Novel Synthesis of Butyl (*S*)-2-Hydroxybutanoate, the Key Intermediate of PPARα Agonist (*R*)-K-13675 from Butyl (2*S*,3*R*)-Epoxybutanoate and Butyl (*S*)-2,3-Epoxypropanoate

Takaaki Araki, Minoru Koura, Yukiyoshi Yamazaki, Kimiyuki Shibuya*

Tokyo New Drug Research Laboratories, Pharmaceutical Division, Kowa Co., Ltd., 2-17-43, Noguchicho, Higashimurayama, Tokyo 189-0022, Japan
Fax +81(42)3950312; E-mail: k-sibuya@kowa.co.jp

Received: 08.02.2013; Accepted after revision: 06.03.2013

Abstract: Novel synthetic methods for the production of butyl (*S*)-2-hydroxybutanoate starting from butyl (2*S*,3*R*)-epoxybutanoate or butyl (*S*)-2,3-epoxypropanoate were established. The former method utilized the regioselective thiolysis of the epoxybutanoate mediated by scandium triflate and subsequent reductive cleavage of the thioether to give butyl (*S*)-2-hydroxybutanoate with stereochemical retention in quantitative yield. The latter method utilized one-step conversion by a combination of methylmagnesium bromide and copper catalyst in high yield.

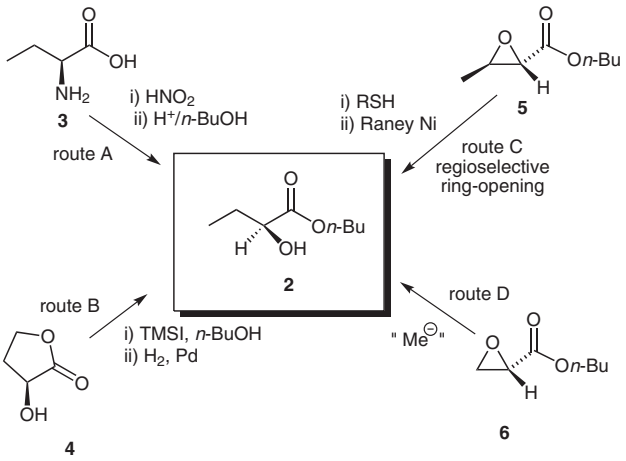
Key words: epoxides, regioselectivity, ring opening, Lewis acids, scandium

Recently we developed the highly potent and selective PPARα agonist, (*R*)-K-13675 (**1**).[1] This agent has shown promise in clinical trials as an excellent candidate for the treatment of hyperlipidemia by reducing plasma triglycerides and increasing HDL cholesterol. In this molecule, the (aryloxy)butanoic acid is the key pharmacophore for the potency and selectivity. Therefore, we regarded butyl (*S*)-2-hydroxybutanoate (**2**) as a useful and key synthon in the preparation of (*R*)-K-13675 (**1**) (Scheme 1).

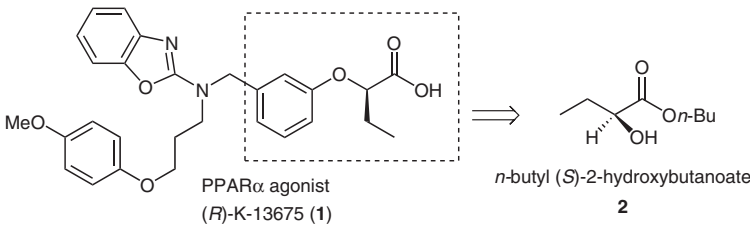
Our initial attempt prepared **2** from inexpensive (*S*)-2-aminobutanoic acid (**3**),[2a–d] but this was accompanied partial racemization (ca. 5% ee)[2e] (Scheme 2, route A). Next, we attempted to establish a practical method to provide **2** via (*S*)-2-hydroxybutyrolactone (**4**) in a multi-kilogram-production scale[3] (Scheme 2, route B). However, the multitude of reaction steps and high cost of goods in this method creates limitations when scaling up to commercial scale manufacture.

Although a number of synthetic methods[4–7] have been reported, most of them are noted as being technically difficult requiring the preparation of special chiral ligands or the tedious handling of enzymes and furthermore are cost prohibitive resulting in the production of waste products due to environmental regulations at pilot scale or larger.

In order to prevent potential racemization or avoid incomplete asymmetric induction, we decided to use chiral templates imbued with the requisite chiral center, such as easily available butyl (2*S*,3*R*)-epoxybutanoate (**5**) and butyl (*S*)-2,3-epoxypropanoate (**6**)[8] (Scheme 2, routes C and D).



