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Iridium Catalysis: Reductive Conversion of Glucan to Xylan

Martin Jæger Pedersen,a Robert Madsenb and Mads Hartvig Clausenc*

By using iridium catalysed dehydrogenative decarbonylation, we converted a partly protected cellobioside into a fully protected xylobioside. We demonstrate good yields with two different aromatic ester protecting groups. The resulting xylobioside was directly used as glycosyl donor in further synthesis of a xyloctaose.

In the last decade a large contribution to glycobiology research and glycomics has been made through the extensive development of epitope-recognizing antibodies, carbohydrate-binding-modules and carbohydrate microarrays.1 The construction of oligosaccharide microarrays, enzymatic studies and development of specific antibodies requires well-defined and pure oligosaccharides in reasonable quantities. These have traditionally been isolated from plant material following partial enzymatic and/or chemical degradation. However, the purity requirement results in a time-consuming purification process and often the resulting glycan are contaminated with closely related structures, which decrease their utility. For this reason, chemical synthesis currently offers a superior method for obtaining sufficient amounts of well characterized structures in high purity.2

The plant cell wall is the single largest source of sustainable biomass on the planet and efficient utilization of cell wall material will be one of the keys to realizing the biobased society of the future.3,4 Glucuronoarabinoxylan (GAX) is one of the major components of feedstocks that are utilized for the production of 2nd generation biofuels.3,4 GAXs are composed of a backbone of β-(1→4)-D-xylopyranose, partially substituted by arabinosyl, glucuronic acid and 4-O-methyl glucuronic acid residues.6,7 Therefore, efficient methods to synthesize well-defined oligoxylans are important to these research areas. The β-1,4-xylosyl backbone has been targeted by different approaches. The first chemical synthesis of a xylan was achieved by Myhre and Smith,8 who synthesized xylobiose. Twenty years later, Kováč and Hirsch made a sequential synthesis of methyl xylotetraoside and xylohexaoside. Both groups employed glycosyl bromides as donors in a linear strategy.9–11 A synthetic blockwise approach was used by Takeo et al., who obtained fully protected xylohexaose as a stepping stone towards xylodecaose,12 and later accessed a whole series of xylans.13 More recently, several examples of enzymatic synthesis of xylans have emerged, however not on a larger scale.14–16 A powerful method for automated synthesis resulted in a broad range of oligoarabinoxylans and xylans made by Schmidt et al. as recently as 2015.17

We wanted to employ a xylobioside building block in order to speed up assembly of larger glycans. Rather than prepare the required disaccharide from xylose, we envisioned a route starting from protected cellobiose (Figure 1). This would offer several advantages as cellobiose octaacetate is readily available by acetolysis of cotton18,19 and commercially available in multi-gram amounts at low cost. Furthermore, the chemistry of glucose is well established and highly regioselective, rendering protecting group manipulations facile. By realizing a transformation from a hexose to pentose, we are accessing a xylobioside building block for oligosaccharide synthesis in a few steps.

A recent description of iridium catalyzed decarbonylation20 and the knowledge of iridium complexes as excellent hydrogen transfer catalysts, inspired the development of homogeneous transformations...
tandem catalytic system. An iridium complex, generated in situ from \([\text{Ir}(\text{cod})\text{Cl}]_2\) and racemic 2,2’-bis(diphenylphosphino)-1,1’-binaphthalene (BINAP), promotes the catalytic dehydrogenation of a primary alcohol and a subsequent decarbonylation leading to release of hydrogen and carbon monoxide. A related sequence has also been achieved by Melnick et al. using stoichiometric amounts of an iridium (I) complex with a pincer ligand, bis-[2-(diisopropylphosphanyl)-4-methylphenyl]amine converting ethanol into methane after photolysis of an intermediate Ir–CO complex. Additionally, Ho et al. used a rhodium (I) complex with tris(4,4-dimethyl-2-oxazolyl)phenylborate to perform photocatalytic dehydrogenative decarbonylation on a range of primary alcohols. The reductive dehydrogenation-decarbonylation of carbohydrates to produce, for example, pentoses from hexoses has not previously been described. Therefore, we set out to investigate, if the protocol developed by Olsen and Madsen could be employed for this purpose.

