Stereoselective Vanadium-catalysed Epoxidation of α,β-Unsaturated Ketones Possessing a Neighbouring Hydroxy Group

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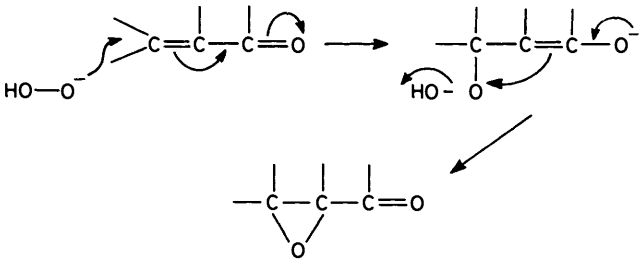
α,β-Unsaturated ketones possessing a hydroxy group two or three bonds away from the β-carbon can be stereoselectively epoxidized with t-butyl hydroperoxide in the presence of bisacetylacetonato-oxovanadium as catalyst. The reaction was applied to steroidal substrates in which the double bond is di- or tri-substituted and the hydroxy group is secondary or tertiary.

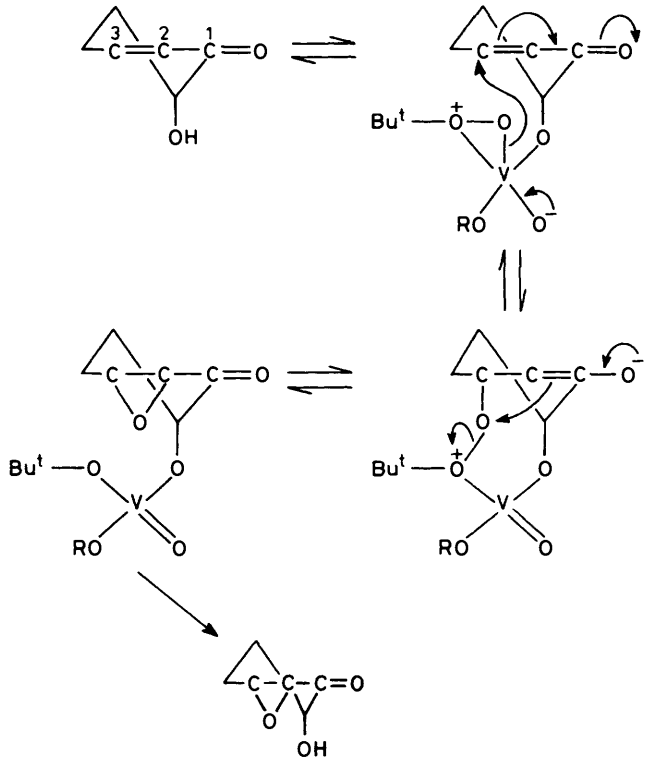
The epoxidation of double bonds conjugated to electron withdrawing groups is usually performed by treating the substrate with hydrogen peroxide in an alkaline medium (the Weitz–Scheffer reaction[1]). This procedure is widely applied to α,β-unsaturated aldehydes and ketones, and to a lesser extent to α,β-unsaturated nitriles, sulphones, *etc.* The reaction is explained by a two step mechanism involving a Michael type addition of the hydroperoxy anion HO_2^- to the β-position of the unsaturated system, followed by epoxide ring formation from the intermediate enolate anion.[2]



An alternative procedure[3] which was developed later, recommends the use of t-butyl hydroperoxide instead of hydrogen peroxide; in most instances, the reactions proceed in the presence of Triton B,[3a] although other basic catalysts are also employed.[3b] This reaction does not take place with hindered enones, not even with cholest-4-en-3-one, which is only slightly hindered. The mechanism of this reaction is most probably analogous to that of the H_2O_2–OH^- process.

