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Enantioselective epoxidation of 2-substituted 1,4-naphthoquinones using *gem*-dihydroperoxides

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ABSTRACT

New *gem*-dihydroperoxides were successfully used for DBU-promoted enantioselective epoxidation of 2-substituted 1,4-naphthoquinones. The corresponding 1,4-naphthoquinone epoxides were obtained in yields up to 97% and ee's up to 82%.

1. Introduction

Enantiomerically pure epoxides are of great importance in organic chemistry. They are versatile building blocks, for example, in the synthesis of pharmaceutical and natural products.[1] While a number of different reliable methods exist for the asymmetric epoxidation of electron-rich alkenes[2,3] and electron-deficient *trans*-alkenes of the chalcone type,[4] enantioselective epoxidations of quinones are not so abundant. In 1980, Pluim and Wynberg reported the synthesis of optically active epoxynaphthoquinones by epoxidation with 30% hydrogen peroxide, aqueous sodium hydroxide and benzylquininium chloride as phase-transfer catalyst (PTC).[5] Enantiomeric excesses up to 45% were realized. In a similar way, Arai et al. achieved up to 76% ee and 47% yield with chinchonium phase-transfer catalysts.[6] Very recently Berkessel et al. reported the epoxidation of 2-methylnaphthoquinone (Vitamin K_3) using modified *cinchona* alkaloid phase-transfer catalysts too, but applying sodium hypochlorite instead of hydrogen peroxide.[7] High enantiomeric excesses (up to 85% ee at 73% yield) were obtained.

In another methodology, Taylor et al. used carbohydrate-derived anomeric hydroperoxides (AHPs) as stoichiometric oxidizing agents for the asymmetric epoxidation of 2-methylnaphthoquinone; a maximum ee of 78% was achieved, however in low yield (32%).[8,9] Chmielewski and co-workers also prepared AHPs and used them for the same purpose, obtaining 47% ee.[10,11] (+)-Norcamphor-derived hydroperoxides were employed by Lattanzi et al. to achieve 51% ee in the epoxidation of Vitamin K_3.[12] Recently, a hydroperoxide derived from a chiral diketopiperazindione was used in our group in the epoxidation of 1,4-naphthoquinones, but unsatisfactory ee's were achieved (maximum 14%).[13]

gem-Dihydroperoxides (DHPs) have received considerable interest because of their relevance as peroxidic antimalarial agents.[14–16] Recently, Iskra and co-workers reported a versatile method for the preparation of DHPs from ketones and H_2O_2 under iodine catalysis.[17,18] Other methods were described, for example, by Terent'ev,[19] Das[20] and Dussault.[21] Primary aliphatic *gem*-DHPs were not obtained by these methods, but were reported very recently by us.[22] In the series of *gem*-dihydroperoxides cyclohexylidenedihydroperoxide was the only example successfully used as oxygen source for the epoxidation of α,β-unsaturated ketones[23] and the oxidation of sulfides.[24] Optically active DHPs are rare. All reported examples were derived from steroids (see for example[16,17,25]). However, to the best of our knowledge, they have not been utilized as oxidants. Because of our continued involvement in epoxidation chemistry,[26] we became interested in using enantiomerically pure DHPs as potential oxidants for asymmetric epoxidation. Herein, we report the synthesis of novel enantiomerically pure DHPs and the first enantioselective epoxidation using optically active DHPs.

2. Results and Discussion

Aside from commercially available enantiopure ketones and ketones with a steroidal structure, a good source for naturally occurring and enantiomerically pure starting materials for the synthesis

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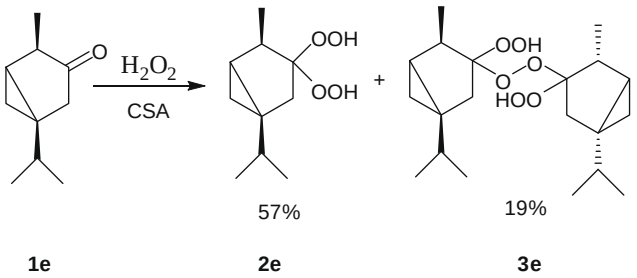
of DHPs is monoterpenones. Thus we prepared dihydroperoxide **2a** from (3*R*)-3-methylcyclohexanone **1a** analogous to Iskra and coworkers[17] while **2b–e** were obtained from *cis*-verbanone **1b**, 5α-cholestan-3-one **1c**, stanolone **1d**, or (−)-α-thujone **1e** and 70% hydrogen peroxide in the presence of camphorsulfonic acid (CSA), adopting an earlier protocol of ours (Scheme 1, Supplementary data).[22]

DHP **2e** was obtained in 57% yield from (−)-α-thujone (**1e**) (Scheme 2). Like the other DHPs, it shows distinctive signals in the NMR spectra, including a signal at 121.4 ppm in the ^{13}C NMR spectrum and one typical proton signal (intensity two protons) at 9.79 ppm in the ^{1}H NMR spectrum. In addition to the DHP **2e** the bis(hydroperoxy)peroxide **3e** was isolated in 19% yield as a mixture of diastereomers as by-product in this reaction (Scheme 2). By crystallization from ethanol one diastereomer could be isolated and characterized. In the synthesis of other *gem*-DHPs **2** only traces of the bis(hydroperoxyperoxides) were found.

