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Two New Seco-Abietanoids with Xanthine Oxidase Inhibitory Activity from *Cryptomeria japonica* D. Don

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Abstract: Two new seco-abietanoids, 12-hydroxy-6-nor-5,6-secoabieta-8,11,13-trien-7-oic acid (**1**) and 7-hydroxy-7,8-secoabieta-8,12-diene-6,11,14-trione (**3**), together with one known seco-abietanoid, 12-hydroxy-6-nor-5-oxo-5,6-secoabieta-8,11,13-trien-7-al (**2**), were isolated from the methanol extract of the bark of *Cryptomeria japonica*. Their structures were elucidated by mean of spectroscopic analysis, as well as on comparison of NMR data with those of known analogues. At a concentration of 50 µM, compounds **1**–**3** showed inhibitory activity toward xanthine oxidase by 38.2%, 55.9%, and 23.0%, respectively.

Keywords: Cupressaceae; *Cryptomeria japonica*; bark; diterpenoid. © 2021 ACG Publications. All rights reserved.

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1. Introduction

Cryptomeria japonica D. Don belongs to monotypic genus of Cypressaceae, endemic to Japan, and is called sugi (Japanese cedar) in Japanese [1]. It is a large evergreen coniferous tree with a height of up to 50 meters. Due to its fast growth rate (20 ft in 20 years), *C. japonica* is one of the most important conifer species in the plantation forestry in Japan. This plant has been widely cultivated in the mountainous areas of Taiwan since 1906 and has become one of the important forestry resources, comprising 39 thousand ha (~13%) of plantation stands [2]. Its wood exhibits aromatic, redidsh-pink in color, soft, lightweight but strong, and waterproof characteristics, so it is one of the excellent materials for construction or wood products in Taiwan. The leaves, heartwood, barks, and roots of *C. japonica* contain diverse chemical constituents including monoterpenoids, sesquiterpenoids, and diterpenoids, and flavanols [3-22]. The crude extracts and secondary metabolites of this species have been reported to have antibacterial [16, 22-24], antifungal [17], cytotoxic [18], anti-inflammatory [19], anti-androgenic [20], antioxidant, anti-lipase, melanin-biosynthesis-inhibition [24], angiotensin I-converting enzyme (ACE) inhibition [21], and insect antifeedant [25] and repellent [12] avtivities. The flavanols, catechin and procyanidin B3 with ACE inhibitory activity were purified from the bark of *C. japonica*. The diterpenes, 6,12-dihydroxyabieta-5,8,11,13-tetraen-7-one, sugiol, ferruginol, and 5-epixanthoperol were identified from the barks of *C. japonica* and were found to inhibit the activity of the androgen receptor (AR) in human prostate cancer (PCa) 22Rv1-derived 103E cells [20]. In addition, ferruginol and isopimaric acid were characterized from the barks of *C. japonica*, showing antibacterial activity against *Escherichia coli*, *Staphylococcus aureus*, methicillin-resistant *S. aureus*, *S. epidermidis*, and *Enterococcus faecalis* [22]. The current study was attempted to search the bioactive compounds from the bark of *C. japonica* and had already reported the isolation of one sesquarterpenoids [26] and twelve abietane-type diterpenoids [27-29]. Herein, the isolation and structure elucidation of two new and one known secoabietane-type diterpenoids and their xanthine oxidase inhibitory activity are described.

2. Materials and Methods

2.1. General Experimental Procedures

Optical rotations were obtained on a JASCO DIP-180 digital polarimeter. A Shimadzu UV-1601PC spectrometer was used to obtain the UV spectra. IR spectra were recorded on a Perkin-Elmer 983 G spectrophotometer. The NMR experiments were performed on a Varian-Unity-Plus-400 spectrometer. The ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ at room temperature, and the residual solvent signals were used as internal references. All chemical shifts (δ) are given in ppm with reference to solvents, and coupling constants (*J*) are given in hertz (Hz). A Jeol-JMS-HX300 mass spectrometer was used to obtain EI-MS and HR-EI-MS. Column chromatography (CC) was carried out on silica gel (230–400 mesh; Merck & Co., Inc.). The fractions were monitored by TLC on pre-coated silica gel plates (Si 60 F_{254}; Merck & Co., Inc.). Semi-preparative HPLC separations were performed on a LDC Analytical-III apparatus using a normal phase column (Purospher STAR Si, 5 mm, 250×10 mm; Merck & Co., Inc.).

