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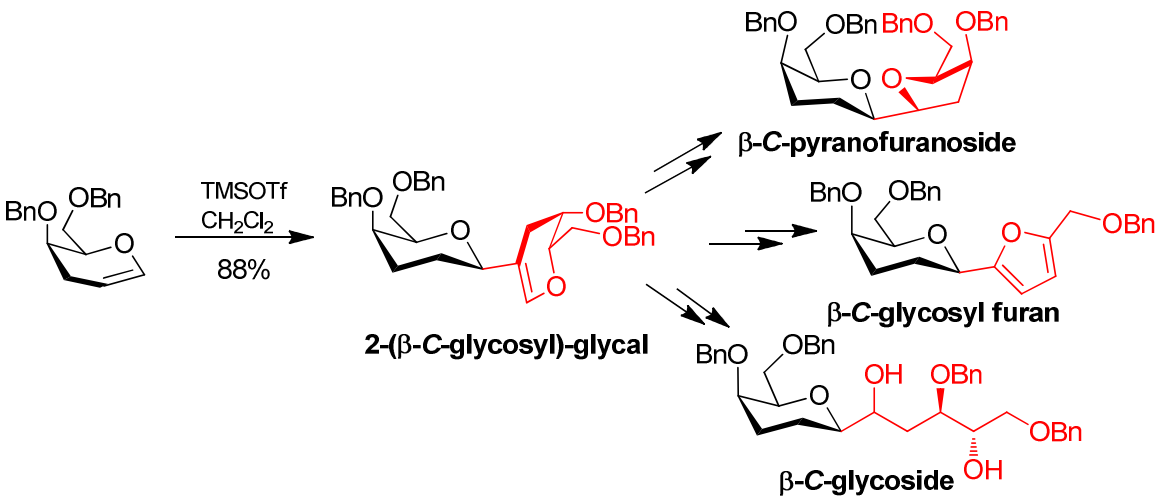
Stereoselective synthesis of 2-(β-*C*-glycosyl)-glycals: An access to the unusual β-*C*-glycosides from 3-deoxy-glycals

Gadi Madhusudhan Reddy, Boddu Uma Maheswara Rao and Perali Ramu Sridhar*

School of Chemistry, University of Hyderabad, Hyderabad – 500 046, INDIA

p_ramu_sridhar@uohyd.ac.in



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.

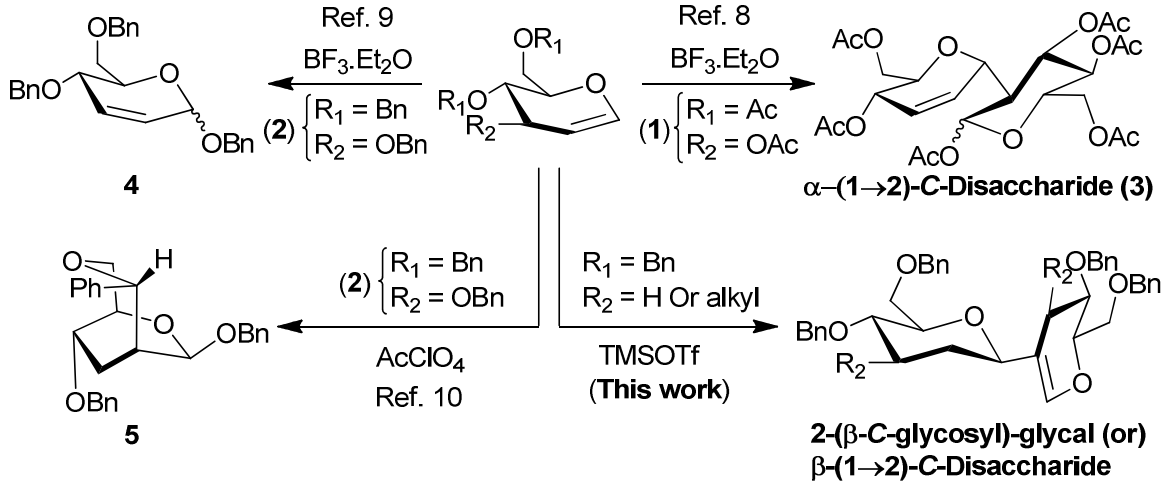
Introduction

The stability of *C*-glycosides[1] to the acids and carbohydrate processing enzymes had 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 method for the synthesis of 2,3-unsaturataed *C*-glycosides.[1g] Recently, palladium catalyzed Heck-type glycosylation of glycals[4] and allylic alkylation[5] have also been reported. However, very few methodologies are available for the synthesis of *C*-saccharides,[6] disaccharides and higher homologues, owing to the difficulties associated in their preparation. Compared to *O*-glycosides, absence of *exo*-anomeric effect and the non-predominant neighbouring 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 the 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 towards the synthesis of *C*-saccharides started from the observation of 3,4,6-tri-*O*-acetyl-D-glucal **1** dimerization using $BF_3.Et_2O$ to provide the 2,3-unsaturated α-(1→2)-*C*-

disaccharide **3** in moderate yield.[8] This reaction is feasible only in 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).



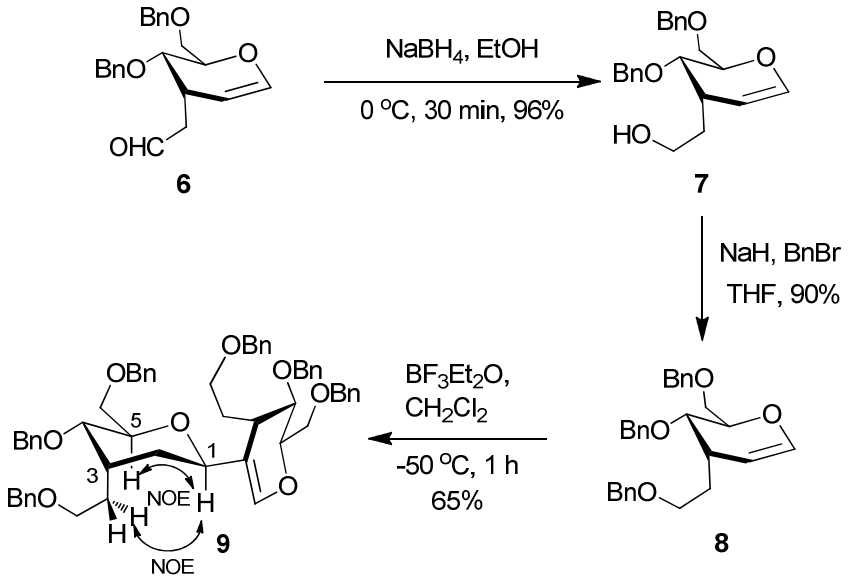
Scheme 1: Reactivity of glycal under Lewis acid conditions.

Surprisingly, to the best of our knowledge, there was no report documented in the literature on the reactivity of 3-deoxy glycals under Lewis acid conditions. The probable reason might be due to the unpredictability in the formation and the fate of the formed oxocarbenium ion in 3-deoxy-glycals. These observations made us curious to investigate the reactivity of 3-deoxy glycals in presence of a Lewis acid. We envisaged that the presence of a leaving group at 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 C4 and C5 via stabilizing the generated oxocarbenium ion intermediate. Thus, herein, we report the reactions of 3-deoxy glycals, 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 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-deoxy glycal derivative, 3-*C*-branched glycal **6**[12] was reduced to the alcohol **7** followed by benzylation provided the glycal **8**. When 3-deoxy-3-*C*-branched glycal **8** in anhydrous CH_2Cl_2 upon treating with $BF_3.Et_2O$ (1 equiv.) at -50 ^oC, 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. On structural analysis, the new compound was found as 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 2D-NOSEY experiment. [13] (Scheme 2).



Scheme 2. Lewis acid mediated dimerization of 3-deoxy 3-*C*-branched glycal.

Exhilarated by this result, the formation of disaccharide **9** was examined under various Lewis acid conditions at different temperatures (Table 1). Trifluoromethanesulfonates of Sc, Ag and Cu were found to be ineffective in catalyzing the reaction at -78 ^{o}C. However, the reaction of **8** with 1 equiv. of $Sc(OTf)_3$ at 0 ^{o}C afforded **9** in 68% yield. Whereas, AgOTf and $Cu(OTf)_2$ were found to be

Table 1. Lewis acid catalyzed electrophilic addition of glycals.

