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Synthesis of a key intermediate, (*S*)-2-[(3-hydroxypropyl)sulfinyl]-1-(*o*-tolyl)imidazole, for the platelet aggregation inhibitor, OPC-29030 via lipase-catalyzed enantioselective transesterification

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Abstract: Optically active 2-[(3-hydroxypropyl)sulfinyl]-1-(*o*-tolyl)imidazole (*S*)-**2** was synthesized by kinetic resolution of (±)-**2** with lipase and hydrolysis of the acetate (*S*)-**3** with potassium carbonate. The reaction mixture of the lipase-catalyzed transesterification was converted to the phthalic acid derivative (*R*)-**4**, and this (*R*)-**4** and the unreacted acetate (*S*)-**3** were fractionated without use of column chromatography. The unrequired recovered alcohol (*R*)-**2** was also racemized and (±)-**2** was repeatedly submitted to the lipase-catalyzed transesterification. © 1997 Elsevier Science Ltd

The sulfinyl derivative (*S*)-(+)-3,4-dihydro-6-[3-(1-*o*-tolyl-2-imidazolyl)sulfinylpropoxy]-2(1*H*)-quinolinone (OPC-29030, **1**)[1] is a new platelet aggregation inhibitor which inhibits the release of 12(*S*)-hydroxyeicosatetraenoic acid (12-HETE) from platelets, and is now under clinical trial. Enantiomerically pure **1** was prepared by using (2*S*)-(+)-glycidyl tosylate as a chiral source in five steps.[1] Generally, the Sharpless oxidation procedure modified by Kagan[2] and Modena[3] is used for the asymmetric synthesis of chiral sulfoxides. Nishi and co-workers prepared the key intermediate (*S*)-**2** for the synthesis of **1** by a modified Sharpless asymmetric oxidation.[4] On the other hand, enzyme-catalyzed processes are some of the most useful synthetic technologies for the preparation of optically active compounds from a racemate. Two groups, Burgess *et al.*[5] and Nagao *et al.*,[6] have reported enzymatic hydrolysis of carboxylic acid ester bearing a sulfinyl group as the prochiral center. We have recently investigated the synthesis of the various key intermediates for medical supplies utilizing enzyme-catalyzed reactions. Herein, we wish to describe the first lipase-catalyzed kinetic resolution of (±)-**2** with a sulfinyl group being remote from the reacting site (Figure 1).

First, we tested the lipases which could be used for the lipase-catalyzed transesterification of (±)-**2** with vinyl acetate. As shown in Table 1, we directed attention to lipase AL and PL which gave the unreacted alcohol in fairly high enantiomeric excess (entries 1 and 2).

Next, we examined the lipase-catalyzed transesterification of (±)-**2** with isopropenyl acetate or vinyl acetate in organic solvent to obtain the convenient reaction conditions as summarized at entries 1–8 in

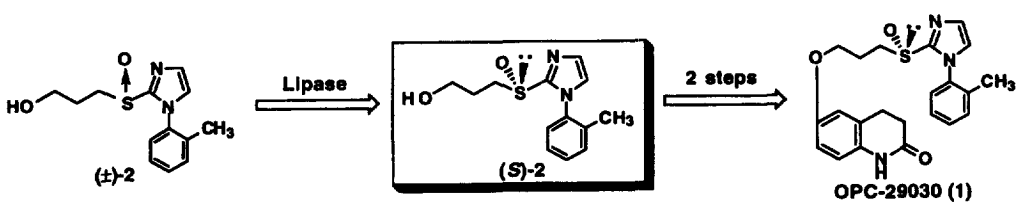

Figure 1.

