Highly Enantioselective Reduction of Ethyl 2-Acyloxy-3-oxobutanoate with Immobilized Baker's Yeast

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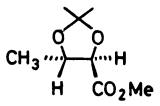
Reduction of ethyl 2-acetoxy-3-oxobutanoate (**4a**) with immobilized baker's yeast in calcium alginate gel gave a 18:19:63 mixture of ethyl (2*R*,3*S*)- and (2*S*,3*S*)-2-acetoxy-3-hydroxybutanoates and ethyl (2*S*,3*S*)-2,3-dihydroxybutanoate each with >95% e.e. in 58% yield. A similar treatment of a 2-benzoyloxy analog of **4a** afforded a 6:94 mixture of ethyl (2*R*,3*S*)- and (2*S*,3*S*)-2-benzoyloxy-3-hydroxybutanoates (>95% e.e.) in 70% yield. Their absolute configurations were determined by comparison with authentic (2*R*,3*S*)- and (2*S*,3*S*)-2,3-dihydroxybutanoic acids. Effects of the immobilization and the pH of culture solution on the product ratio are also discussed.

Chiral (2*S*,3*S*)- and (2*R*,3*S*)-2,3-dihydroxybutanoic acids and their derivatives have been proved to be versatile key intermediates in a variety of natural poroduct syntheses[1-5] and hence convenient synthetic procedure for these compounds is desirable. In the reported method for the preparation of methyl (4*R*,5*S*)-2,2,5-trimethyl-1,3-dioxolane-4-carboxylate (**1**)[1] and its aldehyde analog (**2**),[2] their chiralities are derived from (2*R*,3*R*)-tartaric acid. (4*S*,5*S*)-2,2,5-Trimethyl-1,3-dioxolane-4-carbaldehyde (**3**)[3] has been elaborated from (4*S*,5*R*)-2,2,4-trimethyl-5-(2-phenylethenyl)-1,3-dioxolane which is obtainable from the baker's yeast promoted reaction of cinnamaldehyde with acetaldehyde.[4] Recently, aldehyde **3** has also been prepared efficiently via diastereo- and enantioselective reduction of 2-(1,2-dioxoalkyl)-1,3-dithian with baker's yeast.[5] As shown in these examples, the use of baker's yeast has been growing as one of the powerful synthetic methods for chiral alcohols, because of its high enantioselectivity by a simple procedure.



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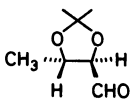

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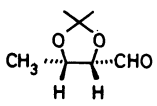

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We describe here a novel, highly enantioselective synthetic method for (2*R*,3*S*)- and (2*S*,3*S*)-2,3-dihydroxybutanoic acid derivatives by the reduction of ethyl 2-acyloxy-3-oxobutanoates (**4a** and **4b**) with baker's yeast which is used by itself (method A) or as an immobilized one in calcium alginate gel[6] (method B) (Table 1). The immobilization of baker's yeast in an appropriate matrix has been realized not only to attain obvious advantages in the isolation and purification procedures,[6] but also to cause a definite change in an optical yield and/or a direction of rotation.[7] These advantages have encouraged us to use immobilized yeast. It enhanced erythro stereoselectivity in the reduction of **4a,b** and optical yields were more than 95% both in methods A and B.

