Xylorumphiins A−D, Mexicanolide Limonoids from the Seed Kernels of *Xylocarpus rumphii*

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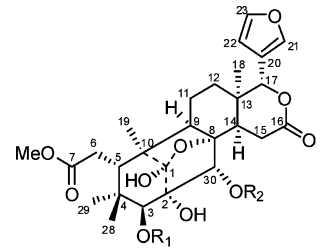
Received June 28, 2010

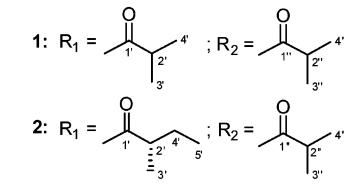
Four new mexicanolide limonoids, named xylorumphiins A−D (**1**−**4**), were isolated from the seed kernels of *Xylocarpus rumphii*, together with three known limonoids. Their structures and configurations were established on the basis of spectroscopic data.

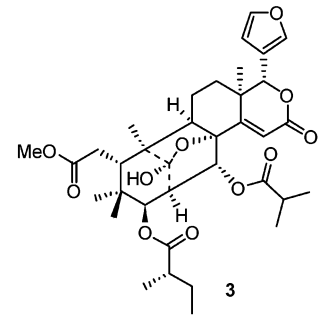
Limonoids are highly oxygenated nortriterpenoids derived from a precursor with a 4,4,8-trimethyl-17-furanylsteroid skeleton. Naturally occurring meliaceous limonoids usually have a β-furanyl ring located at C-17.[1−3] Limonoids have been found in all *Xylocarpus* plants studied, but their distribution and content vary between different species and between plant parts, or geocultivars, of the same species. Previous investigations on plants in this genus, in particular *X. granatum* and *X. moluccensis*, have led to the isolation of an array of structurally diverse limonoids with a wide range of biological activities.[4−10] Recently we reported the isolation and identification of three new protolimonoids and three new phragmalins from the seed kernels of *X. granatum* and *X. moluccensis*, respectively.[11,12] This prompted us to investigate another plant in this genus, *Xylocarpus rumphii* (Kostel.)Mabb.(Meliaceae). In the present study we report the isolation and characterization of four new mexicanolides (**1**−**4**) and three known limonoids from seed kernels of *X. rumphii*.

A MeOH extract of *X. rumphii* seed kernels was partitioned between EtOAc and H_2O to afford an EtOAc extract. The EtOAc extract was then fractionated by silica gel column chromatography (CC). Further silica gel CC and preparative HPLC separations yielded four new mexicanolides (**1**−**4**), which were named xylorumphiins A−D, and three known limonoids, xyloccensins E (**5**)[14] and K (**6**)[6] and methyl angolensate (**7**).[13] The structures of the known compounds were determined by comparison of their NMR spectroscopic data with those in the literature.

Xylorumphiin A (**1**) was obtained as a white, amorphous solid, and its molecular formula was established as $C_{35}H_{48}O_{12}$ by HRESIMS (*m*/*z* 683.3038 $[M + Na]^+$, calcd 683.3043), implying 12 degrees of unsaturation. The ^1H and ^{13}C NMR data indicated that six of the 12 units of unsaturation came from two carbon−carbon double bonds and four ester carbonyls. Therefore, the remaining degrees of unsaturation required **1** to have a hexacyclic core. On the basis of the HSQC results, **1** contained nine methyl, four methylene, 11 methine, and 11 quaternary carbons (including four carbonyls). Analysis of 1D and 2D ($^1H-^1H$ COSY, HSQC, and HMBC) NMR spectra revealed the presence of a β-furanyl ring [δ_H 6.38 (d, J = 0.9 Hz), 7.39 (t, J = 1.6 Hz), 7.53 s; δ_C 109.9 CH, 120.8 qC, 141.6 CH, 143.0 CH], a methoxycarbonyl group [δ_H 3.69 s; δ_C 51.9 CH_3, 173.9 qC], two isobutyryl groups [(δ_H 2.64 m, 1.10 (d, J = 6.8 Hz), 1.22 (d, J = 6.8 Hz); δ_C 18.3 CH_3, 20.1 CH_3, 22.9 CH, 177.8 qC); (δ_H 2.64 m, 1.10 (d, J = 6.8 Hz), 1.08 (d, J = 6.8 Hz); δ_C 17.8 CH_3, 19.6 CH_3, 33.8 CH, 174.4 qC)], and four tertiary methyls [δ_H 0.73 s, 1.04 s, 1.11 s, 1.24 s; δ_C 21.0, 22.1, 22.2, 24.2]. The above NMR data strongly suggested that **1** was a mexicanolide-type limonoid. A proton singlet at δ_H 5.19 was assigned to H-17 by HMBC correlations with the carbon signals of the furan ring (C-20, C-21, and C-23) (Figure 1). A δ-lactone ring was corroborated by the HMBC cross-peaks from H-17 to both bridgehead carbons (C-13 and C-14) and from H-14 to the methylene carbon at δ_C 29.0 (C-15) and to the carbonyl carbon at δ_C 169.7 (C-16). The HMBC correlations between C-7 (δ_C 173.9) and H_2-6 (δ_H 2.27 and 2.33), and the methoxy protons at δ_H 3.69, confirmed the characteristic C-6−C-7 appendage of mexicano-







