PRACTICAL SYNTHESIS OF (*R*)-1-BENZYL-3-HYDROXY-2,5-PYRROLIDINEDIONE AND ITS ACETATE FROM L-TARTARIC ACID

Hiroshi Tomori,[a] Hiroshi Maruyama,[b] and Katsuyuki Ogura*

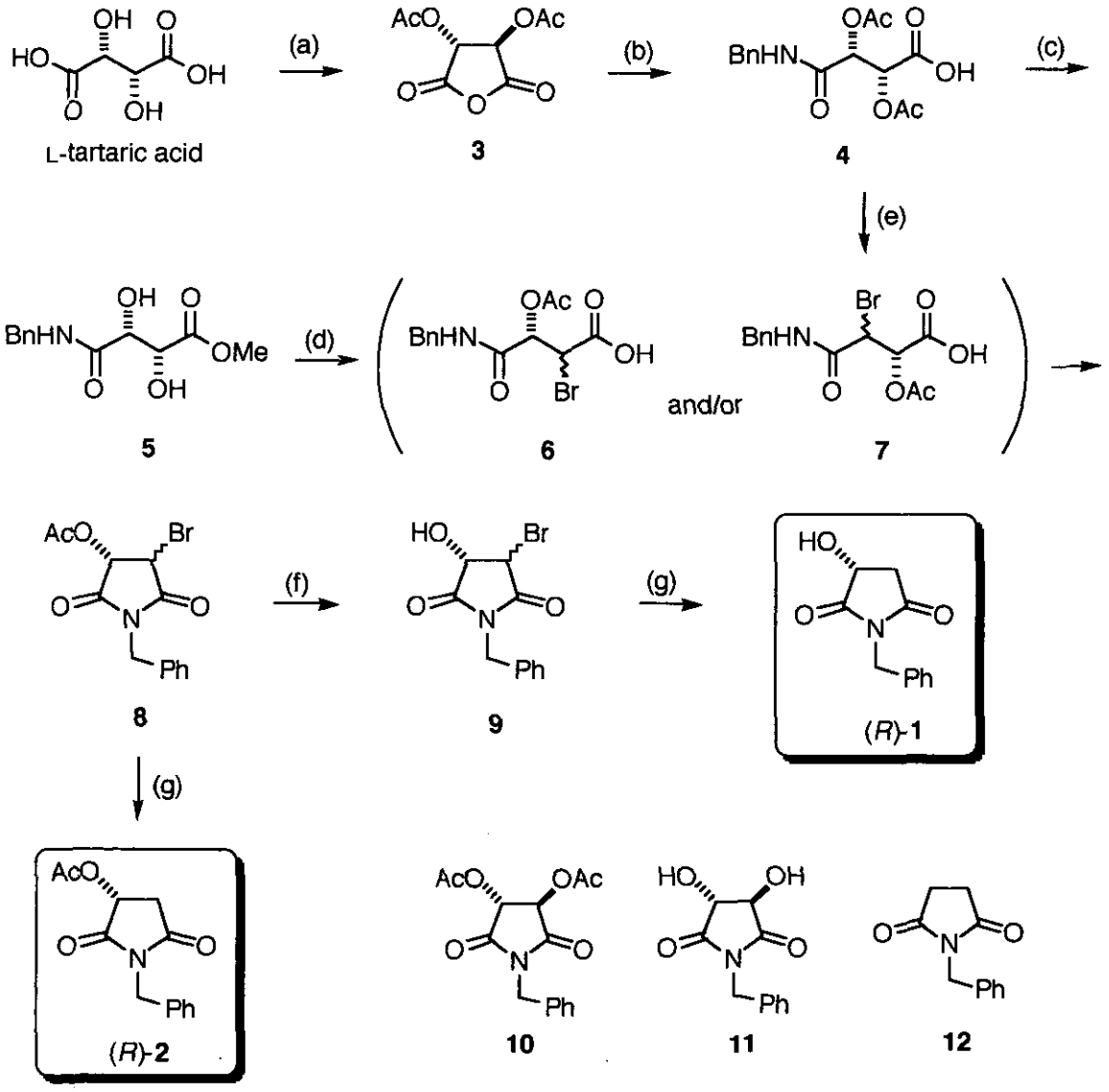
Department of Applied Chemistry, Faculty of Engineering and [a]Graduate School of Science and Technology, Chiba University, 1-33 Yayoicho, Inage-ku, Chiba 263, Japan
[b]Process Development Laboratories, Sankyo Co., Ltd., 1-2-58 Hiromachi, Shinagawa-ku, Tokyo 140, Japan

