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Merrillianin, a unique *seco*-prezizaane-type sesquiterpene, and (6*R*)-pseudomajucin from *Illicium merrillianum*

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Abstract—Novel sesquiterpene lactones, (6*R*)-pseudomajucin (**1**) and merrillianin (**3**), have been isolated from the pericarps of *Illicium merrillianum*, and their structures have been elucidated on the basis of the spectral data. A methanol solution of (6*R*)-pseudomajucin coexisted with (6*R*)-pseudomajucinone (**2**) in a keto/acetal equilibrium, whereas the crystals solely consisted of a keto-type **2**, the structure of which was established by X-ray crystallographic analysis. The absolute stereochemistry of **1** was determined by the X-ray crystallographic analysis of its 7-*O*-methyl-3-*O*-*p*-bromophenylcarbamate. Merrillianin (**3**) is a unique *seco*-prezizaane-type sesquiterpene with an unprecedented dilactone moiety, which may be biosynthesized from pseudomajucin (**4**) or (6*R*)-pseudomajucin (**1**) by oxidative cleavage of the C-6/C-7 bond.

1. Introduction

Illicium sesquiterpenes are a group of structurally unique sesquiterpenes, some of which are elaborated by a tree 'Shikimi' (*Illicium anisatum*) in Japan and classified into three skeletal classes, *seco*-prezizaane,[1–4] anislactone[5,6] and *allo*-cedrane,[7–9] with most belonging to the first class. Their biogenetic relationship has been proposed in our previous papers.[6,7] *Illicium merrillianum* is a small tree or shrub distributed in the southwestern part of China and Myanmar, and its bark and fruits have been locally used as an anti-rheumatic agent. Recently, we have isolated some novel types of anislactone and *allo*-cedrane such as merrilactone A[10] and 11-*O*-debenzoyltashironin[8] with neurotrophic activity from the pericarps of *I. merrillianum*. In our continuing search for structurally unique and biologically interesting *Illicium* sesquiterpenes, three new sesquiterpenes, (6*R*)-pseudomajucin (**1**), (6*R*)-pseudomajucinone (**2**), and merrillianin (**3**) which has an unprecedented dilactone structural unit, along with the previously known sesquiterpenes, anisatin,[1] anislactone B,[5] cycloparvifloralone,[11] 3α-hydroxycycloparvifloralone[8] and pseudomajucin (**4**),[4] were isolated from the pericarps of *I. merrillianum*. This paper reports the isolation and structural elucidation of **1**–**3** (Fig. 1).

2. Results and discussion

The methanol extracts of the pericarps of *I. merrillianum* were subjected to silica gel chromatography to afford fractions A–G. Fraction E was rechromatographed on silica gel to yield three new sesquiterpenes, (6*R*)-pseudomajucin (**1**), (6*R*)-pseudomajucinone (**2**) and merrillianin (**3**), and five known sesquiterpenes (see Section 3). In the purification process, the mixture containing **1** and **2** was incapable of separation even by HPLC under various conditions. It was supposed that they were an equilibrated mixture in

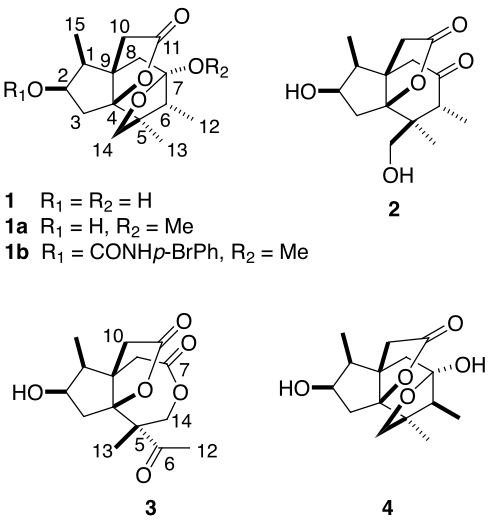

Figure 1. Structures of **1**–**4**.

