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Note

2′-Carboxybenzyl glycosides: glycosyl donors for C-glycosylation and conversion into other glycosyl donors

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Abstract—Glycosylation of various glycosyl acceptors with 2′-carboxybenzyl (CB) 2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranoside and CB 2,3,4,6-tetra-*O*-benzyl-α-D-mannopyranoside as glycosyl donors afforded α-C-glycosides exclusively or predominantly in good yields. CB glycosides were also converted to other well-known glycosyl donors, the corresponding phenyl thioglycoside and the glycosyl fluoride derivatives.

Keywords: C-glycosylation; C-glycosides; CB glycosides; Glycosyl donors

The development of efficient and stereospecific C-glycosylation methodologies has become an increasingly attractive area in synthetic organic chemistry due to the discovery of novel classes of antitumor compounds, such as aquayamycin[1] and pluramycin,[2] and of antibiotic compounds, such as chrysomycin,[3] ravidomycin,[4] and vineomycin,[5] possessing *C*-aryl glycosides as well as a wide variety of medicinally important C-nucleosides.[6] The absence of an oxygen atom between the carbohydrate and the aglycon moiety results in greater stability of these compounds as they are resistant to chemical and enzymatic hydrolysis compared to O-glycosides. C-glycosides are thus hydrolytically stable carbohydrate mimetics with many possible biological applications.[7]

To date several different approaches for the synthesis of C-glycosides have been explored.[8] The most common method for the carbon–carbon bond formation at the anomeric carbon involves the attack of a carbon nucleophile on the electrophilic anomeric center of glycosyl donors. For example, several C-glycosylation methodologies based on efficient glycosyl donors, such as glycosyl fluorides,[9] glycosyl trichloroacetimidates,[10] glycals,[11] lactones,[12] thioglycosides,[13] and glycosyl phosphates,[14] have been employed. Nevertheless, there still remains a need for more study on C-glycosylation methods with respect to stereoselectivity, yields and reaction time.

In our previous endeavors, we reported a novel type of glycosyl donors, 2′-carboxybenzyl (CB) glycosides **B** (Fig. 1) that are useful for stereoselective β-mannopyranosylation,[15] 2-deoxyglucopyranosylation,[16] β-arabinofuranosylation,[17] and are also very effective for the synthesis of complex oligosaccharides by the latent-active glycosylation strategy.[17,18] The CB glycoside **B** was prepared from 2′-(benzyloxycarbonyl)benzyl (BCB) glycoside **A** by the selective removal of its benzyl ester functionality. Treatment of **B** with DTBMP and triflic anhydride followed by the spontaneous lactonization of the resulting glycosyl triflate **D** would afford the oxocarbenium ion **E** by extrusion of stable phthalide. Reaction of **E** with the glycosyl acceptor (nucleophile) would give the desired glycoside **F**. Herein we report a new method for the C-glycosylation using CB glycosides as glycosyl donors. To explore further the scope of this CB glycoside method, we also converted them to other

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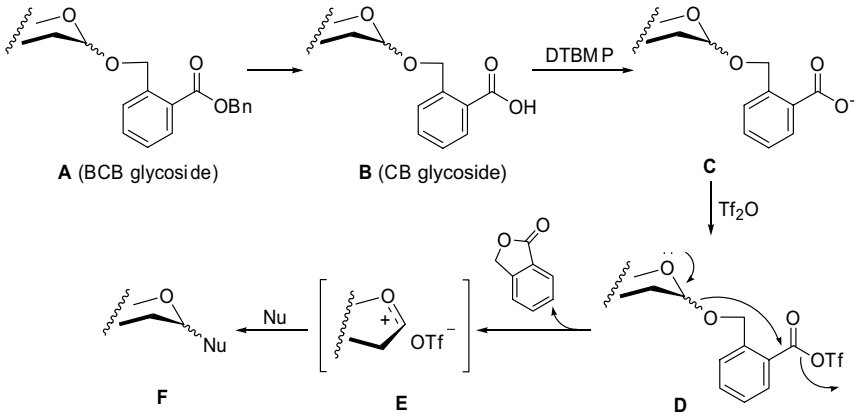
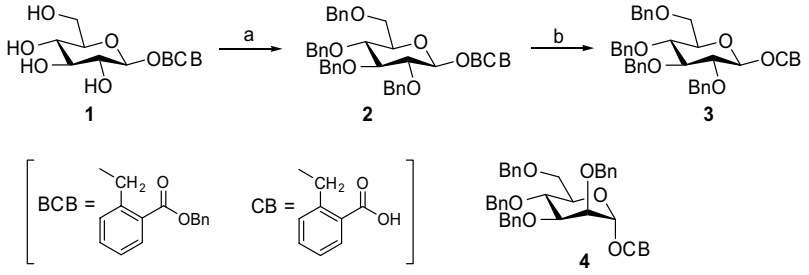


Figure 1.

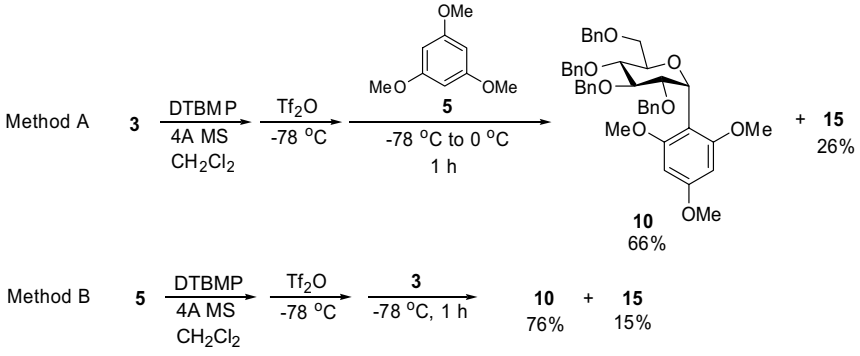
well-known glycosyl donors: thioglycosides and glycosyl fluorides.

CB tetrabenzylglucoside **3** was prepared by the selective hydrogenolysis of BCB tetrabenzylglucoside **2**, which was obtained from BCB glucoside **1** by the known procedure (Scheme 1).[18b] The CB tetrabenzylmannoside **4** was prepared in a similar manner.

