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An Efficient Synthesis of (*R*)-2-Butyl-3-hydroxypropionic Acid

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Abstract:

An efficient synthesis of (*R*)-2-butyl-3-hydroxypropionic acid (1) via a classical resolution of (±)-2-butyl-3-hydroxypropionic acid (7) with (*R*)-α-methylbenzylamine is described. (±)-2-Butyl-3-hydroxypropionic acid (7) was readily available from diethyl butylmalonate (2) in two steps. Results on the enantioselective enzymatic hydrolysis of 2 with pig liver esterase and α-chymotrypsin towards 1 are also described.

Introduction

(*R*)-2-Butyl-3-hydroxypropionic acid (**1**) is a key starting material in the synthesis of LBM415 (Figure 1).[1] Our goal was to develop an efficient large scale synthesis of **1**. Herein we describe the development of an efficient synthesis of **1** by the resolution of (±)-2-butyl-3-hydroxypropionic acid (**7**) with (*R*)-α-methylbenzylamine. Results on the enantioselective enzymatic hydrolysis approach are also described.

Results and Discussion

(*R*)-2-Butyl-3-hydroxypropionic acid (**1**) could be synthesized either by an enantioselective synthesis or by the resolution of racemic material. One must contrast the pros and cons of classical resolution vs an enantioselective synthesis. A resolution is attractive if the racemic material is available readily. We focused our attention on the resolution approach for **1** but decided to investigate both enantioselective enzymatic hydrolysis and classical resolution approaches.

Enantioselective Enzymatic Hydrolysis Approach. Enzymatic catalysis is an attractive methodology in the synthesis of a variety of molecules with high enantiopurity. The lipase promoted asymmetric esterification of 3-butyloxetan-2-one with benzyl alcohol was reported to afford a 32% yield of the (*S*)-enantiomer of benzyl 3-hydroxy-2-butylpropionate with only 36% ee.[2] A patent reported the oxidation of prochiral 2-butyl-1,3-propanediol by Corynebacterium oxydans to afford chiral 2-butyl-3-hydroxypropionic acid in 65% yield and with 97% ee.[3] The absolute configuration of the product was not defined. Since the ee was low for the first

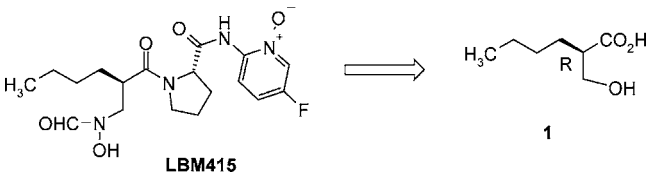

Figure 1.

method and the second method was patented, we sought another enzymatic route. We reasoned that (*R*)-2-butyl-3-hydroxypropionic acid (**1**) can be prepared by an enzymatic desymmetrization of prochiral dialkyl malonates to the chiral monoesters, which can than be converted to either desired enantiomer of 2-butyl-3-hydroxypropionic acid. Commercially available diethyl butylmalonate (**2**) was considered as a suitable substrate to study the enzymatic desymmetrization for the synthesis of **1**. A literature search revealed that pig liver esterase (PLE) has been widely used in the enantioselective hydrolysis of prochiral malonate diesters to give enantiomerically enriched monoester acid. Excellent enantioselectivity is obtained with dialkyl malonates with disubstituted α-carbon, with one of the substituent being an aromatic group.[14b,4,5] Replacement of the aryl group with an alkyl chain such as butyl led to poor ee but gave good ee with the trimethylsilylmethyl chain.[4,6] The substrate with a mono α-alkyl chain that gave excellent enantiopurity was with the *tert*-butyl chain.[7] No results have been reported with diethyl butylmalonate (**2**).

