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J. Org. Chem., **Just Accepted Manuscript** • DOI: 10.1021/jo500860g • Publication Date (Web): 19 May 2014

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Amine-Catalyzed Direct Aldol Reactions of Hydroxy- and Dihydroxyacetone: Biomimetic Synthesis of Carbohydrates

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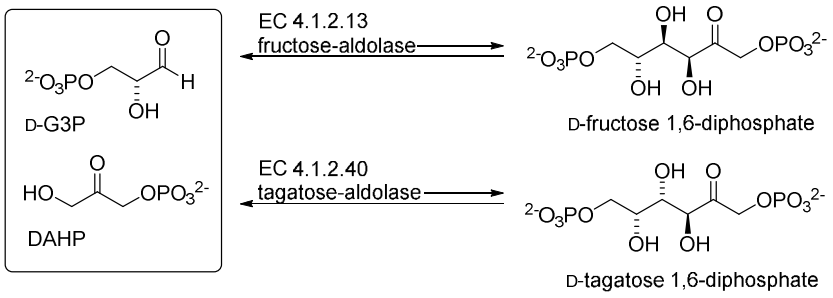
Abstract: This article presents comprehensive studies on application of primary, secondary and tertiary amines as efficient organocatalysts for the *de novo* synthesis of ketoses and

deoxyketoses. Mimicking aldolase enzymes, synthesis of selected carbohydrates was accomplished in aqueous media by using proline- and serine-based organocatalysts. Presented methodology also provides direct access to unnatural L-carbohydrates from the (*S*)-glyceraldehyde precursor. Determination of the absolute configuration of all obtained sugars was feasible using methodology consisting of concerted ECD and VCD spectroscopy.

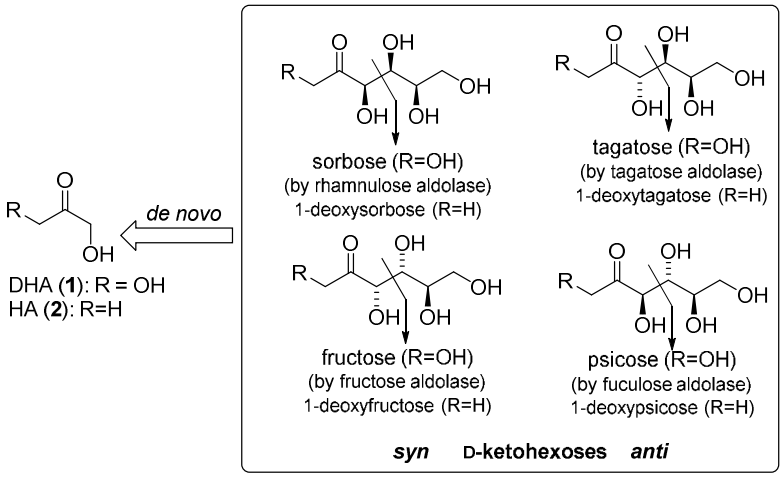
1. Introduction

Dihydroxyacetone (DHA) is one of the most employed donors in nature playing a key role in many vital biotransformations. Particularly, its phosphorylated form is an intermediate in glycolysis and gluconeogenesis. Dihydroxyacetone phosphate (DHAP) participates in an enzyme catalyzed aldol reactions *en route* to carbohydrates.[1] For example, fructose 1,6-biphosphate aldolase (FruA) catalyze *in vivo* the aldol addition of D-glyceraldehyde 3-phosphate (D-G3P) and dihydroxyacetone phosphate (DHAP) to give D-fructose 1,6-biphosphate (Scheme 1). This aldolase controls stereoselective construction of C-C bond with two *syn*-configured hydroxy-substituted stereogenic centers. In contrast, construction of *anti*-configured ketohexose (D-tagatose) is controlled in nature by tagatose aldolase (TagA, Scheme 1).



Scheme 1. Biosynthesis of fructose and tagatose by DHAP-dependent aldolases.

In general, aldolases can catalyze C-C bond formation between dihydroxyacetone phosphate and glyceraldehyde with simultaneous formation of two new stereocenters. As a consequence, four different ketohexose stereoisomers can be obtained in short and efficient C_3+C_3 strategy (Scheme 2). Each aldol reaction generates a single product, whose stereochemistry at C-3 and C-4 is complementary to the others. In addition to one (*R*)-configured stereogenic center delivered from glyceraldehyde substrate, these reactions create two new stereogenic centers in the form of *syn*- (D-fructose and D-sorbose) or *anti*-ketohexoses (D-psicose and D-tagatose) (Scheme 2, R = OPO_3^{2-}).



Scheme 2. Stereochemical complementarity of DHAP-dependent aldolases.

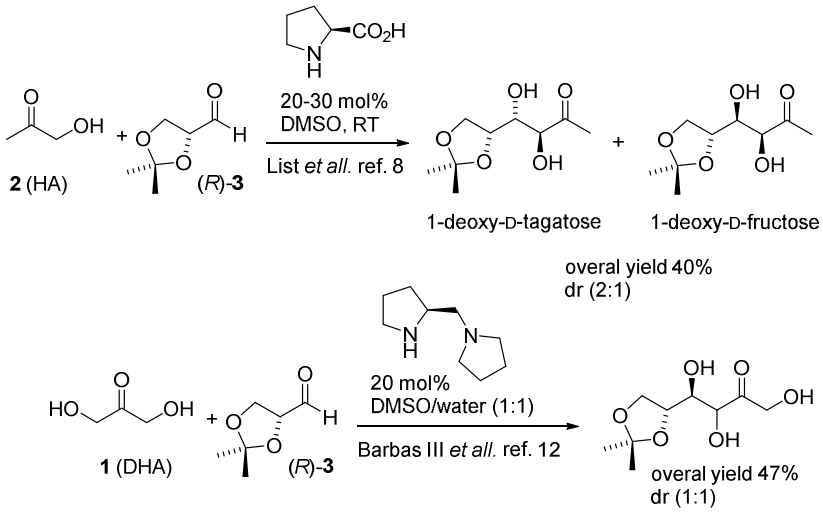
Different aldolases catalyzing the formation of each of those stereoisomers are commercially available and may be adopted to the straightforward synthesis of natural carbohydrates and their derivatives.[2] In this manner, synthesis of remaining diastereoisomeric sorbose and psicose molecules can be accomplished by using rhamnulose and fuculose aldolases, respectively (Scheme 2). All mentioned enzymes have a broad aldehyde specificity while the need for the application of dihydroxyacetone phosphate constitutes important limitation for their synthetic use. Only some aldolase antibodies are capable of using α-hydroxylated ketones such as hydroxyacetone as the donor.[3]

Although chemists developed DHAP-dependent aldolases into important tools for the asymmetric synthesis of carbohydrates, similar straightforward transformations promoted by small organic catalysts remained an elusive goal for a long time. In contrast to the simplicity of presented attempts, existing methodologies for the synthesis of carbohydrates typically need several synthetic steps and tedious protecting group manipulation.[4] Interestingly, versatile and simple C_3+C_3 strategy utilizing DHA donor although most favored by nature is still challenging for organic chemists. A promising strategy for the stereoselective application of hydroxy- and dihydroxyacetone is associated with the rapid development of organocatalytic methods.[5] In analogy to enzymes, organocatalysis allows for the direct catalytic aldol reaction of aldehydes and ketones without the use of preformed enolates.[6] This concept allows also for the organocatalytic synthesis of some carbohydrates but the state-of-the-art in this area is not well recognized especially for unprotected donors.[7]

In 2000 List and Notz described the first enamine-based enantioselective aldol addition of unprotected hydroxyacetone with several enolizable aliphatic aldehydes.[8] Authors demonstrated that protected (*R*)-glyceraldehyde reacted with unprotected hydroxyacetone under (*S*)-proline-promoted direct aldol reaction. D-Tagatose and D-fructose derivatives were isolated with moderate diastereoselectivities of only (2:1) and poor overall yield (40%, Scheme 3). Although unselective, the synthesis of the *anti*- and *syn*-1-deoxyhexoses provided an indication of the utility of these types of asymmetric aldol reactions as applied to carbohydrate synthesis. According to broadly accepted explanation, the *Si*-face of the hydroxyacetone enamine attacks the *Re*-face of the aldehyde to give the *anti*-product (1-deoxytagatose). The enamine double bond is presumed to possess a (*E*)-configuration and observed *anti*-stereoselectivity is consistent with chairlike transition state.[9] Further, enamine-based organocatalytic *anti*-[10] and *syn*-selective[11] direct aldol reaction of unprotected hydroxyacetone has been demonstrated for aromatic and nonchiral aliphatic aldehydes

whereas the diastereoselective reaction with optically pure glyceraldehyde remained neglected.

In 2002, Barbas *et all.* reported for the first time an organocatalyzed cross aldol reaction of unprotected DHA with acetonide of (*R*)-glyceraldehyde. The reaction was promoted by (*S*)-1-(2-pyrrolidinylmethyl)pyrrolidine in an aqueous phosphate buffer.[12] Authors observed unselective formation of all four possible stereoisomeric ketohexoses under physiological conditions by enamine catalysis. Further research also clearly demonstrated that unprotected DHA was not an useful substrate for the enamine-based aldol addition (Scheme 3).[13]



Scheme 3. Amine-catalyzed aldol reactions of unprotected hydroxy- and dihydroxyacetone.

In contrast, application of protected DHA molecules has been far more promising in the field of carbohydrate synthesis. The best results in the direct synthesis of ketohexoses was described when (*S*)-proline was used as a catalyst for the reaction of protected DHA derivatives such as 2,2-dimethyl-1,3-dioxan-5-one.[14] Since (*S*)- and (*R*)-proline catalysts provided versatile access to *anti*-1,2-diols,[13-15] they mimic tagatose and fuculose aldolases. The reaction proceeds through (*E*)-enamine leading to *anti*-selective aldols.

More recently, Luo *et al.* showed that *anti*-selective reaction of dioxanone with aromatic aldehydes can be promoted by chiral primary amines, thus confirmed that reaction stereoselectivity depends on (*E*)-configured enamine formed exclusively from cyclic ketone.[16] Parallel concept of application of primary amine-based organocatalysts to *syn*-selective aldol reaction of unprotected dihydroxyacetone was presented by Barbas and co-workers.[17] These *syn*-selective reactions of DHA with aromatic aldehydes were carried out in the presence of tryptophan or threonine derivatives in combination with methyltetrazole.