Scheme 2 Four synthetic approaches for production of butyl (*S*)-2-hydroxybutanoate (**2**)



Scheme 1 Synthesis of (*R*)-K-13675 (**1**)

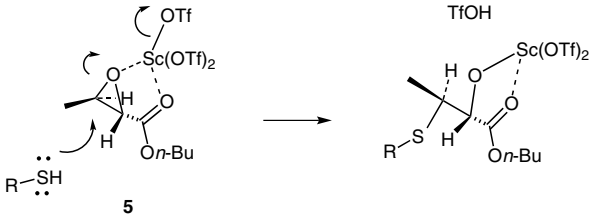
SYNTHESIS 2013, 45, 1319–1324
Advanced online publication: 03.04.2013
DOI: 10.1055/s-0032-1318507; Art ID: SS-2013-F0110-OP

In the first approach, we envisaged the synthesis of **2** via the regioselective ring opening of butyl (2*S*,3*R*)-epoxybutanoate (**5**) using Lewis acids. Our plan was as follows: The nucleophilic attack at the C3 position of **5** by arenethiols or alkanethiols and successive reductive cleavage of the resultant thioether to yield the desired **2**[9,10] (Scheme 2, route C). According to the literature,[11a–d] Riego and Aggarwal both demonstrated the regioselective thiolysis of the 2,3-epoxy ester or amide in moderate yields.[11a,c] These methodologies were based on the coordination of the Lewis acid to the carbonyl and epoxide oxygens and then preferential nucleophilic attack at the C3 position. The first reported method required two nucleophile equivalents and excess Lewis acid, $AlPO_4$-Al_2O_3. Also, these conditions result in a long reaction time because of the low reactivity of $AlPO_4$-Al_2O_3. The second reported method resulted in the regioselective ring opening of phenylglycidic amides by thiophenol in the presence of ytterbium(III) triflate at –78 °C. Regrettably, the substrates were restricted only to phenylglycidic amides that can be easily attacked by the sulfur nucleophiles at the more reactive benzylic position. The application of this reaction scheme to other substrates is uncertain. These issues prompted us to explore methods for 2,3-epoxy ester ring opening with Lewis acids with high regioselectivity and high yield under mild conditions.

A variety of Lewis acids were screened in the reaction of **5** with ethanethiol (Table 1). Starting with typical Lewis acids containing chloride atoms (entry 1–10), some reactions gave the chloride adduct **9** rather than the thioether **7a** or **8a** in dichloromethane (entries 1, 3, 5, and 9). This observation contrasts with previous reports[11e–h] that the use of chloro-substituted Lewis acids ($InCl_3$, $AlCl_3$, $SnCl_2$, $SnCl_4$, $ZnCl_2$, $MgCl_2$, and $CaCl_2$) successfully yielded the thiol adduct and not the chloro adduct. The reactions in tetrahydrofuran (entries 4, 6, 8, and 10) resulted in either complex mixtures or in no reaction product except in the case of zinc chloride[12] (entry 2). We postulate that the nucleophilic thiol[13] is associated with strong Lewis acids and the resulting chloride ion liberated subsequently attacked the C3 position of the epoxy ester. In order to avoid the formation of the chloride adduct, a Lewis acid composed of a less nucleophilic ligand such as triflate was selected for further investigation.

Stoichiometric amounts of scandium triflate[14] were found to be very effective and the regioselective ring opening reaction resulted to give **7a** in satisfactory yield (entry 13). The combinations with other thiols such as dodecanethiol,[15] benzyl mercaptan, and thiophenol also afforded the desired products **7b**–**d** in the same manner (entries 14–16). Thiophenol with stronger acidity compared to other alkanethiols gave a better yield, but it had the potential disadvantage that the successive desulfuration generates benzene as an unwanted byproduct.[16]

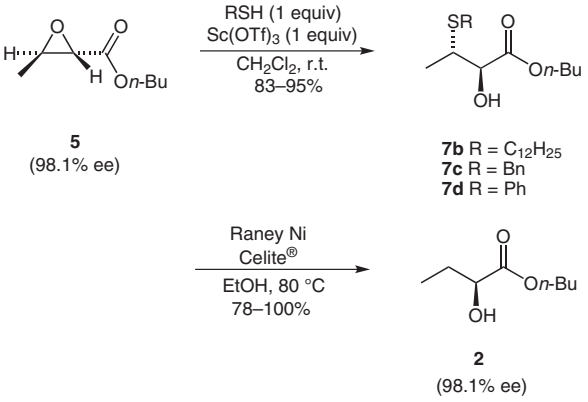
At first glance, scandium triflate can be expected to serve a catalytic function. However, these results suggested that the regioselective thiolysis at C3 of 2,3-epoxybutanoate proceeded by a transition state with the coordination of scandium triflate to both the epoxide and the ester carbonyl oxygen as shown in Scheme 3. When the bond is formed between scandium triflate and the hydroxy group, it was postulated that one equivalent of triflate was liberated from scandium triflate. This is the reason that scandium triflate should be thought of as a mediator, not as the recyclable catalyst as shown in Table 1 (entry 23). In the same way, due to the competitive coordination of Sc(III) with the oxygen of tetrahydrofuran, the thiolysis reaction was inhibited when tetrahydrofuran was used as the solvent and no product resulted (entry 17).



Scheme 3 Plausible transition state of **5** with scandium triflate

Next, we furthermore examined the use of other lanthanide triflates in the thiolysis reaction. Ytterbium(III) triflate gave **7d** in the same manner[11a] (entry 18). Although Sharpless reported a satisfactory result when using lanthanum(III) triflate with glycidic acids and secondary amides,[11b] lanthanum(III) triflate and titanium(IV) isopropoxide did not afford the desired product, **7d** (entry 19 and 20). One speculation is that the coordination of titanium(IV) isopropoxide with the ester might be different from that for acids or amides. In spite of further screening of additional Lewis acids, no other reagents were found to be suitable for the desired reaction.