Keywords: *Illicium merrillianum*; *seco*-prezizaane; pseudomajucin; merrillianin.

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Table 1. ^{1}H NMR spectral data of **1**–**3** (600 MHz, CD_3OD)

H	1	2	3
1	2.11 qd (7.1, 3.5)	1.87 qd (7.1, 3.3)	2.30 qd (7.4, 6.3)
2	4.09 dd (3.8, 3.5)	4.12 dd (4.1, 3.3)	4.30 ddd (6.6, 6.3, 2.2)
3α	2.10 dd (14.8, 3.8)	2.26 dd (15.4, 4.1)	1.84 dd (15.2, 2.2)
β	2.15 d (14.8)	2.37 d (15.4)	2.56 dd (15.2, 6.6)
6	1.97 q (7.6)	2.42 q (6.6)	
8α	1.80 d (14.0)	2.36 d (18.7)	2.75 d (14.6)
β	2.01 d (14.0)	2.70 d (18.7)	2.96 d (14.6)
10α	2.67 d (18.4)	2.22 d (18.9)	2.33 d (18.1)
β	2.88 d (18.4)	3.06 d (18.9)	3.13 d (18.1)
12	1.03 d (7.6)	1.04 d (6.6)	2.28 s
13	1.09 s	0.88 s	1.37 s
14α	3.47 d (8.5)	3.53 d (11.3)	4.52 d (13.7)
β	3.92 d (8.5)	3.62 d (11.3)	4.55 d (13.7)
15	1.04 d (7.1)	1.08 d (7.1)	1.01 d (7.4)

methanol. Fortunately, as the NMR spectra for a mixture of **1** and **2** measured in CD_3OD showed well-separated signals, assignment of proton and carbon signals could be readily made for each one.

2.1. (6*R*)-Pseudomajucin (1) and (6*R*)-pseudomajucinone (2)

The HREI-MS for the mixture of **1** and **2** showed a molecular ion peak at *m/z* 282.1469 corresponding to the molecular formula, $C_{15}H_{22}O_5$. Their IR absorptions at 3429, 1747 and 1706 cm^{-1} were attributable to hydroxyl, γ-lactone and carbonyl groups, respectively. The ^{1}H NMR spectra in CD_3OD revealed the presence of two closely related isomeric sesquiterpenes (**1** and **2**) in a ratio of 2:1. The NMR data were unambiguously assigned (Tables 1 and 2), since all of the ^{1}H and ^{13}C NMR signals could be differentiated clearly to each component. According to these data, the major component **1** contained three methyl groups (δ_H 1.03 (d, *J*=7.6 Hz), 1.04 (d, *J*=7.1 Hz) and 1.09 (s)), four methylene groups, three methine groups and five quaternary carbons, which were very similar to those of pseudomajucin (**4**).[4] Further analysis of 2D NMR spectra supported that **1** had the same planar structure as **4** with a C-7 acetal carbon (δ_C 108.2).

Table 2. ^{13}C NMR spectral data of **1**–**3**

C	1	2	3
1	54.3	52.7	46.7
2	75.0	75.4	73.5
3	45.7	43.9	46.1
4	100.8	101.8	98.3
5	48.5	45.3	59.6
6	50.4	46.3	209.6
7	108.2	212.8	172.9
8	48.2	49.7	39.8
9	50.7	51.9	54.2
10	42.2	40.5	39.6
11	179.5	178.6	176.2
12	10.2	8.8	27.4
13	16.1	15.1	17.7
14	74.9	67.7	69.9
15	10.2	9.8	10.1

150 MHz, CD_3OD.

The ^{13}C NMR data of the minor component **2** were similar to those of **1** except for the disappearance of the acetal signal existing in **1** and the presence of a ketone carbonyl (δ_C 212.8). The ketone carbon must be placed on C-7, since the HMBC correlations of this carbon with H-6, H-8 and H-12 were observed. Consequently, the minor component **2** was elucidated as a keto-form of **1** in a keto/acetal equilibrium.

