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ILLICINOLIDES A AND B, NOVEL SESQUITERPENE LACTONES FROM THE WOOD OF *ILLICIUM TASHIROI*

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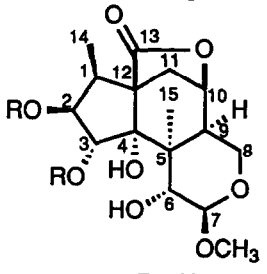
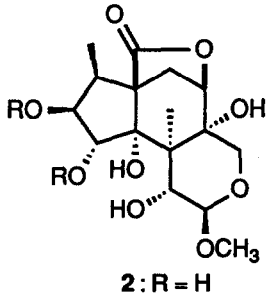
ABSTRACT: A new type of sesquiterpenes, illicinolides A (1) and B (2) has been isolated from *Illicium tashiroi*. The structure of illicinolide A was established by X-ray analysis of the *p*-bromobenzoyl derivative. Illicinolide B was assigned the structure as 9α-hydroxyillicinolide A by spectral data compared with those of illicinolide A. They are biogenetically closely related to anisatin (3) and its derivative.

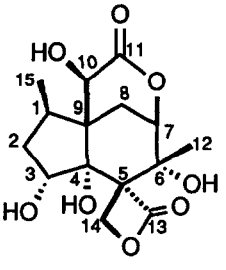
Among approximate 45 plants of *Illicium* species known in the world, the toxic plant, *Illicium anisatum* L., is the sole species indigenous to Japan. In Yaeyama islands located further south from Okinawa islands, however, a variety of this plant, *Illicium tashiroi*, has been widely grown and called "Yaeyamashikimi". The convulsive principle of *I. anisatum*, anisatin (3), was first isolated by Lane[1] and later its full structure was established as a unique sesquiterpene by Hirata and co-workers.[2,3] Since then, the chemical constituents of *I. anisatum* and the Chinese species have been intensively investigated by Kouno *et. al.*, resulting in the discovery of a number of the anisatin-[4,5] and majucin-type[6,7] sesquiterpenes as well as of new type ones.[8] On the other hand, chemical study on *I. tashiroi* has few documentations and there were no other reports but the isolation of several kinds of phytoquinoids[9] represented by illicinone A, though the occurrence of sesquiterpenes is anticipated. This prompted us to investigate chemical constituents of the woods of the title plant collected in Ishigaki island, Japan and thus new sesquiterpenes **1** and **2** with modified anisatin skeleton named illicinolides A[10] and B were successfully isolated. In this paper, we describe the full detail for the structures of these new compounds.



1 : R = H
1a : R = Ac
1b : R = *p*-BrBz



2 : R = H
2a : R = Ac
2b : R = *p*-BrBz



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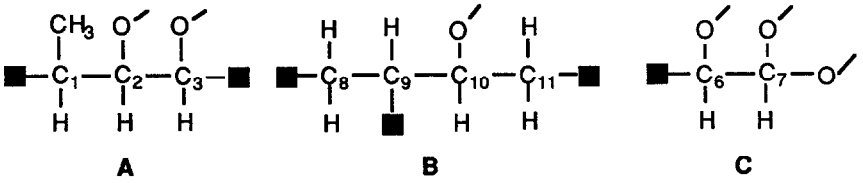
Since the methanol extract had a solubility problem in non-polar organic solvents, the extract was first absorbed on the celite and eluted in order with from less polar solvent to polar one instead of conventional solvent partition. The isolation of illicinolides A (**1**) and B (**2**) from the combined eluents with methylene chloride and EtOAc was achieved by a combination of silica gel and Toyopearl HW-40 chromatographies.

