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thesis entitled

I. A NEW HOST-SPECIFIC TOXIN FROM HELMINTHOSPORIUM CARBONUM

II. A STUDY OF ACYCLIC STEREOSELECTION VIA A CHELATION CONTROLLED [2,3] SIGMATROPIC REARRANGEMENT

presented by

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has been accepted towards fulfillment
of the requirements for

Master of Science degree in Chemistry

Major professor

Date 11/18/85

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By

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A DISSERTATION

Submitted to
Michigan State University
in partial fulfillment for the degree of

MASTER OF SCIENCE

Department of Chemistry

1985

ABSTRACT

I. A NEW HOST-SPECIFIC TOXIN FROM *HELMINTHOSPORIUM CARBONUM*

By

Benjamin A. Horenstein

Previously characterized HC-toxin, elaborated by *Helminthosporium Carbonum*, cyclo-(Pro-Ala-Ala-Aoe), (Aoe = 2-amino-8-oxo-9,10-epoxy decanoic acid), is toxic to susceptible genotype of maize. It has been demonstrated that the epoxy moiety of the Aoe residue is essential for toxicity; however, the actual mode of action of HC-Toxin is not yet understood. In an effort to understand the physiochemical behavior of HC-toxin, the culture filtrate of *Helminthosporium carbonum* was examined for homologous forms of the toxin. This thesis describes the isolation and structural elucidation of two HC-toxin analogs, HC-toxin II and HC-toxin III, cyclo-(Pro-Ala-Gly-Aoe) and cyclo-(3-trans-Hypro-Ala-Ala-Aoe), respectively. Purification of the toxins was achieved by column chromatography on silica gel, followed by reverse-phase HPLC and, finally, normal-phase HPLC. A variety of techniques established the aforementioned structures of HC-toxin II and III, including amino acid analysis, EI- and FAB-mass spectroscopy, ^{1}H-NMR (standard, COSY, NOE-difference), and ^{13}C-NMR (fully decoupled, DEPT).

ABSTRACT

II. ACYCLIC STEREOSELECTION VIA A CHELATION-CONTROLLED [2,3] SIGMATROPIC REARRANGEMENT

By

Benjamin A. Horenstein

The [2,3] Wittig rearrangement of substrates bearing an unstabilized carbanionic center proceeds selectively to yield Z-olefins, given alkyl substitution at the 2-position of the migrating allylic moiety. In the absence of such substituents, the rearrangement occurs in a stereorandom fashion. This thesis describes the synthesis and [2,3] rearrangement of substrates lacking 2-alkyl substitution of the migrating allylic fragment, which are capable of internal chelation of the carbanionic center with an alkoxy group adjacent to the breaking C-O bond. We have observed olefin selectivity of 3.5:1 (Z- to E-), a value higher than that obtained for similarly substituted substrates incapable of internal chelation; a model accounting for these results is discussed.

DEDICATION

This work is dedicated to Professor S. P. Tanis. Professor Tanis' enthusiasm, helpfulness and dedication have been appreciated and will be missed.

ACKNOWLEDGEMENTS

I would like to thank Ms. Tonya Acre for her fine work in preparation of this manuscript. Thanks to Mr. Richard (Red-Shoes) Olsen for his tremendous help in acquisition of many mass spectra. Also, thanks to Mr. Brad Ackermann for his interest, helpful discussions and work on FAB-MS of the HC-toxins. In addition to a rewarding academic experience under the guidance of Professor Tanis, I will always appreciate the good times enjoyed by our group during pursuit of Mexican food, dry-ice ballistics and the B.S.R.I.

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HC-TOXINS INTRODUCTION

Host-selective toxins can be defined as those which originate from microorganisms that are restricted to colonization of certain susceptible plant strains and are toxic only to hosts of the microorganism.

There are a number of reasons for interest in host-selective toxins. Many important crop plants have been attacked by host-selective, toxin-producing microorganisms, including maize, sugarcane, oats, sorghum, pear, citrus, apple, and tomato; significant crop losses have occurred. In all cases, however, resistant host genotypes exist. Indeed, host-selective toxins have been used to screen new hybrids for resistance to fungal attack.[1] Host-selective toxins, in contrast to nonspecific toxins, are required by the parent microorganism for successful colonization of the host. This allows study of disease induction at the molecular level. Ultimately, through a much greater understanding of structure-function relationships and the biochemical role played by host-selective toxins, one may be able to design synthetic host-selective toxins applicable as ecologically sound herbicides.[1]

H. carbonum is a pathogenic fungus, toxic to susceptible genotypes of maize. Examination of culture filtrates of *H. carbonum* resulted in the isolation[2] and structure determination[3-6] of 1 HC-toxin (cyclo(Ala-Ala-Aoe-Pro); Aoe = 2-amino-8-oxo-9,10-epoxy decanoic acid). HC-toxin illicited the same host-selective toxicity to maize as did *H. carbonum*. Related species of *Helminthosporium* also elaborate host-specific toxins, though crops other than maize are affected. The *Helminthospora* fungi, toxins elaborated and their hosts are presented in Table 1. The wide structural diversity displayed by the toxins suggests that the reactive site(s) in plant cells varies from toxin to toxin.

Interestingly, other microorganisms elaborate bioactive tetrapeptidic metabolites containing Aoe and an imino acid (Pro or pipicolic acid). These include Cyl-2, 7, a non-specific plant toxin from *Cylindrocladium scoparium* Morgan and chlamydocin, 8, an anti-tumor agent from *Diheterospora chlamydosporia*. Despite their structural likeness to HC-toxin, these metabolites display markedly different bioactivity, illustrating that changes in the composition of the cyclic tetrapeptides can have an influence upon their biological activity.

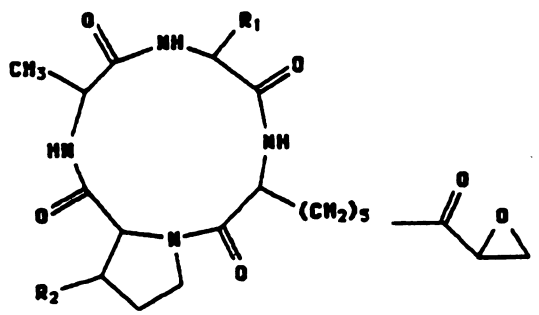
The pathways of amino acid biosynthesis are complex, organism-dependent pathways, though certain generalizations may be made. Carbohydrates are the carbon source for amino

table 1

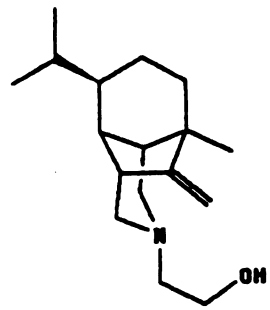
HELMINTHOSPORIUM FUNGI, HOSTS, and TOXINS

FUNGUS	HOST	TOXIN NAME	STRUCTURE[a]
H. carbonum	maize	HC-TOXIN I	1, R_1=Me, R_2=H
		HC-TOXIN II	5, R_1, R_2=H
		HC-TOXIN III	6, R_1=Me, R_2=OH
H. victoriae	oats	HV-TOXIN	2
H. maydis race T	maize	HmT-TOXIN	3
H. sacchari	sugarcane	HS-TOXIN	4a-c R= 5-O-(B-galactofuranosyl)-B-galactofuranoside

adapted from reference 1



1, 5, 6



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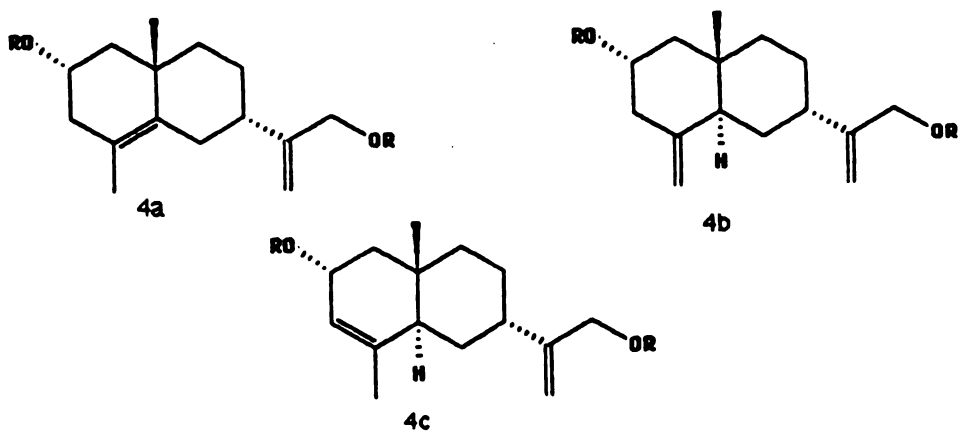
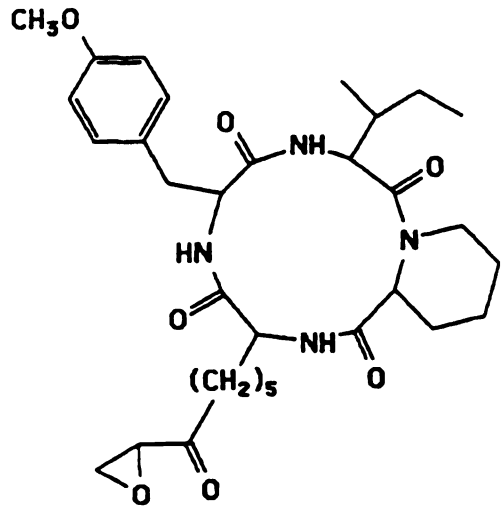


4a, 4b, 4c

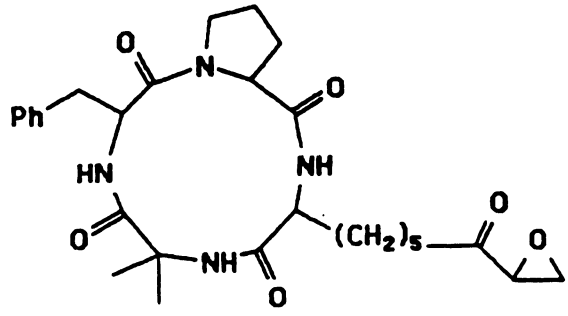
Cyl-2 7

reference 28



chlamydocin
8

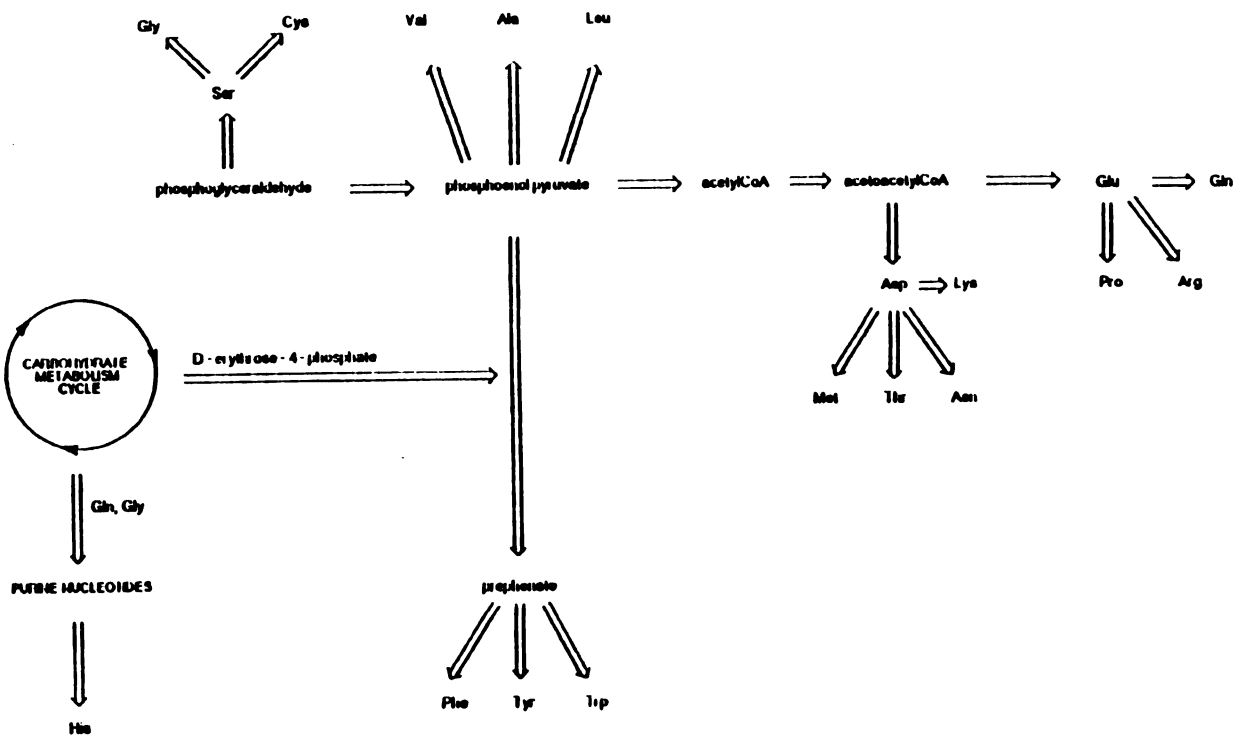
reference 29



acid synthesis; carbohydrate derived phosphoglyceric acid, D-erythrose-4-phosphate, prephenic acid, phosphoenolpyruvate, and acetoacetylCoA are key intermediates from which the amino acids are prepared. Nitrogen can be incorporated via a reductive amination, while various enzymic transformations including methylation, decarboxylation, and transamination complete the functionalization process. Figure 1 presents a very general summation of the pathways involved, the actual pathways in *H. carbonum* have not been reported.

figure 1

GENERAL BIOGENETIC PATHWAY FOR THE COMMON AMINO ACIDS



Early studies of HC-toxin demonstrated that the epoxy moiety of the Aoe residue had to remain intact for toxicity to be observed. Thus, conversion product 9 (Aoe terminal epoxide hydrolyzed to vicinal diol) obtained from the *H. carbonum* culture filtrate[7] and also available via *in vitro* hydrolysis was found inactive towards strains of maize which were susceptible to HC-toxin. This established the first known structure-function relationship for HC-toxin. The possibility that HC-toxin analogs were produced by *H. carbonum* was of tremendous interest, as this might further the understanding of structure-activity relationships in the *H. carbonum*-maize system.

The isolation of HC-toxin analogs was guided routinely by a bioassay. As the culture filtrate of *H. carbonum* contains many components, the bioassay-guided isolation is advantageous, and it allows one to directly identify toxic host-selective fractions at any given stage of the isolation. A root-growth assay was employed where the inhibition of the root growth of susceptible and resistant strains was compared after the addition of aqueous solutions of suspected toxin-containing fractions. Distilled water blanks were employed as controls. Figure 2 provides a schematic illustration of the bioassay.[8]

figure 2

BIOASSAY PROTOCOL

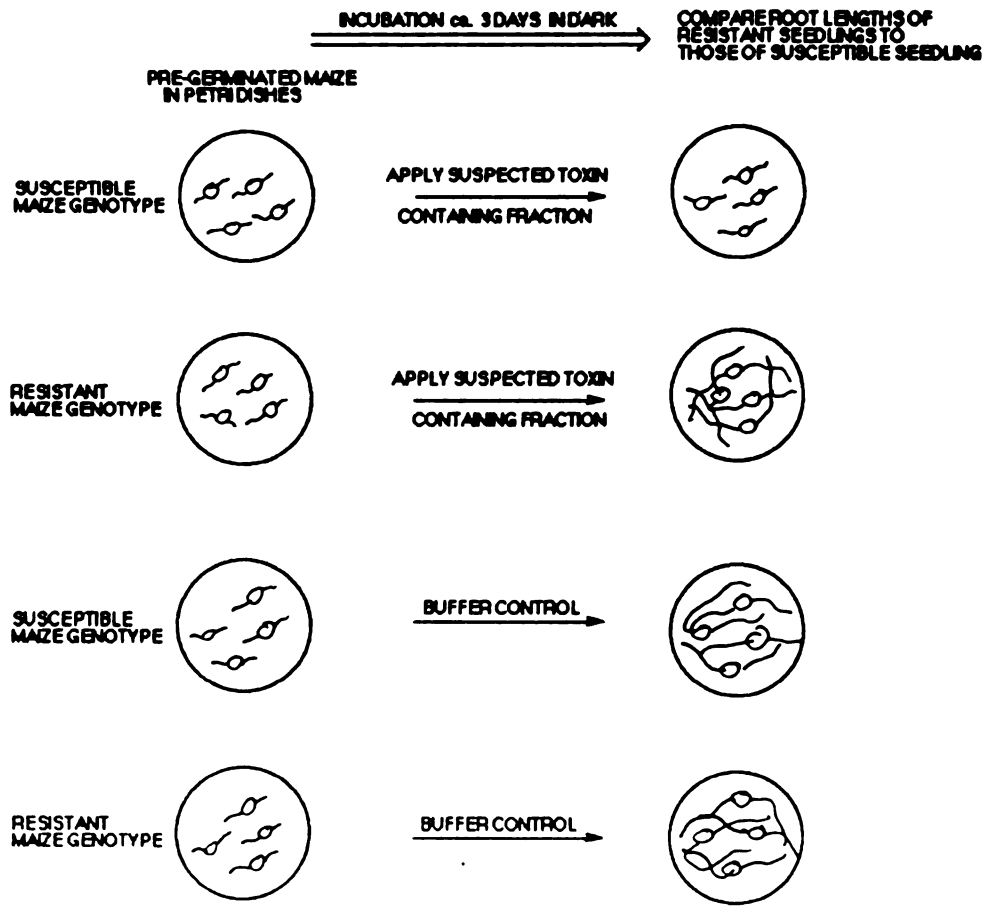
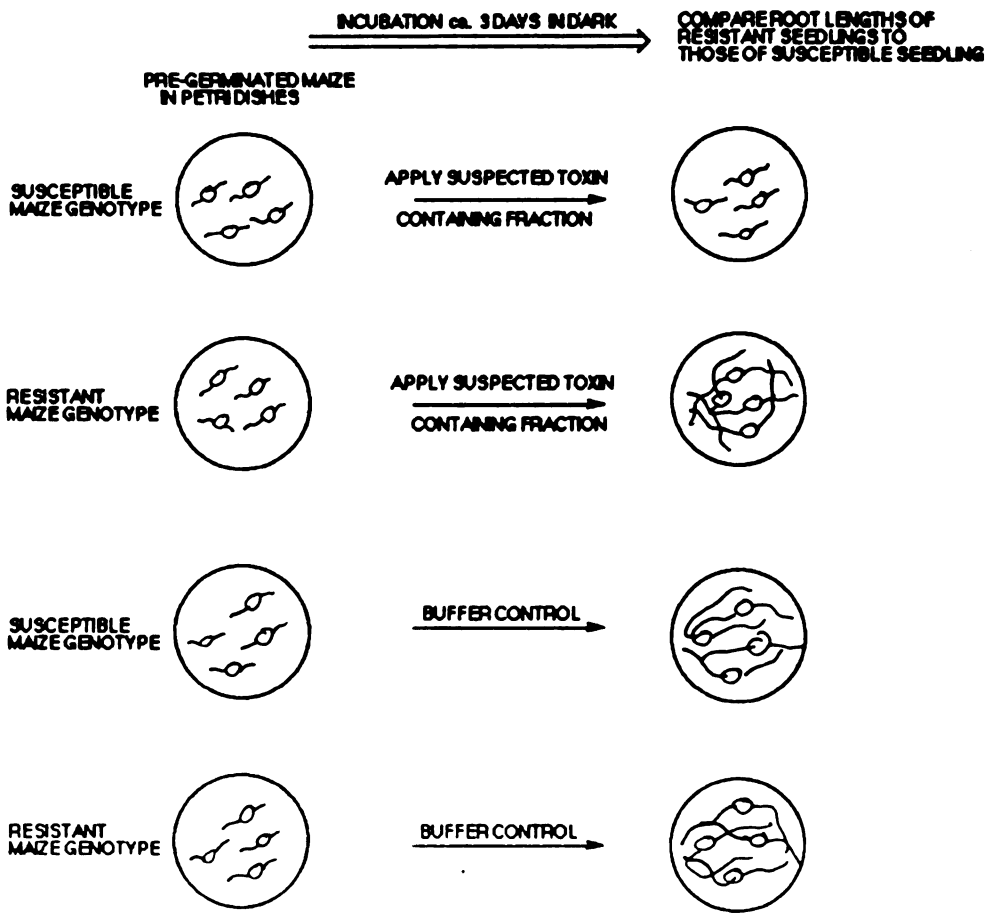


