An Improved Synthetic Method of (*S*)-2-Alkoxypropanals from Ethyl (*S*)-Lactate

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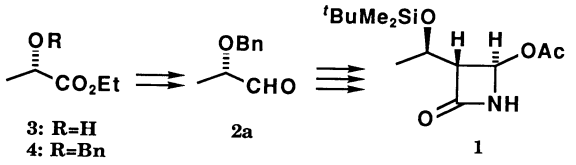
Synopsis. The title synthetic method which undergoes without racemization, was explored employing sequential amidolysis with a secondary amine, alkylation with an alkyl halide under basic conditions, and reduction with sodium bis(methoxyethoxy)aluminium hydride.

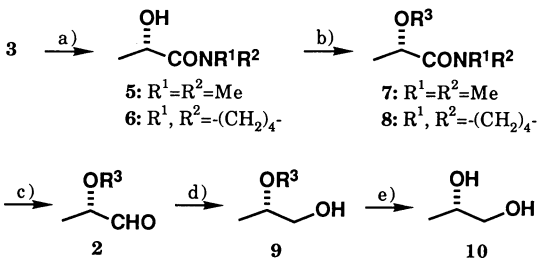
In connection with our ongoing project on the synthesis of the carbapenem key intermediate (**1**),[1] a large quantity of optically pure (*S*)-2-benzyloxypropanal (**2a**)[2] was required as a synthetic intermediate. Initially, the requisite aldehyde (**2a**) could be prepared without racemization by benzylation of commercially available inexpensive ethyl (*S*)-lactate (**3**) with benzyl trichloroacetimidate followed by reduction of formed ethyl (*S*)-2-benzyloxypropionate (**4**) with diisobutylalminium hydride.[1] However, this synthetic scheme turned out to be unrewarding for a large scale preparation of **2a** since the reagent for benzylation is highly expensive. Accordingly, an alternative efficient method was sought which can readily produce **2a** by using inexpensive reagents.



While it has been uncovered that direct benzylation of **3** under basic conditions such as those employing benzyl bromide and sodium hydride in *N*,*N*-dimethylformamide, gives a low yield[3] of **4** and accompanies considerable racemization,[2c] we have now found that **2a** can be readily prepared without racemization by sequential amidolysis of **3** with a secondary amine, benzylation of the formed (*S*)-*N*,*N*-dialkyllactamide under basic conditions, and reduction of the amide group into an aldehyde moiety.

According to the reported method[4] with some modifications, preparation of (*S*)-*N*,*N*-dimethyllactamide (**5**) could be readily achieved in 93% yield by heating a mixture of **3** and liquid dimethylamine in a sealed tube at 70 °C. Benzylation of **5** was effected smoothly by treating with benzyl chloride and sodium hydride[5] or with benzyl chloride and sodium hydroxide[6] under usual phase-transfer conditions, giving rise to the *O*-benzyl derivative (**7a**) in 88 or 86% yield, respectively. Reduction of **7a** with sodium bis(2-methoxyethoxy)aluminium hydride (Vitride®),[7] furnished **2a** in 90% yield.

Since it had been reported that **2a** shows no constant value on measurement of the optical rotation due to its rapid hydration by moisture present in a solvent or air,[2a] determination of the optical purity of **2a** thus



a) For **5**, Me2NH, 70°C, 93%. For **6**, see text. b) For **7**, RCl-NaH in DMF-THF, 0°C, 88% (for **7a**), 76% (for **7b**), 75% (for **7c**), 62% (for **7d**), or BnCl-aqNaOH, BnBu3NCl (cat.), 86% (for **7a**). For **8a**, see text. c) Vitride in THF-toluene, 0°C, 90% (for **2a**), 89% (for **2b**), 80% (for **2c**), 84% (for **2d**). d) NaBH4, in EtOH, 0°C, 89% (for **9a**), 95% (for **9b**), 99% (for **9c**), 85% (for **9d**). e) H2-Pd/C, HCl (cat.), 70% (from **9a**), 56% (from **9b**), 60% (from **9c**).

