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Synthesis of *C*-glycopyranosylphloroacetophenone derivatives and their anomerization facilitated by 1,3-diaxial interactions

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Abstract

The reaction of 2,3,4-tri-*O*-benzyl-6-deoxy-α-D-glucopyranosyl fluoride, 2,3,4,6-tetra-*O*-benzyl-α-D-allopyranosyl fluoride, and 2,3,4-tri-*O*-benzyl-α-L-fucopyranosyl fluoride with 2,4-di-*O*-benzylphloroacetophenone, in the presence of boron trifluoride diethyl etherate, afforded, respectively, the corresponding 3-*C*-β-D-glycopyranosylphloroacetophenone derivatives exclusively in anomerically pure form. Alternatively, the reaction of 2,3,4,6-tetra-*O*-benzyl-α-D-gulopyranosyl fluoride with 2,4-di-*O*-benzylphloroacetophenone afforded both the 3-*C*-β-D-gulopyranosylphloroacetophenone derivative ($^4C_1$ conformation) as the major product and the 3-*C*-α-D-gulopyranosylphloroacetophenone derivative ($^1C_4$ conformation) as the minor product under identical conditions. Including the previously prepared *C*-glycosylphloroacetophenone derivatives that contain 3-*C*-β-D-glucosyl, 3-*C*-β-D-xylosyl, 3-*C*-β-2-deoxy-D-*arabino*-hexosyl, 3-*C*-β-D-galactosyl, 3-*C*-β-L-arabinosyl, and 3-*C*-α-L-arabinosyl moieties, the conformation is dictated primarily by the preference of the bulky aromatic aglycon to orient equatorially, due to the strong repulsion of the aglycon. The anomerization is directed secondarily by the presence of 1,3-diaxial interactions in the sugar moiety.

Keywords: *C*-Glycosylic compound; Aryl *C*-glycoside; *C*-Glycosylflavonoid; 1,3-Diaxial interaction; Conformation

1. Introduction

A number of flavonoids contain aryl *C*-glycosyl moieties as part of their structures and include the naturally occurring *C*-glycosylflavonoids.[1] In this laboratory, our interests are in the synthesis of the glycosylic portion of *C*-glycosyl flavonoids. During the course of our synthetic study on *C*-glycosyl flavonoids, we prepared some *C*-glycosylphloroacetophenone derivatives that contain D-glucopyranosyl,[2] D-xylopyranosyl,[3] 2-deoxy-D-*arabino*-hexopyranosyl (2-deoxy-D-glucopyranosyl),[4] D-galactopyranosyl,[5] L-arabinopyranosyl,[3] D-mannopyranosyl,[4,6] or L-rhamnopyranosyl[6] moieties, respectively, as the *C*-glycosyl moiety. We previously reported that the *C*-glycosylation step in these syntheses was accompanied by an O→C glycosyl rearrangement in the presence of boron trifluoride diethyl etherate as the Lewis acid.[4] During this reaction, the glycosyl moiety is transferred from a hydroxyl group to an ortho position in the aglycon. However, the reaction of 2,3,4-tri-*O*-benzyl-β-L-arabinopyranosyl fluoride with 2,4-di-*O*-benzylphloroacetophenone in the presence of boron trifluoride diethyl etherate afforded both the 3-*C*-α-L-arabinopyranosylphloroacetophenone derivative **15** as the major initial reaction product, which adopted a $^4C_1$ conformation, and the 3-*C*-β-L-arabinopyranosyl derivative **16** as a minor product that was produced via the anomerization of compound **15**, which adopted a $^1C_4$ conformation.[3]

We describe herein the syntheses of *C*-glycosylphloroacetophenone derivatives, which contain 6-deoxy-β-D-glucopyranosyl (**7**), β-D-allopyranosyl (**9**), β-D-gulopyranosyl (**10**), α-D-gulopyranosyl (**11**), and β-L-fucopyranosyl (**14**) moieties, as the glycosyl moiety,

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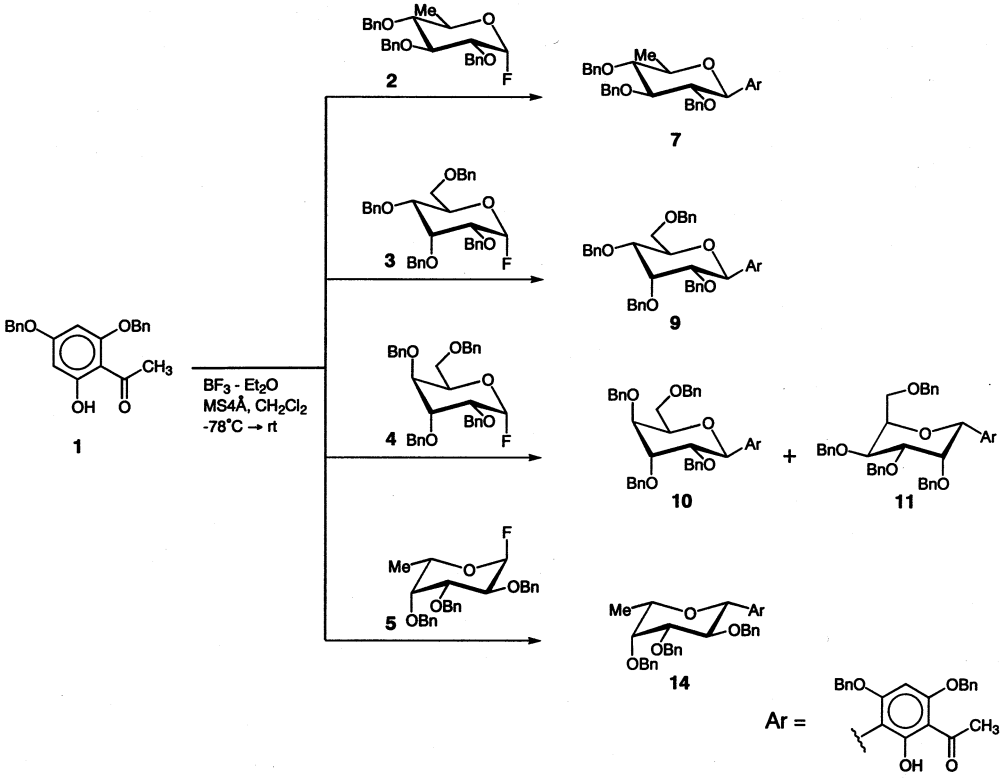
respectively. Including the previously prepared *C*-glycosyl derivatives, the magnitude of 1,3-diaxial interactions in the sugar moiety, which affect the conformation of the *C*-glycosyl derivative produced initially and its anomerization, is discussed.

