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FURTHER FARNESYL-HOMOGENTISIC ACID DERIVATIVES FROM *OTOBA PARVIFOLIA**

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IN HONOUR OF PROFESSOR ANTONIO G. GONZALEZ

Key Word Index—*Otoba parvifolia*; Myristicaceae; farnesyl derivatives; oxocyclohexenylacetic acids; dihydroxy-oxocyclohexanylacetic acid δ-lactone; homogentisic acid pathway.

Abstract—The seeds of *Otoba parvifolia* contain three novel compounds apparently derived from homogentisic acid, *rel*-(1′*R*,5′*R*)-2-(1′-farnesyl-5′-hydroxy-2′-oxocyclohex-3′-en-1′-yl)-acetic acid and its acetate as well as *rel*-(1′*R*,4′*S*,5′*R*)-2-(1′-farnesyl-4′,5′-dihydroxy-2′-oxocyclohexan-1′-yl)-acetic acid δ-lactone. The structure of an additional isolate, previously described as 2-(1′-farnesyl-2′-hydroxy-5′-oxocyclohex-3′-en-1′-yl)-acetic acid γ-lactone was revised to *rel*-(1′*R*,5′*R*)-2-(1′-farnesyl-5′-hydroxy-2′-oxocyclohex-3′-en-1′-yl)-acetic acid δ-lactone.

INTRODUCTION

Fruit kernels of *Otoba parvifolia* (Mkfg.) A. Gentry from the Amazon region have been reported to contain, besides sitosterol and the furofuran lignans xanthoxylol and philygenol, some homogentisic acid (**1**) derived compounds, attributed to structures **2**, **3a**, **4a**, **4b**, **5a** and **5b** [2]. Re-examination of the same material revealed the additional presence of three further compounds, **6a**, **6b** and **7a**. Fruit pericarp was found to contain sitosterol, nerolidol, the neolignan hydroxyotobain [3], the furofuran lignans xanthoxylol and forsythigenol [4], as well as **6b**. Meanwhile, in the quest of a model for **3a**, compound **3b** was synthesized [5]. The spectral data for the synthetic product (IR_{max} 1780 and 1686 cm^{-1}) and the natural isolate (IR_{max} 1742 and 1683 cm^{-1}) were significantly different (see also Tables 1–3). Thus, the present work required not only the structural determination of the novel isolates **6a**, **6b** and **7a**, but also the structural revision of **3a**, now designated **8**.

RESULTS

The ^1H (Tables 1 and 2) and ^{13}C (Table 3) NMR spectra in combination with low resolution mass spectral molecular weight determinations (Table 4) established the formulae $C_{24}H_{36}O_4$ (**6c**), $C_{26}H_{38}O_5$ (**6d**) (the respective methyl esters of **6a** and **6b**) and $C_{23}H_{34}O_4$ (**7a**). Routine examination of the NMR spectra allowed expansion of the formulae to $C_8H_7O_2 \cdot OH \cdot OMe \cdot Fa$ (**6c**), $C_8H_7O_2 \cdot OAc \cdot OMe \cdot Fa$ (**6d**) and $C_8H_8O_3 \cdot OH \cdot Fa$ (**7a**) (Fa = farnesyl) and led to the conclusion that all three must be closely related to the co-occurring known compound $C_8H_7O_3 \cdot Fa$ (**8** = **7a**–H_2O). Indeed the mass spectra of all four compounds are closely comparable (Table 4). IR spectral comparisons showed the δ-lactone of **7a** (ν_{max}^{film} 1741 cm^{-1}), though present in **8** (ν_{max}^{film} 1742 cm^{-1}), to be replaced by an ester in **6c** and **6d** (ν_{max}^{film} 1732 ± 1 cm^{-1}); and the α,β-unsaturated carbonyl of **8** (ν_{max}^{film} 1683 cm^{-1}), though present in **6c** and **6d** (ν_{max}^{film} 1679 ± 2 cm^{-1}), to be replaced by a saturated carbonyl in **7a** (ν_{max}^{film} *ca* 1712 cm^{-1}). Hydrolysis of the lactone of **8** would generate a hydroxyl at a trisubstituted C-5′ as shown in **6c**. Acetylation of this hydroxyl is expected to cause an *ca* 1 ppm paramagnetic shift of the carbinolic proton signal and *ca* 4 ppm paramagnetic shifts of the C-4′ and C-6′ signals. These are precisely the relevant ^1H and ^{13}C NMR spectral modifications upon passing from **6c** to **6d**, all other features remaining closely comparable. The hydroxyls in **6c** and **6d** are both α-oriented. Indeed, only for this conformation, but not for the antipodal orientation shown in the model **6e**, observed and

*Part 38 in the series 'The Chemistry of Brazilian Myristicaceae'. For Part 37 see ref. [1]. Based on part of the Doctorate thesis presented by A. G. F. to Universidade de São Paulo (1990).

