Carbohydrate Synthesis

Direct Amino Acid Catalyzed Asymmetric Synthesis of Polyketide Sugars**

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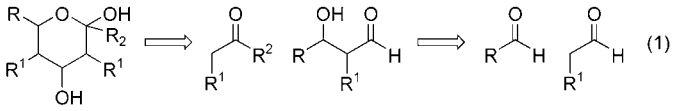
The directed asymmetric assembly of simple achiral building blocks into stereochemically complex molecules like carbohydrates and polyketides has long been accomplished by enzymes in nature.[1,2] The growing interest in glycobiology[3] and the search for novel antibiotics has led to increased activity in developing reaction designs and methods for the synthesis of sugars and polyketides.[1,2,4,5] Among the plethora of methods, the aldol reaction is well established in carbohydrate and triketide synthesis.[6,7] However, it usually requires protective group strategies and subsequent reduction–oxidation steps. One efficient synthetic strategy based on retrosynthetic analysis would be a two-step sugar synthesis involving two iterative aldol reactions with three carbonyl compounds [Eq. (1)]. This potential iterative double-aldol route seems simple and attractive. However, it is challenging to carry out due to the intrinsic chemoselectivity problems with enolizable aldehydes. For example, it is difficult to control whether they would act as donors or acceptors in the sequential aldol reactions.

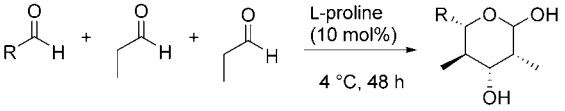


(1)

To date, only enzymes have been able to catalyze sequential one-pot direct aldol reactions with high stereoselectivity.[8] Recently, organocatalysis has been revitalized in the area of asymmetric synthesis.[9] The use of enamine catalysis has enabled the first step of the sequential direct cross-aldol reaction with high stereoselectivity.[10] However, achieving the next amino acid catalyzed aldol step to obtain hexoses with high enantioselectivity has not yet been reported. Initial attempts at conducting one-pot direct catalytic sequential aldol reactions furnished nearly racemic triketide sugars.[10f,g]

Based on retrosynthetic analysis and our interest in developing biomimetic stereoselective transformations catalyzed by amino acids,[11] we envisioned a potential two-step sugar synthesis based on direct amino acid catalyzed selective iterative aldol reactions with aldehydes. Herein, we report the enantioselective de novo synthesis of either enantiomer of natural and unnatural hexoses with up to >99% *ee*. The simplicity and the high stereoselectivity of the hexose formation may support a prebiotic pathway in which amino acids transferred their chiral information to sugars.

In initial experiments we investigated the one-pot direct amino acid catalyzed sequential trimerization of propionaldehyde (Scheme 1). To our delight we were able to signifi-



ent-**1**: R = Et, 31% yield, 85% *ee*
2: R = *i*Pr, traces, *ee* n.d.

Scheme 1. Direct catalytic one-pot enantioselective synthesis of **1**.

cantly increase the *ee* value of the previously reported triketide hexose *ent*-**1** from 49% to 85% *ee* by altering the reaction conditions. However, the new one-pot procedure only provided trace amounts of hexose **2**.

To improve the efficiency and selectivity of the tandem aldol process we decided to isolate the β-hydroxy aldol intermediate from the first aldol transformation prior to the second aldol reaction.[12] The two-step synthetic protocol made it possible to investigate other amino acids as catalysts as well as change the stereochemistry of the amino acid catalyst prior to the second aldol addition. This approach would potentially improve the efficiency and selectivity of the second direct cross-aldol addition. Hence, propionaldehyde was dimerized utilizing L-proline catalysis, and the corresponding isolated β-hydroxy aldehyde was treated with propionaldehyde in the presence of a catalytic amount of D-proline (Table 1, entry 1). To our delight we were able to isolate hexose **1** as a single diastereomer in 29% yield with 99% *ee*.

Encouraged by this result we performed the iterative aldol reactions vide infra with a variety of aldehyde substrates (Table 1). The short synthesis of hexoses proceeded with excellent chemo-, diastereo-, and enantioselectivy. In all cases except one, the corresponding hexoses were isolated as single diastereomers in good overall yield with >99% *ee*. Thus, out of 16 possible stereoisomers amino acid catalysis directs in some cases the creation of a single enantiomer. The yields of the hexoses **1**–**5** were comparable or higher than most conventional multistep sugar syntheses.[6] In addition, this two-step synthesis of sugars is inexpensive and easy to

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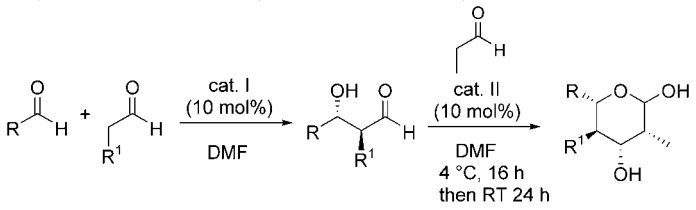
Table 1: Two-step direct amino acid catalyzed enantioselective synthesis of hexoses.



