A General and Enantioselective Approach to Pentoses: A Rapid Synthesis of PSI-6130, the Nucleoside Core of Sofosbuvir

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Supporting Information

ABSTRACT: An efficient route towards biologically relevant pentose derivatives is described. The de novo synthetic strategy features an enantioselective α-oxidation reaction enabled by a chiral amine in conjunction with copper(II) catalysis. A subsequent Mukaiyama aldol coupling allows for the incorporation of a wide array of modular two-carbon fragments. Lactone intermediates accessed via this route provide a useful platform for elaboration, as demonstrated by the preparation of a variety of C-nucleosides and fluorinated pentoses. Finally, this work has facilitated expedient syntheses of pharmaceutically active compounds currently in clinical use.

Carbohydrates represent compounds of both vast abundance and fundamental biological importance. Within this class, five-carbon saccharides (pentoses) are perhaps most readily recognized as the structural monomers composing the backbones of DNA and RNA, which enable the replication, transcription, and translation of genetic information. In addition, the ribose derivative adenosine triphosphate (ATP) represents the molecular unit of energy, while a variety of other elaborated pentoses serve as cofactors crucial to enzyme function. It is not surprising, therefore, that nucleoside frameworks are found at the core of many pharmaceutically active compounds and that significant research effort has been expended to gain synthetic access to non-natural pentose analogs. The most common strategy to build enantiomERICally enriched nucleosides is to employ natural sugars as starting materials; however, these protocols are typically protracted by the need to discriminate among four chemically similar hydroxyl groups, which further limits opportunities for the incorporation of unnatural moieties and stereochemical information. An attractive alternative would involve a de novo synthetic sequence that rapidly and enantioselectively couples prefabricated fragments and is amenable to broad diversification of functional groups and nucleoside stereochemistry.

In 2004, our group described a two-step synthesis of orthogonally protected hexoses applying an enantioselective proline-catalyzed aldol coupling followed by a Lewis acid-mediated, diastereoselective Mukaiyama aldol reaction (eq 1). This approach allows for the rapid and asymmetric construction of gluco-, manno-, and allo-configured carbohydrates from simple starting materials. We questioned whether a similar strategy might provide access to their 5-carbon, nucleoside counterparts, beginning with the enantioselective catalytic production of an α,β-dioxogenated aldehyde (eq 2). By analogy to our hexose synthesis, we envisioned that this enantioenriched aldehyde could undergo aldol coupling to build the requisite nucleoside skeleton. Importantly, such a strategy would employ catalysis-derived starting materials in place of chiral pool precursors (e.g., isopropylidene-protected glyceraldehydes), which have been shown to be poorly or nonselective in similar de novo nucleoside syntheses. Moreover, our building blocks would be easily modified to provide a variety of differentially substituted products and would allow for preinstallation of protecting groups, thereby obviating the need for extraneous protection−deprotection sequences. Herein we describe the successful execution of these design ideals and outline a generic and enantioselective route to nucleoside architecture.
For the preparation of a suitable enantioenriched α,β-dioxyxylated aldehyde, we chose to capitalize on our group’s recently developed protocol for the α-oxygenation of aldehydes. Through the synergistic action of a copper catalyst and an organocatalyst, this technology enables the enantioselective α-coupling of aldehydes with TEMPO. For the specific purposes of nucleoside synthesis, this method has been applied to β-benzoxyprenaldehyde to produce the α,β-dioxyxylated aldehyde in 77% yield and 90% ee. With this critical aldehyde coupling fragment in hand, we envisioned a substrate-controlled, diastereoselective Mukaiyama aldol reaction that would install the remaining two carbons of the sugar skeleton (Table 1, step 1). Reductive cleavage of the TMP ester (step 2), followed by reduction (step 3), would then deliver the desired pentose.

We began our studies by establishing optimal conditions for the Mukaiyama aldol reaction of silyl ketene acetals with α,β-dioxyaldehyde. Evaluation of various reaction parameters revealed dichlorotitanium diisopropoxide (TiCl2(OPr)2) as the Lewis acid of choice, delivering excellent levels of diastereoselectivity in dichloromethane at −20 °C. As shown in Table 1, we applied these general conditions to the reaction of various silyl ketene acetals with α-oxaldehyde to afford a broad array of β-hydroxysters with excellent levels of stereoselectivity. Indeed, we view this finding as critical to our general nucleoside synthetic strategy, given that commonly used glyceraldehyde acetones do not provide high levels of diastereoselective aldol reactions with prochiral nucleophiles reported to date. Subsequent N-O bond cleavage and in situ cyclization were achieved using zinc and aqueous trifluoroacetic acid to provide the corresponding lactones. Reduction of each pentolactone to the desired lactol was then accomplished using diisobutylaluminum hydride (DIBAL-H) in good yield. For all reported β-hydroxysters bearing three stereocenters, only two diastereomers were observed. The stereochemical relationship between substituents at C(3) and C(4) was found to be exclusively anti, while that between substituents at C(2) and C(3) was variable.

