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α-Selective Ribofuranosylation of Alcohols with Ribofuranosyl Iodides and Triphenylphosphine Oxide

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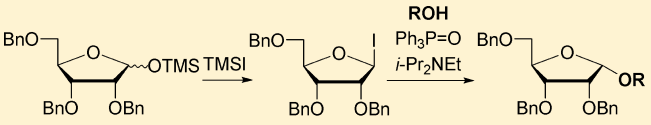
Supporting Information

ABSTRACT: Ribofuranosylation of a variety of alcohols with ribofuranosyl iodides in the presence of a base and triphenylphosphine oxide afforded the corresponding α-ribofuranosides with diastereoselectivities ≥ 99:1. This reaction can be carried out under mildly basic conditions and is thus compatible with acid-sensitive functional groups.



α-Ribofuranosides are key components of various natural products and biomolecules[1,2] such as lampteroflavin[1a,b] and poly(ADP)ribose.[1c,d] Because many such ribofuranosides have intriguing biological activities, the stereocontrolled synthesis of α-ribofuranosides has attracted much attention in recent decades, and a variety of α-selective ribofuranosylation reactions have been developed.[3,4] Glycosyl donors such as thioribofuranosides[4a,b] and ribofuranosyl imidates[1b,4c] are activated by Lewis acids to generate active oxocarbenium ions, which then react with nucleophiles to yield α-ribofuranosides preferentially.[4] Various α-ribofuranosides, including lampteroflavin[1b] and 2′-*O*-(α-D-ribofuranosyl)adenosine,[4c] have been synthesized using such Lewis acid promoted glycosylation reactions. However, the yield and α-selectivity are highly dependent on the structure of the substrate. Moreover, these methods are generally not applicable to the synthesis of acid-sensitive molecules. Mukaiyama et al. have also developed a series of efficient α-selective ribofuranosylation reactions[5] wherein the β-face of the oxocarbenium ion generated upon the activation of glycosyl donors is covered by a perchlorate anion, inducing an α-selective nucleophilic attack;[5,6] however, the α-selectivity is still affected by the structure of the substrates. Moreover, the explosive perchlorate salts and heavy metal compounds such as toxic tin reagents[5a−e] that are used in most of these reactions[5a−i] should be replaced by less hazardous reagents. Furthermore, many of these transformations rely on Lewis acids for the activation of the glycosyl donors, and thus, their application to the synthesis of acid-sensitive molecules is once again limited. Besides the acid-catalyzed reactions, Schmidt et al.[7] have developed the anomeric *O*-alkylation of 2,3,5-protected ribofuranoses in the presence of NaH, while Mukaiyama et al.[8] reported the condensation of a 2,3,5-protected ribofuranose with alcohols in the presence of $LiNTf_2$ and catalytic $Ph_3C^+B(C_6F_5)_4^-$, which they proposed to work cooperatively to isomerize the resulting ribofuranosides to the α-isomers. Both of these reactions afford α-ribofuranosides with almost complete α-selectivity. However, these methods have not been widely applied to the synthesis of α-ribofuranosides.

Under these circumstances, we developed a versatile, heavy-metal-free α-selective ribofuranosylation of alcohols that can be carried out under mildly basic conditions using glycosyl iodides as the glycosyl donors. Glycosyl iodides have been extensively used as glycosyl donors in the synthesis of pyranosides under mildly basic conditions.[9,10] In contrast, furanosyl iodides,[11,12] particularly ribofuranosyl iodides,[11] have not been studied in depth and their properties as glycosyl donors have not yet been fully explored. Thus, we investigated the synthesis of ribofuranosyl iodides and their application to the ribofuranosylation of alcohols to develop a novel α-selective ribofuranosylation reaction.

The compound 1-*O*-trimethylsilyl-2,3,5-tri-*O*-benzyl-D-ribofuranose **1**[5d] was chosen as the starting material, and the ribofuranosyl iodide **2** was synthesized via treatment of **1** with TMSI at 0 °C. TLC monitoring of the reaction showed that compound **1** was completely consumed within 0.5−1 h. Only the crude form of **2** was characterized by ^1H NMR analysis in $CDCl_3$ at low temperature, because the ribofuranosyl iodide **2** was unstable and decomposed even at 0 °C, albeit very slowly. The signal attributable to the anomeric proton of the major product appeared in the spectrum as a singlet at 6.61 ppm,[13] indicating that the major product was the β-ribofuranosyl iodide **2**.

Ribofuranosylation reactions of alcohols using **2** were conducted in one pot from **1**. First, cyclopentanol was used as the glycosyl acceptor to optimize the reaction conditions (Table 1). It has been reported that glycosyl iodides react with alcohols in the presence of tertiary amines, such as *i*-Pr_2NEt.[9,10,12] As shown in entry 1, **2** reacted with cyclopentanol in the presence of *i*-Pr_2NEt to afford the corresponding ribofuranoside **3a** with excellent yield and α-selectivity. The α-selectivity could be improved to >99:1 when **2** was treated with cyclopentanol at −40 °C, though the reaction did not proceed to completion even after 2 h (entry 2). The use of Et_3N, 1,8-bis(dimethylamino)naphthalene (DMAN), and 2,6-di-*tert*-

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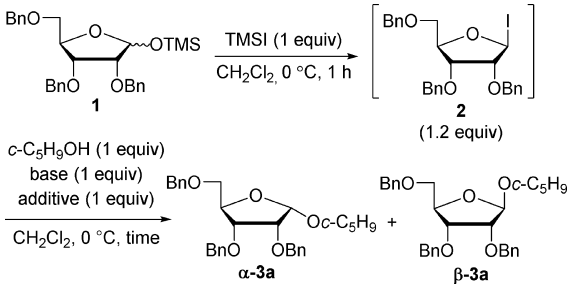
Table 1. Ribofuranosylation of Cyclopentanol with Ribofuranosyl Iodide 2



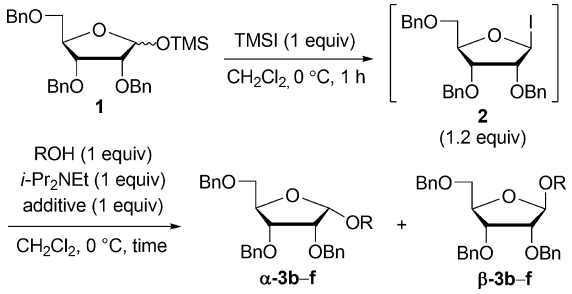
entry	base	additive	time (h)	yield (%)[b]	**α**-3a:**β**-3a
1	*i*-Pr_2NEt		0.5	97	98:2[c]
2[a]	*i*-Pr_2NEt		2	69	>99:1[c]
3	Et_3N		0.5	63	97:3[c]
4	DMAN		0.5	85	95:5[c]
5	DTBMP		0.5	78	87:13[c]
6	*i*-Pr_2NEt	TBAI	0.5	62	83:17[d]
7	*i*-Pr_2NEt	TPPO	0.5	89	99:1[c]
8[a]	*i*-Pr_2NEt	TPPO	2	49	99:1[c]
9	Et_3N	TPPO	0.5	78	>99:1[c]
10	DMAN	TPPO	0.5	87	>99:1[c]
11	DTBMP	TPPO	0.5	84	96:4[c]
12		TPPO	1	92	55:45[d]

[a]Reaction of **2** with cyclopentanol was carried out at −40 °C. [b]Isolated yield of **3a**. [c]Determined by HPLC. [d]Determined by ^{1}H NMR.

butyl-4-methylpyridine (DTBMP) gave comparable or lower α-selectivities (entries 3−5). To further improve the α-selectivity, tetrabutylammonium iodide (TBAI), which has been reported to improve the α-selectivity of glycopyranosylations with glycopyranosyl iodides,[9,10] was employed as an additive. However, both the α-selectivity and the yield of **3a** decreased under these conditions (entry 6). Subsequently, we tested triphenylphosphine oxide (TPPO) as an additive, because phosphine oxides have also been reported by Mukaiyama et al. to improve the α-selectivity of glycopyranosylations using glycopyranosyl iodides, with TPPO giving some of the best results.[9g] We determined that **α-3a** was obtained with d.r. 99:1, although in a slightly lower yield (entry 8). The addition of TPPO at −40 °C did not improve the yield of **α-3a** (entry 2 vs 8). Neither the generation of **2** nor its reaction with cyclopentanol proceeded at −78 °C (data not shown). TPPO was found to suppress the generation of **β-3a** irrespective of the base used (entries 1, 3−5 vs entries 7, 9−11). However, the reaction in the absence of a base afforded **3a** as a 55:45 mixture of diastereomers, though the yield was still high (entry 12). This result can be attributed to the anomerization of the resultant **α-3a** by strongly acidic HI. The relatively low α/β ratios in entries 5 and 11 may also be attributable to the weak basicity of DTBMP.

Next, the scope of the reaction was investigated using 1°, 2°, and 3° alcohols. As shown in Table 2, entries 1−5, the desired α-ribofuranosides were obtained with d.r. ≥ 99:1 from alcohols with various levels of steric hindrance. As in the case of cyclopentanol (Table 1), the use of TBAI as an additive resulted in the generation of diastereomixtures, although the α-isomers were still generated preferentially (entries 6−10). We conducted the ribofuranosylation of 3-phenylpropanol and *t*-BuOH in the absence of TPPO, because the ribofuranosylation of cyclopentanol in the absence of TPPO afforded **α-3a** with

Table 2. Ribofuranosylation of Various Alcohols with Ribofuranosyl Iodide 2



entry	ROH	additive	time (h)	**3**	yield (%)[a,b]
1	$Ph(CH_2)_3OH$	TPPO	0.5	**3b**	84 (99:1[c])
2	*i*-PrOH	TPPO	0.5	**3c**	70 (99:1[c])
3	*c*-$C_6H_{11}OH$	TPPO	0.5	**3d**	88 (>99:1[c])
4	*l*-menthol	TPPO	1	**3e**	84 (>99:1[c])
5	*t*-BuOH	TPPO	2	**3f**	71 (99:1[c])
6	$Ph(CH_2)_3OH$	TBAI	0.5	**3b**	55 (89:11[d])
7	*i*-PrOH	TBAI	0.5	**3c**	76 (87:13[d])
8	*c*-$C_6H_{11}OH$	TBAI	0.5	**3d**	80 (82:18[d])
9	*l*-menthol	TBAI	1	**3e**	67 (78:22[d])
10	*t*-BuOH	TBAI	2	**3f**	67 (90:10[d])
11	$Ph(CH_2)_3OH$		0.5	**3b**	74 (97:3[c])
12	*t*-BuOH		1	**3f**	91 (89:11[c])
13[e]	*t*-BuOH		2	**3f**	83 (>99:1[c])

[a]Isolated yield of **3a**. [b]d.r. (**α**-3:**β**-3) are given in parentheses. [c]Determined by HPLC. [d]Determined by ^{1}H NMR. [e]DMAN was used in place of *i*-Pr_2NEt.

excellent α-selectivity (Table 1, entry 1). When *i*-Pr_2NEt was used as the base, the α-selectivity decreased, particularly with *t*-BuOH (entries 11 and 12). In contrast, only the α-ribofuranoside was obtained from *t*-BuOH when DMAN was used. These results show that, while ribofuranosylation is still highly α-selective in the absence of TPPO, the α-selectivity is dependent on both the glycosyl acceptor and the base. The addition of TPPO suppressed the generation of the β-ribofuranoside virtually completely under various reaction conditions.