Abstract - An efficient method for preparing (*R*)-1-benzyl-3-hydroxy-2,5-pyrrolidinedione and its acetate is described starting from L-tartaric acid, which affords the desired compounds with 99% ee in good overall yields (63-74%).

Enantiomerically pure 3-hydroxypyrrolidines are versatile chiral building blocks for the synthesis of such biologically active compounds as κ-opioid receptor agonists,[1,2] muscarin receptor agonists,[3] calcium antagonist,[4] antibiotics,[5] antihistamine,[6] and prolyl depsipeptides.[7] As a result of their wide range utility in the pharmaceutical industry, considerable efforts have been made for preparing optically active 3-hydroxypyrrolidines and a number of their procedures are now available.[8] Enantiomerically pure 1-benzyl-3-hydroxy-2,5-pyrrolidinedione (**1**) and its acetate (**2**) are among the most promising precursors to access chiral 3-hydroxypyrrolidines.[1,4,9] Furthermore, they serve as synthetic intermediates of chiral β-hydroxy-γ-amino acids[10] and β-substituted γ-lactones.[11] Although the methods to produce the (*S*)-enantiomers of **1** and **2** from relatively inexpensive natural D-malic acid have established, there is no practical method for preparing their antipodes. Hence, our attention was directed to the development of an economical synthesis that is adaptable to a large-scale preparation of the (*R*)-enantiomers of **1** and **2**. In this paper, we report a convenient and efficient method for the production of (*R*)-**1** and (*R*)-**2** starting from natural L-tartaric acid, as summarized in Scheme 1, which involves the acetoxy bromination[12] of *N*-benzyltartaramic acid derivatives (**4** and **5**) as a key to our success.[13] L-Tartaric acid was chosen as the starting material, since it

possesses a C2-symmetric vicinal diol system and its absolute configration is the same to that of the target compounds.

Scheme 1



(a) AcCl/AcOH, 50 °C, quant. (b) $BnNH_2$ (1 equiv), 0 °C–room temperature, 1 h, quant. (c) 1.3 *N* HCl/MeOH, room temperature, quant. (d) HBr (6 equiv)/AcOH, 50 °C; then Ac_2O (3 equiv), 50 °C. (e) HBr (6 equiv)/AcOH and H_2O (1 equiv), 50 °C; then Ac_2O (3 equiv), 50 °C. (f) HBr/AcOH, 50 °C; then MeOH, room temperature–45 °C. (g) H_2 (2 atm), 5% Pd/C, room temperature.

L-Tartaric acid was sequentially treated with acetyl chloride and with 1 molar equiv of benzylamine to afford the half amide (**4**),[14] which was subjected to reaction with 1.3 *N* HCl in methanol to give the amide

ester (**5**). The yields of **4** and **5** were quantitative from L-tartaric acid.

