Microbial *O*-Demethylation, Hydroxylation, Sulfation, and Ribosylation of a Xanthone Derivative from *Halenia elliptica*

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1-Hydroxy-2,3,5-trimethoxyxanthone (**1**), one of the major xanthone derivatives isolated from *Halenia elliptica*, was biotransformed by two fungi, *Trichothecium roseum* and *Paecilomyces marquandii*. Transformation of **1** by *T. roseum* gave 1,5-dihydroxy-2,3-dimethoxyxanthone (**2**), 5-*O*-sulfate-1-hydroxy-2,3-dimethoxyxanthone (**3**), 5-*O*-sulfate-1-hydroxy-2,3,7-trimethoxyxanthone (**4**), 5-*O*-*β*-ribofuranosyl-1-hydroxy-2,3-dimethoxyxanthone (**5**), and 1,5,6-trihydroxy-2,3-dimethoxyxanthone (**6**). Compound **2** was also formed by *P. marquandii*. The structures of the isolated compounds were elucidated by spectroscopic analyses. Among the five microbial-converted compounds, **3**, **4**, **5**, and **6** are new compounds.

Halenia elliptica D. Don (Gentianaceae), a traditional Tibetan medicinal plant, is widely used to treat different kinds of hepatopathies in China. Phytochemical and pharmaceutical studies indicate that xanthones in *H. elliptica* are the most important components for its hepatoprotective activity.[1,2] Additionally, xanthone derivatives also showed other bioactivities such as uricosuric, hypoglycemic, antimalarial, antituberculous, and cytotoxic activities.[3−8] On the basis of these facts, we studied the microbial biotransformation of xanthone derivatives isolated from *H. elliptica*. Our goals are to expand the chemical diversity of xanthone derivatives for further pharmacological research and to attain a better understanding of microbial models of xanthone metabolism. Since 1-hydroxy-2,3,5-trimethoxyxanthone (**1**) is one of the most abundant xanthones in *H. elliptica*, the present work reports the microbial biotransformation of this xanthone.

After a preliminary screening of 23 fungal strains for microbial biotransformation of **1**, *Paecilomyces marquandii* and *Trichothecium roseum* showed the ability to convert the substrate. In the preparative scale biotransformation, 1,5-dihydroxy-2,3-dimethoxyxanthone (**2**) was yielded by *P. marquandii*. Compound **2**, 5-*O*-sulfate-1-hydroxy-2,3-dimethoxyxanthone (**3**), 5-*O*-sulfate-1-hydroxy-2,3,7-trimethoxyxanthone (**4**), 5-*O*-*β*-ribofuranosyl-1-hydroxy-2,3-dimethoxyxanthone (**5**), and 1,5,6-trihydroxy-2,3-dimethoxyxanthone (**6**) were formed by *T. roseum* (Scheme 1).Compound **2** exhibited IR and UV characteristics similar to substrate **1**.[9] The ESIMS of **2** showed an $[M + 1]^+$ quasi-molecular ion peak at *m*/*z* 289, consistent with a molecular formula of $C_{15}H_{12}O_6$. The molecular formula of **2** was also consistent with the disappearance of an oxygenated methyl signal in the ^1H and ^{13}C NMR spectra compared with those of the substrate **1**. Since the two *O*-methyl groups that correlated with C-2 and C-3 in the HMBC spectrum of **2** still existed, it could be deduced that the oxygenated methyl group at C-5 disappeared. The H-4 singlet at *δ* 6.68 showed HMBC correlations with C-2, C-3, C-4a, and C-8b. The remaining ^1H and ^{13}C NMR data were in accordance with a previous report on a xanthone derivative from a Gentianaceae plant, *Schultesia lisianthoides* (Griseb.) Benth & Hook.[10] Thus, **2** was identified as 1,5-dihydroxy-2,3-dimethoxyxanthone.

