Diastereoselective Synthesis of 4-Hydroperoxy-3,5-cyclohexadienones in the Photooxygenation of Hydroxyethyl-Substituted Phenols

Michael Prein,* Michael Maurer, Eva Maria Peters, Karl Peters, Hans Georg von Schnering, and Waldemar Adam

Abstract: Three of the four possible isomeric *para*-substituted hydroxyethylmethylphenols were prepared from readily available starting materials and submitted to photooxygenation. In the case of 3-hydroxy-α,6-dimethylbenzenemethanol (**1a**) and 2-hydroxy-α,5-dimethylbenzenemethanol (**1b**) the corresponding 4-hydroperoxy-3,5-cyclohexadienones were obtained as oxy-functionalized products (≥90%, d.r. 85:15 and 75:15). The stereochemistry of the products was assigned after reduction to the corresponding *p*-quinols. The ready cleavage of the initial oxygenated product, which can be observed at low temperature as a single diastereomer, prevented rigorous assignment of the π-facial selectivity of the singlet oxygen attack for the derivative 4-hydroxy-α,2-dimethylbenzenemethanol (**1c**). The present stereochemical results indicate that the hydroxyl group directing effect, that is, coordination of the incoming singlet oxygen dienophile with the hydroxyl group, is also operating in the photooxygenation of the chiral phenols **1a–c**. However, in the case of the derivative **1b**, hydrogen bonding in the starting material leads to an opposite stereochemical outcome. This conclusion is further substantiated by solvent effects and the fact that the methyl ether **1d** of alcohol **1c** displays a significant lower diastereoselectivity.

Keywords
chiral phenols · facial selectivity · photooxidations · quinols · singlet oxygen

Introduction

Since its discovery 30 years ago by Matsuura et al.,[1] the sensitized photooxygenation of phenols has continued to attract considerable interest in terms of mechanistic[2] studies as well as of synthetic applications.[3] While the photooxygenation of phenols without *para* substituents leads to the corresponding quinones,[2c] the oxyfunctionalized products in case of *para*-substituted phenols are the corresponding 4-hydroperoxy-2,5-cyclohexadienones.[1, 2b, d, e, 3] The acid-[4] and base-catalyzed[5] rearrangements of the latter class of compounds have been extensively studied, while the reduction to 4-hydroxy-2,5-cyclohexadienones (*p*-quinols) is a most useful transformation for preparative purposes. *p*-Quinols have proven to be valuable synthetic intermediates,[6] for instance, as dienophiles in Diels–Alder reactions.[7]

As part of our investigations into diastereoselective singlet oxygen reactions, we have recently established the directing propensity of the hydroxyl group at a stereogenic center in singlet oxygen ene reactions[8] as well as in the [4+2] cycloaddition to chiral naphthyl alcohols.[9] Since the initial step in the formation of 4-hydroperoxy-2,5-cyclohexadienones from *para*-substituted phenols is considered to be a [4+2] cycloaddition of singlet oxygen to the aromatic moiety,[2b] it seemed of particular interest to assess the stereochemical consequences of the hydroxyl group directing effect for the chiral hydroxyethyl-substituted phenols. Were a high diastereoselectivity to operate in the oxygenation step, the resulting hydroperoxy alcohols and their *p*-quinol reduction products should constitute interesting highly functionalized substrates for synthetic applications. Furthermore, careful product studies should provide closer insight into the nature of the hydroxyl group directing effect and the mechanism of phenol photooxygenation in general.

Since the quinones obtained in the photooxygenation of phenols without *para* substituent provide no stereochemical information on the initial attack of singlet oxygen, the chiral *para*-substituted phenols **1a–d** were employed in this study. The phenol derivatives **1c,d** closely resemble the previously examined naphthalene derivatives[9] with respect to the location of the stereogenic center at C-1. In contrast, the phenols **1a,b** derived from *p*-cresol are of special interest, since the chiral directing group is located at C-2 or C-3 of the diene unit in these substrates. So far the stereochemical consequences of a chiral substituent in that position have not been studied in the singlet oxygen [4+2] cycloaddition. Herein, the novel stereochemical results for the photooxygenation of the chiral phenols **1a–d** are presented.

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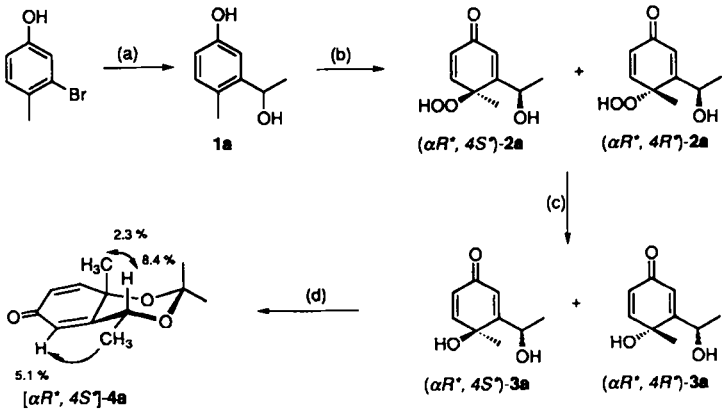
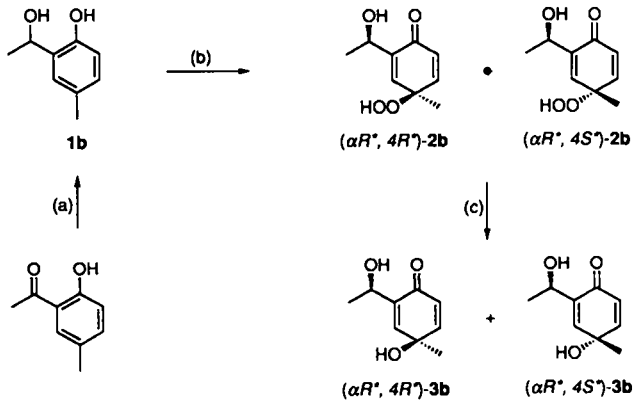
Results

