Lipase-Catalyzed Resolution of Sterically Crowded 1,2-Diols

Vladimir KHLEBNIKOV,*,[a] Kenji MORI,[b] Kohji TERASHIMA,[a] Yuji TANAKA,[a] and Makoto SATO[a]

Research Laboratories, Roussel Morishita Co., Ltd.,[a] 1658, Ohshinohara, Yasu-cho, Yasu-gun, Shiga 520–23, Japan and Department of Chemistry, Science University of Tokyo,[b] Kagurazaka 1–3, Shinjuku-ku, Tokyo 162, Japan.
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An enzymatic method for preparation of the enantiomers of chiral diols 2a,b and their monoacetates 3a,b with 100% enantiomeric purity by using lipase-catalyzed esterification and/or hydrolysis was established. The (*R*)-enantiomers were more reactive in both acetylation of (±)-2a,b and hydrolysis of (±)-3a,b catalyzed by lipase OF-360 from *Candida cylindracea*.

Key words lipase; enzymatic resolution; vicinal diol

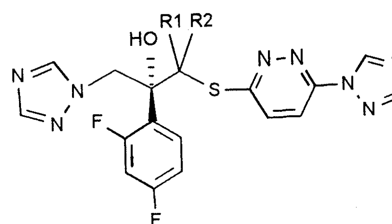
Chiral vicinal diols are useful synthetic intermediates in the synthesis of natural products and pharmaceuticals. These compounds, however, are not always easily available in enantiomerically pure form, in spite of recent advances in asymmetric synthesis, including asymmetric dihydroxylation (AD) of olefins.[1)] In particular, it is difficult to access α,α-disubstituted vicinal diols, where the tertiary hydroxyl group, responsible for the chirality, is adjacent to a primary one. We encountered this problem in the course of preparation of new azole antifungals (for example, representative compounds **1a**,**b**[2)]), where the chiral diols **2a**,**b** were the key intermediates (Fig. 1). The tertiary hydroxyl groups in **2a**,**b** are additionally shielded by two *β*,*β*-substituents, which makes them extremely sterically crowded.

Steric hindrance in the close vicinity of the chiral center sets severe limitations on the possible approach of a reagent and makes the stereoselective synthesis of such compounds very problematic. For example, all attempts to synthesize **2a** *via* Sharpless AD[3)] from the corresponding olefin, or through asymmetric halolactonization reaction[4)] failed due to steric hindrance. Other, not so numerous examples of the creation of the tertiary hydroxyl group *via* asymmetric synthesis (mainly based on the Grignard reaction, see, for example, refs. 5—9), seem to be limited to special classes of substances with simple substituents. We therefore turned our attention to lipase-catalyzed transesterification, which has recently been frequently used to prepare enantiomerically enriched alcohols of various types.[10)]

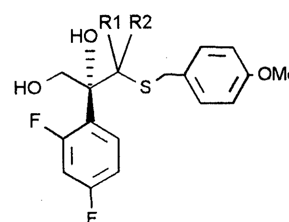
The diols **2a**,**b** are quite dissymmetric molecules, and we expected that some lipases would be able to discriminate their enantiomers in the course of transesterification, even though the primary hydroxyl group, the reactive site, is separated from the chiral center. First, lipase screening was performed in both esterification and hydrolytic modes. In the esterification mode, the substrates [diols (±)-**2a**,**b**] were acetylated by vinyl acetate in an organic solvent in the presence of lipase. In the hydrolytic mode, corresponding monoacetates [(±)-**3a**,**b**] were hydrolyzed in the presence of lipase using a biphasic mixture of organic solvent and aqueous buffer solution (Chart 1). The following lipases were used: lipase A, AK, AY, F, F-AP15, and M from Amano, lipase AF2 and P from Nagase, lipase MY and PS from Takasago, OF-360 from Meito and PPL and CCL from Sigma. The enantiomeric excess (ee) of diols **2a**,**b** and their monoacetates **3a**,**b** during and/or after reaction were determined by HPLC using a chiral stationary phase.

Initially, hexane, diisopropyl ether and acetonitrile were used as solvents for asymmetric esterification of the diol **2a**, in order to examine the influence of the solvent polarity on the reaction course. The results are summarized in Table 1. Without exception, acetylation of the primary hydroxyl group took place exclusively. With all the lipases, the (*R*)-enantiomer of **2a** appeared to be acetylated faster. Peaks of (*R*)- and (*S*)-monoacetates were identified by comparison of their retention times with the retention time of the authentic pure (*R*)-enantiomer.[11)] In the case of diol, the assignment was based on the difference in relative signal intensities of the peaks of enantiomers after enzymatic resolution and comparison with those of the corresponding monoacetate.

