The Mechanism of the β-Acyloxyalkyl Radical Rearrangement: Kinetic and ^{18}O-Labelling Studies[1]

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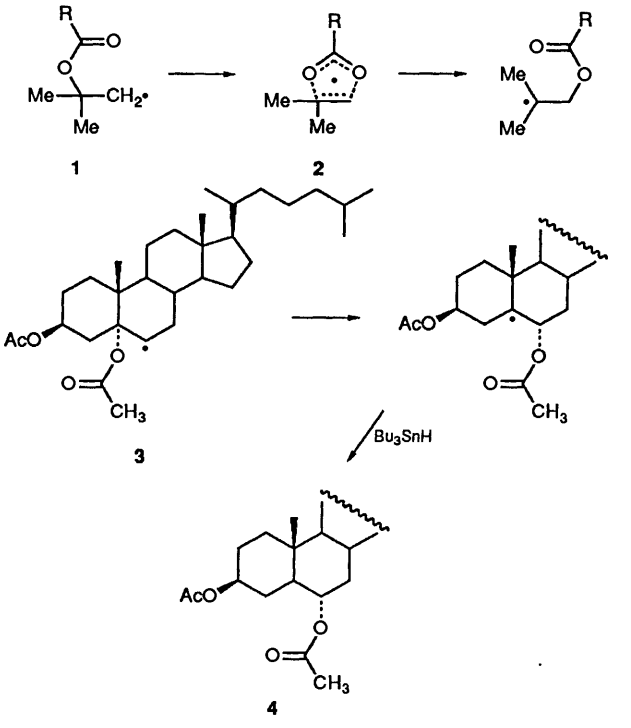
Experiments with ^{18}O-enriched substrates indicate that the rearrangement of 2-butanoyloxy-2,2-dimethyl radical **1** (R = Pr) by migration of the acyloxy group involves complete transposition of the ether and carbonyl oxygen atoms, whereas the similar but much faster rearrangement of the substituted cholestanyl radical **11** proceeds with only 24% transposition. The rearrangement of **1** is considered to involve a five-membered cyclic transition state **2**, while that of **11** probably proceeds *via* a tight anion–radical-cation pair **21**.

Suitably constituted β-acyloxyalkyl radicals (*e.g.* **1**) undergo rearrangement by 1,2-migration of the acyloxy group, a singular process in that, unlike other intramolecular radical reactions, it has no simple intermolecular analogue. Until relatively recently all of the reported investigations of this rearrangement[3–14] were consistent with the view that it proceeds in a concerted fashion *via* a cyclic transition structure **2** in which five electrons are delocalised over five atoms.[6,10,11] It can therefore be classified as an open shell pericyclic reaction, other examples of which include the rearrangements of allylperoxy,[15] acyloxyalkylsilyl,[16] and allylnitroxyl[17] radicals, and the pericyclic reactions of radical cations.[18]

A crucial factor in the elucidation of this mechanism was provided by results obtained from ^{18}O-labelled esters which showed that the ether and carbonyl oxygens in the substrate became completely transposed during the course of the reaction.[6,12] However, these data were recently brought into question by the observation that rearrangement of the steroid β-acetoxy radical **3** with ^{18}O in the ether linkage gave a product **4** in which 77% of the label remained in the ether oxygen.[19] Since this result is clearly inconsistent with the accepted mechanism and is at variance with our earlier labelling studies on simple acyclic esters[6] we were prompted to re-examine both systems using a variety of labelling and kinetic techniques. In this paper we describe our experiments on the rearrangement of the steroid radical **11** and the simple acyclic radical **1** (R = Pr).

