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The Bakers' Yeast Reductions of α- and β-Keto Ester Derivatives in the Presence of a Sulfur Compound

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Abstract: Improvement of the enantioselectivity and enhancement of the reactivity were achieved in the bakers' yeast reduction of the α- and β-keto ester derivatives by the addition of a sulfur compound. High enantioselectivity in the bakers' yeast reduction of keto esters was accomplished by using combination of an addition of a sulfur compound with an appropriate selection of the alcohol part of the ester.

Keywords: bakers' yeast reduction; keto esters; sulfur compound; enantioselectivity

Introduction

Optically active α- and β-hydroxy ester derivatives are important building blocks in the synthesis of natural products. Among the strategies developed for their preparations of the ester derivatives, the bakers' yeast reductions of the corresponding α- and β-keto ester derivatives are one of the most useful methods because of the stability and ready availability of bakers' yeast.[1] Especially the bakers' yeast reduction of β-keto esters has been widely investigated because of the synthetic utility.[2] In most cases so far reported, the results are satisfactory with high chemical yield and high stereoselectivity. However, there have been a lot of examples that afforded unsatisfactory results, low chemical yield, and/or low selectivity, mainly because of the participation of multiple enzymes with different enantioselectivity. A number of methods have been reported for the improvement of the enantioselectivity of the bakers' yeast reduction of β-keto ester analogues, involving some modification of the substrate,[3] addition of an additive as a selective inhibitor of reductase,[4] addition of an inorganic salt,[5] immobilization of bakers' yeast,[6] thermal treatment of bakers' yeast,[7] or use of an organic solvent.[8] On the other hand, the bakers' yeast reduction of α-keto ester derivatives is less popular than that of β-keto ester derivatives.[9] Only a few examples for improvement the enantioselectivity have been reported.[9f, 9h, 9i] However, the rate of reduction and chemical yield usually decreased in such cases. Therefore, more effective methods of improvement of enantioselectivity without decrease of the reactivity in the bakers' yeast reduction of keto esters have been desired. We have already reported that the reactivity and enantioselectivity could be improved using a sulfur compound as an additive in the bakers' yeast reduction of β-keto esters.[10] In this report,

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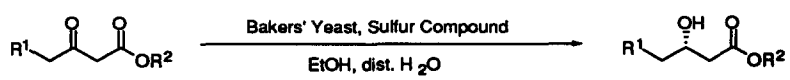
we investigated the bakers' yeast reduction of β-keto ester derivatives in detail for defining the effect of sulfur compounds as an additive and applied the improved method to the bakers' yeast reduction of α-keto esters.

Results and Discussion

The bakers' yeast reduction of ethyl acetoacetate, one of the most popular β-keto esters, was investigated. The results are summarized in Table 1. The reduction of ethyl acetoacetate **1** in the absence of a sulfur compound gave ethyl (*S*)-3-hydroxybutanoate with 94% ee.[11] The use of 1.0 eq of thiophenol as an additive completely loss the activity of the reductase for the reduction of β-keto esters. The enhanced reactivity was observed using 0.5 eq of methyl dithioacetate to the substrate, although the use of 1.0 or 2.0 eq inhibited the reduction. The acceleration of the bakers' yeast reduction using an additive has not been previously reported.[12] The improved enantioselectivity in the bakers' yeast reduction of ethyl acetoacetate was obtained using a sulfur compound such as dimethyl sulfide, dibutyl sulfide, or phenyl vinyl sulfide with up to 99% ee. The highest rate acceleration effect was obtained using L-cysteine as a sulfur compound. The same effects were observed in the bakers' yeast reduction of methyl 3-oxopentanoate **2** to give methyl (*S*)-3-hydroxypentanoate.[13] The use of 2 eq of L-cysteine enhanced the reactivity and improved the enantioselectivity. Butyl 3-oxopentanoate **3** was used as a substrate, because the bakers' yeast reduction of β-keto ester derivatives possessing a long alcohol part gave the reduced product with high enantioselectivity.[3a] The use of 5 eq of L-cysteine effectively enhanced the reactivity and improved the enantioselectivity up to 92% ee, while the reduction of butyl 3-oxopentanoate **3** in the absence of a sulfur compound gave butyl (*S*)-3-hydroxypentanoate with 77% ee, in which the reaction did not reach completion even after 36 h. The butyl (*S*)-3-hydroxypentanoate was transformed into the corresponding methyl ester to establish the absolute stereochemistry. The mercapto group of cysteine would be effective to increase the enantioselectivity and the amino acid part would enhance the reactivity, because the reduction was effectively carried out by the addition of other amino acids, such as L-alanine or L-methionine, although the enantioselectivity was not changed. The best enantioselectivity was achieved using 3 eq of phenyl vinyl sulfide in up to 93% ee. Moreover, the bakers' yeast reduction of pentyl 3-oxopentanoate **4** in the presence of 5 eq of L-cysteine gave pentyl (*S*)-3-hydroxypentanoate with 98% ee.

