Asymmetric Synthesis

Direct Organocatalytic De Novo Synthesis of Carbohydrates**

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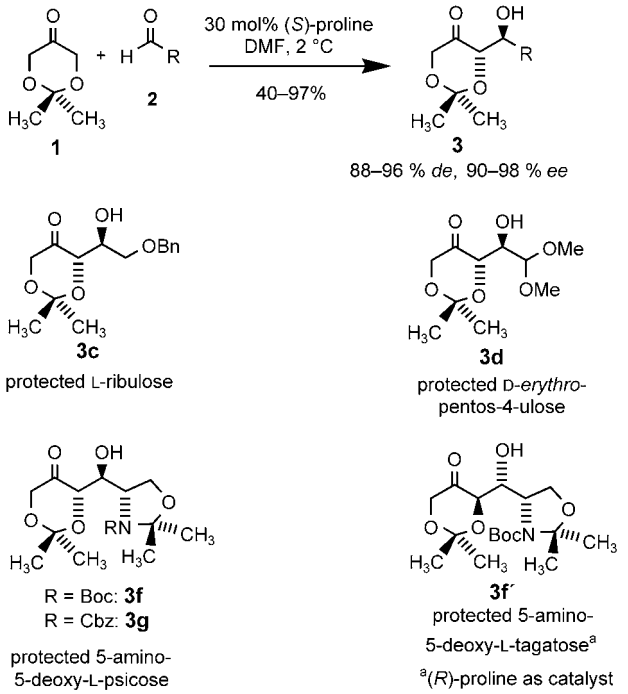
Dedicated to Professor Wilhelm Keim on the occasion of his 70th birthday

Carbohydrates are a class of natural products of great importance in chemical, biological, and medicinal research.[1] Carbohydrates play a key role in many biological processes, for example, as components of glycoproteins, nucleic acids, glycolipids, peptido- and proteoglycans, and liposaccharides.[2] They are both target molecules in modern organic synthesis and sources of enantiopure building blocks (chiron approach)[3] and chiral auxiliaries.[4] An extensive arsenal of methods for the de novo synthesis of carbohydrates is already available, but typically several synthetic steps and extensive protecting group manipulations are necessary.[5] Recently, MacMillan et al. disclosed a "two-step" synthesis of aldohexoses based on an asymmetric proline-catalyzed aldol reaction.[6] Nature also employs a stereoselective aldol reaction in the biosynthesis of carbohydrates; the carbohydrate skeleton is assembled by means of an enzyme-catalyzed aldol reaction of dihydroxyacetone phosphate (DHAP).[7]

The application of DHAP in carbohydrate synthesis has been investigated quite intensively with biological methods in particular,[8] but also chemical methods could be employed successfully with DHA and its derivatives as C_3 building blocks in asymmetric synthesis.[9] A new challenge concerning syntheses with DHA as a C_3 building block is the development of organocatalytic methods. Barbas III et al. described a direct aldol reaction of DHA with different aldehydes, in which proline and various proline derivatives were used as catalysts. While in part good diastereoselectivities were reached, the products turned out to be racemic in all cases.[10]

We now report on the successful development of the first diastereo- and enantioselective organocatalytic aldol reaction with 2,2-dimethyl-1,3-dioxan-5-one (**1**, dioxanone)[11] as a DHA equivalent and methylene component. When suitable aldehyde carbonyl components are employed, this biomimetic C_3+C_n strategy facilitates the direct assembly of selectively protected ketoses in one step.

For our first example we chose 2-methylpropanal (**2a**) as a model system for the aldol reaction with dioxanone and optimized the reaction conditions in terms of chemical yield, enantiomeric excess, and *anti*/*syn* ratio. The best reaction conditions so far call for (*S*)-proline as the catalyst, DMF as the solvent, and a temperature of 2 °C. The *anti* aldol product **3a** was obtained diastereoselectively with an excellent yield of 97 %, an *anti*/*syn* ratio of > 98:2, and a high enantiomeric excess of 94 % *ee*. Subsequently we were also able to show that the aldol reaction of **1** with the α-branched aldehydes **2a**, **b**, **d**–**g** proceeds with good to very good yields, excellent *anti*/*syn* ratios, and enantiomeric excesses in all cases (Scheme 1, Table 1). When the linear aldehyde **2c** was employed, the aldol product **3c** was isolated in only moderate yield (40 %), but still excellent stereoselectivity (*anti*/*syn* = > 98:2, 97 % *ee*). The lower yield may be explained by the fact that linear aldehydes also undergo self-aldol condensation, which is in direct competition with the crossed-aldol reaction. The use of aromatic aldehydes as the carbonyl component reduced the diastereoselectivity. For example, the (*S*)-proline-catalyzed aldol reaction of **1** with *ortho*-chlorobenzaldehyde proceeded with a good yield of 73 % but with an *anti*/*syn*



Scheme 1. (*S*)- and (*R*)-proline-catalyzed asymmetric aldol reaction of dioxanone with various aldehydes.