More specific details of this three-step sequence are summarized in Table 1 and described below. The use of α-oxygenated silyl ketene acetals bearing silyl or alkyl protecting groups provided esters in good yields and excellent selectivities (81−83% yield, >20:1 dr). Cyclization and reduction afforded the corresponding ribonolactols also in good yields (72−87% yield; 2c–2e, 62−70% yield). It should be noted that lactones provide a convenient route to differently protected pentoses without the need to discriminate between similar hydroxyl groups. Interestingly, a reversal of selectivity was observed in the reaction of an unsubstituted silyl ketene acetal, which delivered the lyxo/xylo-configured lactol. Applying BF3·OEt2 as the Lewis acid (in lieu of TiCl2(OPr)2) restored the usual sense of selectivity, providing the ribo/arabino-configured lactol. Silyl ketene acetals bearing alkyl substituents were well-tolerated in the Mukaiyama aldol reaction (7a−16a, 89−98% yield, 11:1 to >20:1 dr). The resulting α-alkylated esters performed
especially well in the cyclization step, affording lactones 7b−16b in 94−99% yield. Reduction then provided C(2)-alkylated lactols 7c−16c (70−89% yield), including examples bearing gem-dimethyl and spirocyclic quaternary centers (13c−16c). It is important to note that the enantiopurity of all isolated lactone intermediates described was not eroded from that of the precursor aldehyde 1. Studies to determine the origins of the observed stereochemical outcomes are ongoing.

At this stage, we hoped to demonstrate the practical utility of our synthetic strategy by preparing nucleoside derivatives of specific interest to the pharmaceutical sciences. In this context, C-nucleosides have found utility in various biochemical settings on the basis of a more metabolically stable C−C bond being utilized in lieu of the naturally occurring anomeric C−N union between the saccharide and base units.15 During the course of our studies, we recognized that the lactone intermediates provided by our synthetic route could be derivatized to a variety of C-nucleosides via a simple and well-precedented two-step sequence.15 Nucleophilic addition of an aryllithium reagent to the lactone of interest would afford an elaborated lactol, which would then be diastereoselectively reduced to provide the desired C-nucleoside.

In practice, direct addition of phenyllithium to the fully protected lactone 17 (Table 2) provided the corresponding lactol in excellent yield (18, 91% yield). In addition, a number of bromoarenes were lithiated and combined with 17 to afford a variety of aryl-substituted lactols as anomeric mixtures (19−23, 72−93% yield).16 Deoxygenation of each product mixture in the presence of BF$_3$·OEt$_2$ and triethylsilane proceeded in good to excellent yield to provide the desired C(1)-arylated ribose as the α-anomer exclusively (24a−29a, 66−97% yield, >20:1 dr). Remarkably, employing Hantzsch ester (diethyl 1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylate) as the reductant provided the corresponding β-anomer of each nucleoside (24b−29b, 66−94% yield, 2:1 to >20:1 dr). To our knowledge, this work represents the first application of Hantzsch ester as a reducing agent for oxocarbonium reduction or carbohydrate formation. Investigations into the origin of the intriguing divergence in selectivity between the Hantzsch ester and triethylsilane protocols are underway.

The growing interest in fluorinated nucleoside analogs as pharmaceutical agents inspired us to further expand our method to the synthesis of these challenging structures.18 We again recognized that our lactone intermediates could be useful synthons for rapid entry to these important fluorinated pentoses. Indeed, after protection of the C(3) hydroxyl group to form lactones of type 30,19 the addition of a fluorine atom at C(2) was performed in one step using the electrophilic fluorinating agent NFSI (N-fluorobenzenesulfinimide) to provide the corresponding 2-fluoro-2-deoxy-ribonolactone or 2-fluoro-2-deoxy-xylono-lactone, respectively (Table 3, 31a and 32a, 72 and 90% yield, >20:1 dr). Preparation of the related 2-methyl derivative required the formation of a silyl ketene acetal from the lactone 7b, which upon treatment with Selectfluor delivered the fluorinated lactone in good yield and excellent diastereoselectivity (33a, 72% yield, >20:1 dr). In all cases, addition of the fluorine atom occurred exclusively away from the bulky silyl protecting group. Finally, reduction of the fluorinated lactones with diisobutylaluminum hydride provided lactols 31b−33b in good to excellent yields (70−90% yield).

