Xylocarpins A−I, Limonoids from the Chinese Mangrove Plant *Xylocarpus granatum*

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Chemical examination of the fruits of the Chinese mangrove plant, *Xylocarpus granatum*, resulted in the isolation and characterization of nine new limonoids, named xylocarpins A−I (**1**−**5**, **7**−**10**), along with nine known limonoids. Xylocarpins A−E were designated as polyoxyphragmalins, xylocarpin I was identified as a phragmalin orthoester, while xylocarpins F−H represented mexicanolides modified by ring oxidation and unusual 9,10-bond cleavage. The structure of xyloccensin U was revised to be 6-dehydroxyxylocarpin D on the basis of 2D spectroscopic data.

The mangrove plant, *Xylocarpus granatum* Koenig (Meliaceae), is used as a folk medicine in Southeast Asia for the treatment of diarrhea, cholera, and fever diseases such as malaria and also as an antifeedant.[1] Since the first limonoid, gedunin, was reported from this plant by Taylor,[2] the unique structural patterns of limonoids have attracted wide attention. Hitherto, more than 40 limonoid derivatives have been isolated from *X. granatum*, and they have been classified into phragmalin, mexicanolide, and andirobin types. The limonoid metabolites have been found in all *Xylocarpus* plants, but their distribution and content vary in different plant parts. The fruits (also named seeds) mainly contain mexicanolides (xyloccensins A−K,[1−8] M, and N and their 3-deacetylated analogues[9−10] X and Y,[11] X_1 and X_2,[12] xylogranatins A−D[13]), polyoxyphragmalins (xyoccensins Y, Z_1, and Z_2[14]), and some minor components involving obacunol and andirobins. The stem and bark are rich in phragmalin orthoesters,[15−17] accompanied by a few unusual polyhydroxyphragmalins.[18]

In a systematic chemical examination of Chinese mangrove plants, we investigated the minor limonoids from the fruit rind of *X. granatum* using HPLC. Nine new limonoid derivatives, xylocarpins A−I (**1**−**5**, **7**−**10**), and nine known limonoids were isolated. Among the latter, proceranolide,[19] khayasin T,[20] and febrifugin A,[21] originally identified from the genus *Khaya* (Swietenieae), were obtained for the first time from the genus *Xylocarpus*. Xyloccensins K, P, and U[13,22] and xylogranatins A−C[23] were also recently reported from this plant. Their structures were elucidated on the basis of IR, MS, ^{1}H and ^{13}C NMR, and 2D NMR spectroscopic data analysis.

Results and Discussion

Xylocarpin A (**1**) was isolated as a white, amorphous powder, and its molecular formula was established as $C_{35}H_{44}O_{14}$ by HRFABMS (*m*/*z* 711.2590 $[M + Na]^+$, calcd 711.2623), which indicated 14 degrees of unsaturation. The IR absorptions at 3416, 1739, and 1700 cm^{-1} suggested the presence of hydroxy, lactone, and ester groups. The ^{1}H NMR spectrum (Table 1) displayed resonances for a β-substituted furan ring at δ 7.45 (1H, s, H-21), 6.38 (1H, s, H-22), and 7.44 (1H, s, H-23), four oxymethines at δ 5.30 (1H, d, J = 11.4 Hz, H-3), 5.40 (1H, br s, H-6), 5.74 (1H, s, H-17), and 5.45 (1H, d, J = 2.3 Hz, H-30), and seven methyl singlets at δ 2.21 (3H, s, Ac), 2.17 (3H, s, Ac), 2.15 (3H, s, Ac), 2.07 (3H, s, Ac), 1.19 (3H, s, H-19), 1.03 (3H, s, H-28), and 1.00 (3H, s, H-18). The ^{13}C NMR and DEPT spectra displayed 35 carbon atoms, involving six carbonyl resonances (δ 170.7, 170.3, 170.2, 169.7, 169.5, and 168.5), four monosubstituted furan carbons, and six oxygenated sp^3 carbons (Table 2). Four of the carbonyl resonances were attributed to acetyl groups, on the basis of HMBC correlations between the acetyl methyl protons and the respective carbonyl resonances (Figure 1). The NMR data (Tables 1 and 2) were indicative of a polyoxygenated phragmalin, similar to those of xyloccensin Z_2, a polyhydroxylated phragmalin also isolated from the fruit of the same plant,[14] with the exception that **1** contains four acetyl groups instead of two. A comparison of the NMR spectra revealed that C-1 of **1** shifted to δ 88.0 (s), ~6.0 ppm farther downfield than the corresponding C-1 of xyloccensin Z_2, while H-6 of **1** was shifted downfield to δ 5.40 (s), in contrast to δ 4.42 (s) of xyloccensin Z_2. These findings suggested the presence of two acetoxy groups at C-1 and C-6, respectively, which were in agreement with the reported data for xyloccensin U.[22] The HMBC correlations between H-3/C=O (δ 169.9, s), H-6/C=O (δ 169.7, s), and H-30/C=O (δ 170.7, s) supported the positions of the other acetoxy groups. The presence of a C-8 hydroxy group was evident from the HMBC correlations of the hydroxy proton at δ 4.34 (br) with C-8 (δ 73.6, s), C-9 (δ 55.6, d), and C-14 (δ 50.7, d).

The relative configuration of **1** could be established on the basis of the NOESY spectrum and coupling constants. Since the pentacyclic rings A_1 and A_2 in a tricyclo[3.3.1.^{2,10}1^{1,4}]decane unit were locked in a "basket" form, the NOE correlations between H-2/H-5 and H-5/H-11b (δ 1.90, m) led to the assignment of the β-orientation for H-2 and H-5, while H-19 should be α-oriented. The *cis*-fused rings B/C and C/D were confirmed by the NOESY correlations between H-2/H-11b and between H_3-18/H-14 (δ 2.04, d), as well as the NOESY correlation from OH-8 (δ 4.34, br s) to H-9 and H-14. These NOE data also defined a β-orientation of H-30. An additional NOE correlation between H-17/H-12b (δ 1.91, m) determined the β-orientation of H-17, which appeared in all meliacins but is not exclusive to phragmalins. The presence of NOE correlations from H-3 to H-29a (δ 2.49, d) and H_3-28 and from H_3-19 to H-29b (δ 2.27, d) and H-6 guided the assignment of H-3α, H_3-19α, and H-5β. The J values ($J_{14/15}$ = 8.4 Hz, and $J_{2/3,30}$ = 2.3, 11.4 Hz) in association with the NOE relationship (Figure 2) indicated that rings B and C adopt boat conformations, while the D ring adopts a semichair form. A singlet representing H-6 of the side chain indicated a 90° dihedral angle with H-5, as observed in the ^{1}H NMR spectra of all phragmalins with an OH or OAc group at C-6. Since the absolute configuration of C-6 in xyloccensin P

