# Studies on the 5β,6β-Epoxide Opening in Withanolides

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The opening of the steroidal 5β,6β-epoxide group, with or without an adjacent 4β-hydroxy-group, was investigated under thermal conditions on a solid support, and in the presence of sodium chloride for several withanolides. The study was expanded with the compounds being treated with sulphuric acid in acetone at various concentrations and temperatures. Different reaction products (diaxial, diequatorial, or rearranged) were obtained depending on the conditions and the presence or absence of a 2,3-double bond in ring A of these 1-keto-steroids.

We recently reported the isolation of some chlorinated withanolides from *Withania* and *Acnistus* species, and we suggested that the chlorine atom in these molecules is derived from sodium chloride present in the plants.[1] A model reaction was therefore performed on withanolide D (1a),[2,3] using sodium chloride adsorbed on an active support (silica gel) and the chlorohydrin (5) was indeed formed in *ca.* 10% yield. The major product of this reaction was, however, the quinone (6) produced, in 60% yield, through an internal rearrangement shown in Scheme 3 (see below).

The structure of compound (6) was established by comparing its u.v. and $^1$H n.m.r. spectra with those of 4-deoxy-4-oxowithanolide U;[1] both compounds were shown to have an indentical A/B ring system. 4-Deoxy-4-oxowithanolide had previously been prepared by manganese dioxide oxidation of the double allylic 4β-hydroxy-group present in withanolide U. The difference between the two compounds is the absence of a 14α-hydroxy-group in structure (6). The structure of the chlorohydrin (5) was confirmed by comparison with an authentic sample from our previous work,[1] and through its oxidation product (7) (Scheme 1).

Jaborosalactone C and E are isomeric chlorinated withanolides which have been described earlier.[4] The former is a 5β-hydroxy-6α-chloro-derivative, and the latter a 5α-chloro-6β-hydroxy-compound. They probably originate from a parent 5β,6β-epoxide in which the absence of any directing influence from a 4β-hydroxy-group could be responsible for their simultaneous formation. To corroborate this assumption, withanolide E (13)[5,6] (no 4-hydroxy-group) was treated with sodium chloride–silica gel as described above. However, in this case chlorination did not occur, presumably due to the ease of $\Delta^4$ formation, and instead the three closely related compounds (14)—(16) were isolated. In compound (14), elimination of the 6-hydroxy-group takes places easily to form the highly conjugated system present in compound (15) which can isomerise at C(8) to form the 8α-H isomer (16) which is the major product in the mixture. It should be noted that the 14α-hydroxy-group, which has been reported to be fairly unstable,[6] does not eliminate under these reaction conditions.

The structures assigned to the above three products are based on u.v., $^1$H n.m.r., and mass spectral measurements. A naturally occurring (8β-H)-2,4,6-trienone has recently been reported[7] from a hybrid of *Withania somnifera*. A comparison of the $^1$H n.m.r. coupling constants of the 8-H in compounds (15) and (16) (Table) shows that the *J* values are 11.4 and 16.2 Hz, respectively, the former being identical with that of the natural trienone.[7] The two compounds have u.v. values which are compatible with their assigned structures, $\lambda_{max.}$ 352 nm (ε 2 100) for (15) and 340 nm (ε 1 300) for (16). An easy isomerisation of the 8β-H- to the 8α-H-isomer in a similar trienone system has been reported in physalins.[8]

Since sodium chloride did not apparently take part in the aforementioned reaction with withanolide E (13), the reaction was repeated without salt and the same products (14)—(16) were again obtained.