figure 2

BIOASSAY PROTOCOL



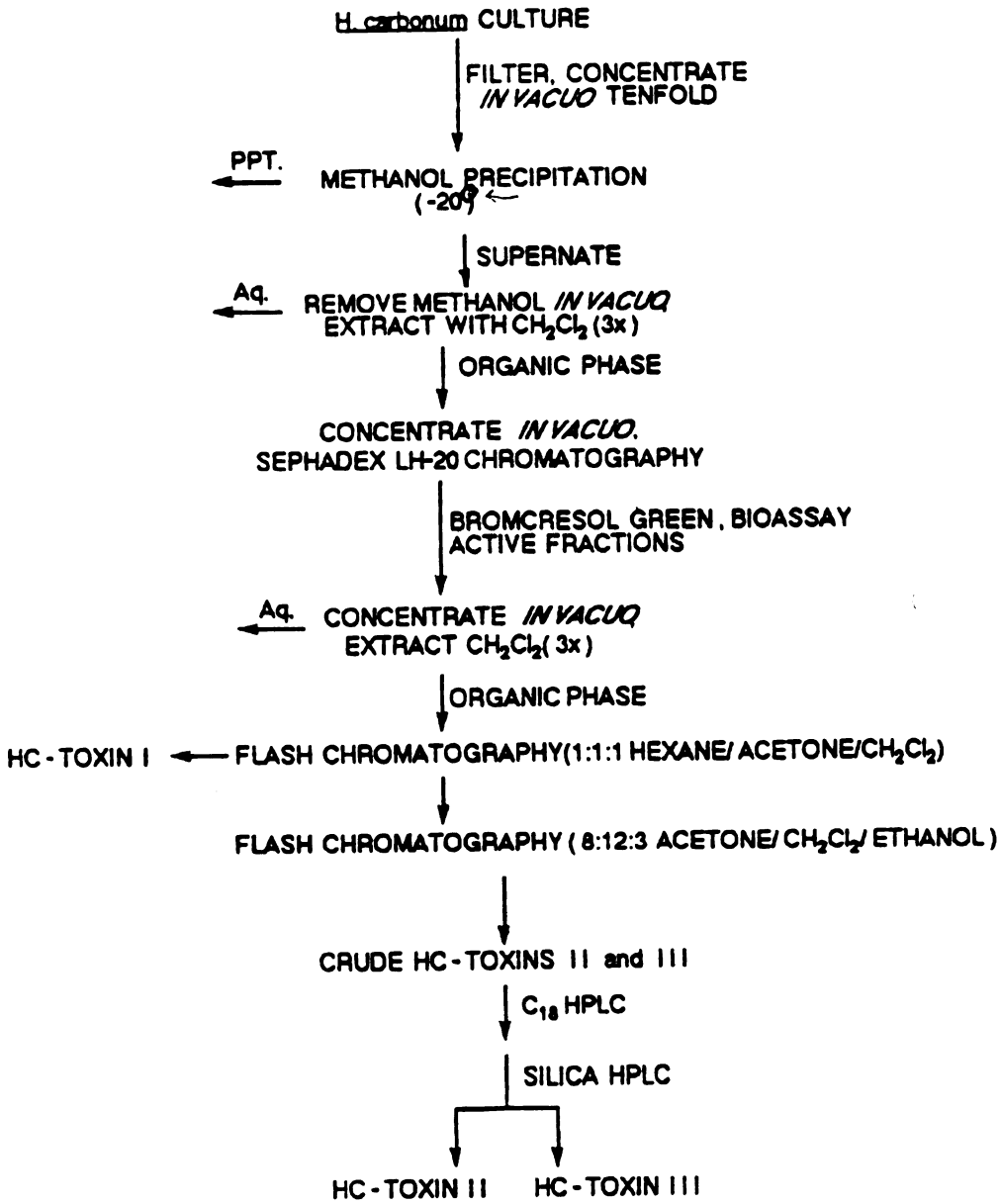
HC TOXINS RESULTS AND DISCUSSION

The isolation and purification of the HC-toxins is outlined in Figure 3. From a 10-20L harvest of culture filtrate, we were typically able to obtain 480 mg of HC-toxin I, 1 4.0 mg of HC-toxin II, 5 and 2.4 mg of HC-toxin III, 6 in a chromatographically pure state. Throughout the course of the isolation, we noted marked simularities in the chromatographic properties of the HC-toxins II and III with those of HC-toxin I. Additionally, the purified toxins exhibited similar levels of toxicity.[9] These two points suggested that HC-toxins II and III might be structurally related to HC-toxin I, a premise supported by the following data.

Fast Atom Bombardment (FAB) mass spectroscopy[10,11] of HC-toxin II gave an $(M+1)^+$ ion at M/Z = 423. High resolution FAB-MS established an empirical molecular formula of $C_{20}H_{30}N_4O_6$ for HC-toxin II. HC-toxin III displayed an $(M+1)^+$ ion at M/Z 453; high resolution FAB-MS established its empirical molecular formula as $C_{21}H_{32}N_4O_7$. Comparison with the known HC-toxin I ($C_{21}H_{32}N_4O_6$) demonstrated that HC-toxins II and III differ from HC-toxin I by CH_2 and an oxygen atom, respectively.

figure 3

ISOLATION FLOW CHART



The low resolution FAB mass spectrum of HC-toxin II displayed a fragmentation pattern similar to that of HC-toxin I (Figure 4); ions observed at M/Z 70 (base) and 170 correspond to the protonated iminium ions[5] derived from Pro and Aoe, respectively. The ion observed at M/Z 226 (M-196) might arise from an Ala, Gly, Pro tripeptide unit on the following basis. The FAB-MS of HC-toxin I contains an ion at M/Z 240 (M-196) arising[12] from the tripeptide unit Ala-Ala-Pro. Given substitution of a Gly for an Ala unit, similar cleavage would still be expected and, hence, an ion 14 amu lower at M/Z 226 should be observed.

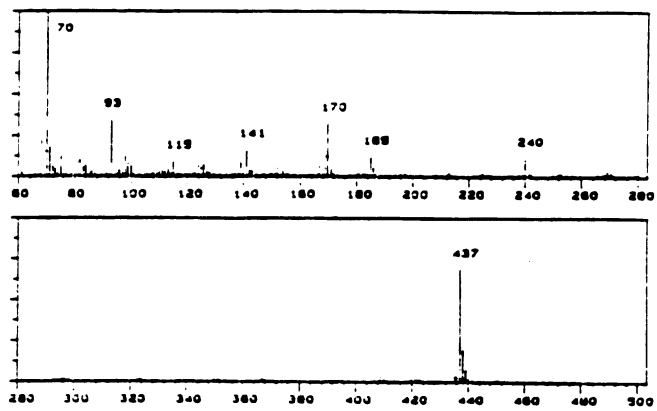
HC-toxin III displayed the Aoe derived ion at M/Z 170; however, the base peak for HC-toxin III was found at M/Z 86 (C_4H_8NO; peak matching[10]), which is assigned to the protonated imminium ion of a hydroxyproline residue. Also, in agreement with the presence of a hydroxyproline residue was the ion observed at M/Z 256 (M-196), which corresponds to a tripeptide fragment ion composed of two Ala units and a hydroxyproline. FAB-MS data indicates that HC-toxin II consists of Ala, Gly, Aoe, and Pro while HC-toxin III consists of 2-Ala, Aoe and hydroxyproline.

Amino acid analysis[13] of HC-toxin II indicated Gly, Ala, and Pro in a 1.00:1.07:0.76 ratio, while analysis of HC-toxin III indicated Ala and an unidentified amino acid in a 2.44:1 ratio. Comparison of the unknown amino acid with Pro, cis- and trans-4-hydroxyproline and cis- and trans-3-

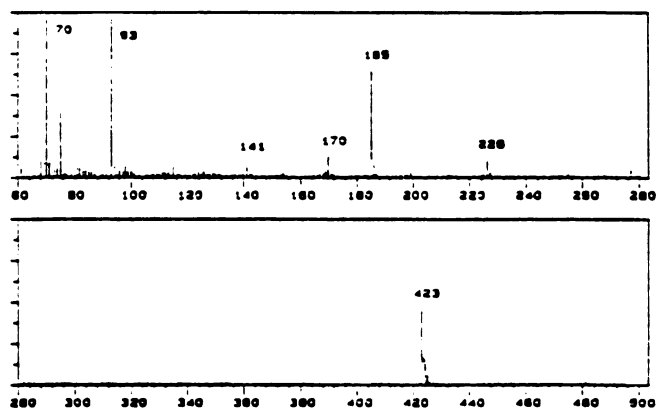
figure 4

FAB-MS OF HC-TOXINS

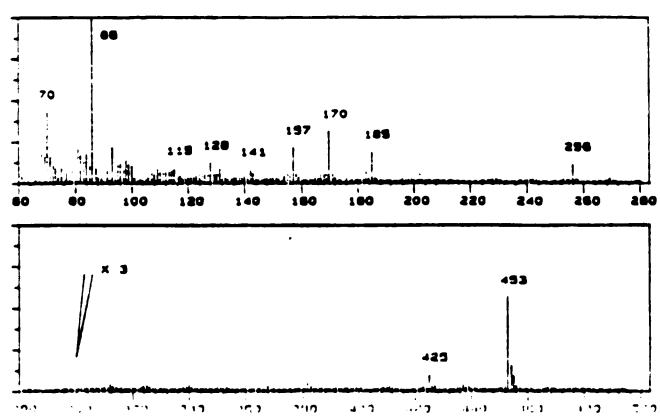
HC-TOXIN I



HC-TOXIN II



HC-TOXIN III



hydroxyproline[14] demonstrated that the unknown amino acid was trans-3-hydroxyproline.

^{13}C-NMR data for HC-toxins II and III is shown in Table 2.[15] In accord with FAB-MS derived empirical formulae, HC-toxins II and III displayed 20 and 21 carbons, respectively, and contain four amide carbonyls, as required for cyclic

TABLE 2

^{13}C-NMR of HC Toxins II and III (68.9 MHz, $CDCl_3$, $CHCl_3$, Ref.)

Amino Acid	Carbon	HC Toxin II	HC Toxin III
Ala	α	47.9	47.3,47.6
	β	14,5	14.1,14.7
Gly	α	44.3	
AOE	α	52.1	51.6
	β γ δ	22.7,25.4,28.7	22.6,25.4,28.4
	ε ζ	29.0,36.2	28.9,35.9
	i θ	53.4,46.1	53.4,46.7
Pro	α	57.8	
	β	25.0	
	γ	24.9	
	δ	47.0	
3-HyPro	α		66.0
	β		71.0
	γ		34.0
	δ		45.0
Amide C=O		171.3	170.4
		172.1	173.5
		173.0	173.7
		174.3	173.9
AOE	η	200.3	201.9

tetrapeptide structures. Like HC-toxin I, both HC-toxins II and III display a ketone carbonyl indicative of the Aoe residue. Note that HC-toxin III exhibits the expected pair

of methyl signals corresponding to two Ala β methyls, and HC-toxin II shows only one methyl carbon, consistant with replacement of one Ala unit with Gly. Consistent with the presence of hydroxyproline, HC-toxin III displays two downfield carbon resonances (66.0, 71.0 ppm) not observed in ^{13}C spectra of HC-toxins I or II.

^{1}H-NMR (250 MHz) spectra of HC-toxins II and III are shown in Figure 5a,b; data and assignments are presented in Table 3. HC-toxin II exhibited 3 amide NH, 5 α-H, three epoxide-H and one methyl resonance, characteristic for a cyclic tetrapeptide comprised of proline, alanine, Aoe and glycine. Assignments were facilitated via a COSY[16] experiment, shown in Figure 6, and are in agreement with those recently reported.[17]

An analysis of the COSY spectrum is shown in Figure 6 where the Ala spin system has been mapped out with heavy lines. Thus, the methyl doublet found at 1.30 ppm is coupled to a resonance at 4.46 ppm by virtue of intersection with off-diagonal peaks (cross-peaks). Referral to the 1-D spectrum leads to assignment of this resonance as the Ala α-H. This hydrogen is in turn coupled to the resonance at 7.04 ppm, which is the Ala NH. In a similar fashion, unambiguous assignment of all resonances was possible, with the exception of the severely congested Aoe side chain.

The ^{1}H-NMR spectrum of HC-toxin III was quite similar to that of HC-toxin I[5] with the exception of those resonances associated with the hydroxyproline residue

figure 5a

250 MHz ^{1}H-NMR HC-TOXIN II

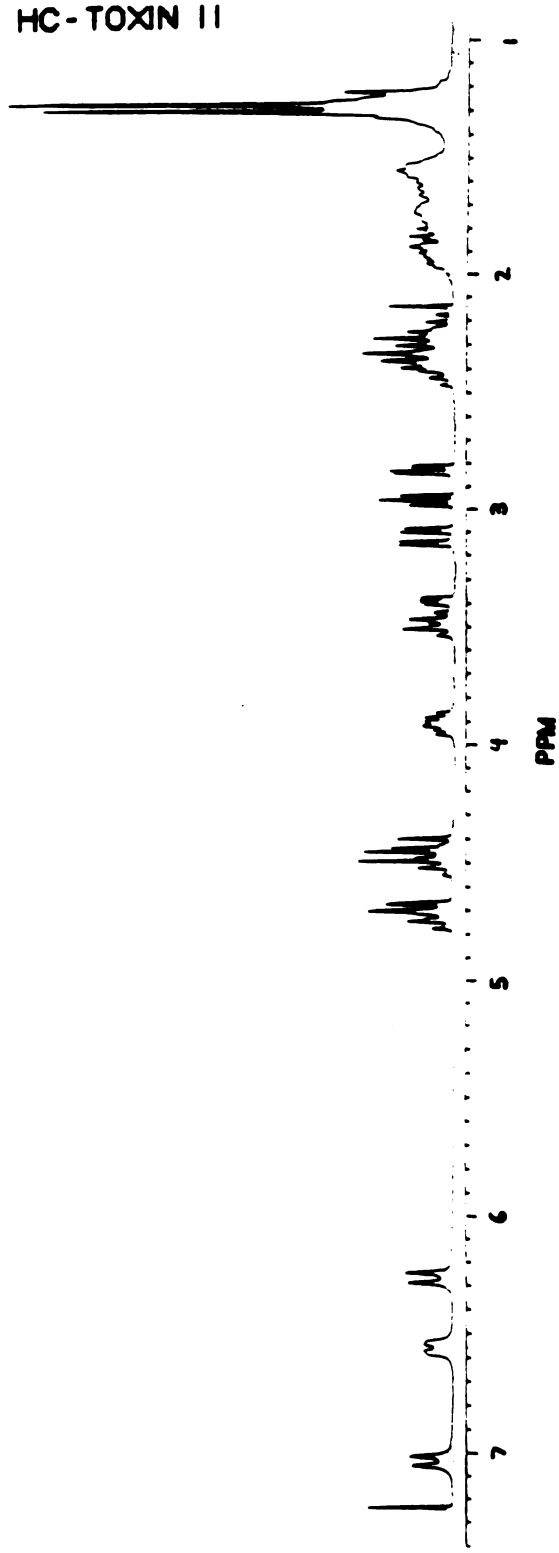


figure 5b

250 MHz ^{1}H-NMR HC-TOXIN III

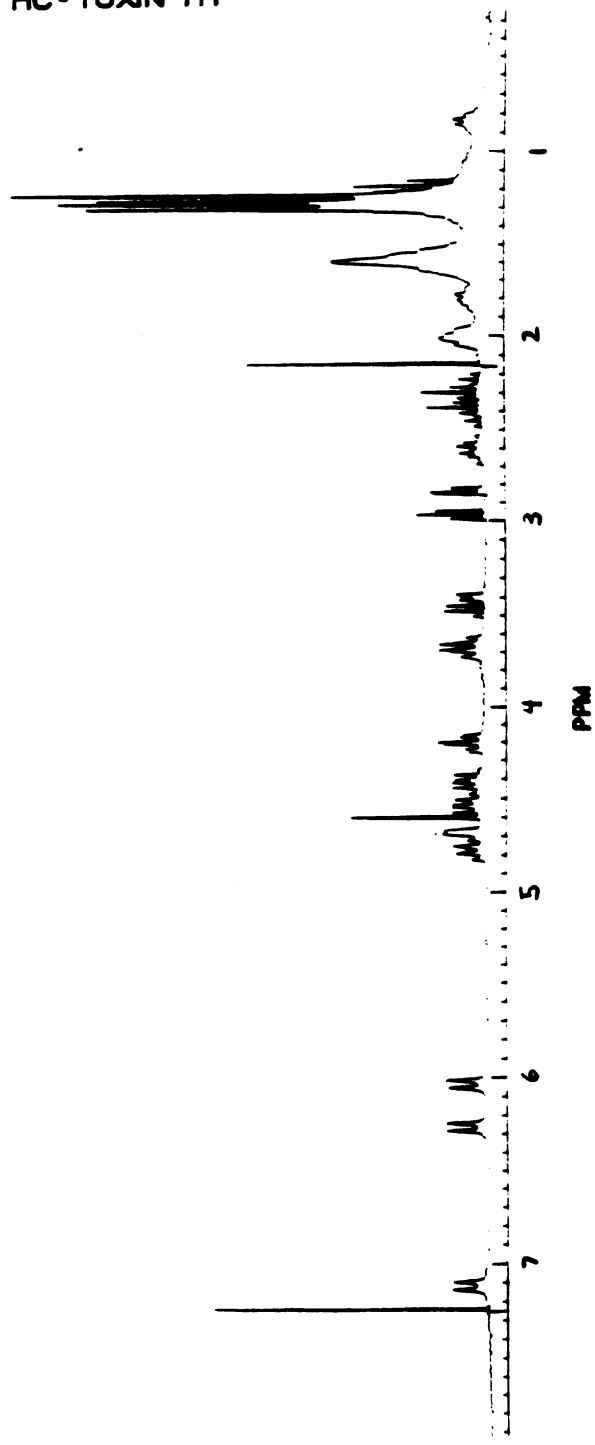


TABLE 3

^{1}H NMR HC Toxins II and III (250 MHz, $CDCl_3$, $CHCl_3$, ref.)

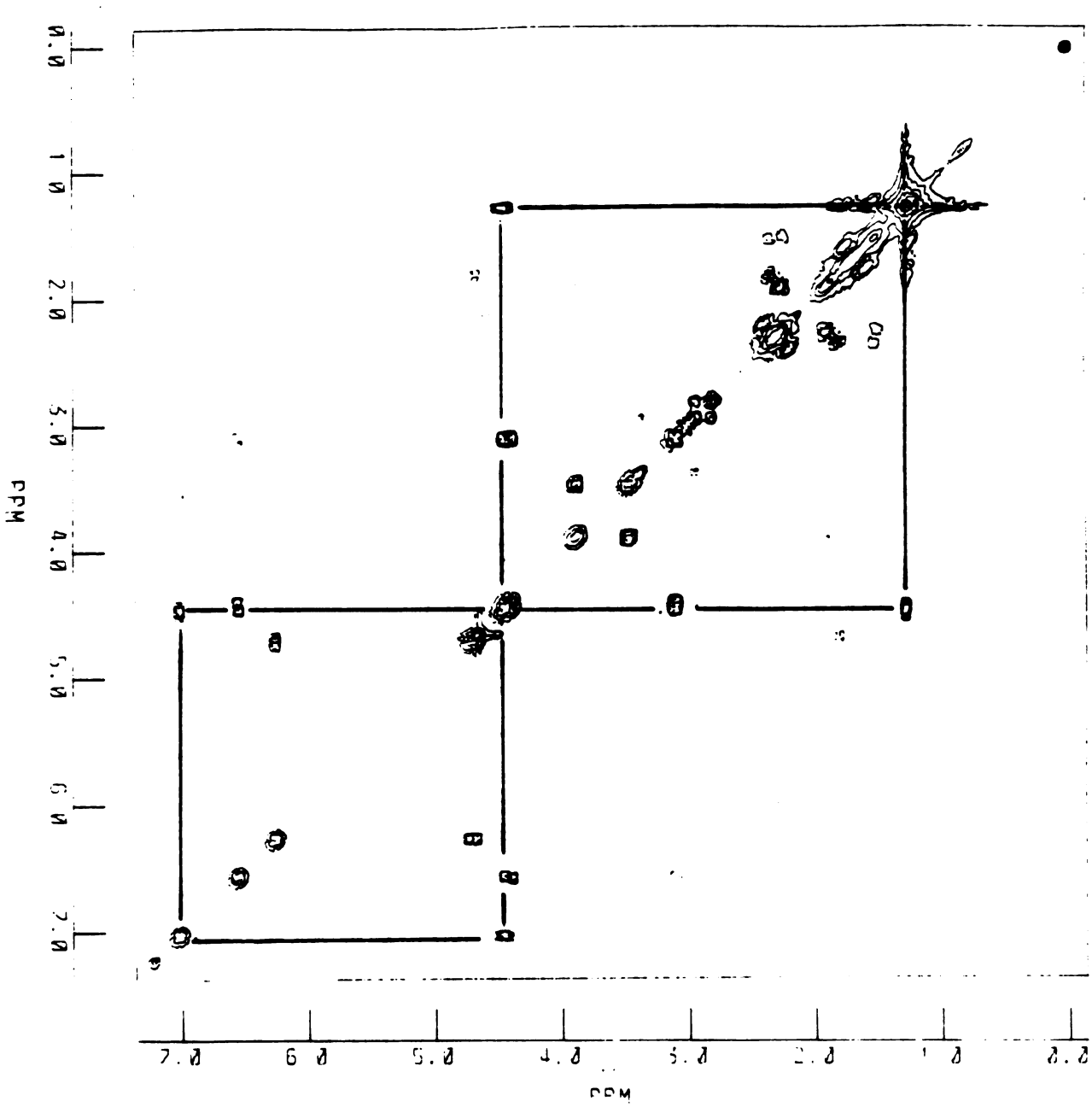
HC Toxin 2

7.04(d) $J_{NH\alpha}$ = 9.96 Hz 1H Ala NH
6.60(dd) $J_{NH\alpha_2}$ = 3.63 Hz $J_{NH\alpha_1}$ = 10.4 Hz 1H GlyNH
6.28(d) $J_{NH\alpha}$ = 10.85 Hz 1H AOENH
4.72(m) $J_{NH\alpha}$ = 10.85 Hz 1H AOEα
4.68(dd) $J\alpha\beta_1$ = 7.23 Hz $J\alpha\beta_2$ = 2.7 Hz 1H Proα
4.46(m) $J_{NH\alpha}$ = 9.95 $J\alpha\beta$ = 6.80 1H Alaα
4.42(dd) $J_{NH\alpha_1}$ = 10.40 Hz $J\alpha_1\alpha_2$ = 13.56 Hz 1H Glyα_1
3.91(m) 1H Proδ_D
3.50(m) 1H Proδ_U
3.39(dd) $J_{\theta\iota_1}$ = 4.75 Hz $J_{\theta\iota_2}$ = 2.73 Hz 1H AOEθ
3.12(dd) $J_{NH\alpha_2}$ = 3.63 Hz $J\alpha_1\alpha_2$ = 13.56 Hz 1H Glyα_2
2.96(dd) $J_{\iota_1\iota_2}$ = 5.88 Hz $J_{\iota_1\theta}$ = 4.75 Hz 1H AOEL_1
2.83(dd) $J_{\iota_1\iota_2}$ = 5.88 Hz $J_{\iota_2\theta}$ = 2.73 Hz 1H AOEL_2
2.37(m) 1H Proβ_D
2.27(m) 1H Proγ_D
2.45-2.2(m) 2H AOEζ
1.92(m) 1H Proγ_U
1.84(m) 1H Proβ_U
1.85(m) 1H AOEβ_D
1.75-1.3 7H AOEβ_U, AOE$\gamma\delta\epsilon$
1.30 $J\alpha\beta$ 6.80 Hz, 3H, Ala β

