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VANADIUM-CATALYZED EPOXIDATIONS. I.
A NEW SELECTIVITY PATTERN FOR ACYCLIC ALLYLIC ALCOHOLS.

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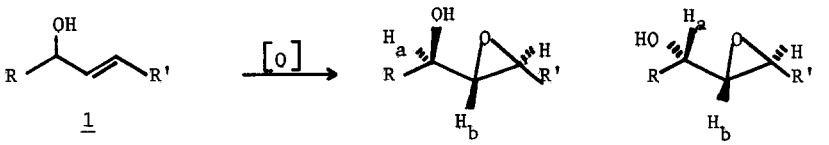
Summary: Vanadium-catalyzed epoxidation of secondary E-allylic alcohols shows opposite stereospecificity to peracid and molybdenum-catalyzed systems.

Extensive interest has been generated in recent years in the development of techniques to selectively introduce chiral centers on acyclic carbon chains. Epoxidations of olefinic alcohols are especially important in this class of reactions for both peracid[1] and metal-catalyzed[2] methods have been shown to display a high degree of selectivity in a number of acyclic cases.[3] In particular the exceptional promise of vanadium-catalyzed epoxidations has drawn much attention. The successful application of this methodology to the stereocontrolled total synthesis of dl-C_{18} *Cecropia* juvenile hormone[2b] and the polyether antibiotic lasalocid A,[4] among others, bears testimony to synthetic chemists' rapid acceptance of this very efficient oxidation reaction. In light of this high degree of interest, it is surprising that few systematic studies of the stereospecificity of this asymmetric synthesis have been reported.[5,6] We describe herein our results on the peracid and metal-catalyzed epoxidations of acyclic secondary E-allylic alcohols (1).

Our studies were initiated by the observation that the alcohol mixture 1a, when treated with $Bu^tOOH/VO(acac)_2$ in toluene, afforded a 2:1 *erythro/threo* mixture of epoxy alcohols 2a.[7]

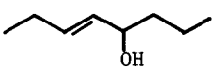
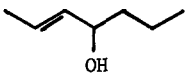
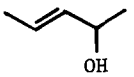
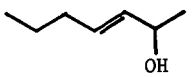
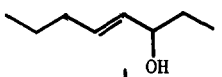
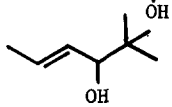


1 *threo*-2 *erythro*-2

1a: R = $(CH_2)_7CO_2CH_3$, R' = $(CH_2)_6CH_3$; and
R = $(CH_2)_7CH_3$, R' = $(CH_2)_6CO_2CH_3$

Peracid epoxidation gave opposite specificity as did the $Bu^tOOH/Mo(CO)_6$ method (Table). These results sharply contrasted with the reported epoxidation of trans-pent-3-en-2-ol (1d), claimed to give ≥90% threo isomer by both peracid[1] and metal-catalyzed[2b,8] processes. Consequently, we investigated a series of alcohols of this structure (1), including pentenol 1d. Our results (Table) indicate that in every case the erythro isomer predominates in vanadium-promoted epoxidation of 1, whereas peracid and molybdenum-catalyzed conditions yield threo enriched epoxy alcohol.[9] This behavior parallels that observed for medium ring cyclic allylic

TABLE: Epoxidation Stereochemistry of Secondary E-Allylic Alcohols

Olefin[a]		$VO(acac)_2/Bu^tOOH$[b]		MCPBA[c]		$Mo(CO)_6/Bu^tOOH$[d]	
		E[e]	T	E	T	E	T
1a		67	33	38	62	39	61
	(1b)	63	37	34	66	40	60
	(1c)	60	40	33	67	37	63
	(1d)	60	40	31	69	39	61
	(1e)	64	36	30	70	41	59
	(1f)	64	36	32	68	40	60
	(1g)	79(81)[f]	21(19)	44(40)[f]	56(60)	45	55

[a]All reactions were done on 5 mmol olefin in 25 ml solvent. Metal-catalyzed reactions employed 1 mole% catalyst and 1.5 equiv of azeotropically dried hydroperoxide (ca. 1 M in benzene). [b]25°C in toluene. [c]m-Chloroperoxybenzoic acid (1.1 equiv) in methylene chloride at 25°C. [d]60°C in benzene. [e]E = % *erythro*; T = % *threo*. [f]At 0°C.

