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GLYCOSYLATIONS VIA *IN SITU* FORMATION OF GLYCOSYL IODIDES FROM GLYCOSYL BROMIDES

By

Son Ngoc Lam

A Thesis Submitted to the Faculty of the

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In the Graduate College

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2001

STATEMENT BY AUTHOR

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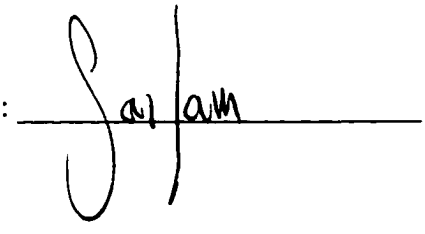
SIGNED: 

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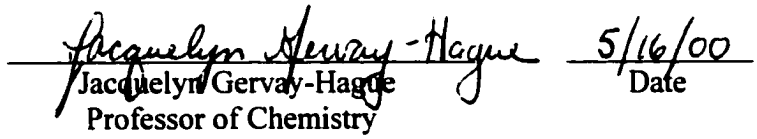

Jacquelyn Gervay-Hague
Professor of Chemistry

5/16/00
Date

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Without my family, I would not have made it this far. I extend to you my warmest thanks and my love for being an indispensable resource. To my mother and father, Anh and Hoa, who gave me life, made sure my stomach was always full, and taught me the important things in life, I am forever indebted. To Loan, Dùng, Jason, Minh, Kelly, Dung, Thanh, and Quang, thank you for all your love and support through all those early mornings and late nights at the airport, the care packages with all the Asian treats, and my favorite pastime the trips to the supermarket.

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Abbreviations

Ag_2O	Silver (I) Oxide
$AgClO_4$	Silver Perchlorate
Ag_2CO_3	Silver (I) Carbonate
AgOTf	Silver triflate
$BF_3 \cdot Et_2O$	Trifluoroborane diethyl etherate
BnBr	Benzyl bromide
BzCl	Benzoyl chloride
Bu_4N-Br	Tetrabutylammonium bromide
Bu_4N-I	Tetrabutylammonium iodide
CH_2Cl_2	Dichloromethane, Methylene Chloride
DAG	1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose, Diacetone glucose
DCM	Dichloromethane, Methylene Chloride
DIPEA	Diisopropylethylamine
DMTSB	
DTBP	2,6-Di-*t*-butylpyridine
DTBPI	2,6-Di-*t*-butylpyridinium iodide
Et_4N-Br	Tetraethylammonium bromide
Et_4N-I	Tetraethylammonium iodide
EtOH	Ethanol
Eq.	Equivalents
Fuc	L-Fucose
Gal	D-Galactose
Glc	D-Glucose
h	hour(s)
$Hg(CN)_2$	Mercuric cyanide
$HgBr_2$	Mercuric bromide
$Hg(TFA)_2$	Mercury trifluoroacetate
HI	Hydrogen iodide
HOAc	Acetic acid
$LiClO_4$	Lithium Perchlorate
$LiOH \cdot H_2O$	Lithium hydroxide monohydrate
M	Molar (moles/Liter)
Man	D-Mannose
min	minute(s)
MeCN	Acetonitrile
MeOH	Methanol
MS	Molecular sieves
Na_2CO_3	Sodium carbonate
$NaHCO_3$	Sodium bicarbonate
NaI	Sodium iodide
NaOEt	Sodium ethoxide
NaOMe	Sodium methoxide

NBS	*N*-Bromosuccinimide
p-NO_2-Bz	*para*-Nitro benzoyl
PhH	Benzene
PhMe	Toluene
P_2O_5	Phosphorous pentoxide
SPOS	Solid Phase Organic Synthesis
SPPS	Solid Phase Peptide Synthesis
TBAI	Tetrabutylammonium iodide
TEABr	Tetraethylammonium bromide
TFA	Trifluoroacetate
TFAA	Trifluoroacetic anhydride
TMSBr	Bromo trimethylsilane
TMSI	Iodo trimethylsilane

Abstract

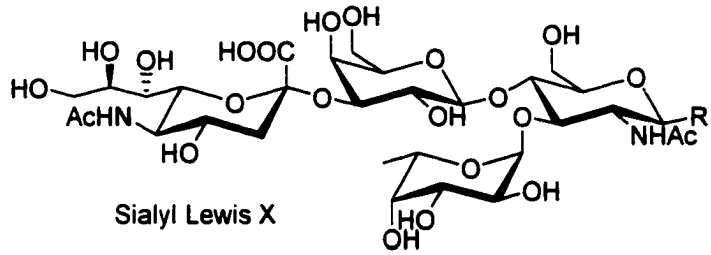
Glycosyl iodides have proven to be highly efficient and stereospecific glycosyl donors. Unfortunately with such high reactivity, they possess short shelf lives. Glycosyl bromides, on the other hand, are more robust than their iodo-counterparts. But, glycosylations using glycosyl bromides in the absence of Lewis acid catalysts are slow. Recently, we have demonstrated conditions augmenting glycosylations involving glycosyl bromides to levels matching the efficiency and stereospecificity of glycosyl iodides. Results of our studies will be discussed.

Introduction

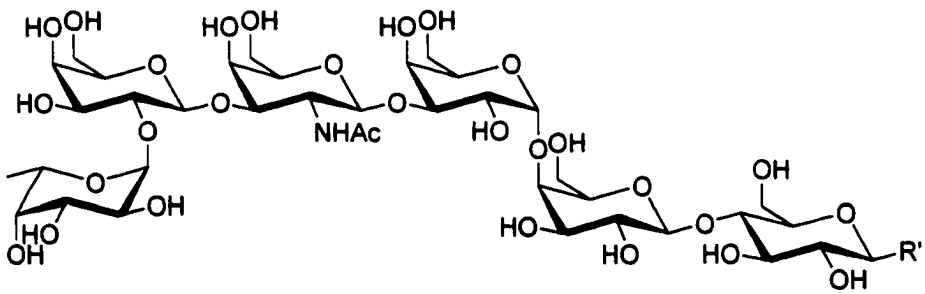
Of the three major classes of biooligomers: polypeptides, oligonucleotides, and oligosaccharides, carbohydrate polymers have seen the least amount of attention in research. This is due to views that oligosaccharides participate primarily as a source of fuel to maintain our livelihood and supporting material for proteins in post-transcriptional glycosylation processes. The lack of research has limited the scope of our knowledge into the biological functions of carbohydrates. With the emergence of glycobiology, which aims to elucidate the role of carbohydrates in influencing the properties of proteins to which they are attached and in recognition events,[1] the biological importance of sugars has gained new perspectives and exciting reevaluations. Apart from the aforementioned, reports have shown carbohydrates, as part of glycoconjugates, to function as: receptors[2,3] for microorganisms, toxins, and antibodies, modulators of protein function,[4] and mediators of cellular adhesion and recognition processes.[5] Glycoconjugates possess protein, lipid, or phospholipid components linked to oligosaccharides; the carbohydrate moieties of these compounds are of equal importance to the biological function.[6] The isolation of oligosaccharides, which mediate such processes, may at times be difficult; as a result, chemical preparation of these targets is a route also taken. This has lead to a resurgence of interest in synthetic carbohydrate chemistry.

