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γ-LACTONES FROM *IRYANTHERA* SPECIES*

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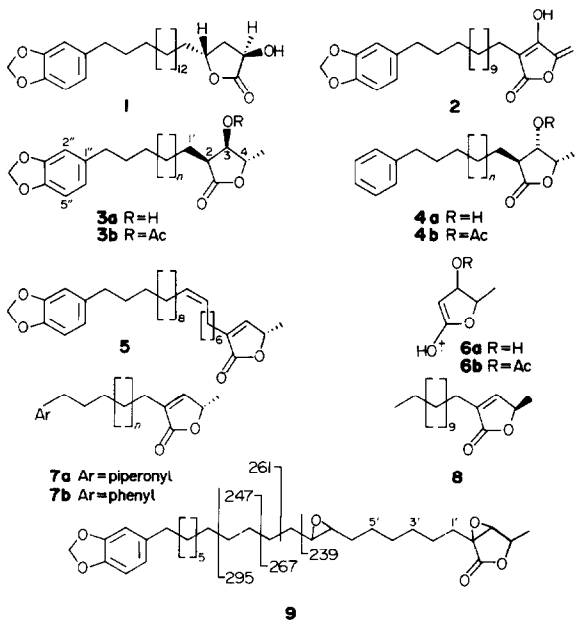
Key Word Index—*Iryanthera grandis*; *I. juruensis*; *I. ulei*; Myristicaceae; juruenolides; grandinolide; 2-(ω-aryl-*n*-alkyl)-γ-lactones.

Abstract—The structure of juruenolide, a constituent of *Iryanthera juruensis* and *I. ulei* is revised to (2*S*, 3*R*, 4*S*)-3-hydroxy-4-methyl-2-(19′-piperonyl-1′-*n*-nonadecyl)-butanolide. The compound is epimeric at C-3 of the γ-lactone unit with grandinolide [(2*S*, 3*S*, 4*S*)-3-hydroxy-4-methyl-2-(19′-phenyl-1′-*n*-nonadecyl)-butanolide] from *I. grandis*. An extract of *I. juruensis* contained additionally juruenolide-B [(4*S*)-4-methyl-2-(19′-piperonyl-1′-*n*-nonadec-7′-enyl)-but-2-enolide]. Analogous products with heptadecyl and pentadecyl side chains co-occur with the respective nonadecyl derivatives.

INTRODUCTION

A previous paper on constituents of the trunk wood of *Iryanthera juruensis* Warb. reported the presence of juruenolide (proposed structure **1**) [2]. A subsequent study on *I. elliptica* Ducke disclosed the presence of iryelliptin (**2**) [3]. A re-examination of juruenolide thus became advisable, since it would be reasonable to expect identical carbon skeletons for the γ-lactone moieties of both compounds. Indeed, as shown in the present paper, the structure of juruenolide must be revised to **3a**. The micromolecular type represented by **2** and **3a** seems to be rather widespread in the genus. Still another species, *I. ulei* (Benth.) Warb., contains **3a** and *I. grandis* Ducke contains the novel grandinolide (**4a**). The careful fractionation of an extract of *I. juruensis*, which had become necessary to secure a fresh sample of juruenolide, yielded additionally a further new product, juruenolide-B (**5**).



*Part 17 in the series "The Chemistry of Brazilian Myristicaceae". For Part 16 see ref. [1].

RESULTS

The ^{1}H NMR spectra (Table 1) suggested **3a** and **4a** to have similar γ-lactone rings (ν_{max} 1750 cm^{-1}) in which an oxymethine (δ4.53 ± 0.01) is represented, in the case of **4a**, by a double quartet. Its proton is thus coupled not only to three methyl protons but also to still another vicinal proton. Comparison of the coupling constants shows this to belong to another oxymethine (δ4.17 ± 0.03) represented, again in the case of **4a**, by a double doublet. The latter oxymethine must thus be coupled to an additional methine group (δ2.6) vicinal to the carbonyl. All these relationships were confirmed by the appropriate decoupling experiments. The last mentioned methine is substituted by the methylene chain ending, in the case of juruenolide (**3a**), in a piperonyl group and, in the case of grandinolide (**4a**), in a phenyl group. The particular γ-lactone moiety formulated for grandinolide is consistent also with the intense mass spectral fragments possibly generated through McLafferty rearrangements of **4a** to **6a** [*m/z* 116 (58%)] and of **4b** to **6b** [*m/z* 158 (28%)].

