Intramolecular Condensation of Steroidal α-Acetoxy-ketones

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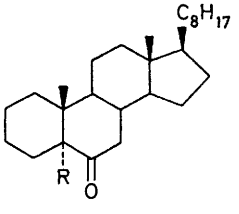
Intramolecular condensation of tertiary α-acetoxy-ketones in the cholestane series takes place in the presence of lithium di-isopropylamide to give products derived from nucleophilic attack of an ester enolate anion upon the adjacent oxo-group. When the acetoxy-group is axial, condensation proceeds rapidly at −78 °C to give the corresponding β-hydroxy-γ-lactone, but when it is equatorial the reaction is less efficient, and is attended by dehydration of the primary product.

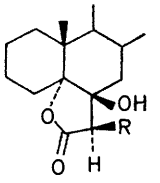
DURING a recent investigation [1,2] into the use of lithium dimethylcuprate (LDC) as a selective reductant for α-functionalised ketones, it was found that, whereas certain secondary α-acetoxy-ketones underwent rapid reduction to the parent ketones, the reaction of 5-acetoxy-5α-cholestan-6-one (2) with LDC in ether at 0 °C proceeded slowly and gave, in addition to the expected 6-ketone (1) (63%), a more polar isomer (35%) of the starting material (2). This product displayed spectroscopic properties consistent with the β-hydroxy-γ-lactone structure (4) [$\nu_{max.}$ 3 600 (OH) and 1 770 cm^{-1} (γ-lactone CO), $\Delta\varepsilon_{max.}$ +2.41 (219 nm), δ 2.33 and 2.85 (1 H doublets, J 16.5 Hz, for an isolated methylene group adjacent to the lactone CO)]. The lower field n.m.r. doublet displayed distinct broadening ($W_{\frac{1}{2}}$ *ca.* 3 Hz) and was assigned to the ' β '-proton, which is uniquely aligned in a planar W-conformation for long-range coupling with the 7β-proton. The configuration at C-6 follows from the mode of formation of the product (see later).

The hydroxy-lactone (4) was not dehydrated by thionyl chloride–pyridine at 0 °C or toluene-*p*-sulphonic acid in refluxing benzene; such dehydration (to the butenolide or the βγ-unsaturated product) would necessitate deformation of the steroidal ring of attachment in order to accommodate the axial C(5)–O bond. Analogous dehydrations have been reported for β-hydroxy-γ-lactones fused to *trans*-decalin,[3] but the relative rigidity of the steroid skeleton probably imposes too high an energy demand upon this process in (4).

In a further experiment, the 5α-propionyloxy-6-ketone (3) reacted with LDC to give the 6-ketone (1) (68%), together with the α-methyl-β-hydroxy-γ-lactone (5) (10%). An n.m.r. spectrum of (5) confirmed the presence of a secondary methyl group (3 H doublet, J 8 Hz, at δ 1.38), and the configuration α to the lactone carbonyl group was suggested by the chemical shift [δ 2.39; *cf.* δ 2.33 for the corresponding proton in (4)] and the absence of long-range coupling in the quartet (J 8 Hz) for the attached ' α '-proton. The formation of (5) is highly stereoselective: no trace of an isomer was detected.



(1) R = H
(2) R = OAc
(3) R = O_2CEt



(4) R = H
(5) R = Me

The formation of the γ-lactones (4) and (5) evidently proceeds *via* proton abstraction α to the ester carbonyl group by an unspecified strong base present in LDC, followed by intramolecular condensation with the adjacent 6-oxo-group. In contrast to the reactions of LDC with secondary α-acetoxy-ketones where no lactonic

[1] J. R. Bull and H. H. Lachmann, *Tetrahedron Letters*, 1973, 3055.

[2] J. R. Bull and A. Tuinman, *Tetrahedron Letters*, 1973, 4349.

[3] G. S. Chappell, *J. Org. Chem.*, 1973, **38**, 240.

products were detected,[2] the reduction pathway in the case of tertiary α-acetoxy-ketones appears to be sufficiently slow to allow this unexpected condensation to intervene.

Following an observation,[4] that base-catalysed intramolecular condensation of a 17α-acetoxy-20-oxo-steroid afforded the corresponding 17-spiro-(β-hydroxy-β-methyl)-γ-lactone and hence the derived butenolide, similar reactions of the 17α-acetoxy-20-ketone system have frequently been noted during attempted base-mediated reactions at other sites in the steroid molecule.[5] The principle has been applied with modest success to the synthesis of a simple, fused-ring butenolide,[6] but no systematic study of the scope of the reaction appears to have been made.

Apart from the potential usefulness of the foregoing reaction in lactone synthesis and in the formal intramolecular transposition of the carbon chain of an ester, the mechanistic implication that a proton α to an ester carbonyl group can be selectively abstracted in the presence of an enolisable ketone system appeared to warrant attention. Accordingly, the base-catalysed intramolecular condensation of a number of steroidal α-acetoxy-ketones was investigated in order to clarify some of the mechanistic and conformational factors involved.

In view of the intrusive reduction pathway during reactions of tertiary α-acetoxy-ketones with LDC, and uncertainty about the basic species implicated in proton abstraction prior to intramolecular condensation, other reagents were sought for this study. Those bases in the presence of which 17α-acetoxy-20-ketones have been reported [4,5] to undergo this reaction were considered to be too unselective to be generally useful.

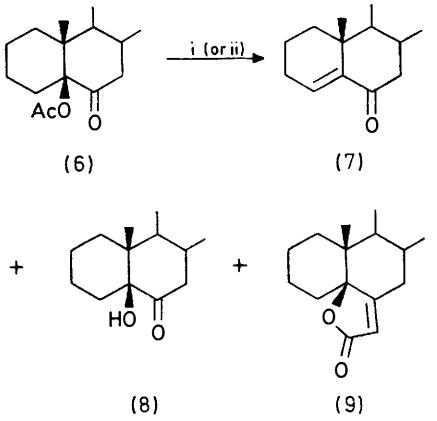
Attention was turned to the alkali metal dialkylamides in view of their known [7] ability to deprotonate esters under mild conditions. An added prospective advantage was that the steric demand of the more hindered amides might facilitate selective ester enolate anion formation in the substrates.

Experiments showed that the slow addition of an α-acetoxy-ketone in ether to a solution of lithium di-isopropylamide (LDA) (generated *in situ* by adding a slight excess of di-isopropylamine to ethereal methyl-lithium at 0 °C) resulted, in favourable cases, in rapid formation of the corresponding β-hydroxy-γ-lactone. In such cases the reactions were conducted at −78 °C, in order to inhibit possible interference through enolisation of the ketone, but higher temperatures and reverse addition techniques were attempted when the milder conditions failed.

The tertiary α-acetoxy-ketones discussed in this work were prepared unexceptionally through treatment of the corresponding α-hydroxy-ketones with toluene-*p*-sulphonic acid in acetic anhydride at 25 °C; under these conditions enol acetylation of the ketones was not observed.