S.No	Lewis Acid	equiv.	Temperature (time)	**9**[a]	**8**[b]
1	$BF_3.OEt_2$	0.3	-78 ^{o}C to rt (8h)	-	92%
		1.0	-78 ^{o}C (1 h)	-	95%
		1.0	-50 ^{o}C (1 h)	65%	5%
2	$ScOTf_3$	0.3	-78 ^{o}C to rt (8 h)	-	95%
		1.0	-78 ^{o}C to -50 ^{o}C (3 h)	-	95%
		1.0	0 ^{o}C 1 h	68%	5%
3	AgOTf	0.3	-78 ^{o}C to rt (8 h)	-	96%
		1.0	-78 ^{o}C to rt (10 h)	-	95%
4	$CuOTf_2$	0.3	-78 ^{o}C to rt (8 h)	-	94%
		1.0	-78 ^{o}C to rt (10 h)	-	95%
5	**TMSOTf**	**0.3**	**-78 ^{o}C (1 h)**	**90%**	**-**
6	Montmorillonite K 10[c]	0.3	-78 ^{o}C to rt (8 h)	-	96%
		1.0	-78 ^{o}C to 0 ^{o}C (6 h)	-	93%
		1.0	rt (12 h)	60%	15%
7	$InCl_3$	0.3	-78 ^{o}C to rt (8 h)	-	94%
		1.0	-78 ^{o}C to 0 ^{o}C (6 h)	-	95%
		1.0	rt (12 h)	5%	75%
8	$BiCl_3$	0.3	-78 ^{o}C to rt (8 h)	-	95%
		1.0	-78 ^{o}C to 0 ^{o}C (6 h)	-	95%
		1.0	rt (12 h)	10%	20%

[a] Yield refers to the pure isolated product. [b] Recovered starting material. [c] Equiv. calculated by w%.

ineffective from -78 ^{o}C to room temperature (Table 1, Entry 2-4). Gratifyingly, when the reaction was conducted using 0.3 equiv. of TMSOTf at -78 ^{o}C in anhydrous CH_2Cl_2 provided 90% of **9** as a single diastereomer (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 in catalyzing the reaction even at 25 ^oC (Table 1, Entry 7-8). Therefore, catalytic TMSOTf was preferred to be the better Lewis acid for the electrophilic addition of deoxy-glycals 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-deoxy glycals under various Lewis acid conditions. The formation of the single diastereomer **9** from **8** could be explained by considering the approach of the nucleophile towards the substituted tetrahydropyran derived oxocarbenium ion. Glycal derived oxocarbenium ions will adopt half-chair conformations of $^3H_4$ and $^4H_3$.[14] Mostly, 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).

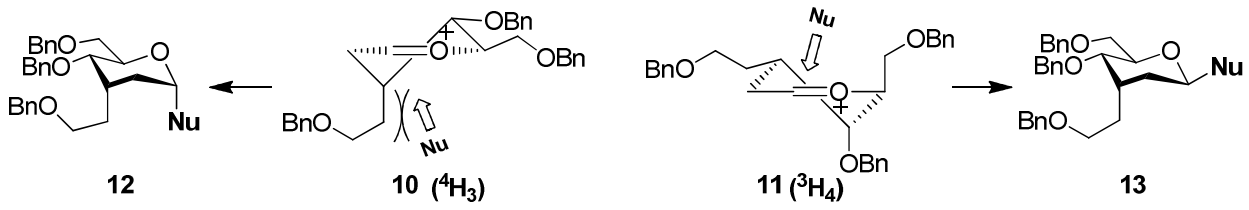
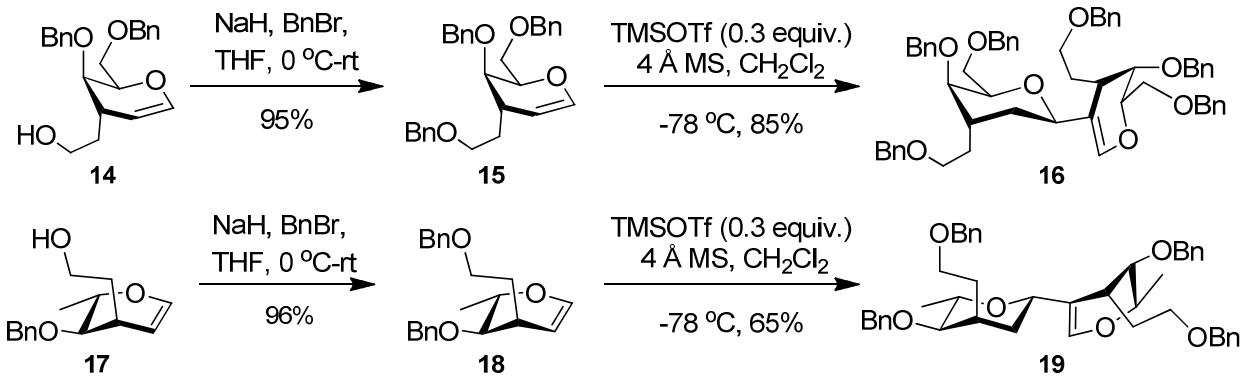


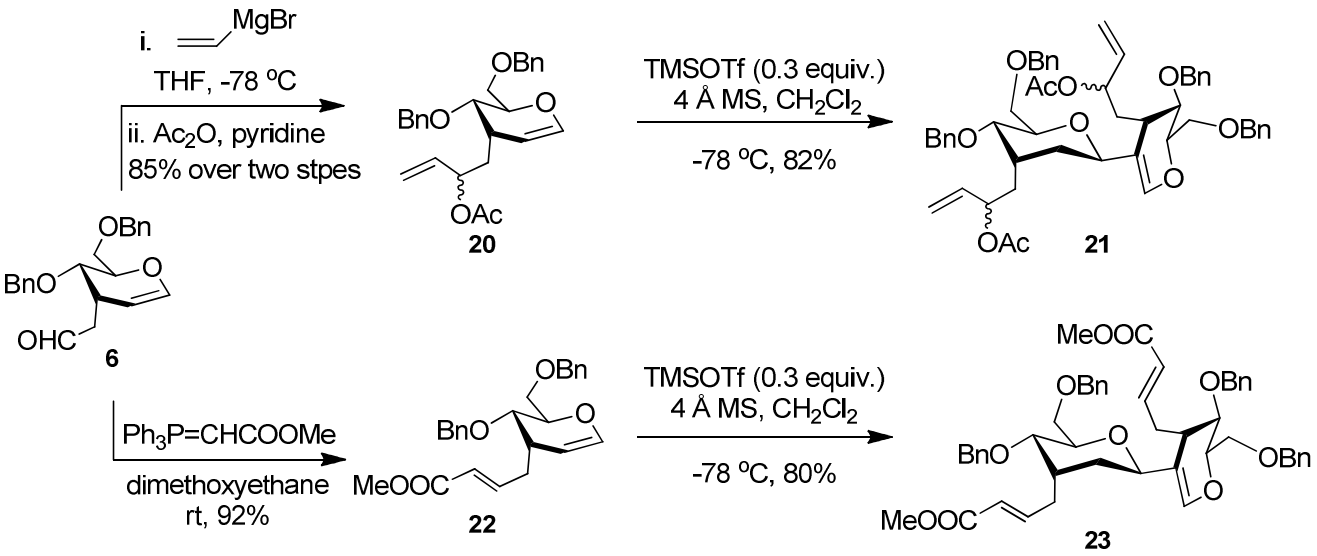
Figure 1. Half-chair conformers of glycal derived oxocarbenium ions and preferred nucleophilic approach to provide the corresponding glycosides.

After having the optimized reaction conditions in hand, the substrate scope of the reaction was investigated. 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 catalytic TMSOTf mediated electrophilic addition reaction. Both the glycals underwent a smooth dimerization reaction providing the diastereomerically pure β-(1→2)-*C*-disaccharides **16** and **19**, respectively, in good yield (Scheme 3).