HC Toxin 3

7.11(d) $J_{NH\alpha}$ = 10.53 Hz 1H Ala$_1$ NH
6.26(d) $J_{NH\alpha}$ = 10.40 Hz 1H AOE NH
6.03(d) $J_{NH\alpha}$ = 9.80 Hz 1H Ala$_2$ NH
4.77(m) $J_{NH\alpha}$ = 10.40 Hz 1H AOEα
4.68(d) $J\beta\gamma$ = 3.85 Hz 1H 3HyProβ
4.60(s) 1H 3HyProα
4.54(dq) $J_{NH\alpha}$ 9.80 Hz $J\alpha\beta$ 7.03 Hz 1H Ala$_2\alpha$
4.41(dq) $J_{NH\alpha}$ 10.53 $J\alpha\beta$ 6.83 Hz 1H Ala$_1\alpha$
4.20(m) $J\delta_U\delta_D$ = 9.75 Hz 1H 3HyProδ_D
3.67(m) $J\delta_U\delta_D$ = 9.75 Hz 1H 3HyProδ_U
3.40(dd) $J\theta\iota_2$ 2.43 $J\theta\iota_1$ 4.27 1H AOEθ
2.97(dd) $J_{\iota_1\iota_2}$ = 5.79 Hz $J_{L_1\theta}$ = 4.27 Hz 1H AOE L_1
2.83(dd) $J_{L_1L_2}$ = 5.79 Hz $J_{L_2\theta}$ = 2.43 Hz 1H AOE L_2
2.60(m) 1H 3HyProγ_D
2.41(dt) $J\zeta_D\zeta_U$ = 17.43 $J\zeta_D\epsilon$ = 7.20 Hz 1H AOEζ_D
2.26(dt) $J\zeta_D\zeta_U$ = 17.43 $J\zeta_U\epsilon$ = 7.20 Hz 1H AOEζ_U
2.00(m) 1H 3HyProγ_U
1.80(m) 1H AOEβ_D
1.57(m) 1H AOEβ_U
1.53(m) 2H AOEϵ
1.6(s) 3-HyPro OH 1H
1.35-1.2(m) 4H AOE$\gamma\delta$
1.29(d) $J\alpha\beta$ 6.83 Hz 3H Ala$_1\beta$
1.25(d) $J\alpha\beta$ 7.03 Hz 3H Ala$_2\beta$

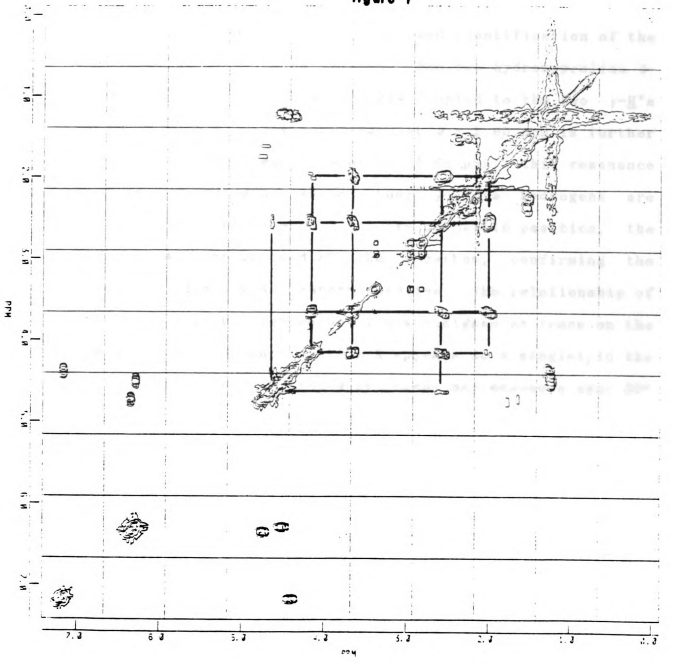
figure 6



(Figure 5b). HC-toxin III displayed three amide NH, 3 epoxide-H, and 2 methyl resonances. However, the region between 4.4 and 4.8 ppm contained five resonances, compared to the four found in the same region of the HC-toxin I.

Examination of the COSY spectrum (Figure 7) established that 3 of the 5 resonances were the α hydrogens of the 2 Ala and Aoe residues. The two remaining resonances at δ = 4.68 and 4.60 ppm were identified as the trans-3-hydroxyproline β- and α-hydrogens, respectively, after consideration of the following data. Irradiation of the Ala-N<u>H</u> at 7.11 ppm

figure 7



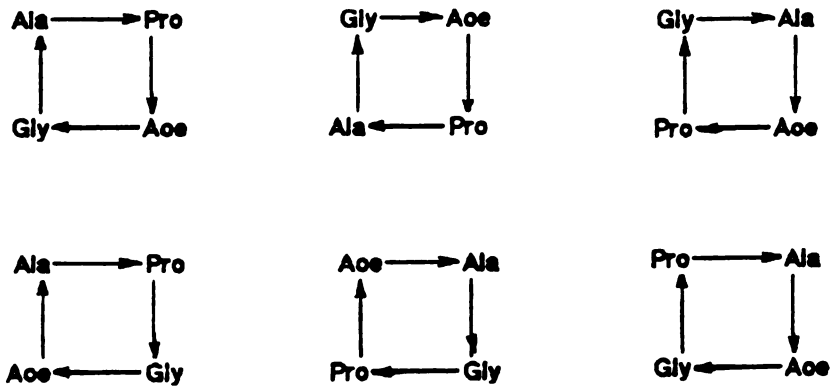
resulted in a 11% NOE of the resonance at δ = 4.60 ppm. Based on this, the noted[4] observation of significant NOE at the α-H of a proline upon irradiation of an Ala-N<u>H</u> preceeding it and inspection of models, the resonance at δ = 4.60 ppm, is assigned as the hydroxyproline α-H. Also, this establishes the proximity of the Ala to the hydroxyproline residue. The COSY spectrum allowed identification of the resonance at δ = 4.68 as follows. The two hydroxyproline δ-<u>H</u>'s (4.20, 3.67 ppm) are strongly coupled to the two γ-<u>H</u>'s (2.60, 2.00 ppm). The γ-hydrogen at δ = 2.60 ppm is further coupled to the resonance at δ = 4.68 ppm; this resonance must be a β-hydrogen. As no other β-hypro hydrogens are present and consistent with its downfield position, the hydroxyl must be located at the β-carbon, confirming the residues' identity as 3-hydroxyproline. The relationship of the hydroxyl to the carbonyl was assigned as trans on the basis of coupling data. The α-H appears as a singlet, in the trans isomer the α and β hydrogens may assume a near 90° relationship resulting in the expected minimum spin-spin coupling. This finding is in agreement with the amino acid analysis.

With the amino acid constitution of HC-toxins II and III established as (Ala, Gly, Aoe, Pro) and (Ala, Ala, Aoe, trans-3-Hypro), respectively, the correct sequence for these cyclic peptides had to be discerned from the possible sequences shown in Figure 8. Previously characterized HC-

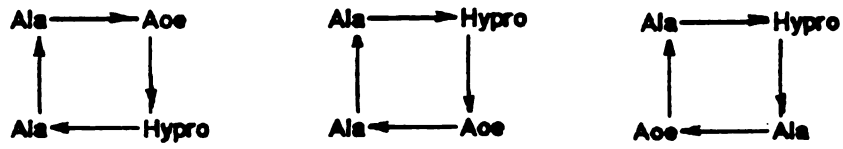
figure 8

POSSIBLE SEQUENCES FOR HC-TOXINS II and III

HC- TOXIN II



HC-TOXIN III



toxin I has been sequenced by FAB-CAD-MS,[12] GC-MS of derivatized partial hydrosylates,[3], 2-D TLC of derivatized partial hydrosylates,[5] and ^{1}H-NMR NOE difference spectroscopy.[4,18] We chose to employ the latter technique both for its operational simplicity and the greater amount of information it offered.

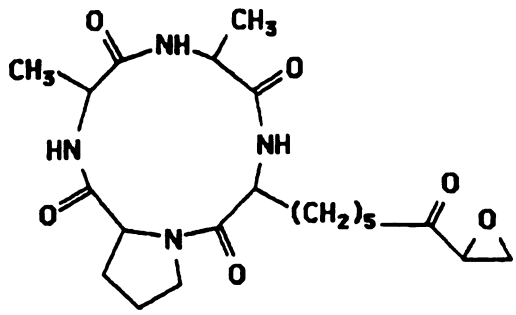
In this approach, irradiation of a nucleus on a given residue may result in a NOE of a neighboring nucleus. If

the two nuclei reside on different amino acids, their proximity and, therefore, a partial sequence is established. As applied to HC-toxins II and III, this methodology yielded the data presented in Table 4 from which overlapping partial sequences were obtained. From this data, structures 5 and 6 for HC-toxins II and III, respectively, are unambiguously established.

table 4

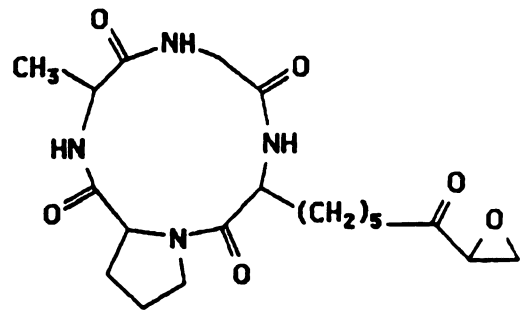
NOE DIFFERENCE EXPERIMENTS
HC-TOXINS II and III

	H IRRADIATED	H ENHANCED	%NOE	PARTIAL SEQUENCE
HC-TOXIN II				
	Gly NH	Ala α	15%	Ala-Gly
	Aoe NH	Gly α	9%	Gly-Aoe
	Ala NH	Pro α	13%	Pro-Ala
	Pro $\delta_{upfield}$	Aoe α	3%	Aoe-Pro
		Pro $\delta_{downfield}$	11%	
	Pro $\delta_{downfield}$	Aoe α	5%	Aoe-Pro
		Pro $\delta_{upfield}$	15%	
HC-TOXIN III				
	Ala_1 NH	t-3-Hypro α	11%	t-3-Hypro-Ala_1
	Aoe NH	Ala_2 α	9%	Ala_2-Aoe
	Ala_2 NH	Ala_1 α	11%	Ala_1-Ala_2
	t-3-Hypro $\delta_{upfield}$	Aoe α	4%	Aoe-t-3-Hypro
		t-3-Hypro $\delta_{downfield}$	21%	
	t-3-Hypro $\delta_{downfield}$	Aoe α	13%	Aoe-t-3-Hypro
		t-3-Hypro $\delta_{upfield}$	18%	



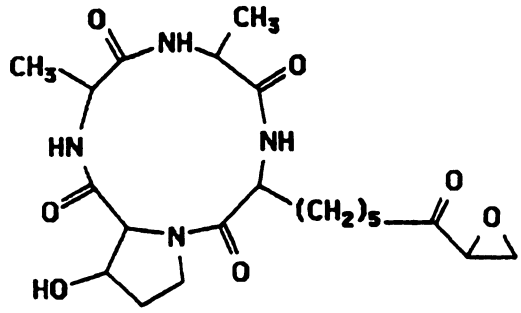
HC-TOXIN I

1



HC-TOXIN II

2



HC-TOXIN III

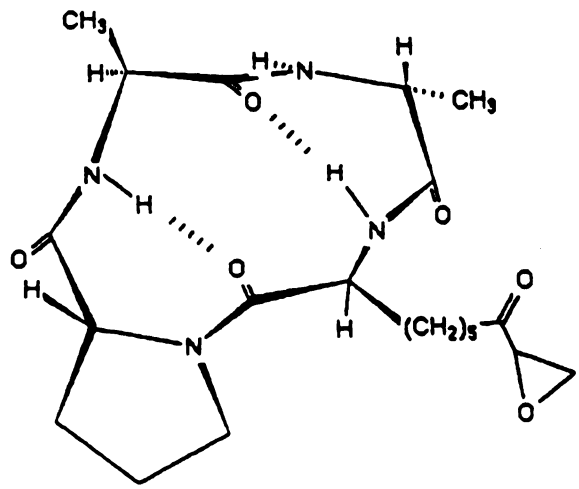
3

It is clear that the three HC-toxins are very similar structurally in that all three contain the Aoe-Pro-Ala subsequence. However, the minor structural perturbations (hydroxylation of Pro, Ala--->Gly) observed have caused a change in their toxicity.[9] Possible reasons include changes in receptor affinity, membrane permeability, conformation, or various combinations of the three. Due to the current lack of information concerning the mode of action for the HC-toxins, the first two possibilities are difficult to investigate. Conformation, however, is subject to investigation; and, indeed, HC-toxin I has had its solution

($CDCl_3$) conformation examined.[4,18,19] Figure 9 presents the suggested conformation for HC-toxin I, determined by ^1H- and ^{13}C-NMR analyses. The conformation shown contains a bis γ turn, characterized by the presence of two sets of 1-3

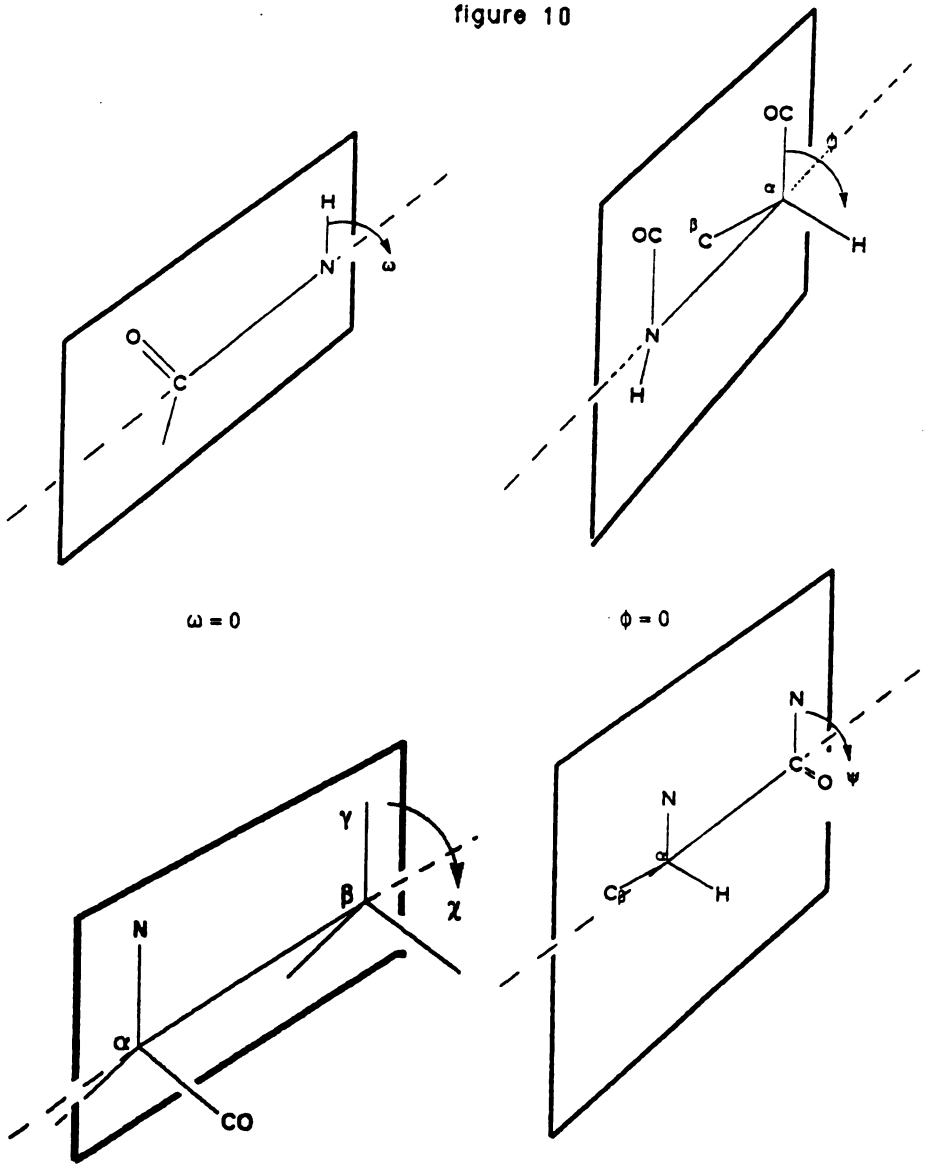
figure 9

HC-TOXIN I SOLUTION CONFORMATION ($CDCl_3$)



hydrogen-bonded amino acid residues and is further supported by a FTIR[19] study which identified hydrogen-bonded and non-hydrogen bonded NH in a 2:1 ratio. The conformation of a peptide can be described by the appropriate combination of bond dihedral angles, as defined in Figure 10. For HC-toxin I, these angles were calculated from measurement of $J_{NH-\alpha H}$ constants and a series of NOE experiments.[4,18] Although presently incomplete, the existing NMR data for HC-toxins II and III may be compared to the data employed in the conformational analysis of HC-toxin I. From a preliminary analysis, we conclude that HC-toxins I, II and III have

figure 10



ω = 0

ϕ = 0

χ = 0°

ψ = 0

rather similar conformations in $CDCl_3$. Thus, φ angles for HC-toxin I were derived from a Karplus-type[20] curve based upon the value of $J_{NH-\alpha H}$. The $J_{NH-\alpha H}$ values for corresponding residues in HC-toxins II and III yield virtually identical values of φ; $J_{NH-\alpha H}$ and φ for all three HC-toxins are presented[21] in Table 5. As for HC-toxin I, the amide bonds in HC-toxins II and III are transoid, as the observation of NH to αH (or Proδ to Aoeα) NOE's is only consistant with transoid amide bonds. For HC-toxin I, Ψ angles were determined from a combination of $J_{NH-\alpha H}$ and extensive NOE data. Presently, there are insufficient data to calculate Ψ angles for HC-toxins II and III; however, the aforementioned data support a general similarity in the conformation of all three HC-toxins.

table 5

φ DIHEDRAL ANGLES FOR HC-TOXINS I-III

	HC-TOXIN		
	I	II	III
AMINO ACID	($J_{NH\alpha H}$, φ)	($J_{NH\alpha H}$, φ)	($J_{NH\alpha H}$, φ)
Ala_1	(10.3,-110°)	(9.95,-120°)	(10.53,-120°)
Ala_2	(9.5,60°)		(9.80,60°)
Gly		(14.03,70°)	
Aoe	(10.5,-120°)	(10.85,-120°)	(10.40,-120°)

HC TOXINS EXPERIMENTAL

Reagent grade solvents were employed for column and thin-layer chromatography and were used as received. HPLC-quality hexanes were used as received for HPLC separations. Flash chromatography was performed with 230-400 nm silica gel (Merck) by the method of Still[22]; conditions are reported as follows: (column outer diameter in mm; solvent system; grams of silica gel employed; fraction sizes collected). TLC was performed on 0.25 mm silica gel plastic-backed plates (Macherery-Nagel, D-5160) which were developed with 4:3 acetone-methylene chloride. HC-toxins were visualized on TLC plates as blue spots when sprayed with 0.05% bromcresol green in acetone, followed by heating. HPLC was performed on a Varian 5000 instrument, equipped with a UV detector operated at 215 nm. Normal-phase HPLC separations utilized a 0.4 x 25 cm Whatman partisil 10 column eluted isochratically with 96:4 hexane-ethanol at a 4 ml/min flow rate. Reverse-phase separations employed a 0.78 x 30 cm Water u-Bondapac C_{18} column eluted with the following gradient: 7% aqueous ethanol to 20% aqueous

ethanol over 30 minutes, 20% aqueous ethanol for 15 minutes, followed by a recycle to 7% aqueous ethanol over 20 minutes.

