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Chemoenzymatic synthesis of both enantiomers of 2-chloro-1-(2-furyl)ethanol

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Abstract—Enzyme catalyzed transesterification of *rac*-2-chloro-1-(2-furyl)ethanol *rac*-**1** using vinyl acetate afforded the enantiomers of 2-chloro-1-(2-furyl)ethanol **1** and 2-chloro-1-(2-furyl)ethyl acetate **2** in high enantiomeric excess. Several lipases were used for the kinetic resolution of racemic 2-chloro-1-(2-furyl)ethanol **l**, in which the lipases from *Pseudomonas cepacia*, *Candida antarctica* and *Candida cylindracea* displayed high enantioselectivity towards **1**.

1. Introduction

Furan ring containing compounds are very useful building blocks for the synthesis of a considerable number of natural products, such as α-amino acids, β-lactams, indolizilines, quinolizidines and piperidine alkaloids.[1] 2-Chloro-1-(2-furyl)ethanol **1** and its acetyl derivative 2-chloro-1-(2-furyl)ethyl acetate **2** are also important precursors for various biologically important molecules. These have been used successfully as a 'conformational toolbox', for example, in the synthesis of antiviral compounds. There are few methods in the literature for the synthesis of **1**.[2,3] Nieman and Tanis obtained (*S*)-**1** by enantioselective reduction of 2-chloro-1-(2-furyl)ethanone **4** using a chiral ruthenium–diamine catalyst. The product is then converted into (*R*)-2-amino-1-(2-furyl)ethanol (98% ee), which is used as a starting material for the synthesis of antiviral compounds.[2a] Takayuki's synthesis is another example of the enantioselective synthesis of (*S*)-**1**. Takayuki et al.[3] synthesized an optically active halohydrin by asymmetric hydrogen transfer reduction of the corresponding α-halo ketone **4** using a chiral rhodium–diamine catalyst.

We recently developed the synthesis of furan containing compounds with high levels of diastereo- and enantioselectivity and the enzyme- and fungus-mediated resolution of alcohols to obtain enantiomerically pure α-hydroxy ketones.[4]

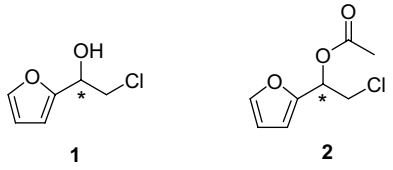

Figure 1.

Herein, we report a simple chemoenzymatic access to both enantiomers of 2-chloro-1-(2-furyl)ethanol **1** and 2-chloro-1-(2-furyl)ethyl acetate **2** starting from 1-(2-furyl)ethanone **3** via α-chlorination with a reduction followed by enzymatic kinetic resolution. To the best of our knowledge, no previous enzymatic kinetic resolution reaction has been carried out with *rac*-**1** (Fig. 1).

2. Results and discussion

The importance of enantiomerically pure **1** led us to explore a chemoenzymatic method for obtaining it in an enantiomerically pure form. As an initial reaction (Scheme 1), chlorination of commercially available 1-(2-furyl)ethanone **3** with SeO_2/TMSCl[5a] or Ce-NH_4NO_3/CH_3COCl[5b] was performed to obtain the chloroketone **4**, in 76–84% yield after purification by column chromatography.[6] BH_3SMe_2 mediated the

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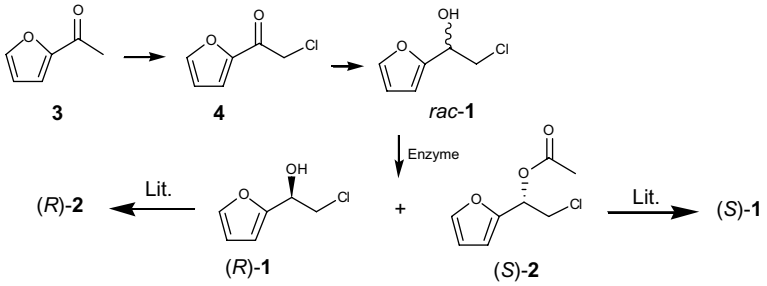

Scheme 1.

reduction of **4** to give *rac*-**1** in 84% yield after purification.