Compounds **3** and **4**, which had similar high polarity on normal-phase silica, were successfully purified on reversed-phase C18 semipreparative HPLC. The EIMS of **3** showed a strong base peak at *m*/*z* 288. However, negative ion ESIMS of **3** showed the strong quasi-molecular ion peak at *m*/*z* 367 $[M - H]^-$ and a strong fragment ion peak at *m*/*z* 287 $[M - 80 - H]^-$. HRESIMS data of *m*/*z* 367.012215 $[M - 1]^-$ were consistent with the molecular formula $C_{15}H_{11}O_9S$, suggesting the occurrence of sulfate conjugation, which was supported by the IR absorption at 1282 cm^{-1} (S═O)[11] and the ratio of isotope peaks at *m*/*z* 367 $[M - H]^-$ and *m*/*z* 369 $[M - H + 2]^-$. The ^1H and ^{13}C NMR data of **3** were very similar to those of **2** except that the C-5 signal shifted to *δ* 142.1, implying that the sulfate moiety was conjugated with 5-OH. Moreover, it could be deduced that H-6 was significantly downfield shifted at *δ* 7.82 because of the *ortho*-effect of the sulfate moiety.[12] Compound **3** was thus presumed a C-5-sulfated derivative of **2** and assigned as 5-*O*-sulfate-1-hydroxy-2,3-dimethoxyxanthone.

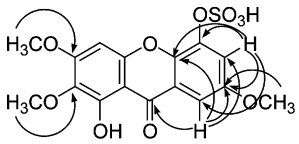

Figure 1. Selective HMBC correlations of **4** (arrows denote HMBC correlations from H to C).

The structure of **4** was postulated to be a xanthone sulfate due to its higher polarity than common xanthones (similar to **3** and lower than the ribosylated **5** on TLC). Negative ion ESIMS of **4** showed a quasi-molecular ion peak at *m*/*z* 397 $[M - H]^-$, corresponding to a molecular formula of $C_{16}H_{13}O_{10}S$, and a strong fragment ion peak at *m*/*z* 317 $[M - 80 - H]^+$, corresponding to a molecular formula of $C_{16}H_{13}O_7$. The molecular formula of **4** was also confirmed by HRESIMS (*m*/*z* 397.022534 $[M - 1]^+$, calcd 397.022945 for $C_{16}H_{13}O_{10}S$). Although a signal for the 1- or 8-hydroxyl protons in the ^1H NMR spectrum of **4** was not apparent, bathochromic shifts observed in the UV spectrum in the presence of $AlCl_3$/HCl indicated a 1- or 8-hydroxyl group.[13] The ^1H and ^{13}C NMR data of ring A of **4** were in accordance with **1**. Singlets at *δ* 7.61 and 7.21 indicated a *meta*-substituted ring B. Important HMBC correlations in Figure 1 supported that **4** should be 5,7-disubstituted. From the molecular formula of **4**, positions 5 and 7 should have a methoxyl and a sulfate group, respectively. According to HMQC and HMBC correlations, the signals at *δ* 7.61 and 7.21 were assigned to H-6 and H-8, respectively. Therefore, sulfate substitution is at C-5 and *O*-methyl substitution at C-7. On the basis of the above analysis, **4** was established as 5-*O*-sulfate-1-hydroxy-2,3,7-trimethoxyxanthone.

The molecular formula of **5** was determined as $C_{20}H_{21}O_{10}$ on the basis of HREIMS data (*m*/*z* 421.113632 $[M + 1]^+$, calcd 421.113475). The ESIMS of **5** showed a quasi-molecular ion peak at *m*/*z* 421 $[M + H]^+$ and a fragment ion peak at *m*/*z* 289 $[M -$

