Journal of Natural Products
Vol. 52, No. 1, pp. 85-94, Jan-Feb 1989

PHOTOOXIDATION OF RESIN ACIDS

BÁRBARA GIGANTE, M. JOÃO MARCELO-CURTO,

LNETI, DTIQ, Serviço de Química Fina, Estrada das Palmeiras, 2745 Queluz, Portugal

ANA M. LOBO,* SUNDARESAN PRABHAKAR,

Secção de Química Orgânica Aplicada, Departamento de Química, FCT, UNL, Quinta da Torre, 2825 Monte da Caparica, Portugal

ALEXANDRA J. SLAWIN, HENRY S. RZEPA, and DAVID J. WILLIAMS

Department of Chemistry, Imperial College of Science and Technology, London SW7 2AY, UK

ABSTRACT.—The photooxidation of methyl dehydroabietate [**1**] has been systematically studied, and the various photoproducts have been identified by ^{1}H-nmr, ms, and X-ray analysis. The unprecedented oxidation at position 2 of ring A is reported.

Resin acids are useful raw materials for the chemical industry and have been the object of intense interest for well over five decades. Among the most salient studies are their conversion to the steroid framework (1–5), the gibberelin skeleton (6,7), a variety of pharmacologically active terpenoids (8,9) as well as additives in polymers (10). Because aging due to aerial oxidation is frequently associated with alteration of the chemical properties of these compounds (11), we report here work on the photo-oxygenation of methyl dehydroabietate [**1**] and methyl 7-oxo-dehydroabietate [**2**], both resin acids easily obtained from crude pine resin.

RESULTS AND DISCUSSION

When a 0.2 M solution of **1** in *t*-BuOH was irradiated for 38 h with a mercury vapor lamp with exposure to air, methyl 7-oxo-dehydroabietate [**2**] and methyl 13-acetyl-7-oxo-podocarpa-8,11,13-trien-15-oate [**3**] were obtained in 37 and 1% isolated yields, respectively, together with unreacted starting material (47%). Compounds **2** and **3** have been previously obtained: **2** by CrO_3 oxidation of **1** (12,13) and **3** by reaction of **2** with molecular O_2 followed by reduction (13,14).

Irradiation of **2** under similar conditions for 73 h yielded 30% of **3**, 21% of **4** (Scheme 1) identified as its acetate **5**, and 12% of **6**, but in a solvent of lower dielectric constant, such as *n*-hexane, the starting material was recovered after ca. 5 days of irradiation with only trace amounts of **3** and **4** being formed.

Compound **6**, $C_{20}H_{22}O_5$ (by ms), mp 206–207.5°, showed in its ir spectrum three more carbonyl absorptions at 1700, 1689, and 1681 cm^{-1}, in addition to the carbonyl ester absorption at 1726 cm^{-1}. Comparison of its ^{1}H-nmr spectrum with that of the diketone **3** showed great similarities, except in the region of δ 3.2–2.4 ppm. Here a complex pattern of 6 one-proton double doublets from irradiation experiments suggested that, apart from the 7-keto function, the molecule contained another carbonyl with two adjacent methylene groups, i.e., at carbon 2 of ring A. An X-ray analysis of **6** (Figure 1) confirmed this assignment. This unprecedented functionalization of C-2 is under study. It is interesting to note that the introduction of the carbonyl function at C-2 in **6** induces a stronger deshielding in the 10-Me function (0.039 ppm) relative to the diketone **3** than in the corresponding 4-Me function (0.004), which remains largely unperturbed. Such an effect is probably the result of the buttressing of ring A coupled with the flattening experienced by ring B from the presence of three sp^2 carbons at C-7, C-8, and C-9. The 10-Me group will thus be directed into the stronger deshielding zone of the aromatic ring (15).

SCHEME 1

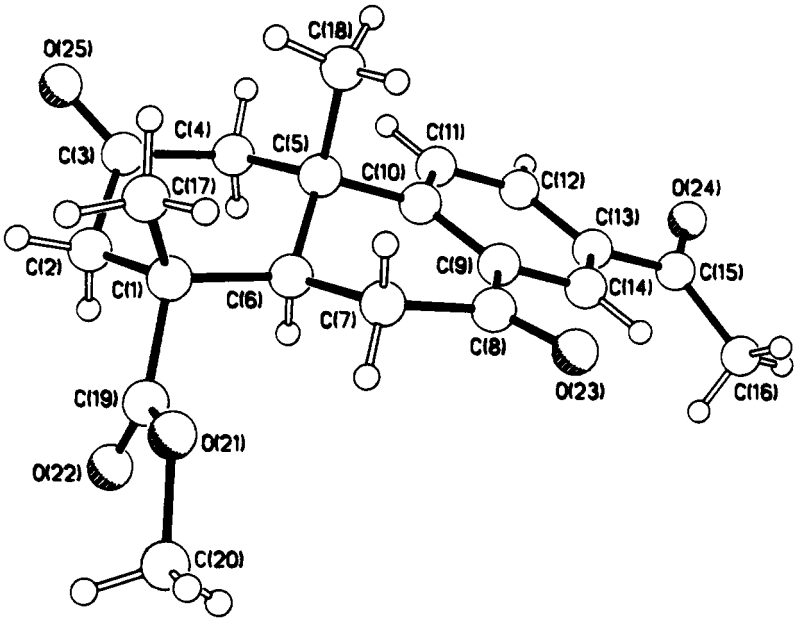


FIGURE 1. 3D Structure for **6** obtained by X-ray analysis with atomic labeling. Oxygen atoms appear as shaded circles.