Illicinolide A (**1**), mp 133-135°C, had the molecular formula $C_{16}H_{24}O_8$ [*pos*-FABMS: *m/z* 345.1566 [M+H]$^+$, calcd 345.1560 for $C_{16}H_{25}O_8$] equivalent to five unsaturations. Its IR spectrum revealed the absorptions attributable to hydroxyl groups (3370, 3230 cm^{-1}) and a γ-lactone moiety (1750 cm^{-1}), and the presence of the latter was supported by the ^{13}C NMR data (δ 179.4). The ^{1}H NMR (C_5D_5N) spectrum (Table I) of **1** contained signals due to a secondary, a tertiary, and a methoxy methyl groups at δ 1.22 (d, J = 7.3 Hz), 1.72 (s), and 3.47 (s), respectively, in addition to well separated signals integrated with eleven protons, the spin networks of which were analyzed by DQFCOSY and ^{13}C-^{1}H COSY, giving rise to the following structural fragments **A**, **B**, and **C**:



Acetylation of **1** yielded diacetate **1a**: in the ^{1}H NMR ($CDCl_3$) spectrum of **1a** the only vicinal carbinyl protons at δ 3.96 (H-2) and 4.48 (H-3) incorporated in the partial unit **A** in **1** were down-field shifted to δ 5.39 and 5.56, indicating free hydroxyl groups bonded at C-2 and C-3. In addition, the ^{13}C NMR spectrum (Table II) and DEPT experiment showed the presence of three quaternary carbons at δ 46.3, 59.7, and 79.0 in addition to a carbonyl carbon. The each partial structure could be readily assembled together with these four quaternary carbons on the basis of HMBC (Table III) according to the following processes: the proton signal (H-1) in **A** was correlated to the carbonyl carbon signal at δ 179.4, and also to the two quaternary carbon signals at δ 59.7 (C-12) and 79.0 (C-4). The latter two carbon signals further showed cross peaks with H-11 in **B** which had a long-range coupling with the lactone carbonyl carbon. Thus, C-1 could be connected to C-11 through C-12 which is adjacent to carbonyl carbon and C-4. The remaining quaternary carbon C-5 (δ 46.3) was correlated not only to the singlet methyl (H-15) and the carbinyl methine (H-6) in **C** but also to the oxygen-bearing methylene protons (H-8) in **B**, which in turn showed clear cross peaks with the acetal carbon signal at δ 105.7 (C-7). This resulted in the formation of a six-membered hemiacetal ring between the C-7 and C-8. These spectral data cumulated in the proposal for the gross structure for illicinolide A as shown in **1**. Although NOE experiments made relative stereochemistry assignable, this unprecedent structure must be substantiated by some direct way. Fortunately, 2,3- di-*p*-bromobenzoyl derivative **1b** gave a single crystal suitable for x-ray analysis. An ORTEP drawing of the molecular structure including the absolute configuration[11] is shown in Fig. 1. Accordingly, the structure of illicinolide A has been established as **1**, having the same absolute configuration with that of **3**.

Illicinolide B (**2**), mp 196-197°C, composed of the molecular formula $C_{16}H_{24}O_9$ [FABMS: *m/z* 361.1493 [M + H]$^+$, calcd 361.1499 for $C_{16}H_{25}O_9$], has one more oxygen atom than **1**. The IR spectrum of **2** showed

Table I. ^{1}H NMR data (400 MHz) of **1**, **1a**, **2**, and **2a**[a]