Spectacular achievements in oligosaccharide syntheses include sialyl Lewis X[7] and Globo H,[8, 9] a human breast cancer antigen, **Figure 1**. Common among the three oligomers shown are the glycosidic linkages and the large number of hydroxyl groups. When assembling these oligomers, a proper protection scheme must be employed to

prevent the occurrence of unwanted side reactions. Furthermore, a method to stereospecifically link the saccharides is also required, **Figure 2**.



Sialyl Lewis X



Hexasaccharide moiety of Globo H

Figure 1: Biologically Active Oligosaccharides: Tetrasaccharide sialyl Lewis X, where R is a lipid, is expressed on the surface of leukocytes and participates in cellular adhesion processes. The hexasaccharide moiety of glycosphingolipid Hakomori MBr1 antigen that specifically binds breast tumors.

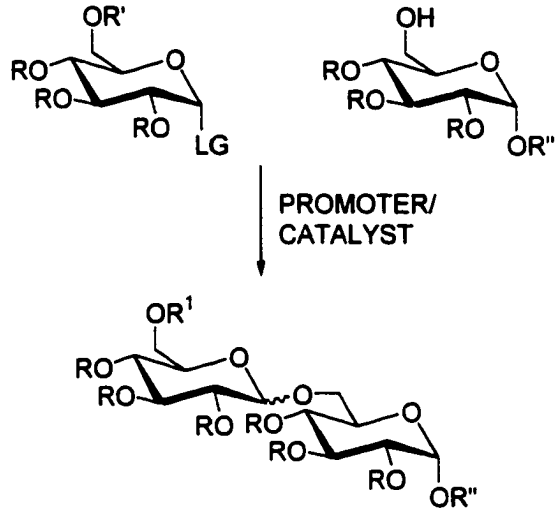


Figure 2: Protection Scheme and Linking Saccharides To glycosidically link two saccharides (1 6), the groups at positions 2, 3, & 4 require robust protecting groups such as benzyls, and the protecting groups at positions 1 & 6 should be temporary groups and orthogonal to the benzyls such as acetates. The saccharide with a leaving group (LG) at C-1, of the glycosyl donor, can be coupled to the hydroxyl at C-6, of the glycosyl acceptor, with assistance from promoters or catalysts.

Many glycosylation strategies now exist to generate *O*-glycosidic linkages, which we owe to the pioneering work of: Fischer,[10] Köenigs and Knorr,[11] Helferich and Olst,[12] Lemieux,[13] Paulsen,[14] Schmidt,[15] Kahne,[16] Danishefsky[17] and others. Of the many glycosylation methods reported, those employing glycosyl halides as donors are arguably well established.

Synthetic Applications of Glycosyl Chlorides and Bromides

Köenigs and Knorr were the first to demonstrate the utility of glycosyl chlorides and bromides as donors in 1901.[11] The solvolyses of per-acetylated α-D-glycopyranosyl chlorides and bromides with alcohols in the presence of insoluble silver catalysts, Ag_2O and Ag_2CO_3, classically illustrate the Köenigs-Knorr reaction, **Figure 3**. The stereochemical outcome of this reaction is dependent upon the nature of the donor, acceptor, and most importantly the catalyst. Glycosylations with insoluble silver promoters generally proceed via a direct displacement of the α-halide to provide a β-glycoside.[12] Many variants of the Köenigs-Knorr reaction now exist which employ soluble silver catalysts, such as: AgOTf[18, 19] and $AgClO_4$[20] or soluble mercury catalysts like $Hg(CN)_2$ and $HgBr_2$ (Helferich conditions).[21] Glycosylations using soluble catalysts generally proceed through an oxonium intermediate;[22] in turn, the participating or non-participating nature of the protecting group at C-2 plays a large role in the stereochemical outcome. Several reviews summarize the application of these methods.[23, 24, 25]

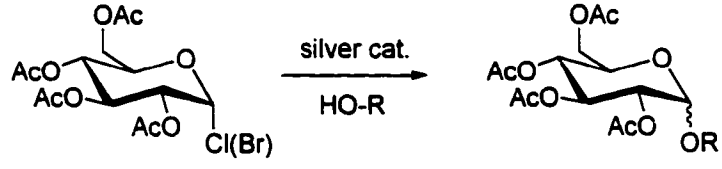


Figure 3: The Köenig's-Knorr reaction uses insoluble silver catalysts such as: Ag_2O and Ag_2CO_3 to promote glycosylations. On the other hand, use of soluble catalyst such as: $Hg(CN)_2$ and $HgBr_2$ is referred to as Helferich conditions.

Glycosylations of glycosyl halides in the absence of Lewis acid promoters, on the other hand, are quite slow. In their attempts to stereospecifically form α-linked glycosides, Lemieux and coworkers (1975) discovered the catalytic activity of tetraalkylammonium halides (Et_4NX) in solvolysis reactions utilizing α-glycosyl bromides as donors.[26] With a non-participating protecting group at the C-2 position, rate enhancements and increased stereocontrol of their glycosylations were observed when activated with Et_4NBr, **Figure 4**.

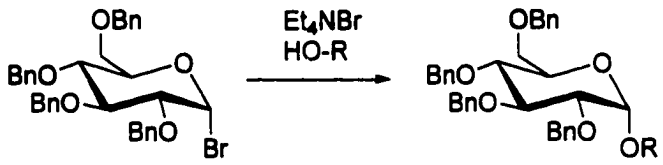


Figure 4: Et_4NBr Catalyzed Glycosylations: Lemieux and coworkers discovered that for glycosylations involving glycosyl bromides an external source of halides can catalyze glycosylations and stereoselectively lead to formation of α-linked glycosides.

Several years earlier, Lemieux reported that α-glycosyl halides exist in equilibrium with the less stable yet more reactive β-glycosyl halides, **Figure 5**.[27] In accord with Le Châtelier's principle, excess bromide ions, provided by Et_4NBr, force the equilibrium to shift toward the less stable β-glycosyl bromides. Fortunately, β-glycosyl bromides, due to conformational destabilization resulting from the anomeric effect, more efficiently undergo nucleophillic attack to form α-linked *O*-glycosides when compared to α-glycosyl bromides.[21, 24, 28, 29]

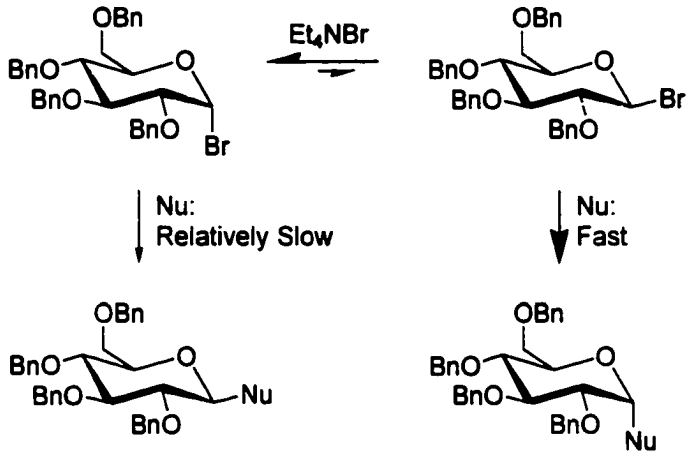


Figure 5: Glycosyl Halides: α/β Equilibrium: With an external source of bromide ions, perbenzylated α-glucosyl bromide can be anomerized to the more reactive perbenzylated β-glucosyl bromide.