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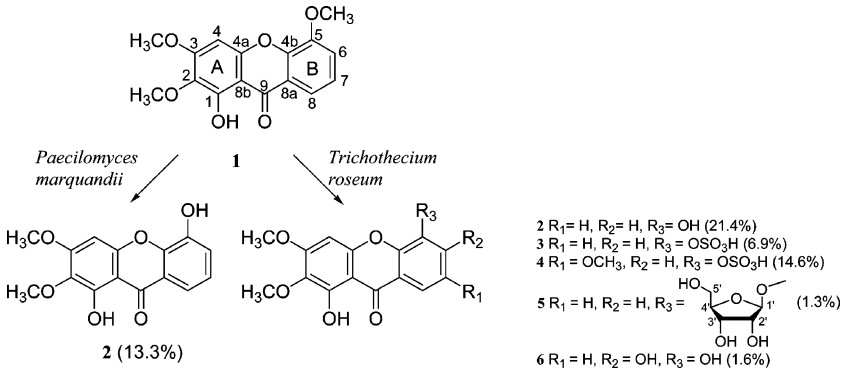
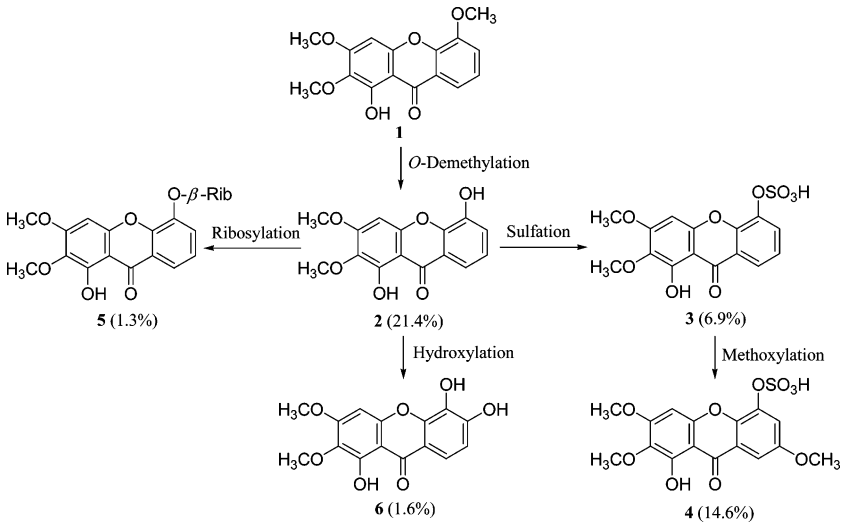
Scheme 1. Transformation of 1-Hydroxy-2,3,5-trimethoxyxanthone (**1**) by *P. marquandii* and *T. roseum*



Scheme 2. Biotransformation of **1** by *T. roseum*



132 + H]$^+$. Together with the information of a set of pentose moiety signals in the ^{1}H and ^{13}C NMR spectra of **5**, it could be inferred that **5** was a product of demethylation and glycosylation of **1**. A downfield signal at δ 12.67 in the ^{1}H NMR spectrum indicated the presence of a phenolic hydroxyl group at C-1 or C-8.[14] Comparing the ^{13}C NMR data of **5** with those of **1** and **2** showed that there was no change in ring A. The upfield chemical shift of C-5 suggested that a pentose was linked to C-5. The conjugated monosaccharide was identified as riboside according to the results of acid hydrolysis. The ^{13}C NMR data of **5** (δ102.2 (C-1′), 71.7 (C-2′), 69.2 (C-3′), 86.6 (C-4′), 61.4 (C-5′)) indicated that the riboside should be ribofuranosyl. From the $^3J_{H-1,H-2}$ coupling constant [δ 5.77 (1H, d, J = 3.4 Hz, H-1′)] and ^{13}C NMR data of the anomeric C-1′ (δ 102.2), the 5-*O*-ribofuranosyl had a β-configuration.[15] Therefore, **5** was concluded to be 5-*O*-β-ribofuranosyl-1-hydroxy-2,3-dimethoxyxanthone.

