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Amino Acid Catalyzed Neogenesis of Carbohydrates: A Plausible Ancient Transformation

Armando Córdova,* Ismail Ibrahem, Jesús Casas, Henrik Sundén, Magnus Engqvist, and Efraim Reyes[a]

Abstract: Hexose sugars play a fundamental role in vital biochemical processes and their biosynthesis is achieved through enzyme-catalyzed pathways. Herein we disclose the ability of amino acids to catalyze the asymmetric neogenesis of carbohydrates by sequential cross-aldol reactions. The amino acids mediate the asymmetric de novo synthesis of natural L- and D-hexoses and their analogues with excellent stereoselectivity in organic solvents. In some cases, the four new stereocenters are assembled with almost absolute stereocontrol. The unique feature of these results is that, when an amino acid is employed as the catalyst, a single reaction sequence can convert a protected glycol aldehyde into a hexose in one step. For example, proline and its derivatives catalyze the asymmetric neogenesis of allose with $>99\,\%$ *ee* in one chemical manipulation. Furthermore, all amino acids tested catalyzed the asymmetric formation of natural sugars under prebiotic conditions, with alanine being the smallest catalyst. The inherent simplicity of this catalytic process suggests that a catalytic prebiotic "gluconeogenesis" may occur, in which amino acids transfer their stereochemical information to sugars. In addition, the amino acid catalyzed stereoselective sequential cross-aldol reactions were performed as a two-step procedure with different aldehydes as acceptors and nucleophiles. The employment of two different amino acids as catalysts for the iterative direct aldol reactions enabled the asymmetric synthesis of deoxysugars with $>99\,\%$ *ee*. In addition, the direct amino acid catalyzed $C_2+C_2+C_2$ methodology is a new entry for the short, highly enantioselective de novo synthesis of carbohydrate derivatives, isotope-labeled sugars, and polyketide natural products. The one-pot asymmetric de novo syntheses of deoxy and polyketide carbohydrates involved a novel dynamic kinetic asymmetric transformation (DYKAT) mediated by an amino acid.

Keywords: aldol reaction · amino acids · asymmetric synthesis · carbohydrates · polyketides

Introduction

Carbohydrates are involved in life-essential processes such as glucolysis, gluconeogenesis, signal transduction, and the immune response.[1] They are also the building blocks of several fundamental oligo- and polysaccharides. The neogenesis of sugars is accomplished through life-essential enzyme-catalyzed pathways from simple achiral precursors, with absolute stereocontrol.[1a] The mechanism of the prebiotic formation of sugars and their role in the formation of ancient RNA analogues are subjects of intense research interest.[2–5] For instance, the neogenesis of hexoses may have occurred by the reaction of glycoaldehyde phosphate under alkaline conditions to provide an achiral mixture of tetrose and hexose derivatives. Moreover, the rapidly growing research areas of carbohydrates and oligomeric interactions of carbohydrates in biological systems have led to an increased demand for the development of reaction design and methodological advancement in the synthesis of sugars.[6] However, most conventional aldose syntheses involve more than eight steps, require protecting group strategies, and subsequent reduction–oxidation steps.[7,8] An alternative approach, for the de novo synthesis of carbohydrates involves the employment of aldolase enzymes as catalysts for the direct asymmetric aldol reaction.[9] Enzyme catalysis has the advantage of both reducing protecting group strategies and also of being highly selective.

Recently, organocatalysis has experienced a renaissance in asymmetric synthesis.[10,11] Enamine-catalysis has been successfully used in direct catalytic cross-aldol reactions with al-

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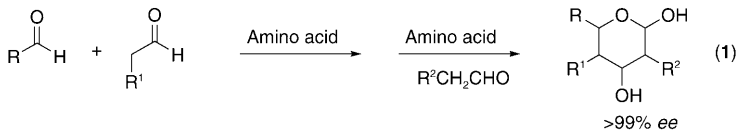
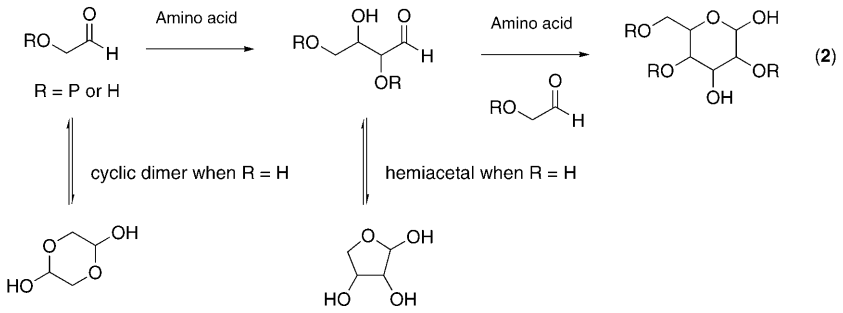
dehydes as nucleophiles.[12] These reactions have been elegantly linked in sequence with the indirect Lewis acid catalyzed Mukaiyama aldol reaction to yield natural hexoses in two steps.[13] Most recently, we reported the first direct amino acid catalyzed, highly enantioselective two-step polyketide sugar synthesis [Eq. (1)].[14]



(1)

Furthermore, we found that amino acids catalyze the asymmetric incorporation of molecular oxygen at the α-position of carbonyl compounds and are able to produce glycol aldehyde derivatives.[15] In the context of this discovery, and given the "intrinsic simplicity" of the hexose structural motif, we investigated whether amino acids can utilize glycoaldehyde derivatives as substrates for the catalytic asymmetric neogenesis of natural hexoses by one-pot sequential aldol reactions [Eq. (2)].[14] Moreover, this plausible ancient catalytic function of amino acids may have played a role in the origin of homochirality in carbohydrates.



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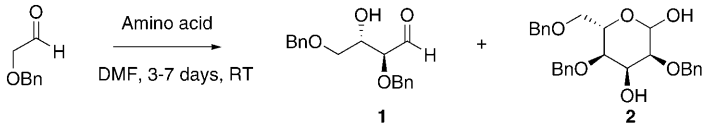
In this paper, we disclose: The results of the amino acid catalyzed asymmetric neogenesis of natural aldoses in organic solvents as well as under prebiotic conditions. The amino acid catalyzed, highly enantioselective de novo syntheses of deoxy and polyketide sugars from simple aldehydes. The mechanisms for the amino acid catalyzed asymmetric neogenesis of carbohydrates, two-step sugar synthesis, and one-pot asymmetric assembly of deoxy and polyketide carbohydrates by dynamic kinetic asymmetric transformations (DYKAT).

Results and Discussion

To begin with, we selected a protected glycoaldehyde as a model substrate in order to prevent cyclic dimerization of the starting glycoaldehyde or the formation of the hemiacetal of the tetrose intermediate; both of which would decrease the rate of hexose generation [Eq. (2)]. Furthermore, the protected tetrose sugar must undergo a sequential amino acid catalyzed cross-aldol addition for hexose generation to occur. In initial experiments, we screened different amino acids for their ability to catalyze the formation of sugars by asymmetric aldol reactions of α-benzyloxyacetaldehyde in organic solvents (Table 1).

We found that all the amino acids tested mediated the direct asymmetric formation of 2,4-di-*O*-benzyl-erythrose (**1**). For instance, the simple chiral amino acids L-alanine and L-valine produced tetrose *ent*-**1** in 67 and 52% yield, with 88 and 81% *ee*, respectively, in addition to trace amounts of hexoses. The cyclic secondary amino acids provided erythrose **1** and *ent*-**1** in good yield with ≥97% *ee*. Importantly, we observed additional products, compounds **2** and *ent*-**2**. NMR and GC–MS analyses of these products revealed that hydroxyproline and proline catalyzed the formation of a tribenzyl protected hexose in one chemical manipulation. Conversion of the sugar to the peracetylated monosaccharide established that hydroxy-L-proline and L-proline had provided 2,4,6-tri-*O*-benzyl-allose **2** as a single diastereomer in 28 and 41% yield, respectively, with >99% *ee*. Thus, out of 16 possible stereoisomers, these amino acids catalyzed the neogenesis of a single enantiomer in one chemical manipulation. The catalytic efficiency as well as the enantio-

Table 1. Amino acid catalyzed asymmetric de novo synthesis of sugars.



1 **2**

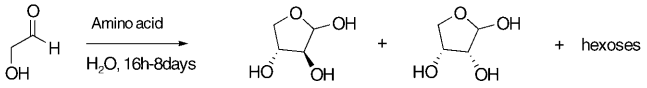
Entry	Amino acid	Tetrose	Yield [%][a]	*dr*[b]	*ee* [%][c]	Hexose	Yield [%][a]	*ee* [%][d]
1	D-alanine	**1**	62	2:1	86	**2**	traces	n.d.
2	D-valine	**1**	51	2:1	80	**2**	traces	n.d.
3	hydroxy-L-proline	**1**	62	5:1	97	**2**	28	>99
4	L-alanine	*ent*-**1**	67	2:1	88	*ent*-**2**	traces	n.d.
5	L-valine	*ent*-**1**	52	2:1	81	*ent*-**2**	traces	n.d.
6	L-phenylalanine	*ent*-**1**	55	2:1	71	*ent*-**2**	traces	n.d.
7	L-proline	**1**	51	4:1	98	**2**	41[e]	>99[e]
8	D-proline	*ent*-**1**	50	4:1	98	*ent*-**2**	40[e]	>99[e]
9	L-proline	**1**	64[f]	4:1	98[f]	**2**	24[f]	>99[f]

[a] Isolated yield after silica-gel column chromatography. [b] The diastereomeric ratio (*dr*) was determined by ^{1}H NMR spectroscopic analysis of the crude product. [c] The enantiomeric excess (*ee*) of **1** and *ent*-**1** was determined by chiral-phase HPLC analysis. [d] The *ee* of hexose **2** and *ent*-**2** was determined by chiral-phase GC analysis of the peracetylated hexose. Racemic hexose **2** was obtained by D,L-proline catalysis. [e] Four days reaction time. [f] Reaction performed in DMSO.

meric excess of the sugars derived from the amino acids tested was found to decrease in the following order: proline > hydroxyproline > alanine > valine and phenylalanine. The yields of the hexoses produced by amino acid catalysis were comparable or higher than most conventional multistep sugar syntheses. The amino acid catalyzed asymmetric assembly of hexoses in DMSO was also found to proceed with excellent stereoselectivity.