The partially protected cellobiosides 5a and 5b were synthesized as shown in Scheme 1, starting from peracetylated cellobiose (1) that was converted to the thiophenyl glycoside [21]. The sequence afforded the desired thiophenyl cellobioside 3 in a high yield. After deacetylation using Zemplén conditions, the resulting thiophenyl cellobioside was selectively protected with 2-naphthylidene, TBS and benzoxazoles to give the fully protected cellobioside 4a. The acetal and silyl protecting groups are orthogonal, however, the optimized order of unmasking the primary alcohols was selectate acetal opening prior to desilylation, which afforded the partly protected cellobioside 5a in 85% yield. When the order was reversed the product was obtained in a mere 23%. The corresponding 4-methoxybenzoylated cellobiose 4b was obtained by debenzoylation of 4a with NaOCH₃ in CH₃OH, followed by treatment with 4-methoxybenzoyl chloride. The product was subjected to identical conditions to give the 4-methoxybenzoylated cellobiose 5b. The dehydrogenative decarbonylation was initially investigated for 5a (Figure 2). Early optimization showed that performing the reactions under a slow flow of argon (as opposed to simply refluxing under argon atmosphere) greatly enhanced the reaction rate and gave the product in 30% yield. We presume this can be ascribed to a more efficient removal of carbon monoxide and/or hydrogen during the reaction. A set of experiments were conducted to investigate the effect of adding hydrogen scavengers (Table 1). Diphenylacetylene and styrene both improved the yield of the reaction compared to not having a scavenger (entries 1–3). Norbornene is an unsaturated, bridged cyclic hydrocarbon and since strain is released upon saturation, norbornene is an excellent candidate for hydrogen scavenging. It was added in different equivalents and we observed a clear effect of the additive (entries 4–6). A positive effect was observed with 1.2 and 2.2 equiv. of norbornene as hydrogen scavenger, but when 4.4 equiv. were used the yield dropped significantly.

After establishing norbornene for optimal hydrogen scavenging, a range of parameters were screened (Table 2). Performing the reaction in diglyme, a high boiling polar aprotic solvent, had in some cases improved decarbonylation reactions, but in our case no conversion of 5a was observed (entry 1). Co-solvents such as N,N-dimethylethamide (DMA) have been reported to stabilize catalytic decarbonylation reactions. Nevertheless, performing the reaction in a 1:9 mixture of DMA and mesitylene (entry 2), did not improve the reaction time nor the yield. By lowering the reaction temperature by refluxing in toluene (boiling point 139 °C, entry 3), we expected prolonged reaction times and less product decomposition. The result, however, was a reduction in reaction yield to merely 16%. In fact, performing this reaction in toluene (boiling point 110 °C) for more than 3 days did not show any significant conversion. Originally, Olsen and Madsen found mesitylene to be the best solvent for the reaction and observed more consistent results when it was saturated with H₂O. This was also the case for substrate 5a (Table 2, entries 4–6), which emphasizes that trace amounts of water are beneficial to the reaction. Addition

