Tetracyclic Triterpenes. Part 2.[1] A Synthetic Approach to Cucurbitacins

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Efficient 19(10 → 9β) methyl migration leading to compounds with the cucurbitane skeleton occurs when 3β-acetoxy-9β,11β-epoxylanostan-7-one (1) is treated with boron trifluoride–diethyl ether in acetic anhydride. The major product (2) has the double bond in the 5,6-position which is common for natural cucurbitacins. The factors influencing the direction of the rearrangement are discussed. Several transformations including the removal of the 7-carbonyl group and epimerization of C-10 are described.

In the triterpenoid series, the skeletons of protostane, lanostane, cycloartane, and cucurbitane are biogenetically closely related and can be interconverted by chemically induced skeletal rearrangements. Examples of such interconversions are: lanostane → protostane,[2] protostane → lanostane,[3] cucurbitane → cycloartane → lanostane,[4] curcurbitane → lanostane,[5] and cycloartane → lanostane.[6] The cucurbitacins,[7] a group of triterpenes of plant origin long known to have weak tumour-inhibitory activity, possess the carbon skeleton of cucurbitane [19(10 → 9β) *abeo*-lanostane], and it is possible to envisage their synthesis from lanostane derivatives by a 1,2-shift of the angular 19-methyl group. Rearrangements involving single 1,2 or multiple methyl and/or hydrogen migrations occur fairly commonly in terpenoid and steroid chemistry.[8] Several attempts have been made to bring about migration of the methyl group from position 10β to 9β, and a few examples of such rearrangement are known in the steroid field.[9] In the lanostane series the only successful approach was based on the Westphalen-type reaction of 3β-acetoxy-9α-hydroxylanostan-11-one,[10] but the total yield of $\Delta^{1(10)}$- and $\Delta^{5(10)}$-cucurbitenes was 34%. Other attempts failed.[2a,11]

Since cucurbitacins possess an oxygen function at C-11 the logical route to the cucurbitane skeleton seemed to be the biomimetic migration of the C-19 methyl group induced by 9,11-epoxide cleavage. However, acid-catalysed opening of 9α,11α-epoxylanostane has been reported to give, besides the 11-ketone, a ' backbone rearrangement ' product, protosta-9(11),13(17)-diene [2a] and no sign of 10β → 9β methyl migration. It appeared, therefore, that appropriate modification of the lanostane molecule was desirable to suppress the ' backbone rearrangement ' and to favour the required methyl migration. Introduction of a C-7 carbonyl function was our choice, and we recently presented preliminary accounts of the acid-catalysed rearrangement of 3β-acetoxy-9β,11β-epoxylanostan-7-one (1).[12] This work is now described in full.

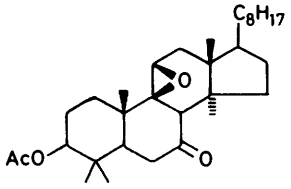
Boron trifluoride-catalysed reaction of the epoxide (1) in acetic anhydride afforded a mixture from which 3β,-11β-diacetoxy-10α-cucurbit-5-en-7-one (2) was isolated as the major product (51—58% yield, depending on conditions). The structure of compound (2) was deduced from its spectral data. Since similar reactions, involving concerted as well as consecutive 1,2-shifts, are believed to proceed in a suprafacial manner, the β-configuration was assigned to C-9. The n.m.r. spectra supported assignment of the 9β- and 10α-configuration. In 3β-acetoxylanostane derivatives of natural configuration, ring A adopts a chair conformation with the 3α-proton having the axial orientation. Consequently, a large coupling is observed between this and the 2β-proton in the n.m.r. spectrum (usually a multiplet with $W_{1/2}$ *ca.* 15 Hz is observed). In compound (2) the 3α-proton is only slightly coupled with the 2α- and 2β-protons and a broadened singlet with $W_{1/2}$ 6 Hz is observed. This clearly results from inversion of the configuration at the ring junction atoms C-9 and C-10, while the 3α-proton adopts an equatorial orientation.

The second most abundant product was 3β-acetoxylanostan-7,11-dione (32% yield). When the rearrangement was carried out on a 1.5-g scale, besides 3β-acetoxylanostane-7,11-dione (31%) and compound (2) (51%), a third product (13%) was isolated. Spectral data suggested structure (6) for this compound, and this assignment was confirmed by oxidation with chromium trioxide in acetic acid. A minor product of this oxidation was assigned structure (10), and the epoxide (9) was also formed; the structure of (9) followed from a comparison of the n.m.r. spectra of the starting material and the product. The i.r. (1 700 cm^{-1}) and mass spectrum (M^+ 558) were also in agreement with structure (9), but the stereochemistry remains uncertain.