Prebiotic studies: Encouraged by the results in organic solvents we next investigated the amino acid catalyzed neogenesis of carbohydrates under prebiotic conditions using glycol aldehyde as the substrate. All the amino acids tested produced the corresponding naturally occurring tetroses and hexoses, such as glucose, with similar catalytic efficiency in water.[16] Proline and valine catalyzed the formation of unprotected carbohydrates with the highest stereoselectivity (Table 2). Thus, the amino acids tested were found to be catalytically active both in water and in organic solvents.

Table 2. The amino acid catalyzed gluconeogenesis in water.



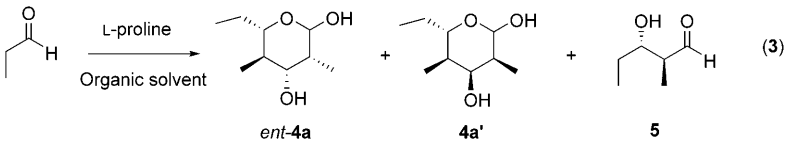
Entry	Amino acid	T [°C]	*erythro*/*threo*[a]	D-threose *ee* [%][b]
1	L-valine	RT	1:1	12
2	L-valine	50	1:1	12
3	L-proline	RT	2:1	-8
4	L-proline	50	1:1	-9
5	L-phenylalanine	RT	1:1	5
6	hydroxy-L-proline	RT	1:1	-7
7	L-serine	RT	1:1	-7
8	L-alanine	RT	1:1	5

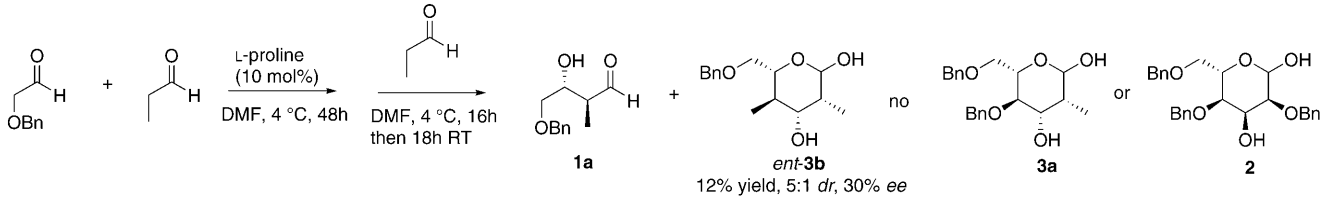
[a] Determined by GC–MS, and ^{1}H NMR analysis of the crude product mixture. [b] Determined by chiral-phase GC analysis of the tetra-acetylated threitol. Hexose formation was determined by chiral-phase GC analysis of the hexa-acetylated hexitols and comparison with authentic samples of hexacetylated D-hexitols.

Previous prebiotic studies have indicated that under specified reaction conditions proline does not catalyze the self-aldolization of glycol aldehyde in water, even though proline is known to exhibit catalytic activity in organic solvents for similar substrates.[4,16] However, our results clearly demonstrate that proline is able to utilize glycol aldehyde as a substrate for the catalytic neogenesis of sugars in water. The stereoselectivity of the reaction is lower than that observed when organic solvents are employed, demonstrating the importance of a hydrophobic transition state to achieve high stereocontrol. The ability of amino acids to catalyze the asymmetric formation of sugars may have prebiotic significance. Extraterrestrial amino acids with up to 9% *ee* have been isolated from the Murchison meteorite.[4,17] The presence of extraterrestrial and prebiotic amino acids with a minor amount of enantiomeric excess suggests, plausibly, that amino acids catalyzed asymmetric aldol reactions according to the routes presented, and transferred their chiral information to tetroses and hexoses,[18] which are the building blocks of prebiotic RNA and most common polysaccarides. In addition, the intrinsic catalytic activity of amino acids when reacting with aldehydes in water to give carbohydrates, according to the mechanism presented, gives rise to the possibility that this reaction may be occurring currently, either on earth, or elsewhere in universe.

One-pot sequential amino acid catalyzed asymmetric synthesis of deoxy and polyketide sugars: Next we investigated the possibility of synthesizing deoxysugars by one-pot, direct amino acid catalyzed sequential aldol reactions. Hence, propionaldehyde and α-benzyloxyacetaldehyde were mixed in the presence of a catalytic amount of L-proline and stirred for 48 h. Additional propionaldehyde was then added slowly to the reaction mixture. The reaction was quenched by aqueous workup and deoxysugar *ent*-**3b** isolated in 12% yield with 5:1 *dr* and 30% *ee*, together with remaining erythrose **1a** (Scheme 1). The reaction proceeded with high chemoselectivity, and without either of the two sugars **3a** or **2** being formed. However, sugar **3a** can be synthesized in one-pot if the erythrose **1** is allowed to form prior to the propionaldehyde addition.

In addition, we investigated the proline-catalyzed asymmetric trimerization of propionaldehyde under various conditions [Eq. (3)].[12f,g]

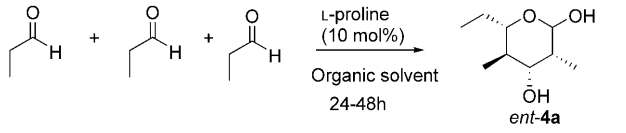




Scheme 1. The highly chemoselective one-pot synthesis of sugar **3b**.

The reactions proceeded smoothly and yielded the corresponding polyketide sugars *ent*-**4a** and insignificant amounts of **4a′**, together with dimer **5**. Selected results from the L-proline-mediated asymmetric synthesis of *ent*-**4a** are shown in Table 3.

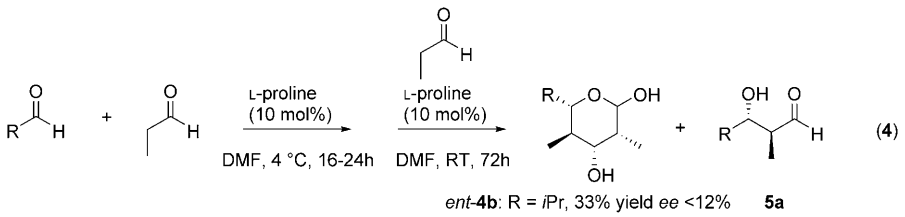
Table 3. Selected examples of proline-catalyzed asymmetric trimerization of propionaldehyde.



Entry	Solvent	Conditions	Yield[a]	*ee* [%][b]
1	DMF	RT[c]	22	33
2	DMF	RT[d]	50	11
3	CH_3CN	RT	16	12
4	DMF	4 °C	11	48
5	DMF	–[e]	17	40
6	DMF	–[f]	31	85
7	DMF	–[g]	12	71
8	Dioxane	RT	16	18

[a] Isolated yield. [b] The *ee* of hexose **4a** was determined by chiral-phase GC analysis. [c] 24 h reaction time. [d] 72 h reaction time. [e] Propionaldehyde at 4 °C over 16 h was added to a reaction mixture of L-proline in DMF. The reaction mixture was then stirred at room temperature for a further 24 h. [f] See Experimental Section. [g] Propionaldehyde (2 mmol) at 4 °C over 16 h was added to a reaction mixture of L-proline and racemic **5b** (1 mmol) in DMF. The reaction mixture was then stirred at room temperature for a further 24 h.[12]

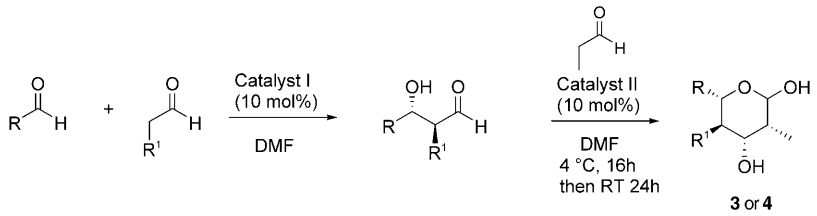
We found that L-proline was able to catalyze the asymmetric formation of *ent*-**4a** with greatest enantioselectivity when DMF was used as the solvent for the reaction. The stereoselectivity of the transformation was dependent upon the reaction time as well as the reaction conditions. For example, the *ee* of *ent*-**4a** decreased with time in DMF at room temperature. The different reaction conditions indicated that the kinetics of the amino acid catalyzed one-pot transformations are very important and may be hard to control. To our encouragement we were able to synthesize *ent*-**4a** as the predominant diastereomer in 31% yield with 85% *ee* in one chemical manipulation by the development of a new reaction procedure (entry 6). Thus, triketide sugar **4a** can now be produced with a high degree of enantioselectivity. However, the one-pot, amino acid catalyzed, sequential aldol reactions afforded triketide sugar *ent*-**4b** as a single diastereomer with modest *ee*, together with corresponding cross-aldol adduct **5a** in one chemical manipulation [Eq. (4)].



Amino acid catalyzed two-step asymmetric synthesis of deoxy and polyketide sugars: The modest enantiomeric excesses of the polyketide carbohydrates derived by one-pot proline catalyzed sequential direct aldol reactions made us embark on the quest to find a new synthetic strategy for the asymmetric synthesis of deoxyaldoses by amino acid catalysis. The results from the one-step allose total synthesis indicated that it would be possible to reach the stereoselectivity of enzyme catalyzed carbohydrate biosynthesis utilizing amino acid catalysis. Retrosynthetic analysis suggested that a two-step carbohydrate synthesis would be an attractive alternative. Moreover, we suspected that the low stereoselectivity of the one-pot L-proline-mediated asymmetric assembly of triketides could be due to a mismatch in the second aldol addition between the L-proline derived enamine and the cross-aldol adduct derived from the first L-proline catalyzed aldol addition. This was also supported by molecular modeling studies, which suggested that nucleophilic attack by the D-proline derived enamine on the cross-aldol adduct derived from the first L-proline catalyzed aldol addition would provide higher enantioselectivity than that observed with the L-proline-derived enamine. In addition, the two-step procedure allows for a change of amino acid catalyst or solvent between the steps. Thus, we utilized a two-step protocol based on sequential L- and D-amino acid catalysis. The tetrose intermediates derived by L-proline catalysis were isolated prior to the second direct D-amino acid catalyzed aldol addition (Table 4).

