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COMMUNICATION

De novo synthesis of deoxy sugar *via* a Wharton rearrangement†‡

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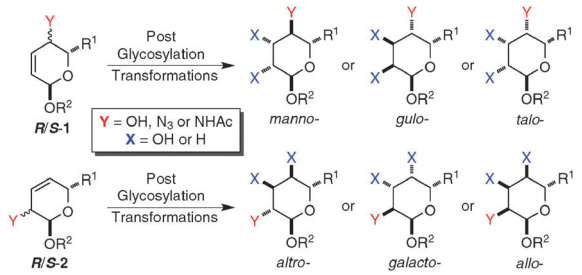
A highly divergent synthesis of α-fuco-, α-6-deoxy-allo-, α-6-deoxy-altro-pyranosides has been achieved. This route utilizes a Wharton rearrangement as part of a new post-glycosylation transformation strategy.

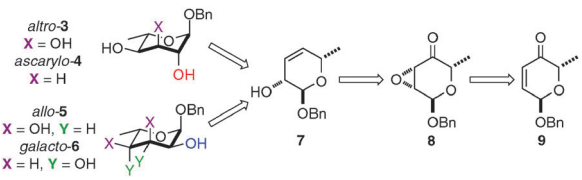
The importance of carbohydrate containing natural products in medicine is indubitable.[1] A survey of the structural motif used in bioactive natural products leads one to notice the reliance on rare sugars with uncommon stereochemistry and patterns of deoxygenation.[2–6] In an effort to mimic nature's use of rare deoxy sugars with unusual stereochemistry, medicinal chemists have long desired new synthetic strategies to provide practical access to a wide range of rare sugar structural motifs. This need has inspired various synthetic approaches.[7]

Similarly, we have developed two *de novo* asymmetric approaches to carbohydrates, where all the carbon atoms of sugars are derived from achiral furans[8] or dienoates.[9] Of these two approaches, the furan approach has proven to be the most powerful. The route links a highly enantioselective Noyori reduction of acylfurans, Achmatowicz oxidative dearomatization, diastereoselective carbonate formation, and Pd(0)-catalyzed glycosylation to stereoselectively transform acylfurans to an aculose sugar with the desired stereochemistry (*e.g.*, **10** to α-/β- and D-/L-**11**, see Scheme 3).[10] Subsequent post-glycosylation transformations provide access to the other pyran sugars.[11] Of particular utility, is the osmium-catalyzed dihydroxylation of the C-2/C-3 pyran double bond ***R*/*S*-1**, which (depending on the C-4 stereochemistry) can be used to install *manno*-, *gulo*-, and *talo*-stereochemistry (Scheme 1).[11] Similarly, regio- and stereoselective *anti*-addition across the same position can be used to access other sugars, such as α-6-deoxy-altrose, α-ascarylose and α-digitoxose (Scheme 1).[12]

We envisioned that the use of the osmium-catalyzed dihydroxylation on the regioisomeric allylic alcohol ***R*/*S*-2** could yield pyranoses with *altro*-, *galacto*- and *allo*-stereochemistry, depending on the C-2 stereochemistry. Herein, we report the successful application of the Wharton rearrangement[13] as a new post-glycosylation transformation, which leads to the synthesis of seven deoxy sugars, *vide infra*.[14] Retrosynthetically, the desired pyran **7** could be derived from the epoxy-ketone **8** *via* a Wharton rearrangement (Scheme 2), which in turn can be prepared *via* nucleophilic epoxidation of α-*aculo*-pyranoside **9**.

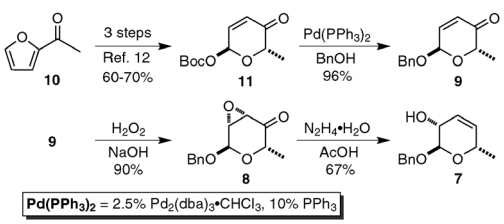


Scheme 1 *De novo* approach toward carbohydrates.



Scheme 2 Retrosynthetic analysis.

As previously reported, Boc-pyranone **11** can be readily prepared in three steps from acylfuran **10** (Scheme 3).[10] Using our Pd(0)-glycosylation, Boc-pyranone **11** was converted into α-benzyl-aculoside **9** with complete retention of anomeric stereochemistry. Epoxidation of **9** with H_2O_2 and a catalytic amount of base (10% NaOH) gave epoxide ketone **8** with high diastereoselectivity (>20 to 1).[5] Next, we explored the potential of Wharton transposition to rearrange **8** into allylic alcohol **7**, which under our optimal condition (Table 1, entry 6) cleanly gave the desired product in 67% yield.



