Xanthone Glycosides from *Polygala tenuifolia* and Their Conformational Analyses

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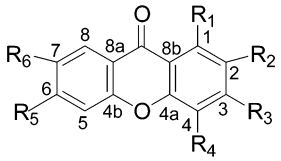
Seven xanthone glycosides were isolated from the cortexes of *Polygala tenuifolia*, and their structures were identified as polygalaxanthones VIII−XI (**1**−**4**), sibiricoxanthone B (**5**), 7-*O*-methylmangiferin (**6**), and lancerin (**7**), on the basis of spectroscopic analyses. Compounds **1**−**4** are new xanthone glycosides, and compounds **4** and **5** exist as rotamers. To explain this phenomenon, conformational analyses were performed on compounds **4** and **5** and other compounds with similar skeletons that were isolated from *P. tenuifolia*.

The roots of *Polygala tenuifolia* Willd., a well-known traditional Chinese medicine, have been used as an expectorant, sedative, and tranquilizing agent.[1] Besides the known saponins, xanthones, and saccharide esters,[2−5] our investigation showed that xanthone glycosides are abundant in this plant species. In this paper, we describe the isolation and structural elucidation of seven xanthone glycosides from *P. tenuifolia*. Among them, compounds **2** and **3** are new xanthone *O*-glycosides, while **1** and **4** are new xanthone *C*-glycosides. Moreover, compounds **4** and **5** exist as rotamers, a phenomenon that is reported for the first time for xanthone glycosides. To explain this phenomenon, conformational analyses were performed on compounds **4** and **5** and other compounds with a similar skeleton, such as compounds **1** and **2**, and the previously reported compound **8**.[6]



1 R_1=R_3=R_5=OH, R_2=Glc(6-1)Ara, R_4=H, R_6=OMe
2 R_1=R_6=OH, R_3=OGlc(2-1)Rha, R_2=R_4=R_5=H
3 R_1=R_2=R_3=R_6=OMe, R_4=H, R_5= OGlc(2-1)Rha
4 R_1=R_3=R_5=OH, R_2=Glc(2-1)Api, R_4=H, R_6=OMe
5 R_1=R_3=R_6=OH, R_2=Glc(2-1)Api, R_4=R_5=H
6 R_1=R_3=R_5=OH, R_2=Glc, R_4=H, R_6=OMe
7 R_1=R_3=OH, R_2=R_5=H, R_4=Glc, R_6=OMe
8 R_1=R_3=R_5=OH, R_2=Glc(6-1)Api, R_4=H, R_6=OMe

Results and Discussion

The *n*-BuOH-soluble parts of the 95% aqueous EtOH extract of *P. tenuifolia* were subjected to macroporous resin D101 column chromatography; elution was with an EtOH−H_2O gradient. The 50% and 20% EtOH−H_2O eluates were then applied to silica gel, ODS, and Sephadex LH-20 column chromatography and finally purified by HPLC to afford compounds **1**−**7**.

Polygalaxanthone VIII (**1**) was obtained as a yellow powder, and its molecular formula was deduced to be $C_{25}H_{28}O_{15}$ from HRSIMS (*m/z* 567.1345 [M − H]$^-$). Its UV spectrum in MeOH (λ_{max} 241, 258, 316, and 362 nm) was similar to that of polygalaxanthone III (**8**),[7] and when NaOAc was added, the UV spectrum of **1** showed a bathochromic shift, indicating the presence of a hydroxyl group at C-3 or C-6.[3] The IR spectrum of **1** showed the presence of hydroxyl groups (3384 cm^{-1}), a hydrogen-bonded ketone (1646 cm^{-1}), and aromatic rings (1611, 1585, 1485 cm^{-1}). The ^{1}H NMR spectrum of **1** contained resonances for two anomeric protons [δ 4.54 (1H, d, J = 7.2 Hz) and 4.08 (1H, d, J = 5.7 Hz)], a hydrogen-bonded hydroxyl proton [δ 13.72 (C-1-OH)], two free phenolic hydroxyl protons (δ 10.86 and 10.69), three uncoupled aromatic protons (δ 7.44, 6.90, and 6.38), and an *O*-methyl group [δ 3.88 (3H, s)]. All these data suggested **1** to be a xanthone glycoside with a disubstituted A ring and a trisubstituted B ring. The NMR data of **1** were similar to those of polyglaxanthone III,[7] except that the signals associated with apiose were replaced by signals consistent with the presence of an arabinose moiety.[8]

