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Highly enantioselective CALB-catalyzed kinetic resolution of building blocks for β -blocker atenolol

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ABSTRACT

Both enantiomers of 4-(3-*chloro*-2-*hydroxypropoxy*)*phenyl*)*acetamide* has been synthesized in 98.5–99% enantiomeric excess by use of lipase B from *Candida antarctica* as catalyst. The *R*-alcohol is a building block for the cardioselective β -blocker (*S*)-atenolol ((*S*)-2-(4-(2-*hydroxy*-3-(*isopropylamino*)*propoxy*) *phenyl*)*acetamide*. Performing kinetic resolutions of 3-chloro-1-phenoxy-2-propanol and 3-bromo-1-phenoxy-2-propanol with vinyl butanoate as acyl donor and the same CALB enzyme, but a different preparation, showed higher *E*-values than previously reported.

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1. Introduction

The amount of approved new racemic drugs, so-called New Molecular Entities (NME's), has decreased in the past 20 years. This can be explained by increased knowledge of the difference in the biological effects of the two enantiomers, in addition to improved asymmetric synthesis. In the years between 1992 and 2011 the amount of racemic NME's approved by The US Food and Drug Administration (FDA) decreased from 21% to 5%. Globally no racemic NME's were approved in 2011, and almost 70% of the approved drugs were enantiomerically pure. The rest were achiral compounds. In the US the number of enantiopure NME's were lower, and a few racemates were also approved by FDA for the American market.^{1,2} Although there is an increasing demand for enantiopure drugs, still several drugs are being sold as the racemate. In 2010 there were still more β -blockers sold as the racemate. however, mostly the S-enantiomers are the active enantiomer (eutomer).³ Some of the *R*-enantiomers can even have adverse effects, rather than any effect at all.⁴ Atenolol is a cardioselective β -blocker, which means that it is selective towards β_1 receptors found in the heart. For a long time atenolol has been a popular choice for treatment of high blood pressure, but has become more controversial in recent years.⁵ Atenolol is also used in the treatment of angina and myocardial infarction.⁶ Atenolol is sold both enantiomerically pure as the *S*-enantiomer as Atpure[®] and racemic as Mylan[®], but it has been found that only the *S*-enantiomer has the desired effect.⁷ The *S*-enantiomer has been found to lack the reported side effect of a lowered heart rate sometimes encountered with the racemate.

Several researchers have used biocatalysis in order to obtain enantiopure atenolol, however *ee*'s of the building blocks have not reached 99%.^{8,9} A recent paper reports kinetic resolution of 4-(3*chloro-2-hydroxypropoxy)phenyl)acetamide* with lipase A from *Candida antarctica* in toluene with an *E*-value of 142 producing enantiomers of the compound.¹⁰ However, optical rotations of these enantiomer products have not been reported previously. (*S*)-Atenolol has also been made from (*R*)-epichlorohydrin.¹¹

Previously, we have achieved 99% *ee* of product enantiomers of secondary phenoxy alcohols with a halogen as a leaving group in 3-position in the side chain in kinetic resolutions using lipase B from *C. antarctica* (CALB),^{12,13} and it was desirable to prepare enantiomerically pure building blocks for atenolol using the same enzyme.

We have used the computer program *E&K* Calculator 2.1b0 PCC for calculations of the *E*-value based on 5–7 *ee*-values for a kinetic resolution.¹⁴ Resolutions of racemic compounds catalyzed by lipases react by a ping-pong bi-bi mechanism and in this program calculations of *E* and *K*_{eq} based on both the ping-pong bi-bi and uniuni kinetic models can be performed.^{15–20}



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2. Results and discussion

2.1. Synthesis of racemic compounds

Racemic 4-(3-chloro-2-hydroxypropoxy)phenyl)acetamide (1) was synthesized from epichlorohydrin and 2-(4-hydroxyphenyl) acetamide in 2.5 M NaOH. A mixture of 1 (70%) and the epoxide 2 (30%) was obtained. In order to open the epoxide 2 Li₂CuCl₄ in tetrahydrofuran was applied as a complexing agent. Scheme 1. NMR spectra were in accordance with previously reported data.¹⁰ Problems with the extraction resulted in lower total yield than previously reported by us in similar reactions.¹²

enantiomers of **1b** (or the acetate enantiomers of **1**) on the OD-H column (one column from 2004 and one from 2014) or other Chiralcel columns.