Basic hydrolysis of the diacetate (2) gave products whose structure and distribution depended on the reaction conditions. Under mild conditions only the 3-acetoxy-group was hydrolysed to afford (3) which could be oxidized with Jones reagent to the 5-ene-3,7-dione (11). In refluxing ethanolic potassium hydroxide two products were formed.† One was simply the diol (4) and the other was assigned structure (12). The n.m.r. spectrum of the diol (12) showed signals characteristic of a 3β,11β-dihydroxycucurbit-5-en-7-one: an olefinic proton at δ 6.10, 3α- and 11α-H at δ 3.39 and 3.94, and 8β-H at δ 2.54. The spectrum of the diacetoxy-derivative (13), showing the corresponding signals at δ 6.11, 5.23, 4.60, and 2.59, was very similar to that of (2). The only, and significant, difference observed was the shape of the signal of the 3α-proton. Whereas in all 10α-cucurbit-5-en-7-ones the 3α-proton appears as a narrow signal (broadened s, $W_{1/2}$ 5—7 Hz, or a multiplet

† When (2) was refluxed in ethanolic potassium hydroxide for 5 h an equilibrium mixture of compounds (4) and (12) was formed in a ratio of *ca.* 2 : 3.

resembling a triplet with J *ca.* 2 Hz), in compounds (12) and (13) it gives a broad multiplet, $W_{1/2}$ 16 Hz, shifted to higher field by *ca.* 0.25 p.p.m. If we assume a change of configuration at C-10 from α to β, the 3α-proton becomes axial and consequently strong magnetic interaction



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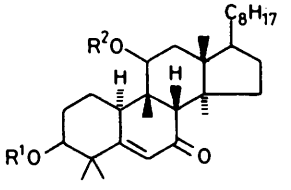
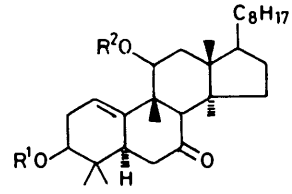
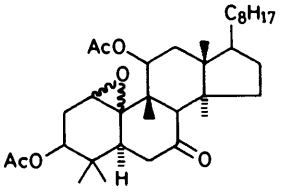


(2) $R^1 = R^2 = Ac$
(3) $R^1 = H$, $R^2 = Ac$
(4) $R^1 = R^2 = H$
(5) $R^1 = Ac$, $R^2 = H$



(6) $R^1 = R^2 = Ac$
(7) $R^1 = H$, $R^2 = Ac$
(8) $R^1 = R^2 = H$



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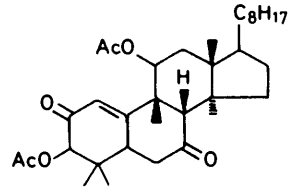

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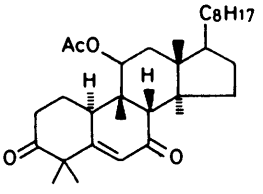

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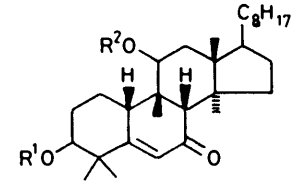
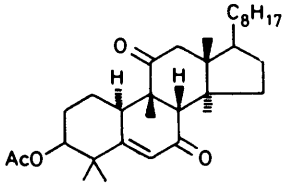


(12) $R^1 = R^2 = H$
(13) $R^1 = R^2 = Ac$

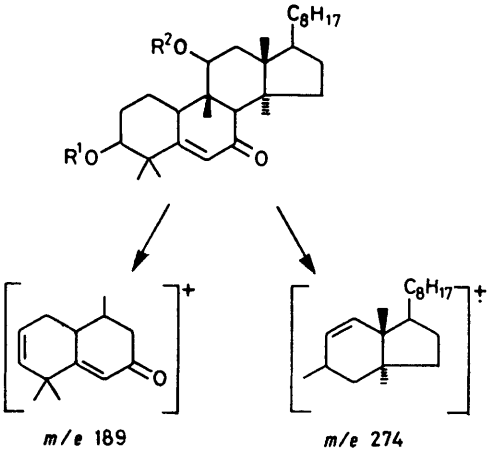


(14)

between this and the 2β-proton is possible. Similar n.m.r. arguments relating to the 11α-proton are also indicative of the 8β-configuration for compounds (12) and (13). Inspection of Dreiding molecular models supported the foregoing assumption. Of the three plausible configurational isomers with a fixed 9β-configuration, the least strained molecule seems to be that having the 8β,9β,10β-configuration, in which rings A and C adopt a chair conformation. The 8α,9β,10α- and 8α,9β,10β-isomers would suffer severe torsional and steric strain, since ring C would be fixed in a boat conformation with the methyl groups at C-9 and C-13 in a 1,4-*cis* relation.

A successful correlation of the synthetic cucurbitanes with a natural cucurbitacin was achieved as follows: acetylation of the diol (4) yielded the 3β-acetoxy-11β-hydroxy-enone (5) (70% yield) and the 3β,11β-diacetoxy-enone (2) (20% yield). Oxidation of (5) with Jones reagent gave 3β-acetoxy-10α-cucurbit-5-ene-7,11-dione (14) which was also obtained when 24-deoxybryogenin acetate [10] (15) was treated with chromium trioxide in acetic acid. The c.d. spectrum of the curcurbitone (14) ($\Delta\varepsilon$ −0.69 at 339 nm, +6.31 at 295 nm) confirmed the 9β-configuration [13] of all *abeo*-compounds described here.

