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MINOR QUINONE METHIDE DITERPENOIDS FROM THE ROOTS OF *SALVIA TEXANA*

ANTONIO G. GONZÁLEZ,* ZAHIRA E. AGUIAR, JAVIER G. LUIS, ANGEL G. RAVELO,

Centro de Productos Naturales Orgánicos "Antonio González", Universidad de La Laguna, 38206 Tenerife, Canary Islands, Spain

and XORGE A. DOMÍNGUEZ

Instituto Tecnológico y de Estudios Superiores de Monterrey, Monterrey, Mexico

ABSTRACT.—Three new methylene quinone diterpenes were isolated from the MeOH extract of the roots of *Salvia texana* and characterized as 2α,11-dihydroxy-5,7,9(11),13-abietatetraen-12-one [**1**], 2α,7,11-trihydroxy-7,9(11),13-abietatrien-12-one [**6**], and 2-oxotaxodione [**12**]. The known product, 2α-hydroxysugiol, was also obtained. The structure of the new natural compounds was determined by chemical and spectroscopic methods.

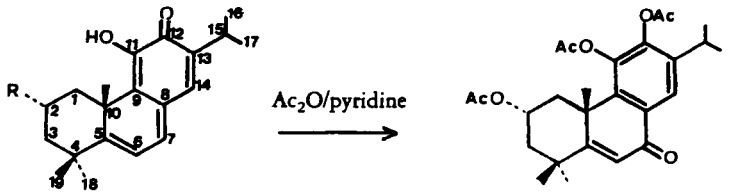
Our intensive study of *Salvia texana* Torr. (Labiatae) has already yielded various new diterpenes (1–3) and two new flavonoids (4). In assays for antibacterial activity (5) carried out on some of these diterpenes (1), all the methylene quinones were effective against Gram-positive *Staphylococcus aureus* and *Bacillus subtilis*, with 6-deoxo-2α-hydroxytaxodione being the most powerful inhibitor. This paper reports the isolation of three new diterpenes **1**, **6**, and **12** and the known 2α-hydroxysugiol [**5**], previously isolated in this laboratory (6), from an MeOH extract of the roots of *S. texana*.

RESULTS AND DISCUSSION

Compound **1** had the molecular formula $C_{20}H_{26}O_3$ and was assigned the structure 2α,11-dihydroxy-5,7,9(11),13-abietatetraen-12-one on the basis of the following evidence: Its uv spectrum was identical to that of fuerstione [**2**] (7), and this established the presence of the same chromophore in the two compounds. Its ir spectrum showed absorption bands for two hydroxyl groups and a conjugated quinone (3660, 3580, and 1600 cm^{-1}). Its ^{1}H-nmr spectrum showed signals for three angular methyls and an isopropyl grouping. A broad multiplet at δ 4.30 was characteristic of the geminal proton of a 2α-OH group (1). A broad singlet at δ 7.36 was attributed to the OH on C-11 and disappeared after D_2O was added, while a singlet at δ 6.92 could be assigned to H-14. The most notable characteristic of the spectrum was the presence of two doublets centered on δ 6.72 and 6.37 ($J = 6.8$ Hz). The low chemical shift of these protons characterized them as the H-6 and H-7 protons of two double bonds conjugated with the quinone system, the H-7 being downfield from the H-6. All these data plus the typical ms fragmentations for this type of compound agreed with the structure and relative stereochemistry given for **1**.

Acetylation of compound **1** (Scheme 1) rather oddly gave compound **3** with the molecular ion $[M]^+$ at *m/z* 456. The ^{1}H-nmr spectrum of **3** showed signals for one aliphatic and two aromatic acetates, a singlet at δ 6.53 assignable to the proton at 6, α to a conjugated ketone, and a singlet at δ 8.13, a characteristic shift when there is a carbonyl group at 7 (1,3). The foregoing agreed with the structure proposed for **3**, which could be obtained from **1** by the Michael addition of H_2O to C-7, followed by dehydrogenation and tautomerization to the acylcatechol form.

