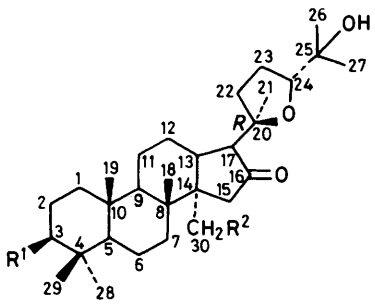
Acid-catalysed Rearrangement of Trevoagenins A and B. The Acetal Function as Electron-donor Group in Heterolytic Fragmentations [1]

Cosme G. Francisco, Raimundo Freire, Rosendo Hernández, José A. Salazar, and Ernesto Suárez *
Instituto de Productos Naturales Orgánicos, C.S.I.C., La Laguna, Tenerife, Spain
Manuel Cortés
Facultad de Química, Pontificia Universidad Católica de Chile, Santiago, Chile

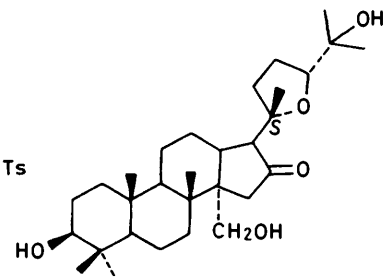
The acid-catalysed rearrangement of trevoagenins A (1) and B (4) gave 3β-hydroxy-24-oxo-16,17-seco-5α-dammar-17(20)*E*-eno-16,30-lactone (5) (40%), its 17(20)*Z*-ene isomer (7) (13%), and (20*R*,24*R*)-3β,25-dihydroxy-15α,30-cyclo-20,24-epoxy-5α-dammaran-16-one (9) (2%). Compounds (5) and (7) were produced through a heterolytic fragmentation mechanism. In order to study the scope of this rearrangement the C-20 epimeric hydroxy acetals (24) and (28) were synthesized starting from trevoagenin B and A, respectively. The reaction of the 20*S*-hydroxy acetal (24) with iodine led to the *Z*-olefin (29) while the 20*R*-hydroxy acetal (28) gave the *E*-olefin (30). The concerted nature of this heterolytic fragmentation, where acetals or hemiacetals are the electron-donor groups, is supported by the observed stereospecificity of the reaction.

The genuine structure of the sapogenin of several dammarane triterpenoid glycosides isolated from species of Rhamnaceae and Scrophulariaceae has been a controversial matter for many years [2] as a consequence of its high sensitivity to acids during hydrolysis, ebelin lactone (13) being the common artefact obtained after the hydrolysis of these glycosides. Recently, jujubogenin [2b] has been isolated from Rhamnaceae species and it has been proposed as the real sapogenin.

In preceding papers [3] we have reported the isolation of the dammarane triterpenes trevoagenins A, B, C, and D from *Trevoa trinervis* Miers (a member of the Chilean Rhamnaceae) whose structures have been unambiguously established by chemical correlations and *X*-ray analysis of trevoagenins A and D. Trevoagenins are more stable to acid than the aforementioned jujubogenin but stronger acid treatment also produced rearranged compounds as we indicated in a preliminary communication.[1] This paper is concerned with a detailed study of the acid-catalysed rearrangements of trevoagenins A and B. We also describe herein the preparation of adequate substrates with the purpose of examining the scope and stereochemistry of this rearrangement.



(1) $R^1 = R^2 = OH$
(2) $R^1 = OAc$, $R^2 = OTs$
(3) $R^1 = OH$, $R^2 = H$



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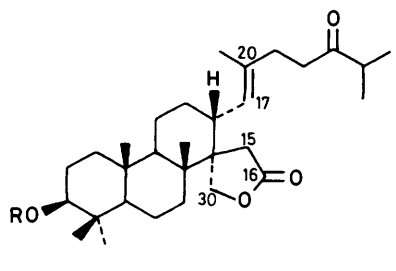
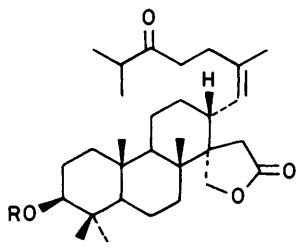
Results and Discussion

As we have already reported,[3] trevoagenins A (1) and B (4) are C-20 epimeric dammarane triterpenes which undergo acid-promoted interconversion with 2.5M ethanolic hydrochloric acid at reflux temperature for 2 h. However, longer reaction times (6 h) led to the rearranged compounds 3β-hydroxy-24-oxo-16,17-seco-5α-dammar-17(20)*E*-eno-16,30-lactone (5) (40%), its 17(20)*Z*-ene isomer (7) (13%), and (20*R*,24*R*)-3β,25-dihydroxy-15α,30-cyclo-20,24-epoxy-5α-dammaran-16-one (9) (2%). This result is obtained irrespective of the starting material (trevoagenin A or B) used.

Compound (5) has the molecular formula $C_{30}H_{48}O_4$ (from quantitative analysis and high-resolution mass spectrometry) that corresponds to the loss of one molecule of water from trevoagenins; however, spectroscopic analysis revealed at once that important structural and functional changes have taken place. Its i.r. spectrum disclosed the presence of hydroxy ($\nu_{max.}$ 3 555 cm^{-1}), saturated carbonyl (1 700 cm^{-1}), and γ-lactone (1 765 cm^{-1}) groups which account for the four oxygen atoms. The fragments [a; R = H] and [b] (Figure) in its mass spectrum,[4] the chemical shift of the 4α-, 4β-, and 10-methyl groups (singlets at δ 0.78, 0.86, and 0.99, respectively), and the position and shape of the 3α-H [multiplet of $W_{\frac{1}{2}}$ 18 Hz at



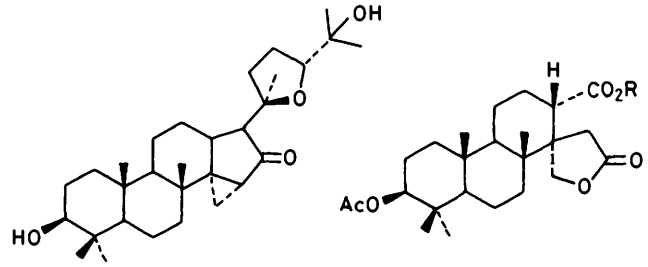
(5) R = H
(6) R = Ac



(7) R = H
(8) R = Ac

Ts = $CH_3C_6H_4SO_2$–

Chemical Abstracts numbering is used throughout this paper, and differs from the IUPAC steroid numbering in the locants assigned to the 4- and 14-methyl groups. The locations used in our previous paper (ref. 3*b*) for C-28 and C-29 should be reversed



