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# New 7-oxoabietane-type diterpenoids from the bark of *Cryptomeria japonica* and their xanthine oxidase inhibitory activity

Chi-I Chang[a], Tzong-Huei Lee[b], Yi-Jen Li[c], Che-Yi Chao[d], Bang-Jau You[e], Ming-Jen Cheng[f,1], Sheng-Yang Wang[g,h,1], Cheng-Chi Chen[i,1], Yueh-Hsiung Kuo[j,k,l,*]

[a] Department of Biological Science and Technology, National Pingtung University of Science and Technology, Pingtung 912, Taiwan
[b] Institute of Fisheries Science, National Taiwan University, Taipei 106, Taiwan
[c] Department of Nutrition and Health Sciences, Chang Jung Christian University, Tainan 711, Taiwan
[d] Department of Health and Nutrition Biotechnology, Asia University, Taichung 413, Taiwan
[e] Department of Chinese Pharmaceutical Sciences and Chinese Mediscine Resources, College of Pharmacy, China Medical University, Taichung 404, Taiwan
[f] Bioresource Collection and Research Center (BCRC), Food Industry Research and Development Institute (FIRDI), 300, Hsinchu, Taiwan
[g] Department of Forestry, National Chung-Hsing University, Taichung 402, Taiwan
[h] Agricultural Biotechnology Research Center, Academia Sinica, Taipei, Taiwan
[i] Department of Chemistry, National Taiwan University, Taipei 106, Taiwan
[j] Department of Chinese Pharmaceutical Sciences and Chinese Medicine Resources, China Medical University, Taichung 404, Taiwan
[k] Department of Biotechnology, Asia University, Taichung 413, Taiwan
[l] Chinese Medicine Research Centser, China Medical University, Taichung 404, Taiwan

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ABSTRACT

Three new 7-oxoabietane-type diterpenoids, 3-oxosugiol methyl ether (**1**), 18-hydroxysugiol (**2**), and 1β-hydroxysugiol (**3**), as well as two known 7-oxoabietane-type diterpenoids, 6α-hydroxysugiol (**4**) and 6α-acetoxysugiol (**5**), were isolated from the bark of *Cryptomeria japonica* D. Don. Their structures were elucidated mainly by NMR and HREIMS, as well as on comparison with the data of known analogues. At the concentration of 75 μM, compounds **2** and **5** exhibited 11.9 and 21.7% xanthine oxidase inhibitory activity, respectively.

## 1. Introduction

The genus *Cryptomeria* (Cupressaceae) comprises of only one species, *Cryptomeria japonica* D. Don, which is endemic to Japan, known as sugi (Japanese cedar) in Japanese and has been widely cultivated as an important plantation coniferous tree species in Taiwan since 1906. *C. japonica* is a massive evergreen coniferous tree, growing up to in height. Its wood has been used as a building material for Japanese-style houses and other wood products due to the aromatic, soft, lightweight but strong, waterproof, and reddish-pink in color properties. Diverse terpenoids, including monoterpenoids, sesquiterpenoids, and diterpenoids (Arihara et al., 2004a, 2004b; Chen et al., 2001; Kofujita et al., 2001, 2002; Morita et al., 1995; Nagahama and Tazaki, 1993; Nagahama et al., 1993, 1996a, 1996b, 1998; Narita et al., 2006; Shibuya, 1992; Shieh et al., 1981; Shimizu et al., 1988; Su et al., 1993, 1994a, 1994b, 1995a, 1995b, 1996; Morisawa et al., 2002; Yoshikawa et al., 2006a, 2006b) were isolated from the leaves, heartwood, and barks of this plant, some of which possess antibacterial (Li et al., 2008), antifungal (Kofujita et al., 2001), cytotoxic (Kofujita et al., 2002), anti-inflammatory (Shyur et al., 2008), anti-androgenic (Tu et al., 2007), and insect antifeedant (Wu et al., 2008), and repellent (Morisawa et al., 2002) properties. 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 7-oxoabietane and cadinane (Chen et al., 2010), ten 7-oxoabietane-type diterpenoids (Chang et al., 2016; Chang et al., 2017a,b), and two sesquarterpenoids (Chang et al., 2017c). Herein, we report the isolation and structure elucidation of three new 7-oxoabietane-type diterpenoids (Fig. 1) and their xanthine oxidase inhibitory activity.

