Total Synthesis of Prostaglandin-E_2 by Rearrangement of a 6,8-Disubstituted-2-oxabicyclo[3.2.1]octan-3-one to a 4,5-Disubstituted-perhydrocyclopenta[*b*]furan-2-one

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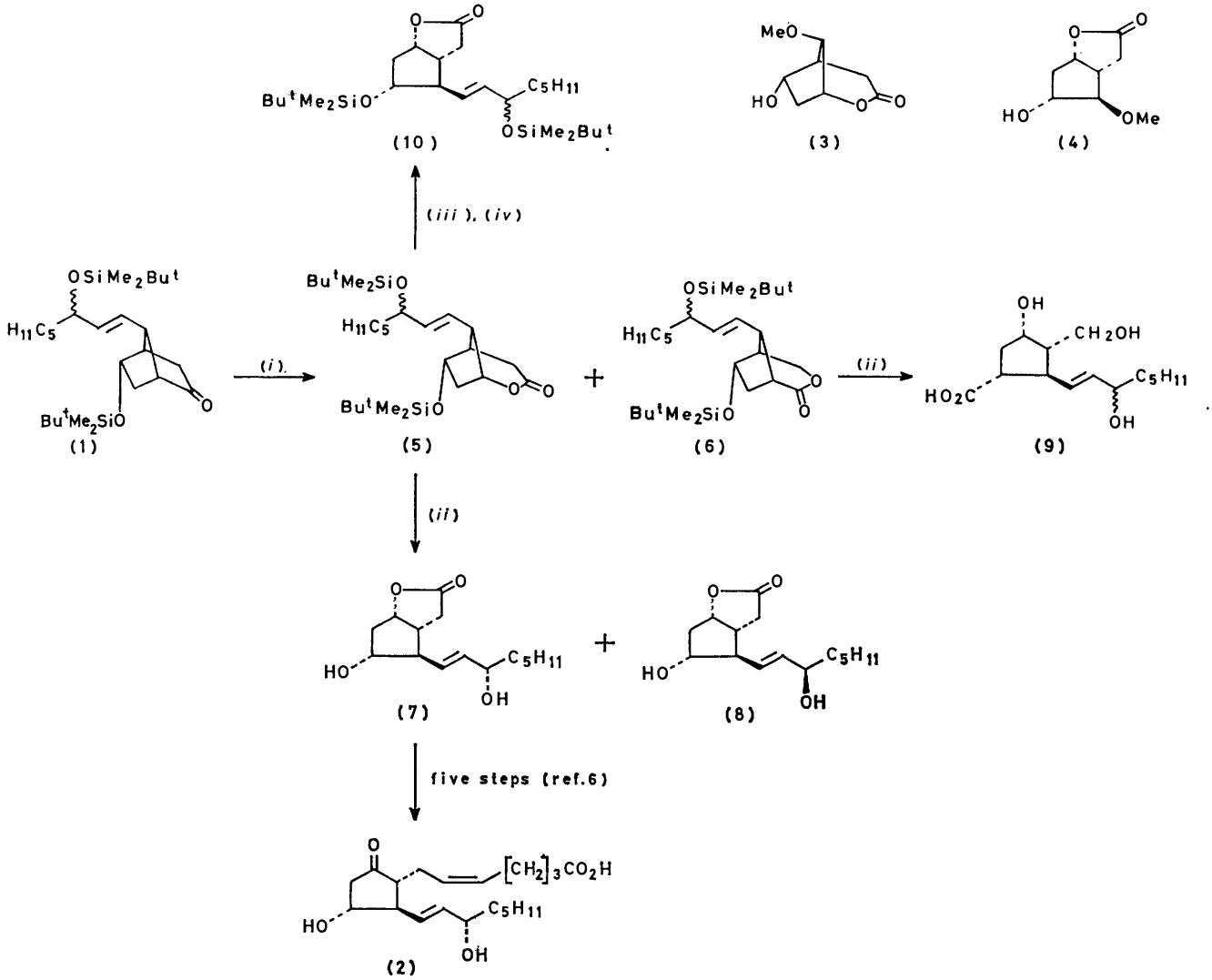
The bis-silyloxylactone (5) has been converted into a prostaglandin-E_2 intermediate (7) using HCl or tetrabutylammonium fluoride.