Lipase type enzymes are used extensively for the synthesis of enantiomerically pure compounds via the resolution of racemic mixtures. The high stereoselectivity in organic media and their low cost make them very useful catalysts for enantioselective resolution.[7]

Different lipases were screened for resolving racemic 2-chloro-1-(2-furyl)ethanol (*RS*)-**1** in the enantioselective transesterification of (*RS*)-**1** using vinyl acetate as an innocuous acyl donor without solvent. The lipases tested for the enantioselective transesterification of (*RS*)-**1** were lipases from *Pseudomonas cepacia*, *Candida antarctica*, Amano *PS*, *Rhizopus niveus*, *Muchor miehei*, *Candida cylindracea* and *hog pancreas*. The transesterification of **1** was carried out at 37 °C at a molar ratio of vinyl acetate to racemic (*RS*)-**1** of 2:1 to ensure complete reaction (Scheme 1). Careful monitoring of the reactions with TLC and HPLC furnished both enantiomers of 2-chloro-1-(2-furyl)ethanol (**1**) and 2-chloro-1-(2-furyl)ethyl acetate **2**. The results of the lipase-catalyzed transesterification of **1** are summarized in Table 1.

In the transesterification of (*RS*)-**1** using lipases from *P. cepacia* and Amano *PS*, (*S*)-**1** was the faster reacting enantiomer, yielding (*S*)-**2** in high ee and leaving (*R*)-**1** as the unreacted enantiomer. The other enzymes showed opposite selectivity. *P. cepacia*, *C. antarctica* and *C. cylindracea* displayed high enantioselectivity towards **1** (Table 1). In regard to the ee of the remaining substrate (*S*)-**1** and that of the product (*R*)-**2** as well as the enantiomeric ratio (E >200), lipase from *C. antarctica* was the best lipase employed in the transesterification of **1**. The lipases from *P. cepacia* and *C. cylindracea* also showed high enantioselectivity towards **1**, however, the enantiomeric ratio E was lower in comparison with the lipase from *C. antarctica* catalyzed transesterification of **1**. Other enzymes showed low to moderate enantioselectivities and reaction rates in the transesterification of **1** (Table 1).

We examined the transesterification of *rac*-**1** with different organic solvents. As shown in Tables 2 and 3 asymmetric transesterification of *rac*-**1** was carried out with lipase from *P. cepacia* and *C. antarctica* using vinyl acetate in toluene, THF and acetonitrile in a molar ratio of vinyl acetate to *rac*-**1** of 2:1. The transesterification of *rac*-**1** lipase from *P. cepacia* displayed high

Table 2. *Pseudomonas cepacia* lipase catalyzed asymmetric transesterification of (*RS*)-**1** using different solvents

Solvent	Time (d)	(*R*)-**1** Ee (%)	(*S*)-**2** Ee (%)	% Conversion	E[8]
Toluene	8	93	30	76	5.4
THF	8	73	77	49	16
Acetonitrile	4	99	42	70	11

Table 3. *Candida antarctica* lipase catalyzed asymmetric transesterification of (*RS*)-**1** using different solvents

Solvent	Time (d)	(*S*)-**1** Ee (%)	(*R*)-**2** Ee (%)	% Conversion	E[8]
Toluene	4	96	33	74	6.6
THF	4	65	96	40	96
Acetonitrile	4	85	34	71	4.9

Table 1. Lipase-catalyzed transesterification of *rac*-**1** without solvent

Lipase	Time (h)	**1** Ee[a] (%)	**2** Ee[a] (%)	% Conversion	E[8]
Pseudomonas cepacia	115	64 (*R*)	96 (*S*)	40	95
Candida antarctica	90	86 (*S*)	99 (*R*)	46	>200
Amano *PS*	85	12 (*R*)	17 (*S*)	41	1.6
Rhizopus niveus	3 weeks	38 (*S*)	39 (*R*)	49	3.2
Muchor miehei	52	22 (*S*)	30 (*R*)	42	2.3
Candida cylindracea	48	20 (*S*)	97 (*R*)	17	79
Hog pancreas	8 d	71 (*S*)	56 (*R*)	56	7.3