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

[a] Overall yield of the isolated hexoses based on the two steps. [b] Determined by chiral-phase GC analyses of the peracetylated products and compared to racemic standards generated by D,L-proline catalysis. [c] 30 mol% hydroxyproline was used. [d] The overall combined yield of a 10:1 mixture of diastereomers (*anti*:*syn*).

conduct, and it generates minimal waste products. The sequential direct catalytic aldol reactions were also readily scaled up and performed on a gram scale. For example, we performed the two-step catalytic asymmetric synthesis of hexose **2** on a 2-g scale, and triketide sugar **2** was obtained in crystalline form in 42% yield with >99% *ee*. Starting the iterative aldol reactions with D-proline as the catalyst furnished the opposite enantiomer of the hexoses without affecting the stereoselectivity of the reaction. Furthermore, performing the two-step synthesis employing sequential D-proline and L-4-hydroxyproline catalysis improved the *ee* of the triketide sugar *ent*-**1** from 99 to >99% *ee*. Moreover, the amino acids are able to catalyze the total synthesis of natural hexoses in one step. For example, L-4-hydroxyproline catalyzed the trimerization of α-benzyloxyacetaldehyde to yield 2,4,6-tri-*O*-benzylallose in 28% yield as a single diastereomer with >99% *ee*. The hexoses obtained from the tandem direct catalytic asymmetric aldol reactions have free hydroxy groups at C1 and C3, 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 hexoses were quantitatively converted into δ-lactones by oxidation with MnO_2. For example, lactones **6** and **7** were prepared in three steps with >99% *ee* (Scheme 2). Thus, the two-step aldol strategy opens up a novel route to enantiomerically pure δ-lactones from simple aldehydes. This type of compounds were previously synthesized in 11 steps by Staunton and co-workers using Evans-type aldol reactions.[6d]

The absolute configurations of sugars **1**–**5** have been assigned based on the crystal structure of the α-anomer of sugar **2** (Figure 1) and synthesis.[13] The crystal structure reveals that the previously suggested relative configuration of triketide sugar **2** is incorrect.[10f] The hexose **2** obtained by proline catalysis has a mannopyranoside configuration and not the previously believed gulopyranoside configuration. Furthermore, sequential L-proline and D-proline catalysis furnished L-hexoses. Accordingly, the observed stereochemistry of the hexoses can be readily explained (Scheme 3). The initial formation of the β-hydroxyaldehyde proceeds by means of a *re*-facial attack on the acceptor aldehyde by the L-proline-derived enamine, which is in accordance with previous reported proline-catalyzed aldol reactions with aldehydes.[8] Next, the D-proline-catalyzed aldol addition proceeds in a highly *anti*-selective fashion with the *anti*-β-hydroxyaldehyde isomer to form the L-mannose structural motif.

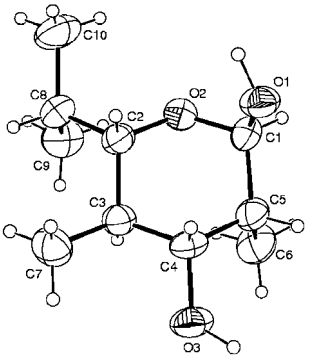
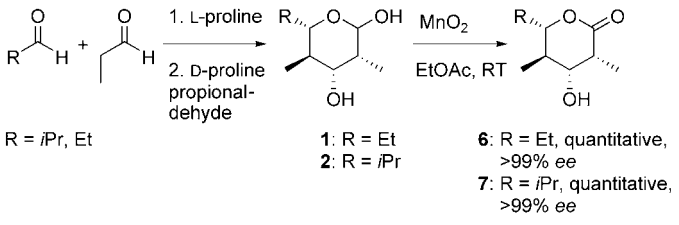
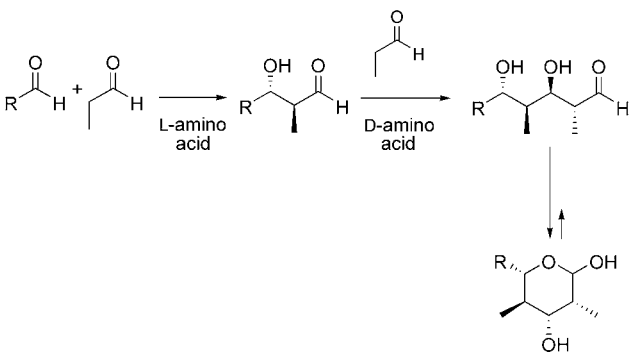


Figure 1. The crystal structure of the α-anomer of hexose **2**.



