Enantioselective Synthesis of the PPARα Agonist (*R*)-K-13675 via (*S*)-2-Hydroxybutyrolactone

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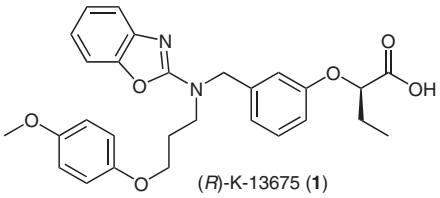
Abstract: Enantioselective synthesis of enantiomerically pure PPARα agonist (*R*)-K-13675 can be achieved starting from (*S*)-2-hydroxybutyrolactone. An important intermediate, 2-(aryloxy)butyrolactone, was prepared by reaction of the phenol with (*S*)-2-hydroxybutyrolactone in excellent yield without loss of enantiomeric purity using the Mitsunobu reaction, followed by conversion into the 2-(aryloxy)butanoic acid via the 2-(aryloxy)-4-iodobutanoate by cleavage of the lactone on exposure to iodotrimethylsilane, followed by hydrogenolysis and hydrolysis.

Key words: Mitsunobu reaction, ethers, ring opening, enantioselective synthesis, PPARα agonist

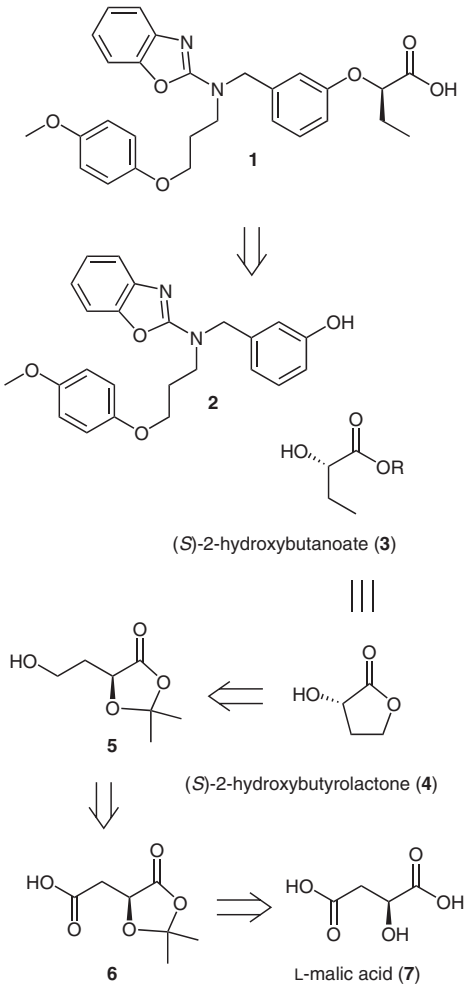
Peroxisome proliferator-activated receptor α (PPARα) is a member of the PPAR nuclear receptor superfamily, activation of which leads to a decrease in triglyceride level and increase in HDL-cholesterol level in humans.[1] During the course of our drug discovery program, we identified (*R*)-2-[3-({benzoxazol-2-yl[3-(4-methoxyphenoxy)propyl]amino}methyl)phenoxy]butanoic acid [(*R*)-K-13675, **1**] as a highly potent and selective PPARα agonist[2] (Figure 1). In a previous study, we obtained enantiomerically pure (*R*)-K-13675 by resolution of the racemate using column chromatography, however, this is very inefficient and wasteful for large-scale production. Therefore, it is necessary to develop a practical synthetic route for (*R*)-K-13675. Although the chiral part corresponding to (*S*)-2-hydroxybutanoate unit **3** is commercially available, it is too expensive to be used in large-scale production. We noted the synthetic equivalent (*S*)-2-hydroxybutyrolactone (**4**), which can be obtained easily starting from L-malic acid (**7**),[3] can be used to replace (*S*)-2-hydroxybutanoate **3**, as shown in Scheme 1. Our strategy involves halogenative cleavage of the lactone moiety on exposure to a Lewis acid (BBr_3 or TMSI) followed by hydrogenolysis, as shown in Scheme 2.

(*S*)-2-Hydroxybutyrolactone (**4**) was prepared efficiently from L-malic acid (**7**) by our modified method. It was reported[3] that the crude product **5** obtained from **6** can be cyclized in the presence of trifluoroacetic acid or 4-toluenesulfonic acid to provide **4** in 55–72% yield. In this step, the formation of byproducts can be monitored by TLC and



(*R*)-K-13675 (**1**)

Figure 1 Structure of (*R*)-K-13675



Scheme 1

the removal of trifluoroacetic acid is the major technical burden in large-scale production.