Treatment of **1** with trimethylorthoformate and methanol in the presence of Amberlyst R 15 afforded a sole 7-*O*-methylated product **1a**, which was then reacted with 4-bromophenyl isocyanate and 1,8-diazabicyclo[5.4.0]-undec-7-ene in toluene to give rise to the *p*-bromophenylcarbamate **1b** as a single crystal suitable for X-ray analysis. Its ORTEP drawing as shown in Fig. 2 revealed the absolute configurations of the chiral centers of **1b** to be 1*S*, 2*R*, 4*S*, 5*S*, 6*R* and 9*R*, and thereby **1** was determined as (6*R*)-pseudomajucin. Accordingly, **2** turns out to be (6*R*)-pseudomajucinone having the same absolute configuration as that of **1b**. Fortunately, **2** was crystallized from an ethyl acetate solution although **1** and **2** coexisted as an equilibrated mixture in solvent. Thus, the stereochemistry of **2** was unambiguously established by X-ray analysis. The structure of **2** was obviously identical with the keto-form of **1** as shown in Fig. 2.

Although some pseudoanisatin-type sesquiterpenes have been reported to occur as an acetal/keto equilibrium,[11] it is the first example that each absolute structure of pseudomajucin-type sesquiterpenes (**1** and **2**) coexisting in an acetal/keto equilibrium has been established independently by X-ray crystallographic analysis. In contrast with (6*S*)-pseudomajucin (**4**) existing as a sole acetal-form, its 6*R*-form **1** readily reaches to a keto-form **2** in equilibration. Although we attempted MM2 calculations to compare the global minimum energy between **1** and **4**, no reasonable

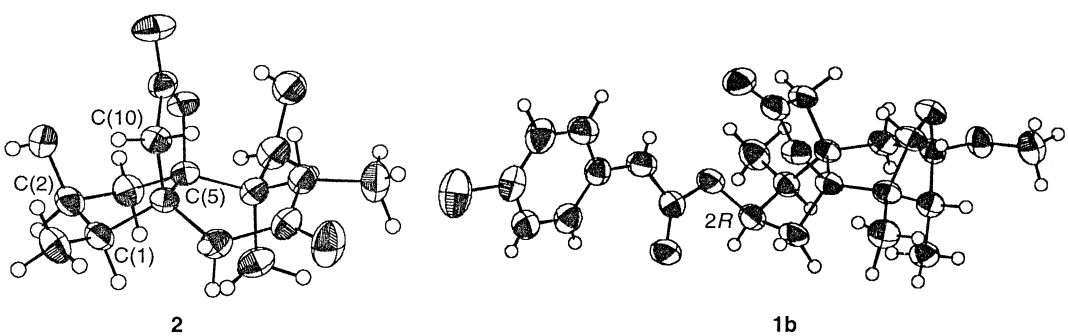


Figure 2. The ORTEP drawings of **2** and **1b**.

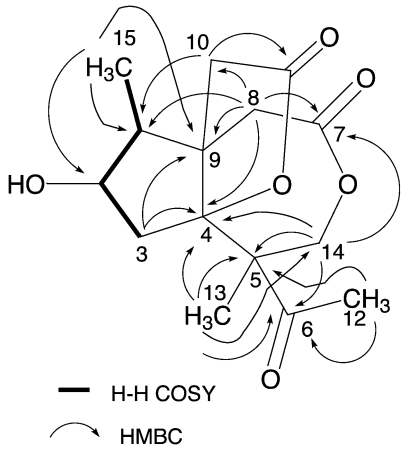


Figure 3. Representative HMBC correlations of **3**.

