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Amino acid catalyzed direct enantioselective formation of carbohydrates: one-step de novo synthesis of ketoses

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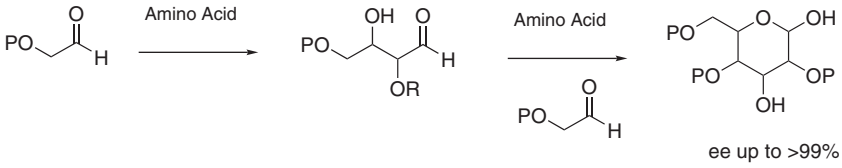
Abstract—The amino acid-catalyzed direct enantioselective one-step de novo synthesis of carbohydrates using dihydroxyacetone phosphate mimetics as donors and aldehydes or in situ generated imines as acceptors is presented. The addition of water significantly accelerates as well as improves the enantioselectivity of the biomimetic aldol and Mannich reactions. The C_3+C_n methodology presented herein is a direct entry to orthogonally protected C-5 and C-6 ketoses (e.g., ribulose, tagatose and piscose) and deoxy- and aminosugars such as 4-amino-4-deoxy-fructose.

Carbohydrates are a class of life essential natural products. They are involved in several metabolic and catabolic processes as well as in cell recognition.[1,2] In Nature, carbohydrates are assembled via enzyme-catalyzed aldol reactions with excellent stereoselectivity.[1a,3] Most aldolase enzymes utilize dihydroxyacetone phosphate (DHAP) as the donor to furnish keto-sugars. For example, fructose 1,6-di-phosphate aldolase catalyzes the reversible aldol transformation between DHAP and glyceraldehyde-3-phosphate that furnishes fructose 1,6-di-phosphate.[1a,3] The high selectivity of aldolase enzymes has made them useful as biocatalysts for the synthesis of carbohydrates and polyhydroxylated natural products.[3,4] However, the aldolase enzymes exhibit poor activities in organic solvents. Inspired by the efficiency and high stereoselectivity of Nature's enzymes, small molecules have been employed as catalysts for enantioselective C–C bond-forming reactions in organic solvents.[3b,5] Chemists have also developed a plethora of methods for the de novo synthesis of carbohydrates.[6] Recently, amino acid catalysis has been used for the synthesis of carbohydrates.[7,8] In particular, the amino acid catalyzed formation of aldoses has been achieved with high selectivity.[9] In this context, we recently synthesized C-6 aldoses with excellent enantioselectivity by one- or two-step amino acid catalyzed cross-aldol reactions (Eq. 1).[9c–e]



(1)

However, the amine mediated cross-aldol reaction between di-hydroxy acetone and aldehydes in aqueous media furnished the corresponding ketoses and polyhydroxylated compounds with low enantioselectivities (Eq. 2).[8c]

Protected dihydroxyacetone derivatives have been employed as synthetic equivalents of 1,3-dihydroxy acetone in the synthesis of carbohydrate derivatives and polyhydroxylated compounds.[6h–l,10] Protected dihydroxyacetone derivatives have the advantages of

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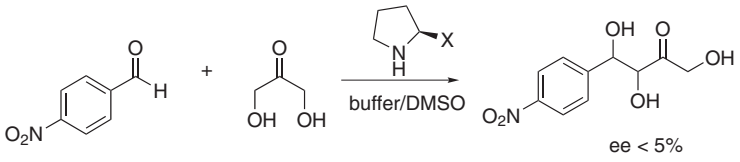
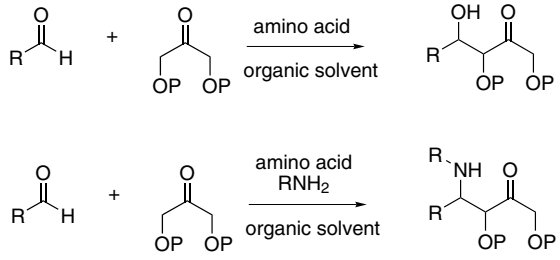


(2)

circumventing dimerization unlike 1,3-dihydroxyacetone, and are soluble in organic solvents.

Based on this research, retrosynthetic analyses and our interest in amino acid catalysis,[11] we envisioned a one-step carbohydrate derivative synthesis via amino acid mediated cross-aldol reactions or Mannich reactions with protected dihydroxy acetone derivatives as nucleophiles (Eq. 3).



