Pergamon

0031-9422(95)00349-5

Phytochemistry, Vol. 40, No. 3, pp. 865–870, 1995

0031-9422/95 $9.50 + 0.00

DITERPENOIDS FROM *TRIPTERIGIUM WILFORDII**

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(*Received* 20 *February* 1995)

Key Word Index—*Tripterigium wilfordii*; Celastraceae; wilforols; abietane, diterpenoids.

Abstract—The acetone extract of the dried root bark of *Tripterigium wilfordii* afforded a novel abietane diterpenoid, wilforol E, while the methanol extract of the dried heartwood of the root afforded another novel abietane diterpenoid, wilforol F. Their structures were established on the basis of chemical and spectroscopic studies.

INTRODUCTION

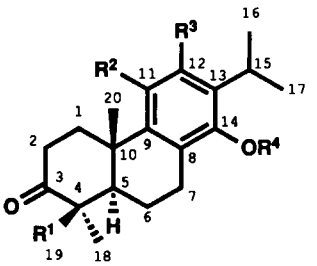
In previous papers, we have reported on the isolation of D:A-friedo-24-noroleanane triterpenoids, triterpenoids and sesquiterpene alkaloids from the root bark of *Tripterigium wilfordii* Hook f. [1–3]. In a continuation of our studies on this plant, we have now investigated the diterpenoids in the bark and the heartwood of the root. One novel diterpenoid, wilforol E (**1**), along with one known triterpenoid (triptonoterpene methyl ether (**3**) was obtained from the bark, and one new diterpenoid, wilforol F (**2**), along with eight known diterpenoids [3, 4, 4a, 9, 10, 10a-hexahydro-8-hydroxy-1-(hydroxymethyl)-1, 4a-dimethyl-7-(1-methylethyl)-2(1H)-phenanthrene (**4**), triptonoterpenol (**5**), triptolide (**6**), triptoquinones B (**7**) and C (**8**), hypolide (triptophenolide, **9**), neotriptophenolide (**10**) and quinone 21 (**11**) was obtained from the heartwood. Compounds **3**–**10** were identified by comparisons of their physicochemical and spectral data with those in the literature [4–10]. Compound **11** was identified by synthesis from **9**. This paper deals with the structural investigations of the two novel diterpenes.

RESULTS AND DISCUSSION

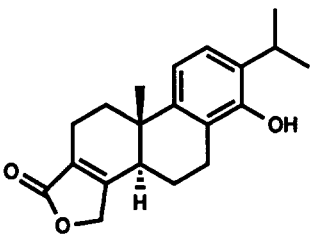
Compound **1** was assigned the molecular formula $C_{21}H_{30}O_3$ (HRMS). The ^1H NMR spectrum showed the presence of one isopropyl group [δ1.362, 1.365 (each 3H, *d*, J = 7.2 Hz), δ3.43 (1H, *sep*, J = 7.3 Hz)], three methyl groups [δ1.12, 1.16, 1.26 (each 3H, *s*)], one methoxyl group [δ3.69 (3H, *s*)], one lone aromatic proton [δ6.41 (1H, *s*)] and an OH group [δ4.73 (1H, *s*, D_2O exchangeable)]. The ^{13}C NMR spectrum showed 21 carbon signals including those assignable to a *penta*-substituted benzene ring [δ109.1 (*d*), 120.9, 125.1, 146.7, 153.6, 156.1 (each *s*)] and an unconjugated ketone [δ217.5 (*s*)]. Based on a comparison of the ^1H and ^{13}C NMR spectral data for **1** with those of the known compounds **3**–**5**, **1** was assumed to be the same type of abietane diterpenoid as these compounds. Since the EI-MS fragmentation pattern and the molecular formula of **1** were the same as those of triptonoterpene methyl ether (**3**) and the NMR data were also similar to those of **3**, **1** was presumed to be a structural isomer of **3**. The ^{13}C NMR signals of **1** assignable to the aliphatic portion were similar to those of **3**, however, those of the aromatic portion were different. This indicates that **1** and **3** differ in the substitutional positions of the functional groups on the C ring. The presence of the same A/B ring system in **1** as in **3** and assignment of all the ^1H and ^{13}C signals ascribable to this part were established by 2D NMR experiments [H–H, C–H COSY, HMBC (Fig. 1) and NOESY (Fig. 2)]. The locations of the three substituents of the C ring (isopropyl, methoxyl and hydroxyl groups) were determined by 2D NOESY (Fig. 2). Thus, the illustrated network of the correlation cross peaks (H-1β—arom. H, arom. H—OH, OH—isopropyl and isopropyl—OMe) led us to determine the positions of the lone aromatic proton at C-11, the hydroxyl group at C-12, the isopropyl group at C-13 and the methoxyl at C-14, respectively. This was further supported by the acylation effects on the C ring revealed in the ^{13}C NMR spectrum of the monoacetate (**1a**) of **1** (Table 1). From the available evidence, the structure of wilforol E was established as **1**. This structure was further confirmed by X ray crystallography of **1a** (Fig. 3).