The electron-impact-induced fragmentation of cucurbit-5-en-7-ones possessing substituents at C-3 and C-11 involves a ready loss of H_2O and/or AcOH as well as an extensive fragmentation of rings B and C directed by the enone unit. The two characteristic fragmentation modes are shown in the Scheme. The fragment of

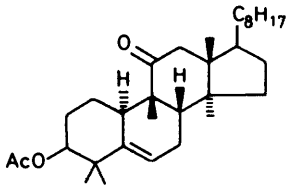


m/e 189 *m/e* 274

m/e 189 is present in the spectra of all compounds with a 3β-OAc or 3β-OH substituent, and is shifted to *m/e* 205 in the spectrum of the 3-ketone (11). The *m/e* 274 peak remains unchanged in the spectra of compounds with an 11β-OR (R = H or Ac) substituent, *e.g.* (2), (3), (5), (11), and (13). Instead, fragmentation of (14) and (15) gives the *m/e* 291 peak which probably arises from a McLafferty-type rearrangement followed by C(7)–C(8) bond cleavage.[14]

Since no natural cucurbitacins possess functionality at C-7, the reduction of the 7-carbonyl to a methylene group was our next goal. Attempts to transform the enone (2) into dithioacetal, toluene-*p*-sulphonylhydrazide, or semicarbazide derivatives failed indicating a remarkably lower reactivity of the 7-carbonyl group, presumably for steric reasons. Reduction under Wolff–Kishner conditions or with $LiAlH_4$–$AlCl_3$ reagent [15] resulted in formation of complicated mixtures. Reduction of the enone (2) with lithium aluminium hydride in ether gave two products. The desired allylic alcohol was formed in 27% yield. Its n.m.r. spectrum showed four low-field signals, 1 H intensity each. The broadened doublet at δ 5.86 was attributed to 7-H, for it collapsed to a broad-

ened singlet upon irradiation of the doublet centred at δ 2.47 (8β-H). 6-H (δ 5.39, $W_{1/2}$ 4.6 Hz) interacts very slightly with 7-H and this might be a consequence of a pseudo-equatorial α-orientation of the 7-acetoxy-group. In such a case the dihedral angle 6-H–7β-H, as estimated from a Dreiding model, is close to 90°. The position of the 6-H signal and the values of the coupling constants are very similar to the corresponding values for a system of similar spatial relation;[16] therefore, structure (16) is proposed for the allylic alcohol triacetate. Considering the steric conditions around the 7-carbonyl group (15-CH_2, 9β-Me, and 14α-Me) it may be assumed that AlH_4^- attack from the top of the molecule implies a reactant-like transition state, and steric-approach control of the reaction operates.



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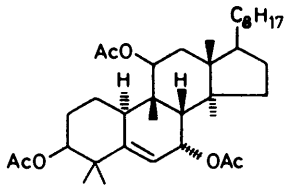

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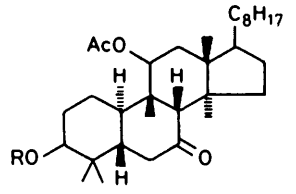
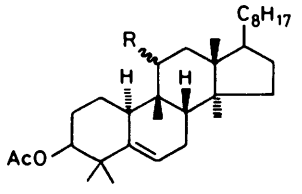
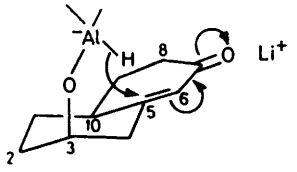


(17) R = H
(18) R = Ac



(19) R = β—OAc
(20) R = α—OAc

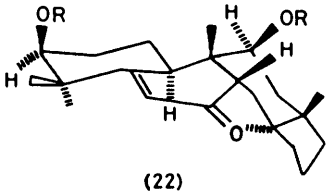


(21)

The spectral data agree with structure (18) for the acetyl derivative of the major product (39%) of the reduction of (2). There are two factors that determine the stereochemistry at C-5: (i) approach of the reducing agent from the α-side is highly inhibited by the 14α-methyl group, and (ii) the resulting 5α-isomer would suffer from severe steric compression of the 9β- and 4β-methyl groups and the 2β-hydrogen. Again, the half-width of the signal for 3α-H ($W_{1/2}$ 4.5 Hz) is characteristic of its equatorial orientation and confirms the 5β-stereochemistry, assuming that ring A exists in a chair conformation. The proportions of the reduction products are rather unusual and might be a result of intramolecular hydride transfer from an alkoxymetal hydride complex (21).[17] Similar reduction of an analogous Δ^5-7-oxo-system derived from litsomentol has been reported [5] to give only a saturated ketone.

The allylic acetate (16) did not react under hydrogenolysis conditions (Pd–C in EtOH, AcOEt, or AcOH).[18] However, it reacted with lithium in ethylamine to give a mixture containing several components from which the major product was isolated in the form of the diacetate and was characterized as the required 7-deoxy-compound (19). Because of the low yield of (19) and the failure to obtain it in crystalline form, it appeared advisable to obtain supporting evidence for its structure. Reduction of (15) ($LiAlH_4$ in tetrahydrofuran) followed by acetylation gave two compounds in the ratio *ca.* 1 : 1. All the physical properties of the more polar product were identical with those of the 7-deoxy-compound (19). The second product, 3β,11α-diacetoxy-10α-cucurbit-5-ene (20), was a crystalline substance showing characteristic n.m.r. signals at δ 5.52 (6-H), 5.21 (11β-H), 4.69 (3α-H), and 2.03 and 1.99 (2 × OAc). The mass spectral fragmentation patterns of both epimers, (19) and (20), were very similar. The outcome of the above reduction was rather surprising in view of the report [19] that reduction of 4,4,14α-trimethyl-19(10 ⟶ 9β)*abeo*-10α-pregn-5-en-11-one under similar conditions gave only one isomer, *i.e.* the corresponding 11β-alcohol