Enantioselective enzymatic hydrolysis of diethyl butylmalonate (**2**) with pig liver esterase (PLE) in phosphate buffer afforded the 2-butyl-propanedioic acid monoethyl ester (**4**) in 95% yield with 54% ee (Scheme 1). Based on the proposed models for PLE hydrolysis,[4] we expected to obtain the monoester enriched with the (*R*)-enantiomer. The (*R*)-configuration of the major enantiomer was further confirmed by reducing the ester to the corresponding (*S*)-2-butyl-3-hydroxypropionic acid (***S*-1**) and comparing it with a known sample. Use of α-chymotrypsin afforded 2-butyl-propanedioic acid monoethyl ester (**4**) in 80% yield with 84% ee. Again, the major enantiomer possessed the *R*-configuration. How-

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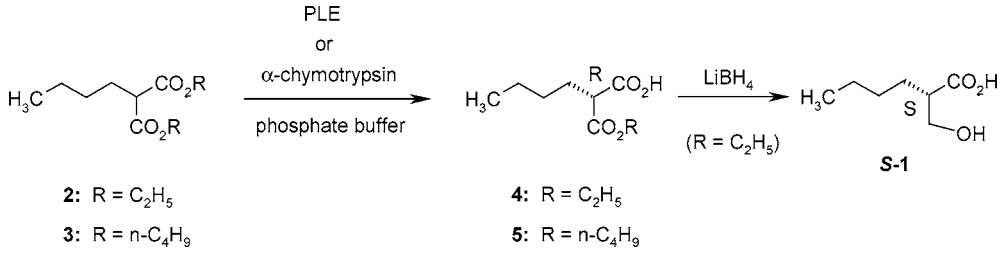
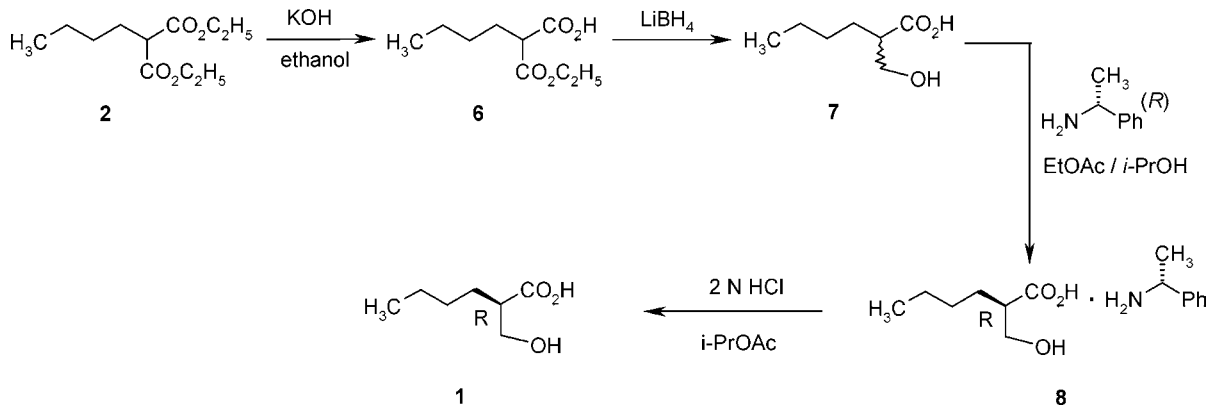
Scheme 1



Scheme 2



ever, the hydrolysis with α-chymotrypsin was much slower compared to PLE and an excess of the enzyme was necessary, making it impractical for large scale preparation. Hydrolysis of the corresponding dibutyl ester (**3**) with PLE afforded only 50% conversion after 60 h, and the enantiopurity of the resulting 2-butyl-propanedioic acid monobutyl ester (**5**) was poor (ee 30%). Hydrolysis of **3** with α-chymotrypsin afforded only a 20% conversion after 3 days with 78% ee of the product. Thus, dibutyl ester (**3**) was a poorer substrate compared to the diethyl ester **2**. These results on enantioselective enzymatic hydrolysis were interesting but not practical for large scale preparation and prompted us to investigate the classical resolution approach for **1**.

