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De Novo Asymmetric Achmatowicz Approach to Oligosaccharide Natural Products

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Abstract: The development and application of the asymmetric synthesis of oligosaccharides from achiral starting materials is reviewed. This *de novo* asymmetric approach centers around the use of asymmetric catalysis for the synthesis of optically pure furan alcohols in conjunction with Achmatowicz oxidative rearrangement for the synthesis of various pyranones. In addition, the use of a diastereoselective palladium-catalyzed glycosylation and subsequent diastereoselective post-glycosylation transformation was used for the synthesis of oligosaccharides. The application of this approach to oligosaccharide synthesis is discussed.

1.0 Introduction

Of the various classes of natural products, the carbohydrate containing ones have seen the least attention from the synthetic and medicinal chemistry communities.[1] This lack of interest is primarily due to a lack of synthetic ability rather than a lack in significant biological activities. In fact, the sugar portions of carbohydrate containing natural products play a crucial role in both the mechanisms of action as well as bioavailability (*e.g.*, target binding, solubility, tissue targeting, and membrane transport). For example, the corresponding aglycons of natural products are often devoid of biological activity.[2] Medicinal chemists have long desired synthetic methods to vary the carbohydrate structures of natural products,[3] which has inspired many de novo asymmetric approaches to monosaccharides.[4,5] This synthetic need is particularly apparent when it comes to the synthesis and medicinal chemistry studies of oligosaccharide containing natural structural motifs.[1,6,7]

In this context, we developed a de novo asymmetric synthetic approach to carbohydrates,[8] which relies upon asymmetric catalysis to set the D-/L-stereochemistry via the synthesis of a furan alcohol and an Achmatowicz rearrangement/carbonate formation to set the α-/β-anomeric stereochemistry.[9] Finally, a Pd-catalyzed glycosylation[10,11,12] is used to stereospecifically transfer the pyranone to various glycosyl acceptors (*e.g.*, *N*-, *O*-, *C*-nucleophiles).[13,14,15] The reaction occurs rapidly and in high yields for all four stereoisomers, with the enone acting as an anomeric directing group (via a Pd-π-allyl).[16] This approach mechanistically stands in contrast to the use of silver and Au, which appears to occur via a Lewis acid glycosylation mechanism.[17] From a stereochemical perspective this approach to hexose sugars is the simplest of all the possibilities. That is to say that it reduces the hexo-pyranoside down from 32 possible stereoisomers to four. This, in theory, should provide access to all the possible hexose stereoisomers. In practice however, we have found ways to make many but not all possible stereoisomers.[18] Herein, we review our successful effort to use this approach for the synthesis of many carbohydrate-based natural products with medicinally relevant biological activity. Key to this approach is the use of Boc-pyranone as Pd-glycosyl donors and in turn oligosaccharide building blocks. The feasibility of this de novo asymmetric approach to carbohydrates is evident by its ability to engender medicinal chemistry studies (*vide infra*).[19]

1.1 Background

In this regard, we have been developing new asymmetric sequences for the *de novo* asymmetric synthesis of carbohydrates.[8] While we and others have developed many enantioselective approaches to monosaccharides from achiral starting materials,[1,Error! Bookmark not defined.,18] it is fair to say that our Achmatowicz approach is the only approach that uses asymmetric catalysis to control the installation of stereochemistry at both the monosaccharide and oligosaccharide level of complexity.[20] Herein we review our development and use of the Achmatowicz approach to carbohydrates natural products with oligosaccharide motifs (*vide infra*).

2.0 *De novo* Asymmetric Approaches to Chiral Furan Alcohols

Key to the success of this Achmatowicz approach is the ease at which furan alcohols can be prepared in enantiomerically pure form from achiral furans (*e.g.*, **1** and **2**).[21] While we have explored many asymmetric approaches to furan alcohols, two preferred methods are the Noyori hydrogen transfer reduction of acylfurans (**1** to **3**) and the Sharpless dihydroxylation of vinylfurans (**2** to **3**) (Scheme 1).[6,22] Application of the Sharpless asymmetric aminohydroxylation (AA)[23] of vinylfurans provides access to azasugars[24] via the aza-Achmatowicz

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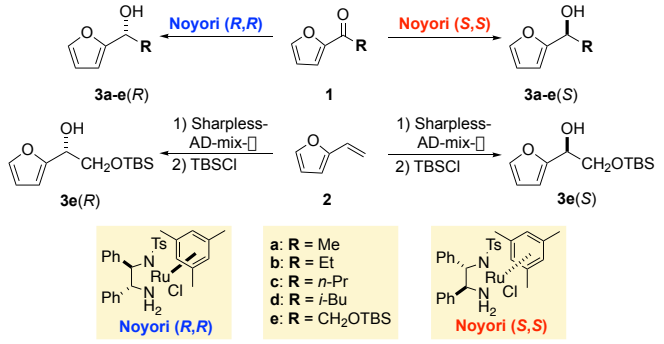
reaction.[25,26] Both routes are quite practical in terms of scalability (> 100 g) and catalyst loading (< 1 % catalyst). The Sharpless route is somewhat limited to the synthesis of hexoses with a *C*-6 hydroxy group (*e.g.*, **3e**, **R** = CH_2OTBS), whereas the Noyori protocol distinguishes itself in its environmentally benign reductant (*e.g.*, *i*-PrOH, HCO_2H)[27] and flexibility to virtually any substitution at the *C*-6 position (*e.g.*, **3a-e**).[28] In addition, the acylfuran (**1**) starting materials are either commercially available or readily available from furan and the corresponding carboxylic acids.

Scheme 1: *De novo* Asymmetric Synthesis of Chiral Furan Alcohols



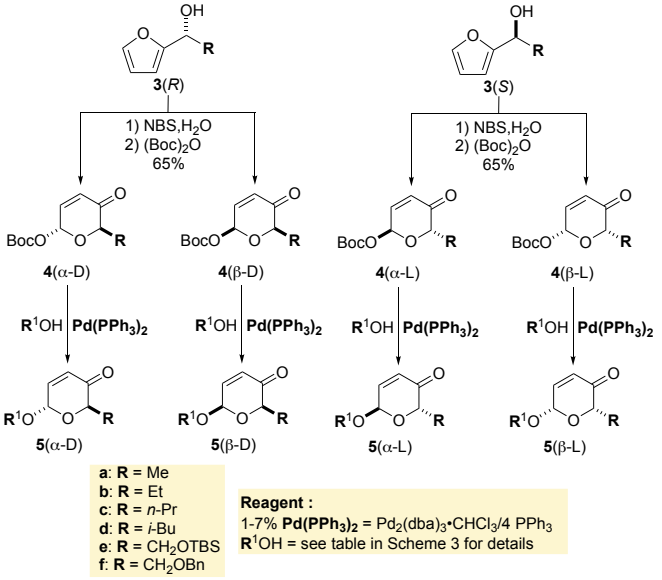
2.1 Achmatowicz Approaches to Hexoses

Key to the overall Achmatowicz approach to carbohydrates is the recognition that furan alcohols like **3**(*S*) can be converted into pyrans like **4**(α-L) and **4**(β-L) with L-sugar stereochemistry (Scheme 2). Analogously furan alcohols with (*R*)-stereochemistry can be converted into D-sugars. The enantio-divergent approach to furan alcohols of type **3**(*S*)/**3**(*R*) enables a highly stereoselective approach to all the possible pyranone stereoisomers **4**(α-L), **4**(β-L), **4**(α-D), and **4**(β-D) by means of an Achmatowicz rearrangement and diastereoselective carbamate formation. The Achmatowicz rearrangement is an oxidative hydration/rearrangement of furfuryl alcohols into 2-substituted 6-hydroxy-2H-pyran-3(6H)-ones. When the pyranone 6-hydroxy group is converted to an acetate or carbonate type Pd-π-allyl leaving group, it becomes the basic pyranone building block for our *de novo* carbohydrate synthesis. The *t*-butyl carbonate formation can selectively give the α-pyranones **4**(α-L) and **4**(α-D) at –78 °C. At higher temperatures (*e.g.*, rt), a 1:1 ratio of the α- and β-Boc protected enones was produced. This procedure is easily scaled for the production of multigram quantities of both α- and β-pyranones in either D- or L-enantiomeric form. The resulting sugar products can exist with variable substitution and stereochemistry. The pyranone subunits **4** can be viewed as a protected form of various monosaccharides or a component to various oligosaccharides (*vide infra*), via highly stereoselective Pd-glycosylation and post glycosylation transformations.

2.2 Pd-Catalyzed Glycosylation

The *de novo* Achmatowicz approach to hexoses has great potential for preparing various D- and L-sugars because the starting 6-*t*-butoxycarboxy-2*H*-pyran-3(6*H*)-ones (**4**) can easily be prepared from optically pure furfuryl alcohols **3** (either (*R*) or (*S*) enantiomers)[29] by a one or 2-step procedures (Scheme 2). Key to the assembly of these building blocks is the use of a Pd-glycosylation reaction.[15,30] This highly diastereoselective process occurs with retention of configuration converting pyranones **4**(α-L), **4**(β-L), **4**(α-D), and **4**(β-D) with a *C*-1 BocO-leaving group into *C*-1 *O*-glycosides **5**(α-L), **5**(β-L), **5**(α-D), and **5**(β-D), with an anomeric alkoxy-group. This approach has also been extended to a Pd-cyclitolization (5a-carbasugar glycosylation).[31]

Scheme 2: Pyranones Form Furan Alcohols via Achmatowicz reaction.

