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A practical synthesis of the PPARα agonist, (*R*)-K-13675, starting from (*S*)-2-hydroxybutyrolactone

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ABSTRACT

A practical synthesis of optically pure PPARα agonist, (*R*)-K-13675, is described. This process is based on the use of (*S*)-2-hydroxybutyrolactone, which can be transformed into the requisite *n*-butyl (*S*)-2-hydroxybutanoate in an efficient manner. A key reaction is the etherification between the phenol and *n*-butyl (*S*)-2-trifluoromethanesulfonyloxybutanoate to give the phenyl ether in excellent yield without loss of optical purity.

1. Introduction

Peroxisome proliferator-activated receptor α (PPARα) is a member of one of the nuclear receptor superfamilies and its activation regulates expression of key genes involved in lipid homeostasis.[1] During the course of drug discovery, we identified (*R*)-2-[3-[[benzoxazol-2-yl[3-(4-methoxyphenoxy)propyl]amino]methyl]phenoxy]butanoic acid ((*R*)-K-13675, **1**) as a highly potent and selective PPARα agonist[2] (Fig. 1) and reported enantioselective synthesis of (*R*)-K-13675 starting from (*S*)-2-hydroxybutyrolactone (**6**).[3] However, the above method involves four steps from the key intermediate **3** as a linear synthetic route and requires the laborious purification by column chromatography after Mitsunobu reaction.[4] As our efforts were focused on developing a practical synthetic route for multi-kg scale preparation, we first have to establish the efficient preparation of *n*-butyl (*S*)-2-hydroxybutanoate (**4**)[5] as an important chiral part, because it is too expensive for use in large-scale production. Our synthetic plan to obtain *n*-butyl (*S*)-2-hydroxybutanoate (**4**) began with the cleavage of (*S*)-2-hydroxybutyrolactone (**6**) by halogen attack at γ-position leading to the halo ester **5**,[6] following hydrogenolysis using palladium carbon under a hydrogen atmosphere (Fig. 1).

2. Results and discussion

The synthesis of *n*-butyl (*S*)-2-hydroxybutanoate (**4**) is illustrated in Scheme 1. (*S*)-2-Hydroxybutyrolactone (**6**) was prepared using L-malic acid according to our modified method in >99% ee.[3] The lactone **6** was reacted with 1.1 equiv of iodotrimethylsilane (TMSI) in the presence of 1.0 equiv of *n*-BuOH in CH_2Cl_2 at room temperature to afford *n*-butyl (*S*)-2-hydroxy-4-iodobutanoate (**5**) in 81% yield. When MeOH or EtOH was used, the yield of the newly formed ester after hydrogenolysis can be decreased due to volatility. Therefore, *n*-BuOH is used to ensure adequate chemical yield. With *n*-butyl (*S*)-2-hydroxy-4-iodobutanoate (**5**) in hand, we performed hydrogenolysis with 10% palladium carbon and triethylamine (Et_3N) under a hydrogen atmosphere to afford *n*-butyl (*S*)-2-hydroxybutanoate (**4**) without loss of optical purity in moderate yield. In this reaction process, the palladium catalyst can be deactivated by the generated hydrogen iodide. Therefore, we added Et_3N to avoid this deactivation.[7]

Next, we investigated the conditions of the etherification of the substituted phenol **3** with *n*-butyl (*S*)-2-hydroxybutanoate (**4**) to obtain the chiral ether **2** in high yield and optical purity. First, we conducted the etherification between the phenol **3** and each sulfonate **7a–c** of *n*-butyl (*S*)-2-hydroxybutanoate (**4**) under basic conditions (Table 1). Unsatisfactory results were obtained on treatment of **3** with the mesylate **7a** or the tosylate **7b** in the presence of K_2CO_3 at room temperature (**7a**=59%, **7b**=10%; entry 1 and 4). When the reaction was performed at 60 °C, the chemical yields of **2** were increased (**7a**=59 to 93%, **7b**=10 to 69%), but this

