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Glycosyl iodides are highly efficient donors under neutral conditions

Michael J. Hadd, Jacquelyn Gervay *

The University of Arizona, Department of Chemistry, Tucson, Arizona 85721, USA

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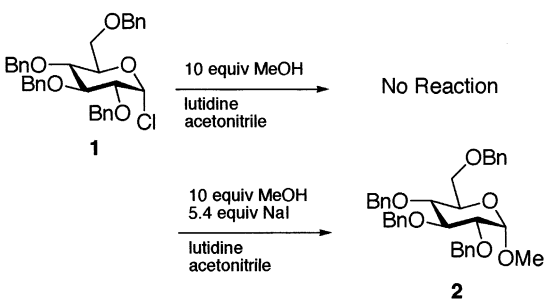
Abstract

Glycosyl iodides have been prepared and subjected to glycosylation under neutral conditions. The reactions are highly efficient, giving α glycosides even with sterically demanding glycosyl acceptors. Glucosyl iodides react with allyl alcohol slowest and require refluxing conditions. Galactosyl iodides are intermediate in reactivity, providing the allyl glycoside in 3 h at room temperature, whereas glycosylation of fucosyl iodides occurs in less than 1 h under similar conditions. The scope and limitations of the reactions were demonstrated with a variety of acceptors, including an anomeric hydroxyl group, to give trehalose analogs. β-Selective glycosylation of glucosyl iodides, in the absence of C-2 participation, could be achieved by simply changing the solvent from benzene to acetonitrile.

Keywords: Glycosyl iodide; Glycosyl bromide; α-Glycosylation; In situ anomerization; Halide-catalyzed anomerization; Trehalose analogs

1. Introduction

Activation of glycosyl halides in the presence of an acceptor alcohol using a Lewis acid promoter is the most widely utilized method of *O*-glycoside formation [1]. However, the use of glycosyl halides in the absence of a Lewis acid promoter has received far less attention, largely due to their low reactivity toward nucleophilic displacement under neutral conditions. For example, Kronzer and Schuerch [2] reported that reaction of 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl chloride (**1**) with 10 equivalents of methanol under neutral conditions in acetonitrile does not proceed, and that the corresponding bromide takes 8 h to react with 5 equivalents of 2-propanol (Scheme 1). They also demonstrated that, upon addition of excess sodium iodide, the glucosyl chloride started to react after 10 min to produce selectively methyl 2,3,4-6-tri-*O*-benzyl-α-D-glycoside (**2**).



Scheme 1. Sodium iodide catalysis of glucosyl chlorides.

Abbreviations: 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose ('diacetoneglucose'), DAG; Ethyldiisopropylamine ('diisopropylethylamine'), DIEA; tetrabutylammonium iodide, TBAI.

* Corresponding author. Tel.: +1-520-621-8843; fax: +1-520-621-8407.

E-mail address: gervay@u.arizona.edu (J. Gervay)

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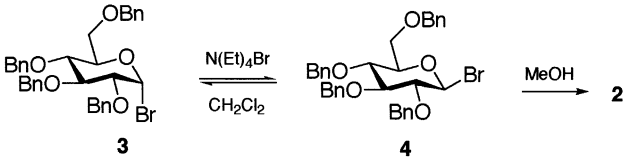


Scheme 2. Tetraethylamonium bromide catalysis of glycosyl bromides.

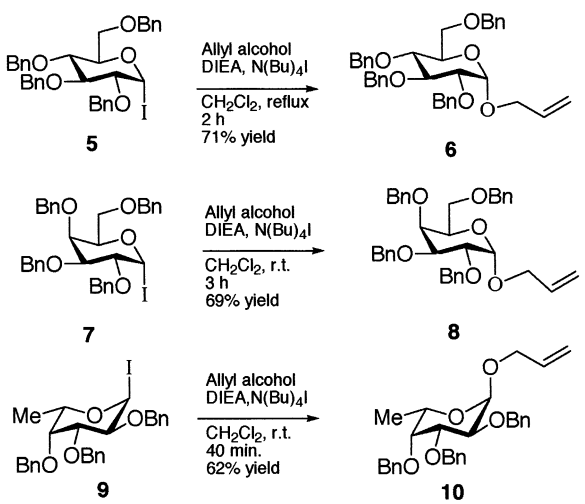
Lemieux and co-workers have also investigated the reaction of anomeric bromides under neutral conditions [3]. They showed that the sluggish reaction rate of glycosyl bromides under neutral conditions could be greatly increased by the addition of tetraethylammonium bromide. The proposed explanation for this rate increase is the in situ formation of the β glycosyl bromide (**4**), which is more reactive than its α counterpart (**3**) (Scheme 2). The highly reactive β glycosyl bromide undergoes S_N2 displacement by the acceptor alcohol to give selectively the α glycoside. Halide-ion catalysis has been shown to work using both simple alcohols and selectively protected carbohydrates as acceptors. However, when glycosyl bromides are employed, the typical procedure calls for a long (4-day) reaction time, and certain secondary alcohols give low yields [4,5].

