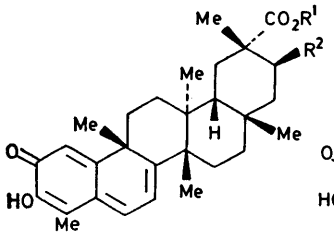
New Triterpene Quinone-methides from Hippocrateaceae

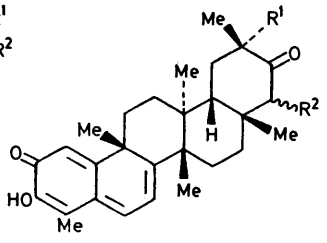
By **Franco Delle Monache, Giovanni B. Marini-Bettòlo,*** and **Massimo Pomponi**, Centro Chimica dei Recettori del C.N.R. presso Università Cattolica del S. Cuore, Via della Pineta Sacchetti 644, Roma, Italy
José F. de Méllo and **O. Gonçalves de Lima**, Instituto de Antibioticos, Universidade Federal de Pernambuco, 50,000 Recife, Brazil
Ronald H. Thomson, Department of Chemistry, University of Aberdeen, Old Aberdeen AB9 2UE, Scotland

In addition to pristimerin and tingenone, the new pigments 21-hydroxypristimerin and hydroxypristimerinene have been isolated from an unidentified *Salacia* sp., while pristimerinene, also new, was found in *Prionostemma aspera*.

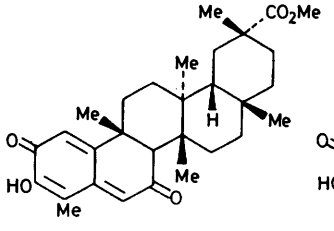
EIGHT triterpene quinone-methides have been identified so far in various genera of the closely related families Celastraceae and Hippocrateaceae. These are celastrol (1a),[1] pristimerin (1b),[1-3] tingenone (2a),[3-5] 20-hydroxytingenone (2b),[4] 22-hydroxytingenone (2c),[6] dispermoquinone (3),[7] iguesterin (4),[8] and a quinone-methide from *Salacia macrosperma* for which structure (5) has been proposed.[9] As several of these compounds show antitumour activity,[10] and tingenone is used clinically in Brazil for the treatment of skin cancer,[11] we have continued our search for quinone-methides and report here three more pigments found in *Prionostemma aspera* (Hippocrateaceae) and an unidentified *Salacia* sp. (Hippocrateaceae). Both plants were collected in north-east Brazil.



(1a) $R^1 = R^2 = H$
(1b) $R^1 = Me, R^2 = H$
(1c) $R^1 = Me, R^2 = OH$



(2a) $R^1 = R^2 = H$
(2b) $R^1 = OH, R^2 = H$
(2c) $R^1 = H, R^2 = OH$



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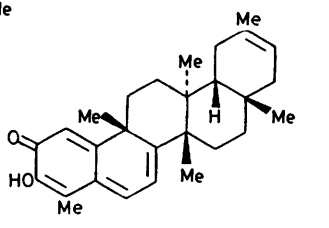

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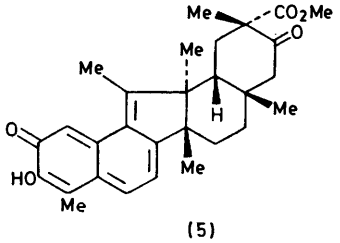

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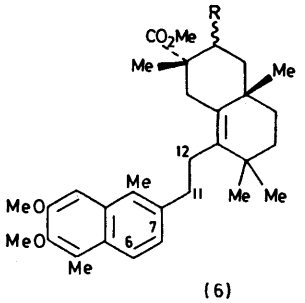
RESULTS AND DISCUSSION

