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Synthesis of Mangiferin, Isomangiferin, and Homomangiferin

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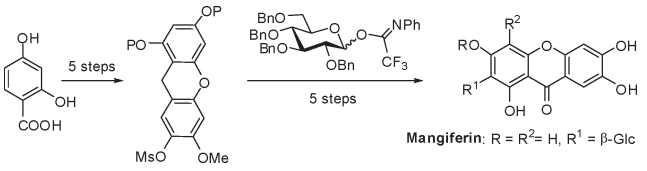
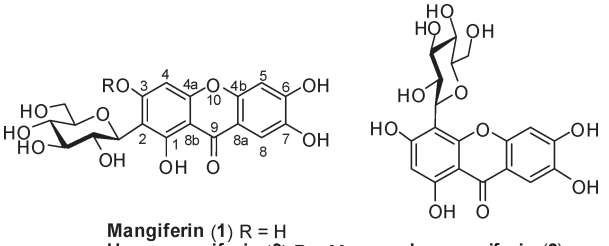


Mangiferin, isomangiferin, and homomangiferin, the xanthone *C*-glycosides with a wide spectrum of pharmacological effects, were synthesized concisely, featuring a *C*-glycosylation of a xanthene derivative with perbenzylglucopyranosyl *N*-phenyltrifluoroacetimidate.

Mangiferin (**1**) was first isolated in 1908 as a coloring matter from the mango tree (*Mangiferin indica* L., Anacardisaceae).[1] Until the 1960s, its structure, namely 2-*C*-*β*-D-glucopyranosyl-1,3,6,7-tetrahydroxyxanthone was convincingly determined by extensive degradation studies.[2,3] The full NMR assignment and X-ray diffraction analysis of this old compound were reported only recently.[4,5] Mangiferin occurs most abundantly in the stem bark of mango;[6] nevertheless, it has also been found in many angiosperm plants and ferns.[7] Isomangiferin (**2**) and homomangiferin (**3**), the 4-*C*-glycoside regioisomer and 3-*O*-methyl derivative of mangiferin, respectively, mainly coexist with mangiferin in the mango leaves and twigs.[8,9]

Mangiferin exhibits a wide spectrum of pharmacological effects, including, among others, immunomodulatory, anti-inflammatory, antitumor, antidiabetic,[10] lipolytic, antimicrobial, and antiallergic activities.[11] Many of these effects could be attributed to its antioxidant property; in fact, mangiferin is a "super antioxidant" which is more potent than vitamins C and E.[11b] Interestingly, this *C*-glycoside could traverse the blood−brain barrier and, thus, has potential to ameliorate the oxidative stress in neurodegenerative disorders.[12]

Mangiferin has been obtained in about 0.1% yield via treatment of the aglycone 1,3,6,7-tetrahydroxyxanthone with a large excess of α-acetobromoglucose in the presence of NaOMe followed by hydrolysis of the formed *O*-glycosidic linkages.[3] However, the chemical synthesis of xanthone *C*-glycosides has never been reported. Herein we present a synthetic approach to mangiferin, isomangiferin, and homomangiferin.



The key to synthesize mangiferin and congeners is the construction of the xanthone *C*-glycosidic linkage. Friedel−Crafts-type reaction between a glycosyl donor and an electron-rich aromatic compound is the most straightforward approach to the synthesis of aryl *C*-glycosides.[13,14] Nevertheless, a xanthone derivative is electron deficient; thus aryl

(1) (a) Wiechowski, W. *Lotos* **1908**, *56*, 61. (b) van Scherpenberg, A. L. *Rec. Trav. Chim.* **1916**, *35*, 346.

(2) (a) Haynes, L. J.; Taylor, D. R. *J. Chem. Soc. C* **1966**, 1685. (b) Bhatla, V. K.; Ramanathan, J. D. *Tetrahedron* **1967**, *23*, 1363. (c) Nott, P. E.; Roberts, J. C. *Phytochemistry* **1967**, *6*, 1597.

(3) (a) Nott, P. E.; Roberts, J. C. *Phytochemistry* **1967**, *6*, 741. (b) Bhatla, V. K.; Seshadri, T. R. *Tetrahedron Lett.* **1968**, *14*, 1741.

(4) Faizi, S.; Zikr-ur-Rehman, S.; Ali, M.; Naz, A. *Magn. Reson. Chem.* **2006**, *44*, 838.

(5) Cruz, J. W., Jr.; Moraes, L. R.; Santos, M. H.; Silva, G. A.; Brigagão, M. R. P. L.; Ellena, J.; Doriguetto, A. C. *Helv. Chim. Acta* **2008**, *91*, 144.