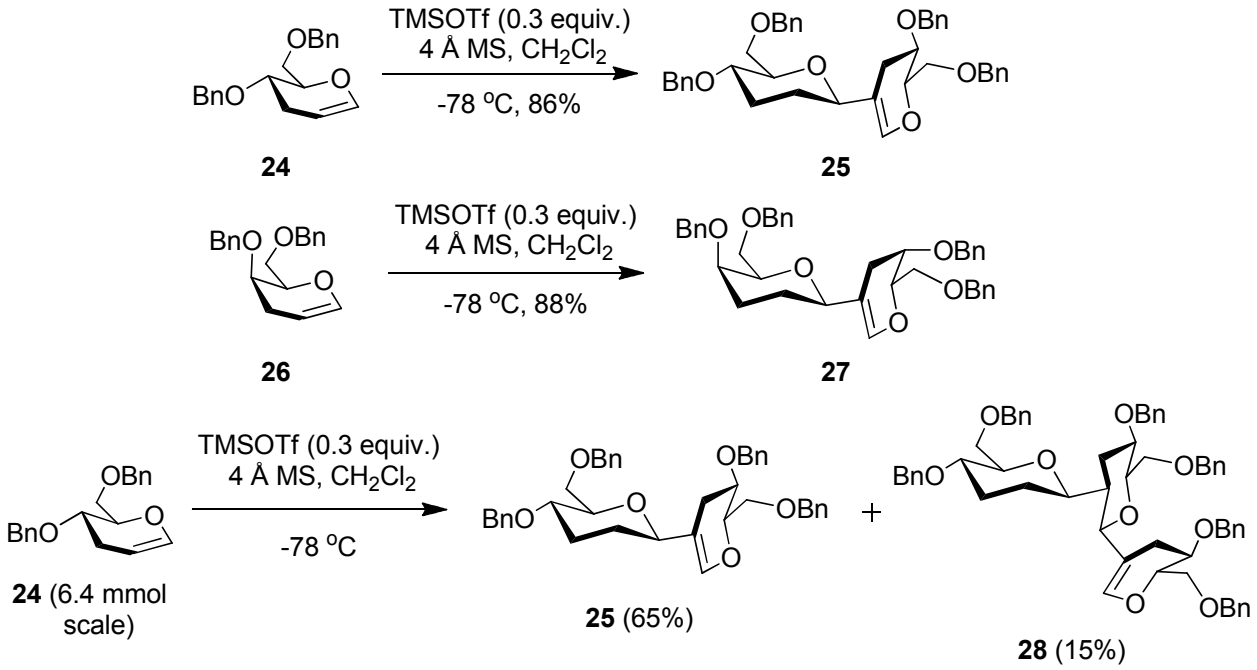
Scheme 3: Synthesis of β-(1→2)-*C*-disaccharides derived from 3-deoxy-3-*C*-branched sugars.

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.



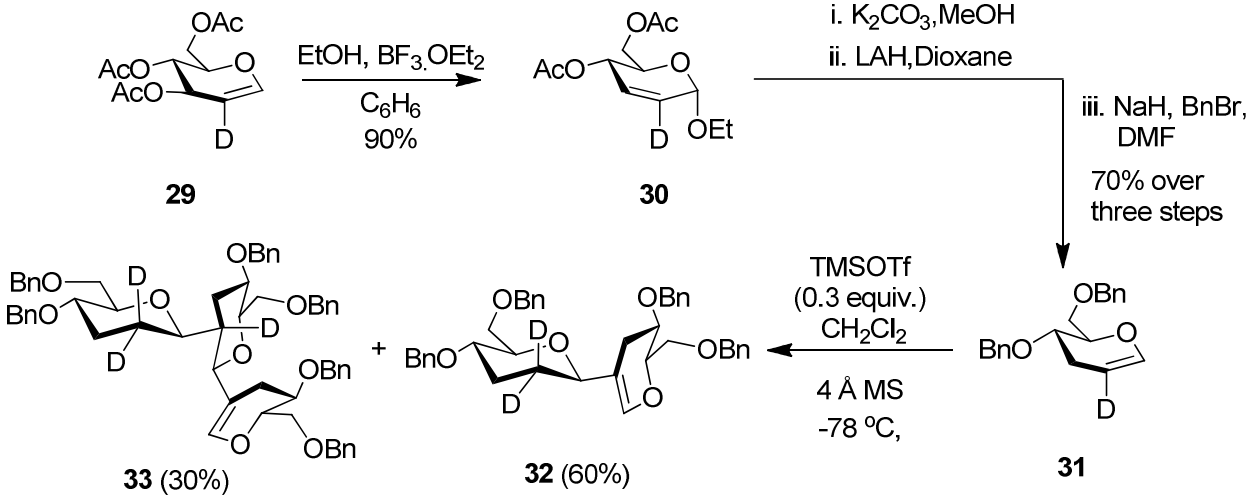
Scheme 4: Synthesis of β-(1→2)-*C*-disaccharides in presence of an external olefin.

Subsequently, to study the importance of the steric effects, 3-deoxy glycals[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 galactose derived 3-deoxy glycals **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, towards the formation of a trisaccharide, glycal **24** was loaded in gram scale and subjected to TMSOTf (0.3 eq) in CH_2Cl_2. Excitingly, the β-(1→2)-*C*-β-(1→2)-*C*-trisaccharide **28** was isolated in 15% yield as a single diastereomer along with the disaccharide **25** in 65% yield (Scheme 5).



Scheme 5: TMSOTf catalyzed stereoselective synthesis of β-(1→2)-*C*-disaccharides from 3-deoxy glycals.

To investigate the mechanism of the reaction, the deuterated 3-deoxy glucal **31** was planned to synthesize from the deuterated glucal derivative **29**.[18] Thus, Ferrier rearrangement of deuterated glucal **29** with ethanol provided the 2,3-unsaturated glycoside **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-deoxy glucal derivative **31**. Subjecting **31** to 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 due to the kinetic isotopic effect. The formation of di-deuterated *C*-disaccharide **32** clearly indicates that the hydrogen present at the 2-position of the starting 3-deoxy glucal **31** is the source of the H^+ in the *C*-saccharide formation.



Scheme 6: Synthesis of isotope labelled di and trisaccharides from the deuterated 3-deoxy glucal.

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 could form the 2-trimethylsilyl glucal derivative **34** and TfOD. Addition of TfOD on glucal **31** would lead to the formation of oxocarbenium ion intermediates **35a** and **35b** possessing $^{4}H_{3}$ and $^{3}H_{4}$ conformations, respectively. Approach of the **34** on to the intermediate **35b**, which is stabilized by the stereo-electronic effect due to the presence of 4-OBn in pseudo-axial position, in an axial trajectory would provide the disaccharide derived oxocarbenium ion intermediates **36a** and **36b**. On regeneration of the catalyst, TMSOTf, would provide the observed *C*-disaccharide **32**. Akin, uninterrupted addition of another molecule of **34** on **32** followed by termination would provide the *C*-trisaccharide **33** (Figure 2).