Remarkably, the reactions proceeded with excellent selectivity and produced the deoxymannoses **3** with high optical purity. The two-step hexose synthesis was more efficient than the one-pot deoxysugar synthesis and provided the desired sugars with increased chemo- and diastereoselectivity. The two-step amino acid catalyzed iterative cross-aldol reactions between aliphatic aldehyde substrates progressed with excellent diastereo- and enantioselectivy and produced the corresponding polyketide sugars **4b**–**4d** as single diastereomers in good overall yield with >99% *ee*. Thus, out of 16 possible stereoisomers amino acid catalysis can allow in some cases for the creation of a single enantiomer with enzymelike selectivity. The yields of the deoxysugars **3** and triketides **4** produced by amino acid catalysis are comparable or higher than most conventional multistep carbohydrate and triketide synthesis, and are determined by the equilibrium of the second aldol reaction. The remaining starting tetrose intermediates were isolated and reused in an additional amino acid catalyzed aldol addition, which further improved the yield. In addition, the direct amino acid catalyzed two-step de novo synthesis of carbohydrates is inexpensive, operationally simple, and minimizes the generation of waste products. The sequential direct catalytic aldol reactions are readily scaled up and performed on a gram scale. The opposite enantiomer of the carbohydrates is

Table 4. Amino acid catalyzed asymmetric formation of deoxysugars **3** and polyketide sugars **4**.



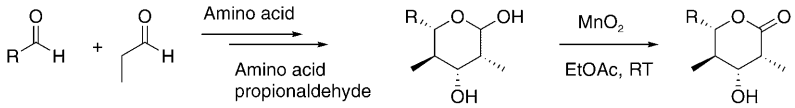
Entry	R	R^1	Cat. I	Cat. II	Sugar	Overall yield [%][a]	*ee* [%][b]
1	$BnOCH_2$	OBn	L-proline	D-proline	**3a**	39[c]	>99
2	$BnOCH_2$	OBn	D-proline	L-proline	*ent*-**3a**	38[c]	>99
3	$BnOCH_2$	Me	L-proline	D-proline	**3b**	30[d]	>99
4	$BnOCH_2$	Me	D-proline	L-proline	*ent*-**3b**	29[d]	>99
5	Et	Me	L-proline	D-proline	**4a**	29[d]	>99
6	*i*Pr	Me	L-proline	D-proline	**4b**	42[d]	>99
7	*i*Pr	Me	D-proline	L-proline	*ent*-**4b**	40[d]	>99
8	Et	Me	D-proline	4-hydroxy-L-proline[e]	*ent*-**4a**	30[d]	>99
9	*i*Pr	Me	D-proline	4-hydroxy-L-proline[e]	*ent*-**4b**	15[d]	>99
10	*i*Bu	Me	L-proline	D-proline	**4c**	24[d]	>99
11	*c*-hexyl	Me	L-proline	D-proline	**4d**	41[d]	>99

[a] Isolated overall yield. [b] The *ee* of hexose **3** and **4** was determined by chiral-phase GC analysis. [c] *dr* determined as $\geq$10:1 by NMR analysis. [d] *dr* determined as >19:1 by NMR analysis.

obtained by starting the reaction sequence with D-proline. For example, the combination of sequential D-proline catalysis and 4-hydroxy-L-proline catalysis produced *ent*-**4a** and *ent*-**4b** with excellent stereoselectivity. In addition, silyl-protected glycolaldehydes can be used as substrates for the amino acid catalyzed two-step carbohydrate synthesis [Eq. (5)]. For example, TBS-protected (TBS= *tert*-butyldimethylsilyl) sugars **3c** and **3d** were assembled in two chemical manipulations. However, TBS protected deoxysugars **3c** and **3d** were isolated in a lower overall yield than that obtained for the benzyl-protected deoxysugars **3a** and **3b**, respectively. The hexoses obtained from the tandem direct catalytic asymmetric aldol reactions have free hydroxyl groups at C-1 and C-3, allowing for introduction of orthogonal protective groups and selective di- or polysaccharide couplings. Furthermore, the aldehyde substrates and the amino acid catalysts can be freely varied potentially providing access to a wide range of deoxyhexoses.

The two-step amino acid catalyzed de novo synthesis of sugars can be utilized for the short synthesis of δ-lactones (Scheme 2). Consequently, lactones **6a** and **6b** were prepared with >99% *ee* in only three chemical manipulations. Thus, the two-step aldol strategy significantly reduced the synthetic steps required when utilizing Evan's type methodology.[7f]

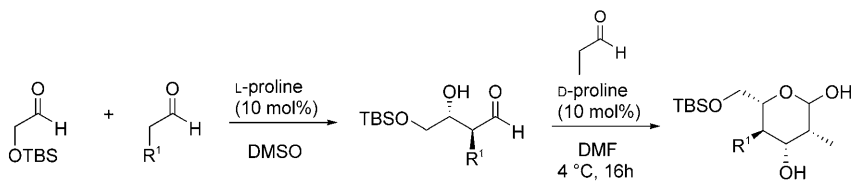
We also treated α-benzyloxyacetaldehyde with formaldehyde in the presence of a catalytic amount of L-proline in DMF (Scheme 3). This reaction lead to the formation of acrylate **7**, which was isolated in high yield. Next, a proline-catalyzed cross-aldol reaction between propionaldehyde and acrylate **7** produced the corresponding cross-aldol adduct **8** in moderate yield and with high stereoselectivity. The unreacted acrylate was recycled in a second cross-aldol reaction to further improve the yield of **8**. The reaction proceeded with excellent chemoselectivity, and the potential Michael product was not detected. Triketide **8** is a protected deoxypentulose and in situ reduction and deprotection should lead to the ketose ("inversion strategy"). In addition, sugar **8** is an important synthon for the synthesis of polyketide natural product segments.[19]



6a: R = OBn, quantitative,>99% *ee*
6b: R = *i*Pr, quantitative, >99% *ee*

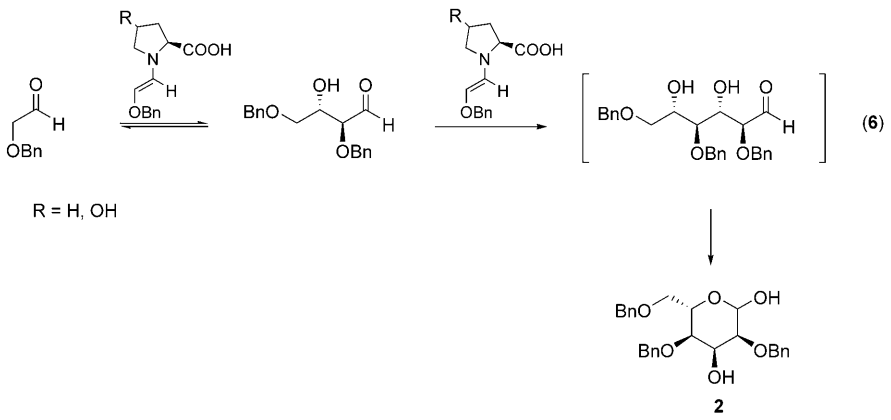
Scheme 2. Direct catalytic enantioselective synthesis of δ-lactones **6**.

Determination of the absolute stereochemistry of sugars 1 and 2: The absolute and relative configuration of the known tetrose **1** confirmed that L-alanine and other primary L-amino acids lead to the formation 2,4-di-*O*-benzyl-D-erythrose. In contrast, the L-proline derivatives produced the L-erythrose derivative. The stereochemical outcome of the neogenesis of sugars in water was the same as that found in



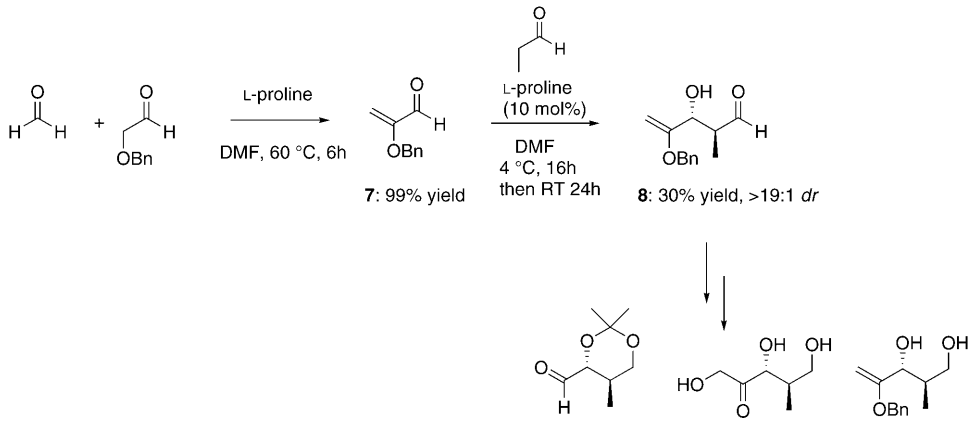
R^1 = Me or OTBS

3c: R^1 = Me, 12% overall yield, >19:1 *dr*, *ee* n.d.
3d: R^1 = OTBS, 7% overall yield, >19:1 *dr*, *ee* n.d.

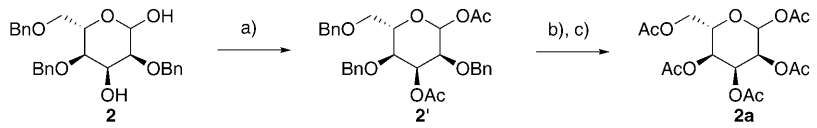


anti-selective aldol reaction occurs with the intermediate erythrose **1** yielding the corresponding hexose [Eq. (6)]. Proline reacts exclusively with the *erythro*-**1** via transition state **I** and not with *threo*-**1** due to steric repulsion between the α-substituent of the threose and the catalytically generated enamine, which would occur in transition state **II** (Figure 2). The rate of the second *anti*-selective aldol reaction is significantly slower than the initial aldol addition. Thus, hexose formation is the rate-determining step.

organic solvents. Thus, all primary amino acids tested except L-serine, produced the naturally occurring D-threose. This was established by comparing the peracetylated threose with the peracetylated commercially available D-threose. The absolute and relative configuration of hexose **2** produced by proline and hydroxyproline catalysis was established by conversion of tri-*O*-benzylated **2** to the corresponding peracetylated hexose **2a**, followed by comparison with the literature and with peracetylated natural hexoses (Scheme 4). This procedure established that hydroxy-L-proline and L-proline catalysis had provided 2,4,6-tri-*O*-benzyl-β-L-(+)-allose **2** in one chemical operation; this subsequently enabled determination of the enantiomeric excess of **2**.



