Pergamon

Tetrahedron Letters, Vol. 35, No. 25, pp. 4331-4334, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $7.00+0.00

0040-4039(94)00850-7

Substituent Effects in the Diastereoselective [4+2] Cycloaddition of Chiral Naphthalene Derivatives with Singlet Oxygen

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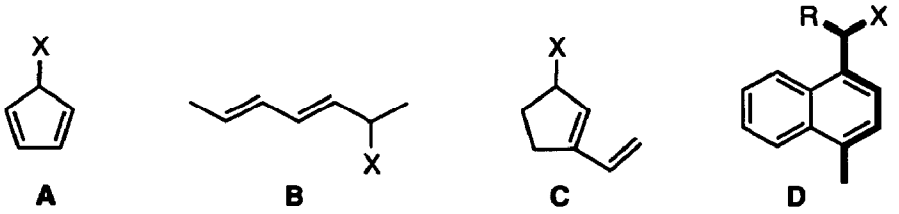
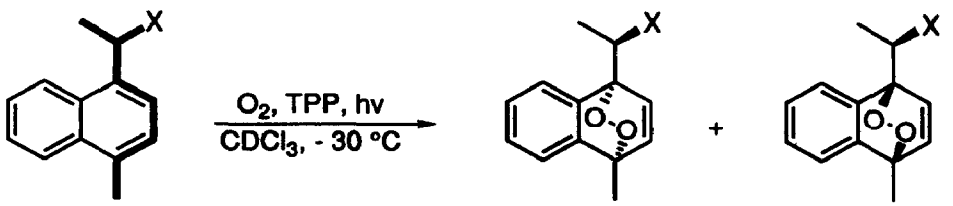
Abstract: *From 1-bromo-4-methylnaphthalene eight chiral derivatives* **1** *with a variety of functional groups at the stereogenic center were prepared, which with singlet oxygen led to the corresponding endoperoxides* **2** *in substituent-dependent π-facial selectivity of stereoelectronic origin.*

The effect of adjacent stereogenic centers on the diastereoselectivity of [4+2] cycloadditions has recently attracted considerable synthetic [1] and theoretical [2] interest. Whereas 5-substituted cyclopentadienes **A** generally exhibit high π-facial selectivity [1a], to date comparatively little is known on the extent and sense of the diastereoselectivity for chiral open-chain [1b] **B**, semicyclic [1c] **C**, and also arene-type [3e] dienes **D**.



A **B** **C** **D**

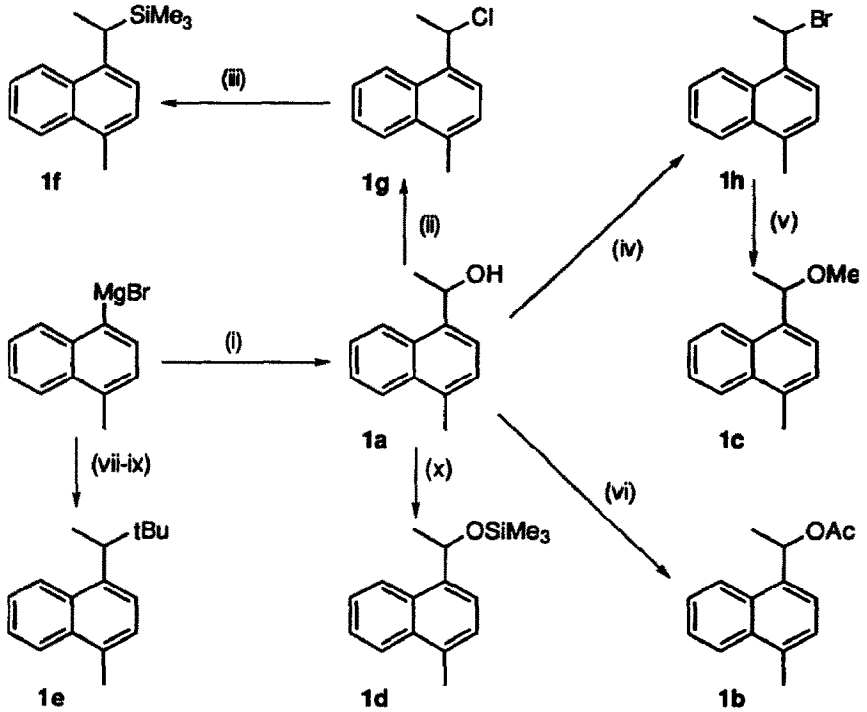
In the context of our work on the diastereoselective oxyfunctionalization of unsaturated compounds by singlet oxygen [3], we recently discovered that chiral naphthyl alcohols (e.g. **1a**, X = OH) give on photooxygenation the corresponding endoperoxides (Scheme 1, X = OH) in good diastereoselectivities (d.r. ≥ 85 : 15). Naphthalene derivatives were chosen as model compounds since they give the desired endoperoxides in high yields [4] (≥ 95 %) without complications by the ene process (Schenck reaction [5]), which allows to make more reliable conclusions on the steering propensity of the substituent at the stereogenic center.



