Sugar Silanes in Carbohydrate Synthesis: Applications Towards Site-Selective Glycosylation

by

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Dedication

This dissertation is dedicated to my parents, Bruce and Catherine Buchan. Without their sacrifices, support, and love I would have never accomplished what I have been able to. I am forever grateful for everything they have done for me.

Acknowledgements

I would like to thank my advisor, Professor John Montgomery, for his guidance during my tenure in graduate school. I was fortunate to have been placed on such a stimulating research project, and to have been granted the level of independence for exploration and learning that I was. The combination of John's mentorship, and his patience in allowing me to work independently in conjunction with a great project played an integral role in my development as a scientist.

Thank you to all of the students I have had the privilege of working with during my time at the University of Michigan. These interactions have allowed me the opportunity to learn a great deal from many people, both in chemistry and in life. A special thanks to Allison Knauff, Aireal Jenkins, Wei Li and Jordan Walk for their assistance in editing early drafts of my dissertation.

Thank you to my committee members for taking the time to review my dissertation and provide thought provoking conversations regarding my graduate research. Thank you to Professor Masato Koreeda, who I developed a special relationship with during my time in graduate school, through teaching and spending time in his lab I learned a great deal. Thank you to Professor John Wolfe, having the opportunity to research under his guidance provided me with training that was highly to my development as a researcher. Thank you to Professor Edwin Vedejs, I learned a great deal from his teachings, and was inspired by his knowledge and passion for organic chemistry.

A special thanks to my family and friends who have supported me during my graduate studies. I am fortunate to have the group of people in my life that I do, and I share my successes with them.

I love my family and my wife more than anything.

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Abstract

Despite numerous elegant advances in the formation of *O*-glycosides, many opportunities for improvement still remain. The site-selective incorporation of glycosides into complex polyfunctional molecules, as well as the need to synthesize the aglycone in a separate operation from glycoside formation still needs to be addressed. In an effort to overcome the current limitations in glycosylation chemistry a carbohydrate-bearing silane reducing agent has been developed to be used in synergy with catalysis for the site-selective glycosylation of complex molecules. A variety of ketones were found to be directly converted into 1,2-*cis* glycosides by their reduction with sugar silanes, followed by glycosylation. This represents the first known example of the glycosylation of a ketone without directly going through a hydroxylic intermediate. Additionally the site-selective glycosylation of hydroxyketones was demonstrated with sugar silanes using both a nickel- and copper-IMes catalyst system.

Sugar silanes were also utilized in the development of a mild, user-friendly method for the dehydrogenative silylation of alcohols. A bench stable, electrophilic triarylborane catalyst was used for the synthesis of silyl-linked compounds for the synthesis of 1,2-*cis* glycosides. This produces hydrogen gas as the only byproduct, and was demonstrated to site-selectively glycosylate secondary and tertiary alcohols in the presence of a ketone. Insight was gained into the site-selective glycosylation of diols by silylation with sugar silanes or a combination of a sacrificial silane and a sugar silane.

This led to a better understanding of the advantages, and limitations, of sugar silanes. Unreactive glycosyl acceptors, such as the 4-hydroxyl group of glucose, did not undergo glycosylation in an appreciable yield using silicon-tethered intramolecular aglycone delivery.

Aglycone synthesis was merged with glycoside incorporation when sugar silanes were employed as reducing agents in the nickel-catalyzed reductive coupling of aldehydes and alkynes, producing carbohydrates tethered to di- and trisubstituted allylic alcohols. Challenges encountered in the glycosylation of tethered allylic alcohols, due to the generation of sensitive intermediates, resulted in the production of the desired allylic alcohol glycosides in low to moderate yield. However, despite these limitations, this method highlights the utility of sugar silanes in the development of novel methods for the synthesis of glycosides.

Chapter 1

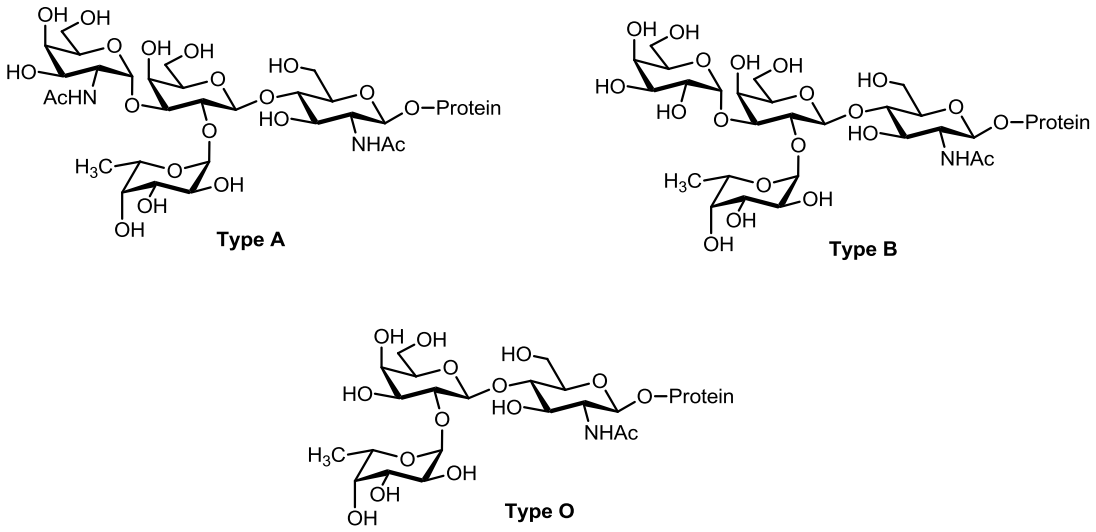
Ketone Hydrosilylation with Sugar Silanes Followed by Intramolecular Aglycone Delivery

1.1 Introduction

1.1.1 Role of Carbohydrates in Nature

Carbohydrates play an important biological role in virtually all living organisms. By their appendage to proteins, lipids, and other conjugates, carbohydrates affect a wide variety of essential biological functions.[1] These functions include, but are not limited to: cell-growth regulation, protein anchoring, cell differentiation, inflammation, bacterial and viral infections, metastasis, and immunological response. One of the most identifiable examples of these characteristics is found in the glycoproteins of human red blood cells, which determine our blood type (Scheme 1.1). A molecular recognition event such as a blood transfusion containing mismatched blood types can result in drastic effects stemming from these seemingly minor differences in glycoforms.

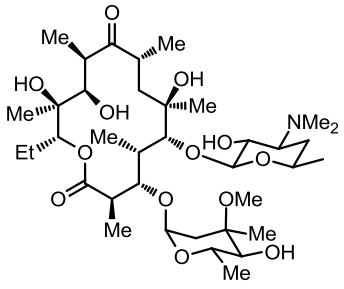
Scheme 1.1 Human Blood Type Determined by Glycoprotein Structure



Carbohydrates may be assembled into a plethora of different structures due to the variety of known monosaccharide units, as well as the positional diversity in which they can be assembled into larger building blocks. The possibility of regioisomeric connections at the 2-, 3-, 4-, and 6-OH, and the fact that glycosidic linkages have two different diastereomers, α and β, present an almost endless possibility of carbohydrate structures.

Nature utilizes enzymes known as glycosyltransferases in late stage transformations to append carbohydrates to a variety of macrolides, enediyne, and other natural products classes. These carbohydrates often play a key role in the compound's activity due to crucial interactions between the carbohydrate and non-carbohydrate functionalities.[2] This is seen in the macrolide erythromycin A where the dimethylamino group of the desosamine sugar unit forms a salt bridge in the enzyme active site resulting in its antibacterial mode of action (Scheme 1.2).[3] In the absence of the desosamine sugar, the compound loses all of its potent antibacterial properties.

Scheme 1.2 Glycosylated Macrolide Antibiotic Erythromycin A



Erythromycin A

1.1.2 Importance of Carbohydrates in Biological Activity

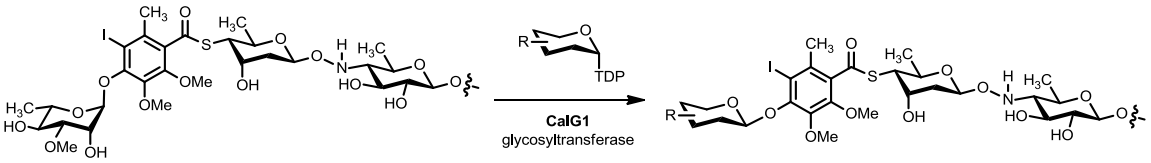
As seen with erythromycin A, carbohydrate-derived interactions can play an important role in the biological activity of a compound. This has provided scientists with an approach to the ongoing search for new and promising biologically active compounds. Modifying appended carbohydrates on small molecules is a popular approach to increasing biological activity. Glycosylated compounds provide an excellent platform for discovering new compounds, and one elegant application of this strategy came from the development of glycorandomization by Thorson and coworkers.[4]

Thorson achieved the glycosylation of highly complex molecules in a very selective fashion with a variety of monosaccharides. This was done through the symbiotic use of nucleotide diphosphate sugars (NDP-sugar) and several glycosyltransferase enzymes. Known glycosyltransferases were subjected to directed evolution to decrease substrate specificity while maintaining high degrees of site-selectivity. This allowed the use of an array of NDP-sugars to selectively modify certain hydroxyl groups on natural products such as calicheamycin and vancomycin (Scheme 1.3).[5]

While the use of enzymology allows for a rapid library synthesis of highly complex glycoconjugates of known active compounds, it is still limited by the need for available glycosyltransferases, as well as a strong understanding of their mode of action.

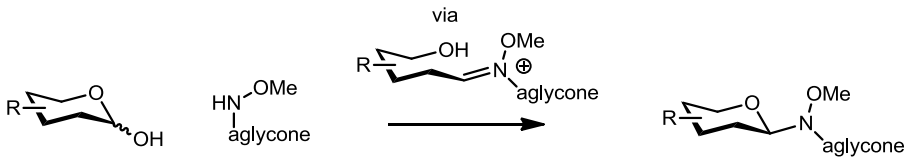
These glycosyltransferases must also be evolved to achieve enough promiscuity to accept a variety of NDP-sugars while still maintaining high efficiency for selective glycosylation of the desired hydroxyl group.

Scheme 1.3 Glycorandomization Approach



In addition to the glycorandomization method, the Thorson laboratory also developed a ligation approach to derivatizing glycosylated molecules, which is known as neoglycorandomization.[6] In this method, the natural carbohydrate is excised from a compound, and the resulting alcohol on the aglycone is oxidized to a ketone, followed by condensation with methoxylamine to form an oxime. This oxime is then reduced to the secondary methoxylamine to give the desired ligation framework. This framework then reacts with a host of unprotected reducing sugars to form the ligated neoglycoside (Scheme 1.4). This methodology allows for the rapid synthesis of a library of neoglycosides for screening new front-line drug candidates. This technique was used to discover a more potent analogue of the glycosylated steroid digitoxin. In the process of developing neoglycorandomization, the investigators gained a better understanding of how minor changes in sugar structure can dramatically modulate the biological activity of a compound.

Scheme 1.4 Neoglycorandomization Method



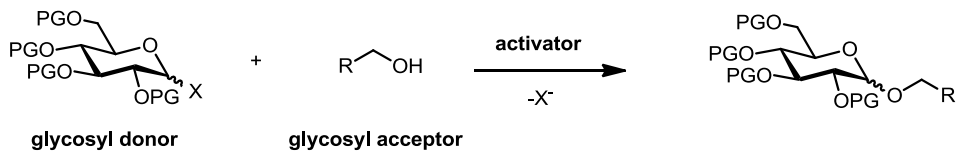
While both of these impressive demonstrations from Thorson and coworkers provided elegant approaches to the modification of compounds with unnatural glycosides, it would be beneficial to develop a purely chemical method to complement this work. This method would not depend on glycosyltransferases or developing an appropriate mode of ligation, instead selective installation of glycosides would be dictated by measures such as the reactivity of various functional groups with site-selective catalysts.

1.2 Glycosylation Methods and Challenges

1.2.1 Glycosylation Background and Nomenclature

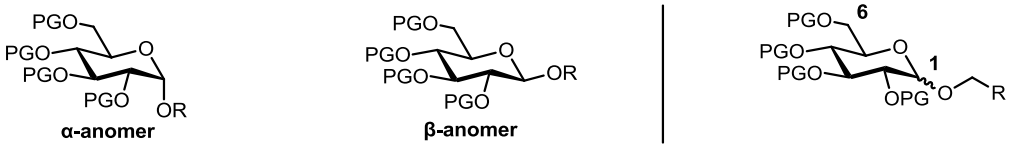
The importance of carbohydrates in biological systems has resulted in a large body of literature focused on their synthesis. *O*-Glycosides are formed by the activation of a glycosyl donor to facilitate the formation of an oxocarbenium ion by assisted displacement of the anomeric leaving group. A wide variety of leaving groups have been developed and utilized in *O*-glycoside formation, most commonly consisting of: halides, thioethers, orthoesters, carbonates, trichloroimidates, 4-pentenyl alcohols, phosphates, sulfoxides, sulfones, and glycals.[7] Upon activation of the glycosyl donor, a hydroxyl group of a glycosyl acceptor adds to the electrophilic oxocarbenium ion to form the desired glycosidic bond (Scheme 1.5). Additionally, 1-hydroxy sugars can be used as nucleophiles to displace an electrophilic species to form the glycosidic bond.[8]

Scheme 1.5 Formation of a Glycosidic Bond



In order to achieve formation of the desired glycosidic bond, all potentially nucleophilic functionalities must be protected on both the glycosyl donor and acceptor. Formation of the *O*-glycosidic bond can occur from either of the two faces of the oxocarbenium ion, resulting in two different anomers of the same product. Since this dissertation will largely involve the use of the D-glucose and D-mannose sugars, the designation of α- and β-anomers will be defined by these sugar configurations. In the D-series of sugars, an axial glycosidic bond is designated α, whereas the corresponding equatorial bond is β. Additionally, these sugars have positional numbers associated with their carbons, numbered one through six, starting with one at the anomeric position and going around the ring to the methylene carbon which is designated six (**Scheme 1.6**). This nomenclature will be used throughout the remainder of this dissertation.

Scheme 1.6 Anomeric Designation and Numbering in D-Sugars

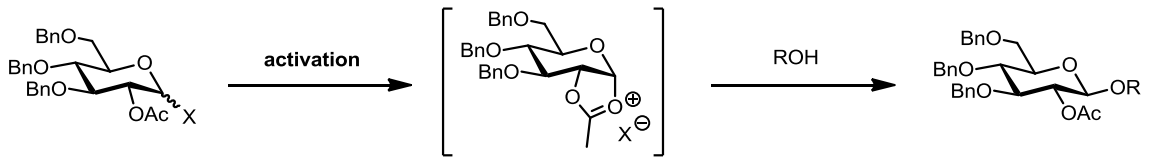


1.2.2 Challenges in Synthesizing Glycosidic Bonds

Great efforts have been devoted to developing methods where compounds are glycosylated with high anomeric selectivity. A common approach to the synthesis of 1,2-*trans* glycosides utilizes neighboring group participation, or anchimeric assistance, in which a group located elsewhere in the glycosyl donor serves to shield the *cis*-face by through-space stabilization of the oxocarbenium ion. This results in high selectivity for addition of the glycosyl acceptor from the opposite face. A common way to employ the neighboring group participation strategy is to protect the 2-hydroxyl position with an acyl group such as an acetate or benzoate ester. This often leads exclusively to the 1,2-*trans*

product (Scheme 1.7) and is commonly used to synthesize β-glucose and α-mannose glycosides.

Scheme 1.7 Neighboring Group Participation in Glycosylations

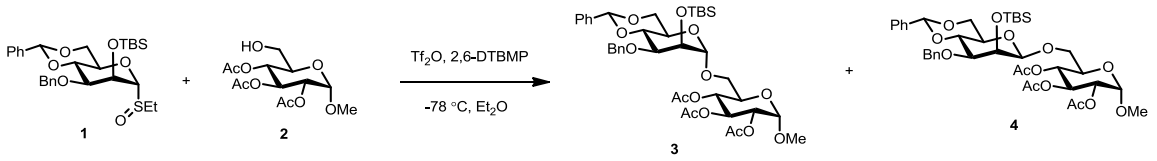


The selective synthesis of 1,2-*cis* glycosides poses a much greater challenge. When considering the synthesis of α-glucosides, one can often achieve good to excellent selectivity for the axial glycosidic bond under thermodynamic glycosylation conditions. The kinetic product for D-glucose, even in the absence of a participating group at the 2-hydroxyl position, is the β-anomer due to the steric repulsion from the 2-hydroxyl group. However, the thermodynamic product is the α-anomer due to the anomeric effect which provides stabilization of the axial C—O bond by lone pair delocalization from the pyran oxygen into the σ*-orbital of the glycosidic bond. Therefore, selectivity for the α-anomer of glucose can be observed under the appropriate thermodynamic conditions.

The synthesis of β-mannosides provides additional challenges because the α-mannoside product is both kinetically and thermodynamically favored. An elegant solution to the synthesis of β-mannosides was developed by Crich and coworkers.[9] When utilizing Kahne's method for sulfoxide activation, they observed a drastic difference in anomeric selectivity based on the order of addition of reagents. When sulfoxide **1** was mixed with glycosyl acceptor **2** and 2,6-di-*tert*-butyl-4-methyl pyridine (2,6-DTBMP) at -78 °C, followed by addition of triflic anhydride (Tf_2O) the glycosidic product was isolated with a 91:9 α:β ratio (**3**:**4**, 64% yield). However, when **1** was first mixed with 2,6-DTBMP and Tf_2O at -78 °C, and allowed to stir for two to five minutes, followed by

addition of glycosyl acceptor **2**, a marked reversal in anomeric selectivity was observed, shifting to a 9:91 α:β ratio (**3**:**4**, 93% yield) (Scheme 1.8).

Scheme 1.8 Crich's Method of β-Mannosylation

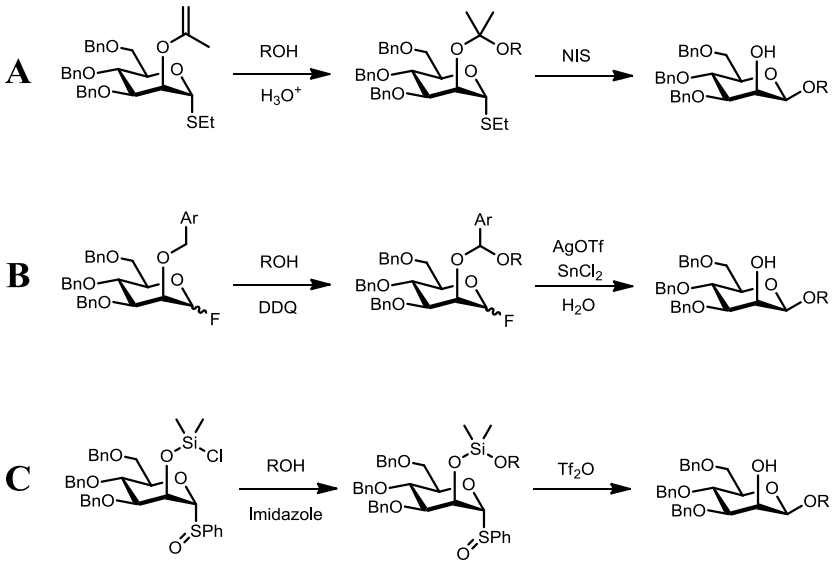


Detailed ^{1}H, ^{13}C, and ^{19}F-NMR studies showed that in Crich's glycosylation protocol the observed selectivity is a result of the formation of an anomeric α-triflate.[10] This leaving group is displaced in a S_N2-like fashion resulting in high selectivity for the β-mannoside. This method continues to be state-of-the-art for the formation of β-mannosides despite the fact that it requires protection of all potentially nucleophilic groups on the glycosyl donor and acceptor. Additionally, modest β-selectivity is observed with some glycosyl acceptors lacking sufficiently nucleophilic hydroxyl groups. A method that overcomes these limitations would prove to be highly useful.

1.2.3 Intramolecular Aglycone Delivery

In the early 1990's, a series of communications were published in an effort to overcome the challenges of synthesizing 1,2-*cis* glycosides, specifically β-mannosides. The unifying strategy in these reports was the use of a temporary linker to tether the glycosyl donor to the acceptor. The acceptor was tethered to the 2-hydroxyl group such that it was spatially oriented for delivery via a 5-membered transition state resulting in formation of the 1,2-*cis* glycoside exclusively (Scheme 1.9).[11]

Scheme 1.9 Intramolecular Aglycone Delivery Methods



The first temporary linkage used for intramolecuar aglycone delivery was reported by Hindsgaul and coworkers.[12] An isopropylidine ether was treated with acid in the presence of the desired glycosyl acceptor to form a dimethyl ketal linker (Scheme 1.9, equation **A**). Activation of the thioethyl leaving group with N-iodosuccinimide (NIS) resulted in good yields of the desired β-mannoside. The use of hindered glycosyl acceptors resulted in low yields for both the ketal and β-mannoside formation, and is a significant limitation of this methodology.

An alternative design for intramolecular aglycone delivery was developed by Ito and Ogawa using a *p*-methoxybenzyl protected 2-hydroxyl group.[13] Treatment of this compound with DDQ in the presence of an alcohol oxidatively formed the desired acetal linkage. Activation of the glycosyl fluorides with AgOTf and $SnCl_2$ in the presence of water gave good yields of the β-mannoside exclusively (Scheme 1.9, equation **B**). This method was further improved by its development with thioglycosides which allowed a greater range of hindered glycosyl acceptors to be glycosylated in good yield.[14]

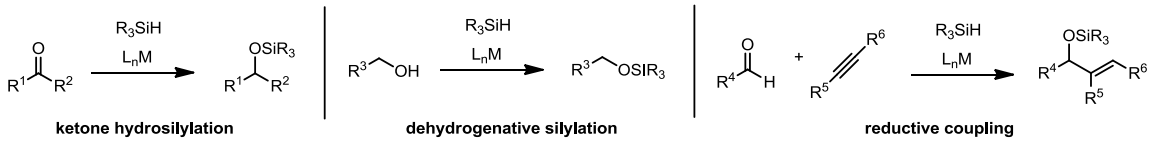
The Stork group used dichlorodimethylsilane to link the 2-hydroxy glycosyl donor to a hydroxyl group on the acceptor resulting in a dimethylsilyl-linker (Scheme 1.9, equation **C**).[15] The sulfur leaving group of the silyl-linked compounds is oxidized to the sulfoxide by *m*-CPBA, and subsequent treatment with Tf_2O provided the β-mannoside as the only isolated anomer. A report using the same dimethylsilyl-linked strategy was simultaneously reported by Bols in the synthesis of α-glucosides.[16] All of these methods provided creative solutions to synthesizing the challenging 1,2-*cis* glycosidic linkage, however they are all limited by the necessity to protect any other nucleophilic functionalities.

1.3 Development of Sugar Silanes

1.3.1 Merging of Carbohydrate Chemistry and Transition Metal Catalysis

Stork and Bols' use of a temporary silyl-linkage to tether glycosyl acceptors and donors for the synthesis of β-mannosides and α-glucosides respectively, provided us with inspiration to develop a new method for the synthesis of these silyl-linked intermediates. Our research group saw this as an opportunity to impart our expertise in the field of transition metal catalysis and utilize the commonly employed silane reducing agent to synthesize silyl-linked compounds for intramolecular aglycone delivery. A variety of transition metal-catalyzed procedures use silanes to synthesize O—Si bonds either by hydrosilylation of ketones, dehydrogenative silylation of alcohols, or reductive coupling of carbonyl compounds with other π-systems (Scheme 1.10).[17]

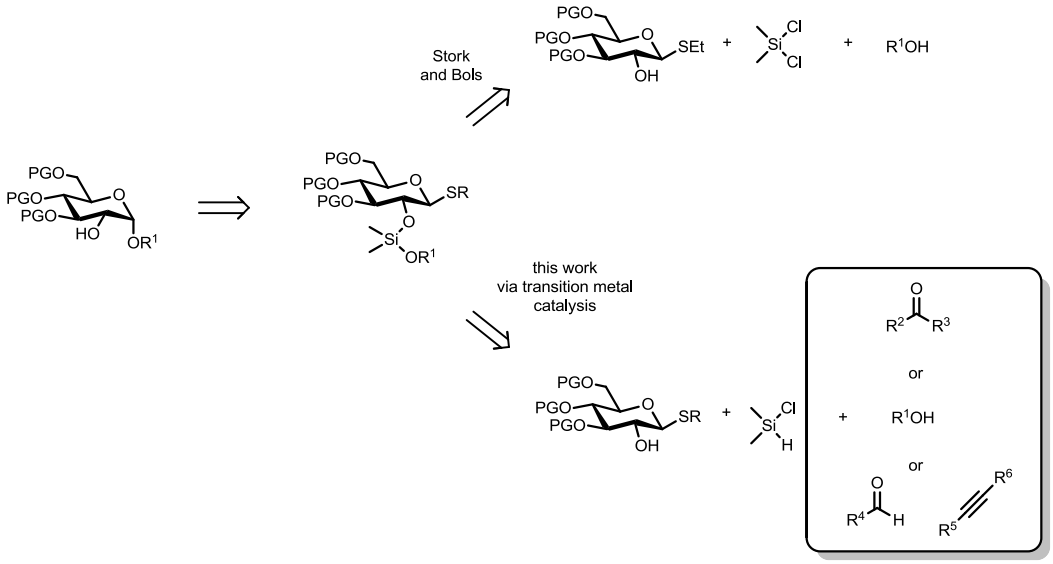
Scheme 1.10 Transition Metal Catalysis Utilizing Silanes



Transition metal catalysis has many advantages such as the ability to finely tune reactivity of a metal complex by altering the choice of ancillary ligands. The opportunity to achieve high levels of chemoselectivity in complex systems comes with the ability to fine-tune the reactivity of metal complexes.

Stork and Bols' use of a silyl-tether to afford high levels of anomeric selectivity provided an excellent solution to the synthesis of 1,2-*cis* glycosides. However, we felt that the way in which the silyl-linked tethers were synthesized could be greatly improved. Instead of using a dichlorodimethylsilane to tether a glycosyl acceptor and donor, we proposed using chlorodimethylsilane to synthesize a carbohydrate-bearing silane reducing agent (Scheme 1.11). This would allow us to synthesize the desired silyl-linked compounds while benefitting from the tunable reactivity of transition metal catalysis, thereby allowing the synthesis of *O*-glycosides from the standard alcohol oxidation state by dehydrogenative silylation. This strategy would also allow the unconventional synthesis of *O*-glycosides from ketones by carbonyl reduction. Additionally, C—C bonds can be formed in the synthesis of aglycones by the silane-mediated reductive coupling of two π-systems. These new opportunities utilizing carbohydrate-bearing silanes could provide useful new avenues for the selective incorporation of glycosides in complex settings and provide a purely chemical method for the rapid discovery of new biologically active compounds.

Scheme 1.11 New Opportunities for Glycosylation with Sugar Silanes



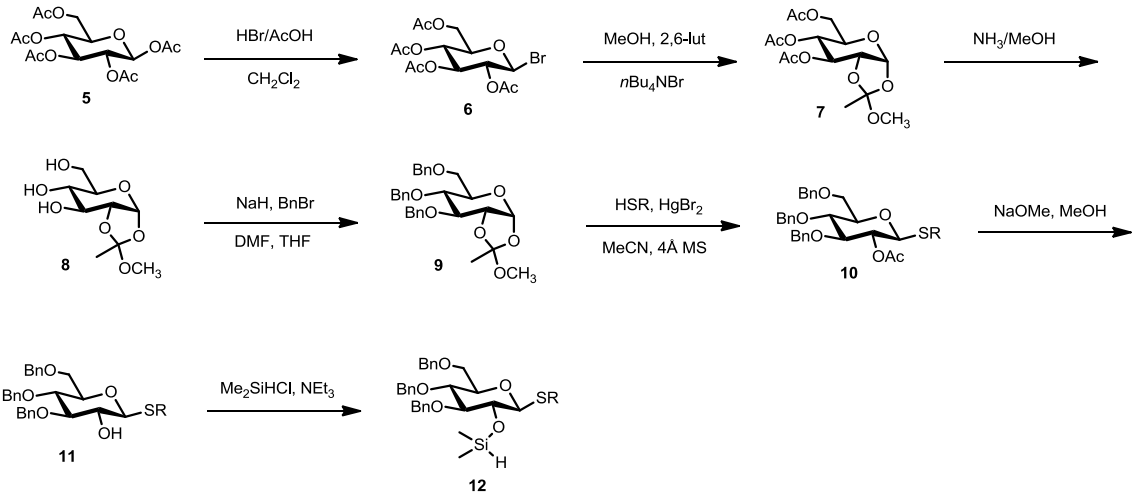
1.3.2 Synthesis of Carbohydrate-Bearing Silane Reducing Agents

Carbohydrate-bearing silane reducing agents were unknown at the time of our proposal, so we envisioned synthesizing a 2-hydroxy glycosyl donor that could be converted into a silane reducing agent, which we have termed a "sugar silane." These silane reducing agents can be synthesized from the commercially available chlorodimethylsilane. A robust, large scale synthesis of sugar silanes was designed starting from inexpensive starting materials, to allow us to explore their applications (Scheme 1.12).[18]

To begin the synthesis of the desired glucose variant of a sugar silane reducing agent, the commercially available glucose pentaacetate **5** was treated with a mixture of hydrobromic and acetic acid in methylene chloride to generate the glycosyl bromide **6**. Refluxing **6** in methylene chloride in the presence of methanol, and tetrabutylammonium bromide with 2,6-lutidine as an acid scavenger, yielded the orthoester **7**, which serves to protect the 2-hydroxy position. Treatment of **7** with an ammonia solution in methanol

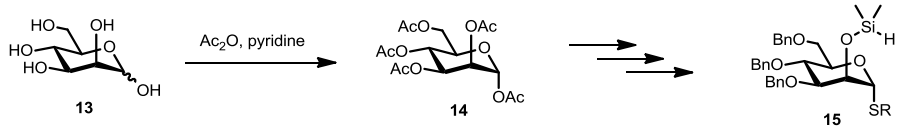
removes the acetate groups to produce triol **8**. Perbenzylation of **8** is achieved by treatment with sodium hydride in the presence of benzylbromide to yield orthoester **9**. The thioglucoside **10** is next synthesized by the mercuric bromide catalyzed opening of the orthoester in the presence of a thiol and 4Å molecular sieves. The 2-hydroxyl position is deacylated in basic methanol to give the 2-hydroxy silane precursor **11**. At this stage in the synthesis, the only chromatographic purification is performed to give the pure 2-hydroxy sugar. It was also found that the purification of 2-hydroxy glucose compounds could be achieved using only a short plug of silica gel to remove non-polar impurities followed by elution of the impure **11** away from the highly polar impurities. Recrystallization from a mixture of methylene chloride and hexanes gave **11** as a white crystalline solid. This can then be silylated with triethylamine and chlorodimethylsilane to give the desired sugar silane **12**. Purity of **11** is paramount as the desired dimethyl sugar silane is not stable to column chromatography; rather, it is obtained pure upon aqueous workup. The sugar silane compound can be stored for months frozen in benzene, or neat under reduced pressure, and used with comparable results to freshly prepared silane. Alternatively, the corresponding 2-hydroxy compound is stable to bench top storage indefinitely.

Scheme 1.12 Synthesis of a Glucose Sugar Silane



The synthesis of a mannose sugar silane begins with peracylation of D-mannose **13** in a mixture of acetic anhydride and pyridine to give peracylated mannose compound **14**. This is then treated to the exact same sequence as described for the synthesis of the glucose sugar silane, with the exception that in the orthoester forming step, no tetrabutylammonium bromide is required (Scheme 1.13). Despite repeated efforts, all attempts to crystallize the 2-hydroxy thiomannosides failed, requiring careful flash chromatography to yield the desired pure 2-hydroxy compound as a colorless oil. Treatment of the mannose alcohol with triethylamine and chlorodimethyl silane produces the desired mannose sugar silane **15**.

Scheme 1.13 Synthesis of a Mannose Sugar Silane



Both the glucose and mannose sugar silanes are readily prepared on multigram scale in seven or eight steps respectively, and begin from widely available inexpensive reagents. The syntheses are robust, generally yielding the desired compound in an overall

40-50% yield (~90% yield per step), with only a single chromatographic purification. Although both the β-thioglucosides and α-thiomannosides are isolated exclusively in this sequence, it has been shown by Stork that the anomeric stereochemistry of the sulfur leaving group is inconsequential in intramolecular aglycone delivery.[15] The first syntheses of sugar silane reducing agents has been now completed, it was time to test our hypothesis for the formation of silyl-linked compounds by employing transition metal catalysis.

1.4 Glycosylation of Ketones

1.4.1 Ketone Hydrosilylation Background

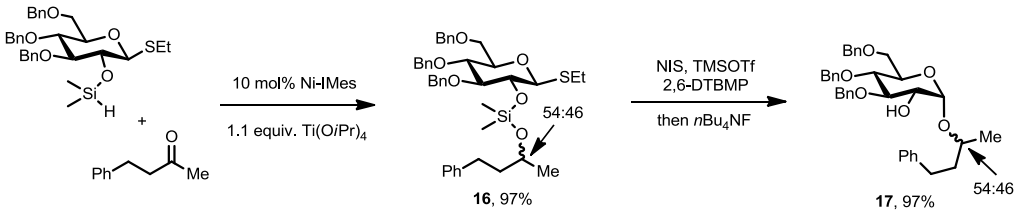
The reduction of carbonyl compounds with silanes has been extensively studied due to the ease of handling silane reducing agents, and wide variety of known catalysts are available to catalyze this transformation. Extensive studies of both asymmetric and non-asymmetric carbonyl hydrosilylations have been reported using ligand-metal frameworks of the metals: gold, silver, copper,[19] platinum, nickel,[20] titanium,[21] rhodium,[22] ruthenium,[23] iridium,[24] iron,[25] and zinc.[26] Additionally, electrophilic borane reagents have been utilized to reduce carbonyl compounds with organosilanes.[27] Each of these catalyst classes has their merits, as well as disadvantages, in various aspects of synthetic utility. The wide variety of options allow one to select the ideal catalyst system based on chemoselectivity, mild reaction conditions, high catalyst turnover, cost of reagent, or generality. Despite all the known ketone hydrosilylation methods, there still remains the need for new synthetically useful methods that expand the utility of this well known transformation.

1.4.2 Developing Conditions for Ketone Reduction by Sugar Silanes

The synthesis of *O*-glycosides generally proceeds through the addition of a nucleophilic alcohol into the electrophilic oxocarbenium ion, or by displacing an activated leaving group, to form the desired glycosidic bond. We were interested to see if glycosylation could be approached from a higher oxidation state through a hydrosilylation/glycosylation sequence utilizing sugar silanes. A variety of nickel(0)-ligand combinations were screened in the hydrosilylation of ketones. Of the various phosphine and N-heterocyclic carbenes, it was found that a nickel(0)-IMes catalyst system was most ideal. A screen of additives also found that reaction rates and yields were improved by the addition of Lewis acidic titanium tetraisopropoxide ($Ti(O\textit{i}Pr)_4$). An optimized procedure was developed by treating 1.0 equivalent of ketone with 1.1 equivalents of sugar silane, 1.1 equivalents of $Ti(O\textit{i}Pr)_4$, and 10 mol% of a Ni(0)-IMes catalyst in a 0.1M solution of dry THF.

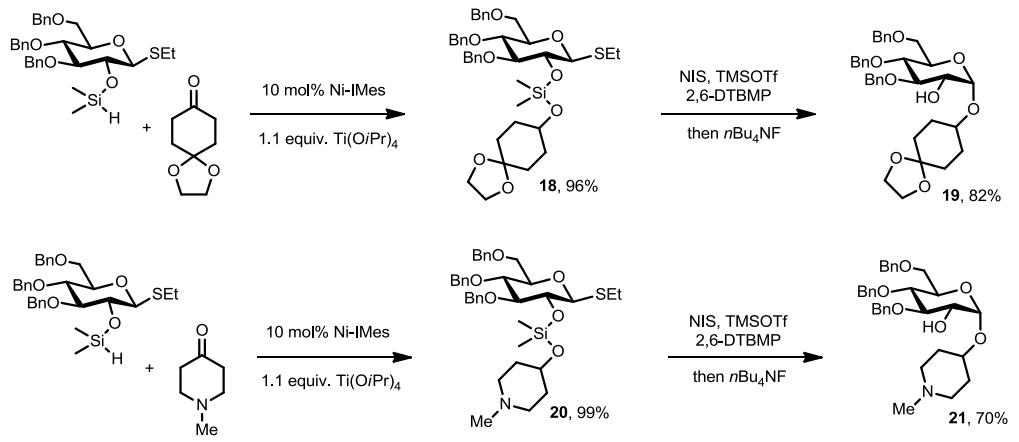
Treatment of benzylacetone with the thioethyl glucose sugar silane under the optimized hydrosilylation procedure resulted in a 97% isolated yield of **16**. It should be noted from the 54:46 dr of **16** that the chirality of the sugar silane does not transfer well to the facial selectivity of the reduction. The silyl-linked compound is then activated for glycosylation with NIS, trimethylsilyl trifluoromethanesulfonate (TMSOTf), and 2,6-DTBMP, followed by addition of $\textit{n}Bu_4NF$ to produce the desired α-glucoside **17** as two readily separable diastereomers in an excellent 97% yield (Scheme 1.14). To our knowledge, this was the first demonstration of a ketone being directly converted to a glycoside without going through a hydroxylic intermediate.

Scheme 1.14 First Example of the Glycosylation of a Ketone



The Ni(0)-IMes catalyzed hydrosilylation of ketones was mild enough to tolerate cyclic ketals in high yield to produce compound **18** in 96% yield. This was converted to the corresponding α-glucoside **19** in 82% yield. A ketone bearing a tertiary basic amine also performed well in the hydrosilylation producing **20** in nearly quantitative yield. The silyl-linked compound was activated using the NIS/TMSOTf procedure to give the α-glucoside **21** in 70% isolated yield (Scheme 1.15).

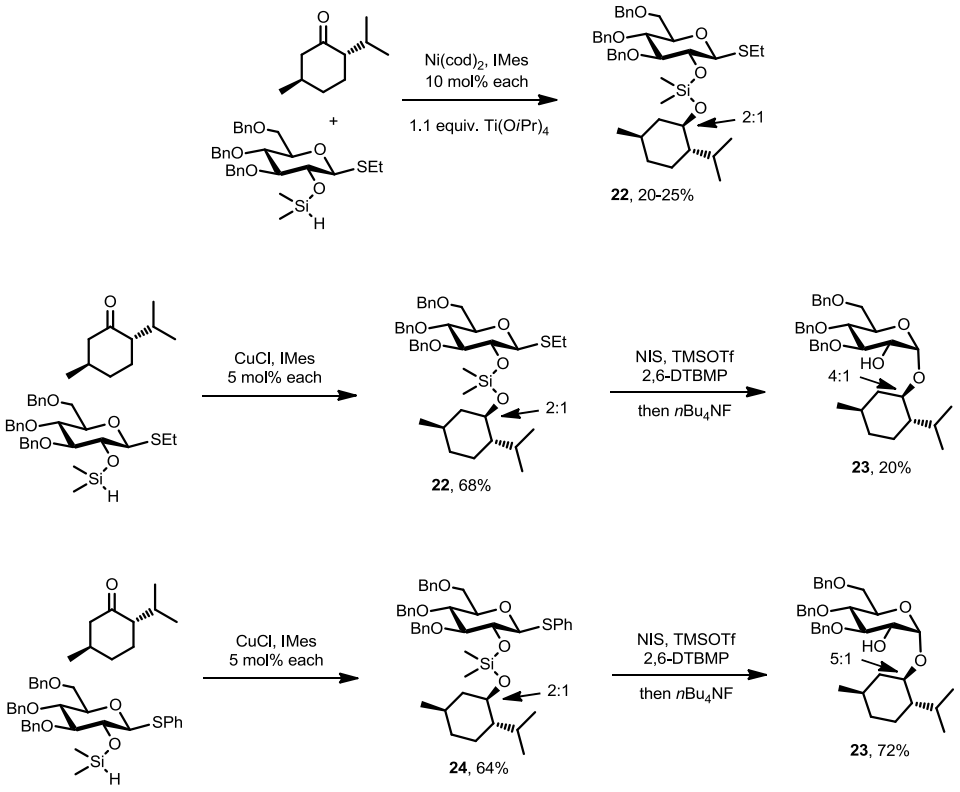
Scheme 1.15 Functional Group Tolerance in Ketone Glycosylation



A limitation of the method was realized when trying to reduce the sterically hindered (-)-menthone using the Ni(0)-IMes conditions, as the desired silyl-linked compound **22** was isolated in 20-25% yield. A survey of the literature led us to a Cu(I)-IMes catalyst developed by Nolan and coworkers for the efficient hydrosilylation of hindered ketones.[28] When the Cu(I)-IMes catalyst was used in the reduction of (-)-menthone with the thioethyl glucose sugar silane, **22** was produced in a synthetically

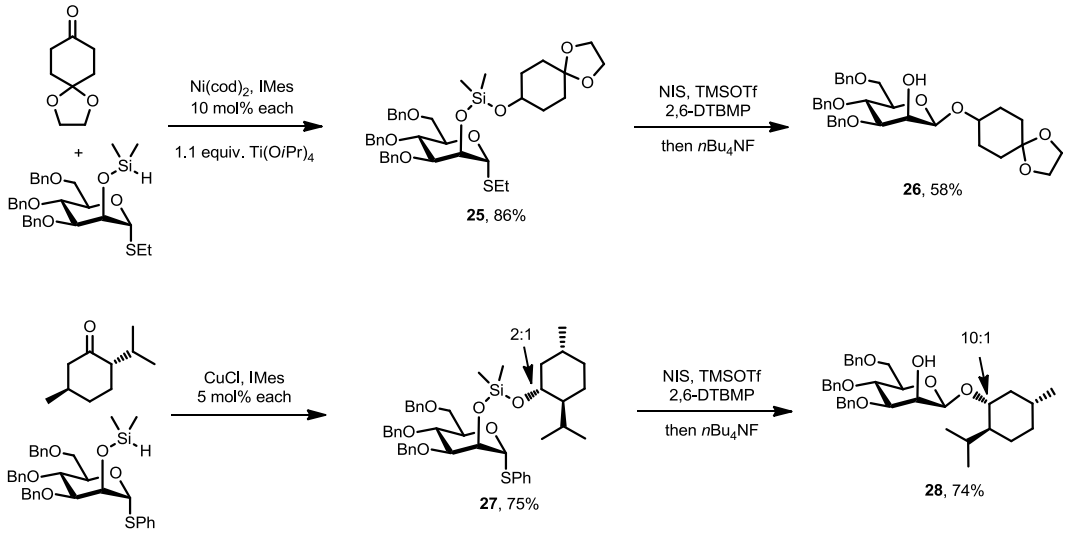
useful 68% yield with a 2:1 dr. Unfortunately, upon activation with NIS/TMSOTf, the desired α-glucoside **23** was only isolated in 20% yield (Scheme 1.16). It was proposed that by switching from thioethyl, to the more active thiophenyl leaving group, a better glycosylation yield could be achieved. The thiophenyl glucose sugar silane and (-)-menthone were treated with Cu(I)-IMes to give **24** in a 64% yield and 2:1 dr. The silyl-linked compound, with the thiophenyl leaving group, was treated with the NIS/TMSOTf glycosylation conditions, resulting in a synthetically useful 72% yield of **23**, with a 5:1 dr. The enhancement of the diastereomeric ratio from **24** (2:1) to **23** (5:1) is the result of the major diastereomer undergoing glycosylation at a much faster rate than the minor diastereomer, producing the observed enhancement of diastereoselectivity.

Scheme 1.16 Glycosylation of Hindered Ketones



Having now demonstrated sugar silanes as effective reagents for the hydrosilylation and glycosylation of ketones to synthesize α-glucosides, we now wished to explore mannose sugar silanes for the synthesis of β-mannosides. The thioethyl mannose sugar silane and ketal-bearing cyclic ketone were treated with the Ni(0)-IMes catalyst system in the presence of Ti(O*i*Pr)$_4$ to give **25** in 86% yield, which upon treatment with NIS/TMSOTf gave the β-mannoside **26** exclusively in a modest 58% yield (Scheme 1.17). Additionally, the utilization of Nolan's Cu(I)-IMes catalyst resulted in the reduction of the hindered ketone (-)-menthone with a thiophenyl mannose silane to produce **27** in 75% with a 2:1 dr. Glycosylation of **27** proceeded in 74% yield to give the β-mannoside **28**. However, in this case there was a drastic difference in the rates of glycosylation of the major and minor diastereomer resulting in a 10:1 dr.

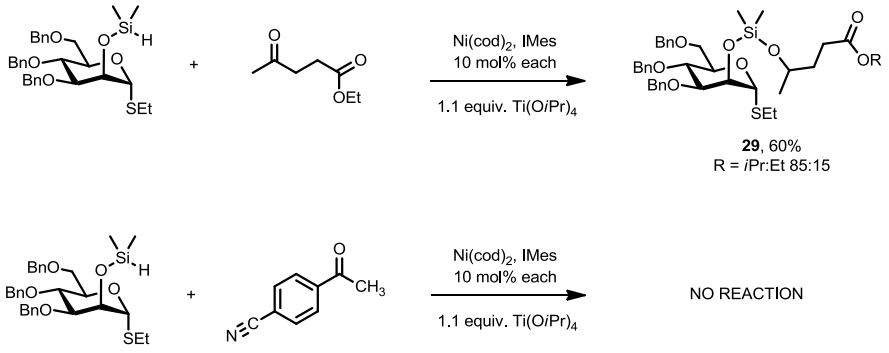
Scheme 1.17 Synthesis of β-Mannosides from Ketones



As we continued to explore the scope of the glycosylation of ketones, we tested the selective reduction of a ketoester. Using the Ni(0)-IMes catalyst resulted in selective reduction of the ketone. However, Ti(O*i*Pr)$_4$ catalyzed a transesterification of the ethyl ester. This reaction, stopped before completion, gave the desired ketone reduction

product **29** in 60% yield of which approximately 85% of the isopropyl ester was present (Scheme 1.18). This undesired background reaction could potentially be masked by using a titanium Lewis acid with the same alkoxide group as the ester. Additionally, treatment of *p*-cyanoacetophenone with a sugar silane and the nickel catalyst resulted in no desired product. The aryl nitrile presumably coordinated to the nickel irreversibly, or oxidized the Ni(0) catalyst, leading to an unproductive reaction.

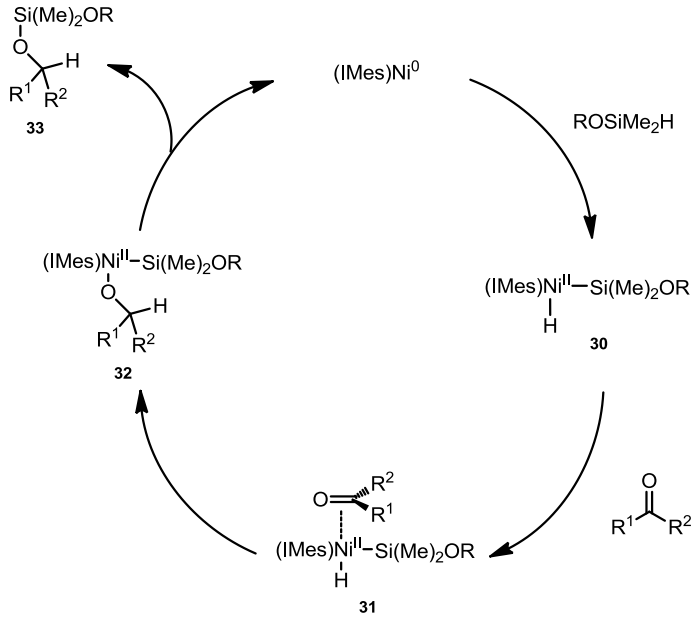
Scheme 1.18 Functional Group Incompatabilities in Ketone Glycosylation



1.4.3 Proposed Mechanism for Ni(0)-IMes and Cu(I)-IMes Hydrosilylation

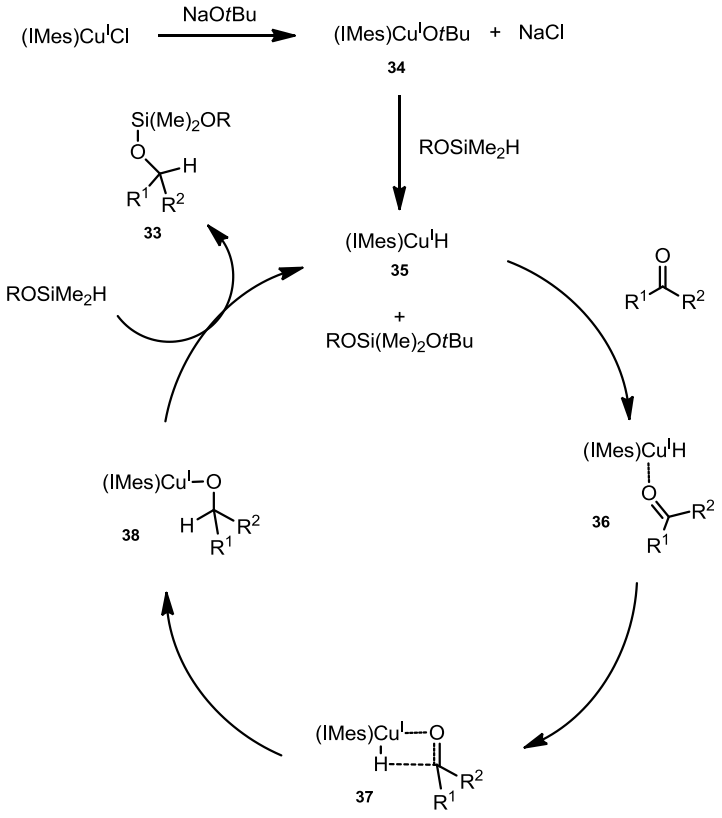
We have now reported the use of sugar silanes in the hydrosilylation of ketones with Ni(0)-IMes and Cu(I)-IMes catalysts. While both of these species are isoelectronic d^{10} metal-ligand combinations, it is proposed that they operate with fundamentally different mechanistic pathways. We proposed that the Ni(0)-IMes catalytic cycle goes through a Ni(0)-Ni(II) cycle which is interchanged by the sugar silane reducing agent (Scheme 1.19). The Ni(0)-IMes catalyst presumably is oxidized by addition to the silicon hydride bond of the sugar silane to form Ni(II) species **30**. Coordination of **30** to the π-bond of a ketone forms complex **31**, which can undergo migratory insertion to produce Ni(II)-alkoxide **32**. Reductive elimination from **32** produces the desired hydrosilylated product **33**, and the active Ni(0)-IMes catalyst for re-entry into the catalytic cycle.

Scheme 1.19 Proposed Catalytic Cycle for Ni(0)-IMes Catalyzed Hydrosilylation



While the sugar silane serves to shuttle nickel between oxidation states, Nolan and coworkers proposed that the copper catalyst remains in the Cu(I) oxidation throughout the entire cycle (Scheme 1.20). They proposed that displacement of chloride from copper with sodium *tert*-butoxide occurs to make **34**, followed by σ-bond metathesis with the organosilanes, producing the active copper hydride **35**. This coordinates to a ketone to give copper complex **36**, which is proposed to undergo migratory insertion across the π-bond (**37**), producing copper alkoxide **38**. Another σ-bond metathesis with the silane generates the desired hydrosilylation product **33**, and regenerates the active copper hydride **35** for additional catalytic turnover.

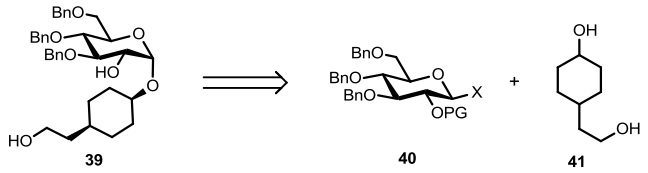
Scheme 1.20 Nolan's Proposed Cu(I)-IMes Hydrosilylation Catalytic Cycle



1.4.4 Site-Selective Glycosylation of Ketones

We have now demonstrated that ketones can effectively be glycosylated by hydrosilylation with a Ni(0)-IMes catalyst to generate 1,2-*cis* glycosides. We ultimately hoped to exploit high levels of selectivity so commonly associated with transition metal mediated processes with an eye towards achieving site-selective glycosylations of polyfunctional substrates. When contemplating how we could apply sugar silanes to improve current methods for glycosylating molecules containing multiple hydroxyl groups, we considered how one would synthesize the glycosylated compound **39** (Scheme 1.21).

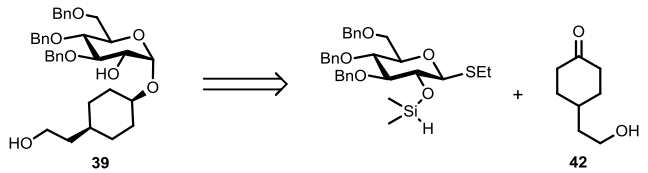
Scheme 1.21 Retrosynthetic Approach to **39** Using Current Methods



Using standard methods for the synthesis of **39**, one would need to consider several different factors. First, the relative stereochemistry of the aglycone must be preassembled prior to any attempts at glycosylation. Second, one must choose a suitable set of glycosylation conditions and protecting group array on the glycosyl donor to ensure high selectivity in forming the desired anomer. Third, and most important, one must block the more nucleophilic primary alcohol in order to glycosylate the less reactive secondary alcohol. This dependence on a protecting group strategy adds two additional steps to the synthesis, as the blocking group must be put on and then removed at a later stage, thereby reducing the efficiency of the synthesis of compound **39**.

In order to overcome these limitations, we proposed approaching the glycosylation from a higher oxidation state with a sugar silane. By doing so, site-selectivity could be achieved between a ketone and an alcohol, relative stereochemistry could be imparted on the aglycone by reduction, and complete control of anomeric stereochemistry could be achieved (Scheme 1.22).

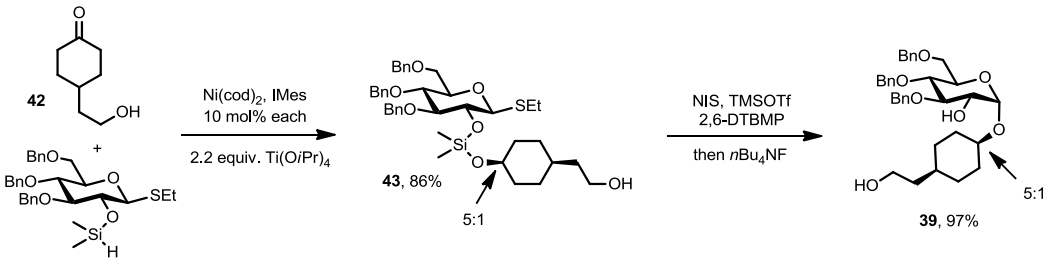
Scheme 1.22 Retrosynthetic Approach to **39** Using a Sugar Silane



With the hope of testing our ketone hydrosilylation strategy in the synthesis of glycoside **39**, hydroxyketone **42** was synthesized and subjected to the Ni(0)-IMes

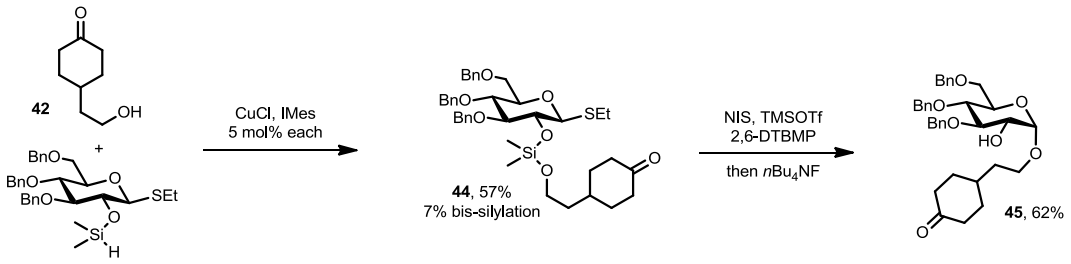
conditions with 2.2 equivalents of Ti(O*i*Pr)$_4$. Gratifyingly, this led almost exclusively to the ketone reduction product **43** in an 86% isolated yield with a 5:1 dr (Scheme 1.23). The silyl-linked compound was then activated using NIS and TMSOTf to yield the desired α-glucoside **39** in 97% yield. Not only was complete control of anomeric stereochemistry achieved, relative stereochemistry of the aglycone was set during the same hydrosilylation step. Glycoside **39** was synthesized without the use of protecting groups to mask the reactivity of the more nucleophilic primary hydroxyl group, highlighting the utility of sugar silanes in streamlining the synthesis of glycosides.