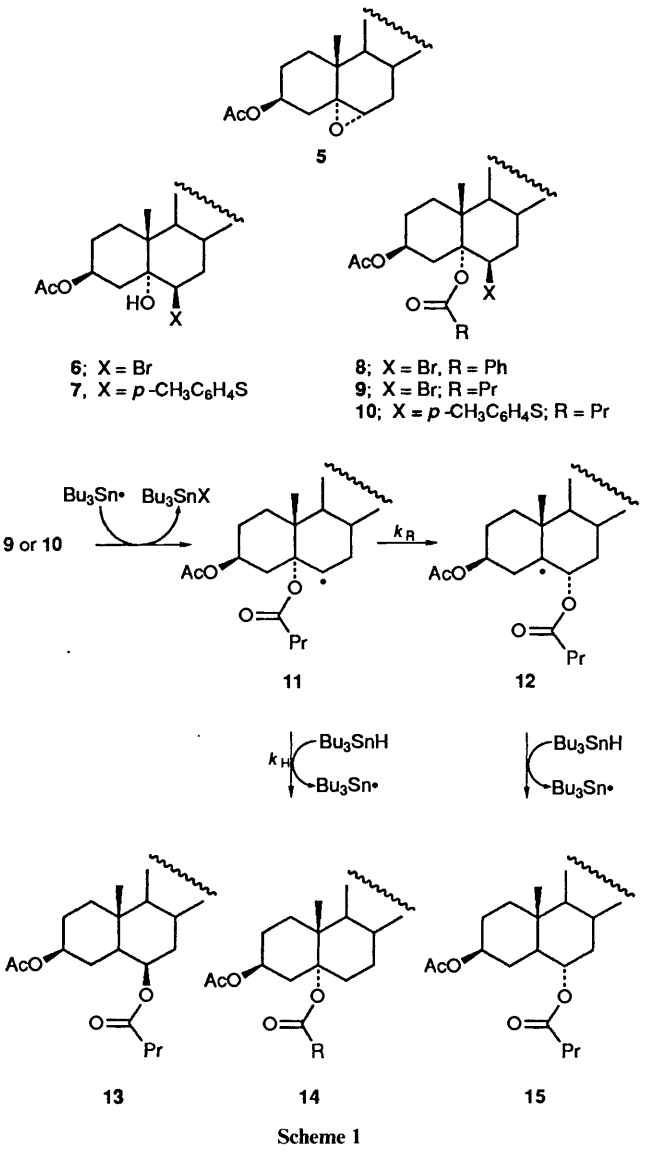


Results

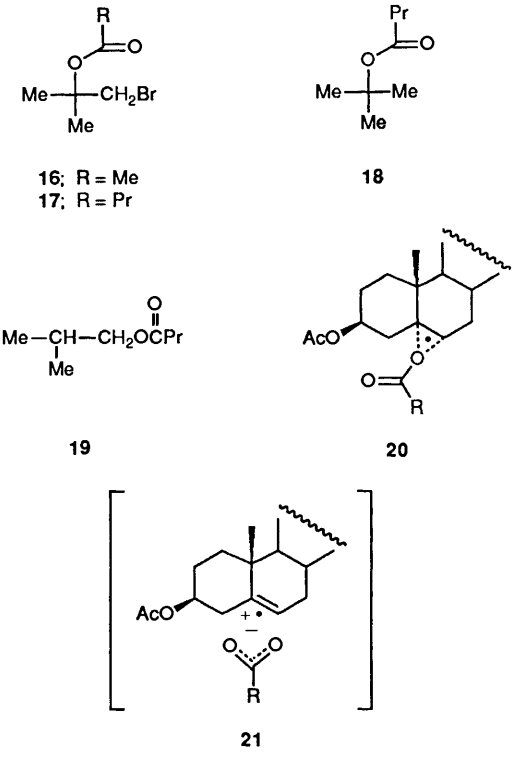
Substrates and Products.—One of the chosen substrates **17** was readily prepared from the corresponding bromohydrin by treatment with butanoic trifluoroacetic anhydride. The preparation of a suitable steroid ester was more difficult. Initially, we had intended to use the benzoate **8**, but all attempts to benzoylate the bromohydrin **6**, including the use of benzoic trifluoroacetic anhydride under forcing conditions, gave only negligible quantities of **8**, the major product in every case being the epoxide **5**. In an attempt to avoid the problem of epoxide formation, the alcohol **7** containing a β-arylthio substituent was chosen as an alternative substrate. However, in this case benzoylation would not proceed even under the most vigorous conditions.

Since the benzoates were apparently beyond reach we chose, instead, the butanoates **9** and **10**. Treatment of each of the alcohols **6** and **7** with butanoyl chloride and *N*,*N*-dimethylaniline gave the required substrates in moderate yield. Labelled substrates were obtained from [^{18}O]butanoyl chloride. Preparation of the latter involved hydrolysis of unlabelled butanoyl chloride wtih H_2O (99 atom% ^{18}O) in dry ether, followed by treatment of the labelled butanoic acid so formed with thionyl chloride. The product contained about 50 atom% ^{18}O. Treatment of the bromohydrin **6** with the labelled butanoyl chloride gave the ester **9** which was shown to contain about 34 atom% ^{18}O incorporated into the carbonyl group (see below). When 2-bromo-1,1-dimethylethanol was treated with butanoyl chloride and *N*,*N*-dimethylaniline some displacement of the bromo substituent by chlorine occurred to give a mixture of the bromoester **17** and its chloro analogue. However, since both of these substrates should react with tributylstannyl radicals to give the same intermediate radical **1** (R = Pr) no attempt was made to separate them.

Authentic samples of compounds expected as products from reactions of **9** or **10** were prepared by unambiguous routes. Reduction of the epoxide **5** with lithium aluminium hydride gave cholestane-3β,5α-diol[20] which was acetylated then treated with butanoyl chloride and *N*,*N*-dimethylaniline to give **14**. Hydroboration of cholesteryl acetate gave 3β-acetoxycholestane-6α-ol which was readily esterified to give **15**. The 6β-butanoate **13** was formed from the corresponding alcohol[21] which was obtained from the triacetate of cholestane-3β,5α,6β-triol *via* the 5β,6β-epoxide.[22]



Scheme 1



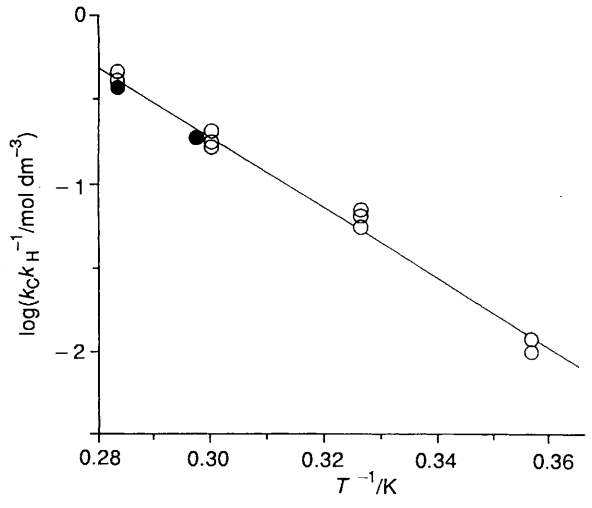


Fig. 1 Temperature dependence of k_R/k_H for the radical **11**

Kinetic Studies.—Heating of a solution of the bromoester **9** with tributylstannane and a catalytic quantity of azo-bis-isobutyronitrile (AIBN) as catalyst in deoxygenated benzene afforded only two products; they were identified as **14** and **15** by comparison with authentic samples. The β-ester **13** could not be detected but since it has rather similar chromatographic properties to its isomer **15**, a further check was carried out on a portion of the stannane reaction mixture which was hydrolysed by treatment with potassium hydroxide in hot methanol. The expected hydrolysis products of **14** and **15**, namely cholestane-3β,5α-diol and cholestane-3β,6α-diol, were formed but no trace could be detected of cholestane-3β,6β-diol. We conclude, therefore, that the rearrangement of **11** is completely stereoselective: migration of the butanoyloxy group is confined to the α-face of the molecule. The putative reaction mechanism is set out in Scheme 1. Bromine atom transfer from **9** to tributylstannyl radicals gives the radical **11** which can either react directly with tributylstannane to afford **14** or undergo rearrangement followed by reduction with stannane to give **15**. The usual steady-state treatment of the mechanism of Scheme 1 gives the rate equation (1) where $[\mathbf{14}]_f$ and $[\mathbf{15}]_f$ represent the final concentrations of the two products, k_R and k_H are the rate constants for rearrangement and hydrogen-atom transfer respectively, and $[Bu_3SnH]_m$ is the average concentration of tributylstannane which must be present in large excess.

$$k_R/k_H/\text{mol dm}^{-3} = ([\mathbf{15}]_f/[\mathbf{14}]_f) \times [Bu_3SnH]_m \quad (1)$$

In a series of kinetic experiments, solutions of **9** and an excess of tributylstannane in known concentration in benzene were heated in sealed ampoules. Experiments were conducted at four different temperatures with three different concentrations at each temperature. Analysis of the product mixtures by HPLC gave the ratio $[\mathbf{14}]_f/[\mathbf{15}]_f$ from which values of k_R/k_H were calculated (Table 1). The proposed mechanistic scheme requires that the results fit eqn. (1); the data in Table 1 show that this is so. Although, as expected for data collected by a refractive index detector, there is some scatter in the results, values of k_R/k_H are independent of $[Bu_3SnH]_m$ as demanded by the mechanism. Other mechanistic possibilities such as reversibility of the rearrangement step can, therefore, be precluded.