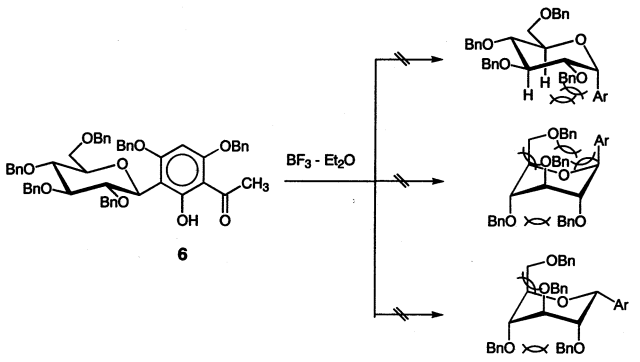
2. Results and discussion

The 3-*C*-6-deoxy-β-D-glucopyranosylphloroacetophenone derivative **7**, the 3-*C*-β-D-allopyranosyl derivative **9**, and the 3-*C*-β-L-fucopyranosyl derivative **14** were synthesized according to methods previously described.[2] In summary, the reaction of 2,4-di-*O*-benzylphloroacetophenone (**1**) with the benzyl-protected glycopyranosyl fluorides **2**, **3**, and **5** in the presence of boron trifluoride diethyl etherate gave the corresponding the *C*-β-glycopyranosylphloroacetophenone derivatives, namely, the *C*-6-deoxy-β-D-glucopyranosyl derivative **7** in 88% yield, the *C*-β-D-allopyranosyl derivative **9** in 87% yield, and the *C*-β-L-fucopyranosyl derivative **14** in 68% yield, respectively (Scheme 1). In the course of these reactions, the initial reaction temperature of −78 °C was slowly elevated to ambient temperature. Thin-layer chromatography (TLC) of these reaction mixtures indicated that the *C*-glycosyl compounds were produced via an O→C glycosyl rearrangement. Bright red–brown spots corresponding to the *C*-glycosy derivatives and the phenolic glycosyl acceptor **1** were observed on the TLC plates after treatment with 5% ethanolic ferric chloride, whereas the *O*-glycosyl derivatives were not colored by the ethanolic ferric chloride. In these reactions, compounds **7**, **9**, and **14** were obtained exclusively in the anomerically pure β-form and were not anomerized to the α isomers by the boron trifluoride diethyl etherate.

^{1}H NMR and COSY experiments of compounds **7**, **9**, and **14** were all conducted at elevated temperatures, 130 °C for compound **7** in Me_2SO-d_6, 140 °C for compound **9** in Me_2SO-d_6, and 120 °C for compound **14** in Me_2SO-d_6, respectively. The reason for this is that the structural assignment by NMR spectroscopy at ambient temperature was hampered by the slow rotation of the C-1–aglycon bond, due to the interaction between the benzyl group at the C-2′ position in the glycosyl moiety and both substituted groups in the aglycon around the glycosyl moiety. The ^{1}H NMR spectra and the COSY spectra indicated coupling constants of $J_{1',2'}$ 9.8 Hz for the 6-deoxy-β-D-glucopyranosyl derivative **7**, $J_{1',2'}$ 9.9 Hz for the β-D-allopyranosyl derivative **9**, and $J_{1',2'}$ 9.6 Hz for the β-L-fucopyranosyl derivative **14**, respectively. In addition, NMR spectra showed that the 6-deoxy-β-D-glucopyranosyl derivative **7** and the β-D-allopyranosyl derivative **9** exist in a $^4C_1$ conformation, while the β-L-fucopyranosyl derivative **14** exists in a $^1C_4$ conformation.



Scheme 1.



Scheme 2.

On the other hand, the reaction of 2,4-di-*O*-benzylphloroacetophenone (**1**) with 2,3,4,6-tetra-*O*-benzyl-α-D-gulopyranosyl fluoride (**4**) afforded the 3-*C*-β-D-gulopyranosylphloroacetophenone derivative **10** in 43% yield and the 3-*C*-α-D-gulopyranosylphloro-acetophenone derivative **11** in 22% yield under reaction conditions identical to those mentioned above (Scheme 1). The yields of the *C*-β-D-gulopyranosyl derivative **10** and the *C*-α-D-gulopyranosyl derivative **11** were determined after acetylation of both compounds, as the acetylated compounds **17** and **18**, respectively. Although compounds **10** and **11** could not be resolved by silica gel chromatography, the acetylated compounds **17** and **18**, which showed different TLC R_f values, were separated.

^{1}H NMR and COSY experiments of the compound **10** were conducted at an elevated temperature of 100 °C in Me_2SO-d_6. The reason for this is as mentioned above. The NMR spectra of the β-D-gulopyranosyl derivative **10** were found to have $J_{1',2'}$10.1 Hz, which indicated a $^4C_1$ conformation. Alternatively, an ^{1}H NMR and the COSY experiment of compound **11** could be conducted in $CDCl_3$ at ambient temperature, due to the absence of severe interactions between the benzyl group at the C-2′ position in the glycosyl moiety and the aglycon. The NMR spectra of the α-D-gulopyranosyl derivative **11** showed $J_{1',2'}$ 1.8 Hz and that it adopted the $^1C_4$ conformation.

Such an anomerization process has been reported by Suzuki and co-workers,[7] Schmidt,[8] Mulzer and co-workers,[9] and our group,[3,6] respectively. The Lewis acid weakens the C-1–O bond by attack at the tetrahydropyran oxygen in the glycosyl moiety, which leads to an open-chain intermediate via a qinone methide intermediate that can then undergo isomerization and subsequent recyclization.

We previously reported on the syntheses of 3-*C*-β-D-glucopyranosyl (**6**), 3-*C*-β-D-xylopyranosyl (**8**), 3-*C*-β-2-deoxy-D-*arabino*-hexopyranosyl (**12**), 3-*C*-β-D-galactopyranosyl (**13**), 3-*C*-α-L-arabinopyranosyl (**15**), and 3-*C*-β-L-arabinopyranosylphloroacetophenone derivative **16** under identical conditions,[3] which are important synthetic intermediates in *C*-glycosyl flavonoid syntheses. Including the synthesis of these new *C*-glycosylphloroacetophenone derivatives in this report, the aglycons of all the *C*-glycosyl compounds are oriented toward the equatorial position. Because of severe unfavorable 1,3-diaxial interactions between the bulky aglycon at C-1 and the substituent group at C-3, as well as C-5, including hydrogen, the *C*-glycosyl derivatives, in which the aglycon oriented toward the axial position, could not be produced initially using boron trifluoride diethyl etherate as the Lewis acid (Scheme 2). Thus, in these reactions, the conformation is dictated primarily by the preference of the bulky aromatic aglycon to orient equatorially, due to the strong repulsion of the aglycon.

