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Note

Synthesis of *C*-mannopyranosylphloroacetophenone derivatives and their anomerization

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Abstract

The reaction of 2,3,4-tri-*O*-benzyl-α-L-rhamnopyranosyl fluoride (6-deoxy-2,3,4-tri-*O*-benzyl-α-L-mannopyranosyl fluoride) with 2,4-dibenzylphloroacetophenone, in the presence of boron trifluoride·diethyl etherate, afforded both the 3-*C*-α-L- and the 3-*C*-β-L-rhamnopyranosylphloroacetophenone derivatives. The 3-*C*-α-L-rhamnoside was produced as a major product, while the 3-*C*-β-L-rhamnoside was produced as a minor product via anomerization of the 3-*C*-α-L-rhamnoside. Alternatively, the reaction of 2,3,4,6-tetra-*O*-benzyl-α-D-mannopyranosyl fluoride with 2,4-dibenzylphloroacetophenone afforded both the 3-*C*-α-D- and the 3-*C*-β-D-mannnopyranosylphloroacetophenone derivatives under identical conditions. The 3-*C*-β-D-mannoside was produced as a major product via anomerization of the 3-*C*-α-D-mannoside during the reaction. These differences in composition result apparently from the magnitude of the 1,3-diaxial interactions between the C-3 and C-5 positions in these sugar moieties.

Keywords: *C*-Glycosylic compound; *C*-Glycosylflavonoid; *C*-Glycoside; *C*-α-D-Mannosyl compound; *C*-β-D-Mannosyl compound; *C*-α-L-Rhamnosyl compound; *C*-β-L-Rhamnosyl compound; Diaxial interaction; Conformation

C-Glycosyl flavonoids are plant constituents, some of which have biological activities.[1] In this laboratory, our interests have been focussed on the synthesis of the glycosylic portion of *C*-glycosyl flavonoids. Among the *C*-glycosyl flavonoids, a *C*-L-rhamnosyl moiety is much less common, comprising only 7% of the sugar moieties in mono-*C*-glycosyl flavonoids, and 2% of sugar moieties in di-*C*-glycosyl flavonoids.[2] In the course of our synthetic study on *C*-glycosyl flavonoids, we previously described the syntheses of a 3-*C*-β-D-xylopyranosylphloroacetophenone derivative, as well as 3-*C*-α-L- and 3-*C*-β-L-arabinopyranosylphloroacetophenone derivatives, which are important synthetic intermediates in *C*-glycosyl flavonoid syntheses. We also described the anomerization of the *C*-α-L-arabinosyl derivative, a reaction which is controlled by diaxial interactions.[3] We describe herein the synthesis of a 3-*C*-α-L-rhamnopyranosylphloroacetophenone derivative **3**, which is the major product formed initially in the reaction, and a 3-*C*-β-L-rhamnopyranosylphloroacetophenone derivative **4**, which is a minor product, produced via the anomerization of the 3-*C*-α-L-rhamnosyl derivative **3**,

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in the presence of boron trifluoride·diethyl etherate. We also report the synthesis of a 3-*C*-α-D-mannopyranosylphloroacetophenone derivative **6**, which is a minor product formed initially in the reaction, and a 3-*C*-β-D-mannnopyranosylphloroacetophenone derivative **7**,[4a] which is a major product, produced via the anomerization of the 3-*C*-α-D-mannosyl compound **6** under identical conditions. To compare the magnitude of 1,3-diaxial interactions between the C-3 and C-5 positions in the sugar moiety, these *C*-D-mannosyl derivatives were synthesized using commercially available D-mannnose, not the commercially unavailable L-mannose, as a starting glycosyl donor. But the isolation of a *C*-mannosyl flavonoid as a natural product from plants has not been described so far.