We used Amberlyst 15 in place of trifluoroacetic acid or 4-toluenesulfonic acid to reduce the amounts of byprod-

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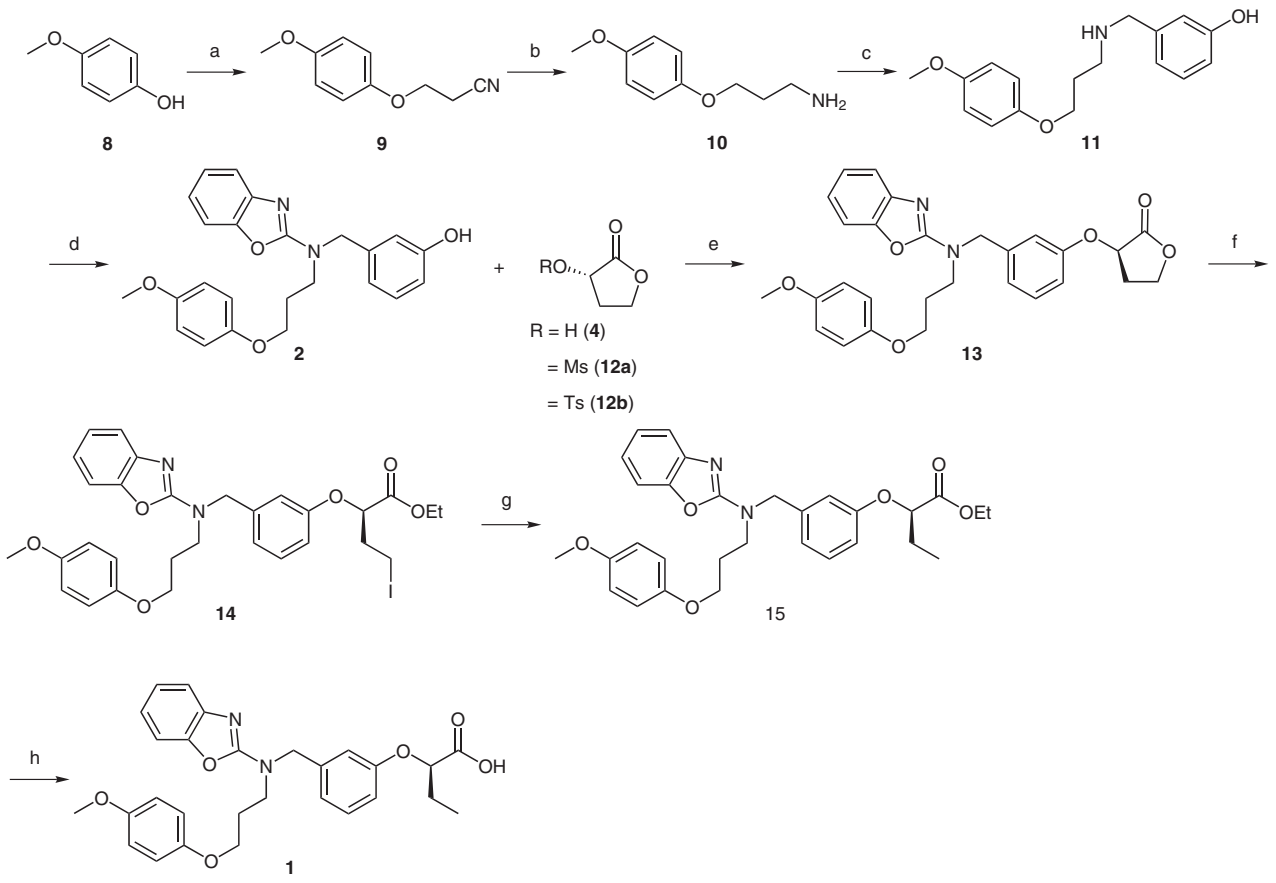

Scheme 2 Synthesis of (*R*)-K-13675. *Reagents and conditions*: (a) Triton B, acrylonitrile; (b) BH_3–THF, THF; (c) 3-hydroxybenzaldehyde, $NaBH_4$, MeOH; (d) 2-chlorobenzoxazole, Et_3N, MeCN; (e) see Table 1; (f) TMSI, EtOH, $CHCl_3$; (g) H_2, 10% Pd/C, Et_3N, EtOH; (h) aq 4 M NaOH, EtOH.

ucts produced in the formation of **4**; this method provided **4** in 89% yield without loss of enantiomeric purity (>99% ee) and it was convenient to filter off the resin on completion of the reaction.[4]

The phenol **2** was prepared as shown in Scheme 2. 4-Methoxyphenol (**8**) was alkylated with acrylonitrile to give the nitrile **9** in 76% yield, followed by reduction with borane–tetrahydrofuran to provide the amine **10** (90% yield). Reductive alkylation of **10** with 3-hydroxybenzaldehyde and sodium borohydride gave the secondary amine **11** in 86% yield, then reaction with 2-chlorobenzoxazole afforded **2** (72% yield).

First, we investigated the conditions for the coupling reaction between the phenol **2** and the sulfonates of (*S*)-2-hydroxybutyrolactone **12a**,**b** in the presence of a base (Table 1). Reaction of **2** with the mesylate **12a** and the tosylate **12b** at room temperature in the presence of potassium carbonate in acetonitrile resulted in unsatisfactory yields and significant loss of enantiomeric purity (entries 1 and 2).

