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CHEMISTRY OF THE PODOCARPACEAE—XV[1]

ELABORATION OF PODOCARPIC ACID

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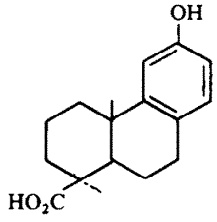
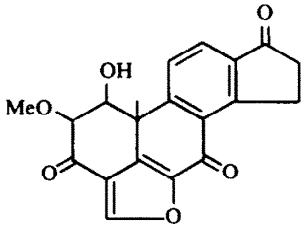
Abstract—The conversion of the diterpenoid resin acid, podocarpic acid, into a tetracyclic system possessing a 5-membered ring D is described The unsubstituted ring with a CO group at C-15* was prepared from the 13-(2'-carboxyethyl) derivative III (R = $CH_2CH_2CO_2H$) in fair yield, but attempted cyclization of compounds possessing a 1'-substituted-2'-carboxyethyl side chain at C-13 was unsuccessful. The C-17 ketone was obtained in low yield from the 13-acrylyl compound, but not at all from the 13-crotonyl compound. Some model experiments involving derivatives of anisole are described.

PODOCARPIC acid, (I) with its oxygenated aromatic ring C and carboxyl group in ring A provides a starting material, readily available in New Zealand, for the elaboration of steroids which may possess biological activity. Ring C aromatic steroids are uncommon. The conversion of ergosterol into such a compound has been reported,[2] while the fungal metabolite, viridin(II)[3] has been shown to possess a steroidal skeleton with an aromatic ring C.



I



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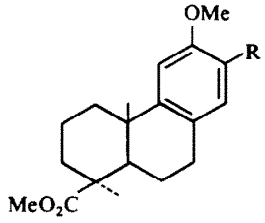


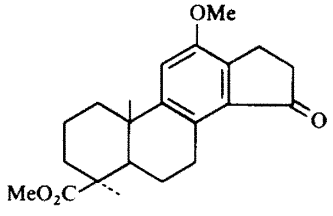
III

In this paper, we describe the elaboration of a 5-membered ring D in the podocarpic acid series, along with other synthetic approaches to this goal. Bible[4] has reported the preparation of such a compound in unstated yield. Friedel–Crafts reactions probably provide the best methods for forming the 2 new C—C bonds at C-13 and C-14 in the methyl ether methyl ester III (R = H). Initial attack *ortho* to the OMe group at C-13 is known to proceed readily with simple acid chlorides,[5] but the formation of a second bond at C-14 might be expected to be more difficult, although there is analogy in the literature in the synthesis of indanones.

As aromatic acylation proceeds more readily than alkylation, the ring closure of

* Steroid nomenclature and numbering is used for all tetracyclic compounds.

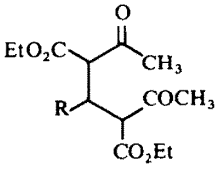
the 13-(2′-carboxyethyl) compound III (R = $CH_2CH_2CO_2H$) appeared to provide a favourable route to the desired molecule. This acid was prepared in two ways. Reaction of the 13-propionyl compound III (R = $COCH_2CH_3$)[5b] with sulphur and morpholine gave the known thiomorpholide[5b] which on acid hydrolysis gave the carboxyethyl compound. In the first of two alternative routes, the 13-acetyl compound III (R = Ac)[5a] was treated with diethyl carbonate and sodium hydride, thus effecting carboethoxylation to give the β-keto ester III (R = $COCH_2CO_2Et$). In another method, this same keto ester was prepared by direct reaction of the methyl ether III (R = H) with ethyl malonyl chloride and aluminium chloride in nitrobenzene. Clemmensen reduction of the β-keto ester III (R = $COCH_2CO_2Et$) followed by alkaline hydrolysis, under such conditions that the tertiary axial carbomethoxyl group at C-4 was unaffected, gave the same acid III (R = $CH_2CH_2CO_2H$) as had been prepared by the Willgerodt reaction. The corresponding acid chloride was prepared and reacted *in situ* with aluminium chloride in nitrobenzene to give the 15-keto compound IV in 45% yield. This product was identified from analytical and spectral data, including IR absorption at 1710 cm^{-1} assigned to a 5-ring ketone conjugated with an aromatic ring.



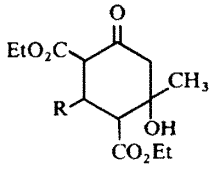
IV

Experiments were then undertaken in an attempt to prepare a C-15 keto compound with a substituent such as carboxyl or carboxyalkyl at C-17. The plan envisaged preparation of the 13-formyl derivative III (R = CHO) which might be condensed with a malonic ester, cyanoacetic ester or acetoacetic ester to give an unsaturated ester of the type III (R = $CH{=}CR_1R_2$) where R_1 and R_2 are electron withdrawing groups. Nucleophilic addition on the benzylic carbon atom in a Michael reaction with the malonyl carbanion, cyanide ion, or the carbanion from acetoacetic ester, respectively, would, after suitable hydrolysis and decarboxylation provide the 13-(1′-substituted-2′-carboxyethyl) derivative. Such reactions are well known in derivatives of benzaldehyde; those model experiments involving new compounds are briefly described in the experimental section.

Ethyl acetoacetate reacts readily with aldehydes in the presence of piperidine to produce bis adducts. There was considerable uncertainty in the literature as to



V



VI

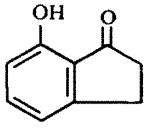
whether these compounds, as normally isolated, were actually 1,5 diketones (V) or whether they had undergone an aldol reaction to give a hydroxycyclohexanone (VI). Finar[6] has shown clearly by IR studies that such compounds generally possess the latter structures and this is confirmed in the present work by an examination of their NMR spectra.

