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Enzyme Catalyzed Addition of Hydrocyanic Acid to Substituted Pivalaldehydes - A Novel Synthesis of (*R*)-Pantolactone[1]

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Abstract: (*R*)-Cyanohydrins (*R*)-**2b-h** are obtained in good optical yields by (*R*)-oxynitrilase catalyzed enantioselective addition of HCN to β-substituted pivalaldehydes **1b-h**. Under optimized reaction conditions with highly purified (*R*)-oxynitrilase, hydroxypivalaldehyde (**1a**) is converted to (*R*)-**2a** in satisfactory chemical and optical yields. By acid-catalyzed hydrolysis the cyanohydrins (*R*)-**2a-h** cyclize directly to give crude (*R*)-pantolactone (*R*)-**3** with *ee*-values of 56-95% which, after recrystallization, go up to ≥98 %*ee* in all cases.

(*R*)-Pantolactone (*R*)-**3** is the most important starting compound for (*R*)-pantothenic acid, a constituent of coenzyme A.[3] (*R*)-**3** serves also for the preparation of (*R*)-panthenol,[4] a bactericide, or (*R*)-pantotheine[5] which is a growth factor. In the synthesis of natural products, (*R*)-pantolactone has been widely used as a chiral auxiliary[6] and as a chiral building block.[7]

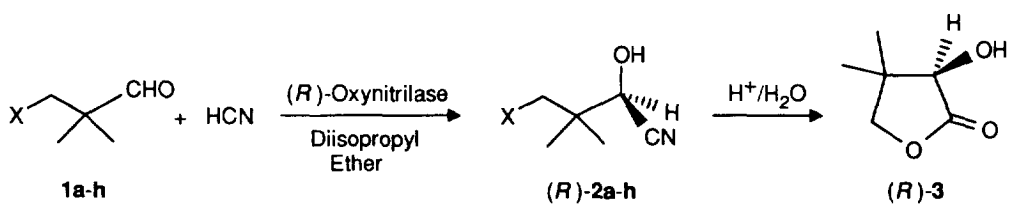
In the last few years great efforts in the development of technical preparations of (*R*)-pantolactone have been made, since vitamins have great importance as food and feed additives. Numerous synthetic procedures for (*R*)-(-)-pantolactone have therefore been developed and described in the literature. Since racemic pantolactone is easily accessible in a "one pot reaction" from hydroxypivalaldehyde, sodium cyanide, hydrochloric acid and calcium chloride,[8] general racemate resolution techniques have been applied to obtain enantiomerically pure (*R*)-pantolactone. The resolution via diastereomeric salts or amides using quinine,[9] D(-)-galactamine,[10] (+)-3-aminomethylpinane,[11] and (1*R*)-3-*endo*-aminoborneol[12] has been applied. 2,4-Dihydroxybutyric acid derived from pantolactone with sodium hydroxide is enantioselectively protonated in the presence of (1*S*)-(+)-10-camphorsulfonic acid and undergoes spontaneous cyclization to (*R*)-pantolactone.[13] Besides the enantioselective hydrolysis of *O*-acyl pantolactones to (*R*)-pantolactone using lipases or esterases,[14] the hydrolysis of racemic pantolactone by a specific fungal hydrolase[15] has been reported. Chromatographic resolutions of racemic pantolactone were performed either directly on chiral phases[16] or after formation of diastereomers using optically active acid chlorides or isocyanates.[17] The enantioselective hydrogenation of ketopantoyl lactone is a further general route to (*R*)-(-)-pantolactone. The catalytic hydrogenation with rhodium or ruthenium complexes containing chiral ligands provides high enantiomeric excesses and excellent chemical yields.[18] An enantioselective hydrogenation with moderate enantiomeric excesses could also be achieved using NADH model compounds.[19] In enzymatic hydrogenations, cells of the genera *Rhodotorula* and *Agrobacterium*[20] or of yeasts[21] have been applied. Also microbial oxidation-reduction processes starting from racemic pantolactone lead to the desired (*R*)-(-)-pantolactone.[22] A very efficient synthesis of

(*R*)-pantolactone was achieved via carboxylation of the chiral carbanion of a 1,3-propanediol, prepared by metalation with *sec*-butyllithium/(-)-sparteine.[23] In a very recent publication a chemical synthesis of (*R*)-**3** was described, where the chirality was introduced by a Sharpless epoxidation.[24]

