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CHIRAL EPOXIDES AS PRECURSORS OF CHIRAL ALLENES

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Summary: We have applied the Sharpless asymmetric epoxidation to allylic alcohols containing a conjugated alkyne. Reaction of dialkyl metallic cuprates with the resulting alkynyl epoxyalcohols gives dihydroxy allenes of high chiral purity. The stereochemistry of the reaction was shown to be exclusively anti when sulfide is present.

The synthesis of chiral allenes is most often effected by SN2' reaction of organometallics with chiral propargylic esters.[1] The stereochemistry of the reaction is reported to be exclusively anti but products of both syn and anti attack are often encountered.[2] Vermeer[3] has recently shown that the apparent lack of stereospecificity in the conversion of propargylic esters to allenes by organocuprates could be due to organocuprate-induced isomerization of the product allenes. It is also reasonable to expect that the stereospecificity of the propargyl ester→allene reaction should vary with the tightness of the transition state. The latter should increase for those propargyl substituents that are poor leaving groups. If leaving groups contain anion stabilizing functions (e.g. C=O, S→O) little effect on stereoselectivity is observed.[4]

Conversion of α-alkynyl epoxides to hydroxy allenes (stereochemistry unknown) occurs with a variety of organometallics.[5] Because of the lack of anion stabilizing groups and the retention of the epoxidic carbon in the allene product, we suspected SN2' rearrangements of these propargyl derivatives should be highly stereoselective.

We have applied the Sharpless asymmetric epoxidation[6] to allylic alcohols containing a conjugated alkyne. This leads to the formation of alkynyl epoxyalcohols (eg. 1→2) with high ee.[7]

Reaction of excess dialkyl magnesium or lithium cuprates with the unprotected alkynyl epoxyalcohols gives diastereomeric dihydroxy allenes which may be differentiated by 400 MHz ^{1}H n.m.r. of the corresponding diacetoxy derivatives. Thus reaction of (-) 2 ($[\alpha]_D^{25}$ -10.3°; c=1.6,$CHCl_3$) with dioctyl magnesium cuprate gave (4) after acetylation of the product (Table 1, Entry 1). The resonances of the diastereotopic hydrogens on C_1 of 4 were each exhibited as quartets in C_6D_6 solvent ($\delta_{A_{syn}}$= 4.17, $\delta_{A_{anti}}$=4.08, J_{AC}=7.5 Hz, J_{AB}= 12 Hz; $\delta_{B_{syn}}$ =5.23, $\delta_{B_{anti}}$=5.24, J_{BC}=3.5 Hz, J_{AB}=12 Hz).

