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The Synthesis Of Stannylated C1 Nucleophilic Monosaccharides For Use In The Stille Coupling Reaction

Michael Rourke
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The Synthesis Of Stannylated C1 Nucleophilic Monosaccharides For Use In The Stille Coupling Reaction

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Undergraduate Thesis
October 30, 2017

University of Colorado at Boulder
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Abstract

The investigation sought to determine whether a transition metal coupling reaction with aryl halides could be utilized to form glycoconjugates, carbohydrate-containing molecules, specifically C-Aryl Glycosides. Our successful novel application in glycochemistry employs the Stille coupling reaction and improves the viability of accessing a range of glycogonjugates for biological and therapeutic screening.\(^1\) The reaction maintains exceptional retention of configuration from the carbohydrate-metal bond in the completed \(sp^3\) carbon – \(sp^2\) carbon bond of the produced glycoside. A synthesized library of C-aryl Glycosides was established utilizing this methodology; from which a selective schema was submitted for publication. This technology provides a route to discrete carbohydrate building blocks that can be assembled with minimal reagents and moderate synthetic knowledge. These building blocks can then be stereo-specifically attached to molecules of interest under a set of general catalytic conditions; expediting the investigation of carbohydrate’s role in biochemical processes that was limited by substrate dependent laborious processes of glycoconjugate formation.
Introduction

Developing a synthetic library of carbohydrate molecules is necessary for advancement in glycoinformatics as there is no template like in DNA, RNA, and proteins, and requires chemical synthesis. Developing the glycomic library has implications for a range of diseases and healthy biology and is a priority to emphasize the importance in the development of new glycomic technology. With the expansion of the glycomic library, including more C-aryl glycoside discoveries, new drug targets can utilize this specific glycoside as they are carbohydrate analogues stable to enzymatic and acid hydrolysis.

Research was founded on the hypothesis that transition metal coupling reactions have potential applications that can revolutionize glycochemistry, with the capability to modify the current approach to the chemistry of glycoconjugate formation. Our methodology demonstrates carbohydrates can be coupled in transition metal coupling reactions with observable complete retention of configuration, that is the configuration of a carbon-metal bond can be absolutely retained in a palladium catalyzed coupling reaction with an electrophile. The objective was to develop a viable route to perform stereospecific coupling reactions of carbohydrates with a multitude of aryl-halide containing molecules. The addition of carbohydrate groups to organic compounds is important as it improves pharmacokinetic properties such as solubility and stability. Moreover, carbohydrates are responsible for mediating numerous cell signaling events such as nutrient sensing, protein degradation, and gene expression.

Traditional methods of carbohydrate synthesis are limited because of arduous synthetic schemes needed to prepare the compounds of interest. Currently the preparation of novel carbohydrate molecules is laborious and primarily restricted to specialized synthetic laboratories.
utilizing anomeric halides and nucleophilic carbon sources.\(^{(8)}\) Furthermore, the application of Friedel-Crafts electrophilic substitution of the aromatic ring by variable glycans in the presence of a Lewis-Acid has been employed, exhibiting limited substrate dependent diastereoselectivity.\(^{(8a)}\)

The chemistry performed in this project enables the synthesis of complex carbohydrate entities in much shorter and efficient ways, and provides a viable route for carbon-carbon bond formation in the presence of fully deprotected sugars. This novel ground work has the capability to enable efficient synthesis of complex carbohydrate-bound targets and provides opportunity for further investigation into selectively applying and refining methodologies of stereoretentive carbon-carbon bond formation. This technology could create a range of new therapeutics and diagnostic applications by providing academic researchers and industry an efficient general protocol that eases the synthetic production of previously complicated carbohydrate reactions that were inherently hard to isolate, purify, and characterize due to glycoconjugates of variable epimeric purity.

**Background**

Possible therapeutic applications within glycochemistry will be imperative in research, industry, and healthcare. Furthermore, as glycans are involved in pathophysiology of human disease, glycochemical research will have the potential to accelerate the addition of glycans into already significantly characterized biological libraries, leading to novel therapeutics.\(^{(9)}\) As surface-bound carbohydrate entities, glycans enable recognition and intercellular communication; it has been known for almost three decades that the carbohydrates residing on the cell surface and their complementary sugar-specific receptors, lectins, play a key role in intercellular signaling and recognition.\(^{(10)}\)
This cell signaling and communication on the surface of pathogens and mammalian cells can be exploited in antibiotics and as biomarkers in biological processes. Thus the addition of the associated epitopes or glycotopes can be attached to immunologically active peptides to investigate minimally explored therapeutics in cancer.\textsuperscript{(11)} The abundance of bonding configurations that carbohydrates exhibit from their branched structures lends to a unique ability for great variability in signaling potential.\textsuperscript{(12)} However, this potential for multiple branching configurations exacerbates the difficulty of synthetic glycochemistry. Efficient investigation of carbohydrates and their associated biologically significant coupling partners across broad signaling pathways will require the continued development of novel synthetic methodology. This will enable viable production of synthesizable industrial or public libraries of glycoconjugates with complex carbohydrates bound to coupling partners beyond aryl halides, including the addition of C-O, and C-N bond formation methodologies.

The development of methods that produce building blocks that can be reproducibly assembled will allow glycochemistry to meet a “sorely needed” niche in the biosciences.\textsuperscript{(13)} Few methods have provided this reproducibility with the potential to provide carbohydrate building blocks in discrete packages that can be assembled under a simple set of reagents and conditions. Utilizing Stille transition metal coupling reactions, we have shown through the formation of glycosylated aromatic structures that developing carbohydrate building blocks and subjecting them to a set of catalytic conditions can expand the availability of structures for investigation, applications in industry, and discovery of potential therapeutic approaches.

**Exploration of Suzuki-Miyaura coupling**

The project began utilizing Suzuki-Miyaura coupling and attempted to develop a methodology that would provide a novel route to C-Aryl Glycosides. The model system was a C1
carbon that was synthesized by ortho-lithiation of 3,4-di-hydro-2H-pyran. This lithium reagent performed a nucleophilic attack on trimethyl borate and after addition of pinacol, the pinacalato boronic ester MR1 was formed. The double bond was saturated to form a racemic molecule with a coupling nucleophile attached to an sp³ C1 for the Suzuki-Miyaura reaction; this screens for any combination of catalytic conditions for sp³ carbon – sp² carbon bond formation. The racemic boronic ester removes factors of selectivity for C1 configuration in catalytic conditions and delays consideration of retention until the carbon bond formation was established.

**Scheme 1:** Synthetic pathway to the saturated pinocatalo boronic ester MR2 that was subjected to a series of unsuccessful coupling conditions with 3-iodotoluene

![Scheme 1](image)

**Table 1:** A depiction of conditions experimentally determined to be unsuccessful for the pinocatalo boronic ester and two simple aryl halides.

<table>
<thead>
<tr>
<th>Catalyst</th>
<th>Reagent</th>
<th>Conditions</th>
<th>Electrophile</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pd(PPh₃)₄, (10 mol%)</td>
<td>Na₃PO₄ (5 eq.), Dioxane 2ml</td>
<td>Freeze, pump cycle, rt. 25 min</td>
<td>Bromobenzene (1 eq.)</td>
<td>No Product</td>
</tr>
<tr>
<td>Pd(PPh₃)₄, (10 mol%)</td>
<td>Na₃PO₄ (5 eq.), Dioxane 2ml</td>
<td>Freeze, pump cycle, rt. 25 min</td>
<td>3-iodotoluene (1 eq.)</td>
<td>No Product</td>
</tr>
<tr>
<td>Pd(PPh₃)₄, (10 mol%)</td>
<td>Cs₂CO₃ (2 eq.), Dioxane:H₂O (1:1) 40ml (1M)</td>
<td>Freeze, pump cycle, rt. 25 min</td>
<td>3-iodotoluene (1 eq.)</td>
<td>No Product</td>
</tr>
<tr>
<td>Pd(PPh₃)₄, (10 mol%) Unsaturated boronic ester</td>
<td>Cs₂CO₃ (2 eq.), Dioxane:H₂O (1:1) 50ml (0.8M)</td>
<td>Freeze, pump cycle, rt. 25 min</td>
<td>3-iodotoluene (1 eq.)</td>
<td>No Product</td>
</tr>
<tr>
<td>Pd(dpdpf)Cl₂, (10 mol%)</td>
<td>Cs₂CO₃ (2 eq.), CuI (1 eq.), Dioxane 1.5ml (0.16M)</td>
<td>Glove box prep, 100°C O/N</td>
<td>3-iodotoluene (1 eq.)</td>
<td>No Product</td>
</tr>
<tr>
<td>NiBr₂ (10 mol%),</td>
<td>n-Hexanol (2 eq.), t-BuOK (1.4 eq.),</td>
<td>In glove box: A. L (12%),</td>
<td>3-iodotoluene (1 eq.)</td>
<td>No Product</td>
</tr>
</tbody>
</table>
Ligand: CAS 29841-69-8 (12 mol %)
Performed x2 variance of boronic ester equivalence with respect to electrophile
1. 1 eq.
2. 2 eq.

