



## ISOLATION AND STRUCTURE OF WIGHTIONAL AND WIGHTIOLIDE FROM *ANDROGRAPHIS WIGHTIANA*

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**Key Word Index**—*Andrographis wightiana*; Acanthaceae; diterpenes; wightional, wightiolide and wightionolide;  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra.

**Abstract**—Two new *ent*-labdane-type diterpenoids, wightional and wightiolide have been isolated from the leaves of *Andrographis wightiana*. Their structures were determined on the basis of extensive  $^1\text{H}$  and  $^{13}\text{C}$ ,  $^1\text{H}$  homonuclear COSY, and HMBC NMR spectroscopic studies. To correlate the newly isolated diterpenes with wightionolide, a number of derivatives of wightionolide have been prepared and characterized.

### INTRODUCTION

*Andrographis wightiana* is a widely distributed herb found in the western Ghats, the hills of Travancore and the Annamalais Hills of India [1]. Isolation and structural determination of wightionolide (**1**), the only example of an *ent*-labdane-type diterpene lactone having geminal hydroxymethyl groups at the C-4 position, was reported earlier [2]. The structure of **1** was derived from chemical and degradation studies and an X-ray crystal diffraction analysis of 13,14-dibromo-17,19,20-tri-*O*-acetyl-wightionolide. The major diterpene in the leaves of *A. wightiana* is **1**. We report in this communication, on the structural determination of two new minor diterpenes, wightional (**2**) and wightiolide (**7**), isolated from the same plant. Some bicyclic *ent*-labdane-type diterpenoids related to **1** and **2** are andrograpanin [3], nivenolide [4], andrographolide [5, 6] and 14-deoxyandrographolide [5, 7].

### RESULTS AND DISCUSSION

From a chloroform extract of the aerial parts of *A. wightiana* Arn. ex Nees (family Acanthaceae) collected in the Annamalais Hills, the diterpenoids **2** and **7** were isolated by chromatographic separation. Compound **2**, mp 99–100°, was homogeneous by TLC, and its EI mass spectrum and elemental analysis were consistent with the molecular formula  $\text{C}_{20}\text{H}_{30}\text{O}_5$  [ $\text{M}]^+ m/z$  350. The mass spectral fragments at  $m/z$  322 [ $\text{M} - 28]^+$  and  $m/z$  319 [ $\text{M} - 31]^+$  indicated that it contains a car-

bonyl and a hydroxymethyl group. The IR spectrum of **2** showed the presence of hydroxyl groups (3520 and 3450  $\text{cm}^{-1}$ ), an  $\alpha,\beta$ -unsaturated  $\gamma$ -lactone (1730  $\text{cm}^{-1}$ ) and an aldehyde (1720  $\text{cm}^{-1}$ ). The presence of the  $\alpha,\beta$ -unsaturated  $\gamma$ -lactone was also supported by a positive Legal colour reaction [8], the signals for a vinyl proton at  $\delta$  7.15 (1H, *d*,  $J = 1$  Hz) and the signals for an adjacent methylene at  $\delta$  4.85 (2H, *s*) in its  $^1\text{H}$  NMR spectrum. The signal at  $\delta$  9.54 (1H, *d*,  $J = 5$  Hz) indicated the presence of a secondary aldehydic group at C-8. Its occurrence along with **1**, and the  $^1\text{H}$  NMR doublet, suggested that the aldehydic group may be located at C-8 and not at C-18 or C-19. The  $^1\text{H}$  and the  $^{13}\text{C}$  NMR spectra of wightional (Table 1) are consistent with the proposed structure **2**. The  $^1\text{H}$ – $^1\text{H}$  COSY correlations are given in Table 2. The  $^{13}\text{C}$  NMR spectrum of **2** showed nearly similar signals for most of the carbons, indicating that the diterpene is a mixture of two epimers, **2A** and **B**, in an approximate ratio of 3:2. The two epimers are most probably due to the aldehydic group, and purification by chromatographic methods failed to separate the epimers.

As accurate  $^1\text{H}$  and  $^{13}\text{C}$  NMR assignments for **1** were not made in the earlier work [2],  $^1\text{H}$ ,  $^{13}\text{C}$ , DEPT,  $^1\text{H}$ – $^1\text{H}$  COSY and HMBC NMR experiments were performed (Table 1). Table 2 shows the significant  $^1\text{H}$  and  $^{13}\text{C}$  long-range correlations observed in the HMBC spectrum and the  $^1\text{H}$ – $^1\text{H}$  COSY correlations. The  $^{13}\text{C}$  NMR data provide important information in deriving the structures of newly isolated diterpenoids. Some of the earlier  $^{13}\text{C}$  NMR spectral data for labdanic diterpenoids depended on multiplicities in the SFORD spectra, making use of the changes produced by substituent(s) and by comparison of the shifts produced

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Table 1.  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectral data for compounds **1** ( $\text{CDCl}_3$ ), **2** ( $\text{CDCl}_3$  + 1 drop of  $\text{DMSO}-d_6$ ) and **7** ( $\text{CDCl}_3$ ),  $\delta$  (ppm); multiplicity ( $J$  in Hz)

