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Dimerization of aldosuloses and aldonolactones into branched higher carbon sugars

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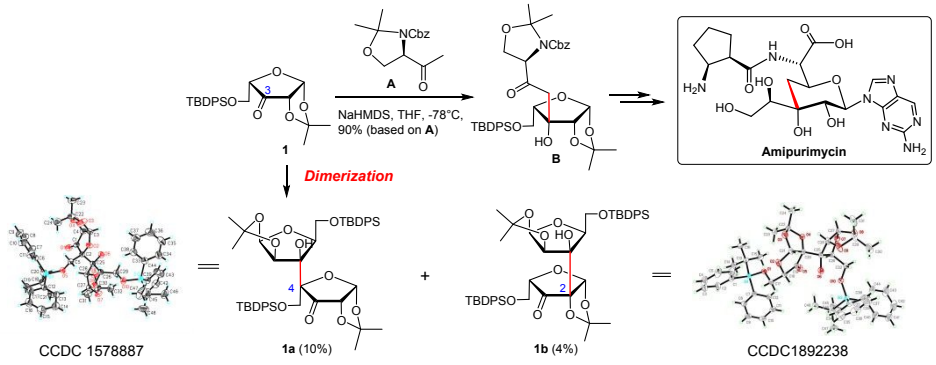
Yachen Zhao,[a] Shengyang Wang,[b] and Biao Yu[a,c]*

In Memory of Prof. Derek Horton



Scheme 1. Homo-dimerization of 3-oxo-furanoside **1** in the cross-aldol reaction with methyl ketone **A** and ORTEP diagrams of the dimers **1a** and **1b** with 30% probability ellipsoids.

Homo-dimerizations of a variety of aldosulose and aldonolactone derivatives via aldol and Claisen condensations have been achieved, leading to novel branched higher carbon sugars in highly stereoselective manner.

In our recent synthesis of amipurimycin, a higher carbon sugar peptidyl nucleoside antibiotic, a stereoselective aldol reaction of 3-oxo-furanoside **1** and methyl aminoketone **A** was employed as a key step to build the branched C9 sugar amino acid skeleton (Scheme 1).[1,2] In decagram-scale syntheses, two minor side products **1a** and **1b** were isolated in 10% and 4% yield, respectively, which were determined to be the homo-dimerization products of 3-oxo-furanoside **1** by X-ray diffraction analysis (CCDC 1578887 and 1892238). Thus, the excess ketone **1** was attacked by the self-derived 4,3-enolate or 2,3-enolate from exclusively the less hindered face. In fact, the homo-dimerization of aldosuloses is not without precedent. In 1969, Horton and Just disclosed a homo-dimerization upon treatment of 1,6-anhydro-2,3-*O*-isopropylidene-4-oxo-derivative of D-mannopyranose with Ac_2O and Et_3N at room temperature.[3] This transformation was also observed in the presence of NaOMe.[4] Later on, similar aldol-type homo-dimerizations were reported with 1,2-*O*-isopropylidene-α-L-glycero-tetros-3-ulofuranose,[5] *tert*-butyl 3,4-*O*-isopropylidene-α-L-erythro-pentopyranosidulose,[6] and 1,6-anhydro-3-deoxy-5-*O*-tosyl-α-L-threo-hexofuranos-2-ulose[7] under varied conditions. In addition, Csuk et al. and Kobayashi et al. disclosed relevant homo-dimerization of aldonolactones via Claisen-type reaction.[8-11] Herein, we examined the homo-dimerization of a series of aldosulose and aldonolactone derivatives in order to provide a general approach to the synthesis of higher carbon sugars bearing novel dimeric skeletons.[12-14]