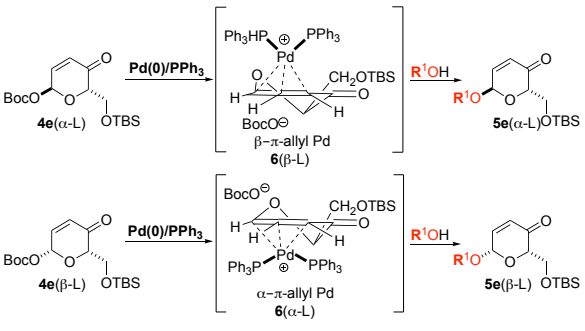


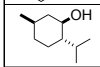
The Pd-reaction occurs via a double inversion/net retention mechanism (*i.e.*, **4**(α-L) to **5**(α-L) via **6**(β-L) and *i.e.*, **4**(β-L) to **5**(β-L) via **6**(α-L); Scheme 3). The Pd-π-allyl reaction occurs rapidly and in high yields for both the α- and β-diastereomers (e.g., **4**(α-L/D) to **5**(α-L/D) systems and works best when $Pd_2(dba)_3{\cdot}CHCl_3$ is used as the Pd(0) source with triphenylphosphine as the ligand in a 1:2 Pd/PPh_3 ratio. Various carboxylate leaving groups (*e.g.*, AcO, BzO, PivO) work in the Pd-glycosylation reaction, however, the *t*-butyl carbonate group (BocO) performs the best. The BocO-group is the best leaving group and serves as the base to form *t*-BuOH, after decarboxylation. The *t*-BuOH that is formed is a poor nucleophile in the Pd-glycosylation reaction, due to its steric hinderance. When performed in conjunction with the Achmatowicz reaction and diastereoselective carbonate formation, the Pd-glycosylation enables a 3-step stereo-divergent pyranone synthesis from chiral furan alcohols. Key to the success of the *de novo* asymmetric Achmatowicz approach is the practical access to all four possible pyranone diastereomers **5**(α-L), **5**(β-L), **5**(α-D), and **5**(β-D) from either furan alcohol enantiomers **3**(*R*) or **3**(*S*).

The resulting approach to sugars has become a viable *de novo* asymmetric alternative to traditional carbohydrate routes. While the comparison of these *de novo* routes to traditional carbohydrate routes is difficult, these *de novo* routes have a clear advantage in terms of D-/L-sugar variability and for rare sugars.[32] In addition, when these *de novo* routes are applied to oligosaccharide targets, they often are executed with the use of fewer protecting groups and sometimes no protecting groups. In our view, the best metric for this evaluation is in terms of synthetic utility and variability, which is highlighted in the following synthetic endeavors (Schemes 4-24).[13] The Pd-glycosylation

reaction, which at first glance does not look like a typical glycosylation reaction, has the ability to use the enone functionality as precursors to mono-, di- and triol products. With various post-glycosylation reactions, we are able to transform the enones into the functional equivalent of variously substituted alcohol/polyol and hence function as atom-less protecting groups (*vide infra*).

Scheme 3: The Mechanism of the Pd-Catalyzed Glycosylation



R^1OH	α(% yield)	β(% yield)
MeOH	87	85
BnOH	89	85
t-BuOH	70	75
	88	80
	82	72

Reagent : 1-7% **$Pd(PPh_3)_2$** = $Pd_2(dba)_3$•$CHCl_3$/4 PPh_3

3.0 De Novo Synthesis of Oligosaccharides

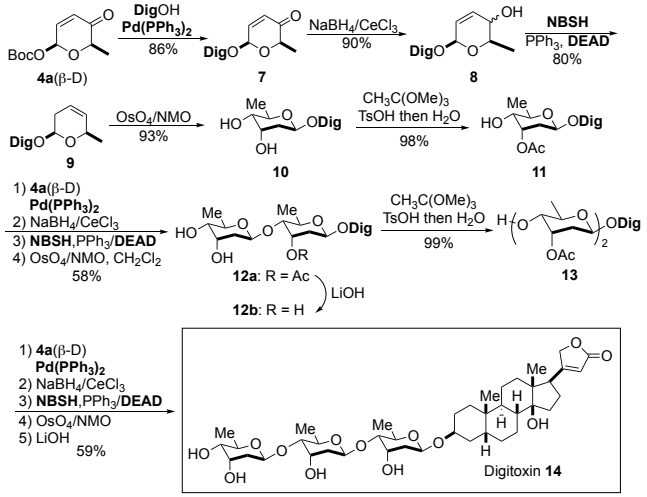
This Achmatowicz-based *de novo* approach to carbohydrates has had success in its application to various monosaccharide targets,[33] however, its full potential is best revealed in its application to oligosaccharide targets.[34] This potential can be measured in terms of its overall synthetic efficiency (*i.e.*, number of steps, the minimal use of protecting groups) and complexity of the targets achieved. The complexity can be measured by the range and variability of the oligosaccharide motifs that can be prepared, as well as the biological and medicinal chemistry structure-activity relationship studies they enable. Of the many ways to compare these *de novo* routes, clearly the best metric is the scope of the synthetic and biological applications. Herein we demonstrate the potential of these de novo asymmetric approaches by reviewing their application to the synthesis of various mono-, di-, tri- tetra-, and heptasaccharide motifs.

3.1 Synthesis of Digitoxin

The first significant application of the Achmatowicz approach to oligosaccharides was its application toward the synthesis of the cardiac glycosides (Scheme 4). The cardiac glycosides, like digitoxin, emanates from a long folk medicine tradition (~1500 BC). The cardiac glycosides are produced in toxic plants (*e.g.*, Digitalis purpurea, Digitalis lanata) and found in amphibians that feed on them. In addition to its cardiotonic effect, the cardiac glycosides have potential as anticancer and antiviral agents.[35] Studies have found that the carbohydrate portion of the cardiac glycosides controls the selectivity for cancer cells/infected cells over the cardiotonic effects.[36,37]

The structure-activity relationship (SAR)-studies of the cardiac glycosides have been limited by the number of naturally occurring cardiac glycosides that are available (*e.g.*, digitoxin, digoxin, and oleandrin). To address these concerns, we have developed a carbohydrate medicinal chemistry SAR-method that allows us to map the carbohydrate oligosaccharide space around the cardiac glycoside structural motifs.[38] These efforts began with the synthesis of natural product digitoxin **14** from its aglycon digitoxigenin (DigOH), which also involved a 4-step synthesis of the digitoxin monosaccharide **10**. In addition, this led to a 10-step synthesis of digitoxin disaccharide **12b** and ultimately a 15-step synthesis of digitoxin **14**.

Scheme 4: Synthesis of Digitoxin, Mono-, Di- and Tri-Saccharides



The synthesis began with a Pd-catalyzed glycosylation between digitoxigenin (DigOH) and the β-D-glycosyl donor **4a** to afford the β-D-pyranone **7**. While not too surprising, it was gratifying to see the selective glycosylation of the axial secondary alcohol in the steroid A-ring over the bridgehead tertiary alcohol. An unselective sodium borohydride 1,2-reduction of the ketone in **7**,[39] afforded a mixture of allylic alcohols **8**. Fortunately, the lack of stereoselectivity did not hurt the throughput, as both diastereomers could be used in the subsequent Myers reductive rearrangement of **8**. Thus, exposure of both diastereomers of **8** to the Mitsunobu conditions with NBSH (*o*-$NO_2PhSO_2NHNH_2$), cleanly provides alkene **9** as a single regio- and diastereo-isomer. Finally, an Upjohn dihydroxylation[40] of alkene **9** (OsO_4/NMO) exclusively gave the digitoxin monosaccharide **10** in good yield and as a single diastereomer. In addition to providing access to the desired monosaccharide **10**, the synthesis demonstrated the compatibility of the Pd-glycosylation and post-glycosylation reaction sequence with the butenolide functional group.

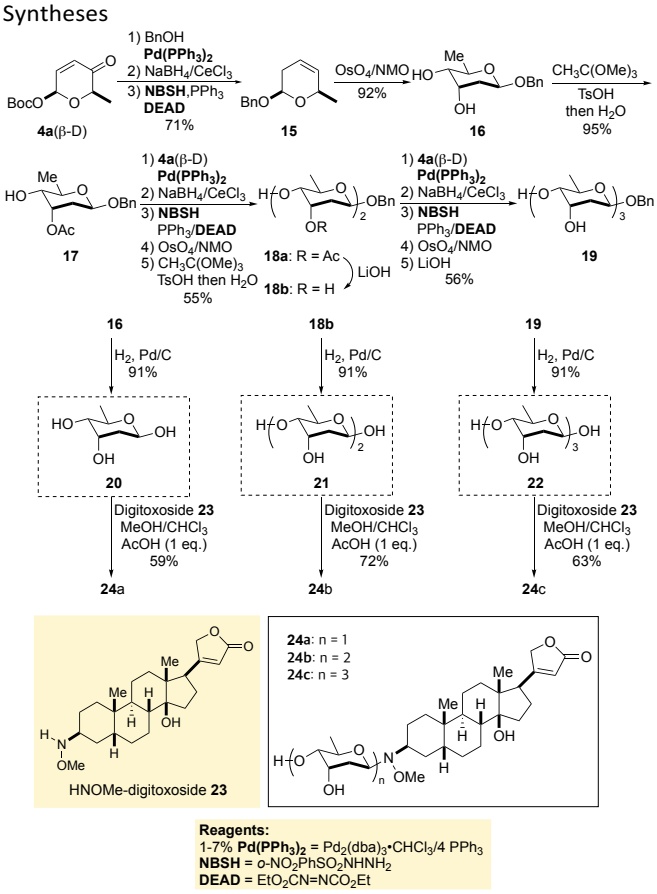
The synthesis of the digitoxin disaccharide **12b** utilized a similar sequence after regioselective protection. To accomplish this, we turned to orthoester chemistry.[41,42] Specifically, the regioselective acylation of the *syn*-3,4-diol in **10** occurred via a one-pot orthoester ($(MeO)_3CCH_3$) formation and acid-catalyzed hydrolysis ($TsOH/H_2O$) to afford axial acetate **11**. Then the Pd-glycosylation of equatorial

alcohol in **11** with **4a** began a 4-step synthesis to give disaccharide **12a**. A LiOH hydrolysis of the axial alcohol in **12a** gave the deprotected disaccharide **12b**. Once again, the same Pd-glycosylation and post-glycosylation sequence can be used for the synthesis of digitoxin **14**. Thus, a regioselective acylation of **12a** gave the diacetate **13**, which via a familiar 5-step sequence was converted it into digitoxin **14**.