We recently reported that α glycosyl iodides are easily accessible from the corresponding anomeric acetate [6], and that they readily undergo nucleophilic displacement with stabilized anions [7]. As a natural extension of that work, we decided to investigate the reaction of glycosyl iodides [8] with alcohols under neutral conditions with the hope that they would be more efficient glycosyl donors than the corresponding bromides.

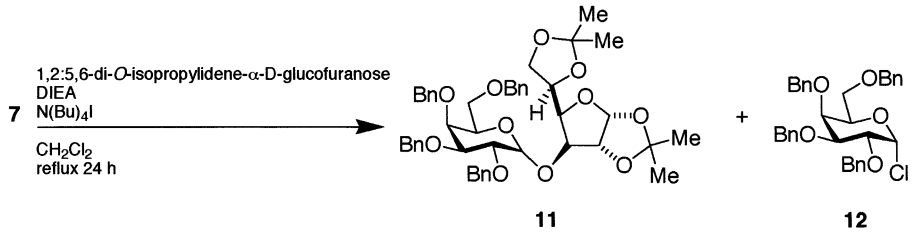
2. Results and discussion

The direct addition of methanol to glycosyl iodides is very slow and does not always lead to stereospecific product formation [9]. Based on the work of Lemieux and co-workers [4], we thought that introduction of a soluble iodide source might catalyze the reaction by in situ formation of the more reactive β-glycosyl iodide, leading to more efficient and stereospecific α glycoside formation than with the corresponding glycosyl bromide. Our initial experiments focused on the formation of allyl glycosides from the corresponding α-glycosyl iodides, using tetrabutylammonium iodide (TBAI) as the soluble iodide source and diisopropylethyl amine as a hindered base (Scheme 3). The reactions proceeded swiftly to give the allyl α-glycosides in good yield with high stereoselectivity. The reactivities of the glycosyl iodides varied tremendously, with the glucosyl iodide **5** reacting slowest, followed by the galactosyl iodide **7**, and the fucosyl iodide **9**, which was fastest.

Although allyl alcohol added to the glycosyl iodides quickly at room temperature, more pressing conditions were necessary for hindered alcohols. 1,2:5,6-Di-*O*-isopropylidene-α-D-glucopyranose (DAG) was chosen as a representative secondary alcohol of moderate reactivity, in order to demonstrate the applicability of this glycosylation method to common glycosyl acceptors. Initially, dichloromethane was used as solvent, and refluxing conditions were employed in order to facilitate the reaction. After 24 h, reaction with the galactosyl iodide produced the α glycoside **11** in low yield (45%) along with a major by-product. Mass spectral and ^{1}H NMR analysis confirmed that the by-product formed was the galactosyl chloride **12** (Scheme 4). Other solvents were employed in an attempt to increase the reaction rate. For example, after 3 h in refluxing THF, all of the galactosyl iodide had been consumed, but



Scheme 3. Reaction of allyl alcohol with glycosyl iodides.



Scheme 4. Reaction of the galactosyl iodide with DAG in CH_2Cl_2.

again a low yield of **11** was obtained and a by-product had formed. Mass spectral and ^1H NMR data were used to assign the byproduct's structure as the THF adduct[1].

In order to avoid solvent reaction with the glycosyl iodides, benzene was employed, even though TBAI solubility was low at room temperature. Reaction of **7** in refluxing benzene with DAG and 2 equiv of TBAI proceeded smoothly in 5.5 h to give a 93% yield of a 9:1 α:β mixture along with a minor amount of the glycal (Scheme 5). Addition of 10 equivalents of TBAI increased the rate of glycosyl iodide disappearance, but the α selectivity did not change, and the rate of glycal formation increased. A lower temperature (40 °C) was also tried, but it only slowed the overall reaction, with little or no gain in selectivity.

Several other glycosyl iodides were reacted with TBAI and DAG. The fucosyl iodide **9** reacted in refluxing CH_2Cl_2 to give a 62% yield of only the α product **14** in 3 h. This result was in agreement with our earlier observation that the fucosyl iodide was more reactive than the galactosyl iodide. The mannosyl iodide differed from the other glycosyl iodides in that no TBAI was needed in order to give α selectivity. Reaction of the mannosyl iodide **15** in refluxing benzene gave a 67% yield of the α glycoside **16**, with the glycal **17** as a by-product. Reaction of **5** gave a 45% yield of the α glycoside **18**, along with a 44% yield of **17**[2]. Attempts to limit elimination by changing to a milder base failed. A comparison between the reactivity of glycosyl iodides and the glycosyl bromides used by Lemieux and co-workers [4] is shown in Table 1.