^{1}H- and ^{13}C-NMR spectra were recorded in $CDCl_3$ at 250 and 68.9 MHz, respectively, on a Bruker WM-250 spectrometer. All chemical shifts are reported in ppm relative to internal $CHCl_3$. ^{13}C-NMR spectra were acquired with broadband noise decoupling; COSY[23] spectra were obtained as 1K x 512W data matrices using a $\pi/2$-T-$\pi/4$-AQ pulse sequence. Data was multiplied by a gaussian function prior to transformation. DEPT[24] subspectra were obtained using the following pulse sequence: $^{1}H(\pi/2-\Delta-\pi-\Delta-\Theta-\Delta-BB)$, $^{13}C(----\pi/2---\pi---AQ)$; editing was performed using the procedure described by Bendall and Pegg.[25] NOE experiments employed a 2-second decoupler irradiation, followed by a $\pi/2$ observation pulse and aquisition of the FID. FID's were multiplied by an exponential function before transformation such that a 2Hz-line broadening was introduced. Substraction of a transformed off-resonance control spectrum from the transformed on resonance spectrum produced the NOE difference spectrum from which NOE's were determined.[26] The ratio of the area of the enhanced peak to the area of the irradiated peak (normalized to equal unity) determined the % NOE. FAB-MS were obtained[10] on a Varian Mat CH5-DF double-focusing mass spectrometer. EI/MS were obtained[27] on a Finnigan 4000 mass spectrometer equipped with an INCOS 4201 data system.

The initial stages of the isolation and purification of HC-toxins and bioassay were performed by Jack B. Rasmussen[8], from initial culture of *Helminthosporium carbonum* (race 1) to Sephadex LH-20 chromatography (refer to Figure 3). Variable quantities of crude HC-toxins were obtained as a function of culture size, age, viability, etc.

In a typical isolation, 2-5 ml of the Sephadex eluate was dissolved in methylene chloride (50 ml), leaving behind a small amount of dark-colored insoluble material. The methylene chloride solution was washed with distilled water (3 x 30 ml), brine (1 x 50 ml) and dried (Na_2SO_4). Concentration *in vacuo* yielded an orange-brown gum which tended to foam at reduced pressures.

This material (2.24g) was purified by flash chromatography[22] (60mm, 2-step gradient: 3L-1:1:1 hexane-acetone-methylene chloride, 4L - 4:3 acetone-methylene chloride; 300g; 1 x 3L, 1 x 300 mL, 1 x 700 mL, 1 x 3L).

After concentration *in vacuo*, fraction 1 yielded 1.45 g of a pale yellow foam. Comparison of this material with an authentic sample of HC-toxin 1 (TLC: 1 spot, R_f 0.64) showed that it consisted primarily of HC-toxin 1; the ^1H-NMR spectrum of this material compared favorably with that of HC-toxin I. Fraction 4 yielded 0.350g of an orange-brown oil which illcited host-specific toxicity (TLC: streak R_f 0.55-0.20). This material was purified by flash chromatography (40 mm, 8:12:3 acetone-methylene chloride-ethanol, 100g, 50 ml initial fraction followed by 20 ml

fractions); fractions 8 and 9 were combined and concentrated *in vacuo* yielding 181 mg of a yellow oil which was active by bioassay (TLC: 2 poorly resolved spots, R_f 0.45-0.25).

The oil was then dissolved in H_2O and passed through a Waters C_{18} Sep-Pak flushed with 40% aqueous ethanol. Reverse-phase HPLC of 35.0 mg of this material separated it into 3 major components, retention times: 25, 35 and 47 minutes, designated RP-1, RP-2 and RP-3, respectively; 11.0 mg of RP-1 was obtained. Normal-phase HPLC of RP-1 (11.0 mg) separated it into two components, with retention times of 25 and 33 minutes, which displayed host-specific toxicity; these were designated HC-toxin II (4.0 mg) and HC-toxin III (2.4 mg) in order of the elution.

HC-toxin II, cyclo[Ala-Gly-(2-amino-8-oxo-9,10-epoxy-decanoyl)-Pro], 5

EI-MS (70eV): 422 (M^+, 5.0%), 170 ($C_9H_{16}O_2N^+$, 76.6%), 70 ($C_4H_8N^+$, base). FAB-MS (glycerol): 423 ($M+1^+$, 48%), 226 (M-196, 10%), 170 ($C_9H_{16}O_2N^+$, 13%), 70 ($C_4H_8N^+$, base). High Resolution FAB-MS (CsI,glycerol) for $C_{20}H_{31}N_4O_6$, calculated 423.22436, found 423.22558; +2.88 ppm. ^1H- and ^{13}C-NMR Tables 3 and 2.

HC-toxin III, cyclo[Ala-Ala-(2-amino-8-oxo-9,10-epoxy-decanoyl)-trans-3-Hypro], 6

EI-MS (70eV): 452 (M^+, 3.9%), 170 ($C_9H_{16}O_2N^+$, base), 86 ($C_4H_8ON^+$, 55.4%). FAB-MS (glycerol): 453 ($M+1^+$, 19%), 156

(M-196, 12%), 170 ($C_9H_{16}O_2N^+$, 30%), 86 ($C_4H_8ON^+$, base). High Resolution FAB-MS (CsI, glycerol) for $C_{21}H_{33}N_4O_2$, calculated 453.23493, found 453.23221; -6.0 ppm. ^1H- and ^{13}C-NMR Tables 3 and 2.

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13. Analysis performed by Professor D. T. A. Lamport and Mr. P. E. Muldoon III, MSU-DOE Plant Research Laboratory, Michigan State University, East Lansing, Michigan 48824.

14. We thank Dr. Ashok Shenji, E. I. DuPont de Nemours and Company (Inc.), Central Research and Development Department, DuPont Experimental Station, Wilmington, Delaware 19898 for authentic samples of cis- and trans-3-hydroxyproline.

15. Assignments were aided by a comparison of ^{13}C-NMR data for 1, 5 and 6; and DEPT experiments.

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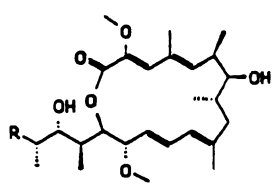
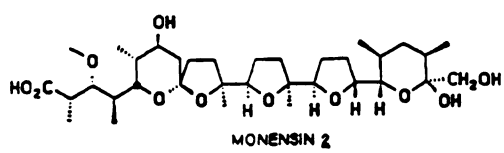
[2,3] INTRODUCTION

The macrolide and polyether classes of natural products often display potent antibiotic activity. This, and the structural complexity of these highly oxygenated bioactive molecules makes them of tremendous interest to synthetic organic chemists. A few examples of the structural diversity these molecules display are shown in Figure 1.

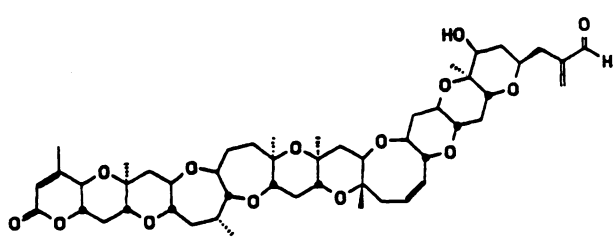
figure 1



BAFILOMYCIN 1

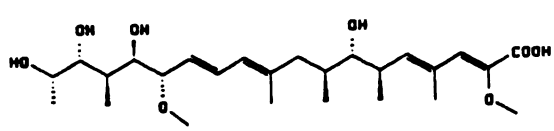


MONENSIN 2



BREVITOXIN B 3

figure 2



ACYCLIC ANALOG OF BAFILOMYCIN

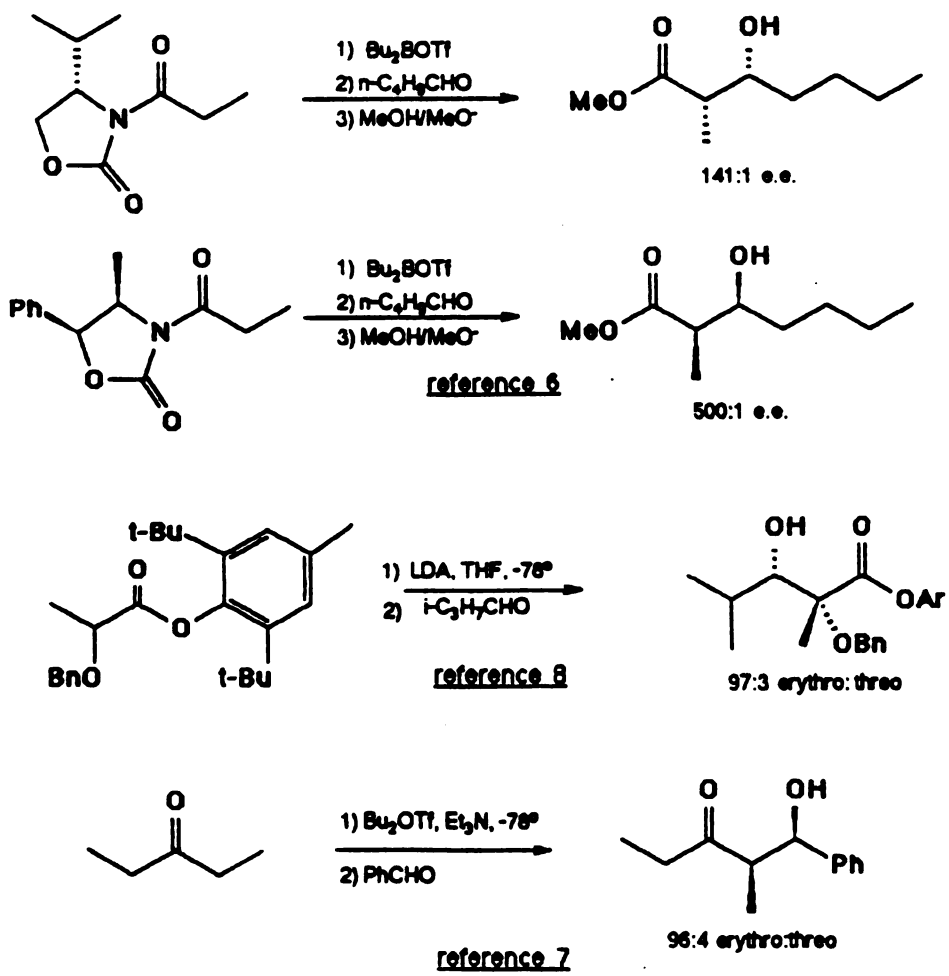
Some structural simplification can be achieved by opening the cyclic array and considering the assemblage of acyclic stereocenters thus produced as the ultimate synthetic target. Consider, for example, the acyclic precursor of bafilomycin (Figure 2). The C_{14}-C_{19} segment of **1** contains five consecutive centers of asymmetry, with both alkyl and oxygen substituents in a variety of stereochemical relationships. Clearly, any efficient synthesis of this molecule must incorporate convergent and flexible techniques of acyclic stereoselection.

For an approach to the synthesis of arrays of acyclic stereocenters to be considered general, the relative and absolute stereochemistry in the target must be accessible in a straightforward manner.[1a,b] Of paramount importance to the rational control of acyclic stereochemistry in the relative or absolute sense is an understanding of the reaction process and various steric and electronic factors responsible for stereo-discrimination in the transition state.[2-5] With such a model in hand, the synthetic chemist has often been able to rationalize and/or predict the outcome of various functional group transformations and carbon-carbon, bond-forming reactions.

One of the most successful techniques of acyclic stereoselection is the "modern" aldol condensation. Exemplifying this is the work of Evans[6], Mukaiyama[7], and Heathcock[8], whose aldol chemistry has achieved high levels

of diastereo- and enantioselection (Figure 3). The success of the aldol reaction depends upon two factors: first, enolates of high geometric purity must be obtained and, second, the homogeneous enolate should produce a preponderance of one aldol diastereomer in the condensation. Since it is generally accepted that the majority of "standard" aldol condensations proceed via the Zimmerman-Traxler[9] chair-like transition state, in which substituents adopt orientations which result in minimum steric interaction, one can generally predict the outcome of the

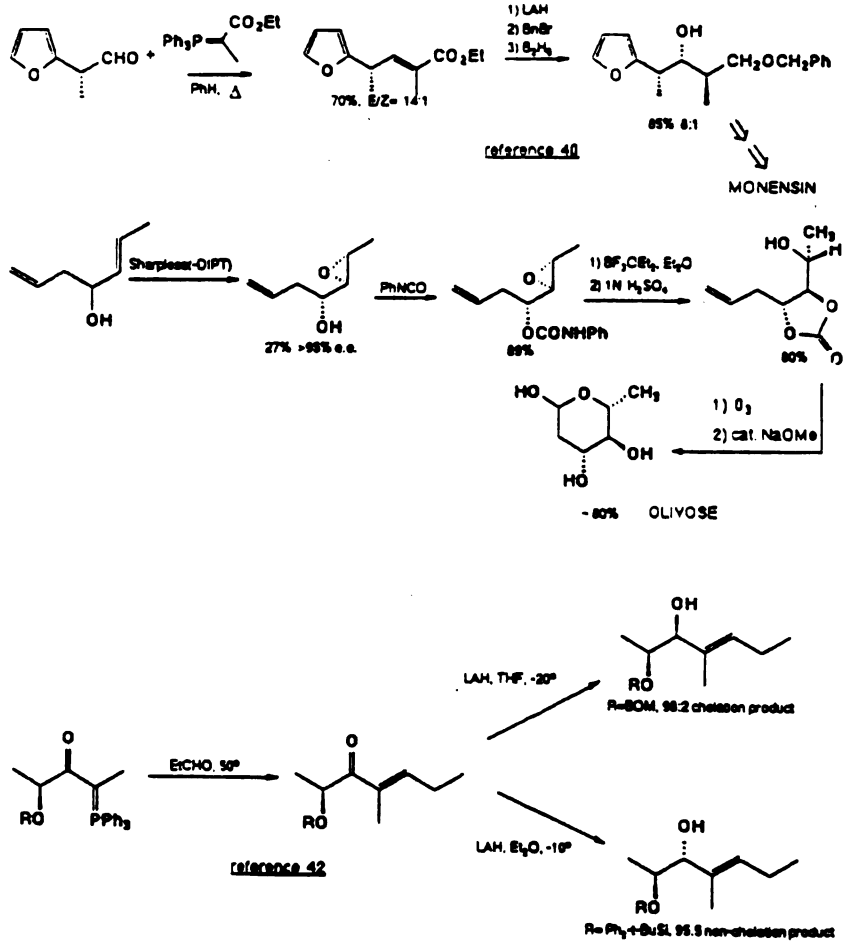
figure 3



process. The absolute configuration in the aldol process has also been controlled, via chiral enolates, and the course of the reaction with chiral aldehydes is relatively well understood. One drawback to the aldol chemistry thus far reported is difficulty in routinely producing the threo- or anti-stereochemistry with the same levels of stereoselection observed for the erythro-syn manifold.

Another technique for the control of relative and absolute acyclic stereochemistry focuses on the development of a carbon-carbon double bond with proximal resident chirality (Figure 4). In this approach, a fragment

figure 4



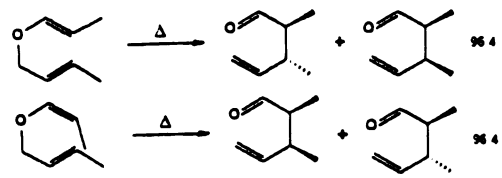
containing the resident chirality is typically coupled with an achiral ylid; the resulting unsaturated center may then be operated upon as demonstrated in Figure 4. Here, success is contingent on obtaining olefins of high geometric purity, a condition which may not always be realized.

Sigmatropic rearrangements are also attractive routes to highly functionalized molecules as these intramolecular processes are often highly stereospecific. A number of variants of the [3,3] sigmatropic rearrangement have met with considerable success in this regard. Figure 5 provides examples of some Claisen and Cope [3,3] rearrangements. Note that in these reactions, the starting asymmetric center is lost, but one or even two centers and double bonds of known configuration are obtained with high transmission of chirality. This self-immolitive process is generally thought to proceed through a six-membered, chair-like transition state[10] wherein substituents assume the most stable orientation.

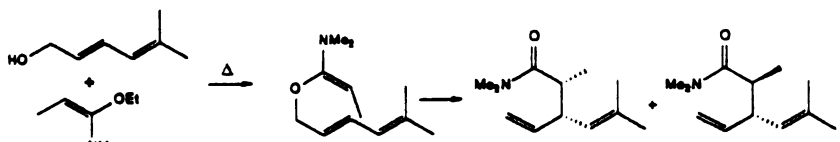
The [2,3] sigmatropic rearrangement has also been employed in natural products synthesis. A number of variants are shown in Figure 6, including the allyl sulfoxide-sulfenate rearrangement, allylic amine oxide rearrangement, the "Buchi"[11] rearrangement and the extensively employed Wittig rearrangement. The stereoselectivity observed in these rearrangements is thought to derive <u>via</u> a cyclic 5-center transition state[12],

figure 5

[3,3] rearrangements

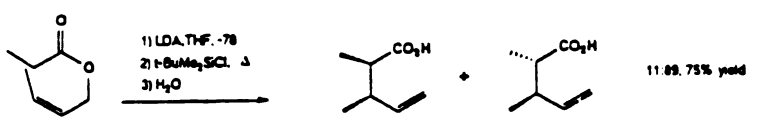


reference 43



reference 44

Santolinatriene



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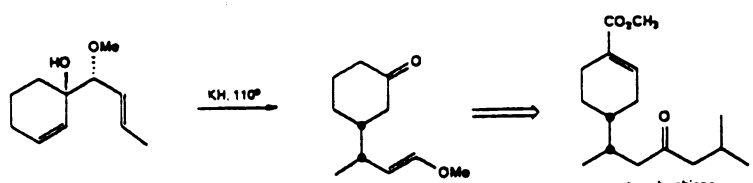
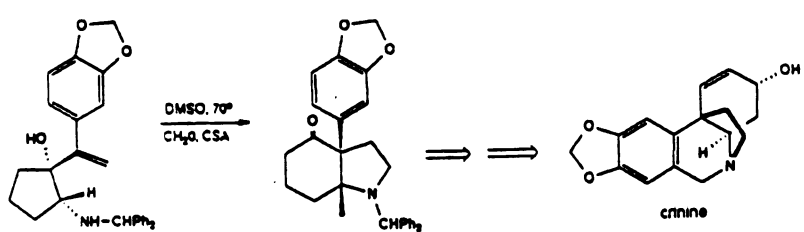


erythro-Juvabione

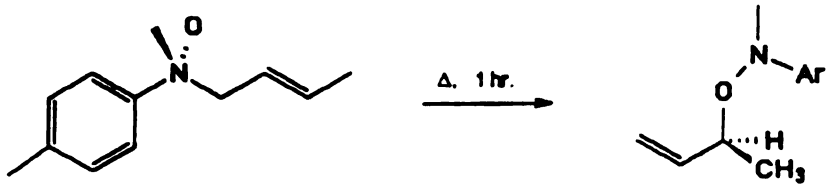
reference 46



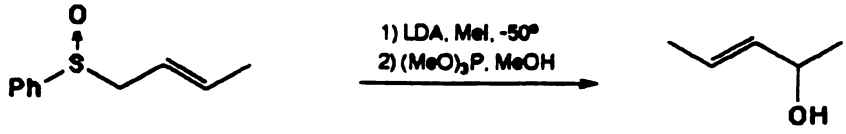
crinine

reference 47

figure 6



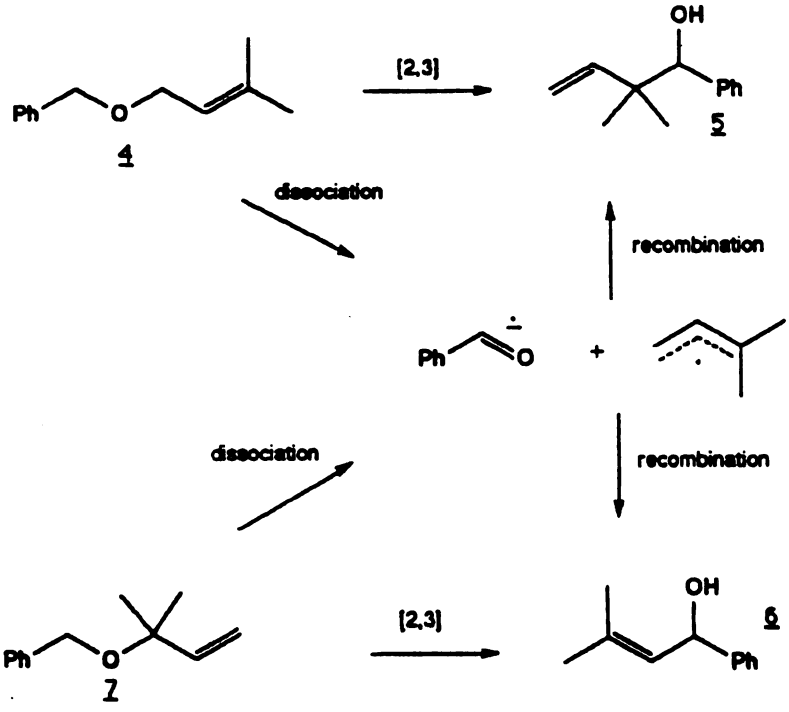
reference 48



reference 49

reference 50

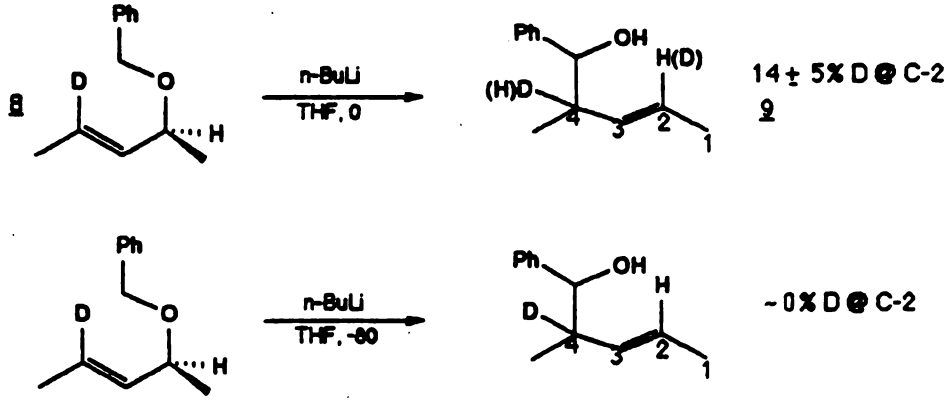
figure 7a



analogous to that of [3,3] rearrangements. Early mechanistic studies of the [2,3] Wittig rearrangement examined the competition of the concerted vs. non-concerted pathways in the rearrangement. Rautenstrauch[13] examined γ,γ-dimethyl allyl benzyl ether 4 in a crossover experiment, shown in Figure 7a. Upon lithiation, he observed an 8:1 mixture of 5 and 6 at -80°C, whereas at 23°C at 6:1 mixture of 5 and 6 was observed. Additionally, rearrangement of 7 α,α-dimethyl allyl benzyl ether at -25° afforded a 1:1.4 mixture of 5 and 6. Two conclusions may be drawn from these experiments; the concerted pathway appears to dominate over the non-concerted at lower temperatures, and the nature of the migrating allyl fragment has some influence on the pathway chosen.

