The Synthesis of (+)-Premnolal

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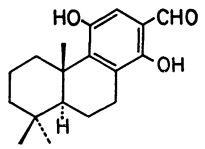
The revised structure of premnolal was confirmed by the following synthesis. Treatment of 12-methoxypodocarpa-8,11,13-triene (**7**), derived from methyl 12-methoxypodocarpa-8,11,13-trien-18-oate, with ethoxyoxalyl chloride and anhydrous aluminium chloride afforded 13-(ethoxyoxalyl) derivative, which was converted into 12-hydroxypodocarpa-8,11,13-triene-13-carbaldehyde (**9**) by alkaline hydrolysis, decarboxylation, and demethylation. The compound **9** was also prepared from **7** by demethylation and formylation. Reduction of **9** with lithium aluminium hydride, followed by partial acetylation, afforded 13-acetoxymethyl derivative which was converted into 13-acetoxymethyl-12-methoxy-11-nitropodocarpa-8,11,13-triene by nitration and methylation. This was then converted into 11,12-dimethoxypodocarpa-8,11,13-triene-13-carbaldehyde (**18**) by a series of reactions: catalytic hydrogenation, diazotization, reduction with lithium aluminium hydride, methylation, and oxidation. Demethylation of **18** gave 11,12-dihydroxypodocarpa-8,11,13-triene-13-carbaldehyde, which was identical with natural premnolal.

Recently, Rao *et al.*[1] reported the isolation of a novel tricyclic bisnorditerpene, premnolal, from the root bark of *Premna latifolia* Roxb. (Verbenaceae). On the basis of chemical and spectroscopic studies, they deduced the structure of premnolal to be 11,14-dihydroxypodocarpa-8,11,13-triene-13-carbaldehyde (**1**). In the previous paper,[2] we have reported the synthesis of 11,14-diacetoxy-13-(acetoxymethyl)podocarpa-8,11,13-triene (**2**), which possesses the proposed structure of 15-acetoxypremnol diacetate derived from natural premnolal. However, the non-identity of the synthetic **2** and 15-acetoxypremnol diacetate led us to propose the revised structure of premnolal to be 11,12-dihydroxypodocarpa-8,11,13-triene-13-carbaldehyde (**3**). To confirm the validity of our proposed structure, we now attempted the synthesis of **3**. This paper will describe the structural confirmation of natural premnolal by the synthesis of (+)-**3** starting from methyl 12-methoxypodocarpa-8,11,13-trien-18-oate (**4**).[3]



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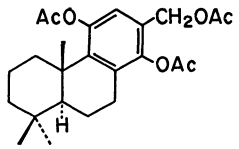

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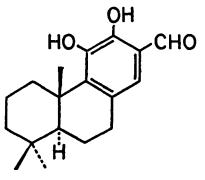

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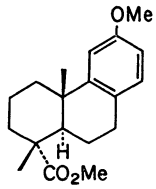


