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Stereoselective Synthesis of 2-(β-*C*-Glycosyl)glycals: Access to Unusual β-*C*-Glycosides from 3-Deoxyglycals

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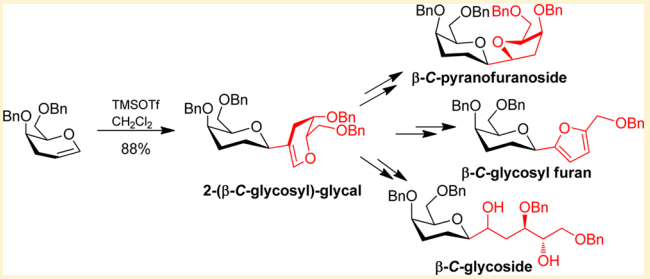
Supporting Information

ABSTRACT: A novel method for the highly stereoselective synthesis of β-(1→2)-*C*-saccharides employing 3-deoxy- and 3-*C*-branched glycals as hermaphroditic substrates is revealed. The generality of the C−C bond formation reaction between the two sugar units is evaluated. The developed methodology is successfully applied to the synthesis of biologically significant subunits that are present in various natural products, which include mixed *C*-disaccharides with adjacent THP−THF rings, *C*-aryl glycosides, and highly functionalized β-*C*-glycosides.



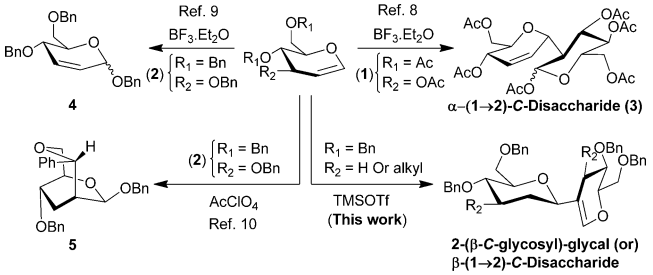
INTRODUCTION

The stability of *C*-glycosides[1] to acids and carbohydrate-processing enzymes has attracted many synthetic organic chemists and biologists worldwide for their exploration as potential mimics to the biologically active *O*-glycosides.[2] This has intensified the search for new *C*-glycosidic structures for the discovery of potential drug candidates in the treatment of various diseases and immunological disorders.[3]

Reaction of glycals with carbon nucleophiles in the presence of a Lewis acid is one of the most widely used methods for the synthesis of 2,3-unsaturated *C*-glycosides.[1g] Recently, palladium-catalyzed Heck-type glycosylation of glycals[4] and allylic alkylation[5] have been reported. However, very few methodologies are available for the synthesis of *C*-saccharides,[6] disaccharides, and higher homologues, owing to the difficulties associated with their preparation. Compared to *O*-glycosides, the absence of an *exo*-anomeric effect and the nonpredominant neighboring group participation are the major drawbacks in the stereoselective synthesis of *C*-glycosides.[7] Further, selective modification of one of the sugar parts in *C*-saccharides is an arduous and important task for the transformation of *C*-saccharides to complex glycosides, natural products, and biologically important skeletons. The insufficient availability of pure *C*-glycosidic compounds from natural sources to study their biological profile provided a strong motivation for the development of synthetic approaches using abundant natural sugars and their derivatives.

Our investigation toward the synthesis of *C*-saccharides started from the observation of 3,4,6-tri-*O*-acetyl-D-glucal **1** dimerization using $BF_3{\cdot}Et_2O$ to provide the 2,3-unsaturated α-(1→2)-*C*-disaccharide **3** in moderate yield.[8] This reaction is feasible only in the presence of an effective leaving group at the C-3 position of a glycal. On the other hand, 3,4,6-tri-*O*-benzyl-D-glucal **2** was reported to provide the benzyl glycoside **4**[9] under similar reaction conditions. Interestingly, using acetyl perchlorate as the Lewis acid, glucal **2** was converted to the bicyclic acetal **5** through an unprecedented 1,7-hydrogen shift[10] (Scheme 1).

Scheme 1. Reactivity of Glycal under Lewis Acid Conditions



Surprisingly, to the best of our knowledge, there was no report documented in the literature on the reactivity of 3-deoxyglycals under Lewis acid conditions. The probable reason might be due to the unpredictability of the formation and the fate of the formed oxocarbenium ion in 3-deoxyglycals. These observations made us curious to investigate the reactivity of 3-deoxyglycals in the presence of a Lewis acid. We envisaged that the presence of a leaving group at the C-3 position might facilitate the Ferrier rearrangement,[11] but its absence might not hinder the general electrophilic addition reaction to give *C*-saccharides. Additionally, the reaction could be driven stereoselectively by the substituents present at C-4 and C-5 by stabilizing the generated oxocarbenium ion intermediate. Thus, herein, we report the reactions of 3-deoxyglycals under a Lewis acid to produce 2-(β-*C*-glycosyl)glycals or β-(1→2)-*C*-saccharides (Scheme 1) in an unusual and highly stereoselective

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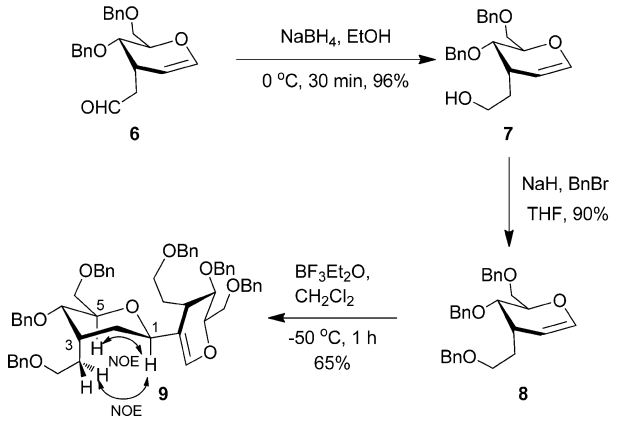
fashion. Further, we also reveal the selective modification of a single sugar unit of the synthesized novel *C*-saccharides to obtain various biologically important *C*-glycoside architectures.

RESULTS AND DISCUSSION

To obtain the appropriately protected 3-deoxyglycal derivative, 3-*C*-branched glycal **6**[12] was reduced to the alcohol **7** followed by benzylation to provide the glycal **8**. When 3-deoxy-3-*C*-branched glycal **8** in anhydrous CH_2Cl_2 was treated with $BF_3{\cdot}Et_2O$ (1 equiv) at −50 °C, most of the starting material was consumed and a new compound, which is slightly more polar than glycal **8**, and a complex polar mixture at the bottom of the TLC were observed. With structural analysis, the new compound was found to be the diastereomerically pure *β*-(1→2)-*C*-disaccharide **9** (65% isolated yield, Scheme 2). The stereochemistry at the anomeric center was assigned based on positive correlation between H-1/H-5 in a 2D NOESY experiment[13] (Scheme 2).

Scheme 2. Lewis Acid Mediated Dimerization of 3-Deoxy-3-*C*-branched Glycal



Exhilarated by this result, we examined the formation of disaccharide **9** under various Lewis acid conditions at different temperatures (Table 1). Trifluoromethanesulfonates of Sc, Ag, and Cu were found to be ineffective at catalyzing the reaction at −78 °C. However, the reaction of **8** with 1 equiv of $Sc(OTf)_3$ at 0 °C afforded **9** in 68% yield, whereas AgOTf and $Cu(OTf)_2$ were found to be ineffective from −78 °C to room temperature (Table 1, entries 2−4). Gratifyingly, when the reaction was conducted using 0.3 equiv of TMSOTf at −78 °C in anhydrous CH_2Cl_2, **9** was provided as a single diastereomer in 90% yield (Table 1, entry 5). Although the reaction proceeded with Montmorillonite K10 at room temperature, the yield was found to be only 60% (Table 1, entry 6). Lewis acids $InCl_3$ and $BiCl_3$ were found to be ineffective at catalyzing the reaction even at 25 °C (Table 1, entries 7 and 8). Therefore, catalytic TMSOTf was validated as the better Lewis acid for the electrophilic addition of deoxyglycals to produce *β*-(1→2)-*C*-saccharides.

In contrast to the carbon−Ferrier rearrangement[1g] of glycals, which mostly produce 2,3-unsaturated *α*-*C*-glycosides, it is surprising to observe the exclusive formation of 2-(*β*-*C*-glycosyl)glycals from 3-deoxyglycals under various Lewis acid conditions. The formation of the single diastereomer **9** from **8** could be explained by considering the approach of the nucleophile toward the substituted tetrahydropyran-derived oxocarbenium ion. Glycal-derived oxocarbenium ions generally adopt half-chair conformations of $^3H_4$ and $^4H_3$.[14] Mostly,

Table 1. Lewis Acid Catalyzed Electrophilic Addition of Glycals

entry	Lewis acid	equiv	temp (time)	**9**[a] (%)	**8**[b] (%)
1	BF_3OEt_2	0.3	−78 °C to rt (8 h)		92
		1.0	−78 °C (1 h)		95
		1.0	−50 °C (1 h)	65	5
2	$ScOTf_3$	0.3	−78 °C to rt (8 h)		95
		1.0	−78 °C to −50 °C (3 h)		95
		1.0	0 °C (1 h)	68	5
3	AgOTf	0.3	−78 °C to rt (8 h)		96
		1.0	−78 °C to rt (10 h)		95
4	$CuOTf_2$	0.3	−78 °C to rt (8 h)		94
		1.0	−78 °C to rt (10 h)		95
5	**TMSOTf**	**0.3**	**−78 °C (1 h)**	**90**	
6	Montmorillonite K10[c]	0.3	−78 °C to rt (8 h)		96
		1.0	−78 to 0 °C (6 h)		93
		1.0	rt (12 h)	60	15
7	$InCl_3$	0.3	−78 °C to rt (8 h)		94
		1.0	−78 to 0 °C (6 h)		95
		1.0	rt (12 h)	5	75
8	$BiCl_3$	0.3	−78 °C to rt (8 h)		95
		1.0	−78 to 0 °C (6 h)		95
		1.0	rt (12 h)	10	20

[a]Yield refers to the pure isolated product. [b]Recovered starting material. [c]Equivanlet was calculated by wt %.

nucleophiles are likely to approach the cation in a pseudoaxial trajectory to attain the maximum orbital overlap.[15] In the case of $^4H_3$ conformer **10**, the approach of nucleophile suffers from unfavorable 1,3-diaxial interactions between the C-3 substituent and the incoming nucleophile. Similarly, in the case of $^3H_4$ conformer **11**, 1,3-diaxial interactions between the incoming nucleophile and the C-6 substituent hinders the nucleophilic approach. However, due to the electrostatic stabilization of oxocarbenium ions by axial 4-OBn,[14] the reaction proceeds through the oxocarbenium ion possessing the $^3H_4$ conformation to provide exclusively the *β*-(1→2)-*C*-disaccharide **13** (Figure 1).

After having the optimized reaction conditions in hand, we investigated the substrate scope of the reaction. Thus, 3-deoxy-3-*C*-branched glycals **15** and **18** were synthesized by benzylation of the corresponding alcohols **14** and **17**,[12] respectively, and subjected to a catalytic TMSOTf-mediated electrophilic addition reaction. Both glycals underwent a smooth dimerization reaction, providing the diastereomerically pure *β*-(1→2)-*C*-disaccharides **16** and **19**, respectively, in good yield (Scheme 3).

To investigate the regioselectivity of the endocyclic double bond over an isolated olefin as well as an electron-deficient olefin, compounds **21** and **23** were synthesized. Thus, the 3-*C*-branched glycal aldehyde **6** was treated with vinylmagnesium bromide, followed by acetylation to provide the allyl acetate substituted glycal **20**. On the other hand, Wittig olefination[16] of **6** provided the *α*,*β*-unsaturated ester-derived glycal **22**. Subjecting compounds **20** and **21** to TMSOTf-mediated C−C bond formation reaction afforded the *β*-(1→2)-*C*-disaccharides **21** and **23**, respectively, as the only products in which the isolated olefins were intact (Scheme 4). This study clearly supports the requirement of an oxocarbenium ion formation for the reaction to proceed.