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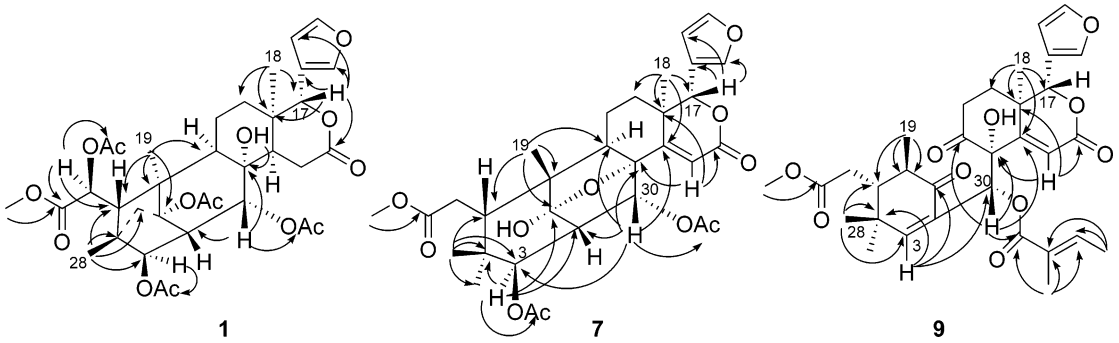


Figure 1. HMBC correlations of xylocarpins A, F, and H (**1**, **7**, **9**).

Table 1. ^{1}H NMR Data of Xylocarpins A−E and Xyloccensin U (**1**−**6**)[a]

position	1	2	3	4	5	6
2	3.00 dd (2.3, 11.4)	3.00 dd (2.3, 11.4)	2.36 dd (2.8, 11.4)	3.03 dd (2.5, 11.5)	3.03 dd (2.5, 11.4)	3.02 dd (2.5, 11.5)
3	5.30 d (11.4)	5.37 d (11.4)	5.31 d (11.4)	5.26 d (11.5)	5.30 d (11.4)	5.36 d (11.5)
5	3.26 br s	3.03 dd (3.5, 10.0)	2.94 dd (3.0, 9.5)	2.92 s	3.20 s	2.97 dd (3.0, 9.0)
6	5.40 br s	2.31 dd (3.5, 16.5)	2.29 dd (3.0, 16.0)	4.29 s	5.40 s	2.23 dd (3.0, 16.0)
		2.25 dd (10.0, 16.5)	2.24 dd (9.5, 16.0)			2.25 dd (9.0, 16.0)
9	1.90 m	1.83 m	2.06 m	2.24 dd (4.0, 14.0)	2.19 m	2.14 m
11	1.76 m	1.80 m	2.20 m	1.86 ddd (4.0, 4.0, 15.0)	1.90 m	1.97 m
	1.43 m	1.92 m	2.00 m	2.05 m	2.00 m	2.12 m
12	1.91 m	1.94 m	4.99 br s	5.03 br s	3.84 br s	5.01 br s
	1.45 m	1.42 ddd (2.5, 11.5, 11.5)				
14	2.04 d (8.4)	2.03 dd (1.5, 8.5)	2.44 d (8.2)	2.44 d (8.5)	2.44 d (8.3)	2.43 d (8.5)
15α	3.38 d (19.2)	3.37 dd (1.5, 19.5)	3.13 br d (19.2)	3.40 d (19.5)	3.35 d (19.5)	3.36 d (19.4)
15*β*	2.76 dd (8.4, 19.2)	2.75 dd (8.5, 19.5)	2.72 dd (8.2, 19.2)	2.69 dd (8.5, 19.5)	2.67 dd (8.3, 19.5)	2.68 dd (8.5, 19.4)
17	5.74 s	5.73 s	5.77 s	5.76 s	5.73 s	5.80 s
18	1.00 s	0.99 s	1.04 s	1.03 s	1.11 s	1.03 s
19	1.19 s	1.11 s	1.06 s	1.42 s	1.19 s	1.09 s
21	7.45 br s	7.46 br s	7.53 br s	7.45 br s	7.46 br s	7.51 br s
22	6.38 br s	6.40 br s	6.41 br s	6.37 br s	6.38 br s	6.41 br s
23	7.44 br s	7.44 br s	7.47 br s	7.47 br s	7.46 br s	7.46 br s
28	1.03 s	0.88 s	0.85 s	0.96 s	1.02 s	0.88 s
29a	2.49 d (11.0)	2.44 d (11.0)	1.96 d (10.8)	2.43 br	2.49 d (10.5)	2.01 d (10.5)
29b	2.27 d (11.0)	1.98 d (11.0)	1.46 d (10.8)	2.43 br	2.26 d (10.5)	2.46 d (10.5)
30	5.45 d (2.3)	5.50 d (2.3)	5.44 d (2.8)	5.45 d (2.5)	5.46 d (2.5)	5.51 d (2.5)
7-OMe	3.78 s	3.71 s	3.71 s	3.87 s	3.78 s	3.71 s
1-OAc	2.15 s	2.16 s		2.17 s	2.26 s	2.10 s
3-OAc	2.17 s	2.18 s	2.16 s	2.12 s	2.15 s	2.17 s
6-OAc	2.21 s				2.22 s	
12-OAc			2.11 s	2.12 s		2.17 s
30-OAc	2.07 s	2.07 s	2.11 s	2.08 s	2.08 s	2.09 s
8-OH	4.34 s	4.34 s		4.49 s	4.19 s	4.43 br s

[a] Measured in $CDCl_3$.

from the same plant was determined by X-ray crystallography,[15] the compatible NMR data and the similarity in the NOE relationship at H-6 of **1** with that of xyloccensin P enabled the assignment of the configuration in **1** as 6*R*. Similar data were also observed for the following phragmalins with 6-oxygenation.

The structures of **2**−**5** were determined to be polyoxygenated phragmalins. They all exhibited the same basic skeleton as **1** but with different substitution patterns, according to spectroscopic data analysis and comparison of their NMR data with those of **1** and xyloccensin U[22] (Tables 1 and 2).

The ^{1}H and ^{13}C NMR data of **2** were similar to those of **1**, except for the presence of an additional methylene group (*δ* 2.25, dd; 2.31, ddd; and 33.6, t) and the absence of the C-6 oxymethine resonance of **1**, thus indicating that **2** was a 6-deacetoxy analogue of **1**. This conclusion was also confirmed by the molecular formula of **2** as $C_{33}H_{42}O_{12}$, 58 amu less than that of **1**, as determined by HRFABMS and NMR data. The COSY correlation between H-5 (*δ* 3.00, dd, J = 3.5, 10.0 Hz) and H_2-6 (*δ* 2.31, dd, J = 3.5, 16.5 Hz; 2.25, dd, J = 10.0, 16.5 Hz) and the HMBC correlation from H_2-6, H-5, and the methoxy protons (*δ* 3.71, s) to a carbonyl carbon at *δ* 173.4 (s, C-7) provided additional evidence that **2** contained a methylene group at C-6. Compounds **2** and **1** both share the same configuration as confirmed by similarities between the NOESY correlations and the NMR data (Tables 1 and 2).

