Structures of Novel Sesquiterpenes from the Pericarps of *Illicium merrillianum*

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Five new sesquiterpenes, named merrillianone (1), cyclomerrillianolide (2), merrillianolide (3), 1α-hydroxy-3-deoxypseudoanisatin (4) and 7-*O*-acetylanislactone B (5), were isolated from the pericarps of *Illicium merrillianum*, a species indigenous to southwestern China and Burma. Their structures were elucidated based on spectroscopic and chemical data. The structure of 1 was confirmed by X-ray crystallographic analysis of its acetylated derivative 1a to consist of a novel cagelike acetal and hemiacetal structure. The NMR data for compounds 2 and 3, which could not be separated due to an equilibrium mixture of keto and hemiacetal forms, were unambiguously assigned, respectively.

Key words *Illicium merrillianum*; merrillianone; cyclomerrillianolide; merrillianolide; 1α-hydroxy-3-deoxypseudoanisatin; 7-*O*-acetylanislactone B

More than 30 highly oxygenated sesquiterpene lactones and their derivatives have been isolated from *Illicium* (Illiciaceae) plants since Yamada *et al.*[1] reported the structure of anisatin, a neurotoxic principle of *Illicium anisatum* in 1968. Most of them are categorized as anisatin-type,[2] pseudoanisatin-type,[3,4] and majucin-type sesquiterpenes.[5] Our continuing studies on biologically active substances in the *Illicium* species have resulted in a number of novel sesquiterpenes and prenylated C_6-C_3 compounds.[6—10] Quite recently, T. J. Schmidt[11] reported the isolation of cycloparvifloralone (**6**) possessing an unprecedented dioxatetracyclic ring system from the leaves of *I. parviflorum*, endemic to central Florida. We have also successfully isolated **6** and its closely related sesquiterpene **1**, named merrillianone, and additional new sesquiterpenes **2**—**5**, along with the known anislactones A (**9**) and B (**10**),[12] anisatin and pseudomajucin[13] from the pericarps of *I. merrillianum*, which is a shrub or small tree indigenous to southwestern China and Burma. In this paper, we report our independent results of studies on the chemical constituents of *I. merrillianum*.

Merrillianone (**1**) has the molecular formula $C_{15}H_{22}O_5$, equivalent to five unsaturations, determined by high resolution (HR)-FAB-MS at *m/z* 283.1534 $[M+H]^+$. Its IR spectrum showed absorptions attributable to hydroxyl groups (3567 and 3483 cm^{-1}), but no absorption due to a carbonyl group. The ^1H- and ^{13}C-NMR data (Tables 1 and 2) of **1** indicated the presence of two tertiary methyl groups (δ_H 1.42 and 1.83), one secondary methyl group [δ_H 1.31 (d, J=7.2 Hz)], a trisubstituted double bond [δ_H 5.81 (br dd, J=2.4, 1.0 Hz); δ_C 123.8 and 150.2] and an isolated methylene [δ_H 2.12 and 2.73 (d, J=12.0 Hz); δ_C 43.3] as well as an oxygen-bearing isolated methylene [δ_H 3.89 and 3.99 (d, J=10.8 Hz); δ_C 75.6]. These spectral data suggested that compound **1** is a *seco*-prezizaane-type sesquiterpene[14] specifically occurring in the *Illicium* species. However, it seemed unusual that no spectral data for **1** revealed the presence of a carbonyl group in the molecule, because all of the known sesquiterpenes isolated from the *Illicium* species contained some carbonyl functions such as lactone and ketone groups. The ^{13}C-NMR spectrum contained two low-field signals resonating at δ_C 98.1 (d) and 100.0 (s), which were presumably assigned to an acetal carbon (C-11) and a hemiacetal carbon (C-7), respectively, in consideration of their shift values. This acetal proton at δ_H 5.73 (d, J=4.8 Hz) was clarified to be coupled to a vicinal proton [δ_H 4.13 (d, J=4.8 Hz)] attached to an oxygen-bearing carbon (δ_C 72.6) by ^1H–^1H correlation spectroscopy (COSY) and heteronuclear multiple quantum coherence (HMQC). Thus, these spectral data implied that **1** consists of a dioxatetracyclic framework with three hydroxyl groups, thereby accounting for its molecular formula. Next, a routine analysis of heteronuclear multiple bond correlation (HMBC), as shown in Fig. 2, enabled us to connect the C-7 hemiacetal carbon, the C-11 acetal carbon and three remaining quaternary carbons at δ_C 49.7 (C-5), 52.6 (C-9) and 78.8 (C-6) to the structural fragments obtained above.