5-Acetoxy-6-ketones.—Treatment of the 5α-acetoxy-6-ketone (2) with LDA resulted in rapid (<5 min by t.l.c.) intramolecular condensation at −78 °C, and the product (4) was obtained in high yield.

By contrast, the 5β-acetoxy-6-ketone (6) did not undergo the desired reaction under these conditions; slightly contaminated starting material (6) was recovered after 4 h in the presence of LDA at −78 °C. When the reaction was repeated at 20 °C an intractable mixture, containing traces of the butenolide (9) among several ill-defined products (t.l.c.), was obtained. However, the reverse addition of an excess of ethereal LDA during 2 h to the substrate (6) in ether at 20 °C afforded a separable mixture comprising the Δ^4-6-ketone (7) (22%), the 5β-hydroxy-6-ketone (8) (20%), and the butenolide (9)



(6) (7) (8) (9)

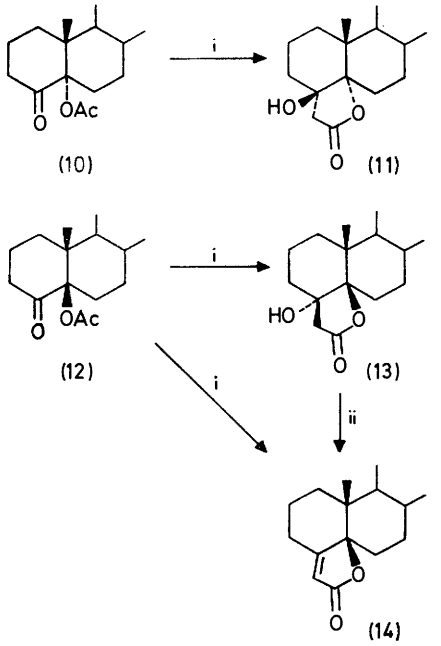
Reagents: i, Pr^i_2NLi–Et_2O, 20 °C; ii, $LiMe_2Cu$–Et_2O, 0 °C

(10%); no other pure products were isolated. The structure of the butenolide (9) was established by its spectroscopic properties [$\nu_{max.}$ 1739 (butenolide CO) and 1 646 cm^{-1} (butenolide C:C), $\Delta\varepsilon_{max.}$ +11.84 (237 nm) and −7.05 (206 nm), and δ 5.59 (1 H, *J* 2 Hz, for the vinylic proton coupled with the 7α-proton)]. This product apparently arose through the desired condensation, followed by β-elimination in the intermediate, which was not detected. In this case the fused butenolide ring of (9) may be accommodated without deformation of the steroidal ring B. The possible origin of the other products obtained in this reaction is discussed below.

It was of interest to compare the efficacy of LDC as the agent for intramolecular condensation since it appeared that (6) was not as rapidly destroyed in this medium as in LDA. Accordingly, (6) was treated with an excess of LDC in ether at 0 °C. After 4 h at 0 °C no starting material remained and the resultant mixture was separated by chromatography. Formation of the

[4] H.-G. Lehmann, *Angew. Chem. Internat. Edn.*, 1965, **4**, 783.
[5] N. H. Dyson, J. A. Edwards, and J. H. Fried, *Tetrahedron Letters*, 1966, 1841; G. W. Moersch, D. E. Evans, and G. S. Lewis, *J. Medicin. Chem.*, 1967, **10**, 254; T. L. Popper, J. N. Gardner, R. Neri, and H. L. Herzog, *ibid.*, 1969, **12**, 393; S. J. Halkes, J. Hartog, L. Morsink, and A. M. de Wachter, *ibid.*, 1972, **15**, 1288.
[6] W. C. Bailey, A. K. Bose, R. M. Ikeda, R. H. Newman, A. V. Secor, and C. Varsel, *J. Org. Chem.*, 1968, **33**, 2819.
[7] For examples see M. W. Rathke and A. Lindert, *J. Amer. Chem. Soc.*, 1971, **93**, 2318; M. W. Rathke and D. F. Sullivan, *ibid.*, 1973, **95**, 3050; R. J. Cregge, J. L. Herrmann, C. S. Lee, J. E. Richman, and R. H. Schlessinger, *Tetrahedron Letters*, 1973, 2425.

Δ^4-6-ketone (7) (5.5%) and the 5β-hydroxy-6-ketone (8) (3%) was less favoured than in the LDA-mediated reaction, whereas the butenolide (9) was obtained in a significantly higher yield (22%). No reduction product [2] was detected, but three further fractions (a) (11%), (b) (5%), and (c) (15.5%), were isolated during chromatography. The properties of compound (a) corresponded closely with those reported [8] for 5-methyl-5β-cholestan-6-one, and compound (b) was shown to be an isomeric methyl ketone ($C_{28}H_{48}O$) containing a secondary methyl group (3 H doublet, J 7 Hz, at δ 1.07). This product has not been identified, but has been shown not to be 4β-methyl-5α-cholestan-6-one,[9] arising from the action of LDC upon the product cholest-4-en-6-one (7). Fraction (c) was evidently a mixture of 6ξ-methyl-5β-cholestane-5,6ξ-diols arising from slow 1,2-methylation [10,11] and



Reagents: i, Pr^i_2NLi–Et_2O, −78 °C; ii, $SOCl_2$–C_5H_5N, 0 °C

ester cleavage of (6). Although n.m.r. spectroscopy revealed the presence of a major component, the mixture (c) could not be separated by repeated chromatography or recrystallisation. However, treatment of (6) with methyl-lithium, to give a similar mixture, confirmed the origin of this material.

5-Acetoxy-4-ketones.—The 5α-acetoxy-4-ketone (10) underwent rapid intramolecular condensation in the presence of LDA at −78 °C to give the expected product (11), whose spectroscopic properties were related to those of (4) in the expected manner. The c.d. data of (4) [$\Delta\varepsilon_{max.}$ +2.41 (219 nm)] and (11) [$\Delta\varepsilon_{max.}$ −2.43 (215 nm)] reflected the mutually antipodal relationship of their lactone chromophores toward the appended steroid rings. The lactone (11) also resisted dehydration.

The 5β-acetoxy-4-ketone (12) in LDA at −78 °C also reacted rapidly; in this case both the β-hydroxy-γ-lactone (13) and the derived butenolide (14) were obtained, in high combined yield. The implied facility with which (13) underwent β-elimination (possibly during work-up) was verified by its smooth conversion into (14) with thionyl chloride–pyridine at 0 °C. Although the conformational factors opposing butenolide formation should also apply to (13), it is possible that this compound differs in behaviour as a consequence of severe 1,3-diaxial interactions between the 4α-hydroxy-group and the C(6)–C(7) and C(10)–C(9) bonds of ring B. The removal of these interactions through dehydration may therefore be energetically advantageous, despite the attendant deformation of ring A.