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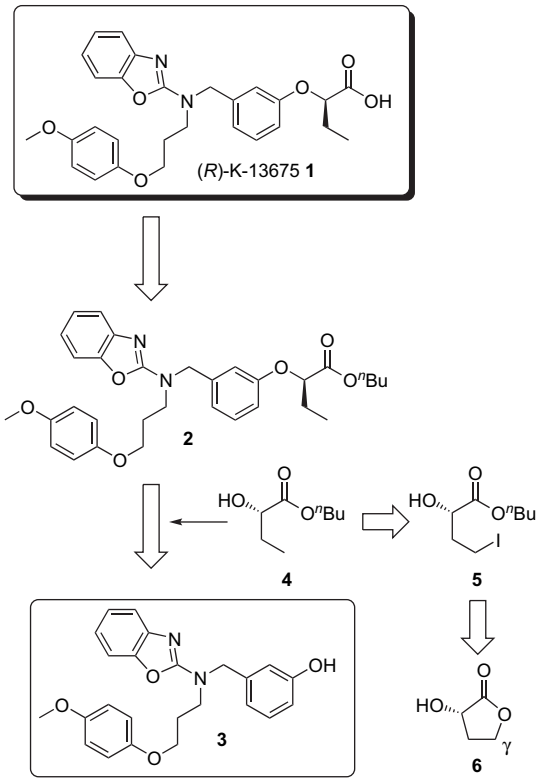
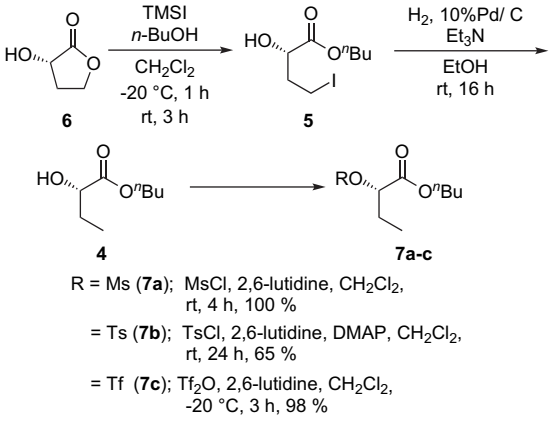


Figure 1. Structure of (*R*)-K-13675 and the synthetic plan.

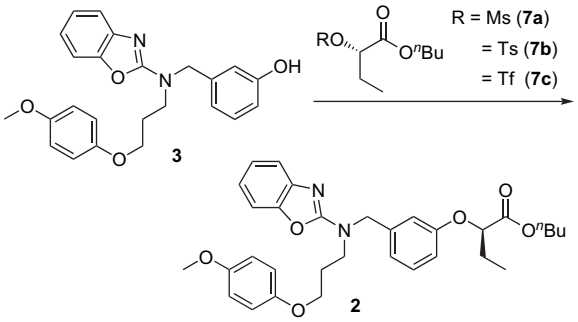


Scheme 1. Synthesis of *n*-butyl (*S*)-2-hydroxybutanoate and the sulfonates.

was accompanied by a loss of optical purity (**7a**=97 to 79% ee, **7b**=>99 to 93% ee; entry 2 and 5). Changing the base from K_2CO_3 to Cs_2CO_3 markedly affected the chemical yield (**7a**=59 to 90%, **7b**=10 to 77%) but lowered the optical purity (**7a**=97 to 77% ee, **7b**=>99 to 93% ee). From these results, we should note the leaving group of **7a** and **7b** to obtain the acceleration effect in this etherification. It was reported previously that a trifluoromethanesulfonyloxy (TfO–) group shows much higher leaving group capability than methanesulfonyloxy (MsO–) and *p*-toluenesulfonyloxy (TsO–) groups (TfO–/MsO–/TsO–=56,000:1:0.7).[8]

Therefore, we used the TfO– group instead of the MsO– or TsO– group. Exposure of the triflate **7c** with the phenol **3** at room temperature in the presence of K_2CO_3 led to excellent results with regard to chemical yield and optical purity (100% and 99% ee; entry 7). By raising the reaction temperature, a slight decrease in optical

