New Hydroxylated *ent*-Kauranoic Acids From *Eupatorium album*[1]

Werner Herz* and Ram P. Sharma

Department of Chemistry, The Florida State University, Tallahassee, Florida 32306

Received October 6, 1975

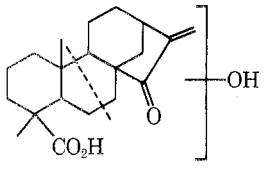
Eupatorium album L. gave four new hydroxylated *ent*-kauran-19-oic acids as well as a small amount of a sesquiterpene lactone mixture. Identification of the new substances as *ent*-11α,15α-dihydroxykaur-16-en-19-oic acid (**1a**), (16*R*)-*ent*-11α-hydroxy-15-oxokauran-19-oic acid (**2a**), *ent*-11α-hydroxy-15-oxokaur-16-en-19-oic acid (**3a**), and *ent*-11α,12α,15α-trihydroxykaur-16-en-19-oic acid (**4a**) by means of chemical correlations, ^{1}H NMR, and ^{13}C NMR spectrometry is described.

A number of sesquiterpene lactones with cytotoxic and antitumor activity has been isolated from *Eupatorium* species *sensu stricto*.[2] In the present paper we describe isolation and structure determination from *Eupatorium album* L. of four new 11-hydroxylated *ent*-kaurane derivatives **1a, 2a, 3a,** and **4a.** Proof of structure was achieved by extensive use of ^{1}H and ^{13}C NMR spectrometry and conversion of **3a** to the known (16*R*)-*ent*-15-oxokauran-19-oic acid (**5**).[3] The sesquiterpene lactone fraction of *E. album* was small and could not be resolved into its constituents.[4]

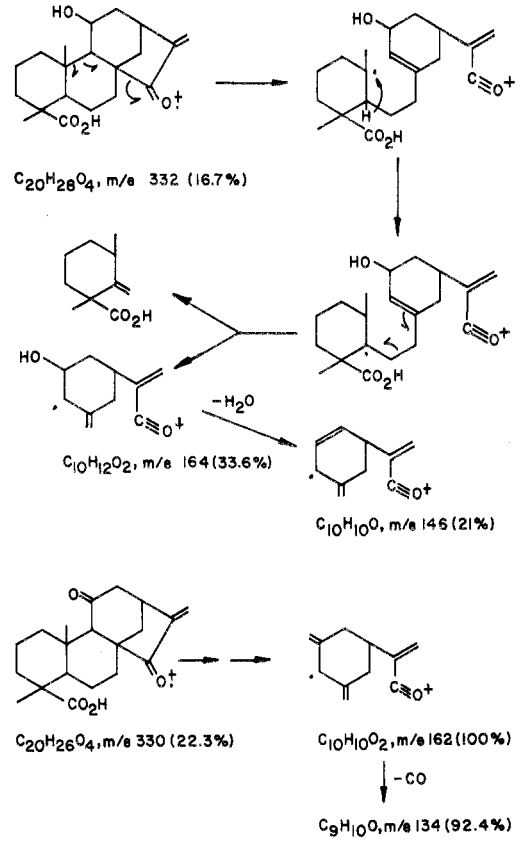
We commence with **3a,** $C_{20}H_{28}O_4$ (elemental analysis and high-resolution mass spectrum), which was an α,β-unsaturated ketone (λ_{max} 237 nm, ϵ_{max} 8000) involving an exocyclic methylene group (NMR singlets at 5.85 and 5.26 ppm) attached to a cyclopentanone (ir band at 1715 cm^{-1}). The presence of a carboxyl group suggested by the ir spectrum (broad absorption in the 2500–3400-cm^{-1} region) was confirmed by treatment with diazomethane; however, instead of the expected methyl ester **3c,** there was obtained the methyl ester pyrazoline **6** whose formation also served to confirm the functionalization of the five-membered ring.

The remaining oxygen atom of the empirical formula was a secondary hydroxyl group revealed by an NMR doublet at 4.05 ppm (sharpened on D_2O exchange) which moved downfield to 5.11 ppm (J = 3 Hz) on acetylation of **3a** to **3b.** Since the NMR spectrum also exhibited two methyl singlets at 1.26 and 0.92 ppm, the new substance was a tetracyclic diterpene which belonged to the kaurene or the phyllocladene series.

The problem of locating the hydroxyl group on the carbon skeleton presented considerable difficulties. The appearance of –CHOR as a doublet appeared to limit the attachment of the hydroxyl group to C-14; however, irradiation at the frequency of H-13 (3.05 ppm)[5] effected no change in the signal at 4.05 ppm. On the assumption that at least one, if not two, coupling constants had to be close to zero, C-1, C-3, C-6, C-7, C-11, and C-12 appeared possible loci for the hydroxyl group. C-12 was eliminated because equatorial orientation of the hydroxyl group on C-12 (to explain absence of coupling between H-12 and H-13) required coupling between H-11α, H-11β, and H-12 and therefore a doublet of doublets or a triplet. C-1, C-3, and C-6 were eliminated on the basis of the mass spectra of **3a** and its oxidation product **7** which exhibited a very strong peak at *m/e* 164 ($C_{10}H_{12}O_2$) and the base peak at *m/e* 162 ($C_{10}H_{10}O_2$), respectively. This corresponds to the fragment on the right resulting from the scission depicted below as the result of the preferred cleavage of the C-9, C-10 bond

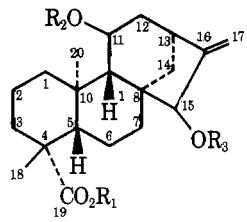


Scheme I. Mass Spectral Fragmentation of 3a and 7

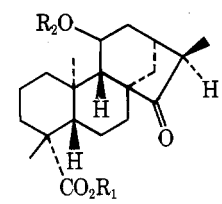


and places the hydroxyl group on C-11 because of the restrictions imposed earlier. A rationalization of some of the significant peaks in the high-resolution mass spectra of **3a** and **7** is presented in Scheme I.

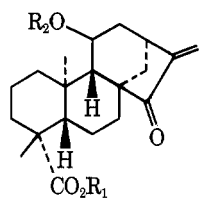
That the hydroxyl group was at C-11 was also indicated by analysis of the ^{13}C NMR spectra (Table I). In kaurene, the triplets of C-2, C-6, and C-11 are found near 20 ppm, the triplets of C-1, C-3, C-5, C-7, and C-12 appearing at much lower field.[7] As the ^{13}C NMR spectrum of **3a** exhibited only two triplets near 20 ppm, it was clear that C-11 was oxygenated, C-2 and C-6 having been eliminated earlier. Moreover, comparison with the ^{13}C NMR spectrum of **3b** showed that the C-9 doublet and the C-12 triplet had undergone diamagnetic shifts of 4.2 and 2.6 ppm, respectively, thus clearly pointing to C-11 as the locus of the hydroxyl group. This was further corroborated by the spectroscopic properties of **7**; in the ^{1}H NMR spectrum the C-20 methyl resonance exhibited the expected paramagnetic shift of about 1 ppm, while in the ^{13}C NMR spectrum the signals of C-9 and C-11 had undergone the expected downfield shifts. The small downfield shift of C-8 may be due to removal of a 1,3 interaction or to deshielding by the