Based upon the data generated in this series of experiments, we concluded that scandium triflate is the most effective Lewis acid for regioselective thiolysis of **5** under mild conditions. Thus the obtained butyl (2*R*,3*S*)-3-(arylalkylthio)-2-hydroxybutanoates **7b**–**d** were successively reduced by Raney nickel in the presence of Celite to afford the desired **2** with complete retention of optical purity[17] (Scheme 4).

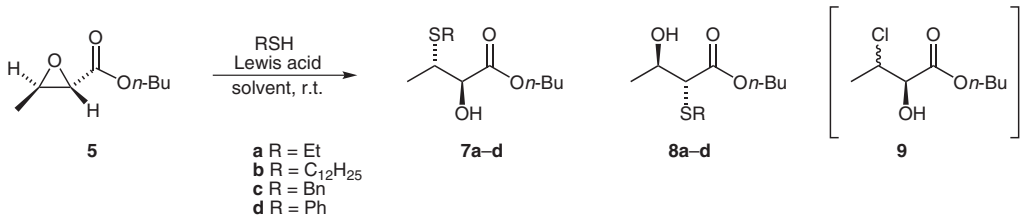


Scheme 4 Synthesis of butyl (*S*)-2-hydroxybutanoate (**2**)

A further study demonstrated that the scandium triflate can be easily recovered after workup, and that it can be recycled and reused without losing activity several times.[18] Thus this result would be environmentally favorable to minimize industrial waste. Herewith we successfully established a useful method for the production of **2**, except that it requires an equivalent amount of scandium triflate even though it is a relatively inexpensive reagent.

Considering the above issue, our attention was directed to catalytic reactions and one-step conversions. First, we reacted **6** with low-order lithium dimethylcuprate and succeeded in obtaining **2** with high regioselectivity in excellent yield (Table 2, entry 1). Next, we attempted to minimize the requisite amount of copper consumption by investigating several copper catalysts including, copper(I) iodide, copper(I) chloride, and copper(I) bromide in combination with a methylmagnesium bromide.[19] Of the cop-

Table 1 Ring-Opening Reaction of Epoxide **5** with Thiols and Lewis Acids

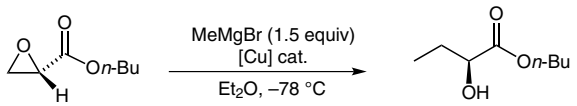


5 **a** R = Et, **b** R = $C_{12}H_{25}$, **c** R = Bn, **d** R = Ph — **7a–d** — **8a–d** — **9**

Entry	RSH (equiv)	Lewis acid (equiv)	Solvent	Time (h)	Yield (%) **7**/**8**/**9**	Recovery of **5**[b]
1	Et (1.2)	$ZnCl_2$ (1.2)	CH_2Cl_2	20	trace:0:98[a]	0
2	Et (1.2)	$ZnCl_2$ (1.2)	THF	20	0:0:46[a]	50
3	Et (1.2)	$ZrCl_4$ (1.2)	CH_2Cl_2	20	trace:0:93[a]	0
4	Et (1.2)	$ZrCl_4$ (1.2)	THF	20	complex mixture	–
5	Et (1.2)	$AlCl_3$ (1.2)	CH_2Cl_2	3	17:0:83[a]	0
6	Et (1.2)	$AlCl_3$ (1.2)	THF	20	complex mixture	–
7	Et (1.2)	Et_2AlCl (1.2)	CH_2Cl_2	3	complex mixture	–
8	Et (1.2)	Et_2AlCl (1.2)	THF	20	complex mixture	–
9	Et (1.2)	VCl_3 (1.2)	CH_2Cl_2	20	0:0:40[a]	54
10	Et (1.2)	VCl_3 (1.2)	THF	20	no reaction	–
11	Ph (1.0)	$Zn(OTf)_2$ (1.0)	CH_2Cl_2	24	no reaction	–
12	Ph (1.0)	$Al(OTf)_3$ (1.0)	CH_2Cl_2	12	complex mixture	–
13	Et (1.0)	$Sc(OTf)_3$ (1.0)	CH_2Cl_2	7	83:0:0[b]	0
14	$C_{12}H_{25}$ (1.0)	$Sc(OTf)_3$ (1.0)	CH_2Cl_2	10	85:0:0[b]	0
15	Bn (1.0)	$Sc(OTf)_3$ (1.0)	CH_2Cl_2	10	90:0:0[b]	0
16	Ph (1.0)	$Sc(OTf)_3$ (1.0)	CH_2Cl_2	10	95:0:0[b]	0
17	Ph (1.0)	$Sc(OTf)_3$ (1.0)	THF	24	no product	0
18	Ph (1.0)	$Yb(OTf)_3$ (1.0)	CH_2Cl_2	24	81:0:0[b]	0
19	Ph (1.0)	$La(OTf)_3$ (1.0)	CH_2Cl_2	24	no reaction	–
20	Ph (1.0)	$Ti(O\textit{i}\text{-}Pr)_4$ (1.0)	CH_2Cl_2	24	no reaction	–
21	Ph (1.0)	BF_3–Et_2O (1.0)	CH_2Cl_2	8	34:trace:0[b]	–
22	Ph (1.0)	Al_2O_3 (1.0)	CH_2Cl_2	24	trace:19:0[b]	0
23	Ph (1.0)	$Sc(OTf)_3$ (0.2)	CH_2Cl_2	24	26:trace:0	70

[a] Yield was determined by ^{1}H NMR analysis.
[b] Isolated yield.