It was obvious from the chromatograms of resolutions of **1** that only one alcohol peak was decreasing. The formed butanoate **1b** was hydrolyzed in phosphate buffer by CALB in order to obtain correct *ee*-values for calculation of the *E*-value. Scheme 4. The *S*alcohol (*S*)-**1** was produced in 98.5% *ee*, thus we present **1b** as (*S*)-**1b** in Scheme 4. Optical rotation (o.r.) values of (*R*)-**1** (99.0% *ee*) is $[\alpha]_D^{23} = -3.0$ (*c* 1.0, MeOH). O. r. for (*S*)-**1** (98.5% *ee*) is $[\alpha]_D^{23} = +3.0$ (*c* 1.0, MeOH). Optical rotation values for these compounds have not been reported previously.



Scheme 1. Synthesis of 4-(3-chloro-2-hydroxypropoxy)phenyl)acetamide, 1.

3-Chloro-1-phenoxy-2-propanol (**3**) was synthesized in high yield and purity by opening benzyl glycidyl ether with conc. hydrochloric acid in dichloromethane according to Chini et al.²¹ 3-Bromo-1-phenoxy-2-propanol (**4**) was synthesized in high yield and purity by opening benzyl glycidyl ether by addition of LiBr in acetic acid according to Bajwa et al.²² Scheme 2. NMR spectra for both compounds were in accordance with previously reported data.^{13,21–23}

2.3. Improvement of enantiomeric ratio (*E*) with new CALB preparation

As model substrates for comparison of *E*-values in CALB resolutions of the series of secondary halogenated aryl alcohols 3-chloro-1-phenoxy-2-propanol (**3**) and 3-bromo-1-phenoxy-2-propanol (**4**) (Scheme 5), have been synthesized and resolved by another batch of CALB (with vinyl butanoate as acyl donor in dry hexane) than previously reported by us.



Scheme 2. Synthesis of 3-chloro-1-phenoxy-2-propanol, 3, and 3-bromo-1-phenoxy-2-propanol, 4.

2.2. Kinetic resolution of 4-(3-chloro-2-hydroxypropoxy) phenyl)acetamide (1) by CALB

Resolution of **1** with CALB (Novozym 435) was performed in dry acetonitrile with vinyl butanoate as acyl donor. The reaction was incubated at 30 °C and stirred at 200 rpm for 27 h. (*R*)-**1** was produced in 99% *ee* in 16% yield, and the butanoate (*S*)-**1b** was obtained in 18% yield. the *E*-value was 238. Scheme 3 and Fig. 1.

The alcohol enantiomers from the transesterification of **1** was analyzed on Daicel Chiralcel OD-H HPLC columns with baseline separation (hexane:2-propanol, 83:17, 1.00 mL min⁻¹, UV 254 nm). However, we were not able to separate the butanoate

The *E*-value in resolution of **3** increased from *E*=11 with the previous CALB preparation (PLU 7000 g⁻¹, no lot information)²³ to *E*=220 with the new enzyme preparation (Novozym 435, PLU 10000 g⁻¹, batch no LC200204). The *E*-value in the resolution of **4** increased from *E*=58 with the previous CALB preparation (PLU 7000 g⁻¹)²³ to *E*=278 with the new enzyme preparation. Chromatographic analyses (GLC) of **3** and **4** have been performed on similar Chirasil DEX columns with the same conditions as previously reported. Different water content in the reaction medium may affect the *E*-value.^{24,25} The water content of the old enzyme preparation was 2.16%, the water content of the newer preparation is 2.0%. Molecular sieve has been used in all reactions. We have





Scheme 3. CALB catalyzed kinetic resolution of 1 with vinyl butanoate in acetonitrile.