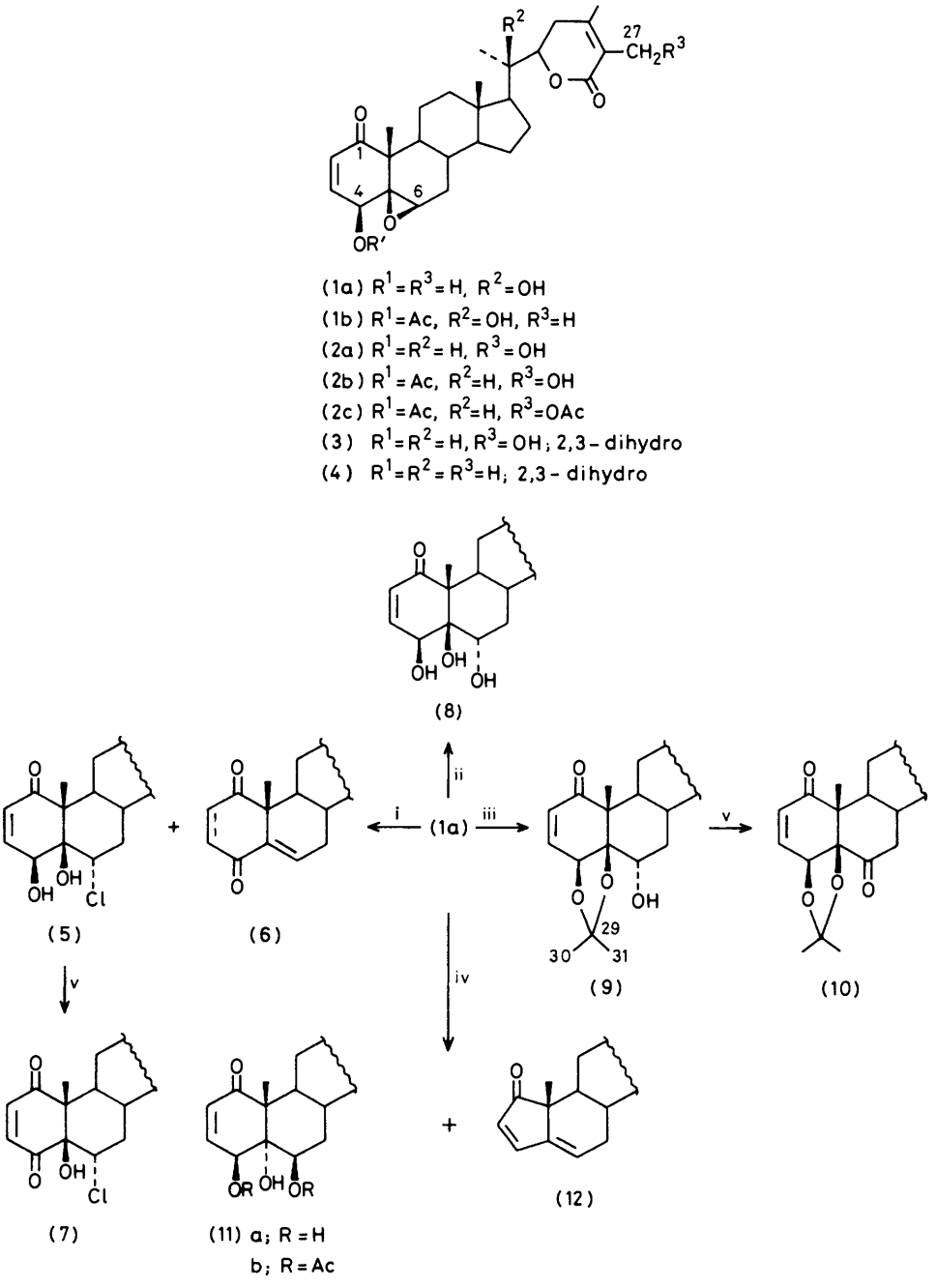
It has been reported that a 4β-hydroxy-5β,6β-epoxycholesterol gave a 5-en-4-one system on treatment with either toluene-*p*-sulphonic acid or alumina, whereas its 1-oxo-analogue produced an aldehyde resulting from a rearrangement in ring A. Thus, it was suggested that, in the latter case, an sp$^2$-hybridised C(1) favours ring contraction.[9] Since, in the preceding reaction with withanolide D (1a) on silica gel under thermal conditions the 2,5-diene-1,4-dione (6) was obtained in spite of the presence of a 1-oxo-function, additional reactions of the 5,6-epoxy-group were investigated.

When compound (1a) was treated with 3% sulphuric acid in acetone for 6 h, the 4β,5β,6α-trihydroxy-compound (8) was produced quantitatively. The reaction with 1% sulphuric acid afforded the corresponding acetonide (9). The structures of compounds (8) and (9) were based on their $^1$H and $^{13}$C n.m.r. data, as well as on those of the oxidation product (10), smoothly obtained from compound (9). It was found that in compound (9) the 6α-hydroxy-group is sterically hindered and thus it was not acetylated with pyridine–acetic anhydride during 48 h. It is worthwhile noting that when the aforementioned acetone–sulphuric acid treatment was repeated with the acetates of withanolide D, (1b),[3] and withaferin A, (2c),[10] the epoxide group remained intact; however, the latter compound gave the 4β-monoacetate (2b).