Scheme 2. Direct catalytic enantioselective synthesis of δ-lactones **6** and **7**.



Scheme 3. The reaction pathway for the amino acid catalyzed triketide hexose synthesis.

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The ability of amino acids to catalyze the asymmetric formation of sugars may have prebiotic significance. In fact, it has been reported that terrestrial and extraterrestrial amino acids catalyze the formation of tetroses under prebiotic conditions.[14] Perhaps amino acids catalyzed asymmetric aldol reactions according to the routes presented and transferred their chiral information to hexoses,[15] which are the building blocks of prebiotic RNA and most common polysaccarides.

In summary, we disclose the direct amino acid catalyzed asymmetric de novo synthesis of hexoses with excellent chemo-, diastereo-, and enantioselectivity. The employment of a two-step direct catalytic synthetic protocol furnished either L- or D-sugars in most cases with $>99\,\%$ *ee*. Thus, the novel synthetic approach allows for the creation of four contiguous stereocenters with excellent stereocontrol. Our hexose synthesis is inexpensive and easy to conduct, and it generates minimal waste products. The iterative aldol reaction methodology allows for variation of both the catalyst and the three carbonyl components, hence facilitating a modular enantioselective synthesis of functional sugars and isotope-labeled sugars. The ability of amino acids to mediate asymmetric formation of natural sugars may support a catalytic prebiotic homochirality pathway in which chiral amino acids transferred their stereochemical information to carbohydrates.

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[1] a) K. M. Koeller, C.-H. Wong, *Nature* **2001**, *409*, 232; b) H. J. M. Gijsen, L. Qiao, W. Fitz, C.-H. Wong, *Chem. Rev.* **1996**, *96*, 443; c) C.-H. Wong, G. M. Whitesides, *Enzymes in Synthetic Organic Chemistry*, Pergamom, Oxford, **1994**.

[2] a) C. Khosla, *J. Org. Chem.* **2000**, *65*, 8127; b) C. Khosla, P. B. Harbury, *Nature* **2001**, *409*, 247; c) N. Wu, F. Kudo, C. Khosla, D. E. Cane, *J. Am. Chem. Soc.* **2000**, *122*, 4847; d) C. N. Boddy, K. Hotta, M. L. Tse, R. E. Watts, C. Khosla, *J. Am. Chem. Soc.* **2004**, *126*, 7436, and references therein.

[3] *Glycochemistry: Principles, Synthesis, and Applications* (Eds.: P. Wang, C. Bertozzi), Marcel Dekker, New York, **2001**.

[4] C. T. Walsh, *Science* **2004**, *303*, 1805.

[5] K. C. Nicolaou, H. J. Mitchell, *Angew. Chem.* **2001**, *113*, 1625; *Angew. Chem. Int. Ed.* **2001**, *40*, 1576.

[6] a) D. A. Evans, E. Hu, J. S. Tedrow, *Org. Lett.* **2001**, *3*, 3133; b) M. P. Sibi, J. Lu, J. Edwards, *J. Org. Chem.* **1997**, *62*, 5864; c) S. G. Davies, R. L. Nicholson, A. D. Smith, *Synlett* **2002**, *10*, 1637; For selected examples of the aldol reaction in assembly of triketides see: d) A. L. Wilkinson, U. Hanefeld, B. Wilkinson, P. F. Leadlay, J. Staunton, *Tetrahedron Lett.* **1998**, *39*, 9827; e) J. R. Gage, D. A. Evans, *Org. Synth.* **1990**, *68*, 83; f) B. C. Raimundo, C. H. Heathcock, *Synlett* **1995**, 1213.

[7] Reviews see: a) D. A. Evans, J. V. Nelson, T. Taber in *Topics in Stereochemistry, Vol. 13*, Wiley, New York, **1982**, p. 1; b) T. D. Machajewski, C.-H. Wong, *Angew. Chem.* **2000**, *112*, 1406; *Angew. Chem. Int. Ed.* **2000**, *39*, 1352; c) C. Palomo, M. Oiarbide, J. M. García, *Chem. Eur. J.* **2002**, *8*, 36; For examples of direct aldol reactions catalyzed by organometallic complexes see: d) Y. M. A. Yamada, N. Yoshikawa, H. Sasai, M. Shibasaki, *Angew. Chem.* **1997**, *109*, 1942; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1871; e) N. Yoshikawa, N. Kumagai, S. Matsunaga, G. Moll, T. Oshima, T. Suzuki, M. Shibasaki, *J. Am. Chem. Soc.* **2001**, *123*, 2466; f) B. M. Trost, H. Ito, *J. Am. Chem. Soc.* **2000**, *122*, 12003; g) B. M. Trost, E. R. Silcoff, H. Ito, *Org. Lett.* **2001**, *3*, 2497; h) D. A. Evans, J. S. Tedrow, J. T. Shaw, C. W. Downey, *J. Am. Chem. Soc.* **2002**, *124*, 392.

