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(Z)-3-Methyl-3-penten-2-ol as Stereochemical Probe for 1,2 *versus* 1,3 Allylic Strain in the Photooxygenation and Epoxidation of Chiral Allylic Alcohols

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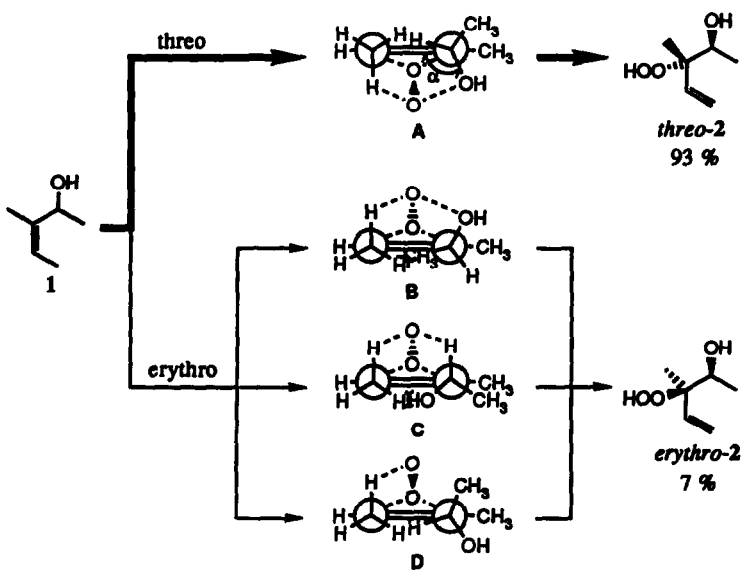
Key Words: Stereochemical Probe, Allylic Strain, Singlet Oxygen, Ene Reaction, Epoxidation.

Abstract: The importance of 1,2 *versus* 1,3 allylic strain in hydroxy-directed reactions can be assessed from reactions of (Z)-3-methyl-3-penten-2-ol, which is demonstrated for the ene reaction of singlet oxygen and the epoxidations by *m*-CPBA and $VO(acac)_2$/*t*-BuOOH; furthermore these results provide insight into transition state geometries for such hydroxy-directed oxygen transfer reactions.

Provided efficient coordination operates between a reagent and the substrate, high diastereoselectivity can be observed through control by allylic strain[1]. Herein we illustrate this mechanistically useful concept in the ene reaction of $^1O_2$ with the chiral allylic alcohol (Z)-3-methyl-3-penten-2-ol (**1**), in which the directing effect of hydroxy coordination[2] and 1,3 allylic strain[1] together are responsible for the large *threo* selectivity (Scheme 1). This is analogous to the stereochemical control established in peracid epoxidations[3], but contrary

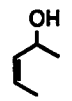
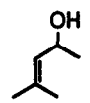
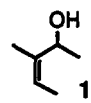


Scheme 1

to the *erythro* preference exercised by $VO(acac)_2$/ *t*-BuOOH[3a,b,4] for which 1,2 allylic strain dominates.

The origin of the stereoselectivities observed for *m*-CPBA and $VO(acac)_2$/*t*-BuOOH derives from coordination of the oxygen-donating reagent with the allylic hydroxy functionality. The stereochemical differentiation is then a consequence of the preferred hydroxy group conformation of the allylic alcohol in the transition state for oxygen transfer. While for the *m*-CPBA epoxidations a C=C-C-O dihedral angle of ca. 120° appears to be optimal[3a,b], for the vanadium-catalyzed reaction an angle of ca. 50° applies[3a,b], to account for the dominating control through 1,3 allylic strain (compare entries 1-3 of column 3 in Table 1) in

Table 1: Stereoselectivities in the Epoxidations and Singlet Oxygen Ene Reactions of Chiral Allylic Alcohols.

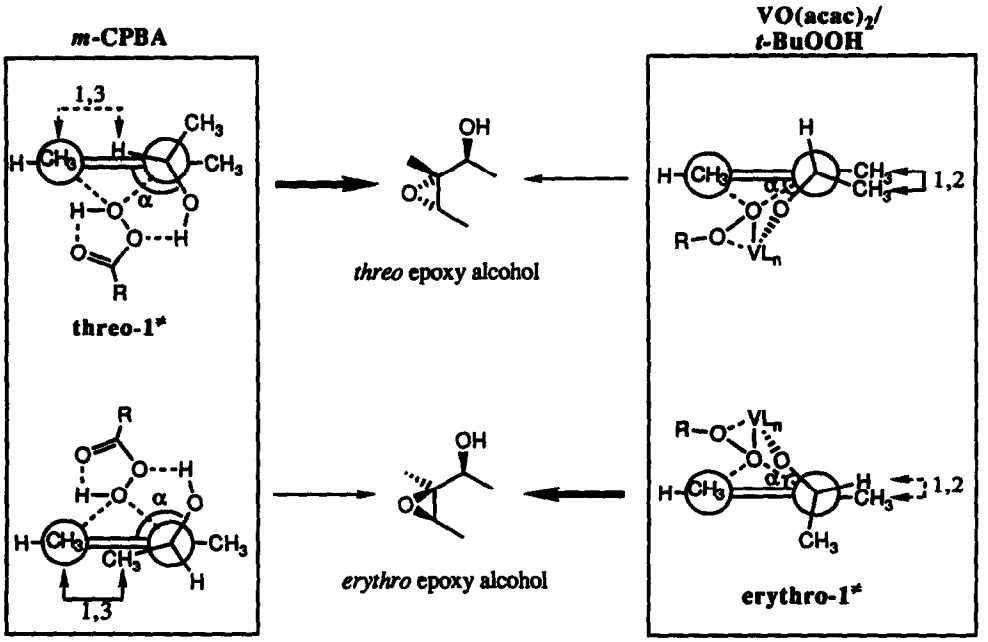
		threo/erythro selectivity		
		epoxidation		ene reaction
		m-CPBA	$VO(acac)_2$/*t*-BuOOH	$^1O_2$
1.		60 : 40[a]	20 : 80[a]	
2.		45 : 55[a]	5 : 95[a]	
3.		95 : 5[a]	71 : 29[a]	93 : 7[a]
4.		95 : 5[a]	86 : 14[a]	93 : 7[b]
5.		90 : 10[c,d]	33 : 67[c,d]	93 : 7[c,e]

