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Chemoenzymatic synthesis of four diastereomers of (6-fluoro-2-chromanyl)oxirane: An intermediate of a potent β-blocker

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Abstract

The synthesis of optically active 5-acetoxy-3-(*p*-fluorophenoxy)-1-pentanol **4**, for the synthesis of the potent β-blocker R-67555, bis[2-(2-chromanyl-6-fluoro)-2-hydroxyethyl]amine **1**, was investigated. The acetylation of 3-(*p*-fluorophenoxy)-1,5-pentanediol **5a** using lipozyme and the hydrolysis of 1,5-diacetoxy-3-(*p*-fluorophenoxy)pentane **5b** using lipase Amano P yielded (3*S*)- and (3*R*)-5-acetoxy-3-(*p*-fluorophenoxy)-1-pentanol **4**, respectively, with high enantiomeric excess. Four diastereomers of (6-fluoro-2-chromanyl)oxirane **2**, important intermediates for the synthesis of R-67555, were synthesized by chemical methods using (*S*)-**4** and (*R*)-**4**. © 1997 Published by Elsevier Science B.V.

Keywords: Asymmetric hydrolysis; Asymmetric acetylation; Lipase; β-blocker

1. Introduction

R-67555, bis[2-(2-chromanyl-6-fluoro)-2-hydroxyethyl]amine, **1** (Scheme 1) has been reported to be a potent β-blocker [1–4]. However, R-67555 exists as a mixture of (*RS/SS*) and (*SR/RR*) configurations [1–4], and the development of drugs for clinical use requires stereochemically pure compounds. For the synthesis of (*RS/SS*) and (*SR/RR*)-R-67555, all four diastereomers of epoxides **2**, which we selected as important intermediates, were required and the synthetic process was also investigated [5]. To introduce the asymmetrical carbon of the 2-position of the chromane structure, we performed hydrolysis and acylation of prochiral compounds **5a** or **5b**. The monoesters thus obtained with high enantiomeric excess were transformed into the four epoxides **2** (Scheme 1).

2. Results and discussion

2.1. Screening of the enzyme

It is possible that monoalcohols with opposite stereochemistry can be obtained by using one kind of lipase, because the lipase may recognize

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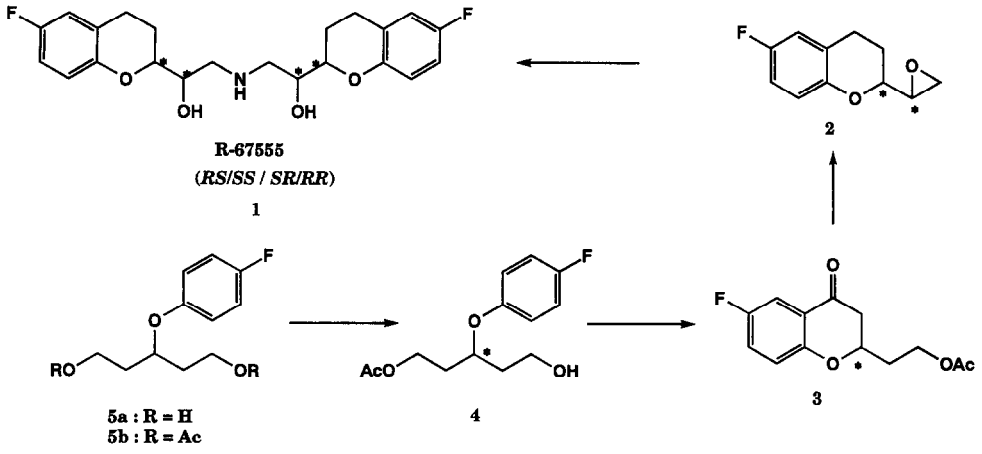


Scheme 1. Strategy.

the same side of the molecule in both hydrolysis and acetylation [6]. That is, hydrolysis may provide a monoacetate bearing an acetyl group at one side of the molecule and acetylation may provide a molecule with the opposite stereochemistry. We thus screened for enzymes capable of acetylation of **5a** and hydrolysis of **5b**. Thirty commercially available lipases were investigated and four lipases were found to catalyze the hydrolysis of diacetate **5b** as shown in Table 1. Among these enzymes, Amano P was chosen for further investigation because of its high activity and enantioselectivity. Amano P catalyzed the hydrolysis of diacetate **5b** to the corresponding monoalcohol **4** with a yield of 82% and with > 99% ee. The optical purity was determined by HPLC analysis of the corresponding MTPA ester of the monoalcohol.