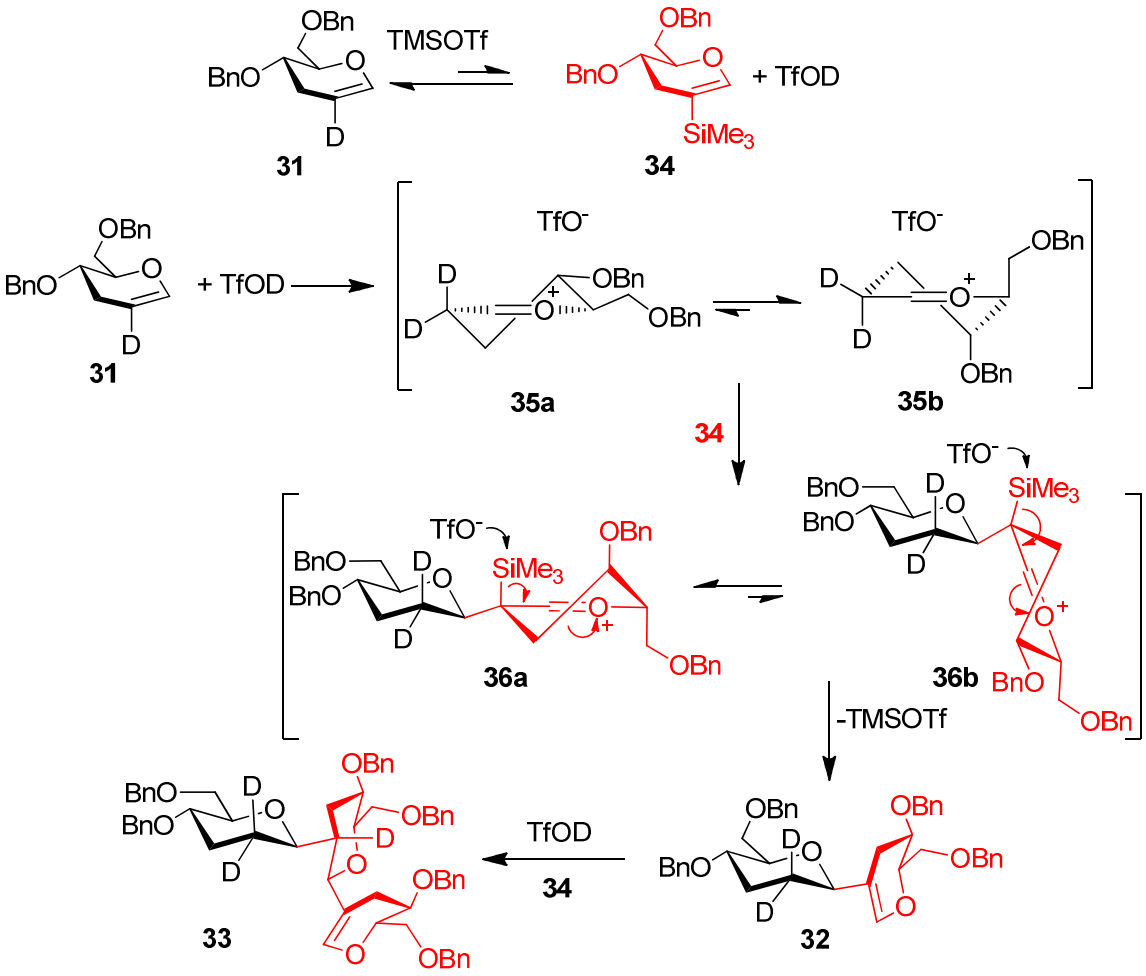


Figure 2. Proposed mechanism for the β-*C*-saccharide formation.

To further demonstrate the importance of the novel one-step *C*-saccharide formation from 3-deoxy glycals, we turned our attention to explore the synthetic applications of glycalic double bond in the 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 possess the carbon linked adjacent THP-THF rings, for example jimenezin (**37**), muconin (**38**) (Figure 3) etc.

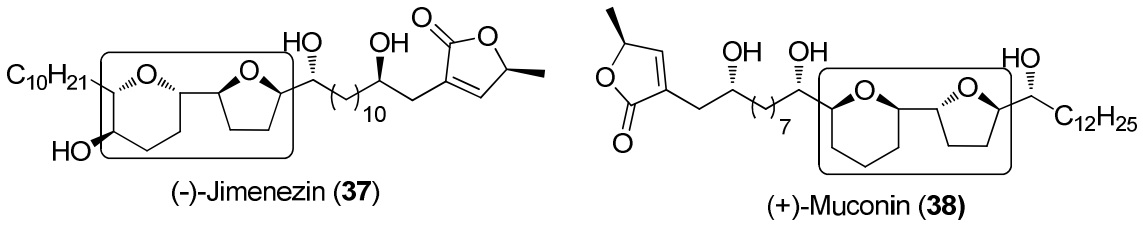
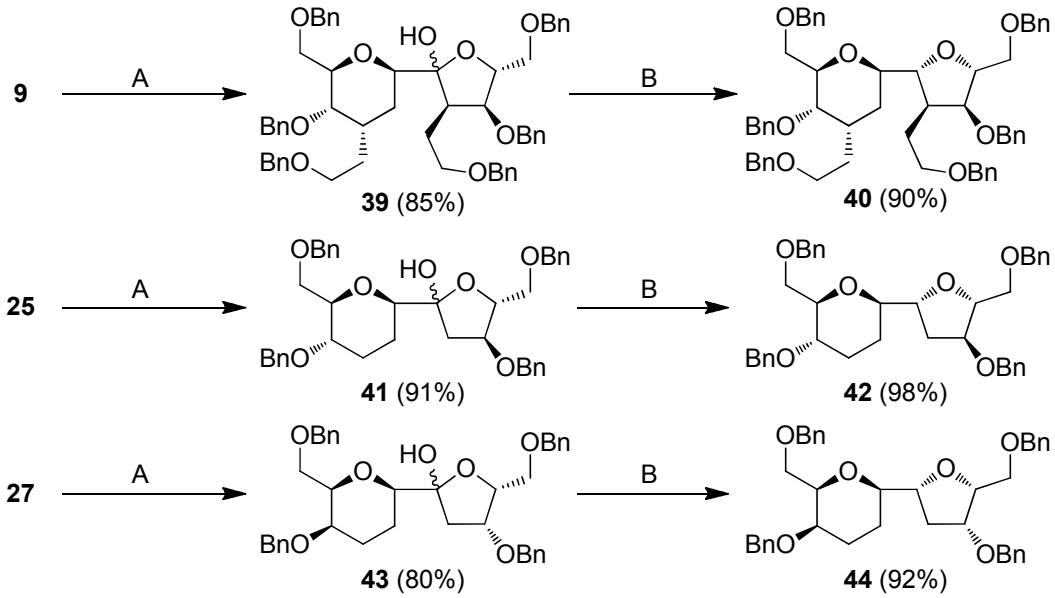


Figure 3: Cytotoxic annonaceous acetogenins from Rollinia mucosa seeds.

Various groups had previously reported the total synthesis of these natural products but, using a multi-step protocol for the formation of adjacent bicyclic core skeleton (adjacent THP-THF rings).[20] However, we had planned to convert the obtained 2-(β-*C*-glycosyl)-glycals to the core skeletons present in these natural products in comparatively less synthetic steps. Towards this, compounds **9**, **25** and **27** were subjected to ozonolysis[12a,21] followed by deformylation with



Condition **A**: i) O_3, CH_2Cl_2,DMS, -78 ^oC, ii) $NaHCO_3$, MeOH
Condition **B**: i) Et_3SiH, $BF_3.OEt_2$, -78 ^oC, CH_2Cl_2

Scheme 7: Synthesis of a mixed *C*-disaccharides possessing adjacent THP-THF rings.

$NaHCO_3$ in MeOH to provide the *C*-disaccharide derived hemi-ketals **39**, **41** and **43** in good yield.[22] These hemi-ketals upon dehydroxylation with Et_3SiH and $BF_3.Et_2O$ afforded the targeted

β-(1→2)-*C*-pyranofuranosides or adjacent THP-THF rings **40**, **42** and **44**, respectively, as single diastereomers (Scheme 7).[6h] Further, functional group modification of these adjacent THP-THF rings to natural acetogenins and their analogs is in progress.

The stereochemistry at the newly formed stereocentre 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, 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.