The chiral benzylic alcohol **1a** (Scheme 1) was prepared in 50% yield by lithiation of 3-bromo-4-methylphenol (BuLi, THF) and subsequent reaction with acetaldehyde. The regioisomeric alcohols **1b,c** were obtained by reduction of the appropriate acetyl



Scheme 1. Preparation and photooxygenation of phenol **1a**: (a) *n*BuLi, THF, −60 °C to RT, 3 h; 2. MeCHO, THF, RT, 15 h, 50% yield; (b) O_2, TPP, *hv*, $CHCl_3$, −30 °C, 24 h, 95% yield; (c) Ph_3P, EtOH, 0 °C, 78% yield; (d) $Me_2C(OMe)_2$, *p*-TsOH, Me_2CO, RT, 4 h, 47% yield.

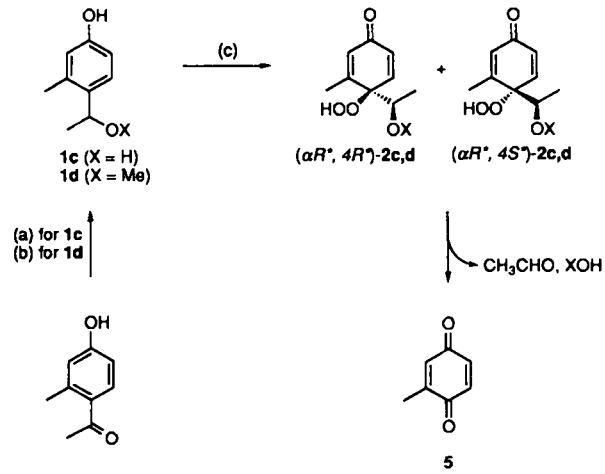
compounds, which were readily available by the Fries rearrangement of the corresponding phenol acetates (Schemes 2 and 3). In the sodium borohydride reduction of 4-acetyl-3-methylphenol in methanol, the methoxy ether **1d** (17%) was formed as a by-product (Scheme 3).



Scheme 2. Preparation and photooxygenation of phenol **1b**: (a) $NaBH_4$, MeOH, RT, 6 h, 63% yield; (b) O_2, TPP, *hv*, $CHCl_3$, −30 °C, 18 h, 95% yield; (c) Ph_3P, EtOH, 0 °C, 74% yield.

The phenol derivatives **1a–d** were photooxygenated in chloroform to give the corresponding hydroperoxycyclohexadienones **2a–d** (Schemes 1–3). For quantitative product studies, the reactions were also conducted directly in deuterated solvents. The reaction conditions and product ratios, which were determined by ^1H NMR spectroscopy on the crude reaction mixtures, are summarized in Table 1.

The photooxygenation of the chiral alcohol **1a** in chloroform (Scheme 1) gave the diastereomeric hydroperoxides **2a** in very



Scheme 3. Preparation and photooxygenation of phenols **1c,d**: (a) $LiAlH_4$, Et_2O, 0 °C to RT, 24 h, 87% yield; (b) $NaBH_4$, MeOH, 0 °C to reflux, 18 h, 17% yield (c) O_2, TPP, *hv*, $CDCl_3$, −30 °C.

good yield (≥95%) and high diastereoselectivity (Table 1, entry 1). When the solvent was changed to the more polar methanol, the diastereoselectivity dropped dramatically to around 50:50 (entry 2). The (α*R**,4*S**) configuration for the major isomer was assigned by NOE experiments on the acetonide **4a**, which was obtained from the hydroperoxide **2a** (Scheme 1) by reduction (Ph_3P, ethanol) and subsequent acetalation of diol **3a** [$Me_2C(OMe)_2$, *p*-TsOH]. Thus, irradiation of the doublet at $\delta = 1.46$ gave significant enhancement (5.1%) of the olefinic proton at $\delta = 6.14$, which confirms the equatorial position of the methyl group at C-4. Also, when the methyl group at C-8a ($\delta = 1.55$) was irradiated, a large enhancement (8.4% and vice versa 2.3%) of the signal for 4-H ($\delta = 4.84$) was observed, which supports the stereochemical assignment.

Table 1. Product studies and diastereoselectivities for the photooxygenation of chiral hydroxyethyl-substituted phenols **1** [a].

Entry	Substrate	Solvent	*T*/h	Conv./%	Yield/%	Product	d.r./% [b]
1	**1a**	$CDCl_3$	6.5	95	95	**2a**	85:15±3 [c]
2	**1a**	CD_3OD	4.5	42	95	**2a**	52:48±3 [c]
3	**1b**	$CDCl_3$	6.5	>98	>98	**2b**	75:25±3 [d]
4	**1c**	$CDCl_3$	0.5	40	47	**2c**	>95:5 [e]
5	**1c**	$CDCl_3$	8	95	85	**5**	–
6	**1c**	$CDCl_3$ [g]	1.5	48	95	**5**	–
7	**1c**	$CDCl_3$ [h]	3	80	95	**5**	–
8	**1c**	CD_3OD	0.5	15	95	**5**	–
9	**1d**	$CDCl_3$	21	93	90	**2d**	62:38±3 [f]

[a] Photooxygenations were carried out at −30 °C with tetraphenylporphine (TPP) as sensitizer, except for entries 2 and 8 in which Rose Bengal was used; ^1H NMR spectra were taken on the crude reaction mixtures at −25 °C. [b] Diastereomeric ratio (d.r.) determined by ^1H NMR spectroscopy of the appropriate, characteristic resonances. [c] (α*R**,4*S**)-**2a** was the major product. [d] (α*R**,4*S**)-**2b** was the major product. [e] Only the (α*R**,4*R**)-**2c** isomer was observed. [f] (α*R**,4*R**)-**2d** was the major product. [g] Additive: pyridine (10 mol%). [h] Additive: $P(OEt)_3$ (5 equiv).