Compound **5** was obtained from more polar fractions than **1**. Its spectra were superimposable upon those of 2α-hydroxysugiol, a substance which we had isolated earlier for the first time (6). When salviol [**4**] was treated with DDQ in dioxan in anhydrous medium, as reported earlier (2), 6,7-dehydrosalviol was obtained. In the



1 R=OH
2 R=H

3

SCHEME 1

presence of H_2O, the same DDQ reaction afforded **5** (Scheme 2) by a similar mechanism to that proposed for the formation of **3**.

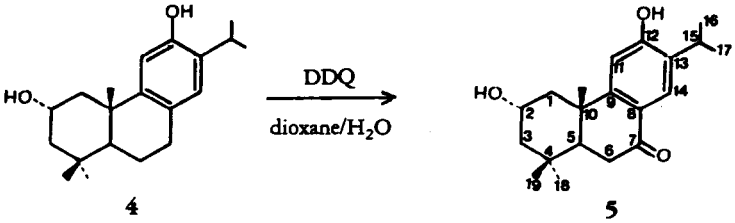
Product **6** could not be isolated as a pure substance and was only obtained as part of a mixture (67:33) with compound **7** which had been isolated previously (1). Their methyl derivatives, **8** and **9**, were prepared and proved equally inseparable. However, acetylation gave a mixture of **10** and **11** which could be separated by preparative tlc.

Allowing for the presence of **7** and subtracting its signals, the following spectral data were observed for **6**: molecular ion $[M]^+$ at *m/z* 332, molecular formula $C_{20}H_{28}O_4$; ^1H nmr showed an isopropyl group, three angular methyls, an ABX system, with the AB part corresponding to protons 5 and 6α, and the X to 6β. This coupling pattern was identical to that seen for compound **5**. The signal for H-5 in the ^1H nmr of **5** and **6** is partly hidden by a broad signal assigned to an -OH, which disappeared when D_2O was added. The ABX system was better studied on **5**.

When the spectra of **5** taken in $CDCl_3$ and C_6D_6 were compared, a huge shift for a multiplet (δ 1.83 to 2.35) was observed, a shift which could only agree with H-6α because this remained in front and on the same side of the carbonyl group and was equatorial, inducing a downfield shift in C_6D_6 (8). NOe experiments bore out this assignment, as irradiation of the C-10 Me showed a strong nOe effect on H-6β (20%), C-4 β Me (36%), and H-2β (46%). Finally, ^1H nmr of **6** shows a heptet for H-15 and a very broad multiplet at δ 4.08, the breadth and multiplicity of which agreed only with H-2β; this determined the stereochemistry of the alcohol group as 2α.

A singlet at δ 7.62 could be assigned to H-14, showing by its shift that there is an enol system at 7 and not a carbonyl group. All these data were in agreement with the structure of 2α,7,11-trihydroxy-7,9(11),13-abietatrien-12-one for **6**, which was confirmed chemically by obtaining a mixture of the monomethylated products **8** and **9** when the mixture of **6** and **7** was treated with CH_2N_2.

The mass spectrum of product **8** showed $[M]^+$ at *m/z* 346 and fragments at 328 and



4

5

SCHEME 2

314 corresponding to the loss of H_2O and MeOH from the molecular ion, confirming the data given above. The ^{1}H-nmr spectrum, in addition to signals for the isopropyl group, angular methyls, and the β geminal proton of the 2-OH group, showed the same coupling pattern as for the ABX system discussed above, and H-5 and H-6 behaved in the same way. The continuance of the enolic system at C-7 was confirmed because the chemical shift of H-14 was identical to that of the same proton in **6**. The methylene quinone system was thus ratified.