The relative configurations at C-5, C-7, C-9 and C-11 are fixed by the cage-like structure of **1**. Fortunately, acetylation

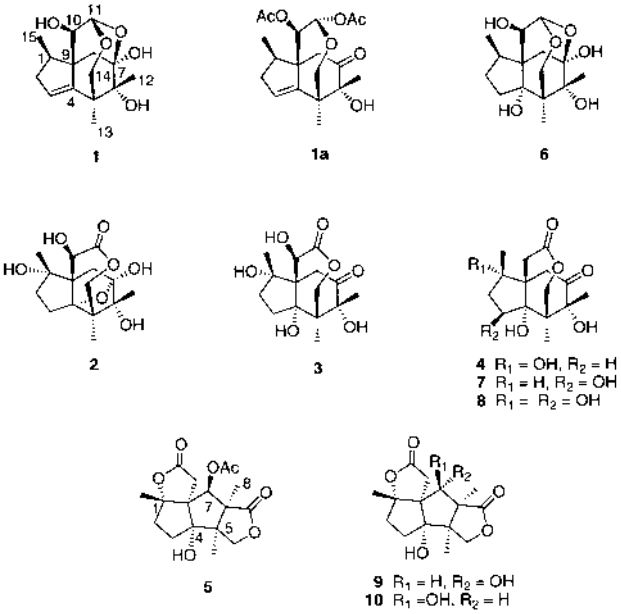

Fig. 1

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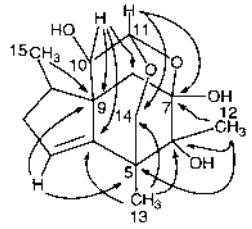

Fig. 2. Representative HMBC Correlations of **1**

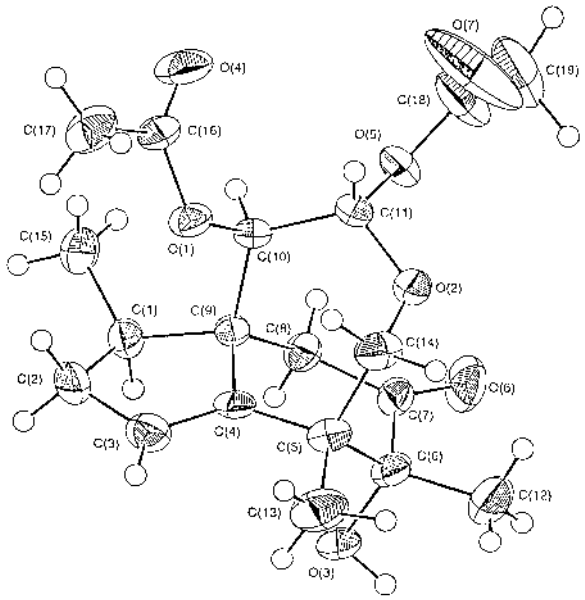

Fig. 3. ORTEP Drawing of **1a**

of **1** afforded diacetate **1a** as a single crystalline compound, which was suitable for X-ray crystallographic analysis (Fig. 3). Accordingly, the relative configurations for the other chiral centers at C-1, C-6 and C-10 were established as depicted in the ORTEP drawing in Fig. 3. It should be noted that **1** is probably equilibrated between an acetal-hemiacetal and a hemiacetal form, which is in turn acetylated to give **1a** in a solution of pyridine-acetic anhydride. Thus, the structure of merrillianone was determined to be **1**. In the course of our structural studies on **1**, we encountered Schmidt's paper reporting the unprecedented structure of cycloparvifloralone (**6**),[11] which we had also isolated from the title plant. Merrillianone (**1**) possesses a unique dioxatetracyclic ring system made up of acetal and hemiacetal functions in the same manner as **6**.