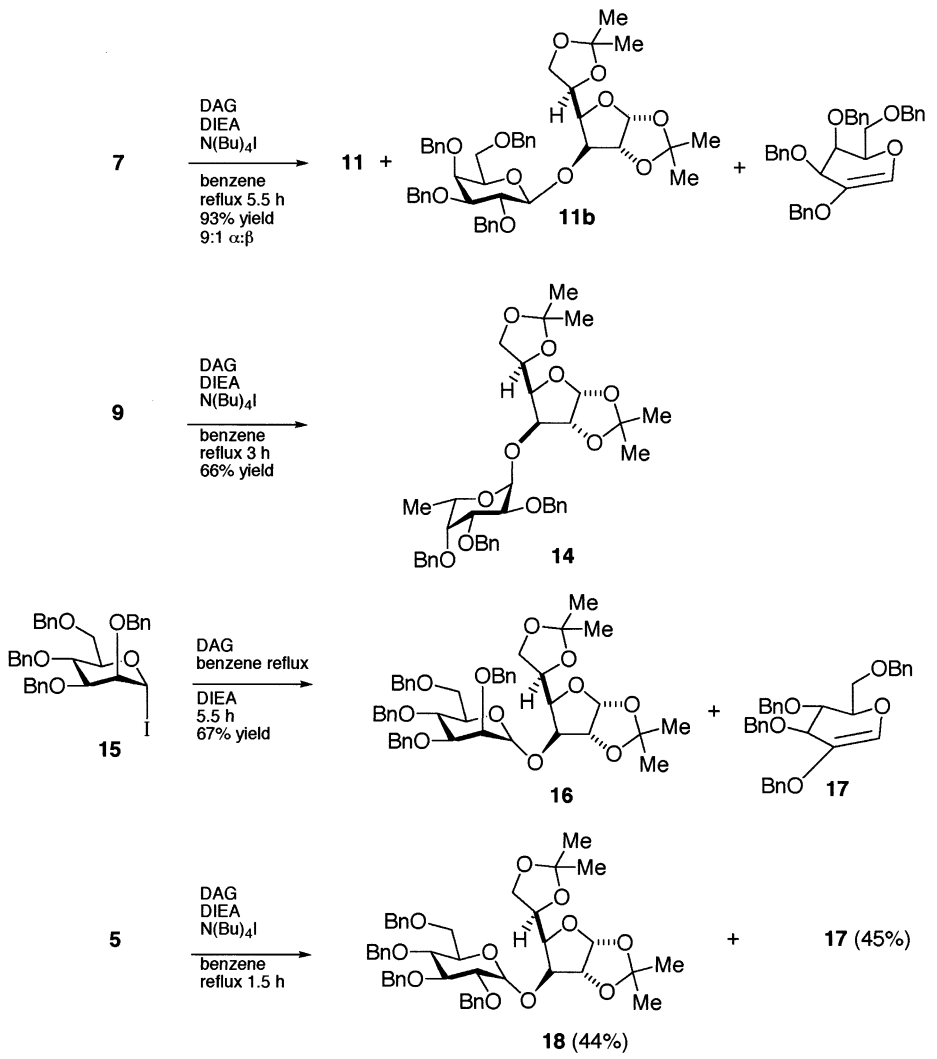
We also looked at the possibility of using glycosyl bromides as donors under TBAI catalysis. In an analogous reaction to that used for the preparation of **9**, the fucosyl bromide was generated by the action of bromotrimethylsilane (2.2 equivalents) on 1-*O*-acetyl-2,3,4-tri-*O*-benzyl-1-fucopyranose. While reaction of the anomeric acetate with iodotrimethylsilane (1.1 equivalents) was complete within 20 min, generation of the glycosyl bromide required 2.5 h. However, subsequent reaction of the bromide under TBAI catalysis proceeded at a similar rate to that for **9**, with complete consumption of the acceptor within 4 h (Table 1, entries 8 and 9). This result suggests that the fucosyl bromide and **9** undergo in situ halide exchange with equal facility. A comparative rate study between bromides and iodides of less reactive donors is currently under investigation, in order to determine the generality of this finding. Nonetheless, the experiments reported herein clearly illustrate the advantages of using glycosyl iodides: shorter reaction times, as well as improved yields, are realized.

In order to investigate the ability of the glycosyl iodides to react with other secondary alcohol acceptors, the C-2 hydroxyl group of 1,6-anhydro-3,4-*O*-isopropylidene-β-D-galactopyranose was chosen as an example of a secondary axial alcohol acceptor. Reaction of **9** with the anhydrosugar and TBAI in dichloromethane at room temperature provided a 91% yield of only the α glycoside **19** in 5.5 h (Scheme 6).

The facility with which the glycosyl iodides underwent glycoside formation prompted us to investigate the possibility of using them as donors in constructing the 1,1′-linkage found

[1] Similar product formation was observed by Iadonisi and co-workers upon activation of trichloracetimidates with air-oxidised samarium diiodide in tetrahydrofuran. M. Adinolfi, G. Barone, A. Iadonisi, R. Lanzetta, *Tetrahedron Lett.*, 39 (1998) 5605–5608.

[2] The yield of **18** is based upon the theoretical yield of the acceptor, which is the limiting reagent. The yield of **17** is based upon using 1.3 equivalents of the glycosyl iodide.