Changing the solvent from acetonitrile to *N*,*N*-dimethylformamide and the base from potassium carbonate to cesium carbonate resulted in a marked increase in the chemical yield of **13**, but not the enantiomeric purity (entries 3 and 4). In this reaction system, we concluded that racemization of sulfonates could not be avoided because the proton at the α-position of the 2-(sulfonyloxy)butyrolactone can be easily abstracted. This may be explained by the increased acidity of H2, the proton between the lactone carbonyl and the sulfonate.[5]

To overcome the problem of racemization, we applied the Mitsunobu reaction[6] for coupling between **2** and **4** under mild conditions (Table 1). Interestingly, we found that the polarity of solvent influenced the reactivity. In polar solvents, the yields were less than 50% (entries 5–10). On the other hand, nonpolar solvents, such as toluene, gave moderate yield, while maintaining enantiomeric purity (63% yield, 97% ee; entry 11). The enantiomeric purity tended to decrease at higher temperatures (100 °C), while the yield increased (73%, 94% ee; entry 12). Next, we examined various azodicarboxylates (entries 13–16). Di-*tert*-butyl azodicarboxylate (DBAD) gave the most satisfactory results for both yield and enantiomeric purity (92% yield, 98% ee; entry 14). Diamide-type reagents resulted in poor yield (<50% yield; entries 15 and 16). Using *tert*-butyl (*S*)-2-hydroxybutanoate instead of 2-hydroxybutyrolactone gave lower yields under the Mitsunobu reaction conditions.[7] For the practical scaleup of production, we selected diisopropyl azodicarboxylate (DIAD; entry 13) because of the ease of separation of **13** from the resultant hydrazine dicarboxylate.

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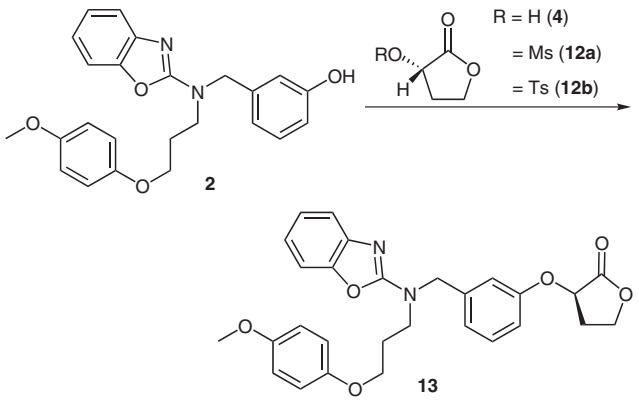
Table 1 Coupling Reaction between **2** and the Lactones **4**, **12a**, and **12b**[a]

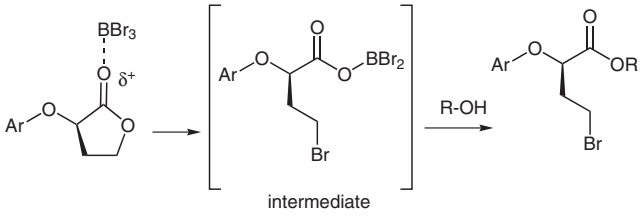


Entry	R	Reagent	Solvent	Yield[b] (%)	ee (%)
1	Ms	K_2CO_3	MeCN	44	11[c]
2	Ts	K_2CO_3	MeCN	35	59[c]
3	Ts	K_2CO_3	DMF	74	62[c]
4	Ts	Cs_2CO_3[d]	DMF	97	54[c]
5	H	DEAD	THF	34	
6	H	DEAD	*t*-BuOMe	26	
7	H	DEAD	MeCN	trace	
8	H	DEAD	EtCN	48	
9	H	DEAD	CH_2Cl_2	14	
10	H	DEAD	DMF	37	
11	H	DEAD	toluene	63	97[c]
12	H	DEAD[e]	toluene	73	94[c]
13	H	DIAD	toluene	77	97[c]
14	H	DBAD	toluene	92	98[c]
15	H	TMAD[f]	toluene	47	
16	H	ADDP[g]	toluene	37	

[a] Conditions: entries 1–4: **2** (100 mg), **12a** or **12b** (1.2 equiv), base (1.2 equiv), r.t., 2 d; entries 5–15: **2** (100 mg), **4** (2.0 equiv), Ph_3P (2.0 equiv), azodicarboxylates or TMAD (2.0 equiv), r.t., 1 d; entry 16: **2** (100 mg), **4** (2.0 equiv), Ph_3P (3.0 equiv), ADDP (3.0 equiv), r.t., 1 d.
[b] Isolated yield.
[c] Determined by HPLC analysis.
[d] Stirred for 12 h.
[e] Reacted at 100 °C.
[f] TMAD = *N*,*N*,*N*′,*N*′-tetramethylazodicarboxamide.
[g] ADDP = 1,1′-(azodicarbonyl)dipiperidine.

