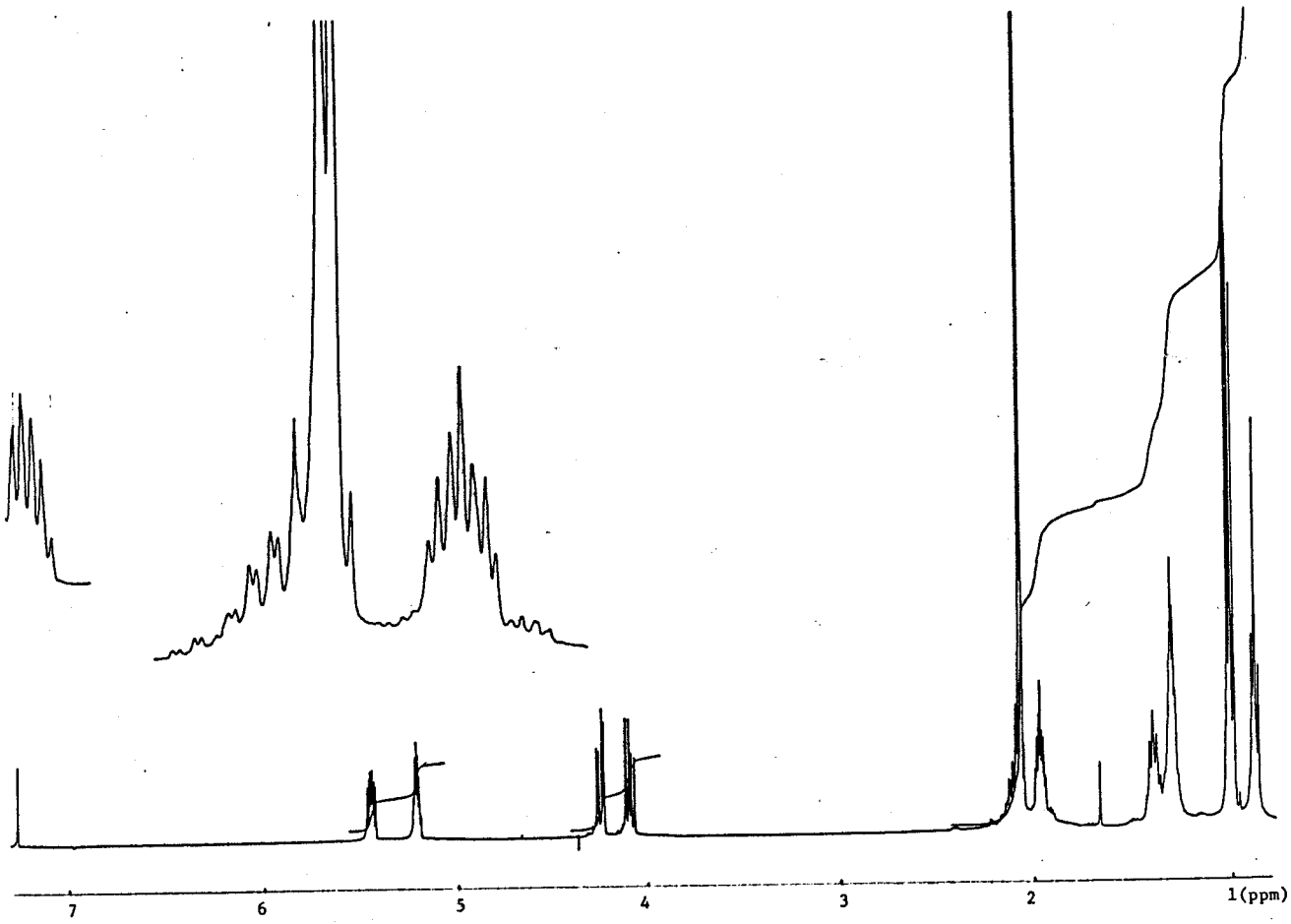


Figure 5: 400 MHz HMR Spectrum of
5-Isopropyl-3,4-decadien-1,2-diacetates, 7d,
Derived from Reaction of 2b with 21a

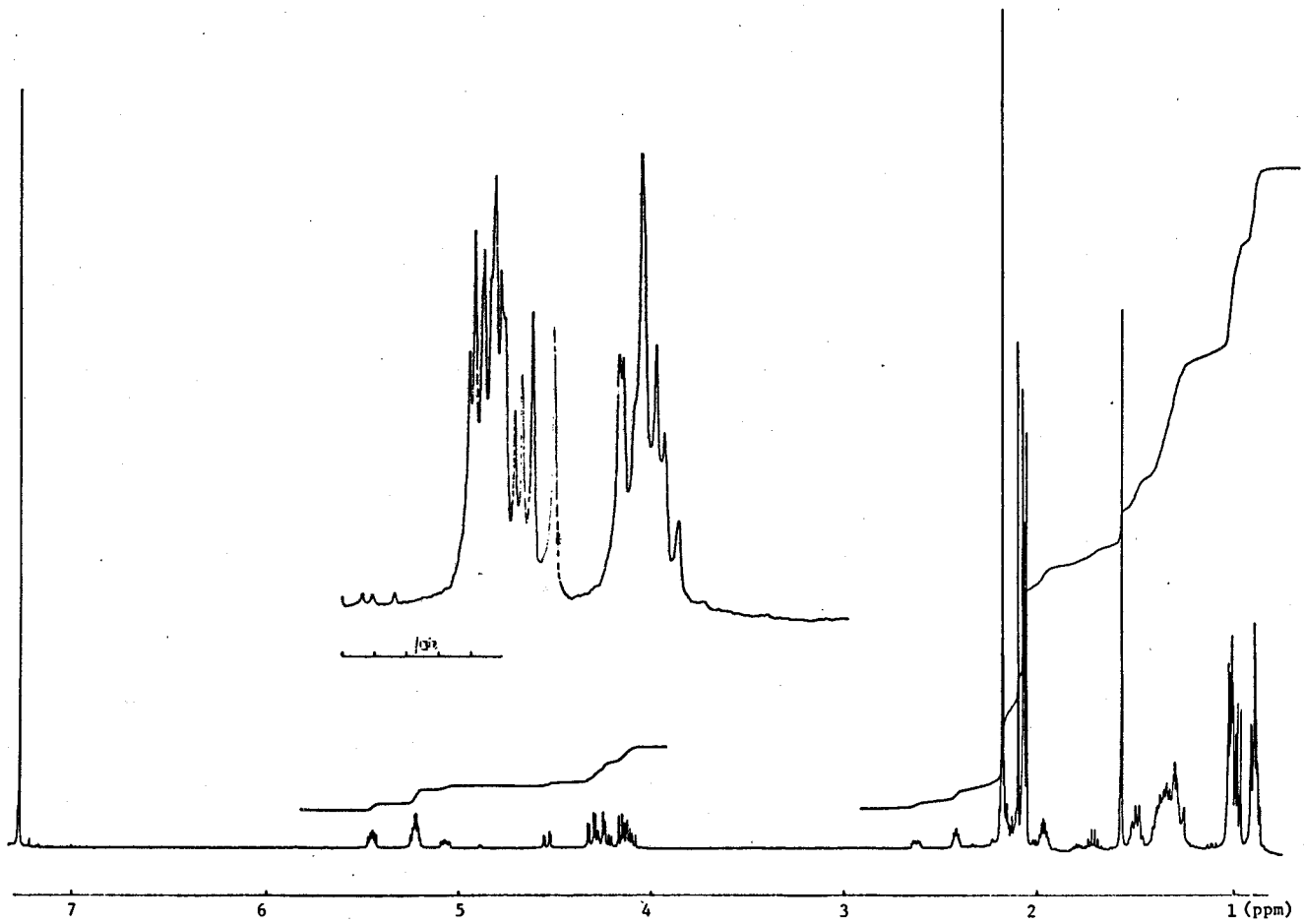


Figure 6: 400 MHz HMR Spectrum of Diastereoisomeric Mixture of 5-Isopropyl-3,4-decadien-1,2-diacetates Derived from Reaction of 2b with Isopropyl Magnesium Bromide

The reaction of **2b** with **21d** yielded **4e** which gave a diacetoxy derivative that was mainly one product by GLPC. The product, **7d**, also exhibited only one AB coupled quartet belonging to H_A on C-1 in its ^1H NMR spectrum (Figure 5, Scheme 8). A minor product was identified as alkylated alkyne **12b**.

Reaction of **2b** and isopropyl magnesium bromide at 0°C for 1 hr gave a mixture of two diastereoisomers of **4e** which were identified by GLPC, ^1H NMR (Figure 6) and IR spectral analyses.

We conclude that the reactions of organocuprates **8a** and **21** with substituted epoxyalkynol **2b** proceed in an anti S_N2' fashion. Examination of Table 1 reveals that most reactions proceeded by anti S_N2' attack. However, as the size of the alkyl group on organocuprate became equal to or smaller than ethyl (ie R"=Et, Me), the diastereoselectivity of the reaction was decreased (Table 1, entries h and i).

5. The Effect of Solvent on the Coupling Reaction

It was previously reported[14] that coupling organocuprates with epoxyalkynols was not highly diastereoselective because the organocuprate caused racemization of the allene products. For example, it was reported that the coupling of **8a** with **2a** became highly

diastereoselective when the cuprate was stabilized by dimethyl sulfide[14]. In the present work, it was found that organocuprate-dimethyl sulfide complexes also function in a highly stereoselective fashion when dimethyl sulfide was used as a cosolvent (for example, compare Table 1 entry b with Table 2 entry q). In addition, the proportion of alkylated alkyne **9** increased (Table 2 entry q) when organocuprate **8a** was reacted with **2b** without dimethyl sulfide solvent. Finally, if the reaction between **2b** and **8a** was conducted at high (2°C) temperature, in the absence of dimethyl sulfide a complex mixture of more than six products was evident by GLPC analysis. (Table 2 entry s).

In an experiment to examine the effect of HMPA, epoxyalkynol, **2b**, was coupled with **21c** in a mixture of diethyl ether and dimethyl sulfide to give allene **4d** with a low diastereomeric excess. If 20% (v/v) of HMPA was added to the reaction immediately after addition of **2b** and the reaction temperature increased slowly to room temperature, the yield and diastereoselectivity of the reaction increased. (Table 1, entries h and l).

6. The Effect of Using Inverse Addition on the Coupling Reaction

Time course GLPC analysis of the reaction mixture generated from coupling **2b** and **8a** revealed that the amount of alkylated allene **4c** did not increase 15 minutes after addition of **2b**. However, the amount of non-alkylated allene **10** and alkyne **11** both increased beyond this time. Moreover, it was found that the proportion of alkylated allene **4c** increased with increasing reaction temperature. We therefore suspected that the coupling reaction of **2b** with **8a** was partly completed during the time taken to add **2b** to the solution of **8a**, and that the intermediates leading to non-alkylated allene **10** and alkyne **11** were produced during that time. Copper(I) catalysis of organic reactions is well known[24] and the product ratios might, therefore, be a function of the concentration of copper(I) or organocuprate during reagent mixing. Inverse addition (*i.e.* method B---adding organocuprate solution to the solution of **2b**) might, therefore, give different product ratios.

Following this line of reasoning we reacted lithium dibutylcyanocuprate **22a** with **2b** using the inverse addition procedure. The reaction was slowly warmed to room temperature and the products isolated. The formation of the alkylated alkyne, **9a**, non-alkylated allene, **10**, and non-alkylated alkyne, **11** was greatly inhibited (Table 4, entry a, Figure 7) while the yield of alkylated allene, **4c**, increased to 72% (isolated after acetylation).

Table 4: Reaction of Organocuprates with Epoxyalkynol 2b Using Inverse Addition Method (Method B)

	Epoxyalkynes R	R'	R"M	Copper(I)	Sol[1]	T[6](C)	Yield of 4+9[2](4/9)[3]	A/S of 4	Yield of 10+11[2](10/11)[3]	A/S of 10	Conversion[3]
a,	n-pentyl	CH_2OH	n-BuLi	CuCN	E	20	70.4(99:1)	>99/1			100
b,	"	"	n-BuMgBr	$CuBrMe_2S$	E/D	20	73.1(99:1)	>99/1			100
c,	"	"	3MeLi	1.5CuCN	E	-30	62.7(90:10)	95/5			100
d,	"	"	MeLi	$CuXMe_2S$[4]	E/D	20	99(96:4)	60/30			100

[1]E/D; Represents three portions of anhydrous diethyl ether to two portions of dimethyl sulfide; E; Represents anhydrous diethyl ether only. [2]Isolated yield by flash column chromatography. [3]Determined by GC and/or ^1H NMR with about +/- 10%. [4]X; represents n-hexynyl. [6]Organocuprate was added to the starting material 2b at -70°C and warmed slowly to the temperature indicated.

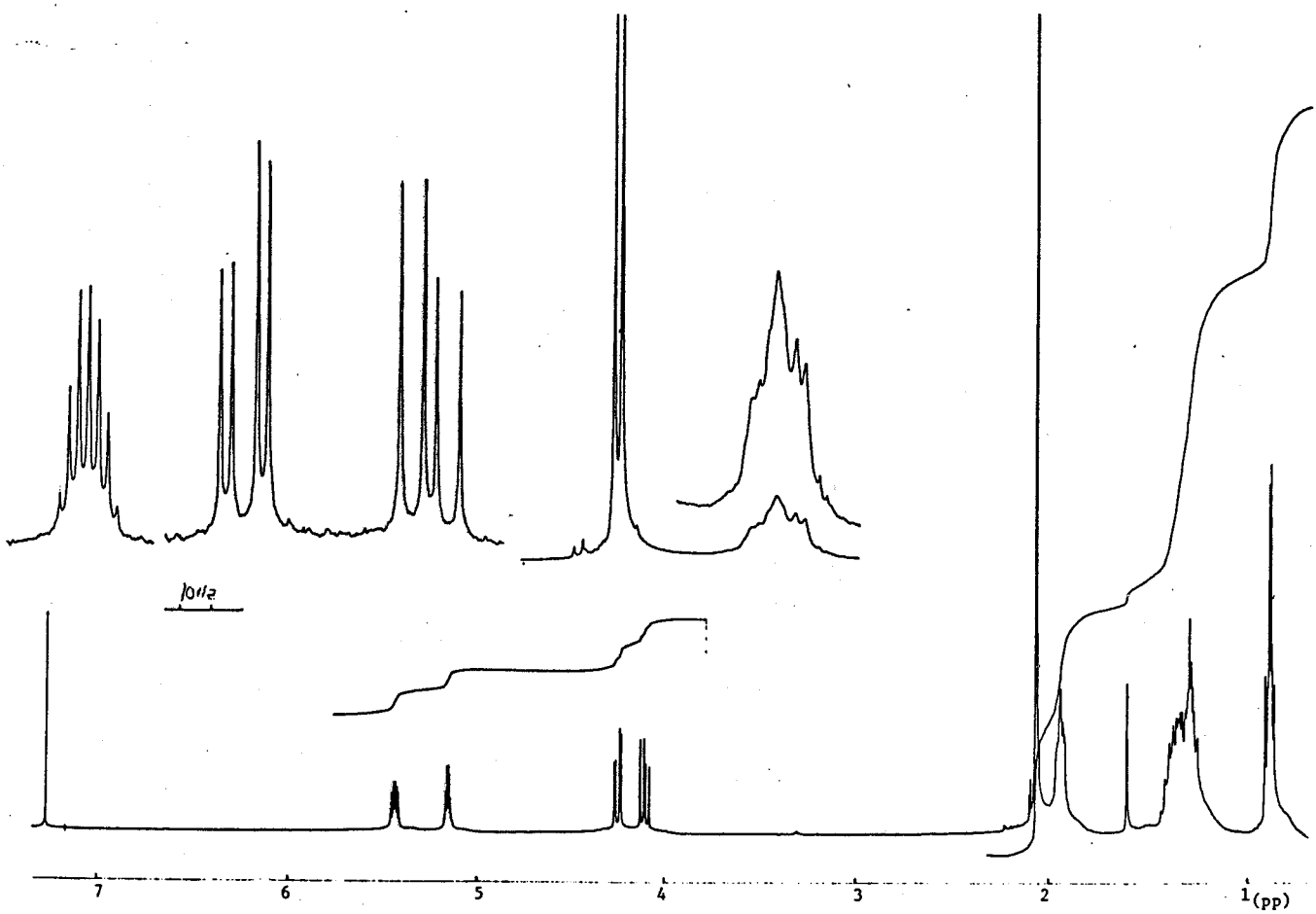


Figure 7: 400 MHz HMR Spectrum of
5-n-Butyl-3,4-decadien-1,2-diacetates, 7b,
Derived from Reaction of 2b with 22a
by Inverse Addition Method

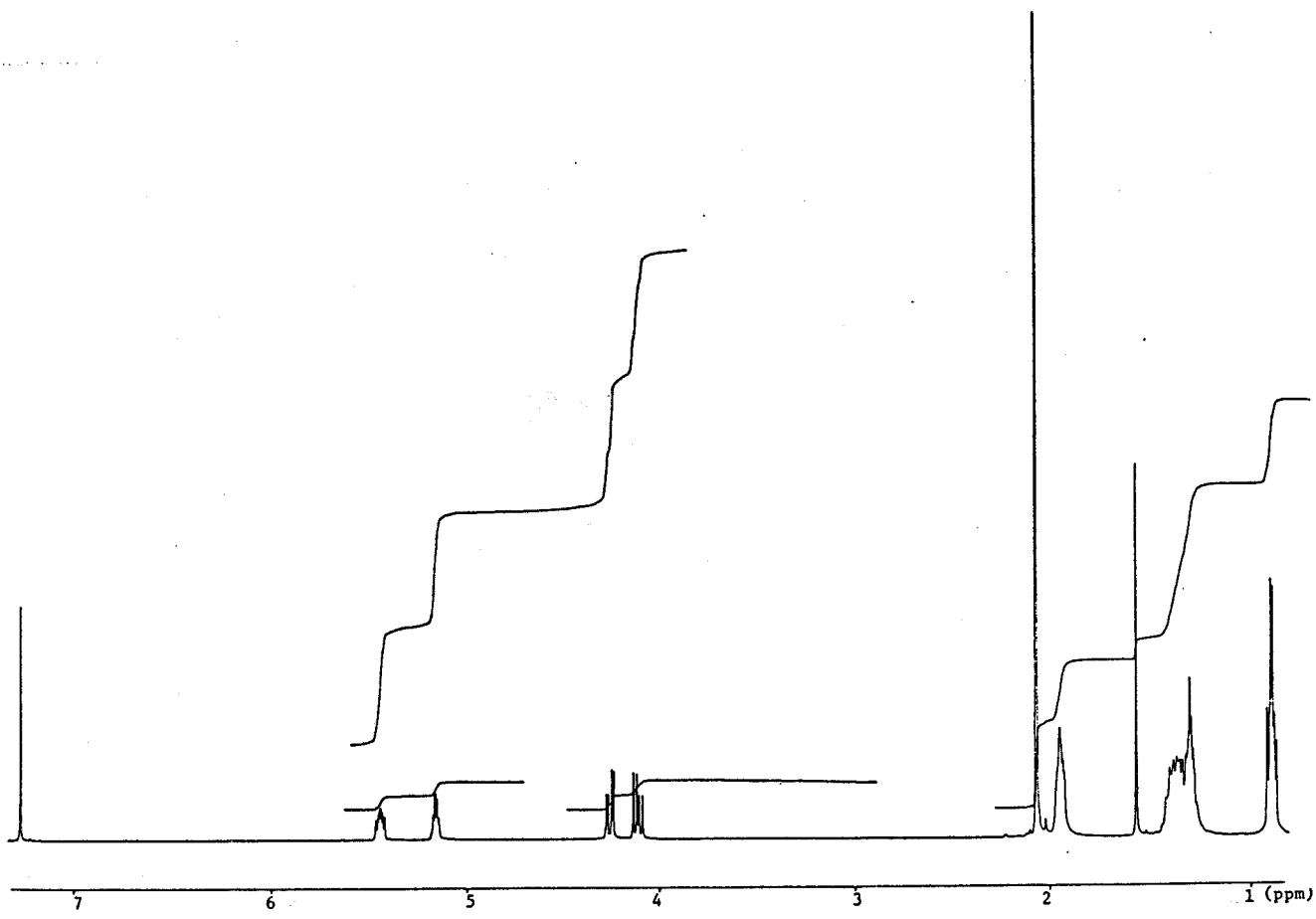


Figure 8: 400 MHz HMR Spectrum of
5-n-Butyl-3,4-decadien-1,2-diacetates, 7b,
Derived from Reaction of 2b with 21d
by Inverse Addition Method