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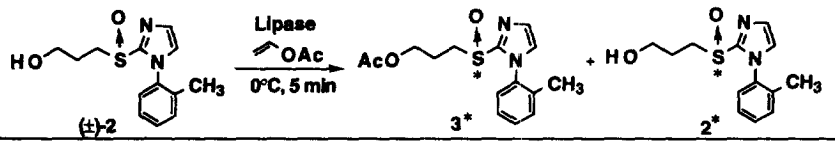
Table 1. Lipase-catalyzed esterification of (±)-**2**[a]



Entry	Lipase[b]	3* C.Y.(%)[c]	3* %ee[d]	2* C.Y.(%)[c]	2* %ee[d]
1	Lipase AL	83	24 (*S*)	17	92 (*R*)
2	Lipase PL	93	2 (*S*)	2	90 (*R*)
3	Lipase OF	34	13 (*R*)	66	6 (*S*)
4	Lipase MY	13	13 (*R*)	86	2 (*S*)
5	Lipase QL	100	racemic	0	–
6	Novozym 435	96	racemic	4	20 (*R*)
7	Lipozyme IM	22	3 (*S*)	77	racemic

a. All reactions were carried out by stirring a mixture of (±)-**2** (10 mg), lipase (10 mg) and vinyl acetate (1 ml) at 0 °C for 5 min. b. AL (Meito, *Alcaligenes sp.*), PL (Meito, *Alcaligenes sp.*), OF (Meito, *Candida cylindracea*), MY (Meito, *Candida cylindracea*), QL (Meito, *Alcaligenes sp.*), Novozym 435 (Novo Nordisk, *Aspergillus oryzae*), Lipozyme IM (Novo Nordisk, *Mucor miehei*). c . Isolated yield. d. Enantiomeric purities were determined by HPLC analyses using a column packed with Daicel Chiralpak AD (solvent; *n*-hexane:EtOH:diethylamine = 600:400:1).

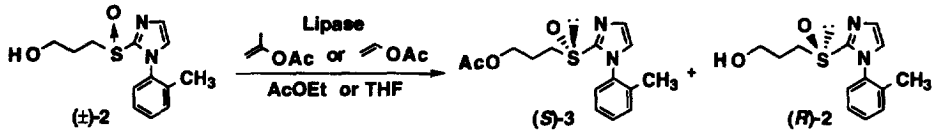
Table 2. From the screening test, the use of lipase AL and isopropenyl acetate in ethyl acetate (AcOEt) gave a good result (entry 2). The acetate (*S*)-**3** and the unreacted alcohol (*R*)-**2** were obtained in 41% yield and 63% ee, and 59% yield and 43% ee, respectively. We futhermore investigated the reaction conditions at the practical scale as shown at entries 9–12 in Table 2. From entries 9 and 10, the used amount of lipase AL towards (±)-**2** hardly influenced the enantioselectivities and enantiomeric purities of the products. The lipase-catalyzed transesterification at 4°C required long reaction times. In fact, it is technically preferable to perform the reaction at room temperature rather than at 4°C. When the reaction was carried out at room temperature, the enantioselectivities and enantiomeric excesses of the products were similar to those at 4°C, and the optical purity of the desired acetate (*S*)-**3** decreased in accordance with an extension of the reaction time (entries 11 and 12).

The desired key intermediate (*S*)-**2** was obtained by methanolysis of the acetate (*S*)-**3** with potassium carbonate (K_2CO_3) in methanol (MeOH). Enantiomerically pure alcohol (*S*)-**2** was prepared by two recrystallizations of 59% ee product from AcOEt (Table 3).

We attempted fractional purification without use of column chromatography (Scheme 1). After the lipase-catalyzed transesterification of (±)-**2**, the mixture was filtered through a Celite pad and the filtrate was evaporated. Instantly, a mixture of the acetate (*S*)-**3** and the alcohol (*R*)-**2** was treated with phthalic anhydride in the presence of 4-dimethylaminopyridine (DMAP) in pyridine to afford the unreacted acetate (*S*)-**3** and the phthalic acid derivative (*R*)-**4** without racemization, and then both of the compounds were separated by extraction. The unreacted acetate (*S*)-**3** was recovered in good yield and the phthalic acid derivative (*R*)-**4** was hydrolyzed with 1 N sodium hydroxide (NaOH) in MeOH to regenerate the alcohol (*R*)-**2**. The recovered alcohol (*R*)-**2** was completely racemized by treatment with 3 N hydrochloric acid (HCl) in 70% yield. The racemized alcohol (±)-**2** was repeatedly used as a substrate for the lipase-catalyzed transesterification.

