Stereospecific Epoxidation by Air of Cholest-5-ene Derivatives catalysed by a Ruthenium Porphyrin

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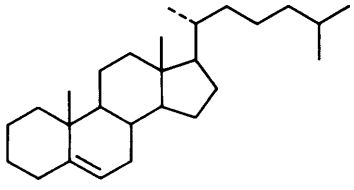
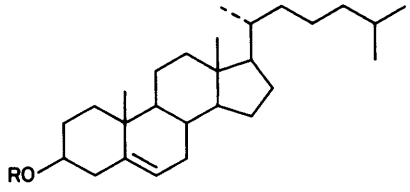
A ruthenium porphyrin catalyses the epoxidation of several cholest-5-ene derivatives by air in high yield and with nearly complete β-stereospecificity; C-3-unprotected cholesterol is unaffected, but cholesteryl acetate gives nearly pure (>99%) 5β,6β-epoxide.

The ability of transition metal–porphyrin complexes to carry out the catalytic epoxidation of various alkenes with suitable oxygen donors under mild conditions is now well documented.[1] The lower reactivity of *trans* than *cis* double bonds has been recognised,[2] and a high degree of stereospecificity of the epoxidation when aliphatic alkenes are used as substrates has been observed in several cases.[2—7] The epoxidation of *cis*- and *trans*-β-methylstyrene has been shown to proceed with nearly complete retention of configuration with chromium,[8] manganese,[6] iron,[9,10] and ruthenium[11] based metalloporphyrin systems. Furthermore, iron porphyrins bearing chiral *meso* substituents catalysed the asymmetric epoxidation of styrene derivatives.[9,12] Few studies have been conducted on the metalloporphyrin catalysed epoxidation of steroids. An estra-5(10),9(11)-diene derivative[13] was converted by FeCl(tpp)–PhIO† to a mixture of its 5,10-epoxides in low yield but with good α-stereoselectivity [α/(α + β) = 0.91]. In contrast, with substrates such as cholesteryl acetate[14] or cholesterol analogues,[15] Δ^5-epoxidation with MCl(tpp)–PhIO (M = Cr, Mn, Fe),[14] or FeCl(tptp)–PhIO[15] was fairly β-stereoselective [β/(α + β) = 0.71—0.89]. The MnCl(tpp)–NaOCl system showed poor stereoselectivity in the epoxidation of cholest-5-ene, while a fair α-selectivity was obtained in the 13,17-epoxidation of a 19-nor steroid precursor [α/(α + β) = 0.80].[16] An iron complex of a steroidal porphyrin intercalated in a phospholipid-bilayer assembly has been shown to induce a profound regioselectivity for the side-chain epoxidation of sterols by PhIO.[15] We report here the remarkable β-stereospecificity observed for the epoxidation of several cholest-5-ene derivatives by atmospheric oxygen in the presence of a sterically hindered ruthenium porphyrin.



(1)



(2) a, R = H
b, R = MeCO
c, R = Me_2Bu^tSi

† Abbreviations: tpp = tetraphenylporphyrinato; PhIO = iodosylbenzene; tptp = tetra-*p*-tolylporphyrinato.

The carbonyl–ruthenium(II) complex of tetramesitylporphyrin was prepared according to literature procedures,[17] and was dissolved in benzene. *In situ* conversion to the corresponding *trans*-dioxoruthenium(VI) complex was effected by addition of a stoicheiometric amount of *m*-chloroperbenzoic acid.[17] Catalytic epoxidations of cholest-5-ene derivatives were conducted by stirring the solutions (5×10^{-3} M in catalyst; 10^{-1} M in substrate) in the dark under air for several hours, in the presence or absence of solid K_2CO_3 (Table 1). Substrate conversion was monitored by t.l.c. until no further change was noticed. The reaction mixture was then chromatographed on silica gel, and the epoxides were isolated and weighed. Relative yields of the α- and β-epoxides were determined by integration of the ^1H n.m.r. signals of C-6-H.[16] Structures were assigned by comparing the ^1H and ^{13}C n.m.r. spectra of the products with those of authentic samples;[18—20] the epoxides of the silyl ether (**2c**)[21—23] (prepared in a *ca.* 1 : 1 ratio by *m*-chloroperbenzoic oxidation) were separated by preparative h.p.l.c. and their structures were assigned by n.m.r. spectroscopy using classical diagnostic criteria.[20]

Product analysis (Table 1) demonstrates that this ruthenium–porphyrin system is a highly efficient and stereoselective catalyst for the epoxidation by atmospheric oxygen of those cholesterol derivatives in which the OH group is protected by an ester (**2b**) or a silyl (**2c**) group; these unsaturated steroids are selectively converted to epoxide in high yield (60—90%) with nearly complete β-stereospecificity, albeit rather slowly. Protection of the OH group is required, as cholesterol itself (**2a**) completely inhibits the catalysis. That the substituent on C-3 is involved in the

Table 1. Stereoselectivity in the epoxidation of cholest-5-ene derivatives with air in the presence of a ruthenium porphyrin (see text).

Substrate	K_2CO_3 present	Reaction time	Epoxide yield(%)[c]	% Stereoisomer α	% Stereoisomer β
(1)	No	3 days[a]	45	20	80
	Yes	3 days[a]	40	20	80
(2a)	No	7 days	<5[b]		
	Yes	7 days	<5[b]		
(2b)	No	5 hours	85	<1	>99
	Yes	3 days	90	<5	>95
(2c)	No	20 hours	60	8	92
	Yes	6 days	72	15	85

[a] Epoxide formation very slow; numerous other unidentified products; reaction stopped after 3 days. [b] May result from a slight excess of *m*-chloroperbenzoic acid. [c] All epoxide yields are based on the substrate.

mechanism, as suggested by the above results, is confirmed by the finding that cholest-5-ene (**1**) is only slowly epoxidized by the catalytic system while cholesteryl acetate (**2b**) gives nearly pure (>99%) 5β,6β-epoxide. The scope of this highly selective and stereospecific catalyst in steroid oxidation is under study.

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