<table>
<thead>
<tr>
<th>Ligands</th>
<th>Solvents</th>
<th>Conditions</th>
<th>Products</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dioxane 1.5 ml (0.16M)</td>
<td>C(10%),dioxane. 30 min rt.</td>
<td>No Product</td>
<td></td>
</tr>
</tbody>
</table>

B. MR2, t-BuOK, n-hexanol.30min rt.
C. Combined, removed,40hr 100°C.

Pd(PPh₃)₄ (5 mol%) Cs₂CO₃(2eq.), Dioxane:H₂O (1:1) Freeze, pump, thaw. Stir 100°C 3-iodotoluene (1 eq.)

Suzuki-Miyaura coupling was a target because of proven research that states pharmaceuticals currently utilizing this method are safe for manufacturing and non-toxic. Furthermore, boron containing compounds and boronic acids were concluded safe and possibly efficacious justifying investigation into their therapeutic value as an active constituent of the final molecule or drug (13).

The unsuccessful coupling of the pinacolato borane MR2 lead to the consideration of a trifluoroborate, as the coupling of the BF₃⁻ nucleophile with aryl-halides has demonstrated has been by Molander et al. (14)

**Scheme 2:** Synthetic pathway from the saturated pinocalato boronic ester MR3 to the trifluoroborate that was subjected to a series of unsuccessful coupling conditions with 3-iodotoluene.
Table 2: Coupling conditions C1-trifluoroborates, proved to be unsuccessful. Note: Dioxane degassed.

<table>
<thead>
<tr>
<th>Catalyst</th>
<th>Reagent</th>
<th>Conditions</th>
<th>Electrophile</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pd(PPh₃)₄ 10%</td>
<td>Cs₂CO₃ (2eq.), Dioxane 1.5 ml (0.14 M)</td>
<td>Glove box prep, 100°C for 72 hr.</td>
<td>3-iodotoluene</td>
<td>No Product</td>
</tr>
<tr>
<td>NiBr₂(diglyme) (10 mol%), Ligand*:CAS2984169-8 (12%)</td>
<td>n-hexanol (2 eq.), t-BuOK (1.2eq), Dioxane 1.5 ml (0.14M)</td>
<td>In glove box: A. L(12%), C(10%), dioxane. 30 min rt. B. MR3, t-BuOK, n-hexanol. 30 min rt. C. Combined, removed, stir 100°C 40hr.</td>
<td>3-iodotoluene</td>
<td>No Product</td>
</tr>
</tbody>
</table>

The C1-trifluoroborate did not successfully form the desired product under the two catalytic conditions, leading to the reconsideration of the pinacolato boronic ester. In attempt to prepare a carbohydrate model for the application of appropriate catalytic conditions, a tetra-O-acetyl-1-bromo-glucose electrophile was subjected to catalytic conditions with bis(pinacolato)diboron.

Scheme 3: Synthetic route to tetra-O-acetyl-1-bromo-D-glucopyranose MR5 from glucose. MR5 was subjected to coupling conditions as an electrophile with no desired product.
Table 3: A depiction of conditions experimentally determined to be unsuccessful for tetra-\(O\)-acetyl-1-Bromo-glucose in a 3-neck anh. flask w/ condenser under an \(N_2\) atmosphere.

<table>
<thead>
<tr>
<th>Catalyst</th>
<th>Reagent</th>
<th>Conditions</th>
<th>Electrophile</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pd(PPh(_3))(_4), (15 mol%)</td>
<td>KOAc (10eq.), DMSO 2.5 ml (0.24 M)</td>
<td>Glove box prep, 80(^0)C, 5 min</td>
<td>Bis(pinacaloto)diboron (1eq.)</td>
<td>No Product</td>
</tr>
<tr>
<td>Pd(PPh(_3))(_4), (20 mol%)</td>
<td>KOAc (10eq.), DMSO 2.5 ml (0.24 M)</td>
<td>Glove box prep, 80(^0)C, 30 min.</td>
<td>Bis(pinacaloto)diboron (1eq.)</td>
<td>No Product</td>
</tr>
<tr>
<td>Pd(PPh(_3))(_4), (20 mol%)</td>
<td>KOAc (10eq.), DMSO 2.5 ml (0.24 M)</td>
<td>Glove box prep, 80(^0)C, 7 hr.</td>
<td>Bis(pinacaloto)diboron (1eq.)</td>
<td>No Product</td>
</tr>
<tr>
<td>Pd(PPh(_3))(_4), (20 mol%)</td>
<td>Na(_3)PO(_4) (10eq.), DMSO 2.5 ml (0.24 M)</td>
<td>Glove box prep, 80(^0)C, 7 hr.</td>
<td>Bis(pinacaloto)diboron (1eq.)</td>
<td>No Product</td>
</tr>
<tr>
<td>Pd(dppf)Cl(_2), (20%)</td>
<td>Cs(_2)CO(_3) (10eq.), DMSO1.5 ml (0.24 M)</td>
<td>Glove box prep, 80(^0)C, 7 hr.</td>
<td>Bis(pinacaloto)diboron (1eq.)</td>
<td>No Product</td>
</tr>
<tr>
<td>Pd(dppf)Cl(_2), (20%)</td>
<td>Na(_3)PO(_4) (10eq.), DMSO1.5 ml (0.24 M)</td>
<td>Glove box prep, 80(^0)C, 7 hr.</td>
<td>Bis(pinacaloto)diboron (1eq.)</td>
<td>No Product</td>
</tr>
</tbody>
</table>

Exploration of the Stille coupling reaction

Approaches to stereo-retentive bond formation utilizing other coupling methods were investigated as we were not able to produce successful reactions with a C1 nucleophilic boronic ester, in consideration with the failed attempts at successfully forming the \(sp^3\) carbon – \(sp^2\) carbon bond via Suzuki coupling. In response, a glycosylstannane utilizing trimethyltin was subjected to catalytic conditions favoring the Stille coupling method. However, the reaction proved to be unsuccessful but remains a defining time in the application of coupling reactions to C-glycoside formation.
**Scheme 4:** Depiction of the trimethyl(tetra-O-benzyl-D-glucopyranosyl)stannane **MAW** and desired coupling product

![Scheme 4 Depiction of the trimethyl(tetra-O-benzyl-D-glucopyranosyl)stannane MAW and desired coupling product](image)

**Table 4:** A depiction of conditions experimentally determined to be unsuccessful for the Stille coupling reaction of tri-methyl(tri-O-benzyl-D-glucopyranosyl)stannane with 3-iodotoluene.

<table>
<thead>
<tr>
<th>Catalyst</th>
<th>Reagent</th>
<th>Conditions</th>
<th>Electrophile</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pd(PPh₃)₄, 5%</td>
<td>CuI (0.1 eq.), CsF (2 eq.), DMF 2 ml (0.1 M)</td>
<td>Reflux under N₂, 100°C, O/N</td>
<td>3-iodotoluene</td>
<td>No Product</td>
</tr>
<tr>
<td>Pd(PPh₃)₄, 10%</td>
<td>CuI (1 eq.), CsF (excess), DMF 2 ml (0.1 M)</td>
<td>Reflux under N₂, 100°C, O/N</td>
<td>3-iodotoluene</td>
<td>No Product</td>
</tr>
<tr>
<td>CuCN (8%)</td>
<td>THF</td>
<td>Pressure tube anh., O/N</td>
<td>3-iodotoluene</td>
<td>No Product</td>
</tr>
</tbody>
</table>

**Scheme 5:** The synthesis of tri-O-benzyl-D-glucal from commercial sources of tri-O-acetyl-D-glucal

![Scheme 5 The synthesis of tri-O-benzyl-D-glucal from commercial sources of tri-O-acetyl-D-glucal](image)

The pursuit of D-glucopyranosyl stannanes began with the glycal building block **MR7**.

Scale up of de-acetylation followed by benzylation of D-glucal proved to be seamless as the same number of equivalents of each reactant was utilized on scales reaching 100 g of **MR7**. On a small scale, the reaction was purified at the second step of D-glucal and decreased the final product yield by 7%, and thus determined to be inefficient and was not applied to large scale synthesis. The
reaction proceeds at room temperature and is sensitive to temperatures above 60 °C, a discovery made by returning to a reaction flask over a hot plate that was unknowingly turned on.