3-Acetoxy-3-methyl-2-ketones.—The results obtained in the LDA-mediated reaction of the 5β-acetoxy-6-ketone (6) suggest that it is not a representative substrate upon which to assess the ability of an equatorial acetoxy-group to condense with an adjacent ketone function. An epimeric pair of substrates was sought in which ring conformations could be unambiguously defined and where the tertiary acetoxy-groups are not subject to the rotational restrictions which obtain at the 5-position.[12] 3α-Acetoxy-3β-methyl- (18) and 3β-acetoxy-3α-methyl-5α-cholestan-2-one (22) were studied.

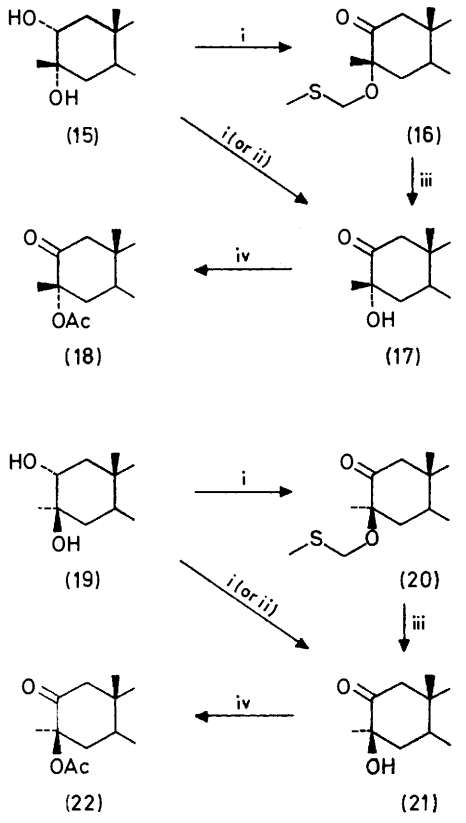
The known [13] 3-methyl-2α,3-diols (15) (40%) and (19) (38%) were prepared as described, by the action of methylmagnesium iodide upon 2α-acetoxy-5α-cholestan-3-one. Attempts to oxidise each diol with 8N-chromic acid were unsatisfactory, owing to extensive ring cleavage, but use of chromium trioxide–pyridine afforded the respective 3-hydroxy-3-methyl-2-ketones (17) and (21) in *ca.* 60% yields. In an attempt to improve this step, a study was made of the oxidation method recently described by Corey and Kim [14] as being suitable for conversion of secondary-tertiary α-glycols into α-hydroxy-ketones.

Treatment of (15) in toluene at −18 °C with 2 mol. equiv. of the *N*-chlorosuccinimide–dimethyl sulphide complex for 3 h resulted in incomplete reaction, but when a larger excess (*ca.* 5 mol. equiv.) of the reagent was used for the same period, the α-hydroxy-ketone (17) was obtained in 43% yield, together with a further product (55%), shown by spectroscopic data to be the 3β-methyl-3α-methylthiomethoxy-2-ketone (16). Brief treatment of (16) with toluene-*p*-sulphonic acid in warm benzene resulted in efficient conversion into the α-hydroxy-ketone (17); in this way the desired product was obtained in an effective overall yield of 83%.

Similarly, the diequatorial diol (19) was oxidised to the 3β-hydroxy-3α-methyl-2-ketone (21) (37%) and the

[8] J. W. Blunt, M. P. Hartshorn, and D. N. Kirk, *Tetrahedron*, 1965, **21**, 559.
[9] J. R. Bull, *J. Chem. Soc.* (*C*), 1969, 1128.
[10] H. O. House, W. L. Respess, and G. M. Whitesides, *J. Org. Chem.*, 1966, **31**, 3128.
[11] D. J. Goldsmith and I. Sakano, *Tetrahedron Letters*, 1974, 2857.
[12] J. R. Bull and P. R. Enslin, *Tetrahedron*, 1970, **26**, 1525.
[13] V. Dovinola, M. Adinolfi, and L. Mangoni, *Gazzetta*, 1970, **100**, 483.
[14] E. J. Corey and C. V. Kim, *Tetrahedron Letters*, 1974, 287.

corresponding methylthiomethyl ether (20); the latter product was converted into the former in the prescribed manner.



Reagents: i, *N*-chlorosuccinimide–Me_2S–PhMe, −18 °C; ii, CrO_3–C_5H_5N, 20 °C; iii, *p*-TsOH–C_6H_6, 50 °C; iv, *p*-TsOH–Ac_2O, 20 °C

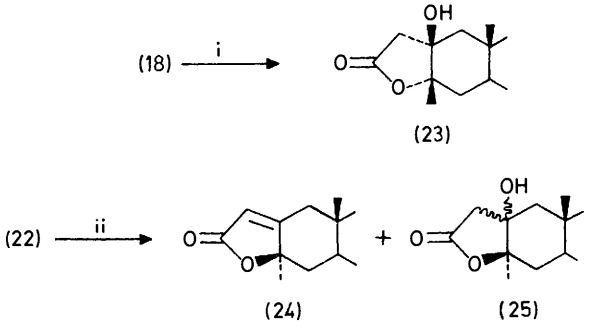
Methylthiomethyl ethers have frequently been encountered during mechanistically related oxidations of alcohols,[15] but their ready formation with tertiary hydroxy-groups under the mild conditons used here was unexpected. The possibility that intramolecular transfer of the group might have taken place, from the initially formed secondary oxysulphonium ion, can be precluded since experiments in progress [16] show that *trans*-diaxial alcohols also afford α-methylthiomethoxy-ketones. Furthermore, 3β-methyl-5α-cholestan-3α-ol has been shown [16] to react under the same conditions to form the corresponding ether at a rate comparable to that observed for the α-glycols. It follows that direct formation of a tertiary oxysulphonium ion is possible, and its subsequent rearrangement (through a one- or two-step mechanism [15]) to the ether proceeds independently of adjacent functionality.

The respective 3-acetoxy-3-methyl-2-ketones (18) and (22) were prepared in the usual way, and spectroscopic examination (see Experimental section) revealed no evidence of unusual conformational features. As expected, LDA-mediated condensation of the axial α-acetoxy-ketone (18) was complete within 5 min at −78 °C, and the β-hydroxy-γ-lactone (23) was obtained. The expectation that the greater conformational mobility at this site might enable the product (23) to undergo dehydration more readily than (4) or (11) was not realised despite prolonged treatment with the appropriate reagents.

The reaction of 3β-acetoxy-3α-methyl-5α-cholestan-2-one (22) in ethereal LDA proceeded slowly at −78 °C and was incomplete after 1 h at this temperature. Although the temperature was raised to 20 °C before work up, traces of starting material were still present. Chromatography afforded several minor and impure products which were not identified; the major product (51%) was the butenolide (24), and a more polar fraction (*ca.* 7%) exhibited properties (M^+ 458, $\nu_{max.}$ 3 600 and 1 770 cm^{-1}) consistent with a β-hydroxy-γ-lactone (25). Multiple-development t.l.c. showed that this fraction comprised two products (*ca.* 3 : 1). Although insufficient material was available for quantitative separation and characterisation of the components, it was demonstrably a mixture of the C-2 epimers (25) since it was smoothly converted into the butenolide (24) upon treatment with thionyl chloride–pyridine at 0 °C.