Photooxygenation of alcohol **1b** in chloroform (Scheme 2; Table 1, entry 3) gave hydroperoxide **2b** in a clean reaction and with a diastereoselectivity of 75:25. The large distance between the stereogenic centers precluded, in this case, the assignment of the relative stereochemistry by means of chemical transformations or by spectroscopy. Nevertheless, the (α*R**,4*S**) configu-

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ration of the major diastereomer could be established unequivocally by means of an X-ray analysis of diol ($\alpha R^*,4S^*$)-**3b**, which was obtained by triphenylphosphine reduction of hydroperoxide **2b** (Fig. 1).[10]

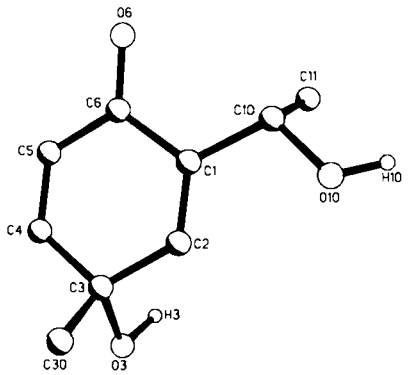


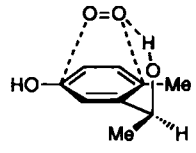
Fig. 1. X-Ray structure of diol ($\alpha R^*,4S^*$)-**3b**.

In view of the labile nature of the hydroperoxide **2c**, the photooxygenation of alcohol **1c** (Scheme 3) proved to be more problematic. The latter readily cleaved into acetaldehyde and 2-methylbenzoquinone (**5**), which was the only product from a prolonged photooxygenation (Table 1, entry 5). When the reaction was run at low conversion, the hydroperoxide **2c** could be detected by low-temperature NMR spectroscopy as a single diastereomer (Table 1, entry 4), but the crude reaction mixture contained already about 50% of the cleavage product **5** (based on converted starting material). Neither addition of pyridine as base (Table 1, entry 6), attempted in situ reduction with triethylphosphite (Table 1, entry 7), or the use of methanol as solvent (Table 1, entry 8) circumvented the fragmentation of **2c**. Therefore, hydroperoxide **2c** could not be isolated and purified, and the relative stereochemistry could not be rigorously established. Nevertheless, on the basis of our previous results on the [4+2] cycloadditon of singlet oxygen with chiral naphthyl alcohols,[9] the ($\alpha R^*,4S^*$) configuration for hydroperoxide **2c** seems reasonable. Like the *peri* hydrogen in the case of the naphthalene derivatives (see Discussion), the *ortho* methyl group dictates the same stereochemical outcome in the photooxygenation of alcohol **1c**.

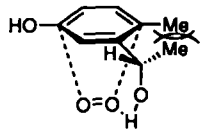
Photooxygenation of the methyl ether **1d** (Scheme 3) proceeded much slower (21 h for almost complete conversion; Table 1, entry 9) than for the alcohols **1a–c**. The hydroperoxide **2d** was the major product (90%), but quinone **5** was also detected as a side-product due to the fragmentation of **2d**. In contrast to the photooxygenation of alcohol **1c**, in which only one diastereomer of the oxyfunctionalized product **2c** was formed, only poor diastereoselectivity (d.r. 62:38) was obtained for the methyl ether **1d**. The assignment of the ($\alpha R^*,4S^*$) stereochemistry for the major diastereomer is based on the close resemblance of its proton NMR data with those of the hydroperoxide **2c**.

Discussion

Inspection of the data in Table 1 shows that strategically placed stereogenic functionalities induce moderate to high diastereoselectivities in the singlet oxygen addition to *para*-substituted phenols. The observed solvent effect for phenol **1a**, that is, loss of stereoselectivity in methanol, is well-known in the photooxygenation of chiral allylic alcohols,[8] chiral allylic amines,[11] and chiral naphthyl alcohols.[9a] It is rationalized in terms of attractive hydrogen bonding in the exciplex between the incoming singlet oxygen and the hydroxyl group. Consequently, reduced ortho strain in the diastereomeric transition state **A*** as compared to **B*** is responsible for the observed stereochemistry.



A*

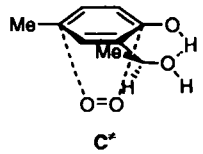


B*

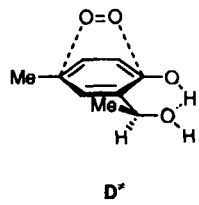
It should be noted that the transition states **A*** and **B*** refer to classical, concerted [4+2] cycloaddition pathways, but the above-mentioned stereochemical argument would also apply if the $^1O_2$ reaction were to proceed through a hydroxy-stabilized exciplex that collapses directly in a subsequent step to the observed products, without intermediacy of the [4+2] cycloadduct. The latter possibility has so far not been suggested in the photooxygenation of phenols.[2, 3] The proposed mechanism is further substantiated by the fact that phenol **1a** with the chiral substituent at C-2 of the diene moiety displays close resemblance in the extent and sense of diastereoselectivity to the previously examined chiral naphthyl alcohols,[9] in which the stereogenic unit is located at C-1. In fact, if the diastereoselectivity were to be attributed to the polarization of the π orbitals of the dienic system, that is, to the different electron densities at the respective diastereotopic faces, a change of the location of the stereogenic unit from the reaction center C-1 to C-2 should result in a remarkable drop of selectivity, since it is a well-known fact that such polarization effects are important only at the carbon atom directly adjacent to the chiral substituent.[12]

