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An Efficient Synthesis of Optically Active Metabolites of Platelet Adhesion Inhibitor OPC-29030 by Lipase-Catalyzed Enantioselective Transesterification

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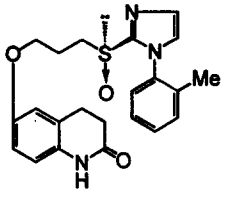
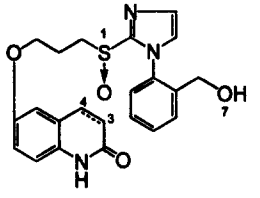
Abstract: The optically active metabolites of (*S*)-3,4-dihydro-6-[3-(1-*o*-tolyl-2-imidazolyl)sulfinyl-propoxy]-2(1*H*)-quinolinone (OPC-29030, **1**), which is a new anti-platelet agent (platelet adhesion inhibitor), were effectively synthesized by the enzyme-catalyzed enantioselective transesterification of the racemic sulfinyl metabolites. The enzymes can recognize a stereogenic sulfur atom remote from the reaction site.

(*S*)-3,4-Dihydro-6-[3-(1-*o*-tolyl-2-imidazolyl)sulfinylpropoxy]-2(1*H*)-quinolinone (OPC-29030, **1**)[1] is a new platelet adhesion inhibitor which suppresses the production of 12(*S*)-hydroxyeicosatetraenoic acid (12-HETE) in platelets and is now under clinical trials (Figure 1). As a part of the drug development study, the metabolism of **1** has been investigated in rats, dogs and humans. The structures of the metabolites (**2a** and **2b**) were proposed on the basis of NMR and MS spectral analyses to be the compounds hydroxylated at the tolyl group. These metabolites have a chiral sulfinyl group as well as **1**. The pharmacological activity of the enantio-isomeric metabolites and the metabolic chiral inversion of the sulfinyl group pose an interesting problem.

On the other hand, the synthetic method for optically active compounds using lipase-catalysis in an organic solvent has recently been generally accepted. However, substrates of the lipase-catalyzed asymmetric reactions were limited to the compounds whose stereogenic carbon atoms were in the neighborhood of the reaction site. There have been some investigations on substrates whose stereogenic carbon atoms are remote from the reacting site.[2] The application of enzymatic methods for the preparation of chiral sulfoxide has been reported by Nagao et al.[3] and other groups.[4] Usually, the enantioselectivity was low in lipase-catalyzed optical resolution which used a primary alcohol. In a previous paper,[5] we also reported the asymmetric synthesis of the key intermediate (**3**) of OPC-29030 from a racemic substrate using the lipase catalyst. However, the low enantioselectivity ($E < 9$)[8] was observed in the reaction of **3** included the flexible primary alcohol, and there was no effect by the added organic solvent. In the course of our investigation we have noted the relationship between the primary hydroxyl- and chiral sulfinyl-group in the enzyme-catalyzed reaction. Herein we wish to describe the synthesis of the optical isomers of the metabolites (**2a** and **2b**), using the lipase-catalyzed reaction of them in which the chiral center and reacting site are distant, when compared with **3**.



1 (OPC-29030)



2a : bond of C(3) and C(4), single
2b : bond of C(3) and C(4), double

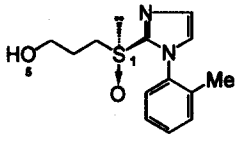


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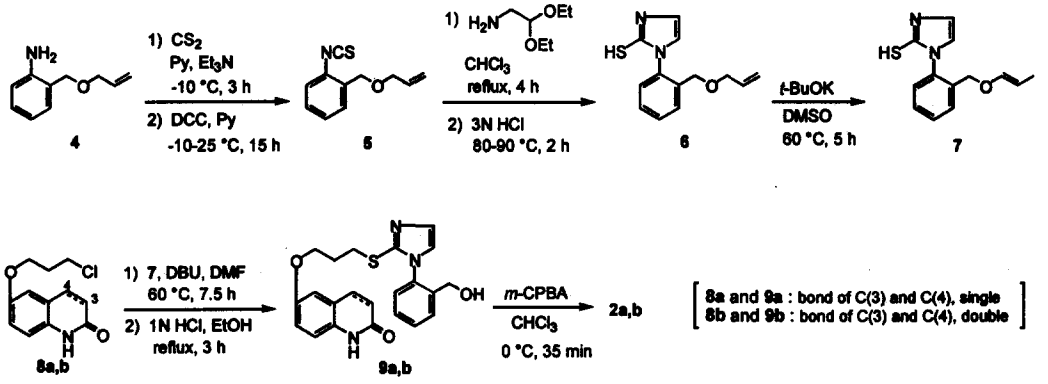
Figure 1