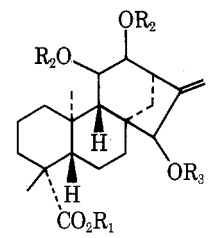
1a, R_1, R_2, R_3 = H
b, R_1 = Me; R_2, R_3 = H



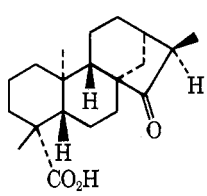
2a, R_1, R_2 = H
b, R_1 = Me; R_2 = H
c, R_1 = Me; R_2 = Ac



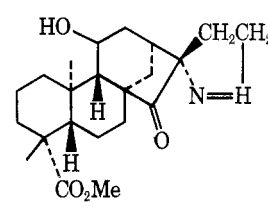
3a, R_1, R_2 = H
b, R_1 = H; R_2 = Ac
c, R_1 = Me; R_2 = H
d, R_1 = H; R_2 = Ms



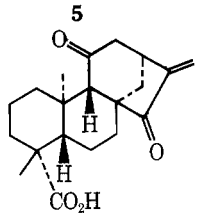
4a, R_1, R_2, R_3 = H
b, R_1 = Me; R_2, R_3 = H
c, R_1 = Me; R_2, R_3 = Ac



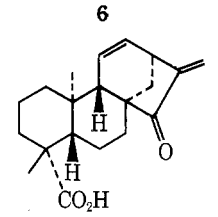
5



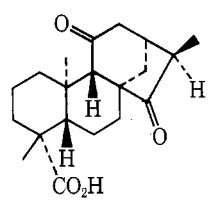
6



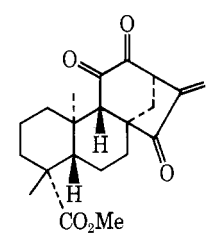
7



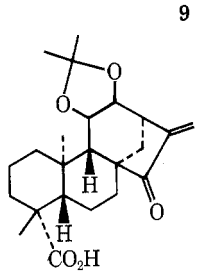
8



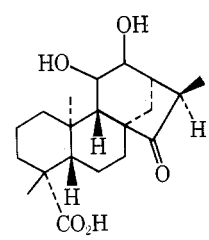
9



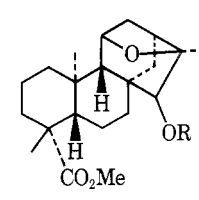
10



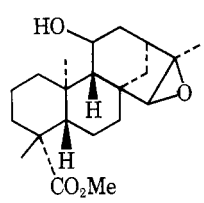
11



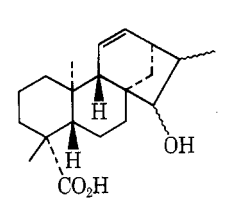
12



13a, R = H
b, R = Ac



14



15

newly formed carbonyl group;[8] the much larger downfield shift of C-10 may be the result of a combination of such effects.[9] The lack of a significant change in the C-12 signal is not explained readily.

Conclusive proof for the attachment of the hydroxyl group to C-11 was provided in the following manner. $POCl_3$–pyridine dehydration of **3a** provided **8**, whose new double bond was located unequivocally between C-11 and C-12. The ^1H NMR spectrum exhibited a new AB system of two vinyl protons ($J_{A,B}$ = 10 Hz) at 5.51 (H-11) and 6.09 (H-12) ppm. Irradiation at the frequency of H-13 (dd br at 3.24 ppm) converted the signal at 6.09 ppm to a broadened doublet ($J_{12,13}$ = 7 Hz) and caused some changes in the methylene region. Irradiation at the frequency of H-12 collapsed the signal of H-11 to a doublet ($J_{9,11}$ = 3 Hz) as well as converting the H-13 resonance to a broadened doublet ($J_{12,14a}$ = 3 Hz).

Before considering the stereochemistry of **3a**, we would like to discuss two other substances, **1a** and **2a**, that were also isolated from *E. album* and could be correlated with **3a**. The empirical formula of **1a**, $C_{20}H_{30}O_4$, combined with the absence of ultraviolet absorption and the ir band at 1715 cm^{-1}, the upfield shift of the exocyclic methylene resonances to 5.11 and 5.03 ppm (broad singlet and doublet), and the additional presence of a proton under hydroxyl (broadened triplet at 3.77 ppm), indicated that it differed from **3a** only by reduction of the ketone to a hydroxyl group. This was confirmed by double resonance experiments, since irradiation at the frequencies of both H-17 protons simultaneously affected H-15, but residual coupling indicated that H-15 was long range coupled to other protons as well. Finally $NaBH_4$ reduction of **3a** (−20 °C) gave **1a** in 80% yield; the latter was converted to a methyl ester which was identical with authentic methyl ester **1b** in every respect.

The third compound **2a**, $C_{20}H_{30}O_4$, was an isomer of **1a**. In the NMR spectrum the two signals of the exocyclic methylene protons were replaced by a methyl doublet at 1.22 ppm (J = 7 Hz); the absence of the multiplet at 3.77 ppm, the absence of conjugation evidenced by the uv spectrum, and the presence of an ir band at 1725 cm^{-1} suggested that **2a** was a dihydro derivative of **3a**. This was confirmed by catalytic hydrogenation of **3a** and subsequent methylation of the product to **2b**. Incidentally, in **1a**, **1b**, **2a**, and **2b**, the signal of H-11 was a broadened doublet or a doublet of doublets, instead of a sharp doublet as in **3a–c**.

As regards the stereochemistry of the three substances **1a**, **2a**, and **3a** the magnitude of the coupling constants involving H-11 in these substances and their derivatives ($J_{9\beta,11} = J_{11,12\beta} \simeq$ 0–2, $J_{9a,11}$ = 3–4.5 Hz) made it obvious that the hydroxyl group was axial. The chemical shift of the C-10 methyl group in all compounds was indicative of the fact that the C-10 methyl and the C-4 carboxyl are cis to each other and therefore both axial. The ORD spectrum of **2a** exhibited a strong negative Cotton effect,[11] hence ring D is β oriented and **1a**, **2a**, and **3** belong to either the phyllocladene or the *ent*-kaurene series. Catalytic hydrogenation of **7** afforded **9** which exhibited a strong positive Cotton effect, thus suggesting that rings B and C are cis fused and that the new substances belong to the *ent*-kaurane series.[11] Finally, hydrogenation of **8** gave a quantitative yield of a substance whose physical properties corresponded in all respects to those reported for 15-oxo(16*R*)-*ent*-kauran-19-oic acid (**5**).[3,12]

Since $NaBH_4$ reduction of **3a** at low temperature resulted in a good yield of **1a** and since the reagent is known to attack from the least hindered side, the C-15 hydroxyl group of **1a** is assigned the β configuration.