In the "one pot reaction" for the preparation of racemic pantolactone,[8] the racemic cyanohydrin is the decisive intermediate, which under the reaction conditions (hydrochloric acid) hydrolyzes and cyclizes to give the lactone (*RS*)-**3**. In recent years, (*R*)-cyanohydrins became easily accessible in high enantiomeric excesses by (*R*)-oxynitrilase catalyzed addition of hydrocyanic acid to aldehydes, especially using organic solvents.[25] The enzyme catalyzed enantioselective addition of HCN to hydroxypivalaldehyde could therefore open a novel and simple route to (*R*)-pantolactone.

In the present paper we report on our investigations of the (*R*)-oxynitrilase [EC 4.1.2.10] catalyzed addition of HCN to β-substituted pivalaldehydes **1a-h** to the corresponding cyanohydrins (*R*)-**2a-h** and the cyclization of the cyanohydrins to (*R*)-(-)-pantolactone (*R*)-**3** (Scheme 1). The addition reactions were carried out at room temperature in diisopropyl ether[25b,26] with an excess of HCN. The (*R*)-oxynitrilase, isolated from bitter almond, was immobilized on cellulose soaked in sodium acetate solution at pH 3.3.[27]

Scheme 1



1a-h (*R*)-**2a-h** (*R*)-**3**

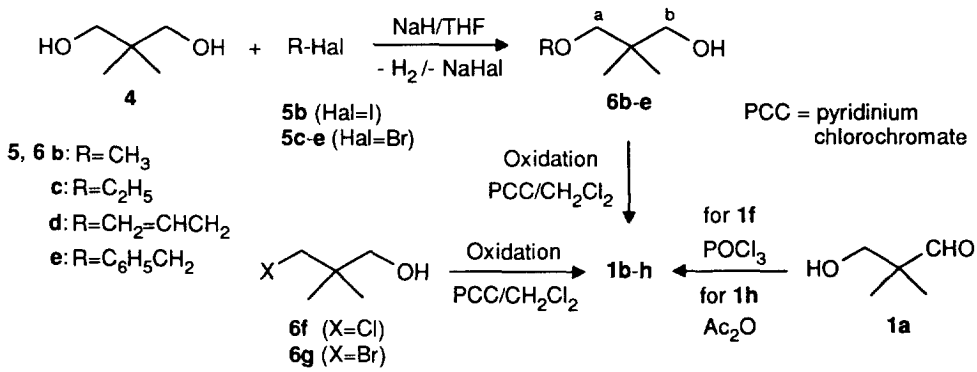
1, 2	a	b	c	d	e	f	g	h
X	OH	CH_3O	C_2H_5O	CH_2=$CHCH_2O$	$C_6H_5CH_2O$	Cl	Br	CH_3CO_2

Hydroxypivalaldehyde (**1a**)[28] exists at room temperature as a crystalline dimer[28a] which can be cleaved into the monomer by heating. The cyanohydrin (*R*)-**2a** is accessible by the enzyme catalyzed reaction under the usual reaction conditions[25] only in unsatisfactory optical yields (61 %*ee*) with distilled or freshly melted **1a** monomer.

We have therefore investigated the (*R*)-oxynitrilase catalyzed addition of HCN to the *O*-protected hydroxy- as well as to halogenated pivalaldehydes **1b-h**.

The oxy-substituted pivalaldehydes **1b-e** were synthesized according to Ref.[29a] starting from 2,2-dimethyl-1,3-propandiol (**4**) via the monoprotected alcohols **6b-e** and their oxidation with pyridinium chlorochromate (PCC)[29b,c] (Scheme 2, Table 6 and 7).

Scheme 2



Chloro- (**1f**) and bromopivalaldehyde (**1g**) were also accessible by oxidation of the corresponding propanols **6f** and **g** with pyridinium chlorochromate (PCC) in dichloromethane[30] (Table 7) as shown in Scheme 2. The chloro compound **1f** can also be obtained by chlorination of hydroxypivalaldehyde (**1a**) with phosphoryl chloride or thionyl chloride in dimethyl formamide according to Ref.[31] Acetoxypivalaldehyde (**1h**) was prepared by acetylation of **1a** with acetic anhydride in presence of pyridine in dichloromethane.

