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Review

Sugar Asymmetry: The Evolution of De Novo Asymmetric Syntheses of Carbohydrates from Hexoses to Oligosaccharides

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Abstract: The ability to recognize hidden symmetry in a highly asymmetric world is a key factor in how we view and understand the world around us. Despite the fact that it is an intrinsic property of the natural world, we have an innate ability to find hidden symmetry in asymmetric objects. The inherent asymmetry of the natural world is a fundamental property built into its chemical building blocks (e.g., proteins, carbohydrates, etc.). This review highlights the role of asymmetry in the structure of the carbohydrates and how these stereochemical complexities present synthetic challenges. This survey starts with an overview of the role synthetic chemistry plays in the discovery of carbohydrates and their 3D structure. This review then introduces various de novo asymmetric synthetic approaches that have been developed for the synthesis of carbohydrates and, in particular, oligosaccharides. The two most successful strategies for oligosaccharide synthesis rely on diastereoselective palladium-catalyzed glycosylation. The first uses an Achmatowicz reaction to asymmetrically prepare pyranose building blocks along with a substrate-controlled Pd-glycosylation. The other strategy couples a ligand-controlled Pd-glycosylation with a ring-closing metathesis for oligosaccharide assembly.

Keywords: carbohydrates; hexoses; pyranoses; oligosaccharides; de novo asymmetric synthesis

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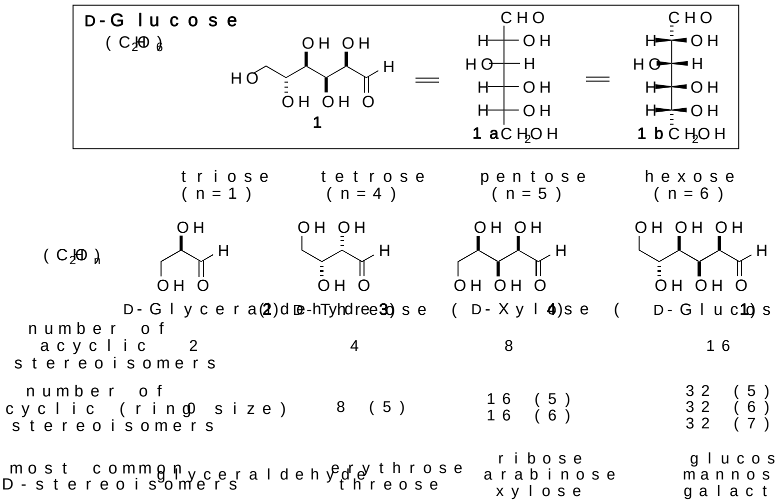
1. Introduction

There appears to be an innate attraction to symmetry. This attraction is evident in how we explain and apply mathematical concepts, especially in geometry, where seeing potential symmetry helps simplify and better understand concepts. In fact, an appreciation for symmetry likely underlies aphorisms such as "symmetrical faces are more beautiful" [1]. The natural tendency to notice hidden symmetry in the physical objects we see and the mathematical formulas we derive is probably best viewed as a generalization of how we view and understand nature rather than a perfect model of nature [2]. This simplification is necessary, as a hallmark of all living organisms is inherent asymmetry. In fact, it has been suggested that the overuse of symmetry is behind our ability to recognize very lifelike robot faces as being artificial (also known as the uncanny valley) [3]. In contrast to humans' preference for seeing symmetry, asymmetry is a hallmark of the natural world.

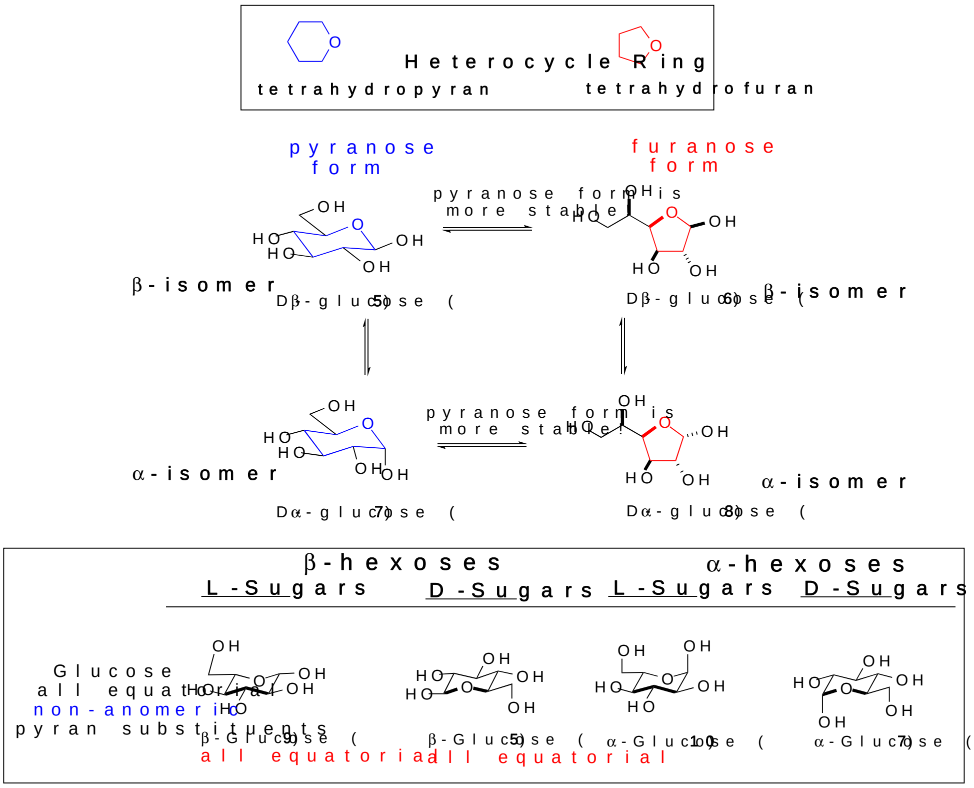
Young artists often encounter nature's asymmetry when taught to break with symmetry in drawing [4], for example, when they lower a branch on one side of a tree to create a more natural appearance. This is a process called desymmetrization. When viewed in this way, inherent asymmetry in natural systems allows for access to more states or the more efficient filling of space. This phenomenon of asymmetrically filling three-dimensional space can also be seen in organic chemistry. Asymmetry arises when four different atoms or groups are attached to a single carbon atom, forming what is called a chiral carbon. The term "chirality" comes from the Greek word for "hand", referring to two mirror-image molecules called enantiomers. In chemistry, enantiomers of chiral molecules are distinguished from one another with (+)/(–), D-/L- or R-/S-labeling systems [5].

There is a fundamental preference for one enantiomer over another in the biomolecules of nature (e.g., D-sugars and L-amino acids) that result from various diastereomeric interactions (i.e., right/right-handed vs. right/left-handed interactions) in biosynthesis. This enantiomeric preference is amplified when nature's chiral building blocks oligomerize into biopolymers. Proteins that are made of many amino acids have more chiral centers, which leads them to exhibit significantly greater asymmetry. This increase in stereochemical complexity can also be seen in the structures of DNA (from nucleosides) and oligosaccharides (from sugars). In this context, stereochemical complexity can be defined in terms of both the number of stereocenters (n) and the possible stereoisomers (2^n). Correspondingly, nature's stereochemical bias is evident by the fact that only one of the possible isomers is produced. One can view nature's predetermined stereochemical bias (e.g., D-sugars, L-amino acids) as resulting from the downstream effect of the diastereoselectivities inherent in the replication chemistry of life. An interesting result of the chiral bias in biosynthesis is that there are a greater number of molecular structures and three-dimensional spaces that are not used in the biomolecules of nature (Scheme 1).



Scheme 1. Monosaccharides and their stereochemical complexity from C-3 to C-6.

Of the building blocks that form biopolymers, carbohydrates possess the greatest degree of stereochemical complexity. For example, the hexose D-glucose **1**, the most common six-carbon carbohydrate, has four chiral centers in its acyclic form and five in its cyclic forms. In their simplest forms, carbohydrates are compositionally defined by the molecular formula $(CH_2O)_n$, where n is the number of carbon atoms in the chain. When the carbon count reaches three (triose), the simplest chiral carbohydrate, glyceraldehyde **2**, is formed, with a single chiral center at the C-2 position. Glyceraldehyde can exist in a D- or L-configuration, where the D-glyceraldehyde has R-configured alcohol at C-2 and the L-glyceraldehyde is S-configured at C-2. This simple choice of D- vs. L-sugars fundamentally establishes the chiral bias of carbohydrates in nature. In four-carbon sugars (tetroses), a second stereocenter arises, resulting in four possible acyclic stereoisomers (2^2) and eight cyclic, five-membered ring (furanose) isomers (2^3). Five-carbon sugars (pentoses), having three chiral centers, yield eight acyclic stereoisomers (2^3). Additionally, they form two sets of sixteen cyclic isomers (2^4), consisting of furanoses and pyranoses (six-membered rings). Finally, hexose sugars, with four stereocenters, yield sixteen acyclic stereoisomers (2^4) and three sets of thirty-two cyclic isomers (2^5), including furanose, pyranose, and septanose (seven-membered ring) forms (Scheme 2).



Scheme 2. Cyclic hexoses in their cyclic furanose and pyranose forms.

Among the eight possible diastereomers of acyclic D-hexoses, nature primarily uses three in its biopolymers: glucose, mannose (C-2 epi-glucose), and galactose (C-4 epi-glucose), with glucose representing the majority of the monosaccharides used. In fact, glucose monomers make up the most prevalent oligosaccharides in nature: cellulose and amylose (also known as starch). When glucose is in an aqueous solution, it exists primarily in its cyclic form (~99%) with only a negligible amount in its acyclic form (<1%). Of the possible cyclic forms, glucose exists almost exclusively in the pyranose form, with minimal amounts (<1%) of the furanose form and undetectable amounts of the septanose forms.

The hydroxy-aldehyde functionality of the hexoses can reversibly form cyclic structures, primarily five- and six-membered rings with a hemiacetal functionality at the C-1 position (Scheme 2). In the case of the furanose and pyranose rings, the equilibrium constant lies heavily in favor of the cyclic structures. In the cyclic form, the C-1 group is called the anomeric position, which is the point of attachment for the glycosidic bond. When in a chair conformation, the newly formed hemiacetal introduces a hydroxyl group and a new chiral center at the anomeric position. When the hydrogen of the anomeric hydroxyl group (OH) is replaced with an alkyl-group (OR), the newly formed acetal product is called an alkyl-glycoside. The anomeric group can have a configuration that is either trans (alpha (α)-stereochemistry) or cis (beta (β)-stereochemistry) relative to the C-6 substituent. There is a balance between countervailing steric and electronic effects that favor the α- and β-stereoisomers. While the equatorial β-isomer is sterically preferred, the axial α-isomer is electronically preferred. This electronic preference, called anomeric effect, arises from the antiperiplanar arrangement, where hyperconjugation provides electronic stabilization to the α-isomer.