(3)

Herein, we present a water accelerated, highly enantioselective, one-step amino acid-catalyzed carbohydrate synthesis. The biomimetic $C_3 + C_n$ methodology presented herein is a direct route to orthogonally protected ketosugars.

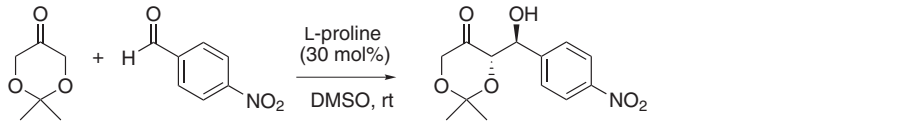
In an initial experiment, *p*-nitrobenzaldehyde and 1,3-dioxan-5-one **1** were stirred vigorously in the presence of a catalytic amount of L-proline in DMSO (Scheme 1). The reaction was quenched after 7 days and the desired β-hydroxy ketone **2a** was isolated in 58% yield an a 12:1 (*anti*:*syn*) dr and 73% ee.[12] Based on the lengthy reaction time, we decided to investigate whether addition of a small amount of water would increase catalyst turnover and as a consequence decrease the reaction time.[13] To our delight, we found that addition of water (5 equiv) to the reaction mixture significantly accelerated the reaction (Scheme 1).[14] The reaction was quenched after 24 h and the corresponding aldol adduct **2a** was isolated in 72% yield in an 18:1 dr and 93% ee. Interestingly, addition of water (5 equiv) also significantly improved the enantioselectivity of the reaction.

Encouraged by this result we decided to utilize ketone **1** as the donor for the amino acid-catalyzed one-step synthesis of carbohydrate derivatives (Table 1).[15]

The reactions proceeded smoothly furnishing the corresponding carbohydrate derivatives **2** with excellent chemo-, diastereo- and enantioselectivity. For example, protected ribulose **2c** was synthesized in 85% yield with >19:1 dr and 98% ee (entry 3).[16] Furthermore, the L-proline catalyzed diastereoselective cross-aldol reaction between **1** and protected D-glyceraldehyde furnished the corresponding D-tagatose[2d] in 74% yield with >19:1 dr and ⩾98% ee (entry 4).[17] In addition, D-proline catalysis furnished D-piscose[2e] in 68% yield with >19:1 dr and ⩾98% ee (entry 5). Hence, amino acid catalysis provides a new entry for the one-step synthesis of C_3+C_n sugars with excellent stereoselectivity.

Next, we investigated the direct proline-catalyzed one-pot three-component enantioselective Mannich reaction with **1** as the nucleophile for the one-step de novo synthesis of aminosugars (Scheme 2).[18,19]

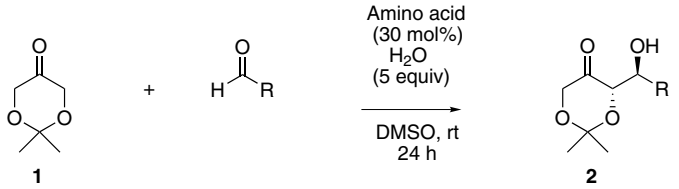
The reactions were performed under the same reaction conditions as the amino acid-catalyzed aldol additions. Consequently, the donor **1** (1 mmol), *p*-anisidine (0.6 mmol), water (2.5 mmol) and acceptor aldehyde (0.5 mmol) in the presence of a catalytic amount of proline (30 mol %) were stirred for 24 h. The reactions were quenched by simple aqueous workup and the corresponding protected aminosugars **3a**–**c** were isolated in good yield with excellent chemo- and enantioselectivity. The addition of water (5 equiv) was of great importance. For example, the L-proline catalyzed reactions between **1**, *p*-anisidine and α-benzyloxyacetaldehyde without addition of water furnished trace amounts of the corresponding *p*-methoxyphenyl (PMP) protected aminosugar **3b**. In contrast, addition of 5 equiv of water to the reaction mixture significantly accelerated the reaction and protected 4-amino-4-deoxy-*threo*-pentulose **3b** was isolated in 70% yield in a 6:1 dr (*syn*:*anti*) and 98% ee.[20] Moreover, the D-proline catalyzed one-pot, three-component, Mannich reaction between dioxanone **1**, *p*-anisidine and D-isopropylideneglyceraldehyde proceeded with high chemo- and diastereo-selectivity and