Protons	**1**[b]	**1**[c]	**1a**[c]	**2**[b]	**2**[c]	**2a**[c]
1	2.93 (dq, 9.0, 7.3)	2.71 (dq, 10.0, 7.8)	2.84 (dq, 10.0, 7.6)	2.97 (dq, 9.3, 7.6)	2.64 (dq, 9.8, 7.3)	2.82 (dq, 10.0, 7.6)
2	4.61 (dd, 9.0, 4.6)	3.96 (br)	5.39 (dd, 10.0, 5.1)	4.66 (dd, 9.3, 5.0)	3.93 (dd, 9.8, 3.0)	5.37 (dd, 10.0, 5.1)
3	5.24 (d, 4.6)	4.48 (d, 3.4)	5.56 (d, 5.1)	5.27 (d, 5.0)	4.52 (d, 3.0)	5.55 (d, 5.1)
6	4.34 (d, 7.3)	3.56 (d, 7.3)	3.70 (dd, 7.3, 2.7)	4.52 (d, 7.2)	3.65 (d, 7.3)	3.68 (d, 7.3)
7	4.59 (d, 7.3)	4.25 (d, 7.3)	4.21 (d, 7.3)	4.79 (d, 7.2)	4.34 (d, 7.3)	4.28 (d, 7.3)
8	4.02 (d, 2.4)	3.96 (d, 1.5)	3.70 (dd, 12.7, 3.3)	4.11 (d, 12.2)	3.69 (d, 12.7)	3.78 (d, 12.4)
			3.94 (dd, 12.7, 1.2)	4.16 (d, 12.2)	3.76 (d, 12.7)	3.69 (d, 12.4)
9	1.84 (t, 2.4)	1.73 (t, 1.5)	1.74 (dd, 3.3, 1.2)	-	-	-
10	4.72 (d, 6.5)	4.73 (d, 5.9)	4.66 (d, 5.9)	4.81 (d, 5.9)	4.60 (d, 5.4)	4.54 (d, 5.6)
11α	2.60 (d, 11.5)	2.34 (d, 11.2)	2.41 (d, 11.5)	3.36 (d, 12.0)	2.68 (d, 12.2)	2.68 (d, 12.7)
11β	2.21 (dd, 11.5, 6.5)	2.30 (d, 11.2, 5.4)	2.24 (d, 11.5, 5.9)	2.25 (dd, 12.0, 5.9)	2.23 (dd, 12.2, 5.4)	2.24 (dd, 12.7, 5.6)
14	1.22 (d, 7.3)	0.98 (d, 7.8)	0.99 (d, 7.6)	1.29 (d, 7.6)	1.07 (d, 7.3)	1.01 (d, 7.6)
15	1.72 (s)	1.29 (s)	1.13 (s)	2.01 (s)	1.33 (s)	1.35 (s)
OCH_3	3.47 (s)	3.46 (s)	3.49 (s)	3.48 (s)	3.50 (s)	3.49 (s)
C_4-OH			2.89 (s)			
C_6-OH			2.24 (d, 2.7)			
$OCOCH_3$			2.05 (s)			2.06 (s)
			2.13 (s)			2.13 (s)

[a] J/Hz in parentheses. [b] in C_5D_5N. [c] in $CDCl_3$.

Table II. ^{13}C NMR data (100 MHz, C_5D_5N) for compounds **1** and **2**[a]

Carbons	**1**	**2**	Carbons	**1**	**2**
1	36.5	36.4	9	45.6	70.8
2	78.2	77.6	10	82.8	84.8
3	83.8	84.1	11	36.2	32.0
4	79.0	80.2	12	59.7	58.5
5	46.3	50.2	13	179.4	179.4
6	70.2	70.8	14	8.2	8.3
7	105.0	105.4	15	18.1	12.5
8	66.0	71.2	OCH_3	55.0	56.1

[a] Assignments were aided by the ^{13}C-^{1}H COSY and HMBC spectra.

Table III. ^{13}C-^{1}H long-range correlation in the HMBC[a] of **1** and **2**

Carbons	H in **1**	H in **2**
1	H-14	H-14
2	H-1, 3, 14	H-1, 14
4	H-1, 6, 11, 15	H-1, 6, 11, 15
5	H-6, 8, 9, 10, 15	H-6, 7, 8, 15
6	H-9, 15	H-15
7	H-6, 8, OCH_3	H- 8, OCH_3
8	H-10	H-10
9	H-11, 15	H-8, 11, 10, 15
10	H-8, 11	H-8, 11
12	H-1, 10, 11, 14	H-1, 11, 14
13	H-1, 10, 11	H-1, 10, 11
14	H-1	H-1
15	H-6, 9	H-6
OCH_3	H-7	H-7

[a] J = 8 Hz, in C_5D_5N.