3.1.1 Synthesis of Analogs

The synthetic approach used for the synthesis of digitoxin was also used in the synthesis of its neo-glycoside analogues (Scheme 5).[43] Additionally, this approach was used to prepare the three reducing sugars with a free alcohol at the anomeric position (digitoxin monosaccharide **20**, disaccharide **21**, and trisaccharide **22**), which were used in the synthesis of the corresponding neo-glycosides **24a-c**.[44] The synthesis began with the β-glycosylation of benzyl alcohol, followed by an unselective reduction and Myers reductive rearrangement to give alkene **15**. A diastereoselective dihydroxylation of **15** gave the digitoxin β-monosaccharide **16** with a benzyl anomeric protecting group. As before, orthoester chemistry was used to regioselectively acylate the *C*-4 axial alcohol in **16** ($(MeO)_3CCH_3$, then $TsOH/H_2O$) to afford the protected monosaccharide **17**. Simply repeating the 5-step Pd-glycosylation, Luche/Myers reduction/dihydroxylation and orthoester acylation converted **17** into the disaccharide **18a** with both sugars with a *C*-3 axial acetate. The two acetates could easily be removed to form **18b** with aqueous LiOH.

Scheme 5: Mono-, Di-, and Tri-Digitoxin Neo-Glycoside Syntheses

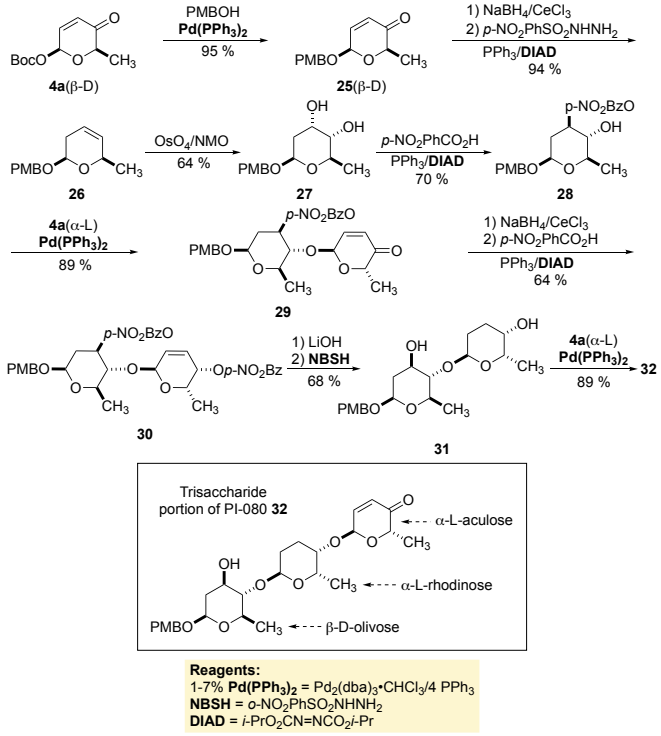


Once again, exposing **18a** was transformed via a similar 4-step sequence (Pd-glycosylation, Luche/Myers reduction, and dihydroxylation) followed by a LiOH ester hydrolysis to give the trisaccharide **19** with a benzyl group at the anomeric position. The two acetates could easily be removed to form **18b** with aqueous LiOH. A Pd-C catalyzed hydrogenolysis was used to cleanly convert Bn-protected monosaccharide **16**, disaccharide **18b**, and trisaccharide **19** into monosaccharide **20**, disaccharide **21**, and trisaccharide **22** with minimal purification to remove the catalyst. Then the three reducing sugars monosaccharide **20**, disaccharide **21** and trisaccharide **22** were converted into the corresponding neoglycoside by exposure to digitoxigenin with a methoxyamine in the A-ring by using the neoglycosylation condition developed by Thorson (AcOH in $MeOH/CHCl_3$). The three *O*-glycosides (**10**, **12b**, and **14**) and corresponding neoglycosides (**24a**, **24b**, and **24c**) were evaluated for their anticancer activity. These studies revealed two trends. The first being that the monosaccharides (**10** and **24a**) were more active than the disaccharides (**12b** and **24b**), which were more active than the trisaccharides (**14** and **24c**). The second trend was that the three *O*-glycosides (**20**, **21**, and **22**) were more active than the corresponding neoglycosides (**24a-c**).[44,45]

3.2 Synthesis of a PI-080 Trisaccharide

In addition to symmetrical linear trisaccharides like the digitoxins, we have also applied this *de novo* approach to the synthesis of trisaccharide with different sugars making up the oligomer. An example of this can be seen in our de novo asymmetric approach to the trisaccharide of PI-080 (**32**) (Scheme 6), which consists of a β-D-olivose, α-L-rhodinose, and α-L-aculose. [46] As with the digitoxin this began with the β-glycosylation of PMBOH with **4a**(β-D) to stereo-specifically give β-D-pyranone **25**. An unselective reduction of **25**(β-D) gave a mixture of allylic alcohols which after a Myers reductive rearrangement gave alkene **26**. Again, a highly diastereoselective dihydroxylation converted **26** into monosaccharide **27** with digitoxose stereochemistry. Then the digitoxose monosaccharide **27** was selectively converted in to a protected olivose sugar **28** by a regioselective and stereospecific Mitsunobu-like inversion ($PPh_3/DEAD/p\text{-}NO_2BzOH$). It worth noting that this combination of diastereoselective dihydroxylation and regioselective inversion of the axial alcohol results in an excellent solution to the problem of 1,2-*trans*-diequatorial addition of a cyclohexene (**26** to **28**). Then the *C*-4 alcohol in **28** was exposed to an α-glycosylation with **4a**(α-L) to give the olivose/aculose disaccharide **29**. A selective Luche reduction and Mitsunobu inversion were used to convert the aculose ring in disaccharide **29** to disaccharide **30** with one rhodinose sugar. Then, disaccharide **30** was exposed to LiOH to hydrolysis of the two nitrobenzoates and diimide to reduce the alkenes to give the olivose/rhodinose disaccharide **31**. Finally, our Pd-catalyzed glycosylation conditions were used to regioselectively and stereospecifically glycosylate the diol in **31** with **4a**(α-L) to give the PI-080 trisaccharide **32**. The trisaccharide **32** displayed significant growth inhibition (GI_{50} from 0.1 to 11 mM) and cytotoxicity (LC_{50} from 5.1 to 100 mM) against a range of cancer cell lines.[47]

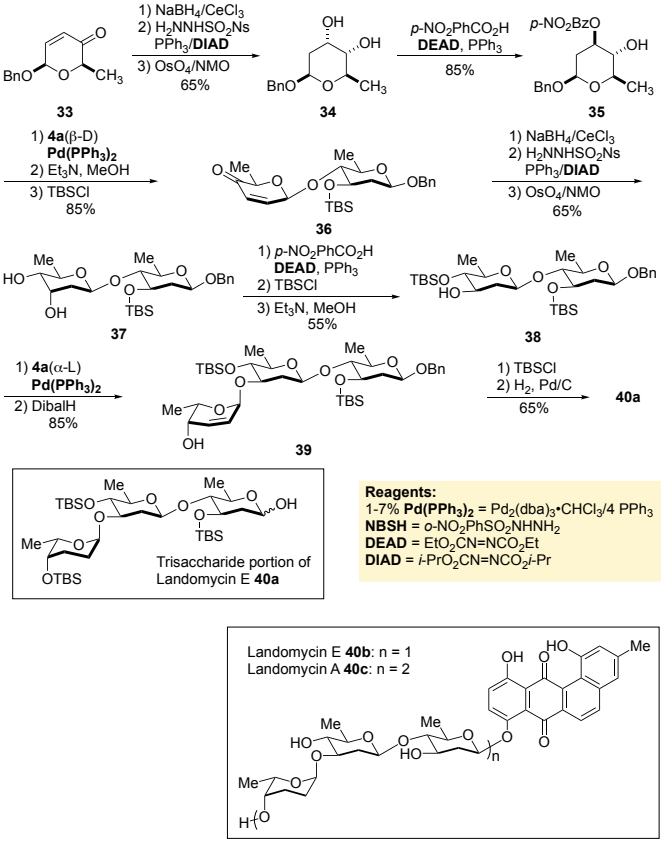
Scheme 6: Synthesis of the PI-080 Trisaccharide



3.3 Landomycin E Trisaccharide Synthesis

A similar approach as the one used for the PI-080 trisaccharide was used for a de novo asymmetric synthesis of the trisaccharide portion of Landomycin E **40b** (Scheme 7).[48,49] The Landomycin E trisaccharide **40a** consists of two β-olivose-sugars terminated by a α-rhodinose. As a result, the route used similar glycosylation and post-glycosylation chemistry as was used for the digitoxins and PI-080 (Schemes 4-6). The synthesis began with a β-glycosylation of benzyl alcohol with **4a**(β-D) to give β-aculose monosaccharide **33**. As above a three-step Luche/Myers reduction and dihydoxylation sequence was used to convert **33** into digitoxose **34**. Another regioselective inversion of the *C*-3 axial alcohol (PPh_3/DEAD/*p*-NO_2BzOH) was used to convert the digitoxose stereochemistry in **34** into a protected olivose sugar **35**. A β-Pd-glycosylation with **4a**(β-D) of the *C*-4 alcohol in **35** followed by nitrobenzoate hydrolysis and TBS-protection was used to convert it into olivose/aculose disaccharide **36**. Once again, the enone functionality in **36** was converted into a digitoxose sugar by a 3-step sequence (Luche/Myers reduction and dihydroxylation) to give the olivose/digitoxose disaccharide **37**. The *C*-3/4 diol of the digitoxose sugar was regioselectively converted into an olivose sugar by a three-step Mitsunobu/TBS-protection and nitrobenzoate hydrolysis to give the bis-olivose disaccharide **38**. A Pd-catalyzed α-glycosylation of the *C*-3 alcohol in **38** with **4a**(β-D) followed by DibalH reduction was used to give trisaccharide **39**. Finally, a TBS protection and alkene hydrogenation gave a protected form of the landomycin E trisaccharide **40a**.