Scheme 1.23 Site-Selective Glycosylation of a Hydroxyketone



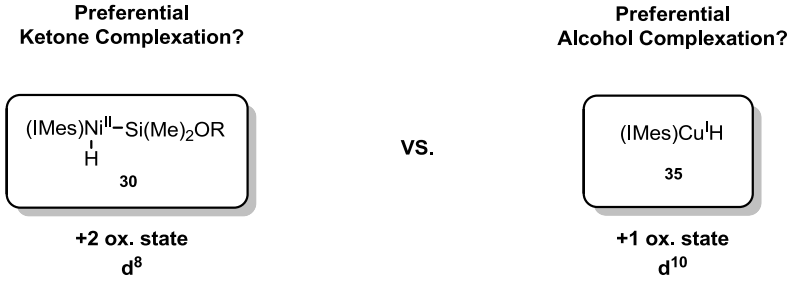
In our continued efforts to explore the role of catalyst-derived selectivity, we also subjected hydroxyketone **42** to the isoelectronic Cu(I)-IMes catalyst conditions. In this case, a complete reversal in site-selectivity was observed. Now dehydrogenative silylation was favored to form compound **44** in 57% yield. This could be converted to the α-glucoside **45** in a moderate 62% yield (Scheme 1.24). In addition to the dehydrogenative silylation product, 7% of the bis-silylated compound was also isolated. This diminished selectivity is a function of the increased reactivity of the Cu(I)-IMes catalyst system.

Scheme 1.24 Copper Catalyzed Reversal of Site-Selectivity with Sugar Silanes



The observed reversal in selectivity in the glycosylation of hydroxyketone **42** is exactly the type of catalyst controlled site-selective glycosylation we hoped to uncover when introducing sugar silanes. Rigorous mechanistic studies have not been conducted to determine the origin of site-selectivity with hydroxyketones between the Ni(0)- and Cu(I)-IMes catalysts. However, we speculate that the catalyst's preference for ketone hydrosilylation or alcohol dehydrogenative silylation is related to the active hydride species of each catalyst (Scheme 1.25).

Scheme 1.25 Proposed Difference in Site-Selectivity for Ni- and Cu-Hydrides

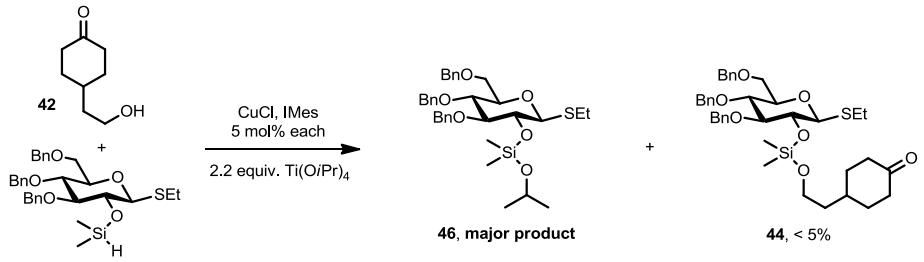


Despite the isoelectronic nature of the nickel and copper catalysts in their inactive species, the active metal hydride species are quite different. The active hydrosilylating species with Ni(0)-IMes is proposed to be the d^8 nickel-hydride species **30**, whereas the active copper-hydride species is a d^{10} Cu(I)-catalyst that lacks the silyl ligand. It is possible that nickel-hydride **30** preferentially binds to the π-system of a ketone, while copper-hydride **35** complexes with alcohols. This is our proposed explanation for the

observed selectivity differences between catalysts reacting with hydroxyketone **42** and a sugar silane.

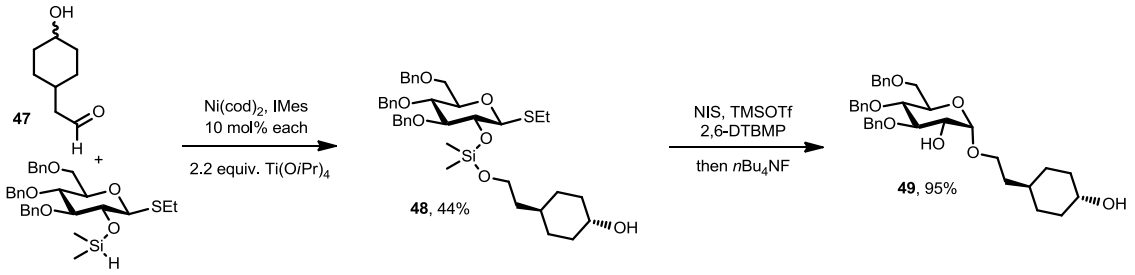
The other main difference in comparing the nickel and copper site-selectivity respectively, is the presence of Ti(O*i*Pr)$_4$ in the ketone hydrosilylation of **42** and its absence in the dehydrogenative silylation. This raised the question about what role the Lewis acid was playing in the ketone reduction. We set out to understand if it was actually acting as an *in situ* protecting group for the primary hydroxyl group, ultimately leading to the observed selectivity for ketone reduction. In order to probe this question, we subjected **42** to the Cu(I)-IMes conditions, in the presence of 2.2 equivalents of Ti(O*i*Pr)$_4$, to see what effect it would have on the selectivity of the silylation (Scheme 1.26). If the selectivity reversed from favoring dehydrogenative silylation, to ketone reduction in the presence of Ti(O*i*Pr)$_4$, it would provide evidence for the *in situ* protection of the primary alcohol by the Lewis acid. When the reaction was conducted, very little silylated **42** was observed. The major product was derived from the dehydrogenative silylation of adventitious isopropanol from Ti(O*i*Pr)$_4$ to form **46**. This provided further evidence for the ketone hydrosilylation selectivity in the Ni(0)-IMes catalyst system with sugar silane reducing agents.

Scheme 1.26 Determining the Role of Ti(O*i*Pr)$_4$ in Site-Selective Glycosylation



In order to further understand the selectivity in the nickel mediated reduction of hydroxyketone **42**, the oxidation states of the ketone and alcohol were interchanged to make hydroxyaldehyde **47**. This was done to explore the possibility of any silyl- or glycosyl-transfer between the primary and secondary alcohol. Treatment of **47** with the Ni(0)-IMes catalyst and 2.2 equivalents of Ti(O*i*Pr)$_4$, resulted entirely in carbonyl reduction to produce **48** in 44% yield (Scheme 1.27). This was isolated predominately as the *trans*-diastereomer, because the *cis*-diastereomer presumably formed an unreactive hemiacetal under the reaction conditions. This was then glycosylated to give the α-glucoside **49** in 95% yield with no evidence of silyl- or glycosyl-transfer.

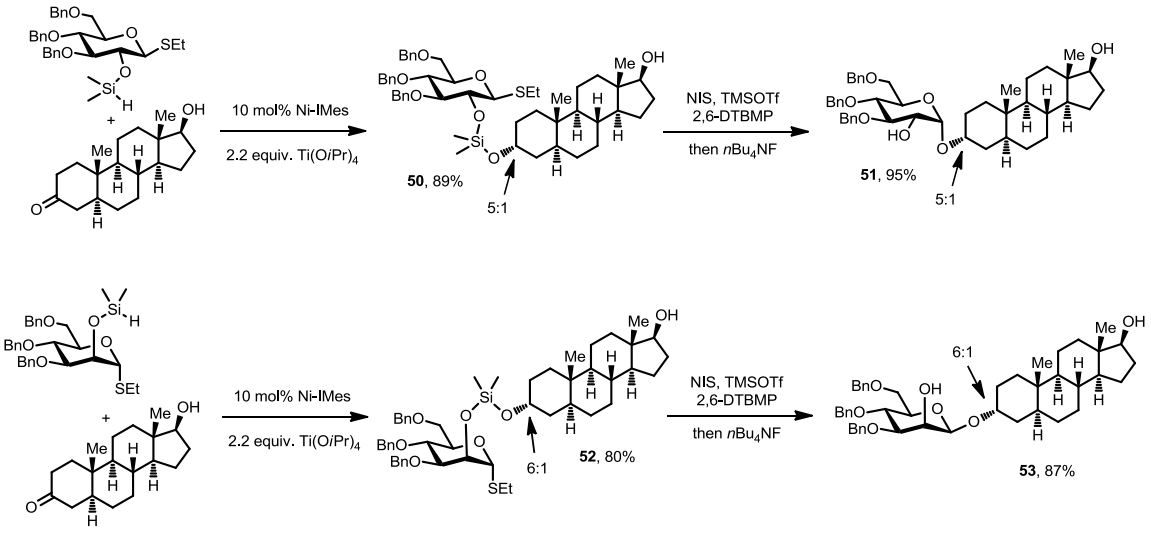
Scheme 1.27 Exploring Silyl- or Glycosyl-Transfer Pathways



With a more thorough understanding of the site-selective glycosylation of hydroxyketones, we explored additional substrates. The steroid dihydrotestosterone was reduced with the thioethyl glucose sugar silane and the Ni(0)-IMes catalyst system to afford **50** in an 89% yield and 5:1 dr with no detection of dehydrogenative silylation (Scheme 1.28). This was glycosylated to give the α-glucosylated steroid **51** in a 95% yield and no change in the dr. Similarly, treatment of dihydrotestosterone with the thioethyl mannose sugar silane under the same conditions yielded **52** in 80% with a 6:1 dr, with no detection of dehydrogenative silylation. Treatment of **52** with NIS and TMSOTf gave β-mannoside **53** in 87% yield (6:1 dr). This again demonstrated the utility

of the site-selective glycosylation of hydroxyketones with transition metal catalysts and sugar silanes.

Scheme 1.28 Site-Selective Glycosylation of Dihydrotestosterone

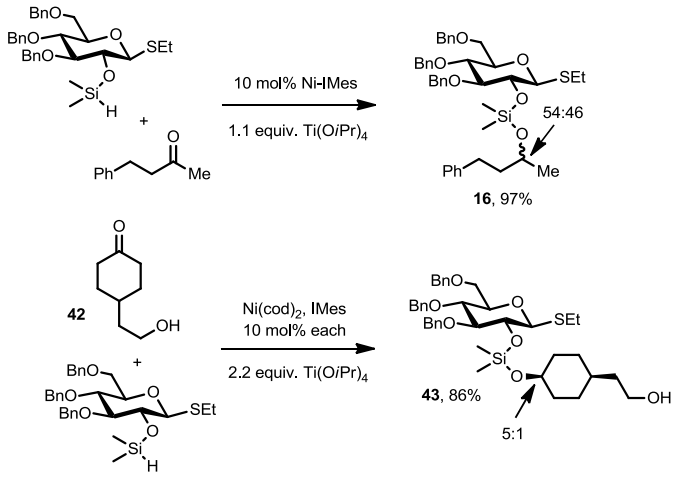


1.5 Future Directions and Ketone Glycosylation Summary

1.5.1 Developing Asymmetric Ketone Reductions with Sugar Silanes

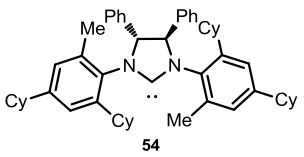
In order to improve the utility of ketone glycosylation, an asymmetric reduction of ketones must be developed. As demonstrated in the reduction of benzylacetone with the thioethyl sugar silane and Ni(0)-IMes, which resulted in a 54:46 dr. The reduction of cyclic ketones such as **42** with Ni(0)-IMes, generally resulted in approximately 5:1 dr, favoring an equatorial approach of the metal-hydride (Scheme 1.29). This is most likely due to the nickel-hydride species also containing the moderately bulky sugar component of the silane. Generally, as steric bulk of a hydride reducing agent increases, the equatorial delivery of the reducing agent to cyclic ketones becomes more favored, resulting in the axial C—O bond.[29]

Scheme 1.29 Diastereoselectivity Observed in Ketone Reduction with Ni(0)-IMes

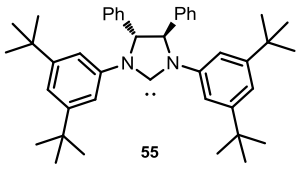


Although each diastereomer can often be obtained in pure form upon chromatographic purification after glycosylation, it would be more synthetically useful to have an asymmetric catalyst that could produce high levels of diastereoselectivity. Ideally, a catalyst system would not only selectively reduce prochiral ketones, but also maintain high levels of site-selectivity in polyfunctional molecules similar to that demonstrated by the Ni(0)-IMes catalyst. In order to find a ligand that provided diastereocontrol in ketone reduction, a quick study was devised with chiral N-heterocyclic carbenes (NHCs) developed in our lab for the asymmetric nickel-catalyzed reductive coupling of aldehydes and alkynes.[30] In order to simplify the determination of selectivity, the less complex triethyl- and triphenylsilane were used as the reducing agent (Scheme 1.30).

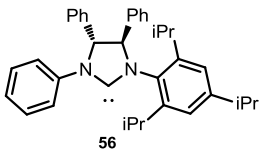
Scheme 1.30 Asymmetric Ketone Reduction Ligand Screen

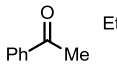


Et_3SiH 6% ee
Ph_3SiH 1% ee

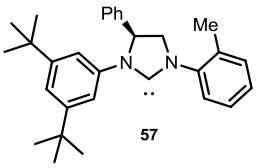


Et_3SiH 12% ee
Ph_3SiH 3% ee





Et_3SiH 6% ee



Et_3SiH no rxn
Ph_3SiH 1% ee

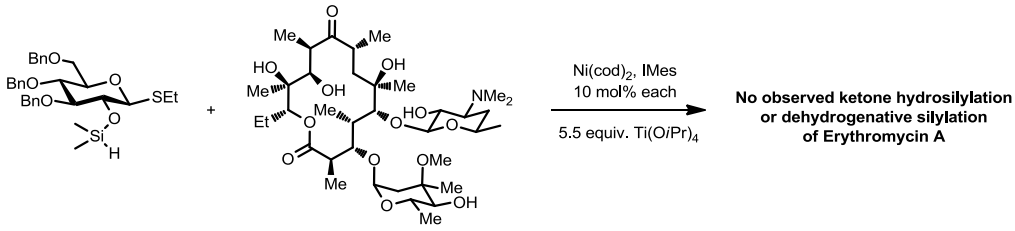
In an attempt to quickly assay several ligands for asymmetric reduction of ketones, acetophenone was chosen, and chiral HPLC conditions were developed for the separation of enantiomers from a non-selective sodium borohydride reduction. Chiral NHCs **54**-**57** and $Ni(cod)_2$ were used with Et_3SiH and Ph_3SiH to reduce acetophenone, followed by addition of nBu$_4$NF, to probe the enantiomeric excess of the alcohol reduction product. It was found that NHC **54** gave 6% ee with Et_3SiH and 1% ee with Ph_3SiH. The bulky C_2-symmetric ligand **55** and Et_3SiH gave a slight increase in enantiomeric excess up to 12% ee, Ph_3SiH resulted in a lower 3% ee. Switching to non-C_2-symmetric NHCs, **56** and **57**, did not improve the enantiomeric excess any further. **56** gave a 6% ee with Et_3SiH, whereas **57** did not react with Et_3SiH and produced nearly no facial selectivity when using Ph_3SiH. It was determined at this point that the chirality transfer from these ligands, designed for the asymmetric reductive coupling of aldehydes and alkynes, did not relate to prochiral facial selectivity in ketone reductions. Therefore, future efforts must focus on expanding the ligands to be screened in order to better

understand how the spatial features of the asymmetric catalyst will transfer to selective ketone reduction.

1.5.2 Ketone Glycosylation in Complex Molecules

The ultimate goal of developing sugar silanes to merge the fields of carbohydrate chemistry and transition metal catalysis is to have the ability to selectively incorporate glycosides into complex molecules based on the functional group, without protecting groups. This would provide the purely chemical complement to the glycorandomization approach of Thorson that was mentioned earlier in this chapter. After developing the glycosylation of ketones and gaining a better understanding for the site-selective glycosylation of hydroxyketones, we wished to push the limits of our method by testing it in a highly complex setting. Erythromycin A was chosen as a target due to its high level of complexity, known biological activity, and single ketone in the presence of many hydroxyl groups (Scheme 1.31).

Scheme 1.31 Attempt at Site-Selective Glycosylation of Erythromycin A



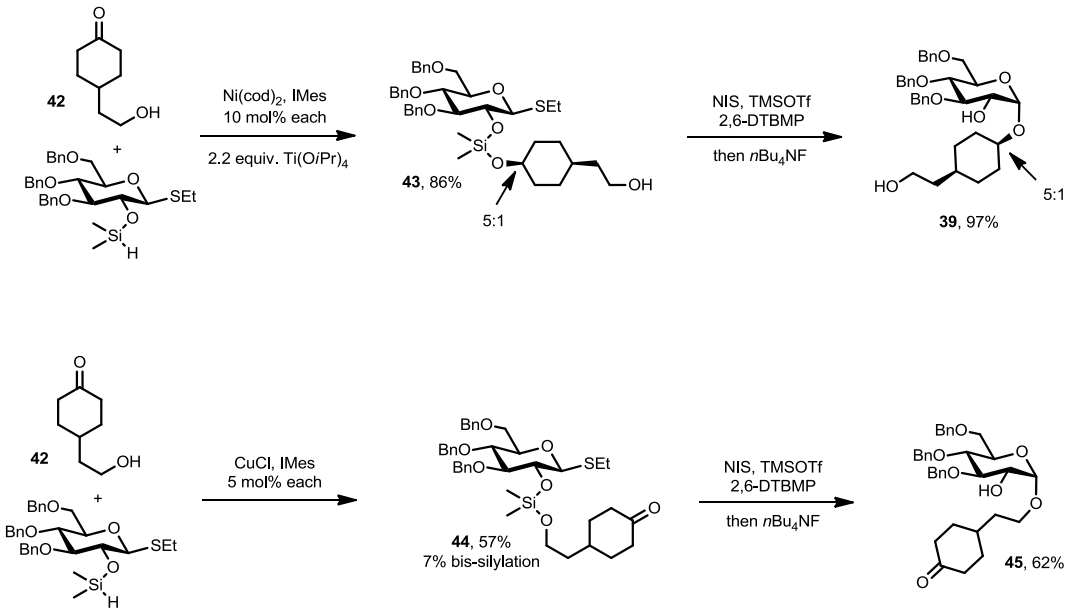
When attempting to hydrosilylate the ketone of Erythromycin A with the thioethyl glucose sugar silane and Ni(0)-IMes catalyst system, no desired product was observed. Additionally, no dehydrogenative silylation of the macrolide was observed. It appeared that solubility of Erythromycin A in THF as well as having 5.5 equivalents of $Ti(O\textit{i}Pr)_4$ were detrimental to the reaction. In order to better understand how polar solvents would affect the Ni(0)-IMes catalyst system, control experiments were conducted with

benzylacetone and THF containing 5% DMF or DMSO. The reaction was completely tolerant of DMF, but DMSO reduced the yield and efficiency of ketone reduction. These solvents would play an important role in the solubility of polar molecules, and their compatibility with the nickel-catalyzed hydrosilylation was important to determine. It would also be beneficial to develop conditions that do not rely on the addition of Lewis acids as complex molecules often contain many Lewis basic sites. This will require the addition of a large excess of the Lewis acid, possibly causing undesired side reactions.

1.5.3 Summary of Sugar Silanes in the Glycosylation of Ketones

This chapter has focused on the development of sugar silanes and their utilization with transition-metal catalysis. An orthogonal glycosylation strategy has been developed in which ketones are directly converted to *O*-glycosides for the first time. This method generally produces high yields in both the reduction of ketones and glycosylation of silyl-linked intermediates which exclusively generate the desired α-glucoside or β-mannoside products. Additionally, the catalyst-controlled site-selective glycosylation of hydroxyketone **42** was demonstrated (Scheme 1.32).

Scheme 1.32 Catalyst-Controlled Site-Selective Glycosylation of a Hydroxyketone



The introduction of sugar silanes as new reagents for glycosylation provides many opportunities for novel, site-selective methods in which compounds can be glycosylated in a more efficient manner.

Chapter 2

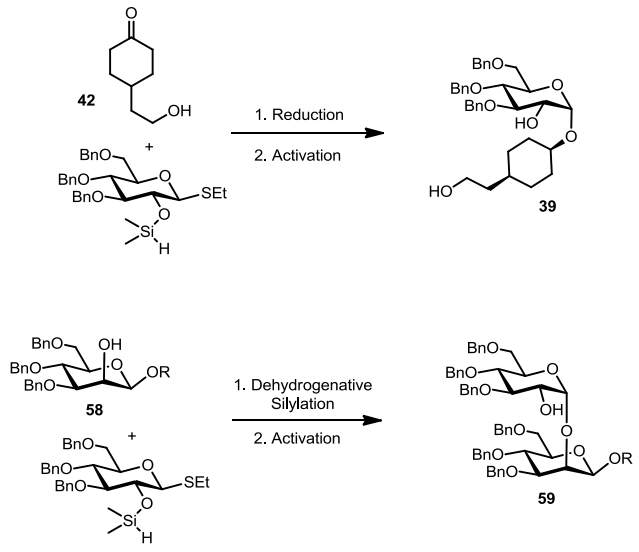
Dehydrogenative Silylation with Sugar Silanes: Progress Towards Streamlining the Synthesis of Disaccharides

2.1 Introduction to Dehydrogenative Silylation

2.1.1 Transitioning from Ketone Hydrosilylation to Dehydrogenative Silylation

The conversion of ketones directly to glycosides without going through a hydroxylic intermediate was a fundamentally new advance in the synthesis of *O*-glycosidic bonds.[18] However, it would be useful to develop complementary conditions for the site-selective dehydrogenative silylation of alcohols. Many substrates of interest, such as carbohydrates, exist in the alcohol oxidation state, and it would be laborious to oxidize then reduce the compound to form the desired glycosidic bond (Scheme 2.1).

Scheme 2.1 Ketone Hydrosilylation vs. Dehydrogenative Silylation with Sugar Silanes

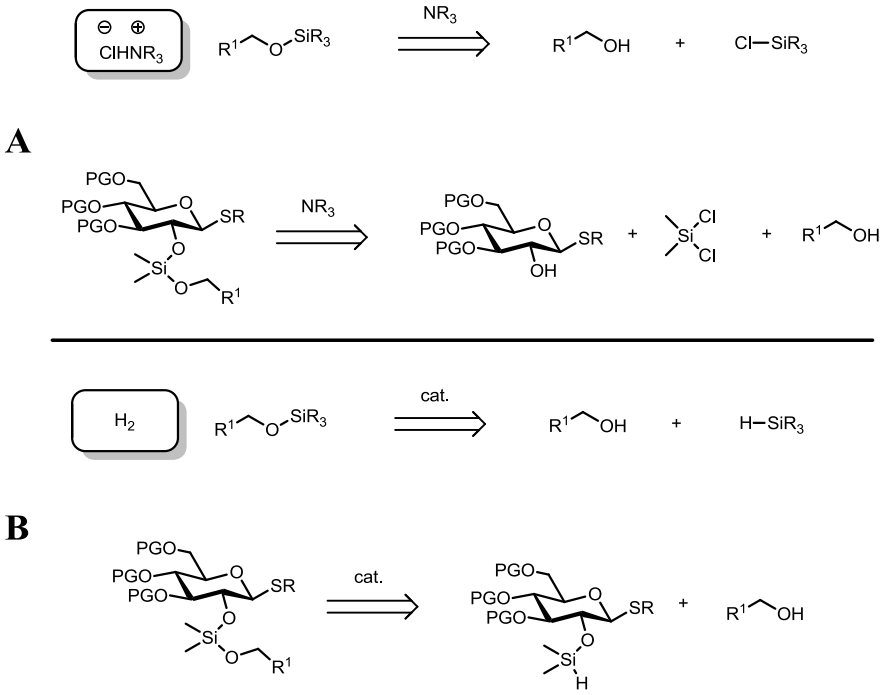


When exploring the glycosylation of carbohydrate alcohols such as **58**, the dehydrogenative silylation pathway is much more practical. Oxidizing the alcohol followed by reduction with a sugar silane would add additional steps as well as erase the existing stereochemical information. With this in mind we wanted to apply sugar silanes to a method aimed at the dehydrogenative silylation of alcohols. Ideally this method will be user friendly, mild, and utilize catalyst derived selectivity for the glycosylation of hydroxyketones as well as diols.

2.1.2 Advantages of Dehydrogenative Silylation with Silanes

Silyl ethers are most commonly synthesized by the nucleophilic addition of an alcohol to an electrophilic silylchloride or silyltriflate species in the presence of an amine base.[31] While this is an effective method for the synthesis of the desired silyl protected alcohol, it requires an aqueous work up to remove the stoichiometric production of ammonium salts. This was used in the synthesis of silyl-linked compounds by Stork and Bols by the sequential addition of two different alcohols to dichlorodimethyl silane.[15,16] Not only does this require the removal of stoichiometric byproducts and purification of sensitive intermediates, but it also requires careful control of addition in order to avoid undesired homocoupling of the alcohols (Scheme 2.2, equation **A**).

Scheme 2.2 Differences in Silyl Ether Synthesis



On the other hand, when silylhydride reagents are utilized with a catalyst to form silyl ethers, the only byproduct is hydrogen gas, which simplifies purification of the desired product. Instead of synthesizing the silyl-linked compounds from dichlorodimethyl silane, we use chlorodimethyl silane to make the sugar silane. The sugar silane is then coupled to the desired alcohol by dehydrogenative silylation to form a silyl-linked compound without any issues of homodimerization (Scheme 2.2, equation **B**).

2.1.3 Choosing a Dehydrogenative Silylation Catalyst

Dehydrogenative silylation of alcohols, similar to hydrosilylation of carbonyls, has been studied by with an extensive variety of metal catalysts. Complexes of the following metals have been utilized: copper,[32] gold,[33] iron,[34] platinum,[35] nickel,[36] iridium,[37] rhodium,[38] and ruthenium.[39] Additionally, the electrophilic tris-

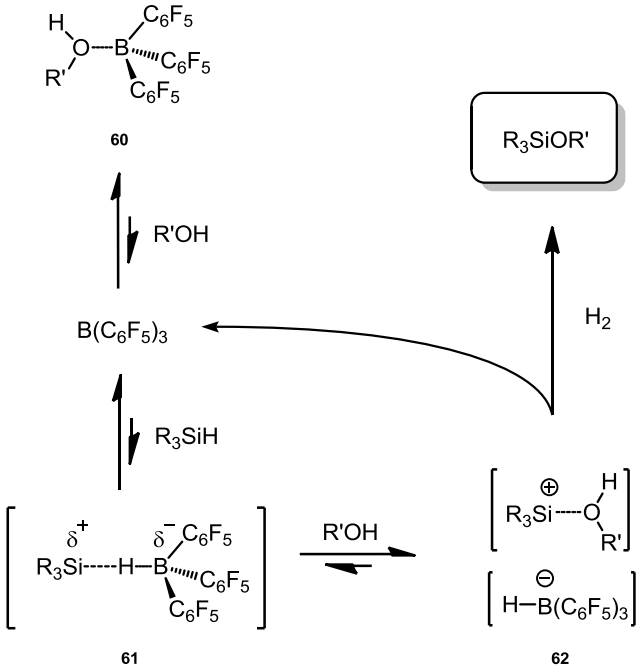
pentafluorophenyl borane has been utilized to silylate alcohols.[40] As demonstrated in the previous chapter, we discovered that Nolan's Cu(I)-IMes catalyst, designed for the hydrosilylation of hindered ketones, was also an effective catalyst for the dehydrogenative silylation of alcohols.[18,28] In addition to this catalyst system, a wide variety of catalysts for dehydrogenative silylation have been reported in the literature. As mentioned previously, we hoped to select a catalyst system that would allow for the user friendly, mild, and selective silylation of alcohols with sugar silanes. One such catalyst that fits this description was tris-pentafluorophenyl borane ($B(C_6F_5)_3$), developed by Piers and coworkers. It was particularly attractive because $B(C_6F_5)_3$ is bench stable, requires no ancillary ligands, operates with low catalyst loading, and proceeds effectively at ambient temperature. In addition to these attributes, $B(C_6F_5)_3$ demonstrated selectivity for dehydrogenative silylation of hydroxyketones as well as chemoselectivity in differentially substituted alcohols. These attributes provided more than enough motivation for us to explore its utility with sugar silanes in the hope of streamlining the synthesis of disaccharides.

2.1.4 Proposed Dehydrogenative Silylation Mechanism with $B(C_6F_5)_3$ and Cu-IMes

Piers and coworkers proposed a mechanism where the highly Lewis acidic $B(C_6F_5)_3$, in the presence of an alcohol, is in equilibrium with complex **60** (Scheme 2.3).[40] Although the equilibrium between the free borane and alcohol and **60** lies further towards the complexed species, the small amount of free $B(C_6F_5)_3$ can interact with a silyl hydride species to form **61**. This produces a positively charged, highly electrophilic silicon species similar to a silyltriflate, which, in the presence of a free alcohol, forms the ion pair **62**. This consists of a protonated silyl ether and a borohydride, which quickly

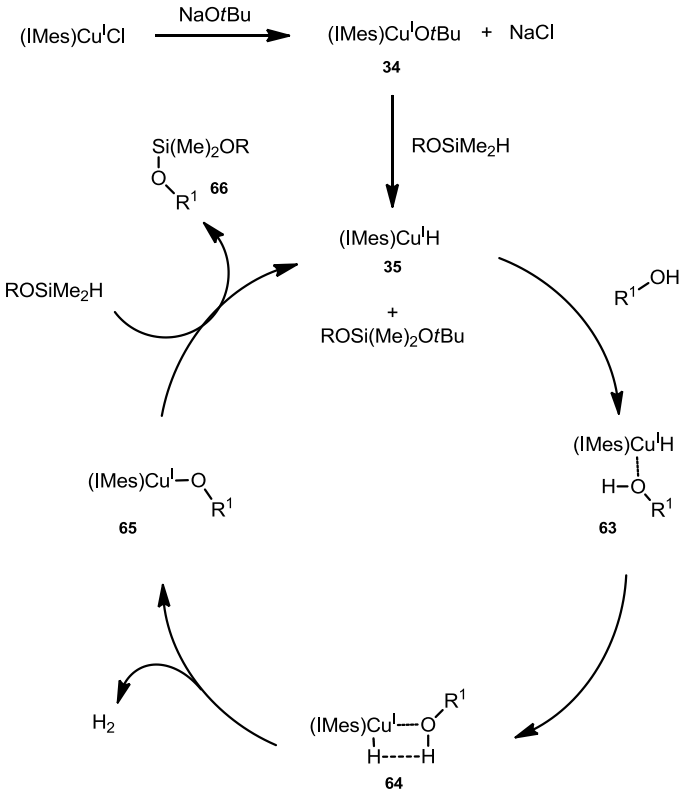
liberate hydrogen gas, producing the desired dehydrogenative silylation product, and regenerating the active $B(C_6F_5)_3$ catalyst species.

Scheme 2.3 Proposed Mechanism of Dehydrogenative Silylation with $B(C_6F_5)_3$



Alternatively, the Cu(I)-IMes catalyzed dehydrogenative silylation of alcohols is proposed to go through a fundamentally different mechanism than that of $B(C_6F_5)_3$ (Scheme 2.4). Similar to the mechanism discussed in the ketone hydrosilylation chapter, sodium *tert*-butoxide displaces chloride from copper to form **34**, followed by σ-bond metathesis with a silane to generate the active copper hydride species **35**. This coordinates to an alcohol, forming complex **63**, followed by σ-bond metathesis (**64**) to liberate hydrogen gas and form copper alkoxide **65**. An additional equivalent of silane will undergo a σ-bond metathesis to form desired product **66**, driven by the strength of a Si—O bond, and regenerate the active copper hydride species to re-enter the catalytic cycle.

Scheme 2.4 Proposed Mechanism for Dehydrogenative Silylation with Cu(I)-IMes

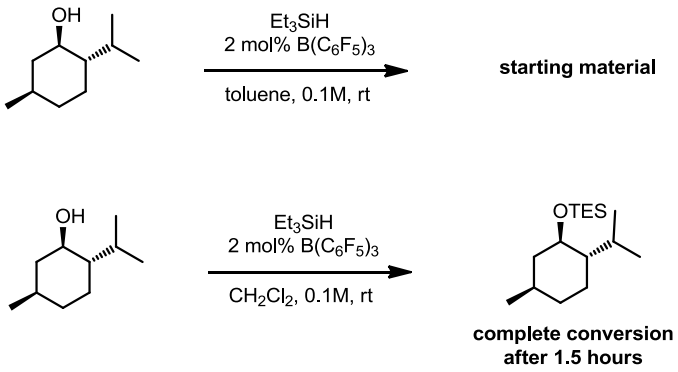


2.2 Dehydrogenative Silylation of Alcohols with Sugar Silanes

2.2.1 Developing Conditions with $B(C_6F_5)_3$ and Sugar Silanes

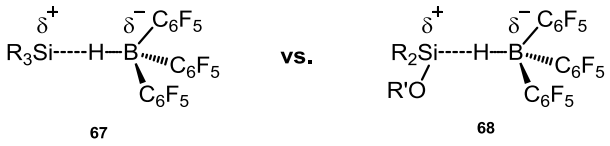
Piers and coworkers found that $B(C_6F_5)_3$ effectively catalyzed the dehydrogenative silylation of alcohols with a variety of silanes, generally using toluene or methylene chloride as the solvent of choice. In order to gain an understanding of the reactivity, an initial screening of conditions was carried out with triethylsilane and (-)-menthol in both of these solvents (Scheme 2.5).

Scheme 2.5 Exploring Solvents in $B(C_6F_5)_3$ Catalyzed Dehydrogenative Silylation



It was found that the dehydrogenative silylation proceeded much faster in methylene chloride, so the initial development of conditions with sugar silanes in the borane-catalyzed dehydrogenative silylation was carried out in methylene chloride. It was found that switching from triethylsilane to the thioethyl mannose sugar silane, the yield was much lower. Upon addition of $B(C_6F_5)_3$, vigorous hydrogen evolution was observed, and undesired byproducts indicative of silane decomposition were observed as well as the desired product. The sugar silane was considerably more reactive than triethyl silane under the same conditions. The observed increase in reactivity when switching from a trialkylsilane (**67**) to a dialkylalkoxysilane (**68**) was not surprising considering the stabilization of the transition state proposed in the borane-mediated hydride abstraction operative in this reaction (Scheme 2.6). It was found that switching back to toluene, or in some cases a toluene: methylene chloride mixture, resulted in higher yield of the desired product.

Scheme 2.6 Explanation for Increased Reactivity with Sugar Silanes

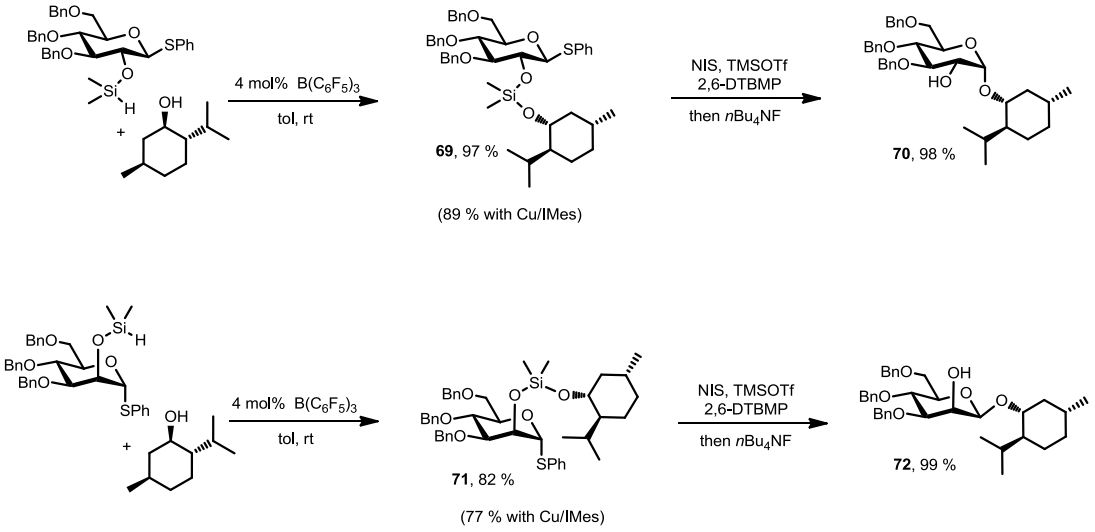


67 68

2.2.2 $B(C_6F_5)_3$ Catalyzed Dehydrogenative Silylation of Alcohols

With a better understanding for the reactivity of sugar silanes in the $B(C_6F_5)_3$ catalyzed dehydrogenative silylation of alcohols, we wanted to apply the method to a variety of alcohols. Using 4 mol% of $B(C_6F_5)_3$ and a thiophenyl glucose sugar silane, (-)-menthol was silylated in 97% yield to give **69** (Scheme 2.7). Activation with NIS/TMSOTf gave the α-glucoside **70** exclusively in 98% isolated yield. Treating (-)-menthol under the same conditions with a thiophenyl mannose silane produced **71** in 82% yield. This was then glycosylated in nearly quantitative yield producing only the β-mannoside **72**. The use of $B(C_6F_5)_3$ in the dehydrogenative silylation of (-)-menthol with both sugar silanes was directly compared to the Cu(I)-IMes procedure, which produced **69** and **71** in 89% and 77% yield, respectively. Based on these results, it was determined that, for the silylation of secondary alcohols, $B(C_6F_5)_3$ is the catalyst of choice.

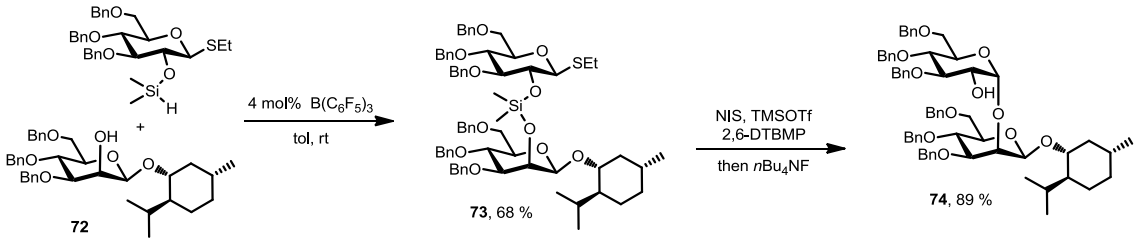
Scheme 2.7 Comparison of Methods for the Dehydrogenative Silylation of (-)-Menthol



An advantage of using the 2-hydroxy group as a tether is that upon glycosylation, the alcohol becomes liberated, allowing further manipulations. Taking **72** and silylating with an equivalent of thioethyl glucose sugar silane gives **73** in 68% (Scheme 2.8).

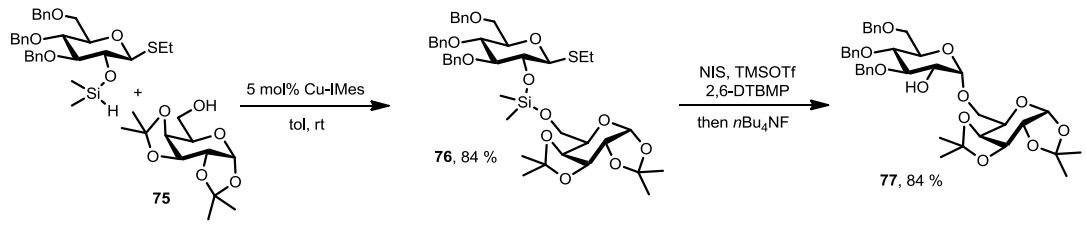
Activating the tethered carbohydrates with NIS/TMSOTf then produces disaccharide **74** in 89% isolated yield, highlighting the utility of iterative glycosylations using $B(C_6F_5)_3$-catalyzed dehydrogenative silylations to form this complex disaccharide in an efficient manner with complete control over the stereochemistry of both anomeric positions.

Scheme 2.8 Iterative Synthesis of a Complex Disaccharide



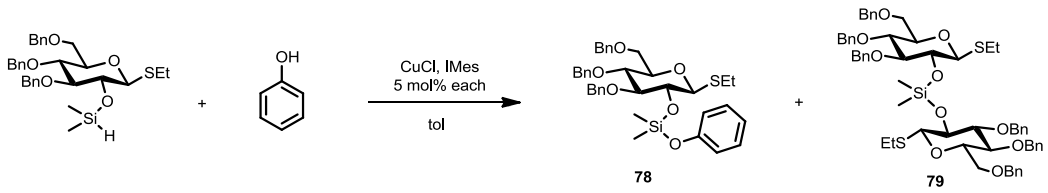
Attempting to silylate the 6-hydroxy galactose compound **75** with the $B(C_6F_5)_3$ catalyst and thioethyl glucose silane produced very little desired product **76**. Increasing catalyst loading, reaction time, and reaction temperature did not lead to synthetically useful yields of **76**. Piers and coworkers reported similarly sluggish, low yielding reactions with primary alcohols. They proposed the more Lewis basic primary alcohol binds strongly to the $B(C_6F_5)_3$ catalyst, rendering it inactive. In order to remedy this limitation, we reverted to the Cu(I)-IMes catalyst system, which reacted with **75** to form **76** in 84% yield (Scheme 2.9). This was glycosylated to form disaccharide **77** in 84% yield. Therefore this demonstration of dehydrogenative silylation established Cu(I)-IMes as an excellent catalyst for the dehydrogenative silylation of primary alcohols.

Scheme 2.9 Dehydrogenative Silylation of Primary Alcohols with Cu(I)-IMes



A limitation of sugar silanes was discovered attempting the dehydrogenative silylation of phenol, when no desired product was observed. Instead the only product observed under the standard Cu(I)-IMes conditions was silyl-dimer **79**. This presumably formed as the increased acidity of phenol led to desilylation of the sugar silane, resulting in a 2-hydroxy sugar, which was then silylated by the sugar silane (Scheme 2.10). It was found that by adding a solution of phenol dropwise to a mixture of the sugar silane and Cu(I)-IMes catalyst system, **78** could be formed, but still in low yields (~30%). Control experiments showed that stirring the sugar silane and copper catalyst did not lead to formation of **79**, as stirring the two together for 5 minutes followed by addition of methanol resulted almost exclusively in dehydrogenative silylation of methanol with little to no formation of **79**. This limitation must be overcome in future efforts as phenolic glycosides represent an important class of biologically active glycoconjugates.[41]

Scheme 2.10 Limitations in the Dehydrogenative Silylation of Phenol

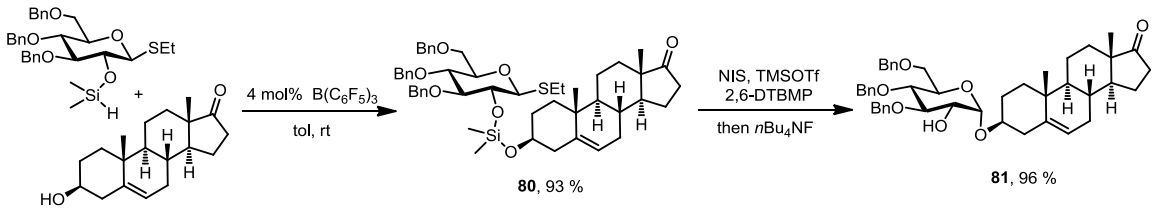


2.2.3 Site-Selective Dehydrogenative Silylation of Hydroxyketones

One of the main goals of developing sugar silanes was to improve the current state of carbohydrate synthesis. In order to achieve this goal, site-selective silylation of polyfunctional molecules is very important. Having already demonstrated catalyst controlled site-selective glycosylation of a hydroxyketone with Ni(0)- and Cu(I)-IMes catalysts, we wanted to explore how $B(C_6F_5)_3$ performed with polyfunctional molecules. Reacting the thioethyl glucose sugar silane with a polyfunctional steroid and 4 mol%

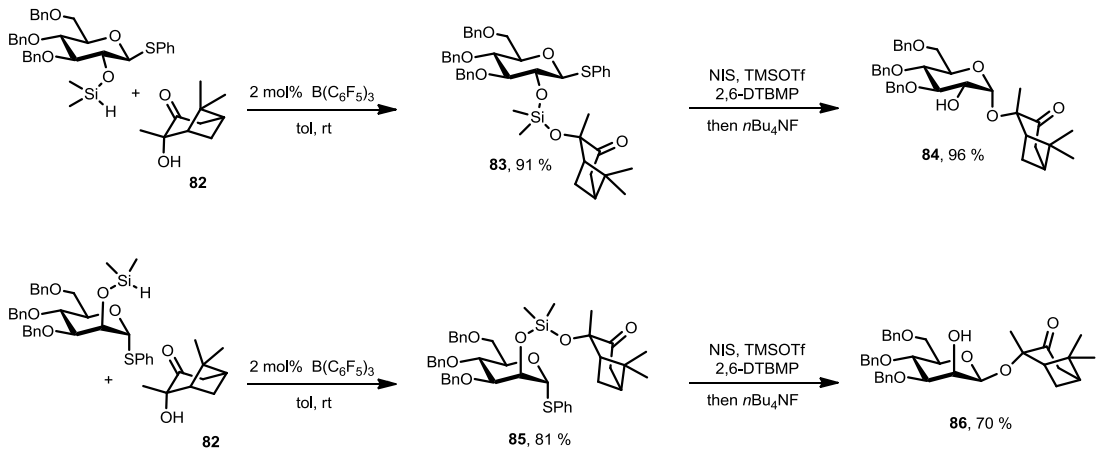
$B(C_6F_5)_3$ resulted exclusively in dehydrogenative silylation of the alcohol to give **80** in 93% yield (Scheme 2.11). This was important to demonstrate, as the aglycone contains an olefin and a ketone, both of which have been shown to be reduced by a combination of silanes and $B(C_6F_5)_3$.[27,42] Silyl-linked compound **80** was activated to yield the α-glucosylated steroid **81** in 96% yield.

Scheme 2.11 Site-Selective Glycosylation of a Polyfunctional Steroid



To this point, only primary and secondary alcohols have been glycosylated with sugar silanes. We wanted to explore the site-selective glycosylation of hydroxyketone **82**, which contains a tertiary alcohol, with $B(C_6F_5)_3$. Not only would this site-selectively glycosylate a hydroxyketone, but it would show the ability to glycosylate a hindered, nonnucleophilic alcohol in the process. Treatment of **82** with the thiophenyl glucose sugar silane and only 2 mol% of $B(C_6F_5)_3$ produced silyl-linked **83** in 91% yield with no detection of ketone reduction (Scheme 2.12). This was readily converted to the 1,2-*cis* glucoside **84** in 96% yield. Not only did this demonstrate the high reactivity of sugar silanes with hindered tertiary alcohols in the dehydrogenative silylation, but also in the glycosylation process.

Scheme 2.12 Glycosylation of a Tertiary Alcohol with Sugar Silanes



Hydroxyketone **82** was also treated with the thiophenyl mannose sugar silane and 2 mol% of $B(C_6F_5)_3$ to give **85** selectively in an 81% yield. When this was subjected to NIS and TMSOTf, the desired β-mannoside **86** was isolated in a 70% yield, demonstrating that the site-selective glycosylation of a tertiary alcohol performed well in both the glucose and mannose sugar silanes.

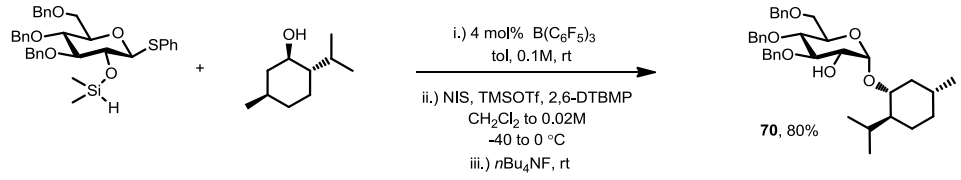
2.2.4 Additional Applications of Sugar Silanes in Dehydrogenative Silylation

Intramolecular aglycone delivery has many advantages, such as the highly selective synthesis of 1,2-*cis* glycosides. This is especially true when the silyl-linked compounds are synthesized in a site-selective manner. However, despite these advantages, intramolecular aglycone delivery is a two pot procedure, in which a linked material is first synthesized and isolated. This is followed by a second step where the linked material is activated to give the penultimate glycoside. This is unlike most traditional glycosylation methods that proceed in a single operation. We therefore opted to investigate a one pot dehydrogenative silylation/glycosylation sequence. The $B(C_6F_5)_3$ catalyzed hydrosilylation was viewed as an ideal scenario for glycosylating in a one pot procedure as the only byproduct of dehydrogenative silylation, hydrogen gas, bubbles out

of solution during the reaction. Additionally, the only species remaining is a catalytic amount of $B(C_6F_5)_3$, as other metal or ligand derived byproducts are not present. Control experiments showed $B(C_6F_5)_3$ had no detrimental effects when added to a NIS/TMSOTf catalyzed glycosylation.

With this understanding of how a catalytic amount of $B(C_6F_5)_3$ would affect a glycosylation sequence, (-)-menthol was selected as an ideal target to test the one pot procedure due to the fact that it was high yielding in both the dehydrogenative silylation and glycosylation step with thiophenyl glucose sugar silane. It was shown that allowing the sugar silane to react with (-)-menthol and 4 mol% $B(C_6F_5)_3$ for 1.5 h, then diluting to 0.02M with CH_2Cl_2 and cooling to -40 °C, followed by treatment with the standard NIS/TMSOTf glycosylation conditions, produced the desired α-glucoside **70** in 80% yield (Scheme 2.13). This shows the possibility of utilizing a one pot dehydrogenative silylation/glycosylation sequence for the synthesis of 1,2-*cis* glycosides.

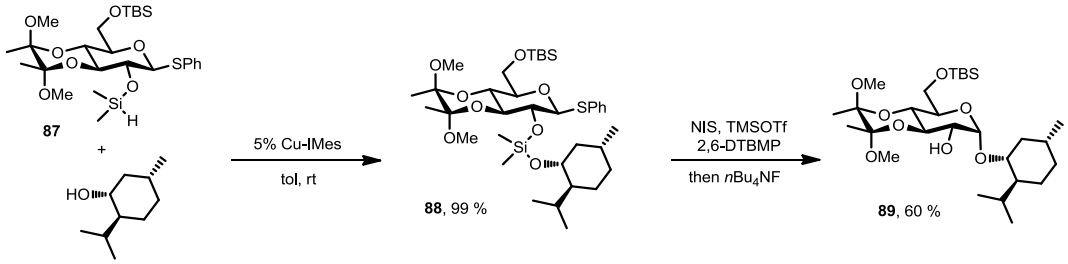
Scheme 2.13 One Pot Dehydrogenative Silylation/Glycosylation of (-)-Menthol



Thus far the development of all sugar silane related procedures has utilized a glycosyl donor containing a thioether leaving group, a dimethylsilyl group linked to the 2-hydroxy group, and benzyl protecting groups at the 3-, 4- and 6-hydroxy positions. While this protecting group array has performed well in all methods without having any detrimental side reactions occasionally associated with protecting groups, it would be nice to develop a sugar silane with a different protecting group array. This would prove highly useful in a scenario where one wishes to further modify the donor sugar after it is

appended to the glycosyl acceptor. Designing a silane with a protecting group array that would allow for selective access to all of the sugar's hydroxyl groups would be advantageous. With that in mind, a new sugar silane **87** was designed with a *tert*-butyldimethyl silyl (TBS) protecting group on the primary 6-hydroxyl group and a Ley acetal linking the 3- and 4-hydroxyl groups together.[43] Using silane **87** and the Cu(I)-IMes catalyst system, the dehydrogenative silylation of (-)-menthol produced **88** in nearly quantitative yield (Scheme 2.14). Compound **88** was treated with NIS and TMSOTf to yield α-glucoside **89** in 60% yield with selective deprotection of the 2-hydroxydimethyl silyl group in the presence of the primary 6-OTBS protecting groups. Protection of the 2-hydroxyl group of **89** followed by standard protecting group conversions will allow selective access to any of the 3-,4- or 6-hydroxyl groups for further manipulations.

Scheme 2.14 Design of a New Sugar Silane for Selective Manipulation



2.3 Site-Selective Glycosylation of Diols

2.3.1 Mechanistic Implications of $B(C_6F_5)_3$ Catalyzed Dehydrogenative Silylation

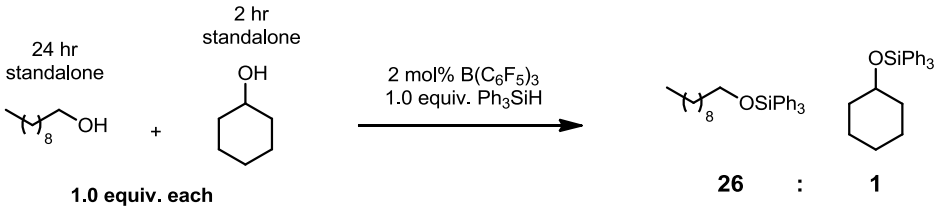
The use of catalysis and sugar silanes has now been demonstrated in several examples where either a ketone or an alcohol can be selectively glycosylated based on catalyst choice. While these are useful in the site-selective synthesis of *O*-glycosides, we would also like to extend this selectivity to diols. An area where this would be particularly useful is in the synthesis of disaccharides in which the glycosyl acceptor has

two free hydroxyl groups that could be selectively glycosylated by judicious choice of reagents and catalyst. Aside from the user-friendly nature of $B(C_6F_5)_3$ and mild reaction conditions, another intriguing feature is its proposed mechanism of action in the dehydrogenative silylation of alcohols.

A revisit to the proposed mechanism reveals why $B(C_6F_5)_3$ is most reactive with tertiary alcohols, and least reactive with primary alcohols (Scheme 2.3). As the Lewis basicity of the alcohol increases, the equilibrium between the free borane and **60** lies towards the complexed species. This prevents formation of any appreciable amount of the electrophilic silyl species **61** when attempting to silylate a primary alcohol. On the other hand as the Lewis basicity decreases with secondary and tertiary alcohols, more free $B(C_6F_5)_3$ is present in solution, allowing formation of the reactive silicon species **61** and then the charge separated **62** which ultimately delivers the desired silylated product.

With the understanding of different rates based on the nucleophilicity of the alcohol, Piers designed a competition experiment between a primary and secondary alcohol. Cyclohexanol and 1-decanol were chosen as the substrates, due to the marked difference in their reactivity. In standalone dehydrogenative silylation experiments, cyclohexanol took 2 hours to go to completion, whereas 1-decanol took 24 hours. In the competition experiment, 1.0 equivalent of both alcohols was treated with 2 mol% $B(C_6F_5)_3$ and 1.0 equivalent of Ph_3SiH (Scheme 2.15). Surprisingly, 1-decanol was silylated almost to the exclusion of cyclohexanol.

Scheme 2.15 Competition Experiment between Differentially Substituted Alcohols

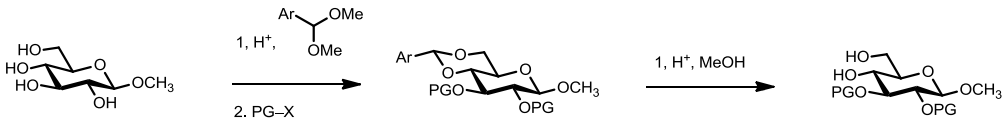


When reevaluating the proposed mechanism of this reaction, this result was readily explained. More Lewis basic alcohols, like 1-decanol, cause formation of the inactive complexed borane species **60** (Scheme 2.3). However, this is only present at a maximum of 2 mol%, leaving behind a large excess of free alcohol to react with any of the electrophilic silane species **61**. As this forms, the more nucleophilic 1-decanol serves to increase the rate of formation of the charge separated species **62** relative to the less nucleophilic cyclohexanol. This explains the high selectivity for silylation of a primary alcohol in the presence of a secondary alcohol despite their drastically different rates of silylation in standalone experiments. This competition study inspired us to study the selective-silylation and glycosylation of differentially substituted diol glycosyl acceptors.