Table 2 Reaction of Butyl (*S*)-2,3-Epoxypropanoate (**6**) with Methylmagnesium Bromide in the Presence of a Copper Catalyst



6 **2**

Entry	Cu source	Cu (equiv)	Time	Yield (%)
1	$LiCuMe_2$	2.0	15 min	99
2	CuI	0.075	3.5 h	83
3	CuI	0.15	15 min	99
4	CuCl	0.15	15 min	79
5	CuBr	0.15	15 min	76
6	CuI	0	2.5 h	–
7	CuI	0.75	15 min	41
8	CuI	1.5	2.5 h	–

per catalysts, copper(I) iodide was found to produce the highest yield as shown in Table 2 (entries 3–5). Interestingly, the chemical yield of **2** was not linear, doubling the amount of copper(I) iodide (entries 7 and 8) did not double the yield. The desired product **2** was obtained with high regioselectivity in quantitative yield when 0.15 equivalents of copper(I) iodide were used (entry 3).

By using a catalytic amount of copper(I) iodide and methylmagnesium bromide, we achieved one-step conversion of **6** into **2** in excellent yield without affecting the ester.[20]

In summary, we have established two methods for the synthesis of butyl (*S*)-2-hydroxybutanoate (**2**) as a key intermediate of (*R*)-K-13675 (**1**) starting from butyl (2*S*,3*R*)-epoxybutanoate (**5**) and butyl (*S*)-2,3-epoxypropanoate (**6**). The method from butyl (2*S*,3*R*)-epoxybutanoate (**5**) is a useful method of production, unfortunately the method requires large amounts of scandium triflate albeit that it is inexpensive and recyclable. The method from butyl (*S*)-2,3-epoxypropanoate uses a Grignard method with catalytic copper reagent and provides an efficient conversion to give **2** in excellent yield. Both results provide a useful demonstration of the nucleophilic opening of 2,3-substituted epoxy esters in a highly regioselective manner. Furthermore, we are, at present, refining a more practical and environmentally friendly production.

Commercially available reagents and solvents were used without further purification. All reactions were carried out under an argon or a nitrogen atmosphere unless otherwise noted. TLC analyses were carried out on silica gel 60 F_{254} plates (Merck). Optical rotations were measured on a JASCO P-2200 polarimeter with sodium (D line) lamp. IR spectra were recorded on a Thermo Nicolet 370 FT-IR (ATR) spectrophotometer. ^{1}H NMR spectra and ^{13}C NMR spectra were obtained on a JEOL JNM-AL 400 MHz spectrometer using $CDCl_3$ as solvent with tetramethylsilane as internal standard unless otherwise noted. Mass spectra were obtained on a JEOL GC-mate MS-BU20, JEOL JMS-T100GCV, Waters Xevo G2 QTof, AB SCIEX API4000 QTRAP apparatus. Elemental analyses (C, H, N) were performed by Yanaco MT-5. The enantiopurities were determined by HPLC analysis (Shimadzu LC-10Avp equipment, CHIRALPAK® AD column, Daicel Chemical Industries, Ltd.).

Butyl (2*R*,3*S*)-3-(Ethylthio)-2-hydroxybutanoate (7a); Typical Procedure

To a stirred soln of butyl (2*S*,3*R*)-2,3-epoxybutanoate (98.1% ee) (**5**, 100 mg, 0.632 mmol) and $Sc(OTf)_3$ (311 mg, 0.632 mmol) in CH_2Cl_2 (5 mL) was added EtSH (39.3 mg, 0.632 mmol) at r.t. The mixture was stirred for 7 h and then diluted with H_2O (20 mL) and extracted with $CHCl_3$ (3 × 20 mL). The combined organic layers were dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by column chromatography (silica gel, *n*-hexane–EtOAc, 5:1) to give **7a** (116 mg, 83%) as a colorless oil; $[\alpha]_D^{25}$ +10.0 (*c* 0.28, $CHCl_3$).

IR (ATR, neat): 3490, 2962, 2873, 1732, 1456, 1209, 1130 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.95 (t, *J* = 7.6 Hz, 3 H), 1.24 (d, *J* = 6.8 Hz, 3 H), 1.28 (t, *J* = 7.6 Hz, 3 H), 1.40 (sextet, *J* = 7.6 Hz, 2 H), 1.63–1.70 (m, 2 H), 2.57–2.71 (m, 2 H), 3.00 (br ds, 1 H), 3.20 (qd, *J* = 6.8, 2.8 Hz, 1 H), 4.17–4.27 (m, 2 H), 4.33 (d, *J* = 2.8 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.6, 14.7, 15.7, 19.0, 25.2, 30.5, 43.4, 65.7, 73.2, 172.8.

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{10}H_{20}O_3S$: 220.1133; found: 220.1141.

Anal. Calcd for $C_{10}H_{20}O_3S$: C, 54.51; H, 9.15. Found: C, 54.45; H, 9.18.

Butyl (2*R*,3*S*)-3-(Dodecylthio)-2-hydroxybutanoate (7b)

Following the typical procedure using **5** (50 mg, 0.316 mmol) and $Sc(OTf)_3$ (156 mg, 0.316 mmol) in CH_2Cl_2 (4 mL) and dodecane-1-thiol (64.0 mg, 0.316 mmol); time: 10 h. Work up and purification by column chromatography (silica gel, *n*-hexane–EtOAc, 5:1) gave **7b** (97.0 mg, 85%) as a colorless oil; $[\alpha]_D^{25}$ +9.34 (*c* 0.77, $CHCl_3$).