The established structure of wilforol E (**1**) is the same as that of 'neotriptonoterpene' reported by Zhou *et al.* [12]; however, some parts of the spectral and physicochemical data for **1** are different from those reported for neotriptonpterpene [12]. We propose that the

* Part 4 in the series 'Chemical Studies on the Root Bark of *T. wilfordii*'. For Part 3 see ref. [3].



	R^1	R^2	R^3	R^4
1:	Me	H	OH	Me
2:	CH_2OH	H	OMe	H
3:	Me	OH	H	Me
4:	CH_2OH	H	H	H
12:	Me	H	OMe	H



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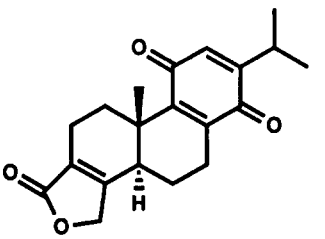

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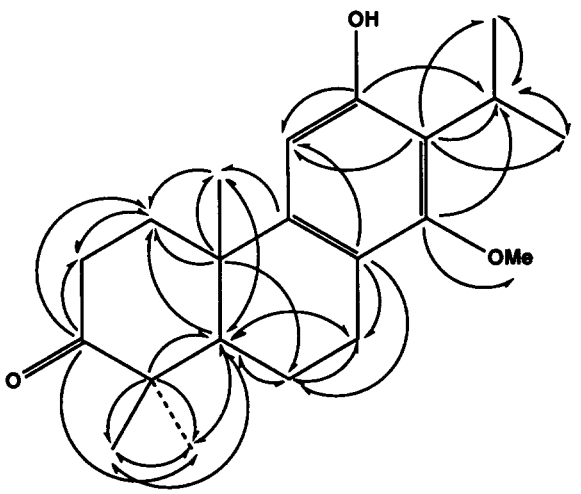

Fig. 1. 2D HMBC data for **1**. Correlation: $^{13}C \rightarrow {}^{1}H$.

structure of this compound or its spectral data [12] may be incorrect.

Compound **2** was assigned the molecular formula $C_{21}H_{30}O_4$ (HR-MS). The ^1H and ^{13}C NMR data suggested an abietane skeleton for **2**. In addition, these spectral data also showed the presence of the following functional groups: one methoxyl group [δ^{13C}: 55.8 (*q*), δ^{1H}: 3.76 (3H, *s*)], one phenolic OH group [δ^{1H}: 4.76 (1H, *s*)], one alcoholic OH group [δ^{1H}: 2.93 (1H, *dd*, J = 9.1, 3.0 Hz], one unconjugated ketone group [δ^{13C}: 220.0 (*s*)] and one hydroxymethyl group [δ^{13C}: 65.7 (*t*), δ^{1H}: 3.54 (1H, *dd*, J = 11.2, 9.1 Hz), 4.07 (1H, *dd*, J = 11.2, 3.0 Hz)]. Comparison of the ^1H NMR spectra of **2** and **4** showed that one of the two aromatic proton signals [δ6.83 (1H, *d*, J = 8.2 Hz), 7.04 (1H, *d*, J = 8.2 Hz)] observed in **4** was replaced by a methoxyl signal in **2**. This indicated that **2**, unlike **4**, had a methoxyl group on the C ring. The signals assignable to the A ring in the ^{13}C NMR spectrum of **2** showed good agreement with those of **4**. Thus, **2** was presumed to have the same A/B ring system as **4** (Table 1). On the other hand, based on a comparison with the ^{13}C NMR spectral data for earlier isolated abietane diterpenoids, the C ring of **2** was assumed to be the same as that of 12-methoxy triptonoterpene (**12**) [11] (Table 1). The A/B *trans* fused ring system as well as the substitution pattern and the coordination of the functional groups in **2** were confirmed by a 2D NOESY experiment (Fig. 4). The lone aromatic proton signal [δ6.36 (1H, *s*)] showed cross peaks between the 1-β-H signal [δ2.44 (1H, *ddd*, J = 13.1, 8.3, 4.6 Hz)] and the methoxyl signal (δ3.76, 3H, *s*). Thus, the positions of the lone aromatic proton and methoxyl group were identified as C-11 and C-12, respectively. Moreover, the position and the coordination of the hydroxymethyl group were determined as 4-β-axial based on the cross peaks (H-20 and H-6β—hydroxymethyl). Upon acetylation of **2**, the expected diacetate (**2a**) was obtained and a significant acylation shift was observed for the signals assignable to C-9, C-13 and C-11 in its ^{13}C NMR spectrum (Table 1). This evidence also supported the substitution system at the C ring. The β-angular methyl at C-10 in abietane diterpenoids was highly probable on biogenetic grounds. Thus, the structure of wilforol F was established as **2**.