Scheme 3. Direct catalytic enantioselective synthesis of polyketide segments **7** and **8**.



Scheme 4. a) Ac_2O, CH_2Cl_2, RT, DMAP. b) cat. Pd/C, MeOH. c) Ac_2O, CH_2Cl_2, RT, pyridine DMAP.

Hence, the cyclic five-membered L-amino acids produced L-hexoses and the corresponding D-amino acids, D-hexoses.

Mechanism of the amino acid catalyzed glycoaldehyde cross-aldol reactions: The stereochemistry of the sugars is determined in the first aldol addition, and depends on the direction of approach of the acceptor glycoaldehyde to the catalytically generated enamines (Figure 1),[12,20] which are formed between the donor glycoaldehyde and the amino acids, ultimately producing tetrose **1**. Next, an additional

Determination of the absolute stereochemistry of sugars 3 and 4: The absolute and relative configurations of sugars **3** and **4** have been assigned based on the crystal structure of the α-anomer of sugar **4b** (Figure 3),[21] NMR studies and chiral-GC analysis.

The crystal structure revealed that hexose **4b** obtained by sequential two-step L- and D-proline catalysis has a manno-pyranoside configuration. Thus, the sequential L-proline and D-proline catalysis produced L-mannose derivatives **3** and **4**. In addition, the L-proline-mediated one-pot asymmetric assembly of polyketide sugars produced the corresponding D-mannose derivatives **3** and **4**, as established by NMR spectroscopy. The NMR spectra of the sugars **3** and **4**, obtained by the one-pot and two-step syntheses, were identical, and therefore the same major diastereomer is formed regardless of which procedure is used. Moreover, chiral-phase GC analysis confirmed that the one-pot L-proline and hydroxyl-

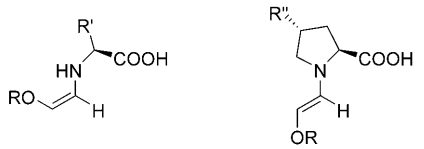


Figure 1. Enamine intermediates.

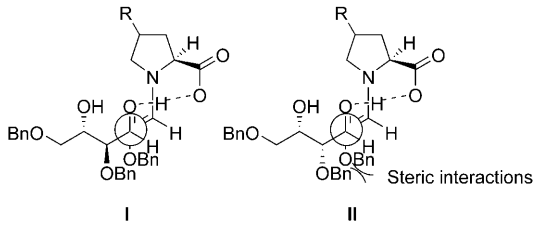


Figure 2. Potential transition states **I** and **II** for the enamine-addition to erythrose and threose, respectively.

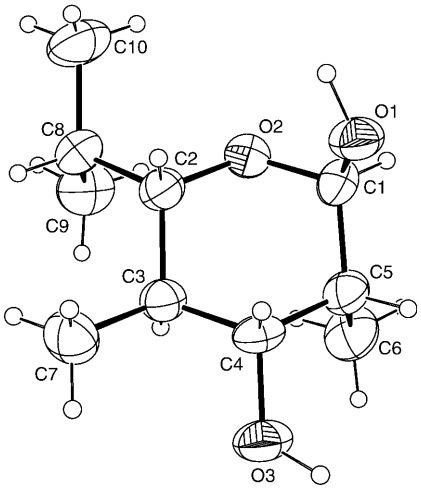


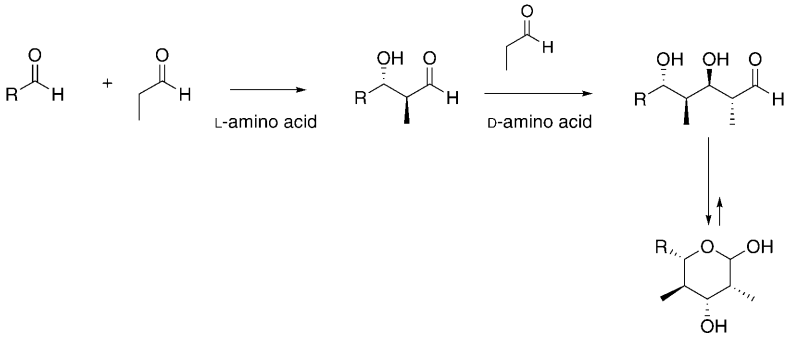
Figure 3. The crystal structure of the α-anomer of hexose **4b**.

L-proline-catalyzed sequential cross-aldol reactions produced the corresponding D-mannose derivatives *ent*-**3** and *ent*-**4**.

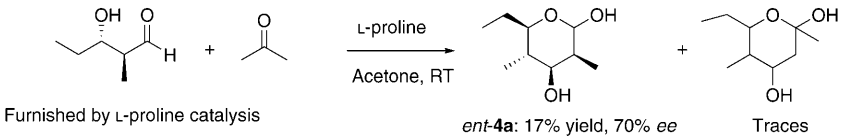
Mechanism of the two-step sugar synthesis: The sequential L- and D-proline catalysis produced L-hexoses. Accordingly, the observed stereochemistry of the hexoses can be readily explained (Scheme 5). The initial formation of the β-hydroxy aldehyde proceeds through *re*-facial attack on the acceptor aldehyde by the L-proline derived enamine, which is in accordance with previously reported proline-catalyzed aldol reactions with aldehydes.[12,20] Next, the D-proline-catalyzed aldol addition proceeds in a highly *anti*-selective fashion with the *anti*-β-hydroxy aldehyde isomer to form the L-mannose structural motive.

The role of the dynamic kinetic asymmetric transformation (DYKAT) in the mechanism of the one-pot amino acid catalyzed asymmetric assembly of polypropionate sugars: The L-proline mediated one-pot asymmetric assembly of polyketide sugars was found, by means of NMR spectroscopy and chiral-phase GC analysis, to produce the corresponding D-mannose derivatives **3** and **4**. This is the opposite absolute configuration to that obtained for the same sugars by sequential L- and D-proline catalysis. Furthermore, we investigated the possibility of performing a sequential L-proline-catalyzed cross-aldol addition between acetone and the (2*R*,3*S*)-*anti*-β-hydroxy aldehyde **5** (4:1 *dr*, 99% *ee*), derived by L-proline catalysis (Scheme 6).

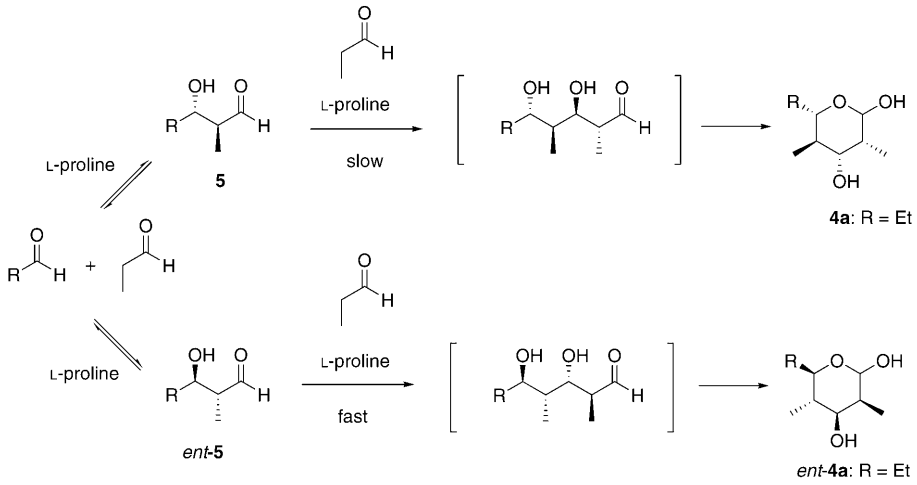
Remarkably, no significant acetone addition occurred and we were able to isolate *ent*-**4a** in 17% yield and with 70% *ee*. The remaining self-aldol adduct **5** was nearly racemic (<10% *ee*). Based on this noteworthy experiment, we propose the following reaction sequence as well as a process for the asymmetric formation of the aldose: L-proline must have initially racemized the β-hydroxyaldehyde adduct **5** by a *retro*-aldol reaction and subsequent dimerization, which produced the opposite enantiomer, *ent*-**5** (Scheme 7). Next, a highly selective cross-aldol addition with the *anti*-β-hydroxy aldehyde *ent*-**5** must have taken place to produce the aldose *ent*-**4a**. Thus, L-proline converted the *anti*-β-hydroxyaldehyde **5** to the corresponding triketide *ent*-**4a** by the means of a dynamic kinetic asymmetric transformation (DYKAT).[22] In addition, the propionate sugars **4a**–**4d** can be synthesized with high enantioselectivity by amino acid catalyzed DYKAT of racemic β-hydroxyaldehydes.[23] The absolute configuration of the triketide sugars *ent*-**4**, derived from the one-pot synthetic protocol utilizing L-proline catalysis, together with the time dependence of the hexose sugars *ent*-**4** *ee*, corroborates that these transformations also involved an amino acid catalyzed DYKAT. In accordance, the reaction sequence starts with the L-proline-catalyzed formation of the *anti*-β-hydroxyaldehyde adducts **5** with high enantioselectivity (Scheme 7). Next, L-proline catalyzes the



Scheme 5. The reaction pathway for the two-step amino acid catalyzed triketide hexose synthesis.



Scheme 6. Proline-catalyzed asymmetric trimerization in acetone.