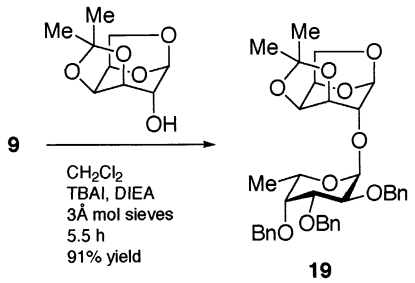
Scheme 5. Reaction of glycosyl iodides in refluxing benzene.

in trehalose. The fucose derivative of trehalose has to our knowledge never been synthesized. For this reason, we chose it as our synthetic target in probing the formation of the 1,1′-glycosidic linkage. Fucosyl iodide **9** was reacted with 2,3,4-tri-*O*-benzyl-L-fucopyranose in refluxing benzene in the presence of 10 equivalents of TBAI and 2 equivalents of DIEA. After 1 h, the reaction gave a 90% yield of a 1.1:1 ratio of the α,α:α,β (**20**:**21**) trehalose derivatives (Scheme 7). Several different mechanistic scenarios, which are currently under investigation in our laboratory, could explain the product mixture. However, it is noteworthy that the α,α:α,β ratio increased to 6.5:1 when only 2 equivalents of TBAI were used and the reaction was performed at room temperature in CH_2Cl_2.

Once it was established that high α selectivity was attainable in glycosylation reactions using glycosyl iodide donors, β-selective glycosylation strategies were investigated. Since the glycosyl donors have a nonparticipating group at the C-2 position, the only viable mechanism that would produce a β linkage would be S_N2 displacement of an α iodide or other leaving group. High α selectivity is achieved in TBAI-catalyzed reactions because the β iodide is a more reactive glycosyl donor than the α anomer due to the anomeric effect [10]. Therefore we considered the possibility of exploiting the anti-anomeric effect in order achieve β selectivity [11]. The anti-anomeric effect arises from the fact that a positively charged anomeric substituent is more stable in the β configuration. Therefore, if an equilibrium be-

Table 1
Halide catalysis: comparison of glycosyl bromides [4,5] with glycosyl iodides

Entry	Donor	Catalyst	Time (h)	Yield (%)
1	Glc-Br (**3**)+DAG	$N(Et)_4Br$	48	42
2	Glc-I (**5**)+DAG	$N(Bu)_4I$	1.5	44
3	Gal-Br+DAG	$N(Et)_4Br$	48	62
4	Gal-I (**7**)+DAG	$N(Bu)_4I$	5.5	93 (9:1 α:β)
5	Fuc-Br+DAG	$N(Et)_4Br$	48	47
6	Fuc-I (**9**)+DAG	$N(Bu)_4I$	3	62
7	Man-I (**15**)+DAG	none	5.5	67
8	Fuc-Br+dodecanol (bromide formed in 2.5 h)	$N(Bu)_4I$	4	Quant.
9	Fuc-I (**9**)+dodecanol (iodide formed in 20 min)	$N(Bu)_4I$	4	Quant.



Scheme 6. 1,6-Anhydrogalactose reactions with fucosyl iodide **9**.

tween the two anomers could be established, the α anomer should be more reactive, selectively producing the β glycoside (Scheme 8).

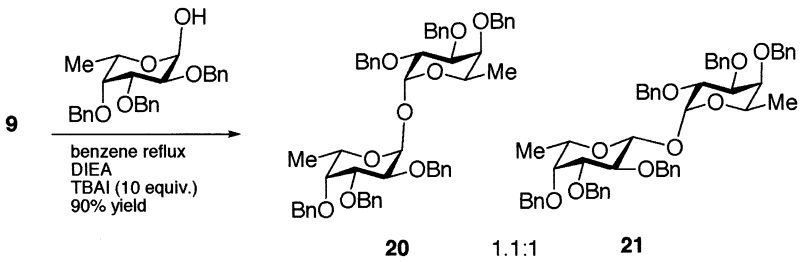
Our plan for setting up such an equilibrium was to utilize an α nitrilium ion [12] that could be formed from either the β glycosyl iodide or the oxonium ion. To test this hypothesis, the glucosyl iodide **5** was reacted with allyl alcohol, DIEA, and TBAI in acetonitrile. After 2 h at room temperature, a 9.8:1 ratio of β:α glycosides was obtained (Scheme 9).

Two mechanisms for the β selectivity were probable, either the α nitrilium ion formed and reacted with the alcohol, or due to the increased polarity of the solvent the α iodide reacted by a type I S_N2 reaction (Scheme 10).

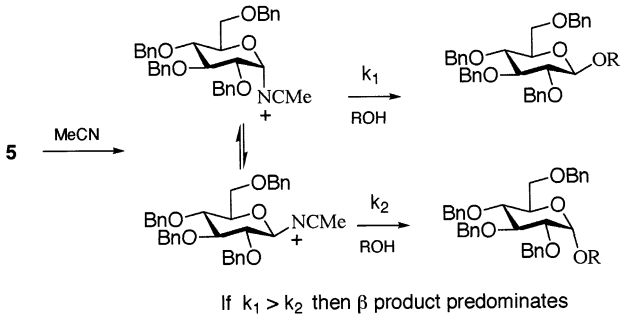
If **5** reacted by the type I S_N2 process, we would expect the galactosyl iodide **7**, which was shown earlier to be more reactive, to show better β selectivity and a faster reaction rate. However, when **7** was reacted under the same conditions, it yielded only the α glycoside after 45 min. One explanation for this result is that the rate of formation of the galactosyl oxonium ion is faster than the rate of formation of the glucosyl oxonium ion, and that the galactosyl oxonium species is trapped by the alcohol with no nitrilium ion intermediate. Support for this theory was recently published by Miljković and co-workers [13], where they demonstrated that oxonium ion formation is stabilized by the presence of an axial substituent at the C-4 position of the pyranose ring, and that this stabilization is greatest if the substituent is an ether. Due to the stabilizing effect of the C-4 axial benzyl ether, the oxonium ion would be formed at a faster rate in the galactose case and might exhibit selectivity for reaction with the alcohol over solvent participation by acetonitrile. Extension of these reaction conditions to the mannosyl iodide gave an approximately 1:1 ratio of α and β anomers both in the presence and absence of TBAI (Scheme 11). This result might be explained by an oxonium ion with a stability that is between that of the glucosyl and galactosyl oxonium species, thus yielding a mixture of anomers. At this point, however, several other mechanistic explanations cannot be discounted, and further research must be done to clearly demonstrate the effects of solvent and carbohydrate structure on the specificity and rate of reaction for the glycosyl iodides in polar solvents.

