Asymmetric Synthesis of Furan Alcohols

by Alhanouf Zakaria Aljahdali
B.S. in Chemistry, Northeastern University

A Thesis submitted to

The Faculty of the
College of Science of
Northeastern University
in partial fulfillment of the requirements
for the Master of Science degree in Chemistry

August 17, 2015

Thesis directed by

George A. O’Doherty
Professor of Chemistry and Chemical Biology
ACKNOWLEDGEMENTS

First, I would like to express my sincere gratitude towards my advisor Prof. George A. O’Doherty for his excellent mentorship, guidance, motivation, and encouragement during my studies at Northeastern University. My gratitude is extended gratitude to Prof. Penny Beuning and Prof. Ke Zhang for being on my dissertation committee, and their valuable suggestions on my thesis. I also would like to thank Cara Shockley for her kindness and all of her help during my undergraduate and graduate years.

I feel that I am fortunate to work in Prof. O’Doherty’s group where all the group members both past and present, were very helpful during my studies. Specifically, I would like to thank Dr. Sumit Bajaj, Dr. Yuzi Ma Dr. Miaosheng Li, Dr. Mingzong Li, Dr. Yanping Wang, Dr. Michael Cuccarese, Dr. Yashan Zhong, Dr. Pei Shi, Debarpita Ray, Yu Li, Jiamin Zheng, Chao Liang, Xiaofan Liu, and Naimah Alhazza.

Therefore, I would like to thank my parents (Zakaria Aljahdali and Nazeeha Aljeddani) for their unconditional support and love, guidance, encouragement and for always keeping me in theirir prayers. My gratitude is extended to my brothers and sisters, Almohaned, Almuthana, Alhatoon and Sondos for their support, motivation and love. I would like to thank my uncle Mohammed Aljeddani as well for his advice, encouragement and support during my educational endeavors. I also would like to thank my grandmother, uncles and aunts and all the family members for their encouragement and love.

I would like to thank my friends Amell Alsudairi and Nisal Gajadeera for their support, help and advice. Thank you for always listening to me and giving me advices. I would also like to thank Amal Bukhari, Anwar Zwawi and all of my friends for their support and love. I would
like to thank my dearest Boshra Rajkhan, for her patient and for always being by my side through my good and bad times. I would like to thank Elissa for her inspirational music. Her soothing voice accompanied me while I was running reactions days and nights. I never felt bored or tired while I am at the lab because of her music. Thank you Elissa.

I would like to thank King Abdullah (may his soul rest in peace) for giving me the opportunity to achieve my dream through this scholarship. I would like to thank Saudi Arabian Culture Mission (SACM) for their financial support.

Finally, I bow down to Allah thanking him for his guidance and showering me with his blessing and giving me strength and patience through the good and bad times.
ABSTRACT

The importance of the role oligosaccharides play in biological has been becoming more and more apparent. In a commensurate fashion there has been an ever-increasing need for synthetic access to oligosaccharide structure motifs. As these studies have evolved, there has been a change in the desire for specific oligosaccharides produced by natural to structures for structure-activity relationship studies. In an effort to address this need a de novo asymmetric synthetic approach to oligosaccharides was developed; where the carbons and asymmetry of the sugar are derived from chiral furan alcohols. To enable this approach highly practical and enantioselective approach to chiral furan alcohols from inexpensive achiral starting materials is required. Herein we will present our latest efforts at the synthesis of substituted furan alcohols from 2-acetyl furan and its application to the synthesis of C-6 substituted D-/L-sugars.
# TABLE OF CONTENTS

Acknowledgements .............................................................................................................. ii

Abstract .............................................................................................................................. iv

Table of contents ................................................................................................................ v

List of figures ....................................................................................................................... vii

List of scheme ................................................................................................................... viii

List of abbreviations ......................................................................................................... ix

Chapter 1. Asymmetric Synthesis of Furan Alcohols .............................................................. 1

1.1 Introduction to Carbohydrates ...................................................................................... 1

1.2 *De Novo* Approach using Pd-catalysis towards glycosylation .................................... 3

1.3 Examples and applications of furan alcohol ................................................................. 6

1.4 Application of *N*-protected alcohol .......................................................................... 9

1.5 Previous methods towards furan alcohol ................................................................... 11

1.6 Previous methods towards *N*-protected alcohol ....................................................... 12

1.7 New approach to furan Alcohols and *N*-protected furan alcohols ............................. 13

1.8 Synthesis of α-Boc-pyranosides ................................................................................. 15

1.9 Conclusions ................................................................................................................ 16

1.10 References .................................................................................................................. 18

Chapter 2. Experimental Section .......................................................................................... 20

2.1 Chapter 1 experimental procedure ............................................................................. 21

2.2 References ................................................................................................................... 29
List of Figures

Figure 1.1: Both enantiomers of Noyori catalysts…………………………………………..5
List of Schemes

Scheme 1. Achmatowicz reaction and its mechanism ......................................................... 3

Scheme 2. Stereospecific palladium-catalyzed glycosylation ........................................... 5

Scheme 3. O’Doherty De Novo Approach to hexoses ....................................................... 6

Scheme 4. Synthesis of Branched α-rhamno-/manno-Trisaccharides Containing Both D- and L- Pyranoses ....................................................................................................................... 7

Scheme 5. A 12-Step Synthesis of Highly Branched All-L-α-manno Heptapyranoside ......... 8

Scheme 6. Synthesis of N-Cbz-Protected 6-aminomono, 6-aminotalose
and 6-aminogulose ........................................................................................................... 10

Scheme 7. O’Doherty’s first approach to protected furan alcohols ..................................... 11

Scheme 8. Another approach to protected furan alcohols .................................................. 12

Scheme 9. Previous method to N-protected furan alcohol .................................................. 12

Scheme 10. Another approach to N-protected furan alcohols ............................................ 13

Scheme 11. New route to protected furan alcohol ............................................................... 14

Scheme 12. New route toward N-protected furan alcohol .................................................. 15

Scheme 13. Synthesis toward α-Boc-pyronside ................................................................. 16
List of Abbreviations:

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ac</td>
<td>Acetyl</td>
</tr>
<tr>
<td>Anal.</td>
<td>Analysis</td>
</tr>
<tr>
<td>Bn</td>
<td>Benzyl</td>
</tr>
<tr>
<td>Boc</td>
<td>t-Butoxycarbonyl</td>
</tr>
<tr>
<td>bp</td>
<td>Boiling point</td>
</tr>
<tr>
<td>Bu</td>
<td>Butyl</td>
</tr>
<tr>
<td>BuLi</td>
<td>n-Butyllithium</td>
</tr>
<tr>
<td>Calcd</td>
<td>Calculated</td>
</tr>
<tr>
<td>CI</td>
<td>Chemical Ionization</td>
</tr>
<tr>
<td>CTAB</td>
<td>Cetyltrimethylammonium bromide</td>
</tr>
<tr>
<td>d</td>
<td>Doublet</td>
</tr>
<tr>
<td>DBA</td>
<td>trans, trans-dibenzylideneacetone</td>
</tr>
<tr>
<td>DBU</td>
<td>1,8-Diazabicyclo[5.4.0]undec-7-ene</td>
</tr>
<tr>
<td>δ</td>
<td>Chemical shift (ppm)</td>
</tr>
<tr>
<td>DMAP</td>
<td>4-Dimethylaminopyridine</td>
</tr>
<tr>
<td>ee</td>
<td>Enantiomeric excess</td>
</tr>
<tr>
<td>EI</td>
<td>Electron ionization</td>
</tr>
<tr>
<td>Symbol</td>
<td>Full Form</td>
</tr>
<tr>
<td>--------</td>
<td>---------------------------</td>
</tr>
<tr>
<td>ent</td>
<td>Enantiomer</td>
</tr>
<tr>
<td>equiv</td>
<td>Equivalent(s)</td>
</tr>
<tr>
<td>Et</td>
<td>Ethyl</td>
</tr>
<tr>
<td>EtOAc</td>
<td>Ethyl acetate</td>
</tr>
<tr>
<td>g</td>
<td>Gram(s)</td>
</tr>
<tr>
<td>h</td>
<td>Hour(s)</td>
</tr>
<tr>
<td>HRMS</td>
<td>High resolution mass spectrum</td>
</tr>
<tr>
<td>Hz</td>
<td>Hertz (cycles per second)</td>
</tr>
<tr>
<td>IR</td>
<td>Infrared</td>
</tr>
<tr>
<td>J</td>
<td>Spin-spin coupling constant</td>
</tr>
<tr>
<td>mol</td>
<td>Mole(s)</td>
</tr>
<tr>
<td>mg</td>
<td>Milligram(s)</td>
</tr>
<tr>
<td>MHz</td>
<td>Megahertz</td>
</tr>
<tr>
<td>MIC</td>
<td>Minimum inhibitory concentration</td>
</tr>
<tr>
<td>min</td>
<td>Minute(s)</td>
</tr>
<tr>
<td>mmol</td>
<td>Millimole(s)</td>
</tr>
<tr>
<td>mp</td>
<td>Melting point</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Full Form</td>
</tr>
<tr>
<td>--------------</td>
<td>-----------</td>
</tr>
<tr>
<td>MS</td>
<td>Mass spectrum</td>
</tr>
<tr>
<td>NBS</td>
<td>N-Bromosuccinimide</td>
</tr>
<tr>
<td>NMR</td>
<td>Nuclear magnetic resonance</td>
</tr>
<tr>
<td>Ph</td>
<td>Phenyl</td>
</tr>
<tr>
<td>Ppm</td>
<td>Parts per million</td>
</tr>
<tr>
<td>Py</td>
<td>Pyridine</td>
</tr>
<tr>
<td>$R_f$</td>
<td>Ratio to front</td>
</tr>
<tr>
<td>rt</td>
<td>Room temperature</td>
</tr>
<tr>
<td>THF</td>
<td>Tetrahydrofuran</td>
</tr>
<tr>
<td>TLC</td>
<td>Thin layer chromatography</td>
</tr>
</tbody>
</table>
Chapter I

Asymmetric Synthesis of Furan Alcohols

1.1 Introduction to Carbohydrates

Carbohydrates have become a major interest of current chemical biology research. Synthetic organic chemists and biochemists have long recognized the antibiotic and anticancer properties of carbohydrate based natural products. Additionally, oligosaccharides have been identified as having diverse biological properties where the stereochemistry ($\alpha/\beta$ and $D/L$) is critically important to these properties. Therefore, the need for efficient synthesis of carbohydrates and oligosaccharides molecules for structure-activity relationship studies (SAR) is apparent.

Traditionally, monosaccharides have been used as the starting materials for more complex sugars; due to the need for nearly perfect enantiomeric purity of the building blocks before assembly.

From the synthetic perspective, syntheses of these molecules have provided a great deal of insight into balancing the substrate and reagent control for complex carbohydrate synthesis. In addition, the new synthetic routes that have been discovered have provided access to unnatural carbohydrates with interesting biological properties. Of long standing interest to the synthetic carbohydrate community has been the developments of novel routes for the synthesis of hexoses. More recently the O’Doherty group has been able to extend these approaches to oligosaccharides. Starting from achiral starting material, our group has used asymmetric catalysis to install all stereocenters of mono-, di-, tri-saccharides. These routes that use asymmetric synthesis are described as “de novo asymmetric”. In the O’Doherty approach, Boc-pyranones are considered as building blocks for oligosaccharides. We are interested in developing synthetic application of the building block for the synthesis of several de novo approaches to the hexoses and oligosaccharides.
Key to the success of the O’Doherty approach to carbohydrates is the reliance on the Achmatowicz rearrangement for the conversion of furan alcohols into pyranones (Scheme 1). The Achmatowicz rearrangement is an oxidative hydration reaction that converts furan into 5-hydroxy-2-en-3-on-als, because of the cis-alkene preference to exist in their cyclic hemiacetal form. In this case, the Achmatowicz reaction was used to convert furan alcohol (I-3) into pyranone (I-4). Because of the unstable hemiacetal functionality in (I-4) the product is often taken to the next step without further purification. Thus, the hydroxyl-group of the hemiacetal is protected as a t-butyl-carbonate (I-5). The Boc-functionality (I-5) is important, as it is the ideal leaving group for the key Pd-catalyzed glycosylation. Similarly, the enone functionality serves as a precursor for the C-2 to C-4 triol of the sugar product, which is installed by two post-glycosylation transformations (e.g., Luche reduction and Upjohn dihydroxylation). Thus in this methodology for making hexoses the pyranone double bond serves as an anomic directing group in the Pd-catalyzed glycosylation (I-5 to I-7) and the enone functions as an atom-less protecting group.
1.2  *De Novo* approach using Pd-catalysis towards glycosylation