Even if the compounds **6**–**9** could be induced to anomerize to the presupported flipped *C*-glycosylic conformers, in which the aromatic aglycons are oriented toward an equatorial position, the unfavorable 1,3-diaxial interactions between the C-2 and C-4 positions would be a problem. In addition, the presupported *C*-glucopyranosyl conformer and the *C*-6-deoxy-glucopyranosyl conformer have unfavorable 1,3-diaxial interactions between the C-3 and the C-5 positions (Scheme 3). However, these effects are absent in the *C*-β-D-gulopyranosyl derivative **10** and the *C*-α-D-gulopyranosyl derivative **11**. Therefore, the *C*-β-D-gulopyranosyl derivative **10** with a $^4C_1$ conformation can be anomerized to give the *C*-α-D-gulopyranosyl derivative **11** with the $^1C_4$ conformation via Lewis acid. In the same manner, even without the 1,3-diaxial interactions between the C-2 and the C-4 positions in the presupported conformers, taking the 1,3-diaxial interactions between the C-3 and C-5 positions into consideration, the anomerization of compounds **12**, **13**, and **14** would not be expected (Scheme 3). Alternatively, these steric effects are not present in the *C*-α-L-arabinosyl derivative **15** and the *C*-β-L-arabinosyl derivative **16**. Therefore, the *C*-α-L-arabinosyl derivative **15**, in a $^4C_1$ conformation, can be anomerized to give the *C*-β-L-arabinosyl derivative **16**, in a $^1C_4$ conformation, via Lewis acid.

These facts provide experimental evidence for the severe repulsion of the aglycon against the C-3 and C-5 positions, for the magnitude of the 1,3-diaxial interactions between the C-2 and the C-4 positions, as well as for the interaction between the C-3 and the C-5 positions, in the sugar moieties.

3. Experimental

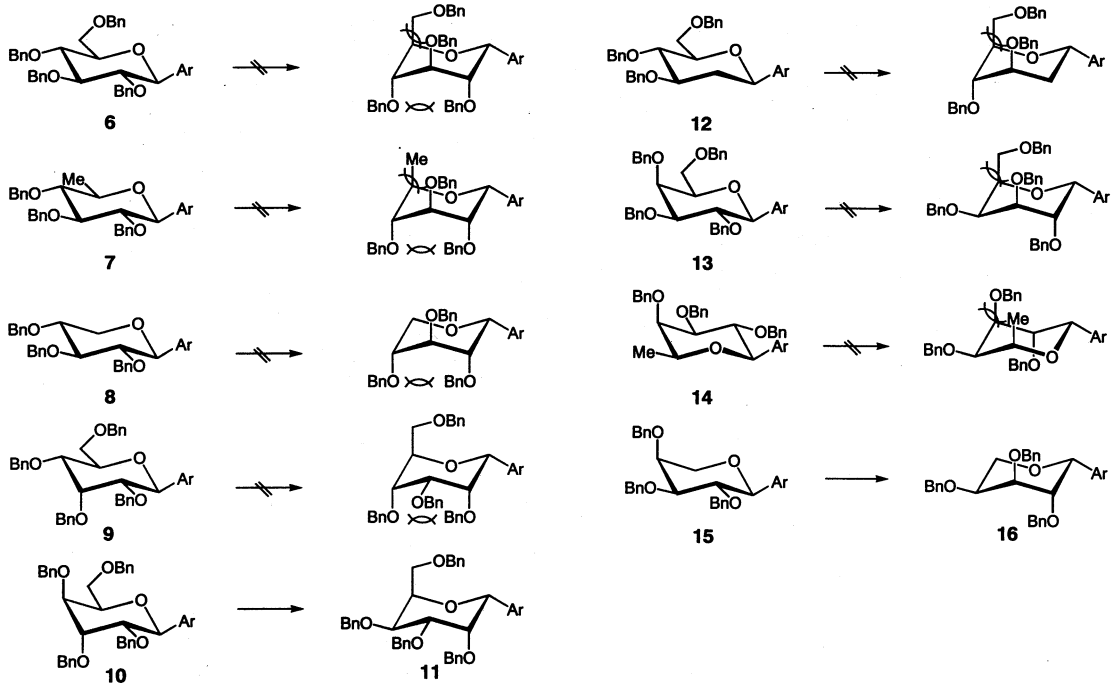
General methods.—All nonaqueous reactions were carried out under an atmosphere of dry Ar using freshly distilled solvents, unless otherwise noted. Reactions were monitored by TLC, which was carried out

on 0.25-mm Silica Gel 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. Fuji Silysia BW-300 was used for silica gel column chromatography. Optical rotations were recorded using $CHCl_3$ as the solvent on a JASCO DIP-370 digital polarimeter. IR spectra were recorded on a Horiba FT-720 IR spectrometer in the form of KBr pellets or as films on an NaCl plate. Mass spectra were recorded on a JEOL JMS-AX-505-HA mass spectrometer under electron-ionization (EI) conditions or under fast-atom bombardment (FAB) conditions using 3-nitrobenzyl alcohol (NBA) as the matrix. ^{1}H NMR spectra were recorded on a Varian Inova 500 instrument using Me_4Si as an internal reference.

2,3,4-Tri-O-*benzyl-6-deoxy-α*-D-*glucopyranosyl fluoride* (**2**), *2,3,4,6-tetra*-O-*benzyl-α*-D-*allopyranosyl fluoride* (**3**), *2,3,4,6-tetra*-O-*benzyl-α*-D-*gulopyranosyl fluoride* (**4**), *2,3,4-tri*-O-*benzyl-α-L-fucopyranosyl fluoride* (**5**).—Compounds **2**–**5** were synthesized according to Noyori's method[10] using 70% HF·pyridine.

