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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.[1] 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.[2] The most common strategy to build enantioenriched nucleosides is to employ natural sugars as starting materials;[3] 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. Clearly, 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.[4−6]

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.[7] 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-dioxygenated 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),[8] which have been shown to be poorly or nonselective in similar *de novo* nucleoside syntheses.[9] 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.

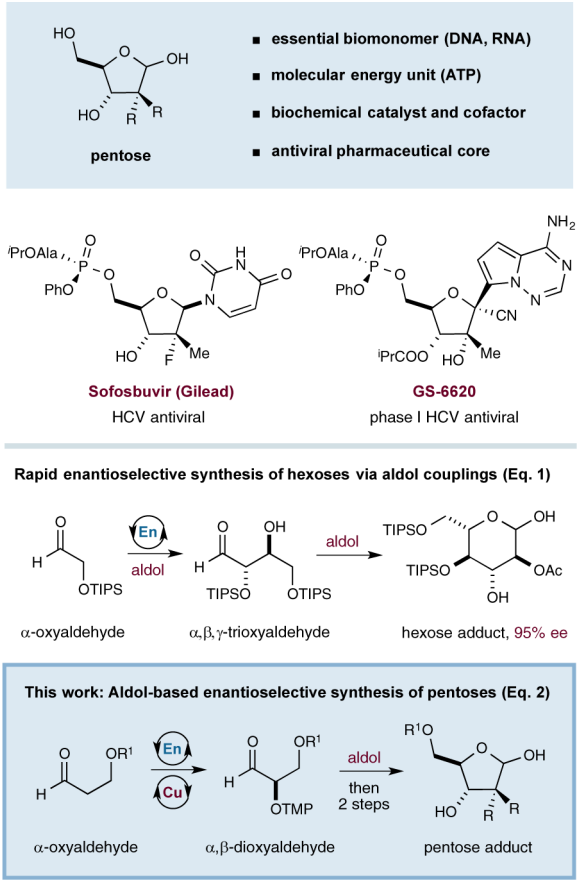

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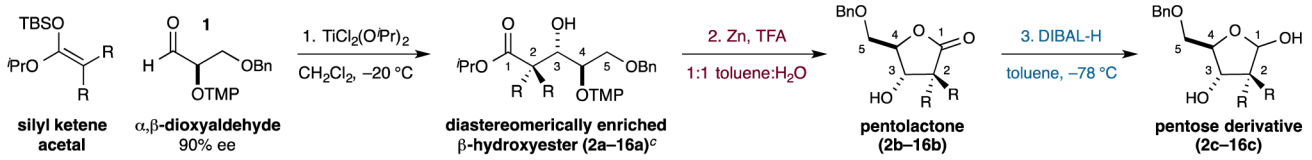
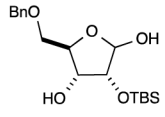
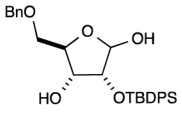
Table 1. Three-Step Synthesis of Pentose Derivatives from α,β-Dioxyaldehyde 1[a,b]

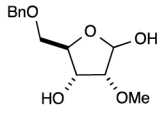




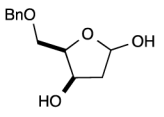
2a 83% yield, >20:1 dr
2b 72% yield, >20:1 dr[g]
2c 64% yield, 90% ee



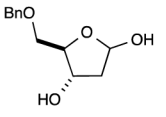
3a 83% yield, >20:1 dr
3b 83% yield, >20:1 dr[i]
3c 62% yield, 91% ee



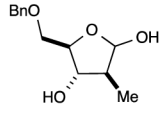
4a 81% yield, >20:1 dr
4b 87% yield, >20:1 dr[g]
4c 70% yield, 89% ee



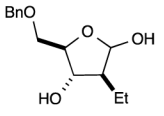
5a 84% yield, 3:1 dr[d]
5b 91% yield, >20:1 dr[i,j]
5c 75% yield, 91% ee



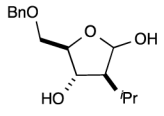
6a 87% yield, 3:1 dr[d,e]
6b 92% yield, >20:1 dr[g,j]
6c 77% yield, 90% ee



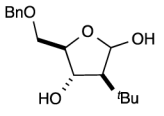
7a 96% yield, 11:1 dr
7b 98% yield, 11:1 dr[g]
7c 82% yield, 89% ee



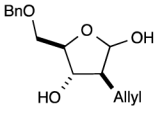
8a 98% yield, 13:1 dr
8b 99% yield, 13:1 dr[i]
8c 84% yield, 90% ee[k]



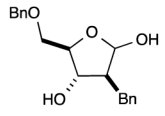
9a 94% yield, >20:1 dr[f]
9b 98% yield, >20:1 dr[i]
9c 89% yield, 89% ee



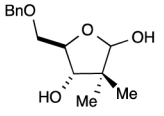
10a 96% yield, >20:1 dr[f]
10b 97% yield, >20:1 dr[i]
10c 89% yield, 91% ee