The traditional glycosylation is a reaction that goes through an oxygen-stabilized carbocation. Over the years, this powerful methodology has been used for the assembly of many types of complex oligosaccharides, however, it does have some disadvantages. For instance, the traditional glycosylation does not give product with predictable stereocontrol, as often products are provided as a mixture of stereoisomers at the anomeric position. To address this issue with stereochemical ambiguity, the O’Doherty group has developed a Pd-catalyzed glycosylation methodology that controls the anomeric selectivity via a reliable stereo-retentive mechanism for product formation. This Pd-catalyzed glycosylation reaction, when used in context with their *de novo* approach to carbohydrate, becomes a powerful approach toward natural and unnatural carbohydrates. In contrast to the harsh Lewis acid condition of the traditional glycosylation, the Pd-catalyzed glycosylation
occurs under the mild reaction conditions (i.e., 0 °C) of Pd-\(\pi\)-allylation chemistry (e.g., Pd\(_2\)(dba)\(_3\)•CHCl\(_3\)/4PPh\(_3\) (2.5 mol%)) (Scheme 2). Because the reaction occurs via a \(\pi\)-allylation double inversion mechanism, the reaction is stereospecific. Thus when starting with \(\alpha\)-pyranones (I-5) the reaction gives exclusively the \(\alpha\)-anomeric product (I-7). Similarly, when the reaction starts with the \(\beta\)-pyranes (I-8) it proceeds to give only the \(\beta\)-product (I-10). Additional benefits of using Pd-catalyzed glycosylation are the compatibility of reaction with a wide variety of solvents and functional groups. Possibly the greatest advantages of the Pd-catalyzed glycosylation are environmental, as the reaction complies with green chemistry principles: for instance, the need of only a catalytic amount of Pd-catalyst and the minimal use of protecting groups. Possibly the mostly important green aspect of the reaction is the excellent stereocontrol (i.e., no complex chromatography is needed to purify the products). When comparing the reaction to traditional glycosylations it is useful to think of the Pd-\(\pi\)-allyl intermediates (I-6) and (I-9) as glycosyl donors that react with various glycosyl acceptors (i.e., the electrophile), which are most often alcohols (i.e., nucleophile.) As the Pd-\(\pi\)-allyl intermediates (I-6) and (I-9) are selectively formed from pyranones (I-5) and (I-8) these pyranones can be viewed as the de facto glycosyl donors. As can be seen in Scheme 2 this method can be applied towards a wide range of alcohol nucleophiles, which react with good yields.
In addition to installing the enone functionality, the Achmatowicz rearrangement uses the initial furan alcohol stereocenter into the D- or L-stereochemistry of the resulting pyranose ring. Thus if the initial furan alcohol is in the R-configuration, D-sugar results and if the furan alcohol is in the S-configuration the resulting sugar is an L-sugars. In the O’Doherty approach a Noyori asymmetric hydrogenation (Figure 1)\(^8\) of acylfurans is used to install the initial furan alcohol stereochemistry. The reaction is used because it occurs in both high yield and with excellent enantiocntrol.\(^10\) Additional features that make the Noyori asymmetric reduction appealing are the availability of both enantiomers of the catalyst and the ease with which this reaction can be run on large scale (e.g., 100 g of furan alcohols).

**Figure 1. Both enantiomers of Noyori catalysts**
1.3 Examples and application of furan alcohol

Starting with furan alcohol, the O’Doherty’s group has successfully synthesized hexoses, which are of great synthetic challenge due to the stereochemical complexity. The approach to hexoses (Scheme 3) was completed without the need of any protection/deprotection steps to install the C-2 and C-4 stereocenters. The methodology begins with the three step conversion of acylfuran (I-11) into Boc-protected pyranone (I-5) (Noyori, Achmatowicz and carbonate formation). The pyranone in turn serves as glycosyl donor (I-5) in the Pd-catalyzed glycosylation, which converts pyranone (I-5) into (I-7). Then in two highly diastereoselective steps, the enone in (I-7) was converted into a pyranose (I-12). This typically involves a Luche reduction (NaBH₄) of (I-7) to form (I-56) and an Upjohn-type alkene dihydroxylation (OsO₄/NMO) of (I-56) to form L-manno-sugar (I-12). Importantly, the route can be applied equally well to D-sugar by simply changing the Noyori catalysts.

Scheme 3. O’Doherty De Novo Approach to hexoses

The successful application can be seen in the synthesis of oligosaccharides. This was accomplished by using the Pd-glycosylation in a bidirectional fashion. For example, the group synthesized highly branched all-L-α-manno-trisaccharide (Scheme 4) and related heptasaccharide (Scheme 5). The bidirectional nature of these applications allows for the synthesis to save steps. An example of this
approach to trisaccharides is outlined in (Scheme 4). Of particular note in this example, is its application to a mixed D-/L-trisaccharide (I-18). Thus with the Boc-pyranone (I-13) on hand, a Pd-catalyzed glycosylation and Luche reduction were applied, followed by a deprotection of the TBS-protecting group to give D-sugar (I-14). A bidirectional glycosylation was applied to install two L-sugar Boc-pyranones providing trisaccharide (I-16). A bis-Luche reduction of trisaccharide (I-16) gave diol (I-17). Finally, a tris-dihydroxylation of the alkenes installed the final C2/C3 stereochemistry in the D-/L-trisaccharide (I-18). It is important to note that regardless of the sugar D-/L-stereochemistry the dihydroxylation occurs to install manno-/rhamno-stereochemistry.