These halide-catalyzed conditions provide an attractive alternative to utilization of harsh Lewis acids as promoters of the Köenigs-Knorr and Helferich reactions. But, long reaction times are commonly seen with glycosyl bromides and chlorides. The reactivity of glycosyl halides depends upon: (1) the protecting groups, whereby electron donating benzyl ethers are more activating than benzoyl and acyl esters, and (2) the halide, with the following trend: fluorides<chlorides<bromides<iodides. With poorer leaving groups than chloride and bromide counterparts, glycosyl fluorides are remarkably stable and can be easily handled. However, glycosyl fluorides require strong Lewis acid promoters such as the combination of $SnCl_2$ and $AgClO_4$ along with benzyl protecting groups. In contrast, glycosyl iodides were long thought to be too reactive for any useful synthetic purposes,[23, 30, 31, 32] until the recent work of Gervay-Hague and coworkers.[33, 34]

Glycosyl Iodides

Fischer and Fischer, in 1910, first reported the preparation of 1-iodo-2,3,4,6-tetra-*O*-acetyl glucopyranose[35] through treatment of β-penta-*O*-acetyl glucopyranose with anhydrous HI in glacial HOAc, **Figure 6**. The electron-withdrawing nature of the acetyl protecting groups sufficiently stabilized the glucosyl iodide to allow for recrystallization from petroleum ether in 54% isolated yield. Although Fischer and Fischer described the glucosyl iodide as unstable and recommended immediate use upon isolation, it can be stored for several weeks in a dessicator with P_2O_5. Under Köenigs-Knorr conditions, using Ag_2CO_3 as a catalyst, 1-iodo-2,3,4,6-tetra-*O*-acetyl glucopyranose was reacted with methanol to form the 2,3,4,6-tetra-*O*-acetyl-β-*O*-methyl-glycoside, **Figure 6**. Optical data showed that the product was impure. However and more importantly, this was the first demonstration of glycosyl iodides serving as glycosyl donors.

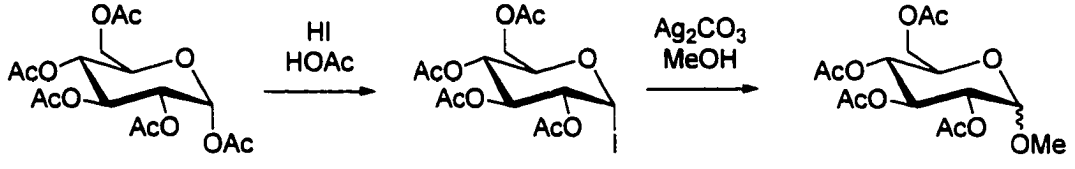


Figure 6: First Preparation of Glucosyl Iodide: Fischer and Fischer synthesized peracetylated glucosyl iodide and demonstrated its utility as a glycosyl donor.

Fischer and Zemplén also synthesized 1-iodo-hepta-*O*-acetyl-cellobiose following the same protocol.[36] Several other groups applied this method in the preparation glycosyl iodides from the per-acetylated sugars.[37]

Glycosylations via *in situ* Formation of Glycosyl Iodides

Since the initial work of Fischer and coworkers on glycosyl iodides, scattered reports have appeared in the literature, showing poor and unpromising results.[38, 39, 40] In 1974, Kronzer and Schuerch were the first to synthesize per-benzylated glycosyl iodides, but they did not attempt isolation for characterization.[41] It was widely accepted that per-benzylated glycosyl iodides readily undergo hydrolysis because the electron-donating nature of the benzyl protecting groups. Their strategy was to form the glycosyl iodide *in situ* with concomitant solvolysis in methanol. Through application of the Finkelstein reaction, the per-benzylated glycosyl iodides were prepared by treatment of per-benzylated α-glycosyl chlorides with excess sodium iodide. In the presence of methanol and 2,6-lutidine, solvolysis reactions were effected, **Figure 7**. α-Selectivity in the glycosylations was observed.

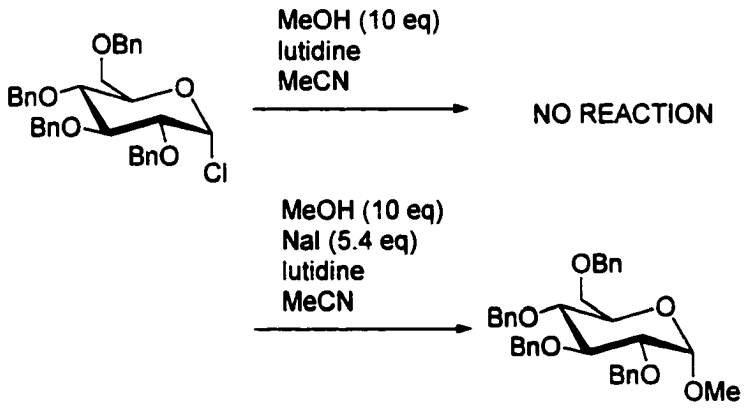


Figure 7: Solvolysis of Perbenzylated Glycosyl Halides: Kronzer and Schuerch demonstrated that *in situ* anomerization of unreactive glucosyl chlorides to glucosyl iodides, using NaI proved to enhance reaction rates and stereocontrol.

It is plausible to suggest that after an S_N2 displacement of the α-chloride to generate the β-glycosyl iodide, concomitant nucleophilic displacement of the β-glycosyl iodide could lead to two other relatively more stable compounds: (1) the α-*O*-methyl glycoside or (2) the α-glycosyl iodide, **Figure 8**. In using a large excess of iodide ions, one would expect the equilibrium between the α- and β-glycosyl iodides to exist while the chloride ions remain as spectator ions, due to the higher nucleophilic nature of iodide over chloride ions. Furthermore, the excess of iodide ions would also force the equilibrium toward the more reactive β-glycosyl iodide. These conditions resemble those of glycosyl bromides with excess bromide ions shown in the Lemieux findings. With glycosyl bromides, one would expect the α-*O*-methyl glycoside to be formed selectively and this is also the case with the glycosyl iodides. In repeating the glycosylation in the absence of NaI, the reaction does not proceed. These results prompted many other groups to employ glycosyl iodides, which were generally formed *in situ*, as donors in their glycosylations,[42, 43] but the perception of glycosyl iodides being too reactive for useful synthetic purposes persisted.