Compounds **2** and **3** could not be separated because of an equilibrium mixture of hemiacetal and keto forms in solution. Both of them have the same molecular formula, $C_{15}H_{22}O_7$, established by high resolution chemical ionization (HR-CI)-MS. The ^{1}H-NMR spectrum revealed that **2** and **3** coexisted in a ratio of approximately 1 : 1 deduced from the integration of each pair of signals. The ^{13}C-NMR spectrum of the mixture showed the presence of fifteen pairs of signals. Thus, we could unambiguously assign all of the well-resolved NMR signals to appropriate the H and C positions of compounds **2** and **3** by using various two-dimensional (2D) NMR methods (Tables 1 and 2). From analyses of ^{1}H–^{1}H COSY and HMQC, compound **3** is closely related to pseudomajucin (**7**),[3,15] but differs in the following: the presence of a new tertiary methyl group at δ_H 1.52 in **3** instead of a secondary methyl group (CH_3-15) occurring in **7**, plus a hydroxylated methine [δ_H 4.95 (d, J=5.5 Hz) and 9.08 (d, J=5.5 Hz, OH); δ_C 77.4 (C-10)] in **3** but not in **7**. In HMBC spectrum, this newly appearing tertiary methyl proton signal showed cross peaks to C-9 (δ_C 54.6), C-2 (δ_C 41.2), and C-1 (δ_C 82.6), which further correlated to a hydroxyl proton signal at δ_H 7.40. On the other hand, newly appearing hydroxylated methine (H-10) showed HMBC correlations with the C-11 carboxyl carbon (δ_C 172.0) and the C-9 quaternary carbon (δ_C 54.6). These spectral data allowed the planar structure of **3** to be assigned as 1,10-dihydroxy-3-deoxypseudoanisatin. Other characteristic HMBC correlations from four hydroxyl protons, as shown in Fig. 4, substantiated the proposed structure for **3**. The relative stereochemistry of **3** was elucidated as shown in Fig. 5 by the nuclear overhauser enhancement and exchange spectroscopy (NOESY) experiment. Thus, the structure of **3** was represented as 1α, 10β-dihydroxy-3-deoxypseudoanisatin.

As compound **2** is regarded as the counterpart of **3** in the equilibrium mixture, it is most likely that the hydroxyl group at C-4 in **3** attacks the C-7 keto group to form the hemiacetal ring in **2**. In fact, the NMR data (Tables 1 and 2) of **2** were very similar to those of **3** except for the presence of a newly appearing hemiacetal-type carbon signal at δ_C 110.3 in **2** instead of the signal due to the C-7 keto group existing in **3**. Although no HMBC correlation was observed over the oxygen bridge between C-4 and C-7 due to both the quaternary carbons, it was evident from the noticeable low-field shift of C-4 resonating at δ_C 97.5 that a hemiacetal ring was formed between C-4 and C-7. The other spectral data, including HMBC and NOESY as shown in Fig. 5, were consistent with the structure **2** having a hemiacetal ring. The structures of compounds **2** and **3** are closely related to those of cycloparviflorolide and parviflorolide recently isolated from a North American *Illicium* plant, *I. parviflorum* by T. J. Schmidt.[11] Cycloparviflorolide and parviflorolide were also isolated as unseparable equilibrium mixture with regard to keto and hemiacetal forms. However, since there is no proof correlating the absolute configurations of **2** and **3** to those of cycloparviflorolide and parviflorolide, which T. J. Schmidt's preceding studies have not refered to, we have named the new compounds **2** and **3** cyclomerrillianolide and merrillianolide, respectively.

