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ALKENE-γ-LACTONES AND AVOCADOFURANS FROM *PERSEA INDICA*: A REVISION OF THE STRUCTURE OF MAJORENOLIDE AND RELATED LACTONES

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Key Word Index—*Persea indica*; Lauraceae; avocadofurans; perseafuran; alkene-γ-lactones; majorenolide.

Abstract—Three avocadofurans and an alkene-γ-lactone have been isolated from *Persea indica*. The data for the lactone are similar to those given for majorenolide to which a δ-lactone structure was previously assigned. We suggest that its structure and those of other analogous lactones, such as majorynolide and majoranolide, should be revised.

INTRODUCTION

Persea indica is endemic to the Canary Islands, where it grows in a relic laurel forest. In a previous work, we have reported on the isolation of the toxic ryanodane diterpenes ryanodol and cinnzeylanol from the stems and leaves of this species, their ecological relation with the wild rats of the forest and their insecticidal effects [1–3]. The essential oil of the leaves of this species has also been studied [4]. In this work, we describe the isolation of three avocadofurans from the fruits of *P. indica* and the structural determination of an alkene-γ-lactone (**4**), which has been obtained from the stems and leaves of this species. We believe that this lactone is identical with majorenolide, the structure of which must, therefore, be revised.

RESULTS AND DISCUSSION

The stems and leaves of *P. indica* contain ryanodane diterpenes, which are highly toxic to mammals and insects, but it is known that the doves of the laurel forest eat the fruits of this species. Thus, in the study of the chemical components of the fruits, as expected, we obtained no toxic diterpenes, only compounds of the avocadofuran type.

We have named one of the avocadofurans isolated from the fruits perseafuran (**1**). This compound was identified from the essential oil of this species and its structure was tentatively assigned by GC–mass spectrometry [4]. We now give its structure on the basis of its ^{1}H and ^{13}C NMR spectra.

The molecular ion of this compound appeared in the mass spectrum at *m/z* 276. Its ^{1}H NMR spectrum showed characteristic signals of a furan ring substituted α to the oxygen function, with signals at δ6.20, 6.35 and 7.31, which are typical of the avocadofurans. There also appeared centred at δ6.18 a doublet (J = 16 Hz) and a multiplet, of intensity two protons, which were assigned to the two hydrogens of the 14, 15 double bond.

The ^{13}C NMR spectrum (Table 1) showed furan carbon signals at δ105.7 (C-2), 111.0 (C-3), 141.1 (C-1) and 152.8 (C-4). Those of a chain double bond appeared at δ118.4 (C-6) and 130.3 (C-5), and of C-7 and C-18 at δ32.8 and 22.6, respectively.

Another two avocadofurans, identified as components of the fruits of this species, were avocadienofuran (**2**) and avocadenynofuran (**3**). These two compounds have previously been obtained from *P. americana* [5] and *Elodea canadensis* [6], respectively. Both have also been found in the essential oil of the leaves of *P. indica* [4]. We have now corrected the assignment of the C-16 and C-17 resonances for the avocadenynofurans (**3**) (Table 1).

An alkene-γ-lactone was isolated from the stems and leaves of *P. indica*. The structure (**4**) assigned to this compound was based on the following considerations. The ^{1}H NMR spectrum showed the signals of the terminal double bond as a multiplet at δ5.80 and a pair of doublets centred at δ4.92 and 4.98, and those of the vinyl proton H-7 as a triplet of triplets at δ6.75. This hydrogen showed a long-range allylic coupling with each one of the two H-4 (2.8 Hz), which resonate as a pair of double-doublets of doublets at δ2.68 and 2.89. In this spectrum, the resonances of the hydrogen at C-5 appear as a multiplet at δ4.66, of the hydroxymethylene group as a pair of doublets centred at δ3.65 and 3.89, of the two methylene groups allylic to the double bonds as two multiplets at δ2.06 and 2.18, and those due to the long methylene chain as a broad singlet at δ1.28.

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Table 1. ^{13}C NMR data for compounds **1**–**3** ($CDCl_3$, 50.3 MHz)

C	1	2	3
1	141.1	141.1	141.3
2	105.7	105.8	105.8
3	111.0	111.0	111.0
4	152.8	153.4	153.4
5	130.3	130.3	130.2
6	118.4	118.4	118.5
7	32.8	32.7	32.7
15	n.a.	33.8	18.4
16	n.a.	139.3	68.0
17	n.a.	114.1	84.8
18	22.6	—	—
19	14.1	—	—

n.a. = signals not assigned.