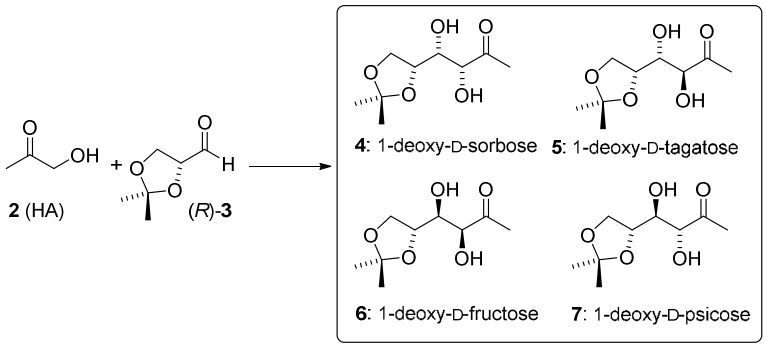
By using the same principles, Barbas and co-workers reported that primary amino acid derivatives could catalyze the *syn*-aldol reaction of protected DHA with optically pure glyceraldehyde. *O*-*tert*-Butyl-D-threonine controlled the aldol reaction of *tert*-butyldimethylsilyl (TBS)-protected dihydroxyacetone with (*R*)-glyceraldehyde to form protected D-fructose with high diastereoisomers ratio (98:2).[18] Similarly, *O*-*tert*-butyl-L-threonine-based amide can act as an efficient catalyst for the reaction of TBS-protected DHA with the acetonide of (*R*)-glyceraldehyde providing the protected D-sorbose derivative in 86% yield and (3:1) *syn/anti* ratio.[19] Applying water tolerant catalysts mimics L-rhamnulose and D-fructose aldolases, respectively.

Despite the fact that many authors claimed to solve the problem of biomimetic reaction of DHA, presented catalysts were active and selective for protected donors only. Although stereoselective synthesis of *syn*- and *anti*-aldols from DHA derivatives is well established, asymmetric reaction of unprotected donors needs further effort, especially for the synthesis of sugars. To address this problem and since divergent biomimetic access to all ketohexoses by using enamine organocatalysis and a C_3-dihydroxyacetone-based strategy from unprotected donor have been still not possible, we present here our effort toward resolving this fundamental synthetic problem.

This article presents first straightforward *de novo* synthesis of all 1-deoxyketohexoses of D- and L-series from hydroxyacetone and to date elusive *syn*-selective formation of ketohexoses from unprotected dihydroxyacetone. In addition to the synthetic value, presented organocatalysts truly mimic aldolases' stereoselectivity and mode of action by forming enamine intermediates in homogeneous aqueous solvents.

2. Results and Discussion

2.1. Reaction of hydroxyacetone (HA) promoted by primary and secondary amine-based organocatalysts. General lack in stereoselective synthesis of carbohydrates from unprotected donors inspired us for comprehensive research in this field. We initially studied the reaction of hydroxyacetone (**2**) and (*R*)-glyceraldehyde acetonide (**3**) as a possible general method for the *de novo* synthesis of 1-deoxyketohexoses. Unselective asymmetric aldol reaction of these substrates may result in the formation of four differently configured 1-deoxyketohexoses (**4**-**7**, Scheme 4). To control the reaction stereoselectively enamine should preferentially attack one of the aldehyde carbonyl group site. Moreover, enamine formation and its reaction with aldehyde should be faster than possible formation of the product under general base mechanism. To achieve high enantioselectivity of the aldol product, diastereoselective control of the C-C bond formation by chiral aldehyde should also be restrained.



Scheme 4. Four possible products of the reaction of hydroxyacetone and (*R*)-glyceraldehyde.

Following results described by List,[8] and to investigate application of both enantiomeric amino acids in various solvents, we started from re-examination of (*S*)-proline-controlled aldol reaction. Preferential formation of (*E*)-enamine between hydroxyacetone and proline molecule should result in selective formation of *anti*-aldol. Indeed, we confirmed observed reaction selectivity (Table 1, entry 1). Surprisingly, application of enantiomeric (*R*)-configured catalyst resulted in visible drop in reaction yield thus confirming additional influence of substrate stereochemistry and confirmed possible formation of matched/mismatched pairs (Table 1, entry 2).

Table 1. Direct aldol reaction of hydroxyacetone **2** with (*R*)-glyceraldehyde **3** promoted by secondary amine-based catalysts.

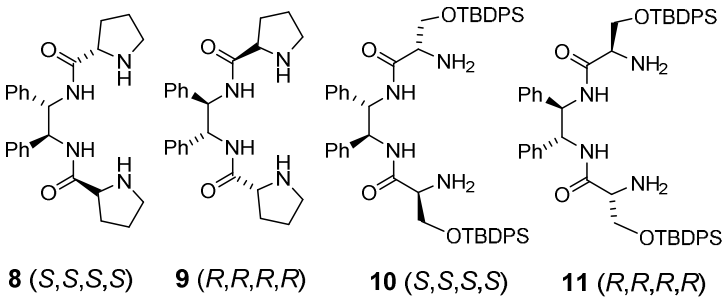
Entry	Catalyst[a]	Solvent	Yield [%][b]	*dr* (**4**:**6**)[c]
1	(*S*)-proline	DMF	39	2.5:1
2	(*R*)-proline	DMF	trace	-
3	(*S*)-proline	DMSO	30	2.5:1
4	(*S*)-proline	THF	45	2:1
5	(*S*)-proline	DMF/H_2O (9:1)	7	1:1
6	pyrrolidine	DMF/H_2O (9:1)	37	1:1
7	(*S*)-proline[d]	-	50	2:1
8	pyrrolidine[d]	-	60	1:7
9	(*S*)-serine	THF	8	2:1[e]
10	(*R*)-serine	THF	10	1:2[e]

[a]Reactions were performed with (*R*)-**3** (1 mmol), HA **2** (5 mmol), catalyst (20 mol-%) in appropriate solvent (2 mL) at RT for 24 h. [b]Total yield of both *syn*-stereoisomers. -[c]Determined by ^{1}H NMR and chiral HPLC analysis. [d]Reactions were performed with (*R*)-**3** (4 mmol), HA **2** (2 mmol), catalyst (20 mol-%) in neat at RT for 24 h. [e]dr Refers to *syn* products (**4**:**6**).

Next, we turned our attention to the reaction in aqueous solvents closely related to biomimetic concept. In fact, synthetically useful direct aldol reactions in aqueous media are rare and mostly limited to less demanding donors such as cyclohexanone or acetone.[20] According to our expectation direct aldol reaction of hydroxyacetone in wet DMF was less efficient and unselective when compared to the reaction in dry solvents (Table 1, entry 5). Proline was an extremely poor catalyst of the reaction, providing unselective formation of the aldols as expected. The addition of water to the mixture completely suppressed stereoselective addition of enamine to aldehyde, probably because of competitive hydrogen bond formation between carbonyl group of aldehyde and water instead of catalyst. Interestingly, reaction promoted by pyrrolidine catalyst resulted in better yield (Table 1, entry 6). Such better reactivity of pyrrolidine when compared to proline was previously observed in aqueous solvents.[12] Most intriguing was however, reaction promoted by pyrrolidine without any solvent (Table 1, entry 8). The reaction afforded *syn*-diol *i.e.* 1-deoxy-D-fructose (**6**) with high level of stereoselectivity (*syn*/*anti*, 7:1) clearly suggesting different reaction mechanism. We assumed that reaction selectivity resulted from hydroxyacetone enol formation which reacts with optically pure glyceraldehyde under Felkin-Anh model. Proposed reaction mechanism will be presented and discussed in the next paragraphs.

Learning from these studies, we attempted to the synthesis of carbohydrates. Based on our earlier success in the development of direct aldol reactions catalyzed by C_2-symmetrical bisamides in water,[21] we decided to apply this methodology to the elusive synthesis of ketohexoses. First, we decided to test previously developed organocatalytic mimics of the aldolases for *anti*- and *syn*-selective aldol reaction of hydroxyacetone with optically pure aldehyde. C_2-Symmetrical bisprolinamides (**8**, **9**) and lipophilic bissiloxyserinamides (**10**, **11**) readily available from (*S*,*S*)-, (*R*,*R*)-diphenylethylenediamine and amino acids have been used as enantioselective organocatalysts for direct aldol reaction of unprotected hydroxyacetone

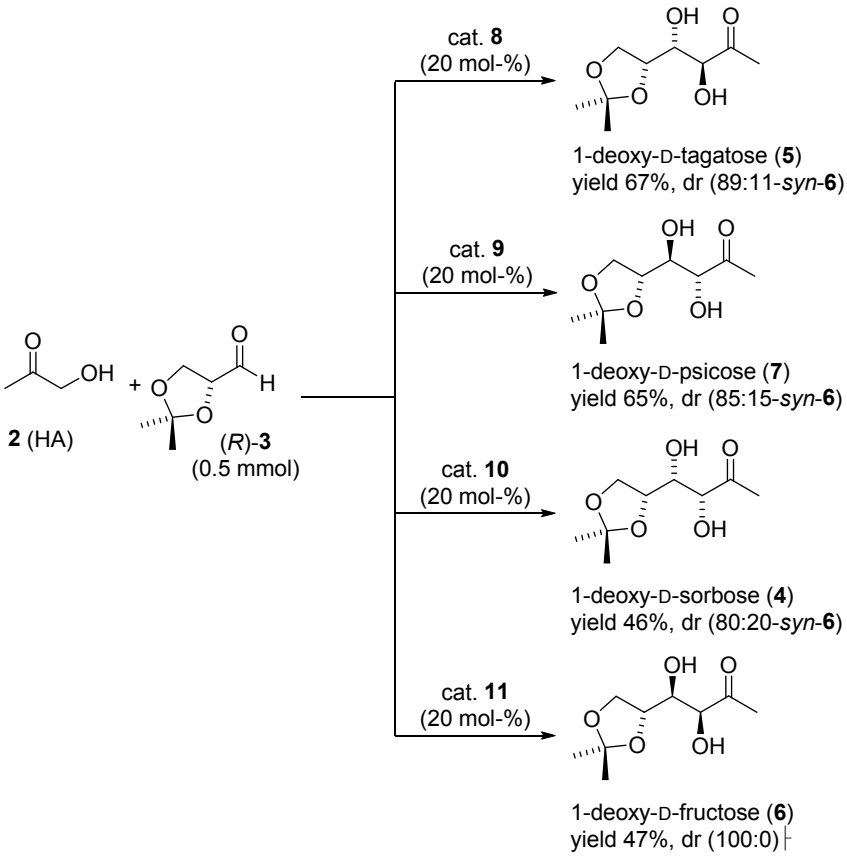
with non-chiral aldehydes. Now, we screened all four catalysts in the aldol reaction of hydroxyacetone with glyceraldehyde acetonide (**3**) (Scheme 5).