Baldwin[14] performed a similar experiment, outlined in Figure 7b. Rearrangement of deuterium labeled 8 at 0°C

figure 7b



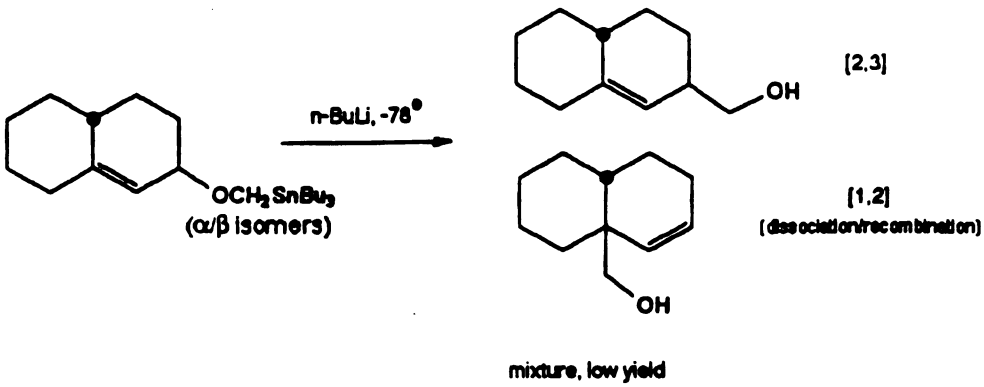
resulted in the production of 9 as a mixture of cis- and trans-isomers. ^{1}H-NMR indicated a vinylic deuterium content of 14±5%. At -80°C, the vinylic deuterium count fell to nearly 0%, indicating the predominance of the [2,3] pathway at low temperature, in agreement with the findings of Rautenstrauch.

In another variant of the Wittig rearrangement, Still reported[15] that the rearrangement of allyl stannyl methyl ethers derived from α and β bicyclo dec-5-ene-7-ol formed [1,2] (non-concerted) and [2,3] Wittig products in low yield. This contrasts with the rearrangement of 3-cyclohexenyl stannyl methyl ether (Figure 7c) which provided the product shown in 93% yield. Still suggests that steric hindrance at the migration terminus (β-carbon) and perhaps conformational problems can promote the non-concerted pathway, relative to the concerted [2,3] process.

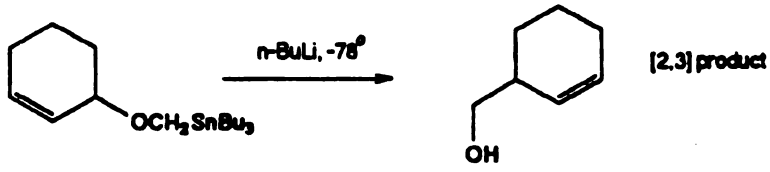
There are two general classifications one may impose upon the Wittig [2,3] rearrangement. The first consists of [2,3] substrates which contain an anion-stabilizing group; Midland[16] and, in particular, Nakai[17,18] have examined this variant extensively (Figure 8). The second type of rearrangement substrate generates an unstabilized carbanion, as exemplified by the work of Still[15] (Figure 9).

Inspection of the rearrangement products of the anion stabilized substrates listed in Figure 8 establishes that these rearrangements typically proceed with good to

figure 7c

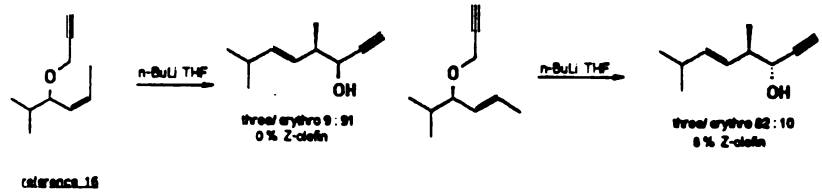


mixture, low yield

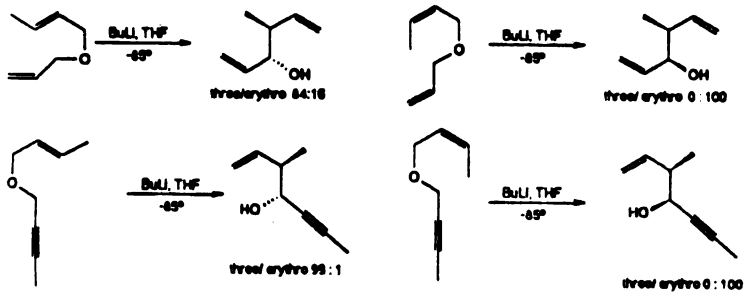


93% yield

figure 8

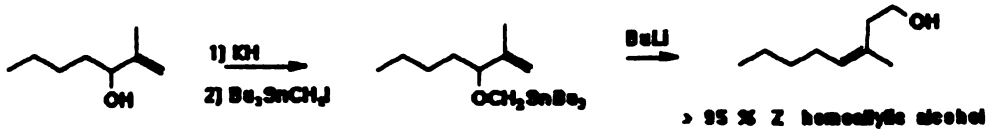


reference 16



reference 17

figure 9



> 95 % Z homoallylic alcohol

selectivity for the E-olefin and can often achieve diastereoselectivities of better than 10:1. There is, however, a drawback to the stabilized Wittig, that is, one must carry along the anion-stabilizing function regardless of its appropriateness to the target structure. Therefore, additional steps may be required to convert this moiety to the desired functionality. In this regard, the unstabilized variant might be the method of choice; as after rearrangement, one is left with a rather versatile primary alcohol for subsequent elaboration. In contrast to the stabilized rearrangement, the unstabilized Wittig rearrangement often yields predominantly Z-olefin. This selectivity is a function of olefin substitution, as the Z-selectivity drops to 60:40[15] when the vinyl carbon adjacent to the breaking C-O bond is unsubstituted (Figure 10). To rationalize these data, Still has suggested the model depicted in Figure 11. Still assumes an early transition state for this exothermic reaction, with a dihedral angle of ca. 30° between the breaking C-O bond and the vinyl moiety. The olefin facial-selectivity, and, thus, the ratio of E- to Z-product alkenes, is determined by $A_{1,2}$ interactions. In the example depicted in Figure 11, the interactions between Me and Bu result in rearrangement through the alternative rotamer, producing predominantly the Z-olefin. When the vinyl substituent is removed, the olefin facial-selectivity drops dramatically, resulting in low Z/E ratios (60:40). The requirement of an alkyl substituent at C-2 of the

figure 10

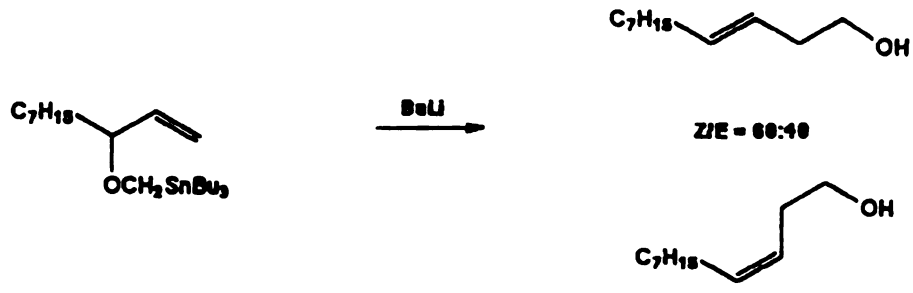
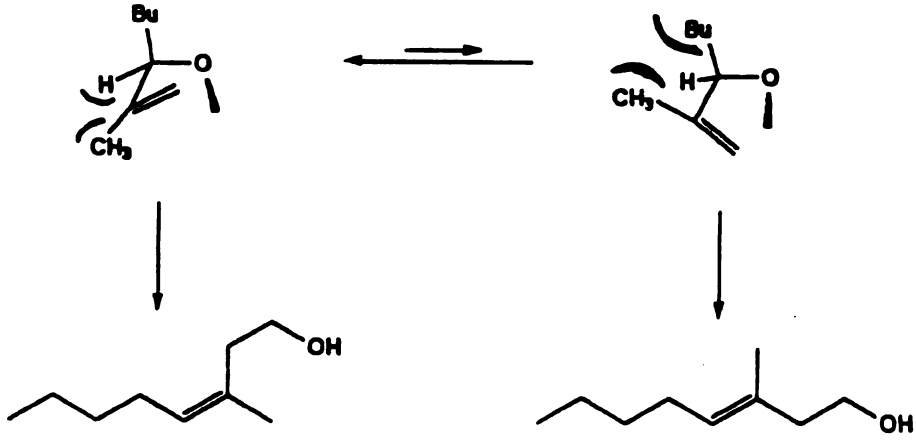


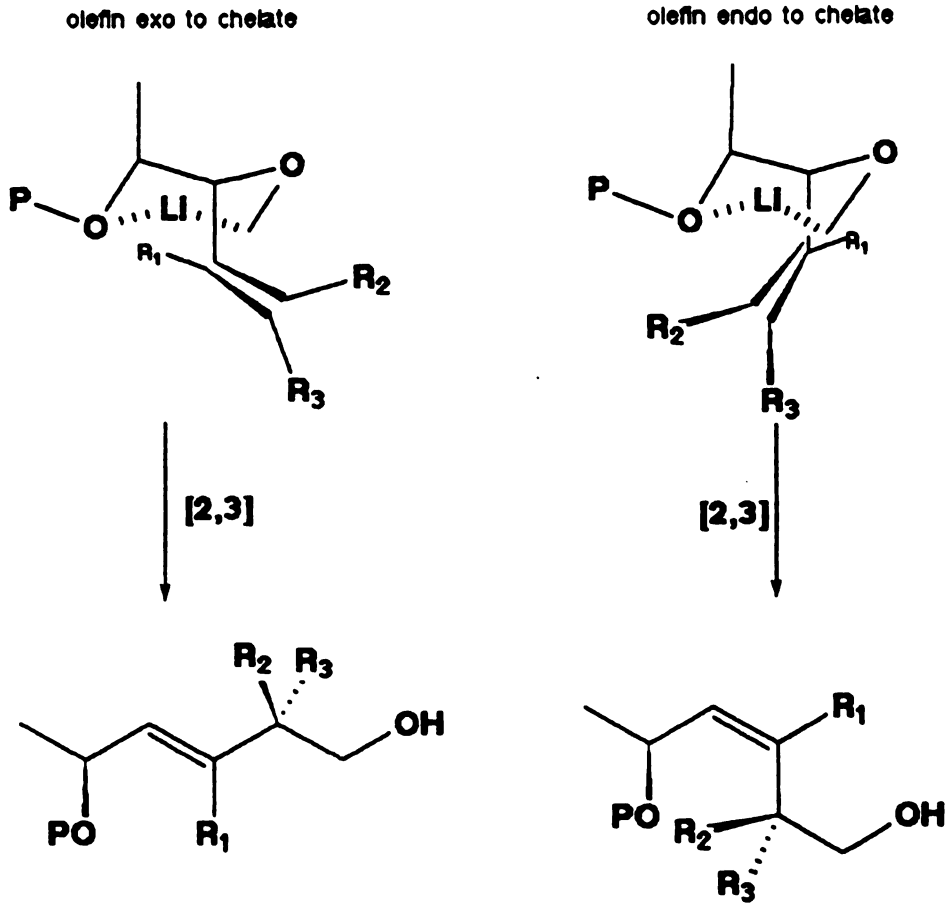
figure 11



substrate allylic alcohol limits the utility of the method; however, if one could routinely select the face of the olefin which is attacked, then the unstabilized Wittig rearrangement would become an attractive technique for acyclic stereoselection.

One possible method for directing olefin facial-selectivity is by organization of the transition state through chelation[19] (Figure 12). If we assume that the

figure 12

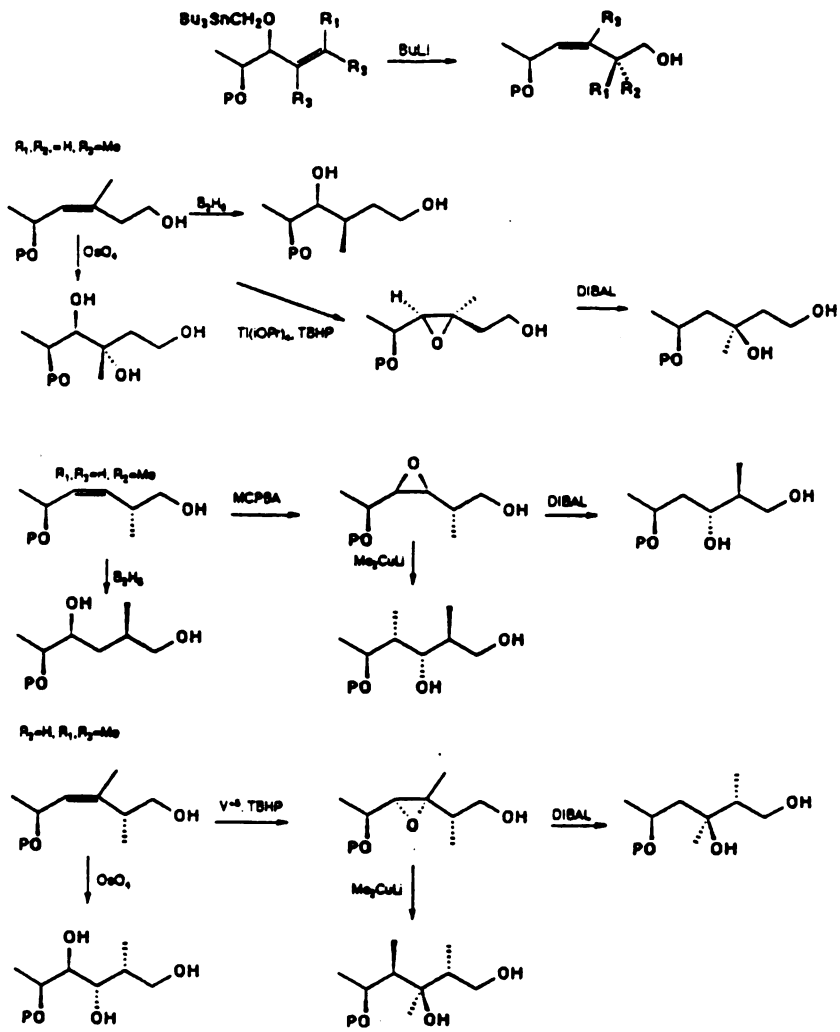


intermediate alkoxy carbanion is internally coordinated[20], providing a six-membered chair-like chelate, then the sense of asymmetry at C-7 and the resulting product olefin geometry will be dictated by the face of the double bond which is attacked. The placement of the vinyl group exo to the chelated ring system, leading to an E-olefin, is appealing for steric reasons; however, stereoelectronic considerations should render such a conformation unproductive. Alternatively, placement of the double bond in the sterically more-congested position, under the ring

plane, leading to a Z-olefin, is attractive as the bond angles and overlap closely approximate those assumed in the transition state proposed by Still. The substrates obtained upon rearrangement should be highly versatile synthetic intermediates, as illustrated in Figure 13.

Many regio- and stereochemical patterns of substitution may be produced from such a substrate using a variety of stereoselective methods. These acyclic pieces are then

figure 13

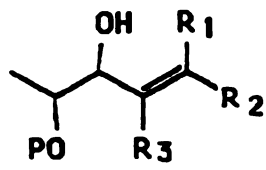


ideally suited for rapid assembly into desired target molecules; for example, the primary hydroxyl group obtained from the rearrangement can serve as an electrophile in an aldol reaction, or could serve as the hydroxyl terminus in a macrolactonization.

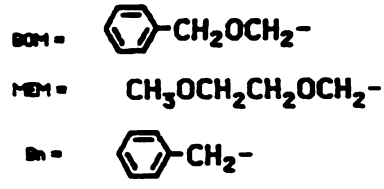
[2,3] RESULTS AND DISCUSSION

To examine the chelation-controlled [2,3] Wittig rearrangement, allylic alcohols of the type shown in Figure 14 are needed. Based on the high diastereomeric ratios

figure 14



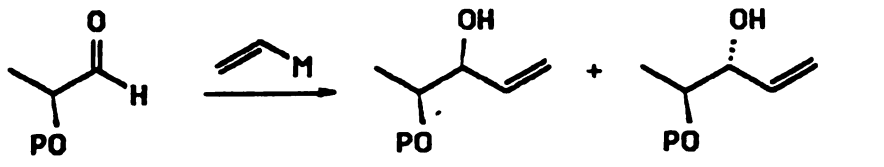
P = BOM, MEM, Bn



noted[21] in the literature for chelation controlled organometallic additions to α-alkoxy carbonyl compounds, a possible route to the desired allylic alcohols involved vinyl organometallic additions to readily available protected lactaldehydes, as depicted in Figure 15.

The two-step transformation of protected ethyl lactates to the desired protected lactaldehydes is shown in Equation 1. With a variety of protected lactaldehydes available, we next investigated the organometallic additions.

figure 15

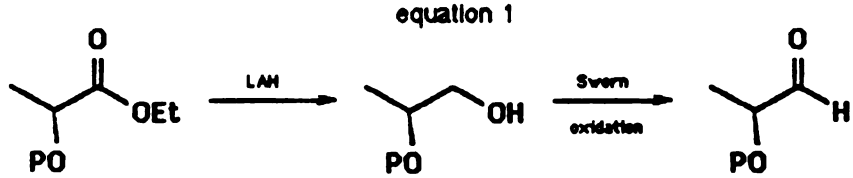


chelation product (a) non-chelation product (b)

10 P=BOM
11 P=MEM
12 P=Bn

13a,b P=BOM
14a,b P=MEM
15a,b P=Bn

equation 1



16 P=BOM
17 P=MEM
18 P=Bn

19 P=BOM
20 P=MEM
21 P=Bn

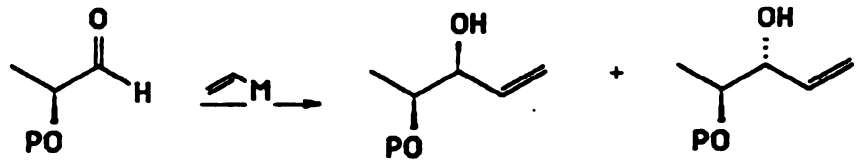
10 P=BOM
11 P=MEM
12 P=Bn

To the best of our knowledge, the only report of highly diastereoselective additions of vinyl organometallic reagents to α-alkoxy aldehydes which has appeared in the literature is that of MacDonald, et. al.[22] Therefore, we surveyed a variety of reaction conditions to ascertain the influence of solvent, protecting group and metals present and/or added on product diastereoselectivity.

A typical experiment consisted of side-by-side runs which examined a given solvent/protected aldehyde combination, with or without zinc halide added to vinyl magnesium bromide. The reactions were performed by adding the aldehyde solution to either vinyl magnesium bromide solution (control) or to a solution (2:1 mol) of the vinyl

Grignard and the desired zinc halide at -78°C, followed by warming to room temperature. Table 1 presents the results of these studies. Based on the general observation[4] that Grignard reagents react with α-alkoxy aldehydes to favor the

table 1



chelation (a) non-chelation (b)

P	solvent	$ZnCl_2$(+/-)	yield(crude)	ratio, a:b ^{1}H-NMR ratio	GC ratio
Benzyl	THF	-	77 %	1.6:1	1.6:1
Benzyl	THF	+	97 %	6.0:1	6.8:1
MEM	THF	-	79 %	1.8:1	-
MEM	THF	+	53 %	7.5:1	-
BOM	THF	-	78 %(purified)	1.8:1	-
BOM	THF	+	83 %	9.3:1	22:1
BOM	Et_2O	+	88 %	3.4:1	4.1:1
BOM	CH_2Cl_2	-	86 %	1.3:1	-
BOM	CH_2Cl_2	+	91 %	8.4:1	8.4:1
BOM	CH_2Cl_2	$ZnBr_2$	79 %	-	12.7:1

product of chelation control[2,3] as the major diastereomer, we assigned product stereochemistry as chelation or non-chelation by comparison of the product distribution in the presence of zinc halide with that obtained from the corresponding Grignard reaction without zinc halide. It is noteworthy that in all cases the addition of zinc halide increased the diastereoselectivity of the reaction relative

to the control. A maximum diastereoselectivity of ≥ 9.3:1 was observed for the BOM/THF/$ZnCl_2$ system. This selectivity is appropriate for synthetic use; however, it is still far below the 49:1 obtained by MacDonald[22] in vinyl copper additions to α,β-dialkoxyaldehydes.