In a further experiment, an excess of LDA was added slowly to the 3β-acetoxy-3α-methyl-2-ketone (22) in ether at 20 °C; after 1 h the butenolide (24) was obtained in a similar yield (48%) to that of the foregoing experiment.

Mechanism and Stereochemistry.—The condensation described here bears a formal resemblance to an intramolecular Reformatsky reaction; the evidence supports selective proton abstraction α to the ester carbonyl group, followed by rapid nucleophilic attack upon the adjacent oxo-group when the conformational requirements are fulfilled. The more acidic [17] protons α to the oxo-group are sterically less vulnerable to abstraction,



Reagents: i, Pr^i_2NLi–Et_2O, −78 °C; ii, as i, −78 to 20 °C

and it is significant that no trace of starting materials, suggestive of synchronous proton abstraction from both α-positions, was ever detected in the fast condensations.

The further possibility, that initial proton abstraction α to the oxo-group is followed by intramolecular proton

[15] W. W. Epstein and F. W. Sweat, *Chem. Rev.*, 1967, **67**, 247; S. M. Ifzal and D. A. Wilson, *J. Chem. Soc.* (*C*), 1969, 2168, and references cited therein.

[16] J. R. Bull, unpublished work.

[17] H. O. House, 'Modern Synthetic Reactions,' 2nd edn., Benjamin, New York, 1972, ch. 9.

transfer from the ester methyl group, either to the former position (resulting in immediate ketonisation) or to oxygen (to give an enol), is unlikely in view of steric requirements and the need for a seven-membered transition

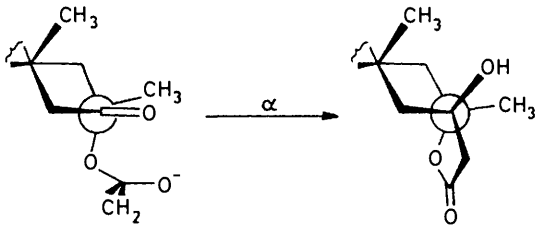


FIGURE 1 Stereoselective intramolecular condensation of 3α-acetoxy-3β-methyl-5α-cholestan-2-one (18) [C(2)–C(3) projections]

state. Furthermore, proton transfer to oxygen, while sterically less demanding, would necessitate ketonisation prior to intramolecular condensation. No products of an intramolecular Claisen condensation or of nucleophilic attack by enolic oxygen were detected.

The rapidity with which axial α-acetoxy-ketones [(2), (10), (12), and (18)] reacted may readily be explained, since the ester enolate anion, once formed, is able to adopt an ideal conformation for perpendicular attack upon the adjacent oxo-group [exemplified by (18) ⟶ (23), Figure 1]. On the other hand, the ester enolate anion derived from the equatorial α-acetoxy-ketone (22) is unable to do so without an improbable deformation of ring A. Furthermore, in this case the direction of attack

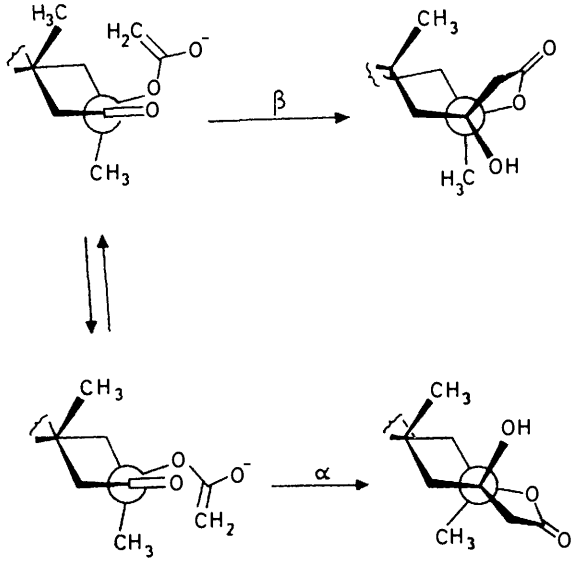


FIGURE 2 Conformers of the 3β-acetoxy-3α-methyl-2-ketone (22) anion, leading to β- and α-directed intramolecular condensation [C(2)–C(3) projections]

cannot be ascertained by inspection; β-directed bond-forming approach of the nucleophile to C-2 is 1,3-diaxially disposed toward the 10β-methyl group, while α-face attack is impeded by remoteness of the reaction centres and possibly also by the 3α-methyl group (Figure 2). This implied lack of stereoselectivity is borne out by the finding that the β-hydroxy-γ-lactone fraction (25) obtained in the reaction of (22) is an epimeric mixture. The ease with which the mixture (25) underwent β-elimination may be ascribed to the consequent relief of strain in either epimer, without deformation of the appended steroid ring.

The 5β-acetoxy-6-ketone (6) is exceptional since the 5β-substituent, while equatorial toward the 6-oxo-group, is axial in ring A, and is severely restricted in rotational freedom.[12] The β-mode of attack is most unlikely since the ester enolate anion would be required to

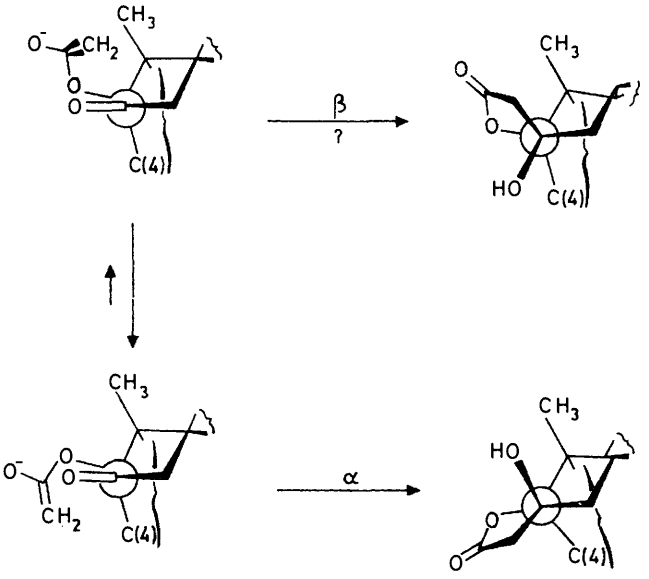


FIGURE 3 Conformers of the 5β-acetoxy-6-ketone (6) anion, leading to β- and α-directed intramolecular condensation [C(6)–C(5) projections]

