Tetrahedron Letters, Vol. 33, No. 36, pp. 5157-5160, 1992
Printed in Great Britain

0040-4039/92 $5.00 + .00
Pergamon Press Ltd

Preparation of Optically Pure L-2-Hydroxyaldehydes with Yeast Transketolase[1]

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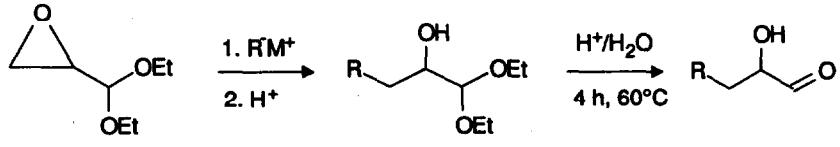
Abstract: L-2-Hydroxyaldehydes L-3 with a great variety of substituents in 3-position are obtained in good chemical and excellent optical yields by kinetic resolution in the transketolase-catalyzed reaction of racemic 2-hydroxyaldehydes with lithium hydroxypyruvate 4 where only the enantiomer (*R*)-3 reacts to 5-deoxy-D-xyluloses 5.

Exclusively the (*R*)-enantiomer of racemic 3-azido-2-hydroxypropanal reacts with lithium hydroxypyruvate 4 and yeast transketolase (EC 2.2.1.1) as catalyst to 5-azido-5-deoxy-D-xylulose;[2] from the reaction mixture the (*S*)-enantiomer can be isolated in good chemical yield and high optical purity.[2] A kinetic resolution of racemic 2-hydroxyaldehydes, which are interesting compounds for various syntheses,[3] with transketolase as catalyst therefore can be reached. Transketolase-catalyzed kinetic separations of racemic 2-hydroxyaldehydes were mentioned in the literature,[4] but were not yet used for the preparation of optically active α-hydroxyaldehydes.

In generally, optically active 2-hydroxyaldehydes can be synthesized by hydrogenation of the corresponding 2-hydroxycarboxylic acid derivatives.[5] Several optically active 2-hydroxyaldehydes were obtained as their diethyl acetals via lipase-catalyzed kinetic resolution of racemic 2-acetoxyaldehyde diethyl acetals.[6] Optically pure glyceraldehydes, important starting compounds for many syntheses,[3] were obtained from natural sources. For example (*R*)-2,3-*O*-isopropylidene glyceraldehyde is accessible from D-mannitol and the corresponding (*S*)-enantiomer starting from L-ascorbic acid.[7] (*R*)- and (*S*)-2-*O*-benzyl glyceraldehyde resp. which are less sensible to racemization can be obtained from the esters of D- or L-tartaric acid.[8]

From the racemic 2-hydroxyaldehydes **3a-g**, used for the transketolase-catalyzed reactions, the aldehydes **3a**, **3c**, and **3g** have not yet been described in the literature; they were obtained by regioselective ring opening of the easily accessible 2-(diethoxymethyl)oxirane[9] **1** with the respective nucleophiles R^-M^+ (Table 1).



1 **2** **3**

The regioselectivity of the oxirane ring opening is influenced by electronic and steric effects.[10] With strong nucleophiles ring opening of **1** occurs exclusively in 3-position to give the acetals **2** which can be isolated and characterized. The hydroxyaldehydes **3** itself, however, received by acid catalyzed hydrolysis

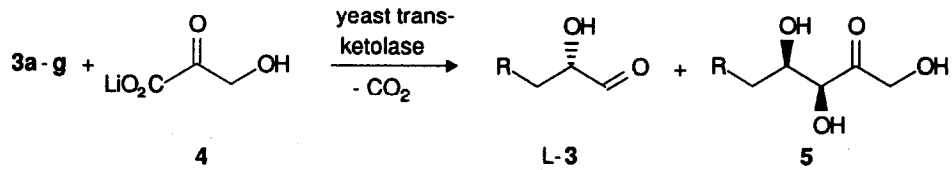
from compounds **2** are obtained in aqueous solution as hydrates or as colorless dimers, for example **3a** and **3g**, whose structure has been established by mass spectrometry.[11]

Table 1. Yields of Diacetals **2** and Hydroxyaldehydes **3** by Nucleophilic Ring Opening of the Oxirane **1** and Subsequent Hydrolysis

R^-	M^+		**2** yield [%]		**3** yield [%]
$PhCH_2O$	Na	**a**	45	**a**	85[a]
HS	K	**c**	95	**c**	92
CN	K	**g**	60	**g**	96[a]

[a] Isolated as dimers.

