Conceivable origins of homochirality in the amino acid catalyzed neogenesis of carbohydrates

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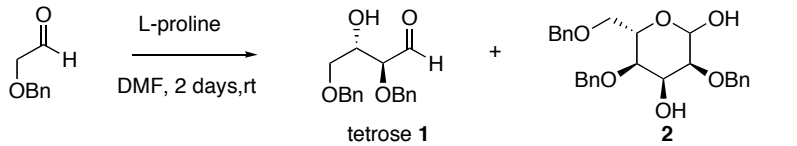
Supporting Information

General. 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 were 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. The spectra were recorded in $CDCl_3$ as solvent at room temperature, TMS served as internal standard (δ = 0 ppm) for ^{1}H NMR, and $CDCl_3$ was used as internal standard (δ = 77.0 ppm) for ^{13}C NMR. GC was carried out using a Varian 3800 GC Instrument. Chiral GC-column used: CP-Chirasil-Dex CB 25m x 0.32mm. Optical rotations were recorded on a Perkin Elemer 241 Polarimeter (λ=589 nm, 1 dm cell). Optical rotations were recorded on a Perkin Elemer 241 Polarimeter (λ=589 nm, 1 dm cell). High resolution mass spectra were recorded on an IonSpec FTMS mass spectrometer with a DHB-matrix.

Typical experimental procedure for one-step proline-catalyzed asymmetric synthesis of allose 1. A solution of benzyloxyacetaldehyde (2 mmol) and proline (10 mol %, the e.e of the proline was varied according to Figure 1) in DMF (2 mL) was stirred at room temperature for 2 days. The reaction was quenched by extraction. The combined aqueous layers were back-extracted with 3 portions of EtOAc. The combined organic layers were dried over anhydrous $MgSO_4$, which was subsequently removed by filtration. Next, the solvent was removed under reduced pressure following purification of the crude product mixture by silica-gel column chromatography (EtOAc:pentane-mixtures or toluene:EtOAc mixtures) to afford the desired tetrose and protected allose **1**. Remaining starting material was reused in a second reaction sequence to further improve the yield.



2, 4-Benzyl-O-D-erythrose: ^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 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 (d, *J* = 2 Hz, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm): 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; $[\alpha]_D^{25}$ = -8.1 (*c* = 3.4, $CHCl_3$); MALDI-TOF MS: 323.1261; $C_{19}H_{20}O_4$ (M+Na^+: calcd 323.1259). The enantiomeric excess of the tetrose was determined by in situ reduction with $NaBH_4$ at 0 ºC to furnish the corresponding diol. HPLC (Daicel Chiralpak AD, hexanes/*i*-PrOH = 96:4, flow rate 0.5 mL/min, λ = 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.

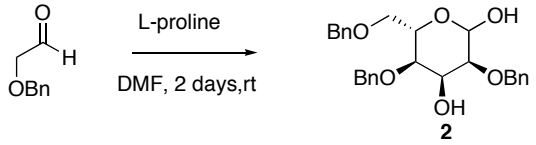
2, 4, 6-tri-*O*-benzyl-allose **2** (α:β-1:2): ^{1}H-NMR (400 MHz, $CDCl_3$) β-anomer: δ (ppm) 3.18 (dd, 1H), 3.51 (m, 1H), 3.61-3.81 (m, 2H), 4.01 (m, 1H), 4.28 (t, 1H), 4.18-4.86 (m, 6H), 5.18 (d, *J* = 8.8 Hz, 1H), 7.28 (m, 15H); α-anomer: δ (ppm) 3.41 (m, 0.5 H), 3.61-3.90 (m, 1H), 4.19 (m, 0.5H), 4.18-4.86 (m, 3H), 5.23 (bs, 0.5H), 7.28 (m, 7.5H); ^{13}C-NMR (100 MHz, $CDCl_3$) α- and β- anomer: δ (ppm) 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. MALDI-TOF MS: 473.1943; $C_{27}H_{33}O_6$ (M+Na^+: calcd 473.194). The allose **1** was peracetylated according to the general procedure and the enantiomeric excess determined.