(6) (a) Selles, A. J. N.; Castro, H. T. V.; Aguero-Aguero, J.; Gonzalez-Gonzalez, J.; Naddeo, F.; Simone, F. D.; Rastrelli, L. *J. Agric. Food Chem.* **2002**, *50*, 762. (b) Berardini, N.; Knodler, M.; Schieber, A.; Carle, R. *Inn. Food Sci. Emerg. Tech.* **2005**, *6*, 442. (c) Makare, N.; Bodhankar, S.; Rangari, V. *J. Ethnopharmacol.* **2001**, *78*, 133.

(7) (a) Hostettmann, K.; Wagner, H. *Phytochemistry* **1977**, *16*, 821. (b) Richardson, P. M. *Biochem. Sys. Ecol.* **1983**, *11*, 371. (c) Richardson, P. M. *Biochem. Sys. Ecol.* **1984**, *12*, 1. (d) Cafferty, S.; Greenham, J.; Williams, C. A. *Biochem. Syst. Ecol.* **1996**, *24*, 173.

(8) (a) Aritomi, M.; Kawasaki, T. *Chem. Pharm. Bull.* **1970**, *18*, 2327. (b) Saleh, N. A. M.; El-Ansari, M. A. I. *Planta Med.* **1975**, *28*, 124. (c) Fujita, M.; Inoue, T. *Chem. Pharm. Bull.* **1982**, *30*, 2342.

(9) Aritomi, M.; Kawasaki, T. *Chem. Pharm. Bull.* **1970**, *18*, 2224.

(10) For a recent development of *C*-aryl glycosides as anti-diabetic agents, see: Zhou, H.; Danger, D. P.; Dock, S. T.; Hawley, L.; Roller, S. G.; Smith, C. D.; Handlon, A. L. *ACS Med. Chem. Lett.* **2010**, *1*, 19.

(11) (a) Wauthoz, N.; Balde, A.; Balde, E. S.; van Damme, M.; Duez, P. *Int. J. Biomed. Pharma. Sci.* **2007**, *1*, 112. (b) Masibo, M.; He, Q. *CRFSFS* **2008**, *7*, 309. (c) Guha, S.; Ghosal, S.; Chattopadhyay, U. *Chemotherapy* **1996**, *42*, 443. (d) Scartezzini, P.; Speroni, E. *J. Ethnopharmacol.* **2000**, *71*, 23. (e) Sanchez, G. M.; Re, L.; Giuliani, A.; Nuonez-Selles, A. J.; Davison, G. P.; Leon-Fernandez, O. *Pharmcol. Res.* **2000**, *42*, 565.

(12) (a) Martinez, G.; Candelario, E.; Giuliani, A.; Leon, O.; Sam, S.; Delgado, R. *Free Radic. Res.* **2001**, *35*, 465. (b) Jung, K.; Lee, B.; Han, S. J.; Ryu, J. H.; Kim, D.-H. *Biol. Pharm. Bull.* **2009**, *32*, 242.

(13) For selected reviews on aryl *C*-glycosides synthesis, see: (a) Jaramillo, C.; Knapp, S. *Synthesis* **1994**, 1. (b) Lee, D. Y. W.; He, M. *Curr. Top. Med. Chem.* **2005**, *5*, 1333.

(14) For selected examples on flavonoid *C*-glycosides synthesis, see: (a) Oyama, K.; Kondo, T. *J. Org. Chem.* **2004**, *69*, 5240. (b) Kumazawa, T.; Kimura, T.; Matsuba, S.; Sato, S.; Onodera, J.-i. *Carbohydr. Res.* **2001**, *334*, 183. (c) Furuta, T.; Nakayama, M.; Suzuki, H.; Tajimi, H.; Inai, M.; Nukaya, H.; Wakimoto, T.; Kan, T. *Org. Lett.* **2009**, *11*, 2233. (d) Yepremyan, A.; Salehani, B.; Minehan, T. G. *Org. Lett.* **2010**, *12*, 1580.