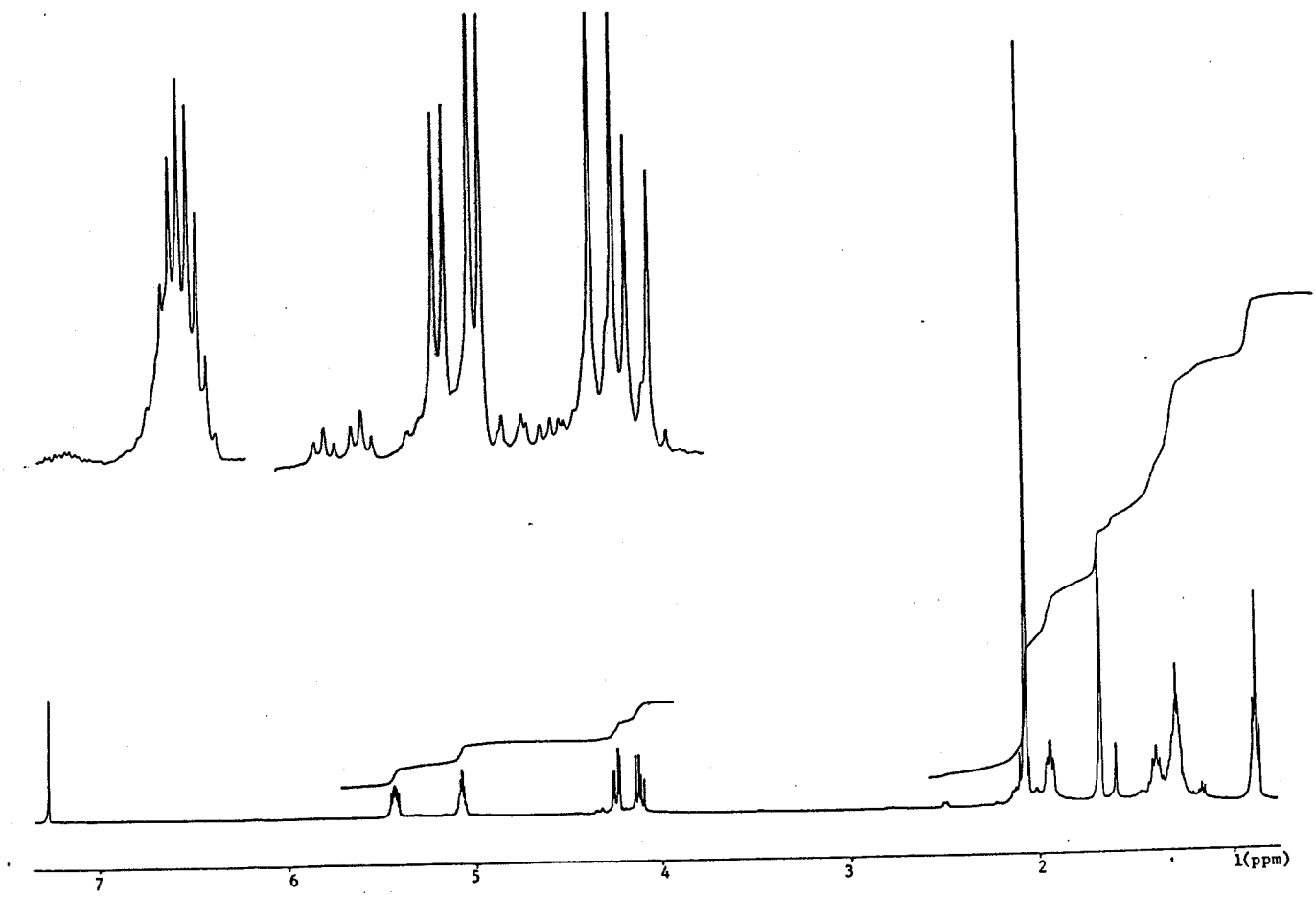


Figure 9: 400 MHz HMR Spectrum of
5-Methyl-3,4-decadien-1,2-diacetates, 7f,
Derived from Reaction of 2b with 22b
by Inverse Addition Method

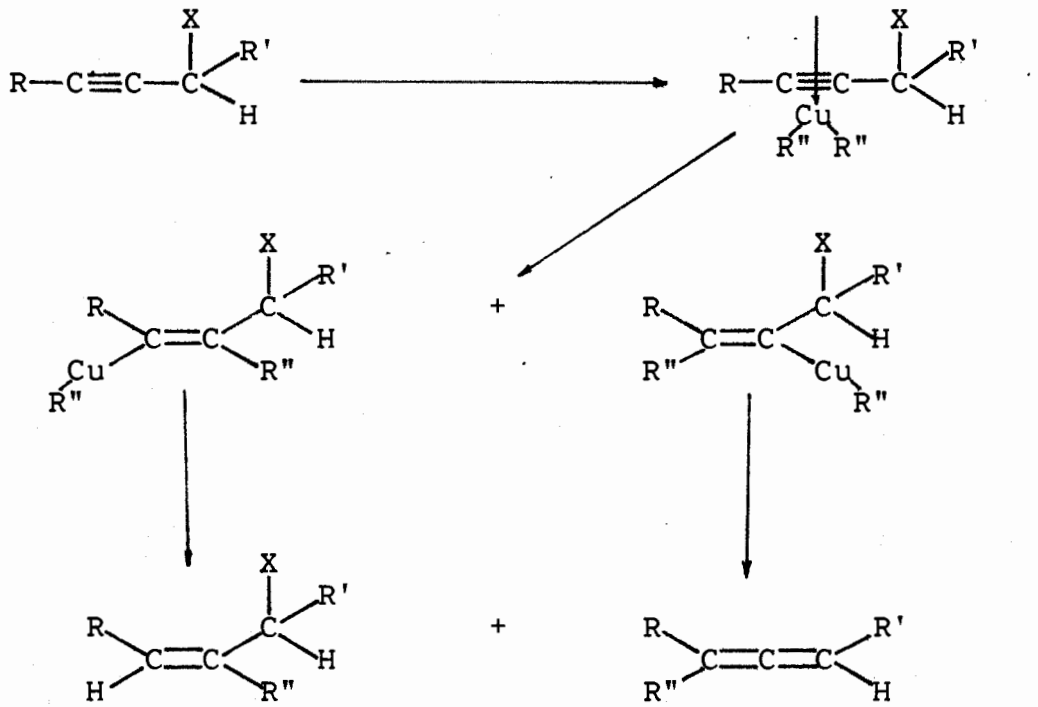
Reaction of **21d** with **2b** by method B, (Table 4, entry b) gave **4c** in high diastereoisomeric purity. Both GLPC and ^{1}H NMR spectral (Figure 8) analyses revealed that the alkylated diacetoxy allene produced from **2b** and **21d** was **7bA**. This result clearly showed that organocuprates prepared from Grignard reagents give anti S_N2' displacement (Table 4).

Lithium dimethylheptynylcuprate, **25**, reacted with **2b** by inverse addition method gave only alkylated allene, **4d**, and alkyne, **9d** (total yield 99%) (Table 4, entry d). The alkylated allene in this reaction was predominantly that expected from anti attack (3 : 1). Lithium dimethylcyanocuprate, **22b**, reacted with **2b** below -30°C, to give 63.7% of alkylated allene **4d** (after acetylation). The diastereoselectivity of this reaction was 95% anti (Table 4 entry c, Figure 9).

7. Mechanistic Considerations on the Coupling Reaction

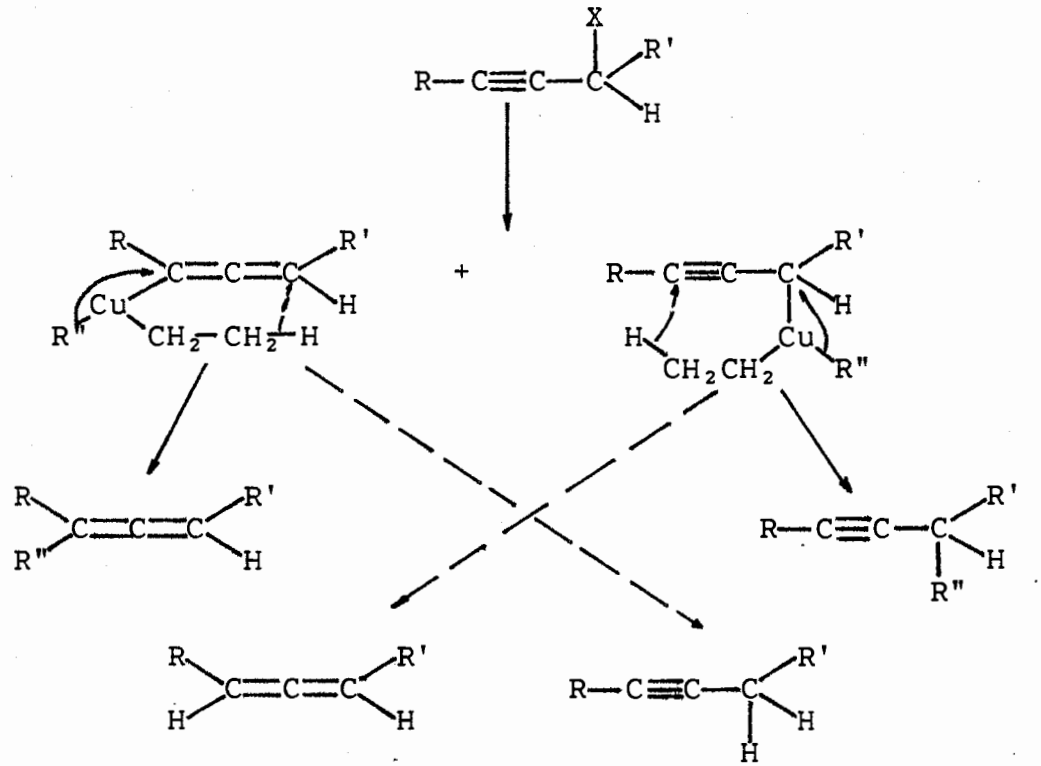
Although several mechanisms have been advanced to explain the formation of both alkylated and non-alkylated products from the reaction of organocuprates with propargyl derivatives, none can fully explain the regio- and stereochemistry of the present reaction. One mechanistic proposal involves formation of an organocuprate-alkyne complex followed by carbocupration to yield regioisomeric

vinyl cuprates[25] (Scheme 10). According to this process, allenes are formed from propargyl derivatives via a carbocupration to give two vinyl cuprate intermediates. Subsequent elimination of one vinyl cuprate regioisomer[25] gives the allene. In the present case no obvious products arising from the alternative vinyl cuprate regioisomer were detected. This proposal also cannot explain how non-alkylated products are formed.



Scheme 10: Carbocupration Mechanism for Reaction of Organocuprates with Propargyl Derivatives.

A second mechanistic proposal (Scheme 11) for which there is experimental evidence involves S_N2'[26] and S_N2[21]



Scheme 11: Alkynyl-Allenyl Cuprate Mechanism for Reaction of Organocuprates with Propargyl Derivatives.

attack of the propargyl system by the cuprate to generate allenyl copper and propargyl copper intermediates respectively. These may undergo reductive elimination to yield alkylated allenes and alkynes[26]. Alternatively, the copper intermediates generated may undergo hydrolysis, or hydride transfer with rearrangement to yield non-alkylated products[21]. Since both alkylated and non-alkylated allenes are derived from the same intermediate by this proposal, both should have the same diastereoisomeric enrichment. In

the present study, high diastereoisomeric selectivity was encountered for formation of alkylated allene products but not for reduced allene products. The mechanism in Scheme 11 cannot explain why reductive elimination should be a highly stereoselective reaction, whereas β-hydrogen transfer should be a non stereoselective process. Since we did not conduct any labelling studies, the mechanism is still unknown.

We can conclude that using the inverse addition method, appropiate temperature and organocuprate one can achieve high regioselectivity and stereoselectivity in additions of these reagents to epoxyalkynes. Moreover, the allene products from S_N2' reaction are formed as a result of anti attack.

SECTION III

CONFORMATIONS OF ALLENYL-1,2-DIOLS AND ALLENYL-1,2-DIACETATES

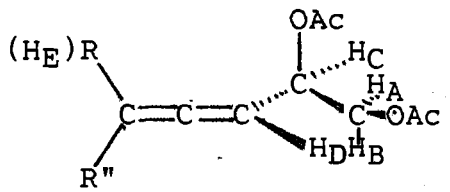
Since allenes are becoming important intermediates for organic synthesis (eg. formation of dienes), the conformation of the allenic functional group in relation to other functional groups is of some interest. We have found the reaction of organocuprates **8**, **21** or **22** with epoxyalkynol **2b** to be a diastereoselective reaction giving moderate yields of alkylated 5-substituted-3,4-decadien-1,2-diols, **4**, and small amounts of 3,4-decadien-1,2-diol, **10**. After acetylation, **4** and **10** gave 5-substituted-3,4-decadien-1,2-diacetate, **7**, and 3,4-decadien-1,2-diacetate, **12**, respectively. The conformations about the C-2 to C-3 bond, and about the C-1 to C-2 bond in allenes **4**, **10**, **7** and **12** based on ^{1}H NMR data will be discussed in this Section.

1. The Conformation about C-2 and C-3 in 3,4-Dienyl-1,2-diacetates

The chemical shifts and hydrogen-hydrogen coupling constants of hydrogens on C-1, C-2 and C-3 of **7** and **12** are shown in Table 5. The ^{1}H NMR spectra of all allenic-diacetates **7** and **12** show one set of multiplets

centered around 5.1 ppm and another set centered around 5.4 ppm. The assignment of these two multiplets was carried out by decoupling techniques, which showed that the multiplet centered at 5.4 ppm exhibits vicinal hydrogen-hydrogen couplings with the two methylene hydrogens (H_A and H_B between 4.0 to 4.3 ppm respectively) on C-1 and with the hydrogen giving rise to the multiplet centered at 5.1 ppm.

Table 5: Chemical Shifts and Coupling Constants for Allenyl-diacetates 7 and 13.



R	R"	H_D (ppm)	H_C (ppm)	$^3J_{CD}$[1]	X_a
$n-C_5H_{11}$	H	5.02	5.46	6.2-6.6	0.2-0.3
$n-C_5H_{11}$	CH_3	5.08	5.43	5.9	0.2
CH_3	$n-C_5H_{11}$	5.08	5.43	6.2	0.3
$n-C_5H_{11}$	C_2H_5	5.18	5.44	6.0	
$n-C_5H_{11}$	$n-C_4H_9$	5.15	5.45	6.1	0.3
$n-C_4H_9$	$n-C_5H_{11}$	5.31	5.42		
$n-C_5H_{11}$	$i-C_3H_7$	5.22	5.44	6.1	0.3

[1]With accuracy +/- 0.4 Hz.

The multiplet centered at 5.1 ppm exhibits both the vicinal hydrogen-hydrogen coupling mentioned above and five-bond hydrogen-hydrogen couplings with hydrogens on C-6 and C-11 (at about 2.0 ppm). Thus the multiplet centered at 5.4 ppm

is characteristic of the C-2 hydrogen (H_C), whereas the multiplet centered at 5.1 ppm is characteristic of the C-3 allenic hydrogen (H_D). The assigments are in agreement with those reported for secondary α-allenylacetates[27].

Diacetates 7 and 13 may exist in three stable conformations about the C-2, C-3 bond: rotamer A, in which H_C and C-1 are gauche to H_D and the C-2 acetate is almost eclipsed with the center allenic carbon (C-4); rotamer B, in which H_C and the C-2 acetate are gauche to H_D and C-1 is approximately eclipsed with C-4; and rotamer C, in which both the C-2 acetate and C-1 are gauche to H_D but H_C is anti to H_D (Figure 10). As the size of R" increases, the vicinal coupling constant $^3J_{CD}$ increases (Table 5). This is most consistent with rotamer A and B as the preferred conformations since any change in rotamer C where H_C and H_D are antiparallel would lead to a smaller coupling between H_C and H_D.

A rationale for A and B as the stable rotamers can be advanced based on steric grounds. It has been reported[31] that the angle between the two σ bonds of the methylene groups in allenes (angle α) are smaller than or equal to 120° (Figure 11). Accordingly the angle between the sigma bonds and the double bond (angle β_1 and β_2) of the methylene groups in allenes are larger than or equal to 120°[31]. In rotamer C, the C-2 acetate and the C-1 acetate

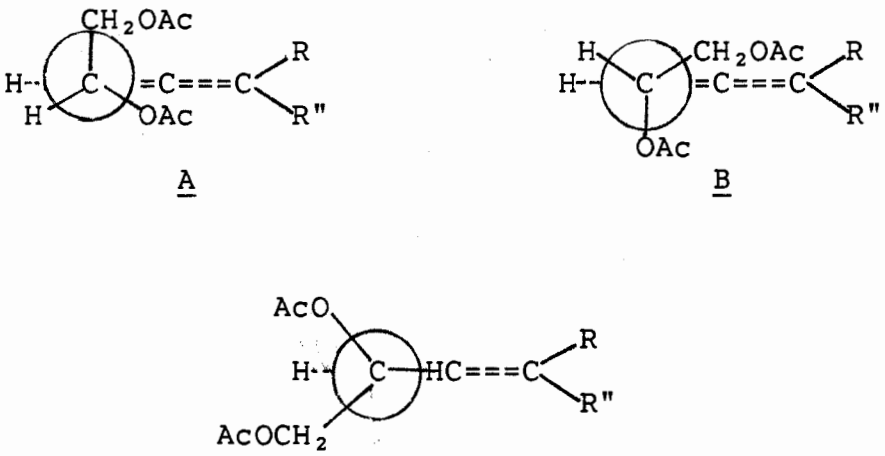


Figure 10: Conformation of 3,4-Dienyl-1,2-diacetates.

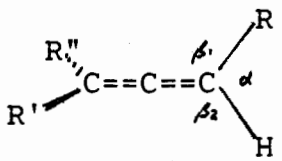


Figure 11: Bond Angles in Allenes.

will create more steric interference with H_D as the angle α decreases. In other words, rotamer C is suspected not to be the preferred conformer. The above argument has also been applied by Sharpless[28] and Doutheau[29] to explain stereoselectivities in the epoxidation of allylic alcohols. In the case of 5-alkyl-3,4-dien-1,2-diacetates, if the C-5

alkyl group (R) is n-pentyl and the other (R") C-5 substituent is hydrogen, methyl, ethyl or n-butyl, rotamer A will become more preferred than B as R is more bulky than R".

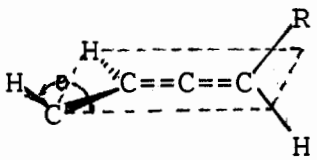
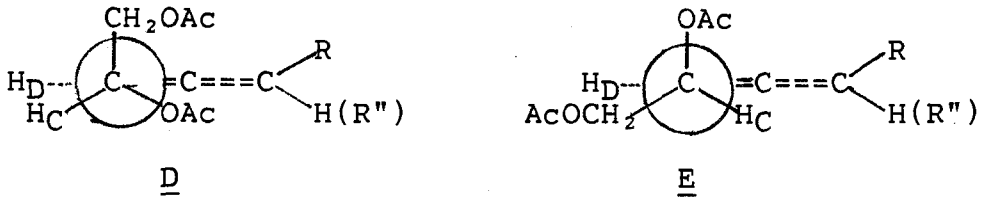


Figure 12: Conformational Analysis of α-Substituted Allenes.

Long range five bond hydrogen-hydrogen coupling constants and short range vicinal coupling constants observed in the ^{1}H NMR spectra of allenes have been used for conformational investigations[32].

$$^5J_{CE} = 2.25\sin^2\theta + 1.18 \quad \text{.....(eq 1)}$$

Equation 1[30] relates the expected five bond coupling ($^5J_{CE}$) to conformation (Figure 12), and has been successfully used in several allene[30-32] systems. In 3,4-dienyl-1,2-diacetates of interest to us, only C-5 monoalkylated allenes such as **13** can produce this long range coupling. The ^{1}H NMR spectrum of **13** gives a value of $^5J_{CE}$ = 2.2 Hz. According to equation 1, θ is near 40° or 140°. The conformation about C-2 and C-3 in allene **13** with θ approximatly 40° (*i.e.* rotamer E) will not be preferred because the C-1 acetate is almost eclipsed with



D E

Figure 13: Conformational Isomerism in 3,4-Dienyl-1,2 Diacetates about the C-2, C-3 Bond.

H_D. The conformation with θ approximatly 140° (*i.e.* rotamer D) is expected to be preferred. The value of θ suggests that H_C on C-2 and H_D on C-3 are gauche to each other.

A conformational analysis of allenes based on vicinal coupling $^3J_{CD}$ has also been performed[31-33], using standard values of $^3J_{CD}$=11 Hz (^3J_a) for H_C trans to H_D and $^3J_{CD}$=4.3 Hz (^3J_g) for gauche arrangements[33]. According to equation 2[33]:

$$^3Jobs = X_a\,^3J_a + (1-X_a)\,^3J_g \quad \text{.....(eq2)}$$

the mole fraction of the anti conformation (X_a) in 7 and **13** are as recorded in Table 5. All X_a's are calculated to be around 0.3, in agreement with calculations using Equation 1 which indicated a conformation with a gauche arrangement of H_C and H_D (A and B).

2. The Conformation about C-1 and C-2 in 3,4-Dienyl-1,2-diacetates

It is well known that the NMR spectrum of an acyclic compound containing both a methylene group with a neighbouring asymmetrically (or pseudoasymmetrically) substituted group can be considerably more complex than would be expected on the basis of simple spin-spin coupling rules. Such methylene hydrogens should exhibit a signal for each methylene hydrogen because the time-averged magnetic environments of the two hydrogens differ, and no rotational process can bring about exchange between these two environments[34]. In such cases methylene hydrogens are diastereotopically related, and distinguishable by NMR.

The C-1 methylene hydrogens in allenyl-1,2-diols **4** and **10** produced from the coupling of organocuprate reagents **8**, **21** and **22** with **2b** are diasterotopically related and are exhibited as two AB coupled quartet in the ^{1}H NMR spectra of these compounds. However, in some cases, if small amounts of acid are present in the sample, interchange with the alcoholic hydrogens will occur and result in broadening of the AB coupled quartet. To prevent this, all allenyl-1,2-diols were acetylated prior to ^{1}H NMR analysis. In spite of the potential for intermolecular hydrogen bonding, conformations of the diols and the corresponding

diacetates are suspected to be similar. Indeed we observed that the coupling constants ($^2J_{AB}$, $^3J_{AC}$, $^3J_{BC}$) within these two sets of AB coupled quartets in the diols and their diacetate derivatives were in close agreement (Table 6).

Table 6: Chemical Shifts and Coupling Constants for Allenyl-1,2-Diacetates 7 and 13.