The steroidal nucleus of cucurbitanes has a folded conformation. Valuable information on conformational changes was gained from n.m.r. spectra of variously functionalized compounds. Since the observed splittings do not necessarily represent true coupling constants [20] the shape of low-field signals and the half-width thereof was used for qualitative evaluation of a ring conformation. From the n.m.r. data and examination of Dreiding models it is apparent that in compounds represented by formula (22) ring A exists in a slightly flattened chair form with an axially oriented 3β-OR group. Ring B adopts a half-chair conformation and ring C is a flattened chair which is distorted to a higher degree in 11β-acetoxy- than in 11β-hydroxy-derivatives, owing to the non-bonded interactions with 9- and 13-methyl groups. The 11α-H signal in the olefin (19) and in the 5β,10α-compounds (17) and (18) is distinctly broader than that in the enones (2)—(5), suggesting for the 11β-acetoxy-group a pseudo-equatorial orient-



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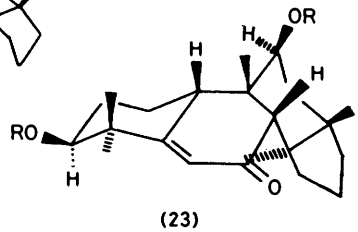

(23)

ation, *i.e.* a twist–boat conformation of ring C.[19] In compound (20) ring C again adopts a flattened chair conformation, as shown by a triplet due to 11β-H. It is proposed that in the hitherto unknown 8β,9β,10β-

cucurbitanes, *e.g.* (12) and (13), ring A adopts a chair, ring B a half-chair, and ring C a flattened chair conformation (23). Such an arrangement gives a molecule with minimal interactions between non-bonded groups or atoms.

The formation of the cucurbitene (2) when the epoxide (1) is treated with boron trifluoride–diethyl ether in acetic anhydride * can be explained by a mechanism involving a non-concerted process [22] in which discrete carbo-cations at C-9, C-10, and possibly at C-5, are intermediates. Formation of a $\Delta^{5(10)}$-olefin, *i.e.* 3β,11β-diacetoxycucurbit-5(10)-en-7-one, as an intermediate product seems to be excluded because its protonation might occur from both α- and β-directions, and consequently both 10α- and 10β-isomers, (2) and (12), should be formed in view of the ready isomerization at C-10 (see above). It has recently been reported [23] that acetolytic cleavage of 2β,11-epoxycholestane with boron trifluoride–diethyl ether involves an intermediate secondary carbo-cation.

In the skeletal transformation of lanostane into cucurbitane described here two points are noteworthy: the use of acetic anhydride as the solvent and the presence of a 7-carbonyl group in the starting epoxide (1). Acetic anhydride is required for this methyl migration since in benzene the 11-ketone is formed.[1] The 7-carbonyl group has a dual role: (i) it totally supresses the ' backbone rearrangement ' leading to protostane derivatives [2] by destabilization of the incipient transition state having carbo-cationic character with the positive charge placed at C-8 and (ii) it affords the possibility of stabilization of the rearranged molecule predominantly at the stage of the 5-en-7-one with the double bond in the position common for natural cucurbitacins.

From the results given here it may be concluded that while rearrangement of 9β,11β-epoxylanostan-7-one seems promising as a route to cucurbitacins, the efficient removal of the 7-carbonyl group remains a problem. The factors responsible for the 1,2-shift of the C-19 methyl group are being investigated and will be reported later.

EXPERIMENTAL

For general experimental directions see ref. 1.

Rearrangement of the Epoxy-ketone (1).—(i) The epoxide (1) [1] (630 mg) dissolved in acetic anhydride (43 ml) was treated under argon with boron trifluoride–diethyl ether (0.63 ml) at room temperature for 15 min. The red solution was poured on ice, then pyridine (45 ml) was added dropwise while the temperature was maintained below 10 °C. Following extraction with benzene–diethyl ether (1 : 1), the organic layer was washed (5% HCl; then 5% $NaHCO_3$; then water) and dried ($MgSO_4$). Evaporation gave a yellow semi-solid, which was chromatographed on a silica column (30 g). Elution with benzene afforded 3β-acetoxylanostane-7,11-dione [24] (200 mg, 32%), m.p. 223—225 °C (from chloroform–methanol), mixed m.p. 221—224 °C. Elution with benzene–ether (5 : 1) gave 3β,11β-*diacetoxy*-10α-*cucurbit*-5-*en*-7-*one* (2) (396 mg, 58%), m.p. 188—190 °C (from hexane), δ 6.07 (slightly broadened s, $W_{1/2}$ 4 Hz, 6-H), 5.27 (br. s, $W_{1/2}$ 9 Hz, 11α-H), 4.86 (br. s, $W_{1/2}$ 6 Hz, 3α-H), 2.63 (s, 8β-H), and 2.05 and 2.00 (2 × s, OAc); $\nu_{max.}$ 1 725, 1 660, 1 260, 1 025, and 975 cm^{-1}; $\lambda_{max.}$ 245 nm (ε 13 500); *m/e* 542 (M^+), 482, 369, 274, 241, 208, and 189 (Found: C, 75.3; H, 9.9. $C_{34}H_{54}O_5$ requires C, 75.2; H, 10.0%).