2.3.2 Using Sugar Silanes for Selective Silylation of Diols

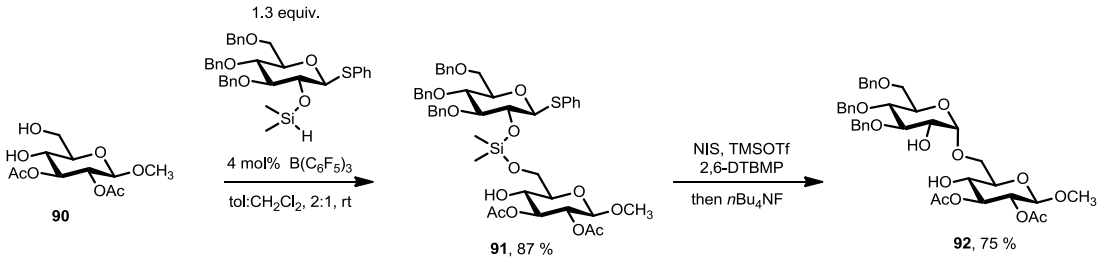
We wanted to explore the selective silylation of a dihydroxysugar compound with the $B(C_6F_5)_3$ catalyst. Sugars with the 2- and 3-hydroxy positions protected and free 4- and 6-hydroxyl groups were targeted due to their ease of synthesis[31] and the fact that they contain differentially substituted alcohols (Scheme 2.16). This would allow rapid access to substrates to test the selective silylation with sugar silanes and $B(C_6F_5)_3$.

Scheme 2.16 Generic Synthesis of 4,6-Dihydroxy Sugars



This general synthesis was used to make the 2,3-diacetoxy-4,6-dihydroxy sugar **90**. It was found that **90** was not soluble in toluene, however a mixture of 2:1-4:1 toluene: methylene chloride worked well at dissolving **90**. Solubility is crucial to selectivity experiments because if the diol is only partially dissolved and is silylated, it will become more soluble than the diol prompting unselective bis-silylation to occur. It was found that mixing **90** and thiophenyl glucose sugar silane in a 1:1 ratio with 4 mol% $B(C_6F_5)_3$ in a 0.04M solution of 2:1 toluene: methylene chloride gave a 67% yield of silyl-linked compound **91**, with approximately 15:1 selectivity for the primary 6-hydroxyl group (Scheme 2.17). Optimization showed that increasing the equivalents of sugar silane from 1.0 to 1.3 further increased the yield of **91** to an excellent 87%. Treatment of **91** with NIS/TMSOTf yielded the desired disaccharide **92** in 75% isolated yield with complete control of anomeric stereochemistry and no need to protect the 4-hydroxyl group of the glycosyl acceptor.

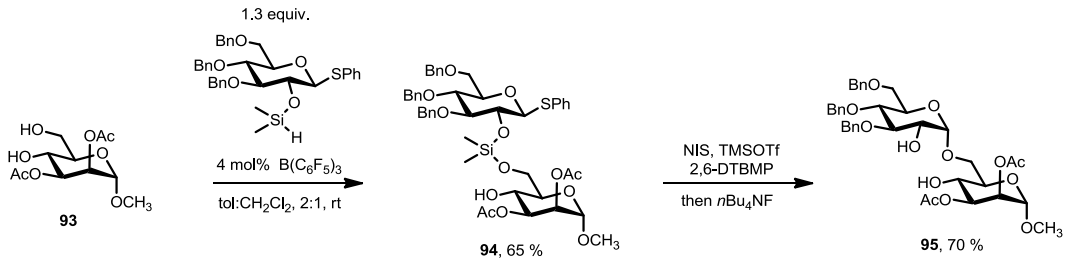
Scheme 2.17 First $B(C_6F_5)_3$ Catalyzed Selective Glycosylation of a Diol



These selective diol glycosylation conditions were next applied to the synthesis of a disaccharide with a mannose glycosyl acceptor. When treating mannose diol **93** under the same conditions as previously described, the silyl-linked compound **94** was obtained as a single regioisomer in 65% yield (Scheme 2.18). This was also converted to the 6-

hydroxy-linked disaccharide **95** in 70% yield without requiring protection of the 4-hydroxyl group of the mannose diol in any step.

Scheme 2.18 Additional $B(C_6F_5)_3$ Catalyzed Synthesis of a Disaccharide



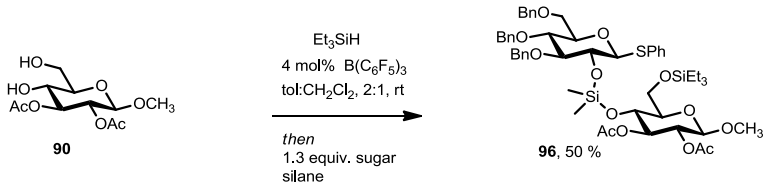
These two examples represent the utility of catalyst-derived selectivity in the dehydrogenative silylation of diols, and how they can be applied to streamlining the synthesis of disaccharides. However, while these represent intriguing new uses of sugar silanes, it would truly be an advance in the field if selective silylation of a secondary alcohol in the presence of a more nucleophilic primary alcohol was achieved. This could provide a very practical, efficient method for the synthesis of various disaccaharides by eliminating laborious protecting group manipulations.

It has been demonstrated in Piers' work, as well as our studies with sugar silanes, that the more nucleophilic of two alcohols will be preferentially silylated in a $B(C_6F_5)_3$ catalyzed dehydrogenative silylation. We set out to use this to our advantage when exploring site-selective glycosylation of a secondary alcohol. Rather than try to discover a catalyst that operates inversely to the nucleophilicity of an alcohol, it was hoped that a sacrificial silane could be used to react with the more reactive primary alcohol. This would then be followed in the same pot by the addition of a sugar silane to form the silyl-linked compound at the less reactive hydroxyl group. Although the use of a sacrificial silane does constitute the use of a protecting group, it is added in the same pot as the

sugar silane and will be removed in the same pot as the glycosylation. This represents a sequence with no additional protection-deprotection steps.

With this strategy for site-selective glycosylation of the less reactive alcohol of a diol in mind, experiments were designed to look at installation of the sugar silane at the 4-hydroxy position of diol **90**. Initially, Et_3SiH was chosen as the sacrificial silane, and a series of experiments showed this strategy was indeed viable. Treatment of **90** with an equivalent of Et_3SiH and 4 mol% $B(C_6F_5)_3$ followed by thiophenyl glucose sugar silane, produced 4-hydroxy silyl-linked compound **96** in one pot and a 50% yield (Scheme 2.19).

Scheme 2.19 First Attempt at Site-Selective Silylation of a Secondary Alcohol

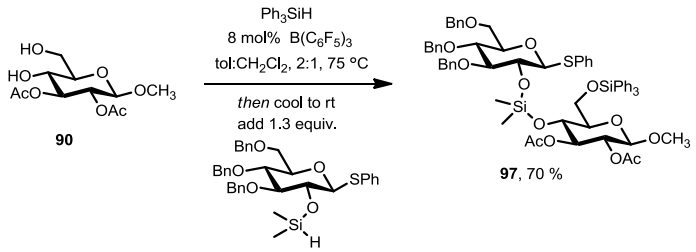


While this achieved the desired goal of tethering at the less-nucleophilic alcohol in a diol, it was not an ideal solution to this challenging problem. The 50% yield was lower than desired, and the selectivity for the primary 6-hydroxyl silylation by Et_3SiH varied. Additionally, the glycosylation of **96** posed some unique problems that will be discussed in greater detail in the following subsection.

Switching the sacrificial silane from Et_3SiH to Ph_3SiH produced very low yields of the desired 6-hydroxy silylated product at room temperature. However, it was found that increasing the catalyst loading slightly, as well as the temperature of the reaction, led to excellent yields of desired monosilylated sugar. This allowed for the development of a one pot silylation procedure with sacrificial triphenylsilane followed by the sugar silane. Reaction of an equivalent of diol **90** with 1.05 equivalents of Ph_3SiH and 8 mol%

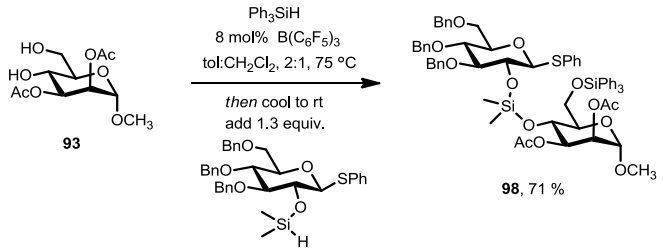
$B(C_6F_5)_3$ at 75 °C followed by cooling to room temperature and addition of 1.3 equivalents of thiophenyl glucose sugar silane as a solution in toluene produced the desired silyl-linked compound **97** in 70% yield (Scheme 2.20).

Scheme 2.20 Utilizing Triphenylsilane as the Sacrificial Silane in the Synthesis of **97**



This result again demonstrates the ability to selectively tether glycosides to polyfunctional molecules for intramolecular aglycone delivery, based on catalyst selection. We also applied these conditions to the selective silylation of mannose diol **93** and observed a nearly identical 71% yield of the desired silyl-linked compound **98** (Scheme 2.21).

Scheme 2.21 Utilizing Triphenylsilane as the Sacrificial Silane in the Synthesis of **98**



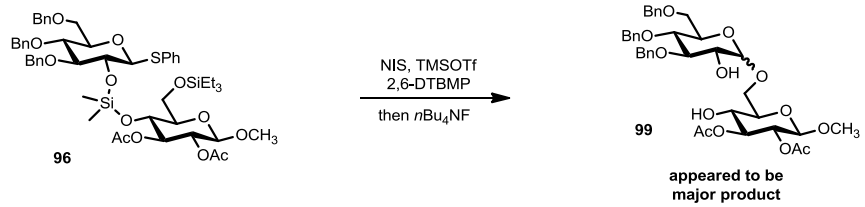
With the ability to tether the sugar silane to either of the alcohols in sugar diols such as **97** and **98** we set out to test the intramolecular aglycone delivery of the 4-hydroxy tethered compounds. It has been demonstrated in this subsection that the primary 6-hydroxyl tethered compounds performed well in the glycosylation, however the same was not observed for 4-hydroxy tethered compounds. Further exploration into the glycosylation of these compounds was necessary to complete the sequence of

glycosylating either alcohol of a differentially substituted diol based on choice of reagents.

2.3.3 Glycosylation of 4-Hydroxy Tethered Compounds

An efficient one pot synthesis was developed for the synthesis of 4-hydroxy tethered silyl-linked compounds from sugar silanes and a 4,6-dihydroxy sugar compound. While this worked with excellent efficiency in the synthesis of compounds such as **97** and **98**, early attempts at their activation for glycosylation did not fare as well. Studies on this glycosylation sequence began with an attempt at glycosylating the 6-triethylsilyl-protected compound **99**. Upon activation with NIS/TMSOTf and subsequent treatment with *n*Bu_4NF, a complex mixture was obtained in which it appeared that the triethylsilyl protected 6-hydroxy group of the glycosyl acceptor had been glycosylated as the major product (Scheme 2.22).

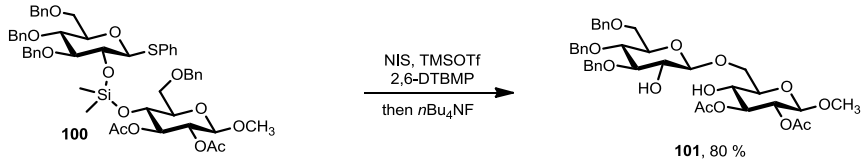
Scheme 2.22 Unexpected Glycosylation Outcome with Triethylsilyl Protecting Group



This result was problematic because the mechanism by which the undesired glycoside **99** was produced was not well understood. Compound **96** could have undergone a silyl-transfer resulting in the sugar silane being tethered to the 6-hydroxy position. Triethylsilyl cleavage could have led to competitive intramolecular aglycone delivery from the untethered 6-hydroxy position. Additionally, both silyl groups could have been cleaved and an intermolecular glycosylation could have occurred at the more reactive primary 6-hydroxyl group. Aside from these pathways it is conceivable that the

triethylsilyl protected 6-hydroxyl was glycosylated followed by desilylation leading to **99**. In order to better understand what might be occurring under the NIS/TMSOTf conditions, a control experiment was designed where the 6-hydroxyl group of the glycosyl acceptor had a 6-*O*-benzyl protecting group instead of a triethylsilyl group. This should serve to rule out any silyl-transfer mechanisms, and given the more robust nature of a benzyl protecting group compared to the triethylsilyl group, also rule out undesired deprotection pathways. To test this, compound **100** was synthesized and treated to the NIS/TMSOTf catalyzed glycosylation conditions. This resulted in an 80% yield of glycoside **101** derived from addition of the 6-*O*-benzyl protected primary alcohol, primarily as the β-anomer, with no detection of the desired 4-hydroxyl glycosylation product (Scheme 2.23).

Scheme 2.23 Control Experiment to Determine Mechanism of Undesired Glycosylation

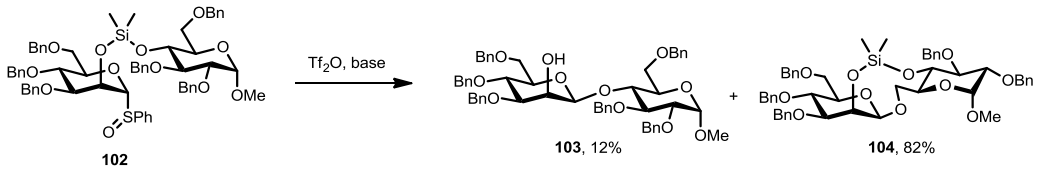


The glycosylation result suggests that the previously observed undesired glycosylation of the triethylsilyl protected 6-hydroxy group most likely occurred by addition to the electrophilic oxocarbenium ion followed by desilylation. It provided strong evidence ruling out a silyl-transfer mechanism, and since it is unlikely the benzyl group was deprotected under the reaction conditions, also ruled out the intermolecular glycosylation pathway. Additional evidence for the glycosylation of the 6-*O*-benzyl protected primary alcohol was observed by low resolution mass spectrometry. The positive ion of the sodium adduct for **101** with the dimethyl silyl-group still linking the 2-

hydroxy and 4-hydroxy group of the glycosyl donor and acceptor, respectively, was the major peak prior to the addition of nBu$_4$NF.

This result is precedented. Looking back at Stork's use of the dimethylsilyl linker for intramolecular aglycone delivery, a very similar result was observed.[44] When attempting to glycosylate the 4-hydroxy silyl-linked compound **102**, using Tf_2O activation of the sulfoxide resulted in only 12% of the desired product **103** (Scheme 2.24). The major product was derived from the addition of the benzyl protected 6-hydroxy group as well, as **104** was isolated in 82%.

Scheme 2.24 Stork's Observation of Similar Undesired Glycosylation Products



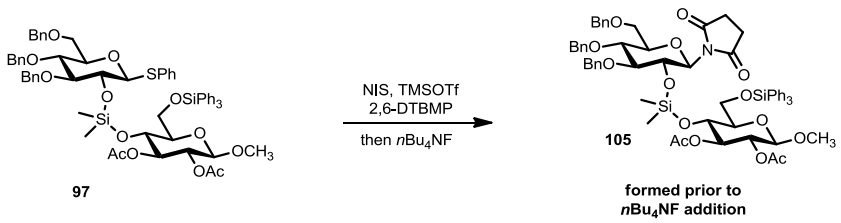
The fact that the undesired glycoside **104** was isolated with the silyl-linkage still intact provides further evidence that the glycosylation occurs directly from the benzyl ether. It is clear from both of these results that the glycosylation of 4-hydroxy-linked sugars were problematic and several factors must be considered when moving forward. First, the protecting group on the 6-hydroxyl group must be sufficiently robust and sterically bulky so that its natural positioning is not within proximity of the reactive oxocarbenium species generated upon activation of the glycosyl donor. Second, a screen of activation conditions must be done to provide a sufficiently reactive intermediate allowing for glycosylation of the weakly nucleophilic 4-hydroxyl group of glucose or mannose.

By switching from triethyl- to the triphenylsilyl protecting group we proposed the first problem could be addressed. This protecting group possesses much greater steric

bulk, and stronger Si—O bond compared to the triethylsilyl protecting group. The use of triphenylsilane proved to be advantageous in the site-selective $B(C_6F_5)_3$ catalyzed dehydrogenative silylation of a diol as well. As described in the previous subsection, Ph_3SiH provided higher yields and better selectivity for selective silylation of the 4,6-hydroxy sugars. With the 4-hydroxy linked compound **97**, possessing a triphenylsilyl protecting group at the 6-hydroxyl position in hand, a screening of glycosylation conditions was possible.

Attempting to glycosylate **97** with NIS and TMSOTf led almost exclusively to the addition of succinimide into the oxocarbenium ion (Scheme 2.25). Although this resulted in no production of the desired disaccharide, we were pleased to observe that the switch to a triphenylsilyl protecting group completely suppressed the undesired addition of the 6-hydroxyl group.

Scheme 2.25 Attempt at Glycosylation of **97** with NIS and TMSOTf

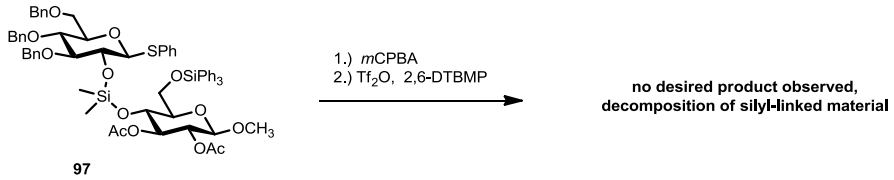


The addition of succinimide, which is a byproduct of activation of the thiophenyl group, prompted us to explore activation conditions that do not produce nucleophilic byproducts that can provide competition in the glycosylation of the desired glycosyl acceptor. A potential solution to this problem was the use of Kahne's method for sulfoxide activation[45] which was utilized by Stork and coworkers in their reports of temporary silicon tethers for intramolecular aglycone delivery. Not only is this method

well known to glycosylate unreactive glycosyl acceptors, but it also does not produce any overly nucleophilic byproducts.

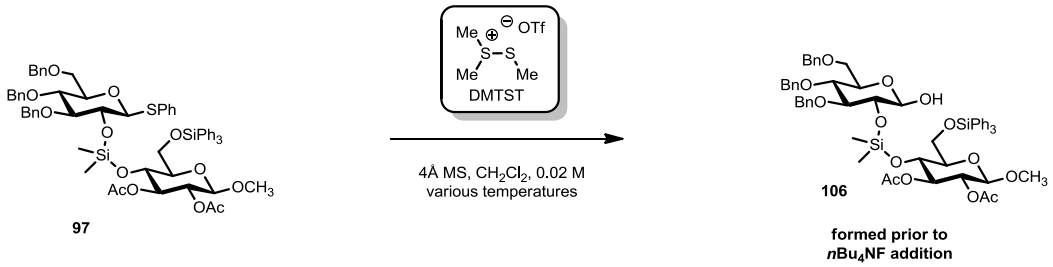
Testing this method by treating **97** with *m*-CPBA to generate the sulfoxide *in situ* followed by treatment with Tf_2O and 2,6-DTBMP led mostly to decomposition of the silyl-linker and further decomposition of the separate sugar components (Scheme 2.26).

Scheme 2.26 Attempt at Glycosylation of **97** with Kahne's Method of Activation



The fact that this worked poorly, in addition to Stork's undesirable results using the same activation method, showed that exploration of additional methods was necessary. Another common method for the activation of thioglycosides is by utilizing dimethyl(methylthio)sulfonium triflate (DMTST), which is generated by treating methyl disulfide with methyl triflate. It produces no nucleophilic byproducts and is quite mild when buffered with a hindered pyridine base such as 2,6-DTBMP. Using Wong's method of generating DMTST, silyl-linked compound **97** was then activated (Scheme 2.27).[46]

Scheme 2.27 Attempt at Glycosylating **97** with DMTST



At temperatures between -40 °C and room temperature, no desired product was formed. Instead, adventitious water added into the oxocarbenium at a greater rate than the

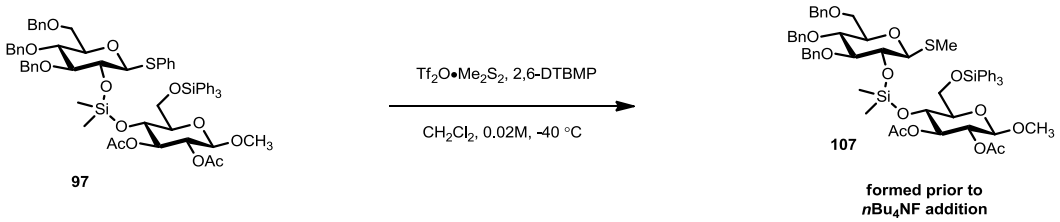
tethered 4-hydroxyl group to produce **106**. This was most likely the result of the stability of the anomeric triflate, which forms after activation of the thiophenyl leaving group with DMTST, and is stable up to room temperature. It is apparent that oxocarbenium formation is readily occurring under the DMTST activation conditions; however, the tethered hydroxyl group is not sufficiently reactive to generate any of the desired product. A set of activation conditions that are known to be even more reactive must be uncovered in order to get the poorly nucleophilic 4-hydroxyl group to glycosylate.

It is known that the 4-hydroxyl position of glucose is a very poor nucleophile, and it has proven no different in the glycosylation studies to this point. One concern was that by choosing the acetate protecting groups, that the inductive withdrawing effects were making the poor nucleophile even worse. A careful survey of the literature was conducted with these considerations in mind. A glycosylation method was desired that results in high yields, specifically for 4-hydroxy glucose glycosyl acceptors containing acetate protecting groups. A method developed by Fugedi and coworkers utilizing an activating complex similar to DMTST seemed to address all of these issues.[47] Fugedi's reagent is made by premixing methyl disulfide and triflic anhydride to make the active $Tf_2O{\cdot}Me_2S_2$ species. An additional perk of this method is that it utilizes only a slight excess of the glycosyl donor relative to the acceptor (1.2:1). This translates well to silyl-tethered intramolecular aglycone delivery as it is inherently a 1:1 ratio of acceptor to donor; methods requiring an excess of either the acceptor or donor to get useful yields are not desired.

With these factors in mind, we hoped to apply this method to the successful glycosylation of **97**. Following the procedure reported by Fugedi and coworkers, **97** was

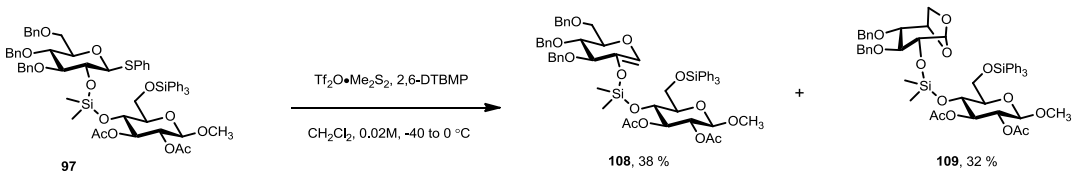
treated with 1.5 equivalents of $Tf_2O{\cdot}Me_2S_2$ at -40 °C with 2,6-DTBMP added to buffer any adventitious acid (Scheme 2.28). Activation of the thiophenyl leaving group occurred rapidly; however, no product generation was observed. Instead, over time, addition of methyl thiolate occurred. The nucleophilic sulfur species presumably forms as the methylsulfenyl triflate reacts with a nucleophile.

Scheme 2.28 Attempt at Glycosylating **97** with $Tf_2O{\cdot}Me_2S_2$ at -40 °C



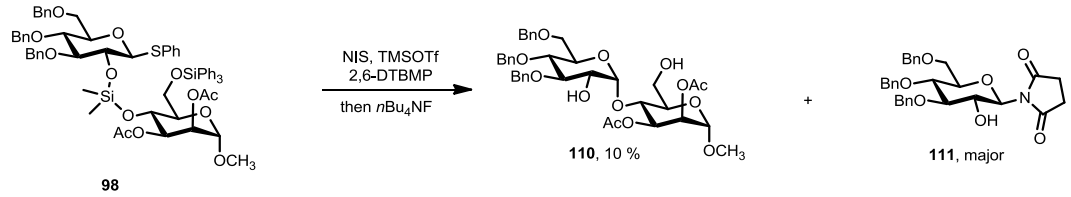
In addition to the formation of **107**, water also underwent glycosylation to form compound **106**, as was seen with the DMTST activation conditions. Running the reaction under the same conditions at room temperature led to almost instantaneous consumption of the starting material with no formation of the desired product. It was hoped that by adding the $Tf_2O{\cdot}Me_2S_2$ reagent at -40 °C followed by warming to 0 °C, an effective balance of reactivity could be realized. Upon attempting this, two major products were detected by low resolution mass spectrometry corresponding to the desired glycoside without a proton and a benzyl group (Scheme 2.29). The reaction was not treated with nBu$_4$NF, and the two major products were isolated. The products obtained were indeed missing a proton and benzyl protecting group, and corresponded to glucal **108**, which was obtained in 38% yield and the 1,6-*anhydro* sugar **109** in 32% yield.

Scheme 2.29 Second Attempt at Glycosylating **97** with Tf_2O-Me_2S_2



Both of these compounds contained the silyl-linkage intact, which demonstrates the lack of reactivity of the tethered 4-hydroxyl group of glucose. It was evident that the poor nucleophilicity of the tethered alcohol required additional screening to achieve the desired glycosylation. We wanted to explore the glycosylation of the sugar silane tethered to the 4-hydroxyl group of a mannose sugar, hoping that a slight change in the acceptor's stereochemistry may lead to increased reactivity. We first treated **98** under the NIS and TMSOTf conditions, and although succinimide addition (**111**) was the major product, the desired disaccharide **110** was also isolated, albeit in 10% yield (Scheme 2.30).

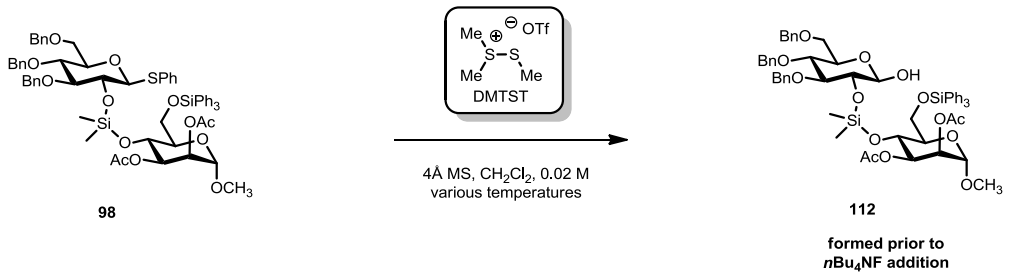
Scheme 2.30 Attempt at Glycosylating **98** with NIS and TMSOTf



This was an exciting result because it suggested the reactivity of the tethered aglycone was sufficient to form the desired glycoside, and switching to an activation method that produces nonnucleophilic byproducts should increase the yield of **110**. Switching to DMTST as the activation method was next explored. Unfortunately the desired product **110** was not produced under several different variations of the DMTST activation conditions (

Scheme **2.31**). Instead the major product was the addition of adventitious water producing **112**, both in the presence and absence of 4Å MS.

Scheme 2.31 Attempt at Glycosylating **98** with DMTST

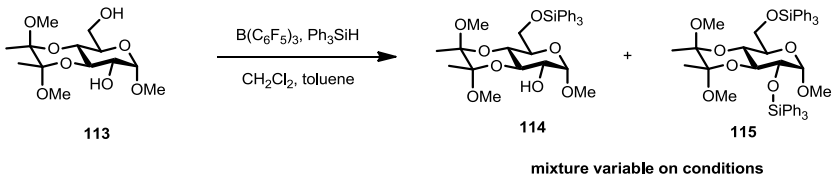


This was disappointing as the small amount of product formed with the NIS/TMSOTf catalyzed conditions suggested that the appropriate reactivity may be there to synthesize the desired disaccharide **110** in synthetically useful yields. It was not the case, and at this stage of the project it was determined that future work would be invested into looking more carefully at the glycosylation of unreactive 4-hydroxy sugar alcohols.

2.3.4 Gaining Additional Insight on Site-Selective Silylation/Glycosylation of Diols

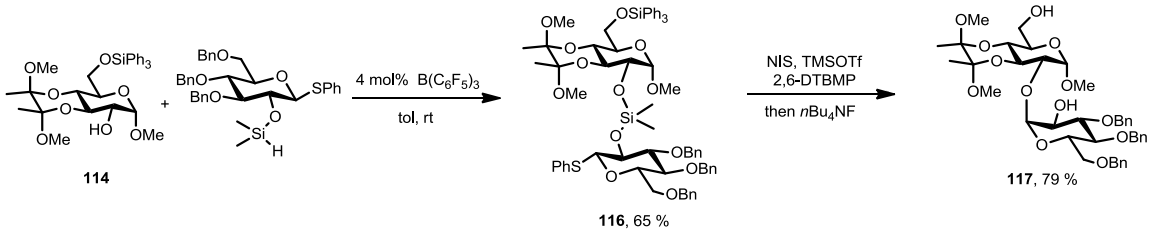
Different substitution patterns on the sugar diols were next explored. It was hoped that a 2,6-diol would lead to better results as the 2-hydroxyl position of glucose is known to be much more nucleophilic than the 4-hydroxyl position.[48] However, it was found that the increased nucleophilicity of the 2-hydroxyl group severely diminished the selectivity for silylation of the primary alcohol (Scheme 2.32). Conditions identical to those used for 4,6-sugar diols led to a mixture of approximately 1:1 mono- to bis-silylated products **114** and **115**, respectively. Reducing the temperature to 50 °C led to less bis-silylation than at 75 °C. Further attempts at lowering catalyst loading led to increased selectivity for desired product **114**; however, as $B(C_6F_5)_3$ was lowered from 8 to 4 to 2 mol%, an increasing amount of starting material **113** remained even after prolonged reaction times.

Scheme 2.32 Attempt at Site-Selective Silylation of a 2,6-Sugar Diol



In order to better understand the interplay between $B(C_6F_5)_3$-catalyzed site-selective silylation of a diol and the reactivity of glycosylation, mono-silylated compound **114** was isolated and silylated with a thiophenyl glucose sugar silane to produce **116** in 65% yield (Scheme 2.33). This silyl-linked compound was then treated to the NIS/TMSOTf glycosylation conditions, providing the desired disaccharide solely as the α-anomer **117** in 79% yield.

Scheme 2.33 Glycosylation of 2-Hydroxy Glucose Compound **114**

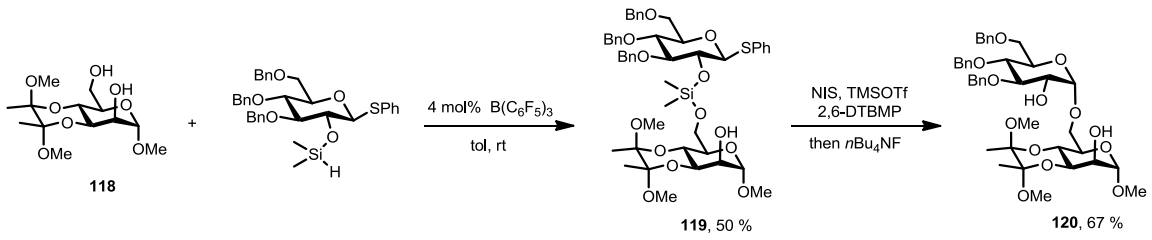


The fact that **116** glycosylated so readily, but performed with poor selectivity in the $B(C_6F_5)_3$-catalyzed site-selective silylation of 2,6-hydroxy sugar diol **113** is problematic for our desired plan. This suggested that, when using this strategy to selectively glycosylate the less reactive alcohol of a diol, a high yielding glycosylation may be preceded by a poorly selective silylation step. However, further exploration of

additional diols was needed in order to better understand the relation between selectivity of silylation and yield of glycosylation.

Since the nucleophilicity of the 2-hydroxyl group in glucose was too similar to the primary 6-hydroxyl group in **113** to attain selectivity in the dehydrogenative silylation, we wanted to explore the comparable mannose 2,6-diol **118**. It is known that axial alcohols are less nucleophilic than their equatorial counterparts, so the slightly increased difference in nucleophilicity between the primary and secondary alcohol in **118** could produce selectivity in the silylation step as well as useful yields in glycosylation. Exploring the site-selective silylation of **118** with the thiophenyl glucose sugar silane and 4 mol% $B(C_6F_5)_3$, a 50% yield of the desired primary alcohol silylation product **119** was obtained as well as some of the bis-silylated compound (Scheme 2.34). This compound was converted into disaccharide **120** in 67% yield upon treatment with NIS and TMSOTf.

Scheme 2.34 Site-Selective Glycosylation of the Primary Alcohol of **118**

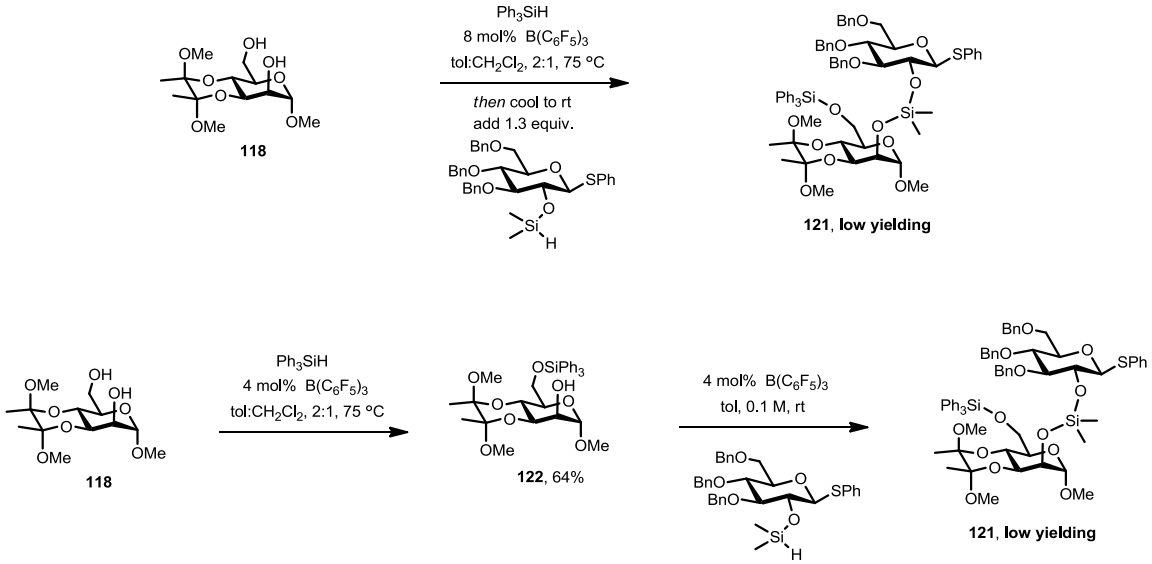


While the glycosylation of the 6-hydroxyl group of a sugar in the presence of unprotected secondary alcohols can often be done effectively in an intermolecular fashion, this result was noteworthy for several reasons. In addition to having complete control of anomeric stereochemistry of the newly formed glycosidic bond, the glycosyl acceptor bearing benzyl protecting groups is "armed." Fraser-Reid has reported the selectivity of silylation of diols such as **114** and **118** is highly dependent on the glycosyl donor being "disarmed" by inductively withdrawing protecting groups such as acetate or

benzoates.[49] The fact that the selectivity for the primary 6-hydroxyl group is based on the silylation catalyst and not the protecting groups could prove useful when strategically installing glycosides with orthogonal protecting groups.

With the successful silylation and glycosylation of the primary alcohol of diol **118**, we next wanted to explore site-selective glycosylation of the axial 2-hydroxyl group. Initial treatment with conditions utilized previously using Ph_3SiH as a sacrificial silane followed by a sugar silane resulted in low yields of the desired silyl-linked compound **121** (Scheme 2.35). In order to make sure the silylation worked, diol **118** was treated with Ph_3SiH to give the desired 6-hydroxy silylated alcohol **122** in 64% yield. Reacting this alcohol with the thiophenyl glucose sugar silane and 4 mol% of the $B(C_6F_5)_3$ catalyst surprisingly produced very low yields of the desired product **121**, thus preventing further study of its glycosylation.

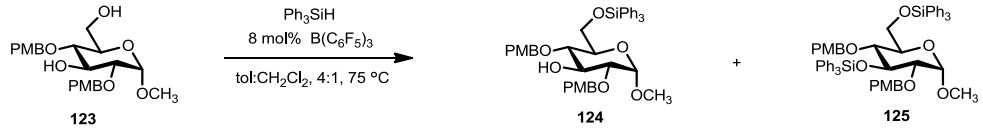
Scheme 2.35 Difficulties in Site-Selective Silylation of the Secondary Alcohol of **118**



With a better understanding of the selective silylation and glycosylation of 2,6-diols we hoped to explore a 3,6-sugar diol in this sequence as well. Diol **123** was

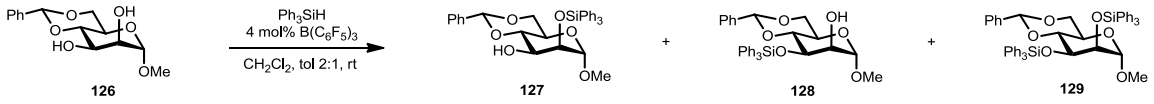
synthesized and it was hoped that the reduced nucleophilicity of the 3-hydroxy group relative to the 2-hydroxy group would provide good selectivity in silylation. This however was not the case, as treatment of **123** with an equivalent of Ph_3SiH resulted in a nonselective mixture of mono-silylated compound **124** and bis-silylated **125** (Scheme 2.36).

Scheme 2.36 Attempt at Selective Silylation of a 3,6-Sugar Diol



Selectivity studies on several sugar diols have been carried out where differentiation between a primary and secondary alcohol was explored. We were also curious to see if selectivity between two secondary alcohols in a sugar could be achieved. A logical starting point for this would be the study between the 2- and 3-hydroxy groups of mannose as one is axial and the other equatorial, providing a difference in nucleophilicity (Scheme 2.37). Attempts at selective silylation of diol **126** again produced a mixture of mono- and bis-silylated compounds **127**, **128**, and **129**.

Scheme 2.37 Attempt at Selective Silylation between Two Secondary Alcohols



2.4 Future Directions and Summary of Dehydrogenative Silylation

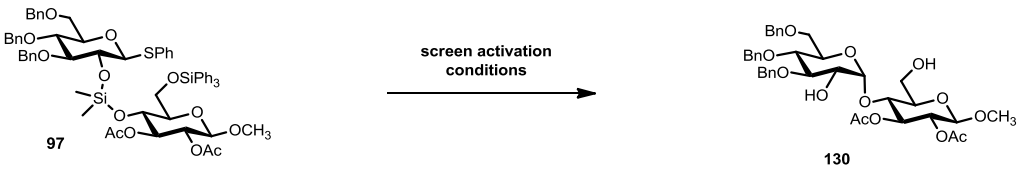
2.4.1 Building Upon Selective Silylation/Glycosylation of Diols Studies

The utilization of $B(C_6F_5)_3$-catalyzed dehydrogenative silylation has been introduced in conjunction with sugar silanes for the site-selective glycosylation of diols based on reactivity patterns and reagent choice. This has been shown to be an effective

strategy for the site-selective glycosylation of primary alcohols in the presence of unprotected secondary alcohols. However, in the case of glycosylating the less reactive alcohol in the presence of a primary alcohol, challenges were observed in either the glycosylation step (with 4,6-sugar diols) or in the selective silylation step (with 2,6- and 3,6- sugar diols). While it has been disappointing that our goal of site-selectively glycosylating both positions of a sugar diol has not come to fruition, a foundation for understanding the reactivity patterns in this strategy has been developed.

The continuation of this project will build from the silylation and glycosylation studies described in the previous section. Additional studies on the use of silyl tethering for the intramolecular aglycone delivery of unreactive nucleophiles such as 4-hydroxy sugars should be conducted in order to uncover which of the numerous methods for thioether activation can lead to the desired product (Scheme 2.38). Additionally, the use of $B(C_6F_5)_3$ for the silylation of diols has in some cases proven highly selective, while in other cases only moderate selectivity was observed. A more thorough screening of dehydrogenative silylation catalysts and conditions with sugar silanes as well as sacrificial silanes would be beneficial. This would produce an understanding of what choice of catalyst should be used based upon predicted reactivity patterns.

Scheme 2.38 Screening Activation Conditions for Glycosylating Unreactive Aglycones

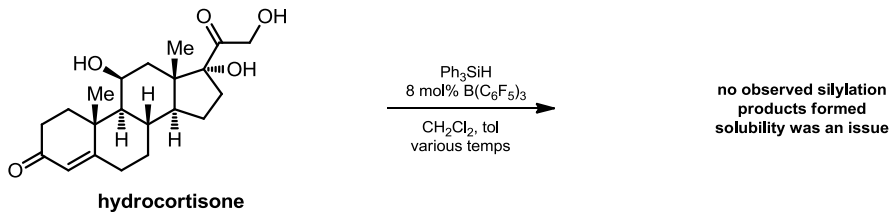


2.4.2 Selective Silylation of Complex Substrates

As discussed in the previous chapter, the ultimate goal in the development of sugar silanes is to be able to have a toolbox of catalysts that enable the selective

silylation/glycosylation of a desired functional group in a complex setting. An attractive compound for exploring the borane-catalyzed dehydrogenative silylation is hydrocortisone. In addition to the ketone and enone functional groups, it possesses a primary, secondary, and tertiary alcohol. It would be a marked advancement in the field of glycosylation to be able to selectively glycosylate each of hydrocortisone's alcohols individually based on choice of catalyst and sacrificial silane. Initial attempts at selective silylation of hydrocortisone with the borane and triphenylsilane were plagued by solubility issues. Toluene and methylene chloride, which are solvents that have been compatible with borane reactivity, would not dissolve hydrocortisone, leading to very little observed reactivity (Scheme 2.39).

Scheme 2.39 Study on Selective Silylation of Hydrocortisone



hydrocortisone

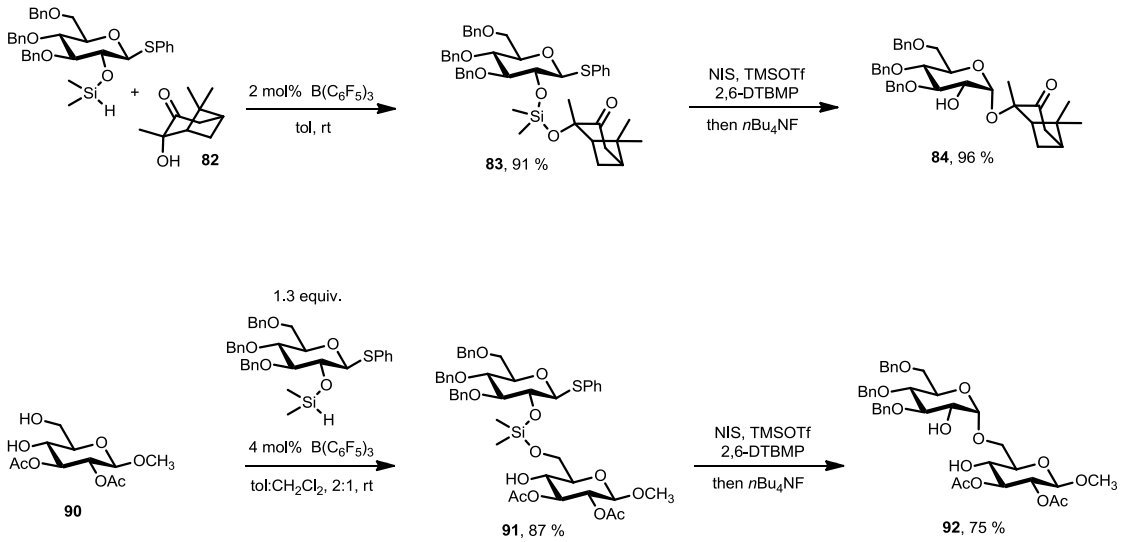
Solvent screening with (-)-menthol and triphenylsilane showed that the addition of polar solvents such as THF, even as a minor component, completely shut down reactivity due to competing borane coordination. This appears to be a major hurdle in the development of site-selective glycosylation of polar molecules with $B(C_6F_5)_3$, and other catalysts, such as those developed by Ito and coworkers,[32,33] should be thoroughly screened.

2.4.3 Summary of Dehydrogenative Silylation with Sugar Silanes

A method utilizing user-friendly dehydrogenative silylation conditions with sugar silanes and $B(C_6F_5)_3$ has been developed. This method has been demonstrated to work

well with secondary and tertiary alcohols and can site-selectively glycosylate hydroxyketones as well as certain diols (Scheme 2.40).

Scheme 2.40 Demonstrating the Utility of Dehydrogenative Silylation with Sugar Silanes



It has been shown that a Cu(I)-IMes catalyst can be utilized on substrates such as primary alcohols that are not high yielding with the $B(C_6F_5)_3$ catalyst. Additionally, by studying the silylation of a variety of sugar diols, reactivity patterns and limitations of the $B(C_6F_5)_3$ catalyst and sugar silanes have been uncovered. These studies should provide future efforts in this area with an understanding of reactivity patterns and hopefully direct research towards a solution to the challenges encountered.

Chapter 3

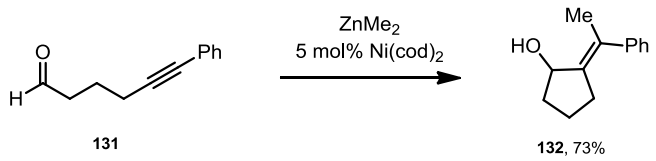
Merging Aglycone Synthesis and Glycosylation by Reductive Coupling with Sugar Silanes

3.1 Reductive Coupling Background

3.1.1 Introduction to Reductive Coupling Strategy

Nickel-catalyzed reductive and alkylative coupling of two π-components has seen a great deal of development over the past two decades.[50,51] These methods utilize the Ni(0)-catalyzed hetero-coupling of differentiated polar and non-polar π-components (Scheme 3.1). In the first example from our lab, ynal **131** was cyclized using a $Ni(cod)_2$ catalyst and dimethylzinc to form the cyclized allylic alcohol **132** in 73% yield with complete stereocontrol of the newly formed tetrasubstituted olefin.[52] A wide variety of π-systems have been utilized in this strategy, such as: aldehydes, enones, enals, ketones, imines, and epoxides as polar components; and alkynes, allenes, and dienes as nonpolar components. These simple and readily accessible starting materials have been used to synthesize a variety of useful organic frameworks.

Scheme 3.1 First Nickel-Catalyzed Aldehyde-Alkyne Coupling



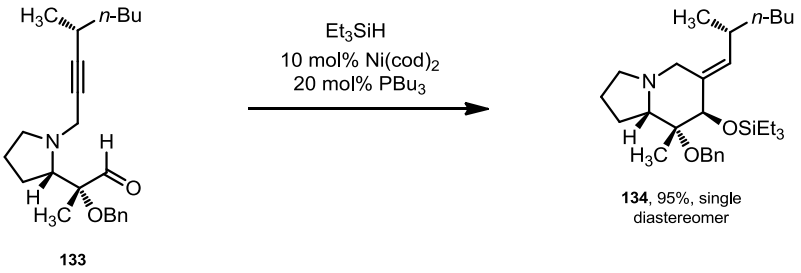
131 **132**, 73%

An advantage of this approach is that it eliminates the need to generate pre-formed organometallic species, instead using a Ni(0)-catalyst in a substoichiometric amount. In order to utilize nickel as a catalytic species, a reducing agent must be used to alter oxidation states in the catalytic cycle. A variety of reducing agents have been employed in these sequences such as dialkyl zinc reagents, trialkylboranes, silanes, and even alcohols.[53] We were particularly interested in processes utilizing silane reducing agents, as they could provide a new application for sugar silanes in site-selective glycosylations.

3.1.2 Use of Silanes as Reducing Agents in Nickel-Catalyzed Reductive Coupling

As nickel-catalyzed reductive couplings have been developed over the past two decades, the reducing agents have become increasingly mild and tolerant of a wide variety of functional groups. Initial efforts in the reductive coupling of π-systems with nickel(0)-phosphine catalysts used dialkyl zinc reducing agents, and later triethylborane, to afford the reductive or alkylative product. Although effective as reducing agents, both of these compounds are pyrophoric and have limited functional group compatibility. When attempting the nickel(0)-catalyzed cyclization of ynal **133** in the key step of the synthesis of (+)-allopumiliotoxin 267A, it was found that no desired allylic alcohol product was formed when using diethylzinc as the reducing agent.[54] Instead, addition of an ethyl group from the zinc species into the aldehyde was the only product observed. However, it was found that when switching to the mild reducing agent triethylsilane, the desired cyclized product **134** was produced in a 95% isolated yield (Scheme 3.2).

Scheme 3.2 Use of Silane as the Reducing Agent in Ni-Catalyzed Reductive Coupling

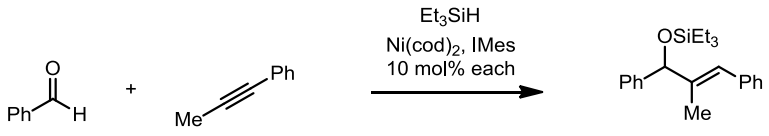


133

134, 95%, single diastereomer

The synthetic utility of the nickel-catalyzed reductive coupling of two π-systems is readily apparent, as demonstrated in the synthesis of compound **134**. The nickel-catalyst enables **134** to be formed from two readily available organic components, an alkyne and aldehyde. The reaction forms a new C—C bond and a new stereocenter as well as a stereodefined olefin. These characteristics enable the rapid development of molecular complexity from simple starting materials. Although silane reducing agents were found to be highly useful in this intramolecular cyclization, it was not until several years later that silanes were demonstrated to be effective reducing agents in the intermolecular coupling of alkynes and aldehydes (Scheme 3.3).[55] It was found that by switching from monodentate phosphine ligands to the more σ-donating N-heterocyclic carbene (NHC) IMes, that intermolecular reductive coupling of benzaldehyde and 1-phenyl-1-propyne produced the desired allylic alcohol **135** in 84% yield.

Scheme 3.3 Intermolecular Reductive Coupling of an Aldehyde and Alkyne

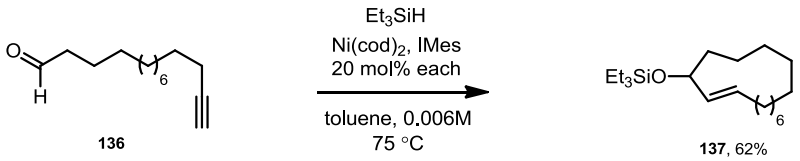


135, 84% >98:2 regiocontrol

Since this important advance in the field of the nickel-catalyzed reductive coupling of aldehydes and alkynes, many additional methodologies have been developed. In 2005 our group reported the application of ynal reductive coupling in the synthesis of

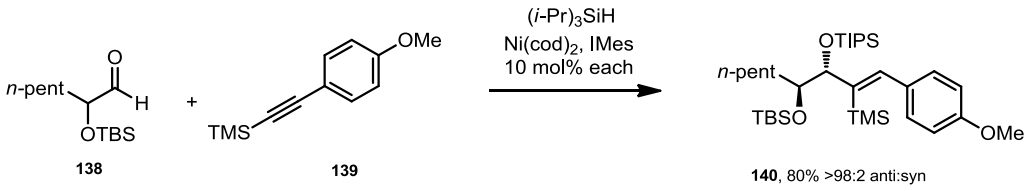
macrocycles.[56] Rings sized between 11- and 22-membered were synthesized, and a ligand-dependent regiochemical outcome between endo- and exo-olefins was discovered. A representative example of this methodology is shown with the cyclization of ynal **136** to give macrocycle **137** in 62% yield (Scheme 3.4).

Scheme 3.4 Ni(0)-IMes Catalyzed Macrocyclization of Ynals



Shortly after the macrocyclization methodology was developed, our group reported the reductive coupling of α-silyloxy aldehydes and alkynes to produce 1,2-*anti* diols in a highly diastereoselective fashion.[57] It was found necessary to protect the α-hydroxyl group with a *tert*-butyldimethyl silyl (TBS) group as well as the terminal alkyne with a trimethyl silyl (TMS) group to achieve the highest levels of diastereoselectivity. When α-silyloxy aldehyde **138** and alkyne **139** were treated with 10 mol% of Ni(0)-IMes the desired 1,2-*anti* diol **140** was formed in 80% yield with >98:2 dr (Scheme 3.5). This methodology was paired with the macrocyclization protocol in the total synthesis of the natural product aigialomycin D.[58]

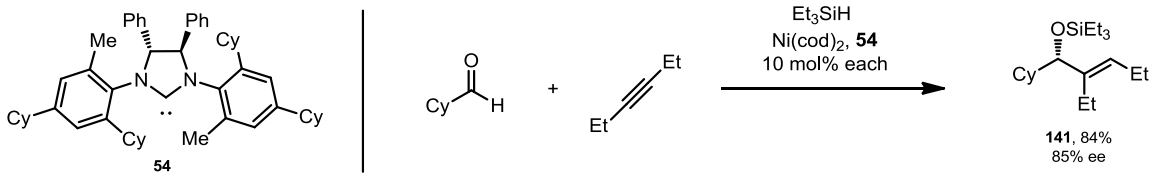
Scheme 3.5 Synthesis of 1,2-*Anti* Diols by Ni(0)-IMes Catalyzed Reductive Coupling



The utility of nickel-catalyzed reductive coupling of aldehydes and alkynes with silane reducing agents has been demonstrated through the development and application of several methods highlighted thus far in this chapter. However, all of the allylic alcohols

have either been formed unselectively or rely on substrate control to achieve enhanced diastereoselectivity. In order to overcome this limitation, our lab reported the development of several new NHC's in 2007 for the asymmetric reductive coupling of aldehydes and alkynes.[30] Optimization studies found that NHC **54** was effective at achieving moderate to high levels of enantioselectivity, with a broad substrate scope, in nickel-catalyzed formation of allylic alcohols. Using 10 mol% of a Ni(0)-**54** catalyst with cyclohexylcarboxaldehyde and 3-hexyne, triethylsilyl protected allylic alcohol **141** was obtained in 84% yield and 85% ee (Scheme 3.6).

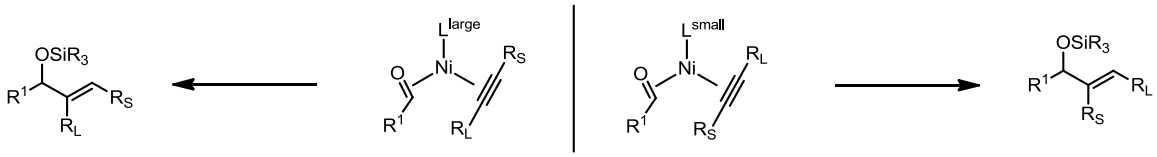
Scheme 3.6 Asymmetric Reductive Coupling of Aldehydes and Alkynes with NHC **54**



The development of NHC **54** was a key advancement in the field of nickel-catalyzed reductive coupling. However, there remained one more element of this reaction that still needed to be addressed, which is the regiocontrolled addition of unbiased alkynes to aldehydes. High levels of regiocontrol can be achieved with alkynes possessing a steric or electronic bias, such as terminal alkynes, ynoates, 1,2- and 1,6-enynes, alkyl-aryl and internal alkynes bearing two substituents with contrasting steric environments. Our group developed a set of ligand-based conditions for achieving high levels of regiocontrol with biased and unbiased substrates based solely upon ligand structure, not the inherent reactivity of the alkyne.[59] Several ligands were identified that served to control the regiochemical addition of the alkyne to the aldehyde based upon the steric environment of the ligand on the alkyne in the formation of the nickellacycle

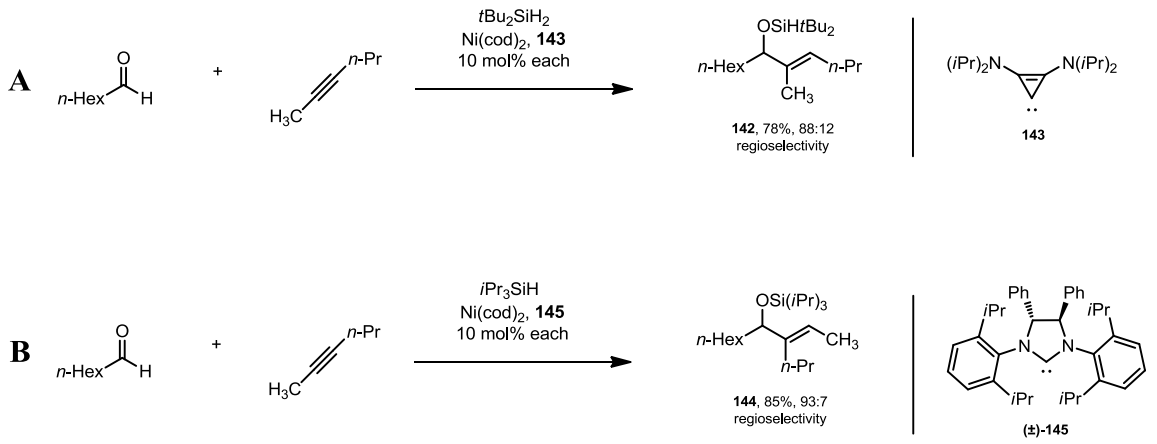
(Scheme 3.7). When a large ligand is used, the steric repulsion between the large group of the alkyne and the ligand led to addition of the alkyne carbon bearing the bulkier substituent to the aldehyde. Conversely, when a small ligand was used, the steric repulsion between the aldehydic substituent and the larger group on the alkyne led to addition of the less hindered end of the alkyne to the aldehyde.