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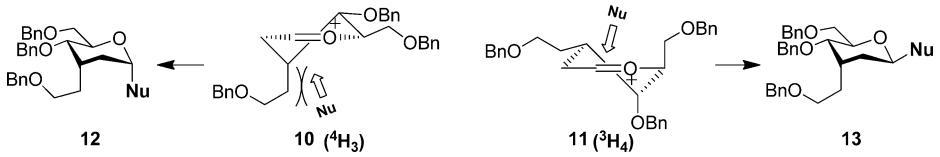
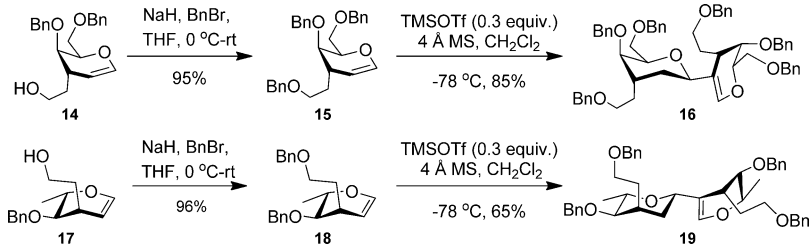
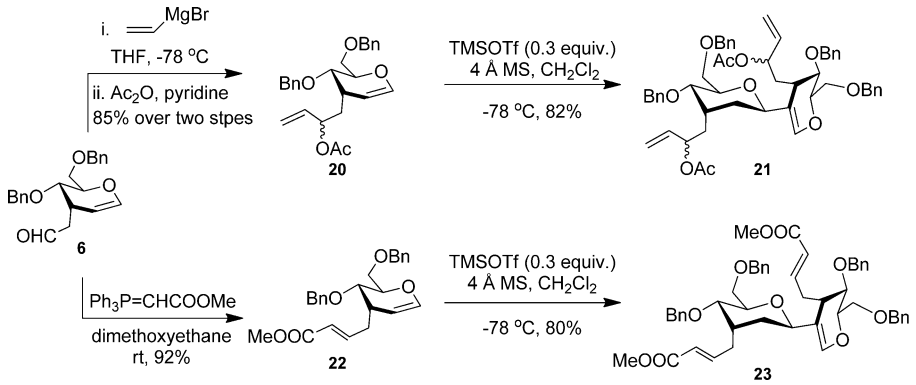


Figure 1. Half-chair conformers of glycal-derived oxocarbenium ions and preferred nucleophilic approach to provide the corresponding glycosides.

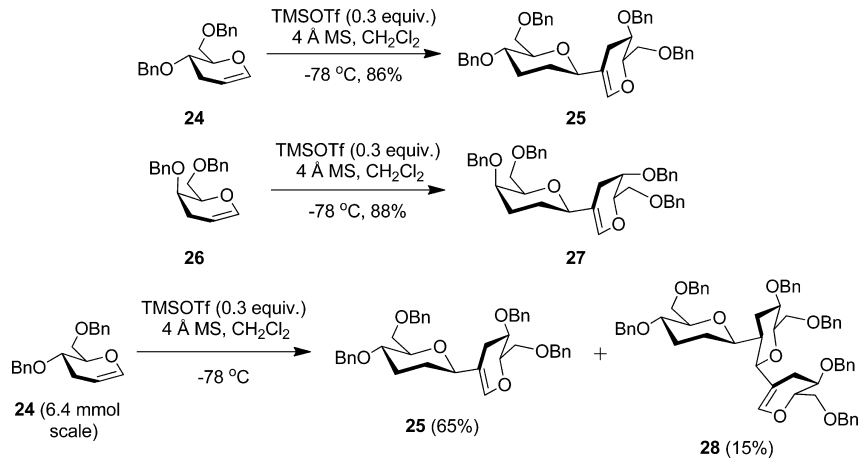
Scheme 3. Synthesis of β-(1→2)-*C*-Disaccharides Derived from 3-Deoxy-3-*C*-branched Sugars



Scheme 4. Synthesis of β-(1→2)-*C*-Disaccharides in the Presence of an External Olefin



Scheme 5. TMSOTf-Catalyzed Stereoselective Synthesis of β-(1→2)-*C*-Disaccharides from 3-Deoxyglycals



To study the importance of the steric effects, 3-deoxyglycals[17] such as **24** and **26** were synthesized and subjected to the optimized *C*-disaccharide formation reaction conditions. Interestingly, in the absence of the 3-*C*-branch ($-CH_2CH_2OBn$), both the glucose- and the galactose-derived 3-deoxyglycals **24** and **26** provided exclusively the β-(1→2)-*C*-disaccharides **25** and **27**, respectively, in good yield. These results provide sufficient evidence that the electrostatic effect is mainly driving the stereochemical outcome of the reaction. Additionally, to explore the inherited glycalic double bond present in the formed disaccharide, toward the formation of a trisaccharide, glycal **24** was loaded in gram scale and subjected to TMSOTf (0.3 equiv) in CH_2Cl_2. The β-(1→2)-*C*-β-(1→2)-*C*-trisaccharide **28** was isolated in 15% yield as a single diastereomer along with disaccharide **25** in 65% yield (Scheme 5).

To investigate the mechanism of the reaction, the deuterated 3-deoxyglucal **31** was synthesized from the deuterated glucal derivative **29**.[18] Thus, Ferrier rearrangement of deuterated glucal **29** with ethanol provided the 2,3-unsaturated glycoside

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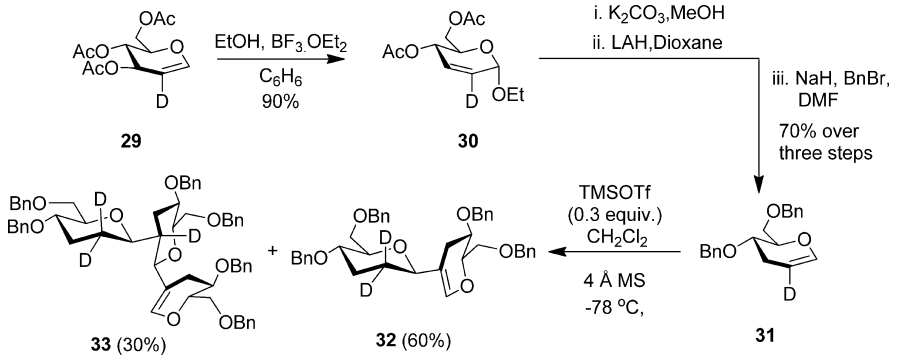
Scheme 6. Synthesis of Isotope-Labeled Di- and Trisaccharides from the Deuterated 3-Deoxyglucal



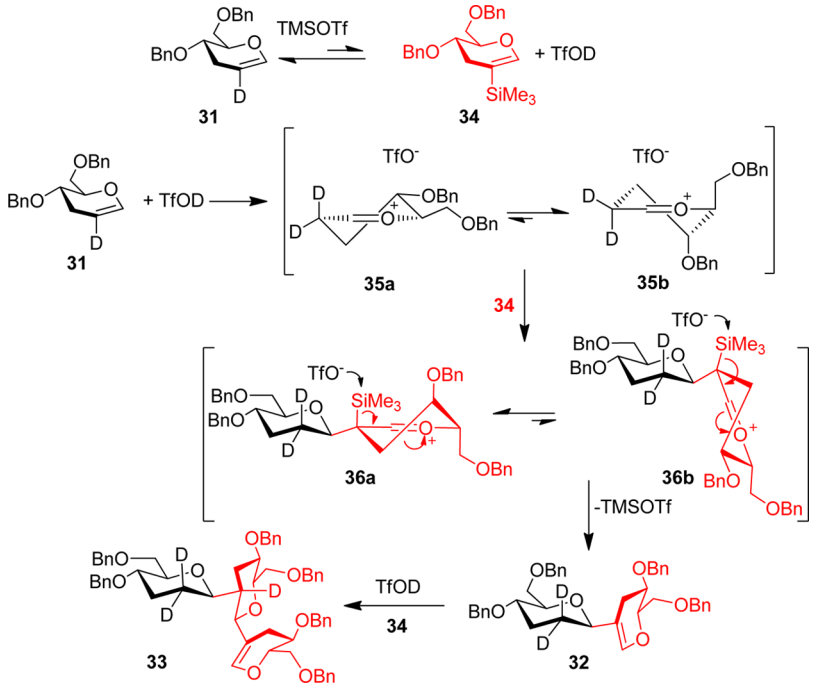


Figure 2. Proposed mechanism for the *β*-*C*-saccharide formation.

30. Deprotection of the acetyl groups followed by subjecting the obtained diol to LAH[17] under reflux conditions provided the 3-deoxyglucal, which was benzylated to afford the required deuterated 3-deoxyglucal derivative **31**. Subjecting **31** to the TMSOTf-mediated *C*-saccharide formation reaction provided the deuterated *C*-disaccharide **32** in 60% yield and deuterated *C*-trisaccharide **33** in 30% yield (Scheme 6). The increased yield in the formation of *C*-trisaccharide **33** could be attributed to the kinetic isotopic effect. The formation of dideuterated *C*-disaccharide **32** clearly indicates that the hydrogen present at the 2-position of the starting 3-deoxyglucal **31** is the source of H^+ in the *C*-saccharide formation.

Based on the above observations, a possible mechanism is proposed for the formation of *β*-*C*-disaccharide under TMSOTf catalysis conditions (Figure 2). Accordingly, glucal **31** upon reaction with TMSOTf might form the 2-trimethylsilyl glucal derivative **34** and TfOD. Addition of TfOD to glucal **31** leads to the formation of oxocarbenium ion intermediates **35a** and **35b** possessing $^4H_3$ and $^3H_4$ conformations, respectively. Approach of **34** to intermediate **35b**, which is stabilized by the stereoelectronic effect due to the presence of 4-OBn in the pseudoaxial position, in an axial trajectory provides the disaccharide-derived oxocarbenium ion intermediates **36a** and **36b**. Regeneration of the catalyst, TMSOTf, provides the observed *C*-disaccharide **32**. Similarly, uninterrupted addition of another molecule of **34** to **32** followed by termination provides *C*-trisaccharide **33** (Figure 2).

To further demonstrate the importance of the novel one-step *C*-saccharide formation from 3-deoxyglycals, we turned our attention to explore the synthetic applications of the glycalic double bond in synthesized 2-(*β*-*C*-glycosyl)glycals. In this context, annonaceous acetogenins are a class of natural products isolated from the Annonaceae species, and they have been highly recognized for their potent biological properties, most importantly hailed for their cytotoxicity.[19] An important subclass of these natural products possesses the carbon-linked adjacent THP−THF rings, for example, jimenezin (**37**) or muconin (**38**) (Figure 3).

Various groups had previously reported the total synthesis of these natural products using a multistep protocol for the formation of an adjacent bicyclic core skeleton (adjacent THP−THF rings).[20] However, we planned to convert the obtained 2-(*β*-*C*-glycosyl)glycals to the core skeletons present in these natural products in comparatively less synthetic steps.

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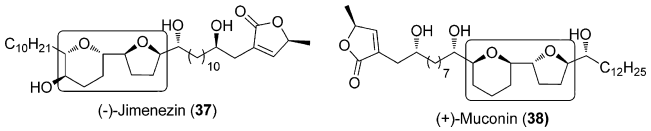
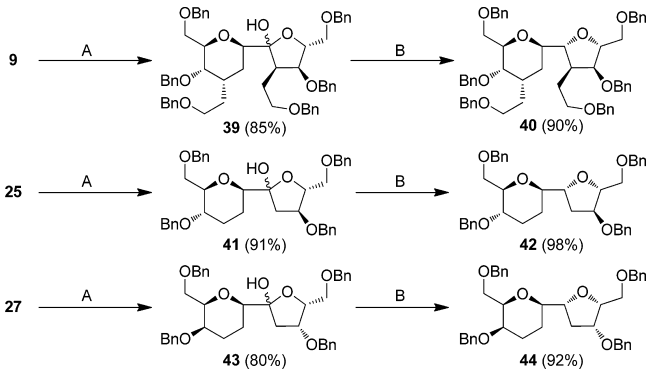


Figure 3. Cytotoxic annonaceous acetogenins from *Rollinia mucosa* seeds.

Toward this, compounds **9**, **25**, and **27** were subjected to ozonolysis,[12a,21] followed by deformylation with $NaHCO_3$ in MeOH to provide the *C*-disaccharide-derived hemiketals **39**, **41**, and **43** in good yield.[22] These hemiketals upon dehydroxylation with Et_3SiH and $BF_3{\cdot}Et_2O$ afforded the targeted β-(1→2)-*C*-pyranofuranosides or adjacent THP−THF rings **40**, **42**, and **44** as single diastereomers (Scheme 7).[6h] Further, functional group modification of these adjacent THP−THF rings to natural acetogenins and their analogues is in progress.