The four lipases described above and two lipases (SP-382 and lipozyme) which were immobilized for use in organic solvents were investigated for asymmetric acetylation. Three lipases were found to acetylate diol **5a**. Of these, lipozyme was selected because of its high reactivity, enantioselectivity and ease of use with organic solvents, compared with Amano P. The lipozyme provided the corresponding monoacetate **4** with a yield of 87% and with > 99% ee. (Table 2).

Monoacetate obtained via hydrolysis of **5b** using lipase Amano P and that via the acetylation of **5a** using lipozyme were found to have opposite stereochemistries. This finding suggests that Amano P and lipozyme recognize the same site of the corresponding substrates.

Table 1
Enzyme screening (asymmetric hydrolysis of **5b**) [a]

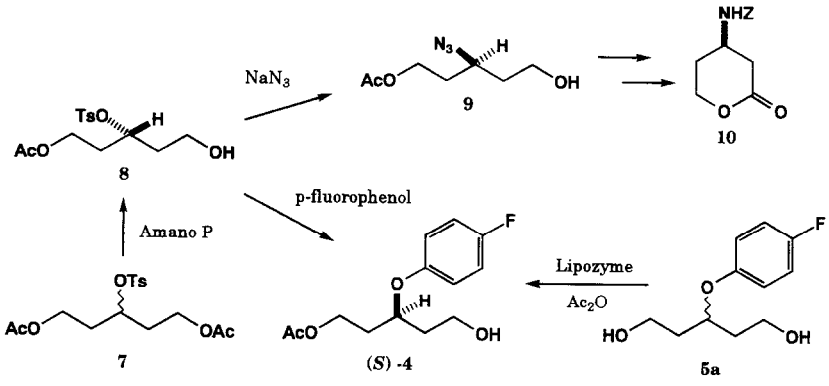
Enzyme	Conversion ratio (%)	% ee of **4**	Time (h)
Newlase	26	77	18
Amano F-AP-15	26	48	18
Amano F-AP-10	30	96	18
Amano P	82	> 99 (R)	2

[a] The substrate was suspended in a 0.1 M potassium phosphate buffer, pH 7.0–0.5% Triton X-100 at a concentration of 20 mg/ml. Enzymes were added to the suspensions at a concentration of 50 mg/ml and stirred at 28°C.

Table 2
Enzyme screening (asymmetric acylation of **5a**) [a]

Enzyme	Conversion ratio (%) [b]	% ee of **4**	Time (h)
Lipozyme	—	> 99 (S)	3
SP-382	—	< 20	3
Amano P	—	> 99	3