The hydroxymethyl-substituted *gem*-DHP **2f** was synthesized using a slightly modified procedure starting with the corresponding hydroxymethyl-β-thujone **1f** which is easily available from (−)-α-thujone and formaldehyde in high yields.[27] **1f** can also be obtained even in larger quantities from naturally occurring cheap essential oil of *thuja occidentalis*. The *gem*-DHP **2f** was isolated in 35% yield after column chromatography with dichloromethane/methanol.

As primary substrate for epoxidation we chose 2-methyl-1,4-naphthoquinone **4a** (R^2 = Me) (Scheme 3). The reaction conditions were adopted from a previously described procedure,[11] using toluene as the solvent and DBU as the base. The DHPs **2a–e** provided unsatisfactory ee's of **6a,** as did the peroxide **3e** (Table 1, entries 1–6).

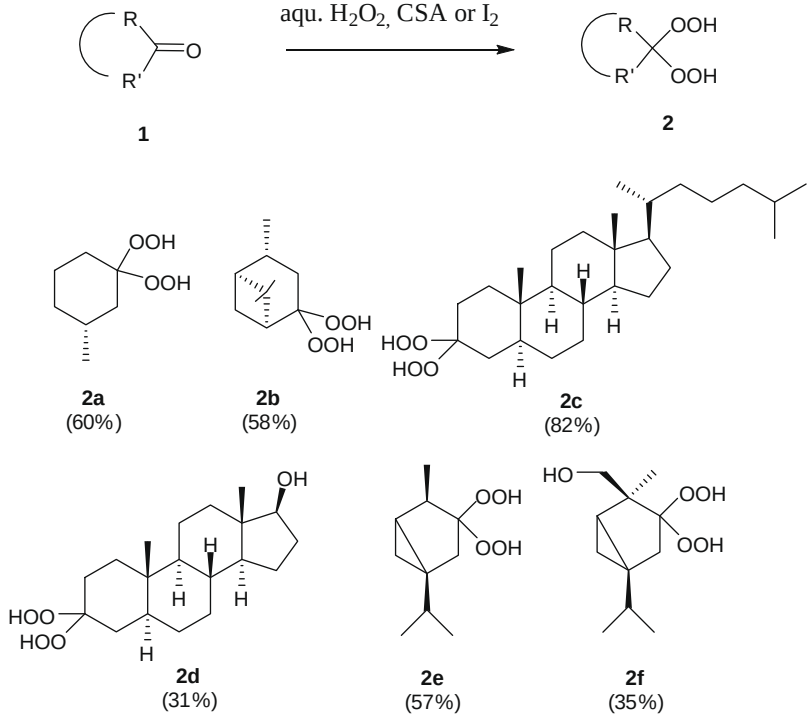
The hydroxymethyl-substituted thujone-derived *gem*-DHP **2f** can be expected to form additional hydrogen bonds via the alcoholic OH group and thus may give rise to a more rigid transition state and higher stereoselectivity in the epoxidation of 1,4-naphthoquinones. Indeed, 2-methyl-1,4-naphthoquinone **4** formed epoxide **6a** in 59% ee (Table 1, entry 7), albeit with a rather low



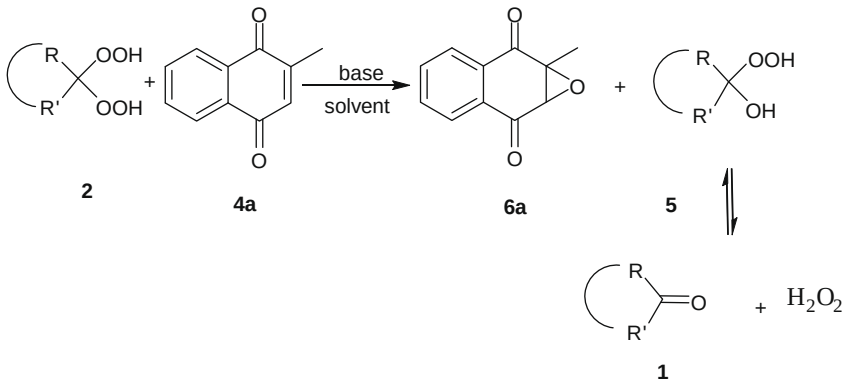
Scheme 2. Transformation of (−)-α-thujone **1e** into the *gem*-dihydroperoxide **2e**.

conversion. Thus the effect of reaction conditions on the conversion and enantiomeric excess was investigated.