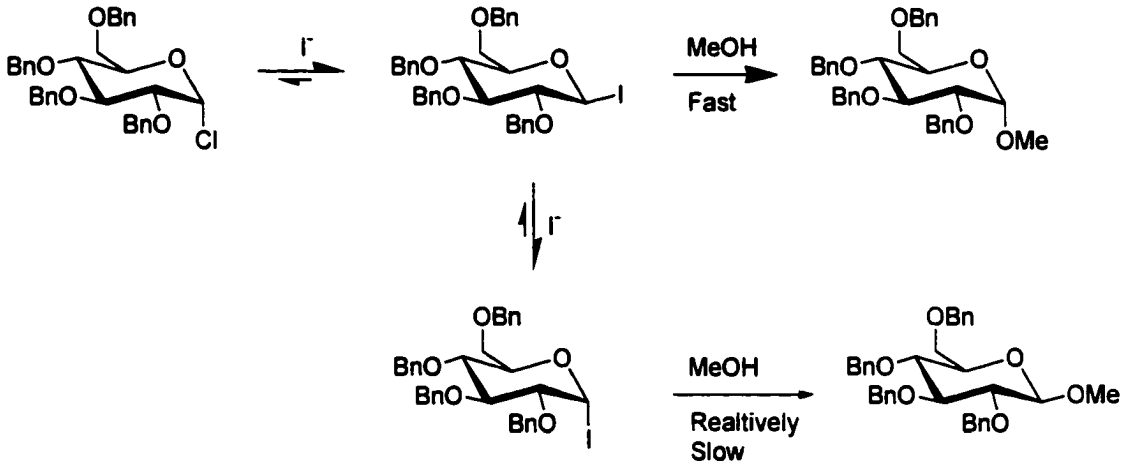


Figure 8: NaI Catalyzed Glycosylations of Glycosyl Chlorides: Proposed catalytic scheme which invokes Le Châtelier's principle through the use of iodide ions to drive the reaction toward the product.

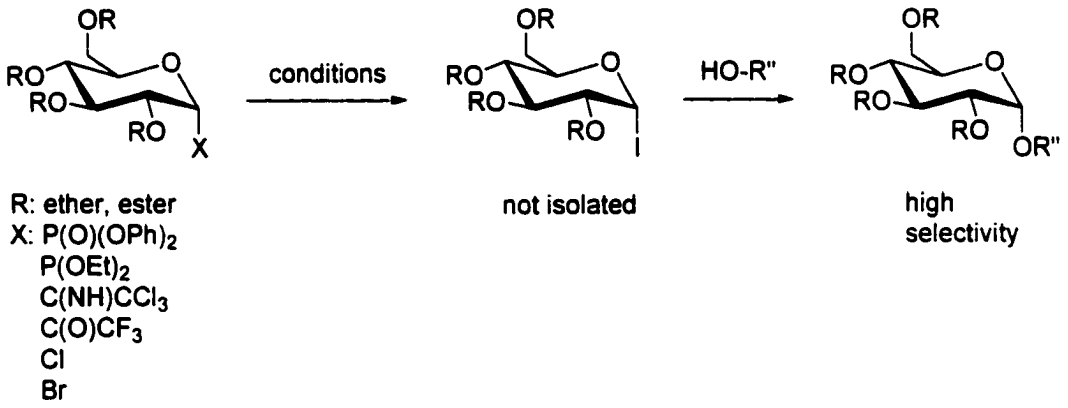


Figure 9: α-*O*-Glycosides From Glycosyl Iodides Formed *in situ*: Recently, several groups also employed *in situ* generation of glycosyl iodides from a wide array of compounds to enhanced their glycosylations.

Recently, several groups also reported the catalytic activity of iodide ions in the promotion of various glycosylations, **Figure 9**. Schmid and Waldmann demonstrated the

conversion of glycosyl phosphates, imidates, trifluoroacetates, chlorides, and bromides to glycosyl iodides by treatment with LiI or NaI in 1M solutions of $LiClO_4$ in CH_2Cl_2.[41, 44] The glycosyl iodides were then treated with acceptors under neutral conditions to selectively form, in moderate yields, α-*O*-glycosides. Hashimoto and coworkers[42] also reported conditions toward stereospecific formation of α-*O*-glycosides. Starting from an anomeric mixture of glycosyl diethyl phosphites, they used 2,6-di-*t*-butylpyridinium iodide, DTBPI, and TBAI as an activating mixture to generate glycosyl iodides *in situ*. TBAI, as a source of excess iodide ions, also contributed to the stereocontrol observed in the formation of the *O*-glycosides. Meanwhile, glycosylations in the absence of TBAI were sluggish.

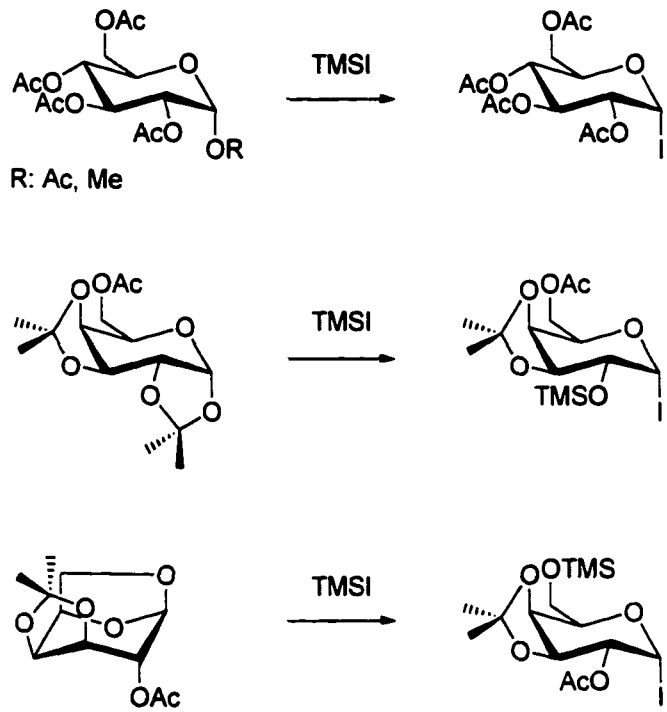
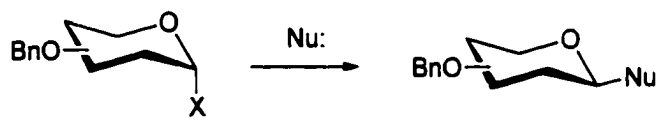


Figure 10: Generation of Glycosyl Iodides Using TMSI: Using TMSI, Thiem and coworkers were able to efficiently generate glycosyl iodides under milder conditions when compared to HI in glacial HOAc.