Two routes to the 13-formyl compound III (R = CHO) were successfully employed. In the first, dichloromethyl n-butyl ether was reacted with III (R = H) under Friedel–Crafts conditions.[7] Decomposition of the relatively unstable α-alkoxybenzyl intermediate III (R = CHCl.O.^{n}Bu) with water gave the 13 formyl derivative III (R = CHO) in 73% yield. The second method involved three steps but proved as convenient as the first. The methyl ether III (R = H) gave the 13-ethyl glyoxylate III (R = $COCO_2Et$) with ethyl oxalyl chloride and aluminium chloride. Hydrolysis to the free α-keto acid and pyrolytic decarboxylation in refluxing aniline yielded the 13-formyl compound III (R = CHO). Reaction of this aldehyde with either ethyl cyanoacetate or diethyl malonate gave the corresponding unsaturated esters in good yield. Addition of the carbanion from diethyl malonate to the unsaturated diethyl ester III (R = $CH{=}C(CO_2Et)_2$) gave the corresponding tetra-ethyl ester as a crystalline solid. Hydrolysis gave the free acid, whose NMR integral showed 4 carboxylic hydrogens, and this on heating at 180° showed a decrease in weight corresponding to the loss of two molecules of CO_2. The resultant di-acid III [R = $CH(CH_2CO_2H)_2$] showed only 2 carboxyl protons in the NMR integral. However, all attempts to cyclise the corresponding acid chloride were unsuccessful. Alternatively, cyanide ion was added in a Michael reaction to the unsaturated cyano ester III (R = $CH{=}C(CN)CO_2Et$) but attempted hydrolysis failed to yield the desired carboxylic acid.

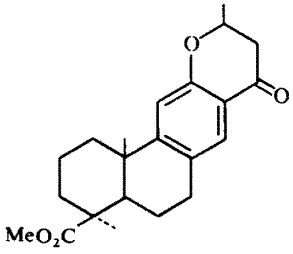
Reaction of the 13-formyl compound with ethyl acetoacetate failed to reveal any of the desired adduct.

Indenones have been prepared by the acid catalysed cyclization of substituted cinnamic acids.[8] Reaction of the 13-formyl compound with malonic acid in pyridine containing a little piperidine at 100° for 3 hr gave the 2′-carboxyvinyl compound III (R = $CH{=}CHCO_2H$) in high yield but again cyclization was unsuccessful.

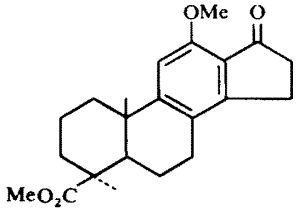
Attention was also directed towards the preparation of a podocarpic acid homologue with a 5-membered ring D possessing a CO group at C-17. 7-Hydroxyindan-1-ones VII have been prepared from monocyclic aromatic substrates by acylation–alkylation reactions involving unsaturated acids or their derivatives. In some cases, the initial step involves the Fries rearrangement of the phenyl ester of an unsaturated or halo acid.



VII



VIII



IX

Initially, the methyl ether III (R = H) was reacted with either crotonic acid and polyphosphoric acid or with crotonyl chloride and aluminium chloride in nitrobenzene. Both routes gave up to 75% of the 13-crotonyl compound III (R = $COCH{=}CHCH_3$). Numerous attempts to effect intramolecular cyclization at C-14 were unsuccessful. In one experiment, demethylation occurred at the C-12 oxygen atom, and the chromanone VIII was isolated and identified by its analytical and spectral properties. The more reactive acrylyl chloride did, in fact, give a low yield of compound identified by spectral evidence as the tetracyclic ketone IX.

In similar reactions, aromatic α and β halo ketones have been utilised for the preparation of indanones.[9] The methyl ether III (R = H) was reacted both with 3-chloropropionic acid and polyphosphoric acid, and also with 3-chloropropionyl chloride and aluminium chloride in nitrobenzene, to give the 3-chloropropionyl ketone III (R = $COCH_2CH_2Cl$). In the latter reaction, the work-up included treatment with charcoal in ethanol solution and recrystallization from ethanol. One of the products isolated was the 3'-ethoxypropionyl compound III (R = $COCH_2CH_2OEt$) identified by analysis and spectral evidence. However, no indanone was detected in the products from the attempted cyclization of the chloroketone.

α-Bromoaralkyl ketones have also been employed in the synthesis of indan-1-ones,[10] and tertiary α-bromo ketones have been shown to cyclize more readily than compounds containing a secondary bromo atom. In the present work, the 13-propionyl III (R = COEt) and 13-isobutyryl ketones III (R = $COCHMe_2$) were treated with bromine in acetic acid to give the bromo ketone, but attempted cyclization was unsuccessful. Demethylation of the C-12 oxygen function was the only reaction observed.

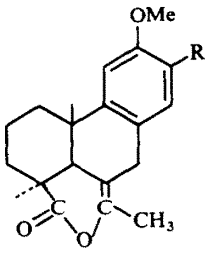
The work reported so far emphasizes the unreactivity of podocarpic acid derivatives towards electrophilic substitution at C-14. This lack of reactivity was very clearly emphasized in the reaction of two C-13 alkyl compounds III (R = Me and R = Et) with acetyl chloride under normal Friedel–Crafts conditions. Alumina chromatography of the product from III (R = Et)[1] afforded three identifiable products:

(a) was starting material (31%).

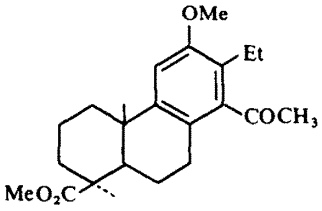
(b) (25%) had m.p. 144·5–146·5°, was analysed for $C_{22}H_{28}O_3$ and showed strong absorption in the IR at 1760 cm^{-1} (CCl_4) or 1745 cm^{-1} ($CHCl_3$), but no absorption at 1730 cm^{-1} indicative of the C-4 ester grouping. The NMR spectrum showed a three-proton singlet at 1·95 δ, ascribed to a vinyl Me group. The absence of vinyl proton resonances suggested a tetrasubstituted double bond. The aromatic ring system present in the starting material was not changed, while a broad two-proton singlet appeared at 3·52 δ. Examination of the mass spectrum confirmed the molecular formula and suggested the presence of the grouping —CO—O—C(Me)=. On this basis, structure X (R = Et) was assigned to this compound.

(c) an oil, (3%) was identified as the 14-acetyl derivative (XI) from spectral data.

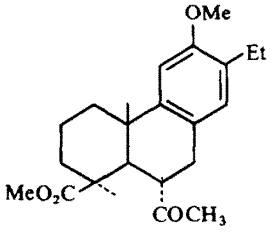
In a similar manner, the 13-Me compound III (R = Me) was prepared by Clemmensen reduction of the 13-formyl derivative and reacted with acetyl chloride and aluminium chloride in nitrobenzene for 3 days at 0° to give both starting material (52%) and the enol δ-lactone X (R = Me; 27%).