We have shown that the 7-*anti*-substituted-5-*endo*-silyloxybicyclo[2.2.1]heptan-2-one (1) is easily prepared by a convergent synthesis and can be converted into prostaglandin-$F_{2\alpha}$ in four steps.[1] Prostaglandin-C_2 can be prepared from similarly substituted bicycloheptanones.[2] We now show that the norbornanone (1) is readily converted into prostaglandin-E_2 (2).[3]

RESULTS AND DISCUSSION

The chance observation in our laboratories that the δ-lactone (3) gave the γ-lactone (4) in 90% yield after chromatography over alumina suggested the following route to prostaglandin-E_2. The ketone (1) was oxidised with peracetic acid to give a mixture of two products in the ratio 85 : 15. These were separated by column



Scheme (*i*) CH_3CO_3H, NaOAc, CH_3CO_2H; (*ii*) HCl, acetone; (*iii*) NBu_4F; (*iv*) $SiMe_2Bu^tCl$, DMF, imidazole

chromatography and the major component was shown to be the lactone (5) by physical methods.[1] The less polar minor component was identified as the lactone (6).[4]

Treatment of the lactone (5) with aqueous HCl in acetone gave a mixture of the dihydroxy-γ-lactones (7) and (8) (81%). These were readily separated by chromatography on silica to give (7) and (8) in 37% and 42% yields, respectively, from (5). The intermediate dihydroxy-δ-lactone was not detected.

Since the unwanted lactone (6) gave the trihydroxy-acid (9) under the same acidic conditions, the difficult chromatographic separation of the lactones (5) and (6) could be avoided. Thus treatment of the mixture of lactones (5) and (6) directly with aqueous HCl in acetone, followed by a sodium hydrogencarbonate work-up procedure, gave a mixture of dihydroxy-γ-lactones (7) and (8). Chromatography over silica afforded (7) (25%) and (8) (25%), based on the ketone (1). Acidification of the sodium hydrogencarbonate extracts allowed isolation of the trihydroxy-acid (9).

Reduction of the more polar lactone (7) with di-isobutyl aluminium hydride and reaction of the resultant lactol with the requisite Wittig reagent afforded (±)-prostaglandin $F_{2\alpha}$ which was identical with an authentic sample. Similarly the less-polar lactone (8) was converted into (±)-15-*epi*-prostaglandin $F_{2\alpha}$. Previous work [5] suggested that lactone (7) was less polar than lactone (8).

The lactone (7) has been converted into prostaglandin-E_2 (2) in five steps.[6] Prostaglandin-E_1 has also been prepared from the same lactone.[7]

In a similar manner the lactone (5) gave the bis-silyloxy-γ-lactone (10) in 68% overall yield, after treatment with tetra-n-butylammonium fluoride to give the γ-lactones (7), (8) followed by direct resilylation using t-butyldimethylsilyl chloride. Further work on the prostaglandin synthon (10) will be reported in due course.

EXPERIMENTAL

^{1}H N.m.r. data refer to solutions in deuteriochloroform and were determined at 90 MHz unless otherwise specified. Mass spectra were determined after ionisation by electron impact at 70 eV (e.i.m.s.) or chemical ionisation using isobutane or ammonia (c.i.m.s.). T.l.c. was carried out with Camlab 'Polygram' pre-coated silica gel plates. Short-column chromatography [8] used Merck Kieselgel H or G. Light petroleum refers to the fraction of b.p. 60—80 °C and all solvents for chromatography were distilled before use.

6-endo-*Hydroxy*-8-anti-*methoxy*-2-*oxabicyclo*[3.2.1]*octan*-3-*one* (3).—6-*endo*-Benzyloxy-8-*anti*-methoxy-2-oxabicyclo-[3.2.1]octan-3-one [4] (1.3 g) in ethyl acetate (50 ml) containing 5% palladium–charcoal (100 mg) was shaken under an atmosphere of hydrogen for 1 h. The solution was filtered and the solvent evaporated to give 6-endo-*hydroxy*-8-anti-*methoxy*-2-*oxabicyclo*[3.2.1]*octan*-3-*one* (3) (99%), $\nu_{max.}$ (film) 1 725 cm^{-1}; τ 5.32 (2 H, m, H-1, H-6), 6.12 (1 H, br s, H-8), 6.25 (1 H, br s, OH), 6.59 (3 H, s, OMe), 6.8—7.9 (4 H, m, 2 × H-4, H-5, and H-7-*exo*), and 8.07 (1 H, dm, *J* 15 Hz, H-7-*endo*) {Found: (e.i.m.s.) M^+, 172.073 9. $C_8H_{12}O_4$ requires *M*, 172.073 4}.