Optically active 4-chloro-3-hydroxybutanoate is a useful intermediate for the synthesis of natural products, such as carnitine.[3] Thus, the effect of a sulfur compound in the reduction of 4-chloroacetoacetate was also investigated. 2-Aminoethanethiol hydrochloride effectively enhanced the enantioselectivity. The absolute stereochemistry was established by its derivatization to 1,3-butanediol with $LiAlH_4$, and comparison of the optical rotation.[14] The best enantioselectivity was obtained using 5 eq of 2-aminoethanethiol hydrochloride, although the chemical yield was low because 2-aminoethanethiol hydrochloride reacted with butyl 4-chloroacetoacetate **5** to give by-products. 4-Chloroacetoacetate possessing a longer alcohol part was used as a



1 ; R^1 = H, R^2 = Et **5 ; R^1 = Cl, R^2 = Bu**
2 ; R^1 = Me, R^2 = Me **6 ; R^1 = Cl, R^2 = Hex**
3 ; R^1 = Me, R^2 = Bu **7 ; R^1 = OBn, R^2 = Et**
4 ; R^1 = Me, R^2 = Pent

Table 1. The Bakers' Yeast Reduction of β-Keto Ester Derivatives

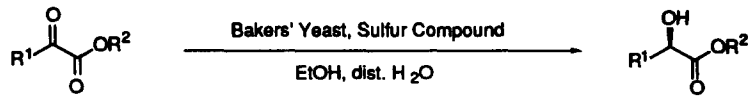
entry	Substrate	Sulfur Compound (equiv.)	Time (h)	% yield[a]	% ee[b]
1	1	none	8	60	94
2	1	PhSH (1.0)	31.5	-	-
3	1	$CH_3CS_2CH_3$ (0.5)	3	54	95
4	1	$CH_3CS_2CH_3$ (1.0)	9	65	93
5	1	$HSCH_2CO_2Et$ (2.0)	47	22	85
6	1	Me_2S (1.0)	3	59	98
7	1	Me_2S (2.0)	4	42	99
8	1	Bu_2S (1.0)	3	52	99
9	1	DMSO (1.0)	2.5	67	98
10	1	$PhSCH=CH_2$ (1.0)	3	64	99
11	1	L-Cysteine (1.0)	2	49	98
12	2	none	37	41	22
13	2	Me_2S (1.0)	21	54	25
14	2	L-Cystine (1.0)	28	52	43
15	2	L-Cysteine (2.0)	25	46	55
16	3	none	36	44	77
17	3	L-Cysteine (1.0)	19	75	81
18	3	L-Cysteine (3.0)	5.5	75	90
19	3	L-Cysteine (5.0)	6.5	72	92
20	3	L-Alanine (1.0)	3	69	76
21	3	L-Methionine (1.0)	4	77	77
22	3	$PhSCH=CH_2$ (1.0)	10	68	86
23	3	$PhSCH=CH_2$ (3.0)	36	67	93
24	4	none	14	46	88
25	4	$PhSCH=CH_2$ (3.0)	11	56	96
26	4	L-Cysteine (5.0)	7	51	98
27	5	none	2	65	22
28	5	$HSCH_2CH_2NH_2 \cdot HCl$ (1.0)	2	65	46
29	5	$HSCH_2CH_2NH_2 \cdot HCl$ (5.0)	1	20	69
30	6	none	3	62	64
31	6	$HSCH_2CH_2NH_2 \cdot HCl$ (1.0)	3	38	75
32	6	$PhSCH=CH_2$ (1.0)	5	76	88
33	6	$PhSCH=CH_2$ (3.0)	96	12	97
34	7	none	5	74	34[c]
35	7	L-Cysteine (2.0)	9	61	54[c]
36	7	$PhSCH=CH_2$ (3.0)	9	64	70[c]
37	7	$PhSCH=CH_2$ (3.0) + L-Cysteine (2.0)	12	18	76[c]
38	7	$PhSCH=CH_2$ (2.0) + $HSCH_2CH_2NH_2 \cdot HCl$ (2.0)	23	58	83[c]
39	7	$PhSCH=CH_2$ (3.0) + $HSCH_2CH_2NH_2 \cdot HCl$ (2.0)	35	46	87[c]

