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Kinetic Resolution of rac-3-(2-Methylphenoxy)propane-1,2-diol (Mephenesin) by Sequential Lipase-Catalyzed Transesterification[1]

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Abstract: The kinetic resolution of rac-3-(2-methylphenoxy)propane-1,2-diol (**rac-1**, *Mephenesin*) by sequential lipase-catalyzed transesterification with vinyl acetate in tetrahydrofuran/triethylamine in the presence of lipase *Amano PS* is described.

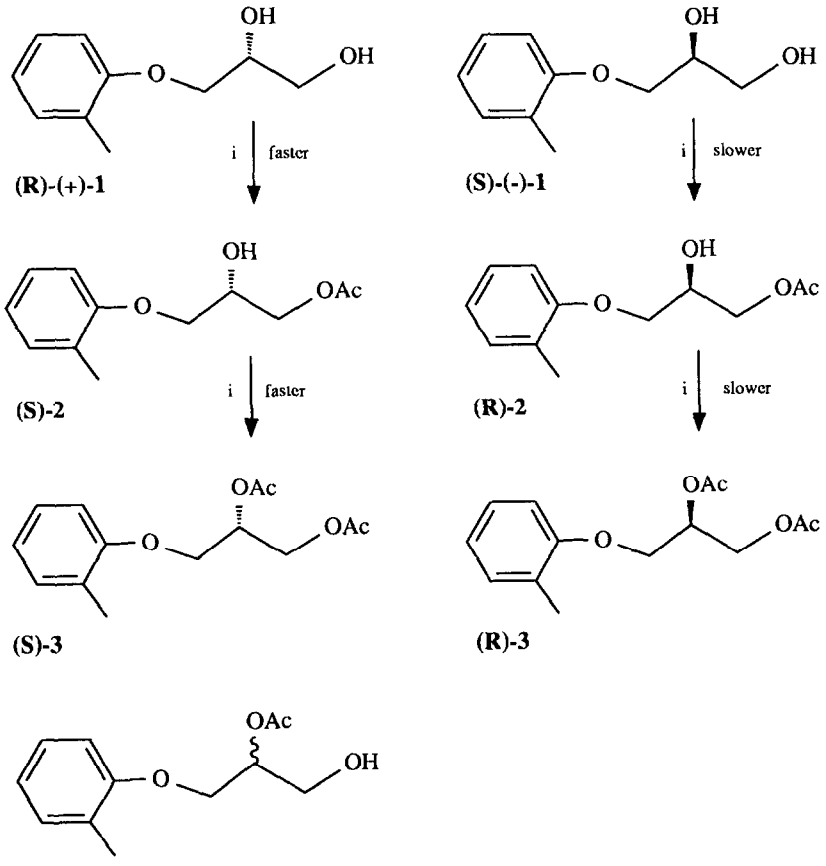
Racemic 3-(2-methylphenoxy)propane-1,2-diol (**rac-1**, *Mephenesin*) is a potent muscle relaxant. Previously **rac-1** has been only incompletely resolved into its enantiomers via the formation of the hemiphthalate which formed diastereomeric salts with quinidine and brucine[2]. A chiral pool synthesis of (R)- and (S)-*Mephenesin* was realized starting from (+)-(2R,3R,4R,5R)-mannitol[3].

Owing to the efficiency of enzyme-catalyzed transformations in asymmetric synthesis[4] and in continuation of our work on lipase-catalyzed transesterifications for enantio- and regioselective functionalizations it has been an attractive aim to separate **rac-1** into its enantiomers as an example for related 1,2-diols of physiological importance.

Primary hydroxy groups are acylated faster than secondary ones and regioselectively by a lipase-catalysis[5b,5e,6]. At the first attempts to realize the separation of **rac-1** into its enantiomers by combination of regioselective monoacetylation with enantioselection, **rac-1** was acetylated with vinyl acetate in tetrahydrofuran/triethylamine[7] in the presence of lipases of different origin. Most of the lipases tested (*Lipozyme M20,* lipase from *Candida sp. 382,* lipase from *Mucor sp.,* lipase from *Yarrowia lipolytica,* and *Pancreatin*) showed a high regioselectivity but a very low enantioselectivity in the monoacetylation step after 50 % conversion of **rac-1**. After separation of the unreacted diol **(S)-(-)-1** from the monoacetate **(S)-2** the enantiomeric excess (e.e.) for both products did not reach more than 5 - 20 %. Only lipase *Amano PS* showed a moderate e.e. for the diol **(S)-(-)-1** and the monoacetate **(S)-2** in the order of 40 - 45 %. This was the starting point for applying the concept of *sequential resolution*[8] to the amplification of a kinetic resolution of a racemic diol.

Indeed, acetylation of **rac-1** with vinyl acetate in tetrahydrofuran/triethylamine in the presence of lipase *Amano PS* afforded the monoacetate **(R)-2** in a chemical yield of 45 - 48 % with an e.e. of 89 - 94 % and the corresponding diacetate **(S)-3** in a chemical yield of 45 - 48 % with an e.e. of 79 - 81 %.