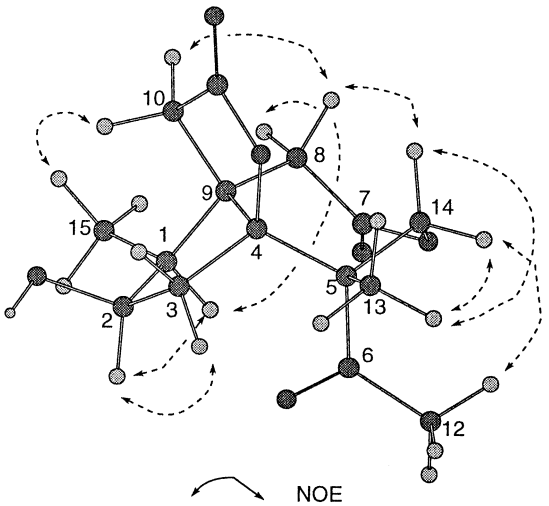


Figure 4. Key NOESY correlations of **3**.

explanation failed to be provided for **1** and **2** coexisting in an acetal/keto equilibrium.

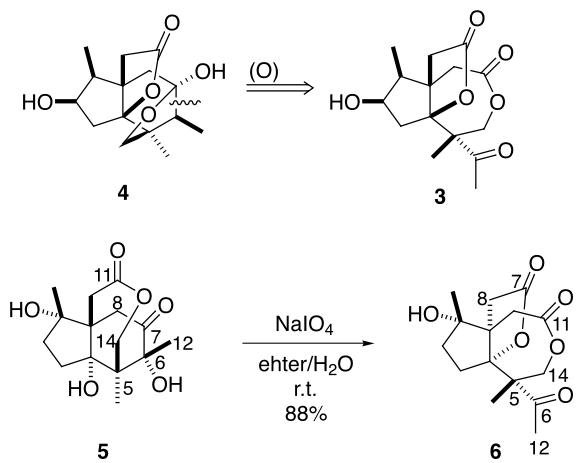
2.2. Merrillianin (3)

Compound **3** was obtained as a colorless amorphous solid. The molecular formula of **3** was established to be $C_{15}H_{20}O_6$ from HREI-MS at *m/z* 296.1255. The ^1H NMR and ^{13}C NMR spectral data including DEPT indicated the presence of three methyl, four methylene, two methine and six quaternary carbons. The presence of a hydroxyl group in the molecular was deduced from the IR absorption band at 3446 cm^{-1}. The ^{13}C NMR data resonating at δ_C 172.9, 176.2 and 209.6 suggested the presence of two ester carbonyl groups and one ketone carbonyl group, which were supported by IR absorption bands at 1738, 1725 and 1710 cm^{-1}. The ketone carbonyl group (δ_C 209.6, C-6) was found to be associated with a methyl group (δ_C 2.28, H-12) on the basis of HMBC correlation, thereby making up a methyl ketone unit. This methyl and another methyl (δ_H 1.37, H-13) groups showed the HMBC correlations with the C-5 quaternary carbon at δ_C 59.6. These spectral features imply that **3** composes of a new skeleton different from those of aforementioned three classes of *Illicium* sesquiterpenes.

The $^1H-^1H$ COSY spectrum showed cross-peaks at H-15/H-1, H-1/H-2, and H-2/H-3, indicating the presence of a structural fragment C-15/C-1 to C-3 as shown with bold line in Fig. 3. The HMBC correlations of H-8 to C-4, C-9 and C-7 as well as of H-14 to C-4, C-5 and C-7 allowed us to construct a seven-membered lactone ring, which could be fused to a five-membered carbon ring on C-4 and C-9 by the HMBC correlations as shown in Fig. 3. The remaining ester carbonyl group (δ_C 176.2) was involved in a γ-lactone ring which was fused on C-4 and C-9 on the basis of the marked downfield-shifted signal (δ_C 98.3) for C-4 and the HMBC correlations of H-10 as shown in Fig. 3. Thus, the plane structure of **3** with an unprecedented dilactone moiety was proposed.