Scheme 4. Synthesis of Branched α-rhamno-/manno-Trisaccharides Containing Both D- and L-Pyranoses

\[
\begin{align*}
I-13 & \xrightarrow{a, b, c} I-14 \\
I-14 & \xrightarrow{d} I-16 \\
I-15 & \xrightarrow{e, f} I-17 \\
I-17 & \xrightarrow{e} I-18: X = OH
\end{align*}
\]

a. BnOH, Pd(0)/PPh\textsubscript{3}, 92%; b. NaBH\textsubscript{4}, −78 °C, 83%; c. TBAF, 90%; d. Pd(0)/PPh\textsubscript{3}, 75%; e. NaBH\textsubscript{4}, −78 °C, 72%; f. OsO\textsubscript{4}, NMO, 94%;

The O’Doherty group has also extended this bi-directional approach for the successful synthesis of heptapyranoside (Scheme 5). Once again, the bidirectional aspect of this approach enables its overall efficiency. In addition, the use of enone atom-less protecting group allows the synthesis to
occur with only one type of protecting group (seven C-6 TBS-groups). As before, two Boc-pyranones were installed at the same time via bidirectional bis-glycosylation of diol (I-20) to (I-21). A bis-Luche reduction of (I-21) gave diol (I-23). Deprotection of the two TBS-groups gave tetraol (I-24). The bidirectional glycosylation was then applied on tetraol (I-24) to install four Boc-pyranones to give heptasaccharide (I-25) after the per-Luche reduction. Finally, a per-dihydroxylation of the seven distinct double bonds in (I-25) was performed to give (I-26).\textsuperscript{11}

**Scheme 5. A 12-Step Synthesis of Highly Branched All-L-\textalpha-manno Heptapyranoside**

\begin{verbatim}
<table>
<thead>
<tr>
<th>Step</th>
<th>Reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>BnOH, Pd(0)/PPh₃</td>
</tr>
<tr>
<td>b</td>
<td>NaBH₄, –78 °C</td>
</tr>
<tr>
<td>c</td>
<td>TBAF</td>
</tr>
<tr>
<td>d</td>
<td>(I-6), Pd(0)/PPh₃</td>
</tr>
<tr>
<td>e</td>
<td>OsO₄, NMO</td>
</tr>
<tr>
<td>f</td>
<td>o-NO₂ArSO₂NHNH₂, Et₃N</td>
</tr>
</tbody>
</table>
\end{verbatim}
1.4 Applications of N-protected alcohol

Because of the importance of aminoglycosides as antibiotics, the O’Doherty group has also applied their de novo approach toward the synthesis of aminosugars. For example, they completed an enantioselective synthesis of three 6-amino-6-deoxy sugars (Scheme 6). The route began with the synthesis of amino alcohol (I-29), which can be prepared from applying the Henry reaction (nitroaldol) on furfural (I-28). Hydrogenation and protection with a Cbz-group gave racemic furan alcohol (I-29). Oxidation of racemic (+/-)-(I-29) was accomplished with the Dess-Martin reagent to give the ketone (I-30). Noyori asymmetric hydrogenation of (I-30) gave optically enriched (+)-furan alcohol (I-29) with a 92% yield and >96% ee. Achmatowicz reaction was applied on (I-29) to form dihydropyranone (I-31). The Achmatowicz reaction was followed by protection with PivCl to give pyranones (I-32) and (I-33). Next, a Luche reduction was applied on (I-32) to give allylic alcohol (I-35). Dihydroxylation of the olefin (I-35) gave mannose sugars (I-36). A similar approach was applied to give D- and L-talose (I-38) and gulose aminosugers (I-39).
Scheme 6. Synthesis of N-Cbz-Protected 6-aminomonoo, 6-aminotalose and 6-aminogulose

1. $\text{CH}_3\text{NO}_2$ to $\text{I-28}$
2. $10\% \text{LiAlH}_4$
3. $\text{H}_2$, Pd/C
4. $\text{CbzCl, K}_2\text{CO}_3$
5. Dess-Martin

$\text{N}\text{Cbz}$-$\text{I-29}$

$\text{I-30}$

$\text{Et}_3\text{N/MeOH}$

$\text{PivCl, Et}_3\text{N}$

$\text{CH}_2\text{Cl}_2$

$\text{I-32}^\alpha$ + $\text{I-33}^\beta$

$\text{I-32}^\alpha$

$\text{I-33}^\beta$

$\text{NaBH}_4/\text{CeCl}_3$

$\text{CH}_2\text{Cl}_2/$MeOH

$\text{I-35}$

$\text{OsO}_4$/NMO

$\text{I-36}$

$\text{NaBH}_4/\text{CeCl}_3$

$\text{CH}_2\text{Cl}_2/$MeOH

$\text{I-37}$

$\text{I-38}$

$\text{I-39}$

$a$: $5\text{ mol}\% \text{OsO}_4$, $50\% \text{NMO/CH}_2\text{Cl}_2$

$b$: 1 equiv TMEDA$+\text{OsO}_4$, $\text{CH}_2\text{Cl}_2$

$c$: $5\text{ mol}\% \text{OsO}_4$, $50\% \text{NMO/t-BuOH}$

$d$: $5\text{ mol}\% \text{OsO}_4$, $50\% \text{NMO/acetone}$
1.5 Previous methods towards furan alcohols

The O’Doherty group has previously synthesized furan alcohols using two different approaches. The first approach (Scheme 7) began with a Petersen olefination of furfural (I-28) followed by asymmetric dihydroxylation of the vinylfuran (I-40) and then TBS-protection to give furan alcohol (I-41) or its enantiomer (I-3) depending upon which chiral ligands were used. While this approach was easily executed on small scale, it was more difficult to scale up. In addition, the enantioexcess of the products were good but too low for oligosaccharide synthesis (e.g., ee = 90-92%).\textsuperscript{15} Thus my task was to develop an alternative approach to furan alcohols.