Table 1
Etherification with phenol **3** and sulfonate (**7a–c**)[a]



Entry	R	Base	Solvent	Temp (°C)	Time (h)	Yield[b] (%)	Optical purity[c] (% ee)
1	Ms	K_2CO_3	MeCN	rt	55	59	97
2	Ms	K_2CO_3	MeCN	60	24	93	79
3	Ms	Cs_2CO_3	MeCN	rt	27	90	77
4	Ts	K_2CO_3	MeCN	rt	24	10	>99
5	Ts	K_2CO_3	MeCN	60	24	69	93
6	Ts	Cs_2CO_3	MeCN	rt	24	77	93
7	Tf	K_2CO_3	MeCN	rt	14	100	99
8	Tf	K_2CO_3	MeCN	30	8	99	99
9	Tf	K_2CO_3	MeCN	40	6	100	99
10	Tf	K_2CO_3	MeCN	50	3	100	99
11	Tf	K_2CO_3	MeCN	60	6	100	98
12	Tf	K_2CO_3	MeCN	90	6	100	94
13	Tf	Et_3N	$CHCl_3$	rt	48	80	99

[a] Conditions: phenol **3** (100 mg), sulfonate **7a–c** (1.2 equiv), base (1.2 equiv), rt.
[b] Isolated yield.
[c] Determined by HPLC analysis.

purity was observed (98% ee; entry 11, 94% ee; entry 12). The use of Et_3N in place of K_2CO_3 yielded satisfactory optical purity, but the reaction was incomplete (80% and 99% ee; entry 13).

In this reaction system, we postulated that the racemization of **7a–c** could occur before formation of the chiral ether **2**. The proton at the α-position of *n*-butyl 2-sulfonyloxybutanoate can be easily abstracted due to the double activation by the neighboring carbonyl and sulfonyloxy groups. To confirm the influence of K_2CO_3, we examined racemization of the triflate **7c** under basic conditions. The triflate **7c** was exposed to K_2CO_3 in MeCN at room temperature for various times. After treatment, the phenol **3** was added to this mixture and stirred for 4 h. The optical purity of **2** was measured by HPLC and the results are summarized in Table 2. In contrast to our expectations, the optical purity of **7c** was maintained even under basic conditions. In fact, we postulated the mechanism of racemization as illustrated in Figure 2.

In the case of the triflate **7c**, the S_N2 reaction (path b) occurred much faster than racemization by phenoxide anion (path a) due to the high leaving capability. These results can be explained in

Table 2
Influence of triflate **7c** under basic conditions[a]

Time (h)	Yield[b] (%)	Optical purity[b] (% ee)
1	98	99
2	98	99
3	98	99
4	97	99
5	98	98
6	98	98
12	97	97
24	97	97

[a] Conditions: phenol **3** (50 mg) was added after treatment of triflate **7c** (1.5 equiv) with K_2CO_3 (1.5 equiv) in MeCN (2 mL) for various times at rt and the mixture was then stirred for 4 h.
[b] Determined by HPLC analysis.

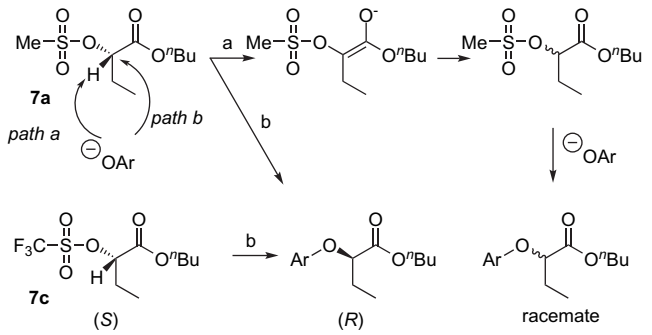


Figure 2. Plausible mechanism of racemization.

accordance with the reactivity (TfO–≫MsO–>TsO–). We concluded that rapid etherification is the key feature in this reaction system. It is important for the synthesis of (*R*)-K-13675 to maintain a high optical purity. Finally, we selected the optimized reaction conditions shown as entry 7 in Table 1.