Despite these elaborate schemes toward implementing glycosyl iodides as donors, isolation of glycosyl iodides for characterization remained difficult. The work of Thiem and Meyer provided a new synthetic route toward the synthesis of glycosyl iodides from anomeric acetates, acetals, methyl glycosides, and anhydrosugars, **Figure 10**.[45] The by-products of these transformations are volatile which provided for facile reaction work-up and a practical means toward obtaining pure glycosyl iodides for characterization. Many other groups have since used TMSI as a highly efficient means toward synthesis of glycosyl iodides.[46, 47, 48] Thiem also demonstrated the preparation of glycosyl bromides in an analogous fashion using TMSBr.[43]

Glycosylations using Isolated Glycosyl Iodides

In attempts to synthesize galactosyl ceramide derivatives, Gervay-Hague and coworkers sought to activate per-acetylated glucopyranose with TMSI followed by nucleophilic displacement with dodecanol. Unfortunately, the reaction did not proceed to a synthetically satisfactory degree. Along with the expected *O*-dodecyl-glycoside a by-product was also isolated after silica gel column chromatography. This product was characterized as 2,3,4,6-tetra-*O*-acetyl glucosyl iodide. In their view, this was a spectacular finding since they too believed that glycosyl iodides are too reactive to be useful.[23, 29, 30, 31] Subsequent review of the early literature convinced them that this was a false belief. With this new perspective on the stability and reactivity of glycosyl iodides, Gervay-Hague and coworkers examined the generation[49] and utility of glycosyl iodides as glycosyl donors.[33]



sugar: Glc, Gal, Man

nuc: NaOPh, NaOCOR, $NaCH(COOEt)_2$, Bu_4NCN, Bu_4NN_3, $KNC_8H_4O_2$

Figure 11: Anionic Additions to Glycosyl Iodides: Gervay-Hague and Hadd demonstrated the wide utility of glycosyl iodides as highly efficient glycosyl donors with a range of nucleophiles under anionic conditions.

In an initial survey, isolated glycosyl iodides were reacted with various nucleophiles under anionic conditions to form *C*-, *N*-, and *O*-glycosides, **Figure 11**.[48] The results showed moderate to high isolated yields with high or exclusive β-selectivity. Gervay-Hague and Hadd then employed glycosyl iodides in a fashion similar to the work of Lemieux and coworkers.[34] Starting from the α-glycosyl iodide, addition of tetrabutylammonium iodide (Bu_4N-I) would form the more reactive β-glycosyl iodide, which upon a S_N2 nucleophilic displacement would provide the α-linked *O*-glycoside, **Figure 12**. On the other hand as iodides are good leaving groups, oxonium intermediates could also be generated from both the α- and β-glycosyl iodides, which selectively undergo α-nucleophilic attack. Both mechanisms are plausible, unfortunately neither have been experimentally verified.

Glycosylations via glycosyl iodides afforded greatly enhanced rates and yields when contrasted with the bromide[25] counterparts. In many instances, reactions that proceeded in days with glycosyl bromides went to completion in minutes or hours with glycosyl iodides. These studies effectively demonstrated the wide utility and efficiency of glycosyl iodides. Yet the use of some glycosyl iodides was still difficult, due to their short shelf lives.

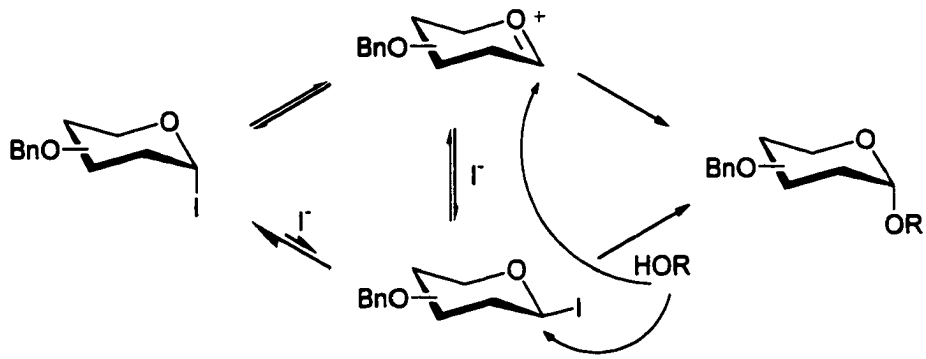
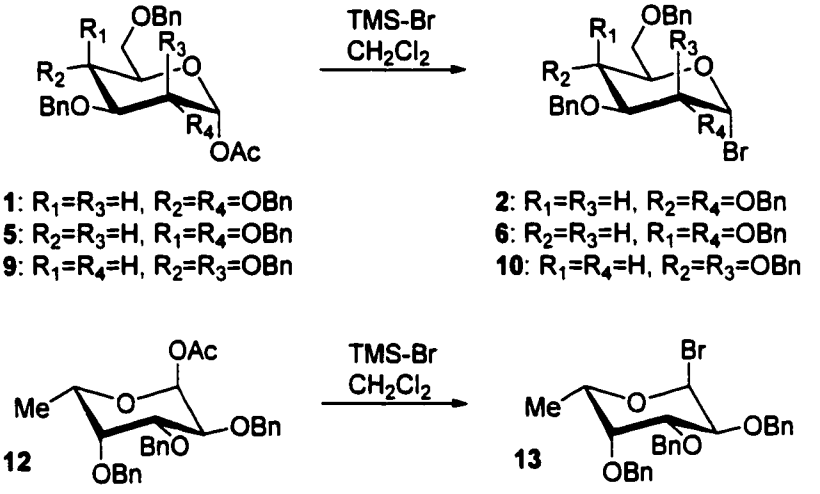


Figure 12: TBAI Catalyzed Glycosyl Iodide Glycosylations: Proposed mechanism for iodide catalyzed glycosylations, where an α-glycosyl iodide can be anomerized to the more reactive β-glycosyl iodide which undergoes nucleophilic attack to form the α-linked product. An oxonium intermediate, generated from both α and β-glycosyl iodides, can also undergo nucleophilic attack to form the α-linked product.

Glycosyl Iodides From Glycosyl Bromides

In an attempt to combine the advantage of glycosyl bromide stability with that of glycosyl iodide reactivity, we investigated reactions involving glycosyl bromides treated with Bu_4N-I to generate β-glycosyl iodides *in situ* followed by coupling to an acceptor. To facilitate accurate comparisons to the work of Lemieux[25] and coworkers, we also examined glycosylations using 1-bromo-2,3,4,6-tetra-*O*-benzyl-α-D-gluco-, galacto-, and manno-α-D-fucopyranoses and 1-bromo-2,3,4-tri-O-benzyl-α-L-fucopyranose as glycosyl donors and using 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (DAG) as a glycosyl acceptor. The bromides were readily prepared by treating the 1-*O*-acetyl-2,3,4,6-tetra-*O*-benzyl-α-D-glycopyranoses and 1-*O*-acetyl-2,3,4-tri-*O*-benzyl-α-L-fucopyranose: **1**, **5**, **9**, **12**, with bromo trimethylsilane[43] in dichloromethane to afford the corresponding bromides: **2**, **6**, **10**, **13**, in quantitative yields as verified through ^{1}H-NMR and ^{13}C-NMR spectroscopy, **Figure 13**. We were able to store these bromides in the freezer for extended periods without degradation as confirmed through ^{1}H-NMR and ^{13}C-NMR spectroscopy.