Scheme 7. O’Doherty’s first approach to protected furan alcohols

To address the problem associated with poor enantio-purity, the O’Doherty group developed an alternative approach (Scheme 8)\textsuperscript{16}. This second approach to furan alcohol (I-3), started with glycolic acid (I-43), which was reacted with pyrrolidine to give amide (I-44). A TBS-protection of (I-44) was used to give TBS-ether (I-45). Addition of 2-lithiofuran to (I-45) gave acylfuran (I-11). A Noyori asymmetric hydrogenation of (I-11) gave furan alcohol (I-3). This approach was scale limited because of the difficulty of using lithium chemistry on large scale.
Scheme 8. Another approach to protected furan alcohols

![Scheme 8](image)

1.6 Previous methods to $N$-protected furan alcohols

A similar approach was developed for the synthesis of $N$-protected furan alcohol (I-29) from vinylfuran (I-40) (Scheme 9). After the Petersen olefination step, an asymmetric amino-hydroxylation was applied on vinylfuran (I-40) to give a mixture of regioisomeric furan amino alcohols (I-42) and (I-29). While the desired region-isomer (I-29) was the major product, the enantioexcess was too low.\textsuperscript{13,17,18} A solution to the problem of low enantio-purity was solved by an oxidation and asymmetric reduction sequence (scheme 6) (I-30) to (I-29).

Scheme 9. Previous method to $N$-protected furan alcohol

![Scheme 9](image)

An alternative approach to $N$-protected furan alcohol was developed by the O’Doherty group (Scheme 10). The approach started with the reaction of $N$-Boc-glycine with 2-lithiofuran to give
acylfuran (I-47). Once again a Noyori asymmetric hydrogenation of (I-47) gave the desired product Boc-protected furan alcohol (I-48). Once again because lithium chemistry was used, the group was not able to make large scale of N-protected furan alcohol. However, using Noyori asymmetric hydrogenation gave a high yield in the end. Therefore, it was desirable that our improved scheme includes this key reduction.

**Scheme 10. Another approach to N-protected furan alcohols**

![Scheme 10. Another approach to N-protected furan alcohols](image)

1.7 **New Approaches to furan alcohols and N-protected furan alcohols**

We needed an improved route to get access to large-scale Boc-pyranones so we could explore more oligosaccharide and amino sugars. At the outset my task was to develop an improved synthesis of furan alcohol and N-protected furan alcohol. Finally, I was challenged to demonstrate the feasibility of my furan synthesis by making large amounts of pyranone. Previously, the group has settled on the Noyori asymmetric hydrogenation to reduce the ketone instead of Sharpless asymmetric dihydroxylation. This decision was based on the fact that the Noyori reduction of acyfuran gives near perfect enantioselectivities. For reasons of practically we were interested in replacing the lithium furan chemistry, as this becomes a safety issue on large scale. However, the new route needed also to produce furan alcohols in a route that avoids silica gel chromatography. This new approach solved these issues by starting with inexpensive materials and only four steps needed to produce the target with the use of only one column chromatography. Most importantly, this new
method was easily scaled up to > 50 g with no difficult air or moisture sensitive chemistry being used. Herein we report our successful development of this alternative approach.

Our next generation route to acyl furan (I-11) began with the addition of bromine to inexpensive 2-acetyl furan (I-49) (60 g) (Scheme 11) to give bromoketone (I-50). Because of the instability of (I-50), sodium bisulfite was added to reduce excess of bromine. Treatment of the crude bromofuran product (I-50) with sodium acetate in acetone/H$_2$O gave the acetate furan (I-51). Hydrolysis of the acetate was accomplished with LiOH in H$_2$O to give furan alcohol (I-52). A TBS-protection of the alcohol (I-52) gave the desired acyl furan (I-11). After we obtained the protected product, a final purification was preformed by filtering through a short column of silica gel to provide 49 g of (I-11).

Scheme 11. New route to protected furan alcohol

One of the more exciting aspects of this new bromofuran (I-50) procedure is the potential application for the synthesis of C-6 substituted furan and corresponding sugar. Once again this new and improved approach to N-protected furan alcohol (Scheme 12) also used no lithium chemistry and should allow access to large-scale synthesis. The first approach starts with the freshly prepared bromofuran (I-50). Addition of potassium phthalimide in DMF to bromo ketone (I-50), gave
phthalimide (I-53). Currently, we are expanding the Noyori asymmetric hydrogenation of (I-53). We are also expanding the synthesis potential of (I-50) by reacting with lists of nucleophiles, such as, azide, $t$-butyl carbamate or benzyl carbamate.

Scheme 12. New route towards N-protected furan alcohol

1.8 Synthesis of $\alpha$-Boc pyranosides

Once we had a large-scale access to acyl furan (I-11) a large-scale synthesis of Boc-pyranone (I-5) was carried out (Scheme 13). This synthesis started with the large-scale Noyori asymmetric hydrogenation of (I-11) to form furan alcohol (I-3). This reaction was preformed on a large enough scale to produce 45 g of furan alcohol (I-3). An Achmatowicz rearrangement was carried out on I-3 and the crude pyranone product was Boc-protected to give the desired Boc-pyranone (I-5). This reaction was also preformed on a scale large enough to produce 20 g of Boc-pyranone (I-5). Because this reaction produces a mixture of $\alpha$- and $\beta$-Boc-pyranone products, extensive silica gel column chromatography was required. At this stage 15 g $\alpha$-Boc-pyranone was supplied to my collaborator, Dr. Yuzhi Ma, who used this material in his convergent heptasaccharide synthesis. In addition, I am using the remaining material for the synthesis of methyl $\alpha$-L-manno-pyranoside (I-58), by the route described in (Scheme 13). This is the rare enantiomeric form of the readily available D-sugar variant. Currently, I am at the stage that Pd-catalyzed glycosylation to form pyranone (I-55) and Luche reduction post glycosylations to give (I-56). Finally, an Upjohn
Dihydroxylation and TBS-deprotection will be performed to prepare methyl α-L-manno-pyranoside (I-58).