## 2. Results and discussion

A methanol extract of the bark of *C. japonica* was suspended in $H_2O$ and then partitioned successively with EtOAc and *n*-BuOH. Fractionation of the EtOAc soluble portion by silica gel column

* Corresponding author at: Department of Chinese Pharmaceutical Sciences and Chinese Medicine Resources, China Medical University, No. 91, Hsueh-Shih Rd., Taichung City, 404, Taiwan.
*E-mail address:* kuoyh@mail.cmu.edu.tw (Y.-H. Kuo).
[1] Equal contribution to first author.

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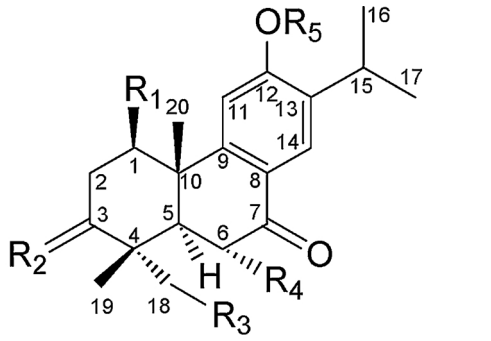


**1** $R_1$= $R_3$= $R_4$= H, $R_2$= O, $R_5$= Me
**2** $R_1$= $R_4$= $R_5$= H, $R_2$= $H_2$, $R_3$= OH
**3** $R_1$= OH, $R_2$= $H_2$, $R_3$= $R_4$= $R_5$= H
**4** $R_1$= $R_3$= $R_5$= H, $R_2$= $H_2$, $R_4$= OH
**5** $R_1$= $R_3$= $R_5$= H, $R_2$= $H_2$, $R_4$= OAc

**Fig. 1.** Structures of compounds **1**–**5**.

chromatography followed by purification using semipreparative NP-HPLC yielded three new 7-oxoabietane-type diterpenoids, 12-methoxyabieta-8,11,13-trien-3,7-dione (**1**), 18-hydroxysugiol (**2**), and 1β-hydroxysugiol (**3**), together with two known 7-oxoabietane-type diterpenoids, 6α-hydroxysugiol (**4**) (Fang et al., 1993) and 6α-acetoxysugiol (**5**) (Kuo et al., 1975) (Fig. 1).

Theof **1** gave a molecular ion at 328.4509, establishing the molecular formula of **1** as $C_{21}H_{28}O_3$, with eight degrees of unsaturation. The UV maximum (278 nm) and IR absorptions (1672, 1600, and 1500 $cm^1$) of **1** indicated the presence of the benzoyl moiety (Kuo and Yu, 1996). An IR absorption for an isolated ketone carbonyl group (1706 $cm^1$) was also observed. The resonances in the $^1$H NMR spectrum of **1** (Table 1) for three tertiary-linked methyls [$_H$ 1.13, 1.19, and 1.45 (each 3H, s, Me-18, Me-19, and Me-20], two *para*-oriented aromatic protons [$_H$ 6.68 (1H, s) and 7.89 (1H, s)], one set of ABX coupling system neighboring to the carbonyl group [$_H$ 2.31 (1H, dd, 14.0, 4.0 Hz), 2.58 (1H, dd, 17.6, 4.0 Hz), and 2.75 (1H, dd, 17.6, 14.0 Hz)], an isopropyl group [$_H$ 1.19 (3H, d, $J$ = 6.8 Hz), 1.21 (3H, d, $J$ = 6.8 Hz), and 3.26 (1H, sept, $J$ = 6.8 Hz)], one methoxy group [$_H$ 3.88 (3H, s)], and a typical downshifted $H_β$-1 signal at $_H$ 2.60 (1H, m) suggested that **1** was a dehydroabietane diterpene (Kuo and Yu, 1996). The $^{13}$C NMR and DEPT spectra spectrum of **1** indicated the presence of 21 carbons, consisting of five methyl, three aliphatic methylene, two aliphatic methine, two aliphatic quaternary, two olefinic methine, four quaternary olefinic, two carbonyl, and one methoxy carbons. The $^1$H and $^{13}$C NMR data of **1** were similar to those of sugiol methyl ether (Kuo and Yu, 1996), the major differences were the $^{13}$C NMR chemical shifts of C-1 ~ C-4, Me-18, Me-19, and Me-20 in ring A. The HMBC correlations between H-2 ($_H$ 1.51)/C-3 ($_C$ 214.1) and Me-19/C-3 (Figure 3) indicated an isolated ketone carbonyl located on C-3. From the above evidences, compound **1** was thus formulated as 12-methoxyabieta-8,11,13-trien-3,7-dione and given the trival name 3-oxosugiol methyl ether. Compound **1** had been synthesized by Burnell and Caron (1992)and was isolated from the natural source for the first time.