IR (ATR, neat): 3471, 2924, 2854, 1733, 1458, 1210, 1129 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.88 (t, *J* = 6.9 Hz, 3 H), 0.95 (t, *J* = 7.6 Hz, 3 H), 1.23–1.45 (m, 23 H), 1.59 (quintet, *J* = 7.6 Hz, 2 H), 1.67 (quintet, *J* = 6.9 Hz, 2 H), 2.54–2.66 (m, 2 H), 2.99 (br ds, 1 H), 3.17 (dq, *J* = 6.9, 3.2 Hz, 1 H), 4.16–4.27 (m, 2 H), 4.32 (d, *J* = 2.8 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.6, 14.0, 15.7, 19.0, 22.6, 28.9, 29.2, 29.3, 29.5, 29.5, 29.6, 29.6, 29.6, 30.5, 31.3, 31.9, 43.8, 65.6, 73.2, 172.8.

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{20}H_{40}O_3S$: 360.2698; found: 360.2684.

Anal. Calcd for $C_{20}H_{40}O_3S$: C, 66.62; H, 11.18; S, 8.89. Found: C, 66.66; H, 11.35; S, 8.83;

Butyl (2*R*,3*S*)-3-(Benzylthio)-2-hydroxybutanoate (7c)

Following the typical procedure using **5** (300 mg, 1.90 mmol) and $Sc(OTf)_3$ (933 mg, 1.90 mmol) in CH_2Cl_2 (10 mL) and BnSH (234 mg, 1.90 mmol); time: 10 h. Workup used H_2O (10 mL) and $CHCl_3$ (2 × 10 mL). Purification by column chromatography (silica gel, *n*-hexane–EtOAc, 5:1) gave **7c** (484 mg, 90%) as a colorless oil; $[\alpha]_D^{20}$ –9.4 (*c* 1.5, $CHCl_3$).

IR (ATR, neat): 3470, 2961, 1732, 1454, 1209, 1127, 700 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.94 (t, *J* = 7.3 Hz, 3 H), 1.18 (d, *J* = 7.3 Hz, 3 H), 1.36 (sextet, *J* = 7.3 Hz, 2 H), 1.61–1.67 (m, 2 H), 2.95 (br ds, 1 H), 3.09 (dq, *J* = 2.8, 7.3 Hz, 1 H), 3.79 (d, *J* = 13.5 Hz, 1 H), 3.85 (d, *J* = 13.5 Hz, 1 H), 4.14–4.24 (m, 2 H), 4.30 (d, *J* = 2.7 Hz, 1 H), 7.22–7.36 (m, 5 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.5, 15.4, 19.0, 30.4, 35.7, 42.9, 65.6, 73.1, 127.0 (2 ×), 128.4, 128.8 (2 ×), 137.9, 172.8.

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{15}H_{22}O_3S$: 282.1290; found: 282.1291;

Butyl (2*R*,3*S*)-2-Hydroxy-3-(phenylthio)butanoate (7d)
Following the typical procedure using **5** (100 mg, 0.632 mmol) and $Sc(OTf)_3$ (311 mg, 0.632 mmol) in CH_2Cl_2 (5 mL) and PhSH (69.6 mg, 0.632 mmol); time 10 h. Workup and purification by column chromatography (silica gel, *n*-hexane–EtOAc, 5:1) gave **7d** (117 mg, 95%) as a colorless oil; $[\alpha]_D^{25}$ +42.8 (*c* 0.95, $CHCl_3$).

IR (ATR, neat): 3484, 2961, 2873, 1732, 1439, 1211, 1129 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 0.94 (t, *J* = 7.6 Hz, 3 H), 1.27 (d, *J* = 6.8 Hz, 3 H), 1.38 (sextet, *J* = 7.6 Hz, 2 H), 1.65 (quintet, *J* = 7.6 Hz, 2 H), 2.98 (d, *J* = 4.6 Hz, 1 H), 3.65 (dq, *J* = 6.8, 2.8 Hz, 1 H), 4.14–4.25 (m, 2 H), 4.28 (br ds, 1 H), 7.24–7.34 (m, 3 H), 7.48 (dt, *J* = 1.4, 6.6 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.6, 14.8, 19.0, 30.5, 47.0, 65.9, 72.3, 127.4, 129.1 (2 ×), 132.2 (2 ×), 134.1, 172.8.

MS (EI): *m*/*z* 268 $[M]^+$.

Anal. Calcd for $C_{14}H_{20}O_3S$: C, 62.66; H, 7.51; S, 11.95. Found: C, 62.66; H, 7.61; S, 11.70.

Butyl (*S*)-2-Hydroxybutanoate (2)
To a stirred soln of butyl (2*R*,3*S*)-2-hydroxy-3-(phenylthio)butanoate (**7d**, 60.0 mg, 0.224 mmol) in EtOH (2 mL) was added Celite (240 mg) and a suspension of Raney Ni (360 mg) in EtOH (3 mL) at r.t. The mixture was stirred at 80 °C for 10 h and then filtered through a pad of Celite. The filtrate was concentrated in vacuo, diluted with H_2O (20 mL) and extracted with Et_2O (3 × 20 mL). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by column chromatography (silica gel, CH_2Cl_2) to give **2** (35.8 mg, 100%) as a colorless oil; 98.1% ee.