The formation of compounds (8) and (9) under the aforementioned conditions, in the presence of an sp$^2$-hybridised C(1), is a different case from that producing the rearrangement in ring A.[11] Such a rearrangement did, however, take place, under the same conditions, with 2,3-dihydrowithaferin A (3) and its 27-deoxy-analogue (4) to give compounds (17) and (18), respectively (Scheme 2).[9,11]

When compound (1a) was heated under reflux in 0.3% sulphuric acid–acetone during 6 h, two main products, (11a) and (12), were identified. Whereas compound (11a), with a 4β,5α,6β-trihydroxy-system, is the product of a regular epoxide opening [compare compound (8)], compound (12) is the results from a pinacol-type rearrangement.

The conditions leading to the rearrangement producing ring-A contraction and the formation of an aldehyde centre at C(4) have been analysed earlier.[9,11,12] In the present case it was found that whereas treatment with sulphuric acid in acetone at room temperature induced an epoxide opening through a C(6)–O cleavage leading to *trans*-diequatorial products as shown in structures (8) and (9), the application of heat gives diaxial products through C(5)–O cleavage, producing both the alcohol (11a) and the ring A-rearranged compound (12) which is formed through a sequence, depicted in Scheme 3, involving the initial formation of an unsaturated keto-aldehyde (A) which is a vinologue of an α-keto aldehyde in




**Scheme 1.** *Reagents and conditions:* i, $SiO_2$–NaCl, 100 °C; ii, 3% $H_2SO_4$–acetone, room temperature, 6 h; iii, 1% $H_2SO_4$–acetone, room temperature, 6 h; iv, 0.3% $H_2SO_4$–acetone, reflux, 6 h; v, $CrO_3$

which the aldehyde, attached to a quaternary carbon atom can easily undergo deformylation followed by elimination of the 6-hydroxy-group from the intermediate (B) leading to compound (12).[11] Both compounds (11a) and (12) are therefore formed from the same C(5) carbocation (C). For the case when ring A is saturated, as in the 2,3-dihydro-derivatives (3) and (4), the rearrangement leading to ring-A contraction takes place at room temperature to produce the C(4) aldehydes [5-formyl compounds] (17) and (18), no driving force for elimination of the aldehyde function existing in this case.

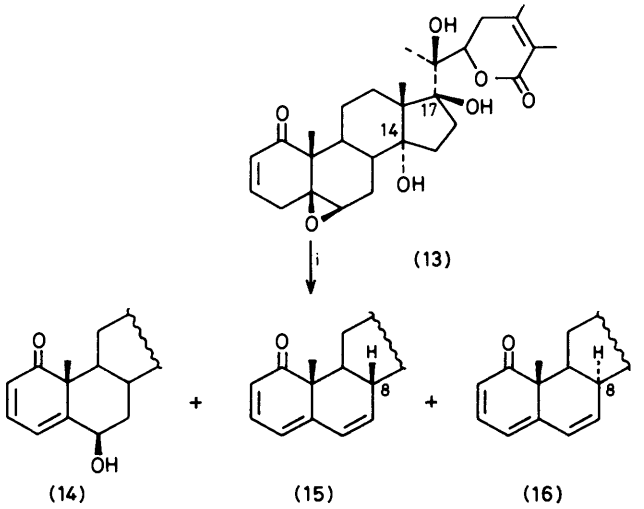
## Experimental

M.p.s were taken on a Fischer–Johns apparatus. Optical rotations were recorded with an automatic Perkin-Elmer 141 polarimeter and refer to solutions in chloroform. I.r. spectra were recorded on a Perkin-Elmer 467 grating spectrophotometer and refer to KBr pellets; u.v. spectra were recorded on a Cary 118 instrument for solutions in ethanol; $^1H$ and $^{13}C$ n.m.r. spectra were determined on Bruker WH-270 and WH-90 (at 22.63 MHz) instruments, respectively, for chloroform