Physicochemical data for **2**: yield, 67% as colorless crystals; mp 62 °C; $[\alpha]_D^{22}$ −3.4° (*c* 1.0, $CHCl_3$); R_f 0.55 (5:1 hexane–EtOAc); IR (KBr): *v* 3089, 3064, 3030, 2989, 2979, 2974, 2918, 2873, 1496, 1454, 1400, 1358, 1215, 1159, 1124, 1082, 1030, 1003, 904, 889, 741, 694 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.27 (d, 3 H, $J_{5,6}$ 6.3 Hz, H-6), 3.18 (t, 1 H, $J_{3,4} = J_{4,5}$ 9.5 Hz, H-4), 3.53 (ddd, 1 H, $J_{1,2}$ 2.7, $J_{2,3}$ 9.8, $J_{2,F}$ 25.6 Hz, H-2), 3.941 (dq, 1 H, $J_{5,6}$ 6.3, $J_{4,5}$ 9.5 Hz, H-5), 3.947 (dd, 1 H, $J_{3,4}$ 9.5, $J_{2,3}$ 9.8 Hz, H-3), 4.64 (d, 1 H, J_{gem} 11.0 Hz, benzylic CH_2), 4.71 (d, 1 H, J_{gem} 11.7 Hz, benzylic CH_2), 4.80 (d, 1 H, J_{gem} 11.7 Hz, benzylic CH_2), 4.85 (d, 1 H, J_{gem} 10.7 Hz, benzylic CH_2), 4.90 (d, 1 H, J_{gem} 11.0 Hz, benzylic CH_2), 4.95 (d, 1 H, J_{gem} 10.7 Hz, benzylic CH_2), 5.46 (dd, 1 H, $J_{1,2}$ 2.7, $J_{1,F}$ 53.2 Hz, H-1), 7.28–7.37 (m, 15 H, ArH); EIMS: *m*/*z* 436 [M$^+$]. Anal. Calcd for $C_{27}H_{29}FO_4$: C, 74.29; H, 6.70. Found: C, 74.03; H, 6.70.

Physicochemical data for **3**: yield, 64% as colorless crystals; mp 60–61 °C; $[\alpha]_D^{22}$ +37° (*c* 1.0, $CHCl_3$); R_f 0.32 (5:1 hexane–EtOAc); IR (KBr): *v* 3087, 3064, 3026, 3006, 2966, 2935, 2927, 2914, 2889, 2864, 2854, 1496, 1452, 1365, 1328, 1207, 1180, 1161, 1144, 1105, 1066, 1053, 1026, 1009, 957, 904, 864, 845, 777, 739, 696 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 3.38 (dt, 1 H, $J_{1,2} = J_{2,3}$ 2.9, $J_{2,F}$ 26.9 Hz, H-2), 3.61 (dd, 1 H, $J_{3,4}$ 2.4, $J_{4,5}$ 10.0 Hz, H-4), 3.72 (dd, 1 H, $J_{5,6a}$ 2.0, J_{gem} 10.7 Hz, H-6a), 3.81 (dd, 1 H, $J_{5,6b}$ 3.0, J_{gem} 10.7 Hz, H-6b), 4.19 (dd, 1 H, $J_{3,4}$ 2.4, $J_{2,3}$ 2.9 Hz, H-3), 4.42 (d, 1 H, J_{gem} 11.6 Hz, benzylic CH_2, and ddd, 1 H, $J_{5,6a}$ 2.0, $J_{5,6b}$ 3.0, $J_{4,5}$ 10.0 Hz, H-5), 4.50 (d, 1 H, J_{gem} 12.2 Hz, benzylic CH_2), 4.51 (d, 1 H, J_{gem} 11.6 Hz, benzylic CH_2), 4.55 (d, 1 H, J_{gem} 12.2 Hz, benzylic CH_2), 4.60 (d, 2 H, J_{gem} 12.2 Hz, benzylic CH_2), 4.85 (d, 1 H, J_{gem} 12.5 Hz, benzylic CH_2), 4.91 (d, 1 H, J_{gem} 12.5 Hz, benzylic CH_2), 5.62 (dd, 1 H, $J_{1,2}$ 2.9, $J_{1,F}$ 54.0 Hz, H-1), 7.20–7.41 (m, 20 H, ArH); EIMS: *m*/*z* 542 [M$^+$]. Anal. Calcd for $C_{34}H_{35}FO_5$: C, 75.26; H, 6.50. Found: C, 75.11; H, 6.58.



Scheme 3.

Physicochemical data for **4**: yield, 57% as a colorless oil; $[\alpha]_D^{22}$ +4.8° (*c* 1.0, $CHCl_3$); R_f 0.38 (5:1 hexane–EtOAc); IR (NaCl): *v* 3087, 3062, 3030, 3008, 2929, 2902, 2870, 1496, 1454, 1358, 1340, 1306, 1250, 1207, 1165, 1117, 1072, 1049, 1028, 1003, 941, 908, 748, 739, 698 cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.52 (dd, 1 H, $J_{5,6a}$ 7.1, J_{gem} 9.5 Hz, H-6a), 3.59 (dd, 1 H, $J_{5,6b}$ 6.3, J_{gem} 9.5 Hz, H-6b), 3.61 (dd, 1 H, $J_{4,5}$ 1.5, $J_{3,4}$ 3.7 Hz, H-4), 3.74 (ddd, 1 H, $J_{1,2}$ 2.7, $J_{2,3}$ 3.2, $J_{2,F}$ 28.2 Hz, H-2), 3.79 (dd, 1 H, $J_{2,3}$ 3.2, $J_{3,4}$ 3.7 Hz, H-3), 4.33 (d, 1 H, J_{gem} 12.0 Hz, benzylic CH_2), 4.36 (d, 1 H, J_{gem} 12.0 Hz, benzylic CH_2), 4.45 (d, 1 H, J_{gem} 12.0 Hz, benzylic CH_2), 4.51 (ddd, 1 H, $J_{4,5}$ 1.5, $J_{5,6b}$ 6.3, $J_{5,6a}$ 7.1 Hz, H-5), 4.536 (s, 2 H, benzylic CH_2), 4.539 (d, 2 H, J_{gem} 12.0 Hz, benzylic CH_2), 4.55 (d, 1 H, J_{gem} 12.5 Hz, benzylic CH_2), 4.74 (d, 1 H, J_{gem} 12.5 Hz, benzylic CH_2), 5.62 (dd, 1 H, $J_{1,2}$ 2.7, $J_{1,F}$ 54.3 Hz, H-1), 7.09–7.36 (m, 20 H, ArH); EIMS: *m*/*z* 542 $[M^+]$. Anal. Calcd for $C_{34}H_{35}FO_5$: C, 75.26; H, 6.50. Found: C, 75.11; H, 6.33.