Scheme 7. Synthesis of Mixed *C*-Disaccharides Possessing Adjacent THP−THF Rings[a]



[a]Condition A: (i) O_3, CH_2Cl_2, DMS, −78 °C; (ii) $NaHCO_3$, MeOH. Condition B: (i) Et_3SiH, $BF_3{\cdot}OEt_2$, −78 °C, CH_2Cl_2.

The stereochemistry at the newly formed stereocenter in the obtained adjacent THP−THF rings was assigned based on the 2D COSY and NOESY experiment. For example, in the case of compound **42**, positive correlations between H-1/H-5, H-1/H-3, and H-1′/H-4′ were observed (Figure 4).[13] The stereochemistry for the other two bicycles were assigned based on the COSY and NOESY correlations, and their spectra are presented in the Supporting Information.

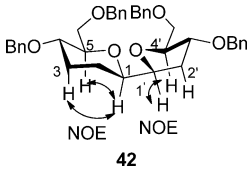
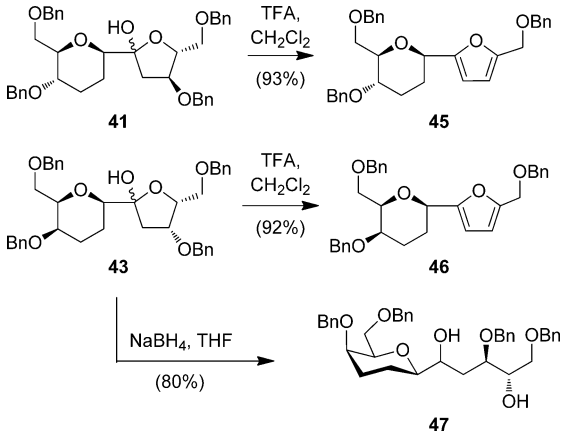


Figure 4. Through-space correlations observed in compound **42** using 2D NOESY experiments.

Another important subclass of the *C*-glycoside family of natural products is *C*-aryl glycosides, which are known for their antibiotic properties.[23] Therefore, a notable approach, from β-(1→2)-*C*-saccharides, for the synthesis of β-*C*-aryl glycosides with functionalized furan moieties would be very interesting. Toward this, the hemiketal derivatives **41** and **43** were treated with trifluoroacetic acid in CH_2Cl_2 to provide the corresponding β-*C*-glycosyl furan derivatives **45** and **46**, respectively, in excellent yield (Scheme 8).[24] On the other hand, methodologies to synthesize the densely functionalized *C*-glycosides[1] are of great importance because of their high structural resemblance to the pharmacologically undermined glycolipids. Hence, $NaBH_4$-mediated reduction of the hemiketal **43** provided the highly functionalized β-*C*-glycoside **47** as a single diastereomer in excellent yield (Scheme 8).

Scheme 8. Synthesis of β-*C*-Glycosyl Furans and β-*C*-Glycosides from *C*-Disaccharide Derivatives

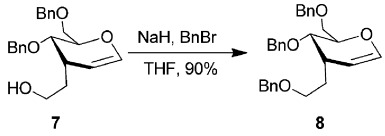


CONCLUSION

In conclusion, a facile protocol for the highly stereoselective synthesis of β-(1→2)-*C*-saccharides or 2-(β-*C*-glycosyl)glycals by TMSOTf-mediated dimerization of 3-deoxyglycals is revealed. The generality and the stereoselectivity for the β-*C*-saccharide formation is investigated. In addition, the developed methodology was extended to prepare a diversity of mixed *C*-disaccharides, *C*-glycosyl furans, and a highly functionalized β-*C*-glycoside. Further functional group transformations to achieve the total synthesis of bioactive natural products is in progress.

EXPERIMENTAL SECTION

General Methods. All reactions were carried out under an inert atmosphere with dry solvents under anhydrous conditions unless otherwise mentioned. Dichloromethane, methanol, THF, dimethoxyethane, dichloroethane, dioxane, and DMF were initially dried and stored in suitable conditions. TLC was run on silica gel 60 F254 plates, and the spots were detected by staining with H_2SO_4 in methanol (5%, v/v) or phosphomolybdic acid in ethanol (5%, w/v) and heating. Silica gel (100−200 mesh) was used as a stationary phase for column chromatography. Yield refers to the isolated products unless otherwise stated. NMR spectra were recorded at 25 °C on a 400 MHz spectrometer (400 MHz for ^1H and 100 MHz for ^{13}C) or 500 MHz spectrometer (500 MHz for ^1H and 125 MHz for ^{13}C) in $CDCl_3$, using residual $CHCl_3$ (δH = 7.26 ppm) as internal standard for ^1H and $CDCl_3$ (δC = 77.0 ppm) as internal standard for ^{13}C. Chemical shifts are given in δ (ppm) and coupling constants (J) in hertz. IR spectra were recorded with a FTIR-5300 instrument. High-resolution mass spectra were recorded on ESI-TOF spectrometer. A Welsbach Ozoniser was used for all ozonolysis reactions.



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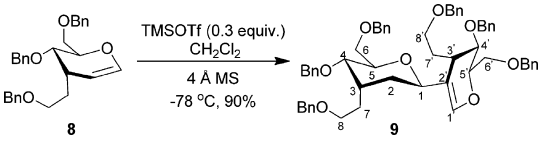
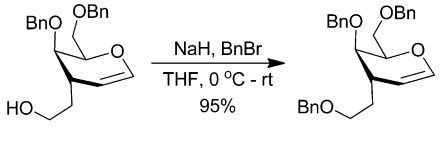
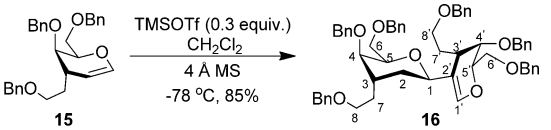
*(2R,3S,4S)-3-(Benzyloxy)-4-(2-benzyloxyethyl)-2-(benzyloxymethyl)-3,4-dihydro-2H-pyran (**8**):* Alcohol derivative **7**[12] (0.5 g, 1.41 mmol) was dissolved in anhydrous THF (10 mL). To this solution, at 0 °C, was added portionwise NaH (68 mg, 2.8 mmol) over 10 min with stirring. After continuous stirring for a further 1 h at 0 °C, benzyl bromide (0.36 g, 2.11 mmol) and TBAI (cat) were added, and the mixture was stirred at 25 °C until completion of the reaction (12 h). The reaction was quenched with the slow addition of cold water and extracted with CH_2Cl_2. The combined organic layers were dried with anhydrous Na_2SO_4 and concentrated under reduced pressure to obtain crude benzylated derivative. Purification of the crude product by column chromatography over silica gel (hexanes/ethyl acetate) provided pure glycal derivative **8** (0.56 g, 90%) as colorless liquid. R_f = 0.8 (20% EtOAc in hexanes). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.33−7.30 (m, 15H), 6.34 (d, J = 6.0 Hz, 1H), 4.69 (t, J = 4.8 Hz, 1H), 4.64−4.60 (m, 3H), 4.53−4.51 (m, 3H), 4.13−4.09 (m, 1H), 3.82−3.79 (m, 1H), 3.75 (d, J = 4.0 Hz, 2H), 3.57 (t, J = 6.0 Hz, 2H), 2.63 (dd, J = 4.8, 9.2 Hz, 1H), 2.12−2.104 (m, 1H), 1.58−1.49 (m, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 142.1, 138.5, 138.1, 138.0, 128.3, 127.8, 127.7, 127.5, 101.6, 73.5, 73.0, 72.9, 72.8, 71.1, 69.4. 67.8, 30.9, 29.6 ppm. IR (neat): ν = 2974, 2920, 2860, 2363, 2334, 1647, 1454, 1362 cm^{-1}. HRMS (ESI): calcd for $C_{29}H_{33}O_4$ $[M + H]^+$ 445.2379; found 445.2377.



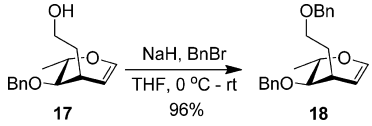
*(2R,3S,4S)-3-(Benzyloxy)-5-(2R,4S,5S,6R)-5-(benzyloxy)-4-(2-(benzyloxyethyl)-6-(benzyloxymethyl)tetrahydro-2H-pyran-2-yl)-4-(2-benzyloxyethyl)-2-(benzyloxymethyl)-3,4-dihydro-2H-pyran (**9**):* Glycal **8** was dried over vacuum for 1 h prior to use. Glycal **8** (0.13 g, 0.3 mmol) was dissolved in freshly distilled dry dichloromethane (10 mL). Powdered 4 Å molecular sieves (100 mg) was added to this solution and stirred for 1 h at room temperature. The solution was cooled to −78 °C and stirred for 15 min at the same temperature. Freshly distilled TMSOTf (16.4 μL, 0.09 mmol) was added at −78 °C and stirred until completion of the reaction (1 h). Triethylamine (12.5 μL, 0.09 mmol) was added at −78 °C to quench the reaction and allowed to reach room temperature. Dichloromethane was evaporated under reduced pressure, and the obtained crude was purified by column chromatography over silica gel (hexanes/ethyl acetate) to obtain the disaccharide **9** (0.12 g, 90%) as a colorless liquid. R_f = 0.45 (20% EtOAc in hexanes). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.36−7.23 (m, 30H, Ar(OBn)), 6.39 (s, 1H, H-1′), 4.64−4.63 (m, 1H, OCH_2Ph), 4.61−4.57 (m, 3H, OCH_2Ph), 4.58 (d, J = 12.0 Hz, 1H, OCH_2Ph), 4.53 (d, J = 12.0 Hz, 1H, OCH_2Ph), 4.52−4.51 (m, 1H, OCH_2Ph) 4.45−4.43 (m, 2H, OCH_2Ph), 4.40−4.38 (m, 1H, OCH_2Ph), 4.37 (d, J = 12.0 Hz, 1H, OCH_2Ph), 4.36 (d, J = 11.5 Hz, 1H, OCH_2Ph), 4.08 (br d, J = 10.5 Hz, 1H, H-1), 4.05−4.02 (m, 1H, H-5′), 3.81−3.62 (m, 7H, H-4, 5, 6_a, 6_b, 3′, 6_a′, 6_b′), 3.56−3.53 (m, 4H, H-8_a, 8_b, 8_a′, 8_b′), 2.90 (q, J = 5.0 Hz, 1H, H-3′), 2.47−2.45 (m, 1H, H-7_a), 2.11−2.09 (m, 1H, H-3), 2.02 (dd, J = 6.0, 13.5 Hz, 1H, H-7_a′), 1.80−1.72 (m, 3H, H-2_a, 2_b, 7_b), 1.24 (t, J = 7.0 Hz. 1H, H-7_b′) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 140.4, 138.8, 138.7, 138.5, 138.4, 138.1, 138.0, 128.2, 127.7, 127.6, 127.5, 127.5, 127.3, 114.6, 75.5, 75.4, 73.6, 73.5, 73.3, 73.0, 72.8, 72.5, 71.2, 71.1, 70.5, 70.4, 69.6, 69.4, 68.9, 31.9, 31.0, 30.3, 29.8, 25.2 ppm. IR (neat): ν = 3651, 2980, 2888, 1657, 1492, 1454 cm^{-1}. HRMS (ESI): calcd for $C_{58}H_{64}O_8Na$ $[M + Na]^+$ 911.4499; found 911.4499.



*(2R,3R,4S)-3-(Benzyloxy)-4-(2-benzyloxyethyl)-2-(benzyloxymethyl)-3,4-dihydro-2H-pyran (**15**):* Alcohol derivative **14**[12] (0.5 g, 1.41 mmol) was dissolved in anhydrous THF (10 mL). To this solution, at 0 °C, was added portionwise NaH (68 mg, 2.8 mmol) over 10 min with stirring. After continuous stirring for a further 1 h at 0 °C, benzyl bromide (0.36 g, 2.11 mmol) and TBAI (cat) were added and the mixture was stirred at 25 °C until completion of the reaction (12 h). The reaction was quenched with slow addition of cold water and extracted with CH_2Cl_2. The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to obtain crude benzylated derivative. Purification of the crude product by column chromatography over silica gel (hexanes/ethyl acetate) provided pure glycal derivative **15** (0.56 g, 95%) as a colorless liquid. R_f = 0.4 (10% EtOAc in hexanes). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36−7.28 (m, 15H), 6.44 (d, J = 6.0 Hz, 1H), 4.72 (t, J = 5.6 Hz, 1H), 4.64 (d, J = 12.0 Hz, 1H), 4.59 (d, J = 12.0 Hz, 1H), 4.52−4.44 (m, 4H), 4.05−4.02 (m, 1H), 3.78 (dd, J = 7.6, 10.0 Hz, 1H), 3.60 (dd, J = 4.8, 10.0 Hz, 1H), 3.55−3.53 (m, 3H), 2.42 (br s, 1H), 1.72−1.64 (m, 1H), 1.61 (dd, J = 6.8, 13.6 Hz, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 142.5, 138.2, 138.0, 137.9, 128.3, 128.0, 127.8, 127.7, 127.6, 102.4, 74.4, 73.4, 73.0, 72.6, 71.2, 69.2, 67.4, 35.3, 31.2 ppm. IR (neat): ν = 3046, 2926, 2857, 2350, 2318, 1650, 1492, 1454 cm^{-1}. HRMS (ESI): calcd for $C_{29}H_{32}O_4Na$ $[M + Na]^+$ 467.2199; found 467.2201.