Racemic 2-hydroxyaldehydes **3a-g** react with lithium hydroxypyruvate **4** and yeast transketolase (EC 2.2.1.1) as catalyst to give the L-2-hydroxyaldehydes L-**3a,b,d-g** and the corresponding 5-substituted 5-deoxy-D-xyluloses **5a-g** in good chemical yields and in excellent optical purity (Table 2).



4 L-**3** **5**

Table 2. Yeast Transketolase (TK)-Catalyzed Reaction of Racemic 2-Hydroxyaldehydes **3a-g** with Equimolar Amounts of Lithium Hydroxypyruvate **4**[12]

educts, reaction conditions				L-3				5	
		TK	time	yield	*ee*	$[\alpha]_D^{20}$	yield	$[\alpha]_D^{20}$
3	R	[U/mmol **3**]	[h]	[%]	[%]	(c, solvent)	[%]	(c, solvent)
3a	$PhCH_2O$	3.0	168	(*S*)-**3a**	75	98	+2.8°(0.25,$CHCl_3$)	**5a**	79	-2.0° (1.0,$CHCl_3$)[a]
3b	CH_3O	2.7	24	(*S*)-**3b**	72	99	-7.5° (0.6,D_2O)	**5b**	72	+5.1° (0.4,H_2O)
3c	SH	5.4	24	(*R*)-**3c**	-	-	-	**5c**	80	-116° (0.3,H_2O)[b]
3d	EtS	2.7	168	(*R*)-**3d**	52	99	-15.7° (0.3,H_2O)	**5d**	74	-37.5° (0.7,EtOH)[c]
3e	F	4.0	24	(*R*)-**3e**	71	96	-12° (1.0,H_2O)	**5e**	79	-2.4° (0.3,D_2O)
3f	CH_3	1.7	84	(*S*)-**3f**	50	99	-23.5° (1.0,H_2O)	**5f**	80	+9.5° (0.4,H_2O)[d]
3g	CN	1.9	24	(*S*)-**3g**	78	97	-22.8° (0.8,D_2O)	**5g**	82	+5.3° (3.6,D_2O)

a) $[\alpha]_D^{20}$ = -2.2° (c = 0.98, $CHCl_3$).[13] b) $[\alpha]_D^{20}$ = -103.8° (c = 3.23, D_2O).[14] c) $[\alpha]_D^{20}$ = -41° (c = 0.9, EtOH).[15]
d) $[\alpha]_D^{20}$ = +6° (c = 2.5, H_2O).[16]

The highest conversion in the yeast transketolase-catalyzed reaction is achieved with lithium hydroxypyruvate **4** and racemic 2-hydroxyaldehydes **3** in equimolar ratio. Despite a partly deactivation of the enzyme, a subsequent addition of transketolase is not necessary. The course of the resolution of the racemic aldehydes **3** was followed either by derivatization (**3a,b,d-g**) or by measuring the optical rotation (**3c**). After incubation at 30°C at the pH optimum 7.6 of the enzyme[17] the reactions were started by addition of the enzyme. The reactions were stopped by addition of Dowex 50WX8 H^+ and Dowex 1X8 HCO_3^- when no change of concentration of **4** nor a change of α_D for L-**3** is observed. The pure 2-hydroxyaldehydes L-**3b,d-g** and the 2-ketoses **5** were isolated by chromatography on Dowex 50WX8 Ca^{2+}. In case of the reaction of **3c** only the ketose **5c** but not L-**3c** could be isolated. (*S*)-**3a** and **5a** were obtained by extraction and perforation with diethyl ether or ethyl acetate followed by column chromatography on silica gel. The L-hydroxyaldehydes L-**3** were converted into the corresponding diethyl acetals and the enantiomeric excess was determined by gas chromatography on a β-cyclodextrine phase. The enantiomerically pure hydroxyaldehydes L-**3** are oily compounds; they do not dimerize in aqueous solution in contrast to the racemic aldehydes **3**.