The molecular formula of **6** was established as $C_{15}H_{12}O_7$ by HREIMS (*m*/*z* 304.058728 [M]$^+$, calcd 304.058305 for $C_{15}H_{12}O_7$). The molecular formula implied that **6** was a demethylation and hydroxylation product of **1**. Only one hydrogen-bonded phenolic hydroxyl singlet at δ 13.04 appeared in the ^{1}H NMR spectrum, which showed that either C-8 or C-1 was hydroxylated.[13] The spectroscopic data of **6** indicated that ring A was identical to that of **1**. The two doublets at δ 7.52 and 6.95 (J = 8 Hz) indicated that ring B was 5,6- or 7,8-*O*,*O*-*o*-disubstituted. C-8 in ring B should not be hydroxylated because there was no hydrogen-bonded phenolic hydroxyl group at about δ 13.[16] Compared with the ^{13}C NMR data of other 5,6-dihydroxylated xanthones, the similar data showed that **6** should have a 5,6-dihydroxy-substituted ring B.[17,18] Compound **6** was thus identified as a new pentaoxygenated xanthone, 1,5,6-trihydroxy-2,3-dimethoxyxanthone.

In conclusion, both the fungi *P. marquandii* and *T. roseum* regiospecifically demethylate the substrate **1**. We obtained five microbial converted products, **2**, **3**, **4**, **5**, and **6**, from **1** by *T. roseum*, the last four compounds being new xanthone derivatives. A comparison of the structures of the substrate and transformed products led to the proposed metabolic pathway in *T. roseum* as shown in Scheme 2:

In the proposed pathway, compound **2** was the major metabolic intermediate generated from **1**, suggesting that *O*-demethylation is the key enzymatic reaction for compound **1** in *T. roseum*. Transformed products **3** (6.9%), **5** (1.3%), and **6** (1.6%) were directly derived from **2**, with 7-*O*-methyl substitution of **3** resulting in the formation of compound **4** (14.6%). Low yields of compounds **5** and **6** demonstrate that *O*-ribosylation at C-5 and hydroxylation at C-6 of the xanthone derivative **2** are relatively difficult to achieve. Sulfation of the xanthone derivative **2** was more easily performed in *T. roseum*, leading to relatively high yields of sulfated products **3** and **4**. Compounds **1**, **2**, and **3** were specific substrates in *T. roseum* for the corresponding microbial *O*-demethylation, hydroxylation, ribosylation, sulfation, and *O*-methylation, which demonstrates the advantages of microbial transformation: functional diversity and substrate specificity of metabolic enzymes.

The present report indicates that *T. roseum*, a common pathogen of cotton, was also capable of performing phase II conjugation in the form of the rare ribosylation and sulfation reactions.[19−21] *T. roseum* may be used as a potential biocatalyst and a new in vitro model system for xanthone metabolism.[22,23] Since many xanthone derivatives isolated from *H. elliptica* showed antioxidant and other activities, the bioactivities of the bioconverted derivatives of **1**, especially the new structures, could be utilized as potential candidates for drug screening. Expanding the xanthone substrates,

more diverse converted xanthone compounds would likely be obtained by this potential biocatalyst.

Experimental Section

General Experimental Procedures. Melting points (uncorrected) were determined on a Reichert Nr-229 micromelting point apparatus. Optical rotations were measured on a Perkin-Elmer 343 digital polarimeter. UV spectra were determined with a Hitachi UV-240 spectrophotometer. IR spectra were recorded on an IMPACT FT-IR 400 (KBr) spectrometer. ^{1}H NMR (500 MHz), ^{13}C NMR (125 MHz), and 2D NMR spectra were recorded on an INOVA-500 spectrometer. HR-mass spectra were performed on a VG-Autospec-300 mass spectrometer.

Microorganisms and Culture Media. *Trichothecium roseum* (Bull.) Link ex S. F. Gray (ACCC30210) was purchased from China Agricultural Culture Collection Center (Beijing), and *Paecilomyces marquandii* (Massee) S. Hughes was a gift from Professor Ying-lan Guo of Institute of Microbiology, Chinese Academy of Sciences. Both of the strains were maintained on barley bran agar slants containing barley bran (50 g), glucose (20 g), sucrose (20 g), peptone (2 g), KH_2PO_4 (1.5 g), and $MgSO_4 \cdot 7H_2O$ (0.75 g) in 1000 mL of H_2O, pH 6.2. Liquid medium containing glucose (20 g), yeast extracts (5 g), peptone (5 g), NaCl (5 g), and KH_2PO_4 (5 g) in 1000 mL of water, pH 6.5, was used for biotransformation experiments.