Xylocarpin C (**3**) had a molecular formula of $C_{33}H_{42}O_{13}$ as determined by HRFABMS, suggesting 12 degrees of unsaturation. The structural pattern of **3** shared the same polyoxygenated phragmalin skeleton as that of **2**. Comparable ^{1}H NMR data displayed three acetyl methyls at *δ* 2.11 (6H, s) and 2.16 (3H, s), correlating with carbonyl carbons at *δ* 170.7 (s), 169.8 (s), and 169.9 (s) in the HMBC spectrum, respectively. Two acetoxy groups were positioned at C-3 and C-30 as previously assigned in **1** and **2** and were confirmed by NMR data and the HMBC correlations between H-3 (*δ* 5.31, d, J = 11.4 Hz)/C═O (*δ* 169.9, s) and H-30 (*δ* 5.44, d, J = 2.8 Hz)/C═O (*δ* 170.7, s). The NMR data revealed that the C-1 resonance of **3** was shifted upfield to *δ* 81.5 (s), a distinction that suggested C-1 to be substituted by a hydroxy group. Moreover, the ^{13}C NMR spectrum exhibited a new hydroxylated methine at *δ* 71.6 (d), which was assignable to C-12, according to the HMBC correlation between H_3-18 (*δ* 1.04, s) and C-12, C-13 (*δ* 39.6, s), and C-17 (*δ* 77.1, d) and in turn between H-12 (*δ* 4.99, br) and C-18 (*δ* 18.9, q) and C-17. Although the HMBC correlation

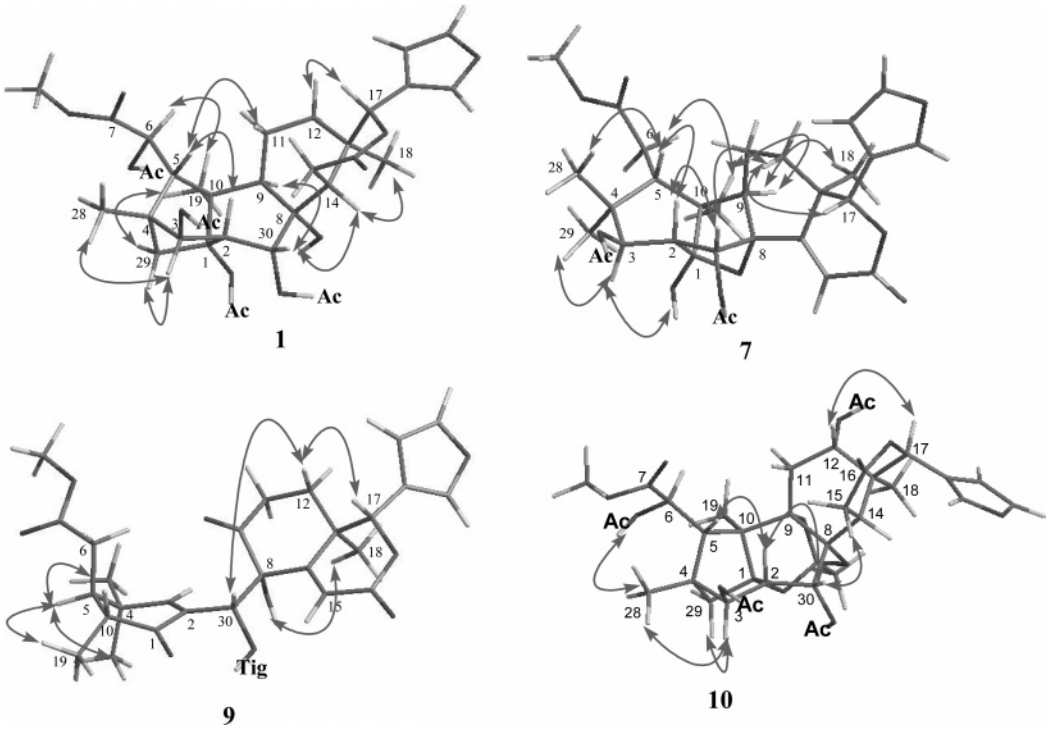


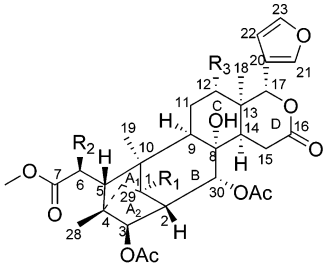
Figure 2. NOE correlations of xylocarpins A, F, H, and I (**1**, **7**, **9**, **10**).

Table 2. ^{13}C NMR Data of Xylocarpins A−E and Xyloccensin U (**1**−**6**)[a]