The 3-*C*-α-L-rhamnopyranosylphloroacetophenone derivative **3** and the 3-*C*-β-L-rhamnopyranosylphloroacetophenone derivative **4** were synthesized according to methods previously described.[4] The reaction of 2,4-dibenzylphloroacetophenone **1** with 2,3,4-tri-*O*-benzyl-α-L-rhamnopyranosyl fluoride (6-deoxy-2,3,4-tri-*O*-benzyl-α-L-mannopyranosyl fluoride) **2**[5] in the presence of boron trifluoride·diethyl etherate gave the 3-*C*-α-L-rhamnoside **3** and the 3-*C*-β-L-rhamnoside **4**. Thin-layer chromatography (TLC) of the reaction mixture indicated that the *C*-α-L-rhamnoside **3** was produced via an O→C glycosylic rearrangement at low temperature and that the resulting *C*-α-L-rhamnosyl compound **3** was subsequently anomerized to give the *C*-β-L-rhamnosyl compound **4** by boron trifluoride·diethyl etherate at temperatures greater than −20 °C. When the initial temperature of −78 °C was slowly elevated to 0 °C, the *C*-α-L-rhamnosyl derivative **3** was obtained in 41% yield, and the *C*-β-L-rhamnosyl derivative **4** in 25% yield. When the reaction mixture reached ambient temperature, the *C*-α-L-rhamnosyl compound **3** was obtained in 40% yield, and the *C*-β-L-rhamnosyl compound **4** in 27% yield. The yields were determined after purification using silica-gel column chromatography. The yield of the *C*-α-L-rhamnosyl derivative **3** was obtained after acetylation of compound **3**, as compound **8**, because purification of the *C*-α-L-rhamnosyl derivative **3** was difficult. TLC monitoring was carried out at reaction temperatures of −78, −42, −20, 0 °C and ambient temperature. The bright red–brown spots corresponding to the phenolic constituents of the reaction mixture were observed by treatment with a 5% ethanolic ferric chloride. Incidentally, the prior *O*-rhamnoside was not colored by the ethanolic ferric chloride. The colored spot corresponding to the *C*-β-L-rhamnosyl compound **4** on the TLC was initially observed at −20 °C, not at −42 °C. After structural analysis of compound **3** and **4** by NMR studies, TLC observation was carried out again, R_f values of the compounds **3** and **4** were verified by comparison between the preserved samples of the reaction mixture at each temperature and these known products. The ^{1}H NMR spectrum showed that the *C*-α-L-rhamnosyl compound **3** exists in a $^4C_1$ conformation, and the *C*-β-L-rhamnosyl compound **4** had a $^1C_4$ conformation. In previous studies, we reported on the preparation of some *C*-glycosylphloroacetophenone derivatives that contain β-D-glucosyl,[4] β-D-galactosyl,[4] β-D-xylosyl,[3] α-L-arabinosyl moieties,[3] respectively, as the glycosyl moiety. The ^{1}H NMR experiments were all conducted at elevated temperatures >100 °C because structural assignment by NMR spectroscopy at ambient temperature was hampered by the slow rotation of the C-1–aglycon bond. In spite of fact that the *C*-α-L-rhamnosyl compound **3** contains equatorial substitutions at 1′ and 2′ positions of the rhamnose moiety, the ^{1}H NMR experiment involving the *C*-α-L-rhamnosyl compound **3** could be conducted at ambient temperature.

The 3-*C*-α-D-mannopyranosylphloroacetophenone derivative **6** and the 3-*C*-β-D-mannopyranosylphloroacetophenone derivative **7**[4a] were synthesized according to methods previously described.[4] The reaction of 2,4-dibenzylphloroacetophenone **1** with 2,3,4,6-tetra-*O*-benzyl-α-D-mannopyranosyl fluoride **5**[5] in the presence of boron trifluoride·diethyl etherate gave the 3-*C*-α-D-mannosyl compound **6** and the 3-*C*-β-D-mannosyl compound **7**. TLC of the reaction mixture indicated that the *C*-α-D-mannosyl compound **6** was produced via an O→C glycoside rearrangement at low temperature

and that the resulting *C*-α-D-mannosyl compound **6** then underwent anomerization to give the *C*-β-D-mannosyl compound **7** by boron trifluoride·diethyl etherate at temperatures greater than −42 °C. When the initial temperature of −78 °C was slowly elevated to 0 °C, the *C*-α-D-mannosyl compound **6** was obtained in 13% yield, and the *C*-β-D-mannosyl compound **7** in 38% yield. When the final temperature was ambient temperature, the *C*-α-D-mannosyl compound **6** was obtained in 11% yield, and the *C*-β-D-mannosyl compound **7** in 28% yield. TLC indicated a slow-decomposition of the *C*-β-D-mannosyl compound **7** at ambient temperature. The red–brown colored spot corresponding to the *C*-β-D-mannosyl compound **7** on the TLC with ferric chloride was initially observed at −42 °C, not at −78 °C. After structural analysis of the compound **6** and **7** by NMR studies, TLC observation was carried out again, and R_f values of compounds **6** and **7** were verified by comparison between the preserved samples of the reaction mixture at each temperature and these known products, mentioned above. The ^{1}H NMR spectrum showed that the *C*-α-D-mannosyl compound **6** adopted the $^1C_4$ conformation, and that the *C*-β-D-mannosyl compound **7** was present in the $^4C_1$ conformation. As mentioned above, the ^{1}H NMR experiment of *C*-α-D-mannosyl compound **6** could be conducted at ambient temperature.