We now report that α,β-unsaturated ketones bearing a hydroxy group two or three bonds away from the β-carbon are smoothly and stereoselectively epoxidized by t-butyl hydroperoxide in aprotic solvents, in the presence of bisacetylacetonato-oxovanadium [$VO(acac)_2$]. The reactions proceed at practically neutral pH and are performed under the same conditions as in the Sharpless epoxidation of allylic alcohols.[4] Attack of the double bond by the hydroperoxide co-ordinated together with the hydroxy group of the substrate in the vanadium complex, is facilitated by the polarization of the π system of the enone. The presence of the hydroxy group is a *sine qua non* condition for the reaction to take place. Simple enones cannot offer a binding site to the catalyst and are not epoxidized by this reagent. The reactions seem to be dependent on the distance between the double bond and the hydroxy group, the possibility of the latter to enter into the co-ordination sphere of the vanadium and by its spatial orientation.

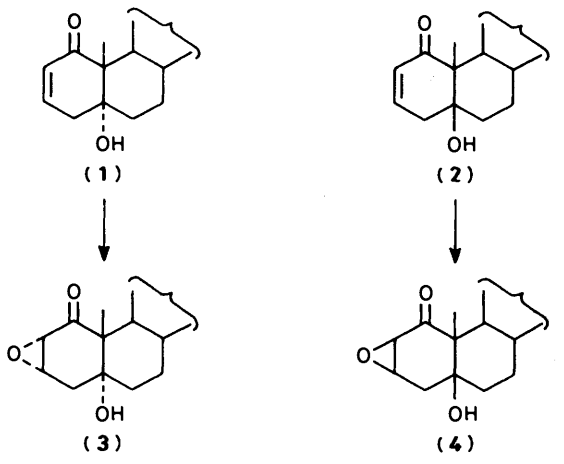
In our opinion, the reaction takes place by nucleophilic attack of the peroxidic oxygen at C-β of the conjugated system. The proximity of this oxygen to the double bond in the intermediate complex compensates probably for its low nucleophilicity in a neutral medium and enables the transfer. A possible mechanism for the epoxidation of a 6-hydroxycyclohex-2-en-1-one system is shown in the following Scheme. In a rigid



Scheme. Possible mechanism for the epoxidation of a 6-hydroxycyclohex-2-en-1-one system

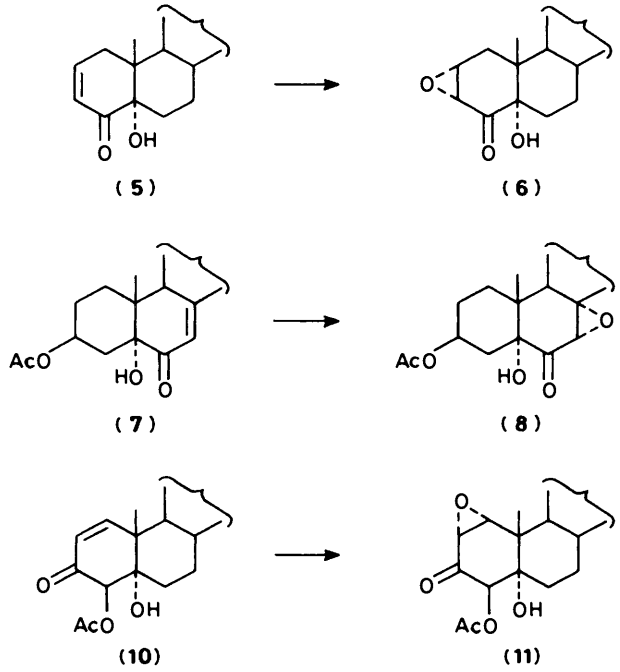
system, the hydroxy group should be suitably oriented in order to allow the juxtaposition between the peroxy group and the double bond to be epoxidized.