Increasing the period of irradiation of **2** (ca. 3 weeks) gave rise (by gc) to **3** (34%), **4** (31%), **6** (4%), as well as to six other compounds: **7** (0.5%), **8** (1.5%), **9** (1%), **10** (1.5%), **11** (0.5%), **12** (0.5%), and **13** (8%); all compounds were quantitated after separation by preparative tlc. The appearance of compound **13** in the gc analyses is an artifact resulting from partial dehydration of **4**. Their ^{1}H-nmr spectra (Table 1) showed that the Me groups at C-4, C-10, and in the ester function had remained intact, as well as the three aromatic protons at H-11, H-12, and H-14, with the exception of compound **11**. However, the typical doublet at δ ca. 1.2 ppm for the isopropyl methyls at C-13 present in **2** became a singlet in compounds **7** and **8** and shifted towards lower field (δ 1.6 ppm) as in the tertiary alcohol **4**, indicating an oxygenated function at C-15. In compounds **9**, **10**, and **11** the isopropyl doublet was also absent and had been replaced by an acetyl group (δ 2.6–2.7 ppm, ν max ca. 1680 cm^{-1}) as in **3** and **6**, which also causes a noticeable shift towards a lower field of the adjacent aromatic protons.

Compound **10**, $C_{20}H_{24}O_5$ by mass measurement, having a hydroxy function (by ir), yielded the triketone **6** on oxidation by CrO_3, showing that the alcohol function is at C-2. The presence of a one-proton multiplet at δ 4.18 (W½ 28 Hz) is characteristic of a 2β-H geminal with a hydroxy group (16,17). The molecular ion of **8** at *m/z* 360 is in agreement with formula $C_{21}H_{28}O_5$. Its strong similarity with the ^{1}H-nmr spectrum of **10**, except for the presence of a 13-hydroxy-isopropyl group, led us to assign the structure depicted.

The lactol structures shown were attributed to compounds **7** and **9**, the only differences being in the groups present at C-13, a hydroxy-isopropyl for **7** and an acetyl group for **9**. The stereochemistry of the ring A/B junction of lactol **9** was compared with the triketone **14** (18) and found by ^{1}H nOe to be *cis* for the former and *trans* for the latter, a conclusion which found theoretical support in molecular modeling studies (19).

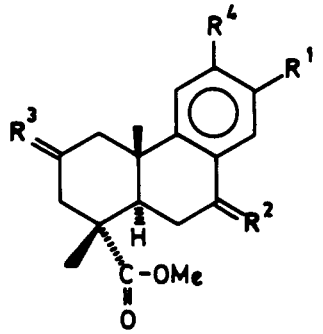
The acid function in both **7** and **9** was put in evidence by the reaction with CH_2N_2 and isolation of the open chain methyl esters **15** and **16** (Scheme 2).

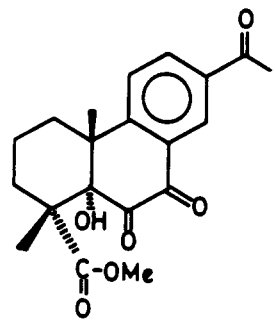
TABLE 1. ^{1}H-nmr Data ($CDCl_3$/TMS).[1]

Compound	4-Me	10-Me	COOMe	Ac	1′-Me_2	H-11	H-12	H-14	H_2-6
1	1.269	1.206	3.656	—	1.218 d (7.5)	7.161 d (9)	6.992 d (9)	6.877	—
2	1.343	1.260	3.652	—	1.248 d (7.5)	7.285 d (9)	7.403 d (9)	7.872	2.718 dd (3,12)
4	1.348	1.265	3.656	—	1.583	7.352 d (10)	7.737 d (10)	8.058	2.728 d (11)
8	1.383	1.304	3.681	—	1.588	7.376 d (9)	7.759 d (9)	8.073	2.691 dd (3,12)
3	1.363	1.289	3.676	2.637	—	7.502 d (7.5)	8.151 d (7.5)	8.548	2.735 dd (3,12)
6	1.367	1.328	3.759	2.652	—	7.392 d (9)	8.200 d (9)	8.592	—
10	1.402	1.328	3.701	2.647	—	7.524 d (9)	8.176 d (9)	8.553	2.730 d (12)
11	1.348	1.269	3.671	2.681	—	6.916	—	8.489	2.681 d (12)
12	1.363	1.247	3.676	—	—	7.499 d (9)	8.212 d (9)	8.705	2.735 d (12)
13	1.348	1.270	3.658	—	—	7.341 d (8)	7.661 d (8)	8.051	2.718 m
5	1.343	1.260	3.656	—	1.759	7.333 d (9)	7.518 d (9)	7.978	2.719 m

Compound	1-Me	3-Me	COOMe	Ac	7′-Me_2	H-6′	H-5′	H-3′	2-OH
7	1.510	1.624	3.838	—	1.598	7.435 d (9)	7.764 d (9)	8.175	6.367
15	1.465	1.553	3.386 3.832	—	1.568	7.420 d (7)	7.536 d (7)	7.822	—
9	1.515	1.671	3.852	2.647	—	7.562 d (9)	8.200 d (9)	8.641	6.445
16	1.505	1.603	3.460 3.862	2.608	—	7.585 d (7)	8.009 d (7)	8.303	—

[1]Data are δ (ppm), multiplicity, and *J* (in parentheses) in Hz.





1 $R^1=Me_2CH$; $R^2=H,H$; $R^3=H,H$; $R^4=H$
5 $R^1=Me_2C(OAc)$; $R^2=O$; $R^3=H,H$; $R^4=H$
6 $R^1=Ac$; $R^2=O$; $R^3=O$; $R^4=H$
8 $R^1=Me_2C(OH)$; $R^2=O$; $R^3=\alpha$-OH,β-H; $R^4=H$
10 $R^1=Ac$; $R^2=O$; $R^3=\alpha$-OH,β-H; $R^4=H$
11 $R^1=Ac$; $R^2=O$; $R^3=H,H$; $R^4=OH$
12 $R^1=CO_2H$; $R^2=O$; $R^3=H,H$; $R^4=H$
13 $R^1=Me(CH_2)C$; $R^2=O$; $R^3=H,H$; $R^4=H$

