A Convenient Synthesis of 5,6β-Epoxides of Some Cholesteryl Esters and Δ^5-Ketosteroid Derivatives by Catalytic β-Stereoselective Epoxidation

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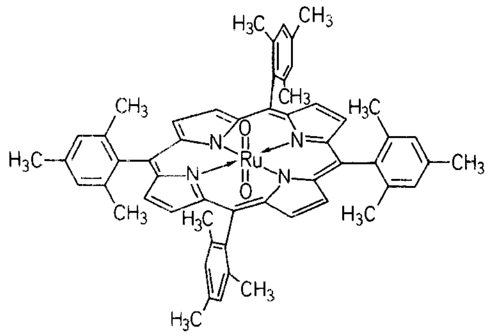
The epoxidation of a series of cholesteryl esters by air in the presence of a catalytic amount of a ruthenium tetramesitylporphyrin complex is described. The preparative procedure, which requires only 4 to 5 mol % of the catalyst, leads to high conversion (76 to 94%) and very high β-stereoselectivity (> 99%). Similar results are obtained in the epoxidation of 3β-acetoxyandrost-5-ene-17-one, 3β-acetoxypregn-5-ene-20-one, and 3,3-ethylenedioxycholest-5-ene.

Catalytic oxidations with molecular oxygen are believed to have a considerable potential for the production of fine chemicals. Their obvious advantages with respect to stoichiometric processes using traditional oxidants are the use of a cheap reagent, namely oxygen, and the absence of by-product problems. On the other hand, their scope in organic synthesis is largely unexplored.[1] We have begun investigating the utilization in steroid epoxidation[2] of a recently described ruthenium porphyrin catalyst.[3]

In 1985, Groves and Quinn have reported that *trans*-dioxo(tetramesitylporphyrinato)ruthenium(VI) [Ru(O)$_2$(tmp), 1], prepared by 3-chloroperoxybenzoic acid oxidation of the corresponding carbonyl-ruthenium(II) complex [Ru(CO)(tmp)] is able to catalyze the epoxidation by air of various olefins (cyclooctene, methylstyrenes, norbornene) at ambient temperature and pressure.[3] In a preliminary communication,[2] we have described the comparative behavior towards aerobic epoxidation in the presence of the Groves-Quinn catalyst of four unsaturated steroids. Cholesterol inhibits the catalytic system, presumably through protonation of the oxo ligand of the active species. Cholest-5-ene is slowly converted to its epoxides in moderate yield (45% after 3 days) and good β-stereoselectivity (80%), but minor unidentified oxidation by-products are also obtained. Cholesteryl chloride is selectively converted to its epoxides in 7 days in high yields (90%) with high β-selectivity (91%). Especially noteworthy is the reaction of cholesteryl acetate, which gives 85% β-epoxide conversion (isolated yield) in 5 hours with nearly complete β-stereoselectivity (> 99%).[2]



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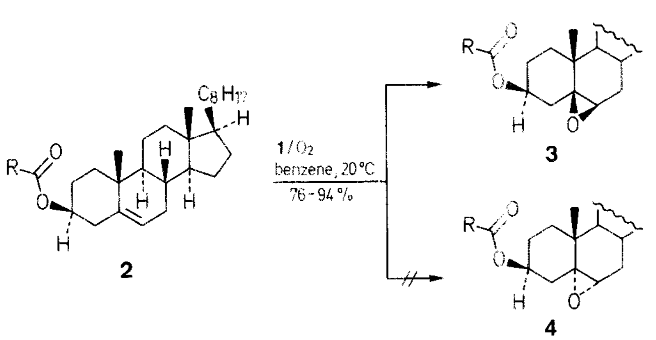
We have now investigated the Groves-Quinn epoxidation of a series of cholesteryl esters of various aliphatic acids, and of one aromatic acid. In addition, we have studied the behavior of a few Δ^5-ketosteroid derivatives (androstenone acetate, pregnenolone acetate, and cholestenone) to check the compatibility of the Groves-Quinn catalyst in the presence of ketone groups on the steroid nucleus. The results of this investigation are described in the present paper.