The molecular formula of $C_{15}H_{22}O_6$ for compound **4** was established by HR-FAB-MS. Its ^{1}H-NMR spectrum (Table 1) contained three sets of signals for isolated methylene groups (H_2-8, H_2-10 and H_2-14) and three tertiary methyl groups. Its ^{13}C-NMR showed a carbonyl group (δ_C 207.1) and a carboxyl group (δ_C 172.3). These data indicated that **4** belongs to a pseudoanisatin-type sesquiterpene lactone such as pseudoanisatin (**7**) and **8**.[16] Compared with the NMR data of **7**,[3] the doublet methyl signal (CH_3-15) of **7** was replaced with a singlet methyl signal resonating at δ_H 1.29 (s) in **4**. Additionally, ^{1}H–^{1}H COSY showed the presence of a –CH_2–CH_2– fragment, and thereby a hydroxyl group should be located at C-1, but not at C-3. The other structural parts of **4** were identical with those of **7**. Moreover, HMBC of **4** confirmed the proposed structure, and the relative stereochemistry of **4** was verified to be the same as that of **7** by the ob-

Table 1. ^{1}H-NMR Spectral Data of **1**—**5**[a)]

H	**1**[b)]	**2**[b)]	**3**[b)]	**4**[b)]	**5**[c)]
1	2.10 qdd (9.6, 9.6, 7.2)				
2	2.38 ddd (14.4, 9.6, 1.0)	2.27 ddd (12.4, 12.4, 4.4)	2.41 ddd (12.0, 12.0, 6.8)	2.06 ddd (14.4, 12.0, 3.6)	1.98—2.06 m
	2.43 ddd (14.4, 9.6, 2.4)	2.52 ddd (12.4, 12.4, 4.4)	2.46 ddd (12.0, 12.0, 3.0)	2.32 ddd (14.4, 10.2, 6.0)	2.28—2.45 m
3	5.81 brdd (2.4, 1.0)	2.05 ddd (12.4, 12.4, 4.4)	2.15 ddd (12.0, 12.0, 3.0)	2.08 ddd (13.8, 10.2, 3.6)	1.50—1.85 m
		2.25 ddd (12.4, 12.4, 4.4)	2.75 ddd (12.0, 12.0, 6.8)	2.41 ddd (13.8, 12.0, 6.0)	2.06—2.12 m
7					5.32 s
8	2.12 d (12.0)	2.17 d (14.0)	2.65 d (16.8)	2.74 d (16.2)	1.21 s
	2.73 d (12.0)	3.06 d (14.0)	3.97 d (16.8)	3.88 dd (16.2, 2.4)	
10	4.13 d (4.8)	5.14 d (4.9)	4.95 d (5.5)	2.84 dd (15.6, 2.4)	2.90 d (16.9)
				2.89 d (15.6)	3.04 d (16.9)
11	5.73 d (4.8)				
12	1.83 s	1.81 s	1.75 s	1.69 s	
13	1.42 s	1.23 s	1.31 s	1.26 s	1.14 s
14	3.89 d (10.8)	4.16 d (13.2)	4.01 d (13.2)	4.00 d (13.8)	3.95 d (9.3)
	3.99 d (10.8)	5.36 d (13.2)	5.25 d (13.2)	4.57 d (13.8)	4.45 d (9.3)
15	1.31 d (7.2)	1.42 s	1.52 s	1.29 s	1.38 s
$COCH_3$					2.05 s
C_1-OH			7.40 s	7.64 s	
C_4-OH			8.06 s	8.14 s	
C_6-OH			7.94 s	8.02 s	
C_{10}-OH		8.65 d (4.9)	9.08 d (5.5)		

a) Coupling constants (*J*) in Hz are given in parentheses. *b*) 600 MHz in pyridine-d_5. *c*) 300 MHz in CD_3OD.