The UV maximum (284 nm) and IR absorptions (1646, 1593, and 1460 $cm^1$) of **2** indicated the presence of the benzoyl moiety (Kuo and Yu, 1996). An IR absorption at 3383 $cm^{-1}$ for hydroxyl group was also observed. The molecular formula was established to be $C_{20}H_{28}O_3$ from itsmolecular ion at 316.4389 and its $^{13}$C NMR data, indicating seven degrees of unsaturation. The $^1$H NMR spectrum of **2** (Table 1) showed resonances for two tertiary-linked methyls [$_H$ 0.88, and 1.18 (each 3H, s, Me-19, and Me-20], two *para*-oriented aromatic protons [$_H$ 6.67 (1H, s) and 7.83 (1H, s)], an isopropyl group [$_H$ 1.19 (3H, d, $J$ = 6.8 Hz), 1.21 (3H, d, $J$ = 6.8 Hz), and 3.13 (1H, sept, $J$ = 6.8 Hz)], an AB-type oxymethylene [$_H$ 3.12 (1H, d, 11.2 Hz) and 3.42 (1H, d, 11.2 Hz)], and a typical downshifted $H_β$-1 signal of dehydroabietane diterpene at $_H$ 2.12 (1H, br d, $J$ = 13.2 Hz). With the aid of $^1$H-$^1$H COSY, one set of ABX coupling system neighboring to the carbonyl group [$_H$ 2.17 (1H, dd, 11.2, 7.2 Hz), 2.56 (1H, m), and 2.57 (1H, m)] was also found. 20 carbon signals were observed in the $^{13}$C NMR spectrum of **2** and were

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

| | **1** | | **2** | | **3** | |
|---|---|---|---|---|---|---|
| No. | $\delta_C$ | $\delta_H$ | $\delta_C$ | $\delta_H$ | $\delta_C$ | $\delta_H$ |
| 1 | 37.0 | 2.04 t d (13.2, 5.2) α, 2.60 m β | 37.4 | 1.74 m α, 2.12 br d (13.2) β | 77.2 | 3.97 dd (9.2, 6.8) |
| 2 | 34.6 | 2.53 ddd (15.2, 5.2, 3.2) β, 2.87 m α | 18.3 | 1.67 m β, 1.73 m | 29.9 | 1.79 m, 1.80 m |
| 3 | 214.1 | | 34.7 | 1.34 m β, 1.50 dt (12.8, 4.0) α | 39.2 | 1.39 m β, 1.51 dt (13.2, 3.2) α |
| 4 | 47.4 | | 37.7 | | 33.2 | |
| 5 | 49.6 | 2.31 dd (14.0, 4.0) | 42.5 | 2.17 dd (11.2, 7.2) | 48.5 | 1.82 m |
| 6 | 36.2 | 2.58 dd(17.6, 4.0) α, 2.75 dd(17.6, 14.0) β | 35.7 | 2.56 m, 2.57 m | 35.7 | 2.63 m, 2.64 m |
| 7 | 196.7 | | 198.4 | | 198.0 | |
| 8 | 123.6 | | 123.9 | | 124.6 | |
| 9 | 153.4 | | 156.1 | | 154.7 | |
| 10 | 37.8 | | 37.5 | | 43.8 | |
| 11 | 104.7 | 6.68 s | 109.7 | 6.67 s | 112.4 | 7.68 s |
| 12 | 161.6 | | 158.7 | | 158.1 | |
| 13 | 135.9 | | 132.8 | | 133.0 | |
| 14 | 125.6 | 7.89 s | 126.4 | 7.83 s | 126.3 | 7.85 s |
| 15 | 26.6 | 3.26 sept (6.8) | 26.8 | 3.13 sept (6.8) | 26.8 | 3.16 sept (7.2) |
| 16 | 22.5 | 1.19 d (6.8) | 22.4 | 1.21 d (6.8) | 22.3 | 1.21 d (7.2) |
| 17 | 22.4 | 1.21 d (6.8) | 22.5 | 1.19 d (6.8) | 22.4 | 1.21 d (7.2) |
| 18 | 25.1 | 1.13 s | 70.7 | 3.12 d (11.2), 3.42 d (11.2) | 32.0 | 0.90 s |
| 19 | 21.6 | 1.19 s | 17.4 | 0.88 s | 21.1 | 0.97 s |
| 20 | 22.7 | 1.45 s | 23.7 | 1.18 s | 16.6 | 1.22 s |
| -$OCH_3$ | 55.5 | 3.88 s | | | | |