In hexane, lipases AY, MY, OF-360 and CCL were active in acetylation of (±)-**2a**. Lipases A, AK, F, F-AP15, M, P and PS also exhibited some activity, but too little



1a (R1,R2 = Me)
b (R1,R2 = CH_2CH_2)



2a (R1,R2 = Me)
b (R1,R2 = CH_2CH_2)

Fig. 1

* To whom correspondence should be addressed.

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to be of practical interest. After 100 h of incubation at room temperature, the ee's of produced monoacetate and remaining diol were determined for the lipases AY, MY, OF-360 and CCL (Table 1). The monoacetate was enriched with (*R*)-enantiomer, and the diol with (*S*)-enantiomer. The large difference in the ee of monoacetate (reaction product) and diol (substrate) is an indication that the conversion rate was very small. The reason for this might be very low solubility of both the diol **2a** and the monoacetate **3a** in hexane.

In diisopropyl ether, lipases AY, MY, OF-360, P and CCL were active, and lipases AK, F-AP15, M and PS had low activity. After 114 h of incubation at room temperature, the ee's of reaction products and remaining substrates were determined for lipases AY, MY, OF-360, P and CCL (Table 1). Although the conversion rate was generally higher compared to esterification in hexane (especially for CCL), it is still not sufficient for practical use and the reaction time is very long. In all the reactions except one, catalyzed by CCL, the conversion rate was far below 50%. In the case of CCL, approximately equal ee's for both produced monoacetate and remaining diol is a good indicator that the conversion rate is about 50%. However, in spite of good stereoselectivity (>90% ee for monoacetate), the long reaction time makes these reactions inconvenient for preparative purposes.

Table 1. Asymmetric Esterification of (±)-**2a** in the Presence of Lipases

Entry	Lipase	Hexane,[a] ee (%)		Isopropyl ether,[b] ee (%)	
		(*R*)-**3a**	(*S*)-**2a**	(*R*)-**3a**	(*S*)-**2a**
1	Lipase AY	77.6	12.4	94.6	19.0
2	Lipase MY	81.2	14.8	93.4	38.8
3	Lipase OF-360	87.2	4.8	91.2	24.2
4	Lipase P	ND[c]	ND	98.8	25.8
5	CCL	84.4	13.8	91.6	81.0

a) For 100 h at room temperature. *b*) For 144 h at room temperature. *c*) Not determined.

Practically no enzyme was found to be active in esterification of the racemic diol (±)-**2a** in acetonitrile under reaction conditions identical to those for hexane and diisopropyl ether. After 100 h of incubation, only lipases AK, OF-360, P and PS produced traces of the monoacetate **3a**. Removal of water from enzyme by acetonitrile probably results in almost complete inhibition of its activity.

Using lipase OF-360, many other solvents were tested, including benzene, 1,2-dichloroethane, methylene chloride, chloroform, ethyl acetate (with and without vinyl acetate), diethyl ether, tetrahydrofuran (THF), dioxane, acetone, dimethylformamide (DMF) and pyridine. The highest activity of lipase was observed in diethyl ether, benzene and 1,2-dichloroethane. Little activity was found in methylene chloride, chloroform, ethyl acetate, THF, dioxane and acetone, and no activity at all in DMF and pyridine. Unfortunately, the reaction was very slow: after 140 h of incubation at room temperature, the conversion rate was only *ca.* 23% for diethyl ether, *ca.* 12% for benzene and *ca.* 7% for 1,2-dichloroethane.

Fortunately, asymmetric hydrolysis of the monoacetate (±)-**3a** occurred at a significantly higher rate. In the case of hydrolysis, the situation is opposite to esterification: the monoacetate **3a** is a substrate, and the diol **2a** is the reaction product, which means that different enantiomers of **2a** and **3a** are generated (Chart 1). Asymmetric hydrolysis was carried out in a biphasic mixture of phosphate buffer solution/isopropyl ether. Results similar to those in the case of asymmetric esterification were obtained: lipases AY, MY, OF-360 and CCL were very highly active, and lipases AK, F-AP15, M and PS showed very low activity. As mentioned above, the enzymatic hydrolysis reaction appeared to be significantly faster than esterification: after 58 h at room temperature, the con-