The dimerized products **1a** and **1b** were obtained as side products in the aldol reaction of 3-oxo-furanoside **1** with methyl aminoketone **A** (Scheme 1). Following a similar procedure, 3-oxo-furanoside **1** was treated with NaHMDS in THF at -78 °C to generate the corresponding enolates followed by addition of another equivalent of **1** (instead of the previous methyl aminoketone **A**); a new dimerized product **1c** was isolated in 44% yield, with the desired dimers **1a** and **1b** being absent (Table 1, entry 1). The generation of olefin derivative **1c** involved elimination of the 5-*O*-*tert*-butyldiphenylsilyl (TBDPS) group, which took place at the enolization stage in the presence of a relatively high concentration of NaHMDS. Thus, the 5'-*O*-TBDPS

[a]*State Key Laboratory of Bioorganic and Natural Products Chemistry, Center for Excellence in Molecular Synthesis, Shanghai Institute of Organic Chemistry, University of Chinese Academy of Sciences, Chinese Academy of Sciences, 345 Lingling Road, Shanghai 200032, China. Email: byu@sioc.ac.cn*
[b]*Innovation Research Institute of Traditional Chinese Medicine, Shanghai University of Traditional Chinese Medicine, 1200 Cai Lun Road, Shanghai 201203, China*
[c]*School of Chemistry and Material Sciences, Hangzhou Institute for Advanced Study, University of Chinese Academy of Sciences, 1 Sub-lane Xiangshan, Hangzhou 310024, China*

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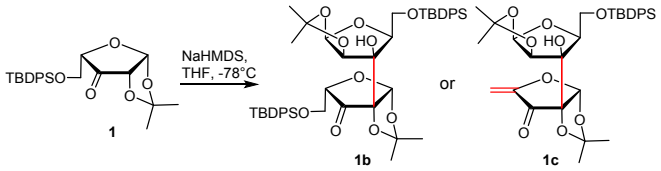
group in the later added ketone **1** remained intact in product **1c**. To avoid this undesired elimination, NaHMDS (0.5

Table 1. Optimization of the dimerization of 3-oxo-furanoside **1**



Entry	Adding Sequence[a]	NaHMDS (equiv)	Product	Isolated Yield
1	A	0.5	**1c**	44%
2	B	0.5	**1b**	52%
3	B	1.0	**1b**	70%

[a] A: 0.5 equiv **1** in THF was added to a solution of NaHMDS in THF; after 10 min, another 0.5 equiv **1** in THF was added. B: A solution of NaHMDS in THF was added to 1.0 equiv **1** in THF.

equiv.) was added to a solution of **1** in THF at -78 °C to avoid the occurrence of high concentration of base in the reaction mixture. Indeed, with this addition sequence, the desired dimerized product **1b** was isolated in a decent 52% yield, whereas dimer **1a** and the elimination product **1c** were not detected (entry 2). Increasing the amounts of NaHMDS to 1.0 equiv. resulted in an increase of the yield of dimer **1b** to 70% (entry 3).

3-Oxo-xylofuranose derivative **2** was also employed in our synthesis of amipurimycin diastereoisomers.[1] Applying the above optimized conditions for the dimerization of **2**, however, led to the dimerized olefin product **2b** as the major product in 42% yield, with the desired dimer **2a** in only 3% yield (Table 2, entry 1). Apparently, the electron-withdrawing 5-*O*-benzoyl group in 3-oxo-furanoside **2** is far more prone to elimination than the 5-*O*-silyl group in **1**. Indeed, the elimination was avoided by replacing the benzoyl group with the electron-donating benzyl group (in **3**). Thus, the aldol reaction of **3** gave a pair of the C4-epimers **3a** and **3b** in 13% and 49% yield, respectively (entry 2). It is not surprising that the desired ketone **3b** could undergo epimerization under basic conditions to give **3a**; in **3a** a strong NOE signal was observed between H1 and H4. We then replaced the 5-*O*-benzyl group with the electron-donating *tert*-butyldimethylsilyl (TBS) group to obtain 3-oxo-furanoside **4** as a substrate for dimerization. Indeed, ketone **4** was converted into dimer **4a** as the only product in a moderate 39% yield (entry 3). It is noteworthy that the dimerization was not observed once the 5-*O*-TBS group in **4** was replaced by the bulkier TBDPS group.