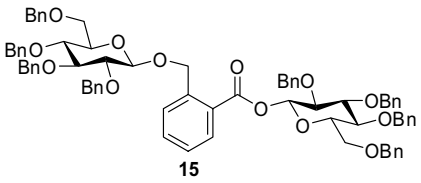
For our initial studies, C-glycosylations of various glycosyl acceptors (**5**–**9**) with the CB tetrabenzylglucoside **3** were carried out by the following standard reaction protocol (Scheme 2, method A): (i) stirring the solution of **3** (100 mg, 1.0 equiv) and 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP, 2.4 equiv) in the presence of 4 Å molecular sieves for 20 min at room temperature in CH_2Cl_2 (10 mL), (ii) addition of Tf_2O (1.2 equiv) to this solution at −78 °C and stirring the reaction mixture for 10 min, (iii) addition of the glycosyl acceptor (2.0 equiv) and stirring the reaction mixture for another 1 h at −78 °C and allowing the solution to warm over 1 h to 0 °C, and (iv) quenching the reaction by the addition of aqueous $NaHCO_3$. Glycosylations of acceptors, 1,3,5-trimethoxybenzene (**5**) and 1,3-dimethoxybenzene (**6**) with the donor **3** afforded exclusively α-C-glycosides **10** and **11** in 66% and 68% yields, respectively, along with the self-condensed ester **15** (Fig. 2) in 26% yields in both cases (Table 1, entries 1 and 2), whereas the



Scheme 1. Reagents and conditions: (a) NaH, BnBr, DMF, rt, 2 h, 80%; (b) H_2, Pd/C, NH_4OAc, CH_3OH, rt, 1 h, 94%.



Scheme 2. Glycosylation of acceptor **5** with CB glycoside **3**.



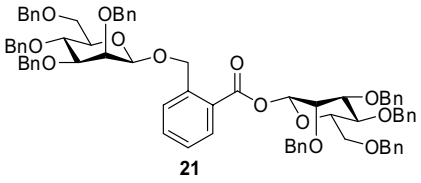
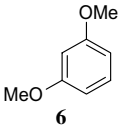
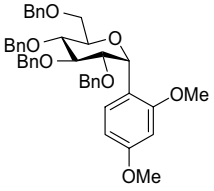
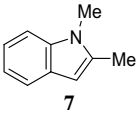
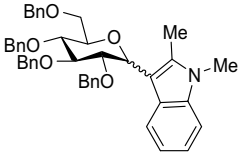
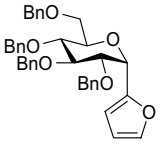
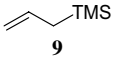
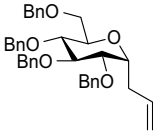


Figure 2.

Table 1. C-glycosylations with the CB glucoside **3** as the glycosyl donor

Entry	Glycosyl acceptor	C-glycoside	Method[a]	Yield (%)[b]	Ratio (α/β)[b]	Self-condensed ester **15** (%)[b]
1	**5**	**10**	A	66	α only	26
			B	76	α only	15
2	 **6**	 **11**	A	68	α only	26
			B	79	α only	12
3	 **7**	 **12**	A	63	1.7:1	30
			B	85	1.7:1	0
4	 **8**	 **13**	A	56	α only	39
			B	73	α only	20
5	 **9**	 **14**	A	56	α only	36
			B	68	α only	20

[a] Method A: The acceptor was added to a solution of the donor (CB glycoside), DTBMP, and Tf_2O. Method B: The donor (CB glycoside) was added to a solution of the acceptor, DTBMP, and Tf_2O. See the text or experimental for details.
[b] Determined after isolation.

reaction of **3** with 1,2-dimethylindole (**7**) gave a mixture of α- and β-C-glycoside **12** (α/β = 1.7:1) in 63% yield (entry 3). On the other hand, the same reaction of **3** with the acceptors furan (**8**) and allyltrimethylsilane (**9**) provided α-C-glycosides **13** and **14** exclusively in 56% yields in both cases, along with the ester **15** in 39% and 36% yields, respectively (entries 4 and 5).

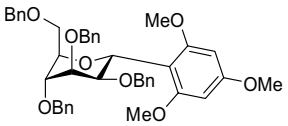
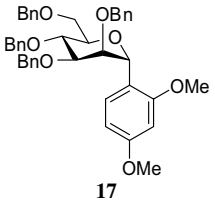
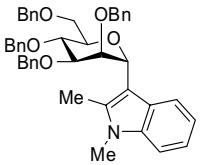
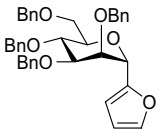
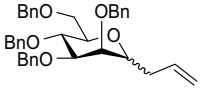
Formation of the self-condensed ester **15** probably resulted from the coupling between the carboxylate anion **C**, which was generated by deprotonation of the CB glycoside **B** by DTBMP, and the oxocarbenium ion **E** as shown in Figure 1. To suppress the formation of the ester **15**, we ran the glycosylation reaction with the reversal of the order of the addition of reactants. Thus, C-glycosylations of acceptors **5**–**9** with the CB tetrabenzylglucoside **3** were carried out under the modified reaction conditions: (Scheme 2, method B): (i) stirring the solution of the glycosyl acceptor (2.0 equiv) and DTBMP (2.4 equiv) in the presence of 4 Å molecular sieves for 20 min at room temperature in CH_2Cl_2 (5 mL), (ii) addition of Tf_2O (1.2 equiv) to this solution at −78 °C, (iii) dropwise addition of **3** (100 mg, 1.0 equiv) in CH_2Cl_2 (5 mL) to the solution over a period of 10 min and stirring the reaction mixture for further

1 h at −78 °C, and (iv) quenching the reaction by the addition of aqueous $NaHCO_3$. Under the modified reaction condition (method B), glycosylations of the acceptors **5**, **6**, **8**, and **9** with the donor **3** afforded only α-C-glycosides **10**, **11**, **13**, and **14**, respectively, in 68–79% yields, along with the ester **15** in 12–20% yields (Table 1, entries 1, 2, 4, and 5). In particular, although the same reaction of **3** with **7** gave a mixture of α- and β-C-glycoside **12** (α/β = 1.7:1), the yield was increased to 85%, without generation of the ester **15** (entry 3). Clearly, the modified reaction condition, method B, reduced the formation of the self-condensed ester **15** and increased the yield of C-glycosylation reaction. It is worthy of note that reactions of the CB tetrabenzylglucoside **3** with acceptors **5**, **6**, **8**, and **9** afforded the corresponding α-C-glycosides exclusively using both reaction conditions.