At first glance, phenol **1b** can be regarded as a perfect analogon to **1a**, in which the phenolic hydroxyl group takes the part of the methyl group in differentiating the energy content of the different reactive rotamers. The reduced size of the hydroxyl group as compared to the methyl group would then account for the reduced diastereoselectivity of 75:25. However, the assignment of the relative stereochemistry of diol **3b** by X-ray analysis (Fig. 1) surprisingly revealed the opposite stereochemistry to what one would have expected when transitions states analogous to **A*** and **B*** were to apply. In other words, hydroperoxide ($\alpha R^*,4S^*$)-**2b** was formed as the major diastereomer in the photooxygenation of alcohol **1b**.

The hydrogen-bonded transition states **C*** and **D*** readily account for this observed preference. Thus, on the basis of the steric bias of the methyl group, attack of singlet oxygen is favored at the "bottom" π face, and transition state **C*** is preferred over **D***. Such hydrogen bonding between the phenolic proton (acidic site) and the aliphatic hydroxyl group (basic site) through the six-membered ring structure is quite likely and



C*



D*

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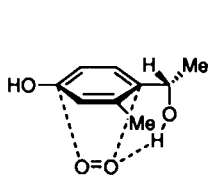
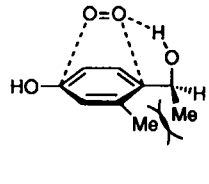
should enhance the reactivity of the aromatic unit towards electrophilic attack. Thus, the aliphatic OH group coordinates as an intramolecular base to the acidic phenolic proton; this explains the importance of transition states **C*** and **D*** in dictating the observed stereochemistry.

In the case of phenol derivative **1c**, it was unfortunately difficult to determine π-facial selectivity, owing to the lability of the oxyfunctionalized product of the photooxygenation. Nevertheless, the high diastereoselectivity obtained in the photooxygenation of the alcohol **1c**, as well as the sharp drop for methyl ether derivative **1d**, agree well with our previous results for the chiral naphthyl alcohols.[9] The latter closely resemble the present phenolic substrates **1c,d** as far as the fixation of the stereogenic unit at C-1 is concerned. Consequently, the *ortho* methyl group is decisive in differentiating the energy content of the transition states **E*** and **F*** in favor of the former and, therefore, plays the



E*



F*

same role as the *peri* hydrogen atom in the naphthalene substrates. The diastereoselectivity of the methyl ether **1d** (Table 1, entry 9) is too low (d.r. 62:38) to speculate upon its origin, but it further substantiates the importance of coordination between the incoming singlet oxygen and the free hydroxyl group for achieving high diastereoselectivities.

Conclusion

A strategically placed chiral hydroxyethyl group gives rise to moderate to good diastereoselectivities in the reaction of *para*-substituted phenols with singlet oxygen. The observed solvent effects as well as the stereochemical outcome for the phenol derivative **1a** further support the hydroxyl group directing effect towards singlet oxygen, that is, the coordination of the incoming dienophile with the unprotected OH group, presumably through hydrogen bonding in the $^1O_2$ exciplex. The hydroperoxides **2a,b** and the corresponding quinols **3a,b** can be prepared in high yields from readily available precursors. Therefore, the opportunity is offered for useful applications of such highly functionalized dienones in organic synthesis.

Experimental Section

General Aspects: Melting points were determined on a Büchi SMP-20 apparatus and are uncorrected. Infrared spectra were recorded with a Perkin-Elmer 1420 ratio-recording infrared spectrophotometer, and ^1H and ^{13}C NMR spectra with a Bruker AC200 and $CDCl_3$ as internal standard. Combustion analyses were performed by the Microanalytical Division of the Institute of Inorganic Chemistry, University of Würzburg. Macherey and Nagel Polygram SIL G/UV$_{254}$ plates were used for TLC; UV detection (254 nm) was employed. Peroxides were detected by means of 10% aqueous KI. Column chromatography was performed on silica gel (63–200 μm) from Woelm, Erlangen. Commercial compounds were used as received; solvents were purified and dried by standard methods. 3-Bromo-4-methylphenol [13], 2-acetyl-4-methylphenol [14], and 4-acetyl-3-methylphenol [15] were prepared according to previously described procedures.

5-Hydroxy-α,2-dimethylbenzenemethanol (1a): To a stirred solution of 3-bromo-4-methylphenol (1.70 g, 9.09 mmol) in THF (40 mL) at −60 °C was added dropwise a 1.5 M solution of *n*-butyllithium in hexane (13.3 mL, 20.0 mmol). The mixture was stirred for 3 h at −60 °C and then allowed to warm up to 0 °C, stirred for 30 min, and then cooled to −30 °C. A solution of acetaldehyde (520 mg, 11.8 mmol) in THF (15 mL) was added dropwise, and the mixture stirred at room temperature overnight. Concentrated aqueous ammonium chloride (70 mL) was added, and the aqueous layer extracted with ether (3 × 100 mL). The combined organic layers were washed with water (2 × 20 mL), dried over anhydrous magnesium sulfate, and the solvent was evaporated at 20 °C/20 Torr. The oily residue was chromatographed on silica gel [petroleum ether (30–50)/methyl *tert*-butyl ether (4:1 to 1:1) as eluent] to give 690 mg (50%) of phenol **1a** as yellowish powder, m.p. 95.5–96.5 °C. ^1H NMR (200 MHz, $CDCl_3$): $\delta = 1.41$ (d, $J = 6.4$ Hz, 3H), 1.80 (br s, 1H), 2.21 (s, 3H), 5.07 (q, $J = 6.4$ Hz, 1H), 5.99 (br s, 1H), 6.64 (dd, $J = 8.2$ Hz, 2.7 Hz, 1H), 6.97 (d, $J = 8.2$ Hz, 1H), 7.04 (d, $J = 2.7$ Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 22.2$ (q), 23.8 (q), 66.9 (d), 111.4 (d), 114.0 (d), 131.4 (d), 133.7 (s), 145.0 (s), 154.5 (s); IR (KBr): $\tilde{\nu} = 3380–3320$, 2960, 2890, 1590, 1480, 1240, 1200, 1155, 1065, 1015 cm^{-1}; $C_9H_{12}O_2$ (152.2): calcd C 71.03, H 7.95; found C 71.00, H 7.99.

