SHORT COMMUNICATION

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Biomimetic *syn*-Aldol Reaction of Dihydroxyacetone Promoted by Water-Compatible Catalysts

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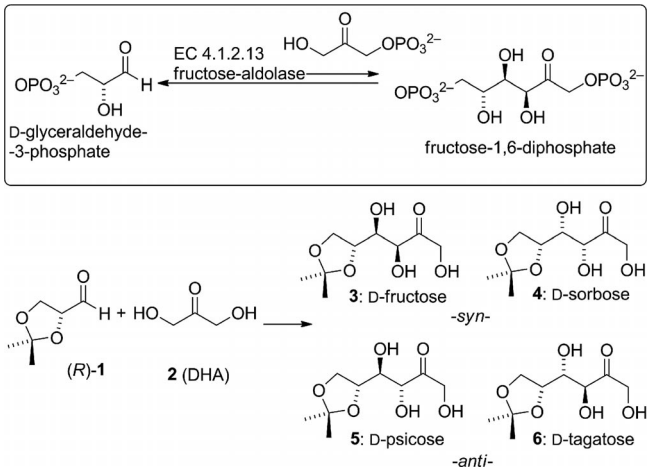
The *syn*-selective direct aldol reaction of unprotected dihydroxyacetone with glyceraldehyde has been catalyzed by serine-based organocatalysts. The application of the catalysts mimics the biosynthesis of ketohexoses in aqueous solvents and leads to fructose and sorbose with excellent diastereoselectivity (up to 95:5 *dr*). The organocatalytic C_3+C_3 methodology presented herein is a versatile direct entry to protected *syn*-configured sugars of both the D and L series.

Introduction

The aldol reaction is one of the most important transformations for the construction of C–C bonds in both the laboratory and in nature.[1] This particular reaction is crucial in the context of living organisms, being the most important biochemical process for the synthesis of naturally occurring carbohydrates. For example, dihydroxyacetone phosphate (DHAP) participates in an enzyme-catalyzed aldol reaction with (*R*)-glyceraldehyde-3-phosphate to form D-fructose-1,6-diphosphate (Scheme 1).[2] In general, the construction of four differently configured sugars is controlled by four different aldolases. In addition to one (*R*)-configured stereogenic center delivered from the glyceraldehyde substrate, these reactions create two new stereogenic centers in the form of *syn*- (fructose and sorbose) or *anti*-ketohexoses (psicose and tagatose; Scheme 1).[3]

This versatile and simple C_3+C_3 strategy involving the DHA synthon, although most favored by nature, is still beyond the reach of organic chemists, especially the synthesis of *syn*-configured ketohexoses.[4] Chemists have long been pursuing simple catalysts to mimic nature's aldolase enzymes, but the asymmetric synthesis of carbohydrates with DHA derivatives as donors[5] has only been achieved recently with enamine-based organocatalysis.[6] The best results in the direct synthesis of ketohexoses were achieved when (*S*)-proline was used as a catalyst, and the reactions were largely limited to cyclic-protected DHA derivatives such as 2,2-dimethyl-1,3-dioxan-5-one.[4] Because (*S*)- and (*R*)-proline catalysts have provided access to *anti*-1,2-diols,[7] they mimic tagatose and fuculose aldolases for dioxanone substrate.[6] More recently, Luo et al. showed that *anti*-selective reactions of dioxanone with aromatic aldehydes can be promoted by chiral primary amines, thus confirming that the stereoselectivity of the reaction depends on *E*-configured enamines formed exclusively from cyclic ketones.[8]



Scheme 1. Biomimetic synthesis of all four D-ketohexoses.

Recently, Barbas and co-workers reported that primary amino acids can catalyze the *syn*-aldol reaction of protected DHA with glyceraldehyde. In addition, *O*-*tert*-butyl-L-threonine (20 mol-%) promoted the aldol reaction of *tert*-butyldiphenylsilyl (TBDPS) protected dihydroxyacetone with (*R*)-glyceraldehyde to form protected D-fructose with a high diastereoisomeric ratio (98:2).[9] Similarly, an *O*-*tert*-butyl-L-threonine-based amide acted as an efficient catalyst for the reaction of TBDPS-protected DHA with the acetonide of (*R*)-glyceraldehyde providing the protected D-sorbose derivative in 86% yield and with a 3:1 *syn*/*anti* ratio.[10] The catalysts used were also water-tolerant making the presented reactions biomimetically even more relevant. This methodology provides a direct route to aldol products of

