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Resolution of α-(4-Fluorophenyl)-4-(5-fluoro-2-pyrimidinyl)-1-piperazinebutanol (BMS 181100) and α-(3-Chloropropyl)-4-fluorobenzenemethanol Using Lipase-Catalyzed Acetylation or Hydrolysis

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Abstract: α-(3-Chloropropyl)-4-fluorobenzenemethanol, a possible intermediate for synthesis of a potential anti-psychotic agent α-(4-fluorophenyl)-4-(5-fluoro-2-pyrimidinyl)-1-piperazine butanol (BMS 181100), was resolved by acetylation using isopropenyl acetate and lipase PS-30 in heptane. *S*-alcohol was obtained in 42% yield with >99% optical purity. *R*-acetate was obtained with 92.6% optical purity by stopping the reaction after 46% conversion. The enzymatically produced acetate was hydrolyzed by lipase PS-30 to give *R*-alcohol with >99% optical purity after 62-72% conversion. BMS 181100 acetate ester was treated with lipase GC-20 in buffer containing 10% toluene to give the *R*-alcohol with 97.9% optical purity after 47.6% conversion. The rate and enantioselectivity of hydrolysis by lipase GC-20 were very dependent on the organic solvent. E values ranged from 1 in the absence of organic solvent to >100 with dichloromethane and toluene.

INTRODUCTION

BMS 181100 (previously BMY 14802) [(*R,S*)-**5**, Fig. 3] is a new anti-psychotic drug candidate being developed at Bristol-Myers Squibb.[1] The *R*-(+)-enantiomer binds about ten times more tightly to the haloperidol-sensitive σ opiate receptor from guinea pig brain than the *S*-(–)-enantiomer.[2] The *R*-(+)-enantiomer is also more potent than the *S*-(–)-enantiomer in most, but not all, of the animal models used for testing potential antipsychotic effects.[3] (*R*)- and (*S*)-**5** were initially resolved by Yevich *et al.*[1] using derivatization with (*R*)-α-methylbenzylisocyanate, crystallization of the R, R-diastereomer and cleavage to give (R)-**5**. A separate reaction sequence with the (*S*)-isocyanate was used to obtain (*S*)-**5**. A more efficient and practical method for preparation or resolution of the enantiomers (*R*)-**5** and (*S*)-**5** was of interest. This report describes the resolution of chloroalcohol (*R,S*)-**1** (Fig. 1), a possible intermediate useful for the synthesis of **5**, using Amano lipase PS-30 from *Pseudomonas*. Better enantioselectivity was achieved using Amano lipase GC-20 from *Geotrichum candidum* for hydrolysis of (*R,S*)-**4**, the racemic acetate of (*R,S*)-**5** (Fig. 3). A previous report from this department described the preparation of (*R*)- and (*S*)-**1** and (*R*)- and (*S*)-**4** by microbial reduction of the corresponding ketones.[4]

RESULTS

Acetylation of (*R,S*)-1

Lipase screening experiments showed that Amano lipase PS30 was useful for resolution of (*R,S*)-1 by treatment with isopropenyl acetate in heptane as depicted in Fig. 1. Lipases GC-20 and AY-30 also gave (*R*)-2, but the reactions were very slow and optical purity was lower. Lipase from *Candida cylindracea*, MAP-10, SAM-2 and porcine pancreatic lipase had little or no activity. Some preliminary experiments were done to optimize reaction conditions before proceeding with a preparative batch. Comparing enol esters, rate of acylation of (*R,S*)-1 was: vinyl acetate > isopropenyl acetate > vinyl butyrate. However, a side product was obtained with vinyl acetate which decreased the yield. The reaction was faster in hexane than toluene and was very slow without solvent. Addition of 0.03 to 0.45 % water decreased the rate of reaction in heptane when using lipase immobilized on Accurel (Karl Fischer water, 0.52%). Addition of 0.04 to 0.1 % water also decreased the reaction rate when using lipase PS30 that was not immobilized (Karl Fischer water, 1.19%). When the enzyme/substrate ratio was held constant, varying the substrate concentration from 2.5 to 10 % of the heptane volume had little effect on the rate of acetylation or enantioselectivity.

