Salaspermic Acid, a New Triterpene Acid from *Salacia macrosperma* Wight

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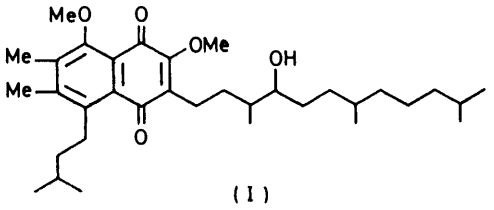
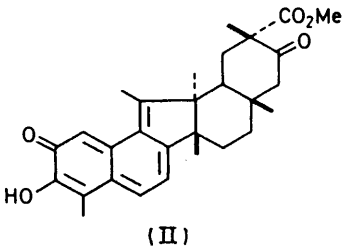
Salaspermic acid, a new triterpene acid isolated from *Salacia macrosperma* Wight, has been shown to be 24-hydroxy-3-oxofriedelan-29-oic acid hemiacetal (IIIa) on the basis of spectral and chemical properties. The structure has been confirmed by an *X*-ray study of compound (VII) obtained from the acid by a sequence involving the enlargement of ring E.

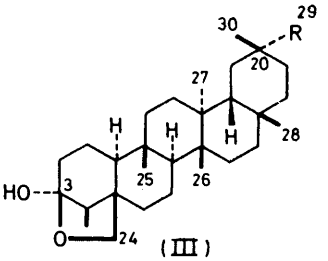
Salacia macrosperma Wight. (family Celastraceae) is a rambling shrub commonly found in Western peninsular India and has been used in native medicine under the name ' Saptarangi '. The water extracts of the leaves and roots have been reported to have hypoglycaemic activity.[1] From the root bark, Krishnan and Rangaswami [2] isolated three quinones, saptarangi quinones-A, -B, and -C, and proposed structure (I) for quinone-A. Later, Reddy *et al.*[3] reported the isolation of pristimerin, tingenone, hydroxytingenone, and a new compound, salacia quinone methide, for which they suggested structure (II).



(I)

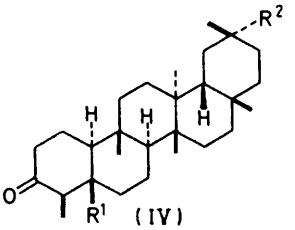


(II)



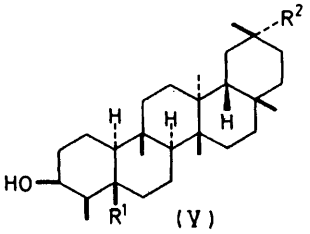
(III)

a; R = CO_2H
b; R = CO_2Me
c; R = CH_2OH



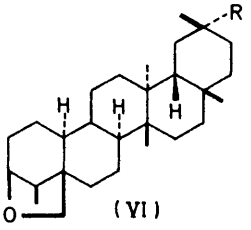
(IV)

a; R^1 = CH_2OCONH(COCCl$_3$), R^2 = CO_2Me
b; R^1 = CH_2OAc, R^2 = CO_2Me
c; R^1 = Me, R^2 = CO_2H
d; R^1 = CHO, R^2 = CO_2Me
e; R^1 = CO_2H, R^2 = CO_2Me
f; R^1 = R^2 = CHO



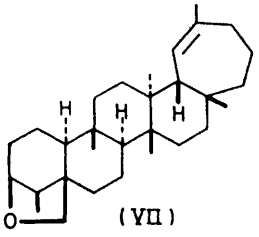
(V)

a; R^1 = CH_2OH, R^2 = CO_2Me
b; R^1 = R^2 = CH_2OH

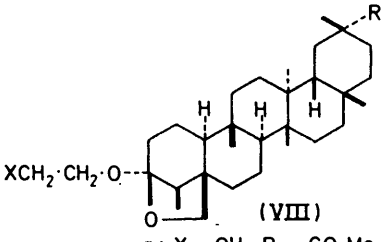


(VI)

a; R = CH_2OTs
b; R = Me
c; R = CH_2OH
d; R = CH_2OAc

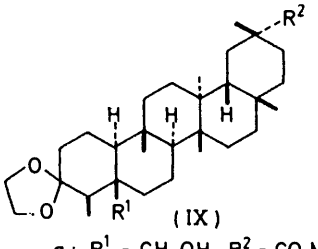


(VII)



(VIII)

a; X = OH, R = CO_2Me
b; X = OTs, R = CO_2Me
c; X = H, R = CH_2OH



(IX)

a; R^1 = CH_2OH, R^2 = CO_2Me
b; R^1 = CH_2OTs, R^2 = CO_2Me
c; R^1 = Me, R^2 = CH_2OH

The present paper deals with the isolation of a new triterpene acid, named salaspermic acid, from the stem-wood and root-wood of the plant and establishment of its structure as (IIIa).