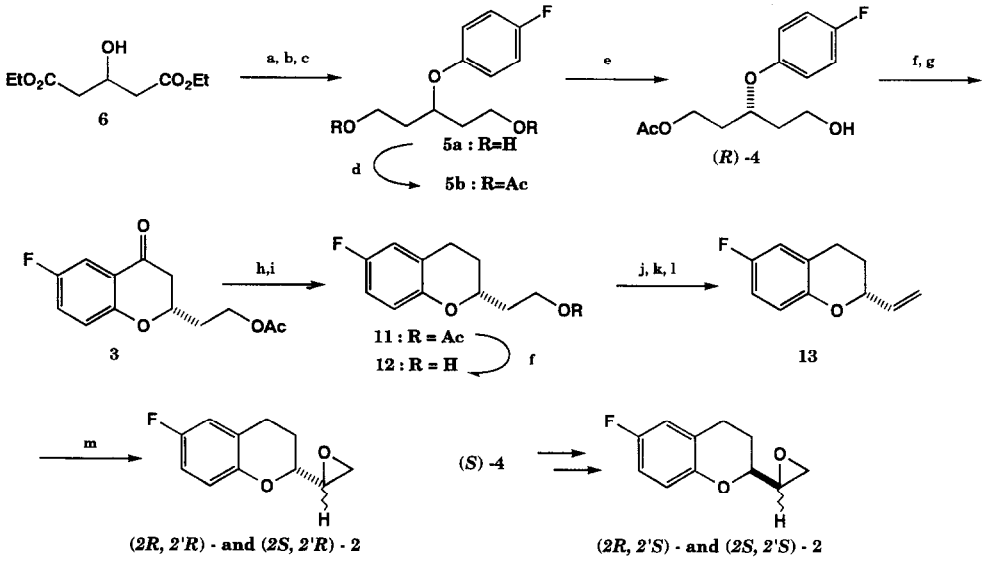
[a] The substrate was dissolved in toluene at a concentration of 20 mg/ml. Acetic anhydride was added to the suspensions as the acyl donor and enzymes were added at a concentration of 10 mg/ml. These mixtures were stirred for 3 h at ambient temperature.
[b] Not measured.



Scheme 2. Determination of the absolute configurations.

2.2. Stereochemistry

Scheme 2 shows the determination of the absolute configuration of compound **4**. Tosylate **7** was hydrolyzed by Amano P yielding monoacetate **8** with high optical purity. Then the tosyl group of monoacetate **8** was substituted for the azide group accompanied by Walden inversion without racemization, affording azide **9**. The optical purity of this compound was determined in the same manner as that described above. Azide **9** was converted to lactone **10**, whose absolute configuration has been reported previously [7]. Lactone **10** exhibited specific rotation of $[\alpha]_D^{24} + 20.5$ (c 2 in $CHCl_3$), lit. + 4.70 (c 1.66 in $CHCl_3$) [7]. From this finding, the absolute configuration of tosylate **8** was determined as (R). Tosylate **8** was also substituted by p-fluorophenol sodium salt in DMF giving (S)-**4**, which was the same as that



Scheme 3. Synthesis of prochiral compounds (**5a** and **5b**) and the epoxides **2**. (a) TsCl 91%, (b) $LiAlH_4$ 59%, (c) sodium p-fluorophenoxide/MeCN 50%, (d) Ac_2O/pyr., (e) Amano P, (f) Jones' Reagent 90%, (g) PPA 73%, (h) $NaBH_4$ (quant.), (i) H_2/Pd–C, (f) NaOH, (j) TsCl/pyr. 68%, (k) NaI/acetone 98%, (l) KO^{t}Bu/DMSO 89%, (m) m-CPBA/CH_2Cl_2.

obtained via acetylation of dialcohol **5a** catalyzed by lipozyme. On the basis of these experiments, it was determined that acetylation of **5b** by lipozyme afforded (*S*)-**4** and asymmetric hydrolysis of **5b** by lipase Amano P afforded (*R*)-**4**.

*2.2.1. Synthesis of epoxides **2a–d** (Scheme 3)*

Diethyl 3-hydroxyglutarate **6** was tosylated and the tosylate thus obtained was reduced using $LiAlH_4$. The tosyl group of the diol thus obtained was substituted for *p*-fluorophenol to give diol **5a**. Diacetate **5b** was obtained by acetylation of diol **5a**. These compounds were transformed into (3*S*)-**4** and (3*R*)-**4** as described above. The oxidation of monoacetate (*R*)-**4** by Jones' reagent (90% yield) followed by cyclization by PPA gave ketone **3** with a yield of 73% [8]. Reduction of the carbonyl group of ketone **3** by sodium borohydride and subsequent hydrogenolysis provided acetate **11**. Then, hydrolysis of acetate **11** gave alcohol **12**. Analysis of the corresponding MTPA ester of alcohol **12** by HPLC confirmed that no racemization had taken place. Transformation of alcohol **12** to iodide via tosylate, followed by its elimination by potassium *t*-butoxide provided olefin **13**. The epoxides, which were the target molecules, could be readily obtained by oxidizing olefin **13** by means of *m*-chloroperbenzoic acid in chloroform.