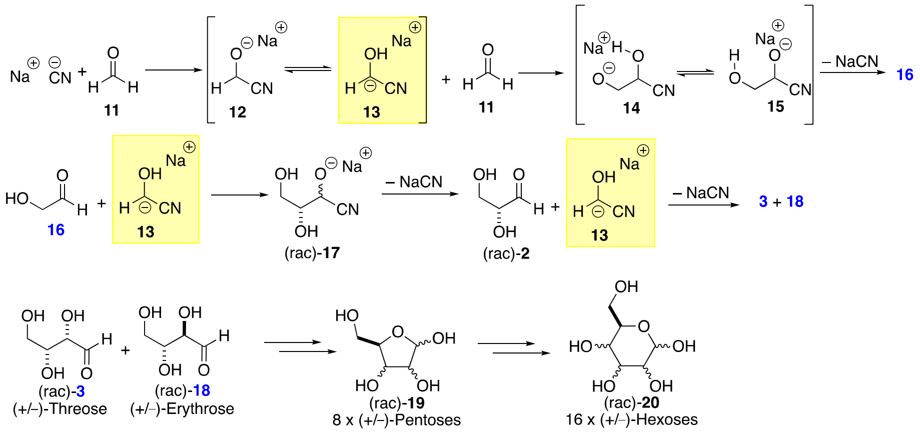
A final element of structural complexity can be introduced when a sugar is connected via the anomeric position to another sugar (i.e., disaccharide). In the disaccharide case, when both hexoses are in their pyranose forms, there are ten possible isomers. This results from a combination of the five possible connections (regioisomers) with two possible stereochemistries (α/β). The structural complexity increases quickly when progressing from disaccharides and trisaccharides to oligosaccharides. In mammalian cells, the most common oligosaccharide connections are limited due to enzymatic specificity and biosynthetic constraints. For example, cellulose is usually a 1,4-linked oligomer of glucose with the anomeric position in the β-configuration, whereas amylose (starch) contains 1,4- and 1,6-linked oligomers of glucose with the anomeric position in the α-configuration. A greater degree of structural complexity in terms of sugars and connectivities exists in the various mammalian glycoprotein and glycolipid structures. This complexity is used by cells and proteins to communicate identity via the immune system. The situation becomes even more complex in the non-mammalian systems, as a significantly larger range of carbohydrate structures and oligosaccharide connectivity can be found therein.

In mammalian cells, there are at least nine common monosaccharides, as defined by sugars that function as enzyme substrates. In addition to the three main monosaccharides in mammalian cells (glucose, mannose, and galactose), there are six other monosaccharides. These include four hexoses (*N*-acetylglucosamine, *N*-acetylgalactosamine, glucuronic acid, and fucose), a pentose (xylose) and, a nonose (sialic acid). Of these mammalian sugars, the hexose fucose is unique in that it is an L-sugar (6-deoxy-L-galactose). Other non-mammalian rare sugars that are commonly contained in natural products are the six-deoxy sugars D-quinovose (6-deoxy-D-glucose) and L-rhamnose (6-deoxy-L-mannose), the 2,6-dideoxy sugars D-olivose (2,6-dideoxy-D-glucose) and D-digitoxose (2,6-dideoxy-D-allose), and the 2,3,6-trideoxy sugars, L-amicetose (2,3,6-trideoxy-L-glucose) and rhodinose (2,3,6-trideoxy-L-galactose).

Historically, organic synthesis has played a critical role in the development of carbohydrate chemistry. This began in the 1800s with the formose synthesis of sugars as part of an effort to prove their molecular formulae $(CH_2O)_n$ [6]. Then, in the 1890s, carbohydrate synthesis evolved into the use of stereodivergent synthesis to assign the stereochemistry of the hexoses. This was followed by the development of glycosylation reaction methods for forming the glycosidic bond stereoselectively. This glycosylation chemistry was developed in combination with protecting group strategies for the regioselective construction of oligosaccharides. As the need for greater structural diversity and complexity grew, synthetic chemistry evolved from diastereoselective synthesis to enantioselective chemistry. This growth in synthetic capability ultimately led to the use of asymmetric catalysis for the synthesis of hexoses, which is called "de novo asymmetric synthesis" [7–10]. Herein, this review will explore the historical development of these asymmetric synthetic methods.

2. Formose Synthesis

The structure and synthesis of sugars was an early topic of discovery during the emergence of organic chemistry in the 19th century. This research effort began with the realization that simple sugars shared the empirical formula CH_2O with formaldehyde **11**, one of the simplest organic molecules ($O{=}CH_2$). Thus, the hexose glucose $(CH_2O)_6$ and the related shorter sugars $(CH_2O)_n$ can be viewed as oligomers of formaldehyde $(CH_2O)_1$. Importantly, this oligomerization mechanism for formose synthesis is significantly different than for the oligomerization process that converts formaldehyde to paraformaldehyde $(O{-}CH_2)_n$ (Scheme 3). The initial attempts to oligomerize formaldehyde into sugars using $Ca(OH)_2$ bases were met with limited success. Better results were found when the base catalyst was switched to cyanide salts. The use of NaCN enabled iterative benzoin-type condensation for carbohydrate chain growth (e.g., **11** to **16** to **3** + **18**) [11]. Further improvements were achieved when the cyanide was replaced with *N*-heterocyclic carbene (NHC) catalysts like thiazolium salts [12]. However, it should be noted that these processes lack the ability to control stereochemistry or the number of carbons in sugar products. When aqueous formaldehyde **11** is treated with NaCN as a catalyst, stereochemically complex mixtures of the two-carbon sugar (glycolaldehyde **16**), trioses (racemic glyceraldehyde **2**), and tetroses (racemic threose **3** and erythrose **18**) are formed. Once sugars capable of forming stable hemiacetals are produced, the oligomerization process begins to slow down, as this hemiacetal formation removes a significant amount of the reactive aldehydes. However, longer-chain sugars like the pentoses (*rac*-**19**) and the hexoses (*rac*-**20**) can also be detected.



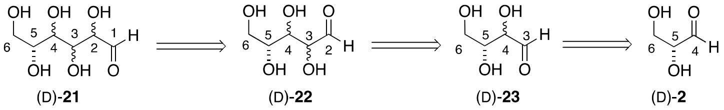
Scheme 3. The formose synthesis of sugars and reaction mechanism.

The mechanism of chain propagation in the formose synthesis begins with the cyanide attack on formaldehyde **11** to form oxyanion **12**, which equilibrates to carbanion **13**. The insight gained from the understanding of this mechanism underlying this equilibrium process was fundamental in the development of many related Stetter-type processes and our understanding of thiamine biochemistry [13–15]. The nucleophilic carbanion **13** can be added to another molecule of formaldehyde **11** to form alkoxide **14**, which can equilibrate further to alkoxide **15**. Because of the proximity of the alkoxide anion in **15** to the cyano group, **15** can eliminate an equivalent of sodium cyanide, forming the simplest of the sugars, glycolaldehyde **16**. Under the same reaction conditions, the aldehyde in **16** can further react with **13** via an analogous addition and proton migration to form **17**, which can similarly eliminate cyanide to form glyceraldehyde **2** as a racemic mixture. After another round of addition/isomerization/elimination between *rac*-glyceraldehyde **2** and **13**, a mixture of the racemic *cis*-triol threose **3** and *trans*-triol erythrose **18** is produced. Further extension by one or two carbons (via carbanion **13**) leads to eight possible pentose diastereomers **19** or 16 possible hexose diastereomers **20**, both as racemates. A full appreciation of the extent of the product mixture formed, including stereochemical diversity and chain lengths, only became possible with the development of modern analytical methods, although it should be noted that this work inspired the synthetically practical stepwise approach of Dondoni [16].

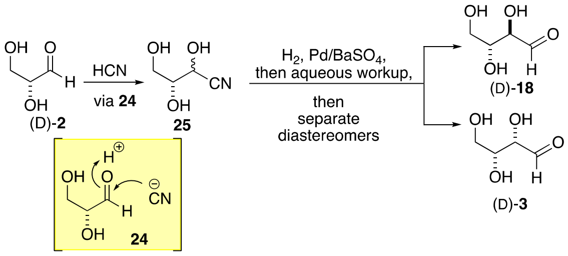
3. Fischer Synthesis of the Hexoses

The full stereochemical complexity of hexoses was not completely understood until the late 19th century. This insight was gained from synthetic and structural chemistry studies by Emil Fischer. The Fischer synthesis and structural proof of hexoses were accomplished through a combination of a stepwise one-carbon homologation (chain growth) and a stepwise one-carbon degradative (chain reduction) reaction sequence. The homologation chemistry involved cyanohydrin formation (HCN addition to the aldehyde carbon of the sugar), followed by reduction and hydrolysis to form the aldehyde carbon of the new sugar. This process builds a two-carbon sugar into the trioses and onward (e.g., glyceraldehyde **2**, to erythrose/threose **23**, etc.).

In contrast to the stereo-randomness of the formose process, the Fischer approach is stepwise and, as a result, introduces only one stereocenter at a time (Scheme 4). This allows for the separation of the diastereomers, which can then be subjected again to the cyanohydrin formation, reduction, and hydrolysis to exclusively prepare two new homologated stereoisomers (Scheme 5). Thus, glyceraldehyde **2** is converted into a mixture of tetrose sugars **23**, which can be separated into erythrose **8** and threose **3**. In turn, the mixture of tetroses can be converted into a mixture of pentoses **22**, and finally to a mixture of hexoses **21** (Scheme 4). Alternatively, the purified erythrose **18** can be selectively converted into arabinose **27** and ribose **26**. Similarly, threose **3** can be selectively converted into xylose **4** and lyxose **31** (Scheme 6).



