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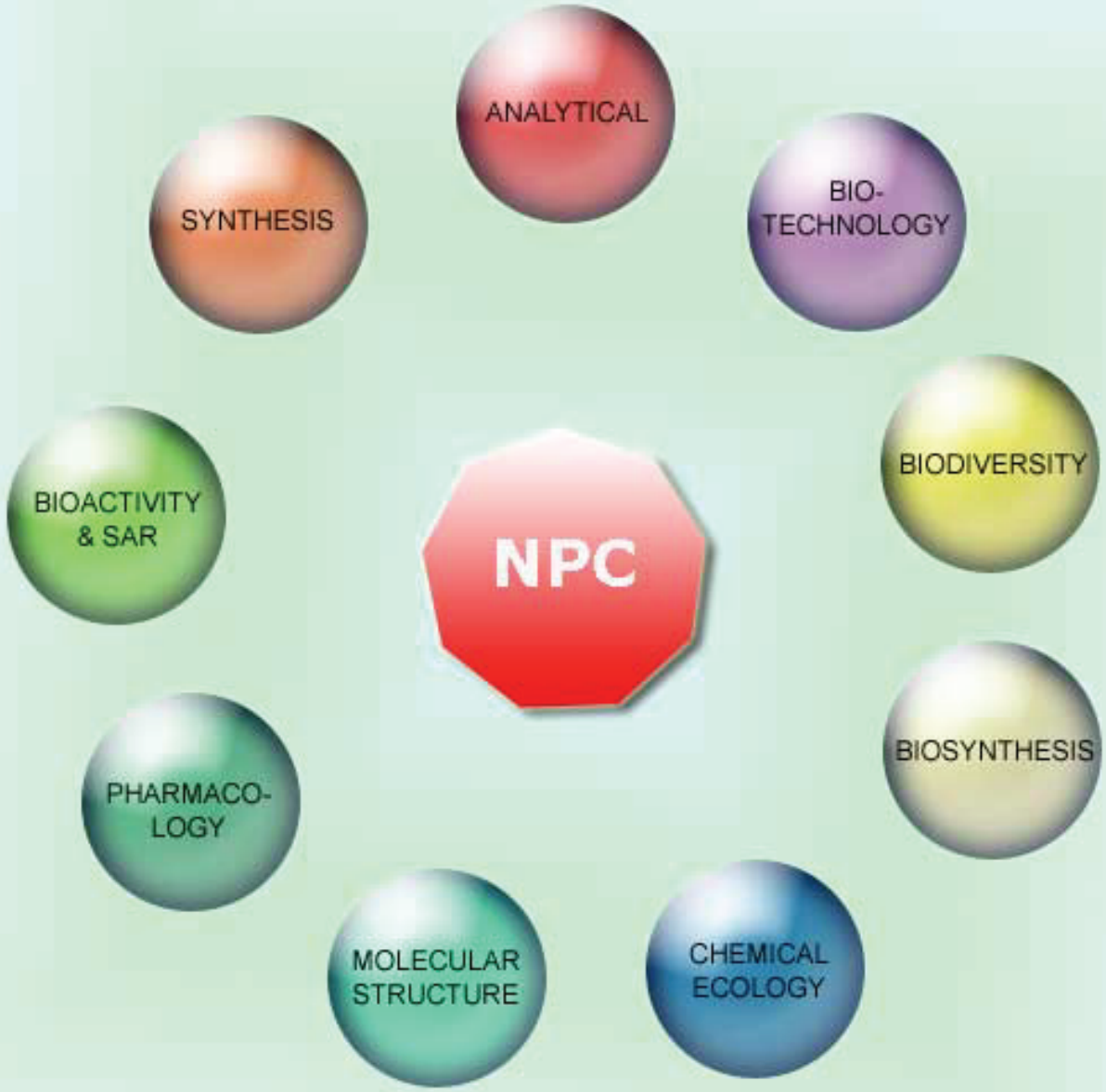