The relative stereochemistry of **3** was established by NOESY experiment (Fig. 4) as follows. NOE correlation between H-15 and H-10β disclosed that the γ-lactone ring should be on the same face as CH_3-15. Respective NOE correlation of H-12 to H-14α and of H-13 to H-14α and H-14β made CH_3-13 assignable as a β configuration. Additionally, the hydroxyl group took a β configuration on the basis of the observed NOE correlations between H-2 and H-1/H-3α. Thus, the relative stereochemistry of merrillianin was elucidated as **3**.

In order to confirm the stereochemistry proposed for **3**, a possible biosynthetic route of **3** was taken into consideration. Its biosynthetic precursor may be pseudomajucin (**4**) or (6*R*)-pseudomajucin (**1**). The oxidative cleavage of C-6/C-7 bond in **4** or **1**, followed by the formation of a seven-membered lactone ring between C-7 and C-14, should lead to **3**. However, the oxidative cleavage of C-6/C-7 bond of pseudoanisatin-type sesquiterpenes[2] also may afford a similar skeleton, which has a spatially revised relationship of two lactone rings in comparison of **3**. Thus we attempted an oxidative cleavage of a pseudoanisatin-type sesquiterpene, 1α-hydroxy-3-deoxypseudoanisatin (**5**), which had been previously isolated from *I. merrillianum* by us.[12] Oxidative cleavage of **5** with sodium periodate in ether and water nicely proceeded to give the product **6** (Scheme 1) in good yield. The structure of **6** was elucidated by extensive analysis of spectroscopic data. Especially, the NOESY spectrum of **6** was carefully compared with that of **3**. The



Scheme 1. Oxidative degradation of **5**.

NOESY spectrum of **6**[13] revealed the presence of an additional correlation between H-8α (δ 2.57) and H-12 (δ 0.97), but no correlation between H-8β and H-15 (δ 1.09). Hence, the γ-lactone ring in **6** is fused down on C-4 and C-9 opposite to that of **3**. This chemical result not only confirms the configuration of the lactone rings in **3**, but also supports that a plausible biosynthetic precursor of **3** may be pseudomajucin (**4**) or (6*R*)-pseudomajucin (**1**).

In conclusion, we have found merrillianin (**3**) to be the first example of C-6/C-7 *seco*-pseudomajucin which can be regarded as a biogenetic significance for a variety of *Illicium* sesquiterpenes, whereas no *seco*-prezizaane sesquiterpene having a 6*R* configuration such as (6*R*)-pseudomajucin (**1**) and (6*R*)-pseudomajucinone (**2**) has been so far reported. Compounds **1**–**3** had neither neurotrophic nor toxic effects on rat cortical neurons at 1 μM.[8,14]

3. Experimental

3.1. General

Optical rotations were measured on a Jasco DIP-1000 digital polarimeter. IR spectra were measured on a Jasco FT-IR 5300 infrared spectrophotometer. NMR spectra were recorded on a Varian Unity 600 or 300 instruments. Chemical shifts were given as δ (ppm) with TMS as internal standard. The MS were recorded on a JEOL AX-500 instrument. Column chromatography was carried out on Kiselgel 60 (70–230 mesh and 230–400 mesh) and Sephadex LH-20.

3.2. Isolation and structure elucidation

3.2.1. Plant material. The ripe fruits of *I. merrillianum* were collected in Yunnan, China in September 1998 and a voucher specimen (94041) has been deposited in Beijing University of Chinese Medicine.