Coupling constants are presented in Hz.

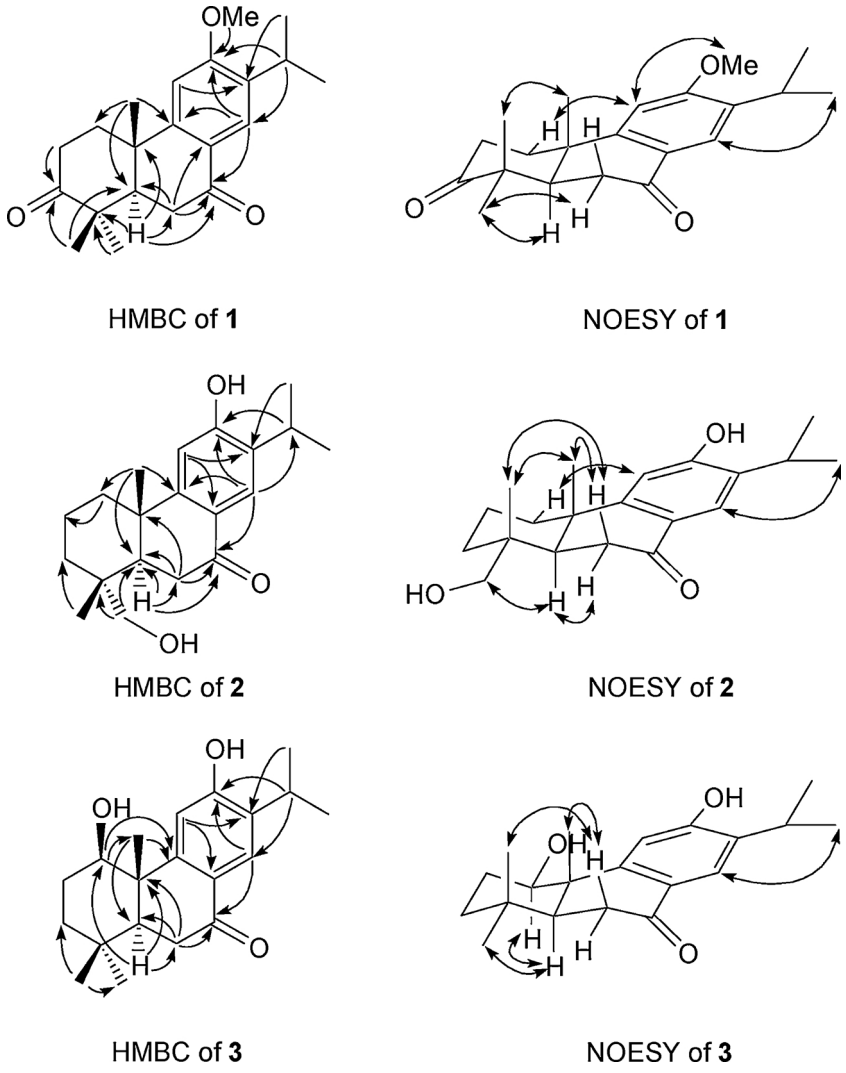


**Fig. 2.** Selected HMBC and NOE correlations of **1**–**3**.

differentiated by DEPT experiments as four methyl, four aliphatic methylene, 2 aliphatic methine,two aliphatic quaternary, one oxygenated methylene, two olefinic methine, four quaternary olefinic, and one carbonyl carbons. The $^{1}H$ and $^{13}C$ NMR data were similar to those of known compound, sugiol (Marcos et al., 2010). By comparing the $^{13}C$ NMR data of **2** with that of sugiol, the major differences were the $^{13}C$ NMR chemical shifts of C-3 ~ C-5, Me-18, and Me-19 in ring A. The HMBC correlations between H-18 ($_H$ 3.12)/C-4 ($_C$ 37.7) and H-18/C-5 ($_C$ 42.5) and NOESY correlation between H-18/H-5 ($_H$ 2.17) suggested that the hydroxyl group was attached on C-18 (Fig. 2). From the above evidences, compound **2** was thus formulated as 18-hydroxysugiol (**2**).