The coordination of a hydroxymethyl in **4** was not mentioned in the literature [5]. However, the same NOE cross peaks as **2** were observed in the 2-D NOESY data for **4** (data not shown). This indicated the presence of a 4-β-axial hydroxymethyl group in **4**.

Since compound **11** was isolated as a minor biproduct of a synthetic procedure, its spectral data were not completely listed in the literature [13]. Salcomine-catalysed oxidation [14] of **9** afforded the corresponding *p*-quinone, which was identical to **11**. This is the first report that **11** is a natural product.

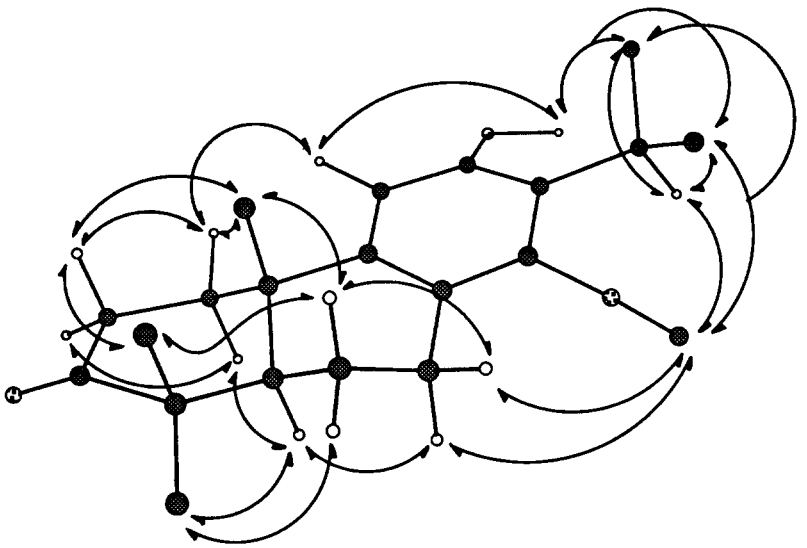

Fig. 2. 2D NOESY data for 1. Cross peaks between *gem* groups were omitted.

Table 1. ^{13}C NMR spectral data for diterpenes from *T. wilfordii* (100 MHz in $CDCl_3$)