2-Hydroxy-α,5-dimethylbenzenemethanol (1b): To a stirred solution of 2-acetyl-4-methylphenol (5.00 g, 33.3 mmol) in methanol (50 mL) at room temperature was added sodium borohydride (1.90 g, 50.0 mmol) in 300 mg portions over 1 h. The mixture was stirred for 6 h, the solvent removed at 20 °C/20 Torr, and the residue dissolved in 2 N HCl (30 mL) and ether (50 mL). The aqueous layer was extracted with ether (2 × 50 mL). The combined ether extracts were washed with water (2 × 15 mL) and dried over anhydrous magnesium sulfate. Evaporation of the solvent at 20 °C/20 Torr gave an oily residue, which was recrystallized from Et_2O/petroleum ether (30–50) to yield 3.20 g (63%) of phenol **1b**, m.p. 92–93 °C (ref. [16] 92 °C). The proton NMR shift data given in ref. [16] were found to be incorrect. ^1H NMR (200 MHz, $CDCl_3$): $\delta = 1.55$ (d, $J = 6.6$ Hz, 3H), 2.27 (s, 3H), 2.56 (br s, 1H), 5.00 (q, $J = 6.6$ Hz, 1H), 6.74–6.99 (m, 3H), 7.72 (br s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 20.4$ (q), 23.4 (q), 71.7 (d), 116.9 (d), 126.9 (d), 128.3 (s), 129.0 (s), 129.3 (d), 152.8 (s); IR (KBr): $\tilde{\nu} = 3340–3260$, 2940, 2890, 1595, 1490, 1240, 1190, 1140, 1055, 810 cm^{-1}.

4-Hydroxy-α,2-dimethylbenzenemethanol (1c): To a suspension of $LiAlH_4$ (0.800 mg, 21.1 mmol) in anhydrous ether (50 mL) was added dropwise at 0 °C a solution of 4-acetyl-3-methylphenol (3.20 g, 21.3 mmol) in ether (250 mL). The mixture was stirred overnight and cautiously hydrolyzed with ice/ammonium chloride (30 mL) and 2 N HCl (5 mL). The aqueous layer was extracted with ether (2 × 50 mL), the combined organic layers were dried over anhydrous magnesium sulfate, and the solvent was evaporated at 20 °C/20 Torr. The residue was crystallized from Et_2O/petroleum ether (30–50) to give 2.78 g (87%) phenol **1c** as colorless plates, m.p. 95.5–96.5 °C. ^1H NMR (200 MHz, $CDCl_3$): $\delta = 1.46$ (d, $J = 6.4$ Hz, 3H), 1.81 (br s, 1H), 2.30 (s, 3H), 5.08 (q, $J = 6.4$ Hz, 1H), 5.46 (br s, 1H), 6.61 (d, $J = 2.7$ Hz, 1H), 6.68 (dd, $J = 8.3$ Hz, 2.7 Hz, 1H), 7.35 (d, $J = 8.3$ Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 18.9$ (q), 23.9 (q), 66.5 (d), 113.0 (d), 117.1 (d), 126.0 (d), 135.6 (s), 136.3 (s), 154.7 (s); IR ($CHCl_3$): $\tilde{\nu} = 3560$, 3480–3120, 2940, 2900, 1590, 1570, 1485, 1250, 1100, 1060 cm^{-1}; $C_9H_{12}O_2$ (152.2): calcd C 71.03, H 7.95; found C 71.32, H 8.13.

4-(1-Methoxyethyl)-3-methylphenol (1d): To a stirred solution of 4-acetyl-3-methylphenol (4.00 g, 26.6 mmol) in methanol (50 mL) was added at room temperature sodium borohydride (2.00 g, 53.2 mmol) in 300 mg portions. The mixture was stirred for 15 h at room temperature and then kept at reflux for 3 h. The solvent was removed at 20 °C/20 Torr, and the residue dissolved in 2 N HCl (30 mL) and ether (50 mL). The aqueous layer was extracted with ether (2 × 50 mL). The combined extracts were washed with water (2 × 15 mL), dried over anhydrous magnesium sulfate, and the solvent evaporated at 20 °C/20 Torr. Column chromatography of the residue on silica gel [petroleum ether(30–50)/EtOAc (6:1 to 3:1) as eluent] gave phenol **1c** (2.12 g, 52%) and the methyl ether **1d** (503 mg, 17%) as colorless powders, m.p. 79.5–80.5 °C. ^1H NMR (200 MHz, $CDCl_3$): $\delta = 1.40$ (d, $J = 6.5$ Hz, 3H), 2.28 (s, 3H), 3.22 (s, 3H), 4.52 (q, $J = 6.5$ Hz, 1H), 5.04 (br s, 1H), 6.64 (d, $J = 2.7$ Hz, 1H), 6.70 (dd, $J = 8.3$ Hz, 2.7 Hz, 1H), 7.28 (d, $J = 8.3$ Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 19.0$ (q), 22.5 (q), 56.1 (q), 75.8 (d), 113.1 (d), 117.0 (d), 126.8 (d), 133.4 (s), 136.8 (s), 154.5 (s); IR (CCl_4): $\tilde{\nu} = 3570$, 2950, 2900, 1590, 1480, 1275, 1220, 1175, 1140, 100 cm^{-1}; $C_{10}H_{14}O_2$ (166.2): calcd C 72.26, H 8.49; found C 72.55, H 8.80.