Next, the new method was applied to the synthesis of both ribofuranosides bearing selected functional groups and disaccharides (Figure 1). α-Ribofuranosides with a C=C bond, amino group, or trityl ether (**α-3g−i**) were obtained in good yields under the same conditions as those used for the synthesis of **α-3a−f**. The compatibility of the amino group and the acid-sensitive trityl ether has demonstrated the advantage of this base-promoted reaction. The method was also applicable to the α-selective synthesis of disaccharides **α-3j−o**. For the synthesis of **α-3j−o**, 1.5 molar equiv of **1** and TMSI relative to the glycosyl acceptors were needed to achieve comparable yields. The synthesis of **α-3o** required an extended reaction time (4.5 h) due to the sterically hindered 2° hydroxy group of 1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose. Notably, for all of these reactions, the corresponding β-isomers could not be detected in the crude mixtures by ^{1}H NMR.

Next, we explored the possibility that the α-selective ribofuranosylation reaction could be carried out without TMSI and a base to expand the scope of substrates. Being inspired by the studies in which glycopyranosyl iodides were generated by the activation of glycosyl phosphites with ammonium iodides,[14] we were able to find that the

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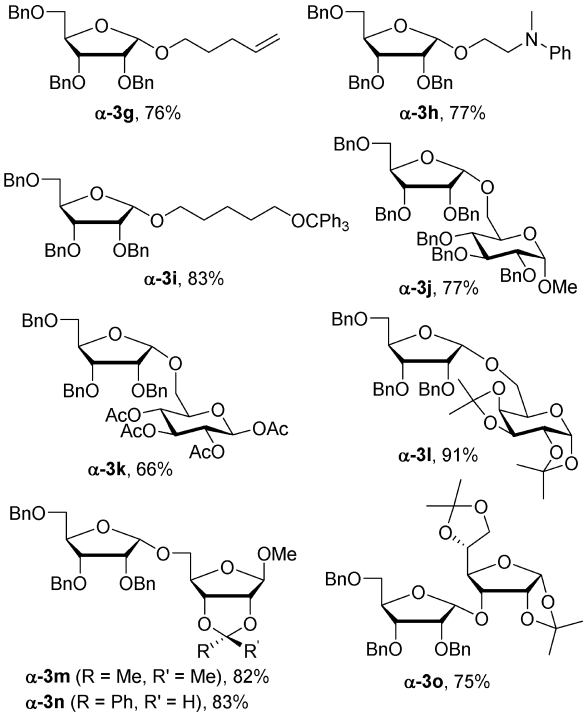
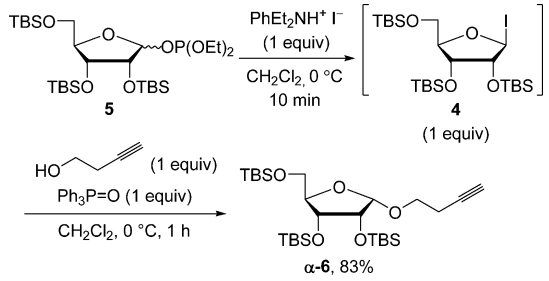


Figure 1. α-Ribofuranosides **α-3g–o** synthesized from ribofuranosyl iodide **2**.

ribofuranosyl iodide **4** could be generated by the activation of the ribofuranosyl phosphite **5** with weakly acidic *N*,*N*-diethylanilinium iodide. Subsequent addition of 3-butyn-1-ol and TPPO gave the corresponding α-ribofuranoside (**α-6**) in good yield with complete α-selectivity (Scheme 1). It is notable

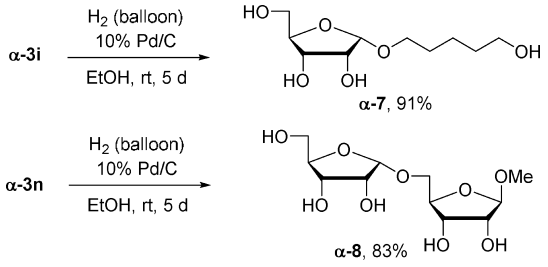
Scheme 1. α-Selective Ribofuranosylation Using Ribofuranosyl Phosphite 5 as Glycosyl Donor



that the silyl-protected glycosyl donor also afforded the coresponding α-ribofuranoside with complete stereoselectivity, indicating that functional groups incompatible with reductive conditions to remove Bn groups (e.g., alkynyl group) can be used.

Finally, three representative products (**α-3i,m,n**) were selected for deprotection. Hydrogenolysis of compounds **α-3i** and **α-3n** (H_2 balloon, 10% Pd/C, EtOH, rt, 5 d) afforded the corresponding fully deprotected ribofuranosides **α-7** and **α-8**, respectively, without any side reactions (Scheme 2). In contrast, attempts to remove the isopropylidene group of compound **α-3m** were not successful even with mildly acidic conditions that have been used for the deprotection of acid-sensitive molecules including other types of glycosides (AcOH/H_2O,[15a] PPTS/MeOH,[15b,c] TFA/CH_2Cl_2,[15d] Amberlyst (H^+)/MeOH[15c]). Cleavage of the α-glycoside bond was the major

Scheme 2. Deprotection of α-Ribofuranosides α-3i,n



side reaction,[13] which indicated the lability of the glycoside bonds of α-ribofuranosides under acidic conditions. This result shows that undesirable side reactions, such as the cleavage of glycoside bonds and epimerization via the resultant oxocarbenium ions, can also occur in acid-promoted ribofuranosylation reactions, which are currently the major approach to α-ribofuranosides. The new ribofuranosylation reaction described in this paper is promoted under mildly basic conditions and thus free from such side reactions. The results have also shown that protecting groups other than those removed under acidic conditions must be employed for the synthesis of α-ribofuranosides as demonstrated by the deprotection of **α-3i** and **α-3n**.

A plausible reaction mechanism is given in Figure 2. Although **2** exists mainly as the β-isomer (**β-2**) as determined by ^{1}H NMR analysis, it should be in equilibrium with the α-isomer (**α-2**) due to repetitive nucleophilic attack of the iodide ions generated by the decomposition of unstable **2** and the progress of the reaction, as is observed for pyranosyl iodides,[9,10] pyranosyl bromides,[16] and ribofuranosyl bromides.[17] The stereocourse of the ribofuranosylation reaction of alcohols with **β-2** and **α-2** without additive (α:β = 87:13 to > 99:1, Table 1, entries 1–5, and Table 2, entries 11–13) can thus be explained by the mechanism proposed by Guindon et al. for the reaction of ribofuranosyl bromides with persilylated pyrimidines (α-selectivity > 20:1).[17] The reaction proceeds via the inside attack[18] of the alcohol in the "exploded" transition states for both isomers,[19] which adopt 5-membered envelop conformations, to form staggered conformations[20] of the resultant ribofuranosides. In the absence of TPPO, TS2, which leads to the formation of **β-3**, is likely to be destabilized by the electronic and steric repulsions between the two eclipsed electronegative groups at the 1- and 2-positions (I and OBn) when compared to TS1, thereby resulting in the preferential generation of **α-3**. It must be mentioned here that the results in this study showed that the formation of the **β-3** was dependent on the reaction conditions and the structures of the substrates. It is then expected that the addition of TBAI will accelerate the exchange between **β-2** and **α-2**, increasing the likelihood of **α-2** reacting with the alcohol, resulting in a decrease in the α-selectivity (α:β = 78:22–90:10; Table 1, entry 6, and Table 2, entries 6–10). However, the observed improvement in α-selectivity on the addition of TPPO irrespective of the reaction conditions tested or the substrates (Table 1, entries 7–11; Table 2, entries 1, 5) suggests that the reaction proceeds with the intermediacy of **β-9** or **α-9**,[21,22] although ^{1}H and ^{31}P NMR analyses of a solution of **2** and TPPO in $CDCl_3$ could not establish the formation of **9**, indicating that the equilibrium is likely to have shifted predominantly toward **2**.[13] The energy difference between TS3 and TS4, which are formed from the reaction of **β-9** and **α-9**, respectively, with an alcohol, is likely to

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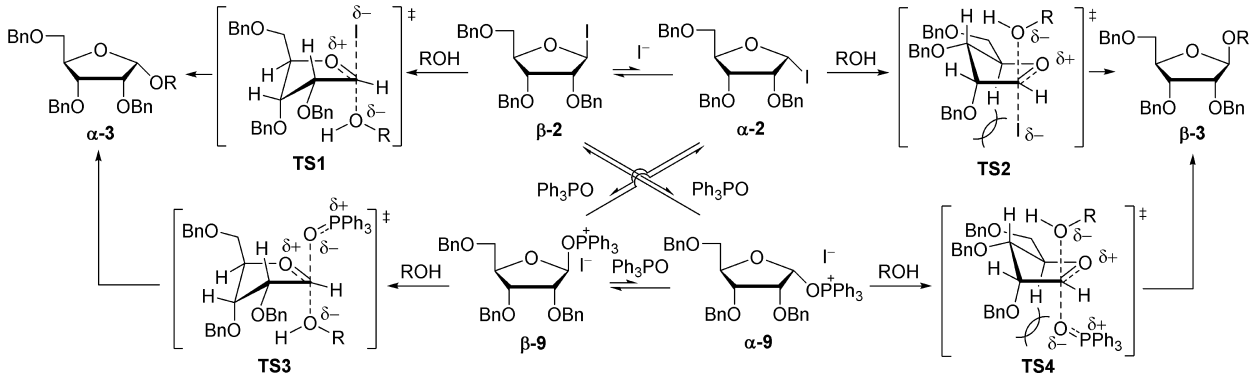

Figure 2. Proposed reaction mechanism.

be larger than that between TS1 and TS2 due to the bulkiness of TPPO, thus leading to the observed improvement in the α-selectivity (α:$\beta \geq$ 99:1, Table 1, entry 3, and Table 2, entries 1−5). The generation of undesired active intermediate ***α*-9** via nucleophilic substitution of ***β*-2** with TPPO may also be hampered by the steric hindrance of the 2-*O*-benzyl group.