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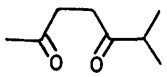
(10) R = H
(11) R = Me



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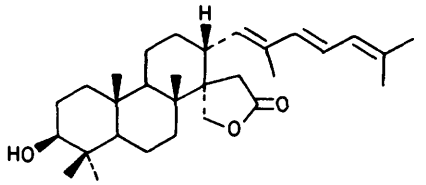

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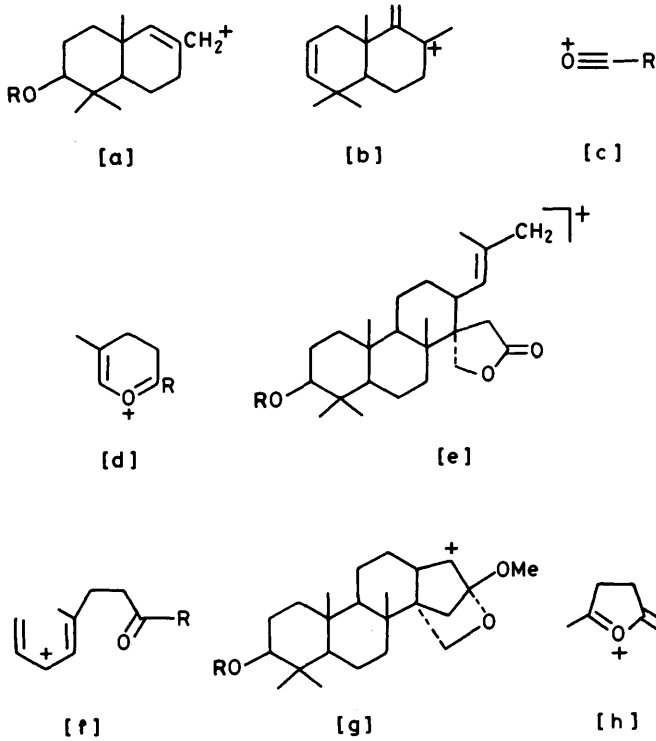


[a] [b] [c]

[d] [e]

[f] [g] [h]

Figure. Important mass-spectral fragmentation ions discussed in the text

δ 3.2 which is shifted downfield to 4.48 on acetylation, compound (6)] in its ^{1}H n.m.r. spectrum (Table), suggest that rings A and B remain unmodified compared with those of the trevoagenins. The ^{1}H n.m.r. spectrum of (5) also shows absorptions due to the presence of a vinylic methyl group [3 H, broad singlet at δ 1.65 ($w_{\frac{1}{2}}$ 3 Hz)] and an olefinic proton [1 H, broad doublet at δ 4.95 (J 10 Hz)]; the two methylene protons at C-30 in the γ-lactone ring are observed as a broad singlet at δ 4.32 ($w_{\frac{1}{2}}$ 3 Hz). Additional information about the structure of the side-chain of compound (5) is obtained from its mass spectrum (Figure): fragment [c; R = Pr^i] indicates the presence of an isopropyl ketone and fragment [d; R = Pr^i] has been observed in γ,δ-enones; [5] likewise, fragments [e; R = H] and [f; R = Pr^i] are produced by allylic cleavage. The presence of the above-mentioned structural features was supported by an examination of the ^{13}C n.m.r. spectrum of (5). Thus, the chemical shifts of carbon atoms in the A-, B-, C-, and γ-lactone rings are almost identical with those of the structurally related ebelin lactone (13) and hovenolactone [6] (see Experimental section); the absorptions at δ_C 124.8 and 137.9 p.p.m. correspond to the C-17 and C-20 olefinic carbons, respectively, and the signal for the C-24 carbonyl appears at δ_C 213.9 p.p.m.

Chemical evidence for the structure of compound (5) was obtained by ozonolysis of its 3-*o*-acetyl derivative (6) followed by oxidation to give the 1,4-diketone (12) [7,*] and the acid (10). The methyl ester of this octanor-acid was identical with that obtained by Simes through oxidative degradation of ebelin lactone (13).[8]

The second compound (7) obtained during the acid treatment of trevoagenins has the molecular formula $C_{30}H_{48}O_4$; it presents the same functional groups as the aforementioned lactone (5), as can be inferred by the similarities of their i.r. and ^{1}H n.m.r. spectra, and its mass spectrum also disclosed the same fragmentation pattern as compound (5). The methyl ester (11) was also obtained by ozonolysis and subsequent methylation of (8). Hence, we can deduce that compounds (5) and (7) differ only in the C-17–C-20 double-bond stereochemistry. The double-bond configuration of each isomer was evident from a detailed analysis of their ^{13}C n.m.r. spectra. The observed deshielding of the C-21 signal from δ_C 17.0 to 23.4 p.p.m. and the shielding of C-22 from δ_C 33.8 to 26.2 p.p.m. when comparing the ^{13}C n.m.r. spectra of (5) and (7) indicate that olefin (5) has 17(20)*E*-stereochemistry and that olefin (7) is its *Z*-isomer; moreover, the chemical shift for C-13, which is *cis* to an α-carbon in both molecules, remains essentially constant (δ_C 38.8 and 38.2 p.p.m., respectively) as expected. The magnitudes of these shifts of steric origin between the allylic carbons (6.4 p.p.m. for the methyl group and 7.6 p.p.m. for the methylene group) agree fairly well with those found for other pairs of stereoisomeric trisubstituted olefins.[9]

A very small amount (2% yield) of the cyclopropane derivative (9) was also produced during the acid treatment of trevoagenins, by intramolecular nucleophilic attack of the 16-keto enol on the protonated C-14 hydroxymethylene group. We have already [3] obtained compound (9) from the 30-tosyl † derivative of trevoagenin A 3-acetate, compound (2), by solvolysis with sodium acetate in acetone followed by saponification. The 20*S*-isomer of compound (9) that would also be expected to be formed in this reaction, if we consider the aforementioned acid-catalysed interconversion between trevoagenin A (1) and trevoagenin B (4), could not be detected.

