Proline-Catalyzed One-Step Asymmetric Synthesis of 5-Hydroxy-(2*E*)-hexenal from Acetaldehyde

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Abstract: For the first time, the L-proline-catalyzed direct asymmetric self-aldolization of acetaldehyde is described affording (+)-(5*S*)-hydroxy-(2*E*)-hexenal **2** with ee's ranging from 57 to 90%. Further transformations of **2** into synthetically valuable building blocks are presented. A mechanism for the formation of **2** is proposed.

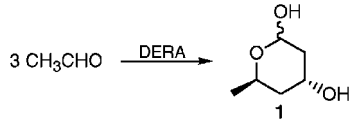
The aldol reaction constitutes an important transformation in several biosynthetic pathways, particularly those involving carbohydrates and polyketides. Whereas carbohydrates are typically synthesized via a direct aldol reaction by an aldolase enzyme,[1] polyketide scaffolds are constructed by modular polyketide synthases (PKSs) via a Claisen condensation of two acyl-CoA units and subsequent reduction of the β-keto moiety to afford the corresponding β-hydroxy acyl-CoA.[2]

In 1994, Wong and co-workers described the stereoselective synthesis of polyketide precursors in a single step. In their scheme, 2-deoxyribose-5-phosphate aldolase (DERA) catalyzed the double-aldol sequence using only acetaldehyde to afford cyclized trimer **1** (Scheme 1).[3]

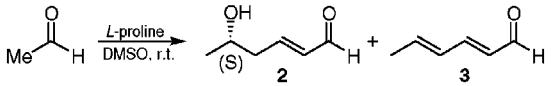
As a complement to natural aldolases, we have developed catalytic antibodies such as 38C2 and 84G3 that have a broad scope for aldol as well as mechanistically related reactions providing products with excellent regio-, diastereo-, and enantioselectivities.[4]

Yet, to date, when aldehydes were used as donors in cross- as well as self-aldolizations, these antibodies have only afforded the corresponding aldol condensation products.[4e] Expanding our efforts in this field, we recently reported the proline-catalyzed direct asymmetric aldol reaction between simple ketones and various aldehydes

Scheme 1. Aldolase-Catalyzed Self-Aldolization of Acetaldehyde



Scheme 2. Proline-Catalyzed Self-Aldol Reaction of Acetaldehyde



$[\alpha]_D$ = +12.7 (57% *ee*)

affording the corresponding cross aldol products under very mild conditions and often with excellent enantioselectivities.[5,6] However, no aldehydes have been employed as aldol donors, and we became interested in whether proline is capable of catalyzing the self-aldol reaction of acetaldehyde to furnish polyketides in a manner similar to DERA.

In an initial experiment, a 4:1 mixture of DMSO/acetaldehyde (10 mL) was treated with L-proline (35 mg) as catalyst for 14 h at 23 °C. We observed the formation of two products, which, after isolation and characterization, were determined to be (+)-(5*S*)-hydroxy-(2*E*)-hexenal **2** and 2,4-hexadienal **3** (Scheme 2).

Triketide **2** was formed in 13% yield (w/w) and 57% ee, together with 5% of **3**. The absolute configuration of the newly formed stereogenic center of **2** was established to be *S* by comparison with its known optical rotation.[7a] The formation of **2** is particularly noteworthy since this transformation can be achieved in a single step by proline catalysis as compared to the multistep syntheses of (*S*)-**2** reported earlier.[7a−c]

Encouraged by this result, we investigated a variety of solvents and reaction temperatures and found pronounced effects on both the yield and ee of **2** (Table 1).