Having developed efficient syntheses of a number of monofluorinated pentoses, we next targeted the synthesis of difluorinated nucleosides, in particular the chemotherapeutic gemcitabine (Scheme 1). To address this challenge, we chose to build upon our established de novo synthetic strategy. We envisaged a route parallel to that outlined in Table 1, beginning with the coupling reaction of α,b-dioxyaldehyde 1 and a nucleophile prefunctionalized with the CF$_2$ motif. More specifically, isopropyl bromofluorooracacetate readily underwent a Reformatsky coupling with 1 in the presence of zinc, facilitating the synthesis of lactol 34 in five steps. Lactol 34 was further elaborated to provide the anticancer agent gemcitabine in nine total steps and 23% overall yield from 1.

Table 2. Two-Step Synthesis of C-Nucleosides from Lactones$^{a,b,c}$

<table>
<thead>
<tr>
<th>Lactol</th>
<th>Yield</th>
<th>Diastereomeric ratio</th>
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<tbody>
<tr>
<td>lactol 18</td>
<td>91%</td>
<td>2β:1α</td>
</tr>
<tr>
<td>lactol 19</td>
<td>93%</td>
<td>2β:1α</td>
</tr>
<tr>
<td>lactol 20</td>
<td>90%</td>
<td>2β:1α</td>
</tr>
<tr>
<td>lactol 21</td>
<td>87%</td>
<td>2β:1α</td>
</tr>
<tr>
<td>lactol 22</td>
<td>81%</td>
<td>2β:1α</td>
</tr>
<tr>
<td>lactol 23</td>
<td>72%</td>
<td>2β:1α</td>
</tr>
</tbody>
</table>

$^{a}$Intermediate lactols 18−23 and α-anomers 24a−29a not depicted.
$^{b}$Diastereomeric ratios determined by $^1$H NMR of crude reaction mixtures.
$^{c}$Relative stereochemistry determined by NOESY.

Sofosbuvir (vide supra) has recently been approved as a therapeutic agent for the treatment of hepatitis C. This prodrug is synthesized via the late-stage nucleoside intermediate PSI-6130 (Scheme 1), which we hypothesized could be accessed rapidly using our pentose strategy. Having prepared the silyl ketene acetal 35, we subjected it to our previously established Mukaiyama aldol conditions using 1 and TiCl$_2$(OPr$_2$)$_3$, as the Lewis acid. To our delight, the aldol coupling proceeded smoothly to provide β-hydroxyster 36 in 79% yield as a single

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Table 3. Synthesis of C(2)-Fluorinated Pentoses from Lactones$^{a,b,c}$

<table>
<thead>
<tr>
<th>Intermediate</th>
<th>Yield</th>
<th>Diastereomeric Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>31a</td>
<td>72%</td>
<td>&gt;20:1 dr</td>
</tr>
<tr>
<td>31b</td>
<td>90%</td>
<td>&gt;20:1 dr</td>
</tr>
<tr>
<td>32a</td>
<td>90%</td>
<td>&gt;20:1 dr</td>
</tr>
<tr>
<td>32b</td>
<td>70%</td>
<td>&gt;20:1 dr</td>
</tr>
<tr>
<td>33a</td>
<td>72%</td>
<td>&gt;20:1 dr</td>
</tr>
<tr>
<td>33b</td>
<td>86%</td>
<td>&gt;20:1 dr</td>
</tr>
</tbody>
</table>

$^{a}$Intermediate fluorinated lactones 31a–33a not depicted. $^{b}$All lactols recovered as amionic mixtures. $^{c}$Diastereomeric ratios determined by $^1$H NMR analysis of isolated material. Relative stereochemistry determined by NOESY.

Scheme 1. Enantioselective Route to Gemcitabine and PSI-6130

The authors declare no competing financial interest.

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5. For a review of the synthesis of carbohydrates from acyclic precursors: Ager, D. J.; East, M. B. *Tetrahedron* 1993, 49, 5683.
13. Reaction of enol silanes was successful in two cases, but silyl ketene acetals provided a more robust scope; details in SI.
16. In some cases, the product mixture also contained the open-chain aryl ketone, which was competent in the reduction step.
19. Use of the bulky TIPS group was found to be essential in order to avoid 3β-elimination during enolization.
22. Absolute stereochemistry of 37 was confirmed by X-ray crystallography (data in SI).