[a] from ref. 3a; [b] from ref. 1; [c] conversion > 95 %, error ± 5 of stated value; [d] for conditions cf. ref. 3; [e] 8 % of 3-methylene-pentane-2,4-diol (d.r. 77 : 23) were formed as side products

the former *versus* 1,2 allylic strain (compare entries 1-3 of column 4 in Table 1) in the latter. These arise from substituents located *cis versus gem* with respect to the alkyl group on the hydroxy-bearing chirality center of the allylic alcohol.

The advantage of the allylic alcohol (Z)-3-methyl-3-penten-2-ol[5] (**1**) as substrate is the fact that it possesses both a *cis* methyl group (1,3 allylic strain) and a *gem* methyl group (1,2 allylic strain), which should allow assessing the relative importance of such steric interactions. For the epoxidation reactions in

question, we would expect for *m*-CPBA a preference for the *threo*-$\mathbf{1}^{\neq}$ transition state (Scheme 2; 1,3 allylic



Scheme 2

strain is minimal) to yield mainly the *threo* epoxide and for $VO(acac)_2$/*t*-BuOOH the *erythro*-$\mathbf{1}^{\neq}$ transition state (Scheme 2; 1,2 allylic strain is minimal) should be favoured to afford predominantly the *erythro* epoxide. The utility of this novel stereochemical probe is demonstrated herein for the above epoxidations and the singlet oxygen ene reaction.

The observed diastereoselectivities are given in Table 1. The large difference in the stereoselectivities for the peracid- and vanadium- catalyzed epoxidations is in accord with the above considerations. Thus, as expected on the basis of coordination by the hydroxy group and allylic strain, for the *m*-CPBA epoxidation of the chiral allylic alcohol **1** 1,3 allylic strain dominates, while for the vanadium-catalyzed epoxidation it is the 1,2 allylic strain (entry 5 in Table 1). Nonetheless, that 1,3 allylic interactions can be important for the $VO(acac)_2$/*t*-BuOOH epoxidations is evident for (Z)-3-penten-2-ol and 4-methyl-3-penten-2-ol as substrates (entries 3 and 4 in Table 1), which also proceed with *threo* selectivity. This is not surprising because through the lack of the 3-methyl group in these chiral allylic alcohols, 1,2 allylic strain is minimal and other steric interactions, i. e. 1,3 allylic strain, become significant (compare entries 3-5 of column 4 in Table 1). Similarly, the slight reduction in the *threo* selectivity for the *m*-CPBA epoxidations of (Z)-3-penten-2-ol and 4-methyl-3-penten-2-ol (compare entries 3-5 of column 3 in Table 1) derives presumably from increased 1,2 allylic interaction in the chiral allylic alcohol **1**.

The most valuable feedback of our mechanistic probe is that the stereochemical course of the singlet oxygen ene reaction is qualitatively similar to that of the *m*-CPBA epoxidation, i. e. high *threo* selectivity (entries 3-5 of columns 3 and 5 in Table 1), which suggests that 1,2 and 1,3 allylic strain operate in the same manner for these oxyfunctionalizations. This implies that the preferred geometries of the transition states for both oxygen transfer reactions must be very similar. Since the C=C-C-O dihedral angle (α) for the *m*-CPBA

epoxidation of allylic alcohols is ca. 120° [3a,b], it follows that for the singlet oxygen ene reaction of **1** α should fall in therange 90-130° (transition state A in Scheme 1). Thus, 1,3 allylic strain nicely accounts for the observed *threo* selectivity in the photooxygenation of chiral allylic alcohols, e. g. for **1** d.r. 93 : 7 in favour of the *threo*-**2** diastereomer (Scheme 1).

Less clear-cut is the mechanistic origin of the *erythro*-**2** isomer, the minor ene product with $^1O_2$ of our stereochemical probe **1**. As counterpart for the *threo* case, it would be tempting to postulate transition state **B** (Scheme 1), in which the coordinating effect of the hydroxy group functions as well. However, other plausible alternatives could be structure C (Scheme 1), in which the conventional *cis* effect[6] operates, or structure **D**, for which 1,3 allylic strain is minimal. Our experimental results cannot differentiate between these alternatives, such mechanistic fine-tuning would require theoretical work[1,7].

In summary, the chiral allylic alcohol (Z)-3-methyl-3-penten-2-ol (**1**) serves as a useful stereochemical probe to assess the relative importance of 1,2 (*erythro* selectivity) *versus* 1,3 allylic strain (*threo* selectivity) on the stereochemical course of HO-directed epoxidations and the ene reaction of singlet oxygen. Knowledge of such stereoselectivity should be important in the logical design of appropriate substrates for synthetic applications. Moreover, it is our contention that the chiral allylic alcohol **1** should prove also valuable as stereochemical probe for other reactions in which hydroxy-directing effects are operating.

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