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Fig. 1. The enantiomeric excess (*ee*) of kinetic resolution of **1** in acetonitrile with CALB and vinyl butanoate as acyl donor, E=238. Circles: *ee* of butanoate ((*S*)-**1b** in excess). Squares: *ee* of remaining alcohol ((*R*)-**1** in excess).



Scheme 4. CALB catalyzed hydrolysis of (S)-1b in phosphate buffer.

3. Experimental

3.1. General

Analytical grade chemicals and solvents were purchased from Sigma–Aldrich, Oslo, Norway. For HPLC-analyses solvents with HPLC grade from Sigma–Aldrich were used. CALB was a gift from Novozymes AS, Bagsværd, Denmark. Enzyme specifications: Novozym 435 (CALB) immobilized on macroporous acrylic resin, activity 10000 PLU g⁻¹, batch nr. LC200204. Flash chromatography was performed with silica gel from Sigma–Aldrich, Oslo, Norway (pore size 60 Å, 230–400 mesh, 40–63 μ m particle size).

The enzyme catalyzed kinetic resolutions were performed in a New Brunswick G24 Environmental Incubator Shaker at 30 °C and 200 rpm. Optical rotations ($[\alpha]_D$) were determined at 23 °C using a Perkin-Elmer 243 B instrument, concentrations are given in g/ 100 mL. NMR spectra were recorded with a Bruker Avance DPX 400 instrument operating at 400 MHz for ¹H and 100 MHz for ¹³C, respectively. Chemical shifts δ are in ppm rel to TMS and coupling constants are in Hertz (Hz). Accurate mass determination in positive and negative mode was performed on a WatersSynapt G2-S Q-TOF instrument with WatersTM Software (Masslynx V4.1 SCN871). Samples were ionized by use of ASAP probe (APCI). Infrared spectroscopy was performed on a Nexus FTIR instrument.

3.2. Chiral analyses

3.2.1. Chiral HPLC-analyses. Chiral HPLC analyses of **1** were performed on an Agilent 1100 HPLC instrument with manual injector Rheodyne 77245i/Agilent, 10 μ L-loop, UV 254 nm. The column was Chiralcel OD-H column (25 cm, i.d 4.6 mm, film density 5 μ m) from Daicel, Chiral Technologies Europe. Eluent **1**: Hexane:2-propanol,



Scheme 5. CALB catalyzed kinetic resolution of 3 and 4.

previously resolved the secondary alcohols **3** and **4** with the older CALB preparation with vinyl butanoate as acyl donor in toluene with fixed water activity (a_w) (a_w =0.18–0.65), resulting in *E*-values ranging from 33 to 21 for **3** depending on the water activity of the medium, and from 12 to 16 for **4** depending on the a_w .¹²

Optical rotation (S)-**3** (96% *ee*) $[\alpha]_D^{22} = +5.3$ (*c* 1.71, EtOH). Reported previously for 97% *ee* of (S)-**3**: $[\alpha]_D^{20} = +3.6$ (*c* 0.56, CHCl₃).²⁶ (S)-**4b** (93% *ee*) $[\alpha]_D^{22} = +14.4$ (*c* 1.71, EtOH). O. r. of (S)-**4** (96% *ee*) $[\alpha]_D^{22} = +5.26$ (*c* 1.71, EtOH) corresponded with previously reported o. r.^{12,22} See Table 1 for *E*-values, *ee*'s and optical rotation values for enantiomers of **1**, **3** and **4**.

83:17, flow rate 1.00 mL min⁻¹. R_t alcohol enantiomers of 1: R_t (*S*)-1=37.70 min, R_t (*R*)-142.75 min, R_S=1.84. R_t butanoate enantiomers of 1: R_t (*S*)-1**b**=21.83 min, (butanoate enantiomers were not separated at R_t 23.48 min (from 1 derivatized with butyric anhydride). After hydrolysis of the butanoate 1**b** it was shown that only one butanoate enantiomer had been produced in the transesterification reaction (giving R_t (*S*)-1=36.91).