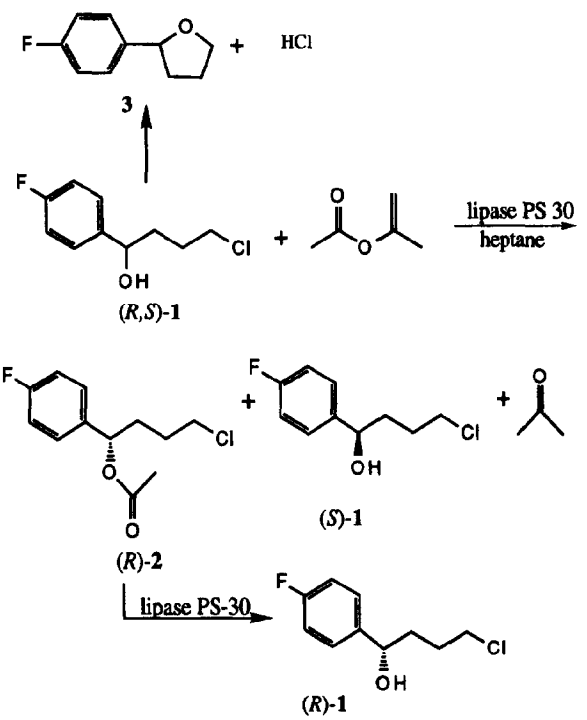

Figure 1. Resolution of α-(3-chloropropyl)-4-fluorobenzene-methanol (1) using lipase PS30.

100 g (*R,S*)-1 was treated with 100 g isopropenyl acetate and 200 g lipase PS30 in 1 L heptane. The time course of the resolution is shown in Figure 2. After 55 h and 46.5% conversion, the optical purity of

remaining alcohol 1 was 90.4% S. Optical purity of the acetate (*R*)-**2** was 93.6% at 31 h and 92.6% at 55 h. The enzyme was removed by filtration and reused in the same procedure to give, after 63 h and 57.8% conversion, >99% *S* alcohol and 87.9% *R* acetate. Because of the limited enantioselectivity of the lipase, the optical purity of acetate **2** was never higher than about 94%, although running the reaction past 50% conversion allowed alcohol 1 to be obtained as 100% *S*-enantiomer.

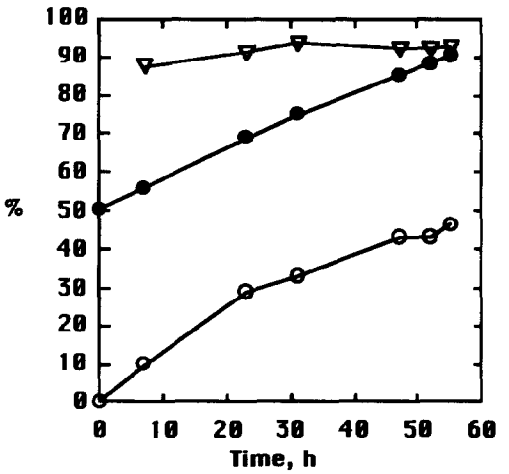

Figure 2. Time course of resolution of **1**. Acetylation of 100 g **1** using lipase PS30 and isopropenyl acetate in heptane was carried out as described in EXPERIMENTAL. o , % conversion; •, optical purity of 1 (% *S*); ∇, optical purity of **2** (% *R*).

Lipase PS30 (1 g) was reused for 7 resolutions of 0.5 g batches of (*R,S*)-**1**. The first use produced *S* alcohol with >99% optical purity and *R* acetate with 91.6% optical purity after 52.4% conversion in 65 h. The seventh use gave 50% conversion in 62 h and yielded *S*-alcohol and *R* acetate with optical purities of 95.9% and 94.2%, respectively.

