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Stereoselective Synthesis of Ribofuranoid *exo*-Glycals by One-Pot Julia Olefination Using Ribofuranosyl Sulfones

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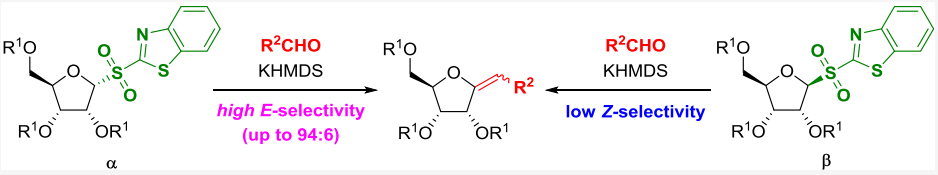

ABSTRACT: One-pot Julia olefination using ribofuranosyl sulfones is described. The α-anomers of the ribofuranosyl sulfones were synthesized with complete α-selectivity via the glycosylation of heteroarylthiols using ribofuranosyl iodides as glycosyl donors and the subsequent oxidation of the resulting heteroaryl 1-thioribofuranosides with magnesium monoperphthalate (MMPP). The Julia olefination of the α-ribofuranosyl sulfones with aldehydes proceeded smoothly in one pot to afford the thermodynamically less stable (*E*)-*exo*-glycals with modest-to-excellent stereoselectivity (up to *E*/*Z* = 94:6) under the optimized conditions. The *E* selectivity was especially high for aromatic aldehydes. In contrast, the (*Z*)-*exo*-glycal was obtained as the main product with low stereoselectivity when the corresponding β-ribofuranosyl sulfone was used (*E*/*Z* = 41:59). The remarkable impact of the anomeric configuration of the ribofuranosyl sulfones on the stereoselectivity of the Julia olefination has been rationalized using density functional theory (DFT) calculations. The protected ribose moiety of the resulting *exo*-glycals induced completely α-selective cyclopropanation on the exocyclic carbon−carbon double bond via the Simmons−Smith−Furukawa reaction. The 2-cyanoethyl group was found to be useful for the protection of the *exo*-glycals, as it could be removed without affecting the exocyclic C═C bond.

INTRODUCTION

Exo-glycals are enol ether derivatives of sugars with an exocyclic carbon−carbon double bond.[1] These sugar derivatives have long been used as versatile synthons for a variety of molecules, such as biologically active natural products[1b,2] and *C*-glycosyl compounds.[1,3] They have also been studied as transition-state analogue inhibitors of sugar-processing enzymes such as glycosidases and glycosyltransferases.[1b,c,4] Furthermore, they have attracted attention as intermediates in various biosynthetic pathways.[5]

Many reports of the synthesis of *exo*-glycals can be found in the literature. Sugar lactones are the most widely used precursors. A variety of reactions, such as the Julia olefination,[6] Wittig reaction,[7] methylenation with the Tebbe reagent or Petasis reagent,[8] dihalomethylenation with tris(dimethylamino)phosphine or triphenylphosphine and carbon tetrahalide,[9] as well as nucleophilic addition of organometallic compounds and subsequent dehydration,[10] are used to synthesize *exo*-glycals from sugar lactones. Many other methods have been reported, such as the Ramberg−Bäcklund rearrangement of glycosyl sulfones,[11] Wittig reaction with glycosyl phosphonium salts,[12] Keck allylation of 1-bromoglycosyl chlorides and dehydrochlorination,[13] Bamford−Stevens reaction,[14] [2,3]-Wittig rearrangement of 1-*C*-alkenylglycosides,[15] β-elimination reaction,[16] Claisen rearrangement[17] or S_N1'-type substitution[18] of 1-*C*-vinylglycosides, and base-promoted alkynol cycloisomerization.[19]

In the synthesis of *exo*-glycals with one substituent or two different substituents on the exocyclic C═C bond, the *E*/*Z* selectivity of the reaction is one of the most important factors to be considered. The thermodynamically more stable (*Z*)-*exo*-glycals are available via various methods. For example, the halogenation of methylene *exo*-glycals with bromine and triethylamine or iodonium di-*sym*-collidine trifluoromethanesulfonate (IDCT) gives (*Z*)-halomethylene *exo*-glycals exclusively, and the subsequent cross-coupling reactions give various monosubstituted (*Z*)-*exo*-glycals.[20] *Z*-selective trifluoromethylation reactions of methylene *exo*-glycals via photoredox and copper catalysis have been reported very recently.[21] Some of the above-mentioned reactions, i.e., the nucleophilic addition of organometallic compounds and dehydration,[10] Keck allylation and dehalogenation,[13] [2,3]-Wittig rearrangement,[15] Claisen rearrangement[17] or S_N1'-type substitution[18] of 1-*C*-vinylglycosides, and base-promoted alkynol cycloisomeri-

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zation[19] also provide (*Z*)-*exo*-glycals exclusively. The Ramberg–Bäcklund rearrangement of glycosyl sulfones[11] and the Wittig reaction of sugar lactones[7] also give (*Z*)-*exo*-glycals with high stereoselectivity in many cases.

In sharp contrast, only a few methods have been reported for the synthesis of the thermodynamically less stable (*E*)-*exo*-glycals with high stereoselectivity. Vincent et al. have reported a base-promoted *Z*-to-*E* isomerization of phosphono-*exo*-glycals. However, the isomerization is not complete and limited to substrates with an electron-withdrawing substituent on the *exo*-methylene group.[22] Wyatt et al. have reported that the Wittig reaction of sugar lactones is *E*-selective for a mannose-derived lactone[7i] but *Z*-selective when glucose- and galactose-derived substrates are used.[7h] Currently, the Julia olefination of sugar lactones reported by Gueyrard et al. has the broadest substrate scope for the stereoselective synthesis of (*E*)-*exo*-glycals.[6] This reaction affords (*E*)-*exo*-glycals that carry an alkyl substituent on the exocyclic C=C bond with high stereoselectivity of up to *E*/*Z* > 9:1. However, it has not been successfully applied to *exo*-glycals with an aryl or electron-withdrawing substituent on the C=C bond due to the low reactivity of both the sugar lactones and the α-carbanions generated from sulfones with an aryl or electron-withdrawing group.[6b] Additionally, the adducts of the sugar lactones and sulfones do not undergo the subsequent Smiles rearrangement smoothly unless treated with an additional base after aqueous workup.[6a]

Under these circumstances, we initiated a study on the synthesis of *exo*-glycals via Julia olefination using glycosyl sulfones as Julia reagents with the expectation that this approach might solve the aforementioned issues associated with the low reactivity of sugar lactones. As the first step toward this goal, an intensive study of the Julia olefination using ribofuranosyl sulfones and aldehydes was carried out. We have recently reported a novel α-selective synthesis of heteroaryl 1-thioribofuranosides **3** from 1-*O*-trimethylsilyl-ribofuranose derivatives **1** via ribofuranosyl iodides **2**.[23] In this study, the heteroaryl 1-thioribofuranosides **3** were used as the precursors to α-ribofuranosyl sulfones **4**, which were applied to Julia olefination with aldehydes for the synthesis of *exo*-glycals **5** (Scheme 1). In addition, the effect of the anomeric configuration of the ribofuranosyl sulfones was examined experimentally by both α-ribofuranosyl sulfones **4** and the corresponding β-ribofuranosyl sulfone, as well as theoretically by density functional theory (DFT) calculations.

RESULTS AND DISCUSSION

Initially, 2-benzothiazolyl 2,3,5-tri-*O*-benzyl-1-thio-α-D-ribofuranoside **3a** was synthesized from 2,3,5-tri-*O*-benzyl-1-*O*-trimethylsilyl-ribofuranose **1a** via ribofuranosyl iodide using our previously reported method[23] in 97% yield with complete α-selectivity. The oxidation of **3a** was then studied (Table 1). An attempt to oxidize **3a** using H_2O_2 and cat. $(NH_4)_6Mo_7O_{24}\cdot 4H_2O$[24] did not afford the desired sulfone **4a**. Instead, a mixture of 2,3,5-tri-*O*-benzyl-ribofuranose and its ethyl and isopropyl ribofuranosides was obtained, indicating that the glycosidic bond of the resulting **4a** or the intermediate sulfoxide was cleaved by water or solvent alcohols (entry 1). In contrast, **4a** was obtained in 85% yield when **3a** was treated with urea hydrogen peroxide (UHP) and trifluoroacetic anhydride (TFAA) in the presence of $NaHCO_3$ (entry 2).[25] The yield of **4a** was further improved to 99% when **3a** was treated with 2 equiv of magnesium monoperphthalate (MMPP) in CH_2Cl_2–MeOH (10:1, v/v) (entry 3).[26] Cleavage of the glycosidic bond of **4a** was not observed during oxidation. The solid-state structure of **4a** was confirmed

Scheme 1. Stereoselective Synthesis of α-Ribofuranosyl Sulfones 4 and Their Application to the Synthesis of *exo*-Glycals 5 by Julia Olefination

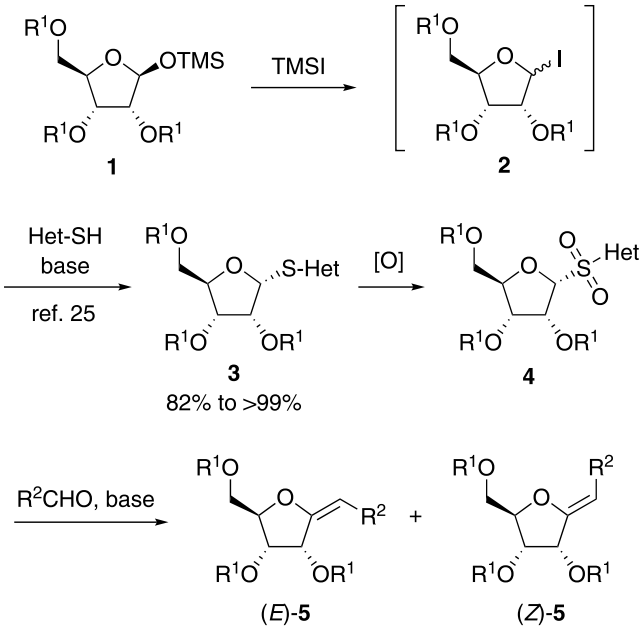
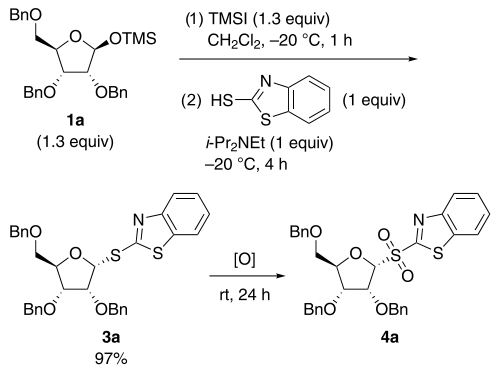


Table 1. Synthesis of Ribofuranosyl sulfone 4a



entry	reagents for the oxidation of **3a**	solvent	yield of **4a** (%)
1	H_2O_2 (9 equiv), $(NH_4)_6Mo_7O_{24}$ (0.2 equiv)	EtOH–*i*-PrOH–AcOEt (4:2:1, v/v/v)	0[a]
2[b]	UHP (3 equiv), TFAA (3 equiv), $NaHCO_3$ (5 equiv)	MeCN	85
3	MMPP (2 equiv)	CH_2Cl_2–MeOH (10:1, v/v)	99
4	MMPP (1.5 equiv)	CH_2Cl_2–MeOH (10:1, v/v)	79
5	MMPP (1 equiv)	CH_2Cl_2–MeOH (10:1, v/v)	45
6	MMPP (2 equiv)	CH_2Cl_2–DMF (10:3, v/v)	5
7	MMPP (2 equiv)	CH_2Cl_2–DMSO (10:3, v/v)	0

[a]2,3,5-Tri-*O*-benzyl-D-ribofuranose, ethyl 2,3,5-tri-*O*-benzyl-D-ribofuranoside, and isopropyl 2,3,5-tri-*O*-benzyl-D-ribofuranoside were generated as byproducts. [b]The reaction mixture was cooled to −40 °C prior to the addition of a mixture of UHP and TFAA in MeCN and then warmed to rt.

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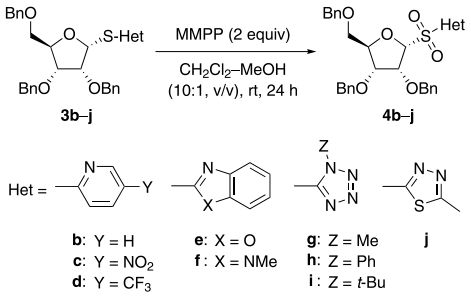
unequivocally by X-ray crystallography.[27] Oxidation did not reach completion when the amount of MMPP was reduced to 1−1.5 equiv (entries 4 and 5). Almost no **4a** was produced when *N*,*N*-dimethylformamide (DMF) or dimethyl sulfoxide (DMSO) was used as the cosolvent instead of MeOH (entries 6 and 7).

The optimized conditions were applied to the oxidation of heteroaryl 1-thio-α-ribofuranosides **3b−j**, which were also synthesized by α-selective ribofuranosylation of heteroarylthiols[28] using ribofuranosyl iodide as the glycosyl donor[23] (Table 2). 2-Pyridyl, 5-nitro-2-pyridyl, and 5-trifluoromethyl-2-pyridyl sulfones **4b−d** were synthesized in good yield (entries 1−3), whereas sulfones **4e−j** were not obtained. Instead, 2,3,5-tri-*O*-benzyl-ribofuranose and methyl 2,3,5-tri-*O*-benzyl-ribofuranoside were formed during oxidation, as was observed in the oxidation of **3a** with H_2O_2 and $(NH_4)_6Mo_7O_{24}$ (Table 1, entry 1). These results suggest that the glycosidic bonds of heteroaryl ribofuranosyl sulfones (or the intermediate sulfoxides) are susceptible to nucleophilic attack and that this susceptibility is affected by the heteroaryl groups.

With α-ribofuranosyl sulfones **4a−d** in hand, we studied the synthesis of *exo*-glycal **5a** by Julia olefination using benzaldehyde as a model compound (Table 3). The reactions were conducted under Barbier conditions in which sulfones **4** were deprotonated by a base in the presence of benzaldehyde. The bases were added at low temperatures, and the mixtures were gradually warmed to room temperature (rt) to promote the reactions. As shown in entries 1−3, the reactions of **4a** with benzaldehyde using LiHMDS, NaHMDS, and KHMDS in CH_2Cl_2 preferentially afforded (*E*)-**5a** over (*Z*)-**5a**. The stereochemistry of (*E*)-**5a** and (*Z*)-**5a** was established using NOESY experiments.[27] The assignment was also confirmed by the ^{1}H NMR spectra, in which the *exo*-C=C*H* signal of (*E*)-**5a** was shifted downfield relative to that of (*Z*)-**5a** due to the effect of endocylic 4-oxygen of the ribose.[1b,29] The highest *E* selectivity among these three reactions was obtained using LiHMDS (entry 1), but the yields were much higher with NaHMDS and KHMDS (entries 2 and 3). The *E* selectivity was improved by changing the solvent from CH_2Cl_2 to toluene (entries 4 and 5). Keeping the temperature at −78 °C throughout the reaction slowed the reaction without improving the stereoselectivity (entry 6). Increasing the initial temperature from −60 to −40 °C slightly improved the yield of **5a** at

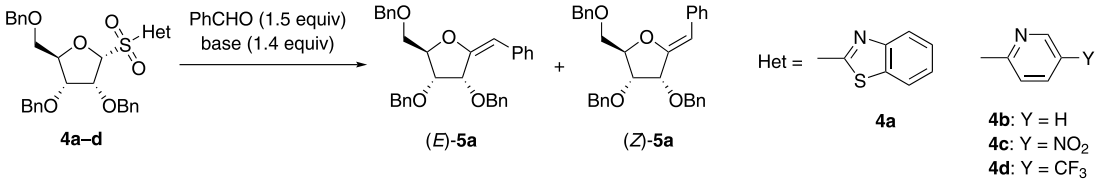
Table 2. Oxidation of 3b−j[a]



entry	Het	yield of **4** (%)
1	**b**	86
2	**c**	98
3	**d**	90

[a]Sulfones **4e−j** were not obtained by the oxidation of **3e−j**. Instead, 2,3,5-tri-*O*-benzyl-D-ribofuranose and methyl 2,3,5-tri-*O*-benzyl-D-ribofuranoside were generated as byproducts.

