Notes

New Bis-secolabdane Diterpenoids from *Excoecaria agallocha*

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Two new bis-secolabdane diterpenoids, excoecarins R1 (**1**) and R2 (**2**), were isolated from the resinous wood of *Excoecaria agallocha*. The structures of **1** and **2** were established on the basis of spectroscopic data interpretation and chemical evidence.

The bark and wood of *Excoecaria agallocha* L. (Euphorbiaceae) have been used in traditional medicines for the treatment of flatulence in Thailand.[1] It is well known that the milky latex exuded from the bark of *E. agallocha* is poisonous and may cause temporary blindness and blistering of the skin.[2] Several skin irritant daphnane and tigliane diterpene esters have been isolated from the latex of *E. agallocha*.[1] Recently, a new phorbol ester acting as an anti-HIV principle was isolated from the stems and leaves of this species collected in northwest Australia.[3] We have previously reported the isolation and structure elucidation of several diterpenes from the resinous wood of *E. agallocha* collected in Okinawa.[4] Furthermore, the antipromoter activities of some of these diterpenes were investigated.[5] In the present study we have isolated two novel bis-secolabdane diterpenoids, named excoecarins R1 (**1**) and R2 (**2**), from the resinous wood of *E. agallocha*. The structures of these two new diterpenoids were elucidated using spectroscopic methods.

Excoecarin R1 (**1**) was isolated as the methyl ester (**1a**), $[\alpha]_D$ −22.5°, by methylation with diazomethane. The IR spectrum of **1a** showed absorption bands attributable to ester carbonyl (1700 cm^{-1}) and olefinic (1145, 1009 cm^{-1}) groups. The ^1H NMR spectrum (Table 1) showed 10 methyls at δ 0.82, 0.88, 1.12, 1.12, 1.21, 1.23, 1.24, 1.26, 1.27, and 1.28, one oxygenated methine proton at δ 3.67 (dd, J = 3.0, 8.0 Hz), two oxygenated methylene protons at δ 3.84 (dd, J = 8.0, 11.5 Hz) and 4.24 (dd, J = 3.0, 11.5 Hz), three olefinic protons at δ 4.93 (dd, J = 0.5, 11.0 Hz), 4.96 (dd, J = 0.2, 17.7 Hz), and 5.99 (dd, J = 11.0, 17.7 Hz), and three methoxyl groups at δ 3.63, 3.66, and 3.68. The ^{13}C NMR spectrum (Table 2) of **1a** showed the presence of 43 carbons including three methoxyl and four ester carbonyl carbons. These carbon signals appeared as paired signals with the exception of three methoxyls and the side-chain carbon signals.

The molecular formula for **1a** was determined by HR-FABMS as $C_{43}H_{70}O_{11}$ on the basis of the quasimolecular ion peaks observed at *m/z* 785 $[M + Na]^+$ and *m/z* 763 $[M + H]^+$. These data suggested a dimeric structure for **1a**. Inspection of the DEPT and HSQC (500 MHz) spectra also revealed the presence of 12 methylene, six methine, and eight quaternary carbons and four ester carbonyl groups. The correlations observed between the methylene protons (δ 3.84, H-15) of unit I and the carbonyl carbons (δ 179.2, C-3) of unit II in the HMBC spectrum of **1a** indicated an ester linkage connecting C-15 of unit I to C-3 of unit II (Figure 1). Detailed analysis of the ^{13}C NMR spectrum showed close correlations between the chemical shifts observed for the methyl group and methylene, methine, and ester carbonyl carbons, suggesting a structural relationship between units I and II.