In the HMBC spectrum of **1**, the arabinose anomeric proton at δ 4.08 correlated with the resonance for C-6 (δ 69.0) of the glucosyl residue, and the glucosyl anomeric proton at δ 4.54 correlated with the resonances for C-2 (δ 107.8), C-1 (δ 161.8), and C-3 (δ 163.9) of the aglycone. Combining this information with the analysis of the chemical shift of the anomeric carbon of the glucosyl moiety (δ 73.0), **1** was deduced to be a xanthone *C*-glycoside, with the sugar chain located at C-2 of the aglycone. Thus, **1** was defined as 2-*C*-[β-D-arabinopyranosyl-(1→6)-β-D-glucopyranosyl]-1,3,7-trihydroxy-6-methoxyxanthone.

Polygalaxanthone IX (**2**) was obtained as a yellow amorphous powder with a molecular formula of $C_{25}H_{28}O_{14}$, as deduced from HRSIMS (*m/z* 551.1413 [M − H]$^-$). Its UV and IR spectra showed characteristic absorptions of xanthone glycosides. Its ^{1}H NMR spectrum contained resonances consistent with an ABX coupled aromatic system [δ 7.52 (1H, d, J = 9.6 Hz), 7.41 (1H, d, J = 3.0 Hz), and 7.30 (1H, dd, J = 9.6, 3.0 Hz)] and a pair of *meta*-coupled aromatic protons [δ 6.60 (1H, d, J = 2.7 Hz) and 6.36 (1H, d, J = 2.7 Hz)]. The ^{13}C NMR data of **2**, for the xanthone core, were similar to those for 1,6-dihydroxy-3-methoxyxanthone,[2] except that downfield shifts of 1.4 ppm for C-2 and of 1.8 ppm for C-4, and an upfield shift of

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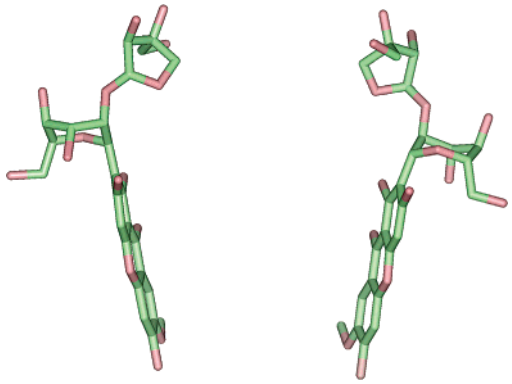

Figure 1. Two conformers of compound **4**.

2.6 ppm for C-3, indicated the sugar moiety to be located at C-3 of the aglycone. The ^{1}H NMR spectrum of **2** also contained resonances consistent with the presence of two anomeric protons [δ 5.25 (1H, d, J = 7.2 Hz, Glc-1) and 5.12 (1H, brs, Rha-1)], while the^{13}C NMR data of the sugar moiety were almost the same as those reported for the equivalent moiety in polygalaxanthone IV.[7] In the HMBC spectrum of **2**, the rhamnose anomeric proton (δ 5.12) was correlated with the resonance for C-2 (δ 76.2) of the glucosyl residue, and the glucosyl anomeric proton (δ 5.25) was correlated with the resonance for C-3 (δ 163.7) of the aglycone. Thus, **2** was identified as 3-*O*-[α-L-rhamnopyranosyl-(1→2)-*β*-D-glucopyranosyl]-1,7-dihydroxyxanthone.