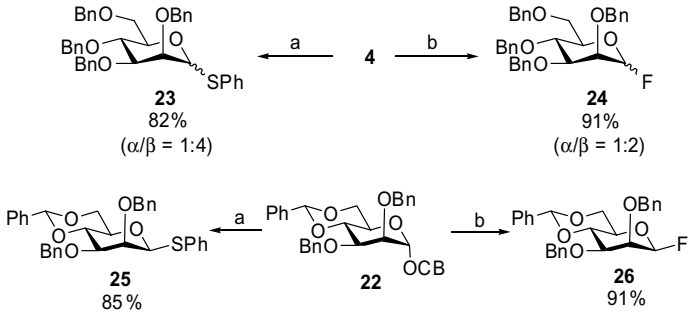
Because the modified reaction condition (method B) resulted in the improved yields for the C-glycoside in case of the CB tetrabenzylglucoside **3** as a glycosyl donor, we also performed C-glycosylation of the glycosyl acceptors **5**–**9** with CB tetrabenzylmannoside **4** under method B conditions (Table 2). Glycosylation of **5**–**8** with **4** under method B afforded α-C-glycosides **16**–**19** exclusively in 52–74% yields, along with the self-condensed ester **21** (Fig. 2) in 18–28% yields (entries 1–4). On the other hand, the same reaction of **4** with acceptor **9** provided a mixture of α- and β-C-glycoside **20** (α/β = 3:1) in 55% yield (entry 5).

It is interesting to note that the values of proton coupling constants, $^{3}J_{H1–H2}$ and $^{3}J_{H3–H4}$ of compound **16** are 8.8 and 4.7 Hz, respectively. These coupling constant values suggest that the pyranose ring of the compound **16**, which has a trimethoxyphenyl group at C-1, favors the $^{1}C_{4}$ conformation rather than the $^{4}C_{1}$ conformation.[19] A 2D-NOESY spectrum (τ_m = 550 ms) also supported the $^{1}C_{4}$ conformation of **16** (entry 1). Thus, strong NOEs were observed between H1 and H6, and between H1 and protons of the C6-*O*-benzyl group.

Table 2. C-glycosylations with the CB mannoside **4** as the glycosyl donor under modified condition (Method B)[a]

Entry	Acceptor	C-glycoside	Yield (%)[b]	Ratio (α/β)[b]	Self-condensed ester **21** (%)[b]
1	**5**	 **16**	69	α only	21
2	**6**	 **17**	71	α only	24
3	**7**	 **18**	52	α only	28
4	**8**	 **19**	74	α only	18
5	**9**	 **20**	55	3:1	20

[a] Method B: The donor (CB glycoside) was added to a solution of acceptor, DTBMP, and Tf_2O. See the text or experimental for details.
[b] Determined after isolation.



Scheme 3. Reagents and conditions: (a) **4** or **22**, DTBMP, Tf_2O, 4 Å molecular sieves, CH_2Cl_2, −78 °C, 10 min, then PhSH, −78 °C to 0 °C, 2 h; (b) **4** or **22**, DTBMP, Tf_2O, 4 Å molecular sieves, CH_2Cl_2, −78 °C, 10 min, then DAST, −78 °C to 0 °C, 2 h.

Besides the C-glycosylation, we attempted to convert the CB mannopyranosides **4** and **22**[15] to other well-known glycosyl donors, for example, thioglycosides and glycosyl fluorides (Scheme 3). Frequently, the conversion between glycosyl donors is very useful in the synthesis of complex oligosaccharides because a specific glycosyl donor gives higher stereoselectivity and better yield for a certain glycosylation reaction. The conversion of CB glycosides into thioglycosides and glycosyl fluorides was carried out under the standard reaction conditions (method A). The reaction of **4** with PhSH afforded a mixture of α- and β-phenyl thioglycosides, **23** in 82% yield (α/β = 1:4), and the same reaction with (diethylamino)sulfur trifluoride (DAST) as a fluoride source also provided a mixture of α- and β-glycosyl fluoride **24** in 91% yield (α/β = 1:2). On the other hand, the reaction of CB 4,6-benzylidenemannopyranoside **22** with PhSH and with DAST gave the previously unknown β-phenyl thioglycoside **25** and β-glycosyl fluoride **26** exclusively in 85% or 92% yield, respectively. It is probable that the exclusive β-stereoselectivity in these reactions is due to the formation of a highly reactive 4,6-*O*-benzylidenemannopyranosyl α-triflate[20] intermediate at low temperature as in the case of our previous β-*O*-mannopyranosylation.[15]

In conclusion, we have developed a highly stereoselective method for the synthesis of C-glycosides by employing CB glycosides **3** and **4** as glycosyl donors. C-glycosylations of various glycosyl acceptors with donors, **3** and **4** afforded exclusively or predominantly α-C-glycosides in good yields. In addition, CB glycosides **4** and **22** were successfully converted to well-known glycosyl donors, thioglycosides and glycosyl fluorides in excellent yields.

1. Experimental

1.1. General methods

All reactions were conducted under a positive pressure of dry argon with dry, freshly distilled solvents unless otherwise noted. All reagents were purchased from commercial suppliers and used without further purification unless otherwise noted. Flash column chromatography was performed employing 230–400 mesh silica gel. Thin-layer chromatography was performed using Silica Gel 60 F254 precoated plates (0.25 mm thickness) with a fluorescent indicator. NMR spectra were recorded on a Bruker 250, 400, or 500 MHz NMR spectrometer. Chemical shifts are reported in parts per million (ppm) downfield from tetramethylsilane (TMS) unless otherwise noted. Optical rotations were measured with a Rudolph Autopol III automatic polarimeter.