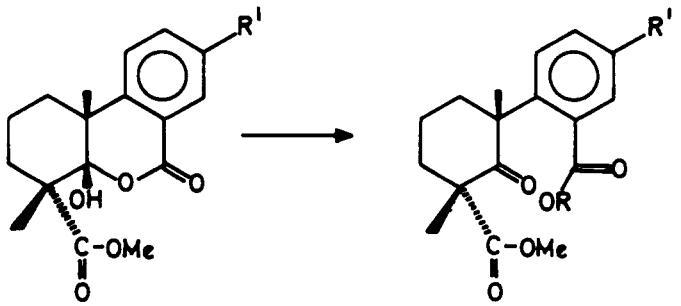
14

Compound **11**, $C_{20}H_{24}O_5$ by mass measurement, had in its ^{1}H-nmr spectrum only two sharp singlets for the aromatic protons (no meta coupling), and an exchangeable proton (D_2O) at low field (δ 12.6). The observation of a strong bathochromic shift in its uv spectrum on addition of an NaOH solution coupled with the absorption at 1640 cm^{-1} in its ir spectrum (typical of an o-hydroxy acetophenone system) indicated that the phenolic function is located at C-12 and not at C-11.

The close similarity of the ^{1}H-nmr spectra of **3** and **12** ($[M]^+$ 330), the typical ir absorption at 3500–2500 and 1706 cm^{-1} for a carboxylic acid function, and rapid reaction with CH_2N_2 led us to assign to **12** the structure depicted, described previously by Ohta (20).

The oxidation by molecular oxygen proposed by Ritchie *et al.* (21) via the intermediate hydroperoxides of type **17**, which subsequently decompose in a protic solvent to give either the corresponding alcohol or the corresponding ketone (Scheme 3), seems to account for the cascade formation of the majority of the products isolated.

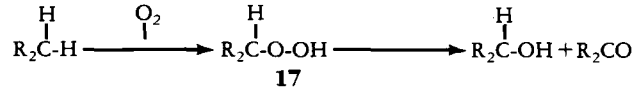
However, two aspects deserve special mention. The first refers to the presence of both lactols **7** and **9**, itself indicative of oxidation occurring also at C-6, which is then rapidly oxidized to the lactol with loss of such carbon. It is interesting to note that



7 $R^1=Me_2C(OH)$
9 $R^1=Ac$

15 R=Me, $R^1=Me_2C(OH)$
16 R=Me, $R^1=Ac$

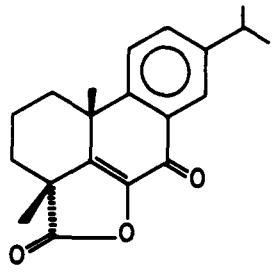
SCHEME 2



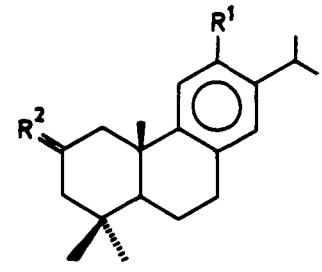
SCHEME 3

Wenkert *et al.* (22) detected the formation in high yield of keto-lactone **18** on exposure of **2** to *t*-BuO_2H, a species which encounters its obvious analogue in the intermediate hydroperoxide at C-15.

The second point is the oxidation at C-2 in compounds **6**, **8**, and **10**, as this position, apart from the fact that it corresponds to the least hindered methylene group in ring A, is deactivated due to the absence of any adjacent functionality. These compounds are structurally related to natural products like salviol [**19**] (23–25) and 2-keto-ferruginol [**20**] (26), for which a biosynthesis along similar lines can thus be envisaged.



18



19 R^1=OH; R^2=α-OH, β-H
20 R^1=OH; R^2=O

EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES.—*Photooxidation reactions were carried out in a* Pyrex flask by irradiation with >300 nm uv light from a Philips HPR 125W mercury lamp. Melting points were determined on a Reichert Thermovar melting point apparatus and are uncorrected. Ir spectra were recorded on a Perkin-Elmer 457 or 298 spectrophotometer. Uv spectra were recorded on a Perkin-Elmer 123 or Hitachi 150-20 spectrophotometer. Optical rotations were measured on a Perkin-Elmer 241 polarimeter. ^{1}H-nmr spectra were recorded on a Brücker CXP 300 MHz spectrometer and are given in ppm (δ) with TMS as internal standard. The abbreviations s, d, t, dd, and m refer to singlet, doublet, triplet, doublet of doublets, and multiplet, respectively. *Mass spectra were determined on an* A.E.I. MS-9 *or on a* Kratos MS 25RF instrument at 70 eV. Gc analyses were performed using the "bonded" methyl silicone DB-1 as a 25 m, 0.1 μ film, fused silica column, with a Carlo Erba HRGC 5160 gas chromatograph; a temperature program (190° for 5 min, followed by a temperature programming up to 210° at 15°/min and 210° for 10 min) was used in most of the work, with He as the carrier gas (split ratio of 100/1). Si gel used for flash column chromatography (27) was Merck Si gel 60 (230–400 mesh). Si gel for analytical and preparative tlc was Merck Si gel GF254. Compounds were visualized by uv light or spraying with 10% H_2SO_4 in EtOH followed by heating. *Microanalysis was performed on a Carlo Erba 1106R microanalizer.* Organic extracts were dried over anhydrous Na_2SO_4. Solvents were purified and dried by standard methods (28).