Unit I of compound **1a** was characterized through analysis of the HMBC spectrum and direct comparison with the ^{13}C NMR data of **3a,**[6] with the exception of the

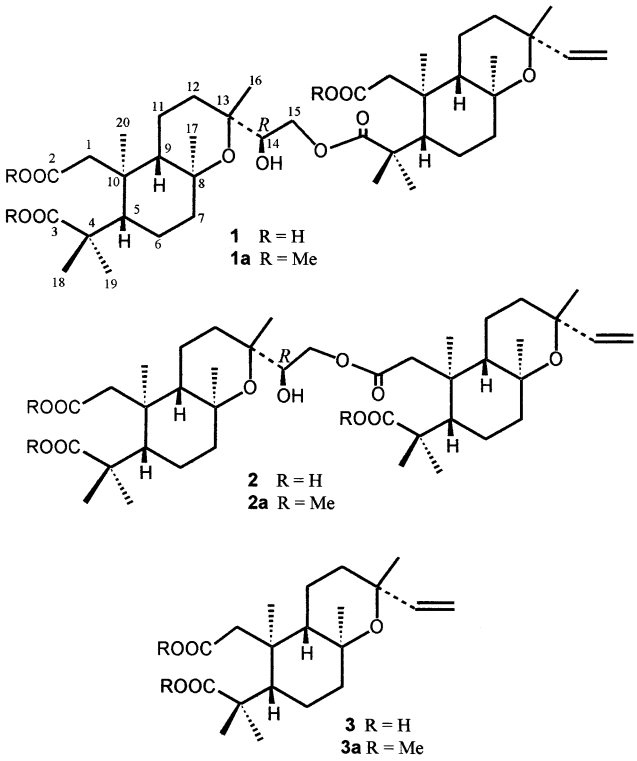

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Table 1. ^{1}H NMR Spectral Data for Compounds **1a** and **2a** in $CDCl_3$[a]

	1a		**2a**	
position	unit I	unit II	unit I	unit II
1	2.33 (d, 18.0)	2.42 (d, 17.0)	2.34 (d, 18.1)	2.44 (d, 17.1)
	2.37 (d, 18.0)	2.52 (d, 17.0)	2.38 (d, 18.1)	2.46 (d, 17.1)
5	2.47 (dd, 5.5, 11.5)	2.55 (dd, 3.0, 11.5)	2.44 (dd, 5.6, 11.6)	2.56 (dd, 3.1, 11.6)
6	1.46 (m)	1.45 (m)	1.48 (m)	1.43 (m)
	1.57 (m)	1.63 (m)	1.58 (m)	1.64 (m)
7	1.50 (m)	1.46 (m)	1.56 (m)	1.48 (m)
	1.74 (ddd, 3.0, 3.0, 12.5)	1.70 (ddd, 3.0, 3.0, 12.5)	1.75 (ddd, 3.0, 3.0, 12.5)	1.71 (ddd, 3.0, 3.0, 12.5)
9	2.49 (dd, 4.2, 12.5)	1.91 (ddd, 2.0, 2.0, 8.5)	2.49 (3.0, 12.0)	2.00 (m)
11	1.44 (m)	1.48 (m)	1.46 (m)	1.48 (m)
	1.50 (m)	1.54 (m)	1.51 (m)	1.57 (m)
12	1.49 (m)	1.43 (m)	1.55 (m)	1.45 (m)
	2.03 (ddd, 5.5, 13.0, 13.0)	2.20 (ddd, 9.0, 10.0, 12.0)	2.03 (ddd, 5.5, 13.0, 13.0)	2.20 (ddd, 9.0, 10.0, 12.0)
14	3.67 (dd, 3.0, 8.0)	5.99 (dd, 11.0, 17.7)	3.74 (dd, 2.0, 8.0)	5.99 (dd, 11.0, 18.0)
15	3.84 (dd, 8.0, 11.5)	4.93 (dd, 0.5, 11.0)	3.88 (dd, 7.8, 11.5)	4.91 (dd, 0.5, 11.0)
	4.24 (dd, 3.0, 11.5)	4.96 (dd, 0.2, 17.7)	4.29 (dd, 3.3, 11.5)	4.96 (dd, 0.2, 18.0)
16	1.12 (s)	1.12 (s)	1.12 (s)	1.12 (s)
17	1.27 (s)	1.21 (s)	1.28 (s)	1.21 (s)
18	1.24 (s)	1.26 (s)	1.22 (s)	1.25 (s)
19	1.23 (s)	1.28 (s)	1.24 (s)	1.25 (s)
20	0.88 (s)	0.82 (s)	0.87 (s)	0.82 (s)
OMe		3.66 (s)	3.68 (s)	3.67 (s)
OMe		3.63 (s)	3.63 (s)	3.65 (s)

[a] Chemical shifts (δ) are expressed in ppm relative to TMS. Multiplicity and coupling constants (J) in Hz are given in parentheses. Values were recorded at 600 MHz.