When the mixture of **8** and **9** was acetylated, **10** and **11** were obtained. The most characteristic signals of **10** were for one aliphatic and one aromatic acetate, a methoxy group, and an aromatic proton at δ 7.97, which were only compatible with structure **10** and could not have been formed from a 7-methoxy derivative of **8**. The experimental data of compound **11** (see Experimental), obviously derived from **7** by a similar process, agree with the structure, 7-oxo-2,6,12-triacetoxy-11-methoxy-abieta-8,11,12-triene. These results indicate that the methoxy group of compound **8** is located at C-11.

The other new product, **12**, molecular formula $C_{20}H_{24}O_4$, had uv spectra very similar to those of 2α-hydroxytaxodione (1), indicating the presence of the same chromophore, a conjugated quinone methide system; this was confirmed by the ir signal at 1675 cm^{-1}. Other ir bands at 1715 and 3300 were typical of a cyclohexanone and a hydroxy group, respectively. The ^{1}H-nmr spectrum had signals for an isopropyl group and three angular methyls, but no signal for the geminal proton of the 2α-OH group, which has been the classic substitution pattern in the diterpenes isolated from the roots of this plant. In this case the substituent was a ketone group on C-2, confirmed by the C-1 and C-3 protons appearing as a double doublet at δ 3.55 (J = 2.3, 13.7 Hz) for H-1β, a doublet at δ 2.95 (J = 13.7 Hz) for H-1α, a double doublet at δ 2.16 (J = 2.3, 12.8 Hz) for H-3β, and a doublet at δ 2.40 (J = 12.8 Hz) for H-3α, established by a double resonance experiment which also showed a long-distance coupling (W) between H-1β and H-3β. The spectrum was rerun in C_6D_6 to check out these assignments and confirmed the spatial relationships proposed (8).

The highest δ (δ $CDCl_3$-δ C_6D_6) is that of H-5α (+0.63 ppm), which confirms the axial position. H-3α and H-1α are also positive (+0.45 and 0.42 ppm) as they are in a 1,3 axial configuration. The ^{1}H-nmr spectrum taken in $CDCl_3$ shows three lowfield singlet signals, one of which (δ 7.58) is exchangeable with D_2O and can be assigned to the 11-OH with the other two corresponding to H-7 and H-14.

All these data are in full agreement with structure 2-oxotaxodione for **12**, which was borne out by chemical evidence. When **12** was treated with Ac_2O in pyridine, a triacetoxy ketone, **13**, was obtained with $[M]^+$ at *m/z* 472; ^{1}H nmr shows signals at δ 2.31, 2.35, and 2.30 for three acetate methyls and at δ 6.40 for the proton geminal to the aliphatic acetate. This low chemical shift suggests that this is at C-7, allylic to the aromatic ring and the C-6 carbonyl. These data agree with structure **13** obtained from **12** by a Michael addition of the acetate followed by acetylation. The α stereochemistry of the 7-acetoxy group was established from the fact that this class of diterpene usually undergoes nucleophilic attack at C-7 on the less hindered α face of the molecule. The chemical shift of H-14 agrees with that of rosmanol triacetate (9).

EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES.—^{1}H nmr spectra were collected on a Bruker WP-200SY (200 MHz) spectrometer with $CDCl_3$ or C_6D_6 as solvents and TMS as internal standard. The ir spectra were taken on a Perkin-Elmer 681 spectrophotometer using either a $CHCl_3$ solution or a film. Uv spectra were recorded on a Perkin-Elmer 550SE spectrophotometer with EtOH as solvent. Mass spectra were run on a VG-Micromass ZAB-2F. Preparative tlc was developed on precoated Schleicher & Schüll foils, F-1500/LS 254. Voucher plant specimens are on file with the Herbarium of the Department of Botany, Instituto Tecnológico y de Estudios Superiores de Monterrey, Monterrey, Mexico.

PLANT MATERIAL.—The finely-cut roots of *S. texana* (3 kg) were extracted with cold MeOH (5 liters). Filtration and evaporation of the solvent in a rotavapor in vacuo gave a reddish-brown extract (48 g) which was chromatographed on Sephadex using *n*-hexane–$CHCl_3$–MeOH (25:25:50) as solvent. Fractions (500 ml) were collected and the medium fractions 40–58 were studied. After repeated chromatography on Si gel with *n*-hexane/EtOAc as solvent, compounds **1**, **5**, **6**, and **12** were isolated.

