

Catalytic β -Stereospecific Epoxidation of Unsaturated Steroids by *trans*-Dioxoruthenium(VI)tetramesitylporphyrin. Stereochemical Grounds for the β -Diastereofacial Selection

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The catalytic epoxidation by dioxygen with *trans*-dioxoruthenium(VI)tetramesitylporphyrin [Ru(O)₂(tmp)] of the acetic esters of cholesterol, 3-epicholesterol and isocholesterol,† as well as of the 7 α -epimer of the latter, is β -stereospecific. Substitution by a methyl group on C-6 of pregnenolone acetate‡ results in reduced reactivity towards catalytic epoxidation and lower β -stereoselectivity. 19-Norsterol esters bearing a double bond at C-8–C-14 or C-14–C-15 are inert towards O₂–Ru(O)₂(tmp) epoxidation. The variable reactivity of these sterol ester substrates is explained by a transition state in which the steroid nucleus approaches the ruthenium–oxo bond approximately perpendicular to the porphyrin ring. The β -selectivity of Δ^5 -sterol ester epoxidation is accounted for in terms of this transition state geometry which provides a good fit between the porphyrin catalyst and the steroid substrate when the β -side faces the oxo ligand. On the other hand, reaction on the α -side involves unfavourable steric interactions between axial hydrogen atoms on C-3 and C-7 of the substrate and the porphyrin ring and a mesityl substituent of the catalyst, respectively. The crystal and molecular structures of cholesteryl ethyl carbonate and of its 5,6 β -epoxide have been determined by single-crystal X-ray diffraction. The overall conformation of the steroid nucleus is nearly planar in the cholesteryl ester, while it is bent at the junction between rings A and B in the 5,6 β -epoxide. This change from pseudo-*trans*- to *cis*-stereochemistry of the A–B ring junction upon epoxidation is proposed to amplify the β -diastereofacial selection. Variable temperature ¹H NMR spectra indicate that in CD₂Cl₂ solution the 5,6 β -epoxide (not the 5,6 α -epoxide) of the cholesteryl acetate coordinates the ruthenium atom of Ru(CO)(tmp) with a nearly perpendicular geometry. These results corroborate the orthogonal substrate approach and the steric origin of the β -stereospecificity in Ru(O)₂(tmp)-catalysed steroid epoxidations.

Various patterns of reactivity and selectivity have been found recently for the Groves–Quinn oxidation of unsaturated steroids, *i.e.* their catalytic oxidation by dioxygen in benzene solution at room temperature in the presence of a small amount of *trans*-dioxoruthenium(VI)tetramesitylporphyrin [Ru(O)₂(tmp)].^{1,2} Cholest-5-ene derivatives bearing a polar group (other than hydroxy³) on C-3 β , such as cholesteryl esters, generally lead to the 5,6 β -epoxide in good yield in a stereospecific but rather slow reaction.⁴ Conjugated 5(6),7(8) diene systems such as those of 7-dehydrocholesteryl acetate or benzoate and ergosteryl acetate are epoxidized regioselectively on the 5,6-double bond in a fast reaction which affords a 1:1 mixture of the α - and β -epoxides in a non-stereoselective process.⁵ The C-8–C-9 double bond of lanosterol acetate is untouched,⁵ while that on C-5–C-10 of 17 β -acetoxyestr-5(10)-en-3-one is found to be shifted to C-4–C-5 in the 10 β -hydroxylated product 17 β -acetoxy-10 β -hydroxyestr-4-en-3-one.⁶ Particularly intriguing is the β -stereospecificity observed in the epoxidation of cholesteryl esters: oxygen atom transfer occurs exclusively on the most sterically crowded β -face of the steroid nucleus,⁴ suggesting a possible *syn*-stereodirecting effect of the homoallylic ester group.⁷ In order to test this hypothesis, we have investigated the catalytic epoxidation of the sterol acetates 2–5. In addition, we have explored the behaviour of 19-norsterol esters 6–9 bearing a double bond at C-8–C-14 in ring C, or at C-14–C-15 in ring D, as substrates of the ruthenium porphyrin catalyst.

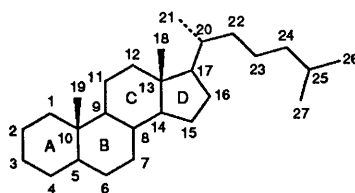
Results and Discussion

Epoxidation.—It was found that epoxidation with Ru(O)₂(tmp)–O₂ (Table 1) is β -stereospecific for the sterol esters 1–4, and fairly β -stereoselective for 5, irrespective of the position and stereochemistry of the ester group. 3-Epicholesteryl acetate 2 affords nearly quantitatively the β -epoxide, which is the sole detectable product by NMR spectroscopy (peracid epoxidation is β -stereoselective for 2^{8,9} and α -stereoselective for 1¹⁰). The isocholesteryl acetates 3 and 4 each yield *ca.* 20% of the corresponding 4,5 β -epoxide, and some 3-ketosteroid allylic oxidation product is also obtained (peracid epoxidation is α -stereoselective for 3,¹¹ and it was found to be 80% β -stereoselective for 4). Methyl substitution on C-6 hinders epoxidation of the C-5–C-6 double bond in 5, and a lower β -stereoselectivity is obtained (peracid epoxidation is α -stereoselective¹²); for the parent pregnenolone acetate 98% β -stereoselectivity is obtained.⁴ Finally, the estradiene derivatives 6 and 7 and the estratetraene derivatives 8 and 9 are inert towards this catalytic system.

The data summarised in Table 1 clearly show that the ruthenium porphyrin-catalysed epoxidation is just as β -stereoselective for a 3 α -substituted cholest-5-ene derivative such as 3-epicholesteryl acetate 2 as for the corresponding 3 β -substituted cholesteryl acetate 1 itself.⁴ This result is not entirely surprising, since the β -side of the steroid 2 is less hindered than that in 1 for which the Ru(O)₂(tmp)-epoxidation is β -stereospecific,⁴ and it affords unambiguous evidence against a possible *syn*-stereodirecting effect of the acetoxy group on C-3. A similar conclusion can be drawn for the acetoxy group on C-7 of 3 and 4. Thus, steric interactions between substrate and catalyst are

† Cholest-4-en-7 β -ol.

‡ 3 β -Acetoxypregn-5-en-20-one.



numbering system for steroid derivatives:
 α -face, below the plane of the paper;
 β -face, above the plane of the paper

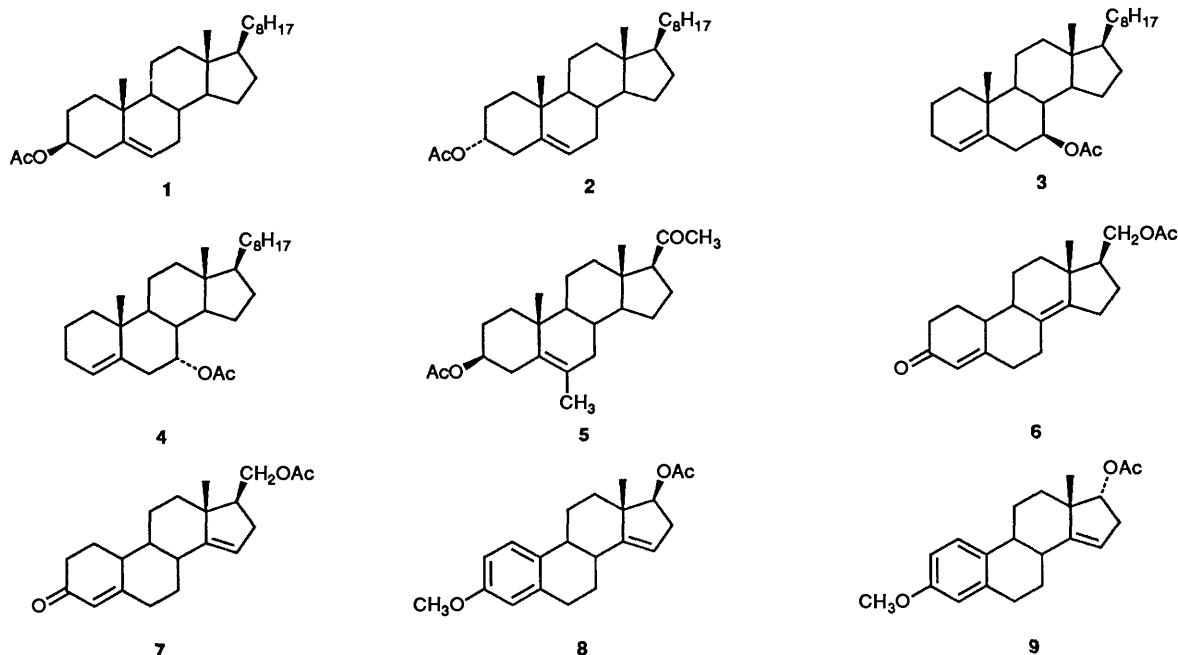


Table 1 Products, epoxide yields and stereoselectivities of the $\text{Ru}(\text{O})_2(\text{tmp})$ -catalysed oxygenation of sterol acetates 1–9