The stereoisomeric 5-hydroxycholest-2-en-1-ones (**1**) and (**2**)[5] were converted into 5α-hydroxy-2α,3α-epoxycholestan-1-one (**3**) and 5β-hydroxy-2β,3β-epoxycholestan-1-one (**4**), respectively. In compound (**1**), the 5α-OH is axial and at nearly 90° with respect to the plane of the enone moiety, whereas in compound (**2**), the 5β-OH is quasi-axial to ring A and at *ca.* 120° with respect to the plane of the enone. In the n.m.r. spectrum of



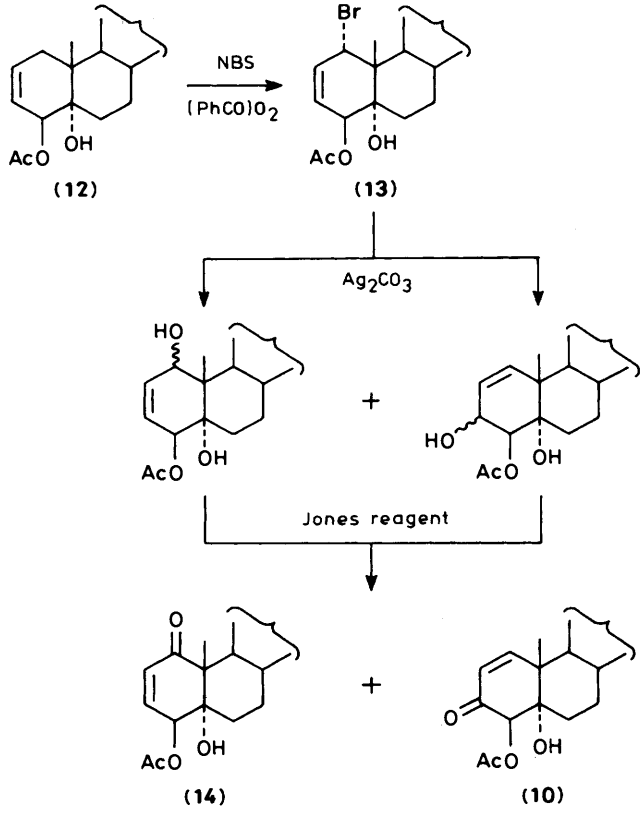
compound (**3**), the epoxidic protons appear at δ 3.32 (d, *J* 3.5 Hz, 2β-H) and 3.59 (m, $w_{\frac{1}{2}}$ 8 Hz, 3β-H), as compared to δ 3.11 (d, *J* 3.5 Hz) and 3.43 (m, $w_{\frac{1}{2}}$ 8 Hz) in 2α,3α-epoxy-5α-cholestan-1-one.[6a] The epoxidic protons of compound (**4**) are at δ 3.29 (d, *J* 3.5 Hz, 2α-H) and 3.65 (m, $w_{\frac{1}{2}}$ 6 Hz, 3α-H), as compared to δ 3.10 (d, *J* 3.5 Hz) and 3.51 (m, $w_{\frac{1}{2}}$ 6 Hz) in 2β,3β-epoxy-5β-cholestan-1-one.[6b]

The α,β-unsaturated ketone (**5**) (5α-hydroxycholest-2-en-4-one)[7] is almost quantitatively transformed into the corresponding 2α,3α-epoxide (**6**), characterized in the n.m.r. spectrum by two epoxidic protons at δ 3.41 (d, *J* 3.7 Hz, 3β-H) and 3.63 (t, *J* 3.7 Hz, 2β-H). This structure was previously assigned[8] to a compound obtained as a by-product (5% yield) in the oxidation of cholesta-2,4-diene with RuO_4. The reported physical constants and n.m.r. data were however different to those of compound (**6**). The structure assigned to the latter was confirmed by its preparation from 5α-hydroxycholest-2-en-4β-yl acetate (**12**) (epoxidation with *m*-chloroperbenzoic acid, followed by hydrolysis of the acetate group and subsequent oxidation with Sarrett reagent).