CRYSTAL DATA FOR COMPOUND **6**.[1]—$C_{20}H_{22}O_5$, M = 342.4, monoclinic, a = 21.701(2), b = 7.747(1), c = 10.913(1) Å, β = 111.70(1)°, U = 1704 Å^3, space group C2, Z = 4, D_C = 1.33 gcm^{-3}, Cu radiation, l = 1.54178 Å, μ (Cu-K_α) = 6 cm^{-1}, F (000) = 591. Data were measured on a Nicolet R3m diffractometer with Cu-K_α radiation (graphite monochromator) using ω-scans. Of the 1256 independent reflections measured ($2\theta \leq 116°$), 1181 had $|F_o| > 3\sigma(|F_o|)$ and were considered to be observed. The data were corrected for Lorentz and polarization factors; no absorption correction was applied. The structure was solved by direct methods. The non-hydrogen atoms were refined anisotropically. The positions of the hydrogen atoms were idealized, C-H = 0.96 Å, assigned isotropic thermal parameters,

[1]Atomic coordinates for this structure have been deposited with the Cambridge Crystallographic Data Centre, and can be obtained on request from Dr. Olga Kennard, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW, UK.

U(H) = 1.2 U_{eq}(C), and allowed to ride on their parent carbon atoms. Refinement was by block-cascade, full-matrix least-squares to R = 0.033, R_w = 0.037 [$w^{-1} = \sigma^2(F) + 0.00063\ F^2$]. The maximum and minimum residual electron densities in the final ΔF map were 0.14 and −0.11 eÅ^{-3}, respectively. The mean and maximum shift/error in the final refinement were 0.009 and 0.049, respectively. Final atomic coordinates are listed in Table 2.

TABLE 2. Atomic Coordinates (× 10^4) and Temperature Factors (Å^2 × 10^3) for Compound **6**.

Atom	*x*	*y*	*z*	U*[a]
C-1	2756(1)	3305(4)	7878(3)	45(1)
C-2	3020(1)	1817(4)	7270(3)	57(1)
C-3	2493(2)	571(4)	6492(3)	51(1)
C-4	1893(2)	1354(4)	5451(3)	51(1)
C-5	1581(1)	2838(4)	5975(3)	42(1)
C-6	2126(1)	4125(4)	6797(2)	40(1)
C-7	1829(1)	5594(4)	7316(3)	48(1)
C-8	1258(1)	6464(4)	6260(3)	44(1)
C-9	953(1)	5571(4)	4969(3)	40(1)
C-10	1096(1)	3858(4)	4814(2)	41(1)
C-11	764(1)	3093(4)	3590(3)	55(1)
C-12	322(2)	4023(5)	2565(3)	62(1)
C-13	195(1)	5743(5)	2705(3)	52(1)
C-14	509(1)	6512(4)	3914(3)	49(1)
C-15	−284(2)	6695(6)	1543(3)	69(1)
C-16	−281(2)	8626(5)	1553(4)	77(2)
C-17	2654(2)	2661(5)	9119(3)	59(1)
C-18	1167(2)	2046(4)	6719(3)	54(1)
C-19	3287(1)	4717(4)	8243(3)	47(1)
C-20	3717(2)	7205(5)	9508(3)	68(1)
O-21	3284(1)	5716(3)	9234(2)	59(1)
O-22	3663(1)	4926(4)	7686(2)	66(1)
O-23	1052(1)	7842(3)	6473(2)	66(1)
O-24	−665(1)	5888(5)	623(3)	109(1)
O-25	2566(1)	−978(3)	6616(2)	75(1)

[a]*Equivalent isotropic U defined as one third of the trace of the orthogonalized U tensor.

PHOTOOXIDATION OF METHYL 13-ISOPROPYL-PODOCARPA-8,11,13-TRIEN-15-OATE [**1**] (METHYL DEHYDROABIETATE).—A 0.2 M solution of **1** (1.87 g) in *t*-BuOH was irradiated for 38 h. The reaction mixture was diluted with CH_2Cl_2 and concentrated to yield a mixture of products which by preparative tlc gave unreacted **1** (47%) and compounds **2** and **3**.

METHYL 7-OXO-13-ISOPROPYL-PODOCARPA-8,11,13-TRIEN-15-OATE [**2**] (METHYL 7-OXO-DEHYDROABIETATE).—Compound **2** (673 mg) (37%): colorless oil; λ max (ε) (EtOH) 252 (10830), 300 (980) nm [lit. (13) 254 nm]; ν max (film) 1726 (C=O, ester), 1681 (C=O, ketone), 1604 (Ar conj. C=C), 1256 (C-O) cm^{-1}; ^{1}H nmr ($CDCl_3$) δ 1.248 (6H, d, *J* = 7.5, 1′-Me_2), 1.260 (3H, s, 10-Me), 1.343 (3H, s, 4-Me), 2.701 (2H, m, H_2-6), 2.926 (1H, m, H-1′), 3.652 (3H, s, COOMe), 7.285 (1H, d, *J* = 9, H-11), 7.403 (1H, d, *J* = 9, H-12), 7.872 (1H, s, H-14) ppm; *m/z* [M]$^+$ 328 (45%), [M − 15]$^+$ 313 (8%), [M − 32]$^+$ 296 (8%), [M − 59]$^+$ 269 (13%), [M − 129]$^+$ 253 (13%), [M − 141]$^+$ 187 (25%), identical with an authentic sample prepared by CrO_3 oxidation of **1** (13).

METHYL 13-ACETYL-7-OXO-PODOCARPA-8,11,13-TRIEN-15-OATE [**3**].—Compound **3** (1.88 mg) (1%): mp 145–146° [lit. (12) 145–145.5°]; ν max (KBr) 1726 (C=O, ester), 1686 and 1683 (C=O, ketones), 1604 (aromatic C=C), 1249 (C-O) cm^{-1}; ^{1}H nmr ($CDCl_3$) δ 1.289 (3H, s, 10-Me), 1.363 (3H, s, 4-Me), 2.431 (1H, t, 5-H), 2.637 (3H, s, Ac), 2.735 (2H, dd, *J* = 3 and 12, H_2-6), 3.676 (3H, s, COOMe), 7.502 (1H, d, *J* = 7.5, H-11), 8.151 (1H, d, *J* = 7.5, H-12), 8.548 (1H, s, H-14) ppm; *m/z* [M]$^+$ 328 (87%), [M − 15]$^+$ 313 (33%), [M − 32]$^+$ 296 (21%), [M − 75]$^+$ 253 (100%), [M − 129]$^+$

199 (21%), $[M-141]^+$ 187 (81%), 155, 43. *Anal.* found C 73.39, H 7.45%; calcd for $C_{20}H_{24}O_4$, C 73.13, H 7.37%.