Classical Resolution Approach. For the classical resolution approach, we needed to develop an efficient preparation of (±)-2-butyl-3-hydroxypropionic acid (**7**). A one-step process for the preparation of (±)-2-butyl-3-hydroxypropionic acid (**7**) had been reported[8] by a reaction of the dianion of hexanoic acid with formaldehyde gas, generated by heating paraformaldehyde at 180−200 °C. While this process was straightforward, it was not deemed suitable for large scale preparation. We investigated alternatives using diethyl butylmalonate (**2**). The first route utilized a selective reduction of **2** to ethyl 2-butyl-3-hydroxypropionate using a known method.[9] However, this reaction did not go to completion with 5.0 equiv of LiAl(O-*t*-Bu)$_3$H over 24 h. In another approach, **2** was treated with paraformaldehyde in the presence of catalytic amounts of sodium ethoxide (0.1 equiv)[10] in ethanol at 60 °C for 30 min to afford diethyl hydroxyl-methyl(butyl)malonate. Basic hydrolysis[11] of this product, however, led to dehydroxymethylation and afforded butylmalonic acid instead of **7**. The chosen approach (Scheme 2) involved the selective hydrolysis[12] of **2** with 1.0 equiv of KOH to afford the monoester **6**, which was then reduced with $NaBH_4$ in THF−water.[13] However, this reduction gave >10% of the diacid, as confirmed by HPLC. Reduction with $LiBH_4$ in the presence of water was not clean.[14] We found that the reduction of **6** was successful using 3.0 equiv of $LiBH_4$ in THF, without preforming the salt of the acid. It afforded (±)-2-butyl-3-hydroxypropionic acid (**7**) in quantitative yield. Thus, (±)-2-butyl-3-hydroxypropionic acid (**7**) can be easily prepared in two steps from commercially available diethyl butylmalonate (**2**).

Classical resolution of **7** was investigated with several resolving agents, e.g., (*R*)-(−)-2-amino-1-butanol, (1*R*,2*S*)-(+)-*cis*-1-amino-2-indanol, (−)-strychnine, and (*R*)-α-methylbenzylamine. Cheap and readily available (*R*)-α-methyl-

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Table 1. **Resolution of 7 (1.0 g) with (*R*)-α-methylbenzylamine (1.0 equiv)**

entry	solvent (ratio)	solvent volume (mL/g of **7**)	enantiopurity of **8** (*R*)/(*S*)	isolated yield (%)
1	CH_3CN/CH_3OH (75:25)	13.6	85.6:14.4	31.0
2	$EtOAc/CH_3OH$ (70:30)	10.0	96.0:4.0	26.7
3	EtOAc/acetone (70:30)	10.0	54.7:45.3	73.3
4	$EtOAc/C_2H_5OH$ (70:30)	10.0	89.3:10.7	36.4
5	EtOAc/2-PrOH (50:50)	12.0	94.1:5.9	41.7
	Recrystallization	**10.0**	**99.3:0.7**	**36.5**

benzylamine gave promising results. Several solvents were investigated (Table 1). We found that a mixture of ethyl acetate and methanol gave the diastereomeric salt **8** with high enantiopurity but with poor yield (entry 2). A mixture of ethyl acetate and 2-propanol was the best solvent mixture for our purposes (entry 5). It afforded the diastereomeric salt **8** in 41.7% (83.4% of theory) yield and with good enantiomeric purity. A further recrystallization from the same solvent mixture afforded the diastereomeric salt **8** with the desired enantiopurity (*R*/*S* = 99.3:0.7) in overall 36.5% yield (73.0% of theory).

The diastereomeric salt **8** was converted to (*R*)-2-butyl-3-hydroxypropionic acid (**1**) in 98% yield by treatment with 2 N HCl followed by an extractive workup with isopropyl acetate. The (*R*)-configuration of **1** was established by converting it to a key intermediate[1a] in the synthesis of LBM415 with a known (*R*)-configuration.

Similarly, resolution of **7** with (*S*)-α-methylbenzylamine afforded the (*S*)-2-butyl-3-hydroxypropionic acid (*S*)-α-methylbenzylammonium salt in 33.2% (66.4% of theory) with excellent enantiopurity (*R*/*S* = 0.4:99.6) that was converted to (*S*)-2-butyl-3-hydroxypropionic acid in 98% yield.