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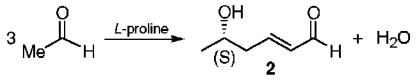
Table 1. Proline-Catalyzed Self-Aldol Reaction of Acetaldehyde under Different Reaction Conditions



solvent	*T* (°C)	time (h)	ee[a] (%)	yield of **2**[b]
acetonitrile	23	14	66	9
acetonitrile	4	5	69	5
DMSO	23	14	57	13
dioxane	23	14	69	7
dioxane	0	5	82	9
EtOAc	23	14	57	3
THF	23	14	69	8
THF	4	14	84	12
THF	0	5	90	10
NMP	23	14	56	4
neat	23	14	57	5
chloroform	23	14	68	2
toluene	23	14	n.d.	traces
MTBE	23	14	n.d.	traces
octane	23	14	n.d.	traces

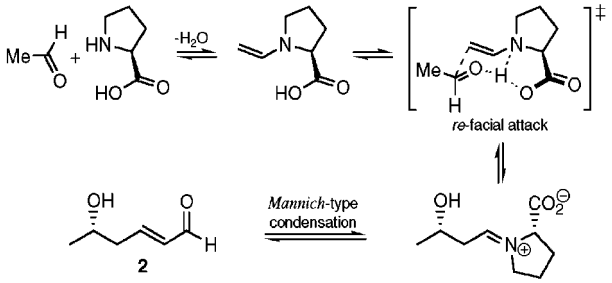
[a] Determined by chiral stationary phase HPLC. See the Experimental Section. [b] Isolated yields in w/w % after column chromatography. In a typical experiment, a mixture of solvent/acetaldehyde (4:1, 10 mL) and L-proline (35 mg) was stirred at the indicated temperature for the indicated period of time. The crude reaction mixture was filtered through silica gel and then purified by column chromatography.

Whereas **2** was readily formed at 23 °C within 14 h in polar aprotic solvents with ee's ranging from 56 to 69%, only trace amounts of **2** were produced in nonpolar solvents such as toluene and octane where the major product formed was diene **3**. Decreasing the reaction temperature to 0−4 °C not only resulted in an increase of the yield and ee of **2** but also diminished the formation of side product **3**.[8] The best results were obtained using anhydrous THF at 0 °C, thereby affording **2** with an ee of 90%. We also performed the reaction on a larger scale (20% acetaldehyde/THF, 500 mL) at 4 °C with D-proline (1.2 g) yielding (*R*)-**2** (2.9 g) with 84% ee together with side product **3** (0.5 g).

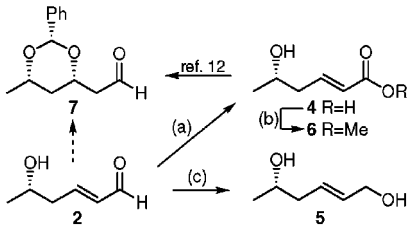
The stereochemical result of this self-aldol reaction is in accordance with our previously proposed transition-state model for the proline-catalyzed aldol reaction of acetone with aldehydes.[5d] In the case of acetaldehyde, an analogous enamine is involved in a *re*-facial attack of the carbonyl group of acetaldehyde (Scheme 3). After the carbon−carbon bond-forming step, however, we assume that the resulting reactive iminium ion, instead of being hydrolyzed, might react further in a Mannich-type condensation[9] to afford **2**.

In contrast to the DERA-catalyzed reaction, where the reaction is terminated after two aldol additions by formation of hemiacetal **1**, the proline-catalyzed reaction does not proceed beyond the formation of **2** since this product is no longer reactive enough to undergo an additional aldol addition with another molecule of acetaldehyde. This is consistent with our earlier observation that no cross-aldolization occurred between acetone and hexenal or cinnamaldehyde.[10] Interestingly, the formation of hemiacetal **1** was not catalyzed by proline.

Scheme 3. Proposed Reaction Mechanism for the Proline-Catalyzed Self-Aldol Reaction of Acetaldehyde



Scheme 4. Transformation of 2 into Synthetically Valuable Synthons 4−7[a]



[a] Reagents and conditions: (a) $NaClO_2$, KH_2PO_4, 2-methyl-2-butene, *t*-BuOH/H_2O, 89%; (b) CH_2N_2, Et_2O, 96%; (c) $NaBH_4$, MeOH/THF, 92%.