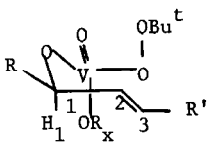
alcohols,[6] but has not been previously reported for acyclic cases. The examples in the table indicate that the vanadium-catalyzed and peracid epoxidations show some variation of specificity with substrate whereas the molybdenum-catalyzed process consistently affords ca. 60:40 *threo/erythro* ratios. The favored formation of the threo isomer in the peracid epoxidation of 1g presented here refutes the previously reported[1,10] exclusive formation of *erythro*-2g and is

significant in terms of the mechanism of peracid epoxidations (*vida infra*). As expected, an increase in asymmetric synthesis was observed as the reaction temperature was lowered (Table, olefin 1g).

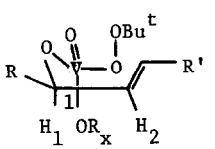
The considerable difficulties encountered in past stereoisomer determinations of this sort prompts us to comment on the methods used in this study. Quantitative isomer ratios were determined by gas chromatographic analysis[11] of the epoxy alcohol mixtures and in those cases where separations were difficult (2a,b,d,e,) the values were confirmed by conversion to the easily resolved acetate derivatives. In all cases, *erythro*-2 had a shorter gc retention time and higher R_f on tlc. Positive isomer identification was facilitated by two distinct characteristics of the ^{1}H NMR spectra: 1) *erythro*-2 invariably displayed J_{ab}=3.25 cps whereas *threo*-2 had $J_{ab} \geq 5.0$ cps, 2) H_a of *erythro*-2 was consistently downfield (δ3.8 $\pm$ 0.1 ppm) from H_a of *threo*-2 (δ3.5 $\pm$ 0.1 ppm). Integration of the H_a absorptions corresponded well to isomer ratios determined by gc. The only exception to these trends was the observation that H_a of *erythro*-2g appeared at δ3.42 (J_{ab}=3.25 cps) with H_a *threo* buried under the epoxy proton absorptions. Pure diastereomers could be obtained from the epoxy alcohol mixtures by medium pressure liquid chromatography.[12] Finally, chemical correlation of 2a to known diols has been reported previously.[7,13]

Although the stereospecificities reported in this work have limited synthetic applicability, we feel that the mechanistic implications of our results are of considerable interest. Preferential formation of *threo*-2 during peracid epoxidation is in accord with Whitham's transition state model[14] which is well established for cyclic allylic alcohols.[6] Recently Pierre et.al. suggested[1] alternate models based largely on their epoxidation of 1g, an assignment shown to be in error by this work. We believe Whitham's model to be fully consistent with observed stereospecificities in both cyclic and acyclic cases and is to be preferred.

We propose that the erythro selectivity of the V^{+5}-catalyzed epoxidations of 1 is consistent with vanadate ester[15] transition states I and II. Steric interactions between OR_x and C_3 in I disfavor this state relative to II, where OR_x is free to rotate past H_1 and H_2 unhindered. Examination of these models predicts erythro selectivity should also be observed for allyl alkyl carbinols (1, R'=H), contrary to reported results.[2b] We have repeated those examples and found the following erythro selectivities: R=Me (65%), R=Et (73%), R=i-Pr (85%). Thus we feel a rational basis is now in hand for determining the direction of asymmetric induction in V^{+5}-promoted epoxidations of acyclic allylic alcohols.



I (gives threo)



II (gives erythro)

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8) The misassignment of erythro as the major isomer[2b] was due to the inaccurate early report of J.-L. Pierre, et.al. [Bull. Soc. Chim. Fr., 1317 (1968)] which was later corrected (ref. 1). We thank Professor Sharpless for bringing this to our attention and for helpful discussions.

9) Professor Sharpless has informed us that they as well have been reinvestigating the epoxidation of 1d and have recently verified our results (see following paper).

10) We have repeated epoxidations of olefins 1d and 1g with p-nitroperoxybenzoic acid and found the same isomer ratios as with MCPBA.

11) We employed 5' x 1/4" 20% SE-30 on 60/80 Chromosorb W in a Varian 202B instrument (TC detector) coupled to a Hewlett Packard 3380A electronic integrator.

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