Table 3. Optimization of the Reaction Conditions for the Synthesis of *exo*-Glycal 5a by Julia Olefination Using Ribofuranosyl Sulfones 4a−d and PhCHO



entry	sulfone	base	solvent	conditions[a]	yield (%)	*E*:*Z*[c]
1	**4a**	LiHMDS	CH_2Cl_2	−60 °C to rt, then 4 h	29	90:10
2	**4a**	NaHMDS	CH_2Cl_2	−60 °C to rt, then 2.5 h	80	83:17
3	**4a**	KHMDS	CH_2Cl_2	−60 °C to rt, then 4 h	84	79:21
4	**4a**	NaHMDS	toluene	−60 °C to rt, then 3 h	69	90:10
5	**4a**	KHMDS	toluene	−60 °C to rt, then 3 h	86	88:12
6	**4a**	KHMDS	toluene	−78 °C, 4 h	51	84:16
7	**4a**	KHMDS	toluene	−40 °C to rt, then 3 h	90	86:14
8	**4a**	KHMDS	THF	−60 °C to rt, then 3 h	96	94:6
9	**4a**	LiHMDS	DMF	−60 °C to rt, then 3 h	62	21:79
10	**4a**	NaHMDS	DMF	−60 °C to rt, then 3 h	78	23:77
11	**4a**	KHMDS	DMF	−60 °C to rt, then 3 h	77	39:61
12	**4a**	NaHMDS	NMP	−20 °C to rt, then 3.5 h[b]	48	28:72
13	**4a**	KHMDS	NMP	−20 °C to rt, then 3.5 h[b]	43	44:56
14	**4a**	NaHMDS	DMPU	−20 °C to rt, then 3.5 h[b]	49	26:74
15	**4b**	KHMDS	toluene	−60 °C to rt, then 3 h	61	63:37
16	**4c**	KHMDS	toluene	−60 °C to rt, then 6 h	53	92:8
17	**4d**	KHMDS	toluene	−60 °C to rt, then 3 h	44	71:29

[a]Unless otherwise noted, the bath temperature was gradually elevated from the initial value to rt over 1 h. [b]The bath temperature was gradually elevated over 0.5 h. [c]Determined using ^{1}H NMR.

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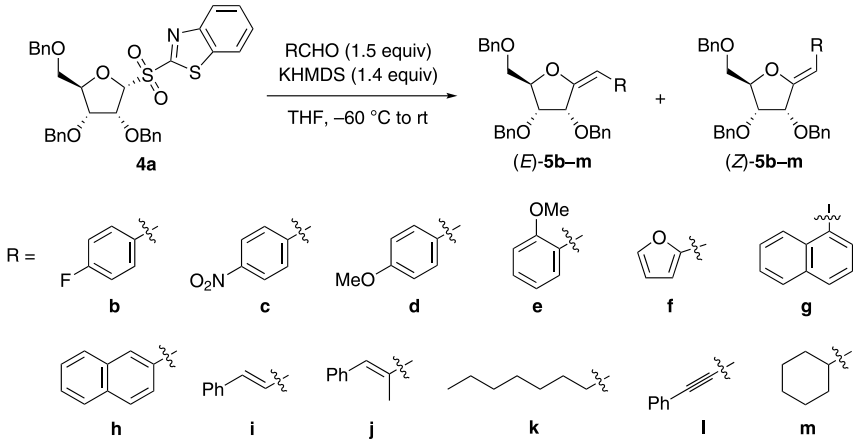
Table 4. Synthesis of *exo*-Glycals 5b−m Using Ribofuranosyl Sulfone 4a and Various Aldehydes



entry	product	yield (%)[a]	*E*:*Z*[b]	entry	product	yield (%)[a]	*E*:*Z*[b]
1	**5b**	91	90:10	7	**5h**	91	91:9
2	**5c**	97	88:12	8	**5i**	71	84:16
3	**5d**	95	93:7	9	**5j**	65	75:25
4	**5e**	79	92:8	10	**5k**	63	71:29
5	**5f**	79	87:13	11	**5l**	82	70:30
6	**5g**	64	89:11	12	**5m**	78	68:32

[a]**5b−j,m** were obtained as (*E*,*Z*) mixtures. (*E*) and (*Z*) isomers of **5k,l** were separated by chromatography. [b]Determined by ^{1}H NMR.

the cost of a small decrease in stereoselectivity (entry 7). Both the yield and stereoselectivity were improved using a more polar solvent tetrahydrofuran (THF, entry 8), whereas the use of even more polar solvents DMF, *N*-methyl pyrrolidinone (NMP), and *N*,*N*′-dimethylpropyleneurea (DMPU) led to modest *Z* selectivity (entries 9−14).[30] 2-Pyridyl sulfones **4b−d** also gave **5a** but in lower yields than that obtained using **4a** (entries 15−17). Thus, under the optimized conditions shown in entry 8, the Julia olefination of the ribofuranosyl sulfone **4a** with benzaldehyde proceeded almost quantitatively in a one-pot manner to give *exo*-glycal **5a** with high *E* selectivity.

Subsequently, sulfone **4a** was allowed to react with various aldehydes under the optimized conditions (Table 4). Aromatic aldehydes **b−h** gave the corresponding *exo*-glycals **5b−h** with high *E* selectivity (*E*/*Z* = 93:7−87:13) (entries 1−7). Aldehydes **d** and **e** with an electron-donating methoxy group at the *para*- or *ortho*-position showed stereoselectivity similar to that of benzaldehyde (entries 3 and 4), while **b** and **c**, which contain an electron-withdrawing fluoro or nitro group at the *para*-position, resulted in a slightly lower stereoselectivity (entries 1 and 2). Aliphatic aldehydes **i−m** gave lower *E* selectivity (*E*/*Z* = 84:16−68:32) compared to the aromatic aldehydes (entries 8−12).

To estimate the energy difference between (*E*)-**5a** and (*Z*)-**5a**, (*E*)-**A** and (*Z*)-**A** were chosen as model compounds (Figure 1). Both structures were optimized via DFT calculations at the B3LYP/6−31G* level of theory, and (*Z*)-**A** was found to be 1.9 kcal/mol more stable than (*E*)-**A**. Although both structures have two intramolecular hydrogen bonds, (*Z*)-**A** is more stabilized by a stronger hydrogen bond between the ribose ring oxygen and one of the *o*-hydrogens of the phenyl group (O−H distance, 2.29 Å). Additionally, the phenylethenyl moiety of (*Z*)-**A** has a planar structure and is stabilized by the overlap of the π-system on C1−C6−C7−C8 (dihedral angle, 2.0°). In contrast, the corresponding dihedral angle in (*E*)-**A** is 31.3°. The reduced overlap of the π-system is attributed to the avoidance of steric repulsion between the 2-H

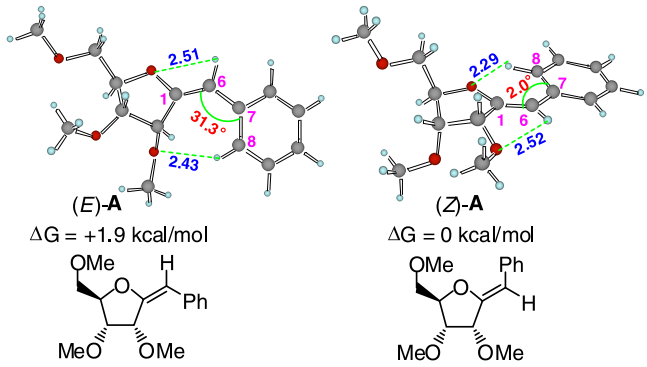


Figure 1. Optimized structures and energies of (*E*)- and (*Z*)-**A**, calculated at the B3LYP/6−31G* level.

of ribose and the phenyl group. Thus, (*E*)-**5** are considered to be kinetic products that are thermodynamically less stable than (*Z*)-**5**. This was also confirmed by the iodine-catalyzed isomerization of alkenes to thermodynamically more stable isomers;[31] **5a** (*E*:*Z* = 94:6) and **5c** (*E*:*Z* = 88:12) completely isomerized to (*Z*)-**5a** and (*Z*)-**5c** upon heating at 50 °C for 1 h in the presence of 0.3 equiv of iodine[31c] (Table 5, entries 1, and 2). However, isomerization was not successful for alkenyl- and alkyl-substituted *exo*-glycals **5i** and **5m** (complex mixtures formed; entries 3 and 4). Therefore, this isomerization should be useful for the synthesis of stereochemically pure aryl-substituted (*Z*)-*exo*-glycals.

One of the objectives of this study was to elucidate the effect of the anomeric configuration of ribofuranosyl sulfones on Julia olefination. For this purpose, the corresponding β-sulfone (β-**4a**) was prepared according to Scheme 2 via Mitsunobu-type β-selective ribofuranosylation (**6** → **7**) developed by Hocek et al.[32] and subjected to Julia olefination with benzaldehyde under the optimized conditions. In fact, the use of β-sulfone changed the stereochemistry of the reaction; (*Z*)-**5a** was

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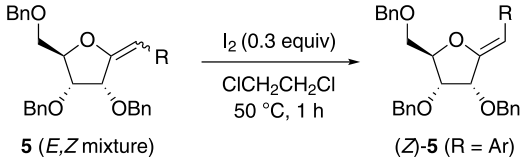
Table 5. Iodine-Catalyzed Isomerization of 5



5 (*E*,*Z* mixture) (*Z*)-5 (R = Ar)

entry	starting material	R	product	yield (%)
1	**5a** (*E*/*Z* = 94:6)	Ph	(*Z*)-**5a**	83
2	**5c** (*E*/*Z* = 88:12)	*p*-$NO_2C_6H_4$	(*Z*)-**5c**	83
3	**5i** (*E*/*Z* = 84:16)	*trans*-PhCH=CH	complex mixture	
4	**5m** (*E*/*Z* = 68:32)	*c*-Hex	complex mixture	

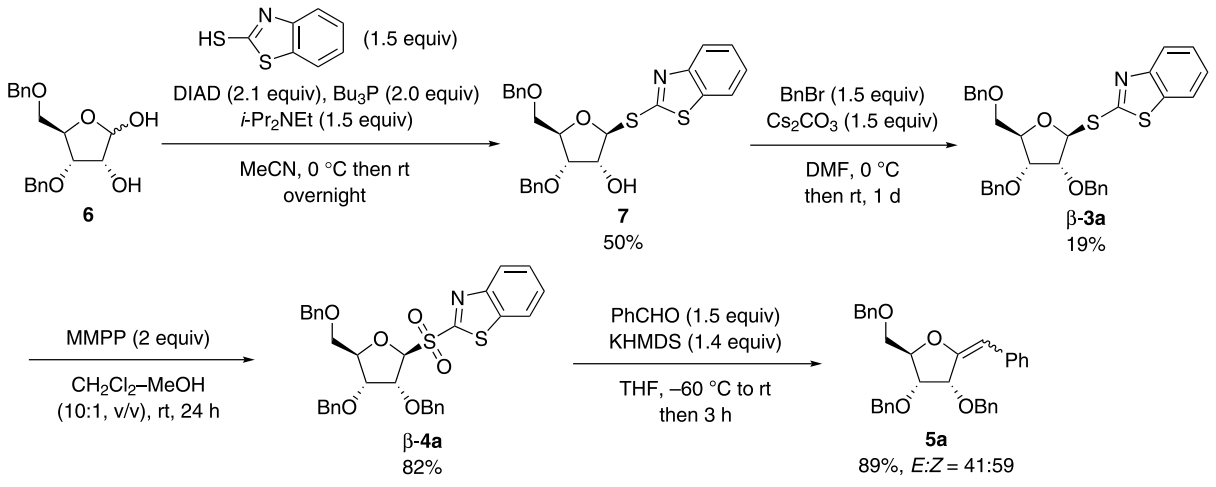
preferentially obtained over (*E*)-**5a** with low stereoselectivity (*E*/*Z* = 41:59).

We also prepared 2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl sulfone β-**4a′**, which was prepared readily via neighboring-group assistance (Scheme 3). However, its application to Julia olefination with benzaldehyde resulted in the formation of *endo*-glycal **10** due to 1,2-*syn*-elimination, which tends to occur when glycosyl sulfones are treated with a strong base.[11g,33]

To elucidate the mechanism of the olefination reactions of the α- and β-ribofuranosyl sulfones in detail, DFT calculations were carried out for the reaction of either α-**B** or β-**B** with PhCHO. The transition structures for the C−C bond formation from the complex (α-**B** and PhCHO) were identified at the B3LYP/6−31G* level (Figure 2).[27] The transition structure ***αE*-TS1** is favored by 3.6 kcal/mol over ***αZ*-TS1**. The C−C distances of the forming bond are 2.33 and 2.22 Å in ***αE*-TS1** and ***αZ*-TS1**, respectively, while the activation free energies are 4.0 and 6.1 (7.6−1.5) kcal/mol, respectively. A careful comparison of the transition structures revealed steric repulsion between the 2-H of ribose and the aldehyde proton. The H−H distance (2.04 Å) is much shorter than the sum of their van der Waals radii (2.40 Å). An intrinsic reaction coordinate (IRC) analysis of these transition structures furnished intermediates ***αE*-Int1** and ***αZ*-Int1**, from which nucleophilic addition to the *ipso* carbon of benzothiazole occurred to give ***αE*-Int2** and ***αZ*-Int2** via transition structures ***αE*-TS2** and ***αZ*-TS2**. The relative Gibbs free energies are −1.2 and 1.3 kcal/mol and the distances of the forming O−C bonds are 1.86 and 1.78 Å in ***αE*-TS2** and ***αZ*-TS2**, respectively. The length of the C=N bond in ***αE*-TS2** (1.32 Å) is only 0.03 Å longer than that in ***αE*-Int1**, while the length of the C−SO_2 bond increased from 1.84 to 1.88 Å. Similar structural changes were seen in ***αZ*-TS2**. Therefore, nucleophilic addition to the C=N bond and elimination of the sulfonyl group occur simultaneously. Finally, the elimination of both SO_2 and a 2(3*H*)-benzothiazolone anion occurs to give the alkene via the transition structures ***αE*-TS3** and ***αZ*-TS3**, whose relative Gibbs free energies are −30.9 and −17.9 kcal/mol, respectively. The rate-determining step is TS1, and ***αE*-TS1** giving the (*E*)-alkene is more stable than ***αZ*-TS1** giving the (*Z*)-alkene by 3.6 kcal/mol. This suggests that the (*E*)-alkene should be formed in high selectivity; thus, these calculations reproduced the experimentally observed product selectivity. The reaction of β-**B** with PhCHO was also analyzed using DFT calculations at the B3LYP/6−31G* level. The reaction occurs in a similar manner to that of α-**B** with PhCHO, and the rate-determining step is TS1. Figure 3 shows only the SM complex and TS1.[27] The α-carbanion β-**B** is more stable than the β-carbanion α-**B**, and the Gibbs free energies of the starting complexes ***βE*-SM** and ***βZ*-SM** relative to ***αE*-SM** are −9.2 and −8.9 kcal/mol, respectively. Transition structure ***βZ*-TS1** is favored over ***βE*-TS1** by 0.6 kcal/mol. This energy difference corresponds to a product ratio of *E*:*Z* = 27:73 at 25 °C, which is consistent with the experimental results. The distances between the C atoms of the forming C−C bond are 2.13 and 2.07 Å in ***βE*-TS1** and ***βZ*-TS1**, respectively, and their relative Gibbs free energies are 7.0 and 6.4 kcal/mol, respectively. A comparison of the transition structures revealed the presence of favorable hydrogen bonds between the aldehyde H and both the 2- and 3-methoxy oxygens in ***βZ*-TS1** with the distances of 2.54 and 2.56 Å, respectively. Therefore, the *Z*-alkene should be obtained as the main product with low selectivity, which is consistent with the experimental results.