3.2.2. Chiral GLC-analyses. Chiral GLC-analyses of **3** and **4** were performed on a Varian 3380 gas chromatograph with a Varian CP-8410 autoinjector and a split injector ($200 \degree C$) and flame ionization

Table 1

E-values from kinetic resolutions of secondary alcohols 1 and 3–4 with CALB (Novozym 435) and vinyl butanoate as acyl donor. For further details, see Experimental section

Substrate, X	E-value	Alcohol, % ee	$[\alpha]_D^{23}$	Butanoate, % ee	$[\alpha]_D^{23}$	Rx time to 50% conv. (h)
1, Cl	238	(R)- 1 , 99	-3.0, (MeOH)			27
		(S)-1, 98.5	+3.0, (MeOH)			
3, Cl	220	(S)- 3 , 96	+5.3, (EtOH)			23
		(S)- 3 , 97	+3.6 (CHCl ₃) ²⁶			
4, Br	278	(S)- 4 , 96	+5.26, (EtOH)	(S)- 4b , 93	+14.0 (EtOH)	10

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detector (FID, 250 °C). The secondary chloro alcohol **3** and the corresponding butanoate **3b** were separated on a Varian CP Chirasil DEX column (25 m, i.d. 0.25 mm, film density 0.25 μ m). Carrier gas H₂ 5.0, flow 7.5 psi, split flow 60 mL min⁻¹, temp program: 110–120 °C/2 °C min⁻¹, 120–140 °C/1 °C min⁻¹, 140–150 °C/0.5 °C min⁻¹, R_t alcohol (*R*)-**3**=38.13 min, R_t (*S*)-**3** 8.67 min. R_S=1.50. R_t butanoates: R_t (*R*)-**3b**=63.57 min and R_t (*S*)-**3b**=64.55 min, R_s=2.30.

The bromo alcohol **4** and the corresponding butanoate **4b** were separated on the same column with H₂ 5.0 carrier gas, flow 9 psi, split flow 80 mL min⁻¹, temp program: 105–115 °C/2 °C min⁻¹, 115–130 °C/1 °C min⁻¹, 130–140 °C/0.5 °C min⁻¹ (5 min hold), 140–150 °C/0.5 °C min⁻¹. Rt alcohols: Rt (*R*)-**4**=51.10 min Rt (*S*)-**4**=51.60 Rs=1.80. Rt butanoates: Rt (*R*)-**4b**=67.53 min and Rt (*S*)-**4b**=67.92 min. R_S=2.40.

3.3. Assignment of absolute configurations

The absolute configuration of the faster reacting enantiomer in lipase catalyzed resolution was determined by the known enantiopreference of CALB²⁷ and by comparing the elution orders of the enantiomers with GLC elution orders of similar enantiopure compounds synthesized from (*S*)-epichlorohydrin.¹² In chiral HPLC analyses, the enantiomers eluted in the opposite order compared to chiral GLC.