Results and Discussion

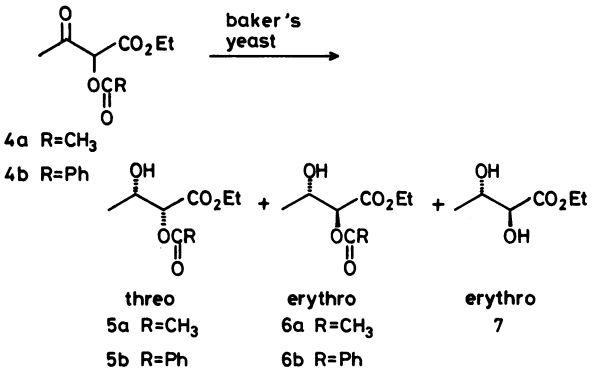
The baker's yeast reduction of ethyl 2-acetoxy-3-oxobutanoate (**4a**)[8] gave ethyl (2*R*,3*S*)- and (2*S*,3*S*)-2-acetoxy-3-hydroxybutanoates (**5a** and **6a**) and ethyl (2*S*,3*S*)-2,3-dihydroxybutanoate (**7**)[9] as a major product (Scheme 1 and Table 1). The relative stereochemistry of **5** (threo) and **6** (erythro) were determined on the basis of ^{1}H NMR analysis which showed $J_{2,3}$=2.3—2.5 Hz for **5** and $J_{2,3}$=4 Hz for **6**.[10] Compound **7** was assigned to erythro after conversion to its acetonide as discussed below. The use of immobilized yeast improved the erythro-selectivity as well as the total yield of the reduction products. Prolonged reaction increased the ratio of **7** up to 63%, and decreased that of **6a**. Threo-(2*R*,3*S*) isomer of **7**, which is expected to be derived

Table 1. Reduction of Ethyl 2-Acyloxy-3-oxobutanoates (**4a, b**) with Fermenting Baker's Yeast

Ester	Method	Reaction Time/h	Product Yield/%[a]	Product Ratio/%[b]		
				5[c]	**6**[c]	**7**[c]
4a	A[d]	48	45	28	18	54
4a	B[e]	12	37	19	58	23
4a	B[e]	43	49	18	26	56
4a	B[e]	53	58	18	19	63
4b	A[d]	23	61	14	86	0
4b	B[e]	21	70	6	94	0
4b	B[f]	21	62	51	49	0

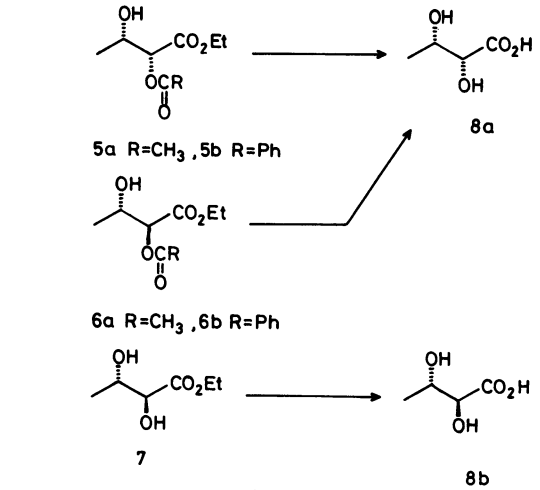
a) Isolated yield. b) Determined after separation by column chromatography. c) Optical purity is more than 95% e.e. d) A: Free baker's yeast was used. e) B: Immobilized baker's yeast was used. f) The pH of the calture solution was controlled at near 7 by addition of aqueous $NaHCO_3$.

from **5a**, was not detected in all cases. These facts suggest that only **6a** was hydrolyzed to **7** under the fermenting conditions. In a similar reduction of ethyl 2-benzoyloxy-3-oxobutanoate (**4b**), erythro-selectivity was further improved up to 94%. It is worth while to note here that the diastereoselection was not observed when the reaction was carried out under neutral conditions.



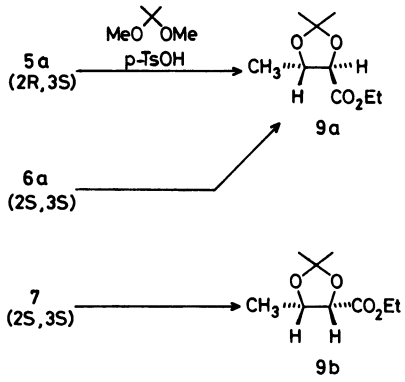
Scheme 1.