The triflate **7c** was prepared on the kg scale from *n*-butyl (*S*)-2-hydroxybutanoate (**4**) on treatment with Tf_2O and pyridine or 2,6-lutidine in CH_2Cl_2 (Fig. 3). In the case of pyridine, 2-pyridinium

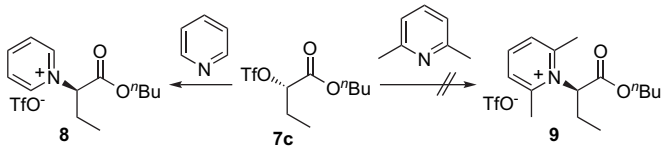
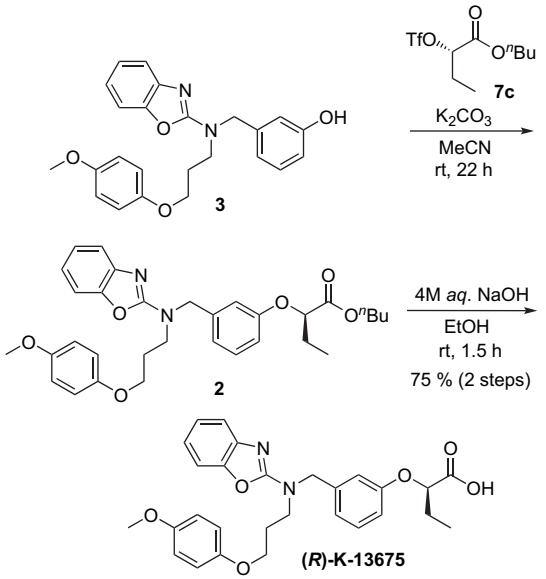


Figure 3.

butanoate **8** could be generated as a major product when the reaction temperature was allowed to warm over 0 °C. Pyridine worked as a nucleophile, not as a base, toward the highly reactive triflate **7c**. To avoid the formation of **8**, we attempted to use 2,6-lutidine. As expected, the reproducible preparation of triflate **7c** was established without regard to the reaction temperature.

The phenyl ether **2** was hydrolyzed with aq NaOH to afford (*R*)-K-13675 in satisfactory yield with excellent optical purity (Scheme 2).



Scheme 2. Synthesis of (*R*)-K-13675 from the phenol **3**.

3. Conclusion

We have established a practical method for synthesis of (*R*)-K-13675 starting from (*S*)-2-hydroxybutyrolactone (**6**) via *n*-butyl (*S*)-2-hydroxybutanoate (**4**). In addition, we demonstrated optimization of etherification between the phenol **3** and triflate of *n*-butyl (*S*)-2-hydroxybutanoate (**4**) in excellent yield and optical purity in large-scale production.

4. Experimental

4.1. General

Commercially available reagents and solvents were used without further purification. TLC analyses were carried out on silica gel 60 F_{254} plates (Merck). ^{1}H NMR and ^{13}C NMR spectra were recorded on a JEOL JNM-LA 400 MHz. Tetramethylsilane was used as an internal standard. Chemical shifts (δ) are given in parts per million (ppm), coupling constants *J* values are given in hertz (Hz) and are reported to the nearest 0.1 Hz. Infrared (IR) spectra were recorded on a Thermo Nicolet 370 FT-IR (ATR) spectrometer. Mass spectra were obtained on a JEOL MS-BU20 mass spectrometer. Elemental analyses (C, H, N) were performed by Yanaco MT-5. Melting points were determined in open glass capillaries on a Buchi B-545 melting point apparatus. The chiral HPLC analyses were performed on a SHIMADZU LC-2010A HT liquid chromatograph using CHIRALPAK AS and AD columns (manufactured by Daicel), 5.0 cm×0.46 cm.