Scheme 3.7 Ligand Steric Control Model



When attempting the regioselective reductive coupling of an alkyne with no inherent substrate bias, such as 2-hexyne, steric control must be derived from the ligand. When utilizing this method, it was found that coupling 2-hexyne and heptanal with carbene ligand **143**, the desired small ligand product **142** was isolated in 78% yield and 88:12 regioselectivity (Scheme 3.8, equation **A**). Switching to the large ligand **145** with 2-hexyne and heptanal completely reversed the regioselectivity to give product **144** in 85% yield and with 93:7 regioselectivity (Scheme 3.8, equation **B**).

Scheme 3.8 Ligand Derived Regiochemical Control in Reductive Coupling



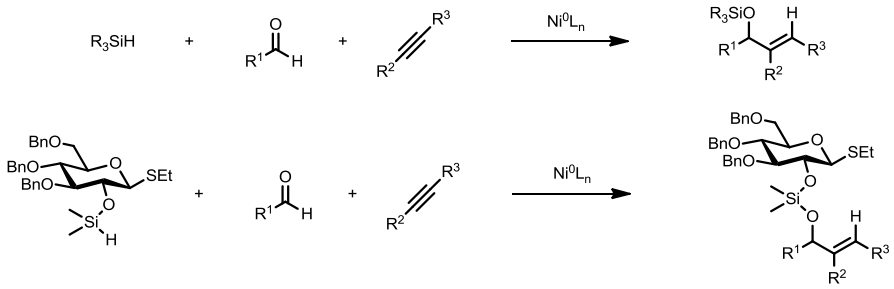
This unprecedented ligand controlled reversal of regiochemistry with an unbiased alkyne represented a great improvement in overcoming the regiochemical challenge that plagued many alkyne addition methodologies. The use of nickel-catalyzed reductive coupling with silane reducing agents has been demonstrated throughout this subsection to be a highly useful method for the synthesis of allylic alcohols. With the expertise developed in this area over the past two decades in our lab, we hoped to employ sugar silanes as the reducing agent to merge aglycone synthesis with site-selective carbohydrate incorporation.

3.2 Nickel-Catalyzed Reductive Coupling with Sugar Silane Reducing Agents

3.2.1 Development of Conditions with Sugar Silanes and Terminal Alkynes

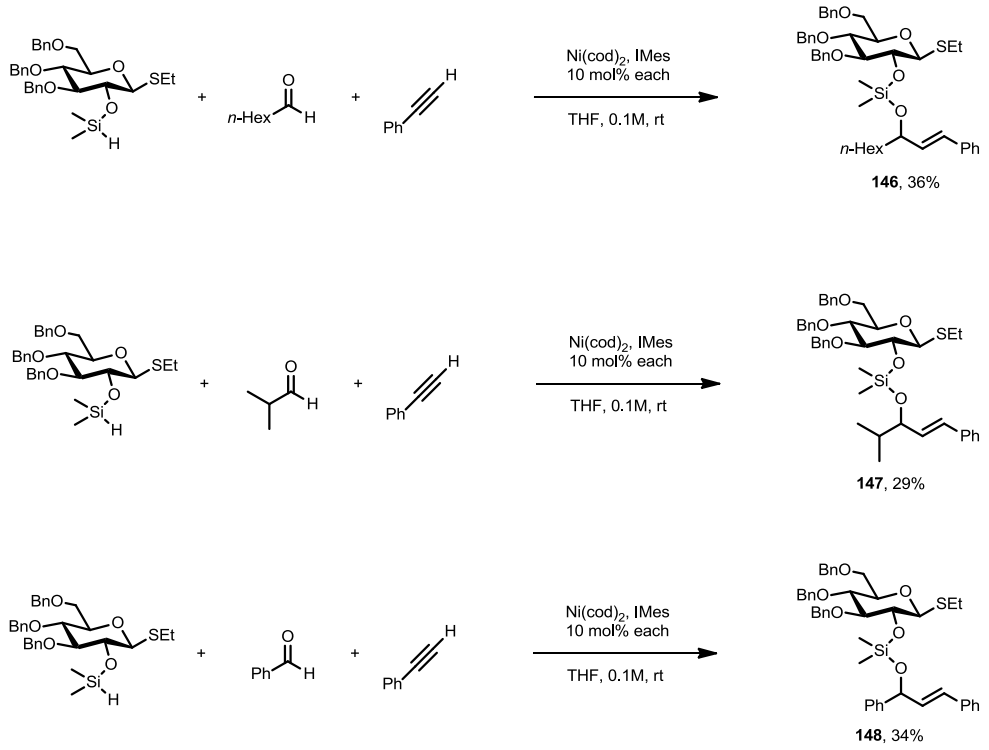
Traditionally, glycosylation is viewed as an operation where a pre-synthesized aglycone and glycosyl donor are coupled to form the desired glycosidic linkage. In this reaction, the synthesis of the aglycone and the glycosylation event are viewed as two distinct operations. With the development of sugar silanes as reducing agents, and the large body of work on nickel-catalyzed reductive coupling of aldehydes and alkynes with silanes, we hoped to merge aglycone synthesis and glycoside incorporation into one highly efficient step (Scheme 3.9). We were optimistic that transitioning from the more conventional triethyl-, triisopropyl-, and di-*tert*-butyl silanes, to a sugar silane would be feasible. Detailed mechanistic studies in our group have shown a zero-order dependence on silane concentration in the nickel-catalyzed reductive coupling of aldehydes and alkynes.[60] Each silane has a distinct reactivity profile, so gaining an understanding of the reactivity of a sugar silane would be the next task.

Scheme 3.9 Merging Aglycone Synthesis with Glycoside Incorporation



Previous work in the group suggested that Ni(0)-IMes would be the most logical catalyst for the desired intermolecular reductive coupling with terminal alkynes, due to its reactivity profile and minimization of alkyne trimerization compared to phosphine ligand-based procedures. Initial attempts at following the previously developed protocol developed with 1.1 equivalents of sugar silane, 1.2 equivalents of alkyne and 1.0 equivalent of aldehyde with 10 mol% Ni(0)-IMes produced the desired allylic alcohols, albeit in low yields (Scheme 3.10).

Scheme 3.10 Initial Attempts at Reductive Coupling with Sugar Silanes

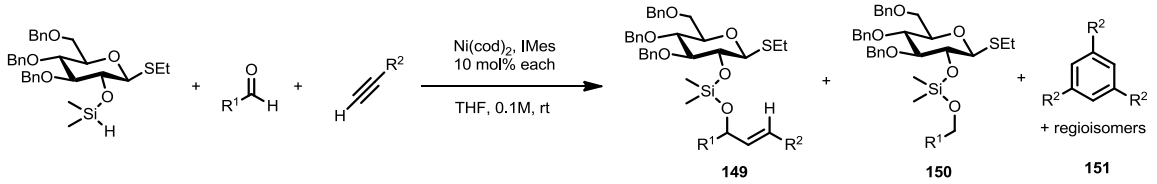


When adding a solution of thioethyl glucose sugar silane, heptanal and phenylacetylene to a pre-formed Ni(0)-IMes catalyst, the desired allylic alcohol **146** was formed in 36% yield. Using the same strategy of adding sugar silane, the corresponding aldehyde and phenylacetylene all at once to the nickel catalyst produced allylic alcohols **147** and **148** in 29% and 34% yield respectively. In each case, it appeared the low yields were a function of competing alkyne trimerization pathways. It was proposed that instead of adding the mixture of sugar silane, aldehyde, and alkyne to the catalyst solution all at once, dropwise addition may slow the trimerization pathway, thus leading to higher yields of the desired allylic alcohol. When testing this hypothesis, a manual dropwise addition of a solution containing sugar silane, heptanal and phenylacetylene over several minutes to the Ni(0)-IMes catalyst increased the yield of **146** from 36% to 68%. While this experiment verified our hypothesis about the slow addition of reagents, it was found

that the yield varied greatly due to the sensitivity of the rate of addition of substrates. An optimization study was needed to develop conditions that were high yielding and highly reproducible in the reductive coupling of terminal alkynes and sugar silanes.

It was found in these early studies that the nickel-catalyzed reductive coupling of aldehydes and terminal alkynes with sugar silanes produced three main products. In addition to the desired silyl-linked allylic alcohol product, alkyne trimerization and aldehyde hydrosilylation byproducts were also observed (Scheme 3.11).

Scheme 3.11 Byproducts Observed in Reductive Coupling of Terminal Alkynes

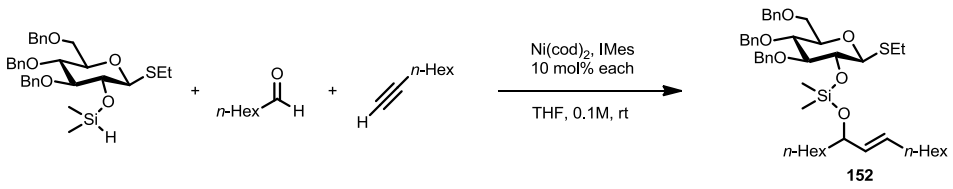


If the addition of the alkyne were too rapid, as was observed when all substrates were added at once, alkyne trimerization product **151** would dominate the reaction. This would lead to consumption of the terminal alkyne with little production of desired allylic alcohol **149**, while the sugar silane and aldehyde remained, eventually producing the hydrosilylation product **150**. Conversely, if the sugar silane and aldehyde are in the presence of Ni(0)-IMes without a sufficient concentration of the alkyne, production of hydrosilylation product **150** dominates followed by generation of trimerization product **151** from the remaining terminal alkyne.

These observations were taken into careful consideration when designing a series of experiments aimed at finding a balance between alkyne trimerization and aldehyde hydrosilylation. An optimization screen was conducted for the reductive coupling of

heptanal, 1-octyne and thioethyl glucose sugar silane with 10 mol% Ni(0)-IMes catalyst (Table 3.1).

Table 3.1 Optimization Studies with Sugar Silanes and Terminal Alkynes



Entry	Alkyne Equiv.	Addition Method	Yield 152 (%)	Notes
1	1.5	substrates added as a solution at once	<30	trimerization accelerated
2	1.5	syringe addition of all substrates over 10 min	39	
3	2.0	syringe addition of all substrates over 10 min	43	
4	1.5	syringe addition of all substrates over 30 min	69	
5	1.5	syringe addition of all substrates over 100 min	64	
6	1.5	syringe addition of all substrates over 200 min	67	
7	1.5	syringe addition of all substrates over 30 min	50	heating to 35 °C, trimerization accelerated
8	1.5	syringe addition of all substrates over 30 min	68	addition of 1.1 equiv. $Ti(OiPr)_4$
9	1.5	syringe addition of alkyne over 90 min	<30	aldehyde hydrosilylation prevalent
10	1.5	syringe addition of alkyne over 45 min	<30	less aldehyde hydrosilylation
11	1.5	syringe addition of alkyne over 25 min	74	**optimized procedure**
12	1.5	syringe addition of alkyne over 8 min	<30	trimerization dominated

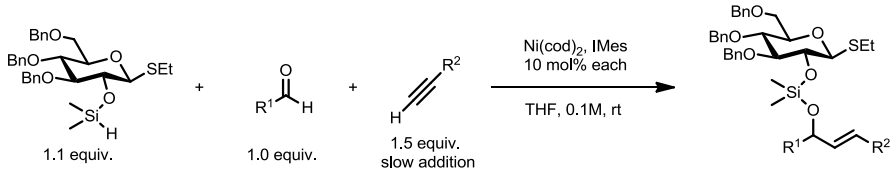
It was proposed that by increasing the amount of alkyne from the reported 1.2 equivalents to 1.5, that more alkyne would be available for the productive formation of **152**, even in the event that some is lost to trimerization. Addition of all substrates to the catalyst mixture with 1.5 equivalents of 1-octyne led to a very low yield as the

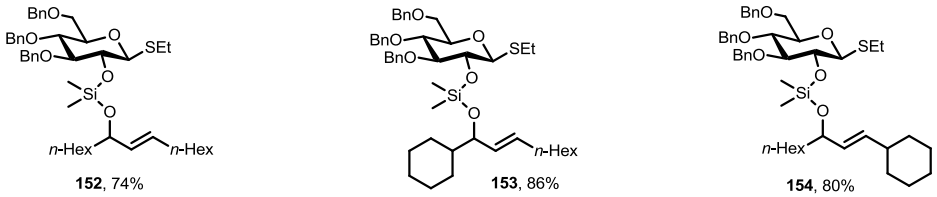
trimerization pathway was accelerated by the increased concentration of 1-octyne (entry 1). Syringe drive addition of the substrates over a ten minute period increased the yield of **152** to 39% (entry 2). Further increasing the equivalents of 1-octyne from 1.5 to 2.0 with a ten minute syringe-drive addition only resulted in a small yield increase to 43%, which suggests that using 1.5 equivalents of alkyne is preferential (entry 3). Reducing the rate of syringe-drive addition of all substrates from ten to thirty minutes increased the yield appreciably to 69% (entry 4). Further reducing the syringe-drive addition rate of a solution of all substrates to the nickel catalyst to 100 or 200 minutes showed no appreciable effect on the yield of **152** (entries 5 and 6). Thirty minute syringe-drive addition of all reagents as a solution to a catalyst mixture heated to 35 °C reduced the yield of **152** to 50% as the rate of trimerization was accelerated by gentle heating (entry 7). Exploring the effect of $Ti(O\textit{i}Pr)_4$ as an additive to the thirty minute syringe-drive addition of a solution of the substrates had no effect on the reaction, leading to a 68% yield (entry 8). It was hypothesized that syringe-drive addition of 1-octyne to a mixture of sugar silane, heptanal and Ni(0)-IMes at the appropriate rate could further increase the yield of **152**. Testing this hypothesis by syringe drive addition of 1-octyne to the silane, aldehyde and nickel-catalyst resulted in a low yield of **152** due to the increased presence of aldehyde hydrosilylation (entry 9). The hydrosilylation suggested that the alkyne was not present in a sufficient concentration, leading to oxidative addition of the Ni(0)-IMes catalyst into the Si—H bond, ultimately resulting in the observed hydrosilylation of heptanal. Increasing the rate of syringe-drive addition of 1-octyne to 45 minutes still resulted in low yields of **152**, however the amount of hydrosilylation was reduced (entry 10). In an effort to find balance in the rate of addition of a solution of 1-octyne, syringe-

drive addition was carried out over 25 minutes, resulting in a 74% yield of **152** (entry 11). Accelerating the syringe-drive addition of the alkyne to eight minutes led to large amounts of the trimerization product (entry 12), demonstrating the balance that must be found in the rate of addition of the alkyne to the aldehyde, silane and catalyst system. That balance was found in the optimized procedure of entry 11, which is as follows: to 10 mol% of a Ni(0)-IMes catalyst in THF, 1.5 equivalents of alkyne is added as a solution in THF by syringe-drive addition. As the first drop of alkyne solution adds to the catalyst mixture, a solution of 1.0 equivalents of aldehyde and 1.1 equivalents of sugar silane are added simultaneously. The syringe drive addition of alkyne is carried out with a 0.6M solution of alkyne in THF at a rate of 1 mL per 50 minutes.

With an optimized procedure developed for the Ni(0)-IMes-catalyzed reductive coupling of aldehydes and terminal alkynes using sugar silane reducing agents, we hoped to apply the conditions to other aldehyde and alkyne combinations (Scheme 3.12).

Scheme 3.12 Reductive Coupling of Terminal Alkynes with Optimized Procedure





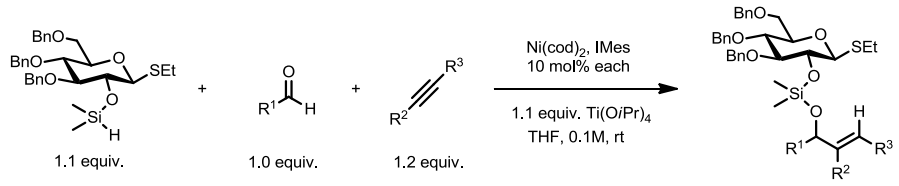
As demonstrated in the optimization studies, the production of **152** proceeded in 74% yield from heptanal and 1-octyne. When using the branched aldehyde

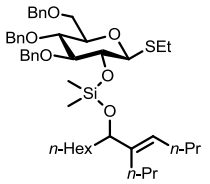
cyclohexylcarboxaldehyde and 1-octyne, **153** was produced in 86% yield. Heptanal underwent reductive coupling with cyclohexylacetylene to produce **154** in 80% yield. These results not only demonstrate the high yielding optimized procedure, but equally as important, they demonstrate the reproducibility as additional trials of these reactions produced the product in nearly identical yields. Further expansion of the scope was not pursued due to issues encountered in the glycosylation of these substrates, which will be highlighted later in this chapter.

3.2.2 Reductive Coupling with Internal Alkynes and Sugar Silanes

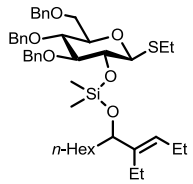
The nickel-catalyzed reductive coupling of aldehydes and internal alkynes generally proceed in higher yields than the corresponding coupling with terminal alkynes. This is due to the decreased tendency of internal alkynes to undergo nickel-catalyzed trimerization reactions. The trimerization side reaction, which required careful optimization to overcome in the previous subsection, is therefore no longer a problem with internal alkynes in reductive coupling. An optimized protocol was developed similar to that of our group's 2004 report, with the exception that adding 1.1 equivalents of $Ti(O\textit{i}Pr)_4$ to the reaction led to more efficient couplings. In this case, a solution of sugar silane, aldehyde and alkyne are added to the pre-formed Ni(0)-IMes catalyst and $Ti(O\textit{i}Pr)_4$, with no syringe drive addition necessary, generally leading to high yields of the trisubstituted allylic alcohol (Scheme 3.13).

Scheme 3.13 Scope of Reductive Coupling with Internal Alkynes and Sugar Silanes

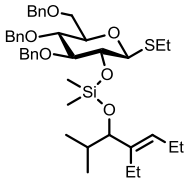




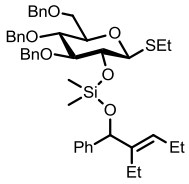
155, 83%



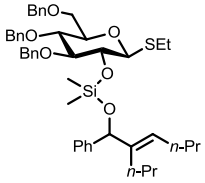
156, 87%



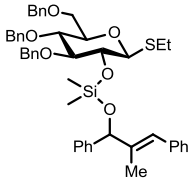
157, 75%



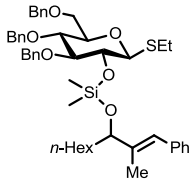
158, 92%



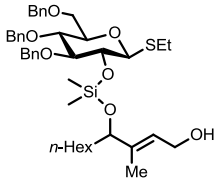
159, 75%



160, 64%, 95:5 rs



161, 99% 93:7 rs



162, No Reaction

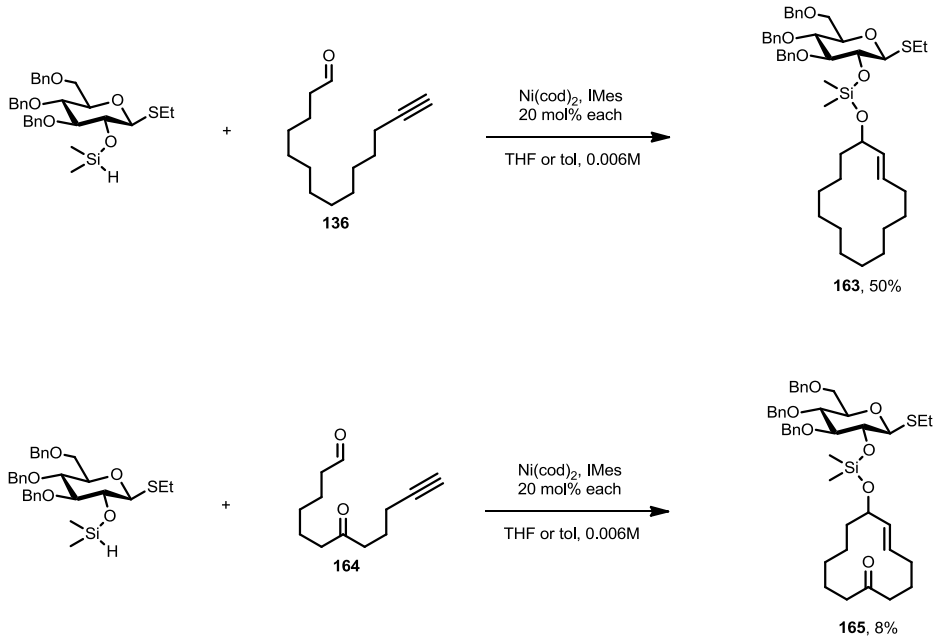
The reductive coupling of the straight-chained aliphatic aldehyde heptanal with 4-octyne and 3-hexyne proceeded to give **155** and **156** in 83% and 87% yield, respectively. The branched aliphatic aldehyde isobutyraldehyde also performed well, coupling with 3-hexyne to produce allylic alcohol **157** in 75% yield. Switching from aliphatic aldehydes to an aromatic aldehyde did not decrease the efficiency of the reaction. Benzaldehyde was coupled with 3-hexyne and 4-octyne and the sugar silane to give **158** and **159** in 92%

and 75% yield, respectively. The reductive coupling of benzaldehyde with 1-phenyl-1-propyne proceeded to give **160** in 64% yield with an excellent 95:5 regioisomeric ratio. Similarly, coupling heptanal with 1-phenyl-1-propyne resulted in a near quantitative yield of **161** with 93:7 regiocontrol. The high levels of regiocontrol observed in the reductive coupling products **160** and **161** are the result of an electronic bias in the aryl-alkyl substituted internal alkyne. We desired to explore the regiocontrolled addition with an internal alkyne bearing a propargylic alcohol. When attempting to couple 1-hydroxy-2-propyne with heptanal, **162** was not detected. Further exploration of free alcohols is needed to understand if this will be a limitation of the methodology. In conclusion, it has been demonstrated that the Ni(0)-IMes catalyzed reductive coupling of both aliphatic and aromatic aldehydes with internal alkynes proceeds in good to excellent yield to produce the desired silyl-linked trisubstituted allylic alcohols.

3.2.3 Reductive Macrocyclizations with Sugar Silanes

As described previously in this chapter, nickel-catalyzed reductive coupling has been utilized for the synthesis of a variety of different-sized macrocyclic rings from the respective ynal precursor. We hoped to explore this approach with sugar silanes because 1,2-*cis* glycosides appended to allylic alcohols of macrocycles are found in natural products such as amphotericin B.[61] Initial studies on macrocyclizations with sugar silane reducing agents produced respectable yields for the 14-carbon ynal **136** giving the desired macrocycle **163** in 50% yield (Scheme 3.14). However, attempts at cyclizing ynal **164**, containing a pendant ketone, produced a complex mixture in which only 8% of **165** was isolated. Additional work must be done in this area as carbohydrate-bearing macrocycles are important biologically relevant molecules.

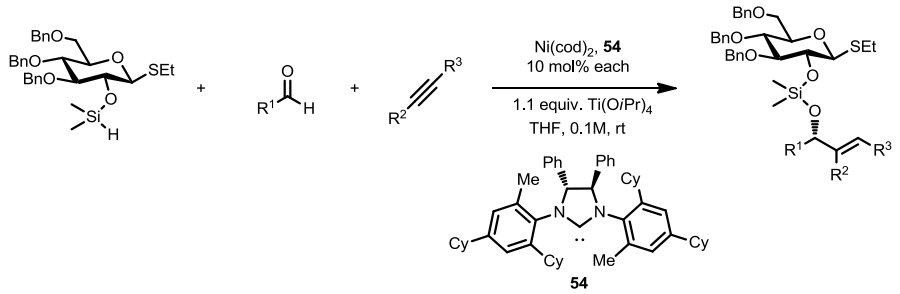
Scheme 3.14 Attempts at Macrocyclization with Sugar Silanes and Ni(0)-IMes

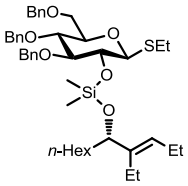


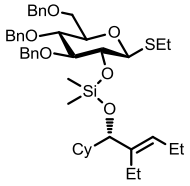
3.2.4 Reductive Coupling with Sugar Silanes Using Chiral NHCs

All reductive coupling products with sugar silanes thus far have been produced non-selectively as a 1:1 mixture of diastereomers at the newly formed stereocenter. It would be useful to apply the chiral NHC ligands developed by our group to produce the allylic alcohol with high levels of diastereocontrol. This process was explored using chiral NHC **54** and conditions for coupling an aldehyde with an internal alkyne using a sugar silane reducing agent (Scheme 3.15).

Scheme 3.15 Diastereoselective Reductive Coupling with Sugar Silanes







Using 10 mol% Ni(0)-**54**, heptanal and 3-hexyne were coupled to produce allylic alcohol **166** in 93% yield with a modest 3:1 dr. In order to have a direct comparison of selectivity, we wished to use an aldehyde-alkyne combination reported in the previous communication on asymmetric reductive coupling, where triethylsilane was used as the reducing agent. This was done by coupling cyclohexylcarboxaldehyde with 3-hexyne to give **167** in 76% yield with a 5.3:1 dr. The reductive coupling product for this aldehyde and alkyne combination in the original communication proceeded in 84% yield and 85% ee. While the yield was comparable when using the sugar silane protocol, the selectivity observed in the newly formed stereocenter was diminished. The 5.3:1 dr observed in the production of **167** corresponds to 68% ee at the carbinol stereocenter. The diminished selectivity is most likely a function of the Ti(O*i*Pr)$_4$, which is not present in the triethylsilane reaction, lowering the energy between diastereomeric transition states. It is unlikely the change in silanes resulted in the diminished selectivity due to the fact that

silanes have been shown to be zero-order in the nickel-catalyzed reductive coupling of aldehydes and alkynes. When attempting the reductive coupling with terminal alkynes and Ni(0)-**54**, low yields were observed due to competing trimerization pathways, necessitating a re-optimization to find a balance in reactivity.

3.3 Glycosylation of Allylic Alcohols

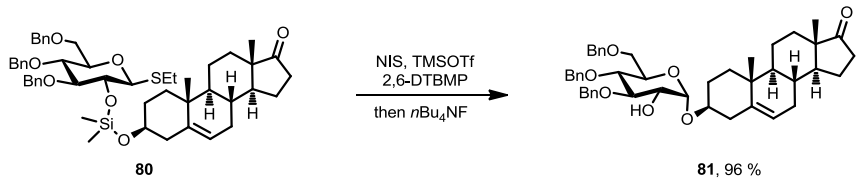
3.3.1 Initial Attempts at Glycosylating Allylic Alcohols

The nickel-catalyzed reductive coupling of aldehydes and alkynes with sugar silane reducing agents has now been demonstrated. The sugar silanes were used to couple both internal and terminal alkynes, to make macrocycles, and to make diastereomerically enriched allylic alcohols with a chiral catalyst system. These advances mark the first step in merging aglycone synthesis with glycoside incorporation; the second is the glycosylation of the newly synthesized allylic alcohol.

Initial attempts at glycosylating the silyl-linked allylic alcohols were carried out with NIS-based activation methods. Reagent combinations such as NIS and TMSOTf had proven to be very successful in the glycosylation of silyl-linked compounds produced in the ketone hydrosilylation and alcohol dehydrogenative silylation projects. Unfortunately, when attempting to glycosylate tethered allylic alcohols with NIS-based methods, very complex reaction mixtures were observed as numerous undesired byproducts were produced, providing low yields of the desired glycoside (~15-30%). Careful consideration of the difference between glycosylating allylic alcohols and those discussed in previous chapters revealed that the presence of the olefin alone was not responsible for the vastly different reactivity with these substrates. This can be observed in the glycosylation of **80** with NIS and TMSOTf. The steroid aglycone contains a homoallylic

alcohol, yet it is glycosylated in an excellent 96% yield producing **81** (Scheme 3.16). This suggests that the undesired side reactions in intramolecular aglycone delivery are a consequence of the unique reactivity of allylic alcohols.

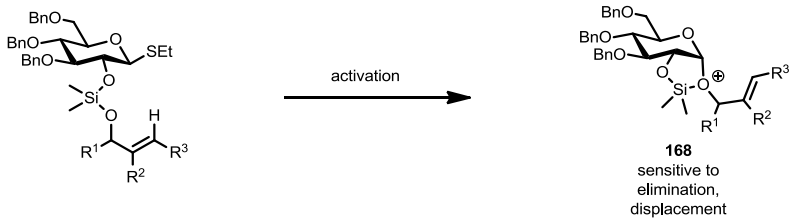
Scheme 3.16 Glycosylation of an Aglycone Containing an Olefin with NIS and TMSOTf



80 **81**, 96 %

While evaluating the unique features of glycosylating an allylic alcohol, we realized that upon activation and delivery of the aglycone, a highly activated leaving group is formed at the allylic position. This intermediate **168** is prone to a variety of side reactions (Scheme 3.17). If a sufficiently basic species is present in the reaction mixture, elimination can occur if R^1 or R^3 contain a proton, leading to an aglycone derived diene byproduct. Additionally, if a sufficiently nucleophilic species is present in the reaction mixture, displacement can occur in an S_N2-like fashion or through an allylic displacement pathway. These unique features presented by the intramolecular aglycone delivery of an allylic alcohol required a careful selection of reagents for the activation of the anomeric leaving group.

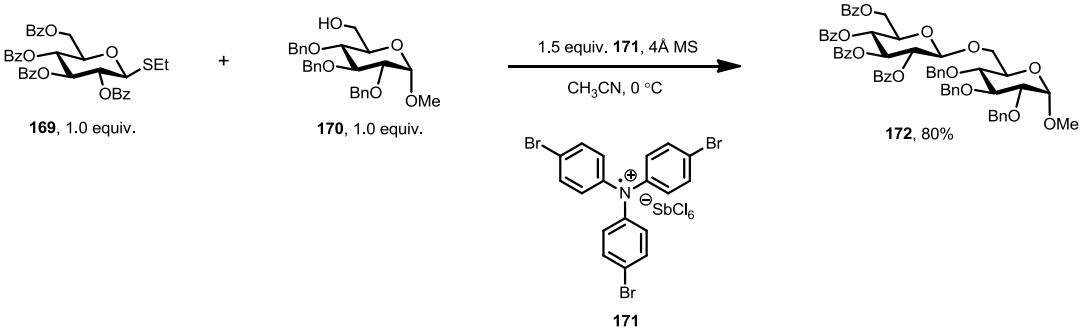
Scheme 3.17 Generation of a Sensitive Intermediate with Allylic Alcohol Glycosylation



Considering the factors discussed regarding the sensitivity of intermediate **168**, a careful review of the literature was conducted to choose a suitable reagent for activation

that would preferentially react under mild conditions without producing any basic or nucleophilic byproducts. Sinay and coworkers developed a method that appeared to fit these parameters, in which the bench stable nitrogen-centered radical cation **171** is used to activate a sulfur leaving group by single electron oxidation, facilitating oxocarbenium formation.[62] It is a notably mild procedure, as the byproducts consist of the corresponding triarylamine and a sulfur-centered radical. A representative example is seen in the glycosylation of primary alcohol **170** with the glycosyl donor **169**, which, upon activation with 1.5 equivalents of radical cation **171**, gave disaccharide **172** in 80% yield and a 25:1 β:α selectivity (Scheme 3.18).

Scheme 3.18 Sinay's Radical Cation **171** Activation Method

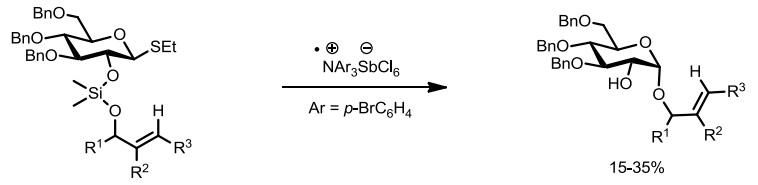


3.3.2 Development of Radical Cation Glycosylation Conditions

The mild features of the radical cation procedure were first tested on the glycosylation of tethered trisubstituted allylic alcohols. Initial screening of conditions did not result in an increase in the yield, and the desired glycosides were produced in a maximum of 35% yield (Scheme 3.19). However, it was noted that the reaction proceeded with a noticeable decrease in undesired side reactions. While using radical cation **171** for activation, the main side reaction appeared to be cleavage of the silyl-linkage prior to glycosylation. This was encouraging, and further screening of conditions

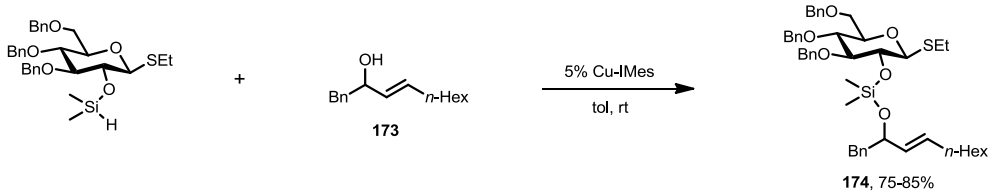
was undertaken to discover conditions to prevent decomposition of the silyl-linker and promote conversion to the desired glycoside.

Scheme 3.19 Initial Screening of Conditions with Radical Cation **171**



It was proposed that switching from the silyl-linked trisubstituted allylic alcohols to 1,2-*trans* allylic alcohols would be a better starting point for screening conditions. We hypothesized that glycosylation would be more facile with less electron rich disubstituted allylic alcohols. This is due to the decreased electron density of the olefin relative to a trisubstituted allylic alcohol, and the diminished steric environment on the aglycone. At the time this screen was to be conducted, the investigation of nickel-catalyzed reductive coupling of aldehydes and terminal alkynes was not yet complete.

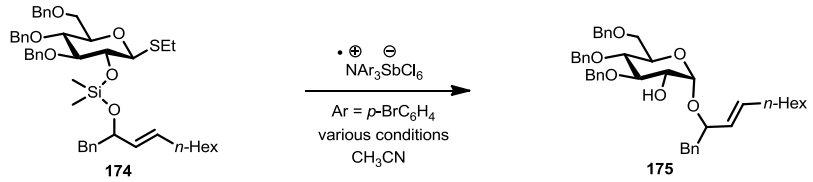
Scheme 3.20 Independent Synthesis of Silyl-Linked Disubstituted Allylic Alcohol



Therefore in order to produce an appreciable quantity of a silyl-linked 1,2-*trans* allylic alcohol, the alcohol was independently synthesized and then tethered to the sugar silane by a Cu(I)-IMes-catalyzed dehydrogenative silylation (**Scheme 3.20**). The synthesis of **174** from the sugar silane and allylic alcohol **173** generally proceeded in a 75-85% yield and easily produced a gram of **174**, which was ideal for screening glycosylation conditions.

To gain a better understanding of the activation of **174** with radical cation **171**, a series of exploratory reactions were conducted (Scheme 3.21). We wanted to know if using a superstoichiometric amount of radical cation **171**, as Sinay and coworkers did, was necessary. Treatment of **174** with 20 mol% of the radical cation led to very low conversion to the desired glycoside **175**. Instead, **174** remained as the major component of the reaction, suggesting that once the radical cation is reduced under the reaction conditions, it is not re-oxidized to the active radical cation form by any other species. This suggested that it was indeed necessary to use the radical cation in a superstoichiometric fashion.

Scheme 3.21 Initial Exploratory Screening in the Glycosylation of **174**



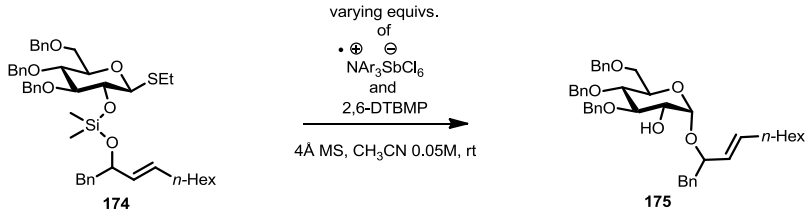
It was proposed that nucleophilic additives could form a pentavalent silicate species, facilitating the delivery of the allylic alcohol aglycone to the oxocarbenium ion. Additionally, this should aid cleavage of the Si—O bond present in the problematic intermediate **168**, prior to any undesired side reactions taking place. The nucleophilic additive must be chosen judiciously, so as to avoid competitive addition to the oxocarbenium ion. In order to overcome this, neutral nucleophiles were chosen so if they did glycosylate, the cation of the nucleophile would be a good leaving group, allowing reversible formation of the oxocarbenium ion.

When activating **174** with 1.5 equivalents each of the radical cation and 2,6-DTBMP, and DABCO as the nucleophilic additive, very little conversion was observed.

This was potentially due to competitive oxidation of DABCO, or the formation of an inactive complex between the two species.[63] When the same reaction was carried out in the absence of 2,6-DTBMP, low conversion was observed. However, when the reaction was allowed to stir for two days, the desired glycoside **175** was isolated in 43% yield. It is unlikely that single electron oxidation of the sulfur leaving group accounted for the observed result. Rather, the prolonged reaction time and mixture of reagents likely resulted in activation of the leaving group by an alternative mechanism. Additional studies with DABCO and radical cation **171** showed that if the equivalents of DABCO were greater than **171**, no reaction was observed, presumably due to the rapid deactivation of the radical cation by DABCO. Activating silyl-linked compound **174** with 1.5 equivalents of the radical cation, 2.0 equivalents 2,6-DTBMP and 5.0 equivalents of THF resulted in a 25% yield of glycoside **175**. These conditions, in the absence of 2,6-DTBMP, led to rapid decomposition of the silyl-linked material producing no desired product. Using 2.0 equivalents of triphenylphosphine as the nucleophilic additive with 1.5 equivalents of radical cation and 2.0 equivalents of 2,6-DTBMP resulted in no activation of the thioethyl leaving group. Instead, cleavage of the silyl-linker was observed, producing the 2-hydroxy sugar and the allylic alcohol. Addition of 3.0 equivalents of pyridine with 1.5 equivalents of radical cation led to no observed reaction, again likely due to the competitive single electron oxidation or formation of an inactive complex with **171**, resulting in large amounts of remaining starting material. Our screen suggested that nucleophilic additives either served to competitively deactivate the radical cation, facilitate decomposition of the silyl-linked starting material, or both.

When treating silyl-linked compound **174** with 1.5 equivalents of radical cation **171** in the absence of added base, no production of the desired glycoside was detected. Instead, rapid decomposition of the starting material was observed. It is possible that upon activation, the hexafluoroantimonate counter ion forms an acidic or nucleophilic species, resulting in the observed decomposition. This suggests the necessity for a base to buffer the reaction, preventing the decomposition of the silyl-linker prior to intramolecular aglycone delivery. Based on previous results, 2,6-DTBMP has been the most compatible organic base, as other bases such as triethylamine, DABCO, and pyridine rapidly deactivate the radical cation reagent. It should be noted that alkoxide bases were not screened due to their potential for competing *O*-glycoside formation. A comprehensive set of experiments was devised to determine the optimal ratio of radical cation to 2,6-DTBMP in the glycosylation of **174** (Scheme 3.22).

Scheme 3.22 Screening Reagent Ratios to Optimize Glycosylation of **174**

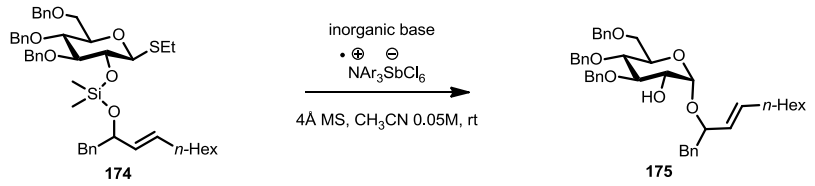


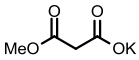
In a series of sixteen experiments with 1.0 equivalent of silyl-linked compound **174**, the amount of radical cation was varied in increments between 1.0 and 2.0 equivalents. The equivalents of 2,6-DTBMP were also varied in increments between 1.0 and 1.8. These experiments revealed that as the ratio of radical cation to 2,6-DTBMP became greater than one, the consumption of starting material increased. However, as this ratio increased, decomposition was a major problem, resulting in low yields of the desired product. As the ratio of radical cation to 2,6-DTBMP decreased to one or less,

reactivity was shut down, and large amounts of starting material remained. This is presumably due to the unproductive oxidation of 2,6-DTBMP, as this hindered pyridine base is unlikely to form a complex by nucleophilic addition to **171**. This study of reagent stoichiometry revealed that the ideal ratio of radical cation **171** to 2,6-DTBMP was 1.5 to 1.1 relative to 1.0 equivalent of **174**. At this optimized level of reactivity with 2,6-DTBMP as the base, the desired 1,2-*cis* glycoside was only produced in 43% yield. It was concluded that 2,6-DTBMP was not a suitable base for the productive intramolecular aglycone delivery utilizing radical cation **171** as the activating agent.

Results with the radical cation suggested that finding a suitable base to buffer the reaction conditions should elevate the yields. However, little success had been realized with organic bases, so we sought to gain an understanding of the compatibility of inorganic bases under the radical cation activation conditions (Table 3.2). When using basic alumina, potassium carbonate, and sodium thiosulfate pentahydrate, small amounts of the desired glycoside **175** were detected, but the major pathway was decomposition of the starting material (entries 1-3). Utilizing magnesium sulfate as the inorganic base produced no detectable amount of **175**, and decomposition of the starting material was rapidly observed (entry 4). Approximately 20% of glycoside **175** was formed when a carboxylate salt was used; however, it appeared to shut down reactivity leading to large amounts of recovered **174** (entry 5). A breakthrough was discovered when employing sodium bicarbonate, producing **175** in 55% yield (entry 6). It was found that sodium sulfate was also a suitable base, as **175** was formed in approximately 35% yield, although decomposition was still an issue (entry 7).

Table 3.2 Screening Inorganic Bases in Radical Cation Glycosylations

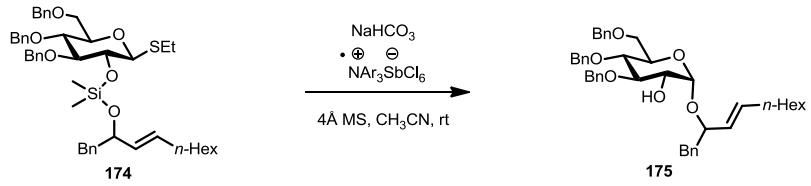


Entry	Inorganic Base	Yield 175 (%)	Notes
1	basic alumina	trace	**174** consumed, decomposition
2	K_2CO_3	trace	**174** consumed, decomposition
3	$Na_2S_2O_3 \bullet 5H_2O$	trace	**174** consumed, decomposition
4	$MgSO_4$	not detected	**174** consumed, decomposition
5		~20%	large amount of **174** remains
6	$NaHCO_3$	55%	promising lead
7	Na_2SO_4	~35%	some decomposition

Sodium bicarbonate was identified as the best base to explore further optimization studies in the glycosylation of **174** (Table 3.3). A control experiment with the silyl-linked compound and $NaHCO_3$ was conducted in the absence of the radical cation (entry 1). This led exclusively to recovery of starting material, which was important not only to determine that $NaHCO_3$ does not aid in glycosylation, but it also does not cleave the silyl-linker in **174**. The starting point for optimization studies comes from the initial reaction conditions discovered in the inorganic base screen, producing **175** in 55% yield (entry 2). When decreasing the equivalents of radical cation to 1.2 with a slight increase of $NaHCO_3$ to 7.0 equivalents, the yield of **175** decreased to 38% (entry 3). It was determined the incorporation of 4Å MS was necessary as attempting the glycosylation in

their absence led to increased glycosylation of adventitious water, resulting in a low yield of **175** (entry 4). Heating the reaction to 50 °C accelerated the decomposition pathway as well as increased the addition of water to the oxocarbenium ion, producing a low yield of **175** (entry 5). Diluting the reaction from 0.05 to 0.02M resulted in a slight increase of the yield of **175** to 59% (entry 6). An additional increase in yield was observed when the silyl-linked **174** was added dropwise to a mixture of radical cation and $NaHCO_3$ as a solution in acetonitrile, resulting in a 64% yield (entry 7). Using the same procedure as entry 7 with $KHCO_3$ resulted in a similar 61% yield of **175**, suggesting negligible counterion effects (entry 8). Increasing the equivalents of $NaHCO_3$ to 20 with the dropwise addition of **174** produced the desired glycoside **175** in an optimized yield of 70% (entry 9). Although it is not ideal to use 20 equivalents of a reagent in a procedure, the reagent is very inexpensive (5 kg $NaHCO_3$ for $137.50, Sigma Aldrich) and has a low molecular weight, resulting in minimal mass addition even at high equivalency. Additionally, using only 5 equivalents of $NaHCO_3$ produced similar yields and can be used as an optimized protocol. It should be noted that nBu$_4$NF is added to all glycosylation experiments following activation to remove the silyl-linkage. The best workup procedure was obtained by filtering off the molecular sieves from the reaction mixture, followed by concentration with silica gel and dry loading for column chromatography.

Table 3.3 Radical Cation Glycosylation with $NaHCO_3$ Optimization Study

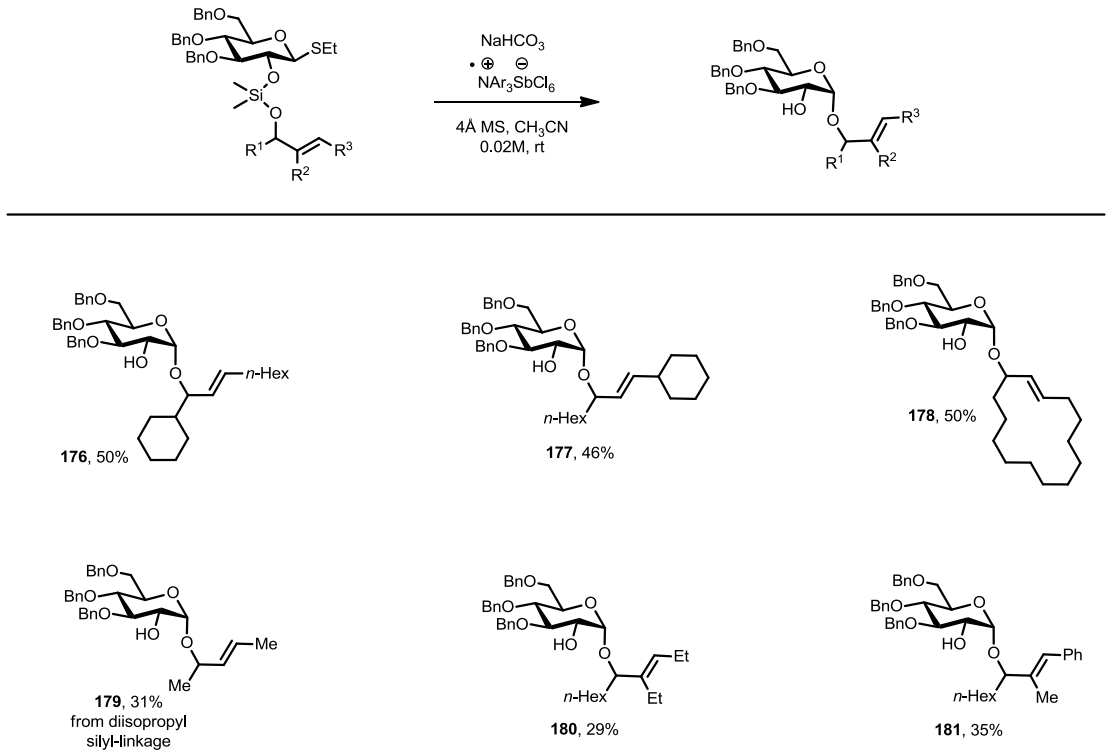


Entry	Equiv. $\bullet\oplus\ \ominus$ NAr_3SbCl_6	Equiv. $NaHCO_3$	Conc.	Yield 175 (%)	Notes
1	0	10	0.05	0	control experiment, no reaction
2	1.5	5	0.05	55	
3	1.2	7	0.05	38	
4	1.5	5	0.05	<30	run without 4Å MS, H_2O addition
5	1.5	5	0.05	<30	H_2O addition, decomposition
6	1.5	5	0.02	59	
7	1.5	5	0.02	64	dropwise addition of **174** over 3 min
8	1.5	5 ($KHCO_3$)	0.02	61	dropwise addition of **174** over 3 min
9	1.5	20	0.02	70	dropwise addition of **174** over 3 min

With a procedure now developed for the glycosylation of 1,2-*trans* allylic alcohols by intramolecular aglycone delivery, we sought to explore the scope and generality of this radical cation based procedure (Scheme 3.23). Applying the radical cation based method to other silyl-tethered disubstituted allylic alcohols resulted in lower yields than those seen with compound **174**. The reductive coupling product of cylcohexylcarboxaldehyde and 1-octyne gave **176** in 50% yield. The reductive coupling product of heptanal and cyclohexylacetylene was activated to give the glycoside **177** in only 46% yield. Similar to the previous two examples, the glycosylated macrocycle **178**

was produced in 50% yield. While these yields were somewhat synthetically useful, they were routinely 10-20% less than yields observed in the glycosylation of **174**. We proposed that switching from a dimethylsilyl to a diisopropylsilyl linker may prevent undesired decomposition pathways. However, when applying the optimized radical cation procedure to the corresponding diisopropylsilyl linked compound of **179**, the desired glycoside was produced in 31% yield. It should be noted that the silyl-linked compound corresponding to **179** was made by dehydrogenative silylation. The sugar silane containing a diisopropylsilane also performed very poorly as a reducing agent in the nickel-catalyzed reductive coupling of aldehydes and alkynes. When attempting to glycosylate trisubstituted allylic alcohols with the radical cation procedure, glycosides **180** and **181** were produced in 29% and 35% yield respectively, which illustrated the additional challenges of glycosylating allylic alcohols containing trisubstituted olefins.

Scheme 3.23 Scope of Radical Cation Glycosylation Method

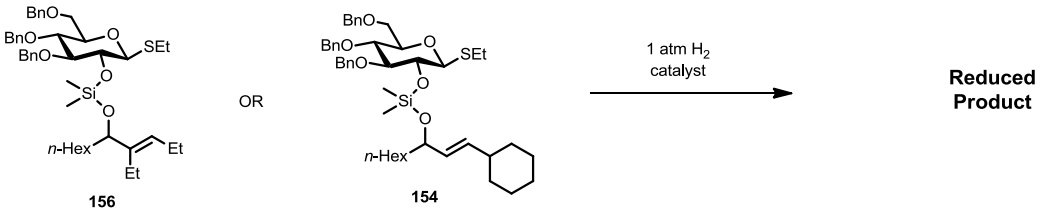


The moderate to poor yields observed while exploring the generality of the optimized radical cation procedure were disappointing. The novelty of merging aglycone synthesis with glycoside incorporation has been limited by the problems glycosylating allylic alcohols presented. We hoped that the advantages of using sugar silanes as reducing agents in the nickel-catalyzed reductive coupling of aldehydes and alkynes would not be lost in these challenges.

3.3.3 Hydrogenation Studies on Silyl-Linked Allylic Alcohols

Studies on the glycosylation of allylic alcohols have shown the inherent challenges that lie within harnessing highly sensitive intermediates. The intramolecular aglycone delivery of allylic alcohols produced by nickel-catalyzed reductive coupling led to poor yields of the desired glycoside. However, intramolecular aglycone delivery of non-allylic alcohol aglycones proceeded in good to excellent yields. We hoped to combine these two strategies by using sugar silanes as reducing agents to produce allylic alcohols, followed by hydrogenation of the olefin, to increase the yields of glycosylation. A screen of hydrogenation conditions was carried out with silyl-linked compounds **154** and **156** (Table 3.4). We searched for a catalyst system that would selectively hydrogenate the olefin in the presence of benzyl protecting groups and be mild enough to prevent decomposition of the silyl linker.

Table 3.4 Screen of Hydrogenation Catalysts for Reducing Allylic Alcohols



Entry	Compound	Catalyst	Solvent	Notes
1	**156**	20% PtO_2	EtOH	decomposition of **156**
2	**156**	10% Pd/C	EtOAc	small amount of reduced product
3	**156**	20% Pd/C	EtOAc	~1:1 **156** to reduced product
4	**156**	20% $Pd(OH)_2$	EtOAc	starting material, silyl-cleavage, debenzylation
5	**156**	20% Pd/C	EtOH	silyl-cleavage
6	**154**	10% Pd/C	MeOH	NH_4HCO_2H used as H_2 surrogate, no reaction
7	**154**	10% Ni(0)-IMes	THF	addition of H_2 following reductive coupling led to silyl-cleavage
8	**154**	20% Pd/C	EtOAc	complete conversion to reduced product

The reduction of trisubstituted allylic alcohol **156** was first explored, and it was found that using PtO_2 in EtOH led to decomposition of the starting material (entry 1). When utilizing 10 mol% Pd/C in EtOAc, no decomposition was observed, and a small amount of the reduced olefin product was detected by low resolution mass spectrometry (entry 2). Increasing catalyst loading to 20 mol% Pd/C in EtOAc improved the conversion to the reduced product (entry 3). However, after 24 hours at room temperature, only 50% of **156** had been converted to the desired product. Using 20 mol%

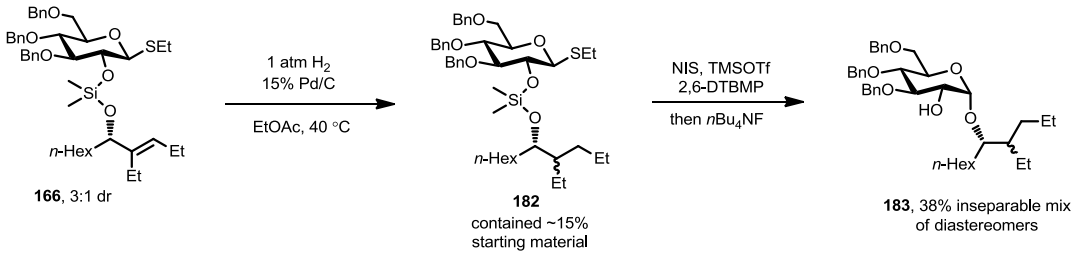
$Pd(OH)_2$ in EtOH resulted in decomposition of the silyl-linker, debenzylation, and recovery of starting material (entry 4). Trying 20 mol% Pd/C in EtOH led only to cleavage of the silyl-linker in **156** (entry 5).

When attempting the reduction of disubstituted allylic alcohol **154** with 10% Pd/C in MeOH, and ammonium formate as a H_2 surrogate, no reaction was observed (entry 6). A one pot reductive coupling-hydrogenation protocol was explored by incorporating a hydrogen atmosphere upon completion of the Ni(0)-IMes catalyzed reductive coupling. This approach only resulted in decomposition of the silyl-linkage (entry 7). Successful reduction of **154** was completed by treatment with 20 mol% Pd/C in EtOAc at room temperature to give complete conversion to the aliphatic product (entry 8). This catalyst system was selected as the ideal choice for the hydrogenation of allylic alcohols tethered to sugar silanes.