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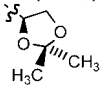
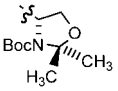
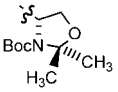
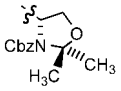
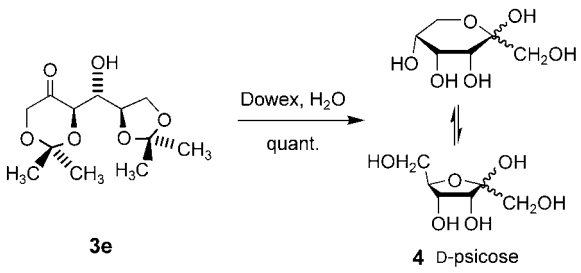
Table 1: (*S*)-proline-catalyzed asymmetric aldol reaction of dioxanone **1** with aldehydes **2** to form the aldol products **3** (see Scheme 1).[a]

3	R	Yield [%][b]	*anti*/*syn* [%][c]	*ee* [%][d]
a	$CH(CH_3)_2$	97	>98:2	94
b	Cy[i]	86	>98:2	90
c	CH_2OBn[i]	40	>98:2	97
d	$CH(OCH_3)_2$	69	94:6	93
e		76	>98:2	≥98[e,f]
f		80	>98:2	≥96[g]
f′		31	>98:2	≥96[e,g]
g		80	>98:2	≥96[h]

[a] General reaction conditions: 2.3 mmol dioxanone, 2.3 mmol aldehyde, 30 mol% (*S*)-proline, 1.2 mL DMF, 2°C, 6 d. [b] Yields of **3** isolated after flash chromatography on silica gel. [c] Determined by ^1H and ^{13}C NMR spectroscopy. [d] Determined by HPLC on chiral stationary phases (Chiralpak AD, Chiralpak IA 5μ, Daicel IA, Daicel OJ, Whelk 01). [e] (*R*)-proline was used as the catalyst. [f] Based on the *ee* value of **2e**. [g] Based on the *ee* value of **2f**. [h] Based on the *ee* value of **2g**. [i] Abbreviations: Bn = benzyl, Boc = tert-butyloxycarbonyl, Cbz = benzyloxycarbonyl, Cy = cyclohexyl.

ratio of only 4:1 and enantiomeric excesses of 86% *ee* (*anti*) and 70% *ee* (*syn*). The aldol products **3** accessible directly by organocatalysis are selectively and partly orthogonal doubly protected sugars and amino sugars, for example, L-ribulose (**3c**), D-*erythro*-pentos-4-ulose (**3d**), 5-amino-5-deoxy-L-psicose (**3f**, **g**), and 5-amino-5-deoxy-L-tagatose (**3f′**). In the case of **3d**, the stereoselective ketose reduction followed by acetal hydrolysis should lead to an aldose ("inversion strategy"),[12] which will greatly expand the potential of this new protocol.

When we used the *S*-configured, enantiomerically pure NBoc- (**2f**) and NCbz-protected Garner aldehydes (**2g**), (*S*)-proline proved to be the appropriate catalyst, since high chemical yields (80%), excellent *anti*/*syn* ratios (>98:2), and high *ee* values (96% *ee*) were obtained for the corresponding aldol products **3f** and **3g**. As expected, (*R*)-proline was not the appropriate catalyst for this aldol reaction because it led to a significant decrease in yield (31%) although the diastereoselectivity remained high (for **3f′**). Consequently, (*R*)-proline was the appropriate catalyst for the reaction of α-branched *R*-configured aldehydes. This could be confirmed by the aldol reaction of **1** with the *R*-configured 2,3-*O*-(isopropylidene)-D-glyceraldehyde (**2e**).[13] The double acetonide-protected D-psicose **3e**,[14] which was obtained with 76% yield in this way, was quantitatively deprotected with an acidic ion-exchange resin (Dowex W50X2-200) to give the parent D-psicose (**4**, Scheme 2). The identity of the ketohexose could be proven unambiguously by spectroscopic comparison (^1H and ^{13}C NMR, HPLC, and optical rotation data) with an authentic, commercially available sample.



