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Tagalsins I and J, Two Novel Tetraterpenoids from the Mangrove Plant, *Ceriops tagal*

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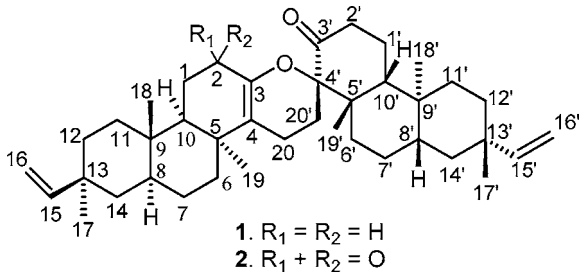
ABSTRACT



1. $R_1 = R_2 = H$
2. $R_1 + R_2 = O$

Two novel bisdolabrane backbone tetraditerpenoids, tagalsins I (1) and J (2), were isolated from the mangrove plant, *Ceriops tagal*, and their structures were elucidated by means of extensive two-dimensional NMR (COSY, HMQC, HMBC, and NOESY), IR, and MS data analysis. The stereochemistry of 1 was further determined by single-crystal X-ray diffraction.

The mangrove plants of the genus *Ceriops* (Rhizophoraceae), represented by two species, *Ceriops decandra* and *Ceriops tagal*, are widely distributed along the sea coast of southern China, India, and other Asian countries.[1] A decoction of the bark of *C. tagal* was used as a folk medicine to treat hemorrhages and malignant ulcers, and the water extract of the leaves of *C. decandra* possessed radical modulation activities in scavenging superoxide anions.[2] In mainland China, the local Chinese on Hainan Island used a decoction of the leaves of *C. tagal* for the treatment of malaria instead of the antimalaria drug, "quinine".[3] The *Ceriops* plants are rich in pentacyclic triterpenoids and tannins.[4] Recently, Anjaneyulu reported diterpenoids, ceriopsins A−F, from the roots of Indian *C. decandra*.[5−7] Our previous chemical study on the plant *C. tagal*, collected from a mangrove forest on Hainan Island, resulted in eight new dolabrane-type diterpenes, tagalsin A−H.[8] In a continuation of our systematic investigation on the chemical diversity of Chinese mangrove

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(1) Shukla, R. S.; Chandel, P. S. *Plant Ecology and Soil Science*; Chand and Company, Ltd.: New Delhi, 1991.
(2) Rastogi, R. P.; Mehrotra, B. N. *Compendium of Indian Medicinal Plants*; Publication and Information Directorate: New Delhi, 1991; Vol. 1.
(3) Lin, P.; Fu, Q. *Environmental Ecology and Economic Utilization of Mangroves in China*; Higher Education Press: Beijing, 1995; pp 1−95.
(4) Ghosh, A.; Misra, S.; Dutta, A. K.; Choudhury, A. *Phytochemistry* **1985**, *24*, 1725−1727.
(5) Anjaneyulu, A. S. R.; Rao, V. L. *Phytochemistry* **2002**, *60*, 777−782.
(6) Anjaneyulu, A. S. R.; Rao, V. L.; Lobkovsky, E.; Clardy, J. *J. Nat. Prod.* **2002**, *65*, 592−594.
(7) Anjaneyulu, A. S. R.; Rao, V. L. *Phytochemistry* **2003**, *62*, 1207−1211.
(8) Zhang, Y.; Deng Z.; Gao T.; Proksch, P.; Lin, W. *Phytochemistry* **2005**, in press.

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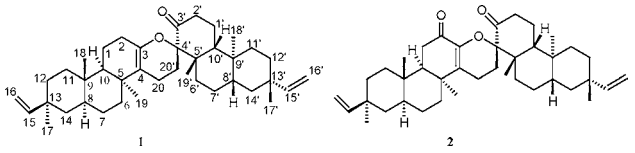

Figure 1. Structures of tagalsins I (**1**) and J (**2**).

plants, two novel bisdolabrane-type tetraterpenoids, tagalsins I (**1**) and J (**2**), were isolated from the same plant.