PHOTOOXIDATION OF METHYL 7-OXO-DEHYDROABIETATE [**2**].—A 0.2 M solution of **2** (656 mg) in *t*-BuOH (or *n*-hexane) was placed in a round-bottomed Pyrex flask and irradiated. The reaction mixture was diluted with CH_2Cl_2 and concentrated to give a transparent glass containing several compounds, separated by preparative tlc or by cc and analyzed for purity by tlc and gc; mixtures of CH_2Cl_2/MeOH of increasing polarity (0.25–6% MeOH) were used to develop the plates and elute the columns. The reaction mixture was irradiated for ca. 3 weeks to yield unreacted **2** (6%) and **3** (34%), together with compounds **13**, **11**, **9**, **6**, **4**, **7**, **10**, **12**, and **8**.

METHYL 13-ISOPROPENYL-7-OXO-PODOCARPA-8,11,13-TRIEN-15-OATE [**13**].—Compound **13** (52.5 mg) (8%): mp 81–83° [lit. (13) 83–84], λ max (ε) (EtOH) 238 (16508), 256 (inf.), 306.8 (1016) nm [lit. (13) 240, 258 (inf.), 316 nm]; ν max ($CHCl_3$) 1722 (C=O, ester), 1680 (C=O, ketone), 1625 (C=C, ethylene), 1602 (Ar conj. C=C) cm^{-1}; ^1H nmr ($CDCl_3$) δ 1.270 (3H, s, 10-Me), 1.348 (3H, s, 4-Me), 2.162 (3H, s, 1′-Me), 2.718 (2H, m, H_2-6), 3.658 (3H, s, COOMe), 5.116 and 5.416 (2 × 1H, s, 1′-CH_2), 7.341 (1H, d, $J=8$, H-11), 7.661 (1H, d, $J=8$, H-12), 8.051 (1H, s, H-14) ppm; *m/z* $[M]^+$ 326 (43%), $[M-59]^+$ 267 (10%), $[M-75]^+$ 259 (100%), $[M-115]^+$ 211 (12%), $[M-141]^+$ 185 (22%). *Anal.* found C 77.52, H 8.01%; calcd for $C_{21}H_{26}O_3$, C 77.26, H 8.03%.

METHYL 13-ACETYL-12-HYDROXY-7-OXO-PODOCARPA-8,11,13-TRIEN-15-OATE [**11**].—Compound **11** (3.3 mg) (0.5%): mp 182–185.5°, $[\alpha]^{25}D$ +35° (*c* = 0.11, $CHCl_3$); λ max (ε) (EtOH) 245 (18000), 276 (2520) nm; λ max (ε) (EtOH + HO^-) 324 (6550) nm; ν max (CCl_4) 3640 (free OH), 3500 (bonded OH), 1725 (C=O, ester), 1680 and 1640 (C=O, ketones), 1603 (Ar, C=C), 1220 (C-O) cm^{-1}; ^1H nmr ($CDCl_3$) δ 1.269 (3H, s, 10-Me), 1.348 (3H, s, 4-Me), 2.377 (1H, t, H-5), 2.681 (2H, d, $J=12$, H_2-6), 2.681 (3H, s, COOMe), 3.671 (3H, s, COOMe), 6.916 (1H, s, H-11), 8.489 (1H, s, H-14), 12.639 (1H, s, 12-OH) ppm; *m/z* $[M]^+$ 344.1620 (100%) (calcd for $C_{20}H_{24}O_5$, 344.1534), $[M-15]^+$ 329 (15%), $[M-18]^+$ 326 (5%), $[M-59]^+$ 285 (55%), $[M-75]^+$ 269 (70%), $[M-115]^+$ 229 (25%), $[M-141]^+$ 203 (55%), 43.

METHYL 3-(4′-ACETYL-2′-CARBOXYPHENYL)-1β,3β-2-OXOCYCLO-HEXANE-CARBOXYLATE (LACTOL) [**9**].—Compound **9** (6.6 mg) (1%): mp 221–223° [lit. (25) 225–227°]; $[\alpha]^{25}D$ −53.0° (*c* = 0.16, $CHCl_3$) [lit. (23) $[\alpha]D$ −59.0° (*c* = 0.5, $CHCl_3$)]; λ max (log ε) (EtOH) 224 (4.36), 245 (inf.) (3.96), 285 (2.88), 295 (2.86) nm [lit. (23) 225 (4.47), 245 (4.03), 291.5 (3.04), 301 (3.02) nm]; λ max (log ε) (EtOH + HO^-) 255 (3.99), 290 (inf.) (2.88) nm; ν max (CCl_4) 3495, 3380 (bonded OH), 1739 (C=O, ester), 1710 and 1696 (C=O, ketones), 1614 (Ar conj. C=C), 1239 (C-O) cm^{-1}; ^1H nmr ($CDCl_3$) δ 1.671 (3H, s, 3-Me), 1.515 (3H, s, 1-Me), 2.647 (3H, s, Ac), 3.852 (3H, s, COOMe), 6.455 (1H, s, 2-OH, exchangeable with D_2O), 7.562 (1H, d, $J=9$, H-6′), 8.200 (1H, d, $J=9$, H-5′), 8.641 (1H, s, H-3′) ppm; *m/z* $[M]^+$ 346.1412 (32%) (calcd for $C_{19}H_{22}O_6$, 346.1416), $[M-18]^+$ 328 (20%), $[M-32]^+$ 314 (35%), $[M-78]^+$ 268 (42%), $[M-91]^+$ 255 (18%), $[M-159]^+$ 187 (82%), $[M-199]^+$ 147 (100%). *Anal.* found C 65.85, H 6.57%; calcd for $C_{19}H_{22}O_6$, C 65.87, H 6.41%.