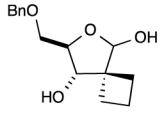
11a 89% yield, 13:1 dr
11b 98% yield, 13:1 dr[i]
11c 80% yield, 91% ee[k]



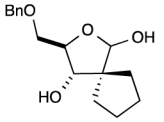
12a 91% yield, 16:1 dr[f]
12b 94% yield, >20:1 dr[i]
12c 85% yield, 90% ee



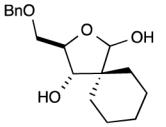
13a 96% yield, >20:1 dr[f]
13b 97% yield, >20:1 dr[g,h]
13c 72% yield, 90% ee



14a 94% yield, >20:1 dr[f]
14b 99% yield, >20:1 dr[i]
14c 70% yield, 90% ee



15a 96% yield, >20:1 dr[f]
15b 98% yield, >20:1 dr[i]
15c 73% yield, 90% ee



16a 97% yield, >20:1 dr[f]
16b 98% yield, >20:1 dr[i]
16c 73% yield, 89% ee

[a]All lactols recovered as anomeric mixtures. [b]Enantioenrichment based on enantiomeric excess of the corresponding lactones. [c]For all reported β-hydroxyesters bearing three stereocenters, only two diastereomers were ever 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. [d]Reaction performed at −40 °C. [e]Reaction performed with $BF_3{\cdot}OEt_2$ as the Lewis acid. [f]Reaction performed using OTMS silyl ketene acetal. [g]Lactone configuration determined by chemical correlation. [h]Lactone configuration confirmed by X-ray crystallography. [i]Lactone configuration determined by analogy. [j]Cyclization performed using only the major diastereomer of the corresponding β-hydroxyester. [k]Lactol configuration confirmed by X-ray crystallography.

For the preparation of a suitable enantioenriched α,β-dioxygenated aldehyde, we chose to capitalize on our group's recently developed protocol for the α-oxyamination of aldehydes.[10] Through the synergistic action of a copper catalyst and an organocatalyst, this technology enables the enantioselective α-coupling of aldehydes with TEMPO.[11] For the specific purposes of nucleoside synthesis, this method has been applied to β-benzyloxypropionaldehyde to produce the α,β-dioxyaldehyde **1** (Table 1) in 77% yield and 90% ee.[10] 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).[12] Reductive cleavage of the TMP (2,2,6,6-tetramethylpiperidinyl) group with concomitant cyclization (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 **1**.[13] Evaluation of various reaction parameters revealed dichlorotitanium diisopropoxide ($TiCl_2(O^iPr)_2$) as the Lewis acid of choice, delivering excellent levels of diastereocontrol 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-oxyaldehyde **1** to afford a broad array of β-hydroxyesters with excellent levels of stereocontrol. Indeed, we view this finding as critical to our general nucleoside synthetic strategy, given that commonly used glyceraldehyde acetonides do not provide high levels of diastereocontrol in analogous Mukaiyama aldol reactions with prochiral nucleophiles reported to date.[14] 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.

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 **2a**−**4a** in good yields and excellent selectivities (81−83% yield, >20:1 dr). Cyclization and reduction afforded the corresponding ribonolactols also in good yields (**2b**−**4b**, 72−87% yield; **2c**−**4c**, 62−70% yield). It should be noted that lactones **2b**−**4b** provide a convenient route to differentially 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 **5c**. Applying $BF_3{\cdot}OEt_2$ as the Lewis acid (in lieu of $TiCl_2(O^iPr)_2$) restored the usual sense of selectivity, providing the ribo/arabino-configured lactol **6c**. 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

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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.

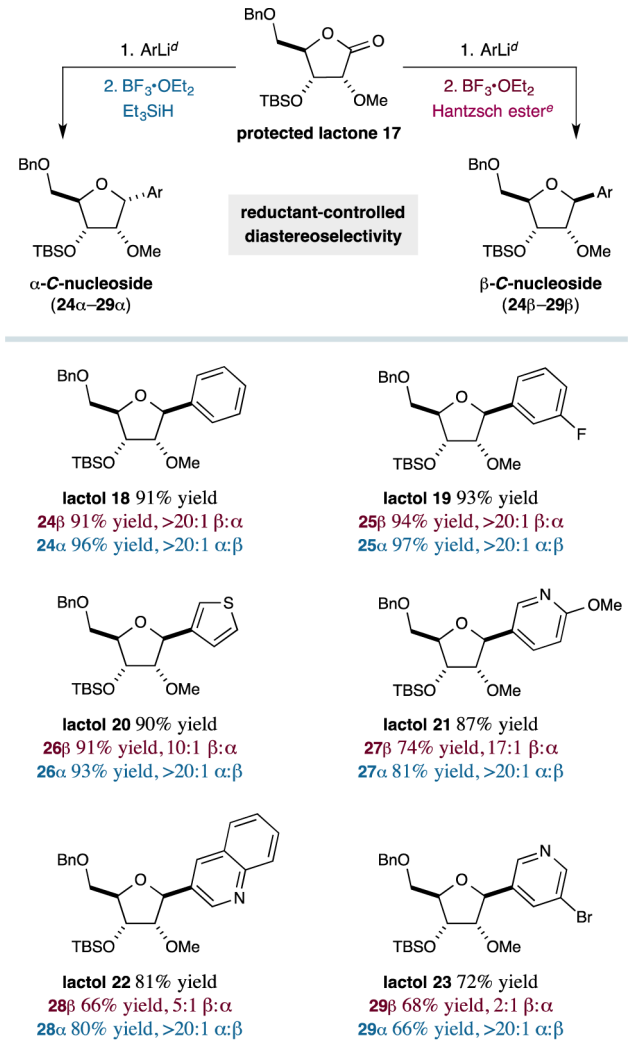
At this stage, we hoped to demonstrate the practical utility of our synthetic strategy by preparing nucleoside derivatives of specific interest to the pharmaceutical sciences. In this context, *C*-nucleosides have found utility in various biochemical settings on the basis of a more metabolically stable 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 $BF_3{\cdot}OEt_2$ and triethylsilane proceeded in good to excellent yield to provide the desired C(1)-arylated ribose as the α-anomer exclusively (**24α**–**29α**, 66–97% yield, >20:1 dr).[17] 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 (**24β**–**29β**, 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 oxocarbenium 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*-fluorobenzenesulfonimide) to provide the corresponding 2-fluoro-2-deoxy-ribonolactone or 2-fluoro-2-deoxy-xylonolactone, 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