1: R_1=R_3=H, R_2=R_4=OBn
5: R_2=R_3=H, R_1=R_4=OBn
9: R_1=R_4=H, R_2=R_3=OBn

2: R_1=R_3=H, R_2=R_4=OBn
6: R_2=R_3=H, R_1=R_4=OBn
10: R_1=R_4=H, R_2=R_3=OBn

12

13

Figure 13: Preparation of Glycosyl Bromides: 1-Bromo-perbenzylated-glycopyranoses can be synthesized in quantitative yield from 1-*O*-acetyl-perbenzylated-glycopyranoses using TMSBr (2 x 4.0 eq. x 2 h.).

With the glycosyl bromides in hand, we envisioned that β-glycosyl iodides could be readily accessible through treatment of the bromide with iodide ions. Starting from α-glycosyl bromides, **2**, **6**, **10**, and **13**, treatment with Bu_4NI could lead to the formation of α-glycosyl iodides, **2b**, **6b**, **10b**, and **13b**, **Figure 14**.

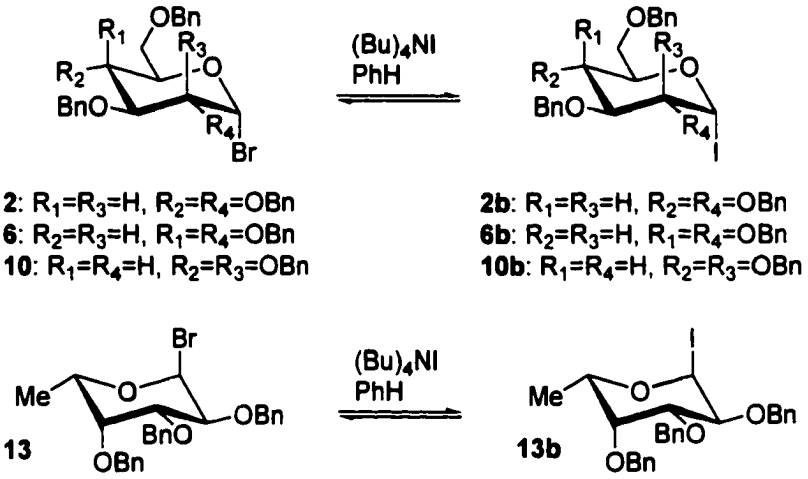


Figure 14: Anomerization of Glycosyl Bromides to Glycosyl Iodides: In order to generate glycosyl iodides, we intended to treat the glycosyl bromides with TBAI.

To test whether the events in **Figure 14** occur, we conducted NMR experiments in hopes to visualize this glycosyl halide anomerization process. Perbenzylated galactosyl bromide (1.0 eq.), **6**, dissolved in CD_2Cl_2 was transferred to an NMR tube containing TBAI (0.5 eq.). ^{1}H-NMR spectrum was periodically taken on a 500 MHz DRX Bruker spectrometer. Upon addition of TBAI, several new peaks appear in the ^{1}H-NMR spectrum. The most distinctive of which was a doublet at 7.04 ppm (J = 3.8 Hz), which corresponded to the C-1 proton of **6b**. At this catalytic amount of TBAI, the integrations of the anomeric protons of **6** and **6b** showed that only 12% of the glycosyl halide mixture consisted of α-glycosyl iodide, **6b**. Despite the 0.5 molar equivalents of TBAI, **6b** did not comprise half of the glycosyl halide mixture. This indicated that the equilibrium between **6** and **6b** lie with the α-glycosyl bromide, **6**. After 5.5 h stored at room temperature, the constituents of the glycosyl halide mixture remained relatively the

same compared to the initial ^{1}H-NMR spectrum. The population of **6b** slightly rose to 14% of the mixture. Knowing that this anomerization scheme, **Figure 14**, provided α-glycosyl iodides, we needed to investigate whether the levels of glycosyl iodides formed would facilitate efficient glycosylations. Provided that **2b**, **6b**, **10b**, and **13b** behave similarly to those reported by the aforementioned groups, we expected similar stereocontrol in the products. The remaining question was whether the events in **Figure 14** would result in diminished overall glycosylation rates relative to glycosylations with purified glycosyl iodides. The glycosylations were carried out using varying amounts of Bu_4NI to catalyze the reactions in order to optimize glycosylation conditions, **Figure 15**.

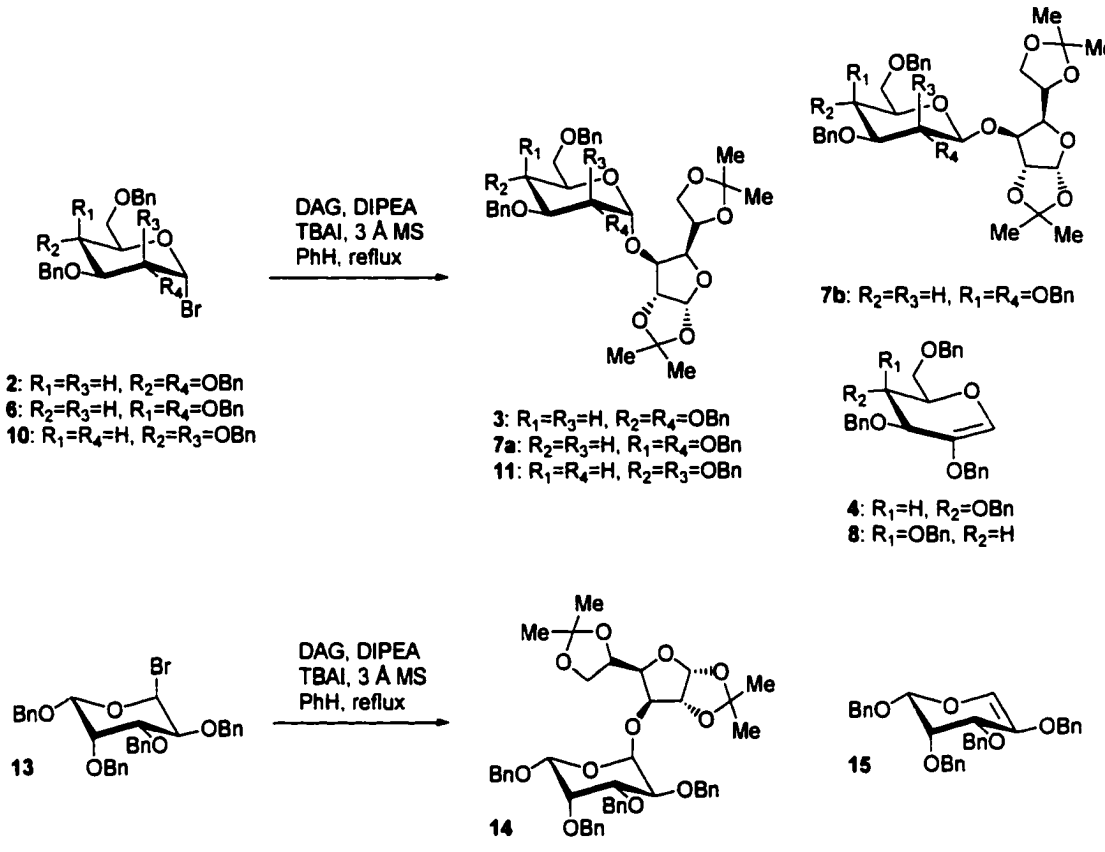


Figure 15: Glycosylations via *in situ* Anomerization: Using DAG (0.75 eq.), Hünig's base (0.75 eq.), 3 A MS. and varying amounts of TBAI with the glycosyl bromides (1.0 eq.), we surveyed the conditions for optimal glycosylations.