C	1	2a	2b	7	H	1	2	7
1	38.2 <i>t</i>	38.6	39.8 <i>t</i>	38.6 <i>t</i>	1	1.80 <i>m</i> 0.85 <i>m</i>	1.80 <i>m</i> 0.90 <i>m</i>	1.90 <i>m</i> 1.1 <i>m</i>
2	17.6 <i>t</i>	—	17.6 <i>t</i>	18.3 <i>t</i>	2a	1.50 <i>m</i>	1.55 <i>m</i>	1.57 <i>m</i>
3	30.0 <i>t</i>	30.2	30.7 <i>t</i>	30.0 <i>t</i>	3a	2.00 <i>m</i>	2.00 <i>m</i>	1.90 <i>m</i>
					3b	1.00 <i>m</i>	0.90 <i>m</i>	1.00 <i>m</i>
4	41.7 <i>s</i>	41.9	42.2 <i>s</i>	42.2 <i>s</i>	4	—	—	—
5	51.3 <i>d</i>	51.9	52.4 <i>d</i>	52.8 <i>d</i>	5	1.00 <i>m</i>	1.11 <i>m</i>	1.05 <i>m</i>
6	26.7 <i>t</i>	26.4	26.9 <i>t</i>	24.5 <i>t</i>	6a	1.60 <i>m</i>	1.71 <i>m</i>	2.00
					6b	1.25 <i>m</i>	1.35 <i>m</i>	1.30
7	30.7 <i>t</i>	—	36.5 <i>t</i>	38.3 <i>t</i>	7a	1.85 <i>m</i>	1.71 <i>m</i>	1.58 <i>m</i>
					7b	1.10 <i>m</i>	1.12 <i>m</i>	—
8	52.1 <i>d</i>	53.4	53.7 <i>d</i>	147.1 <i>s</i>	8	0.80 <i>m</i>	2.25 <i>m</i>	—
9	41.3 <i>d</i>	50.4	50.6 <i>d</i>	56.4 <i>d</i>	9	1.38 <i>m</i>	1.20 <i>m</i>	1.96 <i>m</i>
10	37.7 <i>s</i>	37.5	38.1 <i>s</i>	39.6 <i>s</i>	10	—	—	—
11	21.4 <i>t</i>	20.4	22.2 <i>t</i>	21.8 <i>t</i>	11a	1.60 <i>m</i>	1.75 <i>m</i>	1.75 <i>m</i>
					11b	1.40 <i>m</i>	1.40 <i>m</i>	1.80 <i>m</i>
12	26.9 <i>t</i>	26.9	27.2 <i>t</i>	24.7 <i>t</i>	12a	2.35 <i>m</i>	2.40 <i>m</i>	2.42 <i>m</i>
					12b	2.22 <i>m</i>	2.20 <i>m</i>	2.12 <i>m</i>
13	134.3 <i>s</i>	133.9	134.2 <i>s</i>	134.8 <i>s</i>	13	—	—	—
14	144.3 <i>d</i>	144.4	144.5 <i>d</i>	144.1 <i>d</i>	14	7.14 <i>t</i> ( $J = 1$ )	7.15 <i>d</i> ( $J = 1$ )	7.09 <i>s</i>
15	70.0 <i>t</i>	70.1	70.2 <i>t</i>	70.2 <i>t</i>	15	4.77 <i>dd</i> ( $J = 2, 1$ )	4.85 <i>s</i>	4.76 <i>dd</i> ( $J = 3, 1$ )
16	174.3 <i>s</i>	174.1	174.5 <i>s</i>	174.5 <i>s</i>	16	—	—	—
17	65.1 <i>t</i>	—	204.8 <i>d</i>	107.1 <i>t</i>	17a	3.63 <i>dt</i> ( $J = 10, 5$ )	9.54 <i>d</i> ( $J = 5.4$ )	4.85 <i>d</i> ( $J = 0.5$ )
					17b	3.55 <i>dt</i> ( $J = 10, 5$ )	—	4.57 <i>d</i> ( $J = 0.5$ )
					17-OH	2.82 <i>t</i> ( $J = 5$ )	—	—
18	63.8 <i>t</i>	—	63.8 <i>t</i>	64.3 <i>t</i>	18a	3.86 <i>ddd</i> ( $J = 11, 6, 1$ )	3.85 <i>dd</i> ( $J = 11, 4$ )	3.86 <i>d</i> ( $J = 11$ )
					18b	3.70 <i>ddd</i> ( $J = 11, 6, 1$ )	3.72 <i>dd</i> $J = 11, 4$ )	3.67 <i>dd</i> ( $J = 11, 0.5$ )
					18-OH	3.60 <i>dd</i> ( $J = 6.5, 5$ )	—	—
19	72.3 <i>t</i>	70.1	73.1 <i>t</i>	73.5 <i>t</i>	19a	3.86 <i>dd</i> ( $J = 11, 5$ )	3.80 <i>dd</i> ( $J = 11, 2$ )	3.88 <i>dd</i> ( $J = 11, 0.5$ )
					19b	3.32 <i>dd</i> ( $J = 11, 5$ )	3.40 <i>dd</i> ( $J = 11, 2$ )	3.35 <i>dd</i> ( $J = 11, 0.5$ )
					19-OH	3.63	—	—
20	14.4 <i>q</i>	14.6	15.0 <i>q</i>	15.1 <i>q</i>	20	0.76 <i>s</i>	0.8, 0.82 <i>s</i>	0.63 <i>s</i>

by closely related compounds [9, 10]. The assignments for C-6 and C-11 made earlier [9, 10] in the labdane diterpenoids were reversed in later studies [3, 11] of andrographolides. The  $^{13}\text{C}$  NMR assignments of some andrographolides have been made recently on the basis of 2D COSY and COLOC spectral data [12].