*(2R,3R,4S)-3-(Benzyloxy)-5-(2R,4S,5R,6R)-5-(benzyloxy)-4-(2-benzyloxyethyl)-6-(benzyloxymethyl)tetrahydro-2H-pyran-2-yl)-4-(2-benzyloxyethyl)-2-(benzyloxymethyl)-3,4-dihydro-2H-pyran (**16**):* Glycal **15** was dried over vacuum for 1 h prior to use. Glycal **15** (0.13 g, 0.3 mmol) was dissolved in freshly distilled dry dichloromethane (10 mL). Powdered 4 Å molecular sieves (100 mg) was added to this solution and stirred for 1 h at room temperature. The solution was cooled to −78 °C and stirred for 15 min at the same temperature. Freshly distilled TMSOTf (16.4 μL, 0.09 mmol) was added at −78 °C and stirred until completion of the reaction (1 h). Triethylamine (12.5 μL, 0.09 mmol) was added at −78 °C to quench the reaction and allowed to reach room temperature. Dichloromethane was evaporated under reduced pressure, and the obtained crude was purified by column chromatography over silica gel (hexanes/ethyl acetate) to obtain the disaccharide **16** (0.11 g, 85%) as a colorless liquid. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.38−7.24 (m, 30H, Ar(OBn)), 6.57 (s, 1H, H-1′), 4.63 (d, J = 12.0 Hz, 1H, OCH_2Ph), 4.62 (d, J = 12.0 Hz, 1H, OCH_2Ph), 4.57−4.53 (m, 4H, OCH_2Ph), 4.49 (d, J = 12.0 Hz, 1H, OCH_2Ph), 4.51 (d, J = 12.0 Hz, 1H, OCH_2Ph), 4.42 (d, J = 12.0 Hz, 1H, OCH_2Ph), 4.46 (d, J = 12.0 Hz, 1H, OCH_2Ph), 4.41 (d, J = 12.0 Hz, 1H, OCH_2Ph), 4.39 (d, J = 10.5 Hz, 1H, OCH_2Ph), 4.07 (d, J = 11.0 Hz, 1H, H-1), 4.02 (t, J = 6.0 Hz, 1H, H-5′), 3.87 (dt, J = 1.0, 6.0 Hz, 1H, H-5), 3.75 (dd, J = 6.5, 10.0 Hz, 1H, H-4′), 3.67 (br s, 1H, H-8_a′), 3.63 (dd, J = 2.0, 6.0 Hz, 2H, H-6_a, 6_b), 3.56−3.51 (m, 5H, H-6_a′, 6_a′, 8_b′, 8_a, 8_b), 3.29 (s, 1H, H-4), 2.65 (d, J = 8.0 Hz, 1H, H-3′), 2.38−2.37 (m, 1H, H-3), 2.26−2.20 (m, 2H, H-2_a, 7_a′), 1.81−1.76 (m, 2H, H-7_a, 7_b), 1.38−1.33 (m, 2H, H-2_b, 7_b′) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 141.6, 138.9, 138.6, 138.4, 138.3, 138.2, 138.0, 128.4, 128.3, 128.2, 127.6, 127.5, 127.4, 127.3, 127.3, 114.4, 74.5, 74.2, 73.3, 73.2, 73.0, 72.8, 72.5, 72.2, 71.0, 70.8, 70.4, 69.8, 68.6, 68.3, 34.0, 31.2, 30.2, 28.8 ppm. IR (neat): ν = 3028, 2977, 2917, 2857, 2380, 2354, 1660, 1480 cm^{-1}. HRMS (ESI): calcd for $C_{58}H_{64}O_8Na$ $[M + Na]^+$ 911.4499; found 911.4499.



*(2R,3S,4S)-3-(Benzyloxy)-4-(2-benzyloxyethyl)-2-methyl-3,4-dihydro-2H-pyran (**18**):* Alcohol derivative **17**[12] (0.43 g, 1.73 mmol) was dissolved in anhydrous THF (15 mL). To this solution, at 0 °C, was added portionwise NaH (83 mg, 3.46 mmol) over 10 min with stirring. After continuous stirring for a further 1 h at 0 °C, benzyl bromide (0.59 g, 3.46 mmol) and TBAI (cat) were added and the

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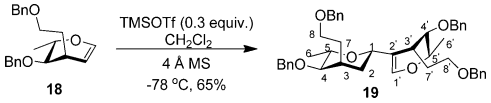
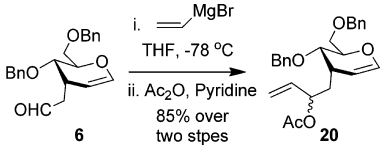
mixture was stirred at 25 °C until completion of the reaction (12 h). The reaction was quenched with slow addition of cold water and extracted with CH_2Cl_2. The combined organic layers were dried with anhydrous Na_2SO_4 and concentrated under reduced pressure to obtain crude benzylated derivative. Purification of the crude product by column chromatography over silica gel (hexanes/ethyl acetate) provided pure glycal derivative **18** (0.56 g, 96%) as a colorless liquid. R_f = 0.6 (10% EtOAc in hexanes). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.37−7.29 (m, 10H), 6.27 (dd, J = 1.2, 6.0 Hz, 1H), 4.67−4.55 (m, 3H), 4.52(s, 2H), 4.09−4.02 (m, 1H), 3.57 (t, J = 5.6 Hz, 2H), 3.42 (dd, J = 5.2, 7.2 Hz, 1H), 2.68−2.62 (m, 1H), 2.10−2.02 (m, 1H), 1.59−1.50 (m, 1H), 1.32 (d, J = 6.4 Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 141.9, 138.6, 138.1, 138.3, 127.8, 127.6, 127.5, 101.6, 77.4, 72.8, 71.1, 69.7, 67.9, 30.8, 29.4, 17.7 ppm. IR (neat): ν = 3056, 3024, 2926, 2857, 1723, 1644, 1489, 1454 cm^{-1}. HRMS (ESI): calcd for $C_{22}H_{26}O_3Na$ [M + Na]$^+$ 361.1780; found 361.1774.

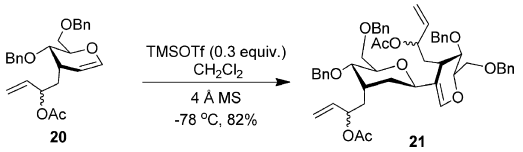


*(2R,3S,4S)-3-(Benzyloxy)-5-(2R,4S,5S,6R)-5-(benzyloxy)-4-(2-benzyloxyethyl)-6-methyltetrahydro-2H-pyran-2-yl)-4-(2-benzyloxyethyl)-2-methyl-3,4-dihydro-2H-pyran (**19**):* Glycal **18** was dried over vacuum for 1 h prior to use. Glycal **18** (0.11 g, 0.32 mmol) was dissolved in freshly distilled dry dichloromethane (10 mL). To this solution was added powdered 4 Å molecular sieves (100 mg) and stirred for 1 h at room temperature. The solution was cooled to −78 °C and stirred for 15 min at the same temperature. Freshly distilled TMSOTf (17.7 μL, 0.09 mmol) was added at −78 °C and stirred until completion (1 h). Triethylamine (13.4 μL, 0.09 mmol) was added at −78 °C to quench the reaction and allowed to reach room temperature. Dichloromethane was evaporated under reduced pressure, and the obtained crude was purified by column chromatography over silica gel (hexanes/ethyl acetate) to obtain the disaccharide **19** (0.07 g, 65%) as a colorless liquid. R_f = 0.4 (10% EtOAc in hexanes). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.34−7.24 (m, 20H, Ar(OBn)), 6.29 (s, 1H, H-1′), 4.64 (d, J = 11.6 Hz, 1H, OCH_2Ph), 4.61 (d, J = 11.6 Hz, 1H, OCH_2Ph), 4.52−4.49 (m, 3H, OCH_2Ph), 4.43 (d, J = 12.0 Hz, 2H, OCH_2Ph), 4.36 (d, J = 11.6 Hz, 1H, OCH_2Ph), 4.04 (t, J = 6.8 Hz, 1H, H-1), 3.93 (dd, J = 6.0, 8.8 Hz, 1H, H-5′), 3.58−3.48 (m, 5H, H-8$_a$, 8$_b$, 8$_a$′, 8$_b$′, 5), 3.38 (dd, J = 5.2, 8.8 Hz, 1H, H-4′), 3.14 (dd, J = 5.2, 9.2 Hz, 1H, H-4), 2.83 (q, J = 5.2 Hz, 1H, H-3′). 2.45−2.40 (m, 1H, H-7$_a$), 2.11−2.02 (m, 1H, H-3), 1.98 (dd, J = 6.4, 14.0 Hz, 1H, H-7$_a$′), 1.75−1.65 (m, 4H, H-2, 2, 7$_b$′, 7$_b$), 1.29 (d, J = 6.0 Hz, 3H, H-6′), 1.23 (d, J = 6.0 Hz, 3H, H-6) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 140.2, 138.8, 138.6, 138.4, 138.2, 128.4, 128.3, 127.8, 127.7, 127.6, 127.5, 127.5, 127.4, 114.8, 81.1, 78.6, 77.3, 72.8, 72.6, 71.7, 71.3, 70.8, 70.4, 69.8, 69.5, 69.0, 32.2, 31.1, 30.4, 30.4, 30.0, 25.3, 19.0. 18.2 ppm. IR (neat): ν = 3651, 2984, 2972, 2882, 2354, 2333, 1657, 1451 cm^{-1}. HRMS (ESI): calcd for $C_{44}H_{52}O_6Na$ [M + Na]$^+$ 699.3662; found 699.3662.

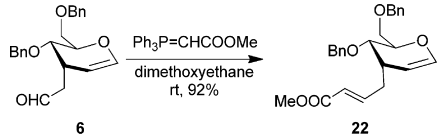


*1-(2R,3S,4S)-3-(Benzyloxy)-2-(benzyloxymethyl)-3,4-dihydro-2H-pyran-4-yl)but-3-en-2-yl acetate (**20**):* To a solution of aldehyde **6**[12] (0.3 g, 0.85 mmol) in anhydrous THF at −78 °C was slowly added vinylmagnesium bromide (3.41 mL, 1 M sol) and stirred until completion (3 h). The reaction was quenched with aq NH_4Cl (2 mL) and brought to room temperature. The reaction mixture was diluted with EtOAc (20 mL) and washed with aq NH_4Cl and brine. The separated organic phase was dried over anhydrous sodium sulfate and concentrated in vacuo. The crude compound was taken forward without purification.

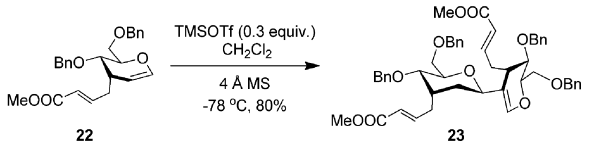
The crude alcohol (0.3 g, 0.78 mmol) was dissolved in pyridine (5 mL) and cooled to 0 °C. Acetic anhydride (0.4 mL, 3.94 mmol) was slowly added and stirred at room temperature for 8 h. The organic phase was evaporated in vacuo and purified by column chromatography over silica gel (hexanes/ethyl acetate) to provide the colorless liquid of acetylated derivative **20** (0.3 g, 85%) as an inseparable mixture of diastereomers. R_f = 0.5 (10% EtOAc in hexanes). IR (neat): ν = 3062, 2933, 2366, 2321, 1793, 1647, 1457 cm^{-1}. HRMS (ESI): calcd for $C_{26}H_{30}O_5Na$ [M + Na]$^+$ 445.1991; found 445.1991.