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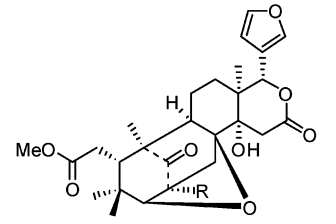

4: R = OH
6: R = H

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10.1021/np100423w
Published on Web 08/02/2010

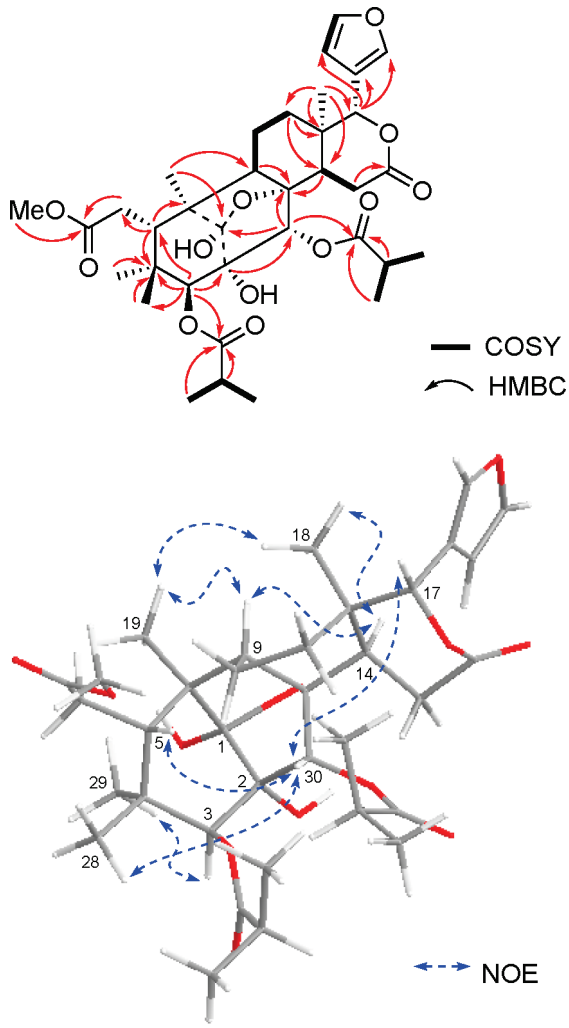

Figure 1. Key ^{1}H−^{1}H COSY, HMBC, and NOE correlations of **1**.

lides.[10] A quaternary carbon at δ_C 107.2 was assignable to C-1, a hemiketal group related to that found in the xylogranatins B−D.[15] The singlet oxymethine proton at δ_H 4.85 was assigned to H-3 through HMBC correlations from this proton to the carbons at C-2, C-4, and C-5, while another singlet proton at δ_H 6.18, showing HMBC correlations to C-1, C-3, and C-9, was assigned to C-30. An OH group was located at C-2, as confirmed by HMBC correlations of H-3 and H-30 with this carbon. Additionally, the strong HMBC cross-peaks from H-3 to an isobutyryl carbonyl at δ_C 177.8 (C-1′) and from H-30 to another isobutyryl carbonyl at δ_C 174.4 (C-1″) clarified the location of both isobutyryl groups at C-3 and C-30, respectively.