Scheme 3 *De novo* synthesis of pyran alcohol **7**.

Our initial attempts to perform the Wharton rearrangement began with the typical condition (3 : 2 of $N_2H_4{\cdot}H_2O$/AcOH,

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‡ Electronic supplementary information (ESI) available: Experimental procedures, characterization data, and NMR spectra are available. See DOI: 10.1039/c1cc13837e

Table 1 Reaction conditions for Wharton rearrangement

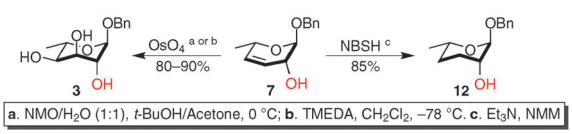
Entry	Reagents (equiv)	Acid/Base (equiv)	Solvent[a]	*t* (h)	Temp.	Yield (%)[b]
1	$N_2H_4{\cdot}H_2O$ (3)	AcOH (2)	MeOH	3	0 °C – rt	48
2	$N_2H_4{\cdot}H_2O$ (3)	AcOH (2)	CH_2Cl_2	18	0 °C – rt	10
3	$N_2H_4{\cdot}H_2O$ (3)	—	MeOH	24	rt	0
4	$N_2H_4{\cdot}H_2O$ (4)	AcOH (1)	MeOH	2	0 °C – rt	55
5	$N_2H_4{\cdot}H_2O$ (4)	Et_3N (1)	MeOH	6	rt	28
6	$N_2H_4{\cdot}H_2O$ (5)	AcOH (3)	MeOH	1.5	0 °C – rt	67
7	$N_2H_4{\cdot}HSO_4$ (3)[c]	Et_3N (3)	CH_3CN	3	rt	22
8	$N_2H_4{\cdot}H_2O$ (5)	—	—	0.3	68 °C	<10

[a] Solvents are used in 0.3 M concentration. [b] Isolated yield. [c] $N_2H_4{\cdot}HSO_4$ are prepared by $N_2H_4{\cdot}H_2O$ and conc. H_2SO_4 (ref. 15).

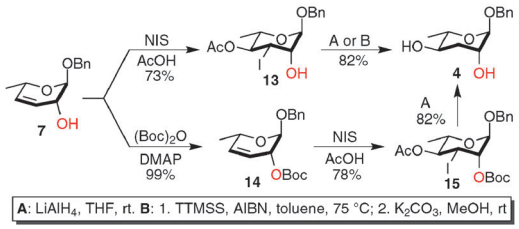
entry 1) in MeOH.[13] The protic solvent, MeOH, appeared to be important for the reaction. Switching to an aprotic solvent CH_2Cl_2 led to much slower reactions (entry 2). Slow reactions occurred also in more polar solvents (*i.e.*, acetonitrile) and in the presence of ammonium salts (entry 7).[15] Running the reaction in neat aqueous hydrazine at elevated temperature led to a faster reaction, although with a significant amount of decomposition (entry 8). We found that acetic acid is critical for the reaction to occur (entry 3), whereas the use of Et_3N as a base gave low conversion to product (entry 5). While increasing the ratio of hydrazine to AcOH (4 : 1) improved the yield (55%, entry 4), increasing both the amount of hydrazine and acetic acid gave the best results (67%, entry 6). We found that it was best to initially add the hydrazine to a methanol solution of **8** to allow for hydrazone formation (~30 min) before adding the AcOH at 0 °C. These conditions work well on the crude reaction product **8** from the enone epoxidation. Thus enone **9** can be converted to **7** on a gram scale using only one column chromatographic purification to give 50% yield.

With allylic alcohol **7** in hand, we explored its reduction and oxidation chemistry. Diimide reduction (*o*-$NO_2PhSO_2NHNH_2$/Et_3N) of **7** cleanly gave a rare α-3,4-dideoxy-rhamnose sugar **12** in 85% yield (Scheme 4). As an alternative, the alkene in **7** can be dihydroxylated under Upjohn conditions to give 6-deoxy-altrose **3** exclusively in 92% yield. These results suggest that the C-2/C-5 flanking substituents dominate the reaction facial selectivity over the competing 1,3-diaxial interactions between C-1-OBn and C-3-oxygen. To our surprise, this facial preference superseded the potential hydrogen bonding interaction between the axial allylic alcohol and the osmate-diamine complex. Thus, when **7** was subjected to the hydroxy-directed dihydroxylation conditions of Donohoe[16] the same *altro*-product **3** was formed.