3. Conclusions

The use of glycosyl iodides as efficient donors in the selective synthesis of α glycosidic linkages has been demonstrated. The advantages of using glycosyl iodides over the corresponding bromides include more rapid generation of the iodide donor, increased rates of glycosylation, and more efficient incorporation of sterically demanding acceptors. Fur-



Scheme 7. Preparation of fucosyl trehalose derivatives.

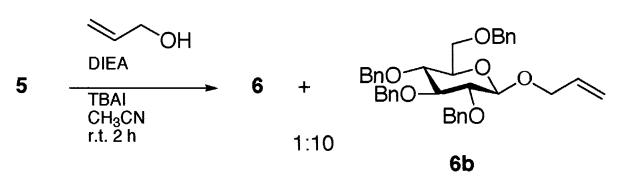


Scheme 8. Utilization of the anti-anomeric effect to obtain β glycosides.

thermore, our initial experiments suggest that glycosyl iodides may also be suitable donors for the construction of β glycosides by simply altering the solvent polarity. The results reported herein raise important mechanistic questions, which are currently under investigation in our laboratory.

4. Experimental

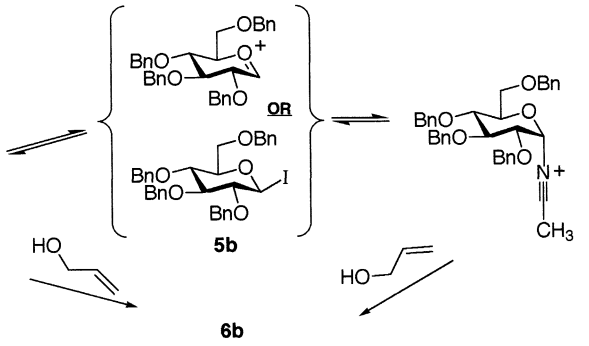
Starting materials and reagents purchased from suppliers were used without further purification. Chemicals were obtained from Fluka Chemical Co.: iodotrimethylsilane, tetra-*O*-benzyl-D-glucopyranose. Solvents were dried by distillation prior to use. Dichloromethane and toluene were dried over calcium hydride, and tetrahydrofuran was dried over sodium–benzophenone ketyl. Chromatography was performed using Silica Gel 60 (230–400 mesh ASTM). Mass spectrometry was performed by the University of Minnesota Mass Spectrometry Service and the University of Arizona Mass Spectrometry Facility. Known compounds showed physicochemical and spectral data that were consistent with those reported in the indicated references.



Scheme 9. Reaction of the glucosyl iodide in acetonitrile.

General procedure for allyl α-glycoside formation (**6, 8** *and* **10**).—To a solution of the 1-*O*-acetyl-tetra-*O*-benzylglycose (0.1 mmol) in 1 mL of CH_2Cl_2 cooled to 0 °C is added iodotrimethylsilane (0.11 mmol for glucose and fucose, and 0.1 mmol for galactose), and the mixture was allowed to stand for 30 min. The solvent was then evaporated in vacuo, and 1.5 mL of toluene was added and again evaporated in vacuo[3]. CH_2Cl_2 (1 mL) was added, and the resulting solution was pipeted into an already stirring solution of CH_2Cl_2 (1 mL), allyl alcohol (14 μL, 0.2 mmol), DIEA (35 μL, 0.2 mmol) and TBAI (74 mg, 0.2 mmol) with 4 Å molecular sieves (150 mg). The solution was then stirred for 40 min (fucose), 3 h (galactose), or 2 h reflux (glucose), and the solvent was evaporated in vacuo. The resulting oil was subjected to flash column chromatography using 9:1 hexanes–ethyl acetate for the fucose reaction or 6:1 hexanes–ethyl acetate for the galactose and glucose reactions to yield the allyl α-glycosides: fucose, 62%; galactose [14], 69%; and glucose [15], 71%. Data for the allyl α-fucoside **8**: ^{1}H NMR (250 MHz, C_6D_6): δ 0.9 (d, 3 H, *J* 6.5Hz), 3.35 (1 H, m), 3.74–3.90 (2 H, m), 4.0–4.12 (2 H, m), 4.25 (1 H, dd, *J* 8.1, 4.5 Hz) 4.41–4.62 (4 H, m), 4.79 (1 H, d, *J* 12.0 Hz), 4.93 (1 H, d, *J* 3.6 Hz, H-1), 5.0–5.07 (2