The stems and twigs of *C. tagal*[9] (3.3 kg) were air-dried and then ground. The powdered sample was percolated with 95% EtOH twice at room temperature. The extract was concentrated in a vacuum to afford a black residue (400 g). The residue was partitioned between H_2O and petroleum ether, and the petroleum ether extract (19 g) was subjected to a silica gel column eluting with petroleum ether−ethyl acetate as a gradient to obtain 10 fractions (A−J). Fraction B (0.7 g, 20:1) was chromatographed on silica gel with petroleum ether−CH_2Cl_2 (9:4) as an eluent to yield compounds **1**[10] (6.2 mg) and **2**[11] (4.3 mg). Compound **1** could be crystallized in a solvent of acetone−CH_2Cl_2 (10:1).

Tagalsin I (**1**) was isolated as a pale yellow crystal, and its molecular formula, $C_{40}H_{60}O_2$, was determined on the basis of HREIMS (*m*/*z* 572.4603, calcd for $[M]^+$ 572.4593) and ^1H and ^{13}C NMR data, which indicated 11 degrees of unsaturation. The IR absorptions at 3076, 1713, 1688, and 1636 cm^{-1} suggested the presence of carbonyl and vinyl groups. The ^1H NMR spectrum exhibited signals for six tertiary methyls at δ_H 0.81 (3H, s, H_3-18′), 0.88 (3H, s, H_3-18), 0.97 (3H, s, H_3-19), 1.01 (3H, s, H_3-17′), 1.03 (3H, s, H_3-17), and 1.19 (3H, s, H_3-19′), two monosubstituted vinylic groups at δ_H 5.82 (2H, dd, J = 10.5, 17.5 Hz, H-15, H-15′), 4.86 (2H, d, J = 10.7 Hz, H-16a, H-16a′), 4.94 (2H, d, J = 17.5 Hz, H-16b, H-16b′). Analysis of ^{13}C NMR, DEPT, and HMQC spectral data revealed the presence of 6 methyls, 18 methylenes, 6 methines, and 10 quaternary carbons, of which the olefinic carbons at δ_C 108.5 (t, C-16), 108.8 (t, C-16′), 151.1 (d, C-15′), and 151.5 (d, C-15) were attributed to two terminal double bonds; two quaternary vinylic carbons at δ_C 112.0 (s, C-4) and 146.8 (s, C-3) were assigned to a tetrasubstituted double bond, and in turn a carbon at δ_C 213.4 (s, C-3′) was assigned to a ketone group. Apart from three double bonds and a ketone group, the remaining elements of unsaturation were assumed to a heptacyclic skeleton in the molecule. A detailed two-dimensional NMR spectral analysis, including $^1H-^1H$ COSY, HMQC, and HMBC experiments, resulted in a gross structure of **1** (Figure 1) composed with two moieties of dolabrane-type diterpenes, partly related to tagalsins[8] and dolabradiene.[12,13]

The HMBC correlations from methyl protons H_3-19 to carbons C-5 (δ_C 37.9, s), C-6 (δ_C 37.8, t), C-10 (δ_C 52.3, d), and C-4, methyl protons H_3-18 to carbons C-11 (δ_C 35.6, t), C-9 (δ_C 36.4, s), C-8 (δ_C 41.8, d), and C-10, methyl protons H_3-17 to carbons C-13 (δ_C 36.4, s), C-14 (δ_C 39.0, t), C-12 (δ_C 31.9, t), and C-15 (δ_C 151.5, d), and olefinic proton H-15