Polygalaxanthone X (**3**) was obtained as a yellow amorphous powder with a molecular formula of $C_{29}H_{36}O_{16}$ as determined by HRSIMS (*m/z* 641.2086 [M + H]$^+$). Its UV spectrum exhibited absorption bands at λ_{max} 246, 274, and 313 nm, which were similar to those of 1,2,3,6,7-pentamethoxyxanthone.[6] The ^{1}H NMR spectrum of **3** showed three uncoupled aromatic protons (δ 7.47, 7.19, and 6.99), two anomeric protons [δ 5.35 (1H, d, J = 7.5 Hz) and 5.26 (1H, brs)], and four methyl groups [δ 3.94, 3.84, 3.83, and 3.75 (each 3H, s)]. The above data suggested **3** to be a xanthone glycoside substituted by four *O*-methyls and a sugar moiety. The ^{1}H NMR and ^{13}C NMR data of **3** were similar to those of polygalaxanthone VI,[6] except for a group of signals from an additional rhamnosyl unit, and the crossing peak observed in the HMBC spectrum of **3** between the rhamnose anomeric proton (δ 5.26) and C-2 (δ 75.1) of the glucosyl moiety, indicating the linkage of the rhamnosyl unit. On the basis of the above analyses, **3** was characterized as 6-*O*-[α-L-rhamnopyranosyl-(1→2)-*β*-D-glucopyranosyl]-1,2,3,7-tetramethoxyxanthone.

Polygalaxanthone XI (**4**) was obtained as a yellow amorphous powder and showed a molecular formula of $C_{25}H_{28}O_{15}$, as confirmed by HRSIMS (*m/z* 567.1345 [M − H]$^-$), and its UV spectrum was similar to that of polygalaxanthone III.[7] It was very unusual for **4** to have NMR signals of the A ring appearing in pairs, but when the temperature was increased to 70 °C, the duplicated signals disappeared; however, when the sample was cooled to room temperature, signal duplication was observed again. Since this phenomenon was similar to that of spinosin rotamers,[9] **4** could thus be deduced to be a pair of rotamers (Figure 1).

In the ^{1}H NMR of **4**, there were a pair of hydrogen-bonded hydroxyl protons [δ 13.81/13.72 (C-1-OH)], three uncoupled aromatic protons [δ 7.42, 6.86, and 6.38/6.35 (each 1H, s)], two anomeric protons [δ 5.20 (1H, brs) and 4.63 (1H, d, J = 10.8 Hz)/4.57 (1H, d, J = 10.8 Hz)], and an *O*-methyl group [δ 3.86 (3H, s)]. The NMR data of **4** were similar to those of polygalaxanthone III, [7] except that

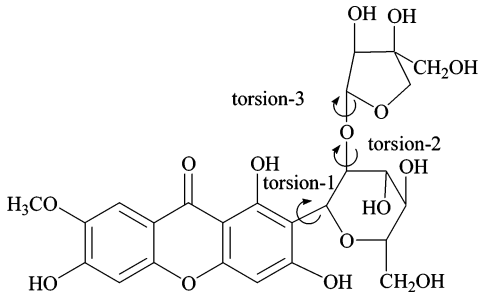

Figure 2. Torsions used in conformation analysis of **4**.

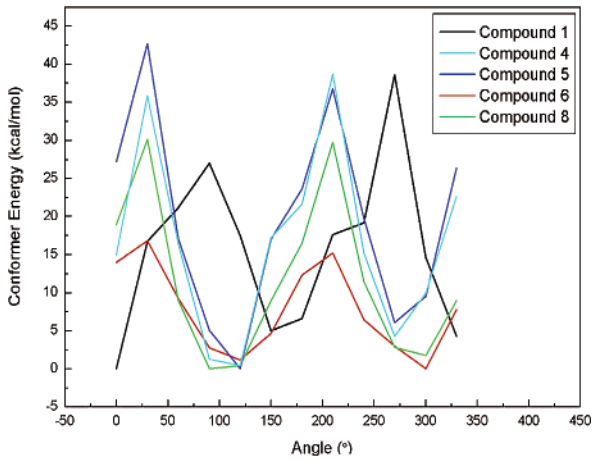

Figure 3. Conformational analysis results of **1**, **4**, **5**, **6**, and **8**.

the linkage of apiose changed from C-6 to C-2 of the glucose. In the HMBC spectrum of **4**, the anomeric proton of the apiose (δ 5.20) correlated with the C-2 signal of glucose at δ 74.1, which confirmed the above elucidation. Thus, **4** was deduced as 6-*O*-[α-L-rhamnopyranosyl-(1→2)-*β*-D-glucopyranosyl]-1,2,3,7-tetramethoxyxanthone.