(ii) To a solution of the epoxide (1) (1.408 g) in acetic anhydride (100 ml) at 40 °C boron trifluoride–diethyl ether (1.4 ml) was added and after 3 min the reaction mixture was poured onto ice. Work-up as just described gave the crude product which was chromatographed on a silica column (85 g) with methylene chloride as eluant. The following compounds were obtained, in order of their elution: 3β-acetoxylanostane-7,11-dione (438 mg, 31%), identical with an authentic sample,[24] 3β,11β-*diacetoxy*-5α-*cucurbit*-1(10)-*en*-7-*one* (6) (205 mg, 13%) as an oil, δ 5.83 (br. s, $W_{1/2}$ 10 Hz, 1-H), 5.65 (br.t, $W_{1/2}$ 9 Hz, J 3.5 Hz, 11α-H), 4.75 (dd, J 10 and 7 Hz, 3α-H), 2.03 (s, 2 × OAc), and 1.00, 0.95, 0.88, and 0.81 (Me); $\nu_{max.}$ 1 723, 1 695, 1 250, and 1 030 cm^{-1}; *m/e* 542 (M^+), 527, 500, 482, 422, 407, 389, 295, and 189 (Found: C, 75.1; H, 10.1%), and 3β,11β-diacetoxy-10α-cucurbit-5-en-7-one (2) (779 mg, 51%), m.p. and mixed m.p. 188—190 °C, identical (i.r., u.v., and n.m.r. spectra) with the compound described in the preceding section.

Oxidation of 3β,11β-*Diacetoxy*-5α-*cucurbit*-1(10)-*en*-7-*one* (6) *with Chromium Trioxide*.—To a stirred solution of compound (6) (71 mg) in acetic acid (5 ml) at room temperature, chromium trioxide (47 mg) was added in portions and the mixture was stirred for 2 h. Dilution with saturated sodium chloride solution (5 ml) followed by extraction with benzene gave the crude product as an oil which was separated by preparative t.l.c. (silica plates, developed twice with chloroform–ethyl acetate, 20 : 1). Two compounds were obtained: 3β,11β-*diacetoxy*-1,10-*epoxy*-5α-*cucurbitan*-7-*one* (9) (27 mg), a thick oil, δ 4.52—4.97 (m, 3α- and 11α-H), 3.62 (br. s, $W_{1/2}$ 6 Hz, 1-H), 2.47—2.60 (m, protons α to 7-carbonyl), 2.02 (s, 2 × OAc), and 0.99, 0.88, and 0.80 (Me); $\nu_{max.}$ 1 735, 1 700, and 1 260 cm^{-1}; *m/e* 558 (M^+), 498, 438, 423, 385, 325, 307, 291, 248, and 221 (Found: C, 72.9; H, 9.8. $C_{34}H_{54}O_6$ requires C, 73.1; H, 9.7%), and 3β,11β-*diacetoxy*-5α-*cucurbit*-1(10)-*ene*-2,7-*dione* (10) (16 mg), an oil, δ 6.43 (br. d, J 2 Hz, 1-H), 5.70 (br. s, $W_{1/2}$ 7 Hz, 11α-H), 5.22 (s, 3α-H), 2.20 (s, 3β-OAc), 2.05 (s, 11β-OAc), and 1.08, 1.04, 0.98, 0.88, and 0.79 (Me); $\nu_{max.}$ 1 745, 1 700, 1 690sh, 1 610, and 1 255 cm^{-1}; $\lambda_{max.}$ 243 nm (ε 9 700); *m/e* 556 (M^+), 306, 264, 233, and 207 (Found: C, 73.1; H, 9.2. $C_{34}H_{52}O_6$ requires C, 73.3; H, 9.4%).

Hydrolysis of 3β,11β-*Diacetoxy*-5α-*cucurbit*-1(10)-*en*-7-*one* (6).—The enone (6) (38 mg) was treated with a saturated solution of potassium carbonate in methanol (2 ml) at room temperature for 24 h. The usual work-up gave the monoacetoxy-enone (7) as an oil, which could not be obtained in a crystalline form, δ 5.90 (br. s, $W_{1/2}$ 11 Hz, 1-H), 5.73 (br. t, J 3.8 Hz, 11α-H), 3.55 (dd, J 11.5 and 8 Hz, 3α-H), 2.02 (s, OAc), and 0.97, 0.90, 0.79, and 0.72 (Me); *m/e* 500 (M^+).

The enone (7) (32 mg) in ethanol (10 ml) containing potassium hydroxide (43 mg) was refluxed for 40 min. The usual work-up gave the dihydroxy-enone (8) (27.3 mg) as a non-crystalline solid, δ 5.64 (br. s, $W_{1/2}$ 8 Hz, 1-H), and

* The i.r. spectrum of BF_3·Et_2O–Ac_2O (1 : 10 to 1 : 1 mixtures) revealed that a complex of the type: CH_3·CO·O·$CH_3CO^+ \cdots {}^-BF_3$·Et_2O is formed. Two additional bands of high intensity were observed at 1 605 [ν(CO)] and 1 490 [$\nu(CH_3)$] cm^{-1}. Analogous bands were observed in the complex AcCl–$AlCl_3$.[21] The absence of a band in the region 2200—2300 cm^{-1} indicates that free or complexed CH_3CO^+ is not formed in an appreciable concentration.