Deacetylation of **(R)-2** yielded crystalline **(S)-(-)-1** and deacetylation of **(S)-3** yielded **(R)-(+)-1**, respectively. The e.e. of both **(S)-(-)-1** and **(R)-(+)-1** could be easily enhanced up to more than 99 % by a single recrystallization from water.



i: vinyl acetate, lipase *Amano PS*, THF, NEt_3, r.t.

Scheme

The e.e's. of **(R)-2** and **(S)-3** were determined by HPLC on a chiral phase[9] after deacetylation to **(S)-(-)-1** and **(R)-(+)-1**, respectively.

The absolute configuration of **(R)-(+)-1** and **(S)-(-)-1**[2,3] was determined on the basis of their CD spectra[3], because the reported optical rotations are contradictory[2,3]. We measured optical rotations in a sufficient magnitude in hexane - 2-propanol[14,15], the solvent system for HPLC, but in ethanol and trichloromethane we did not find an optical rotation.

Lipase-Catalyzed Resolution Procedure. A solution of **rac-1** (1.82 g, 10 mmol) in tetrahydrofuran (25 ml) was treated with triethylamine (0.71 g, 7 mmol), vinylacetate (6.07 g, 70 mmol), and lipase *Amano PS* (1.00 g). The suspension was stirred at room temperature for 96 h. At this time all **rac-1** was consumed. After filtration of the lipase[10] the filter cake was washed with tetrahydrofuran (3 x 10 ml). The filtrate was evaporated to dryness under reduced pressure and separated immediately[11] by flash chromatography on silica gel 60 (0.063 - 0.040 mm) (column size 30 x 4 cm) with hexane - ethyl acetate (1 : 1) yielding **(R)-2**[12] (1.01 g, 45 %) and **(S)-3**[13] (1.28 g, 48 %).

A solution of **(R)-2** (1.01 g, 4.5 mmol) in methanol (10 ml) was treated with the ion exchange resin *Wofatit SBW* (OH^-, 2 g) and stirred at room temperature for 2 h. The ion exchange resin was filtered off and the solvent was removed under reduced pressure yielding **(S)-(-)-1** (0.82 g, 100 %) with an e.e. of 93 %. The same procedure with **(S)-3** (1.28 g, 4.8 mmol) yielded **(R)-(+)-1** (0.87 g, 100 %) with an e.e. of 80 %.

Recrystallization of **(S)-(-)-1** (0.82 g) from water yielded enantiomerically pure **(S)-(-)-1**[14] (0.41 g, 50 %) with an e.e. >99%. Recrystallization of **(R)-(+)-1** (0.87 g) from water yielded enantiomerically pure **(R)-(+)-1**[15] (0.44 g, 51 %) with an e.e. >99 %.

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7. We used this solvent system advantageously for other lipase-catalyzed acylations (ref. 5a - 5e).
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9. Stationary phase: cellulose tris(3,5-dimethylphenyl-carbamate) supported on aminosilica; eluent: hexane - 2-propanol (80 : 20, v : v)
10. The recovered lipase was used at least three times without loss of activity.
11. Storage of the crude monoacetate **2** in racemic or optically active form shows acyl migration affording the secondary monoacetate **4** as a by-product. Purified **2** is stable for several weeks in a refrigerator. Intra- and intermolecular acyl migration during the lipase-catalyzed reaction should be possible diminishing the e.e. of the products.
12. **(R)-2**: colourless oil; ^{1}H NMR (80 MHz, $CHCl_3$): 2.02 (s, 3H, OAc), 2.16 (2, 3H, CH_3), 2.50 (br s, 1H, OH, exchangeable), 3.90 - 4.30 (superimposed signals, 5H, 2 x CH_2 and CH), 6.66 - 7.15 (m, 4H, C_6H_4); ^{13}C NMR (75 MHz, $CDCl_3$): 16.11, 20.77, 6545, 68.54, 68.59, 111.01, 121.01, 126,72, 126.82, 130.78, 156.27, 171.17; MS (70 eV, e.i.): 224 (M, 10), 133 (15), 117 (100), 103 (70), 102 (30), 91 (45); calcd.: C 64.26, H 7.19, found: C 64.31, H 7.29.
13. **(S)-3**: colourless liquid; b.p. 210°C (bath temp./ 3 Pa); ^{1}H NMR (80 MHz, $CDCl_3$): 1.99 (s, 3H, OAc), 2.02 (s, 3H, OAc), 2.14 (s, 3H, CH_3), 4.04 (d, J 7 Hz, 2H, CH_2-O), 4.30 (m, 2H, CH_2-OAc), 5.35 (quin, J 5Hz, CH-OAc), 6.64 - 7.15 (m, 4H, C_6H_4); ^{13}C NMR (75 MHz, $CDCl_3$): 16.04, 20.68, 20.88, 62.60, 66.04, 69.82, 110.98, 121.03, 126.78, 126.93, 130.79, 156.31, 170.17, 170.51; MS (70 eV, e.i.): 266 (M, 40), 207 (10), 159 (100), 108 (25), 99 (25), 91 (25) calcd: C 63.14, H 6.80, found: C 63.58, H 7.09.
14. $[\alpha]_D^{20}$ -19.3 [c 0.9, hexane - 2-propanol (4 : 1)].
15. $[\alpha]_D^{20}$ +19.8 [c 0.9, hexane - 2-propanol (4 : 1)].