The absolute configurations of new chiral centers of these products were confirmed to be (3*S*) by comparison with authentic (2*R*,3*S*)- and (2*S*,3*S*)-2,3-dihydroxybutanoic acids (**8a** and **8b**) (Scheme 2). Thus the hydrolysis of threo esters **5a,b** and erythro ester **7** with 1 mol dm^{-3} methanolic $Ba(OH)_2$ gave the corresponding acids **8a** and **8b**, respectively. Interestingly, a similar treatment of erythro esters **6a,b** also afforded **8a** as a result of epimerization of C-2 position. The relative stereochemistry of **8a** and **8b** is distinguishable by means of ^{13}C NMR spectra (C-4 of **8a**: δ=19.3; that of **8b**[11]: 16.8). The stereochemical assignments are also acceptable in view of the Prelog rule.[12]



Scheme 2.

Optical purities of **5a**, **6a**, and **7** were estimated to be more than 95% e.e. based on the ^1H NMR spectral analysis with chiral shift reagent [Eu(hfc)$_3$] after conversion to acetonides **9a** and **9b** (Scheme 3). Namely, compounds **5a** and **7** could be converted to **9a** (trans) and **9b** (cis) with retention of the stereochemistry in a usual way by using 2,2-dimethoxypropane and *p*-toluensulfonic acid. However, erythro ester **6a** was transformed into **9a** with epimerization at C-2, as observed in the alkaline hydrolysis of **6a** to **8a**. The Eu(hfc)$_3$ induced ^1H NMR signal due to methyl group at C-5 in **9a** and **9b** thus obtained exhibited a doublet only, while that of the racemic ones, prepared from $NaBH_4$ reduction of **4a**, showed a couple of doublets with an equal intensity. The optical purities of **5b** and **6b** were also determined as >95% e.e. by comparing the ^1H NMR signal for C-4 proton in the presence of Eu(hfc)$_3$ with those for the $NaBH_4$ reduction products.



Scheme 3.

Experimental

Evaporative bulb-to-bulb distillation was done using a Büchi Kügelrohrofen. IR spectra were taken on a JASCO Model A-102 spectrometer. ^1H NMR spectra (60 MHz) were measured with a JEOL Model JNM-60 SI spectrometer and ^{13}C NMR spectra (25 MHz) were taken on a JEOL Model FX-100 spectrometer using Me_4Si as an internal standard. Preparative isolation by GLPC was done with Yanagimoto Model G-80 gas chromatograph (Apiezone Grease L on 10% Chromosorb, He 50 ml min^{-1}, oven temperature 140 °C). The preparative TLC was carried out on silica gel (Kieselgel 60 PF_{254}, Merck A. G. Darmstadt). Column chromatography was performed with silica gel (Silica Gel 60, 70—230 mesh, Katayama Chemical Co. Ltd., Tokyo). Elemental analysis was performed by E. A. Compound **4a** was prepared by the procedure of Henecka.[8]

Ethyl 2-Benzoyloxy-3-oxobutanoate (4b). A mixture of ethyl 2-chloro-3-oxobutanoate[8] (16.6 g, 0.101 mol), potassium benzoate·3H_2O (21.5 g, 0.10 mol), tetrabutylammonium bromide (1.51 g, 4.68 mmol) in benzene (150 ml) was heated under reflux for 3 h. The mixture was cooled, washed with aqueous $NaHCO_3$ and then with water, dried over $MgSO_4$, and concentrated. The residue was distilled under vacuum to give **4b** (16.2 g, 65% yield): Bp 115—122 °C (0.2 mmHg) (1 mmHg=133.322 Pa); IR (neat) 1760, 1730 cm^{-1}: ^1H NMR (CCl_4) δ=1.31 (3H, t, J=7 Hz), 2.31 (3H, s), 4.23 (2H, q, J=7 Hz), 5.53 (1H, s), 7.49 (3H, m), 8.09 (2H, m). Found: C, 62.62; H, 5.78. Calcd for $C_{13}H_{14}O_5$: C, 62.39; H, 5.64.