Scheme 7: Synthesis of the Landomycin Trisaccharide



3.4 Synthesis of Cleistetroside

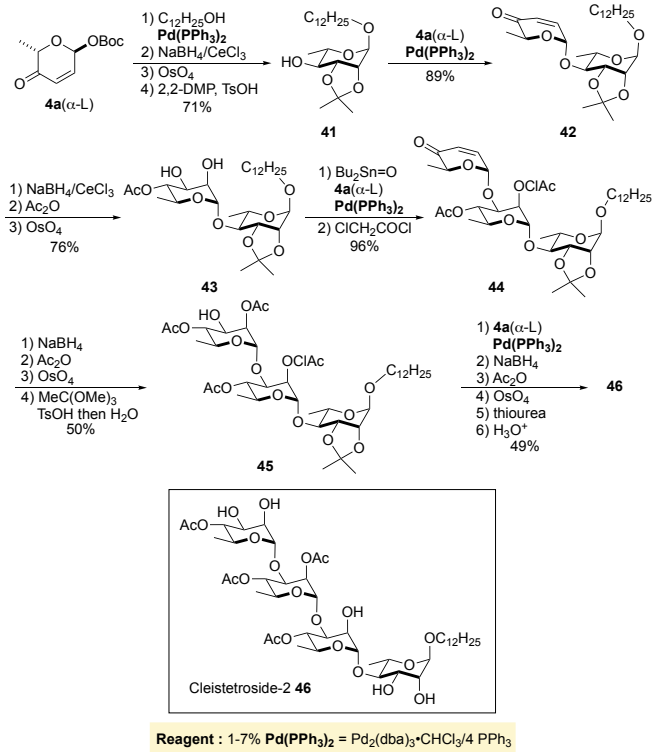
The power of the de novo Achmatowicz approach to natural occurring rare sugar oligosaccharides was demonstrated with the synthesis of digitoxin, PI-080[47] and Landomycin E trisaccharide.[48] We next look to expand the potential of this approach with its application to oligosaccharides that consisted of less rare sugars and the rhamnan set of oligosaccharides seemed ideal for this purpose. As will be revealed (cf., Schemes 8-19), the application of this approach to sugars with α-*rhamno*/*manno*-stereochemistry can be particularly formidable. Our first synthetic foray into this class of oligosaccharides was the synthesis of the partially acylated cleistrioside and cleistetroside class of natural product oligosaccharides.[50] This effort led to the successful synthesis of 2 members of the cleistriosides and 9 members of the cleistetrosides[51,52] For space reasons we have chosen to limit this discussion to the synthesis of cleistetroside-2 (Scheme 8). Key to the practicality of this approach will be its reliance on the minimal use of protecting groups (*i.e.*, chloroacetate and acetonide).

The route to cleistetroside-2 began with a Pd-glycosylation between dodecanol and pyranone **4a**(α-L). After a three-step sequence (Luche reduction, dihydroxylation, and acetonide protection), the protected monosaccharide **41** was obtained. A subsequent Pd-glycosylation of **41** with pyranone **4a**(α-L) yielded the aculose/rhamnose disaccharide **42**, with the *C*-2/3 diol of the *rhamno*-sugar protected as an acetonide and the *C*-2-4 positions of the enone in the aculose sugar serving as an atomlessly protected *rhamno*-sugar. Thus in only three steps (Luche reduction, acylation, and Upjohn

dihydroxylation), the enone in **42** was readily converted into **43** with *rhamno*-sugar stereochemistry and the requisite *C*-4 acetate group already installed.

Next, we need to selectively protect the *C*-2 position and glycosylate the *C*-3 position of **43**. The use of the chloroacetate equivalent of the previously demonstrated very successful ortho-ester chemistry did not work in this situation. Thus, we turned to the novel use of tin acetal chemistry to regioselectively direct a *C*-3 glycosylation. This was accomplished by the use of dibutyltin oxide to perform a *C*-2/3 tin acetal intermediate. The tin intermediate underwent a regioselective Pd-glycosylation reaction with pyranone **4a**(α-L) to give the *C*-3 glycosylated product (*C*-3 to *C*-2, 7:1), which after chloroacylation gave trisaccharide **44**. A 4-step post-glycosylation transformation protocol (Luche reduction, acylation, Upjohn dihydroxylation and orthoester acylation) was used to transform the aculose ring in **44** into **45** a *rhamno*-sugar with a *C*-2/4 diacetate selectively installed. Finally, a 6-step sequence was used to convert **45** into **46**. This involved a glycosylation (Pd(0), **4a**(α-L)), a 3-step post-glycosylation (Luche reduction, acylation, and Upjohn dihydroxylation) and a 2-step chloroacetate/acetonide deprotection (thiourea then H_3O^+). The synthetic cleistetroside-2 (**46**) obtained by this route and its related cleistrioside and cleistetroside oligosaccharides were used in anticancer studies, which demonstrated the synthetic viability of these *de novo* asymmetric approaches for medicinal chemistry studies.

Scheme 8: Synthesis of the Cleistetrosides

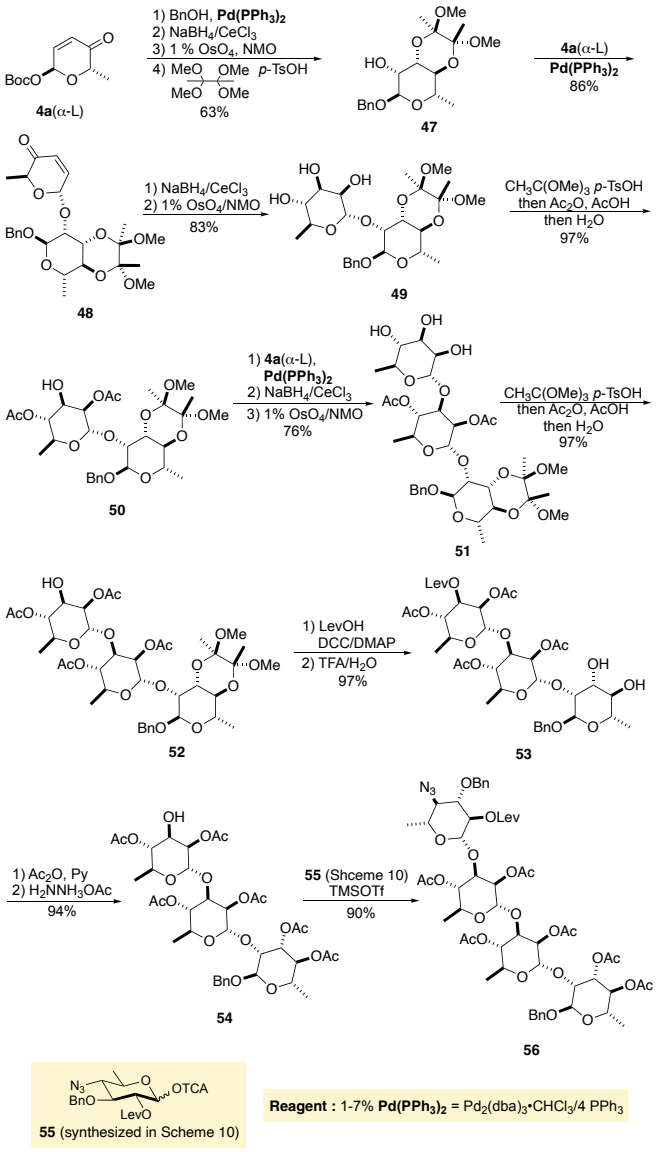


Reagent : 1-7% **Pd(PPh$_3$)$_2$** = Pd$_2$(dba)$_3$•CHCl$_3$/4 PPh$_3$

3.5 Synthesis of Anthrax Tetrassacharide

This asymmetric Achmatowicz approach was also applied to a more complex member of the rhamnan oligosaccharides. More specifically, a unique tetrasaccharide that was isolated from an exosporium glycoprotein (BC1A) from the cell wall of *Bacillus anthracis* spores.[53] *Bacillus anthracis* is one of the most well-known members of the Bacillaceae family. When this Gram-positive spore-forming bacterium is inhaled, it causes the fatal infectious disease called anthrax in humans and other mammals. The anthrax tetrasaccharide **66** (Scheme 11) consists of three L-rhamnose sugars and is terminated by a unique D-sugar, called anthrose. Importantly, the anthrose sugar is unique to Bacillus anthracis and not found in spores from other Bacillus species.[54]