obtained was attempted at the stage of (*S*)-2-benzyloxy-1-propanol (**9a**). Thus, treatment of **2a** with sodium borohydride followed by acylation of **9a** with (*R*)- and (*S*)-2-methoxy-3,3,3-trifluoro-2-phenylpropionyl chloride (MTPACl),[8] yielded the (*R*)- and (*S*)-MTPA esters of **9a**, respectively. As the ^{1}H NMR spectrum of the (*R*)-MTPA ester showed no signals corresponding to those of the (*S*)-MTPA ester, it appeared obvious that **2a** could be produced without racemization.

Taking into account the reagents required for converting **3** into **2a**, the explored synthetic route is undoubtedly more economical than the previous method and can be readily applied to a large scale preparation of **2a**.

In order to extend the developed synthetic scheme to general preparation method of various types of (*S*)-2-alkoxypropanals (**2**) whose protective groups could be introduced under basic conditions, syntheses of **2b—d** were next examined. Thus, alkylation of **5** with *p*-methoxybenzyl chloride, *p*-chlorobenzyl chloride, or benzyloxymethyl chloride,[9] followed by reduction of the *O*-alkyl derivatives (**7b—d**) with Vitride®, smoothly produced **2b—d** in a similar manner to that described for the preparation of **2a**. Since (*S*)-1,2-propanediol (**10**) obtained from **2b,c** by sequential reduction with sodium borohydride and hydrogenolysis exhibited the same optical rotation values as that of **10** independently synthesized from **9a**, it appeared obvious that **2b,c** could be prepared without racemization similarly to **2a**.[10]

As mentioned above, we have succeeded in developing an efficient synthetic method of **2a** required for the synthesis of the carbapenem key intermediate and in extending the explored synthetic scheme to general preparation method of (*S*)-2-alkoxypropanals such as

2b—d.[11] Throughout these studies, **5** was solely used as the substrate for protection of the alcoholic functionality. However, it can be readily realized that (*S*)-*N*,*N*-tetramethylenelactamide (**6**) accessible from **3** and pyrrolidine can be utilized similarly to **5**. The successful preparation of **2a** from **6** by way of the *O*-benzyl derivative (**8a**) has already been briefly mentioned in the separate paper reporting an efficient synthesis of the carbapenem key intermediates.[1b]

Experimental

(*S*)-*N*,*N*-Dimethyllactamide (5). Anhyd dimethylamine (18.0 g, 0.400 mol) was added to **3** (39.6 g, 0.335 mol) in a sealed tube at 0 °C. The mixture was stirred in a sealed tube at 70 °C for 1 d and excess dimethylamine and resulting ethanol were removed in vacuo to afford an oily residue. Additional amount of anhyd dimethylamine (10.0 g, 0.222 mol) was added to the residue and the mixture was further stirred in a sealed tube at 70 °C for 1 d to complete the amidolysis. After complete removal of excess dimethylamine and resulting ethanol in vacuo, the oily residue was purified with distillation (77 °C, 1 mmHg, 1 mmHg=133.322 Pa) to afford **5** as a colorless oil (36.4 g, 93%), $[\alpha]_D^{20}$ +0.98° (*c* 2.03, $CHCl_3$). IR (neat): 3450, 3000, 2950, 1640, 1510, 1450, 1380, 1260, 1120, 1030 cm^{-1}. ^1H NMR ($CDCl_3$): δ=1.33 (3H, d *J*=6.6 Hz, Me), 2.99 (6H, s, NMe_2), 3.66 (1H, bs OH), 4.46 (1H, dq, *J*=6.6 Hz, CH). MS *m/z*: 117 $(M)^+$, 73 $(M-NMe_2)^+$.