		Chemical Shifts		Coupling Constant[1] of diols		diacetates	
R	R"	H_A(ppm)	H_B(ppm)	$^3J_{AC}$	$^3J_{BC}$	$^3J_{AC}$	$^3J_{BC}$
H	$n-C_4H_9$	4.12					
$n-C_4H_9$	H	4.13					
$n-C_5H_{11}$	H	4.13	4.26			7.5	3.6.
H	$n-C_5H_{11}$	4.12	4.27			7.4	3.7
$n-C_5H_{11}$	CH_3	4.11	4.24	7.2	3.5	7.4	3.6
CH_3	$n-C_5H_{11}$	4.10	4.24				
CH_3	$n-C_5H_{11}$	4.10	4.24			7.6	3.7
$n-C_5H_{11}$	CH_3	4.11	4.24			7.4	3.7
C_2H_5	$n-C_5H_{11}$	4.10	4.25	7.3	3.4	7.6	3.7
$n-C_5H_{11}$	C_2H_5	4.10	4.25	7.3	3.4	7.6	3.7
$n-C_5H_{11}$	$n-C_4H_9$	4.10	4.25			7.6	3.7
$n-C_4H_9$	$n-C_5H_{11}$	4.08	4.29			8.3	3.6
$n-C_5H_{11}$	$n-C_4H_9$		4.25			7.6	3.7
$n-C_5H_{11}$	$i-C_3H_7$	4.08	4.24	7.3	3.2	7.6	3.7
$i-C_3H_7$	$n-C_5H_{11}$	4.11					

[1]With accuracy +/- 0.4 Hz

The AB coupled quartets at high field (centered around 4.1 ppm) are assigned to H_A whereas the AB coupled quartets at low field (centered around 4.25 ppm) are assigned to H_B. The vicinal couplings between H_A and H_C ($^3J_{AC}$) of 7 and 13 are approximately 7.5 Hz, whereas the vicinal couplings between H_B and H_C ($^3J_{BC}$) are around 3.5 Hz. Vicinal hydrogen-hydrogen coupling, in general, depends on the

dihedral angle γ and this coupling constant increases in the order gauche ($\gamma = \pi/3$) < cis ($\gamma = 0$) < trans or anti ($\gamma = \pi$) in the absence of influences other than γ[35]. Thus H_A is suspected to be anti to H_C while H_B is gauche to H_C, as the values of $^3J_{AC}$ are about twice as large as the value of $^3J_{BC}$ (Table 6).

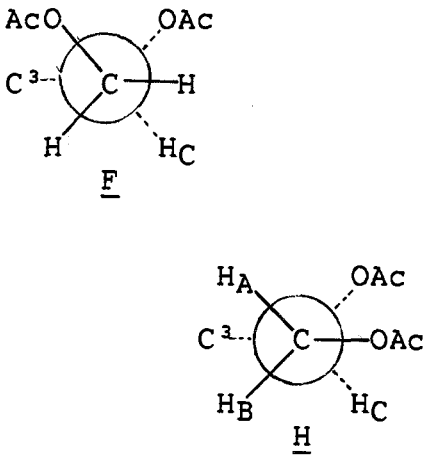


Figure 14: Conformational Isomerism in 3,4-Dienyl 1,2-Diacetates about the C-1, C-2 Bond.

The three probable rotamers about C-1 and C-2 in 7 and 13 are shown in Figure 14. In rotamer F, the C-1 acetate bond bisects the angle between the C-2 acetate and the C2-C3 bond. In this conformation, both methylene hydrogens on C-1 will be gauche to H_C. In rotamer G, the C-1 acetate is gauche to H_C, while H_C is anti to H_A but gauche to H_B. In rotamer H, the C-1 acetate is gauche to the other C-2 acetate which requires

H_C to be in the same relation to H_A and H_B as in rotamer G.

Rotamer F appears to be an unfavorable conformation in the 1,2-diacetoxy-3,4-allenes because there is a significant steric interaction between the C-1 acetate and the C-2 acetate as well as C-3. Furthermore, rotamer F requires both methylene hydrogens on C-1 to be gauche to H_C, suggesting that the values of $^3J_{AC}$ and $^3J_{BC}$ in 7 and 13 should be close, (they are quite different, Table 6). Finally, it has been reported that with three adjacent polar bonds on 1,1,2-trisubstituted ethanes, the conformations wherein all three polar bonds are gauche are not favoured[36].

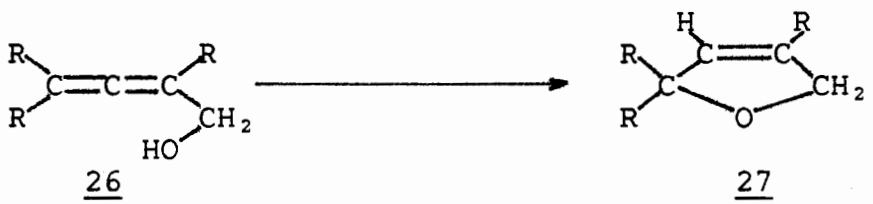
Several different *α*-hydroxy and *β*-hydroxy allenes have been investigated by NMR[37-40]. The methylene hydrogens in some of these allenes, similar to 1,2-diacetoxy-3,4-dienes 7 and 13 give rise to two different vicinal couplings[37]. The larger coupling constants (6 to 11 Hz)[37] are attributed to anti hydrogen coupling, while the smaller coupling constants (2 to 5 Hz)[37] are due to gauche hydrogen coupling.

The above is consistent with the preferred conformation being G or H in 7 and 13 and we expect G and H to be the preferred conformations in 4 and 9. Hydrogen bonding may influence the preference for conformer G and H in 4 and 9. It has been reported that 1,2-diols hydrogen bond[41]. Moreover, intramolecular alcohol hydrogen bonding with

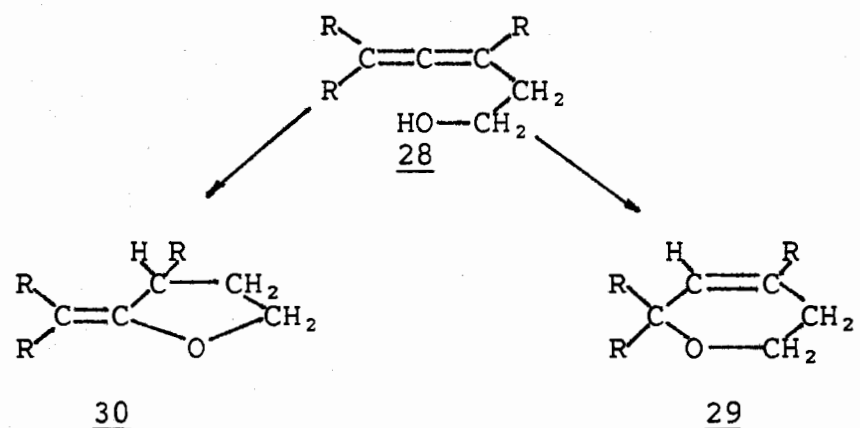
allenes has also been reported[42]. As both **4** and **9** have an allenic function on C-2 and a hydroxy group on C-1 and C-2, the alcohol on C-1 can hydrogen bond to the alcohol on C-2 which in turn could hydrogen bond to the allene. This could yield a more stable conformation than if the two alcohols are each hydrogen bonded to the allene. This analysis suggests that conformation H is more stable than G for the diols as previously suggested for the diacetates[43].

3. Cyclization of 5-Methyl-3,4-decadien-1,2-diol

It has been reported that in the presence of base, acid and metallic salt[44], *α*-allenyl alcohols, **26**, cyclize to



26 **27** (eq 3)

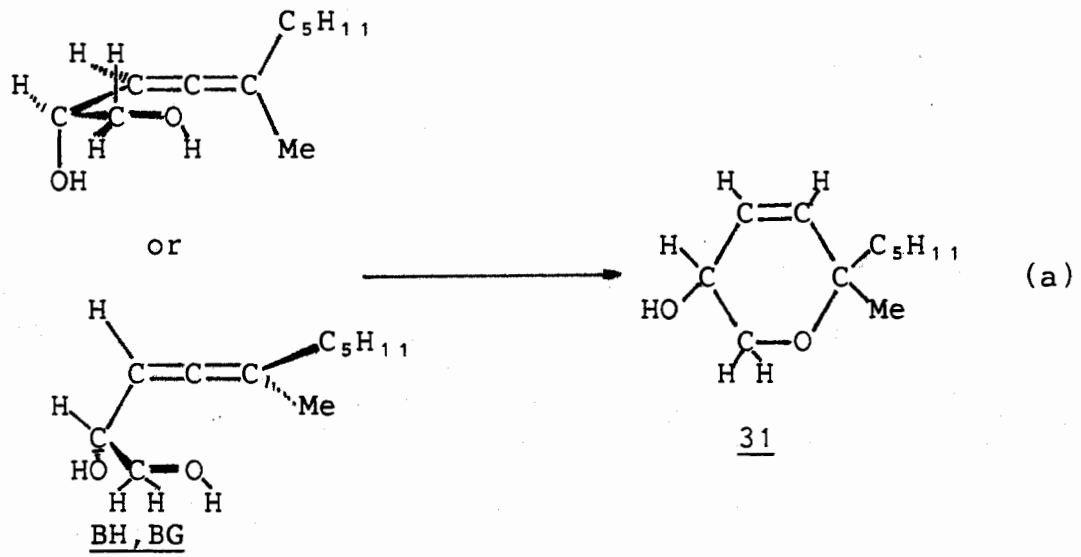


28

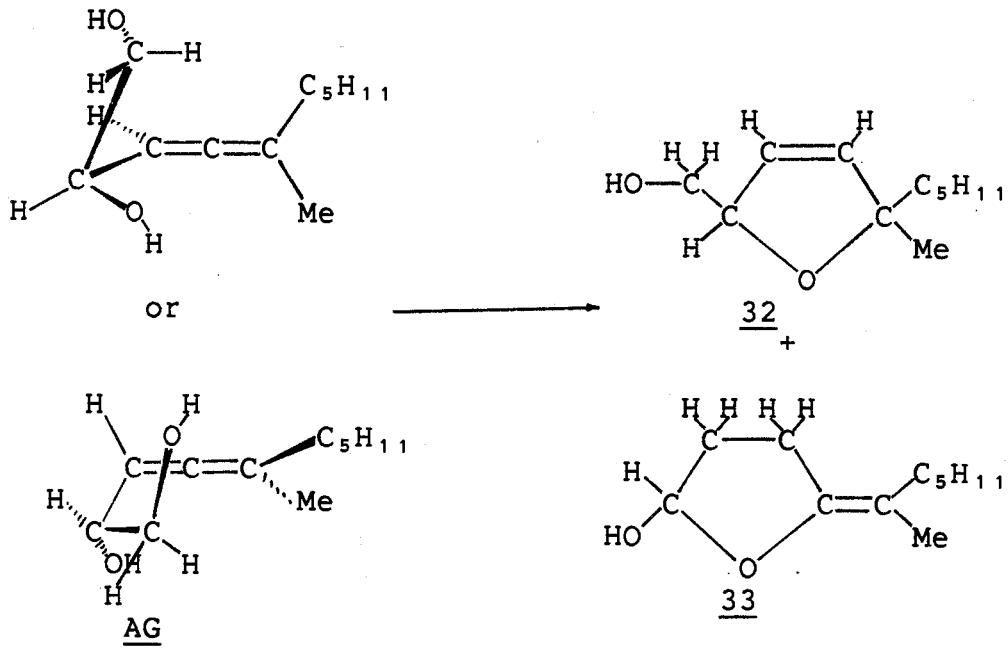
30 **29** (eq 4)

dihydrofurans, 27[45,46] (Equation 3) whereas β-allenyl alcohols, 28, cyclize to dihydropyrans, 29[46,47], or 2-methylenetetrahydrofurans, 30[48] (Equation 4). It has also been found that reactions of 2,4-dinitrobenzenesulphenyl chloride[47], benzeneselenyl chloride[50] or silver nitrate[49] with asymmetrically substituted allenyl alcohols are highly stereoselective. Their reactions are suspected to occur through nonallylic cations[47,51].

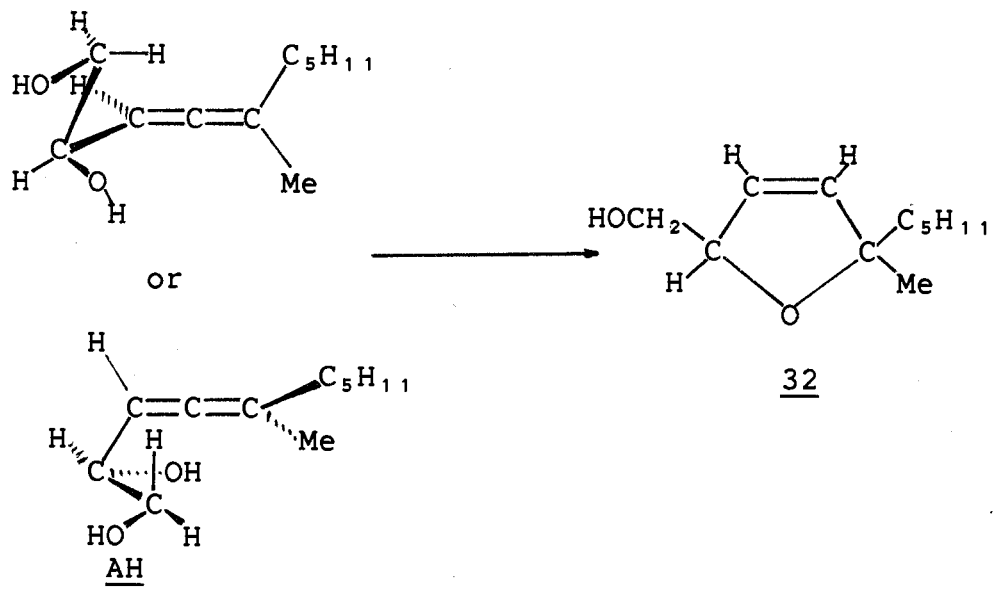
Since allenyl-1,2-diols 4 and 9 have both α and β hydroxyls, three situations which would give reactions may occur. If the diol reacts via the B conformation, wherein the C-1 alcohol is almost eclipsed with the center carbon



Scheme 12: Cyclization of α- and β-Hydroxyallenes with Conformation BH or BG.



Scheme 13: Cyclization of α- and β-Hydroxyallenes with Conformation AG.



Scheme 14: Cyclization of α- and β-Hydroxyallenes with Conformation AH.

(C-4) of the allene (*i.e.* BH or BG), the cyclization will give a 6,6-disubstituted-3-hydroxypyran, 31 (Scheme 12). If the diol reacts via a conformation wherein the C-2 hydroxyl is eclipsed with the allene (*i.e.* AG), cyclization will give a mixture of 1-hydroxymethyl-5,5-disubstituted furan, 32, and (2,2-disubstituted)methylene-2-hydroxy-3,4-dihydrofuran, 33, because the C-2 hydroxyl is in position to form 32 while the C-1 hydroxyl is in position to form 33. A competition between two different cyclizations is expected (Scheme 13). Finally, if the diol reacts via a combined A and H conformation (*i.e.* AH), cyclization will give only 32 (Scheme 14).

When 5-methyl-3,4-decadien-1,2-diol, **4d**, was added to pyridine at ambient temperature and allowed to stand for several days, no cyclization occurred. However, when **4d** was added to silver(I) nitrate in aqueous solvent, cyclization occurred. After flash column chromatography, GLPC and ^{1}H NMR spectral analyses showed that the product was 80% one compound. The ^{1}H NMR spectrum showed the presence of a signal due to two vinyl hydrogens each of which occurred as a quartet. A multiplet of one hydrogen was observed at 4.89 ppm. Two hydrogens were exhibited as an AB coupled octet located at 3.69 ppm and a similar coupled quintet at 3.56 ppm (Figure 15). The ^{1}H NMR spectrum of this compound did not allow us to determine if the product contained a five or

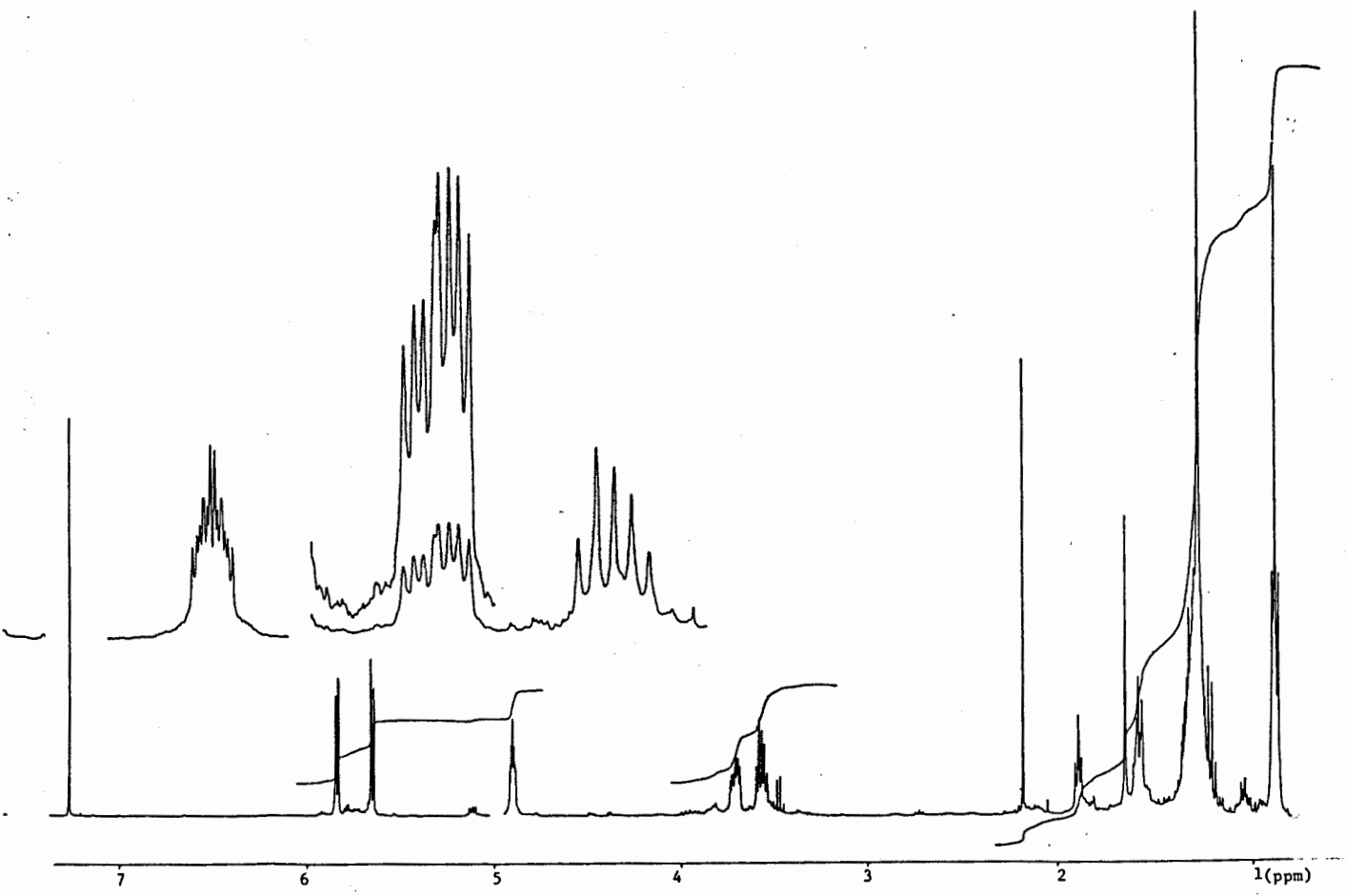


Figure 15: 400 MHz HMR Spectrum of
2-Hydroxymethyl-5-pentyl-5-methylfuran, 32

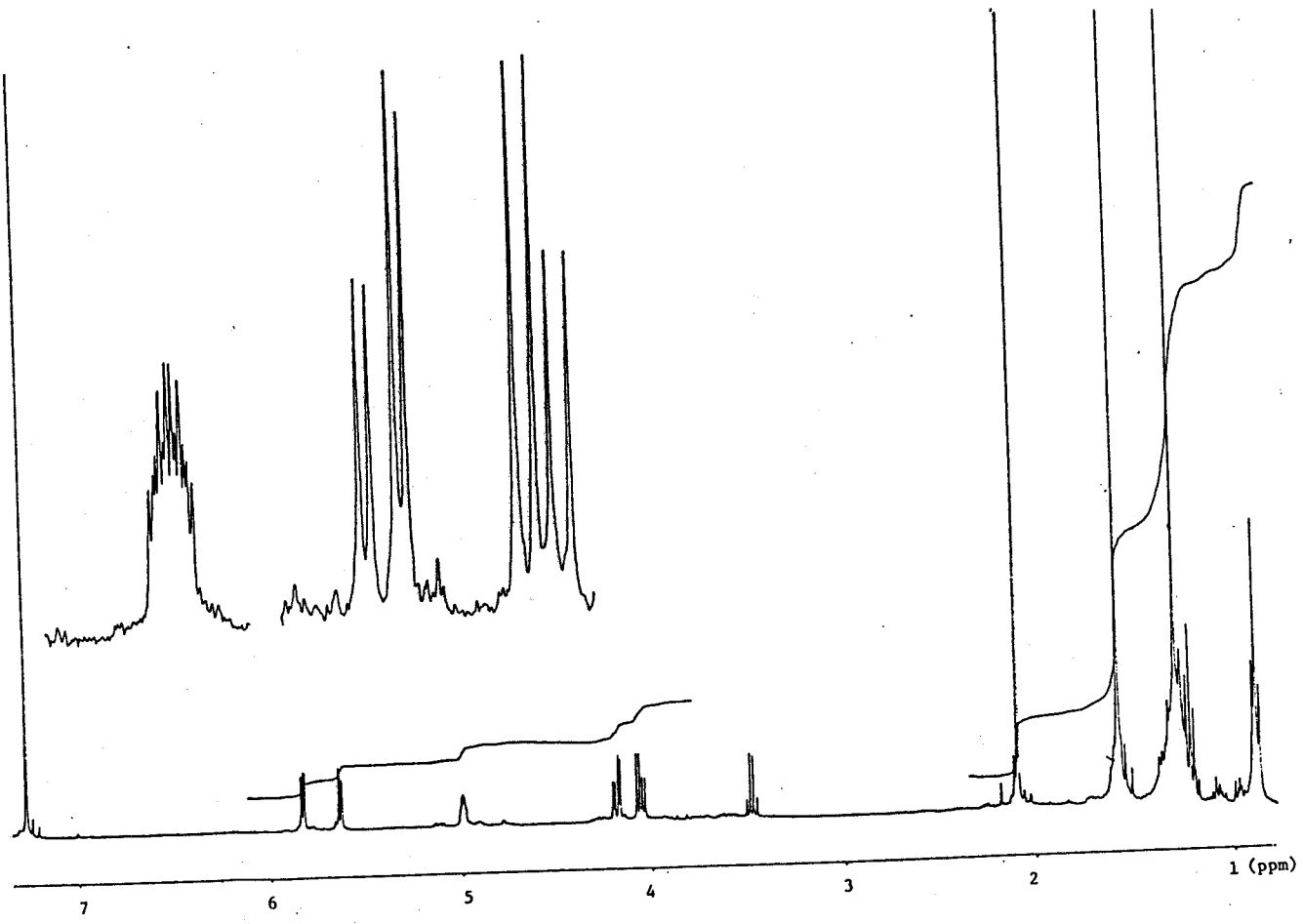


Figure 16: 400 MHz HMR Spectrum of
2-Acetoxymethyl-5-pentyl-methylfuran, 34

six membered ring. After acetylation of the product with pyridine and acetic anhydride, the ^{1}H NMR spectrum of the isolated acetate revealed that the chemical shift of the two vinyl hydrogens and the multiplet did not change significantly. Two observations suggest the product **32** contains a primary alcohol. First, one of the coupling (H-C-O-H) observed in the methylene hydrogens (3-4 ppm) of **32** (Figure 15) disappear when the product is acetylated. Secondary, these hydrogens shift downfield in the acetylated product **34** (Figure 16). Thus, structures **31** and **33** could be ruled out. The ^{1}H NMR spectra of the cyclized compound, **32**, and its acetate, **34**, are consistent with its being 2-hydroxymethyl-5-pentyl-5-methylfuran (Scheme 14).

