1
De Novo Approaches to Monosaccharides and Complex Glycans

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1.1
Introduction

Over the years, considerable effort has been made toward the development of new synthetic routes to monosaccharides [1]. This interest came primarily from the medicinal chemistry community, as these new routes often provided access to unnatural sugars, which could be of use in structure–activity relationship (SAR) studies. In addition, the synthesis of monosaccharides, and in particular hexoses, has served as a challenge and a measuring stick to the synthetic organic community. Of particular interest are the routes to hexoses that start from achiral starting materials, where asymmetric catalysis is used to install the stereochemistry. In the synthetic organic community, these routes are described as "*de novo*" or "*de novo* asymmetric" routes to carbohydrates, whereas in the carbohydrate community, the term *de novo* takes up other meanings. For the purposes of this review, the term *de novo* asymmetric synthesis refers to the use of catalysis for the asymmetric synthesis of carbohydrates from achiral compounds [2]. This then precludes the inclusion of *de novo* process that produced sugars from molecules with preexisting chiral centers (e.g., Seeberger and Reißig) [3, 4].

The challenge of a *de novo* synthetic approach to carbohydrates has been met by many groups (Scheme 1.1). These approaches begin most notably with the seminal work by Masamune and Sharpless [5] (**2** to **5**), which utilized iterative asymmetric epoxidation of allylic alcohols to prepare all eight possible hexoses. More recently, Danishefsky [6] demonstrated the power of asymmetric hetero-Diels–Alder reaction for the synthesis of several glycals (**3** and **4** to **5**), which inspired further studies toward oligosaccharide synthesis. Johnson and Hudlicky [7] turned to the use of enzyme catalysis for the oxidation/desymmetrization of substituted benzene rings to achieve hexopyranoses (**1** to **5**). Alternatively, Wong and Sharpless [8] used a combination of transition metal catalysis (asymmetric dihydroxylation) and an enzyme-catalyzed aldol reaction for the synthesis of several 2-keto-hexoses. More recently, this challenge has been engaged by MacMillan who utilized an iterative aldol reaction approach (a proline-catalyzed aldol followed by a subsequent diastereoselective aldol reaction) to produce various hexoses

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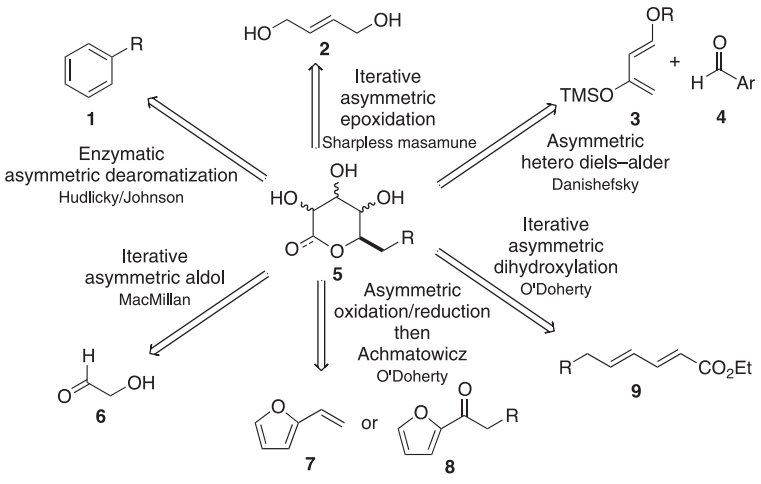
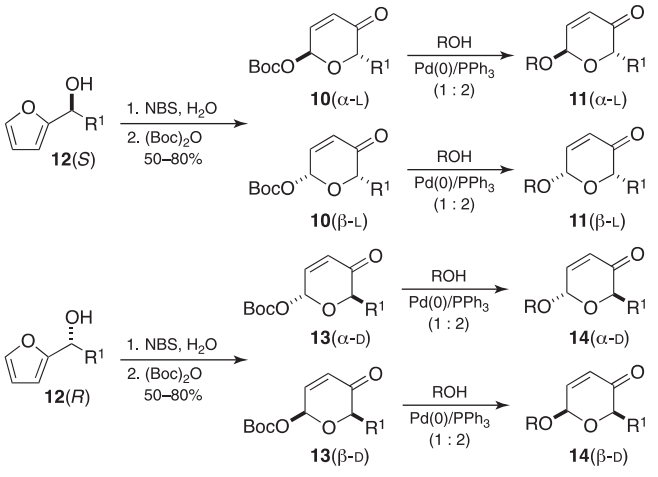


Scheme 1.1 *De novo* approaches to hexoses.

(**6** to **5**) [3]. Of these approaches, only the iterative epoxidation strategy of Masamune and Sharpless provides access to all eight hexoses, but it is also noteworthy that their route required the most steps and protecting groups. It is this latter point, the reduction of steps and avoidance of protecting groups, which guided the development of these synthetic endeavors [9].

We have also developed two practical methods for the *de novo* synthesis of hexoses. These efforts have resulted in the discovery of two orthogonal approaches to hexopyranoses with variable C-6 substitutions. These approaches entail an iterative dihydroxylation strategy to hexose sugar lactones (**9** to **5**) [10] and an Achmatowicz strategy that is amenable to all eight hexose diastereomers (**7** or **8** to **5**) [11] Of the two approaches, the iterative asymmetric dihydroxylation of dienoates (Scheme 1.1) is the most efficient in terms of steps (one step for racemic to three steps for asymmetric) and the minimal use of protecting groups. On the contrary, the Achmatowicz approach is superior in terms of synthetic scope. The potential of this approach can be seen in the highly efficient *de novo* route to various mono-, di-, tri- tetra-, and heptasaccharide motifs, allowing their use for biological and medicinal structure–activity studies.

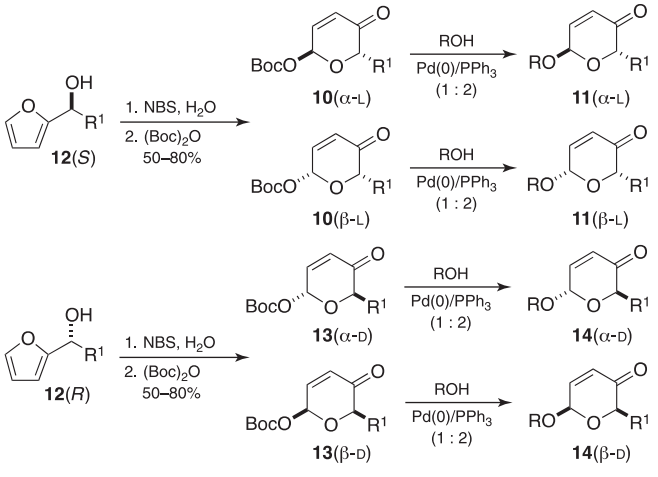
Of the many ways to compare these *de novo* routes (e.g., number of steps, availability of starting materials, and atom economy), clearly the best metric is the scope of its use in synthetic and biological applications. The Achmatowicz approach is distinguished from the other approaches when it comes to practical application to rare sugars, medicinal chemistry, and more specially oligosaccharides. These features result from its compatibility with the Pd-π-allyl-catalyzed glycosylation for the stereospecific formation of the glycosidic bond [12, 13]. As outlined in Scheme 1.2, the Pd(0)-catalyzed glycosylation reaction is both general and stereospecific [14, 15]. The reaction occurs rapidly and in high yields for both the α-**10** to α-**11** and β-**10** to β-**11** systems and works best when $Pd_2(dba)_3{\cdot}CHCl_3$ is used as the Pd(0) source



Scheme 1.2 Stereospecific Pd-catalyzed glycosylation.

with triphenylphospine as the ligand in a 1 : 2 Pd/PPh_3 ratio. While carboxylate-leaving groups also work, the *t*-butoxycarbonate group ($BocO^-$) is critical for the successful implementation of this reaction with alcohol nucleophiles. For example, when the *t*-butoxycarboxy group was replaced with a benzoyl or pivaloyl group, the palladium-catalyzed glycosylation reaction was significantly slower.

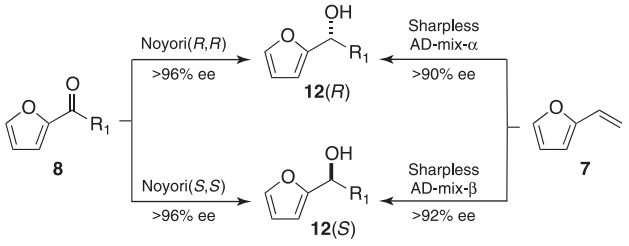
The *de novo* Achmatowicz approach to hexoses has great potential for preparing various D- and L-sugars because the starting 6-*t*-butoxycarboxy-2*H*-pyran-3(6*H*)-ones (**10** and **13**) can easily be prepared from optically pure furfuryl alcohols **12** (either (*R*) or (*S*) enantiomer) [16] by a one or two step procedure (Scheme 1.3). Depending on the temperature of the second step, the *t*-butylcarbonate acylation



Scheme 1.3 Achmatowicz approach to the simplest hexoses.

reaction can selectively give the α-Boc pyranones **10α** and **13α** at −78 °C, whereas at room temperature, a 1 : 1 ratio of the α- and β-Boc protected enones were produced. Thus, this procedure can be used to prepare multigram quantities of both α- and β-pyranones in either enantiomeric form. When the Pd-glycosylation reaction was coupled with the Achmatowicz oxidation of a furan alcohol and diastereoselective *t*-butylcarbonate acylation reaction, a net three-step stereo-divergent pyranone-forming reaction resulted. Key to the success of the *de novo* asymmetric Achmatowicz approach is the practical access to all four possible pyranone diastereomers from either furan alcohol enantiomers **12**(*R*) or **12**(*S*).