C	1	1a	3	2	2a	4	12‡
1	37.7	37.5	35.5	37.3	38.9	37.3	37.6
2	34.6	34.5	34.6	34.9	35.4	35.0	34.7
3	217.5	216.9	219.2	220.0	212.5	220.0	217.2
4	47.3	47.3	47.2	51.0	51.6	51.1	47.3
5	50.5	50.2	52.0	50.9	51.8	50.8	50.1
6	20.0	19.8	20.0	19.1	19.5	19.1	19.6
7	24.9	25.2	26.5	24.4	24.9	24.8	24.2
8	120.9	126.6	131.4	113.9	119.6	120.7	113.9
9	146.7	146.8	131.2	145.3	146.0	130.5	146.0
10	37.3	37.4	38.1	37.1	37.4	36.9	37.3
11	109.1	116.5	148.5	100.9	105.7	117.7	100.5
12	153.6	148.1	111.8	156.9	157.2	123.7	156.8
13	125.1	130.1	139.4	119.4	126.4	145.6	119.2
14	156.1	156.1	150.6	151.6	147.2	150.1	151.6
15*	25.1	25.3	26.1	24.3	26.0	26.9	24.3
16*	21.2	21.6	23.8	20.9	20.6†	22.5	20.9
17	21.1	21.4	23.7	20.8	20.7†	22.7	20.8
18	26.9	26.9	28.4	22.2	20.8†	22.1	26.7
19	21.0	21.1	20.5	65.7	65.9	65.7	21.1
20	24.5	24.5	20.0	25.3	24.9	25.4	24.2
OMe	60.7	60.8	60.7	55.8	55.6		55.7
Ac		21.6			20.8†		
		169.7			21.1		
					169.1		
					170.8		

* †Assignments may be interchangeable in each column.
‡Data were taken from the literature [11].

EXPERIMENTAL

General. Mps: uncorr.; ^1H NMR: 500 or 400 MHz; ^{13}C NMR: 100 MHz with TMS as int. standard; 2D NMR: 500 MHz, standard conditions; EIMS: 70 eV; CC: Kieselgel 60 (70–230 mesh); Prep. HPLC: CIG Si-10 (silica gel, 1.5 i.d. × 30 cm).

Plant material. See ref. [1].

Isolation from bark. The MeOH eluate (60 g) from Diaion HP-20 CC of the mother liquor of demethylzeyrasteral and wilforol B [1] was applied to a MCI CHP 20P CC and eluted with 80% (21 g) then 85% MeOH–H_2O (36 g). 5 g of 85% MeOH–H_2O eluate was chromatographed on silica gel (*n*-hexane–Me_2CO) to