The stereochemistry of the C-16 methyl group of **2a** was

Table I. ^{13}C NMR Spectra of *ent*-Kauranoic Acid Derivatives[a]

Carbon no.	1a	2c	3a	3b	4a	4c	7	10[b]
1	40.5 t	39.6 t	39.8 t	40.1 t	40.5 t	40.6 t	40.1 t	39.7 t
2	19.4 t	18.8 t	19.0 t	18.9 t	19.4 t	19.2 t	18.9 t	18.5 t
3	38.2 t	37.9 t	37.9 t	38.0 t	38.2 t	38.2 t	38.0 t	37.7 t
4	45.0	43.9	43.8	44.1	45.1	44.9	44.1	44.2
5	56.5 d	55.9 d	56.7 d	56.1 d	56.4 d	56.3 d	55.7 d	55.6 d
6	21.6 t	20.1 t	20.1 t	20.1 t	21.5 t	21.3 t	20.1 t	19.9 t
7	39.3 t	34.4 t	34.0 t	33.9	38.4 t	38.2 t	32.3 t	31.6 t
8	42.5	51.1	50.8	50.8	43.9	44.1	52.8	52.5
9	54.4 d	58.1 d	63.1 d	58.9 d	54.5 d	54.2 d	67.3 d	65.9 d
10	38.2	38.7	39.1	39.3	37.9	37.9	51.5	41.7
11	66.5 d	67.5 d	66.1 d	68.6 d	68.3 d	67.2 d	206.7	?
12	39.4 t	31.5 t	41.0 t	38.4 t	72.4 d	73.3 d	40.4 t	?
13	39.3 d	34.5 d	37.2 d	36.9 d	46.1 d	43.4 d	36.6 d	53.7 d
14	36.1 t	37.1 t	36.8 t	36.5 t	36.1 t	36.4 t	35.9 t	36.2 t
15	82.5 d	221.6	210.8	209.3	82.2 d	81.5 d	209.5	?
16	158.1	49.1 d	150.5	150.1	153.2	147.4	147.6	?
17	106.2 t	10.8 q	112.8 t	113.2 t	108.5 t	109.2 t	107.4 t	?
18	29.1 q	28.7 q	29.0 q	29.3 q	29.1 q	28.8 q	29.2 q	28.9 q
19	180.4	177.6	181.4	183.1	180.6	177.5	182.4	?
20	15.7 q	15.5 q	15.7 q	16.0 q	16.4 q	16.2 q	17.2 q	16.5 q

[a] Run in $CDCl_3$ on a Bruker HX-270 instrument. Unmarked signals are singlets. Assignments are based on predicted shifts, comparisons with data in the literature [see, for example, ref 7 and I. Yamaguchi, N. Takahashi, and K. Fujiha, *J. Chem. Soc., Perkin Trans. 1*, 992 (1975)] and selective single frequency off-resonance decoupling. [b] Insufficient sample available to permit clear visualization of signals marked ?. No off-resonance spectrum was recorded.

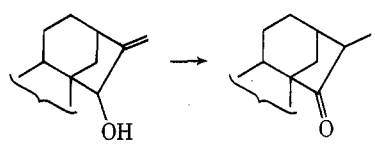
established by double irradiation experiments involving H-16 and H-17 of **2c** which led to the determination of $J_{13,16}$ as 7 Hz. This required that the methyl group be β oriented (expected dihedral angle between H-13 and H-16 $\simeq$ 10°) rather than α (dihedral angle $\simeq$ 90°). The appearance of the H-11 proton as a triplet (J = 3.5 Hz) instead of a doublet of doublets as in **2a** and **2b** indicated a change in conformation of ring C on acetylation. This is attributed to an increase in the strong interaction between the β-oriented hydroxyl group at C-11 and the β-oriented methyl group on C-16 which results in flattening of ring C.[13]

There remains the fourth, most polar compound, **4a,** whose empirical formula $C_{20}H_{30}O_5$, polarity, and NMR spectrum, which exhibited three signals in the regions appropriate for protons under hydroxyl at 3.80, 3.65, and 3.77 ppm, suggested the presence of three secondary hydroxyl groups. This was confirmed by conversion of the methyl ester **4b** to a triacetate **4c.**

Comparison of the ^1H NMR and ^{13}C NMR spectra of **1a** and **4a** made it obvious that the only difference between the two compounds was attachment of the additional hydroxyl group of **4a** to C-12. Aside from the replacement of a triplet at 39.4 ppm by a new doublet at 72.4 ppm, the only significant differences in the ^{13}C NMR spectrum of **4a** were downfield shifts of C-13 (39.3 → 46.1) and C-11 (66.5 → 68.3). This conclusion was fully corroborated by decoupling experiments on **4a.** Irradiation at the frequencies of H-17 (5.08 br and 5.04 d, J = 2.5 Hz) affected the broad triplet (J = 2.5 Hz) of H-15 at 3.77 ppm and vice versa. Irradiation at the frequency of H-13 (2.47 ppm) converted a doublet of doublets at 3.65 ppm (H-12) to a doublet (J = 3.5 Hz), while irradiation at the frequency of H-12 not only affected the resonance of H-13 by collapsing it to a doublet (J = 4.5 Hz), but also collapsed the doublet of H-11 at 3.80 ppm (partially obscured by the H-15 resonance) to a singlet. Irradiation at the frequency of H-11 and H-15 sharpened the signal of H-17 and collapsed the signal of H-12 to a doublet (J = 4.5 Hz).

Oxidation of **4b** furnished the triketone **10** whose properties were in complete agreement with the postulated structure. Successful conversion of **4a** to an acetonide **11** indicated that the two hydroxyl groups were cis. The values of $J_{9,11}$ ($\simeq$ 0), $J_{11,12}$ (3.5 Hz), and $J_{12,13}$ (4.5 Hz) require that the C-11 hydroxyl be axial and the C-12 hydroxyl equatorial.[14] As in the case of **1a, 2a,** and **3a,** the chemical shift of the C-10 methyl group showed that the C-10 methyl and C-4 carboxyl were both axial and the negative Cotton effect of a substance **12** obtained by isomerization of **4a** with 5% Pd–C–H_2[15] indicated that **4a** belonged to the phyllocladene or the *ent*-kaurane series. Thus, although owing to lack of material, correlation of **4a** with an *ent*-kaurane has not yet been achieved, the similarity of chemical shifts exhibited by **1a** and **4a** leaves little doubt that the fourth diterpene isolated from *E. album* is also an *ent*-kaurane and is correctly represented by formula **4a.**

We conclude by recording the behavior of **1b** on treatment with acid, a reaction which normally results in the hydride shift A → B if the 15-hydroxyl group is β oriented,[17]



A B

and confirmed the structure assigned to the substances described in this report. After an NMR tube containing a sample of **1b,** prepared by $NaBH_4$ reduction of **3a** and subsequent methylation, had been allowed to stand at room temperature for 1 month, during which period the $CDCl_3$ solvent had evaporated, fortuitous redetermination of the NMR spectrum revealed that **1b** had undergone conversion to a new compound and that this substance was different from **2b.** Work-up of the material from the sample tube resulted in isolation of an 80% yield of the ether **13a** (vide infra) and a 10% yield of **2b.** During the same period a sample of **1b** prepared directly from **1a** stored in $CDCl_3$ at 0 °C had not undergone any change, but on adding a drop of HCl and shaking the spectrum immediately changed to that of **13a.** Exposure of **1b** to methanolic HCl for 24 h at room temperature[18] again resulted in at least 90% isomerization to **13a.**

The structure **13a** assigned to the new ether was based on the following facts. The two signals of the exocyclic methylene group had been replaced by a methyl singlet at 1.30 ppm. The H-15 signal, formerly a narrowly split

broadened triplet at 3.77 ppm, had changed to a slightly broadened singlet at 2.77 ppm which again moved downfield to 4.40 ppm on acetylation to **13b.** The H-11 signal had experienced a slight downfield shift to 4.27 ppm ($J_{9\beta,11} = J_{11,12\alpha} = 3$; $J_{11,12\beta} = 0$ Hz) and was unaffected by acetylation. These changes, as well as the observation that **13a** was unaffected by further treatment with dilute sulfuric acid, eliminated **14** as an alternative structure. The facile formation of **13a** is obviously due to the proximity of the axial 11-hydroxyl group to C-15 as required by the models which also suggest that the somewhat abnormal upfield shift of H-15 in **13a** is due to shielding by the ether oxygen.