3.4. Synthesis of racemic substrates

3.4.1. 4-(3-Chloro-2-hydroxypropoxy)phenyl)acetamide (1).^{10,11} 2-(4-Hydroxyphenyl)acetamide (2.52 g, 16.6 mmol) and epichlorohydrin (13 mL) was mixed and transferred to a solution of sodium hydroxide (0.50 g, 12.3 mmol) and water (5 mL). The reaction was stirred for 48 h at rt. TLC chromatography (DCM:MeOH, 4:1) showed that both alcohol 1 and the epoxide 2 was produced. The white solid was washed with DCM and filtrated, then Li₂CuCl₄ in THF (0.1 M, 30 mL) was added. The reaction mixture was stirred for 24 h under inert atmosphere. Sodium phosphate buffer (0.1 M, 30 mL) was added. THF was removed and the residue was extracted with ethyl acetate $(5 \times 20 \text{ mL})$ and washed with a satd sodium chloride solution (2×20 mL). Ethyl acetate was removed under reduced pressure and **1** was isolated in 22% yield (0.901 g, 3.70 mmol), mp 129–132 °C. ¹H NMR (MeOD): 7.23-7.21 (m, 2H, aromatic), 6.92-6.90 (m, 2H, aromatic), 4.13-4.10 (m, 1H, -CH-), 4.06-4.02 (m, 2H, -O-CH₂-), 3.77–3.66 (m, 2H, –CH₂–Cl), 3.44 (s, 2H, –CH₂–CONH₂). ¹³C NMR: 177.4, 159.2, 131.3 (2C), 129.4, 115.7 (2C), 71.0, 70.2, 46.8, 42.5. HRMS (APCI/ASAP, *m*/*z*): 244.0744 [M+H]⁺, (calcd. C₁₁H₁₄NO₃Cl, 243.654). IR (cm⁻¹): 3349, 1633, 1241, 706.

3.4.2. 3-Chloro-1-phenoxy-2-propanol (**3**).²¹ HCl (37%, 50 mL) was added to a flask with a solution of 1,2-epoxy-3-phenoxypropane (3.31 g, 22.0 mmol) and DCM (25 mL). The reaction mixture was stirred at 0 °C. TLC showed full conversion of the substrate after 30 min (DCM:acetonitrile, 40:1, R_f =0.42). The organic phase was concentrated under reduced pressure and purified on a silicagel flash column (DCM:acetonitrile, 40:1). The colorless fluid **3** was isolated in 76% yield (3.11 g, 16.7 mmol). ¹H NMR (CDCl₃) 7.29–7.27 (m, 2H, aromatic), 6.98–6.96 (m, 1H, aromatic), 6.91–6.89 (m, 2H, aromatic), 4.21–4.17 (m, 1H, –CH–), 4.08–4.03 (m, 2H, –O–CH₂–), 3.77–3.68 (m, 2H, –CH₂–Cl), 2.81–2.80 (d, 1H, OH; *J*=6.0). ¹³C NMR: 158.3, 129.7 (2C), 121.5, 114.6 (2C), 70.0, 68.5, 46.0. HRMS (APCI/ASAP, *m/z*): 169.0424 [M–OH]⁺, (calcd. C₉H₁₁O₂Cl, 186.628). IR (cm⁻¹): 3405, 751, 690.

3.4.3. 3-Bromo-1-phenoxy-2-propanol (4).^{22,23} 3-Bromo-1-phenoxy-2-propanol (4) was synthesized and characterized as previously described in 99% purity (GLC) and in 82% yield.

3.5. Kinetic resolutions of racemic compounds

3.5.1. Small scale transesterifications. Transesterification reactions were performed in a New Brunswick Incubator Shaker at 30 °C agitating at 200 rpm. Racemic alcohols **1** and **3–4** (1.31×10^{-4} mol) and vinyl butanoate (6.5×10^{-4} mol) were mixed in solvent (acetonitrile, hexane and DCM/hexane, respectively) and the reactions started by addition of immobilized lipase (20 mg) and were incubated for 10–27 h before the enzyme was filtered off and the solvent removed. Two replicates of each reaction were performed. The enantiomers were separated by column chromatography. Chiral GLC and HPLC analyses gave ees- and eep-values from which the degree of conversion was calculated according to $c=ees/(ees+ee_p)$. The *E*-values were calculated using the program *E&K* Calculator 2.1b0 PCC.¹⁴ In control experiments under the same reaction conditions but without enzyme, no acylation was observed.

