Synthesis of *erythro*-L-β-Hydroxyglutamic Acid Hydrochloride from L-Malic Acid

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Facile synthesis of *erythro*-L-β-hydroxyglutamic acid and its derivative, (2*S*,3*S*)-3-acetoxypyroglutamate, from L-malimide is described. The key reaction for the synthesis of 3-oxypyroglutamyl intermediate was the furylation of *N*-acylaminal acetate using zinc bromide–trimethylchlorosilane as an effective catalyst system. Oxidative cleavage of the furyl substituent afforded the 3-acetoxypyroglutamate, which on hydrolysis gave the title amino acid.

Keywords β-hydroxyglutamic acid; *erythro*; acetoxypyroglutamate; furan; α-amino alcohol; aminal; imide; malic acid; zinc bromide; trimethylchlorosilane

Vic-amino alcohol structure occurs in many unusual amino acids and their analogues showing significant physiological activities, so that there is considerable interest in methods for its stereocontrolled construction.[1] Recently, *erythro*- and *threo*-β-hydroxyglutamic acids have been found to show marked pharmacological effects on the giant neurons of an African giant snail.[2] We were therefore interested in developing a facile synthesis of *erythro*-L-β-hydroxyglutamic acid (**1**) as well as its cyclized form, 3-acetoxypyroglutamate (**2**), which may also be a useful compound for the synthesis of natural products such as pyrrolidine alkaloids and carbapenem antibiotics.[3] 3-Acetoxypyroglutamate (**2**) was expected to be synthesized by the condensation of a carboxyl equivalent with an aminal acetate (**3**), which could be regioselectively derived from L-malimide (**4**).[4] During the synthesis of (−)-statine (**5**),[5] we observed that the *N*-benzyl substituent in the γ-lactam (**6**) could not be removed under mild conditions such as hydrogenolysis, though **6** could be hydrolyzed with considerable decomposition, probably involving dehydration. Taking those observations into account, we chose the *N*-unsubstituted imide (**4**) as the starting material. Since the reaction of the diacetate (**3**) with trimethylsilyl cyanide at 0 °C to afford the nitrile (**7**) gave poor yield and stereocontrol (1.25 : 1) in our preliminary experiment, we used a furyl substituent as a carboxyl equivalent.

O-Acetyl malimide (**4**)[4] prepared from L-malic acid was reduced with sodium borohydride ($NaBH_4$) at low temperature, −15 °C, in a mixture of dichloromethane and methanol (2 : 1, v/v), to avoid the over-reduction of the formed aminal (**8**). Addition of dichloromethane reduced the formation of the methyl aminal (**9**) which showed low reactivity in the next alkylation step. After quenching with acetic acid and evaporation, the crude aminal (**8**) was directly acetylated in acetic anhydride with pyridinium perchlorate as a catalyst. The resulting crude aminal acetate (**3**) was almost homogeneous on thin layer chromatography (TLC) and was unstable on silica gel chromatography. Because the configuration at the 2-acetoxy substituent had no influence on stereocontrol in the next alkylation step, compound **3** was used without purification in the subsequent coupling reaction. The aminal acetate (**3**) in nitromethane ($MeNO_2$) was first treated with zinc bromide ($ZnBr_2$) and furan. The reaction took 12 h to complete at room temperature. However, when a small amount of trimethylchlorosilane (TMCS) was added to the reaction mixture, the coupling was extremely accelerated, being completed in 2 h at −15 °C.