The enantioselective addition of HCN to the aldehydes **1b-h** with (*R*)-oxynitrilase as catalyst (1800-3000 U/ml) (Scheme 1) under the usual reaction conditions[25] gives the corresponding (*R*)-cyanohydrins (*R*)-**2b-h** in most cases in excellent chemical and in far better optical yields (Table 1).

Table 1. (*R*)-Cyanohydrins (*R*)-**2** by (*R*)-Oxynitrilase Catalyzed Addition of HCN to the Aldehydes **1b-h** in Diisopropyl Ether at Room Temperature

Aldehydes **1**		Enzyme[a]	React.-	(*R*)-Cyanohydrins (*R*)-**2**			
	X	[U/mmol **1**]	time [h]		Yield [%][b]	ee [%]	$[\alpha]_D^{20}$ (c, CH_2Cl_2); (*ee*%)
b	CH_3O	59	5.5	**b**	100	96	+8.4 (1.4); (95)
c	CH_3CH_2O	182	18	**c**	100	73	+10.9 (1.51); (72)
d	$CH_2=CHCH_2O$	167	8.5	**d**	81	88	+9.6 (1.38); (77)
e	$PhCH_2O$	192	48	**e**	83	61	not determined[d]
f	Cl	163 [c]	3	**f**	100	92	+12.2 (1.54); (88)
g	Br	179	15	**g**	100	89	+3.8 (1.8); (87)
h	CH_3CO_2	150 [c]	6.5	**h**	97	61	not determined

[a] Activity of enzyme solution: 1800 - 3000 U/ml. [b] Determined by ^1H NMR spectroscopy. [c] Specific activity 38 U/mg.
[d] Cyanohydrin (*R*)-**2e** was isolated as mixture with the starting aldehyde **1e**.

Acid-catalyzed hydrolysis of optically active cyanohydrins affords optically active α-hydroxycarboxylic acids without any racemization and with retention of configuration.[25b,c,32] By hydrolyzing the

cyanohydrins (*R*)-**2a-h** in conc. hydrochloric acid unexpectedly in all cases (*R*)-pantolactone was obtained (Scheme 1, Table 2).

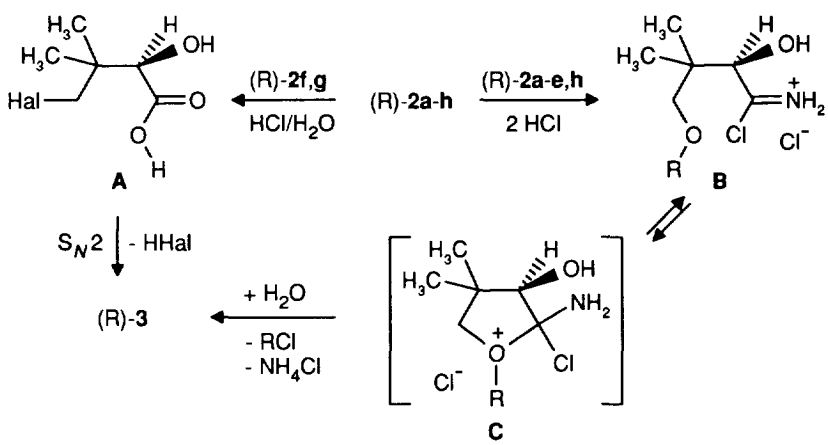
Table 2. Acid-catalyzed Transformation of (*R*)-Cyanohydrins (*R*)-**2a-h** to (*R*)-Pantolactone (*R*)-**3**

	(*R*)-Cyanohydrins (*R*)-**2**		(*R*)-Pantolactone (*R*)-**3**		
	X	(*ee*%)	ee [%][a]	ee [%][b]	Yield [%][b]
a	OH	80[c]	80	98	62
b	CH_3O	95	95	99	78
c	CH_3CH_2O	72	74	98	55
d	CH_2=$CHCH_2O$	77	77	98	62
e	$PhCH_2O$	61	56	93	42
f	Cl	86	86	98	88
g	Br	87	88	-	65[d]
h	CH_3CO_2	52	52	94	45

[a] Crude products. [b] After recrystallization from diethyl ether/petroleum ether; the yields are related to the enantiomeric excess of the crude (*R*)-**3**. [c] Prepared under optimized conditions as described below. [d] After distillation.