Hydrolysis of acetate **2**

Chemically synthesized acetate (*R,S*)-**2** was hydrolyzed by PS30 lipase immobilized on Accurel in heptane containing 0.1 volume of water with $CaCO_3$ to neutralize the acetic acid produced. (*R*)-1 with 95.4% optical purity was obtained after 43% conversion (Table 1, top). The hydrolysis reaction appeared to be slightly more enantioselective than the acetylation reaction, but became very slow as the reaction progressed. (*R*)-**2** produced by lipase-catalyzed acetylation and isolated by flash chromatography was hydrolyzed by PS30 lipase-Accurel in a 1:1 heptane/phosphate buffer biphasic system maintained at pH 7 with a pH stat. The reaction produced (*R*)-1 with 100% optical purity after 62% conversion. Hydrolysis of (*R*)-**2** (87.8% optical purity) was also carried out in heptane containing 0.1 volume of water and $CaCO_3$. Under these conditions, 66.5% hydrolysis of acetate produced (*R*)-1 with >99% optical purity (Table 1, bottom).

Table 1. Hydrolysis of acetate 2 by lipase PS30 immobilized on Accurel

Substrate	Time	Conversion	Optical purity of 1	Optical purity of 2
	h	%	% *R*	% *R*
(*R,S*)-2[a]	48	27.1	96.8	
	90	37.4	96.4	
	162	43.3	95.4	
(*R*)-2[b]	0	0.0		87.8
	24	14.4	100	84.6
	112	46.7	100	84.4
	168	55.1	100	72.1
	281	66.5	100	62.2

[a]1 g (R,S)-2, 0.5 g $CaCO_3$, 1 g Accurel-immobilized lipase PS30, 1 mL water and 10 mL heptane were shaken at 40°C and 250 rpm. The substrate initially contained 0.83 % (*R,S*)-1.
[b]0.5 g (*R*)-2, 0.5 g $CaCO_3$, 0.5 g Accurel-immobilized lipase PS30, 1 mL water and 10 mL heptane were shaken at 25°C and 250 rpm.

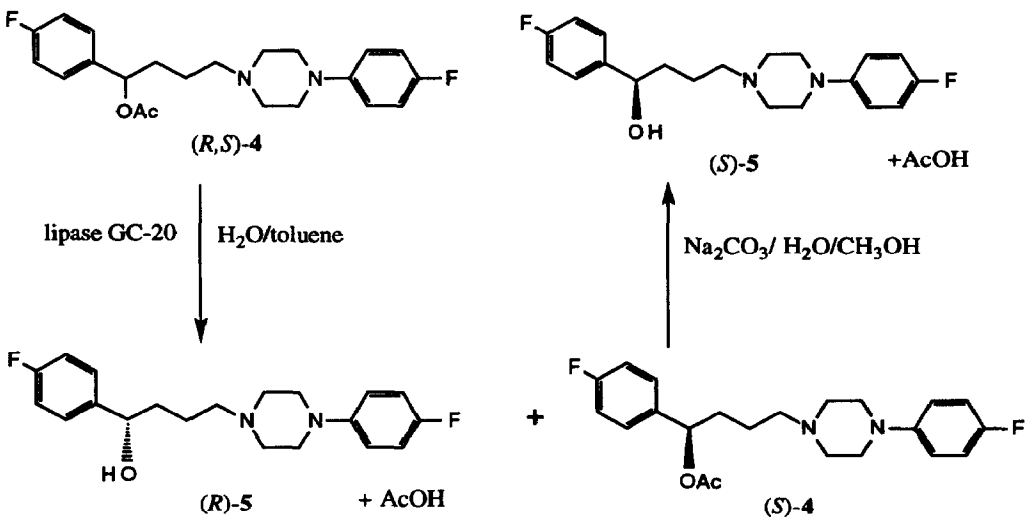

Figure 3. Resolution of α-(4-fluorophenyl)-4-(5-fluoro-2-pyrimidinyl)-1-piperazinebutanol (5) using lipase GC-20.

Hydrolysis of (*R,S*)-4

Fourteen lipases and one esterase were screened for hydrolysis of (*R,S*)-4 in phosphate buffer containing 10% toluene (Table 2). Four lipases produced (*R*)-5 with 95% to 98% optical purity, and lipase from *Aspergillus niger* gave (*S*)-5 with 83.3% optical purity.