1 **2**

Scheme 1.

It was of interest to explore whether other functional groups at the stereogenic center also induce high diastereoselectivities. For this purpose, we prepared from 1-bromo-4-methylnaphthalene a series of eight chiral naphthalene derivatives **1** with a variety of functional groups at the chirality center (Scheme 2). We chose the alcohol derivatives **1b-d** in order to compare their steering propensity to the parent alcohol **1a**, while the hydrocarbon **1e** and its silicon analogon **1f** should provide closer insight into the relative importance of steric and electronic effects on the π-facial selectivity. Finally, the halo derivatives **1g,h** were of particular interest, since apparently little is known on the π-facial selectivity [6] in [4+2] cycloadditions of substrates with conformationally flexible, halogen-substituted stereogenic centers.



(i) MeCHO, THF, 0 °C to RT, 4 h, 68 %; (ii) HCl (g), $CaCl_2$, Et_2O, RT, 8h, 92 %; (iii) Mg (powder), $ClSiMe_3$, THF, RT, 1h, 48 % (ref. 7); (iv) PBr_3, toluene, RT, 20 h, 91 %; (v) MeOH, RT, 14 h, 91 %; (vi) Ac_2O, pyridine, RT, 18 h, 92 %; (vii) tBuCOCl, THF, 0 °C to RT, 18 h; (viii) MeMgI, Et_2O, reflux, 10 h; (ix) H_2, Pd-C, HOAc, $HClO_4$, 40 °C, 1 h, overall 38 %; (x) $ClSiMe_3$, imidazole, CH_2Cl_2, RT, 36 h, 89 %.

Scheme 2.

Photooxygenation [8] of the naphthalene derivatives **1** at -30 °C gave the respective endoperoxides **2** in very high yields (Scheme 1). The diastereomeric ratio of the products was established by NMR spectroscopy on the crude product mixtures, the results are summarized in Table 1 [9].

Unfortunately, due to the inherent thermal lability [4,10] of the endoperoxides **2**, for derivatives **2c,e-h** (entries 3,5-8) their relative stereochemistry could not be assigned; nevertheless, several important mechanistic conclusions can be drawn from the present results. Thus, electron-accepting groups in the benzylic position, e.g. X = OAc and Cl in the naphthalene derivatives **1b,g**, reduce the reactivity, as reflected in the relatively long photooxygenation times, i.e. 12-14 h (entries 2 and 7). Furthermore, steric

crowding, e.g. X = $OSiMe_3$ and tBu in the naphthalene derivatives **1d,e**, also decreases the rate of photooxygenation (entries 4 and 5); however the Me_3Si substituent in **1f**, despite its size, enhances reactivity (entry 6) [11] and is, in fact, the fastest of the substrates investigated herein.