This Issue is Dedicated to
Professor Dr. Mahabir P. Gupta
on the Occasion of his 75th Birthday

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New Abietane-type Diterpenoids from the Bark of *Cryptomeria japonica*

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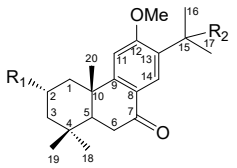
Two new abietane-type diterpenoids, 15-hydroxy-12-*O*-methylsugiol (**1**) and 2α-hydroxy-12-*O*-methylsugiol (**2**) were isolated from the methanol extract of the bark of *Cryptomeria japonica.* Their structures were elucidated on the basis of spectroscopic analysis and comparison of NMR data with those of known analogues. Compounds **2** showed 13.5% inhibition towards xanthine oxidase enzyme at the concentration of 75 μM.

Keywords: Cupressaceae, *Cryptomeria japonica*, Abietane, Diterpenoid, Traditional herbal medicine.

Cryptomeria japonica D. Don (Cupressaceae) is the only species of the monospecific genus *Cryptomeria* and is endemic to Japan, known as sugi (Japanese cedar) in Japanese [1]. It is a massive evergreen coniferous tree, growing up to 50 meters in height. Its wood is one of the best building materials and wood products due to the aromatic, reddish-pink in color, soft, lightweight but strong, and waterproof properties. This plant has been an important cultivated coniferous tree species in Taiwan since 1906. Previous phytochemical investigations of the leaves, heartwood, and barks of *C. japonica* led to the identification of diverse terpenoids, including monoterpenoids, sesquiterpenoids, and diterpenoids [2-24]. A variety of biological activities including cytotoxic [23], antifungal [24], antibacterial [25], antioxidant [26], anti-inflammatory [27], and insect antifeedant [28] and repellent [29] properties have been reported for the crude extracts or secondary metabolites from this species. While searching for the new chemical ingredients of the bark of *C. japonica*, we have already reported the isolation of a cytotoxic sesquarterpene (C_{35}), cryptotrione, with an unprecedented skeleton possessing a conjugated abietane and cadinane [30], ten abietane-type diterpenoids [31-33], and two sesquarterpenoids [34]. In this report, we describe the isolation and structure elucidation of two new abietane-type diterpenoids (Figure 1).



1 R_1= H, R_2= OH
2 R_1= OH, R_2= H
3 R_1= H, R_2= H

Figure 1: Structures of compounds **1** and **2**.

The MeOH extract of the bark of *C. japonica* was suspended in H_2O and partitioned between H_2O and EtOAc. The EtOAc-soluble portion was subjected to repeated silica gel column chromatography and semipreparative normal phase-HPLC to afford compounds **1** and **2**.

Compound **1** has the molecular formula $C_{21}H_{30}O_3$ as determined by a HR-EI-MS molecular ion at *m/z* 330.2200 and its ^{13}C NMR data, representing seven degrees of unsaturation. The ^1H NMR spectrum of **1** (Table 1) displayed signals for five methyl groups [δ_H 0.92, 0.98, 1.23, 1.59, and 1.60 (each 3H, s, Me-18, Me-19, Me-20,

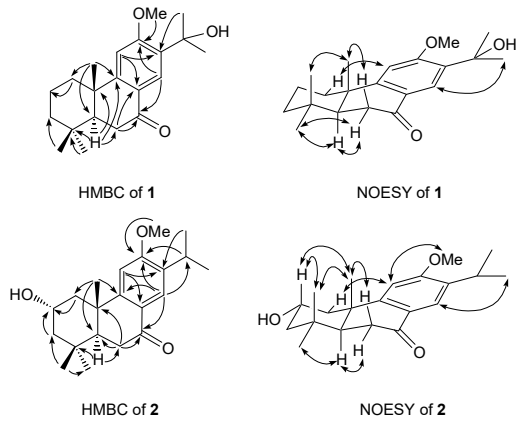


Figure 2: Selected HMBC and NOESY correlations of compounds **1** and **2**.