The epoxide obtained, **2**, was a diastereomeric mixture of (2*R*, 2′*R*)- and (2*S*, 2′*R*)-(6-fluoro-2-chromanyl)oxirane. These molecules could be separated easily by silica gel column chromatography. The distance between the epoxide–oxygen and the chromane–oxygen should be large to reduce the repulsion between both the oxygens. This was also supported by the result of the energy calculation using the Nemesis program (Fig. 1). In the case of (2*S*, 2′*R*)-**2**, it is highly likely that the 2-position C–H bond and the 2′-position C–H bond form a torsion angle of around 180°. Thus, the *J*-value between 2-H and 2′H is relatively large. On the other hand, in the case of (2*R*, 2′*R*)-**2**, a torsion angle of around 0° is preferable and the *J*-value is relatively small. On the basis of this consideration, the compound with 2-H: $\delta = 3.13$–3.26 was determined to be (2*S*, 2′*R*)-**2** and the com-

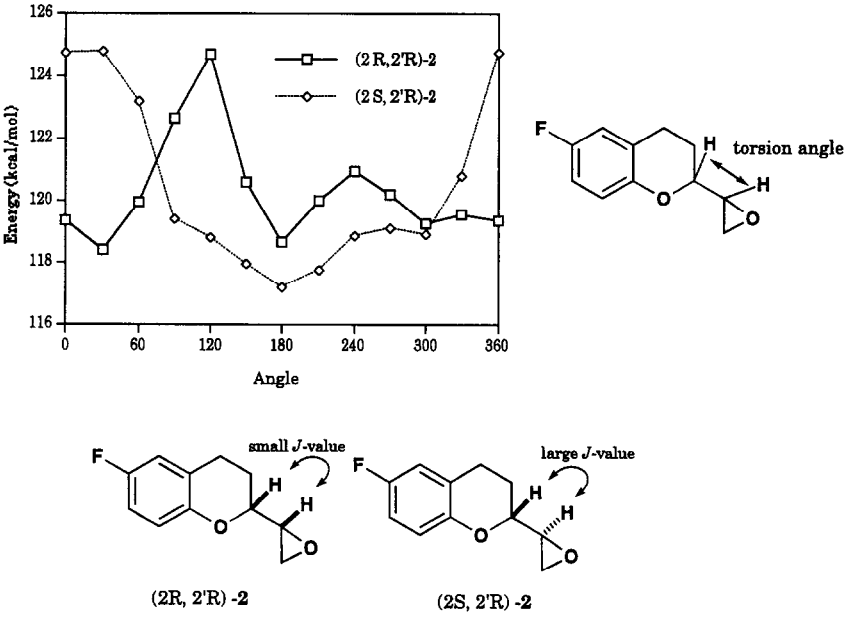


Fig. 1. Energy calculation of epoxide **2** and the determination of its stereochemistries.

pound with 2-H: $\delta = 3.08$–3.18 to be (2*R*, 2′*R*)-**2**. (2*R*, 2′*S*)- and (2*S*, 2′*S*)-**2** could be obtained from monoacetate (*S*)-**4** in an identical way.

In summary, to synthesize optically active β-blocker **1**, (3*S*)- and (3*R*)-5-acetoxy-3-(*p*-fluorophenoxy)-1-pentanol **4** were obtained by enzymatic hydrolysis of **5b** and acetylation of **5a** using Amano P and lipozyme, respectively. Furthermore, the synthetic process to the four diastereomers of the important intermediates epoxides **2** was investigated. These molecules were obtained with excellent diastereomeric purities from optically active monoacetates (*R*)- and (*S*)-**4** in 9 steps, with overall yields of about 10% for each diastereomer.