Substrate	Reaction time	Starting material recovered (%)	Epoxide yield ^a (%)	Stereoisomer (%)		Ref.
				α	β	
1	5 h	0	85	nd ^b	>99	4
2	1 d	3	62 ^c	nd	>99	This work
3	6 d	22	22 ^d	nd	>99	This work
4	4 d	52	16 ^e	nd	>99	This work
5	6 d	35	11 ^f	33	66	This work
6	7 d	83 ^g	nd	—	—	This work
7	4 d	87 ^g	nd	—	—	This work
8	8 d	77 ^g	nd	—	—	This work
9	4 d	82 ^g	nd	—	—	This work

^a After separation by chromatography. ^b Not detected. ^c Diol 15 (30%) is also obtained; crude product contains 97% epoxide as shown by ¹H NMR spectroscopy. ^d Ketone 16 (40%) is also obtained. ^e Ketone 17 (15%) is also obtained. ^f Aldehyde 18 (14%) is also obtained. ^g A few (≥ 3) minor products are seen by TLC, but not by NMR spectroscopy.

left as the most probable origin of the remarkable β -stereospecificity observed in these reactions.

Side-on Approach and Reactivity.—The deleterious effects of a methyl group on C-6 in **5** can be understood on the basis of a steric interaction with the porphyrin ring of the *trans*-dioxoruthenium(vi) species. Similar behaviour has been observed earlier in the epoxidation of *cis*- and *trans*-1,2-disubstituted alkenes by oxometalporphyrins,^{1,13} and it has been accounted for by a mechanism in which the alkene approaches

the metal–oxo bond from the side with a geometry such as **10**. Although alternative geometries have been suggested for alkene approach,^{14–18} they will not be discussed since direct evidence supporting the side-on approach has been found in the X-ray structure of an adduct of styrene oxide with a carbonyl-ruthenium(II)-porphyrin complex,¹⁹ which is likely to be similar to the transition state for alkene epoxidation by oxometalporphyrins. Side-on approach of the C-5–C-6 double bond of **5** towards the metal–oxo group implies that the mean plane of the steroid nucleus be approximately

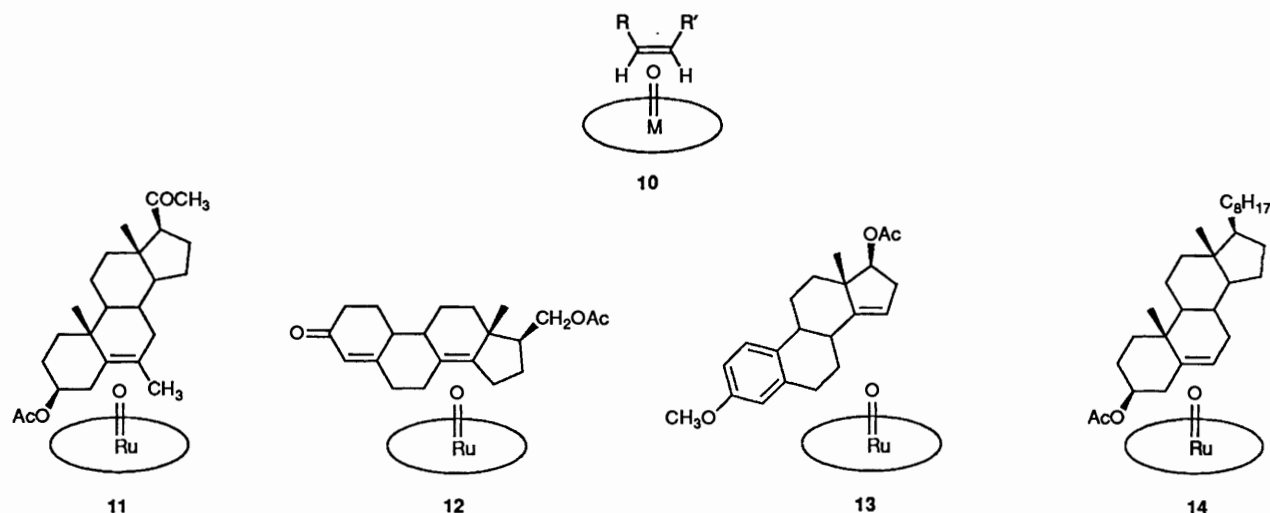


Table 2 Crystal and data collection parameters for cholesteryl ethyl carbonate **19** and 5,6 β -epoxy-5 β -cholestan-3 β -yl ethyl carbonate **20**

Compound	19	20
Formula	C ₃₀ H ₅₀ O ₃	C ₃₀ H ₅₀ O ₄
Molecular mass	458.43	474.43
System	Monoclinic	Monoclinic
<i>a</i> /Å	18.702(5)	18.410(5)
<i>b</i> /Å	11.762(4)	7.155(3)
<i>c</i> /Å	13.573(4)	11.205(4)
β /deg	105.41(5)	106.37(5)
<i>V</i> /Å ³	2878(3)	1416(2)
<i>T</i> /°C	20	20
Systematic absences	0 <i>kl</i> , <i>k</i> \neq 2 <i>n</i>	0 <i>kl</i> , <i>k</i> \neq 2 <i>n</i>
Space group	<i>P</i> 2 ₁ , No. 4	<i>P</i> 2 ₁ , No. 4
<i>Z</i>	4	2
<i>D</i> _c /g cm ⁻³	1.058(1)	1.111(1)
<i>F</i> (000)	1016	522
μ (Cu-K α)/cm ⁻¹	4.41	4.88
Reflections measured	4707	4953
Reflections used for refinements	1811	1664
<i>R</i>	0.088	0.064
<i>R</i> _w	0.091	0.065
<i>S</i>	7.9	3.5

perpendicular to the porphyrin ring with the C-6 methyl group protruding towards the latter as in **11**, thus hindering interaction of the C=C and Ru=O bonds.

The surprising inertia towards Ru(O)₂(tmp)-epoxidation of the sterol acetates **6–9**, which bear a double bond on ring C or D of the steroid nucleus, is consistent with the above picture. Geometries **12** and **13** depict, as typical examples, the unfavourable non-bonded interactions which develop between ring B of **6** and **8** and the porphyrin. These prevent the C=C bond on ring C or D from approaching the Ru=O bond with the rectangular orientation required for reaction, and therefore oxygen transfer cannot occur. The same type of argument can also explain the observed inertia of the 7,8-double bond of 7-dehydrocholesteryl and ergosteryl esters,⁵ as well as the negative results that we have previously obtained in the ruthenium porphyrin epoxidation of 'internal' double bonds, such as C-8–C-9 of lanosteryl acetate⁵ and C-5–C-10 of 17 β -acetoxyestr-5(10)-en-3-one.⁶ Notable in the last-mentioned cases is the occurrence of alternative reaction pathways leading respectively to epoxidation of the C-24–C-25 double bond on the side chain,⁵ and to allylic oxidation of the C-10 methyl group.⁶

Steric Effects and Stereoselectivity.—Steric hindrance of the β -face by the axial methyl groups at C-10 and C-13 is usually

invoked to explain the α -stereoselective epoxidation of cholesterol by peracids.²⁰ In the present case, the absence of α -epoxide product obviously rules out a mechanism in which the steroid would approach the ruthenium–oxo bond with its mean plane parallel to the porphyrin ring. If one now considers the orthogonal approach of a 5,6 steroid double bond towards the ruthenium–oxo bond as depicted in **14** for the β -face of cholesteryl acetate, it is immediately clear that there are no non-bonded interactions between the porphyrin complex and the axial methyl groups at C-10 and C-13 which protrude on the β -face well above the Ru=O and *ortho*-methyl groups.