First the acetoxy bromination of **5** was investigated: **5** was treated with 30 wt% HBr (6 equiv) in acetic acid at 50 °C. Monitoring of the reaction by hplc showed that a complex mixture, which presumably contained **6** and/or **7**, appeared at an early stage and gradually converged to the ring-closure product (**8**), but the cyclization step was very slow. In order to accelerate the cyclization reaction, acetic anhydride (3 equiv) was added after 5–6 h and the resulting mixture was stirred for further 19–20 h at 50 °C. From the ^{1}Hnmr of the crude product, **8** was shown to be a 3:2 diastereomeric mixture contaminated by a small amount of a by-product (**10**)[15] (**8**:**10**=*ca.* 20:1 determined by hplc). The yield of **10** was found to increase with the decreasing mole ratio of HBr to **5**. The ratios of **8**:**10** were 5:1 and 1:1 on treatment with 4 equiv and 2 equiv of HBr, respectively, under the similar conditions. Therefore the use of 6 equiv of HBr is recommendable to minimize the formation of **10**. Hydrogenolysis of the crude **8** with 5% Pd on carbon provided the desired (*R*)-**2** (74% overall yield from L-tartaric acid) together with **10** (4% yield) and an unexpected product (**12**) (5% yield).[16] The enantiomeric excess of (*R*)-**2** thus obtained was determined by hplc analysis to be 99% ee. This reveals that no significant epimerization occurred at the acetoxyl-substituted center throughout these reactions and that the intermediary **8** was a stereoisomeric mixture at the bromine-bearing stereogenic center.

In a similar fashion, sequential treatment of **4** with 6 equiv of HBr/AcOH containing 1 equiv of water and then with 3 equiv of acetic anhydride afforded a *ca.* 10:1 mixture of **8** and **10**, which was subjected to hydrogenolysis with 5% Pd on carbon to give (*R*)-**2** with 99% ee (66% overall yield from L-tartaric acid) together with **10** (7%) and **12** (10%). It should be noted that the ratio of **8**:**10** decreased to approximately 1:1 in the absence of water. Although we have no definitive evidence to explain the precise role of the water, the water probably contributed to the monodeacetylation of **4** to facilitate neucleophilic substitution with bromide ion in acidic media.

Finally, the synthesis of **1** *via* a hydroxy bromide (**9**) was explored. To the reaction mixture that was given by treatment of **5** with 30 wt% HBr (6 equiv) in acetic acid and then with acetic anhydride (3 equiv) in aforementioned manner, was added a large excess of methanol under ice-cooling and the resulting mixture was stirred at room temperature to 45 °C to bring about solvolysis of **8** into **9**. After concentration of the reaction mixture, water was added and the mixture was extracted with "*toluene*". The major by-product (**11**) resulting from the methanolysis of **10** was removed at this extraction stage because of toluene's low extractability toward **11**. Thus concentration of the toluene extract gave crude **9** with a high chemical

purity, which was subjected to hydrogenolysis with 5% Pd on carbon, followed by crystallization from toluene to afford (*R*)-**1** with 99% ee (63% overall yield from L-tartaric acid). Of particular advantage is that no tedious manipulation is required to isolate each of the intermediates. Moreover, crystalline (*R*)-**1** can be obtained with a high enantiomeric excess (99% ee) and a high chemical purity (98%) without any purification process. These facts offer favorable prospects for the present method to be used for the large-scale production of (*R*)-**1**.

In summary, we have developed a practical procedure for the preparation of (*R*)-**1** and (*R*)-**2** starting from L-tartaric acid, which comprises of straightforward processes to elaborate the desired compounds with a high degree of enantiomeric excess (99% ee) in good overall yields (63-74%).