Values of k_R/k_H were fitted to the Arrhenius equation by linear regression analysis to give eqn. (2) where the activation energy is in kJ mol^{-1}. Fig. 1 shows that the Arrhenius equation

Table 1 Relative final concentrations of products **14** and **15** and relative rate constants for the reaction of the radical **11** with tributylstannane[a] in benzene

Substrate	T/°C	$[Bu_3SnH]_m$/ mol dm^{-3}	$[15]_f/[14]_f$	(k_R/k_H)/ mol dm^{-3}
9	8.0	0.008	1.45	0.012
9	8.0	0.016	0.75	0.012
9	8.0	0.029	0.35	0.010
9	33.5	0.029	2.20	0.064
9	33.5	0.062	1.12	0.069
9	33.5	0.113	0.49	0.055
9	60.0	0.108	1.63	0.176
9	60.0	0.203	1.02	0.207
9	60.0	0.404	0.41	0.167
10	63.0	0.203	0.91	0.185
9	80.0	0.203	1.90	0.386
9	80.0	0.404	1.02	0.410
9	80.0	0.599	0.77	0.460
10	80.0	0.103	3.61	0.372

[a] The average concentration during the reaction is listed.

$$\log [(k_R/k_H)/\text{mol dm}^{-3}] = (5.6 \pm 0.4) - (40.3 \pm 2.3)/2.3RT \quad (2)$$

is satisfied over the range of temperatures employed. Unfortunately, no accurate value is available for k_H for the reaction of a radical at C-6 in a steroid with tributylstannane. Accordingly k_H for the corresponding reaction of cyclohexyl radical was employed. The value is given by eqn. (3).[23] It follows from eqns. (2) and (3) that log k_R is given by eqn. (4). It follows from eqn.

$$\log (k_H/\text{dm}^3 \text{ mol}^{-1} \text{ s}^{-1}) = (9.24 \pm 0.78) - (16.6 \pm 4.8)/2.3RT \quad (3)$$

$$\log (k_R/\text{s}^{-1}) = (14.8 \pm 0.8) - (56.9 \pm 5.0)/2.3RT \quad (4)$$

(4) that $k_R = (1.9 \pm 1.1) \times 10^6$ s^{-1} at 75 °C. These data differ so significantly from those previously obtained for the rearrangement of simple acyclic β-acyloxyalkyl radicals ($k_R = 5.1 \times 10^2$ s^{-1} at 75 °C)[9] that it was necessary to consider whether the steroid reaction is, in fact, a radical process. To resolve this question the kinetics of the reaction of tributylstannane with the sulfide **10** were examined. If both **9** and **10** react *via* the radical **11** they should exhibit the same kinetic behaviour, but if other types of intermediate are involved they should behave differently. In the event the behaviour of the sulfide **10** was entirely consistent with that of the bromo compound **9**, and the values of k_R/k_H for both lie close to the best fit of the Arrhenius equation (Fig. 1). Clearly these reactions do not involve the loss of the bromo or arylthio substituent in a kinetically significant step and we conclude, therefore, that both **9** and **10** react *via* the common radical intermediate **11**.

In view of the very large difference in the measured rate constants for rearrangement of **11** and **16** ($k_R^{11}/k_R^{16} \approx 4 \times 10^3$ at 75 °C), we considered it prudent to confirm that k_R for simple acyclic systems had not been underestimated. Treatment of **17** with an excess of tributylstannane (0.022 mol dm^{-3}) in benzene at 100 °C in the usual way gave only the unrearranged product **18** as determined by gas chromatography. If the lower limit of detectability of the method is 5%, it follows that k_R/k_H at 100 °C $\leq$ 0.001 mol dm^{-3}. If k_H is assumed to be the same as that for the neopentyl radical ($k_H = 8.0 = 10^6$ dm^3 mol^{-1} s^{-1} at 100 °C)[24] it follows that $k_R \leq 8 \times 10^3$ s^{-1} at 100 °C. This is consistent with the previous determination ($k_R = 2.3 \times 10^3$ s^{-1} at 100 °C)[9] and confirms that it is not too low.

Experiments with ^{18}O-*Labelled Substrates.*—The butanoate **9** prepared by treatment of the bromohydrin **6** with ^{18}O-labelled butanoyl chloride did not give a molecular ion when subjected to electron ionisation (EI) or chemical ionisation (CI) mass spectroscopy. However, the successful incorporation of the isotopic label into the carbonyl group of the butanoate was verified by the ^{13}C NMR spectrum which showed resonances for the butanoate carbonyl at δ 172.22 (C=^{16}O) and δ 172.18 (C=^{18}O). Only a single resonance was observed for C-5 indicating that there had been no significant scrambling of the label into the ether oxygen.

One sample of the labelled substrate was treated with tributylstannane under conditions ([Bu_3SnH] = 0.59 mol dm^{-3}; 10 °C) designed to produce mainly the unrearranged reduction product **14** while another was treated under conditions ([Bu_3SnH] = 0.01 mol dm^{-3}, 80 °C) designed to produce mainly the rearranged product **15**. Both reactions gave yields >95% as determined by HPLC. The magnitude of the ^{18}O content of each product was determined to be 35 atom% by comparison of the corrected intensities of the peaks at m/z 536 (M + NH_4^+ + 2) and 534 (M + NH_4^+) in the CI (NH_3) mass spectra.

