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.
1. Introduction

Cryptomeria japonica D. Don belongs to monotypic genus of Cypselaceae, 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, reddish-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] activities. 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 sesquiterpenoids [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 spectrophotometer 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 1H and 13C NMR spectra were recorded in CDCl3 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 F254; 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 H2O (1 L). The liquor was partitioned with EtOAc and n-BuOH,
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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 CH2Cl2 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) x 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-secoabiet-8,11,13-trien-7-oic acid (I): Gum. [α]D25 +16.2 (c 0.4, CHCl3). UV (MeOH) λmax (log e): 232 (3.92), 281 (3.67) nm. IR (KBr) νmax: 3200-2500 (carboxylic acid), 1692, 1613, 1580, 1467, 1394, 1268, 1175, 1122, 744 cm⁻¹. 1H and 13C NMR: Table 1. EI-MS (70 eV) m/z (rel. int.): 304 [M]+ (99), 289 [M–CH3]+ (56), 287 (100), 271 (97), 243 (11), 219 (54), 207 (26), 193 (14). HR-EI-MS: m/z 304.2041 (calcd for C20H28O3, 304.2039, [M]+).

7-Hydroxy-7,8-secoabiet-8,12-diene-6,11,14-trione (3): Gum. [α]D25 −4.3 (c 0.5, CHCl3) UV (MeOH) λmax (log e): 258 (3.94) nm. IR (KBr) νmax: 3476, 1719, 1646, 1539, 1460, 1241, 1056, 923 cm⁻¹. 1H and 13C 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 C20H26O4 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-secoabiet-8,11,13-trien-7-oic acid (1) and 7-hydroxy-7,8-secoabiet-8,12-diene-6,11,14-trione (3), together with one known seco-abietanoid, 12-hydroxy-6-nor-5-oxo-5,6-secoabiet-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 C20H28O3 as deduced from the HR-EI-MS molecular ion at m/z 304.2041 and its 13C 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 [δH 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 [δH 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 [δH 6.84 (1H, s, H-11) and 7.38 (1H, s, H-14)]. There are 19 carbon signals containing 6 aromatic carbon signals (δC 114.1, 124.3, 128.7, 130.3, 146.4, and 154.1) and one
conjugated carboxylic acid carbonyl carbon signals (δC 176.8) in the 13C NMR spectrum. Accounting for the total six degrees of unsaturation in 1, the remaining one degree of unsaturation hinted that 1 would be a seco-norabietane diterpene [29]. Comparing the 1H- and 13C-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 13C-NMR signal of carboxylic acid carbonyl carbon [δC 174.4 (s, C-6)] attached on C-5 was absent in 1 and the 1H- and 13C-NMR signals of downfield methine [δH 3.36 (1H, s and δC 58.9 (t, C-5)] were replaced by that of an AX methylene [δH 1.41 (1H, d, J = 14.0 Hz, H-5β), 2.13 (1H, d, J = 14.0 Hz, H-5α)] and δC 49.9 (t, C-5)].

![Diagram](image_url)

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

**Table 1.** 1H and 13C NMR data for compounds 1 and 3 (at 400 and 100 MHz in CDCl₃, δ in ppm, J in Hz)

| Position | 1H   | 13C  | 1H   | 13C  |
|----------|------|------|------|------|
| 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 | |
| 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) | |
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![Figure 2](image)

**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/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 dehydroabietanetype diterpene 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-secoabietane type with a flexible cyclohexane structure in ring A. The conformation of cyclohexane will be inverted to the most stable conformer. H-5a showed the NOESY correlations between Me-18, Me-19, and Me-20 confirmed that H-5a, 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 δH 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-CH3]+, m/z 287 [M-OH]+, m/z 272 [M-CH3-OH]+, and m/z 271 [M-CH3-H2O]+. From the above evidences, compound 1 was thus elucidated as 12-hydroxy-6-nor-5,6-secoabiet-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-ESI-MS of compound 3 showed a molecular ion at m/z 332.1981, consistent with the molecular formula of C20H30O2, 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 13C NMR signals for two carbonyl groups (δC 187.4 (s) and 188.6 (s)) and two double bonds (δC 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 [δH 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 [δH 3.67 (1H, s)], an isopropyl group attached on a quinone ring [δH 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 [δH 6.43 (1H, s, H-12) and 6.62 (1H, s, H-8)], and one set of ABX type methylene protons [δH 3.22 (1H, t, J = 4.0 Hz, 7-OH, exchanged with D2O), 4.20 (1H, dd, J = 15.6, 4.0 Hz, H-7a) and 4.31 (1H, br d, J = 15.6 Hz, H-7b)]. 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-1S,2R)-(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-CH$_2$OH]$^+$ and $m/z$ 273 [M-COCH$_2$OH]$^+$. From the above evidences, compound 3 was determined as 7-hydroxy-7,8-secoabiet-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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References

[1] W. S. Gan (1958). Manual of Medicine Plants in Taiwan Taiwan: National Research Institute of Chinese Medicine, Vol. 1, p. 54.