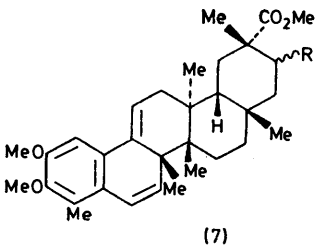
21-Hydroxypristimerin (1c).—Extraction of the root bark of an unidentified *Salacia* sp. yielded pristimerin (1b), tingenone (2a), and a new orange pigment, $C_{30}H_{40}O_5$, which was clearly a hydroxypristimerin. The u.v. spectrum is virtually identical to that of pristimerin (1b) as is the low-field n.m.r. spectrum. At high field the chemical shifts of the seven methyl singlets also correspond closely, and in addition there are signals at δ 4.0 (1 H, dd, *J* 4.5 and 11.5 Hz) and 5.3 (1 H, s, exchanges with D_2O) attributable to a secondary alcohol function. In the i.r. the new pigment shows $\nu_{max.}$ (CCl_4) 3 380, 1 730, and 1 600 cm^{-1}, very similar to pristimerin, while the mass spectra of both compounds show the same major ions (different intensities) with the base peak at *m/e* 201.

On heating in methanol containing a little 2N sulphuric acid the hydroxypristimerin rearranged in the same manner as pristimerin [1,2,12] and related compounds [5,6] to give hydroxyisopristimerin-II and hydroxyisopristimerin-III which were isolated as their dimethyl ethers (6; R = OH) and (7; R = OH), respectively. The structures (and nomenclature) are based on the close similarity of their spectroscopic properties with those [2,6,13] of isopristimerin-II and -III and their dimethyl ethers (6 and 7; R = H). To obtain evidence for the position of the alcoholic hydroxy-group, compound (6) was subjected to a Sarrett [14] oxidation, and the product (M^+, 506) was hydrolysed in aqueous methanolic sodium hydroxide. On acidification and heating, carbon dioxide was liberated leaving a product whose mass spectrum was consistent with di-*O*-methyl isotingenone-II (8) [M^+, 448 (25) and 229 (100)]. Lack of material precluded repetition of this experiment on a larger scale. On this basis the oxidation product was a β-ketoester, and on the reasonable assumption that the methyl ester function in the natural pigment occupies the normal C-20 position it follows that the hydroxyl group in (6) must be at C-21, *i.e.* (6; R = OH). Accordingly the new pigment is 21-hydroxypristimerin (1c), in which the hydroxyl in ring E is equatorial. Inspection of a Dreiding model shows that H-21_{ax} is *trans*-coplanar with H-22_{ax}, consistent with a coupling constant of 11.5 Hz.

Oxidation of di-*O*-methyl hydroxy-isopristimerin-III (7; R = OH) under acidic conditions (Jones reagent [15]) did not give the corresponding ketoester but rather a



(6)



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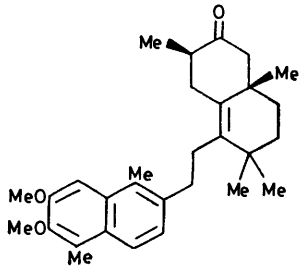

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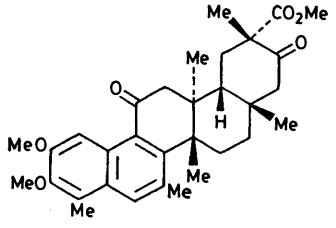
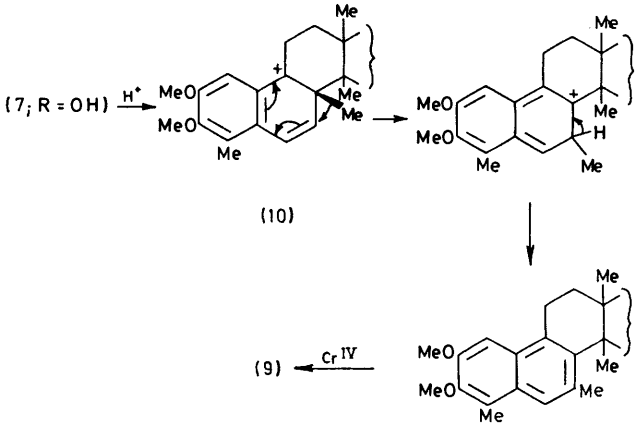