Detailed examination of CPK (Corey–Pauling–Koltun) molecular models reveals further steric interactions between catalyst and substrate in the proposed transition state geometry; these might explain, at least in part, the observed stereoselectivity. The equatorial hydrogen atom on C-4 and the alkenic hydrogen atom on C-6 of cholesteryl esters protrude towards the nitrogen atoms of two adjacent pyrrole rings, but these interactions do not seem to afford a selection factor as they occur for both α - and β -attack on the 5,6-double bond. On the other hand, steric constraints between the axial hydrogen atoms on C-3 and C-7 of the steroid and the porphyrin ring and a mesityl substituent, respectively, upon α -attack seem to favour epoxidation on the less congested β -face (Fig. 1). It could be argued that such a small difference in steric interactions is insufficient to account for the large degree of stereoselectivity (>99%) observed in this system. It must be recalled, therefore, that 7-dehydrocholesterol derivatives with their single proton on C-7 lack a potential discrimination factor, and that they are indeed epoxidized on both faces of the steroid at equal rates on their only accessible 5,6-double bond⁵ (*vide supra*).

The search for additional diastereofacial selection factors led us to examine the detailed structures of both a cholesteryl ester substrate and its β -epoxide. Cholesteryl ethyl carbonate and its 5,6 β -epoxide⁴ were crystallized, and their crystal and molecular structures were solved from X-ray diffraction data. The space groups, unit cell dimensions, and other crystal data are shown in Table 2. Atomic coordinates (Tables 3 and 4), bond distances (Tables 5 and 6) and bond angles (Tables 7 and 8) are also given. ORTEP views of the two molecules are shown in Fig. 2. Simple inspection of these views reveals distinct conformations resulting from different stereochemistries at the A–B ring junction. The conformation of cholesteryl ethyl carbonate does not show reliable differences with the geometry which has been accurately determined for cholesteryl acetate:²¹ ring A has a distorted chair conformation with the ethyl carbonate group in an equatorial position, while ring B is a distorted half-chair, and

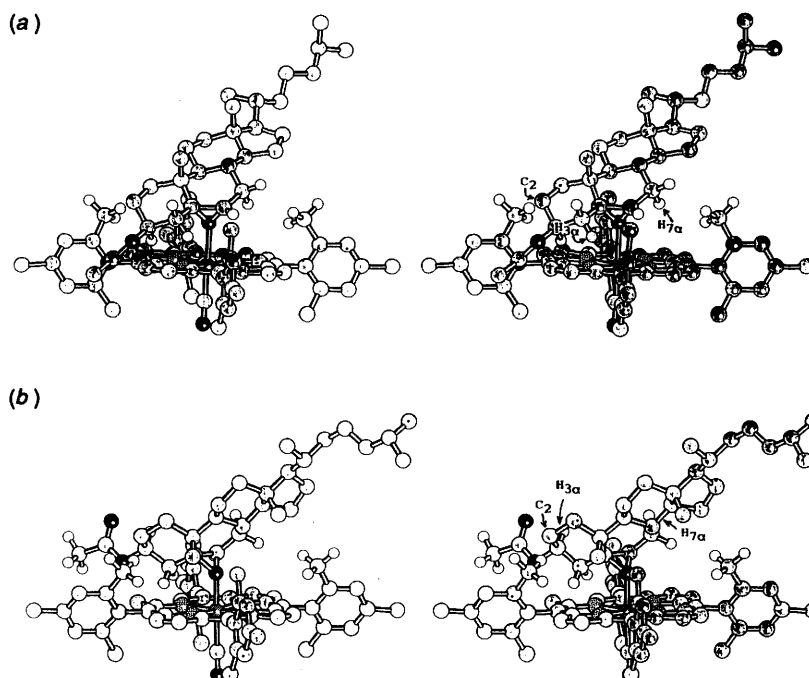


Fig. 1 SYBYL views of proposed transition states for the epoxidation of cholesteryl acetate by $\text{Ru}(\text{O})_2(\text{tmp})$ on the α face (a) and on the β face (b). The geometry of the porphyrin-Ru-epoxide fragment was obtained from the atomic coordinates found in ref. 19. The α -epoxide fragment (a) is a minimised structure obtained with SYBYL. The stereochemistry of the β -epoxide fragment (b) was taken from the X-ray structure of compound **20** (see Table 4). (a) Attack of the C-5-C-6 double bond of cholesteryl acetate on the α face. For clarity, only the hydrogen atoms on C-3, C-4, C-6 and C-7 of the steroid, and on two mesityl *o*-methyl groups of the porphyrin are shown. The axial hydrogen atoms on C-2, C-3 and C-7 of the steroid are proposed to induce steric strain in this transition state geometry (close contacts 0.8, 1.1, 1.7 for H_{2 α} and H_{methyl}, 2.2 for H_{3 α} and N_{porph}, 1.9 for H_{4 α} and N_{porph}, 2.1 for H_{7 α} and H_{methyl}). (b) Attack of the C-5-C-6 double bond of cholesteryl acetate on the β face. For clarity, only the hydrogen atoms on C-3, C-4, C-6, C-7 and acetyl group of the steroid, and on two mesityl *o*-methyl groups of the porphyrin are shown. Note the absence of unfavourable intermolecular contacts between the steroid and the porphyrin in this transition state geometry (close contacts 1.1, 1.6 and 2.3 for H_{2 β} and H_{methyl}, 1.9 for H_{4 α} and N_{porph}, 2.3 for H_{4 β} and N_{porph}).

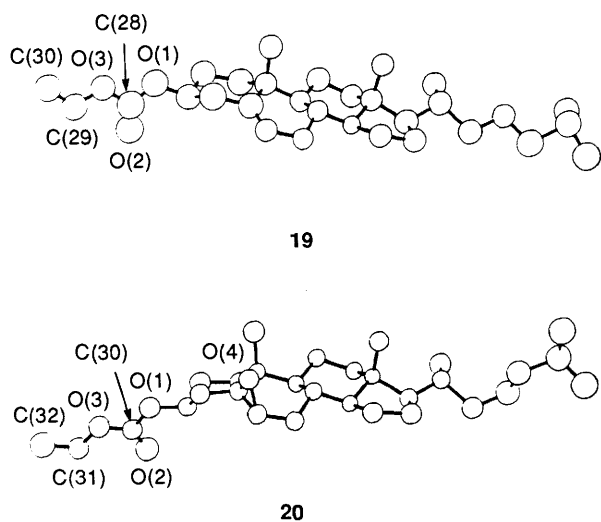


Fig. 2 ORTEP views of cholesteryl ethyl carbonate **19** and of its 5,6 β -epoxide **20** shown with similar orientations. The atom numbering scheme for the ester substituent is indicated. The steroid nucleus is numbered as shown on p. 1323.

the A-B ring junction is pseudo-*trans*. In contrast, this junction is *cis* in the structure of the corresponding 5,6 β -epoxide* (Fig. 2). This change in overall conformation is apparently a result of the formation of the oxirane ring at the C-5-C-6 double bond: bonding of the oxygen atom to C-5 on the β -face requires

folding of the steroid nucleus along C-5-C-10 away from the incoming oxygen atom donor, *i.e.* a *cis* A-B ring junction. Examination of molecular models indicates that no such change is required upon epoxidation of the C-5-C-6 double bond on the α -face; it is therefore assumed that the tetracyclic steroid system maintains its nearly planar conformation in the 5,6 α -epoxides. Similar conclusions are easily arrived at for the steroid derivatives bearing a double bond at C-4-C-5, which would afford nearly planar 4,5 α -epoxides with a *trans* A-B ring junction and bent 4,5 β -epoxides with a *cis* A-B ring junction.²³ An X-ray structure would be desirable to confirm these assumptions. To the best of our knowledge, none is available in the literature for a 5,6 α -epoxide, but an equivalent case is found in the structure of 3 β -acetoxy-5,6 α -dichloromethylene-5 α -androstane-17-one. In this compound, a cyclopropane ring is similarly attached to the C-5 carbon atom of the junction between rings A and B; the X-ray structure shows that indeed the A-B junction is *trans*, and that the overall stereochemistry is nearly planar.²⁴

The distinct conformations of the two possible diastereoisomeric products provide a second explanation for the observed β -stereospecific epoxidation of 5,6-steroid double bonds. Incipient epoxidation on the β -face folds the A-B junction as discussed above. This large conformational change allows a much easier approach for the substrate by releasing the steric strain which results from non-bonded interactions between the ester group on C-3 (or C-7) of the steroid and a mesityl substituent of the porphyrin. In contrast, epoxidation on the α -face has no effect on the A-B junction, and it is therefore disfavoured relative to the former. The notion that steric interactions between the porphyrin mesityl groups and a substituent on C-3 of the substrate do affect the stereoselectivity of this system is supported by earlier experimental evidence.