Attempts were made to prepare **2** from **1**. The hydroxymethyl groups at C-4 were protected by formation of an acetonide (**3**) by the treatment of **1** with acetone and 70%  $\text{HClO}_4$ . Similarly, the dihydro-acetonide (**4**) was prepared from 13,14-dihydro-wightiolide (**5**) [2]. Oxidation of **3** by the Pfitzner-Moffatt procedure [13] furnished the aldehyde (**6**), mp 136–138°. Several attempts to hydrolyse the acetonide-aldehyde (**6**) under different acidic conditions gave a gum which showed a TLC spot corresponding to **2**, but

which failed to give **2**. In a model experiment, we were able to cleave the acetonide by heating **3** with 5%  $\text{HCl}$  at 90° for 15 min to afford **1** in ca 86% yield. However, the acetonide group of the aldehyde (**6**) could not be cleaved under a variety of acidic conditions to afford the desired product, probably because of condensation of the aldehyde with the generated alcohol under the acidic conditions.

Wightiolide **7**, obtained as a colourless crystalline compound, mp 155–157°, analysed for the molecular formula  $\text{C}_{20}\text{H}_{30}\text{O}_4$  (EI mass spectrum,  $[\text{M}]^+ m/z$  334). The IR spectrum showed the presence of hydroxyl (3415) and  $\alpha,\beta$ -unsaturated  $\gamma$ -lactone (1720  $\text{cm}^{-1}$ ) groupings. The  $^1\text{H}$  NMR spectrum exhibited signals at  $\delta$  7.09 (1H, *s*, H-14) and 4.76 (2H, *dd*,  $J = 3$  and 1 Hz, H-15). The presence of an exocyclic methylene was

Table 2.  $^1\text{H}$ - $^1\text{H}$  COSY and  $^1\text{H}$ - $^{13}\text{C}$  HMBC NMR spectral data for compounds **1** and **7**

Position	<b>1</b>		<b>7</b>	
	COSY $^1\text{H}$ - $^1\text{H}$	HMBC $^1\text{H} \rightarrow ^{13}\text{C}$	COSY $^1\text{H}$ - $^1\text{H}$	HMBC $^1\text{H} \rightarrow ^{13}\text{C}$
1a	H-1b, H-2, H-3a	C-2, C-3, C-5, C-10, C-20	H-2, H-3a, H-3b	C-2, C-5, C-10, C-20
2	H-1a, H-3a	C-1, C-3, C-4, C-10	H-1, H-3a	C-1, C-4, C-10
3a	H-1, H-2, H-3b	C-1, C-2, C-4, C-5, C-18	H-1, H-2, H-3b	—
5	H-6a	C-4, C-7, C-10, C-18, C-19, C-20	H-6b, H-19b, CH <sub>3</sub> -20	C-1, C-4, C-10
6a	H-5, H-6b, H-7a	C-5, C-7, C-10	H-6b, H-7a, H-7b	C-1, C-4, C-5, C-9
7a	H-6a, H-6b, H-7b, H-8	C-8, C-9, C-17	H-6, H-7a, H-17a	C-8
8	H-9	C-6, C-7, C-9, C-10, C-17, C-20	—	—
9	H-8, H-11a	C-7, C-8, C-10	—	C-5, C-8, C-10, C-17, C-20
11a	H-11b, H-12b, H-17a, H-17b	C-9, C-10, C-12	H-12a, H-12b, CH <sub>3</sub> -20	C-8, C-12, C-13
12a	H-11a, H-11b, H-12b, H-14	C-13, C-14, C-16	H-11a, H-11b, H-12b, H-14	C-9
12b	H-11a, H-11b, H-12a, H-14	C-13, C-14, C-16	H-11a, H-11b, H-12a, H-14	C-13, C-14
14	H-12a, H-15	C-12, C-13, C-15, C-16	H-12a, H-12b, H-15	C-13, C-15, C-16
15	H-14	C-12, C-13, C-14, C-16	H-12a, H-12b, H-14	C-13, C-14, C-16
17a	H-11a, H-17b, OH-17	C-7, C-8, C-9	H-7a, H-7b, H-17b	C-6, C-7, C-9
17b	H-11a, H-17a, OH-17	C-7, C-8, C-9	H-7a, H-7b, H-17a	C-7, C-8, C-9
17-OH	H-17a, H-17b	—	—	—
18a	H-18b, OH-18	C-3, C-4, C-5, C-19	H-18b	C-3, C-4, C-5
18b	H-18a	C-3, C-4, C-5	H-18a	C-3, C-4, C-5
18-OH	H-18a	—	—	—
19a	H-19b, OH-19	C-3, C-4, C-5, C-18	H-5, H-19b	—
19b	H-19a	C-3, C-4, C-5	H-19a	C-3, C-4, C-5
20	—	C-1, C-5, C-10	H-5, H-11	C-1, C-5, C-9, C-10

