# Diastereoface-Selective Epoxidations: Dependency on the Reagent Electrophilicity**

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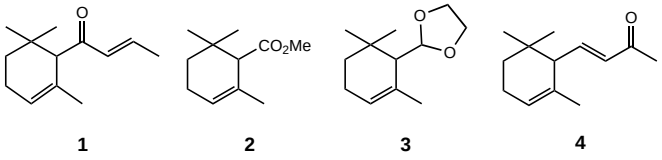
Stereoselective epoxidations have received great attention, as can be judged from the numerous reviews covering the subject.[1] The vast majority of diastereocontrolled epoxidations is based on directing effects that favor the approach of the reagent onto the face containing a polar functional group.[2] In the absence of a steering element, reaction normally takes place on the sterically less hindered side, and conformational analysis is thus essential to predict the π-face selectivity of reactions involving flexible substrates.[3] Mechanistic studies carried out on systems devoid of sterically discriminating groups have evidenced hyperconjugative effects[4] as well as electrostatic (polar) interactions between reagent and substrate as playing a role in the selectivity.[5]

Whereas most of the relevant studies compare substrate reactivities under given conditions, we examined the relationship between the electrophilicity of the reagent (peracid) and the π-facial selectivity for α-damascone (**1**) and six structurally related cyclogeranyl derivatives (**2**–**7**). Remarkably, we

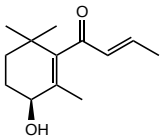



**1** **2** **3** **4**

**5** **6** **7**

found the same trend for all of the cases studied: The stronger the peracid, the higher the *syn* selectivity. These results are rationalized by an increase in the electrostatic interactions between the alkene and the strong peracids, which result from the increased electrostatic potential of the latter.

From a synthetic viewpoint, the diastereocontrolled epoxidation of chiral α-cyclogeranyl systems is of prime importance. Several approaches towards the forskolin[6] and taxane skeleton[7] have taken advantage of this possibility for the construction of the epoxide-cleaved, isomeric alcohol displaying the structural features of (*R*)-**15**. Furthermore, this transformation has proven its usefulness in the synthesis of carotenes,[8] edulanes,[9] strigol,[10] and other terpenoids.[11]

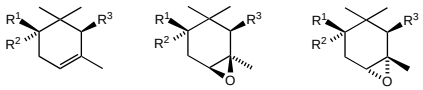



(*R*)-**15**

In the course of this project we became aware of repeated erroneous attributions of epoxide configurations,[6b, 9b, 10b, 11b] in spite of the authoritative work of Eugster.[8] In view of the planned chirality transfer sequence in which (*S*)-**1** is converted into (*R*)-**15**,[12] this stereochemical question is essential.

The known preferential *syn* epoxidation of α-ionone (**4**) with 3-chloroperbenzoic acid (*m*CPBA) in $CHCl_3$ (**11s**/**11a** = 86:14)[8] prompted us to use the same reagent to selectively epoxidize α-damascone (**1**). Whereas *m*CPBA in $CH_2Cl_2$ afforded an 85:15 mixture of epoxy ketones **8s**/**8a** (66:34 in toluene), peracetic acid led to a slightly lower selectivity (80:20 in $CH_2Cl_2$, 58:42 in toluene; Table 1).[13] In contrast, the highly reactive permaleic acid gave rise to a diastereofacial selectivity of 99.3:0.7 (98:2 in toluene) in favor of **8s.** We therefore tested the strongest commonly used peracid, trifluoroperacetic acid, in $CH_2Cl_2$. Even at −50 °C the reaction was very fast and afforded **8s** with excellent diastereofacial selectivity (99.8:0.2) in a yield of 95 %.[14] A net reversal of selectivity was brought about with the system *tert*-butyl hydroperoxide/$[Mo(CO)_6]$:[15] In 1,2-dichloroethane at 70 °C, the *anti*-epoxide **8a** was largely favored (89:11).