Physicochemical data for **5**: yield, 88% as a colorless oil; $[\alpha]_D^{22}$ −16° (*c* 1.0, $CHCl_3$); R_f 0.49 (5:1 hexane–EtOAc); IR (NaCl): *v* 3087, 3064, 3029, 2974, 2937, 2906, 2875, 1496, 1454, 1365, 1380, 1340, 1209, 1174, 1153, 1134, 1119, 1105, 1057, 1028, 1011, 947, 916, 829, 802, 769, 739, 698 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.16 (d, 3 H, $J_{5,6}$ 6.6 Hz, H-6), 3.70 (dd, 1 H, $J_{4,5}$ 1.1, $J_{3,4}$ 2.7 Hz, H-4), 3.94 (dd, 1 H, $J_{3,4}$ 2.7, $J_{2,3}$ 10.1 Hz, H-3), 4.04 (dd, 1 H, $J_{1,2}$ 2.8, $J_{2,3}$ 10.1, $J_{2,F}$ 25.1 Hz, H-2), 4.05 (dq, 1 H, $J_{4,5}$ 1.1, $J_{5,6}$ 6.6 Hz, H-5), 4.66 (d, 1 H, J_{gem} 11.5 Hz, benzylic CH_2), 4.73 (d, 1 H, J_{gem} 11.7 Hz, benzylic CH_2), 4.76 (d, 1 H, J_{gem} 11.7 Hz, benzylic CH_2), 4.85 (d, 1 H, J_{gem} 11.7 Hz, benzylic CH_2), 4.86 (d, 1 H, J_{gem} 11.7 Hz, benzylic CH_2), 4.99 (d, 1 H, J_{gem} 11.5 Hz, benzylic CH_2), 5.57 (dd, 1 H, $J_{1,2}$ 2.8, $J_{1,F}$ 54.0 Hz, H-1), 7.27–7.41 (m, 15 H, ArH); EIMS: *m*/*z* 436 $[M^+]$. Anal. Calcd for $C_{27}H_{29}FO_4$: C, 74.29; H, 6.70. Found: C, 74.47; H, 7.01.

*4,6-Bis-benzyloxy-3-*C*-(6-deoxy-2,3,4-tri-*O*-benzyl-β-*D*-glucopyranosyl)-2-hydroxyacetophenone* (**7**), *4,6-bis-benzyloxy-3-*C*-(2,3,4,6-tetra-*O*-benzyl-β-*D*-allopyranosyl)-2-hydroxyacetophenone* (**9**), *4,6-bis-benzyloxy-3-*C*-(2,3,4-tri-*O*-benzyl-β-*L*-fucopyranosyl)-2-hydroxyacetophenone* (**14**).—To a stirred mixture of glycosyl acceptor **1** (3 equiv), the glycosyl donor (1 equiv), and powdered 4 Å molecular sieves in CH_2Cl_2 at −78 °C, $BF_3{\cdot}Et_2O$ (2.0 equiv) was added dropwise, and the mixture stirred for 30 min. The temperature was then allowed to increase to −42 °C, and the stirring was continued for 30 min, then for 30 min at −20 °C, for 30 min at 0 °C, and finally for 1 h at rt. After adding water, the resulting mixture was filtered through a Celite® pad. The filtrate was extracted with $CHCl_3$, and the organic layer was dried over anhyd $MgSO_4$. The solvent was evaporated under reduced pressure, and the resulting syrup was chromatographed on a silica gel column (hexane–EtOAc) to give the *C*-glycosyl compound.

Physicochemical data for **7**: yield, 88% as a pale, yellowish–green, highly viscous oil; $[\alpha]_D^{22}$ −22° (*c* 1.0, $CHCl_3$); R_f 0.26 (5:1 hexane–EtOAc); IR (NaCl): *v* 3087, 3064, 3030, 3006, 2972, 2931, 2875, 1620, 1597, 1496, 1454, 1431, 1385, 1367, 1352, 1273, 1167, 1147, 1101, 1068, 1029, 1003, 908, 901, 750, 737, 696 cm^{-1}; ^1H NMR (Me_2SO-d_6 at 130 °C): δ 1.18 (d, 3 H, $J_{5',6'}$ 6.1 Hz, H-6′), 2.52 (s, 3 H, ArAc), 3.12 (br. t, 1 H, *J* 9.3 Hz, H-4′), 3.38 (dq, 1 H, $J_{5',6'}$ 6.1, $J_{4',5'}$ 9.3 Hz, H-5′), 3.60 (t, 1 H, $J_{2',3'} = J_{3',4'}$ 9.0 Hz, H-3′), 4.16 (d, 1 H, J_{gem} 11.4 Hz, benzylic CH_2), 4.31 (br. t, 1 H, *J* 9.3 Hz, H-2′), 4.43 (d, 1 H, J_{gem} 11.4 Hz, benzylic CH_2), 4.62 (d, 1 H, J_{gem} 11.4 Hz, benzylic CH_2), 4.75 (d, 1 H, J_{gem} 11.6 Hz, benzylic CH_2), 4.76 (d, 1 H, J_{gem} 11.4 Hz, benzylic CH_2), 4.79 (d, 1 H, J_{gem} 11.6 Hz, benzylic CH_2), 4.83 (d, 1 H, $J_{1',2'}$ 9.8 Hz, H-1′), 5.15 (d, 1 H, J_{gem} 11.9 Hz, benzylic CH_2), 5.18 (d, 1 H, J_{gem} 11.9 Hz, benzylic CH_2), 5.24 (d, 1 H, J_{gem} 12.7 Hz, benzylic CH_2), 5.26 (d, 1 H, J_{gem} 12.7 Hz, benzylic CH_2), 6.40 (s, 1 H, ArH), 6.88–7.47 (m, 25 H, ArH), 13.74 (br. s, 1 H, ArOH); FABMS (positive-ion mode): *m*/*z* 765 $[M+H]^+$; FABMS (negative-ion mode); *m*/*z* 763 $[M-H]^-$. Anal. Calcd for $C_{49}H_{48}O_8$: C, 76.94; H, 6.32. Found: C, 76.81; H, 6.44.