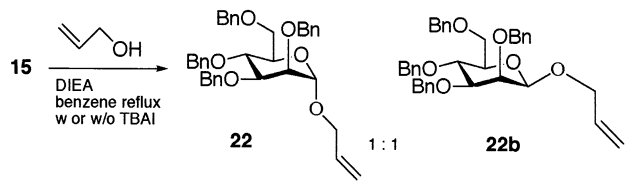
[3] Toluene is added and evaporated in order to remove the trimethylsilyl acetate by azeotropic distillation. Trimethylsilyl acetate adds to the iodide to reform the anomeric acetate. This process competes with glycoside formation.



Scheme 10. Possible mechanistic routes into β glycoside formation.

H, m), 5.27–5.34 (1 H, m), 5.81 (1 H, m) 7.08–7.42 (15 H, m); ^{13}C NMR (62.5 MHz, C_6D_6): δ 16.9, 66.8, 68.5, 73.0, 73.4, 75.4, 77.6, 79.1, 79.4, 97.3, 116.5, 127.6, 127.7, 128.0, 128.4, 128.5, 128.6, 139.6, 139.8; HRFABMS: Anal. Calcd: 473.2328 (MH); Found: 473.2340 (MH); $[\alpha]_D$ −67.0° (*c* 0.04, $CHCl_3$).

*1,2:5,6-Di-*O*-isopropylidene-α-*D*-glucofuranos-3-yl 2,3,4,6-tetra-*O*-benzyl-α-*D*-galactopyranose* (**11**).—To a solution of 1-*O*-acetyl-2,3,4,6-tetra-*O*-benzyl-D-galactopyranose (140 mg, 0.24 mmol) in CH_2Cl_2 cooled to 0 °C was added (34 μL, 0.24 mmol) of iodotrimethylsilane, and the mixture was allowed to stand for 30 min. The solvent was removed in vacuo, and 1.5 mL of toluene was added and again removed in vacuo. Then 1 mL of benzene was added, and the solution was pipeted into an already stirring solution of DAG (48 mg, 0.18 mmol), (DIEA 65 μL, 0.37 mmol), and TBAI (137 mg, 0.37 mmol) in 1 mL of benzene with 4 Å molecular sieves. After refluxing for 5.5 h, the solvent was evaporated in vacuo, and the resulting oil was subjected to flash column chromatography using 6:1 hexanes–ethyl acetate as eluent to yield 7 mg of 3,4,6-tri-*O*-benzyl-D-galactal, 122 mg of the α anomer **11a** [16], and 14 mg of the β anomer **11b**, for a total yield of 93%. Data for **11b**: ^{1}H NMR (250 MHz, C_6D_6): δ 1.14 (s, 3 H), 1.27 (s, 3 H), 1.34 (s, 3 H), 1.49 (s, 3 H), 3.29 (m, 2 H), 3.55 (dd, 1 H), 3.69 (t, 1 H), 3.81 (d, 1 H), 3.92 (dd, 1 H), 4.18–4.72 (m, 14 H), 4.97 (d, 1 H), 5.81 (d, 1 H). ^{13}C NMR (62.5 MHz, C_6D_6): δ 26.2, 26.9, 66.3, 68.7, 73.6, 73.9, 75.1, 79.8, 81.0, 81.3, 82.4, 83.2, 102.5, 105.6, 127.5, 127.6, 127.8, 128.0, 128.1, 128.3, 128.4, 128.6, 138.6, 139.4; HRFABMS: Anal. Calcd: 781.3588



Scheme 11. Reaction of the mannosyl iodide in acetonitrile.

(MH); Found: 781.3605 (MH); $[\alpha]_D$ +42.7° (*c* 0.02, $CHCl_3$).

*1,2:5,6-Di-*O*-isopropylidene-α-*D*-glucofuranos-3-yl 2,3,4-tri-*O*-benzyl-α-*L*-fucopyranose* (**14**).—To a solution of 1-*O*-acetyl-2,3,4-tri-*O*-benzyl-L-fucopyranose (97 mg, 0.20 mmol) in 1 mL CH_2Cl_2 cooled to 0 °C was added iodotrimethylsilane (29 μL, 0.20 mmol), and the mixture was allowed to stand for 20 min. The solvent was evaporated in vacuo, and 1.0 mL of toluene was added and again evaporated in vacuo. CH_2Cl_2 (1 mL) was then added, and the resulting solution was pipeted into an already stirring solution of DAG (41 mg, 0.16 mmol), DIEA (55 μL, 0.31 mmol), and TBAI (116 mg, 0.31 mmol) in 1 mL of CH_2Cl_2 with 4 Å molecular sieves. After refluxing for 3 h, the solvent was evaporated in vacuo, and the resulting oil was subjected to flash column chromatography using 9:1 hexanes–ethyl acetate as eluent to yield 67 mg (62%) of the α glycoside **14** [17].