Several 11β-hydroxylated[19] *ent*-kauranes analogous to **1a, 2a,** and **3a** have been isolated recently from a liverwort.[20] The NMR spectral data given by Connolly and Thornton[20] seem to indicate that two of the three vicinal couplings involving H-11 of these substances were also small or zero, although the authors did not comment on this. The unusual non-acid-catalyzed A → B rearrangement under catalytic hydrogenation conditions was also observed and may be characteristic of kauranes carrying an axial hydroxyl in the 11 position.

Experimental Section

Experimental details have been specified previously.[21] All NMR spectra were run on a Bruker HX-270 NMR spectrometer in $CDCl_3$ solution.

Extraction of *Eupatorium album*. Above-ground parts of *E. album* L., wt 1.33 kg, collected by R. K. Godfrey on Nov 5, 1961, in a clearing 16 miles west of Tallahassee (Godfrey no. 61639), was extracted with $CHCl_3$ and worked up in the usual fashion.[22] The crude gum, wt 20 g, was chromatographed on a column of 500 g of silicic acid (Mallinckrodt 100 mesh) packed in benzene, 200-ml fractions of increasing polarity being collected. Elution with benzene–$CHCl_3$ (1:1) did not furnish any material. Elution with benzene–$CHCl_3$ (1:10, fractions 11–16) gave a gummy sesquiterpene lactone mixture (0.2 g) which could not be separated successfully.

Elution with benzene–$CHCl_3$ (1:10, fractions 17–24) gave a semisolid which on fractional crystallization from ethyl acetate gave first 80 mg of **1a** as needles: mp 155–157 °C; $[\alpha]^{22}D$ −85° (*c* 0.185, MeOH); ir bands (Nujol) at 3400 (OH), 1690 (CO_2H), 1600 (double bond), 1250, 1060, and 970 cm^{-1}; NMR signals ($CDCl_3$ and a drop of pyridine-d_5) at 5.11 br and 5.03 d (2.5, H-17), 4.00 d br (4.5, H-11), 3.77 t br (2.5, H-15), 2.60 m ($W_{1/2}$ = 12 Hz, H-13), 1.24 (H-18 methyl), and 0.90 ppm (H-20). The high-resolution mass spectrum displayed the molecular ion peak (4.9%), other major peaks were at *m/e* (composition, %) 319 ($C_{19}H_{27}O_4$, 5.5), 288 ($C_{19}H_{28}O_2$, 7.1), 273 ($C_{18}H_{25}O_2$, 6.3), 260 ($C_{17}H_{24}O_2$), 255 ($C_{18}H_{23}O$, 7.8), 245 ($C_{16}H_{21}O_2$, 8.5).

Anal. Calcd for $C_{20}H_{30}O_4$: mol wt, 334.2143. Found: mol wt, 334.2131 (MS).

Methylation of 20 mg of **1a** with diazomethane and recrystallization of the product from methanol afforded **1b** as prisms: mp 125–127 °C; $[\alpha]^{22}D$ −90° (*c* 0.70, MeOH); ir bands ($CHCl_3$) at 3400, 1715 (methyl ester), 1600, 1275, 1150, 1100, 1040, 980, and 900 cm^{-1}; NMR signals at 5.11 br and 5.03 d (2.5, H-17), 4.00 d br (4.5, H-11), 3.77 t br (2.5, H-15), 3.65 (methoxyl), 1.18 (H-18), and 0.90 ppm (H-20). The low-resolution mass spectrum afforded the molecular ion peak at *m/e* 348; other major peaks were at *m/e* 330 ($M^+ - H_2O$, 315 ($M^+ - H_2O - CH_3$), 312 ($M^+ - 2H_2O$), 289 ($M^+ - CO_2CH_3$), 288, 287, 271, and 253.

Anal. Calcd for $C_{21}H_{32}O_4$: mol wt, 348.2300. Found: mol wt, 348.2299 (MS).

The second crop from the fractional crystallization of **1a** consisted mainly of **2a.** Repeated recrystallization from ethyl acetate furnished pure **2a** as needles: wt 35 mg; mp 215–217 °C; $[\alpha]^{22}D$ −210° (*c* 0.10, MeOH); ORD curve (MeOH) $[\alpha]_{450}$ −290, $[\alpha]_{320}$ −450 (min), $[\alpha]_{300}$ −225 (max), $[\alpha]_{260}$ −450 (sh), $[\alpha]_{230}$ −750 (last reading); CD (MeOH) $[\theta]_{297}$ −623 (min); ir bands ($CHCl_3$) at 2500–3300 (–OH), 1725 (cyclopentanone), 1690 (CO_2H), 1200, 1015, and 960 cm^{-1}; NMR signals at 3.92 dd (4.5, 2, H-11), 1.23 (H-18), 1.22 d (7, H-17), and 0.90 ppm (H-20). The low-resolution mass spectrum gave the molecular ion peak at *m/e* 334.

Anal. Calcd for $C_{20}H_{30}O_4$: C, 71.82; H, 9.04, O, 191.13. Found: 71.43; H, 9.36; O, 20.42.

It was subsequently discovered that the mixture of **1a** and **2a** could be separated by repeated TLC on silica gel (Merck $PF_{254-356}$, solvent benzene–ethyl acetate, 6:1) by developing the plate several times, although **1a** and **2a** exhibit the same R_f if the plate is developed only once.

Methylation of 20 mg of **2a** with diazomethane and recrystallization from ethyl acetate gave **2b:** mp 195–197 °C; $[\alpha]^{22}D$ −205° (*c* 0.70, MeOH); ir bands ($CHCl_3$) at 3450, 1720 (combination of cyclopentanone and methyl ester), 1200, 1150, 1090, and 980 cm^{-1}; NMR signals at 3.90 dd (4.5, 2, H-11), 3.62 (methoxyl), 1.24 d (7, H-17), 1.18 (H-18), and 0.80 ppm (H-20). The low-resolution mass spectrum exhibited the molecular ion peak at *m/e* 345; other significant peaks were at *m/e* 330 ($M^+ - H_2O$), 289 ($M^+ - CO_2Me$), 288, 287, 271.

Anal. Calcd for $C_{21}H_{32}O_4$: mol wt, 348.2300. Found: mol wt, 348.2299 (MS).