2α,11-DIHYDROXY-5,7,9(11),13-ABIETATETRAEN-12-ONE [**1**].—Compound **1** was isolated as a reddish-yellow oil (4 mg): $[M]^+$ at *m/z* 314.1887 (calcd for $C_{20}H_{26}O_3$, 314.1892); ir cm^{-1} 3660 m, 3580 m, 3000 s, 2950 s, 2920 s, 2860 w, 1600 s, 1520 vs, 1460 w, 1430 w, 1370 m, 1350 m, 1270 m, 1240 m, 1160 w, 1100 w, 1050 w; uv λ max 265, 255 nm; ^{1}H nmr δ 1.18, 1.19 (each 3H, d, J = 7 Hz, Me-16, Me-17), 1.25, 1.28, 1.34 (each 3H, s, Me-18, Me-19, Me-20), 1.97 (1H, br dd, H-1α), 3.16 (1H, hept, J = 7 Hz, H-15), 3.67 (1H, br dd, H-1β), 4.30 (1H, m, W½ = 33 Hz, H-2β), 6.37 (1H, d, J = 6.8 Hz, H-6), 6.72 (1H, d, J = 6.8 Hz, H-7), 6.90 (1H, s, H-14), 7.36 (1H, br s, Ar-O*H*); ms (rel. int.) $[M]^+$ 314 (2), 296 (8), 281 (5), 266 (2), 258 (100), 240 (13), 227 (100), 225 (10), 215 (18), 206 (16), 199 (10).

ACETYLATION OF 2α,11-DIHYDROXY-5,7,9(11),13-ABIETATETRAEN-12-ONE [**1**].—Compound **1** (4 mg) was treated with Ac_2O (0.5 ml) in pyridine (1 ml) overnight at room temperature and after workup and separation by cc on Si gel with *n*-hexane–EtOAc (5:5) gave **3** (Scheme 1) as a pale yellow oil (3 mg): $[M]^+$ at *m/z* 456.2167 (calcd for $C_{26}H_{32}O_7$, 456.2186); ^{1}H nmr δ 1.23, 1.27 (each 3H, d, J = 7 Hz, Me-16, Me-17), 1.34, 1.43, 1.61 (each 3H, s, Me-18, Me-19, Me-20), 2.05 (3H, s, 2α-OAc), 2.32, 2.36 (each 3H, s, 2 × ArOAc), 2.94 (1H, hept, J = 7 Hz, H-15), 3.26 (1H, m, H-1β), 5.31 (1H, m, W½ = 33 Hz, H-2β), 6.53 (1H, s, H-6), 8.13 (1H, s, H-14); ms (rel. int.) $[M]^+$ 456 (11), 428 (1), 414 (6), 396 (4), 372 (13), 354 (32), 339 (9), 312 (100), 297 (64), 269 (19), 243 (32), 213 (8), 165 (14).