Such an anomerization process has been discussed by Suzuki et al.,[6] by Schmidt,[7] and by our group,[3] respectively. Lewis acid weakens the C-1–O bond by attack at the tetrahydropyran oxygen, which leads to an open-chain intermediate that could undergo isomerization and subsequent recyclization. Recently Yamada and co-workers reported on the axial-rich conformation derived form diaxial interactions in the L-rhamnopyranosyl ring and the D-mannopyranosyl ring,[8] and Suzuki and co-workers reported that aryl *C*-α-L-rhamnosyl compounds prefer the flipped $^4C_1$ conformation.[9]

In this study, after the cleavage of the *O*-glycoside, a sugar oxonium ion is attacked from the α-face, because the axial β-benzyloxy group at the C-2 position, together with the anomeric effect, blocks access to the β-face. The resulting *C*-α-glycosyl compounds adopted the conformation in which the aglycon is orientated equatorially in order to avoid unfavorable 1,3-diaxial interactions between the C-1 and C-3 positions at low temperatures. At elevated temperatures, the 1,3-diaxial interactions between the C-3 and C-5 positions of the *C*-α-L-rhamnosyl compounds **3** and *C*-α-D-mannosyl compounds **6** led to anomerization in each case by boron trifluoride·diethyl etherate. On comparing the yields of the *C*-L-rhamnosyl compounds with those of the *C*-D-mannosyl compounds at a final reaction temperature of 0 °C, the 1,3-diaxial interaction between the C-3 and C-5 positions of the *C*-α-L-rhamnosyl compound **3** is weaker than that of the *C*-α-D-mannosyl compound **6**. In fact, the temperature of the conversion from the *C*-α-L-rhamnosyl compound **3** to the *C*-β-L-rhamnosyl compound **4** is higher than that required for the conversion of the *C*-α-D-mannosyl compound **6** to the *C*-β-D-mannosyl compound **7**, and the yield of *C*-α-L-rhamnoside **3** is higher than that of the *C*-β-L-rhamonosyl compound **4**. On the contrary, the yield of the *C*-β-D-mannosyl compound **7** is higher than that of the *C*-α-D-mannosyl compound **6**. Compared with the syntheses of both *C*-L-rhamnosyl and *C*-D-mannosyl compounds, these facts provide experimental evidence for the magnitude of the 1,3-diaxial interaction between the C-3 and C-5 positions in the sugar moieties (Scheme 1).