[2] C. C. Tsai, Y. F. Chang and C.W. Hsu (2011), Effects of thinning treatments on nutrient release from decomposing needle litter of sugi (Cryptomeria japonica D. Don) in northeastern Taiwan, Taiwan J. For. Sci.
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26, 163–177.

[3] M. Shieh, Y. Iizuka and Y. Matsubara (1981). Monoterpenoid and sesquiterpenoid constituents of the essential oil of sugi (*Cryptomeria japonica* D. Don.), *Agric. Biol. Chem.* **45**, 1493–1495.

[4] S. Nagahama, M. Tazaki, H. Nomura, K. Nishimura, M. Tajima and Y. Iwasita (1996). Terpenoids of the wood oil of sugi (*Cryptomeria japonica*) IV. Components of form Yabukuguri, *Mokuzai Gakkaishi* **42**, 1127–1133.

[5] S. Nagahama, M. Tazaki, T. Sanetika, K. Nishimura and M. Tajima (1998). Terpenoids of the wood oil of sugi (*Cryptomeria japonica*) V. Components of from Ayasugi, *Mokuzai Gakkaishi* **44**, 282–286.

[6] S. Morita, M. Yatagai and S. Fujita (1995). Distributions of the extracts and sesquiterpenes in the trunk of Yakusugi (*Cryptomeria japonica*), *Mokuzai Gakkaishi* **41**, 938–944.

[7] H. Narita, M. Yatagai and T. Ohira (2006). Chemical composition of the essential oils from bogwood of *Cryptomeria japonica* D. Don, *J. Essent. Oil Res.* **18**, 68–70.

[8] M. Shimizu, H. Tsuji, H. Shogawa, H. Fukumura, S. Tanaami, T. Hayashi, M. Arisawa and N. Morita (1988). N. Anti-inflammatory constituents of topically applied crude drugs. II. Constituents and anti-inflammatory effect of *Cryptomeria japonica* D. Don, *Chem. Pharm. Bull.* **36**, 3967–3973.

[9] W. C. Su, J. M. Fang and Y. S. Cheng (1996). Diterpenoids from leaves of *Cryptomeria japonica*, *Phytochemistry* **41**, 255–261.

[10] W. C. Su, J. M. Fang and Y. S. Cheng (1995). Synthesis and structure determination of cryptomonanhydride, an uncommon natural terpenic anhydride, *Tetrahedron Lett.* **36**, 5367–5370.

[11] X. H. Chen, C. S. Kim, T. Kashiwagi, S. I. Tebayashi and M. Horiiike (2001). Antifeedants against *Acusta despesta* from the Japanese cedar, *Cryptomeria japonica* II, *Biosci. Biotechnol. Biochem.* **65**, 1434–1437.

[12] J. Morisawa, C. S. Kim, T. Kashiwagi and M. Horiiike (2002). Repellents in the Japanese cedar, *Cryptomeria japonica*, against the pill-bug, *Armadillidium vulgare*, *Biosci. Biotechnol. Biochem.* **66**, 2424–2428.

[13] T. Shibuya (1992). Cryptokoquinemethides D and E, C 30-terpene quinone methides, from *Cryptomeria japonica*, *Phytochemistry* **31**, 4289–4294.

[14] K. Yoshikawa, T. Tanaka, A. Umeyama and S. Arihara (2006). Three abietane diterpenes and two diterpenes incorporated sesquiterpenes from the bark of *Cryptomeria japonica*, *Chem. Pharm. Bull.* **54**, 315–319.

[15] K. Yoshikawa, K. Suzuki, A. Umeyama and S. Arihara (2006). Abietane diterpenoids from the barks of *Cryptomeria japonica*, *Chem. Pharm. Bull.* **54**, 574–578.