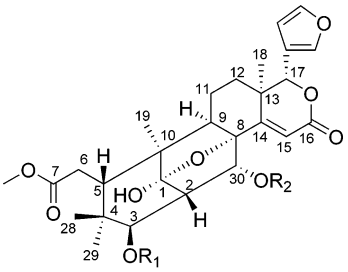
position	1	2	3	4	5	6
1	88.0 qC	88.5 qC	81.5 qC	88.0 qC	87.8 qC	88.2 qC
2	46.2 CH	46.2 CH	51.3 CH	46.3 CH	46.2 CH	46.5 CH
3	76.0 CH	75.6 CH	76.6 CH	76.4 CH	76.0 CH	75.5 CH
4	45.2 qC	45.3 qC	45.3 qC	45.1 qC	45.2 qC	45.3 qC
5	42.4 CH	38.0 CH	39.6 CH	43.3 CH	42.5 CH	38.1 CH
6	71.9 CH	33.6 CH_2	33.4 CH_2	71.2 CH	71.8 CH	33.3 CH_2
7	170.3 qC	173.4 qC	173.4 qC	175.2 qC	170.3 qC	173.1 qC
8	73.6 qC	73.7 qC	75.3 qC	73.4 qC	73.3 qC	73.5 qC
9	55.6 CH	54.8 CH	46.9 CH	49.2 CH	31.0 CH	48.5 CH
10	47.8 qC	46.8 qC	45.4 qC	47.3 qC	47.7 qC	46.4 qC
11	23.4 CH_2	22.5 CH_2	27.7 CH_2	28.7 CH_2	31.9 CH_2	28.1 CH_2
12	34.4 CH_2	34.2 CH_2	71.6 CH	71.3 CH	69.0 CH	71.7 CH
13	35.6 qC	35.5 qC	39.6 qC	39.3 qC	40.0 qC	39.3 qC
14	50.7 CH	50.2 CH	46.8 CH	46.3 CH	45.6 CH	46.4 CH
15	28.5 CH_2	28.3 CH_2	28.0 CH_2	28.1 CH_2	28.3 CH_2	28.0 CH_2
16	170.2 qC	170.5 qC	169.0 qC	169.6 qC	169.8 qC	169.7 qC
17	77.7 CH	77.9 CH	77.1 CH	77.3 CH	77.3 CH	76.9 CH
18	23.7 CH_3	23.6 CH_3	18.9 CH_3	18.8 CH_3	18.8 CH_3	18.9 CH_3
19	22.9 CH_3	23.3 CH_3	22.4 CH_3	23.5 CH_3	22.4 CH_3	22.8 CH_3
20	121.6 qC	121.7 qC	120.5 qC	120.9 qC	121.3 qC	120.7 qC
21	140.1 CH	140.2 CH	140.6 CH	140.4 CH	140.6 CH	140.6 CH
22	109.4 CH	109.5 CH	109.2 CH	109.1 CH	109.4 CH	109.2 CH
23	143.2 CH	143.1 CH	143.9 CH	143.8 CH	143.6 CH	143.7 CH
28	15.7 CH_3	15.3 CH_3	15.6 CH_3	15.7 CH_3	15.6 CH_3	15.1 CH_3
29	40.9 CH_2	39.5 CH_2	43.5 CH_2	40.8 CH_2	41.0 CH_2	39.7 CH_2
30	70.2 CH	70.5 CH	72.2 CH	69.8 CH	69.9 CH	70.1 CH
7-OMe	52.9 CH_3	51.9 CH_3	51.9 CH_3	53.2 CH_3	52.9 CH_3	52.0 CH_3
1-OAc	21.2 CH_3	21.4 CH_3		21.4 CH_3	21.1 CH_3	21.0 CH_3
	168.5 qC	168.6 qC		170.0 qC	168.6 qC	169.8 qC
3-OAc	22.1 CH_3	21.3 CH_3	21.2 CH_3	21.1 CH_3	21.2 CH_3	21.3 CH_3
	169.5 qC	169.9 qC	169.9 qC	169.3 qC	169.6 qC	169.9 qC
6-OAc	21.0 CH_3				21.0 CH_3	
	169.7 qC				170.4 qC	
12-OAc			21.5 CH_3	22.1 CH_3		22.8 CH_3
			169.8 qC	168.4 qC		168.5 qC
30-OAc	21.4 CH_3	22.1 CH_3	21.0 CH_3	22.2 CH_3	21.4 CH_3	21.4 CH_3
	170.7 qC	170.7 qC	170.7 qC	170.3 qC	170.6 qC	170.6 qC

[a] Measured in $CDCl_3$.

between H-12 and the carbonyl carbon of an acetyl group was not observed, the chemical shift of H-12 (~1.0 ppm farther downfield) (Table 1) suggested the presence of an acetoxy group at C-12 rather than at C-8. Irradiation of H-12 caused the NOE enhancement of H-17 and the methyl protons at δ 2.11 (s) and thereby supported the acetyl assignment. Thus, C-8 was considered to be substituted by a hydroxy group. The relative configuration of **3** corresponded to that of **1** on the basis of similar NMR and NOE data, with the

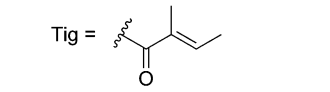


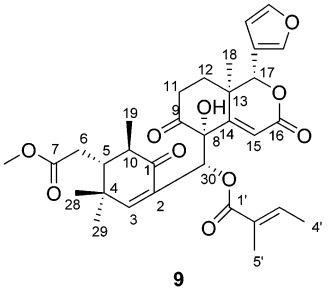
1. $R_1 = R_2 = OAc$, $R_3 = H$
2. $R_1 = OAc$, $R_2 = R_3 = H$
3. $R_1 = OH$, $R_2 = H$, $R_3 = OAc$
4. $R_1 = R_3 = OAc$, $R_2 = OH$
5. $R_1 = R_2 = OAc$, $R_3 = OH$
6. $R_1 = R_3 = OAc$, $R_2 = H$



7. $R_1 = R_2 = Ac$
8. $R_1 = OAc$, $R_2 = Tig$

Tig =





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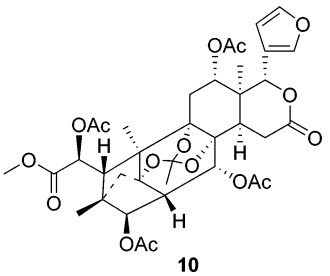

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exception of H-12, which was assumed to be in the β-orientation due to its strong NOESY correlation with H-17 (δ 5.77, s).

The structure of xylocarpin D (**4**) is closely related to that of **3**, as indicated by NMR data. With the exception of carbonyl carbons, seven oxygenated carbons [δ 88.0 (s), 76.4 (d), 71.2 (d), 73.4 (s), 71.3 (d), 77.3 (d), 69.8 (d)] were observed instead of six as shown in **3**. The ^{1}H NMR spectrum indicated four acetyl methyls at δ 2.17 (3H, s), 2.12 (6H, s), and 2.08 (3H, s), which were confirmed by HMBC correlations between the methyl protons and the respective carbonyl carbons. Besides two acetyl groups located at C-3 and C-30 in **1**−**3**, a third acetyl group was positioned at the quaternary C-1 due to the distinguishable carbon resonance at δ 88.0 (s, C-1). The relatively high resonance of a proton at δ 4.28 (1H, s, H-6) was indicative of a hydroxy group positioned at C-6 as opposed to the acetoxy group found in **1**. The remaining acetoxy group was assumed to reside at C-12 according to the downfield resonance of H-12 (δ 5.03, br) and the NOE correlation between H-12 and the acetyl methyl resonance at δ 2.12. A hydroxy singlet at δ 4.49 (s) showing a weak HMBC with C-8 (δ 73.4, s) confirmed the location of the hydroxy group. The ring conformation and the relative orientations at H-3 and H-30 agreed with **1**−**3**, based on similar NOE correlations, and NMR data. The configuration of C-6 was assignable as *R*, while H-12 was in a β-orientation, as deduced from NOESY cross-peaks between H-12 and H-17, and between H-6 and H_3-19, and by the typical zero *J* value of H-6.