5β-*Hydroxy*-4α-*methoxyperhydrocyclopenta*[b]*furan*-2-*one* (4).—The lactone (3) was passed through a column of basic alumina (Type H) using ethyl acetate as eluant to give the 5β-*hydroxy*-4α-*methoxyperhydrocyclopenta*[b]*furan*-2-*one* (4) (90%), m.p. 86—87 °C (petrol–ether–benzene); $\nu_{max.}$ (film) 1 755 cm^{-1}; τ 4.88 (1 H, m, H-6a), 5.71 (1 H, m, H-5), 6.39 (1 H, s, OH), 6.60 (1 H, m, H-4), 6.67 (3 H, s, OMe), 7.15—7.60 (3 H, m, 2 × H-3, H-3a), 7.89 (2 H, m, 2 × H-6) (Found: C, 55.65, H, 7.0. $C_8H_{12}O_4$ requires C, 55.8, H, 7.0%).

Baeyer–Villiger Oxidation of {5-endo-*t-Butyldimethylsilyl-oxy*}-7-anti(E)-[3-(*t-butyldimethylsilyloxy*)*oct*-1-*enyl*]-*bicyclo*[2.2.1]*heptan*-2-*one*.— 5-*endo*-t-Butyldimethylsilyl-oxy-7-*anti*(*E*)-[3-(t-butyldimethylsilyloxy)oct-1-enyl]-bicyclo[2.2.1]heptan-2-one (1) (6.0 g, 12.5 mmol), sodium acetate (10.0 g), glacial acetic acid (300 ml), and commercial 40% peracetic acid (21.25 ml) were stirred at 20 °C for 53 h. Powered sodium thiosulphate was added in portions until the mixture gave a negative starch–iodide test. The solution was evaporated under reduced pressure, the residue treated with water and extracted with ethyl acetate. The combined organic extracts were washed with saturated sodium hydrogencarbonate solution and brine, dried ($MgSO_4$), and evaporated to give a pale yellow oil. G.l.c. analysis (3% OV-275, 240 °C) showed the presence of the two lactone isomers (5) and (6), in the ratio 85 : 15. The mixture was chromatographed on silica gel (MFC, 100—200 mesh) eluting with 5% ethyl acetate–light petroleum, and 300-ml fractions were collected. Evaporation of fractions 15—22 afforded a mixture of lactones (5) and (6) (721 mg), and evaporation of fractions 23—40 gave pure 6-endo-t-*butyldimethylsilyloxy*-8-anti(E)-[3-(*t-butyldimethylsilyloxy*)*oct*-1-*enyl*]-2-*oxabicyclo*[3.2.1]*octan*-3-*one* (5) (3.4 g, 62%) as a colourless oil; $\nu_{max.}$ (film) 1 756 cm^{-1}; τ 4.3—4.8 (2 H, m, CH=CH), 5.4—5.7 (2 H, m, H-1 and CH–O in side chain), 6.00 (1 H, m, H-6-*exo*), 6.90 (1 H, d, H-4-*endo*), 7.10 (1 H, m, H-8-*syn*), 7.3—7.8 (3 H, m, H-4-*exo*, H-5, and H-7-*exo*), 8.20 (1 H, m, H-7-*endo*), 8.4—8.9 (8 H, complex, CH_2-$CH_2CH_2CH_2$), 9.15 (21 H, complex, CH_2Me and 2 × CMe_3), and 10.02 and 10.06 (6 H, 2 × s, 2 × $OSiMe_2$) (Found: C, 65.15; H, 10.6. $C_{22}H_{52}O_4Si_2$ requires C, 65.3; H, 10.8%).