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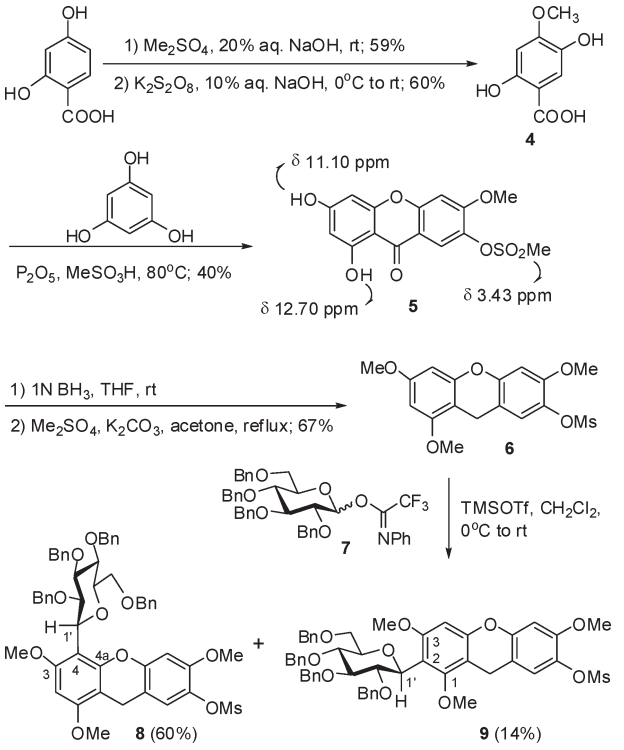
SCHEME 1. Synthesis of Xanthene *C*-Glycosides 8 and 9

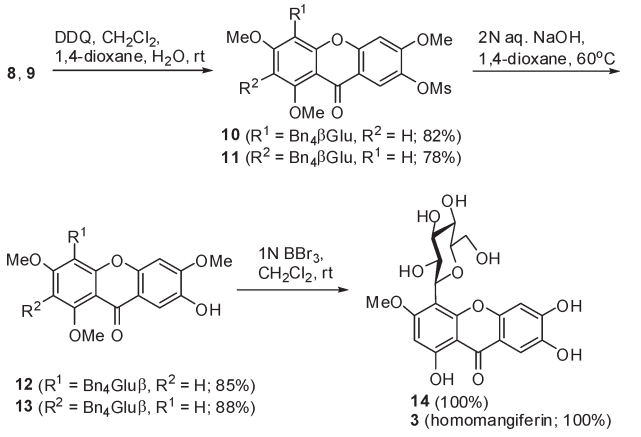


C-glycosylation at a earlier precursor without the C9 carbonyl function would be mandatory.

We first prepared a 1,3,6,7-tetrahydroxyxanthone derivative (**5**) employing modification of the literature transformations (Scheme 1). Thus, the commercially available 2,4-dihydroxybenzoic acid was monomethylated to give 4-methoxy-2-hydroxybenzoic acid (59%), which was then treated with $K_2S_2O_8$ in 10% aqueous NaOH to provide 4-methoxy-2,5-dihydroxybenzoic acid (**4**, 60%).[15] Condensation of benzoic acid **4** with phloroglucinol was effected in the presence of Eaton's reagent (P_2O_5, CH_3SO_3H).[16] Unexpectedly, the resulting xanthone **5** in 40% yield was identified as a 7-*O*-mesyl derivative. The expected 6-methoxy-1,3,7- trihydroxyxanthone was not detected at all.

To effect a nucleophilic *C*-glycosylation, xanthone diol **5** was reduced with 1 N $BH_3 \cdot THF$ followed by methylation to give xanthene derivative **6**. As expected,[17] glycosylation of **6** with 2,3,4,6-tetra-*O*-benzyl-D- glucopyranosyl *N*-phenyltrifluoroacetimidate **7**[18] under the promotion of TMSOTf (0.1 equiv) led to *C*-*β*-glycosides **8** (H-1′: 6.08 ppm, d, $J = 8.0$ Hz) and **9** (H-1′: 5.77 ppm, d, $J = 6.6$ Hz) in a satisfactory overall yield. These two isomers could be easily separated by chromatography on silica gel, with the major isomer determined to be the 4-*C*-glycoside **8** (60%) and the minor 2-*C*-glycoside **9** (14%). Thus, HMBC correlations between signal of the anomeric proton H-1′ with those of C-3 (158.5 ppm), C-4 (107.3 ppm), and C-4a (107.27 ppm) were observed for 4-*C*-glycoside **8**, and the signal of the anomeric proton H-1′ with those of C-1 (159.2 ppm), C-2 (115.8 ppm), and C-3 (158.2 ppm) were observed for 2-*C*-glycoside **9**.