Performing the reaction without the use of 4 Å molecular sieves resulted in a higher conversion but lower ee (Table 1, entry 8). Monitoring the reactions by TLC revealed that the reaction mixture without molecular sieves contained hydrogen peroxide, which could not be detected when mole sieves were used. We assume that the hydrogen peroxide is formed by decomposition of the hemiacetal-like perhydrate **5** which is the primary reaction product of dihydroperoxide **2** after transferring one oxygen atom to naphthoquinone **4** (Scheme 3). The deliberated hydrogen peroxide competes with the dihydroperoxide **2** for the naphthoquinone **4** but leads to racemic products, that is, it lowers the ee of **6**. Obviously, the hydrogen peroxide can be trapped by the molecular sieves, preventing it from non-stereoselective epoxidation of **4** (Scheme 3). As checked in some cases (e.g., **1f**), ketone **1** formed by decomposition of perhydrate **5** can be isolated from the reaction mixture and recycled. Changing the ratio of DHP: substrate **4** affected the conversion without much change of the ee. Reduction of the reaction time (to 1 day) did not significantly change the degree of conversion. To counteract a probable inactivation of the DBU by N-oxide formation an additional equivalent of DBU was added after 7 h (solvent dichloromethane). This led to higher conversion, but side products were formed.



Scheme 1. Synthesis and examples of *gem*-dihydroperoxides **2**.



Scheme 3. Asymmetric epoxidation of 2-methylnaphthoquinone **4a**.

Table 1
Epoxidation of **4a** using DHPs **2**[a] or **3e**

Entry	DHP	Solvent	Conversion of **4a**[b] (%)	ee of **6a**[b] (%)	Configuration of major enantiomer
1	**2a**	Toluene	31	~0	—
2	**2b**	Toluene	100	6	(2*S*,3*R*)
3	**2c**	Toluene	8	8	(2*S*,3*R*)
4	**2d**	Toluene	11	6	(2*S*,3*R*)
5	**2e**	Toluene	14	10	(2*R*,3*S*)
6	**3e**	Toluene	14	17	(2*R*,3*S*)
7	**2f**	Toluene	16	59	(2*R*,3*S*)
8	**2f**	Toluene	24 [c]	45 [c]	(2*R*,3*S*)
9	**2f**	Et_2O	36	56	(2*R*,3*S*)
10	**2f**	DCM	51	66	(2*R*,3*S*)
11	**2f**	EtOAc	44	66	(2*R*,3*S*)
12	**2f**	MeCN	100	46	(2*R*,3*S*)
13	**2f**	MeOH	93	10	(2*R*,3*S*)
14	**2f**	Hexane	49	33	(2*R*,3*S*)
15	**2f**	THF	29	40	(2*R*,3*S*)

[a] Reaction conditions: **2:4a:**DBU = 1:1:1, temperature −30 °C, molecular sieves 4 Å, 3 d.
[b] Determined by HPLC.
[c] Without molecular sieves.

Conversions of **4** and the ee's of epoxide **6** were found highly solvent dependent as can be seen from Table 1 (entries 7, 9–15). While highly polar or typical unpolar solvents (hexane) decrease the ee notably, the best ee values were obtained by using ethyl acetate or dichloromethane. Methanol as protic solvent is especially detrimental to ee but results in high conversion. The application of acetonitrile resulted in full conversion but only in 46% ee.

It should be noted that while conversions are generally higher in other solvents than toluene, colored side products (deeply blue turning to brownish) were observed in these cases.

Variation of temperatures revealed an optimal enantiomeric excess in a temperature range from −30 to 0 °C. Higher temperatures increased the degree of conversion but resulted in a decrease of ee. In some of these experiments we observed changes in colors probably due to unknown decomposition reactions.

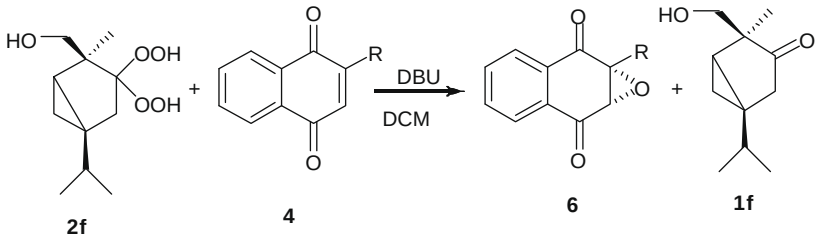
Changing the base from DBU to other organic and inorganic bases also affected the reaction strongly. Contrary to the reports of Chmielewski[11] and Taylor,[8] the use of alkali metal bases showed a very low conversion with dihydroperoxide **2f**, as did the use of DABCO. The stronger basic *N,N*-diethyl-*N′,N′*-dipropyl-*N″*-hexylguanidine gave a rather high conversion (81%), however the formation of unidentified side products was observed. The use of *n*-BuLi similar to the procedure of Lattanzi[28] gave a relatively high conversion (ca. 70%), but low enantiomeric excess (10%).