Scheme 7. The potential mechanism for the one-pot L-proline-catalyzed asymmetric formation of sugar *ent*-**4a**.

catalytic synthetic protocols produces either L- or D-sugars with, in most cases, >99% *ee*. For example, proline and its derivatives catalyze the formation of allose with >99% *ee* in one chemical manipulation. Thus, this novel synthetic approach allows for the creation of four contiguous new stereocenters with excellent stereocontrol. The direct amino acid catalyzed asymmetric syntheses of hexoses are inexpensive, operationally simple, and reduce the generation of waste products. The iterative aldol reaction methodology allows for variation of the catalyst and the three carbonyl components; thereby creating a modular platform in the enantioselective synthesis of sugars, polyketide segments, and their isotope-labeled analogues. In addition, this reaction methodology lays the ground for the direct synthesis of different sugar diastereomers with high enantioselectivity. The mechanistic studies of the one-pot and two-step polyketide sugar synthesis revealed that proline catalyzes the formation of deoxysugars in one chemical manipulation with excellent chemo- and diastereoselectivity by an amino acid catalyzed DYKAT. The DYKAT involves racemization of the β-hydroxyaldehyde intermediates by means of *retro*-aldolization and cross-aldol reactions. Furthermore, all amino acids tested catalyzed the asymmetric neogenesis of natural sugars in water. The intrinsic ability of amino acids to react with carbonyl compounds and mediate the asymmetric for-

racemization of the *anti*-β-hydroxyaldehyde adduct **5** as described vide infra. The accumulated enantiomer *ent*-**5** undergoes a highly diastereoselective cross-aldol reaction with the catalytically generated enamine between L-proline and propionaldehyde to yield the corresponding triketide sugar *ent*-**4** with modest *ee*. However, L-proline catalyzed DYKAT of propionaldehyde can be highly enantioselective, which suggests that if the right kinetic conditions are selected for the one-pot reactions it should be possible to significantly improve the *ee* of the polyketide sugars produced.[23] The allose diastereomer was not observed in the synthesis of polyketide sugars **4b** and **4c**. Thus, the potential transition state **III** is more favored than **IV** (Figure 4). A possible explanation for this may be that hydrogen bonding between the β-hydroxy-group and the carbonyl moiety of **5** significantly decreases the rate of reaction in the second L-proline mediated propionaldehyde addition (Figure 4). In addition, this potential hydrogen-bonding interaction in transition state **IV** may explain why the amino acid catalyzed cross-aldol reaction predominantly yields the corresponding β-hydroxy aldehyde adducts and not hexoses.[12]

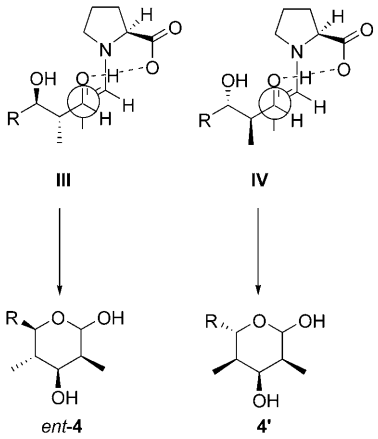


Figure 4. Proposed transition states **III** and **IV** for the one-pot asymmetric assembly of polyketide sugars.

Conclusion

In summary, we have reported the amino acid catalyzed neogenesis of carbohydrates. The direct amino acid catalyzed asymmetric de novo syntheses of hexoses proceeds with excellent chemo-, diastereo-, and enantioselectivty in organic solvents. The employment of one- or two-step direct

mation of carbohydrates may warrant a catalytic prebiotic homochirality pathway for the process whereby extraterrestrial amino acids transferred their stereochemical information. This potentially ancient mechanism suggests that amino acids may have been the first "enzymes", with alanine being the smallest.

Experimental Section

General methods: Chemicals and solvents were either purchased (puriss p. A.) from commercial suppliers or purified by standard techniques. For thin-layer chromatography (TLC), silica gel plates Merck 60 F254 were used and compounds visualized by irradiation with UV light and/or by treatment with a solution of phosphomolybdic acid (25 g), $Ce(SO_4)_2{\cdot}H_2O$ (10 g), conc. H_2SO_4 (60 mL), and H_2O (940 mL) followed by heating or by treatment with a solution of *p*-anisaldehyde (23 mL), conc. H_2SO_4 (35 mL), acetic acid (10 mL), and ethanol (900 mL) followed by heating. Flash chromatography was performed using silica gel Merck 60 (particle size 0.040–0.063 mm). ^{1}H NMR and ^{13}C NMR spectra were recorded on Varian AS 400. Chemical shifts are given in δ relative to tetramethylsilane (TMS); the coupling constants (J) are given in Hz. Spectra were recorded in $CDCl_3$ as the solvent at room temperature. TMS served as internal standard ($\delta = 0$ ppm) for ^{1}H NMR spectra, and $CDCl_3$ was used as internal standard ($\delta = 77.0$ ppm) for ^{13}C NMR spectra. GC was carried out using a Varian 3800 GC Instrument. Chiral GC-column used: CP-Chirasil-Dex CB 25 m × 0.32 mm. HPLC was carried out with a Waters 2690 Millennium with photodiode array detector. Optical rotations were recorded on a Perkin Elemer 241 Polarimeter ($\delta = 589$ nm, 1 dm cell). High-resolution mass spectra were recorded on an IonSpec FTMS mass spectrometer with a DHB-matrix.

General experimental procedure for amino acid catalyzed one-pot trimerization of α-benzyloxyacetaldehyde: A solution of α-benzyloxyacetaldehyde (3 mmol) and the selected amino acid (10 mol% proline or 30 mol% hydroxyproline, alanine, or valine either in DMF or DMSO (3 mL) was stirred at room temperature for 2–7 days. After this time, the reaction was quenched by extraction with water, and the combined aqueous layers were back-extracted with three portions of EtOAc. The organic layers were then combined and dried over anhydrous $MgSO_4$, which was subsequently removed by filtration. Next the solvent was removed in vacuo. After purification of the crude product mixture by silica-gel column chromatography (EtOAc/pentane-mixtures) the solvent was removed in vacuo to afford the desired tetrose and protected hexose. The unreacted starting material α-benzyloxyacetaldehyde was recovered and reused in a second one-pot reaction to further improve the yield.

*2,4-Di-O-benzyl-*D*-erythrose* ***1***: ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 3.62$ (d, $J = 5.2$ Hz, 2H), 3.92 (dd, $J = 5.6$, 2.0 Hz, 1H), 4.13 (m, 1H), 4.51 (d, $J = 4.8$ Hz, 2H), 4.55 (d, $J = 11.6$ Hz, 1H), 4.72 (d, $J = 12.0$ Hz, 1H), 7.30 (m, 10H), 9.71 ppm (d, $J = 2$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 69.6$, 70.6, 73.0, 73.2, 83.5, 127.6, 17.8, 127.9, 128.0, 128.1, 128.2, 136.8, 137.4, 201.8 ppm; $[\alpha]_D^{25} = -8.1$ ($c = 3.4$ in $CHCl_3$); MALDI-TOF MS: m/z calcd for $[M+Na]^+$: 323.1259; found: 323.1261. The enantiomeric excess of tetrose **1** was determined by in situ reduction with $NaBH_4$ at 0°C producing the corresponding diol. HPLC (Daicel Chiralpak AD, hexanes/*i*-PrOH = 96:4, flow rate 0.5 mL min^{-1}, $\lambda = 254$ nm): major isomer: $t_{R(anti)} = 82.33$ min; minor isomer: $t_{R(anti)} = 91.55$ min; major isomer: $t_{R(syn)} = 97.08$ min; minor isomer: $t_{R(syn)} = 98.56$ min.

2,4,6-Tri-O-benzyl-allose **2** (α:β 1:2): ^{1}H NMR (400 MHz, $CDCl_3$) β-anomer: $\delta = 3.18$ (m, 1H), 3.51 (m, 1H), 3.61–3.81 (m, 2H), 4.01 (m, 1H), 4.28 (m, 1H), 4.18–4.86 (m, 6H), 5.18 (d, $J = 8.8$ Hz, 1H), 7.28 ppm (m, 15H); α-anomer: $\delta = 3.41$ (m, 0.5H), 3.61–3.90 (m, 1H), 4.19 (m, 0.5H), 4.18–4.86 (m, 3H), 5.23 (brs, 0.5H), 7.28 ppm (m, 7.5H); ^{13}C NMR (100 MHz, $CDCl_3$; α- and β-anomer): $\delta = 65.1$, 67.1, 68.6, 68.8, 69.4, 70.8, 71.0, 71.9, 72.0, 73.4, 73.8, 92.5, 100.3, 125.6, 128.2, 128.3, 128.5, 128.6, 128.8, 138.1, 138.2 ppm; MALDI-TOF MS: m/z calcd for $[M+Na]^+$: 473.194; found: 473.1943. The allose **2** was acetylated according to the general procedure for the determination of enantiomeric excess.

General experimental procedure for the determination of the enantiomeric excess and absolute configuration of hexose 2: Excess acetic anhydride and a catalytic amount of DMAP (0.1 mol%) was added to a solution of hexose **2** (180 mg) in CH_2Cl_2 (2 mL). The reaction mixture was then stirred at room temperature until all of the hexose **2** had been acetylated, as determined by TLC analysis. After this time, the reaction was quenched by extraction with water, and the combined aqueous layers were back-extracted with three portions of EtOAc. The organic layers were then combined and dried over anhydrous Na_2SO_4, which was subsequently removed by filtration. After purification of the crude product mixture by silica-gel column chromatography (EtOAc/pentane-mixtures), the solvent was removed in vacuo to quantitatively afford the desired 1,3-di-acetyl-2,4,6-tri-*O*-benzyl-hexose. Next, this hexose was dissolved in methanol and hydrogenated in the presence of a catalytic amount of Pd/C (0.1 mol%). After 17 h the catalyst was filtered off and the solvent removed in vacuo. The crude benzyl-free hexose was immediately acetylated vide infra to produce the penta-acetylated sugar. All data of the isolated pure penta-O-acetylated β-anomers of hexose **2** were in accordance with 1,2,3,4,6-penta-*O*-acetyl-β-allopyranoside **2a**.[24]

*1,2,3,4,6-Penta-O-acetyl-*β*-*L*-allopyranoside* ***2a***: ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 2.00$ (s, 3H), 2.01(s, 3H), 2.07(s, 3H), 2.11 (s, 3H), 2.16 (s, 3H), 4.20 (m, 3H), 4.99 (m, 2H), 5.69 (t, $J = 2.9$ Hz, 1H), 6.00 ppm (d, $J = 8.8$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 20.4$, 20.6, 20.9, 21.1, 61.8, 65.5, 68.1, 68.2, 71.0, 90.0, 169.0, 169.6, 170.1, 170.3, 170.9 ppm; GC: (CP-Chirasil-Dex CB); $T_{inj} = 250$°C, $T_{det} = 275$°C, flow = 1.8 mL min^{-1}, $t_i =$ 100°C (10 min), $t_f = 200$°C (1.5°C min^{-1}): major isomer: $t_R = 62.72$ min; minor isomer: $t_R = 61.77$ min; $[\alpha]_D^{25} = +15.1$ ($c = 0.5$ in $CHCl_3$);[24] MALDI-TOF MS: m/z calcd for $[M+Na]^+$: 413.1060; found: 413.1061.