Table 2. Screen for enzymatic hydrolysis of (*R,S*)-4

Enzyme	Source	Time h	Hydrolysis %	o.p. % *R*
AY-30	Amano (*Candida* species)	89	43.6	83.5
Candida cylindracea	Biocatalysts	89	33.2	94.9
GC-20	Amano (*Geotrichum candidum*)	89	31.0	96.3
Aspergillus niger	Biocatalysts	89	28.6	16.7
OF	Mieto-Sangyo (*Candida rugosa*)	89	13.4	98
AK	Amano (*Pseudomonas*)	89	8.3	95.3
Geotrichum candidum	Biocatalysts	89	2.3	
Rhizopus javanicus	Biocatalysts	22	0.9	
Porcine pancreatic	Sigma	22	0.5	
CE	Amano (*Pseudomonas*)	89	0.0	
B1	Enzymatix (*Pseudomonas*)	89	0.0	
SAM-2	Amano (*Pseudomonas*)	89	0.0	
esterase 30000	Gist-Brocades (*Mucor*)	89	0.0	
MAP-10	Amano (*Mucor javanicus*)	22	0.0	
PS30	Amano (*Pseudomonas*)	22	0.0	

50 mg (*R,S*)-4.HCl, 4.5 mL 50 mM potassium phosphate buffer, pH 7.4, 100 mg enzyme (except 200 mg for *Candida cylindracea* and *Aspergillus niger*), and 0.5 mL toluene were shaken at 25°C and 200 rpm. 5 mL 1 M potassium phosphate buffer pH 8 and 10 mL ethyl acetate were added for extraction.

The rate and enantioselectivity of hydrolysis were very dependent on the organic solvent in a biphasic system and the responses were different for the two enzymes studied (Table 3). *Aspergillus niger* lipase, which preferentially hydrolyzed (*S*)-4, showed little enantioselectivity in the absence of organic solvent. For the rate of reaction, estimated by percent conversion after 50 h, the order was: CH_2Cl_2 < toluene < methyl isobutyl ketone < no organic solvent < heptane. The enantiomeric ratio E[5] was highest for toluene and moderate enantioselectivity was obtained with heptane. Lipase GC-20 from *Geotrichum candidum* also gave little enantioselectivity in the absence of organic solvent. Without organic solvent, there was a lag in the reaction with no detectable hydrolysis after 16 h, but 30.1% conversion after 50 h. For the rate of reaction, measured by percent hydrolysis after 50 h, the order was: methyl isobutyl ketone < CH_2Cl_2 < no organic solvent < toluene < heptane. E was highest with toluene and CH_2Cl_2. Although excellent optical purity was obtained with CH_2Cl_2, the reaction rate slowed markedly after about 24 h.

Preparative reactions were carried out using lipase GC-20 in pH 7 phosphate buffer containing 10% toluene as described in EXPERIMENTAL. Using a pH stat to maintain pH 7, (*R*)-5 was obtained with 97.9% optical purity after 47.6% hydrolysis. In another reaction carried to 60% hydrolysis, the remaining acetate was isolated and hydrolyzed to (*S*)-5 (98.2% optical purity) using Na_2CO_3 in aqueous methanol (Figure 3).

Acetylation of (*R,S*)-5

(*R,S*)-5 dissolved in isopropenyl acetate was acetylated about 25% in 16 h at 25° in the absence of lipase. Using vinyl acetate as solvent, (*R,S*)-5 was acetylated only 1.6% after 10 days at room temperature. The rate and enantioselectivity of lipase catalyzed acetylation of (*R,S*)-5 in vinyl acetate was much less than was obtained in the hydrolysis of (*R,S*-4). After 14 days, 24% acetylation by *Aspergillus niger* lipase did not change the optical purity of the remaining alcohol. After 14 days and 49% acetylation by lipase GC-20, the optical purity of the remaining (*R,S*)-5 was 68.2% S. The calculated value of E was 10.6 after 72 h .

Table 3. Effect of solvent on hydrolysis of (*R,S*)-**4** by lipases

Lipase	Solvent	Time h	Conversion %	Optical purity of **5** % *R*	% S	E
Aspergillus niger	toluene	50	11.0		93.8	16.7
	heptane	6	19.9		85.8	7.2
	heptane	50	89.3		54.5	
	MIBK	50	20.4		67.7	2.3
	CH_2Cl_2	50	1.3		nd	
	water	16	54.1		58.2	1.7
	water	50	75.8		58.6	
GC-20	toluene	21	16.4	99.2		149.9
	toluene	50	58.8	88.1		
	heptane	18	32.9	85.8		8.5
	heptane	50	79.6	63.3		
	MIBK	16	1.0	nd		
	MIBK	50	4.9	nd		
	CH_2Cl_2	16	12.3	98.7		84.2
	CH_2Cl_2	21	18.0	98.6		86.7
	CH_2Cl_2	24	24.2	98.4		83.3
	CH_2Cl_2	50	25.8	99.2		180
	CH_2Cl_2	65	39.5	99.0		192
	water	16	0.0	nd		
	water	50	30.1	50.4		1.0
	water	65	45.8	52.2		1.1