*1,2:5,6-Di-*O*-isopropylidene-α-*D*-glucofuranos-3-yl 2,3,4,6-tetra-*O*-benzyl-α-*D*-mannopyranose* (**16**).—To a solution of 1-*O*-acetyl-2,3,4,6-tetra-*O*-benzyl-D-mannopyranose (89 mg, 0.15 mmol) in 1.5 mL of CH_2Cl_2 cooled to 0 °C was added iodotrimethylsilane (22 μL, 0.15 mmol), and the mixture was allowed to stand for 30 min. The solvent was evaporated in vacuo, and 1.5 mL of toluene was added and again evaporated in vacuo. Then 1 mL of benzene was added, and the solution was pipeted into an already stirring solution of DAG (31 mg, 0.18 mmol), and DIEA (40 μL, 0.24 mmol) in 1 mL of benzene with 4 Å molecular sieves. After refluxing for 5.5 h, the solvent was evaporated in vacuo, and the resulting oil was subjected to flash column chromatography using 6:1 hexanes–ethyl acetate as eluent to yield 62 mg (67%) of the α glycoside **16** along with 24 mg of the glycal **17**. Data for α glycoside **16**: ^{1}H

NMR (250 MHz, C_6D_6): δ 1.06 (s, 1 H), 1.21 (s, 3 H), 1.30 (s, 1 H), 1.39 (s, 3 H), 3.76 (d, 2 H, *J* 3.6 Hz), 3.92 (t, 1 H, *J* 2.1 Hz), 4.03–4.14 (4 H), 4.19–4.41 (9 H), 4.62 (s, 2 H), 4.86 (d, 1 H, *J* 3.6 Hz), 4.97 (d, 1 H, *J* 11.2 Hz), 5.40 (d, 1 H, *J* 1.7 Hz, H-1), 5.90 (d, 1 H, *J* 3.6 Hz), 7.07–7.43 (20 H); ^{13}C NMR (62.5 MHz, C_6D_6): δ 25.6, 26.2, 29.9, 67.9, 70.1, 72.2, 72.8, 73.1, 73.5, 73.7, 75.2, 75.5, 75.6, 80.3, 81.7, 84.2, 99.7, 105.8, 109.4, 127.4, 127.6, 127.7, 127.8, 128.0, 128.3, 128.4, 128.5; HRFABMS: Anal. Calcd: 781.3588 (MH); Found: 781.3593 (MH); $[\alpha]_D$ +15.9° (*c* 0.08, $CHCl_3$).

1,2:5,6-Di-O-*isopropylidene*-α-D-*glucofuranos*-*3*-*yl 2,3,4,6-tetra*-O-*benzyl*-α-D-*glucopyranose* (**18**).—To a solution of 1-*O*-acetyl-2,3,4,6-tetra-*O*-benzyl-D-mannopyranose (219 mg, 0.38 mmol) in 1.5 mL of CH_2Cl_2 cooled to 0 °C was added iodotrimethylsilane (54 μL, 0.38 mmol), and the mixture was allowed to stand for 30 min. The solvent was then evaporated in vacuo, and 2.0 mL of toluene was added and again evaporated in vacuo. Then 1.5 mL of benzene was added, and the solution was pipeted into an already stirring solution of DAG (75 mg, 0.29 mmol), TBAI (214 mg, 0.58 mmol), and DIEA (100 μL, 0.24 mmol) in 1 mL of benzene with 4 Å molecular sieves. After refluxing for 1.5 h, the solvent was evaporated in vacuo, and the resulting oil was subjected to flash column chromatography using 7:1 hexanes–ethyl acetate as eluent to yield 102 mg (45%) of the α glycoside **18** [18] along with 86 mg of the glycal **17**.

1,6-Anhydro-3,4-O-*isopropylidene*-D-*galactopyranos*-*2*-*yl 2,3,4-tri*-O-*benzyl*-α-L-*fucopyranoside* (**19**).—To a solution of 1-*O*-acetyl-2,3,4-tri-*O*-benzyl-L-fucopyranose (231 mg, 0.49 mmol) in 2 mL of CH_2Cl_2 cooled to 0 °C was added iodotrimethylsilane (74 μL, 0.52 mmol), and the mixture was let stand for 10 min. The solvent was evaporated in vacuo, and 1.5 mL of toluene was added and again evaporated in vacuo. CH_2Cl_2 (1 mL) was then added, and the resulting solution added to an already stirring solution of 1,6-anhydro-3,4-*O*-isopropylidene-D-galactopyranose (75 mg, 0.37 mmol), TBAI (344 mg, 0.93 mmol), DIEA (110 μL, 0.63 mmol), and 4 Å molecular sieves in 1 mL of CH_2Cl_2. The solution was stirred for 5.5 h, at the end of which time the solvent was evaporated in vacuo, and the resulting oil was subjected to flash column chromatography using 3:1 hexanes–EtOAc) as eluent to yield 209 mg (91%) of the α glycoside **19**: ^{1}H NMR (250 MHz, C_6D_6): δ 1.08–1.12 (m, 6 H), 1.37 (s, 3 H), 3.30 (s, 1 H), 3.42 (t, 1 H, *J* 6.1 Hz), 3.91–4.01 (m, 3 H), 4.09–4.35 (m, 6 H), 4.42–4.59 (m, 5 H), 4.68 (d, 1 H, *J* 11.9), 4.95 (d, 1 H, *J* 6.8 Hz, H-1 fucose), 4.98 (s, 1 H), 5.80 (s, 1 H); ^{13}C NMR (62.5 MHz, C_6D_6): δ 16.8, 24.1, 25.8, 63.3, 67.4, 69.7, 72.5, 73.2, 75.3, 75.4, 77.2, 78.6, 78.8, 79.5, 99.7, 101.1, 108.4, 127.6, 127.8, 128.0, 128.4, 128.5, 139.4; HRFABMS: Anal. Calcd: 617.2751 (MH); Found: 617.2750 (MH); $[\alpha]_D$ −44.2° (*c* 0.3, $CHCl_3$).