1.23, 1.16, 1.04, 0.95, 0.91, and 0.81 (Me), $\nu_{max.}$ 3 630, 3 480, and 1 700 cm^{-1}: *m/e* 458 (M^+), 440, 385, 290, 207, and 189 (Found: C, 78.7; H, 10.7. $C_{30}H_{50}O_3$ requires C, 78.55; H, 11.0).

Mild Hydrolysis of 3β,11β-*Diacetoxy*-10α-*cucurbit*-5-*en*-7-*one* (2).—Compound (2) (95 mg) was dissolved in methanol (2 ml) and saturated methanolic potassium carbonate (0.2 ml) was added. The mixture was kept at room temperature for 3 days. The usual work-up yielded 11β-*acetoxy*-3β-*hydroxy*-10α-*cucurbit*-5-*en*-7-*one* (3), m.p. 214—216 °C (from methylene chloride–methanol), δ 6.07 (s, $W_{1/2}$ 3 Hz, 6-H), 5.25 (br. s, $W_{1/2}$ 8 Hz, 11α-H), 3.62 (br. s, $W_{1/2}$ 5 Hz, 3α-H), 2.58 (s, 8β-H), and 2.06 (s, OAc); $\nu_{max.}$ 3 620, 3450, 1 730, 1 655, 1 625, and 1 260 cm^{-1}; *m/e* 500 (M^+), 440, 274, 207, 189, 166, and 121 (Found: M^+, 500.386 2. $C_{32}H_{52}O_4$ requires *M*, 500.386 3).

Oxidation of 11β-*Acetoxy*-3β-*hydroxy*-10α-*cucurbit*-5-*en*-7-*one* (3) *to the* 3-*Ketone* (11).—Compound (3) (50 mg) was oxidized with Jones reagent to give the *ketone* (11) (48 mg), m.p. 184—186 °C (from methanol), δ 6.12 (br. s, 6-H), 5.27 (br. t, *J* 3 Hz, 11α-H), 2.04 (s, OAc), and 1.32, 1.31, 0.98, 0.92, and 0.79 (Me); $\nu_{max.}$ 1 718, 1 652, 1 620, and 1 250 cm^{-1}; $\lambda_{max.}$ 245 nm (ε 10 500) (Found: M^+, 498.368 8. $C_{32}H_{50}O_4$ requires *M*, 498.370 66).

Vigorous Hydrolysis of 3β,11β-*Diacetoxy*-10α-*cucurbit*-5-*en*-7-*one* (2).—A solution of compound (2) (205 mg) in ethanol (10 ml) containing potassium hydroxide (210 mg) was refluxed under nitrogen for 1 h and then left at room temperature for 3 days. The usual work-up gave the crude product as a slightly yellow oil (183 mg). Two crystallizations from ethyl acetate afforded the 3β,11β-*dihydroxy*-10α-*derivative* (4) (42 mg), m.p. 230—233 °C (from methanol–chloroform), δ 6.11 (br. s, $W_{1/2}$ 3.5 Hz, 6-H), 4.00 (br. s, $W_{1/2}$ 7 Hz, 11α-H), 3.67 (br. s, $W_{1/2}$ 5 Hz, 3α-H), 2.58 (s, 8β-H), and 1.23, 1.11, 1.06, 0.84, and 0.81 (Me); $\nu_{max.}$ (KBr) 3 550, 3 400, 1 650, and 950 cm^{-1}; *m/e* 458 (M^+), 443, 415, 291, 275, 241, 207, 189, and 166 (Found: M^+ 458.381 4. $C_{30}H_{50}O_3$ requires *M*, 458.375 745).

The combined mother liquors from the above crystallization were evaporated and chromatographed on preparative silica plates developed twice with benzene–ethyl acetate (1 : 1). Zone I contained an additional crop of the 3β,11β-dihydroxy-derivative (4) (27 mg). Zone II contained a still impure material (66 mg) which was chromatographed using the conditions just described to give 3β,11β-*dihydroxy*-10β-*cucurbit*-5-*en*-7-*one* (12) (53 mg) as a semi-solid (pure on t.l.c.), δ 6.10 (br. s, $W_{1/2}$ 3.5 Hz, 6-H), 3.94 (br. s, $W_{1/2}$ 7 Hz, 11α-H), 3.39 (m, $W_{1/2}$ 16 Hz, 3α-H), 2.54 (s, 8β-H), and 1.22, 1.03, 0.89, and 0.81 (Me). The crude material was acetylated with pyridine (0.3 ml) and acetic anhydride (0.2 ml) at room temperature for 10 days. Work-up yielded 3β,11β-*diacetoxy*-10β-*cucurbit*-5-*en*-7-*one* (13) (55 mg), m.p. 260—261 °C (from methanol–chloroform), δ 6.11 (br. s, $W_{1/2}$ 3.5 Hz, 6-H), 5.23 (br. s, $W_{1/2}$ 7 Hz, 11α-H), 4.60 (m, $W_{1/2}$ 16 Hz, 3α-H), 2.59 (s, 8β-H), 2.07 and 2.0 (each s, 2 × OAc), and 1.13, 0.97, 0.90, and 0.87 (Me); $\nu_{max.}$ 1 732, 1 660, 1 260, and 1 022 cm^{-1}; $\lambda_{max.}$ 243 nm (ε 10 200); *m/e* 542 (M^+), 482, 440, 422, 274, 240, and 189 (Found: C, 75.4; H, 9.8. $C_{34}H_{54}O_5$ requires C, 75.2; H, 10.0%).