[a] Isolated yield. [b] Determined by HPLC of the corresponding (-)-MTPA ester derivative. [c] Determined by chiral HPLC of the corresponding benzoate derivative.

substrate to improve the enantioselectivity of the bakers' yeast reduction. The use of 1 eq of 2-aminoethanethiol hydrochloride or phenyl vinyl sulfide in the bakers' yeast reduction of hexyl 4-chloroacetoacetate **6** improved the enantioselectivity in which cases hexyl (*R*)-4-chloro-3-hydroxybutanoate was obtained with 75 or 88% ee, respectively. The reduction in the presence of 3 eq of phenyl vinyl sulfide proceeded to give the reduced product with highest enantioselectivity. The use of an excess amount of a sulfur compound decreased the chemical yield and/or the reactivity, although the enantioselectivity was improved. These results would be due to inhibition of the reductase of bakers' yeast or production of by-products by the reaction of the substrate with a sulfur compound.

On the other hand, chiral 3-hydroxybutanoate possessing a hetero-substituent such as an oxygen or sulfur atom at the C-4 position is a useful intermediate for the synthesis of a β-lactam compound,[10b, 15] and thus, ethyl 4-benzyloxyacetoacetate **7** was used as a substrate. The reaction proceeded to give ethyl (*R*)-4-benzyloxy-3-hydroxybutanoate with high enantioselectivity using a sulfur compound such as L-cysteine or phenyl vinyl sulfide.[16] The combined use of 3 eq of phenyl vinyl sulfide and 2 eq of L-cysteine enhanced the enantioselectivity more effectively than that of phenyl vinyl sulfide or L-cysteine alone. The combined use of phenyl vinyl sulfide and 2-aminoethanethiol hydrochloride was the most effective. The best enantioselectivity was achieved using 3 eq of phenyl vinyl sulfide and 2 eq of 2-aminoethanethiol hydrochloride in up to 87% ee.

We extended the effective method of the bakers' yeast reduction of β-keto ester to that of α-keto ester derivatives. The results of the reduction of α-keto ester derivatives in the presence of a sulfur compound are summarized in Table 2. While the reduction of ethyl 2-oxopentanoate **8** in the absence of a sulfur compound gave ethyl (*R*)-2-hydroxypentanoate with 30% ee,[9c] the enantioselectivity was slightly improved using a sulfur compound such as dimethyl sulfide or phenyl vinyl sulfide. 2-Oxopentanoate possessing a longer alcohol part was used as a substrate for improvement of the enantioselectivity. The bakers' yeast reduction of the butyl ester **9** gave butyl (*R*)-2-hydroxypentanoate with 42% ee. The absolute stereochemistry was established by its derivatization to 1,2-pentanediol, and the comparison of the optical rotation with that of authentic sample from ethyl (*R*)-2-hydroxypentanoate. The improved enantioselectivity was obtained using a sulfur compound. The best chemical yield and enantioselectivity were achieved using 3 eq of phenyl vinyl sulfide in which butyl (*R*)-2-hydroxypentanoate was obtained in 56% yield with 86% ee. The bakers' yeast reduction of ethyl 2-oxoheptanoate **10** in the presence of a sulfur compound gave ethyl (*R*)-2-hydroxyheptanoate, while that in the absence of a sulfur compound gave ethyl (*S*)-2-hydroxyheptanoate with low enantioselectivity. The absolute stereochemistry was determined by its derivatization to 1,2-heptanediol, and the comparison of the optical rotation with the reported data.[17] The use of 1 eq of phenyl vinyl sulfide, dimethyl sulfoxide, or methyl dithioacetate improved the enantioselectivity up to 44, 48, or 52% ee respectively. The addition of 1 or 3 eq of L-cysteine as a sulfur compound gave also improved enantioselectivity up to 49 or 58% ee respectively. Moreover, acceleration of the reaction rate of bakers' yeast reduction of ethyl 2-oxoheptanoate **10** was observed using a sulfur compound. Dimethyl sulfoxide was an effective sulfur compound for acceleration of the reaction rate. To our best knowledge, this acceleration of the bakers' yeast reduction of α-keto ester derivatives is the first example. The use of L-cysteine gave the best result in the bakers' yeast reduction of butyl 2-oxoheptanoate **11** in which butyl (*R*)-2-hydroxyheptanoate was obtained in 50% yield with 80% ee, while the bakers' yeast reduction of butyl 2-oxoheptanoate **11** without an added sulfur compound gave the corresponding reduced product with low enantioselectivity.