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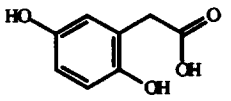

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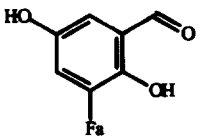

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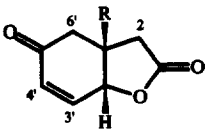

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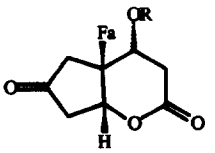
3b R = Me



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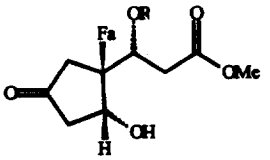
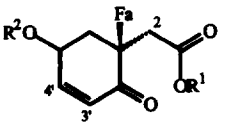
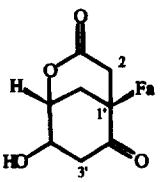
4b R = Et



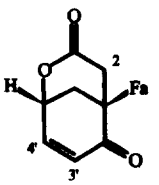
5a R = Me
5b R = Et



6a $R^1 = R^2 = H$, $OR^2\alpha$, C-5'R
6b $R^1 = H$, $R^2 = Ac$, $OR^2\alpha$, C-5'R
6c $R^1 = Me$, $R^2 = H$, $OR^2\alpha$, C-5'R
6d $R^1 = Me$, $R^2 = Ac$, $OR^2\alpha$, C-5'R
6e $R^1 = R^2 = H$, $OR^2\beta$, C-5'S



7a OH eq.
7b OH ax.



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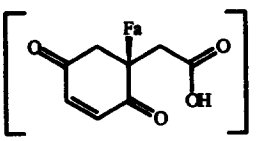

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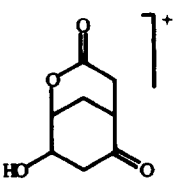
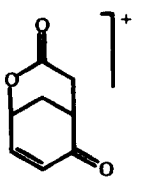
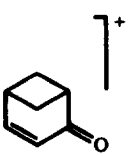


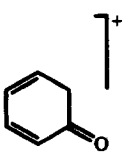
A+



B+



C+



D+

Table 1. ^{1}H NMR spectral data (δ/multiplicity, $CDCl_3$)

H	**6c** (80 MHz)	**6d** (80 MHz)	H*	**7a** (80 MHz)	H*	**8**† (300 MHz)	H	**3b** [5] (200 MHz)
2	2.21 *d*	2.20 *d*	α	2.05 *d*	α	2.57 *dd*	2	2.43 *d*
2	2.91 *d*	2.95 *d*	β	2.40 *d*	β	2.67 *d*	2	2.60 *d*
3′	5.95 *dd*	6.02 *dd*		2.40 *dd*		6.13 *d*	4′	6.16 *dd*
3′	—	—		2.80 *dd*		—		—
4′	6.87 *bd*	6.73 *dt*		3.93 *ddd*		7.13 *ddd*	3′	6.73 *dd*
5′	4.65 *tt*	5.70 *ddt*		4.8 *m*		5.05 *m*	2′	4.77 *dd*
6′	2.3 *m*	2.3 *m*		2.0 *m*	α	2.26 *ddd*	6′	2.48 *d*
6′					β	2.20 *ddd*	6′	2.32 *d*
OMe	3.60 *s*	3.60 *s*		—		—		—
OH	5.1 *m*	—		2.3		—		—
OAc	—	2.10 *s*		—		—		—
1″	1.8–2.4 *m*	1.8–2.5 *m*		2.2–2.5 *m*		2.30 *bdd*	Me	1.30 *s*
1″						2.43 *bdd*		
4″,5″				1.8–2.1 *m*		1.9–2.1 *m*		
8″,9″								
2″	5–5.2 *m*	5–5.3 *m*		4.9–5.2 *m*		5–5.1 *m*		
6″,10″								
12″	1.66 *s*	1.5–1.8 *m*		1.67 *s*		1.68 *d*		
13″	1.59 *s*			1.58 *s*		1.59 *s*		
14″						1.60 *s*		
15″						1.64 *s*		

*For the methylenes of the lactone ring, α refers to hydrogens *cis* to the enone bridge.
†Previously **3a** [2].