SCHEME 2. Synthesis of Homomangiferin 3 and 3-*O*-Methylisomangiferin 14



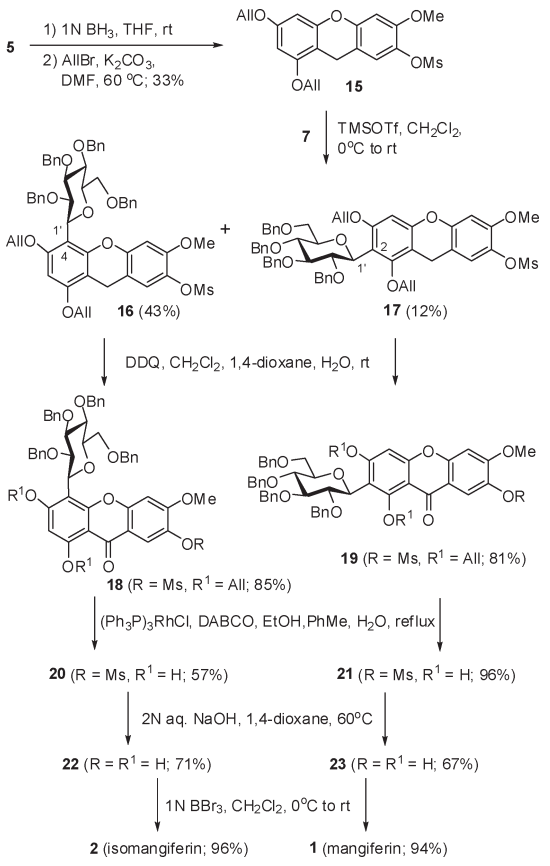
Xanthene *C*-glycosides **8**/**9**, respectively, were then subjected to oxidation with DDQ in a mixed solvent of CH_2Cl_2/1,4-dioxane/H_2O,[19] leading successfully to the desired xanthone *C*-glycosides **10**/**11** in ~80% yields (Scheme 2). The 7-*O*-mesyl group was removed with 2 N NaOH in 1,4-dioxane at 60 °C to afford **12**/**13** in >85% yields.[20] Treatment of **12**/**13** with 1 N BBr_3 in methylene chloride at rt led to mono-*O*-methyl-xanthone *C*-glycosides **14** or **3** in quantitative yields[21] in that the four *O*-benzyl groups on the sugar moiety together with the phenolic 1-*O*-methyl group have been cleaved smoothly.

The ^{1}H NMR of **14** in pyridine-d_5 showed splitting or broadening of several proton signals at room temperature, which coalesced at 70 °C. The ^{13}C NMR at ambient temperature showed a similar phenomenon. These indicated the occurrence of a pair of the rotamers for *C*-glycoside **14** at ambient temperature due to the restricted rotation about the C−C bond between the sugar and the aromatic ring.[22] The 3-*O*-methyl group was assigned according to the HMBC correlation between the signal of *O*-CH_3 (3.89 and 3.87 ppm) with that of C-3 (166.2 and 167.2 ppm). The ^{1}H MNR signal of the 3-*O*-methyl group in compound **3** (homomangiferin) also appeared as two peaks in pyridine-d_5 at ambient temperature (3.70 and 3.61 ppm), which is in accordance with the literature report for the natural compound (3.77 and 3.68 ppm).[9]

The remaining 3-*O*-methyl group on **14**/**3** could not be removed by increasing the amount of BBr_3 or the reaction temperature before the sugar moiety started to decompose. Other conditions, e.g., $BF_3 \cdot OEt_2/Ac_2O$,[23] $AlCl_3$/EtSH,[24] and HI,[25] were also found to be futile in removeing

(15) Evans, J. C.; Klix, R. C.; Bach, R. D. *J. Org. Chem.* **1988**, *53*, 5519.
(16) Pillai, R. K. M.; Naiksatam, P.; Johnson, F.; Rajagopalan, R.; Watts, P. C.; Cricchio, R.; Borras, S. *J. Org. Chem.* **1986**, *51*, 717.
(17) Li, Y.; Wei, G.; Yu, B. *Carbohydr. Res.* **2006**, *341*, 2717.
(18) (a) Yu, B.; Tao, H. *Tetrahedron Lett.* **2001**, *42*, 2405. (b) Yu, B.; Sun, J. *Chem. Commun.* **2010**, *46*, 4668.
(19) (a) Höfler, C.; Rüchardt, C. *Liebigs Ann.* **1996**, 183. (b) Masuo, R.; Ohmori, K.; Hintermann, L.; Yoshida, S.; Suzuki, K. *Angew. Chem., Int. Ed.* **2009**, *48*, 3462.
(20) Rice, J. E.; Hussain, N.; Lavoie, E. J. *J. Labelled. Compd. Radiopharm.* **1987**, *XXIV*, 1043.
(21) (a) Vlattas, I.; Harrison, I. T.; Tökés, L.; Fried, J. H.; Cross, A. D. *J. Org. Chem.* **1968**, *33*, 4176. (b) Grieco, P. A.; Nishizawa, M.; Oguri, T.; Burke, S. D.; Marinovic, N. *J. Am. Chem. Soc.* **1977**, *99*, 5773. (c) Demuynck, M.; Clercq, P. D.; Vandewalle, M. *J. Org. Chem.* **1979**, *44*, 4863.
(22) Jiang, Y.; Zhang, W.; Tu, P.; Xu, X. *J. Nat. Prod.* **2005**, *68*, 875.
(23) Narayanan, C. R.; Iyer, K. N. *J. Org. Chem.* **1965**, *30*, 1734.
(24) Node, M.; Nishide, K.; Fuji, K.; Fujita, E. *J. Org. Chem.* **1980**, *45*, 4275.