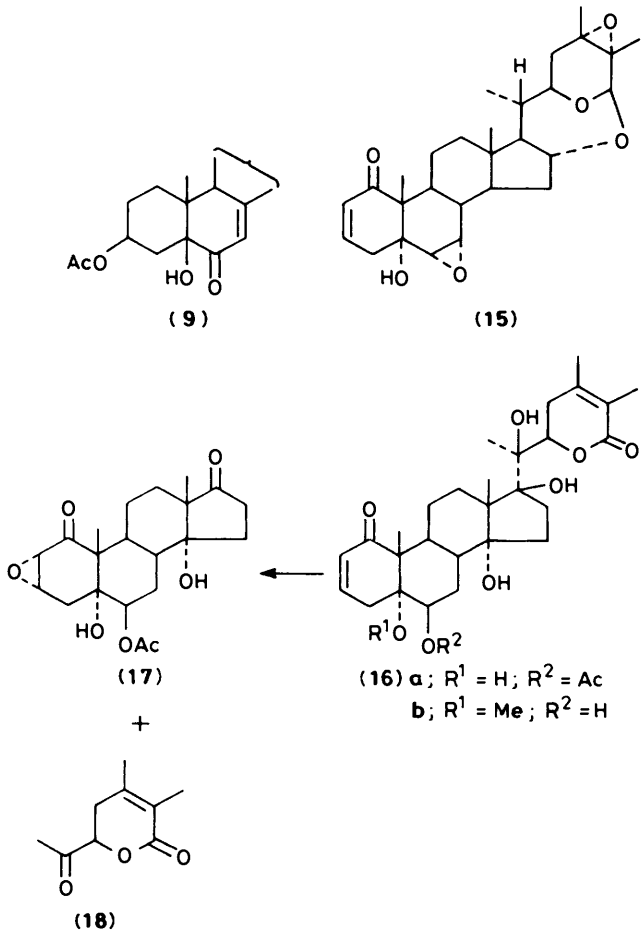


The reaction with t-butyl hydroperoxide in the presence of bisacetylacetonato-oxovanadium also takes place with 5α-hydroxy-6-oxocholest-7-en-3β-yl acetate (**7**), leading in excellent yield to the 7α,8α-epoxy derivative (**8**) which was previously obtained (70% yield) by oxidation of cholesta-5,7-dien-3β-yl acetate with RuO_4.[8] In both compounds (**5**) and (**7**), the 5α-hydroxy group is almost perpendicular to the plane of the double bond and consequently favourably oriented in the intermediate complex for oxygen transfer to the double bond.

As expected, attempted epoxidation of 5β-hydroxy-6-oxocholest-7-en-3β-yl acetate (**9**) with this reagent failed. In our opinion, this is due to the orientation of the 5β-OH with respect to ring B (the angle between this group and the plane of the enone is *ca.* 150°) and to the lack of conformational flexibility of this ring, which precludes oxygen transfer to the double bond.