* This stereochemistry has been found earlier in the structure of 3 β -acetoxy-5,6 β -*N*-nitroaziridinylcholestane.²²

Table 3 Atomic coordinates for cholesteryl ethyl carbonate

Atom	10 ⁴ x	10 ⁴ y	10 ⁴ z
Molecule 1			
C(27)	8 511(20)	5 208(52)	3 649(30)
C(26)	7 650(13)	6 359(57)	2 635(24)
C(25)	8 013(19)	6 174(58)	3 809(21)
C(24)	7 378(1)	5 291(55)	4 080(16)
C(23)	6 704(12)	5 993(55)	4 072(14)
C(22)	6 166(10)	5 271(53)	4 428(12)
C(21)	4 972(10)	6 350(54)	3 358(11)
C(20)	5 411(10)	5 992(54)	4 439(12)
C(17)	4 921(13)	5 217(54)	4 958(15)
C(16)	5 444(10)	4 899(54)	6 159(10)
C(15)	4 859(9)	4 903(54)	6 778(12)
C(14)	4 034(9)	4 886(53)	5 959(10)
C(13)	4 136(10)	5 700(53)	5 108(11)
C(18)	4 270(10)	6 989(53)	5 422(11)
C(12)	3 509(9)	5 496(55)	4 191(10)
C(11)	2 808(10)	5 864(54)	4 506(10)
C(9)	2 727(8)	5 181(54)	5 382(12)
C(8)	3 356(8)	5 179(53)	6 394(11)
C(7)	3 357(8)	4 304(54)	7 170(11)
C(6)	2 630(10)	4 354(53)	7 489(14)
C(5)	2 051(10)	4 919(54)	6 835(15)
C(10)	2 019(10)	5 540(55)	5 754(13)
C(19)	1 997(11)	6 840(54)	5 964(15)
C(4)	1 288(11)	4 972(55)	7 098(15)
C(1)	1 299(11)	5 244(57)	4 896(15)
C(2)	585(13)	5 314(56)	5 316(17)
C(3)	570(14)	4 576(56)	6 107(23)
O(1)	-91(8)	4 857(53)	6 524(14)
C(28)	-476(13)	3 985(56)	6 595(16)
O(2)	-448(9)	3 114(55)	6 276(14)
O(3)	-1 064(8)	4 385(54)	6 892(11)
C(29)	-1 552(13)	3 531(56)	6 921(19)
C(30)	-2 112(16)	4 016(59)	7 285(17)
Molecule 2			
C(27')	11 229(23)	489(65)	-393(40)
C(26')	11 038(25)	2 419(64)	-952(25)
C(25')	10 652(12)	1 276(68)	-863(25)
C(24')	9 985(20)	1 315(66)	-335(21)
C(23')	9 236(16)	1 151(64)	-838(25)
C(22')	8 830(11)	1 114(57)	16(19)
C(21')	7 768(11)	214(55)	-1 190(15)
C(20')	8 065(10)	1 285(54)	-506(13)
C(17')	7 645(8)	1 533(54)	297(12)
C(16')	7 927(9)	2 618(54)	938(13)
C(15')	7 306(10)	3 178(54)	1 249(12)
C(14')	6 624(9)	2 311(53)	875(10)
C(13')	6 785(11)	1 768(53)	-85(12)
C(18')	6 530(11)	2 628(53)	-1 061(11)
C(12')	6 218(10)	713(53)	-408(12)
C(11')	5 383(8)	1 069(53)	-477(12)
C(9')	5 302(8)	1 622(53)	518(10)
C(8')	5 820(9)	2 687(53)	791(9)
C(7')	5 749(9)	3 165(53)	1 835(11)
C(6')	4 960(8)	3 256(54)	1 901(12)
C(5')	4 426(10)	2 723(53)	1 298(10)
C(10')	4 497(8)	1 982(53)	387(10)
C(19')	4 190(9)	2 651(54)	-613(10)
C(1')	4 041(9)	859(53)	402(12)
C(2')	3 222(9)	1 080(53)	452(11)
C(4')	3 658(8)	2 878(53)	1 459(10)
C(3')	3 297(9)	1 737(53)	1 468(13)
O(1')	2 505(6)	1 896(53)	1 457(7)
C(28')	2 323(14)	2 160(54)	2 311(13)
O(2')	2 819(8)	2 218(54)	3 142(10)
O(3')	1 606(7)	2 344(54)	2 194(10)
C(29')	1 327(17)	2 738(62)	3 079(19)
C(30')	586(12)	2 717(59)	2 828(21)

(i) Cholest-5-ene, a substrate devoid of C-3 substitution, is epoxidised with only 80% β -stereoselectivity, compared with

Table 4 Fractional atomic coordinates for 3 β -ethylcarbonyloxy-5,6 β -epoxy-5 β -cholestane

Atom	10 ⁴ x	10 ⁴ y	10 ⁴ z
C(1)	2092(3)	1248(0)	1730(6)
C(2)	2878(4)	1399(14)	1564(6)
C(3)	2931(3)	3199(13)	880(5)
C(4)	2799(4)	4825(13)	1663(6)
C(5)	2067(3)	4734(12)	1957(5)
C(6)	1484(3)	6178(12)	1403(5)
C(7)	669(3)	5905(12)	1323(6)
C(8)	535(3)	4509(11)	2277(5)
C(9)	959(3)	2699(11)	2191(4)
C(10)	1835(3)	2871(11)	2440(4)
C(11)	743(3)	1126(12)	2976(6)
C(12)	-118(3)	840(11)	2661(5)
C(13)	-526(3)	2630(11)	2807(4)
C(14)	-305(3)	4099(11)	1978(5)
C(15)	-838(3)	5728(12)	1979(6)
C(16)	-1581(4)	4793(13)	2006(8)
C(17)	-1414(3)	2655(12)	2230(5)
C(18)	-336(3)	3216(13)	4181(5)
C(19)	2265(4)	2805(16)	3846(5)
C(20)	-1919(3)	1730(12)	2904(5)
C(21)	-1771(4)	-334(14)	3143(7)
C(22)	-2773(3)	1976(14)	2126(7)
C(23)	-3368(5)	1471(16)	2710(8)
C(24)	-3428(7)	2771(21)	3695(9)
C(25)	-4067(6)	2439(22)	4304(10)
C(26)	-3897(8)	3452(30)	5537(11)
C(27)	-4837(10)	2877(37)	3599(15)
C(30)	3819(3)	2658(12)	-259(6)
C(31)	4754(4)	2257(14)	-1244(7)
C(32)	5509(5)	3069(19)	-1183(9)
O(1)	3673(2)	3464(11)	734(4)
O(2)	3355(2)	1745(12)	-1022(4)
O(3)	4507(2)	3033(11)	-250(4)
O(4)	1965(2)	6379(10)	2670(4)

>99% for cholesteryl acetate.²⁵ (ii) Tetraphenylporphyrin complexes as catalysts induce lower β -stereoselectivity for cholesteryl acetate epoxidation (71–89%) than the corresponding tetramesitylporphyrin catalysts (>97%).²⁶

Studies of stable epoxide adducts by NMR spectroscopy shed further light on catalyst–substrate interactions in these systems. Epoxides have been shown to coordinate ruthenium(II) porphyrins,^{19,27} and solution ¹H NMR spectra at 233 K have demonstrated the existence of a styrene oxide adduct as a solute species in CD₂Cl₂.¹⁹ We have investigated the variable-temperature ¹H NMR spectra in CD₂Cl₂ solution of mixtures of Ru(CO)(tmp) and the 5,6 α - or 5,6 β -epoxide of cholesteryl acetate.* Addition of Ru(CO)(tmp) to a CD₂Cl₂ solution of 3 β -acetoxy-5,6 α -epoxy-5 α -cholestane in a molar ratio of approximately 1:3 had no apparent effect on the room temperature NMR resonances of the latter within experimental error. In contrast, addition of Ru(CO)(tmp) to a solution of 3 β -acetoxy-5,6 β -epoxycholestane under the same conditions resulted in shifted and exchange-broadened peaks for the epoxide. Thus, complex formation takes place between the ruthenium porphyrin and the 5,6 β -epoxide, but not with the 5,6 α -epoxide, and there is fast exchange, on the NMR time scale, between free and coordinated steroid at room temperature. Lowering the temperature slowed down the rate of ligand exchange, as anticipated from the study of similar systems,²⁸ and at 233 K the sample exhibited a sharp spectrum indicative of a mixture of the ruthenium porphyrin-5,6 β -epoxide adduct and of the free steroid. The proposed peak assignments were

* Similar results were obtained with the 5,6-epoxides of 7-dehydrocholesteryl acetate.