(9)

diketoester, $C_{32}H_{40}O_6$, which we regard as having the structure (9). The compound has three carbonyl groups (ν_{CO} 1 720, 1 695, and 1 660 cm^{-1}) and is aromatic ($\lambda_{max.}$ 280 and 331 nm). In the n.m.r. spectrum there are singlets for two aromatic protons (δ 8.55 and 7.15), two aromatic methyl (δ 2.74 and 2.60), three *O*-methyl and four tertiary methyl groups. Unresolved signals (4 H) in the region δ 2.57—2.15 can be attributed to methylene protons α to carbonyl. The lower-field aromatic proton signal at δ 8.55 in the n.m.r. spectrum of (9) we ascribe to H-1, which is deshielded [16] by the C-11 carbonyl function [*cf.* δ 7.20 for H-1 in (6)]. A possible mechanism for the rearrangement involved in the conversion of (7; R = OH) into (9) is shown in Scheme 1. A carbonium ion corresponding to (10) is a key intermediate in the rearrangement [2] of pristimerin and isopristimerin-III to isopristimerin-I and -II, and Scheme 1 illustrates yet another transformation of this versatile type of carbonium ion.

Pristimerinene (11; R = H).—Extraction of the wood of *Prionostemma aspera* yielded, besides friedelin [17] and 3,12-diketofriedelane,[17] the pigments tingenone, pristimerin, and pristimerinene. Pristimerinene, $C_{30}H_{38}O_4$, a red amorphous solid, is generally similar to pristimerin but contains two hydrogen atoms less, and there are small differences in the spectra of the chromophore. For example $\lambda_{max.}$ falls at 446 nm (pristimerin 422 nm), and the vinyl proton signals in the n.m.r. spectrum appear at δ 7.10 (1 H, dd, *J* 1 and 7 Hz), 6.48 (1 H, d, *J* 1 Hz), and 6.10 (1 H, d, *J* 7 Hz) compared to δ 6.95 (H-6, dd, *J* 1.5 and 7 Hz), 6.45 (H-1, d, *J* 1.5 Hz), and 6.25 (H-7, d, *J* 7 Hz) for pristimerin. The quinonoid methyl group resonates at δ 2.23 (pristimerin 2.17), and in addition there are singlets for four tertiary methyls in the region δ 1.23—0.80, a vinylic methyl at 1.70, an *O*-methyl at 3.63, and a two-proton signal at 2.1—1.9 assigned to an allylic methylene group. The i.r. spectrum ($\nu_{max.}$ 3 400, 1 715, and 1 590 cm^{-1}) is similar to that of pristimerin but the conjugated carbonyl band at 1 590 cm^{-1} is even more intense, consistent with a more extended conjugated system.[18] All these spectroscopic data can be accommodated by structure (11; R = H) on the assumption that rings D and E are the same as those of pristimerin. Further support for the presence of a double bond in ring C comes from the mass spectrum, where the most important fragment ion at *m/e* 265 (20%), $[C_{18}H_{17}O_2]^+$, appears to arise by normal friedelane cleavage of ring D with hydrogen transfer to give (12) (a naphthotropylium ion structure can also be written).

A quinone-methide of structure (11) having a methylene group at the carbon terminus would be expected to