**Scheme 13. Synthesis toward α-Boc pyronside**

1.9 Conclusions

In summary, the O’Doherty group works on the development of highly efficient routes to complex enantiomerically pure products from simple achiral starting materials using asymmetric catalysis. These synthetic routes are used by the O’Doherty group to allow the study of the biological activity of these products. The key to the success of the O’Doherty methodology to oligosaccharides is the use of: the Noyori asymmetric hydrogen transfer reaction to establish the asymmetry of protected furan alcohol, the Achmatowicz rearrangement to create the pyran ring, a Pd-catalyzed glycosylation to install the α-methyl group, and subsequent post-glycosylation transformation to install the remaining functional group. However, there were some difficulties to get access to large scale of protected furan alcohol and N-protected furan alcohol. For example, using lithium chemistry, getting regioisomer, or getting low enantio excess. Successfully, I was
able to solve these issues by developing an improved synthesis route toward protected furan alcohol and N-protected furan alcohol. The improved route uses inexpensive materials and only one column chromatography purification through four steps. Also it avoids the use of lithium chemistry and most importantly is easy to scale up. We believe that the developed synthesis will help us to explore more oligosaccharides and amino-sugars. Once we have access to oligosaccharides and amino-sugars, we plan to study the structure activity relationship (SAR) of the role of these complex oligosaccharides and amino-sugars.
1.10 References


3) For useful reviews see: (a) Lis, H.; Sharon, N., Lectins: Chemical Reviews 1998, 98, 637-674 (b) S. Houlton, Chemistry in Britain, 2002, 38, 46.


9) Sumit Bajaj, Dissertation Submitted to Northeastern University, Boston, 2015


14) Youn, S. W.; Kim, Y. H. *Synlett* **2000**, 880-882


19) Miaosheng Li’s Dissertation Submitted to the Eberly College of Arts and Sciences at West Virginia University, **2006**
2.1 Chapter 1 experimental procedure

2-Bromo-1-(2-furyl)ethanone (I-50)

To a solution of 2-acetyl furan (30 g, 272 mol) in CH$_3$CN (145 mL, 0.5 M), acetic acid (3 ml, 20 mol%) was added at 0 °C. The solution was stirred for 15-20 min and then bromine (15.6 mL, 1 equiv) was added slowly over a period of 1-2 hr. The reaction continued to stir at rt for 4-5 hr and monitored by TLC until complete. The reaction was diluted with EtOAc and quenched with sodium bisulfite to reduce excess bromine. The HBr was neutralized with saturated NaHCO$_3$ aq and the mixture extracted with ethylacetate. The organic layer was dried over Na$_2$SO$_4$ then concentrated under reduced pressure. The crude product was purified by silica gel flash chromatography eluting with 3% EtOAc/hexanes to give 2-Bromo-1-(2-furyl)ethanone (I-50) as brown solid (37 g, 196 mmol, 69%): $R_f$ (30% EtOAc/hexane) = 0.55. Our spectroscopic data are matched with a literature report of this compound.$^{1,2}$ The reported data are mp 34.5-36 °C; $^1$H NMR (300 MHz, CDCl$_3$): $\delta = 7.64$ (dd, J=1.6, 0.6 Hz, 1H), 7.34 (dd, J=3.7, 0.6 Hz, 1H), 6.55 (dd, J=3.6, 1.8 Hz, 1H), 4.32 (s, 2H). $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta = 180.36$, 150.36, 147.29, 119.13, 112.87, 30.01.$^{1,2}$
2-(2-Furyl)-2-oxoethyl acetate (I-51)

To a solution of (I-50) (37 g, 196 mmol) in acetone (365 mL), a solution of sodium acetate (62 g, 787.2 mmol, in 40 mL H$_2$O) was added solution drop-wise at 0 °C, followed by the addition of TBAB (3.5 g, 5 mol%). The reaction was stirred at rt for 3 hr and monitored by TLC, until the reaction was complete. The reaction was quenched with 1 N HCl solution (50 mL), and extracted with ethylacetate. The combined organic layers were dried over Na$_2$SO$_4$ then concentrated under reduced pressure. The crude product was purified using column chromatography eluting with 7-8% EtOAc/hexane to give 2-(2-Furyl)-2-oxoethyl acetate (I-51) as yellow oil (30 g, 159 mmol, 91%): $R_f$ (30% EtOAc/hexane) = 0.4; Our spectroscopic data are matched with a literature report of this compound.$^3$ The reported data are $^1$IR (KBr): 3422, 3131, 2929, 2856, 1730, 1688, 1570, 1468, 1399, 1276, 1161, 1021 cm$^{-1}$; $^1$H NMR (600 MHz, CDCl$_3$): $\delta$ = 8.23 (s, 1H), 7.65 (d, J = 1.2 Hz, 1H), 7.31 (d, J = 3.6 Hz, 1H), 6.6 (dd, J = 3.5, 1.7 Hz, 1H), 5.29 (s, 2H); $^{13}$C NMR (150 MHz, CDCl$_3$): $\delta$ = 180.5, 159.9, 150.1, 146.9, 117.9, 112.5, 64.4; HRMS (ESI): m/z [M + H]$^+$ calcd for C$_7$H$_6$O$_4$: 192.9930; found: 192.9979.$^3$
1-(2-Furanyl)-2-hydroxyethanone (I-52)

To a solution of furan acetate (I-51) (5 g, 29 mmol) in THF/H₂O (60 mL, 10:1), was added a solution of lithium hydroxide (1.068 g, 44.59 mmol, 4 mL H₂O) drop-wise at 0 °C. The reaction was stirred at rt for 15-20 min and monitored by TLC, until the reaction was complete. The reaction was quenched with 1 N HCl solution (10 mL), and extracted with ethylacetate. The combined organic layers were dried over Na₂SO₄ then concentrated under reduced pressure. The crude product was purified using column chromatography eluting with 12-15% EtOAc/hexane to give 1-(2-furanyl)-2-hydroxyethanone (I-52) as yellow oil (2.43 g, 10.31 mmol, 54%): R_f (30% EtOAc/hexane) = 0.3 ¹H NMR (400 MHz, CDCl₃) δ = 7.63 (d, J = 1.6 Hz, 1H), 7.31 (d, J = 3.6 Hz, 1H), 6.6 (dd, J = 3.6, 1.8 Hz, 1H), 4.74 (s, 2H), 3.25 (broad s, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 187.8, 150.3, 147.3, 118.1, 112.8, 65.2. This spectroscopic data are matched with a literature report of this compound.¹
2-[[1,1-dimethylethyl]dimethylsilyl]oxy]-1-(2-furanyl)- Ethanone (I-11)