In conclusion, we developed a novel ribofuranosylation reaction of alcohols with almost complete α-selectivity using ribofuranosyl iodides and TPPO as the glycosyl donors and additive, respectively. The novel acid-free and heavy-metal-free reaction is advantageous for the synthesis of ribofuranoside derivatives containing acid-sensitive functionalities and should be applicable to the preparation of ribofuranoside derivatives that are intended for use as therapeutic agents.

EXPERIMENAL SECTION

General Methods. Commercially available reagents were used without purification. Dry organic solvents were prepared by appropriate procedures prior to use. The other organic solvents were reagent grade and used as received. All reactions in dry solvents were carried out under argon. Analytical thin-layer chromatography (TLC) was performed on TLC plates precoated with silica gel 60 F_{254}. Silica gel column chromatography was carried out using silica gel 60N (spherical, neutral, 40−50 or 63−210 μm) or 3-aminopropyl-functionalized NH silica gel. Preparative TLC (PTLC) was performed on silica gel 60 F_{254} PLC glass plates (20 × 20 cm, 1 mm thickness). Preparative recycling gel permeation chromatography (GPC) was performed with JAIGEL-1H and −2H columns ($CHCl_3$ as an eluent). The ^{1}H, ^{13}C, and ^{31}P spectra (400, 100, and 161.7 MHz) were recorded at rt, except for the NMR spectra of crude **2** in the absence and presence of TPPO, which were recorded at 4 °C. Tetramethylsilane (TMS) was used as an internal standard for ^{1}H NMR (0.0 ppm). $CDCl_3$ and CD_3OD were used as internal standards for ^{13}C NMR (77.0 and 49.2 ppm, respectively). 85% H_3PO_4 was used as an external standard for ^{31}P NMR in $CDCl_3$ (0.0 ppm). ^{1}H NMR data are reported as follows: chemical shift (multiplicity, coupling constants, integration). Multiplicity is indicated as follows: s (singlet); d (doublet); dd (doublet of doublets); dt (doublet of triplets); t (triplet); q (quartet); m (multiplet). HPLC analyses were carried out using a Mightysil Si60 column (5 μm, 4.6 × 150 mm).

General Procedure A for Ribofuranosylation of Alcohols. Synthesis of Compounds 3a−d,f−h by Ribofuranosylation of Liquid Alcohols in the Presence of TPPO. 1-*O*-Trimethylsilyl-2,3,5-tri-*O*-Bn-D-ribofuranose **1** (0.118 g, 0.24 mmol) was dried by repeated coevaporation with dry toluene and dissolved in dry CH_2Cl_2 (2.0 mL) under argon. MS 4A (0.2 g) was then added, and the mixture was cooled to 0 °C. TMSI (0.0324 mL, 0.24 mmol) was slowly added dropwise to the mixture while stirring, and the mixture was stirred for 1 h at the same temperature. A 0.20 M solution of TPPO, which was dried by repeated coevaporation with dry toluene prior to use, in dry CH_2Cl_2 (1.0 mL, 0.20 mmol), the substrate alcohol (0.20 mmol), which was dried over MS4A prior to use, and dry *i*-Pr_2NEt (0.0348 mL, 0.20 mmol) were successively added, and the mixture was kept stirring for 30 min (for **3a−d**), 1 h (for **3g**), or 2 h (for **3f,h**) at 0 °C. The mixture was then diluted with CH_2Cl_2 (15 mL) and washed with a saturated $NaHCO_3$ aqueous solution (15 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 15 mL), and the combined organic layers were washed with a saturated NaCl aqueous solution (15 mL). The aqueous layer was extracted with CH_2Cl_2 (5 mL), and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was then purified by silica gel column chromatography (silica gel 60N, spherical, neutral, 40−50 or 63-210 μm, hexane−AcOEt). In the cases of compounds **3a−d,f**, all the fractions containing the desired α-ribofuranosides and the trace amounts of minor β-ribofuranosides were collected together, concentrated to dryness under reduced pressure, and analyzed by HPLC.[13]

General Procedure B for Ribofuranosylation of Alcohols. Synthesis of Compounds 3e,i by Ribofuranosylation of Solid Alcohols in the Presence of TPPO. *l*-Menthol (0.0313 g, 0.20 mmol) or 5-triphenylmethoxy-1-pentanol[23] (0.0693 g, 0.20 mmol) and TPPO (0.0556 g, 0.20 mmol) were dried by repeated coevaporation with dry toluene and dissolved in dry CH_2Cl_2 (1.0 mL). Dry *i*-Pr_2NEt (0.0348 mL, 0.20 mmol) was added to the solution. The resultant solution was then added dropwise at 0 °C to a stirred mixture of the ribofuranosyl iodide **2**, which was prepared in advance from compound **1** (0.118 g, 0.24 mmol) and TMSI (0.0324 mL, 0.24 mmol) according to the general procedure A, and MS 4A (0.2 g) in dry CH_2Cl_2 (2.0 mL). The resultant mixture was kept stirring for 1 h (for **3e**) or 2 h (for **3i**) at the same temperature. Aqueous workup and purification by silica gel column chromatography were carried out as in the general procedure A to afford compounds **3e,i**. In the case of compound **3e**, all the fractions containing the desired ***α*-3e** and the trace amount of minor ***β*-3e** were collected together, concentrated to dryness under reduced pressure, and analyzed by HPLC.[13]

General Procedure C for Ribofuranosylation of Alcohols. Synthesis of Disaccharides 3j−o. The corresponding glycosyl acceptor (0.20 mmol) and TPPO (0.0556 g, 0.20 mmol) were dried by repeated coevaporation with dry toluene and dissolved in dry CH_2Cl_2 (1.0 mL). Dry *i*-Pr_2NEt (0.0348 mL, 0.20 mmol) was added to the solution. The resultant solution was then added dropwise at 0 °C to a stirred mixture of the ribofuranosyl iodide **2**, which was prepared in advance from compound **1** (0.148 g, 0.30 mmol) and TMSI (0.0411 mL, 0.30 mmol) according to the general procedure A, and MS 4A (0.2 g) in dry CH_2Cl_2 (2.0 mL). The resultant mixture was kept stirring for 2 h (for **3j−n**) or 4.5 h (for **3o**) at the same temperature. Aqueous workup as in the general procedure A and purification by silica gel column chromatography (**3k,n**), PTLC (**3j,m**), or recycling GPC (**3l**) were carried out to afford the disaccharides **3j−n**.

Cyclopentyl 2,3,5-Tri-*O*-benzyl-D-ribofuranoside (α-3a and β-3a). [Table 1, entry 7] Ribofuranosylation of *c*-$C_5H_{11}OH$ (0.0181 mL, 0.20 mmol) according to the general procedure A gave ***α*-3a** (0.0872 g, 0.178 mmol, 89%, α:β = 99:1, colorless syrup). Conditions

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for silica gel column chromatography: silica gel 60N, spherical, neutral, 63−210 μm, hexane−AcOEt (5:1, v/v).

[Table 1, entry 6] Ribofuranosylation of *c*-$C_5H_{11}OH$ (0.0181 mL, 0.20 mmol) according to the general procedure A except for the use of TBAI in place of TPPO gave a mixture of **α-3a** and **β-3a** (0.060 g, 0.123 mmol, 62%, α:β = 83:17, pale yellow syrup). Conditions for silica gel column chromatography: silica gel 60N, spherical, neutral, 40−50 μm, hexane−AcOEt (100:0 to 90:10, v/v).

Characterization Data of Cyclopentyl 2,3,5-Tri-*O*-benzyl-α-D-ribofuranoside (α-3a). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38−7.21 (m, 15H), 5.09 (d, *J* = 4.3 Hz, 1H), 4.71 (d, *J* = 12.7 Hz, 1H), 4.70 (d, *J* = 12.2 Hz, 1H), 4.61 (d, *J* = 12.4 Hz, 1H), 4.51 (d, *J* = 12.7 Hz, 1H), 4.50 (d, *J* = 12.4 Hz, 1H), 4.43 (d, *J* = 12.2 Hz, 1H), 4.26−4.20 (m, 2H), 3.84 (dd, *J* = 6.8, 4.5 Hz, 1H), 3.77 (dd, *J* = 6.8, 4.3 Hz, 1H), 3.48 (dd, *J* = 10.7, 3.6 Hz, 1H), 3.38 (dd, *J* = 10.7, 4.3 Hz, 1H), 1.86−1.71 (m, 6H), 1.55−1.25 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.5, 138.1, 138.0, 128.3, 128.3, 128.2, 128.0, 127.7, 127.6, 127.6, 127.5, 100.4, 80.7, 79.5, 76.7, 75.5, 73.3, 72.4, 72.1, 69.9, 33.4, 31.9, 23.6, 23.4. HRMS (ESI-TOF) *m*/*z*: $[M + Na]^+$ Calcd for $C_{31}H_{36}NaO_5^+$ 511.2455; Found 511.2470.

Characterization Data of Cyclopentyl 2,3,5-Tri-*O*-benzyl-β-D-ribofuranoside (β-3a). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38−7.26 (m, 15H), 5.07 (d, *J* = 1.2 Hz, 1H), 4.65 (s, 2H), 4.58 (d, *J* = 12.4 Hz, 1H), 4.57 (d, *J* = 12.0 Hz, 1H), 4.54 (d, *J* = 12.4 Hz, 1H), 4.48 (d, *J* = 12.0 Hz, 1H), 4.31 (dt, *J* = 6.5, 4.0 Hz, 1H), 4.17 (m, 1H), 3.99 (dd, *J* = 6.5, 4.9 Hz, 1H), 3.81 (dd, *J* = 4.9, 1.2 Hz, 1H), 3.60 (dd, *J* = 10.8, 4.0 Hz, 1H), 3.52 (dd, *J* = 10.8, 6.5 Hz, 1H), 1.68−1.48 (m, 8H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.3, 138.0, 137.9, 128.4, 128.3, 128.3, 127.9, 127.8, 127.7, 127.7, 127.6, 127.5, 104.0, 80.2, 80.1, 78.9, 78.7, 73.1, 72.3, 72.3, 71.7, 33.1, 31.6, 23.3, 23.2. HRMS (ESI-TOF) *m*/*z*: $[M + Na]^+$ Calcd for $C_{31}H_{36}NaO_5^+$ 511.2455; Found 511.2483.