Table 2. ^{13}C-NMR Spectral Data of **1**—**5**

C	**1**[a)]	**2**[a)]	**3**[a)]	**4**[a)]	**5**[b)]
1	44.9	83.3	82.6	82.8	97.8
2	40.7	42.1	41.2	37.8	39.4
3	123.8	26.0	33.6	31.0	37.0
4	150.2	97.5	89.9	89.4	92.3
5	45.7	52.2	47.3	47.0	57.9[c)]
6	78.8	79.4	78.7	78.5	61.4[d)]
7	100.0	110.3	207.3	207.1	83.8
8	43.3	33.9	38.9	38.5	16.4
9	52.6	58.7	54.6	52.4	68.0
10	72.6	76.1	77.4	40.1	38.4
11	98.1	173.1	172.0	172.3	176.8
12	17.1	19.9	18.6	18.4	178.5
13	17.9	18.1	14.1	13.8	18.6
14	75.6	68.9	69.7	69.9	75.7
15	13.9	23.3	23.6	24.1	21.3
$\underline{C}OCH_3$					169.9
$CO\underline{C}H_3$					21.3

a) 150 MHz in pyridine-d_5. *b*) 75 MHz in CD_3OD. *c*, *d*) Assignments may be interchanged.

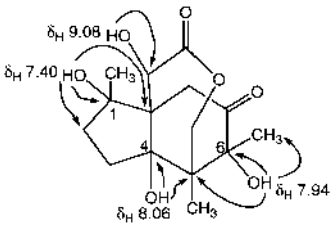

Fig. 4. HMBC Correlations from Hydroxy Protons of **3**

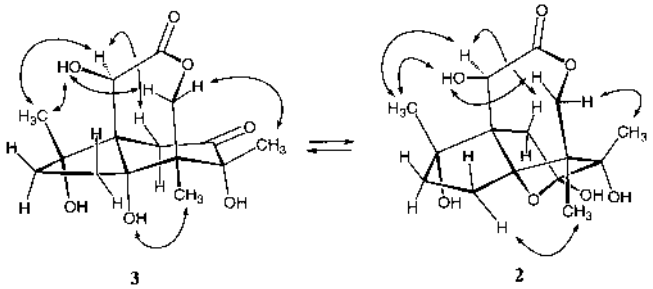

Fig. 5. Relative Configurations of **3** and **2** Based on NOEs Indicated by Arrows

servation of cross peaks between H-15 and H-10, and between H-12 and H-14 in the NOESY spectrum. Thus, the structure of **4** was assigned as 1α-hydroxy-3-deoxypseudoanisatin.

The spectral data for **5** implied that **5** is also a sesquiterpene lactone with three tertiary methyl groups and two carboxyl groups (δ_C 176.8 and 178.5) which are presumably included in γ-lactone moieties (1764 cm^{-1}) and an acetyl group (δ_H 2.05). Such a spectral feature for **5** seems to be characteristic of rarely occurring sesquiterpene lactones, anislactones A (**9**) and B (**10**) isolated from *I. anisatum*,[12] since the pseudoanisatin-type has three methyl groups and only one carboxyl group, and the anisatin- and majucin-types have two carboxyl groups and only two methyl groups. In fact, the ^{1}H-NMR and ^{13}C-NMR spectra (Tables 1 and 2) of **5** were very similar to those of anislactone B (**10**) except for the sole difference that H-7 at δ_H 3.91 in **10** was shifted downfield to δ_H 5.32 in **5**. Thus, **5** was elucidated to be 7-*O*-acetylanislactone B. This structure was confirmed by converting anislactone B into a monoacetate whose ^{1}H-NMR spectrum and specific rotation were identical with those of **5**.

According to T. J. Schmidt's proposal of a biogenetic interrelationship among specific sesquiterpenes occurring in *Illicium* plants,[11] the isolation of **1** from *I. merrillianum* provides an additional example of a biogenetic intermediate leading to a variety of *Illicium* sesquiterpene lactones from a tricyclic prezizaane skeleton.