Biotransformation of 1 by *T. roseum*. The organism was grown at 28 °C for 2 days in conical flasks (500 mL), each containing 100 mL of the liquid medium and shaken at 150 rpm on a rotatory shaker (stage I culture). Each of 67 identical flasks with the same volume of fresh medium was inoculated with 4 mL of the stage I culture and incubated for another 36 h. Then 700 mg of **1** dissolved in 45 mL of mixed solvent (36 mL of acetone, 6 mL of DMSO, and 3 mL of Tween 80) was distributed equally among the 67 stage II culture flasks. The incubation continued for 6 additional days. Filtrate from the broth was extracted four times with the same volume of EtOAc. The combined EtOAc extract was dried over anhydrous Na_2SO_4 and concentrated under vacuum to yield 1.5 g of the residue. This residue was subjected to a silica gel column (160−200 mesh, 90 g) eluted with petroleum ether−EtOAc (1:1), EtOAc, and acetone to MeOH with increased polarity. Fractions 5 and 6 were recrystallized to afford **2** (150 mg, 21.4%). Fractions 15−17 were subjected to preparative TLC with CH_2Cl_2−MeOH (15:1), and **6** (11 mg, 1.6%) was obtained. Fractions 21−28 were developed with CH_2Cl_2−MeOH (10:1) on preparative TLC to give **5** (9 mg, 1.3%). Fractions 41−69 were subjected to semipreparative C18 reversed-phase HPLC (Kromasil 10 μm, 25 cm × 10 mm), eluted with MeOH−H_2O (30:70, v/v) at a flow rate of 3.0 mL/min and detected at 254 nm. Fractions collected at 11 and 20 min gave **3** (48 mg, 6.9%) and **4** (102 mg, 14.6%), respectively.

1,5-Dihydroxy-2,3-dimethoxyxanthone (2): yellow needles (acetone), mp 246−248 °C; UV λ_{max} (MeOH) nm 219, 244, 253, 273, 308, 363; IR bands (KBr) cm^{-1} 3437, 2951, 2829, 1653, 1570, 1498, 1456; ESIMS *m*/*z* 289 [M + 1]$^+$; ^{1}H NMR (DMSO-d_6, 500 MHz) δ 12.75 (1H, s, OH-1), 10.32 (1H, brs, OH-5) 7.67 (1H, dd, J = 2.5 Hz 13 Hz, H-8),7.36 (1H, dd, J = 2.5 Hz 13 Hz, H-6),7.28 (1H, t, J = 13 Hz,H-7), 6.68 (1H, s, H-4) 3.94 (3H, s, OCH_3-3), 3.73 (3H, s, OCH_3-2); ^{13}C NMR (DMSO-d_6, 500 MHz) δ 153.0 (C-1), 131.1 (C-2), 160.1 (C-3), 91.5 (C-4), 152.8 (C-4a), 145.0 (C-4b), 146.2 (C-5), 120.5 (C-6), 124.3 (C-7), 114.5 (C-8), 180.8 (C-9), 120.6 (C-8a), 103.2 (C-8b), 60.1 (OCH_3-2), 56.6 (OCH_3-3).