(*S*)-*N*,*N*-Dimethyl-2-benzyloxypropionamide (7a). a) Preparation with Sodium Hydride and Benzyl Chloride. A solution of **5** (8.12 g, 69.3 mmol) in THF (10 ml) was added slowly to a suspension of sodium hydride (2.00 g, 83.3 mmol) in THF (50 ml) and DMF (36 ml) at 0 °C with vigorous stirring. After stirring for 2 h, the mixture was diluted with THF (15 ml) and DMF (8 ml) and stirred vigorously for additional 6.5 h. Benzyl chloride (8.80 ml, 76.5 mmol) was added to the mixture at 0 °C, and stirring was continued at the same temperature overnight. The resulting mixture was diluted with H_2O (50 ml) and extracted with AcOEt. The combined extracts were washed with satd aq NaCl and dried over anhyd $MgSO_4$. After filtration and concentration in vacuo, the residue was purified with distillation (140 °C, 1 mmHg) to give **7a** as a colorless oil (11.3 g, 88%), $[\alpha]_D^{20}$ −51.5° (*c* 2.90, $CHCl_3$). IR (neat): 3500, 3000, 2950, 1660, 1500, 1458, 1402, 1260, 1118, 700 cm^{-1}. ^1H NMR ($CDCl_3$): δ=1.42 (3H, d, *J*=6.6 Hz Me), 2.95, 3.03 (6H, two s, NMe_2), 4.34 (1H, q, *J*=6.7 Hz, CH), 4.40, 4.60 (2H, two d, *J*=each 11.7 Hz, $\underline{CH_2}Ph$), 7.32 (5H, s, Ph), MS *m/z*: 208 $(M+1)^+$, 135 $(M-\overline{CO}NMe_2)^+$.

b) Preparation with Sodium Hydroxide and Benzyl Chloride in the Presence of a Phase-Transfer Catalyst. Benzyltributylammonium chloride (0.156 g, 0.500 mmol), benzyl chloride (1.52 g, 12.0 mmol), and aq NaOH (50%, 2.80 g, 35.0 mmol) were successively added to a solution of **5** (1.17 g, 10.0 mmol) in CH_2Cl_2 (5.0 ml) at rt. After being vigorously stirred for 12 h, the mixture was diluted with CH_2Cl_2 (10 ml) and H_2O (5 ml). The aqueous layer was separated and the organic layer was washed successively with 1 mol dm^{-3} HCl, and satd aq NaCl, then dried over anhyd $MgSO_4$. After filtration and concentration in vacuo, the residue was purified with column chromatography (SiO_2, hexane–AcOEt 2:3) to give **7a** as a colorless oil (1.78 g, 86%). The ^1H NMR spectrum of this sample were identical with those of **7a** obtained in a).

(*S*)-*N*,*N*-Dimethyl-2-(*p*-chlorobenzyloxy)propionamide (7b). Treatments of **5** (0.828 g, 7.06 mmol) with *p*-chlorobenzyl chloride (1.37 g, 8.51 mmol) under the same conditions as described for the procedure a) of the preparation of **7a** from **5**, gave **7b** as a colorless oil (1.30 g, 76%) after purification with column chromatography (SiO_2, hexane–AcOEt 3:7). $[\alpha]_D^{20}$ −47.2° (*c* 2.05, $CHCl_3$). IR (neat): 3500, 3000, 2950, 1655, 1498, 1400, 1105, 1018, 810 cm^{-1}. ^1H NMR ($CDCl_3$): δ=1.43 (3H, d, *J*=6.8 Hz, Me), 2.96, 3.01 (6H, two s, NMe_2), 4.34 (1H, q, *J*=6.9 Hz, CH), 4.35, 4.56 (2H, two d, *J*=each 11.7 Hz, $\underline{CH_2}Ar$), 7.29 (4H, s, C_6H_4). MS *m/z*: 242 $(M+1)^+$, 125 $(CH_2C_6H_4Cl)^+$.