The molecular formula of xylocarpin E (**5**) was the same as that of **4**, on the basis of HRFABMS data. Its ^{1}H and ^{13}C NMR data were virtually identical to those of **4**, with C-1, C-3, C-6, C-8, C-12, and C-30 being oxygenated. The NMR spectra indicated that **5** contained four acetoxy groups, two residing at C-3 and C-30, according to the comparable NMR and HMBC data with respect to **5** and **4**. Compound **5** was distinguished by the remarkable downfield chemical shift of H-6 (δ 5.40, s) and the HMBC correlations between H-6 and an acetyl carbon at δ 170.4 (s), which permitted the assignment of a third acetyl group at C-6. Since the ^{13}C value of C-1 (δ 87.8, s) was in agreement with an acetoxy group substituent, both C-8 and C-12 were obviously substituted with hydroxy groups. The proton resonances of OH-8 (δ 4.19, s) and H-12 (δ 3.84, br) of **5** shifted ~1.0 ppm farther upfield than those of **3**−**4** also contributed to the assignment. The relative configuration of **5** was identical to that of **4** on the basis of similar NOE correlations.

The ^{1}H and ^{13}C NMR data of **6** were identical to those of xyloccensin U, which was formerly isolated from the stem bark of the same plant.[22] A re-examination of HMBC data revealed a hydroxy singlet at δ 4.42 (1H, s) correlating to C-8 (δ 73.5, s) and C-14 (δ 46.4, d), and in turn, H-12 (δ 5.01, br) and the methyl protons at δ 2.17 (3H, s) correlated to a carbonyl carbon at δ 168.5 (s). These results were consistent with a hydroxy group attached at C-8 and an acetoxy group linked to C-12. Accordingly, the structure of xyloccensin U should be revised as 6-dehydroxyxylocarpin D.

Xylocarpin F (**7**) had the molecular formula $C_{31}H_{38}O_{11}$ as established by HRFABMS (*m*/*z* 609.2302 $[M + Na]^+$, calcd 609.2306), implying 13 degrees of unsaturation. The IR absorptions at 3422, 1737, 1700, and 1625 cm^{-1} suggested the presence of hydroxy, unsaturated lactone, and ester groups. The ^{1}H NMR spectrum displayed four tertiary methyl groups at δ 1.24 (3H, s, H-18), 1.08 (3H, s, H-19), 0.82 (3H, s, H-28), and 1.26 (3H, s, H-29), two acetyl methyl groups at δ 2.01 (3H, s) and 2.04 (3H, s), and a methoxy group at δ 3.72 (3H, s), as well as three oxymethine protons at δ 5.03 (1H, d, $J = 9.1$ Hz, H-3), 5.00 (1H, br s, H-17), and 5.61 (1H, d, $J = 4.4$ Hz, H-30). The downfield shifted proton resonances at δ 7.51 (1H, br, H-21), 6.43 (1H, br, H-22), and 7.44 (1H, br, H-23) were characteristic of a β-substituted furan ring found in all limonoids from this plant. These proton features in association with ^{13}C NMR data (Table 3) were consistent with a mexicanolide-type structure, closely related to those of xylogranatin A.[23] The COSY cross-peaks between H-3/H-2 (δ 2.95, dd, $J = 4.4$, 9.1 Hz) and H-2/H-30 confirmed oxygenation at C-3 and C-30. The singlet oxymethine proton at δ 5.00 (s) was assigned to H-17 through HMBC correlations from this proton to the furan carbons at δ 119.9 (s, C-20), 141.3 (d, C-21), and 109.9 (d, C-22), as well as to a conjugated lactone carbonyl at δ 163.8 (s, C-16). In addition, the α,β-unsaturated δ-lactone of ring D was evident from the olefinic proton at δ 6.09 (1H, s, H-15), which showed HMBC correlations with C-16, C-13 (δ 39.0, s), and C-8 (δ 81.2, s) (Figure 1). The remaining quaternary carbon at δ 107.5 (s) was attributed to C-1, a hemiketal group related to that of xylogranatin A.[23] The HMBC correlations between H-3 and an acetyl carbonyl at δ 170.1 (s) and between H-30 and acetyl carbonyl at δ 170.3 (s) clarified the acetyl substitution. The stereochemical orientations at C-3 and

Table 3. ^{1}H and ^{13}C NMR Data of Xylocarpins F−I (**7**−**10**)[a]

	7		**8**		**9**		**10**	
position	δ_H	δ_C	δ_H	δ_C	δ_H	δ_C	δ_H	δ_C
1		107.5 qC		107.3 qC		198.8 qC		83.1 qC
2	2.95 dd (4.4, 9.1)	53.2 CH	3.01 dd (4.5, 9.1)	53.2 CH		128.9 qC	2.80 dd (4.5, 10.2)	51.5 CH
3	5.03 d (9.1)	74.2 CH	5.04 d (9.1)	74.0 CH	6.99 s	161.8 qC	4.78 d (10.2)	76.5 CH
4		37.3 qC		37.3 qC		36.8 qC		46.8 qC
5	2.65 d (9.5)	40.6 CH	2.68 d (9.8)	40.6 CH	2.26 m	45.3 CH	3.32 br s	40.2 qC
6	2.38 dd (9.6, 16.0)	32.1 CH_2	2.39 dd (9.8, 16.0)	32.2 CH_2	2.45 d (14.5)	34.6 CH_2	6.08 br s	71.5 CH
	2.18 d (16.0)		2.16 d (16.0)		2.25 m			
7		174.0 qC		173.9 qC		173.4 qC		169.7 qC
8		81.2 qC		81.3 qC		80.3 qC		84.8 qC
9	2.17 m	51.4 CH	2.17 m	51.5 CH		208.8 qC		86.3 qC
10		42.9 qC		43.0 qC	2.25 m	42.8 CH		47.7 qC
11	1.80 ddd (11.0, 1.0, 13.5)	14.9 CH_2	1.82 m	15.0 CH_2	3.05 dd (7.0, 20.0)	33.0 CH_2	2.41 dd (1.0, 13.5)	31.6 CH_2
	2.39 m		2.38 m		2.53 ddd (7.0, 12.5, 20.0)		1.82 dd (13.5, 14.0)	
12	1.43 dd (8.5, 13.5)	25.1 CH_2	1.44 dd (8.5, 13.5)	25.0 CH_2	2.64 ddd (7.0, 12.5, 13.5)	25.6 CH_2	4.64 dd (1.0, 14.0)	69.0 CH
	2.10 m		2.17 m		1.64 dd (7.0, 13.5)			
13		39.0 qC		38.9 qC		38.4 qC		38.8 qC
14		160.1 qC		160.0 qC		163.3 qC	2.30 d (10.5)	44.0 CH
15	6.09 s	117.4 CH	6.00 s	117.7 CH	6.07 s	118.5 CH	3.35 d (19.5)	26.6 CH_2
							2.80 dd (10.5, 19.5)	
16		163.8 qC		163.5 qC		169.3 qC		169.9 qC
17	5.00 s	81.6 CH	4.98 s	81.4 CH	5.34 s	80.1 CH	5.69 s	76.8 CH
18	1.24 s	19.4 CH_3	1.22 s	19.4 CH_3	0.95 s	18.5 CH_3	1.23 s	14.1 CH_3
19	1.08 s	20.6 CH_3	1.09 s	20.5 CH_3	1.02 d (6.0)	12.1 CH_3	1.18 s	13.3 CH_3
20		119.9 qC		120.1 qC		119.8 qC		121.0 qC
21	7.51 br s	141.3 CH	7.51 br s	141.0 CH	7.53 br	141.4 CH	7.48 br s	140.9 CH
22	6.43 br s	109.9 CH	6.44 br s	110.0 CH	6.44 br	109.8 CH	6.45 br s	109.7 CH
23	7.44 br s	142.9 CH	7.43 br s	142.9 CH	7.42 br	143.2 CH	7.41 br s	143.1 CH
28	0.82 s	24.5 CH_3	0.83 s	24.5 CH_3	1.18 s	27.9 CH_3	1.14 s	15.5 CH_3
29	1.26 s	21.8 CH_3	1.26 s	21.8 CH_3	1.11 s	20.5 CH_3	2.12 d (10.8)	42.1 CH_2
							2.52 d (10.8)	
30	5.61 d (4.4)	76.5 CH	5.68 d (4.5)	76.4 CH	6.58 s	67.6 CH	6.02 d (4.5)	70.3 CH
7-OMe	3.72 s	52.0 CH_3	3.72 s	52.0 CH_3	3.66 s	51.9 CH_3	3.86 s	52.9 CH_3
1′				166.6 qC		166.8 qC		119.2 qC
2′				127.6 qC		127.8 qC	1.66 s	21.4 CH_3
3′			6.88 qq (1.4, 7.0)	139.8 CH	6.94 qq (1.4, 7.0)	139.9 CH		
4′			1.85 d (7.0)	11.9 CH_3	1.85 d (7.0)	11.6 q CH_3		
5′			1.81 d (1.4)	14.6 CH_3	1.82 d (1.4)	14.6 CH_3		
3-OAc		170.1 qC		170.1 qC				171.6 qC
	2.01 s	20.7 CH_3	1.94 s	20.4 CH_3			2.18 s	21.2 CH_3
30-OAc		170.3 qC						169.8 qC
	2.04 s	21.1 CH_3					2.21 s	21.1 CH_3
6-OAc								169.7 qC
							2.05 s	21.6 CH_3
12-OAc								169.3 qC
							1.65 s	21.4 CH_3
8-OH					3.86 br			