PII: S0040-4039(99)00946-6

The racemic compounds (**2a** and **2b**) were prepared as shown in Scheme 1. The reaction of 2-(allyloxymethyl)aniline (**4**)[6] with carbon disulfide in pyridine-triethylamine followed by treatment with DCC gave the isothiocyanate (**5**). Condensation of **5** with 2,2-diethoxyethylamine afforded the thiourea, which was cyclized in the presence of 3N HCl to give the 2-mercaptoimidazole (**6**). Treatment of this 2-propenyl compound (**6**) with *t*-BuOK afforded the 1-propenyl compound (**7**). The reaction of **7** with the chloride (**8a**)[7] in the presence of DBU gave the sulfide, which was treated with 1N HCl to give the hydroxy compound (**9a**). The desired compound (**2a**) was prepared by the oxidation of **9a** with *m*-CPBA. Another sulfoxide (**2b**) was synthesized from **8b**[7] and **7** by a procedure similar to that used for **2a**.

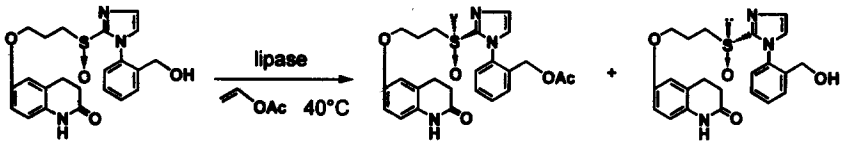
Scheme 1 Preparation of the racemic compounds of **2a** and **2b**



The optical isomers **2a** and **2b** were synthesized as follows. We examined the lipase-catalyzed enantioselective transesterification of the sulfoxide (±)-**2a**. As shown in Table 1, Novozym 435 from *Candida antarctica* (Novo Nordisk) was selected after screening several commercially available lipases in the reaction with (±)-**2a** (Entries 4). Table 2 summarizes the results of the experiments using Novozym 435 and vinyl acetate in various organic solvents. The reaction was usually conducted at 40 °C or room temperature and monitored by HPLC. Under these conditions, it was apparent that the most suitable solvents were dichloromethane and chloroform; good reaction rates and enantioselectivity were achieved at room temperature. Next, a preparative scale reaction was performed. Stopping the reaction at around a 40 % conversion gave (+)-**10a** and (-)-**2a** in high enantiomeric purities (95 % ee and 67 % ee, E = 79).[8] The alcohol (+)-**2a** prepared by hydrolysis of (+)-**10a** (95 % ee) with potassium carbonate was subjected to lipase-catalyzed acylation[9] again and the pure (+)-**10a** (>99 % ee) was obtained. The target compound (+)-**2a** (>99 % ee) was synthesized by the hydrolysis of (+)-**10a** (>99 % ee) with K_2CO_3. The antipodal enantiomer (-)-**2a** (>99 % ee) was similarly obtained as the unreacted alcohol by lipase-catalyzed transesterification[9] of the sample with low optical purity (67 % ee). Compounds (+)- and (-)-**2b**[10] were also synthesized by a procedure similar to that used for (+)- and (-)-**2a**.

The absolute configurations of the above optically active compounds were determined as follows (Scheme 2). The benzyl alcohol (+)-**2a** synthesized from (±)-**2a** via transesterification was treated with mesyl chloride in the presence of Et_3N to give the mesylate, which was converted to the tolyl compound (+)-**1**. The HPLC retention time of this compound was in good agreement with that of the mother compound [**1**, (*S*)-(+)]. The compound (+)-**11** derived from (+)-**10b** agreed with the dehydro compound (*S*)-**11** prepared from (*S*)-(+)-**12**. Accordingly, the absolute configuration for the isomers of (+)-**2a**, (+)-**2b**, (+)-**10a** and (+)-**10b** was assigned *S*.

Table 1. Lipase-catalyzed enantioselective transesterification of (±)-2a[a]



(±)-2a (S)-(+)-10a (R)-(-)-2a

Entry	Lipase[b]	Time (min)	Acetate Yield (%)[c]	Acetate % ee[d]	Unreacted alcohol Yield (%)[c]	Unreacted alcohol % ee[d]	E[e]
1	Lipase PL	660	83	21 (*S*)	17	99 (*R*)	6
2	Lipase MY	660	54	13 (*R*)	46	15 (*S*)	1
3	Lipase OF	30	46	17 (*S*)	54	14 (*R*)	2
4	Novozym 435	30	56	65 (*S*)	44	83 (*R*)	12
5	Lipozyme IM	660	63	28 (*S*)	37	48 (*R*)	3
6	SP 524	660	63	31 (*S*)	37	53 (*R*)	3
7	Toyozyme	120	79	19 (*S*)	21	70 (*R*)	3