[a] The ee value was measured immediately after work-up and determined by HPLC using the chiral column (Chiralcel OD column, UV detection at 254 nm, eluent: hexane/2-propanol = 95:5, flow 0.50 mL min^{-1} 20 °C, using racemic compounds as references) while the configuration was determined from the sign of the specific rotation of the isolated product.[3]

enantioselectivity in acetonitrile and toluene towards **1**, in regard to the ee of the remaining substrate (*R*)-**1** (93%, 99%). Lipase from *C. antarctica* displayed high enantioselectivity in toluene towards **1**, in regard to the ee of the remaining substrate (*S*)-**1** (96%) and in THF towards **1**, in respect to the ee of the product (*R*)-**2** (96%).

C. antarctica lipase was the enzyme of choice used in the transesterification of *rac*-**1** using vinyl acetate without solvent on a preparative scale synthesis of (*R*)-**2**. An *E* value of more than 200 was observed with the reaction terminated after 90 h to afford (*R*)-**2** with more than 99% ee, in 38% yield with alcohol (*S*)-**1** recovered in 86% ee and 34% yield. Compound (*S*)-**1** (96% ee, 41% yield) was obtained in preparative scale by using *C. antarctica* lipase in toluene. For the preparative scale synthesis of (*R*)-**1** lipase from *P. cepacia* was used and transesterification of *rac*-**1** in acetonitrile furnished (*S*)-**2** in 36% yield and 42 % ee and the remaining (*R*)-**1** was isolated in 43% yield and 99% ee. Compound (*S*)-**2** (96% ee, 40% yield) was obtained on a preparative scale by using *P. cepacia* lipase under solvent free condition.

By applying the related literature procedure,[9] hydrolysis of (*S*)-**2** (K_2CO_3/MeOH) furnished (*S*)-**1** in 83% yield while the acetylation of (*R*)-**1** (Et_3N, Ac_2O) furnished (*R*)-**2** in 86% yield (Scheme 1). These processes could be carried out without any loss of enantiomeric excess.

3. Conclusion

In summary, we have reported herein the first efficient synthesis of both enantiomers of 2-chloro-1-(2-furyl)-ethanol **1** and 2-chloro-1-(2-furyl)ethyl acetate **2**, via enzymatic kinetic resolution. Chlorination of 1-(2-furyl)ethanone furnished 2-chloro-1-(2-furyl)ethanone **3** in high yield. Reduction of **3** with BH_3SMe_2 furnished *rac*-**1** in high yield. Enzyme catalyzed transesterification of *rac*-2-chloro-1-(2-furyl)ethanol *rac*-**1** using vinyl acetate afforded both enantiomers of 2-chloro-1-(2-furyl)-ethanol **1** and 2-chloro-1-(2-furyl)ethyl acetate **2** in high enantiomeric excess.

4. Experimental

4.1. Materials and methods

NMR spectra were recorded on a Bruker DPX 400. Chemical shifts δ are reported in ppm relative to $CHCl_3$ (^{1}H: $\delta = 7.27$), $CDCl_3$ (^{13}C: $\delta = 77.0$) and CCl_4 (^{13}C: $\delta = 96.4$) as internal standards. Column chromatography was conducted on silica gel 60 (40–63 μm). TLC was carried out on aluminum sheets pre-coated with silica gel $60F_{254}$ (Merck), and the spots were visualized with UV light ($\lambda = 254$ nm). Enantiomeric excesses were determined by HPLC and LC–MS analysis using a Thermo Finnigan Surveyor equipped with an appropriate chiral phase column, as described in the footnotes of the tables. Optical rotations were measured with a Krüss P3002RS automatic polarimeter.