Table 2. ^{13}C NMR data for compounds **4**, **6** and **7** (50.3 MHz)

C	4 ($CDCl_3$)	6* ($CDCl_3$)	4* (C_6D_6)	7* (C_6D_6)
2	170.9	170.73	170.66	170.24
3	125.6	125.69	127.12	127.01
4	26.7	26.73	26.62	26.54
5	77.3	77.27	77.38	76.95
6	64.5	64.51	64.23	64.10
7	141.6	141.48	139.18	139.71
8	30.3	30.22	30.21	32.30
17	139.2	86.78	139.81	n.a.
18	114.1	68.03	114.55	n.a..

*Data taken from refs [7] and [8] corresponding to structures **9**, **10** and **11**, and now revised in this work to **6**, **4** and **7**, respectively.
n.a. = signals not assigned.

A COSY NMR spectrum and double resonance experiments allowed us to determine the carbon sequence. Thus, irradiation of H-7 cancelled the long-range coupling with H-4 and transformed the signal into a pair of double doublets, also affecting H-8. Conversely, irradiation of H-4 collapsed H-7 to a broad triplet and sharpened the H-5 multiplet. Irradiation of H-5 collapsed H-6 into a clean pair of doublets and H-4 into another pair of broad doublets, while irradiation of H-6 transformed H-5 into a broad triplet.

The ^{13}C NMR spectrum of **4** showed that this compound had no methyl groups and possessed a linear hydrocarbon chain, which ended in a vinylic double bond with signals at δ114.1 (*t*) and 139.2 (*d*). Signals also appeared in this spectrum of other double bonds with resonances at δ125.6 (*s*) and 141.6 (*s*), which indicated a conjugation with a carbonyl group, in this case that of a lactone at δ170.9. The carbon carrying the lactonic oxygen was at δ77.3 and that of the $-CH_2OH$ group appeared at δ64.5. The chemical shifts of these two last carbons were more in accordance with the structure **4** than with a possible alternative such as **10**, with a six-membered ring. Thus, the relatively low chemical shift of the hydroxymethylene carbon (δ64.5) was more typical of a free $-CH_2OH$ group as in **4** than a lactonized one as in **10**. Moreover, the high value of δ77.3 for C-5 was more characteristic of a carbon bearing an esterified secondary hydroxyl, as in **4**, than a free one, as in **10**. HMQC 2D NMR experiments were used for the assignment of the carbon resonances (Table 2).

The ^{1}H NMR spectrum accorded better with a structure such as **4**. Thus, the resonances of H-5 (δ4.66) and the two H-6 (δ3.65 and 3.89) were too high and low, respectively, for a –CHOH and a $-CH_2O$ (CO)–R group as in **10**, and were more in keeping with a –CHO(CO)–R and a CH_2OH, respectively, as in **4**. The coupling constants of H-5, 5.8 and 8.3 Hz (with H-4), and 5 and 3 Hz (with H-6), were better explained with a five-membered ring that with a six-membered one. Moreover, the same long-range coupling (2.8 Hz) observed between H-7 and each one of the two H-4 indicated a planar structure for the molecular ring, thus indicating a five-membered ring, as in **4**.

Acetylation of **4** gave the acetate **5**, which, in its ^{1}H NMR spectrum, showed, as expected, the two H-6 at lower field, δ4.17 and 4.29, compared with δ3.65 and 3.89 in **4**, while H-5 appeared at δ4.66 in the alcohol and at δ4.77 in the acetate. These facts confirmed the existence in the molecule of a hydroxymethylene group and excluded a structure such as **10**, with a secondary hydroxyl group.

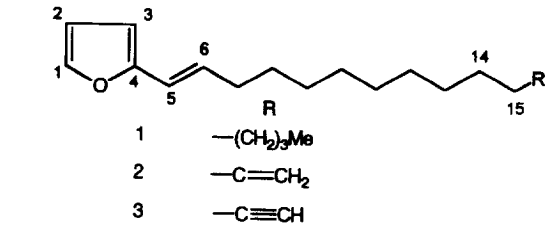
Other lactones of this type, with a six-membered ring, have been isolated from *P. major* and named majorynolide (**9**), majorenolide (**10**) [7] and majoranolide (**11**) [8]. The ^{1}H NMR spectrum described for **10** is identical with that of our lactone (**4**), and the ^{13}C NMR spectra run in different solvents are very similar (Table 2). Unfortunately, we could not take the NMR spectrum in benzene-d_6, because our compound had decomposed with time. On the other hand, the ring carbon resonances of our lactone **4** and those of the parent substance **9**, which were taken in the same solvent (Table 2), are practically identical. Thus, we suggest that the structure given for **10** [8] must be revised to **4**, with a five-membered ring. In the same way, the structures of **9** [7] and **11** [8] should also be revised to **6** and **7**, respectively. To these products an (*E*)-configured double bond had been assigned, because a NOE was observed between H-8 and H-4 [7]. Now, only the stereochemistry at C-5 remains to be established.