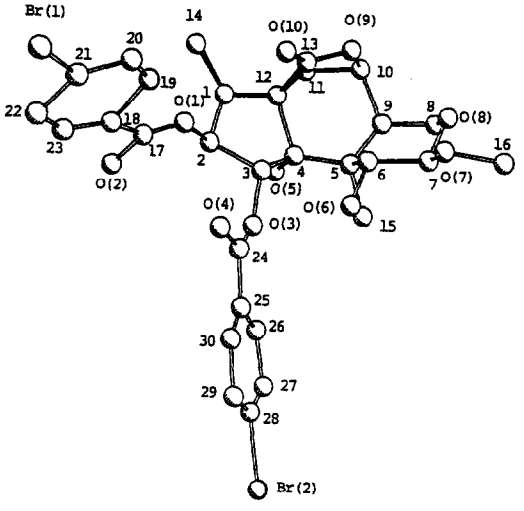


Fig. 1 ORETP drawing of the molecular structure of **1b**

the presence of a γ-lactone ring (1750 cm^{-1}) and hydroxyl groups (3500, 3400 cm^{-1}), and under usual conditions **2** afforded diacetate **2a** closely related to **1a** in ^{1}H NMR (See Table I). ^{1}H and ^{13}C NMR spectra of **2** were very similar to those of **1** except for the missing the H-9 signal of **1** in **2** and new appearance of an oxygen-bearing quaternary carbon resonanced at δ 70.8, disclosing that the H-9 in **1** was just replaced by a hydroxyl group in **2**. This difference from **1** was verified by the facts that both AB type proton signals at δ 4.11 and 4.16 (H-8) and a singlet methyl signal at δ 2.01 (H-15) were correlated to the C-9 (δ 70.8). The other molecular fragments were shown to be identical with those of **1** by the analysis of DQFCOSY and ^{13}C-^{1}H COSY and were readily connected to the remaining five quaternary carbons without any conflict resulting in the construction of the structure **2**, hydroxylated at C-9 position in **1**.

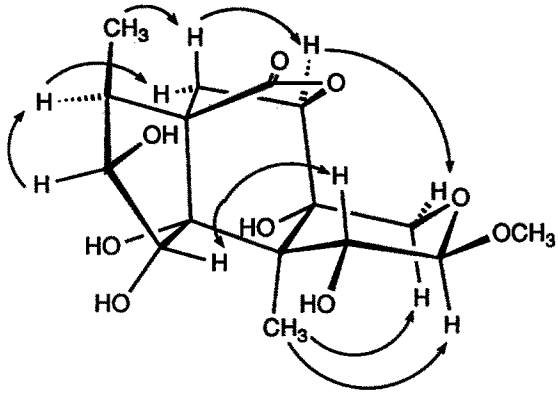
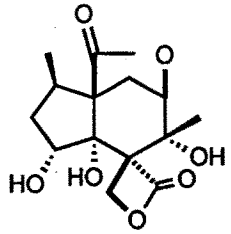


Fig. 2 Stereochemistry of **2** based on NOEs indicated by arrows.

The relative stereochemistry for **2** was elucidated on the basis of the observed NOEs as shown in Fig. 2. It was evident from the J values (J = 7.2 Hz) that the vicinal hydroxyl and methoxy groups at C-6 and C-7 take trans equatorial configuration. Comparison of the ^{1}H NMR data in C_5D_5N revealed that the presence of extra hydroxyl group caused marked down-field shifts on the signal due to C_5-CH_3 and H-11α (Table I), which could be rationalized by the paramagnetic deshielding effect[12] by coordination of pyridine molecule to the neighboring hydroxyl groups. Therefore, the hydroxyl group and the methyl group must have cis disposition. Thus, it turns out to be the relative configuration identical with that in **1**.