2a: 58% yield, 12:1 dr, 73 %ee (7 days, no water)
2a: 72% yield, 18:1 dr, 93 %ee (24 h, 5 equiv. H_2O)

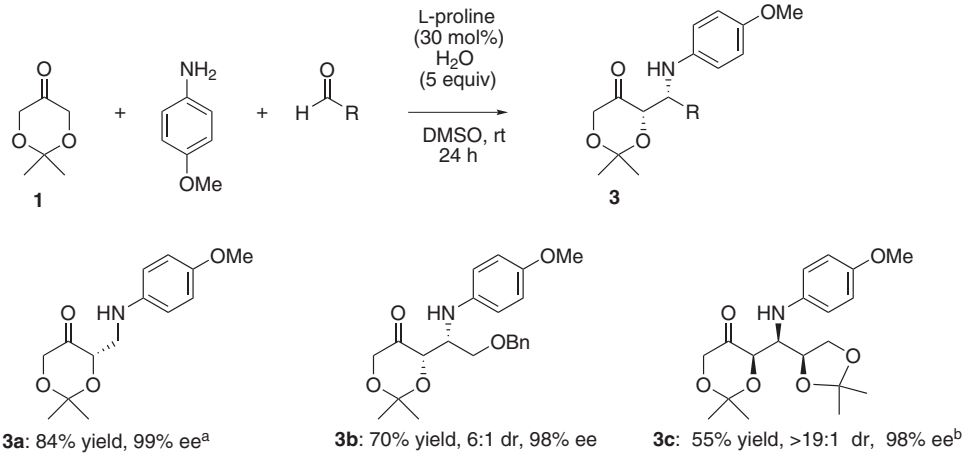
Scheme 1. Proline-catalyzed asymmetric synthesis of **2a**.

Table 1. Direct amino acid-catalyzed synthesis of deoxy- and keto-sugars **2**



Entry	Amino acid	R	Prod.	Yield (%)[a]	dr[b]	ee (%)[c]
1	L-proline	4-NO_2–C_6H_4	**2a**	72	18:1	93
2	L-proline	C_6H_5	**2b**	80	1:1	97
3	L-proline	$BnOCH_2$	**2c**	85	>19:1	98
4	L-proline		**2d**	74	>19:1	⩾98[d]
5	D-proline		**2e**	68	>19:1	⩾98[d]

[a] Isolated yield of the pure products after silica gel chromatography.
[b] dr = *syn*/*anti* Ratio of the products as determined by NMR.
[c] Determined by chiral-phase HPLC analysis. Bn = benzyl.
[d] Based on the ee value of the starting protected D-glyceraldehyde and chiral shift reagents.



Scheme 2. Direct amino acid-catalyzed asymmetric one-step de novo synthesis of protected amino sugars. Reagents and conditions: (a) Purified with neutral aluminium oxide as the stationary phase.[18g] (b) Reaction performed with D-proline.

yielded the corresponding protected 4-amino-4-deoxy-D-fructose **3c** in 55% yield in >19:1 dr and ⩾98% ee.[21]

The stereochemistry of the amino acid-catalyzed one-step carbohydrate derivative synthesis were in accordance with previously reported proline-catalyzed cross-aldol and Mannich reactions.[7–9,18,22] Thus, in the cross-aldol reactions, the *si*-face of the enamine intermediate between **1** and L-proline approaches the *re*-face of the acceptor aldehyde via transition state **I** to furnish the desired *anti*-aldol adducts (Fig. 1a). In contrast, the *si*-face of the enamine intermediate between **1** and L-proline approaches the *si*-face of the acceptor imine to furnish the corresponding desired *syn*-Mannich adducts (Fig. 1b).