Table 2. ^{1}H NMR coupling constants (J) in Hz

Vicinal (J)*	**6c** (obs.)	**6d** (obs.)	**6c, d** (calc.)†	**6e** (calc.)†	**7a** (obs.)	**7a** (calc.)†	**7b** (calc.)†	**8** (obs.)	**8** (calc.)†	**3b** (obs.)	**3b** (calc.)†
H-2′, H-3′	—	—	—	—	—	—	—	—	—	3.3	3.9
H-3′, H-4′	10.5	10	—	—	9	10.6	3.3	10		10.3	—
H-3′, H-4′	—	—	—	—	5	5.8	2.8		—	—	
H-4′, H-5′	2.0	2	2.8	4.7	1.5	2.5	4.1	6	5.8	—	—
H-5′, H-6′	8.5‡	9	10.6	4.1	—	4.7	4.7	3	3.9		—
H-5′, H-6′		6	5.6	2.4	—	1.6	1.6	2.5	1.9	—	—

*Additional J: **6c** H-2 (gem.) 16; H-3′, H-5′ 2. **6d** H-2 (gem.) 16; H-3′, H-5′ 2.5. **7a** H-2 (gem.) 20; H-3′ (gem.) 12. **8** H-2 (gem.) 19.5; H-2, H-6′ 1.5; H-4′, H-6′ 1; H-6′ (gem.) 14.5. **3b** H-2 (gem.) 16.5; H-2′, H-6′ 1.2, H-5′ (gem.) 17.2.

†Molecular modelling was performed using PC MODEL (Serena Software, Bloomington, IN).

‡This is probably an average coupling constant (a small $\Delta\delta$ between the two H-6′ results in this second-order effect).

Table 3. ^{13}C NMR spectral data (δ/multiplicity, 20 MHz, $CDCl_3$)

C	6c	6d	7a	8*	C	3b [5]
1	172.30	171.50 *s*	168.77	168.96	1	173.91
2	40.14†	39.84 *t*	38.45	39.72	1′	44.71
1′	47.48	47.48 *s*	46.14	45.99	2	40.37†
2′	200.86	199.94 *s*	206.46	200.31	5′	195.74
3′	128.00	129.15 *d*	44.06	130.67	4′	131.16
4′	150.92	146.35 *d*	71.71	144.46	3′	140.86
5′	64.93	67.01 *d*	77.75	69.78	2′	79.52
6′	40.00†	36.02 *t*	30.33	33.63†	6′	40.78†
OMe	51.50	51.22 *s*	—	—		—
OAc	—	20.75 *q*	—	—		—
		169.98 *s*				
1″	34.01	34.00 *t*	32.47	33.53†		
2″	117.48	117.17 *d*	117.17	117.57		
3″	139.88	140.01 *s*	140.56	140.56		
4″	39.61	39.45 *t*	39.91	39.99		
5″	26.42	26.25 *t*	26.43	26.46		
6″	123.75	123.71 *d*	123.20	123.45		
7″	135.39	135.12 *s*	135.50	135.34		
8″	39.70	39.53 *t*	39.61	39.82		
9″	26.75	26.61 *t*	26.71	26.78		
10″	124.31	124.26 *d*	124.19	124.31		
11″	132.00	130.98 *s*	130.44	131.28		
12″	25.67	25.45 *q*	25.51	25.69		
13″	17.66	17.45 *q*	17.27	17.69		
14″	16.04	15.85 *q*	15.96	16.05		
15″	16.35	16.16 *q*	16.29	16.41		

*Previously **3a** [2].

†Signals within the same column may be interchanged.

Table 4. MS data

	m/z	6c (%)	6d (%)	7a (%)	8 [2] (%)
$[C_{26}H_{38}O_5]^+$	430	—	0.5	—	—
$[C_{24}H_{36}O_4]^+$	388	1.5	—	—	—
$[C_{23}H_{34}O_4]^+$	374	—	—	3	—
$[C_{23}H_{32}O_3]^+$	356	—	—	—	0.1
Farnesyl$^+$	205	1	1	3	—
Geranyl$^+$	137	9	8	15	20
Prenyl$^+$	69	100	100	100	100
$C_{10}H_{15}^+$	135	17	18	14	41
$C_9H_{11}^+$	121	13	12	12	22
A^+	169	—	—	0.5	—
B^+	151	36	7	36	—
C^+	107	20	22	20	44
D^+	93	28	24	28	30

calculated vicinal coupling constants are compatible (Table 2). With respect to position 1′, it is the farnesyl substituent which is axial. Only in this case, one of the acetic acid methylene protons lies in the plane of the ring carbonyl, as documented by the corresponding NMR signal an extraordinarily low field (δ 2.9).