Table 1: ^{1}H and ^{13}H NMR data for **1** and **2** (400 and 100 MHz in $CDCl_3$).

	1		**2**	
No.	δ_C	δ_H	δ_C	δ_H
1	38.1	1.52 m, 2.28 brd (12.0)	50.7	1.26 dd (12.0, 12.0), 2.64 dd (12.0, 4.0)
2	19.2	1.68 m, 1.72 m	65.1	4.10 dddd (12.0, 12.0, 4.0, 4.0)
3	41.5	1.23 m, 1.52 m	46.7	1.51 dd (12.0, 12.0), 1.88 dd (12.0, 4.0)
4	33.6		34.9	
5	49.7	1.85 dd (13.6, 4.4)	48.9	1.85 dd (13.6, 4.0)
6	36.2	2.59 dd (18.4, 13.6), 2.69 dd (18.4, 4.4)	35.8	2.56 dd (18.0,13.6), 2.69 dd (18.0, 4.0)
7	197.4		197.6	
8	123.8		123.5	
9	157.0		155.0	
10	38.5		39.8	
11	105.5	6.82 s	104.1	6.73 s
12	160.8		161.5	
13	133.5		135.4	
14	125.1	7.96 s	125.7	7.87 s
15	72.3		26.6	3.22 sept (6.8)
16	29.9	1.59 s	22.4	1.19 d (6.8)
17	29.8	1.60 s	22.4	1.17 d (6.8)
18	32.8	0.92 s	32.7	0.98 s
19	21.7	0.98 s	22.6	1.03 s
20	23.6	1.23 s	26.6	1.26 s
-OCH_3	55.7	3.96 s	55.5	3.87 s

[a] Coupling constants are presented in Hz.

Me-16, and Me-17, respectively)], and two *para*-oriented benzene protons [δ_H 6.82 (1H, s, H-11) and 7.96 (1H, s, H-14)], one set of ABX coupling system neighboring to the carbonyl group [δ_H 1.85 (1H, dd, J = 13.6, 4.4 Hz, H-5), 2.59 (1H, dd, J = 18.4, 13.6 Hz, H_β-6), and 2.69 (1H, dd, J = 18.4, 4.4 Hz, H_α-6)], and one methoxy group [δ_H 3.96 (3H, s)]. The ^{13}C NMR experiments (CPD and DEPT 135) revealed 21 carbon signals, comprising five methyl, four methylene, one methine, two quaternary, one oxygenated quaternary, two olefinic methine, four tetra-substituted olefinic, one carbonyl, and one methoxy carbons. The UV absorption band at λ_{max} 276 nm and the IR absorption band at 1672 cm^{-1} indicated the presence of the benzoyl moiety [35]. A typical downshifted H_β-1 signal at δ_H 2.28 (1H, br d, J = 12.0 Hz) and 21 carbon signals in the ^{13}C NMR spectrum including 6 aromatic carbon signals (δ_C 105.5, 123.8, 125.1, 133.5, 157.0, and 160.8) hinted that **1** would be a dehydroabietane diterpene [21]. The ^{1}H and ^{13}C NMR data were similar to those of known compound, sugiol methyl ethe (**3**) [35], except for the signals of isopropyl moiety at C-13, replaced by an 2-hydroxyisopropyl substituent [C-15 (δ_C 72.3), Me-16 (δ_H 1.59, δ_C 29.9), and Me-17 (δ_H 1.60, δ_C 29.8)]. The HMBC correlation between Me-16/C-15 and the NOESY correlation between Me-17/H-14 (δ_H 7.96) (Figure 2) confirmed the above proposal. Based on these above evidences, compound **1** was elucidated as 15-hydroxy-12-*O*-methylsugiol.