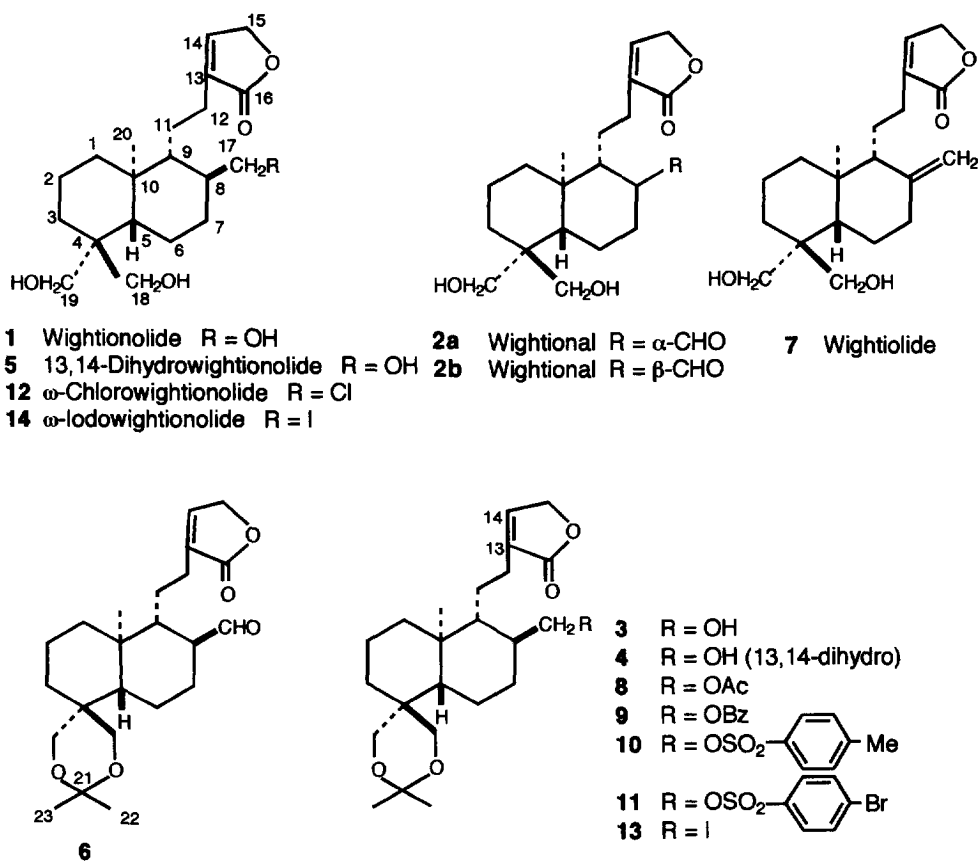
evident from its  $^1\text{H}$  NMR spectrum,  $\delta$  4.57 and 4.85 (1H each, *d*,  $J = 0.5$  Hz), and the  $^{13}\text{C}$  NMR resonances at  $\delta$  147.1 (*s*, C-8) and 107.1 (*t*, C-17). In addition, the  $^1\text{H}$  NMR spectrum of **7** showed the presence of a *tert*-methyl group at  $\delta$  0.63, two methylenes attached to hydroxyl groups at  $\delta$  3.67 and 3.88 (each 1H, *dd*,  $J = 11$  and 0.5 Hz), and 3.35 and 3.86 (each 1H, *dd*,  $J = 11$  and 0.5 Hz). Its occurrence in the plant along with **1** suggested structure **7** for the diterpene. The  $^1\text{H}$  and the  $^{13}\text{C}$  NMR data (Table 1) are in conformity with the proposed structure. The  $^{13}\text{C}$  NMR signals were analysed by the aid of a DEPT spectrum. Table 2 gives the  $^1\text{H}$ - $^{13}\text{C}$  long-range COSY connectivities observed in the HMBC experiment, and the  $^1\text{H}$ - $^1\text{H}$  correlations. To transform **1** into **7**, the acetonide (**3**) was converted to the 17-acetate (**8**), the 17-benzoate (**9**), the 17-*p*-toluenesulphonate (**10**) and the 17-*p*-bromobenzenesulphonate (**11**). All attempts to form the alkene from these esters under pyrolytic conditions failed to give the desired product. The acetonide (**3**) on treatment with  $\text{POCl}_3$  in pyridine afforded 17- $\omega$ -chlorowightionolide (**12**). The *p*-toluenesulphonyl ester (**10**) on refluxing with NaI gave the corresponding 17- $\omega$ -iodo derivative (**13**). Several attempts to dehydrohalogenate under a variety of conditions failed to give the desired olefin.

The acetonide **13** on treatment with methanol-5% HCl gave 17- $\omega$ -iodowightionolide (**14**), which also failed to give **7**. Functionalization of the hydroxymethyl group at C-17 posed no problems; however, the compounds **12** and **13** failed to dehydrohalogenate to give the olefin, probably due to steric hindrance of the lactonic side chain. The structures of **2** and **7** are unusual in that there are no other *ent*-labdane-type diterpenoids, except **1**, which have both geminal methyls at the C-4 position being hydroxylated.