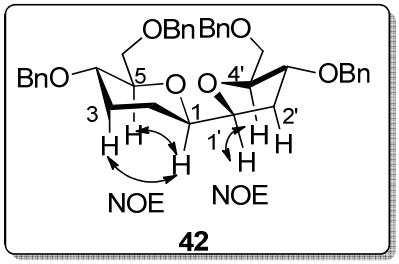
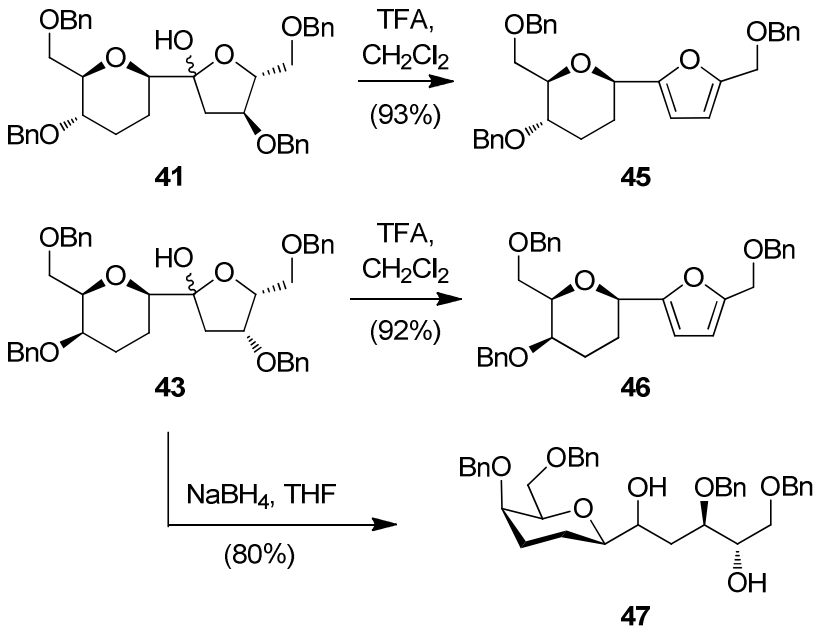


Figure 4: Through space correlations observed in compound **42** using 2D NOESY experiment.

Another important subclass of *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. Towards this, the hemi-ketal 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] is of great importance because of their high structural resemblance to the pharmacologically undermined glycolipids. Hence, $NaBH_4$ mediated reduction of the hemi-ketal **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.

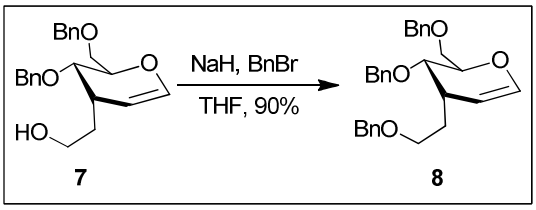
Conclusion

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-deoxy glycals 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 bio-active natural products is in progress.

Experimental Section

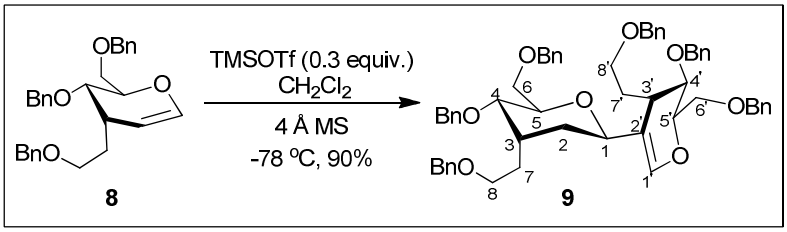
General Methods: All reactions were carried out under an inert atmosphere with dry solvents under anhydrous conditions unless otherwise mentioned. Dichloromethane, methanol, THF,

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 is referred to the isolated products unless otherwise stated. NMR spectra were recorded at 25 ^oC 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) instrument 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 Hz. 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.



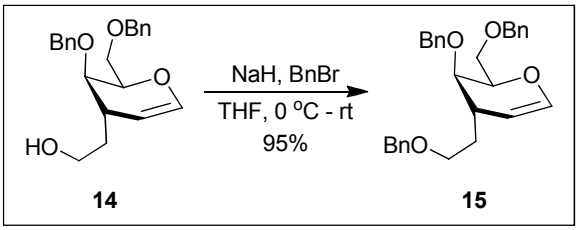
(2R,3S,4S)-3-(benzyloxy)-4-(2-benzyloxyethyl)-2-(benzyloxymethyl)-3,4-dihydro-2H-pyran (**8**): Alcohol-derivative **7**[12] (0.5g, 1.41 mmol) was dissolved in anhydrous THF (10 mL). To this solution, at 0 ^oC, NaH (68 mg, 2.8 mmol) was added portionwise over 10 min with stirring. After continuous stirring for further 1 h at 0 °C, benzyl bromide (0.36 g, 2.11 mmol) and TBAI (cat) were added and the mixture was stirred until completion (12 h) at 25 °C. The reaction was quenched with slow addition of cold water and extracted with CH_2Cl_2. The combined organic layers were dried with anhydrous Na2SO4 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 colourless 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): $\tilde{\nu}$ = 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.



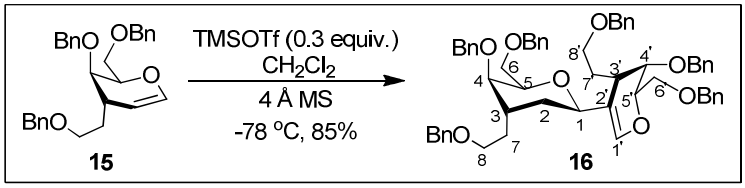
(2R,3S,4S)-3-(benzyloxy)-5-(2R,4S,5S,6R)-5-(benzyloxy)-4-(2-(benzyloxyethyl)-6-(benzyloxymethyl)tetrahydro-2H-pyran-2-yl)-4-(2-benzyloxyethyl)-2-(benzyloxymethyl)-3,4-dihydro-2H-pyran (**9**): Glycal **8** was dried over vacuum for 1 h prior to use. Glycal **8** (0.13 g, 0.3 mmol) was dissolved in freshly distilled dry dichloromethane (10 mL). To this solution, powdered 4 Å molecular sieves (100 mg) was added and stirred for 1 h at room temperature. The solution was cooled to -78 ^{o}C and stirred for 15 min at the same temperature. Freshly distilled TMSOTf (16.4 μL, 0.09 mmol) was added at -78 ^{o}C and stirred until completion of the reaction (1 h). Triethylamine (12.5 μL, 0.09 mmol) was added at -78 ^{o}C to quench the reaction and allowed to reach the 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 colourless 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): $\tilde{\nu}$ = 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.



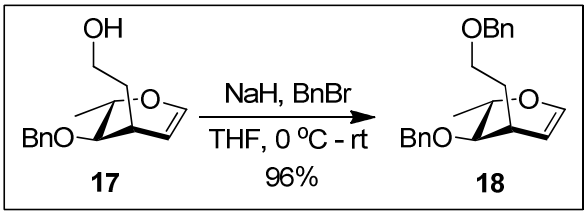
(2R,3R,4S)-3-(benzyloxy)-4-(2-benzyloxyethyl)-2-(benzyloxymethyl)-3,4-dihydro-2H-pyran (**15**): **A**lcohol-derivative **14**[12] (0.5g, 1.41 mmol) was dissolved in anhydrous THF (10 mL). To this solution, at 0 °C, NaH (68 mg, 2.8 mmol) was added portionwise over 10 min with stirring. After continuous stirring for 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 colourless 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): $\tilde{\nu}$ = 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.

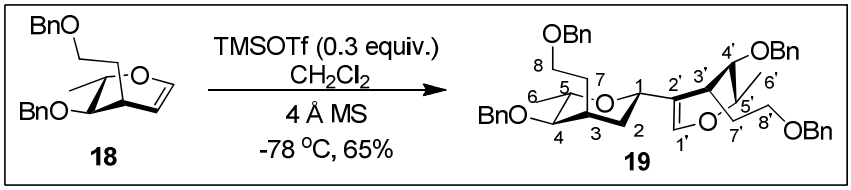


(2R,3R,4S)-3-(benzyloxy)-5-(2R,4S,5R,6R)-5-(benzyloxy)-4-(2-benzyloxyethyl)-6-(benzyloxymethyl)tetrahydro-2H-pyran-2-yl)-4-(2-benzyloxyethyl)-2-(benzyloxymethyl)-3,4-dihydro-2H-pyran (**16**): Glycal **15** was dried over vacuum for 1 h prior to use. Glycal **15** (0.13 g, 0.3 mmol) was dissolved in freshly distilled dry dichloromethane (10 mL). To this solution, powdered 4 Å molecular sieves (100 mg) was added 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 the 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 colourless 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

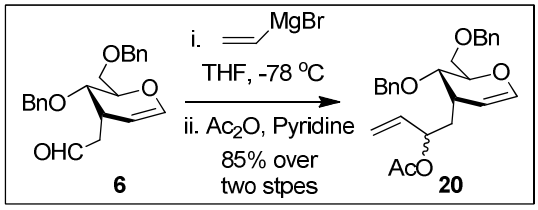
= 8.0 Hz, 1H, H-3'), 2.38-2.37 (m, 1H, H-3), 2.26-2.20 (m, 2H, H-2_a, 7_a'), 1.81-1.76 (m, 2H, H-7_a, 7_b), 1.38-1.33 (m, 2H, H-2_b, 7_b') ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 141.6, 138.9, 138.6, 138.4, 138.3, 138.2, 138.0, 128.4, 128.3, 128.2, 127.6, 127.5, 127.4, 127.3, 127.3, 114.4, 74.5, 74.2, 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): $\tilde{\nu}$ = 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**): **A**lcohol-derivative **17**[12] (0.43 g, 1.73 mmol) was dissolved in anhydrous THF (15 mL). To this solution, at 0 °C, NaH (83 mg, 3.46 mmol) was added portionwise over 10 min with stirring. After continuous stirring for further 1 h at 0 °C, benzyl bromide (0.59 g, 3.46 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 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 colourless 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): $\tilde{\nu}$ = 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.