We envisioned applying this reductive coupling-hydrogenation protocol to a diastereomerically enriched trisubstituted allylic alcohol. Upon hydrogenation of the olefin, a new stereocenter is formed, and the silyl-linked carbohydrate could potentially shield one face of the olefin, leading to a highly diastereoselective reduction. This sequence was tested in the hydrogenation of trisubstituted allylic alcohol **166** (Scheme 3.24). Gentle heating at 40 °C in EtOAc with 15 mol% Pd/C gave approximately 85% conversion to reduced product **182**, which was inseparable from the starting material. The mixture of products complicated accurate determination of the dr of the reduced product, but it was estimated near 10:1. Activation of **182**, still containing ~15% allylic alcohol **166**, with NIS and TMSOTf resulted in only 38% of the desired glycoside **183**. Determination of the relative stereochemistry was again complicated by the inseparable

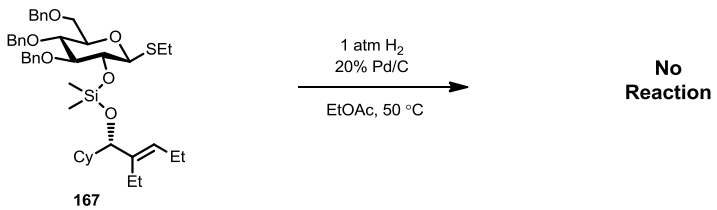
diastereomers of **183**. Further exploration is needed to understand the reasons for the low yielding glycosylation of **182**. It is conceivable that even in small quantities, allylic alcohols generate highly reactive species under NIS/TMSOTf activation conditions which impacted the glycosylation of **182**. Additionally, the thioethyl leaving group may not be reactive enough for the high yielding glycosylation of **182** due to steric hindrance on the aglycone. Using a thiophenyl leaving group and ensuring complete conversion to the reduced product would be important for future studies with the hydrogenation protocol.

Scheme 3.24 Attempt at Hydrogenation/Glycosylation of Trisubstituted Allylic Alcohol



A limitation of the hydrogenation conditions was realized when attempting the reduction of **167** with Pd/C in EtOAc where no reaction resulted (Scheme 3.25). The only difference between **166** and **167** are the *n*-hexyl and cyclohexyl allylic substituents, respectively. A barrier of reactivity was discovered with the small increase in steric bulk. This is a limitation requiring further experimentation, as increased temperatures, reaction times and additional aliquots of catalyst did not produce the desired reduction product.

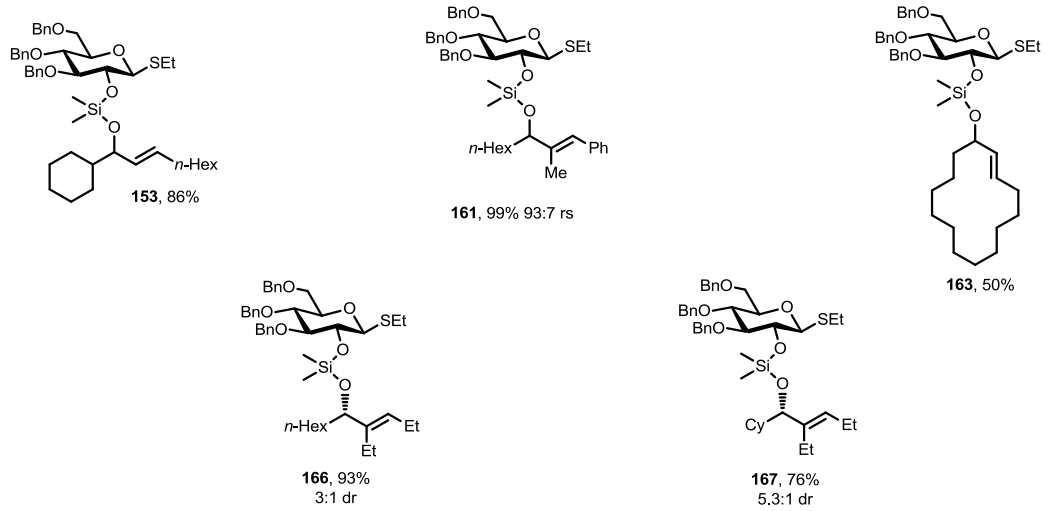
Scheme 3.25 Limitation in the Hydrogenation of Olefins with Increased Steric Bulk



3.4 Summary and Future Directions

The goal of this research project was to merge aglycone synthesis with glycoside incorporation. The first step was accomplished by developing conditions for the Ni(0)-catalyzed reductive coupling of aldehydes and alkynes (Scheme 3.26). This was applied to the intermolecular synthesis of di- and tri-substituted allylic alcohols from terminal and internal alkynes respectively. The intramolecular cyclization of a 14-carbon ynal was carried out to produce a macrocycle in modest yield. Additionally, the utility of chiral NHCs was demonstrated by producing diastereomerically enriched allylic alcohols.

Scheme 3.26 Highlights of Reductive Coupling with Sugar Silanes



153, 86%

161, 99% 93:7 rs

163, 50%

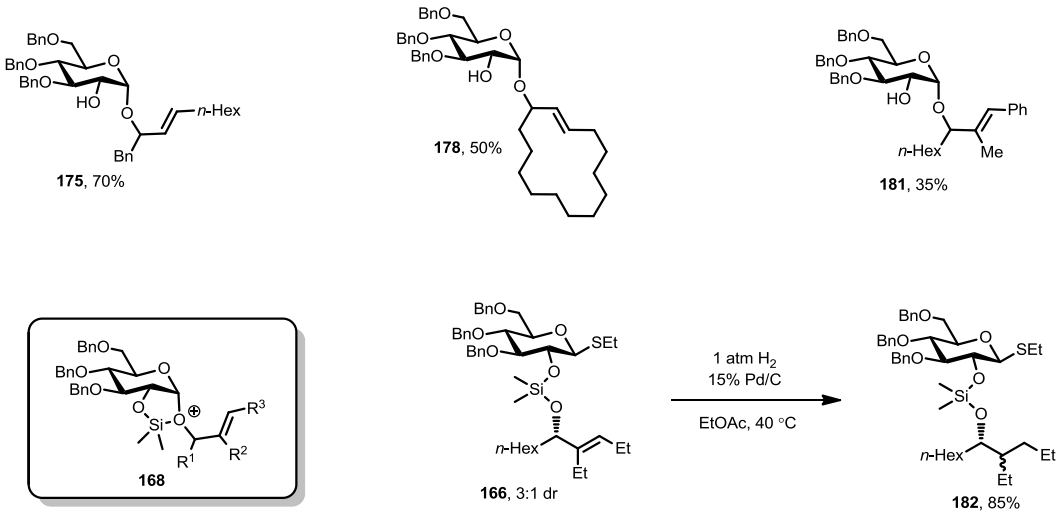
166, 93%
3:1 dr

167, 76%
5.3:1 dr

The glycosylation of the silyl-tethered allylic alcohols by intramolecular aglycone delivery presented a unique challenge due to the proposed generation of sensitive intermediate **168** (Scheme 3.27). Initial studies revealed that NIS-based activation methods were not suitable for the glycosylation of allylic alcohols. A mild radical cation based method was explored, and it was found that buffering the reaction with a base was necessary. Screening revealed sodium bicarbonate was the ideal base paired with radical cation **171** for glycosylation of allylic alcohols. However, optimization studies only

resulted in modest yields of the 1,2-*cis* glycosides when using disubstituted allylic alcohols. The optimized procedure was ineffective at glycosylating trisubstituted allylic alcohols, resulting in yields of approximately 30%. Studies were conducted on the hydrogenation of silyl-tethered allylic alcohols, and conditions using Pd/C in EtOAc were found to be selective for the hydrogenation of unhindered allylic alcohols without debenzylation or silyl-cleavage.

Scheme 3.27 Highlights of Intramolecular Aglycone Delivery with Allylic Alcohols



Glycosyl fluoride-based sugar silanes are currently being explored to determine their effectiveness as reducing agents in the reductive coupling of alkynes and aldehydes, producing silyl-linked allylic alcohols. Mild methods for the activation of fluoride leaving groups are hypothesized to increase the efficiency of intramolecular aglycone delivery with allylic alcohols. The body of work reported in this chapter has improved our understanding of reactive intermediates such as **168**. It is hoped that the shortcomings of our efforts to merge aglycone synthesis with glycoside incorporation provide lessons for the eventual success of this method. Additionally, further exploration into the hydrogenation-glycosylation sequence could provide a useful protocol for generating

glycosides containing two new stereocenters on the aglycone from simple starting materials in rapid fashion. This protocol would be well suited in conjunction with the latest developments in ligand-controlled regioselective addition of unbiased alkynes to aldehydes. These developments would further highlight the applications of sugar silanes and the synthetic utility brought about by merging transition-metal catalysis and carbohydrate chemistry to synthesize glycosides selectively using novel pathways.

Chapter 4

Experimental Procedures and Spectral Data

4.1 Chapter 1 Experimental Procedures and Spectral Data

4.1.1 Chapter 1 Experimental Procedures

All reagents were used as received unless otherwise noted. Solvents were purified under nitrogen using a solvent purification system (Innovative Technology, inc., Model # SPS-400-3 and PS-400-3). $Ni(COD)_2$ (Strem Chemicals, Inc., used as received), CuCl (Sigma-Aldrich, used as received), 1,3-dimesitylimidazolium chloride (IMes·HCl) were stored and weighed in an inert atmosphere glovebox. $Ti(O\text{-}i\text{-}Pr)_4$ and $Me_2Si(H)Cl$ were distilled and stored under inert atmosphere in Schlenk flasks. All nickel reactions were conducted in flame-dried glassware under a nitrogen atmosphere. ^1H and ^{13}C spectra were obtained in $CDCl_3$ at rt, unless otherwise noted, on a Varian Mercury 400 or Varian Unity 500 MHz instrument. Chemical shifts of ^1H NMR spectra were recorded in parts per million (ppm) on the δ scale from an internal standard of residual chloroform (7.27 ppm). Chemical shifts of ^{13}C NMR spectra were recorded in ppm from the central peak of $CDCl_3$ (77.0 ppm) on the δ scale. High resolution mass spectra (HRMS) were obtained on a VG-70-250-s spectrometer manufactured by Micromass Corp. (Manchester UK) at the University of Michigan Mass Spectrometry Laboratory.

General Procedure for the Preparation of Sugar Silanes (General Procedure 4.1)

The respective 2-OH sugar (1.0 equiv) was dissolved in dry CH_2Cl_2 (0.2M) and cooled to 0 °C in an ice bath. Freshly distilled NEt_3 (2.0 equiv) was added and stirred for 3 minutes, $Me_2Si(H)Cl$ (1.5 equiv) was then added. This was allowed to stir for 4 hours then volatiles were removed by rotary evaporation, the resulting oil was extracted from $NaHCO_3$ (aq.) (diluted over ice) 3 times with CH_2Cl_2. The combined organic extracts were dried quickly over $MgSO_4$, filtered, concentrated, and the resulting oil was either used directly or stored frozen in C_6H_6. Note – the sugar silanes are stable for months when stored frozen in benzene, or under high vacuum. Alternatively, the corresponding 2-OH sugars are very stable to be stored for long periods of time on the bench top.

General Procedure for the Ni(0)-IMes Promoted Hydrosilylation of Ketones (General Procedure 4.2)

A solid mixture of $Ni(COD)_2$ (10%), IMes·HCl (10%), and KO-*t*-Bu (10%) was dissolved in dry THF (0.02M) at rt under an inert atmosphere (N_2), and stirred for 10-15 minutes until the catalyst mixture was a dark blue color. $Ti(O\textit{i}\text{-}Pr)_4$ (1.1-2.2 equiv) was then added to the catalyst mixture followed by the addition of the sugar silane (1.1 equiv), and ketone (1.0 equiv) as a solution in dry THF (0.2M). Upon completion of the reaction, as monitored by TLC, the reaction mixture was filtered through a short plug of silica gel with a mixture of EtOAc/hexanes and concentrated by rotary evaporation. The resulting residue was purified via flash chromatography (SiO_2) to afford the desired product. Note – For the site-selective hydrosilylation of a ketone in the presence of a free hydroxyl group, using 2.2 equiv of $Ti(O\text{-}\textit{i}\text{-}Pr)_4$, and a 0.05 M solution in THF results in higher yields of the desired product.

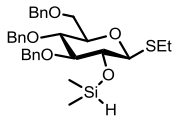
General Procedure for the CuCl/IMes Promoted Hydrosilylation of Ketones (General Procedure 4.3)

A solid mixture of CuCl (5%), IMes·HCl (5%) and KO-*t*-Bu (10%) was dissolved in dry toluene (0.015M) at rt under an inert atmosphere (N_2), and stirred for 20 minutes. A mixture of ketone (1.0 equiv) and silane (1.1 equiv) was dissolved in dry toluene (0.2M), the catalyst was then added to this mixture as a solution in a minimum of dry toluene. Upon completion of the reaction, as monitored by TLC, the reaction mixture was filtered through a short plug of silica gel with a mixture of EtOAc/Hexanes and concentrated by rotary evaporation. The resulting residue was purified via flash chromatography (SiO_2) to afford the desired product.

General Procedure for NIS/TMSOTf Mediated Glycosylation of Silyl-Linked Compounds (General Procedure 4.4)

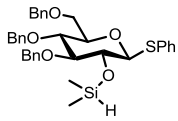
The respective silyl-linked compound (1.0 equiv) was dissolved in dry CH_2Cl_2 (0.02M) and cooled to -40 °C. *N*-iodosuccinimide (NIS) (1.3-1.4 equiv) and 2,6-di-*tert*-butyl-4-methyl pyridine (2,6-DTBMP) (2.0-4.0 equiv) were added and stirred for 3 minutes. To this solution, trimethylsilyl trifluoromethanesulfonate (TMSOTf) (1.2-2.4 equiv) was added, this is stirred for 10-15 minutes and then warmed to 0 °C. Upon disappearance of the silyl-linked compound, as monitored by TLC (generally 30 to 90 min), *n*-Bu_4NF (5-10 equiv, 1M THF) was added, and the reaction was warmed to rt and stirred overnight. The reaction mixture was then quenched with sat. $Na_2S_2O_3$ (aq.) and extracted three times from sat. NH_4Cl (aq.) with EtOAc. The combined organic extracts were dried over $MgSO_4$, filtered, concentrated, and purified by flash chromatography on SiO_2 to afford the desired product.

Thioethyl Glucose Dimethyl Sugar Silane



Following the general procedure **4.1**, ethyl 3,4,6-tri-*O*-benzyl-1-thio-β-D-glucopyranoside (1.237 g, 2.50 mmol), NEt_3 (0.697 mL, 5.00 mmol), and $Me_2Si(H)Cl$ (0.416 mL, 3.75 mmol) were stirred for 4 hours at 0 °C. The product (1.38 g, 2.50 mmol, 100%) was obtained as a red oil after aqueous work up. ^{1}H NMR (500MHz, $CDCl_3$) δ 7.25-7.28 (m, 13H), 7.12-7.16 (m, 2H), 4.91 (d, *J* = 11.5 Hz, 1H), 4.85 (d, *J* = 11.0 Hz, 1H), 4.82 (sept, *J* = 3.0 Hz, 1H), 4.78 (d, *J* = 10.5 Hz, 1H), 4.61 (d, *J* = 12.5 Hz, 1H), 4.553 (d, *J* = 12.5 Hz, 1H), 4.546 (d, *J* = 11.0 Hz, 1H), 4.37 (d, *J* = 9.0 Hz, 1H anomeric), 3.75 (dd, *J* = 10.5, 1.5 Hz, 1H), 3.69 (dd, *J* = 11.0, 4.5 Hz, 1H), 3.53-3.62 (m, 3H), 3.49 (ddd, *J* = 9.5, 5.0, 2.0 Hz, 1H), 2.77 (dq, *J* = 12.5, 7.5 Hz, 1H), 2.71 (dq, *J* = 12.0, 8.0 Hz, 1H), 1.32 (t, *J* = 7.5 Hz, 3H), 0.31 (d, *J* = 3.0 Hz, 3H), 0.25 (d, *J* = 2.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.5, 138.2, 138.0, 128.34, 128.30, 128.27, 127.9, 127.71, 127.69, 127.52, 127.48, 127.45, 87.2, 86.1, 79.2, 77.9, 75.9, 75.6, 75.0, 73.4, 69.1, 24.7, 15.0, -0.6, -0.8; IR (film, cm^{-1}) 2956, 2926, 2864, 2129, 1651, 1385, 1083; HRMS (ES) *m/z* calcd for $C_{31}H_{40}O_5SSi$ $[M+Na]^+$ 575.2263, found 575.2269.

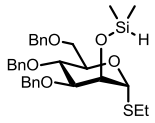
Thiophenyl Glucose Dimethyl Sugar Silane



Following the general procedure **4.1**, phenyl 3,4,6-tri-*O*-benzyl-1-thio-β-D-glucopyranoside (1.00 g, 1.8 mmol), NEt_3 (0.513 μL, 3.7 mmol), and $Me_2Si(H)Cl$ (307 μL, 2.8 mmol) were stirred for 4 hours at 0 °C. The product (1.10 g, 1.8 mmol, 99%) was

obtained as a red oil after aqueous work up. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56-7.59 (m, 2H), 7.24-7.38 (m, 16H), 7.15-7.20 (m, 2H), 4.91 (d, *J* = 11.0 Hz, 1H), 4.87 (d, *J* = 11.5 Hz, 1H), 4.85 (sept, *J* = 3.0 Hz, 1H), 4.79 (d, *J* = 10.5 Hz, 1H), 4.62 (d, *J* = 12.0 Hz, 1H), 4.61 (d, *J* = 9.5 Hz, 1H anomeric) 4.59 (d, *J* = 12.0 Hz, 1H), 4.55 (d, *J* = 12.5 Hz, 1H), 3.80 (dd, *J* = 10.5, 1.5 Hz, 1H), 3.73 (dd, *J* = 11.0, 5.0 Hz, 1H), 3.67 (t, *J* = 9.0 Hz, 1H), 3.65 (t, *J* = 9.0 Hz, 1H), 3.58 (t, *J* = 8.25 Hz, 1H), 3.54 (ddd, *J* = 9.5, 4.5, 1.5 Hz, 1H), 0.29 (d, *J* = 2.5 Hz, 3H), 0.24 (d, *J* = 3.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.4, 138.2, 138.0, 134.1, 131.5, 128.8, 128.4, 128.3, 127.9, 127.8, 127.7, 127.53, 127.49, 127.48, 127.2, 88.8, 87.2, 79.2, 77.8, 75.6, 75.1, 75.0, 73.4, 69.0, -0.6, -0.9; IR (film, cm^{-1}) 3060, 3028, 2864, 2129, 1452, 1362, 1066; HRMS (ES) *m/z* calcd for $C_{35}H_{40}O_5SSi$ $[M+Na]^+$ 623.2263, found 623.2274.

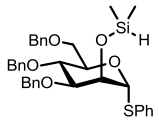
Thioethyl Mannose Dimethyl Sugar Silane



Following the general procedure **4.1**, ethyl 3,4,6-tri-*O*-benzyl-1-thio-α-D-mannopyranoside (1.74 g, 3.5 mmol), NEt_3 (0.98 mL, 7.0 mmol), and $Me_2Si(H)Cl$ (587 μL, 5.3 mmol) were stirred for 4 hours at 0 °C. The product (1.93 g, 3.5 mmol, 100%) was obtained as a red oil after aqueous work up. ^{1}H NMR (500MHz, $CDCl_3$) δ 7.25-7.39 (m, 13H), 7.15-7.18 (m, 2H), 5.27 (d, *J* = 2.0 Hz, 1H anomeric), 4.84 (d, *J* = 11.0 Hz, 1H), 4.76 (sept, *J* = 2.5 Hz, 1H), 4.73 (d, *J* = 11.5 Hz, 1H), 4.68 (d, *J* = 12.0 Hz, 1H), 4.62 (d, *J* = 11.5 Hz, 1H), 4.50 (d, *J* = 11.5 Hz, 1H), 4.49 (d, *J* = 11.0 Hz, 1H), 4.18 (t, *J* = 2.25 Hz, 1H), 4.13 (ddd, *J* = 10.0, 5.0, 2.0 Hz, 1H), 3.95 (t, *J* = 9.5 Hz, 1H), 3.76-3.83 (m, 2H), 3.70 (dd, *J* = 11.0, 2.0 Hz, 1H), 2.67 (dq, *J* = 13.0, 7.0 Hz, 1H), 2.59 (dq, *J* =

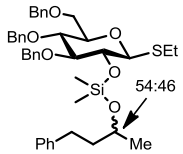
13.0, 7.5 Hz, 1H), 1.29 (t, *J* = 7.5 Hz, 3H), 0.26 (d, *J* = 2.5 Hz, 3H), 0.24 (d, *J* = 2.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.43, 138.40, 138.1, 128.28, 128.25, 128.20, 127.89, 127.65, 127.59, 127.50, 127.4, 85.0, 80.7, 74.9, 74.6, 73.2, 72.5, 72.2, 72.1, 69.1, 25.2, 15.0, -0.6, -0.7; IR (film, cm^{-1}) 3030, 2870, 2122, 1453, 1384, 1250, 1097; HRMS (ES) *m/z* calcd for $C_{31}H_{40}O_5SSi$ $[M+Na]^+$ 575.2263, found 575.2273.

Thiophenyl Mannose Dimethyl Sugar Silane



Following the general procedure **4.1**, phenyl 3,4,6-tri-*O*-benzyl-1-thio-α-D-mannopyranoside (0.765 g, 1.4 mmol), NEt_3 (0.390 mL, 2.8 mmol), and $Me_2Si(H)Cl$ (0.233 mL, 2.1 mmol) were stirred for 4 hours at 0 °C. The product (0.828 g, 1.4 mmol, 98%), was obtained as a red oil after aqueous work up. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48-7.51 (m, 2H), 7.39-7.42 (m, 2H), 7.23-7.37 (m, 14H), 7.18-7.21 (m, 2H), 5.50 (d, *J* = 1.5 Hz, 1H anomeric), 4.87 (d, *J* = 11.0 Hz, 1H), 4.78 (d, *J* = 11.5 Hz, 1H), 4.76 (sept, *J* = 3.0 Hz, 1H), 4.68 (d, *J* = 11.5 Hz, 1H), 4.67 (d, *J* = 12.0 Hz, 1H), 4.52 (d, *J* = 11.0 Hz, 1H),. 4.48 (d, *J* = 12.0 Hz, 1H), 4.34 (t, *J* = 2.0 Hz, 1H), 4.29 (ddd, *J* = 9.5, 4.5, 1.5 Hz, 1H), 4.00 (t, *J* = 9.5 Hz, 1H), 3.79-3.86 (m, 2H), 3.74 (dd, *J* = 11.0, 2.0 Hz, 1H), 0.26 (d, *J* = 3.0 Hz, 3H), 0.22 (d, *J* = 3.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.36, 138.31, 134.4, 131.3, 128.9, 128.32, 128.28, 128.18, 127.9, 127.65, 127.57, 127.4, 127.2, 88.7, 80.5, 75.0, 74.5, 73.2, 72.8, 72.5, 72.3, 69.1, -0.6, -0.7; IR (film, cm^{-1}) 3061, 3030, 2869, 2123, 1453, 1368, 1251, 1101; HRMS (ES) *m/z* calcd for $C_{35}H_{40}O_5SSi$ $[M+Na]^+$ 623.2263, found 623.2248.

Ethyl 2-*O*-dimethyl[(4-phenylbutan-2-yloxy)silane]-3,4,6-tri-*O*-benzyl-1-thio-β-D-glucopyranoside (Scheme 1.14, compound 16)

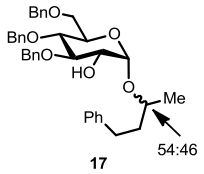


16

Following the general procedure **4.2**, silane (182 mg, 0.33 mmol), freshly distilled (bulb-to-bulb) benzylacetone (45 μL, 0.30 mmol), $Ni(COD)_2$ (8 mg, 0.03 mmol), IMes·HCl (10 mg, 0.03 mmol), KO-*t*-Bu (3 mg, 0.03 mmol) and $Ti(O\text{-}i\text{-}Pr)_4$ (98 μL, 0.33 mmol) were stirred at rt for 13 hours. The desired product was obtained as an inseparable mixture of diastereomers (54:46) (204 mg, 0.29 mmol, 97%, 54:46) as a clear oil, upon purification by flash chromatography on SiO_2 (10% EtOAc/Hex). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.24-7.40 (m, 16H), 7.14-7.19 (m, 2H), 7.09-7.13 (m, 2H), 4.98 (d, *J* = 11.5 Hz, 1H), 4.89 (d, *J* = 11.5 Hz, 0.5H), 4.88 (d, *J* = 11.0 Hz, 0.5H), 4.75 (d, *J* = 10.5 Hz, 0.5H), 4.74 (d, *J* = 11.0 Hz, 0.5H), 4.52-4.63 (m, 3H), 4.40 (d, *J* = 9.5 Hz, 0.5H anomeric), 4.39 (d, *J* = 9.5 Hz, 0.5H anomeric), 4.00-4.08 (m, 1H), 3.67-3.78 (m, 3H), 3.54-3.64 (m, 2H), 3.48-3.52 (m, 1H), 2.66-2.80 (m, 3H), 2.55-2.62 (m, 1H), 1.74-1.84 (m, 1H), 1.65-1.73 (m, 1H), 1.31 (t, *J* = 7.5 Hz, 3H), 1.21 (d, *J* = 6.0 Hz, 1.5H), 1.19 (d, *J* = 6.0 Hz, 1.5H), 0.23 (s, 1.5H), 0.22 (s, 1.5H), 0.19 (s, 1.5H), 0.18 (s, 1.5H), Note – diastereomers are reported as a 1:1 ratio of the total amount of protons; ^{13}C NMR (100 MHz, $CDCl_3$) major and minor diastereomer signals reported δ 142.53, 142.50, 138.8, 138.2, 137.9, 128.3,4, 128.32, 128.24, 128.19, 127.9, 127.7, 127.5, 127.26, 127.24, 127.21, 127.1, 125.58, 125.56, 87.1, 86.2, 79.1, 78.2, 75.18, 75.15, 74.9, 74.48, 74.43, 73.4, 69.1, 68.3, 68.1, 41.0, 32.04, 32.02, 24.7, 23.7, 23.6, 15.1, -0.8, -0.9, -1.2, -1.3; IR (film, cm^{-1}) 3029, 2965,

2923, 2865, 1496, 1453, 1366, 1256, 1134, 1086; HRMS (ES) *m/z* calcd for $C_{41}H_{52}0_6SSi$ $[M+Na]^+$ 723.3152, found 723.3162.

[4-phenylbutan-2]-3,4,6-tri-*O*-benzyl-α-D-glucopyranoside (Scheme 1.14, compound 17)

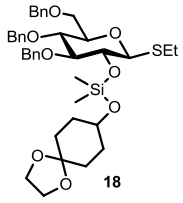


17

Following the general procedure **4.4**, compound **16** (112 mg, 0.16 mmol), NIS (47 mg, 0.21 mmol), TMSOTf (35 μL, 0.19 mmol), 2,6-DTBMP (66 mg, 0.32 mmol) were stirred for 10 min at -40 °C, and 30 min at 0 °C, then excess *n*-Bu_4NF (0.96 mmol, 0.96 mL) was added as a 1M solution in THF and stirred overnight to afford the desired products as a 46:54 mixture of diastereomers as clear oils, which were separated and characterized independently (combined 90 mg, 0.15 mmol, 97%, 54:46) upon purification by flash chromatography on SiO_2 (20% EtOAc/Hex). **Major diastereomer** ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39-7.42 (m, 2H), 7.25-7.36 (m, 13H), 7.13-7.21 (m, 5H), 5.02 (d, *J* = 3.0 Hz, 1H anomeric), 4.97 (d, *J* = 11.0 Hz, 1H), 4.85 (d, *J* = 10.0 Hz, 1H), 4.83 (d, *J* = 10.5 Hz, 1H), 4.62 (d, *J* = 12.5 Hz, 1H), 4.49 (d, *J* = 10.5 Hz, 1H), 4.47 (d, *J* = 12.0 Hz, 1H), 3.83-3.92 (m, 2H), 3.58-3.76 (m, 5H), 2.70-2.78 (m, 1H), 2.60-2.68 (m, 1H), 1.92-2.07 (m, 2H), 1.77-1.85 (m, 1H), 1.23 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.8, 138.8, 138.2, 137.9, 128.35, 128.34, 128.32, 128.27, 127.9, 127.8, 127.66, 127.63, 127.56, 125.8, 96.0, 83.6, 77.3, 75.3, 75.0, 73.5, 72.8, 72.7, 70.8, 68.4, 38.6, 32.0, 19.1; IR (film, cm^{-1}) 3461, 3061, 3029, 2924, 1495, 1453, 1381, 1129, 1065, 1034 ; HRMS (ES) *m/z* calcd for $C_{37}H_{42}O_6$ $[M+Na]^+$ 605.2879, found 605.2877. **Minor diastereomer** ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39-7.42 (m, 2H), 7.26-7.36 (m, 13H), 7.18-7.22 (m, 3H),

7.14-7.17 (m, 2H), 4.99 (d, *J* = 3.5 Hz, 1H anomeric), 4.96 (d, *J* = 11.5 Hz, 1H), 4.84 (d, *J* = 10.5 Hz, 1H), 4.83 (d, *J* = 10.5 Hz, 1H), 4.65 (d, *J* = 12.5 Hz, 1H), 4.50 (d, *J* = 12 Hz, 1H), 4.49 (d, *J* = 10.5 Hz, 1H), 3.89 (d, *J* = 9.0 Hz, 1H), 3.62-3.83 (m, 6H), 2.64-2.75 (m, 2H), 1.90-1.98 (m, 2H), 1.74-1.82 (m, 1H), 1.28 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.7, 138.8, 138.1, 137.9, 128.42, 128.35, 128.32, 128.27, 127.93, 127.87, 127.83, 127.70, 127.63, 127.59, 125.9, 98.5, 83.5, 77.4, 75.28, 75.26, 75.0, 73.5, 73.2, 70.6, 68.5, 38.0, 31.5, 21.3; IR (film, cm^{-1}) 3559, 3471, 3029, 2922, 2864, 1454, 1363, 1129, 1066, 1036; HRMS (ES) *m/z* calcd for $C_{37}H_{42}O_6$ $[M+Na]^+$ 605.2879, found 605.2876.

Ethyl 2-*O*-[(1,4-dioxaspiro[4.5]decan-8-yloxy)dimethylsilane]-3,4,6-tri-*O*-benzyl-1-thio-β-D-glucopyranoside (Scheme 1.15, compound 18)

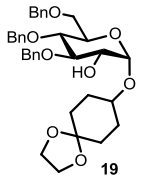


18

Following the general procedure **4.2**, silane (182 mg, 0.33 mmol), 1,4-cyclohexanedione monoethylene acetal (47 mg, 0.30 mmol), $Ni(COD)_2$ (8 mg, 0.03 mmol), IMes·HCl (10 mg, 0.03 mmol), KO-*t*-Bu (3.4 mg, 0.03 mmol), and Ti(O-*i*-Pr)$_4$ (98 μL, 0.33 mmol) were stirred for 3 hr at rt. The product (197 mg, 0.28 mmol, 93%) was obtained as a viscous yellow oil after purification by flash chromatography on SiO_2 (10 to 20% EtOAc/Hex). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.24-7.38 (m, 13H), 7.08-7.12 (m, 2H), 4.93 (d, *J* = 11.5 Hz, 1H), 4.89 (d, *J* = 11.5 Hz, 1H), 4.73 (d, *J* = 11.0 Hz, 1H), 4.61 (d, *J* = 12.0 Hz, 1H), 4.56 (d, *J* = 12.0 Hz, 1H) 4.53 (d, *J* = 11.0 Hz, 1H) 4.40 (d, *J* = 9.5 Hz, 1H anomeric), 4.01 (tt, *J* = 7.5, 3.5 Hz, 1H), 3.90-3.96 (m, 4H), 3.75 (dd, *J* =

11.0, 2.0 Hz, 1H), 3.66-3.73 (m, 2H), 3.60 (t, *J* = 9.25, 1H), 3.55 (t, *J* = 8.75 Hz, 1H), 3.49 (ddd, *J* = 9.5, 5.0, 2.0 Hz, 1H), 2.77 (dq, *J* = 12.75, 7.5 Hz, 1H), 2.71 (dq, *J* = 13.5, 7.5 Hz, 1H), 1.64-1.85 (m, 6H), 1.46-1.54 (m, 2H), 1.31 (t, *J* = 7.5 Hz, 3H), 0.21 (s, 3H), 0.16 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.7, 138.2, 138.0, 128.32, 128.30, 128.2, 127.9, 127.72, 127.69, 127.5, 127.2, 127.0, 108.4, 87.0, 86.2, 79.1, 78.3, 75.1, 74.9, 74.4. 73.4, 69.1, 68.3, 64.17, 64.15, 32.03, 32.00, 31.34, 31.32, 24.6, 15.0, -0.9, -1.3; IR (film, cm^{-1}) 3030, 2929, 1497, 1453, 1363, 1255, 1094; HRMS (ES) *m/z* calcd for $C_{39}H_{52}O_8SSi$ $[M+Na]^+$ 731.3050, found 731.3062.

8-(1,4-dioxaspiro[4.5]decane)-3,4,6-tri-*O*-benzyl-α-D-glucopyranoside (Scheme 1.15, compound 19)

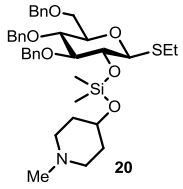


19

Following the general procedure **4.4**, compound **18** (425 mg, 0.60 mmol), NIS (175 mg, 0.78 mmol), 2,6-DTBMP (185 mg, 0.90 mmol), TMSOTf (142 μL, 0.78 mmol) were stirred for 10 min at -40 °C, then warmed to 0 °C and allowed to stir for 1 hour. *n*-Bu_4NF (3.0 mL, 3.0 mmol) was added as a 1M solution in THF, warmed to rt and stirred overnight. The product (289 mg, 0.49 mmol, 82%) was obtained as a colorless oil after flash chromatography on SiO_2 (33% EtOAc/Hex w/ 5% NEt_3). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22-7.38 (m, 13 H), 7.10-7.14 (m, 2H), 4.98 (d, *J* = 3.2 Hz, 1H anomeric), 4.94 (d, *J* = 11.2 Hz, 1H), 4.80 (d, J = 10.8 Hz, 2H), 4.61 (d, *J* = 12.0 Hz, 1H) 4.47 (d, *J* = 12.0 Hz, 1H) 4.45 (d, *J* = 10.8 Hz, 1H), 3.89-3.93 (m, 4H), 3.84 (ddd, *J* = 10.0, 3.2, 2.0 Hz, 1H), 3.57-3.66 (m, 6H), 1.96 (d, *J* = 10.0 Hz, 1H) 1.66-1.91 (m, 6H), 1.50-1.59 (m,

2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.7, 138.1, 137.9, 128.33, 128.31, 127.9, 127.84, 127.80, 127.7, 127.63, 127.56, 108.0, 97.0, 83.6, 75.3, 75.0, 73.5, 73.4, 72.9, 70.6, 68.4, 64.3, 64.2, 31.6, 31.3, 29.9, 28.1; IR (film, cm^{-1}) 3476, 3029, 2937, 1496, 1453, 1365, 1134, 1068, 1028; HRMS (ES) *m/z* calcd for $C_{35}H_{42}O_8$ $[M+Na]^+$ 613.2777, found 613.2786.

Ethyl 2-*O*-[4-(dimethylsilyloxy)-1-methylpiperidine]-3,4,6-tri-*O*-benzyl-1-thio-β-D-glucopyranoside (Scheme 1.15, compound 20)

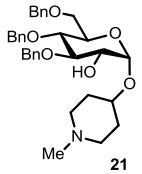


20

Following the general procedure **4.2**, silane (182 mg, 0.33 mmol), N-methyl-4-piperidone (37 μL, 0.30 mmol), Ti(O-*i*-Pr)$_4$ (98 μL, 0.33 mmol), Ni(COD)$_2$ (8 mg, 0.03 mmol), IMes·HCl (10 mg, 0.03 mmol), and KO-*t*-Bu (3 mg, 0.03 mmol) were stirred for 6 hours at rt. The product (200 mg, 0.30 mmol, 100%) was obtained after flash chromatography on SiO_2 (15% MeOH/EtOAc w/ ~1% NEt_3) as a viscous light orange oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.24-7.38 (m, 13H), 7.08-7.12 (m, 2H), 4.95 (d, *J* = 11.0 Hz, 1H), 4.89 (d, *J* = 11.5 Hz, 1H), 4.73 (d, *J* = 10.5 Hz, 1H), 4.61 (d, *J* = 12.0 Hz, 1H), 4.56 (d, *J* = 12.0 Hz, 1H), 4.53 (d, *J* = 10.5 Hz, 1H), 4.39 (d, *J* = 9.5 Hz, 1H anomeric), 3.88 (br s, 1H), 3.75 (dd, *J* = 11.0, 1.5 Hz, 1H), 3.67-3.72 (m, 2H), 3.60 (t, *J* = 9.25 Hz, 1H), 3.55 (t, *J* = 8.75 Hz, 1H), 3.49 (ddd, *J* = 10.0, 5.0, 1.5 Hz, 1H), 2.77 (dq, *J* = 12.5, 7.5 Hz, 1H), 2.72 (dq, *J* = 12.5, 7.5 Hz, 1H), 2.65 (br s, 2H), 2.23 (s, 3H), 1.98-2.10 (m, 2H), 1.74-1.86 (m, 2H), 1.58 (m, 2H), 1.32 (t, *J* = 7.25 Hz, 3H), 0.22 (s, 3H), 0.17 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.7, 138.1, 137.9, 128.33, 128.31, 128.2, 127.9,

127.7, 127.5, 127.3, 127.1, 87.0, 86.1, 79.1, 78.2, 75.1, 74.9, 74.5, 73.4, 69.1, 52.9, 45.9, 34.2, 24.6, 15.1, -0.9, -1.3; IR (film, cm^{-1}) 3030, 2927, 2864, 2780, 1452, 1362, 1255, 1148, 1087; HRMS (ES) *m/z* calcd for $C_{37}H_{51}NO_6SSi$ $[M+H]^+$ 666.3285, found 666.3284.

4-(methylpiperidin-1)-3,4,6-tri-*O*-benzyl-α-D-glucopyranoside (Scheme 1.15, compound 21)

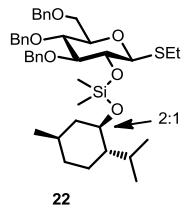


21

Following the general procedure **4.4**, compound **20** (125 mg, 0.19 mmol), NIS (55 mg, 0.24 mmol), 2,6-DTBMP (77 mg, 0.38 mmol), TMSOTf (41 μL, 0.23 mmol) were stirred at -40 °C for 10 min, then warmed to 0 °C and stirred for 1 hour, then excess *n*-Bu_4NF was added (1.14 mL, 1.14 mmol) as a 1M solution in THF, warmed to rt and allowed to stir overnight. The product (73 mg, 0.13 mmol, 70%) was obtained after purification by flash chromatography on SiO_2 (7:1:2 to 3:1:1 EtOAc:MeOH:MeCN w/ ~ 1% NEt_3). ^1H NMR (500 MHz, $CDCl_3$) δ 7.39-7.42 (m, 2H), 7.26-7.37 (m, 11H), 7.13-7.16 (m, 2H), 5.03 (d, *J* = 3.5 Hz, 1H anomeric), 4.99 (d, *J* = 11.0 Hz, 1H), 4.85 (d, *J* = 11.0 Hz, 1H), 4.84 (d, *J* = 10.5 Hz, 1H), 4.64 (d, *J* = 12.0 Hz, 1H), 4.51 (d, *J* = 11.5 Hz, 1H), 4.49 (d, *J* = 10.5 Hz, 1H), 3.87 (ddd, *J* = 10.0, 3.75, 1.75 Hz, 1H), 3.61-3.79 (m, 6H), 2.68 (br s, 2H), 2.28 (s, 3H), 2.20 (br s, OH), 2.16 (br s, 2H), 1.92 (br s, 1H), 1.62-1.77 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.7, 138.0, 137.9, 128.40, 128.37, 128.36, 128.0, 127.9, 127.84, 127.77, 127.69, 127.6, 97.1, 83.6, 77.3, 75.3, 75.1, 73.5, 72.9, 70.7, 68.5, 53.1, 46.1, 32.5, 30.8; IR (film, cm^{-1}) 3453, 3030, 2920, 2850, 2784,

1452, 1384, 1155, 1068, 1043; HRMS (ES) *m/z* calcd for $C_{33}H_{41}NO_6$ $[M+H]^+$ 548.3012, found 548.3019.

Ethyl 2-*O*-[((1R,2S,5R)-2-isopropyl-5-methylcyclohexyloxy)dimethylsilane]-3,4,6-tri-*O*-benzyl-1-thio-β-D-glucopyranoside (Scheme 1.16, compound 22)

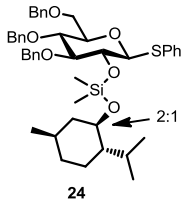


22

Following the general procedure **4.3**, silane (243 mg, 0.44 mmol), (-)-menthone (62 mg, 0.40 mmol), CuCl (2 mg, 0.02 mmol), IMes·HCl (7 mg, 0.02 mmol) and NaO-*t*-Bu (3 mg, 0.04 mmol) were stirred for 8 hours at rt to give the product as an inseparable 2:1 mixture of diastereomers. The product (192 mg, 0.27 mmol, 68%, 2:1) was obtained as a clear oil upon purification by flash chromatography on SiO_2 (10% EtOAc/Hex). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.23-7.41 (m, 13 H), 7.07-7.14 (m, 2H), 5.01 (d, *J* = 11.0 Hz, 0.67H), 4.97 (d, *J* = 11.5 Hz, 0.33H) 4.88 (d, *J* = 12.0 Hz, 0.33H), 4.86 (d, *J* = 11.0 Hz, 0.67H), 4.75 (d, *J* = 11.0 Hz, 0.67H), 4.72 (d, *J* = 11.0 Hz, 0.33H), 4.50-4.63 (m, 3 H), 4.39 (d, *J* = 9.5 Hz, 0.67H anomeric), 4.38 (d, *J* = 9.5 Hz, 0.33H anomeric), 4.26 (br s, 0.33H), 3.66-3.78 (m, 3H), 3.53-3.62 (m, 2.67H), 3.48-3.53 (m, 1H), 2.68-2.81 (m, 2H), 2.20 (septd, *J* = 7.0, 2.5 Hz, 0.67H), 1.99-2.04 (m, 0.67H), 1.78-1.88 (m, 0.67H), 1.48-1.65 (m, 2.33H), 1.26-1.40 (m, 1H), 1.32 (t, *J* = 7.5 Hz, $3H_{major}$), 1.31 (t, *J* = 7.5 Hz, $3H_{minor}$), 0.74-1.15 (m, 10.67H), 0.73 (d, *J* = 7.0 Hz, $3H_{major}$), 0.23 (s, $3H_{major}$), 0.19 (s, $3H_{minor}$), 0.15 (s, $3H_{major + minor}$), Note – diastereomers are reported as a 2:1 ratio of the total amount of protons, the stereochemistry of the major diastereomer and the dr of the reduction was determined on a crude reaction mixture of the silyl-linked compound after

complete desilylation by *n*-Bu_4NF and comparison to known compounds;[4,5] ^{13}C NMR (100 MHz, $CDCl_3$) major and minor diastereomer signals reported δ 138.9, 138.8, 138.24, 138.22, 138.0, 128.34, 128.31, 128.16, 128.13, 127.94, 127.89, 127.7, 127.5, 127.3, 127.2, 127.11, 127.96, 87.2, 87.0, 86.4, 86.3, 79.1, 78.3, 78.2, 75.2, 75.1, 74.9, 74.5, 74.3, 73.4, 72.6, 69.3, 69.2, 68.8, 49.7, 48.8, 45.4, 43.1, 42.6, 35.3, 34.5, 31.6, 28.7, 25.5, 25.2, 24.8, 24.6, 24.0, 22.8, 22.4, 22.2, 21.2, 21.1, 20.9, 15.9, 15.0, -0.4, -1.0, -1.5; IR (film, cm^{-1}) 3029, 2953, 2921, 2866, 1453, 1365, 1254, 1067; HRMS (ES) *m/z* calcd for $C_{41}H_{58}O_6SSi$ $[M+Na]^+$ 729.3621, found 729.3639.

Phenyl 2-*O*-[((1R,2S,5R)-2-isopropyl-5-methylcyclohexyloxy)dimethylsilane]-3,4,6-tri-*O*-benzyl-1-thio-β-D-glucopyranoside (Scheme 1.16, compound 24)

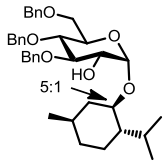


24

Following the general procedure **4.3**, silane (198 mg, 0.33 mmol), (-)-menthone (46 mg, 0.30 mmol), CuCl (2 mg, 0.015 mmol), IMes·HCl (5 mg, 0.015 mmol), and NaO-*t*-Bu (3 mg, 0.03 mmol) were stirred for 5 hours at rt to give the desired product as an inseparable 2:1 mixture of diastereomers. The product (144 mg, 0.19 mmol, 64%, 2:1) was obtained as a clear viscous oil upon purification by flash chromatography on SiO_2 (5% EtOAc/Hex). ^1H NMR (500 MHz, $CDCl_3$) δ 7.52-7.57 (m, 2H), 7.21-7.41 (m, 16H), 7.10-7.17 (m, 2H), 5.02 (d, *J* = 11.0 Hz, 0.67H), 4.98 (d, *J* = 11.5 Hz, 0.33H), 4.89 (d, *J* = 11.5 Hz, 0.33H), 4.86 (d, *J* = 10.5 Hz, 0.67H) , 4.78 (d, *J* = 11.0 Hz, 0.67H) 4.73 (d, *J* = 10.5 Hz, 0.33H), 4.52-4.66 (m, 4H), 4.27 (br s, 0.33H), 3.76-3.86 (m, 2H), 3.69-3.74 (m, 1H), 3.51-3.66 (m, 3.67H), 2.21 (septd, *J* = 6.75, 2.25 Hz, 0.67H), 2.01 (d, *J* =

12.0 Hz, 0.67H), 1.80-1.89 (m, 0.67H), 1.48-1.64 (m, 2.33H), 1.26-1.41 (m, 1.33H), 1.09-1.18 (m, 0.67H), 0.75-1.07 (m, 5.67H), 0.87 (d, J = 7.0 Hz, $3H_{minor}$), 0.85 (d, J = 7.0Hz, $3H_{major}$), 0.84 (d, J = 6.5 Hz, $3H_{minor}$), 0.74 (d, J = 7.0 Hz, $3H_{major}$), 0.25 (s, $3H_{major}$), 0.20 (s, $3H_{minor}$), 0.16 (s, $3H_{minor}$), 0.13 (s, $3H_{major}$), Note – diastereomers are reported as a 2:1 ratio of the total amount of protons, the stereochemistry of the major diastereomer and the dr of the reduction was determined on a crude reaction mixture of the silyl-linked compound after complete desilylation by *n*-Bu_4NF and comparison to known compounds; ^{13}C NMR (100 MHz, $CDCl_3$) δ major and minor diastereomer signals reported 138.8, 138.7, 138.26, 138.24, 138.0, 137.0, 134.5, 131.1, 131.0, 128.8, 128.37, 128.33, 128.30, 128.18, 128.15, 127.90, 127.8, 127.73, 127.69, 127.67, 127.52, 127.51, 127.3, 127.2, 126.97, 126.96, 126.91, 89.1, 88.8, 87.2, 87.0, 79.03, 78.98, 78.16, 78.12, 75.2, 75.1, 74.9, 73.9, 73.8, 73.4, 72.7, 69.14, 69.07, 68.9, 49.7, 48.8, 45.4, 43.2, 35.2, 34.5, 31.6, 28.7, 25.6, 25.2, 24.0, 22.8, 22.3, 22.2, 21.2, 21.1, 20.9, 15.9, -0.4, -1.1, -1.2, -1.4; IR (film, cm^{-1}) 3030, 2953, 2919, 2867, 1454, 1383, 1256, 1067; HRMS (ES) *m/z* calcd for $C_{45}H_{58}O_6SSi$ $[M+Na]^+$ 777.3621, found 777.3635.

(1R,2S,4S)-2-isopropyl-4-methylcyclohexan-3,4,6-tri-*O*-benzyl-α-D-glucopyranoside (Scheme 1.16, compound 23)

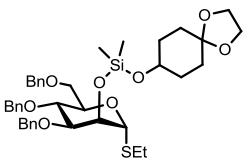


23

Following the general procedure **4.4**, compound **24** (87 mg, 0.12 mmol), NIS (34 mg, 0.15 mmol), 2,6-DTBMP (47 mg, 0.24 mmol) and TMSOTf (25 μL, 0.14 mmol) were stirred for 10 min at -40 °C, warmed to 0 °C and stirred for 45 min, then excess *n*-

Bu_4NF was added (0.72 mL, 0.72 mmol) as a 1M solution in THF, warmed to rt, and stirred overnight. The product (49 mg, 0.08 mmol, 72%, 5:1) was obtained as an inseparable 5:1 mixture of diastereomers as a colorless oil after purification by flash chromatography on SiO_2 (10 to 20% EtOAc/Hex). ^1H NMR (500 MHz, $CDCl_3$) **Major diastereomer** δ 7.26-7.43 (m, 13H), 7.14-7.18 (m, 2H), 4.99 (d, *J* = 4.0 Hz, 1H anomeric), 4.98 (d, *J* = 12.0 Hz, 1H), 4.85 (d, *J* = 11.5 Hz, 1H), 4.84 (d, *J* =10.5 Hz, 1H), 4.66 (d, *J* = 12.0 Hz, 1H), 4.51 (d, *J* = 11.0 Hz, 1H), 4.48 (d, *J* = 10.5 Hz, 1H), 3.95 (d, *J* = 10.0 Hz, 1H), 3.60-3.84 (m, 5H), 3.41 (td, *J* = 10.5, 4.0 Hz, 1H), 2.21 (d, *J* =12.5 Hz, 1H), 2.15 (septd, *J* =7.0, 2.0 Hz, 1H), 1.97 (d, *J* = 9.0 Hz, 1H), 1.56-1.80 (m, 2H), 1.24-1.46 (m, 2H), 0.78-1.05 (m, 3H), 0.93 (d, *J* = 7.0 Hz, 3H), 0.87 (d, *J* = 7.0 Hz, 3H), 0.78 (d, *J* = 7.0 Hz, 3H), diagnostic peaks of the minor diastereomer at 5.03 (d, *J* = 3.5 Hz, 0.2H anomeric), and 4.11 (br s, 0.2H) (aglycone carbinol); ^{13}C NMR (100 MHz, $CDCl_3$) major and minor diastereomer signals reported δ 138.8, 138.2, 138.0, 128.36, 128.33, 128.11, 127.96, 127.92, 127.85, 127.7, 127.64, 127.60, 100.1, 95.4, 83.5, 81.1, 77.5, 75.2, 75.0, 73.6, 73.5, 73.0, 72.6, 70.6, 68.6, 48.7, 48.2, 42.9, 37.3, 34.9, 34.2, 31.6, 28.4, 26.4, 25.5, 22.8, 22.2, 21.2, 21.1, 20.9, 15.7; IR (film, cm^{-1}) 3564, 3030, 2922, 2867, 1453, 1384, 1132, 1067, 1027; HRMS (ES) *m/z* calcd for $C_{37}H_{48}O_6$ $[M+Na]^+$ 611.3349, found 611.3355.

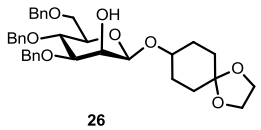
Ethyl 2-*O*-[(1,4-dioxaspiro[4.5]decan-8-yloxy)dimethylsilane]-3,4,6-tri-*O*-benzyl-1-thio-α-D-mannopyranoside (Scheme 1.17, compound 25)



25

Following the general procedure **4.2**, silane (182 mg, 0.33 mmol), 1,4-cyclohexanedione monoethylene acetal (47 mg, 0.30 mmol), Ti(O-*i*-Pr)$_4$ (98 μL, 0.33 mmol), Ni(COD)$_2$ (8 mg, 0.03 mmol), IMes·HCl (10 mg, 0.03 mmol), and KO-*t*-Bu (3 mg, 0.03 mmol) were stirred at room temperature for 4 hours. The product (183 mg, 0.26 mmol, 86%) was obtained as a colorless oil after purification by flash chromatography on SiO_2 (10 to 20% EtOAc/Hex). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.24-7.37 (m, 13H), 7.15-7.18 (m, 2H), 5.28 (d, *J* = 1.5 Hz, 1H anomeric), 4.83 (d, *J* = 10.5 Hz, 1H), 4.71 (d, *J* = 11.5 Hz, 1H), 4.68 (d, *J* = 12.0 Hz, 1H), 4.64 (d, *J* = 11.5 Hz, 1H), 4.52 (d, *J* = 12.0 Hz, 1H), 4.50 (d, *J* = 10.5 Hz, 1H), 4.28 (t, *J* = 2.25 Hz, 1H), 4.13 (ddd, *J* = 10.0, 5.0, 1.5 Hz, 1H), 3.90-4.00 (m, 5H), 3.82 (dd, *J* = 11.0, 5.0 Hz, 1H), 3.77 (dd, *J* = 9.0, 2.5 Hz, 1H), 3.71 (dd, *J* = 10.5, 1.5 Hz, 1H), 2.66 (dq, *J* = 13.0, 7.5 Hz, 1H), 2.58 (dq, *J* = 13.0, 7.5 Hz, 1H), 1.64-1.86 (m, 6H), 1.46-1.55 (m, 2H), 0.17 (s, 3H), 0.15 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.49, 138.47, 138.3, 128.27, 128.25, 128.21, 127.9, 127.8, 127.6, 127.52, 127.49, 127.36, 108.4, 85.4, 80.3, 74.9, 74.8, 73.2, 72.2, 71.0, 69.2, 68.1, 64.20, 64.17, 32.05, 32.00, 31.2, 25.2, 15.0, -1.5, -1.7; IR (film, cm^{-1}) 3030, 2938, 2874, 1452, 1378, 1256, 1099, 1036; HRMS (ES) *m/z* calcd for $C_{39}H_{52}O_8SSi$ $[M+Na]^+$ 731.3050, found 731.3055.

8-(1,4-dioxaspiro[4.5]decane)-3,4,6-tri-*O*-benzyl-β-D-mannopyranoside (Scheme 1.17, compound 26)

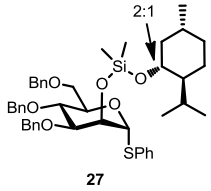


26

Following the general procedure **4.4**, compound **25** (144 mg, 0.20 mmol) NIS (59 mg, 0.26 mmol), 2,6-DTBMP (83 mg, 0.41 mmol) and TMSOTf (44 μL, 0.24 mmol)

were stirred at -40 °C for 15 minutes, warmed to 0 °C and stirred for 45 min, then *n*-Bu_4NF (1.2 mL, 1.2 mmol) was added as a 1M solution in THF and the reaction was warmed to rt and stirred overnight. The product (67 mg, 0.11 mmol, 57%) was obtained as a colorless oil upon purification by flash chromatography on SiO_2 (40 to 50% EtOAc/Hex). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38-7.41 (m, 2H), 7.26-7.36 (m, 11H), 7.21-7.24 (m, 2H), 4.91 (d, *J* = 11.0 Hz, 1H), 4.79 (d, *J* = 12.0 Hz, 1H), 4.68 (d, *J* = 12.0 Hz, 1H), 4.56 (d, *J* = 12.0 Hz, 1H), 4.55 (d, *J* = 11.0 Hz, 1H), 4.52 (s, 1H anomeric), 4.07 (br s, 1H), 3.89-3.98 (m, 5H), 3.86 (t, *J* = 9.5 Hz, 1H), 3.78 (dd, *J* = 10.5, 1.5 Hz, 1H), 3.69 (dd, *J* = 10.5, 5.5 Hz, 1H), 3.58 (dd, *J* = 9.0, 3.0 Hz, 1H), 3.43 (ddd, *J* = 9.5, 5.5, 1.5 Hz, 1H), 2.45 (d, *J* = 1.5 Hz, 1H), 1.70-1.98 (m, 6H), 1.52-1.61 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.3, 138.2, 137.9, 128.5, 128.35, 128.31, 128.1, 127.9, 127.8, 127.7, 127.5, 108.2, 97.4, 81.6, 75.23, 75.16, 74.3, 73.7, 73.4, 71.3, 69.3, 68.8, 64.3, 31.4, 31.3, 29.9, 27.9; IR (film, cm^{-1}) 3476, 3029, 2940, 2872, 1452, 1372, 1100; HRMS (ES) *m/z* calcd for $C_{35}H_{42}O_8$ $[M+Na]^+$ 613.2777, found 613.2781.