With diastereoselective additions of simple vinyl organometallics established, it was of interest to see if the same strategy might be extended to vinyl homologs such as cis- or trans-propenyl organometallics. These reagents, if successfully added, would yield valuable substrates for examination of the [2,3] rearrangement sequence. By simply reversing the geometry of the organometallic reagent, the sense of asymmetry at the methyl-bearing center of the rearranged product could be changed. However, it is difficult to obtain configurationally pure E- or Z- propenyl organometallic species. To circumvent this problem, the plan shown in Figure 16 was developed. Given the availability of E- or Z-propenyl allylic alcohols from precursor propargylic alcohols, we envisioned preparing **22** and **23** by a chelation-controlled addition of a propynyl organometallic reagent to a protected lactaldehyde, followed by a partial hydrogenation or a hydride reduction. This protocol was employed by Hart[24] to prepare [3,3] sigmatropic rearrangement substrates and by Midland[25] to prepare [2,3] rearrangement substrates. Table 2 lists the data from three experiments. The ratios observed for the two Zn mediated reactions are relatively low but demonstrate a reversal of

figure 16

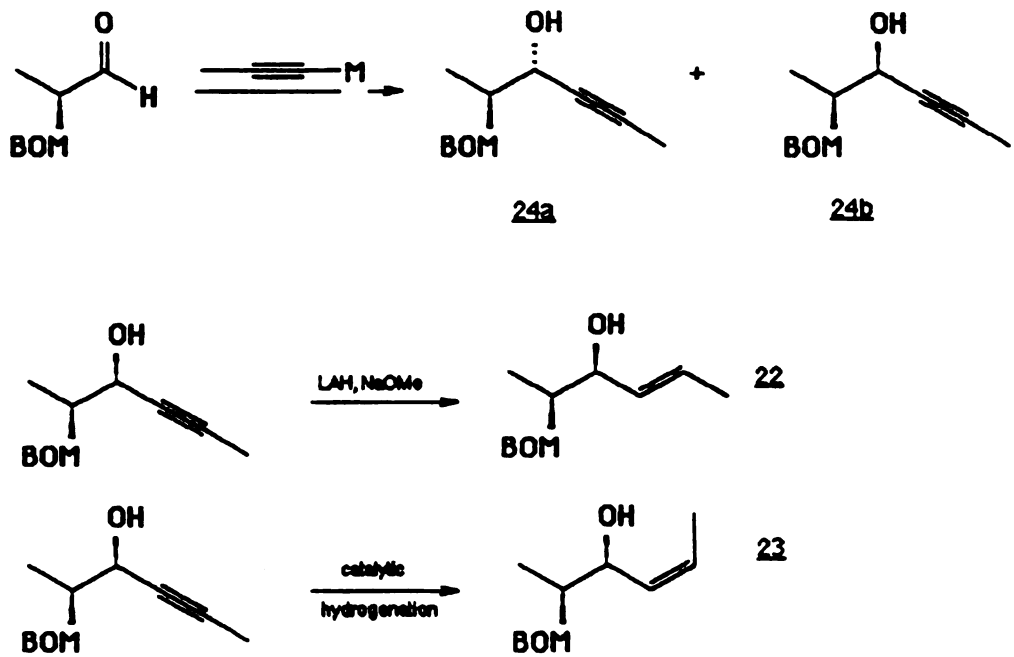
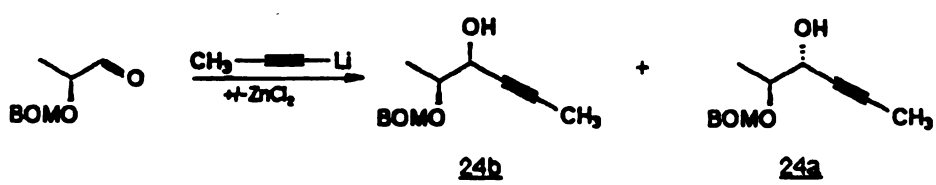


table 2



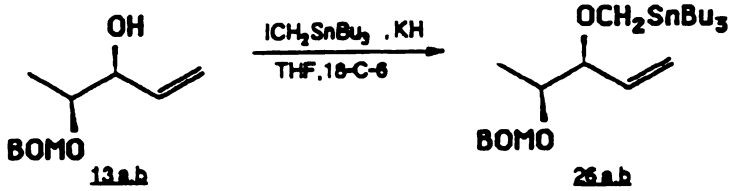
propynyl lithium:$ZnCl_2$	yield(%)	b : a
1:0	87	1:1.7
1:1	93	1.65:1
2:1	86	1.1 : 1

ratios represent an average of GC and NMR data

the diastereoselectivity observed for the propynyl lithium addition. This seems reasonable after consideration of the occasionally observed preference[23] for organolithium reagents to give non-chelation products and on the preference for zinc organometallics to give chelation addition products. Support for these stereochemical assignments is drawn from the $Zn(BH_4)_2$ reduction of ynone **25**, Figure 17, which yields alcohol **24a** as the major product. The indicated stereochemistry of alcohol **24a** is predicted by the work of Oishi.[26a,b] Alcohol **24a** is identical (GC, ^1H NMR) to the major isomer obtained in the propynyl lithium addition, supporting the stereochemistry predicted by the non-chelation model. These data indicate that the stereochemistry of the diastereomeric product from the zinc-mediated addition is that shown in Table 2, in accord with a chelation-controlled addition. As a result of the relatively low diastereoselectivity observed, this route to rearrangement substrates was not pursued further.[27]

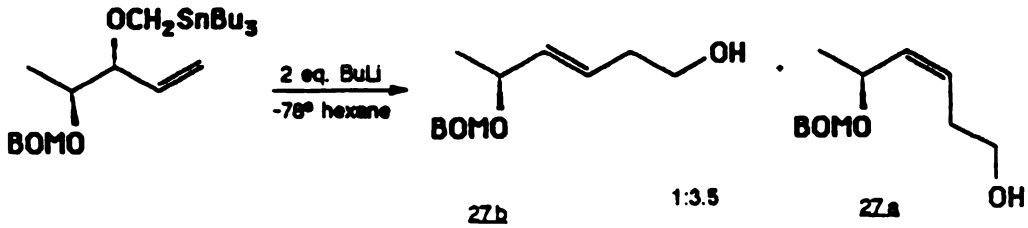
The allylic alcohols obtained from the BOM-lactaldehyde vinyl additions ($ZnCl_2$, THF) were then converted to the corresponding methyl stannyl ethers in preparation for the [2,3] rearrangement (Figure 18). Alkylation of the alkoxides **13a,b** (KH, THF, 18-C-6) with ICH_2SnBu_3 resulted in a 52% isolated yield of **26a,b**. Rearrangement of **26a,b** (Figure 19) was realized after treatment with two equivalents of n-BuLi (hexane, -78°C, 1 hr.) followed by warming to room temperature and quenching with saturated

figure 18



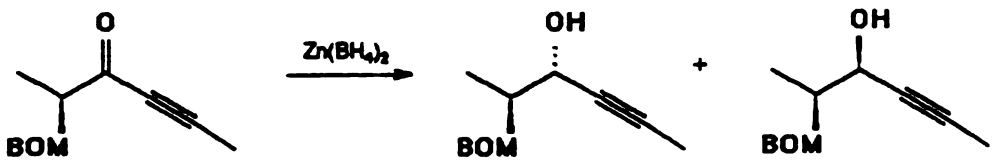
13a,b 26a,b

figure 19



27b 27a

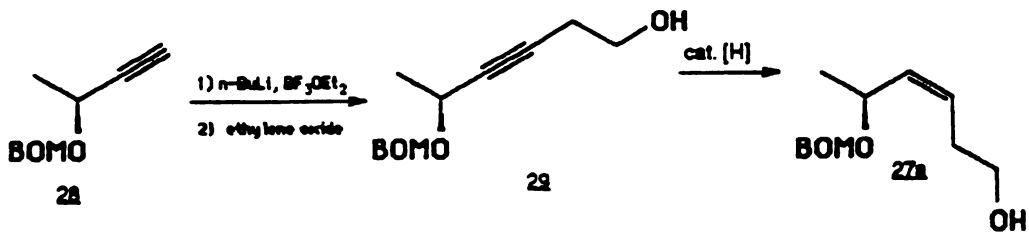
figure 17



25 24a 24b

NH_4Cl (aq.). After workup and silica gel chromatography, a 57% yield of diastereomeric homoallylic alcohols **27a** and **27b** was obtained in 3.5:1 ratio (^{1}H-NMR). The major isomer was assigned as Z- on the basis of a ^{1}H-NMR shift reagent study ($Eu(FOD)_3 \cdot d_{27}$) in which measurement of the vicinal J values for olefinic hydrogens established ^{3}J coupling of 10.5Hz for the major isomer (Z-) and 15.3Hz for the minor (E-) isomer. Confirmation of Z-**27a** as the major isomer was obtained by synthesis of this material by an alternate and unequivocable route,[28] shown in Equation 2. The 3.5:1 Z/E ratio observed

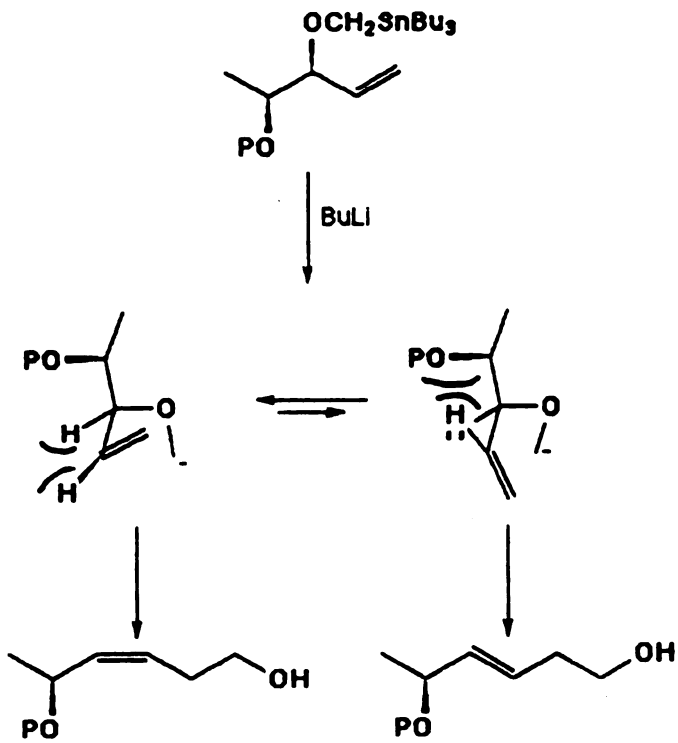
equation 2



in this rearrangement is significant since the Z/E selectivity in the absence of an alkyl substituent on the internal vinylic position of the stannyl methyl ether should have been about 60:40 according to Still's model (refer to Figure 10).

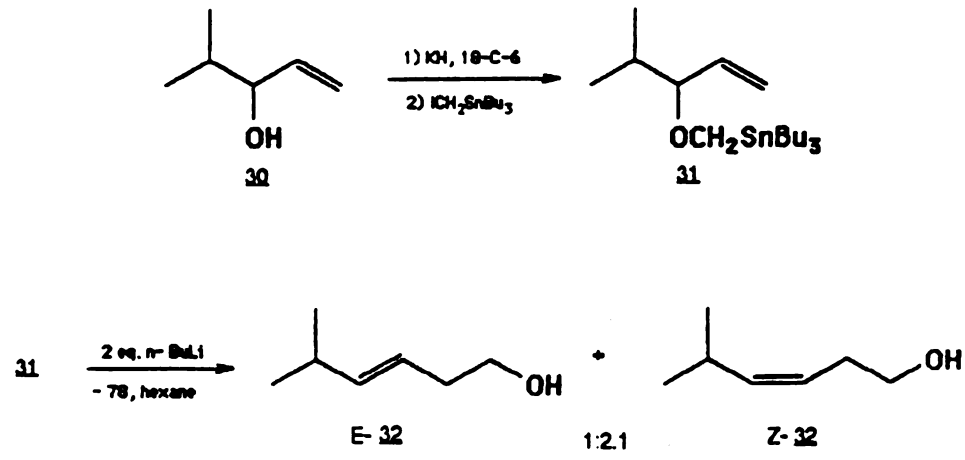
Although our observation of enhanced Z-selectivity is consistant with the chelation model, one might argue that the branching adjacent to the breaking C-O bond (Figure 20) might contribute to the observed Z-selectivity; this factor

figure 20



was not present in Stills' substrates. To test this possibility, a substrate having the desired branching yet incapable of chelation, was needed. Allylic alcohol **30** obtained by addition of vinyl magnesium bromide to isobutyraldehyde was selected for this purpose. Conversion of allylic alcohol **30** to its methyl stannyl ether (ICH_2SnBu_3, KH, 18-C-6, THF), **31**, (87%), and subsequent rearrangement (hexane, 2 equivalents nBuLi, -78°C, 2 hrs.) gave a 2.1:1 ratio of Z- and E-homoallylic alcohols (compound **32**, Figure 21). This ratio is slightly higher than that predicted by the Still model, indicating that

figure 21



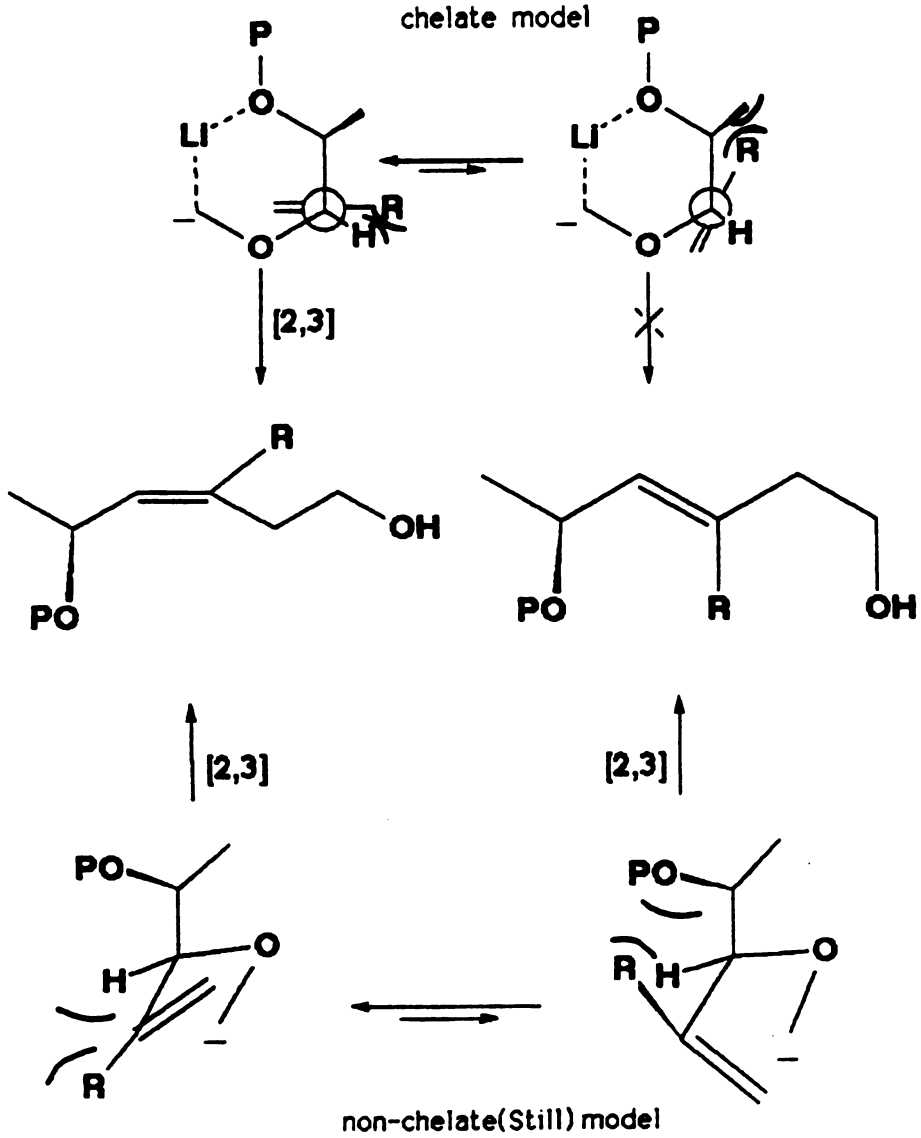
branching of the alkyl group adjacent to the breaking C-O bond has an effect, albeit small, upon rearrangement stereoselectivity.[25] Consequently, it appears that the primary factor responsible for the higher Z-selectivity in this work is, not the branching factor, but the presence of an alkoxy function, capable of chelation.

Chelation control, as an important factor in [2,3] rearrangement stereoselectivity, can be further examined by the rearrangement of substrates having a variety of alkoxy groups such as benzyl, MEM and methyl. The varying ability of these functions to coordinate to the Li counter cation would be expected to effect the degree of diastereoselection. Additionally, the rearrangement could be performed in a variety of solvents and/or exogenous lithium chelating agents could be added. In an attempt to

define solvent effects on the stereochemical outcome of the rearrangement, **26a** was treated with 2 equivalents of n-BuLi (-78°-->0) in methylene chloride and THF. In methylene chloride, a nearly quantitative recovery of starting material was realized; suggesting that transmetallation does not readily occur under standard conditions in methylene chloride. However, rearrangement in THF (2.1 eq. nBuLi; -78°-->RT; 82%) provided a 1.5:1 ratio of alcohols **27a** and **27a**. The lower diastereoselectivity observed for the rearrangement of **26a** in THF vs. rearrangement in hexane is consistant with a chelation model since, in the highly coordinating THF solvent, it is possible that THF-Li^+ association could reduce the efficiency of chelation, leading to lower olefin diastereofacial selection. In hexane, the lack of solvent -Li^+ coordination could facilitate formation of the chelated transition state for rearrangement. Temperature studies should also be conducted in order to determine whether the selectivity is enhanced at low temperature.