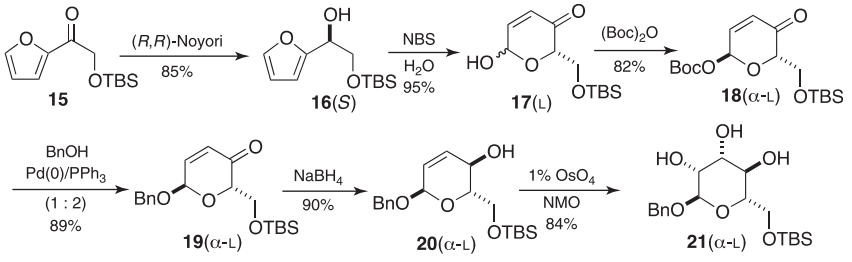
An important aspect of this approach is the ease with which furan alcohols can be prepared in enantiomerically pure form from achiral furans (e.g., **7** and **8**). There are many asymmetric approaches to prepare furan alcohols. The two most prevalent approaches are (i) the Noyori reduction of acylfurans (**8** to **12**) and (ii) the Sharpless dihydroxylation of vinylfurans (**7** to **12**) (Scheme 1.4) [17]. Both routes are readily adapted to 100 g scale synthesis and use readily available reagents. While the Sharpless route is most amenable to the synthesis of hexoses with a C-6 hydroxy group, the Noyori route distinguishes itself in its flexibility to virtually any substitution at the C-6 position. Herein, we review the development of the Achmatowicz approach to the *de novo* synthesis of carbohydrates, with application to oligosaccharide assembly and medicinal chemistry studies.



Scheme 1.4 *De novo* asymmetric approaches to chiral furan alcohols.

1.2
De Novo Synthesis of Monosaccharides

Putting this together, a very practical *de novo* approach to *manno*-hexoses can be carried out in six steps from achiral acylfuran **15**. The route began with a three-step synthesis of Boc-pyranone **18** in an ∼50% overall yield. Thus, in only three highly diastereoselective steps, pyranone **18** was converted into *manno*-pyranose **21** in 45% overall yield. The three-step sequence consists of a Pd-catalyzed glycosylation (**18** to **19**) and two postglycosylation reactions, a Luche reduction ($NaBH_4/CeCl_3$, **19** to **20**) and Upjohn dihydroxylation (OsO_4(cat)/NMO, **20** to **21**) (NMO, *N*-methylmorpholine-*N*-oxide)(Scheme 1.5). This six-step sequence of achiral **15** to partially protected mannose **21** demonstrates the power of asymmetric synthesis.

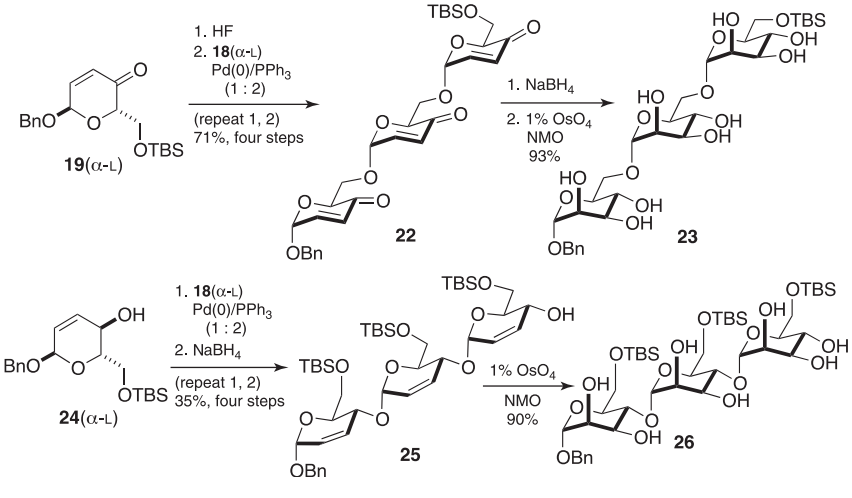


Scheme 1.5 *De novo* asymmetric Achmatowicz approach to L-*manno*-hexoses.

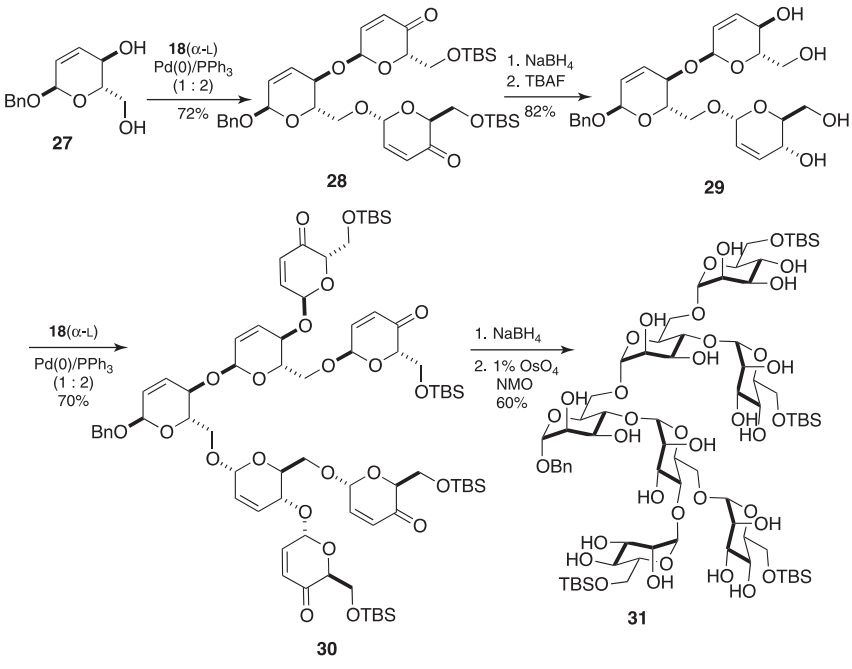
From the point of view of carbohydrate synthesis, this route consists of a three-step asymmetric synthesis of glycosyl donor **18**, which in three additional steps is converted into *manno*-sugar **21**. Viewing this approach from a synthetic perspective becomes more relevant in the subsequent schemes. Other hexose congeners were also prepared using other postglycosylation transformations [18]. Critical to the success of this approach is the chemoselective use of functionality of C–C and C–O π-bonds as atom-less protecting groups (i.e., enone as a protected triol) as well as an anomeric-directing group (via a Pd-π-allyl).

1.3
Iterative Pd-Catalyzed Glycosylation and Bidirectional Postglycosylation

The synthetic efficiency of the approach reveals itself when the Pd(0)-catalyzed glycosylation was applied in an iterative manner for oligosaccharide synthesis (Scheme 1.6 and Scheme 1.7) [19]. The step savings occurred because of the



Scheme 1.6 *De novo* asymmetric approach to 1,6- and 1,4-oligo-hexoses.



Scheme 1.7 *De novo* asymmetric approach to branched 1,4- and 1,6-oligo-L-hexoses.

bidirectional use of postglycosylation Luche and Upjohn reactions. While not always shorter, these routes compare favorably with more traditional carbohydrate approaches and offer exclusive access to enantiomers as well as D-/L-sugar diastereomers. In addition to reducing steps, this highly atom-economical approach avoids the extensive use of protection/deprotection steps. For example, the 1,6-*manno*-trisaccharide **23** was prepared from enone **18** in six steps (nine from achiral furan **15**). The synthesis was accomplished by an iterative use of a *t*-butyldimethylsilyl (TBS)-deprotection/glycosylation strategy to prepare trisaccharide **22**, followed by a tris-reduction and tris-dihydroxylation to install the *manno*-stereochemistry. By simply switching the order of the reduction and glycosylation steps, this route can also be used to prepare 1,4-manno-trisaccharide **23**. Key to the success of this sequence was the highly stereoselective reduction and dihydroxylation reaction, which installed six stereocenters in one transformation (**25** to **26**). This approach was successfully used in the medicinal chemistry SAR study of digitoxin, an anticancer agent [20].

1.3.1
Bidirectional Iterative Pd-Catalyzed Glycosylation and Postglycosylation

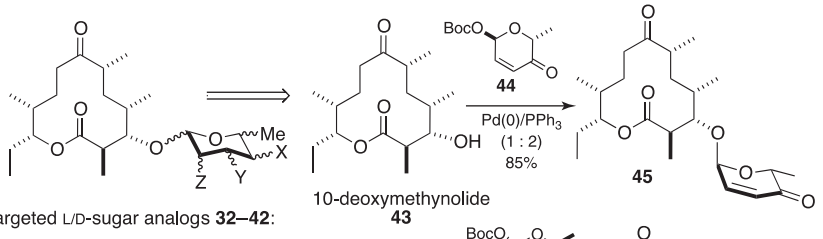
The synthetic efficiency was magnified when the glycosylation reaction was also applied in a bidirectional manner [21]. For example, when the TBS group of pyran

20 was removed, the resulting diol **27** can be bis-glycosylated to form tris-pyran **28**. This bidirectional application of ketone reduction and TBS deprotection gave tetraol **29**. Once again, the tetraol of **29** can be per-glycosylated with excess pyranone **18** to give heptasaccharide **30**. Finally, a ketone per-reduction and double bond per-dihydroxylation gave heptasaccharide **31**. It is worth noting, while there is similar local symmetry around each alkene, they exist in different stereochemical environments.

1.3.2
Synthesis of Monosaccharide Aminosugar Library

While these bidirectional approaches do have some significant synthetic efficiency over traditional approaches, they do suffer from the fact that the routes tend to be linear in nature and do not readily adapt to convergent synthesis. On the contrary, these routes most readily adapt to divergent synthesis. In particular to divergent synthesis, as it is applied to the synthesis of unnatural sugars. This becomes particularly advantageous when it is being used to address problems associated with medicinal chemistry. An example of this application can be seen in our application of this *de novo* Achmatowicz approach for the synthesis of a library of glycosylated methymycin analogs for eventual medicinal chemistry SAR studies [22].