3-Phenylpropyl 2,3,5-Tri-*O*-benzyl-D-ribofuranoside (α-3b and β-3b). [Table 2, entry 1] Ribofuranosylation of 3-phenyl-1-propanol (0.0272 mL, 0.20 mmol) according to the general procedure A gave **α-3b** (0.090 g, 0.167 mmol, 84%, α:β = 99:1, pale yellow syrup). Conditions for silica gel column chromatography: silica gel 60N, spherical, neutral, 40−50 μm, hexane−AcOEt (6:1, v/v).

[Table 2, entry 6] Ribofuranosylation of 3-phenyl-1-propanol (0.0272 mL, 0.20 mmol) according to the general procedure A except for the use of TBAI in place of TPPO gave a mixture of **α-3b** and **β-3b** (0.059 g, 0.110 mmol, 55%, α:β = 89:11, pale yellow oil). Conditions for silica gel column chromatography: silica gel 60N, spherical, neutral, 40−50 μm, hexane−AcOEt (6:1, v/v).

Characterization Data of 3-Phenylpropyl 2,3,5-Tri-*O*-benzyl-α-D-ribofuranoside α-3b.[5h] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37−7.15 (m, 20H), 5.00 (d, *J* = 4.6 Hz, 1H), 4.71 (d, *J* = 12.6 Hz, 1H), 4.68 (d, *J* = 12.4 Hz, 1H), 4.65 (d, *J* = 12.4 Hz, 1H), 4.55 (d, *J* = 12.6 Hz, 1H), 4.49 (d, *J* = 12.4 Hz, 1H), 4.42 (d, *J* = 12.4 Hz, 1H), 4.26 (q, *J* = 4.1 Hz, 1H), 3.86−3.76 (m, 3H), 3.56 (dt, *J* = 10.1, 7.2 Hz, 1H), 3.45 (dd, *J* = 10.8, 4.1 Hz, 1H), 3.37 (dd, *J* = 10.8, 4.1 Hz, 1H), 2.72 (dt, *J* = 7.2, 3.7 Hz, 2H), 2.00 (quintet, *J* = 7.2 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.1, 138.3, 137.9, 128.4, 128.3, 128.2, 128.2, 128.0, 127.9, 127.7, 127.6, 127.5, 125.6, 101.4, 81.5, 77.5, 75.3, 73.4, 72.5, 72.2, 70.0, 67.7, 32.4, 31.3. HRMS (ESI-TOF) *m*/*z*: $[M + Na]^+$ Calcd for $C_{35}H_{38}NaO_5^+$ 561.2611; Found 561.2609.

Characterization Data of 3-Phenylpropyl 2,3,5-Tri-*O*-benzyl-β-D-ribofuranoside β-3b.[5h] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37−7.12 (m, 20H), 5.00 (s, 1H), 4.67 (d, *J* = 12.1 Hz, 1H), 4.63 (d, *J* = 12.1 Hz, 1H), 4.57 (d, *J* = 12.2 Hz, 1H), 4.54 (d, *J* = 12.4 Hz, 1H), 4.51 (d, *J* = 12.4 Hz, 1H), 4.47 (d, *J* = 12.2 Hz, 1H), 4.36−4.32 (m, 1H), 4.03 (dd, *J* = 7.1, 4.9 Hz, 1H), 3.87 (d, *J* = 4.9 Hz, 1H), 3.70 (dt, *J* = 9.6, 6.4 Hz, 1H), 3.60 (dd, *J* = 10.8, 3.9 Hz, 1H), 3.50 (dd, *J* = 10.8, 6.2 Hz, 1H), 3.35 (dt, *J* = 9.6, 6.9 Hz, 1H), 2.59 (t, *J* = 7.3 Hz, 2H), 1.80 (quintet, *J* = 7.3 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.8, 138.2, 137.8, 128.4, 128.3, 128.3, 128.3, 127.9, 127.8, 127.7, 127.7, 127.6, 127.5, 125.7, 105.3, 80.3, 79.7, 78.5, 73.1, 72.3, 72.2, 71.4, 67.1, 32.2, 31.0. HRMS (ESI-TOF) *m*/*z*: $[M + Na]^+$ Calcd for $C_{35}H_{38}NaO_5^+$ 561.2611; Found 561.2624.

Isopropyl 2,3,5-Tri-*O*-benzyl-D-ribofuranoside (α-3c and β-3c). [Table 2, entry 2] Ribofuranosylation of *i*-PrOH (0.0153 mL, 0.20 mmol) according to the general procedure A gave **α-3c** (0.0647 g, 0.140 mmol, 70%, α:β = 99:1, pale yellow syrup). Conditions for silica gel column chromatography: silica gel 60N, spherical, neutral, 40−50 μm, hexane−AcOEt (100:0 to 90:10, v/v).

[Table 2, entry 7] Ribofuranosylation of *i*-PrOH (0.0358 mL, 0.47 mmol) according to the general procedure A except for the use of TBAI in place of TPPO gave a mixture of **α-3c** and **β-3c** (0.165 g, 0.357 mmol, 76%, α:β = 87:13, pale yellow syrup). Conditions for silica gel column chromatography: silica gel 60N, spherical, neutral, 40−50 μm, hexane−AcOEt (100:0 to 90:10, v/v).

^{1}H and ^{13}C NMR spectra of **α-3c** and **β-3c** are consistent with those in the literature.[6b]

Cyclohexyl 2,3,5-Tri-*O*-benzyl-D-ribofuranoside (α-3d and β-3d). [Table 2, entry 3] Ribofuranosylation of cyclohexanol (0.0211 mL, 0.20 mmol) according to the general procedure A gave **α-3d** (0.0885 g, 0.176 mmol, 88%, α:β = >99:1, colorless syrup). Conditions for silica gel column chromatography: silica gel 60N, spherical, neutral, 63−210 μm, hexane−AcOEt (100:0 to 90:10, v/v).

[Table 2, entry 8] Ribofuranosylation of cyclohexanol (0.0211 mL, 0.20 mmol) according to the general procedure A except for the use of TBAI in place of TPPO gave a mixture of **α-3d** and **β-3d** (0.0799 g, 0.159 mmol, 80%, α:β = 82:18, pale yellow syrup). Conditions for silica gel column chromatography: silica gel 60N, spherical, neutral, 40−50 μm, hexane−AcOEt (100:0 to 90:10, v/v).

^{1}H NMR spectra of **α-3d** and **β-3d** are consistent with those in the literature.[24]

***l*-Menthyl 2,3,5-Tri-*O*-benzyl-D-ribofuranoside (α-3e and β-3e).** [Table 2, entry 4] Ribofuranosylation of *l*-menthol (0.0313 g, 0.20 mmol) according to the general procedure B gave **α-3e** (0.0931 g, 0.167 mmol, 84%, α:β = >99:1, colorless syrup). Conditions for silica gel column chromatography: silica gel 60N, spherical, neutral, 40−50 μm, hexane−AcOEt (7:1, v/v). [Table 2, entry 9] Ribofuranosylation of *l*-menthol (0.0313 g, 0.20 mmol) according to the general procedure B except for the use of TBAI in place of TPPO gave a mixture of **α-3e** and **β-3e** (0.0747 g, 0.134 mmol, 67%, α:β = 78:22, colorless syrup). Conditions for silica gel column chromatography: silica gel 60N, spherical, neutral, 40−50 μm, hexane−AcOEt (7:1, v/v).

Characterization Data of *l*-Menthyl 2,3,5-Tri-*O*-benzyl-α-D-ribofuranoside α-3e. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36−7.21 (m, 15H), 5.16 (d, *J* = 4.2 Hz, 1H), 4.72 (d, *J* = 12.4 Hz, 1H), 4.68 (d, *J* = 12.4 Hz, 1H), 4.61 (d, *J* = 12.4 Hz, 1H), 4.55 (d, *J* = 12.4 Hz, 1H), 4.49 (d, *J* = 12.4 Hz, 1H), 4.43 (d, *J* = 12.4 Hz, 1H), 4.26 (q, *J* = 4.0 Hz, 1H), 3.84 (dd, *J* = 6.8, 4.0 Hz, 1H), 3.76 (dd, *J* = 6.8, 4.2 Hz, 1H), 3.46 (dd, *J* = 10.6, 4.0 Hz, 1H), 3.39 (dd, *J* = 10.6, 4.0 Hz, 1H), 3.41−3.35 (m, 1H), 2.35 (m, 1H), 2.14 (m, 1H), 1.62 (m, 2H), 1.45−1.37 (m, 2H), 1.20 (q, *J* = 11.9 Hz, 1H), 1.00−0.80 (m, 2H), 0.90 (d, *J* = 7.2 Hz, 3H), 0.88 (d, *J* = 7.2 Hz, 3H), 0.76 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.6, 138.2, 138.0, 128.3, 128.3, 128.2, 128.0, 127.6, 127.6, 127.6, 127.5, 102.5, 81.1, 79.9, 77.9, 75.3, 73.4, 72.4, 72.1, 70.1, 48.1, 43.3, 34.3, 31.8, 24.9, 22.9, 22.3, 21.2, 15.9. HRMS (ESI-TOF) *m*/*z*: $[M + Na]^+$ Calcd for $C_{36}H_{46}NaO_5^+$ 581.3237; Found 581.3219.

^{1}H NMR spectrum of **β-3e** is consistent with that in the literature.[25]

***tert*-Butyl 2,3,5-Tri-*O*-benzyl-D-ribofuranoside (α-3f and β-3f).** [Table 2, entry 5] Ribofuranosylation of *t*-BuOH (0.0188 mL, 0.20 mmol) according to the general procedure A gave **α-3f** (0.0670 g, 0.141 mmol, 71%, α:β = 99:1, colorless syrup). Conditions for silica gel column chromatography: silica gel 60N, spherical, neutral, 63−210 μm, hexane−AcOEt (100:0 to 90:10, v/v).

[Table 2, entry 10] Ribofuranosylation of *t*-BuOH (0.0188 mL, 0.20 mmol) according to the general procedure A except for the use of TBAI in place of TPPO gave a mixture of **α-3f** and **β-3f** (0.0637 g, 0.134 mmol, 67%, α:β = 90:10, pale yellow syrup). Conditions for silica gel column chromatography: silica gel 60N, spherical, neutral, 40−50 μm, hexane−AcOEt (100:0 to 90:10, v/v).

^{1}H and ^{13}C NMR spectra of **α-3f** and **β-3f** are consistent with the data in the literature[5a] (only those of the anomeric positions are reported).