Aldehyde **2** is a versatile synthon for other synthetically valuable building blocks. For example, the aldehyde functionality of **2** can be readily oxidized ($NaClO_2$) or reduced ($NaBH_4$) to afford the corresponding carboxylic acid **4**[11] or allylic alcohol **5**,[7c] respectively (Scheme 4). Furthermore, carboxylic acid **4** can be readily transformed into aldehyde **7** upon treatment of methyl ester **6** with benzaldehyde and catalytic amounts of KHMDS and subsequent reduction with DIBALH.[12] Thus, the stereogenic center at C-3 that would have been originally obtained from a double aldol addition reaction can be restored with complete stereoselectivity via internal Michael addition of the hemiacetal. Attempts to achieve the direct conversion of **2** to **7**, however, were unsuccessful.[13]

Compounds **2**, **4**, **5**, and **7** and their enantiomers are also structural motifs common to important macrolide antibiotics such as Grahamimycin A and A_1, Carbomycin B and Platenomycin.[7c,11,12a] For implementation of these building blocks in total synthesis, products (*R*)-**2** and (*S*)-**2** could be readily obtained on gram scale in enantiomerically pure form via kinetic resolution by *Candida antarctica* lipase B (CALB) using vinyl acetate as acetyl donor followed by separation of the corresponding acetate (*R*)-**8**[11] and unreacted (*S*)-**2**. Subsequent enzymatic hydrolysis of (*R*)-**8** yielded (*R*)-**2** in > 99% ee and 95% yield (Scheme 5).

(7) Several syntheses of **2** and its enantiomer have been described. See: (a) Lichtenthaler, F. W.; Klingler, F. D.; Jarglis, P. *Carbohydr. Res.* **1984**, *132*, C1. (b) Nakajima, N.; Uoto, K.; Yonemitsu, O.; Hata, T. *Chem. Pharm. Bull.* **1991**, *39*, 64. (c) Keck, G. E.; Palani, A.; McHardy, S. F. *J. Org. Chem.* **1994**, *59*, 3113. For the synthesis of (*S*)-ethyl (*β*)-hydroxybutyrate, see: (d) Seebach, D.; Züger, M. *Helv. Chim. Acta* **1982**, *65*, 495. (e) Noyori, R.; Ohkama, T.; Kitamura, M.; Takaya, H.; Sayo, N.; Kumobayashi, H.; Akutagawa, S. *J. Am. Chem. Soc.* **1987**, *109*, 5856.

(8) Performing the reaction at temperatures below 0 °C did not provide further improvements in the ee of **2**.

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(10) Unpublished results.

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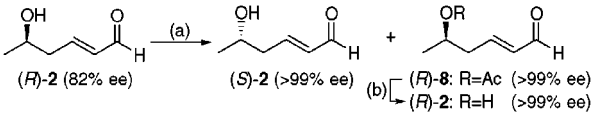
(13) Application of this protocol to the corresponding unsaturated hydroxy ketones by Evans et al. were also unsuccessful. See ref 12b.

Scheme 5. Preparation of Enantiomerically Pure 2 by Kinetic Resolution with *Candida antarctica* Lipase B[a]



[a] Reagents and conditions: (a) *Candida antarctica* lipase B (CALB), vinyl acetate, CH_2Cl_2; (b) CALB, dioxane/PBS buffer (1:1), 95%.

In summary, for the first time, we have demonstrated the proline-catalyzed direct asymmetric self-aldolization of acetaldehyde affording triketide **2** on a multigram scale with high ee. This reaction is operationally facile, and compared to other syntheses, cost and time efficient. Triketide **2** can be readily transformed into a number of other chiral building blocks. Further investigations of this reaction with respect to its mechanism as well as the implementation of **2** in total synthesis are in progress and will be reported in due course.