The absolute stereochemistry was established by comparison between *ent*-**2a** obtained by peracetylation of commercially available D-allose, which has a t_R value of 61.77 min [GC: (CP-Chirasil-Dex CB); $T_{inj} =$ 250°C, $T_{det} = 275$°C, flow = 1.8 mL min^{-1}, $t_i = 100$°C (10 min), $t_f = 200$°C (1.5°C min^{-1})], and the **2a** derived by L-proline derivative catalysis ($t_R =$ 62.72 min), or the *ent*-**2a** produced by D-proline catalysis ($t_R = 61.77$ min).

General experimental procedure for the neogenesis of sugars in water: A solution of glycol aldehyde (2 mmol) and amino acid (30 mol%) in water (2 mL) was stirred at the temperature shown in Table 2 for 16 h and 8 d. Subsequently, the reaction was quenched by removal of water by lyophilization. In the next step, methanol (3 mL) was added to the lyophilized powder and the crude sugar mixture reduced by the addition of excess $NaBH_4$ at 0°C. To quench the reduction 2 M HCl was added at 0°C, and the methanol removed in vacuo. This was followed by the addition of CH_2Cl_2 (5 mL), pyridine (1 mL), acetic anhydride (2 mL), and DMAP (0.2 mmol) to the crude tetrol and hexitol mixture. After 16 h water (3 mL) was added, and the reaction mixture was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic extracts were subsequently washed with 1 N HCl, brine, and water. The organic phase was dried over anhydrous $NaSO_4$, which was subsequently removed by filtration, and the solvent was removed in vacuo, producing a crude mixture of peracetylated tetrol and hexitol products. These products were then dissolved in EtOAc and analyzed by chiral-phase GC analysis.[25] GC tetra-acetylated erythrol: (CP-Chirasil-Dex CB); $T_{inj} = 250$°C, $T_{det} = 275$°C, flow = 1.5 mL min^{-1}, $t_i = 100$°C (10 min), (1.5°C min^{-1}) $t_f = 180$°C (10.0°C min^{-1}) $t_f = 200$°C (10 min): $t_R = 36.71$ min; GC tetra-acetylated threitol: (CP-Chirasil-Dex CB); $T_{inj} = 250$°C, $T_{det} = 275$°C, flow = 1.5 mL min^{-1}, $t_i =$ 100°C (10 min), (180°C min^{-1}) $t_f = 200$°C (10 min): L-isomer: $t_R =$ 38.56 min; D-isomer: $t_R = 38.70$ min. GC peracetylated hexitols: (CP-Chirasil-Dex CB); $T_{inj} = 250$°C, $T_{det} = 275$°C, flow = 1.8 mL min^{-1}, $t_i = 100$°C (10 min), (1.5°C min^{-1}) $t_f = 180$°C (10.0°C min^{-1}) $t_f = 200$°C (10 min): (The hexitols appeared in the range 63–66 min) major glucitol $t_R =$ 64.70 min; mannitol $t_R = 64.30$ min; gulitol = 64.78 min; allitol $t_R =$ 62.71 min. The tetra-acetylated tetrols were also isolated by silica-gel column chromatography (EtOAc:pentane-mixtures). ^{1}H NMR (400 MHz, $CDCl_3$): (*erythro*:*threo* 2:1) $\delta = 2.06$–2.10 (m, 12H; 4OAc), 4.08 (m, 1H; CH_2), 4.16 (m, 1H; CH_2), 4.30 (m, 2H; CH_2), 5.26 (m, 1H; CH),

5.32 ppm (m, 1H; CH); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.88, 20.89, 21.0, 62.0, 69.3, 69.4, 170.0, 170.1, 170.6, 170.7 ppm.

Two-step synthesis of 3a: A solution of benzyloxyacetaldehyde (3 mmol) and L-proline (10 mg, 0.15 mmol) in DMF (3 mL) was stirred at room temperature for 48 h. After this time, the reaction was quenched by extraction with water, and the combined aqueous layers were back-extracted with three portions of EtOAc. The organic layers were then combined and dried over anhydrous $NaSO_4$, which was subsequently removed by filtration. After purification of the crude product mixture by silica-gel column chromatography (EtOAc/pentane mixtures) the solvent was removed in vacuo to afford the desired cross-aldol adduct. For the next step in the synthesis this product was dissolved in DMF (1 mL), along with the L- or D-amino acid (10 mol%). A suspension of propionaldehyde (388 μl, 4 mmol) in DMF (2 mL) was then added slowly to the reaction mixture at 4 °C over the course of 16 h. Once the addition had been completed, the reaction mixture was warmed to room temperature and stirred for a further 24 h. After this time, the reaction was quenched by extraction with water, and the combined aqueous layers were back-extracted with three portions of EtOAc. The organic layers were then combined and dried over anhydrous $NaSO_4$, which was subsequently removed by filtration. After purification of the crude product mixture by silica-gel column chromatography (EtOAc/pentane mixtures) the solvent was removed in vacuo to afford the desired compound **3a**. Unreacted dimmer was also isolated, and subsequently reused in a second addition to further improve the yield. The crude hexose **3a** was then diacetylated, according to the general procedure described previously, producing the corresponding 1, 3-di-*O*-acetylated derivative of **3a**.

1,3-Di-O-acetylated derivative: ^{1}H NMR (400 MHz, $CDCl_3$; α:β-anomer 1:1): δ = 0.88 (d, J = 7.2 Hz, 3H), 1.08 (d, J = 7.3 Hz, 3H), 2.09 (s, 6H), 2.11 (s, 6H), 2.31 (m, 1H), 2.41 (m, 1H), 3.44 (dd, J = 1.6, 3.6 Hz, 1H), 3.58 (d, J = 3.2 Hz, 1H), 3.67 (m, 2H), 3.89 (d, J = 5.2 Hz, 1H), 4.06 (m, 1H), 4.31–4.72 (m, 8H), 5.18 (t, J = 3.2 Hz, 1H), 5.29 (m, 1H), 5.70 (d, J = 9.6 Hz, 1H; β-anomer), 5.98 (d, J = 2.4 Hz, 1H; α-anomer), 7.28 ppm (m, 20H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 11.3, 11.6, 21.2, 21.3 (2C), 21.4, 33.6, 36.4, 68.7, 68.8, 70.0, 71.8, 72.4, 72.8, 73.6, 73.8, 73.9, 74.6, 94.5, 95.8, 127.9, 128.0, 128.2, 128.4, 128.6 (2C), 138.2, 138.4, 169.7, 170.4 ppm; MALDI-TOF MS: m/z calcd for $[M+Na]^+$: 465.1189; found: 465.1192.

1,3,4,6-Tetra-O-acetyl-2-methyl-α-L-mannopyranoside: ^{1}H NMR (400 MHz, $CDCl_3$; α-anomer): δ = 1.14 (d, J = 7.3 Hz, 3H), 2.03 (s, 3H), 2.04 (m, 1H), 2.05 (s, 3H), 2.08 (s, 3H), 2.14 (s, 3H), 4.02 (dq, J = 9.8, 2.2 Hz, 1H), 4.16 (m, 2H), 5.24 (t, J = 9.3 Hz, 1H), 5.33 (dd, J = 9.8, 5.3 Hz, 1H), 5.98 ppm (d, J = 1.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 11.0, 20.6, 20.7, 20.9, 21.0, 36.6, 62.2, 65.5, 70.6, 70.7, 95.1, 169.0, 169.3, 170.1, 170.7 ppm; GC: (CP-Chirasil-Dex CB); T_{inj} = 250 °C, T_{det} = 275 °C, flow = 1.8 mL min^{-1}, t_i = 100 °C (10 min), t_f = 200 °C (1.5 °C min^{-1}): (α-anomer) major isomer: t_R = 53.41 min; minor isomer: t_R = 52.98 min, (β-anomer) major isomer: t_R = 55.43 min; minor isomer: t_R = 56.10 min; $[\alpha]_D^{25}$ = −46.6 (c = 2 in $CHCl_3$); MALDI-TOF MS: m/z calcd $[M+Na]^+$: 369.1162; found 369.1164.

Two-step synthesis of 3b: A solution of benzyloxyacetaldehyde (2 mmol), propionaldehyde (144 μL, 2 mmol), and L-proline (10 mg, 0.15 mmol) in DMF (2 mL) was stirred at 4 °C for 48 h. After this time, the reaction was quenched by extraction with water, and the combined aqueous layers were back-extracted with three portions of EtOAc. The organic layers were then combined and dried over anhydrous $MgSO_4$, which was subsequently removed by filtration. After purification of the crude product mixture by silica-gel column chromatography (EtOAc/pentane mixtures) the solvent was removed in vacuo to afford the desired tetrose **1**. For the next step in the synthesis, this product was dissolved in DMF (1 mL), along with the L- or D-amino acid (10 mol%). A suspension of propionaldehyde (388 μl, 4 mmol) in DMF (2 mL) was then added slowly to the reaction mixture at 4 °C over the course of 16 h. Once the addition had been completed, the solution was warmed to room temperature and stirred for a further 24 h. After this time, the reaction was quenched by extraction with water and the combined aqueous layers were back-extracted with three portions of EtOAc. The organic layers were then combined and dried over anhydrous $MgSO_4$, which was subsequently removed by filtration. Next the solvent was removed in vacuo. After purification of the crude product mixture by silica-gel column chromatography (EtOAc/pentane mixtures) the solvent was removed in vacuo to afford the desired mannose derivative **3b**. The remaining cross-aldol adduct was isolated and reused in a second reaction to further improve the yield. ^{1}H NMR (400 MHz, $CDCl_3$; α:β-anomer 6:1): δ = 0.91 (d, J = 6.6 Hz, 3H), 1.02 (d, J = 7.1 Hz, 3H), 1.75 (m, 1H), 2.07 (m, 1H), 3.59 (m, 3H), 3.80 (m, 1H), 4.54 (d, J = 12.1 Hz, 1H), 4.61 (d, J = 12.1 Hz, 1H), 5.14 (s, 1H; α-anomer), 7.33 ppm (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 10.4, 13.2, 33.9, 38.5, 71.0, 71.1, 73.3, 73.4, 97.1, 127.6, 127.7, 128.3 138.0 ppm; $[\alpha]_D^{25}$ = −39.5 (c = 1 in $CHCl_3$); MALDI-TOF MS: m/z calcd for $[M+Na]^+$: 289.1416; found: 289.1420.