The switch of facial selectivity of the attack on the electrophile in the Mannich transition state **II** as compared to the aldol transition state **I** was originally observed by List and is due to the steric-repulsion between proline and the PMP group, which would occur if a *re*-facial

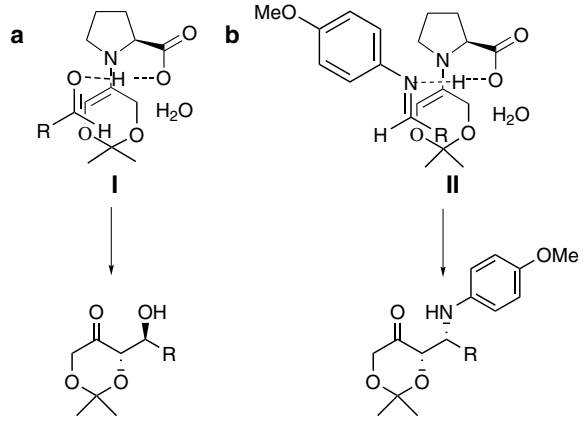


Figure 1. (a) The suggested transition state **I** of the aldol reaction with **1** as the donor. (b) The plausible transition state **II** of the Mannich reaction with **1** as the donor.

attack on the imine took place.[18a] We believe the beneficial effect of water in the amino acid catalyzed synthesis of ketosugars is due to improved catalyst turnover via faster hydrolysis of intermediates of the enamine catalytic cycle as well as suppression of catalyst inhibition.[14a,b,23] Furthermore, a small excess of water will potentially facilitate proton transfer in the transition state, which both lowers the LUMO of the incoming electrophile as well as directs the enantioselectivity of the newly formed stereocentres. Thus, the higher Brønsted acidity of the amino acid when water is added to the polar aprotic organic solvent plausibly accounts for the observed higher stereoselectivity of the water accelerated carbohydrate synthesis.

In summary, the direct amino acid-catalyzed one-step enantioselective de novo synthesis of protected carbohydrate derivatives is presented. The proline-catalyzed direct aldol and Mannich reactions between protected dihydroxyacetone **1** and different acceptor aldehydes or in situ generated imines furnished the corresponding orthogonal protected sugars and amino sugars, respectively, in one step. Moreover, the carbohydrate derivatives were isolated in high yields with excellent chemo-, diastereo- and enantioselectivity. Addition of water significantly accelerates as well as improves the enantioselectivity of the reactions. For example, the reaction times decreased from 6–7 days to 24 h. The C_3+C_n methodology presented herein is a direct entry to orthogonally protected C-4, C-5 and C-6 ketoses in one chemical manipulation. Furthermore, the methodology provides a direct, highly enantioselective entry for the catalytic synthesis of deoxy- and aminosugars. This was exemplified by the one-step de novo syntheses of orthogonally protected ribulose, tagatose, piscose, 4-amino-4-deoxy-*threo*-pentulose and 4-amino-4-deoxy-fructose.