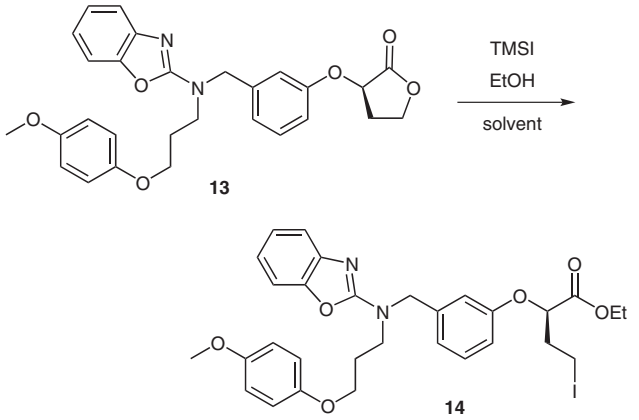
Finally, it was necessary to address the issue of converting the (aryloxy)butyrolactone **13** into the aryloxy ester **15** in an efficient manner.

Our tactic involved cleavage of the lactone ring by halogen attack at the γ-position of **13** leading to the halo ester



Scheme 3 Ring-opening reaction of lactone with boron tribromide

Table 2 Ring-Opening Reaction of **13** with Iodotrimethylsilane and Ethanol[a]



Entry	TMSI (equiv)	EtOH (equiv)	Solvent	Time (h)	Yield[b] (%)
1	1.5	–	EtOH	15	5
2	1.5	1.5	MeCN	15	22
3	1.5	1.5	THF	15	–
4	1.5	1.5	CH_2Cl_2	15	91
5	1.5	5	$CHCl_3$	15	11
6	2.0	5	$CHCl_3$	15	10
7	2.5	5	$CHCl_3$	3	95
8	2.5	1.5	$CHCl_3$	3	72
9	2.5	3	$CHCl_3$	3	90

[a] To a soln of **13** (100 mg) and EtOH in solvent (4 mL) was added TMSI at 0 °C under argon. The mixture was stirred at r.t.
[b] Isolated yield.

14, following by hydrogenolysis using palladium-on-carbon under a hydrogen atmosphere.

Following exposure of **13** to boron tribromide, the resultant intermediate was treated with ethanol according to the conventional method[8] (Scheme 3); this reaction resulted in a complex mixture. Next, we attempted to use iodotrimethylsilane as the ring-opening agent (Table 2).[9] A significant improvement in the isolated yield of **14** was achieved using 2.5 equivalents of iodotrimethylsilane and 5.0 equivalents of ethanol in chloroform at room temperature (95% yield; entry 7). Interestingly, the ring-opening reaction did not proceed in the absence of alcohol. Al-

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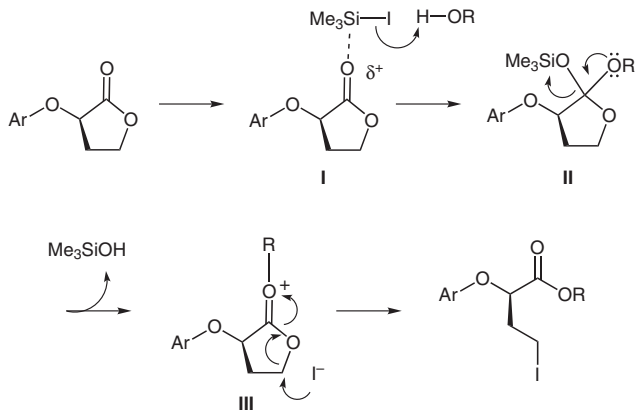

Scheme 4 Plausible mechanism of lactone ring-opening reaction by iodotrimethylsilane

though cleavage of the lactone ring by iodotrimethylsilane was reported in some studies, it required reflux conditions in acetonitrile to form trimethylsilyl 4-iodobutanoate.[10] We presumed that each reaction proceeded by a different mechanism; a plausible mechanism is described in Scheme 4. Initially, iodotrimethylsilane coordinates the carbonyl of the lactone to form the silyl oxonium **I**, which successively adds alcohol and loses silanol. The oxonium intermediate **III** thus formed was attacked by the iodide ion to open the butyrolactone ring, finally leading to the 4-iodobutanoate.

Then, the obtained 2-(aryloxy)-4-iodobutanoate **14** was converted into the final compound (Scheme 2). Hydrogenolysis of **14** was carried out in the presence of triethylamine and 10% palladium on carbon under a hydrogen atmosphere (99% yield). In the absence of triethylamine, this reaction did not proceed due to deactivation of the catalyst by the generated hydrogen iodide. Finally, hydrolysis of the ester **15** furnished (*R*)-K-13675 without racemization at the α-position of the carboxylic acid even under alkaline conditions (90% yield).

In conclusion, we have established a method for the enantioselective synthesis of (*R*)-K-13675 starting from (*S*)-2-hydroxybutyrolactone. In addition, we optimized the Mitsunobu reaction conditions to achieve excellent yield and enantiomeric purity for large-scale production. Furthermore, we developed an efficient method of butyrolactone ring opening, yielding the 4-iodobutanoate using iodotrimethylsilane in the presence of an alcohol under mild conditions.