Determination of the enantiomeric excess of **3b**: Excess MnO_2 (15 mmol) was added to a solution of hexose **3b** (0.27 g, 1 mmol) in EtOAc (5 mL). The resulting reaction mixture was then stirred at room temperature for 3 days. After this time, all solid constituents of the reaction mixture were separated by filtration, and the EtOAC removed in vacuo. Purification of the subsequent crude product mixture by silica-gel column chromatography (EtOAc/pentane mixtures) quantitatively afforded the desired δ-lactone **6a** (0.26 g).

*δ-Lactone **6a***: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.08 (d, J = 6.9 Hz, 3H), 1.28 (d, J = 6.9 Hz, 3H), 2.10 (m, 1H), 2.31 (d, J = 6.9 Hz, 3H), 2.65 (m, 1H), 3.69 (m, 3H), 4.03 (m, 1H), 4.56 (d, J = 11.8 Hz, 1H), 4.63 (d, J = 11.8 Hz, 1H), 7.33 ppm (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 11.4, 16.3, 38.0, 38.7, 70.2, 73.7, 75.0, 81.3, 127.7, 127.8, 128.4, 137.5, 173.6 ppm; $[\alpha]_D^{25}$ = −63.3 (c = 1 in $CHCl_3$); MALDI-TOF MS: m/z calcd $[M+Na]^+$: 287.3067; found: 267.3068. The lactone was converted to the di-acetylated compound according to the general procedure and the enantiomeric excess determined. GC peracetylated lactone: (CP-Chirasil-Dex CB); T_{inj} = 250 °C, T_{det} = 275 °C, flow = 1.8 mL min^{-1}, t_i = 100 °C (35 min), (80 °C min^{-1}), t_f = 200 °C (10 min): major isomer: t_R = 38.15 min; minor isomer: t_R = 38.41 min.

Two-step synthesis of 3c: A solution of proionaldehyde (5 mmol) in DMF (2 mL) was added over a period of 20 h to a solution of α-*tert*-butyldimethylsilyloxyacetaldehyde (1 mmol) and L-proline (10 mg, 0.15 mmol) in DMF (1 mL) at 4 °C. Once the addition had been completed, the reaction was quenched by extraction with water and the combined aqueous layers were back-extracted with three portions of EtOAc. The organic layers were then combined and dried over anhydrous $MgSO_4$), which was subsequently removed by filtration. After purification of the crude product mixture by silica-gel column chromatography (EtOAc/pentane mixtures) the solvent was removed in vacuo to afford the desired β-hydroxy aldehyde. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.07 (s, 6H), 0.89 (s, 9H), 1.10 (d, J = 7.2 Hz, 3H), 2.55 (dq, J = 7.2, 2.2), 2.67 (br s, 1H), 3.60 (dd, J = 10.2, 6.1 Hz, 1H), 3.72 (dd, J = 10.2, 3.9 Hz, 1H), 3.83 (m, 1H), 9.79 ppm (d, J = 2.2, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = −5.6, −5.5, 10.1, 18.2, 25.7, 48.8, 64.6, 72.7, 204.3 ppm. This product (1 mmol) was dissolved in DMF (1 mL), with 10 mol% of D-proline. A suspension of propionaldehyde (4 mmol) in DMF (2 mL) was then added to the reaction mixture at 4 °C over the course of 16 h. Once the addition was complete, the solution was allowed to warm to room temperature and stirred for a further 24 h. The reaction was quenched by extraction with water, and the combined aqueous layers were back-extracted with three portions of EtOAc. The organic layers were then combined and dried over anhydrous $MgSO_4$, which was subsequently removed by filtration. After purification of the crude product mixture by silica-gel column chromatography (EtOAc/pentane mixtures) the solvent was removed in vacuo to afford the desired mannose derivative **3c**. ^{1}H NMR (400 MHz, $CDCl_3$; α-:β-anomer 1:0.4): δ = 0.06 (s, 6H), 0.89 (s, 9H), 0.97 (d, J = 6.2 Hz, 3H), 1.01 (d, J = 7.1 Hz, 3H), 1.84 (m, 1H), 2.06 (m, 1H), 3.72 (m, 2H), 3.82 (dd, J = 9.8, 4.6 Hz, 1H), 5.12 (d, J = 1.8 Hz, 1H), 5.14 ppm (s, 1H; α-anomer); ^{13}C NMR (100 MHz, $CDCl_3$): δ = −5.3, −5.2, 10.5, 13.3, 18.4, 25.9, 33.5, 38.5, 64.1, 71.3, 74.9, 97.2 ppm; $[\alpha]_D^{25}$ = −21.1 (c = 1.5 in $CHCl_3$).

Two-step synthesis of 3d: A solution of α-*tert*-butyldimethylsilyloxyacetaldehyde (2 mmol) and L-proline (0.1 mmol) in DMSO (2 mL) was stirred for 48 h at room temperature. After this time, the reaction was quenched by extraction with water and the combined aqueous layers were back-extracted with three portions of EtOAc. The organic layers

were then combined and dried over anhydrous $MgSO_4$, which was subsequently removed by filtration. After purification of the crude product mixture by silica-gel column chromatography (EtOAc/pentane mixtures) the solvent was removed in vacuo to afford the desired β-hydroxy aldehyde. This product (1 mmol) was dissolved in DMF (1 mL), along with D-proline (10 mol%). A suspension of propionaldehyde (4 mmol) in DMF (2 mL) was then added to the reaction mixture at 4°C over the course of 16 h. Once the addition had been completed, the solution was warmed to room temperature and stirred for a further 24 h. The reaction was quenched by extraction with water and the combined aqueous layers were back-extracted with three portions of EtOAc. The organic layers were then combined and dried over anhydrous $MgSO_4$, which was subsequently removed by filtration. After purification of the crude product mixture by silica-gel column chromatography (EtOAc/pentane mixtures) the solvent was removed in vacuo to afford the desired mannose derivative **3d**. ^{1}H NMR (400 MHz, $CDCl_3$; α-anomer): $\delta = 0.06$ (s, 6H), 0.12 (s, 6H), 0.13 (s, 6H), 0.89 (s, 18H), 1.01 (d, $J = 7.1$ Hz, 3H), 1.91 (d, $J = 4.4$ Hz, 1H), 2.22 (m, 1H), 2.48 (d, $J = 3.0$ Hz, 1H), 3.77 (m, 4H), 3.95 (m, 1H), 5.05 ppm (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = -5.3$, −5.1, −4.7, −4.2, 10.9, 18.2, 18.4, 25.9, 25.9, 39.1, 62.5, 68.8, 71.6, 73.9, 96.8 ppm; $[\alpha]_D^{25} = -12.1$ ($c = 2$ in $CHCl_3$).

General experimental procedure for the two-step synthesis of triketide sugars utilizing direct catalytic asymmetric aldol reactions: A suspension of propionaldehyde (288 μL, 4 mmol) in DMF (2.5 mL) was added over the course of 16–24 h to a stirring suspension of aldehyde (2 mmol) and L- or D-proline (23 mg, 0.2 mmol) in DMF (2.0 mL) at 4°C. After 16 h at 4°C, the resulting solution was diluted with diethyl ether and washed successively with water and brine. The combined aqueous layers were back-extracted with three portions of EtOAc, and the organic layers combined and dried over anhydrous $MgSO_4$, which was subsequently removed by filtration. After purification of the crude product mixture by silica-gel column chromatography (EtOAc/pentane mixtures) the solvent was removed in vacuo to afford the corresponding aldol adduct. The cross-aldol adducts were also synthesized according to Northrup's and MacMillan's procedures.[12b] The cross-aldol product was dissolved in DMF (1 mL), with D-proline (or L-amino acid) (10 mol%). A suspension of propionaldehyde (2 equiv) in DMF (2 mL) was then added to the reaction mixture at 4°C over the course of 16 h. Once the addition had been completed, the solution was warmed to room temperature and stirred for a further 24 h. After this time, the reaction was quenched by extraction with water and the combined aqueous layers were back-extracted with three portions of EtOAc. The organic layers were then combined and dried over anhydrous $MgSO_4$, which was subsequently removed by filtration. After purification of the crude product mixture by silica-gel column chromatography (EtOAc/pentane mixtures) the solvent was removed in vacuo to afford the desired compounds. The remaining β-hydroxyaldehyde was reused in a second cross-aldol addition to further improve the yield.

Triketide ***4a***: ^{1}H NMR (400 MHz, $CDCl_3$; α-anomer): $\delta = 0.94$ (m, 6H), 1.02 (d, $J = 7.2$ Hz, 3H), 1.48 (m, 2H), 1.63 (m, 2H), 2.09 (m, 1H), 2.56 (brs, 1H), 3.54 (ddd, $J = 10.0$, 7.6, 2.8 Hz, 1H), 3.80 (dd, $J = 10.0$, 4.8 Hz, 1H), 5.10 ppm (brs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 9.1$, 10.5, 13.1, 25.2, 36.4, 38.6, 71.1, 74.3, 97.0 ppm; GC peracetylated **2**: (CP-Chirasil-Dex CB); $T_{inj} = 250$°C, $T_{det} = 275$°C, flow = 1.8 mL min^{-1}, $t_i = 100$°C (35 min), $t_f = 200$°C (80°C min^{-1}): (β-anomer) major isomer: $t_R = 35.83$ min; minor isomer: $t_R = 35.73$ min, (α-anomer) major isomer: $t_R = 36.25$ min; minor isomer: $t_R = 36.30$ min; $[\alpha]_D^{25} = -10.2$ ($c = 2$ in $CHCl_3$); MALDI-TOF MS: m/z calcd for $[M+Na]^+$: 197.2272; found: 197.2274.

Triketide ***4b***: ^{1}H NMR (400 MHz, $CDCl_3$; α-anomer): $\delta = 0.89$ (m, 6H), 0.93 (m, 6H), 1.71 (m, 1H), 1.87 (m, 2H), 2.05 (m, 1H), 2.69 (brs, 1H), 3.46 (dd, $J = 10.0$, 2.4 Hz, 1H), 3.77 (dd, $J = 9.4$, 4.6 Hz, 1H), 5.08 ppm (d, $J = 1.6$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 10.6$. 12.9, 14.4, 20.4, 23.1, 34.9, 38.5, 71.7, 77.0, 97.1 ppm; GC peracetylated **4b**: (CP-Chirasil-Dex CB); $T_{inj} = 250$°C, $T_{det} = 275$°C, flow = 1.8 mL min^{-1}, $t_i = 100$°C (35 min), $t_f = 200$°C (80°C min^{-1}): (β-anomer) major isomer: $t_R = 36.12$ min; minor isomer: $t_R = 36.16$ min, (α-anomer) major isomer: $t_R = 36.42$ min; minor isomer: $t_R = 36.55$ min; $[\alpha]_D^{25} = -35.5$ ($c = 1$ in $CHCl_3$); MALDI-TOF MS: m/z calcd for $[M+Na]^+$: 211.1310; found: 211.1311.