The ^{13}C NMR spectra of the products indicated that each had retained the label either completely or predominantly in the carbonyl group of the butanoate. Thus, labelled **14** showed two butanoate carbonyl resonances at δ 172.44 (C = ^{16}O) and δ 172.40 (C=^{18}O) but only one resonance at δ 87.79 for C-5 (C–^{16}O). Similarly, labelled **15** showed two butanoate carbonyl resonances at δ 172.46 (C=^{16}O) and δ 172.42 (C=^{18}O) but only one resonance assigned to C-6 (C–^{16}O) at either δ 72.03 or δ 73.19. Confirmation that the label in **14** was confined to the carbonyl group was obtained when reduction of **14** with lithium aluminium hydride afforded cholestane-3β,5α-diol containing no ^{18}O detectable by EI mass spectroscopy.

Similar reduction of the rearranged product **15** gave cholestane-3β,5α-diol containing ^{18}O. The degree of incorporation (8 atom%) was determined by comparison of its EI mass spectrum with that of an authentic unlabelled sample. The results indicate that the precursor **9** containing 35 atom% ^{18}O in the butanoate carbonyl gives a rearranged product **15** in which the label is distributed between the carbonyl (27 atom% ^{18}O) and ether (8 atom% ^{18}O) oxygens. We conclude that migration of the butanoyloxy group in **11** is accompanied by only 24% transposition of the carbonyl and ether oxygens. Clearly, this result is incompatible with a single concerted mechanism involving a five-membered cyclic transition structure.

Finally, in order to confirm the previous work[6] on ^{18}O-labelled acyclic substrates, the bromoester **17** containing ^{18}O in the carbonyl group was heated in methylcyclohexane at 101 °C while tributylstannane and AIBN were added from a syringe pump over 5 h. The ^{13}C NMR spectrum of the residue showed two resonances assigned to the carbonyl carbon of **18** at δ 172.81 (C=^{16}O) and δ 172.76 (C=^{18}O) but only one resonance for C-6 at δ 79.58 (C–^{16}O). For the rearranged product **19** the ^{13}C NMR spectrum showed two resonances for C-1 at δ 70.17 (C–^{16}O) and δ 70.14 (C-^{18}O) but only one for the carbonyl at δ 173.68 (C=^{16}O). These data are consistent with the complete transposition of the carbonyl and ether oxygens during the rearrangement of the radical **1** (R = Pr).

Discussion

The results described above together with those obtained from earlier experiments[19] indicate clearly that there cannot be a single mechanism for the rearrangement of β-acyloxyalkyl radicals. All of the available information supports the view that simple acyclic radicals such as **1** undergo a relatively slow concerted rearrangement *via* a five-membered cyclic transition structure **2** in which five electrons are delocalised over five

atoms. Both the isotopic labelling studies and the fact that the rate constant is more than three orders of magnitude greater than that for the rearrangement of the acyclic radical **1** (R = Pr) indicate that the conversion of the steroid radical **11** into **12** must proceed, at least in part, by a different mechanism. A process involving elimination of $PrCO_2^{\bullet}$ followed by its addition to the double bond so formed can be precluded since $PrCO_2^{\bullet}$ would certainly undergo decarboxylation. Another mechanistic possibility is that the rearrangement involves a concerted 1,2-migration of the acyloxy group *via* a three-membered cyclic transition structure **20**. Such a process lacks precedent although similar 1,2-oxygen shifts have been invoked to explain the course of some biological reactions.[25] Also, an *ab initio* MO study has indicated that alkyl radicals bearing a protonated oxonium substituent in the β-position should undergo this type of rearrangement.[26] Since a 1,2-acyloxy shift would give no transposition whatsoever of the ether and carbonyl oxygens it alone cannot account for the results of our experiments with ^{18}O labelled steroid substrates or those previously described.[19]

The third possibility involves the dissociation of the parent radical into a carboxylate anion and a radical-cation which exist as a tight ion pair **21** before collapsing to the product. This mechanism is consistent with the observation that radicals containing strongly electron-attracting acyloxy groups undergo particularly rapid rearrangement.[10] Also, the dissociation step is mechanistically related to the well documented elimination of water from the protonated radicals derived from 1,2-diols.[27] At first sight such a process for the rearrangement of **11** should lead to complete scrambling of the carbonyl and ether oxygens in the product and to the concomitant formation of the β-acyloxy compound **13**. However, if the intermediate is a tight ion pair the acyloxy group might be so constrained as to severely hinder the rotation necessary for transposition of the ether and carbonyl oxygen atoms and to confine the migration to the α-face.

Of the various possible mechanisms for rearrangement of the steroid radical **11** we favour that involving the formation of a tight anion–radical-cation pair **21**. It has the virtue of being fully in harmony with all of the experimental evidence including the kinetic data. The increased rate of rearrangement of **11** as compared with that of **1** (R = Pr) is consistent with the view that the formation of the ion pair will relieve the steric strain associated with the presence of the 5α-butanoyloxy group in the former. Evidence of the steric strain associated with 5α-esters is provided by the difficulty in conducting esterification of 5α-alcohols (*vide infra*). Furthermore molecular mechanics calculations show that the strain energy of **14** is decreased by 14.9 kJ mol^{-1} when the butanoyloxy group is replaced by hydrogen, whereas the difference in strain energy between **18** and isobutane is only 7.4 kJ mol^{-1}. Finally, it is noteworthy that the log *A* term [14.8 (s^{-1})] for rearrangement of **11** is greater than that [13.2 (s^{-1})] for rearrangement of **1** (R = Me).[10] This would be expected for a reaction involving ion-pair formation but not for one proceeding *via* a three-membered cyclic transition structure.

Conclusions

Kinetic experiments and experiments with ^{18}O-labelled substrates indicate that the simple acyclic β-acyloxyalkyl radical **1** (R = Pr) undergoes rearrangement by a concerted pericyclic process involving a five-membered cyclic transition structure **2** (R = Pr) in which five electrons are delocalised over five atoms. In the rearrangement of the steroid radical **11** the migration is confined to the α-face of the molecule and proceeds with only 24% transposition of the ether and carbonyl oxygens. The results are consistent with the view that the reaction involves the formation of a tight ion pair **21** incorporating a carboxylate anion and an olefinic radical-cation. However, the possibility that the reaction proceeds partly *via* a three-membered transition structure **20** and partly *via* an ion pair or a 2,3-pericyclic process cannot be unambiguously precluded. Experiments on substrates with structural features expected to favour the dissociation–recombination mechanism are in hand and will be reported shortly.