## EXPERIMENTAL

**General.** Mps were determined by open capillary method and are uncorr. IR spectra were recorded on Perkin-Elmer Infracord Spectrophotometer. EIMS were run on an Atlas-Varian Mat CH-7 instrument.  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra were recorded on Varian XL-400, at 400 MHz for  $^1\text{H}$  and 100 MHz for  $^{13}\text{C}$  spectrometers unless stated otherwise.

**Plant material.** The aerial parts of *A. wightiana* were collected in the Annamalias Hills in 1964–1965. The plant was identified by (the late) Mr T. S. N. Rao and a voucher specimen is deposited in the Herbarium of the



Department of Botany, St. Xavier's College, Bombay, India.

*Isolation of wightionolide (1), wightional (2) and wightiolide (7).* The leaves of *A. wightiana* (10 kg) were extracted with  $CHCl_3$  (25 l  $\times$  2) at 25°, and the extract was evapd *in vacuo* to a thick syrup, diluted with EtOAc and kept overnight. The ppt. was collected (30 g) and chromatographed over silica gel (900 g), eluted with  $CHCl_3$ -5% MeOH, and the sepn was monitored by TLC. The initial frs afforded **1** (11.5 g). For  $^1H$  and  $^{13}C$  NMR spectra: see Table 1.

Further elution and purification by prep. TLC afforded **7** (45 mg; 0.00045%), mp 155–157° (TLC:  $CHCl_3$ -5% MeOH,  $R_f$  0.65); Found: C, 71.6; H, 9.1.  $C_{20}H_{30}O_4$  requires: C, 71.8; H, 9.0%. MS (direct inlet):  $m/z$  334 ( $M^+$ , 60%), 316 ( $M^+ - H_2O$ , 30), 303 ( $M^+ - CH_2OH$ , 35), 298 (316 -  $H_2O$ ,  $M^+$  281, 30), 286 (316 - OH,  $M^+$  245, 100), 285 (45), 271 (40), 258 (70). IR (nujol):  $\nu_{max}$  3415, 1712, 1625, 1300, 1210, 1158, 1145, 1095, 1075, 1062, 1053, 1038, 1027, 1010, 995, 980, 943, 886, 869, 855, 842, 830, 720  $cm^{-1}$ . For  $^1H$  and  $^{13}C$  NMR spectra: see Table 1.

From the above prep. TLC, **2** was isolated; (220 mg; 0.0022%), mp 99–100°;  $[\alpha]_D -12.6^\circ$  (c 0.38, MeOH), (TLC:  $CHCl_3$ -5% MeOH,  $R_f$  0.7). Found: C, 68.1; H, 9.0.  $C_{20}H_{30}O_5$  requires: C, 68.5; H, 8.6%. MS:  $m/z$  350 ( $M^+$ , 5%), 332 ( $M^+ - H_2O$ , 20), 322 ( $M^+ - CO$ , 30), 319 ( $M^+ - CH_2OH$ , 16), 301 (319 -  $H_2O$ , 44), 286 (301 -  $CH_3$ , 44), 283 (46), 274 (90), 271 (60). IR (nujol):  $\nu_{max}$  3520, 3450, 2720, 1730, 1720, 1640,

1300, 1270, 1248, 1203, 1171, 1149, 1130, 1098, 1080, 1052, 1038, 1020, 1000, 975, 960, 942, 895, 868, 848, 830, 803, 770, 720  $cm^{-1}$ . For  $^1H$  and  $^{13}C$  NMR spectra: see Table 1.

*17-Hydroxy-18,19-isopropylidenedioxy-ent-labd-13-en-16,15-olactone (3).* A soln of **1**, (5 g) in  $Me_2CO$  (300 ml) was stirred with 70%  $HClO_4$  (5 ml) at room temp. for 1.5 hr.  $NaHCO_3$  (5 g) was added and stirred for 10 min. The solvent was evapd *in vacuo* and  $H_2O$  (100 ml) was added. The mixt. was extracted with  $CHCl_3$ , the organic layer washed with  $H_2O$  and dried over  $Na_2SO_4$ . Removal of the solvent gave a gum which on crystallization from EtOAc afforded colourless crystals (**3**, 4 g), mp 130–131°.  $^1H$  NMR (250 MHz,  $CDCl_3$ ):  $\delta$  7.10 (1H, s, H-14), 4.74 (2H, s, H-15), 3.75, 3.15 (2H, AB,  $J = 11.4$  Hz, H-19), 3.63 (2H, m, H-17), 3.62 (2H, m, H-18), 1.33, 1.29 (each 3H, s, - $CM_2$ ), 0.67 (3H, s, Me-20).  $^{13}C$  NMR (62.9 MHz,  $CDCl_3$ ): 38.3 (C-1), 17.6 (C-2), 33.3 (C-3), 38.2 (C-4), 53.2 (C-5), 26.9 (C-6), 30.6 (C-7), 51.0 (C-8), 41.4 (C-9), 38.0 (C-10), 21.5 (C-11), 27.0 (C-12), 134.4 (C-13), 144.4 (C-14), 70.8 (C-15), 174.6 (C-16), 65.6 (C-17), 62.0 (C-18), 70.1 (C-19), 14.4 (C-20), 98.6 (C-21), 21.6 (C-22), 25.9 (C-23).