Scheme 9: Synthesis of the Antrax Tetrassacharide

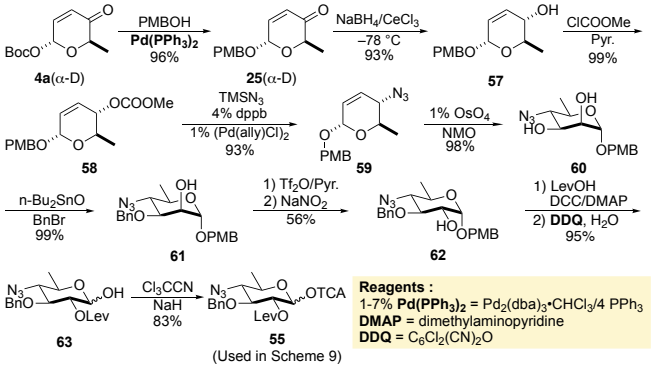


Reagent : 1-7% **Pd(PPh$_3$)$_2$** = Pd$_2$(dba)$_3$•CHCl$_3$/4 PPh$_3$

Our synthesis of the anthrax tetrasaccharide **66** began with the assembly of its tri-rhamnose rhamnan unit in the protected tris-L-*rhamno*-trisaccharide **54** (Scheme 9).[55, 56] This began with a Pd-glycosylation between benzyl alcohol and pyranone **4a**(α-L) which was followed by Luche reduction, dihydroxylation, and Ley spiro-ketal protection[57] to give the L-*rhamno*-sugar **47** with a Bn-protecting group at the anomeric position and a free *C*-2 alcohol. The use of the Ley spiroketal protecting group was critical as it allowed the oligosaccharides to be built with connectivity to the *C*-2 position of the sugar. The *C*-2 alcohol in **47** was then glycosylated with pyranone **4a**(α-L), which provided the disaccharide **48**. A diastereoselective Luche reduction and Upjohn dihydroxylation produced the *rhamno*-triol **49**. Then a 3-step one pot *C*-2/*C*-4 bis-acylation of triol **49** was

accomplished ($CH_3C(OMe)_3$ *p*-$TsOH_{(cat)}$ then Ac_2O then $AcOH/H_2O$) to afford the 2,4-diacetate **50**.[55, 58] Another *rhamno*-sugar was introduced on the *C*-3 alcohol in **50** by a 3-step (Pd-glycosylation (**50** + **4a**(α-L), Luche reduction and dihydroxylation) to form trisaccharide **51**. Once again, the 3-step orthoester bis-acylation of the *C*-2/*C*-4 alcohols of triol **51** was used to form monoalcohol **52**. Unfortunately, we found the Ley spiro-ketal protecting group in **52** did not survive glycosylation with glycosyl-donors like trichloroacetimidate **55** (Scheme 10). To skirt this problem, we decided to protect the *C*-3 alcohol as a levulinate ester, and then the spiroketal was removed with TFA to give diol **53**. The diol in **53** was then protected as a bis-acetate (Ac_2O/Py) and the levulinate was removed with hydrazine to give trisaccharide **54**. Now without the acid-sensitive Ley-protecting group, we found the *C*-3 alcohol in **54** was able to react under the Schmidt type glycosylation condition (*e.g.*, with **55** to form **56**).

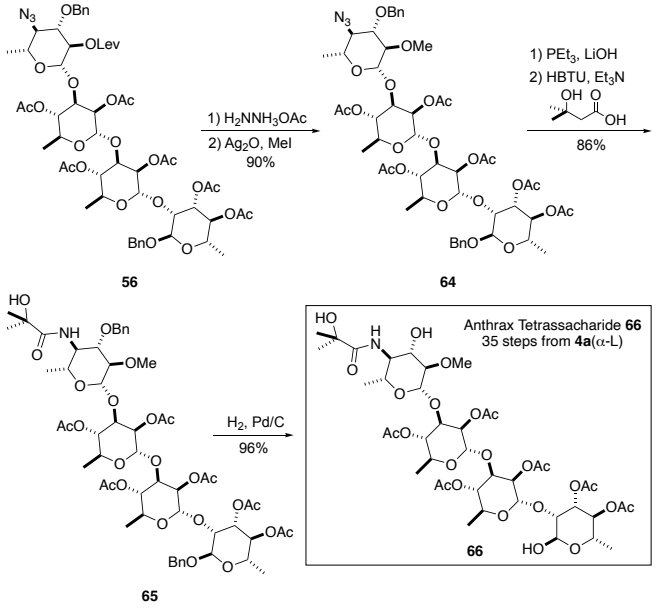
Scheme 10: Synthesis of the Anthrose



With the synthesis of the *rhamno*-trisaccharide **54** accomplished and before it was converted into tetrasaccharide **56**, we needed to develop an Achmatowicz approach to the anthrose portion of the tetrasaccharide (Scheme 10). This began with the Pd-glycosylation between PMBOH and pyranone **4a**(α-D) to give α-D-aculose **25** with the anomeric position protected as a PMB group. We next look to install a *C*-4 azide. This was accomplished with a Luche reduction ($NaBH_4/CeCl_3$) to give allylic alcohol **57**. The allylic alcohol was then converted into methyl carbonate **58** ($ClCO_2CH_3$/DMAP).[59]

Using Pd(0) chemistry, the methyl carbonate group of **58** was regio- and stereo-specifically replaced with an azide group ($TMSN_3$, $(allylPdCl)_2$/dppb) to afford allylic azide **59** (93%).[60] An Upjohn dihydroxylation of **59** (OsO_4/NMO) was used to install the *rhamno*-stereochemistry in **61**. Once again dibutyltin acetal chemistry ($BnBr/Bu_2SnO$) was used to regioselectively protect the diol to form benzyl ether **61**.[41] Then, the *C*-2 axial alcohol in **61** was inverted by a triflation (Tf_2O) and S_N2 displacement/hydrolysis ($NaNO_2$) to give **62** with *gluco*-stereochemistry.[61] The *C*-2 alcohol in **62** was converted into a levulinate (LevOH/DCC/DMAP) and the PMB-group was removed to provide the anomeric alcohol **63**. Then, the anomeric alcohol was converted into trichloroimidate **55**. The final glycosylation step was accomplished with *rhamno*-trisaccharide **54** and trichloroimidate **55** and was catalyzed with TMSOTf to give the tetrasaccharide **56** (Scheme 9).

Scheme 11: Synthesis of the Antrax Tetrassacharide (end game)

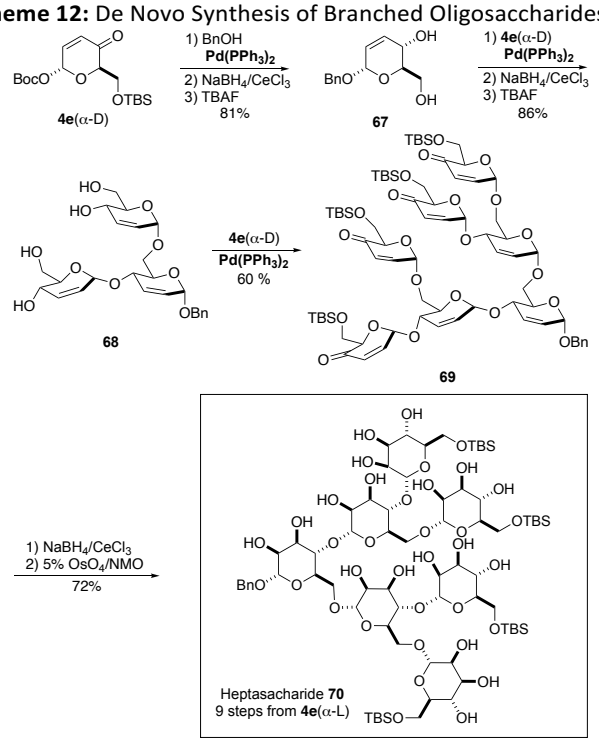


Finally, tetrasaccharide **56** was converted into the anthrax tetrasaccharide **66** in five steps (Scheme 11). This began with the selective levulinate ester hydrolysis (H_2NNH_3OAc), and a silver (I) oxide promoted methylation (Ag_2O in MeI) of the anthrose pyranose in **56** to give **64**. Then a one-pot global deprotection of the acetates in **64** along with azide reduction afforded a primary amine (PEt_3, $LiOH_{(aq)}$), which was selectively coupled with 3-hydroxy-3-methylbutanoic acid ($HBTU/Et_3N$, to give amide **65**. The natural product synthesis was completed by a hydrogenolysis of both benzyl groups (H_2, Pd/C) to give anthrax tetrasaccharide **66**.