The UV and IR spectra of compound **2** indicated the presence of benzoyl moiety (278 nm and 1672 cm^{-1}) and hydroxyl group (3409 cm^{-1}). The molecular formula was established to be $C_{21}H_{30}O_3$ from its HR-EI-MS molecular ion at *m/z* 330.2197, indicating seven degrees of unsaturation. The ^{1}H NMR spectrum of **2** (Table 1) showed resonances for three methyls [δ_H 0.98, 1.03, and 1.26 (each 3H, s, Me-18, Me-19, and Me-20, respectively], one oxymethine [δ_H 4.10 (1H, dddd, J = 12.0, 12.0, 4.0, 4.0 Hz, H-2)], two *para*-oriented benzene protons [δ_H 6.73 (1H, s, H-11) and 7.87 (1H, s, H-14)], one set of ABX coupling system neighboring to the carbonyl group [δ_H 1.85 (1H, dd, J = 13.6, 4.0 Hz, H-5), 2.56 (1H, dd, J = 18.0, 13.6 Hz, H_β-6), and 2.69 (1H, dd, J = 18.0, 4.0 Hz, H_α-6)], an isopropyl group [δ_H 1.17 (3H, d, J = 6.8 Hz, H-17), 1.19 (3H, d, J = 6.8 Hz, H-16), and 3.22 (1H, sept, J = 6.8 Hz, H-15)], and one methoxy group [δ_H 3.87 (3H, s)]. A typical downshifted H_β-1 signal of dehydroabietane diterpene at δ_H 2.64 (1H, dd, J = 12.0, 4.0 Hz) was also found [35]. 21 carbon signals were observed in the ^{13}C NMR spectrum of **2** and were differentiated by DEPT experiments as five methyl, three aliphatic methylene, two aliphatic methine, two aliphatic quaternary, one oxygenated methine, two olefinic methine, four quaternary olefinic, one carbonyl, and one methoxy carbons. By comparing the ^{13}C NMR data of **2** with that of sugiol methyl ether (**3**) [35], the major differences were the ^{13}C NMR chemical shifts of C-1–4, Me-18, Me-19, and Me-20 in ring A. An additional oxymethine (δ_H 4.10, H-2) showed ^{1}H-^{1}H correlations with Hα-1 (δ_H 1.26) and Hα-3 (δ_H 1.51) and NOESY correlation with Me-19 (δ_H 1.03) and Me-20 (δ_H 1.26) suggested that the hydroxyl group was attached on C-2 (δ_C 65.1) in α-equatorial orientation (Figure 2) [36]. From the above evidences, compound **2** was thus formulated as 2α-hydroxy-12-*O*-methylsugiol.

Xanthine oxidase is a key enzyme that catalyzes the oxidation of oxypurines to produce uric acid in the purine metabolic pathway and plays an important role in causing gout [37]. Since sugiol was reported as a potential inhibitor of xanthine oxidase by Lin *et al*. [38], compounds **1** and **2** were evaluated their xanthine oxidase inhibitory activity [39]. Compounds **2** showed 13.5% inhibition towards xanthine oxidase enzyme at the concentration of 75 μM, while compound **1** was inactive.

Experimental

General experimental procedures: Optical rotations were measured using a JASCO DIP-180 digital polarimeter. UV and IR spectra were recorded on a Shimadzu UV-1601PC and a Perkin-Elmer 983 G spectrophotometer, respectively. ^{1}H- and ^{13}C-NMR spectra were recorded in $CDCl_3$ at room temperature on a Varian-Unity-Plus-400 spectrometer with residual solvent signals as internal reference. Chemical shifts are given in δ values and coupling constants (J) are given in hertz (Hz). EI-MS and HR-EI-MS were measured with a Jeol-JMS-HX300 mass spectrometer. Silica gel (230–400 mesh; Merck & Co., Inc.) was used for column chromatography (CC), and pre-coated silica gel plates (60 F-254; Merck & Co., Inc.) were used for TLC. Semi-preparative HPLC was performed using a normal phase column (Purospher STAR Si, 5 mm, 250×10 mm; Merck & Co., Inc.) on a LDC Analytical-III system.