Butyl (2*R*,3*S*)-3-(dodecylthio)-2-hydroxybutanoate (**7b**, 400 mg, 1.11 mmol) or butyl (2*R*,3*S*)-3-(benzylthio)-2-hydroxybutanoate (**7c**, 300 mg, 1.06 mmol) were used instead of **7d** in this procedure giving **2** (139 mg, 78% from **7b**; 159 mg, 94%, from **7c**).

Optical purity of **2** was determined by HPLC as its 4-nitrobenzoate according to the reported method.[3b]

HPLC (Daicel Chiralpak AD, column temperature; 35 °C; hexane–EtOH, 60:40; flow rate; 1.0 mL/min): t_R = 4.85 (*R*-isomer), 6.55 min (*S*-isomer).

$[\alpha]_D^{20}$ –3.53 (*c* 1.01, $CHCl_3$) [Lit.[21] $[\alpha]_D^{25}$ –3.4 (*c* 1.0, $CHCl_3$)].

IR (ATR, neat): 3468, 2962, 1731, 1463, 1244, 1206, 1132 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 0.95 (t, *J* = 7.6 Hz, 3 H), 0.97 (t, *J* = 7.6 Hz, 3 H), 1.39 (qt, *J* = 7.6, 7.3 Hz, 2 H), 1.61–1.74 (m, 3 H), 1.79–1.89 (m, 1 H), 2.81 (d, *J* = 5.6 Hz, 1 H), 4.13–4.25 (m, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 9.0, 13.7, 19.1, 27.6, 30.6, 65.2, 71.5, 175.4.

HRMS (FAB): *m*/*z* $[M + H]^+$ calcd for $C_8H_{17}O_3$: 161.1178; found: 161.1181.

Anal. Calcd for $C_8H_{16}O_3$: C, 59.97; H, 10.07. Found: C, 59.70; H, 9.80.

Butyl (2*R*,3*R*)-3-Hydroxy-2-(phenylthio)butanoate (8d)
To a stirred soln of butyl (2*S*,3*R*)-2,3-epoxybutanoate (**5**, 100 mg, 0.632 mmol) and alumina (64.4 mg, 0.632 mmol) in CH_2Cl_2 (5 mL) was added PhSH (69.6 mg, 0.632 mmol) at r.t. The mixture was stirred for 24 h and then diluted with H_2O (20 mL) and extracted with $CHCl_3$ (3 × 20 mL). The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by column chromatography (silica gel, *n*-hexane–EtOAc, 5:1) to give **8d** (32.2 mg, 19%) as a colorless oil.

$[\alpha]_D^{20}$ +147.0 (*c* 1.1, $CHCl_3$).

IR (ATR, neat): 3466, 2961, 1729, 1160, 691 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 0.90 (t, *J* = 7.3 Hz, 3 H), 1.32 (sextet, *J* = 7.3 Hz, 2 H), 1.40 (d, *J* = 6.4 Hz, 3 H), 1.52–1.60 (m, 2 H), 2.67 (br ds, 1 H), 3.59 (d, *J* = 7.3 Hz, 1 H), 4.09–4.15 (m, 3 H), 7.29–7.34 (m, 3 H), 7.46–7.50 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.5, 18.8, 20.5, 30.3, 57.5, 65.0, 67.7, 127.9 (2 ×), 128.9 (2 ×), 132.6, 133.0, 171.6.

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{14}H_{20}O_3S$: 268.1133; found: 268.1133.

Chloride Adduct 9 (Mixture of Diastereomers) (Table 1, Entries 1–3, 5, and 9)
IR (ATR, neat): 3460, 2962, 1737, 1219 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 0.95 (t, *J* = 7.6 Hz, 2.6 H), 1.24 (d, *J* = 7.3 Hz, 0.4 H), 1.28 (t, *J* = 7.3 Hz, 0.4 H), 1.40 (sextet, *J* = 7.3 Hz, 2 H), 1.54 (d, *J* = 6.8 Hz, 2.6 H), 1.64–1.71 (m, 2 H), 2.59–2.69 (m, 0.3 H), 3.13–3.23 (m, 0.7 H), 4.18–4.35 (m, 4 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.5, 14.6, 15.6, 19.0, 19.6, 25.2, 30.4, 30.5, 43.4, 58.5, 65.6, 66.1, 73.2, 74.7, 171.3, 172.8.

HRMS (EI): *m*/*z* $[M + H]^+$ calcd for $C_8H_{16}ClO_3$: 195.0788; found: 195.0777.

Butyl (2*R*,3*S*)-3-(Benzylthio)-2-hydroxybutanoate (7c); Scaled-Up Synthesis
To a stirred soln of butyl (2*S*,3*R*)-2,3-epoxybutanoate (98.1% ee) (**5**, 80.0 g, 506 mmol) and $Sc(OTf)_3$ (249 g, 506 mmol) in CH_2Cl_2 (1 L) was added BnSH (62.8 g, 506 mmoL) at r.t. The mixture was stirred for 10 h. The mixture was diluted with H_2O (1 L) and extracted with $CHCl_3$ (2 × 500 mL). The combined organic layers were dried (Na_2SO_4, 100 g) and concentrated in vacuo. The residue was purified by column chromatography (silica gel, *n*-hexane–EtOAc, 5:1) to give **7c** (105 g, 74%) as a colorless oil. Spectral data was identical with butyl (2*R*,3*S*)-3-(benzylthio)-2-hydroxybutanoate (**7c**).