Summarized in **Figure 16** are the results of our studies involving glycosylations through *in situ* formation of glycosyl iodides from glycosyl bromides. Using the glycosyl donors (**2**, **6**, **10**, **13**) in excess (1.0 eq.), Bu_4NI (0.50 eq.), Hünig's base (0.75 eq.), and 3 Å MS to pick up residual water under reflux facilitated efficient and stereoselective attack of the nucleophile, DAG (0.75 eq.).

Entry	Donor (1.0 eq.)	Catalyst	Cat. Eq.	Time (h)	Product	% Yield	% Elim.***
1	**Glc-I (2b)***	$(Bu)_4NI$	1.5	1.5	**3**	45	43
2	**Glc-Br (2)**	$(Bu)_4NI$	1	1.5	**3**	26	26
3	**Glc-Br (2)**	$(Bu)_4NI$	0.5	3	**3**	71	34
4	**Glc-Br (2)**	$(Bu)_4NI$	0.1	3	**3**	25	34
5	**Glc-Br (2)****	$(Et)_4NBr$	1	48	**3**	42	nr
6	**Gal-I (6b)***	$(Bu)_4NI$	1.5	5.5	**7a/b**	93 (9:1, α:β)	6
7	**Gal-Br (6)**	$(Bu)_4NI$	1	5.5	**7a/b**	61 (8:1, α:β)	16
8	**Gal-Br (6)**	$(Bu)_4NI$	0.5	9	**7a/b**	94 (8:1, α:β)	8
9	**Gal-Br (6)**	$(Bu)_4NI$	0.1	10	**7a/b**	55 (8:1, α:β)	33
10	**Gal-Br (6)****	$(Et)_4NBr$	1	48	**7**	62	nr
11	**Man-I (10b)***	$(Bu)_4NI$	1.5	5.5	**11**	67	31
12	**Man-Br (10)**	$(Bu)_4NI$	1	5	**11**	42	33
13	**Man-Br (10)**	$(Bu)_4NI$	0.5	8	**11**	70	15
14	**Man-Br (10)**	$(Bu)_4NI$	0.1	8	**11**	56	37
15	**Man-Br (10)****	$(Et)_4NBr$	nr	nr	nr	nr	nr
16	**Fuc-I (13b)***	$(Bu)_4NI$	1.5	3	**14**	62	0
17	**Fuc-Br (13)**	$(Bu)_4NI$	1	4	**14**	60	6
18	**Fuc-Br (13)**	$(Bu)_4NI$	0.5	6	**14**	75	0
19	**Fuc-Br (13)**	$(Bu)_4NI$	0.1	6	**14**	60	14
20	**Fuc-Br (13)****	$(Et)_4NBr$	1	48	**14**	47	nr

Figure 16: Table of Results: Comparison of the results of our survey with those of Lemieux and coworkers and Gervay-Hague and Hadd. nr signifies not reported. * shows the work of Gervay-Hague and Hadd. ** denotes the work of Lemieux and coworkers. *** the percent elimination is based upon the amount of glycosyl donor used which is in excess.

Initially, we attempted the conditions described in entry 17; the results appeared promising with an acceptable 60% yield and a small degree of elimination. Using 1.0 eq. of Bu_4NI, glycosyl bromide **13** readily afforded glycosyl iodide **13b**, which led to **14**, **Figure 17**. Unfortunately, the levels of glycosyl iodide generated also facilitated elimination to **15**.

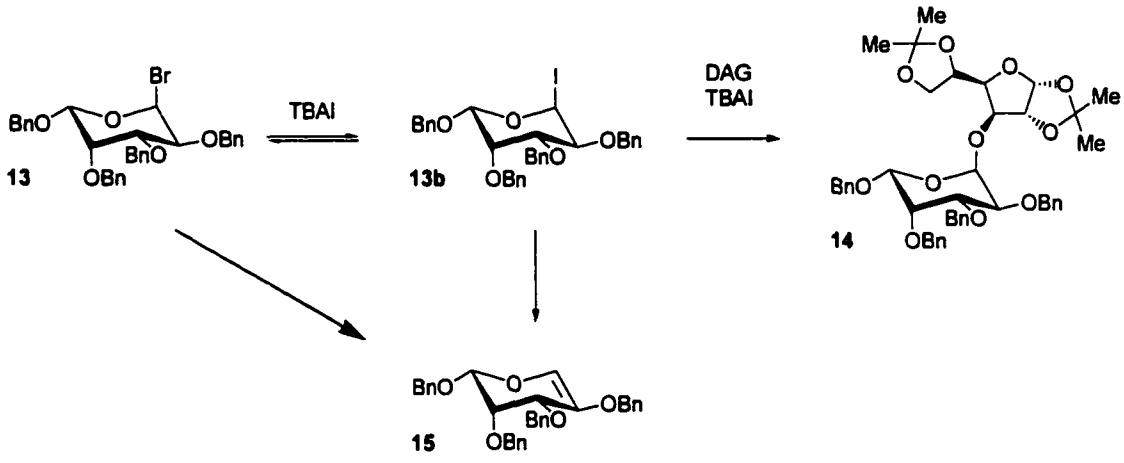


Figure 17: Fucosylation with DAG: Under varying levels of TBAI, the concentration of 13b changes which affects the course of glycosylations.

In an effort to minimize elimination through a reduction of glycosyl iodide concentration, we decreased the amount of Bu_4NI. Lowering the catalyst equivalent to 0.50 (entry 18) was beneficial; it effectively suppressed elimination to an undetectable degree and also enhanced the yield of **14** to a respectable 75%. Further reduction of catalyst amounts to 0.1 equivalents resulted in less efficient glycosylations (entry 19) showing elimination and decreased yield. We believe that 0.10 eq. of TBAI did not provide a sufficient concentration of glycosyl iodide to afford **14**; similarly, the less reactive glycosyl bromide could also undergo elimination.

This glycosylation survey was extended to carbohydrates **2**, **6**, and **10**. In general, conditions employing 0.5 equivalents of Bu_4NI appeared to be optimal (entries **3**, **8**, **13**) and reacted on the same order as glycosylations from purified glycosyl iodide, **2b**, **6b**, **10b**, and **13b**. Once again, decreased yield and increased elimination resulted with other conditions. Entry 3 stood out among the group for it demonstrated a noticeable

enhancement even compared to entry 1. The yield was substantially increased and elimination was suppressed. These conditions, glycosyl bromide glycosylations with Bu_4NI assistance showed substantial improvement when compared to the initial works of Lemieux and coworkers and further improved the work of Gervay-Hague and Hadd. Apart from the aforementioned advantages, one drawback to this method still remains. Generation of the glycosyl bromide through use of TMSBr is inefficient when compared to formation glycosyl iodide with TMSI. Treatment of 1-*O*-acetyl-perbenzylated-α-D-glycopyranose with 1.1 eq. TMSI in CH_2Cl_2 for 45 min. afforded 1-iodo-perbenzylated-α-D-glycopyranose in quantitative yield whereas formation of 1-bromo-perbenzylated-α-D-glycopyranose from 1-*O*-acetyl-perbenzylated-α-D-glycopyranose required 8.0 eq. of TMSBr in CH_2Cl_2 and 4 h reaction time.