Like compound **4**, compound **5** showed the same phenomenon of NMR signal duplication. These two compounds are *C*-glycosides, and there are rotational barriers (C-1 and C-3 hydroxyls) about the C−C bond between the aglycone and the sugar moiety, which inhibited the free rotation of the C−C bond. Compounds **4** and **5** therefore appeared as two conformers at room temperature. This phenomenon was also observed for flavanone *C*-glycosides.[9,10]

On the basis of the structural similarity to the flavanone glycoside rotamers,[9,10] compounds **4** and **5**, together with **1**, **6**, and **8**, were chosen for conformational analyses to define the factors stabilizing the two conformers of **4** and **5** at room temperature. These compounds are *C*-glycosylated at C-2 of the aglycone, and substituents at C-1 and C-3 have provided the steric hindrance to free rotation of the C−C bond at C-2.

For each compound, a conformer energy versus torsion angle 2 graph was plotted, as illustrated in Figure 3. Since the absolute energy cannot be applied for comparison, and only the energy difference between conformers of the same compound is meaningful, we set the minimal conformer energy of each compound as zero for better observation.

In Figure 3, there is obviously an energy barrier between the two energy minima of **4** and **5**, which agrees with the existence of two stable conformers of the two compounds, and the conformers of **4** are shown in Figure 1. In the profiles of **1**, **6**, and **8**, the energy barrier is much lower than that of **4** or **5**; thus these three compounds do not show *iso*-conformers at room temperature. Compounds **1** and **8** have more space for the sugar moiety (C-1 to C-6 liner linkage), and the terminal sugar unit can rotate freely, so

Table 1. ^{1}H NMR and ^{13}C NMR Data of Compounds **1**−**3** (in DMSO-d_6)[a]

	1		**2**		**3**	
position	^{1}H	^{13}C	^{1}H	^{13}C	^{1}H	^{13}C
1		161.8		162.4		152.6
2		107.8	6.36 (d, J = 2.7 Hz)	98.2		139.1
3		163.9		163.7		158.1
4	6.38 (s)	93.4	6.60 (d, J = 2.7 Hz)	94.2	6.99 (s)	96.7
4a		156.2		157.2		154.0
4b		151.7		149.2		149.9
5	6.90 (s)	102.8	7.52 (d, J = 9.6 Hz)	119.2	7.19 (s)	102.5
6		154.7	7.30 (dd, J = 9.6, 3.0 Hz)	125.0		151.6
7		146.1		154.2		146.7
8	7.44 (s)	104.8	7.41 (d, J = 3.0 Hz)	108.0	7.47 (s)	105.1
8a		111.4		120.4		115.4
8b		101.3		103.5		109.5
9		179.0		180.3		172.9
1-OMe					3.83 (s)	61.8
2-OMe					3.75 (s)	61.0
3-OMe					3.94 (s)	56.5
6-OMe	3.88 (s)	55.9	55.9			
7-OMe					3.84 (s)	55.7
1-OH	13.72 (s)		12.86 (s)			
OH	10.86 (s)					
	10.69 (s)					
Glc-1	4.54 (d, J = 7.2 Hz)	73.0	5.25 (d, J = 7.2 Hz)	97.6	5.35 (d, J = 7.5 Hz)	97.5
2		70.0		76.2		75.1
3		78.9		77.0		77.1
4		70.8		69.7		69.7
5		79.8		77.2		77.6
6		69.0		60.5		60.5
Ara			Rha			
1	4.08 (d, J = 5.7 Hz)	103.3	5.12 (brs)	100.5	5.26 (brs)	99.9
2		70.3		70.4		70.4
3		72.5		70.5		70.6
4		67.3		71.8		71.9
5		64.9		68.4		68.5
6			1.19 (d, J = 6.3 Hz)	18.1	1.13 (d, J = 6.0 Hz)	18.1