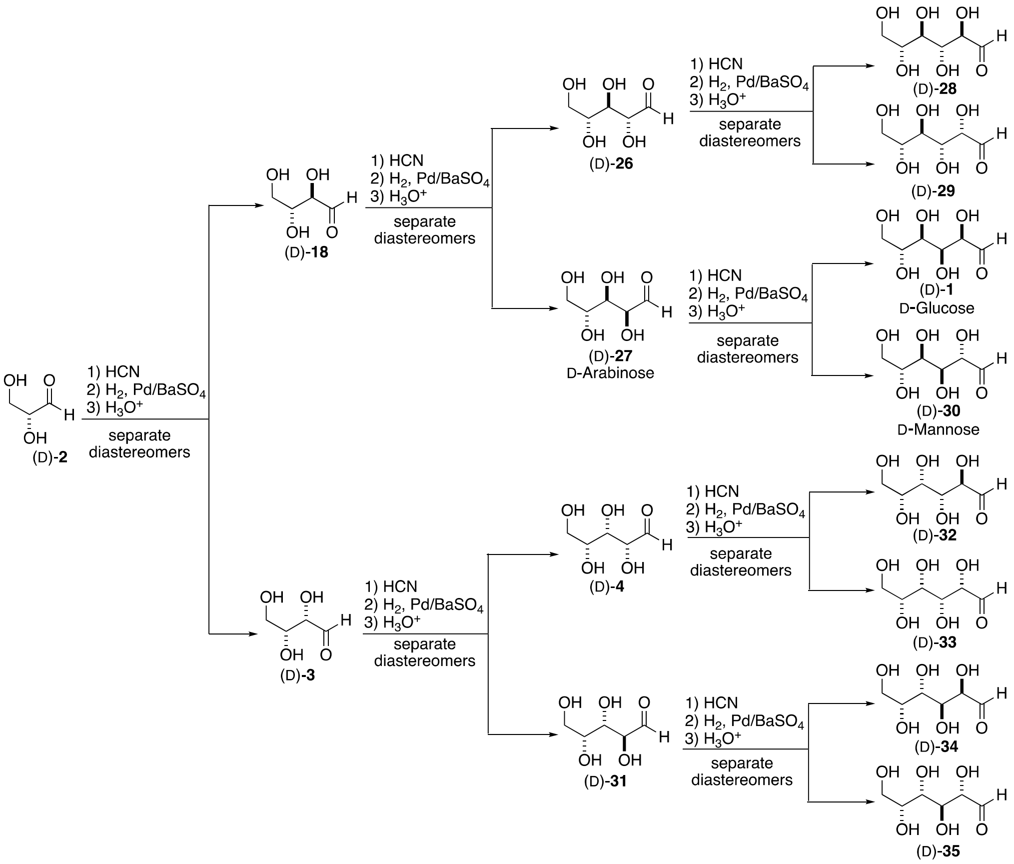
Scheme 4. Retrosynthesis for the Fischer stereodivergent synthesis of the hexoses.



Scheme 5. The Fischer stereodivergent cyanohydrin formation/reduction and separation (chain homologation).

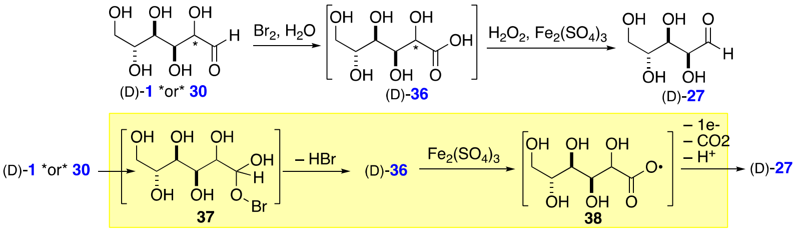
The basic three-step process developed by Fischer is outlined in Scheme 5. This process involved cyanohydrin formation, reduction/hydrolysis, and separation. The process began with the addition of HCN to D- or L-glyceraldehyde **2** with the addition to the D-enantiomer shown. The nucleophilic addition of cyanide to either face of the aldehyde in glyceraldehyde (D)-**2** (via **24**) affords triol **25** as a diastereomeric mixture. The carbon/nitrogen triple bond in nitrile **25** was reduced to form a diastereomeric mixture of aldehydes. At this point, the two aldehydes, (D)-**3** and (D)-**18,** can be separated into optically pure forms. Importantly, the optical purity of (D)-**3** and (D)-**18** is determined by the configuration of the starting D-glyceraldehyde (D)-**2**. Thus, if L-glyceraldehyde (L)-**2** was used as the starting material, the products would be L-erythrose (L)-**18** and L-threose (L)-**3**. Conversely, using racemic glyceraldehyde (*rac*)-**2** would yield racemic erythrose (*rac*)-**18** and threose (*rac*)-**3**.

This same synthetic sequence of one-carbon chain extension and diastereomer separation can be further utilized to construct all the hexoses. Repeating the cyanohydrin formation, reduction/hydrolysis, and separation on the tetrose aldehydes, threose **3** yields the five-carbon sugars xylose **4** and lyxose **31**, featuring C-2/3 syn-stereochemistry derived from threose **3**. A similar three-step transformation was used to convert erythrose **18** into arabinose **27** and ribose **26**. In an analogous fashion, the four pentose sugars ribose **26**, arabinose **27**, xylose **4**, and lyxose **31** can be converted into the eight hexose sugars allose **28**, altrose **29**, glucose **1**, mannose **30**, gulose **32**, idose **33**, galactose **34**, and talose **35**.



Scheme 6. The Fischer synthesis of all the D-hexoses.

In practice, the essentially optically pure form of D- (or L-) glyceraldehyde **2** was obtained from readily available, naturally sourced hexoses via a retro version of the Fischer methodology. This was accomplished using the Ruff degradation reaction (Scheme 7) to dismantle the carbohydrate one carbon at a time, from the reducing end of the sugar. The two-step oxidative degradation begins with an oxidation of the aldehyde to a carboxylic acid via intermediate **37**, followed by an oxidative decarboxylation of the hydroxy acid via intermediate **38** to yield a shortened sugar with a C-1 (formerly C-2) aldehyde. Thus, Ruff degradation can produce pentose sugars from a hexose. For example, either glucose **1** or mannose **30** could be converted into arabinose **27** through the intermediate carboxylic acid **36**. Two further rounds of this chain length reduction would produce D-glyceraldehyde (D-**2**) from any D-hexose, or L-glyceraldehyde (L-**2**) from any L-hexose. Importantly, the resulting pentose sugar is produced as a single diastereomer, where the C-3 to C-5 stereochemistry of the hexose starting material matches the C-2 to C-4 stereochemistry of the pentose product. The high stereospecificity of both the cyanohydrin formation and the Ruff degradation were key factors in enabling Fischer to assign the stereochemistry of all the hexoses.

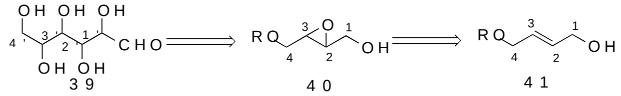


Scheme 7. The conversion of glucose/mannose to arabinose via Ruff degradation.

4. Sharpless De Novo Asymmetric Synthesis of the Hexoses

Since the seminal work of Fischer, synthetic chemists have used the structures of carbohydrates as inspiration for the development of new asymmetric methods for the synthesis carbohydrate motifs. Of particular interest are those routes to sugars that start from achiral starting materials, where asymmetric catalysis is used to install the initial asymmetry (i.e., D- or L-sugar). These asymmetric routes, starting from achiral materials, are referred to as "de novo" or "de novo asymmetric" routes. It should be noted that in the carbohydrate synthesis community the term de novo has taken on very different meanings. The de novo asymmetric synthesis of the hexoses has been an important and ongoing interest to the synthetic community. Of these approaches, only the iterative epoxidation strategy of Masamune and Sharpless provides access to all eight hexoses. Their work utilized iterative asymmetric epoxidation of allylic alcohols to obtain the eight possible L-hexoses [17,18].

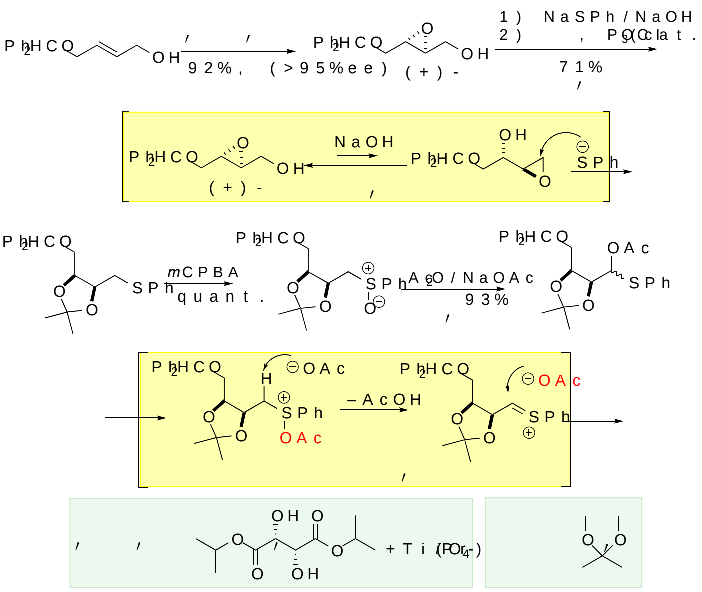
Retrosynthetically, the Masamune–Sharpless approach derives the asymmetry of the hexoses from a single *trans*-epoxide **38**, which can be prepared in either enantiomeric form by means of Sharpless Asymmetric epoxidation of achiral allylic alcohol **39** (Scheme 8). Like the Fischer synthesis of the hexoses, the route developed by Masamune and Sharpless is stereodivergent. That is to say, the route systematically builds stereochemical complexity in a synthetic method that branches to allow for the construction of all possible stereoisomers. The Sharpless epoxidation is accomplished by the use of an alkyl peroxide (e.g., cumene hydroperoxide) as the stoichiometric reagent and a catalytic amount of the complex that from the admixture of $Ti(O_i\text{-}Pr)_4$ and diisopropyl tartrate. As the process is catalytic in its use of chiral reagent, the asymmetric epoxidation can be viewed as a transformation that amplifies the net asymmetry. Thus, a single molecule of the Sharpless reagent can be used to generate a mole of enantiomerically pure chiral epoxide. Importantly, tartaric acid is readily available in both its D- and L-enantiomeric forms.