1.2. Typical experimental protocol for the glycosylation reaction

1.2.1. Method A. A solution of glycosyl donor **3** (100 mg, 0.15 mmol) and DTBMP (74 mg, 0.36 mmol) in CH_2Cl_2 (10 mL) in the presence of 4 Å molecular sieves (500 mg) was stirred for 20 min at rt and cooled to −78 °C, then Tf_2O (30 μL, 0.18 mmol) was added. After the resulting solution was stirred at −78 °C for 10 min, glycosyl acceptor (0.30 mmol) was added and stirred at −78 °C for 1 h and allowed to warm over 1 h to 0 °C. The reaction mixture was quenched by the addition of satd aq $NaHCO_3$ and then extracted with CH_2Cl_2. The combined organic layer was washed with satd aq $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash column chromatography (3:1, hexane/EtOAc) to afford the desired C-glycoside.

1.2.2. Method B. A solution of glycosyl acceptor (0.30 mmol) and DTBMP (74 mg, 0.36 mmol) in CH_2Cl_2 (5 mL) in the presence of 4 Å molecular sieves (500 mg) was stirred for 20 min at rt and cooled to −78 °C, then Tf_2O (30 μL, 0.18 mmol) was added. To the resulting solution was added dropwise a solution of glycosyl donor **3** or **4** (100 mg, 0.15 mmol) in CH_2Cl_2 (5 mL) over 10 min. After stirring at −78 °C for 1 h, the reaction mixture was quenched by the addition of satd

aq $NaHCO_3$, and then extracted with CH_2Cl_2. The combined organic layer was washed with satd aq $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash column chromatography (3:1, hexane/EtOAc) to afford the desired C-glycoside.

All known compounds, **10**,[13b] **11**,[13b] **12β**,[10c] **13**,[10c] **14**,[14b] **15**,[18b] gave acceptable ^{1}H NMR and ^{13}C NMR spectra that matched data reported previously.

1.3. 1,2-Dimethyl-3-(2′,3′,4′,6′-tetra-*O*-benzyl-α-D-glucopyranosyl)-indole (12α)

Colorless oil, $R_f = 0.20$ (10:1:2, hexane/EtOAc/CH_2Cl_2); $[\alpha]_D$ +8.7 (*c* 0.9, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.42 (s, 3H, CH_3), 3.62 (s, 3H, NCH_3), 3.62–3.68 (m, 2H, H-6a, H-6b), 3.75–3.80 (m, 1H, H-5), 3.89–3.93 (m, 2H, H-2, H-4), 4.19 (t, 1H, $J = 7.0$ Hz, H-3), 4.37 and 4.46 (ABq, 2H, $J = 11.6$ Hz, PhCH_2), 4.42 and 4.57 (ABq, 2H, $J = 12.2$ Hz, PhCH_2), 4.54 and 4.79 (ABq, 2H, $J = 11.2$ Hz, PhCH_2), 4.75 and 4.87 (ABq, 2H, $J = 11.2$ Hz, PhCH_2), 5.55 (d, 1H, *J* 4.4 Hz, H-1), 7.03–7.35 (m, 23H, Ar-H), 7.90 (d, 1H, $J = 8.0$ Hz, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 11.9 (*C*H_3), 29.5 (N*C*H_3), 69.9, 70.9, 72.8, 73.2, 73.5, 74.0, 74.3, 77.8, 81.5, 83.0, 108.0 (C′-8), 108.5 (C′-3), [119.2, 120.5, 120.8 (C′-5, C′-6, C′-7)], [127.3, 127.5, 127.6, 127.7, 127.8, 127.9 (2C), 127.97 (2C), 128.0 (2C), 128.2 (2C), 128.22 (2C), 128.4 (2C), 128.44 (2C), 128.6 (2C)(Ar-C)], [136.3, 136.8 (C′-4, C′-9)], [138.4, 138.5, 138.7, 138.74 (Ar-C *ipso*)].

1.4. 1-(2′,3′,4′,6′-tetra-*O*-benzyl-α-D-mannopyranosyl)-2,4,6-trimethoxybenzene (16)

Colorless oil, $R_f = 0.2$ (3:1, hexane/EtOAc); $[\alpha]_D$ +1.3 (*c* 1.4, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.69 (s, 6H, 2OCH_3), 3.78–3.80 (m, 1H, H-4), 3.80 (s, 3H, OCH_3), 3.85 (dd, 1H, $J = 10.0$, 6.0 Hz, H-6a), 3.94 (dd, 1H, $J = 10.0$, 6.8 Hz, H-6b), 4.02–4.04 (dd, 1H, $J = 3.5$, 4.7 Hz, H-3), 4.02–4.23 (m, 1H, H-5), 4.34 (s, 2H, PhCH_2), 4.49 (d, 1H, $J = 12.0$ Hz, PhC*H*H), 4.50 (d, 1H, $J = 12.0$ Hz, PhC*H*H), 4.55–4.60 (m, 3H, 3PhC*H*H), 4.65 (dd, 1H, $J = 9.0$, 3.3 Hz, H-2), 4.72 (d, 1H, $J = 12.5$ Hz, PhC*H*H), 5.56 (d, 1H, $J = 8.8$ Hz, H-1), 6.10 (s, 2H, H-3′, H-5′), 7.06–7.32 (m, 20H, Ar-H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 55.4 (O*C*H_3), 56.0 (2C, O*C*H_3), 65.0, 69.0, 71.7, 71.8, 72.7, 73.4, 74.5, 75.4, 75.8, 76.0, 91.3 (2C, C-3′, C-5′), 108.7 (C-1′), [127.3, 127.4, 127.5 (2C), 127.7 (4C), 127.88 (2C), 127.9 (2C), 128.1 (2C), 128.3 (6C)(Ar-C)], [138.8, 138.87, 138.9, 139.0 (Ar-C *ipso*)], [160.6(2), 161.2 (C-2′, C-4′, C-6′)]. Anal. Calcd for $C_{43}H_{46}O_8$: C, 74.76; H, 6.71. Found: C, 74.73; H, 6.72.