8 ; R^1 = Pr, R^2 = Et **10** ; R^1 = Pent, R^2 = Et
9 ; R^1 = Pr, R^2 = Bu **11** ; R^1 = Pent, R^2 = Bu

Table 2. The Bakers' Yeast Reduction of α-Keto Ester Derivatives.

Entry	Substrate	Sulfur Compound (equiv.)	Time (h)	% yield[a]	% ee[b]
1	**8**	none	1	50	30
2	**8**	Me_2S (1.0)	1.5	53	34
3	**8**	$PhSCH{=}CH_2$ (1.0)	1.5	54	33
4	**9**	none	1.5	42	42
5	**9**	Me_2S (1.0)	2	51	57
6	**9**	$PhSCH{=}CH_2$ (1.0)	1	41	76
7	**9**	$PhSCH{=}CH_2$ (3.0)	2.5	56	86
8	**10**	none	3.5	16	13
9	**10**	$PhSCH{=}CH_2$ (1.0)	2.5	30	44
10	**10**	DMSO (1.0)	1	41	48
11	**10**	$CH_3CS_2CH_3$ (1.0)	2	44	52
12	**10**	L-Cysteine (1.0)	2	38	49
13	**10**	L-Cysteine (3.0)	3	35	58
14	**11**	none	24	15	35
15	**11**	L-Cysteine (1.0)	24.5	50	80

[a] Isolated yield. [b] Determined by HPLC (Hibar column, Merck) analysis of the corresponding (-)-MTPA ester derivative.

Although the effects of a sulfur compound are not obvious at present, the effect could not be due to the role of inhibitor of the reductase, because the rate of the bakers' yeast reduction in the presence of a sulfur compound was accelerated. The sulfur compound possessing a mercapto group may act as a hydride source to reproduce NAD(P)H in the reduction system. On the other hand, the sulfur compound firstly could interact with the substrate at least in the case of addition of the sulfur compound possessing an amino group. Actually, the proton signal of the α-position of the ester on ^1H NMR measurement in D_2O completely disappeared by the addition of 1 eq of L-cysteine. Moreover, the enantioselectivity was effectively improved by the addition of a pre-mixture of the substrate and 1 eq of L-cysteine to a suspension of bakers' yeast in the reduction of butyl 3-oxopentanoate **3** up to 87% ee, while that in the presence of 1 or 3 eq of L-cysteine gave butyl (*S*)-3-hydroxypentanoate with 81 or 90% ee, respectively. The sulfur compound possessing an amino group could act as a base and then as a counter cation species. The resulting interacted species of the substrate with a sulfur compound outwardly act as a substrate possessing a sulfur atom. Therefore, the reactivity and enantioselectivity were improved, because many precedents indicated that introduction of a sulfur atom to the substrate enhanced the reactivity and improved the enantioselectivity.[18] In another assumption, the sulfur compound could act as an organic solvent possessing appropriate polarity. It is known that the addition of organic solvent improve the enantioselectivity.[19] Addition

of a sulfur compound in the bakers' yeast reduction of α-keto ester possessing a bulky alcohol part is more effective than that of α-keto ester possessing a small alcohol part. The result could be due to the solubility to the sulfur compound as an organic solvent. The role of the sulfur compounds possessing an amino group would be different from that of the other sulfur compounds as mentioned above. Therefore, the combined use of phenyl vinyl sulfide and 2-aminoethanethiol hydrochloride improved the enantioselectivity more effectively than that of phenyl vinyl sulfide or 2-aminoethanethiol hydrochloride alone.