A solution of furan alcohol (I-52) (52.4 g, 415 mmol) in CH$_2$Cl$_2$ (790 ml) was cooled to 0 °C. Triethylamine (50.4 ml, 498.9 mmol) was added then the reaction was stirred for 15 min at rt. tert-Butyldimethylsilyl chloride (TBDMSI) (74.5 g, 498 mmol) and 4-dimethylaminopyridine (DMAP) (5.07 g, 41.57 mmol) were added and the solution was stirred for 24 h at rt and monitored by TLC, until the reaction was complete. The reaction was quenched with 1 N HCl solution (200 mL), and extracted with ethylacetate. The combined organic layers were dried over Na$_2$SO$_4$ then concentrated under reduced pressure. The crude product was purified using column chromatography eluting with 3-4% EtOAc/hexane to give 2-((tert-butyldimethylsilyl)oxy)-1-(furan-2-yl)ethan-1-one (I-5) as yellow oil (48 g, 201 mmol, 60%): $R_f$ (40% EtOAc/hexane) = 0.8. Our spectroscopic data are matched with a literature report of this compound.$^5$ The reported data are IR (thin film, cm$^{-1}$) 2952, 2929, 2856, 1698, 1471, 1255, 1150, 1017, 839; $^1$H NMR (270 MHz, CDCl$_3$) $\delta$ 7.58 (dd, $J$=1.7, 0.7 Hz, 1H), 7.32 (dd, $J$=3.5, 0.7 Hz, 1H), 6.54 (dd, $J$=3.5, 1.7 Hz, 1H), 4.73 (s, 2H), 0.94 (s, 9H), 0.13 (s, 6H); $^{13}$C NMR (68 MHz, CDCl$_3$) $\delta$ 187.0, 150.9, 146.3, 118.0, 112.1, 67.1, 25.8, 18.5, −5.4; CI HRMS calcd for [C$_{12}$H$_{20}$O$_3$Si$^+$Na]$^+$: 263.1074, found: 263.1076. $^5$
(S)-2-((tert-butyldimethylsilyl)oxy)-1-(furan-2-yl)ethanol (I-3)

To a 1000 mL flask was added furylketone (I-11) (48 g, 199.6 mmol), HCOONa (67.87 g, 998 mmol), cetyltrimethylammonium bromide (CTAB) (7.27 g, 19.96 mmol), and (R)-Ru(η₆-mesitylene)-(S,S)-TsDPEN (1.2 g, 19 mmol). Deionized water (433 mL) and CH₂Cl₂ (10 mL) were then added to the flask, and the yellow mixture was stirred vigorously under argon for 48 h and monitored by TLC, until the reaction was complete. The resulting solution was transferred to a separatory funnel, followed by addition of satd. aq. NaHCO₃ (300 mL) and EtOAc (300 mL). The organic layer was washed with satd. aq. NaHCO₃ and brine. The organic layer was dried over Na₂SO₄ and concentrated under reduced pressure. The crude product was purified by silica gel flash chromatography eluting with 5% EtOAc/hexanes to give (S)-2-((tert-butyldimethylsilyl)oxy)-1-(furan-2-yl)ethanol (I-3) as colorless oil (31 g, 127 mmol, 64%). Our spectroscopic data are matched with a literature report of this compound. The reported data are [α]D²⁵ = −15.4 (c = 1, CH₂Cl₂); IR (thin film, cm⁻¹) 3420, 2953, 2929, 2884, 2857, 1255, 1117, 837, 778; ¹H NMR (600 MHz, CDCl₃) δ 7.36 (dd, J = 0.6, 1.8 Hz, 1H), 6.33 (dd, J = 3.6, 1.8 Hz, 1H), 6.30 (dd, J = 3.6, 0.6 Hz, 1H), 4.75 (dd, J = 4.2, 6.6 Hz, 1H), 3.87 (dd, J = 4.2, 10.2 Hz, 1H), 3.83 (dd, J = 6.9, 9.9 Hz, 1H), 2.78 (bs, 1H), 0.90 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H); ¹³C NMR (150 MHz, CDCl₃) δ 154.0, 142.2, 110.4, 107.2, 68.6, 65.9, 26.0(3C), 18.5, -5.2, -5.3.⁵
A solution of (I-3) (1.0 g, 4 mmol), in THF (7 mL), and H₂O (1.7 mL) was added to a round bottom flask and cooled to 0 °C. Solid NaHCO₃ (0.69 g, 8 mmol), NaOAc•3H₂O (0.56 g, 4 mmol), and NBS (0.733 g, 4 mmol) were added to the solution and the mixture was stirred at 0 °C for 1 h and monitored by TLC, until the reaction was complete. The reaction was quenched with satd. aq. NaHCO₃ (15 mL) and extracted with Et₂O (3 x 25 mL). The combined organic layers were dried over Na₂SO₄, and concentrated under reduced pressure. The crude product was purified by silica gel flash chromatography eluting with 10% EtOAc/hexanes to give mixture of α-L and β-L (I-4) as yellow oil (0.5 g, 6.62 mmol, 50%): Rf (40% Et2O/hexanes) = 0.40, Our spectroscopic data are matched with a literature report of this compound. The reported data are IR (thin film, cm⁻¹) 3388, 2951, 2929, 2884, 2858, 1699, 1464, 1256; ¹H NMR (270 MHz, CDCl₃) major isomer: δ 6.93 (dd, J = 10.3, 3.3 Hz, 1H), 6.12 (dd, J = 10.4, 0.6 Hz, 1H), 5.79 (dd, J = 5.1, 3.1 Hz, 1H), 4.59 (dd, J = 5.0, 2.8 Hz, 1H), 4.02 (dd, J = 11.2, 5 Hz, 1H), 3.93 (dd, J = 11.2, 2.0 Hz, 1H), 0.87 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H); ¹³C NMR(67.5 MHz, CDCl₃) major isomer: δ 194.9, 145.9, 128.1, 88.1, 76.7, 63.5, 25.8(3C), 18.5, -5.2, -5.3; CIHRMS calcd for [C₁₂H₂₃O₄Si]⁺: 259.1360, found 259.1366.
tert-butyl (2S,6$\text{S}$)-6-(((tert-butyldimethylsilyl)oxy)methyl)-5-oxo-5,6-dihydro-2$H$-pyran-2-yl carbonate (I-6)