[a] Signal assignments were aided by COSY, HMQC, and HMBC spectra.

that the energy gap is much lower that those of **4** and **5**, where the terminal sugar unit is linked to C-2 of the first sugar moiety. Moreover, if the xanthone *C*-glycoside has one sugar unit, such as compound **6**, the energy difference would decrease further, because of the less crowded space. Thus, we deduced that the length of the sugar chain at C-2 of the aglycone and the linkage between the sugars will affect the existence of the xanthone *C*-glycoside rotamers.

The other three compounds, **5**−**7**, were identified as sibiricoxanthone B (**5**),[7] 7-*O*-methylmangiferin (**6**),[11] and lancerin (**7**)[7] by comparing their physical and spectroscopic data with literature values.

Experimental Section

General Experimental Procedures. Optical rotations were measured on a Perkin-Elmer 243B polarimeter. UV spectra were recorded on a TU-1901 spectrophotometer, whereas IR spectra were obtained on an AVATER-360 spectrophotometer. FABMS were obtained on a KYKY-ZHP-5# mass spectrometer. ^{1}H NMR and ^{13}C NMR were measured on a JEOL JNM-A300 spectrometer operating at a basic frequency of 300 MHz, while COSY, HMQC, and HMBC spectra were recorded on a Bruker AM-500 spectrometer operating at a basic frequency of 500 MHz. D101 resin was purchased from Tianjin Chemical Co. Column chromatography silica gel (200−300 mesh) was a Qingdao Marine Chemical Factory product.

Plant Material. The cortexes of *P. tenuifolia* were collected from Shanxi Province, People's Republic of China, in October 2000. The plant was identified by Professor Pengfei Tu, School of Pharmaceutical Sciences, Peking University Health Science Center. A voucher specimen (No. 001020) was deposited in the herbarium of the School of Pharmaceutical Sciences, Peking University, Beijing, People's Republic of China.

Extraction and Isolation. The air-dried cortexes of *P. tenuifolia* (11 kg) were ground and refluxed with 95% aqueous EtOH (77 L) three times, each for 1 h. The extract was combined and evaporated in vacuo to yield 4.9 kg of residue, a portion (2 kg) of which was suspended in water and extracted successively with petroleum, $CHCl_3$, and *n*-BuOH to give the petroleum extract (462.6 g), $CHCl_3$ extract (157.9 g), and *n*-BuOH extract (914.8 g).

A portion of the *n*-BuOH extract (325 g) was subjected to a macroporous resin D101 column (11.5 × 85.5 cm). The adsorbed material was eluted with H_2O, and 20, 50, 70, and 95% EtOH, respectively. The 20% EtOH eluate (19.8 g) was chromatographed on a silica gel (60 g) column and eluted with $CHCl_3$−MeOH−H_2O in a gradient manner (60:10:0 → 60:40:5, 100 mL as one fraction). Fractions 20−39 were further subjected to silica gel chromatography, with $CHCl_3$−MeOH−H_2O (80:20:5, lower phase) as eluting solvent, to give 22 fractions. Fractions 12−22 afforded a yellow powder that was crystallized from MeOH to furnish compound **6** (56.3 mg). Fractions 40−49 were also subjected to silica gel chromatography, eluting with $CHCl_3$−MeOH−H_2O (80:20:2), to give 25 fractions. Fractions 6−8 were purified by Sephadex LH-20 and ODS to give compound **7** (28.8 mg). Fractions 62−90 gave some yellow powder. After filtration, the powder and the mother liquid were subjected to HPLC, respectively. The HPLC separation of the powder was run on a Waters Prep Nova-pak HR C_{18} column (5 μm, 7.8 × 300 mm), with MeOH−H_2O (27:73) as the mobile phase; the flow rate was 3.0 mL/min and 228 and 311 nm were the detecting wavelengths. Through the HPLC separation, 10.8 mg of compound **4** was obtained. The mother liquid was purified by an Alltima C_{18} column (5 μm, 10 × 250 mm), with MeOH−H_2O (40:60) as the mobile phase,