Butyl (*S*)-2-Hydroxybutanoate (2); Scaled-Up Synthesis
To a stirred soln of butyl (2*R*,3*S*)-3-(benzylthio)-2-hydroxybutanoate (**7c**, 5.00 g, 17.7 mmol) in EtOH (150 mL) was added Celite (20.0 g) and a suspension of Raney Ni (30 g) in EtOH (30 mL) at r.t. The mixture was stirred at 80 °C for 10 h and then filtered through a pad of Celite (20 g). The filtrate was concentrated in vacuo. The residue was purified by column chromatography (silica gel, CH_2Cl_2) to give **2** (2.98 g, 100%) as a colorless oil; 98.1% ee. Spectral data was identical with butyl (*S*)-2-hydroxybutanoate (**2**).

Demonstration for the Thiolysis Reaction of 5 with Recycled Scandium Triflate
After the reaction and workup, the consumed $Sc(OTf)_3$ could be recovered quantitatively as follows: The aqueous layer was concentrated and then dried in vacuo at 140 °C for 2 h.

To a stirred soln of butyl (2*S*,3*R*)-2,3-epoxybutanoate (**5**, 500 mg, 3.16 mmol) and thus recovered $Sc(OTf)_3$ (1.56 g, 3.16 mmol) in CH_2Cl_2 (30 mL) was added PhSH (348 mg, 3.16 mmol) at r.t. The mixture was stirred for 4 h and then diluted with H_2O (30 mL) and extracted with $CHCl_3$ (3 × 20 mL). The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by column chromatography (silica gel, *n*-hexane–EtOAc, 5:1) to give **7d** (807 mg, 95%) as a colorless oil; 98.1% ee.

Butyl (*S*)-2-Hydroxybutanoate (2)
To a stirred soln of CuI (594 mg, 3.12 mmol) in anhyd Et_2O (20 mL) was added 0.52 M MeMgBr in THF (60.2 mL, 31.3 mmol) at –15 °C and the mixture was stirred for 20 min under an argon atmosphere. To the mixture was added a soln of butyl (*S*)-2,3-epoxypropanoate (97.0% ee) (**6**, 3.00 g, 20.8 mmol) in Et_2O (8 mL) at –78 °C. The mixture was stirred at this temperature for 20 min and then diluted with sat. aq NH_4Cl (50 mL) and extracted with Et_2O (2 × 50 mL). The combined organic layers were washed with brine (40 mL), dried (Na_2SO_4), and concentrated in vacuo. The residue was

purified by column chromatography (silica gel, *n*-hexane–EtOAc, 5:1) to give **2** (3.37 g, 99%) as a colorless oil; 97.0% ee.

Acknowledgment

We thank Dr. S. Tanabe, Director of Tokyo New Drug Research Laboratories, Kowa Co., Ltd, for his support and also Dr. Kevin Swiss for his help in preparing the manuscript.

References

(1) (a) Yamazaki, Y.; Abe, K.; Toma, T.; Nishikawa, M.; Ozawa, H.; Okuda, A.; Araki, T.; Oda, S.; Inoue, K.; Shibuya, K.; Staels, B.; Fruchart, J. C. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 4689. (b) Kitajima, K.; Miura, S.; Matsuo, Y.; Uehara, Y.; Saku, K. *Atherosclerosis* **2009**, *203*, 75.

(2) (a) Jares-Erijiman, E. A.; Ingrum, A. L.; Carney, J. R.; Rinehart, K. L.; Sakai, R. *J. Org. Chem.* **1993**, *58*, 4805. This mechanism presumably involves anchimeric assistance of the carboxy group in the decomposition of an intermediate diazonium ion, leading to an α-hydroxy acid with retention of configuration. See the following reference: (b) Brewster, F.; Hiron, F.; Hughes, E. D.; Ingold, C. K.; Rao, P. A. D. S. *Nature (London)* **1950**, *166*, 179. (c) Koga, K.; Taniguchi, M.; Yamada, S. *Tetrahedron Lett.* **1971**, *12*, 263. (d) Gringore, O. H.; Rouessac, F. P. *Org. Synth.* **1985**, *63*, 121. The reaction of butyl (*S*)-2-bromobutanoate obtained via diazotization of (*S*)-2-aminobutanoic acid with phenol accompanied with racemization (~81% ee): (e) Sugita, M. JP 2011093869, **2011**.

(3) (a) Yamazaki, Y.; Araki, T.; Koura, M.; Shibuya, K. *Synthesis* **2008**, 1017. (b) Yamazaki, Y.; Araki, T.; Koura, M.; Shibuya, K. *Tetrahedron* **2008**, *64*, 8155.

(4) Davis, F. A.; Chen, B. C. *Chem. Rev.* **1992**, *92*, 919.

(5) (a) Kirschbaum, B.; Fell, R. WO 03005010, **2003**. (b) Senba, N. JP 2000217590, **2000**.