The formation of compounds (5) and (7) can be rationalized in terms of a concerted heterolytic fragmentation [10] followed by a pinacol rearrangement as shown in the Scheme. Two lone sp^3 orbitals of the hemiacetal function are the driving force

* 6-Methylheptane-2,5-dione (12) was directly compared (i.r., ^{1}H n.m.r., and g.l.c.) with a specimen prepared from 6-methylhept-5-en-2-one by hydroboration and subsequent oxidation.
† Tosyl is toluene-*p*-sulphonyl.

Table. ^{1}H N.m.r. data (δ in $CDCl_3$) (multiplicity and J/Hz or $w_{\frac{1}{2}}$/Hz in parentheses)

Compd.	3-H	17-H	30-H	4α-Me	4β-Me	8-Me	10-Me	20-Me	25-Me_2	OMe	OAc
(5)	3.2 (m, 18)	4.95 (br d, 10)	4.32 (br s, 3)	0.78 (s)	0.86 (s)	1.02 (s)	0.99 (s)	1.65 (br s, 3)	1.09 (d, 7)		
(6)	4.5 (m, 18)	4.94 (br d, 10)	4.32 (br s, 3)	0.87 (s)	0.87 (s)	1.03 (s)	0.87 (s)	1.65 (br s, 3)	1.08 (d, 7)		2.04 (s)
(7)	3.2 (m, 18)	4.95 (br d, 10)	4.32 (br s, 3)	0.78 (s)	0.86 (s)	1.04 (s)	0.99 (s)	1.67 (br s, 3)	1.11 (d, 7)		
(8)	4.5 (m, 18)	4.94 (br d, 10)	4.32 (br s, 3)	0.87 (s)	0.87 (s)	1.04 (s)	0.87 (s)	1.67 (br s, 3)	1.11 (d, 7)		2.04 (s)
(11)	4.5 (m, 18)		4.37, 4.57 (AB, 11)	0.86 (s)	0.86 (s)	0.98 (s)	0.86 (s)			3.65 (s)	2.02 (s)
(20)	4.45 (m, 18)		3.94 (br s, 3)	0.83 (s)	0.83 (s)	1.07 (s)	0.83 (s)	1.30 (s)		3.36 (s)	2.01 (s)
(21)	3.2 (m, 18)		3.93 (br s, 4)	0.79 (s)	0.83 (s)	1.03 (s)	0.99 (s)	1.13 (s)	7.3 [a] (m)	3.45 (s)	
(24)	4.45 (m, 18)		3.94 (br s, 4)	0.82 (s)	0.82 (s)	1.03 (s)	0.82 (s)	1.16 (s)	7.4—8.0 [b] (m)	3.47 (s)	2.01 (s)
(26)	4.45 (m, 18)		3.97 (br s, 3)	0.82 (s)	0.82 (s)	1.07 (s)	0.82 (s)	1.34 (s)		3.55 (s)	2.01 (s)
(29) [c]	4.4 (m, 18)	4.93 (br d, 10)	4.18 (br s, 3)	0.82 (s)	0.82 (s)	1.02 (s)	0.85 (s)	1.74 (br s, 3)	7.5—7.9 [b] (m)		1.97 (s)
(30) [c]	4.4 (m, 18)	4.93 (br d, 10)	4.18 (br s, 4)	0.82 (s)	0.82 (s)	1.01 (s)	0.82 (s)	1.71 (br s, 3)	7.5—7.9 [b] (m)		1.97 (s)
(31)	4.45 (m, 18)		3.86, 3.96 (AB, 12)	0.83 [d] (s)	0.83 [d] (s)	0.75 (s)	0.81 [d] (s)	1.32 (s)	7.3 [a] (m)	3.30 (s)	2.01 (s)

[a] 24-Ph_2. [b] 24-Ph. [c] In CCl_4. [d] Assignments may be reversed.

for the ejection of the protonated tetrahydrofuran as the leaving group.[11] The stereochemical requirements for a synchronous mechanism implicate an antiperiplanar relationship among the central C-16–C-17 bond with the C-20–O bond and two non-bonding orbitals of the oxygens in the hemiacetal function. These conditions are fulfilled by both C-20 isomers (14) and (15) (Scheme); at first glance it would appear that, on exposure to acid, trevoagenin A (20*R*) (1) produces the *E*-isomer (5) and trevoagenin B (20*S*) (4) the *Z*-isomer (7). Nevertheless, the formation of the two isomeric olefins (5) and (7) from both trevoagenins can be explained if we consider the previous equilibration of trevoagenins at C-20 under acid conditions through the stabilized allylic cation (16).

A two-step fragmentation mechanism involving carbonium ion at C-20, as shown in (17), can be reasonably ruled out by the following considerations: (a) the C-16 carbonyl group is necessary for the formation of a C-20 carbocation, since compounds lacking it have been shown to be stable to these acid conditions;[3b,4b,12] (b) for the fragmentation process to take place, the presence of the hemiacetal group is essential; indeed, compound (3), which does not bear a hydroxy group at C-30, did not undergo this rearrangement. Obviously, both requirements cannot exist simultaneously.

A totally synchronous mechanism, as indicated in (18) for the formation of compound (5), in which the heterolytic fragmentation and the pinacol rearrangement take place simultaneously, could also be operative.

Acetals and hemiacetals have received little attention as electrofugal groups in heterolytic fragmentation. Eschenmoser [13] used a heterolytic fragmentation involving acetals in his synthetic approach to unsaturated macrolides.*