Acknowledgement: This work was generously supported by the Deutsche Forschungsgemeinschaft.

References and Notes

1. Enzyme-catalyzed Reactions, Part 12.- Part 11: Effenberger, F.; Stelzer, U. *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 873-874.
2. Ziegler, T.; Straub, A.; Effenberger, F. *Angew. Chem. Int. Ed. Engl.* **1988**, *27*, 716-717.
3. Mulzer, J. (R)- and (S)-2,3-Isopropylidene Glyceraldehyde - "Unbiased" Chiral Starting Materials. In *Organic Synthesis Highlights;* Altenbach, H.-J.; Braun, M.; Krohn, K.; Reissig, H. Eds.; VCH-Verlagsgesellschaft: Weinheim, 1991; pp. 243-250.
Bestmann, H.J.; Pecher, B.; Riemer, C. *Synthesis* **1991**, 731-734.
4. Bolte, J.; Demuynck, C.; Samaki, H. *Tetrahedron Lett.* **1987**, *28*, 5525-5528.
Myles, D.C.; Andrulis III, P.J.; Whitesides, G.M. *Tetrahedron Lett.* **1991**, *32*, 4835-4838.
5. Massad, S.K.; Hawkins, L.D.; Baker, D.C. *J. Org. Chem.* **1983**, *48*, 5180-5182.
Hoppe, D.; Tarara, G.; Wilckens, M. *Synthesis* **1989**, 83-88.
Kobayashi, Y.; Takase, M.; Ito, Y.; Terashima, S. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 3038-3040.
Effenberger, F.; Hopf, M.; Ziegler, T.; Hudelmayer, J. *Chem. Ber.* **1991**, *124*, 1651-1659.
6. Von der Osten, C.H.; Sinskey, A.J.; Barbas, C.F.; Pederson, R.L.; Wang, Y.-F.; Wong, C.-H. *J. Am. Chem. Soc.* **1989**, *111*, 3924-3927.
Pederson, R.L.; Liu, K.K.-C.; Rutan, J.F.; Chen, L.; Wong, C.-H. *J. Org. Chem.* **1990**, *55*, 4897-4901.
7. Fischer, H.O.L.; Baer, E. *Helv. Chim. Acta* **1936**, *19*, 519-532.
Dumont, R.; Pfander, H. *Helv. Chim. Acta* **1983**, *66*, 814-823.
Schmid, C.R.; Bryant, J.D.; Dowlatzedah, M.; Phillips, J.L.; Prather, D.E.; Schantz, R.D.; Sear, N.L.; Vianco, C.S. *J. Org. Chem.* **1991**, *56*, 4056-4058.
Takano, S.; Numata, H.; Ogasawara, K. *Heterocycles* **1982**, *19*, 327-328.
8. Jäger, V.; Wehner, V. *Angew. Chem. Int. Ed. Engl.* **1989**, *28*, 469-470.
9. Payne, G.B.; Deming, P.H.; Williams, P.H. *J. Org. Chem.* **1961**, *26*, 659-663.
10. Parker, R.E.; Isaacs, N.S. *Chem. Rev.* **1959**, *59*, 737-799.
Behrens, C.H.; Sharpless, K.B. *Aldrichimica Acta* **1983**, *16*, 67-79.
11. Racemic **3a** (persilylated): MS (70 eV): Calc. 504.2363 Found 504.2360; *m/z* (%): 504 (0.06) [M^+], 324 (0.32) [M^+-2(CH_3)$_3$SiOH], 281 (2.6), 107 (11.2), 91 (100) [$C_7H_7^+$]. Racemic **3g** (persilylated): MS (70 eV): Calc. 342.1431 Found 342.1430; *m/z* (%): 341 (1.5), 191 (18.4), 156 (100).
12. Preparation of 2-hydroxyaldehydes L-**3** and ketoses **5**; general procedure: A freshly prepared solution of the corresponding aldehyde **3a-g**, **4** (each 25 - 50 mM), $MgCl_2$ dihydrate and thiamine pyrophosphate in Tris-HCl buffer (0.5 M, pH 7.6) were incubated at 30°C. The reactions are started by addition of yeast transketolase (EC 2.2.1.1) (Table 2). After the given time (Table 2) the reaction mixture is desalted with Dowex 50WX 8 H^+ and Dowex 1X8 HCO_3^-. The solutions were concentrated and the products L-**3** and **5** were separated by column chromatography on Dowex 50WX 8 Ca^{2+} (column 3 cm x 85 cm) with water as eluent. (*S*)-**3a** was reprocessed by extraction with diethyl ether and perforation of