(*S*)-*N*,*N*-Dimethyl-2-(*p*-methoxybenzyloxy)propionamide (7c). (*S*)-*N*,*N*-Dimethyllactamide (**5**) (0.828 g, 7.06 mmol) was treated with *p*-methoxybenzyl chloride (1.37 g, 8.51 mmol) under the same conditions as described for the procedure a) of the preparation of **7a** from **5**, afforded **7c** as a colorless oil (1.17 g, 75%) after purification with column chromatography (SiO_2, hexane–AcOEt 1:1). $[\alpha]_D^{20}$ −55.6° (*c* 2.03, $CHCl_3$). IR (neat): 3550, 2950, 1650, 1242, 1100, 1030, 820 cm^{-1}. ^1H NMR ($CDCl_3$): δ=1.41 (3H, d, *J*=6.8 Hz, Me), 2.95, 3.05 (6H, two s, NMe_2), 3.80 (3H, s, OMe), 4.32 (1H, q, *J*=6.8 Hz, CH), 4.34, 4.53 (2H, two d, *J*=each 10.6 Hz, $\underline{CH_2}Ar$), 6.85, 7.26 (4H, two d, *J*=8.8 Hz, C_6H_4). MS *m/z*: 238 $(M+1)^+$, 198 $(M-NMe_2)^+$, 121.

(*S*)-*N*,*N*-Dimethyl-2-(benzyloxymethoxy)propionamide (7d). Treatments of **5** (0.847 g, 7.23 mmol) with benzyloxymethyl chloride (1.21 ml, 8.70 mmol) under the same conditions as described for the procedure a) of the preparation of **7a** from **5**, gave **7d** as a colorless oil (1.07 g, 62%) after purification with column chromatography (SiO_2, hexane–AcOEt 3:2). $[\alpha]_D^{20}$ −64.4° (*c* 2.62, $CHCl_3$). IR (neat): 3550, 3120, 3000, 1665, 1518, 1462, 1418, 1120, 1050, 760, 718 cm^{-1}. ^1H NMR ($CDCl_3$): 1.40 (3H, d, *J*=6.8 Hz, Me), 2.94, 3.04 (6H, two s, NMe_2), 4.61 (1H, q, *J*=6.8 Hz, CH), 4.63 (2H, s, OCH_2O), 4.74, 4.84 (2H, two d, *J*=each 7.8 Hz, $\underline{CH_2}Ph$), 6.85, 7.26 (4H, two d, *J*=8.8 Hz, C_6H_4). MS *m/z*: 238 $(M+1)^+$, 198 $(M-NMe_2)^+$, 121.

(*S*)-2-Benzyloxypropanal (2a). General procedure for the reduction with Vitride®. A 1.07 mol dm^{-3} solution of Vitride® in a mixture of toluene and THF (1.60 ml, 3.20 mmol) was added slowly to a solution of **7a** (1.12 g, 5.39 mmol) in THF (15 ml) at 0 °C. After stirring at the same temperature for 2.5 h, the reaction mixture was poured into 1 mol dm^{-3} HCl (15 ml) cooled in an ice bath and extracted with CH_2Cl_2. The combined extracts were washed successively with 0.3 mol dm^{-3} HCl, satd aq NaCl, satd aq $NaHCO_3$, and satd aq NaCl, then dried over anhyd $MgSO_4$. Filtration and concentration in vacuo gave a residue which was purified with bulb-to-bulb distillation (100 °C, 1 mmHg) to give **2a** as a colorless oil (0.800 g, 90%). IR (neat): 3470, 3058, 3000, 2950, 1740, 1500, 1456, 1380, 1210, 1100, 741, 702 cm^{-1}. ^1H NMR ($CDCl_3$): 1.32 (3H, d, *J*=6.8 Hz,Me), 3.88 (1H, dq, *J*=1.8, 6.8 Hz, Me$\underline{CH}$), 4.62 (2H, s, $\underline{CH_2}Ph$), 7.35 (5H, s, Ph), 9.66 (1H, d *J*=1.8 Hz,CHO). MS *m/z*: 181 $(M+OH)^+$, 135 $(M-CHO)^+$.