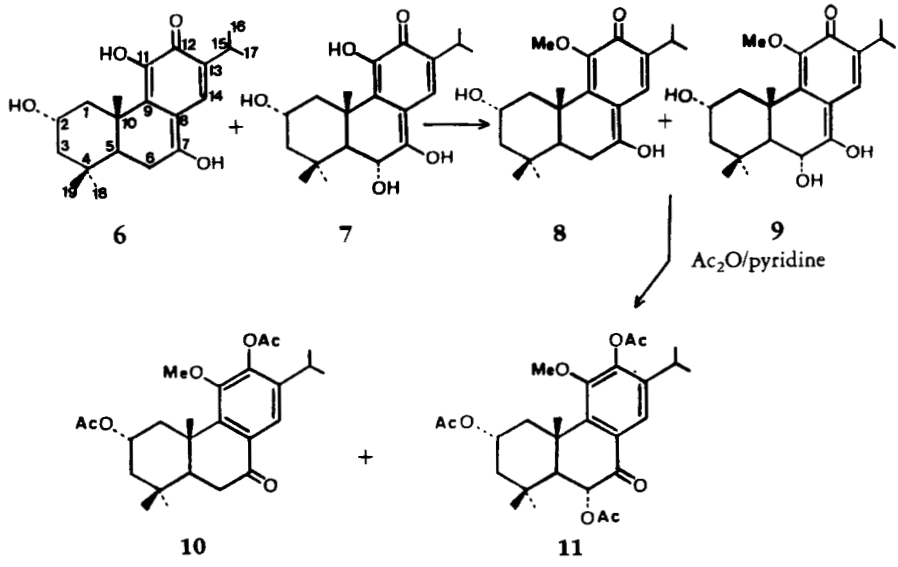
OXIDATION OF SALVIOL.—Salviol [**4**] (13.5 mg) was added to a solution of dioxan with traces of H_2O; the temperature was kept at 0°, and a solution of DDQ (20.3 mg) in dioxan was added. The reaction mixture was stirred continually at room temperature and after 48 h taken to dryness and purified to give product **5** (Scheme 2): ^{1}H nmr ($CDCl_3$) δ 0.99, 1.03 (each 3H, s, 18-Me, 19-Me), 1.22 (3H, s, 20-Me), 1.23, 1.26 (each 3H, d, J = 7.0 Hz, 16-Me, 17-Me), 1.41 (1H, m, H-5α), 1.84 (1H, m, H-6α), 2.59 (1H, m, H-6β), 3.12 (1H, hept, J = 7.0 Hz, H-15), 4.06 (1H, m, W½ = 33 Hz, H-2β), 5.95 (1H, br s, 12-OH), 6.71 (1H, s, H-11), 7.91 (1H, s, H-14); ^{1}H nmr (C_6D_6) δ 0.68, 0.69 (each 3H, s, 19-Me, 20-Me), 0.98 (3H, s, 18-Me), 1.27 (6H, d, J = 7.0 Hz, 16-Me, 17-Me), 1.40 (1H, m, H-5α), 2.35 (1H, m, H-6β), 2.60 (1H, m, H-6α), 3.30 (1H, hept, J = 7.0 Hz, H-15), 3.60 (1H, m, W½ = 33 Hz, H-2β), 6.15 (1H, s, H-11), 6.40 (1H, br s, 12-OH), 8.48 (1H, s, H-14).

2α,7,11-TRIHYDROXY-7,9(11),13-ABIETATRIEN-12-ONE [**6**].—Compound **6** was isolated as a yellow oil formed by a mixture of **6** and **7** (15 mg): $[M]^+$ at *m/z* 332.1988 (calcd for $C_{20}H_{28}O_4$, 332.1989); ir ($CHCl_3$, film) cm^{-1} 3340 m, 2950 s, 2900 s, 2840 m, 1660 s, 1595 s, 1450 m, 1300 m, 1195 w, 1040 w, 860 w; ^{1}H nmr δ 1.00, 1.01 (each 3H, s, Me-18, Me-19), 1.26, 1.28 (each 3H, d, J = 7 Hz, Me-16, Me-17), 1.41 (3H, s, Me-20), 1.83 (1H, m, H-6α), 2.58 (1H, m, H-6β), 3.02 (1H, hept, J = 7 Hz, H-15), 3.63 (1H, br dd, H-1β), 4.08 (1H, m, W½ = 33 Hz, H-2β), 7.62 (1H, s, H-14); ms (rel. int.) $[M]^+$ 332 (14), 314 (55), 299 (100), 271 (30), 243 (50), 232 (39), 217 (25), 215 (13), 177 (13), 149 (27).