**Table.** $^1$H n.m.r. data (δ) of relevant protons in withanolides [a]

| | 2-H | 3-H | 4-H | 6-H | 22-H | Methyl groups C(18) | C(19) | C(21) | C(27) | C(28) | Other groups |
|---|---|---|---|---|---|---|---|---|---|---|---|
| (6) | 6.69 (d, 5.8) | | | 6.84 (dd, 5.8 and 2.4) | 4.22 (dd, 13.4 and 4.4) | 0.92 | 1.39 | 1.31 | 1.90 | 1.96 | |
| (7) | 6.47 (d, 10.6) | 6.58 (d, 5.2) | | 4.27 (dd, 12.9 and 5) | 4.13 (dd, 13.2 and 3.5) | 0.84 | 1.32 | 1.25 | 1.88 | 1.94 | |
| (14) | 6.01 (d, 9.6) | 6.91 (dd, 9.9 and 6) | 6.13 (d, 5.7) | 4.64br (s) | 4.86 (dd, 11.2 and 6.6) | 1.19 | 1.40 | 1.49 | 1.87 | 1.94 | |
| (15) | 5.72 (d, 9.6) | 6.84 (dd, 9.6 and 6) | 5.88 (d, 5.4) | 6.21 (dd, 9.6 and 2.1) | 4.94 (dd, 10.8 and 5.7) | 1.16 | 1.26 | 1.57 | 1.89 | 1.95 | 6.41 (dd, 9.3 and 1.9, 7-H), 2.26 (ddd, 11.4, 3, and 2, 8-H) |
| (16) | 5.93 (d, 10) | 6.97 (dd, 9.6 and 6.3) | 5.94 (d, 6) | 5.99 (dd, 10 and 1.9) | 4.89 (m) | 1.19 | 1.40 | 1.49 | 1.88 | 1.95 | 6.23 (dd, 10 and 3, 7-H), 2.95br (d, 16.2, 8-H) |
| (8) | 5.98 (dd, 10.4 and 2.3) | 6.51 (dd, 10.4 and 2) | 5.21 (m) | 4.11 (m) | 4.21 (dd, 13.4 and 3.4) | 0.82 | 1.21 | 1.23 | 1.88 | 1.94 | |
| (9) | 5.99 (dd, 10.4 and 2.3) | 6.51 (dd, 10.4 and 2.3) | 5.12 (m) | 4.10 (m) | 4.21 (dd, 12.8 and 3) | 0.84 | 1.21 | 1.24 | 1.88 | 1.95 | 1.57 (30- and 31-$H_3$) |
| (10) | 6.01 (dd, 10.4 and 1.4) | 6.67 (dd, 10.4 and 3.4) | 4.97 (dd, 3 and 1.4) | | 4.20 (dd, 13.1 and 3.7) | 0.82 | 1.31 | 1.23 | 1.88 | 1.94 | 1.53 (30-$H_3$), 1.09 (31-$H_3$) |
| (2b) | 6.25 (d, 9.9) | 7.04 (dd, 9.9 and 6.3) | 4.65 (d, 6) | 3.22br (s) | 4.42 (dt, 12.9 and 3) | 0.70 | 1.40 | 0.99 (d, 6.6) | | 2.04 | 2.06 (4-AcO), 4.37 (d, 4.8, $CH_2$OH) |
| (17) | | | | 4.30 (m) | 4.42 (dt, 12.9 and 3) | 0.75 | 1.16 | 1.02 (d, 6.3) | | 2.05 | 9.60 (5-CHO), 4.37 (d, 4.4, $CH_2$OH) |
| (18) | | | | 4.29 (m) [4.52] | 4.36 (dt, 12.9 and 3) [4.37] | 0.74 [0.60] | 1.17 [1.65] | 1.00 (d, 6.6) [0.99] | 1.88 [1.79] | 1.94 [1.95] | 9.60 (5-CHO) [10.07 (5-CHO)] |
| (11a) | 6.06 (d, 10.1) [6.24] | 6.68 (dd, 10.4 and 3.6) [6.92] | 4.84 (d, 3.4) [5.33] | 3.94 (dd,) 11.9 and 5.2) [4.29] | 4.19 (dd, 13.1 and 3.4) [4.40] | 0.82 [1.0] | 1.52 [1.88] | 1.27 [1.39] | 1.88 [1.81] | 1.94 [1.94] | |
| (11b) | 6.08 (dd, 10.5 and 0.3) | 6.68 (dd, 10.5 and 3.9) | 4.90 (dd, 3.6 and 0.3) | 5.07 (dd, 13 and 5) | 4.19 (dd, 13.2 and 3.6) | 0.81 | 1.28 | 1.34 | 1.88 | 1.94 | |
| (12) | 5.96 (d, 5.7) | 7.60 (d, 5.7) | | 5.80 (m) | 4.22 (dd, 13.3 and 3.6) | 0.94 | 1.18 | 1.29 | 1.89 | 1.96 | |

[a] $CDCl_3$ as solvent except for data in square brackets (solvent [$^2H_5$]pyridine). Tetramethylsilane as internal standard. Data in parentheses are: multiplicity, coupling constant/Hz, assignment (where applicable).