SCHEME 3. Synthesis of Mangiferin 1 and Isomangiferin 2[32]



completely the methyl and/or benzyl groups on glycosides **12**−**14** and **3**.

These results prompted us to gauge other protecting groups for the xanthone 3-OH. Thus, starting from xanthone 1,3-diol **5**, upon reduction to xanthene, the 1,3-diol was protected with an allyl group to furnish **15** (Scheme 3). The allylation (AllBr, K_2CO_3, DMF, 60 °C, 40 h)[26] was found to be sluggish, leading to the diallyl product **15** in only 33% yield together with the two monoallyl derivatives. Glycosylation of xanthene **15** with glucosyl imidate **7** under similar conditions for the coupling with xanthene **6** (cf. **6** + **7** → **8**/**9**) led to the 4-*C*- and 2-*C*-*β*-glycosides **16** and **17** in 43% and 12% yield, respectively. It should be noted that glycosylation of the 1,3-di-*O*-benzyl or methoxymethyl counterpart of the diallyl xanthene **15** under similar conditions failed to provide the corresponding *C*-glycosides. Oxidation of **16**/**17** with DDQ gave xanthone glycosides **18**/**19** in good yields (cf. **8**/**9** → **10**/**11**). Deprotection of the allyl groups on **18**/**19** was achieved with $(Ph_3P)_3RhCl$ and DABCO in a mixed solvent of EtOH/PhMe/H_2O under reflux,[27] leading to diol **20** and **21** in 57% and 96% yield, respectively.[28] Several other conditions were also tried, e.g., $PdCl_2$,[29] $HgCl_2$/HgO,[30] $I(CF_2)_7CF_3$/Zn,[31] but failed to give the desired product. Subsequent removal of the 7-*O*-mesyl group was effected without difficulty (2 N aq NaOH in 1,4-dioxane, 60 °C), affording triol **22**/**23**. Finally, treatment of xanthone glycosides **22**/**23** with 1 N BBr_3 in methylene chloride at rt led successfully to the cleavage of the four *O*-benzyl groups on the sugar moiety and the xanthone 6-*O*-methyl group, furnishing isomangiferin (**2**) and mangiferin (**1**) in excellent yields. All of the analytical data of the synthetic **1** and **2** were virtually identical to those recorded for the natural mangiferin and isomangiferin.[4,32]

In summary, mangiferin, isomangiferin, and homomangiferin, the xanthone *C*-glycosides with a wide spectrum of pharmacological effects, were synthesized for the first time, employing the *C*-glycosylation of a xanthene derivative (i.e., **6** or **15**) with perbenzylglucopyranosyl trifluoroacetimidate (**7**) as the key step. Improvement of the overall efficiency of the synthetic approach and synthesis of relevant derivatives for structure−activity relationship studies are our current interest.

Experimental Section[32]

7-Mesyloxy-6-methyloxy-1,3-dihydroxyxanthone (5). To a solution of phosphorus pentoxide (4.4 g, 31.0 mmol) in methanesulfonic acid (30 mL) at 80 °C was added a mixture of phloroglucinol (1.37 g, 10.8 mmol) and acid **4** (1.00 g, 5.4 mmol). The mixture was stirred for 40 min and then poured into ice−water. The precipitate was collected, washed with water, and dried. Purification by silica gel column chromatography (petroleum ether/acetone = 2:1) gave compound **5** (768 mg, 40%) as a white solid: mp 154−156 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.71 (s, 1 H), 11.10 (brs, 1 H), 7.90 (s, 1 H), 7.38 (s, 1 H), 6.37 (d, J = 2.1 Hz, 1 H), 6.21 (d, J = 2.1 Hz, 1 H), 4.00 (s, 3 H), 3.43 (s, 3 H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 178.4, 165.6, 162.6, 157.5, 157.3, 155.4, 135.1, 119.2, 112.7, 102.0, 101.6, 98.3, 94.1, 57.2, 38.2; ESIMS (m/z) 351 $[M - 1]^-$; HRMS (ESI) calcd for $C_{15}H_{12}O_8SNa$ $[M + Na]^+$ 375.0145, found 375.0157.