Phenyl 2-*O*-[((1R,2S,5R)-2-isopropyl-5-methylcyclohexyloxy)dimethylsilane]-3,4,6-tri-*O*-benzyl-1-thio-α-D-mannopyranoside (Scheme 1.17, compound 27)

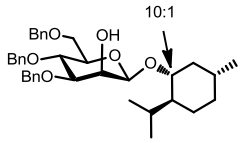


27

Following the general procedure **4.3**, silane (198 mg, 0.33 mmol), (-)-menthone (46 mg, 0.30 mmol), CuCl (1.5 mg, 0.015 mmol), IMes·HCl (5 mg, 0.015 mmol), and NaO-*t*-Bu (3 mg, 0.03 mmol) were stirred for 4 hours at rt to give the desired product as an inseparable 2:1 mixture of diastereomers. The product (171 mg, 0.23 mmol, 75%,

2:1) was isolated as a colorless oil upon purification by flash chromatography on SiO_2 (5% EtOAc/Hex). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47-7.51 (m, 2H), 7.38-7.41 (m, 2H), 7.20-7.36 (m, 16H), 5.54 (d, *J* = 2.0 Hz, 0.33H anomeric), 5.53 (d, *J* = 2.0 Hz, 0.67H anomeric), 4.88 (d, *J* = 11.0 Hz, 0.33H), 4.87 (d, *J* = 10.5 Hz, 0.67H), 4.77 (d, *J* = 11.5 Hz, 1H), 4.65-4.70 (m, 2H), 4.46-4.56 (m, 3H), 4.28-4.34 (m, 1H), 4.19 (br s, 0.33H), 3.97-4.02 (m, 1H), 3.74-3.88 (m, 3H), 3.53 (td, *J* = 10.5, 4.5 Hz, 0.67H), 2.14 (septd, *J* = 7.0, 3.0 Hz, 0.67H), 1.92-1.97 (m, 0.67H), 1.66-1.77 (m, 0.67H), 1.43-1.63 (m, 1.67H), 1.20-1.35 (m, 1.67H), 1.11 (ddt, *J* = 12.25, 9.75, 2.75 Hz, 0.67H), 0.72-1.04 (m, 4H), 0.83 (d, *J* = 7.0 Hz, $3H_{major}$), 0.82 (d, *J* = 6.5 Hz, $3H_{major}$), 0.80 (d, *J* = 7.0 Hz, $3H_{minor}$), 0.78 (d, *J* = 6.5 Hz, $3H_{minor}$), 0.71 (d, *J* = 7.0 Hz, $3H_{major}$), 0.17 (s, $3H_{major}$), 0.16 (s, $3H_{minor}$), 0.15 (s, $3H_{major + minor}$), Note – diastereomers are reported as a 2:1 ratio of the total amount of protons, the stereochemistry of the major diastereomer and the dr of the reduction was determined on a crude reaction mixture of the silyl-linked compound after complete desilylation by *n*-Bu_4NF and comparison to known compounds; ^{13}C NMR (100 MHz, $CDCl_3$) major and minor diastereomer signals reported δ 138.53, 138.47, 138.43, 138.3, 138.2, 134.74, 134.66, 131.7, 131.4, 131.3, 128.9, 128.8, 128.3, 128.2, 127.92, 127.85, 127.77, 127.66, 127.63, 127.58, 127.35, 127.12, 127.09, 89.3, 89.0, 80.3, 75.03, 74.85, 73.16, 73.13, 72.99, 72.86, 72.6, 72.2, 72.1, 70.7, 70.6, 69.28, 69.24, 68.8, 49.8, 48.6, 45.3, 43.1, 35.1, 34.4, 31.6, 28.8, 25.7, 25.5, 25.3, 24.0, 22.8, 22.4, 22.2, 21.1, 21.0, 20.8, 15.8, -1.20, -1.22, -1.36, -1.40; IR (film, cm^{-1}) 3029, 2952, 2915, 2866, 1453, 1255, 1099; HRMS (ES) *m/z* calcd for $C_{45}H_{58}O_8SSi$ $[M+Na]^+$ 777.3621, found 777.3640.

(1R,2S,4S)-2-isopropyl-4-methylcyclohexan-3,4,6-tri-*O*-benzyl-β-D-mannopyranoside (Scheme 1.17, compound 28)

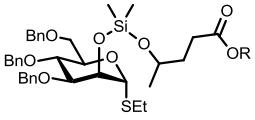


28

Following the general procedure **4.4**, compound **27** (68 mg, 0.09 mmol), NIS (26 mg, 0.12 mmol), 2,6-DTBMP (37 mg, 0.18 mmol), and TMSOTf (20 μL, 0.11 mmol) were stirred at -40 °C for 10 min, then warmed to 0 °C and stirred for 1.5 hours. *n*-Bu_4NF (0.63 mL, 0.63 mmol) was added as a 1M solution in THF and stirred at rt overnight to give the products as a 10:1 mixture of diastereomers. The products (combined 39 mg, 0.07 mmol, 74%, 10:1) were isolated as a white solid and clear oil respectively, and characterized independently after purification by flash chromatography on SiO_2 (10 to 20% EtOAc/Hex). Data for the major diastereomer matches that previously reported. **Major diastereomer** ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38-7.41 (m, 2H), 7.24-7.36 (m, 13H), 4.91 (d, *J* = 11.0 Hz, 1H), 4.80 (d, *J* = 12.0 Hz, 1H), 4.69 (d, *J* = 12.0 Hz, 1H), 4.62 (d, *J* = 12.5 Hz, 1H), 4.60 (d, *J* = 12.0 Hz, 1H), 4.55 (d, *J* = 12.0 Hz, 1H), 4.54 (s, 1H anomeric), 4.04 (br s, 1H), 3.87 (t, *J* = 9.5 Hz, 1H), 3.75 (dd, *J* = 10.5, 1.5 Hz, 1H), 3.71 (dd, *J* = 10.5, 5.0 Hz, 1H), 3.55-3.63 (m, 2H), 3.41 (ddd, *J* = 10.0, 5.0, 2.0 Hz, 1H), 2.38 (s, 1H), 2.29 (septd, *J* = 7.0, 2.0 Hz, 1H), 1.99 (d, *J* = 12.0 Hz, 1H), 1.62-1.70 (m, 2H), 1.24-1.41 (m, 2H), 0.80-1.05 (m, 3H), 0.92 (d, *J* = 6.5 Hz, 3H), 0.91 (d, *J* = 7.0 Hz, 3H), 0.83 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.4, 138.3, 138.0, 128.44, 128.35, 128.29, 128.16, 127.8, 127.75, 127.71, 127.68, 127.5, 96.1, 81.9, 76.5, 75.3, 75.2, 74.4, 73.6, 71.2, 69.7, 69.2, 47.7, 40.4, 34.3, 31.3, 25.3, 23.1, 22.3, 21.0, 15.8; IR (film, cm^{-1}) 3472, 3028, 2950, 2920, 2865, 1452, 1383, 1102; HRMS (ES) *m/z* calcd for $C_{37}H_{48}O_6$ $[M+Na]^+$ 611.3349, found 611.3337. **Minor diastereomer** ^{1}H

NMR (500 MHz, $CDCl_3$) δ 7.38-7.42 (m, 2H), 7.23-7.36 (m, 13H), 4.91 (d, *J* =11 Hz, 1H), 4.81 (d, *J* = 12 Hz, 1H), 4.69 (d, *J* = 11.5 Hz, 1H), 4.64 (d, *J* = 12 Hz, 1H), 4.58 (d, *J* = 11 Hz, 1H), 4.57 (d, *J* = 12 Hz, 1H), 4.44 (s, 1H anomeric), 4.07 (d, *J* = 2.5 Hz, 1H), 4.02 (br s, 1H), 3.69 (t, *J* = 9.0 Hz, 1H), 3.74 (dd, *J* = 11, 2.0 Hz, 1H), 3.70 (dd, *J* = 11, 5.5 Hz, 1H), 3.56 (dd, *J* = 9.5, 3.0 Hz, 1H), 3.41 (ddd, *J* = 9.5, 5.0, 2.0 Hz, 1H), 2.39 (br s, 1H), 2.16-2.22 (m, 1H), 1.81-1.91 (m, 1H), 1.69-1.86 (m, 1H), 1.60-1.68 (m, 1H), 1.20-1.44 (m, 2H), 0.80-1.00 (m, 3H), 0.90 (d, *J* = 7.0 Hz, 3H), 0.89 (d, *J* = 7.0 Hz, 3H), 0.85 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.4, 138.3, 138.0, 128.42, 128.35, 128.31, 128.1, 127.9, 127.73, 127.69, 127.65, 127.5, 101.3, 81.8, 78.5, 75.3, 75.2, 74.3, 73.6, 71.3, 69.5, 69.0, 48.3, 41.1, 35.0, 28.9, 26.2, 24.6, 22.4, 21.3, 20.9; IR (film, cm^{-1}) 3444, 3027, 2917, 2848, 1452, 1383, 1103; HRMS (ES) *m/z* calcd for $C_{37}H_{48}O_6$ $[M+Na]^+$ 611.3349, found 611.3359.

Ketoester Reduction Product (Scheme 1.18, compound 29)

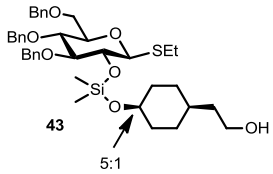


29
R = *i*Pr:Et 85:15

Following the general procedure **4.2**, silane (182 mg, 0.33 mmol), ketoester (43 μL, 0.30 mmol), $Ni(COD)_2$ (8 mg, 0.03 mmol), IMes·HCl (10 mg, 0.03 mmol), KO-*t*-Bu (3.4 mg, 0.03 mmol), and Ti(O-*i*-Pr)$_4$ (195 μL, 0.66 mmol) were stirred for 4.5 hr at rt to give the product as an inseparable 85:15 mixture of silyl-linked esters. The product (125 mg, 0.18 mmol, 60%, 85:15) was obtained as a colorless oil after flash chromatography on SiO_2. ^1H NMR (500 MHz, $CDCl_3$) δ 7.23-7.40 (m, 13H), 7.14-7.22 (m, 2H), 5.27 (s, 1H), 4.96-5.04 (m, 0.26H, indicative of minor product), 4.84 (d, *J* = 11.0 Hz, 1H), 4.62-4.74 (m, 3H), 4.52 (d, *J* = 12.0 Hz, 1H), 4.51 (d, *J* = 11.0 Hz, 1H), 4.27 (br s, 1H), 4.08-

4.18 (m, 2H), 3.94-4.02 (m, 2H), 3.82 (dd, *J* = 11.0, 5.0 Hz, 1H), 3.77 (dd, *J* = 9.5, 2.0 Hz, 1H), 3.72 (d, *J* = 10.5 Hz, 1H), 2.34-2.53 (m, 2H), 2.22-2.48 (m, 2H), 1.66-1.80 (m, 2H), 1.13-1.34 (m, 10H), 0.17 (s, 3H), 0.14 (s, 3H).

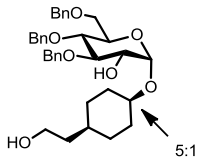
Ethyl 2-*O*- 2-(4-(dimethylsilyloxy)cyclohexyl)ethanol -3,4,6-tri-*O*-benzyl-1-thio-β-D-glucopyranoside (Scheme 1.23, compound 43)



Following the general procedure **4.2**, silane (182 mg, 0.33 mmol), hydroxyketone **42** (43 mg, 0.30 mmol), $Ni(COD)_2$ (8 mg, 0.03 mmol), IMes·HCl (10 mg, 0.03 mmol), KO-*t*-Bu (3.4 mg, 0.03 mmol), and Ti(O-*i*-Pr)$_4$ (195 μL, 0.66 mmol) were stirred for 3 hr at rt to give the desired product as an inseparable 5:1 mixture of diastereomers. Compound **43** (187 mg, 0.26 mmol, 86%, 5:1) was obtained as a viscous colorless oil after purification by flash chromatography on SiO_2 (25 to 30% EtOAc/hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.23-7.39 (m, 13H), 7.07-7.12 (m, 2H), 4.98 (d, *J* = 11.5 Hz, 1H), 4.88 (d, *J* = 11.5 Hz, 1H), 4.73 (d, *J* = 10.5 Hz, 1H), 4.61 (d, *J* = 12.0 Hz, 1H), 4.56 (d, *J* = 12.5 Hz, 1H), 4.52 (d, *J* = 10.5 Hz, 1 H), 4.40 (d, *J* = 9.5 Hz, 1H anomeric), 4.10-4.12 (m, 1H), 3.53-3.78 (m, 7H), 3.49 (ddd, *J* = 9.0, 5.0, 1.75 Hz, 1H), 2.77 (dq, *J* = 12.5, 7.5 Hz, 1H), 2.72 (dq, *J* = 12.5, 7.5 Hz, 1H), 1.59-1.74 (m, 2H), 1.37-1.49 (m, 8H), 1.25-1.39 (m, 1H), 1.32 (t, *J* = 7.5 Hz, 3H), 1.15 (br s, 1H), 0.20 (s, 3H), 0.18 (s, 3H); diagnostic peaks for minor diastereomer: 4.74 (d, *J* = 10.5 Hz, 1H), 1.85-1.97 (m, 1H), 0.22 (s, 3H), 0.17 (s, 3H) Note – the relative stereochemistry of the major and minor diastereomers was confirmed based on the Karplus correlations of the carbinol methine proton of the desilylated diol; ^{13}C NMR (100 MHz, $CDCl_3$) major and minor

diastereomer signals reported δ 138.9, 138.2, 138.0, 129.1, 128.34, 128.32, 128.2, 127.9, 127.74, 127.70, 127.6, 127.2, 127.1, 87.1, 87.0, 86.3, 86.1, 79.1, 78.5, 78.2, 75.1, 74.9, 74.5, 73.4, 71.5, 69.2, 67.6, 60.9, 61.1, 39.6, 38.9, 35.5, 33.2, 32.7, 31.4, 27.13, 27.09, 24.7, 15.1, -0.89, -0.90, -1.16, -1.17; IR (film, cm^{-1}) 3437, 3031, 2926, 2858, 1454, 1364, 1255, 1057, 1028; HRMS (ES) *m/z* calcd for $C_{39}H_{54}O_7SSi$ $[M+Na]^+$ 717.3257, found 717.3283.

2-(4-cyclohexyl)ethanol-3,4,6-tri-*O*-benzyl-α-D-glucopyranoside (Scheme 1.23, compound 39)

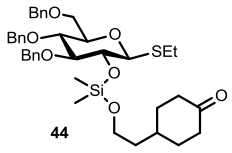


39

Following the general procedure **4.4**, silyl-linked compound **43** (81 mg, 0.12 mmol), NIS (37 mg, 0.16 mmol), 2,6-DTBMP (96 mg, 0.47 mmol), and TMSOTf (51 μL, 0.28 mmol) were stirred at -40 °C for 10 min, then warmed to 0 °C and stirred for 1.5 hr. *n*-Bu_4NF (1.2 mL, 1.2 mmol) was added as a 1M solution in THF, warmed to room temperature and stirred over night. The products **39** (combined 67 mg, 0.11 mmol, 97%, 5:1) were isolated as a clear oil and white crystalline solid respectively, and independently characterized after purification by flash chromatography on SiO_2 (50 to 65% EtOAc/hexanes). **Major diastereomer** ^1H NMR (500 MHz, $CDCl_3$) δ 7.41-7.44 (m, 2H), 7.26-7.37 (m, 11H), 7.14-7.18 (m, 2H), 5.00 (d, *J* = 11.0 Hz, 1H), 4.99 (d, *J* = 4.0 Hz, 1H anomeric), 4.86 (d, *J* = 11.0 Hz, 1H), 4.85 (d, *J* = 10.5 Hz, 1H), 4.65 (d, *J* = 12.0 Hz, 1H), 4.52 (d, *J* = 12.5 Hz, 1H), 4.51 (d, *J* = 11.0 Hz, 1H), 3.85-3.91 (m, 2H), 3.63-3.80 (m, 7H), 2.00 (d, *J* = 10.0 Hz, 1H), 1.81-1.89 (m, 2H), 1.44 -1.60 (m, 7H), 1.22-1.37

(m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.8, 138.1, 137.9, 128.39, 128.35, 128.34, 128.0, 127.9, 127.85, 127.76, 127.66, 127.58, 97.0, 83.7, 77.3, 75.25, 75.15, 73.5, 73.03, 72.97, 70.6, 68.5, 60.7, 39.0, 32.7, 30.8, 28.7, 27.6, 27.5; IR (film, cm^{-1}) 3436, 3031, 2926, 2860, 1453, 1363, 1132, 1067, 1028; HRMS (ES) *m/z* calcd for $C_{35}H_{44}O_7$ $[M+Na]^+$ 599.2985, found 599.2974. **Minor diastereomer** ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38-7.41 (m, 2H), 7.25-7.36 (m, 11H), 7.13-7.17 (m, 2H), 5.04 (d, *J* = 4.0 Hz 1H anomeric), 4.98 (d, *J* = 11.0 Hz, 1H), 4.84 (d, *J* = 11.5 Hz, 1H), 4.83 (d, *J* = 11.0 Hz, 1H), 4.64 (d, *J* = 12.0 Hz, 1H), 4.51 (d, *J* = 11.5 Hz, 1H), 4.49 (d, *J* = 10.5 Hz, 1H), 3.88 (ddd, *J* = 10.0, 3.75, 1.75 Hz, 1H), 3.60-3.79 (m, 7H), 3.56 (tt, *J* = 11.0, 4.25 Hz, 1H), 1.99-2.08 (m, 3H), 1.76-1.85 (m, 2H), 1.48 (q, *J* = 6.5 Hz, 2H), 1.14-1.44 (m, 4H), 0.92-1.04 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.8, 138.2, 138.0, 128.38, 128.37, 128.35, 128.0, 127.8, 127.72, 127.66, 127.57, 97.0, 83.7, 77.4, 75.3, 75.1, 73.5, 73.0, 70.5, 68.6, 60.9, 39.4, 33.33, 33.29, 31.7, 31.3, 31.1; IR (film, cm^{-1}) 3401, 3032, 2924, 2853, 1452, 1353, 1130, 1070, 1040; HRMS (ES) *m/z* calcd for $C_{35}H_{44}O_7$ $[M+Na]^+$ 599.2985, found 599.2971.

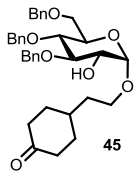
Ethyl 2-*O*- 4-(2-(dimethylsilyloxy)ethyl)cyclohexanone -3,4,6-tri-*O*-benzyl-1-thio-β-D-glucopyranoside (Scheme 1.24, compound 44)



Following the general procedure **4.3**, silane (182 mg, 0.33 mmol), hydroxyketone **42** (43 mg, 0.30 mmol), CuCl (1.5 mg, 0.015 mmol), IMes·HCl (5 mg, 0.015 mmol), and NaO-*t*-Bu) (3 mg, 0.03 mmol) were stirred for 3 hr at rt to give the desired product. Compound **44** (119 mg, 0.17 mmol, 57%) was obtained as a colorless oil after purification by flash chromatography on SiO_2 (20% EtOAc/hexanes). ^{1}H NMR (500

MHz, $CDCl_3$) δ 7.23-7.38 (m, 13H), 7.08-7.11 (m, 2H), 4.94 (d, *J* = 11.5 Hz, 1H), 4.89 (d, *J* = 11.5 Hz, 1H), 4.73 (d, *J* = 11.0 Hz, 1H), 4.61 (d, *J* = 12.5 Hz, 1H), 4.56 (d, *J* = 12.0 Hz, 1H), 4.53 (d, *J* = 10.5 Hz, 1H), 4.40 (d, *J* = 9.5 Hz, 1H anomeric), 3.74-3.78 (m, 3H), 3.67-3.72 (m, 2H), 3.62 (t, *J* = 9.25 Hz, 1H), 3.55 (t, *J* = 8.75 Hz, 1H), 3.49 (ddd, *J* = 9.75, 4.75, 1.75 Hz, 1H), 2.77 (dq, *J* = 12.5, 7.5 Hz, 1H), 2.72 (dq, *J* = 12.5, 7.5 Hz, 1H), 2.20-2.38 (m, 4H), 1.93-2.01 (m, 2H), 1.77-1.86 (m, 1H), 1.49 (q, *J* = 7.0 Hz, 2H), 1.28-1.39 (m, 2H), 1.32 (t, *J* = 7.5 Hz, 3H), 0.22 (s, 3H), 0.20 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 212.3, 138.7, 138.2, 137.9, 128.4, 128.34, 128.26, 127.9, 127.78, 127.76, 127.6, 127.3, 127.1, 87.1, 86.2, 79.2, 78.2, 75.2, 75.0, 74.6, 73.5, 69.1, 60.5, 40.8, 38.0, 32.7, 32.6, 32.4, 24.7, 15.1, -1.95, -2.02; IR (film, cm^{-1}) 3031, 2925, 2865, 1715, 1453, 1384, 1256, 1089, 1029; HRMS (ES) *m/z* calcd for $C_{39}H_{52}O_7SSi$ $[M+Na]^+$ 715.3101, found 715.3095.

4-(2-ethyl)cyclohexanone-3,4,6-tri-*O*-benzyl-α-D-glucopyranoside (Scheme 1.24, compound 45)

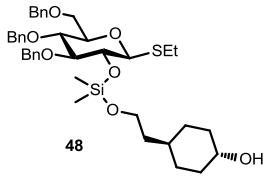


45

Following the general procedure **4.4**, silyl-linked compound **44** (80 mg, 0.12 mmol), NIS (36 mg, 0.16 mmol), 2,6-DTBMP (95 mg, 0.46 mmol), and TMSOTf (50 μL, 0.28 mmol) were stirred at -40 °C for 10 min, then warmed to 0 °C and stirred for 30 min. *n*-Bu_4NF (1.2 mL, 1.2 mmol) was added as a 1M solution in THF, warmed to rt and stirred over night. Compound **45** (41 mg, 0.07 mmol, 62%) was obtained as white crystalline solid after purification by flash chromatography on SiO_2 (50 to 60% EtOAc/hexanes). ^1H NMR (500 MHz, $CDCl_3$) δ 7.38-7.41 (m, 2H), 7.22-7.37 (m, 11H),

7.15-7.19 (m, 2H), 4.95 (d, *J* = 11.0 Hz, 1H), 4.91 (d, *J* = 3.0 Hz, 1H anomeric), 4.88 (d, *J* = 11.0 Hz, 1H), 4.84 (d, *J* = 10.5 Hz, 1H), 4.63 (d, *J* = 12.0 Hz, 1H), 4.54 (d, *J* = 12.0 Hz, 1H), 4.52 (d, *J* = 10.5 Hz, 1H), 3.71-3.85 (m, 5H), 3.68 (dd, *J* = 10.25, 2.25 Hz, 1H), 3.62 (dd, *J* = 9.5, 9.0 Hz 1H), 3.56 (dt, *J* = 10.0, 6.5 Hz, 1H), 2.28 (m, 4H), 2.01-2.10 (m, 3H), 1.81-1.91 (m, 1H), 1.60-1.72 (m, 2H), 1.36-1.48 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.7, 138.6, 138.0, 137.9, 128.42, 128.37, 128.0, 127.85, 127.82, 127.74, 127.69, 98.5, 83.4, 77.5, 75.3, 75.1, 73.6, 72.9, 70.8, 68.6, 66.2, 40.62, 40.60, 35.1, 32.9, 32.7, 32.4; IR (film, cm^{-1}) 3450, 3031, 2926, 1713, 1453, 1357, 1135, 1068, 1028; HRMS (ES) *m/z* calcd for $C_{35}H_{44}O_7$ $[M+Na]^+$ 597.2828, found 597.2818.

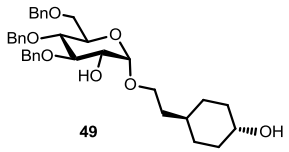
Hydroxyaldehyde Reduction Product (Scheme 1.27, compound 48)



48

Following the general procedure **4.2**, silane (91 mg, 0.17 mmol), hydroxyaldehyde **47** (21 mg, 0.15 mmol), $Ni(COD)_2$ (4.1 mg, 0.015 mmol), IMes·HCl (5.1 mg, 0.015 mmol), KO-*t*-Bu (1.7 mg, 0.015 mmol), and Ti(O-*i*-Pr)$_4$ (97 μL, 0.33 mmol) were stirred for overnight at rt to give the desired product **48**. Compound **48** (46 mg, 0.07 mmol, 44%) was obtained as a colorless oil after purification by flash chromatography on SiO_2 (10 to 30% EtOAc/hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.24-7.38 (m, 13H), 7.08-7.12 (m, 2H), 4.92 (d, *J* = 11.0 Hz, 1H), 4.88 (d, *J* = 11.5 Hz, 1H), 4.60 (d, *J* = 12.0 Hz, 1H), 4.56 (d, *J* = 12.0 Hz, 1H), 4.53 (d, *J* = 10.5 Hz, 1H), 4.39 (d, *J* = 9.5 Hz, 1H), 3.75 (dd, *J* = 11.0, 1.5 Hz, 1H), 3.66-3.74 (m, 4H), 3.61 (t, *J* = 9.0 Hz, 1H), 3.47-3.57 (m, 3H), 2.68-2.81 (m, 2H), 1.89-1.98 (m, 2H), 1.66-1.74 (m, 2H), 1.39 (q, *J* = 6.5 Hz, 2H), 1.14-1.36 (m, 7H) 0.87-0.97 (m, 2H), 0.20 (s, 3H), 0.18 (s, 3H).

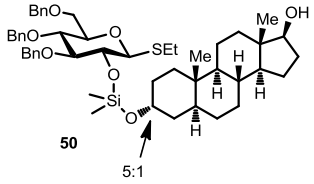
Hydroxyaldehyde Glycosylation Product (Scheme 1.27, compound 49)



49

Following the general procedure **4.4**, compound **48** (36 mg, 0.0.05 mmol), NIS (16 mg, 0.07 mmol), TMSOTf (22 μL, 0.12 mmol), 2,6-DTBMP (42 mg, 0.20 mmol) were stirred for 5 minutes at -40 °C, and 1 hour at 0 °C then excess *n*-Bu_4NF (0.5 mL, 0.5 mmol) was added as a 1M solution in THF and stirred overnight to afford the desired product. The product (27 mg, 0.048 mmol, 95%) was obtained as a colorless viscous oil upon purification by flash chromatography on SiO_2 (50 to 60% EtOAc/Hex). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38-7.41 (m, 2H), 7.26-7.37 (m, 11H), 7.14-7.18 (m, 2H), 4.95 (d, *J* = 11.5 Hz, 1H), 4.89 (d, *J* = 3.5 Hz, 1H), 4.86 (d, *J* = 11.0 Hz, 1H), 4.83 (d, *J* = 11.0 Hz, 1H), 4.64 (d, *J* = 12.0 Hz, 1H), 4.52 (d, *J* = 12.5 Hz, 1H), 4.50 (d, *J* = 10.5 Hz, 1H), 3.60-3.80 (m, 7H), 3.55 (tt, *J* = 11.0, 4.5 Hz, 1H), 3.47-3.53 (m, 1H), 2.06 (d, *J* =7.5 Hz, 1H), 1.94-2.00 (m, 2H), 1.73-1.81 (m, 2H), 1.53 (q, *J* = 7.0 Hz, 2H), 1.20-1.40 (m, 5H), 0.93-1.04 (m, 2H).

Ethyl 2-*O*-[(3R,5S,8R,9S,10S,13S,14S,17S)-3-(dimethylsilyloxy)-10,13-dimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-ol]-3,4,6-tri-*O*-benzyl-1-thio-β-D-glucopyranoside (Scheme 1.28, compound 50)

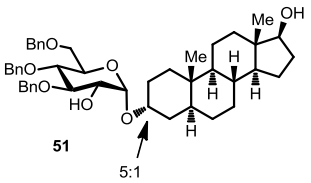


50

Following the general procedure **4.2**, silane (182 mg, 0.33 mmol), dihydrotestosterone (87 mg, 0.30 mmol), $Ni(COD)_2$ (8 mg, 0.03 mmol), IMes·HCl (10

mg, 0.03 mmol), KO-*t*-Bu (3.4 mg, 0.03 mmol), and Ti(O-*i*-Pr)$_4$ (195 μL, 0.66 mmol) were stirred for 6.5 hr at rt to give the product as an inseparable 5:1 mixture of diastereomers. The product (226 mg, 0.27 mmol, 89%, 5:1) was obtained as a viscous yellow oil after flash chromatography on SiO_2 (20 to 25% EtOAc/Hex). ^{1}H NMR 7.24-7.40 (m, 13H), 7.06 (m, 2H), 5.03 (d, *J* = 11.5 Hz, 1H), 4.86 (d, *J* = 11.5 Hz, 1H), 4.71 (d, *J* = 11.0 Hz, 1H), 4.61 (d, *J* = 12.5 Hz, 1H), 4.56 (d, *J* = 12.5 Hz, 1H), 4.51 (d, *J* = 10.5 Hz, 1H), 4.40 (d, *J* = 9.5 Hz, 1H anomeric), 4.17 (t, *J* = 2.5 Hz, 1H) 3.47-3.81 (m, 7H$_{major\ +\ minor}$), 2.68-2.81 (m, 2H), 2.00-2.10 (m, 1H), 0.56-1.82 (m, 31H$_{major\ +\ minor}$) {assignable peaks within this multiplet: 1.32 (t, *J* = 7.5 Hz, 3H$_{major}$), 0.73 (s, 3H$_{major}$), 0.71 (s, 3H$_{major}$)}, 0.21 (s, 3H), 0.19 (s, 3H), diagnostic peaks for minor diastereomer 4.97 (d, *J* = 11.5 Hz, 1H$_{minor}$), 4.90 (d, *J* = 11 Hz, 1H$_{minor}$) benzylic, Note – the stereochemistry of the major diastereomer and the dr of the reduction was determined on a crude reaction mixture of the silyl-linked compound after complete desilylation by *n*-Bu$_4$NF and comparison to known compounds; ^{13}C NMR (100 MHz, $CDCl_3$) major and minor diastereomer signals reported δ 138.9, 138.2, 138.0, 128.34, 128.31, 128.2, 127.95, 127.93, 127.72, 127.69, 127.5, 127.3, 127.0, 87.2, 87.0, 86.2, 82.0, 79.1, 78.3, 78.1, 75.3, 75.1, 74.9, 74.6, 73.4, 71.7, 69.1, 67.2, 54.5, 54.1, 51.01, 50.95, 44.9, 42.9, 38.8, 38.2, 37.1, 36.74, 36.67, 36.4, 35.9, 35.5, 35.4, 32.3, 31.64, 31.57, 31.47, 30.5, 29.7, 29.4, 28.6, 28.4, 24.7, 23.4, 23.3, 20.7, 20.3, 15.1, 12.3, 11.4, 11.1, -0.9, -1.0, -1.1, -1.2; IR (film, cm^{-1}) 3429, 3028, 2925, 2867, 1496, 1452, 1362, 1253, 1133, 1067, 1027; HRMS (ES) *m/z* calcd for $C_{50}H_{70}O_7SSi$ $[M+Na]^+$ 865.4509, found 865.4501.

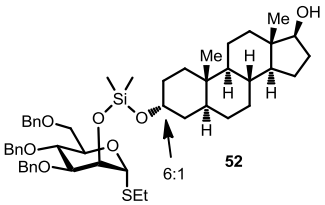
3-(3R,5S,8R,9S,10S,13S,14S,17S)-10,13-dimethylhexadecahydro-1H-cyclopenta[a]phenanthrene-17-ol 3,4,6-tri-*O*-benzyl-α-D-glucopyranoside (Scheme 1.28, compound 51)



Following the general procedure **4.4**, compound **50** (145 mg, 0.17 mmol), NIS (54 mg, 0.24 mmol), TMSOTf (75 μL, 0.41 mmol), 2,6-DTBMP (141 mg, 0.69 mmol) were stirred for 5 minutes at -40 °C, and 1 hour at 0 °C then excess *n*-Bu_4NF (1.7 mL, 1.7 mmol) was added as a 1M solution in THF and stirred overnight to afford the desired products as a 5:1 mixture of diastereomers. The products (combined 117 mg, 0.16 mg, 95%, 5:1) were obtained as colorless viscous oils, separated and characterized independently upon purification by flash chromatography on SiO_2 (30 to 40% EtOAc/Hex). **Major diastereomer** ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41-7.44 (m, 2H), 7.26-7.38 (m, 11H), 7.14-7.17 (m, 2H), 5.02 (d, *J* = 11.0 Hz, 1H), 4.97 (d, *J* = 3.5 Hz, 1H anomeric), 4.87 (d, *J* = 11.0 Hz, 1H), 4.84 (d, *J* = 10.5 Hz, 1H), 4.64 (d, *J* = 12.0 Hz, 1H), 4.51 (d, *J* = 12.0 Hz, 1H), 4.50 (d, *J* = 10.5 Hz, 1H), 3.91 (m, 1H), 3.85 (ddd, *J* = 10.0, 3.5, 1.5 Hz, 1H), 3.78 (dd, *J* = 10.5, 3.5 Hz, 1H), 3.68-3.75 (m, 2H), 3.61-3.68 (m, 3H), 2.02-2.11 (m, 1H), 1.96 (d, *J* = 9.5 Hz, 1H), 1.78-1.81 (m, 2H), 1.52-1.70 (m, 4H), 1.13-1.52 (m, 12 H), 1.07 (td, *J* = 13.0, 4.0 Hz, 1H), 0.85-1.02 (m, 2H), 0.80 (s, 3H), 0.74 (s, 3H), 0.70-0.78 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.9, 138.1, 138.0, 128.44, 128.37, 128.2, 127.90, 127.87, 127.83, 127.7, 127.6, 97.3, 83.8, 82.0, 77.4, 75.2, 73.5, 73.3, 73.1, 70.7, 68.6, 54.3, 51.0, 43.0, 40.2, 36.7, 36.0, 35.5, 33.1, 32.5, 31.4, 30.5, 28.4,

27.4, 23.3, 20.4, 11.4, 11.1; IR (film, cm^{-1}) 3453, 3063, 3030, 2928, 1496, 1453, 1358, 1135, 1067; HRMS (ES) *m/z* calcd for $C_{46}H_6O_7$ $[M+Na]^+$ 747.4237, found 747.4250. **Minor diastereomer** ^1H NMR (500 MHz, $CDCl_3$) δ 7.37-7.41 (m , 2H), 7.26-7.36 (m, 11H), 7.14-7.17 (m, 2H), 5.03 (d, *J* = 3.5 Hz, 1H anomeric), 4.98 (d, *J* = 11.0 Hz, 1H), 4.84 (d, *J* = 11.0 Hz, 1H), 4.64 (d, *J* = 12.5 Hz), 4.51 (d, *J* = 12.0 Hz, 1H), 4.49 (d, *J* = 10.5 Hz, 1H), 3.90 (ddd, *J* = 10.0, 4.0, 2.0 Hz, 1H), 3.55-3.78 (m, 7H), 2.05 (d, *J* = 9.5 Hz, 1H), 2.02-2.10 (m, 1H), 1.84-1.90 (m, 1H), 1.80 (dt, *J* = 12, 3.5 Hz, 1H), 1.74 (dt, *J* = 13.5, 3.5 Hz, 1H), 1.54-1.68 (m, 3H), 1.20-1.47 (m, 10H), 1.01-1.12 (m, 2H), 0.80-0.98 (m, 3H), 0.82 (s,3H), 0.74 (s, 3H), 0.60-0.98 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.8, 138.2, 138.0, 128.35, 128.33, 127.9, 127.8, 127.7, 127.6, 127.5, 97.0, 83.8, 81.9, 77.4, 75.3, 75.0, 73.5, 73.0, 70.5, 68.7, 54.4, 51.0, 45.0, 43.0, 36.8, 36.7, 36.0, 35.6, 35.5, 31.6, 30.5, 29.7, 28.5, 27.8, 23.4, 20.8, 12.3, 11.1; IR (film, cm^{-1}) 3439, 3029, 2928, 1452, 1356, 1207, 1131, 1067, 1025; HRMS (ES) *m/z* calcd for $C_{46}H_{60}O_7$ $[M+Na]^+$ 747.4237, found 747.4258.

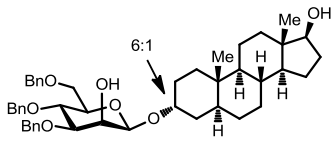
Ethyl 2-*O*-[(3R,5S,8R,9S,10S,13S,14S,17S)-3-(dimethylsilyloxy)-10,13-dimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-ol]-3,4,6-tri-*O*-benzyl-1-thio-α-D-mannopyranoside (Scheme 1.28, compound 52)



Following the general procedure **4.2**, silane (182 mg, 0.33 mmol) dihydrotestosterone (87 mg, 0.30 mmol), $Ni(COD)_2$ (8 mg, 0.03 mmol), IMes·HCl (10 mg, 0.03 mmol), KO-*t*-Bu (3.4 mg, 0.03 mmol), and $Ti(O\text{-}i\text{-}Pr)_4$ (195 μL, 0.66 mmol)

were stirred for 6.5 hr at rt to give the desired product as an inseparable 6:1 mixture of diastereomers. The product (202 mg, 0.24 mmol, 80%, 6:1) was obtained as a viscous off-white oil after flash chromatography on SiO_2 (10 to 20% EtOAc/hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) **Major diastereomer** δ 7.24-7.38 (m, 13H), 7.15-7.18 (m, 2H), 5.32 (d, *J* = 1.5 Hz, 1H anomeric), 4.84 (d, *J* = 11.0 Hz, 1H), 4.73 (d, *J* = 11.5 Hz, 1H), 4.69 (d, *J* = 12.0 Hz, 1H), 4.62 (d, *J* = 12.0 Hz, 1H), 4.52 (d, *J* = 11.0 Hz, 1H), 4.50 (d, *J* = 10.5 Hz, 1H), 4.30 (dd, *J* = 2.5, 2.0 Hz, 1H), 4.12-4.16 (m, 2H), 3.98 (t, 9.5 Hz, 1H), 4.83 (dd, *J* = 11.0, 5.0 Hz, 1H), 3.77 (dd, *J* = 9.0, 2.25 Hz, 1H), 3.72 (dd, *J* = 11.0, 2.0 Hz, 1H), 3.62 (t, *J* = 8.25 Hz, 1H), 2.54-2.70 (m, 2H), 2.01-2.11 (m, 1H), 1.78 (dt, *J* = 12.5, 3.5 Hz, 1H), 1.09-1.66 (m, 17H), 1.29 (t, *J* = 7.5 Hz, 3H), 1.02, (td, *J* = 13.0, 4.0 Hz, 1H), 0.80-0.96 (m, 2H), 0.69-0.78 (m, 1H), 0.76 (s, 3H), 0.73 (s, 3H), 0.16 (s, 3H), 0.15 (s, 3H); diagnostic peak for minor diastereomer at 5.28 (d, *J* = 1.5 Hz, 0.15H anomeric), Note – the stereochemistry of the major diastereomer and the dr of the reduction was determined on a crude reaction mixture of the silyl-linked compound after complete desilylation by *n*-Bu_4NF and comparison to known compounds; ^{13}C NMR (100 MHz, $CDCl_3$) major and minor diastereomer signals reported δ 138.5, 138.3, 128.3, 128.2, 127.9, 127.7, 127.6, 127.5, 127.4, 85.5, 82.0, 80.4, 74.9, 74.8, 73.2, 72.1, 72.0, 70.6, 69.2, 67.0, 54.3, 51.1, 44.9, 43.0, 39.0, 36.7, 36.4, 36.0, 35.5, 25.3, 23.3, 20.3, 15.1, 11.4, 11.1, -1.4, -1.5, -1.7; IR (film, cm^{-1}) 3465, 3030, 2925, 1452, 1371, 1255, 1097, 1047; HRMS (ES) *m/z* calcd for $C_{50}H_{70}O_7SSi$ $[M+Na]^+$ 865.4509, found 865.4484.

3-(3R,5S,8R,9S,10S,13S,14S,17S)-10,13-dimethylhexadecahydro-1H-cyclopenta[a]phenanthrene-17-ol 3,4,6-tri-*O*-benzyl-β-D-mannopyranoside (Scheme 1.28, compound 53)



53

Following the general procedure **4.4**, compound **52** (131 mg, 0.16 mmol), NIS (49 mg, 0.22 mmol), 2,6-DTBMP (128 mg, 0.62 mmol), and TMSOTf (68 μL, 0..37 mmol), were stirred at -40 °C for 10 min, then warmed to 0 °C and stirred for 1.5 hours. *n*-Bu_4NF (1.6 mL, 1.6 mmol) was then added as a 1M solution in THF, and the reaction was taken to rt and stirred overnight to give the products as a 6:1 mixture of diastereomers. The products (combined 103 mg, 0.14 mmol, 92%, 6:1) were isolated as viscous, colorless oils, which were separated and characterized independently upon purification by flash chromatography on SiO_2 (30% EtOAc/Hex). **Major diastereomer** ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38-7.41 (m, 2H), 7.24-7.36 (m, 13H), 7.20-7.23 (m, 2H), 4.91 (d, *J* = 11.0 Hz, 1H), 4.81 (d, *J* = 12.0 Hz, 1H), 4.68 (d, *J* = 11.5 Hz, 1H), 4.61 (d, *J* = 12.5 Hz, 1H), 4.56 (d, *J* = 12.5 Hz, 1H), 4.55 (d, *J* = 10.5 Hz, 1H), 4.49 (s, 1H anomeric), 4.09 (br s, 1H), 4.04-4.07 (m, 1H), 3.87 (t, *J* = 9.0 Hz, 1H), 3.76 (dd, *J* = 10.5, 2.0 Hz, 1H), 3.68 (dd, *J* = 11.0, 5.5 Hz, 1H), 3.64 (t, *J* = 8.5 Hz, 1H), 3.59 (dd, *J* = 9.0, 2.5 Hz, 1H), 3.41 (ddd, *J* = 9.5, 5.0, 2.0 Hz, 1H), 2.52 (s, 1H), 2.02-2.11 (m, 1H), 1.79 (dt, *J* = 12.0, 3.0 Hz, 1H), 1.72 (d, *J* = 14.5 Hz, 1H), 1.10-1.68 (m, 18H), 1.05 (td, *J* = 13.0, 4.0 Hz, 1H), 0.85-1.00 (m, 1H), 0.72-0.82 (m, 1H), 0.80 (s, 3H), 0.74 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.3, 138.2, 137.9, 128.4, 128.33, 128.28, 128.1, 127.8, 127.74, 127.69, 127.5, 97.2, 81.9, 81.8, 75.2, 75.1, 74.3, 73.5, 72.8, 71.2, 69.3, 68.9, 54.2, 51.0, 42.9, 39.4, 36.7, 35.9, 35.5, 34.2, 32.5, 31.4, 30.5, 28.2, 25.0, 23.3, 20.3, 11.4, 11.1; IR (film, cm^{-1}) 3452, 3028, 2926, 2866, 1452, 1363, 1105, 1056; HRMS (ES) *m/z* calcd for $C_{46}H_{60}O_7$ $[M+Na]^+$

747.4237, found 747.4250. **Minor diastereomer** ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37-7.40 (m, 2H), 7.27-7.36 (m, 11H), 7.21-7.24 (m, 2H), 4.90 (d, *J* = 11.0 Hz, 1H), 4.78 (d, *J* = 12.0 Hz, 1H), 4.68 (d, *J* = 11.5 Hz, 1H), 4.62 (d, *J* = 12.0 Hz, 1H), 4.57 (d, *J* = 12.0 Hz, 1H), 4.56 (s, 1H anomeric), 4.55 (d, *J* = 11.5 Hz, 1H), 4.06 (s, 1H), 3.83 (t, *J* = 9.75 Hz, 1H), 3.79 (dd, *J* = 10.75, 1.75 Hz, 1H), 3.60-3.75 (m, 2H), 3.68 (dd, *J* = 10.5, 6.0 Hz, 1H), 3.57 (dd, *J* = 9.0, 3.0 Hz, 1H), 3.43 (ddd, *J* = 9.5, 5.75, 1.75 Hz, 1H), 2.46 (d, *J* = 2.0 Hz, 1H), 2.01-2.10 (m, 1H), 1.92-1.98 (m, 1H), 1.80 (dt, *J* = 12.0, 3.25 Hz, 1H), 1.73 (dt, *J* = 13.25, 2.5 Hz, 1H), 1.67 (dq, *J* = 12.75, 3.25 Hz. 1H), 1.20-1.62 (m, 11H), 0.75-1.10 (m, 6H), 0.82 (s, 3H), 0.74 (s, 3H), 0.58-0.65 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.4, 138.2, 137.9, 128.5, 128.4, 128.3, 128.1, 127.9, 127.8, 127.7, 127.5, 97.2, 82.0, 81.7, 77.4, 75.3, 75.2, 74.4, 73.4, 71.3, 69.4, 68.8, 54.5, 51.0, 44.7, 43.0, 37.0, 36.7, 35.7, 35.5, 34.2, 31.6, 30.5, 29.2, 28.7, 23.4, 20.8, 12.3, 11.1; IR (film, cm^{-1}) 3462, 3028, 2926, 2848, 1452, 1383, 1101, 1071, 1026; HRMS (ES) *m/z* calcd for $C_{46}H_{60}O_7$ $[M+Na]^+$ 747.4237, found 747.4247.

4.2 Chapter 2 Experimental Procedures and Spectral Data

4.2.1 Chapter 2 Experimental Procedures

All reagents were used as received unless otherwise noted. Solvents were purified under nitrogen using a solvent purification system (Innovative Technology, inc., Model # SPS-400-3 and PS-400-3). $B(C_6F_5)_3$ (Sigma-Aldrich, used as received) when stored for long periods of time, an inert atmosphere was used. However, it was found to perform equally well when stored in a vial kept in a dessicator and weighed on the benchtop. CuCl (Sigma-Aldrich, used as received and, 1,3-dimesitylimidazolium chloride (IMes·HCl) were stored and weighed in an inert atmosphere glovebox. All $B(C_6F_5)_3$ and

Cu/IMes reactions were conducted in flame-dried glassware under a nitrogen atmosphere. ^{1}H and ^{13}C spectra were obtained in $CDCl_3$ at rt, unless otherwise noted, on a Varian Mercury 400 or Varian Unity 500 MHz instrument. Chemical shifts of ^{1}H NMR spectra were recorded in parts per million (ppm) on the δ scale from an internal standard of residual chloroform (7.27 ppm). Chemical shifts of ^{13}C NMR spectra were recorded in ppm from the central peak of $CDCl_3$ (77.0 ppm) on the δ scale. High resolution mass spectra (HRMS) were obtained on a VG-70-250-s spectrometer manufactured by Micromass Corp. (Manchester UK) at the University of Michigan Mass Spectrometry Laboratory.

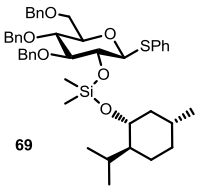
General Procedure for the $B(C_6F_5)_3$ Promoted Dehydrogenative Silylation of Alcohols (General Procedure 4.5)

A mixture of sugar silane (1.0 equiv.) and alcohol (1.0 equiv.) was dissolved in dry toluene (0.10M) at rt under an inert atmosphere (N_2) and stirred until both substrates were completely dissolved. $B(C_6F_5)_3$ (4 mol%) was added as a solid under a gentle stream of nitrogen followed by re-attachment of the septum and nitrogen line. Upon completion of the reaction as monitored by TLC, the reaction mixture was either loaded directly onto a column, or the volatiles were removed by rotary evaporation, and then loaded onto a column for purification by flash chromatography (SiO_2) to afford the desired product. Note – dry dichloromethane was found to be the optimal co-solvent if a substrate is marginally soluble in toluene.

General Procedure for the CuCl-IMes Promoted Dehydrogenative Silylation of Alcohols (General Procedure 4.6)

A solid mixture of CuCl (5%), IMes·HCl (5%) and KO-*t*-Bu (10%) was dissolved in dry toluene (0.015M) at rt under an inert atmosphere (N_2), and stirred for 20 minutes. A mixture of alcohol (1.0 equiv) and silane (1.1 equiv) was dissolved in dry toluene (0.2M), the catalyst was then added to this mixture as a solution in dry toluene. Upon completion of the reaction, as monitored by TLC, the reaction mixture was filtered through a short plug of silica gel with a mixture of EtOAc/Hexanes and concentrated by rotary evaporation. The resulting residue was purified via flash chromatography (SiO_2) to afford the desired product.

Thiophenyl Sugar Silane and (-)-Menthol Silyl-Linked (Scheme 2.7, compound 69)

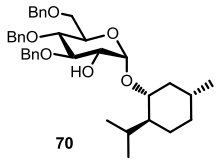


69

Following the general procedure **4.5**, silane (60 mg, 0.10 mmol), (-)-menthol (16 mg, 0.10 mmol), and $B(C_6F_5)_3$ (2 mg, 0.004 mmol) were stirred for 85 minutes at rt. The product (73 mg, 0.097 mmol, 97%) was obtained as a colorless oil upon purification by flash chromatography on SiO_2 (5 to 8% EtOAc/hex). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.53-7.56 (m, 2H), 7.38-7.41 (m, 2H), 7.21-7.35 (m, 14H), 7.14-7.17 (m, 2H), 5.02 (d, *J* = 11.0 Hz, 1H), 4.86 (d, *J* = 11.0 Hz, 1H), 4.78 (d, *J* = 10.5 Hz, 1H), 4.65 (d, *J* = 9.5 Hz, 1H), 4.60 (d, *J* = 12.0 Hz, 1H), 4.57 (d, *J* = 10.5 Hz, 1H), 4.54 (d, *J* = 12.0 Hz, 1H), 3.76-3.81 (m, 2H), 3.71 (dd, *J* = 11.0, 5.0 Hz, 1H), 3.53-3.66 (m, 4H), 2.21 (septd, *J* = 7.0, 2.5 Hz, 1H), 2.01 (d, *J* = 12.0 Hz, 1H), 1.53-1.63 (m, 2H), 1.28-1.37 (m, 1H), 1.12 (dt, *J* = 12.5, 3.0 Hz, 1H), 1.05 (q, *J* = 12.5 Hz, 1H), 0.86-0.97 (m, 1H), 0.86 (d, *J* = 7.0 Hz, 3H), 0.85 (d, *J* = 7.0 Hz, 3H), 0.72-0.82 (m, 1H), 0.74 (d, *J* = 7.0 Hz, 3H), 0.25 (s, 3H), 0.13

(s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.7, 138.23, 137.99, 134.5, 131.1, 128.9, 128.4, 128.3, 128.2, 127.8, 127.73, 127.66, 127.52, 127.50, 127.3, 127.0, 88.8, 87.0, 79.0, 78.2, 75.2, 74.9, 73.9, 73.4, 72.7, 69.0, 49.7, 45.4, 34.5, 31.6, 25.2, 22.8, 22.2, 21.2, 15.9, -1.2,-1.4; IR (film, cm^{-1}) 3030, 2953, 2919, 2868, 1453, 1365, 1254, 1067; HRMS (ES) *m/z* calcd for $C_{45}H_{58}O_6SSi$ $[M+Na]^+$ 777.3621, found 777.3622.

Glucose and (-)-Menthol Glycoside (Scheme 2.7, compound 70)

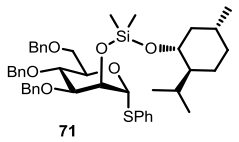


70

Following the general procedure **4.4**, compound **69** (148 mg, 0.20 mmol), NIS (57 mg, 0.25 mmol), TMSOTf (43 μL, 0.24 mmol), and 2,6-DTBMP (80 mg, 0.39 mmol) were stirred at -40 °C for 10 min, then warmed to 0 °C and stirred for 30 min, then excess *n*-Bu_4NF (1.2 mL, 1.2 mmol) was added as a 1M solution in THF, warmed to rt and allowed to stir overnight. The product (113 mg, 0.19 mmol, 98%) was obtained as a colorless oil upon purification by flash chromatography on SiO_2 (10% EtOAc/hex). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39-7.42 (m, 2H), 7.25-7.37 (m, 11H), 7.14-7.17 (m, 2H), 4.99 (d, *J* = 4.5 Hz, 1H), 4.97 (d, *J* = 11.5 Hz, 1H), 4.85 (d, *J* = 11.5 Hz, 1H), 4.84 (d, *J* = 10.5 Hz, 1H), 4.66 (d, *J* = 12.0 Hz, 1H), 4.50 (d, *J* = 11.0 Hz, 1H), 4.48 (d, *J* = 10.0 Hz, 1H), 3.94 (ddd, *J* = 10.0, 3.5, 2.0 Hz, 1H), 3.77 (dd, *J* = 10.75, 4.25 Hz, 1H) 3.60-3.74 (m, 4H), 3.40 (td, *J* = 10.5, 4.0 Hz, 1H), 2.19 (d, *J* = 12.5 Hz, 1H), 2.14 (septd, *J* = 6.5, 2.5 Hz, 1H), 1.96 (d, *J* = 9.0 Hz, 1H) 1.61-1.68 (m, 2H), 1.34-1.45 (m, 1H), 1.25-1.33 (m, 1H), 0.94 – 1.06 (m, 2H), 0.92 (d, *J* = 7.0 Hz, 3H), 0.87 (d, *J* = 6.5 Hz, 3H), 0.78-0.86 (m, 1H), 0.78 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.8, 138.2, 138.0, 128.4, 128.3, 128.0, 127.92, 127.86, 127.7, 127.64, 127.60, 100.0, 83.5, 81.1, 77.4, 75.2,

75.0, 73.6, 73.5, 70.6, 68.6, 48.7, 42.9, 34.1, 31.6, 25.5, 22.8, 22.2, 21.2, 15.7; IR (film, cm^{-1}) 3566, 3062, 3030, 2922, 2868, 1454, 1362, 1133, 1067, 1028; HRMS (ES) *m/z* calcd for $C_{37}H_{48}O_6$ $[M+Na]^+$ 611.3349, found 611.3354.

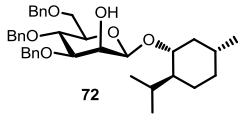
Thiophenyl Mannose Sugar Silane and (-)-Menthol Silyl-Linked (Scheme 2.7, compound 71)



71

Following the general procedure **4.5**, silane (60 mg, 0.10 mmol), (-)-menthol (16 mg, 0.10 mmol) and $B(C_6F_5)_3$ (2 mg, 0.004 mmol) were stirred at rt for 1.5 h. The product (62 mg, 0.082 mmol, 92%) was obtained as a colorless oil upon purification by flash chromatography on SiO_2 (5 to 8% EtOAc/hex). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48-7.51 (m, 2H), 7.38-7.42 (m, 2H), 7.20-7.36 (m, 16H), 5.53 (s, 1H), 4.88 (d, *J* = 10.5 Hz, 1H), 4.78 (d, *J* = 11.5 Hz, 1H), 4.67 (d, *J* = 12.0 Hz, 2H), 4.55 (d, *J* = 11.0 Hz, 1H), 4.50 (d, *J* = 12.0 Hz, 1H), 4.47 (s, 1H), 4.30 (dd, *J* = 9.5, 5.0 Hz, 1H), 4.00 (t, *J* = 9.5 Hz, 1H), 3.85 (dd, *J* = 11.0, 5.0 Hz, 1H), 3.80 (dd, *J* = 9.0, 2.5 Hz, 1H), 3.76 (d, *J* = 11.0 Hz, 1H), 3.54 (td, *J* = 10.0, 4.5 Hz, 1H), 2.09-2.19 (m, 1H), 1.95 (d, *J* = 12.0 Hz, 1H), 1.52-1.63 (m, 2H), 1.25-1.35 (m, 1H), 1.08-1.16 (m, 1H), 1.01 (q, *J* = 12.0 Hz, 1H), 0.75-0.87 (m, 7H), 0.72 (d, *J* = 7.0 Hz, 3H), 0.17 (s, 3H), 0.15 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.5, 138.4, 138.3, 134.7, 131.4, 128.9, 128.3, 128.2, 127.92, 127.86, 127.63, 127.57, 127.3, 127.1, 89.0, 80.3, 75.0, 74.9, 73.2, 73.0, 72.6, 72.2, 70.8, 69.3, 49.8, 45.3, 34.5, 31.6, 25.3, 22.8, 22.2, 21.1, 15.9, -1.35, -1.40; IR and HRMS match previously reported data for a mixture of diastereomers at the (-)-menthol carbinol.