*Hydrolysis of 3 to wightionolide (1).* A soln of **3** (40 mg) in MeOH (5 ml) and 5%  $HCl$  (40 ml) was warmed on a water-bath at ca 90° for 15 min. The solvent was evapd *in vacuo* and the residue crystallized from EtOAc to give **1** (30 mg), mp 176–177°.

*17-Hydroxy - 18,19 - isopropylidenedioxy-ent-labd -*

13,14 - dihydro - 16,15 - olactone (**4**). A soln of **5** (100 mg) in Me<sub>2</sub>CO (200 ml) was stirred with 70% HClO<sub>4</sub> (0.2 ml) for 30 min. NaHCO<sub>3</sub> (1 g) was added and the solvent evapd *in vacuo*. The mixt. was added to H<sub>2</sub>O and extracted with CHCl<sub>3</sub>, washed with H<sub>2</sub>O and dried (Na<sub>2</sub>SO<sub>4</sub>). Removal of the solvent *in vacuo* gave a viscous liquid which was sublimed at 150°/10<sup>-3</sup> mm to afford **4** as an oil which was homogeneous by TLC. Found C, 70.2; H, 10.0. C<sub>23</sub>H<sub>38</sub>O<sub>5</sub> requires: C, 70.0; H, 9.7%.

18,19 - Isopropylidenedioxy - 17 - oxo - ent - labd - 13 - en - 16,15 - olactone (**6**). To a stirred soln of **3**, (500 mg) in DMSO (5 ml), C<sub>6</sub>H<sub>6</sub> (5 ml) and pyridine (5 ml) was added dicyclohexylcarbodiimide (800 mg). The soln was stirred for 1 hr and kept at room temp. for 40 hr. To the mixt. was added C<sub>6</sub>H<sub>6</sub> (30 ml) and a soln of oxalic acid (500 mg) in MeOH (95 ml). This was stirred for 30 min and filtered to remove dicyclohexylurea. The filtrate was washed with 10% NaHCO<sub>3</sub> (50 ml) and then with H<sub>2</sub>O, and the organic layer dried over Na<sub>2</sub>SO<sub>4</sub>. The solvent was removed *in vacuo* to give a gummy residue (450 mg). This was chromatographed over silica gel in C<sub>6</sub>H<sub>6</sub> and the major fr. crystallized from C<sub>6</sub>H<sub>6</sub>-Et<sub>2</sub>O to afford colourless needles (**6**, 140 mg), mp 136–138°. Found: C, 70.9; H, 9.1. C<sub>23</sub>H<sub>34</sub>O<sub>5</sub> requires: C, 70.7; H, 8.8%. IR (nujol):  $\nu_{\max}$  1740, 1690, 1640 cm<sup>-1</sup>. <sup>1</sup>H NMR (60 MHz, CDCl<sub>3</sub>):  $\delta$  9.60 (1H, *d*, *J* = 4 Hz, CHO-17), 7.10 (1H, *t*, H-14), 4.75 (2H, *q*, *J* = 1.5 Hz, H-15), 3.10–3.90 (4H, *m*, OCH<sub>2</sub>-18, 19), 1.35 (6H, *s*, -CM<sub>2</sub>), 0.75 (3H, *s*, Me-20). <sup>13</sup>C NMR (DMSO-*d*<sub>6</sub> + CDCl<sub>3</sub>):  $\delta$  38.1 (C-1), 17.4 (C-2), 33.6 (C-3), 37.8 (C-4), 52.8 (C-5), 26.5 (C-6), 37.5 (C-7), 53.2 (C-8), 49.2 (C-9), 38.1 (C-10), 20.3 (C-11), 26.9 (C-12), 132.9 (C-13), 145.0 (C-14), 70.4 (C-15), 173.6 (C-16), 204.1 (C-17), 61.5 (C-18), 70.0 (C-19), 14.3 (C-20), 98.3 (C-21), 21.7 (C-22), 26.0 (C-23).

Acetoxy-18,19-isopropylidenedioxy-ent - labd - 13 - en - 16,15 - olactone (**8**). To a soln of the acetone (**3**, 180 mg), in HOAc (5 ml) was added Ac<sub>2</sub>O (6 ml) at 5°, and the mixt. was kept at room temp. for 16 hr, when it was poured over crushed ice and extracted with CHCl<sub>3</sub>. The organic layer was washed with NaHCO<sub>3</sub> and then with H<sub>2</sub>O and dried over Na<sub>2</sub>SO<sub>4</sub>. Removal of the solvent gave a gum which crystallized from EtOAc-hexane to afford colourless needles (**8**, 125 mg), mp 114–115°. Found: C, 69.2; H, 9.2. C<sub>25</sub>H<sub>38</sub>O<sub>6</sub> requires: C, 69.1; H, 8.8%. IR (nujol):  $\nu_{\max}$  1740, 1260, 1230 cm<sup>-1</sup>. <sup>1</sup>H NMR (60 MHz, CDCl<sub>3</sub>):  $\delta$  7.12 (1H, *s*, H-14), 4.80 (2H, *m*, H-15), 3.20–4.20 (6H, *m*, -OCH<sub>2</sub>-17, 18, 19), 2.05 (3H, *s*, OAc-17), 1.40 (6H, *s*, -CMe<sub>2</sub>), 0.72 (3H, *s*, Me-20).