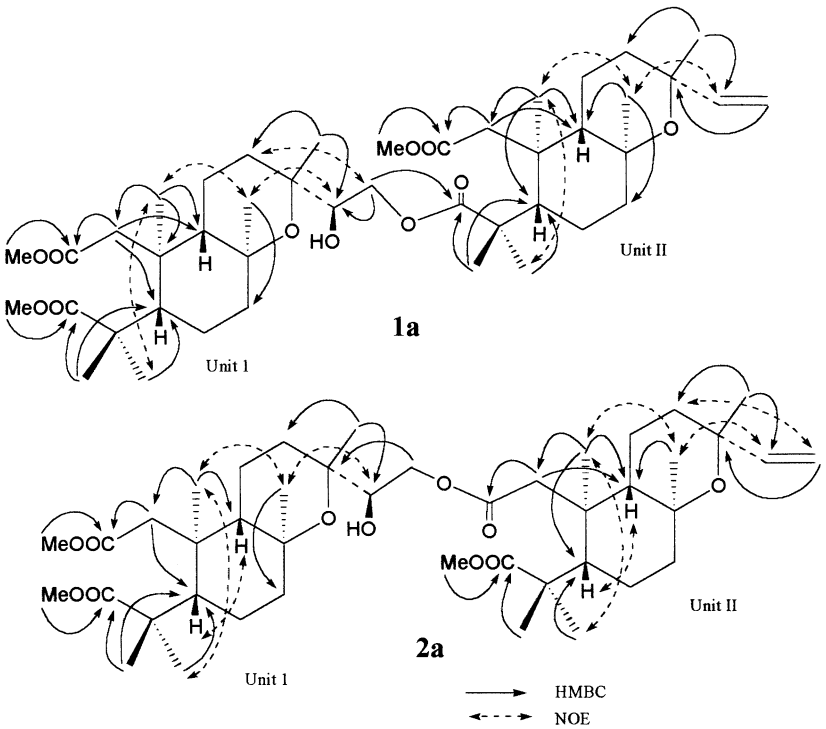

Figure 1. HMBC and NOE Correlations of **1a** and **2a**.

side-chain carbons. Correlations shown between the following atoms indicated a seco-labdane acid skeleton with a dimethyl ester, and a 1,2-dihydroxyl ethyl group as a side chain, i.e., C-9 and C-1 with Me-20; C-5 with Me-18, Me-19, and H-1; the resonance at δ 171.5 with OMe-2; the resonance at δ 179.5 with OMe-3, Me-18, and Me-19; and the hydroxyl methine carbon, C-14, with H_2-15 and Me-16.

The ^{13}C NMR spectrum of unit II of **1a** also showed the chemical shifts characteristic of olefinic carbons (δ 109.7, 147.6) in place of the dihydroxyl ethyl group observed in unit I, and one methoxyl group at δ 3.68. The structure of unit II was also determined on the basis of the observed HMBC correlations of C-2 with OMe-2, C-14 and C-12 with Me-16, C-13 with olefinic protons H-15, C-5 with Me-20, Me-19, and Me-18, and C-9 with Me-17 and Me-20. Thus, the structure of **1a** was established as a dimeric ester of a seco-labdane diacid, as shown in Figure 1. The relative stereostructure of **1a** was deduced by a NOESY experiment, with *cis* relationships between H_3-20, H_3-17, and the side chains (H-14 and H-15) in units I and II determined from the NOE correlations observed (Figure 1). The *R*-configuration of the hydroxyl group at C-14 in unit I was determined by the application of a modified Mosher's method.[7] Alkaline hydrolysis of **1a** with NaOMe gave unit I and **3a**. Oxidation of **3a** with OsO_4 gave unit I (10%) and its 14-isomer (55%).[8] Consequently, the absolute stereostructure of excoecarin R1 was established as **1**.