EXPERIMENTAL

Melting points were determined with a Yamato MP-21 melting point apparatus and are uncorrected. Optical rotations were determined with a Horiba SEPA-300 polarimeter. ^{1}HNmr spectra were recorded on a JEOL JNM-GSX 400 (400 MHz) spectrometer, and chemical shifts were reported in ppm relative to tetramethylsilane as internal standard. Ir spectra were run on a JASCO FT/IR-8900 or JASCO IR-810 spectrophotometer. Column chromatography was performed on a pre-packed glass column (Merck, LiChroprep Si 60, ø 25×310 mm). Preparative hplc was carried out on a reversed-phase column (ODS-525-05-SR, ø 50×250 mm, YMC Co.). Analytical hplc was performed on a Shiseido Capcell Pak C18 SG120 column (ø 4.6×250 mm) [eluent, acetonitrile/0.02 M aq. $AcONH_4$ (2:3); flow rate, 1.0 ml/min; column oven, 40 °C; t_R of **1**=4.1 min, t_R of **2**=7.4 min, t_R of **4**=2.6 min, t_R of **5**=3.2 min, t_R of **8**=12–18 min (broad), t_R of **9**=5.7 and 6.6 min, t_R of **10**=10.7 min, t_R of **11**=3.4 min, t_R of **12**=5.3 min]. All chemicals used herein were reagent grade.

(2*R*,3*R*)-4-(*N*-Benzylcarbamoyl)-2,3-diacetoxybutyric acid (4). To a suspension of L-tartaric acid (4.50 g, 30.0 mmol) in acetic acid (4 ml) was added acetyl chloride (13.5 ml, 190 mmol) and the mixture was heated at 50 °C overnight. The resulting clear solution was concentrated in vacuo to dryness to give crude diacetate of L-tartaric anhydride (6.49 g) as a colorless solid. Then to a solution of the anhydride in CH_2Cl_2 (45 ml) was added dropwise a solution of benzylamine (3.28 ml, 30.0 mmol) in

CH_2Cl_2 (6.5 ml) at 0–10 °C over 30 min. Precipitates formed soon after the addition was complete. After the mixture was stirred at the same temperature for 30 min and then for 30 min at room temperature, methanol (20 ml) was added to the suspension. The resulting clear solution was concentrated in vacuo to dryness to give 10.04 g (quantitative) of **4** as colorless crystals: mp 131.5–132.0 °C (H_2O) [lit.,[14] mp 157–158 °C (ethyl acetate–light petroleum)]; $[\alpha]^{20}_D$ -13.7° (*c* 1.0, methanol); *ir* (KBr) 3500–2400, 1776, 1764, 1732, 1635, 1215, 1201 cm^{-1}; ^{1}Hnmr (CD_3OD) δ 1.97 (s, 3H, C*H*$_3$), 2.16 (s, 3H, C*H*$_3$), 4.29 (dd, *J*=4 and 15 Hz, 1H, NC*H*$_2$Ph), 4.51 (dd, *J*=5 and 15 Hz, 1H, NC*H*$_2$Ph), 5.60 (d, *J*=3 Hz, 1H, C*H*OAc), 5.67 (d, *J*=3 Hz, 1H, C*H*OAc), 7.21–7.32 (m, 5H, Ar*H*), 8.81 (br t-like, 1H, N*H*). The ^{1}Hnmr spectrum of this compound was in agreement with that reported in the literature.[14]

Methyl (2*R*,3*R*)-4-(*N*-benzylcarbamoyl)-2,3-dihyroxybutyrate (5). A solution of **4** (32.3 g, 100 mmol) in 1.3 *N* HCl in methanol (440 ml) was stirred for 16 h at room temperature. The resulting mixture was concentrated in vacuo to dryness to afford 25.8 g (quantitative) of **5** as colorless crystals: mp 124.5–125.0 °C (H_2O); $[\alpha]^{20}_D$ +63.7° (*c* 1.0, methanol); ir (KBr) 3358, 1728, 1660, 1288, 1122, 1067 cm^{-1}; ^{1}Hnmr (CD_3OD) δ 3.77 (s, 3H, C*H*$_3$), 4.43 (d, *J*=15 Hz, 1H, NC*H*$_2$Ph), 4.47 (d, *J*=2 Hz, 1H, C*H*OH), 4.48 (d, *J*=15 Hz, 1H, NC*H*$_2$Ph), 4.61 (1H, *J*=2 Hz, 1H, C*H*OH), 7.20–7.33 (m, 5H, Ar*H*). Anal. Calcd for $C_{12}H_{15}NO_5$: C, 56.91; H, 5.97; N, 5.53. Found: C, 56.92; H, 5.88; N, 5.55.