General Procedure for the Photooxygenations of the Phenols: A solution of the particular phenol (0.100 mmol for NMR and ca. 2.00 mmol for preparative runs) and a catalytic amount of the appropriate sensitizer in the desired solvent (0.8 mL for NMR and ca. 20 mL for preparative runs) was irradiated by means of two external OSRAM Vialox NAV-E (250 W) sodium lamps at −30 °C, while a gentle stream of dried ($CaCl_2$, P_2O_5) oxygen gas was allowed to pass continuously through the reaction mixture. The course of the reaction was monitored by TLC and after all starting material had been converted, the composition of the crude reaction mixture was determined by low-temperature (−25 °C) NMR spectroscopy (for yields and product ratios see Table 1).

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4-Hydroperoxy-3-(1-hydroxyethyl)-4-methyl-2,5-cyclohexadien-1-one (2a): According to the above general procedure, a solution of phenol **1a** (213 mg, 1.40 mmol) in $CHCl_3$ (20 mL) (ca. 3 mg TPP as sensitizer) was photooxygenated for 24 h at −30 °C. After evaporation of the solvent at 20 °C/20 Torr, 264 mg of a green oil was obtained, which contained the diastereomeric hydroperoxides **2a** in high purity (>95%) [(α*R**,4*S**)-**2a**:(α*R**,4*R**)-**2a** = 85:15]. An analytical sample was obtained by low-temperature (−20 °C) column chromatography on silica gel [CH_2Cl_2/MeOH (50:1) as eluent]. $C_9H_{12}O_4$ (184.2): calcd C 58.69, H 6.57; found C 58.93, H 6.84. (α*R**,4*S**)-**2a**: ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.37 (s, 3H), 1.49 (d, *J* = 6.5 Hz, 3H), 2.90 (brs, 1H), 4.77 (m, 1H), 6.37 (dd, *J* = 10.0 Hz, 2.0 Hz, 1H), 6.42 (d, *J* = 2.0 Hz, 1H), 7.01 (d, *J* = 10.0 Hz, 1H), the signal for OOH was not detected; ^{13}C NMR (50 MHz, $CDCl_3$): δ = 21.5 (q), 22.6 (q), 63.8 (d), 80.7 (s), 126.7 (d), 138.7 (d), 152.6 (d), 169.8 (s), 186.8 (s). (α*R**,4*R**)-**2a**: ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.53 (s, 3H), 1.56 (d, *J* = 6.5 Hz, 3H), 6.24 (dd, *J* = 10.0 Hz, 2.0 Hz, 1H), 6.40 (d, *J* = 2.0 Hz, 1H), 6.93 (d, *J* = 10.0 Hz, 1H), only resolved resonances are listed; ^{13}C NMR (50 MHz, $CDCl_3$): δ = 22.8 (q), 23.3 (q), 63.9 (d), 126.5 (d), 128.6 (d), 152.8(d), 186.7 (s), only resolved resonances are listed.

4-Hydroperoxy-2-(1-hydroxyethyl)-4-methyl-2,5-cyclohexadien-1-one (2b): According to the above general procedure, a solution of phenol **1b** (331 mg, 2.20 mmol) in $CHCl_3$ (20 mL) (3 mg TPP as sensitizer) was photooxygenated for 24 h at −30 °C. After evaporation of the solvent at 20 °C/20 Torr, 403 mg of a green oil was obtained, which contained the diastereomeric hydroperoxides **2b** in high purity (≥90%) [(α*R**,4*S**)-**2b**:(α*R**,4*R**)-**2b** = 75:25]. An analytical sample was obtained by low temperature (−20 °C) column chromatography on silica gel [CH_2Cl_2/MeOH (100:1) as eluent]. $C_9H_{12}O_4$ (184.2): calcd C 58.69, H 6.57; found C 58.37, H 6.65. (α*R**,4*S**)-**2b**: ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.30–1.36 (m, 6H) 3.35 (brs, 1H), 4.66 (q, *J* = 6.4 Hz, 1H), 6.25 (d, *J* = 10.0 Hz, 1H), 6.80 (brs, 1H), 6.95 (d, *J* = 10.0 Hz, 1H), 9.42 (brs, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 21.6 (q), 22.7 (q), 66.2 (d), 78.2 (s), 130.1 (d), 142.1 (s), 144.1 (d), 150.3 (d), 186.3 (s). (α*R**,4*R**)-**2b**: ^{1}H NMR (200 MHz, $CDCl_3$): δ = 4.80 (q, *J* = 6.3 Hz, 1H), 6.83 (brs, 1H), 6.93 (d, *J* = 9.9 Hz, 1H), 9.77 (brs, 1H), only resolved resonances are listed; ^{13}C NMR (50 MHz, $CDCl_3$): δ = 22.0 (q), 22.5 (q), 64.9 (d), 78.7 (s), 130.0 (d), 142.8 (s), 143.7 (d), 150.3 (d), 185.8 (s).