[a] Measured in $CDCl_3$.

C-30 were determined to be H-3α and H-30β on the basis of NOESY data between H-2/H-5 (δ 2.65, d) and H-2/H-30 and the $J_{H-2/H-3}$ value (9.1 Hz) for an axial−axial coupling. The NOE relationship between H-17β/H-12b (δ 2.10, m), H-30/H-12b, and H-5/H_3-28, and in turn between H-3/H_3-29, H-19/H-6a (δ 2.38, m), H-19/H-9, and H-9/H_3-18 (Figure 2), led to the assignment of H-9, H_3-18, and H_3-19 occupying the α-face, while the oxygen bridge between C-1 and C-8 was also in the α-orientation. In addition, the hydroxy group at C-1 was in close proximity to H-3, as a weak NOESY correlation was observed between δ 4.24 (br s, OH) and H-3.

Xylocarpin G (**8**) had the same molecular formula as that of xylogranatin B,[23] as established by HRFABMS, and both compounds showed similar NMR data. Spectroscopic data distinguished **8** as having alternate substitution of an acetoxy group at C-3 and, in turn, a tigloxy group at C-30. HMBC correlations were observed between H-30 (δ 5.68, d, J = 4.5 Hz) of **8** and the tigloyl carbonyl at δ 166.6 (s), while the acetoxy group (δ 1.94, 20.7, 170.1) was linked to C-3 on the basis of HMBC correlation between H-3 and the acetyl carbonyl. The comparable NMR and NOE data and specific rotation suggested that **8** had the same relative configuration as xylogranatin B.[23]

The molecular formula of xylocarpin H (**9**) was determined as $C_{32}H_{38}O_{10}$ from HRFABMS (m/z 583.2520 $[M + H]^+$, calcd 583.2543), implying 14 degrees of unsaturation. The ^{1}H NMR spectrum exhibited three tertiary methyls at δ 0.95 (3H, s, H-18), 1.18 (3H, s, H-28), and 1.11 (3H, s, H-29), a methyl doublet at δ 1.02 (3H, d, J = 6.0 Hz, H-19), two olefinic protons at δ 6.99 (1H, s, H-3) and 6.07 (1H, s, H-15), and the resonances for a β-substituted furan ring (δ 7.53, br; 7.42, br; and 6.44 br). The proton resonances at δ 1.85 (3H, d, J = 7.0 Hz), 1.82 (3H, d, J = 1.4 Hz), and 6.94 (1H, qq, J = 1.4, 7.0 Hz) were characteristic of a tigloyl group. These data as well as ^{13}C NMR resonances are similar to those of xylogranatin C,[13] an unusual 9,10-*seco*-

mexicanolide recently isolated from the same fraction. The substitution of a tigloyl group for an acetoxy group at C-30 of **9** was proven by the HMBC correlation from H-30 (δ 6.58, s) to the tigloyl carbonyl at δ 166.8 (s) and to carbon resonances from the basic skeleton at δ 165.0 (s, C-14), 80.3 (s, C-8), 161.8 (d, C-3), 128.9 (s, C-2), and 198.8 (s, C-1). The relative configuration of **9** was determined through NOESY analysis (Figure 2). The NOE correlations between H-30/H-12b (δ 2.64, ddd) and H-17 (δ 5.34, s)/H-12b suggested H-17 and H-30 to be in the β-orientation, while a weak NOE correlation between OH-8 (δ 3.86, s) and H_3-18 assigned the α-orientation of the hydroxy group. A further NOE interaction between H-5 and H_3-19 was indicative that both protons were on the same face. NOESY was unable to establish the relative stereochemical relationship between rings A and B. However, a hypothetical biogenetic pathway (see Supporting Information), in which **9** may derive from a 1,8-oxomexicanolide, such as **7** and **8**, suggested that **9** shares the same backbone configuration.