According to mass spectral evidence (Table 2) both **3a** and **4a** are mixtures of compounds with varying methylene chain lengths. While derivatives with $n = 17$ (uncosyl side chains) appear only in trace amounts, derivatives with $n = 15$ (nonadecyl side chains) are major constituents. Mass spectral indications for derivatives with $n = 13$, 11 and 9 (respectively, heptadecyl, pentadecyl and tridecyl side chains) may be excessively high, since

Table 1. ^{1}H NMR data of natural γ-lactones and their derivatives (100 (**3a**, **3b**) or 60 MHz, CCl_4 (**4b**) or $CDCl_3$, TMS as int. standard)*

	3a	**3b**	**4a**	**4b**	**7a**	**7b**	**5**
H-2	2.46–2.74 *m*	2.57–2.85 *m*	2.45 *m*	—	—	—	—
H-3	4.18 *d* (6)	5.12 *d* (6)	4.14 *dd* (3, 5)	5.10 *dd* (3, 5)	6.87 *dt* (1.5)	6.82 *dt* (1.5)	6.96 *dt* (1.5)
H-4	4.52 *q* (7)	4.49 *q* (7)	4.54 *dq* (5, 6)	4.66 *dq* (5, 6)	4.88 *dq* (1.5, 7)	4.88 *dq* (1.5, 7)	4.96 *dq* (1.5, 7)
Me-4	1.33 *d* (7)	1.39 *d* (7)	1.40 *d* (6)	1.40 *d* (6)	1.38 *d* (7)	1.40 *d* (7)	1.39 *d* (7)
H_2C-2	—	—	—	—	2.21 *dt* (1.5, 7)	2.2 *dt*	2.26 *dt*
$(H_2C)_x$	1.26 *brs*	1.26 *brs*	1.26 *brs*	1.26 *brs*	1.27 *brs*	1.26 *brs*	1.26 *brs*
H_2C-Ar	2.53 *t* (7)	2.53 *t* (7)	2.60 *t* (6)	2.60 *t* (6)	2.50 *t* (7)	2.60 *t* (6)	2.52 *t*
C_6H_5	—	—	7.13, *s*	7.15 *s*	—	7.06 *s*	—
C_6H_3	6.54–6.78 *m*	6.55–6.75 *m*	—	—	6.42–6.75 *m*	—	6.50–6.72 *m*
O_2CH_2	5.90 *s*	5.90 *s*	—	—	5.87 *s*	—	5.86 *s*
AcO-3	—	2.10 *s*	—	2.07 *s*	—	—	—
CH=CH	—	—	—	—	—	—	5.32 *t* (4)
$2C\underline{H}_2$-CH=	—	—	—	—	—	—	1.85–2.15 *m*

*Coupling constants (Hz) in parentheses.

Table 2. Mass spectral data of natural γ-lactones and their derivatives

	3a	**3b**	**4a**	**4b**	**7a**	**7b**
$[M]^+$ ($n = 17$)	530	—	—	—	—	—
	(3)					
$[M]^+$ ($n = 15$)	502	544	458	500	484	440
	(29)	(13)	(5)	(1)	(9)	(2)
$[M]^+$ ($n = 13$)	474	516	430	472	456	412
	(98)	(100)	(29)	(3)	(85)	(29)
$[M]^+$ ($n = 11$)	446	488	402	444	428	384
	(4)		(22)	(10)	(3)	(54)
$[ArCH_2]^+$	135	135	91	91	135	91
	(100)	(96)	(100)	(49)	(100)	(100)

they also refer to ions originating from the fragmentation of molecular ions with $n = 15$.