insinuate itself between the 10β-methyl group and the 6-oxo-group for bond formation (Figure 3). It follows that the extent to which the desired reaction of (6) can proceed is limited by the ability of the nucleophile to adopt a conformation suitable for α-attack at C-6 (Figure 3). That such a conformation is not favoured is suggested by the failure of (6) to undergo any intramolecular condensation at −78 °C, and by the low yields of the butenolide (9) obtained at higher temperatures. It is possible that in this case enolisation of the 6-oxo-group is responsible for suppressing condensation since addition of (6) to an excess of LDA was less successful than the reverse addition. In the latter case the opportunity exists for more selective ester enolate anion formation in the presence of the unchanged 6-oxo-group. However, the intervention of side reactions is not surprising in view of the slowness of the condensation step, although the origin of some of the interfering products is obscure. For example, it is unlikely that formation of the hydroxy-ketone (8) can be ascribed to simple hydrolysis of (6) since stringent precautions were taken to exclude moisture. On the other hand there is no evidence

to suggest that the di-isopropylamide anion is sufficiently nucleophilic to induce ester cleavage. The formation of the Δ^4-6-ketone (7) is also surprising since it implies that effective elimination of the acetoxy-group of (6) can occur through intramolecular abstraction of the very weakly acidic 4-proton (probably β) by the ester enolate anion, or intermolecularly, by the di-isopropylamide anion. Whatever factors are responsible for the formation of (7) and (8) during the LDA-mediated reaction of (6), they are less dominant in the reaction conducted in LDC. This may partly explain the higher yield of the condensation product (9) obtained in the latter medium. However, further work will be necessary to establish the structure and origin of the two methyl ketones (a) and (b) since they cannot readily be rationalised in terms of the known properties of lithium dialkylcuprates.[18]

There is some precedent for 1,2-addition of LDC, albeit slowly, to saturated ketones,[10,11] but the observed ' hydrolysis ' of the 5β-acetoxy-group in the 1,2-addition product (c) also suggests that it could be an artefact of the hydroxy-ketone (8).

An extension of the described method of intramolecular condensation to secondary, and even primary α-acetoxy-ketones would be of considerable synthetic value. However, preliminary results were not encouraging, since treatment of 2α- or 2β-acetoxy-5α-cholestan-3-one with LDA at −78 °C resulted in rapid destruction of starting materials, and no lactonic products were detected in the resultant complex mixtures. In these cases it is probable that the relatively acidic 2-proton is rapidly abstracted and hence, even in the event of concomitant or subsequent ester enolate formation, the intramolecular condensation pathway is blocked. The use of more hindered bases to inhibit abstraction of the secondary proton is being investigated.

EXPERIMENTAL

M.p.s were determined with a Kofler hot-stage apparatus. Spectra were recorded as follows: i.r. spectra, Perkin-Elmer 237, chloroform solutions; u.v. spectra, Unicam SP 800, ethanol solutions; n.m.r. spectra, Varian HA 100, deuteriochloroform solutions with tetramethylsilane as internal standard; and mass spectra, A.E.I. MS 9. Optical rotations were determined for solutions in chloroform (unless otherwise specified) at 24 °C with a Bendix NPL automatic polarimeter, and c.d. spectra were recorded for methanol solutions with a JASCO J-20 instrument. Column chromatography was carried out with Kieselgel 60 (Merck), and t.l.c. with precoated silica gel F_{254} plates (0.25 mm; Merck).

C.d. data for the α-acetoxy-ketones (2), (6), (10), and (12) have been reported;[12] a more detailed discussion of these data for the lactones will be published shortly.

Preparation of α-Acyloxy-ketones.—The appropriate α-hydroxy-ketone was treated with 0.5% toluene-*p*-sulphonic acid in acetic anhydride [or propionic anhydride for (3)] at 25 °C for 15 h, water was added, and the product was isolated by filtration and crystallised to give the corresponding α-acetoxy-ketone. The following compounds were prepared: (a) *5-acetoxy-5α-cholestan-6-one* (2), m.p. 122—124° (from acetone–methanol), $[\alpha]_D$ −13° (*c* 1.1), $\nu_{max.}$ 1 732 and 1 720sh cm^{-1} (Found: C, 78.4; H, 10.9%; M^+, 444. $C_{29}H_{48}O_3$ requires C, 78.3; H, 10.9%; *M*, 444); (b) *5-propionyloxy-5α-cholestan-6-one* (3), m.p. 115—116° (from ether–methanol), $[\alpha]_D$ +53° (*c* 1.0), $\nu_{max.}$ 1 730br cm^{-1}, δ 0.64 (13β-CH_3), 0.82 (10β-CH_3), 1.2 (3 H, t, *J* 7.5 Hz, CO·CH_2·CH_3), and 2.42 (2 H, q, *J* 7.5 Hz, CO·CH_2·CH_3) (Found: C, 78.7; H, 11.1%; M^+, 458. $C_{30}H_{50}O_3$ requires C, 78.55; H, 11.0%; *M*, 458); (c) *5-acetoxy-5β-cholestan-6-one* (6), m.p. 138—141° (from chloroform–methanol), $[\alpha]_D$ −35° (*c* 0.8), $\nu_{max.}$ 1 740 and 1 712 cm^{-1} (Found: C, 78.7; H, 10.8%; M^+, 444); (d) *5-acetoxy-5α-cholestan-4-one* (10), as plates (from acetone–methanol), m.p. 129°, resolidifying as needles, m.p. 149—152°, $[\alpha]_D$ +41° (*c* 1.1), $\nu_{max.}$ 1 730br cm^{-1} (Found: C, 78.4; H, 10.9%; M^+, 444); (e) *5-acetoxy-5β-cholestan-4-one* (12), m.p. 135—138° (from chloroform–methanol), $[\alpha]_D$ +21° (*c* 1.0), $\nu_{max.}$ 1 732br cm^{-1} (Found: C, 78.3; H, 10.7%; M^+, 444); (f) *3α-acetoxy-3β-methyl-5α-cholestan-2-one* (18), m.p. 143—146° (from chloroform–methanol), $[\alpha]_D$ +56° (*c* 0.9), $\nu_{max.}$ 1 740 and 1 720sh cm^{-1}, $\Delta\varepsilon_{max.}$ +2.65 (291 nm) and +0.6 (218 nm), δ 0.66 (13β-CH_3), 0.72 (10β-CH_3), 1.39 (3β-CH_3), 2.09 (3α-OAc), and 2.25 (2 H, s, 1-H_2) (Found: C, 78.5; H, 10.7%; M^+, 458. $C_{30}H_{50}O_3$ requires C, 78.55; H, 11.0%; *M*, 458); (g) *3β-acetoxy-3α-methyl-5α-cholestan-2-one* (22), m.p. 152—154° (from chloroform–methanol), $[\alpha]_D$ +83° (*c* 0.8), $\nu_{max.}$ 1 740 and 1 720 cm^{-1}, $\Delta\varepsilon_{max.}$ +4.76 (289 nm), δ 0.66 (13β-CH_3), 0.99 (10β-CH_3), 1.52 (3α-CH_3), and 2.07 (3β-OAc) (Found: C, 78.2; H, 11.0%; M^+, 458).