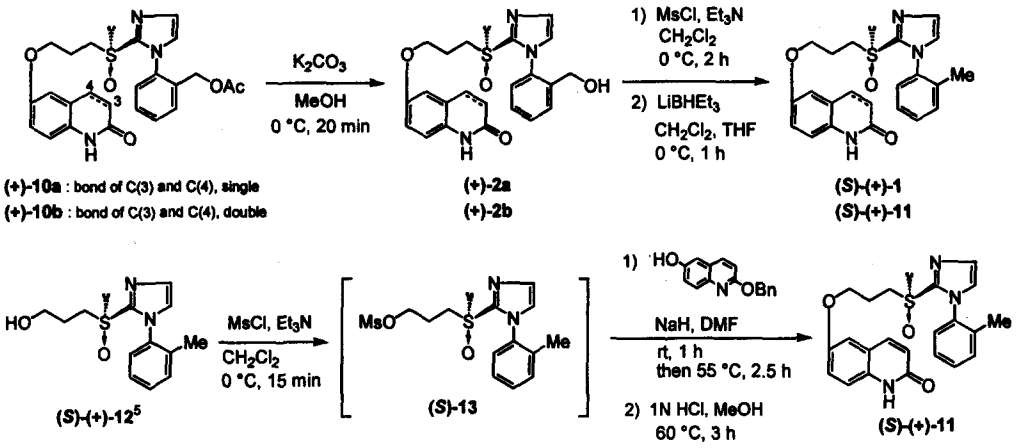
a. All reactions were carried out by stirring a mixture of (±)-2a (10 mg), lipase (10 mg) and vinyl acetate (1 ml) at 40°C. b. PL (Meito, *Alcaligenes sp.*), MY (Meito, *Candida cyclindracea*), OF (Meito, *Candida cyclindracea*), Novozym 435 (Novo Nordisk, *Aspergillus oryzae*), Lipozyme IM (Novo Nordisk, *Mucor miehei*), SP 524 (Novo Nordisk, *Aspergillus orizae*), Toyozyme (Toyo Boseki, *Pseudomonas sp.*). c. HPLC yield. d. Enantiomeric purities were determined by HPLC analyses using a column packed with ULTRON ES-OVM (solvent: acetonitrile : 20 mM KH_2PO_4 = 7 : 93). e. The E value is the ratio of the specificity constant of two enantiomers caluculated according to ref. 8.

Table 2. Lipase-catalyzed enantioselective transesterification of (±)-2a in organic solvents[a]

Entry	Solvent	Temp (°C)	Time (min)	Acetate Yield (%)[b]	Acetate % ee[c]	Unreacted alcohol Yield (%)[b]	Unreacted alcohol % ee[c]	E[e]
1	-	rt	30	38	84	62	51	19
2	i-Pr_2O	40	5	21	68	79	18	6
3	CH_2Cl_2	40	5	37	91	63	54	36
4	CH_2Cl_2	rt	30	47	93	53	82	70
5	$CHCl_3$	rt	30	44	94	56	72	70
6	CCl_4	rt	30	34	85	66	45	19
7	toluene	rt	30	31	92	69	41	36
8	AcOEt	rt	30	50	84	50	85	31
9	THF	rt	30	52	87	48	95	53

a. All reaction were carried out by stirring a mixture of (±)-2a (10 mg), Novozym 435 (10 mg) and vinyl acetate (0.5 ml) in organic solvent (0.5 ml) at room temperature or 40°C. b. HPLC yield. c. Enantiomeric purities were determined by HPLC analyses using a column packed with ULTRON ES-OVM (solvent; acetonitrile : 20 mM KH_2PO_4 = 7 : 93). e. see ref. 8.

Scheme 2 Determination of the absolute configuration of (+)-**10a** and (+)-**10b**



In conclusion, we have established the efficient synthesis of optically active metabolites (**2a** and **2b**) of OPC-29030 using lipase-catalyzed kinetic resolution. The metabolites (**2a** and **2b**) were resolved with excellent enantioselectivity by using Novozym 435 in spite of the reaction site being fairly remote from the stereogenic sulfur atom, in contrast to **3**. There is also significance in addition to expansion of the utility of the lipase-catalyzed transesterification when we consider the reaction mechanism.

References and Notes

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9. The reactions were carried out by stirring a mixture of substrates, Novozym 435 and vinyl acetate in CH_2Cl_2.
10. A mixture of (±)-**2b** (100 mg, 0.24 mmol), vinyl acetate (3.0 ml) and Novozym 435 (100 mg) in CH_2Cl_2 (10 ml) was stirred at room temperature for 4 h. The enzyme was filtered off and washed with CH_2Cl_2. The combined solution was concentrated *in vacuo* and the residue was purified by column chromatography on silica gel to give the acetate (45 mg, 40%, 97 % ee) and the unreacted alcohol (48 g, 46%, 89 % ee, E = 198).[8]