2.2. Collection and Identification of Plant Materials

The bark of *C. japonica* was collected in Sitou, Taiwan in June, 2000. A voucher specimen (TCF13443) deposited at the Herbarium of the Department of Forestry, NCHU, Taiwan, was authenticated by Dr. Yen-Hsueh Tseng at Department of Forestry, National Chung-Hsing University (NCHU).

*2.3. Extraction and Isolation of Compounds **1** – **3***

The air-dried bark of *C. japonica* (16.0 kg) was extracted by maceration in MeOH (100 L×3) for 7 days each time at room temperature. After filtration, the combined extract was evaporated to dryness, and the crude extract (480 g) was suspended in H_2O (1 L). The liquor was partitioned with EtOAc and *n*-BuOH,

successively. The EtOAc soluble fraction (430 g) was subjected to a silica column chromatography, eluted with *n*-hexane–EtOAc and EtOAc–MeOH gradients of increasing polarity. 120 fractions (500 ml each) were collected and were pooled in 11 main 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) on the basis of TLC result. Fr. 4 was further purified by a silica gel column (7x60 cm) eluted with increasing percentage (1-50%) of EtOAc in CH_2Cl_2 to obtain sixteen fractions, 4A-4P. Subfraction 4H was further purified by semi-preparative HPLC using *n*-hexane–EtOAc (5:1) to afford **2** (3.8 mg) and **3** (7.3 mg). Subfraction 4I was further purified by semi-preparative HPLC using *n*-hexane–EtOAc (5:1) to afford **1** (6.6 mg).

2.4. Xanthine Oxidase Inhibition Assay

The XO inhibition assay was performed according to the method of Chen et al. with some modifications [24]. Briefly, 20 μL of the sample solution (final concentration was 50 μM) was added to 35 μL of 0.1 mM phosphate buffer (pH=7.5) and 30 μL of enzyme solution (0.01 units/ml in 0.1 mM phosphate buffer, pH=7.5) and the mixture was pre-incubated at 25 °C for 15 min. Then, 60 μL of substrate solution (150 mM xanthine in the same buffer) was added and was further incubated at 25 °C for 30 minutes. The reaction was stopped by adding 50 μL of 2 N HCl, and the absorbance was measured at 290 nm. The inhibitory activity was calculated based on the following equation: XO Inhibition (%) = (1-B/A) × 100, where A and B are the activities of the enzyme without and with test sample. Quercetin, a known inhibitor of xanthine oxidase, was used as a positive control, whereas negative control was performed without any inhibitor.

2.5. Spectroscopic Data

*12-Hydroxy-6-nor-5,6-secoabieta-8,11,13-trien-7-oic acid (**1**)*: Gum. $[\alpha]_D^{25}$ +16.2 (*c* 0.4, $CHCl_3$) . UV (MeOH) λ_{max} (log *ε*): 232 (3.92), 281 (3.67) nm. IR (KBr) ν_{max}: 3200-2500 (carboxylic acid),1692, 1613, 1580, 1467, 1394, 1268, 1175, 1122, 744 cm^{-1}. ^1H and ^{13}C NMR: Table 1. EI-MS (70 eV) *m/z* (rel. int.): 304 $[M]^+$ (99), 289 $[M–CH_3]^+$ (56), 287 (100), 271 (97), 243 (11), 219 (54), 207 (26), 193 (14) . HR-EI-MS: *m/z* 304.2041 (calcd for $C_{19}H_{28}O_3$ 304.2039, $[M]^+$).

*7-Hydroxy-7,8-secoabieta-8,12-diene-6,11,14-trione (**3**)*: Gum. $[\alpha]_D^{25}$: –4.3 (*c* 0.5, $CHCl_3$). UV (MeOH) λ_{max} (log *ε*): 258 (3.94) nm. IR (KBr) ν_{max}: 3476, 1719, 1646, 1539, 1460, 1241, 1056, 923 cm^{-1}. ^1H and ^{13}C NMR: Table 1. EI-MS (70 eV) *m/z* (rel. int.): 332 $[M]^+$ (9), 316 (55), 301 (100), 287 (34), 273 (60), 231 (23), 217 (24), 203 (44), 178 (39), 161 (28), 149 (25). HR-EI-MS: *m/z* 332.1981 (calcd for $C_{20}H_{28}O_4$ 332.1988, $[M]^+$).