The molecular formula of xylocarpin I (**10**) was established as $C_{37}H_{44}O_{16}$ from HRFABMS (*m*/*z* 767.2513 $[M + Na]^+$, calcd 767.2521) and NMR data. The ^1H and ^{13}C NMR data (Table 3) were consistent with a phragmalin orthoester,[16] characterized by a methyl singlet at δ 1.66 (3H, s) and its HMBC correlation with a quaternary carbon at δ 119.2 (s) for a 1,1,1-trioxyethyl moiety. Typical oxygenated carbon resonances at δ 83.1 (s), 84.8 (s), and 86.3 (s) further substantiated this orthoester identification. The ^1H NMR spectrum exhibited four acetyl methyls at δ 2.18 (3H, s), 2.05 (3H, s), 2.21 (3H, s), and 1.65 (3H, s), as deduced by the HMBC correlation from methyl protons to the respective carbonyl resonances. The HMBC correlations between H-3 (δ 4.78, d, J = 10.2 Hz)/C=O (δ 171.6, s), H-6 (δ 6.08, br s)/C=O (δ 169.7, s) and C-7 (δ 170.0, s), H-12 (δ 4.64, dd, J = 1.0, 14.0 Hz)/C=O (δ 169.3, s), and H-30 (δ 6.02, d, J = 4.5 Hz)/C=O (δ 169.8, s) located acetoxy groups at C-3, C-6, C-12, and C-30, respectively. Obviously, the orthoacetate unit was assembled at C-1 (δ 83.1, s), C-8 (δ 84.8, s), and C-9 (δ 86.3, s) rather than at C-30, C-8, and C-9, as observed for xyloccensins O−V.[15,16,22] In known phragmalins, H-17 was recognized as being exclusively in the β-orientation. The NOE correlations in **10** between H-12/H-17 (δ 5.69, s), H-30/H-15a (δ 3.35, d), H-30/H-2 (δ 2.80, dd), H-3/H-29a (δ 1.53, d), H-3/H_3-28 (δ 1.14, s), and H_3-28/Ac-6 (δ 2.05, s) (Figure 2) led to the assignment of H-30β, H-12β, and H-3α. The oxygen atom at C-1 was determined to be α-oriented by the NOESY relationship between H-2 and H-5, and thus the orthoester unit was fused in the α-orientation. The *R* configuration of C-6 was suggested by NMR data of the side chain, which were compatible with that of xyloccensin P,[15] whose absolute configuration had been established through X-ray diffraction.

The limonoid derivatives such as polyoxyphragmalin- and mexicanolide-type compounds are distributed in all plant parts of *X. granatum*. The phragmalins from the stem bark (or timber) frequently contained an orthoester unit, whereas fruits had a high content of polyoxyphragmalins along with minor amounts of phragmalin orthoesters (only two orthoesters were isolated). Diverse mexicanolides were found in the fruits (or seeds), but these compounds also coexisted in low levels in the stem bark. Biogenetically, mexicanolide is proposed to be the precursor of phragmalins. The high concentration of phragmalin orthoesters in the stem bark of *Xylocarpus* plants may serve as an important chemical defense against ecological invasion, such as by pests and microorganisms.

Strong antifeedant activity against third instar larvae of *Mythimna separate* has been observed for phragamlin orthoesters such as xyloccensins P and Q.[16,17] In contrast, the polyoxyphragmalins such as khyanolides A and B showed only weak antifeeding activity,[18] and mexicanolides xyloccensins I and J showed negative results in a broad screening for antimicrobial, antiviral, and antihelminthic[19] activities. Thus, the orthoester functionality of these natural metabolites appears to play an important ecological function.

The hypothesis of a biogenetic relationship among the isolated limonoids has been depicted (see Supporting Information). The 1,8-hemiacetal is suggested to be a common precursor in biosynthetic routes to establish the biogenetic relationship of the isolated limonoids. Different substitutions at oxygenated positions C-3 and C-30 resulted in the generation of xylocarpins G and H (**7**, **8**) and xylogranatin B, while a transformation of a 1,8-hemiacetal into the ketone at C-1 and the double-bond rearrangement afforded xylogranatin A, proceranolide, khayasin T, and febrifugin A. An 8,9-epoxide was proposed to be an intermediate that produced xylocarpin H (**9**) and xylogranatin C through 9,10-bond cleavage. The polyoxyphragamlins (**1**−**6**) were derived from the 1,8-hemiacetal nucleus by the rearrangement process as described by Taylor.[7]

Experimental Section

General Experimental Procedures. Optical rotations were recorded on a Perkin-Elmer 341 LC polarimeter. IR spectra were determined on a Thermo Nicolet Nexus 470 FT-IR spectrometer, and UV spectra were recorded on Shimadzu UV-210A spectrophotometers. ^1H and ^{13}C NMR spectra were measured on a Bruker Avance DRX 500 spectrometer. ESIMS spectra were recorded on a PE Q-STAR ESITOFMS/MS spectrometer, and HRFABMS data were obtained on a Bruker FTI-CRMS spectrometer. HPLC was performed using an Alltech 426 pump with UV detector and a Chromasil C_{18} column from Pharm Co.

Plant Material. The fresh fruits of the mangrove plant *X. granatum* were collected from the mangrove garden at Hainan Island, Southern China, in May 2003, and the species was identified by Prof. Peng Lin from Xiamen University. A voucher specimen was deposited in State Key Laboratory of Natural and Biomimetic Drugs, Peking University.

Extraction and Isolation. The air-dried fruit rind (3.5 kg) was percolated with 95% EtOH, and the EtOH extract was concentrated in vacuo to yield a residue (706 g). The residue was partitioned between 90% aqueous MeOH and petroleum ether to remove lipids. The aqueous MeOH fraction was concentrated and then re-extracted with H_2O and CH_2Cl_2. The CH_2Cl_2 layer was collected and concentrated to afford a fraction (54.0 g), which was subjected to Si gel CC eluting with a gradient of petroleum ether−acetone (from 5:1 to 1:1) to yield six fractions (Fa−Fg). Fc (1.9 g) was applied on a reversed-phase Si gel CC column (C_{18}) and eluted with MeOH−H_2O (1:1) to yield a sample (250 mg) containing a mixture of limonoids as detected by ^1H NMR spectroscopy. This limonoid mixture was separated by semipreparative HPLC (ODS column, 70% aqueous MeOH−H_2O as mobile phase) to obtain **1** (5.8 mg), **2** (4.1 mg), **3** (4.2 mg), **4** (5.5 mg), **5** (2.2 mg), and **6** (8.2 mg). Fb (12.0 g) was fractionated by Si gel CC by using petroleum ether−acetone (2:1) as an eluant to give a new fraction (423 mg) mainly containing limonoids as monitored by ^1H NMR spectroscopy. This fraction was subsequently separated on a semipreparative HPLC column with 75% MeOH−H_2O as a mobile phase to yield **7** (7.6 mg), **8** (4.7 mg), xylogranatin B (4.2 mg), xylogranatin A (15.3 mg), and **10** (7.5 mg). An aliquot (1.0 g) from the Fa fraction (8.9 g) was subjected to Si gel CC with a gradient of petroleum ether−acetone (from 5:1 to 2:1). This separation yielded six fractions (Faa−Faf). Fac (186 mg) was subjected to Si gel CC and eluted with petroleum ether−acetone (4:1) to afford khayasin T (34.2 mg) and febrifugin A (23.6 mg), while Fae (57.0 mg) was purified in the same manner by using petroleum ether−acetone (3:1) as an eluant to yield xylogranatin C (2.6 mg) and **9** (6.2 mg). Xyloccensin P (32.6 mg), proceranolide (25.6 mg), and xyloccensin K (10.8 mg) were isolated from fraction Faf (124 mg) on Si gel CC eluting with the same solvent system as that of Fae.