3. Experimental

IR spectra were recorded with a JASCO IR-810 instrument and proton NMR spectra were obtained with JEOL FX-100 and PS-100 instruments. Chemical shifts are reported in parts per million (ppm) relative to Me_4Si (TMS) as an internal standard. Optical rotation values were recorded with a JASCO digital polarimeter and HRMS spectra were obtained with a JEOL JMS HX-HX 110A instrument. HPLC analyses of optical purity were performed with a JASCO Trirotor system, using Nucleosil (YMC) (4.6 × 250 mm) monitored at 254 nm and eluting with 9:1 hexane-tetrahydrofuran at a flow rate of 1.0 ml/min. The HPLC retention time of the corresponding MTPA esters of **4** with the (*S*)-configuration was 15.4 min and that with (*R*) was 16.3 min.

3.1. 3-(p-Fluorophenoxy)-1,5-pentanediol (5a)

Diethyl 3-hydroxyglutarate (50 g; 244.8 mmol) **6** was dissolved in pyridine (200 ml) and the solution was cooled by ice-water. *p*-Toluenesulfonic chloride (67 g; 351 mmol) and N,N-dimethylaminopyridine (1 g) was added to the solution and stirred for 24 h allowing the reaction temperature to rise to room temperature. The reaction mixture was concentrated in vacuo and the residue was diluted with ethyl acetate. The solution was washed with 2N HCl, sat. $CuSO_4$, brine and dried over Na_2SO_4, then concentrated and the residue was purified by chromatography to give 3-tosyloxyglutarate (79.8 g; 91%). A solution of diethyl 3-tosyloxyglutarate obtained (17.9 g; 49.9 mmol) in ether (300 ml) was cooled by ice-water and $LiAlH_4$ (2.5 g; 65.9 mmol) was added stepwise to the solution. After the reaction mixture had been stirred at 0°C for 3 h, water (2.5 ml), 15% NaOH (aq) (2.5 ml) and water (7.5 ml) were added to the mixture, again under ice-cooling. The precipitate was filtered and washed with ether. The organic layer was combined and evaporated to give a crude tosylate (8.4 g; 59% yield). The crude tosylate was dissolved in acetonitrile (300 ml) and *p*-fluorophenol sodium salt was added, which had been prepared from 4.48 g (40.0 mmol) of *p*-fluorophenol and 7.7 g (40.0 mmol) of 28% sodium methoxide. The mixture was stirred overnight at room temperature. After the acetonitrile had been evaporated, ethyl acetate was added to the residue and the organic layer was washed with water and brine, then dried over Na_2SO_4 and concentrated. The residue was purified by chromatography to give 6.3 g of 3-(*p*-fluorophenoxy)-1,5-pentanediol **5a** (50% yield). δ_H (100 MHz; $CDCl_3$) 1.96 (4H, m), 2.42 (2H, br s), 3.77 (4H, t, *J* 6), 4.65 (1H, m), 6.96 (4H, m); υ_{max}/cm^{-1} 3350 (OH), 1600, 1505, 1205.

3.2. 1,5-Diacetoxy-3-(p-fluorophenoxy)pentane (5b)

Acetic anhydride (7 ml; 74.1 mmol) was added to a solution of 3-(*p*-fluorophenoxy)-1,5-pentanediol **5a** (6.1 g; 28.5 mmol) in pyridine (20 ml) at 0°C and the solution was allowed to come to room temperature. After the reaction mixture had been stirred overnight, the mixture was poured into water and extracted with ether. The extract was successively washed with saturated $CuSO_4$, water, saturated $NaHCO_3$

and brine, then dried over Na_2SO_4 and evaporated. The residue was purified by silica gel column chromatography to afford 8.0 g of 1,5-diacetoxy-3-(*p*-fluorophenoxy)pentane (**5b**). δ_H (100 MHz; $CDCl_3$) 1.18–2.16 (4H, m), 2.04 (3H, s), 4.18 (4H, t, *J* 6), 4.40 (1H, m), 6.70–7.08 (4H, m); *m/z* (FAB). Found: 298.1211. Calculated for $C_{15}H_{19}O_5F$: 298.1216.