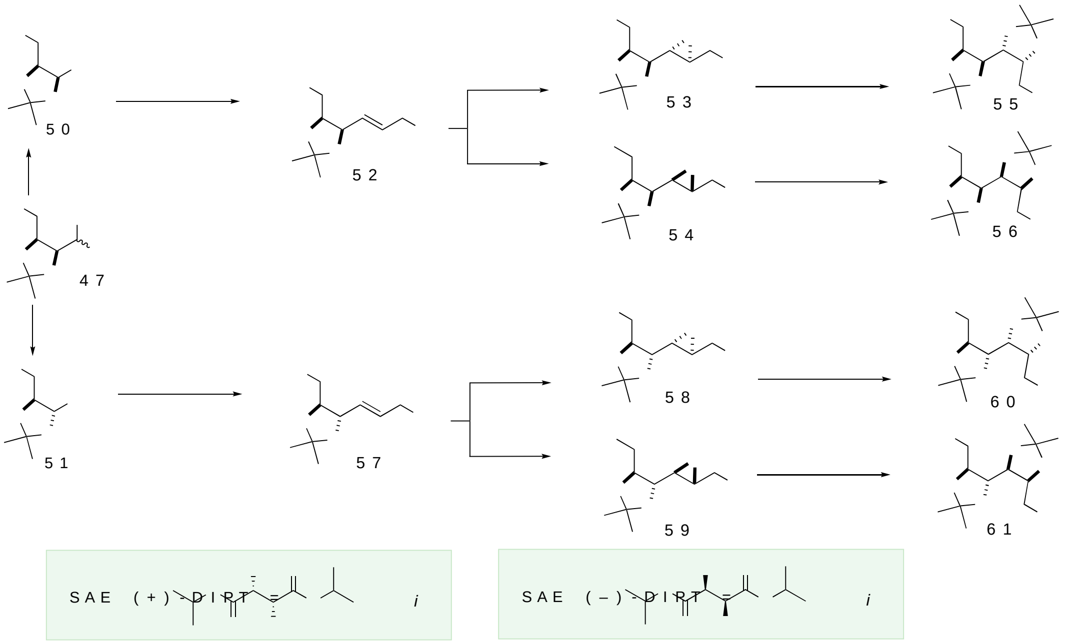
Scheme 8. Retrosynthesis for the Sharpless de novo asymmetric synthesis of the L-hexoses.

The Masamune–Sharpless approach involves the ability to add to hydroxyl groups across the *trans*-alkene of an allylic alcohol from either face in a net syn- or net anti-selective manner. In addition to the Sharpless epoxidation (**42** to **43**), the route developed by Masamune and Sharpless inventively involves the use of a Payne rearrangement (**43** to **45**), Pummerer reaction (**44** to **47**), and acetonide equilibration (**50** to **51**). The use of these reactions is outlined in Schemes 9 and 10.

This Masamune–Sharpless synthesis of the hexoses begins with the asymmetric epoxidation of (E)-4-diphenylmethoxy-2-en-1-ol **42** using the (+)-DIPT ligand system to give epoxide **43** in 92% yield and excellent enantioselectivity. Next, a base-mediated Payne rearrangement of internal epoxide **43** to intermediate terminal epoxide **45** was performed, preceding a regioselective epoxide opening using thiophenol to form a diol, which was acetonide protected as acetonide **44**. Next, thioether **44** was oxidized using *m*CPBA to give sulfoxide **46.** A subsequent Pummerer rearrangement of **46** using Ac_2O/NaOAc afforded acetate ester **47** as a diastereomeric mixture at the thio-substituted carbon (Scheme 9).



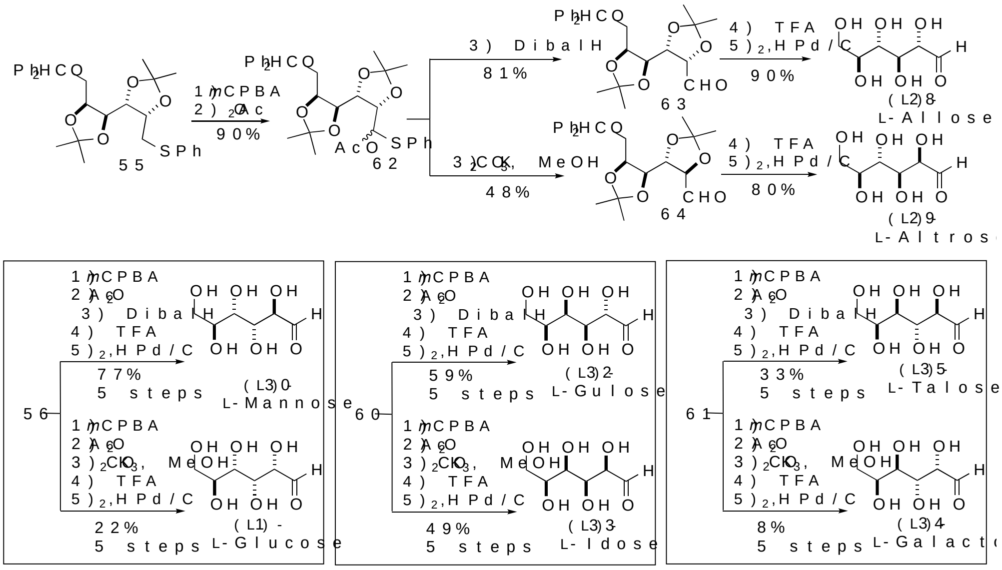
Scheme 9. Sharpless epoxidation/Payne rearrangement for the synthesis of cis-acetonide.



Scheme 10. Sharpless synthesis of C-6 sugars via cis-/trans-acetonide isomerization.

With two stereocenters established in **47**, stereochemical divergence was possible based on the different hydrolysis conditions used. When DIBAL-H was used to hydrolyze **47**, it produced aldehyde **50** in 91% yield without epimerization. Alternatively, when **57** was treated with K_2CO_3/MeOH, hydrolysis occurred in tandem with the desired base catalyzed epimerization at the adjacent stereocenter to form **51**. A Wittig reaction was applied to both **50** and **51** to extend each molecule by two carbons, followed by $NaBH_4$ reduction to afford terminal alcohols **52** and **57**, respectively. Asymmetric epoxidation using either the (+)-DIPT or (–)-DIPT was applied to **52** and **57** to generate four new diastereomeric epoxides—**53**, **54**, **58**, and **59** in 76%, 84%, 71%, and 73%, respectively. These epoxides were subjected to the NaSPH/Payne rearrangement, once again, to induce regioselective epoxide opening and hydrolysis. After acetonide formation, the protected tetraols **55**, **56**, **60**, and **61** were produced in 77%, 63%, 79%, and 86% yields, respectively (Scheme 10).

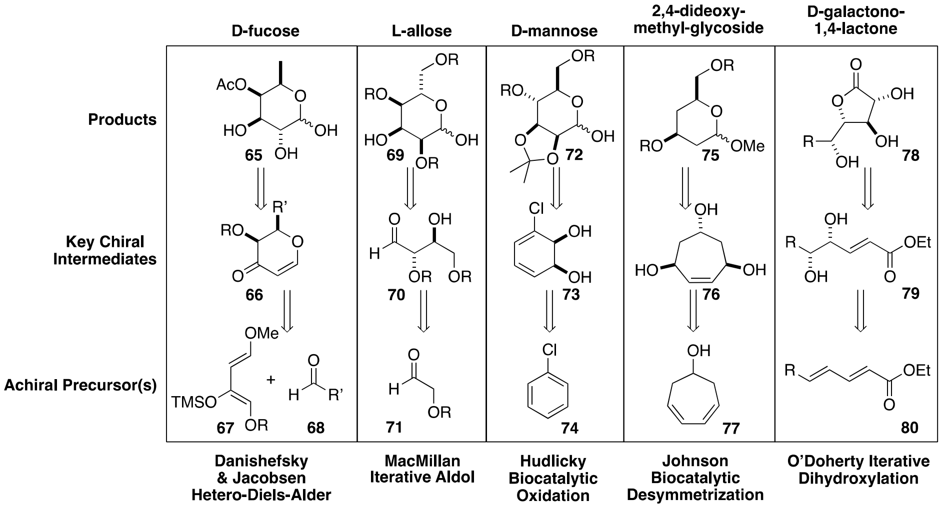
Each of the four acetonides (**55**, **56**, **60**, and **61**) could be converted into two L-sugars through three steps: oxidation, Pummerer rearrangement, and hydrolysis (with or without epimerization). For example, **55** was oxidized and rearranged to afford **62** in 90% yield. Then, **62** was hydrolyzed, with or without epimerization, to afford aldehydes **64** and **63**, respectively. Finally, these two protected L-sugars were acetonide deprotected, followed by hydrogenation to liberate the terminal alcohol, to afford L-allose (L)-**28** and L-altrose (L)-**29** in good yields. Correspondingly, L-mannose (L)-**30** and L-glucose (L)-**1** were produced from **56** in 77% and 22% yields, respectively. L-Gulose (L)-**32** and L-idose (L)-**33** were produced from **60** in 59% and 49% yields, respectively. Lastly, L-talose (L)-**35** and L-galactose (L)-**34** were produced from **61** in 33% and 8% yields, respectively (Scheme 11).



Scheme 11. End game for the Sharpless de novo asymmetric synthesis of the L-hexoses.

5. Other De Novo Asymmetric Carbohydrate Syntheses

In terms of synthetic efficiency, the Masamune–Sharpless approach to the hexoses is particularly impressive in how few total steps are required to prepare all eight hexoses. However, it should be noted that in terms of an asymmetric synthesis of a specific hexose, the Masamune–Sharpless route is step-intensive (~15 steps). In the subsequent years, significantly shorter and more efficient de novo asymmetric approaches have been developed to specific sugars (Scheme 12). Like the Masamune–Sharpless approach, these routes use highly enantio- and diastereo-selective reactions to install the two initial stereocenters, followed by diastereoselective transformations to establish the remaining sugar stereochemistry. A notable example of this can be seen in the use of the Jacobsen variant of the Danishefsky hetero-Diels–Alder reaction (**67** + **68**) for the synthesis of pyran **66**, which was used in the synthesis of fucose sugar **65** [19,20]. An asymmetric approach to an allose sugar **69** was developed by MacMillan from chiral fragment **70**, which was prepared by the dimerization of **71** via a proline-catalyzed aldol reaction [21,22]. Hudlicky developed an enantioselective synthesis of protected mannose derivative **72** from chiral diol **73**, which was prepared by the enzymatic oxidation of chlorobenzene **74** [23,24]. A related biocatalytic approach was developed by Johnson that uses the enzymatic desymmetrization of triol **76** in the synthesis of dideoxyglucose **75** [25,26]. There is also a mixed asymmetric dihydroxylation and enzymatic aldol approach by Wong and Sharpless [27]. Finally, another Sharpless asymmetric oxidation [28,29] was applied in the iterative dihydroxylation of dienoates, such as **80** [30], yielding galacto-lactones through the intermediate diol **79** [31–34]. At the end of the 20th century, the O'Doherty group developed a more systematic de novo asymmetric approach to the hexoses, based on the Achmatowicz oxidation of furan alcohols to pyran ketones (pyranones) in combination with a Pd-glycosylation reaction (vide infra) [35–37].