[16] W. H. Li, S. T. Chang, S. C. Chang and H. T. Chang (2008) Isolation of antibacterial diterpenoids from *Cryptomeria japonica* bark, *Nat. Prod. Res.* **22**, 1085–1093.

[17] H. Kofujita, Y. Fujino, T. Sasaki, M. Hasebe, M. Ota and K. Suzuki (2001) Antifugal activity of the bark of *Cryptomeria japonica* and its relevant components, *Mokuzai Gakkaishi*, **47**, 479–486.

[18] H. Kofujita, M. Ota, K. Takahashi, Y. Kawai and Y. Hayashi (2002). A diterpene quinone from the bark of *Cryptomeria japonica*, *Phytochemistry* **61**, 895–898.

[19] L. F. Shyur, C. C. Huang, C. P. Lo, C. Y. Chiu, Y. P. Chen, S. Y. Wang and S. T. Chang (2008). Hepatoprotective phytochemicals from *Cryptomeria japonica* are potent modulators of inflammatory mediators, *Phytochemistry* **69**, 1348–1358.

[20] W. C. Tu, S. Y. Wang, S. C. Chien, F. M. Lin, L. R. Chen, C. Y. Chiu and P. W. Hsiao (2007). Diterpenes from *Cryptomeria japonica* inhibit androgen receptor transcriptional activity in prostate cancer cells, *Planta Med.* **73**, 1407–1409.

[21] Y. Tsutsumi, A. Shimada, A. Miyano, T. Nishida and T. Mitsunaga (1998). In vitro screening of angiotensin I-converting enzyme inhibitors from Japanese cedar (*Cryptomeria japonica*), *J. Wood Sci.* **44**, 463–468.

[22] S. S. Cheng and S. T. Chang. (2014) Bioactivity and characterization of exudates from *Cryptomeria japonica* bark, *Wood Sci. Tech.* **48**, 831–840.

[23] C. Moiteiro, T. Esteves, L. Ramalho, R. Rojas, S. Alvarez, S. Zacchino and H. Bragança (2013). Essential oil characterization of two Azorean *Cryptomeria japonica* populations and their biological evaluations, *Nat. Prod. Commun.* **8**, 1785–1790.

[24] H. Horiba, T. Nakagawa, Q. Zhu, A. Ashour, A. Watanabe and K. Shimizu (2016). Biological activities of extracts from different parts of *Cryptomeria japonica*, *Nat. Prod. Commun.* **11**, 1337–1342.

[25] B. Wu, T. Kashiwagi, I. Kuroda, X. H. Chen, S. I. Tebayashi and C. S. Kim (2008). Antifeedants against *Locusta migratoria* from the Japanese Cedar, *Cryptomeria japonica* II, *Biosci. Biotechnol. Biochem.* **72**, 611–
614.

[26] C. C. Chen, J. H. Wu, N. S. Yang, J. Y. Chang, C. C. Kuo, S. Y. Wang and Y. H. Kuo (2010). Cytotoxic C₃₅ terpenoid cryptotrione from the bark of Cryptomeria japonica, Org. Lett. 12, 2786–2789.

[27] C. I. Chang, C. C. Chen, S. Y. Wang, C. Y. Chao, L. K. Chao, J. J. Chen, H. H. Ko, C. C. Chen and Y. H. Kuo (2016). Three new abietane-type diterpenes from the bark of Cryptomeria japonica, Helv. Chim. Acta 99, 710–715.

[28] C. I. Chang, C. C. Chen, C. R. Chen, M. D. Wu, M. J. Cheng, P. J. Sung and Y. H. Kuo (2019). Bioactive Dimeric Abietanoid Peroxides from the Bark of Cryptomeria japonica, Molecules 24, E2178.

[29] C. I. Chang, C. C. Chen and Y. H. Kuo (2021). A New Seco-Abietanoid from the Bark of Cryptomeria japonica, Chem. Nat. Compd. 57, 331–334.

[30] Y. Ye, Y. Wang, S. Yao, J. Zhao, C. Tang, W. Xu, C. Ke and C. Xi (2017). Preparation of abietane-type diterpene compounds with lipid-lowering activity, China Patent: CN 106279200 A.

[31] C. H. Chen, H.C. Chan, Y.T. Chu, H.Y. Ho, P.Y. Chen, T.H. Lee and C.K. Lee (2009). Antioxidant activity of some plant extracts towards xanthine oxidase, lipoxygenase and tyrosinase, Molecules 14, 2947–2958.

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