Acetylation of 20 mg at **2b** with 1 ml of acetic anhydride and 0.5 ml of pyridine for 24 h at room temperature followed by the usual work-up and recrystallization from ethyl acetate furnished 18 mg of **2c:** mp 175–177 °C; $[\alpha]^{22}D$ −125° (*c* 0.046, MeOH); ir bands ($CHCl_3$) at 1720 (very strong, combination of cyclopentanone and esters), 1235, 1170, 1020, and 960 cm^{-1}; NMR signals at 5.05 t (3.5, H-11), 3.63 (methoxyl), 1.92 (Ac), 1.16 (H-18), 1.14 d (7, H-17), and 0.83 ppm (H-20). The high-resolution mass spectrum exhibited the molecular ion (2.3%); other major peaks were at 348 ($C_{21}H_{32}O_4$, 2.7), 330 ($C_{21}H_{30}O_3$, 49.8), 315 ($C_{20}H_{27}O_3$, 11.5), 302 ($C_{20}H_{30}O_2$, 9.6), 298 ($C_{20}H_{26}O_2$, 10.8), 287 ($C_{19}H_{27}O_2$, 7.3), 271 ($C_{19}H_{27}O$, 95.4), 270 ($C_{19}H_{16}O$, 32.0), 255 ($C_{18}H_{23}O$, 30.2), 234 ($C_{15}H_{22}O_2$, 38.4), 197 ($C_{15}H_{17}$, 16.8), 150 ($C_{10}H_{14}O$, 27.3), 121 (C_9H_{13}, 100), and 91 (C_7H_7, 78.6).

Anal. Calcd for $C_{23}H_{34}O_5$: mol wt, 390.2405. Found: mol wt, 390.2394 (MS).

Further elution of the column with $CHCl_3$ (fractions 25–30) gave solid **3a,** which was recrystallized from methanol: yield 260 mg; mp 268–270 °C; $[\alpha]^{22}D$ −150° (*c* 0.0225, MeOH); ir bands ($CHCl_3$) at 2500–3300 (–OH), 1715 (cyclopentanone), 1690 (carboxyl), 1640 (conjugated double bond), 1240, 1170, 1050, and 940 cm^{-1}; uv spectrum λ_{max} 237 nm (ϵ_{max} 8000); NMR signals at 5.85 and 5.26 (H-17), 4.05 d (3.5, H-11), 3.05 m ($W_{1/2}$ = 12 Hz, H-13), 1.26 (H-18), and 0.92 ppm (H-20). The high-resolution mass spectrum exhibited the molecular ion peak (16.7%); other major peaks were at *m/e* 288 ($M^+ - CO_2$, $C_{19}H_{28}O_2$, 3.9), 287 ($M - CO_2H$, $C_{19}H_{27}O_2$, 5.4), 286 ($M^+ - CO_2H - H$, $C_{19}H_{26}O_2$, 25.1), 83 (C_5H_7, 100), or are detailed in Scheme I.

Anal. Calcd for $C_{20}H_{28}O_4$: C, 72.26; H, 8.49; O, 19.25; mol wt, 332.1986. Found: C, 72.32; H, 8.33; O, 19.70; mol wt, 332.1988 (MS).

Methylation of 10 mg of **3a** with excess diazomethane in the usual fashion and crystallization of the residue from ethyl acetate afforded 11 mg of **6:** mp 143–145 °C; ir bands ($CHCl_3$) at 3500 (OH), 1770 (cyclopentanone), 1715 (ester), 1235, 1150, 1100, 1040, and 1090 cm^{-1}; NMR signals at 4.05 d (3.5, H-11), 3.67 (OMe), 1.24 (H-18), and 0.92 ppm (H-20).

Anal. Calcd for $C_{22}H_{32}O_4N_2$: mol wt, 388.2361. Found: mol wt, 388.2383 (MS).

Acetylation of 60 mg of **3a** in 1 ml of pyridine with 1.5 ml of acetic anhydride at room temperature for 48 h, at which time TLC analysis indicated that 90% of starting material had reacted, work-up of the mixture in the usual fashion, and purification of the crude product by preparative TLC (silica gel, solvent benzene–ethyl acetate, 3:1) yielded 50 mg of **3b:** mp 253–255 °C; $[\alpha]^{22}D$ −175° (*c* 0.20, MeOH); ir bands ($CHCl_3$) at 3200–2500 (carboxyl –OH), 1730 (cyclopentenone and acetate), 1690 (CO_2H), 1640 (conjugated double bond) 1235, 1035, 1030, and 940 cm^{-1}; NMR signals at 5.88 and 5.23 (H-17), 5.11 d (3, H-11), 3.06 m ($W_{1/2}$ = 12 Hz, H-13), 1.83 (Ac), 1.22 (H-18), and 0.95 ppm (H-20). The low-resolution mass spectrum exhibited peaks at *m/e* 374 (M^+) 332 ($M^+ - C_2H_2O$), 314 ($M^+ - CH_3CO_2H$), 316, 298, 295, 268, 253, 219, 218, 173 (base peak), 148, 147, 146, 121, and 119.

Anal. Calcd for $C_{22}H_{30}O_5$: C, 70.56; H, 8.07; O, 21.36. Found: C, 70.73; H, 8.13, O, 21.44.

Elution of the column with $CHCl_3$–MeOH (49:1, fractions 31–35) gave semisolid material. Repeated recrystallization from methanol and ethyl acetate gave 210 mg of **4a:** mp 215–217 °C; $[\alpha]^{22}D$ −81° (*c* 0.342, MeOH); ir bands ($CHCl_3$) at 3400–2500 (–OH), 1690 (carboxyl), 1200, 1100, and 1030 cm^{-1}; NMR signals ($CDCl_3$ and 2 drops of pyridine-d_5) at 5.08 br and 5.04 d (2.5, H-17), 3.80 d (3.5, H-11), 3.77 t br (2.5, H-15), 3.65 dd (4.5, 3.5, H-12), 2.47 t br (4.5, H-13), 1.15 (H-18), and 0.85 ppm (H-20). The NMR spectrum of the analytical sample indicated the presence of ethyl acetate, also revealed by the elemental analysis. The low-resolution mass spec-

trum exhibited peaks at *m/e* 350 (M^+), 332 ($M^+ - H_2O$), 314 ($M^+ - 2H_2O$), 271, 243, 229, and 213.

Anal. Calcd for $C_{22}H_{30}O_5 \cdot \frac{1}{2}EtOAc$: C, 66.98; H, 8.69; O, 24.33. Found: C, 67.35; H, 8.62; O, 24.01. High-resolution mass spectrum: Calcd for $C_{20}H_{30}O_5$: 350.2093. Found: 350.2110.

Methylation of 20 mg of **4a** and recrystallization of the crude product from ethyl acetate provided **4b:** mp 169–170 °C; $[\alpha]^{22}D$ −105° (*c* 0.188, MeOH); ir bands ($CDCl_3$) at 3400, 1715, 1220, 1150, 1100, 1060, 1030, and 900 cm^{-1}. The high-resolution mass spectrum gave the molecular ion peak (10.8%); other major peaks were at *m/e* (composition, %) 346 ($C_{21}H_{30}O_4$, 1.2), 287 ($C_{19}H_{27}O_2$, 12.3) 285 ($C_{19}H_{25}O_2$, 4.3), 147 ($C_{10}H_{11}O$, 16.5), 123 (C_9H_{15}, 34.8), and 119 (C_9H_{11}, 95.7).