20 mg (*R,S*)-**4**.HCl, 4.5 mL 0.1 M potassium phosphate buffer, pH 8, 0.5 mL solvent, and 200 mg *Aspergillus. niger* lipase or 100 mg lipase GC-20 were shaken at 25°C, 200 rpm. 5 mL 1 M potassium phosphate, pH 8, and 10 mL ethyl acetate were added for extraction. nd, below detection limit; MIBK, methyl isobutyl ketone.

Table 4. Acetylation of (*R,S*)-**5**

Lipase	Time h	Conversion %	optical purity % *S*
none	0	0.0	
	72	0.0	
	240	1.6	
	336	5.1	
GC-20	72	18.7	
	120	25.7	63.5
	168	31.7	66.1
	240	39.7	68.2
	336	48.7	74.5
Aspergillus niger	72	3.3	49.6
	120	6.9	50.3
	168	10.6	50.1
	240	16.0	50.2
	336	24.1	50.7

100 mg (*R,S*)-**5** was dissolved in 20 mL vinyl acetate. 400 mg lipase was added and the flask was shaken at 25°C, 200 rpm.

DISCUSSION

Wong and coworkers[6] introduced the now widely-used (reviewed by Santaniello *et. al.* [7]) technique of using enol esters in lipase-catalyzed resolutions of alcohols to improve rate and enantioselectivity, and to make the acylation irreversible. (*R,S*)-**1**, a potential intermediate for synthesis of BMYS 181100, was resolved by acetylation with isopropenyl acetate using Amano lipase PS30. The *S*-isomer was obtained in close to 100% optical purity and 42% yield. If the lipase has at least moderate enantioselectivity, the unreacted isomer in such a resolution can usually be obtained in high optical purity by increasing the degree of conversion past 50%. The optical purity of the acetate (*R*)-**2** is limited by the enantioselectivity of the enzyme, and a maximum optical purity of 92-93% was obtained. (*R*)-**2** was used to prepare the alcohol (*R*)-**1** with close to 100% optical purity by hydrolysis with lipase PS-30, but the hydrolysis was slow.

A problem with **1** as an intermediate for synthesis of BMS 181100 is formation of impurity **3** at high pH. Acetate (*R*)-**2** has an advantage as a synthon for (*R*)-**5** by precluding intramolecular displacement of chloride by the hydroxyl.

Greater enantioselectivity was found using Amano lipase GC-20 for hydrolysis of the acetate of BMS 181100, (*R,S*)-**4**. (*R*)-**5** was obtained with 97.9% optical purity after 47.6% conversion, and base-catalyzed hydrolysis of the acetate remaining after 60% conversion gave (*S*)-**4** with 98.2% optical purity.

The hydrolysis of (*R,S*)-**4** was carried out in a biphasic system and there was a strong dependence of enantioselectivity on solvent. In the absence of organic solvent, there was little enantioselectivity by either *Aspergillus niger* lipase or lipase GC-20. Organic solvent effects on enantioselectivity have been described by Klibanov and coworkers[8,9] and others[10,11], and recently reversal by the solvent of enantioselectivity with the same enzyme and substrate has been described.[12-14]

EXPERIMENTAL

Synthesis of (±)-α-(3-chloropropyl)-4-fluorobenzenemethanol (*R, S*-**1**)