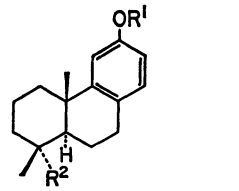
4

Reduction of **4** with lithium aluminium hydride in refluxing ether, followed by tosylation of the resulting alcohol (**5**) with *p*-toluenesulfonyl chloride in pyridine at 80—90 °C, afforded the corresponding tosylate (**6**). This was treated at 110—115 °C with a mixture of sodium iodide and zinc powder in *N,N*-dimethylformamide to give 12-methoxypodocarpa-8,11,13-triene (**7**)[4,5] in 88.9% yield from **4**. Conversion of **7** into 12-hydroxypodocarpa-8,11,13-triene-13-carbaldehyde (**9**) was then carried out by the following two routes. In the first, the methoxy compound **7** was demethylated with boron tribromide in dichloromethane at 5—10 °C to give podocarpa-8,11,13-trien-12-ol (**8**).[4,6] Treatment of **8** with hexamethylenetetramine in refluxing acetic acid under a stream of nitrogen afforded **9** in 34.9% yield from **7**. The second method involved four steps, but proved more convenient than the first. The compound **7** was reacted under Friedel-Crafts conditions with ethoxyoxalyl chloride and anhydrous aluminium chloride in dichloromethane at −15——5 °C to give 13-ethoxyoxalyl-12-methoxypodocarpa-8,11,13-triene (**10**). Hydrolysis of **10** with aqueous sodium hydroxide in refluxing methanol, followed by pyrolytic decarboxylation of the resulting α-keto acid (**11**) in a refluxing mixture of aniline and water, yielded 12-methoxypodocarpa-8,11,13-triene-13-carbaldehyde (**12**). Demethylation of **12** with anhydrous aluminium chloride in refluxing dichloromethane afforded **9** in 60.9% yield from **7**. The ^{1}H NMR spectrum of **9** showed singlet signals at δ 6.78 and 7.10 due to two aromatic protons, at δ 9.75 due to a formyl group, and at δ 10.48 due to a hydroxyl group. Reduction of **9** with lithium aluminium hydride in ether at room temperature gave the corresponding diol, which was partially acetylated with refluxing acetic acid to yield 13-(acetoxymethyl)podocarpa-8,11,13-trien-12-ol (**13**) in 72% yield. The IR spectrum of **13** showed hydroxyl absorptions at 3588 and 3313 cm^{-1} and a carbonyl at 1707 cm^{-1}. The presence of an acetoxymethyl group was also supported by its ^{1}H NMR spectrum, which showed singlet signals at δ 2.06 (3H) and 4.96 (2H). Nitration of **13** with concentrated nitric acid in acetic anhydride at −10——7 °C gave 13-acetoxymethyl-11-nitropodocarpa-8,11,13-trien-12-ol (**14**), which was methylated with methyl iodide and anhydrous potassium carbonate in refluxing ethyl methyl ketone to afford 13-acetoxymethyl-12-methoxy-11-nitropodocarpa-8,11,13-triene (**15**) in 40% yield from **13**. The ^{1}H NMR spectrum of **15** exhibited an acetoxymethyl group at δ 2.07 (3H,

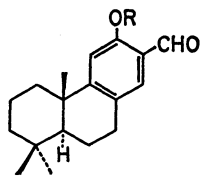
s) and 5.02 (2H, s), a methoxyl group at δ 3.79 (3H, s), and an aromatic proton at δ 7.11 (1H, s). The presence of a nitro group at the C-11 position was supported by the downfield shift of the methyl signal (δ 1.16) at the C-10 position of **13** to δ 1.33 in the ^{1}H NMR spectrum of **15**. Subsequently, the nitro compound **15** was converted into 13-hydroxymethyl-12-methoxypodocarpa-8,11,13-trien-11-ol (**16**) in 42% yield by a series of reactions: Catalytic hydrogenation with PtO_2 in ethanol at room temperature, treatment with sodium nitrite and dilute sulfuric acid in tetrahydrofuran at −15——9 °C and then at 80—90 °C, and reduction with lithium aluminium hydride in ether at room temperature. Methylation of **16** with methyl iodide and anhydrous potassium carbonate in refluxing ethyl methyl ketone afforded 13-hydroxymethyl-11,12-dimethoxypodocarpa-8,11,13-triene (**17**) in 74% yield. The alcohol **17** was then oxidized at room temperature with barium manganate in dichloromethane to yield 11,12-dimethoxypodocarpa-8,11,13-triene-13-carbaldehyde (**18**) in 83% yield. The ^{1}H NMR spectrum of **18** showed singlet signals at δ 7.27 (1H) due to an aromatic proton and at δ 10.41 (1H) due to a formyl group. Demethylation of **18** with anhydrous aluminium chloride in refluxing dichloromethane afforded the desired **3** (mp 133—135 °C, $[\alpha]_D$ +74.1°) in 88% yield. The synthetic **3** was shown to be identical with natural premnolal by comparison of physical and spectral data. Thus, the absolute configuration of premnolal was assigned as 5S and 10S.