*1-(2R,3S,4S,6R)-6-(2R,3S,4S)-4-(2-Acetoxybut-3-en-1-yl)-3-(benzyloxy)-2-(benzyloxymethyl)-3,4-dihydro-2H-pyran-5-yl)-3-(benzyloxy)-2-(benzyloxymethyl)tetrahydro-2H-pyran-4-yl)but-3-en-2-yl acetate (**21**):* Glycal **20** was dried over vacuum for 1 h prior to use. Glycal **20** (0.1 g, 0.23 mmol) was dissolved in freshly distilled dry dichloromethane (10 mL). To this solution was added powdered 4 Å molecular sieves (100 mg) and stirred for 1 h at room temperature. The solution was cooled to −78 °C and stirred for 15 min at the same temperature. Freshly distilled TMSOTf (12.2 μL, 0.07 mmol) was added at −78 °C and stirred until completion (1 h). Triethylamine (9.7 μL, 0.07 mmol) was added at −78 °C to quench the reaction and allowed to reach room temperature. Dichloromethane was evaporated under reduced pressure, and the obtained crude was purified by column chromatography over silica gel (hexanes/ethyl acetate) to obtain the disaccharide **21** (0.82 g, 82%) as a colorless liquid. R_f = 0.4 (10% EtOAc in hexanes). IR (neat): ν = 2986, 2926, 2872, 2366, 2321, 1733, 1650, 1454 cm^{-1}. HRMS (ESI): calcd for $C_{52}H_{64}O_{10}N$ [M + NH_4]$^+$ 862.4530; found 862.4537.



*(E)-Methyl 4-(2R,3S,4S)-3-(Benzyloxy)-2-(benzyloxymethyl)-3,4-dihydro-2H-pyran-4-yl)but-2-enoate (**22**):* To a solution of aldehyde **6**[12] (0.4 g, 1.14 mmol) in dimethoxyethane (20 mL) was added methyl(triphenylphosphoranylidene)acetate (0.95 g, 2.86 mmol) at room temperature and stirred until completion (16 h). The solvent was evaporated under reduced pressure, and the obtained crude was purified by column chromatography over silica gel (hexanes/ethyl acetate) to obtain the pure compound **22** (0.42 g, 92%, *E*:*Z* (86:14)) as a colorless liquid. R_f = 0.65 (10% EtOAc in hexanes). For *E* isomer, ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.35−7.30 (m, 10H), 7.01−6.94 (m, 1H), 6.35 (d, J = 6.0 Hz, 1H), 5.87 (d, J = 15.5 Hz, 1H), 4.63 (dd, J = 5.0, 6.0 Hz, 1H), 4.60−4.53 (m, 4H), 4.11−4.07 (m, 1H), 3.86 (dd, J = 5.5, 8.0 Hz, 1H), 3.75−3.72 (m, 5H), 2.61−2.56 (m, 1H), 2.53−2.49 (m, 1H), 2.18−2.12 (m, 1H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 166.6, 147.2, 142.6, 137.8, 137.6, 127.9, 127.8, 127.7, 127.5, 122.3, 100.8, 73.4, 72.7, 72.7, 71.5, 68.0, 51.2, 33.9, 32.6 ppm. IR (neat): ν = 3059, 3028, 2942, 2857, 2907, 2366, 2328, 1723, 1641, 1498, 1454 cm^{-1}. HRMS (ESI): calcd for $C_{25}H_{32}O_5N$ [M + NH_4]$^+$ 426.2280; found 426.2283.



*(E)-Methyl 4-(2R,3S,4S)-3-(Benzyloxy)-5-(2R,4S,5S,6R)-5-(benzyloxy)-6-((benzyloxymethyl)-4-(E)-4-methoxy-4-oxobut-2-en-1-yl)-tetrahydro-2H-pyran-2-yl)-2-(benzyloxymethyl)-3,4-dihydro-2H-pyran-4-yl)but-2-enoate (**23**):* Glycal **22** was dried over vacuum for 1 h prior to use. Glycal **22** (0.1 g, 0.24 mmol) was dissolved in freshly distilled dry dichloromethane (10 mL). To this solution was added powdered 4 Å molecular sieves (100 mg) and stirred for 1 h at room temperature. The solution was cooled to −78 °C and stirred for 15 min at the same temperature. Freshly distilled TMSOTf (12.7 μL, 0.07 mmol) was added at −78 °C and stirred until completion (1 h).

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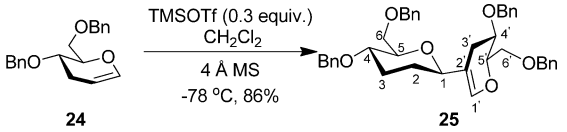
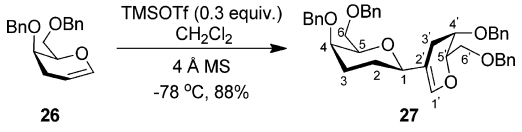
Triethylamine (10.0 μL, 0.07 mmol) was added at −78 °C to quench the reaction and allowed to reach room temperature. Dichloromethane was evaporated under reduced pressure, and the obtained crude was purified by column chromatography over silica gel (hexanes/ethyl acetate) to obtain the disaccharide **23** (0.80 g, 80%) as a colorless liquid. R_f = 0.3 (20% EtOAc in hexanes). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36−7.27 (m, 20H), 7.15−7.07 (m, 1H), 6.97−6.89 (m, 1H), 6.40 (s, 1H), 5.87 (dd, *J* = 6.8, 15.6 Hz, 2H), 4.63−4.55 (m, 6H), 4.47 (d, *J* = 11.2 Hz, 1H), 4.44 (d, *J* = 11.6 Hz, 1H), 4.06 (d, *J* = 10.8 Hz, 1H), 4.02−4.00 (m, 1H), 3.84 (dd, *J* = 5.2, 9.2 Hz, 1H), 3.76 (s, 6H), 3.70−3.67 (m, 6H), 2.93 (q, *J* = 5.6 Hz, 1H), 2.68−2.59 (m, 2H), 2.49 (dd, *J* = 7.2, 14.0 Hz, 1H), 2.44−2.31 (m, 2H), 1.76−1.67 (m, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.9, 166.7, 149.5, 148.2, 141.1, 138.5, 138.0, 137.9, 137.6, 128.3, 128.2, 127.8, 127.7, 127.6, 127.4. 122.4. 121.5, 112.8, 75.2, 75.0, 73.5, 73.3, 73.2, 73.0, 71.6, 71.0, 70.8, 70.2, 60.2, 51.4. 51.3, 33.8, 33.1, 33.0, 31.2, 28.3 ppm. IR (neat): ν = 3664, 2993, 2971, 2961, 2885, 2347, 1717, 1650, 1460 cm^{-1}. HRMS (ESI): calcd for $C_{50}H_{56}O_{10}Na$ $[M + Na]^+$ 839.3771; found 839.3770.



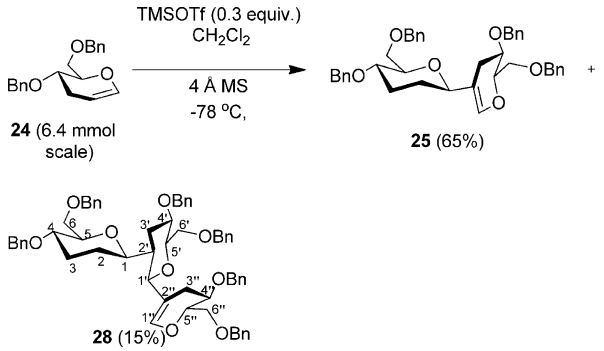
24 **25**

*(2R,3S)-3-(Benzyloxy)-5-(2R,5S,6R)-5-(benzyloxy)-6-(benzyloxymethyl)tetrahydro-2H-pyran-2-yl)-2-(benzyloxymethyl)-3,4-dihydro-2H-pyran (**25**):* Glycal **24** was dried over vacuum for 1 h prior to use. Glycal **24** (0.11 g, 0.35 mmol) was dissolved in freshly distilled dry dichloromethane (10 mL). To this solution was added powdered 4 Å molecular sieves (100 mg) and stirred for 1 h at room temperature. The solution was cooled to −78 °C and stirred for 15 min at the same temperature. Freshly distilled TMSOTf (19.3 μL, 0.10 mmol) was added at −78 °C and stirred until completion (1 h). Triethylamine (14.0 μL, 0.10 mmol) was added at −78 °C to quench the reaction and allowed to reach room temperature. Dichloromethane was evaporated under reduced pressure, and the obtained crude was purified by column chromatography over silica gel (hexanes/ethyl acetate) to obtain the disaccharide **25** (0.09 g, 86%) as a colorless liquid. R_f = 0.4 (20% EtOAc in hexanes). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.37−7.28 (m, 20H, Ar(OBn)), 6.51 (s, 1H, H-1′), 4.70−4.65 (m, 3H, OCH_2Ph), 4.63−4.58 (m, 3H, OCH_2Ph), 4.53 (d, *J* = 11.6 Hz, 1H, OCH_2Ph), 4.48 (d, *J* = 11.6 Hz, 1H, OCH_2Ph), 3.95−3.93 (m, 1H, H-5′), 3.85−3.76 (m, 6H, H-1, 6_a, 6_b, 4′, 6_a′, 6_b′), 3.52−3.50 (m, 1H, H-5), 3.46 (dd, *J* = 4.0, 9.6 Hz, 1H, H-4), 2.55 (dd, *J* = 5.6, 16.0 Hz, 1H, H-3_a′), 2.35−2.30 (m, 1H, H-3_a), 2.16 (dd, *J* = 8.4, 16.4 Hz, 1H, H-3_b′), 1.78−1.74 (m, 1H, H-2_a), 1.63−1.52 (m, 2H, H-2_b, 3_b) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 139.9, 138.6, 138.4, 138.1, 138.1, 128.3, 128.3, 128.2, 127.7, 127.6, 127.5, 127.4, 110.7, 80.8, 77.7, 76.6, 73.4, 73.4, 73.2, 71.0, 70.9, 70.1, 69.9. 68.9, 29.4, 29.1, 26.7 ppm. IR (neat): ν = 3040, 2929, 2888, 2356, 2334, 1679, 1492 cm^{-1}. HRMS (ESI): calcd for $C_{40}H_{44}O_6Na$ $[M + Na]^+$ 643.3036; found 643.3033.

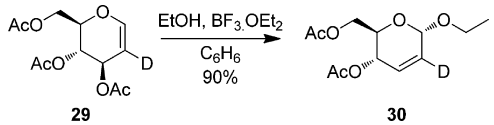


26 **27**

*(2R,3R)-3-(Benzyloxy)-5-(2R,5R,6R)-5-(benzyloxy)-6-(benzyloxymethyl)tetrahydro-2H-pyran-2-yl)-2-(benzyloxymethyl)-3,4-dihydro-2H-pyran (**27**):* Glycal **26** was dried over vacuum for 1 h prior to use. Glycal **26** (0.1 g, 0.24 mmol) was dissolved in freshly distilled dry dichloromethane (10 mL). To this solution was added powdered 4 Å molecular sieves (100 mg) and stirred for 1 h at room temperature. The solution was cooled to −78 °C and stirred for 15 min at the same temperature. Freshly distilled TMSOTf (12.7 μL, 0.07 mmol) was added at −78 °C and stirred until completion (1 h). Triethylamine (10.0 μL, 0.07 mmol) was added at −78 °C to quench the reaction and allowed to reach room temperature. Dichloromethane was evaporated under reduced pressure, and the obtained crude was purified by column chromatography over silica gel (hexanes/ethyl acetate) to obtain the disaccharide **27** (0.88 g, 88%) as a colorless liquid. R_f = 0.4 (20% EtOAc in hexanes). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.39−7.31 (m, 20H, Ar(OBn)), 6.55 (s, 1H, H-1′), 4.69 (d, *J* = 12.0 Hz, 1H, OCH_2Ph), 4.68 (d, *J* = 12.0 Hz, 1H, OCH_2Ph), 4.61 (d, *J* = 12.0 Hz, 1H, OCH_2Ph), 4.58 (d, *J* = 12.0 Hz, 1H, OCH_2Ph), 4.53−4.51 (m, 3H, OCH_2Ph), 4.47 (d, *J* = 12.0 Hz, 1H, OCH_2Ph), 4.16 (t, *J* = 5.5 Hz, 1H, H-5′), 3.92 (q, *J* = 4.0 Hz, 1H, H-4′), 3.84 (d, *J* = 11.5 Hz, 1H, H-1), 3.76−3.64 (m, 5H, H-5, 6_a, 6_b, 6_a′, 6_b′), 3.56 (s, 1H, H-4), 2.37−2.27 (m, 2H, H-3_a′, 3_b′), 2.20 (dd, *J* = 2.5, 14.0 Hz, 1H, H-3_a), 2.02−1.93 (m, 1H, H-2_a), 1.61−1.54 (m, 1H, H-3_b), 1.38 (d, *J* = 13.0 Hz, 1 H, H-2_b) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 139.8, 138.6, 138.2, 138.1, 138.0, 128.2, 128.2, 128.1, 127.9, 127.8, 127.7, 127.6, 127.5, 127.5, 127.4, 127.4. 111.1, 78.7, 78.6, 75.0, 73.3, 73.2, 70.9, 70.6, 70.2, 70.1. 69.4, 68.4, 26.2, 24.5, 23.9 ppm. IR (neat): ν = 3664, 2974, 2882, 2369, 2340, 1669, 1448, 1384 cm^{-1}. HRMS (ESI): calcd for $C_{40}H_{44}O_6Na$ $[M + Na]^+$ 643.3036; found 643.3033.