X

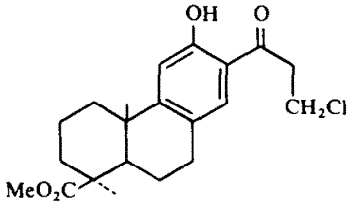


XI



XII

Further evidence for the correctness of structure X (R = Et) was provided by hydrolysis of this lactone with methanolic sodium hydroxide which gave an amorphous acidic product. Reaction of this acid with diazomethane gave an ester, m.p. 124–125·5° to which the structure XII was assigned. Combustion analysis showed it to have formula $C_{23}H_{32}O_4$, while in the IR it showed ν_{max} 1725 cm^{-1} assigned to ester and alkyl ketone C=O. The NMR showed signals due to methoxycarbonyl and aromatic OMe groups and, in particular, a 3-proton singlet at 2·17 δ assigned to the Ac protons. The route by which acylation occurs at C-6 is not clear. In general, the acylation of alkanes in inert solvents takes place through an alkene, formed by an intramolecular hydride shift.[11] It is also possible that cleavage of the C-7,8 bond results in a species which can undergo acylation and reformation of the C-7,8 bond.



XIII

EXPERIMENTAL

For general experimental details, see Part XII.[12] Chromatography was on P. Spence Type H alumina and NMR and IR spectra were measured for CCl_4 solns unless stated otherwise.

Methyl 12-methoxy-13-(2'-carboxyethyl)podocarpa-8,11,13-trien-16-oate (III, R = $CH_2CH_2CO_2H$)

(a) *Via the 13-propionyl compound* III (R = COEt). Methyl 12-methoxy-13-propionylpodocarpa-8,11,13-trien-16-oate was prepared by acylation of III (R = H) employing propionyl chloride and $AlCl_3$ in nitrobenzene. The ketone had m.p. 95·5–96° (lit.[5b] m.p. 103·5–105°), ν_{max} 1730 and 1680 cm^{-1}, δ 1·01 (C-15 Me), 1·09 (t, 3H, J = 7 c/s, C-3' Me), 1·26 (C-17 Me), 2·87 (q, 2H, J = 7 c/s, C-2' methylene), 3·65 (CO_2Me), 3·87 (C-12 OMe), 6·76 (C-11 aromatic), 7·34 (C-14 aromatic), λ_{max} 256, 320 mμ (ε = 10300, 4050). Reaction of III (R = COEt) with morpholine and S gave the thiomorpholide m.p. 174° (lit.[5b] m.p. 177–178·5°). Treatment of this thiomorpholide (1 g) with 50% (w/w) H_2SO_4 (10 ml) in HOAc (5 ml) for 9 hr under reflux gave a product which, after chromatography on silicagel and elution with benzene–ether (19:1), yielded the 13-(2'-*carboxyethyl*) *compound* as rods, from light petroleum—$CHCl_3$, m.p. 133–134°. (Found: C, 70·65; H, 8·1; O, 21·5 $C_{22}H_{30}O_5$ requires: C, 70·6; H, 8·1; O, 21·4%); ν_{max} ($CHCl_3$) 3500–2500 (acid OH), 1715 (acid C=O), 1725 cm^{-1} (ester C=O), δ ($CDCl_3$) 1·04 (C-15 Me), 1·27 (C-17 Me), 3·68 (CO_2 Me), 3·81 (C-12 OMe), 6·74 (C-11 aromatic), 6·84 (C-14 aromatic), 10·00 (CO_2H), λ_{max} 282 mμ (ε = 3900).

(b) *Via the* C-13 *malonyl compound* III (R = $COCH_2CO_2Et$); (i) *From the* C-13 *acetyl compound* III (R = Ac). Diethyl carbonate (24 g) was added to NaH (1·18 g, 50% oil dispersion), followed by III (R = Ac; 2 g)[5a] and the mixture stirred and heated under N_2 for 4 hr. Chromatography of the product gave 12-*methoxy*-13-(2'-*ethoxycarbonylacetyl*) *podocarpa*-8,11,13-*trien*-16-*oate* III (R = $COCH_2CO_2Et$; 1·14 g, 47%); ν_{max} 1745 and 1730 (ester C=O), 1680 cm^{-1} (aryl ketone C=O), δ 1·02 (C-15 Me), 1·22 (3H, t, J = 7 c/s, Me of CO_2Et), 1·25 (C-17 Me), 3·66 (CO_2Me), 3·78 (2H, s, C-2' methylene), 3·86 (C-12 OMe), 4·14 (2H, q, J = 7 c/s, methylene of CO_2Et), 6·80 (C-11 aromatic), 7·54 (C-14 aromatic).

(ii) *From the methyl ether* III (R = H). Partial hydrolysis of diethyl malonate with KOH in abs EtOH gave ethyl hydrogen malonate in 87% yield. Reaction of this half-ester with phthaloyl chloride gave ethyl malonyl chloride.[13] Acylation of III (R = H; 6 g) in nitrobenzene (60 ml) with ethyl malonyl chloride (6 g) and $AlCl_3$ (5·3 g) for 3 days at 5° gave a yellow oil (3·3 g) which on chromatography yielded, in the light petroleum–benzene (4:1) eluate, starting material (1·42 g) followed, in the benzene eluate, by the 13-(2'-ethoxycarbonylacetyl) compound (1·67 g, 50%) identical IR and NMR spectra with a sample prepared in (i) above.

Clemmensen reduction of the 13-(2'-*ethoxycarbonylacetyl*) *compound* (III, R = $COCH_2CO_2Et$)

A soln of III (R = $COCH_2CO_2Et$; 2·8 g) in toluene (10 ml) was added to amalgamated Zn wool (12 g) and HCl (8M, 32 ml) and the mixture heated under reflux for 7 hr. Crystallization of the product from ethanol gave needles of *methyl* 12-*methoxy*-13-(2'-*ethoxycarbonylethyl*)*podocarpa*-8,11,13-*trien*-16-*oate* III (R = $CH_2CH_2CO_2Et$; 1·9 g, 68%), m.p. 98·5–100°. (Found: C, 71·3; H, 8·5; O, 20·2. $C_{24}H_{34}O_5$ requires: C, 71·6; H, 8·5; O, 19·9%); ν_{max} 1730 cm^{-1} (ester C=O), δ 0·97 (C-15 Me), 1·20 (3H, t, J = 7 c/s, Me of CO_2Et), 1·22 (C-17 Me), 3·62 (CO_2Me), 3·75 (C-12 OMe), 4·06 (2H, q, J = 7 c/s, methylene of CO_2Et), 6·62 (C-11 aromatic), 6·73 (C-14 aromatic), λ_{max} 285 mμ (ε = 1340).