3.6. Large scale transesterifications

3.6.1. (*R*)-2-(4-(3-*Chloro-2-hydroxypropoxy)phenyl)acetamide*, (*R*)-**1**. Alcohol **1** (0.56 g, 2.3 mmol) and vinyl butanoate (1.43 g, 12.5 mmol) was added to a flask with dry acetonitrile (40 mL) and molecular sieve. CALB (0.71 g) was added and the reaction was incubated at 30 °C and 200 rpm for 27 h in an incubator shaker. The enzyme and molecular sieve was filtered off and the solvent was removed under reduced pressure. The ester (*S*)-**1b** and the alcohol (*R*)-**1** were separated on a silica column with ethyl acetate as eluent. (*S*)-**1b** was isolated in 99% *ee* and 18% yield (0.13 g, 0.41 mmol). (*R*)-**1** was isolated in 99% *ee* and 16% yield (0.090 g, 0.37 mmol). $[\alpha]_D^{23} = -3.0$ (*c* 1.0, MeOH).

3.6.2. (S)-2-(4-(3-Chloro-2-hydroxypropoxy)phenyl)acetamide, (S)- **1.** Butanoate **1b** (0.092 g, 0.29 mmol) and phosphate buffer (0.1 M, pH=7, 4.0 mL) was mixed in a reaction vessel. CALB (0.8 g) was added and the reaction was incubated for 48 h. The enzyme was filtered off and the mixture was extracted with ethyl acetate (5×2 mL). The solvent was removed under reduced pressure and gave (S)-**1** in 48% yield (0.034 g, 0.14 mmol) 98.5% *ee*, $[\alpha]_D^{23} = +3.0$ (*c* 1.0, MeOH).

3.6.3. (S)-3-Chloro-1-phenoxy-2-propanol, (S)-**3** from butanoate (S)-**3b**. Alcohol **3** (1.00 g, 4.2 mmol) was dissolved in dry hexane (100 mL) with molecular sieve. Vinyl butanoate (3.02 g, 26.4 mmol) and CALB (1.00 g) was added. The suspension was incubated at 30 °C at 200 rpm for 23 h. The enzyme was filtered off and the mixture was extracted with ethyl acetate (5×2 mL). The solvent was removed under reduced pressure and after separation of the enantiomers on silica column (S)-**3b** was hydrolyzed by CALB and gave (S)-**3** in 96% *ee*, optical rotation $[\alpha]_D^{22}$ =+5.3 (*c* 1.71, EtOH).

3.6.4. (*S*)-3-Bromo-1-phenoxy-2-propanol (*S*)-**4** and butanoate (*S*)-**4b**. Alcohol **4** (1.26 g, 5.5 mmol) was dissolved in dry hexane (100 mL) with molecular sieve. Vinyl butanoate (3.15 g, 27.5 mmol) and CALB (0.85 g) was added. The suspension was incubated at 30 °C at 200 rpm for 10 h. The enzyme was filtered off and the mixture was extracted with ethyl acetate (5×2 mL). The solvent was removed under reduced pressure and after separation of the enantiomers on silica column (*S*)-**4b** was produced in 57% yield (0.81 g, 3.2 mmol) ee=93%, $[\alpha]_D^{22}=+14.4$ (*c* 1.71, EtOH). CALB catalyzed hydrolysis of (*S*)-**4b** gave (*S*)-**4** in 96% *ee*, optical rotation $[\alpha]_D^{22}=+5.26$ (*c* 1.71, EtOH) corresponded with previously determined o. r. of this compound in 96% *ee*, which was $[\alpha]_D^{22}=+5.3$ (*c* 1.71, EtOH).^{13,23}

4. Conclusion

An efficient process for synthesis of both enantiomers (*S*)-**1** and (*R*)-**1** (in 98.5 and 99% *ee*, respectively) as building blocks for the β -

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blocker atenolol has been developed using CALB as catalyst and vinyl butanoate as acyl donor. All enantiopure compounds have been extensively characterized. Different preparations of CALB (Novozym 435) show different enantioselectivity in transesterification reactions of the halo alcohols 3 and 4 with the same reaction conditions as in resolutions previously performed by us, which indicates that model reactions should be performed with new enzyme preparations.