Thus we concluded that the best conditions are the use of DBU as the base, dichloromethane as solvent, molecular sieves and a ratio of substrate:oxidant:base = 1:2:2. It further turned out that stirring of the reaction mixture for the whole reaction period is important for high eés, in particular when batch sizes are larger. Most likely, the drop of ee observed otherwise is caused by the formation of free hydrogen peroxide (Scheme 3) which cannot be adsorbed by the molecular sieves fast enough.

These optimum reaction conditions were employed to epoxidize a range of 2-substituted 1,4-naphthoquinones **4** using **2f**. (Scheme 4, Table 2)

It turned out that substituents larger than methyl gave usually higher enantioselectivities. High to moderate yields and enantioselectivities were achieved. Our results successfully compete with those reported in the literature for the epoxidation of 1,4-naphthoquinones applying either asymmetric phase-transfer catalysis or using chiral hydroperoxides.

In summary, we have demonstrated for the first time that enantiomerically pure dihydroperoxides can be used in enantioselective epoxidation. Moderate to good ee's and yields were achieved in the DBU-promoted epoxidation of 2-substituted 1,4-naphthoquinones. Further studies to extend the scope of the application of the thujone-derived dihydroperoxide as well as seeking for other useful chiral dihydroperoxides are currently under way in our laboratories.



Scheme 4. Asymmetric epoxidation of 2-substituted naphthoquinones with hydroxymethyl-substituted thujone-derived *gem*-DHP **2f**.

Table 2
Epoxidation of 1,4-naphthoquinones **4** using DHP **2f** under optimized conditions[a]

Entry	1,4-Naphtho-quinones **4**	R	**6**/Yield (%)[b]	ee (%)[c]	Configuration[d]
1	**4a**	Me	**6a**/92	66	−(2*R*,3*S*)
2	**4b**	Et	**6b**/67	70	−(2*R*,3*S*)
3	**4c**	Bn	**6c**/64	74	−(2*R*,3*S*)
4	**4d**	Ph_2CH	**6d**/97	78	−(2*R*,3*S*)
5	**4e**	*t*-Butyl	**6e**/38[e]	82	+(2*R*,3*S*)
6	**4f**	Cyclohexyl	**6**f/96	60	+(2*R*,3*S*)

[a] Reaction conditions: **2f**:**4**:DBU = 1:2:2, DCM, molecular sieves 4 Å, temperature −20 °C, 16 h, continuous stirring.
[b] Isolated yield after column chromatography.
[c] Determined by HPLC on a chiral column.
[d] Sign of α_{436} value measured.
[e] 59% of the starting material could be recovered.

2. Experimental

Caution: 70% Hydrogen peroxide and peroxidic compounds are potentially explosive and should be handled with precautions (shields, fume hoods, avoidance of transition metal salts).

General procedure for epoxidation (analytical scale): dihydroperoxide **2** or **3e** (0.02 mmol) was added to the corresponding solvent (5 ml), followed by the addition of powdered 4 Å molecular sieves (100 mg). After addition of 0.1 ml of a solution of DBU (0.2 mmol) in the respective solvent (1 ml) the flask was cooled down to −50 to −40 °C and stirred for 10 min. A solution of 2-methylnaphthoquinone (0.1 ml, 0.2 mmol) in the respective solvent (1 ml) was then added and the reaction mixture was stirred at −50 to −40 °C for 1 h. Afterwards the flask was put in a freezer (−30 °C) overnight. The reaction mixture was poured into water (20 ml), extracted with dichloromethane (2 × 20 ml) and dried (sodium sulfate). After evaporation of the solvent the mixture was analyzed by HPLC on a chiral column.

General procedure for asymmetric epoxidation (preparative scale): Into a flask with dihydroperoxide **2f** (0.4 mmol) DCM (50 ml) was added, followed by powdered 4 Å molecular sieves (1 g) and DBU (0.4 mmol). The mixture was stirred at −20 °C for 10 min, naphthoquinone **4** (0.2 mmol) dissolved in DCM (1 ml) was added slowly and the reaction continued to stir overnight. The mixture was then filtered through a pad of Celite® and washed with water (50 ml). The aqueous phase was again extracted with DCM (50 ml), the combined organic phases were dried over sodium sulfate and the solvent evaporated. Purification was done by column chromatography (silica gel, cyclohexane/EtOAc = 95:5, 98:2 or 99:1).

Acknowledgments

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Supplementary data

Supplementary data (general procedures and NMR data of compound) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.05.096.

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