7-Mesyloxy-1,3,6-trimethoxyxanthene (6). To a solution of **5** (785 mg, 2.2 mmol) in anhydrous THF (50 mL) was added BH_3·THF (1 N in THF, 15 mL) at 0 °C under argon. The mixture was allowed to warm to room temperature, stirred for 1 day, and then quenched with water. After removal of the THF under reduced pressure, the mixture was washed with 1 N HCl. The organic layer was concentrated to give a pink solid. To a solution of the above product in dry acetone (18 mL) were added anhydrous K_2CO_3 (895 mg, 6.48 mmol) and dimethyl sulfate (0.82 mL, 8.66 mmol). The mixture was refluxed overnight. After being cooled to room temperature, the mixture was filtered through a Celite pad. The filtrate was concentrated in vacuo and purified by silica gel column chromatography (petroleum ether/EtOAc = 4:1−2:1) to afford **6** (553 mg, 67% for two steps) as a pink solid: mp 167−169 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.11 (s, 1H), 6.64 (s, 1 H), 6.18 (s, 2 H), 3.87 (s, 3 H), 3.81 (s, 3 H), 3.79 (s, 3 H), 3.77 (s, 2 H), 3.17 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.7, 158.2, 152.0, 150.5, 133.5,

(25) Lin, C.; Liou, S.; Ko, F.; Teng, C. *J. Pharm. Sci.* **1992**, *81*, 1109.
(26) Gates, B. D.; Dalidowcz, P.; Tebben, A.; Wang, S.; Swenton, J. S. *J. Org. Chem.* **1992**, *57*, 2135.
(27) Gigg, R. *J. Chem. Soc., Perkin Trans. 1* **1980**, 738.
(28) The anomeric protons in compounds **20**−**23** showed $J_{1',2'}$ = ∼2.0 Hz. Treatment of 1,3-diol **20** with allyl bromide (K_2CO_3, DMF, 60 °C, 96%) gave the corresponding 3-*O*-allyl derivative **S1**, which was also the major product upon treatment of 1,3-di-*O*-allyl compound **18** with $PdCl_2$ (CH_2Cl_2, rt, 91%); the anomeric proton in **S1** showed $J_{1',2'}$ = 5.6 Hz (as in **18**).[32] These results indicated that the change of the $J_{1',2'}$ values was caused by conformation distortion of the bulky perbenzyl-*β*-glucose residue, but not by a possible *β* → α → *β* anomerization (the anomerization might take place via a ortho quinine methide intermediate); see: Hosoya, T.; Ohashi, Y.; Matsumoto, T.; Suzuki, K. *Tetrahedron Lett.* **1996**, *37*, 663.
(29) Mereyala, H. B.; Guntha, S. *Tetrahedron Lett.* **1993**, *34*, 6929.
(30) Gigg, R.; Warren, C. D. *J. Chem. Soc. C* **1968**, 1903.
(31) Yu, B.; Li, B.; Zhang, J.; Hui, Y. *Tetrahedron Lett.* **1998**, *39*, 4871.
(32) Experimental details and characterization data for compounds **1**−**3**, **11**, **13**, **15**−**23**, and **S1** are provided in the Supporting Information.

124.6, 112.5, 101.3, 101.0, 93.4, 92.9, 56.1, 55.6, 55.4, 38.0, 21.5; ESIMS (m/z) 367 $[M + H]^+$, 389 $[M + Na]^+$; HRMS (MALDI) calcd for $C_{17}H_{19}O_7S$ $[M + H]^+$ 367.0846, found 367.0845.

