Facile One-Pot Synthesis of Resorcinol Bis-*C*-Glycosides Possessing Two Identical Sugar Moieties

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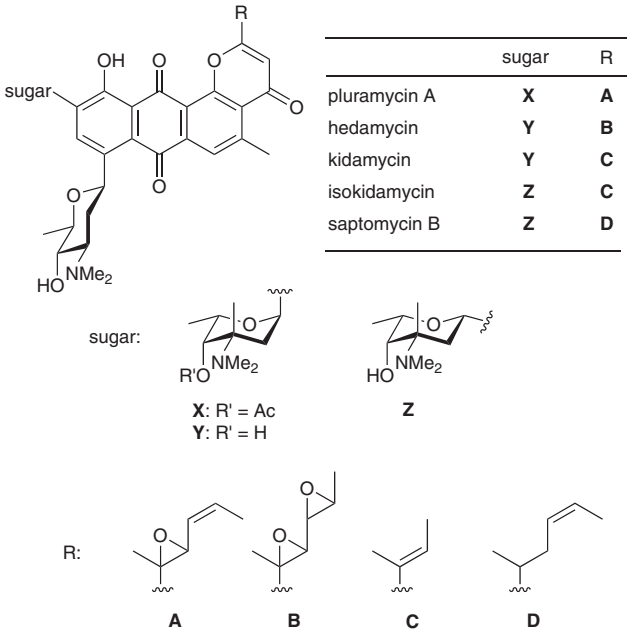
Abstract: Two identical *C*-glycoside moieties were efficiently installed in non-protected resorcinol derivatives by the $Sc(OTf)_3$-catalyzed one-pot procedure.

Key words: bis-*C*-glycoside, rearrangement reactions, resorcinol, scandium(III) triflate, pluramycin

In contrast to the majority of aryl *C*-glycoside antibiotics,[1] some members of the 4*H*-anthra[1,2-*b*]pyran *C*-glycoside family, such as the pluramycins,[2] uniquely have two *C*-glycoside residues (Figure 1). The two sugar residues effect highly sequence-selective interaction with DNA to make these molecules valuable probes in structural studies of DNA.[3]

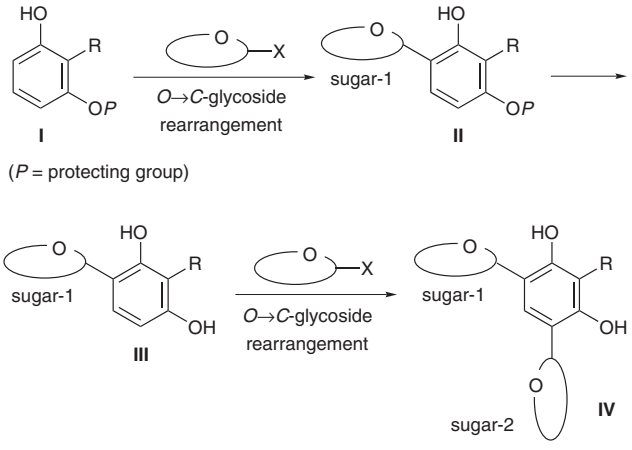


	sugar	R
pluramycin A	**X**	**A**
hedamycin	**Y**	**B**
kidamycin	**Y**	**C**
isokidamycin	**Z**	**C**
saptomycin B	**Z**	**D**

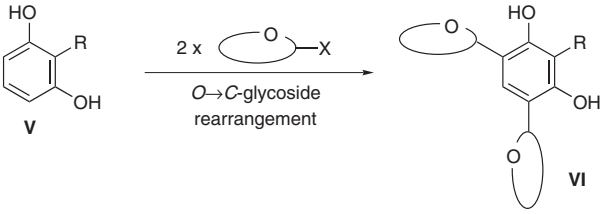
Figure 1 The pluramycin-type bis-*C*-glycoside antibiotics.

In our efforts toward the synthesis of these natural products, we previously reported an efficient approach for constructing the key bis-*C*-glycosyl arene structure by performing the *O*→*C*-glycoside rearrangement twice on a resorcinol derivative (Scheme 1).[4–6] Starting from mono-protected resorcinol **I**, a variety of aryl bis-*C*-glycosides **IV** possessing two identical or different sugar moieties were obtained by utilizing each of the two phenols as the pivot for ensuring regioselective *C*-glycoside formation. We found that the second *C*-glycoside formation was remarkably accelerated by liberating both of the phenols in the mono-*C*-glycoside precursor **III**, and was thereby efficiently catalyzed by various Lewis acids.

These results prompted us to examine the direct installation of two identical sugars onto non-protected resorcinol **V** in one pot as shown in Scheme 2. The reaction, if viable, would substantially simplify access to bis-*C*-glycosides possessing two identical sugars. The resulting bis-*C*-glycosides could serve as useful intermediates to the pluramycin analogues possessing two identical sugar moieties, which would give further insights into the DNA recognition by the *C*-glycoside structures. Now, we describe a facile procedure that realizes the envisioned one-pot bis-C-glycosylation.



Scheme 1 Bis-C-glycosylation of resorcinol derivatives by utilizing the *O*→*C*-glycoside rearrangement.



Scheme 2 One-pot bis-C-glycosylation.