Physicochemical data for **9**: yield, 87% as a pale, yellowish–green, highly viscous oil; $[\alpha]_D^{22}$ −17° (*c* 1.0, $CHCl_3$); R_f 0.22 (5:1 hexane–EtOAc); IR (NaCl): *v* 3087, 3062, 3030, 3006, 2927, 2868, 1622, 1593, 1496, 1454, 1431, 1394, 1367, 1358, 1273, 1238, 1207, 1169, 1119, 1095, 1074, 1055, 1028, 1005, 908, 889, 804, 737, 696 cm^{-1}; ^1H NMR (Me_2SO-d_6 at 140 °C): δ 2.52 (s, 3 H, ArAc), 3.45 (br. d, 1 H, *J* 8.9 Hz, H-4′), 3.58 (dd, 1 H, $J_{5',6'a}$ 5.0, J_{gem} 11.1 Hz, H-6′a), 3.67 (dd, 1 H, $J_{5',6'b}$ 1.7, J_{gem} 11.1 Hz, H-6′b), 3.93 (ddd, 1 H, $J_{5',6'b}$ 1.7, $J_{5',6'a}$ 5.0, $J_{4',5'}$ 9.8 Hz, H-5′), 4.23 (d, 1 H, J_{gem} 12.2 Hz, benzylic CH_2), 4.27 (d, 1 H, $J_{1',2'}$ 9.9 Hz, H-2′), 4.35 (br. s, 1 H, H-3′), 4.41 (d, 1 H, J_{gem} 12.2 Hz, benzylic CH_2), 4.43 (d, 1 H, J_{gem} 12.2 Hz, benzylic CH_2), 4.46 (d, 1 H, J_{gem} 11.9 Hz, benzylic CH_2), 4.49 (d, 1 H, J_{gem} 12.2 Hz, benzylic CH_2), 4.60 (d, 1 H, J_{gem} 11.9 Hz, benzylic CH_2), 4.73 (d, 1 H, J_{gem} 12.0 Hz, benzylic CH_2), 4.81 (d, 1 H, J_{gem} 12.0 Hz, benzylic CH_2), 5.06 (d, 1 H, J_{gem} 12.2 Hz, benzylic CH_2), 5.12 (d, 1 H, J_{gem} 12.2 Hz, benzylic CH_2), 5.23 (d, 1 H, J_{gem} 12.0 Hz, benzylic CH_2), 5.25 (d, 1 H, J_{gem} 12.0 Hz, benzylic CH_2), 5.42 (d, 1 H, $J_{1',2'}$ 9.9 Hz, H-1′), 6.39 (s, 1 H, ArH), 6.97–7.47 (m, 30 H, ArH), 13.43 (br. s, 1 H, ArOH); FABMS (positive-ion mode): *m*/*z* 871 $[M+H]^+$; FABMS (negative-ion mode); *m*/*z* 869 $[M-H]^-$. Anal. Calcd for $C_{56}H_{54}O_9$: C, 77.22; H, 6.25. Found: C, 77.51; H, 6.36.

Physicochemical data for **14**: yield, 68% as a colorless powder; mp 62–63 °C; $[\alpha]_D^{22}$ +17° (*c* 1.0, $CHCl_3$); R_f 0.20 (5:1 hexane–EtOAc); IR (KBr): *v* 3087, 3062,

3030, 3003, 2978, 2931, 2906, 2879, 2870, 1620, 1597, 1585, 1496, 1462, 1454, 1433, 1406, 1389, 1369, 1385, 1275, 1245, 1225, 1178, 1153, 1132, 1117, 1095, 1076, 1041, 1028, 908, 895, 794, 742, 696 cm^{-1}; ^1H NMR (Me_2SO-d_6 at 120 °C): δ 1.16 (d, 3 H, $J_{5',6'}$ 6.4 Hz, H-6′), 2.47 (s, 3 H, ArAc), 3.63 (dq, 1 H, $J_{4',5'}$ 0.9, $J_{5',6'}$ 6.4 Hz, H-5′), 3.68 (dd, 1 H, $J_{3',4'}$ 2.9, $J_{2',3'}$ 9.3 Hz, H-3′), 3.85 (dd, 1 H, $J_{4',5'}$ 0.9, $J_{3',4'}$ 2.9 Hz, H-4′), 4.18 (d, 1 H, J_{gem} 11.4 Hz, benzylic CH_2), 4.50 (d, 1 H, J_{gem} 11.4 Hz, benzylic CH_2), 4.60 (dd, 1 H, $J_{2',3'}$ 9.3, $J_{1',2'}$ 9.6 Hz, H-2′), 4.66 (d, 1 H, J_{gem} 11.7 Hz, benzylic CH_2), 4.69 (d, 1 H, J_{gem} 12.1 Hz, benzylic CH_2), 4.76 (d, 1 H, J_{gem} 12.1 Hz, benzylic CH_2), 4.79 (d, 1 H, $J_{1',2'}$ 9.6 Hz, H-1′), 4.90 (d, 1 H, J_{gem} 11.7 Hz, benzylic CH_2), 5.09 (d, 1 H, J_{gem} 12.9 Hz, benzylic CH_2), 5.13 (d, 1 H, J_{gem} 12.9 Hz, benzylic CH_2), 5.17 (d, 1 H, J_{gem} 11.9 Hz, benzylic CH_2), 5.21 (d, 1 H, J_{gem} 11.9 Hz, benzylic CH_2), 6.35 (s, 1 H, ArH), 6.90–7.44 (m, 25 H, ArH). The phenolic–OH signal was very broad around 13.7 ppm.; FABMS (positive-ion mode): m/z 765 $[M+H]^+$; FABMS (negative-ion mode); m/z 763 $[M-H]^-$. Anal. Calcd for $C_{49}H_{48}O_8$: C, 76.94; H, 6.32. Found: C, 76.77; H, 6.48.

*4,6-Bis-benzyloxy-3-*C*-(2,3,4,6-tetra-*O*-benzyl-β-*D*-gulopyranosyl)-2-hydroxyacetophenone* (**10**), *4,6-bis-benzyloxy-3-*C*-(2,3,4,6-tetra-*O*-benzyl-α-*D*-gulopyranosyl)-2-hydroxyacetophenone* (**11**), *2-acetoxy-4,6-bis-benzyloxy-3-*C*-(2,3,4,6-tetra-*O*-benzyl-β-*D*-gulopyranosyl)acetophenone* (**17**), *2-acetoxy-4,6-bis-benzyloxy-3-*C*-(2,3,4,6-tetra-*O*-benzyl-α-*D*-gulopyranosyl)acetophenone* (**18**).—A reaction using compound **1** (1.62 g, 4.65 mmol, 3.00 equiv), 2,3,4,6-tetra-*O*-benzyl-α-D-gulopyranosyl fluoride (0.842 g, 1.55 mmol), $BF_3{\cdot}Et_2O$ (400 μL, 3.25 mmol, 2.10 equiv), CH_2Cl_2 (30 mL), and powdered 4 Å molecular sieves (3 g) was carried out, and the post-treatment and isolation were also carried out in the same manner as described above. A crude mixture (964 mg) of compound **10** and **11** was obtained as a pale, yellowish–green oil. The mixture was acetylated using acetic anhydride, pyridine, and a catalytic amount of 4-dimethylaminopyridine (DMAP) for 24 h. The reaction mixture was poured into 0.5 M HCl and then extracted with toluene. The organic layer was washed with water and brine, and the solvent was evaporated under reduced pressure. The resulting syrup was chromatographed on silica gel (4:1 hexane–EtOAc) to give compound **17** (593 mg, 43%) and **18** (300 mg, 22%), respectively, as colorless oils. Compound **17** (465 mg) was deacetylated using 25% NaOMe (2 mL) in 1,4-dioxane (2 mL) to give the pure compound **10** (419 mg, 94%) as a pale, yellowish–green oil. Compound **18** (86 mg) was deacetylated under identical conditions to give the pure compound **11** (76 mg, 93%) as a pale, yellowish–green oil.