No CH=CHCO signals appear in the spectra of **7a** where the ketone carbonyl is flanked by a methylene and a quaternary carbon. This locates the hydroxyl, jointly with a sole proton (δ 3.93), at C-4′. In contradistinction such an α,β-unsaturated carbonyl appears again in the additional δ-lactone **8**. The rings in both compounds, **7a** and **8**, must be *cis*-fused. Hence, only the orientation of the free hydroxyl in **7a** remains to be established. This is equatorial. Indeed only for this conformation, but not for the antipodal orientation shown in the model **7b**, observed and calculated vicinal coupling constants are compatible (Table 2).

DISCUSSION

The co-occurrence in *O. parvifolia* of homogentisic acid and of nerolidol rationalizes the formation of the alkylation product **9** as a common intermediate of the oxocyclopentanylpropionic acids **4a**, **b** and **5a**, **b** [2] (via 1′,2′-rearrangement of CH_2CO_2H and ring contraction) and of oxocyclohexanylacetic acids **6a**, **b**, **7b** and **8** (via reduction of the oxo-group).

EXPERIMENTAL

Isolation of constituents. Fruits of *O. parvifolia* were collected by Dr Hipólito Ferreira Paulino Filho in the vicinity of Humaitá, Amazonas State. Botanical material

was identified by Dr William A. Rodrigues, INPA, Manaus. Air-dried fruits were separated into pericarps and seeds.s Ground dry pericarp meal (90 g) was extracted with $CHCl_3$. The extract (19 g) was submitted to CC (240 g Silica gel 60). Elution with $CHCl_3$ gave, in order: fatty material (2 g), nerolidol (35 mg), hydroxyotobain (21 mg), forsythigenol (1 g), xanthoxylol (21 mg), sitosterol (18 mg) and a crude fraction (903 mg), which was treated with CH_2N_2 in Et_2O. The reaction product was purified by prep. TLC (silica gel, hexane–Me_2CO, 4:1) into **6d** (60 mg). Nerolidol and hydroxyotobain were purified by prep. TLC (silica gel, hexane–Me_2CO, 4:1). All other compounds were purified by crystallization from MeOH. The ground dry seed meal (1100 g) was extracted with $CHCl_3$. The extract (380 g) was crystallized from MeOH to fatty material (165 g). The mother liquor was evapd and the residue (8 g) was submitted to CC (280 g Silica gel 60). Elution with $CHCl_3$ gave, in order: fatty material (556 mg), **8** (60 mg), forsythigenol (16 mg), sitosterol (15 mg) and **7a** (10 mg). Elution with $CHCl_3$–EtOAc gave a crude fr. (186 mg) which was treated with CH_2N_2 in Et_2O. The reaction product was sepd by prep. TLC (silica gel, $CHCl_3$–MeOH. 9:1) into **6d** (18 mg) and **6c** (6 mg).

rel-(1′R,5′R)-2-(1′-*Farnesyl*-5′-*hydroxy*-2′-*oxocyclohex*-3′-*en*-1′-*yl*)-*acetic acid methyl ester* (**6c**). Oil. IR ν_{max}^{film} cm^{-1}: 3404, 1731, 1677, 1441, 1365, 1193. UV $\lambda_{max}^{CHCl_3}$ nm: 246 (ε 1100). $[\alpha]_D^{20} = +2°$ (*c* 0.4, $CHCl_3$).

rel-(1′R,5′R)-2-(1′-*Farnesyl*-5′-*acetoxy*-2′-*oxocyclohex*-3′-*en*-1′-*yl*)-*acetic acid methyl ester* (**6d**). Oil. IR ν_{max}^{film} cm^{-1}: 1733, 1681, 1444, 1371, 1233, 1004, 756. $[\alpha]_D^{20} = +11.5°$ (*c* 0.6, $CHCl_3$).

rel-(1′R,4′S,5′R)-2-(1′-*Farnesyl*)-4′,5′-*dihydroxy*-2′-*oxocyclohexan*-1′-*yl*)-*acetic acid δ-lactone* (**7a**). Oil. IR ν_{max}^{film} cm^{-1}: 1741, 1712.

rel-(1′R,5′R)-2-(1′-*Farnesyl*-5′-*hydroxy*-2′-*oxocyclohex*-3′-*en*-1′-*yl*)-*acetic acid δ-lactone* (**8**). Oil. IR ν_{max}^{film} cm^{-1}: 1742, 1683, 1440, 1377, 1313, 1206, 1162, 1093, 1040, 986. UV $\lambda_{max}^{CHCl_3}$ nm: 340 (ε 1300). $[\alpha]_D^{20} = +214°$ (*c* 0.07, $CHCl_3$).

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