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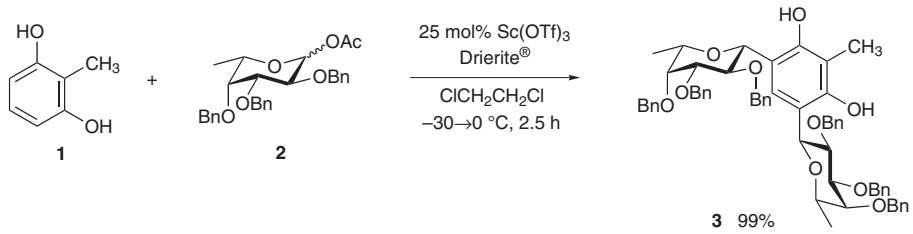


Scheme 3 $Sc(OTf)_3$-catalyzed one-pot bis-C-glycosylation of 2-methylresorcinol (**1**) with fucosyl acetate (**2**).

The initial study was carried out by the reaction of 2-methylresorcinol (**1**) and fucosyl acetate (**2**). Compound **1** and three equivalents of **2** were treated with 25 mol% $Sc(OTf)_3$ in the presence of Drierite® in 1,2-dichloroethane at –30 °C, and the reaction mixture was gradually warmed (Scheme 3). During warming, TLC analysis showed the appearance of some compounds, which converged to one at 0 °C. This final product proved to be the desired bis-*C*-glycoside **3**, whose structure was already verified in the preceding work.[4]

Scheme 4 shows the mechanism of the reaction; the product distribution was investigated by varying the final temperature. It was revealed that the O-glycosylation and the *C*-glycoside formation commenced at below –20 °C and made rapid progress in the temperature range –10 to 0 °C. Notably, the bis-*O*-glycoside **5** was not detected at any stage. This is probably because isomerization of mono-*O*-glycoside **4** to mono-*C*-glycoside **6** is still faster than bis-*O*-glycoside formation.[7]

Also notable are the configuration of the *C*-glycoside linkages in **6**, **7**, and **3**, which were entirely β at any stage. This shows that liberation of the two phenolic hydroxyls serves not only to accelerate the *C*-glycoside formation from the *O*-glycoside but also enables isomerization of the anomeric configuration of the *C*-glycoside linkage to the thermodynamically favored one.

To assess the scope of this one-pot double *C*-glycosylation, a range of glycosyl acetates derived from various sugars were subjected to the reaction with 2-methyl resorcinol (**1**) as the model acceptor (Table 1, entries 1–5).

Rhamnose-derived acetate **8** as a stereoisomer of **2**, 2-deoxy-sugar derived acetates **9** and **10**,[8] and amino-sugar derived acetates **10** and **11**,[9] gave the corresponding bis-*C*-glycosides in good to high yield. In every run, the intermediate *O*-glycoside, mono-*C*-glycoside, and mono-*O*-mono-*C*-glycoside were consumed by raising the reaction temperature, and in the meanwhile the α/β ratio of the *C*-glycoside fully changed to give the bis-β-*C*-glycoside as the sole stereoisomer.

Table 1 One-Pot Double *C*-Glycosylation

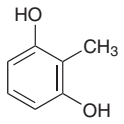
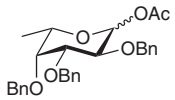
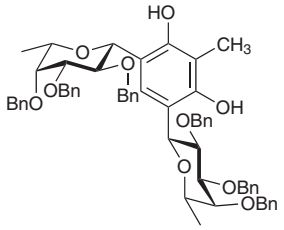
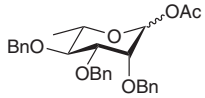
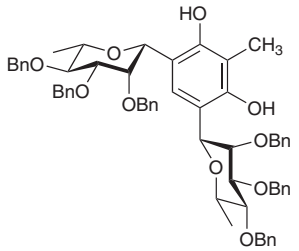
Entry	Resorcinol derivative	Glycosyl donor	Temp (°C)[a]	Product	Yield (%)
1	 **1**	 **2**	0	 **3**	99
2	**1**	 **8**	25	 **12**	79

Table 1 One-Pot Double *C*-Glycosylation (continued)