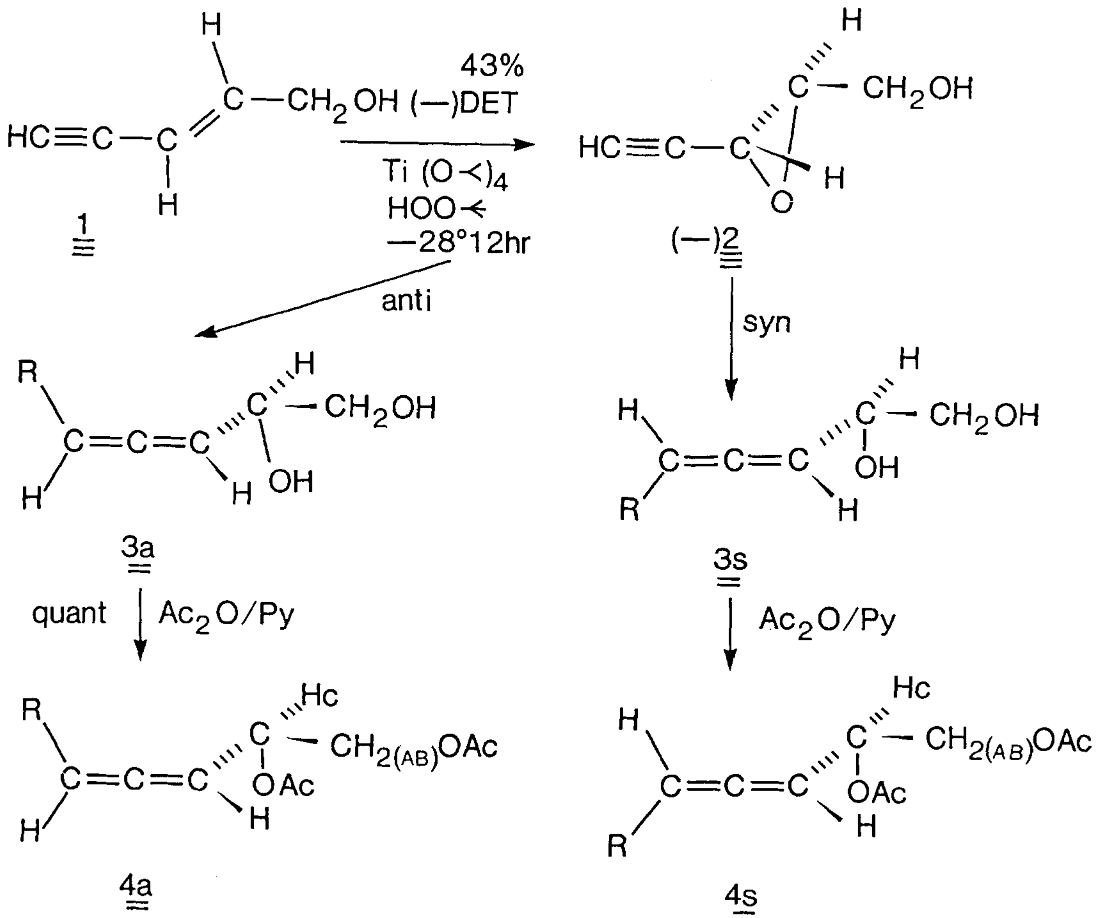


Table 1. Reaction of 2 with Dialkyl Metallic Cuprates in Et_2O[a]

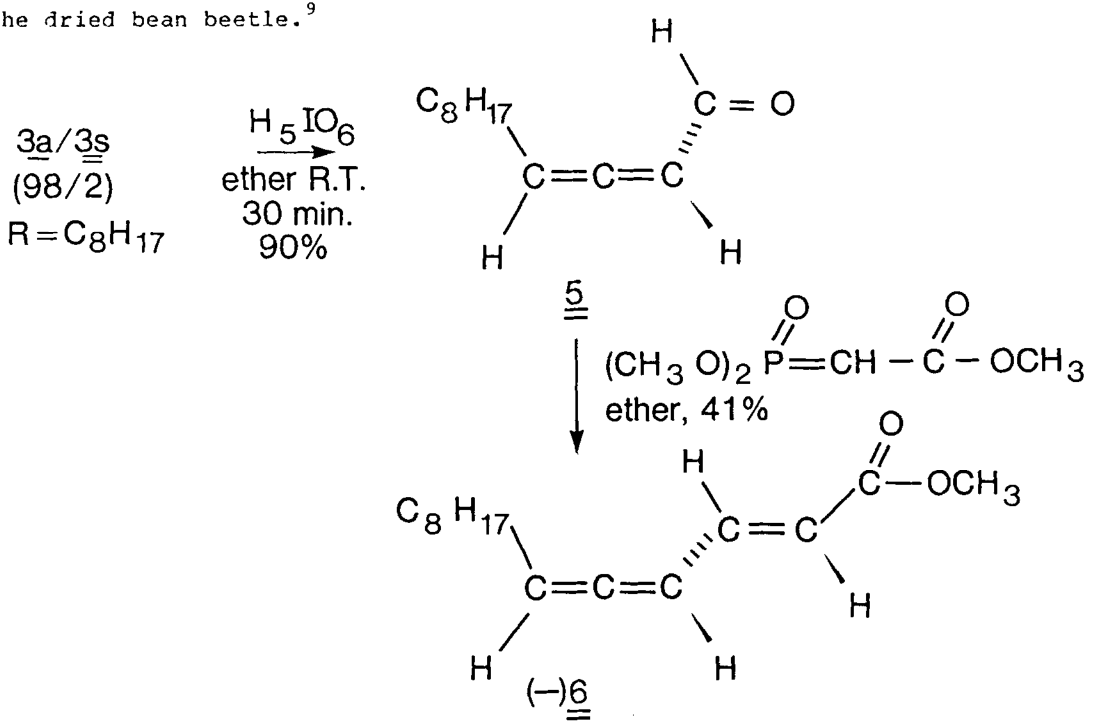
Entry	Reagent	Time(h)	Temp(°C)	Syn/Anti[b]	Yield[c]
1	$(C_8H_{17})_2CuMgBr$	0.5	30-35	60/40	50
2	$(C_4H_9)_2CuLi$	0.5	-60	27/73	63
3	$(C_4H_9)_2CuLi(CH_3)_2S$	1.0	-60	6/94	53
4	$(C_4H_9)_2CuMgBr(CH_3)_2S$	1.5	-60	1/99	68
5	$(C_8H_{17})_2CuMgBr(CH_3)_2S$	1.5	-60	2/98	57
6	$(C_8H_{17})_2CuMgBr(CH_3)_2S$	0.5	-60	4/96	50
7	$(C_8H_{17})_2CuMgBr(CH_3)_2S$	0.5	-30	4/96	52