8 (*S*,*S*,*S*,*S*) **9** (*R*,*R*,*R*,*R*) **10** (*S*,*S*,*S*,*S*) **11** (*R*,*R*,*R*,*R*)

Scheme 5. Organocatalysts used in this study for biomimetic direct aldol reaction of hydroxy- (HA) and dihydroxyacetone (DHA).

Our original design for organocatalysts were both their application for the direct aldol reactions in water and expected reaction selectivity.[22] Thus we selected proline-based catalysts for the *anti*-aldol reaction based on the presumption that (*E*)-enamine formation controlled by the catalysts **8** and **9** will result in the formation of *anti*-aldols. In contrast, design of organocatalysts **10** and **11** for the *syn*-aldols was based on the intermediacy of a (*Z*)-enamine in the transition state. According to this concept, we studied direct aldol reaction of hydroxyacetone (**2**) with (*R*)-glyceraldehyde acetonide (**3**) catalyzed by enantiomeric amides containing secondary- (**8**, **9**) and primary amine functions (**10**, **11**, Scheme 6).[21] Catalysts design and unsuccessful application of simple amides as well as other derivatives of amino acids has been tested and discussed in our previous works.[21-23] In this paper, we present only successful application of the most reactive and stereoselective catalysts.



Scheme 6. Stereoselective synthesis of 1-deoxy-D-ketohexoses. Reactions were performed with (*R*)-**3** (0.5 mmol), catalyst (20 mol-%) in a mixture of THF/HA/water (1:9:1, 2 mL) at RT for 24 h.

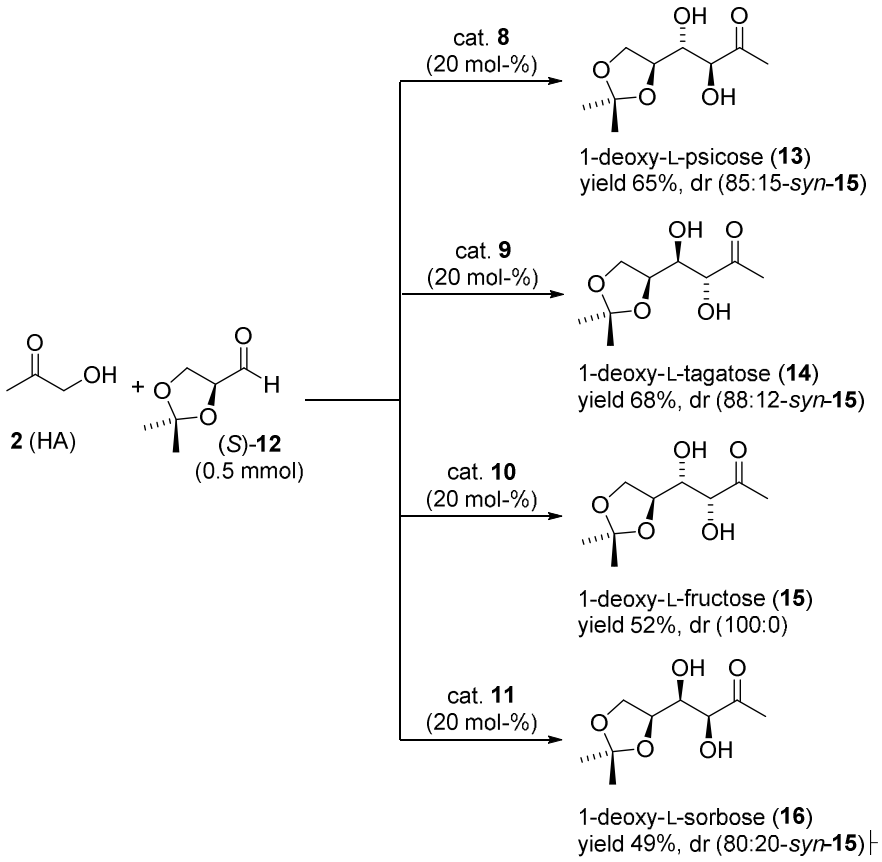
Using optimal conditions elaborated previously for the reaction of non-chiral aldehydes,[21] and performing reaction at RT, we explored the scope of the reaction in the synthesis of deoxyketoses. To our delight, each of four selected catalysts perfectly controlled stereoselective formation of expected sugar with a good yield. First experiments showed that the reaction controlled by catalyst **8** composed of (*S*,*S*)-diphenylethylenediamine and L-proline, resulted in a formation of protected 1-deoxy-D-tagtose (**5**) in a good yield and (89:11) *anti*-favored dr when 20 mol-% of organocatalyst was used (Scheme 6). Interestingly, enantiomeric proline-based catalyst **9** delivered protected 1-deoxy-D-psicose (**7**) in good yield and high stereoselectivity (85:15, Scheme 6). Thus, according to our expectation (*S*)-proline

controls enantioselective formation of (4*S*)-configured 3,4-*anti*-aldol while enantiomeric (*R*)-proline-based catalyst **9** delivered (4*R*)-configured 3,4-*anti*-aldol. Application of the matched catalyst and aldehyde acceptor was essential for the formation of expected sugars.

Based on the same principles, formation of the (4*S*)-configured 3,4-*syn*-aldol was observed for the catalyst **10** composed of L-serine. Catalyst **10** provided 1-deoxy-D-sorbose (**4**) with good chemical yield maintaining essentially the same diastereoselectivity (80:20) compared to proline-based catalysts. Finally, reaction controlled by catalyst **11** resulted in exclusive formation of 1-deoxy-D-fructose (**6**).

It is important to mention that we have not observed any racemisation of optically pure glyceraldehyde nor hexoses during the reaction, and high enantiomeric excess of all products have been confirmed by NMR experiments and chiral HPLC analysis. In fact, enantiomeric excess of the resulting hexoses simply reflects the *ee* of starting material. Presented experiments confirm that elaborated methodology provides a practical and direct route to deoxyketohexoses by using organocatalysts mimicking all four DHAP dependent aldolase enzymes (Scheme 2).

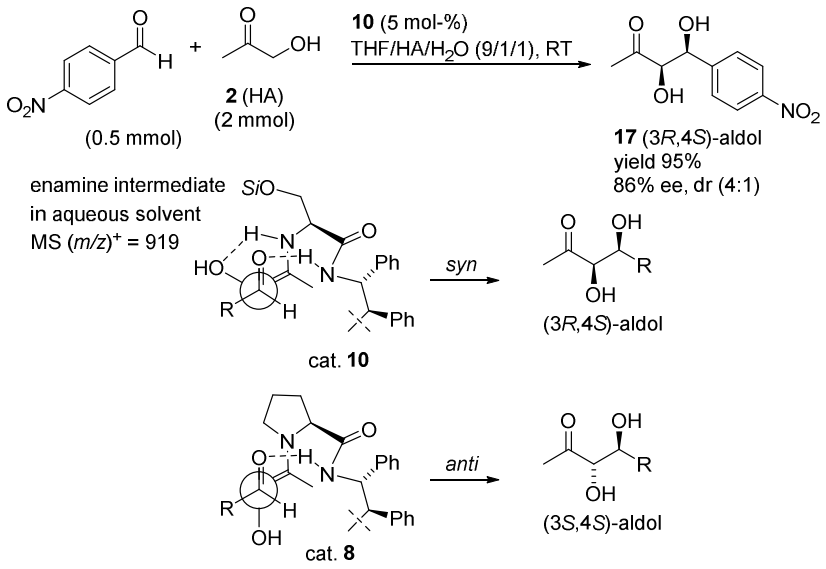
Encouraged by these results we decided to investigate possible synthesis of L-sugars by using developed methodology. This would be valuable achievement in the light of rare and tedious synthesis of this family of compounds.[24] To achieve this goal, the reaction of hydroxyacetone and (*S*)-glyceraldehyde precursor promoted by the same catalysts have been tested (Scheme 7).



Scheme 7. Stereoselective synthesis of 1-deoxy-L-ketohexoses. Reactions were performed with (*S*)-**12** (0.5 mmol), catalyst (20 mol-%) in a mixture of THF/HA/water (1:9:1, 2 mL) at RT for 24 h.

To our delight, the reactions proceeded smoothly and aldol products (**13**-**16**) were isolated in good yields and high diastereoselectivities. Presented amino-acid catalysis provides a new entry to a one-step *de novo* synthesis of 1-deoxy-L-psicose (65%), 1-deoxy-L-tagatose (68%), 1-deoxy-L-fructose (52%) and 1-deoxy-L-sorbose (49%). Application of (*S*)-configured aldehyde additionally confirmed that catalysts control enantioselective formation of *C*-4 stereogenic center with additional control of *syn*- or *anti*-configured aldols (Scheme 7). This observation finally proved that the reaction proceeds *via* enamine formation which, in turn may react preferentially with one site of the aldehyde molecule.

The stereochemistry of presented organocatalytic carbohydrate synthesis are in accordance with previously reported principles for proline- and serine based aldol reactions.[21] In the cross-aldol reaction, the *Si*-face of the (*Z*)-enamine intermediate formed from catalyst **10** and HA approaches the *Re*-face of the acceptor aldehyde furnishing the desired (3*R*,4*S*)-*syn*-aldol adduct as illustrated in Scheme 8. High reaction enantioselectivity observed for the reaction of 4-nitrobenzaldehyde (86% *ee*) confirmed that asymmetric induction is controlled by enamine-based organocatalyst **10**.