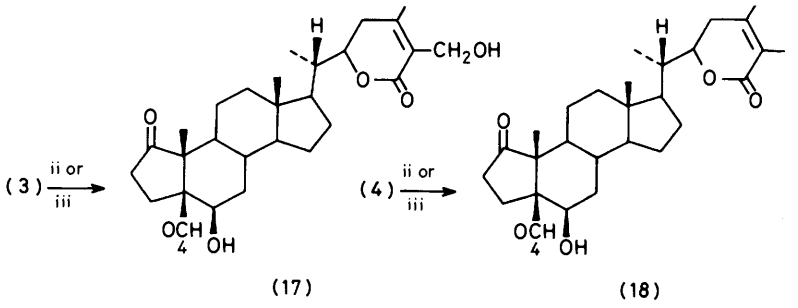



solutions with tetramethylsilane as internal standard. Thin-layer chromatography (t.l.c.) was carried out on chromatoplates (50 × 78 mm) of E. Merck silica gel $R_{254}$. Preparative chromatoplates (150 × 150 mm; silica gel $F_{254}$) (2 mm absorbent thickness) were used for mixture separations. Mass spectra were taken with a Varian MAT 731 HR instrument and an improved Atlas CH4 instrument.

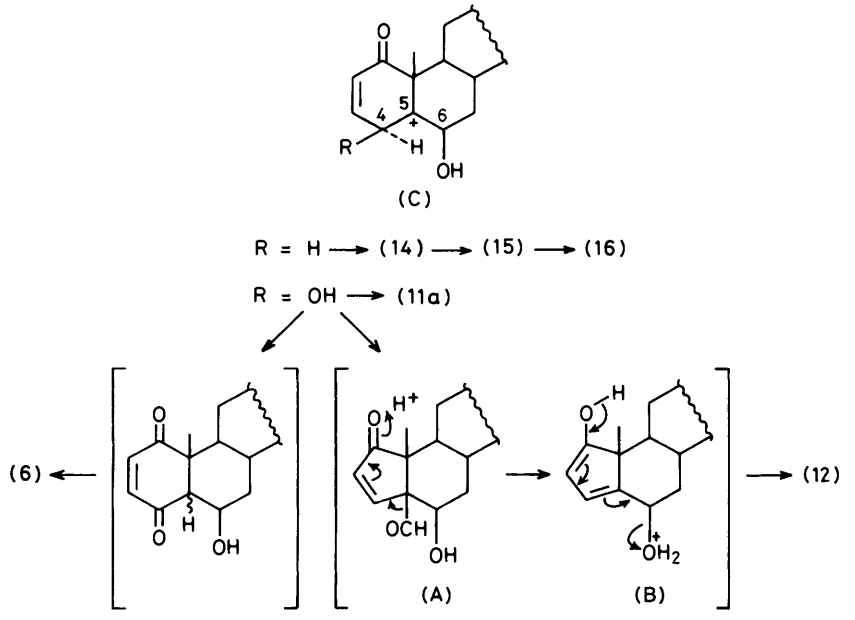
*Starting Compounds.*—Withanolide D (1a) was isolated from *Withania somnifera*[7] while withaferin A (2a), 2,3-dihydrowithaferin A (3), and 2,3-dihydro-27-deoxywithaferin A (4) were isolated from *Acnistus breviflorus*.[13] Withanolide E (13) was available from previous preparations.[5,6]