Rechromatography of the mixed fractions (15—22) gave a pure sample of the isomeric lactone, 6-endo-(*t-butyl*)-*dimethylsilyloxy*)-8-anti(E)-[3-(*t-butyldimethylsilyloxy*)*oct*-1-*enyl*]-3-*oxabicyclo*[3.2.1]*octan*-2-*one* (6) as a colourless oil; $\nu_{max.}$ (film) 1 747 cm^{-1} (C=O); τ (60 MHz) 4.3—4.7 (2 H, m, CH=CH), 5.22 (1 H, br d, *J* 10 Hz, H-4-*endo*), 5.85 (1 H, dd, *J* 10 and 4 Hz, H-4-*exo*), 5.4—6.2 (2 H, m, H-6-*exo* and CH–O in side chain), 7.05 (1 H, br s, H-8), 7.30 (1 H, br s, H-1), 7.4—8.4 (3 H, m, H-7-*exo*, H-7-*endo*, and H-5), 8.5—8.9 (8 H, m, $CH_2CH_2CH_2CH_2$), 9.12 (21 H, s and m, 2 × CMe_3 and CH_2Me), and 9.98 (12 H, s, 2 × $OSiMe_2$) {Found: (c.i.m.s., i-C_4H_9): $[M + H]^+$ 497.344 3. $C_{27}H_{52}OSi_2$ requires *M* + H, 497.348 2}.

Preparation of 3aα,6aα-5β-*Hydroxy*-4α-[(1E)-3-*hydroxyoct*-1-*enyl*]*perhydrocyclopenta*[b]*furan*-2-*ones* (7) *and* (8).—(1) *Acid-catalysed deprotection and rearrangement of* 6-endo-(*t-butyldimethylsilyloxy*)-8-anti(E)-[(3-*t-butyldimethylsilyl-oxy*)*oct*-1-*enyl*]-2-*oxabicyclo*[3.2.1]*octan*-3-*one* (5). Hydrochloric acid (0.3N, 40 ml) was added to the lactone (5) (2.8 g, 5.6 mmol) in acetone (200 ml) at 20 °C. After stirring for 3 d, the solution was diluted with water (500 ml) and extracted with ethyl acetate. The combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated to give a

clear oil (2.0 g). The isomers were separated by short-column chromatography on silica gel (250 g). Elution was with 20% light petroleum–ethyl acetate and 20-ml fractions were collected. Evaporation of fractions 130—170 gave 3aα,6aα-5β-*hydroxy*-4α-[(1E,3R*)-3-*hydroxyoct*-1-*enyl*]*perhydrocyclopenta*[b]*furan*-2-*one* (8) as a colourless oil (624 mg, 42%); $\nu_{max.}$ (film) 3 100—3 700 (OH), 1 760 (C=O), and 970 cm^{-1} (*trans*-CH=CH); τ (270 MHz) 4.35 [1 H, dd, *J* 15 and 6 Hz, CH(OH)CH=CH], 4.50 [1 H, dd, *J* 15 and 7.5 Hz, CH(OH)CH=C*H*], 5.07 (1 H, td, *J* 7, 7, and 3 Hz, H-6a), 5.91 [1 H, q, *J* 6, 6, and 6 Hz, CH=CH-C*H*(OH)], 6.01 (1 H, q, *J* 6.5, 6.5, and 6.5 Hz, H-5), 7.1—7.9 (5 H, m, H-3α, H-3β, H-3aα, H-4, and H-6α), 8.03 (1 H, ddd, *J* 15, 7.5, and 3 Hz, H-6β), 8.3—8.9 (8 H, m, $CH_2CH_2CH_2CH_2$), and 9.11 (3 H, m, CH_2Me) (Found: C, 67.4; H, 9.35. Calc. for $C_{15}H_{24}O_4$: C, 67.15; H, 9.0%).

Evaporation of fractions 181—280 gave 3aα,6aα-5β-*hydroxy*-4α-[(1E,3S*)-3-*hydroxyoct*-1-*enyl*]*perhydrocyclopenta*[b]*furan*-2-*one* (7) as a colourless oil (516 mg, 37%); $\nu_{max.}$ (film) 3 100—3 700 (OH), 1 760 (C=O), and 970 cm^{-1} (*trans*-CH=CH); τ (270 MHz) 4.39 [1 H, dd, *J* 15 and 7 Hz, CH(OH)C*H*=CH], 4.55 [1 H, dd, *J* 15 and 7.5 Hz, CH(OH)-CH=C*H*], 5.09 (1 H, td, *J* 7, 7, and 3 Hz, H-6a), 5.93 [1 H, q, *J* 7, 7, and 7 Hz, C*H*(OH)CH=CH], 6.05 (1 H, q, *J* 7.5, 7.5, and 7.5 Hz, H-5), 7.1—7.9 (5 H, m, H-3α, H-3β, H-3aα, H-4, and H-6α), 8.06 (1 H, ddd, *J* 15, 7.5, and 3 Hz, H-6β), 8.3—8.9 (8 H, m, $CH_2CH_2CH_2CH_2$), and 9.09 (3 H, m, CH_2Me) (Found: C, 67.15; H, 9.2. Calc. for $C_{15}H_{24}O_4$: C, 67.15; H, 9.0%).