Table 1: Diastereoselectivities in the Photooxygenation of the Chiral Naphthalenes **1** [a)]

entry	substrate	substituent	time (h)	conv. (%)	yield [b)] (%)	d.r. (%) [c)]
1	**1a** (ref. 3e)	OH	4	> 98	> 98	85 : 15 ± 3 [d)]
2	**1b** (ref. 3e)	OAc	14	37	95	55 : 45 ± 3 [d)]
3	**1c**	OMe	7	87	> 98	66 : 34 ± 3 [e)]
4	**1d**	$OSiMe_3$	7	98	>98	58 : 42 ± 3 [d)]
5	**1e**	tBu	6	30	95	66 : 34 ± 3 [e)]
6	**1f**	$SiMe_3$	3.5	> 98	95	95 : 5 ± 3 [e)]
7	**1g**	Cl	12	95	> 98	87 : 13 ± 3 [e)]
8	**1h**	Br	4	98	98	95 : 5 ± 3 [e)]

a) Photooxygenations were carried out at - 30 °C in $CDCl_3$ with tetraphenylporphine (TPP) as sensitizer; NMR spectra were taken on the crude product mixture at - 20 °C; b) yield of the corresponding endoperoxides **2**; c) diastereomeric ratio (d.r.) of the isomeric endoperoxides **2**; d) *(αR*,1R*,4S*)*- **2** as major isomer; e) due to the thermal lability of the endoperoxides **2**, the relative stereochemistry could not be assigned.

In regard to the diastereoselectivity of the singlet oxygen [4+2] cycloaddition, it becomes clear that any functionalization of the free hydroxy functionality, either by electron acceptors, e.g. **1b** (entry 2), or by electron donors, e.g. **1c,d** (entries 3 and 4), leads to a substantial drop in the diastereoselectivity. These findings clearly substantiate our previous mechanistic rationalization [3e] that the hydroxy group is responsible for observed π-facial selectivity in the chiral alcohol **1a** (entry 1) by association with the incoming electrophilic singlet oxygen dienophile. Minimization of *peri* strain dictates the conformationally preferred transition state and, consequentely, the observed stereochemical differentiation.

The poor 66 : 34 selectivity in the photooxygenation of *tert*-butyl-substituted naphthalene **1e** (entry 5) clearly demonstrates that steric bias alone is not sufficient to induce a high π-facial selectivity. In contrast, the Me_3Si-substituted analogon **1f** (entry 6) shows very high diastereoselectivity, which emphasizes the importance of electronic effects [12] in the diastereoselective [4+2] cycloaddition; however, the origin of such subtle stereoelectronic factors for singlet oxygen as dienophile would require theoretical scrutiny at a rather sophisticated computational level.

The importance of electronic effects in the diastereoselective [4+2] cycloaddition of singlet oxygen is further substantiated by the results for the halogen-substituted derivatives **1g,h** (entries 7 and 8), which both show even higher π-facial selectivity than the alcohol **1a**. Unfortunately, since the stereochemistry of endoperoxides **2g,h** could not be assigned in view of their thermal lability [13], rationalization of the observed high diastereoselectivity would be too speculative at this point. Nonetheless, whatever the stereochemical outcome, the chiral naphthalenes investigated herein unequivocally establish that stereoelectronic and not steric effects dictate the extent of π-facial selectivity in the singlet oxygen [4+2] cycloaddition. It should be of mechanistic import to probe whether these novel stereoelectronic effects, discovered for the arenes **D**, also operate in the cyclic, open-chain, and semicyclic 1,3 dienic substrates **A-C**. It is hoped that the resulting endoperoxides are sufficiently persistent to permit stereochemical assignment.

Acknowledgment : For generous financial support we thank the *Deutsche Forschungsgemeinschaft* (SFB 347 "Selektive Reaktionen Metall-aktivierter Moleküle"). M.P. is grateful to the *Fonds der Chemischen Industrie* for a doctoral fellowship (1993-95).