Table 5 Bond distances (Å) with standard deviations for cholesteryl ethyl carbonate

Molecule 1		Molecule 2	
C(1)–C(2)	1.528(62)	C(1')–C(2')	1.537(43)
C(2)–C(3)	1.441(68)	C(2')–C(3')	1.532(44)
C(3)–C(4)	1.612(61)	C(3')–C(4')	1.497(43)
C(3)–O(1)	1.393(58)	C(3')–O(1')	1.507(39)
C(4)–C(5)	1.529(52)	C(4')–C(5')	1.494(41)
C(5)–C(6)	1.305(49)	C(5')–C(6')	1.248(41)
C(5)–C(10)	1.604(48)	C(5')–C(10')	1.522(39)
C(6)–C(7)	1.468(45)	C(6')–C(7')	1.492(41)
C(7)–C(8)	1.513(43)	C(7')–C(8')	1.543(41)
C(8)–C(9)	1.526(43)	C(8')–C(9')	1.573(41)
C(8)–C(14)	1.505(41)	C(8')–C(14')	1.551(41)
C(9)–C(10)	1.561(45)	C(9')–C(10')	1.499(39)
C(9)–C(11)	1.430(45)	C(9')–C(11')	1.552(41)
C(10)–C(19)	1.533(49)	C(10')–C(19')	1.556(41)
C(10)–C(1)	1.552(52)	C(10')–C(1')	1.552(40)
C(11)–C(12)	1.499(45)	C(11')–C(12')	1.532(44)
C(12)–C(13)	1.451(44)	C(12')–C(13')	1.582(44)
C(13)–C(14)	1.540(42)	C(13')–C(14')	1.526(42)
C(13)–C(17)	1.625(46)	C(13')–C(17')	1.532(44)
C(13)–C(18)	1.569(44)	C(13')–C(18')	1.614(46)
C(14)–C(15)	1.731(42)	C(14')–C(15')	1.585(42)
C(15)–C(16)	1.491(43)	C(15')–C(16')	1.477(44)
C(16)–C(17)	1.696(45)	C(16')–C(17')	1.600(45)
C(17)–C(20)	1.569(46)	C(17')–C(20')	1.478(47)
C(20)–C(21)	1.548(43)	C(20')–C(21')	1.543(51)
C(20)–C(22)	1.620(45)	C(20')–C(22')	1.406(57)
C(22)–C(23)	1.476(49)	C(22')–C(23')	1.446(84)
C(23)–C(24)	1.467(54)	C(23')–C(24')	1.272(96)
C(24)–C(25)	1.509(81)	C(24')–C(25')	1.606(101)
C(25)–C(26)	1.498(89)	C(25')–C(26')	1.473(97)
C(25)–C(27)	1.431(108)	C(25')–C(27')	1.459(119)
O(1)–C(28)	1.261(54)	O(1')–C(28')	1.344(46)
C(28)–O(2)	1.115(55)	C(28')–O(2')	1.252(50)
C(28)–O(3)	1.282(52)	C(28')–O(3')	1.285(48)
O(3)–C(29)	1.204(59)	O(3')–C(29')	1.449(64)
C(29)–C(30)	1.375(69)	C(29')–C(30')	1.279(79)

made* in keeping with those of the styrene oxide adduct.¹⁹ Particularly noteworthy are the large shifts of the following protons upon complexation: 6 α -H, $\Delta\delta$ –5.00; 4-H, $\Delta\delta$ –3.60, –1.95. The magnitude and the negative sign of these shifts indicate that the corresponding protons sit close to and just above the porphyrin ring in the epoxide complex, *i.e.* a stereochemistry comparable to the perpendicular geometry described above for the transition state of steroid epoxidation.

The fact that the 5,6 β -epoxide of cholesteryl acetate does bind the ruthenium atom in a sterically hindered carbonyl-ruthenium(II)-tetramesitylporphyrin, while the 5,6 α -epoxide does not, affords considerable support to the proposed steric origin of the β -stereoselectivity in this system. If the epoxidation transition state has a structure similar to the epoxide complex, it is clear that non-bonded interactions between substrate and catalyst are weak in the intermediate which leads to the 5,6 β -epoxide, as compared with its α -stereoisomer.

Conclusions

The catalytic epoxidation by Ru(O)₂(tmp) of the sterol esters 1–4 bearing a double bond on C-4–C-5 or C-5–C-6 occurs exclusively on the β -face, irrespective of the stereochemistry of

Table 6 Bond lengths (Å) and standard deviations for 3 β -ethylcarbonyloxy-5,6 β -epoxy-5 β -cholestane

C(1)–C(2)	1.512(18)	C(13)–C(14)	1.531(17)
C(2)–C(3)	1.520(20)	C(13)–C(17)	1.578(17)
C(3)–C(4)	1.519(20)	C(13)–C(18)	1.537(17)
C(3)–O(1)	1.430(17)	C(14)–C(15)	1.522(18)
C(4)–C(5)	1.464(20)	C(15)–C(16)	1.541(20)
C(5)–C(6)	1.485(19)	C(16)–C(17)	1.560(19)
C(5)–C(10)	1.549(18)	C(17)–C(20)	1.503(18)
C(5)–O(4)	1.463(17)	C(20)–C(21)	1.518(20)
C(6)–C(7)	1.483(19)	C(20)–C(22)	1.579(20)
C(6)–O(4)	1.437(17)	C(22)–C(23)	1.459(23)
C(7)–C(8)	1.532(18)	C(23)–C(24)	1.470(27)
C(8)–C(9)	1.531(17)	C(24)–C(25)	1.554(30)
C(8)–C(14)	1.518(17)	C(25)–C(26)	1.481(35)
C(9)–C(10)	1.563(17)	C(25)–C(27)	1.425(39)
C(9)–C(11)	1.547(18)	O(1)–C(30)	1.344(17)
C(10)–C(19)	1.548(19)	C(30)–O(2)	1.211(18)
C(10)–C(1)	1.551(15)	C(30)–O(3)	1.294(17)
C(11)–C(12)	1.540(18)	O(3)–C(31)	1.428(18)
C(12)–C(13)	1.513(17)	C(31)–C(32)	1.490(23)

the acetoxy group on C-3 or C-7. The pregnane derivative 5 with a tetrasubstituted C-5–C-6 double bond shows good β -stereoselectivity under the same conditions. The sterol acetates 6–9, which have a double bond on C-8–C-14 or C-14–C-15, are inert towards this catalytic system. These various reactivity patterns are accounted for by steric interactions between substrate and catalyst which prevent approach of 6–9, but not of 1–5, to the metal–oxo bond in the perpendicular geometry required for reaction. The remarkable β -stereospecificity of epoxidation of cholesterol esters and Δ^5 steroids is proposed to result from specific steric effects. Selection of the β -face occurs as a consequence of unfavourable interactions between the porphyrin catalyst and axial hydrogen atoms on C-3 and C-7 on the α -face of the substrate. This β -diastereofacial selection is then amplified by the change at the A–B ring junction from a pseudo-*trans* to a *cis* stereochemistry which takes place upon epoxidation of the substrate on the β -face exclusively. It is tempting to speculate that specific steric effects of this type might be utilised in a systematic manner for the rational control of enantioselectivity in metal-catalysed reactions.

Experimental

General Methods.—The solvents benzene, heptane, diethyl ether, cyclohexane and ethyl acetate were of reagent grade quality (Prolabo RP Normapur) and they were used as received. Light petroleum (35–60 °C) for analysis was distilled before use. TLC was performed on pre-coated plastic or aluminium sheets of alumina or silica gel (Merck 60F254) with detection by heating (125 °C) after spraying with modified Kagi–Mischer reagent (0.5 cm³ of anisaldehyde and 1 cm³ of concentrated H₂SO₄ in 50 cm³ of AcOH) or spraying with aqueous KMnO₄. Column chromatography was performed on silica gel 60 (Merck, 0.063–0.2 mm). PLC was performed on pre-coated plates of silica gel or alumina (Merck 60F254, 20 × 20 cm³, layer thickness 0.25, 0.5 or 1 mm). M.p.s were determined by the Kofler method or with a hot-stage (Mettler FP800) polarising microscope (Olympus BH-2). Elemental analyses were performed by the *Service d'Analyses du CNRS*, Vernaison.