Summary

The improved enantioselectivity and enhancement of the reactivity in the bakers' yeast reduction of α- and β-keto ester derivatives were observed using a sulfur compound as an additive. Previously the acceleration of the rate of the bakers' yeast reduction has not been reported. High enantioselectivity in the bakers' yeast reduction of keto esters was achieved by combination of an addition of a sulfur compound with an appropriate selection of the alcohol part of the ester.

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Experimental Section

Infrared spectra were determined on a JASCO IR-810 spectrometer. ^{1}H- and ^{13}C-NMR spectra were recorded with JNM EX-270 spectrometers using tetramethylsilane as an internal standard. High performance liquid chromatography (HPLC) was carried out on a Hitachi L-4000 detector and a Hitachi L-6000 pump using a Merck Hibar column or Daicel chiralcel OJ. Optical rotations were measured with a Union PM-101 polarimeter. Exact mass spectra were taken on a JEOL JMS-DX303-HF spectrometer. Tetrahydrofuran was distilled from sodium benzophenone ketyl immediately before use. Purification of products was performed by column chromatography on silica gel Merck Silica Gel-60, and/or preparative TLC on silica gel Merck Kisel Gel PF254.

Ethyl (*S*)-3-Hydroxybutanoate. General Procedure for the Bakers' Yeast Reduction of Ethyl Acetoacetate: A suspension of 9.0 g of dry bakers' yeast (S. I. Lesaffre) in 90 mL of dist. water was stirred for 0.5 hr at ambient temperature. To the resulting suspension was added dimethyl sulfide (0.44 mL, 6.0 mmol). After 0.5 hr stirring, a solution of ethyl acetoacetate (390 mg, 3.0 mmol) in ethanol (9.0 mL) was added to a suspension of bakers' yeast, and the mixture was stirred for 4 hr. Celite and ethyl acetate were added to the reaction mixture, and the whole mixture was stirred for 0.5 hr. The resulting mixture was filtered through a Celite pad. The filtrate was extracted with ether (100 mL x 5). The combined organic extracts were dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (*n*-hexane : ether = 3 : 1 as an eluent) followed by distillation (100 °C/ 30 mmHg, bath temp.) to give the pure title compound as a colorless oil (164 mg, 42 %). $[\alpha]_D^{23}$ = +44.2 (c 1.2, $CHCl_3$): 99% ee; ^{1}H NMR ($CDCl_3$) δ 1.23 (d, *J* = 6.27 Hz, 3H), 1.28 (unresolved t, *J* = 7.09 Hz, 3H), 2.41 (dd, J = 8.25 and 16.5 Hz, 1H), 2.49 (dd, *J* = 3.96 and 16.5 Hz, 1H), 3.05 (d, *J* = 3.63 Hz, 1H), 4.13-4.24 (m, 3H, including unresolved q, *J* = 7.15 Hz); IR ($CHCl_3$) 3500, 2970, 1720, 1450, 1380, 1320, 1180, 1120, 1020 cm^{-1}. The spectral data are in accordance with those in the literature.[11d]

Methyl (*S*)-3-Hydroxypentanoate: bp 100 °C/30 mmHg (bath temp.), $[\alpha]_D^{23}$ = +19 (c 1.0, $CHCl_3$): 55% ee; ^1H NMR ($CDCl_3$) δ 1.03 (t, *J* = 7.26 Hz, 3H), 1.47-1.68 (m, 2H), 2.48 (dd, *J* = 8.75 and 16.3 Hz, 1H), 2.59 (dd, *J* = 3.87 and 16.3 Hz, 1H), 3.18 (brs, 1H), 3.78 (s, 3H), 3.98-4.03 (m, 1H); IR ($CHCl_3$) 3500, 2930, 1720, 1460, 1350, 1160, 1060, 980 cm^{-1}. The spectral data are in accordance with those in the literature.[13]