The relative configuration of **1** was established on the basis of NOE interactions. The significant NOE interactions (Figure 1) observed from H-30 to H-5 and H-17 helped to establish this 30β-H and the corresponding 30α-isobutyryl group, whereas the lack of NOE interaction from H-30 to H-3 indicated α-orientation of H-3. Moreover, the interactions of H_3-18/H-14, H_3-18/H_3-19, H_3-19/H-9, and H-9/H-14 indicated the α-orientation of H-9, H-14, Me-18, and Me-19. The structure of **1** was thus established as shown.

Xylorumphiin B (**2**) was obtained as a white, amorphous solid and had the molecular formula $C_{36}H_{50}O_{12}$, as established by HRESIMS (*m*/*z* 697.3194 [M + Na]$^+$, calcd 697.3200), which was larger than that of **1** by a CH_2 unit. The NMR data of **2** and its 2D NMR studies indicated the presence of a methoxycarbonyl group [(δ_H 3.68 s, δ_C 51.9 CH_3, 173.8 qC)], a 2-methylbutyryl group [δ_H 0.89 (t, J = 7.6 Hz), 1.20 (d, J = 7.2 Hz), 1.41 m, 1.67 m, 2.37 m; δ_C 11.2 CH_3, 25.3 CH_2, 16.8 CH_2, 40.5 CH, 177.3 qC], an isobutyryl group [(δ_H 1.08 (d, J = 6.8 Hz), 1.10 (d, J = 6.8 Hz), 2.67 m; δ_C 17.8 CH_3, 19.7 CH_3, 33.7 CH, 174.3 qC)], and a β-furanyl ring [δ_H 7.53 s, 6.38 (d, J = 1.0 Hz), 7.39 (t, J = 1.7 Hz); δ_C 141.6, 109.9, 143.0, 120.8]. The NMR data of compound **2** were virtually identical to those of **1**, with the only difference being the appearance of a 2-methylbutyryl instead of an isobutyryl group at C-3. This was confirmed by the HMBC correlation of H-30 and the 2-methylbutyryl carbonyl at δ_C 177.3. Both compounds **1** and **2** shared the same relative configuration, as confirmed by their similarities between the NOE correlations.

The absolute configuration at C-2′ of the 2-methylbutyryl group was determined as *S*, supported by the positive sign of the specific rotation of the corresponding acid derived from alkaline hydrolysis ($[\alpha]_D$ −14.3 for (*R*)-2-methylbutyric acid[16] and $[\alpha]_D$ +19.3 for (*S*)-2-methylbutyric acid).[17] Although a mixture of 2-metylbutyric acid and isobutanoic acid was obtained from the above hydrolysis, isobutanoic acid is optically active. Therefore, the absolute configuration at C-2′ of the 2-methylbutyryl group was assigned as *S* from the $[\alpha]^{25}_D$ value of +11 of this mixture. The structure of **2** was thus elucidated as shown.

Xylorumphiin C (**3**), a white, amorphous solid, had the molecular formula $C_{36}H_{48}O_{11}$, as established by HRESIMS (*m*/*z* 697.3095 [M + Na]$^+$, calcd 697.3094). The NMR data of **3** were similar to those of **2**, except for the presence of a $\Delta^{14,15}$ double bond (δ_H 6.00 s; δ_C 117.6 CH, 159.7 qC), an additional methine [δ_H 2.91 (dd, J = 9.1, 4.3 Hz); δ_C 53.2], and the absence of an oxygenated quaternary carbon in **2**. The methine was assigned as C-2 by the ^{1}H−^{1}H COSY correlations from its proton at δ_H 2.91 to H-3 and H-30 and by its HMBC correlations to C-1, C-3, and C-4. The existence of the $\Delta^{14,15}$ double bond was corroborated by HMBC correlations from H-15 to C-13, C-14, and C-16. The similar NOE correlations between **3** and **2** indicated the same stereochemistry for the core skeleton of **3** compared to **2**. The key NOE cross-peak observed in **3** from H-2 to H-3 and Me-29, along with the lack of correlation from H-2 to H-3, confirmed the α-orientation of H-2. The absolute configuration at C-2′ of the 2-methylbutyryl group was characterized as *S*, using the same method as that applied to **2**, from the $[\alpha]^{25}_D$ value of +14 of the corresponding acid.