Table 1. Ratios of *syn* and *anti* conformers (**8s**–**14s**/**8a**–**14a**) obtained from epoxidation of **1**–**7**.[a]




**1 - 7** **8s - 14s** **8a - 14a**

**1**, **8s**, **8a**, $R^1 = R^2 = H$, $R^3 = (E)$-COCH=CHMe
**2**, **9s**, **9a**, $R^1 = R^2 = H$, $R^3 = COOMe$
**3**, **10s**, **10a**, $R^1 = R^2 = H$, $R^3 = CH(OCH_2)_2$
**4**, **11s**, **11a**, $R^1 = R^2 = H$, $R^3 = (E)$-CH=CHCOMe
**5**, **12s**, **12a**, $R^1 = R^2 = H$, $R^3 = Bu$
**6**, **13s**, **13a**, $R^1 = H$, $R^2 = Me$, $R^3 = COOMe$
**7**, **14s**, **14a**, $R^1 = Me$, $R^2 = H$, $R^3 = COOMe$

| | **1** | **2** | **3** | **4** | **5** | **6** | **7** |
|---|---|---|---|---|---|---|---|
| $CF_3CO_3H$[b] | ***99.8:0.2*** | ***99.5:0.5*** | *100:0* | *95:5* | *96:4* | *100:0* | ***81:19*** |
| permaleic acid[c] | *99.3:0.7* | *97:3* | – | – | – | – | *22:78* |
| *m*CPBA[d] | *85:15* | 79:21 | *94:6* | *85:15* | *84:16* | *94:6* | *6:94* |
| $CH_3CO_3H$[e] | (58:42) | (47:53) | (88:12) | 84:16 | *85:15* | (88:12) | *3:97* |
| *t*$BuO_2H$/ $[Mo(CO)_6]$[f] | **11:89** | **14:86** | (71:29) | (60:40) | 74:26 | (71:29) | **2:98** |

[a] Qualitative rate indications: *fast*, moderate, (slow); [b] $CH_2Cl_2$, $Na_2CO_3$, −50 °C. [c] Maleic anhydride, 70 % aqueous $H_2O_2$; $CH_2Cl_2$, 20 °C. [d] $CH_2Cl_2$, 0–20 °C. [e] Toluene, $Na_2CO_3$, 20–50 °C. [f] $ClCH_2CH_2Cl$, 70 °C.

In view of these fascinating results, we extended our study to substrates **2**–**7**, which were submitted to the same epoxidation reagents. Interestingly, all of the alkenes **1**–**7** follow the same reagent-dependent selectivity trend: The highest *syn* preference is found with trifluoroperacetic acid followed by permaleic acid and *m*CPBA. In comparison, peracetic acid in toluene is less reactive and always affords a higher proportion of the *anti* epoxide. The highest preference for *anti* epoxidation is achieved with *tert*-butyl hydroperoxide in the presence of catalytic amounts of $[Mo(CO)_6]$.

As stated by Eugster, the most stable conformer of α-ionone (**4**) is that with a pseudoaxial side chain (**4pa**), and the

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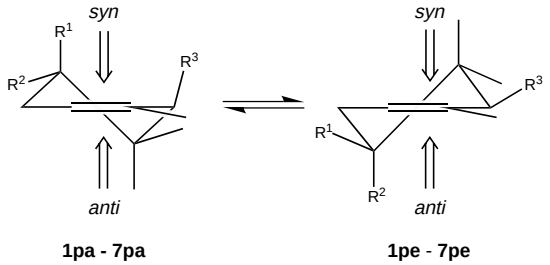
*syn*-selective epoxidation was explained by the fact that the axial methyl group sterically hinders the approach of the peracid from below (*anti*, Scheme 1). This reasoning can

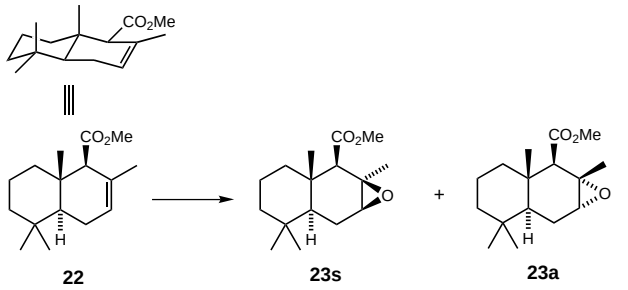



Scheme 1. Conformers of **1**–**7**. $\Delta H$ [kcal mol$^{-1}$] in favor of pseudoaxial conformer (PM3): **1** (1.35), **2** (1.47), **3** (3.18), **4** (0.93), **5** (1.28), and **6** (2.09); in favor of pseudoequatorial conformer: **7** (1.60).

equally be applied to the herein reported epoxidations using *m*CPBA, where both conformers—which are in equilibrium with each other in the case of **1**, **2**, **4**, and **5**—react with great ease. In addition, we can deduce that the pseudoaxial conformers react essentially with *syn* selectivity and the pseudoequatorial conformers with high *anti* selectively, as the observed diastereofacial discriminations approximately parallel the conformational preferences (Table 1). The trends observed by using peracetic acid instead of *m*CPBA are diminished reactivity and decreased *syn* selectivity.[13] Presumably, the more weakly electrophilic peracetic acid is more sensitive to steric factors. As a result, *anti* epoxidations of the pseudoequatorial conformers are faster than *syn* epoxidations of the pseudoaxial conformers. The increased reactivity of **7** relative to its diastereomer **6** (competition experiment) reflects the intrinsic preference of the bis-pseudoequatorial reaction conformer in this system. This trend in favor of *anti* epoxidation is most pronounced with the sterically most demanding Mo-catalyzed epoxidations that lead, for substrates **1** and **2**, to a distinct reversal of diastereofacial selectivity.