4-*C*-(2,3,4,6-Tetra-*O*-benzyl-*β*-D-glucopyranosyl)-7- mesyloxy-1,3,6-trimethoxyxanthene (8) and 2-*C*- (2,3,4,6-Tetra-*O*-benzyl-*β*-D-glucopyranosyl)-7-mesyloxy- 1,3,6-trimethoxyxanthene (9). To a solution of **6** (510 mg, 1.39 mmol) and **7** (1.50 g, 2.10 mmol) in dry CH_2Cl_2 (5 mL) was added TMSOTf (25 μL, 0.14 mmol) dropwise in the presence of freshly activated 4 Å molecular sieves at 0 °C. The mixture was allowed to warm to room temperature and stirred for 1 h. The mixture was then filtered through Celite. The filtrate was concentrated in vacuo. The residue was purified by silica gel column chromatography (petroleum ether/CH_2Cl_2/EtOAc = 6:2:1) to afford **8** (745 mg, 60%) and **9** (173 mg, 14%) as white solids. **8**: mp 61−62 °C; $[\alpha]^{28}_D$ +30.7 (*c* 0.93, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39−6.99 (m, 21 H), 6.75 (s, 1 H), 6.23 (s, 1 H), 6.08 (d, J = 8.0 Hz, 1 H), 4.94 (d, J = 11.2 Hz, 1 H), 4.82 (d, J = 11.2 Hz, 2 H), 4.63−4.34 (m, 6 H), 4.16 (br d, J = 9.2 Hz, 1 H), 4.12−4.08 (m, 1 H), 3.87 (s, 3 H), 3.80 (s, 3 H), 3.89−3.86 (m, 1 H), 3.81−3.78 (m, 1 H), 3.73−3.65 (m, 3 H), 3.27 (br s, 3 H), 3.11 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.5, 157.6, 151.1, 150.6, 150.4, 139.1, 138.7, 138.32, 138.25, 133.6, 128.4, 128.33, 128.29, 128.24, 128.22, 128.0, 127.93, 127.91, 127.88, 127.6, 127.5, 127.3, 124.1, 112.7, 107.3, 101.81, 101.76, 90.6, 83.1, 79.9, 78.8, 74.7, 74.2, 73.9, 73.5, 72.6, 70.0, 68.0, 56.3, 55.7, 55.6, 38.1, 21.7; ESIMS (m/z) 911 $[M + Na]^+$; HRMS (MALDI) calcd for $C_{51}H_{52}O_{12}S$-Na $[M + Na]^+$ 911.3072, found 911.3077. **9**: mp 62−63 °C; $[\alpha]^{28}_D$ +48.3 (*c* 0.74, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35−6.95 (m, 21 H), 6.68 (s, 1 H), 6.40 (s, 1 H), 5.77 (d, J = 6.6 Hz, 1 H), 4.88−4.74 (m, 3 H), 4.59−4.20 (m, 6 H), 4.04−3.96 (m, 2 H), 3.88 (s, 3 H), 3.78 (s, 3 H), 3.70 (s, 3 H), 3.90−3.63 (m, 5 H), 3.18 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.0, 158.2, 152.2, 150.8, 150.6, 138.9, 138.8, 138.4, 138.2, 133.8, 128.29, 128.25, 128.20, 128.0, 127.9, 127.84, 127.81, 127.7, 127.5, 127.4, 124.6, 115.8, 112.5, 106.6, 101.4, 96.3, 83.0, 80.2, 78.2, 74.0, 73.9, 73.3, 72.7, 70.1, 69.6, 62.1, 56.2, 55.7, 53.9, 38.1, 22.2; ESIMS (m/z) 911 $[M + Na]^+$; HRMS (MALDI) calcd for $C_{51}H_{52}O_{12}SNa$ $[M + Na]^+$ 911.3072, found 911.3085.

4-*C*-(2,3,4,6-Tetra-*O*-benzyl-*β*-D-glucopyranosyl)-7-mesyloxy-1,3,6-trimethoxyxanthone (10). To a solution of **8** (141 mg, 0.16 mmol) in CH_2Cl_2/1,4-dioxane/H_2O (8/4/1, 10.4 mL) was added DDQ (360 mg, 1.6 mmol) at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred for 4 h. After the mixture was diluted with EtOAc, DMAP (290 mg, 2.38 mmol) was added. The precipitate was filtered through a Celite pad. The filtrate was concentrated in vacuo. The residue was purified by silica gel column chromatography (petroleum ether/CH_2Cl_2/EtOAc = 3:2:2) to afford **10** (117 mg, 82%) as a white solid: mp 61−62 °C; $[\alpha]^{28}_D$ +29.6 (*c* 0.60, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (s, 1 H), 7.39−6.85 (m, 21 H), 6.37 (s, 1 H), 6.04 (d, J = 6.8 Hz, 1 H), 4.86−4.76 (m, 3 H), 4.61−4.55 (m, 2 H), 4.50−4.46 (m, 2 H), 4.38−4.35 (m, 1 H), 4.30 (br d, J = 9.6 Hz, 1 H); 4.22 (d, J = 11.2 Hz, 1 H); 4.06−4.03 (m, 1 H), 4.03 (s, 3 H), 3.92−3.87 (m, 1 H), 3.87 (s, 3 H), 3.74 (d, J = 2.8 Hz, 2 H), 3.47 (br s, 3 H), 3.20(s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.4, 162.9, 162.0, 157.6, 156.6, 154.4, 138.5, 138.3, 138.1, 137.7, 135.5, 128.5, 128.4, 128.3, 128.02, 127.96, 127.90, 127.81, 127.76, 127.6, 127.5, 120.9, 116.0, 107.3, 106.8, 100.9, 91.1, 81.9, 79.3, 78.6, 74.2, 74.1, 73.7, 73.5, 73.0, 70.2, 68.2, 56.4, 56.3, 56.0, 38.5; ESIMS (m/z) 903 $[M + H]^+$, 925 $[M + Na]^+$; HRMS (MALDI) calcd for $C_{51}H_{51}O_{13}S$ $[M + H]^+$ 903.3045, found 903.3061.