Conclusion

Gervay-Hague demonstrated glycosyl iodides to be highly efficient and stereoselective donors. These results illustrated that glycosylations using glycosyl iodides, formed *in situ* via glycosyl bromides with Bu_4NI, are equally efficient and stereoselective, an enhancement compared to the Lemieux conditions. Prolonged storage of glycosyl bromides as compared to glycosyl iodides, which mandate usage immediately after formation, proved to be advantageous. The efficiency and stereospecificity combined with the stability of glycosyl bromides provided us with attractive means toward synthesis of oligosaccharides.

Experimentals

General Preparation of Glycosyl Bromides: **2**[25, 50, 51, 52], **6**[25, 53] **10**[53], **13**[25, 54]

1-*O*-acetyl-2,3,4,6-tetra-*O*-benzyl-α-D-galactopyranose, **5**, (45 mg, 0.077 mmol, 1.0 eq.) was dissolved in dry CH_2Cl_2 (2 mL) and placed under argon. Upon addition of TMSBr (47 mg, 0.31 mmol, 4.0 eq.) via syringe, the mixture was allowed to react at room temperature. After 2 h, dry toluene was syringed into the reaction flask followed by removal of the solvents *in vacuo*. The resulting light yellow oil was re-dissolved in dry CH_2Cl_2 (2 mL) and re-subjected to TMSBr (47 mg, 0.31 mmol, 4.0 eq.) for an additional 2 h to ensure complete reaction, verified through TLC with 4:1 hexanes: ethyl acetate. Addition of dry toluene followed by removal of the solvents *in vacuo* afforded a yellow oil, 1-bromo-2,3,4,6-tetra-*O*-benzyl-α-D-galactopyranose, **6**, in quantitative yield as verified through ^{1}H-NMR and ^{13}C-NMR. Spectroscopy data are in agreement with those previously reported. The glycosyl bromide was then redissolved in benzene and stored in the freezer.

^{1}H-NMR anomerization study

1-Bromo-2,3,4,6-tetra-*O*-benzyl-α-D-galactopyranose, **6**, was prepared from 1-*O*-acetyl-2,3,4,6-tetra-*O*-benzyl-α-D-galactopyranose, **5**, (45 mg, 0.077 mmol, 1.0 eq.) according to the procedure described above. The glycosyl bromide, **6**, was redissolved in CD_2Cl_2 and the solution was transferred into an NMR tube containing TBAI (xx mg, xx mmol, 0.50 eq.). ^{1}H-NMR spectra were then taken at ambient temperature at times 0 min, 5 min, 10 min, 20 min, and 5.5 h on a 500 MHz DRX Bruker spectrometer.

Preparation of 1,2:5,6-*Di*-*O*-isopropylidene-α-D-glucofuranos-3-yl 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranose: **3**[25, 49, 55, 56, 57]

1-Bromo-2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranose, **2**, (45 mg, 0.074 mmol, 1.0 eq.) was dissolved in dry benzene and transferred to a flask containing DAG (15 mg, 0.056 mmol, 0.75 eq.), TBAI (14 mg, 0.037 mmol, 0.50 eq.), and powdered 3 Å MS (53 mg). Following the addition of Hünig's base (10 μL, 0.06 mmol, 0.75 eq.), the solution was refluxed for 3 h. Removal of the solvent *in vacuo* then silica gel column chromatography, using 7.5:1 hexanes: ethyl acetate, afforded 31 mg of **3** (71% yield) and 13 mg of **4** (34% yield). Products were verified through comparison to previously reported spectroscopic data.

Preparation of 1,2:5,6-*Di*-*O*-isopropylidene-α-D-glucofuranos-3-yl 2,3,4,6-tetra-*O*-benzyl-α-D-galactopyranose: **7a/b**[25, 49, 55, 56]

1-Bromo-2,3,4,6-tetra-*O*-benzyl-α-D-galactopyranose, **6**, (45 mg, 0.074 mmol, 1.0 eq.) was dissolved in dry benzene and transferred to a flask containing DAG (15 mg, 0.056 mmol, 0.75 eq.), TBAI (14 mg, 0.04 mmol, 0.50 eq.), and powdered 3 Å MS (56 mg). Following the addition of Hünig's base (10 μL, 0.06 mmol, 0.75 eq.), the solution was refluxed for 9 h. Removal of the solvent *in vacuo* then silica gel column chromatography, using 7.5:1 hexanes: ethyl acetate, afforded 36 mg of **7a** (82.5% yield), 5 mg of **7b** (11.5% yield), and 3 mg of **8** (8% yield). Products were verified through comparison to previously reported spectroscopic data.

Preparation of 1,2:5,6-*Di*-*O*-isopropylidene-α-D-glucofuranos-3-yl 2,3,4,6-tetra-*O*-benzyl-α-D-mannopyranose: **11**[49, 58]

1-Bromo-2,3,4,6-tetra-*O*-benzyl-α-D-mannopyranose, **10**, (82 mg, 0.14 mmol, 1.0 eq.) was dissolved in dry benzene and transferred to a flask containing DAG (26 mg, 0.10 mmol, 0.75 eq.), TBAI (25 mg, 0.07 mmol, 0.50 eq.), and powdered 3 Å MS (62 mg). Following the addition of Hünig's base (18 μL, 0.10 mmol, 0.75 eq.), the solution was refluxed for 8 h. Removal of the solvent *in vacuo* then silica gel column chromatography, using 7.5:1 hexanes: ethyl acetate, afforded 55 mg of **11** (70% yield) and 10 mg of **4** (15% yield). Products were verified through comparison to previously reported spectroscopic data.

Preparation of 1,2:5,6-*Di*-*O*-isopropylidene-α-D-glucofuranos-3-yl 2,3,4,6-tetra-*O*-benzyl-α-L-fucopyranose: **14**[49]

1-Bromo-2,3,4-tri-*O*-benzyl-α-L-fucopyranose, **13**, (66 mg, 0.14 mmol, 1.0 eq.) was dissolved in dry benzene and transferred to a flask containing DAG (27 mg, 0.10 mmol, 0.75 eq.), TBAI (26 mg, 0.07 mmol, 0.50 eq.), and powdered 3 Å MS (63 mg). Following the addition of Hünig's base (18 μL, 0.10 mmol, 0.75 eq.), the solution was refluxed for 6 h. Removal of the solvent *in vacuo* then silica gel column chromatography, using 8:1 hexanes: ethyl acetate, afforded 36 mg of **14** (75% yield). Products were verified through comparison to previously reported spectroscopic data.

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