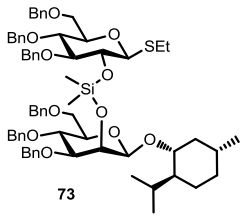
Mannose and (-)-Menthol glycoside (Scheme 2.7, compound 72)



72

Following the general procedure **4.4**, compound **71** (130 mg, 0.17 mmol), NIS (50 mg, 0.22 mmol), TMSOTf (37 μL, 0.21 mmol), and 2,6-DTBMP (70 mg, 0.34 mmol) were stirred at -40 °C for 10 min, then warmed to 0 °C and stirred for 90 min, then an excess of *n*-Bu_4NF (1.36 mL, 1.36 mmol) was added as a 1M solution in THF and allowed to stir at room temperature overnight. The product (100 mg, near quantitative) was isolated as a white crystalline solid upon purification by flash chromatography on SiO_2 (10 to 20% EtOAc/hex). All spectral data matches those previously reported in section 4.1.1.

Thioethyl Sugar Silane and Compound 72 Silyl-Linked (Scheme 2.8, compound 73)

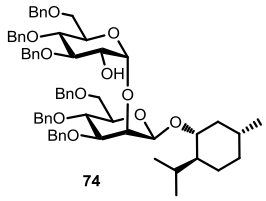


73

Following the general procedure **4.5**, silane (27 mg, 0.049 mmol), compound **72** (29 mg, 0.049 mmol) and $B(C_6F_5)_3$ (2 mg, 0.004 mmol) were stirred at rt overnight. The product (38 mg, 0.033 mmol, 68%) was obtained as an oil upon purification by flash chromatography on SiO_2 (10% EtOAc/hex). ^1H NMR (500 MHz, $CDCl_3$) δ 7.39-7.42 (m, 2H), 7.35-7.38 (m, 2H), 7.18-7.34 (m, 22H), 7.12-7.15 (m, 2H), 7.06-7.10 (m, 2H), 5.22 (d, *J* = 11.0 Hz, 1H), 4.80 (d, *J* = 12.0 Hz, 1H), 4.73 (d, *J* = 11.0 Hz, 1H), 4.70 (d, *J* = 11.0 Hz, 1H), 4.69 (d, *J* = 11.0 Hz, 1H), 4.60 (d, *J* = 12.0 Hz, 1H), 4.55 (d, *J* = 11.0 Hz, 1H), 4.53 (d, *J* = 12.0 Hz, 1H), 4.46 (d, *J* = 12.0 Hz, 1H), 4.423 (d, *J* = 12.0 Hz, 1H), 4.421 (d, *J* = 10.0 Hz, 1H), 4.39 (s, 1H), 4.36 (d, *J* = 9.5 Hz, 1H), 4.23 (d, *J* = 11.0 Hz,

1H), 4.17 (d, *J* = 2.5 Hz, 1H), 3.96 (dd, *J* = 9.5, 8.5 Hz, 1H), 3.73 (dd, *J* = 10.5, 1.5 Hz, 1H), 3.44-3.66 (m, 8H), 3.32-3.38 (m, 1H), 3.28 (dd, *J* = 10.5, 7.0 Hz, 1H), 2.73 (dq, *J* = 13.0, 7.5 Hz, 1H), 2.68 (dq, *J* = 12.5, 7.5 Hz, 1H), 2.57 (septd, *J* = 6.5, 2.0 Hz, 1H), 1.96 (d, *J* = 12.5 Hz, 1H), 1.60-1.68 (m, 2H), 1.27-1.40 (m, 1H), 1.28 (t, *J* = 7.5 Hz, 3H), 1.16-1.24 (m, 1H), 0.77-1.03 (m, 3H), 0.904 (d, *J* = 7.0 Hz, 3H), 0.900 (d, *J* = 6.5 Hz, 3H), 0.84 (d, *J* = 7.0 Hz, 3H), 0.31 (s, 3H), 0.28 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.3, 138.60, 138.56, 138.5, 138.32, 138.31, 128.3, 128.2, 128.1, 128.0, 127.8, 127.7, 127.6, 127.53, 127.46, 127.42, 127.36, 127.2, 96.7, 87.4, 86.2, 82.4, 79.1, 18.0, 76.3, 75.6, 75.4, 75.1, 75.0, 74.8, 74.6, 73.3, 71.2, 70.7, 70.1, 69.3, 47.9, 40.9, 34.4, 31.3, 24.7, 24.5, 22.8, 22.3, 21.6, 15.8, 15.2, -0.7, -1.1.

Glucose and Compound 72 Disaccharide (Scheme 2.8, compound 74)

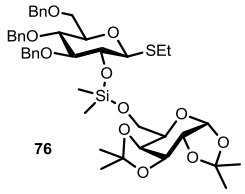


74

Following the general procedure **4.4**, compound **73** (37 mg, 0.032 mmol), NIS (9.5 mg, 0.042 mmol), TMSOTf (7.0 μL, 0.039 mmol), and 2,6-DTBMP (13 mg, 0.065 mmol) were stirred at -40 °C for 10 min, then warmed to 0 °C and stirred for 1.5 hours, then an excess of *n*-Bu_4NF (192 μL, 0.192 mmol) was added as a 1M solution in THF, warmed to rt and allowed to stir overnight. The product (29 mg, 0.028 mmol, 89%) was obtained as a colorless oil upon purification by flash chromatography on SiO_2 (20% EtOAc/hex). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.23-7.39 (m, 27H), 7.16-7.21 (m, 3H), 5.12 (d, *J* = 3.0 Hz, 1H), 4.90 (d, *J* = 11.0 Hz, 1H), 4.85 (d, *J* = 10.5 Hz, 1H), 4.83 (d, *J* = 10.5 Hz, 1H), 4.76 (d, *J* = 11.5 Hz, 1H), 4.72 (d, *J* = 11.5 Hz, 1H),. 4.61-4.70 (m, 4H), 4.56 (d,

J = 12.0 Hz, 1H), 4.54 (d, *J* = 11.0 Hz, 1H), 4.49 (d, *J* = 12.0 Hz, 1H), 4.41 (s, 1H), 4.27 (d, *J* = 9.5 Hz, 1H), 3.92 (d, *J* = 2.5 Hz, 1H), 3.83 (t, *J* = 9.75 Hz, 1H), 3.70-3.81 (m, 6H), 3.58-3.64 (m, 2H), 3.44 (td, *J* = 11.0, 4.0 Hz, 1H), 3.38 (dd, *J* = 9.5, 4.5 Hz, 1H), 3.15 (d, *J* = 7.5 Hz, 1H), 2.30 (sept, *J* = 6.5 Hz, 1H), 1.91 (d, *J* = 12.5 Hz, 1H), 1.58-1.70 (m, 2H), 1.28-1.40 (m, 1H), 1.05-1.12 (m, 1H) 0.73-1.00 (m, 3H), 0.91 (d, *J* = 6.5 Hz, 3H), 0.82 (d, *J* = 7.5 Hz, 3H), 0.77 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.3, 138.9, 138.5, 138.1, 138.0, 137.3, 128.6, 128.4, 128.32, 128.28, 128.25, 128.17, 128.1, 128.0, 127.90, 127.88, 127.87, 127.8, 127.60, 127.56, 127.4, 127.34, 127.26, 100.9, 96.9, 83.9, 82.3, 76.9, 75.6, 75.2, 75.1, 74.9, 74.7, 74.1, 73.6, 73.5, 72.8, 70.5, 69.7, 68.5, 48.0, 41.0, 34.3, 31.4, 24.8, 22.7, 22.2, 21.1, 15.7; IR (film, cm^{-1}) 3428, 3031, 2923, 2867, 1727, 1453, 1273, 1095, 1054; HRMS (ES) *m/z* calcd for $C_{64}H_{76}O_{11}$ $[M+Na]^+$ 1043.5285, found 1043.5297.

Thioethyl Sugar Silane and Galactose 75 Silyl-Linked (Scheme 2.9, compound 76)

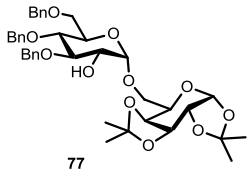


76

Following the general procedure **4.6**, silane (61 mg, 0.11 mmol), alcohol **75** (26 mg, 0.10 mmol), CuCl (0.5 mg, 0.0050 mmol), IMes·HCl (1.7 mg, 0.0050 mmol), and NaO-*t*-Bu (1 mg, 0.010 mmol) were stirred at rt for 15 min. The product (68 mg, 0.084 mmol, 84%) was obtained as an oil upon purification by flash chromatography on SiO_2 (10 to 15% EtOAc/hex). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.23-7.38 (m, 13H), 7.08-7.12 (m, 2H), 5.50 (d, *J* = 5.0 Hz, 1H), 4.96 (d, *J* = 11.5 Hz, 1H), 4.85 (d, *J* = 11.0 Hz, 1H), 4.74 (d, *J* = 10.5 Hz, 1H), 4.60 (d, *J* = 12.0 Hz, 1H), 4.50-4.58 (m, 3H), 4.38 (d, *J* = 9.5

Hz, 1H), 4.27 (dd, *J* = 4.5, 2.0 Hz, 1H), 4.19 (d, *J* = 8.0 Hz, 1H), 3.83-3.92 (m, 3H), 3.66-3.77 (m, 3H), 3.60 (t, *J* = 9.5 Hz, 1H), 3.54 (t, *J* = 8.75 Hz, 1H), 3.49 (ddd, *J* = 9.5, 5.0, 1.5 Hz, 1H), 2.77 (dq, *J* = 13.0, 7.5 Hz, 1H), 2.71 (dq, *J* = 12.5, 7.5 Hz, 1H), 1.49 (s, 3H), 1.42 (s, 3H), 1.29-1.34 (m, 6H), 1.29 (s, 3H), 0.24 (s, 3H), 0.20 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.76, 138.20, 138.00, 128.33, 128.31, 128.23, 127.92, 127.72, 127.54, 127.25, 108.94, 108.38, 96.25, 87.10, 86.20, 79.14, 78.09, 74.94, 74.48, 73.41, 70.77, 70.54, 70.48, 69.12, 68.03, 61.52, 26.11, 25.96, 24.94, 24.67, 24.34, 15.08, -1.90, -2.02; IR (film, cm^{-1}) 3063, 3030, 2978, 2930, 1454, 1382, 1256, 1211, 1070, 1001; HRMS (ES) *m/z* calcd for $C_{43}H_{58}O_{11}SSi$ [M+Na]+ 833.3367, found 833.3408.

Glucose and Galactose 75 Disaccharide (Scheme 2.9, compound 77)

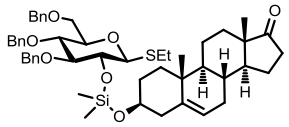


77

Following the general procedure **4.4**, compound **76** (58 mg, 0.072 mmol), NIS (21 mg, 0.093 mmol), TMSOTf (16 μL, 0.086 mmol), and 2,6-DTBMP (29 mg, 0.143 mmol) were stirred at -40 °C for 5 min, then warmed to 0 °C and stirred for 1 hour, then and excess of *n*-Bu_4NF (0.43 mL, 0.43 mmol) was added as a 1M solution in THF and allowed to stir at room temperature overnight. The product (42 mg, 0.061 mmol, 84%) was obtained as a colorless amorphous solid upon purification by flash chromatography on SiO_2 (30 to 45% EtOAc/hex). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25-7.42 (m, 13H), 7.13-7.17 (m, 2H), 5.53 (d, *J* = 5.0 Hz, 1H), 4.99 (d, *J* = 11.0 Hz, 1H), 4.94 (d, *J* = 3.5 Hz, 1H), 4.83 (d, *J* = 11.0 Hz, 1H), 4.82 (d, *J* = 11.0 Hz, 1H), 4.62-4.67 (m, 2H), 4.50 (d, *J* = 12.0 Hz, 1H), 4.49 (d, *J* = 10.5 Hz, 1H), 4.34 (dd, *J* = 5.0, 2.5 Hz, 1H), 4.25 (dd, *J* = 8.0, 1.5 Hz, 1H), 4.00 (td, *J* = 6.5, 1.5 Hz, 1H), 3.92 (dd, *J* = 10.0, 6.5 Hz, 1H), 3.86 (dt, *J*

= 10.0, 2.0 Hz, 1H), 3.63-3.79 (m, 6H), 2.46 (d, *J* = 9.0 Hz, 1H), 1.54 (s, 3H), 1.46 (s, 3H), 1.36 (s, 3H), 1.34 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.84, 138.30, 137.96, 128.35, 128.32, 127.93, 127.90, 127.86, 127.65, 127.62, 127.54, 109.48, 108.69, 99.15, 96.23, 83.41, 77.14, 75.21, 74.95, 73.49, 73.25, 71.04, 70.83, 70.66, 70.50, 68.43, 67.06, 65.71, 26.09, 25.94, 24.88, 24.52; IR (film, cm^{-1}) 3458, 3064, 3031, 2987, 2932, 1383, 1256, 1211, 1070; HRMS (ES) *m/z* calcd for $C_{39}H_{48}O_{11}$ $[M+Na]^+$ 715.3094, found 715.3124.

Thioethyl Glucose Sugar Silane and Ketosteroid Silyl-Linked (Scheme 2.11, compound 80)

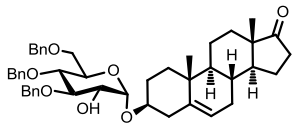


80

Following the general procedure **4.5**, silane (28 mg, 0.050 mmol), steroid (14 mg, 0.050 mmol), and $B(C_6F_5)_3$ (0.5 mg, 0.001 mmol) were stirred at room temperature overnight. The product (39mg, 0.046 mmol, 93%) was obtained as a colorless amorphous solid after purification by flash chromatography on SiO_2 (20% EtOAc/hex). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.24-7.40 (m, 13H), 7.08-7.12 (m, 2H), 5.32 (d, *J* = 4.5 Hz, 1H), 4.97 (d, *J* = 11.0 Hz, 1H), 4.89 (d, *J* = 11.0 Hz, 1H), 4.73 (d, *J* = 11.0 Hz, 1H), 4.61 (d, *J* = 12.0 Hz, 1H), 4.56 (d, *J* = 12.5 Hz, 1H), 4.53 (d, *J* = 10.5 Hz, 1H), 4.40 (d, *J* = 9.5 Hz, 1H), 3.66-3.78 (m, 4H), 3.61 (t, *J* = 9.0 Hz, 1H), 3.56 (t, *J* = 8.5 Hz, 1H), 3.50 (ddd, *J* = 9.5, 5.0, 2.0 Hz, 1H), 2.77 (dq, *J* = 13.0, 7.5 Hz, 1H), 2.72 (dq, *J* = 12.5, 7.5 Hz, 1H), 2.47 (dd, *J* = 19.5, 8.5 Hz, 1H), 2.29 (d, *J* = 7.5 Hz, 2H), 2.04-2.15 (m, 2H), 1.91-1.99 (m, 1H), 1.82-1.88 (m, 1H), 1.72-1.81 (m, 2H), 1.42-1.70 (m, 6H), 1.32 (t, *J* = 7.5 Hz, 3H), 1.22-1.35 (m, 3H), 0.92-1.05 (m, 1H), 0.99 (s, 3H), 0.89 (s, 3H), 0.22 (s, 3H), 0.19

(s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 221.2, 141.6, 138.8, 138.2, 137.9, 128.4, 128.3, 128.2, 128.0, 127.7, 127.6, 127.2, 127.1, 120.5, 87.0, 86.2, 79.1, 78.2, 75.1, 74.9, 74.5, 73.4, 72.0, 69.1, 51.8, 50.2, 47.5, 42.4, 37.2, 36.6, 35.8, 31.7, 31.5, 31.4, 30.8, 24.7, 21.9, 20.3, 19.4, 15.1, 13.5, -0.9, -1.2; IR (film, cm^{-1}) 3064, 3031, 2933, 2863, 1739, 1454, 1372, 1256, 1086, 1030; HRMS (ES) *m/z* calcd for $C_{50}H_{66}O_7SSi$ $[M+Na]^+$ 861.4191, found 861.4193.

Glucose and Ketosteroid Glycoside (Scheme 2.11, compound 81)

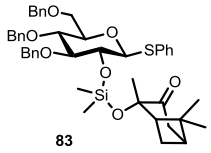


81

Following the general procedure **4.4**, compound **80** (38 mg, 0.045 mmol), NIS (14 mg, 0.063 mmol), TMSOTf (20 μL, 0.108 mmol), and 2,6-DTBMP (37 mg, 0.18 mmol) were stirred at -40 °C for 10 min, then warmed to 0 °C and stirred for 1 hour, then excess *n*-Bu_4NF (0.45 mL, 0.45 mmol) was added as a 1M solution in THF, warmed to rt and allowed to stir overnight. The product (31 mg, 0.043 mmol, 96%) was obtained as a foamy solid upon purification by flash chromatography on SiO_2 (30% EtOAc/hex). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38-7.42 (m, 2H), 7.26-7.37 (m, 11H), 7.15-7.18 (m, 2H), 5.34 (d, *J* = 5.0 Hz, 1H), 5.05 (d, *J* = 3.5 Hz, 1H), 4.98 (d, *J* = 11.0 Hz, 1H), 4.86 (d, *J* = 11.0 Hz, 1H) 4.84 (d, *J* = 10.5 Hz, 1H), 4.65 (d, *J* = 12.0 Hz, 1H), 4.51 (d, *J* = 12.0 Hz, 1H), 4.50 (d, *J* = 10.5 Hz, 1H), 3.91 (ddd, *J* = 11.5, 3.5, 2.0 Hz, 1H), 3.67-3.81 (m, 4H), 3.64 (t, *J* = 9.0 Hz, 1H), 3.54 (tt, *J* = 11.5, 5.0 Hz, 1H), 2.32- 2.52 (m, 3H), 2.04-2.18 (m, 3H), 1.83-2.00 (m, 4H), 1.44-1.72 (m, 6H), 1.22-1.34 (m, 3H), 0.97-1.11 (m, 1H), 1.04 (s, 3H), 0.90 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 221.0, 140.7, 138.8, 138.2, 138.0,

128.4, 128.3, 127.93, 127.86, 127.83, 127.7, 127.64, 127.58, 121.3, 96.9, 83.7, 77.6, 77.5, 75.3, 75.0, 73.5, 72.9, 70.6, 68.6, 51.8, 50.2, 47.5, 40.0, 36.9, 36.8, 35.8, 31.5, 31.4, 30.8, 27.9, 21.9, 20.3, 19.4, 13.5; IR (film, cm^{-1}) 3390, 3031, 2933, 2865, 1737, 1454, 1384, 1274, 1135, 1068, 1029; HRMS (ES) *m/z* calcd for $C_{46}H_{56}O_7$ $[M+Na]^+$ 743.3924, found 743.3928.

Thiophenyl Glucose Sugar Silane and Diterpene 82 Silyl-Linked (Scheme 2.12, compound 83)

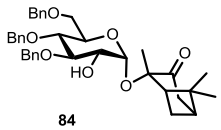


83

Following the general procedure **4.5**, silane (60 mg, 0.10 mmol), hydroxyl ketone **82** (17 mg, 0.10 mmol) and $B(C_6F_5)_3$ (1 mg, 0.002 mmol) were stirred for 80 min. at rt. The product (70 mg, 0.091 mmol, 91%) was obtained as a colorless oil upon purification by flash chromatography on SiO_2 (8% EtOAc/hex). ^1H NMR (500 MHz, $CDCl_3$) δ 7.53-7.56 (m, 2H), 7.21-7.36 (m, 16H), 7.08-7.13 (m, 2H), 4.95 (d, *J* = 11.5 Hz, 1H), 4.86 (d, *J* = 11.5 Hz, 1H), 4.73 (d, *J* = 11.0 Hz, 1H), 4.63 (d, *J* = 9.5 Hz, 1H), 4.59 (d, *J* = 12.0 Hz, 1H), 4.537 (d, *J* = 10.5 Hz, 1H), 4.536 (d, *J* = 11.5 Hz, 1H), 3.82 (t, *J* = 9.0 Hz, 1H), 3.78 (dd, *J* = 11.0, 1.5 Hz, 1H), 3.61 (t, *J* = 9.0 Hz, 1H), 3.57 (t, *J* = 8.5 Hz, 1H), 3.52 (ddd, *J* = 9.0, 5.0, 1.5 Hz, 1H), 2.55 (dt, *J* = 19.0, 3.0 Hz, 1H), 2.48 (dd, *J* = 19.0, 2.0 Hz, 1H), 2.32-2.38 (m, 1H), 2.14 (t, *J* = 6.5 Hz, 1H), 2.02-2.06 (m, 1H), 1.80 (d, *J* = 10.5 Hz, 1H), 1.43 (s, 3H), 1.31 (s, 3H), 0.83 (s, 3H), 0.28 (s, 3H), 0.12 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.8, 138.9, 138.3, 138.0, 134.7, 131.3, 128.8, 128.33, 128.31, 128.2, 128.0, 127.7, 127.5, 127.1, 127.0, 126.9, 89.0, 87.1, 80.2, 79.1, 78.1, 75.1, 74.9, 73.8,

73.4, 69.2, 51.7, 43.5, 38.9, 38.4, 29.0, 27.5, 25.1, 22.7, 1.2, 0.7; HRMS (ES) *m/z* calcd for $C_{45}H_{54}O_7SSi$ $[M+Na]^+$ 789.3252, found 789.3245.

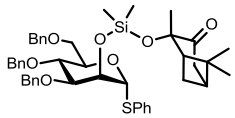
Glucose and Diterpene 82 Glycoside (Scheme 2.12, compound 84)



84

Following the general procedure **4.4**, compound **83** (58 mg, 0.076 mmol), NIS (24 mg, 0.106 mmol), TMSOTf (33 μL, 0.181 mmol), and 2,6-DTBMP (62 mg, 0.302 mmol) were stirred for 5 min at -40 °C, then warmed to 0 °C and stirred for 1 hour, then an excess of *n*-Bu_4NF (0.76 mL, 0.76 mmol) was added as a 1M solution in THF and allowed to stir overnight at rt. The product (44 mg, 0.073, 96%) was obtained as a viscous oil upon purification by flash chromatography on SiO_2 (20 to 30% EtOAc/hex). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25-7.39 (m, 13H), 7.16-7.19 (m, 2H), 5.27 (s, 1H), 4.91 (d, *J* = 11.0 Hz, 1H), 4.84 (d, *J* = 11.0 Hz, 1H), 4.82 (d, *J* = 10.5 Hz, 1H), 4.60 (d, *J* = 12.5 Hz, 1H), 4.51 (d, *J* = 10.5 Hz, 1H), 4.49 (d, *J* = 12.0 Hz, 1H), 3.98-4.02 (m, 2H), 3.63-3.72 (m, 4H), 3.52-3.57 (m, 1H), 2.69 (dd, *J* = 19.0, 1.5 Hz, 1H), 2.57 (dt, *J* = 19.0, 3.0 Hz, 1H), 2.40-2.47 (m, 1H), 2.28 (t, *J* = 6.0 Hz, 1H), 2.04-2.08 (m, 1H), 1.78-1.84 (m, 2H), 1.42 (s, 3H), 1.37 (s, 3H), 0.87 (s, 3H); ^{13}C NMR (100MHz, $CDCl^3$) δ 209.2, 138.7, 138.1, 138.0, 128.40, 128.39, 128.3, 127.9, 127.85, 127.84, 127.7, 127.64, 127.57, 92.8, 83.3, 81.8, 77.7, 75.3, 75.0, 73.5, 72.5, 71.4, 68.8, 49.9, 43.9, 39.2, 38.7, 28.8, 27.5, 22.7, 22.1; IR (film, cm^{-1}) 3443, 3064, 3031, 2925, 1722, 1453, 1273, 1070, 1027; HRMS (ES) *m/z* calcd for $C_{37}H_{44}O_7$ $[M+Na]^+$ 623.2985, found 623.2974.

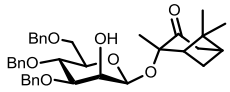
Thiophenyl Mannose Sugar Silane and Terpene 82 Silyl-Linked (Scheme 2.12, compound 85)



85

Following the general procedure **4.5**, silane (60 mg, 0.10 mmol), hydroxyketone **82** (17 mg, 0.10 mmol), and $B(C_6F_5)_3$ (1.0 mg, 0.002 mmol) were stirred at rt for 85 min. The product (62 mg, 0.081 mmol, 81%) was obtained as a colorless oil upon purification by flash chromatography on SiO_2 (8% EtOAc/hex). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.50-7.53 (m, 2H), 7.38-7.41 (m, 2H), 7.20-7.37 (m, 16H), 5.54 (s, 1H), 4.88 (d, *J* = 10.5 Hz, 1H), 4.76 (d, *J* = 11.5 Hz, 1H), 4.663 (d, *J* = 11.5 Hz, 1H), 4.661 (d, *J* = 9.5 Hz, 1H), 4.56 (d, *J* = 11.0 Hz, 1H), 4.50 (d, *J* = 12.0 Hz, 1H), 4.46 (s, 1H), 4.29 (dd, *J* = 10.0, 5.0 Hz, 1H), 3.99 (t, *J* = 9.5 Hz, 1H), 3.85 (dd, *J* = 11.0, 5.0 Hz, 1H), 3.79 (dd, *J* = 9.5, 3.0 Hz, 1H), 3.76 (d, *J* = 11.0 Hz, 1H), 2.46-2.56 (m, 2H), 2.20-2.26 (m, 1H), 2.04 (t, *J* = 6.0 Hz, 1H), 1.97-2.20 (m, 1H), 1.63 (d, *J* = 11.0 Hz, 1H), 1.40 (s, 3H), 1.27 (s, 3H), 0.81 (s, 3H), 0.22 (s, 3H), 0.13 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.9, 138.54, 138.47, 138.3, 134.8, 131.6, 128.9, 128.3, 128.2, 127.9, 127.8, 127.63, 127.56, 127.3, 127.2, 89.2, 80.3, 80.1, 75.0, 74.8, 73.1, 73.0, 72.0, 70.8, 69.3, 51.7, 43.4, 38.9, 28.9, 27.4, 25.2, 22.7, 0.29, 0.27; HRMS (ES) *m/z* calcd for $C_{45}H_{54}O_7SSi$ [M+Na]+ 789.3257, found 789.3282.

Mannose and Terpene 82 Glycoside (Scheme 2.12, compound 86)

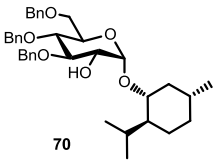


86

Following the general procedure **4.4**, compound **85** (53 mg, 0.069 mmol), NIS (22 mg, 0.097 mmol), TMSOTf (30 μL, 0.166 mmol), and 2,6-DTBMP (57 mg, 0.276 mmol) were stirred for 10 min at -40 °C, then warmed to 0 °C and stirred for 65 min, then an

excess of *n*-Bu_4NF (0.69 mL, 0.69 mmol) was added as a 1M solution in THF and allowed to stir overnight at rt. The product (29 mg, 0.048, 70%) was obtained as a colorless oil upon purification by flash chromatography on SiO_2 (20 to 30% EtOAc/hex). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25-7.39 (m, 13H), 7.20-7.23 (m, 2H), 4.96 (s, 1H), 4.89 (d, *J* = 11.0 Hz, 1H), 4.76 (d, *J* = 11.5 Hz, 1H), 4.63 (d, *J* = 11.5 Hz, 1H), 4.61 (d, *J*, = 12.5 Hz, 1H), 4.53 (d, *J* = 11.5 Hz, 2H), 3.93 (d, *J* = 2.5 Hz, 1H), 3.81 (t, *J* = 9.5 Hz, 1H), 3.73 (dd, *J* = 11.0, 2.0 Hz, 1H), 3.68 (dd, *J* = 10.5, 5.0 Hz, 1H), 3.59 (dd, *J* = 9.0, 3.0 Hz, 1H), 3.46 (ddd, *J* = 9.5, 5.0, 2.0 Hz, 1H), 2.57-2.67 (m, 2H), 2.40-2.47 (m, 1H), 2.36 (br s, 1H), 2.31 (t, *J* = 6.0 Hz, 1H), 2.10 (sept, *J* = 3.0 Hz, 1H), 1.85 (d, *J* = 11.0 Hz, 1H), 1.48 (s, 3H), 1.37 (s, 3H), 0.88 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.63, 138.39, 138.36, 137.84, 94.09, 82.01, 81.87, 75.04, 74.99, 74.09, 73.37, 71.41, 69.42, 69.23, 50.52, 43.60, 39.29, 38.49, 28.61, 27.32, 22.82, 20.58; IR (film, cm^{-1}) 3440, 3064, 3032, 2925, 1720, 1453, 1274, 1109, 1072, 1028; HRMS (ES) *m/z* calcd for $C_{37}H_{44}O_7$ $[M+Na]^+$ 623.2985, found 623.2979.

One Pot Procedure to make Glucose (-)-menthol glycoside (Scheme 2.13, compound 70)

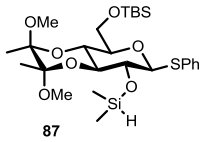


70

Following the general procedure **4.5**, silane (90 mg, 0.15 mmol), (-)-menthol (23 mg, 0.15 mmol), and $B(C_6F_5)_3$ (3 mg, 0.006 mmol) were stirred for 90 minutes at rt. The reaction was then cooled to -40 °C and diluted to 0.02M in dry CH_2Cl_2, NIS (44 mg, 0.20 mmol), and 2,6-DTBMP (62 mg, 0.30 mmol were added followed by TMSOTf (33 μL, 0.18 mmol), were stirred for 10 min at -40 °C, then warmed to 0 °C and stirred for 1 hr,

then an excess of *n*-Bu_4NF (0.75 mL, 0.75 mmol) was added as a 1M solution in THF and allowed to stir overnight at rt. The product (71 mg, 0.12 mmol, 70%) was obtained as a colorless oil upon purification by flash chromatography on SiO_2 (10 to 15% EtOAc/hex). All spectral data was identical to that reported for compound **70** when synthesized by the two-pot protocol.

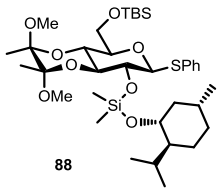
Sugar Silane 87 (Scheme 2.14, compound 87)



87

Following the general procedure **4.1**, 2-hydroxy sugar (0.58 g, 1.16 mmol), NEt_3 (323 μL, 2.32 mmol), and $Me_2Si(H)Cl$ (193 μL, 1.74 mmol) were stirred for 4 hours at 0 °C. The product (0.62 g, 1.11 mmol, 96%) was obtained as a red oil after aqueous work up. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.54-7.57 (m, 2H), 7.22-7.29 (m, 3H), 4.70 (sept, *J* = 2.0 Hz, 1H), 4.56 (d, *J* = 9.5 Hz, 1H), 3.86 (dd, *J* = 11.5, 2.0 Hz, 1H), 3.82 (dd, *J* = 11.5, 4.0 Hz, 1H) 3.72 (t, *J* = 9.5 Hz, 1H), 3.67 (t, *J* = 9.5 Hz, 1H), 3.59 (t, *J* = 9.0 Hz, 1H), 3.45 (ddd, *J* = 9.0, 3.5, 1.5 Hz, 1H), 3.28 (s, 3H), 3.27 (s, 3H), 1.31 (s, 3H), 1.30 (s, 3H), 0.91 (s, 9H), 0.27 (d, *J* = 2.5 Hz, 3H), 0.24 (d, *J* = 2.5 Hz, 3H), 0.93 (s, 3H), 0.57 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 133.94, 131.86, 128.71, 127.18, 99.69, 99.43, 89.09, 78.63, 74.51, 72.45, 64.92, 61.36, 48.03, 47.83, 25.90, 18.36, 17.65, 17.63, -0.45, -0.76, -5.06, -5.44; IR (film, cm^{-1}) 2992, 2954, 2930, 2857, 2131, 1472, 1375, 1252, 1139, 1113, 1075, 1042.

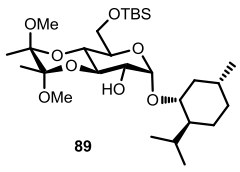
Sugar Silane 87 and (-)-Menthol Silyl-Linked (Scheme 2.14, compound 88)



88

Following the general procedure **4.6**, silane **87** (61 mg, 0.11 mmol), (-)-menthol (16 mg, 0.10 mmol), CuCl (0.5 mg, 0.005 mmol), IMes·HCl (1.7 mg, 0.005 mmol), and NaO-*t*-Bu (1 mg, 0.010 mmol) were stirred at rt for 1 hr. The product (72 mg, 0.010 mmol, 100%) was obtained as a colorless oil upon purification by flash chromatography on SiO_2 (5 to 8% EtOAc/hex). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.50-7.54 (m, 2H), 7.20-7.29 (m, 3H), 4.63 (d, *J* = 8.5 Hz, 1H), 3.87 (dd, *J* = 11.5, 1.5 Hz, 1H), 3.81 (dd, *J* = 11.5, 4.5 Hz, 1H), 3.66-3.75 (m, 3H), 3.62 (td, *J* = 10.5, 4.5 Hz, 1H), 3.46 (ddd, *J* = 9.0, 4.5, 2.0 Hz, 1H), 3.29 (s, 3H), 3.27 (s, 3H), 2.21 (septd, *J* = 7.5, 2.0 Hz, 1H), 2.03-2.09 (m, 1H), 1.54-1.64 (m, 2H), 1.24-1.36 (m, 1H), 1.31 (s, 3H), 1.30 (s, 3H), 1.15 (ddt, *J* = 12.0, 9.5, 2.5 Hz, 1H), 0.76-1.02 (m, 3H), 0.89 (s, 9H), 0.87 (d, *J* = 7.0 Hz, 3H), 0.83 (d, *J* = 6.5 Hz, 3H), 0.73 (d, *J* = 7.0 Hz, 3H), 0.21 (s, 3H), 0.20 (s, 3H), 0.08 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 134.80, 130.93, 128.68, 126.78, 99.65, 99.31, 89.23, 78.50, 74.48, 72.48, 70.67, 65.07, 61.49, 49.88, 48.02, 47.95, 45.16, 34.53, 31.64, 25.87, 25.08, 22.86, 22.15, 21.27, 18.32, 17.64, 17.49, 15.98, -0.32, -1.81, -5.06, -5.48; IR (film, cm^{-1} 2955, 2929, 2870, 1462, 1371, 1255, 1139, 1072, 1042.

Sugar Silane 87 and (-)-Menthol Glycoside (Scheme 2.14, compound 89)

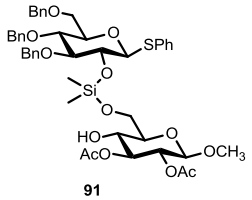


89

Following the general procedure **4.4**, compound **88** (67 mg, 0.094 mmol), NIS (27 mg, 0.122 mmol), TMSOTf (20 μL, 0.113 mmol), and 2,6-DTBMP (39 mg, 0.188 mmol)

were stirred for 10 min at -40 °C, then warmed to 0 °C and stirred for 65 min, then an excess of *n*-Bu_4NF (0.30 mL, 0.30 mmol) was added as a 1M solution in THF and allowed to stir overnight gradually warming to rt. The product (33 mg, 0.06, 60%) was obtained as a colorless oil upon purification by flash chromatography on SiO_2 (10 to 15% EtOAc/hex). ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.96 (d, *J* = 4.0 Hz, 1H), 3.76-3.89 (m, 4H), 3.61-3.68 (m, 3H), 3.40 (dt, *J* = 10.5, 4.0 Hz, 1H), 3.32 (s, 3H), 3.27 (s, 3H), 2.08-2.21 (m, 2H), 1.91 (d, *J* = 10.5 Hz, 1H), 1.56-1.67 (m, 2H), 1.34-1.42 (m, 1H), 1.36 (s, 3H), 1.24-1.32 (m, 1H), 1.31 (s, 3H), 0.76-1.05 (m, 6H), 0.91 (d, *J* = 7.0 Hz, 3H), 0.90 (d, *J* = 6.5 Hz, 3H), 0.89 (s, 9H), 0.79 (d, *J* = 7.0, 3H), 0.06 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 99.65, 99.60, 99.40, 80.59, 70.74, 70.68, 70.41, 65.68, 61.50, 48.76, 47.99, 47.94, 42.84, 34.21, 31.59, 25.93, 25.66, 22.96, 22.28, 21.14, 17.82, 17.70, 15.84, -5.09, -5.40; IR (film, cm^{-1}) 3490, 2954, 2930, 2871, 1638, 1458, 1376, 1252, 1138, 1035; HRMS (ES) *m/z* calcd for $C_{28}H_{40}O_8Si$ $[M+Na]^+$ 569.3480, found 569.3481.

Thiophenyl Glucose Sugar Silane and Diol 90 6-Hydroxy Silyl-Linked (Scheme 2.17, compound 91)

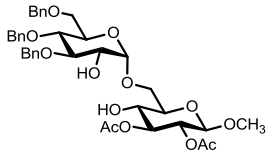


91

Diol **90** (28 mg, 0.10 mmol) was dissolved in a 2:1 mixture of dry CH_2Cl_2 and toluene (0.066M) to this was added $B(C_6F_5)_3$ (2.0 mg, 0.004 mmol) followed by dropwise addition of silane (78 mg, 0.13 mmol) over 20 min as a solution in 1.5 mL toluene, this was stirred at rt for 10 min. The product (76 mg, 0.087 mmol, 87%, 14:1 regioisomeric ratio) was obtained as a white foam upon purification by flash chromatography on SiO_2

(30 to 45% EtOAc/hex). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.57-7.61 (m, 2H), 7.26-7.40 (m, 16 H), 7.12-7.16 (m, 2H), 5.04 (t, *J* = 9.5 Hz, 1H), 4.96 (d, *J* = 11.5 Hz, 1H), 4.86-4.94 (m, 2H), 4.75 (d, *J* = 10.5 Hz, 1H), 4.54-4.68 (m, 4H), 4.35 (d, *J* = 7.5 Hz, 1H), 4.08 (dd, *J* = 11.5, 4.5 Hz, 1H), 4.00 (dd, *J* = 11.5, 4.0 Hz, 1H), 3.67-3.77 (m, 3H), 3.52-3.62 (m, 2H), 3.46 (s, 3H), 3.33 (dt, *J* = 9.5, 4.5 Hz, 1H), 2.81 (br s, 1H), 2.09 (s, 3H), 2.07 (s, 3H), 0.25 (s, 3H), 0.22 (s, 3H);

Glucose and Glucose Diol 90 6-Hydroxy Glycoside (Scheme 2.17, compound 92)

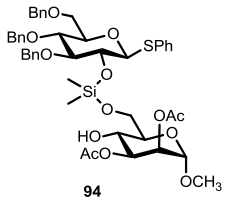


92

Following the general procedure **4.4**, compound **91** (49 mg, 0.056 mmol), NIS (18 mg, 0.078 mmol), TMSOTf (24 μL, 0.134 mmol), and 2,6-DTBMP (46 mg, 0.224 mmol) were stirred for 20 min at -40 °C, then warmed to 0 °C and stirred for 40 min, then an excess of *n*-Bu_4NF (0.56 mL, 0.56 mmol) was added as a 1M solution in THF and allowed to stir overnight at rt. The product (30 mg, 0.042, 75%) was obtained as a white foam upon purification by flash chromatography on SiO_2 (50 to 70% EtOAc/hex). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26-7.40 (m, 13H), 7.12-7.15 (m, 2H), 5.06 (t, *J* = 9.5 Hz, 1H), 4.90-4.96 (m, 3H), 4.86 (d, *J* = 11.0 Hz, 1H), 4.82 (d, *J* = 11.0 Hz, 1H), 4.61 (d, *J* = 12.0 Hz, 1H), 4.54 (d, *J* = 12.0 Hz, 1H), 4.49 (d, *J* = 11.0 Hz, 1H), 4.41 (d, *J* = 8.0 Hz, 1H), 4.10 (dd, *J* = 10.5, 4.0 Hz, 1H), 3.86 (ddd, *J* = 10.5, 5.0, 2.0 Hz, 1H), 3.71-3.81 (m, 4H), 3.69 (dd, *J* = 10.5, 2.0 Hz, 1H), 3.65 (dd, *J* = 10.5, 4.5 Hz, 1H), 3.50-3.59 (m, 3H), 2.55 (br s, 1H), 2.09 (s, 3H), 2.07 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.29, 169.67, 138.57, 137.93, 137.55, 128.43, 128.39, 127.93, 127.91, 127.86, 127.81, 127.79, 127.69,

101.69, 98.83, 83.27, 75.69, 75.39, 75.00, 74.14, 73.44, 72.85, 71.32, 71.01, 69.78, 68.45, 67.60, 57.03, 20.87, 20.76; IR (film, cm^{-1}) 3437, 3064, 3031, 2927, 1753, 1454, 1364, 1243, 1046; HRMS (ES) *m/z* calcd for $C_{38}H_{46}O_{13}$ $[M+Na]^+$ 733.2831, found 733.2830.

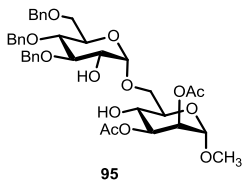
Thiophenyl Glucose Sugar Silane and Diol 93 6-Hydroxy Silyl-Linked (Scheme 2.18, compound 94)



94

Diol **93** (28 mg, 0.10 mmol) was dissolved in a 2:1 mixture of dry CH_2Cl_2 and toluene (0.066M) to this was added $B(C_6F_5)_3$ (2.0 mg, 0.004 mmol) followed by dropwise addition of silane (78 mg, 0.13 mmol) over 20 min as a solution in 1.5 mL toluene, this was stirred at rt for 10 min. The product (57 mg, 0.065 mmol, 65%) was obtained as a white foam upon purification by flash chromatography on SiO_2 (30 to 45% EtOAc/hex). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56-7.60 (m, 2H), 7.23-7.39 (m, 16H), 7.10-7.14 (m, 2H), 5.19-5.21 (m, 1H), 5.17 (dd, *J* =10.0, 3.5 Hz, 1H), 4.93 (s, 2H), 4.73 (d, *J* = 10.5 Hz, 1H) 4.52-4.66 (m, 5H), 4.12 (dd, *J* = 11.5, 4.0 Hz, 1H), 3.95-4.01 (m, 2H), 3.76-3.83 (m, 2H), 3.72 (dd, *J* = 11.0, 5.0 Hz, 1H), 3.68 (t, *J* = 9.0 Hz, 1H), 3.51-3.65 (m, 3H), 3.33 (s, 3H), 2.59 (br s, 1H), 2.07 (s, 6H), 0.26 (s, 3H), 0.21 (s, 3H);

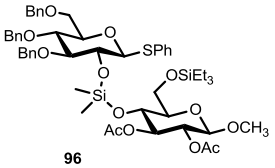
Glucose and Diol 93 6-Hydroxy Glycoside (Scheme 2.18, compound 95)



95

Following general procedure **4.4**, ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26-7.41 (m, 13H), 7.13-7.17 (m, 2H), 5.23 (dd, *J* = 3.0, 1.5 Hz, 1H), 5.19 (dd, *J* = 10.0, 3.5 Hz, 1H), 5.00 (d, *J* = 3.0 Hz, 1H), 4.95 (d, *J* = 11.0 Hz, 1H), 4.84 (d, *J* = 11.0 Hz, 1H), 4.83 (d, *J* = 10.5 Hz, 1H), 4.67 (d, *J* = 1.5 Hz, 1H), 4.63 (d, *J* = 12.0 Hz, 1H), 4.54 (d, *J* = 12.5 Hz, 1H), 4.50 (d, *J* = 10.5 Hz, 1H), 4.12-4.17 (m, 1H), 4.03 (t, *J* = 10.0 Hz, 1H), 3.59-3.92 (m, 8H), 3.59 (s, 3H), 2.59 (br s, 1H), 2.11 (s, 3H), 2.08 (s, 3H).

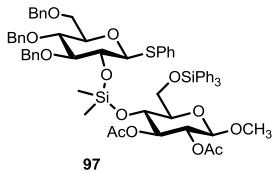
Thiophenyl Glucose Sugar Silane and Diol 90 (6-OSiEt$_3$) 4-Hydroxy Silyl-Linked (Scheme 2.19, compound 96)



96

Diol **90** (28 mg, 0.10 mmol) was dissolved in a 2:1 mixture of dry toluene and CH_2Cl_2 (0.066M) to this was added $B(C_6F_5)_3$ (2.0 mg, 0.004 mmol) and Et_3SiH (16 μL, 0.10 mmol) and allowed to stir for 3 hr 45 min followed by addition of silane (75 mg, 0.125 mmol) as a solution in 0.5 mL toluene, this was stirred at rt overnight. The product (42 mg, 0.042 mmol, 42%) was obtained as an off-white foam upon purification by flash chromatography on SiO_2 (20 to 30% EtOAc/hex). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.55-7.60 (m, 2H), 7.21-7.39 (m, 16H), 7.14-7.20 (m, 2H), 5.11 (t, *J* = 9.5 Hz, 1H), 4.74-4.87 (m, 4H), 4.52-4.63 (m, 4H), 4.29 (d, *J* = 8.0 Hz, 1H), 3.98 (t, *J* = 9.0 Hz, 1H), 3.93 (d, *J* = 11.5 Hz, 1H), 3.76-3.84 (m, 2H), 3.62-3.75 (m, 3H), 3.47-3.54 (m, 2H) 3.44 (s, 3H), 3.20 (dd, *J* = 9.5, 4.0 Hz, 1H), 2.07 (s, 3H), 2.05 (s, 3H), 0.95 (t, *J* = 7.5 Hz, 9H), 0.59 (q, *J* = 8.0 Hz, 6H), 0.23 (s, 3H), 0.09 (s, 3H).

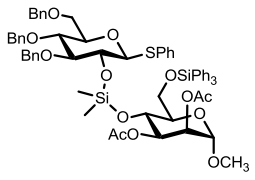
Thiophenyl Glucose Sugar Silane and Diol 90 (6-OSiPh$_3$) 4-Hydroxy Silyl-Linked (Scheme 2.20, compound 97)



97

Diol **90** (28 mg, 0.10 mmol) and Ph_3SiH (27 mg, 0.105 mmol) were dissolved in a 1:2 mixture of dry CH_2Cl_2 and toluene (0.066M) to this was added $B(C_6F_5)_3$ (4.0 mg, 0.008 mmol) and the reaction stirred at 75 °C for 90 min at which point the mixture was cooled to rt followed by dropwise addition of silane (78 mg, 0.13 mmol) over 10 min as a solution in 1 mL toluene, this was stirred at rt for 3.5 hr. The product (80 mg, 0.07 mmol, 70%) was obtained as a white foam upon purification by flash chromatography on SiO_2 (20 to 30% EtOAc/hex). ^1H NMR (500 MHz, $CDCl_3$) δ 7.61-7.64 (m, 6H), 7.51-7.54 (m, 2H), 7.37-7.42 (m, 2H), 7.25-7.36 (m, 18H), 7.15-7.22 (m, 6H), 5.09 (t, *J* = 9.5 Hz, 1H), 4.84 (dd, *J* = 9.5, 7.5 Hz, 1H), 4.68-4.76 (m, 3H), 4.60 (d, *J* = 12.0 Hz, 1H), 4.55 (d, *J* = 11.0 Hz, 1H), 4.53 (d, *J* = 12.5 Hz, 1H), 4.32 (d, *J* = 10.0 Hz, 1H), 4.27 (d, *J* = 8.0 Hz, 1H), 4.13 (dd, *J* = 11.0, 1.5 Hz, 1H), 4.05 (t, *J* = 9.5 Hz, 1H), 3.99 (dd, *J* = 11.5, 5.0 Hz, 1H), 3.77 (dd, *J* = 11.0, 2.0 Hz, 1H), 3.70 (dd, *J* = 11.0, 5.0 Hz, 1H), 3.54 (m, 2H), 3.39-3.44 (m, 1H), 3.40 (s, 3H), 3.24-3.32 (m, 2H), 2.06 (s, 3H), 2.04 (s, 3H), 0.15 (s, 3H), 0.02 (s, 3H).

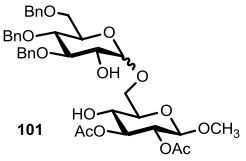
Thiophenyl Glucose Sugar Silane and Diol 93 (6-OSiEt$_3$) 4-Hydroxy Silyl-Linked (Scheme 2.21, compound 98)



98

Diol **93** (38 mg, 0.14 mmol) and Ph_3SiH (37 mg, 0.147 mmol) were dissolved in a 1:2 mixture of dry CH_2Cl_2 and toluene (0.066M) to this was added $B(C_6F_5)_3$ (5.5 mg, 0.011 mmol) and the reaction stirred at 75 °C for 70 min at which point the mixture was cooled to rt followed by dropwise addition of silane (112 mg, 0.19 mmol) over 10 min as a solution in 1.4 mL toluene, this was stirred at rt overnight. The product (114 mg, 0.10 mmol, 71%) was obtained as a white foam upon purification by flash chromatography on SiO_2 (15 to 20% EtOAc/hex). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.58-7.67 (m, 2H), 7.24-7.42 (m, 21H), 7.18-7.24 (m, 4H), 7.13-7.16 (m, 2H), 5.26 (dd, *J* = 3.5, 1.5 Hz, 1H), 5.21 (dd, *J* =10.0, 4.0 Hz, 1H), 4.77 (d, *J* = 11.0 Hz, 1H), 4.64 (m, 3H), 4.60 (d, *J* = 12.0 Hz, 1H), 4.52-4.57 (m, 2H), 4.39 (t, *J* = 9.5 Hz, 1H), 4.29 (d, *J* = 10.0 Hz, 1H), 4.16 (dd, *J* = 11.0, 1.5 Hz, 1H), 3.99 (dd, *J* = 11.0, 6.0 Hz, 1H), 3.77 (dd, *J* = 10.5, 1.5 Hz, 1H), 3.68-3.74 (m, 2H), 3.58 (td, *J* = 9.0, 3.5 Hz, 1H), 3.41 (ddd, *J* = 10.0, 4.5, 2.0 Hz, 1H), 3.28 (s, 3H), 3.24 (t, *J* = 8.5 Hz, 1H), 2.03 (s, 3H), 2.02 (s, 3H), 0.10 (s, 3H), 0.01 (s, 3H).

Thiophenyl Glucose Sugar Silane and Diol 90 (6-OBn) 4-Hydroxy Silyl-Linked (Scheme 2.23, compound 101)

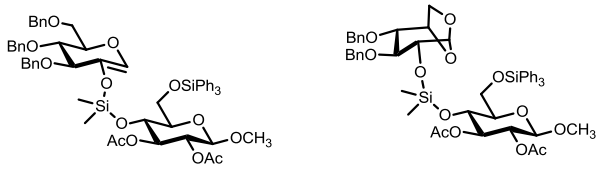


101

Following the general procedure **4.4**, compound **100** (53 mg, 0.055 mmol), NIS (16 mg, 0.071 mmol), TMSOTf (12 μL, 0.066 mmol), and 2,6-DTBMP (23 mg, 0.11 mmol) were stirred for 5 min at -40 °C, then warmed to 0 °C and stirred for 60 min, then an excess of *n*-Bu_4NF (0.28 mL, 0.28 mmol) was added as a 1M solution in THF and allowed to stir overnight gradually warming to rt. The product (30 mg, 0.042, 77%) was obtained as a foam upon purification by flash chromatography on SiO_2 (50 to 75%

EtOAc/hex). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26-7.40 (m, 13H), 7.14-7.20 (m, 2H), 5.07 (t, *J* = 9.0 Hz, 1H), 4.88-4.94 (m, 2H), 4.85 (d, *J* = 11.0 Hz, 1H), 4.82 (d, *J* = 11.0 Hz, 1H), 4.60 (d, *J* = 12.0 Hz, 1H), 4.54 (d, *J* = 12.0 Hz, 1H), 4.53 (d, *J* = 11.0 Hz, 1H), 4.10 (d, *J* = 8.0 Hz, 1h), 4.36-4.40 (m, 1H), 4.17 (dd, *J* = 11.5, 3.5 Hz, 1H), 3.94 (dd, *J* = 11.5, 5.0 Hz, 1H), 3.65-3.80 (m, 5H), 3.46-3.62 (m, 5H), 3.49 (s, 3H), 3.30 (d, *J* = 4.5 Hz, 1H), 2.07 (s, 3H), 2.06 (s, 3H).

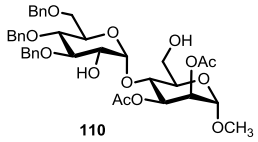
Thiophenyl Glucose Sugar Silane and Diol 90 (6-OSiPh$_3$) Glycosylation to Form 108 and 109 (Scheme 2.29, compounds 108 and 109)



Compound **97** (93 mg, 0.082 mmol), 2,6-DTBMP (34 mg, 0.164 mmol) were dissolved as a 0.02M solution in dry CH_2Cl_2 with and 3Å MS and cooled to -40 °C, $Me_2S_2{\cdot}Tf_2O$[47] (123 μL, 0.123 mmol) was added as a solution in CH_2Cl_2 and after 1 min, the reaction was warmed to 0 °C and stirred for 10 min when the reaction was quenched by an excess of NEt_3 (250 μL, 1.8 mmol). The products glucal **108** (32 mg, 0.031 mmol, 38%) and 1,6-*anhydro* **109** (31 mg, 0.026 mmol, 32%) were obtained upon purification by flash chromatography on SiO_2. **Compound 108** ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.62-7.70 (m, 6H), 7.16-7.47 (m, 24H), 6.27 (s, 3H), 5.10 (t, *J* = 9.5 Hz, 1h), 4.88 (dd, *J* = 9.5, 8.0 Hz, 1H), 4.67 (d, *J* = 11.0 Hz, 1H), 4.62 (d, *J* = 12.0 Hz, 1H), 4.59 (d, *J* = 12.0 Hz, 1H), 4.51-4.59 (m, 3H), 4.39 (d, *J* = 8.0 Hz, 1H), 3.94-4.11 (m, 5H), 3.86 (dd, *J* = 6.5, 4.5 Hz, 1H), 3.76 (dd, *J* = 10.5, 6.0 Hz, 1H), 3.66 (dd, *J* = 11.0, 4.0 Hz 1H), 3.37-3.45 (m, 1H), 3.42 (s, 3H), 2.06 (s, 3H), 2.03 (s, 3H), 0.11 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (100

MHz, $CDCl_3$) δ 107.13, 169.91, 138.28, 137.95, 135.45, 133.81, 132.61, 132.01, 130.03, 128.36, 128.33, 128.29, 127.83, 127.76, 127.73, 127.62, 127.60, 127.53, 101.23, 76.75, 76.36, 75.91, 75.30, 74.20, 73.40, 72.79, 72.28, 71.98, 69.15, 67.98, 62.45, 56.46, 20.91, -2.70, -2.78. **Compound 109** ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.60-7.68 (m, 2H), 7.22-7.47 (m, 24H), 5.25 (s, 1H), 5.09 (t, *J* = 9.5 Hz, 1H), 4.86 (dd, *J* = 9.5, 8.0 Hz, 1H), 4.50-4.58 (m, 4H), 4.38 (d, *J* = 8.0 Hz, 1H), 4.05 (t, *J* = 9.5 Hz, 2H), 3.97 (dd, *J* = 11.0, 4.0 Hz, 1H), 3.81 (d, *J* = 7.0 Hz, 1H), 3.65 (dd, *J* = 7.5, 5.5 Hz, 2H), 3.43-3.47 (m, 1H), 3.32-3.42 (m, 2H), 2.40 (s, 3H), 2.08 (s, 3H), 2.05 (s, 3H), 0.11 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.44, 169.94, 135.49, 133.84, 130.03, 128.42, 128.36, 127.82, 127.75, 127.67, 127.62, 102.61, 101.21, 79.41, 78.20, 76.32, 75.53, 74.58, 72.52, 72.04, 71.14, 68.90, 65.91, 62.43, 56.44, 21.02, 20.79, -2.14, -2.34.