Olefin substitution is another means by which rearrangement diastereoselectivity may be modified. The effect of alkyl substitution at the internal position of the olefin has been examined by Still in a non-chelated variant of the [2,3] rearrangement. The same steric factors are expected to apply in the rearrangement of a suitably substituted chelatable substrate, as shown in Figure 22. In such a case, steric interactions would dictate that the

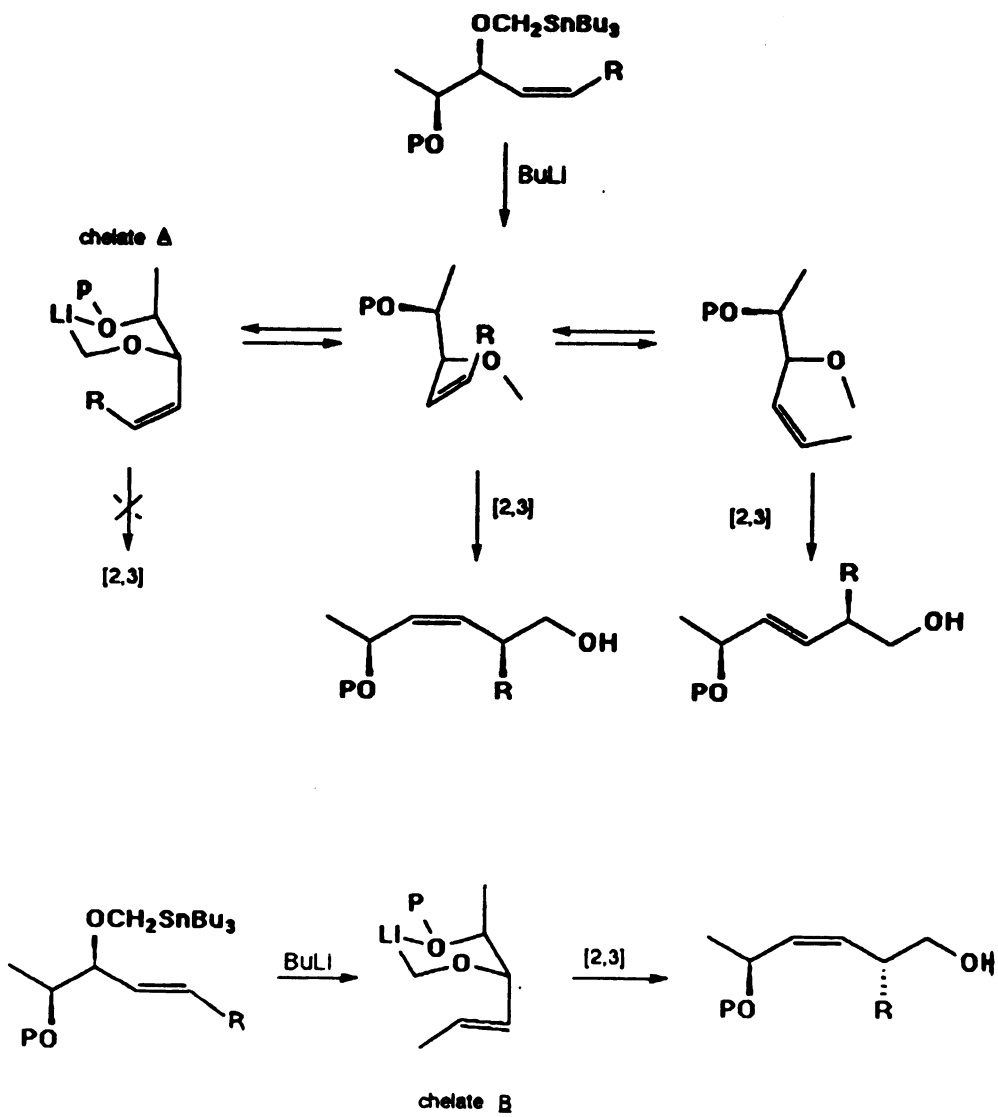
figure 22



olefin swing under the ring to minimize unfavorable $A_{1,2}$ interactions, with rearrangement leading to a predominance of Z-olefin. Note that, whether chelation occurs or not, the same major product is expected. Substitution of the olefin terminus in the Z-position should lead to chelate A in Figure 23. However, it is expected that the olefinic

moiety would be strongly discouraged from residing under the ring due to severe steric interactions. This would inhibit rearrangement from the chelate, perhaps leading to rearrangement <u>via</u> a non-chelated intermediate in which we expect low diastereoselectivity.[30] E-33 (Figure 23) should rearrange <u>via</u> chelate B since the alkyl moiety at the olefin

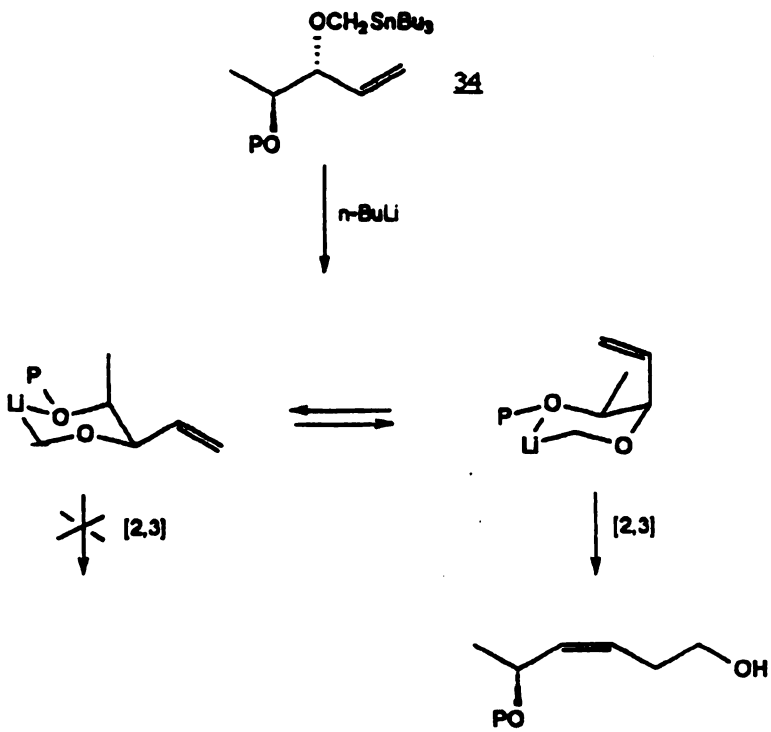
figure 23



terminus resides in a favorable steric environment, away from the chelated-ring. We expect that the product diastereoselectivity should be comparable to that observed for the rearrangement of substrate **26a**.

Alternatively, the stereochemistry of the breaking C-O bond could be inverted which would allow rearrangement of substrates having one less axial substituent (CH_3) in the transition state (Figure 24). This remains to be examined experimentally.

figure 24



The rearrangement of substrates having substitution at the olefin terminus (Figure 25, $R_1 \neq R_2$) results in the transmission of chirality from the resident C-O bond to the new C-C bond. The sense of chirality installed at this center is dependent on two variables, the stereochemistry of the breaking C-O bond and the olefin geometry. The result of altering one of these variables while holding the other constant is presented in Figure 25. Therefore, one can manipulate the sense of asymmetry at the newly formed C-C bond either by variation of olefin geometry or C-O bond stereochemistry. We have suggested that manipulation of asymmetry, based upon reversal of the geometry of a vinyl organometallic, is impractical on steric grounds and from a consideration of organometallic precursor availability. However, a manipulation of the C-O stereochemistry for the control of chirality in the rearrangement appears to be a superior approach[25] (Figure 26).

The precursor to substrate **26b** has been prepared in an unoptimized diastereomeric ratio of 7:1 as shown in Equation 3. Treatment of **34** with ICH_2SnBu_3 should yield **26b**, rearrangement of which will provide insight as to the effect of alternate C-O stereochemistry upon product olefin diastereoselectivity.

This chelation variant of the [2,3] Wittig rearrangment is clearly effective for the rearrangement of substrates lacking alkyl substitution at the internal position of the

figure 25

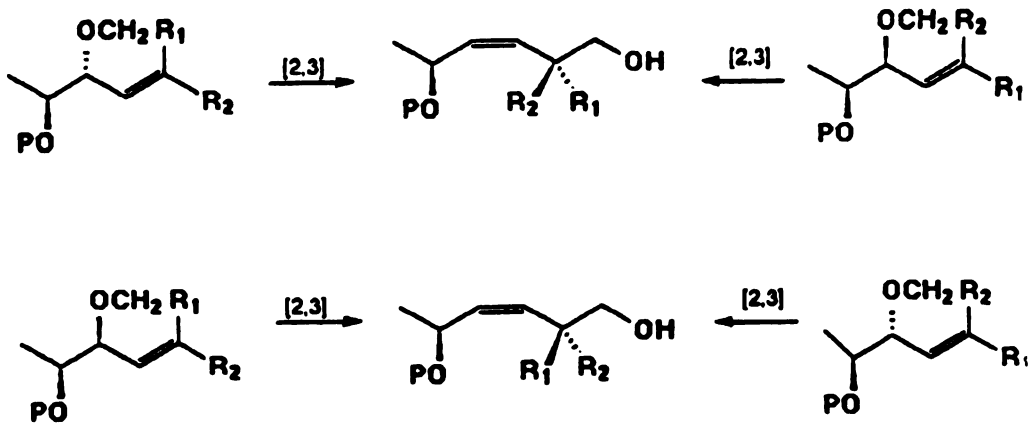
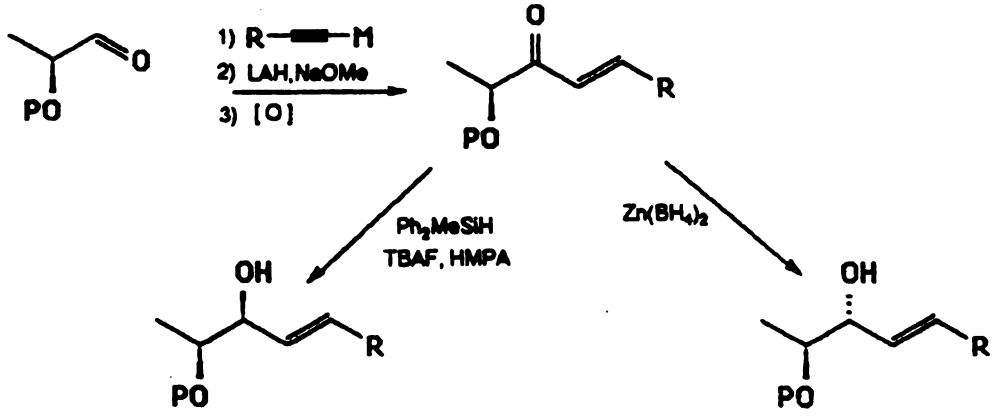
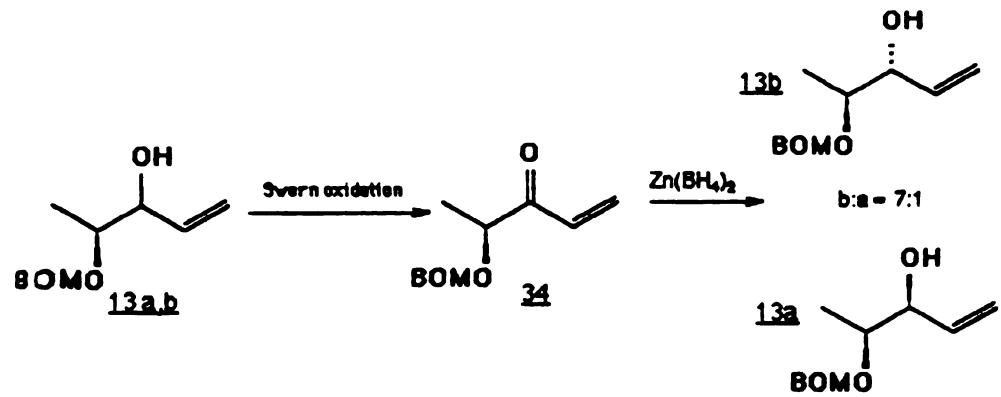


figure 26



equation 3



olefin. The effects of chelation, olefin substitution pattern, and C-O stereochemistry need to be further examined in order to define the scope and utility of this technique.

[2,3] EXPERIMENTAL

All reactions were conducted under Ar, with rigorous exclusion of moisture from glassware and reagents unless otherwise noted. Hexane, ether, and THF were dried by distillation from Na/benzophenone ketyl. Methylene chloride, triethylamine, and diisopropyl ethylamine were dried by distillation from calcium hydride. Dimethyl sulfoxide was dried by distillation at reduced pressure from P_2O_5. Zinc chloride was dried by fusion under Ar, then was crushed and stored in a dry box. Zinc bromide was dried in an abderhalen (xylene) for 48 hours using P_2O_5 dessicant, then stored in a dry box. Ethyl-L-(+)-lactate (Aldrich, 98%) was used as received. n-Butyl lithium was purchased as a solution in hexane from Aldrich Chemical Co., Milwaukee, WI and was titrated by the method[31] of Watson and Eastham. Vinyl magnesium bromide stock solution was prepared from 20 mesh Mg^0 and vinyl bromide in THF; the Grignard solution was titrated by the method of Watson and Eastham. Vinyl addition product diastereomeric ratios were measured by Capillary GC (carbowax column) or 250 MHz ^1H-NMR.

^{1}H-NMR spectra were recorded at 60, 80, or 250 MHz, as indicated, on Varian T-60, Varian FT-80 or Bruker WM-250 spectrometers, respectively. Broadband decoupled ^{13}C-NMR spectra were recorded at 68.9 MHz on a Bruker WM-250 spectrometer. Spectra were recorded in $CDCl_3$ unless noted otherwise. Chemical shifts are reported in ppm relative to a Me_4Si internal standard unless noted otherwise. Coupling constants are reported in Hz; data are reported as follows: chemical shift (multiplicity, coupling constant, integration), multiplicities are defined as s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, br=broad. IR spectra were recorded on a Perkin Elmer Model 599 Spectrometer. Mass spectra were obtained on a Finnigan 4000 mass spectrometer equipped with an INCOS 4201 data system. Spectra were obtained in either electron impact (EI) or chemical ionization (CI) mode; for CI, methane was employed as ionizing gas. Gas chromatography was performed on a Hewlett-Packard 5880 Level 3 capillary gas chromatograph equipped with an FID detector. Methyl silicone (12.5m, He carrier) or carbowax (50m, H_2 carrier) columns were employed.

Ethyl-2-(benzyloxymethyl)-(s)-lactate, 16

To 54.6g (0.35 mol) of benzyloxymethyl chloride[37] in 200 ml of methylene chloride, cooled to 0°C in an ice-water bath, was added 61.0 ml (0.35 mol) of N-ethyl diisopropyl

amine over a five-minute period. After stirring for 5 minutes, 28.3 ml (0.25 mol) of ethyl-(s)-lactate was added to the reaction vessel over ten minutes. The reaction mixture was warmed to room temperature and stirred for 12 hours. The resulting yellow solution was cast into CH_2Cl_2 (100 ml), washed with 0.1 N HCl, saturated aq. $NaHCO_3$, brine (100 ml each), and dried (Na_2SO_4). Concentration *in vacuo* provided 49.06g of a yellow oil, which, after distillation, yielded 30.16g (51%) of **16**, $BP_{0.5}$ 113-117°C.
^{1}H-NMR (60 MHz): δ = 1.1-1.5 (m, 6H), 3.95-4.4 (m, 3H), 4.62 (s, 2H), 4.82 (s, 2H), 7.34 (br s, 5H). CI-MS: 239 (M^{+1}, 1%), 131 (M-107, 86%), 91 ($C_7H_7^+$, base). IR (neat): 3065 (m), 2985 (s), 1740 (s), 1210 (s), 1175 (s), 1115 (s) cm^{-1}.

Ethyl-(2S)-(methoxyethoxymethyl)-lactate, **17**

According to the procedure for synthesis of **16**, treatment of 35.25g (0.3 mol) of ethyl-(s)-lactate, 65 ml (0.373 mol) of N-ethyl-diisopropyl amine and 46.50g (0.373 mol) of methoxyethoxymethyl chloride[32] provided, after distillation, 34.78g (56%) of **17**, $BP_{0.85}$ 79-90°C.
^{1}H-NMR (60 MHz): δ = 1.3 (t, J=7Hz, 3H), 1.43 (d, J=6Hz, 3H), 3.4-3.85 (m, 4H), 4.20 (q, J=7Hz, 2H), 4.24 (q, J=6Hz, 1H), 4.8 (s, 2H). CI-MS: 207 (M+1, 0.3%), 131 (M-75, 71%), 59 (M-147, base). IR (neat): 2990 (s), 2940 (s), 2890 (s), 1745 (s), 1180 (s), 1030 (s), 1100 (s) cm^{-1}.

(2S)-(methoxyethoxymethyl)-propanediol, 20

To a suspension of 2.02g (0.053 mol) of lithium aluminum hydride in 500 ml of anhydrous ether was added 17.56g (0.085 mol) of 17 in 50 ml of ether at such a rate so as to maintain a gentle reflux. After the addition was complete, the mixture was heated under reflux for 7 hours. The reaction mixture was then cooled in an ice bath, and with rapid mechanical stirring, was cautiously quenched with 20% aqueous sodium hydroxide (ca. 80 ml). The resulting heterogeneous solution was filtered through a pad of celite; the filter pad was rinsed with ether. The biphase filtrate was transfered to a separatory funnel and the aqueous layer drawn off. The organic layer was washed with H_2O (2 x 200 ml), brine (100 ml) and dried (Na_2SO_4). Concentration *in vacuo* yielded 12.58g of a pale green oil. Distillation provided 9.18g (66%) of 20, $BP_{0.9}$ 73-80°C.
^{1}H-NMR (60 MHz): δ 1.04 (d, J=6Hz, 3H), 2.89 (s, 1H), 3.24-3.84 (m, 7H), 4.79 (s, 2H). CI-MS: 165 (M+1, 11%), 89 (M-75, base). IR (neat): 3450 (s), 2970 (s), 2930 (s), 1450 (m), 1115 (s), 1040 (s) cm^{-1}.

(2S)-(benzyloxymethyl)-propanediol, 19

According to the procedure employed for 20, 55.7g (0.234 mol) of 16 was treated with 5.54g (0.146 mol) of lithium aluminum hydride. In a modified workup, the Al salts collected by filtration were dissolved in a large

volume of dilute sodium hydroxide and extracted with ether (4 x 50 ml). The resulting ether extracts were combined with the organic phase obtained from the filtrate of the quenched reaction mixture and were washed with brine (200 ml) and dried (Na_2SO_4). Concentration *in vacuo* yielded 47.19g of a clear colorless oil. Distillation afforded 40.15g (88%) of **19**, $BP_{1.5}$ 122-124°C.

^{1}H-NMR (60 MHz): δ = 1.2 (d, J=6Hz, 3H), 2.7 (s, 1H), 3.5 (m, 2H), 3.83 (m, 1H), 4.64 (s, 2H), 4.83 (s, 2H), 7.32 (br s, 5H). CI-MS: 197 (M+1, 2%), 179 (M-17, 8%), 91 ($C_7H_7^+$, base). IR (neat): 3475 (m), 3100 (w), 3070 (w), 2980 (s), 1040 (s), 1105 (s) cm^{-1}.

(2S)-(benzyloxymethyl)-propanal, **10**

The procedure described[33] by Wuts and Bigelow was employed. 5.0 ml (0.055 mol) of oxalylchloride in 100 ml of dry methylene chloride was cooled to -60°C ($CHCl_3/CO_2$). 8.5 ml (0.110 mol) of dry DMSO in 25 ml of methylene chloride was slowly added to the stirring chilled solution, keeping the solution temperature below -50°. After the addition was complete, stirring was continued for 20 minutes. Then 3.92g (0.020 mol) of **19** in 25 ml of methylene chloride was added to the solution over 10 minutes, resulting in a cloudy white solution. After stirring for 15 minutes, 35 ml of triethylamine (0.250 mol) was added, keeping the temperature below -40°C. The flask was warmed to room temperature and the reaction mixture cast into 2:1 H_2O/methylene chloride

(300 ml). The aqueous phase was extracted with methylene chloride (2 x 50 ml); the combined organic phases were washed with 1% HCl (50 ml), 5% Na_2CO_3 (50 ml), brine (50 ml) and dried (Na_2SO_4). After concentration *in vacuo*, Kugelrohr distillation (100°C, 0.02mmHg) afforded 3.50g (98%) of **10**. ^{1}H-NMR (60 MHz): δ = 1.3 (d, J=6Hz, 3H), 4.1 (dq, J=2,6Hz, 1H), 4.66 (s, 2H), 4.84 (s, 2H), 7.36 (br s, 5H), 9.6 (d, J=2Hz, 1H). EI-MS (70eV): 165 (M-29, 4%), 107 ($C_7H_7O^+$, 42%), 91 ($C_7H_7^+$, base). IR (neat): 3035 (m), 2895 (s), 2720 (w), 1735 (s), 1105 (s), 1040 (s) cm^{-1}.

(2S)-(methoxyethoxymethyl)-propanal, **11**

Using the procedure employed for the preparation of **10**, 5.13g (0.031 mol) of **20** provided 3.30g (65%) of **11**, $BP_{0.005}$ 40-45°C.

^{1}H-NMR (60 MHz): δ = 1.33 (d, J=6Hz, 3H), 3.4 (s, 3H), 4.45-4.8 (m, 4H), 4.15 (dq, J=2,6Hz, 1H), 4.82 (s, 2H), 9.62 (d, J=2Hz, 1H). CI-MS: 163 (M+1, 1%), 89 (M-73, base). IR (neat): 2980 (s), 2935 (s), 2725 (w), 1735 (s), 1100 (s), 1035 (s) cm^{-1}.

(2S)-benzyloxypropanal, **12**

Using the procedure employed for preparation of **10**, 5.20g (0.031 mol) of **21**[34] provided 4.72g (92%) of **12** after distillation (Kugelrohr, $100°_{0.05}$).

^{1}H-NMR (60 MHz): δ = 1.34 (d, J=6Hz, 3H), 3.9 (dq, J=2,6Hz, 1H), 4.62 (s, 2H), 7.34 (br s, 5H), 9.62 (d, J=2Hz, 1H).

EI-MS (70eV): 164 (M^+, 0.8%), 163 (M-1, 6%), 135 (M-29, 22%), 91 ($C_7H_7^+$, base). IR (neat): 3035 (m), 2980 (s), 2940 (s), 2718 (m), 1735 (s), 1160 (s) cm^{-1}.

General Procedure for Vinyl Organometallic Additions to Protected Lactaldehydes

The reactions were performed at ca. 1 mmol scale. One equivalent of anhydrous zinc halide was introduced to a round bottom flask in a dry box and 10 ml of dry solvent (ether, THF, or CH_2Cl_2) was added to both the zinc halide flask and a control flask. The flasks were cooled to -78° in a dry ice/acetone bath. With stirring, 2 equivalents of vinyl magnesium bromide were added to the zinc halide-containing flask, while one equivalent of vinyl Grignard was introduced into the control flask. The resulting solutions were stirred at -78°C for 15-30 minutes, after which time, a slow addition of 1 equivalent of protected lactaldehyde in ca. 1 ml of reaction solvent was made. Stirring was continued at -78°C for 30 minutes, followed by slow warming to room temperature over ca. 60 minutes. The reactions were cast into 50 ml of 1:1 ether/saturated NH_4Cl.

The aqueous phase was extracted three times with Et_2O. The combined organic layers were washed with saturated $NaHCO_3$, saturated brine (50 ml each) and dried (Na_2SO_4). Concentration *in vacuo* yielded diastereomeric allylic alcohols which were analyzed with no further purification.

Table 1 reports yields and ratios for product **13a,b**, **14a,b**, and **15a,b** as a function of various reaction parameters.

Sample Procedure for a $ZnCl_2$-mediated Preparation of **13a,b**

0.38g (2.79 mmol) of $ZnCl_2$) was introduced to a flask in a dry box. 10 ml of dry THF was added to the flask and was cooled to -78° (CO_2/acetone). 6.2 ml (5.6 mmol) of vinyl magnesium bromide was added to the flask; the resulting solution was stirred for 30 minutes, after which time 0.500g (2.6 mmol) of **10** in 3 ml THF was slowly added. Stirring was continued for 30 minutes at -78°C, after which time, the reaction mixture was gradually warmed (over 1 hour) to room temperature and was cast into 50 ml of 1:1 ether-saturated NH_4Cl. The aqueous layer was extracted with ether (3 x 25 ml); the combined organic phases were washed with saturated $NaHCO_3$ (40 ml), brine (50 mL), and dried (Na_2SO_4). Concentration *in vacuo* yielded 0.480g (84%) of a yellow oil.