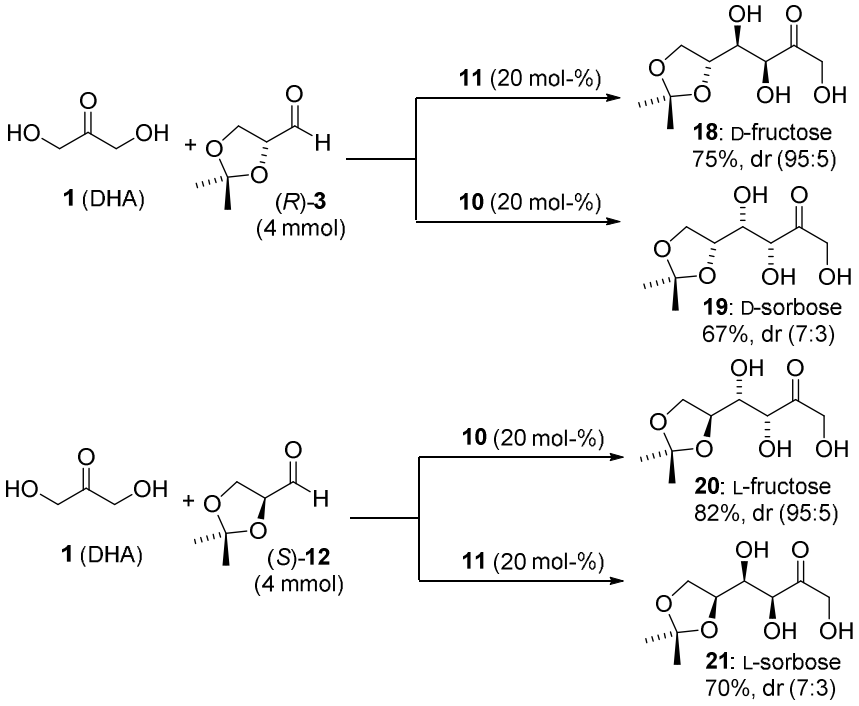


Scheme 8. Possible structures of transition states leading to *syn*- and *anti*-aldols.

Formation of an enamine in the reaction mixture was previously confirmed by high resolution MS spectra: signal at m/z 919 matches expected molecular weight. Isotopic pattern of this signal corresponds with calculated pattern of expected enamine structure.[25] Organocatalyst **10** can form hydrogen-bond-stabilized (*Z*)-enamine. In contrast, preferential formation of (*E*)-enamine between proline-based catalys **8** resulted in preferential formation of *anti*-aldols (Scheme 8).

2.2. Reaction of dihydroxyacetone (DHA) promoted by primary amine-based organocatalysts. In contrast to unexplored field of direct aldol reaction of hydroxyacetone its DHA variant has been well recognized although only for protected donors. Particularly successful development of diastereo- and enantioselective organocatalytic aldol reaction with 2,2-dimethyl-1,3-dioxan-5-one as a ketone equivalent was shown as practical tool for the synthesis of *anti*-configured carbohydrates mimicking tagatose and fuculose aldolases.[15] Among screened catalysts, enantiomeric prolines proved to be superior in the construction of various carbohydrate scaffolds. Less studied *syn*-selective direct aldol reaction of silyloxy-protected DHA provided a direct route to aldol products of the type synthesized with the DHAP aldolase enzymes L-rhamnulose 1-phosphate and D-fructose 1,6-diphosphate.[18,19]

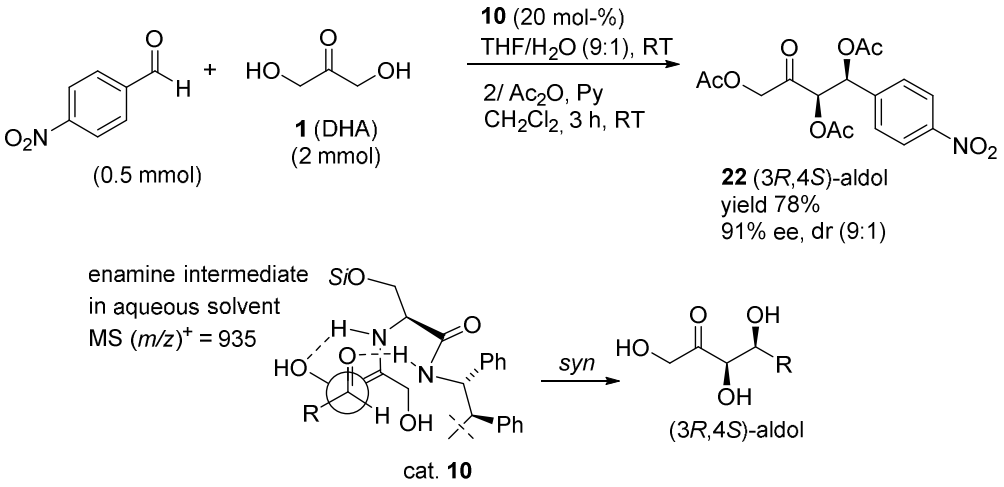
To scope the synthesis of ketohexoses from DHA by using direct C_3+C_3 protocol we tested the same catalysts containing serine motifs (**10**, **11**, Scheme 5).[23] In our efforts, we focused mostly on the *syn*-selective reaction as the *anti*-selective variant has been well explored by other authors. Initial tests for proline-based catalysts **8** and **9** demonstrated also their ineffectiveness, especially in terms of stereoselectivity. Having in hand efficient enantiomeric catalysts **10** and **11** we tested reaction of both enantiomeric glyceraldehyde acetonides (*R*)-**3** and (*S*)-**12** possibly giving short and elegant entries to D- and L-hexoses, respectively.[23] As indicated in Scheme 9 dihydroxyacetone and glyceraldehyde were suitable substrates when the reaction was conducted in wet DMF at ambient temperature. Application of dry DMF or increasing of amount of water in the solvent resulted in the decreasing reaction yield and stereoselectivity.



Scheme 9. Stereoselective synthesis of D- and L-ketohexoses. Reactions were performed with (*R*)-**3** or (*S*)-**12** (1 mmol), DHA (2 mmol of a dimer), catalyst (20 mol-%) in a mixture of DMF/water (9:1, 1 mL) at RT for 24 h.

In the case of optically pure (*R*)- and (*S*)-aldehyde application of appropriate D- or L-serine-based catalyst resulted in a clean and selective formation of expected aldols as a result of formation of a matched pair. In the case of (*R*)-glyceraldehyde, application of catalyst **11** resulted in a formation of D-fructose in high yield (75%) and dr (95:5). In contrast, catalyst **10** may be used for stereoselective formation of D-sorbose (**19**) with good diastereoisomers ratio (7:3). Interestingly, reactions performed in dry DMF were less efficient and delivered aldols in lower yield (ca. 20%). Starting from (*S*)-glyceraldehyde, protected L-fructose **20** was formed under **10**-promoted reaction with high yield (82%) and high stereoselectivity (95:5) while efficient synthesis of L-sorbose derivative **21** was achieved *via* the matched chiral pair between catalyst **11** and (*S*)-glyceraldehyde substrate (70%, Scheme 9).

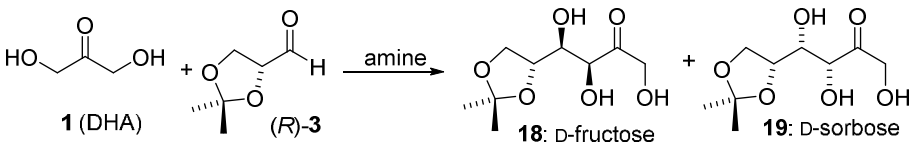
The plausible transition state for the elaborated *syn*-selective aldol reaction of unprotected DHA is based on the assumption that hydroxyacetone enamine attacks aldehyde enantioselectively. This mechanism was additionally confirmed *via* enantioselective direct aldol reaction of DHA to 4-nitrobenzaldehyde in an aqueous solvent (Scheme 9). An important feature for *syn*-selective transition state leading to (3*R*,4*S*)-aldol is the hydrogen bond supported (*Z*)-enamine formation presented in Scheme 10.



Scheme 10. Possible structure of transition state in *syn*-selective aldol reactions promoted by primary amine-based catalyst **10**.

2.3. Reaction of dihydroxyacetone (DHA) promoted by tertiary amines. Previously, we have shown that addition of hydroxy- and dihydroxyacetone to isopropylidene glyceraldehyde may result in controlled formation of aldol adducts under enamine-catalyzed aldol reaction. It was interesting, however, that reaction mixtures was contaminated by the same *syn*-aldol, in all cases. Formation of 1-deoxy-D-fructose (Scheme 6) or D-fructose (Scheme 9) was obviously an alternative reaction pathway leading to the same product despite of the catalyst used. To solve this interesting problem and venturing into reaction mechanism we investigated the reaction of dihydroxyacetone with and (*R*)-glyceraldehyde acetonide (**3**) promoted by various achiral amines (Scheme 11). All performed experiments confirmed

exclusive formation of *syn*-aldols suggesting one common mechanism for all kind of tested amines.



Scheme 11. *syn*-Selective aldol reaction of DHA promoted by tertiary amines.

Table 2 shows that reactions promoted by representative examples of tertiary (entries 1-3), secondary (entries 4-5) and even primary amines (entry 6) resulted in preferential formation of D-fructose from (*R*)-glyceraldehyde. Similar stereoselectivity favoring formation of natural fructose was observed for reactions carried out in wet DMF (entry 1). Previously, in Table 1 we also showed that application of pyrrolidine instead of proline for the reaction of hydroxyacetone in neat switched the reaction selectivity favoring formation of *syn*-aldol (Table 1, entries 7, 8). This tendency is also visible for dihydroxyacetone donor (Table 2, entry 4).

Table 2. Direct aldol reaction of dihydroxyacetone **1** with (*R*)-glyceraldehyde **3** promoted by tertiary amines.

