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Amino acid-catalyzed dynamic kinetic asymmetric transformations (DYKAT): one-step de novo synthesis of polyketide sugars from racemic β-hydroxy aldehydes

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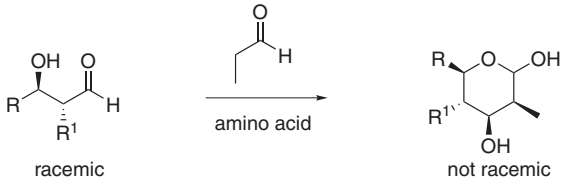
Abstract—The ability of amino acids to catalyze dynamic kinetic asymmetric transformation (DYKAT) with excellent stereoselectivity is presented. The novel DYKAT process was applied in the proline-catalyzed one-step de novo synthesis of triketide- and deoxysugars, which were formed with excellent diastereoselectivity and up to 99% ee. The de novo synthesis is accomplished via an enzyme-like DYKAT process, which includes continuous amino acid-mediated racemization of the acceptor β-hydroxy aldehyde in combination with amino acid-catalyzed direct selective aldol addition.

Hexose carbohydrates take part in essential biological processes such as energy generation, signal transduction, immune response, and cell-recognition.[1,2] In Nature, carbohydrates and polyketides are asymmetrically assembled via enzyme-catalyzed pathways with excellent stereoselectivity.[1a,3] The development of glycobiology and carbohydrate based pharmaceuticals demands novel methodology for the selective construction of natural and unnatural carbohydrates.[2]

In this research area, the de novo synthesis of carbohydrates is of immense importance. Thus chemists have developed a plethora of methods for the de novo synthesis of carbohydrates.[4,5] However, such methods usually require 8–14 chemical steps and protecting group strategies. Aldolase enzymes have also been successfully used as biocatalysts for the synthesis of carbohydrates and polyhydroxylated natural products.[3,6] However, aldolase enzymes exhibit poor activities in organic solvents. Recently, amino acid catalysis was added to the repertoire of carbohydrate synthesis.[7,8] For example, amino acids have been used as catalysts for the de novo synthesis of C_6 aldoses and ketoses with excellent enantioselectivity.[9,10] More recently, we observed a plausible dynamic kinetic resolution process in the amino acid-catalyzed asymmetric amplification of the enantiomeric excess of carbohydrates.[9d] In addition, amino acid catalysis has been employed in dynamic kinetic resolutions.[11] Bearing these observations in mind together with our previous experiences in organocatalysis,[12] we became interested in the development of a possible one-step de novo synthesis of carbohydrates from racemic β-hydroxy aldehydes via amino acid-catalyzed direct aldol additions (Eq. 1).



(1)

Herein, we show that amino acids are able to catalyze highly enantioselective dynamic kinetic asymmetric transformations (DYKAT).[13] The novel amino acid-mediated DYKAT process was applied in the proline-catalyzed one-step de novo synthesis of triketide- and deoxysugars, which were formed with excellent chemo- and diastereoselectivity and up to 99% ee.

Keywords: DYKAT; Carbohydrates; Triketides; Proline; Asymmetric synthesis; Aldehydes.
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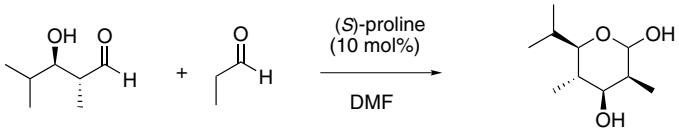
Firstly, the (*S*)-proline-catalyzed aldol reaction between propionaldehyde and β-hydroxy aldehyde **1a** was investigated under various conditions (Eq. 2).



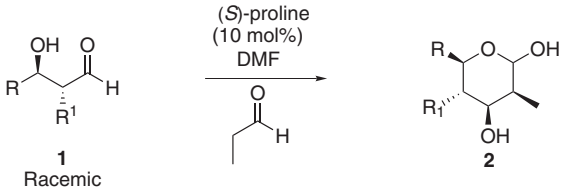
1a: racemic

2a: 14% yield, >19:1 dr, 98% ee
74% Yield based on recovered starting material

(2)