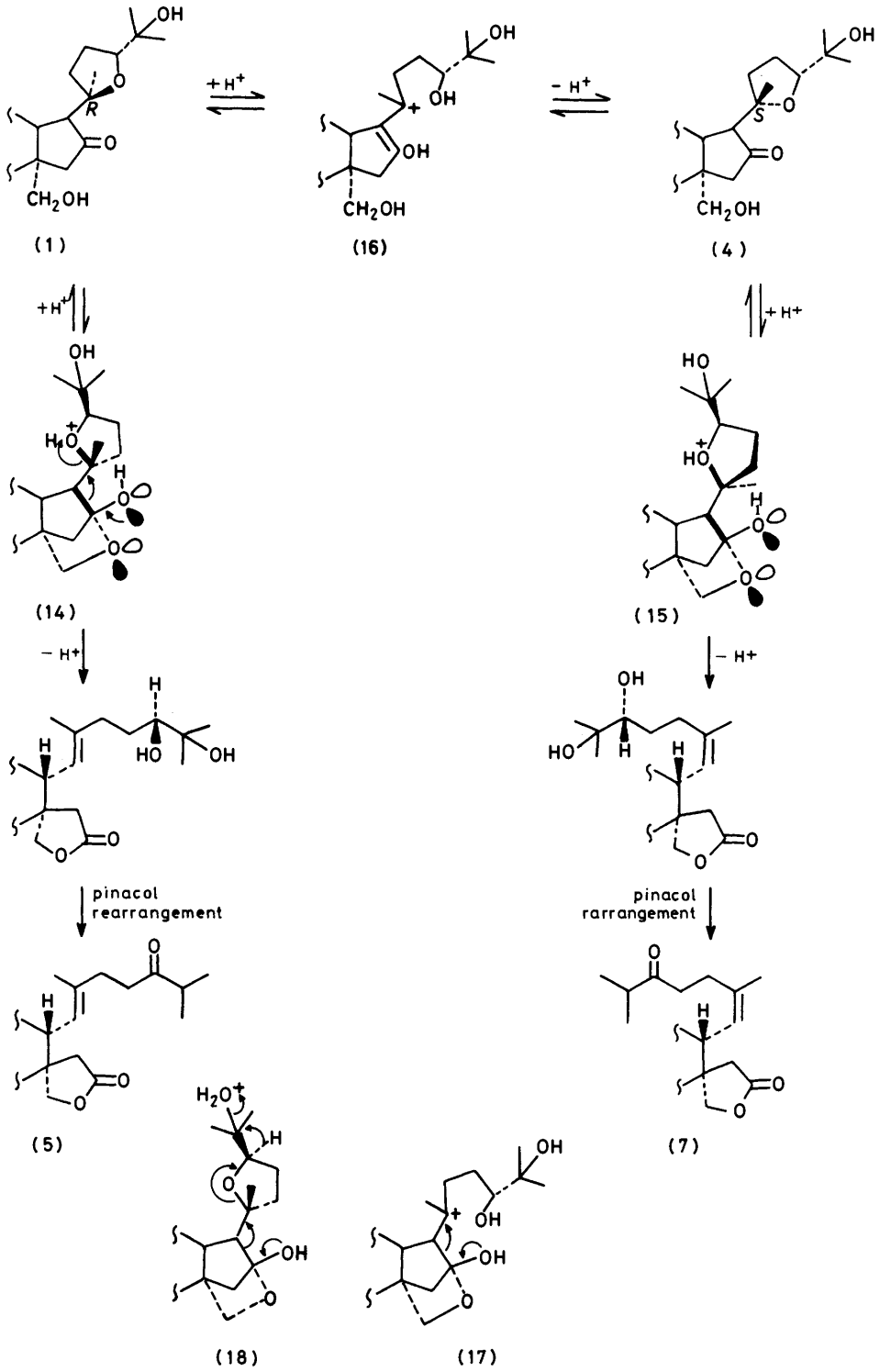
In order to test further the scope of acetals as electron-donor groups in heterolytic fragmentations we have prepared the epimeric hydroxy acetals (24) and (28). Compound (24) was prepared from trevoagenin B (4) by the following sequence. Reaction of (4) with methanolic hydrogen chloride gave the methyl acetal (19), which after acetylation of the 3-hydroxy group, was oxidized with Jones reagent [3b,14] to afford the lactone (20) whose i.r. spectrum shows absorptions at 1 760 cm^{-1} (γ-lactone) and 1 725 cm^{-1} (ester) and in whose ^{1}H n.m.r. spectrum the acetal methyl appears as a singlet at δ 3.36. In the high-resolution mass spectrum of (20) the cleavage of the C-17–C-20 bond produced the intense fragments [g; R = Ac] and [h; R = O] (Figure), as expected. Treatment of the lactone (20) in benzene with an ethereal solution of phenylmagnesium bromide gave a 4 : 1 mixture of the diphenyl carbinol (21) and the phenyl ketone (23). Compound (21) has an i.r. absorption at 3 460 cm^{-1} (hydroxy group) and an examination of its ^{1}H n.m.r. spectrum shows signals for ten aromatic protons [δ 7.3, (m)], a tertiary methyl carbinol [δ 1.13, (s)], and a methoxy group [δ 3.45, (s)]. Acetylation of (23) gave the monoacetyl derivative (24) which presents an i.r. absorption at 1 680 cm^{-1} corresponding to a phenyl ketone, the other spectroscopic data being in agreement with its structure (see Experimental section).

A similar sequence of reactions starting from the previously described [3b] methyl acetal (25) was accomplished to obtain the 20*R*-isomers (27) and (28).

Heterolytic fragmentations of the 20*S* and 20*R* epimeric alcohols (24) and (28), performed using iodine as a Lewis acid to prevent the cleavage of the acetal group prior to fragmentation, gave exclusively the *Z*-olefin (29) from (24) whereas the 20*R*-isomer (28) led to the *E*-olefin (30).† Both products (29) and (30) display very similar spectral data (see Experimental section) with the exception of the chemical shift of the 20-Me group in the ^{1}H n.m.r. spectra (C_6D_6), the

* For other Grob fragmentations with two heteroatoms see ref. 10 and S. Julia and G. Linstrumentelle, *Bull. Soc. Chim. Fr.*, 1966, 3490; W. Eisele, C. A. Grob, E. Renk, and H. von Tschammer, *Helv. Chim. Acta*, 1968, **51**, 816; P. G. Gassman and J. M. Hornback, *J. Am. Chem. Soc.*, 1969, **91**, 5817.

† Attempts to achieve the heterocyclic fragmentation of (22) with iodine were unsuccessful, giving the tetrahydrofuran derivative (31) as the only product as a consequence of the higher stability of the C-24 carbocation.



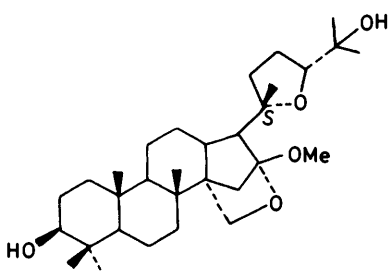
Scheme.

signal for the *E*-isomer (30) being more shielded than that of the corresponding *Z*-isomer (29) ($\Delta\delta = 0.09$ p.p.m.) (*cf.* Table). The spectroscopic behaviour of the isomeric pair (7) and (5), obtained from trevoagenins by heterolytic fragmentation, is also very similar.