METHYL 3-(4′-ACETYL-2′-METHYL-PHENYLCARBOXYLATE)-1β,3β-DIMETHYL-2-OXOCYCLO-HEXANE-CARBOXYLATE [**16**].—Methylation of **9** with excess CH_2N_2 gave **16** as an oil, ν max (CCl_4) 1730 (C=O, esters), 1705 and 1690 (C=O), ketones), 1602 (aromatic conjugated (C=C), 1230 (C-O) cm^{-1}; ^1H nmr ($CDCl_3$) δ 1.603 (3H, s, 3-Me), 1.505 (3H, s, 1-Me), 2.608 (3H, s, Ac), 3.460 (3H, s, 2′-COOMe), 3.862 (3H, s, 1-COOMe), 7.585 (1H, d, $J=7$, H-6′), 8.009 (1H, d, $J=7$, H-5′), 8.303 (1H, s, H-3′) ppm; *m/e* $[M]^+$ 360.1573 (12%) (calcd for $C_{20}H_{24}O_6$, 360.1565), $[M-116]^+$ 244 (8%), $[M-128]^+$ 232 (14%), $[M-175]^+$ 185 (11%), 43 (16%), 32 (100%).

METHYL 13-ACETYL-2,7-DIOXO-PODOCARPA-8,11,13-TRIEN-15-OATE [**6**].—Compound **6** (26.2 mg) (4%): mp 206–207.5°, $[\alpha]^{25}D$ −6.25° (*c* = 0.16, $CHCl_3$); λ max (ε) (EtOH) 228 (14325), 245 (inf.) (10222), 290 (8015), 300 (8009) nm; ν max (KBr) 1726 (C=O, ester), 1700, 1689, and 1681 (C=O, ketones), 1608 (Ar C=C), 1248 (C-O) cm^{-1}; ^1H nmr ($CDCl_3$) δ 1.328 (3H, s, 10-Me), 1.367 (3H, s, 4-Me), 2.463 (1H, dd, $J=3$ and 13.2, H-5), 2.595 (1H, dd, $J=4.2$ and 13.8, H_a-1), 2.652 (3H, s, Ac), 2.809 (1H, dd, $J=4.5$ and 13.8, H_e-6), 2.860 (1H, d, $J=13.2$, H_a-6), 3.051 (1H, d, $J=13.2$, H_e-1), 3.115 (1H, d, $J=14$, H_e-3), 3.203 (1H, dd, $J=3$ and 14, H_a-3), 3.759 (3H, s, COOMe), 7.392 (1H, d, $J=9$, H-11), 8.200 (1H, d, $J=9$, H-12), 8.592 (1H, s, H-14) ppm; *m/z* $[M]^+$ 342.1442 (25%) (calcd for $C_{20}H_{22}O_5$, 342.1467), $[M-15]^+$ 327 (58%), $[M-75]^+$ 267 (100%), $[M-103]^+$ 239 (20%), $[M-129]^+$ 213 (25%), $[M-157]^+$ 187 (32%), $[M-171]^+$ 171 (25%), 127, 43. *Anal.* found C 70.15, H 6.48%; calcd for $C_{20}H_{22}O_5$, C 70.15, H 6.48%.

METHYL 13-HYDROXY-ISOPROPYL-7-OXO-PODOCARPA-8,11,13-TRIEN-15-OATE [**4**].—Compound **4** (203 mg) (31%): oil, $[\alpha]^{25}D$ 4.5° (*c* = 1.0, Me_2CO); λ max (EtOH) 247, 296 nm; ν max (film)

3460 (OH), 1726 (C=O, ester), 1680 (C=O, ketone), 1600 (Ar conj. C=C), 1260 (C-O), 1122 (C-OH, 3° OH) cm^{-1}; ^1H nmr ($CDCl_3$) δ 1.265 (3H, s, 10-Me), 1.348 (3H, s, 4-Me), 1.583 (6H, s, 1′-Me_2), 2.362 (1H, t, H-5), 2.728 (2H, d, J = 11, H_2-6), 3.656 (3H, s, COOMe), 7.352 (1H, d, J = 10, H-11), 7.737 (1H, d, J = 10, H-12), 8.058 (1H, s, H-14) ppm; *m/z* $[M]^+$ 344 (5%), $[M-15]^+$ 329 (100%), $[M-18]^+$ 326 (5%), $[M-75]^+$ 269 (20%), $[M-93]^+$ 251 (8%), 43.

METHYL 13-ACETOXY-ISOPROPYL-7-OXO-PODOCARPA-8,11,13-TRIEN-15-OATE [**5**].—Ac_2O (0.25 ml) was added to a solution of **4** (31.5 mg) in pyridine (0.25 ml) and the reaction mixture left at room temperature for 8 days. The mixture was diluted with H_2O (5 ml) and extracted with Et_2O (4 × 10 ml); the Et_2O extract was washed with H_2O to pH 7, dried, and concentrated under reduced pressure to give a product (22 mg) that was crystallized from MeOH to give **5**: white needles, mp 132–135° [lit. (13) 133–134°], λ max (ε) (EtOH) 210 (29500), 250.8 (18300), 295.2 (950) nm; ν max ($CHCl_3$) 1725 (C=O, ester), 1679 (C=O, ketone), 1610 (aromatic conjugated C=C) cm^{-1}; ^1H nmr ($CDCl_3$) δ 1.260 (3H, s, 10-Me), 1.343 (3H, s, 4-Me), 1.759 (6H, s, 1′-Me_2), 2.093 (3H, s, 1′-OAc), 2.719 (2H, m, H_2-6), 7.333 (1H, d, J = 9, H-11), 7.518 (1H, d, J = 9, H-12), 7.978 (1H, s, H-14) ppm; *m/z* $[M]^+$ 386 (15%), $[M-60]^+$ 326 (50%), $[M-119]^+$ 267 (10%), $[M-135]^+$ 259 (100%), $[M-175]^+$ 211 (15%). *Anal.* found C 71.10, H 7.85%; calcd for $C_{23}H_{30}O_5$, C 71.46, H 7.83%.