3.3. (3R)-5-Acetoxy-3-(p-fluorophenoxy)-1-pentanol (R)-4. Asymmetric hydrolysis of 1,5-diacetoxy-3-(p-fluorophenoxy)pentane 5b

To a solution of phosphate buffer (pH 7.0) containing 0.5% tritonX-100 was added 5 g (16.8 mmol) of 1,5-diacetoxy-3-(*p*-fluorophenoxy)pentane (**5b**) and 3 g of lipase Amano P. The solution was stirred at 30°C, at pH 7.0 for 4 h. The mixture was then saturated with sodium chloride and filtered. The filtrate was extracted with ethyl acetate three times and the organic layer was washed with brine, dried over Na_2SO_4 and then concentrated. The residue was purified by silica gel column chromatography to give the 3.6 g of (3*R*)-5-acetoxy-3-(*p*-fluorophenoxy)-1-pentanol (*R*)-**4** (82% yield). The enantiomeric excess was > 99% ee. δ_H (100 MHz; $CDCl_3$) 1.80–2.16 (4H, m), 2.00 (3H, s), 3.76 (2H, t, *J* 5), 4.16 (2H, t, *J* 5), 4.30 (1H, q, *J* 5), 6.70–7.10 (4H, m); *m/z* (FAB). Found: 256.1109. Calculated for $C_{13}H_{17}O_4F$: 256.1111.

3.4. (3S)-5-Acetoxy-3-(p-fluorophenoxy)-1-pentanol (S)-4. Asymmetric acetylation of 3-(p-fluorophenoxy)-1,5-pentanediol 5a

3-(*p*-Fluorophenoxy)-1,5-dihydroxypentane (6 g; 28.0 mmol) (**5a**) was dissolved in 20 ml of tetrahydrofuran and 200 ml of toluene and 1.2 eq. of acetic anhydride was added to the solution. Then 6 g of lipozyme was added and the mixture was stirred at 30°C for 3 h. The lipozyme was removed by filtration and the filtrate was washed with sat. $NaHCO_3$ and brine and then concentrated. The residue was purified by silica gel column chromatography to give 5.9 g of (3*S*)-5-acetoxy-3-(*p*-fluorophenoxy)-1-pentanol (*S*)-**4** (86% yield). The spectra of ^{1}H-NMR and IR were identical with those of (*R*)-**4**.

3.5. (2R)-2-(2'-Acetoxyethyl)-6-fluorochromane (11)

Jones' reagent was added to a solution of 1 g (3.90 mmol) of (3*R*)-5-acetoxy-3-(*p*-fluorophenoxy)-1-pentanol (*R*)-**4**, which was obtained by asymmetric hydrolysis using lipase Amano P, until the red color remained and was stirred at room temperature for 1 h. After the reaction had finished, 2-propanol was added to the reaction mixture and poured into water. The mixture was extracted with ether and the organic layer was washed with brine, dried over Na_2SO_4 and concentrated to give 1.2 g of (3*R*)-3-(*p*-fluorophenoxy)-5-acetoxypentanoic acid. It (800 mg; 3.05 mmol) was added to polyphosphoric acid (2 g) and stirred slowly at 70 °C for 2 h. The mixture was cooled to room temperature and poured into ice water and then extracted with ether. The ether layer was washed with brine, dried over Na_2SO_4 and then concentrated. The residue was purified by silica gel column chromatography to give 548 mg of (2*S*)-2-(2'-acetoxyethyl)-6-fluoro-4-oxochromane **3** as a brown oil. δ_H (100 MHz; $CDCl_3$) 2.06 (3H, s), 2.12 (2H, m), 2.70 (2H, d), 4.28 (2H, t, *J* 6), 4.52 (1H, m), 6.80–7.60 (3H, m); υ_{max}/cm^{-1} 1740 (CO), 1695 (PhCO), 1620, 1480, 1190, 1180, 1120, 1050, 1000; *m/z* (FAB). Found: 253.0876. Calculated for $C_{13}H_{14}O_4F$: 253.0876. The spectral data of the antipode were identical to those described above.

