

NEW CONGENERS OF CYTOTOXIC NOR-DITERPENOID DILACTONES
IN PODOCARPUS NAGI: C₁₉ LACTONES OF AN α -PYRONE TYPE
AND A 7:8,9:11-DIENOLIDE TYPE

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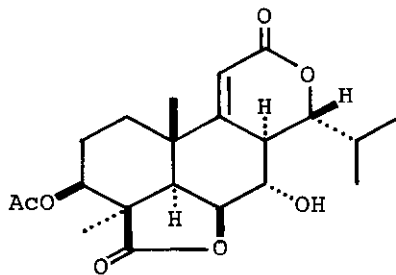
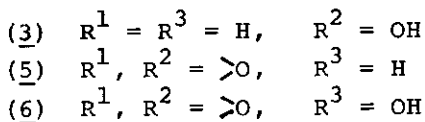
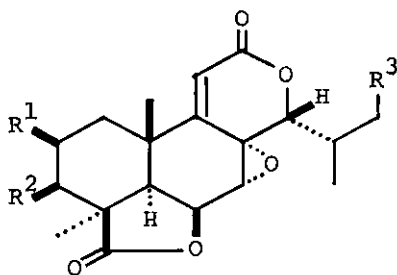
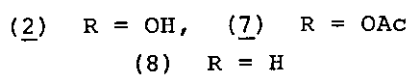
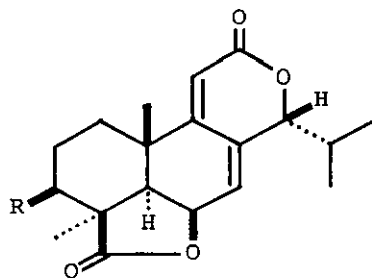
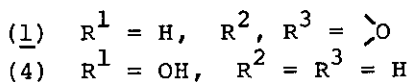
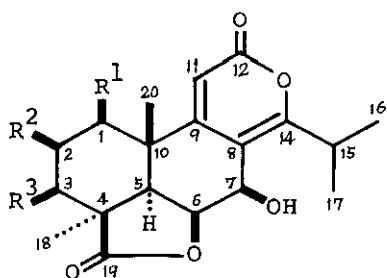
Two new members of the cytotoxic nor-diterpenoid dilactones were obtained from root bark of Podocarpus nagi and the structures were established by the correlation with the known lactones.

In the continuous studies of the cytotoxic components¹⁾ of Podocarpus plants, we have recently reported several new members of nor- or bisnor-diterpenoid dilactones^{2,3)} isolated from seeds and root bark of P. nagi (Thunberg) Pilger⁴⁾. This paper describes the structures of two additional active dilactones, (1) and (2), both of which originate from the root bark and include a C₁₉ carbon skeleton. The biologically active dilactones of Podocarpus species are classified into three major subgroups depending on

the types of the unsaturated lactone part on the B/C ring system: (A) α -pyrone (8:14,9:11-dienolide) type, (B) 7:8-epoxy-9:11-enolide type, and (C) 7:8,9:11-dienolide type. One of the new components described here belongs to the subgroup A, which was clarified by the spectral properties, and the other to the subgroup C, which was determined by derivation from a known type-B dilactone, nagilactone E (3), the most abundant component of the root bark⁵⁾.

The compound (1), mp 300° (sublime), $C_{19}H_{22}O_6$ ¹²⁾, gives the following spectral data: m/e (20 eV) 346 (M^+ , 2), 331 (6), 317 (6), 303 (73), 287 (23), 285 (23), 275 (46), 257 (35), 201 (42); λ_{max}^{EtOH} 299 nm (ϵ : 6800); ν_{max}^{KBr} 3400, 1770, 1695, 1635, 1550 cm^{-1} . The uv and ir spectra indicate the presence of an α -pyrone group (299 nm, 1695, 1635, 1550 cm^{-1}), a γ -lactone group (1770 cm^{-1}), and a hydroxyl group. The ¹H-nmr parameters (Table 1) of ring-B protons, H-5 α , H-6 α , and H-7 α , are very similar to those of nagilactone A (4) and other 7 β -hydroxylated type-A lactones^{2a,b)}. This fact establishes the position of the hydroxyl group to be at C-7. Additional two carbonyl proton signals at 3.32 and around 3.42 ppm reveal the presence of an epoxide group, which should be placed at 2 β :3 β -position by the comparisons with 2 β :3 β -epoxypodolide (5)^{2c,11)} and sellowin B (6)⁶⁾. The location of the epoxide group (2:3- but not 1:2-position) is fully supported by the ¹³C-nmr spectrum (Table 2). The carbon C-10 of 1 shows a comparable δ -value (35.8 ppm) with those (35~36 ppm) of nagilactone E (3) and other related lactones which are not oxygenated at C-1, but is more shielded by 3~6 ppm (β -effect) than those of

1-oxygenated lactones, e.g. nagilactone A. A reverse effect is observed on the C-20 (methyl carbon at C-10) chemical shift: It appears at 22.0 ppm in 1 (more generally, 21~25 ppm in other related lactones without oxygen function at C-1), while 1-oxygenated dilactones exhibit the signal at higher field (15~19 ppm)⁷⁾. The iso-propyl group is placed at C-14 from the δ -value (3.46ppm) and the multiplicity (symmetrical quintet) of the H-15 signal. Thus, 1-deoxy-2 β :3 β -epoxynagilactone A is given for the structure of 1.