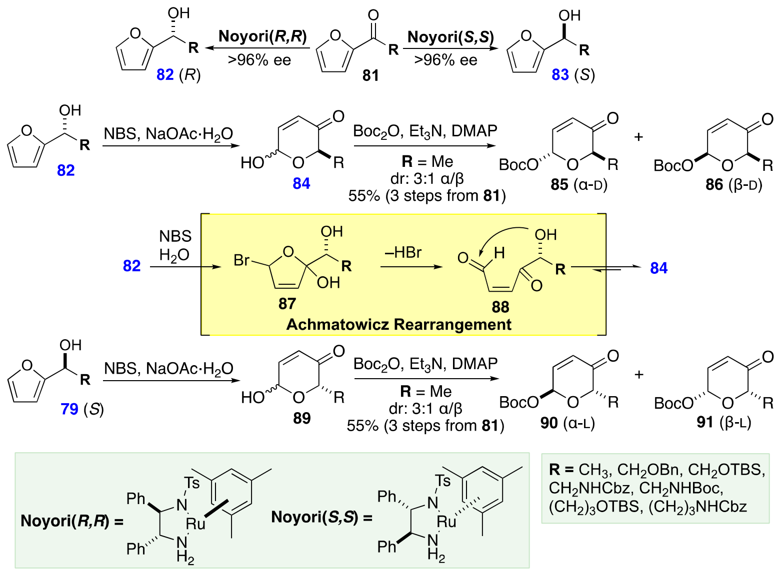


Scheme 12. Other de novo asymmetric syntheses of hexoses.

6. De Novo Asymmetric Achmatowicz Approach to Carbohydrates

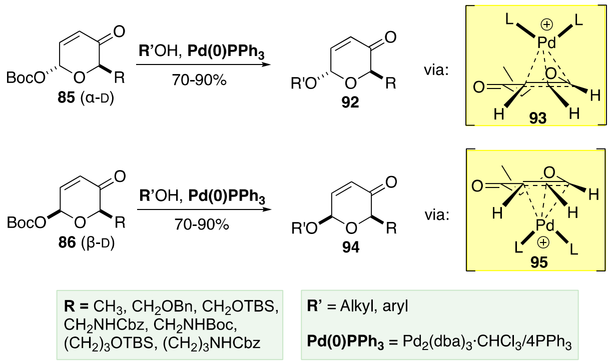
The O'Doherty approach to de novo synthesis of sugars is based on the idea of simplifying all the pyranoses into just four pyranones (Scheme 13). These four pyranones each contain two chiral centers, at C-1 (setting α/β configuration) and C-5 (setting D-/L-configuration). In terms of absolute stereochemistry, the enantiocontrol is established in a furan alcohol by means of an asymmetric reduction in an acylfuran or oxidation of a vinylfuran [38,39]. An Achmatowicz rearrangement can convert the furan alcohol into a pyranone ring where the stereochemistry at C-5 is derived from the furan alcohol A diastereoselective acylation or carbonate formation can then be used to control the C-1 stereochemistry (α or β). A stereochemically retentive Pd-allylation is then used to transfer the α- or β-stereochemistry to the pyranone product, which can then be converted into various pyranoses (vide infra) [40,41].

In practice, the process begins with achiral furyl ketone **81**, which can be functionalized at the α-methyl position (C-6) with a variety of useful substituents. Then ketone **81** can then be reduced to the *R*- or *S*-chiral alcohol (**78** or **79,** respectively), with excellent enantioselectivity, via Noyori asymmetric hydrogenation using a chiral ruthenium catalyst [42–45]. Next, these alcohols are subjected to Achmatowicz rearrangement (via intermediates **87** and **88**) to pyran alcohols **84** and **89**, from furan alcohols **82** and **83**, respectively, with the C-5 stereochemistry being set by the previous asymmetric reduction. Next, the equilibrating mixture of anomers is OH-protected, locking the pyranone into the α-configuration (**85** and **90**) or the β-configuration (**86** or **91**). The α/β ratio can be controlled by altering the protecting groups, or reaction conditions (Scheme 13). When the anomeric protecting group is an ester or carbonate group, it also serves as a Pd-π-allyl-leaving group for a Pd-catalyzed allylation reaction for coupling carbon, nitrogen, and oxygen nucleophiles [46–48].



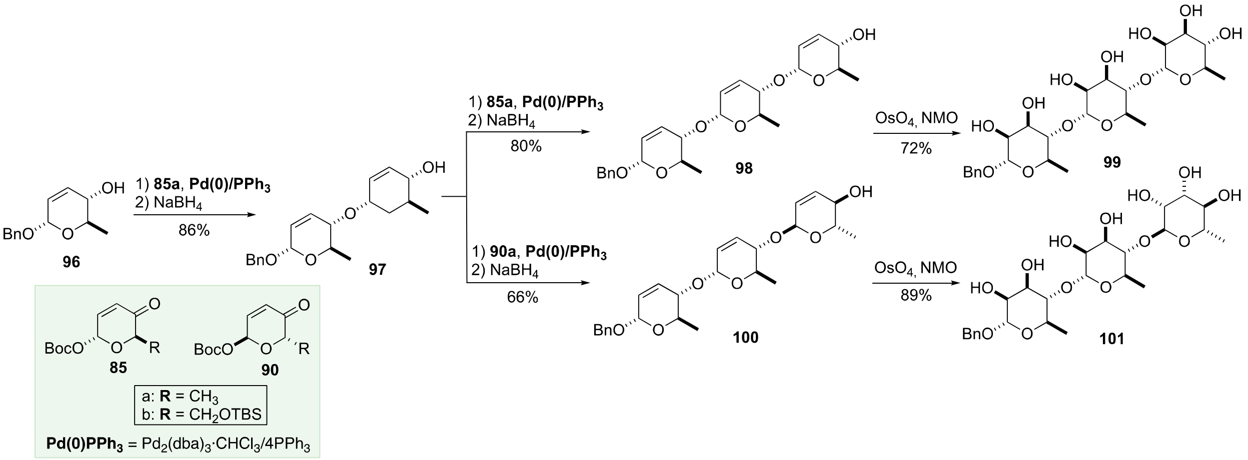
Scheme 13. O'Doherty de novo asymmetric synthesis of pyranone based Pd-glycosylation donors.

The next critical part of O'Doherty methodology is the utilization of a highly diastereoselective Pd-catalyzed Tsuji–Trost glycosylation (Scheme 14) [49–52]. This allows the anomeric position to be functionalized with a variety of different nucleophiles with complete stereochemical retention of the established C-1 stereochemistry. The diastereoselectivity of these transformations stems from the stereochemistry of the intermediate Pd complex. For example, α-pyranone **85** is converted into α-pyranone **92** via the β-intermediate **93** in 70–90% yield. The Pd catalyst coordinates to form the π-allyl on the opposite face of the C-1 leaving group. Therefore, when the alcohol attacks the π-allyl, it must approach from the opposite face as the Pd-group, which leads to the overall stereochemical retention. The same principle guides the transformation of β-**86** to β-**94** through the α-transition state **95** with a similarly strong yield. The route has been successfully applied to several oligosaccharide targets [53–58], with no or minimal use of protecting groups [59].

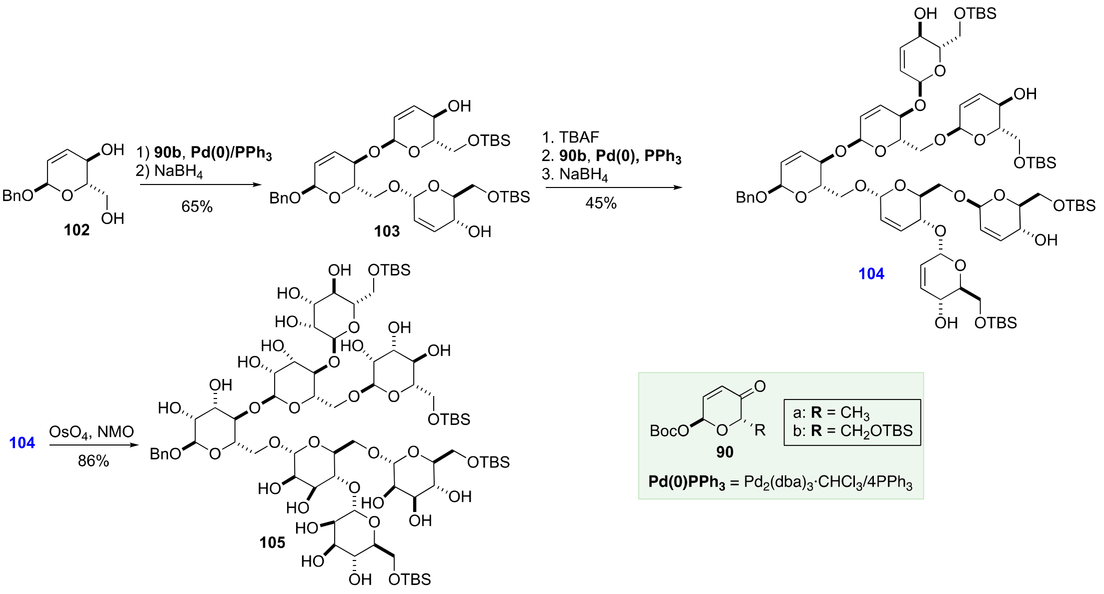


Scheme 14. Diastereoselective Pd-glycosylation.

Where the Achmatowicz approach really distinguishes itself from the other de novo asymmetric approaches to carbohydrates is in its application to oligosaccharides, where the C-2/C-3 alkene can function as an atomless-protecting group (Schemes 15 and 16). By carrying the alkene functionality to the end of the oligosaccharide, these routes have excellent step economy when applied to both linear and branched oligosaccharides [60,61]. The route to the linear sugars started with allylic alcohol **96**, which was prepared from ketone **85a** in two steps (Scheme 15). A Pd-catalyzed glycosylation was accomplished using pyranone **85a**, followed by a reduction to afford disaccharide precursor **97**. By repeating this diastereoselective elongation of **97** (glycosylation/reduction) with two possible D/L-diastereomeric α-pyranones, trisaccharide precursors **98** and **199** were synthesized; **98** was synthesized by glycosylation and reduction using pyranone **85a**, and **100** was synthesized through glycosylation and reduction using pyranone **90a**. These two diastereomeric routes occurred with equivalent excellent overall efficiency and stereochemical control. A similar diastereoselective osmium-catalyzed dihydroxylation of the trienes **98** and **100** afforded trisaccharides **99** and **101**, respectively (Scheme 15).



Scheme 15. O'Doherty de novo asymmetric synthesis of 1,4-linked oligosaccharides.