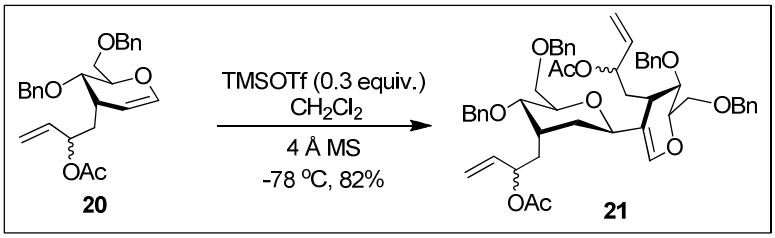


(2R,3S,4S)-3-(benzyloxy)-5-(2R,4S,5S,6R)-5-(benzyloxy)-4-(2-benzyloxyethyl)-6-methyl tetrahydro-2H-pyran-2-yl)-4-(2-benzyloxyethyl)-2-methyl-3,4-dihydro-2H-pyran (**19**): Glycal **18** was dried over vacuum for 1 h prior to use. Glycal **18** (0.11 g, 0.32 mmol) was dissolved in freshly distilled dry dichloromethane (10 mL). To this solution, powdered 4 Å molecular sieves (100 mg) was added 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 the 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 colourless 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): $\tilde{\nu}$ = 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.



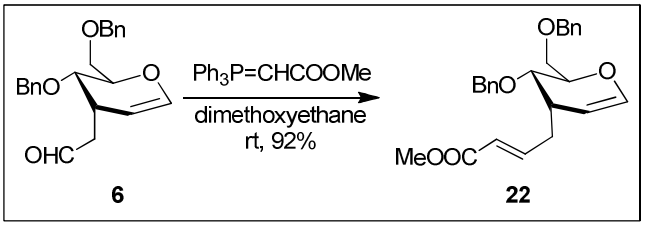
1-(2R,3S,4S)-3-(benzyloxy)-2-(benzyloxymethyl)-3,4-dihydro-2H-pyran-4-yl)but-3-en-2-yl acetate (**20**): To a solution of aldehyde **6**[12] (0.3 g, 0.85 mmol) in anhydrous THF at -78 °C was slowly added vinylmagnesium bromide (3.41 mL, 1M sol.) and stirred until completion (3 h). The reaction was quenched with aq. NH_4Cl (2 mL) and brought to the 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 sulphate 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 colourless 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): $\tilde{\nu}$ = 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.



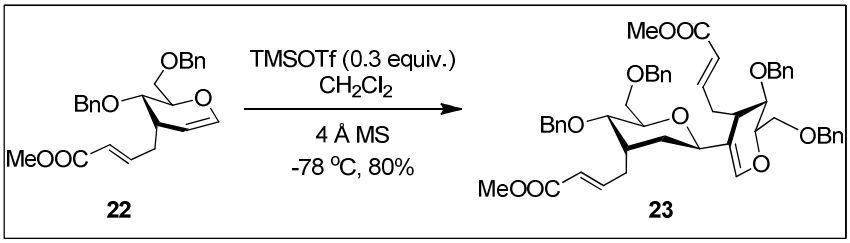
1-(2R,3S,4S,6R)-6-(2R,3S,4S)-4-(2-acetoxybut-3-en-1-yl)-3-(benzyloxy)-2-(benzyloxymethyl)-3,4-dihydro-2H-pyran-5-yl)-3-(benzyloxy)-2-(benzyloxymethyl) tetrahydro-2H-pyran-4-yl)but-3-en-2-yl acetate (**21**): Glycal **20** was dried over vacuum for 1 h prior to use. Glycal **20** (0.1 g, 0.23 mmol) was dissolved in freshly distilled dry dichloromethane (10 mL). To this solution,

powdered 4 Å molecular sieves (100 mg) was added and stirred for 1 h at room temperature. The solution was cooled to -78 ^{o}C and stirred for 15 min at the same temperature. Freshly distilled TMSOTf (12.2 μL, 0.07 mmol) was added at -78 ^{o}C and stirred until completion (1 h). Triethylamine (9.7 μL, 0.07 mmol) was added at -78 ^{o}C to quench the reaction and allowed to reach the 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 colourless liquid. R_f = 0.4 (10% EtOAc in Hexanes). IR (neat): $\tilde{\nu}$ = 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.



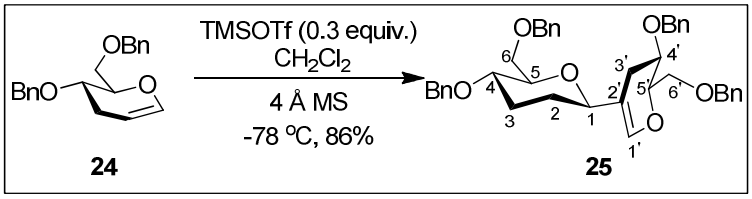
(E)-methyl 4-(2R,3S,4S)-3-(benzyloxy)-2-(benzyloxymethyl)-3,4-dihydro-2H-pyran-4-yl) but-2-enoate (**22**): To a solution of aldehyde **6**[12] (0.4 g, 1.14 mmol) in dimethoxyethane (20 mL) was added methyl(triphenylphosphoranylidene)acetate (0.95 g, 2.86 mmol) at room temperature and stirred until completion (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 colourless 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): $\tilde{\nu}$ = 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.

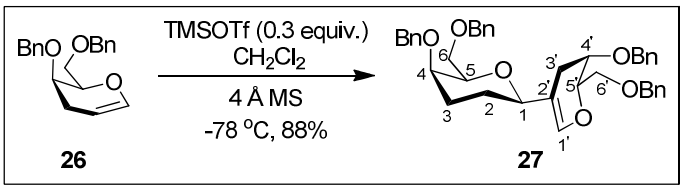


(E)-methyl4-(2R,3S,4S)-3-(benzyloxy)-5-(2R,4S,5S,6R)-5-(benzyloxy)-6-((benzyloxymethyl)-4-(E)-4-methoxy-4-oxobut-2-en-1-yl)tetrahydro-2H-pyran-2-yl)-2-(benzyloxymethyl)-3,4-dihydro-2H-pyran-4-yl)but-2-enoate (**23**): Glycal **22** was dried over vacuum for 1 h prior to use. Glycal **22** (0.1 g, 0.24 mmol) was dissolved in freshly distilled dry dichloromethane (10 mL). To this solution, powdered 4 Å molecular sieves (100 mg) was added and stirred for 1 h at room temperature. The solution was cooled to -78 ^oC and stirred for 15 min at the same temperature. Freshly distilled TMSOTf (12.7 μL, 0.07 mmol) was added at -78 ^oC and stirred until completion (1 h). Triethylamine (10.0 μL, 0.07 mmol) was added at -78 ^oC to quench the reaction and allowed to reach the 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 colourless liquid. R_f = 0.3 (20% EtOAc in Hexanes). ^1H 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): $\tilde{\nu}$ =

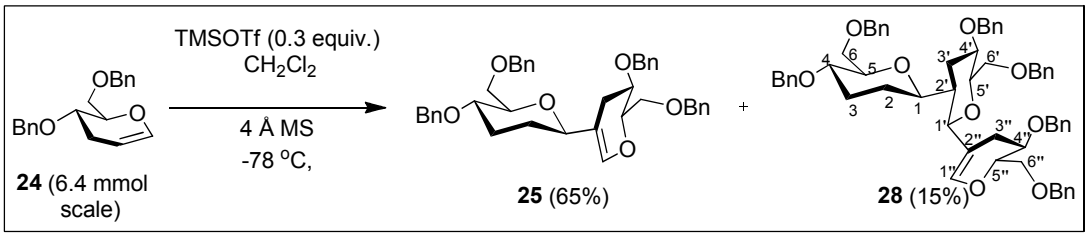
3664, 2993, 2971, 2961, 2885, 2347, 1717, 1650, 1460 cm^{-1}. HRMS (ESI): Calcd. for $C_{50}H_{56}O_{10}Na$ $[M + Na]^+$ 839.3771; found 839.3770.