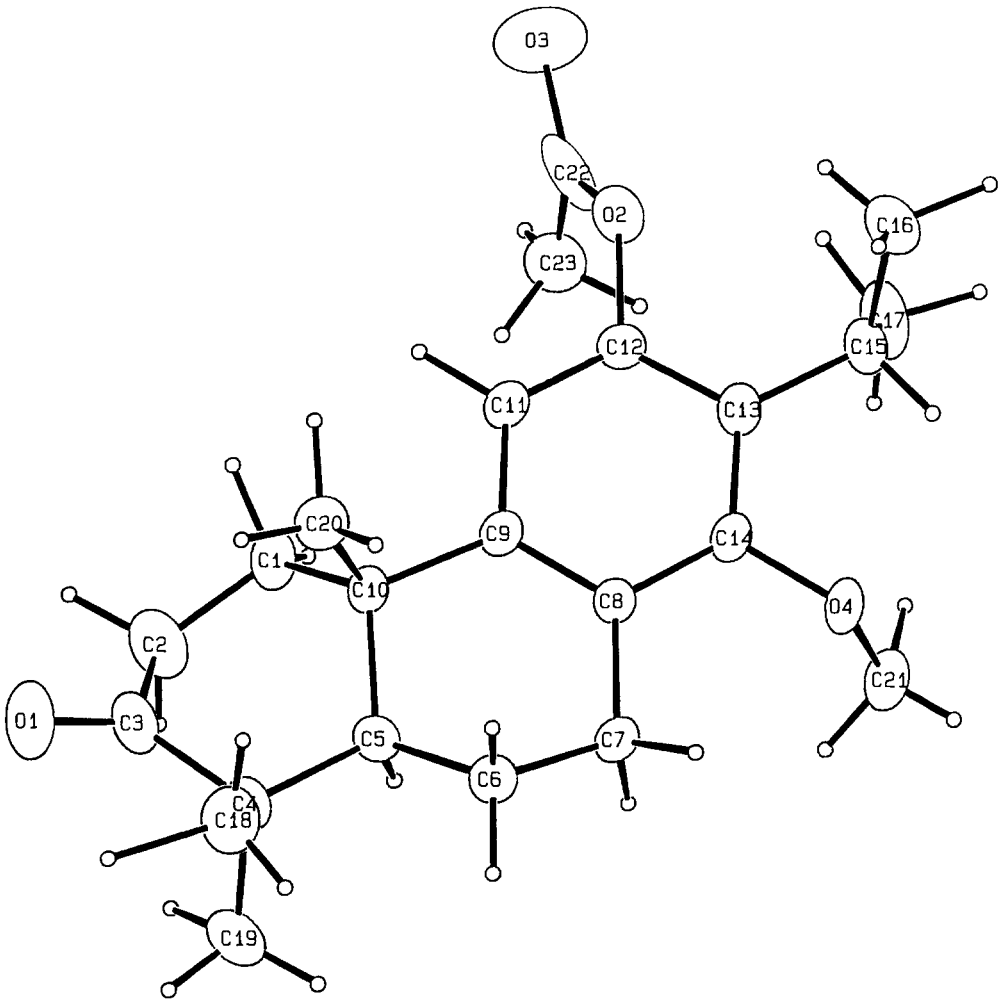

Fig. 3. X-Ray stereoscopic view of **1a**.

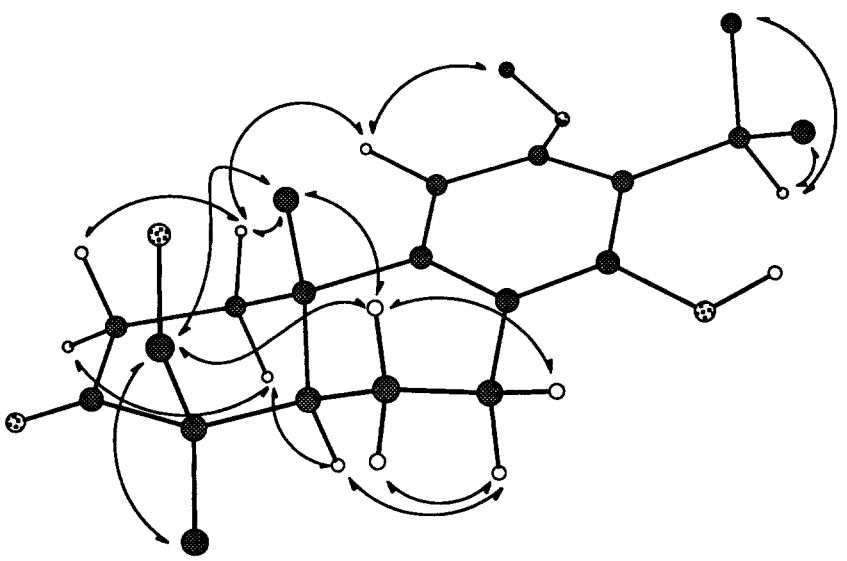

Fig. 4. 2D NOESY data for **2**. Cross peaks between *gem* groups were omitted.

give four frs. Fr. 1 (160 mg) was further purified by prep. HPLC (10% EtOAc–*n*-hexane) and crystallized from Et_2O–*n*-hexane to give **3** (57 mg). Fr. 2 (127 mg) was crystallized from MeOH to give **1** (59 mg).

Isolation from heartwood. Dried heartwood of the root of *T. wilfordii* (20 kg) was extracted with MeOH (100 l) under reflux. The solvent was removed under reduced pressure to give the MeOH extract (1.1 kg). This was dissolved in H_2O and successively extracted with *n*-hexane, EtOAc and *n*-BuOH. The EtOAc layer was further washed with H_2O (×3). The organic layer was evapd *in vacuo* to afford 145 g EtOAc extract. This was divided into four frs, C-1 (3.5 g), C-2 (52 g), C-3 (28 g) and C-4 (39 g), by silica gel CC with the solvent system C_6H_6–EtOAc. Fr. C-2 was further chromatographed on silica gel CC (EtOAc–*n*-hexane) to give 10 frs (C-21 ~ 30). Fr C-24 (6.2 g) was chromatographed on silica gel CC (Me_2CO–C_6H_6) to give seven frs (C-241 ~ 247). Fr. C-246 (720 mg) was crystallized from MeOH to give **5** (408 mg). Crystallization of fr. C-243 (1.1 g) with EtOAc–*n*-hexane afforded **7** (457 mg). Fr. C-242 (1.4 g) was purified by prep. HPLC (3% Me_2CO in *n*-hexane) to afford three compounds, two of them were crystalline and were crystallized from EtOH to give **9** (380 mg) and **10** (45 mg). The other one was an amorphous powder (**11**, 480 mg). Fr. C-244 (1.5 g) was purified by prep. HPLC (7% Me_2CO in C_6H_6) to give two compounds which were crystallized from EtOH to give **6** (60 mg) and **8** (20 mg). Fr. C-246 (750 mg) was repeatedly chromatographed by prep. HPLC (Me_2CO–C_6H_6, EtOAc–*n*-hexane) and finally a fr. which contained two diterpenes was sepd by prep. HPLC (column: TSK ODS 80 TM, mobile phase MeCN–H_2O, (1:1) into **4** (370 mg) and **2** (80 mg).