Butyl (*S*)-3-Hydroxypentanoate: bp 130 °C/30 mmHg (bath temp.), $[\alpha]_D^{23}$ = +26.6 (c 2.1, $CHCl_3$): 93% ee; ^1H NMR ($CDCl_3$) δ 0.93 (t, *J* = 7.26 Hz, 3H), 0.96 (t, *J* = 7.58 Hz, 3H), 1.25-1.31 (m, 2H), 1.45-1.57 (m, 2H), 1.60-1.67 (m, 2H), 2.40 (dd, *J* = 8.74 and 16.3 Hz, 1H), 2.52 (dd, *J* = 3.47 and 16.3 Hz, 1H), 3.08 (brs, 1H), 3.89-3.98 (m, 1H), 4.12 (t, *J* = 6.93 Hz, 2H); IR ($CHCl_3$) 3500, 2960, 1720, 1470, 1350, 1180, 1120, 990 cm^{-1}. MS (CI) *m/z* 175 $[M+H^+]$ (100), HRMS (EI) Calcd for $C_9H_{18}O_3$ $[M^+]$: 174.1256, found: 174.1283.

Pentyl (*S*)-3-Hydroxypentanoate: bp 140 °C/30 mmHg (bath temp.), $[\alpha]_D^{23}$ = +27.0 (c 0.7, $CHCl_3$): 98% ee; ^1H NMR ($CDCl_3$) δ 0.91 (unresolved t, *J* = 5.45 Hz, 3H), 0.97 (unresolved t, *J* = 7.42 Hz, 3H), 1.25-1.36 (m, 4H), 1.38-1.70 (m, 4H), 2.40 (dd, *J* = 8.91 and 16.49 Hz, 1H), 2.52 (dd, *J* = 3.30 and 16.49 Hz, 1H), 2.98 (unresolved d, *J* = 3.30 Hz, 1H), 3.93-3.97 (m, 1H), 4.11 (unresolved t, *J* = 6.77 Hz, 2H); IR ($CHCl_3$) 3450, 2925, 1720, 1460, 1340, 1170, 980 cm^{-1}. MS (CI) *m/z* 189 $[M+H^+]$ (100), HRMS (EI) Calcd for $C_{10}H_{20}O_3$ $[M^+]$: 188.1412, found: 188.1223.

Butyl (*R*)-4-Chloro-3-Hydroxybutanoate: bp 170 °C/30 mmHg (bath temp.), $[\alpha]_D^{23}$ = +10.7 (c 0.43, $CHCl_3$): 69% ee; ^1H NMR ($CDCl_3$) δ 0.94 (t, *J* = 7.26 Hz, 3H), 1.32-1.53(m, 2H), 1.58-1.69 (m, 2H), 2.56-2.70 (m, 2H), 3.15 (d, *J* = 4.95, 1H), 3.56-3.67 (m, 2H), 4.13 (t, *J* = 6.77 Hz, 2H), 4.21-4.29 (m, 1H); IR ($CHCl_3$) 3550, 2950, 1730, 1380, 1270, 1180, 1040 cm^{-1}. MS (CI) *m/z* 195 $[M+H^+]$ (100).

Hexyl (*R*)-4-Chloro-3-Hydroxybutanoate: bp 90 °C/2 mmHg (bath temp.), $[\alpha]_D^{23}$ = +12.1 (c 1.16, $CHCl_3$): 97% ee; ^1H NMR ($CDCl_3$) δ 0.89 (t, *J* = 6.78 Hz, 3H), 1.23-1.40(m, 6H), 1.59-1.69 (m, 2H), 2.56-2.63 (m, 1H), 2.65-2.71 (m, 1H), 3.22 (brs, 1H), 3.60 (d, *J* = 0.99 Hz, 1H), 3.62 (d, *J* = 0.99 Hz, 1H), 4.12 (t, *J* = 6.77 Hz, 2H), 4.17-4.29 (m, 1H); IR ($CHCl_3$) 3550, 2930, 1725, 1330, 1180, 1080 cm^{-1}. MS (CI) *m/z* 223 $[M+H^+]$ (100).