Experimental Section

Melting points were determined on a Buchi 535 melting point apparatus. ^{1}H and ^{13}C NMR spectra were recorded on a Brucker 300 instrument. The enantiomeric purity of diastereomeric salts **8** was determined, after generating the free acid **1** from the salt, by chiral HPLC on a Rainin Dynamax system using a Chiralpak AD-H column (4.6 mm × 250 mm) and a mixture of hexane−isopropanol (95.0:5.0) as the mobile phase (isocratic at a flow rate of 1.0 mL/min and UV detector at 220 nm). The retention times of *R*-(**1**) and *S*-(**1**) enantiomers were 15.5 and 13.6 min, respectively. The enantiopurity of 2-butylpropanedioic acid monoethyl ester (**4**) was determined by chiral HPLC on a Rainin Dynamax system using a Chiralpak AD-H column (4.6 mm × 250 mm) and a mixture of hexane−isopropanol (95.0:5.0) as the mobile phase (isocratic at a flow rate of 1.0 mL/min and UV detector at 220 nm). The retention times of *R* and *S* enantiomers were 7.2 and 7.6 min, respectively. The enantiopurity of 2-butylpropanedioic acid monobutyl ester (**5**) was also determined by the same chiral HPLC method. The retention times of *R* and *S* enantiomers were 6.7 and 7.3 min, respectively. The phosphate buffer was prepared by dissolving Na_2HPO_4 (7.12 g) in water (1.0 L) and adjusting the pH to 7.12 (from 9.2) with concd H_3PO_4.

Enantioselective Enzymatic Hydrolysis of Diethyl Butylmalonate (2) with PLE. To a suspension of diethyl butylmalonate (**2**, 21.7 g, 100.0 mmol) in 50 mM phosphate buffer (pH 7.1, 100.0 mL) was added pig liver esterase (0.2 g), and the mixture was stirred at an internal temperature at 22−24 °C. The pH of the reaction mixture was maintained at 6.8−7.2 by slow addition of 2 N sodium hydroxide (total 48.0 mL) over a period of 6 h while maintaining the same internal temperature. The mixture was cooled to an internal temperature of 0−5 °C, and 2 N HCl (48.0 mL) was added to adjust the pH to 3.0 while maintaining the same internal temperature. The mixture was extracted with ethyl acetate (200.0 mL), and the organic layer was washed with brine and concentrated in vacuo to afford 2-butylpropanedioic acid monoethyl ester (**4**, 18.0 g, 95%); oil; (*R*)/(*S*) = 77:23; ^{1}H NMR ($CDCl_3$, δ) 0.9 (t, 3H), 1.2−1.45 (m, 7H), 1.8−2.0 (m, 2H), 3.38 (t, 1H), 4.23 (q, 2H, *J* = 7.1 Hz), 11.37 (br, 1H); ^{13}C NMR ($CDCl_3$, δ) 13.79, 14.06, 22.33, 28.56, 29.42, 51.82, 61.70, 169.44, 175.66; MS (ESI) 187.15 (M − H).

Enantioselective Enzymatic Hydrolysis of Diethyl Butylmalonate (2) with α-Chymotrypsin. To a suspension of diethyl butylmalonate (**2**, 2.0 g, 9.25 mmol) in 50 mM phosphate buffer (pH 7.1, 110.0 mL) was added α-chymotrypsin (2.4 g), and the mixture was stirred at an internal temperature of 22−24 °C. The pH of the reaction mixture was maintained at 6.8−7.2 by the addition of 2 N sodium hydroxide (total 4.0 mL) over a period of 20 h while maintaining the same internal temperature. The mixture was diluted with 5% HCl (100.0 mL) and ethyl acetate (200.0 mL). The organic layer was separated, the aqueous layer was extracted with dichloromethane (2 × 100.0 mL), and the combined organic layers were concentrated in vacuo to afford 2-butylpropanedioic acid monoethyl ester (**4**, 1.4 g, 80%); oil; (*R*)/(*S*) = 92.0:8.0.

Preparation of 2-Butylpropanedioic Acid Monoethyl Ester (6). A 100-L Buchi reactor was charged with diethyl butylmalonate (**2**, 3.07 kg; 14.18 mol) and ethanol (8.52 L). The solution was cooled to an internal temperature of 15−18 °C over a period of 30 min, and a solution of potassium hydroxide (876.0 g; 15.6 mol; 90% purity) in ethanol (8.52 L) was added over a period of 40 min while maintaining an internal temperature of 15−25 °C. The lines were rinsed with ethanol (1.2 L), and the rinse was added to the reaction mixture. The hazy solution was stirred for 8 h. The reaction mixture was concentrated under a vacuum (20 mbar; jacket temperature 35−40 °C) to collect ∼18.3 L of solvent and to obtain a cloudy viscous suspension (3.66 kg). This suspension was diluted with water (12.0 L) and *tert*-butyl methyl ether (6.0 L), and the biphasic mixture was stirred for 15 min. The organic layer was separated, and the aqueous layer was extracted with *tert*-butyl methyl ether (6.0 L). The aqueous layer was cooled to 15−18 °C (internal temperature) and acidified with concentrated sulfuric acid (0.45 L) to pH