In a 1-L three-necked flask, 10 g (0.26 mol) of sodium borohydride was dissolved in 300 mL of methanol, then chilled to 4°C. To the stirred solution, 50 g (0.25 mol) of 4-chloro-4'-fluorobutyrophenone was added dropwise from an addition funnel. After the completion of the reaction, 110 mL (0.33 mol) of 3N acetic acid was added dropwise to the stirred reaction mixture. The solution was then concentrated to a volume of 150 mL by removing methanol under reduced pressure, then extracted three times with 75 mL of dichloromethane. The organic phases were combined, then washed twice with 100 mL of luke warm water. The organic layer was dried over anhydrous sodium sulfate, then solvents were removed under reduced pressure to produce a viscous yellow oily liquid, 40.6 g (0.2 mol, 81 % yield). ^{1}H-NMR, 300 MHz, ($CDCl_3$), δ 1.8 (m,4H), 3.6 (t,2H), 4.8 (t,1H), 7.1 (t,2H), 7.4 (t,2H). IR (neat) cm^{-1} 3400, 1698, 1605, 1511, 1225. MS (70 ev) M/e 202 (M^+), 184, 165, 135, 125, 109, 97, 77. Anal. Calc.: $C_{10}H_{12}ClFO$ C, 59.27; H, 5.97; Cl, 17.49; F, 9.37; Found: C, 59.72; H, 6.10; Cl, 17.03; F, 9.37.

Synthesis of (±)-α-(3-chloropropyl)-4-fluorobenzenemethanol acetate ester (*R,S*-**2**)

Alcohol **1** (7.1 g, 35 mmoles) was dissolved in 50 mL THF. To this solution, acetic anhydride (4.30 g, 42 mmoles), triethylamine (4.26 g, 42 mmoles) and 4-dimethyaminopyridine (56 mg, 0.458 mmoles) were added. The reaction was complete after 1 hr at 22°C by TLC (silica-gel, CH_2Cl_2). Ethyl acetate (50 mL) was added to the reaction mixture and the resulting solution was washed with water (100 mL, then 0.33 N aqueous

HCl (100 mL), and then water (100 mL). The ethyl acetate phase was separated, dried with anhydrous Na_2SO_4 and evaporated in vacuo to give 8.5 g (99% yield) of the acetate **2**.

IR (CH_2Cl_2): (C=O) 1741 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ, 1.66-2.06 (m,4H), 2.07 (s,3H), 3.53 (t, 2H, J=6.3 Hz), 5.73 (dd,1H, J=7.4 and 6.2), 7.0-7.34 (m,4H); ^{13}C-NMR ($CDCl_3$): δ, 21.2, 28.6, 33. 6, 44.4, 74.6, 115.3, 115.6, 128.2, 128.3, 136.0, 160.8, 164.1, 170.2; MS : $[M+NH4]^+$ 262, 50% rel. abundance.

Enzymatic acetylation of (*R, S*-1)

Two 1-L flasks each containing 50 g (0.247 moles) of (*R,S*)-**1**, 50 g (0.499 moles) of distilled isopropenyl acetate, 100 g of Amano lipase PS-30, and 500 mL of heptane were shaken at 25°C and 250 rpm. Samples of 0.15 mL were removed periodically, diluted 10-fold with heptane, filtered and analyzed for alcohol and acetate enantiomers by chiral HPLC. After 55 h, the lipase was removed from each flask by filtration and washed three times each with 50 ml of heptane. The combined filtrate and washings contained 53.94 g (0.266 moles) of (*S*)-**1** (90.4% S) and 56.38 g (0.230 moles) of (*R*)-**2** acetate ester (92.6% R).

Isolation of (*R*)-α-(3-chloropropyl)-4-fluorobenzenemethanol acetate ester [(*R*)-**2**] and (*S*-α-(3-chloropropyl)-4-fluorobenzenemethanol (*S*)-**1**]

After a smaller scale resolution, the reaction mixture (65 mL was filtered, then washed with brine (50 mL). The organic phase was dried over anhydrous sodium sulfate, then solvents were removed under reduced pressure to produce a light yellow liquid (5.3 g). Chromatography of this material on 100 g of silica gel, which was prewashed with 300 mL of hexane-ether (95:5), afforded 1.77 gm of (*R*)-**2**, when eluted with 300 mL of hexane-ether (90:10). Eluting further with 300 mL of hexane-ether (80:20) produced 1.5 g of (*S*)-**1** as a light yellow viscous oil that solidified on standing, $[\alpha]_D$= –34.9, c=1, cyclohexane. The NMR spectrum of the alcohol was identical to that of racemic alcohol , (±)-**1**. (*R*)-**2** ^{1}H-NMR,($CDCl_3$) δ 1.8 (m,4H), 2.07 (s,3H), 3.6 (t,2H), 5.75 (dd,1H, J=7.3 and 6.0), 7.1 (t,2H), 7.4 (t,2H). MS (70 ev) M/e 244 (M^+), 202 ($M-OCH_2$), 184, 163, 156, 125, 109, 95 and 75. $[\alpha]_D$= +34.2, c=1, cyclohexane. Anal. Calc.: $C_{12}H_{14}ClFO_2$ C, 58.90; H, 5.77; Cl, 14.49; F, 7.76; Found: C, 59.19; H, 5.91; Cl, 14.57; F, 7.65.