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. TMS was used as an internal standard. Chemical shifts are reported to the nearest 0.1 Hz. IR spectra were recorded on a Thermo Nicolet 370 FT-IR (ATR) spectrophotometer. 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 Buche B-545 melting point apparatus. The chiral HPLC analyses were performed on a Shimadzu LC-2010A HT liquid chromatograph using Chiralpak AS and AD (manufactured by Daicel), 5.0 cm × 0.46 cm.

(*S*)-2-Hydroxybutyrolactone (4)

To a soln of 2-[(4*S*)-2,2-dimethyl-5-oxo-1,3-dioxolan-4-yl]acetic acid[3] (**6**, 100 g, 0.574 mol) in THF (900 mL) was added BH_3·SMe_2 (65.3 mL, 0.689 mol) dropwise over 30 min at –10 °C under argon; the mixture was stirred at r.t. for 20 h. MeOH (200 mL) was added to the mixture over 10 min at –10 °C and it was stirred for 1 h then concentrated in vacuo. The residue was dissolved in $CHCl_3$ (500 mL) and Amberlyst 15 (8.03 g) was added at r.t. The mixture was stirred at r.t. for 16 h and the resin was filtered off through a pad of Celite. The filtrate was concentrated in vacuo and the residue was purified by column chromatography (silica gel, $CHCl_3$–MeOH, 20:1) to give **4** as a colorless oil (52.0 g, 89%).

IR (neat): 3413, 1767, 1219, 1175, 1121, 1013, 991 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.24–2.35 (m, 1 H), 2.58–2.66 (m, 1 H), 3.49 (br s, 1 H), 4.21–4.28 (m, 1 H), 4.42–4.55 (m, 2 H).

(*S*)-2-(4-Nitrobenzoyloxy)butyrolactone; Determination of the Enantiomeric Purity of 4

To a soln of **4** (86.0 mg, 0.84 mmol) and pyridine (0.5 mL) in CH_2Cl_2 (0.5 mL) was added 4-nitrobenzoyl chloride (156 mg, 0.84 mmol) at r.t. and it was then stirred at this temperature for 1 h. The mixture was diluted with EtOAc and the organic layer was washed with 4 M HCl, H_2O, and brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by column chromatography (silica gel, *n*-hexane–EtOAc, 3:1) to give a colorless solid (130 mg, 62%); >99% ee [HPLC (Chiralpak AS, 35 °C, *n*-hexane–EtOH, 60:40, flow rate: 1 mL/min): t_R = 8.00 min (*S*-isomer), 8.80 min (*R*-isomer)].

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.41–2.52 (m, 1 H), 2.82–2.87 (m, 1 H), 4.38 (dt, *J* = 9.9, 6.5 Hz, 1 H), 4.56 (dt, *J* = 9.3, 2.3 Hz, 1 H), 5.68 (dd, *J* = 9.8, 8.8 Hz, 1 H), 8.24 (dt, *J* = 9.0, 1.9 Hz, 2 H), 8.30 (dt, *J* = 9.0, 1.9 Hz, 2 H).

(*R*)-3-[3-({Benzoxazol-2-yl[3-(4-methoxyphenoxy)propyl]amino}methyl)phenoxy]dihydrofuran-2(3*H*)-one (13); Typical Procedure for Sulfonates

To a soln of **2** (263 mg, 0.65 mmol) and Cs_2CO_3 (319 mg, 0.98 mmol) in DMF (10 mL) was added (*S*)-(tosyloxy)butyrolactone (**12b**; 250 mg, 0.98 mmol) and it was stirred for 12 h. The mixture was diluted with EtOAc and the organic layer was washed with H_2O and brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by column chromatography (silica gel, *n*-hexane–EtOAc, 1:1) to give **13** as a colorless oil (307 mg, 97%).

For the physicochemical data refer to the scaled-up synthesis.

Scale-up Synthesis of (*R*)-K-13675

3-(4-Methoxyphenoxy)propanenitrile (9)

To a soln of acrylonitrile (684 g, 12.9 mol), 4-methoxyphenol (800 g, 6.44 mol) and Triton B (56.0 mL) were added at r.t. and the mixture was stirred at 80 °C under argon for 24 h. The mixture was diluted with EtOAc (3.2 L) and the organic layer was washed with 5% aq NaOH, H_2O, 1 M HCl, H_2O, sat. $NaHCO_3$, and brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was recrystallized [EtOAc (0.8 L)–*n*-heptane (4.0 L)] to give **9** as pale yellow prisms (870 g, 76%); mp 64–65 °C.

IR (solid sample): 2254, 1507, 1230, 1055, 1032, 833, 804 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.79 (t, *J* = 6.5 Hz, 2 H), 3.77 (s, 3 H), 4.15 (t, *J* = 6.5 Hz, 2 H), 6.85 (d, *J* = 6.9 Hz, 4 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.72, 55.77, 63.61, 114.83, 116.09, 117.35, 151.82, 154.71.

MS (EI): *m*/*z* = 177 [M$^+$].