Xylorumphiin D (**4**) was obtained as colorless crystals and had the molecular formula $C_{27}H_{34}O_9$, as established by HRESIMS (*m*/*z* 525.2101 [M + Na]$^+$, calcd 525.2101). NMR studies revealed the characteristic signals for a mexicanolide limonoid including four methyls [δ_H 0.62 s, 0.99 s, 1.06 s (2 × CH_3); δ_C 16.2, 16.8, 19.1, 28.2], a β-furanyl ring [δ_H 6.48 s, 7.44 s, 7.55 s; δ_C 140.9 CH, 110.0 CH, 143.1 CH, 120.6 qC], a methoxycarbonyl [δ_H 3.71 s; δ_C 52.0 CH_3, 174.2 qC], a ketone carbonyl (δ_C 214.8), and a lactone carbonyl (δ_C 169.7). In addition, the NMR data of **4** (Table 1) were very similar to those of xyloccensin K (**6**),[6] except for the presence of an oxygenated quaternary carbon (δ_C 85.5) and the absence of a methine group in xyloccensin K. This quaternary carbon was assigned as C-2 by HMBC correlations of this carbon with H-3 and H-30 (Figure 2). An HMBC cross-peak from H-3 to C-8 clarified the existence of an *O*-bridge between C-3 and C-8. The single-crystal X-ray diffraction analysis of **4** (Figure 3) confirmed its planar structure and allowed the determination of its relative configuration. Therefore, the structure of **4** was identified as 2-hydroxy-xyloccensin E as shown.

Experimental Section

General Experimental Procedures. Melting points were measured with a Fisher-Johns melting point apparatus. Optical rotations were measured on a Perkin-Elmer 341 polarimeter. UV spectra were recorded on a CARY 50 Probe UV−visible spectrophotometer. IR spectra were recorded on a Perkin-Elmer model 1760X Fourier transform infrared spectrophotometer. NMR spectra were recorded on a Bruker AV400 spectrometer at 400 MHz for ^{1}H NMR and at 100 MHz for ^{13}C NMR using TMS (tetramethylsilane) as the internal standard. HRESIMS spectra were obtained with a Bruker micrOTOF spectrometer. Prepara-

Table 1. NMR Spectroscopic Data (400 MHz, $CDCl_3$) for Xylorumphiins A−D (**1**−**4**)