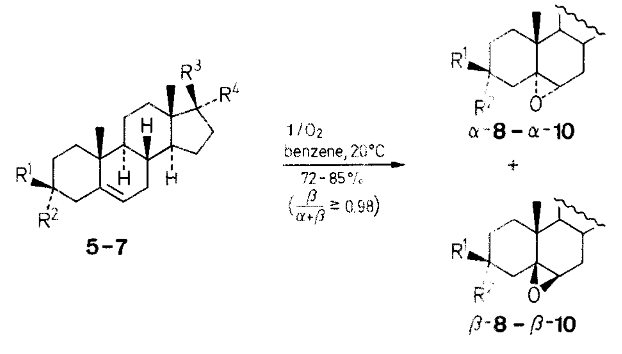
The ruthenium porphyrin catalytic system is particularly effective in the aerobic epoxidation of cholesteryl esters (see Table). Scheme A summarizes the results obtained for this class of substrates. A high conversion rate (76 to 94%) is obtained, and the 5,6β-epoxide is formed with nearly complete stereoselectivity (> 99%). The reaction is quite rapid (complete in 5 h) in the case of the acetic ester **2b**; aliphatic esters with longer alkyl chains **2c–e** require longer reaction times, generally 3–5 days, but the stereoselectivity remains high (> 99%). The formic-**2a**, pivalic-**2f**, and benzoic-**2g** esters behave similarly. The steric bulk of pivalic ester does not seem to affect the stereoselectivity or the kinetics of the reaction in a significant fashion. In contrast, the presence of a phenyl group in the benzoic ester does result in a slower reaction (6 days), but again a high degree of β-stereoselectivity (> 99%) is obtained.



2	R	2	R
a	H	**e**	n-$C_{17}H_{35}$
b	CH_3	**f**	t-C_4H_9
c	n-C_5H_{11}	**g**	Ph
d	n-C_8H_{17}	**h**	EtO

Scheme **A**

The results obtained for the catalytic epoxidation of the keto-steroid derivatives **5–7** (see Table) are summarized in Scheme **B**. The presence of a keto group on the steroid nucleus does not affect the epoxidation process, except in the case (not shown in Scheme **B**) of a carbonyl group conjugated with the olefin bond



	R^1	R^2	R^3	R^4
5, 8 (α, β)	OAc	H	=O	
6, 9 (α, β)	OAc	H	CH_3CO	H
7, 10 (α, β)	OCH_2CH_2O		C_8H_{17}	H

Scheme **B**

(cholest-4-ene-3-one), where 85% of the starting material is recovered after 9 days. Ketalization of the conjugated carbonyl group shifts the double bond to the 5,6-position; the resulting ketal **7** is then readily epoxidized. The epoxidation is highly β-stereoselective for the three compounds **5–7**, and fair to good epoxide yields (72–85%) are obtained, but long reaction times (4-7 days) are required.

The stereoisomers of the 5,6-epoxy derivatives of substituted 5-cholestenes exhibit distinctive signals in their 200 MHz ^{1}H-NMR spectra. The signal of the 6β-proton of the 5α,6α-epoxide is a doublet centered at $\delta = 2.9$ ($J = 4$ Hz), clearly distinct from the ill-resolved doublet at $\delta = 3.1$ ($J = 2$ Hz) observed for the 6α-proton of the 5β,6β-epoxide. Detection and ratio of both stereoisomers are thus readily carried out by NMR[16–18] (Scheme **B**).

The catalytic process that we report for epoxidation of cholesteryl esters and Δ^5-ketosteroid derivatives is easy to carry out, it uses a cheap reagent (air), and it affords a stereochemically pure

Table. β-Stereoselective Epoxidation of Cholesteryl Esters and Δ^5-Ketosteroid Derivatives