1.5. 1-(2′,3′,4′,6′-tetra-*O*-benzyl-α-D-mannopyranosyl)-2,4-dimethoxybenzene (17)

Colorless oil, $R_f = 0.5$ (2:1, hexane/EtOAc); $[\alpha]_D$ +12.7 (*c* 1.3, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$): δ 3.68 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3), 3.81–3.93 (m, 4H, H-3, H-4, H-6a, H-6b), 4.14 (d, 1H, $J = 10.5$, 5.4 Hz, H-5), 4.23 (dd, 1H, $J = 6.2$, 2.7 Hz, H-2), 4.46 (s, 2H, PhCH_2), 4.50–4.64 (m, 6H, 3PhCH_2), 5.32 (d, 1H, $J = 6.2$ Hz, H-1), 6.40–6.47 (m, 2H, H-3′, H-5′), 7.06–7.32 (m, 21H, Ar-H, H-6′); ^{13}C NMR (63 MHz, $CDCl_3$): δ 55.5 (2C, O*C*H_3), 69.3 (2C), 71.8, 72.5, 73.0, 73.3, 75.35, 75.38, 76.4, 77.3, 98.8 (C-3′), 104.4 (C-5′), 120.0 (C-1′), [127.4, 127.5, 127.6, 127.7, 127.8 (2C), 127.9 (4C), 128.0 (2C), 128.2 (2C), 128.4 (4C), 128.5 (2C), 129.1 (Ar-C, C-6′)], [138.5, 138.69, 138.7, 138.8 (Ar-C *ipso*)], [158.5, 160.5 (C-2′, C-4′)]. Anal. Calcd for $C_{42}H_{44}O_7$: C, 76.34; H, 6.71. Found: C, 76.37; H, 6.71.

1.6. 1,2-Dimethyl-3-(2′,3′,4′,6′-tetra-*O*-benzyl-α-D-mannopyranosyl)-indole (18)

Colorless oil, $R_f = 0.30$ (10:1:2, hexane/EtOAc/CH_2Cl_2); $[\alpha]_D$ +2.2 (*c* 0.8, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.33 (s, 3H, CH_3), 3.59 (s, 3H, NCH_3), 3.58–3.62 (m, 1H, H-5), 3.80–3.88 (m, 4H, H-2, H-3, H-6a, H-6b), 4.16 (t, 1H, $J = 9.6$ Hz, H-4), 4.14 and 4.48 (ABq, 2H, $J = 11.2$ Hz, PhCH_2), 4.59 and 4.71 (ABq, 2H, $J = 12.4$ Hz, PhCH_2), 4.68 and 4.96 (ABq, 2H, $J = 10.8$ Hz, PhCH_2), 4.70 (s, 2H, PhCH_2), 4.83 (br s, 1H, H-1), 6.89–7.34 (m, 23H, Ar-H), 7.63 (d, 1H, $J = 8.0$ Hz, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 11.6 (*C*H_3), 29.4 (N*C*H_3), 69.9, 72.2, 73.5, 74.9, 75.3, 75.4, 76.2, 78.2, 80.3, 84.8, 108.4 (C′-8), 108.5 (C′-3), [119.0, 119.3, 120.5 (C′-5, C′-6, C′-7)], [126.8, 127.1 (2C), 127.4 (2C), 127.66 (2C), 127.7 (2C), 127.8 (2C), 128.2 (2C), 128.22 (2C), 128.4 (2C), 128.47 (2C), 128.5 (2C)(Ar-C)], [134.6, 136.6 (C′-4, C′-9)], [138.76, 138.85, 138.9, 139.0 (Ar-C *ipso*)]. Anal. Calcd for $C_{44}H_{45}NO_5$: C, 79.13; H, 6.79; N, 2.10. Found: C, 78.88; H, 7.04; N, 1.93.

1.7. 2-(2′,3′,4′,6′-tetra-*O*-benzyl-α-D-mannopyranosyl)-furan (19)

Colorless oil, $R_f = 0.43$ (4:1, hexane/EtOAc); $[\alpha]_D$ +3.4 (*c* 3.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.72–3.82 (m, 3H, H-5, H-6a, H-6b), 3.84 (dd, 1H, $J = 8.0$, 3.2 Hz, H-3), 4.00 (t, 1H, $J = .0$ Hz, H-4), 4.16 (t, 1H, $J = 3.2$ Hz, H-2), 4.51 (d, 1H, $J = 10.8$ Hz, PhC*H*H), 4.54 (d, 1H, $J = 12.0$ Hz, PhC*H*H), 4.61–4.80 (m, 6H, 3PhCH_2), 5.12 (d, 1H, $J = 3.2$ Hz, H-1), 6.12 (d, 1H, $J = 3.6$ Hz, H′-3), 6.28 (dd, 1H, $J = 3.6$, 2.0 Hz, H′-4), 7.18–7.36 (m, 21H, Ar-H, H′-5); ^{13}C NMR (100 MHz, $CDCl_3$): δ 69.3, 70.5, 72.2, 72.4, 73.4, 74.6, 74.76, 74.8, 75.0, 79.1 (C-1), [108.9, 110.5 (C′-3, C′-4)], [127.55,

127.6, 127.72, 127.74, 127.8, 127.9, 128.0 (2C), 128.06 (2C), 128.13 (2C), 128.2 (2C), 128.38 (2C), 128.44 (2C), 128.5 (2C)(Ar-C)], [138.3, 138.4(2), 138.5 (Ar-C *ipso*)], 142.3 (C′-5), 151.2 (C′-2). Anal. Calcd for $C_{38}H_{38}O_6$: C, 77.26; H, 6.48. Found: C, 77.39; H, 6.45.