	xylorumphiin A (**1**)		xylorumphiin B (**2**)		xylorumphiin C (**3**)		xylorumphiin D (**4**)	
position	δ_C, mult	δ_H (*J* in Hz)	δ_C, mult	δ_H (*J* in Hz)	δ_C, mult	δ_H (*J* in Hz)	δ_C, mult	δ_H (*J* in Hz)
1	107.2, C		107.2, C		107.5, C		214.8, C	
2	82.2, C		82.1, C		53.2, CH	2.91 dd (4.3, 9.1)	85.5, C	
3	80.6, CH	4.85, s	80.5, CH	4.86, s	73.8, CH	5.11, d (9.1)	93.1, CH	3.99, s
4	38.9, C		38.9, C		37.8, C		37.2, C	
5	40.3, CH	2.63, m	40.4, CH	2.60, m	40.6, CH	2.62, d (10.2)	32.6, CH	2.19, m
6	32.3, CH_2	2.33, m	32.3, CH_2	2.27, m	32.1, CH_2	2.35, m	43.7, CH_2	3.11, dd (2.4, 10.8)
		2.27, m		2.31, m		2.16, m		
7	173.9, C		173.8, C		173.8, C		174.2, C	
8	81.0, C		81.0, C		81.5, C		80.7, C	
9	63.2, CH	1.48, m	63.2, CH	1.48, m	51.5, CH	2.14, m	52.3, CH	2.00, dd (4.8, 12.0)
10	42.6, C		42.6, C		42.9, C		50.2, C	
11	19.7, CH_2	1.88, m	19.5, CH_2	1.87, m	15.0, CH_2	2.36, m	18.0, CH_2	2.61, m
		1.68, m		1.67, m		1.81, m		1.51, m
12	35.8, CH_2	1.83, m	35.8, CH_2	1.83, m	24.9, CH_2	2.19, m	28.8, CH_2	1.68, m
		1.32, m		1.32, m				1.53, m
13	36.2, C		36.2, C		38.9, C		40.1, C	
14	46.4, CH	2.22, m	46.4, CH	2.20, m	159.7, C		74.4, C	
15	29.0, CH_2	3.14, d (19.7)	29.0, CH_2	3.14, d (19.6)	117.6, CH	6.00, s	37.5, CH_2	3.30, d (18.0)
		2.73, m		2.75, m				2.54, d (18.0)
16	169.7, C		169.8, C		163.7, C		169.7, C	
17	77.1, CH	5.19, s	77.1, CH	5.19, s	81.3, CH	5.02, s	76.4, CH	6.18, s
18	22.2, CH_3	1.04, s	22.1, CH_3	1.04, s	19.7, CH_3	1.20, s	16.2, CH_3	0.99, s
19	21.0, CH_3	1.11, s	20.9, CH_3	1.11, s	20.5, CH_3	1.07, s	28.2, CH_3	1.06, s
20	120.8, C		120.8, C		120.0, C		120.6, C	
21	141.6, CH	7.53, s	141.6, CH	7.53, s	142.9, CH	7.41, s	140.9, CH	7.55, s
22	109.9, CH	6.38, d (0.9)	109.9, CH	6.38, d (1.0)	109.9, CH	6.42, s	110.0, CH	6.48, s
23	143.0, CH	7.39, t (1.6)	143.0, CH	7.39, t (1.7)	141.2, CH	7.49, s	143.1, CH	7.44, s
28	24.2, CH_3	0.73, s	24.2, CH_3	0.73, s	21.9, CH_3	1.25, s	19.1, CH_3	0.62, s
29	22.1, CH_3	1.24, s	22.0, CH_3	1.24, s	24.6, CH_3	0.78, s	16.8, CH_3	1.06, s
30	75.6, CH	6.18, s	75.5, CH	6.20, s	76.2, CH	5.54, d (4.3)	48.7, CH_2	2.71, d (12.0)
								1.95, d (12.0)
7-OMe	51.9, CH_3	3.69, s	51.9, CH_3	3.68, s	51.9, CH_3	3.68, s	52.0, CH_3	3.71, s
30-Acyl								
1″	174.4, C		174.3, C		176.4, C			
2″	33.8, CH	2.64, m	33.7, CH	2.67, m	34.1, CH	2.47, m		
3″	19.6, CH_3	1.10, d (6.8)	19.7, CH_3	1.10, d (6.8)	18.8, CH_3	1.10, d (6.8)		
4″	17.8, CH_3	1.08, d (6.8)	17.8, CH_3	1.08, d (6.8)	18.9, CH_3	1.10, d (6.8)		
3-Acyl								
1′	177.8, C		177.3, C		175.8, C			
2′	33.9, CH	2.64, m	40.5, CH	2.37, m	41.1, CH	2.28, m		
3′	18.3, CH_3	1.10, d (6.8)	16.8, CH_3	1.20, d (7.2)	16.1, CH_3	1.13, d (7.4)		
4′	20.1, CH_3	1.22, d (6.8)	25.3, CH_2	1.67, m	26.2, CH_2	1.64, m		
				1.41, m				
5′			11.2, CH_3	0.89, t (7.6)	11.5, CH_3	0.88, t (7.4)		

tive HPLC was performed using a GL Science column (length 250 mm, i.d. 20 mm) packed with C18 (3 μm) stationary phase.

Plant Material. The seed kernels of *X. rumphii* were collected from Rayong Province, Thailand, during April 2009. Plant material was identified by the Royal Forest Department, Bangkok, Thailand. A voucher specimen (BKF No. 163884) was deposited at the Forest Herbarium, Royal Forest Department, Bangkok, Thailand.