Preparation of Immobilized Baker's Yeast in Calcium Alginate Gel. The following preparation was done by the modification of the reported procedure.[6] Sodium alginate (14 g) was suspended in water (750 ml) by vigorous stirring at 50 °C for 1 h. To this was added dry baker's yeast

(14 g) (Oriental Yeast Co., Ltd., Tokyo; 98.5% yeast and 1.5% sorbitan fatty acid ester) and the mixture was stirred for additional 2 h untill it became as homogeneous as possible. The resulting suspension was added dropwise from a dropping funnel with a glass tube of 6 mm diameter into a 10% aqueous solution (750 ml) of $CaCl_2 \cdot 2H_2O$ with stirring to form small pieces of spherical calcium alginate gel with ca. 4 mm diameter immediately. Washing with water gave ca. 600 ml of immobilized baker's yeast gel which can be stored in a refrigerator for several weeks.

Typical Procedure for Baker's Yeast Reduction of Ethyl 2-Acyloxy-3-oxobutanoate. Reduction of Ethyl 2-Acetoxy-3-oxobutanoate (4a) with Immobilized Baker's Yeast. A culture solution involving $CaCO_3$ (2.5 g), $NH_4H_2PO_4$ (1 g), KH_2PO_4 (1 g), $MgSO_4$ (0.5 g, glucose (70 g) and boiled water (500 ml) was generally used. To this was added 350 ml of immobilized baker's yeast (8.2 g of baker's yeast) and stirred magnetically for 30 min at 35 °C. When brisk fermentation was confirmed by observing gel pieces to rise up to the surface of the mixture, compound **4a** (9.2 g, 48.9 mmol) was added and the stirring was continued for 20 h at 35 °C. Another batch of glucose (70 g) was added to the solution and the fermentation was continued for additional 23 h. The degree of its consumption was monitored by using glucose-test paper (Diasticks II, Mils-Sankyo Co. Ltd., Tokyo) in the course of the reaction and at the end of the reaction. The gel pieces and the aqueous layer were extracted with ethyl acetate separately. Combined organic layer was dried over $MgSO_4$ filtered and then concentrated. The residual oil was fractionated by column chromatography (140 g of silica gel; hexane–ethyl acetate–ether–acetic acid,30:10:10:0.5) to give **5a** (0.823 g, 9% yield), **6a** (1.19 g, 13% yield), and **7** (2.02 g, 28% yield). **5a**: $[\alpha]_D^{27}$ −30.0° (*c* 1.61, CH_2Cl_2); IR (neat) 3500, 1745 cm^{-1}: ^1H NMR (CCl_4) δ=1.27 (3H, t, *J*=7 Hz), 1.30 (3H, d, *J*=7 Hz), 1.96 (3H, s), 3.34 (1H, br s), 4.00 (1H, d, *J*=2.4 Hz), 4.18 (2H, q, *J*=7 Hz), 5.13 (lH, dq, *J*=2.4 Hz and 7 Hz); ^{13}C NMR ($CDCl_3$) δ=14.1 (q), 19.1 (q), 20.5 (q), 62.0 (t), 67.0 (d), 76.4 (d), 168.7 (s), 170.7 (s). Found: C, 50.59; H, 7.40. Calcd for $C_8H_{14}O_5$: C, 50.50; H, 7.42. **6a**: $[\alpha]_D^{27}$ +31.9° (*c* 1.71, CH_2Cl_2); IR (neat) 3490, 1742 cm^{-1}: ^1H NMR (CCl_4) δ=1.20 (3H, d, *J*=7 Hz), 1.27 (3H, t), 2.12 (3H, s), 3.19 (1H, br s), 3.8—4.30 (1H, m), 4.17 (2H, q, *J*=7 Hz), 4.76 (1H, d, *J*=4 Hz); ^{13}C NMR ($CDCl_3$) δ=14.2 (q), 16.1 (q), 20.9 (q), 62.0 (t), 71.1 (d), 73.0 (d), 170.2 (s), 172.3 (s). Found: C, 50.51; H, 7.69. Calcd for $C_8H_{14}O_5$: C, 50.50; H, 7.42. **7**: $[\alpha]_D^{27}$ +9.3° (*c* 1.69, CH_2Cl_2); IR (neat) 3440, 1730 cm^{-1}: ^1H NMR (CCl_4) δ=1.13 (3H, d, *J*=7 Hz) 1.30 (3H, t, *J*=7 Hz), 3.75—4.15 (2H, m), 4.20 (2H, q, *J*=7 Hz); ^{13}C NMR ($CDCl_3$) δ=14.2 (q), 17.3 (q), 61.6 (t), 69.2 (d), 74.8 (d), 172.7 (s). Found: C, 48.42; H, 8.15. Calcd for $C_6H_{12}O_4$; C, 48.64; H, 8.16.