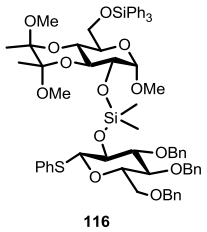
Thiophenyl Glucose Sugar Silane and Diol 93 4-Hydroxy Glycoside (Scheme 2.30, compound 110)



110

Following the general procedure **4.4**, compound **97** (111 mg, 0.098 mmol), NIS (29 mg, 0.127 mmol), TMSOTf (21 μL, 0.118 mmol), and 2,6-DTBMP (40 mg, 0.196 mmol) were stirred for 5 min at -40 °C, then warmed to 0 °C and stirred for 60 min, then an excess of *n*-Bu_4NF (0.49 mL, 0.49 mmol) was added as a 1M solution in THF and allowed to stir overnight at rt. The product (8 mg, 0.011, 11%) was obtained as a yellowish foam upon purification by flash chromatography on SiO_2 (50 to 80% EtOAc/hex). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.42 (dd, *J* = 9.5, 3.5 Hz, 1H), 5.20 (dd, *J* = 3.5, 2.0 Hz, 1H), 5.19 (d, *J* = 3.5 Hz, 1H, **glu α-anomer**), 4.69 (s, 1H, **man α-anomer**).

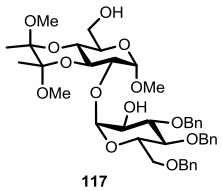
Thiophenyl Glucose Sugar Silane and Compound 114 Silyl-Linked (Scheme 2.33, compound 116)



116

Following the general procedure **4.5**, silane (45 mg, 0.08 mmol), alcohol **114** (39 mg, 0.07 mmol) and $B(C_6F_5)_3$ (1.5 mg, 0.003 mmol) were stirred for overnight at rt. The product (42 mg, 0.036 mmol, 51%) was obtained as a viscous oil upon purification by flash chromatography on SiO_2 (10 to 15% EtOAc/hex). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.62-7.66 (m, 6H), 7.56-7.60 (m, 2H), 7.22-7.44 (m, 22H), 7.14 (m, 3H), 7.09-7.12 (m, 2H), 4.92 (d, *J* = 12.0 Hz, 1H), 4.89 (d, *J* = 11.5 H, 1H), 4.85 (d, *J* = 3.5 Hz, 1H), 4.71 (d, *J* 10.5 Hz, 1H), 4.52-4.64 (m, 4H), 3.92-4.04 (m, 4H), 3.68-3.88 (m, 5H), 3.64 (t, *J* = 9.5 Hz, 1H), 3.51-3.58 (m, 2H), 3.28 (s, 3H), 3.22 (s, 3H), 3.08 (s, 3H), 1.23 (s, 3H), 1.22 (s, 3H), 0.22 (s, 3H), 0.20 (s, 3H).

Glucose and Compound 114 Glycoside (Scheme 2.33, compound 117)

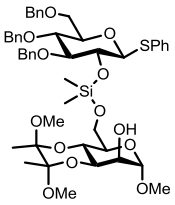


117

Following the general procedure **4.4**, compound **116** (42 mg, 0.036 mmol), NIS (11 mg, 0.047 mmol), TMSOTf (8 μL, 0.043 mmol), and 2,6-DTBMP (15 mg, 0.072 mmol) were stirred for 5 min at -40 °C, then warmed to 0 °C and stirred for 60 min, then an excess of *n*-Bu_4NF (0.29 mL, 0.29 mmol) was added as a 1M solution in THF and allowed to stir overnight at rt. The product (21 mg, 0.028, 79%) was obtained as a white

foam upon purification by flash chromatography on SiO_2 (60 to 75% EtOAc/hex). ^1H NMR (500 MHz, $CDCl_3$) δ 7.24-7.39 (m, 13H), 7.15-7.19 (m, 2H), 4.98 (d, *J* = 11.0 Hz, 1H), 4.98 (d, *J* = 4.0 Hz, 1H), 4.85(2H) (d, *J* = 11.0 Hz, 1H; d, *J* = 4.0 Hz, 1H), 4.80 (d, *J* = 11.0 Hz, 1H), 4.65 (d, *J* = 12.0 Hz, 1H), 4.54 (d, *J* = 11.5 Hz, 1H), 4.46 (d, *J* = 12.0 Hz, 1H), 4.16-4.22 (m, 1H), 4.05 (t, *J* = 9.5 Hz, 1H), 3.82-3.89 (m, 2H), 3.65-3.81 (m, 8H), 3.42 (s, 3H), 3.27 (s, 3H), 3.25 (s, 3H), 2.54 (br d, *J* = 6.0 Hz, 1H), 1.89 (br s, 1H), 1.30 (s, 3H), 1.25 (s, 3H).

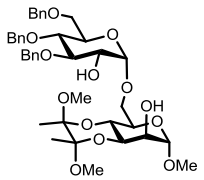
Thiophenyl Glucose Sugar Silane and Diol 118 6-Hydroxy Silyl-Linked (Scheme 2.34, compound 119)



119

Diol **118** (31 mg, 0.10 mmol) was dissolved in toluene (0.1M) to this was added $B(C_6F_5)_3$ (2.0 mg, 0.004 mmol) followed by dropwise addition of silane (78 mg, 0.13 mmol) over 5 min as a solution in 1.0 mL toluene, this was stirred at rt for 10 min. The product (45 mg, 0.05 mmol, 50%) was obtained as a white foam upon purification by flash chromatography on SiO_2 (30 to 45% EtOAc/hex). ^1H NMR (500 MHz, $CDCl_3$) δ 7.56-7.60 (m, 2H), 7.22-7.40 (m, 16H), 7.08-7.12 (m, 2H), 4.95 (d, *J* = 11.0 Hz, 1H), 4.89 (d, *J* = 11.5 Hz, 1H), 4.72 (d, *J* = 11.0 Hz, 1H), 4.68 (s, 1H), 4.51-4.66 (m, 4H), 3.84-4.10 (m, 5H), 3.49-3.80 (m, 7H), 3.30 (s, 3H), 3.27 (s, 3H), 3.19 (s, 3H), 2.35 (br s, 1H), 1.32 (s, 3H), 1.26 (s, 3H), 0.21 (s, 6H).

Glucose and Diol 118 6-Hydroxy Glycoside (Scheme 2.34, compound 120)



120

Following general procedure **4.4**, compound **119** (45mg, 0.05 mmol), NIS (16 mg, 0.07 mmol), TMSOTf (22 μL, 0.12 mmol), and 2,6-DTBMP (41 mg, 0.20 mmol) were stirred at -40 °C for 5 min then warmed to 0 °C and stirred for 2.5 h, then an excess of *n*-Bu_4NF (0.50 mL, 0.50 mmol) was added as a 1M solution in THF and allowed to stir overnight at rt. The product (25 mg, 0.034, 67%) was obtained as a white foam upon purification by flash chromatography on SiO_2 (60 to 75% EtOAc/hex). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37-7.40 (m, 2H), 7.25-7.36 (m, 11H), 7.13-7.17 (m, 2H), 5.07 (d, *J* = 2.5 Hz, 1H), 4.96 (d, *J* = 11.5 Hz, 1H), 4.84 (d, *J* = 11.0 Hz, 1H), 4.83 (d, *J* = 11.0 Hz, 1H), 4.72 (d, *J* = 1.0 Hz, 1H), 4.63 (d, *J* = 12.5 Hz, 1H), 4.51 (d, *J* = 12.5 Hz, 1H), 4.49 (d, *J* = 11.0 Hz, 1H), 4.16 (t, *J* = 10.0 Hz, 1H), 3.95-4.03 (m, 2H), 3.81-3.92 (m, 3H), 3.70-3.80 (m, 4H), 3.68 (dd, *J* = 11.0, 2.0 Hz, 1H), 3.59-3.66 (m, 1H), 3.35 (s, 3H), 3.28 (s, 3H), 3.24 (s, 3H), 2.52 (br s, 2H), 1.33 (s, 3H), 1.29 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.71, 138.36, 137.98, 128.35, 128.31, 128.00, 127.88, 127.77, 127.65, 127.59, 127.56, 100.96, 100.31, 99.93, 99.80, 83.13, 77.24, 75.10, 74.89, 73.47, 73.36, 70.72, 70.03, 69.58, 68.57, 67.95, 66.49, 63.03, 54.95, 48.07, 47.98, 17.72; IR (film, cm^{-1}) 3438, 3029, 2928, 1453, 1378, 1129, 1046 ; HRMS (ES) *m/z* calcd for $C_{40}H_{52}O13$ $[M+Na]^+$ 763.3300, found 763.3299.

4.3 Chapter 3 Experimental Procedures and Spectral Data

4.3.1 Chapter 3 Experimental Procedures

All reagents were used as received unless otherwise noted. Solvents were purified under nitrogen using a solvent purification system (Innovative Technology, inc., Model # SPS-400-3 and PS-400-3). $Ni(COD)_2$ (Strem Chemicals, Inc., used as received), and 1,3-dimesitylimidazolium chloride (IMes·HCl) were stored and weighed in an inert atmosphere glovebox. $Ti(O\text{-}i\text{-}Pr)_4$ and $Me_2Si(H)Cl$ were distilled and stored under inert atmosphere in Schlenk flasks. All nickel reactions were conducted in flame-dried glassware under a nitrogen atmosphere. ^1H and ^{13}C spectra were obtained in $CDCl_3$ at rt, unless otherwise noted, on a Varian Mercury 400 or Varian Unity 500 MHz instrument. Chemical shifts of ^1H NMR spectra were recorded in parts per million (ppm) on the δ scale from an internal standard of residual chloroform (7.27 ppm). Chemical shifts of ^{13}C NMR spectra were recorded in ppm from the central peak of $CDCl_3$ (77.0 ppm) on the δ scale. High resolution mass spectra (HRMS) were obtained on a VG-70-250-s spectrometer manufactured by Micromass Corp. (Manchester UK) at the University of Michigan Mass Spectrometry Laboratory.

General Procedure for Ni(0)-IMes Catalyzed Reductive Coupling of Aldehydes and Terminal Alkynes (General Procedure 4.7)

A solid mixture of $Ni(COD)_2$ (10%), IMes·HCl (10%), and KO-*t*-Bu (10%) was dissolved in dry THF (0.04M) at rt under an inert atmosphere (N_2), and stirred for 10-15 minutes until the catalyst mixture was a dark blue color. Sugar silane (1.1 equiv.), and aldehyde (1.0 equiv., freshly distilled) were added to the catalyst as a solution in dry THF (0.2M) at the same instance the first drop of alkyne (1.5 equiv., freshly distilled) was

added to the catalyst via syringe drive addition. The alkyne is added as a 0.6M solution in THF at a rate of 1 mL/50 min. Upon completion of the reaction, as monitored by TLC, the reaction mixture was filtered through a short plug of silica gel with a mixture of EtOAc/hexanes and concentrated by rotary evaporation. The resulting residue was purified via flash chromatography (SiO_2) to afford the desired product.

General Procedure for Ni(0)-IMes Catalyzed Reductive Coupling of Aldehydes and Internal Alkynes (General Procedure 4.8)

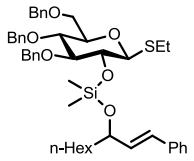
A solid mixture of $Ni(COD)_2$ (10%), IMes·HCl (10%), and KO-*t*-Bu (10%) was dissolved in dry THF (0.02M) at rt under an inert atmosphere (N_2), and stirred for 10-15 minutes until the catalyst mixture was a dark blue color. $Ti(O\textit{i}\text{-}Pr)_4$ (1.1 equiv.) was then added to the catalyst mixture followed by the cannula addition of the sugar silane (1.1 equiv.), and aldehyde (1.0 equiv, freshly distilled) and alkyne (1.2 equiv.) as a solution in dry THF (0.2M). Upon completion of the reaction, as monitored by TLC, the reaction mixture was filtered through a short plug of silica gel with a mixture of EtOAc/hexanes and concentrated by rotary evaporation. The resulting residue was purified via flash chromatography (SiO_2) to afford the desired product.

General Procedure for Radical Cation Glycosylation (General Procedure 4.9)

A solid mixture of $NaHCO_3$ (20 equiv.) and 4Å MS was stirred in dry acetonitrile (70% total solvent volume) for 15 min, radical cation **171** (1.5 equiv.) was then added followed by drop wise addition over 3-5 min of the silyl-linked compound (1.0 equiv.) as a 0.067M solution in dry acetonitrile. Upon completion of the reaction, as monitored by TLC, the reaction mixture was quenched with $n\text{Bu}_4\text{NF}$ (5.0 equiv.) as a 1M solution in THF. The reaction is then filtered through a short plug of silica gel with a mixture of

EtOAc/hexanes, and concentrated with SiO_2 added. The resulting solid mixture was purified via flash chromatography (SiO_2) to afford the desired product. Note – comparable yields were observed using 5.0 equiv. $NaHCO_3$.

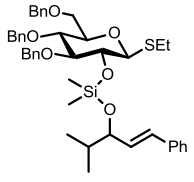
Reductive Coupling of Heptanal and Phenylacetylene (Scheme 3.10, compound 146)



146

Following the general procedure **4.8**, without Ti(O*i*Pr)$_4$, silane (330 mg, 0.55 mmol), heptanal (70 μL, 0.50 mmol), phenylacetylene (66 μL, 0.60 mmol), Ni(COD)$_2$ (14 mg, 0.05 mmol), IMes·HCl (17 mg, 0.05 mmol), and KO-*t*-Bu (6 mg, 0.05 mmol) were stirred overnight. The product (148 mg, 0.18 mmol, 36%, 1:1 dr) was obtained as a colorless oil after purification by flash chromatography on SiO_2 (5 to 10% EtOAc/Hex). ^{1}H NMR (500MHz, $CDCl_3$) δ 6.47 (d, *J* = 16.0 Hz, 0.5H), 6.44 (d, *J* = 16.5 Hz, 0.5H), 6.09-6.17 (m, 1H) (**diagnostic olefin protons**), 4.40 (d, *J* = 9.5 Hz, 0.5H), 4.38 (d, *J* = 9.5 Hz, 1H) (**diagnostic anomeric proton**).

Reductive Coupling of Isobutyraldehyde and Phenylacetylene (Scheme 3.10, compound 147)

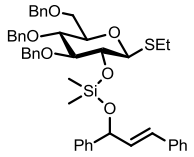


147

Following the general procedure **4.8**, without Ti(O*i*Pr)$_4$, silane (500 mg, 0.90 mmol), isobutyraldehyde (85 μL, 0.82 mmol), phenylacetylene (135 μL, 1.23 mmol), Ni(COD)$_2$ (23 mg, 0.08 mmol), IMes·HCl (28 mg, 0.08 mmol), and KO-*t*-Bu (9 mg, 0.08

mmol) were stirred overnight. The product (175 mg, 0.24 mmol, 30%, 1:1 dr) was obtained as a colorless oil after purification by flash chromatography on SiO_2 (10% EtOAc/Hex). ^{1}H NMR (400MHz, $CDCl_3$) δ 6.47 (d, *J* = 16.0 Hz, 0.5H), 6.45 (d, *J* = 16.0 Hz, 0.5H), 6.14 (dt, *J* = 16.0, 7.0 Hz, 1H) (**diagnostic olefinic protons**), 4.40 (d, *J* = 9.6 Hz, 0.5H), 4.37 (d, *J* = 9.6 Hz, 0.5H) (**diagnostic anomeric proton**).

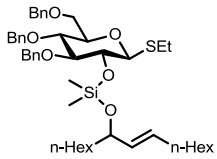
Reductive Coupling of Benzaldehyde and Phenylacetylene (Scheme 3.10, compound 148)



148

Following the general procedure **4.8**, without Ti(O*i*Pr)$_4$, silane (182 mg, 0.33 mmol), benzaldehyde (30 μL, 0.30 mmol), phenylacetylene (40 μL, 0.36 mmol), Ni(COD)$_2$ (8 mg, 0.03 mmol), IMes·HCl (10 mg, 0.03 mmol), and KO-*t*-Bu (3.4 mg, 0.03 mmol) were stirred overnight. The product (77 mg, 0.10 mmol, 34%, 1:1 dr) was obtained as a colorless oil after purification by flash chromatography on SiO_2 (5 to 10% EtOAc/Hex).

Reductive Coupling of Heptanal and 1-Octyne (Scheme 3.12, compound 152)

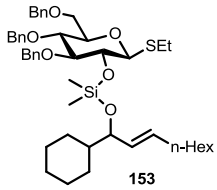


152

Following the general procedure **4.7**, silane (122 mg, 0.22 mmol), heptanal (28 μL, 0.20 mmol), 1-octyne (44 μL, 0.30 mmol), Ni(COD)$_2$ (5.5 mg, 0.02 mmol), IMes·HCl (7 mg, 0.02 mmol), and KO-*t*-Bu (2.2 mg, 0.02 mmol) were stirred for 2 hr

after completion of syringe drive. The product (115 mg, 0.15 mmol, 74%, 1:1 dr) was obtained as a colorless oil after purification by flash chromatography on SiO_2 (5 to 10% EtOAc/Hex). ^{1}H NMR (500MHz, $CDCl_3$) δ 7.24-7.39 (m, 13H), 7.09-7.14 (m, 2H), 5.44-5.55 (m, 1H), 5.30-5.40 (m, 1H), 5.00 (d, *J* = 11.5 Hz, 1H), 4.85 (d, *J* = 11.0 Hz, 0.5H), 4.84 (d, *J* = 11.0 Hz, 0.5H), 4.75 (d, *J* = 10.5 Hz, 0.5H), 4.74 (d, *J* = 10.5 Hz, 0.5 H), 4.50-4.63 (m, 3H), 4.35-4.42 (m, 1H), 4.20 (quint, *J* =7.0 Hz, 1H), 3.66-3.78 (m, 3H), 3.47-3.61 (m, 3H), 2.67-2.81 (m, 2H), 1.96 (q, *J* = 7.5 Hz, 1H), 1.47-1.58 (m, 2H), 1.16-1.45 (m, 19H), 0.86-0.91 (m, 6H), 0.19 (s, 3H), 0.17 (s, 1.5H), 0.16 (s, 1.5H).

Reductive Coupling of Cyclohexylacetylene and 1-Octyne (Scheme 3.12, compound 153)

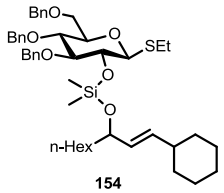


153

Following the general procedure **4.7**, silane (122 mg, 0.22 mmol), cyclohexylcarboxaldehyde (24 μL, 0.20 mmol), 1-octyne (44 μL, 0.30 mmol), $Ni(COD)_2$ (5.5 mg, 0.02 mmol), IMes·HCl (7 mg, 0.02 mmol), and KO-*t*-Bu (2.2 mg, 0.02 mmol) were stirred for 2 hr 15 min after completion of syringe drive. The product (133 mg, 0.17 mmol, 86%, 1:1 dr) was obtained as a colorless oil after purification by flash chromatography on SiO_2 (10% EtOAc/Hex). ^{1}H NMR (500MHz, $CDCl_3$) δ 7.23-7.40 (m, 13H), 7.08-7.12 (m, 2H), 5.41-5.55 (m, 1H), 5.30-5.38 (m, 1H), 5.02 (d, *J* = 11.5 Hz, 0.5H), 5.01 (d, *J* = 11.5 Hz, 0.5H), 4.82-4.88 (m, 1H), 4.74 (d, *J* = 10.5 Hz, 1H), 4.50-4.62 (m, 4H), 4.39 (d, *J* = 9.5 Hz, 0.5H), 4.36 (d, *J* = 9.5 Hz, 0.5 H), 3.93 (t, *J* = 7.0 Hz, 0.5H), 3.90 (t, *J* = 7.0 Hz, 0.5H), 3.66-3.78 (m, 3H), 3.46-3.61 (m, 3H), 2.67-2.80 (m,

2H), 1.94-2.02 (m, 2H), 1.81 (t, *J* = 11.5 Hz, 1H), 1.58-1.73 (m, 4H), 1.22-1.38 (m, 12H), 1.05-1.20 (m, 3H), 0.80-0.95 (m, 5H), 0.173 (s, 3H), 0.167 (s, 1.5H), 0.14 (s, 1.5H).

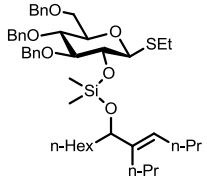
Reductive Coupling of Heptanal and Cyclohexylacetylene (Scheme 3.12, compound 154)



154

Following the general procedure **4.7**, silane (122 mg, 0.22 mmol), heptanal (28 μL, 0.20 mmol), cyclohexylacetylene (39 μL, 0.30 mmol), $Ni(COD)_2$ (5.5 mg, 0.02 mmol), IMes·HCl (7 mg, 0.02 mmol), and KO-*t*-Bu (2.2 mg, 0.02 mmol) were stirred for 2 hr after completion of syringe drive. The product (124 mg, 0.16 mmol, 80%, 1:1 dr) was obtained as a colorless oil after purification by flash chromatography on SiO_2 (5 to 10% EtOAc/Hex). ^{1}H NMR (500MHz, $CDCl_3$) δ 7.24-7.40 (m, 13H), 7.08-7.12 (m, 2H), 5.40-5.49 (m, 1H), 5.26-5.34 (m, 1H), 5.00 (d, *J* = 11.5Hz, 1H), 4.85 (d, *J* = 11.5 Hz, 0.5H), 4.84 (d, *J* = 11.0 Hz, 0.5H), 4.74 (d, *J* = 11.0 Hz, 1H), 4.50-4.62 (m, 3H), 4.39 (d, *J* = 9.5 Hz, 0.5H), 4.37 (d, *J* = 9.5 Hz, 0.5H), 4.14-4.22 (m, 1H), 3.66-3.78 (m, 3H), 3.46-3.61 (m, 3H), 2.67-2.81 (m, 2H), 1.86-1.94 (m, 1H), 1.60-1.74 (m, 4H), 1.46-1.56 (m, 2H), 0.98-1.42 (m, 16H), 0.85-0.90 (m, 3H), 0.183 (s, 1.5H), 0.180 (s, 1.5H), 0.17 (s, 1.5H), 0.15 (s, 1.5H).

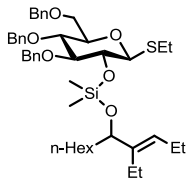
Reductive Coupling of Heptanal and 4-Octyne (Scheme 3.13, compound 155)



155

Following the general procedure **4.8**, silane (182 mg, 0.33 mmol), heptanal (42 μL, 0.30 mmol), 4-octyne (53 μL, 0.36 mmol), Ti(O*i*Pr)$_4$ (98 μL, 0.33 mmol), Ni(COD)$_2$ (8 mg, 0.03 mmol), IMes·HCl (10 mg, 0.03 mmol), and KO-*t*-Bu (3.4 mg, 0.03 mmol) were stirred overnight. The product (193 mg, 0.25 mmol, 83%, 1:1 dr) was obtained as a colorless oil after purification by flash chromatography on SiO_2 (5% EtOAc/Hex). ^{1}H NMR (500MHz, $CDCl_3$) δ 7.23-7.40 (m, 13H), 7.07-7.11 (m, 2H), 5.24-5.32 (m, 1H), 5.01 (d, *J* = 11.5 Hz, 0.5H), 5.00 (d, *J* = 11.5 Hz, 0.5H), 4.86 (d, *J* = 11.5 Hz, 0.5H), 4.85 (d, *J* = 11.5 Hz, 0.5H), 4.74 (d, *J* = 10.5 Hz, 0.5H), 4.73 (d, *J* = 10.5 Hz, 0.5H), 4.60 (d, *J* = 12.5 Hz, 1H), 4.56 (d, *J* = 12.0 Hz, 1H), 4.52 (d, *J* = 11.0 Hz, 0.5H), 4.51 (d, *J* = 11.0 Hz, 0.5H), 4.39 (d, *J* = 9.5 Hz, 0.5H), 4.37 (d, *J* = 9.5 Hz, 0.5H), 4.18 (t, *J* = 6.0 Hz, 0.5H), 4.14 (t, *J* = 5.5 Hz, 0.5H), 3.66-3.88 (m, 3H), 3.46-3.61 (m, 3H), 2.67-2.80 (m, 2H), 1.90-2.00 (m, 4H), 1.10-1.53 (m, 17H), 0.84-0.92 (m, 9H), 0.16 (s, 1.5H), 0.15 (s, 3H), 0.12 (s, 1.5H).

Reductive Coupling of Heptanal and 3-Hexyne (Scheme 3.13, compound 156)

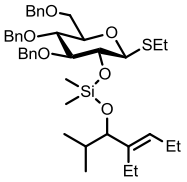


156

Following the general procedure **4.8**, silane (182 mg, 0.33 mmol), heptanal (42 μL, 0.30 mmol), 3-hexyne (41 μL, 0.36 mmol), Ti(O*i*Pr)$_4$ (98 μL, 0.33 mmol), Ni(COD)$_2$ (8 mg, 0.03 mmol), IMes·HCl (10 mg, 0.03 mmol), and KO-*t*-Bu (3.4 mg, 0.03 mmol) were stirred overnight. The product (195 mg, 0.26 mmol, 87%, 1:1 dr) was obtained as a colorless oil after purification by flash chromatography on SiO_2 (5% EtOAc/Hex). ^{1}H NMR (500MHz, $CDCl_3$) δ 7.23-7.40 (m, 13H), 7.08-7.12 (m, 2H), 5.26 (t, *J* = 7.5 Hz,

0.5H), 5.23 (t, *J* = 7.5 Hz, 0.5H), 5.01 (d, *J* = 11.0 Hz, 0.5H), 5.00 (d, *J* = 11.0 Hz, 0.5H), 4.86 (d, *J* = 11.0 Hz, 0.5H), 4.85 (d, *J* =11.5 Hz, 0.5H), 4.75 (d, *J* = 10.5 Hz, 0.5H), 4.74 (d, *J* = 10.5 Hz, 0.5H), 4.61 (d, *J* =12.5 Hz, 1H), 4.50-4.58 (m, 2H), 4.39 (d, *J* = 9.5 Hz, 0.5H), 4.37 (d, *J* = 10.0 Hz, 0.5H). 4.12-4.19 (m, 1H), 3.66-3.78 (m, 3H), 3.47-3.62 (m, 3H), 1.94-2.05 (m, 4H), 1.42-1.54 (m, 2H), 1.10-1.34 (m, 11H), 0.84-1.00 (m, 9H), 0.16 (s, 1.5H), 0.153 (s, 1.5H), 0.147 (s, 1.5H), 0.13 (s, 1.5H).

Reductive Coupling of Isobutyraldehyde and 3-Hexyne (Scheme 3.13, compound 157)

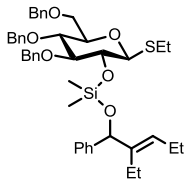


157

Following the general procedure **4.8**, silane (365 mg, 0.66 mmol), isobutyraldehyde (55 μL, 0.60 mmol), 3-hexyne (82 μL, 0.72 mmol), Ti(O*i*Pr)$_4$ (195 μL, 0.66 mmol), Ni(COD)$_2$ (17 mg, 0.06 mmol), IMes·HCl (20 mg, 0.06 mmol), and KO-*t*-Bu (7 mg, 0.06 mmol) were stirred overnight. The product (316 mg, 0.45 mmol, 75%, 1:1 dr) was obtained as a colorless oil after purification by flash chromatography on SiO_2 (5 to 10% EtOAc/Hex). ^{1}H NMR (500MHz, $CDCl_3$) δ 7.23-7.40 (m, 13H), 7.08-7.12 (m, 2H), 5.23 (q, *J* = 6.0 Hz, 1H), 5.03 (d, *J* = 11.0 Hz, 0.5H), 5.01 (d, *J* = 11.5 Hz, 0.5H), 4.87 (d, *J* = 11.5 Hz, 0.5H), 4.86 (d, *J* = 11.5 Hz, 0.5H), 4.74 (d, *J* = 10.5 Hz, 0.5H), 4.73 (d, *J* = 11.0 Hz, 0.5H), 4.61 (d, *J* = 12.5 Hz, 1H), 4.56 (d, *J* = 12.5 Hz, 1H), 4.53 (d, *J* = 11.0 Hz, 0.5H), 4.52 (d, *J* = 10.5 Hz, 0.5H), 4.37 (q, *J* = 9.0 Hz, 1H), 3.66-3.81 (m, 4H), 3.46-3.62 (m, 3H), 2.67-2.80 (m, 2H), 1.94-2.06 (m, 4H), 1.66-1.76 (m, 1H), 1.29-1.34

(m, 3H), 0.88-1.01 (m, 8H), 0.77 (t, *J* = 7.0 Hz, 3H), 0.16 (s, 1.5H), 0.15 (s, 1.5H), 0.14 (s, 1.5H), 0.11 (s, 1.5H).

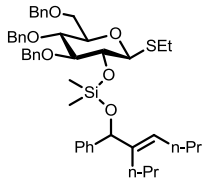
Reductive Coupling of Benzaldehyde and 3-Hexyne (Scheme 3.13, compound 158)



158

Following the general procedure **4.8**, silane (365 mg, 0.66 mmol), benzraldehyde (61 μL, 0.60 mmol), 3-hexyne (82 μL, 0.72 mmol), Ti(O*i*Pr)$_4$ (195 μL, 0.66 mmol), Ni(COD)$_2$ (17 mg, 0.06 mmol), IMes·HCl (20 mg, 0.06 mmol), and KO-*t*-Bu (7 mg, 0.06 mmol) were stirred overnight. The product (407 mg, 0.55 mmol, 92%, 1:1 dr) was obtained as a colorless oil after purification by flash chromatography on SiO_2 (5 to 10% EtOAc/Hex). ^{1}H NMR (500MHz, $CDCl_3$) δ 7.15-7.37 (m, 18H), 7.07-7.11 (m, 2H), 5.51 (q, *J* = 7.5 Hz, 1H), 5.35 (d, *J* = 11.5 Hz, 1H), 4.81-4.94 (m, 2H), 4.69-4.75 (m, 1H), 4.50-4.62 (m, 3H), 4.37 (d, *J* = 9.5 Hz, 0.5H), 4.34 (d, *J* = 9.5 Hz, 0.5H), 3.65-3.78 (m, 3H), 3.44-3.61 (m, 3H), 2.60-2.78 (m, 2H), 1.99-2.10 (m, 3H), 1.79-1.96 (m, 2H), 1.24-1.29 (m, 4H), 0.99 (t, *J* = 7.0 Hz, 1.5H), 0.98 (t, *J* = 7.0 Hz, 1.5H), 0.71 (t, *J* = 7.5 Hz, 1.5H), 0.70 (t, *J* = 7.5 Hz, 1.5H), 0.171 (s, 1.5H), 0.166 (s, 3H), 0.12 (s, 3H).

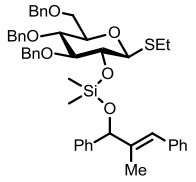
Reductive Coupling of Benzaldehyde and 4-Octyne (Scheme 3.13, compound 159)



159

Following the general procedure **4.8**, silane (182 mg, 0.33 mmol), benzaldehyde (30 μL, 0.30 mmol), 4-octyne (53 μL, 0.36 mmol), Ti(O*i*Pr)$_4$ (98 μL, 0.33 mmol), Ni(COD)$_2$ (8 mg, 0.03 mmol), IMes·HCl (10 mg, 0.03 mmol), and KO-*t*-Bu (3.4 mg, 0.03 mmol) were stirred overnight. The product (173 mg, 0.22 mmol, 75%, 1:1 dr) was obtained as a faint pink oil after purification by flash chromatography on SiO_2 (5 to 10% EtOAc/Hex). ^{1}H NMR (500MHz, $CDCl_3$) δ 7.14-7.36 (m, 18H), 7.06-7.10 (m, 2H), 5.54-5.58 (m, 1H), 5.34 (d, *J* = 14.0 Hz, 1H), 4.80-4.93 (m, 2H), 4.72 (t, *J* = 11.5 Hz, 1H), 4.49-4.69 (m, 3H), 4.36 (d, *J* = 9.5 Hz, 0.5H), 4.33 (d, *J* = 10.0 Hz, 0.5 H), 3.64-3.77 (m, 3H), 3.44-3.61 (m, 3H), 2.59-2.76 (m, 2H), 1.74-2.04 (m, 2H), 1.72-1.90 (m, 2H), 1.35-1.44 (m, 2H), 1.23-1.29 (m, 4H), 1.12-1.22 (m, 1H), 0.99-1.09 (m, 1H), 0.88-0.94 (m, 3H), 0.72-0.77 (m, 3H), 0.163 (s, 3H), 0.157 (s, 1.5H), 0.11 (s, 1.5H).

Reductive Coupling of Benzaldehyde and 1-Phenyl-1-propyne (Scheme 3.13, compound 160)

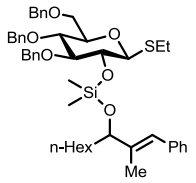


160

Following the general procedure **4.8**, silane (182 mg, 0.33 mmol), benzaldehyde (30 μL, 0.30 mmol), 1-phenyl-1-propyne (45 μL, 0.36 mmol), Ti(O*i*Pr)$_4$ (98 μL, 0.33 mmol), Ni(COD)$_2$ (8 mg, 0.03 mmol), IMes·HCl (10 mg, 0.03 mmol), and KO-*t*-Bu (3.4 mg, 0.03 mmol) were stirred overnight. The product (149 mg, 0.19 mmol, 64%, 1:1 dr, 95:5 regioselectivity) was obtained as a colorless oil after purification by flash chromatography on SiO_2 (5 to 15% EtOAc/Hex). ^{1}H NMR (300MHz, $CDCl_3$) δ 6.69 (br

s, 1H) (**diagnostic olefin proton**), 4.39 (d, *J* = 9.3 Hz, 0.5H), 4.37 (d, *J* = 9.3 Hz, 0.5H) (**diagnostic anomeric proton**).

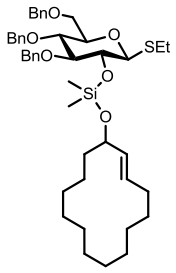
Reductive Coupling of Heptanal and 1-Phenyl-1-propyne (Scheme 3.13, compound 161)



161

Following the general procedure **4.8**, silane (122 mg, 0.22 mmol), heptanal (28 μL, 0.20 mmol), 1-phenyl-1-propyne (30 μL, 0.24 mmol), Ti(O*i*Pr)$_4$ (65 μL, 0.22 mmol), Ni(COD)$_2$ (5.5 mg, 0.02 mmol), IMes·HCl (7 mg, 0.02 mmol), and KO-*t*-Bu (2.2 mg, 0.02 mmol) were stirred overnight. The product (155 mg, 0.20 mmol, 99%, 1:1 dr, 93:7 regioselectivity) was obtained as a colorless oil after purification by flash chromatography on SiO_2 (5 to 10% EtOAc/Hex). ^{1}H NMR (500MHz, $CDCl_3$) δ (**major regioisomer**) 7.15-7.40 (m, 18H), 7.06-7.12 (m, 2H), 6.41 (s, 0.5H), 6.37 (s, 0.5H), 4.97-5.02 (m, 1H), 4.85-4.90 (m, 1H), 4.73 (t, *J* = 10.0 Hz, 1H), 4.48-4.62 (m, 3H), 4.40 (t, *J* = 9.5 Hz, 1H), 4.34 (t, *J* = 7.0 Hz, 0.5H), 4.31 (t, *J* = 7.0 Hz, 0.5H), 3.64-3.80 (m, 3H), 3.47-3.62 (m, 3H), 2.68-2.81 (m, 2H), 1.789 (d, *J* = 13.0 Hz, 1.5H), 1.786 (d, *J* = 13.0 Hz, 1.5H), 1.50-1.66 (m, 2H), 1.20-1.35 (m, 11H), 0.85-0.91 (m, 3H), 0.22 (s, 1.5H), 0.204 (s, 1.5H), 0.199 (s, 1.5H), 0.17 (s, 1.5H). (**diagnostic olefin proton for minor regioisomer**) 5.72-5.81 (m, 0.04H).

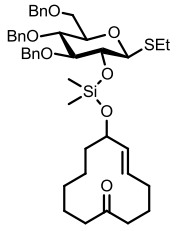
Macrocyclization of 14-Membered Ynal 136 (Scheme 3.14, compound 163)



163

Following general procedure,[56] silane (199 mg, 0.36 mmol), ynal (63 mg, 0.30 mmol), $Ni(COD)_2$ (17 mg, 0.06 mmol), IMes·HCl (20 mg, 0.06 mmol), and KO-*t*-Bu (7 mg, 0.06 mmol) were stirred for 13.5 hr. The product (114 mg, 0.015 mmol, 50%) was obtained as a colorless oil after purification by flash chromatography on SiO_2 (5 to 15% EtOAc/hex). ^{1}H NMR (500MHz, $CDCl_3$) δ 7.23-7.40 (m, 13H), 7.08-7.13 (m, 2H), 5.24-5.44 (m, 2H), 4.994 (d, *J* = 11.5 Hz, 0.5H), 4.988 (d, *J* = 11.5 Hz, 0.5H), 4.87 (d, *J* = 11.0 Hz, 0.5H), 4.86 (d, *J* = 11.0 Hz, 0.5H), 4.75 (d, *J* = 11.0 Hz, 0.5H), 4.74 (d, *J* = 11.0 Hz, 0.5H), 4.50-4.63 (m, 3H), 4.40 (d, *J* = 9.5 Hz, 0.5H), 4.38 (d, *J* = 9.5 Hz, 0.5H), 4.21-4.27 (m, 1H), 3.66-3.78 (m, 3H), 3.47-3.62 (m, 3H), 2.67-2.81 (m, 2H), 2.10-2.17 (m, 1H), 1.87-1.97 (m, 1H), 1.10-1.47 (m, 23H), 0.19 (s, 3H), 0.174 (s, 1.5H), 0.165 (s, 1.5H).

Macrocyclization Ynal 164 (Scheme 3.14, compound 165)

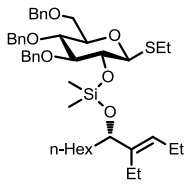


165

Following the general procedure,[56] silane (194 mg, 0.36 mmol), ynal **164** (58 mg, 0.30 mmol), 3-hexyne (41 μL, 0.36 mmol), $Ni(COD)_2$ (17 mg, 0.06 mmol), IMes·HCl (20 mg, 0.06 mmol), and KO-*t*-Bu (7 mg, 0.06 mmol) were stirred overnight at rt. The product (18 mg, 0.02 mmol, 8%, 1:1 dr) was obtained as a colorless oil after several

purifications by flash chromatography on SiO_2 (10 to 20% EtOAc/Hex). ^{1}H NMR (500MHz, $CDCl_3$) δ 5.16-5.36 (m, 2H) (**diagnostic olefin protons**), 4.38 (d, *J* = 9.0 Hz, 0.5H), 4.37 (d, *J* = 9.5 Hz, 0.5H) (**diagnostic anomeric proton**).

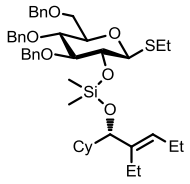
Asymmetric Reductive Coupling of Heptanal and 3-Hexyne (Scheme 3.15, compound 166)



166

Following the general procedure **4.8**, silane (122 mg, 0.22 mmol), heptanal (28 μL, 0.20 mmol), 3-hexyne (27 μL, 0.24 mmol), Ti(O*i*Pr)$_4$ (65 μL, 0.22 mmol), Ni(COD)$_2$ (5.5 mg, 0.02 mmol), **54**·HBF$_4$ (16 mg, 0.02 mmol), and KO-*t*-Bu (2.2 mg, 0.02 mmol) were stirred overnight. The product (140 mg, 0.19 mmol, 93%, 3:1 dr) was obtained as a colorless oil after purification by flash chromatography on SiO_2 (7.5 to 10% EtOAc/Hex). ^{1}H NMR (500MHz, $CDCl_3$) δ 5.26 (t, *J* = 7.0 Hz, 0.75 H), 5.22 (t, *J* = 7.5 Hz, 0.25H) (**diagnostic olefin proton**) all other spectral data matched that of the non-selective reaction to produce **156**.

Asymmetric Reductive Coupling of Cyclohexylcarboxaldehyde and 3-Hexyne (Scheme 3.15, compound 167)

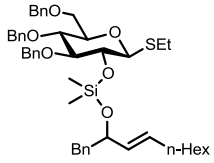


167

Following the general procedure **4.8**, silane (61 mg, 0.11 mmol), cyclohexylcarboxaldehyde (12 μL, 0.10 mmol), 3-hexyne (14 μL, 0.12 mmol), Ti(O*i*Pr)$_4$

(33 μL, 0.11 mmol), $Ni(COD)_2$ (3 mg, 0.01 mmol), **54**·HBF_4 (8 mg, 0.01 mmol), and KO-*t*-Bu (1 mg, 0.01 mmol) were stirred overnight. The product (57 mg, 0.07 mmol, 76%, ~5.3:1 dr) was obtained as a colorless oil after purification by flash chromatography on SiO_2 (5 to 8% EtOAc/Hex). ^{1}H NMR (500MHz, $CDCl_3$) δ (**major diastereomer**) 7.23-7.40 (m, 13H), 7.07-7.10 (m, 2H), 5.17 (t, *J* = 7.5 Hz, 1H), 5.03 (d, *J* = 11.5 Hz, 1H), 4.85 (d, *J* = 11.5 Hz, 1H), 4.73 (d, *J* = 11.0 Hz, 1H), 4.60 (d, *J* = 12.5 Hz, 1H), 4.55 (d, *J* = 12.5 Hz, 1H), 4.52 (d, *J* = 10.5 Hz, 1H), 4.36 (d, *J* = 9.5 Hz, 1H), 3.71-3.77 (m, 2H), 3.68 (dd, *J* = 11.0, 4.5 Hz, 1H), 3.47-3.61 (m, 3H), 2.67-2.80 (m, 2H), 1.92-2.08 (m, 5H), 1.58-1.74 (m, 3H), 1.42-1.48 (m, 1H), 1.25-1.40 (m, 4H), 1.03-1.20 (m, 3H), 0.99 (t, *J* = 8.0 Hz, 3H), 0.95 (t, *J* = 7.0 Hz, 3H), 0.77-0.90 (m, 2H), 0.14 (s, 3H), 0.13 (s, 3H), (**diagnostic peak for minor diastereomer**) 4.39 (d, *J* = 10.0 Hz, 0.19 H).

Thioethyl Glucose Sugar Silane and Allylic Alcohol 173 Silyl-Linked (Scheme 3.20, compound 174)

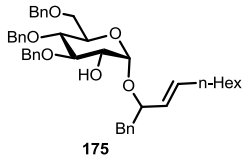


174

Following the general procedure **4.6**, silane (427 mg, 0.77 mmol), alcohol **173** (143 mg, 0.70 mmol), CuCl (3.5 mg, 0.035 mmol), IMes·HCl (12 mg, 0.035 mmol), and NaO-*t*-Bu (7 mg, 0.07 mmol) were stirred at rt overnight. The product (400 mg, 0.53 mmol, 76%) was obtained as a colorless oil upon purification by flash chromatography on SiO_2 (10% EtOAc/hex). ^{1}H NMR (500MHz, $CDCl_3$) δ 7.21-7.40 (m, 15H), 7.08-7.18 (m, 5H), 5.36-5.51 (m, 2H), 4.97 (d, *J* = 11.0 Hz, 0.5H), 4.93 (d, *J* = 11.5 Hz, 0.5H), 4.85 (d, *J* = 11.5 Hz, 1H), 4.75 (d, *J* = 11.0 Hz, 0.5H), 4.73 (d, *J* = 10.5 Hz, 0.5H), 4.51-4.63

(m, 3H), 4.40-4.47 (m, 1H), 4.343 (d, *J* = 9.5 Hz, 0.5H), 4.340 (d, *J* = 9.5 Hz, 0.5H), 3.73-3.38 (m, 1H), 3.63-3.71 (m, 2H), 3.46-3.60 (m, 3H), 2.64-2.88 (m, 4H), 1.88-1.98 (m, 2H), 1.19-1.33 (m, 7H), 0.84-0.88 (m, 3H), 0.07 (s, 1.5H), 0.06 (s, 1.5H), 0.03 (s, 1.5H), 0.01 (s, 1.5H).

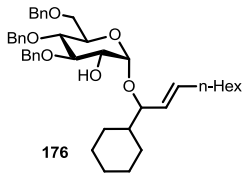
Compound 174 Glycoside (Table 3.3, entry 9, compound 175)



175

Following the general procedure **4.9**, silyl-linked compound **174** (78 mg, 0.10 mmol), radical cation **171** (127 mg, 0.15 mmol), $NaHCO_3$ (173 mg, 2.06 mmol) were stirred at rt for 30 min. *n*Bu_4NF (0.50 mL, 0.50 mmol) was added as a 1M solution in THF and the reaction was allowed to stir overnight. The product (46 mg, 0.07 mmol, 70%) was obtained as an oil upon purification by flash chromatography on SiO_2 (10 to 20% EtOAc/hex). ^{1}H NMR (500MHz, $CDCl_3$) δ (**more polar diastereomer**) 7.36-7.40 (m, 2H), 7.19-7.35 (m, 16H), 7.12-7.16 (m, 2H), 5.61 (dt, *J* = 15.5, 6.5 Hz, 1H), 5.48 (dd, *J* = 15.5, 8.0 Hz, 1H), 4.91 (d, *J* = 11.0 Hz, 1H), 4.81 (d, *J* = 10.5 Hz, 1H), 4.79 (d, *J* = 3.5 Hz, 1H), 4.77 (d, *J* = 11.0 Hz, 1H), 4.63 (d, *J* = 12.0 Hz, 1H), 4.47 (d, *J* = 12.0 Hz, 1H), 4.46 (d, *J* = 10.5 Hz, 1H), 4.15-4.21 (m, 1H), 3.84 (d, *J* = 9.0 Hz, 1H), 3.74 (dd, *J* = 10.5, 3.0 Hz, 1H), 3.52-3.67 (m, 4H), 2.82-2.89 (m, 2H), 1.92-2.02 (m, 2H), 1.42 (d, *J* = 10.5 Hz, 1H), 1.22-1.35 (m, 4H), 0.88 (t, *J* = 7.0 Hz, 3H).

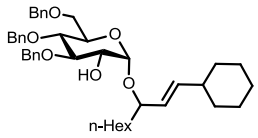
Glycoside of Reductive Coupling Product From Cyclohexylcarboxaldehyde and 1-Octyne (Scheme 3.23, compound 176)



176

Following the general procedure **4.9**, silyl-linked compound **153** (100 mg, 0.11 mmol), radical cation **171** (159 mg, 0.20 mmol), $NaHCO_3$ (108 mg, 1.29 mmol) were stirred at rt for 15 min. *n*Bu_4NF (0.65 mL, 0.65 mmol) was added as a 1M solution in THF and the reaction was allowed to stir overnight. The product (43 mg, 0.065 mmol, 50%) was obtained as an oil upon purification by flash chromatography on SiO_2 (8 to 12% EtOAc/hex).

Glycoside of Reductive Coupling Product From Heptanal and Cyclohexylacetylene (Scheme 3.23, compound 177)

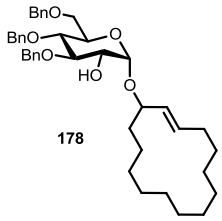


177

Following the general procedure **4.9**, silyl-linked compound **154** (100 mg, 0.13 mmol), radical cation **171** (159 mg, 0.20 mmol), $NaHCO_3$ (218 mg, 2.60 mmol) were stirred at rt for 2 hr. *n*Bu_4NF (0.65 mL, 0.65 mmol) was added as a 1M solution in THF and the reaction was allowed to stir overnight. The product (39 mg, 0.06 mmol, 46%) was obtained as an oil upon purification by flash chromatography on SiO_2 (10% EtOAc/hex). ^{1}H NMR (500MHz, $CDCl_3$) δ (**more polar diastereomer**) 7.39-7.42 (m, 2H), 7.25-7.36 (m, 11H), 7.14-7.18 (m, 2H), 5.54 (dd, *J* = 16.0, 7.0 Hz, 1H), 5.33 (dd, *J* = 15.5, 8.0 Hz, 1H), 5.00 (d, *J* = 3.0 Hz, 1H), 4.97 (d, *J* = 11.5 Hz, 1H), 4.85 (d, *J* = 11.0 Hz, 1H), 4.83 (d, *J* = 10.5 Hz, 1H), 4.64 (d, *J* = 12.5 Hz, 1H), 4.51 (d, *J* = 10.5 Hz, 1H), 4.50 (d, *J* = 12.5 Hz, 1H), 3.96 (q, *J* = 7.0 Hz, 1H), 3.81-3.86 (m, 1H), 3.65-3.77(m, 4H),

3.58 (dd, *J* = 10.5, 1.5 Hz, 1H), 2.04 (d, *J* = 8.5 Hz, 1H), 1.86-1.95 (m, 1H), 1.60-1.75 (m, 6H), 1.42-1.50 (m, 1H), 0.97-1.34 (m, 16H).

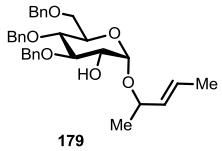
Glycoside of Reductive Coupling Product From Ynal 136 (Scheme 3.23, compound 178)



178

Following the general procedure **4.9**, silyl-linked compound **163** (75 mg, 0.10 mmol), radical cation **171** (121 mg, 0.15 mmol), $NaHCO_3$ (41 mg, 0.49 mmol) were stirred at rt for 30 min. *n*Bu_4NF (0.50 mL, 0.50 mmol) was added as a 1M solution in THF and the reaction was allowed to stir overnight. The product (32 mg, 0.05 mmol, 50%) was obtained as an oil upon purification by flash chromatography on SiO_2 (10% EtOAc/hex). ^{1}H NMR (500MHz, $CDCl_3$) δ 5.44-5.62 (m, 1H), 5.34 (dd, *J* = 15.5, 8.0 Hz, 0.5H), 5.18 (dd, *J* = 15.0, 8.5 Hz, 0.5H) (**diagnostic olefin protons**), 5.03 (d, *J* = 3.5 Hz, 1H) (**diagnostic anomeric proton**).

Glycoside of Reductive Coupling Product From Corresponding Diisopropyl Silyl-Linked Compound (Scheme 3.23, compound 179)

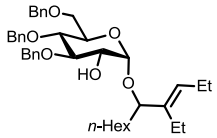


179

Following the general procedure **4.9**, silyl-linked compound (80 mg, 0.12 mmol), radical cation **171** (141 mg, 0.17 mmol), $NaHCO_3$ (193 mg, 2.30 mmol) were stirred at rt for 15 min. *n*Bu_4NF (0.60 mL, 0.60 mmol) was added as a 1M solution in THF and the

reaction was allowed to stir overnight. The product (23 mg, 0.037 mmol, 31%) was obtained as an oil upon purification by flash chromatography on SiO_2 (10 to 20% EtOAc/hex). Note - the product was isolated as the diisopropylsilanol at the 2-hydroxy position.

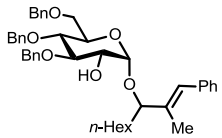
Glycoside of Reductive Coupling Product From Heptanal and 3-Hexyne (Scheme 3.23, compound 180)



180

Following the general procedure **4.9**, silyl-linked compound **156** (75 mg, 0.10 mmol), radical cation **171** (122 mg, 0.15 mmol), $NaHCO_3$ (168 mg, 2.0 mmol) were stirred at rt for 100 min. nBu$_4$NF (0.50 mL, 0.50 mmol) was added as a 1M solution in THF and the reaction was allowed to stir overnight. The product (18 mg, 0.03 mmol, 30%) was obtained as an oil upon purification by flash chromatography on SiO_2 (5 to 10% EtOAc/hex). ^{1}H NMR (500MHz, $CDCl_3$) δ 7.25-7.42 (m, 13H), 7.14-7.18 (m, 2H), 5.37 (t, J = 7.5 Hz, 0.5H), 5.32 (t, J = 7.5 Hz, 0.5H), 4.94-5.01 (m, 1.5H), 4.91 (d, J = 4.0 Hz, 0.5H), 4.80-4.87 (m, 2H), 4.65 (t, J = 13.0 Hz, 1H), 4.45-4.54 (m, 2H), 3.98 (t, J = 7.5 Hz, 0.5H), 3.92 (t, J = 7.0 Hz, 0.5H), 3.62-3.84 (m, 5.5H), 3.53-3.57 (m, 0.5H), 1.92-2.13 (m, 5H), 1.50-1.70 (m, 3H), 1.20-1.36 (m, 3H), 0.86-1.05 (m, 9H).

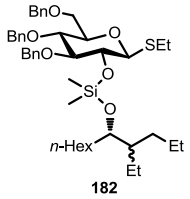
Glycoside of Reductive Coupling Product From Heptanal and 1-Phenyl-1-Propyne (Scheme 3.23, compound 181)



181

Following the general procedure **4.9**, silyl-linked compound **161** (78 mg, 0.10 mmol), radical cation **171** (122 mg, 0.20 mmol), $NaHCO_3$ (168 mg, 2.0 mmol) were stirred at rt for 60 min. nBu$_4$NF (0.50 mL, 0.50 mmol) was added as a 1M solution in THF and the reaction was allowed to stir 1 hr. The product (23 mg, 0.035 mmol, 35%) was obtained as an oil upon purification by flash chromatography on SiO_2 (5 to 20% EtOAc/hex). ^{1}H NMR (500MHz, $CDCl_3$) δ 7.21-7.42 (m, 18H), 7.12-7.19 (m, 2H), 6.49 (s, 0.5), 6.45 (s, 0.5H), 5.07 (d, J = 3.0 Hz, 0.5H), 4.95-5.00 (m, 1.5H), 4.79-4.89 (m, 2H), 4.69 (d, J = 12.0 Hz, 0.5H), 4.59 (d, J = 12.0 Hz, 0.5H), 4.42-4.56 (m, 2H), 4.19 (t, J = 7.0 Hz, 0.5H), 4.07 (t, J = 7.0 Hz, 0.5H), 3.85-3.89 (m, 0.5H), 3.64-3.83 (m, 5H), 3.53 (dd, J = 10.5, 2.0 Hz, 0.5H), 1.840 (dd, J = 6.5 Hz, 1.5H), 1.837 (d, J = 6.0 Hz, 1.5H), 1.58-1.79 (m, 2H), 1.22-1.38 (m, 12H).

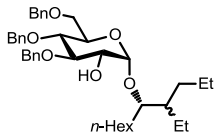
Hydrogenation of Compound 166 (Scheme 3.24, compound 182)



182

Compound **166** (41 mg, 0.05 mmol), and Pd/C (8 mg, 0.008 mmol), were allowed to stir 26 hr as a 0.05M soln in wet EtOAc at 40 °C under an atmosphere of hydrogen gas. The product (41 mg, 0.05 mmol, 85%, ~15% starting material remained, dr undetermined) was obtained as an oil after filtration through a plug of SiO_2 and celite. ^{1}H NMR (500MHz, $CDCl_3$) δ 5.00 (d, J = 11.5 Hz, 1H), 4.85 (d, J = 11.0 Hz, 1H), 4.74 (d, J = 10.5 Hz, 1H), 4.61 (d, J = 12.0 Hz, 1H), 4.56 (d, J = 12.5 Hz, 1H), 4.37 (d, J = 9.5 Hz, 1H) (**diagnostic benzylic and anomeric protons**).

Glycoside of Hydrogenation Product 182 (Scheme 3.24, compound 183)



183

Following the general procedure compound for NIS/TMSOTf glycosylation **182** (37 mg, 0.05 mmol), NIS (15 mg, 0.065 mmol), TMSOTf (11 μL, 0.06 mmol), and 2,6-DTBMP (21 mg, 0.10 mmol) were stirred at -40 °C for 10 min, then warmed to 0 °C and stirred for 30 min, then excess *n*-Bu_4NF (0.25 mL, 0.25 mmol) was added as a 1M solution in THF, warmed to rt and allowed to stir overnight. The product (12 mg, 0.022 mmol, 44%, dr undetermined) was obtained as a colorless oil upon purification by flash chromatography on SiO_2 (10 to 15% EtOAc/hex). ^1H NMR (500MHz, $CDCl_3$) δ 7.16-7.20 (m, 2H), 7.25-7.44 (m, 13H), 4.96 (m, 2H), 4.82-4.86 (m, 2H), 4.66 (d, *J* = 12.5 Hz, 1H), 4.51 (d, *J* = 11.0 Hz, 1H), 4.50 (d, *J* = 12.0 Hz, 1H), 3.77-3.91 (m, 2H), 3.62-3.75 (m, 5H), 2.00 (d, *J* = 10.0 Hz, 1H), 1.15-1.58 (m, 17H), 0.84-0.95 (m, 9H).

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