*Reaction of Withanolide D* (1a) *with Sodium Chloride–Silica Gel.*—Compound (1a) (100 mg) in absolute ethanol (50 ml) was adsorbed over a powdered mixture of silica gel H (E. Merck) and sodium chloride (mixture 25 g, 2 : 1). The solvent was removed under reduced pressure and the dry residue was heated at 100 °C for 24 h. The products were desorbed (ethyl acetate), and the residue was separated by preparative layer chromatography (p.l.c.) using hexane–ethyl acetate (1 : 1) as developer into three compounds: unchanged (1a) (45 mg recovery), the chlorohydrin (5) (5 mg, 5%), and the dienedione (6) (30 mg, 30%). (22R)-20$\alpha_F$-*Hydroxy*-1,4-*dioxowitha*-2,5,24-*trienolide* (6),* m.p. 268—270 °C (from ethyl acetate); $[\alpha]_D$ −7.0° (*c*, 0.1); $\lambda_{max.}$ 225 and 280 nm (ε 20 800 and 2 300); *m/z* (%) 452 ($M^+$) (2), 328 (6), 256 (8), 167 (10), 153 (13), and 125 (100) (Found: C, 74.2; H, 8.2. $C_{28}H_{36}O_5$ requires C, 74.30; H, 8.01%).

* Semi-systematic nomenclature used in the Experimental section: ' withanolide ' refers to 22-hydroxyergostan-26-oic and δ-lactone.




**Scheme 2.** *Reagents and conditions:* as for Scheme 1




**Scheme 3**

(22R)-6α-*Chloro*-5β,20α$_F$-*dihydroxy*-1,4-*dioxowitha*-2,24-*dienolide* (7).—A solution of compound (2) (15 mg) in acetone (15 ml) was treated for 5 min with Jones' reagent (4 drops); the excess of reagent was destroyed with methanol and after the usual work-up the mixture gave the *chlorohydrin* (7) (12 mg, 80%); m.p. 238—240 °C (from ethyl acetate); $[\alpha]_D$ +32.5° (*c*, 0.25); $\lambda_{max.}$ 222 nm (ε 16 000); $\delta_C$ 198.9 [C(1)], 137 and 138.3 [C-(2) and -(3)] 195.5 [C(4)], 77.2 [C(5)], 61.2 [C(6)], 13.6 [C(18), 9.5 [C(19)], 20.7 [C(21)], 80.8 [C(22)], 149 [C(24)], 122 [C(25), 166.1 [C(26)], 12.5 [C(27)], and 20.6 p.p.m. [C(28)]; *m/z* (%) ($M^+$) 504.2196 (3) and 506.2228 (2) (Found: C, 66.4; H, 7.7. $C_{28}H_{37}ClO_6$ requires C, 66.59; H, 7.38%).

*Reaction of Withanolide E* (13) *with Sodium Chloride–Silica Gel.*—Compound (13) (100 mg) was heated, as described above, on silica gel at 100 °C for 24 h both with and without sodium chloride. In both cases identical mixtures of products were obtained: (14) (16 mg, 16%), (15) (35 mg, 35%), and (16) (45 mg, 45%). The components were separated by p.l.c. (hexane–ethyl acetate, 3 : 2 as developer) to give (i) (22R)-6β,14α,17β,20α$_F$-*tetrahydroxy*-1-*oxowitha*-2,4,24-*trienolide* (14), m.p. 285—287 °C; $[\alpha]_D$ −39° (*c*, 0.1); $\lambda_{max.}$ 310, 237, and 225 nm (4 700, 9 000, and 12 000sh); *m/z* (%) 486 ($M^+$) (0.3), 468 ($M - H_2O$) (3), 450 ($M - 2H_2O$) (15), 325 (11), 238 (46), 169 (51), and 125 (100) (Found: C, 68.85; H, 8.0. $C_{28}H_{38}O_7$ requires C, 69.11; H, 7.87%); (ii) (22R)-14α,17β,20α$_F$-*trihydroxy*-1-*oxo-witha*-2,4,6,24-*tetraenolide* (15), m.p. 242—244 °C; $[\alpha]_D$ − 14.6° (*c*, 0.1); $\lambda_{max.}$ 352 and 223 nm (ε 2 100 and 9 800); *m/z* (%) 468 ($M^+$) (8), 450 ($M - H_2O$) (37), 414 ($M - 3H_2O$) 70), 307 (38), 225 (81), and 169 (100) (Found: C, 71.65; H, 7.9. $C_{28}H_{36}O_6$ requires C, 71.77; H, 7.74%); and (iii) (22R)-(8α*H*)-14α,17β,20α$_F$-*trihydroxy*-1-*oxowitha*-2,4,6,24-*tetraenolide* (16), m.p. 244—246 °C, $[\alpha]_D$ −3.4° (*c*, 0.12); $\lambda_{max.}$ 340 and 224 nm (ε 1 300 and 8 400); *m/z* (%) 468.2431 ($M^+$) (6.4), 450.2400 ($M - H_2O$) (10), 343.1908 ($M - C_7H_9O_2$) (11), 238.1346 ($M - C_{11}H_{18}O_5$) (32), and 152.0806 ($C_9H_{12}O_2$) (47) (Found: C, 71.5; H, 7.95. $C_{28}H_{36}O_6$ requires C, 71.77; H, 7.74%).