2,3,4-Tri-O-*benzyl*-α-L-*fucopyranosyl 2,3,4-tri*-O-*benzyl*-α-L-*fucopyranoside* (**20**) *and 2,3,4-tri*-O-*benzyl*-β-L-*fucopyranosyl 2,3,4-tri*-O-*benzyl*-α-L-*fucopyranoside* (**21**).—To a solution of 1-*O*-acetyl-2,3,4-tri-*O*-benzyl-L-fucopyranose (100 mg, 0.21 mmol) in 1.5 mL CH_2Cl_2 cooled to 0 °C was added iodotrimethylsilane (30 μL, 0.21 mmol), and the mixture was allowed to stand for 20 min. The solvent was evaporated in vacuo, and 1.5 mL of toluene was added and again evaporated in vacuo. Benzene (1 mL) was added, and the resulting solution was pipeted into an already stirring solution of 2,3,4-tri-*O*-benzyl-L-fucopyranoside (70 mg, 0.16 mmol), TBAI (600 mg, 1.62 mmol), and DIEA (56 μL, 0.32 mmol) preheated to reflux in 1 mL of benzene with 4 Å molecular sieves. The reaction was refluxed for 1 h, at the end of which time the solvent was evaporated in vacuo, and the resulting oil was subjected to flash column chromatography using 7:1 hexanes–EtOAc as eluent to yield 66 mg of the α,α **20**, 58 mg of the α,β **21**, and 6 mg of 3,4,6-tri-*O*-benzyl-L-fucal. The overall yield is 90% with a 1.14:1, α,α:α,β ratio of anomers. Data for α,α anomer **20**: ^{1}H NMR (250 MHz, C_6D_6): δ 1.25 (d, 6 H, *J* 6.5 Hz, H-6), 3.40 (d, 2 H, *J* 1.5 Hz), 4.14 (dd, 2 H, *J* 10.2, 2.8 Hz), 4.29 (dd, 2 H, *J* 10.1, 3.5 Hz), 4.35 (q, 2 H, *J* 6.6 Hz), 4.48 (d, 4 H, *J* 11.5 Hz), 4.56 (d, 2 H, *J* 8.5 Hz), 4.60 (d, 2 H, *J* 8.5 Hz), 4.71 (d, 2 H, *J* 11.7 Hz), 4.98 (d, 2 H, *J* 11.3 Hz), 5.50 (d, 2 H, *J* 3.5 Hz, H-1,H-1′), 7.00–7.40 (m, 20 H); ^{13}C NMR

(62.5 MHz, C_6D_6): δ 17.1, 67.2, 73.0, 73.4, 75.4, 77.2, 78.7, 79.9, 94.2, 127.6, 127.7, 128.0, 128.3, 128.4, 128.6; HRFABMS: Anal. Calcd: 849.4003; Found: 849.4031 (MH); $[\alpha]_D$ −100.5° (c 0.04, $CHCl_3$). Data for α,β anomer **21**: ^{1}H NMR (250 MHz, C_6D_6): δ 1.22 (d, 3 H, *J* 6.3 Hz, H-6), 1.30 (d, 3 H, *J* 6.3 Hz, H-6), 3.10 (q, 1 H, *J* 7.2 Hz), 3.18 (d, 1 H, *J* 2.8 Hz), 3.33 (dd, 1 H, *J* 9.7, 2.6 Hz), 3.37 (s, 1 H), 4.07–4.19 (m, 2 H), 4.26 (dd, 1 H, *J* 10.3, 3.3 Hz), 4.40–4.72 (m, 10 H), 4.82 (d, 1 H, *J* 11.6 Hz), 4.99 (d, 2 H, *J* 11.4 Hz), 5.33 (d, 1 H, *J* 11.8 Hz), 5.39 (d, 1 H, *J* 3.5 Hz, H-1$^{\alpha}$), 6.95–7.45 (m, 20 H); ^{13}C NMR (62.5 MHz, C_6D_6): δ 16.8, 17.2, 67.7, 70.7, 73.1, 73.3, 74.9, 75.2, 75.3, 77.1, 77.5, 78.8, 79.7, 80.1, 82.9, 100.4, 104.2, 127.2, 127.4, 127.6, 127.9, 128, 128.4, 128.6, 139.6, 139.7; HR-FABMS: Anal. Calcd: 849.4003; Found: 849.4031 (MH); $[\alpha]_D$ −59.1° (*c* 0.04, $CHCl_3$).

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