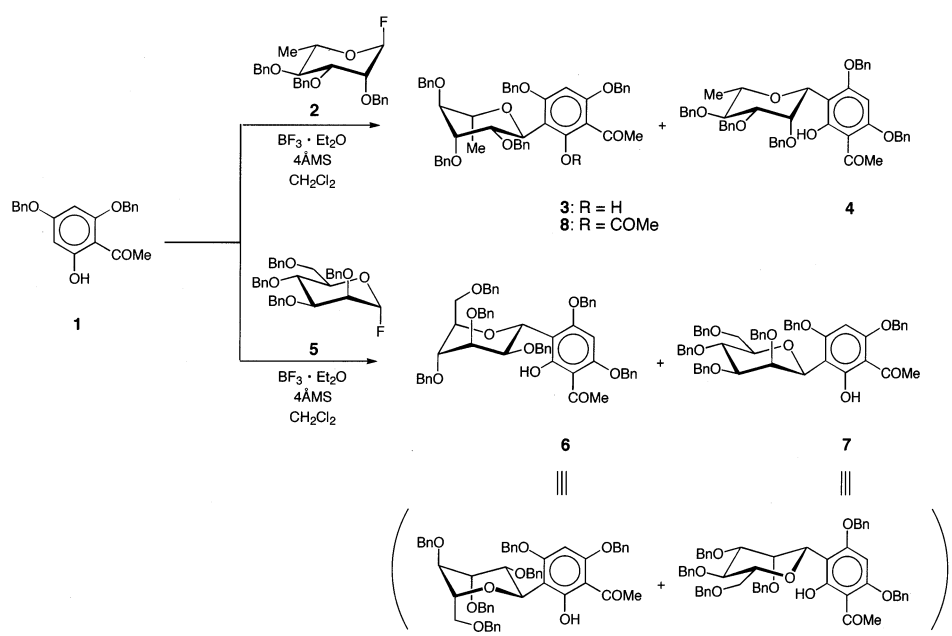
1. Experimental

General methods.—All nonaqueous reactions were carried out under an atmosphere of dry Ar using freshly distilled solvents, unless otherwise noted. All reactions were monitored by TLC, which was carried out on 0.25 mm Silica Gel 60 F_{254} plates (E. Merck) using either UV light, a 5% ethanolic solution of ferric chloride or a 5% ethanolic solution of phosphomolybdic acid with heat as developing agents. Wakogel C-300® (particle size 0.045–0.075 mm) was used for column chromatography. Optical rotations were recorded

using $CHCl_3$ as solvent on a JASCO DIP-370 digital polarimeter. IR spectra were recorded on a Horiba FT-200 IR spectrometer as films on NaCl plates. Mass spectra were recorded on a JEOL JMS-AX-505-HA mass spectrometer under conditions of fast-atom bombardment (FAB) using 3-nitrobenzyl alcohol as the matrix. ^{1}H NMR spectra were recorded on a Varian Inova 500 instrument using Me_4Si as the internal reference.

*4,6-Bis-benzyloxy-2-hydroxy-3-*C*-(2,3,4-tri-*O*-benzyl-α-*L*-rhamnopyranosyl)acetophenone* (**3**), *4,6-bis-benzyloxy-2-hydroxy-3-*C*-(2,3,4-tri-*O*-benzyl-β-*L*-rhamnopyranosyl)acetophenone* (**4**), *and 2-acetoxy-4,6-bis-benzyloxy-3-*C*-(2,3,4-tri-*O*-benzyl-α-*L*-rhamnopyranosyl)-acetophenone* (**8**).—To a stirred mixture of **1** (2.39 g, 6.87 mmol, 3 equiv), 2,3,4-tri-*O*-benzyl-α-L-rhamnopyranosyl fluoride (**2**, 1.00 g, 2.29 mmol) and powdered 4 Å molecular sieves (3 g) in CH_2Cl_2 (30 mL) at −78 °C, $BF_3{\cdot}Et_2O$ (592 μL, 4.81 mmol, 2.1 equiv) was added dropwise, and the mixture was stirred for 30 min. The temperature was then allowed to increase to −42 °C with continued stirring for 30 min, then to −20 °C with continued stirring for 30 min, and finally to 0 °C for 1 h. After adding ice-water, the resulting mixture was filtered through a Celite® pad. The filtrate was extracted with $CHCl_3$, and the organic layer was washed with water and brine and then dried over anhyd $MgSO_4$. The solvent was evaporated in vacuo. The residual syrup was column chromatographed on silica gel (5:1 hexane–EtOAc) to give **4** (443 mg, 25%) as a colorless, highly viscous oil, and pure **3** (12 mg, 0.7%) as a colorless, highly viscous oil, and a crude fraction of compound **3**. The fraction containing **3** was acetylated using Ac_2O, pyridine, and a catalytic amount of 4,4-dimethylaminopyridine to give the acetylated compound **8** (737 mg, 40%) as a colorless, highly viscous oil.

Physicochemical data for (**3**): $[\alpha]_D^{20}$ −32° (*c* 1.0, $CHCl_3$); R_f 0.44 (3:1 hexane–EtOAc); IR (NaCl): 3088, 3062, 3030, 3005, 2968, 2931, 2872, 1622, 1593, 1497, 1454, 1429, 1369, 1273, 1155, 1113, 1028, 912, 795, 737cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.39 (d, 3 H, *J* 6.9 Hz, H-6′), 2.57 (s, 3 H, ArAc), 3.50 (dd, 1 H, *J* 3.1, 4.3 Hz, H-4′), 3.97 (dd, 1 H, *J* 3.2, 4.3 Hz, H-3′), 4.16 (dq, 1 H, *J* 3.1, 6.9 Hz, H-5′), 4.36 (d, 1 H, *J* 12.3 Hz, benzylic CH_2), 4.42 (d, 1 H, *J* 12.3 Hz, benzylic CH_2), 4.50 (s, 2 H, benzylic CH_2), 4.53 (d, 1 H, *J* 12.4 Hz, benzylic CH_2), 4.69 (d, 1 H, *J* 12.4 Hz, benzylic CH_2), 4.73 (dd, 1 H, *J* 3.2, 9.0 Hz, H-2′), 4.98 (d, 1 H, *J* 12.1 Hz, benzylic CH_2), 5.06 (d, 1 H, *J* 12.1 Hz, benzylic CH_2), 5.07 (s, 2 H,