Triketide ***4c***: ^{1}H NMR (400 MHz, $CDCl_3$; α-anomer): $\delta = 0.87$ (d, $J = 6.6$ Hz, 3H), 0.92 (m, 6H), 1.02 (d, $J = 7.3$ Hz, 3H), 1.32 (m, 1H), 1.41 (m, 1H), 1.52 (m, 2H), 1.83 (m, 1H), 2.08 (m, 1H), 2.39 (brs, 1H), 3.62 (dd, $J = 10.0$, 2.4 Hz, 1H), 3.73 (dd, $J = 9.4$, 4.6 Hz, 1H), 5.08 ppm (d, $J = 1.6$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 10.8$, 13.3, 21.3, 23.9, 24.1, 38.3, 38.4, 42.2, 71.5, 71.7, 97.1 ppm; GC peracetylated **4c**: (CP-Chirasil-Dex CB); $T_{inj} = 250$°C, $T_{det} = 275$°C, flow = 1.8 mL min^{-1}, $t_i = 100$°C (35 min), $t_f = 200$°C (80°C min^{-1}): (β-anomer) major isomer: $t_R = 36.65$ min; minor isomer: $t_R = 36.68$ min, (α-anomer) major isomer: $t_R = 36.91$ min; minor isomer: $t_R = 36.99$ min; $[\alpha]_D^{25} = -34.0$ ($c = 0.6$ in $CHCl_3$); MALDI-TOF MS: m/z calcd for $[M+Na]^+$: 225.2803; found: 225.2803.

Triketide ***4d***: ^{1}H NMR (400 MHz, $CDCl_3$; α-anomer): $\delta = 0.91$ (m, 6H), 1.18 (m, 5H), 1.47 (m, 3H), 1.71 (m, 6H), 2.05 (m, 1H), 3.42 (m, 1H), 3.77 (dd, $J = 9.3$, 4.4 Hz, 1H), 5.08 ppm (d, $J = 1.5$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 10.7$, 13.1, 25.0, 26.5, 30.8, 34.2, 38.4, 38.5, 71.9, 77.0, 97.2 ppm; GC peracetylated **4**: (CP-Chirasil-Dex CB); $T_{inj} = 250$°C, $T_{det} = 275$°C, flow = 1.8 mL min^{-1}, $t_i = 100$°C (35 min), $t_f = 200$°C (5°C min^{-1}): (β-anomer) major isomer: $t_R = 52.41$ min; minor isomer: $t_R = 52.55$ min, (α-anomer) major isomer: $t_R = 53.03$ min; minor isomer: $t_R = 53.19$ min; $[\alpha]_D^{25} = -29.4$ ($c = 1.0$ in $CHCl_3$); MALDI-TOF MS: m/z calcd for $[M+Na]^+$: 251.3176; found: 251.3180.

General experimental procedure for the one-pot chemoselective formation of deoxyhexose 3b: A solution of α-benzyloxyacetaldehyde (2 mmol), propionaldehyde (2 mmol), and L-proline (10 mol%) in DMF (2 mL) was stirred at room temperature for 48 h. Next, a suspension of propionaldehyde (3 mmol) in DMF (2 mL) was added to the reaction mixture at 4°C over the course of 16 h. Once the addition had been completed, the solution was warmed to room temperature and stirred for a further 24 h. After this time, the reaction was quenched by extraction with water, and the combined aqueous layers were back-extracted with three portions of EtOAc. The organic layers were then combined and dried over anhydrous $MgSO_4$, which was subsequently removed by filtration. After purification of the crude product mixture by silica-gel column chromatography (EtOAc/pentane mixtures) the solvent was removed in vacuo to afford hexose **3b**. The starting α-benzyloxyacetaldehyde and remaining cross-aldol dimer was re-reacted in a second one-pot operation. The hexose **3b** was oxidized with MnO_2 to the corresponding lactone **6a** and converted to the peracetylated compound according to the general procedure previously described.

One-pot proline catalyzed asymmetric formation of triketide 4a: (Table 3, entry 6) A mixture of propionaldehyde (2 mmol) and L-proline (10 mol%) in DMF (2 mL) was stirred at 4°C for 16 h. Next, a suspension of propionaldehyde (2 mmol) in DMF (2 mL) was added to the reaction mixture at 4°C over the course of 16 h. Once the addition had been completed, the solution was warmed to room temperature and stirred for a further 24 h. The reaction was quenched by extraction with water and the combined aqueous layers were back-extracted with three portions of EtOAc. The organic layers were then combined and dried over anhydrous Na_2SO_4, which was subsequently removed by filtration. After purification of the crude product mixture by silica-gel column chromatography (EtOAc/pentane mixtures) the solvent was removed in vacuo to afford triketide *ent*-**4a** as the major diastereomer.

General procedure for δ-lactone synthesis: The sugar (1 mmol) was dissolved in EtOAc (10 mL), and MnO_2 (15 mmol) added in one portion. After 48 h the reaction mixture was filtered to remove all solid constituents, and EtOAc removed in vacuo. Purification of the crude product by silica-gel column chromatography (EtOAc/pentane mixtures) quantitatively afforded the desired δ-lactones.

δ-Lactone ***6b***: ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.95$ (d, $J = 7.2$ Hz, 3H), 1.05 (d, $J = 6.8$ Hz, 3H), 1.07 (d, $J = 6.8$ Hz, 3H), 1.26 (d, $J = 6.8$, 3H), 1.70 (brs, 1H), 1.92 (m, 2H), 2.67 (dq, $J = 6.8$, 4.0 Hz, 1H), 3.73 (dd, $J = 11.2$, 2.0 Hz, 1H), 3.75 ppm (t, $J = 3.6$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 11.2$, 14.6, 16.0, 19.9, 29.2, 38.8, 39.4, 75.7, 85.3, 174.7 ppm; $[\alpha]_D^{25} = -46.3$ ($c = 1.0$ in $CHCl_3$); (CP-Chirasil-Dex CB); $T_{inj} = 250$°C, $T_{det} = 275$°C, flow = 1.8 mL min^{-1}, $t_i = 100$°C (10 min), $t_f = 200$°C (1.5°C min^{-1}): major isomer: $t_R = 36.32$ min; minor isomer: $t_R = 36.49$ min. MALDI-TOF MS: m/z calcd for $[M+Na]^+$: 209.1145; found: 209.1148.

δ-Lactone ***6c***: ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.03$ (t, $J = 7.2$ Hz, 3H), 1.06 (d, $J = 7.2$ Hz, 3H), 1.27 (d, $J = 7.2$ Hz, 3H), 1.61 (m, 2H), 1.80 (m, 2H), 1.90 (br s, 1H), 2.67 (dq, $J = 7.2$, 3.6 Hz, 1H), 3.74 (t, $J = 3.6$ Hz, 1H), 3.76 ppm (ddd, $J = 10.8$, 8.2, 3.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 9.3$, 11.1, 15.9, 26.1, 38.9, 41.7, 75.5, 82.6, 174.5 ppm; $[\alpha]_D^{25} = -69.0$ ($c = 1.5$ in $CHCl_3$); (CP-Chirasil-Dex CB); $T_{inj} = 250\,^\circ$C, $T_{det} = 275\,^\circ$C, flow = 1.8 mL min^{-1}, $t_i = 100\,^\circ$C (35 min), $t_f = 200\,^\circ$C (80 °C min^{-1}): major isomer: $t_R = 36.28$ min; minor isomer: $t_R = 36.37$ min.; MALDI-TOF MS: m/z calcd for $[M+Na]^+$: 195.0992; found: 195.0991.

Direct catalytic synthesis of acrylate **7**: A mixture of α-benzyloxyacetaldehyde (1.5 mmol), aqueous formaldehyde (1 mmol, 36% aqueous solution), and L-proline (10 mol%) in DMF (2 mL) was vigorously stirred at 50 °C. After 8 h the reaction was cooled to room temperature. The reaction was quenched by extraction with water, and the combined aqueous layers were back-extracted with three portions of EtOAc. The organic layers were then combined and dried over anhydrous Na_2SO_4, which was subsequently removed by filtration. After purification of the crude product mixture by silica-gel column chromatography (EtOAc/pentane mixtures) the solvent was removed in vacuo to afford compound **7**. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 4.93$ (s, 2H), 5.14 (d, $J = 3.1$ Hz, 3H), 5.24 (d, $J = 3.1$ Hz, 1H), 7.32–7.38 (m, 5H), 9.13 ppm (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 70.1$, 103.7, 127.3, 128.1, 128.6, 135.5, 158.1, 188.0 ppm.

Direct catalytic synthesis of β-hydroxy aldehyde ***8***: Acrylate **7** (1 mmol) was dissolved in DMF (1 mL), along with L-proline (10 mol%). Next, a suspension of propionaldehyde (2 mmol) in DMF (2 mL) was added to the reaction mixture at 4 °C over the course of 16 h. Once the addition had been completed, the solution was allowed to warm to room temperature and was stirred for a further 24 h. The reaction was quenched by extraction with water, and the combined aqueous layers were back-extracted with three portions of EtOAc. The organic layers were then combined and dried over anhydrous $MgSO_4$, which was subsequently removed by filtration. After purification of the crude product mixture by silica-gel column chromatography (EtOAc/pentane mixtures) the solvent was removed in vacuo to afford the desired cross-aldol adduct **8**. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.12$ (d, $J = 7.1$ Hz, 3H), 2.77 (m, 1H), 4.25 (d, $J = 2.7$ Hz, 1H), 4.36 (d, $J = 2.7$ Hz, 1H), 4.56 (m, 1H), 4.79 (s, 2H), 7.28–7.41 (m, 5H), 9.77 ppm (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 7.8$, 49.5, 69.7, 71.6, 83.7, 127.5, 128.0, 128.5, 128.5, 136.3, 160.7, 204.1 ppm. $[\alpha]_D^{25} = -3.7$ ($c = 1.0$ in $CHCl_3$).

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