Plant material: The bark of *C. japonica* D. Don was collected in Sitou, Taiwan in June, 2000. The plant material was identified by Prof. Shao-Shun Ying, Department of Forestry, National Taiwan University. A voucher specimen (TCF13443) has been deposited at the Herbarium of the Department of Forestry, NCHU, Taiwan.

Extraction and isolation: The air-dried bark of *C. japonica* (16.0 kg) was extracted by maceration with MeOH (100 L) three times

(7 days each time) at room temperature. The combined MeOH extract was concentrated under reduced pressure to afford a crude extract (480 g), which was suspended in H_2O (1 L), and then partitioned between H_2O and EtOAc (1 L) for three times. The EtOAc soluble fraction (430 g) was subjected to a silica gel (4.0 kg) column, eluted with *n*-hexane–EtOAc and EtOAc–MeOH mixtures to give 11 fractions, fr. 1 (2.6 g), 2 (29.4 g), 3 (47.8 g), 4 (92.4 g), 5 (21.6 g), 6 (18.1 g), 7 (22.5 g), 8 (35.8 g), 9 (19.2 g), 10 (44.2 g), and 11 (72.2 g). Fr. 3 from hexane/AcOEt (9:1) elution (47.8 g) was further purified through a silica gel column (7×60 cm), eluted with hexane/CH_2Cl_2 (1:0 – 0:1) to obtain nine fractions, 3A – 3I. Further purification of subfraction 3E by HPLC gave **1** (2.1 mg) using hexane/AcOEt (9:1). Fr. 4 from *n*-hexane–EtOAc (4:1) elution (92.4 g), was further purified through a silica gel column (7×60 cm), eluted with a gradient mixture of CH_2Cl_2–EtOAc (100:1 to 0:1) to obtain sixteen fractions, 4A–4P. Further purification of subfraction 4F by HPLC afforded **2** (1.9 mg) using *n*-hexane–EtOAc (4:1).

15-Hydroxy-12-*O*-methylsugiol (1)
Gum.
$[\alpha]^{25}_D$: +32.3 (*c* 0.50, $CHCl_3$).
IR (KBr) ν_{max}: 3462, 1672, 1600, 1495, 1460, 1261, 1208, 1036, 950, 850, 731 cm^{-1}.
UV (MeOH) λ_{max} (log ε): 229 (4.60), 276 (4.60) nm.
^1H and ^{13}C NMR data: Table 1.
EI-MS (70 eV) *m/z* (rel. int.): 330 $[M]^+$(2), 315 ($[M–CH_3]^+$, 100), 312 ($[M–H_2O]^+$, 47), 297 (40), 255 (8), 229 (15), 215 (10).
HR-EI-MS: *m/z* 330.2200 (calcd for $C_{21}H_{30}O_3$ 330.2196, $[M]^+$).

2α-Hydroxy-12-*O*-methylsugiol (2)
Gum.
$[\alpha]^{25}_D$: +17.2 (*c* 0.40, $CHCl_3$).
IR (KBr) ν_{max}: 3409, 1672, 1593, 1493, 1460, 1255, 1043 cm^{-1}.
UV (MeOH) λ_{max} (log ε): 229 (4.68), 278 (4.58) nm.
^1H and ^{13}C NMR data: Table 1.
EI-MS (70 eV) *m/z* (rel. int.): 330 $[M]^+$(78), 315 ($[M–CH_3]^+$, 100), 297 ($[M –CH_3–H_2O]^+$, 60), 255 (19), 217 (17), 175 (25).
HR-EI-MS: *m/z* 330.2197 (calcd for $C_{21}H_{30}O_3$ 330.2196, $[M]^+$).

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