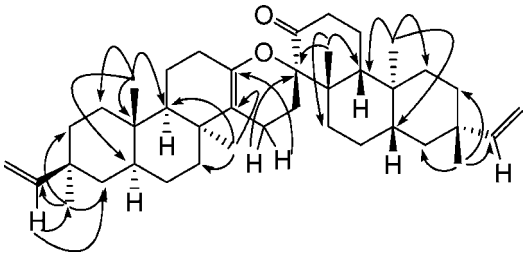

Figure 2. Main HMBC correlations of **1**.

to C-12, C-13, C-14, and C-17 (δ_C 23.0, q) in association with the COSY correlations and by comparison of its NMR data with those of tagalsins,[8] led to the assignment of the partial structure of rings A, B, and C in **1** as a dolabrane-type molecule, closely identical to dolabradiene,[13] with the exception of ring D where a double bond lay at C-4 in **1**. Furthermore, the COSY correlations between H_2-20 (δ 1.99, 2.05, m) and H_2-20′ (δ 1.91, 1.94, m), along with the HMBC correlation of H_2-20 with C-5, C-3 (δ 146.8, s), and C-4′ (δ 85.7, s), allowed the establishment of ring D as a 20-dihydropyran ring. Following the same manner as mentioned using two-dimensional NMR spectral analysis, the other partial structure for rings E, F, and G was established to be a dolabrane skeleton similar to rings A, B, and C. Meanwhile, the HMBC correlations between H_3-19′ (δ_H 1.19, s) and C-5′ (δ_C 43.5, s), C-10′ (δ_C 53.0, d), and C-4′ and between H_2-2′ (δ_H 2.36, 2.42) and C-3′ (δ_C 213.4, s), C-4′, C-1′ (δ_C 20.7, t), C-10′, and C-5′, together with COSY correlations between H_2-2′/H_2-1′ (δ_H 1.92, 1.94, m) and H_2-1′/H-10′ (δ_H 1.38, m), suggested the location of the ketone group at C-3′ and constructed a spiro-ring between rings D and E at an oxygenated quaternary carbon C-4′. The relative stereochemistry of **1** was mainly assigned by NOESY spectrum and by comparison of its NMR spectral data with those of tagalsins. The presence of NOE correlations between H_3-17 (δ_H 1.03, s)/H-8 (δ_H 1.33, m), H_3-19 (δ_H 0.97, s)/H-8, H_3-19/H-10 (δ_H 1.08, m), H_3-17′ (δ_H 1.01, s)/H-8′ (δ_H 1.70, m), H_3-19′ (δ_H 1.19, s)/H-8′, and H_3-19′/H-10′ (δ_H 1.38, m) and the absence of NOE correlation between H_3-18/H-8 and H_3-18′/H-8′ indicated *trans* fusions between A/B and F/G and *cis* fusions between C/D and E/F. The stereochemistry of the spiral configuration at C-4′ was still uncertain, since NOESY did not provided proton correlation between rings D and E. At this stage, X-ray crystallographic analysis of **1** was carried

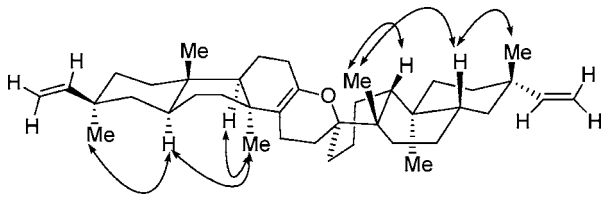

Figure 3. Main NOESY correlations of **1**.