Isolation of (*R*)-α-(3-chloropropyl)-4-fluorobenzenemethanol [(*R*)-**1**]

This alcohol was generated by stereoselective hydrolysis of (*R*)-**2** by lipase PS-30 . After hydrolysis, the reaction mixture was filtered (30 mL), extracted three times (25 mL) with dichloromethane, the organic layer was then washed once with brine (25 mL), then dried over anhydrous sodium sulfate. Solvents were then removed under reduced pressure, to produce a light yellow liquid (1.1 g). This oil was subjected to silica gel chromatography; washing the column with hexane-ether (75:25) afforded 0.47 gm of (*R*)-**1** as a pale yellow liquid. $[\alpha]_D$= +36.6 (c=2, cyclohexane); optical purity was >99% when determined by chiral HPLC. ^{1}H-NMR was identical to racemic (±)-**1**.

2-(4-Fluorophenyl) tetrahydrofuran (**3**)

To 25 mL of 50 mM phosphate buffer, pH 6.0, 2.02 g (10 mmol) of (±)-**1** was added, and the mixture was stirred overnight at 37-40°C. The aqueous solution was extracted twice with dichloromethane (25 mL), and the combined extracts were dried over anhydrous sodium sulfate. The organic solvent was then removed under reduced pressure to produce 1.8 g of yellow oil. The oil was chromatographed on 20 g of silica with hexane-ether (85:15) to produce 0.8 g (49% yield) of colorless liquid. ^{1}H-NMR ($CDCl_3$) δ 1.83 (m,4H), 3.73 (m,3H), 7.0-7.31 (m,4H); ^{13}C-NMR ($CDCl_3$) δ 27.0, 35.34, 62.4, 115.7, 116.0, 130.8, 130.95. MS (70ev) M/e 165 (M^+), 162, 133.

Hydrolysis of α-(4-fluorophenyl)-4-(5-fluoro-2-pyrimidinyl)-1-piperazine butanol, acetate ester, hydrochloride salt, [(*R,S*)-**4**]

(*R,S*)-**4** (200 mg [0.468 mmoles]), 1 mL of 1 M potassium phosphate buffer (pH 7.4), 17 mL of water and 2 mL of toluene were brought to pH 7 with 1 N sodium hydroxide. Amano lipase GC-20 (400 mg) was added and the reaction was maintained at 25° and pH 7 with 1 N NaOH using a Brinkmann pH stat and magnetic stirrer. To monitor the conversion, 0.1 mL samples were added to 0.1 mL of 1 M potassium phosphate buffer, pH 8, and 0.8 mL ethyl acetate. The tubes were vortexed and centrifuged and the ethyl acetate extract was analyzed by GC. After 69 h, the pH of the reactor was raised to 8 with 5 N sodium hydroxide, 20 mL ethyl acetate was added and stirred 5 min for extraction. The extract contained 77.8 mg of (*R*)-**5** (0.223 mmoles, 47.6% yield, 97.9% *R*).