Reduction of 4a with Free Baker's Yeast. To the culture solution (300 ml) prepared as before mentioned, was added dry baker's yeast (12 g) and stirred at 35 °C for 30 min. Compound **4a** (4.7 g, 25 mmol) was added and stirring was continued for 18 h at 35 °C. After addition of glucose (25 g) again, the mixture was stirred for additional 20 h. Celite was added to the mixture and filtered with suction. The organic layer was extracted with ethyl acetate and treated in a manner similar to that described above to give **5a** (607 mg, 13% yield), **6a** (390 mg, 8% yield), and **7** (898 mg, 25% yield).

Reduction of Ethyl 2-Benzoyloxy-3-oxobutanoate (4b) with Immobilized Baker's Yeast. A mixture of immobilized baker's yeast (50 ml) and **4b** (0.494 g, 1.97 mmol) in the culture solution (70 ml) was stirred at 35 °C for 20 h and worked up in a similar way. Crude products were fractionated by preparative TLC (hexane–ethyl acetate–ether, 1:1:1) to give ethyl (2*S*,3*S*)-2-benzoyloxy-3-hydroxybutanoate (**6b**) (R_f 0.47—0.70, 323 mg, 65.8% yield) and its (2*R*,3*S*)-isomer (**5b**) (R_f 0.70—0.75, 22 mg, 4.2% yield). **6b**: $[\alpha]_D^{21}$ +9.80° (*c* 1.96, CH_2Cl_2); IR (neat) 3500, 1730, 1600 cm^{-1}; ^1H NMR (CCl_4) δ=1.26 (3H, t, *J*=7 Hz), 1.27 (3H, d, *J*=7 Hz), 3.03 (1H, br s), 4.22 (2H, q, *J*=7 Hz), 4.00—4.30 (1H, m), 5.07 (1H, d, *J*=4 Hz, 2-H); ^{13}C NMR ($CDCl_3$) δ=14.0 (q), 19.2 (q), 61.7 (t), 67.3 (d), 76.6 (d), 128.5 (d), 129.2 (s), 129.9 (d), 133.4 (d), 166.0 (s), 168.6 (s).Found: C, 61.78; H, 6.40. Calcd for $C_{13}H_{16}O_5$: C, 61.90; H, 6.39. **5b**: $[\alpha]_D^{21}$ +21.4° (*c* 1.91, CH_2Cl_2); IR (neat) 3500, 1730, 1600 cm^{-1}; ^1H NMR (CCl_4) δ=1.16 (3H, t, *J*=7 Hz), 1.43 (3H, d, *J*=7 Hz), 2.96 (1H, s), 4.09 (2H, q, *J*=7 Hz), 4.00—4.35 (1H, m), 5.36 (1H, dq, *J*=2.5 Hz and 7 Hz), 7.40 (3H, m), 7.92 (2H, m); ^{13}C NMR ($CDCl_3$) δ=14.0 (q), 16.1 (q), 62.1 (t), 71.7 (d), 73.1 (d), 128.4 (d), 129.6 (d), 129.9 (s), 133.1 (d), 165.6 (s), 172.5 (s). Found: C, 61.96; H, 6.49. Calcd for $C_{13}H_{16}O_5$: C, 61.90; H, 6.39.