Photooxygenation of Phenol 1c: According to the above general procedure, a solution of phenol **1c** (10.0 mg, 65.7 μmol) in deuteriochloroform (1 mL) was photooxygenated for 0.5 h at −30 °C. Rapid low-temperature (−30 °C) spectroscopy on the crude product mixture showed 40% conversion of the starting material. Besides the hydroperoxide **2c** (47%, only one diastereomer detected), the solution also contained ca. 53% of the cleavage products acetaldehyde and 2-methylbenzoquinone (**5**), which was identified by comparison to the known [17] spectral data. On prolonged photooxygenation, only the cleavage products acetaldehyde and quinone **5** were detected, even in the presence of 10 mol% of pyridine or 5 equiv of triethyl phosphite (for details, see Table 1).

(α*R,4*R**)-4-Hydroperoxy-4-(1-hydroxyethyl)-3-methyl-2,5-cyclohexadien-1-one (2c):** ^{1}H NMR (200 MHz, $CDCl_3$, −30 °C): δ = 0.98 (d, *J* = 6.5 Hz, 3H), 2.02 (s, 3H), 4.15 (q, *J* = 6.5 Hz, 1H), 6.62–6.82 (m, 2H), 7.26 (d, *J* = 9.9 Hz, 1H), 9.90 (brs, 1H), the OH signal could not be unequivocally assigned in presence of the starting material **1c**. The thermal lability of the hydroperoxide **2c** combined with its low solubility precluded acquisition of a ^{13}C NMR spectrum as well as purification and complete characterization.

4-Hydroperoxy-4-(1-methoxyethyl)-3-methyl-2,5-cyclohexadien-1-one (2d): According to the above general procedure, a solution of phenol **1d** (20.1 mg, 0.121 mmol) in $CDCl_3$ (1 mL) was photooxygenated for 21 h at −30 °C. Low-temperature (−20 °C) NMR spectroscopy on the crude product mixture showed 95% diastereomeric hydroperoxides **2d** [(α*R**,4*R**)-**2d**:(α*R**,4*S**)-**2d** = 62:38] and 5% of 2-methylbenzoquinone **5** at 93% conversion of the starting phenol **1d**. The tendency of hydroperoxide **2d** to undergo cleavage to the quinone **5** precluded purification and complete characterization. (α*R**,4*R**)-**2d**: ^{1}H NMR (200 MHz, $CDCl_3$, −20 °C): δ = 0.95 (d, *J* = 6.4 Hz, 3H), 2.04 (s, 3H), 3.45 (s, 3H), 3.63 (q, *J* = 6.4 Hz, 1H), 6.19 (d, *J* = 1.8 Hz, 1H), 6.45 (dd, *J* = 10.2 Hz, 1.8 Hz, 1H), 7.14 (d, *J* = 10.2 Hz, 1H), 8.90 (brs, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.8 (q), 18.2 (q), 59.0 (q), 79.5 (d), 87.8 (s), 129.8 (d), 132.1 (d), 147.3 (d), 157.9 (s), 185.9 (s). (α*R**,4*S**)-**2d**: ^{1}H NMR (200 MHz, CDCl3): δ = 1.16 (d, *J* = 6.4 Hz, 3H), 2.14 (s, 3H), 3.33 (s, 3H), 3.57 (q, *J* = 6.4 Hz, 1H), 6.27 (d, *J* = 1.8 Hz, 1H), 6.36 (dd, *J* = 10.2 Hz, 1.8 Hz, 1H), 6.90 (d, *J* = 10.2 Hz, 1H), 8.90 (brs, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 15.0 (q), 19.0 (q), 58.4 (q), 78.4 (d), 85.9 (s), 130.0 (d), 132.0 (d), 147.4 (d), 157.9 (s), 185.9 (s).

4-Hydroxy-3-(1-hydroxyethyl)-4-methyl-2,5-cyclohexadien-1-one (3a): To a stirred solution of hydroperoxide **2a** (213 mg, 1.16 mmol) [(α*R**,4*S**)-**2a**:(α*R**,4*R**)-**2a** = 85:15] in ethanol (5 mL) was added at 0 °C a solution of triphenylphosphine (304 mg, 1.16 mmol) in ethanol (5 mL). The mixture was stirred for 30 min, and the solvent evaporated at 20 °C/20 Torr. The oily residue was chromatographed on silica gel [CH_2Cl_2/MeOH (50:1) as eluent] to give 152 mg (78%) of the diastereomeric alcohols **3a** [(α*R**,4*S**)-**3a**:(α*R**,4*R**)-**3a** = 90:10] as yellowish oil. IR (neat): $\tilde{\nu}$ = 3530–3100, 2950, 2900, 1645, 1605, 1355, 1280, 1140, 1065, 895 cm^{-1}; $C_9H_{12}O_3$ (168.2): calcd C 64.27, H 7.19; found C 64.44, H 7.30. (α*R**,4*S**)-**3a**: ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.44 (d, *J* = 6.4 Hz, 3H), 1.48 (s, 3H), 4.84 (q, *J* = 6.4 Hz, 1H), 6.07 (dd, *J* = 10.0 Hz, 1.1 Hz, 1H), 6.18 (d, *J* = 1.1 Hz, 1H), 6.86 (d, *J* = 10.0 Hz, 1H), the signals for of the two hydroxyl groups could not be assigned; ^{13}C NMR (50 MHz, $CDCl_3$): δ = 22.1 (q), 26.6 (q), 65.4 (d), 69.4 (s), 123.3 (d), 125.8 (d), 153.6 (d), 165.6 (s), 186.9 (s). (α*R**,4*R**)-**3a**: ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.43 (d, *J* = 6.4 Hz, 3H), 1.58 (s, 3H), 4.82 (q, *J* = 6.4 Hz, 1H), 6.06 (dd, *J* = 10.0 Hz, 1.0 Hz, 1H), 6.17 (d, *J* = 1.0 Hz, 1H), 6.84 (d, *J* = 10.0 Hz, 1H), the signals for of the two hydroxyl groups could not be assigned; ^{13}C NMR (50 MHz, $CDCl_3$): δ = 24.6 (q), 27.2 (q), 67.4 (d), 69.5 (s), 123.3 (d), 125.8 (d), 153.6 (d), 165.7 (s), 186.9 (s).