In conclusion, we have established an efficient synthesis of (*S*)-2-[(3-hydroxypropyl)sulfinyl]-1-

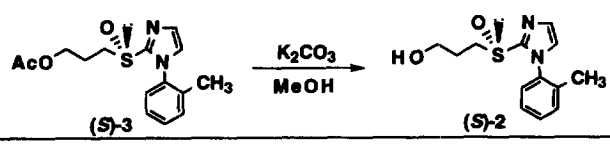
Table 2. Lipase-catalyzed esterification of (±)-**2**[a]



Entry	Lipase[b]	Solvent	Acetate	Temp. (°C)	Time (hr)	(*S*)-3		(*R*)-2	
						C.Y.(%)[c]	%ee[d]	C.Y.(%)[c]	%ee[d]
1	AL	AcOEt	vinyl	4	18	77	27	23	45
2	AL	AcOEt	isopropenyl	4	18	41	63	59	43
3	AL	THF	vinyl	4	18	27	59	73	20
4	AL	THF	isopropenyl	4	18	1	—	99	—
5	PL	AcOEt	vinyl	4	18	83	17	17	76
6	PL	AcOEt	isopropenyl	4	18	28	60	72	2
7	PL	THF	vinyl	4	18	62	43	38	66
8	PL	THF	isopropenyl	4	18	3	> 99	97	racemic
9	AL	AcOEt	isopropenyl	4	96	58	60	42	65
10	AL*	AcOEt	isopropenyl	4	96	58	51	42	73
11	AL	AcOEt	isopropenyl	rt	23	55	46	45	51
12	AL	AcOEt	isopropenyl	rt	28	63	38	37	60

a. The reactions (entries 1– 8) were carried out by stirring a mixture of (±)-**2** (10 mg), lipase (catalytic amount), acyl donor (1 drop) and organic solvent (1 ml) at 4 °C and the reactions (entries 9– 12) were carried out by stirring a mixture of (±)-**2** (264 mg, 1 mmol), lipase AL (50 mg, *100 mg), isopropenyl acetate (200 mg, 2 mmol) and AcOEt (12 ml). b. AL (Meito, *Alcaligenes sp.*), PL (Meito, *Alcaligenes sp.*), c. HPLC yield. d. Enantiomeric purities were determined by HPLC analyses using a column packed with Daicel Chiralpak AD (solvent; *n*-hexane:EtOH:diethylamine = 600:400:1).

Table 3. Conversion of acetate (*S*)-3 to the corresponding alcohol (*S*)-2



(*S*)-3	(*S*)-2	1st Recrys.(AcOEt)	2nd Recrys.(AcOEt)
3.06 g	2.64 g	1.74 g	1.19 g
59 %ee	quant., 59 %ee	66 %, 88 %ee	45 %, 100 %ee

(*o*-tolyl)imidazole (*S*)-**2** by means of the lipase-catalyzed kinetic resolution and fractional purification of both products without use of column chromatography. The unrequired recovered alcohol (*R*)-**2** was converted to (±)-**2** by treatment with 3 N HCl and the racemized alcohol (±)-**2** could be submitted to lipase-catalyzed transesterification.

Acknowledgements

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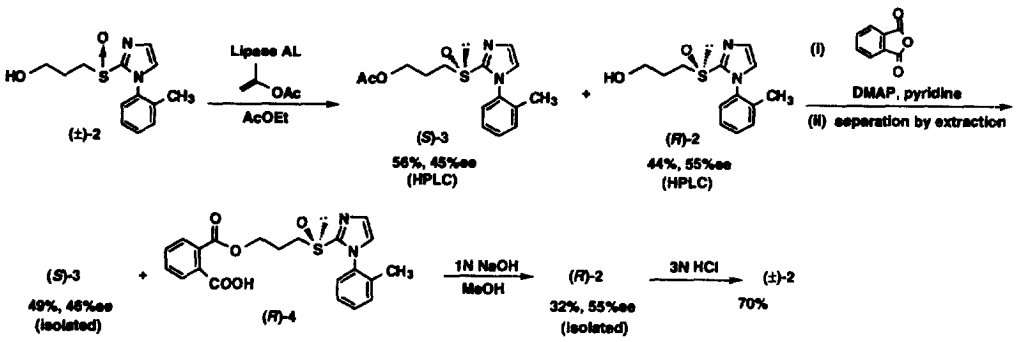

Scheme 1.

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