Table 2. ^{1}H NMR and ^{13}C NMR Data of Compounds **4** and **5** (in DMSO-d_6)

	4				**5**			
	^{1}H		^{13}C		^{1}H		^{13}C	
position	22 °C	70 °C	22 °C	70 °C	22 °C	70 °C	22°C	70 °C
1			162.7/160.9	162.7			162.7/161.1	161.6
2			107.6	107.3			107.7/107.6	107.4
3			164.5/163.3	163.7			165.3/163.8	164.4
4	6.38/6.35 (1H, s)	6.37 (1H, s)	93.8/92.6	93.2	6.43/6.39 (1H, s)	6.39 (1H, s)	93.7/92.6	93.3
4a			156.3	156.0			156.5/156.3	156.3
4b			151.8	151.6			148.8	148.7
5	6.86 (1H, s)	6.89 (1H, s)	102.8	102.6	7.48 (1H, d, J = 8.5 Hz)	7.43 (1H, d, J = 9.0 Hz)	119.0	118.5
6			155.0	154.5	7.28 (1H, dd, J = 2.5, 8.5 Hz)	7.26 (1H, dd, J = 3.0, 9.0 Hz)	124.4	124.0
7			146.2	145.9			153.9	153.6
8	7.42 (1H, s)	7.48 (1H, s)	104.8	105.2	7.42 (1H, d, J = 2.5 Hz)	7.44 (1H, d, J = 3.0 Hz)	108.0	108.0
8a			111.2	111.3			120.4	120.2
8b			101.4/100.9	101.0			101.3/101.5	101.4
9			179.0/178.7	178.6			179.7	179.5
7-OMe	3.86 (3H, s)	3.89 (3H, s)	55.9	55.8				
1-OH	13.81/13.72 (1H, s)	13.61 (1H, s)			13.53/13.48 (1H, s)	13.42 (1H, s)		
Glc-1	4.63 (1H, d, J = 10.8 Hz)/ 4.57 (1H, d, J = 10.8 Hz)	4.69 (1H, d, J = 9.9 Hz)	71.5/71.2	71.2	4.66/4.59 (1H, d, J = 10 Hz)	4.69 (1H, d, J = 10 Hz)	71.3/71.1	71.2
2			74.1	74.3			74.1	74.3
3			79.4	79.0			79.4/79.3	79.0
4			70.7	70.6			71.0/70.7	70.5
5			81.5	80.9			81.5	80.9
6			61.7/61.4	61.2			61.7/61.4	61.2
Api-1	5.20 (1H, s)	5.19 (1H, s)	108.9	108.7	5.22/5.20 (1H, s)	5.20 (1H, s)	109.1/108.9	108.7
2			75.7	75.8			75.6	75.9
3			79.0	79.0			79.0	79.0
4			73.7/73.5	73.2			73.6/73.4	73.2
5			64.5	64.2			64.5	64.2

228 and 311 nm as the detecting wavelength, and 3.0 mL/min as the flow rate to furnish compounds **1** (11.2 mg) and **5** (22.5 mg).

The 50% EtOH aqueous eluate (78 g) was chromatographed on a silica gel column (1.6 kg), eluted with $CHCl_3$−MeOH−H_2O in a gradient manner (90:10:0 → 60:40:5, 500 mL as one fraction). Fractions 61−69 were subjected to Sephadex LH-20 and eluted with MeOH to afford 12 fractions, and subfractions 4 and 5 were further purified by HPLC (Waters Prep Nova-pak HR C_{18} as column, 5 μm, 7.8 × 300 mm, MeOH−H_2O (23:77) as mobile phase, flow rate 3.0 mL/min, detecting wavelengths 228 and 311 nm) to furnish compound **3** (22.3 mg). The recrystallized mother liquor of fractions 70 and 71 from MeOH was subjected to a silica gel column with $CHCl_3$−MeOH−H_2O (80:20:5 lower phase) as eluent to afford 50 fractions, and subfractions 30−45 were further purified by sephadex LH-20 and HPLC (Alltima C_{18} column, 5 μm, 10 × 250 mm, MeOH−H_2O (30:70) as mobile phase, flow rate 2.5 mL/min, detecting wavelengths 228 and 311 nm) to give compound **2** (8.52 mg).