The epoxidation of tri-\textit{O}-benzyl-glucal MR7 and subsequent opening via LiSnBu$_3$ established a synthetic route to tri-\textit{n}-butyl(3,4,6-tri-\textit{O}-benzyl-\textit{\beta}-D-glucopyranosyl)stannane ZF1 that produced an unsatisfactory yield of 8%. Dr. Zhu optimized the final step in the synthesis by using an alternative MeMgSnBu$_3$, which is a sensitive reagent that requires precise execution of anhydrous/degassed techniques in preparation and utilization. Thus, the yields for other group members using this reagent were miniscule. This led Dr. Zhu to perform the last step of epoxide opening via MeMgSnBu$_3$ across a broad range of carbohydrates. Utilizing ZF1 modifications at C2 allowed for screening of coupling reaction conditions that allowed the reactions to proceed with retention of configuration.

\textbf{ZF1} and \textbf{ZF2} were utilized in the optimization of the reaction and required the production of large amounts of tri-\textit{O}-benzyl-D-glucal MR7, over 1 Kg. The financially viable product that is available commercially is tri-\textit{O}-acetyl-D-glucal. This was de-acetylated followed by benzylolation. The scale up of this reaction coincided with the pace of the project as this molecule was the substrate material for the glucopyranosyl C1 nucleophiles exhibited in the project.\textsuperscript{(15)}
Scheme 6: Scope of D-glucopyranosylstannanes synthesized from D-glucal, MR7. (5)

Synthesis of Tri-n-butyl-(2-deoxy-D-glucopyranosyl)stannanes

Tri-O-benzyl-D-Glucal MR7 afforded a synthetic route to several glycosylstannanes that were modified to provide 8 examples of nucleophilic stannylated carbohydrates for the coupling
reaction. The first course of action was executing the synthesis of 3,4,6-tri-O-benzyl-2-deoxy-α-D-glucopyranosyl chloride.\(^{(16)}\) This crude anomeric chloride was utilized to form the α or β 2-deoxy stannanes using the published protocol of Lesimple et al.\(^{(17)}\) This article introduced our group to another approach of forming stannane nucleophiles, “tributylstanannyllithium in oxolane”, (oxolane is tetrahydrofuran). This was made by subjecting tributyltin hydride to LDA, producing a nucleophilic tin reagent that directly displace the chloride, inverting the configuration to produce MR10 tri-\(n\)-butyl-(3,4,6-tri-O-benzyl-2-deoxy-β-D-glucopyranosyl)stannane.\(^{(18)}\) Reactions in pursuit of the β-stannane were run using tributyltin hydride with \(n\)-BuLi with no desired product. The α-glucopyranosyl performs a halide lithium exchange, retaining its anion axially due to configuration stability at reduced temperatures, forming an organolithium reagent, that then produces a nucleophile to displace the chloride from tributyltin chloride, forming MR13 tri-\(n\)-butyl-(3,4,6-tri-O-benzyl-2-deoxy-α-D-glucopyranosyl)stannane.\(^{(19)}\)
**Scheme 7:** Synthetic scheme from the anomeric chloride MR9 to products: tri-$n$-butyl-(3,4,6-tri-$O$-benzyl-2-deoxy-$\beta$-D-glucopyranosyl)stannane MR10 and its anomer tri-$n$-butyl-(3,4,6-tri-$O$-benzyl-2-deoxy-$\alpha$-D-glucopyranosyl)stannane MR13, followed by the subsequent de-benzylation to produce MR11/MR14, and acylation to produce MR12/MR15.

These molecules were then reduced via Birch reduction to remove the three benzyl groups to provide trihydroxyl sugars: tri-$n$-butyl-(2-deoxy-$\beta$-D-glucopyranosyl)stannane MR11 and its anomer tri-$n$-butyl-(2-deoxy-$\alpha$-D-glucopyranosyl)stannane MR14. After characterization, the molecules underwent an acylation procedure to produce tri-$n$-butyl-(3,4,6-tri-$O$-acetyl-2-deoxy-$\beta$-D-arabino-hexopyranosyl)stannane MR12 and tributyl-(3,4,6-tri-$O$-acetyl-2-deoxy-$\alpha$-D-arabino-hexopyronsyl)stannane MR15.

**Synthesis of tri-$n$-butyl(tetra/tri-$O$-benzyl-$\alpha$-D-glucopyranosyl)stannanes**

The majority of coupling reactions were run based on a tri-$n$-butyl(tri-$O$-benzyl-$\beta$-D-glucopyranosyl)stannane model and the synthesis of the corresponding $\alpha$-D-glucopyranosyl was important as the contrasting anomer of our model system, supporting the complete retention of configuration for both anomers. Modification of the tri-$O$-benzyl-D-gluco MR7 was converted
via K$_2$OsO$_4$ to produce the diol MR16. This was dissolved in Et$_2$O/CHCl$_3$ followed by the bubbling of HCl at 0 °C, then sealed in a reaction flask with activated molecular sieves, and allowed to proceed in a cold room. It is important to note that ethanol is a stabilizer for chloroform that diminishes with several washes with water; the washed CHCl$_3$ was exposed to a drying agent, preventing side reactions with EtOH/H$_2$O. This mechanism may proceed by the formation of complimentary Lewis acid/base pair reagents; at C1, a resonance stabilized carbocation forms after the protonated hydroxyl leaves as water and is removed by the sieves. The reaction proceeds by a chlorine anion attacking the C1 carbocation forming the bond observed in MR17.

Scheme 8: The synthetic route to tri-$n$-butyl(tri-$O$-benzyl-$\alpha$-$D$-glucopyranosyl)stannane MR18, and tri-$n$-butyl(tetra-$O$-benzyl-$\alpha$-$D$-glucopyranosyl)stannane MR19.

The formation of the $\alpha$-stannane from the chloride is a temperamental reaction run at -100 °C, proceeding by a halide lithium exchange and requires $n$-BuLi to remove the proton from the C2-hydroxyl. This reaction was required to run on a relatively small scale (0.5 mmol); thus the reactions were run in parallel and combined for work up prior to benzylation of the C2 hydroxyl to form MR19.
Tri-\textit{n}-butyl(2,3,4-Tri-\textit{O}-benzyl-D-arabino-hexapyranosyl)stannane synthesis (MR25/ZF3)

The glycosylstannane of arabinose expands our nucleophilic monosaccharide library. This saccharide upon coupling, could allow for the characterization of synthetic products that provide comparative examples for naturally occurring flavonoid glycosides collected in the laboratory, as investigators report difficulties in the differentiation of xylose and arabinose by UV-vis spectra.\textsuperscript{(20)}

The bromonation of synthesized tetra-\textit{O}-acetyl-D-arabinal formed MR21, and was subjected to a Zn/CuSO\textsubscript{4} reduction, forming di-\textit{O}-acetyl-D-arabinal MR22. The production of a glycal, a C1-C2 double bond formation, is a recurring theme through the methodology, offering several routes to variable glycosylstannes and consequentially synthesis of C-aryl glycosides. After de-acylation the product MR23 was subjected to benzylation arriving at di-\textit{O}-benzyl-arabinal MR24. This was epoxidized and opened by Dr Zhu’s ring opening procedure.\textsuperscript{(5,21)}

\textbf{Scheme 9:} A synthetic pathway to 3,4-di-\textit{O}-benzyl-D-arabinal MR24 from the commercially available D-arabinal. This glycal was epoxidized to form MR25 and opened to form ZF3.

Synthesis of hexa-\textit{O}-benzyl-lactal (MR28)

The lactal disaccharide example is highlighting the synthetic routes to establish modification of carbohydrates via alkenes adjacent to heterocyclic atoms, glycals, allowing for the selective formation of C1 nucleophilic glycosylstannanes of exceptional anomeric purity.
**Scheme 10:** The synthetic route to hexa-\(O\)-benzyl-lactal MR28 from the commercially available hepta-\(O\)-acetyl-1-bromo-D-lactoside MR26.

**Discussion**

There are many different configurations of monosaccharides, single carbohydrate subunits. The methodology successfully synthesized a catalog of monosaccharides utilizing an anomic tributyltin in the Stille coupling reaction. These tin-containing monosaccharides (organostannane) have been proven to be viable nucleophiles for the stille coupling reaction, and were later coupled with an aryl halide compound, in the presence of palladium and a specific ligand. The nucleophiles proceeded in a reaction in which the carbon-carbon bond formation proceeded with retention (>99:1) configuration. The scope of the project includes the variation of two components of our reaction, the organostannane and the aromatic group to which the carbohydrate group will be bound following the successful completion of the reaction. The nucleophilic stannylated carbohydrates utilized in this coupling were the monosaccharides D-glucose, D-galactose, N-acetyl-D-glucosamine, and C2-deoxy glucopyranosyls; 2 anomers of each saccharide. The D-arabinose and D-lactose were applied as only \(\beta\)-Anomers. In this methodology, the coupling partners were aromatic groups that all contained a halide (iodine, bromine or chlorine). The employed aryl-halides included: simple aromatic compounds, heteroaromatics, amino acids/peptides, and other systems of interest. The coupling pairs upon subjection to our catalytic conditions provided a novel route to the formation of \(sp^3\) carbon – \(sp^2\) carbon bonds in the synthesis of C-Aryl glycosides. These coupling conditions were optimized for the tributyl(tetra-\(O\)-benzyl-\(\beta\)-glucopyranosyl)stannane model and were extended to other carbohydrate nucleophiles and
continues to provide a collection of unique glycoconjugates. The products of these reactions have been analyzed using Nuclear Magnetic Resonance spectroscopy (NMR) and mass spectrometry. Upon the analysis of each successful reaction, conditions were optimized for yield and the products fully characterized using $^1$H NMR, $^{13}$C NMR, 2D-NMR, and high resolution mass spectrometry.