As described in the Introduction section, *exo*-glycals have been used as versatile precursors for the synthesis of various compounds through modifications of the exocyclic C=C bonds. To elucidate the effect of the chiral ribose moiety on the stereochemistry of *exo*-C=C modifications, (*E*)-**5a** and (*Z*)-**5a** were subjected to the Simmons−Smith−Furukawa reaction.[34] The cyclopropanation occurred exclusively from the α-face to afford **11** and its epimer (*epi*-**11**) from (*E*)-**5a** and

Scheme 2. Synthesis of β-4a and Its Application to Julia Olefination with PhCHO



https://dx.doi.org/10.1021/acs.joc.0c02297
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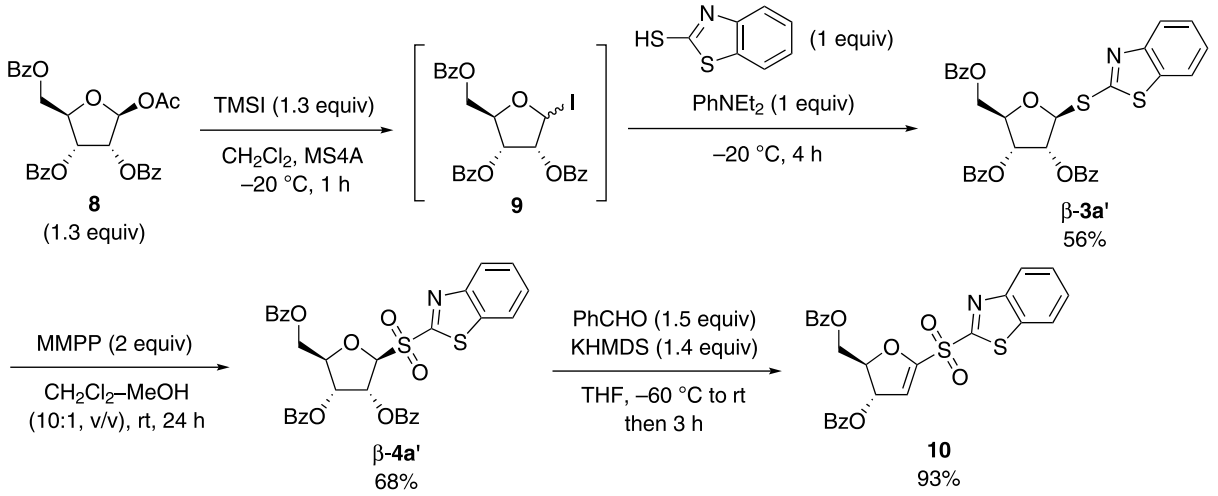
Scheme 3. Synthesis of *β*-4a′ and Its Attempted Julia Olefination with PhCHO



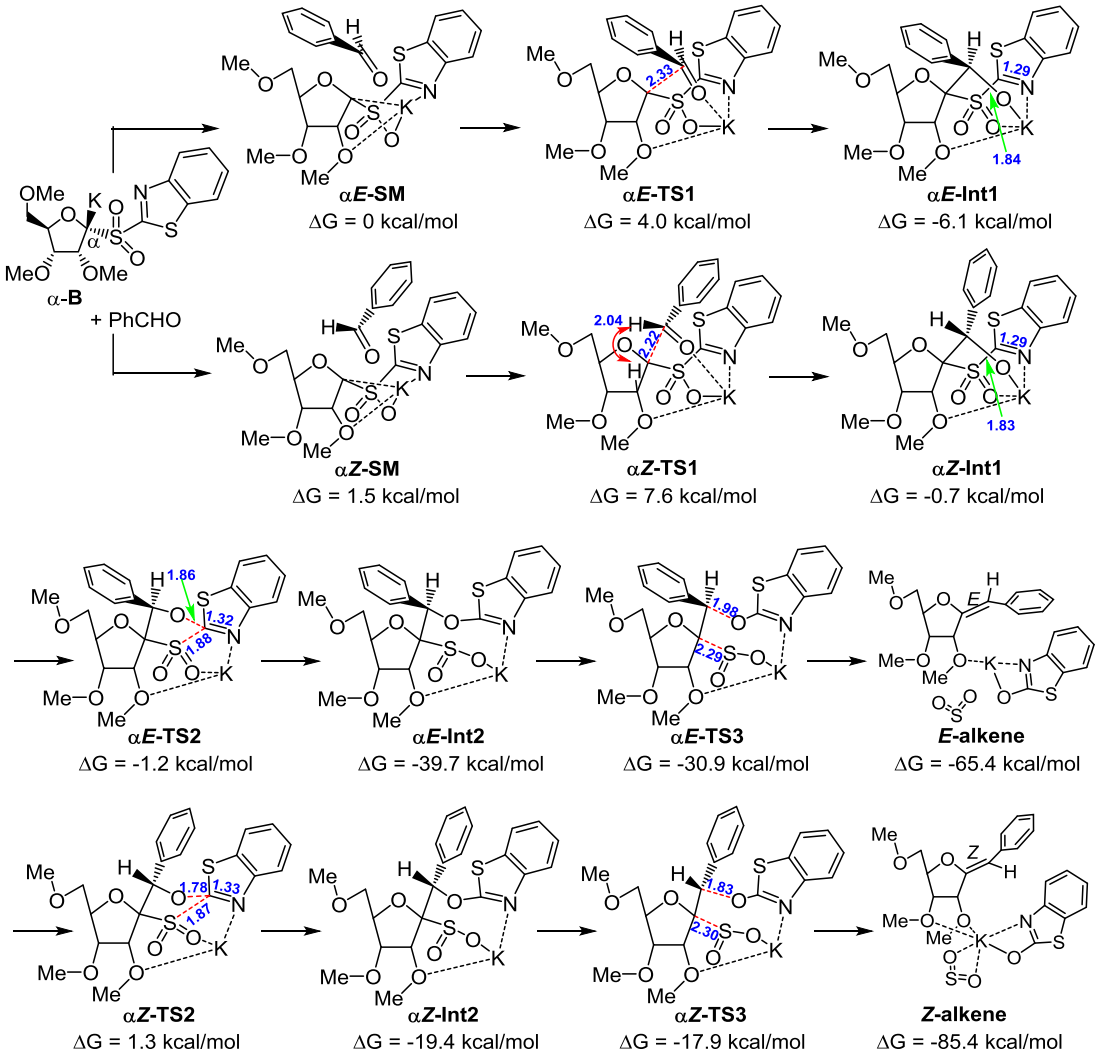


Figure 2. Reaction mechanism of the one-pot Julia olefination of *α*-ribofuranosyl sulfone with PhCHO, calculated at the B3LYP/6−31G* level (all distances in Å).

(*Z*)-**5a**, respectively (Schemes 4 and 5). The stereochemistry of **11** and *epi*-**11** was confirmed using NOESY experiments.[27] *α*-Selectivity in the Simmons−Smith−Furukawa reaction has also been reported for a benzyloxymethyl-protected uridine derivative bearing a 4′-*exo*-C═C bond.[34e] Our study indicates that the benzyl-group-protected ribose moiety also directs the zinc carbenoid to the *α*-face with its 2′- and 3′-ether moieties,

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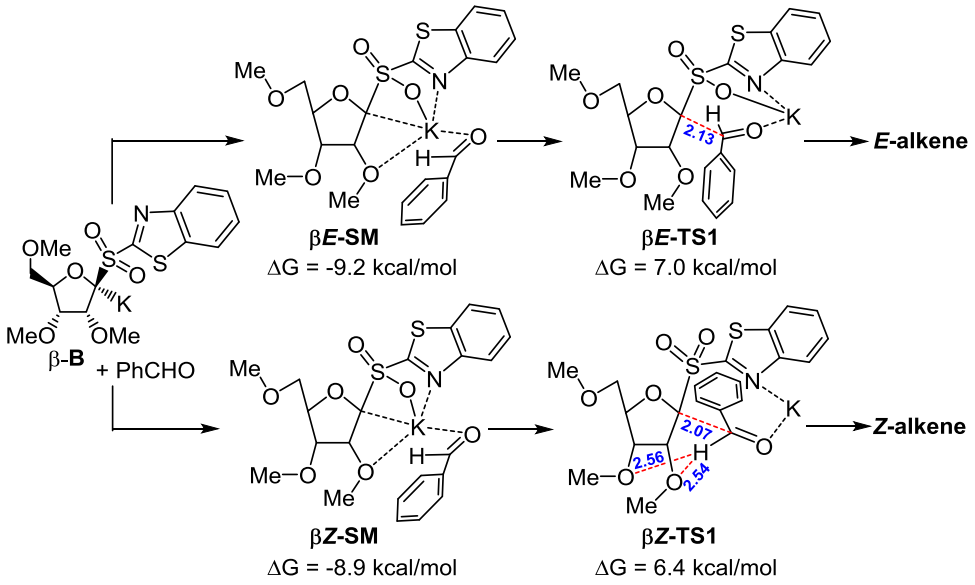
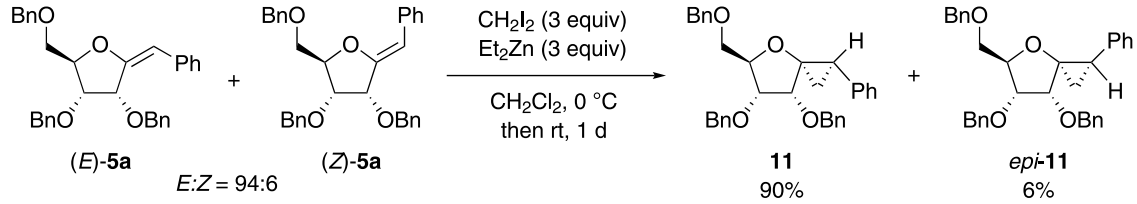
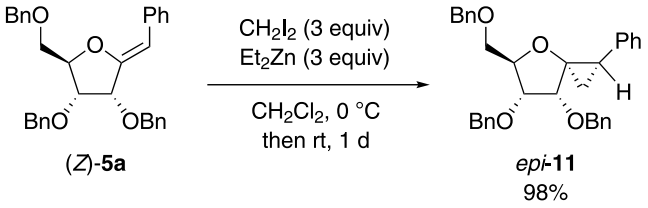


Figure 3. Rate-limiting step of the one-pot Julia olefination of β-ribofuranosyl sulfone with PhCHO, calculated at the B3LYP/6−31G* level (all distances in Å). The Gibbs free energies of SM and TS1 are shown relative to that of ***αE*-SM**.

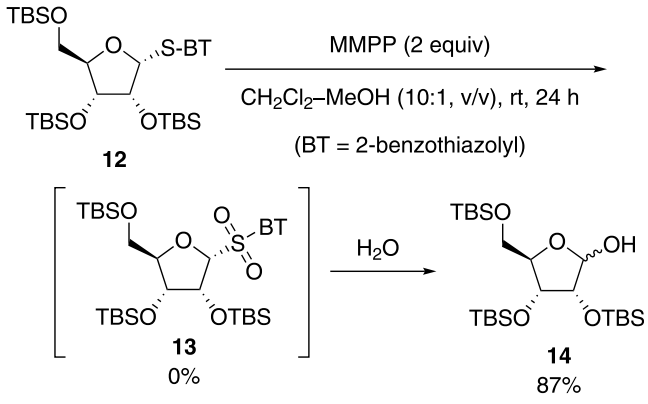
Scheme 4. Cyclopropanation of 5a (*E*:*Z* = 94:6)



Scheme 5. Cyclopropanation of (*Z*)-5a



Scheme 6. Attempted Synthesis of 2-Benzothiazolyl 2,3,5-tri-*O*-TBS-ribofuranosyl Sulfone 13



as was proposed for the α-selective cyclopropanation of the BOM-protected uridine derivative.[34e]

Benzyl protection is useful for the synthesis of *C*-glycosyl compounds without C═C bonds, but a different protecting group must be used for the synthesis of compounds in which an exocyclic C═C bond is to be retained. To expand the scope of this method, we examined the applicability of other protecting groups that could be removed in the presence of the *exo*-C═C bond. Initially, the *tert*-butyldimethylsilyl (TBS) group was chosen because it can be removed using fluoride ions without affecting the C═C bond. 2-Benzothiazolyl 2,3,5-tri-*O*-TBS-1-thioribofuranoside **12** was synthesized via the α-selective ribofuranosylation of 2-mercaptobenzothiazole using the corresponding ribofuranosyl iodide[23] and subjected to oxidation with MMPP under the optimized conditions for the benzyl-protected sulfones described above (Scheme 6). However, the desired sulfone **13** was not obtained, but hemiacetal **14** was formed during the oxidation. Thus, TBS-protected sulfone **13** was found to be more sensitive to acids due to its silyl-protection[35] compared to benzyl-protected sulfone **4a**, which could be synthesized virtually quantitatively under the same oxidation conditions.