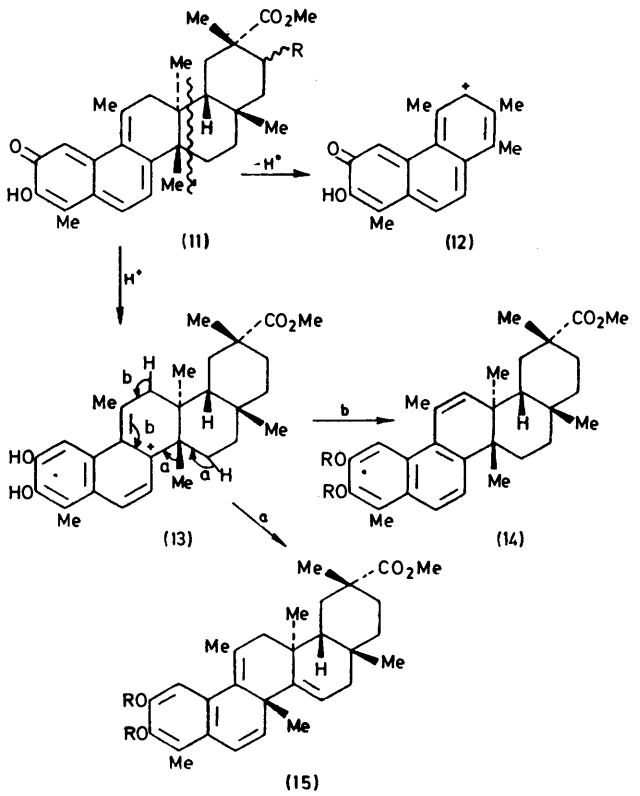
Scheme 1

aromatise easily under acid conditions to give the naphthalene (14; R = H). Accordingly pristimerinene was subjected to the acidic conditions used for the rearrangement of 21-hydroxypristimerin. The initial dark red acidic solution showed $\lambda_{max.}$ 470 nm which gradually changed to pale brown ($\lambda_{max.}$ 308 nm) during 30 min as the carbonium ion (13) rearranged. Two isomeric products were formed which were isolated as their dimethyl ethers. The major product was not the expected (14; R = Me) but instead (15; R = Me) (di-*O*-methyl isopristimerinene-III) showing excellent spectroscopic agreement with isopristimerin-III (15; R = H,

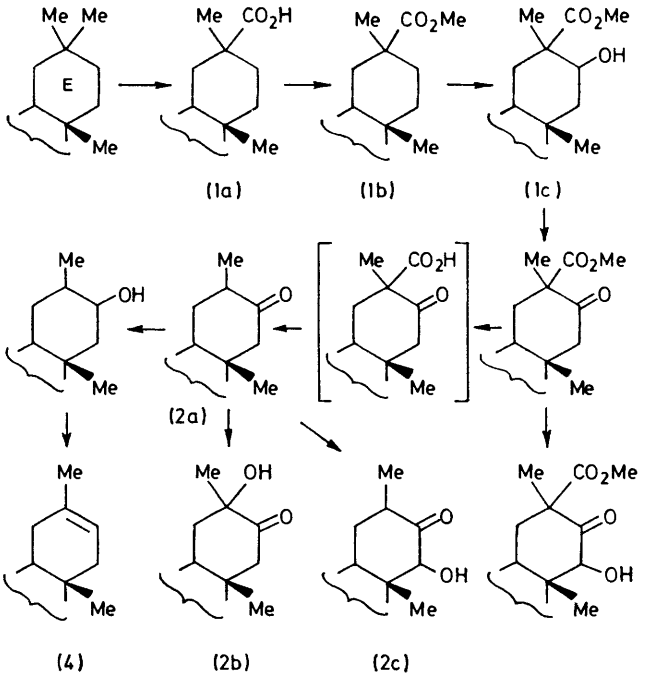
no double bond in ring D) and its dimethyl ether.[2] In particular it showed intense u.v. absorption at 256 and 309 nm (log ε 4.6 and 4.0) appropriate to an *o*-divinylbenzene not conjugated to the remaining double bond. The n.m.r. spectrum showed singlets for four tertiary methyls, a vinylic methyl, an aromatic methyl, and three *O*-methyl groups, an aromatic proton signal at δ 6.7, an AB system centred at δ 6.40 and 6.33 for H-6 and H-7, and a multiplet (4 H) for two allylic methylene groups at δ 2.1—1.9. A broad one-proton signal at δ 5.40 is attributed to H-15.

The minor product from the acid-catalysed rearrangement of pristimerinene, after methylation, was probably (14; R = Me). It had $\lambda_{max.}$ 239, 288, and 332 (sh) nm, and in its n.m.r. spectrum aromatic proton, methyl, and methoxy-signals in good agreement with those of (6) and (8). In addition the spectrum includes a third methoxy-singlet, four tertiary methyls, and a broad vinylic methyl signal at δ 1.83 coupled to a vinyl proton (C-12) at δ 5.33.