(2*S*)-2-(2'-Acetoxyethyl)-6-fluoro-4-oxochromane **3** (412 mg; 1.63 mmol) was dissolved in 3 ml of ethanol and sodium borohydride (120 mg; 3.17 mmol) was added to the solution. The reaction mixture was stirred at room temperature for 1 h and then neutralized with hydrochloric acid and concentrated. To the residue was added water and the mixture was extracted with ether three times. The combined extracts were washed with brine and dried over Na_2SO_4,

then concentrated to give 424 mg of (2*S*)-2-(2′-acetoxyethyl)-6-fluoro-4-hydroxychromane as an oily compound (quant.). The alcohol was dissolved in 4 ml of acetic acid containing 0.1 ml of concentrated hydrochloric acid and 10% Pd-carbon was added to the solution, then the mixture was stirred vigorously in a hydrogen atmosphere for 3 h at 40°C. After filtration of the catalyst, the filtrate was concentrated, and the residue was purified by silica gel column chromatography (EtOAc/Hexane) to give 308 mg (99% yield) of (2*R*)-2-(2′-acetoxyethyl)-6-fluorochromane **11** as a colorless oil. δ_H (100 MHz; $CDCl_3$) 1.5–2.2 (4H, m), 2.04 (3H, s), 2.75 (2H, m), 3.88–4.20 (1H, m), 4.24 (2H, t, *J* 6), 6.60–7.00 (3H, m); ν_{max}/cm^{-1} 1740 (CO), 1490, 1435, 1140, 1100, 1090, 1060, 1030. The spectral data of the antipode were identical to those described above.

3.6. 6-Fluoro-2-(2′-hydroxyethyl)chromane (12)

An aqueous solution of sodium hydroxide (2 N) was added to a solution of (2*R*)-2-(2′-acetoxyethyl)-6-fluorochromane **11** (245 mg; 1.03 mmol) in methanol (3 ml) at 0°C and the mixture was stirred for 1 h. Then the reaction mixture was concentrated and water was added to the residue, then extracted with ether. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated to give 209 mg (quant.) of 6-fluoro-2-(2′-hydroxyethyl)chromane **12** as an oily compound. δH (100 MHz; $CDCl_3$) 1.6–2.6 (4H, m), 2.75 (2H, m), 3.87 (2H, t, *J* 6), 4.16 (1H, m), 6.7 (3H, m); ν_{max}/cm^{-1} 3400 (OH),1490, 1140, 1070, 1020; *m/z* (FAB). Found: 196.0894. Calculated for $C_{11}H_{13}O_2F$: 196.0899. The spectral data of the antipode were identical to those described above.

3.7. (2R)-6-Fluoro-2-vinylchromane (13)

(2*R*)-6-Fluoro-2-(2′-hydroxyethyl)chromane **12** (474 mg; 2.42 mmol) and *p*-toluenesulfonic chloride (800 mg; 4.20 mmol) were dissolved in pyridine (2 ml) and the mixture was stirred for 2 h at room temperature. The mixture was poured into water and extracted with ether 3 times. The organic layer was washed with sat. $CuSO_4$, brine and dried over Na_2SO_4, then concentrated to give (2*R*)-6-fluoro-2-(2′-p-toluenesulfonyloxyethyl)chromane (200 mg; 0.57 mmol). Then it was dissolved in acetone (3 ml) and sodium iodide (172 mg; 1.05 mmol) was added to the solution. The reaction mixture was stirred under reflux for 1 h. After the mixture had been cooled to room temperature, it was diluted with ethyl acetate and washed with sat. $Na_2S_2O_3$, brine, dried over Na_2SO_4 and then concentrated. The residue was purified by silica gel column chromatography to give 183 mg of (2*R*)-6-fluoro-2-(2′-iodoethyl)chromane as an oily compound (99% yield). δ_H (100 MHz; $CDCl_3$) 1.55–2.45 (4H, m), 2.75 (2H, m), 3.37 (2H, t, *J* 6), 4.05 (1H, m), 6.70 (3H, m); ν_{max}/cm^{-1} 1620, 1500, 1430, 1170, 1140, 1040. The spectral data of the antipode were identical to those described above.