Scheme 1.

benzylic CH_2), 5.73 (d, 1 H, *J* 9.0 Hz, H-1′), 6.02 (s, 1 H, ArH), 7.05–7.42 (m, 25 H, ArH), 14.25 (s, 1 H, ArOH); FABMS (positive-ion): *m/z* 765 $[M+H]^+$; FABMS (negative-ion): *m/z* 763 $[M-H]^-$. Anal. Calcd for $C_{49}H_{48}O_8$: C, 76.94; H, 6.32. Found: C, 76.68; H, 6.11.

Physicochemical data for (**4**): $[\alpha]_D^{20}$ −39° (*c* 1.0, $CHCl_3$); R_f 0.53 (3:1 hexane–EtOAc); IR (NaCl): 3317, 3089, 3063, 3030, 3007, 2974, 2931, 2904, 2873, 1699, 1614, 1533, 1497, 1454, 1368, 1352, 1273, 1163, 1120, 1079, 1028, 912, 797, 750, 735 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.38 (d, 3 H, *J* 6.1 Hz, H-6′), 2.53 (s, 3 H, ArAc), 3.45 (dq, 1 H, *J* 6.1, 9.3 Hz, H-5′), 3.63 (dd, 1 H, *J* 2.9, 9.3 Hz, H-3′), 3.72 (t, 1 H, *J* 9.3 Hz, H-4′), 3.98 (dd, 1 H, *J* 1.1, 2.9 Hz, H-2′), 4.40 (d, 1 H, *J* 11.7 Hz, benzylic CH_2), 4.56 (d, 1 H, *J* 11.8 Hz, benzylic CH_2), 4.63 (d, 1 H, *J* 11.8 Hz, benzylic CH_2), 4.66 (d, 1 H, *J* 11.7 Hz, benzylic CH_2), 4.67 (d, 1 H, *J* 10.9 Hz, benzylic CH_2), 4.80 (d, 1 H, *J* 11.6 Hz, benzylic CH_2), 4.83 (d, 1 H, *J* 11.6 Hz, benzylic CH_2), 4.91 (d, 1 H, *J* 1.1 Hz, H-1′), 4.96 (d, 1 H, *J* 10.9 Hz, benzylic CH_2), 5.06 (d, 1 H, *J* 11.9 Hz, benzylic CH_2), 5.08 (d, 1 H, *J* 11.9 Hz, benzylic CH_2), 5.98 (s, 1 H, ArH), 7.03–7.41 (m, 25 H, ArH), 11.02 (br.,s, 1 H, ArOH); FABMS (positive-ion): *m/z* 765 $[M+H]^+$; FABMS (negative-ion): *m/z* 763 $[M-H]^-$. Anal. Calcd for $C_{49}H_{48}O_8$: C, 76.94; H, 6.32. Found: C, 76.68; H, 6.16.