Experimental

IR spectra were recorded on a Perkin-Elmer 683 spectrometer. ^1H NMR spectra were recorded in deuteriochloroform with tetramethylsilane as internal reference at 200 MHz on a Varian XL-200 or JEOL PNM FX-200 instrument. All *J* values are given in Hz. ^{13}C NMR spectra were recorded in deuteriochloroform with tetramethylsilane as internal reference at 50 MHz on a JEOL PNM FX-200, or Varian XL-200 instrument. Assignment of hydrogen substitution of carbons, where appropriate, was made by use of the 'attached proton test' (APT).[28] Electron impact (EI) mass spectra and chemical ionisation (CI) mass spectra with ammonia as the reagent gas were measured on a VG Micromass 7070F mass spectrometer operating at 70 eV. High resolution mass spectra were recorded on an AEI MS 902 instrument. Flash chromatography on silica was carried out as previously described.[29] High pressure liquid chromatography (HPLC) was conducted on a Waters Radial-Pak 5μ HPLC cartridge, and the eluate was scanned with a Waters R403 differential refractometer. Gas liquid chromatography (GC) was carried out on a 25 m × 0.2 mm vitreous silica chromatography column (δGE 25QC 2/BP1 1.0) in a Varian 6000 or Varian 3400 gas chromatograph fitted with a flame ionisation detector and a Hewlett Packard 3390A integrator. Solvents and reagents were purified according to published procedures.[30] 'Ether' refers to diethyl ether. Melting points were determined on a Reichert hot-stage microscope and are uncorrected. Elemental analyses were carried out by the Australian National University Microanalytical Service.

3β-*Acetoxy*-5α,6α-*epoxycholestane* **5**.—Acetylation of 5α,6α-epoxycholestane-3β-ol[31] (4.65 g, 11.5 mmol) with acetyl chloride (1.8 g, 23 mmol) and pyridine (3.6 g, 44 mmol) in dry ether (56 cm^3) gave **5**[32] (4.4 g, 91%) m.p. 97.5–98.5 °C; δ_H(200 MHz) 0.61 (3 H, s, 18-Me), 0.80–0.93 (9 H, m, 21-Me, 26-Me, 27-Me), 1.08 (3 H, s, 19-Me), 2.02 (3 H, s, $MeCO_2$), 2.90 (1 H, d, *J* 4, 6β-H), 4.87–5.03 (1 H, m, 3α-H).

3β-*Acetoxy*-6β-*bromo*-5α-*butanoyloxycholestane* **9**.—The foregoing epoxide (2.0 g, 4.5 mmol) in chloroform (225 cm^3) was stirred for 15 min with 48% aqueous hydrobromic acid (225 cm^3), then tipped into ice and water. After being washed with aqueous sodium hydrogen carbonate and with water, the organic layer was concentrated to afford crude **5**[33] (2.2 g, 93%), m.p. 172–174 °C. A sample (400 mg, 0.76 mmol) of the crude bromohydrin was heated under reflux with butanoyl chloride (120 mg, 1.12 mmol) and *N*,*N*-dimethylaniline (120 mg, 1.1 mmol) in toluene (10 cm^3) for 44 h. After being cooled, the mixture was diluted with pentane and washed with iced water, dilute sulfuric acid, aqueous sodium hydrogen carbonate and brine. Evaporation of the solvent, and flash chromatography of the residue afforded the butanoate **9** (270 mg, 60%) as small plates from methanol, m.p. 125–127 °C (Found: C, 66.4; H, 9.4. $C_{33}H_{55}BrO_4$ requires C, 66.5; H, 9.3%); ν_{max}(KBr)/cm^{-1} 1740, 1733 (ester); δ_H 0.73 (3 H, s, 18-Me), 0.75–0.85 (9 H, m, 21-Me, 26-Me, 27-Me), 0.94 (3 H, t, *J* 6, CH_2CH_3), 1.22 (3 H, s, 19-Me), 1.94 (3 H, s, $MeCO_2$), 2.25 (2 H, t, *J* 6, CH_2CO), 2.80 (1 H, dd, *J* 5 and 14, 4α-H), 4.55–4.75 (1 H, m, 3α-H), 5.05 (1 H, br s, 6α-H); δ_C 12.17, 13.80, 18.51, 18.64, 18.95, 21.07, 21.27, 22.54, 22.80,

23.74, 24.03, 26.36, 27.99, 28.12, 29.55, 31.41, 32.63, 35.41, 35.69, 37.45, 39.46, 39.79, 40.44, 42.69, 45.49, 55.46, 56.11, 56.37, 70.05 (C-3), 88.63 (C-5), 170.29 (MeC=O), 172.22 (C_3H_7C=O); *m/z* 384 (100%) and 369 (26); *m/z* (CI) 532 (1%), 427 (25), 385 (77), 369 (83) and 367 (100).

3β-*Acetoxy*-6β-(4-*methylphenylthio*)*cholestan*-5α-*ol* **7**.—The epoxide **5** (3.3 g, 8.2 mmol) in methanol (130 cm^3) was added with stirring to a solution of potassium *p*-methylthiophenoxide [formed from *p*-toluenethiol (1.45 g, 11.6 mmol) and potassium methoxide (20 cm^3, 0.5 mol dm^{-3}) in methanol (130 cm^3)], and the mixture was heated under reflux for 24 h. The methanol was then evaporated, and the residue, after being dissolved in ether, was washed with aqueous sodium hydroxide and with brine, and dried. Evaporation of the solvent afforded the crude diol which was stirred with acetyl chloride (1.0 g, 12.7 mmol) and pyridine (2.10 g, 26.4 mmol) in dry ether (50 cm^3) at *ca.* 20 °C for 14 h. After addition of ether the mixture was poured into iced water, and the organic layer was washed with dilute hydrochloric acid, aqueous sodium hydrogen carbonate, and brine. The residue obtained by evaporation of the solvent was subjected to flash chromatography to afford the required sulfide **7** (3.2 g, 65%) which crystallised from methanol in needles, m.p. 121–123 °C (Found: C, 75.95; H, 10.4. $C_{36}H_{56}O_3S$ requires C, 76.0, H, 9.9%); ν_{max}(film)/cm^{-1} 3340 (OH) and 1713 (ester); δ_H(200 MHz) 0.70 (3 H, s, 18-Me), 0.82–0.97 (9 H, m, 21-Me, 26-Me, 27-Me), 1.19 (3 H, s, 19-Me), 2.02 (3 H, s, $MeCO_2$), 2.30 (3 H, s, ArCH_3), 2.95 (1 H, br s, 6α-H), 5.05–5.25 (1 H, m, 3α-H), 7.08 (2 H, d, *J* 8, o-ArH), 7.28 (2 H, d, *J* 8, *m*-ArH); δ_C 12.21, 17.23, 18.65, 21.00, 21.17, 21.40, 22.54, 22.78, 23.97, 24.18, 26.67, 27.97, 28.21, 30.66, 32.59, 35.09, 35.85, 36.18, 39.19, 39.28, 39.51, 39.92, 42.78, 45.70, 55.48, 56.39, 58.05, 71.45 (C-3), 77.62 (C-5), 129.70, 132.12, 134.06, 136.95, 170.85 (C=O); *m/z* 568 (M, 3%), 386 (4) and 369 (4).