Hydroxypristimerinene.—This red amorphous compound, $C_{30}H_{38}O_5$, obtained from the *Salacia* sp., corresponds to pristimerinene with one oxygen atom more. The u.v. spectra of the two compounds are superimposable, the n.m.r. are closely similar, indeed identical at low field, with the addition of broad one-proton signals at δ 4.0 and 5.25 arising from a secondary alcohol function in the $C_{30}H_{38}O_5$ compound. The mass spectra of both pigments are identical below *m/e* 300 indicating that all the major ions arise from the usual ring D



SCHEME 2



SCHEME 3

fragmentation. We conclude that this minor pigment is a hydroxypristimerinene, the hydroxyl group being in rings D or E.

Biogenesis.—Most of the triterpenoid pigments in this series vary only in ring E. Their formation can be explained by the sequential reactions outlined in Scheme 3 which draws attention to three likely, but as yet unknown, natural products. Obviously a similar series of pigments based on pristimerinene is also possible. We think it also possible that the *Salacia* quinone-methide (5) may be identical, rather than isomeric, with pristimerinene but unfortunately we have been unable to obtain a sample. The available evidence [9] for structure (5) is limited.

EXPERIMENTAL

N.m.r. spectra were run at 60 MHz in $CDCl_3$ solution.

Extraction of the Salacia *sp.**—The powdered root bark (1.5 kg) was extracted with hexane–ether (1 : 1). The red extract (4.8 g) was chromatographed on a silica gel column in benzene, followed by benzene–ethyl acetate (9 : 1) yielding pristimerin (300 mg) and tingenone (80 mg), and further elution with benzene–ethyl acetate (8 : 2) gave 21-hydroxypristimerin (130 mg), and hydroxypristimerinene (40 mg). 21-*Hydroxypristimerin* (1c), orange crystals, m.p. 238—241 °C (from methanol) (Found: C, 74.9; H, 8.5%; M^+, 480.2 876. $C_{30}H_{40}O_5$ requires C, 75.0; H, 8.3%; M^+, 480.2 866); $\lambda_{max.}$ (EtOH) 250 and 421 nm (log ε 3.94 and 4.08); $\nu_{max.}$ (CCl_4) 3 380, 1 730, and 1 600 cm^{-1}; δ 6.96 (1 H, dd, *J* 7.0 and 1.5 Hz, H-6), 6.46 (1 H, d, *J* 1.5 Hz, H-1), 6.23 (1 H, d, *J* 7 Hz, H-7), 5.30 (1 H, s, exchangeable with D_2O, OH), 4.00 (1 H, dd, *J* 11.5 and 4.5 Hz, H-21), 3.53 (3 H, s, CO_2Me), 2.20 (3 H, s, quinone-Me), 2.42 (3 H, s, Me),

* A voucher specimen, No. 4764, is deposited in the Herbarium of the Instituto de Antibioticos, Universidade Federal de Pernambuco, Recife, Brazil.

1.23 (3 H, s, Me), 1.22 (3 H, s, Me), 1.03 (3 H, s, Me), and 0.47 (3 H, s, Me); *m/e* 480 (27%), 241 (22), 227 (14), 215 (13), 202 (27), 201 (100), and 200 (12).