![Figure 2](image-url)  
**Figure 2** Dehydrogenative decarbonylation resulted in successfully converting partly protected cellobiose 5a and 5b to fully protected xylosides 6a and 6b.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Scavenger</th>
<th>Equivalents</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td></td>
<td>30</td>
</tr>
<tr>
<td>2</td>
<td>Diphenylacetylene</td>
<td>2.2</td>
<td>43</td>
</tr>
<tr>
<td>3</td>
<td>Styrene</td>
<td>2.2</td>
<td>43</td>
</tr>
<tr>
<td>4</td>
<td>Norbornene</td>
<td>1.1</td>
<td>41</td>
</tr>
<tr>
<td>5</td>
<td>Norbornene</td>
<td>2.2</td>
<td>48</td>
</tr>
<tr>
<td>6</td>
<td>Norbornene</td>
<td>4.4</td>
<td>23</td>
</tr>
</tbody>
</table>

| Notes: | | |
|-------| | |
| a | Reactions were performed by in situ generation of the catalyst, using 15 mol % [Ir(cod)Cl]₂ and 30 mol % (rac)-BINAP. The reactions were performed at reflux in mesitylene and stopped after 16 hours, when TLC indicated full conversion of 5a. Relative to the amount of disaccharide 5a. | | |
| b | Average of two reactions. | | |

**Scheme 1** Synthesis of the partially protected cellobiose 5a and 5b. a) (i) HBF₄, AcOH, Ac₂O, (ii) triphenylphosphine, Na₂CO₃, TBAI/ISO, H₂O/CHCl₃, 72% (2 steps); b) NaOCH₃, CH₃OH, quant; c) (i) 2-naphthylacetaldehyde, CH₂OH, 10 mol% PTA/CH₂O, CHCN, 60 °C, (ii) TBC, DMAP, py, 0–22 °C, (iii) Bu₂Cl, DMAP, py, CH₂Cl₂, 0–22 °C, 70% (3 steps); d) (i) NaOCH₃, CH₂OH/CH₃CN, 60 °C, (ii) MCl₂, DMAP, Bu₂N, py, CH₂Cl₂, 0–22 °C, 68% (2 steps), e) (i) BH₃·THF, 20 mol% Cu/DTPh, CH₂Cl₂, 0–22 °C; (ii) H₂O, 15 mol% PTA/CH₂O, 85% (2 steps, 5a), 48% (2 steps, 5b).
of LiCl has been shown to increase the reaction rate, but that was not the case for 5a, instead the yield dropped significantly (entry 7).

When potassium chloride with crown ether was added to produce more accessible chloride ions the yield improved, however not to the levels obtained without additive (compare entry 8 with entries 5 and 6).

The dehydrogenative decarbonylation protocol originally used achiral substrates, hence no difference in performance was expected using the two different antipodes of the ligand. As the substrate has multiple stereocenters, we tested both antipodes of BINAP and observed a significant difference in catalytic efficiency (entries 9 and 10). (R)-BINAP (entry 9) resulted in more than twice the amount of isolated product compared to (S)-BINAP (entry 10), however, the reaction with (R)-BINAP was still lower yielding than when using the racemic ligand (entry 6). Madsen and co-workers showed that the reaction operates through two coupled catalytic cycles (see also Supporting Information). We hypothesize that either the two antipodes of BINAP have different efficiency in the two cycles or alternatively that the iridium complexes formed from each enantiomer matches up differently with the two molecules of glucose in cellobiose, as they represent different chiral environments. The latter would help explain why complexes formed from the racemic ligand had the best overall efficiency. This is also in agreement with the main byproducts observed, resulting from a single chain shortening (Glu-Xyl and Xyl-Glu disaccharides, see Supporting Information). Reducing the catalyst loading to 15 mol% gave a lower isolated yield (entry 11), but an increase to 60 mol% resulted in a faster reaction without a significant improvement in the yield (entry 12). When the concentration of the reactions was varied with fixed times, a significant influence on the outcome was observed (entries 13–16). The isolated yields were diminished at lower concentrations (entries 13 and 14), and this effect was even stronger when concentrations were increased (entries 15 and 16). Furthermore, TLC analysis during the reactions showed more decomposition when concentrations were above 0.1 M. The optimized reaction conditions were applied to the 4-methoxybenzoylated cellobioside 5b giving an acceptable 37% yield (entry 17).