4-Hydroxy-2-(1-hydroxyethyl)-4-methyl-2,5-cyclohexadien-1-one (3b): Treatment of hydroperoxide **2b** (650 mg, 3.53 mmol) with triphenylphosphine (926 mg, 3.53 mmol) as described above for the reduction of **2a** gave, after column chromatography [CH_2Cl_2/MeOH (50:1) as eluent], 446 mg (75%) of the diol **3b**; isomeric ratios ranged from ca. 50:50 to 90:10 in the eluted fractions. Recrystallization of the latter from MeOH gave colorless prisms suitable for X-ray analysis, m.p. 119–120 °C. IR (CCl_4): $\tilde{\nu}$ = 3500–3240, 2940, 2820, 1710, 1650, 1615, 1440, 1350, 1060, 900 cm^{-1}; $C_9H_{12}O_3$ (168.2): calcd C 64.27, H 7.19; found C 64.59, H 7.41. (α*R**,4*S**)-**3b**: ^{1}H NMR (200 MHz, CDCl3): δ = 1.29 (d, *J* = 6.5 Hz, 3H), 1.41 (s, 3H), 3.50 (brs, 2H), 4.67 (qd, *J* = 6.5 Hz, 1.0 Hz, 1H), 6.09 (d, *J* = 9.9 Hz, 1H), 6.80 (dd, *J* = 3.1 Hz, 1.0 Hz, 1H), 6.89 (dd, *J* = 9.9 Hz, 3.1 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 21.5 (q), 26.5 (q), 67.1 (d), 67.2 (s), 126.8 (d), 139.3 (s), 146.7 (d), 153.1 (d), 186.1 (s). X-ray crystallographic data [10]: crystal size, 0.8 × 1.4 × 0.7 mm; number of reflections measured, 1185; number of reflections $F > 3(F)$, 1103; *R*, R_w, 0.057, 0.056; space groups, *Pa*; crystal system, monoclinic, lattice constants (standard deviation), *a* = 894.5(4), *b* = 953.5(4), *c* = 1735.1(4), in pm, β = 97.43(3)°; *V*, 444.5(3) × 10^6 pm^3; molecules/elemental cell, 2; ρ_{calcd}, 1.256 gcm^{-3}. (α*R**,4*R**)-**3b**: ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.34 (d, *J* = 6.4 Hz, 3H), 1.43 (s, 3H), 3.50 (brs 2H), 4.55 (qd, *J* = 6.4 Hz, 1.1 Hz, 1H), 6.08 (d, *J* = 9.9 Hz, 1H), 6.79 (dd, *J* = 3.1 Hz, 1.1 Hz, 1H), 6.88 (dd, *J* = 9.9 Hz, 3.1 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 22.0 (q), 26.6 (q), 64.2 (s), 66.5 (d), 127.0 (d), 138.7 (s), 146.9 (d), 152.9 (d), 186.4 (s).

Acetalation of Diol 3a to the Acetonide 4a: To a solution of diol **3a** [(α*R**,4*S**)-**3a**:(α*R**,4*R**)-**3a** = 85:15] (120 mg, 0.713 mmol) in dry acetone (3 mL) and 2,2-dimethoxypropane (3 mL) was added *p*-toluenesulfonic acid (20.0 mg, 96.0 μmol), and the mixture was stirred for 5 h. Solid sodium carbonate (100 mg) was added, the mixture stirred for 30 min, the precipitate removed by filtration, and the solvent evaporated at 20 °C/20 Torr. Column chromatography of the residue on silica gel [petroleum ether(30–50)/ether (10:1) as eluent] gave 80.1 mg of acetonide **4a** [(*R**,*S**)-**4a**:(*R**,*R**)-**4a** = 90:10] as yellowish oil. $C_{12}H_{16}O_3$ (208.3): calcd C 69.21, H 7.74; found C 69.49, H 7.98. (*R**,*S**)-**4a**: ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.24 (s, 3H), 1.44 (s, 3H), 1.46 (d, *J* = 6.4 Hz, 3H), 1.55 (s, 3H), 4.84 (qd, *J* = 6.4 Hz, 1.9 Hz, 1H), 6.11 (dd, *J* = 10.0 Hz, 1.8 Hz, 1H), 6.14 (brs, 1H), 6.99 (d, *J* = 10.0 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 18.4 (q), 28.1 (q), 29.0 (q), 30.1 (q), 66.0 (d), 71.2 (s), 100.3 (s), 121.8 (d), 125.9 (d), 154.4 (d), 162.9 (s), 185.6 (s). (*R**,*R**)-**4a**: ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.65 (s, 3H), 6.05 (dd, *J* = 10.0 Hz, 1.9 Hz, 1H), 6.80 (d, *J* = 10.0 Hz, 1H), only resolved resonances are listed; ^{13}C NMR (50 MHz, $CDCl_3$): δ = 22.7 (q), 24.7 (q), 29.2 (q), 30.3 (q), 68.3 (d), 70.3 (s), 100.6 (s), 121.6 (d), 125.1 (d), 151.9 (d), 163.2 (s), 185.1 (s).

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