To obtain further confirmation on the structure of **3**, it was reduced with lithium aluminium hydride in ether. The resulting triol was immediately acetylated with acetic anhydride in pyridine to give 11,12-diacetoxy-13-(acetoxymethyl)podocarpa-8,11,13-triene (**19**), which was identical with 15-acetoxypremnol diacetate. The synthetic **19** was finally oxidized with chromium trioxide in aqueous acetic acid at room temperature to give 11,12-diacetoxy-13-(acetoxymethyl)podocarpa-8,11,13-trien-7-one (**20**). The ^{1}H NMR spectrum of **20** showed an acetoxymethyl group at δ 2.00 (3H, s) and 4.99 (2H, s), two acetoxyl groups at δ 2.24 (6H, s), and an aromatic proton at δ 8.01 (1H, s). The downfield shift of an aromatic proton (δ 6.94) in **19** to δ 8.01 in the ^{1}H NMR spectrum of **20** must be caused by a deshielding effect of the carbonyl group at the C-7 position. This supported the presence of the aromatic proton at the C-14 position.

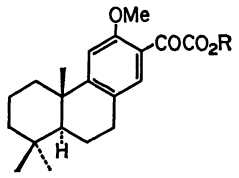
From the present study, the structure of premnolal was conclusively assigned as **3**.



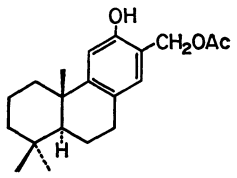
5 R^1=Me, R^2=CH_2OH
6 R^1=Me, R^2=CH_2OTs
7 R^1=R^2=Me
8 R^1=H, R^2=Me



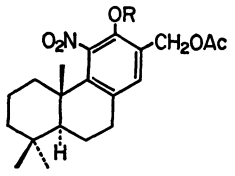
9 R=H
12 R=Me



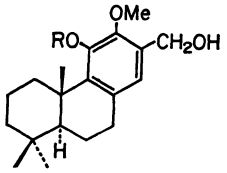
10 R=Et
11 R=H



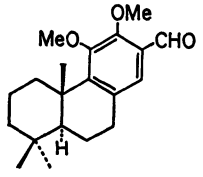
13



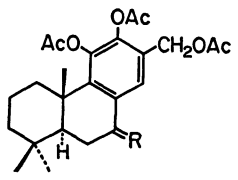
14 R=H
15 R=Me



16 R=H
17 R=Me



18



19 R=H_2
20 R=O

Experimental

All melting points are uncorrected. The IR spectra and optical rotations were measured in chloroform, and the ^{1}H NMR spectra in carbon tetrachloride at 60 MHz, with tetramethylsilane as an internal standard, unless otherwise stated. The chemical shifts are presented in terms of δ values; s: singlet, bs: broad singlet, d: doublet, dd: double doublets, t: triplet, q: quartet, m: multiplet, dm: doublet of multiplet. The column chromatography was performed using Merck silica gel.

12-Methoxypodocarpa-8,11,13-trien-18-ol (5). A solution of methyl 12-methoxypodocarpa-8,11,13-trien-18-oate (**4**)[3] (20.048 g) in dry ether (50 ml) was added dropwise to a stirred suspension of lithium aluminium hydride (2.52 g) in dry ether (100 ml) with cooling in an ice–water bath. The mixture was refluxed for 1.5 h, cooled, poured into a mixture of ice and dilute hydrochloric acid, and extracted with ether. The ether extract was washed with brine, dried over sodium sulfate, and evaporated *in vacuo* to give **5** (17.944 g: 98.6%) which, without purification, was used in the next reaction. The crude **5** (200 mg) obtained from another experiment was purified by column chromatography on silica gel (20 g), using ether–benzene (3:97) as the eluent, to give pure **5** (160 mg) as an oil; $[\alpha]_D$ +61.3° (*c* 2.15), ^{1}H NMR: δ 0.79 (3H, s, C_4–CH_3), 1.17 (3H, s, C_{10}–CH_3), 2.18 (1H, s, –OH), 3.00 (1H, d, J=11 Hz) and 3.36 (1H, d, J=11 Hz, –CH_2OH), 3.68 (3H, s, –OCH_3), 6.47 (1H, dd, J=8.5 and 2.5 Hz, C_{13}–H), 6.64 (1H, d, J=2.5 Hz, C_{11}–H), 6.79 (1H, d, J=8.5 Hz, C_{14}–H). Found: C, 78.54; H, 9.41%. Calcd for $C_{18}H_{26}O_2$: C, 78.79; H, 9.55%.