Hydrolysis of the 13-(2'-*ethoxycarbonylethyl*) *compound*. Treatment of the ester (300 mg) in aq MeOH (13 ml) with KOH (1 g) under reflux for 4 hr gave the 13-(2'-carboxyethyl) compound, m.p. 132–133°, identical mixed m.p. with sample prepared in (a).

4β-*Methoxycarbonyl*-4α-*methyl*-12-*methoxy*-18-*norandrosta*-8,11,13-*trien*-15-*one* (IV)

PCl_5 (810 mg) was reacted with III (R = $CH_2CH_2CO_2H$; 900 mg) for 1 hr at 80° to give the acid chloride which was treated with $AlCl_3$ (510 mg) in nitrobenzene (10 ml) at 5° for 3 days. Chromatography of the product on alumina, elution with benzene, and crystallization from light petroleum–$CHCl_3$ gave needles of 4β-*methoxycarbonyl*-4α-*methyl*-12-*methoxy*-18-*norandrosta*-8,11,13-*trien*-15-*one* (IV; 390 mg, 45%), m.p. 161–161·5°. (Found: C, 74·3; H, 8·0. $C_{22}H_{28}O_4$ requires: C, 74·1; H, 7·9%); ν_{max} 1730 (ester C=O), 1710 cm^{-1} (aryl ketone C=O), δ 1·01 (C-15 Me), 1·25 (C-17 Me), 3·63 (CO_2Me), 3·82 (C-12 OMe), 6·85 (C-11 aromatic), λ_{max} 260, 325 mμ (ε = 8500, 3560).

Methyl 12-*methoxy*-13-*formylpodocarpa*-8,11,13-*trien*-16-oate (III, R = CHO)

(a) *Via the* 13-(*chloromethyl-n-butyl ether*) [III, R = CH(Cl)O^{n}Bu]. Dichloromethyl n-butyl ether (20·2 g) was added, during 30 min, to a cold stirred mixture of III (R = H; 26 g) and $AlCl_3$ (17·3 g) in nitrobenzene (250 ml). After 3 days at 0° the product, isolated in the usual way, was taken up in ether and treated with sat $NaHSO_3$aq for 4 days. Decomposition of the addition product gave the 13-*formyl compound* III (R = CHO; 22 g, 73%) recrystallized from aq EtOH to give needles, m.p. 123·5–125·5°. (Found: C, 72·5; H, 8·2; O, 19·4. $C_{20}H_{26}O_4$ requires: C, 72·7; H, 7·9; O, 19·4%); ν_{max} 1730 (ester C=O), 1690 cm^{-1} (aldehyde C=O), δ 1·00 (C-15 Me), 1·25 (C-17 Me), 3·64 (CO_2Me), 3·85 (C-12 OMe), 6·75 (C-11 aromatic), 7·37 (C-14 aromatic), 10·02 (C-13 CHO), λ_{max} 265, 335 mμ (ε = 10,700, 1900). A similar preparation using $AlCl_3$ in CS_2 gave the 13-formyl compound in 49% yield.

(b) *Via the* 13-(*ethyl glyoxylate*) (III, R = $COCO_2Et$). The methyl ether III (R = H) was reacted under standard Friedel–Crafts conditions with ethyl oxalyl chloride to give the 13-*ethyl glyoxylate* III (R = $COCO_2Et$) as needles from aq EtOH, m.p. 112–113·5°. (Found: C, 68·5; H, 7·6; O, 24·2. $C_{23}H_{30}O_6$ requires: C, 68·6; H, 7·5; O, 23·85%); ν_{max} 1730 (ester C=O), 1680 cm^{-1} (aryl ketone C=O), δ 1·02 (C-15 Me), 1·25 (C-17 Me), 1·37 (3H, t, J = 7 c/s, Me of CO_2Et), 3·64 (CO_2Me), 3·78 (C-12 OMe), 4·28 (2H, q, J = 7 c/s, methylene of CO_2Et), 6·77 (C-11 aromatic), 7·47 (C-14 aromatic); λ_{max} 270, 340 mμ (ε = 11,700, 4500).

Methyl 12-*methoxy*-13-(*glyoxylic acid*)*podocarpa*-8,11,13-*trien*-16-*oate*

The ethyl ester (5 g) was heated under reflux with 2N NaOH (75 ml) for 30 min to give the 13-*glyoxylic*

acid III (R = $COCO_2H$; 4 g, 88%), m.p. 174–176°. (Found: C, 67·3; H, 7·15; O, 25·8. $C_{21}H_{26}O_6$ requires: C, 67·4; H, 7·0; O, 25·6%); ν_{max} ($CHCl_3$) 3500–2500 (acid OH), 1725 (acid, ester C=O), 1675 cm^{-1} (aryl ketone C=O). δ ($CDCl_3$) 1·07 (C-15 Me), 1·30 (C-17 Me), 3·70 (CO_2Me), 3·85 (C-12 OMe), 6·91 (C-11 aromatic), 7·60 (C-14 aromatic), 9·75 (CO_2H). λ_{max} 265, 332 mμ (ε = 9750, 3380).

Methyl 12-*methoxy*-13-*formylpodocarpa*-8,11,13-*trien*-16-*oate*

The keto-acid III (R = $COCO_2H$; 8·2 g) was heated under reflux with aniline (2 g) and water (2 ml) for 45 min. An ethereal extract of this product was washed with 2N HCl and water, and concentrated to a pale yellow oil. Crystallization from aq EtOH gave needles of the 13-formyl compound III (R = CHO, 5·7 g, 81%), m.p. and mixed m.p. 123–125°, identical NMR spectrum

Model experiments

2-(2′-*Cyano*-2′-*ethoxycarbonylvinyl*)*anisole*. To 2-methoxybenzaldehyde (4·3 g) in ethyl cyanoacetate (3·7 g) was added piperidine (125 mg) and the soln stood at 20° for 2 hr, giving yellow needles of 2-(2′-*cyano*-2′-*ethoxycarbonylvinyl*)*anisole* (6·2 g, 87%) from aq EtOH, m.p. 75–76°. (Found: C, 67·2; H, 5·55; N, 5·85. $C_{13}H_{13}NO_3$ requires: C, 67·5; H, 5·7; N, 6·1%); ν_{max} 2220 (αβ-unsat C≡N), 1735 (ester C=O), 1600 cm^{-1} (C=C). δ 1·40 (3H, t, J = 7 c/s, Me of CO_2Et), 3·90 (OMe), 4·35 (2H, q, J = 7 c/s, methylene of CO_2Et), 8·61 (1H, s, vinyl H). λ_{max} 295, 355 mμ (ε = 13,000, 11,200).