*(2R,2′R,3′S,5S,5′S,6R,6′R)-5,5′-Bis(benzyloxy)-2′-((2R,3S)-3-(benzyloxy)-2-(benzyloxymethyl)-3,4-dihydro-2H-pyran-5-yl)-6,6′-bis-(benzyloxymethyl)octahydro-2H,2′H-2,3′-bipyran (**28**):* Glycal **24** was dried over vacuum for 1 h prior to use. Glycal **24** (2.0 g, 6.4 mmol) was dissolved in freshly distilled dry dichloromethane (100 mL). To this solution was added powdered 4 Å molecular sieves (1.0 g) and stirred for 1 h at room temperature. The solution was cooled to −78 °C and stirred for 15 min at the same temperature. Freshly distilled TMSOTf (0.35 mL, 1.92 mmol) was added at −78 °C and stirred until completion (1 h). Triethylamine (0.27 mL, 1.92 mmol) was added at −78 °C to quench the reaction and allowed to reach room temperature. Dichloromethane was evaporated under reduced pressure, and the obtained crude was purified by column chromatography over silica gel (hexanes/ethyl acetate) to obtain the pure compound of disaccharide **25** (1.3 g, 65%) and trisaccharide **28** (0.3 g, 15%) as colorless liquids. Data for trisaccharide **28**, R_f = 0.15 (20% EtOAc in hexanes). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.40−7.27 (m, 30H, Ar(OBn)), 6.45 (s, 1H, H-1″), 4.69−4.65 (m, 4H, OCH_2Ph), 4.63−4.59 (m, 4H, OCH_2Ph), 4.50−4.44 (m, 4H, OCH_2Ph), 4.12 (br t *J* = 5.2 Hz, 1H, H-5), 4.04−4.00 (m, 1H, H-5″), 3.80−3.79 (m, 3H, H-4″, 6_a″, 6_b″), 3.78 (d, *J* = 4.0 Hz, 1H, H-5′), 3.62 (dd, *J* = 5.6, 16.0 Hz, 3H, H-4, 6_a, 6_b), 3.54−3.49 (m, 5H, 1, 1′, 4′, 6_a′, 6_b′), 2.60−2.50 (m, 2H, H-2′, 3_a″), 2.33−2.27 (m, 1H, H-3_b″), 2.04−1.96 (m, 1H, H-3_b), 1.90−1.87 (m, 1H, H-2_b), 1.74−1.68 (m, 1H, H-3_a), 1.42−1.32 (m, 2H, 3_a′, 3_b′), 1.27 (dd, *J* = 2.4, 12.4 Hz, 1H, H-2_a) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 141.57, 138.6, 138.5, 138.3, 138.0, 137.9, 128.3, 128,3, 128.3, 128.3, 128.3, 127.7, 127.6, 127.5, 127.5. 127.5, 127.4, 127.4, 127.3. 109.6, 80.7, 76.7, 74.6, 73.5, 73.4, 73.3, 73.1, 71.3, 70.6, 70.7, 70.5, 70.1, 69.9, 69.6, 68.9. 68.9, 68.7, 41.5, 29.7, 25.2, 23.8, 20.4 ppm. IR (neat): ν = 2929, 2860, 2359, 2331, 1669, 1495, 1451 cm^{-1}. HRMS (ESI): calcd for $C_{60}H_{70}O_9N$ $[M + NH_4]^+$ 948.5051; found 948.5051.



29 **30**

*(2R,3S,6S)-[5-^{2}H]-3-acetoxy-6-ethoxy-3,6-dihydro-2H-pyran-2-yl)-methyl acetate (**30**):* 1,2-Dideoxy-[2-^{2}H]-3,4,6-tri-*O*-acetyl-D-arabino-

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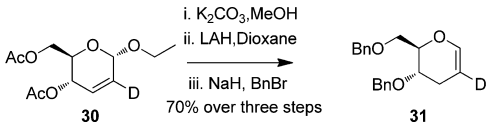
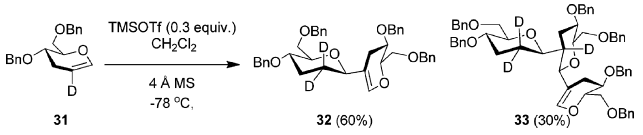
1-hexenopyranose[18] **29** (1.5 g, 5.48 mmol) was dissolved in anhydrous benzene (25 mL). To this solution, at 0 °C, were added ethanol (0.50 mL, 8.61 mmol) and $BF_3{\cdot}OEt_2$ (0.23 mL, 1.80 mmol). The solution was allowed to slowly reach room temperature and stirred until completion (3 h). The reaction was quenched with Et_3N (0.3 mL, 2.22 mmol) at 0 °C and concentrated under vacuo. The obtained crude was purified by column chromatography over silica gel (hexanes/ethyl acetate) to obtain colorless 2,3 unsaturated compound **30** (1.28 g, 90%) as the inseparable mixture of anomers (α:β, 9:1) with α as the major isomer. Data for α anomer, R_f = 0.7 (30% EtOAc in hexanes). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.84 (br s, 1H), 5.27 (dd, J = 1.2, 9.6 Hz, 1H), 5.00 (s, 1H), 4.20 (d, J = 5.2 Hz, 1H), 4.14 (dd, J = 2.0, 12.0 Hz, 1H), 4.01−4.06 (m, 1H), 3.81−3.77 (m, 1H), 3.57−3.50 (m, 1H), 2.05 (s, 3H), 2.04 (s, 3H), 1.21 (t, J = 6.8 Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.7, 170.2, 128.8, 94.1, 65.7, 65.2, 64.2. 62.9, 20.8, 20.7, 15.2 ppm. IR (neat): ν = 2986, 2895, 2366, 2311, 1733, 1444, 1365 cm^{-1}. HRMS (ESI): calcd for $C_{12}H_{17}DO_6Na$ $[M + Na]^+$ 282.1064; found 282.1062.

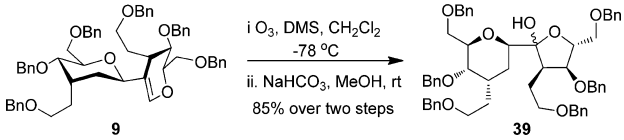


*(2R,3S)-[5-^{2}H]-3-(Benzyloxy)-2-(benzyloxymethyl)-3,4-dihydro-2H-pyran (**31**):* To a solution of β,γ-unsaturated compound **30** (1.24 g, 4.78 mmol) in MeOH (20 mL) was added anhydrous solid K_2CO_3 (66 mg, 0.47 mmol) and stirred until completion (2 h). MeOH was completely evaporated in vacuo and coevaporated with toluene (2 × 10 mL). The crude compound was dried for 20 min in vacuo and dissolved in anhydrous dioxane (15 mL) with stirring. Lithium aluminum hydride (LAH) (0.19 g, 5.0 mmol) was added and heated to reflux until completion (12 h). The reaction was slowly quenched at 0 °C with aq NH_4Cl (10 mL) and stirred for 30 min at room temperature. The precipitated solid material was removed by filtration through Celite. The crude product was dissolved in EtOAc and washed with aq NH_4Cl and brine and concentrated in vacuo to obtain the crude glycal, which was used in the next step without further purification.

The crude glycal was dried in vacuo for 30 min and dissolved in anhydrous THF (10 mL). NaH (0.24 g, 10 mmol) was added slowly portionwise in 10 min at 0 °C and stirred for 15 min at the same temperature. BnBr (1.12 mL, 10 mmol) and TBAI (cat) were added at 0 °C and stirred at 25 °C until completion of the reaction (12 h). The reaction was slowly quenched with aq NH_4Cl (2 mL). The mixture was diluted with EtOAc and washed with aq NH_4Cl and brine and concentrated in vacuo. The obtained crude was purified by column chromatography over silica gel (hexanes/ethyl acetate) to obtain the pure deuterated glycal **31** (1.2 g, 70% over three steps) as colorless liquid. R_f = 0.5 (10% EtOAc in hexanes). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.37−7.27 (m, 10H), 6.38 (s, 1H), 4.66−4.62 (m, 2H), 4.60−4.48 (m, 1H), 4.53 (d, J = 11.5 Hz, 1H), 3.94−3.90 (m, 1H), 3.82−3.78 (m, 3H), 2.40 (ddd, J = 1.5, 6.0, 16.5 Hz, 1H), 2.10 (ddd, J = 2.5, 8.5, 16.5 Hz, 1H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 143.1, 138.3, 138.2, 128.4, 128.3, 127.8, 127.7, 127.6, 127.6, 73.5, 71.1. 70.5, 69.1, 26.5 ppm. IR (neat): ν = 3060, 3031, 2928, 2359, 2331, 1644, 1492 cm^{-1}. HRMS (ESI): calcd for $C_{20}H_{21}DO_3Na$ $[M + Na]^+$ 334.1529; found 334.1530.



*Deuterated Disaccharide **32** and Trisaccharide **33**:* Glycal **31** was dried over vacuum for 1 h prior to use. Glycal **31** (0.4 g, 1.2 mmol) was dissolved in freshly distilled dry dichloromethane (20 mL). To this solution was added powdered 4 Å molecular sieves (200 mg) and stirred for 1 h at room temperature. The solution was cooled to −78 °C and stirred for 15 min at the same temperature. Freshly distilled TMSOTf (63.5 μL, 0.36 mmol) was added at −78 °C and stirred until completion (1 h). Triethylamine (48.5 μL, 0.36 mmol) was added at −78 °C to quench the reaction and allowed to reach room temperature. Dichloromethane was evaporated under reduced pressure, and the obtained crude was purified by column chromatography over silica gel (hexanes/ethyl acetate) to obtain the pure compounds of disaccharide **32** (0.24 g, 60%) and trisaccharide **33** (0.12g, 30%) as color less liquids. Data for disaccharide (**32**), R_f = 0.4 (20% EtOAc in hexanes). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.38−7.23 (m, 20 H), 6.44 (s, 1 H), 4.67 (d, J = 11.5 Hz, 1 H), 4.66 (d, J = 12.0 Hz, 1H), 4.61−4.57 (m, 4 H), 4.51 (d, J = 11.5 Hz, 1 H), 4.46 (d, J = 11.5 Hz, 1 H), 3.92−3.89 (m, 1 H), 3.83 (dd, J = 5.5, 8.0 Hz, 1 H), 3.80−3.77 (m, 3 H), 3.74−3.71 (m, 2 H), 3.50−3.47 (m, 1 H), 3.44−3.39 (m, 1 H), 2.52 (dd, J = 5.5, 16.5 Hz, 1 H), 2.30 (td, J = 4.5, 12.0 Hz, 1 H), 2.17−2.12 (m, 1 H), 1.53−1.48 (m, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 139.9, 138.7, 138.5, 138.3, 138.2, 128.4, 128.3, 128.3, 127.7, 127.7. 127.6, 127.6. 127.5, 127.4, 110.8, 80.9, 77.7, 73.5, 73.5, 73.3, 71.0, 70.9, 70.3, 70.0. 69.0, 29.4, 26.8 ppm. IR (neat): ν = 3654, 3548, 2990, 2071, 2879, 2353, 1676, 1470, 1444 cm^{-1}. HRMS (ESI): calcd for $C_{40}H_{43}D_2O_6$ $[M + H]^+$ 623.3342; found 623.3340. Data for trisaccharide (**33**), yield 30%, R_f = 0.6 (20% EtOAc in hexanes). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.36−7.27 (m, 30H), 6.45 (s, 1H), 4.66 (d, J = 11.5 Hz, 1H), 4.65−4.63 (m, 2H), 4.62−4.60 (m, 2H), 4.58−4.57 (m, 2H), 4.56−4.55 (m, 1H), 4.46−4.42 (m, 4H), 4.07 (br t, J = 5.0 Hz, 1H), 3.99−3.95 (m, 1H), 3.78−3.73 (m, 4H), 3.61−3.53 (m, 3H), 3.50−3.47 (m, 3H), 3.46−3.43 (m, 2H), 2.52 (dd, J = 4.0, 12.0 Hz, 1 H), 2.48 (dd, J = 5.0 Hz, 16.5 Hz, 1H), 2.27−2.22 (m, 1H), 1.93−1.90 (m, 1H), 1.35−1.28 (m, 2H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 141.6, 138.7, 138.6, 138.4, 138.1, 138.0, 138.0, 128.3, 128.3, 128.3, 128.2, 127.7, 127.6, 127.6, 127.5, 127.5, 127.4, 127.3, 109.6. 80.7, 77.3, 76.7. 74.6, 73.5, 73.5, 73.4, 73.2, 71.3, 71.0, 70.6, 70.2, 70.0, 69.7, 69.0, 68.8, 29.7, 25.3, 23.7 ppm. IR (neat): ν = 3658, 2977, 2885, 2366, 2334, 1663, 1467, 1448 cm^{-1}. HRMS (ESI): calcd for $C_{60}H_{63}D_3O_9K$ $[M + K]^+$ 972.4532; found 972.4535.