METHYLATION OF 2α,7,11-TRIHYDROXY-7,9(11),13-ABIETATRIEN-12-ONE [**6**].—The mixture of **6** and **7** (15 mg) was dissolved in Et_2O, and a solution of CH_2N_2 in Et_2O (1 ml) was slowly added. The reaction mixture was kept at low temperature, and after 0.5 h the reaction was completed, giving a mixture of **8** and **9** (10 mg) (8): $[M]^+$ at *m/z* 346.2146 (calcd for $C_{21}H_{30}O_4$, 346.2148); ir ($CHCl_3$, film) cm^{-1} 3400 m, 2940 m, 2900 s, 2800 m, 1670 vs, 1590 s, 1240 m, 1195 m, 1170 w, 1040 s, 1010 s, 1000 m; ^{1}H nmr δ 1.01, 1.02 (each 3H, s, Me-18, Me-19), 1.24, 1.25 (each 3H, d, J = 7 Hz, Me-16, Me-17), 1.42 (3H, s, Me-20), 1.90 (1H, m, H-6α), 2.60 (1H, m, H-6β), 3.20 (1H, hept, J = 7 Hz, H-15), 3.63 (1H, br dd, H-1β), 3.81 (3H, s, 11-OMe), 4.07 (1H, m, W½ = 33 Hz, H-2β), 7.62 (1H, s, H-14); ms (rel. int.) $[M]^+$ 346 (45), 328 (30), 314 (24), 313 (100), 300 (3), 296 (1), 285 (9), 272 (26), 257 (22), 229 (6).

ACETYLATION OF THE MIXTURE OF **8** AND **9**.—This mixture (10 mg), dissolved in pyridine (1 ml), was treated with Ac_2O (1 ml) and left to stand overnight at room temperature. After workup and Si gel preparative tlc separation using *n*-hexane–C_6H_6–EtOAc (1:7.5:1.5), 7-oxo-2,12-diacetoxy-11-methoxyabieta-8,11,13-triene [**10**] (5 mg) and 7-oxo-2,6,12-triacetoxy-11-methoxyabieta-8,11,13-triene [**11**] (3 mg) were obtained (Scheme 3).

Compound **10**.—$[M]^+$ at *m/z* 430.2355 (calcd for $C_{25}H_{34}O_6$, 430.2355); ^{1}H nmr δ 1.01, 1.05 (each 3H, s, Me-18, Me-19), 1.22, 1.26 (each 3H, d, J = 7 Hz, Me-16, Me-17), 1.40 (3H, s, Me-20), 2.07 (3H, s, 2α-OAc), 2.34 (3H, s, 12-OAc), 2.70 (1H, m, H-6β), 3.25 (1H, hept, H-15), 3.76 (3H, s,



6 7 8 9

10 11

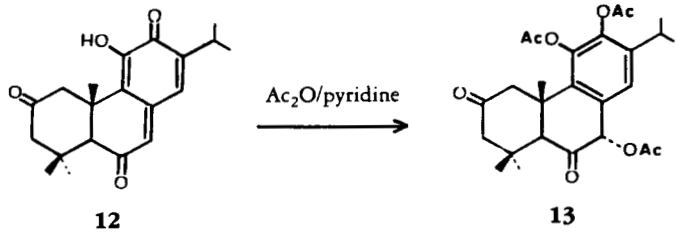
SCHEME 3

11-OMe), 5.10 (1H, m, W½ = 33 Hz, H-2β), 7.97 (1H, s, H-14); ms (rel. int.) *m/z* $[M]^+$ 430 (12), 388 (35), 371 (1), 370 (1), 355 (1), 345 (1), 329 (27), 328 (93), 314 (23), 313 (100), 300 (7), 285 (11), 253 (4).

Compound **11**.—$[M]^+$ at *m/z* 488.2427 (calcd for $C_{27}H_{36}O_8$, 488.2444); ^{1}H nmr δ 1.13 (3H, s, Me-18), 1.21 (3H, s, Me-19), 1.22 (6H, d, J = 7 Hz, Me-16, Me-17), 1.55 (3H, s, Me-20), 2.05 (3H, s, 2α-OAc), 2.25 (3H, s, 6α-OAc), 2.35 (3H, s, 12-OAc), 3.76 (3H, s, 11-OMe), 5.80 (1H, d, J = 13 Hz, H-6β), 7.98 (1H, s, H-14); ms (rel. int.) *m/z* $[M]^+$ 488 (4), 446 (9), 386 (28), 371 (2), 344 (17), 326 (44), 311 (100), 297 (20), 283 (15), 241 (6).