On t.l.c. in ethyl acetate, lactone (7) had R_F 0.40 and the unnatural epimer (8) was less polar with R_F 0.43. Thus the relative polarities disagree with those given in the literature.[5] Reported values for the same solvent system are R_F 0.35 for lactone (7) and R_F 0.33 for lactone (8).

(2) *Preparation from the bicyclo*[2.2.1]*heptan*-2-*one* (1) *avoiding chromatography of the intermediate* δ-*lactones* (5) *and* (6). Compound (1) (16.0 g, 33 mmol) was treated with anhydrous sodium acetate (26.6 g), acetic acid (800 ml), and commercial 40% peracetic acid (37 ml) for 48 h at 20 °C. Work-up in the manner described previously afforded a mixture of lactones (5) and (6) (ratio 86 : 14 by g.l.c.) as a yellow oil (16.2 g). This mixture was dissolved in acetone (1 500 ml) and treated with 0.3N hydrochloric acid (300 ml). After 4 d at 20 °C the solution was diluted with water and extracted with ether. The combined extracts were washed with 8% aqueous sodium hydrogencarbonate, dried ($MgSO_4$), and evaporated. Short-column chromatography of the residue on silica gel (1 500 g) eluting with 20% light petroleum–ethyl acetate afforded the lactone (8) [2.0 g, 25% yield from (1)] identical (i.r., n.m.r., and t.l.c.) with the material described above, together with some mixed fractions of (7) and (8) (278 mg, 3%), and the pure lactone (7) [2.01 g, 25% yield from (1)] identical with the material isolated previously. Acidification of the sodium hydrogencarbonate washings in this preparation afforded 4-*hydroxy*-3-(*hydroxymethyl*)-2-(3-*hydroxyoct*-1-*enyl*)*cyclopentane*-1-*carboxylic acid* (9). Spectroscopic data were obtained on a sample purified by chromatography; $\nu_{max.}$ (film) 3 600—2 200 (br) (bonded OH), 1 710(br (C=O), and 970 cm^{-1} (*trans*-CH=CH); τ 4.2—4.7 (2 H, m, CH=CH), 5.4—6.4 [4 H, m, C*H*(OH)CH=CH, H-3 and CH_2-OH], 6.9—8.3 (5 H, m, H-1, H-2α, H-2, H-4, and H-5), 8.4—8.9 (8 H, m, $CH_2CH_2CH_2CH_2$), and 9.10 (3 H, m, CH_2-*Me*) {Found (c.i.m.s., i-C_4H_9) $[M + H]^+$, 287.186 5; $[M - H]^+$, 285.172 7. $C_{15}H_{26}O_5$ requires (*M* + H), 287.185 8; (*M* − H), 285.170 2}.