Anal. Calcd for $C_{21}H_{32}O_5$: C, 69.20; H, 8.85; O, 21.95; mol wt, 364.2249. Found: C, 69.67; H, 8.80; O, 21.86; mol wt, 364.2244 (MS).

Acetylation of 80 mg of **4b** for 48 h at room temperature followed by the usual work-up and recrystallization of the crude product from ethyl acetate–MeOH yielded 75 mg of **4c:** mp 165–167 °C; ir bands ($CHCl_3$) at 1730 (very strong), 1600, 1235, 1150, 1100, 1080, 1030, and 915 cm^{-1}; NMR signals at 5 c (H-17, H-15, H-11), 2.67 br ($W_{1/2}$ = 12 Hz, H-13), 2.16, 1.98, 1.92 (Ac), 1.17 (H-18), and 0.86 ppm (H-20). The low-resolution mass spectrum had peaks at *m/e* 490 (M^+), 448 ($M - C_2H_2O$), 430 ($M^+ - CH_3CO_2H$), 388 ($M - C_2H_2O - CH_3CO_2H$), 370 ($M - 2CH_3CO_2H$), 328 ($M - 2CH_3CO_2H - C_2H_2O$), 310 ($M^+ - 3CH_3CO_2H$), 268, 251, and 234.

Anal. Calcd for $C_{27}H_{38}O_8$: mol wt, 490.2566. Found: mol wt, 490.2572 (MS).

Further elution of the column with $CHCl_3$–MeOH (49:1, fractions 36–38) gave 0.3 g of a gummy mixture of sesquiterpene lactones.

Conversion of to 3a 1b. A solution of 15 mg of **3a** in 5 ml of MeOH was stirred with 20 mg of $NaBH_4$ at −20 °C. After 5 h 80% of starting material had been consumed (TLC control). The mixture was diluted with water, acidified with dilute acetic acid, and extracted with chloroform. The washed and dried extract was evaporated and the residue esterified with diazomethane. Preparative TLC (solvent benzene–ethyl acetate, 2:1) and elution of the major product gave **1b** (80%), identical in every respect with material prepared from **1a.**

Hydrogenation of 3a. A solution of 10 mg of **3a** in 15 ml of ethanol was hydrogenated with 50 mg of 5% Pd/C for 1 h. Filtration and evaporation gave **2a** which, for ease of comparison, was esterified to **2b** (yield quantitative), identical with **2b** prepared from **2a** in every respect.

Catalytic Isomerization of 1b. Attempted reduction of **1b** with 5% Pd/C in a hydrogen atmosphere as described above followed by the usual work-up gave **2b** in quantitative yield.

Preparation of 7. A solution of 50 mg of **3a** in 25 ml of AR acetone was oxidized with 0.2 ml of Jones reagent by stirring at room temperature. After 15 min excess reagent was destroyed by addition of 2-propanol. The mixture was diluted with water and extracted with $CHCl_3$. The washed and dried extract was evaporated; the residue was purified by preparative TLC (silica gel, solvent benzene–ethyl acetate, 3:1), and recrystallized from ethyl acetate: yield 20 mg; mp 295 °C dec; ir bands ($CHCl_3$) at 2600–3400 (OH), 1715 (cyclopentenone and cyclohexanone), 1690 (carboxyl), 1640 (conjugated double bond), 1200, 1135, and 1050 cm^{-1}; NMR signals at 6.01 and 5.40 (H-17), 3.26 m (H-13), 1.28 (H-18), and 1.02 ppm (H-20); uv spectrum λ_{max} 230 nm (ϵ_{max} 10 000). The high-resolution mass spectrum exhibited the molecular ion peak (22.3%); other major peaks were at *m/e* (composition, %) 312 ($M^+ - H_2O$, $C_{20}H_{24}O_3$, 9.6), 284 ($M^+ - CO_2H - H$, $C_{19}H_{24}O_2$, 33), 269 ($M^+ - CO_2H - H - CH_3$, $C_{18}H_{21}O_2$, 33), 256 ($C_{18}H_{24}O$, 8.2), 215 ($C_{14}H_{15}O_2$, 13.1), 149 ($C_{10}H_{13}O$, 41.2), 148 ($C_{10}H_{12}O$, 26), 91 (C_7H_7, 53.6), and the peaks shown in Scheme I.

Anal. Calcd for $C_{20}H_{26}O_4$: mol wt, 330.1830. Found: mol wt, 330.1827 (MS).

Hydrogenation of 7. A solution of 5 mg of **5** in 10 ml of ethanol was hydrogenated over 50 mg of 5% Pd/C at atmospheric pressure for 2 h and filtered. The filtrate and washings were evaporated. The residue **9** was recrystallized from MeOH: mp 185–187 °C dec; ir bands ($CHCl_3$) at 1720 (cyclopentanone), 1705 (cyclohexanone and carboxyl), 1200, 1110, and 980 cm^{-1}; ORD curve (MeOH) $[\alpha]_{450}$ −72, $[\alpha]_{340}$ +455 (max), $[\alpha]_{315}$ 0, $[\alpha]_{300}$ −650 (last reading); CD (MeOH) $[\theta]_{300}$ +3980.

The high-resolution mass spectrum exhibited the molecular ion peak (4%); other major peaks were at *m/e* (composition, %) 304 ($M^+ - CO$, $C_{19}H_{28}O_3$, 19.7), 286 ($M^+ - CO_2H - H$, $C_{19}H_{26}O_2$, 19.1), 258 ($M^+ - CO_2H - H - CO$, $C_{18}H_{26}O$, 12.3), 203 ($C_{14}H_9O$, 19.8), 175 ($C_{13}H_{19}$, 17.8), 151 ($C_{10}H_{15}O$, 43.5), 149 ($C_8H_5O_3$, 65.4), 138 ($C_9H_{14}O$, 100), 123 ($C_8H_{11}O$, 33.4), 121 (C_8H_9O, 15.7).

Anal. Calcd for $C_{20}H_{28}O_4$: mol wt, 332.1986. Found: mol wt, 332.1992 (MS).

Conversion of 3a to 8. A. An ice-cold mixture of 11 mg of **3a,** 0.5 ml of dry pyridine, and 0.1 ml of $POCl_3$ was stirred at 0 °C for 15 min and then at room temperature for 0.5 h. The mixture was poured on ice–water and extracted with water. The washed and dried extract was evaporated and the residue purified by preparative TLC (silica gel, solvent benzene–ethyl acetate, 6:1). Recrystallization from ethyl acetate afforded 6 mg of **8:** mp 165–167 °C; ir bands ($CHCl_3$) at 2600–3400, 1720 (cyclopentenone), 1690 (carboxyl), 1640 (double bond), 1250, and 1170 cm^{-1}; NMR signals at 6.09 dd br (10, 7, H-12), 5.58 (H-17a), 5.51 dd (10, 3, H-11), 5.01 (H-17b), 3.24 dd br (7, 3, H-13), 1.26 (H-18), and 0.87 ppm (H-20). The low-resolution mass spectrum exhibited the molecular ion peak at *m/e* 314; other major peaks were at *m/e* 268 and 158.

Anal. Calcd for $C_{20}H_{26}O_3$: mol wt, 314.18818. Found: mol wt, 314.18809 (MS).