1-Hydroxy-2,3-dimethoxyxanthone-5-*O*-sulfate (3): yellow powder; R_f 0.48 (silica gel, CH_2Cl_2−MeOH, 4:1); UV λ_{max} (MeOH) nm 239, 307, 359; IR bands (KBr) cm^{-1} 3500, 3089, 2939, 2831, 1658, 1603, 1574; EI-MS *m*/*z* 288 [M − 80]$^+$, 273 [M − 80 − 15]$^+$, 245 [M − 80 − 43]$^+$; ESIMS *m*/*z* 367 [M − 1]$^-$; HRESIMS *m*/*z* 367.012215 [M − 1]$^+$ (calcd 367.012380 for $C_{15}H_{11}O_9S$); ^{1}H NMR (DMSO-d_6, 500 MHz) δ 12.72 (1H, s, OH-1), 7.98(1H, d, J = 8 Hz, H-8), 7.82 (1H, d, J = 8 Hz, H-6), 7.39 (1H, t, J = 8 Hz, H-7), 6.82 (1H, s, H-4), 3.98 (3H, s, OCH_3-3), 3.74 (3H, s, OCH_3-2); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 180.4 (C-9), 160.1 (C-3), 153.2 (C-1), 152.8 (C-4a), 147.1 (C-4b), 142.1 (C-5), 131.2 (C-2), 125.8 (C-7), 123.6 (C-6), 120.5 (C-8a), 118.5 (C-8), 103.2 (C-8b), 91.6 (C-4), 60.04 (OCH_3-2), 56.65 (OCH_3-3).

1-Hydroxy-2,3,7-trimethoxyxanthone-5-*O*-sulfate (4): yellow powder; R_f 0.48 (silica gel, CH_2Cl_2−MeOH, 4:1); UV λ_{max} (MeOH) nm 243, 264, 302, 374; UV λ_{max} (MeOH + $AlCl_3$) nm 231, 276, 330, 426; UV λ_{max} (MeOH + $AlCl_3$ + HCl) nm 231, 276, 330, 426; IR bands (KBr) cm^{-1} 3282, 3120, 2947, 2835, 1662, 1579, 1493; EIMS *m*/*z* 318 [M]$^+$, 303 [M − 15]$^+$, 275 [M − 43]$^+$; HRESIMS *m*/*z* 397.022534 [M − 1]$^+$ (calcd 397.022945 for $C_{16}H_{13}O_{10}S$); ^{1}H NMR (DMSO-d_6, 500 MHz) δ 7.61 (1H, s, H-6), 7.21 (1H, s, H-8), 6.81 (1H, s, H-4),3.97 (3H, s, OCH_3-3), 3.85 (3H, s, OCH_3-7),3.74 (3H, s, OCH_3-2); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 180.0 (C-9), 160.0 (C-3), 155.0 (C-7), 152.9 (C-1), 152.6 (C-4a), 143.2 (C-5), 142.3 (C-4b), 131.1 (C-2), 120.2 (C-8a), 114.9 (C-6), 103.0 (C-8b), 98.3 (C-8), 91.4 (C-4), 60.0 (OCH_3-2), 56.6 (OCH_3-3), 55.7 (OCH_3-7).

5-*O*-β-Ribofuranosyl-1-hydroxy-2,3-dimethoxyxanthone (5): yellow powder; $[\alpha]^{20}_D$ −103.4 (*c* 0.0145, MeOH); R_f 0.55 (silica gel, CH_2Cl_2−MeOH, 10:1); UV λ_{max} (MeOH) nm 217, 241, 305; IR bands (KBr) cm^{-1} 3572, 3477, 3249, 2898, 1657, 1579, 1496, 1452; ESIMS *m*/*z* 443 [M + H + Na]$^+$, 421 [M + H]$^+$, 289 [M − 132 + H]$^+$; ESIMS *m*/*z* 421289 [M − 132 + 1]$^+$; HRESIMS *m*/*z* 421.113632 [M + 1]$^+$ (calcd 421.113475 for $C_{20}H_{21}O_{10}$); ^{1}H NMR (DMSO-d_6, 500 MHz) δ 12.67 (1H, s, OH-1), 7.77 (1H, d, J = 8 Hz, H-8), 7.64 (1H, d, J = 8 Hz, H-6), 7.39 (1H, t, J = 8 Hz, H-7), 6.80 (1H, s, H-4), 3.96 (3H, s, OCH_3-3), 3.74 (3H, s, OCH_3-2), 5.77 (1H, d, J = 3.4 Hz, H-1′), 4.70−5.10 (3H, OH-2′, OH-3′, OH-5′), 4.20−3.90 (3H, H-2′, H-3′, H-4′), 3.48 (1H, H-5′); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 160.0 (C-3), 152.6 (C-4a), 146.8 (C-4b), 145.4 (C-5), 131.2 (C-2), 124.0 (C-7), 122.7 (C-6), 120.5 (C-8a), 117.4 (C-8), 91.5 (C-4), 60.05 (OCH_3-2), 56.54 (OCH_3-3), 102.2 (C-1′), 71.7 (C-2′), 69.2 (C-3′), 86.6 (C-4′), 61.4 (C-5′). (Signals of C-1, C-9, C-8b were not observed in ^{13}C NMR due to a small quantity of determined samples.)