Entry	Catalyst[a]	Solvent	Yield [%][b]	*dr* (**18**:**19**)[c]
1	DBU	DMF/H_2O (9:1)	46	80:20
2	DBU	$CHCl_3$	trace	-
3	triethylamine	DMF/H_2O (9:1)	30	75:25
4	pyrrolidine	DMF/H_2O (9:1)	26	75:25
5	piperidine	DMF/H_2O (9:1)	16	75:25
6	benzylamine	DMF/H_2O (9:1)	55	85:15
7	quinine	DMF/H_2O (9:1)	trace	-
8	quinine	$CHCl_3$	48	80:20

9	quinidine	$CHCl_3$	45	80:20
10	cinchonine	$CHCl_3$	46	75:25
11	cinchonidine	$CHCl_3$	54	75:25

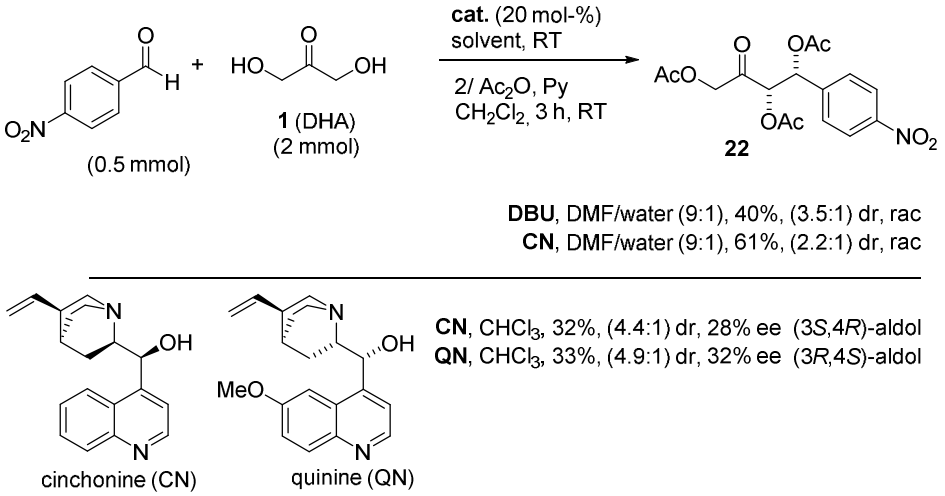
[a]Reactions were performed with (*R*)-**3** (0.5 mmol), DHA **1** (2 mmol as a dimer), catalyst (20 mol-%) in $CHCl_3$ (1 mL) at RT for 24 h or in DMF/water (9:1, 1mL) at RT for 72 h. [b]Total yield of *syn*-isomers. [c]Determined by ^{1}H NMR and chiral HPLC analysis.

Formation of *syn*-aldols from hydroxyketones is in full accordance with previously published results however it needs additional comments and should be seen as an important competitive reaction *en route* to enamine-controlled formation of aldols from hydroxyketones. Our predecessors observed also unexpected *syn*-selectivity in the reaction of unprotected HA[8] and DHA[12] controlled by proline-based catalysts (Scheme 3). Assuming that amine catalysts can simply act as a base, formation of enol from hydroxyketone may be an important threat to the stereoselective addition of expected enamine to aldehyde. Thus formation of protected D-fructose most likely goes through general base mechanism instead of enamine-controlled reaction. Especially in the case of (*S*)-1-(2-pyrrolidinylmethyl)-pyrrolidine used by Barbas, formation of fructose may have resulted from competitive enol formation promoted by secondary-primary amine catalyst (Scheme 3).[12]

However, the use of tertiary amines in the reaction requires clarification. In the mid twentieth century, Gutsche and co-workers demonstrated that in addition to hydroxide ion,[26] tertiary amines are an effective catalyst for unselective addition of glyceraldehyde and dihydroxyacetone.[27] In 2007, Mahrwald showed examples of tertiary-amine promote *syn*-selective aldol reactions.[28] According to authors, DBU-catalyzed aldol addition of DHA to **3** resulted in unselective formation of *syn*-aldols (fructose and sorbose). In contrast, reaction promoted by cinchonine resulted in extremely high stereoselectivity of the fructose formation. In our hand,[29] reaction promoted by either DBU (Table 2, entry 1) or *cinchona* alkaloids

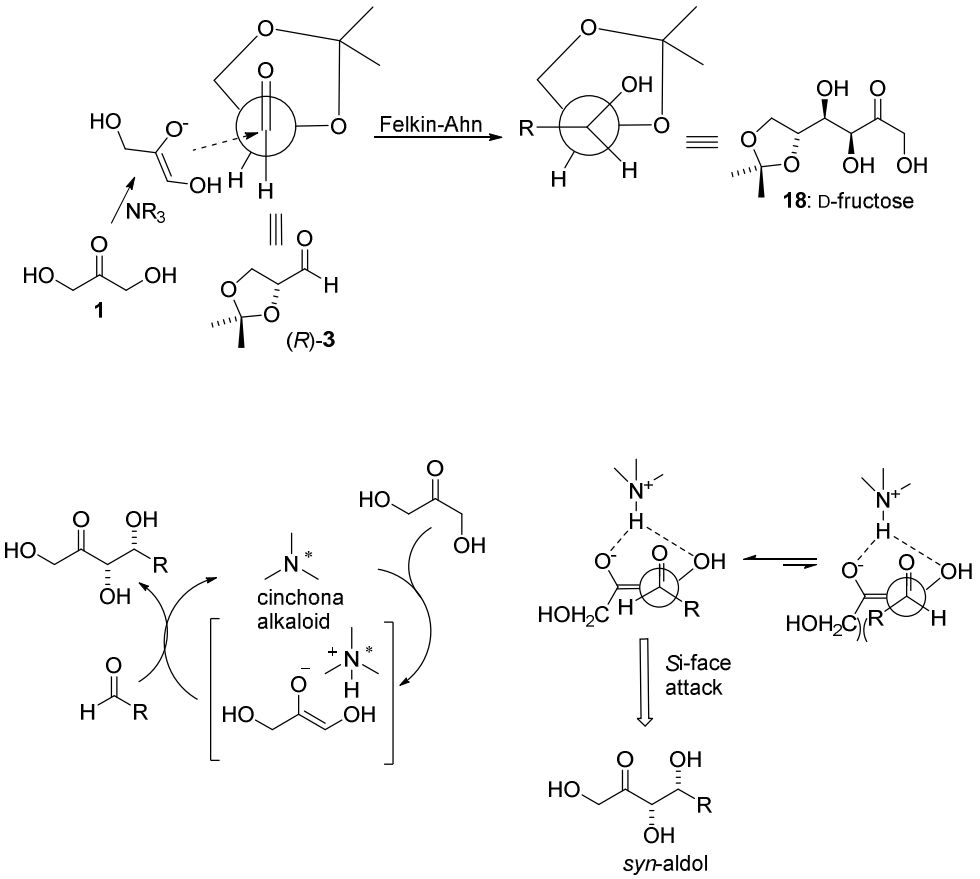
(Table 2, entries 7-11) resulted in the formation of fructose and sorbose with the same level of stereoselectivity (ca. 4:1) suggesting the same mechanism for both reactions.

Nevertheless, some level of enantioselectivity provided by *cinchona* alkaloids may also be considered by using alternative reaction mechanism. Previously, we discovered that unmodified *cinchona* alkaloids work effectively with hydroxyacetone[30] and aromatic hydroxyketones as highly *syn*-selective aldol catalysts providing aldols from non-chiral aldehydes with good enantioselectivities up to 60-70%.[31] To investigate possible enantioselective aldol reaction between DHA and non-chiral aldehydes we used 4-nitrobenzaldehyde as a case study (Scheme 12). Application of 20 mol-% of tertiary amines in wet DMF at RT resulted in preferential formation of *syn*-aldol **22** in good yields ranging 40% for DBU and 61% for cinchonine catalysts. Reaction yield for more reactive aromatic aldehyde was far better than in case of glyceraldehyde (Table 2, entry 7). However, application of cinchonine in aqueous solvent resulted in racemic aldol **22**. Further careful optimization revealed that reaction promoted by 20 mol-% of cinchonine in $CHCl_3$ at RT resulted in formation of aldol **22** in good *syn*-selectivity (4.4:1) and poor enantioselectivity (28% *ee*). Commenting on the correlation between structure of the catalyst and resulting aldol it should be noted that application of **CN** and 'local pseudoenantiomeric' **QN** delivers expected enantiomeric aldols (Scheme 12).



Scheme 12. *syn*-Selective aldol reaction of DHA with 4-nitrobenzaldehyde promoted by tertiary amines.

Taking into account all observations we postulate that the reaction promoted by tested tertiary amines proceeds more likely by enol formation and their subsequent stereoselective addition to optically pure aldehyde. Considering Felkin-Anh transition state oxygen at *C*-2 of aldehyde, being electronegative, will lie perpendicular to the carbonyl group in the most reactive conformer (Scheme 13). This reaction delivers D-fructose as a result of least hindered direction of attack of enolate on (*R*)-**3**. This explanation supports common formation of fructose under general base mechanism.



Scheme 13. Possible structures of transition states in the reaction promoted by tertiary amines (upper) and asymmetric aldol reaction promoted by *cinchona* alkaloids (lower).

While in all cases reaction of a ketone involves initial deprotonation by the amine catalyst the high *syn*-selectivity observed for *cinchona* alkaloids in aprotic solvents could be explained by (*Z*)-enol formation from the hydroxyketone which then attacks the *Si* face of the aldehyde. Reaction at the *Re* face of the aldehyde is more difficult due to the steric repulsion between the two larger substituents.[31]

Reaction of primary, secondary and tertiary amines could be explained in a similar way. The reaction of glyceraldehyde with inorganic bases in aqueous solution to yield fructose and sorbose has been quite well-studied[27] although it cannot be used for the sugar synthesis described above because of at least partial racemization of optically pure glyceraldehyde.

2.4. Determination of the structure of sugars. Confirmation of the structures of resulting sugars was not trivial and constitutes additional problem. Among all presented deoxyhexoses only structures of protected 1-deoxy-D-psicose and 1-deoxy-D-tagatose have been previously described in the literature but presented low resolution NMR (80 MHz) spectra were not useful for unambiguous determination of their complex structures.[32] Determination of the structures of protected fructose also required more attention especially in the light of difficult distinction of two diastereoisomeric *syn*-aldols formed in the reaction.[12] Simply deprotection and cyclisation resulted in a complex mixture of anomers existing in both furanose and pyranose forms. To conclude this subject and undoubtedly confirm absolute configuration of aldols we decided to use CD techniques allowing for insight into structures of unmodified sugars.