Excoecarin R2 (**2**) was purified as a methyl ester derivative (**2a**), $[\alpha]_D$ −11.5°. The IR spectrum of **2a** showed ester carbonyl and olefinic absorptions at 1700, 1143, and 1004 cm^{-1}. A dimeric structure for **2a** was indicated from the molecular formula of $C_{43}H_{70}O_{11}$ $[M]^+$ observed in the HREIMS. The ^1H and ^{13}C NMR (Table 2) spectra closely resembled those of **1a**. Paired signals were evident in the ^{13}C NMR spectrum with the exception of three methoxyls and the side-chain carbons. Extensive analysis of its 2D NMR spectra indicated that the planar structure of **2a** was a further bis-secolabane-type diterpenoid, as observed for **1a**. In the HMBC spectrum of **2a** (Figure 1), the observation of cross-peaks from three methoxyl signals at δ 3.63, 3.67, and 3.65 to C-3 (δ 179.5) and C-2 (δ 171.5) of unit I, and C-3 (δ 179.7) of unit II, respectively, indicated that the C-2 carbonyl carbon on unit II was linked via an ester bond to the C-15 carbinyl carbon of unit I. The relative stereochemistry of **2a** was disclosed from the NOESY spectrum (Figure 1), with NOEs observed between H-20 and H-17 and between H-17 and H-14 in both units. These data provided evidence that **2a** has a similar relative stereochemistry to **1a**. Alkaline hydrolysis of **2a** with NaOMe gave **3** and unit I, which was identified as one of the oxidation products of **3a** with OsO_4, as found for **1**.[8] The absolute configuration of C-14 of unit I was analyzed by the modified Mosher's method as mentioned earlier, resulting in *R*-stereochemistry.[7] Thus, the absolute stereostructure of excoecarin R2 was established as **2**.

Experimental Section

General Experimental Procedures. Melting points were determined on a Yanagimoto micromelting point apparatus and are uncorrected. IR spectra were recorded using a Shimadzu FTIR-8100A instrument with KBr pellets. Optical rotations were recorded in $CHCl_3$ using a Horiba DIP-370 digital polarimeter. ^1H NMR (300, 500, and 600 MHz) and ^{13}C NMR (75, 125, and 150 MHz) spectra were recorded on a Varian XL-300, a Varian INOVA-500, or a GE NMR Omega 600 spectrometer in $CDCl_3$ with TMS as internal standard. Coupling constants (*J*) are given in Hz. MS were obtained with a JEOL MS-BU 20 or a JEOL LMS-SX-120A QQ mass spectrometer. Column chromatography was performed with silica gel 60 (70−230 mesh, Merck), Lichroprep RP-18 (40−63 μm, 10 mm × 200 mm, i.d., Merck), and Sephadex LH-20 (Pharmacia). Silica gel 60 F_{254} (0.25 mm, Merck) and RP-18 F_{254}s (0.25 mm, Merck) were used for analytical TLC. HPLC was run using a Shimadzu LC-10AS Micro pump with a Shimadzu RID-2A RI detector. For HPLC, a Nova-Pak Cartridge C_{18} (Millipore Co. Ltd., Milford, MA; 100 mm × 5 mm i.d.) was used.

Plant Material. The resinous wood of *Excoecaria agallocha* was collected in August 1996, on Okinawa Island, Japan. A voucher specimen (KPU 001950) has been deposited in the Herbarium of the Department of Pharmaceutical Sciences of Natural Resources, Kyoto Pharmaceutical University, Japan.