(2*R*,3*S*)-2,3-Dihydroxybutanoic Acid (8a). A mixture of ethyl (2*R*,3*S*)-2-acetoxy-3-hydroxybutanoate (**5a**) (300 mg, 1.6 mmol) in 5 ml of 1 mol dm^{-3} methanolic $Ba(OH)_2$ was stirred at room temperature for 10 h. After being acidified with 10% HCl and washed well with ether, the solvent was removed under reduced pressure. From the residue, organic material was extracted with several portions of methanol, bubled with carbon dioxide and filtered. Concentration of the filtrate gave an oil together with remaining inorganic materials. To this was added methanol and decanted. The procedure was repeated. Finaly, evaporation of the solvent gave spectroscopically pure **8a** (161 mg, 75% yield): $[\alpha]_D^{16}$ +8.8°[13] (*c* 1.0, H_2O) (lit,[11] $[\alpha]_D^{16}$ −13.51° (*c* 6.0, H_2O) for (2*S*,3*R*)-enantiomer); IR (neat) 3700—2300, 1735, 1310, 1238, 1146, 1083, 1070 cm^{-1}: ^1H NMR (CD_3OD) δ=1.22 (lH, d, *J*=6 Hz), 3.73—4.40 (2H, m),5.13 (3H, br s); ^{13}C NMR (CD_3OD) δ=19.6 (q), 69.7 (d), 75.7 (d), 176.2 (s).

A similar treatment of **5b**, **6a**, and **6b** also gave **8a**. The specific rotation[13] and yield in each experiment are as follows: $[\alpha]_D^{21}$ +13.1° (*c* 1.90, H_2O), 81% yield; $[\alpha]_D^{28}$ +9.1° (*c* 10.6, H_2O), 84% yield; $[\alpha]_D^{24}$ +8.4° (*c* 1.50, H_2O), 76% yield.

(2*S*,3*S*)-2,3-Dihydroxybutanoic Acid (8b).[11] Ester **7** was treated in a way similar to that described above to give **8b** (60% yield) as a viscous oil: $[\alpha]_D^{16}$ +8.8° (*c* 1.0, H_2O) [lit,[11] $[\alpha]_D^{20}$ +9.3° (*c* 0.5, H_2O)]; IR (neat) 3700—2300, 1735, 1260, 1220, 1190, 1082, 1060 cm^{-1}: ^1H NMR (CD_3OD) δ=1.19 (3H, d, *J*=6 Hz), 3.73—4.40 (2H, m), 5.13 (3H, br s); ^{13}C NMR (CD_3OD) δ=17.7 (q), 69.9 (d), 76.0 (d), 175.9 (s).

Ethyl (4*R*,5*S*)-2,2,5-Trimethyl-1,3-dioxolane-4-carboxylate (9a). A mixture of ester **5a** (130 mg, 0.68 mmol), 2,2-dimethoxypropane (140 mg, 1.34 mmol), and *p*-toluenesulfonic acid (1 mg, 0.006 mmol) in dichloromethane (0.75 ml) was heated under reflux for 45 h. The mixture was washed with aqueous $NaHCO_3$, dried over $MgSO_4$, and concentrated under reduced pressure. The residual oil was distilled to give **9a** (82 mg, 64% yield): Bp 60—65 °C (3 mmHg) (1 mmHg=133.322 Pa); $[\alpha]_D^{23}$ +15.2° (*c* 1.2, $CHCl_3$); IR (neat) 1760, 1730 cm^{-1}; ^1H NMR (CCl_4) δ=1.10—1.55 (12H, m), 3.65-4.20 (2H, m), 4.13 (2H, q); ^{13}C NMR ($CDCl_3$) δ=14.2 (q), 18.5 (q), 25.7 (q), 27.2 (q), 61.2 (t), 75.2 (d), 80.5 (d), 110.5 (s), 170.5 (s).