Starting Steroid	Reaction Time	Product	Yield[a] (%)	mp (°C)[b] (solvent)	Molecular Formula[c] or Lit. mp (°C)	^{1}H-NMR (CDCl$_3$/TMS)[d,e] δ, J (Hz)	^{13}C-NMR (CDCl$_3$/TMS)[d,e] δ
2a	3d	**3a**	81	132–133 (*n*-hexane)	$C_{28}H_{46}O_3$ (430.7)	0.64 (s, 3H, H-18); 0.86 (d, 6H, H-26 + 27); 0.88 (d, 3H, J = 6.3, H-21); 1.01 (s, 3H, H-19); 3.07 (d, 1H, J = 1.6, H-6α); 4.90 (m, 1H, H-3α); 8.00 (s, 1H, HCO)	11.8 (C-18); 17 (C-19); 50.9 (C-9); 56.2 (C-14, 17); 62.2 (C-5); 63.3 (C-6); 71.1 (C-3); 160.3 (HCO)
2b	5h	**3b**	85	110 (PE)	111[4–8]	0.64 (s, 3H, H-18); 0.87 (d, 6H, H-26 + 27); 0.88 (d, 3H, J = 6.4, H-21); 1.00 (s, 3H, H-19); 2.02 (s, 3H, CH_3CO); 3.07 (d. 1H, J = 2.2, H-6α); 4.8 (m, 1H, H-3α)	11.8 (C-18); 17 (C-19); 51 (C-9); 56.2 (C-14, 17); 62.5 (C-5); 63.5 (C-6); 71.3 (C-3); 170.4 (CH_3CO_2)
2c	4d	**3c**	91	74–75 (PE)	$C_{33}H_{56}O_3$ (500.8)	0.64 (s, 3H, H-18); 0.87 (d, 6H, H-26 + 27); 0.89 (d, 3H, J = 6.4, H-21); 1.00 (s, 3H, H-19); 3.08 (d, 1H, J = 1.75, H-6α); 4.78 (m, 1H, H-3α)	11.8 (C-18); 17.1 (C-19); 51.1 (C-9); 56.3 (C-14, 17); 62.6 (C-5); 63.6 (C-6); 71.1 (C-3); 173.3 (CO_2)
2d	1d	**3d**	76	56–58 ($EtOH/H_2O$)	$C_{36}H_{62}O_3$ (542.9)	0.64 (s, 3H, H-18); 0.86 (d, 6H, H-26 + 27); 0.88 (d, 3H, J = 6.3, H-21); 1.00 (s, 3H, H-19); 3.08 (1H, H-6α); 4.80 (s, 1H, H-3α)	11.8 (C-18); 17.0 (C-19); 51.1 (C-9); 56.3 (C-14, 17); 62.4 (C-5); 63.4 (C-6); 71.0 (C-3); 173.0 (CO_2)
2e	7d	**3e**	77	84 (PE)	$C_{45}H_{80}O_3$ (669.1)	0.65 (s, 3H, H-18); 0.86 (d, 6H, H-26 + 27); 0.88 (d, 3H, J = 6.4, H-21); 1.01 (s, 3H, H-19); ~1.26 [br, 32H, $(CH_2)_{16}$]; 3.08 (1H, H-6α); 4.80 (m, 1H, 3α)	11.8 (C-18); 17.0 (C-19); 51.1 (C-9); 56.3 (C-14, 17); 62.5 (C-5); 63.5 (C-6); 71.0 (C-3); 173.1 (CO_2)
2f	2d	**3f**	94	156–157 ($MeOH/H_2O$)	$C_{32}H_{54}O_3$ (486.8)	0.64 (s, 3H, H-18); 0.87 (d, 6H, H-26 + 27); 0.89 (d, 3H, J = 6.6, H-21); 1.01 (s, 3H, H-19); 1.17 (s, 9H, *t*-C_4H_9); 3.075 (d, 1H, J = 2.1, H-6α); 4.50 (m, 1H, H-3α)	11.8 (C-18); 17.1 (C-19); 51.0 (C-9); 56.3 (C-14, 17); 62.5 (C-5); 63.5 (C-6); 70.9 (C-3); 172.9 (CO_2)
2g	6d	**3g**	93	173 (Et_2O/ *n*-heptane)	172–174[4] 174–175[9]	0.65 (s, 3H, H-18); 0.88 (d, 6H, H-26 + 27); 0.90 (d, 3H, J = 6.8, H-21); 1.06 (s, 3H, H-19); 3.12 (d, 1H, J = 1.25, H-6α); 5.00 (m, 1H, H-3α); 7.38–7.54 (m, 3H, $H_{m,p}$-C_6H_5); 8.02 (m, 2H, H_o-C_6H_5)	11.8 (C-18); 17.1 (C-19); 51.0 (C-9); 56.3 (C-14, 17); 62.5 (C-5); 63.5 (C-6); 71.9 (C-3); 128.3, 129.6, 130.6, 132.8 (C_6H_5); 165.9 (CO_2)
2h	2d	**3h**	90	101 ($MeOH/H_2O$)	$C_{30}H_{50}O_4$ (474.7)	0.65 (s, 3H, H-18); 0.88 (d, 6H, H-26 + 27); 0.90 (d, 3H, J = 6.1, H-21); 1.00 (s, 3H, H-19); 1.31 (t, 3H, J = 7.1, $C\underline{H}_3CH_2$); 3.09 (d, 1H, J = 2.05, H-6α); 4.19 (q, 2H, J = 7.1, $CH_3C\underline{H}_2$); 4.6 (m, 1H, H-3α)	11.6 (C-18); 17.0 (C-19); 51.0 (C-9); 56.3 (C-14, 17); 62.4 (C-5); 63.5 (C-6); 75.1 (C-3); 154.7 (CO_2)
5	7d	**8**	73	189 ($EtOH/H_2O$)	189–190[10–12]	0.85 (s, 3H, H-18); 1.04 (s, 3H, H-19); 2.03 (s, 3H, CH_3CO); 3.15 (d, 1H, J = 2.2, H-6α); 4.78 (m, 1H, H-3α)	13.5 (C-18); 17.1 (C-19); 62.5 (C-5); 63.1 (C-6); 71.1 (C-3); 170.4 (CO_2); 220.4 (C-17)
6	7d	**9**	72	134–135	133[13,14]	0.60 (s, 3H, H-18); 1.00 (s, 3H, H-19); 2.03 (s, 3H, CH_3CO_2); 2.10 (s, 3H, CH_3CO); 3.15 (d, 1H, J = 2.12, H-6α); 4.78 (m, 1H, H-3α)	13.1 (C-18); 17.0 (C-19); 62.4 (C-5); 63.3 (C-6); 71.2 (C-3); 170.5 (CO_2); 209.1 (C-20)
7	3d	**10**	85	128 (PE)	128–129[15]	0.64 (s, 3H, H-18); 1.00 (s, 3H, H-19); 3.07 (s, 1H, H-6α); 3.92 (br s, 4H, OCH_2CH_2O)	11.8 (C-18); 17.1 (C-19); 109.5 (C-3)

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[a] Isolated yield after chromatographic separation.