The original mistake concerning the structure of juruenolide was a consequence of the fact that the Me-4 resonance is partly included in the low field portion of the broad methylene envelope of the ^{1}H NMR spectrum. Recent work on the mahuba lactones [4], however, sharpened our perception of the corresponding doublet ($\delta 1.37 \pm 0.03$) which, furthermore, can be seen clearly in spectra taken in the presence of lanthanides. The complete registry of lanthanide-induced shifts (Table 3) revealed the cause for the differences in the coupling constants for the three methines of the lactone rings of **3a** and **4a** (Table 1). The complexing site (HO-3) is located on the same face as H-4 and CH_2-2 in **3a** and as Me-4 and H-2 in **4**. These spacial relationships are expressed in the formulae **3a** and **4a** which also represent absolute configurations.

Indeed, compounds **3a** and **4a** gave, by successive acetylation (Ac_2O, C_5H_5N) and elimination of acetic acid (Al_2O_3, C_5H_{12}), the endocyclic α,β-unsaturated γ-lactones **7a** and **7b**, respectively. These are dextrorotatory ($[\alpha]_D + 16° \pm 1$) in contrast to the laevorotatory compound **8** ($[\alpha]_D - 29.8°$) of known absolute stereochemistry [4, 5].

Mass spectral analysis revealed compound **5** to lack two hydrogen atoms with respect to **7a**. The fact that lactone ring and aryl ^{1}H NMR signals of both products are superimposable requires the inclusion of a double bond in the *n*-alkyl chain of **5**. The ^{1}H (Table 1) and ^{13}C NMR

Table 3. $Eu(fod)_3$-induced ^{1}H NMR $\Delta\delta$ values*

	3a	**4a**
H-2	3.2	6.2
H_2C-2	4.2	—
H-4	4.0	1.5
Me-4	1.2	3.1

*Shift studies were carried out by step-wise addition of known amounts of $Eu(fod)_3$ to *ca* 0.8 μM solns of substrate in $CDCl_3$. The $\Delta\delta$ values were obtained by graphic extrapolation of observed shifts to 1:1 shift reagent–substrate ratio.

data confirm the existence of this group and suggest its *cis* geometry. Indeed, reciprocal γ-effects cause protection of two allylic carbons in **5** (δ27.2 and 27.4) precisely as in oleic acid (δ27.0). In contrast, the analogous carbons in elaidic acid do not interact and the corresponding signals appear at lower field (δ32.5) [6].

Oleic acid is the perfect model compound for comparison, since this acid probably functions as one of the biosynthetic precursors of **5**. This would require the

double bond to be situated between C-7′ and C-8′ of the *n*-alkyl chain. Inspection of the mass spectrum of **9**, the di-epoxylated derivative of **5**, confirms this postulate through three conspicuous series of peaks. Within each series the peaks are spaced 28 a.m.u. apart. Two series, one starting at *m/z* 261 (1%), and continuing with 233 (1), 205 (2), 177 (3) and 149 (7), and the other starting at *m/z* 247 (2) and continuing with 219 (1), 191 (2), 163 (4) and 135 (100), indicate the connection of the piperonyl moiety to at least 10 methylene groups. The third series starts at *m/z* 295 (1) and continues with 267 (2) and 239 (1). The termination of this series at *m/z* 239 places the side chain epoxide group at C-7′ and C-8′.

Compound **5** is again dextrorotatory and thus possesses the same absolute stereochemistry as **7a** and **7b**.

DISCUSSION

From the biosynthetic point of view the entire group of compounds can be considered to be derived by condensation of a cinnamyl (or a benzoyl) CoA and a pyruvyl CoA with, respectively, the methyl and the α-methylene of myristic (**3a**, **4a**, $n = 11$), palmitic (**3a**, **4a**, $n = 13$), stearic (**3a**, **4a**, $n = 15$) and oleic (**5**) acids. The conspicuous involvement of C_{18}-fatty acids in these processes is rather surprising. The acids from a typical myristicaceous seed fat are composed chiefly of myristic acid (65%) accompanied by lesser quantities of lauric (15%), palmitic (10%), stearic (1%) and other acids [7]. It should not be forgotten, however, that only grandinolide (**4a**) was isolated from fruits. The juruenolides (**3a**, **5**) occur in wood.