4-*C*-(2,3,4,6-Tetra-*O*-benzyl-*β*-D-glucopyranosyl)-7-hydroxy-1,3,6-trimethoxyxanthone (12). To a solution of **10** (40 mg, 0.044 mmol) in 1,4-dioxane (35 mL) was added 2 N aq NaOH (7.5 mL). The solution was heated to 60 °C and stirred for 24 h. After the solution was cooled to room temperature, the 1,4-dioxane was removed in vacuo, and the resulting mixture was neutralized with 1 N HCl and extracted with CH_2Cl_2. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (petroleum ether/CH_2Cl_2/EtOAc = 1:1:1) to afford **12** (31 mg, 85%) as a white solid: mp 80−81 °C; $[\alpha]^{28}_D$ +23.1 (*c* 0.52, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.87 (d, J = 4.2 Hz, 1 H), 7.39−6.87 (m, 20 H), 6.80 (s, 1 H), 6.35 (s, 1 H), 6.07 (d, J = 6.9 Hz, 1 H), 4.90−4.77 (m, 3 H), 4.63−4.42 (m, 5 H), 4.27 (d, J = 11.7 Hz, 2 H), 4.11−4.03 (m, 1 H), 4.03 (s, 3 H), 3.93−3.86 (m, 1 H), 3.86 (s, 3 H), 3.73 (s, 2 H), 3.50 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.4, 162.6, 162.0, 157.7, 152.4, 150.0, 143.0, 138.7, 138.5, 138.1, 137.8, 128.4, 128.3, 128.24, 128.20, 128.01, 127.96, 127.93, 127.8, 127.72, 127.66, 127.53, 127.45, 116.3, 109.5, 107.0, 98.9, 90.7, 82.4, 79.5, 78.6, 74.3, 74.1, 73.8, 73.6, 73.0, 70.0, 68.2, 56.3, 56.04, 55.95; ESIMS (m/z) 825 $[M + H]^+$, 847 $[M + Na]^+$; HRMS (MALDI) calcd for $C_{50}H_{49}O_{11}$ $[M + H]^+$ 825.3269, found 825.3268.

4-*C*-*β*-D-Glucopyranosyl-3-methoxy-1,6,7-trihydroxyxanthone (14). To a solution of **12** (40 mg, 0.049 mmol) in anhydrous CH_2Cl_2 (1.5 mL) was added BBr_3 (1N in CH_2Cl_2, 0.97 mL) at 0 °C. The mixture was allowed to warm to room temperature. After 3 h, the reaction was quenched with water. The mixture was concentrated in vacuo. The residue was purified by column chromatography on Sephadex LH-20 (CH_2Cl_2/MeOH = 1:1) to afford **14** (21 mg, 100%) as a yellow solid: mp 183−184 °C; $[\alpha]^{24}_D$ +7.8 (*c* 0.36, CH_3OH); ^{1}H NMR (400 MHz, CD_3OD) δ 7.35 (d, J = 12.0 Hz, 1 H), 6.86/6.79 (s, 1 H), 6.39 (d, J = 9.2 Hz, 1 H), 5.02/4.93 (d, J = 10.4 Hz, 1 H), 4.35−4.29 (m, 1 H), 3.93−3.91 (m, 1 H), 3.91 (s, 3 H), 3.73−3.67 (m, 1 H), 3.58−3.49 (m, 2 H), 3.43−3.40 (m, 1 H); ^{13}C NMR (100 MHz, CD_3OD) δ 181.8/181.7, 166.2/167.2, 165.1/164.9, 157.7, 155.7, 153.4, 145.2/145.1, 113.7, 109.3/109.2, 105.8/105.5, 104.3, 103.9/103.7, 95.0/95.9, 82.6/82.8, 80.5/80.7, 74.9/75.4, 73.1, 72.7/72.5, 63.8/63.7, 57.1/56.9; ESIMS (m/z) 825 $[M - 1]^+$; HRMS (ESI) calcd for $C_{20}H_{19}O_{11}$ $[M - 1]^+$ 435.0933, found 435.0922.

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Supporting Information Available: Experimental details, characterization data, and the ^{1}H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.