2-*Methoxyphenylsuccinic acid*. The homogeneous soln prepared by the addition of NaCN (1·6 g in 2 ml water) to a suspension of 2-(2′-cyano-2′-ethoxycarbonylvinyl)anisole (5·8 g) in EtOH (4 ml) was stood at 20° for 18 hr. Addition of water (20 ml) and conc HCl (60 ml) and heating under reflux for 4 hr gave 2-methoxyphenylsuccinic acid as needles from hot water (4·3 g, 67%), m.p. 175° (lit.[14] m.p. 182–184°).

Methyl 12-*methoxy*-13-(2′-*cyano*-2′-*ethoxycarbonylvinyl*)*podocarpa*-8,11-13-*trien*-16-*oate*

A mixture of III (R = CHO; 2 g), ethyl cyanoacetate (760 mg) and piperidine (100 mg) was heated under reflux in benzene (20 ml) for 5·5 hr using a water separator. The crude product (2·5 g, 97%) was distilled to give the *cyano-ethoxycarbonyl compound* III [R = CH=C(CN)CO_2Et], b.p. 246°/0·05 mm, m.p. 55°. (Found: N, 3·3. $C_{25}H_{31}NO_5$ requires: N, 3·3%); ν_{max} 2210 (αβ unsat C≡N), 1730 (ester C=O), 1600 cm^{-1} (C=C). δ 1·02 (C-15 Me), 1·25 (C-17 Me), 1·40 (3H, t, J = 7 c/s, Me of CO_2Et), 3·61 (CO_2Me), 3·84 (C-12 OMe), 4·30 (2H, q, J = 7 c/s, methylene of CO_2Et), 6·73 (C-11 aromatic), 7·90 (C-14 aromatic), 8·50 (C-1′ vinyl H). λ_{max} 314, 380 mμ (ε = 12,600, 9700).

Methyl 12-*methoxy*-13-(1′,2′-*dicyano*-2′-*ethoxycarbonylethyl*)*podocarpa*-8,11,13-*trien*-16-*oate*

KCN (2·2 g) in water (18 ml) was added to the C-13 2′-cyano-2′-ethoxycarbonylvinyl compound (7 g) in EtOH (64 ml) and the soln heated at 100° for 2 hr, to give the *dicyano derivative* III [R = CH(CN)CH(CN)CO_2Et] as an oil (5 g, 67%). δ 1·01 (C-15 Me), 1·13 (3H, t, J = 7 c/s, Me of CO_2Et), 1·25 (C-17 Me), 2·80 (1H, d, J = 7 c/s, C-1′ methine), 3·36 (2H, q, J = 7 c/s, methylene of CO_2Et), 3·60 (CO_2Me), 3·80 (C-12 OMe), 4·25 (d, J = 7 c/s, C-2′ methine), 6·72 (C-11 aromatic), 7·02 (C-14 aromatic). Attempted hydrolysis of this dicyano compound yielded no pure compounds.

Reaction of aromatic aldehydes with ethyl acetoacetate

The aromatic aldehydes were reacted with ethyl acetoacetate and piperidine according to published methods,[6,15] to give products with quoted m.p. values. The NMR spectra showed the absence of the COMe group, and the presence of the grouping Me—C(—O)— and of two different ethoxycarbonyl groups.

VI R =	δ	
	tert-Me	$CO_2CH_2CH_3$
Phenyl	1·34	0·88, 1·03
o-Methoxyphenyl	1·34	0·78, 1·03
p-Methoxyphenyl	1·33	0·85, 1·07
3,4-Dimethoxyphenyl	1·34	0·90, 1·09

Reaction of III (R = CHO) failed to yield any of the desired adduct.

Methyl 12-*methoxy*-13-(2′,2′-*diethoxycarbonylvinyl*)*podocarpa*-8,11,13-*trien*-16-*oate*

A soln of diethyl malonate (7·3 g), piperidine (1·2 ml) and III (R = CHO, 10 g) in benzene (150 ml) was heated under reflux for 4 hr under a water separator. Working up gave an oil which crystallized from aq EtOH as needles of *methyl* 12-*methoxy*-13-(2′,2′-*diethoxycarbonylvinyl*)*podocarpa*-8,11,13-*trien*-16-*oate* [III, R = CH=C(CO$_2$Et)$_2$] (10·3 g, 73%), m.p. 107–108·5°. (Found: C, 68·6; H, 7·8; O, 23·5. $C_{27}H_{36}O_7$ requires: C, 68·6; H, 7·7; O, 23·7%); ν_{max} 1730 (ester C=O), 1615 cm^{-1} (C=C), δ 1·00 (C-15 Me), 1·25 (C-17 Me), 1·23 and 1·34 (each 3H, triplets, Me of CO$_2$Et), 3·60 (CO$_2$Me), 3·78 (C-12 OMe), 6·66 (C-11 aromatic), 6·98 (C-14 aromatic), 7·80 (1H, s, C-1′ vinyl), λ_{max} 292, 345 mμ (ε = 9050, 5850).

Methyl 12-*methoxy*-13-(1′-*diethoxycarbonylmethyl*-2′,2′-*diethoxycarbonylethyl*)*podocarpa*-8,11,13-*trien*-16-*oate*

The C-13 2′,2′-diethoxycarbonylvinyl compound (1 g) in benzene (5 ml) was added to a soln of sodio diethyl malonate [from diethyl malonate (515 mg) and Na (48 mg)] in benzene (5 ml) and the mixture stood on the steam bath for 24 hr, and at 20° for 3 months. Crystallization of the product from aq EtOH gave flakes of the *tetra-ethyl ester* III, R = CH[CH(CO$_2$Et)$_2$]$_2$, m.p. 92–94·5°. (Found: C, 64·9; H, 7·7. $C_{34}H_{48}O_{11}$ requires: C, 64·5; H, 7·6%); ν_{max} 1755 (α-diester C=O), 1730 cm^{-1} (ester C=O), δ 0·96 (C-15 Me), 1·26 (C-17 Me), 3·62 (CO$_2$Me), 3·82 (C-12 OMe), 6·60 (C-11 aromatic), 6·87 (C-14 aromatic), λ_{max} 290 mμ (ε = 3600).