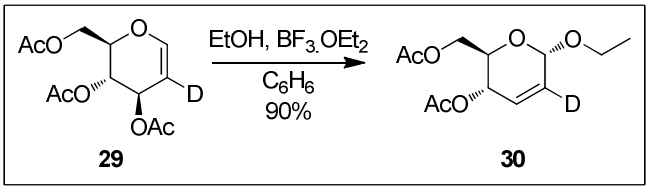
(2R,3S)-3-(benzyloxy)-5-(2R,5S,6R)-5-(benzyloxy)-6-(benzyloxymethyl)tetrahydro-2H-pyran-2-yl)-2-(benzyloxymethyl)-3,4-dihydro-2H-pyran (**25**): Glycal **24** was dried over vacuum for 1 h prior to use. Glycal **24** (0.11 g, 0.35 mmol) was dissolved in freshly distilled dry dichloromethane (10 mL). To this solution, powdered 4 Å molecular sieves (100 mg) was added 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 the 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 colourless 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): $\tilde{\nu}$ = 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.



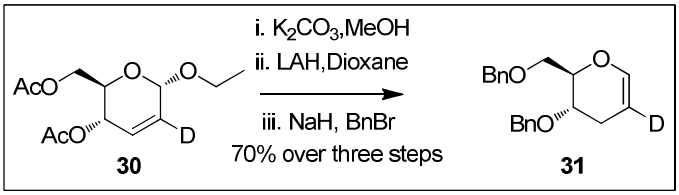
(2R,3R)-3-(benzyloxy)-5-(2R,5R,6R)-5-(benzyloxy)-6-(benzyloxymethyl)tetrahydro-2H-pyran-2-yl)-2-(benzyloxymethyl)-3,4-dihydro-2H-pyran (**27**): Glycal **26** was dried over vacuum for 1 h prior to use. Glycal **26** (0.1 g, 0.24 mmol) was dissolved in freshly distilled dry dichloromethane (10 mL). To this solution, powdered 4 Å molecular sieves (100 mg) was added 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 the 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 colourless 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): $\tilde{\nu}$ = 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, powdered 4 Å molecular sieves (1.0 g) was added 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 the 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 colourless 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): ν̃ = 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.



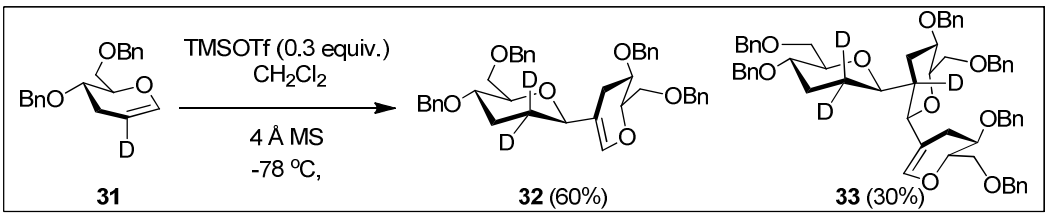
(2R,3S,6S)-[5-^{2}H]-3-acetoxy-6-ethoxy-3,6-dihydro-2H-pyran-2-yl)methyl acetate (**30**): 1,2-Dideoxy-[2-^{2}H]-3,4,6-tri-O-acetyl-D-arabino-1-hexenopyranose[18] **29** (1.5 g, 5.48 mmol) was dissolved in anhydrous benzene (25 mL). To this solution, at 0 ^oC, was added ethanol (0.50 mL, 8.61 mmol) and $BF_3.OEt_2$ (0.23 mL, 1.80 mmol) respectively. The solution was allowed slowly to reach room temperature and stirred until completion (3 h). The reaction was quenched with Et_3N (0.3 mL, 2.22 mmol) at 0 ^oC and concentrated under vacuo. The obtained crude was purified by column chromatography over silica gel (hexanes/ethyl acetate) to obtain colourless 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). ^1H 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): $\tilde{\nu}$ = 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

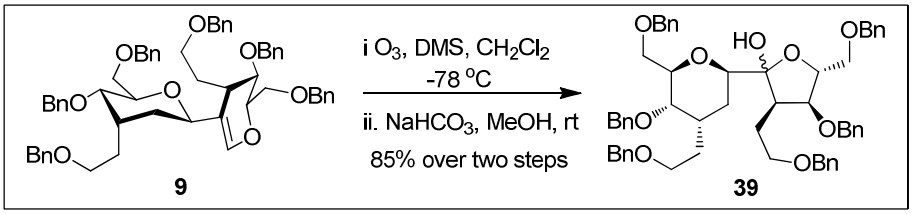
in vacuo and co-evaporated with toluene (2×10 mL). The crude compound was dried for 20 min in vacuo and dissolved in anhydrous dioxane (15 mL) with stirring. Lithium aluminium hydride (LAH) (0.19 g, 5.0 mmol) was added and heated to reflux until completion (12 h). The reaction was slowly quenched at 0 ^{o}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, 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 over portion wise in 10 min at 0 ^{o}C and stirred for 15 min at the same temperature. BnBr (1.12 mL, 10 mmol) and TBAI (cat) were added at 0 ^{o}C and stirred until completion (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, 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 colourless 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 (125MHz, $CDCl_3$): 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): $\tilde{\nu}$ = 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

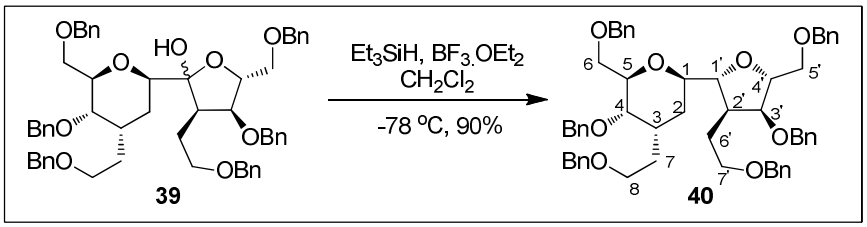
(20 mL). To this solution, powdered 4 Å molecular sieves (200 mg) was added and stirred for 1 h at room temperature. The solution was cooled to -78 ^{o}C and stirred for 15 min at the same temperature. Freshly distilled TMSOTf (63.5 μL, 0.36 mmol) was added at -78 ^{o}C and stirred until completion (1 h). Triethylamine (48.5 μL, 0.36 mmol) was added at -78 ^{o}C to quench the reaction and allowed to reach the 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 colour 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 (125MHz, $CDCl_3$): 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): $\tilde{\nu}$ = 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 (125MHz, $CDCl_3$): 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): $\tilde{\nu}$ = 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.