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***tert*-Butyl 2,3,5-Tri-*O*-benzyl-α-D-ribofuranoside (α-3f).** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39−7.22 (m, 15H), 5.32 (d, *J* = 4.1 Hz, 1H), 4.76 (d, *J* = 12.6 Hz, 1H), 4.70 (d, *J* = 12.6 Hz, 1H), 4.62 (d, *J* = 12.6 Hz, 1H), 4.51 (d, *J* = 12.4 Hz, 1H), 4.50 (d, *J* = 12.6 Hz, 1H), 4.43 (d, *J* = 12.4 Hz, 1H), 4.27 (m, 1H), 3.88 (dd, *J* = 6.4, 5.2 Hz, 1H), 3.75 (dd, *J* = 6.4, 4.1 Hz, 1H), 3.51 (dd, *J* = 10.8, 3.5 Hz, 1H), 3.40 (dd, *J* = 10.8, 3.9 Hz, 1H), 1.32 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.5, 138.3, 138.1, 128.2, 128.2, 128.1, 127.9, 127.5, 127.4, 127.4, 96.3, 80.1, 77.1, 75.7, 74.8, 73.2, 72.3, 72.0, 69.8, 28.8. HRMS (ESI-TOF) *m*/*z*: [M + Na]$^+$ Calcd for $C_{30}H_{36}NaO_5^+$ 499.2455; Found 499.2481.

***tert*-Butyl 2,3,5-Tri-*O*-benzyl-β-D-ribofuranoside (β-3f).** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37−7.26 (m, 15H), 5.27 (d, *J* = 2.0 Hz, 1H), 4.68 (s, 2H), 4.62−4.50 (m, 4H), 4.27 (q, *J* = 5.3 Hz, 1H), 3.97 (t, *J* = 5.3 Hz, 1H), 3.76 (dd, *J* = 5.3, 2.0 Hz, 1H), 3.61−3.54 (m, 2H), 1.19 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.4, 138.1, 138.0, 128.4, 128.3, 128.3, 127.9, 127.9, 127.7, 127.7, 127.5, 100.4, 81.0, 80.1, 78.4, 75.0, 73.2, 72.3, 72.2, 71.8, 28.8. HRMS (ESI-TOF) *m*/*z*: [M + Na]$^+$ Calcd for $C_{30}H_{36}NaO_5^+$ 499.2455; Found 499.2486.

4-Penten-1-yl 2,3,5-Tri-*O*-benzyl-α-D-ribofuranoside (α-3g). Ribofuranosylation of 4-penten-1-ol (0.0203 mL, 0.20 mmol) according to the general procedure A gave **α-3g** (0.0740 g, 0.151 mmol, 76%, pale yellow syrup). Conditions for silica gel column chromatography: silica gel 60N, spherical, neutral, 40−50 μm, hexane−AcOEt (6:1, v/v). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37−7.20 (m, 15H), 5.83 (m, 1H), 5.04−4.93 (m, 2H), 5.00 (d, *J* = 4.2 Hz, 1H), 4.70 (d, *J* = 12.4 Hz, 1H), 4.67 (d, *J* = 12.4 Hz, 1H), 4.63 (d, *J* = 12.4 Hz, 1H), 4.54 (d, *J* = 12.4 Hz, 1H), 4.49 (d, *J* = 12.2 Hz, 1H), 4.42 (d, *J* = 12.2 Hz, 1H), 4.23 (q, *J* = 4.0 Hz, 1H), 3.83 (dd, *J* = 6.9, 4.0 Hz, 1H), 3.77 (dd, *J* = 16.8, 6.8 Hz, 1H), 3.78 (dd, *J* = 6.9, 4.2 Hz, 1H), 3.54 (dt, *J* = 9.6, 6.8 Hz, 1H), 3.44 (dd, *J* = 10.4, 4.0 Hz, 1H), 3.37 (dd, *J* = 10.4, 4.0 Hz, 1H), 2.19−2.13 (m, 2H), 1.81−1.74 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.4, 138.4, 138.0, 128.3, 128.3, 128.2, 128.1, 128.0, 127.7, 127.6, 127.5, 114.6, 101.4, 81.5, 77.5, 75.3, 73.4, 72.5, 72.2, 70.0, 67.7, 30.4, 28.8. HRMS (ESI-TOF) *m*/*z*: [M + Na]$^+$ Calcd for $C_{31}H_{36}NaO_5^+$ 511.2455; Found 511.2472.

2-(Methylphenylamino)ethyl 2,3,5-Tri-*O*-benzyl-α-D-ribofuranoside (α-3h). Ribofuranosylation of 2-(methylphenylamino)-ethanol (0.0283 mL, 0.20 mmol) according to the general procedure A gave **α-3h** (0.0854 g, 0.154 mmol, 77%, pale yellow syrup). Conditions for silica gel column chromatography: silica gel 60N, spherical, neutral, 40−50 μm, hexane−AcOEt (6:1, v/v). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34−7.27 (m, 13H), 7.22−7.17 (m, 4H), 6.72 (d, *J* = 8.0 Hz, 2H), 6.67 (t, *J* = 7.4 Hz, 1H), 4.99 (d, *J* = 4.4 Hz, 1H), 4.69 (d, *J* = 12.4 Hz, 1H), 4.62 (s, 2H), 4.54 (d, *J* = 12.4 Hz, 1H), 4.49 (d, *J* = 12.0 Hz, 1H), 4.42 (d, *J* = 12.0 Hz, 1H), 4.22 (q, *J* = 4.0 Hz, 1H), 3.90−3.83 (m, 2H), 3.79−3.72 (m, 2H), 3.61 (m, 2H), 3.43 (dd, *J* = 10.5, 4.0 Hz, 1H), 3.37 (dd, *J* = 10.5, 4.0 Hz, 1H), 2.96 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.2, 138.3, 137.9, 137.9, 129.1, 128.3, 128.3, 128.2, 128.1, 127.9, 127.8, 127.6, 127.6, 116.0, 112.0, 101.8, 81.8, 77.8, 75.3, 73.4, 72.5, 72.3, 70.0, 65.3, 52.3, 38.8. HRMS (ESI-TOF) *m*/*z*: [M + H]$^+$ Calcd for $C_{35}H_{40}NO_5^+$ 554.2901; Found 554.2896.

5′-Triphenylmethoxypentyl 2,3,5-Tri-*O*-benzyl-α-D-ribofuranoside (α-3i). Ribofuranosylation of 5-triphenylmethoxy-1-pentanol (0.0693 g, 0.20 mmol) according to the general procedure B gave **α-3i** (0.125 g, 0.167 mmol, 83%, colorless syrup). Conditions for silica gel column chromatography: silica gel 60N, spherical, neutral, 63−210 μm, hexane−AcOEt (9:1 to 3:1, v/v). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45−7.19 (m, 30H), 4.97 (d, *J* = 4.4 Hz, 1H), 4.66 (d, *J* = 12.4 Hz, 1H), 4.64 (d, *J* = 12.6 Hz, 1H), 4.60 (d, *J* = 12.6 Hz, 1H), 4.51 (d, *J* = 12.4 Hz, 1H), 4.48 (d, *J* = 12.4 Hz, 1H), 4.41 (d, *J* = 12.4 Hz, 1H), 4.20 (q, *J* = 4.0 Hz, 1H), 3.81 (dd, *J* = 6.8, 4.0 Hz, 1H), 3.77−3.70 (m, 2H), 3.50 (dt, *J* = 9.6, 6.8 Hz, 1H), 3.43 (dd, *J* = 10.6, 4.0 Hz, 1H), 3.35 (dd, *J* = 10.6, 4.0 Hz, 1H), 3.04 (t, *J* = 6.6 Hz, 2H), 1.69−1.61 (m, 4H), 1.47−1.39 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.5, 138.3, 138.0, 128.7, 128.3, 128.3, 128.2, 128.1, 128.0, 127.7, 127.6, 127.5, 126.8, 101.3, 86.3, 81.4, 77.4, 75.2, 73.4, 72.4, 72.1, 70.0, 68.3, 63.6, 29.9, 29.5, 22.9. HRMS (ESI-TOF) *m*/*z*: [M + Na]$^+$ Calcd for $C_{50}H_{52}NaO_6^+$ 771.3656; Found 771.3651.

Methyl (2,3,5-Tri-*O*-benzyl-α-D-ribofuranosyl)-(1→6)-2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (α-3j). Ribofuranosylation of methyl 2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (0.0929 g, 0.20 mmol) according to the general procedure C gave **α-3j** (0.133 g, 0.153 mmol, 77%, colorless syrup). Purification was performed by PTLC (CH_2Cl_2−MeOH (99:1, v/v)). ^{1}H and ^{13}C NMR spectra are consistent with the data in the literature (only the signal corresponding to the anomeric position is reported for ^{13}C NMR).[6,7] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38−7.17 (m, 30H), 5.15 (d, *J* = 3.6 Hz, 1H), 4.93 (d, *J* = 10.8 Hz, 1H), 4.81 (d, *J* = 10.8 Hz, 1H), 4.76 (m, 1H), 4.73 (s, 3H), 4.67 (d, *J* = 12.0 Hz, 1H), 4.62−4.56 (m, 3H), 4.50 (d, *J* = 12.0 Hz, 1H), 4.43 (d, *J* = 11.4 Hz, 1H), 4.42 (d, *J* = 12.0 Hz, 1H), 4.23−4.20 (m, 1H), 4.15 (dd, *J* = 11.0, 3.0 Hz, 1H), 3.95 (t, *J* = 9.2 Hz, 1H), 3.90−3.86 (m, 2H), 3.78−3.65 (m, 3H), 3.49−3.38 (m, 3H), 3.33 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.1, 138.7, 138.3, 138.2, 138.0, 128.4, 128.3, 128.3, 128.2, 128.0, 127.9, 127.8, 127.6, 127.4, 127.4, 102.1, 98.1, 82.0, 81.4, 80.0, 77.8, 76.1, 75.5, 75.0, 73.4, 72.4, 72.4, 70.2, 69.8, 66.6, 55.1. HRMS (ESI-TOF) *m*/*z*: [M + Na]$^+$ Calcd for $C_{54}H_{58}NaO_{10}^+$ 889.3922; Found 889.3896.