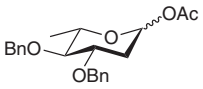
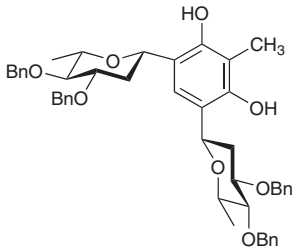
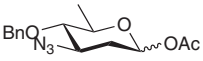
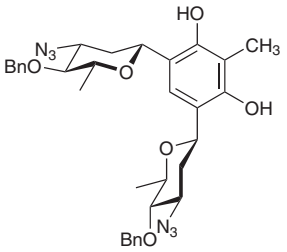
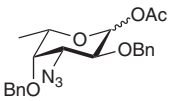
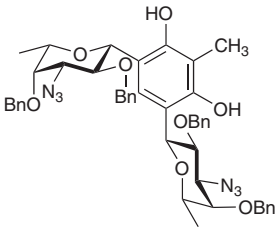
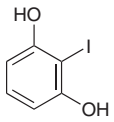
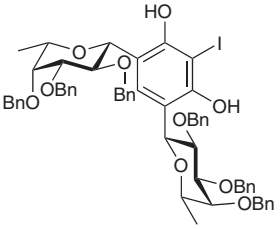
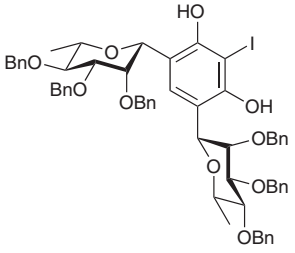
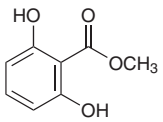
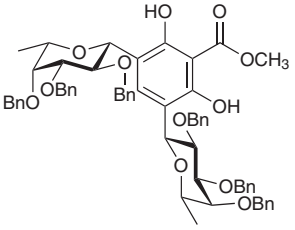
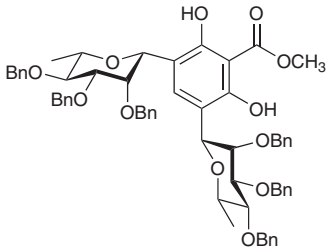
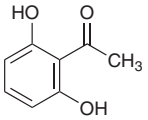
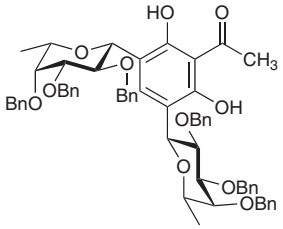
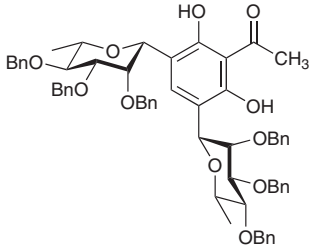
Entry	Resorcinol derivative	Glycosyl donor	Temp (°C)[a]	Product	Yield (%)
3	**1**	 **9**	–20	 **13**	91
4	**1**	 **10**	20	 **14**	62
5	**1**	 **11**	25	 **15**	86
6	 **16**	**2**	10	 **19**	98
7	**16**	**8**	25	 **20**	78
8	 **17**	**2**	5	 **21**	73

Table 1 One-Pot Double *C*-Glycosylation (continued)

Entry	Resorcinol derivative	Glycosyl donor	Temp (°C)[a]	Product	Yield (%)
9	**17**	**8**	15	 **22**	79
10	 **18**	**2**	–20	 **23**	55
11	**18**	**8**	20	 **24**	71

[a] The reaction, starting from –30 °C, was gradually warmed and quenched at this temperature.

Application to the three resorcinol derivatives, which differ in the C2 substituent, broadened the scope of the present method (Table 1, entries 6–11).

Iodine, ester, and ketone proved to be suitable substituents. Particularly notable is that the reaction is not affected by conjugation of the aromatic ring with an electron-accepting group (ester, ketone).

These C2 substituents, in association with the phenolic hydroxyls, would allow flexible manipulation of the aromatic ring and hence the synthesis of a variety of functionalized mono- and polyaromatic compounds with a bis-*C*-glycoside structure.

In summary, we have developed a facile procedure for the one-pot double C-glycosylation of non-protected resorcinol derivatives, which will find application in the synthesis of biologically significant analogues of natural bis-*C*-glycosides.

DCE was distilled over CaH_2. All experiments were performed under an Ar atmosphere. Melting points were determined on a Yanako MP-S3 apparatus and are uncorrected. Optical rotations were measured on a JASCO RIP-1000 polarimeter. IR spectra were obtained on a Horiba FT-710 spectrometer. NMR experiments were recorded on either a JEOL JNMAL-300 or Lambda-400 MHz, instrument. Combustion analyses were performed by the Microanalytical Laboratory, Department of Chemistry, Tokyo Institute of Technology on a Perkin-Elmer 2400 instrument.

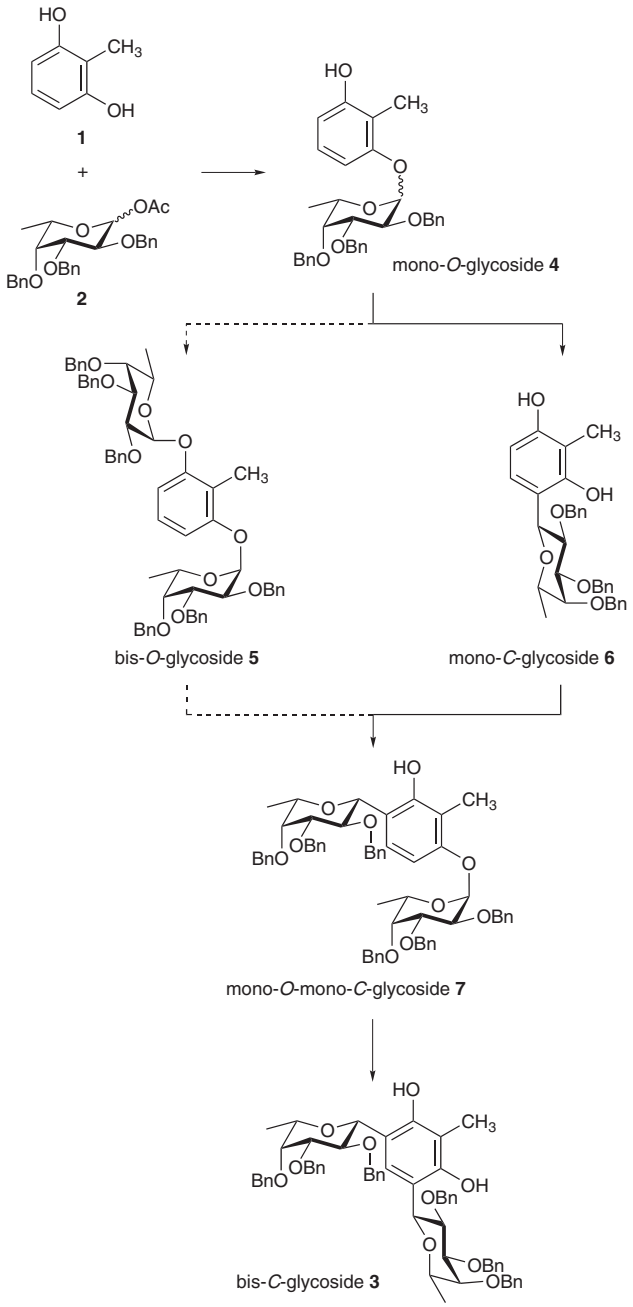
Bis-*C*-Glycosides; 1,3-Dihydroxy-2-methyl-4,6-bis(2,3,4-tri-*O*-benzyl-β-L-fucopyranosyl)benzene (3); Typical Procedure