Therefore, we turned our attention to the 2-cyanoethyl (CE) group. The CE group has been used for the synthesis of oligoribonucleotides and can be removed quickly from the 2′-hydroxy groups of ribonucleosides by treatment with tetra-*n*-butylammonium fluoride (TBAF).[36] Scheme 7 depicts the synthesis of a CE-protected ribofuranosyl sulfone and its application to Julia olefination. Ribose **15** was converted into methyl ribofuranoside **16**, and the hydroxy groups were protected with CE groups via treatment with acrylonitrile and Cs_2CO_3 in *t*-BuOH.[37] The β-isomer of **17** was separated using chromatography and hydrolyzed to give hemiacetal **18**, which

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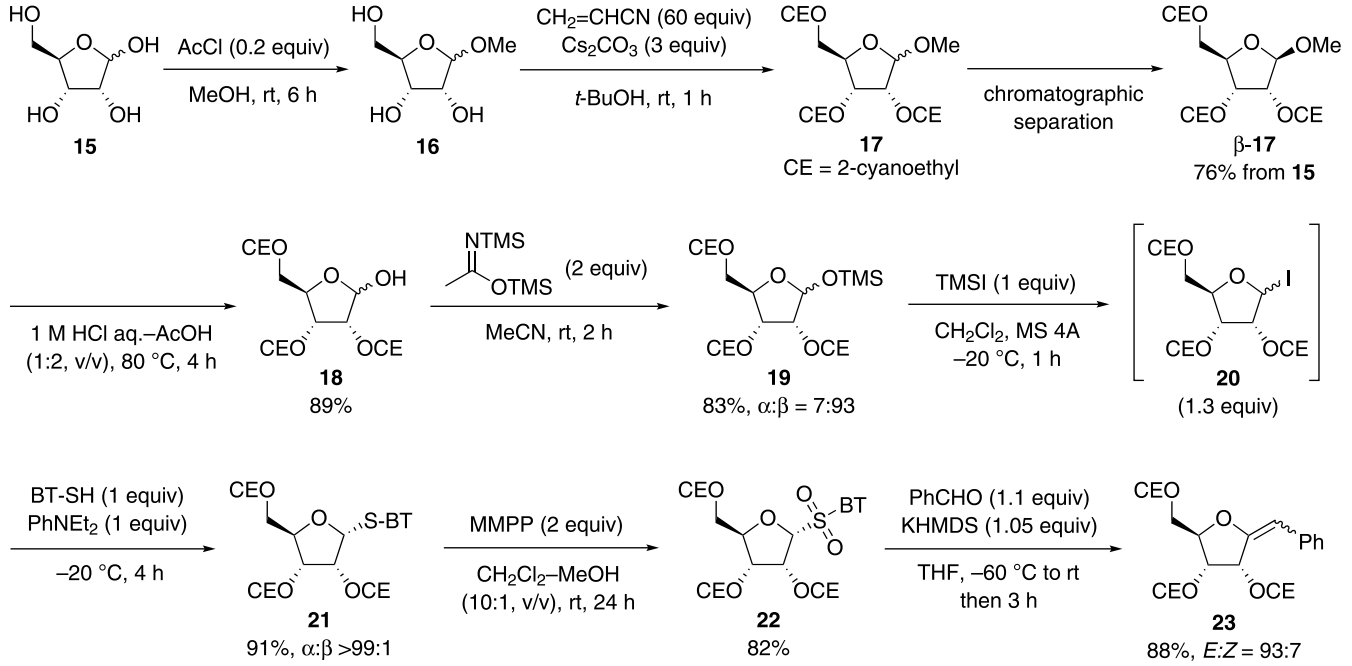
Scheme 7. Stereoselective Synthesis of 2-Benzothiazolyl 2,3,5-tri-*O*-(2-cyanoethyl)-α-D-ribofuranosyl Sulfone 22 and Its Application to Julia Olefination



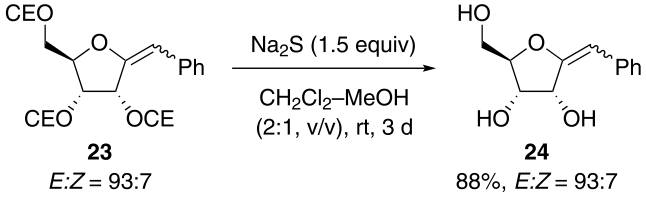
was then silylated at the anomeric position to give **19**. Treatment of **19** with TMSI gave ribofuranosyl iodide **20**, which was then allowed to react *in situ* with 2-mercaptobenzothiazole to give 1-thioribofuranoside **21** with complete α-selectivity. Oxidation with MMPP under the aforementioned conditions afforded the desired sulfone **22** in good yield. As expected, **22** was less susceptible to hydrolysis than TBS-protected sulfone **13** on account of its electron-withdrawing CE groups. A one-pot Julia olefination with benzaldehyde was conducted with a reduced amount of KHMDS to prevent the undesired cleavage of the CE groups. The desired *exo*-glycal **23** was obtained in 88% yield with E/Z = 93:7.

Finally, the deprotection of **23** was examined. It was first attempted by treatment with 1 M TBAF in THF.[36] The deprotection was complete after 24 h at 60 °C, and the desired product (**24**) was generated almost quantitatively. However, the isolation of **24** from the residual tetrabutylammonium salts was difficult. Therefore, we used instead the easily removable Na_2S[38] and found that the deprotection of **23** could be completed via treatment with 1.5 equiv of Na_2S in CH_2Cl_2–MeOH at rt for 3 days (Scheme 8). The fully deprotected *exo*-glycal **24** was isolated in 88% yield without any side reactions.

CONCLUSIONS

In conclusion, a novel one-pot Julia olefination using α-ribofuranosyl sulfones has been developed. Ribofuranosyl sulfones were obtained via α-selective glycosylation of heteroarylthiols and oxidation with MMPP. Among the heteroaryl sulfones tested, 2-benzothiazolyl sulfone was the most advantageous in terms of stability and performance as an olefination reagent. Its application to the Julia olefination with aldehydes afforded the thermodynamically less stable (*E*)-*exo*-glycals efficiently in a one-pot manner with modest-to-excellent stereoselectivity. The *E* selectivity was especially high when aromatic aldehydes were used. Such aryl-substituted (*E*)-*exo*-glycals cannot be easily synthesized using the methods reported to date. The higher *E* selectivity observed for aryl-substituted *exo*-glycals compared to alkyl-substituted ones in this novel Julia olefination is complementary to that of the Julia olefination of sugar lactones, which gives alkyl-substituted (*E*)-*exo*-glycals efficiently but not aryl-substituted ones. The effect of the anomeric configuration, which is one of the most important concerns in using glycosyl sulfones, was elucidated experimentally by carrying out the Julia olefination using a β-ribofuranosyl sulfone, which resulted in slight *Z* selectivity, as well as theoretically using DFT calculations. The successful application of 2-cyanoethyl protection to the synthesis of *exo*-glycals suggested that it should be useful for the synthesis of various sugar derivatives having unsaturated carbon–carbon bonds.

Scheme 8. Deprotection of *exo*-Glycal 23



EXPERIMENTAL SECTION

General Information. Commercially available reagents were used without purification. Dry organic solvents were prepared by appropriate procedures prior to use. The other organic solvents were of reagent grade and used as received. All reactions in dry solvents were carried out under argon. Analytical thin-layer chromatography (TLC) was performed on Merck TLC plates (No. 5715) precoated with silica gel 60 F_{254}. Column chromatography on silica gel was carried out using Kanto silica gel 60N (spherical, neutral, 40–50 or 63–210 μm). Preparative TLC (PTLC) was performed on silica gel 60 F_{254} PLC glass plates (20 cm × 20 cm, 1 mm thickness). Melting points were determined using a Yanaco MP-J3 micro melting point apparatus and were uncorrected. Optical rotations were

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measured using a Horiba SEPA-300 high-sensitivity polarimeter. The ^{1}H (400 MHz) and ^{13}C (100 MHz) NMR spectra were recorded on a JNM-AL-400 or a JNM-ECS-400 spectrometer (JEOL). Tetramethylsilane (TMS; 0.0 ppm in $CDCl_3$) and DMSO-d_5 (2.50 ppm in DMSO-d_6) were used as the internal standards for ^{1}H NMR measurements. $CDCl_3$ (77.0 ppm in $CDCl_3$) and DMSO-d_6 (39.5 ppm in DMSO-d_6) were used as the internal standards for ^{13}C NMR measurements. ^{1}H NMR data are reported as follows: chemical shift (multiplicity, integration, coupling constants). Multiplicity is indicated as follows: s (singlet); d (doublet); dd (doublet of doublets); ddd (doublet of doublet of doublets); dt (doublet of triplets); t (triplet); td (triplet of doublets); q (quartet); quint (quintet); sext (sextet); m (multiplet). Structural assignments were made with additional information from NOESY experiments. High-resolution mass spectra were recorded on a Waters Xevo Q-ToF mass spectrometer (ESI-ToF).

*2-Benzothiazolyl 2,3,5-Tri-O-benzyl-1-thio-α-D-ribofuranoside (**3a**).* **3a** (pale-yellow oil, 5.53 g, 9.71 mmol, 97%) was synthesized from 2-mercaptobenzothiazole (1.67 g, 10.0 mmol) and **1a** (6.40 g, 13.0 mmol) according to the procedure that we reported previously.[23] The NMR spectra were identical to those previously reported.[23]

*2-Benzothiazolyl 2,3,5-Tri-O-benzyl-α-D-ribofuranosyl sulfone (**4a**): General Procedure for the Synthesis of **4a**–**d**.* MMPP (1.55 g, 4.00 mmol) was added to a stirred solution of **3a** (1.14 g, 2.00 mmol) in CH_2Cl_2/MeOH (10:1, v/v; 44.0 mL) at rt. Stirring was continued for 24 h before a saturated aqueous solution of $NaHCO_3$ (30 mL) was added. The resulting mixture was extracted with CH_2Cl_2 (3 × 30 mL). The organic layers were combined and washed with a saturated aqueous solution of $NaHCO_3$ (30 mL). The aqueous layer was re-extracted with CH_2Cl_2 (30 mL). The organic layers were combined, dried over Na_2SO_4, and filtered, and the filtrate was concentrated under reduced pressure. The residue was washed with hexane and dried *in vacuo* to afford **4a** (1.20 g, 1.99 mmol, 99%) as pale-yellow crystals. M.P. = 111−113 °C. $[\alpha]_D$ = +148.2 (*c* 1.02, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.18 (d, 1H, *J* = 7.6 Hz), 7.94 (d, 1H, *J* = 7.6 Hz), 7.56 (m, 2H), 7.40−7.15 (m, 15H), 5.65 (d, 1H, *J* = 5.6 Hz), 4.96 (d, 1H, *J* = 11.4 Hz), 4.73 (d, 1H, *J* = 11.4 Hz), 4.63 (t, 1H, *J* = 5.6 Hz), 4.59 (m, 1H), 4.55 (d, 1H, *J* = 12.0 Hz), 4.45 (d, 1H, *J* = 12.0 Hz), 4.38 (d, 1H, *J* = 12.0 Hz), 4.36 (d, 1H, *J* = 12.0 Hz), 4.03 (dd, 1H, *J* = 7.8, 5.6 Hz), 3.70 (dd, 1H, *J* = 11.6, 1.8 Hz), 3.50 (dd, 1H, *J* = 11.6, 3.2 Hz). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 166.0, 152.4, 137.6, 137.3, 137.2, 137.1, 128.3, 128.2, 128.2, 128.1, 127.8, 127.7, 127.6, 127.5, 127.2, 125.3, 122.0, 94.6, 82.3, 77.2, 76.8, 74.6, 73.2, 72.8, 67.6. HRMS (ESI-TOF) *m*/*z*: [M + Na]$^+$ calcd for $C_{33}H_{31}NNaO_6S_2^+$ 624.1485; found 624.1498.

*2-Pyridyl 2,3,5-Tri-O-benzyl-α-D-ribofuranosyl Sulfone (**4b**).* **4b** (colorless oil, 1.10 g, 2.01 mmol, 86%) was obtained from **3b** (1.20 g, 2.33 mmol) according to the general procedure described for **4a**. Purification was carried out by column chromatography on silica gel (hexane/AcOEt = 1:0 → 1:1, v/v). The ^{1}H and ^{13}C NMR spectra were identical to those previously reported.[39] ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.69−8.67 (m, 1H), 8.06 (d, 1H, *J* = 7.6 Hz), 7.80 (dt, 1H, *J* = 7.6, 2.0 Hz), 7.45−7.40 (m, 3H), 7.34−7.25 (m, 9H), 7.23−7.20 (m, 2H), 7.18−7.15 (m, 2H), 5.68 (d, 1H, *J* = 5.4 Hz), 4.95 (d, 1H, *J* = 11.2 Hz), 4.73 (d, 1H, *J* = 11.2 Hz), 4.61 (t, 1H, *J* = 5.4 Hz), 4.54 (d, 1H, *J* = 11.8 Hz), 4.52 (m, 1H), 4.44 (d, 1H, *J* = 12.2 Hz), 4.38 (d, 1H, *J* = 11.8 Hz), 4.36 (d, 1H, *J* = 12.2 Hz), 4.00 (dd, 1H, *J* = 8.2, 5.4 Hz), 3.68 (dd, 1H, *J* = 11.4, 2.2 Hz), 3.50 (dd, 1H, *J* = 11.4, 3.2 Hz). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 157.3, 149.9, 137.7, 137.6, 137.5, 137.4, 128.3, 128.3, 128.2, 127.8, 127.8, 127.7, 127.6, 127.5, 127.0, 123.8, 91.9, 81.8, 77.1, 77.0, 74.7, 73.2, 72.7, 67.7. HRMS (ESI-TOF) *m*/*z*: [M + Na]$^+$ calcd for $C_{31}H_{31}NNaO_6S^+$ 568.1764; found 568.1770.

*5-Nitro-2-pyridyl 2,3,5-Tri-O-benzyl-α-D-ribofuranosyl Sulfone (**4c**).* **4c** (white foam, 1.08 g, 1.83 mmol, 98%) was obtained from **3c** (1.05 g, 1.87 mmol) according to the general procedure described for **4a**. Purification was carried out by column chromatography on silica gel (hexane/AcOEt = 9:1 → 7:3, v/v). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.27 (d, 1H, *J* = 2.0 Hz), 8.26 (dd, 1H, *J* = 8.4, 2.2 Hz), 8.06 (d, 1H, *J* = 8.4 Hz), 7.34−7.17 (m, 15H), 5.60 (d, 1H, *J* = 5.6 Hz), 4.70 (s, 2H), 4.59 (t, 1H, *J* = 5.6 Hz), 4.52 (d, 1H, *J* = 12.0 Hz), 4.51−4.47 (m, 1H), 4.50 (d, 1H, *J* = 12.0 Hz), 4.42 (d, 1H, *J* = 12.0 Hz), 4.41 (d, 1H, *J* = 12.0 Hz), 4.07 (dd, 1H, *J* = 7.0, 5.6 Hz), 3.71 (dd, 1H, *J* = 11.2, 1.8 Hz), 3.53 (dd, 1H, *J* = 11.2, 2.6 Hz). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 162.1, 145.0, 144.8, 137.6, 137.1, 136.8, 132.5, 128.4, 128.4, 128.2, 128.1, 127.8, 127.6, 124.0, 94.5, 82.7, 77.3, 74.4, 73.5, 73.1, 68.0. HRMS (ESI-TOF) *m*/*z*: [M + Na]$^+$ calcd for $C_{31}H_{30}N_2NaO_8S^+$ 613.1615; found 613.1625.

*5-Trifluoromethyl-2-pyridyl 2,3,5-Tri-O-benzyl-α-D-ribofuranosyl Sulfone (**4d**).* **4d** (white crystals, 1.46 g, 2.38 mmol, 90%) was obtained from **3d** (1.54 g, 2.64 mmol) according to the general procedure described for **4a**. Purification was carried out by column chromatography on silica gel (hexane/AcOEt = 19:1 → 17:3, v/v). M.p. = 87−88 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.86 (d, 1H, *J* = 1.2 Hz), 8.09 (d, 1H, *J* = 8.4 Hz), 7.92 (dd, 1H, *J* = 8.4, 1.2 Hz), 7.35−7.27 (m, 11H), 7.22−7.18 (m, 4H), 5.65 (d, 1H, *J* = 5.6 Hz), 4.82 (d, 1H, *J* = 11.0 Hz), 4.71 (d, 1H, *J* = 11.0 Hz), 4.60 (t, 1H, *J* = 5.6 Hz), 4.55 (d, 1H, *J* = 11.8 Hz), 4.50−4.47 (m, 1H), 4.47 (d, 1H, *J* = 12.2 Hz), 4.41 (d, 1H, *J* = 11.8 Hz), 4.38 (d, 1H, *J* = 12.2 Hz), 4.04 (dd, 1H, *J* = 8.0, 5.6 Hz), 3.69 (dd, 1H, *J* = 11.6, 2.4 Hz), 3.50 (dd, 1H, *J* = 11.6, 3.2 Hz). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 160.6, 146.7 (q, $^3J_{CF}$ = 3.8 Hz), 137.6, 137.3, 137.1, 135.0 (q, $^3J_{CF}$ = 2.8 Hz), 129.3 (q, $^2J_{CF}$ = 33.4 Hz), 128.4, 128.3, 128.2, 128.2, 127.9, 127.8, 127.8, 127.7, 127.6, 123.4, 122.5 (q, $^1J_{CF}$ = 272.7 Hz), 93.1, 82.1, 77.1, 77.0, 74.6, 73.3, 72.9, 67.7. HRMS (ESI-TOF) *m*/*z*: [M + Na]$^+$ calcd for $C_{32}H_{30}F_3NNaO_6S^+$ 636.1638; found 636.1638.