Acknowledgements

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15. In a typical experiment, the aldehyde (0.5 mmol) was added to a round-bottomed flask charged with proline (30 mol %) and 2 mL DMSO. Next, the ketone **1** (1 mmol) and water (2.5 mmol) were added to the flask and the reaction was vigorously stirred for 24 h at room temperature. The reaction was quenched by addition of brine followed by extraction with EtOAc. The aqueous-phase was back-extracted with EtOAc (3×15 mL). The combined organic layers were dried over anhydrous $NaSO_4$, filtered and concentrated. The pure protected sugars **2** were obtained by silica gel column chromatography (toluene/EtOAc mixtures).
16. (−)-5-Benzyl-*O*-1,3-*O*-isopropylidine-L-ribulose **2c**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.45 (s, 3H), 1.48 (s, 3H), 3.16 (d, J = 4.2 Hz, 1H), 3.70–3.67 (m, 2H), 4.03 (d, J = 17.2 Hz, 1H), 4.21 (m, 1H), 4.27 (d, J = 17.2 Hz, 1H), 4.45 (d, J = 6.2 Hz, 1H), 4.56–4.63 (m, 2H), 7.27–7.37 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 23.5, 24.2, 66.9, 69.9, 70.2, 73.7, 74.04, 101.1, 127.9, 128.5, 129.2, 138.1, 210.0; $[\alpha]_D^{23}$ −129.7 (*c* 3.3, $CHCl_3$) [Literature: $[\alpha]_D^{25}$ −106.7 (*c* 1.0, $CHCl_3$)][3i]; HPLC (Daicel Chiralpak AD, hexanes/*i*-PrOH = 96:4, flow rate 0.5 mL/min, λ = 254 nm): major isomer: t_R = 46.02 min; minor isomer: t_R = 40.73 min; MALDI-TOF MS: 303.1211; $C_{15}H_{20}O_5$ ($M+Na^+$: calcd 303.1208).
17. (−)-1,3:5,6-Di-*O*-isopropylidene-D-tagatose **2d**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.07 (s, 3H), 1.24 (s, 3H), 1.45 (s, 3H), 1.47 (s, 3H), 3.17 (d, J = 3.5 Hz, 1H), 3.82–3.91 (m, 2H), 3.98–4.10 (m, 2H), 4.25–4.32 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 23.5, 23.6, 25.6, 26.3, 65.6, 66.7, 70.1, 73.4, 75.2, 101.3, 109.1, 210.4; $[\alpha]_D^{23}$ −166.1 (*c* 0.9, $CHCl_3$) [Literature: $[\alpha]_D^{25}$ −167.2 (*c* 1.1, $CHCl_3$)];[3f] MALDI-TOF MS: 283.277; $C_{12}H_{20}O_6$ ($M+Na^+$: calcd 283.2734).
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19. In a typical experiment, the aldehyde (0.5 mmol) and *p*-anisidine (1.65 mmol) were added to a round-bottomed flask charged with proline (30 mol %) and 2 mL DMSO. The reaction was stirred for 30–40 min at room temperature. Next, the ketone **1** (1 mmol) and water (2.5 mmol) were added to the flask and the reaction was vigorously stirred for 24 h. The reaction was quenched by addition of brine followed by extraction with EtOAc. The aqueous-phase was back-extracted with EtOAc (3×15 mL). The combined organic layers were dried with anhydrous $NaSO_4$, filtered and concentrated. The pure protected sugars **3** were obtained by silica gel column chromatography (toluene/EtOAc mixtures).
20. Protected 4-amino-4-deoxy-*threo*-pentulose **3b**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.45 (s, 3H), 1.50 (s, 3H), 3.49–3.54 (m, 1H), 3.59–3.64 (m, 2H), 3.74 (s, 3H), 3.98 (d, J = 16.4 Hz, 1H), 4.22 (dd, J = 16.4, 1.8 Hz, 1H), 4.46–4.59 (m, 2H), 4.63 (m, 1H), 6.64 (d, J = 8.9 Hz, 2H), 6.76 (d, J = 8.9 Hz, 2H), 7.33 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 23.4, 25.0, 54.1, 55.9, 67.5, 68.0, 73.4, 74.4, 100.6, 115.1, 115.8, 127.7, 127.9, 128.6, 138.2, 140.8, 152.9, 208.3; $[\alpha]_D^{23}$ +40.9 (*c* 4.5, $CHCl_3$); HPLC (Daicel Chiralpak AD, hexanes/*i*-PrOH = 98:2, flow rate 0.5 mL/min, λ = 254 nm): major isomer: t_R = 23.11 min; minor isomer: t_R = 33.51 min; MALDI-TOF MS: 408.1788; $C_{22}H_{27}NO_5$ ($M+Na^+$: calcd 408.1787).
21. Protected 4-amino-4-deoxy-fructose **3c**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.31 (s, 3H), 1.41 (s, 3H), 1.46 (s, 3H), 1.47 (s, 3H), 3.70 (s, 3H), 3.97–3.92 (m, 2H), 4.02 (m, 1H), 4.08 (m, 1H), 4.22 (d, J = 17.2 Hz, 1H), 4.42–4.46 (8m, 1H), 4.52 (m, 1H), 6.64 (d, J = 8.9 Hz, 2H), 6.73 (d, J = 8.9 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 23.4, 24.9, 25.0, 26.5, 54.9, 55.7, 65.6, 67.3, 73.9, 74.6, 100.6, 109.3, 114.9, 115.7, 140.7, 152.7, 207.8; $[\alpha]_D^{23}$ −18.7 (*c* 3.0, $CHCl_3$); MALDI-TOF MS: 388.177; $C_{19}H_{27}NO_6$ ($M+Na^+$: calcd 388.1736).
22. (a) Córdova, A. *Acc. Chem. Res.* **2004**, *37*, 102; (b) Bahmanyar, S.; Houk, K. N. *Org. Lett.* **2003**, *5*, 1249, and references cited therein.
23. List, B.; Hoang, L.; Martin, H. J. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5839.