The acid (IIIa), $C_{30}H_{48}O_4$, *m/e* 472 (M^+), m.p. 335°, reacts with diazomethane to yield a methyl ester (IIIb),

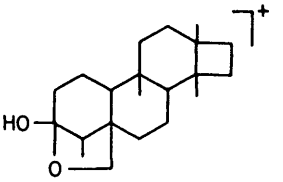
$C_{31}H_{50}O_4$, m.p. 300°. Examination of the n.m.r. spectrum of the ester reveals the presence of a methoxycarbonyl group, one hydroxy, five tertiary CMe, one secondary CMe, and two protons appearing as doublets at δ 4.17 and 3.58 (*J* 9 Hz) assigned to a cyclic O–CH_2–C(–C)(–C)–C group. The presence of a cyclic hemiacetal function in the ester was indicated by the changes brought about in its n.m.r. spectrum by addition of trichloroacetyl isocyanate [4] to the solution in the n.m.r. probe. This resulted in the isomerisation to the keto-alcohol structure followed by reaction of the alcoholic hydroxy with the isocyanate to yield the urethane (IVa). The new n.m.r. signals which appeared were at δ 8.29 (NH) and two doublets at δ 4.62 and 4.23 (*J* 11 Hz) assigned to the C(–C)(–C)–CH_2OCONHCOCCl_3 group. Acetylation of the ester (IIIb) with pyridine and acetic anhydride effected a similar conversion to yield the keto-acetate (IVb), whose i.r. spectrum showed three peaks at 1 740, 1 725, and 1 710 cm^{-1} due to the two ester groups and the ketone group respectively. The n.m.r. spectrum of (IVb) showed the C(–C)(–C)–CH_2–OAc as an AB quartet at δ 4.32 and 4.05 (*J* 13 Hz), very similar to the reported n.m.r. spectrum of 24-acetoxyfridelan-3-one.[5]

The n.m.r. spectrum of the ester (IIIb) and the absence of unsaturation in it indicated that it had a friedelane skeleton. The related plants *Salacia prinoides* DC [6] and *S. fruticosa* Heyne [7] have also been found to contain friedelane-type compounds. The ester (IIIb) could be easily hydrolysed with both base and acid to yield the acid (IIIa) and this, in conjunction with mass spectral data, indicated that the carboxy group in the latter was unhindered and equatorially disposed at C_{20}. The presence of the hemiacetal function in ring A was in keeping with the o.r.d. of the ester (IIIb) which showed a plain positive curve due to the absence of a free keto group and that of the keto-acetate (IVb) which showed a negative Cotton effect near 305 nm in agreement with a 3-oxofriedelane skeleton.[8]

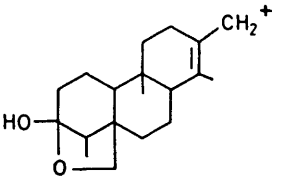
In the light of the known mass spectral fragmentation of friedelanes,[9-11] the mass spectrum of ester (IIIb) accorded well with its formulation, with the major fragments (a)—(f).

The presence of fragment (e) at *m/e* 169, which is shifted to *m/e* 155 for the acid (IIIa), is indicative of a hydrogen transfer from C-27 to the ester or carboxy at C-29 as in maytenonic acid (IVc) [12] (*cf.* polpunonic acid,[13] octandronic acid,[14] 3-oxofriedelan-29-oic acid [7]).

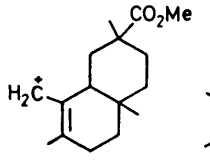
Reduction of the ester (IIIb) with sodium borohydride yielded the diol (Va) whereas oxidation of (IIIb) with pyridine–chromium trioxide yielded the keto-aldehyde (IVd) and the keto-carboxylic acid (IVe). Reduction of the ester (IIIb) with lithium aluminium hydride (LAH) yielded the triol (Vb) which on oxidation with pyridine–chromium trioxide gave, in poor yields, the keto-dialdehyde (IVf). The mass spectral fragmentations of all these derivatives were in agreement with the proposed structures.