Preparation of the 3-Methyl-5α-cholestane-2α,3-diols (15) *and* (19).—2α-Acetoxy-5α-cholestan-3-one (2 g) in ether was added during 10 min to ethereal 2M-methylmagnesium iodide (22 ml) at 20 °C under nitrogen, and the mixture was gently refluxed for 20 min. The excess of reagent was destroyed, and the product (1.83 g) was isolated by extraction with ether and adsorbed on silica gel (150 g). Elution with ethyl acetate–benzene (1 : 1) afforded the 3β-methyl-2α,3α-diol (15) (0.76 g), m.p. 189—192° (from chloroform–methanol), $[\alpha]_D$ +26° (*c* 0.9), δ 0.66 (13β-CH_3), 0.79 (10β-CH_3), 1.24 (3β-CH_3), and 3.5 (1 H, q, *J* 12 and 5 Hz, 2β-H) (lit.,[13] m.p. 188—189°, $[\alpha]_D$ +25°). Further elution with the same solvent gave unidentified material (0.046 g) followed by the 3α-methyl-2α,3β-diol (19) (0.713 g), m.p. 211—215° (from acetone–methanol), $[\alpha]_D$ +26° (*c* 0.6), δ 0.64 (13β-CH_3), 0.86 (10β-CH_3), 1.19 (3α-CH_3), and 3.7 (1 H, q, *J* 12 and 4 Hz, 2β-H) (lit.,[13] m.p. 203—205°, $[\alpha]_D$ +26°).

Oxidation of 3β-Methyl-5α-cholestane-2α,3α-diol (15).—(*a*) The diol (15) (0.05 g) in pyridine (1.5 ml) was added to stirred chromium trioxide (0.1 g) in pyridine (1 ml) at 0 °C. After 1 h at 0 °C the mixture was kept at 20 °C for 15 h then poured into aqueous sodium hydrogen carbonate and ice. Extraction with benzene afforded a product which was chromatographed on silica gel (5 g) with ethyl acetate–benzene (1 : 9) to give *3α-hydroxy-3β-methyl-5α-cholestan-2-one* (17) (0.028 g), m.p. 196—199° (from ethyl acetate–methanol), $[\alpha]_D$ +81° (*c* 0.8), $\nu_{max.}$ 3 580 and 1 704 cm^{-1}, $\Delta\varepsilon_{max.}$ +2.96 (302 nm), δ 0.66 (13β-CH_3), 0.72 (10β-CH_3), 1.28 (3β-CH_3), and 2.24 and 2.65 (each 1 H, d, *J* 12 Hz, 1-H_2) (Found: C, 80.8; H, 11.6%; M^+, 416. $C_{28}H_{48}O_2$ requires C, 80.7; H, 11.6%, *M*, 416).

(*b*) Dimethyl sulphide (1.7 ml, *ca.* 23 mmol) was added to stirred *N*-chlorosuccinimide (2.94 g, *ca.* 22 mmol) in dry toluene (60 ml) at 0 °C under nitrogen. The mixture was cooled to −18 °C and a suspension of the 3β-methyl-2α,3α-

[18] J. F. Normant, *Synthesis*, 1972, 63.

diol (15) in toluene (20 ml) was added. The mixture was stirred at −18 °C for 3 h, after which triethylamine (3.2 ml) in toluene (5 ml) was added, and the cooling bath was removed. After 15 min ethyl acetate was added to the mixture and the organic layer was washed successively with cold N-hydrochloric acid and aqueous sodium chloride, and evaporated *in vacuo*. The residue (2.1 g) was adsorbed on silica gel (160 g); elution with ethyl acetate–benzene (1 : 9) afforded oily material (0.15 g) followed by 3β-*methyl*-3α-*methylthiomethoxy*-5α-*cholestan*-2-*one* (16) (1.05 g), m.p. 60—63° (from methanol), $[\alpha]_D$ +95° (*c* 0.8), $\nu_{max.}$ 1 705 cm^{-1}, $\Delta\varepsilon_{max.}$ +2.72 (307 nm) and −0.94 (226 nm), δ 0.65 (13β-CH_3), 0.7 (10β-CH_3), 1.23 (3β-CH_3), 2.2 (SCH_3), 2.27 and 2.54 (each 1 H, d, *J* 12 Hz, 1-H_2), and 4.26 and 4.48 (each 1 H, d, *J* 11 Hz, OCH_2S) (Found: C, 75.8; H, 10.8; S, 6.7%; M^+, 476. $C_{30}H_{52}O_2S$ requires C, 75.6; H, 10.9; S, 6.7%; *M*, 476). Further elution with the same solvent afforded the 3α-hydroxy-3β-methyl-2-ketone (17) (0.71 g), m.p. and mixed m.p. 196—199°.

The ether (16) (1 g) in benzene (50 ml) was treated at 50 °C with toluene-*p*-sulphonic acid (0.05 g). After 10 min the product was isolated and chromatographed on silica gel (80 g) to give the hydroxy-ketone (17) (0.63 g).

Oxidation of 3α-*Methyl*-5α-*cholestane*-2α,3β-*diol* (19).—(*a*) The diol (19) (0.11 g) was treated with chromium trioxide in pyridine as described in the previous experiment (*a*). Chromatography of the product afforded 3β-*hydroxy*-3α-*methyl*-5α-*cholestan*-2-*one* (21) (0.07 g), double m.p. 119—120 and 128—130° (from acetone–methanol), $[\alpha]_D$ +89° (*c* 0.9) $\nu_{max.}$ 3 470br and 1 700 cm^{-1}, $\Delta\varepsilon_{max.}$ +4.46 (288 nm), δ 0.64 (13β-CH_3), 0.71 (10β-CH_3), 1.38 (3α-CH_3), and 2.19 and 2.45 (each 1 H, d, *J* 13 Hz, 1-H_2) (Found: C, 80.6; H, 11.4%; M^+, 416).

(*b*) Treatment of the diol (19) (0.836 g) in toluene (40 ml) with *N*-chlorosuccinimide (1.47 g) and dimethyl sulphide (0.85 ml) as described in the previous experiment (*b*), followed by addition of triethylamine (1.6 ml) in toluene (2.5 ml) prior to work-up, afforded a product which was chromatographed on silica gel (80 g) with ethyl acetate–benzene (1 : 9) to give oily material (0.09 g), followed by 3α-*methyl*-3β-*methylthiomethoxy*-5α-*cholestan*-2-*one* (20) (0.49 g), m.p. 85—90° (from chloroform–methanol), $[\alpha]_D$ +75° (*c* 0.8), $\nu_{max.}$ 1 708 cm^{-1}, $\Delta\varepsilon_{max.}$ +4.02 (297 nm) and +0.08 (226 nm), δ 0.66 (13β-CH_3), 0.77 (10β-CH_3), 1.5 (3α-CH_3), 2.26 (SCH_3), 2.12 and 2.38 (each 1 H, d, *J* 13 Hz, 1-H_2), and 4.7 (2 H, s, OCH_2S) (Found: C, 75.6; H, 11.0; S, 6.7%; M^+, 476). Further elution with the same solvent gave the 3β-hydroxy-3α-methyl-2-ketone (21) (0.305 g), m.p. and mixed m.p. 119—120 and 128—130°.