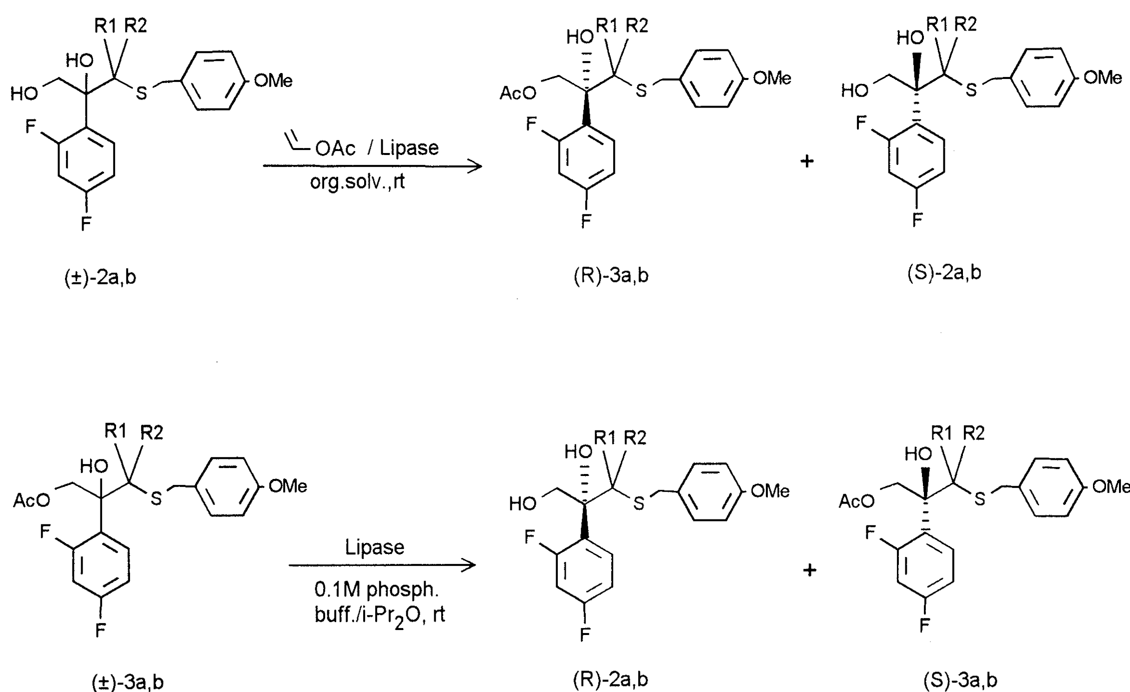

Chart 1

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version rate was about 50% for lipases AY and CCL, slightly below 50% for lipase MY, and over 50% for lipase OF-360 (Table 2), based on a comparison of the ee of produced diol and unreacted monoacetate. Generally speaking, all the lipases demonstrated a high degree of stereoselectivity (ee about 90% or higher for the reaction product). In the case of lipase OF-360, the ee of the recovered monoacetate was 100%, but the chemical yield was low because of the high conversion rate. Therefore, lipase OF-360 was the most active enzyme in this reaction and it was chosen for further optimization.

First, dependence of the ee of both **2a** and **3a** upon the conversion rate in the course of enzymatic hydrolysis was briefly investigated. As expected, the ee of remaining monoacetate (*S*)-**3a** increased steadily with the conversion rate, reaching *ca.* 95% at 50% conversion, and 100% at conversion 55—60% or higher. Accordingly, the ee of the produced diol (*R*)-**2a** was approximately 100% at the beginning, then decreased slowly to *ca.* 95% at 50% conversion, and dropped rapidly when the conversion exceeded 50%. The reaction speed became very low at 50% conversion, which demonstrated that the enantioselectivity of enzymatic hydrolysis was high. The conversion rate of 50% seems to be optimal for preparation of both (*S*)-**3a** and (*R*)-**2a** with high optical and chemical yields. The ee of the monoacetate (*S*)-**3a**, which is a solid, can easily be increased to 100% by a single recrystallization after separation from (*R*)-**2a** (chromatography on silica gel). The optically active diol (*R*)-**2a**, unlike its racemate, is an oil, but after conversion to the monoacetate or mono-3,5-dinitrobenzoate, its ee can be increased to 100% in a similar way.