2,3,5-Tri-*O*-benzyl-α-D-ribofuranosyl-(1→6)-1,2,3,4-tetra-*O*-acetyl-β-D-glucopyranose (α-3k). Ribofuranosylation of 1,2,3,4-tetra-*O*-acetyl-β-D-glucopyranose (0.0697 g, 0.20 mmol) according to the general procedure C gave **α-3k** (0.0984 g, 0.131 mmol, 66%, white powder). Purification was performed by silica gel column chromatography (conditions: silica gel 60N, spherical, neutral, 63−210 μm, hexane−AcOEt (5:1 to 0:1, v/v)). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39−7.21 (m, 15H), 5.72 (d, *J* = 8.4 Hz, 1H), 5.24 (t, *J* = 9.4 Hz, 1H), 5.11 (q, *J* = 9.4 Hz, 2H), 4.98 (d, *J* = 3.6 Hz, 1H), 4.66 (d, *J* = 12.0 Hz, 1H), 4.64 (d, *J* = 12.0 Hz, 1H), 4.60 (d, *J* = 12.4 Hz, 1H), 4.55 (d, *J* = 12.4 Hz, 1H), 4.49 (d, *J* = 12.4 Hz, 1H), 4.43 (d, *J* = 12.4 Hz, 1H), 4.24 (q, *J* = 4.0 Hz, 1H), 3.90−3.79 (m, 4H), 3.74 (dd, *J* = 11.4, 3.0 Hz, 1H), 3.46 (dd, *J* = 10.7, 4.0 Hz, 1H), 3.39 (dd, *J* = 10.7, 4.0 Hz, 1H), 2.03 (s, 3H), 2.02 (s, 3H), 1.99 (s, 3H), 1.97 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.3, 169.6, 169.3, 169.0, 138.5, 138.1, 128.4, 128.3, 128.2, 128.2, 127.8, 127.7, 127.6, 101.5, 91.8, 81.5, 77.7, 75.3, 73.8, 73.5, 73.2, 72.7, 72.1, 70.6, 70.0, 69.2, 66.2, 20.8, 20.7, 20.7, 20.7. HRMS (ESI-TOF) *m*/*z*: [M + Na]$^+$ Calcd for $C_{40}H_{46}NaO_{14}^+$ 773.2780; Found 773.2817.

2,3,5-Tri-*O*-benzyl-α-D-ribofuranosyl-(1→6)-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (α-3l).[4a] Ribofuranosylation of 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (0.0521 g, 0.20 mmol) according to the general procedure C gave **α-3l** (0.120 g, 0.181 mmol, 91%, pale yellow syrup). Purification was performed by recycling GPC ($CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37−7.20 (m, 15H), 5.51 (d, *J* = 5.0 Hz, 1H), 5.14 (d, *J* = 4.2 Hz, 1H), 4.73 (d, *J* = 12.4 Hz, 2H), 4.62 (d, *J* = 12.4 Hz, 1H), 4.57 (dd, *J* = 8.0, 2.0 Hz, 1H), 4.55 (d, *J* = 12.4 Hz, 1H), 4.49 (d, *J* = 12.0 Hz, 1H), 4.42 (d, *J* = 12.0 Hz, 1H), 4.39 (dd, *J* = 8.0, 2.2 Hz, 1H), 4.29 (dd, *J* = 5.0, 2.2 Hz, 1H), 4.25 (q, *J* = 4.0 Hz, 1H), 4.13 (m, 1H), 3.89 (dd, *J* = 10.1, 5.4 Hz, 1H), 3.86 (dd, *J* = 6.9, 4.0 Hz, 1H), 3.80 (dd, *J* = 6.9, 4.2 Hz, 1H), 3.78 (dd, *J* = 10.1, 8.8 Hz, 1H), 3.46 (dd, *J* = 10.6, 4.0 Hz, 1H), 3.39 (dd, *J* = 10.6, 4.0 Hz, 1H), 1.52 (s, 3H), 1.44 (s, 3H), 1.32 (s, 3H), 1.29 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.4, 138.0, 138.0, 128.3, 128.2, 128.0, 127.8, 127.7, 127.6, 127.5, 108.9, 108.5, 102.1, 96.3, 81.5, 77.5, 75.4, 73.4, 72.2, 72.1, 70.8, 70.6, 70.5, 69.8, 66.6, 65.8, 26.1, 26.0, 24.9, 24.4. HRMS (ESI-TOF) *m*/*z*: [M + Na]$^+$ Calcd for $C_{38}H_{46}NaO_{10}^+$ 685.2983; Found 685.2953.

Methyl (2,3,5-Tri-*O*-benzyl-α-D-ribofuranosyl)-(1→5)-2,3-*O*-isopropylidene-β-D-ribofuranoside (α-3m).[4a] Ribofuranosylation of methyl 2,3-*O*-isopropylidene-β-D-ribofuranoside (0.0408 g, 0.20 mmol) according to the general procedure C gave **α-3m** (0.0994 g, 0.164 mmol, 82%, colorless syrup). Purification was performed by PTLC (hexane−AcOEt (2:1, v/v)). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37−7.22 (m, 15H), 5.04 (d, *J* = 4.3 Hz, 1H), 4.94 (s, 1H), 4.87 (d, *J* = 6.4 Hz, 1H), 4.69 (d, *J* = 12.4 Hz, 1H), 4.65 (s, 2H), 4.56−4.49 (m, 4H), 4.42 (d, *J* = 12.0 Hz, 1H), 4.30 (q, *J* = 3.6 Hz, 1H), 3.86 (dd, *J* = 6.6, 3.6 Hz, 1H), 3.81 (dd, *J* = 6.6, 4.3 Hz, 1H), 3.74 (dd, *J* = 10.8, 5.6 Hz, 1H), 3.66 (t, *J* = 10.8 Hz, 1H), 3.45 (dd, *J* = 10.6, 3.6 Hz, 1H), 3.38 (dd, *J* = 10.6, 3.6 Hz, 1H), 3.28 (s, 3H), 1.47 (s, 3H), 1.28 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.3, 137.9, 137.9, 128.3, 128.3,

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128.2, 128.1, 128.0, 127.8, 127.6, 127.6, 127.6, 112.0, 109.5, 102.2, 85.2, 85.1, 82.0, 81.7, 77.9, 75.4, 73.3, 72.5, 72.2, 69.9, 69.3, 54.7, 26.5, 24.9. HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{35}H_{42}NaO_9^+$ 629.2721; Found 629.2726.

Methyl 2,3-*O*-Benzylidene-*β*-D-ribofuranoside.[26] AcCl (0.028 mL, 0.40 mmol) was added dropwise to dry MeOH (2.00 mL), and the resultant solution was added dropwise a stirred mixture of D-ribose (1.00 g, 6.67 mmol) and dry MeOH (13.0 mL) at rt under argon. After stirring for 5 h, $NaHCO_3$ (0.40 g, 4.8 mmol) was added to the mixture, and the solid was filtered off and washed with MeOH (40 mL). The filtrate was then concentrated under reduced pressure. The residue was dried by repeated coevaporation with dry pyridine and dry toluene and dissolved in dry MeCN (60 mL) under argon. Benzaldehyde dimethyl acetal (1.99 mL, 13.3 mmol) and PPTS (0.335 g, 1.33 mmol) were added, and the resultant mixture was stirred for 25 h at 90 °C. The mixture was allowed to cool to rt, and Et_3N (0.37 mL, 2.7 mmol) was added. The mixture was then diluted with AcOEt (50 mL), washed successively with water (2 × 50 mL), saturated $NaHCO_3$ aqueous solutions (2 × 50 mL), and a saturated NaCl aqueous solution (20 mL). The aqueous layers were combined and extracted with AcOEt (20 mL). The organic layers were combined, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was then purified by silica gel column chromatography (silica gel 60N, spherical, neutral, 63−210 μm, hexane−AcOEt (1:1, v/v)). The fractions containing the *β*-isomer were collected and concentrated to dryness to afford the title compound (1.25 g, 4.95 mmol, 74%, white solid) as a 96:4 mixture of the *endo*- and *exo*-isomers. The ^{1}H NMR spectrum is consistent with that in the literature.[26b,c] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52−7.47 (m, 2H), 7.41−7.38 (m, 3H), 5.77 (s, 1H), 5.13 (s, 1H), 4.92 (d, J = 6.0 Hz, 1H), 4.70 (d, J = 6.0 Hz, 1H), 4.61 (t, J = 2.8 Hz, 1H), 3.77−3.63 (m, 2H), 3.47 (s, 3H), 3.26 (dd, J = 10.4, 2.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.9, 129.8, 128.4, 126.9, 109.6, 105.8, 88.1, 86.3, 82.5, 63.9, 55.5. HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{13}H_{16}NaO_5^+$ 275.0890; Found 275.0889.

Methyl (2,3,5-Tri-*O*-benzyl-*α*-D-ribofuranosyl)-(1→5)-2,3-*O*-benzylidene-*β*-D-ribofuranoside (*α*-3n). Ribofuranosylation of methyl 2,3-*O*-benzylidene-*β*-D-ribofuranoside (0.0505 g, 0.20 mmol) according to the general procedure C gave ***α*-3n** (0.108 g, 0.165 mmol, 83%, white solid). Purification was performed by silica gel column chromatography (conditions: silica gel 60N, spherical, neutral, 63−210 μm, hexane−AcOEt (2:1, v/v)). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51−7.17 (m, 20H), 5.70 (s, 1H), 5.08 (s, 1H), 5.05 (d, J = 4.0 Hz, 1H), 4.97 (d, J = 6.4 Hz, 1H), 4.74−4.63 (m, 5H), 4.53 (d, J = 12.4 Hz, 1H), 4.48 (d, J = 12.2 Hz, 1H), 4.39 (d, J = 12.2 Hz, 1H), 4.30 (q, J = 3.6 Hz, 1H), 3.86−3.70 (m, 4H), 3.43 (dd, J = 10.6, 3.8 Hz, 1H), 3.35 (dd, J = 10.6, 3.8 Hz, 1H), 3.31 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.2, 137.8, 137.8, 136.2, 129.6, 128.2, 128.1, 128.0, 127.9, 127.7, 127.5, 127.5, 126.9, 109.1, 105.8, 102.1, 85.7, 84.8, 82.7, 81.7, 77.9, 75.4, 73.2, 72.5, 72.2, 69.9, 69.0, 54.7. HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{39}H_{42}NaO_9^+$ 677.2721; Found 677.2723.