(9)

The compound (2), mp 252°, C₁₉H₂₄O₅, m/e(20 eV) 332(M⁺,15), 289(45), 261(55), 243(100), 215(73); λ_{max}^{EtOH} 261 nm (ε:10100); ν_{max}^{KBr} 3440, 1760, 1610 cm⁻¹, possesses the 7:8,9:11-dienolide system (261 nm, 1610 cm⁻¹), a γ-lactone group, and a hydroxyl group [monoacetate (Ac₂O-pyridine): 7¹²]. The relationship of the functional protons, H-6, H-7, H-11, and H-14, around the dienolide system was proved by the nmr experiments: ¹H homo-spin decoupling and the comparisons with nagilactone F (8)⁵ (Table 1 and 2) and ponalactone A⁸). The significant allylic (H-7 ↔ H-14, 2.0 Hz) and homoallylic (H-6 ↔ H-14, 2.0 Hz) couplings observed in these cases (2 and 8) are well explained by the consideration of the mutual bond angles between the protons and the plane of the dienolide system¹³): H-6 and H-14 are located, approximately, in the plane and perpendicular to the plane, respectively. A broad signal around 3.65 ppm is assigned to the axial 3α-carbinyl proton, based upon the following chemical correlation of 2 with nagilactone E (3).

Hydrogenation of nagilactone E acetate with 10% Pd-C in ethanol⁹) (room temperature, 20 min.) gave a 7α-hydroxy compound (9)¹⁰, mp 272°(sublime), C₂₁H₂₈O₇¹², λ_{max}^{EtOH} 216 nm (ε:8900), ν_{max}^{CHCl₃} 3380, 1772, 1713, 1700^{sh} cm⁻¹. The stereochemistry of H-8 is assigned as α-orientation on the basis of the ¹H-nmr spectrum (Table 1; J_{7,8} = 11.2, J_{8,14} = 11.2, J_{8,11} = 2.5 Hz). The hydrogen attack at C-8 takes place at the α-side of the molecule on the epoxide ring cleavage, since the β-face would be severely hindered by the axial methyl group (at C-10) and

the γ -lactone group. Dehydration of 9 with POCl_3 in pyridine (75° , 5 hrs.) gave, in good yield, a 7:8,9:11-dienolide compound which was identical in all respects with the acetate (7) of the compound (2). It is noted that this transformation is the first case of the chemical correlation of the type-C dilactone with the type-B dilactone.

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Table 1. Proton nmr spectra of the lactones.

Lactones	H ¹	H ²	H ³	H ⁵	H ⁶	H ⁷	H ¹¹	H ¹⁴	H ¹⁵	H ¹⁶	H ¹⁷	CH ₃ [*]
(1) [#]	†	3.40 3.45 m	3.32 d (3.9)	1.75 d (5.9)	5.18 dd (5.9, 8.8)	5.62 d (8.8)	6.13 s	---	3.46 m (6.8)	1.22 d (6.8)	1.31 d (6.8)	1.50 1.89
(2) ^{##}	**	**	3.60 3.75 m	1.92 d (4.5)	5.04 td (2.0, 4.5, 4.5)	6.12 dt (2.0, 2.0, 4.5)	5.70 d (2.0)	4.82 q (2.0)	**	0.98 d (6.0)	1.19 d (6.0)	1.23 1.53
(4) [#]	4.1 br,m	**	**	1.83 d (5.7)	5.17 dd (5.7, 8.6)	5.67 d (8.6)	7.38 s	---	3.51 m (6.6)	1.26 d (6.6)	1.26 d (6.6)	1.33 2.01
(8) ^{##}	**	**	**	1.93 d (4.5)	5.04 td (2.0, 4.5, 4.5)	6.18 dt (2.0, 2.0, 4.5)	5.74 d (2.0)	4.85 q (2.0)	**	0.98 d (6.5)	1.19 d (6.5)	1.15 1.33
(9) ^{#,††}	**	**	5.15 5.35 br,m	2.26 d (5.4)	5.19 dd (5.4, 4.5)	4.73 dd (4.5, 11.2)	6.01 d (2.5)	4.42 dd (1.7, 11.2)	**	1.20 d (6.8)	1.24 d (6.8)	1.30 1.44

* Singlet methyl signals. ** Signals overlap each other. # Pyridine-d₅ as solvent.
 ## Chloroform-d as solvent. † H^{1α}: 1.78 dd (1.5, 14.5), H^{1β}: 2.35 dd (2.5, 14.5).
 †† H^{8α}: 3.01 dt (2.5, 11.2, 11.2).

Table 2. Carbon-13 nmr spectra of the lactones.

Carbon No.	Lactones				
	<u>1</u> pyr-d ₅	<u>2</u> CDCl ₃	<u>3</u> ⁷⁾ CDCl ₃	<u>4</u> ⁷⁾ pyr-d ₅	<u>8</u> CDCl ₃
1	33.2	29.9	28.9	71.0	30.1
2	52.3	28.8	28.4	28.0	17.6
3	53.1	72.4	73.0	29.8	27.9
4	44.4	45.0	44.3	43.2	42.9
5	49.4	49.7	45.4	50.1	47.6
6	75.3	73.3	73.0	74.9	71.9
7	60.3	121.1	53.6	60.5	121.8
8	111.4	135.4	58.7	111.9	134.2
9	170.5	158.3	158.2	169.5	159.2
10	35.8	35.7	36.4	41.6	35.2
11	105.1	111.8	116.8	108.0	112.0
12	162.2	163.9	163.4	162.7	164.3
14	166.0	82.9	82.9	166.0	83.1
15	29.6	29.8	26.8	29.6	29.8
16	20.0	15.2	16.5	20.2	15.3
17	20.8	19.7	21.3	20.7	19.7
18	24.8	23.5	24.2	24.6	25.0
19	178.1	179.9	179.3	181.2	180.9
20	22.0	22.3	21.7	16.1	24.3

References and Notes

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