Preparation of (*R*)-3-Acetoxy-1-benzyl-2,5-pyrrolidinedione ((*R*)-2) from 5. A typical procedure. Compound (**5**) (0.76 g, 3.0 mmol) was placed in a 25 ml one-neck round-bottomed flask equipped with a magnetic stirring bar, and 30 wt% HBr in AcOH (3.6 ml, 9.0 mmol of HBr) was added. The flask was fitted with a serum cup, and the mixture was heated at 50 °C for 6 h and then cooled to room temperature. After acetic anhydride (0.85 ml, 9.0 mmol) was added, the mixture was heated again at 50 °C for 19 h and then poured into ice-water (20 ml) and toluene (20 ml). The organic layer was separated and the aqueous layer was extracted with toluene (20 ml). The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo to afford crude mixture of (3*R*,4*S*)- and (3*R*,4*R*)-3-acetoxy-4-bromo-2,5-pyrrolidinediones (**8**) (908 mg) as a pale yellow oil, which was shown by ^{1}Hnmr to be a 3:2 diastereomeric mixture. In order to obtain its analytical sample, a part of the crude product was purified by column chromatography (ethyl acetate/hexane, 1:3). Data for a 3:2 diastereomeric mixture: a colorless oil; ir (neat) 1755, 1720, 1395, 1222, 1167 cm^{-1}; ^{1}Hnmr ($CDCl_3$) δ 2.20 (s, 3H×0.6, C*H*$_3$), 2.25 (s, 3H×0.4, C*H*$_3$), 4.69 (d, *J*=4.6 Hz, 1H×0.6, C*H*Br), 4.72 (d, *J*=14.3 Hz, 1H×0.6, NC*H*$_2$Ph), 4.73 (d, *J*=14.1 Hz,

1H×0.4, NCH_2Ph), 4.75 (d, J=14.1 Hz, 1H×0.4, NCH_2Ph), 4.78 (d, J=14.3 Hz, 1H×0.6, NCH_2Ph), 4.90 (d, J=7.3 Hz, 1H×0.4, CHBr), 5.50 (d, J=4.6 Hz, 1H×0.6, CHOAc), 5.52 (d, J=7.3 Hz, 1H×0.4, CHOAc), 7.3–7.4 (m, 5H, ArH). Anal. Calcd for $C_{13}H_{12}NO_4Br \cdot 0.1CH_3CO_2C_2H_5$: C, 47.86; H, 3.87; N, 4.20; Br, 23.94. Found: C, 48.00; H, 3.84; N, 4.09; Br, 24.04.

The crude **8** (850 mg) obtained above was placed in an autoclave. Then dioxane (40 ml), water (20 ml), and 5% Pd/C (85 mg) were added. The resulting mixture was stirred vigorously for 75 min under hydrogen atmosphere (2 atm) at room temperature. The catalyst was filtered off and washed with dioxane. After the filtrate and the washing were combined and evaporated to remove dioxane, the residual solution was extracted with toluene (15 ml). The organic extract was dried (Na_2SO_4) and concentrated in vacuo to afford an oil (721 mg). Preparative hplc (acetonitrile/water=2:3; flow rate=40 ml/min) of the oil (700 mg) afforded 500 mg (74% overall yield from L-tartaric acid) of (*R*)-**2** as a colorless solid together with **10** (31 mg: 4%) and **12** (28 mg: 5%). The enantiomeric excess of (*R*)-**2** was determined to be 99% ee [Hplc analysis: column, Daicel Chiralcel OJ (ø 4.6×250 mm); eluent, IPA/hexane (1:2); flow rate, 0.6 ml/min; t_R of (*R*)-**2**= 38.4 min, t_R of (*S*)-**2**= 40.7 min].

