REGIOSELECTIVE EPOXIDATION BY AIR OF STEROL ESTERS BEARING SEVERAL DOUBLE BONDS USING A RUTHENIUM PORPHYRIN CATALYST

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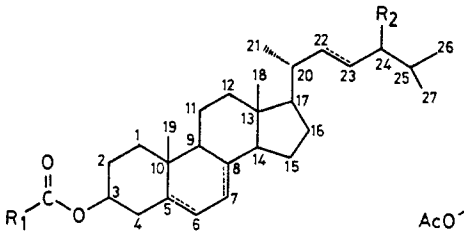
A series of sterol esters bearing varying patterns of unsaturation on the nucleus, side chain, and acyl substituent were epoxidized using trans-dioxoruthenium(VI) tetramesitylporphyrin as catalyst and air as source of oxygen. Attack at the steroid nucleus is generally favored, and a high degree of β-stereoselectivity is obtained except for conjugated 5,7 diene systems which yield a ca. 1:1 mixture of 5,6α and 5,6β epoxides.

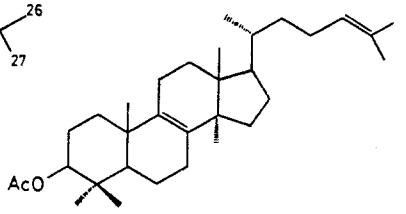
1. Introduction

Recently, the solutions obtained by m-chloroperbenzoic acid oxidation of carbonylruthenium(II)tetramesitylporphyrin Ru(CO)(tmp) have been found to catalyze the aerobic epoxidation of various Δ^5 steroids (in which a double bond is present at the 5,6 position of the tetracyclic nucleus) [1,2]. This catalytic system exhibits unique features which makes it well suited to applications in synthetic organic chemistry: it uses a cheap oxidant (air), it affords a clean conversion of the Δ^5 steroid to its epoxides in high yield (72–90%), and it shows a high degree of β-stereoselectivity ($> 80\%$) [1]. It is believed that the active species is the trans-dioxoruthenium(VI) complex $Ru(O)_2(tmp)$, which is known to be reactive in oxygen transfer reactions to olefins [3], phosphines [4], and thioethers [5], both stoichiometrically and catalytically. We have described very recently an application of this catalytic system to the stereoselective synthesis of the 5,6β-epoxides of a series of cholesteryl esters and Δ^5 steroids (androstenone acetate, pregnenolone acetate, cholestenone ethyleneketal) which are not readily accessible using traditional methods [6].

Continuing our studies on the scope of this catalyst in synthetic steroid chemistry, we have investigated its behavior towards a series of sterol esters bearing several olefinic bonds. In addition to a double bond in the B ring of the steroid nucleus, these substrates exhibited unsaturation either on the nucleus (dehydrocholesterol esters), or on the side chain (stigmasterol acetate, lanosterol



1 – 4
6 – 12



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	R_1	R_2	Position(s) of double bond(s) (N′ = carbon N of acyl chain)
1	CH_3	H	5,7
2	C_6H_5	H	5,7
3	CH_3	CH_3	5,7,22
4	CH_3	C_2H_5	5,22
6	$C_6H_5CH_2$	H	5
7	n-Pr	H	5
8	$CH_3CH{=}CH$(trans)	H	5,2′
9	$C_6H_5(CH_2)_2$	H	5
10	$C_6H_5CH{=}CH$(trans)	H	5,2′
11	$CH_3(CH_2)_7CH{=}CH(CH_2)_7$(cis)	H	5,9′
12	$CH_3(CH_2)_7CH{=}CH(CH_2)_7$(trans)	H	5,9′

Scheme I.

acetate), or both (ergosterol acetate), or finally on the acyl substituent (cholesterol crotonate, cinnamate, oleate, and elaidate). This communication describes the regio- and stereo-selective behaviour of the ruthenium tetramesitylporphyrin catalyst towards this class of substrates (Scheme I).