Rearrangement of 21-*Hydroxypristimerin*.—21-Hydroxypristimerin (120 mg) in methanol (30 ml) containing 2M sulphuric acid (0.5 ml) was heated under reflux for 30 min. The dark red solution changed to pale yellow. The methanol was evaporated under reduced pressure at room temperature, and the residue, diluted with ice–water, was extracted with ethyl acetate which was washed with water, dried (Na_2SO_4), and evaporated. The crude product in acetone (50 ml) was heated under reflux with dimethyl sulphate (2.0 ml) and anhydrous potassium carbonate. Standard work-up followed by chromatography on a silica gel column in benzene–ethyl acetate (9 : 1) yielded di-*O*-methyl 21-hydroxy-isopristimerin-II (30 mg) and di-*O*-methyl 21-hydroxy-isopristimerin-III (40 mg). *Di*-O-*methyl* 21-*hydroxyisopristimerin*-II (6; R = OH), m.p. 104—105 °C (from methanol) (Found: C, 75.3; H, 8.4%; M^+, 508. $C_{32}H_{44}O_5$ requires C, 75.6; H, 8.7%; M, 508); $\lambda_{max.}$ (MeOH) 233, 288, and 324 nm (log ε 4.56, 3.61, and 2.84); $\nu_{max.}$ (KBr) 3 450, 1 720, and 800 cm^{-1}; δ 7.63 (1 H, d, *J* 8 Hz, H-5), 7.17 (1 H, s, H-1), 7.13 (1 H, d, *J* 8 Hz, H-6), 3.96 (1 H, obscured by methoxy-resonance, H-21), 4.00 and 3.86 (each 3 H, s, OMe), 3.67 (3 H, s, CO_2Me), 7.0—7.2 (2 H, m, 11-H_2), 2.50 and 2.40 (each 3 H, s, Ar-*Me*), 7.9—8.1 (4 H, m, 12-H_2 and 19-H_2), and 1.33, 1.23, 1.12, and 1.00 (each 3 H, s, Me); *m/e* 508 (20%), 243 (60), and 229 (100). *Di*-O-*methyl* 21-*hydroxyisopristimerin*-III (7; R = OH), m.p. 200—203 °C (from hexane–dichloromethane) (Found: C, 75.3; H, 8.4%; M^+, 508. $C_{32}H_{44}O_5$ requires C, 75.6; H, 8.7%; *M*, 508); $\lambda_{max.}$ (MeOH) 254 and 298 nm (log ε 4.50 and 3.90); $\nu_{max.}$ (KBr) 3 500 and 1 725 cm^{-1}; δ 6.67 (1 H, s, H-1), 6.27 (2 H, dd, *J* 8.5 Hz, H-6 and H-7), 5.57 (1 H, m, H-11, X proton of AMX system, corresponding M proton (H-12) found by decoupling in C_6D_6 solution at 3.05, J_{AM} 13.8 Hz), 4.0 (1 H, dd, *J* 12.0 and 4.5 Hz, H-21), 3.83 and 3.70 (each 3 H, s, OMe), 3.50 (3 H, s, CO_2Me), 2.17 (3 H, s, Ar-*Me*), and 1.23 (3 H), 0.94 (6 H), and 0.75 (methyl groups).

Oxidation of Di-O-*methyl* 21-*Hydroxyisopristimerin*-II (6; R = OH).—The hydroxyester (20 mg) in pyridine (3 ml) was added to a yellow suspension of chromium trioxide (90 mg) in pyridine (1 ml). The reaction flask was stoppered and left overnight at room temperature. The mixture was poured into water and extracted with chloroform. Work-up in the usual way gave, after p.l.c. in benzene–ethyl acetate (9 : 1), an amorphous solid with an R_F greater than that of the starting material, an unchanged u.v. spectrum, and M^+ 506 (10%) with the base peak at *m/e* 229. This compound was hydrolysed by heating with 0.05M methanolic sodium hydroxide (30 ml) for 60 min. Acidification of the solution with 2M hydrochloric acid, and heating, liberated carbon dioxide which was passed through a solution of barium hydroxide and gave an intense white precipitate (a blank reaction was negative). Work-up of the organic mixture gave, after t.l.c. in benzene-ethyl acetate (9 : 1) a compound with *m/e* 448 (M^+, 25%), 243 (30), 229 (100), and 215 (10).