Methyl 12-*methoxy*-13-(1′-*carboxymethyl*-2′-*carboxyethyl*)*podocarpa*-8,11,13-*trien*-16-*oate* [III, R = CH(CH$_2$CO$_2$H)$_2$]

The tetra-ethyl ester (5 g) was heated under reflux with 50% KOH in MeOH (100 ml) for 2 hr. Isolation of the acidic component gave the tetra-acid (3·68 g, 89%), NMR spectrum integral 4H at 8·80 δ (CO$_2$H). The tetra-acid (2·98 g) was heated at 180° for 1·5 hr, the decarboxylation reaction being monitored by the loss in weight of the starting material, to give the *di-acid* (2·1 g, 84%) as a glass, ν_{max} (CHCl$_3$) 3500–2500 (acid OH), 1725 cm^{-1} (acid and ester C=O), δ (CDCl$_3$) 1·07 (C-15 Me), 1·30 (C-17 Me), 3·68 (CO$_2$Me), 3·86 (C-12 OMe), 6·85 (C-11 aromatic), 7·21 (C-14 aromatic), 9·65 (2H, CO$_2$H). The corresponding acid chloride was prepared in the usual manner with PCl$_5$ but attempted ring closure (AlCl$_3$–PhNO$_2$) gave a product whose spectral properties did not indicate the presence of the desired indanone.

Methyl 12-*methoxy*-13-(2′-*carboxyvinyl*)*podocarpa*-8,11,13-*trien*-16-*oate* (III, R = CH=CHCO$_2$H)

A soln of III (R = CHO; 3·6 g), malonic acid (1·9 g), pyridine (18 ml) and piperidine (0·05 g) was heated at 100° for 3 hr, to give needles of III (R = CH=CHCO$_2$H; 3·4 g, 84%), m.p. 178–179·5. (Found: C, 70·8; H, 7·7; O, 21·25. $C_{22}H_{28}O_5$ requires: C, 70·9; H, 7·6; O, 21·5%); ν_{max} (CHCl$_3$) 3500–2500 (acid OH), 1720 (ester C=O), 1690 (α,β-unsat acid C=O), 1630 cm^{-1} (conj C=C), δ (CDCl$_3$) 1·05 (C-15 Me), 1·28 (C-17 Me), 3·68 (CO$_2$Me), 3·85 (C-12 OMe), 6·52 (1H, d, J = 16 c/s, C-2′ vinyl), 6·80 (C-11 aromatic), 7·72 (C-14 aromatic), 8·03 (1H, d, J = 16 c/s, C-1′ vinyl). Attempted ring closure of the corresponding acid chloride was unsuccessful.

3,4-*Dimethyl*-6-*crotonylanisole*

3,4-Dimethylanisole (9 g) and crotonic acid (9·9 g) in polyphosphoric acid (60 g) were stirred at 56° for 45 min. The soln was poured on to ice and worked up to give 3,4-*dimethyl*-6-*crotonylanisole* (7·5 g, 56%), b.p. 110–114°/0·05 mm. (Found: C, 76·6; H, 8·1; O, 15·55. $C_{13}H_{16}O_2$ requires: C, 76·4; H, 7·9; O, 15·7%); ν_{max} 1670 (C=O) and 1625 cm^{-1} (C=C), δ 1·87 (3H, m, vinyl Me), 2·17 and 2·22 (each 3H, Ar–Me), 3·74 (3H, OMe), 6·50–6·67 (3H, m, C-2 aromatic and vinyl H), 7·15 (1H, d, J = 1 c/s, C-5 aromatic), λ_{max} 267, 330 mμ (ε 8500, 3860).

Methyl 12-*methoxy*-13-*crotonylpodocarpa*-8,11,13-*trien*-16-*oate*

(a) Compound III (R = H; 364 mg) and crotonic acid (175 mg) were added to polyphosphoric acid (5 g) and the mixture stirred at 28° for 3 hr. The mixture was poured on to ice and extracted to yield the 13-*crotonyl compound* III (R = COCH=CHMe; 333 mg, 75%), m.p. 104–105·5° (from light petroleum). (Found: C, 74·5; H, 8·3; O, 17·5. $C_{23}H_{30}O_4$ requires: C, 74·6; H, 8·2; O, 17·3%); ν_{max} 1730 (ester C=O), 1670 (αβ unsat C=O), 1625 cm^{-1} (conj C=C), δ 1·00 (C-15 Me), 1·23 (C-17 Me), 1·89 (m, vinyl Me), 3·58 (CO$_2$Me), 3·75 (C-12 OMe), 6·67 (3H, m, C-11 and vinyl H), 7·05 (1H, d, J = 1 c/s, C-14 aromatic H), λ_{max} 245, 274 and 335 mμ (ε = 14,600, 10,700, 4080)

(b) The methyl ether III (R = H; 2·05 g) anhydrous AlCl$_3$ (1·8 g) and nitrobenzene (20 ml) were stirred

at 0° until homogenous. Crotonyl chloride (790 mg) was added over 10 min, the mixture stirred for 15 min and stood at 0° for 3 days. Chromatography of the total product gave starting material (315 mg, 23%) followed by the crotonyl compound (1·45 g, 77%), m.p. and m.m.p. 104–105·5°.

Attempted cyclization of methyl 12-*methoxy*-13-*crotonylpodocarpa*-8,11,13-*trien*-16-*oate*

(a) $AlCl_3$–CS_2 (α) crotonyl chloride (1 g) and $AlCl_3$ (2·6 g) were added to CS_2 (10 ml) and the mixture heated to reflux. Methyl 12-methoxypodocarpa-8,11,13-trien-16-oate (1·96 g) was added and the mixture heated to reflux for 2 hr. Chromatography of the product on alumina gave (i) from light petroleum–benzene (1:1), starting material (90 mg, 5%), (ii) from benzene, *methyl* 1′-*oxo*-3′-*methyl*-4′-*oxacyclohexano*(5′,6′:12,-13)*podocarpa*-8,11,13-*trien*-16-*oate* (VI; 617 mg, 30%), as needles from EtOH, m.p. 175–175·5°. (Found: C, 73·8; H, 8·0; O, 18·1. $C_{22}H_{28}O_4$ requires: C, 74·1; H, 7·9; O, 18·0%); ν_{max} 1730 (ester C=O) and 1695 cm^{-1} (aryl ketone C=O), δ 1·00 (C-15 Me), 1·27 (C-17 Me), 1·47 (d, J = 6 c/s, C-3′ Me), 2·51 (d, J = 7 c/s, C-2′ methylene), 3·65 (CO_2Me), 4·16–4·65 (m, C-3′ methine), 6·80 (C-11 aromatic), 7·47 (C-14 aromatic), λ_{max} 264, 338 mμ (ε = 18,500, 5450). (iii) from benzene–ether (1:1), the 13-crotonyl compound (360 mg, 18%), m.p. and mixed m.p. 104–105·5°.