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 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), concentrated H_2SO_4 (60 mL), and H_2O (940 mL) followed by heating or by treatment with a solution of *p*-anisaldehyde (23 mL), concentrated 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). HPLC was carried out using a Hitachi organizer consisting of a D-2500 Chromato-Integrator, a L-4000 UV-detector, and a L-6200A intelligent pump. Optical rotations were recorded on a Perkin-Elmer 241 polarimeter ($\lambda = 589$ nm, 1 dm cell). The lipase (component B) Novozym 435 derived from *C. antarctica* is a product of Novo Nordisk A/S Denmark. The enzyme used was an immobilized preparation on a macroporous poly(acrylic) resin, containing 1% (w/w) enzyme, with a catalytic activity of approximately 25 000 LU/g preparation. CALB was dried in a desiccator over P_2O_5 prior to use.

(5*S*)-Hydroxy-(2*E*)-hexenal ((*S*)-2). A mixture of THF/acetaldehyde (4:1, 500 mL) and L-proline (1.2 g) was stirred for 14 h at 4 °C. The crude reaction mixture was filtered through silical gel and then purified by flash column chromatography (hexanes/ethyl acetate = 1:1) to afford (*S*)-**2** (2.9 g) together with **3** (0.5 g). The ee was determined by chiral stationary-phase HPLC analysis using a Chiralpak Daicel AD-RH column and eluting with 15% acetonitrile/water (0.1% TFA), flow rate 0.7 mL/min, $\lambda = 272$ nm. (*S*)-enantiomer of **2**: $t_R = 15.74$ min. (*R*)-enantiomer of **2**: $t_R = 19.96$ min.

1,(5*S*)-Dihydroxy-(2*E*)-hexene (5). To a solution of (*S*)-**2** (114 mg, 1 mmol) in MeOH/THF (10 mL, 1:1) was added sodium borohydride, and the mixture was stirred for 15 min. The solvent was removed, and after addition of water and extraction with diethyl ether, the organic phase was dried ($MgSO_4$), concentrated in vacuo, and purified by flash column chromatography (hexanes/ethyl acetate = 1:4) to afford **5**[7c] (106 mg, 92%).

Methyl (5*S*)-Hydroxy-(2*E*)-hexenoate (6). To a magnetically stirred solution of (*S*)-**2** (100 mg, 0.87 mmol) in *tert*-butyl alcohol/water (5:1, 10 mL) were added successively NaH_2PO_4 (180 mg, 1.5 mmol), 2-methyl-2-butene (3 mL, 2 M solution in THF, 6.0 mmol), and $NaClO_2$ (270 mg, 3.0 mmol). The resulting mixture was stirred for 4 h until the yellow solution turned colorless. The solvent was removed under reduced pressure, and the residue was extracted with ethyl acetate, washed with water and brine, and dried over $MgSO_4$. The combined organic layers were concentrated, and the residual acid **4**[11] was dissolved in diethyl ether (10 mL) and treated with excess diazomethane in diethyl ether, the excess being consumed by addition of acetic acid. Concentration in vacuo, coevaporation with toluene, and purification of the residue by flash chromatography (hexanes/ethyl acetate = 1:1) afforded methyl ester **6**[12] (106 mg, 0.73 mmol, 85%).

Kinetic Resolution with CALB. A 0.87 M solution of (*R*)-**2** (ee = 82%) in anhydrous dichloromethane was treated with 1 equiv of vinyl acetate and 100 mg of CALB for 16 h at room temperature. After filtration of the enzyme, the reaction mixture was concentrated and the residue purified by flash column chromatography (hexanes/ethyl acetate = 1:1) affording quantitatively enantiomerically pure (*S*)-**2** and (*R*)-**8**.[11] (*R*)-**8** was subsequently deacetylated in a 1:1-mixture of dioxane/PBS buffer (20 mL) using CALB (100 mg) to provide enantiomerically pure (*R*)-**2**.

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