3.6 (1→4),(1→6)-branched oligosaccharides

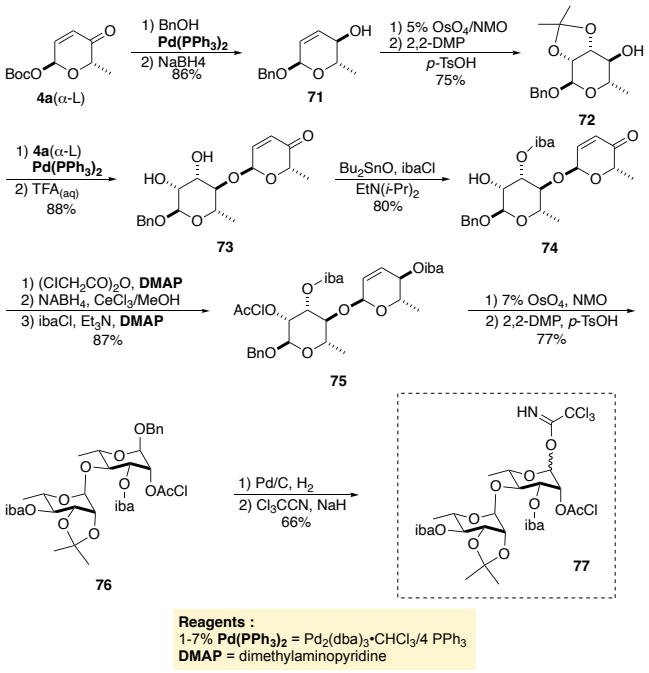
The asymmetric Achmatowicz approach to oligosaccharides has also been used for the synthesis of unnatural oligosaccharides. This has been successfully applied for the synthesis of 1,4- and 1,6-linked trisaccharides with rhamnose and amecitose stereochemistry. Outlined in Scheme 12 is the use of this approach to 1,4-/1,6-branched oligosaccharides.[62] This began with the synthesis and bidirectional glycosylation of *C*-4 and *C*-6 diol **67**. The synthesis of diol **67** was accomplished from Boc pyranone **4e**(α-D) in 3 steps by a Pd-glycosylation of BnOH, Luche reduction, and TBS-deprotection. A Pd-catalyzed bis-glycosylation of diol **67** with two equivalents of pyranone **4e**(α-D) followed by diastereoselective bis-1,2-reduction and bis-TBS-protection gave the trisaccharide **68**. A tetra-Pd-glycosylation of **68** with excess pyranone **4e**(α-D) gave heptasaccharide **69**. Exposure of **69** to excess $NaBH_4$ reduced the four enone groups to give a tetra-allylic alcohol, which was per-dihydroxylation (OsO_4/NMO) to give **70**. The all α-*manno*-hepta-saccharide **70** was prepared in only 9 steps from pyranone **4e**(α-D). The route is equally amenable to the all-L-enantiomer as well as the various D-/L-stereoisomers and deoxy congeners. It is important to note the acid-sensitivity of the glycosidic bonds in deoxy hepta-saccharides **69** and **70**, which might not survive the strongly acidic conditions of a traditional glycosylation.

Scheme 12: De Novo Synthesis of Branched Oligosaccharides



acetonide protection gave **76**. Finally, the *C*-1 position was deprotected, and the anomeric alcohol was converted into a Schmidt trichloroacetimidate **77**.[71]

Scheme 13: Synthesis of the Merremoside D Disaccharide



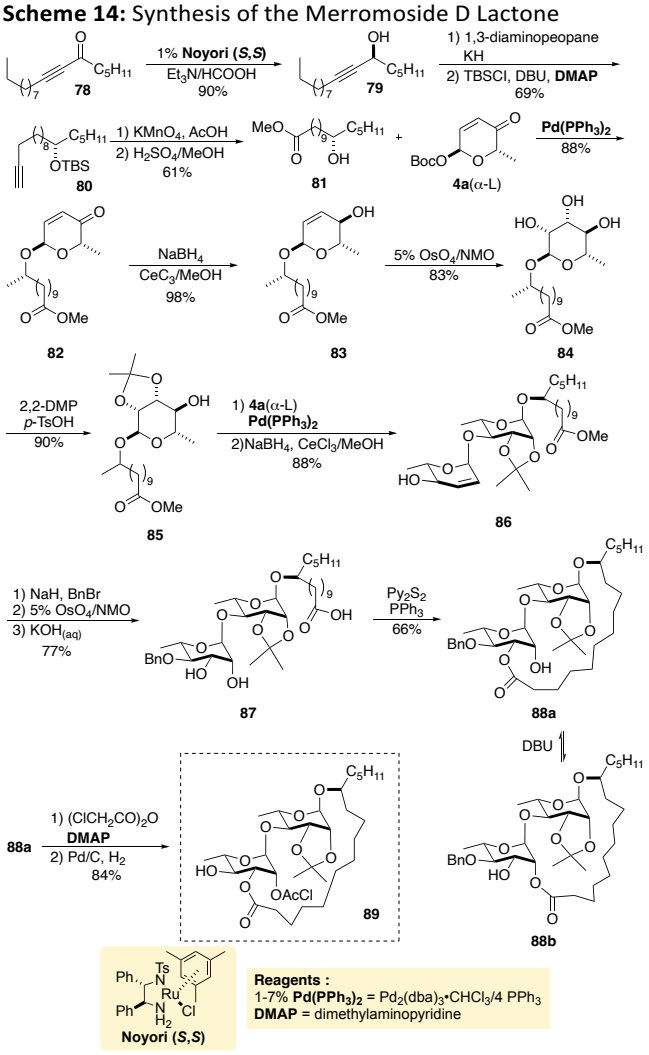
3.7 Synthesis of Merremoside D

Our success with the glycosylated lipid oligosaccharides, like the cleistriosides and cleistetrosides, emboldened us to apply the asymmetric Achmatowicz approach to the resin glycoside class of macrolactone oligosaccharides.[63,64,65] We identified merremoside D as the ideal test case for our development of a synthetic approach. The merremoside D (**92**) is a member of the family of resin glycoside natural products, isolated by Kitagawa from the tuber of *Merremia mammosa* (Lour.) Hall. f. (Convolvulaceae).[66] The Indonesian plant, *Merremia mammosa*, has been used in traditional medicine for an array of illnesses. This structurally complex macrolactone/oligosaccharide consist of a bis-rhamnose disaccharide bridged by jalapinolic acid containing lactone at the *C*-1 and *C*-3' position. The amphiphilic nature of the resin glycosides has been suggested to be the source of its ionophoretic activity (i.e., membrane transporter).[67]

The convergent approach began with the synthesis of two disaccharide fragments, a disaccharide donor **77** and macrolactone/disaccharide acceptor **89** (Schemes 13 and 14). The synthesis of the donor disaccharide **77** began with the Pd-glycosylation between BnOH and pyranone **4a**(α-L) and Luche reduction to give allylic alcohol **71**. The allylic alcohol was dihydroxylated using the Upjohn procedure and acetonide protected to form the *rhamno*-pyranosides **72** with a free *C*-4 alcohol.[68,69] The alcohol in **72** was glycosylated with pyranone **4a**(α-L) and deprotected (TFA) to give disaccharide **73**. Using tin-acetal chemistry, the *C*-3 equatorial alcohol in **73** was acylated to give **74** with a *C*-3 *i*-butyrate ester (iba).[70] The remaining *C*-2 alcohol was chloroacylated and the enone was reduced and the resulting *C*-4 allylic alcohol was acylated to give disaccharide **75**. A subsequent Upjohn dihydroxylation, and

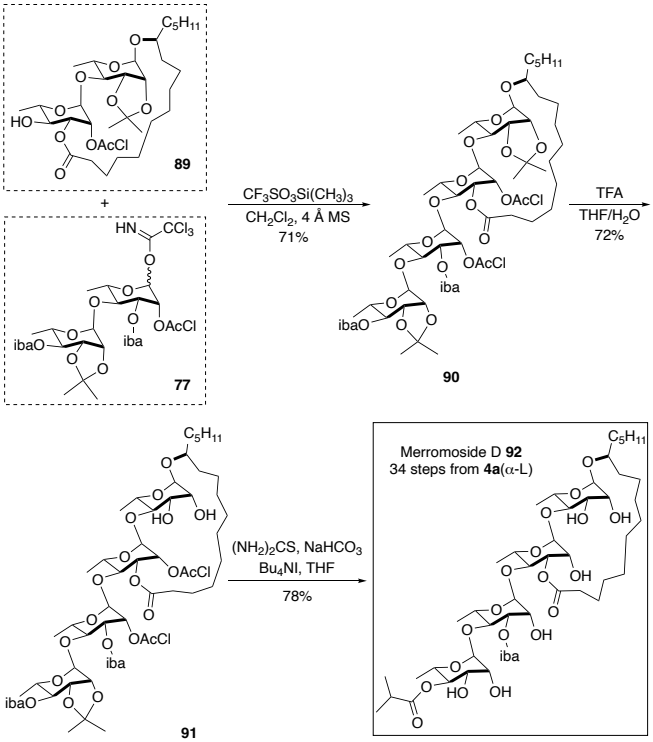
The approach to the macrolactone fragment **89** began with the synthesis of the methyl jalapinolate **81**, which is the aglycon portion of the macrolactone (Scheme 14). This *de novo* asymmetric aglycon synthesis began with the Noyori asymmetric reduction of achiral ynone **78** to give propargyl alcohol **79**. An alkyne-zipper isomerization and TBS-protection were used to convert **79** into terminal alkyne **80**. An oxidative alkyne cleavage and Fisher esterification with concomitant TBS-deprotection were used to prepare the methyl jalapinolate **81**. A Pd-catalyzed glycosylation between **81** and pyranone **4a**(α-L) gave monosaccharide **82**. A Luche reduction of **82** gave allylic alcohol **83**, followed by an Upjohn dihydroxylation to form *rhamno*-sugar **84**. An acetonation of the *C*-2/3 diol of **84** gave **85** with a free *C*-4 alcohol, which was Pd-glycosylated with pyranone **4a**(α-L) to give monosaccharide **86** after a Luche reduction. A protection of the *C*-4 alcohol in **84** followed by Upjohn dihydroxylation and ester hydrolysis gave seco-lactone **87**. A Corey-Nicolaou macrolactonization of **87** gave a mixture of regioisomeric macrolactones **88a** and **88b** (1:4),[72] which was unfortunately biased toward the wrong regioisomer **88b**. It should be noted that Yang *et al*. generated a similar mixture.[64] The minor isomer could be separated from this mixture, and the major isomer could be equilibrated to afford a 1:2 ratio of **88a** to **88b**. The minor macrolactone, isolated from both of these mixtures, could be protected as a chloroacetate, and the Bn-group could be removed by hydrogenolysis to afford the desired fragment **89**.