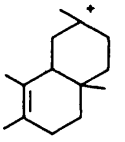
(a) *m/e* 318

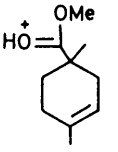


(b) *m/e* 289

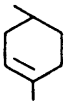


(c) *m/e* 249

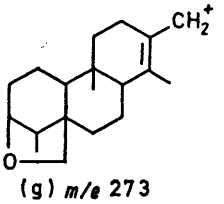

(d) *m/e* 191



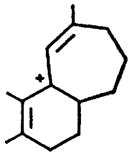
(e) *m/e* 169


(f) *m/e* 109

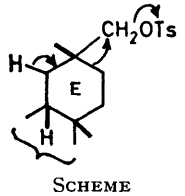
Treatment of the triol (Vb) with toluene-*p*-sulphonyl chloride and pyridine gave a mixture of the expected tosylate (VIa) and the olefin (VII). The latter, m.p. 285—287°, $C_{30}H_{48}O$, *m/e* 424 (M^+), shows, in its n.m.r. spectrum, the presence of a vinylic proton at δ 5.25 (d, *J* 7 Hz), a vinylic CMe at δ 1.75 (s), an AB quartet for two protons at δ 4.22 and 3.40 (d, *J* 8 Hz) due to the cyclic –O–CH_2–C(–C)(–C) protons, and a doublet at δ3. 83 (*J* 4 Hz) due to 3-H. The region δ 3.3—4.3 was very similar to that of the known ether (VIb).[15] The 27-protons of the tertiary CMe appeared to low field as a singlet at δ 1.36 due to deshielding by the double bond. The mass spectrum of (VII) shows, in addition to the molecular ion at *m/e* 424, the significant fragments (g) and (h).



(g) *m/e* 273


(h) *m/e* 203

The structure of (VII) was confirmed by an *X*-ray study [16] carried out by Professor D. Rogers, Imperial College, London. The structure has the D and E rings in the chair conformation and is strain-free. It evidently



SCHEME

arises by ring enlargement of the tosylate (VIa) (Scheme), the driving force being the release of steric strain.

Reduction of the tosylate (VIa) with LAH gave the carbinol (VIc) and none of the desired known compound (VIb).[15] Acetylation of (VIc) gave the acetate (VId) in which the CH_2OAc protons appear, in the n.m.r. spectrum, at δ 3.79 in agreement with its formulation as an equatorial substituent on ring E.[17] The ease of hydrolysis of the ester (IIIb) also shows the ester to be equatorially oriented. Previous *X*-ray studies on friedelanes [18,19] have shown them to have rings A—C as chairs and rings D and E as *cis*-fused boats. The carboxy in salaspermic acid, being equatorial, would have the α-configuration as shown in formula (IIIa).

In an attempt to correlate salaspermic acid (IIIa) with 3-oxofriedelan-29-oic acid (IVc),[7,12-14] the ester (IIIb) was reacted with ethylene glycol and toluene-*p*-sulphonic acid. It was hoped that the hemiacetal ring would open to yield the ethylene diacetal (IXa) which could be converted into the tosylate (IXb) and thence to the carbinol (IXc).[7,13,14] However, the reaction with ethylene glycol gave, instead of (IXa), the acetal (VIIIa). Conversion into the tosylate (VIIIb), followed by reduction with lithium aluminium hydride, yielded the acetal-alcohol (VIIIc), $C_{32}H_{54}O_3$, *m/e* 486 (M^+). Hydrolysis of the latter with acid gave the carbinol (IIIc), $C_{30}H_{50}O_3$, *m/e* 458 (M^+). The desired correlation could not therefore be carried out.

Salaspermic acid is a rare example of a triterpene having a hemiacetal function, benulin [20] being another such compound.

EXPERIMENTAL

M.p.s are uncorrected. I.r. spectra, unless otherwise stated, were taken for KBr discs. N.m.r. spectra were run in $CDCl_3$. Mass spectral fragments are reported with the relative intensity of the ions in parentheses.

Isolation of Salaspermic Acid (IIIa).—The powdered root-wood or stem-wood (20 kg) of *Salacia macrosperma* was defatted with hexane and then extracted thrice with hot EtOAc. Chromatography of the hexane extract yielded sitosterol. The EtOAc extract was concentrated and kept in an ice-chest for a week. The solid that separated was crystallised from excess $CHCl_3$–MeOH to yield *3-oxo-friedelan-29-oic acid hemiacetal* (1.2 g), m.p. 335°, $\nu_{max.}$ 3 440 and 1 690 cm^{-1} (Found: C, 74.6, 74.7; H, 10.4, 10.6. $C_{30}H_{48}O_4,\frac{1}{2}H_2O$ requires C, 74.8; H, 10.3%); *m/e* 472 (M^+, 36%), 442 (4), 395 (5), 318 (5), 302 (8), 289 (15), 287 (7), 259 (14), 250 (12), 249 (8), 235 (40), 203 (17), 191 (30), 189 (35), 177 (17), 175 (20), 163 (18), 155 (15), 135 (26), and 125 (100).