(β) Repetition of the above experiment with refluxing for 6 hr gave the chromanone VI in 56% yield.

(γ) Repetition at 20° for 4 days gave starting material (23%) and the crotonyl compound (75%).

(δ) Repetition of the experiment as in (α) with a stream of anhyd HCl bubbling through the reaction mixture gave starting material (1%), the chromanone (18%) and the crotonyl compound (39%).

(b) Attempted cyclization of the crotonyl compound with $AlCl_3$, with H_2SO_4, with formic acid–polyphosphoric acid, or with hydrogen fluoride gave either starting material or unidentifiable mixtures.

4β-*Methoxycarbonyl*-4α-*methyl*-12-*methoxy*-18-*norandrosta*-8,11,13-*trien*-17-*one* (IX)

Reaction of III (R = H; 3·34 g) with acrylyl chloride (1·5 g) and $AlCl_3$ (3·7 g) in nitrobenzene (30 ml) for 3 days at 20° gave an oil (2·99 g) which on chromatography on alumina and elution with benzene yielded the androstane derivative as an oil, (118 mg, 3%), ν_{max} 1730 (ester C=O), 1710 cm^{-1} (aryl ketone (C=O), δ 1·02 (C-15 Me), 1·25 (C-17 Me), 3·62 (CO_2Me), 3·80 (C-12 OMe), 6·80 (C-11 aromatic H).

Methyl 12-*methoxy*-13-(3′-*chloropropionyl*)*podocarpa*-8,11,13-*trien*-16-*oate* (III, R = $COCH_2CH_2Cl$)

(a) The methyl ether III (R = H; 441 mg) and 3-chloropropionic acid (270 mg) in polyphosphoric acid (5 g) were stirred at 35° for 75 min, to give *methyl* 12-*methoxy*-13-(3′-*chloropropionyl*)*podocarpa*-8,11,13-*trien*-16-*oate* (363 mg, 63%) as needles from aq EtOH, m.p. 90–91°. (Found: C, 67·5; H, 7·8; O, 16·1. $C_{22}H_{29}ClO_4$ requires: C, 67·2; H, 7·4; O, 16·3%); ν_{max} 1730 (ester C=O) and 1675 cm^{-1} (aryl ketone C=O), δ 1·02 (C-15 Me), 1·27 (C-17 Me), 3·67 (CO_2Me), 3·92 (C-12 OMe), 6·80 (C-11 aromatic H), 7·44 (C-14 aromatic H), λ_{max} 259, 323 mμ (ε = 10,200, 3740).

(b) The methyl ether III (R = H; 1·68 g), 3-chloropropionyl chloride (1·8 g) and $AlCl_3$ (1·56 g) in nitrobenzene were stood at 0° for 4 days. Working up in the usual way gave a brown solid which was dissolved in EtOH and decolourised with charcoal. Addition of water gave the 13-(3′-chloropropionyl) ketone (503 mg, 30%). Concentration of the ethanolic mother liquors and addition of ether gave needles of *methyl* 12-*methoxy*-13-(3′-*ethoxypropionyl*)*podocarpa*-8,11,13-*trien*-16-*oate* III (R = $COCH_2CH_2OEt$; 1·04 g, 62%) from EtOH, m.p. 125·5–126°. (Found: C, 71·8; H, 8·55; O, 19·8. $C_{24}H_{34}O_5$ requires: C, 71·6; H, 8·5; O, 19·9%); ν_{max} 1730 (ester C=O), 1680 cm^{-1} (aryl ketone C=O), δ 1·02 (C-15 Me), 1·15 (C-17 Me), 3·11 (2H, t, J = 6 c/s, C-2′ methylene), 3·47 (2H, q, J = 7 c/s, methylene of C-3′ OEt), 3·65 (CO_2Me), 3·72 (2H, t, J = 6 c/s, C-3′ methylene), 3·90 (C-12 OMe), 6·80 (C-11 aromatic), 7·38 (C-14 aromatic), λ_{max} 257, 320 mμ (ε = 11,600, 3860).

Attempted cyclization of the 13-(3′-*chloropropionyl*) *ketone*

3-Chloropropionyl chloride (2·9 g) was added to a refluxing mixture of III (R = H; 4·62 g) and $AlCl_3$ (6·15 g) in CS_2 (50 ml). After 6 hr the mixture was worked up to give a solid (5·13 g) which was chromatographed on silicagel. Elution with benzene yielded needles of *methyl* 12-*hydroxy*-13-(3′-*chloropropionyl*)-*podocarpa*-8,11,13-*trien*-16-*oate* XIII (3·9 g, 70%) from MeOH, m.p. 108·5–109·5°. (Found: C, 66·4; H, 7·3; O, 17·2. $C_{21}H_{27}ClO_4$ requires: C, 66·6; H, 7·2; O, 16·9%); ν_{max} 1732 (ester C=O) and 1650 cm^{-1} (aryl ketone C=O), δ 1·01 (C-15 Me), 1·27 (C-17 Me), 3·66 (CO_2Me), 6·83 (C-11 aromatic), 7·34 (C-14 aromatic), λ_{max} 266, 346 mμ (ε = 13,200, 3640).

Methyl 12-methoxy-13-(2'-methylpropionyl)podocarpa-8,11,13-trien-16-oate (III, R = $COCHMe_2$)

Acylation of III (R = H; 9 g) with isobutyryl chloride (3 g) in nitrobenzene (90 ml) containing $AlCl_3$ (4·9 g) gave the *13-(2'-methylpropionyl) compound* (8·9 g, 80%), m.p. 85–87°, b.p. 265–275°/0·5 mm. (Found: C, 74·1; H, 8·7; O, 17·0. $C_{23}H_{32}O_4$ requires: C, 74·2; H, 8·7; O, 17·2%); ν_{max} 1730 and 1680 cm^{-1}, δ 1·01 (C-15 Me), 1·05 (6H, d, J = 7 c/s Me_2CH), 1·24 (C-17 Me), 3·64 (CO_2Me), 3·84 (C-12 OMe), 6·75 (C-11 aromatic), 7·18 (C-14 aromatic), λ_{max} 257, 315 mμ (ε = 6900, 2530).