The unexpected direct formation of (*R*)-pantolactone by treatment of the very differently substituted cyanohydrins (*R*)-**2a-h** with conc. hydrochloric acid can be explained as outlined in Scheme 3.

Scheme 3



The halogen substituted cyanohydrins **2f** and **2g** are hydrolyzed to the corresponding carboxylic acids **A**, which then in a S_N2 reaction which is highly favoured by forming a five-membered ring,[33a] cyclize to give (*R*)-**3**. For the *O*-substituted cyanohydrins (*R*)-**2a-e,h** it is assumed, that the imide chlorides **B** formed pri-

marily, react via the tetrahedral intermediates **C** to give (*R*)-**3**. Comparative rate studies have shown that reactions via a five-membered tetrahedral intermediate such as **C** are about 10^5 times faster than reactions without this neighboring group participation.[33b]

The acid-catalyzed conversion of the cyanohydrins (*R*)-**2a-h** proceeds without any racemization as shown by comparison of the *ee*-values of the educts (*R*)-**2** and the obtained crude pantolactone (*R*)-**3** (Table 2). In each reaction listed in Table 2, (*R*)-**3** was completely characterized by elemental analysis, NMR spectroscopy and comparison of specific rotation values with literature data.[9b,10,21a] After crystallization from diethyl ether/petroleum ether[21a] (*R*)-pantolactone with high optical purity was obtained in all cases (Table 2), even from cyanohydrins with comparable low *ee*-values like (*R*)-**2e** and **h**.

For a technical synthesis of (*R*)-pantolactone, hydroxypivalaldehyde (**1a**) would be the most suitable starting compound. The unsatisfactory optical yield of (*R*)-**2a** (61 %*ee*) derived from hydroxypivalaldehyde **1a** under the reaction conditions applied for the preparation of (*R*)-**2b-h** required therefore an optimization of the enzyme catalyzed reaction.

By varying the reaction parameters it became obvious that mainly two factors influence the optical yield of the reaction: the purity of the enzyme and the concentration of aldehyde **1a**. By using highly purified (*R*)-oxynitrilase[34] the enantiomeric excess and the chemical yield of (*R*)-**2a** increase considerably (Table 3).

Table 3. Variation of Specific Activity and Amount of (*R*)-Oxynitrilase in the HCN Addition to Hydroxypivalaldehyde (**1a**) in Diisopropyl Ether at Room Temperature

(*R*)-Oxynitrilase		React.-time [h]	Cyanohydrin (*R*)-**2a**	
[U/mmol **1a**]	Spec. Act. [U/mg]		Yield [%][a]	ee [%]
112	11	17	60	61
130	31	1.5	43	68
150	38	2.25	55	83
175	74	1.75	84	89
425	136	1.75	77	89

[a] Determined by ^{1}H NMR spectroscopy.

As can be seen from Table 3, there is a limit where a further increase of the specific activity of the enzyme as well as the amount of enzyme does not improve the optical and the chemical yield of (*R*)-**2a** further.

Table 4 shows the influence of the concentration of aldehyde **1a**. Increasing concentrations of **1a** result in a diminished chemical and optical yield of cyanohydrin (*R*)-**2a**. The reaction is independent on the concentration of HCN varying between twofold and fivefold excess; enantiomeric excesses in the range of 86 to 88% were determined in all cases.

Table 4. Variation of the Concentration of Aldehyde **1a** in the (*R*)-Oxynitrilase[a] Catalyzed Addition of HCN in Diisopropyl Ether at Room Temperature

1a Conc. [mol/l]	React.-time [h]	(*R*)-**2a** Yield [%][b]	ee [%]
0.22	2	68	89
0.44	2.25	44	84
0.87	2	48	79

[a] 200 Units/mmol **1a**, specific activity: 91 U/mg. [b] Determined by ^{1}H NMR spectroscopy.

Our further investigations have shown, that the influence of all other parameters on the enzyme catalyzed reaction of **1a** with HCN is negligible. Neither the variation of reaction time in the range of 0.5 to 6.5 hours and the reaction temperature between 23°C and 40°C nor changing the support (cellulose, kieselguhr) used for enzyme immobilization (Table 5) gives a remarkable improve of optical and chemical yields.