the aqueous phase with ethyl acetate within 48 h. The combined organic phases were dried (Na_2SO_4), concentrated and chromatographed on silica gel with methanol/dichloromethane/petroleum ether (1+2+4). All compounds gave correct elemental analyses and were characterized by ^{1}H-NMR spectroscopy.

	^{1}H-NMR data (250 MHz, δ)
(*S*)-**3a**	1.76 (s, 1 H, OH), 3.40-3.70 and 5.10-5.40 (m, 4 H, 1-,2-,3-H), 4.54 (s, 2 H, C*H*$_2$Ph), 7.30-7.39 (m, 5 H, Ph)
(*S*)-**3b**	3.40 (s, 3 H, CH_3), 3.53 (dd, $J_{2,3}$=3.0 Hz, $J_{3,3}$=-10.5 Hz, 1 H, 3-H), 3.64 (dd, $J_{2,3}$=6.9 Hz, 1 H, 3-H), 3.69 (ddd, $J_{1,2}$=5.3 Hz, 1 H, 2-H), 4.93 (d, 1 H, 1-H)
(*R*)-**3d**	1.25 (t, *J*=7.3 Hz, 3 H, CH_3), 2.63 (q, 2 H, C*H*$_2$CH$_3$), 2.65 (dd, $J_{2,3}$=8.5 Hz, $J_{3,3}$=-13.8 Hz, 1 H, 3-H), 2.88 (dd, $J_{2,3}$=3.6 Hz, 1 H, 3-H), 3.66 (ddd, $J_{1,2}$=5.1 Hz, 1 H, 2-H), 4.95 (d, 1 H, 1-H)
(*R*)-**3e**	3.75 (dddd, $J_{F,2}$=23.8 Hz, $J_{2,3}$=3.1 Hz, $J_{2,3}$=5.1 Hz, $J_{1,2}$=6.0 Hz, 1 H, 2-H), 4.58 (dd, $J_{3,3}$=-10.2 Hz, $J_{F,3}$=47.2 Hz, 1 H, 3-H), 4.63 (dd, 1 H, 3-H), 5.00 (d, 1 H, 1-H)
(*S*)-**3f**	0.96 (t, 3 H, CH_3), 1.40-1.80 (m, 2 H, CH_2), 3.40-3.90 (m, 1 H, 2-H), 4.30-5.30 (m, 1 H, 1-H)
(*S*)-**3g**	2.74 (dd, $J_{2,2}$=-17.2 Hz, $J_{2,3}$=7.2 Hz, 1 H, 2-H), 2.84 (dd, $J_{2,3}$=4.5 Hz, 1 H, 2-H), 3.86 (dddd, $J_{3,4}$=5.3 Hz, 1 H, 3-H), 4.97 (d, 1 H, 4-H)
5a	1.70, 2.70, 3.00 (3s, 3 H, OH), 3.60-3.70 (m, 2 H, 5-H), 4.12 (m, 1 H, 4-H), 4.33 and 4.41 (AB system, 2 H, 1-H), 4.40 (d, 1 H, 3-H), 4.55 (s, 2 H, C*H*$_2$Ph), 7.30-7.40 (m, 5 H, Ph)
5b	3.38 (s, 3 H, CH_3), 3.53 (dd, $J_{4,5}$=7.2 Hz, $J_{5,5}$=-10.4 Hz, 1 H, 5-H), 3.60 (dd, $J_{4,5}$=5.2 Hz, 1 H, 5-H), 4.18 (ddd, $J_{3,4}$=2.5 Hz, 1 H, 4-H), 4.39 (d, 1 H, 3-H), 4.50, 4.60 (AB syst., $J_{1,1}$=-19.4 Hz, 2 H, 1-H)