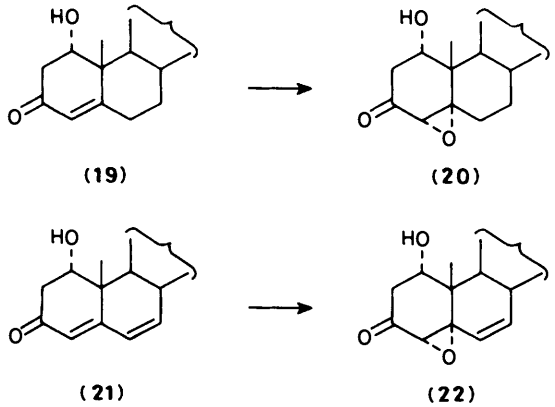


5α-Hydroxy-3-oxocholest-1-en-4β-yl acetate (**10**) was converted in practically quantitative yield into the 1α,2α-epoxide (**11**). Compound (**10**) was prepared in three steps from 5α-hydroxycholest-2-en-4β-yl acetate (**12**)[7] which was obtained by the reduction of the unsaturated ketone (**5**) with $NaBH_4$ and subsequent acetylation. Allylic bromination of compound (**12**) with *N*-bromosuccinimide in CCl_4, in the presence of benzoyl peroxide (an adaptation of the procedure developed for allylic bromination of 5α-cholest-2-en-1-one[9]) afforded 1α-bromo-5α-hydroxycholest-2-en-4β-yl acetate (**13**) as the major component. Displacement of the bromine in (**13**) with freshly prepared silver carbonate, proceeded with allylic rearrangement to give a mixture of allylic alcohols (Δ^1-3-OH and Δ^2-1-OH) which was oxidized with Jones' reagent to a 4:1 mixture of compounds (**10**) and (**14**).[5] The n.m.r. signals of the two vinylic protons in the unsaturated ketone (**10**) (d, *J* 10.5 Hz, at δ 6.05 and 7.15) were replaced in the epoxy ketone (**11**) by two signals at δ 3.62 and 3.76 (d, *J* 3.7 Hz).



In contrast to the facile epoxidation of the double bond in the 5α-hydroxycholest-2-en-1-one (**1**), the reaction failed with compound (**15**) (nicalbin B[10]) in which the tertiary hydroxy group is flanked by a *cis* epoxide; the latter probably hinders the hydroxy group and does not allow its inclusion in the co-ordination sphere of the vanadium complex. Indeed, the reaction easily takes place with compound (**16a**) (withanolide S 6-acetate[11]) in which the 5-OH is flanked by a β-OAc group (*trans*-diaxial relationship) which cannot hinder the binding of the OH group to the vanadium catalyst. Withanolide S, in addition to the ring A enone, possesses a ditertiary 17,20-glycol which is easily cleaved by the catalyst.[12] Treatment of compound (**16a**) with the reagent afforded therefore the epoxyandrostanedione (**17**) and the lactone (**18**).

In the enones presented heretofore, the double bond was



secondary or tertiary, whereas the OH group was always tertiary. The epoxidation proceeds also with enones possessing a secondary OH group, two bonds away from the double bond. Thus, 1α-hydroxycholest-4-en-3-one (**19**), easily obtained from cholest-4-ene-1α,3α-diol[5] by MnO_2 oxidation, afforded in good yield the corresponding 4α,5α-epoxide (**20**). The reaction also proceeded with the corresponding hydroxy dienone (**21**)[13] (obtained by MnO_2 oxidation of cholesta-4,6-diene-1α,3α-diol[14]). The 4α,5α-epoxide (**22**) resulted, however, in lower yield (*ca.* 70%),[15] most probably due to its instability (allylic epoxide).

A more remote hydroxy group is ineffective in triggering the epoxidation of enones. For instance, the only reaction taking place on treatment of withanolide S 5-methyl ether (**16b**) with Bu^tO_2H–vanadium catalyst is cleavage of the 17,20-ditertiary glycol.[12]

The scope and limitations of the vanadium-catalysed t-butyl hydroperoxide epoxidation of enones are being further investigated with appropriate systems.

Experimental

M.p.s were taken with a Fisher-Johns apparatus. Optical rotations were recorded with an automatic Perkin-Elmer 141 polarimeter and refer to solutions in chloroform. ^{1}H N.m.r. spectra were determined at 80 MHz on a Varian FT-80A spectrometer for *ca.* 5% solutions in deuteriochloroform containing Me_4Si. Flash chromatography was performed on silica gel 60, 230—400 mesh (Merck); t.l.c. was carried out on plates of silica gel 60 F_{254} (Merck). Yields are given in mg of isolated product showing one spot on a chromatoplate and no traces of unchanged material or other impurities detectable in the n.m.r. spectrum. Mass spectra (chemical ionization) were taken with a Finnigan 4000 instrument.