Compounds related to **4** are the litsenolides, a group of six alkene-γ-lactones, which have been obtained from another Lauraceae, *Litsea japonica* [9]. An example of these substances is litsenolide A_1 (**8**).

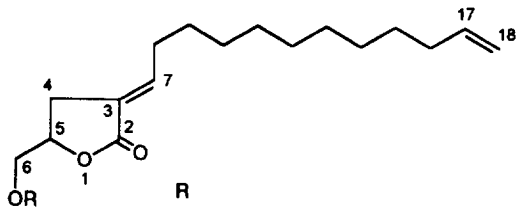
EXPERIMENTAL

Mps: uncorr.; MS: 70 eV (probe); ^{1}H NMR: $CDCl_3$; CC: silica gel, 0.063–0.2 mm.

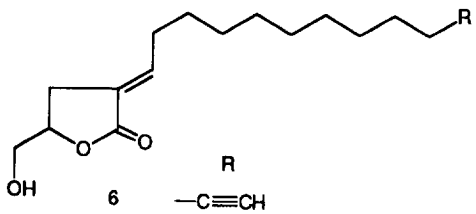
Extraction of the fruits. The mature fruits of *P. indica* were collected in the gardens of the Instituto de Productos Naturales (La Laguna, Tenerife) in July and the



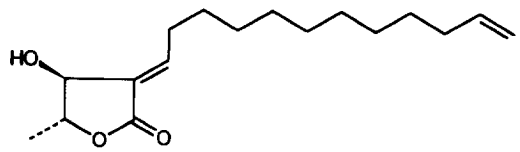
1 —$(CH_2)_3Me$
2 —$C{=}CH_2$
3 —$C{\equiv}CH$



4 H
5 Ac



6 —$C{\equiv}CH$
7 —$(CH_2)_3Me$



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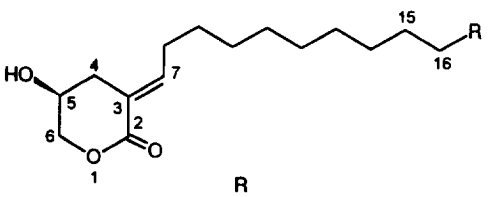

9 —$C{\equiv}CH$
10 —$C{=}CH_2$
11 —$(CH_2)_3Me$

pulp was sepd from the seed. The pulp (265 g) was extracted with EtOH in a Soxhlet apparatus for 40 hr. Evapn of the solvent *in vacuo* led to a syrupy material (174 g), a portion of which (6 g) was chromatographed, eluting with petrol to give in order of elution perseafuran (**1**), avocadienofuran (**2**) and avocadynenofuran (**3**).

Perseafuran (**1**). ^{1}H NMR (200 MHz): δ0.93 (3H, *s*), 1.28 (nCH_2, *br s*), 2.18 (2H, *m*, H-7), 6.16 (2H, complex signal. H-5 and H-6), 6.20 (1H, *d*, J = 3 Hz, H-3), 6.35 (1H, *dd*, J = 3, 2 Hz, H-2), 7.31 (1H, *d*, J = 2 Hz, H-1); MS *m/z* (rel. int.): 276 $[M]^+$ (22), 248 (8), 219 (3), 204 (12), 189 (4), 161 (23), 135 (12), 134 (10), 123 (12), 119 (17), 107 (68), 94 (100), 81 (78), 79 (39), 77 (36).

Avocadienofuran (**2**). ^{1}H NMR (200 MHz): δ1.29 (nCH_2, *br s*), 2.04 (2H, *dd*, H-15), 2.16 (2H, *dd*, H-7), 4.92 (1H, *br d*, J = 10 Hz, H-17), 4.98 (1H, *br d*, J = 16, H-17), 5.80 (1H, *m*, H-16), 6.15 (2H, complex signal, H-5 and H-6), 6.18 (1H, J = 3 Hz, H-3), 6.33 (1H, *dd*, J = 3, 2 Hz, H-2), 7.30 (1H, *d*, J = 2 Hz, H-1); MS *m/z* (rel. int.): 246 $[M]^+$ (42), 175 (4), 161 (5), 149 (12), 135 (14), 133 (6), 121 (14), 107 (97), 94 (100), 81 (29), 79 (50), 77 (38).