Table 5. Variation of the Support in the Enzyme Catalyzed HCN Addition to Aldehyde **1a** in Diisopropyl Ether at Room Temperature

(*R*)-Oxynitrilase Spec. Act.	[U/mmol **1a**]	Support[a]	React.-time [h]	Cyanohydrin (*R*)-**2a** Yield [%][b]	ee [%]
74 U/mg	175	Avicel (cellulose)	1.75	84	89
91 U/mg	200	P100PSC (cellulose)	2	68	89
91 U/mg	200	Celite (kieselguhr)	1.75	77	82
136 U/mg	425	Celite (kieselguhr)	1.75	85	87

[a] Soaked in 0.02 M sodium acetate solution, pH 3.3. [b] Determined by ^{1}H NMR spectroscopy.

The supports used for the enzyme immobilization were soaked in sodium acetate solution at pH 3.3 as described above. By treatment at pH 5.4, the pH optimum of (*R*)-oxynitrilase,[35] the enantiomeric excess decreases from 89% at pH 3.3 to values below 84%. The application of kieselguhr for enzyme immobilization affords chemical and optical yields comparable with those of cellulose (Table 5) whereas other supports such as ion exchange resins are not suitable because both the conversion and the enantiomeric excess markedly decrease.

Hydroxypivalaldehyde (**1a**) which is easily accessible, provides the cyanohydrin (*R*)-**2a** in relatively high optical yields by using highly purified enzyme. Since the enantiomeric excess of the crude (*R*)-pantolactone obtained by acid-catalyzed cyclization increases to ≥98 *%ee* after one recrystallization, the route for the preparation of (*R*)-(-)-pantolactone described in this paper is an interesting alternative to procedures reported.

In summary, the described novel route to (*R*)-(-)-pantolactone via enzyme catalyzed synthesis of the chiral cyanohydrin is an alternative to the large scale preparations of (*R*)-pantolactone applied today.

Experimental

Materials and Methods: Hydroxypivalaldehyde (**1a**) was purchased from Fluka or prepared according to Ref.[28a] 2,2-Dimethyl-1,3-propandiol (**4**) and pyridinium chlorochromate (PCC) were purchased from Fluka, 3-chloro- (**6f**) and 3-bromo-2,2-dimethyl-1-propanol (**6g**) from Aldrich, Avicel cellulose from Merck, Celite from Fa. Roth and Elcema P100PSC from Degussa. All solvents were purified and dried as described in the literature. ^{1}H NMR spectra were recorded on a Bruker ACF 250 with TMS as int. standard. Optical rotations were performed in a Perkin-Elmer polarimeter 241 LC. Gas chromatography: Hewlett Packard 5700A and 5710 A with FID, 30 ml/min nitrogen, glass columns 2.3 m x 2 mm, phases OV 7,17,101,225 on chromosorb W. Capillary GC for determination of enantiomeric excess: a) Carlo Erba Fractovap 4160 with FID, Spectra Physics minigrator, 0.5 bar hydrogen, column 50 m, phase OV 1701 with 10% permethylated β-cyclodextrin; b) Carlo Erba HRGC 5300 Mega Series with FID, Carlo Erba Mega Series integrator, 0.5 bar hydrogen, column 20 m, phases OV 1701 and PS 086 with 10% permethylated β-cyclodextrin; c) Hewlett Packard 5890 Series II with FID, 0.42 bar hydrogen, column 50 m x 25 mm, phase FS-Lipodex C (Macherey Nagel) or column 30 m x 32 mm, phase Chiraldex B-TA (ICT).

Preparation of O-protected 2,2-dimethyl-1-propanols **6b-e**; *general procedure according to Ref.*[29a]: At room temperature a solution of 2,2-dimethyl-1,3-propandiol (**4**) in THF (see Table 6) is dropped with stirring within 1-1.5 h to a suspension of NaH in THF and then the reaction mixture is refluxed for 1 h. After cooling to room temperature the corresponding alkyl halides **5b-e** are dropped within 1 h and the reaction mixture then is either refluxed for 16 h (**5e**) or stirred at room temperature followed by refluxing (times given in Table 6). Then 15-20 ml water are added, the aqueous phase is separated and extracted three times with 60 ml diethyl ether. The combined organic phases are dried ($MgSO_4$), concentrated, and the resulting alcohol **6** is fractionated *in vacuo*.