[a] Reaction conducted by adding 1.1 eq. of CuI to 2.5 eq. of alkyl magnesium bromide or alkyl lithium in ether followed by addition of the epoxide in ether. Alternatively, CuI was replaced by 1.1 eq. of $CuBr{\cdot}(CH_3)_2S$ in ether:$(CH_3)_2S$ (3:2 v/v).

[b] Syn/Anti ratios were determined by g.l.p.c. analysis of 4a and 4s on a 15 m × 0.25 mm Durabond DB1 fused silica column.

[c] Yield of 3 after chromatography on silica gel using hexane:ethyl acetate, 4:1 v/v as eluant.

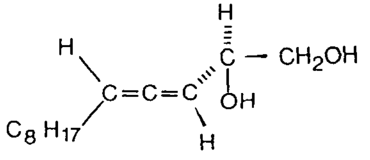
The major diastereomer was assigned to the product of anti attack by conversion of the diastereomeric mixture of diols from Entry 5 (Table 1) to 6 for which the absolute configuration is known.[8] Thus diol mixture 3a,b ($R=C_8H_{17}$, $[\alpha]_D^{25}$-67.4°, c=0.9, hexane) was oxidized with periodic acid in ether to 5 (unstable). Aldehyde 5 was converted without prior purification to 6 ($[\alpha]_D^{25}$-79.5, c=1.1, hexane) with trimethylphosphonoacetate. The estimated ee of 6 was 62% based on the maximum reported[8] rotation for 6 the sex pheromone of the dried bean beetle.[9]



It can be seen from Table 1 that the reaction of 2 with organocuprates gives nearly exclusive anti product when $(CH_3)_2S$ is present but mixtures of syn and anti product in its absence.

Organocuprates cause isomerization of allenes, probably via electron transfer.[3] We found (Table 2) that $(CH_3)_2S$ slows this process.

Table 2. Isomerization of 3a:3s (98:2) by Dibutyl Lithium Cuprate with and without added $(CH_3)_2S$.



3s/3a (Entry 5, Table 1)
syn/anti
2 98

		syn/anti[a]
$(C_4H_9)_2CuLi\cdot(CH_3)_2S$		
2 h, -60°, Et_2O	→	2/98
2 h, -20°, Et_2O	→	9/91
$(C_4H_9)_2CuLi$		
2 h, -60°, Et_2O	→	7/93
2 h, -20°, Et_2O	→	27/73

[a] Ratio of 4s:4a determined by g.l.p.c. as above.

A report of the full details of this investigation is in preparation.

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7. The enantiomeric excess of (-) 2 was determined by 400 ^{1}H n.m.r. analysis of the (+) α-methoxy-α-trifluoromethylphenylacetate.
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9. We assume that epimerization occurred in the conversion of 3 to 5 since reduction of 5 to the corresponding alcohol with $NaBH_4$ followed by derivatization with (+)-α-methoxy-α-trifluoromethylphenylacetyl chloride gave a mixture of diastereoisomeric esters as judged from 400 MHz ^{1}H n.m.r.

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