As a general observation, longer reaction times did not promote higher yields, even though intermediate products are converted continuously. One reason could be decomposition: in a qualitative experiment, a sample of starting material and one of product were heated in mesitylene and monitored by TLC, which revealed a slow, but steady decomposition, more pronounced for the product than for the starting material. When scaling up the reaction we initially observed a dramatic decrease in yield; however, this was solved by performing a thorough degassing by freeze-pump-thaw prior to heating and formation of the active complex. In this manner, we obtained an effective reaction on up to a five-gram scale affording the same result as the 200 mg entries shown in Table 2.

Interestingly, substrates with neighboring endocyclic oxygen were previously shown to react more slowly by Olsen. This effect was clearly visible when compound 7 and 8 were subjected to dehydrogenative decarbonylation (Scheme 2). The pronounced effect of the endocyclic oxygen on the reaction rate compared to the methylene adduct, leads us to hypothesize that the endocyclic oxygen can coordinate to iridium, stabilizing a catalytic intermediate and thus negatively impact the kinetics of the reaction. Subjecting a 2,3,4-tri-tribenzoylated methyl glucoside to the same reaction conditions resulting in the corresponding methyl xylose in 13% yield, together with 48% of a byproduct, where the 4-O-Bz group had migrated to the 6-position of glucose (not shown).

With the thio-xylobioside 6a in hand, a reducing end building block for oligosaccharyl assembly was prepared by coupling to benzyl alcohol, which gave the benzyl β-xylobioside in 55%, along with the α-adduct in 17% yield (Scheme 3). The Nap group was removed with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ), affording acceptor 11a in a near quantitative yield (98%). Coupling with 6a required NIS in combination with TFOH and resulted in the xylotetraoside in a moderate yield,

\[
\begin{align*}
7 & : X = \text{CH}_3 \\
8 & : X = \text{O} \\
9 & : X = \text{CH}_3, 16 \text{ hours}, 87\% \\
10 & : X = \text{O}, 60 \text{ hours}, 79\%
\end{align*}
\]

**Scheme 2** Dehydrogenative decarbonylation of substrates with and without adjacent endocyclic oxygen. Using 2.5 mol% [Ir(cod)Cl], 30 mol% (rac)-BINAP, 10 mol% LiCl and H2O saturated mesitylene.

which was readily deprotected with DDQ to give acceptor 12a. When 12a was subjected to glycosylation conditions with the thio-xylobioside 6a, we observed no conversion of the

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acceptor and only hydrolyzed donor and unreacted acceptor was recovered. Despite numerous attempts, we were unable to optimize the reaction to produce more than trace amounts of product and we ascribe this to a mismatch between the xylotetraoside acceptor and the biose donor.

Instead, we turned to donor 6b, carrying 4-methoxybenzoyl protection. Through a similar sequence of reactions, we could very rapidly access the benzyl xylotetraoside (12b), –hexaoside (13) and –octaoside (14) in very good yields. This example highlights the importance of protecting groups in carbohydrate chemistry, as they clearly have a profound impact on reactivity in this case. Finally, the fully protected benzyl xylooctaoside 14 was globally deprotected by Zemplén deesterification followed by hydrogenolysis, affording octasaccharide 15 after purification by size exclusion chromatography.

In conclusion, we successfully accomplished the conversion of partly protected cellobiose to xylobiose. This is the first example of a 1-pot reaction forming pentoses from hexoses, and 6b was directly used as glycosylation donor in the synthesis of xyans 12–14. The iridium-catalyzed dehydrogenative decarbonylation proved to be a robust method also on a gram scale. Meticulously degassing prior to reaction was crucial to obtaining good yields when scaling up.

Acknowledgements

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Conflicts of interest

There are no conflicts to declare.

Notes and references

Iridium catalyzed dehydrogenative decarbonylation is used to convert cellobiosides to xylobiosides, which is used in rapid assembly of oligoxylans.