When compound (2) (111 mg) was refluxed with base for 10 min and the mixture was left at room temperature for 15 h, compound (3) (34 mg, 33%) crystallized out. The mother liquor was left at room temperature for an additional 3 days; the usual work-up and t.l.c. separation (as just described) then gave the 3β,11β-dihydroxy-compound (4) (37 mg, 39%) and 3β,11β-dihydroxy-10β-cucurbit-5-en-7-one (12) (11 mg, 12%).

Acetylation of 3β,11β-*Dihydroxy*-10α-*cucurbit*-5-*en*-7-*one* (4).—A solution of the dihydroxy-compound (4) (42 mg) in pyridine (0.5 ml) and acetic anhydride (0.5 ml) was left at room temperature for 15 h. Work-up gave the crude product (50 mg) as a two-component mixture, which was separated by preparative t.l.c. (silica gel, benzene–ethyl acetate, 1 : 1) to yield the 3β,11β-diacetoxy-compound (2) (10 mg, 20%), m.p. 188—190 °C (from hexane), identical (n.m.r. and i.r. spectra) with an authentic sample, and 3β-*acetoxy*-11β-*hydroxy*-10α-*cucurbit*-5-*en*-7-*one* (5) (32 mg, 70%), m.p. 252—254 °C (from chloroform–methanol), δ 6.09 (br. s, $W_{1/2}$ 3 Hz, 6-H), 4.82 (br. s, $W_{1/2}$ 4.5 Hz, 3α-H), 3.98 (t, *J* 1.7 Hz, 11α-H), 2.62 (s, 8β-H), 1.99 (s, OAc), and 1.19, 1.09, 0.96, 0.91, 0.85, and 0.82 (Me); $\nu_{max.}$ 3 635, 3 480, 1 730, 1 655, and 1 250 cm^{-1}; $\lambda_{max.}$ 244 nm (ε 11 200) (Found: C, 77.1; H, 10.7. $C_{32}H_{52}O_4$ requires C, 76.75; H, 10.5%).

3β-*Acetoxy*-10α-*cucurbit*-5-*ene*-7,11-*dione* (14).—A solution of 3β-acetoxy-11β-hydroxy-10α-cucurbit-5-en-7-one (5) (23 mg) in acetone (2 ml) was treated with Jones reagent. Work-up gave 3β-*acetoxy*-10α-*cucurbit*-5-*ene*-7,11-*dione* (14) (22 mg), m.p. 225—227 °C (from methanol), δ 6.13 (d, *J* 2.5 Hz, 6-H), 4.83 (br. s, $W_{1/2}$ 5 Hz, 3α-H), 2.92 (d, *J* 15 Hz, 12β-H), 2.57 (d, *J* 15 Hz, 12α-H), 2.55 (s, 8β-H), 2.00 (s, OAc), and 1.17, 1.14, 1.06, 0.90, and 0.79 (Me); $\nu_{max.}$ 1732, 1700, 1663, and 1255 cm^{-1}; $\lambda_{max.}$ 243 nm (ε 13 300); c.d. Δε −0.69 (339 nm) and +6.31 (295 nm); *m/e* 498 (M^+), 438, 291, 249, 190, 189, and 121 (Found: C, 77.2; H, 10.4. $C_{32}H_{50}O_4$ requires C, 77.1; H, 10.1%).

Oxidation of Deoxybryogenin Acetate (15).—To a solution of 24-deoxybryogenin acetate (15) (51 mg) in acetic acid (5 ml) a solution of chromium trioxide (50 mg) in acetic acid (1 ml) was added and the mixture was set aside at room temperature for 2 h. Dilution with water followed by extraction with benzene afforded the crude product which was filtered through a short alumina column (1 g) in benzene to give the diketone (14) (42 mg), m.p. 225—227 °C (from methanol), $\lambda_{max.}$ 243 nm (ε 13 700), identical (i.r., n.m.r., and mass spectra) with the substance obtained in the preceding experiment.

Reduction of 3β,11β-*Diacetoxy*-10α-*cucurbit*-5-*en*-7-*one* (2).—To a solution of compound (2) (354 mg) in ether (50 ml) lithium aluminium hydride (355 mg) was added in portions over 15 min. The mixture was refluxed for 75 min, then a saturated magnesium sulphate solution (a few ml) was added carefully. Benzene (30 ml) was added and the organic layer was dried ($MgSO_4$) and evaporated to give the crude product (289 mg), which was acetylated with acetic anhydride (4 ml) and pyridine (4 ml). Addition of water and extraction with benzene gave an oil, which was shown on t.l.c. to be a mixture of two components of very similar polarity. This was chromatographed three times on preparative t.l.c. plates (silica gel, benzene–ethyl acetate, 10 : 1) to give chromatographically pure 3β,7α,11β-*triacetoxy*-10α-*cucurbit*-5-*ene* (16) (102 mg, 27%) as an oil, δ 5.86 (br. d, *J* 7 Hz, 7β-H), 5.39 (br. s, $W_{1/2}$ 4 Hz, 6-H), 5.17 (br. s, $W_{1/2}$ 6 Hz, 11α-H), 4.73 (br. s, $W_{1/2}$ 4.5 Hz, 3α-H), 2.47 (d, *J* 7 Hz, 8β-H), 2.04, 2.01, and 1.98 (3 × s, OAc), and 1.02, 0.92, 0.88, and 0.82 (Me); $\nu_{max.}$ 1 725, 1 255, and 1 030 cm^{-1}; *m/e* 526 (M^+ — AcOH), 484, 469, 406, 391, 252, and 173 (Found: C, 73.5; H, 10.0. $C_{36}H_{58}O_6$ requires C, 73.7; H, 10.0%), and 3β,11β-*diacetoxy*-5β,10α-*cucurbitan*-7-*one* (18) (137 mg, 39%), m.p. 200—203 °C (from methanol),