17-Benzoyloxy - 18,19 - isopropylidenedioxy - ent - labd - 13 - en - 16,15 - olactone (**9**). To a soln of **3**, (500 mg) in pyridine (1.5 ml) was added benzoyle chloride (1.5 g) at 0° and the mixt. was kept at room temp. for 16 hr. The mixt. was poured over crushed ice and extracted with CHCl<sub>3</sub>, washed with 10% HCl and H<sub>2</sub>O and the organic layer dried (Na<sub>2</sub>SO<sub>4</sub>). Removal of

the solvent *in vacuo* gave a gum which crystallized from EtOAc-hexane as colourless needles, mp 176–177°. Found: C, 72.7; H, 8.3. C<sub>30</sub>H<sub>40</sub>O<sub>6</sub> requires: C, 72.6; H, 8.1%. IR (nujol):  $\nu_{\max}$  1740  $\alpha,\beta$ -unsaturated  $\gamma$ -lactone), 1720 (ester), 1455, 1375, 1350, 1310, 1280, 1225 cm<sup>-1</sup>. <sup>1</sup>H NMR (250 MHz, CDCl<sub>3</sub>):  $\delta$  8.00 (2H, *m*, 2',6'-Ar-H), 7.58 (1H, *m*, 4'-Ar-H), 7.53 (2H, *m*, 3',5' Ar-H), 7.03, (1H, *s*, H-14), 4.70 (2H, *s*, H-15), 3.20, 3.65 (2H, AB, *J* = 11.3 Hz, H-19), 3.65 (2H, AB, *J* = 11.7 Hz, H-18), 2.21 (2H, *m*, H-12), 0.85, 2.15 (2H, *m*, H-7), 1.31, 1.69 (2H, *m*, H-6), 0.88, 1.80 (2H, *m*, H-1), 1.75 (1H, *m*, H-9), 1.51 (2H, *m*, H-2), 1.30 (2H, *m*, H-11), 1.30, 1.32 (each 3H, *s*, -C(Me)<sub>2</sub>), 0.89 (1H, *m*, H-5), 0.88 (1H, *m*, H-8), 0.72 (3H, *s*, Me-20). <sup>13</sup>C NMR (62.9 MHz, CDCl<sub>3</sub>): 38.297 *t* (C-1), 17.6 *t* (C-2), 31.1 *t* (C-3), 38.3 *s* (C-4), 52.0 *d* (C-5), 26.6 *t* (C-6), 33.3 *t* (C-7), 53.4 *d* (C-8), 38.9 *d* (C-9), 38.3 *s* (C-10), 21.5 *t* (C-11), 27.2 *t* (C-12), 134.1 *s* (C-13), 144.3 *d* (C-14), 70.8 *t* (C-15), 174.1 *s* (C-16), 68.1 *t* (C-17), 62.0 *t* (C-18), 70.0 *t* (C-19), 14.4 *q* (C-20), 98.7 *s* (C-21), 21.5 *q* (C-22), 25.8 *q* (C-23), 166.6 *s* (-O-CO), 130.2 *s* (C-1'), 129.5 *d* (C-2', C-6'), 128.4 *d* (C-3', C-5'), 133.0 *d* (C-4'). The assignments are based on HETCOR and DEPT spectra.

18,19 - Isopropylidenedioxy - 17 - *p* - toluenesulphonyloxy - ent - labd - 13 - en - 16,15 - olactone (**10**). To a soln of **3** (1.5 g) in pyridine was added *p*-toluenesulphonyl chloride (1.3 g) at 0° and the mixt. was kept at room temp. for 3 hr. The mixt. was poured over crushed ice, the crude product collected by filtration and crystallized from CH<sub>2</sub>Cl<sub>2</sub>-EtOH to afford colourless needles (**10**, 1.5 g), mp 165–166°. Found: C, 66.2; H, 8.0. C<sub>30</sub>H<sub>42</sub>O<sub>7</sub> requires: C, 65.9; H, 7.7%. IR (nujol)  $\nu_{\max}$  1740, 1630, 1590 cm<sup>-1</sup>. <sup>1</sup>H NMR (250 MHz, CDCl<sub>3</sub>):  $\delta$  7.74 (2H, *d*, *J* = 7.5 Hz, 2',6'-Ar-H), 7.10 (1H, *br s*, H-14), 7.30 (2H, *d*, *J* = 7.5 Hz, 3',5' Ar-H), 4.73 (2H, *s*, H-15), 3.98 (2H, *m*, H-18), 3.15–3.68 (2H, AB, *J* = 9.5 Hz, H-19), 3.56 (2H, *t*, *J* = 9.4 Hz, H-17), 2.44 (3H, *s*, Ar-Me), 2.14 (2H, *m*, H-12), 1.30, 1.32 (each 3H, *s*, -CMe<sub>2</sub>), 0.73 (3H, *s*, Me-20). <sup>13</sup>C NMR (62.9 MHz, CDCl<sub>3</sub>): 38.9 (C-1), 17.6 (C-2), 30.3 (C-3), 39.1 (C-4), 50.4 (C-5), 26.4 (C-6), 33.2 (C-7), 53.1 (C-8), 39.0 (C-9), 39.1 (C-10), 21.7 (C-11), 26.7 (C-12), 132.7 (C-13), 144.8 (C-14), 70.8 (C-15), 174.1 (C-16), 70.1 (C-17), 62.0 (C-18), 73.4 (C-19), 14.2 (C-20), 98.7 (C-21), 21.7 (C-22), 25.6 (C-23), 133.0 (C-1'), 129.9 (C-2', C-6'), 127.9 (C-3', C-5'), 133.8 (C-4').