Experimental

Melting points were determined on a PHMK05 melting point apparatus and are uncorrected. Optical rotations were measured with a Jasco DIP-1000

digital polarimeter. IR spectra were recorded on a Nicolet 20SXB or a Jasco FT-IR 5300 infrared spectrophotometer. 1D- and 2D-NMR spectra were recorded on a Varian Unity 600 or 300 instrument. Chemical shifts were given as δ (ppm) with tetramethylsilane as an internal standard. MS were recorded on a JEOL AX-500 instrument.

Plant Materials The ripe fruit of *I. merrillianum* A. C. SMITH were collected in Yunnan, China and a voucher specimen (94041) has been deposited in the Herbarium of Beijing University of Chinese Medicine.

Extraction and Purification The dried powder (4 kg) of the pericarps of *I. merrillianum* was extracted with MeOH at room temperature for 1 week. The MeOH extract was concentrated under reduced pressure to give light yellow powder (1196 g). The powder was suspended in water and then extracted successively with *n*-hexane, $CHCl_3$ and EtOAc. The $CHCl_3$ soluble part (30 g) was chromatographed on silica gel (Merck, 100—200 mesh) and eluted with $CHCl_3$–MeOH gradient, and the eluent was separated into 1—10 fractions. Fraction 2 was washed with ether and crystallized from EtOAc to give 7-*O*-acetylanislactone B (**5**) (6 g). The EtOAc soluble part was fractionated into 11—30 fractions by column chromatography on silica gel with $CHCl_3$–MeOH gradient as the eluent. 1α-hydroxy-3-deoxypseudoanisatin (**4**) (120 mg), anisatin (20 mg), anisalactones A (**9**) (13 mg) and B (**10**) (7 g), and pseudomajucin (50 mg) were obtained from fractions 14, 12, 13 and 15 by repeated recrystallization, respectively. Fractions 16—18 were subjected to silica gel chromatographic column using petroleum ether–EtOAc gradient to give a 1 : 1 mixture (120 mg) of cyclomerrillianolide (**2**) and merrillianolide (**3**), merrillianone (**1**) (2 g) and cycloparviflorolide (**6**) (140 mg).

Merrillianone (**1**): White powder (from petroleum ether–EtOAc), mp 165—167 °C, $[\alpha]_D^{21.5}$ +8.1° (c=1.33, MeOH). IR (KBr) cm^{-1}: 3567, 3483, 3393 (OH). FAB-MS *m/z*: 305 $[M+Na]^+$, 283 $[M+H]^+$. HR-FAB-MS *m/z*: 283.1534 $[M+H]^+$ (Calcd for $C_{15}H_{23}O_5$: 283.1546). ^{1}H- and ^{13}C-NMR: Tables 1 and 2.

Acetylation of **1**: To a solution of **1** (5 mg) in 0.25 ml dry pyridine was added two drops of Ac_2O and a piece of 4-*N*,*N*-dimethylaminopyridine. This solution was left overnight at room temperature and concentrated under reduced pressure to leave a residue, which was purified by silica gel chromatography to give a diacetate, **1a** (3 mg). **1a**: colorless prisms (from methanol), mp 165—166 °C. IR (film) cm^{-1}: 3482 (OH), 1740, 1714 (C=O). FAB-MS *m/z*: 389 $[M+Na]^+$. ^{1}H-NMR (200 MHz, pyridine-d_5) δ: 0.96 (3H, d, J=6.6 Hz, 15-H_3), 1.28 (3H, s, 13-H_3), 1.64 (3H, s, 12-H_3), 1.96 (3H, s, CH_3CO), 2.06 (3H, s, CH_3CO), 2.12 (1H, m, 1-H), 2.27—2.43 (2H, m, 2-H), 3.01 (1H, d, J=16.8 Hz, 8-H), 3.17 (1H, d, J=16.8 Hz, 8-H), 3.53 (1H, d, J=12.4 Hz, 14-H), 3.96 (1H, d, J=12.4 Hz, 14-H), 5.29 (1H, d, J=1.4 Hz, 10-H), 5.95 (1H, br s, 3-H), 6.06 (1H, d, J=1.4 Hz, 11-H). ^{13}C-NMR (100 MHz, $CDCl_3$): 13.4 (C-15), 14.1 (C-12), 16.0 (C-13), 20.9 ($\underline{C}H_3CO$), 21.3 ($\underline{C}H_3CO$), 39.6 (C-2), 45.8 (C-1), 48.6 (C-5), 51.0 (C-8), 52.3 (C-9), 72.5 (C-14), 77.7 (C-10), 79.7 (C-6), 100.1 (C-11), 130.5 (C-3), 144.1 (C-4), 168.6 ($CH_3\underline{C}O$), 169.6 ($CH_3\underline{C}O$), 203.5 (C-7).