The observed stereospecificity in these Grob fragmentations accounts for a one-step process where the acetals or hemiacetals are the electron-donor groups.

Experimental

M.p.s were determined with a Kofler hot-stage apparatus and are uncorrected. Optical rotations were measured for solutions in $CHCl_3$. ^1H N.m.r. spectra were recorded with a Perkin-Elmer R-12B (60 MHz) or a R-32 (90 MHz) instrument and ^{13}C n.m.r. spectra on a Varian C.F.T.-20 (20 MHz) instrument for solutions in $CDCl_3$ (unless otherwise stated)



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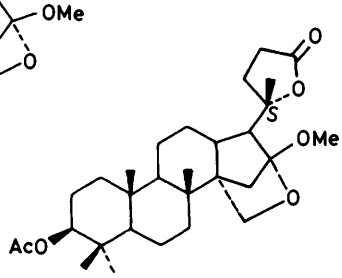

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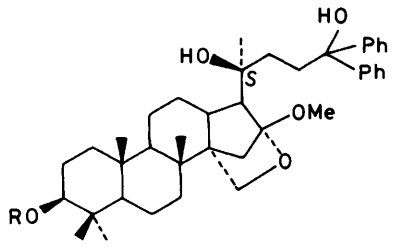
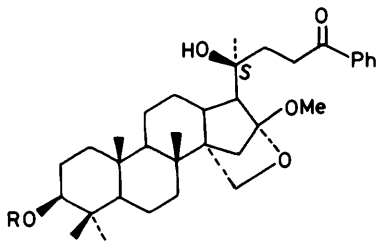
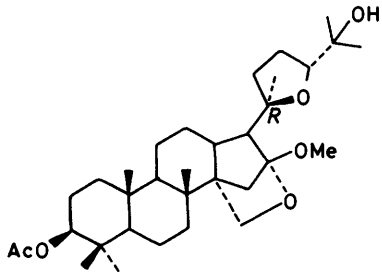


(21) R = H
(22) R = Ac



(23) R = H
(24) R = Ac



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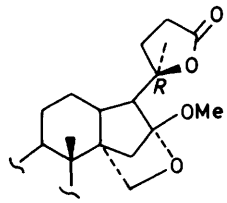

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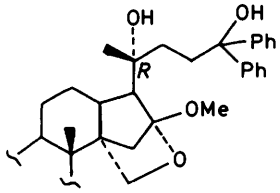

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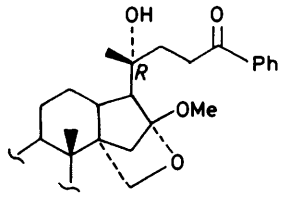

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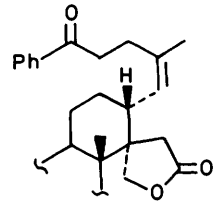

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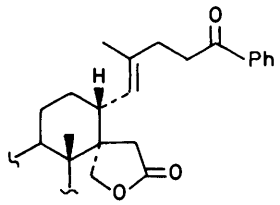

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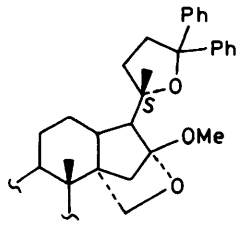

(31)

with Me_4Si as internal reference. I.r. spectra were measured on a Perkin-Elmer 257 spectrophotometer, and u.v. spectra on a Perkin-Elmer 402 spectrophotometer. Mass spectra were recorded with Hewlett-Packard 5930A and VG Micromass ZAB-2F spectrometers. Gas-liquid chromatography was performed with a Hewlett-Packard 5710A instrument. T.l.c. was performed on Merck silica gel 60 and column chromatography on Merck silica gel (0.063—0.2 mm). The spray reagent for t.l.c. was H_2SO_4–AcOH–H_2O (1 : 20 : 4).

Acid Treatment of Trevoagenin A (1).—To a solution of trevoagenin A (1) (1 g) in ethanol (22 ml) was added 6.5M aqueous hydrochloric acid (13 ml) and the mixture was refluxed for 5 h. After addition of water, the solution was neutralized with aqueous $NaHCO_3$ and was extracted with ethyl acetate. The extract was washed with water, dried (Na_2SO_4), and evaporated to dryness under reduced pressure. Column chromatography of the residue [benzene–ethyl acetate (85 : 15) as eluant] afforded 3β-*hydroxy*-24-*oxo*-16,17-*seco*-5α-*dammar*-17(20)E-*eno*-16,30-*lactone* (5) (0.38 g), its 17(20)Z-*isomer* (7) (0.12 g), and a small amount of (20*R*,24*R*)-3β,25-dihydroxy-15α,30-cyclo-20,24-epoxy-5α-dammaran-16-one (9) (0.02 g).[3b]