Physicochemical data for (**8**): $[\alpha]_D^{20}$ +34° (*c* 1.0, $CHCl_3$); R_f 0.40 (3:1 hexane–EtOAc); IR (NaCl): 3088, 3062, 3030, 3007, 2968, 2931, 2873, 1770, 1693, 1605, 1585, 1497, 1454, 1369, 1350, 1319, 1250, 1203, 1155, 1092, 1028, 914, 885, 810, 739 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.40 (d, 3 H, *J* 7.1 Hz, H-6′), 2.03 (s, 3 H, ArOAc), 2.46 (s, 3 H, ArAc), 3.45 (dd, 1 H, *J* 1.3, 3.8 Hz, H-4′), 3.93 (dd, 1 H, *J* 2.9, 3.8 Hz, H-3′), 4.07 (dq, 1 H, *J* 1.3, 7.1 Hz, H-5′), 4.31 (d, 1 H, *J* 12.2 Hz, benzylic CH_2), 4.34 (d, 1 H, *J* 12.2 Hz, benzylic CH_2), 4.37 (d, 1 H, *J* 11.7 Hz, benzylic CH_2), 4.41 (d, 1 H, *J* 11.7 Hz, benzylic CH_2), 4.45 (dd, 1 H, *J* 2.9, 9.8 Hz, H-2′), 4.57 (d, 1 H, *J* 12.2 Hz, benzylic CH_2), 4.78 (d, 1 H, *J* 12.2 Hz, benzylic CH_2), 4.96 (d, 1 H, *J* 12.0 Hz, benzylic CH_2), 5.02 (d, 1 H, *J* 12.0 Hz, benzylic CH_2), 5.05 (d, 1 H, *J* 12.1 Hz, benzylic CH_2), 5.07 (d, 1 H, *J* 12.1 Hz, benzylic CH_2), 5.70 (d, 1 H, *J* 9.8 Hz, H-1′), 6.41 (s, 1 H, ArH), 7.14–7.40 (m, 25 H, ArH); FABMS (positive-ion): *m/z* 807 $[M+H]^+$; FABMS (negative-ion): *m/z* 805 $[M-H]^-$. Anal. Calcd for $C_{51}H_{50}O_9$: C, 75.91; H, 6.25. Found: C, 75.69; H, 5.98.

*4,6-Bis-benzyloxy-2-hydroxy-3-*C*-(2,3,4,6-tetra-*O*-benzyl-α-*D*-mannopyranosyl)acetophenone* (**6**) *and 4,6-bis-benzyloxy-2-hydroxy-3-*C*-(2,3,4,6-tetra-*O*-benzyl-β-*D*-mannopyranosyl)acetophenone* (**7**).—The reaction conditions, post-treatment and isolation were carried out in the same manner as described above. An analytically pure sample of compound **6** was obtained by HPLC.

Physicochemical data for (**6**): $[\alpha]_D^{20}$ +20° (*c* 1.0, $CHCl_3$); R_f 0.46 (3:1 hexane–EtOAc); IR (NaCl): 3088, 3063, 3030, 3007, 2929, 2864, 1621, 1593, 1497, 1454, 1429, 1367, 1271, 1169, 1113, 1097, 1028, 1003, 910, 797, 737 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.57 (s, 3 H, ArAc), 3.73 (dd, 1 H, *J* 2.4, 4.3 Hz, H-4′), 3.78 (dd, 1 H, *J* 6.2, 10.2 Hz, H-6′a), 3.88 (dd, 1 H, *J* 6.9, 10.2 Hz, H-6′b), 3.93 (dd, 1 H, *J* 3.1, 4.3 Hz, H-3′), 4.23 (ddd, 1 H, *J* 2.4, 6.2, 6.9 Hz, H-5′), 4.34 (d, 1 H, *J* 12.2 Hz, benzylic CH_2), 4.36 (d, 1 H, *J* 12.3 Hz, benzylic CH_2), 4.39 (d, 1 H, *J* 12.2 Hz, benzylic CH_2), 4.46 (d, 1 H, *J* 12.4 Hz, benzylic CH_2), 4.47 (d, 2 H, *J* 12.3 Hz, benzylic CH_2), 4.51 (d, 1 H, *J* 12.4 Hz, benzylic CH_2), 4.62 (d, 1 H, *J* 12.3 Hz, benzylic CH_2), 4.76 (dd, 1 H, *J* 3.1, 9.3 Hz, H-2′), 4.94 (d, 1 H, *J* 12.0 Hz, benzylic CH_2), 5.05 (d, 1 H, *J* 12.0 Hz, benzylic CH_2), 5.07 (d, 1 H, *J* 12.4 Hz, benzylic CH_2), 5.09 (d, 1 H, *J* 12.4 Hz, benzylic CH_2), 5.68 (d, 1 H, *J* 9.3 Hz, H-1′), 6.02 (s, 1 H, ArH), ~7.06–7.43 (m, 30 H, ArH), 14.28 (s, 1 H, ArOH); FABMS (positive-ion): *m/z* 871 $[M+H]^+$; FABMS (negative-ion): *m/z* 869 $[M-H]^-$. Anal. Calcd for $C_{56}H_{54}O_9$: C, 77.22; H, 6.25. Found: C, 77.25; H, 6.24.

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