3β-*Acetoxy*-5α-*butanoyloxy*-6β-(4-*methylphenylthio*)*cholestane* **10**.—Treatment of **7** (1.6 g, 2.8 mmol) with butanoyl chloride (0.45 g, 4.3 mmol) and *N*,*N*-dimethylaniline (0.51 g, 4.2 mmol) in toluene (10 cm^3) as described above gave the *butanoate* (0.60 g, 34%) as needles from methanol, m.p. 110–114 °C (Found: C, 74.8; H, 10.2. $C_{40}H_{62}O_4S$ requires C, 75.2; H, 9.8%); ν_{max}(KBr)/cm^{-1} 1735 (ester); δ_H 0.73 (3 H, s, 18-Me), 0.82–1.03 (17 H, m, 19-Me, 21-Me, 26-Me, 27-Me, CH_2CH_3), 2.00 (3 H, s, $MeCO_2$), 2.27–2.37 (5 H, m, ArCH_3, $COCH_2$), 2.99 (1 H, dd, *J* 4 and 14, 4α-H), 4.40 (1 H, br s, 6α-H), 4.65–4.85 (1 H, m, 3α-H), 7.10 (2 H, d, *J* 8, *o*-ArH), 7.33 (2 H, d, *J* 8, *m*-ArH); δ_C 12.33, 13.85, 17.50, 18.55, 18.72, 21.03, 21.26, 22.57, 22.81, 23.83, 24.18, 26.60, 28.03, 28.18, 30.34, 32.33, 32.74, 33.64, 35.77, 36.21, 37.67, 39.57, 40.04, 40.74, 42.84, 45.93, 49.64, 55.77, 56.33, 70.46 (C-3), 90.26 (C-5), 129.82, 131.78, 133.85, 136.94, 170.32, (MeC=O), 172.48 (PrC=O); *m/z* 490 (14%), 385 (5), 367 (2).

3β-*Acetoxy*-5α-*butanoyloxycholestane* **14**.—Acetylation of cholestan-3β,5α-diol[20] with acetic anhydride–pyridine gave the 3-acetate,[32] a sample of which (250 mg, 0.56 mmol) was treated with butanoyl chloride (90 mg, 0.9 mmol) and *N*,*N*-dimethylaniline (116 mg, 0.9 mmol) in toluene as described above. Flash chromatography of the crude product gave the butanoate (210 mg, 73%) as fine needles from methanol, m.p. 84.5–86.5 °C (Found: C, 76.8; H, 10.5. $C_{33}H_{56}O_4$ requires C, 76.7; H, 10.9%); ν_{max}(KBr)/cm^{-1} 1732 (ester C=O); δ_H 0.65 (3 H, s, 18-Me), 0.80–0.95 (9 H, m, 21-Me, 26-Me, 27-Me), 0.98–1.04 (6 H, m, 19-Me, CH_2CH_3), 1.99 (3 H, s, $MeCO_2$), 2.30 (2 H, t, *J* 7, CO_2CH_2), 2.53 (1 H, dd, *J* 5 and 14, 6α-H), 2.77 (1 H, dd, *J* 5 and 14, 4α-H), 4.70–4.90 (1 H, m, 3α-H); δ_C 12.16, 13.59, 15.85, 18.64, 21.31, 22.53, 22.79, 23.76, 24.00, 26.09, 26.62, 26.83, 27.82, 27.87, 27.99, 28.19, 30.51, 33.60, 34.64, 35.72, 36.12, 37.55, 39.48, 39.72, 39.99, 42.68, 45.64, 56.15, 56.23, 69.92 (C-3), 87.79 (C-5), 170.32 (MeC=O), 172.22 (PrC=O); *m/z* 428 (1%), 386 (2), 369 (31), 368 (100); *m/z* (CI) 534 (M + 18, 59%), 446 (12), 429 (12), 386 (9), 369 (100).

3β-*Acetoxy*-5α-*cholestan*-6α-*ol*.—A solution of boron trifluoride–THF complex in THF (1.0 cm^3; 1.0 mol dm^{-3}) was added over 10 min to a stirred solution of cholesteryl acetate (200 mg, 0.47 mmol) in THF (7 cm^3) at 0 °C. The mixture was stirred for 2.5 h at 0 °C, and a few drops of water were then added followed by caustic soda solution (1 cm^3; 1 mol dm^{-3}) and hydrogen peroxide (0.5 cm^3; 30%). After the mixture had been stirred for a further hour at room temperature, potassium carbonate was added, and the organic layer was separated, dried, and concentrated. Flash chromatography of the residue gave the required monoacetate (59 mg, 28%) as needles from acetone, m.p. 137–139 °C (lit.,[34] 138–139 °C); δ_H 0.64 (3 H, s, 18-Me), 0.80–0.92 (12 H, m, 19-Me, 21-Me, 26-Me, 27-Me), 2.02 (3 H, s, $MeCO_2$), 3.30–3.49 (1 H, m, 6β-H), 4.58–4.78 (1 H, m, 3α-H).

