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# CATALYTIC ASYMMETRIC WEITZ-SCHEFFER REACTION IN THE PRESENCE OF BOVINE SERUM ALBUMIN

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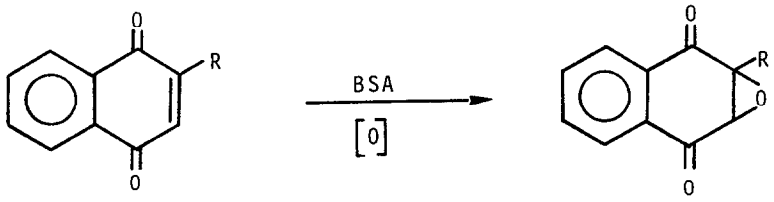
ABSTRACT: Epoxidation of 2-substituted 1,4-naphthoquinones with t-BuOOH or $H_2O_2$ in the presence of a catalytic amount of bovine serum albumin afforded the corresponding epoxynaphthoquinones in up 70% e.e.

The Weitz-Scheffer reaction[1] represents a useful tool for the synthesis of optically active epoxides, particularly if it is performed under catalytic conditions. Valuable substrates for this epoxidation are quinones, in view of the importance of vitamins K and their epoxides in metabolic processes. Inter alia, 2-methyl-3-phytyl-1,4-naphthoquinone (vitamin $K_1$, phylloquinone) is indispensable for maintaining the function of the blood coagulation system and phylloquinone 2,3-epoxide is its major metabolite in the liver.[2]

Recently vitamin $K_3$ epoxide, which has equal or higher vitamin K activity than vitamin $K_1$,[3] has been prepared by Pluim and Wynberg in a optically active form, together with a variety of 2,3-epoxynaphthoquinones, under phase transfer conditions.[4]

We decided to take advantage of the well-known binding ability of bovine serum albumin (BSA), a carrier protein in biological systems, towards species having a negative charge. For these reasons we have examined the Weitz-Scheffer epoxidation of 2-substituted 1,4 naphthoquinones (1-5) and of other electron- poor olefins in the presence of a catalytic amount of BSA.




1, 6 R = $CH_3$
2, 7 R = $C_6H_5$
3, 8 R = $C_4H_9^t$
4, 9 R = $C_6H_{11}$
5, 10 R = $C_3H_7^i$

The reaction was performed by stirring at room temperature the enone (1 mmol) and the oxidizing agent (2 mmol) in 12.5 ml pH 11 buffer solution containing 0.05 molar equivalents of BSA. Reaction time, chemical and optical yield are reported in the Table. The enantiomeric excess of the asymmetric synthesis was determined by $^1H$ NMR with $Eu(dcm)_3$ or $Eu(tfc)_3$ as chiral shift reagents.

The highest enantioselectivity (70%) was obtained in the epoxidation of 2-cyclohexyl-1,4-naphthoquinone (4) with t-BuOOH. In all cases examined t-BuOOH is the oxidant of choice from the stereoselective point of view.

The stereochemistry of the reaction is very sensitive to minor structural variation of the substrates, in agreement with the results previously found by Sugimoto in the oxidation of sulphides to sulphoxides in the presence of BSA.[6] As a matter of fact the Weitz-Sheffer reaction on 2-methyl, 2-cyclohexyl and 2-isopropyl-1,4-naphthoquinones with $H_2O_2$ or t-BuOOH afforded the corresponding epoxides (6), (9) and (10) with opposite sign of optical rotation, whereas starting from quinone (2) the (+) or the racemic 2-phenyl-1,4-naphtoquinone derivative (7) was obtained depending on the oxidizing species.

Steric effects are also important since 2-t-butyl-1,4-naphthoquinone was recovered unchanged after a very long reaction time either with $H_2O_2$ or with tBuOOH.

The degree of asymmetric induction in the catalytic epoxidation with bovine serum albumin and t-BuOOH is generally more relevant than in the

reaction under phase-transfer conditions with $H_2O_2$. In our case epoxides (6), (7) and (9) have 20, 50 and 70% e.e., respectively, compared to 20, 45 and 39% e.e., respectively, under the conditions of Pluim and Wynberg.

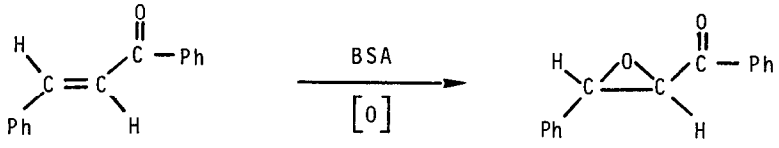
On the basis of the CD spectra the vitamin $K_3$ 2,3 epoxide (6), and by analogy the 2-substituted 1,4-naphthoquinone epoxides (7)-(10), have the (-)-(2R, 3S) absolute configuration.[4,7]

Table Enantioselective Weitz-Scheffer reaction in a buffer solution (pH 11) containing bovine serum albumin at 25°C.

| R | Oxidizing agent | Time (days) | $[\alpha]_{436}$ [a] | Yield % | e.e. ± 2% | PTC e.e. |
|---|---|---|---|---|---|---|
| $CH_3$ | $H_2O_2$ | 3 | (+) | 32 | 3 [b] | 5 |
| | $t\text{-}C_4H_9OOH$ | 3 | (-) | 34 | 20 [b] | |
| $C_6H_5$ | $H_2O_2$ | 8 | | 42 | 0 [c] | 45 |
| | $t\text{-}C_4H_9OOH$ | 8 | (+) | 46 | 50 [c] | |
| $t\text{-}C_4H_9$ | $H_2O_2$ | 9 | - | - | - | 23 |
| | $t\text{-}C_4H_9OOH$ | 9 | - | - | - | |
| $C_6H_{11}$ | $H_2O_2$ | 7 | (-) | 68 | 2 | 39 |
| | $t\text{-}C_4H_9OOH$ | 7 | (+) | 64 | 70 | |
| $i\text{-}C_3H_7$ | $H_2O_2$ | 6 | (+) | 60 | 15 | 31 |
| | $t\text{-}C_4H_9OOH$ | 6 | (-) | 56 | 21 | |

[a] The (+) enantiomer has (2S, 3R) absolute configuration. [b] Determined in the presence of $Eu(dcm)_3$ as shift reagent. [c] Determined in the presence of $Eu(hfc)_3$ as shift reagent.

We have also examined the epoxidation of an acyclic $\alpha,\beta$ unsaturated ketone, namely trans chalcone (11). The reaction with $H_2O_2$ and t-BuOOH gave epoxides (+)12 and (-)(12); $[\alpha]_{578}$ -25.5° and +27°, 12% and 13% e.e., respectively. The lower optical yield of trans epoxychalcone (12) with respect to 2,3 epoxy-1,4-naphthoquinones leads to the conclusion that the larger conformational mobility of the starting material gives rise to a lower enantioselectivity of this Weitz-Scheffer oxidation.




(11) (12)

Finally it should be mentioned that the stereoelectronic effects of the substituent at C-2 in the epoxidation of 1,4-naphthoquinones in the presence of BSA are in agreement with the mechanism proposed for the epoxidation of $\alpha,\beta$-unsaturated ketones in alkaline medium. A bulky substituent, such as a t-butyl group, disfavours the conjugate addition of hydroperoxide anion to the double bond in the rate-determining step. On the other hand a phenyl substituent stabilizes the intermediate carbanion, thus increasing the reaction rate.

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