Epoxidation of 5α-*Hydroxycholest*-2-*en*-1-*one* (**1**).[5]—The reaction was carried out in a three necked flask, under nitrogen, according to the usual procedure for reactions with t-butyl hydroperoxide in the presence of bis-acetylacetonato-oxovanadium as the catalyst.[4,16] To a solution of (**1**) (21 mg, 0.05 mmol) in dry benzene (10 ml), was added a freshly prepared solution of $[VO(acac)_2]$ (0.06 mg, 2.3×10^{-4} mmol) in dry benzene (0.1 ml), followed by a solution of t-butyl hydroperoxide (3M; 0.02 ml, 0.06 mmol) in the same solvent. After 24 h at 40 °C, the reaction mixture was filtered through a short column of Florisil (100—200 mesh) (2 g) and the product was eluted with dichloromethane–ethyl acetate (7:3). The product (**3**), isolated after evaporation of the solvent, showed one spot on a chromatoplate, and δ 0.65 (s, 18-H_3), 1.14 (s, 19-H_3), 3.32 (d, *J* 3.5 Hz, 2-H), and 3.59 (m, $w_{\frac{1}{2}}$ 6 Hz, 3-H). 5α-Hydroxy-2α,3α-epoxycholestan-1-one (**3**) had m.p. 175—177 °C (from methanol); $[\alpha]_D$ +25° (*c*, 0.05); *m*/*z* 417.4 (MH^+, 12.5%), 399.6 ($MH^+ - H_2O$, 100), and 381.5 ($MH^+ - 2H_2O$, 13) (Found: C, 77.9; H, 10.8. $C_{27}H_{44}O_3$ requires C, 77.8; H, 10.65%).

Epoxidation of 5β-*Hydroxycholest*-2-*en*-1-*one* (**2**).[5]—The reaction was carried out as described above. Compound (**2**) (13 mg) afforded a product (**4**) (11 mg), which showed one spot on a chromatoplate. 5β-Hydroxy-2β,3β-epoxycholestan-1-one (**4**) had m.p. 139—142 °C (from methanol); *m*/*z* 417.4 (MH^+, 9.6%), and 399.6 ($MH^+ - H_2O$, 100); δ 0.63 (s, 18-H_3), 1.19 (s, 19-H_3), 3.29 (d, *J* 3.5 Hz, 2-H), and 3.65 (m, $w_{\frac{1}{2}}$ 6 Hz, 3-H).

Epoxidation of 5α-*Hydroxycholest*-2-*en*-4-*one* (**5**).[7]—The reaction was carried out as described for compound (**1**). Compound (**5**) (20 mg) afforded (**6**) (18 mg), which showed one spot on a chromatoplate; δ 0.63 (s, 18-H_3), 0.93 (s, 19-H_3), 3.41 (d, *J* 3.7 Hz, 3-H), and 3.63 (t, *J* 3.7 Hz, 2-H). 5α-Hydroxy-2α,3α-

epoxycholestan-4-one (**6**) had m.p. 112—114 °C (from methanol); $[\alpha]_D$ +54° (*c* 0.5) {lit.,[8] m.p. 156—157 °C; $[\alpha]_D$ +37.5°}; *m/z* 417.4 (MH^+ 5.5%), 399.6 ($MH^+ - H_2O$, 100%), 383.4 ($M^+ - H_2O - 0$, 27.5), and 381.4 ($MH^+ - 2H_2O$, 34.5) (Found: C, 77.7; H, 10.5. $C_{27}H_{44}O_3$ requires C, 77.8; H, 10.65%).

Epoxidation of 3β-*Acetoxy*-5α-*hydroxycholest*-7-*en*-6-*one* (**7**).[17]—The reaction with (**7**) (32 mg) was carried out as described for compound (**1**) and afforded compound (**8**) (30 mg). The physical constants and n.m.r. data were as reported.[8]