1−2 (addition time of sulfuric acid was 30 min while maintaining the internal temperature at <25 °C). Heptane (13.5 L) was added, and the mixture was stirred for 30 min. The organic layer was separated and washed with water (3.0 L). The organic layer was concentrated under a vacuum (20 mbar; jacket temperature 45−55 °C) to collect ∼14.9 L of solvent to obtain 2-butylpropanedioic acid monoethyl ester[12] (**6**, 2.55 kg; 95% crude yield; purity 99% by HPLC) as a clear liquid; MS (ESI) 187.15 (M-1); ^{1}H NMR ($CDCl_3$, δ) 0.8−1.0 (m, 3H), 1.2−1.45 (m, 7H), 1.8−2.0 (m, 2H), 3.38 (t, 1H, J = 7.4 Hz), 4.23 (q, 2H, J = 7.1 Hz), 11.37 (br, 1H); ^{13}C NMR ($CDCl_3$, δ) 13.79, 14.06, 22.33, 28.56, 29.42, 51.82, 61.70, 169.44, 175.66.

Preparation of (±)-2-Butyl-3-hydroxypropionic Acid (7). A 12-L, four-necked, round-bottomed flask, equipped with a mechanical stirrer, digital thermometer, and nitrogen inlet−outlet was charged with 2-butylpropanedioic acid monoethyl ester (**6**, 450.0 g, 2.39 mol) and 2-propanol (4.5 L). The solution was cooled to an internal temperature at 15−18 °C, and a 2 M solution of lithium borohydride (2.4 L, 4.8 mol) in tetrahydrofuran was added over a period of 1.5 h while maintaining the internal temperature at 15−25 °C. The stirring was continued for an additional 3 h. The reaction mixture was cooled to an internal temperature of 10−13 °C and quenched by the addition of 2 N HCl (2.4 L) over a period of 1 h while maintaining the internal temperature at 10−25 °C. The reaction mixture was concentrated at 35−40 °C (20 mbar) to collect ∼7.5 L of the solvent to obtain a suspension (∼1.9 kg). This suspension was diluted with water (2.0 L) and ethyl acetate (2.5 L), and the biphasic mixture was stirred for 1 h. The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (2.0 L). The combined organic layers were washed with 20% aqueous solution of sodium chloride (1.0 L) and concentrated under a vacuum (20 mbar) until no further solvent distilled to afford crude (±)-2-butyl-3-hydroxypropionic acid[8] (**7**, 349.4 g, 100%) as a colorless liquid, which was used as such in the next step.

Resolution of (±)-2-Butyl-3-hydroxypropionic Acid (7). A 5-L, four-necked, round-bottomed flask, equipped with a mechanical stirrer, digital thermometer, reflux condenser, addition funnel with nitrogen inlet−outlet, and heating mantle, was charged with (*R*)-α-methylbenzylamine (280.7 g, 2.316 mol), 2-propanol (1.9 L), and ethyl acetate (1.63 L). The solution was stirred and heated to an internal temperature at 60−65 °C, and a solution of (±)-2-butyl-3-hydroxypropionic acid (**7**, 322.5 g, 2.206 mol) in ethyl acetate (0.2 L) was added over a period of 15 min while maintaining the internal temperature at 60−70 °C. The addition funnel was washed with ethyl acetate (0.2 L) and added to the mixture. The solution was cooled to 20−25 °C over a period of 2 h, and the resulting suspension was stirred at the same temperature for an additional 5 h. The solids were collected by filtration, washed with a mixture of ethyl acetate−2-propanol (2:1 v/v) in two equal portions of 0.5 L each, and dried at 50−53 °C (13−49 mbar) to afford crude (*R*)-2-butyl-3-hydroxypropionic acid (*R*)-α-methylbenzylammonium salt (**8**, 246.3 g; 41.7%); (*R*)/(*S*) = 94.1:5.9.