Next, the dimerization of 1,6-anhydro-pyranose ketones **5** and **6** were examined. Unexpectedly, addition of NaHMDS to a THF solution of **5** or **6** at -78 °C resulted in complete decomposition of the starting material. Under milder reaction conditions with a catalytic amount of NaOMe as the base (DME, RT), the homo-coupling of 2-oxo-pyranoside **5** proceeded smoothly, giving the desired dimer **5a** in 68% yield (entry 4). Under similar conditions, 4-oxo-pyranoside **6** was converted into dimer **6a** in 58% yield (entry 5).[4] The structure

Table 2. Aldol-type dimerization of aldosulose derivatives **2-6**

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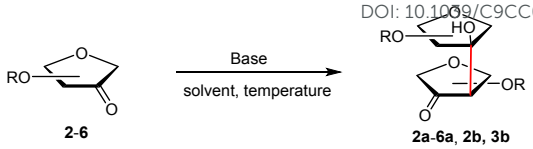
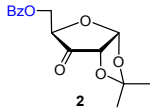
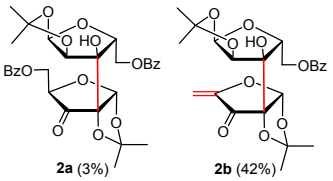
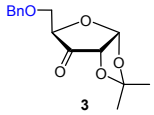
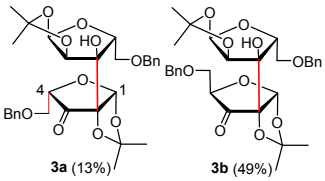
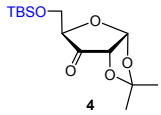
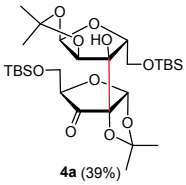
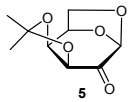
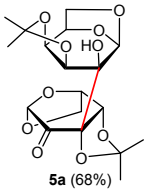
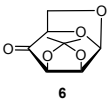
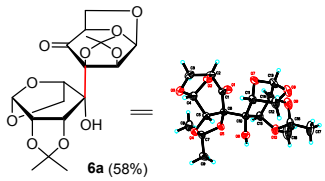


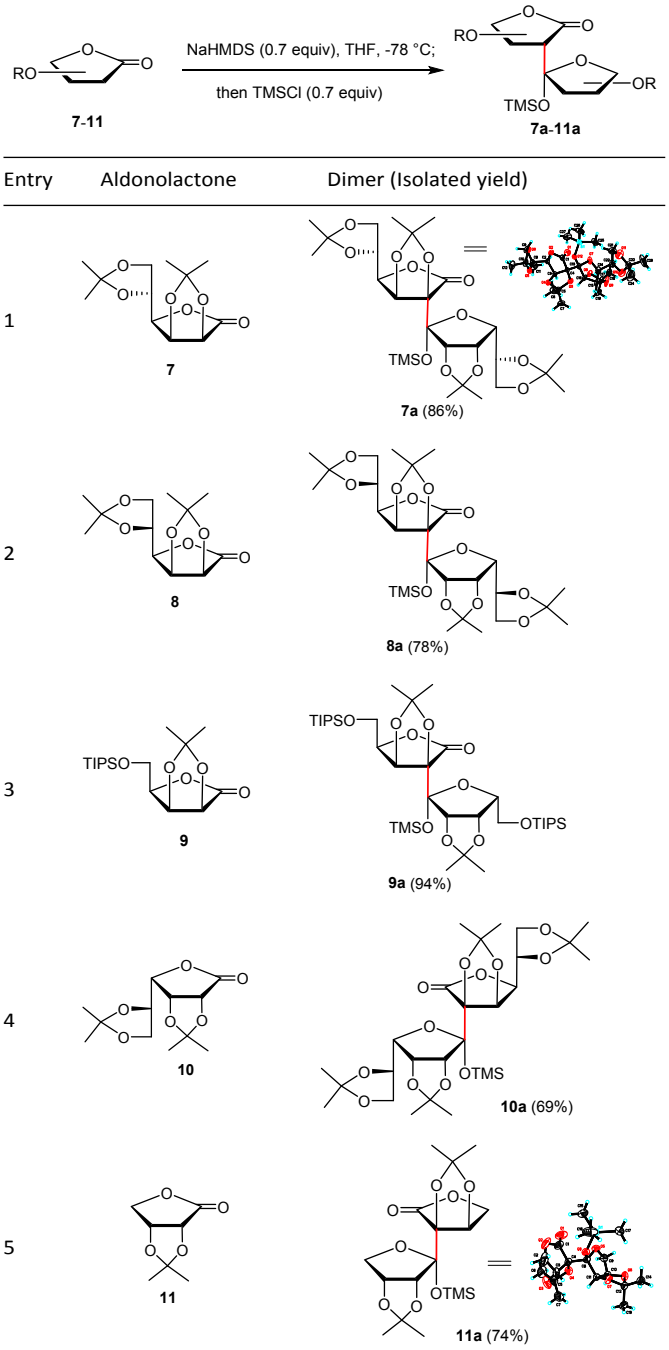
Entry	Aldosulose	Dimers[a] (Isolated yield)
1[b]		
2[c]		
3[c]		
4[d]		
5[d]		