3. Results and Discussion

3.1. Structure Elucidation

A MeOH extract of the bark of *C. japonica* was partitioned successively with EtOAc and *n*-BuOH. From EtOAc-soluble fraction, two new seco-abietanoids, 12-hydroxy-6-*nor*-5,6-secoabieta-8,11,13-trien-7-oic acid (**1**) and 7-hydroxy-7,8-secoabieta-8,12-diene-6,11,14-trione (**3**), together with one known seco-abietanoid, 12-hydroxy-6-*nor*-5-oxo-5,6-secoabieta-8,11,13-trien-7-al (**2**), were purified through repeated silica gel column chromatography and normal phase semipreparative HPLC (Figure 1).

Compound **1** was assigned the molecular formula $C_{19}H_{28}O_3$ as deduced from the HR-EI-MS molecular ion at *m/z* 304.2041 and its ^{13}C NMR data, representing six degrees of unsaturation. Its UV and IR spectra showed the presence of carboxylic acid (3200-2500, 1692 cm^{-1}), and aromatic (1613, and 1467 cm^{-1}) groups. The ^1H NMR spectrum of **1** (Table 1) showed resonances for three tertiary methyls [δ_H 0.47, 0.88, and 1.45 (each 3H, s, Me-18, Me-19, and Me-20, respectively)], an isopropyl group attached to a phenyl group [δ_H 1.24 (3H, d, *J* = 7.0 Hz, Me-16), 1.26 (3H, d, *J* = 7.0 Hz, Me-17) and 3.13 (1H, sept, *J* = 7.0 Hz, H-15)], and two *para* aromatic protons [δ_H 6.84 (1H, s, H-11) and 7.38 (1H, s, H-14)]. There are 19 carbon signals containg 6 aromatic carbon signals (δ_C 114.1, 124.3, 128.7, 130.3, 146.4, and 154.1) and one

conjugated carboxylic acid carbonyl carbon signals (δ_C 176.8) in the ^{13}C NMR spectrum. Accounting for the total six degrees of unsaturation in **1**, the remaining one degrees of unsaturation hinted that **1** would be a seco-norabietane diterpene [29]. Comparing the ^{1}H- and ^{13}C-NMR data of **1** with those of the known compound, 12-hydroxy-6,7-seco-abieta-8,11,13-triene-6,7-dioic acid [23], indicated that both compounds exhibited identical structure in ring C. The differences were that the another ^{13}C-NMR signal of carboxylic acid carbonyl carbon [δ_C 174.4 (s, C-6)] attached on C-5 was absent in **1** and the ^{1}H- and ^{13}C-NMR signals of downfield methine [δ_H 3.36 (1H, s and δ_C 58.9 (t, C-5)] were replaced by that of an AX methylene [δ_H 1.41 (1H, d, J = 14.0 Hz, H-5$_\beta$), 2.13 (1H, d, J = 14.0 Hz, H-5$_\alpha$) and δ_C 49.9 (t, C-5)].

1 R_1=2H, R_2=CO_2H
2 R_1=O, R_2=CHO

3

Figure 1. Structures of compounds 1–3 from *C. japonica*

Table 1. ^{1}H and ^{13}C NMR data for compounds **1** and **3** (at 400 and 100 MHz in $CDCl_3$, δ in ppm, J in Hz)