(*S*)-(*p*-Chlorobenzyloxy)propanal (2b). Reduction of **7b** (0.800 g, 3.31 mmol) performed in a similar manner to that described for the preparation of **2a**, gave **2b** as a colorless oil (0.586 g, 89%) after purification with column chromatography (SiO_2, hexane–AcOEt 97:3). IR (neat): 2990, 2860, 1738, 1490, 1082, 1010, 802 cm^{-1}. ^1H NMR ($CDCl_3$): δ=1.34 (3H, d, *J*=7.0 Hz, Me), 3.88 (1H, dq, *J*=1.7, 7.0 Hz, CH), 4.51, 4.65 (2H, two d, *J*=each 11.9 Hz, $\underline{CH_2}Ar$), 7.31 (4H, s, C_6H_4), 9.66 (1H, d, *J*=1.5 Hz, CHO). MS *m/z*: 169 $(M-CHO)^+$, 125 $(CH_2C_6H_4Cl)^+$.

(*S*)-(*p*-Methoxybenzyloxy)propanal (2c). Treatment of **7c** (0.427 g, 1.80 mmol) under the conditions similar to those described for the reduction of **7a** afforded **2c** as a colorless oil (0.278 g, 80%) after purification with column chromatography (SiO_2, hexane–AcOEt 24:1). IR (neat): 2950, 2850, 1728, 1610, 1518, 1250, 1030, 820 cm^{-1}. ^1H NMR ($CDCl_3$): δ= 1.30 (3H, d, *J*=7.0 Hz,Me), 3.80 (3H, s, MeO), 3.90 (1H, dq, *J*=1.8, 7.0 Hz, CH), 4.55 (2H, s, $\underline{CH_2}Ar$), 6.88, 7.29 (4H, two

d, J=8.8 Hz, C_6H_4), 9.62 (1H, d, J=1.8 Hz, CHO). MS m/z: 194 $(M)^+$, 121 $(M-CH_2C_6H_4OMe)^+$.

(*S*)-(Benzyloxymethoxy)propanal (2d). Reduction of **7d** (0.724 g, 3.05 mmol) carried out in a similar manner to that described for the preparation of **2a**, gave **2d** as a colorless oil (0.500 g, 84%) after purification with column chromatography (SiO_2, hexane–AcOEt 24:1—4:1). IR (neat): 3050, 2900, 1738, 1450, 1380, 1040, 740, 700 cm^{-1}. ^1H NMR ($CDCl_3$): δ=1.32 (3H, d, J=6.8 Hz, Me), 4.10 (1H, dq, J=1.5, 6.8 Hz, CH), 4.67 (2H, s, OCH_2O), 4.86 (2H, s, $\underline{CH_2}Ph$), 7.33 (5H, s, Ph), 9.64 (1H, d, J=1.5 Hz, CHO). MS m/z: 165 $(M-CHO)^+$.