5c	2.63 (dd, $J_{4,5}$=9.2 Hz, $J_{5,5}$=-10.3 Hz, 1 H, 5-H), 3.08 (dd, $J_{4,5}$=7.3 Hz, 1 H, 5-H), 3.66 (s, 2 H, 1-H), 3.80 (d, $J_{3,4}$=9.4 Hz, 1 H, 3-H), 4.34 (ddd, 1 H, 4-H)
5d	1.22 (t, *J*=7.4 Hz, 3 H, CH_3), 2.60 (q, 2 H, CH_2), 2.70 (dd, $J_{4,5}$=7.5 Hz, $J_{5,5}$=-13.8 Hz, 1 H, 5-H), 2.73 (dd, $J_{4,5}$=6.6 Hz, 1 H, 5-H), 4.13 (ddd, $J_{3,4}$=2.2 Hz, 1 H, 4-H), 4.51 (d, 1 H, 3-H), 4.53, 4.62 (AB syst., $J_{1,1}$=-19.5 Hz, 2 H, 1-H)
5e	4.33 (dddd, $J_{F,4}$=15.9 Hz, $J_{4,5}$=6.2 Hz, $J_{4,5}$=5.0 Hz, $J_{3,4}$=2.1 Hz, 1 H, 4-H), 4.49 (d, 1 H, 3-H), 4.58 (ddd, $J_{5,5}$=-9.7 Hz, $J_{F,5}$=46.6 Hz, 1 H, 5-H), 4.65 (ddd, 1 H, 5-H), 4.56, 4.66 (AB syst., $J_{1,1}$=-19.5 Hz, 2 H, 1-H)
5f	0.93 (t, $J_{5,6}$=7.4 Hz, 3 H, CH_3), 1.58 (m, 2 H, CH_2), 3.89 (ddd, $J_{4,5}$=7.4 Hz, $J_{4,5}$=6.6 Hz, 1 H, 4-H), 4.34 (d, $J_{3,4}$=2.3 Hz, 1 H, 3-H), 4.48, 4.58 (AB syst., $J_{1,1}$=-19.4 Hz, 2 H, 1-H)
5g	2.87 (d, 2 H, 2-H), 4.43 (d, $J_{3,4}$=2.3 Hz, 1 H, 4-H), 4.48 (ddd, 1 H, 3-H), 4.58, 4.68 (AB syst., $J_{6,6}$=-19.6 Hz, 2 H, 6-H)

13. Bednarski, M.D.; Simon, E.S.; Bischofberger, N.; Fessner, W.-D.; Kim, M.-J.; Lees, W.; Saito, T.; Waldmann, H.; Whitesides, G.M. *J. Am. Chem. Soc.* **1989**, *111*, 627-635.
14. Straub, A. *Dissertation*, Univ. Stuttgart **1989**.
15. Jones, J.K.N.; Mitchell, D.L. *Can. J. Chem.* **1959**, *37*, 1561-1566.
16. Gorin, P.A.J.; Hough, L.; Jones, J.K.N. *J. Chem. Soc.* **1955**, 2699-2705.
17. Kochetov, G.A. *Methods Enzymol.* **1982**, *90*, 209-223.
Datta, A.G.; Racker, E. *J. Biol. Chem.* **1961**, *236*, 624-628.

(Received in Germany 12 June 1992)