EXPERIMENTAL

Isolation of the constituents of Iryanthera juruensis. This was described previously in detail [2]. The mother liquor which remained after crystallization of juruenolide was evaporated. The residue (1.6 g) was washed with EtOH. The insoluble portion was crystallized from MeOH to give **3a** (70 mg). The EtOH soln was evaporated and the residue was purified by TLC (Si gel, C_6H_6–C_6H_{14}–Me_2CO 17:2:1) to give **5** (21 mg).

Isolation of the constituents of Iryanthera ulei. A specimen collected at Itaituba, Pará State, identified by Dr. William A. Rodrigues (INPA, Manaus), gave a trunk wood sample (1 kg) which was dried, powdered and extracted with C_6H_6. The extract (8 g) was chromatographed on Si gel. Mixtures of $CHCl_3$–EtOAc of gradually increasing polarities eluted two useful fractions F1 (1.4 g) and F2 (400 mg). Crystallized from MeOH, F1 gave sitosterol (900 mg) and F2 gave **3a** (360 mg).

Isolation of the constituents of Iryanthera grandis. Fruits of a specimen, identified by Dr. William A. Rodrigues (INPA, Manaus), were collected at Itaituba, Pará State. After drying, the fruits were reduced to a powder (400 g) which was extracted with C_6H_6. The extract (90 g), crystallized from EtOH, gave triglycerides (60 g). The mother liquor was evaporated and the residue (27 g) was chromatographed on Si gel. Mixtures of petrol–EtOAc of gradually increasing polarities eluted 35 fractions (250 ml). Fraction 34 (220 mg), crystallized from MeOH, gave **4a** (80 mg).

(2S, 3R, 4S)-3-*Hydroxy*-4-*methyl*-(19′-*piperonyl*-1′-*n*-*nonadecyl*)-*butanolide* (*juruenolide*, **3a**). Mp 89–90° (MeOH), $[\alpha]_D$ +12.5° (MeOH) [2]. ^{13}C NMR (25.2 MHz, $CDCl_3$): δ 177.8 (*s*, C-1), 43.7 (*d*, C-2), 73.5 (*d*, C-3), 82.7 (*d*, C-4), 17.9 (*q*, Me-4), 23.3 (*t*, C-1′), 27.6 (*t*, C-2′), 29.1 (*t*, C-3′), 29.6 (*t*, $n = 15$: C-4′–C-17′; $n = 13$: C-4′–C-15′; $n = 11$: C-4′–C-13′), 31.7 (*t*, $n = 15$: C-18′; $n = 13$: C-16′; $n = 11$: C-14′), 35.6 (*t*, $n = 15$: C-19′; $n = 13$: C-17′; $n = 11$: C-15′), 136.6 (*s*, C-1″), 107.8 (*d*, C-2″), 147.2 (*s*, C-3″), 147.1 (*s*, C-4″), 108.7 (*d*, C-5″), 120.8 (*d*, C-6″), 100.5 (*t*, CH_2O_2). *Acetate* (**3b**): mp 83–85° (MeOH).