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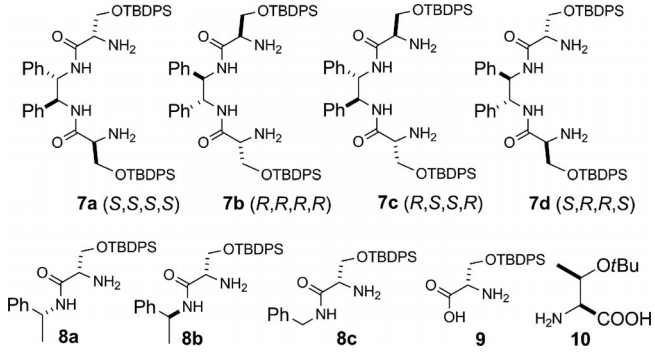
the type synthesized with DHAP aldolase enzymes, but still requires a protected ketone donor. Reactions of unprotected DHA have so far been unselective[11] or limited to non-chiral aldehydes.[10,12]

Because biomimetic access to *syn*-1,2-diols by enamine organocatalysis and a C_3-dihydroxyacetone-based strategy with an unprotected donor are still not possible, we present herein our attempt towards resolving this fundamental problem. This communication presents a versatile and stereoselective access to *syn*-configured D- and L-ketohexoses from DHA and (*R*)- and (*S*)-glyceraldehyde, respectively. To meet the biomimetic criteria, we focused on water-tolerant organocatalysts that form enamine intermediates in homogeneous aqueous solvents. The presented aldol reaction is also a rare example of the practical synthesis of natural products in an aqueous environment.[13]

Results and Discussion

Based on our earlier development of *syn*-aldol reactions of hydroxyacetone catalyzed by amino acids,[14,15] we initially screened various bis(amides) containing primary amines. The four isomeric bis(serinamides) **7a**–**7d** demonstrated activity and stereoselectivity superior to that obtained previously by other authors. We decided to use *O*-*tert*-butyldiphenylsilyl-protected bis(serinamides) as these catalysts are very hydrophobic, mimicking the nature and mode of action of enzymes. The idea behind this was that more bulky substituents can effectively protect reactive sites from water molecules and also shield one of the sites from nucleophilic attack resulting in higher enantioselectivity (Scheme 2).



Scheme 2. Organocatalysts used in this study for the *syn*-selective direct aldol reaction of DHA.

The four catalysts **7a**–**7d**, which are readily available from (*S*,*S*)- and (*R*,*R*)-diphenylethylenediamine and the two serine enantiomers,[14,16] were initially screened in the aldol reaction of (*R*)-glyceraldehyde (**1**, 1 mmol) and unprotected dihydroxyacetone (**2**, 4 mmol). In an effort to improve the reaction rates and stereoselectivities, we evaluated different solvents and various conditions. The best results observed in DMF/water are collected in Table 1. All the bis(amides) were observed to catalyze the reaction very smoothly, affording preferential and exclusive formation of *syn*-aldols. The first experiments showed that the reaction controlled by catalyst **7a**, composed of (*S*,*S*)-diphenylethylenediamine and L-serine, resulted in the formation of protected D-sorbose (**4**) in good yield and with a 7:3 *syn*/*anti dr* when 20 mol-% of the organocatalyst was used (Table 1, Entry 2). Interestingly, enantiomeric catalyst **7b** delivered protected D-fructose (**3**) in very good yield and with high stereoselectivity (9:1, Table 1, Entry 3). It is important to mention that we did not observe racemization of the glyceraldehyde or the hexoses during the reaction, and high enantiomeric excesses were confirmed for all the products by NMR experiments and chiral HPLC analysis.

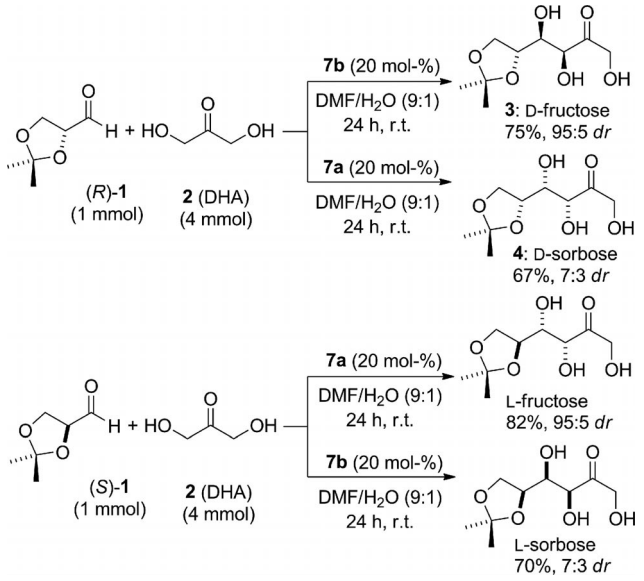
Table 1. Direct aldol reaction of dihydroxyacetone (**2**) with (*R*)-glyceraldehyde **1**.[a]