B. Hydrogenation of 4 mg of **8** in 10 ml of ethanol with 50 mg of 5% Pd/C at atmospheric pressure for 2 h and recrystallization from MeOH afforded 4 mg of **5:** mp 225–227 °C; $[\alpha]^{22}D$ −105° (*c* 0.09, $CHCl_3$) [reported[3] mp 226–228 °C, $[\alpha]D$ −99° (*c* 0.192, $CHCl_3$)]; ir bands ($CHCl_3$) at 2600–3400, 1725 (cyclopentanone), 1690 (carboxyl), 1260, and 1180 cm^{-1} [reported ir bands (CS_2) 1723, 1692 cm^{-1}]; NMR signals at 1.23 (H-18), 1.09 d (7, H-17), and 1.00 ppm (H-20). The low-resolution mass spectrum exhibited the molecular ion peak at *m/e* 318; other major peaks were at *m/e* 303 ($M^+ - CH_3$), 274 ($M^+ - CO_2$), 259 ($M^+ - CO_2 - CH_3$), and 244 ($M^+ - CO_2 - 2CH_3$).

Anal. Calcd for $C_{20}H_{30}O_3$: mol wt, 318.2194. Found: mol wt, 318.2193 (MS).

Reaction of 17 mg of **3a** in 0.35 ml of pyridine and 0.1 ml of methanesulfonyl chloride overnight at room temperature followed by the usual work-up gave 18 mg of **3d** which was purified by preparative TLC (silica gel, solvent benzene–ethyl acetate, 4:1) and was characterized by its NMR spectrum only, signals at 5.90 and 5.30 (H-17), 5.15 d br (3.5, H-11), 2.83 (methanesulfonate), 1.22 (H-18), and 0.98 ppm (H-20). The product, wt 15 mg, was dissolved in 10 ml of Me_2SO and heated with 50 mg of $NaBH_4$ at 100 °C for 12 h. The cooled reaction mixture was diluted with water and extracted with $CHCl_3$. The washed and dried extracts were evaporated and the residue was purified by preparative TLC and identified as **15** by its NMR spectrum, signals at 5.85 dd (10, 9, H-12) and 5.58 dd (10, 3, H-11), 3.51 d br (10.5, H-15), 1.21 (H-18), 0.88 d (7, H-17), and 0.84 ppm (H-20). The low-resolution mass spectrum gave a very weak molecular ion peak at *m/e* 318 (M^+); other peaks were at *m/e* 300 ($M^+ - H_2O$), 285 ($M^+ - H_2O - CH_3$), 270 ($M^+ - H_2O - 2CH_3$), and 255 ($M^+ - H_2 - CO_2H$).

Anal. Calcd for $C_{20}H_{30}O_3$: mol wt, 318.2194. Found: mol wt, 318.2199 (MS).

Because of the very poor yield of **15,** this route was abandoned.

Reactions of 4a and 4b. A. Oxidation of 80 mg of **4b** in 50 ml of AR acetone with 0.2 ml of Jones reagent in the manner described for **3a** and preparative TLC of the crude product over silica gel (solvent benzene–ethyl acetate, 4:1) furnished 22 mg of **10** as a gum: ir bands at 1720 (very broad), 1650, 1150, 1100, and 970 cm^{-1}; uv spectrum λ_{max} 232 nm (ϵ_{max} 6000); NMR signals at 6.30 br, 5.66 br (H-17), 3.95 d br (4, H-13), 3.64 (methoxyl), 1.26 (H-18), and 0.86 ppm (H-20). The high-resolution mass spectrum gave the molecular ion (37.2%); other major peaks were at *m/e* (composition, %) 330 ($C_{20}H_{26}O_4$, 8.8), 302 ($C_{19}H_{26}O_3$, 31.5), 283 ($C_{18}H_{19}O_3$, 25.3), 270 ($C_{18}H_{22}O_2$, 7.9), 242 (34.3), and 227 ($C_{16}H_{19}O$, 13.2).

Anal. Calcd for $C_{21}H_{26}O_5$: mol wt, 358. 1779. Found: mol wt, 358.1776 (MS).

B. A solution of 9 mg of **4a** in 1 ml of acetone containing a crystal of *p*-toluenesulfonic acid was allowed to stand overnight at room temperature, placed on a column of silica gel (1 g), and eluted with an additional 20 ml of acetone. Evaporation of the eluate and crystallization of the residue gave 8 mg of the acetonide **11:** mp 255–257 °C; ir bands (Nujol) at 3400, 1690, 1260, and 1170 cm^{-1}; NMR signals at 5.27 br and 5.13 d (1.8, H-17), 4.12 m (H-11 and H-12), 3.75 t br (1.8, H-15), 2.55 t br (4.5, H-13), 1.45 and 1.30 (acetonide methyls), 1.24 (H-18), and 0.88 ppm (H-20). The low-resolution mass spectrum exhibited the molecular ion at *m/e* 390; other major peaks were at *m/e* 375 ($M^+ - CH_3$), 332 ($M^+ - C_3H_6O$), 314 ($M^+ - C_3H_6O - CH_3$), 299 ($M^+ - C_3H_6O - CH_3 - H_2O$), 287, and 268.

Anal. Calcd for $C_{23}H_{32}O_5$: mol wt, 390.2406. Found: mol wt, 390.2410 (MS).

C. Catalytic isomerization of 7 mg of **4a** to **12** with 5% Pd/C in a hydrogen atmosphere was carried out in the same manner as previously described for **1a.** The product **12,** wt 7 mg, was recrystallized from methanol: mp 225–227 °C; ir bands (Nujol) at 3400, 1720, 1690, 1260, 1170, and 1060 cm^{-1}; NMR signals ($CDCl_3$ plus 2 drops of pyridine-d_5) at 3.95 m (H-11 and H-12), 2.61 br ($W_{1/2}$ = 12 Hz, H-13), 13.7 d (7, H-17), 1.23 (H-18), and 0.93 ppm (H-20); ORD curve (MeOH) $[\alpha]_{150}$ −60, $[\alpha]_{400}$ −60, $[\alpha]_{317}$ −240 (min), $[\alpha]_{300}$ −60 (max), $[\alpha]_{275}$ −125, $[\alpha]$ −250 (sh), $[\alpha]_{235}$ −360 (last reading). The low-resolution mass spectrum gave the molecular ion peak at *m/e* 350; other peaks were at *m/e* 332 ($M^+ - H_2O$), 314 ($M^+ - 2H_2O$), 304 ($M^+ - CO_2H - H$), 287 ($M^+ - CO_2H - H_2O - H$), 271, 259, and 213.

Anal. Calcd for $C_{20}H_{30}O_5$: mol wt, 350.2093. Found: mol wt, 350.2110 (MS).