12-Methoxy-18-tosyloxypodocarpa-8,11,13-triene (6). A mixture of the crude **5** (17.944 g) and *p*-toluenesulfonyl chloride (14.96 g) in pyridine (80 ml) was heated at 80—90 °C for 3 h. The mixture was cooled, poured into a

mixture of ice and dilute hydrochloric acid, and extracted with ether. The ether extract was washed with brine, dried over sodium sulfate, and evaporated *in vacuo* to give the crude **6** (27.264 g: 97.3%) which, without purification, was used in the next reaction. The crude **6** (213 mg) obtained from another experiment was purified by column chromatography on silica gel (20 g), using benzene as the eluent, to give pure **6** (140 mg); $[\alpha]_D$ +57.9° (*c* 2.23); ^{1}H NMR: δ 0.89 (3H, s, C_4–CH_3), 1.17 (3H, s, C_{10}–CH_3), 2.43 (3H, s, $-C_6H_4C\underline{H}_3$), 3.69 (3H, s, $-OCH_3$), 6.48 (1H, dd, J=8.5 and 2 Hz, C_{13}–H), 6.62 (1H, d, J=2 Hz, C_{11}–H), 6.81 (1H, d, J=8.5 Hz, C_{14}–H), 7.25 (2H, d, J=8 Hz) and 7.71 (2H, d, J=8 Hz, $-C_6\underline{H}_4CH_3$). Found: C, 70.03; H, 7.66%. Calcd for $C_{25}H_{32}O_4S$: C, 70.06; H, 7.53%.

12-Methoxypodocarpa-8,11,13-triene (7). A stirred mixture of the crude **6** (27.264 g), sodium iodide (47.7 g), and zinc powder (20.8 g) in *N*,*N*-dimethylformamide (110 ml) was heated at 110—115 °C for 6 h. The mixture was cooled, diluted with benzene, and then filtered. The filtrate was further diluted with ether and washed successively with dilute hydrochloric acid, aqueous sodium thiosulfate, and brine. After drying over sodium sulfate, the solution was evaporated *in vacuo*. The residue was chromatographed on silica gel (200 g), using hexane–benzene (7:3) as the eluent, to give **7** (15.246 g: 88.9% from **4**); ^{1}H NMR: δ 0.95 (6H, s, $-\dot{C}(CH_3)_2$), 1.18 (3H, s, C_{10}–CH_3), 3.70 (3H, s, $-OCH_3$), 6.47 (1H, dd, J=8.5 and 2 Hz, C_{13}–H), 6.63 (1H, d, J=2 Hz, C_{11}–H), 6.81 (1H, d, J=8.5 Hz, C_{14}–H). Found: C, 83.79; H, 9.84%. Calcd for $C_{18}H_{26}O$: C, 83.66; H, 10.14%.

Podocarpa-8,11,13-trien-12-ol (8). A solution of boron tribromide (1.1 ml) in dichloromethane (2.0 ml) was added dropwise to a stirred solution of **7** (1.010 g) in dichloromethane (5.0 ml) at 5—10 °C. The mixture was stirred at this temperature for 1 h, poured into a mixture of ice and water, and extracted with ether. The ether extract was washed successively with aqueous sodium thiosulfate and brine, dried over sodium sulfate, and evaporated *in vacuo*. The residue was chromatographed on silica gel (50 g), using benzene as the eluent, to give **8** (796 mg: 83%); IR: 3590, 3320 cm^{-1}; ^{1}H NMR: δ 0.94 (6H, s, $-\dot{C}(CH_3)_2$), 1.10 (3H, s, C_{10}–CH_3), 5.75 (1H, bs, –OH), 6.45 (1H, dd, J=8.5 and 2 Hz, C_{13}–H), 6.59 (1H, d, J=2 Hz, C_{11}–H), 6.77 (1H, d, J=8.5 Hz, C_{14}–H).