2,3,5-Tri-*O*-benzyl-*α*-D-ribofuranosyl-(1→3)-1,2:5,6-di-*O*-isopropylidene-*α*-D-allofuranose (*α*-3o). Ribofuranosylation of 1,2:5,6-di-*O*-isopropylidene-*α*-D-allofuranose (0.0521 g, 0.20 mmol) according to the general procedure C with an extended reaction time (4.5 h) gave ***α*-3o** (0.0986 g, 0.149 mmol, 75%, colorless syrup). Purification was performed by silica gel column chromatography (conditions: silica gel 60N, spherical, neutral, 63−210 μm, hexane−AcOEt (5:1 to 1:1, v/v)). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40−7.19 (m, 15H), 5.88 (d, J = 4.1 Hz, 1H), 5.30 (d, J = 3.6 Hz, 1H), 4.88 (d, J = 12.2 Hz, 1H), 4.77 (t, J = 4.1 Hz, 1H), 4.73 (d, J = 12.2 Hz, 1H), 4.66 (d, J = 12.2 Hz, 1H), 4.56 (d, J = 12.2 Hz, 1H), 4.53−4.40 (m, 5H), 4.30 (dd, J = 8.2, 7.0 Hz, 1H), 4.25 (dd, J = 8.8, 2.0 Hz, 1H), 3.89−3.84 (m, 3H), 3.46 (dd, J = 10.6, 3.6 Hz, 1H), 3.39 (dd, J = 10.6 Hz, 4.0 Hz, 1H), 1.51 (s, 3H), 1.48 (s, 3H), 1.37 (s, 3H), 1.35 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.3, 138.2, 137.9, 128.3, 128.3, 128.1, 128.0, 127.8, 127.6, 127.5, 127.4, 112.7, 109.4, 104.4, 98.4, 82.0, 78.2, 77.6, 76.9, 75.7, 73.8, 73.3, 72.2, 71.7, 71.5, 69.9, 63.9, 26.8, 25.9, 24.7. HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{38}H_{46}NaO_{10}^+$ 685.2983; Found 685.3017.

Diethyl 2,3,5-Tris-*O*-*tert*-butyldimethylsilyl-D-ribofuranosyl Phosphite (5). 2,3,5-Tris-*O*-*tert*-butyldimethylsilyl-D-ribofuranose[27] (0.246 g, 0.50 mmol) was dried by repeated coevaporation with dry toluene and dissolved in dry CH_2Cl_2 (5.0 mL) under argon. Dry Et_3N (0.209 mL, 1.5 mmol) and $(EtO)_2PCl$ (0.0865 mL, 0.60 mmol) were added dropwise with stirring, and the mixture was allowed to stir for 1 h. The mixture was then treated with a saturated $NaHCO_3$ aqueous solution (15 mL). The aqueous layer was separated and extracted with CH_2Cl_2 (3 × 15 mL). The organic layers were combined, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Finally, the residue was purified by silica gel column chromatography (conditions: 3-aminopropyl-functionalized NH silica gel, hexane−AcOEt (20:1 to 2:1, v/v) containing 3 vol % Et_3N) to afford **5** (0.275 g, 0.45 mmol, 90%, α:β = 62:38) as a colorless syrup. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.46−5.40 (m, 1H), 4.20−3.63 (m, 9H), 1.28−1.21 (m, 6H), 0.93−0.89 (m, 27H), 0.11−0.03 (m, 18H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 100.6 (d, $^2J_{PC}$ = 17.0 Hz), 97.0 (d, $^2J_{PC}$ = 29.4 Hz), 87.0, 83.3, 77.5 (d, $^3J_{PC}$ = 6.1 Hz), 74.1 (d, $^3J_{PC}$ = 9.4 Hz), 71.6, 71.1, 63.4, 63.2, 58.4 (d, $^2J_{PC}$ = 18.4 Hz), 58.1 (d, $^2J_{PC}$ = 10.8 Hz), 57.8 (d, $^2J_{PC}$ = 9.2 Hz), 26.0, 25.9, 25.9, 25.8, 25.8, 18.5, 18.4, 18.3, 18.1, 18.0, 16.8, 16.7, −4.3, −4.4, −4.6, −4.8, −4.9, −5.3, −5.4, −5.5. ^{31}P NMR (161.7 MHz, $CDCl_3$) δ 138.9, 138.0. HRMS (ESI): m/z calcd for $C_{27}H_{61}NaO_7PSi_3^+$ $[(M + Na)^+]$ 635.3355, found 635.3354.

3-Butyn-1-yl 2,3,5-Tris-*O*-*tert*-butyldimethylsilyl-*α*-D-ribofuranoside (*α*-6). Compound **5** (0.0613 g, 0.10 mmol) was dried by repeated coevaporation with dry toluene and dissolved in dry CH_2Cl_2 (1.0 mL) under argon. MS 4A (0.2 g) was then added, and the mixture was cooled to 0 °C. A solution of *N*,*N*-diethylanilinium iodide (0.0277 g, 0.10 mmol) in dry CH_2Cl_2 (2.0 mL) was added dropwise, and the mixture was allowed to stir for 10 min. A solution of 3-butyn-1-ol (7.5 μL, 0.10 mmol) and TPPO (0.0278 g, 0.10 mmol) in dry CH_2Cl_2 (1.0 mL) was then added, and the mixture was stirred for 1 h. The mixture was then treated with a saturated $NaHCO_3$ aqueous solution (15 mL). The aqueous layer was separated and extracted with CH_2Cl_2 (3 × 15 mL). The organic layers were combined, washed with a saturated NaCl aqueous solution (10 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was dissolved in Et_2O (20 mL) and then washed with 0.1 M HCl aqueous solutions (2 × 15 mL) and a saturated NaCl aqueous solution (10 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Finally, the residue was purified by PTLC (hexane−AcOEt (10:1, v/v)) to afford ***α*-6** (0.0454 g, 0.083 mmol, 83%) as a colorless syrup. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.91 (d, J = 4.4 Hz, 1H), 4.07 (dd, J = 5.4, 3.4 Hz, 1H), 4.02−3.98 (m, 2H), 3.84 (dt, J = 9.4, 7.4 Hz, 1H), 3.68 (dd, J = 11.4, 3.0 Hz, 1H), 3.65 (dd, J = 11.4, 3.0 Hz, 1H), 3.59 (dt, J = 9.4, 7.4 Hz, 1H), 2.48 (dt, J = 7.4, 2.6 Hz, 1H), 1.92 (t, J = 2.6 Hz, 1H), 0.91 (s, 9H), 0.89 (s, 9H), 0.89 (s, 9H), 0.09 (s, 3H), 0.07 (s, 3H), 0.07 (s, 3H), 0.06 (s, 6H), 0.05 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 102.5, 85.2, 81.5, 73.9, 71.4, 69.0, 65.9, 62.9, 26.0, 25.9, 25.9, 20.1, 18.4, 18.3, 18.1, −4.4, −4.5, −4.6, −4.9, −5.3, −5.5. HRMS (ESI): m/z calcd for $C_{27}H_{56}NaO_5Si_3^+$ $[(M + Na)^+]$ 567.3328, found 567.3308.

5′-Hydroxypentyl *α*-D-Ribofuranoside (*α*-7). A mixture of compound ***α*-3i** (0.0375 g, 0.050 mmol), 10% Pd/C (2.5 mg), and dry EtOH (0.50 mL) was stirred under H_2 (balloon) for 5 days at rt. The mixture was then filtered, and the filtrate was concentrated under reduced pressure. The residue was dissolved in H_2O (20 mL) and washed with Et_2O (20 mL). The organic layer was extracted with H_2O (3 × 20 mL). The aqueous layers were combined and lyophilized to afford ***α*-7** (0.0107 g, 0.045 mmol, 91%) as a colorless syrup. ^{1}H NMR (400 MHz, CD_3OD) δ 4.96 (d, J = 4.4 Hz, 1H), 3.99−3.96 (m, 2H), 3.93−3.91 (m, 1H), 3.77 (dt, J = 9.6, 6.6 Hz, 1H), 3.66 (dd, J = 12.0, 3.6 Hz, 1H), 3.59 (dd, J = 12.0, 4.4 Hz, 1H), 3.56 (t, J = 6.6 Hz, 2H), 3.50 (dt, J = 9.6, 6.4 Hz, 1H), 1.65 (m, 2H), 1.60−1.53 (m, 2H), 1.48−1.40 (m, 2H). ^{13}C NMR (100 MHz, CD_3OD) δ 103.7, 86.5, 73.2, 71.5, 69.4, 63.4, 63.0, 33.5, 30.6, 23.6. HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{10}H_{20}NaO_6^+$ 259.1152; Found 259.1176.

Methyl *α*-D-Ribofuranosyl-(1→5)-*β*-D-ribofuranoside (*α*-8). A mixture of compound ***α*-3n** (0.0613 g, 0.0936 mmol), 10% Pd/C (4.7 mg), and dry EtOH (1.00 mL) was stirred under H_2 (balloon) for 5

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days at rt. The mixture was then filtered, and the filtrate was concentrated under reduced pressure. The residue was dissolved in H_2O (40 mL) and washed with Et_2O (40 mL). The organic layer was extracted with H_2O (3 × 20 mL). The aqueous layers were combined and lyophilized to afford **α-8** (0.0231 g, 0.0780 mmol, 83%) as a white solid. ^{1}H NMR (400 MHz, CD_3OD) δ 5.03 (d, J = 4.4 Hz, 1H), 4.76 (s, 1H), 4.17−4.14 (m, 1H), 4.10−3.99 (m, 3H), 3.95−3.91 (m, 2H), 3.85 (dd, J = 10.4, 5.6 Hz, 1H), 3.68−3.58 (m, 3H), 3.35 (s, 3H). ^{13}C NMR (100 MHz, CD_3OD) δ 110.4, 103.8, 87.0, 83.0, 76.3, 73.6, 73.5, 71.6, 70.3, 63.4, 63.4, 55.8. HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{11}H_{20}NaO_9^+$ 319.1000; Found 319.1007.

■ ASSOCIATED CONTENT

Supporting Information

HPLC profiles and NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Isobe, M.; Uyakul, D.; Goto, T. *Tetrahedron Lett.* **1988**, *29*, 1169. (b) Isobe, M.; Takahashi, H.; Goto, T. *Tetrahedron Lett.* **1990**, *31*, 717. (c) Miwa, M.; Saito, H.; Sakura, H.; Saikawa, N.; Watanabe, F.; Matsushima, T.; Sugimura, T. *Nucleic Acids Res.* **1977**, *4*, 3997. (d) Hakmé, A.; Wong, H.-K.; Dantzer, F.; Schreiber, V. *EMBO Rep.* **2008**, *9*, 1094.