*2,5-Anhydro-3,4,6-tri-O-benzyl-1-deoxy-1-phenyl-D-ribo-hex-1-enitol (**5a**): General Procedure for the Synthesis of **5a**–**m**.* **4a** (0.602 g, 1.00 mmol) and benzaldehyde (0.153 mL, 1.50 mmol) were dissolved in dry THF (10.0 mL) under argon and cooled to −60 °C. Under stirring, a 0.5 M KHMDS solution in toluene (2.80 mL, 1.40 mmol) was added dropwise. The mixture was gradually warmed to rt over 1 h. Stirring was continued for 3 h, before a saturated aqueous solution of NH_4Cl (20 mL) and H_2O (30 mL) were added. The resulting mixture was extracted with CH_2Cl_2 (3 × 30 mL). The organic layers were combined and washed with H_2O (30 mL). The aqueous layer was re-extracted with CH_2Cl_2 (30 mL). The organic layers were combined, dried over Na_2SO_4, and filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane/AcOEt = 1:0 → 9:1, v/v) to afford **5a** (0.474 g, 0.963 mmol, 96%, *E*:*Z* = 94:6) as a pale-yellow oil. $[\alpha]_D$ = −26.3 (*c* 1.66, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz): (*E*)-**5a**: δ 7.39−7.26 (m, 17H), 7.19−7.16 (m, 3H), 6.23 (s, 1H, *exo*-C=C*H*), 4.80 (d, 1H, *J* = 4.8 Hz), 4.72 (d, 1H, *J* = 11.5 Hz), 4.65−4.49 (m, 6H), 4.10 (dd, 1H, *J* = 8.8, 4.8 Hz), 3.81 (dd, 1H, *J* = 11.3, 2.3 Hz), 3.63 (dd, 1H, *J* = 11.3, 4.6 Hz). (*Z*)-**5a**: 5.42 (s, 1H, *exo*-C=C*H*). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): (*E*)-**5a**: δ 155.4, 137.8, 137.3, 136.0, 128.4, 128.3, 128.2, 128.1, 128.0, 127.9, 127.8, 127.8, 127.6, 127.5, 125.8, 106.2, 80.3, 78.2, 73.3, 72.7, 72.4, 70.4, 68.7. HRMS (ESI-TOF) *m*/*z*: [M + Na]$^+$ calcd for $C_{33}H_{32}NaO_4^+$ 515.2193; found 515.2208.

*2,5-Anhydro-3,4,6-tri-O-benzyl-1-deoxy-1-(4-fluorophenyl)-D-ribo-hex-1-enitol (**5b**).* **5b** (pale-yellow oil, 0.0464 g, 0.0909 mmol, 91%, *E*/*Z* = 90:10) was obtained from **4a** (0.0602 g, 0.100 mmol) and 4-fluorobenzaldehyde (0.0161 mL, 0.150 mmol) according to the general procedure described for **5a**–**m**. ^{1}H NMR ($CDCl_3$, 400 MHz): (*E*)-**5b**: δ 7.38−7.17 (m, 17H), 6.98−6.92 (m, 2H), 6.17 (s, 1H, *exo*-C=C*H*), 4.75−4.72 (m, 2H), 4.66−4.50 (m, 6H), 4.11 (dd, 1H, *J* = 8.6, 5.0 Hz), 3.80 (dd, 1H, *J* = 11.2, 2.4 Hz), 3.62 (dd, 1H, *J* = 11.2, 4.5 Hz). (*Z*)-**5b**: δ 5.39 (s, 1H, *exo*-C=C*H*). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): (*E*)-**5b**: δ 161.2 (d, J_{CF} = 244.1 Hz), 155.3, 137.9, 137.8, 137.4, 132.1 (d, J_{CF} = 3.8 Hz), 129.5 (d, J_{CF} = 7.7 Hz), 128.4, 128.4, 128.3, 128.1, 128.0, 127.9, 127.8, 127.7, 127.7, 115.3 (d, J_{CF} = 21.9 Hz), 105.2, 80.6, 78.3, 73.5, 72.9, 72.7, 70.5, 68.8. HRMS (ESI-TOF) *m*/*z*: [M + Na]$^+$ calcd for $C_{33}H_{31}FNaO_4^+$ 533.2099; found 533.2060.

*2,5-Anhydro-3,4,6-tri-O-benzyl-1-deoxy-1-(4-nitrophenyl)-D-ribo-hex-1-enitol (**5c**).* **5c** (pale-yellow oil, 0.0521 g, 0.0970 mmol, 97%, *E*:*Z* = 88:12) was obtained from **4a** (0.0602 g, 0.100 mmol) and 4-nitrobenzaldehyde (0.0227 g, 0.150 mmol) according to the general procedure described for **5a**–**m**. ^{1}H NMR ($CDCl_3$, 400 MHz): (*E*)-

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5c: δ 8.07 (d, 2H, *J* = 8.8 Hz), 7.38−7.20 (m, 17H), 6.21 (s, 1H, *exo*-C=C*H*), 4.81 (d, 1H, *J* = 5.2 Hz), 4.77−4.52 (m, 7H), 4.19 (dd, 1H, *J* = 8.1, 5.2 Hz), 3.81 (dd, 1H, *J* = 11.3, 2.4 Hz), 3.63 (dd, 1H, *J* = 11.3, 4.2 Hz). (*Z*)-**5c**: δ 5.51 (s, 1H, *exo*-C=C*H*). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): (*E*)-**5c**: δ 159.1, 145.4, 143.3, 137.7, 137.4, 137.2, 128.5, 128.4, 128.2, 128.2, 128.1, 128.1, 127.8, 127.8, 123.8, 104.6, 81.5, 78.1, 73.7, 73.6, 72.9, 70.9, 68.5. HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ calcd for $C_{33}H_{32}NO_6^+$ 538.2224; found 538.2194.

*2,5-Anhydro-3,4,6-tri-O-benzyl-1-deoxy-1-(4-methoxyphenyl)-D-ribo-hex-1-enitol (**5d**).* **5d** (pale-yellow oil, 0.0495 g, 0.0947 mmol, 95%, *E*:*Z* = 93:7) was obtained from **4a** (0.0603 g, 0.100 mmol) and *p*-anisaldehyde (0.0182 mL, 0.150 mmol) according to the general procedure described for **5a**−**m**. ^1H NMR ($CDCl_3$, 400 MHz): (*E*)-**5d**: δ 7.36−7.18 (m, 17H), 6.84−6.80 (m, 2H), 6.19 (s, 1H, *exo*-C=C*H*), 4.78 (d, 1H, *J* = 4.9 Hz), 4.73 (d, 1H, *J* = 11.5 Hz), 4.65−4.49 (m, 6H), 4.09 (dd, 1H, *J* = 8.8, 4.9 Hz), 3.80 (dd, 1H, *J* = 11.2, 2.4 Hz), 3.80 (s, 3H), 3.62 (dd, 1H, *J* = 11.2, 4.6 Hz). (*Z*)-**5d**: δ 5.37 (s, 1H, *exo*-C=C*H*). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): (*E*)-**5d**: δ 158.0, 154.2, 138.1, 138.0, 137.5, 129.2, 128.6, 128.4, 128.3, 128.2, 128.2, 127.9, 127.8, 127.6, 127.6, 113.9, 105.9, 80.4, 78.4, 73.4, 72.7, 72.6, 70.4, 68.9, 55.2. HRMS (ESI-TOF) *m*/*z*: $[M + Na]^+$ calcd for $C_{34}H_{34}NaO_5^+$ 545.2298; found 545.2294.

*2,5-Anhydro-3,4,6-tri-O-benzyl-1-deoxy-1-(2-methoxyphenyl)-D-ribo-hex-1-enitol (**5e**).* **5e** (pale-yellow oil, 0.0412 g, 0.0788 mmol, 79%, *E*:*Z* = 92:8) was obtained from **4a** (0.0602 g, 0.100 mmol) and *o*-anisaldehyde (0.0181 mL, 0.150 mmol) according to the general procedure described for **5a**−**m**. ^1H NMR ($CDCl_3$, 400 MHz): (*E*)-**5e**: δ 7.34−7.18 (m, 15H), 7.09 (dd, 2H, *J* = 6.7, 2.9 Hz), 6.89−6.84 (m, 2H), 6.32 (s, 1H, *exo*-C=C*H*), 4.68−4.55 (m, 6H), 4.44 (t, 2H, *J* = 11.2 Hz), 4.06 (dd, 1H, *J* = 8.8, 4.6 Hz), 3.81 (dd, 1H, *J* = 11.3, 2.4 Hz), 3.79 (s, 3H), 3.64 (dd, 1H, *J* = 11.3, 4.8 Hz). (*Z*)-**5e**: δ 5.87 (s, 1H, *exo*-C=C*H*). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): (*E*)-**5e**: δ 156.8, 155.3, 138.1, 138.0, 137.5, 129.5, 128.4, 128.3, 128.1, 127.9, 127.8, 127.6, 127.6, 127.5, 125.2, 120.5, 110.4, 101.3, 80.4, 78.2, 73.4, 72.5, 72.4, 70.3, 69.0, 55.3. HRMS (ESI-TOF) *m*/*z*: $[M + Na]^+$ calcd for $C_{34}H_{34}NaO_5^+$ 545.2298; found 545.2294.

*2,5-Anhydro-3,4,6-tri-O-benzyl-1-deoxy-1-(2-furanyl)-D-ribo-hex-1-enitol (**5f**).* **5f** (pale-yellow oil, 0.0381 g, 0.0790 mmol, 79%, *E*:*Z* = 87:13) was obtained from **4a** (0.0602 g, 0.100 mmol) and furfural (0.0124 mL, 0.150 mmol) according to the general procedure described for **5a**−**m**. ^1H NMR ($CDCl_3$, 400 MHz): (*E*)-**5f**: δ 7.34−7.24 (m, 16H), 6.36 (dd, 1H, *J* = 3.2, 1.9 Hz), 6.10 (dt, 1H, *J* = 3.2, 0.7 Hz), 5.98 (s, 1H, *exo*-C=C*H*), 5.12 (d, 1H, *J* = 4.6 Hz), 4.75−4.50 (m, 7H), 4.09 (dd, 1H, *J* = 8.9, 4.6 Hz), 3.80 (dd, 1H, *J* = 11.4, 2.3 Hz), 3.61 (dd, 1H, *J* = 11.4, 4.7 Hz). (*Z*)-**5f**: δ 5.54 (s, 1H, *exo*-C=C*H*). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): (*E*)-**5f**: δ 154.8, 150.6, 140.7, 138.6, 138.0, 137.5, 128.4, 128.3, 128.1, 127.9, 127.9, 127.7, 127.7, 127.6, 127.4, 111.3, 107.0, 95.7, 80.4, 78.0, 73.5, 73.4, 72.4, 70.6, 68.6. HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ calcd for $C_{31}H_{31}O_5^+$ 483.2166; found 483.2186.

*2,5-Anhydro-3,4,6-tri-O-benzyl-1-deoxy-1-(1-naphthyl)-D-ribo-hex-1-enitol (**5g**).* **5g** (pale-yellow oil, 0.0350 g, 0.0645 mmol, 64%, *E*:*Z* = 89:11) was obtained from **4a** (0.0602 g, 0.100 mmol) and 1-naphthaldehyde (0.0204 mL, 0.150 mmol) according to the general procedure described for **5a**−**m**. ^1H NMR ($CDCl_3$, 400 MHz): (*E*)-**5g**: δ 8.09−8.05 (m, 1H), 7.89−7.85 (m, 1H), 7.77 (dd, 1H, *J* = 7.2, 2.3 Hz), 7.52−7.11 (m, 17H), 6.77 (d, 2H, *J* = 7.2 Hz), 6.65 (s, 1H, *exo*-C=C*H*), 4.69−4.54 (m, 5H), 4.40 (d, 2H, *J* = 11.7 Hz), 4.14−4.08 (m, 2H), 3.87 (dd, 1H, *J* = 11.3, 2.2 Hz), 3.69 (dd, 1H, *J* = 11.3, 4.6 Hz). (*Z*)-**5g**: δ 6.10 (s, 1H, *exo*-C=C*H*). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): (*E*)-**5g**: δ 156.7, 138.0, 137.6, 137.3, 133.6, 133.3, 132.5, 128.4, 128.0, 127.9, 127.9, 127.7, 127.6, 127.5, 127.1, 126.7, 126.1, 125.9, 125.5, 125.0, 103.0, 80.6, 77.9, 73.5, 72.3, 72.0, 70.3, 68.8. HRMS (ESI-TOF) *m*/*z*: $[M + Na]^+$ calcd for $C_{37}H_{34}NaO_4^+$ 565.2349; found 565.2333.

*2,5-Anhydro-3,4,6-tri-O-benzyl-1-deoxy-1-(2-naphthyl)-D-ribo-hex-1-enitol (**5h**).* **5h** (pale-yellow oil, 0.0495 g, 0.0912 mmol, 91%, *E*:*Z* = 91:9) was obtained from **4a** (0.0602 g, 0.100 mmol) and 2-naphthaldehyde (0.0234 g, 0.150 mmol) according to the general procedure described for **5a**−**m**. ^1H NMR ($CDCl_3$, 400 MHz): (*E*)-**5h**: δ 7.80−7.66 (m, 4H), 7.45−7.12 (m, 18H), 6.37 (s, 1H, *exo*-C=C*H*), 4.86 (d, 1H, *J* = 4.8 Hz), 4.73 (d, 1H, *J* = 11.6 Hz), 4.69−4.51 (m, 7H), 4.15 (dd, 1H, *J* = 8.7, 4.8 Hz), 3.84 (dd, 1H, *J* = 11.3, 2.4 Hz), 3.65 (dd, 1H, *J* = 11.3, 4.5 Hz). (*Z*)-**5h**: δ 5.59 (s, 1H, *exo*-C=C*H*). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): (*E*)-**5h**: δ 155.9, 137.9, 137.9, 137.4, 133.6, 131.8, 128.4, 128.4, 128.2, 128.0, 127.9, 127.9, 127.8, 127.7, 127.6, 127.5, 126.8, 126.3, 126.1, 125.4, 106.3, 80.5, 78.4, 73.5, 73.1, 72.7, 70.6, 68.7. HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ calcd for $C_{37}H_{35}O_4^+$ 543.2530; found 543.2542.