13-Ethoxyoxalyl-12-methoxypodocarpa-8,11,13-triene (10). Anhydrous aluminium chloride (1.30 g) was added to a stirred solution of **7** (2.034 g) and ethoxyoxalyl chloride (1.20 ml) in dichloromethane (15 ml) at −35——25 °C. The mixture was stirred at −15——5 °C for 1.5 h, poured into a mixture of ice and dilute hydrochloric acid, and extracted with ether. The ether extract was washed with brine, dried over sodium sulfate, and evaporated *in vacuo*. The residue was chromatographed on silica gel (100 g), using benzene as the eluent, to give **10** (2.039 g: 72%); IR: 1735, 1665, 1605 cm^{-1}; ^{1}H NMR: δ 0.96 (6H, s, $-\dot{C}(CH_3)_2$), 1.17 (3H, s, C_{10}–CH_3), 1.36 (3H, t, J=7 Hz, $-OCH_2C\underline{H}_3$), 3.80 (3H, s, $-OCH_3$), 4.27 (2H, q, J=7 Hz, $-OC\underline{H}_2CH_3$), 6.79 (1H, s, C_{11}–H), 7.46 (1H, s, C_{14}–H).

12-Methoxypodocarpa-8,11,13-triene-13-carbaldehyde (12). A mixture of **10** (2.039 g) and aqueous sodium hydroxide (25%: 2.0 ml) in methanol (15 ml) was refluxed for 30 min. The mixture was concentrated *in vacuo*, acidified with dilute hydrochloric acid, and extracted with ether. The ether extract was washed with brine, dried over sodium sulfate, and evaporated *in vacuo* to give the crude acid (**11**) (2.025 g).

A mixture of the crude **11** (2.025 g), aniline (10 ml), and water (5.0 ml) was refluxed for 45 min. The mixture was cooled, diluted with water, and extracted with ether. The ether extract was washed successively with dilute hydrochloric acid and brine, dried over sodium sulfate, and evaporated *in vacuo*. The residue was chromatographed on silicic acid (Mallinckrodt CC-7, 100 g), using benzene as the eluent, to give **12** (1.519 g: 93% from **10**); IR: 1673, 1607 cm^{-1}; ^{1}H NMR: δ 0.96 (6H, s, $-\dot{C}(CH_3)_2$), 1.17 (3H, s, C_{10}–CH_3), 3.86 (3H, s, $-OCH_3$), 6.75 (1H, s, C_{11}–H), 7.36 (1H, s, C_{14}–H), 10.36 (1H, s, –CHO).

12-Hydroxypodocarpa-8,11,13-triene-13-carbaldehyde (9).

a): A mixture of **8** (629 mg) and hexamethylenetetramine (433 mg) in acetic acid (5.0 ml) was refluxed for 30 min in a stream of nitrogen. After the addition of dilute hydrochloric acid (10%: 2.0 ml), the mixture was further refluxed for 5 min. The mixture was cooled, diluted with water, and extracted with a mixture of ether and chloroform. The extract was washed successively with aqueous sodium hydrogencarbonate and brine, dried over sodium sulfate, and evaporated *in vacuo*. The residue was chromatographed on silicic acid (Mallinckrodt CC-7, 50 g), using benzene as the eluent, to give **9** (295 mg: 42%). This was recrystallized from hexane; mp 131—133 °C (softened at *ca.* 129 °C); $[\alpha]_D$ +79.8° (*c* 2.57); IR: 3195, 1650 cm^{-1}; ^{1}H NMR (90 MHz): δ 0.95 (3H, s) and 0.97 (3H, s, $-\dot{C}(CH_3)_2$), 1.19 (3H, s, C_{10}–CH_3), 6.78 (1H, s, C_{11}–H), 7.10 (1H, s, C_{14}–H), 9.75 (1H, s, –CHO), 10.48 (1H, s, –OH). Found: C, 79.10; H, 8.89%. Calcd for $C_{18}H_{24}O_2$: C, 79.37; H, 8.88%.

b): A stirred mixture of **12** (1.136 g) and anhydrous aluminium chloride (800 mg) in dichloromethane (15 ml) was refluxed for 7 h. The mixture was cooled, poured into water, and extracted with ether. The ether extract was washed with brine, dried over sodium sulfate, and evaporated *in vacuo*. The crude product was purified by column chromatography on silicic acid (Mallinckrodt CC-7, 70 g), using benzene as the eluent, to give **9** (979 mg: 91%), whose IR spectrum was identical with that of the sample in *a)*.