It was found that the stereoselectivity of the hydrolysis does not depend significantly upon the amount of enzyme (5, 10, 20%), the reaction temperature (5, 20, 35 °C) or the substrate concentration in the organic phase (0.033, 0.167 and 0.2 g/ml). Within the limits of experimental error, the data from different experiments exhibited the same dependence of the ee on the conversion rate for both **2a** and **3a**. However, the reaction conditions very much affected the reaction rate. Decreasing and increasing the temperature, as well as decreasing the amount of enzyme, slowed down the reaction dramatically. Increasing the substrate concentration in the organic phase had the opposite effect. For practical purposes, by using a substrate concentration of 0.17—0.2 g/ml and 20% lipase (w/w relative to substrate), a conversion of *ca.* 50% can be achieved after 20 h at 20 °C.

Due to the close structural similarity between the dimethyl and cyclopropyl derivatives used in this study, careful lipase screening for **2b** and **3b** was not required. Lipase OF-360, which gave the best result for **2a** and **3a**, was employed. The absolute configurations of the enantiomers of **2b** and **3b** were assigned assuming the same stereochemical output of enzymatic resolution as in the case of the dimethyl analogs **2a**, **3a**. It appeared that, in the case of the cyclopropyl analogs **2b** and **3b**, both asymmetric hydrolysis and esterification, catalyzed by lipase OF-360, were significantly faster, but enantioselectivity was lower. This is consistent with the less demanding sterical properties of the cyclopropyl group, compared to the dimethyl fragment. Because of the higher reaction speed, asymmetric esterification of the racemic diol (±)-**2b** seems to be practical. The experimental procedure for asymmetric esterification with vinyl acetate is simpler than that for asymmetric hydrolysis, and provides some other ways for optimization. In particular, we tried to carry out asymmetric esterification with strictly controlled water content (in the presence of molecular sieves). However, the reaction rate dropped sharply, together with the optical yield (Table 3). A better result was obtained with crude lipase containing some "natural" water, which gave both (*S*)-**2b** and (*R*)-**3b** with *ca.* 80% ee. Later it was found that the ee of the monoacetate **3b** can be increased to 100% after a single recrystallization with the minimal losses, which is sufficient for practical purposes. The enantiomeric purity of the diol **2b** can also be increased by several recrystallizations, but in this case the yield is low, and conversion of **2b** into **3b** before recrystallization is therefore preferable. Because of that, further optimization of the reaction conditions in the case of cyclopropyl derivatives **2b** and **3b** became unnecessary.

When this work was finished, several short communications describing successful enzymatic resolution of tertiary-primary 1,2-diols with similar, although simpler structure, appeared.[12-14] Interestingly, good results were achieved with lipases from *Pseudomonas* sp. (for example, lipase AKG,[12] PFL[13]) or PPL.[14] It is noteworthy that PPL was used earlier to discriminate primary/secondary and primary/tertiary hydroxyl groups in different 1,2- and 1,3-diols, but enantioselectivity was disappointingly low.[14] In our case, lipases from *Candida cylindracea* (AY, OF-360 and CCL) were the best enzymes. Lipase MY from Mucor gave a similar result; PPL was practically inactive and lipase P from *Pseudomonas fluorescence* had good enantioselectivity in asymmetric esterification of **2a**,

Table 2. Asymmetric Hydrolysis of (±)-**3a** in 0.1 M Phosphate Buffer Solution/iso-Pr_2O (Room Temperature, 58 h)

Entry	Lipase	(*S*)-**3a**, ee (%)	(*R*)-**2a**, ee (%)
1	Lipase AY	87.4	89.0
2	Lipase MY	77.2	90.0
3	Lipase OF-360[a]	100	69.6
4	CCL	80.4	91.0

a) Conversion more then 50%.

Table 3. Asymmetric Esterification of (±)-**2b** in iso-Pr_2O

Entry	Reaction conditions[a]	Time (h)	Conversion (%)	(*R*)-**3b**, ee (%)	(*S*)-**2b**, ee (%)
1[b]	200% lipase, room temp., mol. sieves 3A	53	12	53	7
2	200% lipase, room temp., mol. sieves 3A	52	21	51	13
3	50% lipase, room temp.	1	55	75	92
4	20% lipase, 5 °C	19	53	80	79

a) Amount of lipase relatively to (±)-**2b** (w/w). *b*) Vinyl acetate was used as a solvent instead of iso-Pr_2O.

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however the reaction rate was very low. This comparison clearly demonstrates that even structurally similar substrates may have quite different requirements for enzyme active site, and traditional screening remains the most reliable and often used general method for choosing an enzyme for a particular transformation.