The molecular formula of **3** was assigned as $C_{20}H_{28}O_3$ byat 316.4399, representing seven degrees of unsaturation. The IR absorptions indicated the presence of hydroxyl (3303 $cm^{1}$) group and benzoyl moiety (1653, 1600 and 1460 $cm^{1}$). The UV absorption band at 290 nm was further confirmed the benzoyl moiety. The $^{1}H$ NMR spectrum of **3** (Table 1) displayed the signals for three tertiary-linked methyls [$_H$ 0.90, 0.97, and 1.22 (each 3H, s, Me-18, Me-19, and Me-20], one oxymethine [$_H$ 3.97 (1H, dd, $J$ = 9.2, 6.8 Hz, H-1)], two *para*-oriented aromatic protons [$_H$ 7.68 (1H, s) and 7.85 (1H, s)], and an isopropyl group on the benzene ring [$_H$ 1.21 (6H, d, $J$ = 6.8 Hz) and 3.16 (1H, sept, $J$ = 6.8 Hz)]. An ABX coupling system [$_H$ 1.82 (1H, m), $_H$ 2.63 (1H, m), and 2.64 (1H, m)] was also assured by their $^{1}H$-$^{1}H$ COSY correlations. Similarities in the $^{1}H$ and $^{13}C$ NMR spectroscopic data hinted that **3** should be an analogue of **2**. The absence of a typical $H_\beta$-1 of dehydroabietane diterpene, replacing by an oxymethine [$_H$ 3.97 (1H, dd, $J$ = 9.2, 6.8 Hz, H-1)], along with a downshifted H-11 proton signal [$_H$ 7.68 (1H, s)] hinted that the hydroxyl group was located at C-1 (Abdul-Wahab et al., 2012). Furthermore, the HMBC correlations between H-1 ($_H$ 3.97)/C-9 ($_C$ 154.7) and C-20 ($_C$ 16.6) and NOESY correlation between H-1/H-5 ($_H$ 1.82) confirmed that the hydroxyl group was attached on C-1 inβ-equatorial orientation (Fig. 2), which caused the downshifted H-11 at $_H$ 7.68. Thus, compound **3** was identified as 1β-hydroxysugiol.

Compounds **1**-**5** were evaluated their xanthine oxidase inhibitory activity (Chen et al., 2009). At the concentration of 75 μM, compounds **2** and **5** exhibited 11.9 and 21.7% xanthine oxidase inhibitory activity, respectively, while compounds **1**, **3**, and **4** were inactive.

## 3. Experimental

### 3.1. General experimental procedures

Optical rotations were obtained with a Jasco-DIP-180 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 and 2D NMR spectra were recorded on a Varian-Unity-Plus-400 spectrometer with residual solvent signals as internal reference. EI-MS and HR-EI-MS were determined on a Jeol-JMS-HX300 mass spectrometer. Column chromatography (CC) was carried out with Silica gel mesh;

Merck & Co., Inc.). Thin-layer chromatography (TLC) was performed on pre-coated silica gel plates (silica gel 60 $F_{254}$; Merck & Co., Inc.). Semi-preparative HPLC was performed using a normal phase column (Purospher STAR Si, 5 μm, 250 × 10 mm; Merck & Co., Inc.) on a LDC Analytical-III system.

### 3.2. Plant Material

The bark of *C. japonica* D. Don was collected in Sitou, Taiwan in. The plant material was identified by Dr. Yen-Hsueh Tseng, Department of Forestry, National Chung-Hsing University (NCHU). A voucher specimen (TCF13443) has been deposited at the Herbarium of the Department of Forestry, NCHU, Taiwan.