Compound (5) was crystallized from methanol, m.p. 212—214 °C; $[\alpha]_D$ 0° (*c*, 0.15); *m/z* 472.3552 (100%, $C_{30}H_{48}O_4$ = 472.3552, M^+), 454.3422 (15, $C_{30}H_{46}O_3$ = 454.3447, $M^+ - H_2O$), 429.3015 (6, $C_{27}H_{41}O_4$ = 429.3005, $M^+ - Pr^i$), 411.2924 (7, $C_{27}H_{39}O_3$ = 411.2899, $M^+ - Pr^i - H_2O$), 387.2860 (3, $C_{25}H_{39}O_3$ = 387.2899, [e; R = H]), 369.2809 (14, $C_{25}H_{37}O_2$ = 369.2794, [e; R = H] − H_2O), 207.1722 (15, $C_{14}H_{23}O$ = 207.1748, [a; R = H]), 203 (7, [b]), 189.1592 (26, $C_{14}H_{21}$ = 189.1643, [a; R = H] − H_2O), 179.1377 (20, $C_{12}H_{19}O$ = 179.1436, [f; R = Pr^i]), 139.1101 (36, $C_9H_{15}O$ = 139.1123, [d; R = Pr^i]), and 71.0524 (80, C_4H_7O = 71.0497, [c; R = Pr^i]); $\nu_{max.}$ (KBr) 3 555, 1 765, and 1 700 cm^{-1}; δ_H (C_6D_6) 0.63, 0.66, 0.79, and 1.03 (total 12 H, 4 × s, 4 × Me), 1.02 (6 H, d, *J* 7 Hz, 25-Me_2), 1.51 (3 H, br s, $w_{\frac{1}{2}}$ 3 Hz, 20-Me), 3.05 (1 H, m, $w_{\frac{1}{2}}$ 18 Hz, 3α-H), 3.93 (2 H, br s, $w_{\frac{1}{2}}$ 4 Hz, 30-H_2), and 4.95 (1 H, br d, *J* 10 Hz, 17-H); δ_C 213.9 (C-24), 177.1 (C-16), 137.9 (C-20), 124.8 (C-17), 78.5 (C-3), 69.5 (C-30), 55.2 (C-5), 52.9 (C-9), 51.7 (C-14), 40.9 (C-8), 39.9 (C-25), 38.9 (C-4), 38.8 (C-1), 38.8 (C-13), 38.6 (C-23), 37.2 (C-10), 34.6 (C-15), 34.6 (C-7), 33.8 (C-22), 29.1 (C-12), 28.1 (C-28), 27.3 (C-2), 20.1 (C-11), 18.3 (C-6), 18.3 (C-26 and C-27), 18.0 (C-18), 17.0 (C-21), 16.0 (C-19), and 15.5 p.p.m. (C-29) (Found: C, 76.3; H, 10.4. $C_{30}H_{48}O_4$ requires C, 76.2, H, 10.2%).

Acetylation of compound (5) with acetic anhydride and pyridine at room temperature gave a *monoacetate* (6) which was crystallized from methanol, m.p. 156—158 °C; $[\alpha]_D$ +7° (*c*, 0.19); $\nu_{max.}$ 1 770, 1 730, and 1 710 cm^{-1} (Found: C, 74.4; H, 9.8. $C_{32}H_{50}O_5$ requires C, 74.7; H, 9.8%).

Compound (7) was crystallized from methanol, m.p. 203—205 °C; $[\alpha]_D$ −13° (*c*, 0.21); *m/z* 472 (100%, M^+), 454 (15, $M^+ - H_2O$), 429 (6, $M^+ - Pr^i$), 411 (7, $M^+ - Pr^i - H_2O$), 387 (3, [e; R = H]), 369 (14, [e; R = H] − H_2O), 207 (15, [a; R = H]), 203 (7, [*b*]), 189 (26, [a; R = H] − H_2O), 179 (20, [f; R = Pr^i]), 139 (36, [d; R = Pr^i]), and 71 (80, [c; R = Pr^i]); $\nu_{max.}$ (KBr) 3 505, 1 765, and 1 700 cm^{-1}; δ_H (C_6D_6) 0.61, 0.77, 0.77, and 1.02 (total 12 H, 4 × s, 4 × Me), 0.90 and 0.93 (total 6 H, 2 × d, each *J* 7 Hz, together 25-Me_2), 1.58 (3 H, br s, $w_{\frac{1}{2}}$ 3 Hz, 20-Me), 3.98 (2 H, br s, $w_{\frac{1}{2}}$ 4 Hz, 30-H_2), and 4.95 (1 H, br d, *J* 10 Hz, 17-H); δ_C 213.6 (C-24), 177.2 (C-16), 137.6 (C-20), 125.9 (C-17), 78.5 (C-3), 69.5 (C-30), 55.1 (C-5), 52.8 (C-9), 51.4 (C-14), 41.0 (C-8), 39.9 (C-25), 38.9 (C-4), 38.6 (C-1), 38.4 (C-23), 38.2 (C-13), 37.2 (C-10), 34.6 (C-7 or C-15), 34.5 (C-15 or C-7), 29.5 (C-12), 28.0 (C-28), 27.2 (C-2), 26.2 (C-26), 23.4 (C-21), 20.0 (C-11), 18.2 (C-26 and C-27), 18.2 (C-6), 18.0 (C-18), 15.9 (C-19), and 15.4 p.p.m. (C-29) (Found: C, 76.2; H, 10.5. $C_{30}H_{48}O_4$ requires C, 76.2; H, 10.2%).

Acetylation of compound (7) gave a monoacetate (8), amorphous, $[\alpha]_D$ −5° (*c*, 0.3); $\nu_{max.}$ ($CHCl_3$) 1 760, 1 720, and 1 710 cm^{-1}.

Compound (9) had i.r. and ^1H n.m.r. spectra superimposable with those previously described.[3]

Acid Treatment of Trevoagenin B (4).—A solution of trevoagenin B (4) in ethanol was refluxed with aqueous hydrochloric acid as described above for trevoagenin A (1). The same products in the same yields were obtained.

Ozonolysis of 3β-*Acetoxy*-24-*oxo*-16,17-*seco*-5α-*dammar*-17(20)E-*eno*-16,30-*lactone* (6).—A stream of ozone was introduced into a solution of compound (6) (0.2 g) in chloroform (30 ml) at −78 °C until the blue colour persisted for more than 2 min. The excess of ozone was removed by bubbling oxygen through the solution at −78 °C. The mixture was allowed to warm to room temperature and the solvent was evaporated off under reduced pressure. The residue was dissolved in acetone and treated with an excess of Jones reagent at room temperature. The excess of reagent was destroyed with methanol and the mixture was then poured into water and extracted with diethyl ether. The extract was washed thoroughly with aqueous $NaHCO_3$, dried (Na_2SO_4), and concentrated under reduced pressure. The residue (50 mg) was distilled (bulb-to-bulb) to give 6-methylheptane-2,5-dione (12)[7] (25 mg). The combined $NaHCO_3$ aqueous washings were acidified with aqueous hydrochloric acid and extracted with diethyl ether. After being washed with saturated aqueous NaCl the extract was dried (Na_2SO_4) and evaporated to dryness under reduced pressure. The crude residue, compound (10), was methylated with an excess of an ethereal solution of diazomethane and purified by column chromatography [benzene–ethyl acetate (95 : 5) as eluant] to give the methyl ester (11) (0.105 g).