To a stirred mixture of $Sc(OTf)_3$ (102 mg, 0.207 mmol), 2-methylresorcinol (**1**; 100 mg, 0.806 mmol), and powdered Drierite® (2.4 g) in DCE (20 mL), was added fucosyl acetate (**2**; 1.24 g, 2.60 mmol) in DCE (20 mL) at –30 °C. The mixture was gradually warmed to 0 °C over 1.5 h, stirred at this temperature for 1 h, and then poured into a sat. aq solution of $NaHCO_3$ (20 mL). After filtration through a pad of Celite, the products were extracted with EtOAc (1 × 60 mL, then 2 × 10 mL), and the combined organic extracts were washed with brine (20 mL), and dried over Na_2SO_4. Removal of the solvents in vacuo and purification by silica gel chromatography (hexane–acetone, 30:1) afforded *C*-glycoside **3**; colorless prisms (Et_2O); mp 131–132 °C; $[\alpha]_D^{30}$ –18 (*c* 1.0, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.26 (d, *J* = 6.0 Hz, 6 H), 2.17 (s, 3 H), 3.60–3.61 (m, 4 H), 3.71 (d, *J* = 1.6 Hz, 2 H), 3.84 (d, *J* = 10.2 Hz, 2 H), 4.14–4.15 (m, 4 H), 4.46 (d, *J* = 10.2 Hz, 2 H), 4.76 (d, *J* = 12.0 Hz, 2 H), 4.77 (d, *J* = 12.2 Hz, 2 H), 4.82 (d, *J* = 12.0 Hz, 2 H), 5.11 (d, *J* = 12.2 Hz, 2 H), 6.71 (s, 1 H), 7.04–7.41 (m, 30 H), 7.95 (s, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 8.2, 17.5, 72.7, 74.4, 74.6, 75.3, 76.6, 78.5, 82.3, 83.9, 113.6, 114.3, 127.3, 127.4, 127.48, 127.53, 127.90, 127.95, 128.2, 128.4, 128.7, 137.9, 138.56, 138.64, 154.9.

Anal. Calcd for $C_{61}H_{64}O_{10}$: C, 76.54; H, 6.74. Found: C, 76.24; H, 6.81.



Final temp. (°C)[a]	Yield (%)				
	2	**4**[b]	**6**[c]	**7**[d]	**3**[e]
–20	31	33	19	2	0
–15	27	20	20	15	8
–10	0	11	17	22	44
0	0	0	0	0	98

[a] The temperature at which the reaction was quenched.
[b] Total yield of the α-*O*- and β-*O*-glycosides.
[c] Yield of the β-*C*-glycoside. The α-*C*-glycoside was not detected.
[d] Yield of the α-*O*-β-*C*-glycoside. The β-*O*-β-*C*-glycoside was not detected.
[e] Yield of the bis-β-*C*-glycoside. Neither α-*C*-β-C- nor bis-α-*C*-glycoside was detected.

Scheme 4 Mechanism of the reaction of 2-methylresorcinol (**1**) and fucosyl acetate **2**.

1,3-Dihydroxy-2-methyl-4,6-bis(2,3,4-tri-*O*-benzyl-β-L-rhamnopyranosyl)benzene (12)
White foamy solid; mp 50–51 °C; $[\alpha]_D^{31}$ –19 (*c* 1.0, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.42 (d, *J* = 6.0 Hz, 6 H), 2.15 (s, 3 H), 3.47 (dq, *J* = 9.3, 6.0 Hz, 2 H), 3.66 (dd, *J* = 9.3, 2.2 Hz, 2 H), 3.70 (t, *J* = 9.3 Hz, 2 H), 3.91 (d, *J* = 2.2 Hz, 2 H), 4.36 (d, *J* = 11.1 Hz, 2 H), 4.36 (s, 2 H), 4.60 (d, *J* = 11.1 Hz, 2 H), 4.65 (d, *J* = 12.0 Hz, 2 H), 4.68 (d, *J* = 10.7 Hz, 2 H), 4.71 (d, *J* = 12.0 Hz, 2 H), 4.97 (d, *J* = 10.7 Hz, 2 H), 6.33 (s, 1 H), 7.13–7.34 (m, 30 H), 8.08 (s, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 8.2, 18.3, 72.0, 75.2, 75.6, 76.6, 79.1, 79.9, 82.5, 83.9, 113.3, 113.4, 123.8, 127.4, 127.5, 127.6, 127.8, 128.0, 128.1, 128.36, 128.39, 128.41, 137.8, 138.2, 138.3, 155.0.