According to the Curtin and Hammett principle[52], the reacting conformation bears no relation to the ground state conformation of a molecule for most reactions. Since **32** is the only cyclized product, it indicates the reacting conformation of **4d** has H_C gauche rather than anti to H_D and the C-2 alcohol is almost eclipsed with the plane of the allene. The experimental result also suggests that in the reacting conformation, the C-1 alcohol is gauche to the C-2 hydroxyl *i.e.* conformation H. Since we have already argued that the ground state conformation of allenyl-1,2-diols is H, this is not unreasonable.

SECTION IV

EXPERIMENTAL SECTION

1. General Procedures

Routine GLC analyses were carried out with Hewlett Packard 5880A or 5890A gas chromatographs equipped with gas capillary inlet systems and flame-ionization detectors. The columns were 15 m x 0.21 mm ID DURABOND-1 fused silica. Helium was the carrier gas. Injection port and detector temperatures were 275°C.

Column chromatography was performed by the flash chromatography method[17] on Silica gel (Kieselgel 60, 40-63 μm, E. Merck No. 9385). Chromatographic solvents were distilled before use.

Boiling points are uncorrected and recorded during distillation. Boiling points indicated as air-bath temperatures refer to short path (Kugelrohr) distillations.

Infrared (IR) spectra were determined on a Perkin-Elmer 599B infrared spectrophotometer. Samples were run as neat films on NaCl plates. Signal positions are given in ν (cm^{-1}). Intensity and assignment are indicated in parentheses.

Nuclear magnetic resonance ^{1}H NMR and ^{13}C NMR were recorded on a Bruker WM 400 NMR spectrometer. Signal positions are given in δ (ppm) units, with chloroform-D (7.259) as the internal standard. The multiplicity, number of protons, assigments and coupling constants (where possible) are indicated in parentheses. For compounds exhibiting ABX type spectra, the quoted values of J are measured from the line positions, although these values only approximate the actual coupling constants[53].

Low resolution mass spectra were obtained via GLC inlet on a Hewlett-Packard 5985B coupled gas chromatograph-mass spectrometer. All samples were run using electron-impact ionization (70 eV) unless otherwise specified. Samples run with chemical ionization (denoted by CI) were run with isobutane as the ionizing gas unless otherwise stated. High-resolution mass spectra were obtained on a Kratos/AEI MS-50 instrument by Dr. G. Eigendorf at the University of British Columbia.

Elemental analyses were performed by Mr. M. Yang (Department of Biological Sciences, Simon Fraser University) on a Perkin-Elmer Model 240 elemental analyzer.

2. Solvents and Reagents

All reactions requiring anhydrous and/or oxygen free conditions were run under a positive pressure of argon in flamed dried glassware. Tetrahydrofuran (THF) was freshly distilled immediately prior to use. Dry ether and dimethyl sulfide were used directly as commercially supplied.

Cuprous bromide was prepared by the method of Vogel[54], and used after washing with methanol[56] and drying under vacuum.

Cuprous bromide-dimethyl sulfide complex was prepared by the method of House[55].

All other reagents were used as commercially supplied.

Cold temperatures were maintained by use of the following baths[54]: aqueous sodium chloride/ice (0°C), acetone/CO_2 (-70°C), isopropanol/CO_2 (-78°C).

3. Synthesis of (E)-2,3-Epoxydec-4-yn-1-ol (2b)

Preparation of 1-Iodo-hept-1-yne:

A solution of 1-heptyne (9.6 g, 0.10 mol) in anhyd. ether (100 mL) was cooled to -25°C and n-butyllithium (0.11 mol, 2.4 M in hexane) was added via syringe. The mixture was stirred for 20 min, and then finely powdered iodine (28.9 g,

0.11 mol) was added over 15 min. After stirring for an additional 40 min, the mixture was poured into ice water (100 g). Then $Na_2S_2O_3$ was added to destroy excess free iodine. After vigorous shaking, the upper layer was separated. The aqueous layer was extracted with ether (3 X 30 mL), and the combined organic phase was dried over anhyd. $MgSO_4$, and concentrated in vacuo. Distillation of the residue gave 1-iodo-1-hept-1-yne 21.7 g, 98%, bp 90-91°C/18 torr [lit.[11] bp. 78°C/10 torr]. This material exhibited: mass spectrum m/e (relative intensity) 222 (M^+, 100), 213 (1) 207 (1), 165 (57), 95 (55), 67 (77); IR (film) ν 2195 (broad, weak, C C) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.9 (t, 3H, Me), 1.33 (m, 4H), 1.52 (q, 2H, HC-4), 2.37 (t, 2H, HC-3).

Preparation of Deca-2,4-diyn-1-ol:

To a suspension of cuprous chloride (0.19 g, 0.001 mol), propargyl alcohol (6.4 g, 0.11 mol), hydroxylamine hydrochloride (0.75 g) methanol (37.8 mL) and aqueous ethylamine (50 mL, 0.01 mol, 33% in H_2O), was added dropwise, under argon, 1-iodo-1-heptyne (16 g, 0.07 mol). After stirring for 45 min, NaCN (2 g) was added. The mixture was then poured into water (60 mL), and extracted with ether (5 X 50 mL). The combined organic extracts were backwashed with water (25 mL), dried over anhyd. $MgSO_4$, and concentrated under reduced pressure. Distillation of the residue gave deca-2,4-diyn-1-ol (9.16 g, 79%) bp

90-91°C/0.05 torr. This material exhibited: mass spectrum m/e (relative intensity) 150 (M^+, 5.1), 149 (4), 91 (69), 79 (75), 77 (100), 65 (47); IR (film) ν 3340 (broad, strong, OH), 2262 (sharp, medium, C C), 1025 (broad, strong, C-O) cm^{-1}.

Preparation of (E)-Dec-4-yn-2-en-1-ol:

[57] Lithium tetrahydridoaluminate (2.36 g, 0.06 mol) was added, in small portions, to a solution of deca-2,4-diyn-1-ol (8.9 g, 0.06 mol) in anhyd. ether (100 mL) at 0°C, and the mixture was stirred at room temperature for 45 min. The mixture was again cooled to 0°C, and slowly hydrolyzed by addition of water (2.36 mL), aqueous NaOH (3 X 2.36 mL, 15%) and again water (3 X 2.36 mL). After filtration of the salts through 0.5 cm of Celite, the organic phase was dried over anhyd. $MgSO_4$, and concentrated in vacuo. Distillation of the residue gave (E)-dec-4-yn-2-en-1-ol (6.65 g, 74%) bp 78-80°C/0.25 torr. This material exhibited: mass spectrum m/e (relative intensity) 152 (M^+, 8), 95 (100), 81 (26) 79 (15) 67 (34); IR (film) ν 3340 (very broad, strong, OH), 2221 (sharp, medium, C C), 1635 (broad, medium, C=C), 1095 (broad, strong, C-O), 957 (broad, strong, C=C) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.9 (t, 3H, Me), 1.35 (m, 4H, C_2H_4), 1.47 (s, 1H, OH), 1.53 (q, 2H, HC-7), 2.3 (dt, 2H, HC-6, J = 1.9, 7), 4.18 (broad, 2H, HC-1), 5.73 (dq, 1H, HC-3, J = 16.3, 1.9), 6.16

(td, 1H, HC-2, J = 16.3, 5.5).

Preparation of (E)-2,3-Epoxydec-4-yn-1-ol (2b):

To a solution of (E)-dec-4-yn-2-en-1-ol (3.34 g, 0.022 mol) in dichloromethane (70 mL), m-chloroperbenzoic acid (4.54 g, 85% pure, 0.023 mol) was added in small portions. The mixture was stirred for 7 hr. Excess m-chloroperbenzoic acid was destroyed by addition of soldium sulfite solution (10%). The reaction mixture was washed with 5% $NaHCO_3$ (50 mL), water (50 mL) and saturated brine (2 X 50 mL). The organic phase was dried over anhyd. $MgSO_4$, concentrated under reduced pressure, and chromatographed on Silica gel 60 using hexane:ethyl acetate (4:1) as eluant to give **2b** (3.32 g, 90%) bp 93-94°C/0.1 torr. This material exhibited: mass spectrum CI m/e 169 ($M^+ + 1$); IR (film) ν 3400 (broad, strong, OH), 2229 (sharp, medium, C C), 854, 874 (broad, medium, trans epoxy C-O-C) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.89 (t, 3H, Me), 1.32 (m, 4H, C_2H_4), 1.51 (q, 2H, HC-7), 1.59 (s, 1H, OH), 2.21 (dt, 2H, HC-6), 3.28 (m, 1H, HC-2), 3.44 (m, 1H, HC-3), 3.71 (m, 1H, HC-1), 3.95 (m, 1H, HC-1); ^{13}C NMR ($CDCl_3$) δ 13.51, 18.35, 21.81, 27.74, 30.69, 42.96 (C-2), 59.92 (C-3), 60.40 (C-1), 75.90 (C-4), 85.05 (C-5). **Anal.** calcd. for $C_{10}H_{16}O_2$: C, 71.39%; H, 9.58%. Found: C, 71.66%; H, 9.78%.

Preparation of (E-2,3-Epoxy-1-(tert-butyldimethyl)siloxydec-4-yne (23):

To a stirred solution of **2b** (1 g, 5.9 mmol), and imidazole (1 g, 14.9 mmol) in dry N,N-dimethyl formamide (8 mL) at 0°C, t-butyldimethylsilyl chloride (0.9 g, 6.2 mmol) was added in one portion. The reaction mixture was stirred for 2 hr, and quenched by addition of water (2 mL). The organic phase was extracted with pentane (4 X 25 mL) and the extract was backwashed with saturated brine. The extract was dried over anhyd. $MgSO_4$, concentrated in vacuo, and chromatographed on Silica gel 60 using hexane:ethyl acetate (4:1) as eluant to give **23** (1.2 g, 70%). The material exhibited: IR (near) ν 2240 (sharp, weak, C C), 1255 (sharp, strong, C-O), 839 (sharp, strong, epoxy C-O-C) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.075 (m, 6H, Me-Si), 0.93 (m, 12H, 4Me), 1.33 (m, 4H, C_2H_4), 1.50 (q, 2H, HC-7), 2.19 (dt, 2H, HC-6), 3.20 (m, 1H, HC-2), 3.31 (m, 1H, HC-3), 3.73 (ABq, 1H, HC-1), 3.84 (ABq, 1H, HC-1).

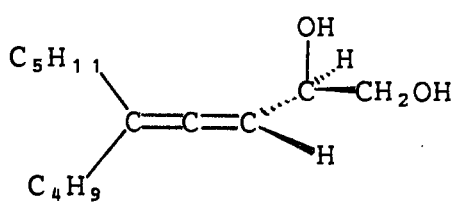
4. Reaction of Organocuprates with 2b by Normal Addition Method (Method A)

General Procedure for the Reactions of (E)-2,3-Epoxydec-4-yn-1-ol (2b) with Organocuprates:

A solution of $CuBrMe_2S$ (1.1 m mol) in a mixture anhyd. ether (6.5 mL) and dimethyl sulfide (4 mL) was cooled to -70°C. To this solution was added the organolithium (2.2 mmol, 2.4 M in hexane) or organomagnesium bromide (2.2 mmol,

3.2 M in ether) via syringe. The mixture was stirred for 30 min. and **2b** (1.0 mmol in 5 mL anhyd. ether) was added over 10 min. The reaction was allowed to increase to the indicated temperature (see Table 1) quickly and then stirred for 1 hr. The reaction mixture was then hydrolyzed by addition 10 mL of a 10% aqueous NH_4Cl solution, and was extracted with ether (4 X 30 mL). The combined extracts were filtered through 2 cm of coarse Silica gel, followed by an ether wash (2 X 10 mL). The ether solution was dried over anhyd. $MgSO_4$ and concentrated in vacuo. The products were isolated by chromatography on Silica gel 60 using hexane:ethyl acetate (1:2) as the eluant. Product yields are given in Table 1.

Isolation of 5-n-Butyl-3,4-decadien-1,2-diol (4c):

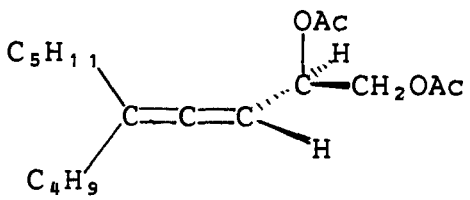


4c

Following the general procedure A outlined above, **2b** (0.168 g, 1 mmol) was reacted with lithium dibutylcuprate-dimethyl sulfide, **8a**, (1.1 mmol) in a solution of anhyd. ether (11.5 mL) and dimethyl sulfide (4 mL) at -70°C and then warmed to r.t. for 1 hr. Normal workup, followed by flash chromatography afforded **4c** (0.14 g, 62%) which distilled (air-bath temperature 90°C/0.06

torr) as a clear liquid. This material exhibited: m/e (relative intensity) 97 (79), 95 (100), 93 (42), 81 (71); IR (film) ν 3350 (very broad, strong, OH), 1951 (sharp, medium, C=C=C) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.9 (m, 6H, $2CH_3$), 1.30, 1.38 (m, m, 10H, C_3H_6, C_2H_4), 1.97 (m, 4H, 2HC-6, 2HC-11), 2.05 (m, 2H, 2OH), 3.5 (m, 1H, H_AC-1), 3.67 (m, 1H, H_BC-1), 4.22 (m, 1H, HC-2), 5.2 (m, 1H, HC-3). **Exact** mass calcd. for $C_{14}H_{26}O_2$ (M^+-H_2O): 208.1827. Found (ms): 208.1825.

Preparation of 5-n-Butyl-3,4-decadien-1,2-diacetate (7bA):

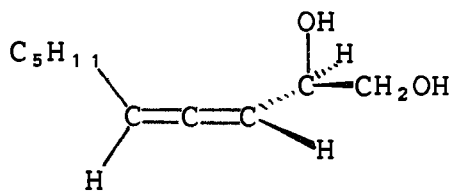


7bA

Reaction of **4c** with acetic anhydride and pyridine gave **7bA**, which distilled (air-bath temperature 115°C/0.1 torr) as a clear liquid. This material exhibited: mass spectrum m/e (relative intensity) 151 (85), 109 (100), 95 (80), 68 (97); IR (film) ν 1960 (sharp, medium, C=C=C), 1745 (broad, strong, C=O), 1220 (broad, strong, C-O) cm^{-1}; ^1H NMR (C_6D_6) δ 0.97 (m, 6H, $2CH_3$), 1.30, 1.46 (m, m, 10H, C_3H_6, C_2H_4), 1.73 (s, 3H, Ac), 1.77 (s, 3H, Ac), 1.93 (m, 4H, 2HC-6, 2HC-11), 4.23 (ABq, 1H, H_AC-1, $^2J_{AB}$ = 11.7 Hz, $^3J_{AC}$ = 7.6 Hz), 4.41 (ABq, 1H, H_BC-1, $^2J_{AB}$ = 11.7 Hz, $^3J_{BC}$ = 3.7 Hz), 5.27 (m, 1H, HC-3), 5.75 (m, 1H,

H_CC-2, $^3J_{BC}$ = 3.7 Hz, $^3J_{AC}$ = 7.6 Hz, $^3J_{CD}$ = 6.7 Hz); ^{1}H NMR ($CDCl_3$) δ 0.88 (m, 6H, $2CH_3$), 1.33 (m, 10H, C_3H_6, C_2H_4), 1.95 (m, 4H, 2HC-6, 2HC-11), 2.07 (d, 6H, 2Ac), 4.0998 (ABq, 1H, H_AC-1 $^3J_{AC}$ = 7.6 Hz, $^2J_{AB}$ = 11.8 Hz), 4.25 (ABq, 1H, H_BC-1 $^2J_{AB}$ = 11.7 Hz, $^3J_{BC}$ = 3.7), 5.15 (m, 1H, HC-3), 5.45 (m, 1H, H_CC-2); ^{13}C NMR ($CDCl_3$) 13.81, 13.92, 20.65, 20.96, 22.35, 22.43, 27.09, 29.64 (C-6 or C-11), 31.48 (C-6 or C-11), 32.02, 32.28, 65.02 (C-1), 70.13 (C-2), 88.51 (C-3), 108.36 (C-5), 169.98 (C=O), 170.54 (C=O), 201.70 (C-4). **Exact** mass calcd. for $C_{18}H_{30}O_4$: 310.2144. Found (ms): 310.2118.

Isolation of 3,4-Decadien-1,2-diol (10):

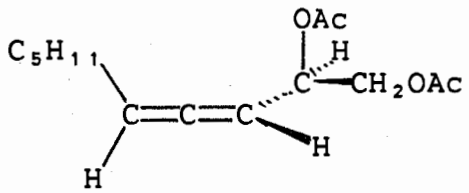


10

Following general procedure A outlined above, **2b** (0.168 g, 1 mmol) was reacted with lithium dialkylcuprate **8a** in a solution of anhyd. ether (11.5 mL) and dimethyl sulfide (4 mL) at -70°C then warmed to r.t. for 1 hr. Normal workup, followed by flash chromatography afforded **10** (in most cases less than 13%). The material exhibited: G.C./C.I (methane) M^++1/e 171; IR (film) ν 3500 (broad, strong, OH), 1960 (broad, weak, C=C=C) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.9 (t, 3H, CH_3), 1.32 (m, 4H, $-C_2H_4-$), 1.42 (m, 2H, HC-7), 1.64 (s, 2H,

2OH), 2.03 (m, 2H, 2HC-6), 3.54 (m, 1H, H_AC-1), 3.69 (m, 1H, H_BC-1), 4.25 (m, 1H, HC-2), 5.22 (m, 1H, HC-3), 5.36 (m, 1H, HC-5).

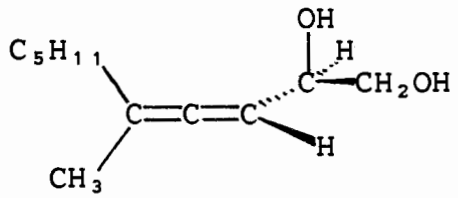
Preparation of 3,4-Decadien-1,2-diacetate (13):



13

Reaction of 10 with acetic anhydride and pyridine gave 13, which distilled (air-bath temperature: 92°C/0.06 torr) as a clear liquid. This material exhibited: IR (film) ν 1964 (broad, weak, C=C=C), 1743 (broad, strong, C=O), 1252, 1240 (doublet, strong, C-O) cm^{-1}; ^{1}H NMR (C_6D_6) δ 0.9 (m, 3H, CH_3), 1.32 (m, 6H, C_3H_6), 1.73 (q, 6H, 2Ac), 1.91 (m, 2H, 2HC-6), 4.18 (ABq, H(anti), H_AC-1), 4.19 (ABq, H(syn), H_AC-1), 4.35 (ABq, 1H, H_BC-1), 5.21 (m, 1H, HC-3), 5.28 (m, 1H, HC-5), 5.73 (m, 1H, H_CC-2); $^3J_{BC}$ = 3.5 Hz(synB), 3.4 Hz(antiB), $^3J_{AC}$ = 7.2 Hz, $^2J_{AB}$ = 11.9 Hz); ^{1}H NMR ($CDCl_3$) δ 0.9 (t, 3H, CH_3), 1.32 (m, 4H, C_2H_4), 1.41 (m, 2H, CH_2), 2.02 (m, 2H, 2HC-6), 2.08 (d, 6H, 2Ac), 4.122 (ABq, H(syn), H_AC-1), 4.129 (ABq, H(anti), H_AC-1), 4.27 (ABq, 1H, H_BC-1), 5.02 (m, 1H, HC-3), 5.33 (m, 1H, HC-5), 5.46 (m, 1H, HC-2), $^2J_{AB}$ = 11.8 Hz, $^3J_{AC}$ = 7.4 Hz(antiA), 7.5. Hz(synA), $^5J_{CE}$ = 2.2 Hz; ^{13}C NMR ($CDCl_3$) 31.0 (Ac), 31.0 (C-6), 31.2 (Ac), 64.0 (C-1), 69.6 (C-2), 87.8 (C-3), 94.5 (C-5), 195.1 (C-4).