METHYL 3-(4′-HYDROXY-ISOPROPYL-2′-CARBOXYPHENYL)-1β,3β-DIMETHYL-2-OXOCYCLOHEXANE-CARBOXYLATE (LACTOL) [**7**].—Compound **7** (3.3 mg) (0.5%): mp 105–107°; $[\alpha]^{25}D$ −21° (c = 0.12 $CHCl_3$); λ max (EtOH) 242, 290 nm; ν max (CCl_4) 3600 (free OH), 3495, 3440 (bonded OH), 1727 (C=O, ester and lactone), 1689 (C=O, ketone), 1608 (Ar C=O), 1235 (C-O), 1120 (C-OH, 3° OH) cm^{-1}; ^1H nmr ($CDCl_3$) δ 1.510 (3H, s, 1-Me), 1.598 (6H, s, 7′-Me_2), 1.642 (3H, s, 3-Me), 3.838 (3H, s, COOMe), 6.367 (1H, s, 2-OH, exchangeable with D_2O), 7.435 (1H, d, J = 9, H-6′), 7.764 (1H, d, J = 9, H-5′), 8.175 (1H, s, H-3′) ppm; *m/z* $[M]^+$ 362.1723 (2.6%) (calcd for $C_{20}H_{26}O_6$, 362.1729), $[M-18]^+$ 344 (11%), $[M-75]^+$ 265 (81%), $[M-143]^+$ 219 (7%), 203, 69, 44.

METHYL 3-(4′-HYDROXY-ISOPROPYL-2′-METHYLPHENYLCARBOXYLATE)-1β,3β-DIMETHYL-2-OXOCYCLOHEXANE-CARBOXYLATE [**15**].—Methylation of **7** with excess CH_2N_2 gave **15** as an oil: ν max (CCl_4) 1735 (C=O, esters), 1686 (C=O, ketone), 1610 (conjugated C=C) cm^{-1}; ^1H nmr ($CDCl_3$) δ 1.465 (3H, s, 1-Me), 1.553 (3H, s, 3-Me), 1.568 (6H, s, 7′-Me_2), 3.386 (3H, s, 2′-COOMe), 3.832 (3H, s, 1-COOMe), 7.420 (1H, d, J = 7, H-6′), 7.536 (1H, d, J = 7, H-5′), 7.822 (1H, s, H-14) ppm; *m/z* $[M]^+$ 376.1958 (10%) (calcd for $C_{21}H_{28}O_6$, 376.1878), $[M-30]^+$ 346 (50%), $[M-30-18]^+$ 328 (22%), $[M-62]^+$ 314 (40%), $[M-108]^+$ 268 (72%), 187 (100%), 69 (72%).

METHYL 13-ACETYL-2α-HYDROXY-7-OXO-PODOCARPA-8,11,13-TRIEN-OATE [**10**].—Compound **10** (9.6 mg) (1.5%): glass, $[\alpha]D$ −10° (c = 0.52, $CHCl_3$); λ max (ε) (EtOH) 230 (35000), 290–300 (600) nm; ν max ($CHCl_3$) 3420 (OH), 1725 (C=O, ester), 1691, 1685 (C=O, ketones), 1605 (C=C Ar) cm^{-1}; ^1H nmr ($CDCl_3$) δ 1.328 (3H, s, 10-Me), 1.402 (3H, s, 4-Me), 2.509 (1H, t, H-5), 2.647 (3H, s, Ac), 2.730 (2H, d, J = 12, H_2-6), 3.701 (3H, s, COOMe), 4.176 (1H, m, W½ = 28, H-2), 7.524 (1H, d, J = 9, H-11), 8.176 (1H, d, J = 9, H-12), 8.553 (1H, s, H-14) ppm; *m/z* $[M]^+$ 344.1620 (10%) (calcd for $C_{20}H_{24}O_5$, 344.1534), $[M-15]^+$ 329 (14%), $[M-18]^+$ 326 (4%), $[M-157]^+$ 187 (15%), 43 (100%).

Compound **10** was oxidized as follows: To a solution of **10** (2.2 mg) in glacial HOAc (0.1 ml) was added dropwise a solution of CrO_3 (3.0 mg) in 80% HOAc (0.5 ml). The reaction mixture was stirred overnight at room temperature. An excess of CrO_3 (3.0 mg) was added, and the reaction mixture was kept at 100° for 30 min, diluted with H_2O (20 ml), and extracted with CH_2Cl_2 (3 × 20 ml). The organic layer was washed with H_2O (5 × 50 ml) to pH 7, dried, and concentrated to give a gum (1.7 mg) which was separated to tlc to give unreacted **10** (0.5 mg) and the triketone **6** (1.2 mg), as confirmed by comparison (tlc with several solvents, ^1H nmr) with an authentic sample.

METHYL 7-OXO-PODOCARPA-8,11,13-TRIEN-13-OIC-15-OATE [**12**].—Compound **12** (0.5%), glass; λ max (ε) (EtOH) 223 (40225), 300 (12502) nm [lit. (20) 224 (40738), 291 (13490), 301 (13182) nm]; ν max ($CHCl_3$) 3520 (bonded OH), 3500—2500 (acid OH), 1728 (C=O, ester), 1706 (C=O, acid), 1690 (C=O, ketone), 1603 (C=C Ar), 1430, 1240 (C-O) cm^{-1}; ^1H nmr ($CDCl_3$) δ 1.247 (3H, s, 10-Me), 1.363 (3H, s, 4-Me), 2.735 (2H, d, J = 12, H_2-6), 3.676 (3H, s, COOMe), 7.499 (1H, d, J = 9, H-11), 8.212 (1H, d, J = 9, H-12), 8.705 (1H, s, H-14) ppm; *m/z* $[M]^+$ 330 (25%), $[M-32]^+$ 298 (22%), $[M-44]^+$ 286 (18%), $[M-75]^+$ 255 (100%), 217.