Ethyl (*R*)-4-Benzyloxy-3-Hydroxybutanoate: $[\alpha]_D^{23}$ = +6.1 (c 0.62, $CHCl_3$): 87% ee; ^1H NMR ($CDCl_3$) δ 1.26 (t, *J* = 7.26 Hz, 3H), 2.54 (d, *J* = 6.27 Hz, 2H), 3.00 (d, *J* = 4.29 Hz, 1H), 3.44-3.55 (m, 2H) 4.15 (q, *J* = 7.26 Hz, 2H), 4.21-4.29 (m, 1H), 4.56 (s, 2H), 7.27-7.38 (m, 5H); IR ($CHCl_3$) 3500, 2950, 1740, 1360, 1280, 1150 cm^{-1}. The spectral data are in accordance with those in the literature.[17b]

Ethyl (*R*)-2-Hydroxypentanoate: bp 80 °C/20 mmHg (bath temp.), $[\alpha]_D^{23}$ = +2.4 (c 2.2, EtOH): 34% ee; ^1H NMR ($CDCl_3$) δ 0.95 (t, *J* = 7.26 Hz, 3H), 1.31 (unresolved t, *J* = 7.09 Hz, 3H), 1.37-1.79 (m, 4H), 2.71 (d, *J* = 5.61 Hz, 1H), 4.14-4.29 (m, 3H, including unresolved q, *J* = 7.14 Hz); IR ($CHCl_3$) 3500, 2950, 1720, 1450, 1260, 1130 cm^{-1}. The spectral data are in accordance with those in the literature.[9f]

Butyl (*R*)-2-Hydroxypentanoate: bp 120 °C/20 mmHg (bath temp.), $[\alpha]_D^{23}$ = +5.8 (c 1.1, EtOH): 86% ee; ^{1}H NMR ($CDCl_3$) δ 0.95 (t, *J* = 7.26 Hz, 6H), 1.28-1.51 (m, 4H), 1.53-1.83 (m, 4H), 2.14 (d, *J* = 5.94 Hz, 1H), 4.12-4.29 (m, 3H); IR ($CHCl_3$) 3500, 2950, 1730, 1280, 1120, 1100 cm^{-1}. MS (CI) *m/z* 175 [M+H$^+$] (100), HRMS (EI) Calcd for $C_6H_{12}O_3$ [M$^+$-C_3H_6] : 132.0786, found: 132.0777.

Ethyl (*R*)-2-Hydroxyheptanoate: bp 105 °C/20 mmHg (bath temp.), $[\alpha]_D^{23}$ = +1.2 (c 0.67, EtOH): 58% ee; ^{1}H NMR ($CDCl_3$) δ 0.89 (t, *J* = 6.6 Hz, 3H), 1.26-1.56 (m, 9H, including unresolved t, *J* = 7.09 Hz), 1.58-1.68 (m, 1H), 1.72-1.80 (m, 1H), 2.72 (d, *J* = 5.94 Hz, 1H), 4.13-4.29 (m, 3H, including unresolved q, *J* = 6.93 Hz); IR ($CHCl_3$) 3500, 2920, 1735, 1460, 1370, 1280, 1135,1080 cm^{-1}. The spectral data are in accordance with those in the literature.[20]

Butyl (*R*)-2-Hydroxyheptanoate: bp 130 °C/20 mmHg (bath temp.), $[\alpha]_D^{23}$ = +5.7 (c 0.77, EtOH): 80% ee; ^{1}H NMR ($CDCl_3$) δ 0.89 (t, *J* = 6.6 Hz, 3H), 0.95 (t, *J* = 7.26 Hz, 3H), 1.22-1.49 (m, 8H), 1.56-1.82 (m, 4H), 2.73 (d, *J* = 5.61 Hz, 1H), 4.12-4.26 (m, 3H); IR ($CHCl_3$) 3510, 2950, 1720, 1460, 1360, 1130, 1080 cm^{-1}. MS (CI) *m/z* 203 [M+H$^+$] (100). HRMS (EI) Calcd for $C_{11}H_{22}O_3$ [M$^+$] : 202.1569, found: 202.1532.

Methyl (*S*)-3-Hydroxypentanoate. Determination of Absolute Stereochemistry of Butyl 3-Hydroxypentanoate: A solution of butyl (*S*)-3-hydroxypentanoate (100 mg, 0.57 mmol) in 1.5 mL of ethanol was stirred at ambient temperature. To the solution was added 1.5 mL of water solution of potassium hydroxide (48 mg, 0.86 mmol), and the mixture was allowed to stand at ambient temperature for 6 h. Ethanol in the reaction mixture was removed under reduced pressure, the water layer was acidified with 2N hydrochloride, and extracted with dichloromethane (10 mL x 3). The combined organic extracts were dried over anhydrous sodium sulfate, and concentrated in vacuo to give a crude residue. To a tetrahydrofuran (1.0 mL) solution of the crude material was treated with an ether solution of diazomethane. The resulting solution was concentrated in vacuo to give a crude oil. The residue was purified by distillation (100 °C/30 mmHg, bath temp.) to give the pure title compound as a colorless oil (30 mg, 40 %). $[\alpha]_D^{23}$ = +22.1 (c 0.38, $CHCl_3$).