Experimental

Melting points were determined on a Yanaco micro melting point apparatus and are uncorrected. TLC analyses were performed on silica gel/alumina precoated plates (Kieselgel 60 F_{254}, Merck). Wakogel C-200 (100—200 mesh) was used for column chromatography. Infrared (IR) spectra were measured on a Jasco A-102 or Hitachi 270-30 infrared spectrophotometer. ^{1}H-NMR spectra were recorded on a Bruker AC-250 spectrometer in $CDCl_3$ with tetramethylsilane (TMS) as an internal standard. Optical rotation was measured at sodium D line (589 nm) on a JASCO DIP-370 automatic digital polarimeter. HPLC analyses were performed on Hitachi L-series and Shimadzu liquid chromatographs with UV detection at 254 nm using Chiralcel OD, OG or OJ analytical columns (Daicel Chemical Industries, Ltd.) and hexane/isopropyl alcohol mixture as a mobile phase. Lipases A, AK, AY F, F-AP15 and M were obtained from Amano Pharmaceutical Company, lipases AF2 and P from Nagase Biochemical Industries Ltd., lipases MY and PS from Takasago Corp., lipase OF-360 from Meito Sangyo Co., Ltd., PPL and CCL from Sigma Chemical Company. Phosphate buffer solution (0.1 M, pH 7.0) was prepared by dissolving KH_2PO_4 (0.55 g) and $Na_2HPO_4 \cdot 12H_2O$ (2.15 g) in deionized water and adjusting the volume to 100 ml. The starting diols **2a,b** were prepared according to the published procedure[2] and converted to the monoacetates **3a,b** by a standard method.

General Procedure for Lipase Screening Esterification Mode: Vinyl acetate (95 mg, *ca.* 100 μl, 1.1 mmol) was added *via* a syringe to a suspension of the racemic diol **2a** or **2b** (*ca.* 30 mg, *ca.* 0.11 mmol) and lipase (*ca.* 15 mg) in the appropriate solvent (2 ml), and the reaction mixture was stirred at room temperature.

Hydrolytic Mode: A solution of the racemic monoacetate **3a** or **3b** (*ca.* 30 mg) in iso-Pr_2O (0.5 ml) was added to a suspension of lipase (*ca.* 15 mg) in 0.1 M phosphate buffer solution (1.5 ml), and the reaction mixture was stirred at room temperature. The progress of the reaction was monitored by TLC (hexane/ethyl acetate, 3 : 1).

(*R*)-2-(2,4-Difluorophenyl)-3-[(4-methoxyphenyl)methylthio]-3-methylbutane-1,2-diol [(*R*)-2a] and (*S*)-1-Acetoxy-2-(2,4-difluorophenyl)-3-[(4-methoxyphenylthio]-3-methylbutan-2-ol [(*S*)-3a] Typical Procedure: A solution of the monoacetate ($\pm$)-**3a** (1.0 g, 2.4 mmol) in iso-Pr_2O (30 ml) was added to a suspension of lipase OF-360 (0.2 g) in 0.1 M phosphate buffer solution (60 ml), and the reaction mixture was stirred at room temperature for 38 h. The aqueous layer was saturated with NaCl to destroy the emulsion and all the reaction mixture was filtered through Celite. The aqueous layer was separated and extracted with iso-Pr_2O. The combined organic phases were washed with saturated NaCl, dried over Na_2SO_4 and concentrated in a vacuum (1.1 g). This mixture was chromatographed on silica gel (hexane–ethyl acetate, 10 : 1→4 : 1) to give (*R*)-**2a** (0.49 g, 54%, ee 96.4% by HPLC) and (*S*)-**3a** (0.59 g, 59%, ee 84.2% by HPLC). The combined yield of (*R*)-**2a** and (*S*)-**3a** slightly exceeds 100% due to the presence of the residual organic solvents.

The diol (*R*)-**2a** was converted into the mono-3,5-dinitrobenzoate in the usual manner, and this was recrystallized from iso-Pr_2O/ethyl acetate and hydrolyzed with aqueous NaOH to give a sample of 100% ee (HPLC) as a colorless oil, $[\alpha]_D^{27}$ +35.3° (c=1.06, MeOH). Lit.[2]: $[\alpha]_D^{25}$ +32.1° (c=1.02, MeOH).