Isolation of *S*-Acetate **4**

(*R,S*)-**4**.HCl (3 g [7.03 mmoles]), 27 mL of 1 M potassium phosphate buffer (pH 8), 243 ml water, 30 mL of toluene, and 6 g of Amano lipase GC-20 were adjusted to pH 7.4 with 5 N NaOH and shaken at 25°C, 300 rpm. pH was maintained near 7 by periodic addition of NaOH. After 60.4% conversion, the mixture of acetate **4** and alcohol **5** was adjusted to pH 7.5 with dropwise addition of 1N NaOH. The precipitated alcohol and the acetate were extracted with 150 mL of ethyl acetate. The ethyl acetate layer was separated, dried with anhydrous Na_2SO_4 and filtered. The ethyl acetate was evaporated to give 2.1 g of crude mixture. The crude product was applied to a silica gel column (82 g, Baker flash grade silica) and eluted with 50% ethyl acetate-hexane. Fractions containing 100 mL were collected. Each fraction was checked for acetate **4** by TLC (Silica-gel plates, 250 mm, 5 cm x 10 cm, were developed with 50% ethyl acetate in hexane) and similar fractions were combined. Evaporation of the eluent gave 1.27 g of the acetate (84.7% yield).

Hydrolysis of *S*-Acetate **4**

The acetate from the chromatography was dissolved in 43 mL of methanol. To this solution 20 mL of water and 882 mg of Na_2CO_3 were added. The mixture was stirred overnight (~16 h) at room temperature. At the end of this period 100 mL of water was added and the mixture was extracted with ethyl acetate twice (100 mL each). The ethyl acetate layer was dried with Na_2SO_4, filtered and evaporated to give 1.15 g of crude (*S*)-**5**. This material was crystallized from 20 mL of isopropanol by addition of 324 mL of concentrated (37%) HCl. The isopropanol solution was kept at 4°C for 2 hours and filtered on a Buchner funnel to give 0.96 g (91.4% yield) of *S*-**5**.IR(KBr): cm-1, 3383, 2668, 2600, 1507, 1491; 1H-NMR(DMSO-d6) δ, 1.59-1.64 (m,2H), 1.73-1.84 (m,2H), 2.98-3.09 (m,4H), 3.41-3.52 (m,4H), 4.54-4.59 (m,3H), 5.43 (broad s,1H), 7.11-7.41 (m,4H), 8.55 (s,2H), 11.25 (broad s,1H); ^{13}C-NMR(DMSO-d6); δ, 19.7, 36.1, 41.0, 50.2, 55.4, 70.8, 114.5, 114.8, 127.5, 127.6, 141.9, 145.6, 145.9, 150.3, 153.5, 157.8, 159.4, 162.6; MS(CI):[M^{+1}] 349, 100 % rel. abundance; mp. 228-229° C, optical purity (HPLC): 98.2 % *S* (–), $[\alpha]_D$ (H_2O) = –4.14.

Analytical Methods

(*R,S*)-**1** was resolved into *R* and *S* alcohols using a Chiralcel OB (25 x 0.46 cm) HPLC column. The mobile phase was 94% hexane and 6% isopropanol, temperature was 25°C (ambient), detection wavelength was 270 nm and flow rate was 1 mL/min. R and S alcohols were resolved and separated from the corresponding acetate **2** by this column, but racemic acetate **2** was not resolved. This method was used for determining concentrations of **1** and **2** as well as optical purity of **1**. Optical purity of **2** was determined using a Chiralcel OK (25 x 0.46 cm) column with 2% butanol, 2% ethanol, 96% hexane mobile phase, 270 nm detection

wavelength, ambient temperature, and 0.5 mL/min flow rate. Analyses were performed with a Hewlett Packard 1090 HPLC equipped with a diode array detector.

4 and **5** were determined using a HP ultra 2, 25 m x 0.32 mm, 0.17 mm film thickness, capillary column containing 5% phenyl methyl silicone. Analyses were performed with a Hewlett Packard 5890 gas chromatograph equipped with an automatic sampler and flame ionization detector. Injector temperature was 230°C, column temperature was 245°C and detector temperature was 270°. Optical purity of **5** was determined by HPLC using a Chiralcel OD 25 x 0.46 cm column with 2.5% n-butanol, 0.5% isopropanol, 97% heptane mobile phase, 240 nm detection wavelength, 20°C column temperature, and 0.7 mL/min flow rate.

Materials

Commercial sources were: chiral HPLC columns, Daicel Chemical Industries, LTD; HP ultra 2 capillary GC column, Hewlett Packard; vinyl acetate and isopropenyl acetate, Aldrich; vinyl butyrate, Monomer-Polymer and Dajac Laboratories, Inc. Lipase sources are indicated in Table 2.

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