Potassium *t*-butoxide (140 mg; 1.25 mmol) was added to a solution of (2*R*)-6-fluoro-2-(2′-iodoethyl)chromane (278 mg; 0.91 mmol) in dimethylsulfoxide (2 ml) and the mixture was stirred at room temperature for 30 min. To the mixture was added ethyl acetate and washed with brine, dried over Na_2SO_4 and then concentrated. The residue was purified by silica gel column chromatography to give 150 mg of (2*R*)-6-fluoro-2-vinylchromane 13 (89% yield). δ_H (100 MHz; $CDCl_3$) 1.62–2.32 (2H, m), 2.80 (2H, t, *J* 5), 4.50 (1H, m), 5.24 (1H, d, *J* 12), 5.36 (1H, d, *J* 20), 5.80–6.20 (1H, m), 6.70 (3H, m); ν_{max}/cm^{-1} 1490, 1260, 1220, 1200, 1140, 1040, 1000; *m/z* (FAB). Found: 178.0759. Calculated for $C_{11}H_{11}OF$: 178.0794. The spectral data of the antipode were identical to those described above.

3.8. (6-Fluoro-2-chromanyl)oxirane (2)

m-CPBA (110 mg; 0.64 mmol) was added to a solution of (2*R*)-6-fluoro-2-vinylchromane **13**

(300 mg; 1.68 mmol) in $CHCl_3$ (10 ml) and the mixture was stirred for 3 days at room temperature. To the mixture was added ether, and washed with sat. Na_2SO_3, $NaHCO_3$, brine, dried over Na_2SO_4 and then concentrated to give a mixture of two diastereomers in a ratio of 1:1. These diastereomers could be easily separated by silica gel column chromatography to give (2*S*, 2′*R*)-(6-fluoro-2-chromanyl)oxirane 2 (45 mg) and (2*R*, 2′*R*)-(6-fluoro-2-chromanyl)oxirane 2 (52 mg). The spectral data of (2*S*, 2′*R*)-2: δ_H(100 MHz; $CDCl_3$) 1.75–2.15 (2H, m), 2.60–3.95 (4H, m), 3.13–3.26 (1H, m), 3.75–3.93 (1H, m), 6.50–6.85 (3H, m); υ_{max}/cm^{-1} 3060 (epoxide), 3000, (epoxide), 2930, 1490, 1435, 1420, 1260, 1220, 1140, 1050; *m/z* (FAB). Found: 194.0757. Calculated for $C_{11}H_{11}O_2F$: 194.0743; $[\alpha]_D^{23}$ −76.9 (*c* 1.0 in $CHCl_3$). The spectral data of (2*R*,2′*S*)-2 (via asymmetric acetylation using lipozyme) were identical to those described above. Its specific rotation: $[\alpha]_D^{23}$ + 72.9 (*c* 1.0 in $CHCl_3$). The spectral data of (2*R*, 2′*R*)-2: δ_H (100 MHz; $CDCl_3$) 1.75–2.15 (2H, m), 2.60–3.95 (4H, m), 3.08–3.18 (1H, m), 3.75–3.93 (1H, m), 6.50–6.85 (3H, m); υ_{max}/cm^{-1} 3060 (epoxide), 3000 (epoxide), 2930, 2900, 1490, 1440, 1435, 1260, 1220, 1140, 1050; $[\alpha]_D^{23}$ −75.9 (*c* 1.0 in $CHCl_3$). The spectral data of (2*S*,2′*S*)-2 (via asymmetric acetylation using lipozyme) were identical with those described above. Its specific rotation: $[\alpha]_D^{23}$ + 72.6 (*c* 1.0 in $CHCl_3$).

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