The monoacetate (*S*)-**3a** was recrystallized directly from iso-Pr_2O/hexane to give, after one recrystallization, a sample of 100% ee (HPLC) as colorless needles, mp 78—79 °C, $[\alpha]_D^{23}$ −16.2° (c=0.96, MeOH), yield 0.43 g (43%). ^{1}H-NMR, δ: 1.33 (s, 3H, Me), 1.37 (d, 3H, J=2.7 Hz, Me), 1.92 (s, 3H, Ac), 3.69 (s, 1H, OH), 3.79 (s, 5H, MeO and CH_2S), 4.78 and 4.98 (dd, 1H each, J_{AB}=11.7 Hz, J=2.6 Hz, CH_2O), 6.72—6.98 (m, 2H, arom.), 6.83 and 7.22 (d, 2H each, J=8.7 Hz, C_6H_4), 7.67—7.82 (m, 1H, arom.). IR (KBr): 3450, 3370 (OH), 1710 (C=O) cm^{-1}. *Anal.* Calcd for $C_{21}H_{24}F_2O_4S$: C, 61.45; H, 5.89. Found: C, 61.42; H, 5.79.

Cyclopropyl analogs (*R*)-**2b** and (*S*)-**3b** were obtained in a similar manner.

(*R*)-1-(2,4-Difluorophenyl)-1-[1-(4-methoxyphenyl)methylthiocycloprop-1-yl]ethane-1,2-diol [(*R*)-2b] Colorless flakes from iso-Pr_2O, mp 71—72 °C, $[\alpha]_D^{27}$ +21.2° (c=1.0, $CHCl_3$), ee 100% (HPLC), yield 11%. ^{1}H-NMR δ: 0.84—1.0, 1.07—1.17 and 1.2—1.3 (m, 2H, 1H, and 1H, cyclopropyl), 2.22 (m, 1H, $CH_2O\underline{H}$), 3.26 and 3.41 (d, 1H each, J_{AB}=11.9 Hz, CH_2S), 3.37 (d, 1H, J=2.7 Hz, OH), 3.76 (s, 3H, MeO), 3.89—4.03 and 4.22—4.36 (m, 1H each, $C\underline{H}_2OH$), 6.72—7.01 (m, 2H, arom.), 6.78 and 7.02 (d, 2H each, J=8.7 Hz, C_6H_4), 7.62—7.77 (m, 1H, arom.). IR (Nujol): 3608, 3536, 3380 (OH) cm^{-1}. *Anal.* Calcd for $C_{19}H_{20}F_2O_3S$: C, 62.28; H, 5.50. Found: C, 62.52; H, 5.50.

(*S*)-2-Acetoxy-1-(2,4-difluorophenyl)-1-[1-(4-methoxyphenyl)methylthiocyclprop-1-yl]ethan-1-ol [(*S*)-3b] Colorless prisms from ethyl acetate/hexane, mp 120—121 °C, $[\alpha]_D^{26}$ −19.6° (c=1.0, $CHCl_3$), ee 100% (HPLC), yield 30%. ^{1}H-NMR δ: 0.85—1.05, 1.06—1.15 and 1.3—1.4 (m, 2H, 1H, and 1H, cyclopropyl), 1.97 (s, 3H, Ac), 3.27 and 3.47 (d, 1H each, J_{AB}=11.8 Hz, CH_2S), 3.32 (d, 1H, J=1.6 Hz, OH), 3.75 (s, 3H, MeO), 4.56 and 4.96 (dd, 1H each, J_{AB}=11.7 Hz, J=2.0, 1.8 Hz, $C\underline{H}_2OH$), 6.74—6.98 (m, 2H, arom.), 6.77 and 7.04 (d, 2H each, J=8.7 Hz, C_6H_4); 7.58—7.71 (m, 1H, arom.). IR (Nujol): 3480 (OH), 1736 (C=O) cm^{-1}. *Anal.* Calcd for $C_{21}H_{22}F_2O_4S$: C, 61.75; H, 5.43. Found: C, 61,94; H 5.49.

(*R*)-**3b** was obtained by asymmetric acetylation of ($\pm$)-**2b** with vinyl acetate in iso-Pr_2O in the presence of lipase OF-360 in 33% yield. mp 120—121 °C, $[\alpha]_D^{26}$ +18.8° (c=1.08, $CHCl_3$), ee 100% (HPLC). *Anal.* Calcd for $C_{21}H_{22}F_2O_4S$: C, 61.75; H, 5.43. Found: C, 61.81; H, 5.34.

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