The dione (12)[7] [$\nu_{max.}$ ($CHCl_3$) 1 700 cm^{-1}; δ_H (CCl_4) 1.07 (6 H, d, *J* 7 Hz, 6-Me_2), 2.11 (3 H, s, 1-H_3), 2.58 (4 H, s, 3- and 4-H_2), and 2.58 (1 H, m, $w_{\frac{1}{2}}$ 30 Hz, 6-H); *m/z* 142 (2%, M^+), 99 (100), 45 (65), and 71 (33)] was identical with an authentic sample [i.r. and ^1H n.m.r. spectra, and g.l.c. (QF-1; 80 °C and OV-1; 100 °C)] prepared from 6-methylhept-5-en-2-one by hydroboration and oxidation with Jones reagent.

The methyl ester (11) was crystallized from acetone–n-hexane, m.p. 213—215 °C; $[\alpha]_D$ −2° (*c*, 0.2) (lit.,[8] m.p. 213—214 °C; $[\alpha]_D$ 0°); $\nu_{max.}$ (KBr) 1 780, 1 730, and 1 240 cm^{-1} (Found: C, 69.4; H, 9.05. Calc. for $C_{25}H_{38}O_6$: C, 69.1; H, 8.8%). Compound (11) was identical (i.r. and ^1H n.m.r. spectra, m.p. and mixed m.p., t.l.c.) with an authentic reference sample.

Ozonolysis of 3β-*Acetoxy*-24-*oxo*-16,17-*seco*-5α-*dammar*-17(20)Z-*eno*-16,30-*lactone* (8).—The methyl ester (11) was also obtained in identical yield from compound (8) by ozonolysis, oxidation with Jones reagent, and methylation as described above for the 17(20)*E*-isomer (6).

(20S)-3β-*Acetoxy*-16-*methoxy*-16α,30-*epoxy*-24,25,26,27-*tetranor*-5α-*dammarane*-23,20-*carbolactone* (20).—To a solution of trevoagenin B (4) (1 g) in dry methanol (60 ml) was added a saturated solution of hydrogen chloride in methanol (0.5 ml) and the mixture was kept at room temperature for 2 d, then diluted with water and extracted with chloroform. The extract was washed in turn with aqueous $NaHCO_3$ and water, and then evaporated to dryness. The crude methyl acetal (19) (0.95 g), without purification, was acetylated and then oxidized with Jones reagent in acetone. The usual work-up and column chromatography purification gave the *lactone* (20) (570 mg) which was crystallized from n-hexane, m.p. 270—272 °C; $[\alpha]_D$ −27° (*c*, 0.27); *m/z* 502.3303 (18%, $C_{30}H_{46}O_6$ = 502.3294, M^+), 458.3403 (30, $C_{29}H_{46}O_4$ = 458.3396, $M^+ - CO_2$), 443.3147 (14, $C_{28}H_{43}O_4$ = 443.3161, $M^+ - CO_2 - Me$), 403.2805 (32, $C_{25}H_{39}O_4$ = 403.2848, [g; R = Ac]), 401.2694 (11, $C_{25}H_{37}O_4$ = 401.2692), 237.1061 (9, $C_{13}H_{17}O_4$ = 237.1126), 189.1624 (17, $C_{14}H_{21}$ = 189.1644, [a; R = Ac] − AcOH), and 99.0463 (100, $C_5H_7O_2$ = 99.0446, [h; R = O]); $\nu_{max.}$ ($CHCl_3$) 1 760 and 1 725 cm^{-1} (Found: C, 71.5; H, 9.5. $C_{30}H_{46}O_6$ requires C, 71.7; H, 9.2%).

Reaction of the Lactone (20) *with Phenylmagnesium Bromide*.—To a cold (−20 °C) solution of compound (20) (0.8 g, 1.6 mmol) in dry benzene was added, under nitrogen, a solution of phenylmagnesium bromide (8 mmol) in diethyl ether. After being stirred for 3 h, the mixture was poured into aqueous H_2SO_4 (10%) and was extracted with ethyl acetate. The extracts were dried (Na_2SO_4) and concentrated under reduced pressure, and the residue was chromatographed [benzene–ethyl acetate (75 : 25) as eluant] to give saponified starting material (20; 3β-OH) (0.3 g), the *diphenyl carbinol* (21) (0.12 g), and the *phenyl ketone* (23) that was purified as its *acetyl derivative* (24) (30 mg).

Compound (21) was crystallized from n-hexane, m.p. 215—217 °C; *m/z* 616.4092 (2%, $C_{40}H_{56}O_5$ = 616.4128, M^+), 598.4001 (11, $C_{40}H_{54}O_4$ = 598.4021, $M^+ - H_2O$), 580.3865 (2, $C_{40}H_{52}O_3$ = 580.3917, $M^+ - 2H_2O$), 521.3613 (6, $C_{34}H_{49}O_4$ = 521.3630, $M^+ - Ph - H_2O$), 405.2984 (26, $C_{25}H_{41}O_4$ = 405.3005), 362.2743 (95, $C_{23}H_{38}O_3$ = 362.2821, [g; R = H] + H), 361.2733 (96, $C_{23}H_{37}O_3$ = 361.2742, [g; R = H]), 237.1272 (100, $C_{17}H_{17}O$ = 237.1279), 219.1221 (23, $C_{17}H_{15}$ = 219.1174), 207.1654 (17, $C_{14}H_{23}O$ = 207.1749, [a; R = H]), 193.1086 (29, $C_{15}H_{13}$ = 193.1017), 183.0836 (45, $C_{13}H_{11}O$ = 183.0810), 180.0951 (22, $C_{14}H_{12}$ = 180.0939), 167.0842 (17, $C_{13}H_{11}$ = 167.0860), 125.0621 (50, $C_7H_9O_2$ = 125.0602), 105.0352 (77, C_7H_5O = 105.0341), and 99.0465 (33, $C_5H_7O_2$ = 99.0446); $\nu_{max.}$ (KBr) 3 460 cm^{-1}.