Table 6. Preparation of Alcohols **6b-e** and ^{1}H NMR data

4 g (mmol)	THF (ml)		**5** g (mmol)	NaH g (mmol)	THF (ml)	Reaction- time[h]	temp.[°C]	**6**	Yield g (%)	bp [°C/Torr]
34.4 (330)	150	**b**	51.1 (360)	7.92 (330)	300	18; 4	23; 90	**b**	27.7 (71)	55-69/16
17.7 (170)	70	**c**	20.2 (180)	4.10 (170)	180	14; 10	23; 90	**c**	9.4 (42)	61/10
17.2 (165)	75	**d**	21.8 (180)	4.00 (170)	150	15; 10	23; 90	**d**	17.9 (75)	87-90/10
17.2 (165)	75	**e**	31.7 (180)	4.00 (170)	150	16	90	**e**	24.2 (75)	80-84/0.01

	^{1}H NMR ($CDCl_3$, δ)
6b	0.92 (s, 6 H, CH_3), 2.70 (t, *J*=5.8 Hz, 1 H, OH), 3.25 (s, 2 H, a-CH_2), 3.34 (s, 3 H, CH_3O), 3.44 (d, 2 H, b-CH_2)
6c	0.92 (s, 6 H, CH_3), 1.19 (t, *J*=7.0 Hz, 3 H, CH_3CH_2), 2.97 (t, *J*=5.6 Hz, 1 H, OH), 3.29 (s, 2 H, a-CH_2), 3.43-3.52 (m, 4 H, CH_3CH_2, b-CH_2)
6d	0.93 (s, 6 H, CH_3), 2.69 (t, *J*=5.9 Hz, 1 H, OH), 3.30 (s, 2 H, a-CH_2), 3.45 (d, 2 H, b-CH_2), 3.97 (dt, J_1=1.4, J_2=5.5 Hz, 2 H, CH_2CHCH_2), 5.15-5.30 (m, 2 H, CH_2CHCH_2), 5.81-5.97 (m, 1 H, CH_2CHCH_2)
6e	0.93 (s, 6 H, CH_3), 2.49 (s, 1 H, OH), 3.32 (s, 2 H, a-CH_2), 3.46 (s, 2 H, b-CH_2), 4.51 (s, 2 H, $PhCH_2$), 7.25-7.39 (m, 5 H, Ph)

Preparation of the pivalaldehydes **1b-g**; *general procedure according to Ref.*[29a,30]: A solution of the corresponding alcohol **6** in absolute dichloromethane is added at room temperature to a suspension of pyridinium chlorochromate (PCC) and sodium acetate (**6d,e**) in absolute dichloromethane. The reaction mixture is stirred for the given time (see Table 7) and then diethyl ether is added (volume see Table 7). The solvent is decanted and the remaining solid is extracted four times with 100 ml diethyl ether. The combined extracts are filtered through a silica gel column (12 x 3 cm), concentrated and the residue is fractionated.

Table 7. Oxidation of Alcohols **6** to the Aldehydes **1** and ^{1}H NMR data

6	g (mmol)	PCC g (mmol)	CH_2Cl_2 (ml)[a]	Et_2O (ml)	R.-time [h]	**1**	Yield g (%)	bp [°C/Torr]
b	15.0 (127.0)	42.2 (195.8)	160; 160	500	7	**b**	6.30 (43)	131/760
c	5.0 (38.0)	12.3 (57.0)	50; 50	100	7	**c**	3.62 (74)	71/40
d	7.7 (53.4)	23.4 (109.0)[b]	20; 80	320	16/6.5[c]	**d**	4.75 (62)	55-57/10
e	8.1 (41.7)	18.0 (83.5)[b]	15; 60	250	16/10[c]	**e**	4.03 (50)	78-80/0.1
f	16.6 (135.4)	43.9 (203.6)	180; 170	400	7	**f**	10.8 (66)	38/10
g	10.0 (60.0)	19.5 (90.5)	75; 75	500	7	**g**[d]	6.15 (62)	49-50/13