X-Ray Crystallographic Analysis of **1a**: Crystal data: orthorhombic, space group $P2_1P2_1P2_1$ (Z=4), a=10.173 (0) Å, b=11.555 (0) Å, c=15.942 (0) Å, radiation=MoK_α (λ=0.71073 Å), D_{calc}=1.50 g/cm^3, final R=0.049; Data Collection: MXC (MAC Science); Cell refinement: MXC (MAC Science); Data reduction: CRYSTAN; Program(s) used to solve structure: CRYSTAN SIR-92[17]; Program(s) used to refine structure: CRYSTAN; Molecular graphics: CRYSTAN; Software used to prepare material for publication: CRYSTAN.

Cyclomerrillianolide (**2**) and merrillianolide (**3**): (data for a 1 : 1 mixture of **2** and **3**) Colorless grains (from petroleum ether–EtOAc), mp 142—144 °C, $[\alpha]_D^{23.5}$ +38.7° (c=0.64, MeOH). HR-CI-MS *m/z*: 315.1455 $[M+1]^+$ (Calcd for $C_{15}H_{23}O_7$: 315.1444). CI-MS *m/z* (rel. int.): 315 $[M+1]^+$ (31), 279 $[M-2H_2O]^+$ (100). IR (KBr) cm^{-1} 3381 (OH), 1711 (C=O). ^{1}H- and ^{13}C-NMR: Tables 1 and 2.

1α-Hydroxy-3-deoxypseudoanisatin (**4**): Colorless needles (from EtOAc), mp 198—200 °C, $[\alpha]_D^{18.6}$ −43.8° (c=0.63, MeOH). HR-FAB-MS *m/z*: 321.1299 $[M+Na]^+$ (Calcd for $C_{15}H_{22}O_6Na$: 321.1314). FAB-MS *m/z* (rel. int.): 321 $[M+Na]^+$, 154 (100). IR (film) cm^{-1}: 3239 (OH), 1730 (C=O), 1713 (C=O). ^{1}H- and ^{13}C-NMR: Tables 1 and 2.

7-*O*-Acetylanislactone B (**5**): Colorless plates (from EtOAc), mp 188—190 °C, $[\alpha]_D^{23.5}$ +3.4° (c=1.23, MeOH). IR (KBr) cm^{-1}: 3397 (OH), 1764 (C=O), 1740 (C=O). EI-MS *m/z* (rel. int.): 320 $[M-H_2O]^+$, 278(4), 113(100). HR-FAB-MS m/z: 339.1456 $[M+H]^+$ (Calcd for $C_{17}H_{23}O_7$: 339.1443). ^{1}H- and ^{13}C-NMR: Tables 1 and 2.

Acetylation of anislactone B (**10**): Anislactone B (**10**) (5 mg) was acetylated with 0.5 ml of pyridine and two drops of Ac_2O. The usual work-up gave a residue which was purified by silica gel chromatography to afford a monoacetate. Its ^{1}H-NMR data was identical with that of **5**.

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