Extraction and Isolation. The chopped resinous wood (1.2 kg) was extracted three times with diethyl ether at room temperature. Removal of the solvent from the combined diethyl ether extracts gave a brown syrup (240 g). A portion (100 g) of this brown syrup was subjected to column chromatography over silica gel using solvent mixtures of increasing polarity from hexane through EtOAc to give 10 fractions. Fraction 8 (13.5 g) was chromatographed on silica gel with $CHCl_3$−MeOH (20:1, 10:1), $CHCl_3$−MeOH−H_2O (10:1:0.1), and MeOH to yield fractions 11−20. Fraction 18 (2.03 g) was subjected to passage over a silica gel column [$CHCl_3$−MeOH−H_2O (4:1:0.1), MeOH] to give fractions 21−30. Fraction 26 (230 mg) was found to contain carboxylic acids by spraying with 2,6-dichlorophenolindophenol sodium salt on TLC.[9] Fraction 26 was treated with diazomethane for esterification. The methyl-esterified fraction 26-M was subjected to passage over Lichroprep RP-18 chromatography (87.5% MeOH) to give fractions 31−34. Fraction 31 (34 mg) was subjected to HPLC (77% MeOH) to afford the methyl esters of excoecarins R1 (**1a**, 9.4 mg) and R2 (**2a**, 7.4 mg).

Table 2. ^{13}C NMR Spectral Data for Compounds **1a** and **2a** in $CDCl_3$[a]

	1a		2a	
carbon	unit I	unit II	unit I	unit II
1	40.7 t	41.8 t	40.8 t	41.7 t
2	171.5 s	171.8 s	171.5 s	171.4 s
3	179.5 s	179.2 s	179.5 s	179.7 s
4	46.0 s	46.7 s	46.1 s	46.4 s
5	46.1 d	47.8 d	46.6 d	48.0 d
6	22.4 t	22.0 t	22.1 t	22.0 t
7	42.6 t	41.7 t	42.5 t	41.8 t
8	75.1 s	75.6 s	75.3 s	75.6 s
9	48.4 d	51.2 d	48.3 d	50.8 d
10	41.6 s	41.9 s	41.6 s	41.8 s
11	16.7 t	15.2 t	16.8 t	15.4 t
12	29.8 t	34.8 t	30.4 t	34.8 t
13	74.0 s	73.2 s	73.9 s	73.2 s
14	74.6 d	147.6 d	75.0 d	147.5 d
15	66.0 t	109.7 t	65.6 t	109.8 t
16	24.4 q	32.4 q	24.4 q	32.5 q
17	24.4 q	23.0 q	24.2 q	23.0 q
18	27.8 q	26.8 q	27.8_	27.3 q
19	23.8 q	24.7 q	23.8 q	24.1 q
20	19.0 q	19.6 q	19.1 q	19.7 q
OMe	51.0 (C-2)	51.2 (C-2)	51.0 (C-2)	
OMe	51.8 (C-3)		51.8 (C-3)	52.0 (C-3)

[a] Chemical shifts (δ) are expressed in ppm relative to TMS; assignments were made from DEPT, HSQC, and HMBC experiments. Values are recorded at 150 MHz.

Excoecarin R1 methyl ester (1a): colorless needles (MeOH); mp 152−153 °C; $[\alpha]^{22}_D$ −22.5° (*c* 0.7, $CHCl_3$); IR (KBr) 3300, 1745, 1728, 1640, 1525, 1253, 1145, 1090, 1010, 970, 910 cm^{-1}; ^1H NMR, see Table 1; ^{13}C NMR, see Table 2; EIMS *m/z* 747 (4) $[M - Me]^+$, 353 (100), 321 (88); FABMS *m/z* 785 $[M + Na]^+$, 763 $[M + H]^+$; HRFABMS *m/z* 763.4991 $[M + H]^+$ (calcd for $C_{43}H_{71}O_{11}$, 763.4997).