Table 2. Two-Step Synthesis of *C*-Nucleosides from Lactones[a,b,c]



[a]Intermediate lactols **18**–**23** and α-anomers **24α**–**29α** not depicted. [b]Diastereomeric ratios determined by ^{1}H NMR of crude reaction mixtures. [c]Relative stereochemistry determined by NOESY. [d]Aryllithium addition to provide arylated lactols **18**–**23**. [e]Hantzsch ester = diethyl 1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylate.

our established *de novo* synthetic strategy. We envisaged a route parallel to that outlined in Table 1, beginning with the coupling reaction of α,β-dioxyaldehyde **1** and a nucleophile prefunctionalized with the CF_2 motif. More specifically, isopropyl bromodifluoroacetate readily underwent a Reformatsky coupling with **1** in the presence of zinc,[9a,20] 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**.

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),[21] 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 $TiCl_2(O^iPr)_2$ as the Lewis acid. To our delight, the aldol coupling proceeded smoothly to provide β-hydroxyester **36** in 79% yield as a single

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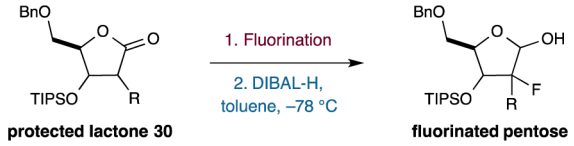
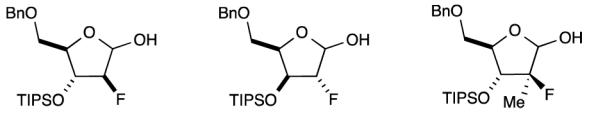
Table 3. Synthesis of C(2)-Fluorinated Pentoses from Lactones[a,b,c]





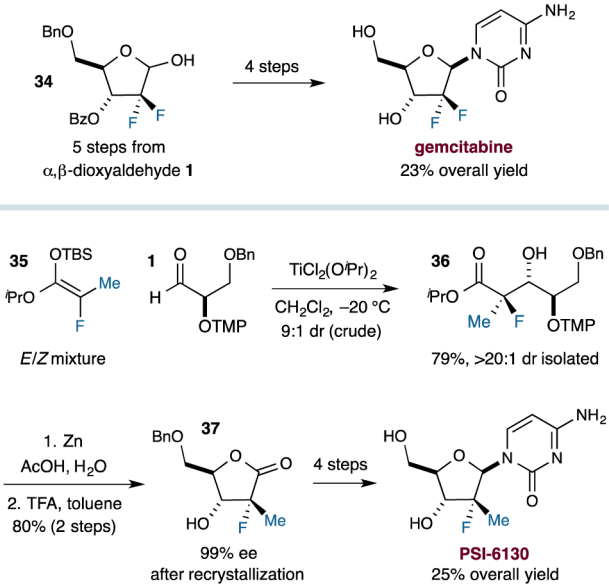
31a 72% yield, >20:1 dr
31b 90% yield

32a 90% yield, >20:1 dr
32b 70% yield

33a 72% yield, >20:1 dr
33b 86% yield

[a]Intermediate fluorinated lactones **31a–33a** not depicted. [b]All lactols recovered as anomeric 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



diastereomer after isolation. Cleavage of the OTMP group under reducing conditions followed by treatment with acid promoted cyclization to form lactone **37**. We were pleased to find that the lactone was obtained as a crystalline solid and that its enantiopurity could be increased to 99% ee after recrystallization.[22] Further elaboration of **37** delivered PSI-6130 in 25% yield and seven total steps from α,β-dioxyaldehyde **1**.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details and crystallographic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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