1.8. 3-(2′,3′,4′,6′-tetra-*O*-benzyl-D-mannopyranyl)-propene (20)

Compound **20α**: colorless oil, $R_f = 0.4$ (8:1:10, hexane/EtOAc/CH_2Cl_2); $[\alpha]_D$ +16.7 (*c* 2.7, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.30–2.36 (m, 2H, H′-1a, H′-1b), 3.61–3.62 (m, 1H, H-3), 3.70 (dd, 1H, $J = 10.1$, 3.0 Hz, H-6a), 3.75–3.88 (m, 4H, H-1, H-2, H-4, H-6b), 4.05 (dd, 1H, $J = 11.4$, 6.5 Hz, H-5), 4.50–4.73 (m, 8H, 4PhC*H*$_2$), 4.99–5.03 (m, 2H, H′-3a, H′-3b), 5.70–5.78 (m, 1H, H′-2), 7.18–7.36 (m, 20H, Ar-H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 34.7 (C′-1), 69.1, 71.5, 72.0, 72.4, 73.3, 73.6, 74.0, 74.8, 74.9, 76.9, 117.4 (C′-3), [127.6, 127.8 (4C), 128.0 (3C), 128.1 (4C), 128.4 (4C), 128.5 (4C)(Ar-C)], 134.3 (C′-2), [138.2 (3C), 138.4 (Ar-C *ipso*)]. Anal. Calcd for $C_{37}H_{40}O_5$: C, 78.69; H, 7.14. Found: C, 78.70; H, 7.13. Compound **20β**: colorless oil, $R_f = 0.5$ (8:1:10, hexane/EtOAc/CH_2Cl_2); $[\alpha]_D$ −18.8 (*c* 0.8, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.29–2.35 (m, 1H, H′-1a), 2.48–2.53 (m, 1H, H′-1b), 3.33 (t, 1H, $J = 6.8$ Hz, H-3), 3.46 (dd, 1H, $J = 8.6$, 5.9 Hz, H-5), 3.62 (dd, 1H, $J = 9.3$, 2.1 Hz, H-2), 3.68 (dd, 1H, $J = 10.7$, 5.9 Hz, H-6a), 3.75–3.80 (m, 2H, H-1, H-6b), 3.90 (t, 1H, $J = 9.5$ Hz, H-4), 4.53 (d, 1H, $J = 10.7$ Hz, PhC*H*H), 4.58 and 4.61 (ABq, 2H, $J = 12.2$ Hz, PhC*H*$_2$), 4.69 (d, 1H, $J = 11.6$ Hz, PhC*H*H), 4.72 and 4.79 (ABq, 2H, $J = 11.7$ Hz, PhC*H*$_2$), 4.87 (d, 1H, $J = 10.6$ Hz, PhC*H*H), 5.00–5.05 (m, 3H, H′-3a, H′-3b, PhC*H*H), 5.63–5.71 (m, 1H, H′-2), 7.15–7.38 (m, 20H, Ar-H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 35.7 (C′-1), 69.7, 72.5, 73.5, 74.4, 74.5, 75.38, 75.44, 78.3, 79.8, 85.5, 117.5 (C′-3), [127.6 (3C), 127.8 (2C), 128.1 (2C), 128.2 (4C), 128.4 (7C), 128.6 (2C)(Ar-C)], 134.7 (C′-2), [138.3, 138.4 (2C), 138.8 (Ar-C *ipso*)]. Anal. Calcd for $C_{37}H_{40}O_5$: C, 78.69; H, 7.14. Found: C, 78.67; H, 7.12.

1.9. Self-condensed ester of CB mannopyranoside (21)

Colorless oil, $R_f = 0.30$ (4:1, hexane/EtOAc); $[\alpha]_D$ +4.8 (*c* 1.1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.70–3.83 (m, 6H), 3.87–3.88 (m, 1H), 3.90–3.97 (m, 2H), 4.00 (dd, 1H, $J = 9.6$, 3.2 Hz, H-6a), 4.05–4.12 (m, 1H), 4.18 (t, 1H, $J = 9.8$ Hz, H-4), 4.50–5.09 (m, 18H, 9PhC*H*$_2$), 5.05 (br s, 1H, H-1), 6.43 (d, 1H, $J = 1.6$ Hz, H′-1), 7.18–7.49 (m, 43H, Ar-H), 7.75 (d, 1H, $J = 8.0$ Hz, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 67.4, 69.0, 69.3, 72.2, 72.3, 72.5, 72.65, 72.7, 73.6, 73.7, 74.0, 74.4, 74.8, 75.0, 75.1, 75.4, 75.6, 79.2, 80.2, 92.3 (C′-1), 98.0 (C-1), [127.6 (2C), 127.7 (4C), 127.8 (5C), 127.87 (3C), 127.89 (3C), 127.91, 127.92, 127.97, 128.0, 128.07, 128.1 (2C), 128.2 (2C), 128.3 (2C), 128.39 (2C), 128.43, 128.45 (2C), 128.46 (2C), 128.48 (3C), 128.52 (3C), 128.54 (3C)(Ar-C)], [130.8, 133.2, 138.0, 138.1, 138.35, 138.4, 138.5, 138.6 (2C), 141.4 (Ar-C *ipso*)], 164.1 (C=O). Anal. Calcd for $C_{76}H_{76}O_{13}$: C, 76.23; H, 6.40. Found: C, 76.32; H, 6.23.