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Anal. Calcd for $C_{10}H_{11}NO_2$: C, 67.78; H, 6.26; N, 7.90. Found: C, 67.71; H, 6.28; N, 7.82.

3-(4-Methoxyphenoxy)propylamine (10)

To a soln of **9** (600 g, 3.39 mol) in anhyd THF (2.4 L) was added BH_3·THF (1.0 mol/L, 3.56 L, 3.56 mol) dropwise at 65 °C under argon. The mixture was stirred at 65 °C for 5 h and then allowed to cool to r.t. 4 M NaOH (4.2 L) was added slowly to the mixture at 5 °C and it was stirred at 65 °C for 16 h. The mixture was allowed to cool to r.t. and diluted with toluene (12 L). The organic layer was washed with H_2O (3 ×) and brine, dried (Na_2SO_4) and, concentrated to give **10** as a colorless solid (551 g, 90%); mp 36–37 °C.

IR (solid sample): 3360, 3341, 1507, 1225, 1031, 1002, 819 cm^{-1}.

^1H NMR (400 MHz, CD_3OD): δ = 2.05 (quint, *J* = 7.1 Hz, 2 H), 3.07 (t, *J* = 7.3 Hz, 2 H), 3.71 (s, 3 H), 4.01 (t, *J* = 5.9 Hz, 2 H), 6.79–6.85 (m, 4 H).

^{13}C NMR (100 MHz, CD_3OD): δ = 31.22, 39.23, 56.07, 67.28, 115.64, 116.45, 154.59, 155.44.

MS (EI): *m*/*z* = 181 [M^+].

3-({[3-(4-Methoxyphenoxy)propyl]amino}methyl)phenol (11)

To a soln of **10** (551 g, 3.04 mol) in MeOH (2.7 L) was added 3-hydroxybenzaldehyde (371 g, 3.04 mol) at r.t. and the mixture was stirred for 5 h. A soln of $NaBH_4$ (115 g, 3.04 mol) in H_2O (5.4 L) was added slowly at 0 °C and the mixture was stirred at r.t. for 1 h, then it was filtered and the thus-obtained solid was washed with H_2O. The solid was dried in vacuo to give **11** as pale yellow crystals (750 g, 86%); mp 140–141 °C.

IR (solid sample): 3274, 2948, 1510, 1282, 1227, 1034, 831 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 1.82 (quint, *J* = 6.6 Hz, 2 H), 2.60 (t, *J* = 6.8 Hz, 2 H), 3.35 (br s, 1 H), 3.60 (s, 2 H), 3.68 (s, 3 H), 3.95 (t, *J* = 6.6 Hz, 2 H), 6.60 (d, *J* = 7.8 Hz, 1 H), 6.73 (t, *J* = 7.6 Hz, 1 H), 6.74 (s, 1 H), 6.83 (s, 4 H), 7.07 (t, *J* = 7.8 Hz, 1 H), 9.34 (s, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 29.29, 45.48, 53.04, 55.30, 66.35, 113.40, 114.54, 114.74, 115.26, 118.46, 128.95, 142.42, 152.67, 153.20, 157.26.

MS (EI): *m*/*z* = 287 [M^+].

Anal. Calcd for $C_{17}H_{21}NO_3$: C, 71.06; H, 7.37; N, 4.87. Found: C, 70.75; H, 7.40; N, 4.96.

3-({Benzoxazol-2-yl[3-(4-methoxyphenoxy)propyl]amino}methyl)phenol (2)

To a soln of **11** (740 g, 2.58 mol) in DMF (3.0 L) and Et_3N (292 g, 2.88 mol) was added 2-chlorobenzoxazole (396 g, 2.58 mol) at 75 °C and it was stirred for 2 h. The mixture was concentrated in vacuo and the thus-obtained residue was dissolved in EtOAc and washed with H_2O and brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by column chromatography (silica gel, *n*-hexane–EtOAc, 1:1) to give a yellow oil. The yellow oil was dissolved with *t*-BuOMe and allowed to stand at r.t. for overnight. The crystals were filtered off and dried in vacuo to give **2** as colorless needles (753 g, 72%); mp 103–104 °C.

IR (solid sample): 3065, 2998, 1638, 1582, 1508, 1460, 1225 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 2.01 (quint, *J* = 6.8 Hz, 2 H), 3.41 (t, *J* = 6.8 Hz, 2 H), 3.76 (s, 3 H), 3.88 (t, *J* = 6.8 Hz, 2 H), 4.63 (s, 2 H), 6.67–6.83 (m, 7 H), 6.91–6.97 (m, 2 H), 7.04 (dt, *J* = 7.2, 2.0 Hz, 1 H), 7.13 (t, *J* = 8.1 Hz, 2 H), 9.41 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 27.62, 45.11, 52.06, 55.73, 65.33, 108.93, 113.04, 114.64, 115.24, 115.30, 115.36, 118.84, 120.66, 123.99, 129.79, 137.65, 141.58, 148.20, 152.72, 153.87, 157.75, 162.27.