[a] All reactions were conducted with addition of the base directly to the solutions of 1.0 equiv. aldosuloses. [b] NaHMDS, (1.0 equiv), THF, -78 °C. [c] NaHMDS (0.5 equiv), THF, -78 °C. [d] MeONa (0.1 equiv.), DME, rt.

of dimer **6a** was unambiguously confirmed by X-ray diffraction analysis (CCDC 1892033). The excellent regioselectivity of these dimerizations originated from the required planarity of the enolates; the enolization at C1 in **5** or C5 in **6**, the bridgehead of the [3.2.1] bicyclic system, is considered to be sterically unfavored (Bredt's rule).[3] The moderate yields might be ascribed to the reversibility of these aldol reactions.

The dimerizations of the easily accessible aldonolactones **7-11** were also examined (Table 3). Compared to the previous aldol-type dimerization of aldosuloses, the Claisen-type dimerizations of aldonolactones were found to be much effective under the optimal reaction conditions (0.7 equiv. NaHMDS, THF, -78 °C). The resultant dimeric ketoses could

Table 3. Claisen-type dimerization of aldonolactone derivatives **7**-**11**



exist as mixtures of anomers and open-chain hydroxyl ketones, therefore were immediately protected by silylation for the convenience of isolation and characterization. These two-step transformations provided the corresponding dimeric 1'-*O*-trimethylsilyl (TMS) derivatives **7a**-**11a** in satisfactory yields (69%-94%). The structures of dimers **7a** and **11a**[8] were confirmed unambiguously by X-ray diffraction analysis (CCDC 1892035 and 1892034). It is noteworthy that dimers **8a** and **10a**, which were prepared from L/D-gulose lactones, respectively, can be regarded as the homo-coupling products of D/L-glucose.

In summary, the aldol-type dimerization of six aldosuloses and Claisen-type dimerization of five aldonolactones have been realized. These transformations provide a novel type of branched higher carbon sugars effectively, wherein the regio- and stereo-selectivities can be well controlled by the substituents on the starting aldosuloses/aldonolactones. It is noteworthy that the isopropylidene group installed at the α,β-position of the carbonyl group in the monosaccharide substrates plays an indispensable role in these reactions. Otherwise, α-epimerization and β-elimination of the carbonyl compounds having hetero-atoms at the α/β positions can occur easily under basic conditions. Further transformations of the resultant higher carbon sugars into biologically active compounds are a current project of us and the results will be reported in due course.

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