4.2. General procedure for the lipase-catalyzed asymmetric transesterification of (±)-1

Racemic alcohol **1** (293 mg, 2 mmol) and vinyl acetate (344 mg, 4 mmol) were dissolved in the appropriate organic solvent (8 mL) while lipases (200–300 mg) were added [reactions without organic solvents: a mixture of racemic alcohol **1** (292 mg, 2 mmol), vinyl acetate (344 mg, 4 mmol) and lipase (200–300 mg) were stirred at 37 °C].The reaction mixture was stirred at 37 °C. The reaction was monitored by TLC and HPLC and when the maximum conversion was reached, the reaction was terminated by way of filtration. Substrate **1** and product **2** were separated by flash chromatography over silica (*n*-hexane/ethyl acetate, 4:1).

4.2.1. (*R*)-2-Chloro-1-(2-furyl)ethanol (*R*)-1.[3] Colourless oil (126 mg, 43%, 99% ee), $[\alpha]_D^{25} = -21.7$ (*c* 0.42, $CHCl_3$), {lit.[3] $[\alpha]_D^{20} = +23$ (*c* 0.52, $CHCl_3$) for (*S*)-**1**}. HPLC: Chiralcel OD column, UV detection at 254 nm, eluent: hexane/2-propanol = 95:5, flow 0.50 mL min^{-1} 20 °C (retention time: 18 min). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.60 (br s, 1H, OH), 3.71–3.81 (m, 2H), 4.87–4.93 (m, 1H), 6.27 (d, $J = 3.1$ Hz, 1H), 6.32 (dd, $J = 1.6$, 3.1 Hz, 1H), 7.25 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 47.3, 68.0, 107.5, 112.8, 142.3, 152.9.

4.2.2. (*S*)-2-Chloro-1-(2-furyl)ethanol (*S*)-1. Colourless oil (120 mg, 41%, 96% ee), $[\alpha]_D^{25} = +18.3$ (*c* 0.35, $CHCl_3$) HPLC: Chiralcel OD column, UV detection at 254 nm, eluent: hexane/2-propanol = 95:5, flow 0.50 mL min^{-1} 20 °C (retention time: 22 min).

4.2.3. (*S*)-2-Chloro-1-(2-furyl)ethyl acetate (*S*)-2. Colourless oil (150 mg, 40%, 96% ee), $[\alpha]_D^{25} = +14.5$ (*c* 0.2, $CHCl_3$). HPLC: Chiralcel OD column, UV detection at 254 nm, eluent: hexane/2-propanol = 95:5, flow 0.50 mL min^{-1} 20 °C (retention time: 12.5 min). ^{1}H NMR ($CDCl_3$): δ 2.01 (s, 3H), 3.73–3.81 (m, 2H), 5.93 (dd, $J = 5.9$ Hz, 1H), 6.25–6.28 (m, 1H), 6.32 (d, $J = 3.2$ Hz, 1H), 7.33 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 20.7, 43.0, 96.1, 109.8, 110.4, 142.8, 149.5, 169.1. Anal. Calcd for $C_8H_9ClO_3$ (188.6): C, 50.94; H, 4.81. Found: C, 50.75; H, 4.72.

4.2.4. (*R*)-2-Chloro-1-(2-furyl)ethyl acetate (*R*)-2. Colourless oil (142 mg, 38%, 99% ee), $[\alpha]_D^{25} = -16.6$ (*c* 0.2, $CHCl_3$). HPLC: Chiralcel OD column, UV detection at 254 nm, eluent: hexane/2-propanol = 95:5, flow 0.50 mL min^{-1} 20 °C (retention time: 14 min).