Scheme 14: Synthesis of the Merromoside D Lactone



The two fragments were stitched together by means of a convergent TMSOTf-catalyzed Schmidt glycosylation (Scheme 15). This was accomplished by treating a 2:1 mixture of disaccharide glycosyl donor **77** and disaccharide glycosyl acceptor **89** with TMSOTf (12%, $CF_3SO_3Si(CH_3)_3$) to afford tetrasaccharide **90** with complete α-selectivity via the anchimeric assistance of the *C*-2 chloroacetate (Scheme 15). The tetrasaccharide **90** was deprotected by a 2-step procedure. Specifically, the acetonide of **90** could be removed with TFA to furnish tetraol **91**. Finally, the two chloroacetate groups in **91** were removed with thiourea to provide merremoside D (**92**). While the preponderance of evidence suggests that the synthetic material was consistent with the natural material (specific rotation, melting point and HRMS), the comparison of the spectral data was complicated by the limited NMR data reported for the isolated merremoside D.[66]

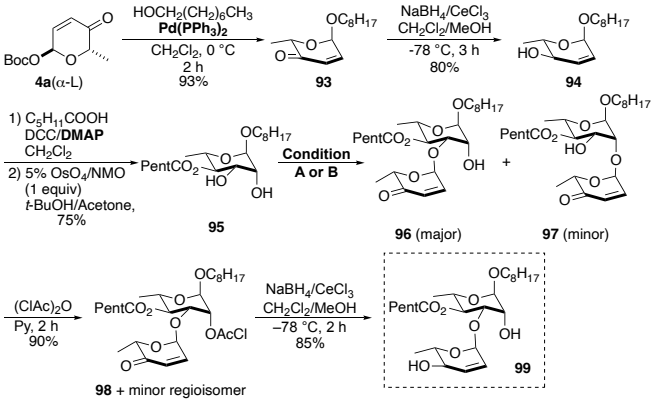
Scheme 15: Synthesis of the Merromoside D (end game)



3.8 Synthesis of Mezzettiaside

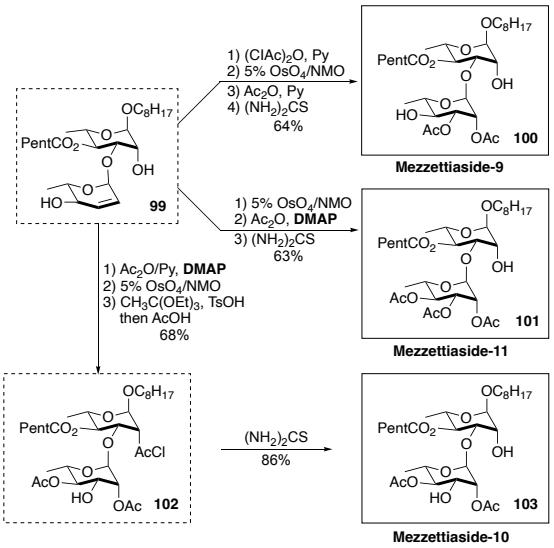
Our final application of this asymmetric Achmatowicz approach to oligosaccharides was one aimed at the family of natural products known as the messettiasides.[73] Like the cleistriosides and cleistetrosides, the messettiasides make up a family of acetylated rhaman type oligosaccharides (Schemes 16-19).[74,75] In our approach to this class of natural products was aimed at an efficient synthesis of the entire class of the natural products, which minimizes the use of protecting groups and the total number of steps to the all the member of the natural product

Scheme 16: Synthesis of the Mezzettiaside Core Disaccharide



family. Our approach to the mezzettiaside family of natural products was based upon a modular strategy with the identification of three key building blocks, disaccharide **99**, trisaccharide **106** and tetrasaccharide **111**.

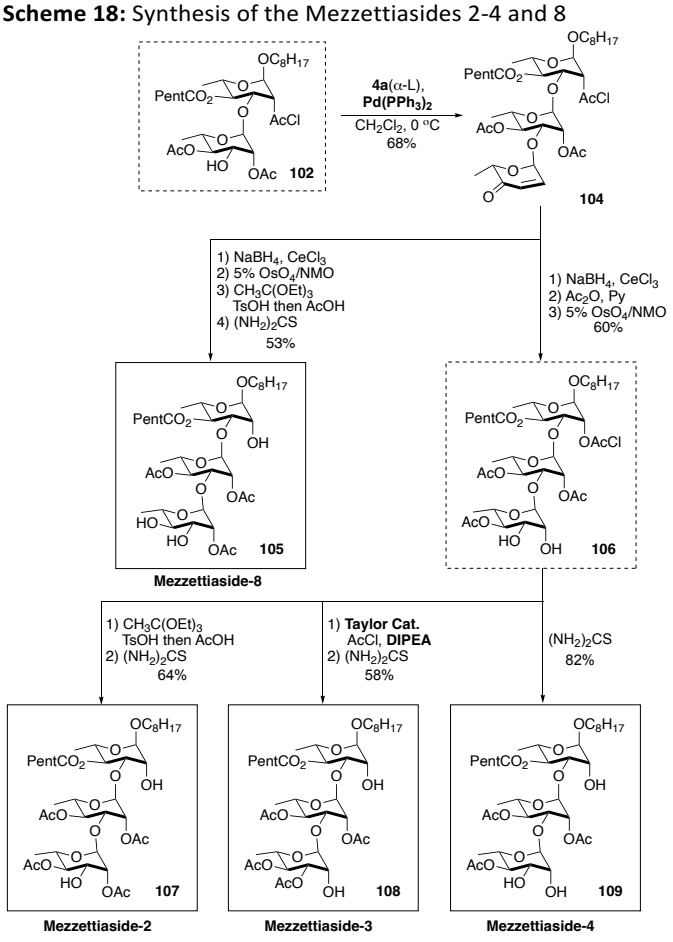
Scheme 17: Synthesis of the Mezzettiasides 9-10



The synthesis of the key disaccharide **99** began with the Pd-catalyzed glycosylation of *n*-octanol with pyranone **4a**(α-L) to give aculose sugar **93** (Scheme 16). A 1,2-reduction of enone **93** under the Luche condition gave allylic alcohol **94**. This allowed for the selective installation of an *n*-hexanoate group at *C*-4, followed by an Upjohn dihydroxylation to give diol **95** with *rhamno*-stereochemistry. As with our cleistrioside/cleistetroside syntheses, the regio- and stereo-selective glycosylation/chloroacylation of monosaccharide **95** could be accomplished using stochiometric tin acetal chemistry (*e.g.*, $Bu_2Sn{=}O$).[51] Without the use of tin acetal chemistry, the wrong regioisomer was produced as the major product. Specifically, a 1:2 mixture of regioisomer *C*-3 vs *C*-2 (*i.e.*, **96**:**97**) was produced when the Pd-glycosylation was performed on diol **95**. Although it was difficult to reproduce, we have found that when the tin acetal of diol **95** was glycosylated under our typical Pd-glycosylation conditions, the desired regioisomer **96** was selectively produced (~7:1 of **96**:**97**).[73] A practical alternative to this reproducibility problem emerged when we turned to the use of the Taylor catalyst ($Ph_2BOCH_2CH_2NH_2$)[76] over the stochiometric tin acetal chemistry. The resulting dual nucleophilic/electrophilic catalytic system resulted in a much more reactive B/Pd-catalyst system. Presumably, this increased reactivity is due to the anionic nature of the borinate complex make them an ideal coupling partner with the cationic Pd-π-allyl complex. Our optimized conditions using the Taylor catalyst (3% $Pd_2(dba)_3{\cdot}CHCl_3/4PPh_3$, 15 mol% $Ph_2BOCH_2CH_2NH_2$ in CH_2Cl_2) typically used a 3:1 ratio of boron to palladium. Using these conditions, CH_3CN/THF (10:1) as solvents gave a 8:1 ratio of **96** to **97**. The *C*-2 alcohol of the mixture could be chloroacylated ($(ClAc)_2O$, 10 mol% DMAP in Py) to form a similar mixture of regioisomer **98**. Then the enone could be reduced under the Luche condition to form the key disaccharide **99**, at this point the minor regioisomer could be removed chromatographically.

At this stage, the key disaccharide **99** served as a lynch pinpoint in the synthesis providing access to three disaccharide mezzettiasides, specifically, mezzettiaside-**9**, **10**, and **11** (Scheme 17). This began a combination of allylic alcohol acylation, de-chloroacylation, and dihydroxylation. For the synthesis of mezzettiaside-**9** (**100**) the transformation was accomplished in four steps and started with the chloroacetylation of **99** at the *C*-4 position ($(ClAc)_2O$, 10 mol% DMAP in Py), followed by an Upjohn dihydroxylation (OsO_4/NMO(aq)), bis-acetylation (Ac_2O/Py) and finally bis-deprotection of the two chloroacetate groups (thiourea, $NaHCO_3$ and n-Bu_4NI) to give mezzettiaside-**9** (**100**). By simply not including the chloroacetylation step, the sequence resulted in a three steps mezzettiaside-**11** (**101**) synthesis. Using a slightly different sequence, the regioisomeric diacetate mezzettiaside-**10** (**103**) was prepared in four steps, *C*-4 acetylation, dihydroxylation, and *C*-2 ortho-ester regioselectively acetylation to form **102**. Then, a selective removal of the *C*-2 chloroacetate group gave mezzettiaside-**10** (**103**).