(2) (a) Brink, N. G.; Holly, F. W.; Shunk, C. H.; Peel, E. W.; Cahill, J. J.; Folkers, K. *J. Am. Chem. Soc.* **1950**, *72*, 1866. (b) Okami, Y.; Takashio, M.; Umezawa, H. *J. Antibiot.* **1981**, *34*, 344. (c) Takashio, M.; Ohnuki, T.; Okami, Y. *Agric. Biol. Chem.* **1982**, *46*, 2449. (d) Altman, E.; Schäffer, C.; Brisson, J.-R.; Messner, P. *Carbohydr. Res.* **1996**, *295*, 245. (e) Murata, M.; Yasumoto, T. *Nat. Prod. Rep.* **2000**, *17*, 293. (f) Winn, A. M.; Wilkinson, S. G. *Carbohydr. Res.* **2001**, *330*, 279. (g) Kocharova, N. A.; Mieszala, M.; Zatonsky, G. V.; Staniszewska, M.; Shashkov, A. S.; Gamian, A.; Knirel, Y. A. *Carbohydr. Res.* **2004**, *339*, 321. (h) Chistoserdova, L.; Rasche, M. E.; Lidstrom, M. E. *J. Bacteriol.* **2005**, *187*, 2508. (i) Li, Y.; Li, X.; Lee, U.; Kang, J. S.; Choi, H. D.; Son, B. W. *Chem. Pharm. Bull.* **2006**, *54*, 882. (j) Pospíšil, S.; Sedmera, P.; Halada, P.; Petříček, M. *J. Nat. Prod.* **2007**, *70*, 768.

(3) Bogusiak, J. *Pol. J. Chem.* **2002**, *76*, 1.

(4) (a) Mereyala, H. B.; Kulkarni, V. R.; Ravi, D.; Sharma, G. V. M; Rao, B. V.; Reddy, G. B. *Tetrahedron* **1992**, *48*, 545. (b) Kurosu, M.; Li, K. *J. Org. Chem.* **2008**, *73*, 9767. (c) Van der Heden van Noort, G. J.; Overkleeft, H. S.; Van der Marel, G. A.; Filippov, D. V. *Org. Lett.* **2011**, *13*, 2920. (d) Bogusiak, J.; Szeja, W. *Tetrahedron Lett.* **2001**, *42*, 2221. (e) Mukaiyama, T.; Hayashi, Y.; Hashimoto, Y. *Chem. Lett.* **1985**, *14*, 1087. (f) Larsen, C. H.; Ridgway, B. H.; Shaw, J. T.; Smith, D. M.; Woerpel, K. A. *J. Am. Chem. Soc.* **2005**, *127*, 10879. (g) Schmidt, R. R.; Hermentin, P. *Chem. Ber.* **1979**, *112*, 2659. (h) Bock, K.; Refn, S. *Acta Chem. Scand.* **1988**, *42B*, 324.

(5) (a) Mukaiyama, T.; Hashimoto, Y.; Shoda, S. *Chem. Lett.* **1983**, *12*, 935. (b) Mukaiyama, T.; Shimpuku, T.; Takashima, T.; Kobayashi, S. *Chem. Lett.* **1989**, *18*, 145. (c) Mukaiyama, T.; Matsubara, K.; Suda, S. *Chem. Lett.* **1991**, *20*, 981. (d) Mukaiyama, T.; Matsubara, K. *Chem. Lett.* **1992**, *21*, 1041. (e) Mukaiyama, T.; Matsubara, K.; Hora, M. *Synthesis* **1994**, *12*, 1368. (f) Mukaiyama, T.; Shimomura, N. *Chem. Lett.* **1993**, *22*, 781. (g) Suda, S.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **1993**, *66*, 1211. (h) Shimomura, N.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **1994**, *67*, 2532. (i) Mukaiyama, T.; Kobayashi, S.; Shoda, S. *Chem. Lett.* **1984**, *13*, 907. (j) Uchiro, H.; Mukaiyama, T. *Chem. Lett.* **1996**, *25*, 79.

(6) (a) Hashizume, N.; Kobayashi, S. *Carbohydr. Lett.* **1996**, *2*, 157. (b) Suzuki, T.; Watanabe, S.; Yamada, T.; Hiroi, K. *Tetrahedron Lett.* **2003**, *44*, 2561.

(7) Schmidt, R. R.; Reichrath, M. *Angew. Chem., Int. Ed.* **1979**, *18*, 466.

(8) Uchiro, H.; Mukaiyama, T. *Chem. Lett.* **1996**, *25*, 271.

(9) (a) Gervay, J.; Hadd, M. J. *J. Org. Chem.* **1997**, *62*, 6961. (b) Hadd, M. J.; Gervay, J. *Carbohydr. Res.* **1999**, *320*, 61. (c) Lam, S. N.; Gervay-Hague, J. *Org. Lett.* **2002**, *4*, 2039. (d) Lam, S. N.; Gervay-Hague, J. *Carbohydr. Res.* **2002**, *337*, 1953. (e) Du, W.; Kulkarni, S. S.; Gervay-Hague, J. *Chem. Commun.* **2007**, 2336. (f) Kulkarni, S. S.; Gervay-Hague, J. *Org. Lett.* **2008**, *10*, 4739. (g) Kobashi, Y.; Mukaiyama, T. *Chem. Lett.* **2004**, *33*, 874. (h) Fischer, E.; Fischer, H. *Ber. Dtsch. Chem. Ges.* **1910**, *43*, 2521. (i) Helferich, B.; Gootz, R. *Ber. Dtsch. Chem. Ges.* **1929**, *62B*, 2788. (j) Kronzer, F. J.; Schuerch, C. *Carbohydr. Res.* **1974**, *34*, 71.

(10) (a) Shoda, S.; Kulkarni, S. S.; Gervay-Hague, J. In *Handbook of Chemical Glycosylation: Advances in Stereoselectivity and Therapeutic Relevance*; Demchenko, A. V., Ed.; Wiley-VCH: Weinheim, 2008; pp 29−93. (b) Meloncelli, P. J.; Martin, A. D.; Lowary, T. L. *Carbohydr. Res.* **2009**, *344*, 1110.

(11) (a) Točík, Z.; Earl, R. A.; Beránek, J. *Nucleic Acids Res.* **1980**, *8*, 4755. (b) Marquez, V. E.; Liu, P. S.; Linevsky, J. K. *J. Org. Chem.* **1982**, *47*, 1712. (c) Takamura-Enya, T.; Watanabe, M.; Totsuka, Y.; Kanazawa, T.; Matsushima-Hibiya, Y.; Koyama, K.; Sugimura, T.; Wakabayashi, K. *Proc. Natl. Acad. Sci. U.S.A.* **2001**, *98*, 12414.

(12) (a) Ernst, B.; Winkler, T. *Tetrahedron Lett.* **1989**, *30*, 3081. (b) Baldoni, L.; Marino, C. *J. Org. Chem.* **2009**, *74*, 1994. (c) Baldoni, L.; Marino, C. *Carbohydr. Res.* **2012**, *362*, 70. (d) Baldoni, L.; Marino, C. *Carbohydr. Res.* **2013**, *374*, 75.

(13) See the Supporting Information.

(14) (a) Tanaka, H.; Sakamoto, H.; Sano, A.; Nakamura, S.; Nakajima, M.; Hashimoto, S. *Chem. Commun.* **1999**, 1259. (b) Matsumura, F.; Tatsumi, S.; Oka, N.; Wada, T. *Carbohydr. Res.* **2010**, *345*, 1211.

(15) (a) Yadav, J. S.; Chander, M. C.; Reddy, K. K. *Tetrahedron Lett.* **1992**, *33*, 135. (b) Van Rijsbergen, R.; Anteunis, M. J. O.; De Bruyn, A. *J. Carbohydr. Chem.* **1983**, *2*, 395. (c) Zhu, J.; Ma, D. *Angew. Chem., Int. Ed.* **2003**, *42*, 5348. (d) Wakharkar, R. D.; Sahasrabuddhe, M. B.; Borate, H. B.; Gurjar, M. K. *Synthesis* **2004**, 1830.

(16) Lemieux, R. U.; Hendriks, K. B.; Stick, R. V.; James, K. *J. Am. Chem. Soc.* **1975**, *97*, 4056.

(17) Prévost, M.; St-Jean, O.; Guindon, Y. *J. Am. Chem. Soc.* **2010**, *132*, 12433.

(18) (a) Larsen, C. H.; Ridgway, B. H.; Shaw, J. T.; Woerpel, K. A. *J. Am. Chem. Soc.* **1999**, *121*, 12208. (b) Larsen, C. H.; Ridgway, B. H.; Shaw, J. T.; Smith, D. M.; Woerpel, K. A. *J. Am. Chem. Soc.* **2005**, *127*, 10879.

(19) Crich, D.; Chandrasekera, N. S. *Angew. Chem., Int. Ed.* **2004**, *43*, 5386.

(20) (a) Krumper, J. R.; Salamant, W. A.; Woerpel, K. A. *Org. Lett.* **2008**, *10*, 4907. (b) Krumper, J. R.; Salamant, W. A.; Woerpel, K. A. *J. Org. Chem.* **2009**, *74*, 8039.

(21) Similar active intermediates have been proposed for ribofuranosylation reactions wherein the glycosyl donors (2,3,5-tri-*O*-benzyl-ribofuranose and ribofuranosyl dithiocarbamates) are activated with $Bu_3P{=}O$ and Tf_2O or $(Me_2N)_3P{=}O$ and AgOTf. In both cases, the addition of the phosphine oxides has improved the α-selectivity of the ribofuranosylation of alcohols (α:β up to 87:13 and 91:9, respectively). See ref 22.

(22) (a) Mukaiyama, T.; Suda, S. *Chem. Lett.* **1990**, *19*, 1143. (b) Bogusiak, J.; Szeja, W. *Synlett* **1997**, 661. (c) Bogusiak, J.; Szeja, W. *Carbohydr. Res.* **2001**, *330*, 141.
(23) (a) Valentijn, A. R. P. M.; van der Marel, G. A.; Sliedregt, L. A. J. M.; van Berkel, T. J. C.; Biessen, E. A. L.; van Boom, J. H. *Tetrahedron* **1997**, *53*, 759. (b) Komiotis, D.; Currie, B. L.; LeBreton, G. C.; Venton, D. L. *Synth. Commun.* **1993**, *23*, 531.
(24) Hirooka, M.; Mori, Y.; Sasaki, A.; Koto, S.; Shinoda, Y.; Morinaga, A. *Bull. Chem. Soc. Jpn.* **2001**, *74*, 1679.
(25) Vidadala, S. R.; Gayatri, G.; Sastry, N.; Hotha, S. *Chem. Commun.* **2011**, *47*, 9906.
(26) (a) Barker, G. R.; Noone, T. M.; Smith, D. C. C.; Spoors, J. W. *J. Chem. Soc.* **1955**, 1327. (b) Hanessian, S.; Plessas, N. R. *J. Org. Chem.* **1969**, *34*, 1053. (c) Clode, D. M. *Can. J. Chem.* **1977**, *55*, 4071.
(27) Liav, A.; Swiezewska, E.; Ciepichal, E.; Brennan, P. J. *Tetrahedron Lett.* **2006**, *47*, 8781.

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