Methymycin is one of the several 12-membered ring-glycosylated macrolide antibiotics isolated from *Streptomyces venezuelae* ATCC 15439 (ATCC, American Type Culture Collection; Scheme 1.8). Similar to other macrolide antibiotics, the rare deoxy-aminosugar portion of methymycin (desosamine) is important for their bioactivity. Thus, its modifications hold promise as a valuable approach



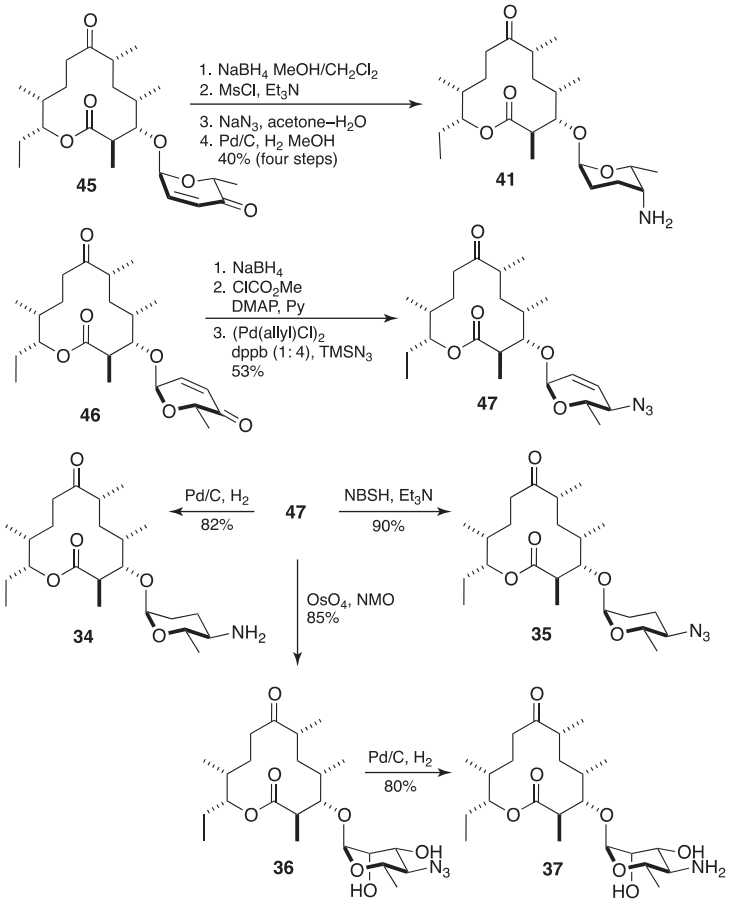
Targeted L/D-sugar analogs **32–42**:

32: X = OH, Y = H, Z = H (α-L-sugar)
33: X = OH, Y = OH, Z = OH (α-L-sugar)
34: X = NH_2, Y = H, Z = H (α-L-sugar)
35: X = N_3, Y = H, Z = H (α-L-sugar)
36: X = N_3, Y = OH, Z = OH (α-L-sugar)
37: X = NH_2, Y = OH, Z = OH (α-L-sugar)
38: X = OH, Y = OH, Z = H (β-L-sugar)
39: X = OH, Y = H, Z = H (α-D-sugar)
40: X = OH, Y = OH, Z = OH (α-D-sugar)
41: X = NH_2, Y = H, Z = H (α-D-sugar)
42: X = OH, Y = OH, Z = H (β-D-sugar)

Scheme 1.8 *De novo* synthesis of a methymycin monosaccharide library.

toward preparing new macrolide antibiotics with improved and/or altered biological properties. Our *de novo* approach to a library of methymycin analogs is retrosynthetically outlined in Scheme 1.8, where the macrolide aglycon 10-deoxymethynolide was glycosylated in a stereo-divergent manner (with D- or L-Boc pyranones **44** or *ent*-**44**, respectively) to give either α-D-glycoside **45** or its diastereomer α-L-glycoside **46**. Subsequent postglycosylation transformations were used to provide various sugar congeners and stereoisomers, in particular, unnatural deoxy-aminosugar isomers.

The installation of amino-functional groups, in practice, was most easily accomplished at the C-4 position (Scheme 1.9). For instance, the α-D-pyranone ring on methymycin analog **45** could be converted into a 4-aminosugar **41** with α-D-*rhodino*-stereochemistry in four steps, via a reduction, activation of the resulting alcohol, azide inversion, and reduction strategy. Alternatively, this approach is

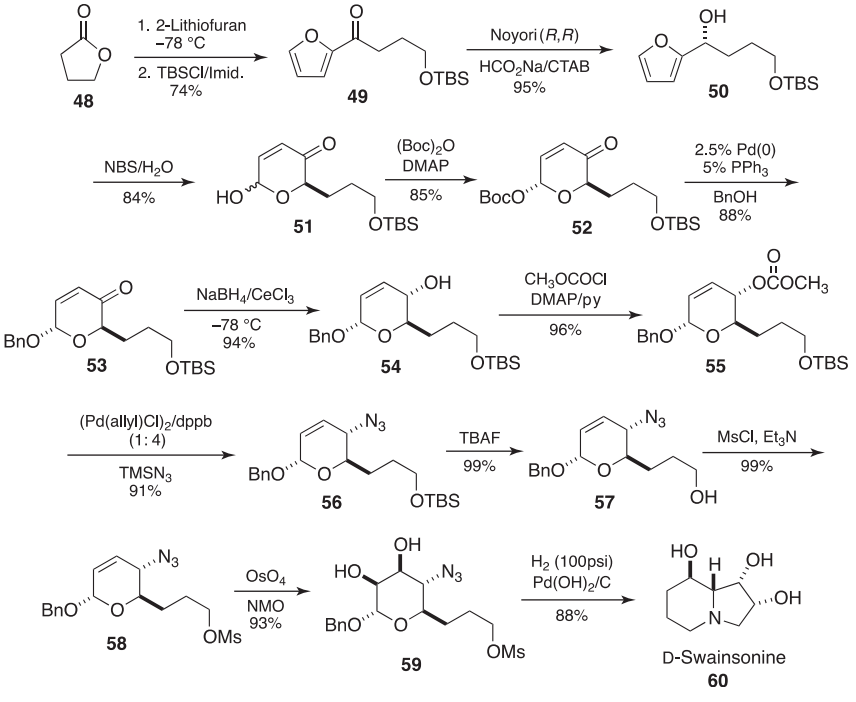


Scheme 1.9 *De novo* synthesis of a methymycin monosaccharide aminosugar library.

also compatible with the installation of equatorial amino groups at the C-4 position. This is accomplished by means of a net retention of stereochemistry in the substitution reaction at the C-4 position. The reaction occurred via a Pd-catalyzed π-allyl reaction with trimethylsilyl azide ($TMSN_3$) as the nucleophile to give allylic azide **47** from α-D methymycin analog **46**. In turn, azide **47** could be converted into azido-/azasugar methymycin analogs with α-L-*rhamno*- (**36** and **37**) and α-L-*amiceto*-stereochemistries (**34** and **35**).

1.4
Synthesis of Monosaccharide Azasugar

Among the polyhydroxylated indolizidine alkaloids, the most well-known member is D-swainsonine **60** (Scheme 1.10) [23–25]. Swainsonine is known as a *potent inhibitor* of both lysosomal α-mannosidase [26] and mannosidase II [27] and has shown promise as an anticancer agent [28]. Fleet *et al.* [29] have shown that the enantiomer (L-swainsonine) selectively inhibited narginase (L-rhamnosidase, $K_i = 0.45\ \mu M$), whereas the D-swainsonine showed no inhibitory activity toward this enzyme. Owing to the biological importance of both D- and L-swainsonines, several epimers and analogs have become attractive targets for syntheses [30, 31].



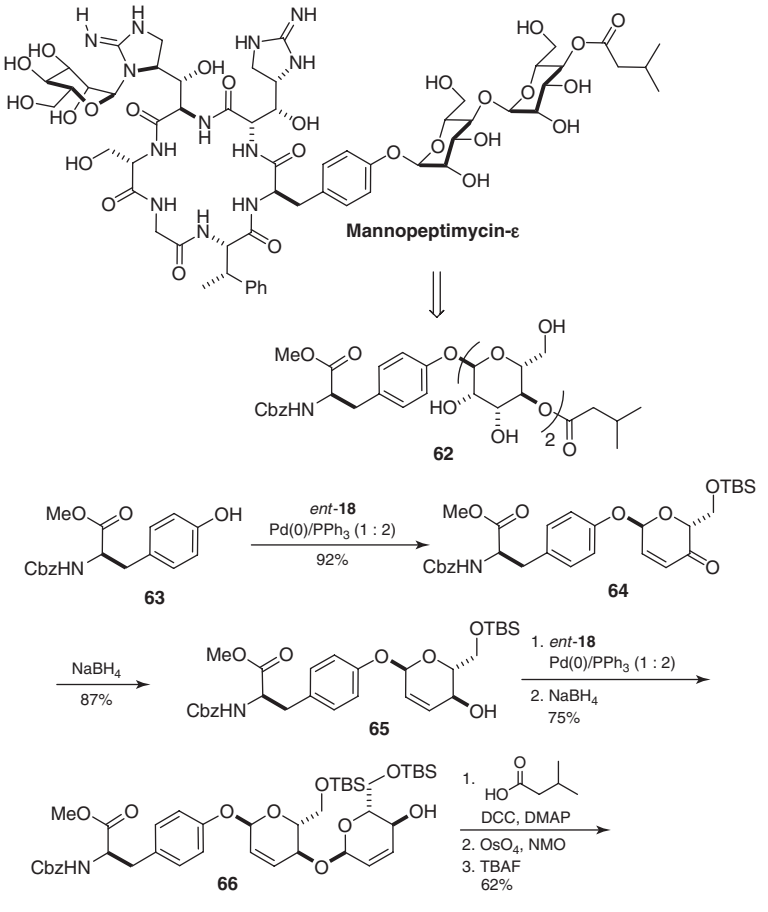
Scheme 1.10 *De novo* synthesis of D-swainsonine.