Extraction and Isolation. Air-dried and powdered seed kernels of *X. rumphii* (0.5 kg) were extracted with MeOH (2 L × 3, each for 2 days) at room temperature. Extracts were pooled, and the solvent was removed under reduced pressure. The combined MeOH crude extract was then suspended in H_2O (250 mL) and partitioned with EtOAc (200 mL × 3) to afford the crude EtOAc extract (4.10 g). The EtOAc extract was chromatographed on a silica gel column eluted with a gradient of acetone−hexane (10%−50%) to yield 15 fractions (I−XV). Fraction XIII was subjected to CC over silica gel eluting with acetone−CH_2Cl_2 (5%−15%) to give xylorumphiin C (**3**, 11.0 mg). Fraction IX was chromatographed using silica gel CC and acetone−CH_2Cl_2 (5%−100%) to obtain methyl angolensate (**7**, 34.6 mg). Fraction XI was subjected to silica gel CC eluting with acetone−benzene (10%−15%) and further separated by preparative HPLC (C18) silica gel using a mixture of MeOH−H_2O (80%) to afford xylorumphiins A (**1**, 19.1 mg) and B (**2**, 30.5 mg), respectively. Fraction XII was separated on a silica gel column eluting with MeOH−CH_2Cl_2 (2%−5%) and then crystallized from MeOH to obtain xyloccensin E (**5**, 79.0 mg). Fraction XIII was chromatographed on a silica gel column using acetone−CH_2Cl_2 (15%) to furnish xyloccensin K (**6**, 44.9 mg) and xylorumphiin D (**4**, 26.1 mg), respectively.

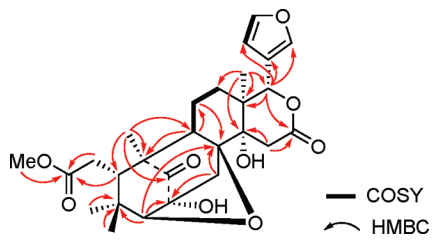

Figure 2. Key $^1H-^1H$ COSY and HMBC correlations of **4**.

Xylorumphiin A (1): white, amorphous solid; mp 124−126 °C; $[\alpha]_D^{20}$ −115 (*c* 0.1, $CHCl_3$); UV ($CHCl_3$) λ_{max} (log ε) 243 (3.10) nm; IR (KBr) ν_{max} 3460, 2978, 1733, 1456, 1385, 1189, 1151, and 1017 cm^{-1}; ^1H and ^{13}C NMR ($CDCl_3$) see Table 1; HRESIMS *m/z* 683.3038 $[M + Na]^+$ (calcd for $C_{35}H_{48}O_{12}Na$, 683.3043).

Xylorumphiin B (2): white, amorphous solid; mp 115−117 °C; $[\alpha]_D^{20}$ −38 (*c* 0.1, $CHCl_3$); UV ($CHCl_3$) λ_{max} (log ε) 241 (2.66) nm; IR (KBr) ν_{max} 3445, 2965, 1730, 1460, 1386, 1291, 1195, and 1147 cm^{-1}; ^1H and ^{13}C NMR ($CDCl_3$) see Table 1; HRESIMS *m/z* 697.3197 $[M + Na]^+$ (calcd for $C_{36}H_{50}O_{12}Na$, 697.3200).

Xylorumphiin C (3): white, amorphous solid; mp 180−182 °C; $[\alpha]_D^{20}$ −13 (*c* 0.1, $CHCl_3$); UV ($CHCl_3$) λ_{max} (log ε) 245 (3.48) nm; IR (KBr) ν_{max} 3393, 2973, 1723, 1461, 1380, 1294, 1256, 1189, and 1151

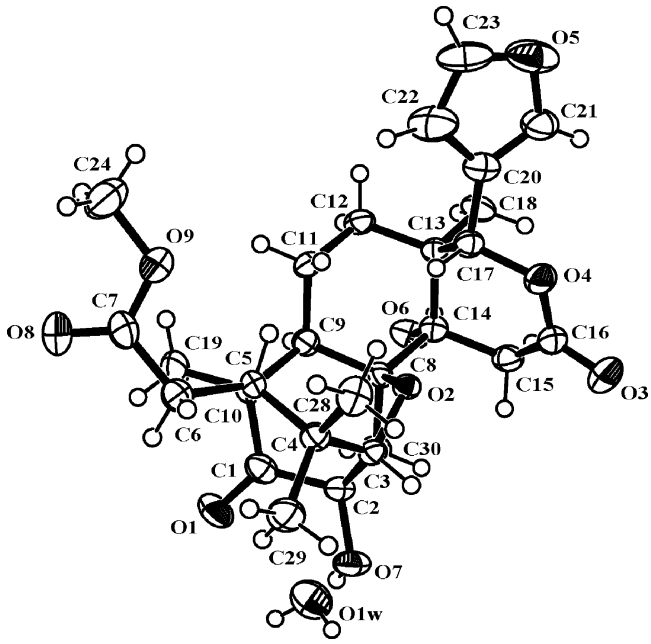

Figure 3. ORTEP diagram of **4**.