Physicochemical data for **10**: $[\alpha]_D^{18}$ −27° (*c* 1.0, $CHCl_3$); R_f 0.22 (5:1 hexane–EtOAc); IR (NaCl): ν 3087, 3062, 3030, 3006, 2906, 2868, 1622, 1616, 1593, 1496, 1454, 1431, 1394, 1367, 1358, 1274, 1207, 1169, 1115, 1095, 1076, 1028, 1003, 989, 912, 802, 737, 698 cm^{-1}; ^1H NMR (Me_2SO-d_6 at 100 °C): δ 2.50 (s, 3 H, ArAc), 3.50 (dd, 1 H, $J_{5',6'a}$ 6.3, J_{gem} 10.0 Hz, H-6′a), 3.58 (dd, 1 H, $J_{5',6'b}$ 6.3, J_{gem} 10.0 Hz, H-6′b), 3.65 (dd, 1 H, $J_{4',5'}$ 1.5, $J_{3',4'}$ 3.7 Hz, H-4′), 4.01 (dt, 1 H, $J_{4',5'}$ 1.5, $J_{5',6'a} = J_{5',6'b}$ 6.3 Hz, H-5′), 4.02 (dd, 1 H, $J_{2',3'}$ 2.7, $J_{3',4'}$ 3.7 Hz, H-3′), 4.16 (d, 1 H, J_{gem} 12.1 Hz, benzylic CH_2), 4.28 (d, 1 H, J_{gem} 12.1 Hz, benzylic CH_2), 4.40 (d, 1 H, J_{gem} 12.2 Hz, benzylic CH_2), 4.44 (d, 1 H, J_{gem} 12.2 Hz, benzylic CH_2), 4.45 (d, 1 H, J_{gem} 12.2 Hz, benzylic CH_2), 4.48 (d, 1 H, J_{gem} 12.2 Hz, benzylic CH_2), 4.57 (d, 1 H, J_{gem} 12.2 Hz, benzylic CH_2), 4.60 (d, 1 H, $J_{2',3'}$ 2.7, $J_{1',2'}$ 10.1 Hz, H-2′), 4.67 (d, 1 H, J_{gem} 12.2 Hz, benzylic CH_2), 5.09 (d, 1 H, J_{gem} 12.7 Hz, benzylic CH_2), 5.17 (d, 1 H, J_{gem} 12.7 Hz, benzylic CH_2), 5.23 (d, 1 H, J_{gem} 12.0 Hz, benzylic CH_2), 5.25 (d, 1 H, J_{gem} 12.0 Hz, benzylic CH_2), 5.40 (d, 1 H, $J_{1',2'}$ 10.1 Hz, H-1′), 6.41 (s, 1 H, ArH), 6.96–7.48 (m, 30 H, ArH), 13.45 (br. s, 1 H, ArOH); FABMS (positive-ion mode): m/z 871 $[M+H]^+$; FABMS (negative-ion mode); m/z 869 $[M-H]^-$. Anal. Calcd for $C_{56}H_{54}O_9$: C, 77.22; H, 6.25. Found: C, 76.77; H, 6.08.

Physicochemical data for **11**: $[\alpha]_D^{18}$ −7.8° (*c* 1.0, $CHCl_3$); R_f 0.20 (5:1 hexane–EtOAc); IR (NaCl): ν 3307, 3087, 3062, 3030, 3006, 2925, 2906, 2868, 1616, 1593, 1496, 1454, 1427, 1367, 1350, 1273, 1205, 1157, 1119, 1092, 1028, 910, 798, 737, 698 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.54 (s, 3 H, ArAc), 3.78 (dd, 1 H, $J_{5',6'a}$ 3.7, J_{gem} 10.7 Hz, H-6′a), 3.84 (dd, 1 H, $J_{5',6'b}$ 6.5, J_{gem} 10.7 Hz, H-6′b), 3.92 (dd, 1 H, $J_{2',3'}$ 2.9, $J_{3',4'}$ 9.0 Hz, H-3′), 3.99 (dd, 1 H, $J_{1',2'}$ 1.8, $J_{2',3'}$ 2.9 Hz, H-2′), 4.30 (dd, 1 H, $J_{4',5'}$ 6.3, $J_{3',4'}$ 9.0 Hz, H-4′), 4.33 (d, 1 H, J_{gem} 11.6 Hz, benzylic CH_2), 4.47 (d, 1 H, J_{gem} 12.4 Hz, benzylic CH_2), 4.50 (d, 1 H, J_{gem} 12.4 Hz, benzylic CH_2), 4.55 (ddd, 1 H, $J_{5',6'a}$ 3.7, $J_{4',5'}$ 6.3, $J_{5',6'b}$ 6.5 Hz, H-5′), 4.61 (d, 1 H, J_{gem} 11.9 Hz, benzylic CH_2), 4.63 (d, 1 H, J_{gem} 11.6 Hz, benzylic CH_2), 4.64 (d, 1 H, J_{gem} 11.9 Hz, benzylic CH_2), 4.65 (d, 1 H, J_{gem} 11.6 Hz, benzylic CH_2), 4.79 (d, 1 H, J_{gem} 11.6 Hz, benzylic CH_2), 4.82 (d, 1 H, J_{gem} 12.2 Hz, benzylic CH_2), 4.85 (d, 1 H, J_{gem} 12.2 Hz, benzylic CH_2), 5.04 (s, 2 H, benzylic CH_2), 5.45 (d, 1 H, $J_{1',2'}$ 1.8 Hz, H-1′), 5.94 (s, 1 H, ArH), 6.99–7.41 (m, 30 H, ArH), 11.96 (br. s, 1 H, ArOH); FABMS (positive-ion mode): m/z 871 $[M+H]^+$; FABMS (negative-ion mode); m/z 869 $[M-H]^-$. Anal. Calcd for $C_{56}H_{54}O_9$: C, 77.22; H, 6.25. Found: C, 77.31; H, 6.01.