(2S, 3S, 4S)-3-*Hydroxy*-4-*methyl*-(19′-*phenyl*-1′-*n*-*nonadecyl*)-*butanolide* (*grandinolide*, **4a**). Mp 55–56° (MeOH) (M^+ found: 458.3889; $C_{30}H_{50}O_3$ requires: 458.3895). MS *m/z* (rel. int.): 458 $[M]^+$ (5), 430 (29), 402 (22), 269 (1), 255 (1), 241 (1), 227 (1), 213 (1), 199 (1), 185 (1), 171 (1), 148 (3), 129 (32), 116 (58), 104 (45), 91 (100), 57 (95); IR ν_{max}^{KBr} cm^{-1}: 3570, 1750, 1490, 1470, 1385, 1330, 1235, 1190, 1055, 990, 935, 745, 730, 670; $[\alpha]_D^{24}$ −34.7° (MeOH). *Monoacetate* (**4b**): oil. IR ν_{max}^{film} cm^{-1}: 1775, 1745, 1490, 1460, 1370, 1235, 1190, 1150, 1020, 750, 725, 705; MS *m/z* (rel. int.): 500 $[M]^+$ (1), 472 (3), 444 (10), 385 (17), 158 (28), 104 (15), 99 (24), 91 (49), 57 (24), 55 (32), 43 (100).

Elimination of HOAc from **3b** *and* **4b**. The compounds (30 mg) were placed on top of a column of Al_2O_3 (Brockman activity II/III, 5 g). Elution with C_5H_{12} gave **6a** (23 mg, ex **3b**) and **6b** (21 mg ex **4b**).

(4S)-4-*Methyl*-2-(19′-*piperonyl*-1′-*n*-*nonadec*-7′-*enyl*)-*but*-2-*enolide* (*juruenolide-B*, **5**). Oil (M^+ found: 482.3560; $C_{31}H_{46}O_4$ requires: 482.3576). IR ν_{max}^{film} cm^{-1}: 1755, 1485, 1440, 1320, 1240, 1190, 1120, 1080, 1040, 870, 820; UV λ_{max}^{EtOH} nm: 236 sh, 290 (ε 3300, 3900); ^{13}C NMR (20 MHz, $CDCl_3$): δ 173.8 (*s*, C-1), 134.4 (*s*, C-2), 148.8 (*d*, C-3), 77.4 (*d*, C-4), 19.2 (*q*, Me-4), 25.2 (*t*, C-1′), *ca* 29 (*ca t*, C-2′–C-5′, C-10′–C-15′), 27.2 and 27.4 (*t*, C-6′, C-9′), 129.9 (*d*, C-7′, C-8′), 31.7 (*t*, C-16′), 35.7 (*t*, C-17′), 136.8 (*s*, C-1″), 108.0 (C-2″), 147.4 (*s*, C-3″), 145.5 (*s*, C-4″), 108.8 (*d*, C-5″), 121.0 (*d*, C-6″), 100.7 (CH_2O_2); MS *m/z* (rel. int.): 482 $[M]^+$ (26), 454 (28), 135 (100); $[\alpha]_D^{25}$ +15° (MeOH). *Di-epoxide* (**9**): submitted directly after preparation (**5**, *m*-chloroperbenzoic acid, CH_2Cl_2, room temp., 100 hr) to mass spectrometry *m/z* (rel. int.): 295 (1), 267 (2), 239 (1), 211 (1), 261 (1), 247 (2), 233 (1), 219 (1), 205 (2), 191 (2), 177 (3), 163 (4), 149 (7), 135 (100).

(4S)-4-*Methyl*-2-(19′-*piperonyl*-1′-*n*-*nonadecyl*)-*but*-2-*enolide* (**7a**). Mp 56–58° (C_5H_{12}). IR ν_{max}^{KBr} cm^{-1}: 1755, 1490, 1470, 1250, 870, 810; UV λ_{max}^{MeOH} nm: 230, 290 (ε 3200, 4100). $[\alpha]_D^{25}$ +15° (MeOH).

(4S)-4-*Methyl*-2-(19′-*phenyl*-1′-*n*-*nonadecyl*)-*but*-2-*enolide* (**7b**). Oil. IR ν_{max}^{film} cm^{-1}: 1755, 1490, 1460, 1370, 1320, 1200, 1115, 1075, 1030, 750, 725, 705; MS *m/z* (rel. int.): 440 $[M]^+$ (2), 412 (29), 384 (54), 91 (100), 84 (25), 83 (27), 69 (41), 67 (37), 57 (50), 55 (68), 43 (88), 41 (97); $[\alpha]_D^{25}$ +17° (MeOH).

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