Anal. Calcd for $C_{61}H_{64}O_{10}$: C, 76.54; H, 6.74. Found: C, 76.26; H, 6.69.

1,3-Dihydroxy-2-methyl-4,6-bis(3,4-di-*O*-benzyl-2-deoxy-β-L-*arabino*-hexopyranosyl)benzene (13)
Colorless needles (hexane); mp 76–77 °C, $[\alpha]_D^{30}$ –31 (*c* 1.0, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.38 (d, *J* = 6.0 Hz, 6 H), 1.94 (ddd, *J* = 13.6, 13.4, 11.9 Hz, 2 H), 2.12 (s, 3 H), 2.32 (ddd, *J* = 13.4, 5.0, 1.7 Hz, 2 H), 3.21 (dd, *J* = 9.2, 8.9 Hz, 2 H), 3.53 (dq, *J* = 9.2, 6.0 Hz, 2 H), 3.74 (ddd, *J* = 13.6, 8.9, 5.0 Hz, 2 H), 4.51 (dd, *J* = 11.9, 1.7 Hz, 2 H), 4.62 (d, *J* = 11.8 Hz, 2 H), 4.69 (d, *J* = 11.0 Hz, 2 H), 4.70 (d, *J* = 11.8 Hz, 2 H), 4.99 (d, *J* = 11.0 Hz, 2 H), 6.42 (s, 1 H), 7.27–7.33 (m, 20 H), 7.95 (s, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 7.9, 18.6, 37.4, 71.3, 75.4, 76.1, 78.4, 80.3, 83.5, 114.0, 116.0, 121.4, 127.58, 127.63, 127.8, 128.1, 128.39, 128.41, 138.27, 138.33, 154.1.

Anal. Calcd for $C_{47}H_{52}O_8$: C, 75.78; H, 7.04. Found: C, 75.89; H, 7.04.

1,3-Dihydroxy-2-methyl-4,6-bis(2-azido-4-*O*-benzyl-2,3-dideoxy-β-D-*arabino*-hexopyranosyl)benzene (14)
Colorless plates (EtOAc–hexane); mp 161–162 °C, $[\alpha]_D^{30}$ +32 (*c* 1.5, $CHCl_3$).

IR (KBr): 2100 cm^{-1} (N=N=N).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.39 (d, *J* = 6.0 Hz, 6 H), 1.92 (ddd, *J* = 13.2, 12.0, 11.7 Hz, 2 H), 2.11 (s, 3 H), 2.21 (ddd, *J* = 13.2, 4.8, 1.8 Hz, 2 H), 3.09 (t, *J* = 9.3 Hz, 2 H), 3.56 (dq, *J* = 9.3, 6.0 Hz, 2 H), 3.67 (ddd, *J* = 12.0, 9.3, 4.8 Hz, 2 H), 4.56 (dd, *J* = 11.7, 1.8 Hz, 2 H), 4.66 (d, *J* = 10.7 Hz, 2 H), 4.91 (d, *J* = 10.7 Hz, 2 H), 6.44 (s, 1 H), 7.31–7.39 (m, 10 H), 7.80 (s, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 7.9, 18.5, 37.2, 63.4, 75.4, 76.6, 78.4, 83.1, 114.2, 115.6, 121.5, 128.1, 128.3, 128.5, 137.3, 154.0.

Anal. Calcd for $C_{33}H_{38}N_6O_6$: C, 64.48; H, 6.23; N, 13.67. Found: C, 64.49; H, 6.51; N, 13.41.

1,3-Dihydroxy-2-methyl-4,6-bis(3-azido-2,4-di-*O*-benzyl-3,6-dideoxy-β-L-galactopyranosyl)benzene (15)
Amorphous solid; mp 57–58 °C; $[\alpha]_D^{31}$ +56 (*c* 1.1, $CHCl_3$).

IR (NaCl): 2100 cm^{-1} (N=N=N).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.26 (d, *J* = 6.3 Hz, 6 H), 2.21 (s, 3 H), 3.59–3.66 (m, 8 H), 4.11 (s, 4 H), 4.39 (d, *J* = 9.9 Hz, 2 H), 4.71 (d, *J* = 11.7 Hz, 2 H), 5.02 (d, *J* = 11.7 Hz, 2 H), 6.64 (s, 1 H), 7.10–7.44 (m, 20 H), 7.90 (s, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 8.1, 17.2, 66.8, 74.7, 75.1, 75.3, 77.4, 77.8, 82.7, 113.8, 114.1, 127.3, 127.7, 127.8, 127.97, 128.02, 128.4, 128.9, 137.1, 137.8, 155.3.

Anal. Calcd for $C_{47}H_{50}N_6O_8$: C, 68.26; H, 6.09; N, 10.16. Found: C, 68.00; H, 6.13; N, 9.90.

1,3-Dihydroxy-2-iodo-4,6-bis(2,3,4-tri-*O*-benzyl-β-L-fucopyranosyl)benzene (19)

Amorphous solid; mp 60–61 °C; $[\alpha]_D^{30}$ +31 (*c* 1.4, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.24 (d, *J* = 6.3 Hz, 6 H), 3.58–3.64 (m, 4 H), 3.70 (d, *J* = 2.2 Hz, 2 H), 3.87 (d, *J* = 10.5 Hz, 2 H), 4.05–4.15 (m, 4 H), 4.51 (d, *J* = 10.5 Hz, 2 H), 4.72–4.80 (m, 4 H), 4.78 (d, *J* = 11.9 Hz, 2 H), 5.07 (d, *J* = 11.9 Hz, 2 H), 6.82 (s, 1 H), 6.99–7.02 (m, 4 H), 7.12–7.17 (m, 6 H), 7.27–7.40 (m, 20 H), 8.70 (s, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 17.4, 72.6, 74.3, 74.8, 75.3, 75.4, 76.0, 78.2, 81.6, 83.9, 114.6, 127.3, 127.5, 127.6, 128.0, 128.2, 128.3, 128.4, 128.6, 130.6, 137.6, 138.3, 138.4, 156.0.