	1		**3**	
Position	**δ_C**	**δ_H**	**δ_C**	**δ_H**
1	39.1	2.23 br d (14.0), 1.38 m	31.7	1.83 m, 1.98 m
2	20.0	1.56 m, 1.58 m	18.3	1.62 m, 1.63 m
3	40.1	1.20 m, 1.24 m	34.4	1.17 m, 1.82 m
4	31.6		33.9	
5	49.9	1.41 d (14.0), 2.13 d (14.0)	55.7	3.67 s
6			212.5	
7	176.8		72.4	4.20 dd (15.6, 4.0), 4.31 br d (15.6)
8	124.3		132.6	6.62 s
9	146.4		153.3	
10	39.4		40.2	
11	114.1	6.84 s	188.6	
12	154.1		132.3	6.43 s
13	130.3		153.5	
14	128.7	7.38 s	187.4	
15	27.0	3.13 sept (7.0)	26.5	2.99 sept (6.8)
16	22.7	1.24 d (7.0)	21.5	1.12 d (6.8)
17	22.6	1.26 d (7.0)	21.3	1.12 d (6.8)
18	27.8	0.47 s	29.9	0.79 s
19	33.1	0.88 s	28.0	0.77 s
20	33.3	1.45 s	28.8	1.09 s
7-OH				3.22 t (4.0)

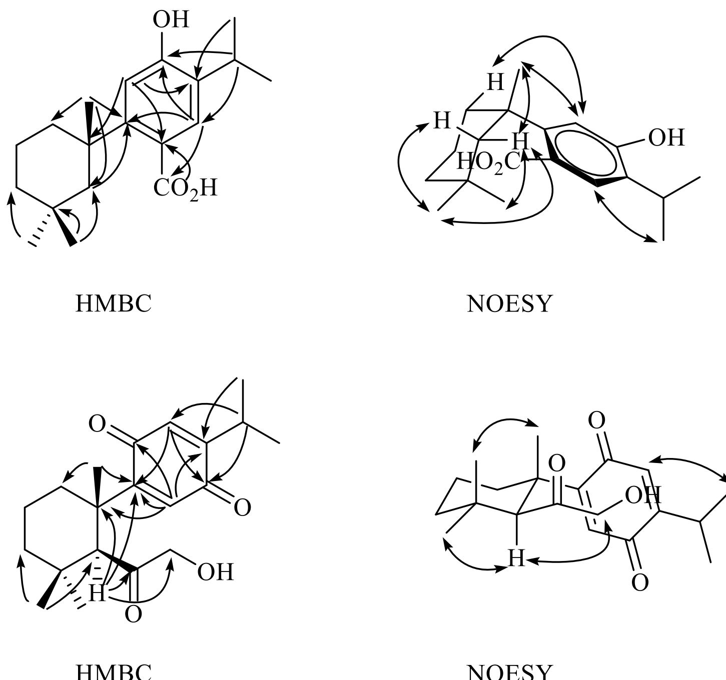

Figure 2. Selected HMBC and NOESY correlations of compounds **1** and **3**

The HMBC correlations between Me-18, Me-19, and Me-20/C-5 and H-5$_{\beta}$/C-9 further confirmed that **1** was a 6-*nor*-5,6-secoabietane diterpene. Furthermore, the HMBC correlations between H-11/C-10, C-12, and C-13; H-14/C-7, C-9, and C-12; H-15/C-12 and C-14; Me-16/C-13; Me-18/C-3; Me-19/C-4; and Me-20/C-1 and C-9 (Figure 2) helped to construct the planar structure of **1**. The skeleton of dehydroabietane-type dietrpene is rigid, although the two methyl groups, Me-19 and Me-20, are positioned in 1,3-diaxial orientations with steric hindrance. When the single bond between C-6 and C-7 of dehydroabietane was broken, the skeleton was thus changed to be 6,7-secoabeitane type with a flexible cyclohexane structure in ring A. The conformation of cyclohexane will be inverted to the most stable conformer. H-5$_{\alpha}$ showed the NOESY correlations between Me-18, Me-19, and Me-20 confirmed that H-5α, Me-19, and Me-20 were all in equatorial orientation in **1**, instead of axial orientation in dehydroabietane. As shown in Figure 2, both Me-18 and ring C were situated in the axial direction. A special highfield proton signal at δ_H 0.47 was assigned as Me-18, which received the anisotropic effect from the aromatic ring of ring C. The proposed structure was also supported by the fragment ion peaks in the EI-MS at *m/z* 289 $[M-CH_3]^+$, *m/z* 287 $[M-OH]^+$, *m/z* 272 $[M-CH_3-OH]^+$, and *m/z* 271 $[M-CH_3-H_2O]^+$. From the above evidences, compound **1** was thus elucidated as 12-hydroxy-6-*nor*-5,6-secoabieta-8,11,13-trien-7-oic acid. The compound **1** was isolated from nature for the first time. However, it was synthesized and patented earlier by Yang et al. [30].