Treatment of the ether (20) (0.376 g) with toluene-*p*-sulphonic acid (0.02 g) in benzene (20 ml) at 50 °C for 10 min, and crystallisation of the product from acetone–methanol gave further hydroxy-ketone (21) (0.31 g).

Reactions of 5-*Acyloxy*-6-*ketones with Lithium Dimethylcuprate* (*LDC*). *Method.*—Methyl-lithium (1.8 mol of an ethereal 2M-solution) was added to a stirred suspension of copper(I) iodide in ether at 0 °C under nitrogen. After 30 min the acyloxy-ketone (0.2 mol) in ether was added dropwise with stirring, and the mixture was kept at 0 °C for the stated interval. Aqueous ammonium chloride was added to destroy the excess of reagent, and the product was extracted with benzene or chloroform; the extract was then washed with aqueous sodium chloride and evaporated *in vacuo*.

(*a*) Treatment of the 5α-acetoxy-6-ketone (2) (0.66 g) with LDC for 26 h and chromatography of the product on silica gel with methanol–chloroform (1 : 49) afforded 5α-cholestan-6-one (1) (0.364 g), m.p. and mixed m.p. 100—101°, and 3′,4′-*dihydro*-6β-*hydroxy*-5α-*cholestano*[5,6-b]*furan*-5′-*one* (4) (0.232 g), m.p. 253—255° (from acetone), $[\alpha]_D$ +5° (*c* 1.1), $\nu_{max.}$ 3 600 and 1 770 cm^{-1}, $\Delta\varepsilon_{max.}$ +2.41 (219 nm), δ 0.68 (13β-CH_3), 1.16 (10β-CH_3), and 2.33 and 2.85 (each 1 H, d, *J* 16.5 Hz, CH_2·CO) (Found: C, 78.1; H, 11.0%; M^+, 444. $C_{29}H_{48}O_3$ requires C, 78.3; H, 10.9%; *M*, 444).

(*b*) The reaction of the 5α-propionyloxy-6-ketone (3) (0.66 g) with LDC for 18 h afforded a mixture which was adsorbed on silica gel (70 g). Elution with ethanol–chloroform (1 : 150) gave the 6-ketone (1) (0.368 g), m.p. and mixed m.p. 99—100°, and (4′R)-3′,4′-*dihydro*-6β-*hydroxy*-4′-*methyl*-5α-*cholestano*[5,6-b]*furan*-5′-*one* (5) (0.065 g), double m.p. 195 and 250—251° (from acetone), $[\alpha]_D$ +18° (*c* 1.0), $\nu_{max.}$ 3 595 and 1 762 cm^{-1}, $\Delta\varepsilon_{max.}$ −0.32 (233 nm) and strong positive absorption below 200 nm, δ 0.69 (13β-CH_3), 1.18 (10β-CH_3), 1.38 (3 H, d, *J* 8 Hz, collapsing to s on irradiation at δ 2.39, 4′-CH_3), and 2.39 (1 H, q, *J* 8 Hz, collapsing to s on irradiation at δ 1.38, 4′-H) (Found: C, 78.6; H, 11.3%; M^+, 458. $C_{30}H_{50}O_3$ requires C, 78.55; H, 11.0%; *M*, 458).

(*c*) The reaction of 5-acetoxy-5β-cholestan-6-one (10) (0.5 g) with LDC for 4 h gave an oil which was adsorbed on silica gel (50 g). Elution with ethyl acetate–benzene (1 : 19) afforded a mixture (0.079 g), which was separated by rechromatography on silica gel (16 g) with benzene–hexane (1 : 1), to give fractions (a) (0.05 g), m.p. 84—85° (from ethanol), $[\alpha]_D$ −62° (*c* 0.6), $\nu_{max.}$ 1 693 cm^{-1}, δ 0.62, 0.97, and 1.02 (each 3 H, s) (Found: C, 84.3; H, 12.0%; M^+, 400. Calc. for $C_{28}H_{48}O$: C, 83.9; H, 12.0%; *M*, 400) (lit.,[8] for 5-methyl-5β-cholestan-6-one, m.p. 83.5—84°, $[\alpha]_D$ −55°); and (b) (0.024 g), m.p. 66—69° (from ethanol), $[\alpha]_D$ +26° (*c* 0.3), $\nu_{max.}$ 1 693 cm^{-1}, δ 0.62 and 0.66 (each 3 H, s), and 1.07 (3 H, d, *J* 7 Hz) (Found: M^+, 400).

Further elution with ethyl acetate–benzene (1 : 19) gave a second mixture (0.051 g), which was separated by rechromatography on silica gel (8 g) with chloroform to give the Δ^4-6-ketone (7) (0.024 g), m.p. and mixed m.p. 105—106°, indistinguishable from authentic material by spectral comparison, and the 5β-hydroxy-6-ketone (8) (0.014 g), m.p. and mixed m.p. 102—104°.

Further elution with ethyl acetate–benzene (1 : 19) afforded 5β-*cholestano*[5,6-b]*furan*-5′-*one* (9) (0.105 g), m.p. 177—180° (from ethanol), $[\alpha]_D$ +101° (*c*. 0.8), $\nu_{max.}$ 1 739 and 1 646 cm^{-1}, $\Delta\varepsilon_{max.}$ +11.84 (237 nm) and −7.05 (206 nm), δ 0.61 (10β-CH_3), 0.67 (13β-CH_3), 2.65br (1 H, d, *J* 13, $W_{\frac{1}{2}}$ 5 Hz, 7β-H), and 5.59 (1 H, d, *J* 2 Hz, 4′-H) (Found: C, 81.2; H, 10.9%; M^+, 426. $C_{29}H_{46}O_2$ requires C, 81.6; H, 10.9%; *M*, 426). Further elution of the column afforded material (c) (0.073 g) which, after several recrystallisations from ethanol, had m.p. 135—140°, $\nu_{max.}$ 3 560 cm^{-1}, δ 0.68, 1.05, and 1.12 (each 3 H, s) (Found: M^+, 418. Calc. for $C_{28}H_{50}O_2$: *M*, 418).

Reactions of α-*Acetoxy-ketones with Lithium Di-isopropylamide* (*LDA*). *Method.*—Unless otherwise specified, the following procedure was employed. Di-isopropylamine (1.1 mol. equiv.) was added to ethereal M-methyl-lithium at 0 °C. After 5 min at 0 °C the solution was cooled to −78 °C and the α-acetoxy-ketone (0.2 mol. equiv.) in ether was added dropwise with stirring. The reaction was monitored at intervals by t.l.c. of samples quenched in dilute acetic acid. When the starting material was consumed, the mixture was poured into dilute acetic acid and extracted

with chloroform or ethyl acetate; the extract was washed with aqueous sodium chloride and evaporated *in vacuo*.