**Further Investigation**

The catalytic method developed through this project provides a viable route to synthesize a broad scope of C-Aryl glycosides that upon characterization can accelerate the integration of glycochemistry into proteomics and genomic libraries, as proteins are currently characterized without determination of their corresponding glycan. Utilizing this methodology requires thorough consideration and investigation into the concentration of alkyl tin in the final products as it could be problematic for human therapeutics. This may require specific removal processes for application in the pharmaceutical industry but offers novel opportunities in biochemistry research, specifically glycan-proteomic characterization as comparative structures can be applied in computational methods to determine glycan arrangement probability. This will open opportunities to comprehensively assess glycan roles in proteomics as we gain understanding of the location of glycans in respect to how a protein interacts with other entities and furthermore how gene expression effects glycan structure, placement, and density. Moving to organo-tin reagents presents toxicity concerns in the application of this technology to life sciences.\(^{(24)}\)

The stannylated sugars remain configurationally stable while stored at room temperature; this advancement has implications for synthetic approaches to the acquisition of unexplored/synthetically unobtainable natural products. Investigators working with a 3D electrochemical structure of lectins or other structures that selects for, or interacts with, carbohydrates of interest may soon be able to uniquely modify mono, di, tri or oligosaccharides
through simple, widely applicable catalytic methodologies. These types of reactions will allow for an extremely large number of coupling pairs, creating molecular libraries that will provide an assessment of a molecule’s value to science, society, and prosperity.

With a growing interest in glycochemistry, the near future may allow investigators, biotech industries, and pharmaceutical companies to utilize carbohydrate chains/webs or monosaccharides that only require a proprietary catalyst, ligands, electrophile or nucleophile, solvent kit, and glovebox for assembly. The goal through these advancements is offering a technology with an ability to access the C-N, C-O and C-C bonds utilizing nontoxic reagents.
Supporting Information

Materials

All chemicals were purchased as reagent grade and used without further purification, unless otherwise noted. Solvents were filtered through a column of activated alumina prior to use. All reactions were carried out under dry N₂ in oven-dried glassware. m-Xylene was distilled under nitrogen over sodium and degassed prior to use. Anhydrous 1,4-dioxane, Pd₂(dba)₃, L1-6 and CuCl were purchased from Sigma-Aldrich. Anhydrous KF was purchased from Strem Chemicals, Inc. Aromatic substrates were purchased from Sigma-Aldrich, TCI, Acros Organic, Oakwood Products Inc., AK Scientific, CHEM-IMPEX INT’L INC. CD₃OH, CD₃CN, CDCl₃ was purchased from Cambridge Isotope Laboratories and used as received. TLC analyses were performed on Merck TLC plates and visualizations were performed with UV light and/or Hanessian stain and/or sulfuric acid stain (5% H₂SO₄ in MeOH). Column chromatography was performed on silica gel (230-400 mesh). ¹H and ¹³C NMR spectra were recorded on Bruker/Varian 300/400/500 MHz instruments and are reported as follows: chemical shift (δ), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), coupling constants (Hz), and integration. The residual solvent reference peaks were used from published literature. 2D-NMR experiments were performed using standard parameters (200 and More NMR Experiments, S. Berger, S. Braun, Wiley-VCH, 2004). IR measurements were performed on Agilent Cary 630 FT/IR instrument and optical rotations were measured on JASCO P-1030 and are reported as the average of five data points. ⁵
MR7

3,4,6-tri-O-benzyl-D-glucal (MR7) \(^{15}\). To a solution of tri-O-acetyl-D-glucal (25.0 g, 91.7 mmol) in MeOH (175 mL), sodium methoxide (4.30 g, 79.6 mmol) was added and the reaction mixture was stirred 12 h at rt under a nitrogen atmosphere. The reaction mixture was passed through a plaque of silica and concentrated to give a crude oil (15.5 g). Under a nitrogen atmosphere, the crude material was dissolved in anh. THF (150 mL). Tetra-n-butylammonium iodide (7.53 g, 20.4 mmol) and NaH (20.0 g, 500 mmol, 60% dispersion in mineral oil) were added and the reaction mixture was allowed to stir at rt for 30 min. The reaction mixture was cooled to 0°C, benzyl bromide (52.3 g, 306 mmol) was added, and the mixture was stirred at rt for 18 h. The reaction mixture was then quenched with MeOH, concentrated, and purified by chromatography on SiO\(_2\) (Hexanes/EtOAc, 1:0 then 10:1) to afford tri-O-benzyl-D-glucal MR7 (33.0 g, 86%) as a white solid. A cautionary consideration as the scale up of this reaction proceeds is the excess NaH increases and can become highly exothermic upon quenching with MeOH.

\[ \delta (400 \text{ MHz, CDCl}_3) \delta 7.25 - 7.16 (15H), 6.35 (dd, J = 6.1, 1.1 Hz, 1H), 4.80 (dd, J = 6.2, 2.7 Hz, 1H), 4.76 (d, J = 11.3 Hz, 1H), 4.56 (d, J = 11.3 Hz, 1H), 4.55 (d, J = 11.8 Hz, 1H), 4.54 - 4.45 (m, 3H), 3.99 (ddd, J = 8.2, 5.0, 2.9 Hz, 1H), 3.79 (dd, J = 8.7, 6.2 Hz, 1H), 3.74 (dd, J = 10.7, 5.0 Hz, 1H), 3.69 (dd, J = 10.7, 2.9 Hz, 1H). \]

MR8

3,4,6-tri-O-benzyl-2-deoxy-D-glucopyranose (MR8). To a solution of tri-O-benzyl-D-glucal MR7 (5.00 g, 12.0 mmol) in THF (50 mL), a solution of HCl (3.0 mL, 2.0 M in water) was added and stirred at rt for 40 h. The reaction mixture was quenched with Et\(_3\)N (0.85 mL, 6 mmol) followed by toluene (20 mL). The volatiles were removed \textit{in vacuo} and the residue was purified by chromatography on SiO\(_2\) (Hexanes/EtOAc, 5:1) to afford MR8 (4.40 g, 84%) as a white powder. \( \delta (400 \text{ MHz, CDCl}_3) \delta 1.95-2.03 (1H, m), 2.05-2.12 (1H, m), 2.17-2.19 (1H, m), 2.73-2.80 (1H, m), 3.32 (2H, s), 3.43-3.59 (5H, m), 3.67-3.74 (3H, m), 3.97-4.01 (1H, m), 4.12 (1H, d, J=3.4 Hz), 4.41 and 4.91 (2H, 2d, J=11.2 Hz), 4.58 and 4.86 (2H, 2d), 4.58 and 4.86 (2H, 2d, J=12.6 Hz), 4.76-4.81 (9H, m), 5.43 (1H,s), 7.22-7.41 (30H, m)\(^{25}\).

MR9

3,4,6-tri-O-benzyl-2-deoxy-\(\alpha\)-D-arabino-hexopyransyl chloride (MR9) \(^{16}\). To a solution of MR8 (565 mg, 1.3 mmol) in DCM (22.6 ML), DMF (1 mL) was added followed by stirring at 0°C. To the vented flask, oxalyl chloride (495 mg, 3.9 mmol) was added dropwise and the reaction
mixture was stirred at 0°C for 20 min. Immediately following removal from the ice bath, oxalyl chloride (0.334 mL, 2.6 mmol) was added, the reaction mixture was then allowed to stir at rt for 20 min producing a white precipitate. To the reaction mixture toluene (10 mL) was added and the white precipitate filtered off. The volatiles were concentrated, followed by two co-evaporations with toluene, in vacuo at 30°C. The contents placed on high vacuum for 45 min and the resulting yellow oil used directly in the synthesis of MR10. 1H NMR (500 MHz, CDCl3) δ 7.24-7.13 (m, 15H), 6.21 (d, J = 3.1 Hz, 1H), 4.79 (d, J = 10.9 Hz, 1H), 4.54 (dd, J = 11.6, 3.3 Hz, 2H), 4.49 (d, J = 11.9 Hz, 1H), 4.37 (d, J = 11.9 Hz, 1H), 4.02 (ddd, J = 11.0, 9.1, 4.6 Hz, 1H), 3.96 (dd, J = 7.1, 3.9 Hz, 1H), 3.58-3.54 (m, 2H), 2.43 (dd, J = 8.9, 4.8 Hz), 1.96-1.91 (m, 1H).