Methyl 12-methoxy-13-(2'-bromo-2'-methylpropionyl)podocarpa-8,11,13-trien-16-oate

Bromine (570 mg) in HOAc (4 ml) was added to III (R = $COCHMe_2$; 1·1 g) in HOAc (30 ml) containing HBr (6 drops) during 15 min and stirring was continued for 30 min. Working up gave needles (from MeOH) of the *bromo-ketone* III (R = $COCBrMe_2$; 970 mg, 72%), m.p. 142–143·5°. (Found: C, 61·0; H, 6·8; O, 14·4. $C_{23}H_{31}BrO_4$ requires: C, 61·0; H, 6·9; O, 14·1%); ν_{max} 1735 and 1705 cm^{-1}, δ 1·03 (C-15 Me), 1·27 (C-17 Me), 1·90 (6H, s, $—CBrMe_2$), 3·68 (CO_2Me), 3·78 (C-12 OMe), 6·80 (C-11 aromatic), 7·13 (C-14 aromatic), λ_{max} 285 mμ (ε = 2850). Attempted cyclization of this bromo-ketone with $AlCl_3$–CS_2 was unsuccessful.

Acetylation of methyl 12-methoxy-13-ethylpodocarpa-8,11,13-trien-16-oate (III, R = Et)

A mixture of cold (0°) nitrobenzene (40 ml), $AlCl_3$ (2·44 g) and AcCl (1·44 g) was stirred until homogeneous. The C-13 ethyl compound III (R = Et; 4 g) was added slowly with stirring and the mixture was held at 0° for 3 days. The red oily product (4·2 g) was chromatographed on alumina to yield:

(i) Light petroleum–benzene (4:1), starting material (1·29 g, 31%), m.p. and mixed m.p. 110–111°.

(ii) Light petroleum–benzene (1:1), the *enol lactone* X (R = Et; 1·05 g, 25%), m.p. 144·5–146·5°. (Found: C, 76·7; H, 8·1; O, 14·2. $C_{22}H_{28}O_3$ requires: C, 77·6; H, 8·3; O, 14·1%); ν_{max} (CCl_4) 1760, ($CHCl_3$) 1745 cm^{-1} (γ,δ-unsat δ-lactone C=O), δ 0·97 (C-15 Me), 1·25 (C-17 Me), 1·95 (s, 3H, vinyl Me), 3·52 (2H, C-7 methylene), 3·78 (C-12 OMe), 6·58 (C-11 aromatic), 6·78 (C-14 aromatic), λ_{max} 285 mμ (ε = 3000).

(iii) Benzene, an oil, the 14-acetyl derivative (XI; 142 mg, 3%), ν_{max} 1730 ester C...O), 1700 cm^{-1} (aryl C=O), δ 1·02 (C-15 Me), 1·24 (C-17 Me) 2·37 (s, 3H, C-14 Ac), 3·65 (CO_2Me), 3·80 (C-12 OMe), 6·74 (C-11 aromatic).

Methyl 6-acetyl-12-methoxy-13-ethylpodocarpa-8,11,13-trien-16-oate (XII)

The lactone VIII (R = Et; 824 mg) was heated with NaOH in MeOH for 4 hr to give an orange oil (174 mg, 20%). Treatment with ethereal diazomethane gave a solid, crystallized from aq EtOH as flakes of *methyl 6-acetyl-12-methoxy-13-ethylpodocarpa-8,11,13-trien-16-oate* (XII; 122 mg, 55%), m.p. 124–125·5°. (Found: C, 74·4; H, 8·8; O, 17·3. $C_{23}H_{32}O_4$ requires: C, 74·2; H, 8·7; O, 17·2%); ν_{max} 1725 cm^{-1} (alkyl ketone and ester C=O), δ 0·97 (C-15 Me), 1·25 (C-17 Me), 2·17 (s, 3H, C-6 Ac), 3·66 (CO_2Me), 3·77 (C-12 OMe), 6·68 (2H, C-11, 14 aromatics), λ_{max} 282 mμ (ε = 2100).

Methyl 12-methoxy-13-methylpodocarpa-8,11,13-trien-16-oate (III, R = Me)

Amalgamated Zn wool (35 g) was added to a soln of III (R = CHO, 9 g) in toluene (60 ml) and 6M HCl (100 ml). The mixture was heated under reflux for 7 hr to give flakes of *methyl 12-methoxy-13-methylpodocarpa-8,11,13-trien-16-oate*, from EtOH, m.p. 115–116°. (Found: C, 75·6; H, 8·9; O, 15·2. $C_{20}H_{28}O_3$ requires: C, 75·9; H, 8·9; O, 15·2%); ν_{max} 1730 cm^{-1} (ester C=O), δ 0·98 (C-15 Me), 1·23 (C-17 Me), 2·08 (C-13 Me), 3·63 (CO_2Me), 3·75 (C-12 OMe), 6·58 (C-11 aromatic), 6·68 (C-14 aromatic), λ_{max} 282 mμ (ε = 2900).

Acetylation of methyl 12-methoxy-13-methylpodocarpa-8,11,13-trien-16-oate

Reaction of III (R = Me; 4 g) in nitrobenzene (40 ml) with AcCl (1·5 g) and $AlCl_3$ (2·5 g) gave a red oil. Chromatography afforded: (i) light petroleum–benzene (4:1), starting material (2·13 g, 52%) and (ii) benzene, the *unsaturated lactone* X (R = Me; 1·12 g, 27%) as needles from aq EtOH, m.p. 117–119°. (Found: C, 77·0; H, 8·2; O, 14·6. $C_{21}H_{26}O_3$ requires: C, 77·3; H, 8·0; O, 14·7%); ν_{max} (CCl_4) 1760, ($CHCl_3$) 1745 cm^{-1} (γ,δ-unsat δ-lactone C=O), δ 0·97 (C-15 Me), 1·25 (C-17 Me), 1·95 (3H, vinylic Me), 2·12 (C-13 Me), 3·52 (2H, C-7 methylene), 3·77 (C-12 OMe), 6·58 (C-11 aromatic), 6·80 (C-14 aromatic), λ_{max} 280 mμ (ε = 4080).

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