3aα,6aα-5β-(*t-Butyldimethylsilyloxy*)-4α-[(1E)-3-(*t-butyldimethylsilyloxy*)*oct*-1-*enyl*]*perhydrocyclopenta*[b]*furan*-2-*one* (10).—A solution of the δ-lactone (5) (500 mg, 1 mmol) and tetra-n-butylammonium fluoride (1.5 g, 6 mmol) in tetrahydrofuran (10 ml) was set aside at 20 °C for 3 d. Water (25 ml) was added and the mixture extracted with ethyl acetate. The combined extracts were washed with brine, dried ($MgSO_4$), and evaporated. The product was dissolved in dry dimethylformamide (5 ml) and treated with t-butyldimethylsilyl chloride (375 mg, 2.5 mmol) and imidazole (340 mg, 5 mmol). After 48 h at 20 °C, water (20 ml) was added, and the mixture extracted with ether. The organic extracts were combined, washed with brine, dried ($MgSO_4$), and evaporated to give an oil (420 mg). Chromatography on silica gel and elution with 5% ethyl acetate–light petroleum gave 3aα,6aα-5β-(*t-butyldimethylsilyloxy*)-4α-[(1E)-3-(*t-butyldimethylsilyloxy*)*oct*-1-*enyl*]-*perhydrocyclopenta*[b]*furan*-2-*one* (10) (340 mg, 68%); $\nu_{max.}$ ($CHBr_3$) 1 765 (C=O) and 970 cm^{-1} (*trans*-CH=CH); τ 4.3—4.8 (2 H, m, CH=CH), 5.10 (1 H, m, H-6a), 5.8—6.2 (2 H, m, H-5 and CH=CHC*H*-O), 7.2—8.4 (6 H, m, H-3α, H-3β, H-3a, H-4, H-6α, and H-6β), 8.4—8.9 (8 H, m, $CH_2CH_2CH_2CH_2$), 9.12 (21 H, s and m, 2 × CMe_3 and CH_2-*Me*), and 9.9—10.0 (12 H, several s, 2 × $OSiMe_2$) (Found: C, 65.4; H, 10.8. $C_{27}H_{52}O_4Si_2$ requires C, 65.2; H, 10.65%),

(±)-*Prostaglandin* $F_{2\alpha}$.—Di-isobutylaluminium hydride (3.4 ml of a 2.2M solution in hexane, 7.5 mmol) was added dropwise to a solution of the dihydroxy-lactone (7) (250 mg, 0.93 mmol) in anhydrous dimethoxyethane (15 ml) at −70 °C under nitrogen. After stirring for 1 h, methanol (15 ml) was added and the mixture set aside at room temperature for 16 h. The precipitate was filtered off (through Hyflo) and washed well with ethyl acetate. The combined filtrate and washings were evaporated to give the lactol as a clear oil (240 mg). This was dissolved in anhydrous tetrahydrofuran (10 ml) and added to a stirred mixture of potassium t-butoxide (0.8 g, 7 mmol) and (4-carboxybutyl)triphenylphosphonium bromide (1.58 g, 3.5 mmol) in dry tetrahydrofuran (20 ml) at 20 °C under nitrogen. The reaction mixture was stirred for 2 h, then quenched by addition of saturated aqueous ammonium chloride (10 ml) followed by 2N hydrochloric acid (4 ml). The organic layer was separated and the aqueous layer extracted with ethyl acetate (3 × 10 ml). The combined extracts were washed with brine (20 ml), dried ($MgSO_4$), and evaporated to give an orange oil (1.6 g). Short-column chromatography on silica gel eluting with acetic acid–light petroleum–ethyl acetate (1 : 10 : 90) gave (±)-prostaglandin $F_{2\alpha}$ (204 mg, 62%) which was identical (t.l.c., i.r., n.m.r., c.i.m.s.) with an authentic sample.

(±)-15-epi-*Prostaglandin* $F_{2\alpha}$.—In the same manner as above, the less polar of the lactone isomers (8) (250 mg) was converted into (±)-15-*epi*-prostaglandin $F_{2\alpha}$ (185 mg, 57%). The i.r., n.m.r., and mass spectrum were similar to those of natural prostaglandin $F_{2\alpha}$ but the 15-*epi*-isomer had a higher R_F on t.l.c.; $\nu_{max.}$ (film) *ca.* 3 400(br) (OH), *ca.* 2 700(br) (CH_2H), 1 712 (C=O), and 970 cm^{-1} (*trans*-CH=CH); τ 4.2—4.8 (4 H, m, olefinic protons), 4.92 (4 H, br, CO_2H and 3 × OH), 5.7—6.2 (3 H, m, H-9, H-11, and H-15), 7.4–7.8 (8 H, m, 2 × H-2, 2 × H-7, H-8, 2 × H-10, and H-12), 8.0—8.9 (12 H, m), 9.10 (3 H, br t, CH_2Me) [Found (c.i.m.s., NH_3): $[M + NH_4]^+$, 372.275; [*M* +

$NH_4 - H_2O]^+$ 354.262 5. Calc. for $C_{20}H_{34}O_5$ ($M + NH_4$) 372.275 0; ($M + NH_4 - H_2O$) 354.264 4}.

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