Anal. Calcd for $C_{60}H_{61}IO_{10}$: C, 67.41; H, 5.75. Found: C, 67.25; H, 5.82.

1,3-Dihydroxy-2-iodo-4,6-bis(2,3,4-tri-*O*-benzyl-β-L-rhamnopyranosyl)benzene (20)

Colorless oil; $[\alpha]_D^{28}$ +3.9 (*c* 1.4, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.41 (d, *J* = 6.1 Hz, 6 H), 3.44–3.53 (m, 2 H), 3.65–3.74 (m, 4 H), 3.94 (br s, 2 H), 4.29 (d, *J* = 11.5 Hz, 2 H), 4.44 (s, 2 H), 4.59 (d, *J* = 11.5 Hz, 2 H), 4.63–4.73 (m, 6 H), 4.95 (d, *J* = 10.7 Hz, 2 H), 6.76 (s, 1 H), 7.06–7.35 (m, 30 H), 8.13 (s, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.3, 72.1, 74.8, 75.6, 77.4, 77.7, 78.3, 79.9, 80.5, 84.0, 114.4, 127.2, 127.4, 127.5, 127.7, 127.8, 128.08, 128.13, 128.14, 128.40, 128.43, 137.7, 138.2, 138.3, 154.8.

Anal. Calcd for $C_{60}H_{61}IO_{10}$: C, 67.41; H, 5.75. Found: C, 67.16; H, 5.52.

Methyl 2,6-Dihydroxy-3,5-bis(2,3,4-tri-*O*-benzyl-β-L-fucopyranosyl)benzoate (21)

Amorphous solid; mp 54–55 °C; $[\alpha]_D^{26}$ –8.6 (*c* 1.1, $CHCl_3$).

IR (NaCl): 1655 cm^{-1} (O=C–O).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.19 (d, *J* = 6.4 Hz, 6 H), 3.58–3.65 (m, 2 H), 3.67–3.70 (m, 4 H), 4.02 (s, 3 H), 4.02 (d, *J* = 10.8 Hz, 2 H), 4.14 (dd, *J* = 9.7, 9.5 Hz, 2 H), 4.57 (d, *J* = 9.5 Hz, 2 H), 4.43 (d, *J* = 10.8 Hz, 2 H), 4.70–4.77 (m, 6 H), 5.07 (d, *J* = 12.1 Hz, 2 H), 6.95–6.98 (m, 4 H), 7.10–7.12 (m, 6 H), 7.23–7.43 (m, 20 H), 7.68 (s, 1 H), 10.1 (s, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 17.4, 52.6, 72.7, 74.4, 74.7, 76.7, 77.3, 79.1, 84.8, 103.0, 117.6, 127.1, 127.36, 127.41, 127.44, 127.7, 127.97, 128.01, 128.1, 128.3, 135.7, 138.3, 138.7, 138.9, 158.6, 170.7.

Anal. Calcd for $C_{62}H_{64}O_{12}$: C, 74.38; H, 6.44. Found: C, 74.12; H, 6.30.

Methyl 2,6-Dihydroxy-3,5-bis(2,3,4-tri-*O*-benzyl-β-L-rhamnopyranosyl)benzoate (22)

Granular crystals (Et_2O–hexane); mp 112–114 °C; $[\alpha]_D^{29}$ –43 (*c* 1.0, $CHCl_3$).

IR (NaCl): 1670 cm^{-1} (O=C–O).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.43 (d, *J* = 6.0 Hz, 6 H), 3.51 (dq, *J* = 8.4, 6.4 Hz, 2 H), 3.71 (dd, *J* = 9.6, 8.4 Hz, 2 H), 3.75 (dd, *J* = 9.6, 1.6 Hz, 2 H), 4.04 (s, 3 H), 4.13 (d, *J* = 1.6 Hz, 2 H), 4.21 (d, *J* = 11.7 Hz, 2 H), 4.52 (d, *J* = 11.7 Hz, 2 H), 4.64 (s, 2 H), 4.68 (d, *J* = 10.8 Hz, 2 H), 4.69 (d, *J* = 11.8 Hz, 2 H), 4.74 (d, *J* = 11.8 Hz, 2 H), 4.96 (d, *J* = 10.8 Hz, 2 H), 7.01–7.04 (m, 4 H), 7.08–7.10 (m, 6 H), 7.22–7.39 (m, 20 H), 7.84 (s, 1 H), 9.85 (s, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.4, 52.6, 71.9, 74.4, 75.2, 75.4, 76.3, 80.5, 84.5, 99.1, 117.0, 126.9, 127.4, 127.5, 127.6, 127.7, 128.06, 128.11, 128.31, 128.34, 134.9, 138.5, 138.6, 138.7, 155.8, 170.7.

Anal. Calcd for $C_{62}H_{64}O_{12}$: C, 74.38; H, 6.44. Found: C, 74.10; H, 6.57.