Thus, we became interested in the *de novo* asymmetric synthesis of both enantiomers of swainsonine and various epimers for further biological studies [32]. We envisioned a similar postglycosylation transformation, in which the installation of the 4-amino-*manno*-stereochemistry in methymycin analog **47** could be instrumental in the development of a *de novo* Achmatowicz approach to the indolizidine natural product swainsonine **60** (Scheme 1.10). In practice, this required access to acylfuran **49**, which was prepared in two steps from 2-lithiofuran and butyrolactone **48**. After Noyori reduction, Achmatowicz reaction, and diastereoselective acylation, **49** was converted into pyranone **52**. Glycosylation of benzyl alcohol with **52** installed the required C-1-protecting group. As before, Luche reduction, carbonate formation, and Pd-π-allyl allylic azide displacement installed the C-4 azido group in **56**. Before the C-2/C-3 double bond was dihydroxylated, the TBS ether is converted into a mesylate-leaving group as in **58**. Finally, a diastereoselective dihydroxylation (**58** to **59**) and exhaustive hydrogenolysis (**59** to **60**) cleanly provided D-swainsonine in an optically pure form. Thus, in only 13 steps, either D- or L-swainsonine can be prepared from achiral starting material. This is of particular note because both enantiomers have been valued as known inhibitors of glycosidase enzymes (D-swainsonine for α-D-mannosidases and α-L-swainsonine for α-L-rhamnosidases). This route has also been used to prepare various diastereoisomers of swainsonine, which are also known to be effective glycosidase inhibitors [32].

1.5
Oligosaccharide Synthesis for Medicinal Chemistry

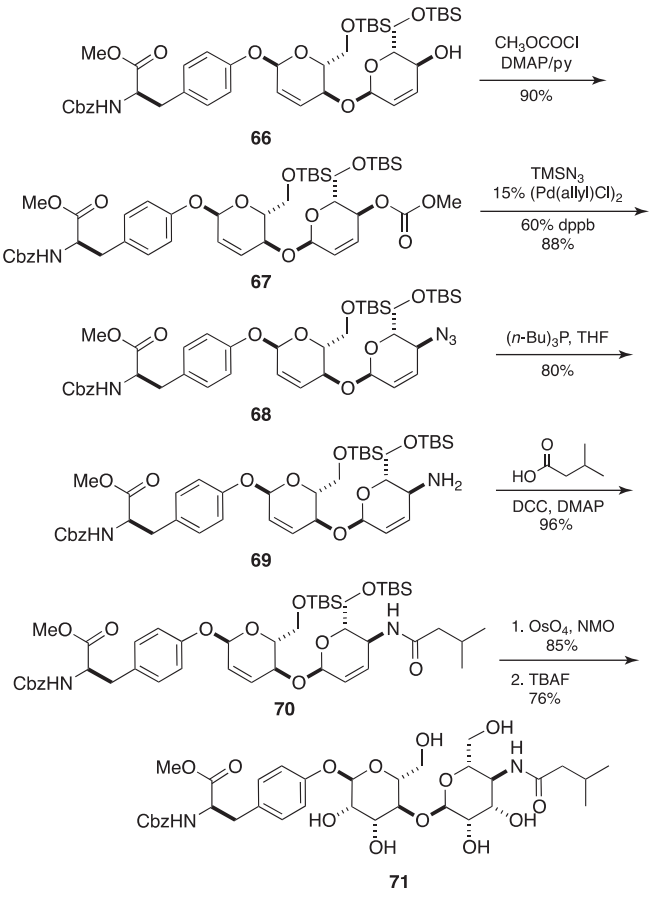
As part of the continuing search for new antibiotics against bacterial resistance [33], the cyclic hexapeptide mannopeptimycin-ε **61** was isolated from the fermentation broths of *Streptomyces hygroscopicus* LL-AC98 and related mutant strains [34]. The key structural features of the mannopeptimycins are a cyclic hexapeptide core with alternating D- and L-amino acids, three of which are rare. Two of the amino acids (β-D-hydroxyenuricididine and D-tyrosine) are glycosylated with mannose sugars. The glycosylated amino acids are an N-glycosylated β-hydroxyenuricididine with an α-mannose, and an O-glycosylated tyrosine with an α-(1,4-linked)-bis-mannopyranose disaccharide portion. The unique structure and unprecedented biological activity have inspired both biological [35] and synthetic studies from us and others.

Our *de novo* asymmetric Achmatowicz approach was also applied to the synthesis of the glycosylated tyrosine portion of the antibiotic mannopeptimycin-ε [36]. Specifically, we targeted a protected tyrosine with bis-manno-1,4-disaccharide with an isovalerate at the C-4′ position. This approach was used to prepare the amino acid portion of the natural product **62** as well as the disaccharide portion in the unnatural L/L-configuration. The linear route involved the application of the iterative bis-glycosylation, acylation, and bis-dihydroxylation of protected tyrosine in only six steps (Scheme 1.11).



Scheme 1.11 Assembly of the mannopeptimycin-ε disaccharide.

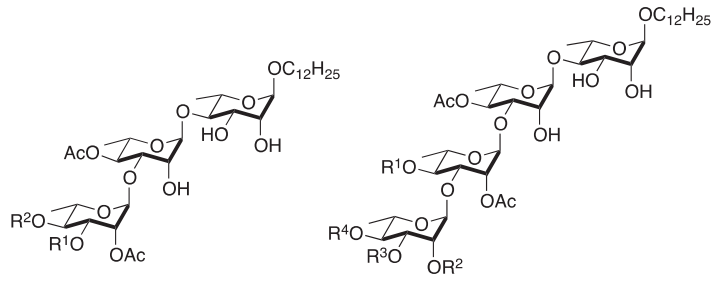
As part of further SAR studies of the antibiotic mannopeptimycin, access to the C-4 amide analogs **42** was also desired [37]. As before, this was also accomplished using the Pd-π-allyl-catalyzed allylic azide alkylation in conjunction with azide reduction and acylation. Specifically, allylic alcohol **66** was converted into methyl carbonate **67**, and the allylic carbonate was converted into allylic azide **68**. In turn, the azide was selectively reduced and the corresponding amine **69** was acylated. The remaining double bonds of **70** were dihydroxylated, and the TBS groups were removed to provide the desired target tyrosine disaccharide **71** (Scheme 1.12). Key to the success of this approach was the somewhat surprisingly selective ionization of the equatorial allylic carbonate in **67** without any sign of ionizing the anomeric phenol in the axial configuration.



Scheme 1.12 Elaboration to C-4″ aza-mannopeptidomycin.

1.5.1
Tri- and Tetrasaccharide Library Syntheses of Natural Product

As part of a high-throughput-based search for new natural products with unique structures and interesting biological activity, two partially acetylated trisaccharide (cleistrioside-5/-6, **72** and **73**) and six partially acetylated tetrasaccharide (cleistetroside-2/-3/-4/-5/-6/-7, **74–81**) natural products were discovered (Figure 1.1) from the leaves and bark of trees with a folk medicinal tradition [38–40]. These dodecanyl tri- and tetrarhamnoside structures with various degrees of acylation were isolated from *Cleistopholis patens* and *Cleistopholis glauca* [36, 37]. The structures of the cleistriosides and cleistetrosides were assigned by detailed NMR analysis and later confirmed by total synthesis by us [41] and others [42, 43]. In addition to clarifying the structural issues, our synthetic interest in these



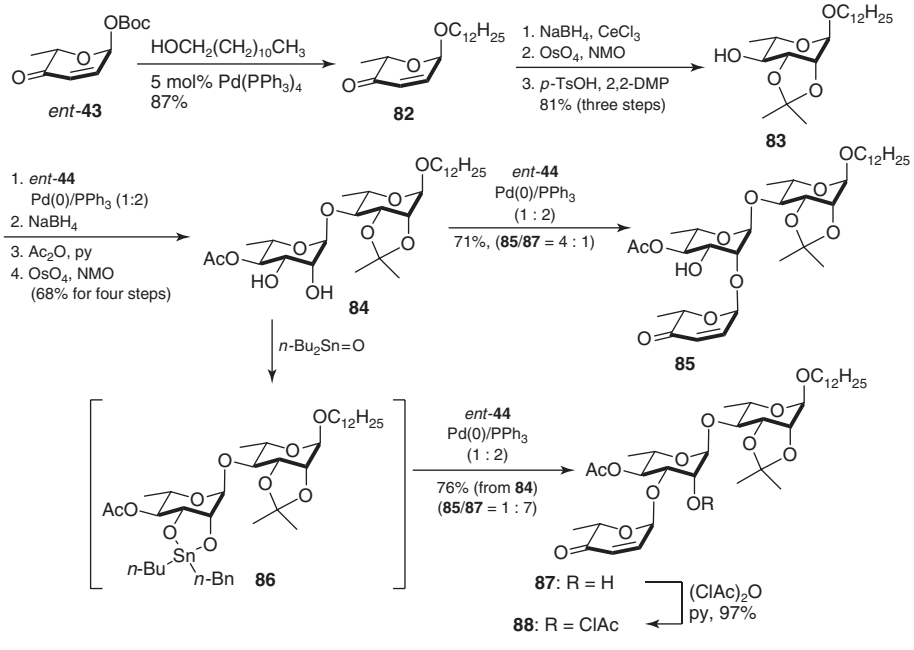
72: Cleistrioside-5: R^1 = H, R^2 = Ac
73: Cleistrioside-6: R^1 = Ac, R^2 = H

74: Cleistetroside-2: R^1 = R^4 = Ac, R^2 = R^3 = H
75: Cleistetroside-3: R^1 = R^2 = Ac, R^3 = R^4 = H
76: Cleistetroside-4: R^1 = Ac, R^2 = R^3 = R^4 = H
77: Cleistetroside-5: R^1 = R^2 = R^3 = R^4 = H
78: Cleistetroside-6: R^1 = R^2 = R^4 = Ac, R^3 = H
79: Cleistetroside-7: R^1 = R^2 = R^3 = R^4 = Ac
80: Cleistetroside-9 (new): R^1 = R^2 = R^3 = H, R^4 = Ac
81: Cleistetroside-10 (new): R^1 = H, R^2 = R^3 = R^4 = Ac

Figure 1.1 The cleistriosides, cleistetrosides, and analogs.