4.2. Synthesis of *n*-butyl (*S*)-2-hydroxy-4-iodobutanoate (5)

To a solution of (*S*)-2-hydroxybutyrolactone (**6**) (1.60 kg, 15.7 mol) and *n*-BuOH (1.16 kg, 15.7 mol) in CH_2Cl_2 (7.0 L) was added TMSI (3.31 kg, 16.7 mol) at −10 °C over 0.5 h under a nitrogen atmosphere and stirred for 1 h. The reaction mixture was allowed to warm to room temperature and stirred for 3 h. The mixture was diluted with water (7.0 L) and extracted with CH_2Cl_2 (5.5 L). The organic layer was washed with saturated aq $NaHCO_3$ (3.0 L), 1% aq $NaHSO_3$ (4.0 L), and brine (3.0 L), dried over Na_2SO_4, and concentrated in vacuo to give **5** as a yellowish oil (3.67 kg, 81%). An analytically pure sample was obtained via silica gel column chromatography: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.89 (t, *J*=7.4 Hz, 3H), 1.33 (qt, *J*=7.5, 7.4 Hz, 2H), 1.60 (tt, *J*=7.1, 7.1 Hz, 2H), 1.98–2.07 (m, 1H), 2.22–2.29 (m, 1H), 2.75 (d, *J*=4.6 Hz, 1H), 3.23–3.29 (m, 2H), 4.12–4.18 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 0.71, 13.56, 18.99, 30.41, 37.95, 65.81, 70.23, 174.27; IR (neat) 3448, 2960, 1732, 1464, 1212, 1148, 1086 cm^{-1}; MS (EI) *m*/*z* 286 [M$^+$]. Anal. Calcd for $C_8H_{15}IO_3$: C, 33.58; H, 5.28. Found: C, 33.53; H, 5.23; $[\alpha]_D^{20}$ −6.14 (*c* 1.08, $CHCl_3$).

4.3. Synthesis of *n*-butyl (*S*)-2-hydroxybutanoate (4)

To a solution of **5** (3.61 kg, 12.6 mol) and Et_3N (3.83 kg, 37.8 mol) in EtOAc (5.5 L) was added 10% Pd/C (365 g) at room temperature under a nitrogen atmosphere. The reaction mixture was stirred at room temperature for 16 h under a hydrogen atmosphere and then was diluted with water (2.0 L). The catalyst was removed by filtration through a pad of Celite and washed with EtOAc (2.5 L) and water (1.0 L). The organic layer was partitioned and washed with 1 M HCl (4.0 L×5), water (4.0 L), saturated aq $NaHCO_3$ (4.0 L), and brine (2.0 L), dried over Na_2SO_4, and concentrated in vacuo to give a yellowish oil. The oil was distilled under reduced pressure (0.8–1.6 kPa, 55–72 °C) to give **4** as a colorless oil (1.18 kg, 59%):[9] ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.93 (t, *J*=7.8 Hz, 3H), 0.94 (t, *J*=7.8 Hz, 3H), 1.37 (qt, *J*=7.5, 7.4 Hz, 2H), 1.59–1.72 (m, 3H), 1.77–1.85 (m, 1H), 2.71 (d, *J*=5.6 Hz, 1H), 4.11–4.23 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 8.72, 13.40, 18.85, 27.31, 30.41, 65.14, 71.25, 175.13; IR (neat) 3468, 2962, 1731, 1463, 1244, 1206, 1132 cm^{-1}; MS (EI) *m*/*z* 161 [M$^+$+1]. Anal.

Calcd for $C_8H_{16}O_3$: C, 59.97; H, 10.07. Found: C, 59.71; H, 9.88; $[\alpha]_D^{20}$ −3.53 (*c* 1.01, $CHCl_3$).