Mass spectra were obtained on Kratos MS 50 (EI ID in beam) and VG ZAB SEQ (conventional EI ID) spectrometers. ¹H and ¹³C NMR spectra were recorded on a Bruker AC200 instrument. Spectra were obtained in C₆D₆ because some epoxides were unstable in CDCl₃. Chemical shifts are reported as δ values with (CH₃)₄Si as an internal reference and coupling constants (*J*) are reported in Hz with a precision of

* Selected ¹H NMR spectroscopic data for 3 β -acetoxy-5,6 β -epoxy-5 β -cholestane–Ru(CO)(tmp) adduct (δ in CD₂Cl₂ at 233 K). Porphyrin: 1.73 (s, *o*-CH₃), 1.79 (s, *o*-CH₃), 2.47 (s, *p*-Me), 7.0–7.3 (m, *m*-H) and 8.29 (s, pyrrole); coordinated 3 β -acetoxy-5,6 β -epoxy-5 β -cholestane: –2.05 (s, 6-H), –1.65 (br s, 4-H) and 0.0 (s, 4-H); for free 3 β -acetoxy-5,6 β -epoxy-5 β -cholestane at 233 K, δ 2.95 (s, 6-H) and 1.95 (t, 4-H). The large number of overlapping signals in the δ 0.5–2.0 region precludes further peak assignments.

Table 7 Bond angles (deg) for cholesteryl ethyl carbonate

Molecule 1		Molecule 2	
C(27)–C(25)–C(26)	100.6(10.1)	C(27')–C(25')–C(26')	109.5(12.5)
C(27)–C(25)–C(24)	106.3(10.6)	C(27')–C(25')–C(24')	119.6(13.8)
C(26)–C(25)–C(24)	110.9(10.0)	C(26')–C(25')–C(24')	114.0(11.6)
C(25)–C(24)–C(23)	111.6(7.8)	C(25')–C(24')–C(23')	137.4(15.6)
C(24)–C(23)–C(22)	110.5(6.0)	C(24')–C(23')–C(22')	119.4(13.0)
C(23)–C(22)–C(20)	113.4(5.4)	C(23')–C(22')–C(20')	113.4(8.7)
C(22)–C(20)–C(21)	112.5(4.9)	C(22')–C(20')–C(21')	106.9(6.0)
C(22)–C(20)–C(17)	109.3(4.8)	C(22')–C(20')–C(17')	111.6(6.3)
C(21)–C(20)–C(17)	110.2(4.9)	C(21')–C(20')–C(17')	114.1(5.8)
C(20)–C(17)–C(16)	106.1(4.5)	C(20')–C(17')–C(16')	112.4(5.2)
C(20)–C(17)–C(13)	121.0(5.6)	C(20')–C(17')–C(13')	121.2(5.8)
C(16)–C(17)–C(13)	105.5(4.4)	C(16')–C(17')–C(13')	100.0(4.2)
C(17)–C(16)–C(15)	104.3(4.4)	C(17')–C(16')–C(15')	110.2(5.0)
C(16)–C(15)–C(14)	107.3(4.4)	C(16')–C(15')–C(14')	103.5(4.4)
C(15)–C(14)–C(13)	101.5(3.9)	C(15')–C(14')–C(13')	103.0(4.2)
C(15)–C(14)–C(8)	120.3(4.9)	C(15')–C(14')–C(8')	119.7(5.1)
C(13)–C(14)–C(8)	115.6(4.9)	C(13')–C(14')–C(8')	118.8(5.1)
C(17)–C(13)–C(14)	101.2(4.2)	C(17')–C(13')–C(14')	103.8(4.4)
C(17)–C(13)–C(18)	105.8(4.5)	C(17')–C(13')–C(18')	112.6(5.0)
C(17)–C(13)–C(12)	113.4(5.2)	C(17')–C(13')–C(12')	120.7(5.5)
C(14)–C(13)–C(18)	112.6(4.9)	C(14')–C(13')–C(18')	110.2(4.8)
C(14)–C(13)–C(12)	108.5(4.8)	C(14')–C(13')–C(12')	105.4(4.5)
C(18)–C(13)–C(12)	114.5(5.2)	C(18')–C(13')–C(12')	103.7(4.4)
C(13)–C(12)–C(11)	106.7(4.9)	C(13')–C(12')–C(11')	116.7(5.3)
C(12)–C(11)–C(9)	115.2(5.6)	C(12')–C(11')–C(9')	113.1(4.8)
C(11)–C(9)–C(8)	118.4(5.6)	C(11')–C(9')–C(8')	110.8(4.5)
C(11)–C(9)–C(10)	117.7(5.6)	C(11')–C(9')–C(10')	112.5(4.6)
C(8)–C(9)–C(10)	103.3(4.5)	C(8')–C(9')–C(10')	110.9(4.5)
C(14)–C(8)–C(9)	103.2(4.3)	C(14')–C(8')–C(9')	109.4(4.5)
C(14)–C(8)–C(7)	108.2(4.6)	C(14')–C(8')–C(7')	113.1(4.7)
C(9)–C(8)–C(7)	118.5(5.3)	C(9')–C(8')–C(7')	108.2(4.4)
C(8)–C(7)–C(6)	111.8(5.1)	C(8')–C(7')–C(6')	112.8(4.7)
C(7)–C(6)–C(5)	118.7(6.5)	C(7')–C(6')–C(5')	125.8(6.2)
C(6)–C(5)–C(10)	128.2(7.1)	C(6')–C(5')–C(10')	123.0(5.9)
C(6)–C(5)–C(4)	122.7(7.0)	C(6')–C(5')–C(4')	117.1(5.6)
C(10)–C(5)–C(4)	109.1(5.4)	C(10')–C(5')–C(4')	119.8(5.1)
C(9)–C(10)–C(5)	111.4(5.1)	C(9')–C(10')–C(5')	111.7(4.5)
C(9)–C(10)–C(19)	112.4(5.3)	C(9')–C(10')–C(19')	110.6(4.5)
C(9)–C(10)–C(1)	110.6(5.3)	C(9')–C(10')–C(1')	107.4(4.3)
C(5)–C(10)–C(19)	108.9(5.2)	C(5')–C(10')–C(19')	110.4(4.4)
C(5)–C(10)–C(1)	109.3(5.3)	C(5')–C(10')–C(1')	107.3(4.2)
C(19)–C(10)–C(1)	103.8(5.1)	C(19')–C(10')–C(1')	109.4(4.4)
C(5)–C(4)–C(3)	123.1(7.1)	C(10')–C(1')–C(2')	114.9(4.9)
C(10)–C(1)–C(2)	119.1(7.0)	C(1')–C(2')–C(3')	107.8(4.7)
C(1)–C(2)–C(3)	118.0(8.3)	C(5')–C(4')–C(3')	110.7(4.8)
C(4)–C(3)–C(2)	104.4(6.8)	C(2')–C(3')–C(4')	112.9(5.1)
C(4)–C(3)–O(1)	110.6(6.9)	C(2')–C(3')–O(1')	104.1(4.3)
C(2)–C(3)–O(1)	115.5(8.1)	C(4')–C(3')–O(1')	110.7(4.7)
C(3)–O(1)–C(28)	114.2(7.3)	C(3')–O(1')–C(28')	120.9(5.6)
O(1)–C(28)–O(2)	129.0(10.1)	O(1')–C(28')–O(2')	116.2(7.0)
O(1)–C(28)–O(3)	104.9(6.8)	O(1')–C(28')–O(3')	111.9(6.4)
O(2)–C(28)–O(3)	124.3(9.4)	O(2')–C(28')–O(3')	131.8(8.6)
C(28)–O(3)–C(29)	117.5(8.1)	C(28')–O(3')–C(29')	119.0(7.3)
O(3)–C(29)–C(30)	122.9(10.2)	O(3')–C(29')–C(30')	118.0(10.3)

approximately 0.3 Hz. Optical rotations were measured with a Jobin Yvon Digital Micropolarimeter. $[\alpha]_D$ Values are given in units of 10^{-1} deg $\text{cm}^2 \text{g}^{-1}$.

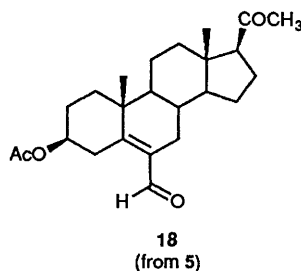
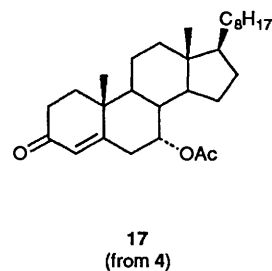
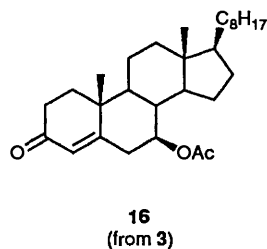
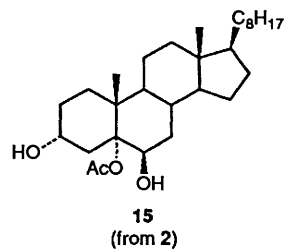
X-Ray Data Collection and Structure Determination.—Single crystals of rather poor quality (approximate dimensions: $0.2 \times 0.2 \times 0.5$ mm) were obtained by slow evaporation of light petroleum solutions of cholesteryl ethyl carbonate **19** and its β -epoxide **20**. The crystals were mounted on a Philips PW1100 four-circle diffractometer using Cu-K α radiation (1.5418 Å at 20 °C) and a graphite monochromator. Unit cell parameters (Table 2) were obtained from a least-squares fit of 25 reflections in the range $20 < \theta < 25^\circ$. Corrections for Lorentz and polarisation effects were applied but not for absorption. Three standard reflections (2,5,5, 8,2,0 and $-2, -5, -5$ for **19**, 8,0,0, $-5,3,2$ and $-8,0,0$ for **20**) monitored every hour showed no indication of crystal decay.