Data for (*R*)-**2**: mp 59–60 °C; $[\alpha]^{20}_D$ +42.4° (*c* 0.50, methanol) [lit.,[10b] mp 58–60 °C; $[\alpha]^{20}_D$ of (*S*)-**2**: -42° (*c* 1.18, methanol)]; ir (Nujol) 1760, 1705, 1430, 1405, 1225 cm^{-1}; ^{1}Hnmr ($CDCl_3$) δ 2.16 (s, 3H, CH_3), 2.67 (dd, J=5.0 and 18.3 Hz, 1H, CH_2C(=O)N), 3.17 (dd, J=8.8 and 18.3 Hz, 1H, CH_2C(=O)N), 4.69 (d, J=14.1 Hz, 1H, NCH_2Ph), 4.72 (d, J=14.1 Hz, 1H, NCH_2Ph), 5.45 (dd, J=5.0 and 8.8 Hz, 1H, CH(OAc)), 7.26–7.40 (m, 5H, ArH). These spectral data were identical with those reported for the (*S*)-enantiomer.[11a] The spectral data for **10** and **12** agreed with the corresponding authentic samples prepared from **3** and succinic anhydride, respectively.

Preparation of (*R*)-2 from 4. A mixture of **4** (0.97 g, 3.0 mmol), 30% HBr/AcOH (3.6 ml, 9.0 mmol of HBr), and water (54 μl, 3.0 mmol) was heated at 50 °C for 21.5 h and then acetic anhydride (0.87 ml, 10 mmol) was added. The resulting mixture was heated again at 50 °C for 5.5 h and poured into ice-water (20 ml). After the mixture was extracted with toluene (2×20 ml), the combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo to afford crude **8**, to which were added dioxane (50 ml), water (25 ml), and 5% Pd/C (90 mg). The resulting mixture was stirred vigorously under hydrogen atmosphere (2 atm) for 30 min, and the catalyst was filtered off and washed with dioxane. After the filtrate and the washing were combined and evaporated to remove dioxane, the residual aqueous solution was extracted

with toluene (2×20 ml). The combined organic extracts were concentrated and purified by preparative hplc under the similar conditions described above to give 493 mg (66% overall yield from L-tartaric acid) of (*R*)-**2** with 99% ee together with **10** (55 mg: 7%) and **12** (55 mg: 10%)

Preparation of (*R*)-1-Benzyl-3-hydroxy-2,5-pyrrolidinedione ((*R*)-1) from 5. A mixture of **5** (6.33 g, 25.0 mmol) and 30% HBr/AcOH (30 ml, 0.15 mol) was heated at 50 °C for 5 h. After cooling to room temperature and addition of acetic anhydride (7.1 ml, 75 mmol), the resulting mixture was heated again at 50 °C for 20 h. Then methanol (30 ml) was added under ice-cooling and the resulting mixture was warmed up to room temperature. After being stirred for 42 h at room temperature and for 6 h at 45 °C, the reaction mixture was concentrated to *ca.* 20 ml and water (15 ml) was added. The aqueous solution was extracted with toluene (2×40 ml). The combined organic extracts were washed with water (3 ml), dried (Na_2SO_4), and concentrated in vacuo to afford a 5:2 diastereomeric mixture of crude mixture of (3*S*,4*R*)- and (3*R*,4*R*)-3-bromo-4-hydroxy-2,5-pyrrolidinediones (**9**) (6.72 g) as a viscous yellow oil, which was used in the next step without further purification. An analytical sample of **9** was obtained by column-chromatographic purification (ethyl acetate/hexane, 1:2) of the crude product prepared in the strictly same manner.