Preparation of 4β-*Acetoxy*-5α-*hydroxycholest*-1-*en*-3-*one* (**10**).—(*a*) *Allylic bromination of* 5α-*hydroxycholest*-2-*en*-4β-*yl acetate* (**12**).[7] The reaction was carried out essentially as described for the allylic bromination of 5α-cholest-2-en-1-one.[9] Commercial benzoyl peroxide (250 mg) was dissolved in carbon tetrachloride (25 ml). The turbid solution was dried (Na_2SO_4), filtered, and washed on the filter with an additional portion of CCl_4 (5 ml). To the clear solution obtained, was added compound (**12**) (200 mg) and *N*-bromosuccinimide (400 mg), and the mixture was heated to reflux, with stirring, for 1 h. The crude mixture was loaded onto a dry column of silica gel 60 (25 g) and the product was eluted with light petroleum (b.p. 60—80 °C)–ether (95:5) and the fractions containing the bromo derivative were combined according to their t.l.c. pattern (160 mg). 1α-Bromo-5α-hydroxycholest-2-en-4β-yl acetate (**13**), one spot on a chromatoplate, was used as such in the next step. δ 0.70 (s, 18-H_3), 1.17 (s, 19-H_3), 2.05 (s, OCOMe), 4.58 (d, *J* 5.5 Hz, 1-H), 5.13 (d, *J* 4.5 Hz, 4-H), 5.85 (dd, *J* 10, 4.5 Hz, 3-H), and 6.27 (dd, *J* 10, 5.5 Hz, 2-H).

(*b*) *Hydrolysis of the bromo derivative* (**13**) *and oxidation of the crude product.* Freshly prepared silver carbonate (240 mg) (*cf. Org. Synth.*, vol. III, p. 435) was added to a cold solution of compound (**13**) (420 mg) in pure acetone (15 ml) containing 10 drops of water. The suspension was stirred for 75 min at 0 °C and the temperature was then allowed to rise gradually to 15 °C. The mixture was filtered and the precipitate washed with acetone. The combined filtrates were concentrated to a final volume of *ca.* 3 ml and then diluted with water. The residue was then extracted with chloroform and the extract dried (Na_2SO_4) and evaporated. The crude product (350 mg) so obtained was dissolved in pyridine (4 ml) at 0 °C and added to a suspension of Sarrett reagent [prepared from CrO_3 (250 mg) and pyridine (5 ml)] kept at the same temperature. The mixture was kept overnight at room temperature after which the product was extracted with ether and the extract washed with dilute HCl solution and with brine. The crude product (270 mg) was chromatographed over silica gel 60 (70—230 mesh) (25 g). The fractions obtained by elution with hexane–ether (3:2) were combined according to t.l.c. 4β-Acetoxy-5α-hydroxycholest-1-en-3-one (**10**) (150 mg) had m.p. 176—178 °C (from methanol); $[\alpha]_D$ +98° (*c* 0.05); δ 0.69 (s, 18-H_3), 1.25 (s, 19-H_3), 2.13 (s, OCOMe), 5.17 (s, 4-H), 6.05 (d, *J* 10.5 Hz, 2-H), and 7.15 (d, *J* 10.5 Hz, 1-H) (Found: C, 75.9; H, 10.2. $C_{29}H_{46}O_4$ requires C, 75.9; H, 10.1%). Subsequent fractions contained 4β-acetoxy-5α-hydroxycholest-2-en-1-one (**14**) (30 mg). The compound was identified by comparison with an authentic sample.[5]

Epoxidation of 4β-*Acetoxy*-5α-*cholest*-1-*en*-3-*one* (**10**).—The reaction was performed with compound (**10**) (30 mg) as described for compound (**1**), to give a product (28 mg) which showed one spot on a chromatoplate; δ 0.65 (s, 18-H_3), 1.11 (s, 19-H_3), 2.10 (s, OCOMe), 3.62 (d, *J* 3.7 Hz, 1-H), 3.76 (d, *J* 3.7 Hz, 2-H), and 5.39 (s, 4-H). 3β-Acetoxy-5α-hydroxy-1α,2α-epoxycholestan-3-one (**11**) had m.p. 136—138 °C (from methanol) $[\alpha]_D$ +79° (*c* 0.1); *m/z*, 475.5 MH^+, 19%), 457.6 $MH^+ - H_2O$, 95), 415.5 (MH^+ – AcOH, 100), and 397.5 ($MH^+ - H_2O$ – AcOH, 59) (Found: C, 73.5; H, 10.0. $C_{29}H_{46}O_5$ requires C, 73.4; H, 9.8%).