(22R)-4β,5β,6α,20α$_F$-*Tetrahydroxy*-1-*oxowitha*-2,24-*dienolide* (8).—A solution of compound (1a) (100 mg) in acetone (50 ml) was treated for 6 h at room temperature with concentrated sulphuric acid (1.5 ml). The mixture was poured into water and the product was extracted with chloroform to give the *tetraol* (8) (92 mg, 92%) as crystals from ethyl acetate, m.p. 255—257 °C; $[\alpha]_D$ +37.8° (*c*, 0.11); $\lambda_{max.}$ 228 nm (ε 16 000) (Found: C, 68.25; H, 8.4. $C_{28}H_{40}O_7$ requires C, 68.82; H, 8.25%).

*The* 4,5-*Acetonide* (9) *of* (22R)-4β,5β,6α,20α$_F$-*Tetrahydroxy*-1-*oxowitha*-2,24-*dienolide*.—A solution of compound (1a)

(100 mg) in acetone (50 ml) was treated with concentrated sulphuric acid (0.5 ml) for 6 h and the mixture was worked up as before to give the *cyclic acetal* (9) (95 mg, 95%) as crystals from ethyl acetate, m.p. 263—265 °C; $[\alpha]_D$ +47.9° (*c*, 0.1); $\lambda_{max.}$ 224 nm (ε 15 200); $\delta_C$ 202.3 [C(1)], 129.2 [C(2)], 142.5 [C(3)], 66.7 [C(4)], 72.2 [C(5)], 70.7 [C(6)], 13.6 [C(18)], 10.8 [C(19), 21.9 [C(21)], 80.8 [C(22)], 12.5 [C(27)], 20.6 [C(28)], 110.1 [C(29)], and 22.6 p.p.m. [C-(30) and -(31)]; $\lambda_{max.}$ 224 nm (ε 15 200); *m/z* (%) 528 ($M^+$) (1), 496 (8), 470 (17), 387 (47), 152 (61), 126 (100), and 125 (66) (Found: C, 70.1; H, 8.2. $C_{31}H_{44}O_7$ requires C, 70.42; H, 8.39%).

*The* 4,5-*Acetonide* (10) *of* (22R)-4β,5β,20$\alpha_F$-*Trihydroxy*-1,6-*dioxowitha*-2,24-*dienolide*.—In a similar manner to the preparation of the chlorohydrin (7), compound (9) was oxidised with Jones' reagent and, after work-up, the product (10) crystallised from ethyl acetate, m.p. 261—262 °C; $[\alpha]_D$ +16.6° (*c*, 0.11); *m/z* (%) 526 ($M^+$) (1), 401 ($M$ − 125) (36), 344 (10), 343 (45), 169 (16), and 126 (100) (Found: C, 70.5; H, 8.0. $C_{31}H_{42}O_7$ requires C, 70.69; H, 8.03%).