Data for a less polar isomer (major): colorless crystals; mp 97.5–98.5 °C (ether–hexane); $[\alpha]^{20}_D$ +36.7° (*c* 0.53, ethanol); ir (KBr) 3447, 3319, 1713, 1696, 1176 cm^{-1}; ^{1}Hnmr ($CDCl_3$) δ 3.13 (d, *J*=4 Hz, 1H, O*H*), 4.58 (d, *J*=5 Hz, 1H, C*H*Br), 4.70 (d, *J*=14 Hz, 1H, NCH_2Ph), 4.73 (d, *J*=14 Hz, 1H, NCH_2Ph), 4.76 (dd, *J*=4 and 5 Hz, 1H, C*H*OH), 7.28–7.37 (m, 5H, Ar*H*). Anal. Calcd for $C_{11}H_{10}NO_3Br$: C, 46.50; H, 5.79; N, 4.93; Br, 28.12. Found: C, 46.60; H, 5.50; N, 4.96; Br, 27.96.

Data for a more polar isomer (minor): colorless crystals; mp 126.5–128.0 °C (ether); $[\alpha]^{20}_D$ +66.8° (*c* 0.26, ethanol); ir (KBr) 3432, 1693, 1135, 747, 720 cm^{-1}; ^{1}Hnmr ($CDCl_3$) δ 2.95 (d, *J*=6.7 Hz, 1H, O*H*), 4.65 (t, *J*=6.7 Hz, 1H, C*H*OH), 4.70 (d, *J*=14.3 Hz, 1H, NCH_2Ph), 4.73 (d, *J*=14.3 Hz, 1H, NCH_2Ph), 4.80 (d, *J*=6.7 Hz, 1H, C*H*Br), 7.28–7.37 (m, 5H, Ar*H*). Anal. Calcd for $C_{11}H_{10}NO_3Br$: C, 46.50; H, 5.79; N, 4.93; Br, 28.12. Found: C, 46.27; H, 5.80; N, 4.89; Br, 27.88.

A mixture of the above obtained crude **9** (6.72 g) and 5% Pd/C (0.67 g) in methanol–water (4:1, 150 ml) was stirred vigorously under hydrogen atmosphere (2 atm) at room temperature. After 1 h, the catalyst was filtered off and washed with methanol. The filtrate and the washing were combined and concentrated to *ca.* 40 ml, and water (20 ml) was added. The mixture was extracted with ethyl acetate (2×40 ml) and the

combined organic extracts were washed with water (20 ml), dried (Na_2SO_4), and concentrated in vacuo. The residue was crystallized from toluene (24 ml) to afford 3.24 g (63% overall yield from L-tartaric acid) of (*R*)-**1** (98% chemical purity) as colorless crystals. The enantiomeric excess of (*R*)-**1** was determined to be 99% ee [Hplc analysis: column, Daicel Chiralcel OJ (ø 4.6×250 mm); eluent, IPA/hexane (1:6); flow rate, 0.6 ml/min; t_R of (*R*)-**1**=31.1 min, t_R of (*S*)-**1**=27.7 min]. mp 101–103 °C; $[\alpha]^{20}_D$ +62.7° (*c* 0.50, ethanol) [lit.,[4] mp 99–101 °C; $[\alpha]^{20}_D$ of (*S*)-**1** with 80% ee: -51.1° (*c* 0.50, ethanol)]; ir (KBr) 3367, 1687, 1434, 1344, 1179 cm^{-1}; ^{1}Hnmr ($CDCl_3$) δ 2.68 (dd, *J*=4.9 and 18.2 Hz, 1H, C*H*$_2$C(=O)N), 3.07 (dd, *J*=8.5 and 18.2 Hz, 1H, C*H*$_2$C(=O)N), 3.19 (br d, *J*=2.8, 1H, O*H*), 4.60–4.64 (m, 1H, C*H*(OH)), 4.66 (s, 2H, NC*H*$_2$Ph), 7.26–7.38 (m, 5H, Ar*H*). The spectral data for this compound were identical with those reported in the literature.[17]

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15. Compound (**10**) remained unchanged during the reaction with 30 wt% HBr/AcOH.

16. Compound (**12**) presumably arose by the hydrogenation of *N*-benzylmaleimide resulting from elimination of AcOH from (*R*)-**2**.

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