Both crystal structures were solved by a multiresolution method using the MULTAN 77 package,²⁹ which led to the location of the carbon and oxygen atoms of the steroid nucleus. Full-matrix least-squares refinement of the coordinates, followed by three-dimensional electron density difference synthesis revealed all the other non-hydrogen atoms. At this stage, the temperature factors of the two end-chain atoms were very high. After further cycles of refinement, the temperature factors of the non-hydrogen atoms were made anisotropic. A few hydrogen atoms appeared on the Fourier maps. The positions of most of the hydrogen atoms were calculated. Atomic positional parameters are in Tables 3 and 4. Tables of thermal parameters and hydrogen atom co-ordinates have been deposited at the Cambridge Crystallographic Data Centre.*

* For details of the CCDC deposition scheme see 'Instructions for Authors (1992)', *J. Chem. Soc., Perkin Trans. 2*, issue 1.

Table 8 Bond angles (deg) for 3 β -ethylcarbonyloxy-5,6 β -epoxy-5 β -cholestane

C(2)–C(1)–C(10)	116.7(2.0)	C(11)–C(12)–C(13)	112.0(2.0)
C(1)–C(2)–C(3)	108.9(2.1)	C(12)–C(13)–C(14)	106.8(1.8)
C(2)–C(3)–C(4)	108.2(2.2)	C(12)–C(13)–C(17)	116.9(2.1)
C(2)–C(3)–O(1)	111.6(2.2)	C(12)–C(13)–C(18)	110.8(2.0)
C(4)–C(3)–O(1)	106.4(2.1)	C(14)–C(13)–C(17)	99.7(1.6)
C(3)–C(4)–C(5)	114.0(2.4)	C(14)–C(13)–C(18)	113.6(2.0)
C(4)–C(5)–C(6)	119.4(2.5)	C(17)–C(13)–C(18)	108.7(1.9)
C(4)–C(5)–C(10)	118.4(2.4)	C(8)–C(14)–C(13)	115.1(2.1)
C(4)–C(5)–O(4)	111.2(2.2)	C(8)–C(14)–C(15)	117.6(2.2)
C(6)–C(5)–C(10)	119.2(2.4)	C(13)–C(14)–C(15)	104.0(1.8)
C(6)–C(5)–O(4)	58.3(0.9)	C(14)–C(15)–C(16)	103.7(2.0)
C(10)–C(5)–O(4)	114.0(2.1)	C(15)–C(16)–C(17)	107.2(2.2)
C(5)–C(6)–C(7)	123.5(2.6)	C(13)–C(17)–C(16)	102.2(1.8)
C(5)–C(6)–O(4)	60.0(0.9)	C(13)–C(17)–C(20)	120.6(2.2)
C(7)–C(6)–O(4)	115.0(2.3)	C(16)–C(17)–C(20)	112.9(2.2)
C(5)–O(4)–C(6)	61.6(0.9)	C(17)–C(20)–C(21)	114.3(2.3)
C(6)–C(7)–C(8)	112.6(2.2)	C(17)–C(20)–C(22)	109.7(2.1)
C(7)–C(8)–C(9)	108.7(1.9)	C(21)–C(20)–C(22)	108.2(2.2)
C(7)–C(8)–C(14)	108.8(2.0)	C(20)–C(22)–C(23)	118.4(2.7)
C(9)–C(8)–C(14)	109.2(1.9)	C(22)–C(23)–C(24)	113.8(3.1)
C(8)–C(9)–C(10)	116.2(2.1)	C(23)–C(24)–C(25)	117.2(3.6)
C(8)–C(9)–C(11)	110.9(2.0)	C(24)–C(25)–C(26)	109.8(3.7)
C(10)–C(9)–C(11)	111.9(2.0)	C(24)–C(25)–C(27)	116.6(4.3)
C(1)–C(10)–C(5)	108.3(1.8)	C(26)–C(25)–C(27)	107.6(4.1)
C(1)–C(10)–C(9)	107.2(1.8)	O(1)–C(30)–O(2)	123.0(2.8)
C(1)–C(10)–C(19)	110.6(1.9)	O(1)–C(30)–O(3)	109.3(2.3)
C(5)–C(10)–C(9)	112.4(2.0)	O(2)–C(30)–O(3)	127.7(3.0)
C(5)–C(10)–C(19)	105.8(1.9)	C(32)–C(31)–O(3)	107.8(2.4)
C(9)–C(10)–C(19)	112.5(2.1)	C(3)–O(1)–C(30)	117.4(2.3)
C(9)–C(11)–C(12)	112.3(2.0)	C(30)–O(3)–C(31)	115.8(2.3)



Calculations were performed on a NAS 90-80 computer for the structure solution with MULTAN 77, and on a MD/570-CX using AFFINE (a modified version of ORFLS)³⁰ for the structure refinement and for drawing with ORTEP.³¹

Reagents.—Ru(O)₂(tmp) was prepared according to Leung and Che.² 3-Epicholesterol was prepared by reduction of cholest-5-en-3-one (Fluka) by NaBH₄–MeOH.³² As epicholesterol is obtained in a poor yield (approximately 10%) with cholesterol as major product, repetitive crystallisations in ethanol were carried out to discard the bulk of the cholesterol with minimum loss of 3-epicholesterol; the latter is obtained pure after chromatography on silica (overall yield 10%).

Isocholesterol was obtained by reduction of cholest-3,5-dien-7-one (Aldrich) by Na–propanol at reflux.³³ After chromatography on silica the following products were obtained: cholest-

4-en-7 α -ol (15% yield, m.p. 87–88 °C), cholest-4-en-7 β -ol (ischolesterol, 42% yield, m.p. = 122.5–124.5 °C) and a crude mixture of both these compounds (22%).

The acetic esters **2** and **3** were obtained by reaction of the appropriate sterol with an acetic anhydride–pyridine mixture^{8,12} for 24 h at room temp. Cholest-4-en-7 α -yl acetate **4** was obtained under the same conditions in 7 d [m.p. 103–104 °C; *m/z* (*M* – AcOH)⁺ (Found: M⁺, 368.3448. Calc. for C₂₇H₄₄: *M*, 368.3443); δ_{H} 0.65 (s, 3 H, 18-CH₃), 0.92 (d, 6 H, 26- and 27-CH₃, *J* 6.4), 0.94 (s, 3 H, 19-CH₃), 1.0 (d, 3 H, 21-CH₃, *J* 6.4), 1.76 (s, 3 H, 7 α -acetoxy), 5.06 (br s, 1 H, 7 β -H, *w*_z 6), 5.30 (br s, 1 H, 4-H, *w*_z 9)].

The pregnane derivative **5** was purchased from Steraloids. Compounds **6–9** were generous gifts from Dr. Schubert (Zentralinstitut für Mikrobiologie und Experimentelle Therapie, Jena, Germany).