*(3S,4R,5S)-4-(Benzyloxy)-2-(2R,4S,5S,6R)-5-(benzyloxy)-4-(2-benzyloxyethyl)-6-(benzyloxymethyl)tetrahydro-2H-pyran-2-yl)-3-(2-benzyloxyethyl)-5-(benzyloxymethyl)tetrahydrofuran-2-ol (**39**):* CH_2Cl_2 (10 mL) was added to the disaccharide **9** (0.15 g, 0.17 mmol) in a two-neck round-bottomed flask with a gas outlet on one neck and a gas inlet on the other neck. The solution was cooled to −78 °C using an EtOAc/liquid nitrogen bath. Ozone was bubbled through the gas inlet into the solution until the pale blue color persisted. Then, oxygen followed by nitrogen was passed through the inlet until the pale blue color disappeared. Dimethyl sulfide (0.5 mL) was added to the reaction mixture at −78 °C, which was then allowed to warm to 25 °C. The solvent was evaporated in vacuo to obtain the crude formate ester, which was used in the next step without purification.

The obtained crude product was dissolved anhydrous MeOH (10 mL). To this solution was added solid $NaHCO_3$ (0.13 g, 1.57 mmol) and stirred until completion (2 h). MeOH was evaporated in vacuo, and the obtained crude was purified by column chromatography over silica gel (hexanes/ethyl acetate) to obtain the inseparable anomeric mixture of pure hemiketal **39** (0.12 g, 85% over two steps, α:β (9:1)) as colorless liquid. R_f = 0.4 (20% EtOAc in hexanes). For α anomer, ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.37−7.27 (m, 30H), 4.65 (d, J = 11.5 Hz, 1H), 4.62 (d, J = 11.5 Hz, 1H), 4.52 (m, 3H), 4.49−4.45 (m, 5H), 4.39 (d, J = 11.5 Hz, 1H), 4.37 (d, J = 12.0 Hz, 1H), 4.36 (d, J = 11.5 Hz, 1H), 4.01 (d, J = 4.5 Hz, 1H), 3.88 (s, 1H), 3.71 (d, J = 8.5 Hz, 1H), 3.67−3.62 (m, 3H), 3.61−3.55 (m, 3H), 3.52−3.96 (m, 3H), 3.29 (dd, J = 8.5, 10.0 Hz, 1H), 2.68−2.63 (m, 1H), 2.48−2.46 (m, 1H), 2.12−2.07 (m, 1H), 2.01−1.96 (m, 1H), 1.91−1.82 (m, 2H), 1.79 (s, 1H), 1.73−1.66 (m, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.6, 138.5, 138.3, 137.4, 128.4, 128.3, 128.3, 128.2, 128.2, 128.1, 127.8, 127.7, 127.6, 127.5, 127.5, 127.4, 127.4, 127.3, 107.0, 81.2, 80.4,

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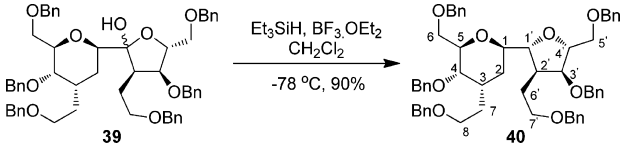
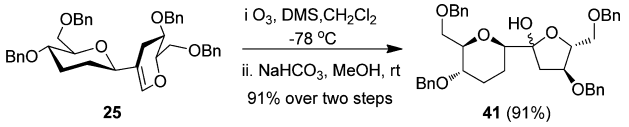
75.5, 75.5, 73.3, 72.8, 72.6, 71.4, 71.4, 70.7, 70.3, 70.3, 68.9, 68.7, 41.5, 30.3, 27.0, 25.2, 23.2 ppm. IR (neat): ν = 3031, 2933, 2853, 1950, 1489, 1448, 1362 cm^{-1}. HRMS (ESI): calcd for $C_{57}H_{64}O_9Na$ $[M + Na]^+$ 915.4448; found 915.4445.



39 40

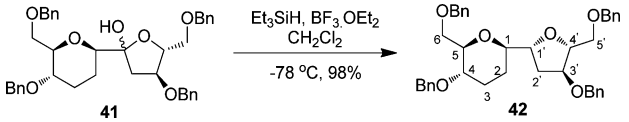
*(2R,3S,4S,6R)-3-(Benzyloxy)-6-(2R,3S,4R,5S)-4-(benzyloxy)-3-(2-benzyloxyethyl)-5-(benzyloxymethyl)tetrahydrofuran-2-yl)-4-(2-benzyloxyethyl)-2-(benzyloxymethyl)tetrahydro-2H-pyran (**40**):* A solution of hemiketal **39** (0.07 g, 0.08 mmol) in anhydrous dichloromethane (5 mL) was cooled to −78 °C. Et_3SiH (32 μL, 0.2 mmol) and $BF_3{\cdot}OEt_2$ (20 μL, 0.15 mmol) were added at the same temperature. The reaction mixture was slowly allowed to reach room temperature and stirred until completion (2 h). The organic phase was washed with aq $NaHCO_3$ and brine and concentrated in vacuo. The crude was purified by column chromatography over silica gel (hexanes/ethyl acetate) to obtain the pure pyranofuranoside **40** (0.06 g, 90%) as a colorless liquid. R_f = 0.7 (20% EtOAc in hexanes). ^1H NMR (500 MHz, $CDCl_3$): δ = 7.40−7.27 (m, 30H, Ar(OBn)), 4.61−4.56 (m, 3H, OCH_2Ph), 4.52−4.51 (m, 4H, OCH_2Ph), 4.49−4.38 (m, 5H, OCH_2Ph), 4.25−4.22 (m, 1H, H-5), 3.92 (dd, J = 2.0, 5.5 Hz, 1H, H-4,), 3.80 (dd, J = 2.0, 9.0 Hz, 1H, H-8_a), 3.72 (d, J = 8.5 Hz, 1H, H-4′), 3.65−3.59 (m, 3H, H-1′, 5_a′, 8_b), 3.54−3.50 (m, 3H, H-1, 6_a, 5_b′), 3.49−3.48 (m, 4H, H-6_b, 3′, 7_a′, 7_b′), 2.46−2.42 (m, 2H, H-3, 7_a), 2.10−2.06 (m, 1H, H-6_a′), 2.05−1.98 (m, 1H, H-2_a), 1.92−1.86 (m, 1H, H-2′), 1.74−1.64 (m, 3H, H-2_b, 7_b, 6_b′) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.5, 138.4, 138.2, 129.5, 128.5, 128.3, 128.3, 128.2, 128.2, 128.2, 127.8, 127.7, 127.6, 127.5, 127.5, 127.4. 127.3, 126.9, 84.6, 81.4, 81.25, 75.6, 75.4, 73.3, 73.2, 72.8, 72.7, 71.2, 71.0, 70.8, 70.8, 70.4, 69.1, 68.8, 39.3, 30.9, 30.2, 25.6, 25.3 ppm. IR (neat): ν = 3651, 3639, 2980, 2888, 2347, 1717, 1495, 1451 cm^{-1}. HRMS (ESI): calcd for $C_{57}H_{64}O_8Na$ $[M + Na]^+$ 899.4499; found 899.4499.



25 41 (91%)

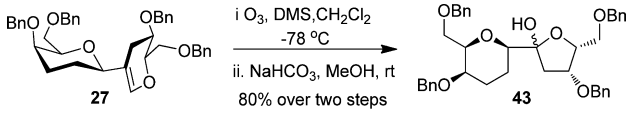
*(2R,4R,5S)-4-(Benzyloxy)-2-(2R,5S,6R)-5-(benzyloxy)-6-(benzyloxymethyl)tetrahydro-2H-pyran-2-yl)-5-(benzyloxymethyl)-tetrahydrofuran-2-ol (**41**):* CH_2Cl_2 (20 mL) was added to the disaccharide **25** (0.25 g, 0.4 mmol) in a two-neck round-bottomed flask with a gas outlet on one neck and a gas inlet on the other neck. The solution was cooled to −78 °C using an EtOAc/liquid nitrogen bath. Ozone was bubbled through the gas inlet into the solution until the pale blue color persisted. Then, oxygen followed by nitrogen was passed through the inlet until the pale blue color disappeared. Dimethyl sulfide (1.0 mL) was added to the reaction mixture at −78 °C, which was then allowed to warm to 25 °C. The solvent was evaporated in vacuo to obtain the crude formate ester, which was used in the next step without purification.

The obtained crude product was dissolved anhydrous MeOH (20 mL). To this solution was added solid $NaHCO_3$ (0.32 g, 3.8 mmol) and stirred until completion (2 h). MeOH was evaporated in vacuo and the obtained crude was purified by column chromatography over silica gel (hexanes/ethyl acetate) to obtain the inseparable anomeric mixture of pure hemiketal **41** (0.21 g, 91% over two steps, α:β (1:1)) as colorless liquid. R_f = 0.3 (30% EtOAc in hexanes). HRMS (ESI): calcd for $C_{39}H_{48}O_7N$ $[M + NH_4]^+$ 642.3431; found 642.3429.



41 42

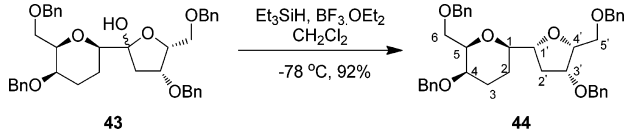
*(2R,3S,6R)-3-(Benzyloxy)-6-(2R,4R,5S)-4-(benzyloxy)-5-(benzyloxymethyl)tetrahydrofuran-2-yl)-2-(benzyloxymethyl)-tetrahydro-2H-pyran (**42**):* A solution of hemiketal **41** (0.08 g, 0.12 mmol) in anhydrous dichloromethane (5 mL) was cooled to −78 °C. Et_3SiH (47.8 μL, 0.3 mmol) and $BF_3{\cdot}OEt_2$ (30.4 μL, 0.24 mmol) were added at the same temperature. The reaction mixture was slowly allowed to reach room temperature and stirred until completion (2 h). The organic phase was washed with aq $NaHCO_3$ and brine and concentrated in vacuo. The crude was purified by column chromatography over silica gel (hexanes/ethyl acetate) to obtain the pure pyranofuranoside **42** (76 mg, 98%) as a colorless liquid. R_f = 0.4 (20% EtOAc in hexanes). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.41−7.28 (m, 20H, Ar(OBn)), 4.67 (d, J = 12.0 Hz, 1H, OCH_2Ph), 4.63 (d, J = 11.2 Hz, 1H, OCH_2Ph), 4.59−4.55 (m, 5H, OCH_2Ph), 4.48 (d, J = 11.6 Hz, 1H, OCH_2Ph), 4.26−4.20 (m, 2H, H-1′, 4′), 4.11−4.09 (m, 1H, H-3′), 3.84 3.75 (m, 2H, H-6_a, 6_b), 3.62 (dd, J = 4.8, 10.0 Hz, 1H, H-5_a′), 3.50−3.46 (m, 3H, H-4, 5, 5_b′), 3.40−3.36 (m, 1H, H-1), 2.33−2.30 (m, 1H, H-3_a), 2.05−1.99 (m, 1H, H-2_a′), 1.94−1.87 (m, 1H, H-2_b′), 1.69−1.66 (m, 1H, H-3_b), 1.52−1.50 (m, 2H, H-2_a, 2_b) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.5, 138.4, 138.3, 138.1, 128.3, 128.2, 128.2, 127.7. 127.6, 127.5 127.5, 127.5, 127.4, 127.3. 83.2, 80.7, 80.4, 80.3, 79.2, 73.3, 73.2, 73.1, 70.9, 70.8, 69.8, 34.1, 29.0, 26.3 ppm. IR (neat): ν = 3062, 3024, 2933, 2853, 2350, 2300, 1495, 1451 cm^{-1}. HRMS (ESI): calcd for $C_{39}H_{44}O_6Na$ $[M + Na]^+$ 631.3036; found 631.3037.