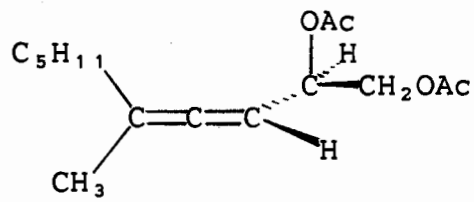
Isolation of 5-Methyl-3,4-decadien-1,2-diol (4d):



4d

Following general procedure A outlined above, **2b** (0.168 g, 1 mmol) was reacted with lithium dimethylcuprate-dimethyl sulfide **8b** (1 mmol) in a solution of anhyd. ether (11.5 mL) and dimethyl sulfide (4 mL) at -70°C then warmed to r.t. for 1 hr. Normal workup, followed by flash chromatography afforded **4d** (0.04 g, 21.5%) as a clear liquid. This material exhibited: G.C./C.I. (methane) M^++1/e 185; IR (film) ν 3410 (very broad, strong, OH), 1975 (sharp, medium, C=C=C) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.89 (t, 3H, CH_3), 1.30, 1.41 (m, m, 6H,C_2H_4, CH_2), 1.72 (m, 3H, HC-11), 1.95 (m, 2H, 2HC-6), 2.45 (broad, 2H, 2OH), 3.5 (ABq, 1H, H_AC-1 $^2J_{AB}$ = 11.5 Hz, $^3J_{AC}$ = 7.2 Hz), 3.66 (ABq, 1H, H_BC-1, $^2J_{AB}$ = 11.5 Hz, Jba= 3.5 Hz), 4.19 (m, 1H, H_CC-2). 5.12 (m, 1H, HC-3),

Preparation of 5-Methyl-3,4-decadien-1,2-diacetate (7f):

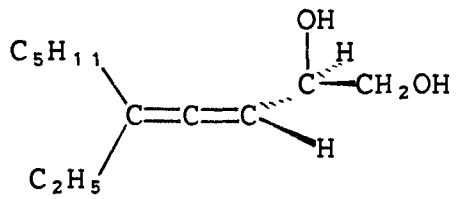


7f

Reaction of **4d** with acetic anhydride and pyridine gave

7f, which distilled (air-bath temperature 92°C/0.06 torr) as a clear liquid. This material exhibited: mass spectrum m/e (relative intensity) 110 (45), 109 (100), 95 (47), 81 (25); ^{1}H NMR ($CDCl_3$) δ 0.89 (t, 3H, CH_3), 1.3 (m, 4H, C_2H_4), 1.40 (q, 2H, CH_2), 1.7 (m, 3H, HC-11), 1.95 (t, 2H, HC-6), 2.04 (d, 6H, 2Ac), 4.102 (ABq, H(syn), H_AC-1 $^3J_{AC}$ = 7.6 Hz, $^2J_{AB}$ = 11.9 Hz), 4.115 (ABq, H(anti), H_BC-1 $^2J_{AB}$ = 11.9 Hz, $^3J_{AC}$ = 7.5), 4.25 (ABq, 1H, HC-2, $^2J_{AB}$ = 11.9 Hz, $^3J_{BC}$ = 3.72 Hz), 5.08 (m, 1H, HC-3), 5.43 (m, 1H, H_CC-2). **Exact** mass calcd. for $C_{15}H_{24}O_4$ (M^+ - CH_2=C=O): 226.1569. Found (ms): 226.1578.

Isolation of 5-Ethyl-3,4-decadien-1,2-diol (4f):

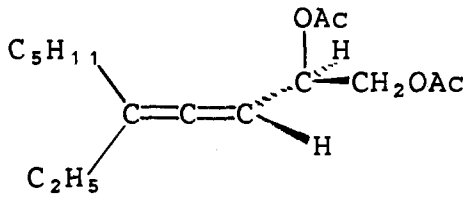


4f

Following general procedure A outlined above, **2b** (0.168 g, 1 mmol) was reacted with magnesium bromide diethylcuprate-dimethyl sulfide, **21b**, (1 mmol) in a solution of anhyd. ether (11.5 mL) and dimethyl sulfide (4 mL) at -70°C then warmed to r.t. for 1 hr. Normal workup, followed by flash chromatography afforded 4f (0.06 g, 31%) which distilled (air-bath temperature 92°C/0.15 torr) as a clear liquid. The material exhibited: G.C./C.I. (methane) M^++1/e 199; mass spectrum m/e (relative intensity) 180 (12), 81

(71), 79 (67), 67 (90), 55 (100); IR (film) ν 3380 (very broad, strong, OH), 1973 (sharp, medium, C=C=C) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.88 (t, 3H, CH_3), 0.99 (m, 3H, HC-12), 1.31, 1.42 (m, m, 6H, C_2H_4, CH_2), 1.60 (s, 2H, 2OH), 1.99 (m, 4H, 2HC-6, 2HC-11), 3.53 (m, 1H, H_AC-1), 3.68 (m, 1H, H_BC-1), 4.22 (m, 1H, H_CC-2), 5.27 (m, 1H, HC-3). **Exact** mass calcd. for $C_{12}H_{22}O_2$ ($M^+ - H_2O$): 180.1514. Found (ms): 180.1517.

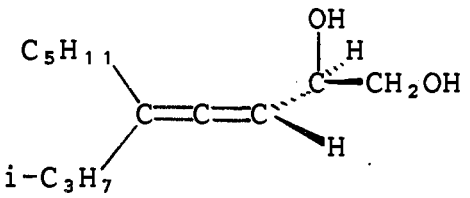
Preparation of 5-Ethyl-3,4-decadien-1,2-diacetate (7e):



7e

Reaction of 4f with acetic anhydride and pyridine gave 7e as a clear liquid. This material exhibited: mass spectrum m/e (relative intensity) 240 (35), 180 (49), 123 (100), 109 (40); ^1H NMR ($CDCl_3$) δ 0.88 (t, 3H, CH_3), 0.98 (m, 3H, HC-12), 1.29 (m, 4H, C_2H_4), 1.40 (q, 2H, CH_2), 1.95 (m, 4H, 2HC-6, 2HC-11), 2.07 (d, 6H, 2Ac), 4.098 (ABq, H(syn), H_AC-1 $^3J_{AC}$ = 7.6 Hz, $^2J_{AB}$ = 11.9 Hz), 4.105 (ABq, H(anti), H_AC-1 $^2J_{AB}$ = 11.9 Hz, $^3J_{AC}$ = 7.6), 4.2476 (ABq, H(syn), H_BC-1, $^2J_{AB}$ = 11.9 Hz, $^3J_{BC}$ = 3.7 Hz), 4.2505 (ABq, H(anti), H_BC-1, $^3J_{BC}$ = 3.7 Hz, $^2J_{AB}$ = 11.9 Hz), 5.19 (m, 1H, HC-3), 5.44 (m, 1H, H_CC-2). **Exact** mass calcd. for $C_{16}H_{26}O_4$ ($M^+ - CH_2=C=O$): 240.1726. Found (ms): 240.1704.

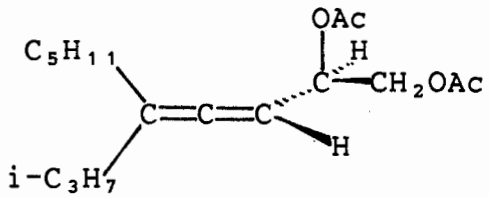
Isolation of 5-Isopropyl-3,4-decadien-1,2-diol (4e):



4e

Following general procedure A outlined above, **2b** (0.168 g, 1 mmol) was reacted with magnesium bromide diisopropylcuprate-dimethyl sulfide, **21a**, (1 mmol) in a solution of anhyd. ether (11.5 mL) and dimethyl sulfide (4 mL) at -70°C then warmed to r.t. for 1 hr. Normal workup, followed by flash chromatography afforded **4e** (0.11 g, 53%) which distilled (air-bath temperature 99°C/0.2 torr) as a clear liquid. This material exhibited: G.C./C.I. (methane) M^++1/e 213; mass spectrum m/e (relative intensity) 125 (95), 81 (66), 69 (100), 55 (74); IR (film) ν 3400 (very broad, strong, OH), 1970 (sharp, medium, C=C=C) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.89 (t, 3H, CH_3), 1.02 (m, 6H, 2MeC-11), 1.31, 1.40 (m, m, 6H, C_2H_4, CH_2), 1.98 (m, 2H, 2HC-6), 2.08 (broad, 2H, OH), 2.13 (m, 1H, HC-11), 3.52 (m, 1H, H_AC-1), 3.68 (m, 1H, H_BC-1), 4.21 (m, 1H, HC-2), 5.27 (m, 1H, HC-3). **Exact** mass calcd. for $C_{13}H_{24}O_2$ ($M^+ - H_2O$): 194.1671. Found (ms): 194.1673.

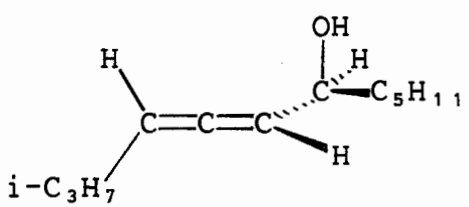
Preparation of 5-Isopropyl-3,4-decadien-1,2-diacetate (7d):



7d

Reaction of 4e with acetic anhydride and pyridine gave 7d, which distilled (air-bath temperature 99°C/0.1 torr) as a clear liquid. This material exhibited: mass spectrum m/e (relative intensity) 137 (63), 123 (78), 95 (50), 68 (100); ^{1}H NMR ($CDCl_3$) δ 0.89 (t, 3H, CH_3), 0.99 (q, 6H, 2MeC-11), 1.30 (m, 4H, C_2H_4), 1.39 (q, 2H, CH_2), 1.96 (m, 2H, 2HC-6), 2.05 (d, 6H, 2Ac), 2.09 (m, 1H, HC-11), 4.08 (ABq, 1H, H_AC-1 $^3J_{AC}$ = 7.5 Hz, $^2J_{AB}$ = 11.7 Hz), 4.24 (ABq, 1H, H_BC-1, $^3J_{BC}$ = 3.8 Hz, $^2J_{AB}$ = 11.7 Hz), 5.22 (m, 1H, HC-3), 5.44 (m, 1H, H_CC-2). Exact mass calcd. for $C_{17}H_{28}O_4$ (M^+ - CH_2=C=O): 254.1882. Found (ms): 254.1881.

Isolation of 2-Methyl-3,4-undecadien-6-ol (4g):

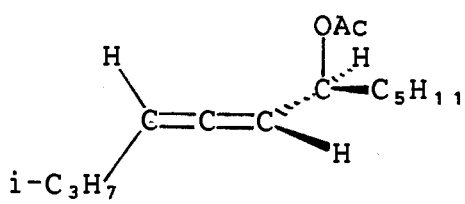


4g

Following general procedure A outlined above, 24 (0.138 g, 1 mmol) was reacted with magnesium bromide diisopropylcuprate-dimethyl sulfide (21a) (1 mmol) in a solution of anhyd. ether (11.5 mL) and dimethyl sulfide (4

mL) at -70°C then warmed to r.t. for 1 hr. Normal workup, followed by flash chromatography afforded **4g** (0.12 g, 67%) as a clear liquid. The material exhibited: G.C./C.I. (methane) M^++1/e 183; IR (film) ν 3368 (very broad, strong, OH), 1971 (sharp, medium, C=C=C) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.90 (t, 3H, CH_3), 1.02 (q, 6H, 2MeC-2), 1.33, 1.41 (m, m, 6H, C_2H_4, CH_2), 1.57 (m, 1H, HC-7), 1.63 (m, 1H, HC-7), 2.31 (m, 1H, HC-2), 4.12 (m, 1H, HC-6), 5.25 (m, 1H, HC-5), 5.32 (m, 1H, HC-3).

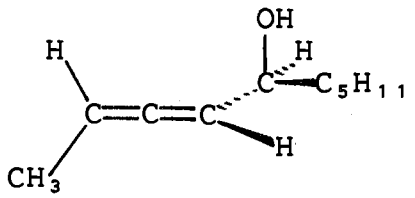
Preparation of 2-Methyl-3,4-undecadien-6-acetate (7g):



7g

Reaction of **4g** with acetic anhydride and pyridine gave **7g** as a clear liquid. This material exhibited: ^1H NMR (C_6D_6) δ 0.91 (t, 3H, CH_3), 1.01 (d, 6H, 2MeC-2), 1.27, 1.38 (m, m, 6H, C_2H_4, CH_2), 1.65 (m, 1H, HC-7), 1.75 (m, 1H, HC-7), 1.80 (s, 3H, Ac), 2.39 (m, 1H, HC-2), 5.30 (m, 1H, HC-3), 5.38 (m, 1H, HC-5), 5.55 (m, 1H, HC-6), $^3J_{AC}$ = 6 Hz, $^2J_{AB}$ = 6 Hz, $^3J_{BC}$ = 2 Hz.

Isolation of 2,3-Decadien-5-ol (4h):



4h

Following general procedure A outlined above, **24** (0.138 g, 1 mmol) was reacted with magnesium bromide dimethylcuprate-dimethyl sulfide (**21c**) (1 mmol) in a solution of anhyd. ether (11.5 mL) and dimethyl sulfide (4 mL) at -70°C then warmed to r.t. for 1 hr. Normal workup, followed by flash chromatography afforded **4h** (0.05 g, 33.5%) as a clear liquid. The material exhibited: G.C./C.I. (methane) M^++1/e 155; IR (film) ν 3475 (very broad, strong, OH), 1974 (sharp, medium, C=C=C) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.92 (t, 3H, CH_3), 1.33, (m, 6H, C_3H_6), 1.55 (m, 2H, HC-6), 1.71 (m, 3H, 3HC-1, J = 3.2, 6.8 Hz), 4.13 (m, 1H, HC-5, $^3J_{CD}$ = 6.8 Hz, $^5J_{CE}$ = 2.3 Hz, J = 6.4 Hz), 5.18 (m, 1H, HC-4, J_{DE} = 6.1 Hz, $^3J_{CD}$ = 6.8 Hz, J = 3.2 Hz), 5.28 (dq, 1H, HC-2, $^5J_{CE}$ = 2.3 Hz, J_{DE} = 6.1 Hz, J = 6.8 Hz).

5. Preparation of 7 from Reaction of Organometallics with **2b**

Reaction of n-Butyllithium with 2":

To a dry THF solution (17mL) of dec-4-yn-2,3-epoxy-1-ol (0.168g 1m mol) was added dropwise, at -70°C, n-butyllithium (2 mmol, 2.4 M in hexane). The reaction temperature rose to

-35°C over 1 hr., water (10 mL) was added, and the organic layer was extracted with ether (4 X 50mL). The organic extract was dried over anhyd. $MgSO_4$, and concentrated in vacuo. The product was isolated by flash chromatography on Silica gel 60 using hexane:ethyl acetate (1:2) as eluant to give mixture of diastereoisomers of **4c**. This mixture was acetylated with pyridine and acetic anhydride to give a mixture which was identified as **7bA** and **7bS** by ^1H NMR.

Reaction of Isopropyl Magnesium Bromide with 2b:

To a dry THF solution (17mL) of dec-4-yn-2,3-epoxy-1-ol (0.168g 1m mol) was added dropwise, at -70°C, isopropyl magnesium bromide (2 mmol, 3.2 M in ether). The reaction mixture was warmed to 0°C over 1 hr. After which water (10 mL) was added. The aqueous layer was extracted with ether (4 X 50mL). The organic extract was dried over anhyd. $MgSO_4$ and concentrated in vacuo. The product was isolated by flash chromatography on Silica gel 60 using hexane:ethyl acetate (1:2) as eluant to give mixture of diastereoisomers of **4e**. The product was acetylated with pyridine and acetic anhydride to give a mixture which was identified as **7dA** and **7dS** by ^1H NMR.

6. Synthesis of 5-n-Butyl-3,4-decadien-1,2-diacetate (7**bS**)

Preparation of 5-n-Butyl-3,4-decadien-1,2-diol (4cS):

Following the method of Ganem[22], n-butyllithium (1.06 mmol, 2.4 M in hexane) was added dropwise to a stirred solution of $BF_3.Et_2O$ (0.13 mL, 1.06 mmol) in dry THF (10 mL) at -70°C. Neat **23** (0.1 g, 0.35 mmol) was added quickly, and the solution stirred for 10 min. The reaction was quenched at -70°C by addition of sat. aqueous $NaHCO_3$ (1 mL), and warmed to room temperature. THF was removed in vacuo, H_2O (1 mL) was added, and the aqueous layer was extracted with ether (4 X 10 mL). The organic extract was dried over anhyd. $MgSO_4$, concentrated in vacuo and chromatographed on Silica gel 60 using hexane:ethyl acetate (12 : 1) as eluant to give 0.065 g (54%) of product. The product was desilylated with tetrabutylammonium fluoride (6 mL, <5% in THF) in THF (10 mL). The reaction mixture was stirred for 1 hr. then diluted with ethyl acetate (10 mL) and washed with 15 mL of H_2O, 15 mL of 5% HCl, 15 mL of H_2O, 15 mL of sat. $NaHCO_3$ solution and 15 mL of H_2O. The organic layer was dried over anhyd. $MgSO_4$ and concentrated in vacuo to give **4cS**. This material exhibited: IR (film) ν 3380 (very broad, strong, OH), 1961 (sharp, medium, C=C=C) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.92 (m, 6H, $2CH_3$), 1.37 (m, 10H, C_3H_6, C_2H_4), 2.0 (m, 4H, 2HC-6, 2HC-11), 2.05 (m, 2H, 2OH), 3.53 (m, 1H, H_AC-1), 3.73 (m, 1H H_BC-1), 4.06 (m, 1H,

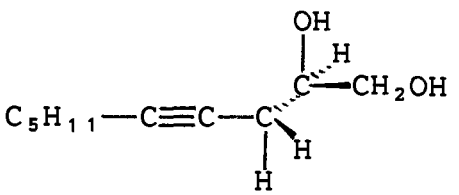
H_CC-2), 5.43 (m, 1H, HC-3).

Preparation of 5-n-Butyl-3,4-decadien-1,2-diacetate (7bS):

Reaction of **4cS** with acetic anhydride and pyridine gave **7bS**. This material exhibited: mass spectrum m/e (relative intensity) 151 (67.5), 138 (34.3), 109 (38.7), 95 (52.1) 81 (37), 43 (100); ^{1}H NMR ($CDCl_3$) δ 0.88 (t, 6H, CH_3, J=4.322 Hz), 1.24-1.42 (m, 10H, C_2H_4, C_3H_6), 1.97 (m, 4H, 2HC-6, 2HC-11), 2.04, 2.07 (2s, 6H, 2Ac), 4.094 (ABq, H(syn), H_AC-1), 4.291 (ABq, 1H, H_BC-1), 5.31 (m, 1H, HC-3), 5.42 (m, 1H, HC-2), $^3J_{AC}$ = 8.27 Hz, $^3J_{BC}$ = 3.572 Hz, $^2J_{AB}$ = 11.8 Hz.

7. Synthesis of Dec-4-yn-1,2-diacetate (14)

Preparation of Dec-4-yn-1,2-diol (11):

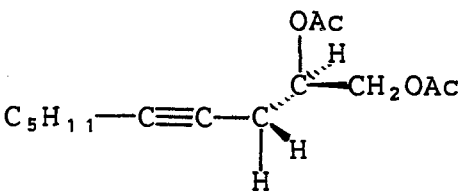


11

To a stirred dry THF solution (25mL) of lithium tetrahydroaluminate (6 mmol) was added dropwise, at -60°C, **2b** (3 mmol) in dry THF (10 mL). The stirred reaction mixture was warmed to room temperature and stirred for 4 hr. The reaction was cooled to 0°C, and 0.2g of water was added dropwise, followed by 0.55 g of 10% NaOH and 0.55 g of

water. After filtration of the salts through 0.5 cm of Celite 545, the organic phase was dried over anhyd. $MgSO_4$ and concentrated in vacuo. The product was isolated by flash chromatography on Silica gel 60 using eluant hexane:ethyl acetate (1:1) to give 0.23 g (45.5%) of **11** which with its diacetate gave ^1H NMR and mass spectra identical to those derived **11** produced by reaction of **2b** with **8**. Distillation (air-bath temperature 85°C/0.06 torr) gave **11** as a clear liquid. This material exhibited: G.C./C.I (methane) M^++1/e 171; mass spectrum m/e (relative intensity) 95 (100), 83 (80), 82 (71), 81 (89); ^1H NMR ($CDCl_3$) δ 0.917 (t, 3H, CH_3), 1.35 (m, 4H, C_2H_4), 1.50 (m, 2H, HC-7), 2.15 (m, 2H, HC-6), 2.33 (s, 1H, OH), 2.40 (m, 2H, HC-3), 2.58 (s, 1H, OH), 3.58 (m, 1H, H_AC-1), 3.74 (m, 1H, H_BC-1), 3.83 (m, 1H, HC-2). **Exact** mass calcd. for $C_{10}H_{18}O_2$ (M^+): 170.1307. Found (ms): 170.1307.

Preparation of Dec-4-yn-1,2-diacetate (14):



14

Reaction of **11** with acetic anhydride and pyridine gave **14** as a clear liquid. This material exhibited: mass spectrum m/e (relative intensity) 151 (51), 109 (26), 96 (100), 95 (51), 81 (66); ^1H NMR ($CDCl_3$) δ 0.9 (t, 3H, CH_3), 1.32 (m,

4H, C_2H_4), 1.48 (m, 2H, HC-7), 2.08 (s, 6H, 2Ac), 2.13 (m, 2H, HC-6), 2.5 (m, 2H, HC-3), 4.18 (ABq, 1H, H_AC-1 $^2J_{AB}$ = 11.8 Hz, $^3J_{AC}$ = 6.18 Hz), 4.34 (ABq, 1H, H_BC-1 $^2J_{AB}$ = 11.8 Hz, $^3J_{BC}$ = 3.5 Hz), 5.09 (m, 1H, HC-2). **Exact** mass calcd. for $C_{14}H_{22}O_4$ (M^+ - $MeCO_2H$): 194.1307. Found (ms) 194.1277.