[8] a) A. Heine, G. DeSantis, J. G. Luz, M. Mitchell, C.-H. Wong, I. A. Wilson, *Science* **2001**, *294*, 369; b) H. J. M. Gijsen, C.-H. Wong, *J. Am. Chem. Soc.* **1994**, *116*, 8422; c) H. J. M. Gijsen, C.-H. Wong, *J. Am. Chem. Soc.* **1995**, *117*, 7585; d) H. J. M. Gijsen, C.-H. Wong, *J. Am. Chem. Soc.* **1995**, *117*, 2947; e) J. Liu, C.-H. Wong, *Angew. Chem.* **2002**, *114*, 1462; *Angew. Chem. Int. Ed.* **2002**, *41*, 1404.

[9] a) P. I. Dalko, L. Moisan, *Angew. Chem.* **2001**, *113*, 3840; *Angew. Chem. Int. Ed.* **2001**, *40*, 3726; b) B. List, *Tetrahedron* **2002**, *58*, 5573; c) E. R. Jarvo, S. J. Miller, *Tetrahedron* **2002**, *58*, 2481; d) R. O. Duthaler, *Angew. Chem.* **2003**, *115*, 1005; *Angew. Chem. Int. Ed.* **2003**, *42*, 975; e) P. I. Dalko, L. Moisan, *Angew. Chem.* **2004**, *116*, 5248; *Angew. Chem. Int. Ed.* **2004**, *43*, 5138.

[10] a) A. Córdova, W. Notz, C. F. Barbas III, *J. Org. Chem.* **2002**, *67*, 301; b) A. B. Northrup, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2002**, *124*, 6798; c) A. Bøgevig, N. Kumaragurubaran, K. A. Jørgensen, *Chem. Commun.* **2002**, 620; d) N. Mase, F. Tanaka, C. F. Barbas III, *Angew. Chem.* **2004**, *116*, 2474; *Angew. Chem. Int. Ed.* **2004**, *43*, 2420; e) C. Pidathala, L. Hoang, N. Vignola, B. List, *Angew. Chem.* **2003**, *115*, 2474; *Angew. Chem. Int. Ed.* **2003**, *42*, 2785; f) N. S. Chowdari, D. B. Ramachary, A. Córdova, C. F. Barbas III, *Tetrahedron Lett.* **2002**, *43*, 9591; g) A. Córdova, *Tetrahedron Lett.* **2004**, *45*, 3949; h) J. Casas, H. Sundén, A. Córdova, *Tetrahedron Lett.* **2004**, *45*, 6117; i) A. B. Northrup, I. K. Mangion, F. Hettche, D. W. C. MacMillan, *Angew. Chem.* **2004**, *116*, 2204; *Angew. Chem. Int. Ed.* **2004**, *43*, 2152.

[11] a) A. Córdova, H. Sundén, M. Engqvist, I. Ibrahem, J. Casas, *J. Am. Chem. Soc.* **2004**, *126*, 3914; b) A. Bøgevig, H. Sundén, A. Córdova, *Angew. Chem.* **2004**, *116*, 1129; *Angew. Chem. Int. Ed.* **2004**, *43*, 1109; c) A. Córdova, H. Sundén, A. Bøgevig, M. Johansson, F. Himo, *Chem. Eur. J.* **2004**, *10*, 3673; d) A. Córdova, *Chem. Eur. J.* **2004**, *10*, 1987; e) A. Córdova, *Acc. Chem. Res.* **2004**, *37*, 102; f) A. Córdova, *Synlett* **2003**, 1651, and references therein.

[12] After the submission of this manuscript MacMillan and co-workers reported an excellent short synthesis of hexoses based on a proline-catalyzed dimerization of protected glycoaldehydes followed by Lewis acid mediated indirect tandem Mukaiyama aldol addition cyclization reactions. A. B. Northrup, D. W. C. MacMillan, *Science* **2004**, *305*, 1752.

[13] CCDC-251202 contains the crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB21EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk).

[14] S. Pizarello, A. L. Weber, *Science* **2004**, *303*, 1151. For a Zn/amino acid mediated sugar synthesis under prebiotic conditions see: J. Kofoed, M. Machuqueiro, J.-L. Reymond, T. Darbre, *Chem. Commun.* **2004**, *26*, 1540.

[15] a) L. E. Orgel, *Science* **2000**, *290*, 1306; b) N. Hall, *Chem. Commun.* **2004**, 1247, and references therein.

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