Stereoelectronic Control of the Diastereoselectivity in the Photooxygenation (Schenck Ene Reaction) of an Electron-Poor Allylic Alcohol and Its Ethers

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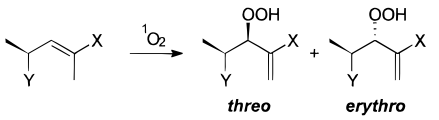
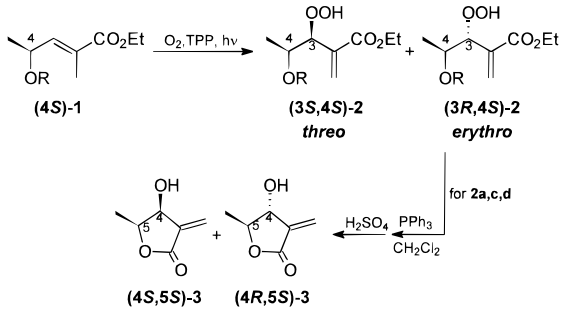
The diastereoselectivity of the Schenck ene reaction (singlet oxygen) has been recently intensively investigated, in which the chiral alkene substrates are conformationally fixed through 1,3-allylic strain ($A^{1,3}$).[1] While electron-poor (X = CO_2Me) and electron-rich olefins (*X* = Me) with alkyl or aryl substituents (Y = Ph, ^{t}Bu) at the stereogenic center afford with singlet oxygen preferentially the *erythro* diastereomeric hydroperoxides (eq 1),[2] electron-rich (*X* = Me, $SnBu_3$; Y = OH, OR, $OSiR_3$) allylic alcohols and their ether derivatives react *threo*-selectively.[3] The highest *threo* control is observed for the free allylic alcohols in nonpolar solvents. The latter *threo* diastereoselectivity was rationalized in terms of irreversible formation of a perepoxide-like intermediate (exciplex), stabilized through intramolecular hydrogen bonding with the allylic hydroxy functionality in the singlet-oxygen complex.[1,4]



(eq 1)

Since for the ene reaction of singlet oxygen with electron-rich versus electron-poor olefins distinct rate-determining steps have been proposed,[1,5] which also has been rationalized theoretically,[6] it was of interest to probe the consequences of such electronic differences on the π-facial selectivity in chiral allylic alcohols. For this purpose, we chose the chiral, electron-poor allylic alcohol **1a** and its ether derivatives **1b**−**d** to assess the importance of intramolecular hydrogen bonding in the singlet oxygen ene reaction of such low-reactive, acyclic substrates, conformationally fixed by means of $A^{1,3}$ strain. Our present results reveal that a novel stereoelectronic effect (Houk model[7]) rather than intramolecular hydrogen bonding or steric congestion determine the diastereoselectivity in these photooxygenations.

Scheme 1. Photooxygenation of the Allylic Alcohol Derivatives (4*S*)-1 and Subsequent Transformation of the Hydroperoxides 2 to the Lactones 3



The synthesis of the known allylic substrates **1a**−**c** followed the literature procedures,[8] and the unknown silyl ether **1d** was prepared from the allylic alcohol **1a** by standard silylation procedures.[9] In the photooxygenations of the substrates **1** the corresponding hydroperoxides **2** are formed quantitatively (Scheme 1, Table 1). The *threo* diastereoselectivities increase with the size of the R substituent in the order H ≈ CH_2Ph < $SiMe_2{}^t$Bu < $Si(^i Pr)_3$ (entries 1 and 3−5). In contrast to the photooxygenation of electron-rich allylic alcohols,[3] the nature of the solvent exerts no significant influence on the diastereoselectivity (entries 1 and 2).

The conformational assignment of the hydroperoxides **2a**,**c**,**d** was achieved by means of chemical correlation (Scheme 1). After reduction by triphenylphosphine and subsequent acid-catalyzed cyclization, the known lactones **3** were obtained.[3d]

The stereochemical results in Table 1 exhibit clearly that the ene reaction of singlet oxygen with these chiral, electron-poor allylic alcohols **1a**−**d** proceeds in all cases *threo*-selectively, regardless of whether the hydroxy functionality is free or masked by alkyl or silyl groups. In contrast, the corresponding olefin with a phenyl substituent (Y = C_6H_5, X = CO_2Me) at the allylic stereogenic center reacts *erythro*-selectively.[2c] Steric effects alone cannot adequately rationalize these conflictive stereochemical results; instead, we propose that Houk's stereoelectronic effect is responsible.[7] The transition state **A** (Figure 1) of the rate-determining hydrogen-atom transfer is favored for **1a**−**d**, in which singlet oxygen abstracts the allylic hydrogen on the π face opposite to the methyl group, while the oxygen functionality resides preferentially in the *outside* position to minimize $A^{1,3}$ strain; consequently, the *threo* product is preferred for these substrates. The transition state **B**, which should apply for purely sterically controlled photooxygenations of olefins (Ph instead of OR) and affords predominantly the *erythro* diastereomer,[2c] is for the allylic alcohol derivatives **1a**−**d** unfavorable, because in this conformation the σ^*(CO)/π interaction removes electron density from the already electron-deficient activated complex.[7] Furthermore, the higher *threo* diastereoselectivity with increasing size of the OR substituent at the allylic site may be accounted for by the fact that transition state **C**, which leads to the *erythro* product, becomes depreciated with increasing $A^{1,3}$ strain.