The crude sample of (I-4) (14 g, 54 mmol) was dissolved in CH$_2$Cl$_2$ (45 mL) and the solution was cooled to -78 °C. A CH$_2$Cl$_2$ (9.8 ml) solution of (Boc)$_2$O (14.14 g, 64 mmol) and a catalytic amount of DMAP (0.65 g, 5 mmol) was added to the reaction mixture. The reaction was stirred at -78 °C for 1 h and monitored by TLC, until the reaction was complete. The reaction was quenched with satd. aq. NaHCO$_3$ (50 mL) and extracted with Et$_2$O (3 x 50 mL). The combined organic layers were dried over Na$_2$SO$_4$, and concentrated under reduced pressure. The crude product was given $\alpha$-L and $\beta$-L with 5:3 ratio then purified by silica gel flash chromatography eluting with 6% EtOAc/hexanes to give (I-6) (8 g, 8.20 mmol, 41%): $R_f$ (20% Et2O/hexanes) = 0.70. Our spectroscopic data are matched with a literature report of this compound.$^5$ The reported data of $\alpha$-L(I-6) are $[\alpha]_{D}^{21} = +47.7$ (c = 1.5, CH2Cl2); IR (thin film, cm$^{-1}$) 2956, 2932, 2858, 1754, 1703, 1472, 1371, 1277, 1257; 1H NMR (270 MHz, CDCl3) δ 6.88 (dd, J = 10.2, 3.7 Hz, 1H), 6.45 (d, J = 3.5 Hz, 1H), 6.23 (d, J = 10.2 Hz, 1H), 4.54 (dd, J = 3.5, 3.3 Hz, 1H), 4.05 (d, J = 3.5 Hz, 1H), 4.03 (d, J = 3.5 Hz, 1H), 1.51 (s, 9H), 0.84 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H); 13C NMR (67.5 MHz, CDCl3) δ 193.6, 151.7, 141.4, 129.3, 89.2, 83.6, 77.7, 62.6, 27.6(3C), 25.8(3C), 18.3, -5.4(2C); CIHRMS calcd for [C$_{17}$H$_{30}$O$_6$SiNa]$^+$: 381.1704, found 381.1716.$^5$
(+/-) 2-((tert-butyldimethylsilyl)oxy)-1-(furan-2-yl)ethan-1-ol (I-3)

A CH₂Cl₂ (2 mL) solution of (I-5) (50 mg, 0.20 mmol) and CeCl₃/MeOH (0.52 mL) was cooled to –78 °C. NaBH₄ (23 mg, 0.62 mmol) was added and the reaction mixture was stirred at –78 °C for 3 h and monitored by TLC, until the reaction was complete. The reaction mixture was diluted with Et₂O (20 mL) and quenched with satd. aq. NaHCO₃ (5 mL) and extracted with Et₂O (3 x 5 mL). The combined organic layers were dried over Na₂SO₄, and concentrated under reduced pressure. The crude product was purified by silica gel flash chromatography eluting with 5% EtOAc/hexanes to give mixture of 2-((tert-butyldimethylsilyl)oxy)-1-(furan-2-yl)ethan-1-ol (I-3) as yellow oil (28 mg, 0.11 mmol, 56%). Rf (10% Et₂O/hexanes) = 0.33. Our spectroscopic data are matched with a literature report of this compound. The reported data are ¹H NMR (600 MHz, CDCl₃) δ 7.36 (dd, J = 0.6, 1.8 Hz, 1H), 6.33 (dd, J = 3.6, 1.8 Hz, 1H), 6.30 (dd, J = 3.6, 0.6 Hz, 1H), 4.75 (dd, J = 4.2, 6.6 Hz, 1H), 3.87 (dd, J = 4.2, 10.2 Hz, 1H), 3.83 (dd, J = 6.9, 9.9 Hz, 1H), 2.78 (bs, 1H), 0.90 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H); ¹³C NMR (150 MHz, CDCl₃) δ 154.0, 142.2, 110.4, 107.2, 68.6, 65.9, 26.0(3C), 18.5, -5.2, -5.3.
2-(2-(furan-2-yl)-2-oxoethyl)isoindoline-1,3-dione (I-53)

To a solution of furan bromide (I-50) (30 mg, 0.159 mmol) in DMF (0.5 mL) was added potassium phthalimide (35 mg, 0.190 mmol) at rt. The reaction was stirred at rt for 3 hr and monitored by TLC, until the reaction was complete. The reaction was quenched with satd. aq. NaHCO₃ (1 ml), then washed with water and extracted with ethylacetate. The combined organic layers were dried over Na₂SO₄ then concentrated under reduced pressure. The crude product was purified using column chromatography eluting with 20-25% EtOAc/hexane to give 2-(2-(furan-2-yl)-2-oxoethyl)isoindoline-1,3-dione (I-53) as yellow solid (30 g, 159 mmol, 91%): $R_f$ (40% EtOAc/hexane) = 0.68; $^1$H NMR (400 MHz, CDCl₃) $\delta$ = 7.89 (dd, $J$ = 5.2, 3.2 Hz, 2H), 7.75 (dd, $J$ = 6.4 Hz, 2H), 7.64 (d, $J$ = 2.1Hz, 1H), 7.31 (d, $J$ = 3.6 Hz, 1H), 6.60 (dd, $J$ = 3.6, 2 Hz, 1H), 4.99 (s, 2H); $^{13}$C NMR (100 MHz, CDCl₃) $\delta$ 180.7, 168.0, 151.1, 147.1, 134.3, 132.3, 123.8, 118.2, 112.9, 43.8.1.
2.2 References