27 43

*(2R,4R,5R)-4-(Benzyloxy)-2-(2R,5R,6R)-5-(benzyloxy)-6-(benzyloxymethyl)tetrahydro-2H-pyran-2-yl)-5-(benzyloxymethyl)-tetrahydrofuran-2-ol (**43**):* CH_2Cl_2 (20 mL) was added to the disaccharide **27** (0.25 g, 0.4 mmol) in a two-neck round-bottomed flask with a gas outlet on one neck and a gas inlet on the other neck. The solution was cooled to −78 °C using an EtOAc/liquid nitrogen bath. Ozone was bubbled through the gas inlet into the solution until the pale blue color persisted. Then, oxygen followed by nitrogen was passed through the inlet until the pale blue color disappeared. Dimethyl sulfide (1.0 mL) was added to the reaction mixture at −78 °C, which was then allowed to warm to 25 °C. The solvent was evaporated in vacuo to obtain the crude formate ester, which was used in the next step without purification.

The obtained crude product was dissolved anhydrous MeOH (20 mL). To this solution was added solid $NaHCO_3$ (0.32 g, 3.8 mmol) and stirred until completion (2 h). MeOH was evaporated in vacuo, and the obtained crude was purified by column chromatography over silica gel (hexanes/ethyl acetate) to obtain the inseparable anomeric mixture of pure hemiketal **43** (0.18 g, 80% over two stpes, α:β (1:1)) as a colorless liquid. R_f = 0.3 (30% EtOAc in hexanes). HRMS (ESI): calcd for $C_{39}H_{48}O_7N$ $[M + NH_4]^+$ 642.3431; found 642.3429.



43 44

*(2R,3R,6R)-3-(Benzyloxy)-6-(2R,4S,5S)-4-(benzyloxy)-5-(benzyloxymethyl)tetrahydro furan-2-yl)-2-(benzyloxymethyl)-tetrahydro-2H-pyran (**44**):* A solution of hemiketal **43** (0.08 g, 0.12 mmol) in anhydrous dichloromethane (5 mL) was cooled to −78 °C. Et_3SiH (47.8 μL, 0.3 mmol) and $BF_3{\cdot}OEt_2$ (30.4 μL, 0.24 mmol) were added at the same temperature. The reaction mixture was slowly allowed to reach room temperature and stirred until completion (2 h). The organic phase was washed with aq $NaHCO_3$ and brine and concentrated in vacuo. The crude was purified by column chromatography over silica gel (hexanes/ethyl acetate) to obtain the pure pyranofuranoside **44** (72 mg, 92%) as colorless liquid. R_f = 0.4 (20% EtOAc in hexanes). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.35−7.26 (m, 20H, Ar(OBn)), 4.63 (d, J = 12.0 Hz, 1H, OCH_2Ph), 4.62 (d, J = 12.0 Hz, 2H, OCH_2Ph), 4.54 (d, J = 12.0 Hz, 1H, OCH_2Ph), 4.52(d, J = 12.0 Hz, 1H, OCH_2Ph), 4.88−4.39 (m, 3H, OCH_2Ph), 4.17−4.11 (m, 3H, H-1′, 3′, 4′), 3.76 (d, J = 4.8 Hz, 1H, H-5_a′), 3.71

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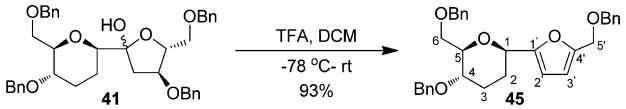
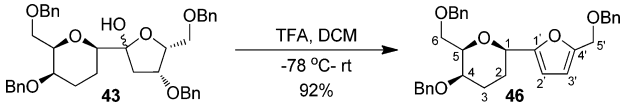
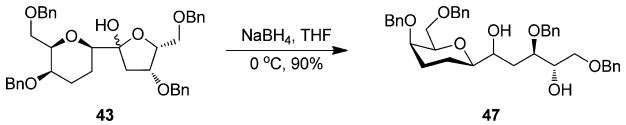
(d, J = 6.0 Hz, 1H, H-5$_b$′), 3.64−3.61 (m, 3H, H-5, 6$_a$, 6$_b$), 3.52 (br s, 1H, H-4), 3.43−3.38 (m, 1H, H-1), 2.28−2.23 (m, 1H, H-2$_a$′), 2.18−2.13 (m, 1H, H-3$_a$), 2.03−2.00 (m, 1H, H-2$_b$′), 1.65−1.62 (m, 2H, H-2$_a$, 2$_b$), 1.50−1.46 (m, 1H, H-3$_b$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.6, 138.3, 128.3, 128.7, 128.2, 127.8, 127.7, 127.6, 127.5, 127.4, 127.4, 127.3. 81.1, 80.1, 80.0, 79.2, 78.7, 73.4, 71.0, 70.6, 70.5, 70.2, 68.9, 33.7, 25.7, 23.2 ppm. IR (neat): ν = 2932, 2853, 1746, 1444, 1093 cm^{-1}. HRMS (ESI): calcd for $C_{39}H_{44}O_6Na$ [M + Na]$^+$ 631.3036; found 631.3037.



*(2R,3S,6R)-3-(Benzyloxy)-2-(benzyloxymethyl)-6-(5-(benzyloxymethyl)furan-2-yl)tetrahydro-2H-pyran (**45**):* A solution of hemiketal **41** (0.1 g, 0.16 mmol) in anhydrous dichloromethane (5 mL) was cooled to −78 °C. Trifluoroacetic acid (TFA) (37 μL, 0.48 mmol) was added at the same temperature. The reaction mixture was slowly allowed to reach room temperature and stirred until completion (3 h). The organic phase was washed with aq $NaHCO_3$ and brine and concentrated in vacuo. The crude was purified by column chromatography over silica gel (hexanes/ethyl acetate) to obtain the pure pyranofuranoside **45** (74 mg, 93%) as a colorless liquid. R_f = 0.5 (20% EtOAc in hexanes). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36−7.29 (m, 15H, Ar(OBn)), 6.27 (d, J = 5.2 Hz, 2H, H-2′, 3′), 4.67−4.60 (m, 3H, OCH_2Ph), 4.56 (br s, 2H, H-5$_a$′, 5$_b$′), 4.48 (br s, 3H, OCH_2Ph), 4.45 (s, 1H, H-1), 3.83 (d, J = 10.4 Hz, 1H, H-6$_a$), 3.77 (dd, J = 4.0, 10.8 Hz, 1H, H-6$_b$), 3.63−3.60 (m, 1H, H-5), 3.58−3.52 (m, 1H, H-4), 2.40 (d, J = 12.4 Hz, 1H, H-3$_a$), 2.04 (d, J = 12.8 Hz, 1H, H-2$_a$), 1.94 (dd, J = 12.8, 24.8 Hz, 1H, H-2$_b$), 1.62−1.59 (m, 1H, H-3$_b$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 154.6, 151.1, 138.4, 138.3, 137.9. 128.4, 128.3, 128.5, 127.9, 127.8, 127.7, 127.6, 127.6. 127.4, 109.9, 107.3, 80.96, 73.4, 73.0, 72.8, 71.8, 71.0. 69.4, 64.0, 29.3, 28.9 ppm. IR (neat): ν = 3658, 2986, 2967, 2888, 2356, 2309, 1463 cm^{-1}. HRMS (ESI): calcd for $C_{32}H_{34}O_5Na$ [M + Na]$^+$ 521.2304; found 521.2305.



*(2R,3R,6R)-3-(Benzyloxy)-2-(benzyloxymethyl)-6-(5-(benzyloxymethyl)furan-2-yl)tetrahydro-2H-pyran (**46**):* A solution of hemiketal **43** (0.1 g, 0.16 mmol) in anhydrous dichloromethane (5 mL) was cooled to −78 °C. Trifluoroacetic acid (TFA) (37 μL, 0.48 mmol) was added at the same temperature. The reaction mixture was slowly allowed to reach room temperature and stirred until completion (3 h). The organic phase was washed with aq $NaHCO_3$ and brine and concentrated in vacuo. The crude was purified by column chromatography over silica gel (hexanes/ethyl acetate) to obtain the pure pyranofuranoside **46** (73 mg, 92%) as a colorless liquid. R_f = 0.6 (20% EtOAc in hexanes). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.35−7.27 (m, 15H, Ar(OBn)), 6.28 (q, J = 3.2 Hz, 2H, H-2′, 3′), 4.67 (d, J = 12.4 Hz, 1H, H-6), 4.54 (br s, 3H, OCH_2Ph), 4.47 (d, J = 12.0 Hz, 2H, OCH_2Ph), 4.46 (d, J = 12.0 Hz, 1H, OCH_2Ph), 4.45 (br s, 2H, H-5$_a$′,5$_b$′), 3.80 (dt, J = 1.2, 6.4 Hz, 1H, H-5), 3.70−3.64 (m, 2H, H-6$_a$, 6$_b$), 3.00 (br.s, 1H, H-4), 2.26−2.20 (m, 2H, H-2$_a$,3$_b$), 1.76−1.61 (m, 2H, H-2$_a$,3$_b$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.5, 138.2, 137.9, 128.3, 128.3, 128.2, 127.9, 127.8, 127.8, 127.6, 127.5, 127.5, 109.9, 107.3, 78.9, 73.4, 73.2, 71.7, 70.9, 70.0, 69.7, 63.9, 26.2, 24.0 ppm. IR (neat): ν = 3654, 2977, 2802, 2879, 1498, 1454 cm^{-1}. HRMS (ESI): calcd for $C_{32}H_{34}O_5Na$ [M + Na]$^+$ 521.2304; found 521.2304.



*(3R,4S)-3,5-Bis(benzyloxy)-1-(2R,5S,6R)-5-(benzyloxy)-6-(benzyloxymethyl)tetrahydro-2H-pyran-2-yl)pentane-1,4-diol (**47**):* To a solution of hemiketal **43** (0.05 g, 0.08 mmol) in anhydrous THF (4 mL) was added $NaBH_4$ (10 mg, 0.24 mmol) at 0 °C and stirred at the same temperature until completion (12 h). The reaction was quenched with aq NH_4Cl (1 mL) and extracted with EtOAc (10 mL). The organic phase was concentrated in vacuo and purified by column chromatography over silica gel (hexanes/ethyl acetate) to obtain pure *C*-glycoside **47** (0.045 mg, 90%) as colorless liquid. R_f = 0.4 (40% EtOAc in hexanes). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.34−7.28 (m, 20H), 4.72 (d, J = 10.8 Hz, 1H), 4.62 (d, J = 12.0 Hz, 1H), 4.57 (d, J = 11.2 Hz, 1H), 4.52−4.48 (m, 5H), 4.41 (d, J = 12.0 Hz, 1H), 3.95−3.91 (m, 1H), 3.80−3.73 (m, 2H), 3.63−3.62 (m, 2H), 3.53−3.51 (m, 3H), 3.27−3.22 (m, 1H), 2.59 (br S, 1H), 2.18−2.14 (m, 1H), 1.83−1.69 (m, 3H), 1.63−1.60 (m, 1H), 1.51−1.48 (m, 1H), 1.45 (br S, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.4, 138.3, 138.1, 138.0, 128.4, 128.3, 128.0, 127.9, 127.8, 127.7, 127.6, 127.6, 81.42, 78.70, 76.0, 73.9, 73.4, 73.3, 72.7, 71.3, 70.9, 70.6, 70.5, 70.1, 34.9, 25.7, 22.0 ppm. IR (neat): ν = 3015, 2986, 2359, 2350, 2377, 1454 cm^{-1}. HRMS (ESI): calcd for $C_{39}H_{46}O_7Na$ [M + Na]$^+$ 649.3141; found 649.3143.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b02879.

Copies of ^{1}H and ^{13}C NMR and HRMS spectra for all new compounds and 2D COSY and 2D NOESY spectra of *C*-saccharides (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

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