cm^{-1}; ^1H and ^{13}C NMR ($CDCl_3$) see Table 1; HRESIMS *m/z* 697.3095 $[M + Na]^+$ (calcd for $C_{36}H_{48}O_{11}Na$, 697.3094).

Xylorumphiin D (4): colorless crystals; mp 208−210 °C; $[\alpha]_D^{20}$ +4 (*c* 0.1, $CHCl_3$); UV ($CHCl_3$) λ_{max} (log ε) 242 (2.32) nm; IR (KBr) ν_{max} 3445, 2949, 1723, 1452, 1375, 1270, 1165, and 1041 cm^{-1}; ^1H and ^{13}C NMR ($CDCl_3$) see Table 1; HRESIMS *m/z* 525.2101 $[M + Na]^+$ (calcd for $C_{27}H_{34}O_9Na$, 525.2101).

X-ray Crystallographic Analysis of Xylorumphiin D (4). Crystal data: colorless crystal (MeOH); $C_{27}H_{36}O_{10}$, $M_r = 520.56$, orthorhombic, $P2_12_12_1$, $a = 10.0323(4)$ Å, $b = 10.9812(5)$ Å, $c = 22.1156(10)$ Å, $Z = 4$, and $V = 2472.76(19)$ Å^3, Mo Kα radiation, $\lambda = 0.71073$ Å. The intensity data were collected at 293 K to a maximum 2θ value of 56.56°. Of the 13 069 reflections collected, 6104 were unique ($R_{int} = 0.0484$). The crystal structure was solved by direct methods using the SHELXS97[18] program. Refinements were made by full-matrix least-squares on all F^2 data using SHELXL97[19] to final *R* values [$I > 2\sigma(I)$] of $R_1 = 0.0428$, $wR_2 = 0.0854$ and goodness of fit on $F^2 = 0.888$. All non-hydrogen atoms were anisotropically refined. All hydrogen atoms were added at calculated positions and refined using a rigid model. Crystallographic data for **4** have been deposited with the Cambridge Crystallographic Data Centre (deposition number CCDC 782257). Copies of the data can be obtained, free of charge, via www.ccdc.cam.ac.uk/data_request/cif, or by e-mailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK: fax: +44 1223 336033.

Absolute Configurations at C-2′ of the 2-Methylbutyryl Moiety of Xylorumphiins B (2) and C (3). Compound **2** (10 mg) was dissolved in EtOH (0.5 mL), then treated with 10% aqueous KOH solution (1 mL) at room temperature. After stirring overnight, the mixture was concentrated and washed with EtOAc (×3). The aqueous layer was then acidified with HCl to pH 3.0 and extracted with CH_2Cl_2 (×3). The combined organic layer was subjected to Sephadex LH-20 CC (CH_2Cl_2−MeOH, 1:1) to yield a mixture of 2-methylbutyric acid and isobutanoic acid (2.3 mg). Since isobutanoic acid is optically active, the absolute configuration at C-2 of 2-methylbutyric acid was identified as *S* by the $[\alpha]^{25}_D$ +11 (*c* 0.1, acetone). In a similar fashion, the absolute configuration at C-2′ of the 2-methylbutyryl group of **3** was also indicated as *S*.

Acknowledgment. This work was supported by The 90th Anniversary of Chulalongkorn University Fund (Ratchadaphisek Somphot Endowment Fund), the Ratchadaphisek Somphot Endowment Fund (AG001B), and the Thai Government Stimulus Package (TKK2555) under the Project for Establishment of Comprehensive Center for Innovative Food, Health Products and Agriculture. We also thank the Center for Petroleum, Petrochemicals, and Advanced Materials, Chulalongkorn University, for partial support.

Supporting Information Available: HRESIMS and NMR spectra of compounds **1**−**4** are available free of charge via the Internet at http://pubs.acs.org.

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NP100423W