A similar treatment of compound **6a** also gave **9a** (73% yield): Bp 60—65 °C (3 mmHg).

Ethyl (4*S*,5*S*)-2,2,5-Trimethyl-1,3-dioxolane-4-carboxylate

(9b). Yield 72%; bp 60—65 °C (3 mmHg) (1 mmHg= 133.322Pa); $[\alpha]_D^{16}$ +24.7° (*c* 2.4, $CHCl_3$); IR (neat) 1760, 1730 cm^{-1}; ^1H NMR (CCl_4) δ=1.05—1.50 (12H, m), 4.07 (2H, q, *J*=7 Hz), 3.9—4.4 (2H, m); ^{13}C NMR ($CDCl_3$) δ=14.7 (q), 15.6 (q), 25.6 (q), 27.0 (q), 60.9 (t), 73.6 (d), 77.8 (d), 110.3 (s), 170.2 (s). Found: C, 57.74, H, 8.63. Calcd for $C_9H_{16}O_4$: C, 57.43; H, 8.57.

Ethyl (4*RS*,5*SR*)- and (4*RS*,5*RS*)-2,2,5-Trimethyl-1,3-dioxolane-4-carboxylates [(±)-9a and (±)-9b]. To a solution of ester **4a** (1.0 g, 5.26 mmol) in ethanol (5 ml), was added $NaBH_4$ (70 mg, 1.85 mmol). After being stirred at 4 °C for 10 min, the mixture was acidified with 10% HCl and ethanol was removed under reduced pressure. The residual oil[14] (762 mg) was added to a mixture of 2,2-dimethoxypropane (1.25 g, 12 mmol) and *p*-toluenesulfonic acid (5 mg, 0.03 mmol) in dichloromethane (3 ml). It was stirred under reflux for 12 h, cooled, washed with aqueous $NaHCO_3$, dried over $MgSO_4$, and then concentrated. The residue was purified by preparative TLC (hexane–ethyl acetate, 3:1; R_f 0.40—0.85) to give 228 mg (23% yield) of a mixture of (±)-**9a** and (±)-**9b**, which were separated by preparative GLPC [(±)-**9a**: retention time 7.3 min; (±)-**9b**: 9.3 min)].

Ethyl (2*RS*,3*SR*)- and (2*RS*,3*RS*)-2-Benzoyloxy-3-hydroxybutanoates [(±)-5b and (±)-6b]. Ester **4b** (504 mg, 3.02 mmol) was allowed to react with $NaBH_4$ (24.6 mg, 0.677 mmol) in ethanol (3 ml) at 0 °C for 5 min and worked up in a similar way. Crude products were fractionated by preparative TLC (hexane–ethyl acetate–ether, 1:1:1) to give (±)-**5b** (R_f 0.69—0.79, 165 mg, 33% yield) and (±)-**6b** (R_f 0.57—0.69, 49 mg, 10% yield).[15]

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12) V. Prelog, *Pure Appl. Chem.*, **9**, 119 (1964).
13) The specific rotation was not maximized because of difficulty in further purification of the compound but satisfactory to comfirm its direction.
14) Attempts for purification of the crude products were not successful. The products seem to involve racemic **5a** and **6a** together with their 3-acetoxy-2-hydroxy derivatives and so on.
15) Although HPLC analysis of **5b** and **6b** obtained showed a single peak (column SI-60, 8 mmϕ×250 mm; hexane–ethyl acetate–ethanol–ether, 20:10:9:1; 1.0 ml min^{-1}; (±)-**5b**: retention time 10.2 min; (±)-**6b**: 10.6 min), ^1H and ^{13}C NMR spectra of each compound indicate the presence of a small amount of impurities, probably due to 2-hydroxy-3-benzoyloxy analogs.