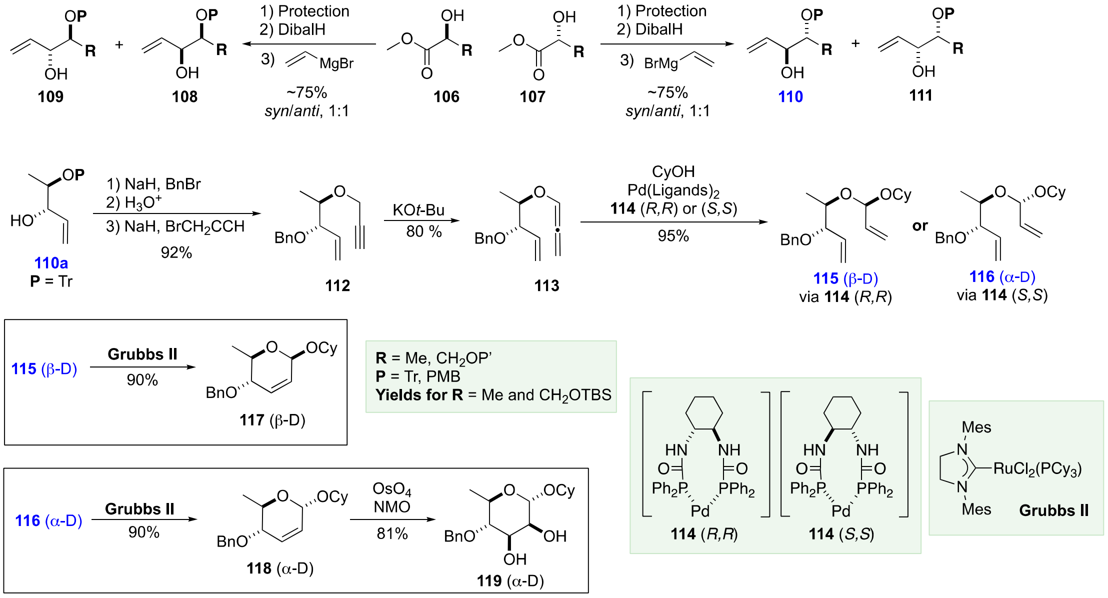


Scheme 16. O'Doherty de novo asymmetric synthesis of branched 1,4-/1,6-linked oligosaccharides.

The power of the de novo Achmatowicz approach in terms of step economy is particularly preannounced in the application to the branched oligosaccharides. This route began with a Pd-catalyzed bis-glycosylation of two equivalents of pyranone **90b** with diol **102**, which was synthesized from **90b** in three steps. Following reduction with $NaBH_4$, allylic alcohol **103** was obtained in 65% yield. Following TBAF-mediated removal of the two TBS groups, the resulting tetraol was again subjected to the two-step protocol of glycosylation (with four equivalents of **90b**) and reduction to yield heptasaccharide precursor **104** in 45% yield over three steps. Finally, dihydroxylation was performed using the Upjohn conditions of OsO_4/NMO to give the manno-hepta-saccharide **105** in 86% yield. When viewed from the perspective of its high degree of stereochemical complexity, it is worth noting the heptasaccharide **105**, with its 35 stereocenters, was prepared in only 11 steps from an achiral furan starting material (Scheme 16).

7. Rhee Synthesis of Carbohydrates

More recently, Rhee and co-workers developed an alternative de novo approach to hexose sugars [62,63], which is particularly compatible with oligosaccharide synthesis. Like the Achmatowicz approach, the Rhee approach relies on the use of a Pd-allylation reaction. This alternative approach builds upon the use of asymmetric Pd-allylation of alcohols with alkoxy-allenes that was developed by Trost and Lee [64,65]. In the Rhee application, the chiral ligands on the palladium catalyst (**114**(*R*,*R*) or **114**(*S*,*S*)) are used to control the sugar acetal stereochemistry in the asymmetric allylation (**113** to **115** or **116**). After the allylation, a ring-closing metathesis (RCM) reaction is used to close the pyran ring (**115** to **117** and **116** to **119** via **118**). The approach is compatible with all the D-/L- and α-/β-sugar stereochemical combinations (Scheme 17).



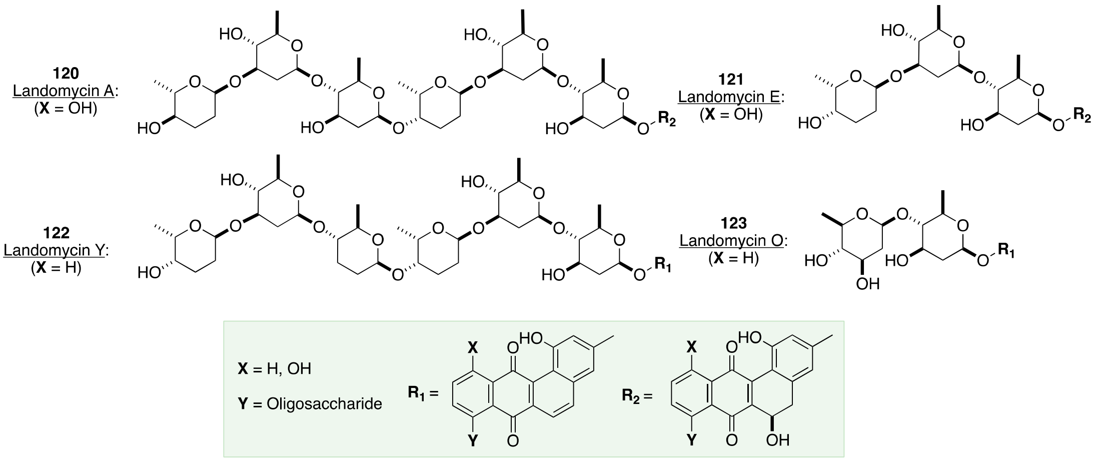
Scheme 17. Rhee asymmetric synthesis of hexoses via a Pd-glycosylation (Pd-allylation/RCM).

In lieu of asymmetric catalysis, Rhee's synthesis derives its asymmetry from lactic acid, which is readily available in either D- or L-enantiomeric form. Therefore, the Rhee de novo carbohydrate synthesis is technically not a de novo asymmetric approach (Scheme 17). Nevertheless, the Rhee synthesis begins with the conversion of either D- or L-lactic acid into the four possible ene-diols **108–111** that contain the C-3 to C-6 sugar fragment. Thus, in three steps, (i.e., protection, DibalH reduction, and vinyl Grignard addition) D-lactic acid was converted into a separable mixture of a variably protected syn- and anti-diols (**108** (D, syn) or **109** (D, anti)). Similarly, L-lactic acid can be converted into syn- and anti-diols (**111** (L, syn) or **110** (L, anti)). These chiral fragments can be converted into the desired pyran by a six-step protocol. The approach begins with a four-step introduction of an allenyl ether at the C-4 position, which functions as a Pd-glycosylation precursor. The key to the approach is a two-step allenylation propargylation (NaH/$BrCH_2CCH$) and isomerization (KOt-Bu) to an allene (**112** to **113**).

Using a Pd(0) complex with the Trost C-2 symmetric chiral ligand Pd(0) (**114** (*R*,*R*)), Rhee showed that allenyl ethers like **113** (D, anti) could be converted into diastereomeric acetals **115** or **116**. After Grubbs II-catalyzed ring-closing metathesis reaction, diene **113** can be converted into pyran **115** (β-D). Thus, the two-step Pd-allylation/RCM reaction results in a net β-glycosylation, where the anomeric stereochemistry is controlled by the chiral ligand on the Pd catalyst. Similarly, the α-isomer **118** can be prepared by Grubbs II-catalyzed RCM on **116**. A subsequent osmium-catalyzed dihydroxylation converted **118** into the α-rhamno-sugar **119** (α-D). To prove the utility of his approach, Rhee applied this approach to the synthesis of numerous oligosaccharide motifs, such as, cervimycin K [66], saccharomicin [67], and landomycin (vide infra) [68].

8. The De Novo Asymmetric Synthesis of Landomycins

Landomycins (Scheme 18) are a family of glycosylated angucycline anticancer antibiotics with an unusual structural motif that were first isolated in the 1990s. Of the landomycins, landomycin A **120** has received the most attention from the synthetic community, as it is reported to have a novel mechanism of anticancer activity. Landomycin A consists of a novel deoxygenated hexasaccharide with two repeating trisaccharides (α-L-rhodinose-(1→3)-β-D-olivose-(1→4)-β-D-olivose). More recently, the landomycin family has grown with the discovery of the 11-Deoxylandomycins, which has an alternative dehydrated aglycon motif and the same basic oligosaccharide repeat unit. Of the 11-Deoxylandomycins, the largest member of this family of angucycline natural products is landomycin Y **122** with the same landomycin A hexasaccharide. Most synthetic approaches to the landomycin oligosaccharides have focused on using traditional carbohydrate approaches to assemble the deoxy sugar oligomer [69–81]. In contrast to these more conventional approaches, there have been two de novo approaches to the landomycin carbohydrates. The first de novo approach was by O'Doherty and used the asymmetric Achmatowicz chemistry, and the other by Rhee used a mixed traditional carbohydrate/de novo approach. This approach (Pd-allylation/RCM) also heavily relies on the 2-deoxy-sugar glycosylation chemistry developed by Bennett [82–84].