[b] Measured with an Olympus BH2 polarizing microscope fitted with a Mettler FP800 hot stage. PE = petroleum ether (bp 35–60 °C).

[c] Satisfactory microanalyses obtained: C ± 0.36, H ± 0.19, O ± 0.34.

[d] Recorded on a Bruker AC200 spectrometer.

[e] Only representative signals are given.

product in good yield. This result contrasts with those obtained earlier in the epoxidation of cholesteryl acetate by iodosylbenzene in the presence of chromium, manganese, or iron tetraphenylporphyrins,[19] which requires an expensive oxidant and shows only good β-stereoselectivity (71–89%). The present procedure seems therefore to be of a higher synthetic utility. It is useful to recall that epoxidation of the "hindered" β-side of unsaturated steroids is usually carried out via *trans*-halohydrins in two or three steps with a moderate overall yield.[20] Our procedure, which involves a one-pot catalytic aerobic reaction, therefore offers a more convenient alternative access to the 5,6β-epoxides of some Δ^5-unsaturated steroids. The mutagenicity and cytotoxicity of the related cholesterol epoxides are the topic of active current research.[21,22]

All but one of the steroid compounds used as substrates in this study were commercially available samples from Aldrich, BDH, Eastman, Sigma, or Steraloids, and they were used as received after a check of their purity had been made by TLC. The solvents benzene, *n*-heptane, and ether were R.P. Normapur (Prolabo), and they were used as received. Cholesteryl pivalate was prepared in 96% yield by reacting cholesterol with pivaloyl chloride in pyridine solution; mp 159–161 °C (Lit.[23] mp 160–162 °C). Carbonylruthenium(II)(tetramesitylporphyrin)[24] was prepared according to a literature procedure.[25]

The formation of oxidation products was followed by TLC on silica gel plates (Merck 60F254). After elution with suitable solvent mixture (generally EtOAc/cyclohexane, 1:9), the plates were sprayed with a modified Kagi-Mischer reagent (solution of 0.5 mL of anisaldehyde and 1 mL of conc. H_2SO_4 in 50 mL of AcOH), then heated at 125 °C for 10 min for optimal color formation.

Melting points were measured by the Kofler method, or with a polarizing microscope (Olympus BH-2) fitted with a hot stage (Mettler FP800). Analyses were performed by the Service d'Analyses du CNRS, Vernaison. ^{1}H- and ^{13}C-NMR spectra were run with a Bruker AC 200 spectrometer on $CDCl_3$ solutions with TMS as internal standard.

Catalytic β-Stereoselective Epoxidation of Steroids; General Procedure: A two-necked 10-mL round-bottomed flask is charged with Ru(CO)(tmp) (20 mg, 0.022 mmol), 3-chloroperoxybenzoic acid, (85% purity, 8.7 mg, 0.043 mmol), and benzene (3 mL). The mixture is stirred magnetically for 3 min for complete dissolution of the reactants and generation of the catalytically active species $Ru(O)_2(tmp)$ (**1**).[24] The unsaturated steroid (200 to 300 mg, ca. 0.5 mmol) is then added, the flask (unstoppered) is wrapped with aluminum foil to exclude stray light, and the solution is stirred until complete disappearance of the substrate. This is checked by visual examination of TLC plates as described above, and it is obtained after a period of 5 h to 7 d,[26] depending on the substrate. *n*-Heptane (20 mL) is added, and the volume of the reaction mixture is reduced under aspiration at 60–70 °C to near dryness. This procedure is repeated to give 3–5 mL of the mixture. This is chromatographed on a column containing silica gel (30–40 g) slurried in petroleum ether (bp 35–60 °C); elution is performed with ether/petroleum ether (bp 35–60 °C) mixtures of increasing polarity (0, 1, 2, 5, 10, 20, 30, 40% ether). The epoxide product is usually found in 3–5 50 mL fractions eluted with 40% ether. These fractions are analyzed by ^{1}H- and ^{13}C-NMR spectroscopy. The relative yields of α- and β-epoxides are obtained by integration of the signals of the C-6 protons (Scheme **B**). A final recrystallization from EtOH/water affords an analytically pure product free from detectable porphyrin impurities (Table).

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