	^{1}H NMR ($CDCl_3$, δ)
1b	1.08 (s, 6 H, CH_3), 3.33 (s, 3 H, CH_3O), 3.38 (s, 2 H, CH_2), 9.55 (s, 1 H, CHO)
1c	1.08 (s, 6 H, CH_3), 1.16 (t, *J*=7 Hz, 3 H, CH_3CH_2), 3.42-3.50 (m, 4 H, CH_2, CH_3CH_2), 9.58 (s, 1 H, CHO)
1d	1.09 (s, 6 H, CH_3), 3.43 (s, 2 H, CH_2), 3.96 (dt, J_1=1.4, J_2=5.5 Hz, 2 H, CH_2CHCH_2), 5.14-5.31 (m, 2 H, CH_2CHCH_2), 5.78-5.95 (m, 1 H, CH_2CHCH_2), 9.58 (s, 1 H, CHO)
1e	1.09 (s, 6 H, CH_3), 3.45 (s, 2 H, CH_2), 4.50 (s, 2 H, $PhCH_2$), 7.28-7.38 (m, 5 H, Ph), 9.57 (s, 1 H, CHO)
1f	1.20 (s, 6 H, CH_3), 3.60 (s, 2 H, CH_2), 9.53 (s, 1 H, CHO)
1g	1.23 (s, 6 H, CH_3), 3.46 (s, 2 H, CH_2), 9.49 (s, 1 H, CHO)

[a] Volume in which **6** (1. value) and PCC (2. value) are dissolved. [b] Addition of about 0.37 mol sodium acetate per mol alcohol. [c] Reaction time under reflux. [d] Ref.[30]

3-Chloro-2,2-dimethyl-propionaldehyde (**1f**):[31] After addition of $SOCl_2$ or $POCl_3$ to absolute DMF within 30 min at room temperature the solution is stirred for 15 min, cooled to 0°C, and a solution of freshly

melted **1a** in 10 ml DMF is dropped within 30 min. The reaction mixture is warmed up to room temperature and refluxed for 6 h. Then the twofold volume of water is added and the reaction mixture extracted four times with 100-150 ml diethyl ether. The combined extracts are washed with 100 ml water, dried with $MgSO_4$, concentrated, and the residue is fractionated *in vacuo*. Physical data see Table 7.

Chloride	g (mmol)	DMF (ml)	**1a** g (mmol)	**1f** Yield g (%)
$POCl_3$	18.5 (120.6)	74	10.3 (100.8)	6.10 (51)
$SOCl_2$	7.9 (66.4)	40	5.1 (50.0)	2.23 (37)

3-Acetoxy-2,2-dimethyl-propionaldehyde (**1h**): A solution of 3.0 g (29.4 mmol) freshly melted **1a**, 3.63 g (46.0 mmol) pyridine and 9.0 g (88.2 mmol) acetic anhydride in 90 ml dichloromethane is stirred at 60°C for 40 h. Then the reaction mixture is filtered through a silica gel column (5 x 3 cm), concentrated and the residue is fractionally distilled *in vacuo*; yield 2.2 g (52%), bp 75°C/10 Torr. ^{1}H NMR ($CDCl_3$) δ = 1.12 (s, 6 H, CH_3), 2.05 (s, 3 H, CH_3CO_2), 4.12 (s, 2 H, CH_2), 9.52 (s, 1 H, CHO).

Enzyme catalyzed HCN addition to the aldehydes **1**; *general procedure according to Ref.*[25a,32c]: A solution of (*R*)-Oxynitrilase (amount and spec. activities are given in Tables 1,3-5) is dropped on the support (e.g. Avicel cellulose, 1.5 g, soaked in 10 ml 0.02 M sodium acetate solution, pH 3.3). 4-5 ml of diisopropyl ether are added followed by 100 µl of the aldehyde **1** and a two- to threefold molar excess of hydrocyanic acid, and the reaction mixture is stirred for the given time and temperature (see Tables 1, 3-5). The catalyst is filtered off and washed with diethyl ether. The combined filtrates are concentrated to give the (*R*)-cyanohydrins (*R*)-**2**. The reaction can be performed up to an amount of the aldehyde of about 20 mmol.