*(1E,3E)- and (1E,3Z)-4,7-Anhydro-5,6,8-tri-O-benzyl-1,2,3-trideoxy-1-phenyl-D-ribo-1,3-octadienitol (**5i**).* **5i** (pale-yellow oil, 0.0366 g, 0.0706 mmol, 71%, *E*:*Z* = 84:16) was obtained from **4a** (0.0602 g, 0.100 mmol) and *trans*-cinnamaldehyde (0.0189 mL, 0.150 mmol) according to the general procedure described for **5a**−**m**. ^1H NMR ($CDCl_3$, 400 MHz): (*E*)-**5i**: δ 7.40−7.16 (m, 20H), 6.70 (dd, 1H, *J* = 15.5, 11.4 Hz), 6.38 (d, 1H, *J* = 15.5 Hz), 5.97 (d, 1H, *J* = 11.4 Hz, *exo*-C=C*H*), 4.82−4.73 (m, 3H), 4.64−4.48 (m, 5H), 4.07 (dd, 1H, *J* = 8.4, 4.6 Hz), 3.78 (dd, 1H, *J* = 11.4, 2.4 Hz), 3.60 (dd, 1H, *J* = 11.4, 4.5 Hz). (*Z*)-**5i**: δ 5.39 (d, 1H, *J* = 11.0 Hz, *exo*-C=C*H*). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): (*E*)-**5i**: δ 156.2, 137.9, 137.9, 137.7, 137.4, 128.7, 128.5, 128.5, 128.4, 128.3, 128.1, 128.0, 127.8, 127.8, 127.7, 127.6, 126.8, 125.9, 124.0, 106.8, 81.0, 77.4, 73.4, 72.4, 71.5, 70.0, 68.6. HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ calcd for $C_{35}H_{35}O_4^+$ 519.2530; found 519.2544.

*(1E,3E)- and (1E,3Z)-4,7-Anhydro-5,6,8-tri-O-benzyl-1,2,3-trideoxy-2-methyl-1-phenyl- D-ribo-1,3-octadienitol (**5j**).* **5j** (pale-yellow oil, 0.0344 g, 0.0646 mmol, 65%, *E*:*Z* = 75:25) was obtained from **4a** (0.0603 g, 0.100 mmol) and α-methyl-*trans*-cinnamaldehyde (0.0209 mL, 0.150 mmol) according to the general procedure described for **5a**−**m**. ^1H NMR ($CDCl_3$, 400 MHz): (*E*)-**5j**: δ 7.41−7.18 (m, 20H), 6.47 (s, 1H), 5.86 (s, 1H, *exo*-C=C*H*), 4.87 (d, 1H, *J* = 4.8 Hz), 4.79−4.46 (m, 7H), 4.11 (dd, 1H, *J* = 8.8, 4.8 Hz), 3.80 (dd, 1H, *J* = 11.3, 2.3 Hz), 3.61 (dd, 1H, *J* = 11.3, 4.4 Hz), 2.03 (s, 3H). (*Z*)-**5j**: δ 5.15 (s, 1H, *exo*-C=C*H*). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): (*E*)-**5j**: δ 154.4, 138.2, 138.1, 138.0, 137.5, 133.2, 129.1, 128.4, 128.3, 128.3, 128.1, 128.0, 128.0, 128.0, 127.9, 127.8, 127.6, 127.6, 127.5, 126.1, 111.4, 79.9, 78.6, 73.4, 73.4, 72.7, 70.7, 68.7, 18.2. HRMS (ESI-TOF) *m*/*z*: $[M + Na]^+$ calcd for $C_{36}H_{36}NaO_4^+$ 555.2506; found 555.2485.

*(2R,3R,4R)-3,4-Bis(benzyloxy)-2-benzyloxymethyl-5-octylidenetetrahydrofuran (**5k**).* (*E*)-**5k** (pale-yellow oil, 0.0229 g, 0.0445 mmol, 45%) and (*Z*)-**5k** (pale-yellow oil, 0.0093 g, 0.018 mmol, 18%) were obtained from **4a** (0.0602 g, 0.100 mmol) and octanal (0.0234 mL, 0.150 mmol) according to the general procedure described for **5a**−**m**. Purification was carried out by column chromatography on silica gel (hexane/AcOEt = 1:0 → 97:3, v/v) and PTLC (hexane/AcOEt = 3:1, v/v). (*E*)-**5k**: ^1H NMR ($CDCl_3$, 400 MHz): δ 7.38−7.27 (m, 15H), 5.03 (t, 1H, *J* = 7.8 Hz, *exo*-C=C*H*), 4.72 (d, 1H, *J* = 11.6 Hz), 4.70 (d, 1H, *J* = 11.4 Hz), 4.60 (d, 1H, *J* = 12.0 Hz), 4.57 (d, 1H, *J* = 11.6 Hz), 4.54−4.48 (m, 3H), 4.44 (ddd, 1H, *J* = 8.8, 4.6, 2.4 Hz), 3.98 (dd, 1H, *J* = 8.8, 4.8 Hz), 3.75 (dd, 1H, *J* = 11.4, 2.4 Hz), 3.58 (dd, 1H, *J* = 11.4, 4.6 Hz), 2.08−1.92 (m, 2H), 1.41−1.19 (m, 10H), 0.88 (t, 3H, *J* = 7.0 Hz). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ 152.3, 138.4, 138.1, 137.6, 128.4, 128.3, 127.9, 127.9, 127.7, 127.6, 104.5, 79.9, 77.9, 73.4, 72.3, 71.8, 70.2, 69.0, 31.8, 30.6, 29.2, 29.2, 27.3, 22.6, 14.1. HRMS (ESI-TOF) *m*/*z*: $[M + Na]^+$ calcd for $C_{34}H_{42}NaO_4^+$ 537.2975; found 537.2952. (*Z*)-**5k**: ^1H NMR ($CDCl_3$, 400 MHz) δ 7.39−7.27 (m, 15H), 4.74 (d, 1H, *J* = 12.2 Hz), 4.62 (d, 1H, *J* = 11.8 Hz), 4.60 (d, 1H, *J* = 12.2 Hz), 4.55−4.44 (m, 5H, PhC*H* × 3, C4-*H*, *exo*-C=C*H*), 4.09 (d, 1H, *J* = 4.4 Hz), 3.95 (dd, 1H, *J* = 7.8, 4.4 Hz), 3.74 (dd, 1H, *J* = 11.4, 2.6 Hz), 3.59 (dd, 1H, *J* = 11.4, 4.6 Hz), 2.17−2.07 (m, 2H), 1.43−1.25 (m, 10H), 0.87 (t, 3H, *J* = 7.0 Hz). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ 151.3, 138.3, 138.1, 137.6, 128.4, 128.3, 128.0, 128.0, 127.8, 127.6, 127.6, 127.5, 104.0, 81.1, 74.8, 73.3, 71.9, 69.3, 69.1, 31.9, 29.8, 29.3, 29.2, 24.7, 22.7, 14.1. HRMS (ESI-TOF) *m*/*z*: $[M + Na]^+$ calcd for $C_{34}H_{42}NaO_4^+$ 537.2975; found 537.2969.

*4,7-Anhydro-5,6,8-tri-O-benzyl-1,3-dideoxy-1-phenyl-D-ribo-oct-3-en-1-ynitol (**5l**).* (*E*)-**5l** (pale-yellow oil, 0.0296 g, 0.0573 mmol, 57%) and (*Z*)-**5l** (pale-yellow oil, 0.0131 g, 0.0254 mmol, 25%) were

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obtained from **4a** (0.0602 g, 0.100 mmol) and 3-phenyl-2-propinal (0.0195 g, 0.150 mmol) according to the general procedure described for **5a**−**m**. Separation of (*E*)-**5l** and (*Z*)-**5l** was carried out by column chromatography on silica gel (hexane/AcOEt = 1:0 → 9:1, v/v). The ^{1}H and ^{13}C NMR spectra of (*Z*)-**5l** were identical to those reported in the literature.[19] (*E*)-**5l**: ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.42−7.26 (m, 20H), 5.39 (s, 1H, *exo*-C═C*H*), 4.94 (d, 1H, *J* = 12.0 Hz), 4.76 (d, 1H, *J* = 12.0 Hz), 4.74 (d, 1H, *J* = 4.5 Hz), 4.66−4.63 (m, 1H), 4.64 (d, 1H, *J* = 11.7 Hz), 4.58 (d, 1H, *J* = 12.1 Hz), 4.52 (d, 1H, *J* = 12.1 Hz), 4.45 (d, 1H, *J* = 11.7 Hz), 4.05 (dd, 1H, *J* = 8.8, 4.5 Hz), 3.79 (dd, 1H, *J* = 11.5, 2.2 Hz), 3.60 (dd, 1H, *J* = 11.5, 4.6 Hz). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 165.6, 138.2, 137.8, 137.3, 131.0, 128.4, 128.4, 128.3, 128.3, 128.0, 127.9, 127.7, 127.7, 127.6, 123.8, 91.1, 86.3, 85.1, 82.3, 76.8, 73.4, 73.4, 72.3, 71.4, 68.3. HRMS (ESI-TOF) *m*/*z*: [M + H]$^+$ calcd for $C_{35}H_{33}O_4^+$ 517.2373; found 517.2388. (*Z*)-**5l**: ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.45−7.43 (m, 2H), 7.37−7.26 (m, 18H), 4.90 (s, 1H, *exo*-C═C*H*), 4.72 (d, 1H, *J* = 12.0 Hz), 4.69−4.65 (m, 1H), 4.63−4.51 (m, 5H), 4.32 (d, 1H, *J* = 4.8 Hz), 4.07 (dd, 1H, *J* = 6.0, 4.8 Hz), 3.77 (dd, 1H, *J* = 11.5, 3.0 Hz), 3.63 (dd, 1H, *J* = 11.5, 3.8 Hz). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 163.1, 137.9, 137.4, 137.3, 131.4, 128.5, 128.4, 128.4, 128.1, 128.1, 128.0, 127.9, 127.7, 127.6, 124.0, 93.0, 84.2, 83.8, 81.8, 76.3, 75.5, 73.4, 72.0, 70.6, 68.4. HRMS (ESI-TOF) *m*/*z*: [M + H]$^+$ calcd for $C_{35}H_{33}O_4^+$ 517.2373; found 517.2380.

*2,5-Anhydro-3,4,6-tri-O-benzyl-1-cyclohexyl-1-deoxy-D-ribo-hex-1-enitol (**5m**).* **5m** (pale-yellow oil, 0.0391 g, 0.0784 mmol, 78%, *E*:*Z* = 68:32) was obtained from **4a** (0.0602 g, 0.100 mmol) and cyclohexanecarboxaldehyde (0.0181 mL, 0.150 mmol) according to the general procedure described for **5a**−**m**. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.38−7.27 (m, 15H, (*E*, *Z*)-Ar-*H*), 4.92 (d, 1H, *J* = 10.5 Hz, (*E*)-*exo*-C═C*H*), 4.75−4.45 (m, 7H, (*E*, *Z*)-PhC*H*$_2$, (*E*)-C2-*H*, (*Z*)-C4-*H*), 4.43 (ddd, 1H, *J* = 8.8, 4.8, 2.4 Hz, (*E*)-C4-*H*), 4.33 (d, 1H, *J* = 9.0 Hz, (*Z*)-*exo*-C═C*H*), 4.06 (d, 1H, *J* = 4.6 Hz, (*Z*)-C2-*H*), 3.98 (dd, 1H, *J* = 8.8, 4.8 Hz, (*E*)-C3-*H*), 3.94 (dd, 1H, *J* = 8.0, 4.6 Hz, (*Z*)-C3-*H*), 3.75 (dd, 1H, *J* = 11.3, 2.4 Hz, (*E*)-C5-*H*), 3.74 (dd, 1H, *J* = 11.3, 2.5 Hz, (*Z*)-C5-*H*), 3.59 (dd, 1H, *J* = 11.3, 4.8 Hz, (*Z*)-C5-*H*), 3.59 (dd, 1H, *J* = 11.3, 4.8 Hz, (*E*)-C5-*H*), 2.50−2.40 (m, 1H, (*Z*)-C*H*(CH$_2$)$_5$), 2.05−1.95 (m, 1H, (*E*)-C*H*(CH$_2$)$_5$), 1.79−1.62 (m, 4H, (*E*, *Z*)-*c*-Hex), 1.38−1.01 (m, 6H, (*E*, *Z*)-*c*-Hex). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 151.1, 149.9, 147.4, 142.7, 140.9, 138.3, 138.3, 138.1, 138.1, 137.9, 137.4, 128.5, 128.4, 128.3, 128.3, 128.0, 128.0, 127.9, 127.9, 127.8, 127.7, 127.6, 127.6, 127.6, 127.5, 127.5, 126.9, 110.6, 110.1, 103.9, 81.2, 79.8, 78.2, 74.9, 74.2, 73.4, 73.2, 72.3, 71.8, 71.6, 70.1, 69.1, 69.1, 69.0, 65.3, 64.4, 36.4, 34.5, 34.3, 34.1, 33.6, 33.3, 33.0, 32.7, 26.4, 26.1, 25.9, 25.8. HRMS (ESI-TOF) *m*/*z*: [M + Na]$^+$ calcd for $C_{33}H_{38}NaO_4^+$ 521.2662; found 521.2654.

*Synthesis of (Z)-**5a** by Iodine-Catalyzed Isomerization.* A solution of **5a** (*E*:*Z* = 94:6, 0.0493 g, 0.100 mmol) and I_2 (0.0076 g, 0.030 mmol) in dry 1,2-dichloroethane (1.00 mL) was stirred for 1 h at 50 °C in an oil bath under argon. Subsequently, the mixture was cooled to rt, before a saturated aqueous solution of $Na_2S_2O_3$ (2 mL) and a saturated aqueous solution of $NaHCO_3$ (2 mL) were added. The resulting mixture was extracted with CH_2Cl_2 (3 × 10 mL). The organic layers were combined, dried over Na_2SO_4, and filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane/AcOEt = 19:1 → 9:1, v/v) to afford (*Z*)-**5a** (yellow solid, 0.0408 g, 0.0828 mmol, 83%). $[\alpha]_D$ = +83.5 (*c* 1.06, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.61 (d, 2H, *J* = 7.2 Hz), 7.41−7.26 (m, 17H), 7.17−7.13 (m, 1H), 5.42 (s, 1H, *exo*-C═C*H*), 4.78 (d, 1H, *J* = 12.1 Hz), 4.72 (ddd, 1H, *J* = 7.0, 4.4, 2.8 Hz), 4.67−4.51 (m, 5H), 4.33 (d, 1H, *J* = 4.7 Hz), 4.06 (dd, 1H, *J* = 7.0, 4.7 Hz), 3.81 (dd, 1H, *J* = 11.3, 2.8 Hz), 3.66 (dd, 1H, *J* = 11.3, 4.4 Hz). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 153.4, 138.0, 137.8, 137.5, 135.5, 128.4, 128.4, 128.4, 128.2, 128.1, 128.1, 128.0, 127.9, 127.8, 127.6, 127.5, 125.8, 102.8, 83.0, 76.7, 76.3, 73.3, 72.0, 70.0, 69.0. HRMS (ESI-TOF) *m*/*z*: [M + Na]$^+$ calcd for $C_{33}H_{32}NaO_4^+$ 515.2193; found 515.2181.