MR10
Tributyl-(3,4,6-tri-O-benzyl-2-deoxy-β-D-arabino-hexopyranosyl)stannane (MR10) 17. To a dry flask under a nitrogen atmosphere, anh./degassed THF (10 mL) and distilled (i-Pr)2NH (0.800 mL, 5.7 mmol) was added, cooled to 0°C, followed by the dropwise addition of n-BuLi (3.125 mL, 5 mmol), the reaction mixture were allowed to stir at 0°C for 5 min. Then tributyltin hydride (1.32 mL, 1.45 g, 5 mmol) was added and the reaction was left to stir at 0°C for 20 min producing a tributyltin lithium reagent. To a dry flask under a nitrogen atmosphere, containing a stirring solution of the crude chloride MR9 (2.6 mmol) in anh./degassed THF (10 mL), the stannane reagent (11.89 mL, 3.9 mmol) was added at 0°C over 20 min. The reaction was left to stir at 0°C for 1.5 hr, followed by quenching with Et2O/H2O (50 mL, 3:2) then extracted three times with Et2O, organic layers dried over MgSO4 and the volatiles concentrated in vacuo. The resultant residue was purified by chromatography on SiO2 (Hexanes/EtOAc, 1:0, 10:1) to afford the MR4 (1.04 g, 56%) as a clear oil. [α]D26 = -9.08 (c = 1.00, CHCl3); IR (ATR) ν = 2851, 1746, 1452, 1358, 1095, 875, 730, 694, 595 cm⁻¹; 1H NMR (400 MHz, CDCl3) δ 7.39-7.29 (m, 15H), 4.90 (d, J = 10.8 Hz, 1H), 4.67 (d, J = 12.0 Hz, 2H), 4.62 (d, J = 11.2 Hz, 2H), 4.54 (d, J = 12.3 Hz, 1H), 3.71 - 3.67 (m, 2H), 3.62 (dd, J = 13.3, 1.8 Hz, 1H), 3.58 – 3.50 (m, 1H), 3.47 (t, J = 9.0 Hz, 1H), 3.26 - 3.16 (m, 1H), 2.12 (ddd, J = 13.1, 5.0, 2.0 Hz, 1H), 1.89 - 1.75 (m, 1H), 1.58 - 1.39 (m, 6H), 1.37 - 1.05 (m, 6H), 1.02 - 0.71 (m, 15H); 13C NMR (101 MHz, CDCl3) δ 139.0 (2), 138.9, 128.5 (2), 128.4, 128.2, 127.8, 127.7, 127.6, 127.4, 83.2, 83.0, 79.3, 75.3, 73.5, 71.7, 70.8, 70.1, 37.1, 29.2, 27.6, 13.9, 8.7; FT-HRMS (ESI) calcd for C39H56O4SnNa [M + Na]+: 731.3093, found 731.3102

MR13
Tributyl-(3,4,6-tri-O-benzyl-2-deoxy-α-D-arabino-hexopyranosyl)stannane (MR13) 17. To a flask containing the crude chloride MR9 (1.30 mmol), anh./degassed THF (11 mL) was added
under a nitrogen atmosphere followed by stirring at -78°C. Then, freshly prepared 1M lithium naphthalenide (4.55mL, 4.55 mmol) was added dropwise over 5 min, followed immediately by tributyltin chloride (1.23 mL, 4.55 mmol), and the reaction mixture was allowed to stir at -78°C for 30 min. The reaction mixture was then quenched with Et2O/H2O (25 mL, 3:2), extracted three times with Et2O, organic layers dried over MgSO4 and the volatiles concentrated in vacuo. The residue was purified by chromatography on SiO2 (Hexanes/EtOAc, 1:0 then 5:1) to afford MR13 (370 mg, 42%) as a colorless oil: [α]D25 = +77.83 (c = 0.083, CHCl3); IR (ATR) ν = 3029, 2920, 2858, 2359, 1453, 1359, 1201, 1086, 1016, 731, 694, 594 cm−1; 1H NMR (400 MHz, CD3Cl) δ 7.43 -7.24 (m, 15H), 4.97 (d, J = 11.1 Hz, 1H), 4.75 (d, J = 11.9 Hz, 1H), 4.68 (d, J = 11.89 Hz, 1H), 4.66 (d, J = 12.3 Hz, 1H), 4.60 (d, J = 11.1 Hz, 1H), 4.57 (t, J = 4.16 Hz, 1H), 4.54 (d, J = 12.2 Hz, 1H), 3.78 (dd, J = 10.4, 4.2 Hz, 1H), 3.71 (dd, J = 10.3, 2.2 Hz, 1H), 3.66 -3.57 (m, 1H), 3.58 (t, J = 8.5 Hz, 1H) 3.22 (dt, J = 6.9, 2.1 Hz, 1H), 2.24 (dd, J = 7.0, 3.8 Hz, 2H), 1.57 -1.45 (m, 6H), 1.39 -1.29 (m, 9H), 0.99 -0.87 (m, 12H); 13C NMR (101 MHz, CD3Cl) δ 138.9, 138.7, 138.4, 80.9, 79.3, 74.9, 73.6, 72.0, 71.4, 69.5, 36.3, 29.3, 27.6, 13.8, 10.1; FT-HRMS (ESI) calculated for C39H56O4SnNa [M + Na]+: 731.3093, found 731.3109.

MR11
Tri-n-butyl-(2-deoxy-β-D-glucopyranosyl)stannane (MR11). Freshly cut sodium (0.547 g, 23.8 mmol) was added to liquid NH3 (ca. 40 mL) at -78 °C followed by a solution of MR10 (0.209 g, 0.295 mmol) in anhydrous dioxane (2 mL). This dark blue reaction mixture was stirred under reflux (-34 oC) for 2 h, was cooled to -78 °C and solid NH4Cl was added portionwise until the blue color disappeared. The resulting suspension was allowed to warm up to rt, the residue was washed with EtOAc (3x), filtered, and concentrated. Purification by column chromatography on SiO2 (CH2Cl2 then CH2Cl2:EtOAc, 1:1) afforded MR11 (64.0 mg, 50%) as a colorless oil: [α]D24 = -9.2 (c = 0.65, CHCl3); IR (ATR): 3354, 2920, 2867, 1459, 1375, 1251, 1200, 1048, 870, 658, 593 cm−1; 1H NMR (500 MHz, CDCl3) δ 4.00 (br, 1H), 3.76 (m, 3H), 3.56 (m, 1H), 3.51 (br, 1H), 3.38 (t, J = 9.0 Hz, 1H), 3.08 (dt, J = 9.3, 3.9 Hz, 1H), 2.42 (br, 1H), 2.01 (ddd, J = 13.1, 5.0, 2.0 Hz, 1H), 1.81 (td, J = 13.3, 10.8 Hz, 1H), 1.49 (m, 6H), 1.37 -1.23 (m, 6H), 0.89 (m, 15H); 13C NMR (101 MHz, CDCl3) δ 82.2, 74.6, 73.4, 71.2, 63.0, 38.9, 29.2, 29.1, 63.0, 71.2, 73.4, 74.6, 82.2; HRMS (ESI) calculated for C18H36O4Sn [M + Na]+: 461.16834 found 461.1681.

MR14
Tri-n-butyl-(2-deoxy-α-D-glucopyranosyl)stannane (MR14). Freshly cut sodium (0.580 g, 25.2 mmol) was added to liquid NH3 (ca. 40 mL) at -78 °C followed by a solution of MR13 (0.203 g, 0.287 mmol) in anhydrous dioxane (2 mL). This dark blue reaction mixture was stirred under reflux (-34 oC) for 2 h, was cooled to -78 °C and solid NH4Cl was added portionwise until the blue color disappeared. The resulting suspension was allowed to warm up to rt, the residue was
washed with EtOAc (3x), filtered, and concentrated. Purification by column chromatography on SiO2 (CH2Cl2 then CH2Cl2:EtOAc, 1:1) afforded MR14 (66.0 mg, 53%) as a colorless oil; $[\alpha]_{D}^{25} = +36.6$ (c = 0.50, CHCl3); IR (ATR): 3354, 2920, 2857, 1459, 1375, 1251, 1200, 1048, 870, 658, 593, 503 cm$^{-1}$; $^1$H NMR (500 MHz, CD$_3$CN) $\delta$ 4.47 (dd, $J = 4.4$, 3.4 Hz, 1H), 3.68 (ddd, $J = 11.6$, 6.2, 3.1 Hz, 1H), 3.56 (dt, $J = 11.5$, 5.7 Hz, 1H), 3.40 (qd, $J = 8.4$, 3.8 Hz, 1H), 3.30 (d, $J = 4.4$ Hz, 1H), 3.17 (d, $J = 4.3$ Hz, 1H), 3.01 - 1.96 (m, 2H), 1.59 - 1.44 (m, 6H); $^13$C NMR (101 MHz, CD$_3$CN) $\delta$ 81.5, 74.2, 73.7, 73.1, 63.4, 39.5, 29.8, 28.2, 13.9, 10.7; HRMS (ESI) calculated for C$_{18}$H$_{38}$O$_4$Sn $[M + Na]^{+}$ 461.1684, found 461.1686.