Scheme 2. Deprotection of **3e** to give D-psicose (**4**) (mixture of the four isomers α,β-D-psicofuranose and α,β-D-psicopyranose).

The formation of the *anti* aldol products **3** and the absolute configurations given are consistent with related proline-catalyzed aldol reactions.[15] The absolute configurations were also confirmed by polarimetric comparison with independently synthesized aldol products.[16] The observed relative topicity can be explained by the Houk–List model for proline-catalyzed aldol reactions with cyclic ketones, where an enamine intermediate and an intermolecular hydrogen bond play the decisive role (Figure 1).[17]

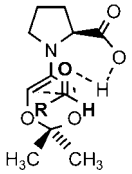
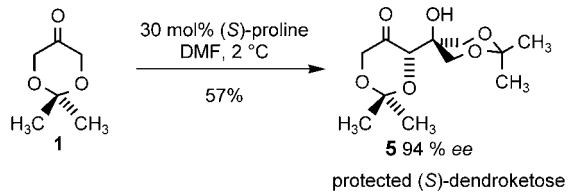


Figure 1. Postulated transition state (Houk–List model) for the (*S*)-proline-catalyzed one-step de novo synthesis of simple sugars and derivatives.

Further investigations revealed that under proline catalysis compound **1** underwent self-aldol condensation to give the adduct **5**, which represents a direct precursor of (*S*)-dendroketose (Scheme 3).[18] The aldol addition proceeded with high enantioselectivity (94% *ee*) and a moderate yield of 57%. This observation shows that in principle ketones can act as carbonyl components under formation of quaternary stereogenic centers. It is unnecessary to point out that a simple change of (*S*)- to (*R*)-proline as catalyst leads to the opposite absolute configurations at the aldol C_3/C_4 centers (here (*R*)-dendroketose, see also **3e** and **3f′**).



Scheme 3. (*S*)-proline-catalyzed asymmetric self-aldol condensation of dioxanone **1** to give the double acetonide-protected (*S*)-dendroketose **5**.

In conclusion, our asymmetric, (*S*)-proline-catalyzed aldol reaction of the DHA equivalent **1** with various aldehydes generates the same relative and absolute configuration as the enzyme tagatose aldolase (TagA). Whereas the TagA catalyzed aldol reaction proceeds unselectively,[19] our organocatalytic approach offers a viable alternative. As shown with the asymmetric synthesis of the rare ketosugar D-psicose (**4**) and related simple sugars and amino sugars, this new protocol

opens an impressively simple, biomimetic direct approach to selectively and differently protected simple carbohydrates and related compounds in practically one step. At present, we are optimizing and extending this procedure by varying the methylene and carbonyl components as well as the organocatalyst.

Experimental Section

Unless otherwise stated, all chemicals are commercially available and were used without further purification. All new compounds were fully characterized (IR, NMR, MS, elemental analysis, optical rotation).

3e: Compound **1** (1.0 g, 7.69 mmol) was dissolved in dimethylformamide (4 mL) in a 10-mL round-bottomed flask, and (*R*)-proline (266 mg, 2.31 mmol) was added with stirring. The suspension was stirred for 30 min after which freshly prepared **2e** (1.0 g, 7.69 mmol) was added. The flask was evacuated, flushed with argon and stored at 2 °C for 6 d. The suspension was quenched with sat. aq. ammonium chloride solution (2 mL) and extracted with ethyl acetate (3 × 5 mL). The combined organic layers were concentrated and purified by flash column chromatography using silica gel (diethyl ether/pentane, 2:1). Product **3e** (1.52 g, 76 %) was obtained as a colorless oil. $[\alpha]_D^{24} = 126.8$ ($c = 1.02$ in $CHCl_3$); IR ($CHCl_3$): $\tilde{\nu} = 3461$ (s), 3133 (s), 2988 (m), 2939 (m), 1747 (s), 1378 (s), 1224 (s), 1157 (m), 1069 (s), 990 (w), 948 (w), 889 (m), 853 (s), 758 cm^{-1} (s); ^1H NMR (400 MHz, $CDCl_3$): $\delta = 1.33$ (s, 3H, CCH_3), 1.37 (s, 3H, CCH_3), 1.47 (s, 6H, $C(CH_3)_2$), 2.96 (s, 1H, O*H*), 3.98–4.09 (m, 4H), 4.27–4.34 (m, 2H), 4.45 ppm (dd, $J = 3.3$ Hz, $J = 1.3$ Hz, 1H, C*H*); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 23.2$ (CH_3), 24.5 (CH_3), 25.2 (CH_3), 26.3 (CH_3), 66.1 (CH_2), 66.7 (CH_2), 71.9 (*C*H), 74.9 (*C*H), 76.1 (*C*H), 100.5 ($C(CH_3)_2$), 109.2 ($C(CH_3)_2$), 206.9 ppm (*C*O); MS (CI, isobutane): *m/z* (%): 261 (1) [$M^+ + 1$], 245 (82) [$M^+ - CH_3$], 202 (15) [$M^+ - CO(CH_3)_2$], 187 (41) [$C_8H_{11}O_5^+$] , 131 (32) [$C_6H_{11}O_3^+$], 101 (100) [$C_4H_5O_3^+$], 72 (14) [$C_3H_4O_2^+$], 59 (50) [$C_3H_7O^+$]; elemental analysis calcd for $C_{12}H_{20}O_6$ (%): C 55.37, H 7.74; found: C 55.02, H 7.73.