(*S*)-2-Benzyloxy-2-propanol (9a). General procedure for the reduction with sodium borohydride. Sodium borohydride (0.166 g, 4.39 mmol) was added to a solution of **2a** (0.282 g, 1.72 mmol) in EtOH (2 ml) at 0 °C. After stirring for 2 h at the same temperature, the mixture was diluted with 1 mol dm^{-3} HCl to decompose the excess reducing agent and extracted with AcOEt. The combined extracts were washed successively with satd aq NaCl, satd aq $NaHCO_3$ and satd aq NaCl, then dried over anhyd $MgSO_4$. Filtration and concentration in vacuo gave an oily residue which was purified with column chromatography (SiO_2, hexane–AcOEt 4:1) to give **9a** as a colorless oil (0.272 g, 95%), $[\alpha]_D^{20}$ +44.7° (c 3.47, $CHCl_3$) [lit,[2b] $[\alpha]_D^{25}$ +43.1° (c 3, $CHCl_3$) lit,[2c] $[\alpha]_D$ +45.86° (c 6.4, $CHCl_3$)]. IR (neat): 3450, 3050, 2970, 2940, 2870, 1950, 1880, 1818, 1500, 1450, 1050, 700 cm^{-1}. ^1H NMR ($CDCl_3$): δ=1.15 (3H, d, J=6.0 Hz, Me), 2.41 (1H, bs, OH), 3.51—3.65 (3H, m, $CHCH_2O$), 4.44, 4.63 (2H, two d, J=each 11.7 Hz, $\underline{CH_2}Ph$), 7.31 (5H, bs, Ph). MS m/z: 166 $(M)^+$, 91, 65. The optical purity of this sample was determined by comparing the ^1H NMR spectra of its (*R*)- and (*S*)-MTPA esters prepared according to the method reported by Mosher et al.[8] The (*R*)- and (*S*)-MTPA esters of **9a** were obtained in 72% and 66% yields, respectively. The (*R*)-MTPA ester of **9a**: $[\alpha]_D^{20}$ +45.7° (c 1.35, $CHCl_3$). IR (neat): 3000, 2950, 1745, 1445, 1270, 1240, 1162, 1020, 700 cm^{-1}. ^1H NMR ($CDCl_3$): δ=1.21 (3H, d, J=6.4 Hz, Me), 3.54 (3H, dd, J=1.3, 2.4 Hz, MeO), 3.78—3.90 (1H, m, CH), 4.29—4.39 (2H, m, $CH\underline{CH_2}O$), 4.52 (2H, s, $\underline{CH_2}Ph$), 7.23—7.62 (10H, m, Ph×2). MS m/z: 382 $(M)^+$, 244. The (*S*)-MTPA esters of **9a**: $[\alpha]_D^{20}$ −32.7° (c 2.24, $CHCl_3$). IR (neat): 3000, 2950, 1742, 1442, 1270, 1240, 1160, 1020, 695 cm^{-1}. ^1H NMR ($CDCl_3$): δ=1.20 (3H, d, J=6.4 Hz, Me), 3.53 (3H, dd, J=1.2, 2.3 Hz, MeO), 3.77—3.90 (1H, m, CH), 4.33 (2H, d, J=5.7 Hz, $CH\underline{CH_2}O$), 4.51 (2H, s, $\underline{CH_2}Ph$), 7.22—7.61 (10H, m, Ph×2). MS m/z: 382 $(M)^+$, 244. The ^1H NMR spectrum of the (*R*)-MTPA ester showed no signals corresponding to the (*S*)-MTPA ester. Accordingly, it appeared obvious that **2a** could be prepared from **3** without racemization.

(*S*)-2-(*p*-Chlorobenzyloxy)-1-propanol (9b). Reduction of **2b** (0.408 g, 2.05 mmol) performed as described for the preparation of **9a** from **2a**, gave **9b** as a colorless oil (0.390 g, 95%) after purification with column chromatography. $[\alpha]_D^{20}$ +36.8° (c 1.72, $CHCl_3$). IR (neat): 3450, 2950, 1918, 1610, 1500, 1100, 890 cm^{-1}. ^1H NMR ($CDCl_3$): δ=1.17 (3H, d, J=6.2 Hz, Me), 2.00 (1H, bs, OH), 3.48—3.73 (3H, m, $CHCH_2O$), 4.44, 4.63 (2H, two d, J=each 11.8 Hz, $\underline{CH_2}Ar$), 7.31 (4H, bs, C_6H_4). MS m/z: 200 $(M)^+$, 125 $(CH_2C_6H_4Cl)^+$.

(*S*)-2-(*p*-Methoxybenzyloxy)-1-propanol (9c). Treatments of **2c** (0.216 g, 1.11 mmol) under the same conditions as described for the preparation of **9a** from **2a**, gave **9c** as a colorless oil (0.217 g, 99%) after purification with column chromatography. $[\alpha]_D^{20}$ +41.2° (c 4.10, $CHCl_3$). IR (neat): 3450, 2950, 1610, 1510, 1242, 1030, 820 cm^{-1}. ^1H NMR ($CDCl_3$): δ=1.15 (3H, d, J=5.2 Hz, Me), 2.20 (1H, br, OH), 3.44—3.74 (3H, m, $CHCH_2O$), 3.79 (3H, s, OMe), 4.38, 4.52 (2H, two d, J=each 11.2 Hz $\underline{CH_2}Ar$), 6.87, 7.26 (4H, two d, J=8.6 Hz, C_6H_4). MS m/z: 196 $(M)^+$, 152, 137.