13-(Acetoxymethyl)podocarpa-8,11,13-trien-12-ol (13). A mixture of **9** (2.114 g) and lithium aluminium hydride (300 mg) in dry ether (30 ml) was stirred at room temperature for 1.5 h. The mixture was poured into a mixture of ice and dilute hydrochloric acid and extracted with ether. The ether extract was washed with brine, dried over sodium sulfate, and evaporated *in vacuo*.

The residue was dissolved in acetic acid (5.0 ml) and refluxed for 5 min. The cooled solution was neutralized with aqueous sodium hydrogencarbonate and extracted with ether. The ether extract was washed with brine, dried over sodium sulfate, and evaporated *in vacuo*. The crude product was chromatographed on silica gel (170 g), using ether–benzene (2:98) as the eluent, to give **13** (1.442 g); IR: 3588, 3313, 1707 cm^{-1}; ^{1}H NMR: δ 0.97 (6H, s, $-\dot{C}(CH_3)_2$), 1.16 (3H, s, C_{10}–CH_3), 2.06 (3H, s, $-OCOCH_3$), 4.96 (2H, s, $-CH_2O-$), 6.68 (1H, s) and 6.78 (1H, s, C_{11}–H and C_{14}–H).

Further elution with ether–benzene (1:9) afforded 13-(hydroxymethyl)podocarpa-8,11,13-trien-12-ol (349 mg) which was similarly acetylated for 15 min with refluxing acetic acid (1.5 ml) to give some additional **13** (331 mg).

13-Acetoxymethyl-11-nitropodocarpa-8,11,13-trien-12-ol (14). Nitric acid (d=1.38: 6 drops) was added to a stirred suspension of **13** (500 mg) in acetic anhydride (3.5 ml) at −10——7 °C. The mixture was stirred at this temperature for 30 min, diluted with ice–water, and extracted with ether. The ether extract was washed successively with aqueous sodium hydrogencarbonate and brine, dried over sodium

sulfate, and evaporated *in vacuo*. The crude product was chromatographed on silicic acid (Mallinckrodt CC-7, 90 g), using benzene as the eluent, to give **14** (294 mg); ^{1}H NMR: δ 0.96 (6H, s, $-C(CH_3)_2$), 1.36 (3H, s, $C_{10}-CH_3$), 2.10 (3H, s, $-OCOCH_3$), 4.94 (2H, s, $-CH_2O-$), 6.97 (1H, s, $C_{14}-H$), 8.07 (1H, bs, -OH).

*13-Acetoxymethyl-12-methoxy-11-nitropodocarpa-8,11,13-triene (**15**).* A stirred mixture of **14** (587 mg), methyl iodide (0.2 ml), and anhydrous potassium carbonate (400 mg) in ethyl methyl ketone (5.0 ml) was refluxed for 5 h. The mixture was cooled, diluted with water, and extracted with ether. The ether extract was washed with brine, dried over sodium sulfate, and evaporated *in vacuo*. The crude product was chromatographed on silicic acid (Mallinckrodt CC-7, 50 g), using benzene as the eluent, to give **15** (478 mg); $[\alpha]_D$ +169° (*c* 3.50); IR: 1735, 1525 cm^{-1}; ^{1}H NMR: δ 0.93 (3H, s) and 0.96 (3H, s, $-C(CH_3)_2$), 1.33 (3H, s, $C_{10}-CH_3$), 2.07 (3H, s, $-OCOCH_3$), 3.79 (3H, s, $-OCH_3$), 5.02 (2H, s, $-CH_2O-$), 7.11 (1H, s, $C_{14}-H$). Found: C, 67.40; H, 7.85; N, 3.53%. Calcd for $C_{21}H_{29}O_5N$: C, 67.18; H, 7.79; N, 3.73%.

*13-Hydroxymethyl-12-methoxypodocarpa-8,11,13-trien-11-ol (**16**).* A solution of **15** (345 mg) in ethanol (16 ml) was hydrogenated for 3 h using PtO_2 (150 mg) at room temperature in an atmosphere of hydrogen. After the usual work-up, it gave the corresponding amino compound (313 mg) which, without purification, was used in the next reaction.