To determine the absolute configuration (AC) of aldols (diols) **4**-**7** and **18**-**21** the so-called *in situ* methodology of electronic circular dichroism spectroscopy (ECD) with dimolybdenum tetraacetate acting as auxiliary chromophore has been used.[33] Recently, this methodology has gained increasingly widespread application in solving stereochemical problems of transparent molecules. This can be evidenced by its escalated use for three-dimensional structure determination of 1,2-diols.[34] Certainly, the evidenced escalation of the *in situ* method is due to its simplicity consisting of nothing less than mixing a chiral ligand with an achiral auxiliary chromophore and recording the spectra. The exchange of ligand(s) results in transferring the chirality of ligand to the chiral complex, which is formed in solution. Application of the *in situ* method involves linking a positive/negative sign of the Cotton effects (CEs) occurring in the 300-400 nm spectral range in the spectra of resultant complexes with the positive/negative O-C-C-O torsion angle of the diol unit. This relationship, called the helicity rule, allows assignment of AC of *vic*-diols with confidence through this rule.[33,35]

In the current case, however, the *in situ* methodology had to be modified due to strongly overlapping carbonyl bands with the bands of resultant Mo_2-complexes at around 300 nm. Workaround the issue was made by subtracting from the complex spectrum of free ligand recorded under the same measurement conditions. The ECD data for diols **4**-**7** and **18**-**21** resulting after such treatment are collected in Table 3.

Table 3. Difference ECD data for the in-situ formed Mo_2-complexes of *vic*-diols **4**-**7** and **18**-**21**. Values are given as $\Delta\varepsilon'$(nm).*

	ECD $\Delta\varepsilon$ (λ_{max})						
comp.	band I	band II	band III	band IV	band V	A	B
4	+0.08 (280.0)	+0.96 (312.5)	-0.05 (353.5)	+0.22 (395.5)	-	+	+
5	+0.26 (276.0)	+[b]	-0.38 (344.5)	+0.19 (428.5)	-0.07 (542.5)	+/-	-
6	+1.06 (277.5)	-1.69 (312.0)	+[b]	-0.78 (371.0)	-	-	-
7	-0.08 (274.0)	+0.54 (312.0)	-[a]	+0.14 (378.5)	-0.06 (429.5)	+/-	+
18	+0.20 (277.5)	-[a]	+0.28 (315.0)	-0.82 (372.5)	+0.31 (459.0)	-	-
19	-0.46 (262.0)	+0.08 (308.0)	-[a]	+0.02 (355.5)	-0.13 (421.5)	+	+
20	-0.22 (277.0)	+[b]	-0.15 (319.0)	+0.63 (373.0)	-0.25 (453.5)	+	+
21	+0.09 (273.0)	-0.13 (307.0)	+0.19 (336.0)	-0.27 (382.0)	+0.13 (462.5)	-	-

A – predicted sign of the O–C–C–O torsion angle. B – sign of the O–C–C–O torsion angle from ECD; [a]Positive minimum. [b]Negative minimum. *Since the real complex structure as well as the concentration of the chiral complex formed in solution is not known the ECD data are presented as the artificial $\Delta\varepsilon'$ values which are calculated in the usual way as $\Delta\varepsilon' = \Delta A/c \times d$, where c is the molar concentration of the chiral ligand, assuming 100%complexation.

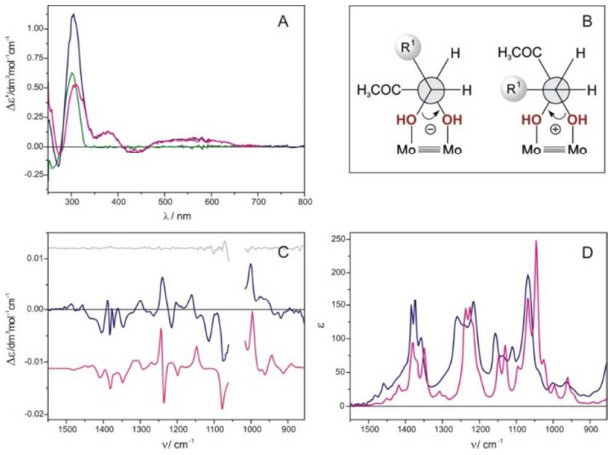
Based on the positive signs of CEs at ~320 and ~380 nm the (3*R*,4*R*) AC was assigned to diols **4**, **19**, and **20**. Again in accordance with helicity rule and negative signs of CEs in the same spectral region (3*S*,4*S*) AC was assigned to diols **6**, **18**, and **21**. Sets of ECD spectra for all diols are presented in the Supporting Information material.

A relatively more complex situation is observed for *erythro* diols **5** and **7**. In their case, there are two possible conformations of the diol unit after ligation to the Mo_2-core. This is because, in contrast to the threo diols, in *erythro* 1,2-diols two O-C-C-R groups cannot adopt an antiperiplanar conformation simultaneously. This leads to two possible arrangements of the diol unit characterized by opposite signs of decisive CEs for the same absolute configuration as shown in Scheme14, chart B. However, based on the previous statement,[36] that flexible *erythro vic*-diols fall also under the helicity rule and follow signs of crucial CEs in the spectra of their Mo_2-complexes the (3*S*,4*R*) and (3*R*,4*S*) AC was assigned to the diols **5** and **7**, respectively.

In an effort to corroborate the conclusions made on the basis of the in situ dimolybdenum method, the vibrational circular dichroism (VCD) spectra were performed. This was particularly important for *erythro* diols as calculated Gibbs free energy difference between conformers was relatively small. Thus, ECD spectroscopy alone is not sufficient for a reliable AC determination here and independent confirmation of the results significantly increases the confidence level of assignment.

The experimental and population weighted IR and VCD spectra for diol **7** are summarized in Scheme 14 charts C,D. As one can see, the overall agreement of the predicted and experimental spectra for this diol is excellent, and the confidence level of (3*R*,4*S*) AC assignment is equal 100% according to the CompareVOA™ program.[37] The VCD results for remaining diols collected in the Supporting Information section positively verify the absolute

configuration pre-assignment made by means of the in situ dimolybdenum method. Thus, one can conclude that the assignment of absolute configuration of diols under study was done in a reliable manner.



Scheme 14. A: ECD data of diol **7**: navy blue line – chiral Mo_2-complex, green line – free ligand, purple line – difference spectrum (complex spectrum minus free ligand spectrum); B: Two possible arrangements of the *erythro* 1,2-diol unit in the chiral complex formed after complexation with the Mo2-dimer; C: VCD data of diol **7**: navy blue line – experimental spectrum, purple line – population weighted spectrum for (3*R*,4*S*,5*R*)-isomer, gray line – noise; D: IR data of diol **7**: navy blue line – experimental spectrum, purple line – population weighted spectrum for (3*R*,4*S*,5*R*)-isomer.

3. Conclusion

In summary, we disclosed short and elegant *de novo* synthesis of deoxyketoses and ketoses by amino acid-catalyzed bond forming reactions with hydroxyacetone and dihydroxyacetone, respectively. Proline- and serine-based amides proved to be excellent catalysts in term of yield and stereoselectivity in the construction of various carbohydrates in aqueous solvents. Presented enamine-based C_3+C_3 methodology provided direct entry the synthesis of various

D- and L-ketohexoses. Its synthetic potential have been demonstrated in the direct biomimetic synthesis of a series of ketohexoses and deoxyketohexoses.

In this study (*S*)-proline-based catalyst act as an organocatalytic mimic of tagatose aldolase, whereas its (*R*)-configured enantiomer can be regarded as a mimic of fuculose aldolase. Application of enantiomeric serine-based organocatalysts delivered the product with the stereoselectivity similar to that controlled by rhamnulose and fructose aldolases in nature. These enamine-based *syn*- and *anti*-aldol additions represent a very easy and elegant approach to ketohexoses with good yields and high degree of stereoselectivity. Based on the elaborated methodology four deoxyketohexoses: D-deoxyfructose, D-deoxysorbose, D-deoxypsicose and D-deoxytagatose have been obtained from hydroxyacetone and (*R*)-glyceraldehyde in an asymmetric manner. The same set of catalysts allows for the formation of L-deoxyhexoses from hydroxyacetone and (*S*)-glyceraldehyde.

Furthermore, stereoselective addition of dihydroxyacetone to optically pure glyceraldehyde has been demonstrated to operate under primary-, secondary- and tertiary amine control. This reaction cannot be compared with the aldol addition catalyzed by amino acids with regards to the reaction mechanism although it results in a stereoselective formation of *syn*-configured D-fructose as a result of the Felkin-Anh mechanism. Enantioselective version of the reaction promoted by *cinchona* alkaloids seems to be also possible, and we believe that the procedure described above will influence the development of asymmetric synthesis and will lead to the discovery of more selective tertiary amine-based organocatalysts.

Structures of all ketohexoses have been unambiguously established by using CD spectroscopy. The results of combined *in situ* method and VCD spectra analysis of all aldols allowed one to assign three-dimensional molecular structure of all deoxyhexoses and hexoses with great certainty. Thus, the methodology consisting of concerted ECD and VCD

spectroscopy to solve structural and stereochemical problems has demonstrated its possibilities and excellent effectiveness in the case of this class of compounds, for the first time.

4. Experimental Section

General Information. All starting materials and reagents were obtained from commercial sources and used as received unless otherwise noted. All solvents used were freshly distilled prior to use. Optical rotations were measured at room temperature with a polarimeter. High-resolution mass spectra were acquired using electrospray ionization mode with a time-of-flight detector. Infrared (IR) spectra were recorded on a Fourier transform infrared (FT-IR) spectrometer as either a thin film on a NaCl plate (film) or as an KBr pellet (KBr). ^{1}H NMR spectra were recorded on spectrometers operating at 300, 400, 500 and 600 MHz in $CDCl_3$ or acetone-d_6. Data were reported as follows: chemical shifts in parts per million (ppm) from tetramethylsilane as an internal standard, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, dd = double-doublet, m = multiplet, br = broad), coupling constants (in Hz), and assignment. ^{13}C NMR spectra were measured at 75, 100, 125 or 150 MHz with complete proton decoupling. Chemical shifts were reported in ppm from the residual solvent as an internal standard. Reactions were controlled using TLC on silica [alu-plates (0.2 mm)]. Plates were visualized with UV light (254 nm) and by treatment with: ethanolic *p*-anisaldehyde with sulfuric and glacial acetic acid followed by heating, aqueous cerium(IV) sulfate solution with molybdic and sulfuric acid followed by heating or ethanolic ninhydrin solution followed by heating. All organic solutions were dried over anhydrous sodium sulfate. Reaction products were purified by flash chromatography using silica gel 60 (240-400 mesh). HPLC analysis were performed on HPLC system equipped with chiral stationary phase columns, detection at 254 nm.