Entry	Catalyst (mol-%)	Yield[b] [%]	Fructose(**3**)/sorbose(**4**)[c]
1	**7a** (10)	29	25:75
2	**7a** (20)	67	30:70
3	**7b** (20)	75	90:10
4	**7c** (20)	52	90:10
5	**7d** (20)	53	50:50
6	**8a** (20)	27[d]	55:45
7	**8a** (40)	35[d]	55:45
8	**8b** (20)	27[d]	60:40
9	**8b** (40)	35[d]	65:35
10	**8c** (20)	32[d]	70:30
11	**9** (20)	traces	–
12	**10** (20)	traces	–

[a] Reactions were performed with (*R*)-**1** (1 mmol), DHA (**2**; 2 mmol as a dimer) and catalyst (20 or 40 mol-%) in DMF/H_2O (9:1, 1 mL) at room temp. for 24 h. [b] Yield of the isolated product. [c] Determined by ^{1}H NMR analysis. [d] Reaction time of 72 h.

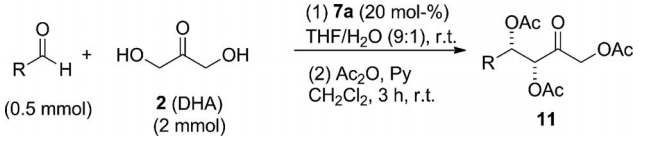
The diastereoisomeric catalysts **7c** and **7d** were less efficient, revealing that the stereochemistry of the amino acid motif has a significant effect on the stereoselectivity of the reaction. Thus, the application of (*R*)-configured serine in bis(amide) **7c** supports the formation of D-fructose (Table 1, Entry 4). Interestingly, the stereochemistry of the whole catalyst molecule seems to be essential for the formation of a monosaccharide. The unselective formation of fructose and sorbose (1:1, Entry 5) by catalyst **7d**, as well as the lower yields observed for mismatched catalysts **7c** and **7d** strongly support the hypothesis that a chiral catalyst and chiral aldehyde molecule should work together and match each other. Interestingly, mono(serinamides) **8a**–**8c** induced poorer stereoselectivity and yields even when used in two-fold excess, further demonstrating the need for a C_2-symmetrical bis(amide) catalyst (Entries 6–10). The use of *O*-*tert*-butyldiphenylsilyl-protected L-serine **9** and *O*-*tert*-butyl-L-threonine **10**[12] were unsuccessful in the tested aldol reaction.

Having in hand the efficient enantiomeric catalysts **7a** and **7b**, we tested the ability of the reactions of both enantiomeric glyceraldehyde acetonides (*R*)-**1** and (*S*)-**1** to give rapid and direct access to D- and L-hexoses, respectively. Under the optimized conditions, the reactions were complete in 24 h at room temperature (Scheme 3).



Scheme 3. Stereoselective synthesis of D- and L-fructose and -sorbose.

Table 2. Enantioselective direct aldol reaction of dihydroxyacetone (**2**).[a]



Entry	Aldol (R)	Yield[b] [%]	*syn*/*anti*[c]	*ee*[d] [%]
1	**11a** (4-$O_2NC_6H_4$)	78[e]	9:1	91
2	**11b** (4-NCC_6H_4)	71	6:1	92
3	**11c** (4-$F_3CC_6H_4$)	61	8:1	89
4	**11d** (4-ClC_6H_4)	51[f]	9:1	92
5	**11e** (2-ClC_6H_4)	49	10:1	91
6	**11f** (C_6H_5)	15	8:1	86
7	**11g** (CH_2OBn)	22[f]	9:1	85

[a] Reactions were performed with aldehyde (0.5 mmol), DHA (**2**; 1 mmol as a dimer) and catalyst **7a** (20 mol-%) in THF/H_2O (9:1, 1 mL) at room temp. for 48 h. [b] Yield of the isolated product. [c] Determined by ^1H NMR spectroscopy and HPLC analysis. [d] The enantiomeric excess of the *syn* isomer was determined by HPLC analysis on a chiral phase column (Chiralpak OD-H and AS-H). [e] Reaction time of 24 h. [f] Reaction time of 72 h.