1.10. Phenyl 2,3,4,6-tetra-*O*-benzyl-1-thio-D-mannopyranoside (23)

A solution of **4** (158 mg, 0.23 mmol) and DTBMP (115 mg, 0.56 mmol) in CH_2Cl_2 (15 mL) in the presence of 4 Å molecular sieves was stirred for 20 min at rt and cooled to −78 °C, then Tf_2O (47 μL, 0.28 mmol) was added. After the resulting solution was stirred at −78 °C for 10 min, benzenethiol (36 μL, 0.35 mmol) was added and stirred at −78 °C for 1 h and allowed to warm over 1 h to 0 °C. The reaction mixture was quenched with satd aq $NaHCO_3$, and then extracted with CH_2Cl_2. The combined organic layer was washed with satd aq $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash column chromatography (7:1, hexane/EtOAc) to afford α-thioglycoside **23α** (24 mg, 16%) and then β-thioglycoside **23β** (98 mg, 66%). Compound **23α**: colorless oil, $R_f = 0.3$ (7:1, hexane/EtOAc); $[\alpha]_D$ +8.1 (*c* 1.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.75 (d, 1H, $J = 11.2$, 1.8 Hz, H-6a), 3.82–3.88 (m, 2H, H-3, H-6b), 3.99–4.00 (m, 1H, H-2), 4.07 (t, 1H, $J = 9.4$ Hz, H-4), 4.26–4.31 (m, 1H, H-5), 4.48 (d, 1H, $J = 12.0$ Hz, PhC*H*H), 4.54 (d, 1H, $J = 10.8$ Hz, PhC*H*H), 4.60–4.66 (m, 4H, 2PhC*H*$_2$), 4.73 (d, 1H, $J = 12.4$ Hz, PhC*H*H), 4.90 (d, 1 H, $J = 10.8$ Hz, PhC*H*H), 5.61 (d, 1H, $J = 1.6$ Hz, H-1), 7.19–7.45 (m, 25H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 69.3, 72.0, 72.2, 72.9, 73.4, 75.1, 75.3, 76.4, 80.3, 85.9 (C-1), [127.5, 127.6, 127.75, 127.82 (2C), 127.86 (2C), 127.95 (2C), 128.0 (2C), 128.1 (2C), 128.4 (2C), 128.47 (2C), 128.5 (2C), 128.54 (2C), 129.1 (2C), 131.8 (2C)(Ar-C)], 134.5 (Ar-S *ipso*), [138.1, 138.3, 138.5, 138.6 (Ar-C *ipso*)]. Anal. Calcd for $C_{40}H_{40}O_5S$: C, 75.92; H, 6.37. Found: C, 75.98; H, 6.34. Compound **23β**: colorless oil, $R_f = 0.28$ (7:1, hexane/EtOAc); $[\alpha]_D$ −4.1 (*c* 5.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.53–3.55 (m, 1H, H-5), 3.61 (dd, 1H, $J = 9.2$, 2.8 Hz, H-3), 3.74 (dd, 1H, $J = 10.8$, 6.4 Hz, H-6a), 3.83 (dd, 1H, $J = 10.8$, 1.6 Hz, H-6b), 3.94 (t, 1H, $J = 9.6$ Hz, H-4), 4.13 (d, 1H, $J = 2.4$ Hz, H-2), 4.53–4.61 (m, 3H, 3PhC*H*H), 4.67 and 4.71 (ABq, 2H, $J = 11.8$ Hz, PhC*H*$_2$), 4.76 (br s, 1H, H-1), 4.85 (d, 1H, $J = 11.2$ Hz, PhC*H*H), 4.88 (d, 1 H, $J = 10.8$ Hz, PhC*H*H), 5.04 (d, 1H, $J = 11.6$ Hz, PhC*H*H), 7.17–7.52 (m, 25H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 69.9, 72.7,

73.5, 75.0, 75.2, 75.3, 77.6, 80.2, 84.4, 87.7 (C-1), [127.0, 127.5, 127.7 (2C), 127.8 (2C), 127.83 (2C), 127.9 (2C), 128.1 (2C), 128.26 (2C), 128.3 (3C), 128.4 (2C), 128.6 (2C), 129.0 (2C), 130.6 (2C)(Ar-C)], 135.8 (Ar-S *ipso*), [138.1, 138.3, 138.4, 138.6 (Ar-C *ipso*)]. Anal. Calcd for $C_{40}H_{40}O_5S$: C, 75.92; H, 6.37. Found: C, 76.11; H, 5.99.

1.11. 2,3,4,6-Tetra-*O*-benzyl-D-mannopyranosyl fluoride (24)

A solution of **4** (128 mg, 0.19 mmol) and DTBMP (94 mg, 0.46 mmol) in CH_2Cl_2 (12 mL) in the presence of 4 Å molecular sieves was stirred for 20 min at rt and cooled to −78 °C, then Tf_2O (38 μL, 0.23 mmol) was added. After the resulting solution was stirred at −78 °C for 10 min, DAST (50 μL, 0.38 mmol) was added and stirred at −78 °C for 1 h and allowed to warm over 1 h to 0 °C. The reaction mixture was quenched with satd aq $NaHCO_3$, and then extracted with CH_2Cl_2. The combined organic layer was washed with satd aq $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash column chromatography (4:1, hexane/EtOAc) to afford α-glycosyl fluoride **24α** (32 mg, 31%) and then β-glycosyl fluoride **24β** (62 mg, 60%). Compound **24α**: pale yellow oil, $R_f = 0.53$ (4:1, hexane/EtOAc); $[\alpha]_D$ +2.9 (*c* 1.4, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 3.71 (dd, 1H, $J = 11.2$, 1.8 Hz, H-6a), 3.77 (dd, 1H, $J = 11.2$, 4.4 Hz, H-6b), 3.86–3.93 (m, 3H, H-2, H-3, H-5), 4.07 (t, 1H, $J = 9.4$ Hz, H-4), 4.53 (d, 2H, $J = 11.2$ Hz, PhCH_2), 4.61–4.70 (m, 4H, 2PhCH_2), 4.80 (d, 1H, $J = 12$ Hz, PhC*H*H), 4.87 (d, 1H, $J = 10.8$ Hz, PhC*H*H), 5.59 (dd, 1H, $J_{1,F} = 50.6$, $J_{1,2} = 1.6$ Hz, H-1), 7.15–7.36 (m, 20H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 68.8 (C-6), 72.7 (Ph*C*H$_2$), 73.4 (Ph*C*H$_2$), 73.56 (Ph*C*H$_2$), 73.6 (d, *J* 34 Hz, C-2), 74.2 (C-3/4/5), 74.3 (C-3/4/5), 75.2 (Ph*C*H$_2$), 79.3 (C-3/4/5), 106.5 (d, *J* 221 Hz, C-1), [127.6, 127.7 (3C), 127.8 (3C), 127.9, 128.0 (2C), 128.1 (2C), 128.46 (2C), 128.5 (2C), 128.6 (4C)(Ar-C)], [138.0, 138.27, 138.3, 138.34 (Ar-C *ipso*)]. Anal. Calcd for $C_{34}H_{35}FO_5$: C, 75.26; H, 6.50. Found: C, 75.31; H, 6.46. Compound **24β**: pale yellow oil, $R_f = 0.38$ (4:1, hexane/EtOAc); $[\alpha]_D$ −2.2 (*c* 2.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 3.61 (dd, 1H, $J = 7.6$, 3.2 Hz, H-3), 3.68–3.72 (m, 1H, H-5), 3.78 (dd, 1H, $J = 10.4$, 5.6 Hz, H-6a), 3.84 (dd, 1H, $J = 10.4$, 3.6 Hz, H-6b), 3.92–3.95 (m, 2H, H-2, H-4), 4.49–4.60 (m, 5H, 5PhC*H*H), 4.72 and 4.82 (ABq, 2H, $J = 12.4$ Hz, PhCH_2), 4.73 (d, 1H, $J = 11.2$ Hz, PhC*H*H), 5.33 (d, 1H, $J_{1,F} = 50.8$ Hz, H-1), 7.16–7.35 (m, 20H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 69.5 (C-6), 72.1 (Ph*C*H$_2$), 73.0 (d, *J* 19 Hz, C-2), 73.4 (C-5), 73.56 (Ph*C*H$_2$), 73.9 (Ph*C*H$_2$), 74.3 (Ph*C*H$_2$), 75.3 (C-4), 78.6 (C-3), 107.1 (d, $J = 218$ Hz, C-1), [127.7, 127.8, 127.83, 127.85, 127.9 (2C), 128.0 (2C), 128.1 (2C), 128.2 (2C), 128.43 (2C), 128.44 (2C), 128.5 (2C), 128.51 (2C)(Ar-C)], [138.0, 138.06, 138.1, 138.3 (Ar-C *ipso*)]. Anal. Calcd for $C_{34}H_{35}FO_5$: C, 75.26; H, 6.50. Found: C, 75.25; H, 6.57.