MR12
Tributyl-(3,4,6-tri-O-acetyl-2-deoxy-ß-D-arabino-hexopyranosyl)stannane (MR12)$^{17}$. To a flask containing (MR11) (100 mg), pyridine (5.00 mL) was added followed by Ac$_2$O (1.00 mL) and DMAP (10.0 mg, 0.08 mmol). The reaction mixture was placed under a nitrogen atmosphere and allowed to stir at rt for 12 hr. The reaction mixture was combined with H$_2$O (50 mL) in a separatory funnel and extracted three times with EtOAc. The organic layer was washed with sat. CuSO$_4$, DI H$_2$O, then sat. NaCl. The volatiles concentrated in vacuo and chromatography on SiO$_2$ (Hexanes:EtOAC, 10:1 then 5:1) to afford MR12 (99.0 mg, 77%). Light yellow oil; $[\alpha]_{D}^{25} = -24.56^{\circ}$ (c = 1.00, CHCl3); IR (ATR) ν = 2923, 2851, 1743, 1455, 1364, 1225, 1043, 908, 695, 599 cm$^{-1}$; $^1$H NMR (400 MHz, CD$_3$Cl) $\delta$ 4.98 - 4.82 (m, 1H), 4.12 (dd, $J = 12.0$, 5.3 Hz, 1H), 4.04 (d, $J = 2.4$ Hz, 1H), 2.12 (ddd, $J = 12.8$, 4.9, 2.0 Hz, 1H), 2.02 (d, $J = 6.2$ Hz, 1H), 1.91 (td, $J = 13.3$, 10.2 Hz, 1H), 1.55 - 1.37 (m, 6H), 1.28 (dq, $J = 14.7$, 7.4 Hz, 9H), 1.00 - 0.81 (m, 15H); $^13$C NMR (101 MHz, CD$_3$CN) $\delta$ 171.0, 170.8, 170.1, 79.2, 74.0, 70.5, 70.1, 63.4, 36.3, 29.1, 27.4, 21.2, 20.9 (2), 13.8, 8.8; FT-HRMS (ESI) calcd for C$_{24}$H$_{44}$O$_7$SnNa $[M + Na]^{+}$: 587.2001, found 587.2018.

MR15
Tributyl-(3,4,6-tri-O-acetyl-2-deoxy-α-D-arabino-hexopyranosyl)stannane (MR10)$^{17}$. To a flask containing MR14 (51.0 mg), pyridine (5.00 mL) was added followed by Ac$_2$O (1.00 mL) and DMAP (10.0 mg, 0.08 mmol). The reaction mixture was placed under a nitrogen atmosphere and allowed to stir at rt for 12 hr. The reaction mixture was combined with H$_2$O (50 mL) in a separatory funnel and extracted three times with EtOAc. The organic layer was washed with sat. CuSO$_4$, DI H$_2$O, then sat. NaCl. The volatiles concentrated in vacuo and chromatography on SiO$_2$ (Hexanes:EtOAC, 10:1 then 5:1) to afford MR15 (50.0 mg, 78%). Light yellow oil; $[\alpha]_{D}^{25} = +39.12$ (c = 0.38, CHCl3); IR (ATR) ν = 3029, 2922, 2859, 2359, 1744, 1453, 1364, 12225, 1053, 909, 732, 695, 598 cm$^{-1}$; $^1$H NMR (300 MHz, CD$_3$CN) $\delta$ 4.94 - 4.84 (m, 2H), 4.51 (t, $J = 4.3$ Hz, 1H), 4.26 (dd, $J = 12.1$, 5.7 Hz, 1H), 4.03 (dd, $J = 12.1$, 2.4 Hz, 1H), 3.37 (ddd, $J = 8.8$, 5.7, 2.3 Hz, 1H), 2.90 (ddd, $J = 9.0$, 5.5, 3.1 Hz, 1H), 2.65 (t, $J = 6.2$ Hz, 1H), 2.01 - 1.96 (m, 2H), 1.59 - 1.44 (m, 6H); $^13$C NMR (101 MHz, CD$_3$CN) $\delta$ 81.5, 74.2, 73.7, 73.1, 63.4, 39.5, 29.8, 28.2, 13.9, 10.7; HRMS (ESI) calculated for C$_{18}$H$_{38}$O$_4$Sn $[M + Na]^{+}$ 461.1684, found 461.1686.
MR16
To a solution of (MR7) (6.00 g, 14.4 mmol) in Acetone/H₂O (300 mL, 2:1), K₂OsO₄ (106 mg, 0.144 mmol) and 4-methylmorpholine 4-oxide (8.43 g, 72 mmol) was added. The reaction mixture was allowed to stir for 12 hr at rt, then the volatiles were removed in vacuo. The residual mixture was extracted three times with EtOAc, the organic layer washed with brine and volatiles removed in vacuo, the residue purified with chromatography on SiO₂ (Hexanes:EtOAc, 5:1 the 0:1) to afford (MR16) (5.86 g, 90%). ¹H NMR (CDCl₃, 300 MHz) δ = 7.34–7.06 (m), 5.18 (d, J = 4.7 Hz), 4.85–4.71 (m), 4.55–4.38 (m), 4.03–3.94 (m), 3.74 (t, J = 9.1 Hz), 3.67–3.53 (m), 3.53–3.39 (m); ¹³C NMR (CDCl₃, 90 MHz): δ = 138.6, 138.5, 138.1, 137.9, 137.7, 128.4, 128.3, 128.0, 127.9, 127.8, 127.7, 96.7, 92.3, 84.4, 82.5, 77.6, 75.6, 75.3, 75.1, 74.9, 74.8, 73.5, 72.8, 70.4, 68.8.

MR17
3,4,6-tri-O-benzyl-2-deoxy-α-D-arabino-hexopyranosyl chloride (MR17). To a dry flask under a nitrogen atmosphere containing a solution of (MR16) in anh. Et₂O/Chloroform (165 mL, 10:1), HCl was bubbled at 0°C for 15 min. The flask was fitted with a glass stopper and the reaction mixture was allowed to stir at 0°C for 48 hr. The reaction mixture was placed under light vacuum to remove HCl via aspiration, before volatiles removed in vacuo to afford crude (MR17) (2.402 g) as a yellow solid.
(3,4,6-Tri-O-benzyl-α-D-glucopyranosyl)tri-n-butylstannane (MR18). A dry flask under a nitrogen atmosphere containing a solution of (MR17) (422 mg, 0.900 mmol) in anhyd./degassed THF (9 mL), was cooled to -100°C by a MeOH/N₂ bath. To the reaction mixture, n-BuLi (0.771 mL, 1.08 mmol) was added drop-wise followed by the immediate drop-wise addition of a 1M lithium naphthalenide solution (1.98 mL, 1.98 mmol) in anhy./degassed THF, the dark red reaction mixture was stirred at -100°C for 15 min. Tri-n-butyltin chloride was added and the resulting light yellow reaction mixture was stirred at -100°C for 1 hr. The reaction mixture was then allowed to reach room temperature over 1 hr before quenching with H₂O (10 mL). The resulting mixture was extracted three times with DCM, the organic layer dried over Na₂SO₄, and the volatiles removed in vacuo. The resultant residue purified by chromatography on SiO₂ (Hexanes/EtOAc, 1:0 then 10:1, then 5:1) to afford MR18 (313 mg, 48%): [α]²⁶_D = +59.84 (c = 1.00, CHCl₃); IR (ATR) ν = 3301, 3029, 2919, 2857, 1453, 1357, 1206, 1070, 864, 731, 694, 596 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.37-7.19 (m, 15H), 4.85 (d, J = 11.6 Hz, 1H), 4.75 (d, J = 11.1 Hz, 1H), 4.67 (d, J = 11.7 Hz, 1H), 4.61 (d, J = 12.0 Hz, 1H), 4.57 (J = 8.31, 2.4 Hz, 1H), 4.51 (d, J = 12.1 Hz, 1H), 3.95 (ddd, J = 12.0 Hz, 1H), 3.78 (dd, J = 10.4, 4.5 Hz, 1H), 3.68 (dd, J = 10.4, 2.9 Hz, 1H), 3.62 (t, J = 7.7 Hz, 1H), 3.43 (t, J = 7.7 Hz, 1H), 3.37 (ddd, J = 7.6, 4.4, 2.9 Hz, 1H), 2.47 (d, J = 4.5 Hz, 1H), 1.57-1.42 (m, 6H), 1.31 (h, J = 7.1 Hz, 6H), 0.90 (q, J = 7.6, 7.1 Hz, 25H); ¹³C NMR (75 MHz, CDCl₃) δ 138.7, 138.3, 128.8, 128.5 (2), 128.0, 128.0, 127.9, 127.9, 127.9, 127.7, 83.9, 78.3, 77.4, 75.7, 74.6, 74.1, 73.7, 68.8, 29.3, 27.6, 13.9, 10.4; FT-HRMS (ESI) calcd for C₃₉H₅₆O₅SnNa [M + Na]⁺: 747.3042, found 747.3048.