Excoecarin R2 methyl ester (2a): colorless amorphous powder; $[\alpha]^{22}_D$ −11.5° (*c* 0.9, $CHCl_3$); IR (KBr) 3340, 1748, 1725, 1639, 1525, 1254, 1144, 1087, 1010, 965, 910 cm^{-1}; ^1H NMR, see Table 1; ^{13}C NMR, see Table 2; EIMS *m/z* 762 (0.5) $[M]^+$, 747 (9) $[M - Me]^+$, 353 (100), 321 (76); FABMS *m/z* 785 $[M + Na]^+$, 763 $[M + H]^+$; HREIMS *m/z*, 762.4931 $[M]^+$ (calcd for $C_{43}H_{70}O_{11}$ 762.4918); HRFABMS *m/z* 763.4994 $[M + H]^+$ (calcd for $C_{43}H_{71}O_{11}$, 763.4997).

Preparation of (*S*)-(−)- and (*R*)-(+)-MTPA Ester Derivatives of 1a. Compound **1a** (1 mg) was treated with (*R*)-(−)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (10 μL) in pyridine (50 μL) at room temperature overnight, and ice water (3 mL) was then added. The water solution was passed through a Sep-Pak C_{18} cartridge, washed with 4 mL of MeOH−H_2O (7:3), and then eluted with MeOH. The MeOH solution was removed in vacuo, and the residue subjected to silica gel column chromatography by elution with hexane−EtOAc (5:1) to obtain the *S*-(−)-Mosher ester, **1a*S***: ^1H NMR ($CDCl_3$, 300 MHz) unit I δ 0.77 (H_3-20), 1.03 (H_3-16), 1.14 (H_3-17), 1.17 (H_3-18), 1.21 (H_3-19), 2.16 (H-12), 2.19 (H-1), 2.28 (H-1), 2.41 (H-5), 2.56 (H-9), 3.61 (OMe-2), 3.64 (OMe-3), 3.86 (H-15), 4.73 (H-14), 5.18 (H-15); unit II δ 0.79 (H_3-20), 1.19 (H_3-16, H_3-17), 1.22 (H_3-19, H_3-18), 2.11 (H-9), 2.15 (H-12), 2.27 (H-1), 2.35 (H-1), 2.52 (H-5), 3.59 (OMe-3), 4.91 (H-15), 4.97 (H-15), 5.99 (H-14). Treatment of **1a** (1.0 mg) with (*S*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride, as described above, yielded the *R*-(+)-Mosher ester, **1a*R***: ^1H NMR ($CDCl_3$, 300 MHz) unit I δ 0.87 (H_3-20), 1.12 (H_3-16), 1.21 (H_3-17, H_3-19), 1.24 (H_3-18), 2.28 (H-12, H-1), 2.38 (H-1), 2.45 (H-5), 2.63 (H-9), 3.63 (OMe-2), 3.66 (OMe-3), 3.67 (H-15), 4.56 (H-14), 5.29 (H-15); unit II δ 0.80 (H_3-20), 1.19 (H_3-16, H_3-17, H_3-18), 1.21 (H_3-19), 2.02 (H-9), 2.08 (H-12), 2.27 (H-1), 2.34 (H-1), 2.53 (H-5), 3.54 (OMe-3), 4.92 (H-15), 4.98 (H-15), 5.99 (H-14).

Preparation of (*S*)-(−)- and (*R*)-(+)-MTPA Ester Derivatives of 2a. Similar to the above procedure described for compound **1a**, treatment of **2a** (each 1.0 mg) with (*R*)-(−)- and (*S*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride yielded the *S*-(−)-Mosher ester, **2a*S***, and the *R*-(+)-Mosher ester, **2a*R***, respectively.