The absolute configuration for C-2 and C-3 were established as *S* and *R* on the basis of the CD dibenzoate chirality rule, since *p*-bromobenzoyl derivative **2b** showed first positive Cotton effect at 262 nm and negative one at 235 nm which were consistent with those observed in the CD spectrum of **1b**. Thus, the absolute structure of illicinolide B (**2**) was determined as 9α-hydroxyillicinolide A.

While illicinolides A (**1**) and B (**2**) appear to be closely related to the previously reported anisatin and majucin, the structural feature containing γ-lactone ring closed between C-10 and C-12 is rather similar to noranistain (**4**),[13] an oxidatively degraded product of anisatin (**3**). This highly oxygenated abnormal structure may be rationalized biogenetically by assuming that the C-7 carbon in **1** would originate from the C-11 in normal anisatin skeleton through, for example, a tetracyclic intermediate **5**.



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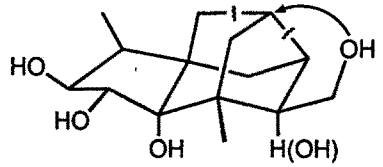

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We acknowlege Drs. H. Murata and M. Nishikawa for identification of *Illicium tashiroi*.

Experimental

All melting points were determined on a Yanagimoto hot-stage melting apparatus and are uncorrected. UV spectra were measured in EtOH on a Shimadzu UV-300 spectrophotometer. IR spectra were recorded on a

Hitachi IR 260-10 spectrometer. NMR spectra were recorded on a JEOL GX-400 spectrometer operating at 400 MHz for ^1H and 100 MHz for ^{13}C nuclei. NOE and 2-dimensional experiments were performed on the same apparatus. Chemical shifts are reported in ppm relative to tetramethylsilane as internal standard. *J*-values are given in Hz. Optical rotations were taken in EtOH with a JASCO DIP-181 polarimeter. CD spectra were recorded in EtOH on a JEOL JMS-SX 102. Merck Kiesel gel 60 (70-230 mesh, 230-400 mesh) and Wakogel (C-300) were used for silica gel column chromatography. Precoated Kiesel gel 60 F_{254} or RP8 F_{254} plates were used for analytical TLC and spots were visualized by UV (254 nm) and 2% $CeSO_4$ in H_2SO_4 after heating.

Extraction and Isolation of Illicinolides A (1) and B (2).

Dried and powdered woods (40 Kg) of *Illicium tashiroi* collected in Ishigaki island, Japan, were immersed in methanol at room temperature for 1 month. The methanol was evaporated *in vacuo* to give a gummy extract (661 g). The extract (320 g) mixed with celite (400 g) in methanol (1 l) was dried under reduced pressure. The obtained solids were pulverized, packed into a glass column, and eluted in order with *n*-hexane (1.5 l), methylene chloride (2 l), EtOAc (2 l), and methanol (2.5 l). The combined fractions (64.5 g) eluted with methylene chloride and EtOAc were divided into frs. 1 - 11 by silica gel (Kiesel gel 70 - 230 mesh, 650 g) chromatography eluting with methylene chloride (3 l) and then EtOAc (2 l). The frs.10 - 11 (1.7 g) were subjected to Toyopearl HW-40F (170 ml) chromatography eluting with methanol followed by further purification using silica gel chromatography (Wakogel C-300, 65 g; $CHCl_3$-MeOH, 9 : 1) to afford illicinolide A (**1**) (140 mg) and illicinolide B (**2**) (50 mg) as crystals.

Illicinolide A (1). Colorless needles (from *n*-hexane-methylene chloride), mp 133 - 135°C. $[\alpha]_D^{20}$ -14.6° (c 0.58). *pos*-FABMS: *m/z* 367 $[M + Na]^+$, 345.1566 $[M + H]^+$ (calcd 345.1560 for $C_{16}H_{25}O_8$). IR: ν_{max}^{KBr} 3370, 3230 (OH), 1750 (γ-lactone) cm^{-1}. ^1H and ^{13}C NMR: see Tables I and II.