	^{1}H NMR ($CDCl_3$, δ)
(*R*)-**2a**	1.04 (s, 3 H, CH_3), 1.13 (s, 3 H, CH_3), 3.50, 3.80 (AB system, *J*=-10.8 Hz, 2 H, CH_2), 4.37 (s, 1 H, CH)
(*R*)-**2b**	1.03 (s, 3 H, CH_3), 1.16 (s, 3 H, CH_3), 3.40 (s, 3 H, CH_3O), 3.27, 3.63 (AB system, *J*=-9.2 Hz, 2 H, CH_2), 4.24 (s, 1 H, CH)
(*R*)-**2c**	1.03 (s, 3 H, CH_3), 1.17 (s, 3 H, CH_3), 1.23 (t, *J*=7.0 Hz, 3 H, CH_3CH_2), 3.48-3.61 (m, 2 H, CH_3CH_2), 3.31, 3.69 (AB system, *J*=-9.3 Hz, 2 H, CH_2), 4.23 (s, 1 H, CH)
(*R*)-**2d**	1.04 (s, 3 H, CH_3), 1.18 (s, 3 H, CH_3), 3.32, 3.68 (AB system, *J*=-9.3 Hz, 2 H, CH_2), 3.95-4.05 (m, 2 H, CH_2CHCH_2), 4.26 (s, 1 H, CH), 5.21-5.33 (m, 2 H, CH_2CHCH_2), 5.81-5.96 (m, 1 H, CH_2CHCH_2)
(*R*)-**2e**	1.03 (s, 3 H, CH_3), 1.17 (s, 3 H, CH_3), 3.35, 3.70 (AB system, *J*=-9.2 Hz, 2 H, CH_2), 4.28 (s, 1 H, CH), 4.51, 4.60 (AB system, *J*=-11.8 Hz, 2 H, $PhCH_2$), 7.28-7.41 (m, 5 H, Ph)
(*R*)-**2f**	1.17 (s, 3 H, CH_3), 1.19 (s, 3 H, CH_3), 3.41, 3.67 (AB system, *J*=-11.1 Hz, 2 H, CH_2), 4.56 (s, 1 H, CH)
(*R*)-**2g**	1.18 (s, 3 H, CH_3), 1.24 (s, 3 H, CH_3), 2.97 (s, 1 H, OH), 3.32, 3.57 (AB system, *J*=-10.4 Hz, 2 H, CH_2), 4.58 (s, 1 H, CH)
(*R*)-**2h**	1.10 (s, 3 H, CH_3), 1.13 (s, 3 H, CH_3), 2.12 (s, 3 H, CH_3CO_2), 3.99, 4.06 (AB system, *J*=-11.4 Hz, 2 H, CH_2), 4.31 (s, 1 H, CH)

Determination of the enantiomeric excess: 50 µl acetic anhydride and 10 µl pyridine are added to a solution of 10 µl (*R*)-**2** in 250 µl dichloromethane. After standing at 60°C for 4 h the reaction mixture is filtrated through a silica gel column (3 x 0.5 cm) with 3-4 ml dichloromethane. The enantiomeric excess of **2** is determined directly from the filtrate by capillary gas chromatography on OV 1701 and PS 086 phases with 10% permethylated β-cyclodextrin.

Transformation of cyanohydrins (*R*)-**2a-h** *to (R)-pantolactone* (*R*)-**3**; *general procedure according to Ref.*[32c]: A solution of (*R*)-**2b-h** in an excess of conc. HCl is stirred 16 h at room temperature and heated for 5 h at 115°C, (*R*)-**2a** is stirred in conc. HCl 8.5 h at room temperature. The excess of HCl is removed *in vacuo*, the residue taken up in diethyl ether, dried (Na_2SO_4), concentrated and distilled *in vacuo* or recrystallized from diethyl ether/petroleum ether to give (*R*)-pantolactone (*R*)-**3**, bp 100°C/0.01 Torr,[8,9,21a] mp 90.5°C,[8,9b,21a] $[\alpha]_D^{20}$ = -49 (c 0.6, H_2O),[9b,10,21a] (99% ee). ^1H NMR ($CDCl_3$) δ = 1.09 (s, 3 H, CH_3), 1.24 (s, 3 H, CH_3), 3.95, 4.04 (AB system, *J*=-8.9 Hz, 2 H, CH_2), 4.14 (s, 1 H, CH). ^{13}C NMR ($CDCl_3$) δ = 18.8 and 22.9 (CH_3), 40.9 (C3), 75.5 (C2), 76.5 (C4), 177.9 (C1). The enantiomeric excess is determined without derivatization on chiral β-cyclodextrin phases (Chiraldex B-TA) by capillary gas chromatography. (*R*)-**3** is characterized at each conversion by ^1H and ^{13}C NMR, elemental analysis and comparison of optical rotation values.

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