### 3.3. 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. After filtration and evaporation, the crude extract (480 g), was suspended in $H_2O$ (1 L) and 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 with increasing polarity to yield 11 fractions. 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 - 4 P. Further purification of subfraction 4C (0.9 g) by HPLC gave **5** (3.2 mg, $t_R$ = 18.1 min) using *n*-hexane–EtOAc (4:1). Subfraction 4 G (1.6 g) by HPLC afforded **1** (1.5 mg, $t_R$ = 46.2 min) using *n*-hexane–EtOAc (4:1). Fr. 5 from *n*-hexane–EtOAc (7:3) elution (21.6 g) was further purified over a silica gel column (5 × 45 cm), eluted with *n*-hexane$_2$Cl$_2$ - EtOAc (8:8:1 to 0:1:1) to yield fifteen fractions, 5A - 5O. Further purification of subfraction 5E (1.2 g) by HPLC gave **4** (12.9 mg, $t_R$ = 38.1 min) using *n*-hexane–EtOAc (7:3). Subfraction 5 F (2.0 g) by HPLC gave **2** (2.5 mg, $t_R$ = 43.1 min) and **3** (1.9 mg, $t_R$ = 46.1 min) using *n*-hexane–EtOAc (7:3).

#### 3.3.1. 12-Methoxyabieta-8,11,13-trien-3,7-dione (1)

Gum; $[\alpha]_D^{25}$ = +3.5 (*c* 0.4, $CHCl_3$); IR (dry film) $\nu_{max}$ 1706, 1672, 1600, 1500, 1460, 1288, 1255, 1175, 1029 $cm^{-1}$; UV (MeOH) $\lambda_{max}$ (log $\varepsilon$) 229 (4.69), 278 (4.58) nm; $^1H$ and $^{13}C$ NMR data, see Table 1; EI-MS (%) 328 ($M^+$, 71) $[M]^+$, 313 ($[M_3]^+$, 100), 271 (7), 243 (9), 125 (7). HR-EI-MS $[M]^+$ 328.4509 (calcd for $C_{21}H_{28}O_3$ 328.4504).

#### 3.3.2. 18-Hydroxysugiol (2)

Gum; $[\alpha]_D^{25}$ = +1.8 (*c* 0.25, $CHCl_3$); IR $_{max}$ 3383, 1646, 1593, 1460, 1381, 1308, 1268, 1182, 1043 $cm^{-1}$; UV (MeOH) $\lambda_{max}$ (log $\varepsilon$) 232 (3.82), 284 (3.75) nm; $^1H$ and $^{13}C$ NMR data, see Table 1; EI-MS (%) 316 (41) $[M]^+$, 301 ($[M_3]^+$, 24), 283 ($[M_3—H_2O]^+$, 30), 243(17), 215 (24), 203 (100), 59 (47), 55 (32). HR-EI-MS $[M]^+$ 316.4389 (calcd for $C_{20}H_{28}O_3$ 316.4394).

#### 3.3.3. 1β-Hydroxysugiol (3)

Gum; $[\alpha]_D^{25}$ = +30.5 (*c* 0.32, $CHCl_3$); IR $_{max}$ 3303, 1653, 1600, 1566, 1460, 1381, 1301, 1268, 1182, 1009, 897 $cm^{-1}$; UV (MeOH) $\lambda_{max}$ (log $\varepsilon$) 232 (4.28), 290 (4.22) nm; $^1H$ and $^{13}C$ NMR data, see Table 1; EI-MS (%) 316 (100) $[M]^+$, 301 ($[M_3]^+$, 91), 283 ($[M_3—H_2O]^+$, 16), 257 (38), 217 (46), 201 (44), 175 (43). HR-EI-MS $[M]^+$ 316.4399 (calcd for $C_{20}H_{28}O_3$ 316.4394).

### 3.4. Xanthine oxidase inhibition assssay

The xanthine oxidase inhibitory activity was carried out using the method of Chen et al. with some modifications (Chen et al., 2009). In brief, 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) solution was added to 20 μL of the sample solution (final concentration was 75 μM). After preincubation at 25 °C for, the reaction was initiated by the addition of 60 μL of substrate solution (150 mM xanthine in the same buffer). The solution was mixed thoroughly by vortexing and preincubated for 30 min at 25 °C, and then 60 μL of substrate solution (150 mM xanthine in the same buffer) was added. The reaction mixture was incubated for further 30 min at 25 °C, and the absorbance was measured at 290 nm. The percentage activity of xanthine oxidase was calculated according to the following equation: (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.

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