2. Experimental

The catalyst preparation and the general procedures for catalytic steroid epoxidation and product detection, isolation, and identification by n.m.r. methods have been detailed in a previous publication [6]. Dehydrocholesterol acetate 1 and benzoate 2, stigmasterol acetate 4, cholesterol phenylacetate 6, butyrate 7, crotonate 8, hydrocinnamate 9, cinnamate 10, oleate 11, and elaidate 12 were purchased from Sigma or Steraloids, Ergosterol acetate 3 and lanosterol acetate 5 were prepared by reaction of acetic anhydride in pyridine on the parent com-

Table 1
Ruthenium porphyrin catalyzed epoxidation of sterol esters

Substrate	Reaction time (hours)	Double bond(s) epoxidized [a]						
		5,6		7,8	8,9	22,23	24,25	
		%α	%β	%	%	%	%R	%S
dehydrocholesterol acetate **1**	1	38	34	<1	–	–	–	–
dehydrocholesterol benzoate **2**	1	dec [b]	47	<1	–	–	–	–
ergosterol acetate **3**	4	38	41	<1 [c]	–	<1	–	–
stigmasterol acetate **4**	24	2	85	–	–	<1	–	–
lanosterol acetate **5**	72	–	–	–	<1	–	15	15

[a] Yield of isolated epoxidized material; products in yield indicated <1% were undetected by ^{1}H n.m.r..
[b] Product detected by analytical TLC but decomposed on preparative TLC.
[c] 3% of starting material is recovered.

pound; ergosterol was obtained from Sigma, and lanosterol from Research Plus (the latter was 70% pure at best). All new compounds were characterized by elemental analysis and/or high resolution mass spectrometry, as well as by ^{1}H and ^{13}C n.m.r. spectroscopy.

3. Results

Table 1 summarizes the results obtained for the catalytic epoxidation of sterol esters **1**-**3** which exhibit a conjugated 5,7 diene system, and **4**-**5** which have a single double bond on the nucleus and an additional unsaturation at C22 or C24 on the side chain. Experimental data obtained for cholesterol esters of unsaturated carboxylic acids **8** and **10**-**12** are reported in table 2, together with comparative information on the corresponding esters of saturated carboxylic acids **6**, **7**, and **9**.

The catalytic epoxidation of conjugated dienes **1**-**3** is highly regioselective, but not stereoselective: a mixture of the two isomeric 5,6α and 5,6β epoxides only in a ca. 1:1 ratio is obtained, but the two compounds are easily separated by chromatography on alumina. For the sake of comparison, let us recall that peracid epoxidation of dehydrocholesterol acetate **1** affords only the 5,6α epoxide, and/or the 5,6α-7,8α diepoxide [7,8]; the 5,6β epoxide is accessible in moderate yield from cholesterol acetate in four steps [7]. Obviously, our catalytic method offers a quick and efficient alternative access to the latter epoxide. In the case of

Table 2
Regio- and stereo-selective epoxidation of cholesterol esters of unsaturated carboxylic acids

Cholesterol ester	Reaction time (days)	Double bond(s) epoxidized [a,b]				
		5,6		2′,3′	9′,10′	5,6+9′,10′
		%α	%β	%	%	%
phenylacetate **6**	2	<1	88	–	–	–
butyrate **7**	1	<1	90	–	–	–
crotonate **8**	1	<1	79 [c]	<1	–	–
hydrocinnamate **9**	1	<1	91	–	–	–
cinnamate **10**	7	<1	18	<1	–	–
oleate **11**	7	<1	18	–	19	30
elaidate **12**	2	<1	57 [d]	–	<1	<1

[a] Yield of isolated epoxidized material; products in yield indicated <1% were undetected by ^{1}H n.m.r..
[b] Primed numbers refer to acyl chain carbon atoms.
[c] Unidentified by-products in an overal yield of ca. 7% are detected.
[d] Unidentified polar by-products (presumably derived from acyl chain autoxidation) are detected in an overall yield of ca. 26%; 5% of starting material is recovered.