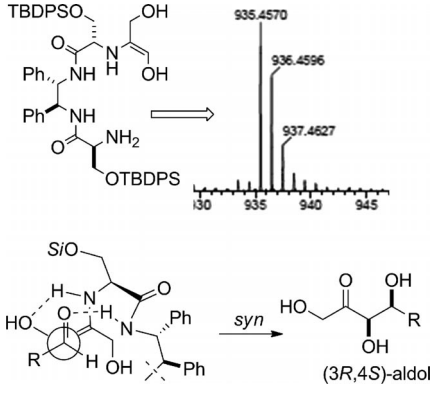
When used with chiral (*R*)- and (*S*)-aldehydes in the presence of D- and L-serine-based catalysts, a matched/mismatched situation becomes apparent. In the case of (*R*)-glyceraldehyde, application of catalyst **7b** resulted in the formation of D-fructose in high yield and *dr*, whereas the use of catalyst **7a** led to the stereoselective formation of D-sorbose with a good diastereoisomeric ratio. Again, we confirmed the exclusive formation of two *syn*-aldols. In contrast, L-fructose was formed with **7a** and (*S*)-**1**, whereas L-sorbose resulted from the **7b**/(*S*)-glyceraldehyde matched chiral pair.

These results are interesting not only in terms of a biomimetic synthesis of natural carbohydrates, but, significantly, protected unnatural L-carbohydrates are also formed, which otherwise are most efficiently prepared by difficult unnatural enzymatic reactions or from the chiral pool.[17]

To understand better the reaction mechanism and discuss the competition between enamine formation and the general base mechanism, we also studied the enantioselective direct organocatalytic *syn*-aldol reaction of unprotected dihydroxyacetone with achiral aldehydes. Under the optimized conditions, the reactions were performed in aqueous THF solution in the presence of catalyst **7a**. For practical reasons, the triol products were peracetylated and the resulting esters **11** analyzed by HPLC on a chiral stationary phase. The results of these experiments are collected in Table 2.

The reaction of unprotected dihydroxyacetone with a variety of aromatic aldehydes provided the desired *syn*-aldol products in moderate to good yields and with excellent diastereo- and enantioselectivity. As expected, the activated aromatic aldehydes were the more reactive substrates (Table 1, Entries 1–3), and benzaldehyde was a much less reactive acceptor (Entry 6). In all cases, however, high stereoselectivity was observed, which confirms the efficient formation of the enamine in the aqueous media and its highly stereoselective nucleophilic addition to the aldehyde.

The organocatalytic enantioselective reaction of dihydroxyacetone presented above took place in a homogeneous organic aqueous solution. To gain a deeper insight into the enamine mechanism of hydroxyacetone activation by primary amine catalyst **7a** we used ESI-MS. The results of the analysis of a mixture of unprotected DHA and catalyst **7a** (1:1) in an aqueous DMF solution are presented in Scheme 4. The high-resolution mass spectrum confirms the formation of an enamine in the aqueous medium: The signal at m/z = 935 is in accord with the expected molecular weight. The isotopic pattern of this signal corresponds to the calculated pattern of the expected enamine structure.[16] A plausible enamine-based transition state for the *syn*-aldol reaction of dihydroxyacetone catalyzed by **7a** is presented in Scheme 4. The (3*R*,4*S*) absolute configuration of the aldols **11** was assigned by analogy to previously published



Scheme 4. HRMS (ESI) spectrum of the enamine formed in situ from dihydroxyacetone (**2**) and catalyst **7a** in aqueous solution and the plausible structure of transition state based on enamine formation.

results.[12] Organocatalyst **7a** can form a hydrogen-bond-stabilized (*Z*)-enamine, which attacks the aldehyde from the *Re* face resulting in the formation of *syn*-(3*R*,4*S*)-aldols.

Conclusions

We have presented a highly enantioselective *syn*-aldol reaction of unprotected dihydroxyacetone (**2**) with aldehydes including achiral and optically pure acceptors. The presented serine-based organocatalysts **7a** and **7b** are active not only with aromatic aldehydes, but can also efficiently promote the stereoselective synthesis of D- and L-configured *syn*-hexoses. In all cases, *syn*-aldols were formed exclusively without substrate racemization. The reactions of chiral glyceraldehydes promoted by enantiomeric bis(serinamides) mimic the reactions catalyzed by fructose and rhamnulose aldolases, but also give direct access to unnatural L-carbohydrates from the (*S*)-glyceraldehyde precursor. Such a stereoselective methodology closely related to the biosynthesis of sugars from unprotected dihydroxyacetone in an aqueous environment and at ambient temperature has never been published previously. This study not only describes biomimetic aldol reactions but also provides one of the most efficient de novo syntheses of sugars by enamine-based organocatalysis.[18]

Supporting Information (see footnote on the first page of this article): Detailed experimental procedures and HPLC analysis as well as ^{1}H and ^{13}C NMR spectra of all catalysts and aldol products.

Acknowledgments

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