Methylation of Salaspermic Acid.—The acid (IIIa) (1 g) was suspended in MeOH and treated with excess ethereal CH_2N_2. The product was chromatographed over silica gel in CH_2Cl_2 to yield the *methyl ester* (IIIb) (0.8 g), m.p. 300° (from $CHCl_3$–MeOH), $\nu_{max.}$(CH_2Cl_2) 3 600 and 1 720 cm^{-1} (Found: C, 76.7; H, 10.7. $C_{31}H_{50}O_4$ requires C, 76.5; H, 10.4%); δ (100 MHz) 4.17 (1 H, d, *J* 9 Hz), 3.63 (3 H, s, CO_2Me), 3.58 (1 H, d, *J* 9 Hz), 2.83 (1 H, s, OH), 1.18 (3 H, s, CMe), 1.06 (3 H, s, CMe), 0.95 (3 H, s, CMe), 0.95 (3 H, d, *J* 6 Hz, CHMe), and 0.81 (6 H, s, 2 CMe). Addition of trichloroacetyl isocyanate [4] to the solution in the n.m.r. tube changes the spectrum to give signals due to structure (IVa) at δ 8.29 (1 H, s, NH), 4.62 (1 H, d, *J* 11 Hz), 4.23 (1 H, d, *J* 11 Hz), 3.63 (3 H, s, CO_2Me), 1.18 (3 H, s, CMe), 1.07 (3 H, s, CMe), 1.02 (3 H, s, CMe), 0.98 (3 H, d, *J* 6 Hz, CHMe), and 0.86 (3 H, s, 2 CMe). Mass spectrum of (IIIb); *m/e* 486 (M^+, 8%), 330 (12), 310 (7), 289 (10), 264 (6), 259 (6), 249 (15), 223 (9), 217 (8), 203 (10), 191 (14), 189 (25), 175 (16), 169 (38), 163 (32), 161 (20), 149 (27), 147 (26), 137 (35), 135 (45), 133 (35), 125 (100), 123 (50), 121 (80), 109 (90), 107 (70), 95 (70), and 93 (60), o.r.d. (*c* 0.079, dioxan) $[\phi]_{400}$ +37, $[\phi]_{340}$ +123, $[\phi]_{310}$ +98, $[\phi]_{231}$ +2 025, and $[\phi]_{210}$ +123°.

Hydrolysis of the Ester (IIIb).—(a) The ester (0.1 g) was refluxed with KOH (0.2 g) in dioxan (4 ml) containing H_2O (0.5 ml) for 3 h. The solution was acidified to yield the acid (IIIa) (60 mg), m.p. 335°, identical with the original acid.

(b) The ester (0.1 g) was refluxed with concentrated HCl (0.5 ml) in dioxan (3 ml) and H_2O (1 ml) to yield the acid (50 mg) identical with the original acid.

Acetylation of the Ester (IIIb).—The ester (0.2 g) was heated at 60° for 3 h with pyridine (2 ml) and Ac_2O (2 ml). The solution was evaporated *in vacuo* and the residue chromatographed over silica gel in CH_2Cl_2 to yield the keto-acetate (IVb) (0.1 g), m.p. 173° (from CH_2Cl_2–MeOH), $\nu_{max.}$ 1 740, 1 725, and 1 710 cm^{-1} (Found: C, 75.0; H, 10.2. $C_{33}H_{52}O_5$ requires C, 75.0; H, 9.9%); δ 4.32 and 4.05 (2 H, AB q, *J* 13 Hz), 3.67 (3 H, s, CO_2Me), 1.92 (3 H, s, $OCOCH_3$), 1.19 (3 H, s, CMe), 1.08 (3 H, s, CMe), 0.98 (3 H, s, CMe), 0.91 (3 H, d, *J* 7 Hz, CHMe), and 0.85 (3 H, s, CMe); *m/e* 528 (M^+, 3%), 496 (6), 468 (13), 271 (25), 264 (10), 249 (15), 245 (14), 231 (17), 229 (15), 223 (27), 217 (17), 203 (16), 191 (35), 189 (35), 175 (20), 169 (100), 163 (75), 149 (37), 137 (72), 123 (60), 121 (90), and 109 (95); o.r.d. (*c* 0.073, dioxan) $[\phi]_{600}$ −145, $[\phi]_{311}$ −3 488, $[\phi]_{305}$ −3 234, $[\phi]_{303}$ −3 270; $[\phi]_{265}$ +3 888, $[\phi]_{250}$ +3 597, $[\phi]_{232.5}$ +4 142, and $[\phi]_{205}$ −5 813°.