Avocadynenofuran (**3**). ^{1}H NMR (200 MHz): δ1.29 (nCH_2, *br s*), 1.93 (1H, *t*, J = 2.6 Hz, H-17), 2.18 (4H, *m*, H-7, H-15), 6.15 (2H, complex signal, H-5, H-6), 6.19 (1H, *d*, J = 3 Hz, H-3), 6.34 (1H, *dd*, J = 3, 2 Hz, H-2), 7.31 (1H, *d*, J = 2 Hz, H-1); MS *m/z* (rel. int.): 244 $[M]^+$ (21), 187 (2), 173 (3), 161 (4), 147 (11), 133 (11), 119 (10), 107 (92), 94 (100), 81 (49), 79 (62), 77 (58).

Extraction of the aerial parts. P. indica branches (1.3 kg), collected at Monte de Las Mercedes (Tenerife) in March, were air-dried, chopped and then extracted with EtOH in a Soxhlet apparatus. The cold extract was filtered and concd *in vacuo* to afford a syrupy gum (307 g). This syrup was treated with EtOAc and the soln sepd by filtration. The solvent was evapd and the residue (138 g) chromatographed on silica gel, eluting with petrol–EtOAc mixts. The frs eluted with petrol–EtOAc (7:3) (6.2 g) were rechromatographed on silica gel, giving **4** and several ryanodane diterpenes.

Lactone **4**. ^{1}H NMR (200 MHz): δ1.28 (nCH_2), 2.06 (2H, *m*, H-16), 2.18 (2H, *m*, H-8), 2.68 (1H, *ddd*, J = 16, 5.8, 2.8 Hz, H-4), 2.89 (1H, *ddd*, J = 16, 8.3, 2.8 Hz, H-4), 3.65 (1H, *dd*, J = 12.4, 5 Hz, H-6), 3.89 (1H, *dd*, J = 12.4, 3 Hz, H-6), 4.66 (1H, *m*, H-5), 4.92 (1H, *br d*, J = 8 Hz, H-18), 4.98 (1H, *br d*, J = 16 Hz, H-18), 5.80 (1H, *m*, H-17), 6.75 (1H, *tt*, J = 7.4, 2.8 Hz, H-7).

Acetate **5**. ^{1}H NMR (200 MHz): δ1.28 (nCH_2), 2.06 (2H, *m*, H-16), 2.09 (3H, *s*, –OAc), 2.18 (2H, *m*, H-8), 2.60 (1H, *ddd*, J = 16, 5, 2.8 Hz, H-4), 2.95 (1H, *ddd*, J = 16, 8, 2.8 Hz, H-4), 4.17 (1H, *dd*, J = 12, 5 Hz, H-6), 4.29 (1H, *dd*, J = 12, 3 Hz, H-6), 4.77 (1H, *m*, H-5), 4.92 (1H, *br d*, J = 8 Hz, H-18), 4.98 (1H, *br d*, J = 16 Hz, H-18), 5.79 (1H, *m*, H-17), 6.76 (1H, *tt*, J = 7.6, 2.8 Hz, H-7).

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REFERENCES

1. González-Coloma, A., Hernández, M. G., Perales, A. and Fraga, B. M. (1990) *J. Chem. Ecol.* **16**, 2723.
2. González-Coloma, A., Cabrera, R., Castañera, P., Gutiérrez, C. and Fraga, B. M. (1992) *Phytochemistry* **31**, 1549.
3. González-Coloma, A., Cabrera, R., Socorro, A. R. and Fraga, B. M. (1993) *Phytochemistry* **34**, 397.

4. Weyerstahl, P., Marschall, H. and Scora, R. W. (1993) *Flav. Fragr. J.* **8**, 201.
5. Malghaes Alves, H., Coxon, D. T., Falshaw, C. P., Godtfredsen, W. O. and Ollis, W. D. (1970) *An. Acad. Brasil Cienc.* **42**, 45.
6. Previtera, L., Merola, D. and Monaco, P. (1985) *Phytochemistry* **24**, 1838.
7. Ma, W., Anderson, J. E., Chang, C., Smith, D. L. and McLaughlin, J. L. (1989) *J. Nat. Prod.* **52**, 1263.
8. Ma, W., Anderson, J. E., Chang, C., Smith, D. L. and McLaughlin, J. L. (1990) *Phytochemistry* **29**, 2698.
9. Takeda, K., Sakurawi, K. and Ishii, H. (1972) *Tetrahedron* **28**, 3757.