1.12. Phenyl 4,6-*O*-benzylidene-2,3-di-*O*-benzyl-1-thio-β-D-mannopyranoside (25)

CB glycoside **22** (670 mg, 1.15 mmol) was subjected to the same reaction conditions as that for the preparation of **23** from **4**. The reaction mixture was purified by flash column chromatography (7:1, hexane/EtOAc) to give the title compound **25** (529 mg, 85%, β only) as a colorless oil. $R_f = 0.38$ (9:1:1, hexane/EtOAc/CH_2Cl_2); $[\alpha]_D$ −0.78 (*c* 1.1, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 3.37–3.43 (m, 1H, H-5), 3.74 (dd, 1H, $J = 9.6$, 3.2 Hz, H-3), 3.95 (t, 1H, $J = 10.2$ Hz, H-4), 4.18 (d, 1H, $J = 2.0$ Hz, H-2), 4.29–4.34 (m, 2H, H-6a, H-6b), 4.74 and 4.89 (ABq, 2H, $J = 12.4$ Hz, PhCH_2), 4.85 (d, 1H, $J = 0.8$ Hz, H-1), 4.86 and 5.11 (ABq, 2H, $J = 11.2$ Hz, PhCH_2), 5.64 (s, 1H, PhC*H*O$_2$), 7.25–7.51 (m, 20H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 68.6, 71.8, 73.3, 76.0, 78.8, 79.1, 79.9, 89.2 (C-1), 101.6 (Ph*C*HO$_2$), [126.2 (2C), 127.6, 127.8 (2C), 127.87, 127.9, 128.3 (4C), 128.6 (2C), 128.8 (2C), 129.0,129.1 (2C), 129.3, 131.2 (2C)(Ar-C)], 135.1 (Ar-S *ipso*), [137.6, 138.1, 138.4 (Ar-C *ipso*)]. Anal. Calcd for $C_{33}H_{32}O_5S$: C, 73.31; H, 5.97. Found: C, 73.36; H, 5.96.

1.13. 4,6-*O*-Benzylidene-2,3-di-*O*-benzyl-β-D-mannopyranosyl fluoride (26)

CB glycoside **22** (57 mg, 0.098 mmol) was subjected to the same reaction conditions as that for the preparation of **24** from **4**. The reaction mixture was purified by flash column chromatography (4:1, hexane/EtOAc) to give the title compound **26** (40 mg, 91%, β only) as a pale yellow oil. $R_f = 0.55$ (3:1, hexane/EtOAc); $[\alpha]_D$ −3.0 (*c* 1.1, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 3.37–3.43 (m, 1H, H-5), 3.65 (dd, 1H, $J = 9.6$, 2.8 Hz, H-3), 3.94 (t, 1H, $J = 10.4$ Hz, H-4), 4.00–4.01 (m, 1H, H-2), 4.24 (t, 1H, $J = 9.6$ Hz, H-6a), 4.35 (dd, 1H, $J = 10.4$, 4.8 Hz, H6b), 4.64 and 4.76 (ABq, 2H, $J = 12.4$ Hz, PhCH_2), 4.83 and 4.89 (ABq, 2H, $J = 12.0$ Hz, PhCH_2), 5.28 (dd, 1H, $J_{1,F} = 49.2$ Hz, $J_{1,2} = 0.8$ Hz, H-1), 5.62 (s, 1H, PhC*H*O$_2$), 7.29–7.50 (m, 15H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 67.0 (C-3/4/5), 68.5 (C-6), 72.9 (Ph*C*H$_2$), 74.9 (C-3/4/5), 75.1 (d, *J* 16 Hz, C-2), 76.8 (C-3/4/5), 78.3 (Ph*C*H$_2$), 101.7 (Ph*C*HO$_2$), 107.7 (d, *J* 216 Hz, C-1), [126.2 (2C), 127.8 (2C), 127.9, 128.0, 128.4 (2C), 128.45 (2C), 128.5 (4C), 129.1 (Ar-C)], [137.4, 137.9, 138.1 (Ar-C *ipso*)]. Anal. Calcd for $C_{27}H_{27}FO_5$: C, 71.98; H, 6.04. Found: C, 71.91; H, 6.09.

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