(6) (a) Nakamura, K.; Inoue, K.; Ushio, K.; Oka, S.; Ohno, A. *J. Org. Chem.* **1988**, *53*, 2589. (b) Nakamura, K.; Yamanaka, R.; Matsuda, T.; Harada, T. *Tetrahedron: Asymmetry* **2003**, *14*, 2659.

(7) Burk, M. J.; Kalberg, C. S.; Pizzano, A. *J. Am. Chem. Soc.* **1998**, *120*, 4345.

(8) Both compounds are commercially available from Osaka Organic Chemical Industry Ltd.; they can be easily prepared from the corresponding racemic epoxypropanoate and *trans*-2,3-epoxybutanoate by the treatment with protease: Akaishi, R.; Tsutsumi, A.; Araki, S.; Hirose, Y.; Ohno, A. JP 2000166592, **2000**.

(9) (a) Behrens, C. H.; Sharpless, K. B. *J. Org. Chem.* **1985**, *50*, 5696. (b) Chong, J. M.; Sharpless, K. B. *Tetrahedron Lett.* **1985**, *26*, 4683. (c) Amantini, D.; Fringuelli, F.; Pizzo, F.; Vaccaro, L. *J. Org. Chem.* **2001**, *66*, 4463. (d) Gleason, J. G.; Hall, R. F.; Perchonock, C. D.; Erhard, K. F.; Frazee, J. S.; Ku, T. W.; Kondrad, K.; McCarthy, M. E.; Mong, S. *J. Med. Chem.* **1987**, *30*, 959.

(10) Refer to the following articles: (a) Koura, M.; Yamazaki, Y.; Shibuya, K. WO 2007013555, **2007**. (b) Compagnone, R. S.; Rapoport, H. *J. Org. Chem.* **1986**, *51*, 1713. (c) Romanelli, M. N.; Bartolini, A.; Bertucci, C.; Dei, S.; Ghelardini, C.; Giovannini, M. G.; Gualtieri, F.; Pepeu, G.; Scapecchi, S.; Teodori, E. *Chirality* **1996**, *8*, 225.

(11) (a) Riego, J.; Costa, A.; Saa, J. M. *Chem. Lett.* **1986**, 1565. (b) Chong, J. M.; Sharpless, K. B. *J. Org. Chem.* **1985**, *50*, 1560. (c) Aggarwal, V. K.; Charmant, J. P. H.; Fuentes, D.; Harvey, J. N.; Hynd, G.; Ohara, D.; Picoul, W.; Robiette, R.; Smith, C.; Vasse, J. L.; Winn, C. L. *J. Am. Chem. Soc.* **2006**, *128*, 2105. (d) Flisak, J. R.; Gombatz, K. J.; Holmes, M. M.; Jarmas, A. A.; Lantos, I.; Mendelson, W. L.; Novack, V. J.; Remich, J. J.; Snyder, L. *J. Org. Chem.* **1993**, *58*, 6247. (e) Puschmann, I.; Erker, T. *Heterocycles* **1995**, *41*, 709. (f) Hashiyama, T.; Inoue, H.; Takeda, M.; Murata, S.; Nagao, T. *Chem. Pharm. Bull.* **1985**, *33*, 2348. (g) Hashiyama, T.; Inoue, H.; Konda, M.; Takeda, M. *J. Chem. Soc., Perkin Trans. 1* **1984**, 1725. (h) Ranu, B. C.; Mandal, T. *Can. J. Chem.* **2006**, *84*, 762.

(12) We postulated that THF can be cleaved under these conditions. Whereas $ZnCl_2$ is too weak a Lewis acid to open the THF ring.

(13) March, J. *Advanced Organic Chemistry*, 4th ed.; Wiley-VCH: Weinheim, **1992**, 350.

(14) $Sc(OTf)_3$ in bulk for multi-kg scale is commercially available from Shanghai Synchem Technology and Sinofluoro Scientific Co., Ltd. (China).

(15) Node, M.; Kumar, K.; Nishide, K.; Ohsugi, S.; Miyamoto, T. *Tetrahedron Lett.* **2001**, *42*, 9207.

(16) Benzene in pharmaceutical products must be controlled to less than 2 ppm as organic volatile impurities under the ICH Q3C guidelines.

(17) The optical purity of **2** was determined by converting it into its 4-nitrobenzoate and then examining it by HPLC analysis, see also ref. 3b.

(18) Refer to the following articles: (a) Kobayashi, S. *Chem. Lett.* **1991**, 2187. (b) Barrett, A. G. M.; Braddock, D. C. *Chem. Commun.* **1997**, 351.

(19) (a) Ashby, E. C.; Smith, R. S.; Goel, A. B. *J. Org. Chem.* **1981**, *46*, 5133. (b) Larcheveque, M.; Perit, Y. *Tetrahedron Lett.* **1987**, *28*, 1993.

(20) (a) Perrone, M. G.; Santandrea, E.; Nunno, L. D.; Scilimati, A.; Tortorella, V.; Capitelli, F.; Bertolasi, V. *Tetrahedron: Asymmetry* **2005**, *16*, 783. (b) Diaz, M.; Ibarzo, J.; Ortuno, R. M. *Tetrahedron: Asymmetry* **1994**, *5*, 37. (c) Diaz, M.; Ortuno, R. M. *Tetrahedron: Asymmetry* **1995**, *6*, 1845.

(21) Parida, S.; Dordick, J. S. *J. Am. Chem. Soc.* **1991**, *113*, 2253.