5,6 β -Epoxy-5 β -cholestan-3 α -yl Acetate **21.**—In a two-necked 10 cm³ round bottomed flask (unstoppered and wrapped with aluminium foil to exclude stray light), 3-epicholesteryl acetate (210 mg, 0.49 mmol), Ru(O)₂(tmp) (20 mg, 0.022 mmol) and benzene (3 cm³) were stirred at room temp. until disappearance of the unsaturated steroid occurred (1 d). After evaporation of benzene under reduced pressure the ¹H NMR spectrum indicated the presence of epoxide **21** as the sole steroid product. The crude product was chromatographed on silica gel and it afforded epicholesteryl acetate **2** (7 mg) (5% diethyl ether–light petroleum), epoxide **21** (136 mg, 62%) as glassy product (50% diethyl ether–light petroleum; efforts to crystallise this made it less pure as previously described⁹); 5 α -acetoxycholestan-3 α ,6 β -diol **15** (69 mg, 30%) (MeOH). NMR spectroscopic data for **21** and **15** were consistent with literature values.⁹

Oxidation of Cholest-4-en-7 β -yl Acetate **3.**—Compound **3** (210 mg, 0.49 mmol), Ru(O)₂(tmp) (20 mg, 0.022 mmol) and benzene (3 cm³) were stirred at room temp. for 6 days. The crude product was chromatographed on silica gel (20 g), and it afforded: the title compound **3** (47 mg) (3% diethyl ether–light petroleum); 4 β ,5-epoxy-5 β -cholestan-7 β -yl acetate **22** (48 mg, 22%) (20% diethyl ether–light petroleum) as a glassy product, m.p. 54–59 °C, [α]_D²⁰ +24 (c 1, CHCl₃) [lit.,¹¹ [α]_D²⁰ +18.5 (c 2.05, CHCl₃) for the β -epoxide and [α]_D²⁰ +85 (c 1.08, CHCl₃) for the α -epoxide]; 7 β -acetoxycholest-4-en-3-one **16** (87 mg, 40%) (50% diethyl ether–light petroleum), m.p. 99–100 °C, *m/z* (*M* – AcOH)⁺ (Found: M⁺, 382.3241. Calc. for C₂₇H₄₂O: *M*, 382.3235); δ_{H} 0.61 (s, 3 H, 18-CH₃), 0.69 (s, 3 H, 19-CH₃), 0.94 and 0.95 (2 d, 6 H, 26- and 27-CH₃, *J* 6), 1.05 (d, 3 H, 21-CH₃, *J* 6.5), 1.75 (s, 3 H, 7 β -acetoxy), 4.68 (m, 1 H, 7 α -H) and 5.85 (d, 1 H, 4-H, *J* 2.3); δ_{C} 12.1 (C-18), 75.5 (C-7), 125.9 and 163.9 (C-4 and C-5, tentative), 169.5 (7 β -acetoxy) and 196.7 (C-3).

Oxidation of Cholest-4-en-7 α -yl Acetate **4.**—Compound **4** (105 mg, 0.24 mmol), Ru(O)₂(tmp) (10 mg, 0.011 mmol) and benzene (3 cm³) were stirred at room temp. for 4 d. PLC of the crude product on silica with 5% AcOEt–cyclohexane afforded unchanged starting material (55 mg), 4 β ,5-epoxy-5 β -cholestan-7 α -yl acetate **23** (17 mg, 16%) as a glassy product, m.p. 88–94 °C, *m/z* (*M* – AcOH)⁺ (Found: M⁺, 384.3391. Calc. for C₂₇H₄₄O: *M*, 384.3392); δ_{H} 0.58 (s, 3 H, 18-CH₃), 0.92 (d, 6 H, 26- and 27-CH₃, *J* 6.3), 0.98 (d, 3 H, 21-CH₃, *J* 6.2), 0.99 (s, 3 H, 19-CH₃), 1.69 (s, 3 H, 7 α -acetoxy), 2.71 (d, 1 H, 4 α -H, *J* 4.3) and 5.09 (s, 1 H, 7 β -H); δ_{C} 11.9 (C-18), 61.3, 61.8 (C-4, C-5), 71.9 (C-7) and 169.4 (7 α -acetoxy); 7 α -acetoxycholest-4-en-3-one **17** (16 mg, 15%), m.p. 138–139 °C, *m/z* (*M* – AcOH)⁺ (Found: M⁺, 382.3240. Calc. for C₂₇H₄₂O: *M*, 382.3235); δ_{H} 0.57 (s, 3 H, 18-CH₃), 0.66 (s, 3 H, 19-CH₃), 0.93 (d, 6 H, 26- and 27-CH₃, *J* 6.9), 0.98 (d, 3 H, 21-CH₃, *J* 6.9), 1.67 (s, 3 H, 7 α -

acetoxy), 4.99 (m, 1 H, 7 β -H) and 5.79 (d, 1 H, 4-H, *J* 1.8); δ_C 11.9 (C-18), 70.9 (C-7), 126.8 (C-4), 164.8 (C-5), 169.8 (7 α -acetoxy) and 196.6 (C-3).

4 β ,5-Epoxy-5 β -cholestan-7 α -yl acetate **23** and 4 α ,5-epoxy-5 α -cholestan-7 α -yl acetate. Compound **4** (50 mg, 0.12 mmol) and *m*-chloroperbenzoic acid (27 mg, 87%, 0.13 mmol) in CH₂Cl₂ (2 cm³), stirred for 1 d, afforded, after work-up, a 4:1 mixture (50 mg) of the 4 β ,5 β - and 4 α ,5 α -epoxides. PLC on silica (5% AcOEt–cyclohexane) gave 4 β ,5 β -epoxide **23** (32 mg, 64%) and 4 α ,5-epoxy-5 α -cholestan-7 α -yl acetate (8 mg, 16%); δ_H 0.65 (s, 3 H, 18-CH₃), 0.78 (s, 3 H, 19-CH₃), 0.93 (d, 6 H, 26- and 27-CH₃, *J* 6.8), 1.03 (d, 3 H, 21-CH₃, *J* 6.8), 1.94 (s, 3 H, 7 α -acetoxy), 2.45 (d, 1 H, 4 β -H, *J* 4) and 5.05 (m, 1 H, 7 β -H, *w*₄ 5.5).

Oxidation of 3 β -Acetoxy-6-methylpregn-5-en-20-one 5.—Compound **5** (182.5 mg, 0.49 mmol), Ru(O)₂(tmp) (20 mg, 0.022 mmol) and benzene (3 cm³) were stirred at 20 °C for 6 d. The crude product, chromatographed on silica gel (20 g), afforded with 20% diethylether–light petroleum, starting material (65 mg); with 30% diethylether–light petroleum 3 β -acetoxy-5,6 β -epoxy-6 α -methyl-5 β -pregnan-20-one **24** (8 mg, 4%) as a glassy product, *m/z* M⁺ (Found: M⁺, 388.2607. Calc. for C₂₄H₃₆O₄: M, 388.2614); δ_H 0.52 (s, 3 H, 18-CH₃), 0.97 (s, 3 H, 19-CH₃), 1.26 (s, 3 H, 6-CH₃), 1.71 and 1.79 (2 s, 6 H, 3 β -acetoxy and 21-CH₃) and 4.9 (m, 1 H, 3 α -H, *w*₄ 33); δ_C 13.0 (C-18), 63.6 (C-17), 64.2 and 66.6 (C-5 and C-6), 71.3 (C-3), 169.6 (3 β -acetoxy) and 207.0 (C-21); with 40% diethylether–light petroleum a 1:1 mixture of epoxide **24** and its α -isomer **25** (13 mg, 7%); δ_H 0.51 (s, 18-CH₃), 0.74 (s, 19-CH₃ of 5,6 α -isomer), 0.97 (s, 19-CH₃ of 5,6 β -isomer), 1.08 (s, 6 β -CH₃ of 5,6 α -isomer), 1.26 (s, 6 α -CH₃ of 5,6 β -isomer), 1.72, 1.74, 1.79 (3 s, 3 β -acetoxy and 21-CH₃ of the two isomers), 4.9 (m, 3 α -H of 5,6 β -isomer, *w*₄ 33) and 5.28 (m, 3 α -H of 5,6 α -isomer, *w*₄ 28); with 50% diethyl ether–light petroleum 3 β -acetoxy-20-oxopregn-5-ene-6-carbaldehyde **18** (31 mg, 14%), *m/z* (M – AcOH)⁺ (Found: M⁺, 326.2239. Calc. for C₂₂H₃₀O₂: M, 326.2246); δ_H 0.53 (s, 3 H, 18-CH₃), 0.69 (s, 3 H, 19-CH₃), 1.77 and 1.80 (2 s, 6 H, 3 β -acetoxy and 21-CH₃), 4.65 (m, 1 H, 3 α -H, *w*₄ 26) and 10.2 (s, 1 H, CHO); δ_C 13.1 (C-18), 63.3 (C-17), 72.8 (C-3), 133.7 and 156.9 (C-6 and C-5, tentative), 169.4 (3 β -acetoxy), 189.7 (CHO) and 206.6 (C-20).

Molecular Graphics.—The structures of the proposed transition states were generated with the Sybyl software (Tripos) on a Silicon Graphics 4D20 workstation. The CrysIn interface was used for input of crystallographic coordinates. Files of atomic coordinates were converted to a format suitable for drawing 'ball-and-stick' figures with MolDraw³⁴ on a MacIntosh LC.

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