(*a*) Treatment of 5-acetoxy-5α-cholestan-6-one (2) (0.15 g) with lithium di-isopropylamide (LDA) at −78 °C for 5 min, and crystallisation of the product from acetone afforded the β-hydroxy-γ-lactone (4) (0.125 g), m.p. and mixed m.p. 253—255°.

(*b*) Ethereal 0.2M-LDA was added at *ca.* 1.9 ml h^{-1} to the 5β-acetoxy-6-ketone (6) (0.132 g) in ether (4 ml) at 20 °C under nitrogen. T.l.c. showed that, after the addition of 1.5 ml of base (*ca.* 1 mol. equiv.), compound (6) was still present, but had disappeared after 2 h when 3.8 ml had been added. The product (0.13 g) was adsorbed on silica gel (16 g) and eluted with ethyl acetate–benzene (1 : 19) to give a mixture (0.071 g) which, after rechromatography (*cf.* reaction with LDC), afforded the Δ^4-6-ketone (7) (0.025 g) and the 5β-hydroxy-6-ketone (8) (0.024 g), both identical with authentic samples. Further elution with the same solvent gave the butenolide (9) (0.012 g) m.p. and mixed m.p. 177—179°.

(*c*) Treatment of the 5α-acetoxy-4-ketone (10) (0.2 g) with LDA at −78 °C for 5 min afforded 3′,4′-*dihydro*-4β-*hydroxy*-5α-*cholestano*[5,4-b]*furan*-5′-*one* (11) (0.167 g), m.p. 229—232° (from acetone), $[\alpha]_D$ +5° (*c* 0.9), $\nu_{max.}$ 3 600 and 1 765 cm^{-1}, $\Delta\varepsilon_{max.}$ −2.43 (215 nm), δ 0.67 (13β-CH_3), 1.16 (10β-CH_3), and 2.34 and 2.87 (each 1 H, d, *J* 16.5 Hz, CH_2·CO) (Found: C, 78.1; H, 10.9%; M^+, 444).

(*d*) Treatment of the 5β-acetoxy-4-ketone (12) (0.3 g) with LDA at −78 °C for 5 min gave a product which was adsorbed on silica gel (30 g). Elution with ethyl acetate–benzene (1 : 4) afforded 5β-*cholestano*[5,4-b]*furan*-5′-*one* (14) (0.062 g), m.p. 164—165° (from acetone–methanol), $[\alpha]_D$ −51° (*c* 0.8), $\nu_{max.}$ 1 730 and 1 642 cm^{-1}, $\Delta\varepsilon_{max.}$ −3.61 (239 nm) and +4.84 (212 nm), δ 0.67 (13β-CH_3), 0.72 (10β-CH_3), 2.72br (1 H, d, *J* 14, $W_{\frac{1}{2}}$ 7 Hz, 3β-H), and 5.65 (1 H, d, *J* 1 Hz, 4′-H) (Found: C, 81.8; H, 10.9%; M^+, 426). Further elution with the same solvent gave 3′,4′-*dihydro*-4α-*hydroxy*-5β-*cholestano*[5,4-b]*furan*-5′-*one* (13) (0.208 g), m.p. 193—195° (from acetone–methanol), $[\alpha]_D$ +32° (*c* 0.9), $\nu_{max.}$ 3 600 and 1 760 cm^{-1}, $\Delta\varepsilon_{max.}$ +1.63 (214 nm), δ 0.67 (13β-CH_3), 1.04 (10β-CH_3), and 2.34 and 3.0 (each 1 H, d, *J* 16.5 Hz, CH_2·CO) (Found: C, 78.5; H, 10.85%; M^+, 444).

Treatment of the β-hydroxy-γ-lactone (13) (0.025 g) in pyridine (0.5 ml) at 0 °C with thionyl chloride (0.1 ml) for 25 min afforded the butenolide (14) (0.02 g), m.p. and mixed m.p. 164—165°.

(*e*) The reaction of the 3α-acetoxy-2-ketone (18) (0.2 g) with LDA at −78 °C for 5 min, and crystallisation of the product from chloroform–ethanol, afforded 3′,4′-*dihydro*-2β-*hydroxy*-3β-*methyl*-5α-*cholestano*[3,2-b]*furan*-5′-*one* (23) (0.13 g), m.p. 251—256°, $[\alpha]_D$ +19° (*c* 1.0), $\nu_{max.}$ 3 600 and 1 770 cm^{-1}, $\Delta\varepsilon_{max.}$ −2.23 (215 nm), δ (C_5D_5N) 0.66 (13β-CH_3), 1.15 (10β-CH_3), 1.56 (3β-CH_3), and 2.6 and 3.18 (each 1 H, d, *J* 16 Hz, CH_2·CO) (Found: C, 78.6; H, 10.9%; M^+, 458).

(*f*) 3β-Acetoxy-3α-methyl-5α-cholestan-2-one (22) (0.43 g) was treated with LDA in the usual way. After 1 h at −78 °C starting material was still present and the mixture was allowed to attain room temperature before work up. Chromatography of the product on silica gel (40 g) with ethyl acetate–benzene (1 : 19) gave impure fractions (0.01 g) and starting material (22) (0.01 g) followed by 3α-*methyl*-5α-*cholestano*[3,2-b]*furan*-5′-*one* (24) (0.211 g), m.p. 179—181° (from chloroform–methanol), $[\alpha]_D$ −74° (*c* 0.9), $\nu_{max.}$ 1 740 and 1 645 cm^{-1}, $\Delta\varepsilon_{max.}$ −13.18 (228 nm) and strong positive absorption below 200 nm, δ 0.66 (13β-CH_3), 0.68 (10β-CH_3), 1.47 (3α-CH_3), 2.68 (1 H, d, *J* 12 Hz, 1β-H), and 5.63 (1 H, d, *J* 1 Hz, 4′-H) (Found: C, 81.9; H, 11.0%; M^+, 440. $C_{30}H_{48}O_2$ requires C, 81.8; H, 11.0%; *M*, 440).

Further elution with the same solvent gave impure fractions (0.027 g), and elution with ethyl acetate–benzene (1 : 9) gave crystalline material (0.032 g), $\nu_{max.}$ 3 600 and 1 770 cm^{-1} (Found: M^+, 458), shown by t.l.c. to be a mixture (*ca.* 3 : 1) of two compounds, presumed to be the C-2 epimers of (25). Treatment of a portion (0.02 g) of this material with thionyl chloride (0.1 ml) and pyridine (0.5 ml) at 0 °C for 20 min gave the butenolide (24) (0.014 g), m.p. and mixed m.p. 178—180°.

(*g*) Ethereal 0.2M-LDA was added to the 3β-acetoxy-3α-methyl-2-ketone (22) (0.066 g) in ether (2 ml) at 20 °C, as described in (*b*). After 1 h the product was isolated and chromatographed on silica gel (7 g). Impure fractions, corresponding (t.l.c.) to those obtained in experiment (*f*), were obtained, together with the butenolide (24) (0.03 g), m.p. and mixed m.p. 178—180°.

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