Wilforol E (**1**). Needles, mp 218–219°, $[\alpha]_D^{25}$ + 117.1° (*c* 0.18, $CHCl_3$). EI-MS *m/z* (rel. int.): 330.2197 (calc. for $C_{21}H_{30}O_3$: 330.2195, M^+) (100), 315 (63), 273 (29), 245 (14), 217 (19); UV λ_{max}^{EtOH} nm (log ε): 206 (4.06), 225 (3.88), 284 (3.41); IR ν_{max}^{KBr} cm^{-1}: 3356, 2952, 2872, 1684; ^1H NMR (500 MHz in $CDCl_3$): δ 1.12 (3H, *s*, H-19), 1.16 (3H, *s*, H-18), 1.26 (3H, *s*, H-20), 1.362, 1.365 (each 3H, *d*, *J* = 7.2 Hz, H-16, 17), 1.68 (1H, *dq*, *J* = 12.6, 5.8 Hz, H-6β), 1.84 (1H, *ddt*, *J* = 12.6, 6.7, 2.0 Hz, H-6α), 1.86 (1H, *dd*, *J* = 12.6, 2.0 Hz, H-5α), 1.93 (1H, *ddd*, *J* = 13.2, 9.9, 7.5 Hz, H-1α), 2.34 (1H, *ddd*, *J* = 13.2, 7.5, 4.2 Hz, H-1β), 2.57 (1H, *ddd*, *J* = 15.8, 7.5, 4.2 Hz, H-2α), 2.60 (1H, *ddd*, *J* = 17.1, 12.6, 6.7 Hz, H-7α), 2.67 (1H, *ddd*, *J* = 15.8, 9.9, 7.5 Hz, H-2β), 3.01 (1H, *ddd*, *J* = 17.1, 5.8, 2.0 Hz), 3.43 (1H, *sep*, *J* = 7.2 Hz, H-15), 3.69 (3H, *s*, 14-OMe), 4.73 (1H, *s*, 12-OH), 6.41 (1H, *s*, H-11); ^{13}C NMR: Table 1.

12-O-*Acetyl wilforol E* (**1a**). Needles (EtOH), mp 134–135°, $[\alpha]_D^{24}$ + 101.2° (*c* 0.84, $CHCl_3$). EI-MS *m/z* (rel. int.): 372.2287 (calc. for $C_{23}H_{32}O_4$: 372.2300, M^+) (18), 330 (100), 315 (38), 273 (12), 245 (6); IR ν_{max}^{KBr} cm^{-1}: 2968, 2872, 1752, 1698; ^1H NMR (400 MHz in $CDCl_3$): δ 1.13 (3H, *s*, H-19), 1.17 (3H, *s*, H-18), 1.263, 1.269 (each 3H, *d*, *J* = 7.1 Hz, H-16, 17), 1.28 (3H, *s*, H-20), 1.72 (1H, *dq*, *J* = 12.5, 5.8 Hz, H-6β), 1.87 (1H, *ddt*, *J* = 12.5, 6.8, 2.0 Hz, H-6α), 1.89 (1H, *dd*, *J* = 12.5, 2.0 Hz, H-5α), 1.96 (1H, *ddd*, *J* = 13.2, 9.9, 7.6 Hz, H-1α), 2.31 (3H, *s*, 12-OAc), 2.35 (1H, *ddd*, *J* = 13.2, 7.6, 4.3 Hz, H-1β), 2.56 (1H, *ddd*, *J* = 16.0, 7.6, 4.3 Hz, H-2α), 2.61 (1H, *m*, H-7α), 2.67 (1H, *ddd*, *J* = 16.0, 9.9, 7.6 Hz, H-2β), 3.07 (1H, *ddd*, *J* = 17.3, 5.8, 2.0 Hz, H-7β), 3.36 (1H, *sep*, *J* = 7.1 Hz, H-15), 3.71 (3H, *s*, 14-OMe), 6.69 (1H, *s*, H-11); ^{13}C NMR: Table 1.