*Synthesis of (Z)-**5c** by Iodine-Catalyzed Isomerization.* (*Z*)-**5c** (pale-yellow solid, 0.0448 g, 0.0833 mmol, 83%) was obtained from **5c** (*E*:*Z* = 88:12, 0.0537 g, 0.100 mmol) according to the procedure described for (*Z*)-**5a**. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.15−8.11 (m, 2H), 7.70−7.67 (m, 2H), 7.38−7.22 (m, 15H), 5.51 (s, 1H, *exo*-C═C*H*), 4.75−4.47 (m, 8H), 4.09 (t, 1H, *J* = 4.9 Hz), 3.75 (dd, 1H, *J* = 11.2, 3.1 Hz), 3.63 (dd, 1H, *J* = 11.2, 3.8 Hz). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 158.3, 144.8, 142.8, 137.6, 137.3, 137.2, 128.5, 128.5, 128.4, 128.2, 128.1, 128.1, 128.0, 127.8, 127.5, 123.6, 99.7, 84.5, 77.3, 75.7, 73.4, 72.0, 71.3, 68.8. HRMS (ESI-TOF) *m*/*z*: [M + Na]$^+$ calcd for $C_{33}H_{31}NNaO_6^+$ 560.2044; found 560.2066.

*2-Benzothiazolyl 3,5-Di-O-benzyl-1-thio-β-D-ribofuranoside (**7**).* **7** was synthesized according to the β-selective ribofuranosylation reported by Hocek et al.[32] **6**[40] (0.661 g, 2.00 mmol) and 2-mercaptobenzothiazole (0.502 g, 3.00 mmol) were dried by repeated coevaporation with dry MeCN (5 × 5 mL) and dissolved in dry MeCN (2.00 mL). The solution was cooled to 0 °C, before dry *i*-Pr$_2$NEt (0.523 mL, 3.00 mmol), diisopropyl azodicarboxylate (DIAD, 0.827 mL, 4.20 mmol), and Bu_3P (0.989 mL, 4.00 mmol) were added under stirring, and stirring was continued overnight at rt. Subsequently, the mixture was concentrated under reduced pressure and the residue was purified by column chromatography on silica gel (hexane/AcOEt = 1:0 → 4:1, v/v) to afford **7** (0.479 g, 0.999 mmol, 50%) as a colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.93 (d, 1H, *J* = 8.4 Hz), 7.77 (d, 1H, *J* = 8.8 Hz), 7.43 (t, 1H, *J* = 8.4 Hz), 7.38−7.28 (m, 11H), 6.00 (d, 1H, *J* = 4.4 Hz), 4.65 (s, 2H), 4.58 (d, 1H, *J* = 12.2 Hz), 4.53 (d, 1H, *J* = 12.2 Hz), 4.45 (q, 1H, *J* = 4.4 Hz), 4.34 (q, 1H, *J* = 4.4 Hz), 4.24 (t, 1H, *J* = 4.4 Hz), 3.62 (dd, 1H, *J* = 10.8, 4.4 Hz), 3.57 (dd, 1H, *J* = 10.8, 4.4 Hz), 3.25 (d, 1H, *J* = 4.4 Hz). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 164.0, 152.9, 137.7, 136.8, 135.4, 128.5, 128.3, 128.2, 128.0, 127.6, 127.6, 126.0, 124.5, 122.0, 120.8, 90.3, 82.5, 78.5, 75.2, 73.4, 72.6, 69.7. HRMS (ESI-TOF) *m*/*z*: [M + Na]$^+$ calcd for $C_{26}H_{25}NNaO_4S_2^+$ 502.1117; found 502.1103.

*2-Benzothiazolyl 2,3,5-Tri-O-benzyl-1-thio-β-D-ribofuranoside (**β-3a**).* **7** (0.250 g, 0.520 mmol) was dried by repeated coevaporation with dry pyridine (3 × 3 mL) and dry toluene (3 × 3 mL) and dissolved in dry DMF (0.50 mL) under argon. Cs_2CO_3 (0.254 g, 0.780 mmol) was added under stirring at 0 °C and stirring was continued for 30 min. Subsequently, BnBr (0.0928 mL, 0.780 mmol) was added dropwise and stirring was continued for 10 min and for 1 d at rt, before H_2O (30 mL) was added. The resulting mixture was extracted with AcOEt (30 mL). The organic layer was washed with H_2O (30 mL), and the aqueous layer was re-extracted with AcOEt (30 mL). The organic layers were combined, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane/AcOEt = 1:0 → 17:3, v/v) to afford β-**3a** (0.0571 g, 0.100 mmol, 19%) as a pale-yellow oil. ^{1}H NMR spectrum was identical to that we reported previously.[23]

*2-Benzothiazolyl 2,3,5-Tri-O-benzyl-β-D-ribofuranosyl Sulfone (**β-4a**).* β-**4a** (pale-yellow oil, 0.0495 g, 0.0823 mmol, 82%) was obtained from β-**3a** (0.0571 g, 0.100 mmol) according to the general procedure described for **4a**. Purification was carried out by column chromatography on silica gel (hexane/AcOEt = 1:0 → 4:1, v/v). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.24 (dd, 1H, *J* = 7.4, 1.0 Hz), 7.98 (dd, 1H, *J* = 7.2, 1.6 Hz), 7.66−7.57 (m, 2H), 7.41−7.21 (m, 15H), 5.51 (d, 1H, *J* = 1.6 Hz), 4.80 (d, 1H, *J* = 12.0 Hz), 4.70 (dd, 1H, *J* = 5.2, 1.6 Hz), 4.61 (d, 1H, *J* = 12.0 Hz), 4.51 (d, 1H, *J* = 11.4 Hz), 4.42 (d, 1H, *J* = 12.0 Hz), 4.45 (d, 1H, *J* = 12.0 Hz), 4.45−4.41 (m, 1H), 4.40 (d, 1H, *J* = 11.4 Hz), 4.08 (dd, 1H, *J* = 8.2, 5.2 Hz), 3.65 (dd, 1H, *J* = 11.2, 3.4 Hz), 3.60 (dd, 1H, *J* = 11.2, 6.0 Hz). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 163.2, 152.8, 137.9, 137.5, 137.0, 136.3, 128.5, 128.4, 128.3, 128.2, 128.1, 128.0, 127.9, 127.6, 127.5, 125.6, 122.1, 96.7, 83.1, 78.2, 75.5, 73.2, 72.5, 72.3, 70.0. HRMS (ESI-TOF) *m*/*z*: [M + Na]$^+$ calcd for $C_{33}H_{31}NNaO_6S_2^+$ 624.1485; found 624.1495.

*2-Benzothiazolyl 2,3,5-Tri-O-benzoyl-1-thio-β-D-ribofuranoside (**β-3a′**).* 1-*O*-Acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose (**8**) (0.328 g, 0.650 mmol) was dried by repeated coevaporation with dry toluene (3 × 5 mL) and dissolved in dry CH_2Cl_2 (6.00 mL) under argon. Subsequently, MS4A (1.0 g) were added, and the mixture was cooled to −20 °C. Under stirring, TMSI (0.0891 mL, 0.650 mmol) was added dropwise, and stirring was continued for 1 h. 2-Mercaptobeozothiazole (0.0836 g, 0.500 mmol) and a solution of

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dry *N*,*N*-diethylaniline (0.0800 mL, 0.500 mmol) in dry CH_2Cl_2 (0.50 mL) were added successively, and stirring was continued for 4 h, before a saturated aqueous solution of $NaHCO_3$ (20 mL) was added. The mixture was extracted with CH_2Cl_2 (3 × 30 mL). The organic layers were combined, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane/AcOEt = 1:0 → 177:23, v/v) to afford *β*-**3a′** (0.172 g, 0.280 mmol, 56%) as a white foam. ^{1}H NMR ($CDCl_3$, 400 MHz): *δ* 8.09 (d, 2H, *J* = 8.0 Hz), 8.01 (d, 2H, *J* = 8.0 Hz), 7.94−7.91 (m, 3H), 7.75 (d, 1H, *J* = 8.4 Hz), 7.56 (quint, 3H, *J* = 8.0 Hz), 7.44−7.30 (m, 8H), 6.46 (d, 1H, *J* = 3.6 Hz), 6.07 (dd, 1H, *J* = 5.6, 3.6 Hz), 6.00 (t, 1H, *J* = 5.6 Hz), 4.83 (dt, 1H, *J* = 5.6, 4.0 Hz), 4.76 (dd, 1H, *J* = 12.0, 4.0 Hz), 4.60 (dd, 1H, *J* = 12.0, 4.0 Hz). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): *δ* 166.0, 165.2, 164.8, 161.9, 152.9, 135.6, 133.5, 133.5, 133.1, 129.8, 129.7, 129.7, 129.3, 128.7, 128.6, 128.4, 128.3, 126.1, 124.8, 122.2, 120.9, 87.4, 80.7, 75.4, 71.9, 63.6. HRMS (ESI-TOF) *m*/*z*: [M + Na]$^+$ calcd for $C_{33}H_{25}NNaO_7S_2^+$ 634.0965; found 634.0966.

*2-Benzothiazolyl 2,3,5-Tri-O-benzoyl-β-D-ribofuranosyl Sulfone (**β-4a′**).* *β*-**4a′** (white foam, 0.257 g, 0.399 mmol, 68%) was obtained from *β*-**3a′** (0.361 g, 0.591 mmol) according to the general procedure described for **4a**. Purification was carried out by column chromatography on silica gel (hexane/AcOEt = 1:0 → 1:1, v/v). ^{1}H NMR ($CDCl_3$, 400 MHz): *δ* 8.22 (dd, 1H, *J* = 7.4, 1.2 Hz), 8.06 (dd, 2H, *J* = 8.0, 1.2 Hz), 7.97−7.94 (m, 3H), 7.87 (dd, 2H, *J* = 8.0, 1.2 Hz), 7.64−7.50 (m, 5H), 7.40 (dt, 4H, *J* = 8.0, 3.2 Hz), 7.32 (t, 2H, *J* = 8.0 Hz), 6.52 (dd, 1H, *J* = 5.4, 2.8 Hz), 6.03 (dd, 1H, *J* = 6.2, 5.4 Hz), 5.81 (d, 1H, *J* = 2.8 Hz), 4.82 (m, 1H), 4.69 (dd, 1H, *J* = 12.4, 4.0 Hz), 4.59 (dd, 1H, *J* = 12.4, 5.4 Hz). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): *δ* 166.0, 164.8, 164.4, 162.7, 152.7, 137.4, 133.8, 133.6, 133.2, 129.8, 129.8, 129.7, 129.2, 128.5, 128.4, 128.3, 128.3, 128.2, 127.7, 125.6, 122.2, 95.3, 81.8, 72.1, 71.2, 63.3. HRMS (ESI-TOF) *m*/*z*: [M + Na]$^+$ calcd for $C_{33}H_{25}NNaO_9S_2^+$ 666.0863; found 666.0881.

*(4S,5R)-2-Benzothiazolylsulfonyl-4-benzoyloxy-5-benzoyloxymethyl-4,5-dihydrofuran (**10**).* *β*-**4a′** (0.0644 g, 0.100 mmol) and benzaldehyde (0.0153 mL, 0.150 mmol) were dissolved in dry THF (1.00 mL) under argon, and the solution was cooled to −60 °C. Under stirring, a 0.5 M KHMDS solution in toluene (0.28 mL, 0.140 mmol) was added dropwise. The temperature was gradually increased to rt over 1 h. Stirring was continued for 3 h, before a saturated aqueous solution of NH_4Cl (2 mL) and H_2O (3 mL) were added. The resulting mixture was then extracted with CH_2Cl_2 (3 × 10 mL). The organic layers were combined and washed with H_2O (10 mL). The aqueous layer was re-extracted with CH_2Cl_2 (15 mL). The organic layers were combined, dried over Na_2SO_4, and filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane/AcOEt = 1:0 → 7:3, v/v) to afford **10** (0.0484 g, 0.0928 mmol, 93%) as a pale-yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz): *δ* 8.07−8.03 (m, 3H), 7.90−7.86 (m, 1H), 7.72 (d, 2H, *J* = 7.8 Hz), 7.61 (t, 1H, *J* = 7.6 Hz), 7.57−7.44 (m, 5H), 7.30 (t, 2H, *J* = 7.8 Hz), 6.50 (d, 1H, *J* = 3.2 Hz), 6.17 (t, 1H, *J* = 3.2 Hz), 5.19−5.17 (m, 1H), 4.66 (dd, 1H, *J* = 12.0, 3.4 Hz), 4.57 (dd, 1H, *J* = 12.0, 4.0 Hz). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): *δ* 165.9, 165.6, 162.8, 157.8, 152.5, 137.4, 133.8, 133.2, 129.8, 129.5, 128.7, 128.5, 128.3, 128.3, 127.7, 125.8, 122.1, 109.2, 87.8, 77.5, 63.5. HRMS (ESI-TOF) *m*/*z*: [M + Na]$^+$ calcd for $C_{26}H_{19}NNaO_7S_2^+$ 544.0495; found 544.0485.

*(1S,3R,5R,6R,7R)-6,7-Bis(benzyloxy)-5-benzyloxymethyl-1-phenyl-4-oxaspiro[2.4]heptane (**11**).* **5a** (*E*/*Z* = 94:6, 0.443 g, 0.900 mmol) was dissolved in dry CH_2Cl_2 (0.50 mL) under argon. CH_2I_2 (0.218 mL, 2.70 mmol) was added dropwise to a mixture of 1.0 M Et_2Zn in hexane (2.7 mL, 2.7 mmol) and dry CH_2Cl_2 (1.50 mL) under argon in a separate flask at 0 °C under stirring and stirring was continued for 10 min. Subsequently, the latter solution was added dropwise to the former at 0 °C under stirring; then, stirring was continued for 1 d at rt. The mixture was subsequently diluted with CH_2Cl_2 (20 mL) and washed with a saturated aqueous solution of NH_4Cl (20 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The organic layers were combined and washed with a saturated aqueous solution of NaCl (20 mL). The aqueous layer was re-extracted with CH_2Cl_2 (20 mL). The organic layers were combined, dried over Na_2SO_4, and filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane/AcOEt = 1:0 → 17:3, v/v) to afford **11** (0.412 g, 0.814 mmol, 90%, pale-yellow oil) and *epi*-**11** (0.0029 g, 0.0057 mmol, 6%, pale-yellow oil). **11**: ^{1}H NMR ($CDCl_3$, 400 MHz): *δ* 7.38−7.21 (m, 13H), 7.16−7.12 (m, 5H), 6.78−6.74 (m, 2H), 4.59 (d, 2H, *J* = 11.8 Hz), 4.50 (d, 1H, *J* = 11.8 Hz), 4.48 (d, 1H, *J* = 12.1 Hz), 4.38 (d, 1H, *J* = 11.8 Hz), 4.32 (d, 1H, *J* = 12.1 Hz), 4.32−4.28 (m, 1H), 3.97 (dd, 1H, *J* = 7.4, 4.7 Hz), 3.67 (dd, 1H, *J* = 10.6, 3.1 Hz), 3.55 (dd, 1H, *J* = 10.6, 4.3 Hz), 3.33 (d, 1H, *J* = 4.7 Hz), 2.22 (dd, 1H, *J* = 9.8, 8.0 Hz), 1.47−1.40 (m, 2H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): *δ* 138.3, 138.1, 137.5, 137.4, 128.3, 128.2, 128.2, 128.2, 128.1, 128.0, 127.8, 127.7, 127.5, 127.2, 125.7, 79.5, 78.6, 75.4, 73.3, 72.4, 71.6, 70.5, 69.8, 27.8, 12.1. HRMS (ESI-TOF) *m*/*z*: [M + Na]$^+$ calcd for $C_{34}H_{34}NaO_4^+$ 529.2349; found 529.2350. The ^{1}H NMR spectrum of *epi*-**11** was identical to that of the product obtained from (*Z*)-**5a** shown below.