1,5,6-Trihydroxy-2,3-dimethoxyxanthone (6): yellow powder; UV λ_{max} (MeOH) nm 254, 280, 325; IR bands (KBr) cm^{-1} 3381, 2951, 2829, 1652, 1577, 1498, 1454; EIMS *m*/*z* 304 [M]$^+$(100%), 289 [M − 15]$^+$ (100%), 261 [M − 43]$^+$ (63%); HREIMS *m*/*z* 304.058728 [M]$^+$ (calcd 304.058305 for $C_{15}H_{12}O_7$); ^{1}H NMR (DMSO-d_6, 500 MHz) δ 13.04 (1H, s, OH-1), 7.52 (1H, d, J = 8 Hz, H-8), 6.95 (1H, d, J = 8 Hz, H-7), 6.74 (1H, s, H-4), 3.94 (3H, s, OCH_3-3), 3.73 (3H, s, OCH_3-2); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 180.2 (C-9), 159.3 (C-3), 153.4 (C-1), 152.7 (C-4a), 152.0 (C-6), 146.2 (C-4b), 132.5 (C-5), 130.9 (C-2), 115.8 (C-8), 113.2 (C-8a), 112.7 (C-7), 102.5 (C-8b), 91.0 (C-4), 60.05 (OCH_3-2), 56.43 (OCH_3-3).

Biotransformation of 1 by *P. marquandii*. The organism was grown at 28 °C for 2 days in 15 conical flasks (500 mL), each containing 100 mL of the liquid medium and shaken at 150 rpm on a rotatory shaker. The substrate **1** (150 mg) dissolved in 15 mL of acetone with 1.5 mL of Tween 80 was distributed equally among these 15 flasks and the incubation continued for another 6 days. The same extraction procedure mentioned previously was utilized, and 80 mg of a residue was obtained. The residue was subjected to silica gel column chromatography (160−200 mesh) eluted with petroleum ether−acetone, 5:1. Similar fractions, monitored by TLC, were combined and developed on preparative TLC (petroleum ether−acetone, 5:3) to afford 20 mg of pure **2** (13.3%).

1,5-Dihydroxy-2,3-dimethoxyxanthone (2): same physical data as the biotransformed product of **1** by *T. roseum*.

Acid Hydrolysis of 5. A solution of **5** (5 mg) in 5 mL of 0.2 M HCl−dioxane (1:1, v/v) was heated under reflux for 2.5 h. The solution was evaporated under vacuum to remove dioxane and then was extracted with EtOAc (3 × 5 mL). The EtOAc layers were combined and concentrated to yield a residue. The residue was purified by preparative TLC (petroleum ether−acetone, 5:3, v/v) to give **2** (2 mg), which was identified by comparison of the spectroscopic data obtained previously. The aqueous layer was lyophilized to obtain the sugar fraction. Sugar analysis was performed on normal-phase TLC (7:3:1 $CHCl_3$−MeOH−H_2O, v/v/v). By comparison with the standard sugars, the pentose in the hydrolysis products was identified as ribose (R_f = 0.68).

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