Acetylation of 1. To a solution of **1** (12 mg) in pyridine (1 ml) was added acetic anhydride (0.7 ml) and the mixture was allowed to stand at room temperature for 24 h. The reaction mixture was diluted with cold water and extracted with ether. The extracts were washed with water, 10% $Cu(NO_3)_2$, and saturated $NaHCO_3$, and brine. After drying over $MgSO_4$, solvent was evaporated *in vacuo* and the residue was chromatographed on silica gel (methylene chloride-EtOAc, 4 : 1) to give **1a** (10 mg). Colorless needles (from ether), mp >250°C. *pos*-FABMS : *m/z* 477 $[M + Li]^+$, 429 $[M + H]^+$, 397 $[M + H - 42]^+$. IR: ν_{max}^{KBr} 3385, 1763, 1728 cm^{-1}. ^1H NMR: see Table I.

2, 3-Di-*p*-Bromobenzoate of 1. To a solution of **1** (10.2 mg) in pyridine (1.5 ml) was added *p*-bromobenzoyl chloride (20 mg) and the mixture was allowed to stand at room temperature for 48 h. The reaction mixture was diluted with cold water and extracted with ether. The extracts were washed with 10% $Cu(NO_3)_2$, water, saturated $NaHCO_3$, and brine. After drying over $MgSO_4$, solvent was evaporated *in vacuo* and the residue was chromatographed on alumina (methylene chloride-methanol, 4 : 1) to give **1b** (18.7 mg). Colorless prisms (from ether-methylene chloride), mp >250°C. *pos*-FABMS (rel. int.): *m/z* 713 $[M + H]^+$ (1), 711 (2), 709 (1), 681 $[M - 31]^+$ (1), 679 (2), 679 (1). IR: ν_{max}^{KBr} 3450 (OH), 1750 (γ-lactone), 1720 (ester C=O), 1590 cm^{-1}. UV: λ_{max} 201 (ε 10900), 244 (ε 9400) nm. CD: Δε (252 nm) 30.7, Δε (233 nm) -8.8. ^1H NMR ($CDCl_3$): δ 1.07 (3 H, d, *J* = 7.6, H-14), 1.35 (3 H, s, H-15), 1.80 (1 H, d, *J* = 2.7, H-9), 2.24 (1 H, d, *J* = 2.0, C_6-OH), 2.34 (1 H, dd, *J* = 11.5, 5.9, H-11β), 2.50 (1 H, d, *J* = 11.5, H-11α), 3.04 (1 H, dq, *J* = 9.8, 7.6, H-1), 3.49 (3 H, s, OCH_3), 3.78 (1 H, dd, *J* = 7.3, 2.0, H-6), 3.97 (1 H, dd, *J* =

12.7, 2.7, H-8), 4.02 (1 H, d, J = 12.7, H-8), 4.73 (1 H, d, J = 5.9, H-10), 5.68 (1 H, dd, J = 9.8, 4.7, H-2), 5.98 (1 H, d, J = 4.7, H-3), 7.56 (2 H, d, J = 8.6), 7.61 (2 H, d, J = 8.6), 7.89 (2 H, d, J =8.6), 8.11 (2 H, d , J =8.6).

Illicinolide B (2). Colorless needles (from *n*-hexane-methylene chloride), mp 196 - 197°C. $[\alpha]_D^{20}$ -32.2 (c 0.51). *pos*-FABMS: *m/z* 383 $[M + Na]^+$, 361.1493 $[M + H]^+$ (calcd 361.1499 for $C_{16}H_{25}O_9$). IR: ν_{max}^{KBr} 3500, 3400 (OH), 1750 (γ-lactone). ^1H and ^{13}C NMR: see Tables I and II. Anal. calcd for $C_{16}H_{24}O_9$: C, 53.33; H, 6.71. found: C, 53.58; H, 6.55.