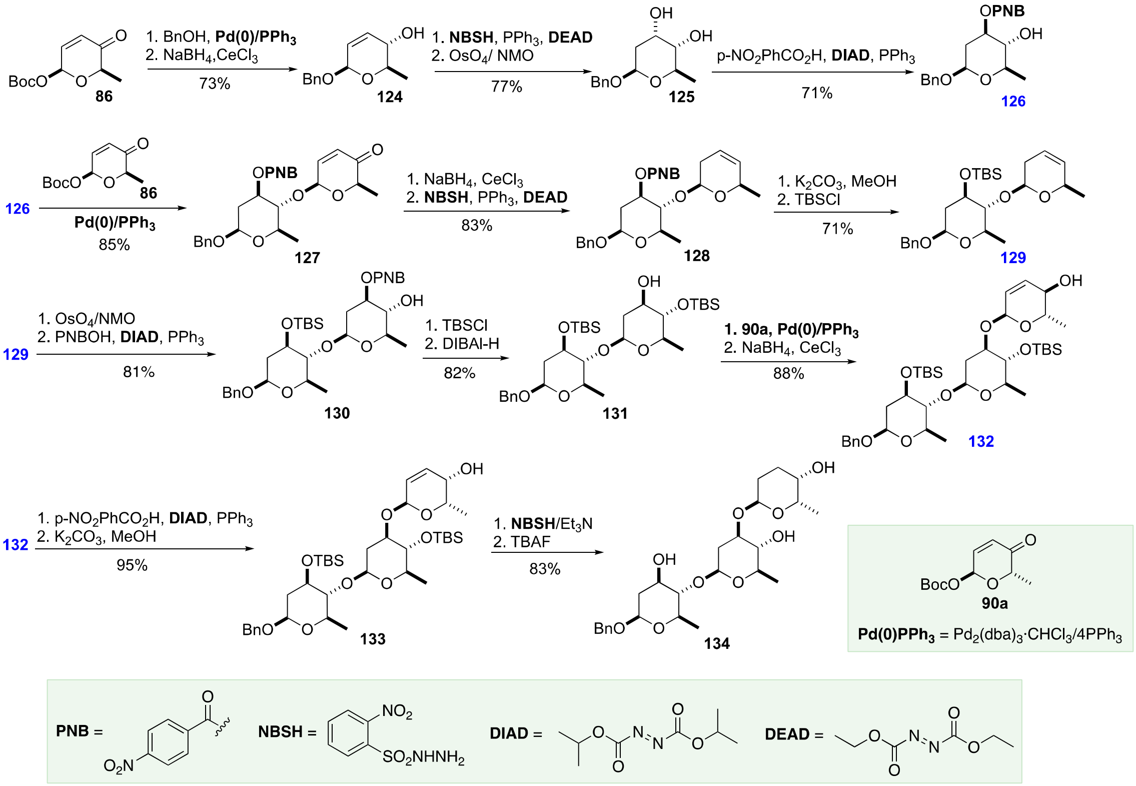


Scheme 18. The landomycin family of oligosaccharides.

The landomycin oligosaccharides offer an excellent opportunity to apply the de novo Achmatowicz approach to a sugar oligomer that repeats the sugar subunit. For example, the trisaccharide repeat unit of the hexasaccharide landomycin A has two rare β-D-olivose sugars and one α-L-rhoodinose. This asymmetry of the oligomer chain is another form of structural complexity, which adds steps when compared to the oligosaccharide syntheses of Schemes 15 and 16. Note that these de novo approaches, compared to traditional ones, save steps in the preparation of the monosaccharide building blocks.

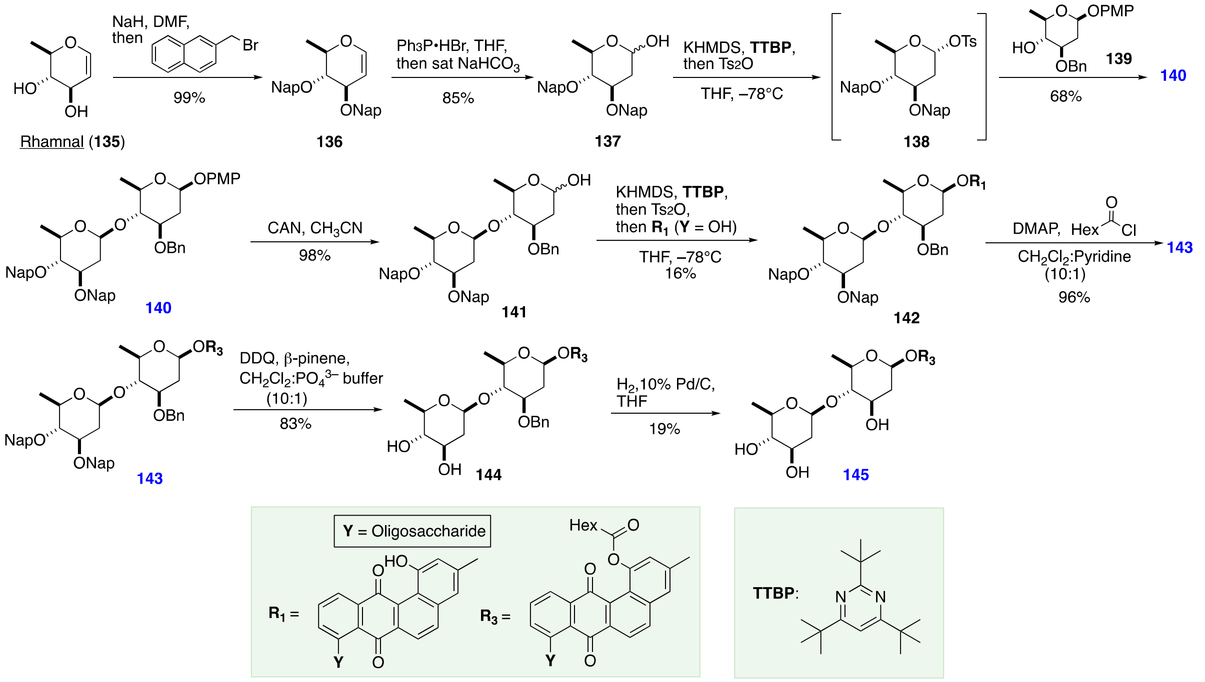
The application of the de novo Achmatowicz approach to the landomycins begins with β-pyranone **86**, which can be prepared in three steps from commercially available

2-acetylfuran. Pyranone **86** was subjected to a palladium-catalyzed glycosylation with BnOH followed by a Luche reduction in the keto group to yield allylic alcohol **124**. This alcohol was then subjected to a Myers' reductive 1,3-allylic transposition followed by a stereoselective Upjohn dihydroxylation to afford diol **125** in 56% overall yield over four steps. Mitsunobu reaction conditions were then utilized to selectively invert the axial C-3 alcohol, converting **125** into a protected β-D-olivose **126** in 71% yield [85,86]. Next, **126** was used to glycosylate pyranone **86** using the typical palladium-catalyzed glycosylation conditions to form the *C*-4 glycosylated disaccharide **127** in 85% yield. A Luche reduction in the keto group in **127** yielded a diastereomeric mixture of allylic alcohols. However, when this mixture was exposed to the Myers' reductive 1,3-allylic transposition conditions, the desired olefin **128** was produced in good yield. Next, the *p*-nitrobenzoate group of **128** was hydrolyzed and the resulting free alcohol protected with TBSCl to give silyl ether **129** in 71% yield. Following subjection of **129** to OsO_4-catalyzed dihydroxylation, the resulting diol was applied to a regioselective Mitsunobu reaction to produce benzoate **130**. The remaining free alcohol was then protected with a TBS group, after which the PNB-protected alcohol was liberated via DIBAL-H reduction to afford the desired glycosyl acceptor **131**. Next, pyranone **90a** was glycosylated with **131**, producing allylic alcohol **132** after Luche reduction, providing an intermediate trisaccharide precursor. The allylic alcohol **132** was inverted using the Mitsunobu reaction followed by the removal of the resulting benzoate, affording axial alcohol **133** in 95% yield. Lastly, olefin **133** was reduced to provide the protected trisaccharide, which was liberated by TBAF-mediated protection with TBSCl to afford benzyl glycoside **134** in 83% yield over the final two steps (Scheme 19).



Scheme 19. O'Doherty de novo asymmetric synthesis of the trisaccharide repeat of landomycin A.

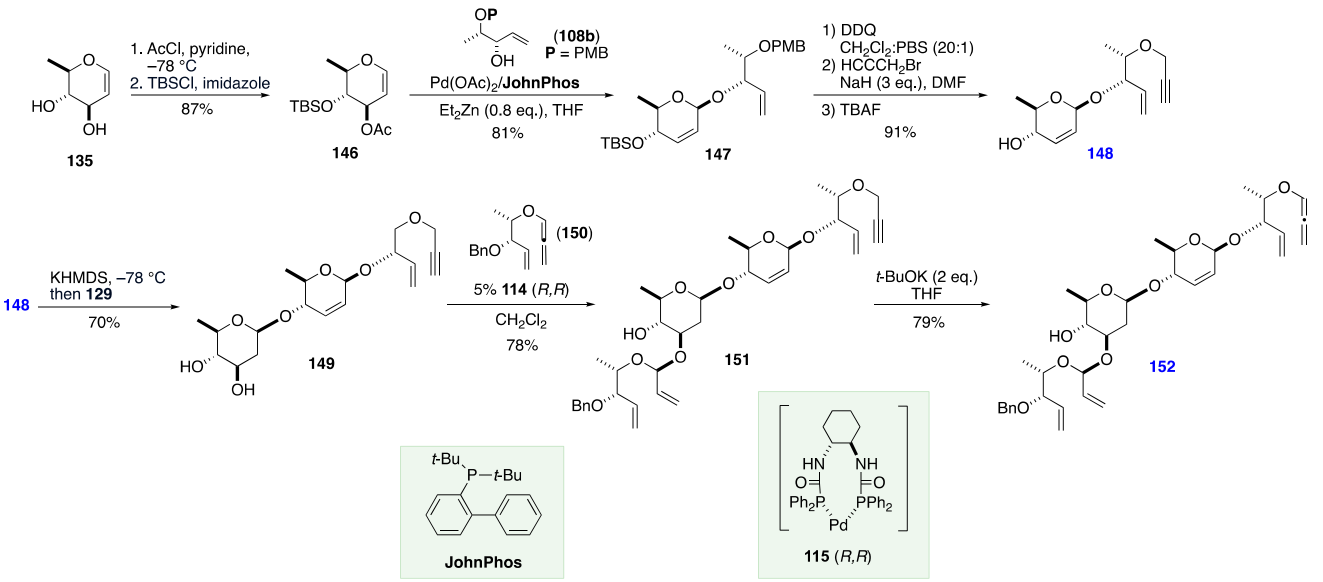
The Rhee groups' synthesis of landomycin Y began with naphthyl-protection of rhamnal **135** to form **136** in nearly quantitative yield. Next, glycal **136** was converted to a 2-deoxy sugar **137**, as an equilibrating mixture of unprotected anomers. Then, **137** was selectively converted to α-tosylate intermediate **138**, followed by glycosylation with C-4 unprotected sugar **139** to afford protected disaccharide **140**. Next, the anomeric PMP group was selectively removed via ceric ammonium nitrate (CAN) oxidation to afford acetal **141**. Next, the aglycone component was coupled at the liberated anomeric position to afford **142** with the desired β-configuration, followed by protection of the phenol in the aglycone as *n*-hexyl ester **143**. Then, **143** was sequentially deprotected—first by oxidative removal of the naphthyl groups with DDQ, followed by hydrogenation of the benzyl group, affording the first key coupling partner **145** (Scheme 20).