4.4. Determination of optical purity of 4

To a solution of **4** (30.0 mg, 0.19 mmol) and pyridine (0.02 mL) in CH_2Cl_2 (1.0 mL) was added 4-nitrobenzoyl chloride (35.0 mg, 0.19 mmol) at 0 °C and stirred at room temperature for 5 h. The reaction mixture was diluted with EtOAc and the organic layer was washed with 4 M HCl, water, and brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by preparative TLC (silica gel, *n*-hexane/$CHCl_3$=1:1) to give a colorless oil (31.0 mg, 54%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.83 (t, *J*=7.3 Hz, 3H), 1.03 (t, *J*=7.6 Hz, 3H), 1.25–1.34 (m, 2H), 1.53–1.60 (m, 2H), 1.95–2.02 (m, 2H), 4.10–4.14 (m, 2H), 5.16 (dd, *J*=6.8, 5.4 Hz, 1H), 8.18 (d, *J*=8.9 Hz, 2H), 8.23 (d, *J*=8.9 Hz, 2H); optical purity: >99% ee. HPLC condition: column; CHIRALPAK AD, column temperature; 35 °C, eluent; *n*-hexane/EtOH=60:40, flow rate; 1 mL/min, retention time; 6.55 min (*R*-form; 4.85 min).

4.5. Synthesis of *n*-butyl (*S*)-2-trifluoromethanesulfonyloxybutanoate (7c)

To a stirred solution of **4** (1.55 kg, 9.67 mol) and 2,6-lutidine (1.14 kg, 10.6 mol) in CH_2Cl_2 (15 L) was added dropwise Tf_2O (3.00 kg, 10.6 mol) at −20 °C during 2 h under a nitrogen atmosphere. After stirring for 2 h, further 2,6-lutidine (104 g, 0.97 mol) and Tf_2O (273 g, 0.97 mol) were added additionally to this mixture at same temperature and stirred for 1 h. The reaction mixture was quenched with 0.1 M aq $KHSO_4$ (8.0 L) at 0 °C and the organic layer was partitioned, washed with 0.1 M aq $KHSO_4$ (8.0 L×2), water (8.0 L), and brine (6.0 L), dried over Na_2SO_4, and concentrated in vacuo to give a reddish oil. The oil was dissolved in $CHCl_3$ (5.0 L) and silica gel (1.3 kg) was added to the solution at room temperature. The mixture was stirred at room temperature for 10 min, filtered off the silica gel. The filtrate was concentrated in vacuo to give **7c** as a reddish oil (2.76 kg, 98%). An analytically pure sample was obtained via silica gel column chromatography: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.93 (t, *J*=7.3 Hz, 3H), 1.05 (t, *J*=7.3 Hz, 3H), 1.34–1.43 (m, 2H), 1.65 (quintet, *J*=7.1 Hz, 2H), 1.97–2.08 (m, 2H), 4.23 (td, *J*=6.7, 2.9 Hz, 2H), 5.06 (dd, *J*=7.1, 4.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 8.80, 13.44, 18.84, 25.48, 30.32, 66.36, 84.78, 118.45 (q, *J*=317.8 Hz), 167.05; IR (neat): 2966, 1763, 1418, 1245, 1203, 1146, 947 cm^{-1}; MS (EI) *m*/*z* 293 [M^++1]. Anal. Calcd for $C_9H_{15}F_3O_5S$: C, 36.98; H, 5.17. Found: C, 36.82; H, 5.11; $[\alpha]_D^{20}$ −39.7 (*c* 1.01, $CHCl_3$).