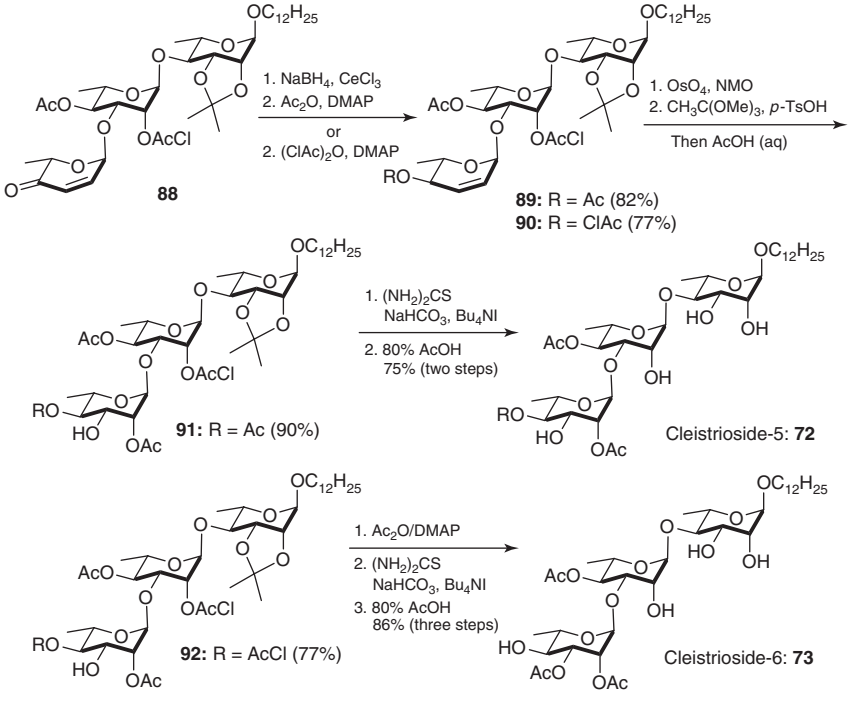
oligosaccharides was aimed at supplying sufficient material for SAR-type studies and as a test of our synthetic methodology [44].

The route began with pyranone *ent*-**44**, which was easily prepared in three steps from commercially available acetylfuran (Scheme 1.13). In four steps (glycosylation, reduction, dihydroxylation, and acetonide protection), glycosyl donor *ent*-**44** was



Scheme 1.13 Synthesis of trisaccharide **88**.

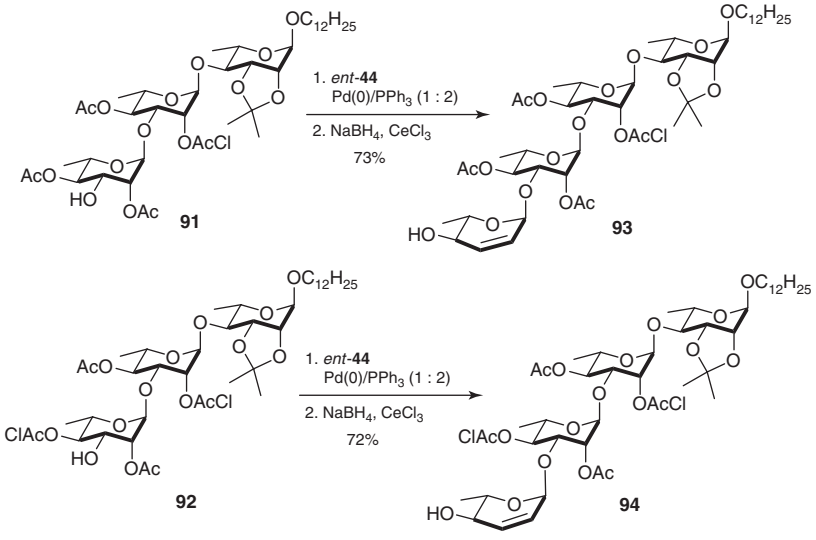
converted into protected rhamnose **83**. A subsequent glycosylation, reduction, acylation, and dihydroxylation gave diol disaccharide **84**. Unfortunately, when diol **84** was exposed to our typical Pd-catalyzed glycosylation conditions, the trisaccharide **85** with the wrong regiochemistry was formed. To our delight, this substrate regioselectivity (4 : 1) could be reversed via the formation of tin acetal **86**. Thus, a tin-directed regioselective (7 : 1) glycosylation gave trisaccharide **87** with the required carbohydrate at the C-3 position. A subsequent chloro-acylation gave trisaccharide **88**, which was ready for further elaboration into both the cleistrioside and cleistetroside natural products (Scheme 1.14, Scheme 1.16, and Scheme 1.17).



Scheme 1.14 Synthesis of cleistrioside-5 and -6.

The pyranone ring in trisaccharide **88** is perfectly situated for further elaboration into a rhamnose ring with the desired acylation pattern for cleistrioside-5 and -6. This was accomplished by Luche reduction and acylation or chloro-acylation to give **89** and **90**. A subsequent dihydroxylation and ortho-ester-mediated C-2 acylation gave trisaccharides **91** and **92**, which could be converted into cleistrioside-5 and -6 (**72** and **73**) by a selective removal of the chloro-acetates over the other acetates (removed with thiourea) and acetonide-protecting groups (hydrolyzed with $AcOH/H_2O$).

In addition, the trisaccharides **91** and **92** can be further converted into eight members of the cleistetroside family of natural products (Scheme 1.16 and Scheme 1.17). This divergent route began with the selective Pd-catalyzed glycosylation of the free C-3 alcohol in **91** and **92** and a subsequent Luche reduction to afford tetrasaccharides **93** and **94** (Scheme 1.15).

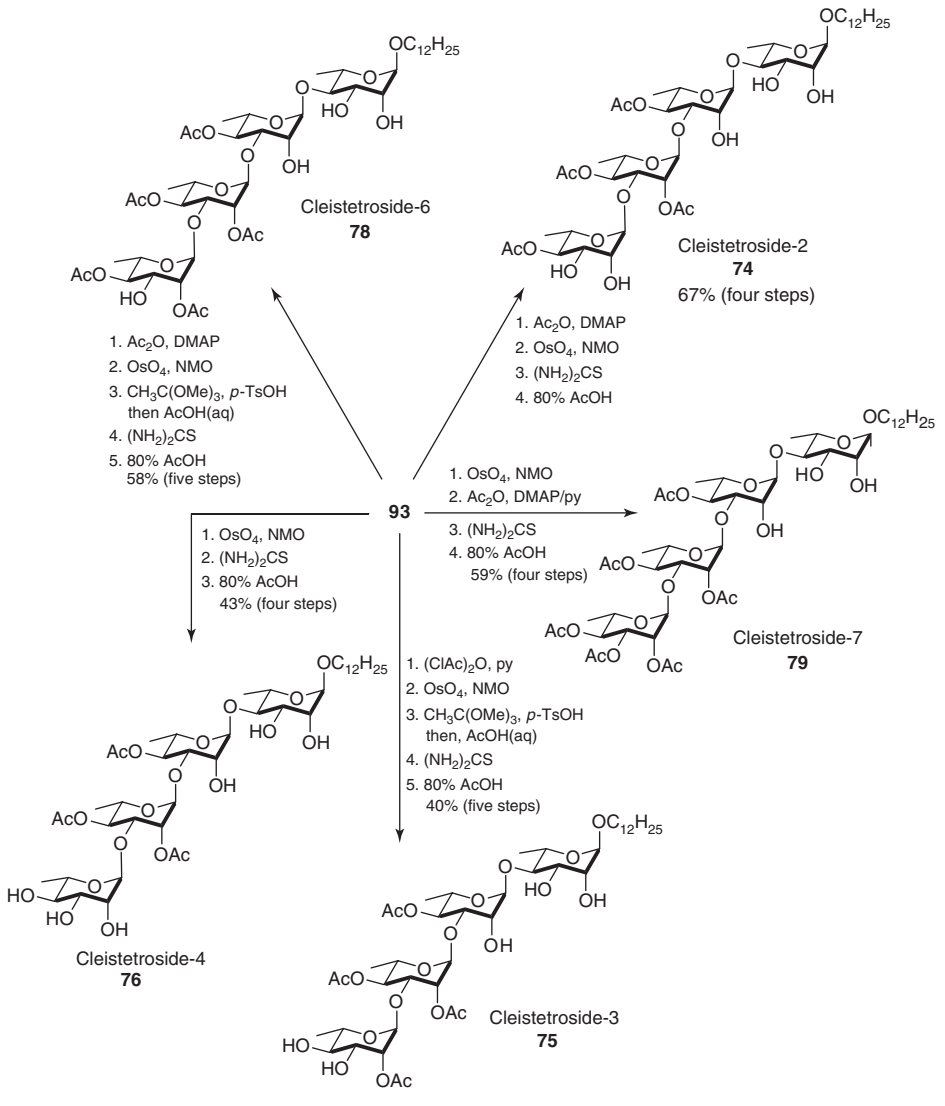


Scheme 1.15 Synthesis of tetrasaccharides **93** and **94**.