X-Ray analysis of compound **1a**. The crystal size of **1a** was 0.25 × 0.30 × 0.30 mm. The unit cell dimension was obtained by least-squares refinement using 25 centred reflections for which 20° < θ < 30° (graphite monochromatized CuK_α, λ = 1.54184 Å). Intensity data were collected at ω/2θ scans on an Enraf-Nonius CAD-4 with three check reflections at intervals of 100 reflections. Other crystal data were: $C_{23}H_{32}O_4$, orthorhombic, space group $P2_12_12_1$, *Z* = 4, *a* = 9.4194(4) Å, *b* = 9.6914(3) Å, *c* = 23.2966(8) Å, *V* = 2126.7(1) $Å^3$, D_{calc} = 1.170 g cm^{-3} and (Cu K_α) with 5.9 cm^{-1}. Intensities were measured for 2508 reflections in the range 5° ≦ 2θ ≦ 148.6° with 2125 considered as observed by the criteria $I > 3\sigma$ (I). The data were corrected for Lorentz and polarization effects. No absorption correction was applied. The structure was solved by the direct-method program Multan and was refined by full-matrix least-squares, using the Enraf-Nonius MOLEN programs. All the non-H atoms were refined anisotropically. The locations of the H atoms at C_{23} were determined by calculation. The others were located from difference maps. The last difference Fourier map was essentially featureless with no peaks greater than 0.931 $eÅ^{-3}$. The final discrepancy index was *R* = 0.088.

Wilforol F (**1**). Amorphous powder. $[\alpha]_D^{30}$ + 104.1° (*c* 0.22, $CHCl_3$); EI-MS *m/z* (rel. int.): 346.2139 (calc. for $C_{21}H_{30}O_4$: 346.2143, M^+, 20), 331 (20), 316 (48), 301 (100). UV λ_{max}^{EtOH} nm (log ε): 225 (3.97), 275 (3.13), 282 (3.17); IR ν_{max}^{KBr} cm^{-1}: 3448, 2952, 2872, 1702, 1612; ^1H NMR (400 MHz in $CDCl_3$): δ 1.29 (3H, *s*, H-20), 1.31 (6H, *d*, *J* = 7.1 Hz, H-16, 17), 1.34 (3H, *s*, H-18), 1.68 (1H, *dq*, *J* = 13.2, 6.0 Hz, H-6β), 1.96 (1H, *dddd*, *J* = 13.2, 6.7, 2.2, 1.7 Hz, H-6α), 2.04 (1H, *ddd*, *J* = 13.1, 9.0, 8.3 Hz, H-1α), 2.10 (1H, *dd*, *J* = 13.2, 2.2 Hz, H-5α), 2.44 (1H, *ddd*, *J* = 13.1, 8.3, 4.6 Hz, H-1β), 2.49 (1H, *ddd*, *J* = 16.1, 13.2, 6.7 Hz, H-7α), 2.62 (1H, *dt*, *J* = 16.0, 8.3 Hz, H-2α), 2.71 (1H, *ddd*, *J* = 16.0, 9.0, 4.6 Hz, H-2β), 2.80 (1H, *ddd*, *J* = 16.1, 6.0, 1.7 Hz, H-7β), 2.93 (1H, *dd*, *J* = 9.1, 3.0 Hz, 18-OH), 3.46 (1H, *sep*, *J* = 7.1 Hz, H-15), 3.54 (1H, *dd*, *J* = 11.2, 9.1 Hz, H-18), 3.76 (3H, *s*, 12-OMe), 4.07 (1H, *dd*, *J* = 11.2, 3.0 Hz, H-19), 4.76 (1H, *s*, 14-OH), 6.36 (1H, *s*, H-11); ^{13}C NMR: Table 1.