2a*S*: ^{1}H NMR ($CDCl_3$, 300 MHz) unit I δ 0.77 (H_3-20), 1.01 (H_3-16), 1.14 (H_3-17, H_3-18), 1.17 (H_3-19), 2.18 (H-12, H-1), 2.28 (H-1), 2.41 (H-5), 2.50 (H-9), 3.61 (OMe-2), 3.64 (OMe-3), 3.88 (H-15), 4.70 (H-14), 5.15 (H-15); unit II δ 0.80 (H_3-20), 1.18 (H_3-17), 1.19 (H_3-16), 1.21 (H_3-19, H_3-18), 2.07 (H-9), 2.09 (H-12), 2.37 (H-1), 2.44 (H-1), 2.47 (H-5), 3.65 (OMe-2), 4.91 (H-15), 4.96 (H-15), 6.00 (H-14). **2a*R***: ^{1}H NMR ($CDCl_3$, 300 MHz) unit I δ 0.88 (H_3-20), 1.13 (H_3-16), 1.20 (H_3-17), 1.24 (H_3-18), 1.25 (H_3-19), 2.21 (H-12), 2.26 (H-1), 2.33 (H-1), 2.44 (H-5), 2.65 (H-9), 3.63 (OMe-2), 3.65 (OMe-3), 3.76 (H-15), 4.43 (H-14), 5.26 (H-15); unit II δ 0.80 (H_3-20), 1.18 (H_3-17), 1.19 (H_3-16), 1.20 (H_3-19), 1.21 (H_3-18), 1.98 (H-9), 2.01 (H-12), 2.37 (H-1), 2.43 (H-1), 2.47 (H-5), 3.66 (OMe-2), 4.91 (H-15), 4.96 (H-15), 5.99 (H-14).

Alkali Hydrolysis of 1a and 2a. A mixture of **1a** (3 mg) or **2a** (4 mg) and NaOMe (2 mL) was stirred for 30 min under N_2. After addition of acetic acid, the reaction mixture was concentrated under reduced pressure. Each residue was purified by HPLC (MeOH−H_2O, 3:2) to give unit I and **3**.

OsO_4 Oxidation of 3a. To a solution of **3a** (50 mg) in acetone was added a reaction mixture composed of 2 mL of 0.5% osmium tetroxide catalyst solution, and 2 mL of 30% hydrogen peroxide was added. The reaction mixture was stirred for 16 h at room temperature and subsequently concentrated. The residue was extracted with chloroform three times. The chloroform solution was evaporated and purified by silica gel column chromatography ($CHCl_3$−MeOH, 50:1) to give unit I (10%) and its C-14-isomer (50%). **C-14-isomer**: colorless needles (hexane−EtOAc); mp 103−105 °C; $[\alpha]^{23}_D$ −20.5° (*c* 1.5, MeOH); ^{1}H NMR($CDCl_3$, 300 MHz) δ 0.89 (3H, s H_3-20), 1.19 (3H, s, H_3-16), 1.21 (3H, s, H_3-18), 1.22 (3H, s, H_3-19), 1.24 (3H, s, H_3-17), 1.75 (1H, ddd, J = 3.0, 3.5, 9.0 Hz, H-7), 2.03 (1H, ddd, J = 8.5, 9.0, 13.0 Hz, H-12), 2.32 (2H, s, H-1), 2.49 (1H, dd, J = 3.0, 12.0 Hz, H-5), 2.70 (1H, dd, J = 7.3, 11.5 Hz, H-9), 2.79 (1H, s, OH), 3.52 (1H, dd, J = 9.0, 11.0 Hz, H-15), 3.56 (1H, dd, J = 2.5, 11.0 Hz, H-15), 3.62 (3H, s, OMe), 3.66 (3H, s, OMe), 3.73 (1H, dd, J = 2.5, 9.0 Hz, H-14); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.4 (C-11), 18.8 (C-20), 21.9 (C-6), 23.5 (C-19), 24.4 (C-16), 25.3 (C-17), 26.6 (C-12), 28.0 (C-18), 40.4 (C-1), 41.4 (C-10), 42.8 (C-7), 44.0 (C-5), 45.8 (C-4), 48.5 (C-9), 51.0 (OMe-3), 51.8 (OMe-2), 63.0 (C-15), 74.9 (C-13), 75.2 (C-8), 77.5 (C-14), 171.5 (C-2), 179.5 (C-3); HRFABMS *m*/*z* 415.2702 $[M + H]^+$ (calcd for $C_{22}H_{39}O_7$ 415.2688).

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