As outlined in Scheme 1.16, tetrasaccharide **93** was divergently converted into five of the six desired cleistetroside-2, -3, -4, -6, and -7. This was accomplished in a range of three to five steps by subtle variations of the postglycosylation reactions (dihydroxylation, acylation, and chloro-acylation), followed by global deprotection (thiourea then $AcOH/H_2O$).

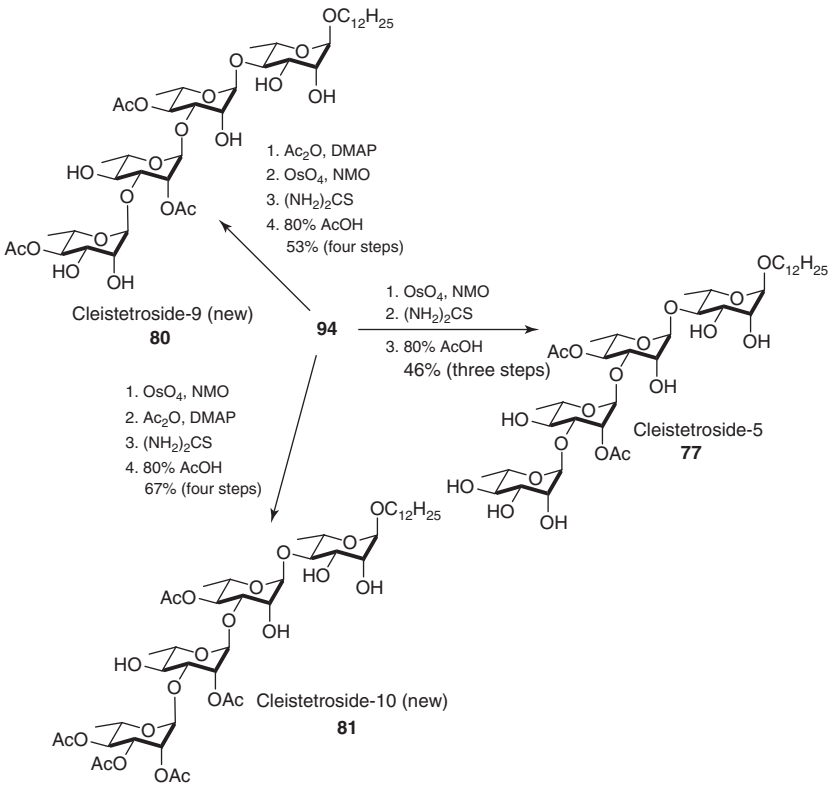
By applying the same postglycosylation/deprotection reaction sequence on tetrasaccharide **94**, the remaining cleistetroside-5 was prepared in three steps. In addition, the revised route was also used to prepare two previously unknown analogs, cleistetroside-9 and -10. This was accomplished in a range of one to three steps by modular application of the postglycosylation reactions (dihydroxylation, acylation, and chloro-acylation) (Scheme 1.17).

It is worth noting that the route to any of the cleistetrosides is quite comparable to the two previously reported routes to cleistetroside-2 in terms of total number of steps. What distinguished it from these more traditional routes is its flexibility to diverge to any of the possible natural product isomers. Thus, we have found that this divergent approach is particularly amenable to medicinal chemistry studies. In this regard, our synthetic access to these eight natural products (two



Scheme 1.16 Synthesis of cleistetroside-2, -3, -4, -6, and -7.

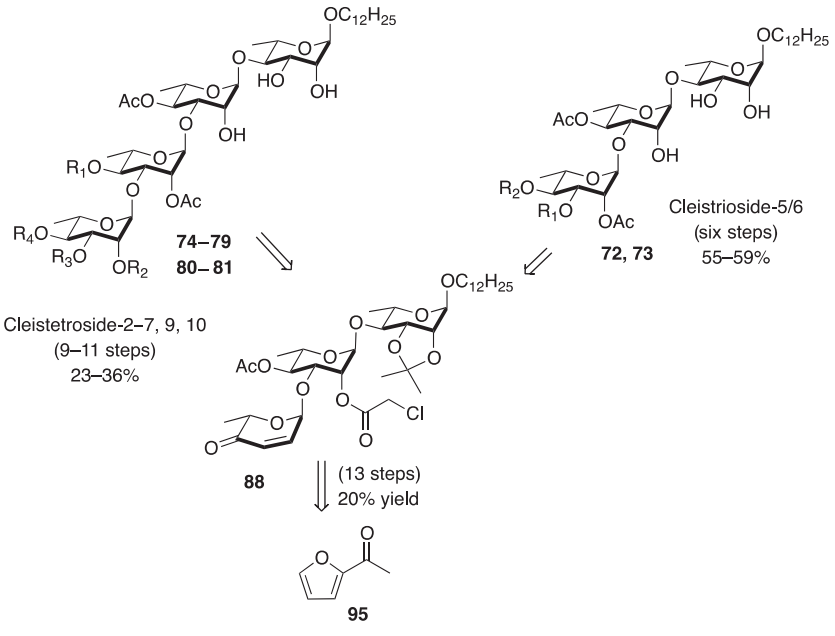
trisaccharides and six tetrasaccharides) and additional two natural product analogs enabled detailed medicinal chemistry SAR studies. The divergent nature of the approach is graphically displayed in Scheme 1.18, where in only 13 steps and in 20% overall yield, the key trisaccharide **88** could be prepared from achiral furan **95**. Trisaccharide **88** serves as the linchpin molecule that can, in 6–11 steps, be converted into any of the desired natural products, in sufficient quantities for further studies.



Scheme 1.17 Synthesis of cleistetroside-5, -8, and -10.

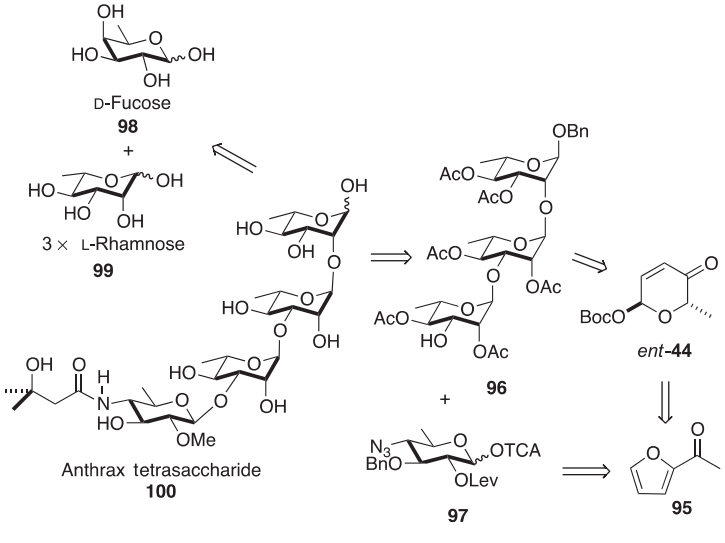
1.5.2
Anthrax Tetrasaccharide Synthesis

Possibly the most elaborate application of this *de novo* Achmatowicz approach to oligosaccharides was the synthesis of the anthrax tetrasaccharide **100**. The approach to this tetrasaccharide natural product merged well with our efforts to C-4 aminosugars with the synthesis of rhamnose-containing oligosaccharides (Scheme 1.19) [45, 46]. Anthrax is a zoonotic disease caused by the spore-forming bacterium *Bacillus anthracis* [47]. In an effort to find a unique structural motif associated with the bacterium, the anthrax tetrasaccharide **100** was discovered. The tetrasaccharide **100** consists of three L-rhamnose sugars and a rare sugar, D-anthrose [48]. The uniqueness of the D-anthrose sugar and the resistance of carbohydrate structures to evolutionary change make the anthrax tetrasaccharide an interesting target for synthesis [49]. Several carbohydrate approaches to the anthrax tetrasaccharide and one to a related trisaccharide have been reported [49a, 50], which derive their stereochemistry from the known but less common sugar L-rhamnose and the rare D-fucose. Our *de novo* approach to the tetrasaccharide **100** was envisioned as occurring through a traditional glycosylation between trisaccharide **96** with

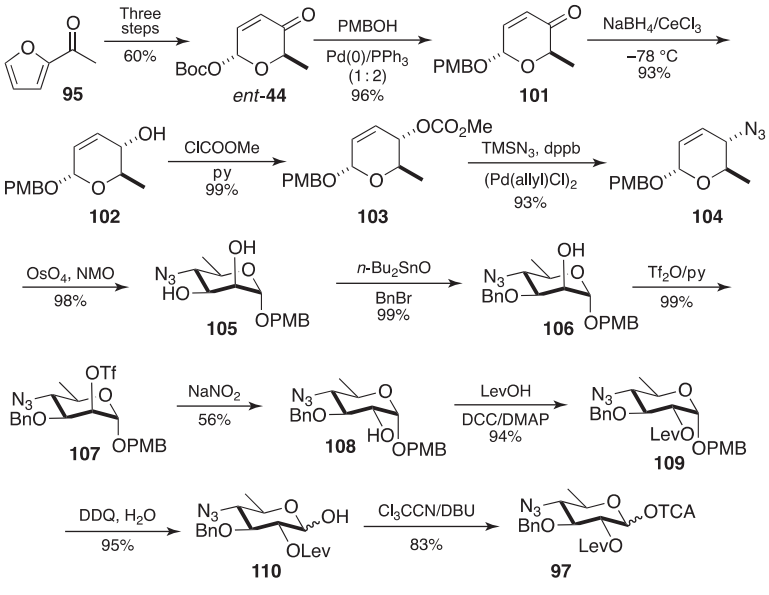


Scheme 1.18 Divergent synthesis retrosynthetic summary.

trichloroacetimidate **97** (Scheme 1.19). In turn, our *de novo* approach was planned to prepare both of these fragments (**96** and **97**) from the achiral acetylfuran **95**, which it is worth noting are significantly less expensive than either L-rhamnose or D-fucose.