3.2.2. Extraction and isolation. The dried pericarps of *I. merrillianum* (3.7 kg) were powdered and extracted with methanol at room temperature to give 1 kg of pale yellow extract. The extract (430 g) was chromatographed on silica gel (70–230 mesh) eluted successively with CH_2Cl_2, CH_2Cl_2/EtOAc (9:1, 1:1), EtOAc, EtOAc/MeOH (7:3) and MeOH to yield seven fractions (A–G). Fraction E (3.7 g) was divided by column chromatography on Sephadex LH-20 eluting with methanol to give fractions 1–4. Fraction 2 (3 g) was further subjected to column chromatography on silica gel eluting with *n*-hexane/EtOAc (1:4) to afford fractions 5–12. Anisatin (41 mg), anislactone B (264 mg), cycloparvifloralone (180 mg), 3α-hydroxycycloparvifloralone (803 mg) and pseudomajucin (**4**) (861 mg) were isolated from the fractions 5–11. Fraction 12 (447 mg) was purified first by reverse phase ODS column chromatography with MeOH/H_2O (1:2) to yield fractions 13–16, the fraction 14 (207 mg) of which was subjected to silica gel chromatography eluting with $CHCl_3$/MeOH (10:1) to give a mixture (19 mg) of (6*R*)-pseudomajucin (**1**) and (6*R*)-pseudomajucinone (**2**), merrillianin (**3**) (8 mg), and pseudomajucin (**4**) (3.3 mg).

3.2.3. (6*R*)-Pseudomajucin (1) and (6*R*)-pseudomajucinone (2). $[\alpha]_D^{22}=-96.7°$ (*c* 1.48, MeOH); IR (film) 3429, 1747, 1706 cm^{-1}; HREI-MS: *m*/*z* 282.1469 (calcd for $C_{15}H_{22}O_5$, 282.1467); EI-MS: *m*/*z* (rel. int.): 282 (1), 264 (10), 234 (39), 175 (100), 113 (82); ^1H and ^{13}C NMR data: see Tables 1 and 2.

X-Ray crystallographic analysis of ***2***. Mp 192–194°C (from EtOAc); crystal data: orthorhombic, space group $P2_12_12_1$ (*Z*=8), *a*=11.1330(0), *b*=14.6620(0), *c*=17.2900(0) Å, *V*=2822.2(0) $Å^3$, radiation=Mo Kα, final *R* factor=0.053; data collection: DIP image plate; data reduction: maXus; program used to solve structure: maXus SIR92; program used to refine structure: maXus; molecular graphics: maXus.[15]

3.2.4. Methylation of 1. To a solution of **1** and **2** (8.5 mg) in methanol (1 mL) was added trimethylorthoformate (0.2 mL) and three grains of Amberlyst R 15. The mixture was stirred at room temperature for 48 h. The reaction mixture was condensed in vacuo to give the residue, which was purified by preparative TLC to afford **1a** (4.7 mg). $[\alpha]_D^{23}=-75.7°$ (*c* 0.95, $CHCl_3$); IR (film): 3499, 1765 cm^{-1}; HRFAB-MS: *m*/*z* 297.1704 (calcd for $C_{16}H_{25}O_5$, 297.1702); ^1H NMR ($CDCl_3$, 600 MHz): δ 0.97 (3H, d, *J*=7.7 Hz, H-12), 1.09 (3H, d, *J*=7.1 Hz, H-15), 1.12 (3H, s, H-13), 1.71 (1H, d, *J*=14.0 Hz, H-8), 2.07 (1H, qd, *J*=7.1 and 3.6 Hz, H-1), 2.09 (1H, dd, *J*=14.8 and 3.8 Hz, H-3), 2.11 (1H, dd, *J*=14.0 and 2.2 Hz, H-8), 2.19 (1H, q, *J*=7.7 Hz, H-6), 2.21 (1H, d, *J*=14.8 Hz, H-3), 2.79 (1H, dd, *J*=18.4 and 2.2 Hz, H-10), 2.90 (1H, d, *J*=18.4 Hz, H-10), 3.31 (3H, s, OCH_3), 3.45 (1H, d, *J*=8.8 Hz, H-14), 4.12 (1H, d, *J*=8.8 Hz, H-14), 4.20 (1H, dd, *J*=3.8 and 3.6 Hz, H-2); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 176.6 (C-11), 109.5 (C-7), 98.5 (C-4), 74.8 (C-14), 74.3 (C-2), 53.3 (C-1), 48.9 (OCH_3), 48.8 (C-9), 48.1 (C-5), 45.8 (C-8), 45.2 (C-3), 43.1 (C-6), 40.7 (C-10), 16.0 (C-13), 9.8 (C-15), 9.7 (C-12).