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6. For reports on high π-facial selectivity of halogen-substituted cyclopentadienes cf. ref. 1a. Examples of diastereoselective epoxidation of allylic flourides are given in Fujita, M.; Ishizuka, H.; Ogura, K. *Tetrahedron Lett.* **1991**, *32*, 6355-6358.
7. As a by-product also 1-ethyl-4-methylnaphthalene (33 %) was formed, which could not be removed by attempted chromatography and, thus, the mixture was submitted to photooxygenation.
8. The substrates **1** were dissolved in 0.8 mL of $CDCl_3$ in a 20-mL test tube and irradiated by means of two OSRAM Vialox NAV-E (250 W) sodium lamps, while a gentle stream of dried ($CaCl_2$, P_2O_5) oxygen gas was allowed to pass continuously through the reaction mixture. Control experiments assured that the chiral endoperoxides were stable under the reaction conditions, i.e. the d.r. values did not change on prolonged photooxygenation.
9. The diastereomeric ratios of the endoperoxides **2** were determined for the 2-H, 3-H, α-H and/or Me-H NMR signals. The assignment of the stereochemistry of the endoperoxides **2a,b** has been previously described[3e]. The stereochemisty of the silyl ether **2d** was assigned by desilylation (NBu_4F) and comparison with the spectral data of endoperoxide **2a**. The diastereomeric endoperoxides **2a** exhibit the following spectral data: *(aR*,1R*,4S*)*-**2a**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.55 (d, J = 6.5 Hz, 3 H), 1.84 (s, 3 H), 2.38 (br d, J = 3.5 Hz, 1 H), 4.70 (qd, J = 6.5 Hz, 3.5 Hz, 1 H), 6.75 (d, J = 8.2 Hz, 1 H), 6.89 (d, J = 8.2 Hz, 1 H), 7.19-7.33 (m, 4 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 15.9 (q), 18.1 (q), 65.5 (d), 79.0 (s), 83.1 (s), 120.3 (d), 121.6 (d), 126.5 (d), 126.6 (d), 134.3 (d), 139.4 (s), 140.0 (d), 141.1 (s). *(aR*,1S*,4R*)*-**2a**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.51 (d, J = 6.5 Hz, 3 H), 1.84 (s, 3 H), 2.27 (br s, 1 H), 4.62 (q, J = 6.5 Hz, 1 H), 6.71 (d, J = 8.1 Hz, 1 H), 6.91 (d, J = 8.1 Hz, 1 H), 7.20-7.52 (m, 4 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 15.9 (q), 18.2 (q), 66.1 (d), 78.7 (s), 82.7 (s), 120.1 (d), 121.5 (d), 126.5 (d), 126.5 (d), 135.4 (d), 138.3 (s), 139.1 (d), 141.4 (s).
10. On standing in solution at room temperature, all endoperoxides **2** reverted quantitatively and fast to the respective naphthalenes **1** by extrusion of molecular oxygen. Only the bromo-substituted endoperoxide **2h** afforded also an unidentified side-product (ca. 10 %).
11. The activating effect of allylic silyl substituents on the adjacent double bond is well documented: a) Schweig, A.; Weidner, U.; Manuel, G. *J. Organomet. Chem.* **1973**, *54*, 145-148: b)Schweig, A.; Weidner, U.; Manuel, G. *J. Organomet. Chem.* **1977**, *67*, C4-C6.
12. Other examples of π-facial selectivity induced by silyl substituents are given in ref. 1d) and Fleming, I.; Williams, R.V. *J. Chem. Soc. Perkin Trans. I* **1981**, 684-688. In these cases the observed diastereoselectivity was explained in terms of FMO theory.
13. For the chloro- and bromo-substituted cyclopentadienes A the opposite sense of π-facial selectivity has been reported (cf. ref 1a).

(*Received in Germany* 25 *February* 1994; *accepted* 26 *April* 1994)