The HR-EI-MS of compound **3** showed a molecular ion at *m/z* 332.1981, consistent with the molecular formula of $C_{20}H_{28}O_4$, indicating seven degrees of unsaturation. The IR spectrum showed the presence of hydroxyl (3476 cm^{-1}), isolated carbonyl (1719 cm^{-1}) and conjugated carbonyl (1646 cm^{-1}) groups. The ^{13}C NMR signals for two carbonyl groups [δ_C 187.4 (s) and 188.6 (s)] and two double bonds [δ_C 132.3 (d), 132.6 (d), 153.3 (s) and 153.5 (s)] and the UV maximum at 258 nm indicated that **3** should include a di-substituted *p*-quinone moiety [14]. The ^1H NMR spectrum of **3** (Table 1) showed resonances for three tertiary methyl groups [δ_H 0.77, 0.79, and 1.09 (each 3H, s, Me-18, Me-19, and Me-20, respectively], one methine proton adjacent to carbonyl group [δ_H 3.67 (1H, s)], an isopropyl group attached on a quinone ring [δ_H 1.12 (6H, d, J = 6.8 Hz, Me-16,17) and 2.99 (1H, sept, J = 6.8 Hz, H-15)], two quinone protons [δ_H 6.43 (1H, s, H-12) and 6.62 (1H, s, H-8)], and one set of ABX type methylene protons [δ_H 3.22 (1H, t, J = 4.0 Hz, 7-OH, exchanged with D_2O), 4.20 (1H, dd, J = 15.6, 4.0 Hz, H-7$_a$) and 4.31 (1H, br d, J = 15.6 Hz, H-7$_b$)]. After subtracting the six degrees of unsaturation attributable to the *p*-benzoquinone unit and one

carbonyl group, the remaining one unsaturation indicated that compound **3** would be a seco-abietane derivative. By comparison of the ^{1}H- and ^{13}C-NMR data with those of the known compound, (rel-1*S*,2*R*)-(4'-isopropyl-1,3,3-trimethyl'3',6'-dioxo-bicyclohexyl-1',4'-dien-2-yl)-acetic acid [15], indicated that both compounds exhibited identical *p*-benzoquinone moiety in ring C. The HMBC correlations between H-8/C-9, C-10, C-11, and C-13; H-12/C-9 and C-14; H-15/C-12 and C-14; Me-16/C-13; Me-19/C-4 and C-5; and Me-20/C-1, C-5, C-9 and C-10 (Figure 2) confirmed the planar structure of **3**. Additionally, a 2-hydroxyacetyl moiety attached on C-5 in β orientation, which was assured by both the HMBC correlations between H-5/C-9, C-10, C-6, and C-7 and the NOESY correlations H-5/H-7 and Me-18 (Figure 2). The proposed structure was also supported by the fragment ion peaks in the EI-MS at *m/z* 301 $[M\text{-}CH_2OH]^+$ and *m/z* 273 $[M\text{-}COCH_2OH]^+$. From the above evidences, compound **3** was determined as 7-hydroxy-7,8-secoabieta-8,12-diene-6,11,14-trione. Complete ^{1}H- and ^{13}C-NMR chemical shifts were established by ^{1}H-^{1}H COSY, HMQC, HMBC, and NOESY spectra.

3.2. Xanthine Oxidase Inhibitory Activity

Xanthine oxidase is a key enzyme in the pathway of purine metabolism. It catalyzes the oxidation of oxypurines to produce uric acid and plays an important role in causing gout. The enzyme inhibitory activities of compounds **1**-**3** were evaluated [31]. At the concentration of 50 μM, compounds **1**–**3** inhibited xanthine oxidase activity by 38.2, 55.9, and 23.0%, respectively, whereas the positive control, quercetin, inhibited xanthine oxidase activity by 35.1%.

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Supporting Information

Supporting information accompanies this paper on http://www.acgpubs.org/journal/records-of-natural-products

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