Table 1. ^{1}H NMR Data of Tagalsins I (**1**) and J (**2**)

position	**1**	**2**	position	**1**	**2**
1	2.03 (m)	2.73 (d, 18.5)	1′	1.92 (m)	1.87 (m)
	2.19 (m)	2.81 (dd, 6.5, 18.5)		1.94 (m)	2.22 (m)
2	1.61 (m)		2′	2.36 (ddd, 5.0, 8.5, 19.0)	2.27 (ddd, 4.0, 7.5, 19.0)
	2.31 (m)			2.42 (ddd, 7.5, 7.5, 19.0)	2.37 (ddd, 8.5, 8.5, 19.0)
6	1.14 (m)	1.22 (m)	6′	1.32 (m)	1.33 (m)
	1.60 (m)	2.02 (ddd, 3.5, 3.5, 14.0)		1.67 (m)	1.69 (m)
7	1.03 (m)	1.14 (m)	7′	1.13 (m)	1.15 (m)
	1.05 (m)	1.16 (m)		1.66 (m)	1.68 (m)
8	1.33 (m)	1.39 (m)	8′	1.70 (m)	1.69 (m)
10	1.08 (m)	1.60 (d, 6.5)	10′	1.38 (m)	1.52 (m)
11	1.11 (m)	1.14 (m)	11′	1.16 (m)	1.30 (m)
	1.71 (m)	1.71 (m)		1.61 (m)	1.65 (m)
12	1.21 (m)	1.23 (m)	12′	1.21 (m)	1.22 (m)
	1.57 (ddd, 4.0, 14.0, 14.0)	1.54 (m)		1.48 (ddd, 4.0, 14.0, 14.0)	1.47 (ddd, 3.5, 14.0, 14.0)
14	0.98 (m)	1.01 (m)	14′	1.16 (m)	1.21 (m)
	1.35 (m)	1.37 (m)		1.22 (m)	1.24 (m)
15	5.82 (dd, 10.5, 17.5)	5.80 (dd, 10.5, 17.5)	15′	5.82 (dd, 10.5, 17.5)	5.81 (dd, 10.5, 17.5)
16	4.86 (d, 10.5)	4.86 (d, 10.5)	16′	4.94 (d, 17.5)	4.86 (d, 10.5)
	4.94 (d, 17.5)	4.94 (d, 17.5)		4.86 (d, 10.5)	4.94 (d, 17.5)
17	1.03 (s)	1.04 (s)	17′	1.01 (s)	1.01 (s)
18	0.88 (s)	0.69 (s)	18′	0.81 (s)	0.79 (s)
19	0.97(s)	1.17 (s)	19′	1.19 (s)	1.30 (s)
20	1.99 (m)	2.23 (m)	20′	1.91 (m)	1.87 (m)
	2.05 (m)	3.00 (m)		1.94 (m)	2.23 (m)

out. As shown in Figure 2, it became clear that the absolute configuration for C-4′ was assigned to the (*S*)-form. The molecular formula of tagalsin J (**2**) was determined as $C_{40}H_{58}O_3$ on the basis of HRFABMS (*m*/*z* 587.4449, calcd for $[M + H]^+$ 587.4458), with one oxygen atom more but two hydrogens less than that of **1**. The IR absorptions at 1711, 1674, and 1623 cm^{-1} suggested the presence of an unsaturated ketone and vinyl groups. The ^{1}H and ^{13}C NMR spectral data of **2** were closely comparable with those of **1**, except for the presence of an additional ketal carbon at δ_C 191.5 (s) and the absence of a methylene group assigned to C-2 of **1**, indicating that C-2 of **1** was replaced by a ketone group to conjugate with a double bond at C-3/C-4. The evidence of the olefinic carbon assigned to C-4 shifted downfield at δ_C 138.0 (s) in **2** in comparison with that of **1**, and a pair of geminal protons H_2-1 [δ_H 2.73 (d, J = 18.5 Hz); 2.81 (dd,