Scheme 1.19 Retrosynthesis of anthrax tetrasaccharide **100**.

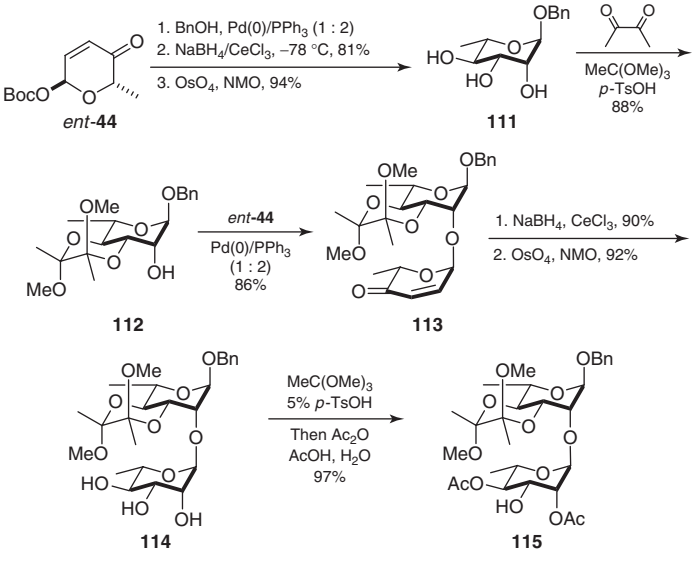


Scheme 1.20 *De novo* synthesis of a D-anthrose sugar trichloroacetimidate.

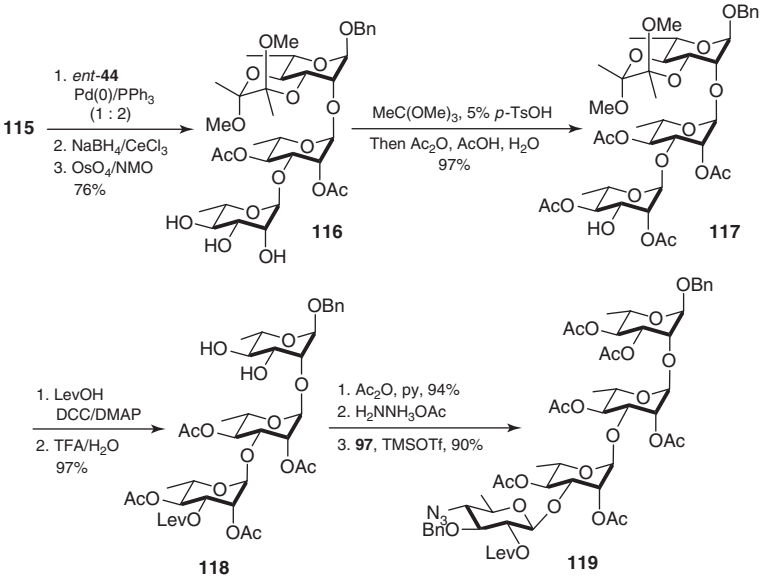
Our synthesis of the anthrose monosaccharide **97** is described in Scheme 1.20 and involved two Pd-π-allylation reactions. The route began with the synthesis of (*p*-methoxybenzyl)PMB-protected pyranone **101** from **95** via *ent*-**44**. Using the Pd-catalyzed C-4 allylic azide chemistry previously described, pyranone *ent*-**44** was converted into allylic azide **104** and dihydroxylated to give rhamno-sugar **105**. The 6-deoxy-*gluco*-stereochemistry is then installed by a protection/C-2 inversion strategy to give anthrose sugar **108**. Finally, a Lev-protection, PMB-deprotection strategy, and trichloroacetimidate formation were used to convert **108** into the glycosyl donor sugar **97** (14 steps from achiral acetylfuran **95**).

The *de novo* Achmatowicz approach to the tris-rhamno portion of the anthrax tetrasaccharide began with the synthesis of disaccharide **115** from pyranone *ent*-**44** and benzyl alcohol (Scheme 1.21). After glycosylation and postglycosylation transformations to install the *rhamno*-stereochemistry (*ent*-**44** to **111**), the 1,2-*trans*-diol of **111** was then protected with the Ley-spiroketal to provide monosaccharide **112** with a free C-2 hydroxyl group. After a similar three-step glycosylation (**112** and **113**) and postglycosylation sequence, **113** was converted into disaccharide **114**, which in a one-pot ortho-ester protocol was protected to give disaccharide **115** with a free C-3 alcohol.

Simply repeating the same three-step glycosylation and postglycosylation sequence converted disaccharide **115** into trisaccharide **116** (Scheme 1.22). Once again the one-pot ortho-ester formation/acylation/hydrolysis sequence gave trisaccharide **117** with the free C-3 alcohol, ready for glycosylation with an anthrose sugar fragment. Unfortunately, any attempt at glycosylation of trisaccharide **117** failed because of the instability of the Ley-spiroketal to the Lewis acidic nature of



Scheme 1.21 Synthesis of disaccharide **115**.

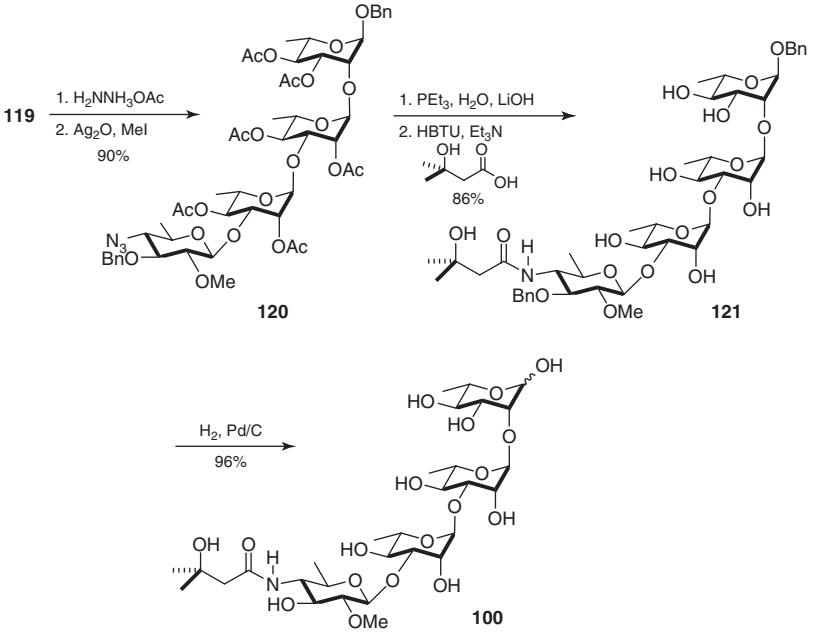


Scheme 1.22 Synthesis of tetrasaccharide **119**.

the traditional glycosylation conditions. Undaunted, we turned to an alternative protecting group strategy. Thus, the C-3 hydroxyl group of **117** was protected as a levulinate ester, and the Ley-spiroketal-protecting group was removed to form **118**. Then, the anthrose sugar was installed by an acylation, selective levulinate

deprotection (using hydrazine), and glycosylation with anthrose monosaccharide **97** delivering the corresponding tetrasaccharide **119**.

Finally, we turned to the deprotection of tetrasaccharide **119** into anthrax tetrasaccharide **100**. Deprotection of levulinate-protecting groups followed by an etherification (MeI/Ag_2O) delivered the methyl ether **120**. A one-pot condition was employed to reduce and acylate azide **120** along with global deprotection of the acetate groups to generate the free alcohol ($PEt_3/LiOH/H_2O$), which upon selective peptide coupling of primary amine and 3-hydroxy-3-methylbutanoic acid ($HBTU/Et_3N$) (HBTU, *O*-(benzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate) afforded amide **121**. Removal of the benzyl groups in **121** under hydrogenolysis conditions provided the natural product anthrax tetrasaccharide **100** (Scheme 1.23).



Scheme 1.23 Synthesis of anthrax tetrasaccharide **100**.

1.6 Conclusion and Outlook

For the last 25 years, various groups have been investigating the use of asymmetric catalysis for the synthesis of hexoses. When beginning with achiral starting materials and when asymmetric catalysis is used for the installation of asymmetry, these syntheses are called "*de novo asymmetric*" or "*de novo*" for short. While these *de novo* approaches have been quite impressive in terms of the scope of products

prepared and the brevity of steps, they were lacking in terms of application to oligosaccharide synthesis. As part of these efforts, we have developed two orthogonal *de novo* asymmetric approaches to hexoses: an iterative dihydroxylation strategy and an Achmatowicz strategy. Owing to its compatibility with a Pd-catalyzed glycosylation reaction, this later Achmatowicz *de novo* approach to hexoses has seen significant application for the assembly of oligosaccharides.

Of particular note is the flexibility of the *de novo* Achmatowicz route to a myriad of carbohydrate motifs. The approach couples asymmetric catalysis with the Achmatowicz rearrangement for the synthesis of D- and L-pyranones and utilizes highly diastereoselective glycosylation and postglycosylation reactions for the assembly of oligosaccharides. Heavily featured in the glycosylation and postglycosylation reactions was the Pd-π-allyl-catalyzed allylic substitution reaction for substitution at both the anomeric C-1 and C-4 positions of the hexose. What made these allylic substitution reactions so powerful is the one-step double inversion mechanism of the Pd-catalyzed reaction, which in a highly stereospecific manner reliably provides products with net retention of stereochemistry.