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References

1. (a) Zhou, W. S.; Lu, Z. H.; Xu, Y. M.; Liao, L. Y.; Wang, Z. M. *Tetrahedron* **1999**, *55*, 11959; (b) Cinfolini, M.; Hermann, C. Y. W.; Dong, Q.; Shimizu, T.; Swaminathan, S.; Yi, N. *Synlett* **1998**, 105; (c) Chen, W. P.; Roberts, S. M. *J. Chem. Soc., Perkin Trans. 1* **1999**, 103; (d) Kasai, M.; Ziffer, H. *J. Org. Chem.* **1983**, *48*, 2346; (e) Aehmatowicz, O.; Bukowski, P.; Szechner, B.; Zwierzchowska, Z.; Zamojski, A. *Tetrahedron* **1971**, *27*, 1973; (f) Boulton, A. J.; McKillop, A. In *Comprehensive Heterocyclic Chemistry*; Katritzsky, A. R., Rees, C. W., Eds.; Pergamon: Oxford, 1984; Vol. 2, part 2A, p 90; (g) Shono, T.; Matsumura, Y.; Tsubata, K.; Inoue, K.; Nishida, R. *Chem. Lett.* **1983**, 21; (h) Shono, T.; Matsumura, Y.; Tsubata, K.; Tanaka, J. *Chem. Lett.* **1981**, 1121, and the references cited therein; (i) Ciufolini, M. A.; Wood, C. W. *Tetrahedron Lett.* **1986**, *27*, 5085.
2. (a) Nieman, J. A.; Tanis, S. P. Process to produce enantiomerically enriched 1-aryl- and 1-heteroaryl-2-aminoethanols. PCT Int. Appl. 2004, 37 pp. CODEN: PIXXD2 WO 2004085414 A1 20041007 CAN 141:314165 AN 2004:817874 CAPLUS; (b) Brown, W. H.; Sawatzky, H. *Can. J. Chem.* **1956**, *34*, 1147; (c) Smith, L. R. Preparation of furylethanolamines as intermediates for herbicide antidotes. US 4,962,212.
3. Hamada, T.; Torii, T.; Izawa, K.; Ikariya, T. *Tetrahedron* **2004**, *60*, 7411.
4. (a) Demir, A. S. *Pure Appl. Chem.* **1997**, *69*, 105; (b) Demir, A. S.; Sesenoglu, O.; Gerçek-Arkın, Z. *Tetrahedron: Asymmetry* **2001**, *12*, 2309; (c) Demir, A. S.; Sesenoglu, O.; Ulku, D.; Arici, C. *Helv. Chim. Acta* **2003**, *86*, 91; (d) Demir, A. S.; Sesenoglu, O.; Aksoy-Cam, H.; Kaya, H.; Aydogan, K. *Tetrahedron: Asymmetry* **2003**, *14*, 1335; (e) Demir, A. S.; Sesenoglu, O. *Helv. Chim. Acta* **2004**, *87*, 106; (f) Demir, A. S.; Senocak, D. *Tetrahedron: Asymmetry* **2004**, *15*, 2641.
5. (a) Lee, G. L.; Park, I. S.; Seo, J. W. *Bull. Korean Chem. Soc.* **2002**, *23*, 1333; (b) Roy, C. S.; Rana, K. K.; Guin, C.; Baberjee, B. *ARKIVOC* **2003**, *9*, 34.
6. The compound is identified by the spectral data described in the literature; Dubac, J.; Gaset, A.; Maraval, M. *Synth. Commun.* **1991**, *21*, 11.
7. (a) Faber, K. *Biotransformations in Organic Chemistry*, 4th ed.; Springer: New York, 2000; (b) Liese, A.; Seelbach, K.; Wandrey, C. *Industrial Biotransformations*; Wiley-VCH Verlag GmbH: Weinheim, 2000; (c) Roberts, S. M. *Biocatalysts for Fine Chemical Synthesis*; John Wiley and Sons: New York, 1999; (d) Halgas, J. *Biocatalysts in Organic Synthesis (Studies in Organic Chemistry 46)*; Elsevier: Amsterdam, 1992.
8. Chen, C.-S.; Fujimoto, Y.; Girdaukas, G.; Sih, C. J. *J. Am. Chem. Soc.* **1982**, *104*, 7294.
9. (a) Demir, A. S.; Sesenoglu, O. *Org. Lett.* **2002**, *4*, 2021; (b) Bevinakatti, H. S.; Banerji, A. A.; Newadkar, R. V. *J. Org. Chem.* **1989**, *54*, 2453.