8. Synthesis of 3-n-Butyldec-4-yn-1,2-diacetate (**12a**)

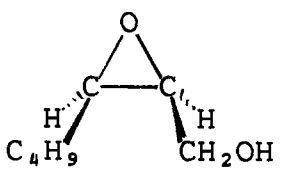
Preparation of Hept-2-yn-1-ol (18):

To a stirred dry THF solution (50mL) of 1-hexyne (60 mmol) was added dropwise, at 0°C, n-butyllithium (2.4M in hexane, 61 mmol). After a clear solution was obtained, paraformaldehyde (60.9 mmol) was added over 45 min. The reaction temperature was increased to room temperature, and the mixture was stirred over night. The clear solution was poured into ca 50 g of ice. The mixture was vigorously stirred, and the water layer was extracted with ether (4 X 40 mL). The combined extract was dried over anhyd. $MgSO_4$, and concentrated in vacuo. Distillation of the residue (bp 83°C/12 torr) gave **18** in 85% yield (5.7 g). This material exhibited: IR (film) ν 3340 (very broad, strong, OH), 2235, 2300 (sharp, weak, C C), 1013 (broad, strong, C-O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.90 (t, 3H, CH_3), 1.4 (m, 4H, C_2H_4), 2.19 (m, 2H, HC-4), 4.22 (m, 2H, HC-1).

Preparation of (Z)-2-Hepten-1-ol (19):

P-2 nickel (13 mmol) was prepared from $Ni(C_2H_3O_2)_2.6H_2O$ (3.25 g, 13 mmol), 1 M ethanolic $NaBH_4$ solution (13 mL, 13 mmol with 5mL 2N NaOH present) and ethylenediamine (1.8 mL, 27 mmol) in ethanol (130 mL, 95%) under H_2. Neat 18 (3 g, 26.8 mmol) was added dropwise, and the solution was stirred for 45 min. The solution was then filtered through 1 cm of activated charcoal. The filtrate was diluted with water (50 mL) and extracted with ether (5 X 25 mL). The combined extract was backwashed with water (25 mL), dried over anhyd. $MgSO_4$, and concentrated in vacuo. Distillation of the residue (bp 77°C/11 torr) gave 19 (2.44 g, 80%). This material exhibited: IR (film) ν 3320 (very broad, strong, OH), 1720 (broad, weak, C=C), 1019 (broad, strong, C-O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.90 (t, 3H, CH_3), 1.33 (m, 4H, C_2H_4), 2.07 (q, 2H, HC-4), 4.19 (d, 2H, HC-1), 5.57 (m, 2H, HC-2, HC-3).

Preparation of (Z)-2,3-Epoxyheptan-1-ol (15):

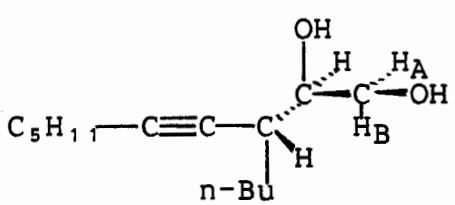


18

To a stirred CH_2Cl_2 solution (15mL) of m-chloroperbenzoic acid (3 g, 15 mmol) was added dropwise 19 (1.7 g, 14.9m mol) in CH_2Cl_2 (20 mL) over 0.5 hr. The

reaction mixture was stirred at room temperature for 3 hrs. Starch paper showed no peracid was left, and G.C. showed all **19** was reacted. Saturated $NaHCO_3$ solution (20 mL) was added to the mixture. After extraction with CH_2Cl_2 (3 X 25 mL), the organic layer was washed with H_2O (20 mL) and sat. NaCl solution (2 X 20 mL). The organic layer was dried over anhyd. $MgSO_4$ and concentrated in vacuo. The product was chromatographed on Silica gel 60 using hexane:ethyl acetate (10:1) as eluant to give 1.72 g of **15** (89%). This material exhibited: IR (film) ν 3440 (broad, strong, OH), 1115 (broad, medium, C-O), 1045 (broad, strong, C-O), 843, 809 (doublet, medium, Z-epoxy C-O-C); ^1H NMR ($CDCl_3$) δ 0.90 (t, 3H, CH_3), 1.37 (m, 1H, C_2H_4), 1.54 (m, 2H, HC-4), 2.08 (broad, 1H, OH), 3.01 (m, 1H, H_CC-2), 3.14 (m, 1H, HC-3), 3.64 (ABq, 1H, H_AC-1), 3.84 (ABq, 1H, H_BC-1), $^2J_{AB}$ = 12.2 Hz, $^3J_{BC}$ = 3.9 Hz, $^3J_{AC}$ = 7.07 Hz.

Preparation of 3-n-Butyldec-4-yn-1,2-diol (9a):

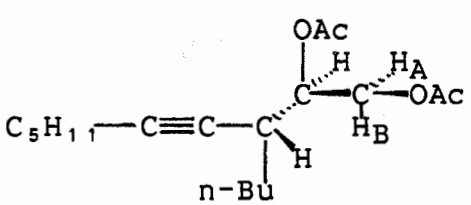


9a

To a stirred hexane solution (20mL) of 1-heptynyl lithium (11.5 mmol) was added dropwise, at 0°C, diethyl aluminum chloride (11.5 mmol, 1M in hexane). The mixture was stirred at room temperature for 1hr. Then (0.5 g, 3.8 mmol)

of (Z)-2,3-epoxyheptan-1-ol, **15**, in hexane (1 mL) was added to the reaction mixture at 0°C. After stirring for 20 min. the reaction mixture was warmed to room temperature and allowed to stir for 4 hrs. The suspension was poured into CH_2Cl_2 (40 mL) containing KF (6.7 g), and 2 mL of water was added. The resulting suspension was vigorously stirred for 0.5 hr. After filtration, the organic layer was dried over anhyd. $MgSO_4$, and concentrated in vacuo. The crude oil was chromatographed on Silica gel 60 using hexane:ethyl acetate (1:1) as eluant to give 0.05 g (6%) of **9a**. The ^1H NMR spectrum of diacetoxy **9a** (**12a**) derived from **15** matched that of diacetoxy **9a** derived from reaction of **2b** with **8a**. The material exhibited: ^1H NMR ($CDCl_3$) δ 0.91 (m, 6H, $2CH_3$), 1.35 (m, 8H, $2C_2H_4$), 1.50 (m, 2H, HC-7), 2.18 (m, 2H, HC-6), 2.52 (m, 1H, HC-3), 3.57 (m, 1H, H_AC-1), 3.67 (m, 2H, H_BC-1, HC-2).

Preparation of 3-n-Butyldec-4-yn-1,2-diacetate (12a):



12a

Reaction of **9a** with acetic anhydride and pyridine gave **12a**, which distilled (air-bath temperature 101°C/0.06 torr) as a clear liquid. This material exhibited: mass spectrum m/e (relative intensity) 207 (93), 165 (45), 151 (88), 137

(81), 103 (100); ^{1}H NMR ($CDCl_3$) δ 0.91 (t, 6H, $2CH_3$), 1.3 (m, 8H, $2C_2H_4$), 1.49 (p, 2H, CH_2), 2.08 (d, 6H, 2Ac), 2.16 (m, 2H, HC-6), 2.62 (m, 1H, HC-3), 4.17 (ABq, 1H, H_AC-1), 4.32 (ABq, 1H, H_BC-1), 5.12 (m, 1H, H_CC-2), $^2J_{AB}$ = 11.76 Hz, $^3J_{BC}$ = 3.7 Hz, $^3J_{AC}$ = 7.7 Hz. **Exact** mass calcd. for $C_{18}H_{30}O_4$ (M^+ - $MeCO_2H$): 250.1933. Found (ms): 250.1966.

9. Reaction of Organocuprates with **2b** by Inverse Addition Method (Method B)

Procedure for Coupling the $Bu_2CuCNLi_2$ with 2b:

To a stirred ethereal solution (7mL) of **2b** (0.1g, 0.59 mmol) was added dropwise over 10 min, at -70°C, under argon, lithium di-n-butylcyanocuprate, **22a**, (0.65 mmol) prepared from 0.54mL (1.3 mmol) of n-butyllithium (2.4M in hexane) and 0.058g (0.65 mmol) of cuprous cyanide in 12mL of anhyd. ether. The reaction mixture was warmed slowly to room temperature over 45 min, then hydrolyzed by stirring with water (1.3 g) and NH_4Cl (3 g) for 0.5 hr. The suspension was filtered through 1 cm of coarse Silica gel and the residue was washed with ether (3 X 10 mL). The combined filtrate was dried over anhyd. $MgSO_4$, and concentrated in vacuo. The concentrate was further dried under high vacuum for 15 min. to give 0.103 g (77%) of product. The product was acetylated with dry pyridine (1 mL) and of acetic anhydride (1 mL) in the same flask. This mixture was stirred overnight, then

quenched with water (4 mL), and extracted with ether (4 X 25 mL). The combined ether extracts were washed with 5 mL of 5% HCl, 5 mL of H_2O, 5 mL of sat. $NaHCO_3$, and 5 mL of H_2O. The organic phase was then dried over anhyd. $MgSO_4$, and concentrated in vacuo. The acetylated product was flash chromatographed on Silica gel 60 using hexane:ethyl acetate (1:2) as eluant to give 0.13g (72% overall yield) of clear liquid as 5-n-butyl-3,4-decadien-1,2-diacetate, **12a**. GLPC analysis of this liquid showed that it consisted of only one (>99%) component with a retention time identical to that of allenyl diacetate **12aA**. ^1H NMR spectroscopy also confirmed this identity.

Reaction of 2b with Magnesium Bromide Di-n-butylcuprate (21d):

Following method B outlined above, **2b** (0.1 g, 0.59 mmol) was reacted with magnesium bromide di-n-butylcuprate, **21d**, (0.65 mmol) in a mixture of anhyd. ether (10 mL) and dimethyl sulfide (5 mL) at -70°C and then at 20°C for 1 hr. Normal workup, acetylation and chromatographic isolation yielded **12aA** (0.13 g, 73%) confirmed by ^1H NMR.

Reaction of 2b with Lithium Dimethylhept-1-ynylcuprate (25):

Following method B outlined above, **2b** (0.1 g, 0.59 mmol) was reacted with lithium dimethylhept-1-ynylcuprate, **25**, (0.65 mmol) in 10 mL of anhyd. ether and 5 mL of dimethyl

sulfide at -70°C and at 20°C for 1 hr. Normal workup, acetylation and chromatographic isolation yielded **12a** (0.15 g, 99%). GLPC and ^{1}H NMR analyses revealed that this material was a 70:30 mixture of diastereoisomers.

Reaction of 2b with Lithium Dimethylcyanocuprate (22b):

Following method B outlined above, **2b** (0.1 g, 0.59 mmol) was reacted with lithium dimethylcyanocuprate (25d) (0.89 mmol) in 19 mL of anhyd. ether at -70°C and below -30°C for 1 hr. Normal workup, acetylation and chromatographic isolation yielded **12d** (0.10 g, 63.9%) which was ca 95% one diastereoisomer by GLPC and ^{1}H NMR.

10. Cyclization of 5-Methyl-3,4-decadien-1,2-diol (**4d**):

Preparation of 2-Hydroxymethyl-5-pentyl-5-methylfuran (32):

In the dark, 5-methyl-3,4-decadien-1,2-diol (**4d**) (0.046 g, 0.25 mmol) was added to a solution of silver nitrate (0.13 g, 0.75 mmol) in H_2O (1 mL) and acetone (2 mL). The solution was refluxed for 4 hr, until TLC analysis showed no **4d**. The reaction mixture was then extracted with ether (3 X 10 mL). The combined organic phase was dried over anhyd. $MgSO_4$, concentrated in vacuo and chromatographed on Silica gel 60 using hexane:ethyl acetate (5:1) as eluant to give **32** (24.7 mg, 54%). The material exhibited: mass spectrum m/e

(relative intensity) 184 (M^+, 0.09), 153 (100), 113 (93.5), 97 (37.1), 95 (30.1), 83 (99.2), 81 (41.9); IR (gc/ir) ν 1113 (sharp, medium, C-O), 1045 (sharp, strong, C-O), 729 (sharp, weak, cis olefin C-H); ^{1}H NMR ($CDCl_3$) δ 0.87 (t, 3H, Me), 1.26 (m, 9H, MeC-4, C_3H_6), 1.58 (m, 2H, HC-1"), 1.64 (s, 1H, OH), 3.56 (m, 1H, H_AC-1'), 3.69 (dq, 1H, H_BC-1'), 4.89 (m, 1H, H_CC-2), 5.64 (ABq, 1H, H_DC-3, J_{DE} = 6.1 Hz, J_{CD} = 1.39 Hz), 5.83 (ABq, 1H, H_EC-4, J_{CE} = 2.41 Hz). The assignment of HC-3 and HC-4 were based on the observation that the coupling of HC-2 and HC-3 ($^3J_{CD}$ = 1.39 Hz) matched similar couplings in (Z)-2,5-diisopropyldihydrofuran[33], and that the signal due to the hydrogen on C-3 was shifted more than the hydrogen on C-4 upon acetylation.

Preparation of the Acetate of 32:

Reaction of **32** with acetic anhydride and pyridine gave **34**. This material exhibited: ^{1}H NMR ($CDCl_3$) δ 0.89 (t, 3H, Me, J = 6.96 Hz), 1.27 (m, 6H, C_3H_6), 1.56 (m, 5H, MeC-4, 2HC-1"), 2.08 (s, 3H, Ac), 4.04 (ABq, 1H, H_AC-1', $^2J_{AB}$ = 11.47 Hz, $^3J_{AC}$ = 6.29 Hz), 4.17 (ABq, 1H, H_BC-1', $^3J_{BC}$ = 3.52 Hz), 4.98 (m, 1H, H_CC-2), 5.63 (ABq, 1H, H_DC-3, J_{DE} = 6.08 Hz, $^3J_{CD}$ = 1.41 Hz), 5.82 (ABq, 1H, H_EC-4, J_{CE} = 2.42 Hz).

SECTION V

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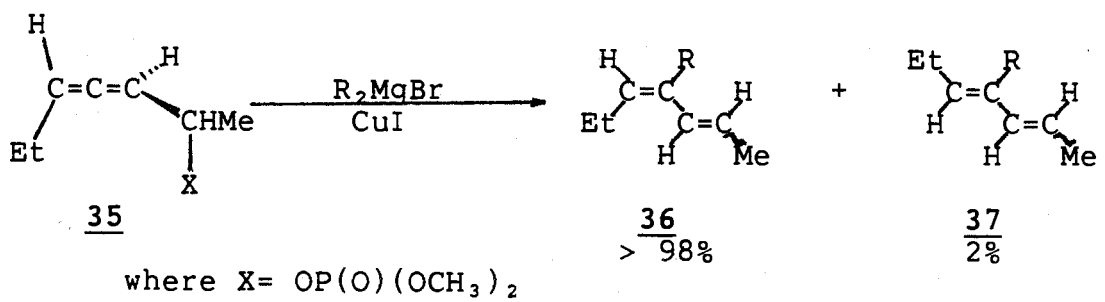
PART B

FORMATION OF 1,3-DIENES FROM THE REACTION OF α-ALLENYL PHOSPHATES AND ORGANOCUPRATES

SECTION I

INTRODUCTION

There are many ways to synthesize 1,3-dienes[1], but stereospecific synthesis wherein a third substituent is located on the β- or γ- carbon of a 1,3-diene is not easy. Gore and co-workers[2] have reported that reaction of magnesium bromide organocuprates with α-allenyl phosphates, 35, gave 1,3-dienes, 36 and 37, wherein the new substituent is mainly trans to the group initially located on the remote allenic carbon[2] (Scheme 15). The stereochemistry of the formation of the other double bond has not been studied.



Scheme 15: Conversion of α-Substituted Allenes to 1,3-Dienes.

This question can only be addressed in α-allenyl alcohols with known configurational relationships between the allene and the α-hydroxyl-bearing carbon. The previous study described in this thesis and that of Czyzewska[3] showed that reaction of alkynyl epoxides with organocuprates gave

α-allenyl alcohols of high diastereoisomeric purity and known relative configuration. Herein, we take adventage of this to study the stereochemistry of the reaction of lithium dimethylhex-1-ynylcuprate with two diastereoisomers of α-allenyl phosphates of known relative configuration.

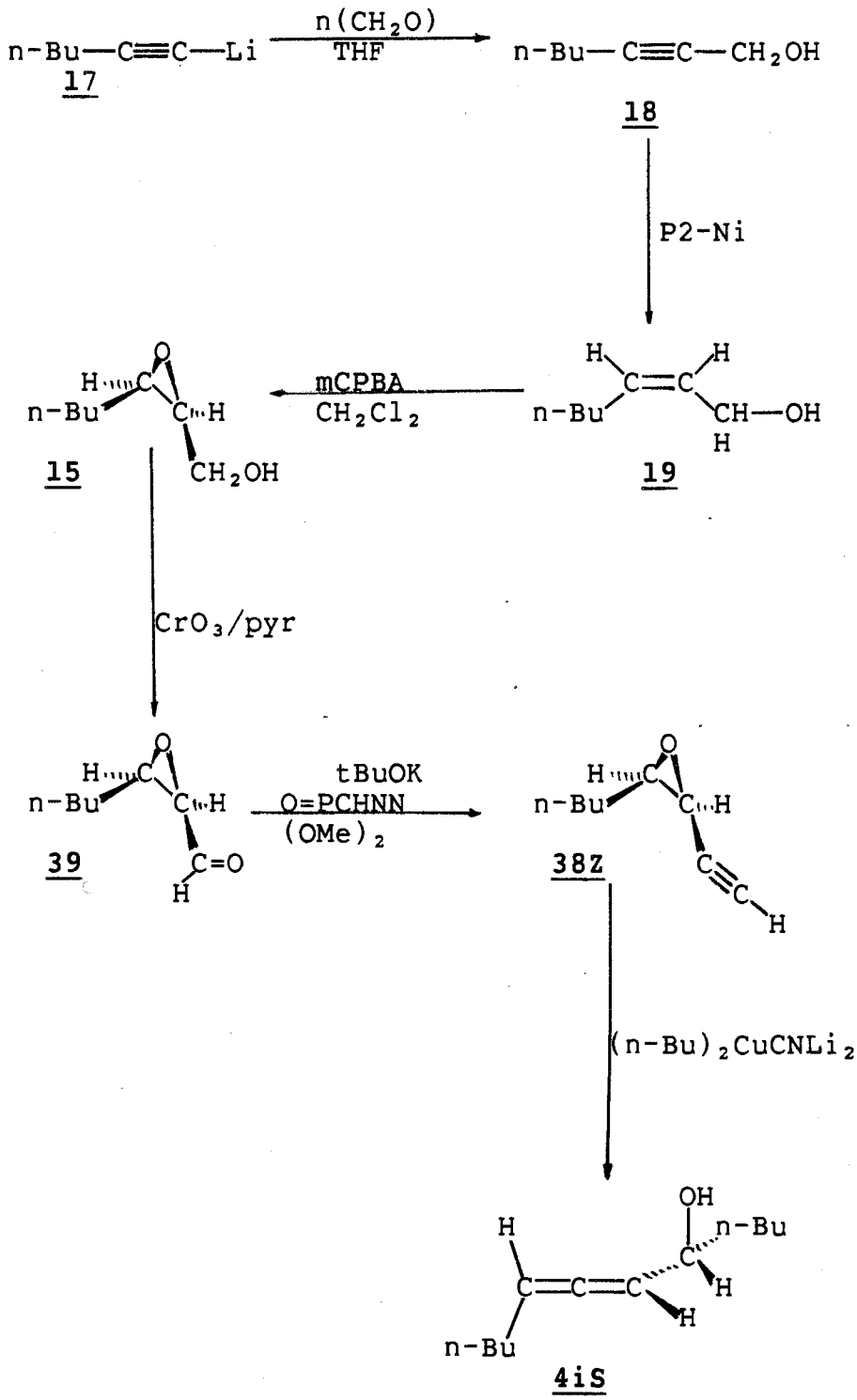
SECTION II

RESULTS AND DISCUSSION

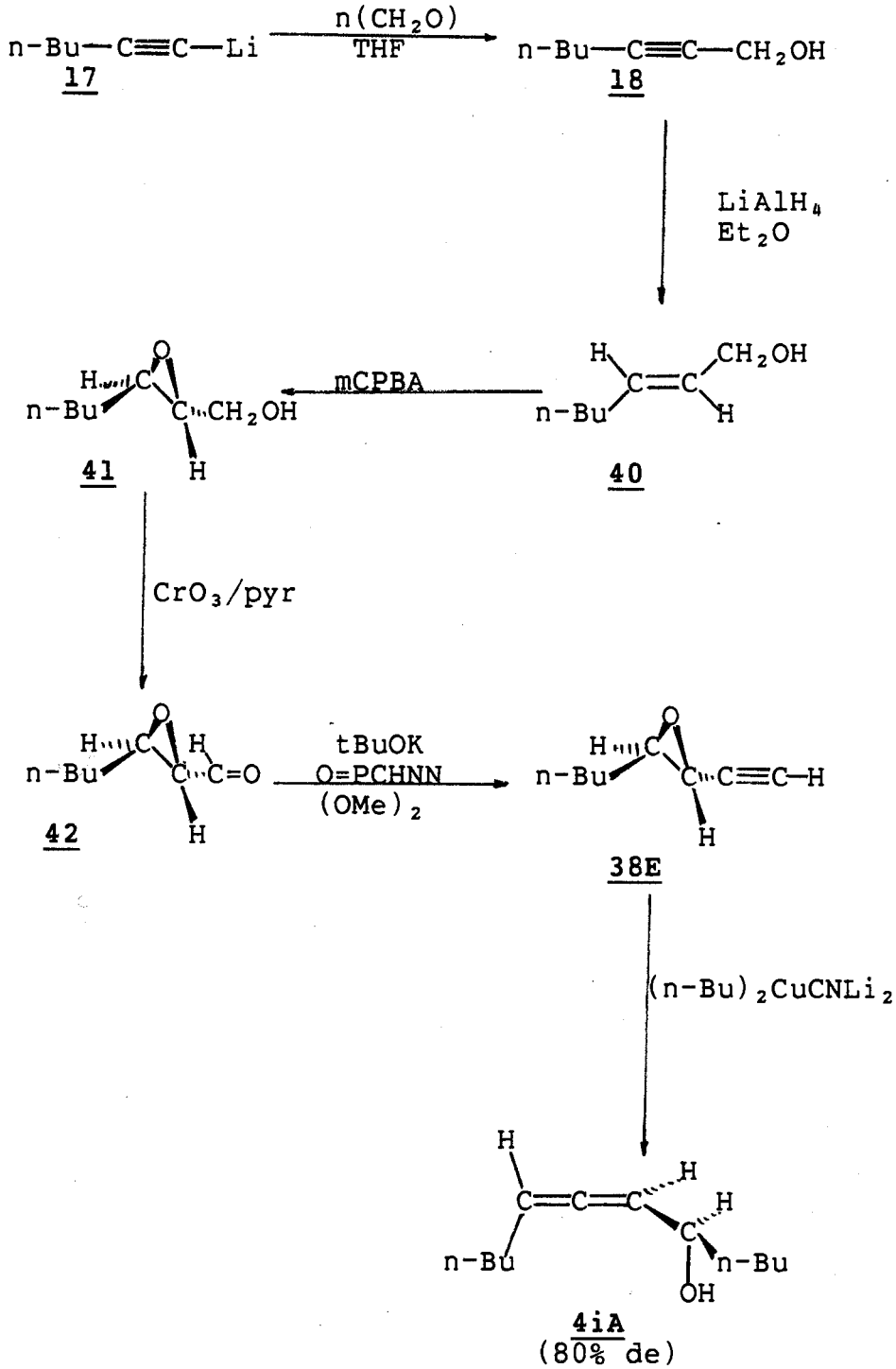
1. Synthesis of Diasteroisomers of α-Allenyl Alcohols

It has already been shown that organocuprate reagents 8, 21 and 22 react with epoxyalkynes via an anti S_N2' process. Thus the reaction of organocuprate with (Z)-epoxyalkyne, 38Z (Scheme 16), and (E)-epoxyalkyne, 38E (Scheme 17), should give 4iS and 4iA respectively with high diastereoisomeric excess.