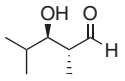
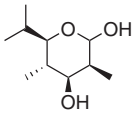
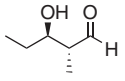
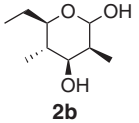
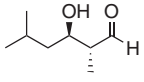
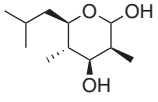
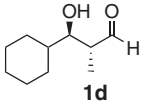
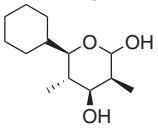
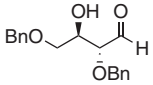
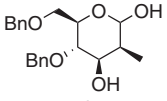
Remarkably, we found that (*S*)-proline was able to catalyze the formation of triketide sugar **2a** in 14% yield (74% based on recovered starting material) with >19:1 dr and up to 98% ee. The remaining β-hydroxy aldehyde **1a** was isolated in 81% yield with >19:1 dr and 0% ee and reused in a second crossed-aldol reaction to furnish additional triketide sugar **2a** with >19:1 dr and 98% ee.[14] Thus, an amino acid-catalyzed plausible DYKAT had occurred. The total combined yield of sugar **2a** was 21% based on the starting β-hydroxy aldehyde **1a**. Moreover, we believe that the low conversion of β-hydroxy aldehyde is because the equilibrium position of the dynamic reaction lies towards the β-hydroxy

Table 1. Proline-catalyzed DYKAT of different racemic β-hydroxyaldehydes[a]



1
Racemic

2

Entry	Acceptor	ee (%)[b]	Product	Yield (%)[c]	dr[d]	ee (%)[e]
1	 **1a**	0	 **2a**	21	>19:1	98
2	 **1b**	0	 **2b**	9[f]	>19:1	94
3	 **1c**	0	 **2c**	19	>19:1	93
4	 **1d**	50	 **2d**	19	>19:1	90
5	 **1e**	n.d.	 **2e**	22[f]	>19:1	99

[a] Experimental conditions: To a mixture of racemic **1** (1 mmol) in DMF (2.5 mL) in the presence of a catalytic amount of (*S*)-proline (10 mol %) was added over 12 h at 4 °C a solution of propionaldehyde (2 mmol, 2.5 mL DMF). Next, the reaction mixture was stirred for an additional 24 h at room temperature. The crude product **2** obtained after aqueous work-up was purified by column chromatography and the recovered starting material was reused in the second DYKAT cycle.

[b] The enantiomeric excess of the remaining β-hydroxy aldehyde **1**.

[c] Isolated yield of the pure products after silica gel column chromatography after two DYKAT cycles based on the starting β-hydroxy aldehyde **1**.

[d] The diastereomeric ratio determined by NMR analyses.

[e] Determined by chiral-phase GC analyses of the peracetylated sugars **2**.

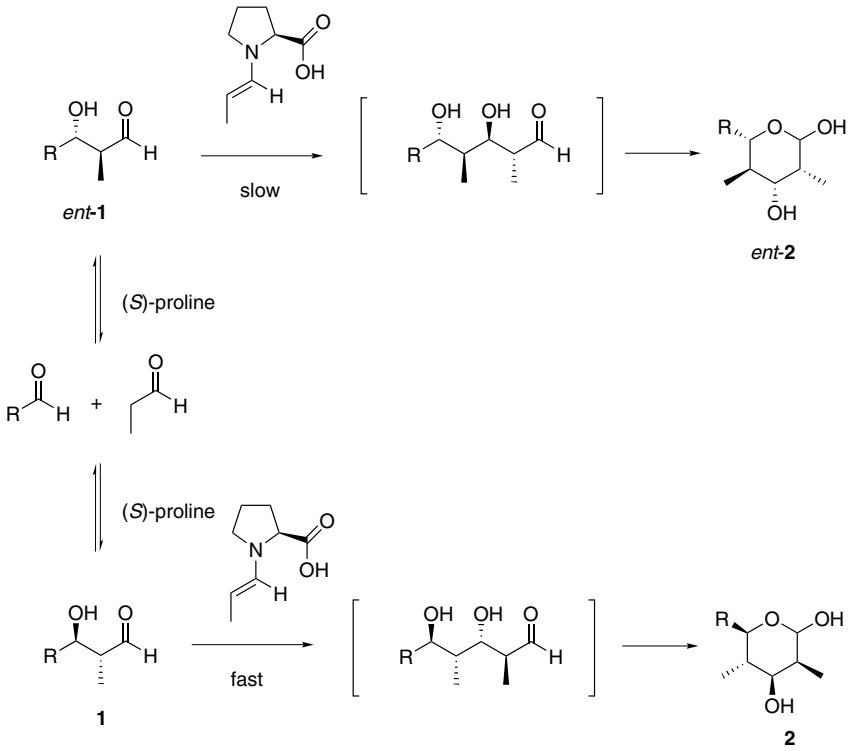
[f] Isolated yield of the pure products after silica gel column chromatography after one DYKAT cycle.

aldehyde. In addition, increasing the reaction time at room temperature slightly increased the conversion of the β-hydroxy aldehyde and decreased the ee of sugar **2a** to 81% ee. We also investigated the effect of adding water to the reaction mixture, since it can increase the efficiency of proline-catalyzed reactions.[9h,11b] However, the presence of water did not increase the yield of **2a**. Nevertheless, the proline-catalyzed DYKAT furnished triketide sugar **2a** with excellent stereoselectivity in one step. With these results in hand, we decided to perform the proline-catalyzed direct asymmetric crossed-aldol reactions for a set of different β-hydroxy aldehydes **2** (Table 1).