MS (EI): *m*/*z* = 404 [M^+].

Anal. Calcd for $C_{24}H_{24}N_2O_4$: C, 71.27; H, 5.98; N, 6.93. Found: C, 71.20; H, 6.06; N, 6.87.

(*R*)-3-[3-({Benzoxazol-2-yl[3-(4-methoxyphenoxy)propyl]amino}methyl)phenoxy]dihydrofuran-2(3*H*)-one (13); Formation Using the Mitsunobu Reaction

To a soln of **2** (558 g, 1.38 mol), (*S*)-2-hydroxybutyrolactone (**4**, 213 g, 2.09 mol), and Ph_3P (548 g, 2.09 mol) in toluene (5.0 L) was added 40% DIAD in toluene (1.1 L, 2.09 mol) under argon at ca. 6 °C. The mixture was stirred at 28 °C for 21 h and then it was washed with H_2O and brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by column chromatography (silica gel, *n*-hexane–EtOAc, 3:1) to give **13** as a colorless oil (411 g, 61%); 97% ee [HPLC (Chiralpak AS, 35 °C, *n*-hexane–EtOH, 60:40, flow rate: 1 mL/min): t_R = 9.37 min (*R*-isomer), 6.86 min (*S*-isomer)].

$[\alpha]_D^{25}$ +26.1 (*c* 1.04, $CHCl_3$).

IR (neat): 1786, 1637, 1578, 1508, 1459, 1230, 756 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 2.14 (quint, *J* = 6.6 Hz, 2 H), 2.36–2.44 (m, 1 H), 2.60–2.67 (m, 1 H), 3.71 (t, *J* = 7.0 Hz, 2 H), 3.76 (s, 3 H), 3.96 (t, *J* = 5.9 Hz, 2 H), 4.25–4.31 (m, 1 H), 4.43–4.49 (m, 1 H), 4.77 (s, 2 H), 4.89 (t, *J* = 7.9 Hz, 1 H), 6.81 (s, 4 H), 6.95–7.03 (m, 4 H), 7.17 (t, *J* = 7.6 Hz, 1 H), 7.22–7.28 (m, 2 H), 7.37 (d, *J* = 7.8 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 27.54, 29.65, 45.12, 52.07, 55.65, 65.21, 65.47, 72.20, 108.74, 114.58, 114.75, 115.13, 115.35, 116.05, 120.40, 121.53, 123.92, 129.90, 138.80, 143.34, 148.83, 152.71, 153.82, 157.52, 162.60, 173.30.

MS (EI): *m*/*z* = 488 [M^+].

HRMS (EI): *m*/*z* [M^+] calcd for $C_{28}H_{28}N_2O_6$: 488.1947; found: 488.1967.

Ethyl (*R*)-2-[3-({Benzoxazol-2-yl[3-(4-methoxyphenoxy)propyl]amino}methyl)phenoxy]-4-iodobutanoate (14)

To a soln of **13** (542 g, 1.11 mol) and EtOH (256 g, 5.55 mol) in $CHCl_3$ (5.4 L) was added TMSI (555 g, 2.78 mol) at ca. –2 °C under argon and the mixture was stirred at 20 °C for 6 h. It was then washed with 2% $Na_2S_2O_3$, sat. $NaHCO_3$, H_2O, and brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by column chromatography (silica gel, *n*-hexane–EtOAc, 2:1) to give **14** as a colorless oil (586 g, 82%).

$[\alpha]_D^{25}$ +22.1 (*c* 0.37, $CHCl_3$).

IR (neat): 1752, 1637, 1578, 1508, 1459, 1230, 755 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.78 (t, *J* = 7.2 Hz, 3 H), 2.14 (quint, *J* = 6.6 Hz, 2 H), 2.37–2.43 (m, 2 H), 3.33 (t, *J* = 7.1 Hz, 2 H), 3.70 (t, *J* = 7.1 Hz, 2 H), 3.76 (s, 3 H), 3.96 (t, *J* = 5.9 Hz, 2 H), 4.09–4.18 (m, 2 H), 4.70 (dd, *J* = 7.8, 4.9 Hz, 1 H), 4.76 (s, 2 H), 6.76–6.81 (m, 5 H), 6.89 (s, 1 H), 6.93 (d, *J* = 7.6 Hz, 1 H), 7.01 (t, *J* = 7.6 Hz, 1 H), 7.16 (t, *J* = 7.6 Hz, 1 H), 7.22–7.26 (m, 2 H), 7.37 (d, *J* = 7.8 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.36, 27.87, 36.70, 45.50, 52.38, 56.02, 61.88, 65.82, 76.68, 77.32, 109.06, 114.48, 115.00, 115.12, 115.71, 116.47, 120.71, 121.53, 124.26, 130.20, 139.13, 143.75, 149.20, 153.10, 154.19, 158.28, 162.92, 170.90.

MS (EI): *m*/*z* = 644 [M^+].

HRMS (EI): *m*/*z* [M^+] calcd for $C_{30}H_{33}IN_2O_6$: 644.1383; found: 644.1386.