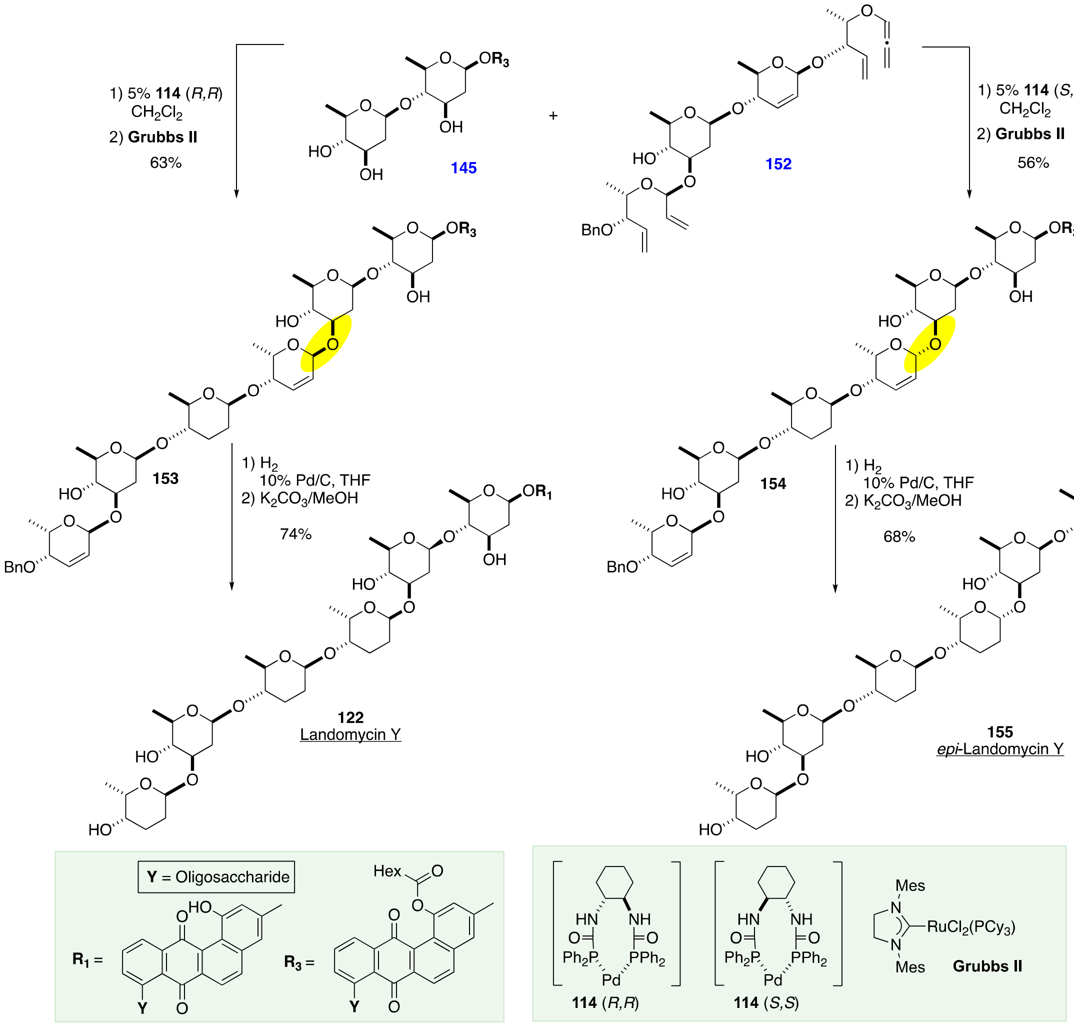
Scheme 20. Rhee asymmetric synthesis of the landomycin disaccharide.

The synthesis of the second coupling partner also began with **135**, which was iteratively protected as a C-3 acetate and C-4 TBS ether **146**. Next, mono-protected diol **108b** was coupled using Pd(II) chemistry to afford **147** with the desired β-linkage. Next, the PMB-group was removed, followed by propargyl addition to the resulting alcohol, and then TBS-deprotection yielding allylic alcohol **148**. This alcohol was coupled with **135** to give the β-linked trisaccharide precursor **149**. This was coupled with allene **150** using the appropriate chiral Pd catalyst to yield C-3 α-linked tetra saccharide precursor **151**. Finally, terminal alkyne **151** was isomerized to allene **152** under standard isomerization conditions (Scheme 21).

Allene **152** and alcohol **145** were coupled together with both the (*R*,*R*) and (*S*,*S*) Pd catalysts to install the α- or β-linkage, respectively. This was followed by ring-closing metathesis using the Grubbs catalyst to cyclize the terminal sugar residue, giving hexasaccharide precursors **153** and **154**, respectively. Finally, the benzyl groups were removed by hydrogenation, and the *n*-hexyl esters of the aglycones were subjected to base hydrolysis to afford landomycin Y **122** in two steps from **153**, and *epi*-landomycin Y **155** from **154**. The use of **114**(*R*,*R*) versus **114**(*S*,*S*) to produce either **122** or **155** demonstrates the stereochemical versatility of this reagent-controlled approach to anomeric stereochemical control (Scheme 22).



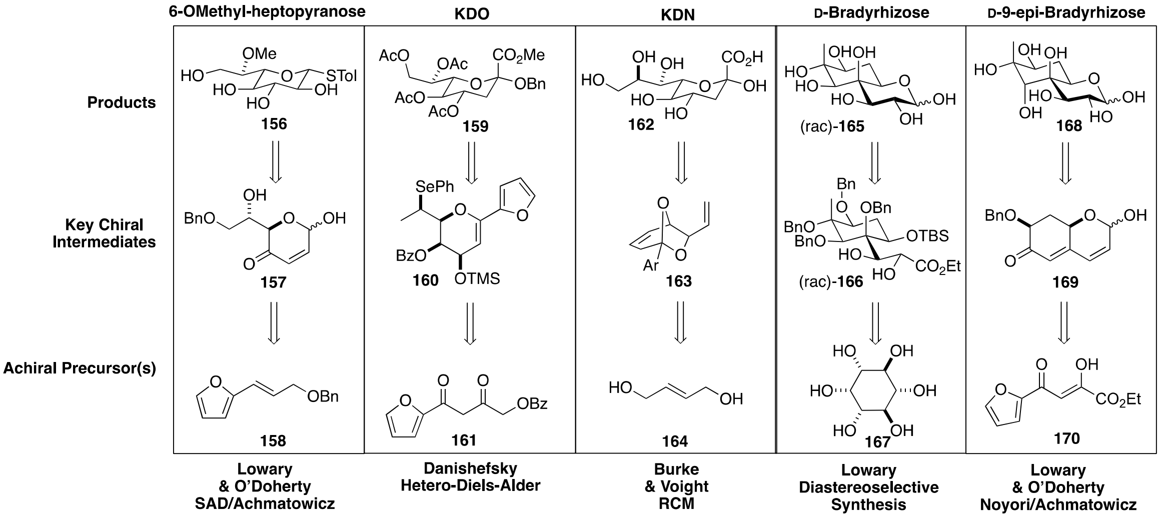
Scheme 21. Rhee Pd-allylation approach to a landomycin tetrasaccharide precursor.



Scheme 22. Rhee Pd-allylation and RCM approach to a landomycin Y.

9. De Novo Approaches to Higher Order Sugars

As demonstrated in the synthesis of the landomycin oligosaccharides, these de novo asymmetric approaches have the greatest utility when they allow for access to rare sugars. The most common de novo asymmetric approaches are to the hexoses with uncommon stereochemistry or deoxy-substitutions. In addition to hexoses, de novo asymmetric routes have also been developed to the C-7 and C-9 sugars (Scheme 23). The Lowary group, in collaboration with the O'Doherty group, developed a de novo asymmetric approach to the C-7 monosaccharide 6-*O*-methyl-heoropyranose **156** [87]. The approach used the Achmatowicz approach via pyranone **157**, which could be prepared from achiral vinylfuran **158**. The route derived its asymmetry by means of a Sharpless asymmetric dihydroxylation of vinylfurans. Another notable example is the de novo synthesis of the C-8 sugar KDO **159**, by Danishefsky [88]. The Danishefshy route utilizes a hetereo-Diels–Alder reaction to make the key pyran building block **160** from a diene derived from achiral furan **161**. More recently, Burke and Voight developed an asymmetric synthesis of the related C-9 sugar KDN **162** [89]. Their approach asymmetrically builds **162** from the spiro-ketal **163**, which can be prepared enantioselectively from achiral alkene **164**, via the use of a diastereoselective RCM reaction. More recently a de novo asymmetric synthesis was developed for the C-10 monosaccharide bradyrhizose **165**. The Lowary group first developed an enantio-divergent approach to racemic **165** from achiral inositol **167** [90]. Additionally, in collaboration with the O'Doherty group, Lowary and coworkers developed a de novo asymmetric approach to several diastereomers of bradyrhizose, like the C-9 epimer, **168**. This de novo approach used an Achmatowicz reaction to create a bicyclic pyran **169**. The de novo approach derived its asymmetry from a double Noyori reduction in achiral furan **170** [91]. Several of these de novo asymmetric carbohydrate approaches have also been applied to other sugars with additional carbons at C-1 [92–95].



Scheme 23. De novo asymmetric syntheses of higher-order sugars.

10. Conclusions

In summary, this review introduces the concept of de novo asymmetric synthesis in the context of carbohydrate synthesis, particularly for the synthesis of oligosaccharides. This was accomplished by introducing the role asymmetry plays in nature and natural substances and describing how asymmetry is particularly prevalent in the chemistry of biomolecules, especially carbohydrates with their many chiral carbon centers. As asymmetry plays an important role in the structure of carbohydrates, it also plays a similarly critical role in their syntheses. As our ability to synthesize carbohydrate motifs advances, the complexity of the targets that can be accessed synthetically has also progressed. This can be seen in the progression of the early diastereoselective syntheses to enantioselective syntheses, and finally, to de novo asymmetric syntheses. This advancement culminated in the development of two de novo asymmetric synthetic methods for oligosaccharides, with application to oligosaccharide medicinal chemistry [96–102]. The first approach was the Achmatowicz approach, which relies on the asymmetric synthesis of furan alcohols, a Pd-glycosylation reaction, and post-glycosylation reactions. The Achmatowicz approach synthesizes stereochemically simplified D- and L-pyranones with α- and β-stereochemistry. The Achmatowicz approach reduces the 32 possible hexose monosaccharides to just 4 stereoisomers. The second approach developed by the Rhee group led to an alternative method for pyran construction with similar applications to oligosaccharides like the landomycins. Of particular note to the Rhee method is its ability to allow for more convergent approaches with a late-stage control of a single anomeric stereocenter. In addition, the approach showed an excellent degree of compatibility with more traditional carbohydrate approaches. The results covered herein bode well for a future where the application of these and other de novo approaches to carbohydrate synthesis and medicinal chemistry are prevalent.

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