METHYL 13-HYDROXY-ISOPROPYL-2α-HYDROXY-7-OXO-PODOCARPA-8,11,13-TRIEN-15-OATE [**8**].—Compound **8** (9.9 mg) (1.5%): glass, $[\alpha]D$ −8° (c = 0.05, $CHCl_3$), λ max (ε) (EtOH) 205 (35400), 250 (12273), 298 (2418) nm; ν max ($CHCl_3$) 3590 (free OH), 3420 (bonded OH), 1726 (C=O, ester), 1670 (C=O, ketone), 1607 (C=C Ar) cm^{-1}; ^1H nmr ($CDCl_3$) δ 1.304 (3H, s, 10-Me), 1.383 (3H, s, 4-

Me), 1.588 (6H, s, 1′-Me_2), 2.451 (1H, t, H-5), 2.691 (2H, dd, $J=3$ and 12, H_2-6), 3.681 (3H, s, COOMe), 4.156 (1H, m, $W½=28$, H_β-2), 7.376 (1H, d, $J=9$, H-11), 7.759 (1H, d, $J=9$, H-12), 8.073 (1H, s, H-14) ppm; *m/z* $[M]^+$ 360.1936 (7%) (calcd for $C_{21}H_{28}O_5$, 360.1929), $[M-15]^+$ 354 (100%), $[M-18]^+$ 342 (27%), $[M-31]^+$ 329 (17%), $[M-73]^+$ 267 (8%), $[M-109]^+$ 251 (37%), $[M-157]^+$ 203 (18%), 43.

LITERATURE CITED

1. A. Tahara, M. Shimagaki, M. Itoh, Y. Harigaya, and M. Onda, *Chem. Pharm. Bull. Jpn.*, **23**, 3189 (1975).
2. Y. Harigaya, M. Onda, and A. Tahara, *Chem. Lett.*, 919 (1974).
3. T. Wirthlin, H. Wehrli, and O. Jeger, *Helv. Chim. Acta*, **57**, 351, 368 (1974).
4. J.W. Huffman, *J. Org. Chem.*, **35**, 478 (1970).
5. B. San Miguel, B. Maillard, and B. Delmond, *Tetrahedron Lett.*, **28**, 2127 (1987).
6. T. Nakata, Y. Ohtsuka, A. Tahara, and S. Takeda, *Chem. Pharm. Bull. Jpn.*, **23**, 2318 (1975).
7. T. Nakata and A. Tahara, *Tetrahedron Lett.*, 1515 (1976).
8. H. Mizuno, T. Ohsawa, and A. Tahara, *Chem. Pharm. Bull. Jpn.*, **24**, 1527 (1976).
9. E.E. van Tamelen, J.P. Demers, E.G. Taylor, and K. Koller, *J. Am. Chem. Soc.*, **102**, 5424 (1980).
10. D.F. Zinkel, in: "Organic Chemicals from Biomass." CRC Press, Boca Raton, 1981, p. 163.
11. Y.T. Pratt, *J. Am. Chem. Soc.*, **73**, 3803 (1951).
12. H. Erdtman and M. Malmborg, *Acta Chem. Scand.*, **24**, 2252 (1970).
13. P.F. Ritchie, T.F. Sanderson, and L.F. McBurney, *J. Am. Chem. Soc.*, **76**, 723 (1954).
14. P.F. Ritchie, T.F. Sanderson, and L.F. McBurney, *J. Am. Chem. Soc.*, **75**, 2610 (1953).
15. E. Wenkert, A. Afonso, P. Beak, R.W.J. Carney, P.W. Jeffs, and J.D. McChesney, *J. Org. Chem.*, **30**, 713 (1965).
16. J.E. Bridgeman, P.C. Cherry, A.S. Clegg, J.M. Evans, E.R.H. Jones, A. Kasal, V. Kumar, G.D. Meakins, Y. Moriasawa, E.E. Richards, and P.O. Woodgate, *J. Chem. Soc. C*, 250 (1970).
17. N.S. Bhacca and D.H. Williams, "Applications of NMR Spectroscopy in Organic Chemistry," 2nd ed., Holden-Day, San Francisco, 1966, p. 309.
18. J.F. Grove and B.J. Riley, *J. Chem. Soc.*, 1105 (1961).
19. B. Gigante, A.M. Lobo, M.J. Marcelo-Curto, S. Prabhakar, and H.S. Rzepa, *Tetrahedron Computer Methodology*, **1**, 133 (1988).
20. M. Ohta, *Pharm. Bull. Jpn.*, **4**, 273 (1956).
21. P.F. Ritchie, T.F. Sanderson, and L.F. McBurney, *J. Am. Chem. Soc.*, **83**, 4440 (1961).
22. E. Wenkert, R.W. Carney, and C. Kaneko, *J. Am. Chem. Soc.*, **83**, 4440 (1961).
23. A. Tahara and H. Mizuno, *Tetrahedron Lett.*, 523 (1974).
24. H. Mizuno, T. Ohsawa, and A. Tahara, *Chem. Pharm. Bull. Jpn.*, **24**, 1527 (1976).
25. T. Hayashi, T. Handa, M. Ohashi, H. Kakisawa, H.Y. Hsu, and Y.P. Chen, *J. Chem. Soc., Chem. Commun.*, 541 (1971).
26. T. Matsumoto, S. Usui, H. Kawashina, and M. Mitzuki, *Bull. Chem. Soc. Jpn.*, **54**, 581 (1981).
27. W.C. Still, M. Khan, and A. Mitra, *J. Org. Chem.*, **43**, 2923 (1978).
28. D.D. Perrin, W.L.F. Armarego, and D.R. Perrin, "Purification of Laboratory Chemicals," 2nd ed., Pergamon Press, London, 1983.

Received 13 June 1988