Physicochemical data for **17**: $[\alpha]_D^{22}$ +13° (*c* 1.0, $CHCl_3$); R_f 0.40 (3:1 hexane–EtOAc); IR (NaCl): ν 3087, 3062, 3030, 3008, 2916, 2871, 1770, 1689, 1606, 1585, 1496, 1454, 1429, 1367, 1350, 1321, 1250, 1207, 1165, 1092, 1076, 1028, 1003, 987, 912, 885, 810, 750, 739, 698 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.90 (s, 3 H, ArOAc), 2.44 (s, 3 H, ArAc), 3.47 (dd, 1 H, $J_{5',6'a}$ 5.6,

J_{gem} 9.3 Hz, H-6′a), 3.52 (dd, 1 H, $J_{5',6'b}$ 7.5, J_{gem} 9.3 Hz, H-6′b), 3.63 (dd, 1 H, $J_{4',5'}$ 1.2, $J_{3',4'}$ 2.7 Hz, H-4′), 3.90 (dd, 1 H, $J_{2',3'}$ 1.8, $J_{3',4'}$ 2.7 Hz, H-3′), 4.10 (ddd, 1 H, $J_{4',5'}$ 1.2, $J_{5',6'a}$ 5.6, $J_{5',6'b}$ 7.5 Hz, H-5′), 4.23 (d, 1 H, J_{gem} 12.2 Hz, benzylic CH_2), 4.26 (d, 1 H, J_{gem} 12.2 Hz, benzylic CH_2), 4.32 (d, 1 H, J_{gem} 11.5 Hz, benzylic CH_2), 4.34 (d, 1 H, J_{gem} 11.5 Hz, benzylic CH_2), 4.35 (dd, 1 H, $J_{2',3'}$ 1.8, $J_{1',2'}$ 10.0 Hz, H-2′), 4.43 (d, 1 H, J_{gem} 12.0 Hz, benzylic CH_2), 4.50 (d, 1 H, J_{gem} 12.0 Hz, benzylic CH_2), 4.60 (d, 1 H, J_{gem} 12.0 Hz, benzylic CH_2), 4.81 (d, 1 H, J_{gem} 12.0 Hz, benzylic CH_2), 4.988 (d, 1 H, J_{gem} 11.7 Hz, benzylic CH_2), 4.994 (d, 1 H, J_{gem} 12.0 Hz, benzylic CH_2), 5.03 (d, 1 H, J_{gem} 12.0 Hz, benzylic CH_2), 5.04 (d, 1 H, J_{gem} 11.7 Hz, benzylic CH_2), 5.58 (d, 1 H, $J_{1',2'}$ 10.0 Hz, H-1′), 6.38 (s, 1 H, ArH), 7.09–7.37 (m, 30 H, ArH); Neither the protonated molecular ion nor the deprotonated molecular ion was identified in FABMS spectra using any matrix. Anal. Calcd for $C_{58}H_{56}O_{10}$: C, 76.30; H, 6.18. Found: C, 76.20; H, 6.01.

Physicochemical data for **18**: $[\alpha]_D^{22}$ −9.2° (*c* 1.0, $CHCl_3$); R_f 0.26 (3:1 hexane–EtOAc); IR (NaCl): *v* 3087, 3062, 3030, 3008, 2925, 2908, 2871, 1770, 1755, 1695, 1606, 1585, 1496, 1454, 1429, 1365, 1352, 1323, 1246, 1213, 1155, 1090, 1028, 912, 885, 810, 752, 737, 698 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.08 (s, 3 H, ArOAc), 2.47 (s, 3 H, ArAc), 3.76 (dd, 1 H, $J_{5',6'a}$ 2.7, J_{gem} 10.7 Hz, H-6′a), 3.82 (dd, 1 H, $J_{5',6'b}$ 5.1, J_{gem} 10.7 Hz, H-6′b), 3.88 (dd, 1 H, $J_{1',2'}$ 1.5, $J_{2',3'}$ 3.0 Hz, H-2′), 3.91 (dd, 1 H, $J_{4',5'}$ 2.9, $J_{3',4'}$ 9.0 Hz, H-4′), 4.25–4.28 (m, 2 H, H-3′, 5′) 4.37 (d, 1 H, J_{gem} 11.7 Hz, benzylic CH_2), 4.43 (d, 1 H, J_{gem} 12.5 Hz, benzylic CH_2), 4.46 (d, 1 H, J_{gem} 12.5 Hz, benzylic CH_2), 4.55 (d, 1 H, J_{gem} 12.0 Hz, benzylic CH_2), 4.59 (d, 1 H, J_{gem} 12.0 Hz, benzylic CH_2), 4.60 (d, 1 H, J_{gem} 11.7 Hz, benzylic CH_2), 4.65 (d, 1 H, J_{gem} 11.7 Hz, benzylic CH_2), 4.70 (d, 1 H, J_{gem} 11.7 Hz, benzylic CH_2), 4.787 (d, 1 H, J_{gem} 11.7 Hz, benzylic CH_2), 4.795 (d, 1 H, J_{gem} 11.7 Hz, benzylic CH_2), 5.05 (s, 2 H, benzylic CH_2), 5.31 (d, 1 H, $J_{1',2'}$ 1.5 Hz, H-1′), 6.26 (s, 1 H, ArH), 7.05–7.41 (m, 30 H, ArH); Neither the protonated molecular ion nor the deprotonated molecular ion was identified in FABMS spectra using any matrix. Anal. Calcd for $C_{58}H_{56}O_{10}$: C, 76.30; H, 6.18. Found: C, 76.14; H, 6.09.

References

1. Harborne J. B. *The Flavonoids*: *Advances in Research Since* 1986; Chapman and Hall: London, 1994; pp 57–93.
2. Kumazawa T.; Kimura T.; Matsuba S.; Sato S.; Onodera J. *Carbohydr. Res.* **2001**, *334*, 183–193.
3. Kumazawa T.; Saito T.; Matsuba S.; Sato S.; Onodera J. *Carbohydr. Res.* **2000**, *329*, 855–859.
4. Kumazawa T.; Akutsu Y.; Matsuba S.; Sato S.; Onodera J. *Carbohydr. Res.* **1999**, *320*, 129–137.
5. Kumazawa T.; Chiba M.; Matsuba S.; Sato S.; Onodera J. *Carbohydr. Res.* **2000**, *328*, 599–603.
6. Kumazawa T.; Sato S.; Matsuba S.; Onodera J. *Carbohydr. Res.* **2001**, *332*, 103–108.
7. (a) Hosoya T.; Ohashi Y.; Matsumoto T.; Suzuki K. *Tetrahedron Lett.* **1996**, *37*, 663–666;
   (b) Hosoya T.; Takashiro E.; Matsumoto T.; Suzuki K. *Tetraherdon Lett.* **1994**, *35*, 4591–4594.
8. (a) Schmidt B. *Org. Lett.* **2000**, *2*, 791–794;
   (b) Schmidt B. *J. Chem. Soc., Perkin Trans. 1* **1999**, 2627–2637.
9. (a) Martin H. J.; Drescher M.; Kählig H.; Schneider S.; Mulzer J. *Angew. Chem., Int. Ed. Engl.* **2001**, *40*, 3186–3188;
   (b) *Review on sp^2–sp^3 Atropisomerism*; Eliel, E. L.; Wilen, S. H., Eds.; Stereochemistry of Organic Compounds; Wiley: New York, 1994; p 1150.
10. Hayashi M.; Hashimoto S.; Noyori R. *Chem. Lett.* **1984**, 1747–1750.