4.6. Synthesis of *n*-butyl (*R*)-2-[3-[[benzoxazol-2-yl-[3-(4-methoxyphenoxy)propyl]amino]methyl]-phenoxy]butanoate (2)

To a solution of **3** (3.03 kg, 7.49 mol) and K_2CO_3 (1.55 kg, 11.2 mol) in MeCN (58 L) was added a solution of **7c** (2.63 kg, 8.99 mol) in MeCN (6.0 L) for 5 min under a nitrogen atmosphere and stirred at room temperature for 22 h. The reaction mixture was filtered off and the filtrate was concentrated in vacuo. The residue was dissolved in EtOAc (27 L) and washed with water (19 L), brine (12 L). The organic layer was dried over Na_2SO_4, concentrated in vacuo to give crude product **2** as a brown oil (4.52 kg). An analytically pure sample was obtained via silica gel column chromatography: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.83 (t, *J*=7.3 Hz, 3H), 1.03 (t, *J*=7.3 Hz, 3H), 1.18–1.29 (m, 2H), 1.44–1.55 (m, 2H), 1.93 (quintet, *J*=7.3 Hz, 2H), 2.12 (quintet, *J*=6.5 Hz, 2H), 3.67 (t, *J*=7.1 Hz, 2H), 3.74 (s, 3H), 3.94 (t, *J*=6.0 Hz, 2H), 3.98–4.13 (m, 2H), 4.51 (t, *J*=6.2 Hz, 1H), 4.72 (d, *J*=3.2 Hz, 2H), 6.74 (dd, *J*=8.3, 2.0 Hz, 1H), 6.78 (s, 4H), 6.84 (t, *J*=2.0 Hz, 1H), 6.88 (d, *J*=7.6 Hz, 1H), 6.99 (td, *J*=7.8, 1.2 Hz, 1H), 7.14 (td, *J*=7.8, 1.2 Hz, 1H), 7.19–7.24 (m, 2H), 7.34 (dd, *J*=7.8, 0.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 9.65, 13.58, 18.92, 26.16, 27.54, 30.49, 45.12, 52.08, 55.71, 64.95, 65.55, 77.63, 108.75, 113.77, 114.65, 114.68, 115.42, 116.16, 120.37, 120.69, 123.94, 129.82, 138.67, 143.50, 148.92, 152.83, 153.89, 158.33, 162.65, 171.65; IR (neat) 1751, 1637, 1578, 1508, 1459, 1230, 1058 cm^{-1}; MS (EI) *m*/*z* 546 [M^+]. Anal. Calcd for $C_{32}H_{38}N_2O_6$: C, 70.31; H, 7.01; N, 5.12. Found: C, 70.40; H, 7.09; N, 5.10; $[\alpha]_D^{20}$ +22.4 (*c* 0.51, $CHCl_3$).

4.7. Synthesis of (*R*)-2-[3-[[benzoxazol-2-yl[3-(4-methoxyphenoxy)propyl]amino]methyl]phenoxy]butanoic acid; (*R*)-K-13675 (1)

To a solution of **2** (5.28 kg, 9.67 mol) in EtOH (23 L) was added 4 M aq NaOH (3.9 L) at 0 °C. The reaction mixture was stirred at room temperature for 1.5 h and then concentrated in vacuo. The residue was dissolved in water (30 L) and washed with *tert*-butyl methyl ether (16 L×2). The aqueous layer was acidified with concd HCl (1.7 L) at 0 °C and extracted with EtOAc (30 L). The organic layer was washed with brine (20 L), dried over Na_2SO_4 (1.0 kg), and concentrated in vacuo. The residue was recrystallized from EtOAc (54 L)/*n*-heptane (94 L) to give (*R*)-K-13675 as pale yellow needles (3.24 kg, 75%). All spectroscopic data were identical with those already reported (see Ref. 3): mp 98–99 °C; $[\alpha]_D^{25}$ +17.0 (*c* 1.00, $CHCl_3$); optical purity: 99% ee. HPLC condition: column; CHIRALPAK AD, column temperature; 35 °C, eluent; *n*-hexane/2-propanol/trifluoroacetic acid=100:30:0.1, flow rate; 2 mL/min, retention time; 4.19 min (*S*-form; 3.68 min). An analytically pure sample for elemental analysis was obtained via recrystallization from EtOAc/*n*-heptane. Anal. Calcd for $C_{28}H_{30}N_2O_6$: C, 68.56; H, 6.16; N, 5.71. Found: C, 68.63; H, 6.23; N, 5.69.

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9. In order to ensure the production of the triflate **7c** from *n*-butyl (*S*)-2-hydroxybutanoate (**4**), we decided to conduct the purification of **4** by distillation. As a result, the yield was significantly decreased in a kg scale operation. On the contrary, this reaction process showed 76% of yield in a 50 g scale operation.