The unusual lack of a solvent effect on the diastereoselectivity in the photooxygenation of the free alcohol **1a** (Table

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Table 1. Diastereoselectivities in the Photooxygenation of the Chiral, Electron-Poor Allylic Alcohol 1 and Its Ether Derivatives 1b−d

	R	solvent	*T* (°C)	time (h)	convn (%)[a,b]	diastereoselectivity[a] (3*S*,4*S*)-2 : (3*R*,4*S*)-2
1a	H	CCl_4	−5	60	≥95	84 : 16
1a	H	CD_3OD[c]	−7	54	61	86 : 14
1b	CH_2Ph	CCl_4	−10	164	85	83 : 17
1c	$SiMe_2{}^tBu$	CCl_4	−5	160	≥95	93 : 7
1d	$Si(^iPr)_3$	CCl_4	0	120	≥95	≥95 : ≤5

[a] Determined by ^{1}H-NMR analysis directly of the crude product mixture; error ±5% of the stated values. [b] The hydroperoxides **2** were formed quantitatively. [c] Methylene blue as sensitizer, all others tetraphenylporphine (TPP).

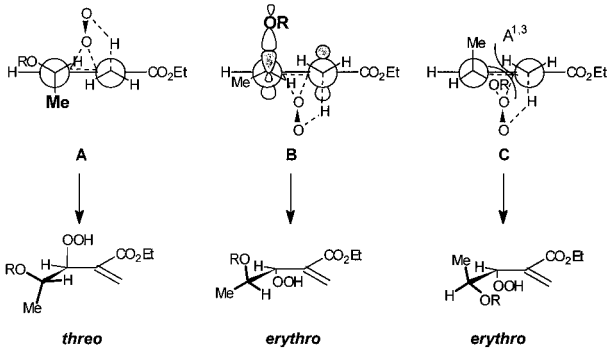


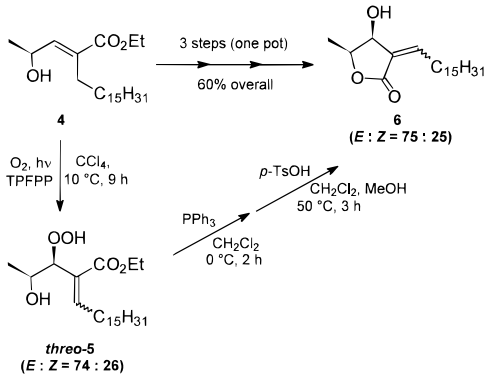
Figure 1. Transition-state geometries **A**−**C** for the rate-determining hydrogen abstraction in the singlet oxygen ene reaction of chiral, electron-poor allylic alcohols.

1, entries 1 and 2) speaks against a strongly polarized transition state stabilized by hydrogen bonding, unlike the situation previously documented for the electron-rich allylic alcohols.[3] This confirms that for electron-poor olefins the perepoxide-structured exciplex intermediate is formed reversibly and not in the rate-determining step (cf. Figure 4b in ref 1). The enhanced reactivity for the free alcohol **1a** compared to the ethers **1b**−**c** (Table 1) originates most likely from steric effects, since the π systems of the bulky ethers **1b**−**d** are less accessible for the attacking singlet oxygen compared to the free alcohol **1a**.

Our present results demonstrate for the first time that the *threo* diastereoselectivity in the singlet oxygen ene reaction of electron-poor allylic alcohol derivatives may be controlled effectively by means of bulky silyl substituents at the allylic oxygen functionality. The steering effect comes about through the synergistic interplay between conformational ($A^{1,3}$) and stereoelectronic [σ^*(CO)/π interactions] factors rather than solely steric influence. This novel *threo*-diastereoselective control applies also to the free alcohol **1a**, rather than intramolecular hydrogen bonding of the allylic hydroxy group with singlet oxygen, as in the case of electron-rich derivatives.[3]

The synthetic value of this for photooxygenations unprecedented stereoelectronic effect is illustrated by the preparation of the enantiomerically pure *dihydromahubanolide B* [(*Z*)-**6**] and *isodihydromahubanolide B* [(*E*)-**6**] in Scheme 2.[10]

Scheme 2. Highly Efficient and *Threo*-Selective Synthesis of Enantiomerically Pure Mahubalactones 6



The photooxygenation [with tetrapentafluorophenylporphine (TPFPP) as sensitizer[11]] of the optically active allylic alcohol **4** [prepared through the Wittig−Horner reaction of optically active ^{t}BuMe$_2$Si-protected lactaldehyde, followed by desilylation] led to a 74:26 *E*/*Z* mixture of the allylic hydroperoxides **5**; reduction by triphenylphosphine and subsequent acid-catalyzed cyclization afforded the desired lactones **6** (*E*:*Z* = 75:25) in 60% overall yield. This sequence constitutes to date the most efficient and convenient synthesis of these natural products in optically pure form.[10]

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Supporting Information Available: Experimental details (22 pages).

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