Trifluoroperacetic acid is by far the most reactive epoxidation agent and displays an outstanding preference for *syn* epoxidation for all the substrates investigated (followed by permaleic acid). Remarkably, this statement holds even for hydrocarbon **5**, which is devoid of any polar groups that are able to undergo complexation by hydrogen bonding.

The preferential *syn* epoxidation of alkenes **1**–**6**, in which the pseudoaxial conformers dominate, is not surprising. However, the extent of *syn* selectivity in **1** and **2** (>200:1) implies that the pseudoequatorial conformers **1pe** and **2pe** also undergo preferential *syn* epoxidation. Indeed, ester **7**, with a pseudoequatorial groundstate conformation, gives an epoxide mixture that is rich in the *syn* conformer (**14s**:**14a** = 81:19). To confirm the contrasteric reactivity of **7**, the rigid *trans*-decalin derivative **22**[16] with a pseudoequatorial ester group was submitted to epoxidation. Whereas the epoxidation with *m*CPBA affords the *anti* epoxide **23a**,[16] $CF_3CO_3H$ preferentially reacts from the more hindered face (**23s**:**23a** = 82:18). Permaleic acid shows an intermediate reactivity (22:78, Scheme 2).




Scheme 2. Epoxidation of *trans*-decalin derivative **22,** which possesses a pseudoequatorially fixed ester group. *syn*:*anti* = 82:18 (with $CF_3CO_3H$ in $CH_2Cl_2$), 22:78 (with permaleic acid in $CH_2Cl_2$), 5:95[16] (with *m*CPBA in $CH_2Cl_2$), 3:97 (with $CH_3CO_3H$ in toluene).

This result is contrasteric (and probably contraelectronic),[17] but can be rationalized on the basis of the electrostatic interactions, which become important with $CF_3CO_3H$, possessing a very high electrostatic potential (partial positive charge). In these very fast and exothermic reactions, little polarization is required for attaining the early transition state, but the approach of $CF_3CO_3H$ is governed by Coulombic attractions with the more electron-rich $\pi$ face.[18] This reactivity–selectivity relationship is contrary to the commonly accepted principle that a better discrimination between diastereomeric transition states is achieved with a reagent of moderate reactivity.

Houk et al.[5a] have demonstrated that the *syn* additions of strong electrophiles ($AcCl-AlCl_3$ or $:CCl_2$) to isopropylidenebenzonorbornenes result from preassociations between the electrophiles and the aromatic ring, whereas weak electrophiles (for example *m*CPBA or NBS) preferentially react from the opposite side, where polarization is facilitated by involvement of the $\pi$ orbital. The present work compares different electrophiles of the same reaction type and describes for the first time, how electrostatic effects can be exploited for improving the $\pi$-face selectivity of epoxidations.

*syn*-Selective epoxidations of certain pseudoaxially locked alkoxycyclohexenes using $CF_3CO_3H$ have been observed,[14a] but seemed to be limited to special cases. More recently, *m*CPBA has been shown to effect moderate to excellent *syn* epoxidations with various cyclohexenes and cyclopentenes possessing an amide, ester,[2a, b] or ketone[2c] functionality.

To illustrate that our findings are not limited to particular substrate classes, esters **24** and **25** as well as ketone **26** were epoxidized using either $CF_3CO_3H$ or *m*CPBA (Table 2). Because the *anti* epoxides **27a**–**29a** are prone to cleavage reactions in the presence of acids, these epoxidations were performed in aqueous $NaHCO_3/CH_2Cl_2$. Careful analysis by gas chromatography (GC) indicated that the *syn*:*anti* ratios increase during the reaction and isolation. Contrary to the claim of Armstrong et al.,[2c] ketone **26** only exhibits very high *syn* selectivity when $CF_3CO_3H$ is used as the reagent.[19]

*Experimental Section*

(−)-**8s**: A 70 % aqueous solution of $H_2O_2$ (1.62 g, 33.4 mmol) was added to a solution of $(CF_3CO)_2O$ (14.8 g, 9.9 mL, 70 mmol) in $CH_2Cl_2$ (25 mL) at 0 °C. After 30 min this solution was added dropwise to a suspension of (*S*)-(−)-**1** (99 % *ee*)[20] (4.80 g, 25.0 mmol) and $Na_2CO_3$ (7.80 g, 75.0 mmol) in

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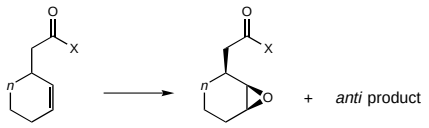
Table 2. Epoxidation of olefinic esters **24** and **25** as well as ketone **26** and comparison with literature results.