Acetylation of 2. To a solution of **2** (5 mg) in pyridine (0.7 ml) was added acetic anhydride (0.5 ml) and the mixture was allowed to stand at room temperature for 24 h. The reaction mixture was diluted with cold water and then extracted with ether. The extracts were washed with 10% $Cu(NO_3)_2$, water, saturated $NaHCO_3$, and brine. After drying over $MgSO_4$, solvent was evaporated *in vacuo* and the residue was chromatographed on silica gel (methylene chloride-EtOAc, 4 : 1) to give diacetate **1a** (6.1 mg). Colorless needles (from ether), mp >250°C. pos-FABMS: *m/z* 445 $[M + H]^+$. IR: ν_{max}^{KBr} 3490, 1770, 1736 cm^{-1}. ^1H NMR: see Tables I.

2, 3-Di-*p*-Bromobenzoate of 2. To a solution of **2** (5.6 mg) in pyridine (0.8 ml) was added p-bromobenzoyl chloride (12 mg) and the mixture was stood at room temperature for 48 h. The reaction mixture was poured onto an ice-water and extracted with ether. The extracts were washed with 10% $Cu(NO_3)_2$, saturated $NaHCO_3$, and brine. After drying over $MgSO_4$, solvent was removed *in vacuo* to leave the residue, which was chromatographed on alumina (methylene chloride-methanol, 4 : 1) to give 2, 3-di-*p*-bromobenzoate **2a** (7.2 mg). Colorless prisms (from ether-methylene chloride), mp >250°C. *pos*-FABMS: *m/z* (rel. int.) 729 $[M + H]^+$ (1), 727 (2), 725 (1). IR: ν_{max}^{KBr} 3500 (OH), 1780 (γ-lactone), 1720 (ester C=O), 1580 cm^{-1}. UV: λ_{max} 202 (ε 9500), 244 (ε 10900) nm. CD: Δε (262 nm) 35.1, Δε (235 nm) -10.6. ^1H NMR ($CDCl_3$): δ 1.08 (3 H, d, J = 7.6, H-14), 1.39 (3 H, s, H-15), 2.33 (1 H, d, J = 12.7, 5.6, H-11β), 2.75 (1 H, d, J = 12.7, H-11α), 3.01 (1 H, dq, J = 9.5, 7.6, H-1), 3.47 (3 H, s, OCH_3), 3.69 (1 H, d, J = 12.5, H-8), 3.81 (1 H, d, J = 12.5, H-8), 3.84 (1 H, d, J = 7.1, H-6), 4.22 (1 H, d, J = 7.1, H-7), 5.70 (1 H, dd, J =9.5, 4.9, H-2), 5.95 (1 H, d, J = 4.9, H-3), 7.52 (2 H, d, J = 8.5), 7.60 (2 H, d, J = 8.5), 7.78 (2 H, d, J = 8.5), 8.08 (2 H, d, J = 8.5).

Crystal Data for 1b. $C_{30}H_{30}O_{10}Br_2$, Mw = 710.37, monoclinic, space group $P2_1$ (#4), a = 7.15 (1), b = 18.29 (2), c = 11.622 (8) Å, β = 104.25 (9)°, V = 1473 (3) $Å^3$, D_{calc} = 1.601 g/cm^3, μ(MoKα) = 27.77 cm^{-1}, and T = 296 K.

X-Ray Analysis of 1b. A single crystal used for the x-ray analysis was crystallized from ether-methylene chloride. Intensity data were obtained on a Rigaku AFC-5S apparatus equipped with graphite-monochromated MoKα radiation and using the ω−θ scan type ($2\theta_{max}$ = 49.9°). Of 2267 independent reflections measured, only 749 were considered as observed on the basis of criterion (I>3.00 σ (I)). The structure was solved by direct methods using MULTAN[14] and refined by the block-diagonal least-squares method. The final R value was 0.065. The absolute configuration of the molecule was determined by Bijovet's anomalous dispersion method[15] based on the observed and calculated structure factors of 10 Friedel pairs.

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