1-[2,6-Dihydroxy-3,5-bis(2,3,4-tri-*O*-benzyl-β-L-fucopyranosyl)phenyl]ethanone (23)

Colorless oil; $[\alpha]_D^{27}$ –21 (*c* 3.1, $CHCl_3$).

IR (NaCl): 1622 cm^{-1} (C=O).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.24 (d, *J* = 6.4 Hz, 6 H), 2.69 (s, 3 H), 3.63 (q, *J* = 6.4 Hz, 2 H), 3.68 (dd, *J* = 9.2, 2.5 Hz, 2 H), 3.71 (q, *J* = 2.5 Hz, 2 H), 3.91 (d, *J* = 10.9 Hz, 2 H), 4.04 (dd, *J* = 9.4, 9.2 Hz, 2 H), 4.28 (d, *J* = 10.9 Hz, 2 H), 4.56 (d, *J* = 9.4 Hz, 2 H), 4.71 (s, 4 H), 4.75 (d, *J* = 11.8 Hz, 2 H), 5.11 (d, *J* = 11.8 Hz, 2 H), 6.90–6.95 (m, 4 H), 7.06–7.13 (m, 6 H), 7.24–7.48 (m, 20 H), 7.59 (s, 1 H), 11.23 (br, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$, 40 °C): δ = 17.4, 33.7, 72.6, 74.5, 74.56, 74.59, 77.2, 78.1, 79.1, 84.5, 110.8, 117.1, 127.1, 127.3, 127.41, 127.45, 127.48, 127.8, 128.0, 128.2, 128.3, 135.8, 138.3, 138.6, 138.8, 160.3, 205.7.

Anal. Calcd for $C_{62}H_{64}O_{11}$: C, 75.59; H, 6.55. Found: C, 75.38; H, 6.34.

1-[2,6-Dihydroxy-3,5-bis(2,3,4-tri-*O*-benzyl-β-L-rhamnopyranosyl)phenyl]ethanone (24)

Colorless oil; $[\alpha]_D^{27}$ –48 (*c* 1.1, $CHCl_3$).

IR (NaCl): 1622 cm^{-1} (C=O).

^{1}H NMR (500 MHz, DMSO-d_6): δ = 1.28 (d, *J* = 5.1 Hz, 6 H), 2.53 (s, 3 H), 3.49–3.54 (m, 4 H), 3.83–3.86 (m, 2 H), 3.99 (d, *J* = 11.5 Hz, 2 H), 4.06 (d, *J* = 2.4 Hz, 2 H), 4.43 (d, *J* = 11.5 Hz, 2 H), 4.63 (d, *J* = 11.8 Hz, 2 H), 4.64 (d, *J* = 11.1 Hz, 2 H), 4.73 (d, *J* = 11.8 Hz, 2 H), 4.80 (s, 2 H), 4.84 (d, *J* = 11.1 Hz, 2 H), 7.05–7.07 (m, 4 H), 7.15–7.20 (m, 6 H), 7.27–7.40 (m, 20 H), 7.58 (s, 1 H), 11.45 (br, 2 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 19.1, 34.3, 71.7, 75.0, 75.2, 76.2, 76.9, 77.5, 80.6, 83.9, 110.8, 116.9, 128.1, 128.19, 128.27 (2 C), 128.35, 128.7, 128.8, 129.06, 129.13, 135.4, 139.2, 139.5, 158.6, 206.6.

Anal. Calcd for $C_{62}H_{64}O_{11}$: C, 75.59; H, 6.55. Found: C, 75.36; H, 6.42.

Mechanistic Study (Scheme 4)

The reaction of 2-methylresorcinol (**1**) and fucosyl acetate (**2**) was quenched after warming to –20 °C, –15 °C, or –10 °C. The crude mixture was carefully purified by silica gel chromatography (hexane–acetone, 30:1) to give mono-*O*-mono-*C*-glycoside **7**, bis-*C*-glycoside **3**, mono-α-*O*-glycoside α-**4**, mono-*C*-glycoside **6**, and a mixture of mono-*C*-glycoside **6** and mono-β-*O*-glycoside β-**4**, which were eluted in that order.

3-Hydroxy-2-methylphenyl 2,3,4-Tri-*O*-benzyl-α- and -β-L-fucopyranoside (α-4 and β-4)

α-4

Colorless oil; $[\alpha]_D^{22}$ –74 (*c* 1.3, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.11 (d, *J* = 6.4 Hz, 3 H), 2.15 (s, 3 H), 3.71 (d, *J* = 2.6 Hz, 1 H), 4.00 (q, *J* = 6.4 Hz, 1 H), 4.14 (dd, *J* = 10.2, 2.6 Hz, 1 H), 4.20 (dd, *J* = 10.2, 3.2 Hz, 1 H), 4.66 (d, *J* = 11.4 Hz, 1 H), 4.69 (d, *J* = 11.4 Hz, 1 H), 4.79 (d, *J* = 11.2 Hz, 1 H), 4.81 (d, *J* = 12.0 Hz, 1 H), 4.82 (s, 1 H), 4.92 (d, *J* = 12.0 Hz, 1 H), 5.03 (d, *J* = 11.2 Hz, 1 H), 5.47 (d, *J* = 3.2 Hz, 1 H), 6.47 (d,

J = 8.0 Hz, 1 H), 6.70 (d, *J* = 8.4 Hz, 1 H), 6.95 (dd, *J* = 8.4, 8.0 Hz, 1 H), 7.21–7.43 (m, 15 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 8.4, 16.7, 67.3, 72.9, 73.2, 74.9, 76.4, 77.7, 78.8, 97.0, 107.6, 109.0, 113.8, 126.4, 127.3, 127.4, 127.5, 127.6, 128.1, 128.28, 128.34, 138.45, 138.50, 138.7, 154.3, 156.5.