Xylocarpin A (1): white, amorphous powder; $[\alpha]_D^{25}$ +43 (*c* 1.1, MeOH); UV (MeOH) λ_{max} 221 nm; IR (KBr) ν_{max} 3416, 2937, 1739, 1700, 1626, 1441, 1375, 1234 cm^{-1}; ^1H and ^{13}C NMR data, see Tables 1 and 2; HRFABMS *m*/*z* 689.2810 $[M + H]^+$ (cacld for $C_{35}H_{45}O_{14}$, 689.2809), 711.2590 $[M + Na]^+$ (calcd for $C_{35}H_{44}O_{14}Na$, 711.2629).

Xylocarpin B (2): white, amorphous powder; $[\alpha]_D^{25}$ +53 (*c* 1.8, MeOH); UV λ_{max} 221 nm; IR (KBr) ν_{max} 3426, 2956, 2920, 2850, 1730, 1700, 1628, 1466, 1238, 1157 cm^{-1}; ^1H and ^{13}C NMR data, see Tables 1 and 2; HRFABMS *m*/*z* 631.2742 $[M + 1]^+$ (calcd for $C_{33}H_{43}O_{12}$, 631.2747), 653.2542 $[M + Na]^+$ (calcd for $C_{33}H_{42}O_{12}Na$, 653.2568).

Xylocarpin C (3): white, amorphous powder; $[\alpha]_D^{25}$ +46 (*c* 1.3, MeOH); UV (MeOH) λ_{max} 221 nm; IR (KBr) ν_{max} 3421, 2924, 2853, 1738, 1695, 1601, 1464, 1384, 1240, 1122, 863 cm^{-1}; ^1H and ^{13}C NMR data, see Tables 1 and 2; ESIMS *m/z* 669 $[M + Na]^+$, 685 $[M + K]^+$; HRFABMS *m/z* 647.2700 $[M + 1]^+$ (calcd for $C_{33}H_{43}O_{13}$, 647.2697).

Xylocarpin D (4): white, amorphous powder; $[\alpha]_D^{25}$ +57 (*c* 1.8, MeOH); UV (MeOH) λ_{max} 221 nm; IR (KBr) ν_{max} 3431, 2921, 2852, 1739, 1700, 1690, 1660, 1629, 1473, 1378, 1239, 1023 cm^{-1}; ^1H and ^{13}C NMR data, see Tables 1 and 2; ESIMS (positive) *m/z* 705 $[M + H]^+$, 722 $[M + NH_4]^+$, 727 $[M + Na]^+$; HRFABMS *m/z* 705.2762 $[M + 1]^+$ (calcd for $C_{35}H_{45}O_{15}$, 705.2752).

Xylocarpin E (5): white, amorphous powder; $[\alpha]_D^{25}$ +43 (*c* 0.9, MeOH); UV (MeOH) λ_{max} 221 nm; IR (KBr) ν_{max} 3422, 2927, 1734, 1700, 1623, 1569, 1420, 1384, 1117 cm^{-1}; ^1H and ^{13}C NMR data, see Tables 1 and 2; ESIMS *m/z* 705 $[M + 1]^+$, 722 $[M + NH_4]^+$, 727 $[M + Na]^+$; HRFABMS *m/z* 705.2743 $[M + 1]^+$ (calcd for $C_{35}H_{45}O_{15}$, 705.2752).

Xylocarpin F (7): white, amorphous powder; $[\alpha]_D^{25}$ −42 (*c* 0.7, MeOH); UV (MeOH) λ_{max} 252 nm; IR (KBr) ν_{max} 3422, 2950,1737, 1700, 1625, 1426, 1384, 1150 cm^{-1}; ^1H and ^{13}C NMR data, see Table 3; ESIMS *m/z* 587 $[M + H]^+$, 609 $[M + Na]^+$; HRFABMS *m/z* 609.2302 $[M + Na]^+$ (calcd for $C_{31}H_{38}O_{11}Na$, 609.2306).

Xylocarpin G (8): white, amorphous powder; $[\alpha]_D^{25}$ −61 (*c* 0.4, MeOH); UV (MeOH) λ_{max} 253 nm; IR (KBr) ν_{max} 3425, 2951, 1732, 1700, 1636, 1381, 1262, 1150, 1072 cm^{-1}; ^1H and ^{13}C NMR data, see Table 3; ESIMS *m/z* 627 $[M + H]^+$, 649 $[M + Na]^+$; HRFABMS *m/z* 627.2796 $[M + 1]^+$ (calcd for $C_{34}H_{43}O_{11}$, 627.2799).

Xylocarpin H (9): white, amorphous powder; $[\alpha]_D^{25}$ +95 (*c* 0.4, MeOH); UV (MeOH) λ_{max} 212 nm; IR (KBr) ν_{max} 3432, 2964, 1728, 1680, 1640, 1606, 1262, 1097, 1032 cm^{-1}; ^1H and ^{13}C NMR data, see Table 3; ESIMS *m/z* 583 $[M + H]^+$, 605 $[M + Na]^+$; HRFABMS *m/z* 583.2543 $[M + 1]^+$ (calcd for $C_{32}H_{39}O_{10}$, 583.2537).

Xylocarpin I (10): white, amorphous powder; $[\alpha]_D^{25}$ +62 (*c* 0.8, MeOH); UV (MeOH) λ_{max} 221 nm; IR (KBr) ν_{max} 3424, 2954, 1744, 1702, 1619, 1384, 1225, 1183, 1134 cm^{-1}; ^1H and ^{13}C NMR data, see Table 3; ESIMS *m/z* 767 $[M + Na]^+$, 783 $[M + K]^+$; HRFABMS *m/z* 767.2513 $[M + Na]^+$ (calcd for $C_{37}H_{44}O_{16}Na$, 767.2521).

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Supporting Information Available: IR, MS, 1D and 2D NMR spectra of new compounds (**1**−**5**, **7**−**10**). A possible biogenetic relationship among the isolated limonoids is described in Scheme 1. This material is available free of charge via the Internet at http://pubs.acs.org.

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