17-*p*-Bromobenzenesulphonyloxy - 18,19 - isopropylidenedioxy - ent - labd - 13 - en - 16,15 - olactone (**11**). To a soln of **3** (500 mg) in pyridine (1 ml) was added *p*-bromobenzenesulphonyl chloride (600 mg) at 0° and the mixt. was kept at room temp. for 3 hr. The mixt. was poured over crushed ice, the ppt. collected by filtration (600 mg) and crystallized from 80% EtOH to afford colourless plates, mp 148–150°. Found: C, 57.1; H, 6.8. C<sub>29</sub>H<sub>39</sub>BrO<sub>7</sub>S requires: C, 57.0; H, 6.4%.

17- $\omega$ -Chlorowightionolide (**12**). To a soln of **3** (120 mg) in pyridine (0.5 ml), was added POCl<sub>3</sub> (0.5 ml) at 0° and kept for 14 hr. The mixt. was poured over

crushed ice, extracted with  $\text{CHCl}_3$ , washed with 10%  $\text{HCl}$  and  $\text{H}_2\text{O}$ , dried over  $\text{Na}_2\text{SO}_4$  and the solvent removed *in vacuo*. The residue was chromatographed over silica gel and crystallized from  $\text{EtOAc}$  to afford colourless plates (**12**, 25 mg), mp 190–191°. Found, C, 65.0; H, 8.6.  $\text{C}_{20}\text{H}_{31}\text{ClO}_4$  requires: C, 64.8; H, 8.4%.

17- $\omega$ -Iodo-18,19-isopropylidenedioxy-ent-labd-13-en-16,15-olactone (**13**). To a soln of **10** (1 g) in dry  $\text{Me}_2\text{CO}$  (200 ml) was added  $\text{NaI}$  (500 mg) and the mixt. heated under reflux for 22 hr. The residue was filtered, washed with  $\text{Me}_2\text{CO}$  and the filtrate evapd *in vacuo* and crystallized from  $\text{EtOH}$  to afford colourless plates (**13**, 600 mg), mp 149–150°. Found: C, 54.8; H, 7.3.  $\text{C}_{23}\text{H}_{35}\text{IO}_4$  requires: C, 55.0, H, 7.0%.  $^1\text{H}$  NMR (60 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.20 (1H, t, H-14), 4.85 (2H, d,  $J = 2$  Hz, H-15), 3.10–3.90 (6H, m,  $-\text{OCH}_2$ -17, 18, 19), 1.50 (6H, s,  $-\text{CMe}_2$ ), 0.80 (3H, s, Me-20).

17- $\omega$ -Iodowightionolide (**14**). A soln of **13** (300 mg) in  $\text{MeOH}$  (30 ml) and 5%  $\text{HCl}$  (20 ml) was heated on a water-bath at 80° for 10 min. The solvent was removed *in vacuo*,  $\text{H}_2\text{O}$  (25 ml) added and extracted with  $\text{CHCl}_3$ . The  $\text{CHCl}_3$  layer was washed with  $\text{H}_2\text{O}$ , dried over  $\text{Na}_2\text{SO}_4$  and the solvent evapd to give a gum which crystallized from  $\text{CH}_2\text{Cl}_2$ –hexane to afford colourless needles (**14**, 165 mg), mp 134–135°. Found: C, 52.2; H, 6.8.  $\text{C}_{20}\text{H}_{31}\text{IO}_4$  requires: C, 52.0; H, 6.8%. IR (nujol):  $\nu_{\text{max}}$  1740, 1455, 1452, 1370, 1260, 1220  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (250 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.12 (1H, s, H-14), 4.75 (2H, s, H-15), 3.72, 3.56 (2H, AB,  $J = 11.5$  Hz, H-17), 3.15, 3.62 (2H, AB,  $J = 11$  Hz, H-19), 3.26, 3.43 (2H, AB,  $J = 9.4$  Hz, H-18), 1.33, 1.30 (each 3H, s,  $-\text{CMe}_2$ ), 0.69 (3H, s, C-20).  $^{13}\text{C}$  NMR (62.9 MHz,  $\text{CDCl}_3$ ): 38.3 (C-1), 17.6 (C-2), 33.2 (C-3), 38.3 (C-4), 53.3 (C-5), 27.0 (C-6), 34.6 (C-7), 53.8 (C-8), 40.2 (C-9), 38.3 (C-10), 21.5 (C-11), 27.4 (C-12), 134.3 (C-13), 144.3 (C-14), 70.8 (C-15), 174.2 (C-16), 62.1 (C-17), 62.1 (C-18), 70.1 (C-19), 14.8 (C-20), 98.7 (C-21), 21.5 (C-22), 25.9 (C-23).

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