General determination of the enantiomeric excesses of allose 2: The hexose (180 mg) was dissolved in 2 mL CH_2Cl_2 followed by addition of excess acetic anhydride and a catalytic amount of DMAP (0.1 mol%). The reaction was stirred at room temperature until all the hexose **2** had been acetylated as determined by TLC analyses. The reactions were quenched by extraction. The combined aqueous layers were back-extracted with 3 portions of EtOAc. The combined organic layers were dried over anhydrous Na_2SO_4, which was subsequently removed by filtration. Next, the solvent was removed under reduced pressure following purification of the crude product mixture by silica-gel column chromatography (EtOAc:pentane-mixtures) to quantitatively afford the desired 1, 3-di-acetyl-2, 4, 6-tri-O-benzyl-hexoses. Next, the hexoses were dissolved in MeOH and hydrogenated in the presence of a catalytic amount of Pd/C (0.1 mol%). After 17h the catalyst was filtered off and the solvent removed under reduced pressure. The crude benzyl-free hexoses were immediately acetylated vide infra to furnish the penta-acetylated sugars. All data of the isolated pure penta-*O*-acetylated β-anomers of hexose **2** was in accordance with 1, 2, 3, 4, 6-Penta-*O*-acetyl-β-L-allopyranoside.[1]

1, 2, 3, 4, 6-Penta-O-acetyl-β-L-allopyranoside: ^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 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 (d, *J* = 8.8 Hz, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm): 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; GC: (CP-Chirasil-Dex CB); T_{inj} = 250 °C, T_{det} = 275 °C, flow = 1.8 mL/min, t_i = 100 °C (10 min), t_f = 200°C (1.5 °C/ min): major isomer: t_R = 62.72 min;

minor isomer: t_R = 61.77 min; $[\alpha]_D^{25}$ = +15.1 (*c* = 0.5, $CHCl_3$, >99% e.e.); MALDI-TOF MS: 413.1061; $C_{16}H_{22}O_{11}$ (M+Na^+: calcd 413.1060).[1]

Table 1S. The relation of the enantiomeric excess of L-proline and that of the newly formed sugar **2**.



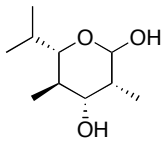
2

Entry	L-proline Ee (%)	**2** Yield (%)[a]	**2** Ee (%)[b]
1	>99	26	>99
2	80	23	>99
3	60	20	>99
4	50	15	99
5	40	<15	99
6	30	<15	88
7	20	n.d.[c]	55
8	10	n.d.[c]	33
9	0	23	0

[a] Isolated yield after silica-gel column chromatography. [b] The ee of hexose **2** was determined by chiral-phase GC analyses of the peracetylated hexose. Racemic hexose **2** was obtained by D,L-proline catalysis.[c] not determined.

Direct amino acid catalyzed synthesis of 4. The cross-aldol adduct **3** was synthesized according to MacMillan's and ours procedures utilizing D,L-proline (10 mol%) as the catalyst.[2] The racemic cross-aldol product **3** was dissolved in 1 mL of DMF, with 10 mol% of D-proline. Next, a suspension of propionaldehyde (2 equivalents) in 2 mL DMF was added slowly over the course of 16h to the reaction mixture at 4 °C. Next, the solution was allowed to react at room temperature and stirred for 24h. The reaction was quenched by extraction. The combined aqueous layers were back-extracted with 3 portions of EtOAc. The combined organic layers were dried over anhydrous $MgSO_4$, which was subsequently removed by filtration. Next, the solvent was removed under reduced pressure following purification of the crude product mixture by silica-gel column chromatography (EtOAc:pentane-mixtures) to afford the desired hexose **4** together with the starting aldehyde **3**. The remaining racemic β-hydroxyaldehyde **3** was reused in a second cross-aldol addition to further improve the yield.

[1] All the data were in accordance with the peracetylated commercially available β-D-(-)-allopyranose obtained from Sigma. Litt. $[\alpha]_D$ = -15.0 (c = 0.5, $CHCl_3$). E. Lee, P. Browne, P. McArdle, D. Cunningham, *Carbohydr. Res.*, **224**, 285. (1992).; R. U. Lemieux, J. D. Stevens, *Can. J. Chem.*, **43**, 2059 (1965).



4

^{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 (bs, 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), 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; GC peracetylated **3**: (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 = 36.12 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, $CHCl_3$); MALDI-TOF MS: 211,1311; $C_{10}H_{20}O_3$ ($M+Na^+$: calcd 211.1310).

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[2] (a) A. B. Northrup, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2002**, *124*, 6798. (b) J. Casas, M. Engqvist, B. Kaynak, *Angew. Chem. Int. Ed.* **2005**, Early view.