$NaBH_4$ *Reduction of the Ester* (IIIb).—The ester (90 mg) in a mixture of dioxan (5 ml) and MeOH (2 ml) was heated with $NaBH_4$ (0.3 g) at 60° for 4 h, diluted with H_2O and extracted with CH_2Cl_2 to give the *diol* (Va), m.p. >310° (from excess $CHCl_3$–MeOH) (Found: C, 75.8; H, 11.0. $C_{31}H_{52}O_4$ requires C, 76.2; H, 10.7%); *m/e* 488 (M^+, faint), 440 (35%), 412 (100), 290 (40), 273 (28), 217 (30), 177 (30), 163 (38), 161 (32), 149 (55), 135 (32), and 123 (30).

Pyridine–Chromium Trioxide Oxidation of the Ester (IIIb). The ester (0.3 g) in pyridine (2 ml) was added to a complex prepared from pyridine (4 ml) and CrO_3 (0.4 g) at 5—10°, stirred for 4 h at 10—20°, and diluted with C_6H_6. The solution was filtered and the filtrate was washed with dilute HCl and H_2O, dried, and evaporated. The residue was chromatographed over silica gel in CH_2Cl_2 to yield the *keto-aldehyde* (IVd) (50 mg), m.p. 254—256° (from CH_2Cl_2–MeOH), $\nu_{max.}$ 1 720 and 1 700 cm^{-1} (Found: C, 76.9; H, 10.2. $C_{31}H_{48}O_4$ requires C, 76.8; H, 10.0%); δ 9.72 (1 H, s, CHO) and 3.63 (3 H, s, CO_2Me); *m/e* 484 (M^+, faint), 316 (17%), 287 (16), 249 (18), 223 (28), 207 (24), 201 (33), 191 (32), 189 (48), 175 (32), 169 (100), 163 (90), 161 (52), 149 (53), 137 (90), 123 (80), 121 (90), and 109 (90).

Oxidation for a longer time gave the keto-acid (IVe), m.p. >325° (from CH_2Cl_2–MeOH), $\nu_{max.}$ 1 730, 1 720, and 1 705sh cm^{-1}; *m/e* 500 (M^+, 8%), 279 (24), 249 (22), 189 (30), 169 (65), 155 (73), 141 (90), 121 (60), and 109 (100).

LAH Reduction of the Ester (IIIb).—The ester (0.8 g) in dry tetrahydrofuran (THF) (100 ml) was refluxed for 5 h with LAH (2 g), left overnight at room temperature, and decomposed with H_2O to yield the *triol* (Vb) (0.5 g), m.p. >330° (from excess $CHCl_3$–MeOH) (Found: C, 78.2; H,

11.4. $C_{30}H_{52}O_3$ requires C, 78.2; H, 11.4%); *m/e* 460 (M^+, 3%), 412 (20), 290 (30), 273 (25), 234 (25), 221 (31), 217 (34), 209 (32), 207 (27), 205 (30), 203 (33), 189 (33), 177 (63), 163 (62), 123 (100), 121 (95), and 109 (95).

Reaction of the Triol (Vb) *with Toluene-*p*-sulphonyl Chloride.*—The triol (0.6 g) was heated at 60° for 3 h with pyridine (15 ml) and *p*-TsCl (3.5 g). The solution was evaporated *in vacuo* and the residue diluted with H_2O. The solid was filtered and chromatographed over silica gel, the column being eluted with CH_2Cl_2–hexane (1 : 1) and then with CH_2Cl_2. The earlier fractions gave the *olefin* (VII) (0.2 g), m.p. 285—287° (from excess $CHCl_3$–MeOH) (Found: C, 81.3; H, 11.3. $C_{30}H_{48}O,H_2O$ requires C, 81.4; H, 11.4%); δ (90 MHz; Fourier transform) 5.25 (1 H, d, *J* 7 Hz), 4.22 (1 H, d, *J* 8 Hz), 3.83 (1 H, d, *J* 4 Hz), 3.40 (1 H, d, *J* 8 Hz), 1.75 (3 H, s, C=CMe), and 1.36 (3 H, s, CMe); *m/e* 424 (M^+, 25%), 409 (25), 274 (30), 273 (100), 232 (50), 231 (60), 218 (26), 203 (20), 136 (20), 135 (19), and 123 (65).