MR19
(2,3,4,6-Tetra-O-benzyl-α-D-glucopyranosyl)tri-n-butylstannane (MR19). A solution of MR18 (313 mg, 0.432 mmol) in anhydrous THF (5 mL) was cooled to 0 °C, and a 0.5 M solution of KHMDS (1.72 mL, 0.864 mmol) was added. The solution stirred for 0.25 hr at 0 °C before the addition of benzyl bromide (0.154 mL, 1.30 mmol). The resulting solution stirred at 0 °C for 0.5 hr then for 2 hr at rt. After, the reaction is concentrated and directly purified by flash column chromatography (Hexanes/EtOAc, 1:0 then 20:1) to yield MR19 (299 mg, 85%) as a light yellow oil: [α]²⁶_D = +29.79 (c = 0.43, CHCl₃); IR (ATR) ν = 3029, 2920, 2359, 1452, 1357, 1069, 864, 731, 695, 596 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.33-7.21 (m, 18H), 7.13 (d, J = 7.4, 2.2 Hz, 2H), 4.90 (d, J = 10.9 Hz, 1H), 4.80 (d, J = 9.8 Hz, 2H), 4.69 (d, J = 11.7 Hz, 1H), 4.65 (d, J = 6.9 Hz, 2H), 4.57 (d, J = 12.1 Hz, 1H), 4.50-4.42 (m, 2H), 3.99-3.93 (m, 1H), 3.64 (qd, J = 10.4, 2.9 Hz, 2H), 3.58-3.49 (m, 2H), 3.18-3.07 (m, 1H), 1.54-1.37 (m, 6H), 1.31-1.20 (m, 6H), 1.00-0.85 (m, 5H), 0.83 (t, J = 7.3 Hz, 10H); ¹³C NMR (101 MHz, CDCl₃) δ 138.8, 138.6, 138.5, 138.2, 128.5, 128.4, 128.4, 128.4, 128.1, 128.0, 127.9, 127.7, 127.7, 127.7, 86.5, 81.4, 79.3, 78.1, 76.3, 75.6, 75.4, 73.7, 73.6, 69.2, 29.3, 27.7, 13.9, 10.6; FT-HRMS (ESI) calcd for C₄₆H₆₂O₅SnNa [M + Na]⁺: 837.3511, found 837.3521.
MR20

**1,2,3,4-Tetra-O-acetyl-D-arabinose (MR20)**\(^{13}\). To a flask containing a solution of D-arabinose (7.00g, 46.6 mmol) in pyridine (50 mL), Ac\(_2\)O (20 mL, 212 mmol) and 4-Dimethylaminopyridine (500 mg, 4.09 mmol) was added. The reaction mixture was allowed to stir for 12 hr at rt before dilution with H\(_2\)O (250 mL). The reaction mixture was then extracted three times with EtOAc and the organic layers washed with sat CuSO\(_4\), DI H\(_2\)O, then brine. The organic layer was dried over NaSO\(_4\) and volatiles removed *in vacuo* to afford crude MR20 (18.2 g).

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MR21

**2,3,4-Tri-O-acetyl-β-D-arabinopyranosyl bromide (MR21).** To a dry flask containing a solution of crude MR20 (18.2 g, assumed 46.6 mmol from previous reaction) in anh. DCM (46.5 mL), Ac\(_2\)O (4.65 mL, 49.2 mmol) and 33% HBr/AcOH (37.3 mL) was added at 0°C. The reaction mixture was then allowed to stir at 0°C for 18 hr. The reaction mixture was then diluted with DCM, H\(_2\)O then sat. NaCO\(_3\)H at 0°C. The reaction mixture was then extracted three times with EtOAc, the organic layers washed with sat. NaCO\(_3\)H, sat. NaCl, dried over NaSO\(_4\) and the volatiles removed *in vacuo* to afford crude MR21; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 2.03(s, 3H), 2.11(s, 3H), 2.15(s, 3H), 3.94(d, 1H, J=13.4 Hz), 4.21(d, 1H, J=13.4 Hz), 5.09(dd, 1H, H-2, J=10.0, 3.8 Hz), 5.40—5.42(m, 2H, H-3, H-4), 6.70(d, 1H, H-1, J=3.8 Hz).

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MR22

**3,4-di-O-acetyl-D-arabinal (MR22).** To a flask, CuSO\(_4\)•5H\(_2\)O (582 mg, 2.33 mmol), activated Zn (16.8 g, 257 mmol), and NaOAc•3H\(_2\)O (30.2 g, 222 mmol) was added. To the mixture, a 60% AcOH:H\(_2\)O solution (72.9 mL) was added, and the heterogeneous reaction mixture was stirred at rt for 10 min. Then a solution of crude MR21 (15.8 g, 46.6 mmol) in THF (50 mL) was added, and the reaction mixture was allowed to stir for 18hr. The reaction mixture was then filtered through celite, and the celite pad washed with EtOAc. To the resultant mixture, H\(_2\)O (50 mL) was added, followed by extraction three times with EtOAc. The organic layer was washed with sat. NaHCO\(_3\), DI H\(_2\)O, sat. NaCl, dried over NaSO\(_4\) and the volatiles removed *in vacuo*. The resultant oil was purified by chromatography on SiO\(_2\) (Hexanes/EtOAc, 5:1) to afford D-arabinal MR22 (4.00g, 43% over 3 steps) as a clear oil. \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 6.52 (d, 1H, J = 6.0 Hz),
5.46 (t, 1H, J = 4.3 Hz), 5.23–5.17 (m, 1H), 4.89–4.84 (m, 1H), 4.07–3.97 (m, 2H), 2.09 (s, 3H), 2.08 (s, 3H). (26)

MR23

3,4-di-O-benzyl-D-arabinal (MR23) 13. To a flask containing a solution of MR22 (2.00 g, 10 mmol) in MeOH (100 mL), NaOMe (108 mg, 2 mmol) was added. The reaction mixture was allowed to stir for 12 hours before the volatiles were removed in vacuo. The resultant residue was placed on high vacuum for one hour then placed under a nitrogen atmosphere. To the flask tetra-n-butylammonium iodide (1.61 g, 5.00 mmol) and NaH (2.4 g, 50 mmol, 50% dispersion in mineral oil) were added and the reaction mixture was allowed to stir at rt for 30 min. The reaction mixture was cooled to 0°C, benzyl bromide (8.52 g, 5.00 mmol) was added, and the mixture was stirred at rt for 18 h. The reaction mixture was then quenched with MeOH, concentrated, and purified by chromatography on SiO2 (Hexanes/EtOAc, 1:0 then 10:1) to afford 3,4-di-O-benzyl-D-arabinal MR23 (1.8 g, 61%) as a clear oil: [α]D25 = +114.2 (c = 1.00, CHCl3); IR (ATR) ν = 3029, 2924, 2870, 2360, 1882, 1723, 1640, 1495, 1452, 1355, 1059, 914, 736, 697 cm−1; 1H NMR (300 MHz, CDCl3) δ 7.51–7.22 (m, 10H), 6.42 (d, J = 6.0 Hz, 1H), 4.90 (dd, J = 6.0, 5.2 Hz, 1H), 4.67 (q, J = 12.1 Hz, 4H), 4.12–4.00 (m, 3H), 3.77 (dt, J = 10.3, 3.9 Hz, 1H); 13C NMR (75 MHz, CDCl3) δ 146.6, 138.8, 138.0, 128.5, 128.4, 127.8, 127.8, 127.7, 127.6, 98.8, 73.2, 71.1, 70.8, 66.7, 63.3.