4: The aldol product **3e** (520 mg, 2 mmol) was stirred with 10 mL deionized water in a 10-mL round-bottomed flask, and Dowex W50X2-200 ion-exchange resin (350 mg) was added. After complete conversion (followed by TLC) the ion-exchange resin was removed by filtration over glass wool, and the aqueous solution was lyophilized, affording D-psicose (**4**) (360 mg, 100 %). If necessary, D-psicose was purified using silica gel (ethyl acetate/methanol, 6:1). $[\alpha]_D^{24} = +3.02$ (c = 1.16 in H_2O); Lit.: $[\alpha]_D^{20} = +3.1$ (c = 1.62 in H_2O);[20] ^1H NMR (400 MHz, D_2O) mixture of α,β-D-psicofuranose and α,β-D-psicopyranose: $\delta = 3.31$ (d, $J = 11.8$ Hz), 3.43–3.71 (m), 3.81–3.95 (m), 4.07 (m), 4.20 ppm (dd, $J = 7.7$ Hz, $J = 4.7$ Hz); ^{13}C NMR (125 MHz, D_2O): $\delta = 60.0$ (*C*HOH), 61.4 (*C*HOH), 62.4 (CHOH), 62.9 (CH_2), 63.1 (*C*HOH), 63.3 (CH_2), 64.0 (*C*HOH), 64.2 (*C*HOH), 65.1 (*C*HOH), 65.5 (CH_2), 65.9 (*C*HOH), 69.0 (CH_2), 70.2 (CH_2), 70.3 (CH_2), 71.0 (*C*HOH), 71.7 (*C*HOH), 74.7 (*C*HOH), 82.7 (*C*HOH; CH_2), 97.6 ($C(OH)OCH_2$), 98.4 ($C(OH)OCH_2$), 103.2 ($C(OH)OCH_2$), 105.6 ppm ($C(OH)OCH_2$).

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[1] a) K. C. Nicolaou, H. J. Mitchell, *Angew. Chem.* **2001**, *113*, 1625 – 1672, *Angew. Chem. Int. Ed.* **2001**, *40*, 1576 – 1624; b) *Carbohydrats Mimics* (Ed.: Y. Chapleur), Wiley-VCH, Weinheim, **1998**.

[2] a) M. Sznaidman in *Bioorganic Chemistry: Carbohydrates* (Ed.: S. M. Hecht), Oxford University Press, New York, **1999**, pp. 1 – 56; b) K. M. Koeller, C.-H. Wong, *Chem. Rev.* **2000**, *100*, 4465 – 4493; c) A. Varki, *Glycobiology* **1993**, *3*, 97 – 130.

[3] S. Hanessian, *Total Synthesis of Natural Products: The "Chiron" Approach*, Pergamon, Oxford, **1983**.

[4] H. Kunz, K. Rück, *Angew. Chem.* **1993**, *105*, 355 – 377; *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 336 – 358.

[5] a) T. Ogawa, *Chem. Soc. Rev.* **1994**, *23*, 397 – 407; b) S. J. Danishefsky, M. T. Bilodeau, *Angew. Chem.* **1996**, *108*, 1482 – 1522; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1380 – 1520; c) S. Hanessian, *Preparative Carbohydrate Chemistry*, Marcel Dekker, New York, **1997**; d) T. Hudlicky, D. A. Entwistle, K. K. Pitzer, A. J. Thorpe, *Chem. Rev.* **1996**, *96*, 1195 – 1220.

[6] a) A. B. Northrup, I. K. Mangion, F. Hettche, D. W. C. MacMillan, *Angew. Chem.* **2004**, *116*, 2004 – 2006; *Angew. Chem. Int. Ed.* **2004**, *43*, 2152 – 2154; b) A. B. Northrup, D. W. C. MacMillan, *Science* **2004**, *305*, 1752 – 1755.