Diastereoisomer 38Z was synthesized (Scheme 16) from reaction of n-hex-1-ynyllithium, 17, with paraformaldehyde to give 85% 2-heptyn-1-ol, 18, which was hydrogenated with P-2 nickel in ethanol to give a 80% yield of (Z)-2-hepten-1-ol, 19. The alkenol 19 was oxidized to 15 with m-chloroperbenzoic acid in 89% yield. Epoxide 15 was oxidized with dipyridine chromium trioxide to give 33.7% of (Z)-2,3-epoxyheptanal, 39. The aldehyde 39 was treated with dimethyl diazomethylphosphonate[4] in THF in the presence of a slurry of potasium tert-butoxide to give 46.9% of (Z)-3,4-epoxy-1-octyne, 38Z, which was finally converted in 60% yield to 6,7-dodecadien-5-ol, 4iS, with lithium di-n-butylcyanocuprate, 22a. GLPC analysis revealed that the 4iS was more than 99% one diastereoisomer (Scheme16).



Scheme 16: Synthesis of **4iS**.



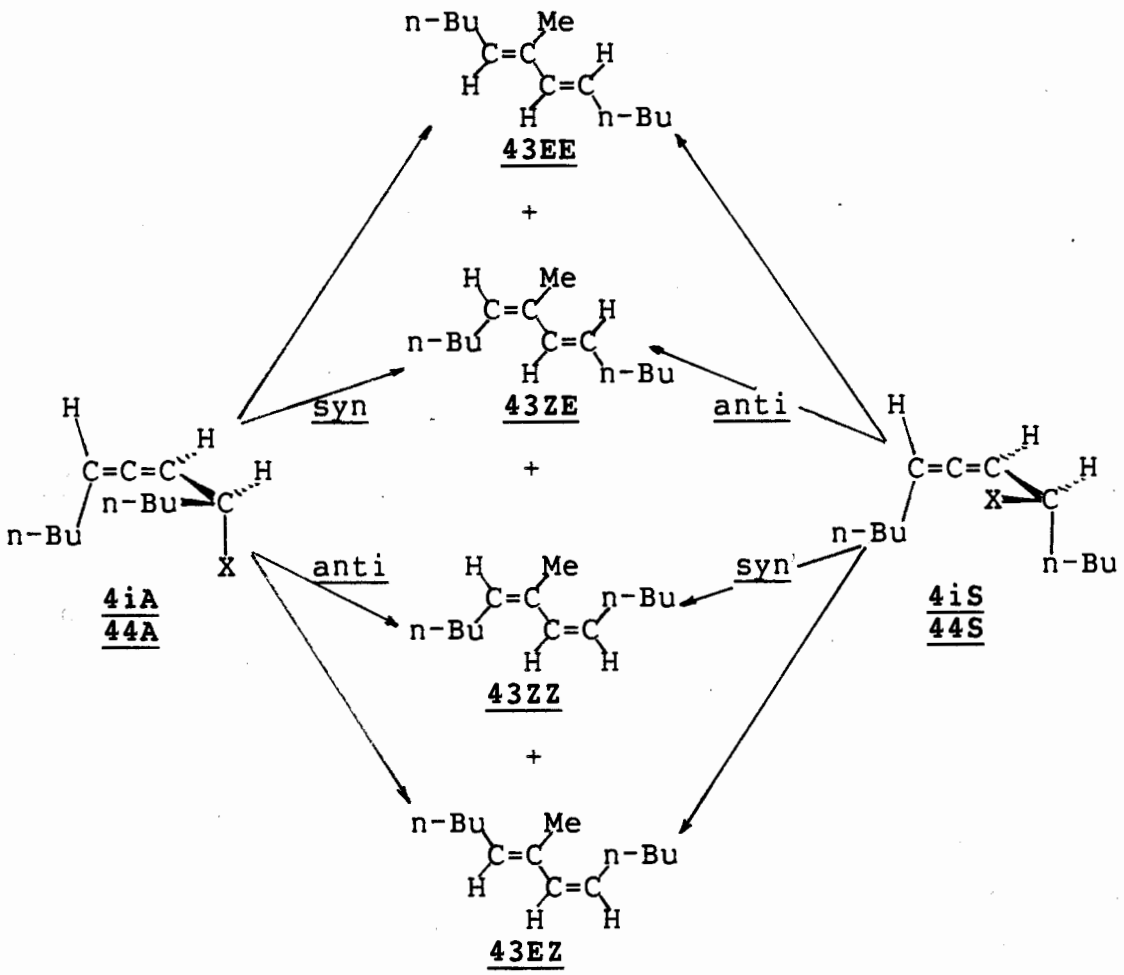
Scheme 17: Synthesis of **4iA**.

The other diastereoisomeric α-allenyl alcohol, **38E**, was synthesized (Scheme 17) by a similar synthetic method, but using a different reducing agent. Thus alkynol **18** was reduced by lithium tetrahydridoaluminate in anhydrous ether to give 83.6% (E)-2-hepten-1-ol, **40**. The alkenol **40** was oxidized with m-chloroperbenzoic acid to yield 86.8% (E)-2,3-epoxyheptan-1-ol, **41**, and then oxidized with dipyridine chromium trioxide to give 39% (E)-2,3-epoxyheptan-1-ol, **42**, which was converted to (E)-3,4-epoxy-1-octyne, **38E**, with dimethyl diazomethyl phosphonate in the presence of a slurry of potassium tert-butoxide. The epoxyalkyne **38E** was coupled with lithium di-n-butylcyanocuprate, **22a**, to give 6,7-dodecadien-5-ol, **4iA**, in which the configuration of the α-carbon with respect to the allene was opposite to that in **4iS**. Because the acetates of the two diastereoisomers could not be differentiated by ^{1}H NMR spectral analysis, the diasteroisomeric purity was determined by GLPC analysis and found to be 90% **4iA** and 10% **4iS**.

2. The Stereochemistry of Diene Formation from α-Allenyl Phosphastes

The conversion of α-allenyl esters to 1,3-dienes by reaction with organocuprates can occur either via an anti

or syn S_N2' process[4]. If the reaction involves a syn S_N2' process, **4iS** would give diene **43ZZ** (Scheme 18), and **4iA** would give diene **43ZE** (Scheme 18). If the reaction proceeds via an anti S_N2' process, **4iS** would produce diene **43ZE** and **4iA** would produce diene **43ZZ** (Scheme 18).



where 4i: X = OH
44: X = $OP(O)(OCH_3)_2$

Scheme 18: Conversion of Diastereoisomeric *a*-Allenyl Esters to 1,3-Dienes.

We phosphorylated allenyl alcohols **4iA** and **4iS** with dimethylchlorophosphate and pyridine[2]. Since the allenyl phosphate products, **44A** and **44S** (Scheme 18), decomposed on Silica gel TLC plates, the crude phosphorylation mixtures were directly reacted with lithium dimethyl-n-hex-1-ynylcuprate, **25**. The results are summarized in Table 7. The structure of the major 1,3-diene isomer from the organocuprate reaction with **44S** was assigned as **43ZE** on the basis of ^{1}H NMR analysis. The ^{1}H NMR spectrum of **43ZE**

Table 7: Formation of 1,3-Diene from Diastereoisomers of *a*-allenyl alcohol **4iA** and **4iS**

a-allenyl alcohol (diastereoisomers)	Diene 43ZE	43ZZ	other isomers	Yield
4iS (99%)	84%	16%	<2%	80%
4iA (10% **4iS**, 90% **4iA**)	10%	90%	<2%	75%

exhibited a doublet of doublets near 6.42 ppm which contained a large vinyl vicinal coupling (J = 15.6 Hz) with the hydrogen on C-8 (Figure 17). The ^{1}H NMR spectrum of **43ZZ** exhibited a doublet near 5.84 ppm containing a smaller vinyl vicinal coupling (J = 11.5 Hz) with the hydrogen on C-8 (Figure 18). These spectral characteristics are consistent with the assignment given for each compound[2,5]. Isomer composition in each reaction was estimated by GLPC

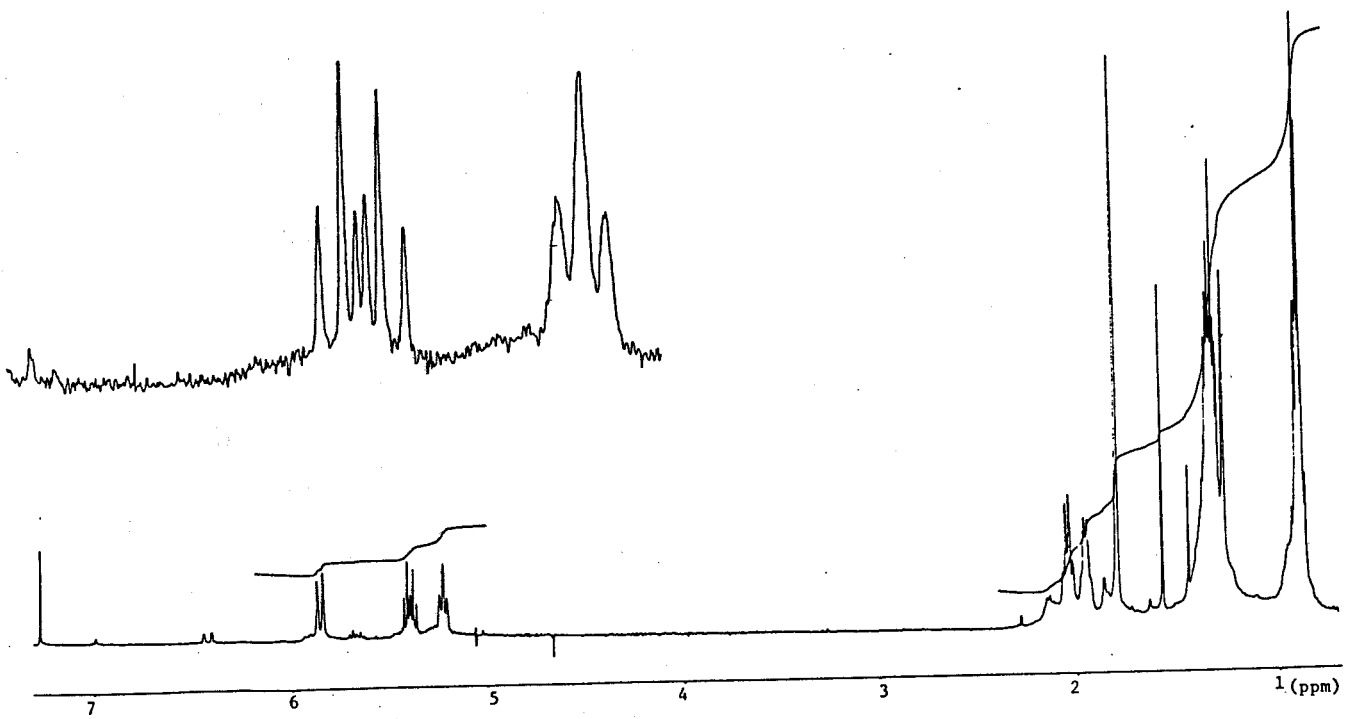


Figure 17: 400 MHz HMR Spectrum of
(Z,Z)-6-Methyl-5,7-dodecadiene, 43ZZ

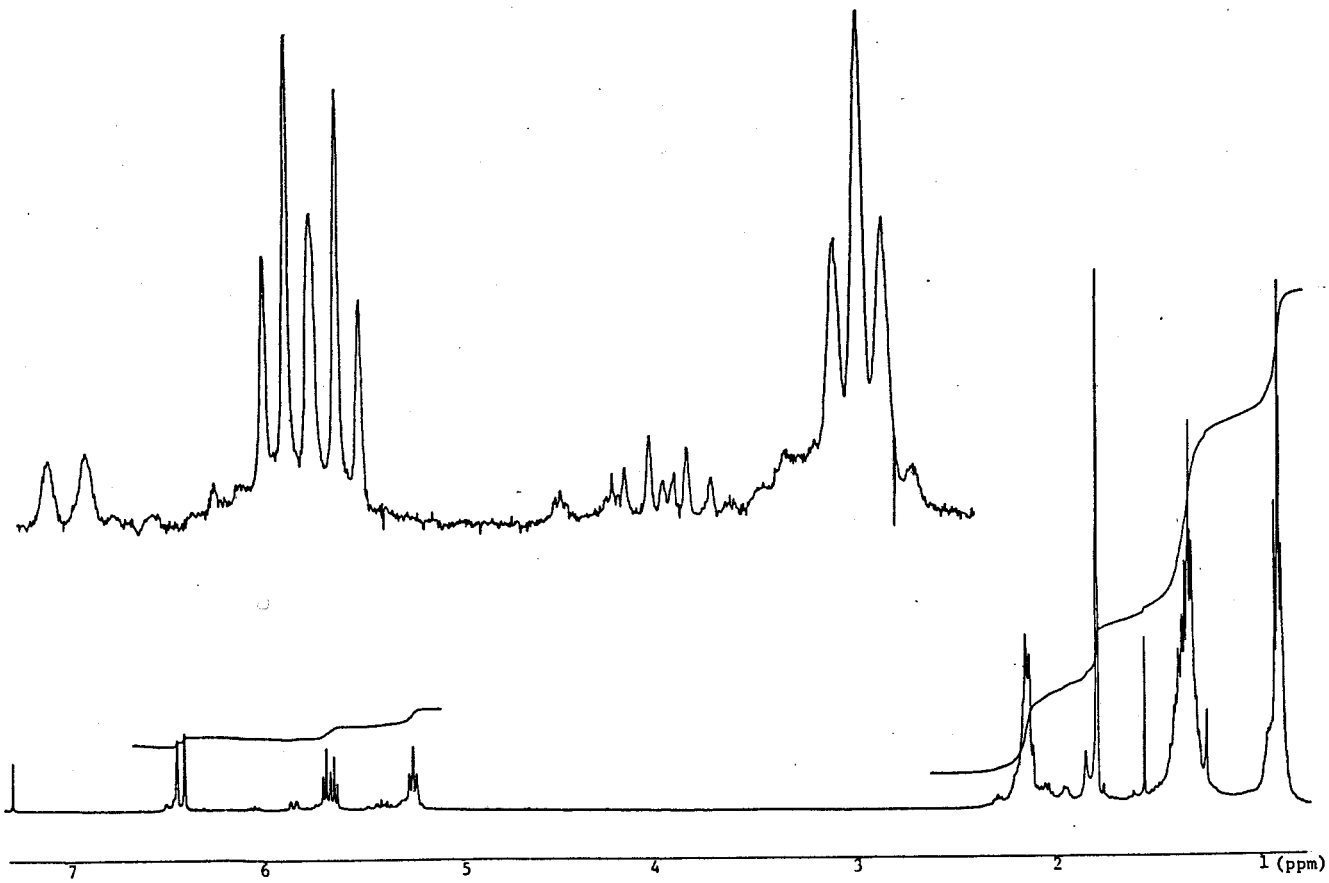


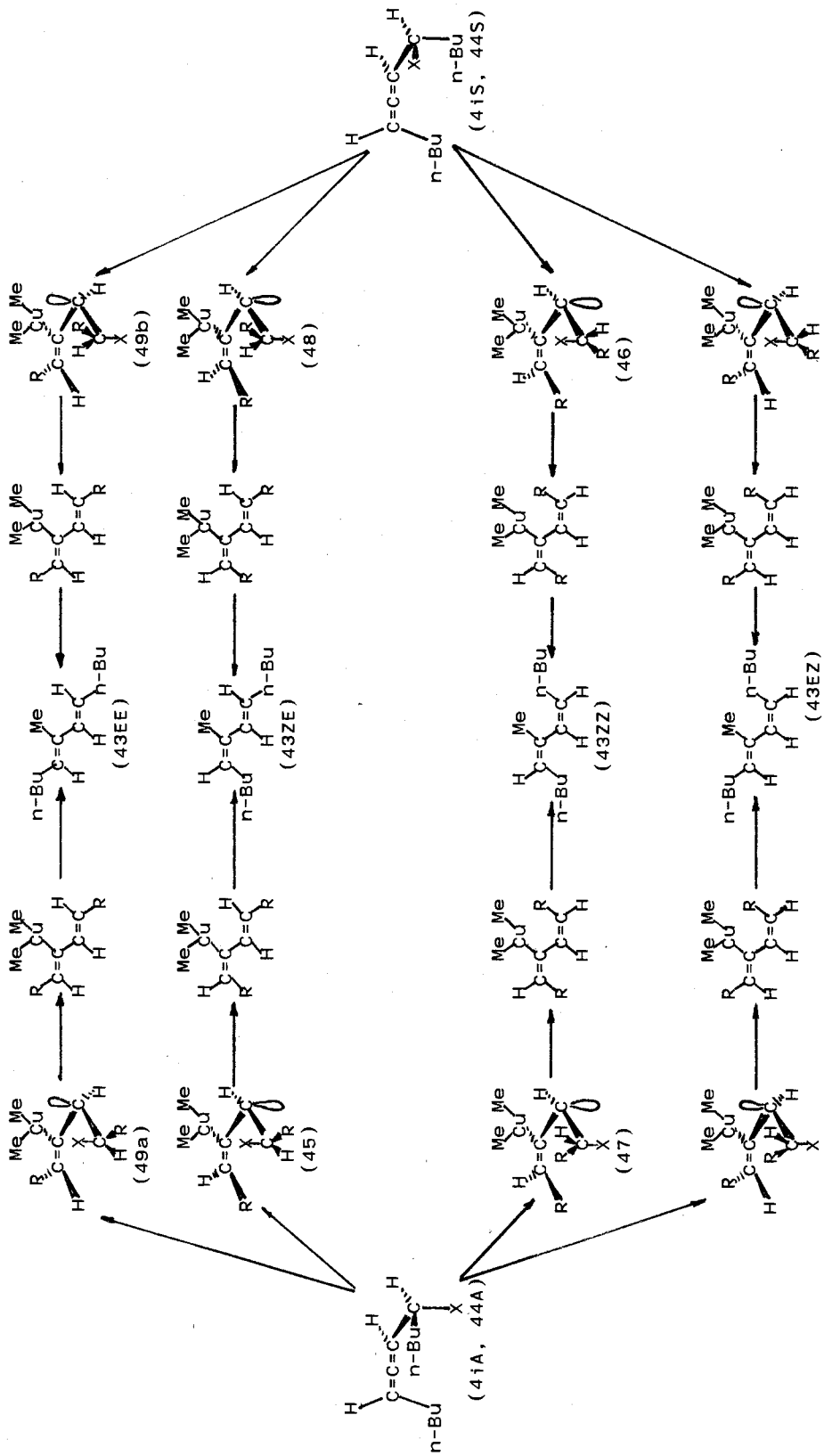
Figure 18: 400 MHz HMR Spectrum of
(Z,E)-6-Methyl-5,7-dodecadiene, 43ZE

(Table 7). Thus *a*-allenyl phosphate **44A** gave exclusively anti S_N2' reaction, whereas **44S** gave major anti S_N2' reaction.