Xanthone VIII (1): yellow amorphous powder, $[\alpha]^{20}_D$ −7.98° (*c* 0.11, MeOH); UV λ_{max} (MeOH) nm 241, 258, 316, 362; λ_{max} (MeOH+NaOAC) nm: 240, 369; IR (KBr) ν_{max} cm^{-1} 3396 (OH), 1657 (C=O), 1619, 1472 (aromatic ring); HRSIMS (negative mode) *m/z* 567.1345 ($C_{25}H_{30}O_{15}$ [M − H]$^-$, requires 567.1355); FABMS (positive mode) *m/z* 569 [M + H]$^+$; ^{1}H NMR and ^{13}C NMR data, Table 1.

Xanthone IX (2): yellow amorphous powder, $[\alpha]^{20}_D$ +69.1° (*c* 0.10, MeOH); UV λ_{max} (MeOH) nm 219, 259, 302, 371; IR (KBr) ν_{max} cm^{-1} 3402 (OH), 1651 (C=O), 1610, 1478 (aromatic ring); HRSIMS (negative mode) *m/z* 551.1413 ($C_{25}H_{30}O_{15}$ [M − H]$^-$, requires 569.1406); FABMS (positive mode) *m/z* 553 [M + H]$^+$; ^{1}H NMR and ^{13}C NMR data, Table 1.

Xanthone X (3): yellow amorphous powder, $[\alpha]^{20}_D$ −77.3° (*c* 0.12, MeOH); UV λ_{max} (MeOH) nm 246, 274, 313; IR (KBr) ν_{max} cm^{-1} 3399 (OH), 1651 (C=O), 1620, 1503, 1474 (aromatic ring); HRSIMS (positive mode) *m/z* 641.2086 ($C_{29}H_{37}O_{16}$ [M + H]$^+$, requires 641.2076); ^{1}H NMR and ^{13}C NMR data, Table 1.

Xanthone XI (4): yellow amorphous powder, $[\alpha]^{20}_D$ −11.6° (*c* 0.10, MeOH); UV λ_{max} (MeOH) nm 211, 241, 258, 315, 363; λ_{max} (MeOH + NaOAC) nm 211, 242, 259, 371; IR (KBr) ν_{max} cm^{-1} 3408 (OH), 1650 (C=O), 1614, 1587, 1485 (aromatic ring); HRSIMS (negative mode) *m/z* 567.1345 ($C_{25}H_{30}O_{15}$ [M − H]$^-$, requires 567.1355); FABMS (positive mode) *m/z* 569 [M + H]$^+$; ^{1}H NMR and ^{13}C NMR data, Table 2.

Conformational Analysis. The conformational analyses was done using the TRIPOS Sybyl software package.[12] The MMFF94 force field[13] was chosen to assign parameters. The conformers of compound **4** were built using the Insight II molecular simulation package.[14] Systematic search was used as the method for conformer search. The steric hindrance formed by the C-1 and C-3 hydroxyls to the free rotation of the C−C bond in the *C*-glycoside and of the two bonds linking the two sugars seems to be the main reasons for the existence of the two similar conformers. Torsions 1, 2, and 3 were considered in the conformational search. The three torsions of **4** are illustrated in Figure 2. All the torsions involved were rotated from 0° to 330° and once per 30°, thus 1728 conformations were generated for **1**, **4**, **5**, and **8** and 12 conformations were generated for **6**. To avoid the irrational interatom distance generated by the conformation, which would cause system energy rise to an unreasonable level, each conformer obtained in the rotation was minimized from its current state to a reasonable conformer.

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