(*R*)-Glyceraldehyde acetonide ((*R*)-**3**) was prepared from D-mannitol according to procedure found in the literature.[38] (*S*)-Glyceraldehyde acetonide ((*S*)-**12**) was prepared from L-ascorbic acid according to procedure found in the literature.[39]

Synthesis and spectroscopic data for organocatalysts **8**-**11** were described previously.[21,23,40]

General Methods for CD measurement and calculations. The ECD measurements of in situ formed chiral Mo_2-complexes of diols (1.2–3 mg of ligand, ca. 0.003 M) with stock complex $[Mo_2(O_2CCH_3)_4]$ (2.8-4 mg, ca. 0.002 M) were dissolved in DMSO (2.5-5 mL) so that the molar ratio of the stock complex to ligand was about (1.5:1), in general. The measurement parameters 0.5 nm/step with an integration time of 0.25 s over the range 245–800 nm with 200 nm/min scan speed. For difference spectra the ECD measurements of diols with concentration ca. 0.001 M were acquired at room temperature in DMSO (for UV-Spectroscopy) on a spectropolarimeters and were collected with the same parameters as for chiral complexes. UV–Vis spectra were measured in DMSO (for UV-Spectroscopy). The VCD and IR spectra of compounds **4**-**7** and **18**-**21** were measured by VCD spectrometer at a resolution of 4 cm^{-1} using CD_3CN. FT-VCD spectrometer was equipped with dual sources and dual PEM's technology. Solutions (0.25-0.39 M) were measured in a BaF_2 cell with a path length of 102 μm assembled in rotating holder (14 s/cycle) at room temperature. The ZnSe photo elastic modulator of the instrument was set to 1400 cm^{-1}. To improve the S/N ratio, the spectra were measured between 6 and 24 h. Baseline correction was achieved by subtracting the spectrum of a reference CD_3CN obtained under the same conditions.

Computational details. The conformational search was performed with ComputeVOA[41] using MMF94 force field within 5 kcal/mol energy ranges. The further optimization was carried out at DFT level using meta-hybrid B3LYP functional and the aug-cc-pVDZ basis set. The polarizable continuum model (PCM) implemented in the Gaussian09[42] was applied for

acetonitrile. VCD and IR calculations were carried out for the same level of theory, *i.e.* B3LYP/aug-cc-pVDZ/PCM(CH_3CN). The final spectrum was obtained by Boltzmann averaging (T=298 K) according to the population percentages of individual conformers based on the relative Gibbs energies calculated at the same level of theory.

Representative Procedure for Aldol Reaction of Hydroxyacetone (HA, Scheme 6).

Solution of freshly distilled glyceraldehyde acetonide **3** (65 mg, 0.5 mmol) in THF/hydroxyacetone/water (1:9:1, 2 mL) and catalyst (20 mol%) was stirred under room temperature for 24 h and then directly purified through flash column chromatography on a silica gel (toluene/EtOH, 20:1) to afford the pure aldols.

5,6-*O*-isopropylidene-1-deoxy-D-sorbose (4, Scheme 6).

38 mg (37%); ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.31 (dd, J = 12.4, 6.2 Hz, 1H), 4.11 (dd, J = 8.5, 6.5 Hz, 2H), 3.95 (d, J = 4.9 Hz, 1H), 3.88 (dd, J = 8.5, 6.2 Hz, 1H), 3.66 (d, J = 3.3 Hz, 1H), 2.54 (d, J = 6.9 Hz, 1H), 2.32 (s, 3H), 1.47 (s, 3H), 1.39 (s, 3H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 207.7, 110.2, 77.9, 77.4, 72.3, 66.2, 26.8, 26.0, 25.4; HRMS (ESI): exact mass calcd for $C_9H_{16}O_5Na$ *m/z* 227.0895 ($[M+Na]^+$), found *m/z* 227.0869 ($[M+Na]^+$); IR (neat): 3436, 2987, 2928, 1715, 1372, 1215, 1066, 852 cm^{-1}; $[\alpha]^{22}_D$ = –28.3 (*c* 0.91, $CHCl_3$).

5,6-*O*-isopropylidene-1-deoxy-L-sorbose (16, Scheme 7).

40 mg (39%); ^{1}H NMR (600 MHz, $CDCl_3$): δ 4.31 (q, J = 6.2 Hz, 1H), 4.11 (dd, J = 8.5, 6.5 Hz, 2H), 3.95 (td, J = 6.1, 2.2 Hz, 1H), 3.88 (dd, J = 8.5, 6.2 Hz, 1H), 3.67 (d, J = 4.5 Hz, 1H), 2.56 (d, J = 6.4 Hz, 1H), 2.31 (s, 3H), 1.47 (s, 3H), 1.39 (s, 3H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$): δ 207.7, 110.2, 77.9, 76.7, 72.3, 66.2, 26.8, 26.0, 25.4; HRMS (ESI): exact mass calcd for $C_9H_{16}O_5Na$ *m/z* 227.0895 ($[M+Na]^+$), found *m/z* 227.0881 ($[M+Na]^+$); IR (neat): 3437, 2987, 2930, 1715, 1371, 1215, 1065, 852 cm^{-1}; $[\alpha]^{22}_D$ = +27.1 (*c* 1.00, $CHCl_3$).

5,6-*O*-isopropylidene-1-deoxy-D-fructose (6, Scheme 6).

48 mg (47%); ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.41 (d, J = 1.5 Hz, 1H), 4.16-4.12 (m, 2H), 4.07 (dd, 1H), 3.90 (dd, J = 11.1, 4.8 Hz, 1H), 3.77 (d, J = 3.5 Hz, 1H), 2.34 (s, 1H), 2.29 (s, 3H), 1.46 (s, 3H), 1.37 (s, 3H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 208.1, 109.6, 76.9, 75.7, 72.5, 66.9, 27.1, 25.2, 25.2; HRMS (ESI): exact mass calcd for $C_9H_{16}O_5Na$ *m/z* 227.0895 ([M+Na]$^{+}$), found *m/z* 227.0876 ([M+Na]$^{+}$); IR (neat): 3436, 2988, 2934, 1717, 1372, 1216, 1067, 846 cm^{-1}; $[\alpha]^{22}_{D}$ = +73.4 (*c* 1.10, $CHCl_3$).

5,6-*O*-isopropylidene-1-deoxy-L-fructose (15, Scheme 7).

53 mg (52%); ^{1}H NMR (600 MHz, $CDCl_3$): δ 4.41 (s, 1H), 4.18–4.10 (m, 2H), 4.09–4.04 (m, 1H), 3.91 (d, J = 6.4 Hz, 1H), 3.79 (s, 1H), 2.42 (s, 1H), 2.29 (s, 3H), 1.46 (s, 3H), 1.37 (s, 3H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$): δ 208.1, 109.6, 76.9, 75.7, 72.5, 66.9, 27.1, 25.3, 25.2; HRMS (ESI): exact mass calcd for $C_9H_{16}O_5Na$ *m/z* 227.0895 ([M+Na]$^{+}$), found *m/z* 227.0888 ([M+Na]$^{+}$); IR (neat): 3437, 2988, 2931, 1717, 1371, 1216, 1066, 846 cm^{-1}; $[\alpha]^{22}_{D}$ = –76.3 (*c* 1.13, $CHCl_3$).

5,6-*O*-isopropylidene-1-deoxy-D-psicose (7, Scheme 6).[32]

56 mg (55%); ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.26 (t, J = 4.4 Hz, 1H), 4.17–4.08 (m, 2H), 4.03 (dd, J = 4.0, 1.4 Hz, 1H), 3.92–3.83 (m, 1H), 3.79 (d, J = 4.4 Hz, 1H), 2.57 (d, J = 7.6 Hz, 1H), 2.31 (s, 3H), 1.40 (s, 3H), 1.31 (s, 3H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 207.0, 109.9, 78.6, 74.5, 73.4, 66.8, 26.8, 26.5, 25.1; HRMS (ESI): exact mass calcd for $C_9H_{16}O_5Na$ *m/z* 227.0895 ([M+Na]$^{+}$), found *m/z* 227.0885 ([M+Na]$^{+}$); IR (neat): 3435, 2985, 2929, 1716, 1377, 1216, 1071, 849 cm^{-1}; $[\alpha]^{22}_{D}$ = –36.1 (*c* 1.00, $CHCl_3$).

5,6-*O*-isopropylidene-1-deoxy-L-psicose (13, Scheme 7).

56 mg (55%); ^{1}H NMR (600 MHz, $CDCl_3$): δ 4.27 (d, J = 4.4 Hz, 1H), 4.13 – 4.11 (m, 2H), 4.04–4.02 (m, 1H), 3.88 (dd, J = 6.5, 4.7 Hz, 1H), 2.31 (s, 3H), 1.40 (s, 3H), 1.31 (s, 3H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$): δ 207.0, 109.9, 78.6, 74.5, 73.4, 66.9, 26.7, 26.5, 25.0; HRMS (ESI): exact mass calcd for $C_9H_{16}O_5Na$ *m/z* 227.0895 ($[M+Na]^+$), found *m/z* 227.0871 ($[M+Na]^+$); IR (neat): 3436, 2985, 2932, 1716, 1376, 1216, 1070, 849 cm^{-1}; $[\alpha]^{22}_D$ = +34.0 (*c* 1.00, $CHCl_3$).

5,6-*O*-isopropylidene-1-deoxy-D-tagatose (5, Scheme 6).[32]

61 mg (60%); ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.36 (td, J = 6.6, 4.3 Hz, 1H), 4.10 (ddd, J = 8.6, 6.5, 2.9 Hz, 2H), 3.89 (dd, J = 8.6, 6.5 Hz, 1H), 3.54 (d, J = 6.3 Hz, 1H), 3.46 (ddd, J = 8.0, 6.6, 4.3 Hz, 1H), 2.75 (d, J = 6.6 Hz, 1H), 2.39 (s, 3H), 1.46 (s, 3H), 1.39 (s, 3H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 210.0, 109.6, 77.9, 76.2, 72.5, 66.5, 28.1, 26.5, 25.2; HRMS (ESI): exact mass calcd for $C_9H_{16}O_5Na$ *m/z* 227.0895 ($[M+Na]^+$), found *m/z* 227.0890 ($[M+Na]^+$); IR (neat): 3437, 2987, 2934, 1713, 1372, 1215, 1064, 854 cm^{-1}; $[\alpha]^{22}_D$ = +58.2 (*c* 1.10, $CHCl_3$).