*(1R,3R,5R,6R,7R)-6,7-Bis(benzyloxy)-5-benzyloxymethyl-1-phenyl-4-oxaspiro[2.4]heptane (**epi-11**).* *epi*-**11** (pale-yellow oil, 0.0990 g, 0.195 mmol, 98%) was obtained from (*Z*)-**5a** (0.0988 g, 0.201 mmol) according to the procedure described for **11**. Purification was carried out by column chromatography on silica gel (hexane/AcOEt = 1:0 → 37:3, v/v). ^{1}H NMR ($CDCl_3$, 400 MHz): *δ* 7.39−7.21 (m, 15H), 7.18−7.09 (m, 5H), 4.82 (d, 1H, *J* = 11.9 Hz), 4.71 (d, 1H, *J* = 11.9 Hz), 4.66 (d, 1H, *J* = 11.8 Hz), 4.57 (d, 1H, *J* = 11.8 Hz), 4.34 (td, 1H, *J* = 6.2, 3.8 Hz), 4.22 (d, 1H, *J* = 12.1 Hz), 4.06 (d, 1H, *J* = 12.1 Hz), 4.00 (dd, 1H, *J* = 6.2, 4.8 Hz), 3.88 (d, 1H, *J* = 4.8 Hz), 3.27 (dd, 1H, *J* = 10.6, 3.8 Hz), 2.98 (dd, 1H, *J* = 10.6, 6.2 Hz), 1.86 (dd, 1H, *J* = 10.2, 7.2 Hz), 1.55 (dd, 1H, *J* = 10.2, 7.2 Hz), 1.36 (t, 1H, *J* = 7.2 Hz). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): *δ* 138.4, 138.3, 137.8, 137.7, 128.3, 128.1, 127.9, 127.8, 127.7, 127.7, 127.6, 127.4, 127.3, 125.6, 80.8, 80.1, 79.8, 73.0, 72.2, 71.7, 70.8, 69.8, 26.5, 13.9. HRMS (ESI-TOF) *m*/*z*: [M + Na]$^+$ calcd for $C_{34}H_{34}NaO_4^+$ 529.2349; found 529.2359.

*Methyl 2,3,5-Tri-O-(2-cyanoethyl)-β-D-ribofuranoside (**β-17**).* AcCl (0.725 mL, 10.0 mmol) was mixed with dry MeOH (30.0 mL) under argon and added to a stirred mixture of ribose (7.51 g, 50.0 mmol) in dry MeOH (100.0 mL) at rt. The stirring was continued for 6 h, before $NaHCO_3$ (5.05 g, 60.0 mmol) was added. After the insoluble materials were removed by suction filtration, the filtrate was concentrated under reduced pressure. The residue was then dried by repeated coevaporation with dry pyridine (3 × 10 mL) and dry toluene (3 × 10 mL) and dissolved in dry *t*-BuOH (250 mL). Acrylonitrile (197 mL, 3.00 mol) and Cs_2CO_3 (48.9 g, 150 mmol) were added to the solution under stirring at rt under argon. The stirring was continued for 1 h, before insoluble materials were removed by suction filtration through a pad of celite. The filtrate was concentrated under reduced pressure to give a crude mixture containing *α*-**17** and *β*-**17** (ca. 2:8). Purification by column chromatography on silica gel (CH_2Cl_2/AcOEt = 1:0 → 7:3 then AcOEt/MeOH = 4:1, v/v) afforded *β*-**17** (12.3 g, 37.9 mmol, 76% from ribose) as a pale-yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz): *δ* 4.90 (d, 1H, *J* = 1.4 Hz), 4.19 (dt, 1H, *J* = 6.5, 4.7 Hz), 4.09 (dd, 1H, *J* = 6.5, 4.7 Hz), 3.90−3.74 (m, 7H), 3.69−3.62 (m, 2H), 3.38 (s, 3H), 2.69−2.62 (m, 6H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): *δ* 118.0, 117.9, 117.9, 106.1, 81.5, 79.9, 79.7, 71.8, 66.0, 65.5, 65.4, 55.3, 19.2, 19.1, 18.9. HRMS (ESI-TOF) *m*/*z*: [M + Na]$^+$ calcd for $C_{15}H_{21}N_3NaO_5^+$ 346.1373; found 346.1382.

*2,3,5-Tri-O-(2-cyanoethyl)-D-ribofuranose (**18**).* A mixture of *β*-**17** (12.3 g, 37.9 mmol) with AcOH (190.0 mL) and 1 M HCl aq. (95.0 mL) was stirred for 4 h at 80 °C in an oil bath. The mixture was then cooled to rt and concentrated under reduced pressure. The residue was dissolved in AcOEt (150 mL) and washed successively with saturated aqueous solutions of $NaHCO_3$ (150 mL) and NaCl (100 mL). The aqueous layers were combined and extracted with AcOEt (10 × 100 mL). The organic layers were combined, dried over Na_2SO_4, and filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography on

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silica gel (CH_2Cl_2/AcOEt = 6:4 → 0:1 then AcOEt/MeOH = 4:1, v/v) to afford **18** (10.5 g, 33.8 mmol, 89%) as a pale-yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.37−5.33 (m, 1H), 4.31−3.56 (m, 11H), 2.80−2.61 (m, 6H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ 118.2, 118.0, 117.8, 99.9, 95.7, 82.3, 80.8, 79.9, 79.2, 78.8, 78.8, 71.1, 70.6, 66.2, 66.0, 65.8, 65.3, 65.3, 65.0, 19.2, 19.1, 19.1, 18.9, 18.8. HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{14}H_{19}N_3NaO_5^+$ 332.1217; found 332.1205.

*1-O-Trimethylsilyl-2,3,5-tri-O-(2-cyanoethyl)-D-ribofuranose (**19**).* **18** (10.5 g, 33.8 mmol) was dried by repeated coevaporation with dry toluene (3 × 10 mL) and dissolved in dry MeCN (169.0 mL) under argon. *N,O*-Bis(trimethylsilyl)acetamide (16.5 mL, 67.6 mmol) was added to the solution at rt under stirring. After 2 h of stirring, H_2O (100 mL) was added, and the mixture was extracted with AcOEt (3 × 100 mL). The organic layers were combined and washed with H_2O (100 mL). The aqueous layer was extracted with AcOEt (100 mL). The organic layers were combined, dried over Na_2SO_4, and filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (CH_2Cl_2/AcOEt = 1:0 → 2:1, v/v) to afford **19** (10.7 g, 28.1 mmol, 83%, α:β = 7:93) as a pale-yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.46 (d, 1H, J = 3.8 Hz, α), 5.28 (d, 1H, J = 1.5 Hz, β), 4.25−4.04 (m, 2H, α, β), 4.00−3.64 (m, 9H, α, β), 2.73−2.60 (m, 6H, α, β), 0.19 (s, 9H, α), 0.16 (s, 9H, β). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): α-**19**: δ 118.2, 117.9, 96.4, 80.1, 79.6, 70.3, 66.1, 65.5, 65.5, 19.2, 18.9, 0.2. β-**19**: 117.9, 117.9, 117.8, 99.9, 83.3, 79.6, 79.5, 72.0, 65.8, 65.4, 19.2, 19.1, 18.9, 0.0. HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{17}H_{27}N_3NaO_5Si^+$ 404.1612; found 404.1626.

*2-Benzothiazolyl 2,3,5-Tri-O-(2-cyanoethyl)-α-D-ribofuranoside (**21**).* **19** (2.48 g, 6.50 mmol) was dried by repeated coevaporation with dry toluene (3 × 10 mL) and dissolved in dry CH_2Cl_2 (60.0 mL) under argon. Subsequently, MS4A (10.0 g) were added, and the mixture was cooled to −20 °C. Under stirring, TMSI (0.891 mL, 6.50 mmol) was added dropwise to the mixture, and stirring was continued for 1 h at the same temperature. 2-Mercaptobenzothiazole (0.836 g, 5.00 mmol) and a solution of dry *N,N*-diethylaniline (0.799 mL, 5.00 mmol) in dry CH_2Cl_2 (5.00 mL) were added dropwise, and stirring was continued for 4 h before a saturated aqueous solution of $NaHCO_3$ (50 mL) was added. The mixture was warmed to rt and extracted with CH_2Cl_2 (3 × 50 mL). The organic layers were combined, dried over Na_2SO_4, and filtered, and the filtrate was concentrated under reduced pressure. The residue was then purified by column chromatography on silica gel (CH_2Cl_2/AcOEt = 1:0 → 1:1, v/v) to afford **21** (2.09 g, 4.57 mmol, 91%, α:β > 99:1) as a pale-yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.91 (d, 1H, J = 8.0 Hz), 7.77 (d, 1H, J = 8.0 Hz), 7.42 (t, 1H, J = 8.0 Hz), 7.32 (t, 1H, J = 8.0 Hz), 6.80 (d, 1H, J = 5.6 Hz), 4.45 (t, 1H, J = 5.6 Hz), 4.35 (q, 1H, J = 3.0 Hz), 4.19 (dd, 1H, J = 5.6, 3.8 Hz), 4.11 (dt, 1H, J = 9.7, 5.6 Hz), 3.97 (dt, 1H, J = 9.1, 5.6 Hz), 3.89−3.69 (m, 6H), 2.79−2.63 (m, 6H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ 165.4, 152.9, 135.5, 126.0, 124.5, 121.9, 120.9, 118.0, 117.5, 88.8, 82.0, 79.9, 78.5, 69.7, 66.2, 66.1, 65.8, 19.3, 19.0, 18.9. HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{21}H_{22}N_4NaO_4S_2^+$ 481.0975; found 481.0974.

*2-Benzothiazolyl 2,3,5-Tri-O-(2-cyanoethyl)-α-D-ribofuranosyl Sulfone (**22**).* **22** (white foam, 1.83 g, 3.73 mmol, 82%) was obtained from **21** (2.09 g, 4.57 mmol) according to the general procedure described for **4a**. Purification was carried out by column chromatography on silica gel (hexane/AcOEt = 1:0 → 0:1, v/v). $[\alpha]_D$ = +154.4 (c 1.05, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.25−8.23 (m, 1H), 8.04−8.01 (m, 1H), 7.67−7.58 (m, 2H), 5.69 (d, 1H, J = 5.8 Hz), 4.72 (t, 1H, J = 5.8 Hz), 4.56 (dt, 1H, J = 6.8, 2.3 Hz), 4.26−4.19 (m, 2H), 4.02−3.92 (m, 2H), 3.80−3.76 (m, 1H), 3.75−3.74 (m, 2H), 3.68 (t, 2H, J = 6.0 Hz), 2.87−2.48 (m, 6H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ 165.1, 152.3, 137.2, 127.9, 127.4, 125.3, 122.2, 118.0, 117.9, 117.8, 94.1, 82.3, 79.1, 77.9, 68.4, 67.7, 66.2, 65.8, 18.8, 18.7. HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{21}H_{22}N_4NaO_6S_2^+$ 513.0873; found 513.0883.

*2,5-Anhydro-3,4,6-tri-O-(2-cyanoethyl)-1-deoxy-1-phenyl-D-ribo-hex-1-enitol (**23**).* **22** (0.0491 g, 0.100 mmol) and benzaldehyde (0.0112 mL, 0.110 mmol) were dissolved in dry THF (1.00 mL) under argon and cooled to −60 °C. Under stirring, a 0.5 M KHMDS solution in toluene (0.210 mL, 0.105 mmol) was added dropwise. The mixture was gradually warmed to rt over 1 h and stirring was continued for 3 h, before a saturated aqueous solution of NH_4Cl (2 mL) and H_2O (3 mL) were added. The mixture was then extracted with CH_2Cl_2 (3 × 10 mL). The organic layers were combined and washed with H_2O (10 mL). The aqueous layer was re-extracted with CH_2Cl_2 (15 mL). The organic layers were combined, dried over Na_2SO_4, and filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane/AcOEt = 1:0 → 17:3, v/v) to afford **23** (0.0336 g, 0.0881 mmol, 88%, E:Z = 93:7) as a pale-yellow oil. $[\alpha]_D$ = −52.6 (c 1.29, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz): (E)-**23**: δ 7.35−7.20 (m, 5H), 6.24 (s, 1H, *exo*-C=C*H*), 4.84 (d, 1H, J = 5.0 Hz), 4.38 (ddd, 1H, J = 8.6, 3.7, 2.4 Hz), 4.18 (dd, 1H, J = 8.6, 5.0 Hz), 3.97 (dt, 1H, J = 9.5, 5.8 Hz), 3.90−3.67 (m, 7H), 2.71 (t, 2H, J = 6.0 Hz), 2.65 (t, 2H, J = 6.0 Hz), 2.60−2.47 (m, 2H). (Z)-**23**: δ 5.48 (s, 1H, *exo*-C=C*H*). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): (E)-**23**: δ 153.7, 135.1, 128.5, 127.7, 126.3, 117.9, 117.8, 117.8, 107.0, 79.8, 78.6, 73.3, 69.2, 66.0, 65.2, 63.1, 18.9, 18.9, 18.7. HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{21}H_{23}N_3NaO_4^+$ 404.1581; found 404.1573.

*2,5-Anhydro-1-deoxy-1-phenyl-D-ribo-hex-1-enitol (**24**).* A solution of **23** (0.0382 g, 0.100 mmol) and Na_2S (0.0117 g, 0.150 mmol) in CH_2Cl_2/MeOH (2:1, v/v; 0.30 mL) was stirred for 3 days at rt, before being concentrated under reduced pressure. The residue was then purified by column chromatography on silica gel (CH_2Cl_2/MeOH = 1:0 → 94:6, v/v) to afford **24** (0.0195 g, 0.0877 mmol, 88%, E:Z = 93:7) as a pale-yellow solid. $[\alpha]_D$ = −293.8 (c 2.19, MeOH). ^{1}H NMR (DMSO-d_6, 400 MHz): (E)-**24**: δ 7.40 (d, 2H, J = 7.4 Hz), 7.26 (t, 2H, J = 7.4 Hz), 7.11 (t, 1H, J = 7.4 Hz), 5.82 (s, 1H), 5.32 (d, 1H, J = 5.0 Hz), 5.23 (d, 1H, J = 6.8 Hz), 4.85 (t, 1H, J = 5.6 Hz), 4.37 (t, 1H, J = 5.0 Hz), 4.03 (ddd, 1H, J = 8.8, 5.0, 2.2 Hz), 3.85 (ddd, 1H, J = 8.8, 6.8, 5.6 Hz), 3.72 (ddd, 1H, J = 12.4, 5.6, 2.2 Hz), 3.45 (dt, 1H, J = 12.4, 5.6 Hz). (Z)-**24**: δ 5.30 (s, 1H, *exo*-C=C*H*). $^{13}C\{^1H\}$ NMR (DMSO-d_6, 100 MHz): (E)-**24**: δ 159.2, 136.5, 128.3, 127.1, 125.1, 102.9, 82.5, 70.4, 68.7, 60.4. HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{12}H_{14}NaO_4^+$ 245.0784; found 245.0767.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.0c02297.

FAIR data includes the primary NMR FID files for compounds **4a−d**, **5a−m**, (Z)-**5a,c**, **7**, β-**4a**, β-**3a′**, β-**4a′**, **10**, **11**, *epi*-**11**, β-**17**, **18**, **19**, and **21−24** (ZIP)

X-ray crystal data for **4a**; X-ray structure analysis, crystal data, structure refinement results, bond lengths, and bond angles of **4a**; computational details; NMR spectra (PDF)

Accession Codes

CCDC 2009571 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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