**24 - 26** **27s - 29s** **27a - 29a**

| | *n* | X | Peracid | *syn*:*anti* (yied [%]) |
|---|---|---|---|---|
| **24** | – | OMe | $CF_3CO_3H$ | 94:6[a] |
| | | | $CF_3CO_3H$ | 100:0 (84)[b] |
| | | | *m*CPBA | 78:22 (91)[a, b] (X = *i*Pr: 3:1[2b]) |
| **25** | $CH_2$ | OMe | $CF_3CO_3H$ | 96:4[a] |
| | | | $CF_3CO_3H$ | 99:1 (63)[b] |
| | | | *m*CPBA | 68:32 (87)[a, b] (4:1[2a]) |
| **26** | $CH_2$ | Me | $CF_3CO_3H$ | 100:0 (77)[a, b] |
| | | | *m*CPBA | 80:20[a] |
| | | | *m*CPBA | 88:12 (86)[b] (100:0 (61)[2c]) |

[a] First reaction sample. [b] Distilled product.

$CH_2Cl_2$ (30 mL) at $-50\,^{\circ}C$. After complete addition (30 min) the mixture was poured into aqueous $Na_2SO_3$ and extracted with diethyl ether. The organic phase was washed successively with $H_2O$, saturated $NaHCO_3$, and saturated NaCl, dried ($Na_2SO_4$), evaporated, and distilled bulb-to-bulb (oven temperature 80–90 °C/0.7 Torr). Yield: 5.06 g of (−)-**8s** (95 %); $[\alpha]_D^{20} = -136$ ($c = 0.03$ in $CHCl_3$), 99 % *ee* by GC on a chiral phase; $^1H$ NMR (360 MHz, $CDCl_3$): $\delta = 2.59$ (C(6)H); $^{13}C$ NMR (360 MHz, $CDCl_3$): $\delta = 31.8$ (C(2)).

(−)-**8a**: A mixture of $[Mo(CO)_6]$ (56 mg, 0.21 mmol), dichloroethane (6 mL), and *t*BuOOH (3 M in isooctane, 6 mL, 18 mmol) was heated at 70 °C for 30 min and introduced within 15 min into a stirred, heated (80 °C) mixture of (*S*)-(−)-**1** (99 % ee)[20] (2.00 g, 10.4 mmol), $Na_2HPO_4$ (11 mg), and dichloroethane (12 mL). After 1 h the mixture was cooled and isolated as above. The distilled mixture (1.84 g; **8a**/**8s** = 89:11; GC: 90 %, yield: 76 %) was separated by chromatography ($SiO_2$; cyclohexane/AcOEt 98/2). (−)-**8a**: 1.32 g (61 %); $[\alpha]_D^{20} = -66$ ($c = 0.06$ in $CHCl_3$), 99 % *ee* by GC on a chiral phase; $^1H$ NMR (360 MHz, $CDCl_3$): $\delta = 3.12$ (C(6)H); $^{13}C$ NMR (360 MHz, $CDCl_3$): $\delta = 32.6$ (C(2)).

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[17] The *anti* π face of **7pe** displays a higher electron density in the HOMO than the *syn* face (PM3).

[18] A calculation (PM3) of the electron density surfaces encoded by the electrostatic potential[5] for **1pa**–**7pa**, **1pe**–**7pe**, and **22** showed that the *syn* faces exhibit a more negative electrostatic field.

[19] A referee suggested citing the work of T. Linker, K. Peters, E.-M. Peters, and F. Rebien (*Angew. Chem.* **1996**, *108*, 2662; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2487) as an example of *syn*-selective epoxidation of a cyclohexene ester. According to these authors, the selectivity is entirely the result of the steric control exerted by the *trans*-oriented phenyl group. However, preliminary experiments performed in our laboratory show that the same facial selectivity is observed in the absence of the phenyl group, and that $CF_3CO_3H$ gives the highest *syn* selectivity.

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