In marked contrast to the osmylation, pyran **7** reacted with the opposite facial selectivity with "I^+" type reagents (NIS/HOAc), suggesting that the iodonium formation is more sensitive to the developing 1,3-diaxial interaction with the presence of anomeric oxygen. For instance, when pyran **7** was exposed to NIS in acetic acid, the β-acetoxy iodide **13** with



Scheme 4 Synthesis of *altro*- and 3,4-dideoxy-*rhamno*-se.



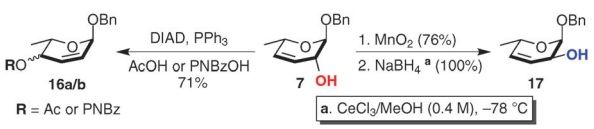
Scheme 5 Synthetic approaches toward α-ascarylose **4**.

manno-stereochemistry was formed as a single diastereomer (Scheme 5). In addition to the stereochemistry, we were surprised by the regioselectivity of addition to the iodonium intermediate, (*i.e.*, *trans*-diequatorial addition). This peculiar regioselectivity could be explained by the destabilizing effects of the C-2 axial hydroxyl group on the partial positive charge that is required for addition at the C-3 position.

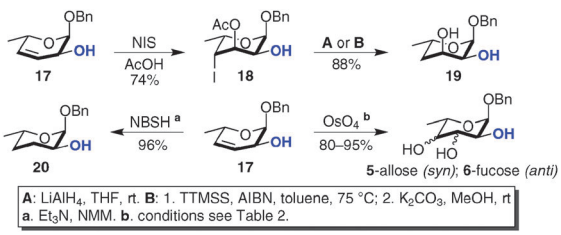
To test for reversibility in the iodonium formation, we decided to perform the reaction on the *t*-butyl carbonate **14**, which could trap the stereoisomeric iodonium intermediate. When carbonate **14** was exposed to the identical conditions as above only *trans*-diequatorial iodide **15** was observed. Both iodo-esters **13** and **15** were easily reduced in one-pot with $LiAlH_4$ to give α-ascarylose **4** in good yields. Alternatively, in a milder condition, iodide **13** was removed under radical conditions with tris(trimethylsilyl)silane (TTMSS) and AIBN, followed by hydrolysis to obtain α-ascarylose **4** with a similar yield over two steps (Scheme 5).

We next decided to explore the facial selectivity of the stereoisomeric allylic alcohol **17** (Scheme 6). Our initial attempts to invert the stereochemistry of allylic alcohol **7** *via* a Mitsunobu reaction failed leading to only products of S_N2' allylic transposition (**7** to **16**).[17] To avoid this problem, we turned to an oxidation/reduction strategy. The allylic alcohol **7** was oxidized with MnO_2, and reduced under Luche conditions to provide the allylic alcohol **17** in 76% overall yield as a single diastereomer.

With allylic alcohol **17** in hand, we first investigated the stereo- and regio-selectivity of the halo-acetoxy formation. Under the same NIS/HOAc conditions, allylic alcohol **17** was converted to β-iodoacetate **18** as a single regio- and stereoisomer in 74% yield (Scheme 7). The *gulo*-stereochemistry of **18** was the result of a net *trans*-diaxial addition. Thus, changing the C-2 allylic alcohol stereochemistry of **7** to **17** did not

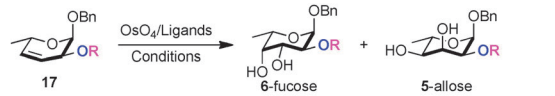


Scheme 6 Inversion of allylic alcohol **7**.



Scheme 7 Synthesis of α-fucose, α-6-deoxy-allose, 4,6-dideoxy-allose, and 3,4-dideoxy sugar congener.