12-O-*Acetyl wilforol F* (**2a**). Needles, mp 171–172°, $[\alpha]_D^{25}$ + 38.8° (*c* 0.71, $CHCl_3$); EI-MS *m/z* (rel. int.): 430 (M^+, 39), 388 (100), 373 (80), 313 (9); IR ν_{max}^{KBr} cm^{-1}: 2964, 2932, 2872, 1762, 1740, 1708; ^1H NMR (400 MHz in $CDCl_3$, 45°C*): δ 1.20 (3H, *s*, H-20), 1.24, 1.25 (each 3H, *d*, *J* = 6.9 Hz), 1.43 (3H, *s*, H-18), 2.00, 2.30 (each 3H, *s*, Ac), 3.10 (1H, *sep*, *J* = 6.9 Hz), 4.03, 4.65 (each 1H, *d*, *J* = 12.0 Hz, H-19), 6.67 (1H, *s*, H-11). (*The resolution was very low due to the 4-axial acetyl group.)

Chemical formation of **11** *from* **9**. Compound **9** (52 mg) was dissolved in 3 ml THF, and 5 mg salcomine was added to the soln. The mixture was stirred for 1 hr at room temp. under O_2. Work up and purification by prep. HPLC (3% Me_2CO in C_6H_6) afforded the corresponding *p*-quinone (40 mg, 78%), which was identical to **11** as a yellow amorphous powder, $[\alpha]_D^{26}$ + 110.3° (*c* 0.28, $CHCl_3$). EI-MS *m/z* (rel. int.): 326.1514 (M^+, calc. for $C_{20}H_{22}O_4$, 100), 311 (32), 298 (9), 283 (14), 267 (14); UV λ_{max}^{EtOH} nm (log ε): 219 (4.17), 260 (4.15); IR ν_{max}^{KBr} cm^{-1}: 3488, 2968, 2936, 2876, 1758, 1680, 1646, 1598; ^1H NMR (400 MHz in $CDCl_3$): δ 1.12 (3H, *d*, *J* = 6.9 Hz), 1.13 (3H, *d*, *J* = 6.9 Hz), 1.16 (3H, *d*, *J* = 0.6 Hz), 1.49 (1H, *ddd*, *J* = 13.3, 11.1, 7.2, 0.7 Hz), 1.70 (1H, *ddt*, *J* = 13.3, 11.2, 6.2 Hz), 1.89 (1H, *dddd*, *J* = 13.3, 7.7, 2.7, 1.1 Hz), 2.41 (2H, *m*), 2.52 (1H, *ddd*, *J* = 20.5, 11.2, 7.7 Hz), 2.62 (1H, *m*), 2.80 (1H, *ddd*, *J* = 20.5, 6.2, 1.1 Hz), 3.02 (1H, *dsep*, *J* = 6.9, 1.2 Hz), 3.12 (1H, *ddd*, *J* = 13.3, 6.1, 1.7 Hz), 4.71 (1H, *ddd*, *J* = 17.2, 3.5, 2.0, 1.7 Hz), 4.81 (1H, *ddt*, *J* = 17.2, 2.9, 1.7 Hz), 6.42 (1H, *d*, *J* = 1.2 Hz). ^{13}C NMR ($CDCl_3$): δ 18.3 (*t*), 18.5 (*t*), 18.7 (*q*), 21.3 (*q*), 21.4 (*q*), 24.3 (*t*), 26.5 (*d*), 30.9 (*t*), 36.8 (*s*), 42.5 (*d*), 70.2 (*t*), 125.7 (*s*), 131.7 (*s*), 142.6 (*s*), 147.8 (*s*), 153.6 (*s*), 161.3 (*s*), 173.7 (*s*), 187.3 (*s*), 187.5 (*s*).

Acknowledgements—The authors are grateful to Dr T. Wakamatsu for suggesting the salcomine-catalysed oxidation. We thank Dr K. Suguma, Miss Y. Imamura and Miss N. Kanda for 1D and 2D NMR spectra, and Mr K. Kano and Miss J. Nishizawa for MS. We also thank the personnel from the Zhong Shan Hospital who helped in the extraction of the plant. We are also indebted to Dr T. Tamaki, Hachiouji Medical Center, Tokyo Medical University, and Drs Y. Ikeya, H. Nishimura and Y. Komatsu, Mr T. Yoshino, Dr H. Kawamura, Dr H. Maruyama and other members of Tsumura & Co. for supporting the work.

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