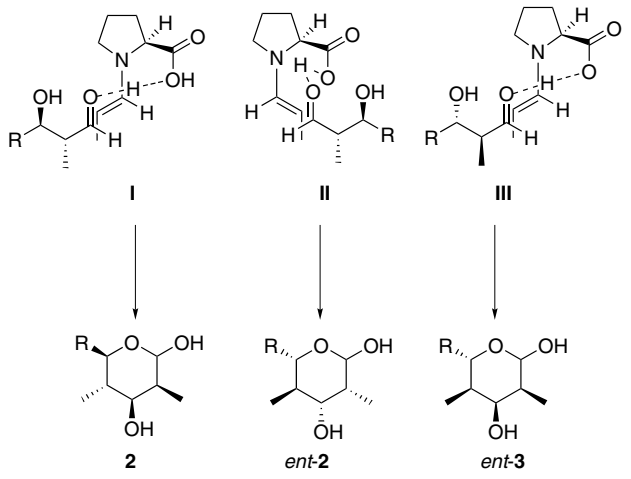
The reactions proceeded with high stereoselectivity and the desired polyketide sugars **2a**–**e** were isolated in yields comparable to most multi-step sugar syntheses with >19:1 dr and up to 99% ee.[15] Thus, the polyketide sugars were asymmetrically assembled with excellent stereoselectivity in one-step. It should be mentioned that the opposite enantiomer of the sugars *ent*-**2** were readily obtained by performing the DYKAT with (*R*)-proline as the catalyst. For example, *ent*-**2a** was synthesized in one-step in 22% yield with >19:1 dr and 95% ee. Moreover, the reactions are operationally simple and significantly decrease the generation of waste products compared to multi-step synthesis. Notably, due to the high chemoselectivity of the reaction, the starting β-hydroxy aldehyde can be reused in subsequent DYKAT cycles, which increases the yield. The ees of the remaining starting β-hydroxy aldehyde were 0% in all cases except for one, which means to that the racemization of the β-hydroxy aldehyde is faster than the C–C bond formation in all cases except one. In addition, the (*S*)-proline-catalyzed racemization of *ent*-**1b** with 99% ee was investigated. Thus, *ent*-**1b** with 99% ee was treated with a catalytic amount of (*S*)-proline (10 mol %) in DMF at 4 °C. After 24 h of stirring at this temperature, *ent*-**1b** was isolated with 98% ee and no hexose **1b** was formed. However, when performing the same experiment at room temperature, **1b** was isolated as a racemate (0% ee) and sugar **2b** was formed. Thus, the (*S*)-proline-catalyzed racemization is much faster at room temperature.

Comparison with the known absolute and relative stereochemistry of the mannose derivatives **2** established that (*S*)-proline asymmetrically assembled (*R*)-mannose sugars and (*R*)-proline furnished (*S*)-mannose sugars by DYKATs of racemic β-hydroxy aldehydes **1**.[9c] Based on the absolute stereochemistry of the mannose sugars **2**, we propose the following reaction scheme for the proline-catalyzed DYKAT of racemic aldehydes **1** (Scheme 1).

Initially, (*S*)-proline forms a catalytic chiral enamine intermediate with propionaldehyde. Next, the *Re*-face of the (*S*)-proline derived enamine is approached by the *Si*-face of aldehyde **1** via transition state **I** to form (*R*)-mannose **2**. This is in accordance with previously reported proline-catalyzed aldol reactions.[9,11,16] In parallel to this transformation, (*S*)-proline catalyzes the racemization of β-hydroxy aldehyde **1** via a plausible retro-aldol and aldol addition process. We ascribe the high stereoselectivity of the reaction to the transition state **I**, which must be more favored than the other two possible transition states **II** and **III**, which would form *ent*-**2a** and allose *ent*-**3**, respectively.



Scheme 1. Reaction scheme for the (*S*)-proline-catalyzed DYKAT of β-hydroxy aldehydes.