Table 2 Optimization of OsO_4 dihydroxylation



A = 1% OsO_4, 1 M NMO/H_2O (1:1), 0.3 M *t*-BuOH/Acetone, 0 °C
B = 4% OsO_4, 1 M NMO/H_2O (1:1), 0.3 M CH_2Cl_2, 0 °C
C = 4% $K_2OsO_2(OH)_4$, 10% **Ligand**, 3 eq $K_3Fe(CN)_6$, 3 eq K_2CO_3, 3 eq $MeSO_2NH_2$, 0.05 M *t*-BuOH/H_2O (1:1), 0 °C
D = 20% OsO_4, NMO/H_2O (70% w/v), 50% **Ligand** or w/o ligand, 0.03 M CH_2Cl_2, –78 °C
E = 1 eq OsO_4, 1.5 eq TMEDA, 0.05 M CH_2Cl_2, –78 °C

Entry	R	Condition	Ligand	Ratio (6 : 5)[a]	Yield (%)[b]
1	–H	**A**	—	2 : 1	95
2	–H	**B**	—	1 : 3	84
3	–H	**D**	—	1 : 4	80
4	–H	**E**	—	2 : 1	65
5	–H	**C**	$(DHQ)_2PHAL$	1 : 1.5	94
6	–H	**C**	$(DHQD)_2PHAL$	1 : 1.2	89
7	–H	**C**	$(DHQD)_2DPP$	1 : 5	97
8	–H	**D**	DHQ	1 : 6	88
9	–H	**D**	DHQD	1 : 1	82
10	–H	**D**	$(DHQ)_2PHAL$	1 : 4	85
11	–H	**D**	$(DHQD)_2PHAL$	1 : 2	88
12	–H	**D**	$(DHQD)_2DPP$	1 : >10	92
13	–Piv	**A**	—	5 : 1	90
14	–TBS	**A**	—	7 : 1	95

[a] Diastereomeric ratio are based on crude NMR analysis in the comparison of anomeric H1. [b] Combined yield after flash column purification.

affect the inherent facial preference of **17** with "I^+" type reagents. In contrast, switching the C-2 alcohol from axial to equatorial did change the regio-selectivity of iodonium ring opening. A similar removal of both iodide and acetate moiety was achieved successfully under either hydride **A** or radical-reduction condition **B** to give a rare 4,6-dideoxy-allose sugar **19**. Allylic alcohol **17** was further reduced with diimide to give 3,4,6-trideoxy-glucose **20**.

Although switching the C-2 hydroxyl stereochemistry had no effect on the stereochemistry of iodonium formation, it greatly influenced the facial selectivity of dihydroxylation. For instance, when **17** was exposed to typical Upjohn conditions, it gave a 2 to 1 mixture of *fuco*-sugar **6** and 6-deoxy-*allo*-sugar **5** (Table 2, entry 1). The facial selectivity of **17** may result from many competing factors, such as solvent effect, reaction temperature and the presence of chiral ligands. For example, when *t*-BuOH was changed to aprotic CH_2Cl_2, the facial preference switched from fucose to allose (entry 2). The preference for *allo*-stereochemistry in CH_2Cl_2 was increased by lowering the reaction temperature (entry 3). Unfortunately, the hydroxy-directing Donohoe conditions gave the same selectivity as the Upjohn condition (entry 4). The addition of the Sharpless chiral ligands to the reaction in *t*-BuOH switched the selectivity from fucose to allose (entries 5–7) with $(DHQD)_2DPP$ being the best ligand. This effect could be enhanced by switching to CH_2Cl_2 and cooling to −78 °C (entries 8–12). In general, switching between the dimeric *pseudo*-enantiomeric ligands has little effect, whereas the monomeric ligands cause a significant difference at −78 °C (entries 8–9). The best allose selectivity came from the use of $(DHQD)_2DPP$ at −78 °C (entry 12). In order to increase fucose selectivity, the C-2 allylic alcohol had to be protected either as a pivaloate or TBS-ether (entries 13 or 14).

In conclusion, we have found that by incorporating the Wharton reaction into post-glycosylation transformation, new rare deoxy sugars can be easily obtained. These sugars include 6-deoxy-*altro*-/*fuco*-/*allo*-, *ascarylo*-, 3,4,6-trideoxy *gluco*-/*manno*- and 4,6-dideoxy-*allo*-pyranosides, which can be prepared in either D- or L-enantiomeric series. The route allows for the divergent synthesis of a range of sugars from the advanced stage intermediate. Future work in exploring the potential of employing this strategy in medicinal chemistry is currently ongoing.

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