NEW CONGENERS OF CYTOTOXIC NOR-DITERPENOID DILACTONES IN *PODOCARPUS NAGI*: C_{19} LACTONES OF AN α-PYRONE TYPE AND A 7:8,9:11-DIENOLIDE TYPE

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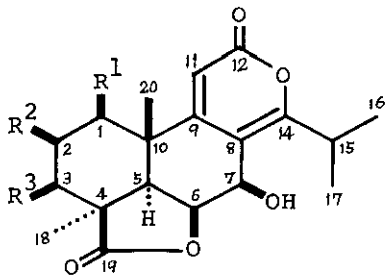
Two new members of the cytotoxic nor-diterpenoid dilactones were obtained from root bark of *Podocarpus nagi* and the structures were established by the correlation with the known lactones.

In the continuous studies of the cytotoxic components[1] 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) Pilger[4]. This paper describes the structures of two additional active dilactones, (1) and (2), both of which originate from the root bark and include a C_{19} carbon skeleton. The biologically active dilactones of *Podocarpus* species are classified into three major subgroups depending on

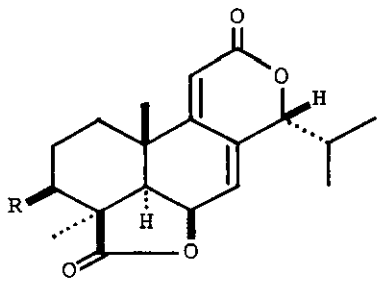
the types of the unsaturated lactone part on the B/C ring system: (A) α-pyrone (8:14,9:11-dienolide) type, (B) 7:8-epoxy-9:11-enolide type, and (C) 7:8,9:11-dienolide type. One of the new components described here belongs to the subgroup A, which was clarified by the spectral properties, and the other 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 bark[5].

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 ^{1}H-nmr parameters (Table 1) of ring-B protons, H-5α, H-6α, and H-7α, are very similar to those of nagilactone A (4) and other 7β-hydroxylated type-A lactones[2a,b]. This fact establishes the position of the hydroxyl group to be at C-7. Additional two carbinyl proton signals at 3.32 and around 3.42 ppm reveal the presence of an epoxide group, which should be placed at 2β:3β-position by the comparisons with 2β:3β-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 ^{13}C-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

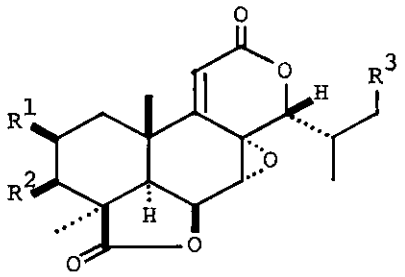
1-oxygenated lactones, e.g. nagilactone A. A reverse effect is observed on the C-20 (methyl carbon at C-10) chemical shift: It appears at 22.0 ppm in 1 (more generally, 21~25 ppm in other related lactones without oxygen function at C-1), while 1-oxygenated dilactones exhibit the signal at higher field (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-2β:3β-epoxynagilactone A is given for the structure of 1.



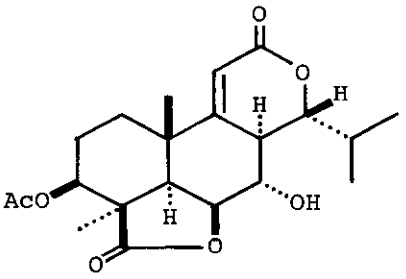
(1) R^1 = H, R^2, R^3 = =O
(4) R^1 = OH, R^2 = R^3 = H



(2) R = OH, (7) R = OAc
(8) R = H



(3) R^1 = R^3 = H, R^2 = OH
(5) R^1, R^2 = =O, R^3 = H
(6) R^1, R^2 = =O, R^3 = OH



(9)

The compound (2), mp 252°, $C_{19}H_{24}O_5$, 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 (Ac_2O-pyridine): 7[12)]]. 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 A[8)]. 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 system[13)]: 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 ethanol[9)] (room temperature, 20 min.) gave a 7α-hydroxy compound (9)[10)], mp 272°(sublime), $C_{21}H_{28}O_7$[12)], λ_{max}^{EtOH} 216 nm (ε:8900), $\nu_{max}^{CHCl_3}$ 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-d_5 as solvent.
Chloroform-d as solvent. † $H^{1\alpha}$: 1.78 dd (1.5, 14.5), $H^{1\beta}$: 2.35 dd (2.5, 14.5).
†† $H^{8\alpha}$: 3.01 dt (2.5, 11.2, 11.2).

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

Carbon No.	Lactones				
	1 pyr-d_5	2 $CDCl_3$	3[7] $CDCl_3$	4[7] pyr-d_5	8 $CDCl_3$
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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4 "Podocarpus nagi (Thunberg) Pilger" was found to be the correct name of the plant "nagi" by the courtesy of Professor Holger Erdtman of Royal Institute of Technology, Stockholm, (private communication). This name, therefore, will be used hereafter in place of the other, "P. nagi Zoll. et Moritzi", which has been improperly adopted in the previous reports of this series.

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11 Proton nmr parameters (pyr-d_5) of the ring-A protons of 2β:3β-epoxypodolide (5): H-1α 1.73 dd (1.5, 14.5); H-1β 2.23 dd (2.0, 14.5); H-2α 3.39 m; H-3α 3.27 d (4.0).

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