Table 2. ^{13}C NMR Data of Tagalsins I (**1**) and J (**2**)

position	**1**	**2**	position	**1**	**2**
1	25.1	35.2	1′	20.7	21.7
2	34.1	191.5	2′	36.4	36.3
3	146.8	146.1	3′	213.4	213.0
4	112.0	138.0	4′	85.7	86.2
5	37.9	38.4	5′	43.5	43.7
6	37.8	37.3	6′	25.5	25.9
7	27.1	26.7	7′	23.9	23.8
8	41.8	41.3	8′	33.1	32.8
9	36.4	38.0	9′	37.3	37.4
10	52.3	54.0	10′	53.0	52.1
11	35.6	33.9	11′	37.2	37.0
12	31.9	31.6	12′	32.3	32.2
13	36.4	36.2	13′	36.7	36.4
14	39.0	38.9	14′	40.3	40.2
15	151.5	150.9	15′	151.1	151.1
16	108.5	108.9	16′	108.8	108.8
17	23.0	23.0	17′	22.4	22.4
18	11.9	13.7	18′	14.2	14.2
19	33.5	33.1	19′	27.1	26.6
20	17.2	20.2	20′	18.5	20.1

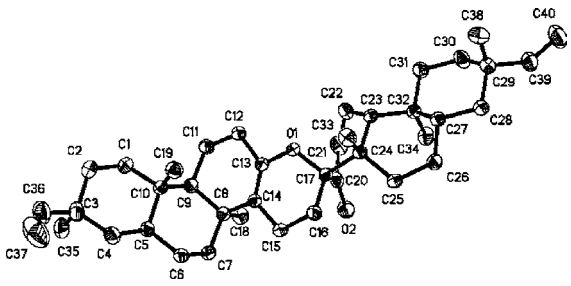

Figure 4. X-ray structure of tagalsin I (**1**).

(9) **Plant Material.** The stem and twig of *Ceriops tagal* were collected at the mangrove garden of Hainan Island, People's Republic of China, in July of 2002. The plant was identified by Prof. Lin Peng of Xia Men University. A voucher specimen (HN-032) was deposited at the State Key Laboratory of Natural and Biomimetic Drugs, Peking University.

(10) **Compound 1:** pale yellow crystals; mp 163−164×c1âC.; $[\alpha]^{25}_D$ + 4.6° (*c* 0.12, $CHCl_3$); IR (KBr) υ_{max} 3076, 2970, 2921, 2855, 1713, 1687, 1636, 1453, 1411, 1377, 1200, 1095, 1071, 1056, 1001, 905 cm^{-1}; ^{1}H and ^{13}C NMR see Table 1; HREIMS (*m*/*z* 572.4603 $[M]^+$, calcd 572.4593)

$J = 6.5, 18.5$ Hz)] showed COSY correlation with H-10 (δ_H 1.60, d, $J = 6.5$ Hz); the HMBC correlations between H_2-1 and the carbons at δ_C 191.5 (s, C-2), 146.1 (s, C-3), 38.0 (s, C-9), and 38.4 (s, C-5) supported the location of the ketal carbon at C-2. The stereochemistry of **2** was in agreement with that of **1** due to the similar NOESY correlations and by the comparison of NMR data with both compounds.

(11) **Compound 2:** white amorphous powder; $[\alpha]^{25}_D$ +37.6° (*c* 0.59, $CHCl_3$); IR (KBr) υ_{max} 3075, 2951, 2920, 2855, 1710, 1673, 1623, 1465, 1413, 1378, 1336, 1302, 1275, 1196, 1094, 1066, 999, 903 cm^{-1}; ^1H and ^{13}CNMR see Table 1; HRFABMS *m*/*z* 587.4449 (calcd for $C_{40}H_{59}O_3$, 587.4458).

(12) Nagashma, F.; Tori, M.; Asakawa, Y. 1991. *Phytochemistry* **1991**, *30*, 849−851.

(13) Koike, K.; Cordell, G. A.; Farnsworth, N. R. *Tetrahedron* **1980**, *36*, 1167−1172.

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Supporting Information Available: MS, HREIMS, and ^1H and ^{13}C NMR spectra involving two-dimensional NMR spectra of compounds **1** and **2**, and X-ray data of **1**. This material is available free of charge via the Internet at http://pubs.acs.org.

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