δ 5.39 (m resembling dd, $W_{1/2}$ 10 Hz, 11α-H), 4.64 (br. s, $W_{1/2}$ 4.5 Hz, 3α-H), 2.56 (s, 8β-H), 1.99 (s, 2 × OAc), and 0.95 (Me); $\nu_{max.}$ 1 730, 1 720sh, 1 690, 1 255, 1 020, and 975 cm^{-1}; *m/e* 544 (M^+), 484, 469, 458, 442, 424, and 371 (Found: C, 74.8; H, 10.5. $C_{34}H_{56}O_5$ requires C, 74.95; H, 10.4%).

Hydrolysis of 3β,11β-*Diacetoxy*-5β,10α-*cucurbitan*-7-*one* (18).—To a solution of the diacetoxy-ketone (18) (43 mg) in methanol (5 ml) a saturated solution of potassium carbonate in methanol (1 ml) was added and the mixture was left at room temperature for 10 days. After the usual work-up a single product was obtained: 11β-*acetoxy*-3β-*hydroxy*-5β,10α-*cucurbitan*-7-*one* (17), m.p. 219—222 °C (from methanol–acetone), δ 5.41 (br. d, *J* 4 Hz, $W_{1/2}$ 10 Hz, 11α-H), 3.45 (br. s, $W_{1/2}$ 5 Hz, 3α-H), 2.56 (s, 8β-H), 2.00 (s, OAc), and 1.00, 0.90, and 0.80 (Me); $\nu_{max.}$ 3 630, 3500, 1720, 1683, 1255, and 1020 cm^{-1}.

Reduction of 3β,7α,11β-*Triacetoxy*-10α-*cucurbit*-5-*ene* (16) *with Lithium in Ethylamine*.—To a solution of compound (16) (36 mg) in ethylamine (2 ml) lithium (25 mg) was added and the stirred mixture was heated under reflux until a blue colour developed (40 min). After a further 10 min diethyl ether (15 ml) was added and the solution was washed (water; 5% HCl; 5% $NaHCO_3$; water). The organic layer was dried ($MgSO_4$), filtered, and evaporated to give an oil (27 mg) which was acetylated with acetic anhydride (0.5 ml) in pyridine (0.5 ml). The mixture was kept at room temperature for 24 h then at 60 °C for 2 h. Work-up gave an oil (30 mg) which was shown by t.l.c. to be a mixture. It was chromatographed on t.l.c. plates (silica gel, benzene–ethyl acetate, 5 : 1) and 3β,11β-*diacetoxy*-10α-*cucurbit*-5-*ene* (19) (12 mg, 37%) was isolated as an oil, δ 5.52 (m, $W_{1/2}$ 10 Hz, 6-H), 5.16 (m, $W_{1/2}$ 8 Hz, 11α-H), 4.72 (br. s, $W_{1/2}$ 6 Hz, 3α-H), 2.03 and 1.99 (2 × s, OAc), and 1.03, 0.89, and 0.79 (Me); $\nu_{max.}$ 1 720, 1 255, 1 027, and 985 cm^{-1}; *m/e* 528 (M^+), 468, 426, 408, 393, 304, 290, and 275 (Found: C, 77.4; H, 10.8. $C_{34}H_{56}O_4$ requires C, 77.2; H, 10.7%).

Reduction of 24-*Deoxybryogenin Acetate* (15) *with Lithium Aluminium Hydride*.—To a solution of the ketone (15) (23 mg) in tetrahydrofuran (2 ml) lithium aluminium hydride (10 mg) was added and the mixture was refluxed for 1.5 h. The usual work-up gave an oil which was acetylated with acetic anhydride (0.5 ml) and pyridine (1 ml) at room temperature for 18 h followed by 2.5 h at 65 °C. Water was added and the product extracted with benzene. After work-up an oil was obtained which was shown by t.l.c. to be a mixture of two major and three other compounds. Preparative t.l.c. (silica gel, methylene chloride) gave two compounds: 3β,11β-diacetoxy-10α-cucurbit-5-ene (19) (7 mg), an oil, whose spectral properties were identical with those of the compound obtained in the previous experiment, and the less polar 3β,11α-*diacetoxy*-10α-*cucurbit*-5-*ene* (20) (7.5 mg), m.p. 94—96 °C (from methanol–chloroform), δ 5.52 (m, $W_{1/2}$ 11 Hz, 6-H), 5.21 (t, *J* 9 Hz, 11β-H), 4.69 (br. s, $W_{1/2}$ 5 Hz, 3α-H), 2.03 and 1.99 (2 × s, OAc), and 1.09, 1.02, 0.96, 0.89, 0.85, and 0.80 (Me) (Found: C, 77.2; H, 10.5%).

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