Isomerization of 1b to 13a. A. A sample of **1b** prepared by $NaBH_4$ reduction of **3a,** subsequent methylation, and preparative TLC (vide supra) was used almost entirely for determination of the NMR spectrum. After 1 month at room temperature, during which time the solvent had evaporated, the NMR spectrum was redetermined and exhibited the significant differences mentioned in the Discussion. TLC indicated the presence of two constituents (approximately 9:1). Preparative TLC on silica gel resulted in isolation of the less polar product **13a,** crude wt ~15 mg. After recrystallization from ethyl acetate, it melted at 95–97 °C: ir bands ($CHCl_3$) at 3500 (OH), 1715 (ester), 1225, 1160, 1090, 1070, 980, and 830 cm^{-1}; NMR signals at 4.27 t (J = 3 Hz, H-11), 3.63 (methoxyl), 2.88 (slightly broadened, H-15), 1.30 (H-17), 1.17 (H-18), and 0.87 ppm (H-20). The low-resolution mass spectrum gave the molecular ion peak at *m/e* 348; other major peaks were at *m/e* 333 ($M^+ - CH_3$), 330 ($M^+ - H_2O$), 289 ($M^+ - CO_2Me$), 288, 287, and 274.

Anal. Calcd for $C_{21}H_{32}O_4$: mol wt, 348.2300. Found: mol wt, 348.2303 (MS).

Acetylation of **13a** in the usual fashion gave, after recrystallization from ethyl acetate, **13b:** mp 118–120 °C; ir bands at 1720, 1235, 1070, and 970 cm^{-1}; low-resolution mass spectral peaks at *m/e* 390 (M^+), 348 ($M^+ - C_2H_2O$), 330 ($M^+ - CH_3CO_2H$), 315 ($M^+ - CH_3CO_2H - CH_3$), 306, 287, and 271.

Anal. Calcd for $C_{23}H_{34}O_5$: mol wt, 390.2406. Found: mol wt, 390.2410 (MS).

The minor material, crude wt ~3 mg, was originally thought to be starting material since **1b** and **2b** have the same R_f. Recrystallization from ethyl acetate and determination of the melting point and the NMR spectrum identified it as **2b.**

B. A solution of 5 mg in **1b** in 1 ml of methanol and 5 drops of 10% aqueous HCl was allowed to stand at room temperature. The solvent was evaporated, first under the water pump and then in vacuo. The NMR spectrum of the residue was that of **13a,** indicating that the proportion of **2b** was 10% or less.

C. A 10-mg sample of pure **13a** was refluxed with 0.5 ml of sulfuric acid and 0.5 ml of water in 10 ml of ethanol for 24 h. After the usual work-up of the reaction mixture, TLC analysis of the crude product indicated absence of **2b** and recovery of **13a** which was subsequently isolated in nearly quantitative yield.

Registry No.—**1a,** 57719-76-3; **1b,** 57719-77-4; **2a,** 57719-78-5; **2b,** 57719-79-6; **2c,** 57719-80-9; **3a,** 57719-81-0; **3b,** 57719-82-1; **3d,** 57719-83-2; **4a,** 57719-84-3; **4b,** 57719-85-4; **4c,** 57719-86-5; **5,** 57793-40-5; **6,** 57719-87-6; **7,** 57719-88-7; **8,** 57719-89-8; **9,** 57719-90-1; **10,** 57738-57-5; **11,** 57719-91-2; **12,** 57719-92-3; **13a,** 57719-93-4; **13b,** 57719-94-5; **15,** 57719-95-6.

References and Notes

(1) This work was supported in part by Grant CA-13121 from the U.S. Public Health Service through the National Cancer Institute. We are greatly indebted to Mr. John Shedd for carrying out the chromatographic separation of the crude extract.
(2) For references to earlier work and to a redefinition of the genus *Eupatorium,* see our previous paper on constituents of *E. hyssopifolium* L.: W. Herz and R. P. Sharma, *J. Org. Chem.,* preceding paper in this issue.
(3) D. E. U. Ekong and A. U. Ogan, *J. Chem. Soc.,* 311 (1968).
(4) The flavonoid constituents of the polar extract of *E. album* have been described earlier: H. Wagner, M. A. Iyengar, L. Hörhammer, and W. Herz, *Phytochemistry,* **11,** 1504 (1972).
(5) For a recent reference to the chemical shift of H-13 in 15-oxo-16-kaurenes, see I. Kubo, T. Kamikawa, T. Isabe, and T. Kubota, *Bull. Chem. Soc. Jpn.,* **47,** 1277 (1974).
(6) Analogous with the primary process in the mass spectra of 11-keto steroids; see H. Budzikiewicz in "Biochemical Applications of Mass Spectrometry", G. R. Waller, Ed., Wiley-Interscience, New York, N.Y., 1972, p 251.
(7) We are indebted to Dr. J. R. Hanson, University of Sussex, for this information. Valuable data on ^{13}C NMR spectra of kaurenolides appear in an article by J. R. Hanson, G. Savona, and M. Siverns, *J. Chem. Soc., Perkin Trans. 1,* 2001 (1974).
(8) For an analogy, see the comparison between 11α-hydroxyandrostane[9] and 11-ketoandrostane.[10]
(9) H. Eggert, C. L. VanAntwerp, N. S. Bhacca, and C. Djerassi, *J. Org. Chem.,* **41,** 71 (1976).
(10) H. Eggert and C. Djerassi, *J. Org. Chem.,* **38,** 3788 (1973).
(11) L. H. Briggs, R. C. Cambie, and P. S. Rutledge, *J. Chem. Soc.,* 5374 (1963).
(12) An unsuccessful attempt to relate **3a** to a known compound via the mesylate **3d** is described in the Experimental Section.
(13) A. J. McAlees and R. McCrindle, *J. Chem. Soc., Perkin Trans. 1,* 861 (1975).
(14) In the ^{13}C NMR spectrum of the triacetate **4c,** only C-12 experienced the expected downfield shift (72.4 → 73.3), whereas the signals of C-11 and C-15 were shifted upfield (68.3 → 67.3, 82.2 → 81.5). Similarly only C-13 and C-16 exhibited a β shift (46.0 → 43.4, 153.2 → 146.4) whereas C-8 and C-9 remained essentially unchanged. Somewhat similar seemingly anomalous results have been observed in the acylation of 1,3-diols of the olean-12-enes: K. Tori, S. Seo, A. Shimaoka, and Y. Tomita, *Tetrahedron Lett.,* 4227 (1974).
(15) Rearrangement under these conditions normally occurs on acid catalysis and is limited to substances containing a β-oriented C-15 hydroxyl group,[16,17] In a similar way, treatment of **1a** with 5% Pd/C–H_2 caused isomerization to **2a.** For an account of the behavior of **1b** on treatment with acid, see below.
(16) J. R. Cannon, P. W. Chow, P. R. Jefferies, and G. V. Meehan, *Aust. J. Chem.,* **19,** 861 (1966).
(17) M. F. Barnes and J. MacMillan, *J. Chem. Soc.,* 361 (1967).
(18) These are the conditions ordinarily employed for the A → B isomerization.
(19) The rules used for nomenclature of diterpenoids are clear but frequently lead to confusion. The prefix ent indicates that the substance in question belongs to the enantiomeric series. Since in a systematic name the prefix precedes the number specifying the location of the substituent, an 11β-hydroxylated *ent*-kaurane becomes an *ent*-11α-hydroxykaurane.
(20) J. D. Connolly and I. M. S. Thornton, *J. Chem. Soc., Perkin Trans. 1,* 737 (1973).
(21) W. Herz, A. Srinivasan, and P. S. Kalyanaraman, *Phytochemistry,* **14,** 233 (1975).
(22) W. Herz and G. Högenauer, *J. Org. Chem.,* **27,** 905 (1962).