3.2.5. *p*-Bromophenylcarbamate (1b). To a solution of **1a** (4.7 mg) in toluene (2 mL) was added 4-bromophenylisocyanate (3 mg) and DBU (1 mg). The reaction mixture was refluxed for 18 h and then purified by silica gel chromatography with hexane/EtOAc (4:1) to give **1b** (7.6 mg) as crystals. Recrystallization from CH_2Cl_2 gave colorless plates: mp 191–192°C.

X-Ray crystallographic analysis of ***1b***. Crystal data: orthorhombic, space group $P2_12_12_1$ (*Z*=4), *a*=8.09, *b*=11.00, *c*=24.34(0) Å, *V*=2166.60 $Å^3$, radiation=Mo Kα, final *R* factor=0.0392; data collection: DIP image plate; data reduction: maXus; program used to solve structure: maXus SIR92; program used to refine structure: maXus; molecular graphics: maXus.[15]

3.2.6. Merrillianin (3). Colorless amorphous solid. $[\alpha]_D^{23}=-14.0°$ (*c* 0.61, MeOH); IR (film): 3446, 1738, 1725, 1710 cm^{-1}; HREI-MS: *m*/*z* 296.1255 (calcd for $C_{15}H_{20}O_6$, 296.1260). EI-MS: *m*/*z* 296 (1), 271 (10), 253 (20), 212 (38), 195 (69), 177 (32), 149 (34), 121 (33); ^1H and ^{13}C NMR data: see Tables 1 and 2.

3.2.7. Oxidative degradation of 1α-hydroxy-3-deoxy-pseudoanisatin (5). To a solution of **5** (4.7 mg) in H_2O and

ether (1 and 2 mL) was added $NaIO_4$ (9.8 mg, 0.046 mmol) at room temperature. After stirring the mixture for 30 min, the water layer was extracted with EtOAc three times. The combined organic layers were dried over $MgSO_4$ and condensed in vacuo to afford **6** (4.1 mg, 88%) as an oil. $[\alpha]_D^{23}$=2.9° (*c* 0.29, MeOH); IR (film): 3408 (OH), 1755 (γ-lactone), 1734 (C=O), 1716 (C=O) cm^{-1}; EI-MS: *m/z* (rel. int.): 296 (M^+, 5), 278 (7), 212 (13), 85 (34), 43 (100); HREI-MS: *m/z* 296.1254 (calcd for $C_{15}H_{20}O_6$, 296.1260); ^1H NMR (CD_3OD, 600 MHz): δ 1.37 (3H, s, H-13), 1.38 (3H, s, H-15), 1.90 (1H, dd, *J*=14.0 and 9.9 Hz, H-2α), 1.93 (1H, dd, *J*=13.7 and 9.1 Hz, H-3α), 2.16 (1H, ddd, *J*=13.7, 11.6 and 9.9 Hz, H-3β), 2.29 (3H, s, H-12), 2.34 (1H, ddd, *J*=14.0, 11.6 and 9.1 Hz, H-2β), 2.56 (1H, d, *J*=13.5 Hz, H-10α), 2.57 (1H, d, *J*=17.8 Hz, H-8α), 2.93 (1H, d, *J*=13.5 Hz, H-10β), 3.08 (1H, d, *J*=17.8 Hz, H-8β), 4.35 (1H, brd, *J*=14.3 Hz, H-14), 4.46 (1H, brd, *J*=14.3 Hz, H-14); ^{13}C NMR (CD_3OD, 150 MHz): δ 214.7 (C-6), 178.2 (C-7), 174.6 (C-11), 98.9 (C-4), 88.4 (C-1), 69.6 (C-14), 57.9 (C-5), 56.3 (C-9), 37.2 (C-8), 36.9 (C-10), 35.1 (C-2), 34.1 (C-3), 28.6 (C-12), 24.3 (C-15), 19.1 (C-13).

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