Anal. Calcd for $C_{34}H_{36}O_6$: C, 75.53; H, 6.71. Found: C, 75.77; H, 6.96.

β-4 (Selected Data)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.18 (s, 3 H, ArCH_3), 4.95 (d, *J* = 7.7 Hz, 1 H, anomeric H), 6.48 (d, *J* = 8.0 Hz, 1 H, *ortho* to OH), 6.63 (d, 1 H *J* = 8.0 Hz, *para* to OH), 6.97 (t, *J* = 8.0 Hz, 1 H, *meta* to OH).

1,3-Dihydroxy-2-methyl-4-(2,3,4-tri-*O*-benzyl-β-L-fucopyranosyl)benzene (6)

Colorless oil; $[\alpha]_D^{28}$ +16 (*c* 3.5, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.21 (d, *J* = 6.4 Hz, 3 H), 2.14 (s, 3 H), 3.59 (q, *J* = 6.4 Hz, 1 H), 3.63 (dd, *J* = 2.4, 8.9 Hz, 1 H), 3.69 (d, *J* = 2.4 Hz, 1 H), 3.92 (d, *J* = 10.1 Hz, 1 H), 4.16 (dd, *J* = 9.4, 8.9 Hz, 1 H), 4.24 (d, *J* = 9.4 Hz, 1 H), 4.44 (d, *J* = 10.1 Hz, 1 H), 4.74 (d, *J* = 12.0 Hz, 1 H), 4.76 (d, *J* = 12.0 Hz, 1 H), 4.79 (d, *J* = 12.0 Hz, 1 H), 4.92 (s, 1 H), 5.10 (d, *J* = 12.0 Hz, 1 H), 6.30 (d, *J* = 8.2 Hz, 1 H), 6.85 (d, *J* = 8.2 Hz, 1 H), 7.02–7.08 (m, 2 H), 7.16–7.42 (m, 13 H), 7.93 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 8.0, 17.4, 72.7, 74.4, 74.5, 75.3, 76.5, 78.0, 82.2, 83.9, 106.0, 111.8, 116.0, 126.9, 127.4, 127.5, 127.58, 127.62, 127.9, 128.1, 128.2, 128.4, 128.6, 137.8, 138.48, 138.52, 154.8, 155.0.

Anal. Calcd for $C_{34}H_{36}O_6$: C, 75.53; H, 6.71. Found: C, 75.28; H, 6.86.

3-Hydroxy-2-methyl-4-(2,3,4-Tri-*O*-benzyl-β-L-fucopyranosyl)phenyl 2,3,4-Tri-*O*-benzyl-α-L-fucopyranoside (7)

Colorless oil; $[\alpha]_D^{21}$ –33 (*c* 1.2, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.08 (d, *J* = 6.8 Hz, 3 H), 1.22 (d, *J* = 6.4 Hz, 3 H), 2.18 (s, 3 H), 3.60 (q, *J* = 6.4 Hz, 1 H), 3.64 (dd, *J* = 9.2, 2.8 Hz, 1 H), 3.71 (d, *J* = 1.6 Hz, 2 H), 3.91 (d, *J* = 10.0 Hz, 1 H), 3.98 (q, *J* = 6.8 Hz, 1 H), 4.15–4.20 (m, 3 H), 4.25 (d, *J* = 9.2 Hz, 1 H), 4.45 (d, *J* = 10.0 Hz, 1 H), 4.67–4.70 (m, 2 H), 4.74–4.83 (m, 5 H), 4.92 (d, *J* = 12.0 Hz, 1 H), 5.02 (d, *J* = 11.6 Hz, 1 H), 5.11 (d, *J* = 12.0 Hz, 1 H), 5.48 (d, *J* = 2.8 Hz, 1 H), 6.60 (d, *J* = 8.6 Hz, 1 H), 6.89 (d, *J* = 8.6 Hz, 1 H), 7.01–7.04 (m, 2 H), 7.11–7.43 (m, 28 H), 7.89 (s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 8.6, 16.6, 17.4, 67.3, 72.7, 73.1, 73.3, 74.4, 74.5, 74.9, 75.3, 76.4, 76.5, 77.3, 77.7, 78.0, 79.0, 82.3, 84.0, 96.9, 106.1, 115.8, 117.4, 126.8, 127.37, 127.44, 127.53, 127.59, 127.63, 127.9, 128.19, 128.22, 128.26, 128.36, 128.40, 128.42, 128.5, 137.8, 138.5, 138.6, 138.7, 138.8, 154.5, 156.6.

Anal. Calcd for $C_{61}H_{64}O_{10}$: C, 76.54; H, 6.74. Found: C, 76.79; H, 6.71.

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(7) Another possible explanation is that bis-*O*-glycoside **5**, once formed immediately rearranges to mono-*O*-mono-*C*-glycoside **7**. However, this is unlikely since it was previously shown that protection of one hydroxyl group of a resorcinol derivative remarkably retards the *O*→*C*-glycoside rearrangement at the other hydroxyl; see ref. 4.

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