(*S*)-2-(*p*-Benzyloxymethoxy)-1-propanol (9d). Reduction of **2d** (0.431 g, 2.17 mmol) under the same conditions described for the preparation of **9a** from **2a**, afforded **9d** as a colorless oil (0.361 g, 85%) after purification with column chromatography. $[\alpha]_D^{20}$ +51.8° (c 1.51, $CHCl_3$). IR (neat): 3460, 2950, 2900, 1458, 1380, 1040, 700 cm^{-1}. ^1H NMR ($CDCl_3$): δ=1.18 (3H, d, J=6.4 Hz, Me), 2.61 (1H, bs, OH), 3.53 (2H, m, $\underline{CH_2}OH$), 3.86 (1H, m, CH), 4.65 (2H, s, OCH_2O), 4.85 (2H, s, $\underline{CH_2}Ph$), 7.34 (5H, s, Ph). MS m/z: 181 $(M-Me)^+$, 165 $(M-CH_2OH)^+$.

(*S*)-1,2-Propanediol (10). Palladium on carbon (10%, 25.8 mg) and one drop of 5 mol dm^{-3} solution of HCl in EtOH were added to a solution of **9a** (0.204 g, 1.23 mmol) in EtOH (3 ml) and the mixture was stirred under a hydrogen atmosphere for 1 h. The catalyst was filtered off and the filtrate was concentrated in vacuo. The concentration residue was purified with bulb-to-bulb distillation (110 °C, 18 mmHg) to give **10** as a colorless oil (65.0 mg, 70%). By the same procedure as described above, **9b, c** could be derived to **10** (56% from **9b** and 60% from **9c**). $[\alpha]_D^{20}$ +27.4° (c 3.00, $CHCl_3$) (from **9a**), $[\alpha]_D^{20}$ +27.5° (c 2.38, $CHCl_3$) (from **9b**), $[\alpha]_D^{20}$ +28.0° (c 2.31, $CHCl_3$) (from **9c**), [lit,[12] $[\alpha]_D^{24.2}$ +30.0° (c 3.00, $CHCl_3$)]. These specific rotation values clearly confirmed that no racemization had taken place during the preparation of **2b,c** from **3**. IR (neat): 3400, 3000, 2950, 1650, 1140, 1040, 840 cm^{-1}. ^1H NMR ($CDCl_3$): δ=1.15 (3H, d, J=6.4 Hz, Me), 3.10 (2H, bs, OH×2), 3.38—3.99 (3H, m, $\underline{CHCH_2}O$). MS m/z: 61 $(M-Me)^+$, 59 $(M-OH)^+$.

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5) Since the sodium alkoxide prepared from **5** and sodium hydride was found to be fairly unstable at rt, it should be treated blow 0 °C.

6) Sodium hydroxide was used as an aqueous solution or as a powder.

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9) The *O*-allyl derivative (**7**: R^3=allyl) was similarly prepared in 71% yield by treating **5** with sodium hydride and allyl chloride though the corresponding propanal derivative (**2**: R^3=allyl) could not be obtained by the subsequent reduction.

10) Since hydrogenolysis of **9d** produced by the reduction of **2d** with sodium borohydride turned out to be unsuccessful, the optical purity of **2d** could not be rigorously ascertained. However, based on the results obtained for **2a—c**, **2d** prepared from **5** by way of **7d** was expected to be optically pure.

11) Application of this methodology to the synthesis of (*R*)- or (*S*)-3-benzyloxybutanal, one of the useful chiral building blocks, from commercially available methyl (*R*)- or (*S*)-3-hydroxybutyrate, resulted in exclusive formation of the elimination product (the crotonamide derivative) in the step of benzylation.

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