A solution of sodium nitrite (107 mg) in water (0.7 ml) and tetrahydrofuran (1.5 ml) was added dropwise at −15—−9 °C to a stirred mixture of the crude amino compound (313 mg) and dilute sulfuric acid (2%: 3.0 ml) in tetrahydrofuran (13 ml) over a period of 5 min. The mixture was stirred at this temperature for 30 min, poured into water (60 °C), cooled, and washed with ether. The aqueous solution was heated at 80—90 °C for 5 min, cooled, and extracted with ether. The ether extract was washed with brine, dried over sodium sulfate, and evaporated *in vacuo* to give the corresponding phenol (178 mg) which, without purification, was used in the next reaction.

A mixture of the crude phenol (178 mg) and lithium aluminium hydride (30 mg) in dry ether (3.0 ml) was stirred at room temperature for 1.5 h. The mixture was poured into a mixture of ice and dilute hydrochloric acid, and extracted with ether. The ether extract was washed with brine, dried over sodium sulfate, and evaporated *in vacuo*. The crude product was purified by column chromatography on silicic acid (Mallinckrodt CC-7, 10 g), using ether–benzene (2:98) as the eluent, to give **16** (116 mg: 42%); $[\alpha]_D$ +74° (*c* 1.25); ^{1}H NMR: δ 0.95 (6H, s, $-C(CH_3)_2$), 1.26 (3H, s, $C_{10}-CH_3$), 3.68 (3H, s, $-OCH_3$), 4.43 (2H, s, $-CH_2O-$), 6.10 (1H, s, -OH), 6.38 (1H, s, $C_{14}-H$). Found: C, 75.05; H, 9.37%. Calcd for $C_{19}H_{28}O_3$: C, 74.96; H, 9.27%.

*13-Hydroxymethyl-11,12-dimethoxypodocarpa-8,11,13-triene (**17**).* A stirred mixture of **16** (116 mg), methyl iodide (0.3 ml), and anhydrous potassium carbonate (90 mg) in ethyl methyl ketone (3.0 ml) was refluxed for 10 h. The mixture was cooled, diluted with water, and extracted with ether. The ether extract was washed with brine, dried over sodium sulfate, and evaporated *in vacuo*. The crude product was chromatographed on silicic acid (Mallinckrodt CC-7, 10 g), using ether–benzene (1:99) as the eluent, to give **17** (90 mg: 74%); $[\alpha]_D$ +84.4° (*c* 2.12); IR: 3600, 3450 cm^{-1}; ^{1}H NMR 0.95 δ (6H, s, $-C(CH_3)_2$), 1.26 (3H, s, $C_{10}-CH_3$), 2.22 (1H, s, -OH), 3.74 (3H, s) and 3.79 (3H, s, 2-OCH_3), 4.44 (2H, s, $-CH_2O-$), 6.61 (1H, s, $C_{14}-H$). Found: C, 75.14; H, 9.79%. Calcd for $C_{20}H_{30}O_3$: C, 75.43; H, 9.50%.

*11,12-Dimethoxypodocarpa-8,11,13-triene-13-carbaldehyde (**18**).* A mixture of **17** (87 mg) and barium manganate (210 mg) in dichloromethane (2.5 ml) was stirred at room temperature for 24 h. The mixture was diluted with ether and passed through a short column packed with silicic acid (Mallinckrodt CC-7). The eluate was evaporated *in vacuo*. The crude product was chromatographed on silicic acid (CC-7, 10 g), using benzene as the eluent, to give **18** (72 mg: 83%); $[\alpha]_D$ +86.6° (*c* 2.20); IR: 1682, 1595 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 0.96 (6H, s, $-C(CH_3)_2$), 1.33 (3H, s, $C_{10}-CH_3$), 3.91 (6H, s, 2-OCH_3), 7.27 (1H, s, $C_{14}-H$), 10.41 (1H, s, -CHO). Found: C, 76.05; H, 9.17%. Calcd for $C_{20}H_{28}O_3$: C, 75.91; H, 8.92%.