dehydrocholesterol benzoate **2**, only the 5,6β epoxide can be isolated as the 5,6α isomer is very unstable in preparative thin layer chromatography. For ergosterol acetate **3**, the yields of 5,6 epoxides are similar, and no epoxidation of the side double bond is detected after 1 day. Stigmasterol acetate **4** with its Δ^5 nucleus and trans double bond on the side chain behaves in a fashion similar to the cholesterol esters of trans unsaturated acids (vide infra); the observed Δ^5 regioselectivity is higher than that found with the iron tetra-p-tolylporphyrin/iodosylbenzene system [9]. Lanosterol acetate **5** is attacked on the trisubstituted 24,25 double bond of the side chain, and not on the tetrasubstituted 8,9 double of the steroid nucleus; the latter probably is too hindered to react readily with a bulky ruthenium tetramesitylporphyrin species. The catalytic reaction yields regiospecifically a racemic mixture of the diastereoisomeric (24R) and (24S) epoxides which are separated by selective dissolution of the latter in warm methanol [10].

The catalytic epoxidation reaction is region- and stereo-selective for the cholesterol esters of trans unsaturated carboxylic acids **8**, **10**, and **12**. The 5,6β epoxides are obtained in good yield and high stereoselectivity (>99%). The absence of reaction of the trans double bond on the acyl chain is consistent with the lower reactivity of trans olefins, as compared to cis olefins, in a similar catalytic system [3]. In contrast, cholesterol oleate **11** is attacked both on the Δ^5 nucleus and on the cis double bond of the oleyl chain; the reaction yields a mixture of 5,6β-epoxide, 9′,10′-epoxides (presumably two diastereoisomers with the original cis configuration) [11], and a diepoxide, which are separated by chromatography. It seems that the presence of the cis olefinic bond on the acyl

chain slows down the reaction, the oleyl group behaving as a competitive inhibitor of the epoxidation on the steroid nucleus. Adverse kinetic effects of bulky acyl substituents close to the steroid nucleus are apparent: whereas a reaction time of 6 days is needed for complete epoxidation of cholesterol benzoate [6], epoxidation of the corresponding phenylacetate **6** requires only 2 days, and that of the hydrocinnamate **9** one day.

4. Conclusion

Δ^5 sterol esters bearing an additional double bond of trans stereochemistry on a side chain are readily epoxidized by air, in a highly regioselective and stereoselective fashion, to their 5,6β epoxides in the presence of the ruthenium tetramesitylporphyrin catalyst. This catalytic system also provides a convenient access to the 5,6β epoxides of conjugated 5,7 diene systems of sterol esters in a single step in fair yield.

References and notes

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[11] A referee pointed out that high field n.m.r. data on the 9′,10′-epoxide could reveal the presence of the two diastereoisomeric products, and thus indicate a possible asymmetric induction. Our ^{13}C n.m.r. data (C_6D_6, δ_{ppm}/TMS: 73.8 (C–3); 139.9 (C–5); 122.9 (C–6); 56.6, 56.9 (C–9′, C–10′); 172.5 (C=O), Bruker AC-200) show a single set of peaks for C–9′ and C–10′. The chiral centres of the steroid nucleus are probably too far away from the epoxide group to induce detectable shifts in the resonances of the C–9′ and C–10′ atoms of the two diastereoisomers. Thus, the data are consistent with the presence of either one or two of the diastereoisomeric epoxides. We plan to run ^{13}C n.m.r. measurements at higher fields to see if asymmetric induction occurs in this system where the chiral steroid template is loosely bound to the olefinic bond by a chain of seven methylene groups, allowing unpredictable transition state geometries in the epoxidation process. We also plan to investigate the behaviour of cholesterol esters in which the double bond on the acyl chain is closer to the steroid nucleus. We thank a referee for this interesting suggestion.