Oxidation of Di-O-*methyl* 21-*Hydroxyisopristimerin*-III (7; R = OH).—Jones reagent (0.5 ml) was added, dropwise, to a stirred solution of the hydroxyester (36 mg) in acetone (20 ml). Precipitation was observed. The mixture was then concentrated, diluted with water, and extracted with ether; the ether extract was washed with water, and dried (Na_2SO_4). Removal of the solvent under reduced pressure left a crystalline residue, which was recrystallised from acetone to give the *diketoester* (9) (17 mg), m.p. 170—171 °C (Found: C, 73.5; H, 8.0%; M^+, 520. $C_{32}H_{40}O_6$ requires C, 73.8; H, 7.7%; M, 520); $\lambda_{max.}$ ($CDCl_3$) 268, 280, and 331.5 (log ε 4.32, 4.42, and 3.90); $\lambda_{infl.}$ 252 and 332 (log ε 4.16 and 3.89); $\lambda_{min.}$ 273 and 295 (log ε 4.31 and 3.55); $\nu_{max.}$ ($CDCl_3$) 1 720, 1 695, and 1 660 cm^{-1}; δ 8.55 (1 H, s, H-1), 7.15 (1 H, s, H-6), 4.00, 3.80, and 3.55 (each 3 H, s, OMe), 2.74 and 2.60 (each 3 H, s, Ar-*Me*), 2.57—2.15 (4 H, m, H-12 and H-22), and 1.53, 1.43, 1.33, and 0.50 (each 3 H, s, Me).

Extraction of Prionostemma aspera.*—The powdered root bark (2 kg) was extracted with cold methanol. On concentration friedelin [17] and 3,12-diketofriedelane [17] deposited, and were removed by filtration. Evaporation of the filtrate left a residue which was treated with chloroform, and insoluble material [19] was filtered off. The filtrate was evaporated and the residue (12 g) treated with a little methanol. The insoluble material, mainly friedelin, 3,12-diketofriedelane, and hydroxy-3,12-diketofriedelanes,[17] was removed, and the soluble fraction was transferred to a column of silica gel. Elution with benzene and benzene–ethyl acetate (9 : 1 and 8 : 2) gave pristimerin (380 mg), tingenone (80 mg), and pristimerinene (180 mg). *Pristimerinene* (11; R = H), was a red amorphous solid (Found: C, 77.6; H, 8.5%; M^+, 462.2 769. $C_{30}H_{38}O_4$ requires C, 77.9; H, 8.2%; *M*, 462.2 769); $\lambda_{max.}$ (MeOH) 256 and 446 nm (log ε 4.05 and 4.09); $\nu_{max.}$ ($CHCl_3$) 3 400, 1 715, 1 650w, 1 640w, and 1 590 cm^{-1}; δ 7.10 (1 H, dd, *J* 7 and 1 Hz, H-6), 7.00 (1 H, s, exchangeable with D_2O, OH), 6.48 (1 H, d, *J* 1 Hz, H-1), 6.10 (1 H, d, *J* 7 Hz, H-7), 3.63 (3 H, s, CO_2Me), 2.23 (3 H, s, quinone-Me), 2.4 (1 H, br d, *J* 18 Hz, H-12) (the other allylic proton signal is not distinguishable), 1.70 (3 H, br s, =C–Me), 1.5—1.0 (9 H, m), 1.23 (6 H, s, Me), and 1.07 and 0.80 (each 3 H, s, Me); *m/e* 462 (M^+, 100%), 445 (15), 279 (16), ($C_{19}H_{19}O_2$ requires 279.1 384; found 279.1 380), 265 (20), ($C_{18}H_{17}O_2$ requires 265.1 228; found 265,1 227), 251 (18), and 239 (16) ($C_{16}H_{15}O_2$ requires 239.1 071; found 239.1 069). *Hydroxypristimerinene* was also a red amorphous solid (Found: C, 75.2; H, 8.3%; M^+, 478.2 718. $C_{30}H_{38}O_5$ requires C, 75.3; H, 7.9%; *M*, 478.2 719); $\lambda_{max.}$ (MeOH) 256 and 446 nm (log ε 4.05 and 4.09); $\nu_{max.}$ ($CHCl_3$) 3 500, 1 715, 1 650w, 1 640w, 1 590 cm^{-1}; δ 7.17 (1 H, dd, *J* 7 and 1 Hz, H-6), 6.53 (1 H, d, *J* 1 Hz, H-1), 6.16 (1 H, d, *J* 7 Hz, H-7), 5.25 (1 H, s, exchangeable with D_2O, OH), 4.00 (1 H, m, >C*H*(OH)), 3.73 (3 H, s, CO_2Me), 2.23 (3 H, s, quinone-Me), 2.0—1.8 (2 H, m, =C(Me)CH_2–), 1.73 (3 H, bs, =C–Me), and 1.39, 1.29, 1.13, and 0.75 (each 3 H, s, Me), 1 OH not observed; *m/e* 478 (M^+, 100%), 463 (10), 279 (20), 265 (15), 251 (15), and 239 (10).