(4S,3S)- and (4S,3R)-4-(benzyloxymethyl)-3-hydroxy-1-pentene **13a,b**

13a: ^{1}H-NMR (250 MHz): δ = 1.2 (d, J=6Hz, 3H), 2.57 (br s, 1H), 3.66 (quintet, J=6Hz, 1H), 3.97 (br t, J=6Hz, 1H), 4.65 (ABq, ν_{AB}=17Hz, J=12.5Hz, 2H), 4.85 (m, 2H), 5.23 (br d, J=10.4Hz, 1H), 5.38 (br d, J=17Hz, 1H), 5.79-5.96 (m, 1H), 7.23-7.4 (m, 5H).

13b: 1.18 (d, J=6Hz, 3H), 2.57 (br s, 1H), 3.85 (dq, J=3.2,6Hz, 1H), 4.15 (m, 1H), 4.63 (ABq, ν_{AB}=17Hz, J=12.5Hz, 2H), 4.85 (m, 2H), 5.19 (br d, J=10.2Hz, 1H), 5.28 (br d, J=16.3Hz, 1H), 5.78-5.92 (m, 1H), 7.25-7.4 (m, 5H). CI-MS: 223 (M+1, 1.4%), 205 (M-17, 5.4%), 91 ($C_7H_7^+$, base). IR (neat): 3450 (s), 3095 (m), 3082 (m), 2990 (s), 2895 (s), 1100 (s), 990 (s) cm^{-1}.

(4S,3S)- and (4S,3R)-4-benzyloxy-3-hydroxy-1-pentene, **15a,b**

15a: ^{1}H-NMR (250 MHz, C_6D_6, relative to Me_2CO): δ = 1.12 (d, J=6Hz, 3H), 2.66 (br s, 1H), 3.35 (quintet, J=6Hz, 1H), 4.07 (br t, J=6Hz, 1H), 4.40 (ABq, ν_{AB}=26Hz, J=11.9Hz, 2H), 5.20 (br d, J=10Hz, 1H), 5.45 (br d, J=16.7Hz, 1H), 5.86-6.00 (m, 1H), 7.16-7.40 (m, 5H).

15b: 1.18 (d, J=6Hz, 3H), 2.66 (br s, 1H), 3.45 (m, 1H), 4.07 (br t, J=6Hz, 1H), 4.42 (ABq, ν_{AB}=26Hz, J=11.9Hz, 2H), 5.20 (br d, J=10Hz, 1H), 5.45 (br d, J=16.7Hz, 1H), 5.86-6.00 (m, 1H), 7.16-7.40 (m, 5H). CI-MS: 193 (M+1, 11.5%), 91 ($C_7H_7^+$, base). IR (neat): 3440 (s), 3090 (w), 3030 (m), 2980 (s), 1185 (s), 990 (s) cm^{-1}.

(3S,4S)- and (3R,4S)-3-hydroxy-4-(methoxyethoxymethyl)-1-pentene **14a,b**

14a: ^{1}H-NMR (250 MHz, C_6H_6): δ = 1.06 (d, J=6.2Hz, 3H), 3.11 (s, 3H), 3.28 (t, J=6Hz, 2H), 3.45-3.65 (m, 5H), 4.0 (br t, J=6Hz, 1H), 4.58 (s, 2H), 5.11 (br d, J=9.2Hz, 1H), 5.4 (br d, J=16.6Hz, 1H), 5.76-5.91 (m, 1H).

14b: 1.12 (d, J=6.2Hz, 3H), 3.09 (s, 3H), 3.25 (t, J=6Hz, 2H), 3.51-3.71 (m, 5H), 4.22 (br m, 1H), 4.56 (s, 2H), 5.13 (br d, J=9.2Hz, 1H), 5.42 (br d, J=16.6Hz, 1H), 5.82-5.97 (m, 1H). CI-MS: 191 (M+1, 3.4%), 89 (M-101, base). IR ($CHCl_3$): 3470 (s), 3080 (w), 3030 (w), 2980 (s), 1130 (s), 1110 (s), 1040 (s) cm^{-1}.

(5S,4R)- and (5S,4S)-5-(benzyloxymethyl)-4-hydroxy-2-hexyne, **24a,b** via lithium methylacetylide

Approximately 5 ml of propyne was condensed into a flask at -78°C, then diluted with 4 ml of THF. To this solution was added 0.67 ml (1.46 mmol) of 2.18N n-BuLi over ca. 1 minute; the resulting cloudy white solution was stirred for 30 minutes at -78°. To the lithium acetylide mixture was added 0.120g (0.73 mmol) of **10** in 4.0 ml of THF over 3 minutes. The reaction was monitored by capillary GC (methyl-silicone column) and after 3.5 hours at -78°C, only 7% conversion was observed. The reaction mixture was then warmed slowly to room temperature (3.5 hours), then let stir an additional hour. The mixture was cast into 50 ml of 1:1

ether/saturated NH_4Cl solution; the organic layer was separated and washed with brine (25 ml) then dried (Na_2SO_4). Concentration *in vacuo* yielded 99.0 mg of a crude yellow oil which contained a 67% yield of **24a,b** as shown by GC analysis.

24a: ^{1}H-NMR (250 MHz): δ = 1.28 (d, J=7Hz, 3H), 1.82 (d, J=2.8Hz, 3H), 2.80 (br d, J=4.9Hz, 1H), 3.77 (quintet, J=7Hz, 1H), 4.2 (m, 1H), 4.65 (ABq, ν_{AB}=14.8Hz, J=11.5Hz, 2H), 4.79-4.9 (m, 2H), 7.27-7.36 (m, 5H).

24b: 1.25 (d, J=7.0Hz, 3H), 1.85 (d, J=7.8Hz, 3H), 3.25 (br d, J=8.8Hz, 1H), 3.82 (m, 1H), 4.31 (m, 1H), 4.68 (ABq, ν_{AB}=53Hz, J=11.5Hz, 2H), 4.79-4.9 (m, 2H), 7.27-7.36 (m, 5H). CI-MS: 235 (M+1, 0.6%), 217 (M-17, 1.3%), 91 ($C_7H_7^+$, base). IR ($CHCl_3$): 3440 (m), 3070 (m), 3040 (m), 2980 (m), 2230 (w), 1040 (s), cm^{-1}.

24a,b via 1:1 $ZnCl_2$-Li-C≡C-CH_3

In a procedure analogous to that employed for the Zn mediated vinyl additions, 2 mmol of $CH_3C{\equiv}C$-Li (5 ml of a 0.40 M THF solution) was added to 0.270g (2 mmol) of $ZnCl_2$ in 5 ml of THF at 0° over a two-minute period. Stirring was continued for 30 minutes, after which time 0.164g (1 mmol) of **10** in one ml of THF was added, all in one portion. Stirring was maintained for five hours at 0°C, then continued at room temperature overnight. The reaction mixture was cast into ether/saturated aqueous NH_4Cl (50 ml, 1:1). The organic layer was separated and washed with brine

(50 ml) and dried (Na_2SO_4). Concentration *in vacuo* yielded 0.189g (93%) of a yellow oil, shown to consist (GC/^{1}H-NMR) of **24b** and **24a** in a ca. 1.65:1 ratio.

24a,b via 2:1 $CH_3-C\equiv C-Li/ZnCl_2$

The procedure and conditions employed were identical to those of the preceding reaction. Addition of 0.164g (1 mmol) of **10** to a 4 mmol:2 mmol mixture of lithium methylacetylide and zinc chloride yielded 0.176g (86%) of a yellow oil shown to consist (GC/^{1}H-NMR) of **24b** and **24a** in a 1.1:1 ratio.

24a,b via $Zn(BH_4)_2$ reduction of ynone **25**

To 30.1mg (0.15 mmol) of **25** in 4 ml of dry ether, cooled to -78°C, was added 2.5 ml of 0.18M $Zn(BH_4)_2$[35] in ether (0.45 mmol) over five minutes. After stirring for one hour at -78°, the reaction mixture was warmed to room temperature then cast into 1:1 ether/saturated NH_4Cl (50 ml), the aqueous layer was separated and extracted with ether (3 x 25 ml). The organic phases were combined and washed with saturated aq. $NaHCO_3$ (50 ml), brine (50 ml), and dried (Na_2SO_4). Concentration *in vacuo* yielded 31 mg of a cloudy white oil. Chromatography (10 mm, 2:1 ether/hexane, 10g) yielded 13.8 mg (45%) of **24a** and diastereomer **24b** in a 6.3:1 ratio (^{1}H-NMR).

(2S)-benzyloxymethyl-hex-4-yn-3-one, **25**

According to the procedure for **10**, Swern oxidation[36] of **24a,b** (0.147g, 0.72 mmol) yielded 0.134g (92%) of **25** as a pale yellow oil.

^{1}H-NMR (60 MHz): δ = 1.4 (d, J=7Hz, 3H), 2.0 (s, 3H), 4.29 (q, J=7Hz, 1H), 4.65 (s, 2H), 4.8 (s, 2H), 7.3 (br s, 5H). EI-MS (70eV): 165 (M-67, 0.15%), 107 ($C_7H_7O^+$, 28%), 91 ($C_7H_7^+$, base). IR (neat): 3090 (m), 3060 (m), 2980 (s), 2218 (s), 1675 (s), 1040 (s) cm^{-1}.

(4S,3S)-4-benzyloxymethyl-pent-1-en-3-(tributylstannylmethyl)-ether, **26a**

To 0.250g (6.25 mmol) of KH (23.6% in oil), washed 3 times with pentane, then suspended in 25 ml of dry THF was added 1.11g (5.0 mmol) of **13a** (which contained 4% **13b** by GC analysis) in 10 ml of THF over 1 hour. The stirring was continued for 1 hour at room temperature, then 0.55g (2.08 mmol) of 18-crown-6 was added, followed by a slow addition of 2.37g (5.5 mmol) of iodomethyltributylstannane in 10 ml THF. Stirring was continued at room temperature for 4.0 hours; the reaction mixture was then carefully decanted into 300 ml of 20:19:1 saturated NH_4Cl/hexane/ether. The organic phase was separated, washed with saturated brine (100 ml) and dried (Na_2SO_4). Concentration *in vacuo* provided a crude product which was purified by flash[37] chromatography (15:1

hexane/ether) yielding 1.35g (52%) of **26a** as a colorless oil.

^{1}H-NMR (60 MHz): δ = 0.8-1.7 (m, 30H), 3.35-3.9 (m, 4H), 4.60 (s, 2H), 4.75 (s, 2H), 5.5-5.8 (m, 3H), 7.28 (br s, 5H). CI-MS: 469 (M-57, 3%, for ^{120}Sn), 467 (M-57, 2.5%, for ^{118}Sn), 91 ($C_7H_7^+$, base). IR (neat): 3035 (w), 3018 (w), 2980 (s), 1645 (m), 1585 (m), 1105 (s), 695 (m) cm^{-1}.

E- and Z-(5S)-benzyloxymethyl-hex-3-en-1-ol, **27a,b**

To allyl stannyl methyl ether **26a** (0.262g, 0.5 mmol) in 15 ml of dry hexane, cooled to -78° (CO_2/acetone) was added 0.4 ml (1.0 mmol) of n-BuLi (2.5M/hexane) over a two-minute period. Stirring was continued for 1 hour at -78°, after which time the reaction mixture was slowly warmed to room temperature and quenched by casting into saturated NH_4Cl/ether (100 ml, 50:50). The organic phase was separated and washed with saturated $NaHCO_3$ (50 ml), brine (50 ml), and dried (Na_2SO_4). Concentration *in vacuo* yielded 0.240g of a biphase oil. Purification by flash chromatography (1:1 hexane/ether) yielded 67.5 mg (57%) of a 3.5:1 Z/E mixture of **27**.

^{1}H-NMR (250 MHz): δ = 1.20 (d, J=6.2Hz, 3H), 1.85 (br s, 1H), 1.93-2.2 (m, 2H), 3.40 (br t, J=7Hz, 2H), 4.55 (ABq, ν_{AB}=24Hz, J=5.9Hz, 2H), 5.3-5.46 (m, 2H), 7.0-7.35 (m, 5H). CI-MS: 107 ($C_7H_7O^+$, 10%), 99 (M-137, base), 91 ($C_7H_7^+$, 61%). IR (neat): 3410 (s), 3060 (w), 3020 (w), 2980 (s), 2940 (s),

1100 (s) cm^{-1}. ^{13}C-NMR (C_6D_6): δ = Z-**27a**: 21.7, 31.5, 61.9, 67.4, 69.3, 91.7, 129.3, 133.8, 138.7; E-**27b**: 21.7, 36.0, 61.9, 67.4, 73.2, 91.7, 129.5, 134.4, 138.7 (some aromatic signals obscured by solvent).

(I)-3-benzyloxymethyl-1-butyne, **28**

Following the procedure described for preparation of **16**, 3.50g (0.050 mol) of (±)-1-butyne-3-ol was treated with 10.92g (0.070 mol) of benzyloxymethyl chloride yielding 6.91g (77%) of **28**, $BP_{0.25}$ 84-91°C.
^1H-NMR (60 MHz): δ = 1.4 (d, J=7Hz, 3H), 2.4 (d, J=2Hz, 1H), 4.60 (dq, J=2,7Hz, 1H), 4.82 (ABq, ν_{AB}=20Hz, J=14Hz, 2H), 5.22 (s, 2H), 7.3 (br s, 5H).

(±)-5-benzyloxymethyl-hex-3-yn-1-ol **29**

1.90g (0.010 mol) of **28** in 20 ml of dry THF was cooled to -78°. 4.6 ml (10 mmol) of 2.18N n-BuLi/hexane was added over 5 minutes; stirring was continued for 15 minutes, after which time, 1.33 ml $BF_3 \cdot OEt_2$[38] was slowly added, stirring was continued for 10 minutes. Ca. 40 ml of ethylene oxide was introduced to the reaction vessel over a 15 minute period. The mixture was stirred at -78° for 45 minutes, then warmed to room temperature. Removal of excess ethylene oxide was facilitated by partial evacuation of the reaction vessel with aspirator suction for ca. 10 minutes. The mixture was subsequently cast into 1N NH_4Cl, and filtered through a pad of celite. The celite pad was rinsed (100 ml

Ethyl acetate); and the organic phase was separated and washed with saturated $NaHCO_3$ (50 ml), saturated brine (50 ml) and dried (Na_2SO_4). Concentration *in vacuo* yielded 11.69g of a milky fluid. Flash chromatography (2 times), (6:4 hexane/ethyl acetate) of a portion of this material (3.35g) yielded 104 mg of a clear oil shown by GC analysis to consist of 80% **29** (12% yield).

^{1}H-NMR (60 MHz): δ = 1.42 (d, J=7Hz, 3H), 2.43 (dt, J=2,7Hz, 2H), 2.64 (br s, 1H), 3.61 (t, J=7Hz, 2H), 4.3-4.7 (m, 1H), 4.6 (s, 2H), 4.85 (ABq, ν_{AB}=18Hz, J=9Hz, 2H), 7.3 (br s, 5H). Impurity Peaks[28]: δ = 1.8-1.6 (m, 1.5H), 3.6-3.35 (3H). EI-MS (70eV): 234 (M^+, 0.1%), 91 ($C_7H_7^+$, 37%), 40 (M-194, base). IR (neat): 3430 (s), 2980 (m), 2940 (s), 2960 (s), 2238 (w), 1100 (s), 1035 (s) cm^{-1}.

Z-(±)-benzyloxymethyl-hex-3-en-1-ol, **27a**

In a procedure similar to that employed by Cram and Allinger[39], 104 mg (0.43 mmol) of **29** was semi-hydrogenated (2 mg, 5%, Pd-$BaSO_4$, 2 mg quinoline, 10 ml methanol, 1.5 atm.H_2, 45 minutes). Workup was effected by filtration through a pad of celite, concentration of the filtrate *in vacuo*, and redissolution of the crude product in ether (20 ml). This ethereal solution was washed (2 x 20 ml) with saturated NH_4Cl solution and dried (Na_2SO_4). Concentration *in vacuo* yielded a yellow oil which was purified by flash chromatography (65:35 ether/hexane) yielding 43 mg (41%) of

I-Z-**27a**, spectroscopically identical to Z-**27a** obtained via [2,3] rearrangement of **26a**.

4-methyl-pen-1-en-3-ol **30**

To 0.020 mol of vinyl magnesium bromide in 25 ml of THF at 0°C was added 0.72g (0.010 mol) of isobutyraldehyde in 5 ml of THF over 5 minutes. Stirring was continued for 1 hour at the end of which time the mixture was cast into 1:1 ether/saturated NH_4Cl (50 ml). The aqueous layer was extracted with ether (2 x 25 ml) and the combined organic phases washed with brine (50 ml) and dried (Na_2SO_4). After concentration *in vacuo*, Kugelrohr distillation (120°, 760mmHg) afforded 0.433g (43%) of **30**.
^{1}H-NMR (60 MHz): δ = 0.90 (d, J=6Hz, 6H), 1.75 (s, 1H), 1.3-1.8 (m, 1H), 3.84 (m, 1H), 5.0-5.4 (m, 2H), 5.6-6.2 (m, 1H). EI-MS (70eV): 100 (M^+, 7.1%), 83 (M-17, base), 82 (m-18, 54%). IR (neat): 3380 (s), 3080 (m), 2965 (s), 2880 (s), 1470 (m), 1385 (m), 990 (s) cm^{-1}.

(±)-4-methyl-pent-1-en-3-(tributylstannylmethyl) ether, **31**

Following the procedure for **26a**, 1.72g (17.2 mmol) of **30** was treated with 8.14g (18.9 mmol) of iodomethyltributylstannane, yielding 7.23g of a pale green oil. Purification by flash chromatography (hexane, 2.15g of crude employed) afforded 2.08g (87%) of **31** as a colorless oil.

^{1}H-NMR (60 MHz): δ = 0.8-2.0 (m, 34H), 3.1 (br t, J=6Hz, 1H), 3.62 (ABq, ν_{AB}=24Hz, J=10Hz, 2H), 5.0-6.0 (m, 3H). EI-MS (70eV): 347 (M-57, 5.1% for ^{120}Sn), 345 (M-57, 3.8%, ^{118}Sn), 177 (M-267, base). IR (neat): 3077 (w), 2960 (s), 2920 (s), 1585 (s), 1050 (s), 992 (m) cm^{-1}.

Z- and E-5-methyl-hex-en-1-ol **32**

Following the procedure for **27a,b**, 0.449g (1.1 mmol) of **31** was treated with 0.82 ml (2.2 mmol) of nBuLi (2.5M/hexane) to provide a pale yellow oil after workup. Flash chromatography (pentane-ether, 2:1) afforded 15.1 mg (12%) of E- and Z-**32** in a 1:2 ratio as shown by a ^{1}H-NMR shift reagent study.

^{1}H-NMR (250 MHz, C_6D_6): δ = 0.93 (major isomer, d, J=6.1Hz, 6H), 0.90 (minor isomer, d, J=6.1Hz, 6H), 2.0-2.15 (m, 2H), 2.42-2.56 (m, 1H), 3.30-3.42 (m, 2H), 5.12-5.41 (m, 2H). CI-MS: 114 (M^+, 2.2%), 96 (M-18, 63%), 81 (M-33, base). IR (neat): 3350 (s), 3008 (m), 2960 (s), 2935 (s), 1465 (s), 1380 (m), 1045 (s) cm^{-1}.

Attempted Wittig Rearrangement of **26a** in CH_2Cl_2

Following the procedure employed for rearrangement of **26a** in hexane, treatment of **26a** with 2 equivalents of n-BuLi in CH_2Cl_2 failed to provide a rearrangement product with 94% recovery of **26a** as realized by TLC and NMR data.

(2S)-benzyloxymethyl)-pent-1-en-3-one 34

Follwing the procedure employed for Swern oxidation of 19, 2.02g (9.1 mmol) of 13 was converted to the desired enone 34 (0.30g, 15%) after isolation by flash chromatography (hexane-ethyl acetate, 10:1).
^{1}H-NMR (80 MHz, C_6D_6): δ = 1.15 (d, J=8Hz, 3H), 4.12 (q, J=8Hz, 1H), 4.4 (s, 2H), 4.5 (s, 2H), 5.1-5.3 (m, 1H), 6.6-6.2 (m, 2H), 7.1 (br s, 5H). CI-MS: 221 (M+1, 0.84%), 113 (M-107, 39%), 91 ($C_7H_7^+$, base). IR (neat): 3100 (m), 3035 (m), 2980 (m), 2940 (m), 1700 (s), 1107 (s), 1030 (s) cm^{-1}.

(4S,3R)- and (4S,3S)-4-benzyloxymethyl-3-hydroxy-1-pentene, 13b,a

To 0.134g (0.61 mmol) of 34 in 15 ml of dry ether, cooled to -22° (CO_2, CCl_4), was added slowly 1.2 ml of ethereal 0.17M $Zn(BH_4)_2$. After the addition was complete, stirring was continued for 25 minutes, then the reaction mixture was cast into 75 ml of 1:1 ether-H_2O. The aqueous layer was drawn off and acidified to pH 3 and extracted (2 x 25 ml) with ether. The ether fractions were combined, washed with brine (50 ml) and dried ($MgSO_4$). Concentration *in vacuo* yielded 0.133g (98%) of 13b and 13a in a 7:1 ratio (GC, carbowax column). ^{1}H-NMR data compared identically with that of 13a,b obtained from vinyl addition to 10.

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