MR25/ZF3

To a solution of 3,4-di-O-benzyl-D-arabinal (500 mg, 1.69 mmol) in a cooled (0 °C), vigorously stirring biphasic solution of DCM (10 mL), satd. aq. NaHCO3 (18 mL), and acetone (1 mL), a solution of Oxone® (4.16 g, 6.76 mmol) in H2O (18 mL) is added dropwise over 15 min. After the addition, the mixture stirs for 0.5 hr at 0 °C then for 2 hr at rt. The organic phase is then separated, and the aq phase is extracted with DCM (2x 10 mL). The combined organic phases are dried over Na2SO3 and concentrated to afford the epoxide as a white solid. The crude epoxide is then dissolved in anhydrous, degassed THF (15 mL) under N2 and cooled to -20 °C (ice salt bath) for the addition of MeMgSnBu3 (837 mg, 2.53 mmol). The solutions stirs at -20 °C for 2 hr and is then quenched with H2O (18 mL). The mixture is filtered twice through Celite® and the organic phase is separated. The aqueous phase is extracted with DCM (3x 15 mL), and the combined organic layers are dried over sodium sulfate and concentrated. The crude material was taken directly to the benzylation step and dissolved in anhydrous THF (5 mL) was cooled to 0 °C, and a 0.5 M solution of KHMDS (5.06 mL, 2.53 mmol) was added. The solution stirred for 0.25 hr at 0 °C before the addition of benzyl bromide (0.602 mL, 5.07 mmol). The resulting solution stirred at 0 °C for 0.5 hr then for 2 hr at rt. After, the reaction is concentrated and directly purified by flash column chromatography (Hexanes/EtOAc, 1:0 then 20:1) to yield ZF3 (340 mg, 29%) as a light yellow oil: [α]D26 = -9.92 (c = 1.00, CHCl3); IR (ATR) ν = 3029, 2921, 2919, 2850, 2359, 1452, 1356, 1088, 864, 731, 694, 594 cm−1; 1H NMR (300 MHz, CDCl3) δ 7.59–7.22 (m, 10H), 5.14 (d, J =
11.3 Hz, 1H), 4.80 (d, J = 12.5 Hz, 1H), 4.75 - 4.63 (m, 3H), 4.58 (d, J = 11.7 Hz, 1H), 4.18 - 4.02 (m, 2H), 3.87 (td, J = 3.3, 1.6 Hz, 1H), 3.63 (dd, J = 8.1, 3.1 Hz, 1H), 3.57 (d, J = 9.5 Hz, 1H), 3.24 (dd, J = 12.3, 1.6 Hz, 1H), 1.66 - 1.40 (m, 6H), 1.40 - 1.21 (m, 6H), 1.00 - 0.73 (m, 15H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) δ 138.9, 138.6, 138.3, 128.4, 128.3, 128.2, 127.8, 127.6 (2), 127.5, 127.3, 83.7, 78.0, 75.2, 74.1, 73.0, 71.4, 70.8, 69.2, 29.3, 29.1, 29.0, 27.5, 13.7, 9.4; FT-HRMS (ESI) calcd for C\(_{38}\)H\(_{54}\)O\(_4\)SnNa [M + Na]\(^+\): 717.2936, found 717.2945.

**MR27**

**Hexa-O-acetyl lactal (MR27)**\(^{22}\). To a flask, CuSO\(_4\)5H\(_2\)O (35.7 mg, 0.143 mmol), activated Zn (1.03 g, 15.7 mmol), and NaOAc•3H\(_2\)O (1.85g, 13.6 mmol) was added. To the mixture, a 60% AcOH:H\(_2\)O solution (4.45 mL) was added, and the heterogeneous reaction mixture was stirred at rt for 10 min. Then a solution of bromo-hepta-acetyl-D-lactoside ( 2.00g, 2.86 mmol) in THF (25 mL) was added. The reaction mixture was allowed to stir and monitored by TLC for 4 hr at rt. Then, a second addition of activated Zn (1.03 g, 15.7 mmol) was added and the reaction mixture was left to stir at rt for 12 hr. The reaction mixture was then filtered through celite, and the celite pad washed with EtOAc. To the resultant mixture, H\(_2\)O (30 mL) was added, followed by extraction three times with EtOAc. The organic layer was washed with sat. NaHCO\(_3\), Di H\(_2\)O, sat. NaCl, dried over NaSO\(_4\), and the volatiles removed in vacuo to afford crude hexa-O-acetyl lactal MR27 (1.58 g), as a clear oil. \(^1\)H NMR (500 MHz, CDCl\(_3\)) δ 6.39 (d, 1H, J = 6.1 Hz), 5.41–5.36 (m, 1H), 5.34 (d, 1H, J = 3.2 Hz), 5.17 (dd, 1H, J = 10.4, 8.0 Hz), 4.98 (dd, 1H, J = 10.5, 3.4 Hz), 4.82 (dd, 1H, J = 6.0, 3.4 Hz), 4.64 (d, 1H, J = 8.0 Hz), 4.41 (dd, 1H, J = 11.7, 2.4 Hz), 4.20–4.03 (m, 4H), 3.98 (dd, 1H, J = 7.3, 5.5 Hz), 3.89 (t, 1H, J = 6.8 Hz), 2.13 (s, 3H), 2.09 (s, 3H), 2.06 (s, 3H), 2.04 (s, 3H), 2.03 (s, 3H). \(^{26}\)

**MR28**

**Hexa-O-Benzyl-lactal (MR28)**\(^{22}\). The crude oil MR19 was dissolved in MeOH (20 mL) and NaOMe (152 mg, 2.82 mmol) was added. The reaction mixture was placed under a nitrogen atmosphere and allowed to stir at rt for 18 hours. The volatiles were then removed in vacuo, and the resulting opaque solid placed on high vacuum for 1 hr. The flask containing the solid was placed under a nitrogen atmosphere, followed by the addition of anh. THF (100 mL). Then tetra-
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*n*-butylammonium iodide (277 mg, 0.855 mmol) and NaH (1.48 g, 37.1 mmol, 60% dispersion in mineral oil) was added and the contents allowed to stir at rt for 30 min. The contents were then cooled to 0°C, BnBr (5.07 mL, 42.8 mmol) was added and the reaction mixture was stirred at rt for 48 hr. The reaction was quenched with MeOH and the volatiles removed *in vacuo*. The resulting semisolid material was purified with chromatography on SiO₂ (Hexanes/EtOAc, 1:0 then 15:2) to afford MR28* (902 mg, 37%) as a clear oil. \(^1\)H NMR (CDCl₃, 300 MHz) δ 7.39–7.27 (m, 30H, Ph), 6.43 (dd, J=6.2, 1.1 Hz, 1H, H-1), 4.92 (d, J=10.8 Hz, 1H), 4.86 (dd, J=6.3, 3.6 Hz, 1H, H-2), 4.82 (d, J=11.7 Hz, 1H), 4.71 (d, J=9.6 Hz, 1H), 4.70 (brs, 2H), 4.55 (m, 7H), 4.35 (dd, J=4.2, 1.0 Hz, 2H), 4.29 (m, 1H), 4.14 (m, 2H), 3.86 (s, 1H), 3.83–3.74 (m, 2H), 3.65 (m, 1H), 3.54–3.41 (m, 5H). \(^{22}\)

*Delivered to Dr. Feng Zhu for epoxide and opening.*
$^{45}=\text{ZF coupling product of MR10}$ with 3-iodotoluene
Rourke

45 = ZF coupling product of MR10

with 3-iodotoluene
45 is the ZF coupling product of MR10 with 3-iodotoluene.
45 = ZF coupling product of MR10 with 3-iodotoluene
46 = ZP coupling product of MR13 with 3-iodotoluene

\[ \text{ZF coupling product of MR13 with} \]
46 = ZF coupling product of MR13 with 3-iodotoluene
46 – ZF coupling product of MR5 with 3-iodotoluene.
46 is the ZF coupling product of MR13 with 3-iodotoluene.
Rourke 53

53 = ZF coupling product of MR11 with 3-iodotoluene
53 = ZF coupling product of MR11 with 3-iodotoluene
53= ZF coupling product of MR11 with 3-iodotoluene
53 = ZF coupling product of MR11 with 3-iodotoluene
3-iodotoluene

54=ZF coupling product of MR14 with
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3-Iodotoluene

54 = ZF coupling product of MRIA with

Diagram of 3-iodotoluene and its structure.
54 = ZF coupling product of MR14 with 3-iodotoluene
54: ZF coupling product of MR14 with 3-iodotoluene
MR18 with 3-iodotoluene

48 = ZF coupling product of
MR 18 with 3-iodotoluene

48 = $^{1}J_{RF}$ coupling product of
48 = ZF coupling product of MR18 with 3-iodotoluene
48 = ZF coupling product of MR18 with 3-iodotoluene
MR19 with 3-iodotoluene
40 = ZF coupling product of
MR19 with 3-iodotoluene

40=ZF coupling product of
40= ZF coupling product of MR19 with 3-iodotoluene
40 = ZF coupling product of MR19 with 3-iodotoluene
References


(8b) Gong, H.; Gagné, M. R. *J. Am. Chem. Soc.* **2008**, *130* (36), 12177