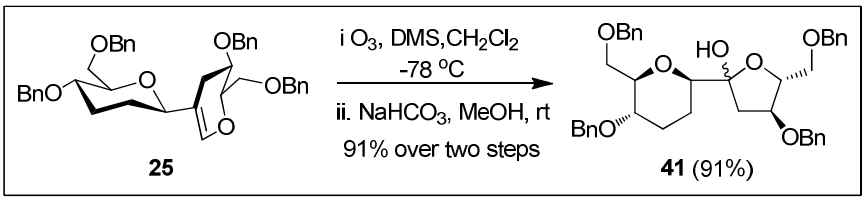
(3S,4R,5S)-4-(benzyloxy)-2-(2R,4S,5S,6R)-5-(benzyloxy)-4-(2-benzyloxyethyl)-6-(benzyloxymeth--yl)tetrahydro-2H-pyran-2-yl)-3-(2-benzyloxyethyl)-5-(benzyloxymethyl)tetrahydrofuran-2-ol (**39**): CH_2Cl_2 (10 mL) was added to the disaccharide **9** (0.15 g, 0.17 mmol) in a two-necked round-bottomed flask 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 colour persisted. Then, oxygen followed by nitrogen were passed through the inlet until the pale blue colour 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, solid $NaHCO_3$ (0.13 g, 1.57 mmol) was added 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 colourless 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, 75.5, 75.5, 73.3, 72.8, 72.6, 71.4, 71.4, 70.7,

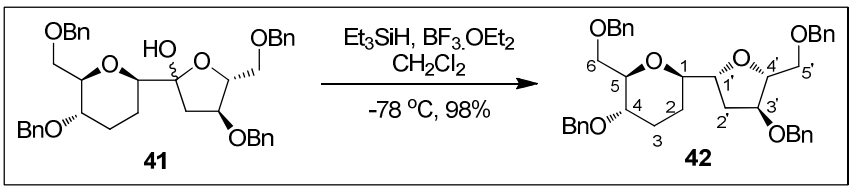
70.3, 70.3, 68.9, 68.7, 41.5, 30.3, 27.0, 25.2, 23.2 ppm. IR (neat): $\tilde{\nu}$ = 3031, 2933, 2853, 1950, 1489, 1448, 1362 cm^{-1}. HRMS (ESI): Calcd. for $C_{57}H_{64}O_9Na$ $[M + Na]^+$ 915.4448; found 915.4445.



(2R,3S,4S,6R)-3-(benzyloxy)-6-(2R,3S,4R,5S)-4-(benzyloxy)-3-(2-benzyloxyethyl)-5-(benzyloxy- -methyl)tetrahydrofuran-2-yl)-4-(2-benzyloxyethyl)-2-(benzyloxymethyl)tetrahy-dro-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, 0.2mmol), $BF_3.OEt_2$ (20 µL, 0.15 mmol) were added respectively 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. $NaHCO_3$, 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 colourless 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): $\tilde{\nu}$ = 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.

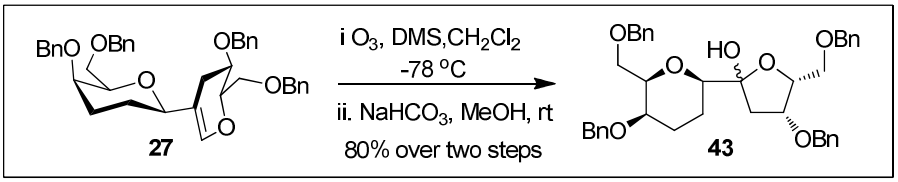


(2R,4R,5S)-4-(benzyloxy)-2-(2R,5S,6R)-5-(benzyloxy)-6-(benzyloxymethyl)tetrahydro-2H-pyran-2-yl)-5-(benzyloxymethyl)tetrahydrofuran-2-ol (**41**): CH_2Cl_2 (20 mL) was added to the disaccharide **25** (0.25 g, 0.4 mmol) in a two-necked round-bottomed flask with a gas outlet on one neck and a gas inlet 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 colour persisted. Then, oxygen followed by nitrogen were passed through the inlet until the pale blue colour 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, solid $NaHCO_3$ (0.32 g, 3.8 mmol) was added 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 colourless 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.



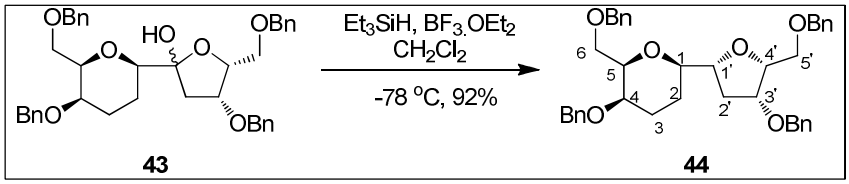
(2R,3S,6R)-3-(benzyloxy)-6-(2R,4R,5S)-4-(benzyloxy)-5-(benzyloxymethyl)tetrahydrofuran-2-yl)-2-(benzyloxymethyl)tetrahydro-2H-pyran (**42**): A solution of hemiketal **41** (0.08 g, 0.12 mmol) in anhydrous dichloromethane (5 mL) was cooled to -78 °C. Et_3SiH (47.8 µL, 0.3mmol), $BF_3.OEt_2$ (30.4 µL, 0.24 mmol) were added respectively 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. $NaHCO_3$, 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 colourless liquid. R_f = 0.4 (20% EtOAc in Hexanes). ^{1}H 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): $\tilde{\nu}$ = 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.



(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-necked 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 colour persisted. Then, oxygen followed by nitrogen were passed through the inlet until the pale blue colour 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.

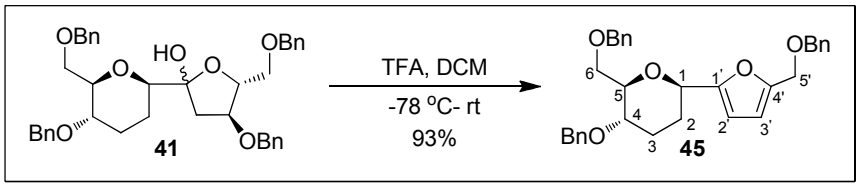
The obtained crude product was dissolved anhydrous MeOH (20 mL). To this solution, solid $NaHCO_3$ (0.32 g, 3.8 mmol) was added and stirred until completion (2 h). MeOH was evaporated in vacuo and the obtained crude was purified by column chromatography over silica gel (hexanes/ethyl acetate) to obtain the inseparable anomeric mixture of pure hemiketal **43** (0.18 g, 80% over two stpes, α:β (1:1)) as a colourless 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.



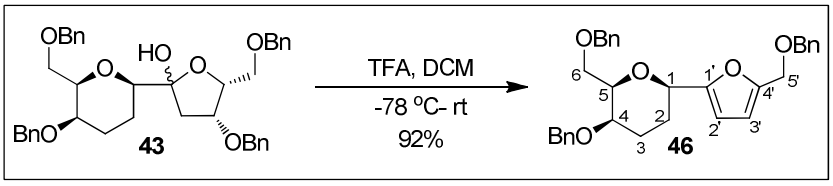
43 **44**

(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, 0.3mmol), $BF_3.OEt_2$ (30.4 µL, 0.24 mmol) were added respectively 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. $NaHCO_3$, 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 colourless 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 (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): ν̃

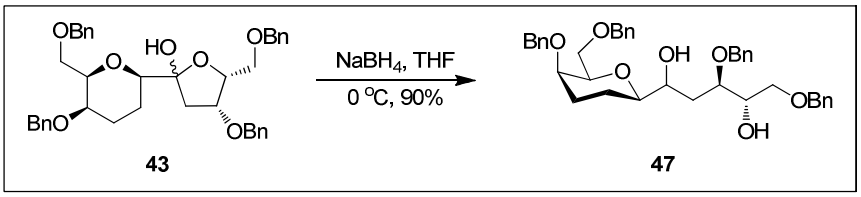
= 2932, 2853, 1746, 1444, 1093 cm^{-1}. HRMS (ESI): Calcd. for $C_{39}H_{44}O_6Na$ $[M + Na]^+$ 631.3036; found 631.3037.



(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) were added respectively 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. $NaHCO_3$, 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 colourless liquid. R_f = 0.5 (20% EtOAc in Hexanes). ^1H 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): $\tilde{\nu}$ = 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 ^{o}C. Trifluoroacetic acid (TFA) (37 µL, 0.48 mmol) were added respectively 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. $NaHCO_3$, 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 colourless 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): $\tilde{\nu}$ = 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.



43 47

(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 ^{o}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 colourless 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): $\tilde{\nu}$ = 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.

Acknowledgements

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Supporting Information

Copies of ^1H, ^{13}C NMR and HRMS spectra for all new compounds and 2D COSY and 2D NOESY spectra of *C*-saccharides are available free of charge via the Internet at http://pubs.acs.org.

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