(*S*)-1,3-Butanediol: Hexyl 4-chloro-3-hydroxypentanoate(224 mg, 1.0 mmol, $[\alpha]_D^{23}$ = +9.9 (c 2.02, $CHCl_3$)) was added to a suspension of lithium aluminum hydride (38 mg, 1.0 mmol) in tetrahydrofuran (6.7 mL) at 0 °C under an argon atmosphere, and the mixture was allowed to stand at ambient temperature for 17 h. To the reaction mixture was added 0.3 mL of sat. aq. sodium sulfate at 0 °C, and the resulting mixture was stirred for 0.5 h. The mixture was filtered through a Celite pad. The filtrate was concentrated in vacuo. The residue was purified by distillation (80 °C/1 mmHg, bulb to bulb) to give the pure title compound as a colorless oil (71.8 mg, 80%). $[\alpha]_D^{23}$ = +17.9 (c 1.36, EtOH); ^{1}H NMR ($CDCl_3$) δ 1.22 (d, *J* = 6.27 Hz, 3H), 1.64-1.71 (m, 2H), 3.72-3.89 (m, 4H), 3.98-4.09 (m, 1H); IR (neat) 3250, 2960, 1650, 1460, 1050 cm^{-1}. The spectral data are in accordance with those of the authentic sample.

(*R*)-1,2-Pentanediol: A suspension of lithium aluminum hydride (18 mg, 0.44 mmol, 74% ee) in tetrahydrofuran (3 mL) was stirred at 0 °C under an argon atmosphere. To the suspension was added a 1 mL of tetrahydrofuran solution of butyl (*R*)-2-hydroxypentanoate (64 mg, 0.37 mmol), and the mixture was allowed to

stand at ambient temperature for 18 h. To the reaction mixture was added 0.12 mL of sat. aq. sodium sulfate at 0 °C, and the resulting mixture was stirred for 0.5 h. The mixture was filtered through a Celite pad. The filtrate was concentrated in vacuo. The residue was purified by silica gel column chromatography (*n*-hexane : ethyl acetate = 1 : 3 as an eluent) to give the pure title compound as a colorless oil (12 mg, 31 %). $[\alpha]_D^{23}$ = +7.0 (c 0.2, EtOH); ^{1}H NMR ($CDCl_3$) δ 0.94 (t, *J* = 7.26 Hz, 3H), 1.31-1.52 (m, 4H), 2.46 (br, 2H), 3.41 (dd, *J* = 7.91 and 11.21 Hz, 1H), 3.62-3.77 (m, 2H); IR (neat) 3400, 2950, 1460, 1080 cm^{-1}. The spectral data are in accordance with those in the literature.[21]

(*R*)-1,2-Heptanediol: To 10.3 mL of an ethanol solution of ethyl (*R*)-2-hydroxyheptanoate (100 mg, 0.57 mmol) was added sodium borohydride (20 mg, 0.57 mmol) at 0 °C under an argon atmosphere. The mixture was heated under reflux for 6 h. The reaction mixture was cooled to ambient temperature. To the reaction mixture was added 2N hydrochloride, and then ethanol was removed under reduced pressure. The residue was extracted with ether (10 mL x 5). The combined organic extracts were dried over anhydrous sodium sulfate, and concentrated in vacuo. The residue was purified by distillation (120 °C/ 20 mmHg, bath temp.) to give the pure title compound as a colorless oil (45 mg, 59 %). $[\alpha]_D^{23}$ = +8.5 (c 0.5, EtOH); ^{1}H NMR ($CDCl_3$) δ 0.90 (t, *J* = 6.60 Hz, 3H), 1.31-1.56 (m, 8H), 1.95 (br, 2H), 3.41-3.49 (m, 1H), 3.64-3.73 (m, 2H); IR ($CHCl_3$) 3450, 2920, 1720, 1460, 1080 cm^{-1}. The spectral data are in accordance with those in the literature.[9f]

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