3. Mechanistic Consideration for the Reaction of *a*-Allenyl Esters with Organocuprates

Two mechanisms have been postulated to explain the reaction of organocuprates with *a*-allenyl esters. One proposal involves S_N2' attack of the organocuprates at the center carbon of the allene to generate vinyl copper(III) intermediates[6], **62**, **63**, **64**, **65** and **66** (Scheme 19). These intermediates may undergo reductive elimination to yield 3-substituted 1,3-dienes. In this mechanism, nucleophilic attack attended by oxidation of copper(I) to copper(III) is suspected to be a slow step, while the rearrangement of the double bond and elimination of the leaving group are fast.

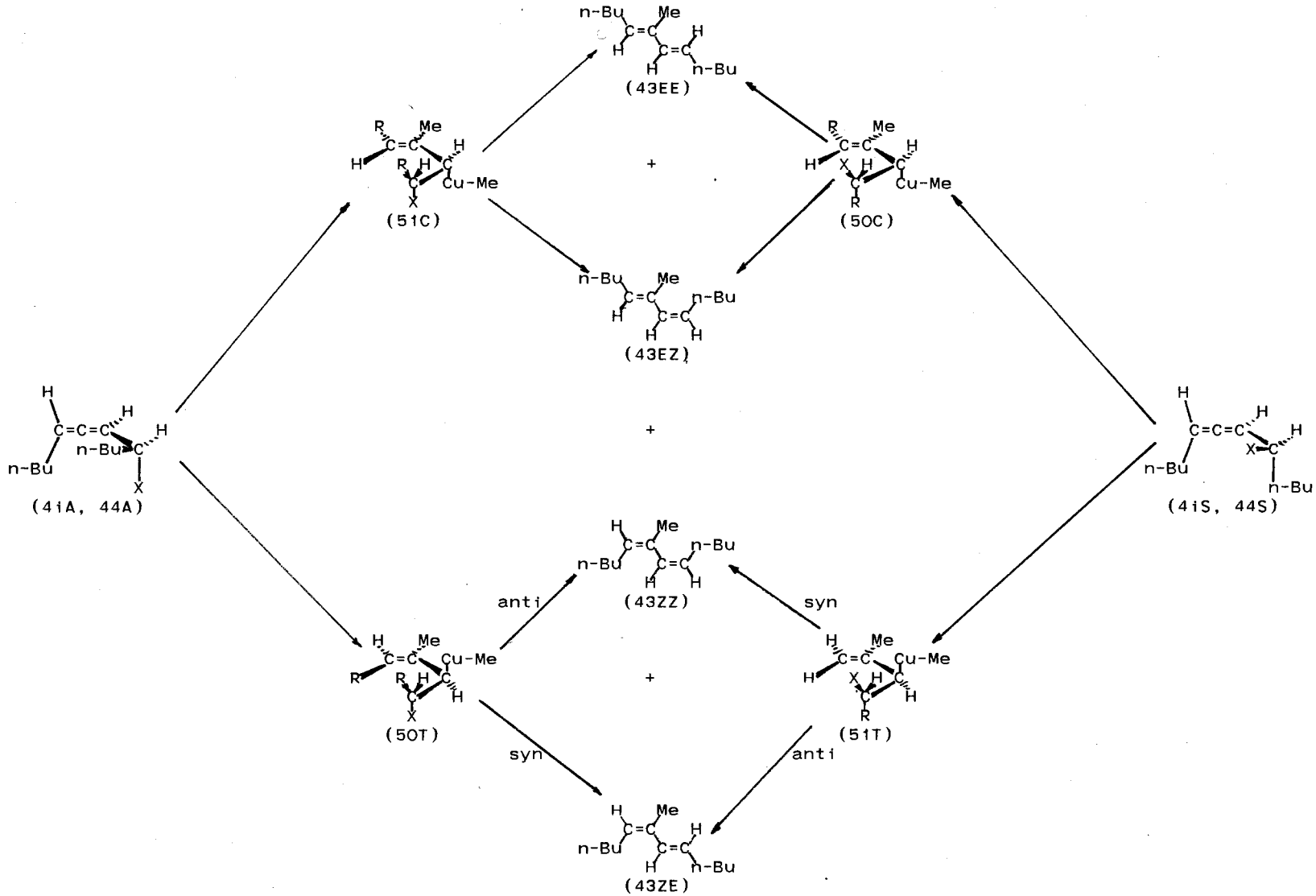
The present reaction parallels the known anti S_N2' reaction of organocuprates with allylic esters[7]. The factors which favour the anti mode of reaction in allylic systems are not understood[8]. However, it is easy to see that in both allylic and allenic systems, S_N2' reaction of organocuprates will generate an electron pair periplanar to the leaving group.



Scheme 19: Vinyl Copper Mechanism for Conversion of α-Allenyl Phosphates to 1,3-Dienes by Organocuprates.

A second mechanistic proposal involves carbocupration to yield cuprates **50** and **51**[8](Scheme 20). According to this process, 1,3-dienes are formed from α-allenyl esters via subsequent decomposition of the cuprates **50** and **51**. The phosphate ester group or the alkyl group may be perpendicular to the allenic function. Their location is dependent on the size of the substituents on the other side of the allene. Thus, the n-butyl group of **44S** is suspected to be perpendicular to the allene (Scheme 20), whereas, the phosphate group of **44A** is suspected to be perpendicular to the allene (Scheme 20).

It has been reported that substitution on the allenic carbon will lower the reactivity of the reaction of organocuprates with allene[9]. Assuming that carbocupration occurs from the less hindered side, **44A** should give intermediate **50T** and **44S** should give intermediate **51T**. After carbocupration, the electron pair of **50T**, coordinating to the copper(I), is suspected to be antiperiplanar to the leaving group. This intermediate is favored stereoelectronically. Decomposition of **50T** results in the formation of diene **43ZZ**, and stereoselectivity should be high (Scheme 20). In intermediate **51T**, the electron pair is not antiperiplanar to the leaving group, and bond rotation must occur before elimination. Thus stereoselectivity for the formation of



Scheme 20: Carbocupration Mechanism for Conversion of α-Allenyl Phosphates to 1,3-Dienes by Organocuprates.

diene **43ZE** from **44S** would be lower (Scheme 20). These rationales fit the experimental results. Therefore, it is most probable that reaction of organocuprates with *a*-allenyl phosphates is by carbocupration.

To conclude, we found that the stereochemistry of the reaction of organocuprates with *a*-allenyl phosphates is highly anti and can be explained by assumption that the reaction proceeds through carbocupration.

SECTION III

EXPERIMENTAL SECTION

General Procedures

See Experimental Part A (p 58).

Solvents and Reagents

See Experinental Part A (p 60).

Methyl (diazomethyl)phosphonate was prepared from N-hydroxymethyl phthalimide[10] by the method of Seyferth[4].

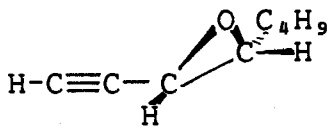
Synthesis of 6,7-Dodecadien-5-ol (4iS)

Preparation of (Z)-2,3-Epoxyheptan-1-al (39):

To 118.2 g (1.46 mol) of pyridine in 195 mL CH_2Cl_2 at 0°C, was added 6.92 g (0.69 mol) of chromium troxide. The solution was stirred for 0.5 hr, and then 10 g (77 mmol) of (Z)-2,3-epoxyheptan-1-ol, 15, was added dropwise. The reaction mixture was stirred at room temperature for 1 hr after which thin layer chromatographic analysis revealed the reaction was complete. The reaction mixture was filtered through 3 cm of coarse Silica gel with ether wash (3 X 25 mL). The solvent was removed in vacuo and the concentrate

filtered through 2 cm of Silica gel 60. The clear liquid was chromatographed on Silica gel 60 using hexane:ethyl acetate (8:1) as eluant to give 39 (3.32 g, 33.7%).

Preparation of (Z)-3,4-Epoxyoct-1-yne (38Z):

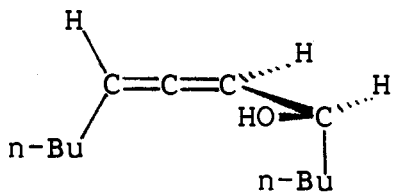


38Z

To a stirred slurry of potassium tert-butoxide (4.07 g, 0.029 mol), in dry THF (36 mL) at -70°C under argon, methyl (diazomethyl)phosphonate (4.28 g, 0.028 mol) in dry THF (55 mL) was added dropwise over a period of 10 min. and allowed to stir for 5 min. Then 39 (3.32 g, 0.026 mol) in dry THF (12 mL) was added slowly. The reaction mixture was diluted with 48 mL of dry THF, stirred at -70°C for 15 hr, and slowly warmed to room temperature over 5 hr. Water (200 mL) was added, and the mixture was extracted with CH_2Cl_2 (3 X 300 mL). The combined extract was backwashed with sat. NaCl solution (50 mL), dried over anhyd. $MgSO_4$, concentrated in vacuo, and chromatographed on Silica gel 60 using hexane:ethyl acetate (8:1) as eluant to give 38Z (1.5 g, 46.9%). This material exhibited: mass spectrum m/e (relative intensity) 95 (60), 81 (72), 70 (100) 55 (63); ^1H NMR ($CDCl_3$) δ 0.93 (t, 3H, Me, J = 7 Hz), 1.49 (m, 4H, C_2H_4), 1.70 (m, 2H, HC-5), 2.34 (d, 1H, HC-1, J = 1.71 Hz), 3.03

(m, 1H, HC-4, J = 4.0 Hz), 3.41 (dd, 1H, HC-3, J = 1.71, 4.0 Hz); ^{13}C NMR $CDCl_3$ δ 13.90, 22.44, 27.99, 28.90, 44.70 (C-4) 57.86 (C-3), 73.45 (C-1), 79.06 (C-2). **Exact** mass calcd. for $C_8H_{12}O$: 124.0888. Found (ms) 124.0881.

Preparation of 6,7-Dodecadien-5-ol (4iS):



4iS

Following the general method B outlined in Part A, **38Z** (0.1 g, 0.8 mmol) was reacted with lithium dimethylcyanocuprate, **22b**, (0.88 mmol) in 17 mL of anhyd. ether at -73°C for 0.5 hr. The stirred mixture was warmed slowly to -30°C over 0.5 hr. Then H_2O (1.7 mL) and NH_4Cl (7.2 g) were added at -30°C to quench the reaction. Normal work up gave **4iS** (0.08 g, 60%). This material exhibited: mass spectrum m/e (relative intensity) 164 (13), 85 (100), 83 (78), 81 (72), 69 (88); IR (film) ν 3320 (broad, strong, OH), 1967 (sharp, medium, C=C=C); ^1H NMR ($CDCl_3$) δ 0.89 (m, 6H, 2Me), 1.34 (m, 8H, $2C_2H_4$), 1.54 (m, 2H, HC-4), 1.58 (brd, 1H, OH), 2.02 (m, 2H, HC-9, J = 6.82 Hz), 4.11 (dq, 1H, HC-5, J = 2.46, 6.15 Hz), 5.22 (m, 1H, HC-6, J = 3.02 Hz, $^3J_{CD}$ = 6.03 Hz), 5.28 (dq, 1H, HC-8, $^5J_{CE}$ = 2.46 Hz, J = 6.56 Hz). **Exact** mass calcd. for $C_{12}H_{22}O$: 182.1670. Found

(ms): 182.1641.

Synthesis of 6,7-Dodecadien-5-ol (**4iA**)

Preparation of (E)-2-Hepten-1-ol (40):

Lithium tetrahydridoaluminate (2.47 g, 62.4 mmol) was added, in small portions, to a solution of 2-heptyn-1-ol, **18**, (6.9 g, 62.0 mmol) in anhyd. ether (150 mL) at ice-bath temperature. The reaction mixture was stirred at room temperature overnight. Water (2.5 g) was added dropwise, followed by 7.5 mL of 15% NaOH solution and a further 7.5 mL of H_2O. After filtration of salts through 0.5 cm of Celite, the organic phase was dried over anhyd. $MgSO_4$, and concentrated in vacuo. Distillation of the residue (bp 85°C/18.5 torr) gave **40** (5.9 g, 83.6%). This material exhibited: ^1H NMR ($CDCl_3$) δ 0.88 (t, 3H, Me, J = 7 Hz), 1.33 (m, 4H, C_2H_4), 1.6 (s, 1H, OH), 2.03 (m, 2H, HC-4), 4.07 (d, 2H, HC-1, J = 4.98 Hz), 5.65 (m, 2H, HC-2, HC-3).

Preparation of (E)-2,3-Epoxyheptan-1-ol (41):

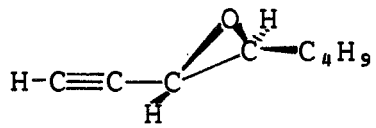
To a solution of **40** (4.79 g, 42 mmol) in CH_2Cl_2 (90 mL), m-chloroperbenzoic acid (9.5 g, 44 mmol) was added in small portions. The reaction was stirred at room temperature for 4 hr. Then potassium fluoride (approx 10 g) was added and the mixture stirred for 0.5 hr. After filtration of salts, the organic phase was concentrated, and chromatographed on

Silica gel 60 using hexane:ethyl acetate (6:1) as eluant to give **41** (5.54 g, 86.8%). This material exhibited: IR (film) ν 3405 (broad, strong, OH), 889, 865 (doublet, medium, trans C-O-C); ^{1}H NMR ($CDCl_3$) δ 0.90 (t, 3H, Me, J = 7 Hz), 1.36 (m, 4H, C_2H_4), 1.55 (m, 2H, HC-4), 1.92 (t, 1H, OH, J = 6.2 Hz), 2.94 (m, 2H, HC-2, HC-3), 3.60 (m, 1H, H_AC-1), 3.88 (m, 1H, H_BC-1).

Preparation of (E)-2,3-Epoxyheptan-1-al (42):

Chromium trioxide (32.8 g, 0.328 mol) was added to a solution of pyridine (56 mL, 0.693 mol) in dichloromethane (100 mL) at ice bath temperature. The mixture was warmed to room temperature over 0.5 hr. then **41** (4.74 g, 0.036 mol) was added dropwise, and the mixture was stirred at room temperature for 1 hr. Thin layer chromatographic analysis revealed the reaction was complete after this time. The mixture was filtered through 3 cm of coarse Silica gel with ether wash (3 X 25 mL). Solvent was removed at reduced pressure and the concentrate filtered through 2 cm of Silica gel 60. The clear solution was concentrated and chromatographed on Silica gel 60 using hexane:ethyl acetate (8:1) as eluant to give **42** (1.8 g, 39%). This material exhibited: ^{1}H NMR ($CDCl_3$) δ 0.90 (t, 3H, Me), 1.32 (m, 2H, HC-6), 1.47 (m, 2H, HC-5), 1.66 (m, 2H, HC-4), 3.11 (dd, 1H, HC-2), 3.22 (td, 1H, HC-3), 8.99 (d, 1H, HC-1, J = 10 Hz).

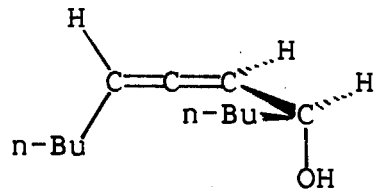
Preparation of (E)-3,4-Epoxyoct-1-yne (38E):



38E

Methyl (diazomethyl)phosphonate (0.44 g, 2.9 mmol) in dry THF (7.5 mL) was added dropwise to a stirred slurry of potassium tert-butoxide (0.33 g, 3.9 mmol) in dry THF (3.6 mL) at -70°C under argon. The solution was stirred for 5 min. and subsequently **42** (0.34 g, 2.6 mmol) in dry THF (7.5 mL) was added slowly. The reaction mixture was stirred at -70°C for 8 hr, and warmed to room temperature for 13 hr. Water (80 mL) was added and the resulting solution extracted with CH_2Cl_2 (4 X 80 mL). The combined extract was backwashed with sat. brine (25 mL), dried over anhyd. $MgSO_4$, and concentrated in vacuo. Flash chromatography on Silica gel 60 using hexane:ethyl acetate (8:1) gave **38E** (0.079 g, 24.6%). This material exhibited: mass spectrum m/e (relative intensity) 95 (41), 81 (45), 70 (100), 55 (64); IR (film) ν 3295 (broad, strong, C C-H), 2130 (sharp, weak, C C), 1270, 1245 (doublet, strong, C-O), 918, 885 (doublet, strong, trans epoxy C-O-C); ^1H NMR ($CDCl_3$) δ 0.92 (t, 3H, Me), 1.33 (m, 4H, C_2H_4), 1.57 (m, 2H, HC-5), 2.32 (d, 1H, HC-1), 3.10 (m, 2H, HC-3, HC-4). **Exact** mass calcd. for $C_8H_{12}O$: 124.0888. Found (ms): 124.0884.

Preparation of 6,7-Dodecadien-5-ol (4iA):

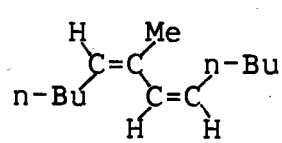


4iA

Following the general method B outlined in Part A, **38E** (0.05 g, 0.4 mmol) was reacted with **22b** (0.44 mmol) in 8.5 mL of anhyd. ether at -65°C for 0.5 hr. The stirred mixture was warmed slowly to -30°C over 0.5 hr. then H_2O (1 mL) and NH_4Cl (3.7 g) were added at -30°C to quench the reaction. Normal work up gave **4iA** (0.03 g, 48%). This material exhibited: IR (film) ν 3330 (broad, strong, OH), 1961 (sharp, strong, C=C=C); ^1H NMR ($CDCl_3$) δ 0.92 (m, 6H, 2Me), 1.34 (m, 8H, $2C_2H_4$), 1.59 (m, 2H, HC-3), 1.61 (s, 1H, OH), 2.02 (m, 2H, HC-9), 4.12 (m, 1H, HC-5), 5.2 (m, 1H, HC-6, J = 3, 6.1 Hz), 5.29 (dq, 1H, HC-8, J = 2.3, 6.4 Hz).

Reaction of Organocuprates with α-Allenyl Phosphates

Preparation of Z,Z-6-Methyl-5,7-dodecadiene (43ZZ):

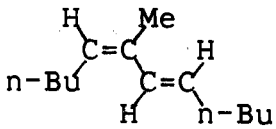


43ZZ

To a solution of **4iS** (0.07 g, 0.38 mmol) in CH_2Cl_2 (2

mL) at ice-bath temperature, pyridine (0.12 mL, 1.52 mmol) and diethylchlorophosphate (0.13 mL, 0.76 mmol) were added. The reaction mixture was warmed slowly to room temperature, and stirred overnight. The solution was diluted with CH_2Cl_2 (5 mL), and H_2O (3 mL). Then the mixture was acidified to pH 3 with 1 N HCl, and washed with H_2O (3 mL), sat. $NaHCO_3$ (3 mL), H_2O (3 mL) and sat. brine (3 mL). The organic phase was dried over anhyd. $MgSO_4$, and concentrated in vacuo. Without purification, the concentrate **44S** was dissolved in anhyd. ether (7 mL), and cooled to -73°C. To this solution, was added dropwise over a 10-min period, under argon, lithium dimethylhex-1-ynlcuprate, **25**, (0.42 mmol) prepared from n-hexynllithium (4.2 mmol), cuprous bromide-dimethyl sulfide (0.085 g, 0.42 mmol) and methyllithium (0.84 mmol, 1.6 M in ether) in 4.5 mL anhyd. ether and 3 mL dimethyl sulfide. The reaction mixture was stirred below -35°C for 1 hr. Following normal work up, the residue was chromatographed on Silica gel 60 using pentane as eluant to give **43ZZ** (0.054 g, 80%). This material exhibited: mass spectrum m/e (relative intensity) 180 (M^+, 34), 123 (23), 109 (22), 95 (44), 81 (100); IR (gc/ir) ν 729 (sharp, weak, cis olefin C-H); ^1H NMR ($CDCl_3$) δ 0.87 (m, 6H, 2Me), 1.31 (m, 8H, $2C_2H_4$), 1.78 (d, 3H, HC-13, J = 0.65 Hz, 1.94 (m, 2H), 2.02 (m, 2H), 5.21 (t, 1H, HC-5, J = 7.6 Hz), 5.38 (dt, 1H, HC-8, J =11.56, 7.28 Hz), 5.8 (d, 1H, HC-7, J = 11.51 Hz). **Exact** mass calcd. for $C_{13}H_{24}$: 180.1878. Found (ms): 180.1852.

Preparation of Z,E-6-Methyl-5,7-dodecadiene (43ZE):



43ZE

Following the procedure for the conversion of **4iS** to **43ZZ** outlined above, **4iA** (0.023 g, 0.13 mmol) in 1 mL CH_2Cl_2 was phosphorylated by reaction of **4iA** with pyridine (0.04 mL, 0.52 mmol) and diethylchlorophosphate (0.04 mL, 0.26 mmol). The phosphate **44A** in 1 mL dimethyl sulfide and 8.5 mL of anhyd. ether was reacted with **25** (0.14 mmol) at -73°C and then below -35°C for 1 hr. Normal work up and chromatography gave **43ZE** (0.017 g, 75%). This material exhibited: mass spectrum m/e (relative intensity) 180 (M^+, 56), 137 (22), 123 (41), 95 (45), 81 (100); IR (gc/ir) ν 962 (sharp, weak, trans olefin C-H); ^1H NMR ($CDCl_3$) δ 0.90 (m, 6H, 2Me), 1.33 (m, 8H, $2C_2H_4$), 1.79 (d, 3H, HC-13, J = 1.06 Hz), 2.13 (m, 4H, 2HC-4, 2HC-9), 5.24 (t, 1H, HC-5, J = 7.45 Hz), 5.66 (dt, 1H, HC-8, J = 7.07, 15.50 Hz), 6.42 (dd, 1H, HC-7, J = 15.59, 0.8 Hz). **Exact** mass calcd. for $C_{13}H_{24}$: 180.1878. Found (ms): 180.1891.

SECTION IV

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