Compound (24) was crystallized from acetone, m.p. 195—197 °C; *m/z* 580.3777 (1%, $C_{36}H_{52}O_6$ = 580.3764, M^+), 562.3685 (25, $C_{36}H_{50}O_5$ = 562.3658, $M^+ - H_2O$), 403.2822 (56, $C_{25}H_{39}O_4$ = 403.2848, [g; R = Ac]), 401.2689 (27, $C_{25}H_{37}O_4$ = 401.2691), 178.1006 (15, $C_{11}H_{14}O_2$ = 178.0994), 125.0630 (19, $C_7H_9O_2$ = 125.0603), 105.0387 (100, C_7H_5O = 105.0340, [c; R = Ph]), and 99.0446 (37, $C_5H_7O_2$ = 99.0446); $\nu_{max.}$ ($CHCl_3$) 3 490, 1 720, and 1 680 cm^{-1}.

(20R)-3β-*Acetoxy*-16-*methoxy*-16α,30-*epoxy*-24,25,26,27-*tetranor*-5α-*dammarane*-23,20-*carbolactone* (26).—The acetate of trevoagenin A 16,30-methyl acetal (25)[3b] (0.85 g) in acetone (50 ml) was oxidized with Jones reagent. The usual work-up gave the *title lactone* (26) which was crystallized from n-hexane, m.p. 231—233 °C; $[\alpha]_D$ −7° (*c*, 0.19); $\nu_{max.}$ ($CHCl_3$) 1 760 and 1 730 cm^{-1} (Found: C, 71.4; H, 9.0. $C_{30}H_{46}O_6$ requires C, 71.7; H, 9.2%).

Reaction of the Lactone (26) *with Phenylmagnesium Bromide*.—The lactone (26) (0.7 g, 1.4 mmol) was treated with a solution of phenylmagnesium bromide (7 mmol) in diethyl ether as previously described for compound (20) to give, after acetylation and chromatography, the starting lactone (26) (0.25 g; main product) and a mixture (0.18 g) of the diphenylcarbinol (27) and the phenyl ketone (28). After repeated chromatography of this mixture compound (27) could not be isolated and compound (28) was still contaminated with a small amount (*ca.* 10%, as detected by ^1H n.m.r.) of (27). The impure compound (28) could not be crystallized; $\nu_{max.}$ (KBr) 3 490, 1 720, and 1 680 cm^{-1}; δ_H 0.82 (9 H, s, 4α-, 4β-, and 10-Me), 1.03 (3 H, s, 8-Me), 1.16 (3 H, s, 20-Me), 2.01 (3 H, s, OAc), 3.46 (3 H, s, OMe), 3.95 (2 H, br s, $w_{\frac{1}{2}}$ 5 Hz, 30-H_2), 4.45 (1 H, m, $w_{\frac{1}{2}}$ 18 Hz, 3α-H), and 7.4 and 8.0 (total 5 H, m, Ph).

Treatment of the Phenyl Ketone (24) *with Iodine*.—A solution of compound (24) (30 mg) in toluene (5 ml) containing iodine (20 mg) was refluxed for 8 h under nitrogen. The solution was washed with dilute aqueous sodium thiosulphate, dried (Na_2SO_4), and evaporated to dryness under reduced pressure. The residue was purified by column chromatography [benzene–ethyl acetate (85 : 15) as eluant] to give the *lactone* (29) (15 mg) which crystallized from methanol, m.p. 198—200 °C; *m/z* 548.3509 (50%, $C_{35}H_{48}O_5$ = 548.3501, M^+), 488 (9, M^+ − AcOH), 429 (4, [e; R = Ac]), 387 (2), 369 (5), 213 (5, [f; R = Ph]), 173 (12, [d; R = Ph]), 105 (100, [c; R = Ph]), and 77 (20); $\lambda_{max.}$ (EtOH) 242 nm (ε 12 400); $\nu_{max.}$ ($CHCl_3$) 1 770, 1 725, and 1 685 cm^{-1}; δ_H (C_6D_6) 0.57, 0.64, 0.83, and 0.88 (total 12 H, 4 × s, 4α,- 4β-, 8-, and 10-Me), 1.61 (3 H, s, $w_{\frac{1}{2}}$ 3 Hz, 20-Me), 1.78 (3 H, s, OAc), 4.02 (2 H, s, 30-H_2), 4.65 (1 H, m, $w_{\frac{1}{2}}$ 18 Hz, 3α-H), and 5.03 (1 H, br d, *J* 9 Hz, 17-H) (Found: C, 76.3; H, 9.0. $C_{35}H_{48}O_5$ requires C, 76.6; H, 8.8%).

Treatment of the Phenyl Ketone (28) *with Iodine*.—A solution of compound (28) (70 mg), contaminated with *ca.* 10% of the diphenylcarbinol (27), in toluene (5 ml) containing iodine (50 mg) was refluxed for 8 h under nitrogen as previously described for compound (24). After the usual work-up, the residue was purified by column chromatography [benzene–ethyl acetate (85 : 15) as eluant] to give the *lactone* (30) (30 mg), amorphous; *m/z* 548.3513 (40%, $C_{35}H_{48}O_5$ = 548.3501, M^+), 488 (5, M^+ − AcOH), 429 (5, [e; R = Ac]), 387 (2), 369 (4), 213 (7, [f; R = Ph]), 173 (10, [d; R = Ph]), 105 (100, [c; R = Ph]), and 77 (30); δ_H (C_6D_6) 0.57, 0.61, 0.83, and 0.87 (total 12 H, 4 × s, 4α-, 4β-, 8-, and 10-Me), 1.52 (3 H, s, $w_{\frac{1}{2}}$ 3 Hz, 20-Me), 1.77 (3 H, s, OAc), 3.97 (2 H, s, 30-H_2), 4.65 (1 H, m, $w_{\frac{1}{2}}$ 18 Hz, 3α-H), and 4.97 (1 H, br d, *J* 9 Hz, 17-H).

Treatment of the Diphenylcarbinol (22) *with Iodine*.—A solution of compound (22) (70 mg) and iodine (45 mg) in toluene (10 ml) was refluxed for 8 h under nitrogen as previously described for compound (24). After the usual work-up, the residue was chromatographed [benzene–ethyl acetate (85 : 15) as eluant] to give *compound* (31) (48 mg), which was crystallized from methanol, m.p. 240—243 °C; *m/z* 640 (5%, M^+), 581 (4), 458 (4), 447 (4), 403 (100, [g; R = Ac]), 343 (6, [g; R = Ac] − AcOH), and 237 (70, [h; R = Ph_2]); $\nu_{max.}$ ($CHCl_3$) 1 720 cm^{-1}.

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