Crude (*R*)-2-butyl-3-hydroxypropionic acid (*R*)-α-methylbenzylammonium salt (**8**, 246.3 g) was transferred to a 5-L, four-necked, round-bottomed flask, equipped with a mechanical stirrer, digital thermometer, reflux condenser, addition funnel with nitrogen inlet−outlet, and a heating mantle. Ethyl acetate (1.225 L) and 2-propanol (1.225 L) were added. The suspension was stirred and heated to an internal temperature of 70−80 °C over a period of 1 h to obtain a solution. The solution was cooled to 20−25 °C over a period of 2 h, and the resulting suspension was stirred at the same temperature for an additional 5 h. The solids were collected by filtration, washed with a mixture of ethyl acetate−2-propanol (2:1 v/v) in two equal portions of 0.4 L each, and dried at 50−53 °C (13−49 mbar) to afford pure (*R*)-2-butyl-3-hydroxypropionic acid (*R*)-α-methylbenzylammonium salt (**8**, 215.6 g; 36.5%; 73.0% of theory); mp 145−147 °C; $[\alpha]_D$ +8.8 (c = 1.0, CH_3OH); (*R*)/(*S*) = 99.3:0.7; ^{1}H NMR ($CDCl_3$, δ) 0.88 (t, 3H), 1.2−1.4 (m, 4H), 1.4−1.6 (m, 2H), 1.61 (d, 3H, J = 6.9 Hz), 2.3−2.4 (m,1H), 3.5−3.6 (m, 1H), 3.6−3.7 (m, 1H), 4.42 (q, 1H, J = 6.9 Hz), 5.13 (s, 4H), 7.3−7.5 (m, 5H); ^{13}C NMR ($CDCl_3$, δ) 14.88, 21.64, 24.42, 30.84, 31.54, 52.58, 52.69, 65.59, 128.08, 130.27, 130.58, 140.96, 183.6. Anal. Calcd for $C_{15}H_{25}NO_3$: C, 67.38; H, 9.42; N, 5.24. Found: C, 67.46; H, 9.45; N, 5.23.

(*R*)-2-Butyl-3-hydroxypropionic Acid (1). (*R*)-2-Butyl-3-hydroxypropionic acid (*R*)-α-methylbenzylammonium salt (**8**, 10.0 g) was dissolved in 2 N HCl (40.0 mL), and isopropyl acetate (50.0 mL) was added to the mixture. After mixing for 5 min, the organic layer was separated, and the aqueous layer was extracted with isopropyl acetate (3 × 50.0 mL). The combined organic layers were washed with water (20.0 mL) and concentrated under a vacuum (20 mbar) until no further solvent distilled to afford (*R*)-2-butyl-3-hydroxypropionic acid (**1**, 5.4 g, 98%); oil; $[\alpha]_D$ +6.5 (c = 1.0, CH_3OH); (*R*)/(*S*) = 99.3:0.7; ^{1}H NMR ($CDCl_3$, δ) 0.9 (t, 3H), 1.25−1.44 (m, 4H), 1.44−1.59 (m, 1H), 1.59−1.75 (m, 1H), 2.5−2.7 (m, 1H), 3.7−3.9 (m, 2H), 7.04 (br, 2H); ^{13}C NMR ($CDCl_3$, δ) 14.21, 22.96, 28.36, 29.67, 47.92, 63.35, 180.80. Anal. Calcd for $C_7H_{14}O_3$: C, 57.51%; H, 9.65%. Found: C, 57.31%; H, 9.90%.

(*S*)-2-Butyl-3-hydroxypropionic Acid. (*S*)-2-Butyl-3-hydroxypropionic acid was prepared by the resolution of (±)-2-butyl-3-hydroxypropionic acid (**7**) with (*S*)-α-methylbenzylamine in a similar manner as that described above for the (*R*)-enantiomer. (*S*)-2-Butyl-3-hydroxypropionic acid (*S*)-α-methylbenzylammonium salt, yield 33.2% (66.4% of theory); mp 145−147 °C; $[\alpha]_D$ −8.9 (c = 1.0, CH_3OH); (*R*)/(*S*) = 0.4:99.6.

(*S*)-2-Butyl-3-hydroxypropionic acid: yield 98%; oil; $[\alpha]_D$ −6.6 (c = 1.0, CH_3OH); (*R*)/(*S*) = 0.4:99.6.

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