Oxidation of Withanolide S 6-*Acetate* (**16a**).[11]—The reaction was carried out with compound (**16a**) (50 mg), as described for compound (**1**), but with twice the molar amounts of t-butyl hydroperoxide and catalyst. After filtration through Florisil, the crude product (two spots on a chromatoplate) was separated by flash chromatography, with dichloromethane–ethyl acetate (1:2) as eluant. Fractions were combined according to t.l.c.; the first fractions contained the lactone (**18**)[12] (11 mg); subsequent fractions contained 6β-acetoxy-5α,14α-dihydroxy-2α,3α-epoxyandrostane-1,17-dione (**17**) (28 mg); δ 1.01 (s, 18-H_3), 1.28 (s, 19-H_3), 2.13 (s, OCOMe), 3.36 (d, *J* 3.3 Hz, 2-H), 3.69 (dt, *J* 3.3 and 1.4 Hz, 3-H), and 4.86 (t, *J* 2.4 Hz, 6-H). The compound could not be crystallized: *m/z* 393.2 (MH^+, 2.8%), 375.3 ($MH^+ - H_2O$, 100), 357.3 ($MH^+ - 2H_2O$, 18.3), and 297.1 ($MH^+ - 2H_2O$ – AcOH, 96.5%).

Attempted Epoxidation of 5β-*Hydroxy*-6-*oxocholest*-7-*en*-3β-*yl Acetate* (**9**),[18] *Nicalbin B* (**15**)[10] *and Withanolide S* 5-*Methyl Ether* (**16b**).[12]—Compounds (**9**) and (**15**) remained unchanged under similar conditions as those used for the epoxidation of compound (**1**). The only reaction which took place with compound (**16b**) was cleavage of the 17—20 bond.[12]

Preparation of 1α-*Hydroxycholest*-4-*en*-3-*one* (**19**).—To a solution of cholest-4-ene-1α,3α-diol[5] (150 mg) in chloroform–ethyl acetate [(3:5); 25 ml], was added freshly prepared MnO_2 (700 mg) and the mixture was stirred overnight at room temperature. After filtration and evaporation of the solvent, almost pure 1α-hydroxycholest-4-en-3-one (**19**) (125 mg) was obtained; δ 0.68 (s, 18-H_3), 1.15 (s, 19-H_3), 4.06 (m, $w_{\frac{1}{2}}$ 9 Hz, 1-H), and 5.75 (narrow m, $w_{\frac{1}{2}}$ 3 Hz, 4-H). The product was used as such in the following step.

Epoxidation of 1α-*Hydroxycholest*-4-*en*-3-*one* (**19**).—Epoxidation of compound (**19**) (90 mg) was performed as described for compound (**1**). 1α-Hydroxy-4α,5α-epoxycholestan-3-one (**20**) (86 mg) had m.p. 126—127 °C (from methanol); $[\alpha]_D$ −32° (*c* 0.1); δ 0.73 (s, 18-H_3), 1.08 (s, 19-H_3), 3.13 (s, 4-H), and 3.67 (t *J* 3.6 Hz, 1-H); *m/z* 417.5 (MH^+, 27.3%), 399.6 ($MH^+ - H_2O$, 100); 381.6 ($MH^+ - 2H_2O$, 17.6) (Found: C, 77.6; H, 10.7. $C_{27}H_{44}O_3$ requires C, 77.8; H, 10.65%).

Acknowledgements

This work was supported in part by a grant from the US–Israel Binational Agricultural Research and Development Fund (BARD). We are grateful to Dr. M. Weissenberg (ARO, Volcani Center) for a sample of compound (**2**) and to Dr. M. Cojocaru (Bar Ilan University) for the mass spectra.

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Received 4th July 1985; *Paper* 5/1128