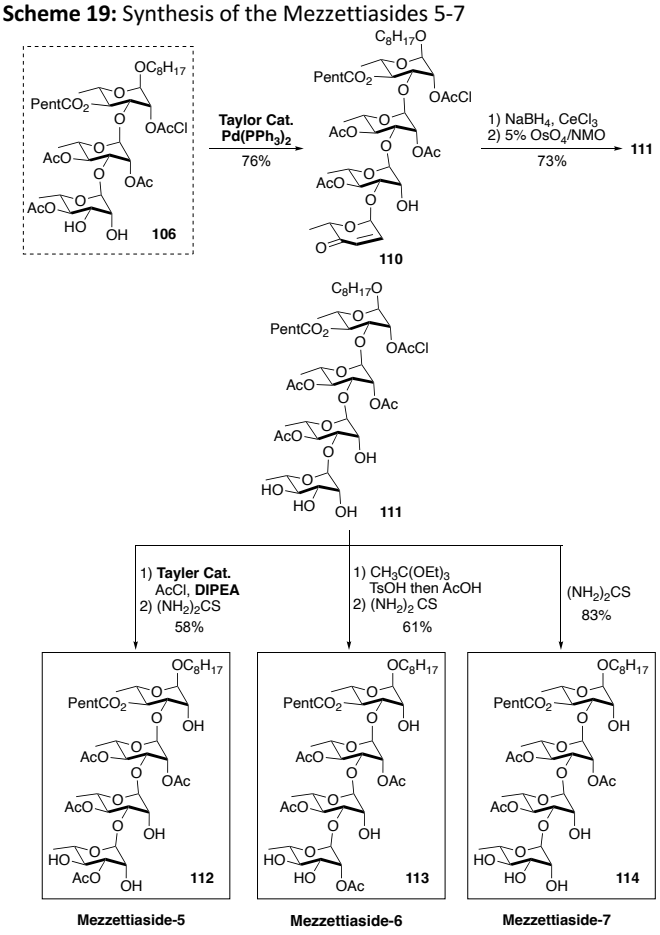
Scheme 18: Synthesis of the Mezzettiasides 2-4 and 8



The fully protected intermediate **102**, from the synthesis of mezzettiaside-**10** (**103**), was also the lynchpin for the syntheses of the larger trisaccharide mezzettiasides (Scheme 18). The approach to the trisaccharide mezzettiasides **2**-**4** and **8** (**109**, **108**, **107**, and **105**) began with the Pd-catalyzed glycosylation of disaccharide **102** with pyranone **4a**(α-L) to give trisaccharide **104**. A 4-step sequence (reduction, dihydroxylation, *C*-2 acylation, and chloroacetate

deprotection) was used to convert trisaccharide **104** into mezzettiaside-**8** (**105**). A 3-step sequence (reduction, *C*-4 acylation, dihydroxylation) on trisaccharide **104** was used to convert it into pivotal trisaccharide intermediate **106**, which could be used to prepare messettiasides **2**-**4**. For the conversion to messettiaside-**4** (**109**), all that was need was the deprotection of the chloroacetate with thiourea. A 2-step procedure was used (*C*-2 acetylation and chloroacetate deprotection) for the conversion to messettiaside-**3** (**108**). Similarly, a 2-step procedure was used (*C*-3 acetylation and chloroacetate deprotection) for the conversion to messettiaside-**2** (**107**).

Scheme 19: Synthesis of the Mezzettiasides 5-7

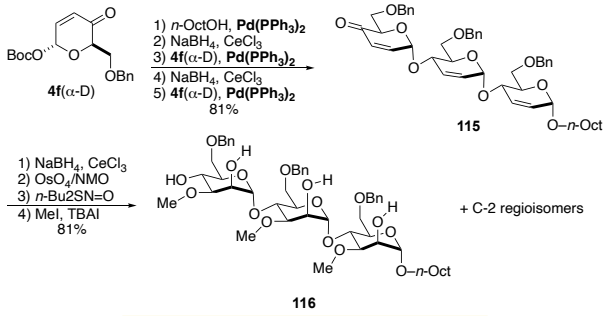


The key tris-*rhamno*-trisaccharide intermediate **106** for the trisaccharide mezzettiasides syntheses was also used for the synthesis of the tetrasaccharide mezzettiasides (mezzettiaside **5**-**7**) (Scheme 19). This was accomplished with a *C*-3 regioselective dual B-nucleophilic/Pd-electrophilic catalyzed glycosylation (2.5 mol% $Pd_2(dba)_3$•$CHCl_3$/4PPh_3, 15 mol% $Ph_2BOCH_2CH_2NH_2$ in THF/CH_3CN) to give tetrasaccharide enone **110**. The enone in **110** was converted into a *rhamno*-sugar **111** by a Luche reduction and Upjohn dihydroxylation. A regioselective borinate-catalyzed *C*-3 acetylation followed by chloroacetate deprotection was used to convert **111** into mezzettiaside-**5** (**112**). Similarly, an orthoester-mediated *C*-2 acetylation and chloroacetate deprotection were used to give mezzettiaside-**6** (**113**). Finally, a direct chloroacetate deprotection of **111** provided the final tetrasaccharide natural product, mezzettiaside-**7** (**114**).

3.9 Pd-glycosylations in oligosaccharide synthesis by others

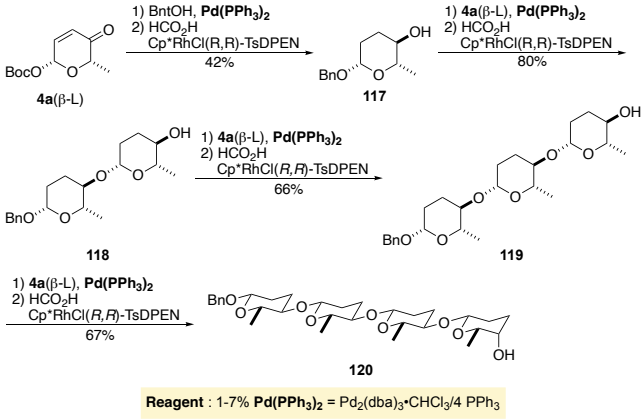
The overall acceptance of this approach can be seen by its use by others in the synthesis of carbohydrate-based natural products and oligosaccharides (Scheme 20 and 21). An example of this is the Lowary synthesis of the *C*-3 *O*-Me-mannose trisaccharide **116**. The synthesis began with the iterative Pd-glycosylation of *n*-octanol with **4f**(α-D), Luche reduction to give enone containing trisaccharide **115**. A subsequent Luche reduction of **115** followed by a per-dihydroxylation gave a tris-*manno*-trisaccharide, which was selectively methylated at the three *C*-3 positions to give **116**.[77]

Scheme 20: Lowary Synthesis of 1,4-Oligomers



An alternative example of this approach can be seen in the Tang synthesis of the tetrasaccharide **120** (Scheme 21).[34] A novel feature of the Tang approach was the development of a chiral catalyst to give a reagent control enone reduction to install an amecitose or rhodinose sugar. The Tang synthesis of **120** began with the Pd-glycosylation of BnOH with **4a**(β-L), followed by a Rh-catalyzed per-reduction of the enone to give the amecitose monosaccharide **117**. Simply repeating this 2-step process gave disaccharide **118** and then again trisaccharide **119**. Finally, the orthogonality of the reagent control was demonstrated by the introduction of a rhodinose sugar to form **120**. This was accomplished with the Pd-glycosylation of **119** with **4a**(β-L), followed by a Rh-catalyzed per-reduction with the enantiomeric ligand system to give the rhodinose sugar of tetrasaccharide **120**.

Scheme 21: Tang Synthesis of 1,4-Oligomers



4.0 Conclusions

For the last 25 years, we have been exploring the use of asymmetric catalysis in combination with Achmatowicz rearrangement for the "de novo asymmetric synthesis of carbohydrate". We refer to these syntheses as "de novo asymmetric" when the synthesis begins with achiral starting materials and when asymmetric catalysis is used for the installation of all the asymmetry. As part of these efforts, we have developed two orthogonal de novo asymmetric approaches to hexoses: an iterative dihydroxylation strategy and an Achmatowicz strategy. While there have been numerous de novo asymmetric approaches to carbohydrates, their applications to oligosaccharides have been a noticeable deficiency. In contrast to the other approaches, the asymmetric Noyori/Achmatowicz approach to carbohydrates has shown great capacity for the synthesis of oligosaccharide targets. This is presumably due to the compatibility of the Pd-catalyzed glycosylation reaction to a myriad of functional groups. Key to the success of the approach is the coupling of asymmetric catalysis with the Achmatowicz rearrangement for the synthesis of stereochemically simplified D- and L-pyranones with α- and β-stereochemistry. Thus, simplifying the 32 possible hexose monosaccharides down to 4 stereoisomers. For this approach to be viable, it relies upon a growing set of highly diastereoselective post-glycosylation reactions for the installation of the rest of the desired monosaccharide stereochemistry. The overall efficiency of these approaches is the result of the strategic use of the enone functionality in the pyranone as atom-less protecting groups. While this use of atom-less protecting groups has been under-explored in carbohydrate chemistry, the success of the above approaches suggests that this strategy should be given more attention by the synthetic organic chemistry community. The overall practicality of these syntheses can be seen in their ability to provide material for medicinal chemistry studies, often in ways that are not readily available by traditional carbohydrate syntheses.[1,6]

Conflicts of interest

There are no conflicts to declare.

Author Contribution

This article was composed and edited collaboratively with all the authors contributing.

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