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References and notes

- 1. Lin, G.-Q.; You, Q.-D.; Cheng, J.-F. Chiral Drugs: Chemistry and Biological Action; John Wiley & Sons Ltd, 2011; p 456.
- 2. Agranat, I.; Wainschtein, S. R.; Zusman, E. Z. Nat. Rev. Drug Discov. 2012, 11, 972-973
- З Agustian, J.; Kamaruddin, A. H.; Bhatia, S. Process Biochem. 2010, 45, 1587–1604.
- 4. Stoschitzky, K.; Lindner, W.; Zernig, G. J. Clin. Bas. Cardiol. 1998, 1, 15-19.
- 5. Che, Q.; Shreiber, M. J.; Rafey, M. A. Cleve. Clin. J. Med. 2009, 76, 533-542.
- http://www.felleskatalogen.no/medisin/atenolol-mylan-546528. 6.
- Stoschitzky, K.; Egginger, G.; Zernig, G.; Klein, W.; Lindner, W. Chirality 1993, 5, 7. 15-19.

- 8. Bevinakatti, H. S.; Banerji, A. A. J. Org. Chem. 1992, 57, 6003-6005.
- Barbosa, O.; Ortiz, C.; Torres, R.; Fernandez-Lafuente, R. J. Mol. Catal. B: Enzym. 9. 2011, 71, 124-132.
- 10. Dwivedee, B. P.; Ghosh, S.; Bhaumik, J.; Banoth, L.; Banerjee, U. C. RSC Adv. 2015, 5, 15850-15860.
- 11. Mehta, S. R.; Bhawal, B. M.; Deshpande, V. H.; Gurjar, M. K. 2006, US Patent US6982349 B1.
- 12. Jacobsen, E. E.; Hoff, B. H.; Anthonsen, T. Chirality 2000, 12, 654-659.
- 13 Jacobsen E. E. Anthonsen T. Can J. Chem 2002, 80, 577–581
- Anthonsen, H. W.; Hoff, B. H.; Anthonsen, T. Tetrahedron: Asymmetry 1996, 7, 14. 2633-2638.
- 15. Chen. C.-S.: Wu. S.: Girdaukas, G.: Sih, C. I. I. Am. Chem. Soc. 1987, 109. 2812-2817.
- 16. Sih, C. J.; Wu, S.-H. Top. Stereochem. 1990, 19, 63-125.
- Strathof, A. J. J.; Jongejan, J. A. Enzyme Microb. Technol. 1997, 21, 559–571.
 Chen, C.-S.; Fujimoto, Y.; Girdaukas, G.; Sih, C. J. J. Am. Chem. Soc. 1982, 104, 7294-7299
- 19. Straathof, A. J. J.; Rakels, J. L. L.; Heinen, J. J. Biocatalysis 1992, 7, 13-27.
- Rakels, J. L. L.; Straathof, A. J. J.; Heijnen, J. J. Enzyme Microb. Technol. 1993, 15, 20 1051-1056.
- 21. Chini, M.; Crotti, P.; Gardelli, C.; Macciha, F. Tetrahedron 1992, 48, 3805–3812.
- 22. Baiwa, J. S.; Anderson, R. C. Tetrahedron Lett. 1991, 32, 3021–3024.
- 23. Hoff, B. H.; Ljones, L.; Rønstad, A.; Anthonsen, T. J. Mol. Catal. B: Enzym. 2000, 8, 51 - 60
- 24. Hanefeld, U. Org. Biomol. Chem. 2003, 1, 2405–2415.
- 25. Sjursnes, B.; Kvittingen, L.; Anthonsen, T.; Halling, P. In Biocatalysis in Nonconventional Media; Tramper, J., Vermüe, M. H., Beeftink, H. H., von Stockar, U., Eds.; Elsevier Science Publishers: 1992; pp 451-457.
- Hsin, L.-W.; Dersch, C. M.; Baumann, M. H.; Stafford, D.; Glowa, J. R.; Rothman, 26. R. B.; Jacobson, A. E.; Rice, K. C. J. Med. Chem. 2002, 45, 1321-1329.
- 27. Hoff, B. H.; Anthonsen, T. Chirality 1999, 11, 760-767.