3β-*Acetoxy*-6α-*butanoyloxycholestane* **15**.—The foregoing alcohol (80 mg, 0.18 mmol) was heated with butanoyl chloride (38 mg, 0.36 mmol), *N*,*N*-dimethylaniline (33 mg, 0.28 mmol) and a few mg of DMAP in chloroform (5 cm^3) for 14 h. The usual work up procedure, including flash chromatography, gave the required diester (75 mg, 80%) as needles from methanol, m.p. 85–87 °C (Found: C, 76.3; H, 11.3. $C_{33}H_{56}O_4$ requires C, 76.7; H, 10.9%); ν_{max}(KBr)/cm^{-1} 1739 and 1734 (ester C=O); δ_H 0.66 (3 H, s, 18-Me), 0.80–1.00 (15 H, m, 19-Me, 21-Me, 26-Me, 27-Me, CH_2CH_3), 2.02 (3 H, s, $MeCO_2$), 2.25 (2 H, t, *J* 7, $COCH_2$), 4.55–4.78 (2 H, m, 3α-H, 6β-H); δ_C 12.04, 13.28, 13.69, 18.55, 18.68, 21.10, 21.45, 22.58, 22.84, 23.86, 24.12, 27.15, 28.03, 28.18, 28.35, 34.12, 35.78, 36.15, 36.53, 36.59, 36.90, 37.69, 39.51, 39.74, 42.63, 48.52, 53.59, 56.14, 56.21, 72.03, 73.19, 170.59 (MeC=O), 172.46 (PrC=O); *m/z* (CI) 534 (M + NH_4^+, 100%), 429 (3), 369 (12).

5α-*Cholestane*-3β,6β-*diol*.—3β,5α,6β-Triacetoxycholestane[35] was converted by a literature method[35] into 5β,6β-epoxycholestan-3β-ol, m.p. 128–130 °C (lit.,[22] 129–131 °C), a sample (57 mg, 0.14 mmol) of which was reduced in the usual way with lithium aluminium hydride (30 mg, 0.75 mmol) in dry ether (10 cm^3). Flash chromatography of the crude product gave the 3β,6β-diol (25 mg, 45%), m.p. 190–193 °C (lit.,[21] 190–192 °C); δ_H 0.68 (3 H, s, 18-Me), 0.82–0.95 (9 H, m, 21-Me, 26-Me, 27-Me), 1.02 (3 H, s, 19-Me), 3.56–3.73 (1 H, m, 3α-H), 3.80 (1 H, d, *J* 3, 6α-H).

2-*Bromo*-1,1-*dimethylethyl Butanoate* **17**.—Butanoic acid (0.47 g, 5.0 mmol) was added to trifluoroacetic anhydride (5 cm^3) at 0 °C and stirred for 5 min as previously described.[36] 2-Bromo-1,1-dimethylethylethanol[6] (0.77 g, 5 mmol) was then added dropwise and the stirred mixture was allowed to warm to 20 °C over 1.5 h. Benzene (5 cm^3) was added to the mixture which was cooled in ice while aqueous sodium hydroxide was slowly added until two layers clearly separated. The usual work-up gave the ester **17** (0.95 g, 92%) as an oil, b.p. 84 °C/15 mmHg (Found: C, 43.0; H, 6.75. $C_8H_{15}BrO_2$ requires C, 43.1; H, 6.8%); ν_{max}/cm^{-1} 1735 (C=O) and 675 (C-Br); δ_H 0.96 (3 H, t, *J* 7, CH_2CH_3), 1.52 [6 H, s, $C(CH_3)_2$], 1.59–1.70 (2 H, m, CH_2CH_3), 2.26 (2 H, t, *J* 7, $COCH_2$), 3.76 (2 H, s, CH_2Br); δ_C 13.61 (CH_2CH_3), 18.52 (CH_2CH_3), 25.14 [$C(CH_3)_2$], 37.17 ($COCH_2$), 40.12 (C-Br), 79.16 [$OC(CH_3)_2$], 172.92 (C=O).

1,1-*Dimethylethyl Butanoate* **18**.—Treatment of *tert*-butyl alcohol with trifluoroacetic anhydride and butanoic acid[36] gave the butanoate **18**; δ_H 0.94 (3 H, t, *J* 7, CH_2CH_3), 1.44 [9 H, s, $C(CH_3)_3$], 1.58–1.69 (2 H, m, CH_2CH_3), 2.19 (2 H, t, *J* 7,

$COCH_2$); δ_C 13.55 (CH_2CH_3), 18.61 (CH_2CH_3), 28.12 [C-$(CH_3)_3$], 37.52 ($COCH_2$), 79.83 [$C(CH_3)_3$], 173.07 (C=O).

2-Methylpropyl Butanoate **19**.—Treatment of isobutanol with butanoyl chloride in pyridine afforded the butanoate **19**; δ_H 0.90–1.10 (9 H, m, 3 × CH_3), 1.60–1.73 (2 H, m, CH_2CH_3), 1.86–2.00 [1 H, m, *J* 7, $CH(CH_3)_2$], 2.30 (2 H, t, *J* 7, $COCH_2$), 3.85 (2 H, d, *J* 7, OCH_2); δ_C 13.58 (CH_2CH_3), 18.46, 18.90 [CH_2CH_3 and $C(CH_3)_2$], 27.71 [$CH(CH_3)_2$] 36.24 ($COCH_2$), 70.28 (OCH_2), 173.68 (C=O).

Reaction of 3β-Acetoxy-6β-bromo-5α-butanoyloxycholestane **9** *with Tributylstannane*.—A degassed solution of the bromide **9** (300 mg, 0.51 mmol), tributylstannane (198 mg, 89%, 0.60 mmol) and AIBN (4 mg) in benzene (60 cm^3) was heated at 80 °C for 50 min. The solvent was then removed by evaporation under reduced pressure and the residue was subjected to flash chromatography to afford the rearranged product **15** (265 mg, 99%) and cholesteryl acetate (2 mg, 1%).

Reaction of 2-Bromo-1,1-dimethylethyl Butanoate **17** *with Tributylstannane*.—A solution of the bromide (25 mg, 0.11 mmol) and tributylstannane (377 mg, 86%, 1.1 mmol) in *tert*-butylbenzene (50 cm^3) was heated at 100 °C for 1 h. GC analysis of the mixture showed 1,1-dimethylethyl butanoate **18** to be the only detectable product.