5,6-isopropylidene-1-deoxy-L-tagatose (14, Scheme 7).

61 mg (60%); ^{1}H NMR (600 MHz, $CDCl_3$): δ 4.36 (td, J = 6.6, 4.3 Hz, 1H), 4.10 (dd, J = 8.6, 6.7 Hz, 2H), 3.89 (dd, J = 8.6, 6.5 Hz, 1H), 3.53 (d, J = 5.5 Hz, 1H), 3.48 – 3.43 (m, 1H), 2.74 (d, J = 6.0 Hz, 1H), 2.39 (s, 3H), 1.46 (s, 3H), 1.39 (s, 3H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$): δ 210.0, 109.6, 77.9, 76.2, 72.5, 66.5, 28.1, 26.6, 25.2; HRMS (ESI): exact mass calcd for $C_9H_{16}O_5Na$ *m/z* 227.0895 ($[M+Na]^+$), found *m/z* 227.0892 ($[M+Na]^+$); IR (neat): 3436, 2987, 2927, 1713, 1373, 1215, 1065, 854 cm^{-1}; $[\alpha]^{22}_D$ = –55.8 (*c* 0.98, $CHCl_3$).

Representative Procedure for Aldol Reaction of Dihydroxyacetone (DHA, Scheme 9).

To a solution of freshly distilled glyceraldehyde acetonide **3** (130 mg, 1 mmol) in DMF/H_2O (9:1, 1 mL), 1,3-dihydroxyacetone dimer (360 mg, 2 mmol; 4 mmol as a monomer) was added. After the substrates were dissolved organocatalyst (20 mol%) was added to the flask and reaction mixture was stirred at room temperature and monitored by TLC. After indicated time, the reaction was poured directly on silica gel column and eluted with toluene/EtOH (90:10) to yield desired aldol.

5,6-*O*-isopropylidene-D-fructose (18, Scheme 9).[12]

165 mg (75%); ^{1}H NMR (400 MHz, acetone-d_6): δ 4.57-4.48 (m, 2H), 4.45 (s, 1H), 4.43-4.35 (m, 1H), 4.17 (ddd, J = 8.3, 6.1, 5.1 Hz, 2H), 4.05 (dd, J = 8.5, 6.1 Hz, 1H), 3.96 (dd, J = 8.5, 5.1 Hz, 1H), 3.94-3.83 (m, 2H), 1.36 (s, 3H), 1.28 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, acetone-d_6): δ 213.1, 109.6, 76.5, 76.0, 73.9, 67.6, 67.5, 27.2, 25.6; HRMS (ESI): exact mass calcd for $C_9H_{16}O_6Na$ *m/z* 243.0845 ([M+Na]$^+$), found *m/z* 243.0845 ([M+Na]$^+$); IR (film, CH_2Cl_2): 3392, 2955, 2925, 2854, 1734, 1375 cm^{-1}; $[\alpha]^{22}_D$ = +14.6 (*c* 0.95, acetone).

5,6-*O*-isopropylidene-L-fructose (20, Scheme 9).

181 mg (82%); ^{1}H NMR (400 MHz, acetone-d_6): δ 4.56 – 4.48 (m, 2H), 4.45 (s, 1H), 4.43-4.34 (m, 1H), 4.17 (ddd, J = 8.3, 6.1, 5.1 Hz, 2H), 4.05 (dd, J = 8.5, 6.1 Hz, 1H), 3.96 (dd, J = 8.5, 5.1 Hz, 1H), 3.93-3.82 (m, 2H), 1.36 (s, 3H), 1.28 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, acetone-d_6): δ 213.1, 109.6, 76.5, 76.0, 73.9, 67.6, 67.5, 27.2, 25.6; HRMS (ESI): exact mass calcd for $C_9H_{16}O_6Na$ *m/z* 243.0845 ([M+Na]$^+$), found *m/z* 243.0843 ([M+Na]$^+$); IR (film, CH_2Cl_2): 3391, 2986, 2925, 2854, 1727, 1373 cm^{-1}; $[\alpha]^{24}_D$ = –16.0 (*c* 0.83, acetone).

5,6-*O*-isopropylidene-D-sorbose (19, Scheme 9).

148 mg (67%); ^{1}H NMR (400 MHz, acetone-d_6): δ 4.56-4.39 (m, 2H), 4.33-4.25 (m, 3H), 4.22-4.17 (m, 1H), 4.04 (dd, J = 8.2, 6.5 Hz, 1H), 3.96-3.91 (m, 1H), 3.85 (dd, J = 8.2, 7.0

Hz, 2H), 1.35 (s, 3H), 1.29 (s, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, acetone-d_6): δ 212.2, 109.8, 77.8, 77.3, 73.4, 67.5, 66.4, 26.8, 25.8; HRMS (ESI): exact mass calcd for $C_9H_{16}O_6Na$ *m/z* 243.0845 ($[M+Na]^+$), found *m/z* 243.0846 ($[M+Na]^+$); IR (film, CH_2Cl_2): 3390, 2986, 2923, 2852, 1727, 1373 cm^{-1}; $[\alpha]^{22}_D = -4.3$ (*c* 0.78, acetone).

5,6-*O*-isopropylidene-L-sorbose (21, Scheme 9).

154 mg (70%); ^{1}H NMR (400 MHz, acetone-d_6): δ 4.56-4.40 (m, 2H), 4.38-4.25 (m, 3H), 4.23-4.15 (m, 1H), 4.04 (dd, *J* = 8.2, 6.5 Hz, 1H), 3.98-3.91 (m, 1H), 3.85 (dd, *J* = 8.2, 7.0 Hz, 2H), 1.35 (s, 3H), 1.29 (s, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, acetone-d_6): δ 212.2, 109.8, 77.8, 77.3, 73.5, 67.5, 66.4, 26.8, 25.8; HRMS (ESI): exact mass calcd for $C_9H_{16}O_6Na$ *m/z* 243.0845 ($[M+Na]^+$), found *m/z* 243.0842 ($[M+Na]^+$); IR (film, CH_2Cl_2): 3392, 2986, 2925, 2854, 1727, 1373 cm^{-1}; $[\alpha]^{24}_D = +4.1$ (*c* 0.80, acetone).

Enantioselective Direct Aldol Reaction of 1,3-Dihydroxyacetone and 4-Nitrobenzaldehyde (Scheme 10).

To a vial containing bis(siloxyserinamide) **10** (86 mg, 0.1 mmol) in THF/H_2O (9:1) (1 mL) 4-nitrobenzaldehyde (75 mg, 0.5 mmol) and 1,3-dihydroxyacetone dimer (180 mg, 1 mmol; 2 mmol as a monomer) were added. Reaction was stirred at room temperature and monitored by TLC. The reaction mixture was poured directly on silica gel. The aldol product was purified by flash column chromatography (toluene/EtOH = 90/10) and submitted for acetylation.

Acetylation was achieved by dissolving the aldol product (0.35 mmol) in DCM (2 mL) and pyridine (142 µL, 138 mg, 1.75 mmol). Acetic anhydride (165 µL, 179 mg, 1.75 mmol) was added and the reaction was stirred at room temperature for 3 h. Reaction mixture was diluted with DCM and washed with water and brine. Organic phase was dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by flash column chromatography

(hexane/ethyl acetate, 70:30). Racemate of the aldol product was obtainted in the same manner using DMF/H_2O (9:1) as a solvent and DBU as a catalyst.

(3*R*,4*S*)-4-(4-nitrophenyl)-1,3,4-triacetoxy-butan-2-one (22).[17]

93 mg (78%); ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.22 (d, J = 8.7 Hz, 2H), 7.52 (d, J = 8.7 Hz, 2H), 6.33 (d, J = 3.4 Hz, 0.89H), 6.20 (d, J = 5.6 Hz, 0.11H), 5.53 (d, J = 3.4 Hz, 0.89H), 5.48 (d, J = 5.6 Hz, 0.11H), 4.98 (d, J = 17.4 Hz, 0.89H), 4.91 (d, J = 17.5 Hz, 0.11H), 4.74 (d, J = 17.5 Hz, 0.11H), 4.67 (d, J = 17.4 Hz, 0.89H), 2.17 (s, 3H), 2.17 (s, 3H), 2.07 (s, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 197.8, 169.9, 169.4, 169.3, 148.2, 142.6, 127.7, 124.0, 77.4, 73.0, 67.0, 20.7, 20.5, 20.4; HRMS (ESI): exact mass calcd for $C_{16}H_{17}NO_9Na$ *m/z* 390.0801 ($[M+Na]^+$), found *m/z* 390.0800 ($[M+Na]^+$); IR (film, $CHCl_3$): 1752, 1524, 1374, 1349, 1211 cm^{-1}; HPLC (Chiralpak OD-H, hexane/*i*-PrOH = 90:10, flow rate 1.0 mL/min, λ = 254 nm): t_R= 29.7 min (major *anti* enantiomer), t_R= 35.7 min (minor *anti* enantiomer), t_R= 47.3 min (minor *syn* enantiomer) and t_R= 58.4 min (major *syn* enantiomer).

Acknowledgements

This project was operated within the Foundation for Polish Science TEAM Programme co-financed by the EU European Regional Development Fund. Financial support from the Polish National Science Centre (grant number NCN 2011/03/B/ST5/03126) is gratefully acknowledged. This work was also supported by the Ministry of Science and Higher Education, grant No N N204 187439 and grant No. G34-15 for computational time at the Interdisciplinary Centre for Mathematical and Computational Modelling (ICM) of University of Warsaw, Poland and Wrocław Centre for Networking and Supercomputing (WCSS) of Technical University of Wrocław, Poland.

Associated Content

Supporting Information. Investigation of the absolute configuration (ECD and VCD spectra) and ^{1}H and ^{13}C NMR spectra of all aldol products **4-7**, **13-16** and **18-21**, ESI-MS spectra of ketones with catalyst **10**. This material is available free of charge via the Internet at http://pubs.acs.org.

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