Rearrangement of Pristimerinene.—Pristimerinene (120 mg) was refluxed for 30 min in methanol (30 ml) containing 2M sulphuric acid (0.5 ml). The dark red solution [$\lambda_{max.}$ (CH_3OH) 470 nm] changed to pale brown ($\lambda_{max.}$ 308 nm). After addition of ice, the methanol was removed *in vacuo* at room temperature, and the crude product was taken into ethyl acetate which was washed and dried (Na_2SO_4). On evaporation, the residue was heated under reflux in dry acetone (50 ml) with dimethyl sulphate (2 ml) and anhydrous potassium carbonate for 4 h. Working up in the usual way gave di-*O*-methyl isopristimerinene II (15 mg) and di-*O*-

* Voucher specimen No. 1374; see footnote on page 3129.

methyl-isopristimerinene-III (32 mg). *Di*-O-*methyl isopristimerinene*-II (14; R = Me) was an amorphous solid (Found: C, 78.7; H, 8.7%; M^+, 490.3 082. $C_{32}H_{42}O_4$ requires C, 78.4; H, 8.6%; M^+, 490.3 082); $\lambda_{max.}$ (MeOH) 239, 288, and 332(sh) nm (log ε 4.90, 4.00, and 3.40); $\nu_{max.}$ (KBr) 1 725, 1 615w, 1 600w, and 805 cm^{-1}; δ 7.50 (1 H, d, *J* 7 Hz, H-6), 7.18 (1 H, s, H-1), 2.97 (1 H, d, *J* 7 Hz, H-7), 5.33 (1 H, br s, $W_{\frac{1}{2}}$ 3 Hz, H-12), 3.97 and 3.83 (each 3 H, s, OMe), 3.65 (3 H, s, CO_2Me), 2.53 (3 H, s, Ar-*Me*), 1.83 (3 H, br s, $-C(Me)=CH-$), 1.20 (6 H, s, Me), and 1.13 and 0.85 (each 3 H, s, Me); *m/e* 490 (M^+, 85%), 475 (20), 293 (10), 278 (40), 250 (60), and 235 (100). *Di*-O-*methyl isopristimerinene*-III (15; R = Me) was an amorphous solid, (Found: C, 78.7; H, 8.7%; M^+, 490.3 082. $C_{32}H_{42}O_4$ requires C, 78.4; H, 8.6%; *M*, 490.3 082); $\lambda_{max.}$ ($CHCl_3$) 256 and 309 nm (log ε 4.6 and 4.0); $\nu_{max.}$ (KBr) 1 720, 1 630w, 1 590w, 830w, and 790 cm^{-1}; δ 6.70 (1 H, d, *J* 1 Hz, H-1), 6.40 (1 H, dd, *J* 9 and 1 Hz, H-6), 6.33 (1 H, d, *J* 9 Hz, H-7), 5.40 (1 H, br s, $W_{\frac{1}{2}}$ 10 Hz, H-15), 3.80 and 3.83 (each 3 H, s, OMe), 3.60 (3 H, s, CO_2Me), 3.00 (1 H, d, *J* 12 Hz, H-12), 2.23 (3 H, s, Ar-*Me*), 2.1—1.9 (3 H, m, $=C(Me)CH-$ and $=CH-CH_2-$), 1.80 (3 H, br s, $=C(Me)CH_2-$), and 1.17 (6 H, s, Me), 1.07 and 0.60 (each 3 H, s, Me); *m/e* 490 (M^+, 100%), 475 (56), 322 (10), 307 (18), 245 (41), 241 (15), 229 (22), 215 (10), and 187 (14).

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