Kinetic Studies on the Reactions of **9** *and of* **10** *with Tributylstannane*.—The purity of the tributylstannane was determined by measuring the volume of hydrogen evolved when a known quantity (*ca.* 50 mg) was injected into a flask containing dichloroacetic acid. For kinetic experiments a solution of the steroid (0.08 mmol) and tributylstannane (277 mg, 85%, 0.8 mmol) in benzene was prepared in a 2.0 cm^3 volumetric flask. An aliquot (1.0 cm^3) was placed in an ampoule with AIBN (*ca.* 0.5 mg) and degassed by repeated freeze–thaw cycles. The ampoule was sealed under vacuum and heated in a constant temperature bath. After an appropriate time (*e.g.* 2 h at 80 °C), the contents of the ampoule were passed through a Waters Sep-Pak, then analysed by HPLC (5% ethyl acetate–hexane; Waters 5μ Radial Pak silica column; refractive index detector; flow rate of 2 cm^3 min^{-1}). The detector had been previously calibrated with standard mixtures of **14** (retention time = 9.0 min) and **15** (retention time = 10.3 min). The results are recorded in Table 1.

^{18}O-Enriched Butanoyl Chloride.—Butanoyl chloride (3.0 cm^3, 28 mmol) was stirred in dry ether to which $H_2{}^{18}O$ (20 atom%, 0.56 cm^3, 31 mmol) had been added. Careful removal of the solvent by distillation under reduced pressure afforded ^{18}O-labelled butanoic acid which was heated under reflux with freshly distilled thionyl chloride. Distillation of the mixture afforded [^{18}O]butanoyl chloride (2.5 cm^3, 83%), the isotopic content of which was estimated to be about 10 atom% ^{18}O by mass spectrometry of a sample of ethyl butanoate prepared from it. [^{18}O]Butanoyl chloride (*ca.* 45 atom% ^{18}O) was similarly prepared from $H_2{}^{18}O$ (99 atom%).

^{18}O-Enriched 3β-Acetoxy-6β-bromo-5α-butanoyloxycholestane.—Treatment of the bromohydrin **6** (0.40 g, 0.75 mmol) with ^{18}O-labelled butanoyl chloride (45 atom%, 0.12 cm^3, 1.1 mmol) as described above for the preparation of **9** gave the required ^{18}O-labelled butanoate (270 mg, 60%), m.p. 122–124 °C. The ^{13}C NMR spectrum showed a resonance at δ 172.18 assigned to the butanoate C=^{18}O group. Otherwise the NMR spectra were identical with those of **9**.

Esterification of 2-Bromo-1,1-dimethylethanol with ^{18}O-Enriched Butanoyl Chloride.—2-Bromo-1,1-dimethylethanol (240 mg, 1.5 mmol) was heated in toluene (2 cm^3) under reflux with [^{18}O]butanoyl chloride (45 atom%, 0.225 cm^3, 2.2 mmol), *N,N*-dimethylaniline (0.270 cm^3; 2.2 mmol) and a catalytic amount of DMAP for 2 days. The product, isolated by flash chromatography as an oil, comprised a mixture (77 mg, 28%) of ^{18}O-enriched 2-bromo-1,1-dimethylethyl butanoate and the corresponding 2-chloro compound. The NMR spectra were identical with those of the unlabelled ester **17** except for additional resonances at δ_H 3.83 (CH_2Cl) and at δ_C 50.55 (CH_2Cl) and 172.90 (C=^{18}O).

Reactions of ^{18}O-labelled 3β-Acetoxy-6β-bromo-5α-butanoyloxycholestane **9** *with Tributylstannane*.—A solution of the bromide **9** (70 mg, 0.12 mmol) labelled specifically with ^{18}O in the butanoate carbonyl group, AIBN (4 mg), and tributylstannane (378 mg), 90%, 1.17 mmol) in benzene (2 cm^3) was degassed, then kept at 10 °C overnight while being irradiated with UV light. In a second experiment the same quantities of reagents were dissolved in 117 cm^3 of benzene and heated at 80 °C for 1 h. Evaporation of the mixtures and HPLC of the products as described above showed the first reaction to afford only **14** (>95%). The unrearranged product **14** had *m/z* (CI) 536 (M + 2 + NH_4, 59.4), 534 (M + NH_4^+, 100%) indicating that it contained 35% of the isotopically labelled compound, while the product **15**, *m/z* (CI) 536 (M + 2 + NH_4^+, 44.8%), 535 (M + NH_4^+, 75.1), also contained 35% of labelled material. The NMR spectra for the products were identical with those recorded above for the unlabelled materials except for extra ^{13}C resonances at δ 172.40 for **14** and δ 172.42 for **15**. Each product (53 mg, 0.01 mmol) was reduced with lithium aluminium hydride (16 mg, 0.4 mmol) in ether (5 cm^3). The cholestane-3β,5α-diol obtained from **14** had a CI mass spectrum identical with that of an authentic sample of the unlabelled compound;[20] *m/z* 404 (M, 23%), 386 (15), 369 (100). The cholestane-3β,6α-diol formed from **15** had *m/z* 406 (4.2%), 404 (40.3%). A reference sample of unlabelled 3β, 6α-diol[34,37] had *m/z* 406 (M + 2, 0.36%), 404 (M, 22), 386 (58), 371 (100) 369 (38).

Reaction of ^{18}O-Enriched 2-Halogeno-1,1-dimethylethyl Butanoate with Tributylstannane.—A deoxygenated solution of the stannane (200 mg, 81%, 0.56 mmol) and AIBN (10 mg) in methylcyclohexane (5 cm^3) was added from a syringe pump over 5 h to a solution of a mixture of ^{18}O-enriched 2-bromo- and 2-chloro-1,1-dimethylbutanoate (77 mg, prepared as described above) in methylcyclohexane heated under reflux. After the addition the heating was continued for a further 3 h by which time all of the halogeno compounds had been consumed (GC). The ratio of unrearranged to rearranged product was 0.44:1.0. The mixture was then placed in a U-tube and concentrated by evaporation of the solvent at room temperature under reduced pressure (*ca.* 16 mmHg) in a closed system. The ^{13}C NMR spectrum of the residue showed peaks at δ 172.81 (C=^{16}O) and 172.76 (C=^{18}O) for ^{18}O-enriched **18** and 70.17 (C-^{16}O) and 70.14 (C-^{18}O) for ^{18}O-enriched **19** together with those recorded above for **18** and **19**.

Calculation of Strain Energies.—The strain energies of the esters **14** and **18**, and of the corresponding compounds in which the butanoyloxy group has been replaced by a hydrogen atom were calculated by the MM2 molecular mechanics programme.[38] Lone pairs were included on the ether oxygens for the ester calculations. The strain energies were reduced when the lone pairs were omitted but the strain energy differences between the steroid and acyclic systems were unaltered.

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