[7] M. Calvin, *Angew. Chem.* **1962**, *74*, 165 – 175; *Angew. Chem. Int. Ed. Engl.* **1962**, *1*, 65 – 75.

[8] a) "Enolates, Organocatalysis, Biocatalysis and Natural Product Synthesis": W.-D. Fessner in *Modern Aldol Reactions*, *Vol. 1* (Ed.: R. Mahrwald), Wiley-VCH, Weinheim, **2004**, 201 – 272; b) C.-H. Wong, T. D. Machajewski, *Angew. Chem.* **2000**, *112*, 1206 – 1230; *Angew. Chem. Int. Ed.* **2000**, *39*, 1352 – 1375; c) W.-D. Fessner, C. Walter, *Top. Curr. Chem.* **1996**, *184*, 97 – 194; d) S. Takayama, G. J. McGarvey, C.-H. Wong, *Chem. Soc. Rev.* **1997**, *26*, 407 – 415; e) M. Schürmann, M. Schürmann, G. A. Sprenger, *J. Mol. Catal. B* **2002**, *8*, 19 – 20, 247 – 252.

[9] Review: D. Enders, M. Voith, A. Lenzen, *Angew. Chem.* **2005**, *117*; *Angew. Chem. Int. Ed.* **2005**, *44*, in press.

[10] a) A. Córdova, W. Notz, C. F. Barbas III, *Chem. Commun.* **2002**, 3024 – 3025; b) For an efficient proline-catalyzed aldol reaction of hydroxy acetone with aldehydes see: W. Notz, B. List, *J. Am. Chem. Soc.* **2000**, *122*, 7386 – 7387.

[11] Dioxanone **1** can be synthesized easily by undergraduate students on a 1-mol scale from simple precursors and is also commercially available. a) D. Enders, M. Voith, S. J. Ince, *Synthesis* **2002**, 1775 – 1779; b) D. Enders, B. Bockstiegel, *Synthesis* **1989**, 493 – 496.

[12] C. W. Borysenko, A. Spaltenstein, J. A. Straub, G. M. Whitesides, *J. Am. Chem. Soc.* **1989**, *111*, 9275 – 9276.

[13] Freshly prepared **2e** was used for the aldol reaction due to its tendency for polymerization and racemization.

[14] M. Majewski, P. Nowak, *J. Org. Chem.* **2000**, *65*, 5152 – 5160.

[15] a) B. List, *Acc. Chem. Res.* **2004**, *37*, 548 – 557; b) B. List, L. Hoang, H. J. Martin, *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 5839 – 5842; c) "Enolates, Organocatalysis, Biocatalysis and Natural Product Synthesis": B. List in *Modern Aldol Reactions*, *Vol. 1* (Ed.: R. Mahrwald), Wiley-VCH, Weinheim, **2004**, 161 – 200.

[16] a) D. Enders, O. Prokopenko, G. Raabe, J. Runsink, *Synthesis* **1996**, 1095 – 1100; b) D. Enders, S. J. Ince, *Synthesis* **2002**, 619 – 624.

[17] a) S. Bahmanyar, K. N. Houk, H. J. Martin, B. List, *J. Am. Chem. Soc.* **2003**, *125*, 2475 – 2479; L. Hoang, S. Bahmanyar, K. N. Houk, B. List, *J. Am. Chem. Soc.* **2003**, *125*, 16 – 17; c) S. Bahmanyar, K. N. Houk, *J. Am. Chem. Soc.* **2001**, *123*, 12911 – 12912.

[18] H. C. Jarrell, W. A. Szarek, J. K. N. Jones, A. Dmytraczenko, E. B. Rathbone, *Carbohydr. Res.* **1975**, *45*, 151 – 159; b) W. A. Szarek, G. W. Schnarr, H. C. Jarrell, J. K. N. Jones, *Carbohydr. Res.* **1977**, *53*, 101 – 108.

[19] a) W.-D. Fessner, O. Eyrisch, *Angew. Chem.* **1992**, *104*, 76 – 78; *Angew. Chem. Int. Ed. Engl.* **1992**, *31*, 56 – 58; b) O. Eyrisch, G. Sinerius, W.-D. Fessner, *Carbohydr. Res.* **1993**, *238*, 287 – 306; c) E. Garcia-Junceda, G. J. Shen, T. Sugai, C.-H. Wong, *Bioorg. Med. Chem.* **1995**, *3*, 945 – 953.

[20] M. Steiger, T. Reichstein, *Helv. Chim. Acta* **1936**, *19*, 184 – 189.