In summary, we have found that amino acids can catalyze highly chemo-, diastereo-, and enantioselective dynamic kinetic asymmetric transformations of racemic β-hydroxy aldehydes. The remarkably high selectivity of proline was utilized in the novel one-step de novo synthesis of deoxy- and polyketide sugars with up to 99% ee. The proline-catalyzed DYKAT process is a combination of an amino acid-mediated racemization of the β-hydroxyaldehyde acceptor via retro-aldol and aldol additions and a subsequent amino acid-catalyzed direct stereoselective aldol addition to the racemic β-hydroxyaldehyde acceptor with an aldehyde nucleophile. Further mechanistic investigations of the racemization process as well as application of the novel DYKAT concept to de novo synthesis of functional sugars are ongoing.

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14. To a mixture of racemic **1a** (1 mmol) in DMF (2.5 mL) in the presence of a catalytic amount of (*S*)-proline (10 mol %) was added over 12 h at 4 °C a solution of propionaldehyde (2 mmol, 2.5 mL DMF). Next, the reaction mixture was stirred for an additional 24 h at room temperature. The crude product **2a** was obtained after extraction with brine (5 mL) and EtOAc (3 × 15 mL). The aqueous layer was back extracted with EtOAc (3 × 15 mL) and the combined organic extracts were dried with anhydrous Na_2SO_4 followed by filtration. Next, the organic phase was concentrated under reduced pressure and the crude product was purified by silica gel column chromatography (EtOAc–pentane, 1:2) to furnish the desired triketide sugar **2a** and recovered the starting material **1a**. The recovered starting material was reused in a second DYKAT cycle, which further improved the yield. Compound **2a**: ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): (α-anomer) 0.89 (m, 6H), 0.93 (m, 6H), 1.71 (m, 1H), 1.87 (m, 2H), 2.05 (m, 1H), 2.69 (br s, 1H), 3.46 (dd, $J = 10.0$, 2.4 Hz, 1H), 3.77 (dd, $J = 9.4$, 4.6 Hz, 1H), 5.08 (d, $J = 1.6$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 10.6, 12.9, 14.4, 20.4, 23.1, 34.9, 38.5, 71.7, 77.0, 97.1. The enantiomeric excess of **2a** was determined by chiral-phase GC analysis of the peracetylated **2a**: (CP-Chirasil-Dex CB); $T_{inj} = 250$ °C, $T_{det} = 275$ °C, flow = 1.8 mL/min, $t_i =$ 100 °C (35 min), $t_f = 200$ °C (80 °C/min): (β-anomer) major isomer: $t_R = 36.16$ min; minor isomer: $t_R = 36.12$ min, (α-anomer) major isomer: $t_R = 36.52$ min; minor isomer: $t_R = 36.42$ min; $[\alpha]_D^{25}$ +35.3 (*c* 1, $CHCl_3$); MALDI-TOF MS: *m*/*z* 211.1311; $C_{10}H_{20}O_3$ ($M+Na^+$: calcd 211.1310). The ee of **1a** was determined by GC analysis of the acetal derived from 2,2-dimethylpropane-1,3-diol according to the method of Yamamoto. (Furuta, K.; Shimizu, S.; Miwa, S.; Yamamoto, H. *J. Org. Chem.* **1989**, *54*, 1481.) GC (CP-Chirasil-Dex CB): $T_{inj} = 250$ °C; $T_{det} = 275$ °C flow = 1.8 mL/min, $t_i = 100$ °C, hold 35 min, $t_f = 200$ °C rate = 80 °C/min, hold 10 min. Major isomer: $t_r = 35.514$ min, minor isomer $t_r = 35.778$ min.
15. To a mixture of racemic **1** (1 mmol) in DMF (2.5 mL) in the presence of a catalytic amount of (*S*)-proline (10 mol %) was added over 12 h at 4 °C a solution of propionaldehyde (2 mmol, 2.5 mL DMF). Next, the reaction mixture was stirred for an additional 24 h at room temperature. The pure triketide sugar **2** and the recovered starting material **1** was obtained by the same procedure as described in Ref. 14. The recovered starting material was reused in a second DYKAT cycle, which further improved the yield. In order to determine the enantiomeric excesses of the triketide sugars **2b–d** they were peracetylated by treatment with Ac_2O and cat. DMAP in $CHCl_3$ according to Ref. 9e. Next, chiral-phase GC analyses gave the ee. The ees of the recovered β-hydroxy aldehydes **1b–d** were determined by GC analysis of the acetal derived from 2,2-dimethylpropane-1,3-diol according to Yamamoto's method (see Ref. 14). For the determination of the ee **2e** see Ref. 9e.
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