Ethyl (*R*)-2-[3-({Benzoxazol-2-yl[3-(4-methoxyphenoxy)propyl]amino}methyl)phenoxy]butanoate (15)

To a soln of **14** (758 g, 1.18 mol) and Et_3N (239 g, 2.36 mol) in EtOH (7.0 L) was added 10% Pd/C (75.8 g) at r.t. under argon. The

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mixture was stirred at r.t. under H_2 for 8 h. The catalyst was removed by filtration and washed with EtOH. The filtrate was concentrated in vacuo and the residue was purified by column chromatography (silica gel, *n*-hexane–EtOAc, 1:1) to give **15** as a colorless oil (606 g, 99%).

$[\alpha]_D^{25}$ +26.9 (*c* 1.19, $CHCl_3$).

IR (neat): 1750, 1733, 1637, 1578, 1508, 1459, 1231 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.05 (t, *J* = 7.3 Hz, 3 H), 1.17 (t, *J* = 7.1 Hz, 3 H), 1.96 (quint, *J* = 7.3 Hz, 2 H), 2.14 (quint, *J* = 6.6 Hz, 2 H), 3.70 (t, *J* = 7.1 Hz, 2 H), 3.76 (s, 3 H), 3.96 (t, *J* = 5.9 Hz, 2 H), 4.04–4.18 (m, 2 H), 4.51 (t, *J* = 6.2 Hz, 1 H), 4.75 (s, 2 H), 6.77–6.81 (m, 5 H), 6.86 (s, 1 H), 6.90 (d, *J* = 7.8 Hz, 1 H), 7.01 (d, *J* = 7.7 Hz, 1 H), 7.16 (t, *J* = 7.7 Hz, 1 H), 7.21–7.26 (m, 2 H), 7.37 (d, *J* = 7.8 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 9.59, 14.07, 26.07, 27.48, 45.09, 52.03, 55.66, 61.09, 65.47, 77.58, 108.70, 113.83, 114.56, 114.58, 115.36, 116.10, 120.33, 120.67, 123.90, 129.78, 138.62, 143.43, 148.86, 152.76, 153.83, 158.27, 162.59, 171.50.

MS (EI): *m*/*z* = 518 [M^+].

HRMS (EI): *m*/*z* [M^+] calcd for $C_{30}H_{34}N_2O_6$: 518.2417; found: 518.2412.

(*R*)-2-[3-({Benzoxazol-2-yl[3-(4-methoxyphenoxy)propyl]amino}methyl)phenoxy]butanoic Acid [(*R*)-K-13675, 1]

To a soln of **15** (605 g, 1.17 mol) in EtOH (4.5 L) was added 4 M NaOH (1.2 L) and the mixture was stirred at r.t. for 1.5 h. After evaporation of EtOH, the mixture was diluted with H_2O and washed with *i*-Pr_2O. The aqueous layer was acidified with concd HCl with ice cooling, and the mixture was extracted with EtOAc. The organic layer was washed with H_2O and brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was recrystallized [EtOAc (4.5 L)–*n*-heptane (9.0 L)] to give (*R*)-K-13675 as colorless needles (515 g, 90%); mp 98–99 °C; 99.5% ee [HPLC (Chiralpak AD, 35 °C, *n*-hexane–*i*-PrOH–TFA, 100:30:0.1, flow rate: 2 mL/min): t_R = 4.19 min (*R*-isomer), 3.68 min (*S*-isomer).

$[\alpha]_D^{25}$ +21.4 (*c* 0.51, $CHCl_3$).

IR (solid sample): 2940, 1713, 1636, 1583, 1510, 1463, 1236 cm^{-1}.

^1H NMR (400 MHz, CD_3OD): δ = 0.94 (t, *J* = 7.4 Hz, 3 H), 1.76–1.88 (m, 2 H), 1.99 (quint, *J* = 6.1 Hz, 2 H), 3.60 (t, *J* = 6.8 Hz, 2 H), 3.61 (s, 3 H), 3.85 (t, *J* = 5.9 Hz, 2 H), 4.40 (t, *J* = 5.9 Hz, 1 H), 4.65 (s, 2 H), 6.69–6.80 (m, 7 H), 6.91 (dt, *J* = 7.2, 1.0 Hz, 1 H), 7.05 (dt, *J* = 7.2, 1.2 Hz, 1 H), 7.12–7.18 (m, 3 H).

^{13}C NMR (100 MHz, CD_3OD): δ = 9.86, 27.04, 28.65, 46.64, 53.06, 56.08, 66.73, 78.45, 109.96, 115.34, 115.46, 115.64, 116.47, 116.51, 121.61, 121.98, 125.27, 130.67, 139.93, 143.77, 149.95, 154.30, 155.40, 159.85, 164.11, 175.11.

MS (EI): *m*/*z* = 490 [M^+].

Anal. Calcd for $C_{28}H_{30}N_2O_6$: C, 68.56; H, 6.16; N, 5.71. Found: C, 68.56; H, 6.16; N, 5.71.

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References and Notes

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