The later fractions in the chromatography yielded the *tosylate* (VIa) (0.2 g), m.p. 210—211° (from CH_2Cl_2–MeOH) (Found: C, 74.8; H, 9.5. $C_{37}H_{56}O_4S$ requires C, 74.5; H, 9.5%).

LAH Reduction of the Tosylate (VIa).—The tosylate (0.4 g) was refluxed for 6 h with LAH (0.5 g) in THF (50 ml) to yield the *alcohol* (VIc) (0.2 g), m.p. 296—299° (from CH_2Cl_2–MeOH) (Found: C, 81.3; H, 11.4. $C_{30}H_{50}O_2$ requires C, 81.4; H, 11.4%). Acetylation of (VIc) (0.2 g) with pyridine (2 ml) and Ac_2O (2 ml) at 80° for 5 h yielded the acetate (VId) (0.1 g), m.p. 176—177° (from CH_2Cl_2–MeOH), $\nu_{max.}$ 1 735 cm^{-1} (Found: C, 76.2; H, 10.9. $C_{32}H_{52}O_3$,MeOH requires C, 76.1; H, 11.2%); δ 4.28 (1 H, d, *J* 8 Hz), 3.85 (1 H, d, *J* 4 Hz), 3.79 (2 H, s, CH_2OAc), 3.45 (1 H, d, *J* 8 Hz), and 2.1 (3 H, s, $OCOCH_3$); *m/e* 484 (M^+).

Pyridine–Chromium Trioxide Oxidation of the Triol (Vb).—The triol (0.3 g) in pyridine (3 ml) was added to a complex of CrO_3 (1 g) and pyridine (10 ml), stirred for 2 h at 10—20°, and worked up as above to yield, after chromatography, the keto-dialdehyde (IVf) (10 mg), m.p. 270° (from CH_2Cl_2), *m/e* 454 (M^+, 3%), 356 (100), 341 (40), 287 (85), 201 (35), 163 (53), 161 (42), and 109 (30).

Reaction of the Ester (IIIb) *with Ethylene Glycol.*—The ester (1 g) in C_6H_6 (100 ml) was refluxed for 12 h with *p*-TsOH (0.1 g) and ethylene glycol (4 ml) using a Dean–Stark water separator. The solution was washed with aqueous Na_2CO_3, dried, evaporated, and the residue chromatographed over silica gel in CH_2Cl_2 to yield the *acetal* (VIIIa) (0.5 g), m.p. 195—197° (from CH_2Cl_2–MeOH), $\nu_{max.}$ 3 420br and 1 720 cm^{-1} (Found: C, 72.7; H, 10.5. $C_{33}H_{54}O_5$,MeOH requires C, 72.7; H, 10.4%); *v* 4.2 (1 H, d, *J* 8 Hz), 3.7 (4 H, s, O·CH_2·CH_2·OH), 3.65 (3 H, s, CO_2Me), and 2.4 (1 H, s, OH); *m/e* 530 (M^+).

The acetal (VIIIa) (0.3 g) in pyridine (3 ml) was heated at 50° with *p*-TsCl (0.4 g) to yield the tosylate (VIIIb) (0.2 g) which was, without purification, reduced with LAH (0.4 g) in refluxing THF (25 ml) for 2 h. Chromatography of the product over silica gel in CH_2Cl_2 yielded the *acetal-alcohol* (VIIIc) (50 mg), m.p. 250° (from CH_2Cl_2–MeOH), $\nu_{max.}$ 3 470 cm^{-1} (Found: C, 76.8; H, 11.3. $C_{32}H_{54}O_3$,MeOH requires C, 76.4; H, 11.3%); *m/e* 486 (M^+).

The acetal-alcohol (VIIIc) (50 mg) in acetone (10 ml) was refluxed with concentrated HCl (0.2 ml) for 12 h to yield the *hemiacetal* (IIIc) (30 mg), m.p. 255° (from CH_2Cl_2–MeOH), $\nu_{max.}$ 3 420br cm^{-1} (Found: C, 75.4; H, 10.6. $C_{30}H_{50}O_3$,MeOH requires C, 75.9; H, 11.1%); *m/e* 458 (M^+).

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