2-OXOTAXODIONE [**12**].—Compound **12** was isolated as a yellow oil (5 mg): $[M]^+$ at *m/z* 328.1671 (calcd for $C_{20}H_{24}O_4$, 328.1668); ir ($CHCl_3$, film) cm^{-1} 3300 m, 2970 vs, 2920 s, 2870 w, 1715 vs, 1675 vs, 1645 m, 1630 vs, 1620 vs, 1470 w, 1425 s, 1395 s, 1350 vs, 1305 s, 1250 m, 1225 m, 1195 w, 1170 w, 1060 w, 1040 w, 990 w, 910 w; uv (λ max) nm 336, 324; ^{1}H nmr ($CDCl_3$) δ 1.17, 1.18 (each 3H, d, J = 7 Hz, Me-16, Me-17), 1.27 (3H, s, Me-20), 1.29 (3H, s, Me-19), 1.31 (3H, s, Me-18), 2.16 (1H, dd, J_1 = 2.26, J_2 = 12.8 Hz, H-3β), 2.40 (1H, d, J = 12.8 Hz, H-3α), 2.95 (1H, d, J = 13.7 Hz, H-1α), 3.10 (1H, hept, J = 7 Hz, H-15), 3.15 (1H, s, H-5α), 3.55 (1H, dd, J_1 = 2.3, J_2 = 13.7 Hz, H-1β), 6.29 (1H, s, H-7), 6.93 (1H, s, H-14), 7.58 (1H, s, 11-OH); ^{1}H nmr (C_6D_6) δ 0.99, 1.05 (each 3H, d, J = 7 Hz, Me-16, Me-17), 1.13 (3H, s, Me-20), 1.22 (3H, s, Me-19), 1.35 (3H, s, Me-18), 1.95 (1H, d, J = 12.3 Hz, H-3α), 2.09 (1H, dd, J_1 = 2.06, J_2 = 12.3 Hz, H-3β), 2.52 (1H, s, H-5α), 2.53 (1H, d, J = 13.6 Hz, H-1α), 3.00 (1H, hept, J = 7 Hz, H-15), 3.60 (1H, dd, J_1 = 2.1, J_2 = 13.6 Hz, H-1β), 5.78 (1H, s, H-7), 6.34 (1H, s, H-14), 7.48 (1H, s, 11-OH); ms (rel. int.) $[M]^+$ 328 (46), 313 (100), 295 (10), 285 (14), 257 (58), 244 (15), 229 (15), 214 (2).

ACETYLATION OF 2-OXOTAXODIONE **12**.—Compound **12** (5 mg) was treated with Ac_2O (0.5 ml) in pyridine (1 ml) overnight at room temperature (Scheme 4). After workup, 2,6-dioxo-7α,11,12-triacetoxyabieta-8,11,13-triene [**13**] was obtained as a pale yellow oil (5 mg): ^{1}H nmr ($CDCl_3$) δ 1.16



12 13

SCHEME 4

(6H, s, Me-18, Me-19), 1.18 (6H, d, $J=7$ Hz, Me-16, Me-17), 1.35 (3H, s, Me-20), 2.30 (3H, s, 7α-OAc), 2.31, 2.35 (each 3H, s, 2 × ArOAc), 3.48 (1H, s, H-5α), 6.40 (1H, s, H-7β), 7.17 (1H, s, H-14); ms (rel. int.) $[M]^+$ 472 (51), 430 (90), 415 (26), 388 (100), 387 (18), 368 (23), 346 (77), 313 (58), 288 (64), 260 (39).

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