*Acid Treatment of Withanolide D* (1a) *under Reflux*.—A solution of compound (1a) (100 mg) in acetone (100 ml) was heated under reflux for 6 h with concentrated sulphuric acid (0.5 ml) until the starting material had been completely consumed (t.l.c.). The product was worked up in the usual manner and was purified by p.l.c. (hexane–ethyl acetate, 3 : 2 as developer); bands corresponding to the two major products (11a) and (12) were worked up to afford (22R)-4β,5α,6β, 20$\alpha_F$-*tetrahydroxy*-1-*oxowitha*-2,24-*dienolide* (11a), m.p. 285—287 °C (from ethyl acetate) (Found: C, 68.4; H, 8.4. $C_{28}H_{40}O_7$ requires C, 68.82; H, 8.25%). The *diacetate* (11b) was obtained by treatment with pyridine–acetic anhydride and had m.p. 272—273 °C; $[\alpha]_D$ +45.8° (*c*, 0.1); $\lambda_{max.}$ 224 nm (ε 17 800); *m/z* 572 ($M^+$) (1), 387 (21), 327 (81), 169 (55), and 126 (100) (Found: C, 66.8; H, 7.95. $C_{32}H_{44}O_9$ requires C, 67.11; H, 7.74%. Also obtained was (22R)-20$\alpha_F$-*hydroxy*-1-*oxo*-4-*norwitha*-2,5,24-*trienolide* (12) as crystals from ethyl acetate, m.p. 208—210 °C; $[\alpha]_D$ +25.8° (*c*, 0.1); $\lambda_{max.}$ 288 and 223 nm (ε 880 and 6 500); *m/z* (%) 424 ($M^+$) (2), 416 (14), 339 (7), 299 (100), 263 (40), 126 (95), and 125 (83) (Found: C, 76.25; H, 8.75. $C_{27}H_{36}O_4$ requires, C, 76.37; H, 8.54%).

(22R)-4β-*Acetoxy*-5β,6β-*epoxy*-27-*hydroxy*-1-*oxowitha*-2,24-*dienolide* (2b).—A solution of withaferin A diacetate (2c) (100 mg) in acetone (50 ml) was treated with concentrated sulphuric acid (1.5 ml) for 6 h. The mixture was then worked up and the products were separated and purified [p.l.c. hexane–ethyl acetate, 1 : 1 as developer). Together with unchanged starting material, the *monoacetate* (2b) was obtained, as crystals from ethyl acetate, m.p. 240—241 °C; $[\alpha]_D$ +102.4° (*c*, 0.16); $\lambda_{max.}$ 224 nm (ε 17 200); *m/z* (%) 512 ($M^+$) (3), 452 ($M$ − AcOH) (5), 434 ($M$ − AcOH − $H_2O$) (6), 416 ($M$ − AcOH − $2H_2O$) (6), 347 (55), 197 (27), 141 (71), and 124 (98) (Found: C, 70.15; H, 7.8. $C_{30}H_{40}O_7$ requires C, 70.29; H, 7.86%).

*Ring* A-*Contraction in Compound* (3) *to give Compound* (17).—A solution of compound (3) (100 mg) in acetone (50 ml) was treated with concentrated sulphuric acid (1.5 ml) for 6 h Following work-up the only product which was obtained was (22R)-5β-*formyl*-6β,27-*dihydroxy*-1-*oxo*-4-*norwith*-24-*enolide* (17) (85 mg, 85%) which crystallised from ethyl acetate, m.p. 272—274 °C; $\lambda_{max.}$ 221 nm (ε 6 500); $\nu_{max.}$ 1 700 $cm^{-1}$; $\delta_C$ 216.3 [C(1)], 204.5 [C(4)], 68.1 [C(5)], 60.8 [C(6)], 12.0 [C(18)], 13.2 [C(19)], 13.4 [C(21)], 78.8 [C(22)], 152.7 [C(24)], 126 [C(25)], 167 [C(26)], 57.5 [C(27)], and 20 p.p.m. [C(28)] (Found: C, 70.9; H, 8.75. $C_{28}H_{40}O_6$ requires C, 71.15; H, 8.53%).

*Ring* A-*Contraction in Compound* (4) *to give Compound* (18).—In a similar manner, compound (4) was treated with sulphuric acid. The product was crystallised from ethyl acetate to afford (22R)-5β-*formyl*-6β-*hydroxy*-1-*oxo*-4-*norwith*-24-*enolide* (18), m.p. 235—236 °C; $\lambda_{max.}$ 222 nm (ε 6 800); $\nu_{max.}$ 1 700 $cm^{-1}$; $\delta_C$ 216.7 [C(1)], 204.8 [C(4)], 68.0 [C(5)], 61.0 [C(6)], 12.2 [C(18)], 13.2 [C(19)], 13.7 (C (21)], 78.7 [C(22)], 149.2 [C(24)], 167.2 [C(26)], 12.7 [C(27)], and 20.7 p.p.m. [C(28)]; *m/z* (%) 456 ($M^+$) (33), 410 (47), 409 (64), 331 (42), 181 (100), and 135 (60) (Found: C, 73.6; H, 8.95. $C_{28}H_{40}O_5$ requires C, 73.65; H, 8.83%).

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