Whether these approaches were used in linear and/or bidirectional manner, highly efficient syntheses of natural and unnatural mono-, di-, and oligosaccharides resulted. The overall efficiency of these approaches was the result of the strategic use of the enone functionality in the pyranone as atom-less protecting groups. While the use of atom-less protecting groups has been under-explored in carbohydrate chemistry, the success of the above-mentioned approaches suggest that this strategy should be given more attention from 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 [51].

1.7 Experimental Section

(*R*)-(+)-1-(2-furyl)ethanol: To a 250 ml flask, 2-acetylfuran (22.0 g, 0.20 mol), CH_2Cl_2 (100 ml), formic acid/triethylamine (1 : 1, 108 ml), and Noyori asymmetric transfer hydrogenation catalyst (*R*)-Ru(η^6-mesitylene)-(*R*,*R*)-TsDPEN (585 mg, 0.95 mmol) were added. The resulting solution was stirred at room temperature for 24 h. The reaction mixture was diluted with water (150 ml) and extracted with Et_2O (3 × 150 ml). The combined organic layers were washed with saturated aqueous $NaHCO_3$, dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by silica gel flash chromatography and eluted with 20% Et_2O/hexanes to give *(R)-(+)-1-(2-furyl)ethanol* (21.5 g, 0.19 mmol, 96%) as a clear liquid.

6-Hydroxy-2-methyl-(2*R*)-2*H*-pyran-3(6*H*)-one: *(R)-(+)-1-(2-furyl)ethanol* (8.9 g, 79.5 mmol): Tetrahydrofuran (THF) (100 ml) and H_2O (25 ml) were added to a round bottom flask and cooled to 0 °C. Solid $NaHCO_3$ (13.4 g, 159 mmol), $NaOAc{\cdot}3H_2O$ (10.8 g, 79.5 mmol) and *N*-bromosuccinimide

(NBS) (14.9 g, 83.5 mmol) were added to the solution and the mixture was stirred at 0 °C for 1 h. The reaction was quenched with saturated aqueous $NaHCO_3$ (200 ml), extracted with Et_2O (3 × 200 ml), dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by silica gel flash chromatography and eluted with 35% EtOAc/hexanes to give *6-hydroxy-2-methyl-(2R)-2H-pyran-3(6H)-one* (9.67 g, 75.5 mmol, 95%, α:β = 2.6 : 1) as a clear liquid.

Carbonic acid, (2*R*,6*R*)-5,6-dihydro-6-methyl-5-oxo-2*H*-pyran-2-yl-1,1-dimethylethyl ester (*ent*-44): 6-Hydroxy-2-methyl-(2*R*)-2*H*-pyran-3(6*H*)-one (3.70 g, 28.9 mmol) was dissolved in CH_2Cl_2 (15 ml) and the solution was cooled to −78 °C. A CH_2Cl_2 (15 ml) solution of $(Boc)_2O$ (9.46 g, 43.4 mmol), and a catalytic amount of dimethylaminopyridine (DMAP) (350 mg, 2.89 mmol) was added to the reaction mixture. The reaction was stirred at −78 °C for 5 h. The reaction was quenched with saturated aqueous $NaHCO_3$ (50 ml), extracted with Et_2O (3 × 50 ml), dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by silica gel flash chromatography and eluted with 7% EtOAc/hexanes to give two diastereomers of *tert*-butyl((6*R*)-6-methyl-5-oxo-5,6-dihydro-2*H*-pyran-2-yl) carbonate (5.72 g, 25.1 mmol, 87%) in 3 : 1 (α:β) ratio *ent*-**44**.

(2*R*,6*S*)-2*H*-6-[(4-Methoxyphenyl)methoxy]-2-methyl-pyran-3(6*H*)-one (101): To a solution of Boc-protected pyranone, *ent*-**44** (13 g, 57.0 mmol), and *para*-methoxy benzyl alcohol (157.3 g, 114.0 mmol) in dry CH_2Cl_2 (57 ml), $Pd_2(dba)_3{\cdot}CHCl_3$ (294 mg, 1 mol% Pd) and PPh_3 (297 mg, 2.0 mol%) at 0 °C were added under argon atmosphere. After stirring for 2 h, the solution was warmed to room temperature, the reaction mixture was quenched with 300 ml of saturated $NaHCO_3$, extracted (3 × 300 ml) with Et_2O, dried (Na_2SO_4), and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography and eluted with 5% EtOAc/hexane to give PMB ether **101** (13.6 g, 54.7 mmol, 96%) as a colorless oil.

(2*R*,3*S*,6*S*)-2*H*-3,6-Dihydro-6-[(4-methoxyphenyl)methoxy]-2-methyl-pyran-3-ol (102): A solution of pyranone **101** (13.5 g, 54.4 mmol) in dry CH_2Cl_2 (54.4 ml) and 0.4 M $CeCl_3$/MeOH (54.4 ml) was cooled to −78 °C. $NaBH_4$ (2.08 g, 55.5 mmol) was added, and the reaction mixture was stirred for 4 h at −78 °C. The resulting solution was diluted with Et_2O (400 ml) and was quenched with 200 ml of saturated $NaHCO_3$, extracted (3 × 400 ml) with Et_2O, dried (Na_2SO_4), and concentrated under reduced pressure. The crude product was purified using silica gel chromatography and eluted with 40% EtOAc/hexane to give 12.6 g (50.6 mmol, 93%) of allylic alcohol **102** as a white solid.

Carbonic acid, (2*R*,3*S*,6*S*)-3,6-Dihydro-6-[(4-methoxyphenyl)methoxy]-2-methyl-2*H*-pyran-3-yl methyl ester (103): To a stirred solution of allylic alcohol **102** (20 g, 80 mmol), pyridine (38.8 ml, 480 mmol), and DMAP (1.96 g) in dry CH_2Cl_2 (400 ml), methyl chloroformate was added dropwise (33.9 ml, 480 mmol) at 0 °C. After reacting for 1 h at 0 °C, water (300 ml) was

added and the reacted mixture was extracted with CH_2Cl_2 (3 × 400 ml), dried (Na_2SO_4), and concentrated under reduced pressure. The crude product was purified using silica gel flash chromatography and eluted with 10% EtOAc/hexane to give 24.4 g (79.2 mmol, 99%) of carbonate **103** as colorless oil.

(2*R*,3*S*,6*S*)-2*H*-3-Azido-3,6-dihydro-6-[(4-methoxyphenyl)methoxy]-2-methyl-pyran (104): To a stirred solution of carbonate **103** (30 g, 97.4 mmol), allylpalladium chloride dimer (378 mg, 1.0 mmol%), and 1,4-bis(diphenylphosphino)butane (1.68 g, 4.0 mmol%) in dry THF (97.2 ml) $TMSN_3$ (15.5 ml, 116.9 mmol) was added under argon atmosphere. The reaction mixture was stirred at room temperature for 0.5 h, the solvent was evaporated under reduced pressure and purified using silica gel flash chromatography, and eluted with 7% EtOAc/hexane to obtain 24.9 g (90.6 mmol, 93%) allylic azide **104** as colorless oil.

(4-Methoxyphenyl)methyl-4-azido-4,6-dideoxy-α-D-mannopyranoside (105): To a mixture of *t*-butanol, acetone (145.4 ml, 1 : 1 (v/v), 1 M) and solution of allylic azide **104** (20 g, 72.7 mmol) at 0 °C, a solution of *N*-methyl morpholine *N*-oxide/water (50% w/v, 50 ml) was added. Crystalline OsO_4 (185 mg, 1 mol%) was added and the reaction mixture was allowed to stir for 24 h. The reaction mixture was quenched with 200 ml saturated $Na_2S_2O_3$ solution, extracted with EtOAc (3 × 500 ml), dried with (Na_2SO_4), concentrated under reduced pressure, and then purified using silica gel flash chromatography, eluting with 90% EtOAc/hexane to give diol **105** (22.0 g, 71.2 mmol, 98%).

List of Abbreviations

Ac	Acetyl
AD-mix-α	3 equiv $K_3Fe(CN)_6/K_2CO_3$, 1 equiv $MeSO_2NH_2$, 5% OsO_4, and 6% $(DHQ)_2PHAL$
AD-mix-β	3 equiv $K_3Fe(CN)_6/K_2CO_3$, 1 equiv $MeSO_2NH_2$, 5% OsO_4, and 6% $(DHQD)_2PHAL$
ATCC	American Type Culture Collection
Bn	Benzyl
Boc	*t*-Butoxycarbonyl
Bu	Butyl
Cbz	Carbobenzoxy
ClAc	Chloroacetyl
CTAB	Cetyltrimethylammonium bromide
DCC	Dicyclohexylcarbodiimide
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DMAP	Dimethylaminopyridine
DMP	Dess–Martin periodinane
dppb	1,4-Bis(diphenylphosphino)butane
Et	Ethyl

HBTU	*O*-(Benzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate
Lev	Levulinoyl
NBS	*N*-Bromosuccinimide
NMO	*N*-Methylmorpholine-*N*-oxide
Noyori	(*S*,*S*) (*R*)-Ru(η^6-mesitylene)-(*S*,*S*)-TsDPEN
p-TsOH	*p*-Toluenesulfonic acid
Ph	Phenyl
PMB	*p*-Methoxybenzyl
py	Pyridine
SAR	Structure Activity Relationship
TBAF	Tetrabutylammonium fluoride
TBS	*t*-Butyldimethylsilyl
Tf	Trifluoromethanesulfonyl
THF	Tetrahydrofuran
TMS	Trimethylsilyl
TsDPEN	PhCH(TsN)CH(NH)Ph

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