*Premnolal (11,12-Dihydroxypodocarpa-8,11,13-triene-13-carbaldehyde) (**3**).* A mixture of **18** (37.3 mg) and anhydrous aluminium chloride (63 mg) in dichloromethane (4.0 ml) was refluxed for 6 h. The mixture was cooled, diluted with ether and dilute hydrochloric acid, and extracted with ether. The ether extract was washed with brine, dried over sodium sulfate, and evaporated *in vacuo*. The crude product was chromatographed on silica gel (5.0 g), using hexane–benzene (1:1) as the eluent, to give **3** (29.9 mg: 88%). This was recrystallized from hexane, mp 133—135 °C, $[\alpha]_D$ +74.1° (*c* 0.58) (lit,[1] mp 135—135.5 °C, $[\alpha]_D$ +67.5°); IR (CCl_4): 3531, 3125, 1665 cm^{-1}; ^{1}H NMR (90 MHz): δ 0.94 (3H, s) and 0.97 (3H, s, $-C(CH_3)_2$), 1.32 (3H, s, $C_{10}-CH_3$), 2.82 (2H, dd, J=8 and 4 Hz, C_7-H_2), 3.24 (1H, dm, J=13 Hz, $C_{1\beta}-H$), 5.84 (1H, s, $C_{11}-OH$), 6.73 (1H, s, $C_{14}-H$), 9.72 (1H, s, -CHO), 10.81 (1H, s, $C_{12}-OH$). The ^{1}H NMR spectrum of the synthetic **3** was identical with that of natural premnolal. Found: C, 74.68; H, 8.55%. Calcd for $C_{18}H_{24}O_3$: C, 74.97; H, 8.39%.

*11,12-Diacetoxy-13-(acetoxymethyl)podocarpa-8,11,13-triene (**19**).* A mixture of **3** (19.9 mg) and lithium aluminium hydride (10 mg) in dry ether (2.0 ml) was stirred at room temperature for 1 h. After the usual work-up, the crude alcohol (18.1 mg) was acetylated at 70—75 °C with acetic anhydride (0.8 ml) in pyridine (0.8 ml) for 1.5 h. The crude acetate was purified by column chromatography on silica gel (2.0 g), using ether–benzene (2:98) as the eluent, to give **19** (17.7 mg: 61.6%); IR (CCl_4): 1778, 1745 cm^{-1}; ^{1}H NMR (90 MHz): δ 0.93 (3H, s) and 0.96 (3H, s, $-C(CH_3)_2$), 1.22 (3H, s, $C_{10}-CH_3$), 1.96 (3H, s), 2.17 (3H, s) and 2.19 (3H, s, 3-$OCOCH_3$), 4.89 (2H, s, $-CH_2O-$), 6.94 (1H, s, $C_{14}-H$). The ^{1}H NMR spectrum of **19** was identical with that of natural 15-acetoxypremnol diacetate. Found: C, 69.02; H, 7.96%. Calcd for $C_{24}H_{32}O_6$: C, 69.21; H, 7.74%.

*11,12-Diacetoxy-13-(acetoxymethyl)podocarpa-8,11,13-trien-7-one (**20**).* A solution of chromium trioxide (7.4 mg) in 80% aqueous acetic acid (0.04 ml) was added to a stirred solution of **19** (10.4 mg) in acetic acid (0.2 ml) at room temperature. The mixture was stirred at room temperature for 1.5 h, poured into brine, and extracted with ether. The ether extract was washed successively with aqueous sodium hydrogencarbonate and brine, dried over sodium sulfate, and evaporated *in vacuo*. The crude product was chromatographed on silica gel (5.0 g), using ether–benzene (7:93) as the eluent, to give the starting **19** (1.2 mg: 12%). Further elution with the same solvent afforded **20** (5.3 mg: 49%); MS (*m/e*): 430 (M^+); IR: 1780, 1740, 1688 cm^{-1}; ^{1}H NMR (90 MHz): δ 1.00 (6H, s, $-C(CH_3)_2$), 1.33 (3H, s, $C_{10}-CH_3$), 2.00 (3H, s, $C_{15}-OCOCH_3$), 2.24 (6H, s, $C_{11}-OCOCH_3$

and C_{12}–$OCOCH_3$), 4.99 (2H, s, $-CH_2O-$), 8.01 (1H, s, C_{14}–H).

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