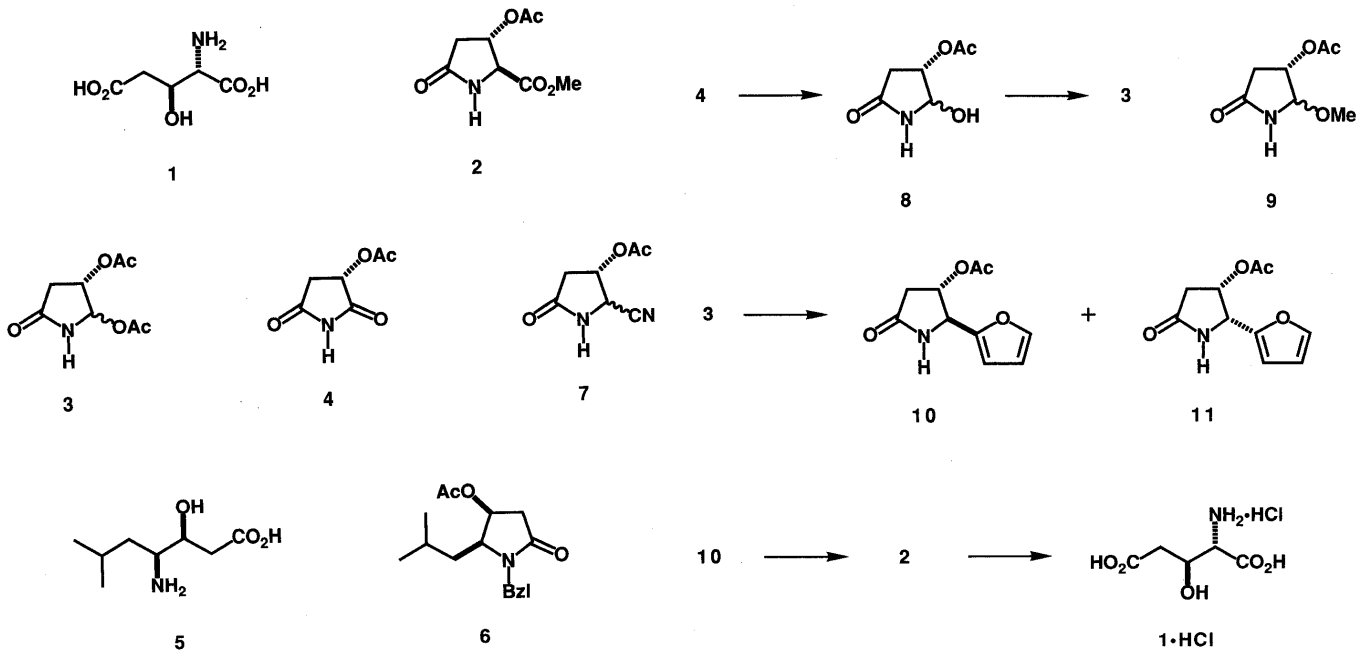

Fig. 1 Chart 1

The coupling reaction gave two diastereomeric compounds (**10** and **11**), which were easily separable on usual silica gel chromatography. The yield was 71% in three steps and the ratio of **10** to **11** was 67:33. The stereochemistries at the C-2 position of the furylates (**10** and **11**) were determined by comparison of the coupling constant (J) between H-2 and H-3. The $J_{2,3}$ value of 0.9 Hz for the *trans* product (**10**) was smaller than that for the *cis* derivative (**11**), $J_{2,3}=7.0$ Hz. This stereoselectivity was considered to be caused by the steric hindrance of the C-3 acetoxy substituent group. Considering the lability of the furyl substituent to acid, the acceleration of the furylation reaction with a weak acid catalyst system of $ZnBr_2$–TMCS seems noteworthy.

Oxidative cleavage of the furan ring of **10** with ozone,[6] followed by esterification with diazomethane without isolation of the resulting acid, gave methyl (2*S*,3*S*)-3-acetoxypyroglutamate (**2**), $[\alpha]_D^{23}$ +60.4°. Overall yield from the imide (**4**) was 42%. Hydrolysis of the pyroglutamate (**2**) in refluxing 6 N hydrochloric acid afforded *erythro*-L-β-hydroxyglutamic acid hydrochloride (**1**·HCl), $[\alpha]_D^{22}$ +19.8° {lit.[7] $[\alpha]_D^{18}$ +19.8° ($c=1.86$, H_2O)}.

In summary, we have shown that *erythro*-L-β-hydroxyglutamic acid and its derivative, (2*S*,3*S*)-3-acetoxypyroglutamate, can be efficiently synthesized from L-malic acid. The mechanism of the catalytic system of $ZnBr_2$–TMCS and application of the procedure to synthesis of biologically active natural products are under investigation.

Experimental

General Procedures Melting points are not corrected. Infrared (IR) spectra were recorded on a JASCO A-100S spectrophotometer. Nuclear magnetic resonance (NMR) spectra were taken on JEOL FX-90A and JEOL GX-500 spectrometers using tetramethylsilane (TMS) as an internal or an external reference. Mass spectra (MS) were measured on JEOL JMS-OISG-2 and JEOL DX-303 spectrometers. Optical rotations were recorded on a JASCO DIP-304 automatic polarimeter.

(2*S*,3*S*)-3-Acetoxy-2-(2-furyl)-5-oxopyrrolidine (10) $NaBH_4$ (567 mg, 15 mmol) was added to a stirred solution of the imide (**4**, 2.35 g, 15 mmol) in a mixture of dichloromethane and methanol (60 ml, 2:1, v/v) at −15 °C. The mixture was stirred for 20 min, then acetic acid (3.5 ml) was added and stirring was continued for 5 min at the same temperature. The solvent was removed *in vacuo*. The residue was suspended in acetic anhydride (30 ml) and pyridinium perchlorate (268 mg, 1.5 mmol) was added. The suspension was stirred for 3 h at room temperature under a nitrogen atmosphere. After evaporation, the residue was dissolved in ethyl acetate, washed with water and brine, dried with magnesium sulfate, and concentrated to dryness. The residue was dissolved in $MeNO_2$ (20 ml), then $ZnBr_2$ (33.7 mg, 0.15 mmol), furan (10.9 ml, 150 mmol) and TMCS (0.095 ml, 0.75 mmol) were added at −15 °C. The mixture was stirred for 2 h at the same temperature under a nitrogen atmosphere, and washed with saturated aqueous sodium bicarbonate, water and brine. The organic layer was dried over magnesium sulfate and evaporated *in vacuo*. The residue was purified by silica gel chromatography using a mixture of *n*-hexane and ethyl acetate (1:1, v/v) as an eluent to give **10** (1.52 g, 48%) and **11** (764 mg, 23%), each as a crystalline solid. Analytical samples of **10** and **11** were recrystallized from a mixture of *n*-hexane and ethyl acetate to give colorless needles, in each case. **10**, mp 117—118 °C. $[\alpha]_D^{26}$ +65.0° ($c=1.15$, $CHCl_3$). IR (KBr): 3210, 1730, 1660, 890 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 90 MHz) δ: 2.11 (s, 3H, CH_3COO), 2.34 (dd, $J=18.0$, 2.0 Hz, 1H, H-4$_\alpha$), 2.93 (dd, $J=18.0$, 6.5 Hz, 1H, H-4$_\beta$), 4.74 (d, $J=0.9$ Hz, 1H, H-2), 5.34 (ddd, $J=6.5$, 2.0, 0.9 Hz, 1H, H-3), 6.26—6.40 (m, 2H, H-3′, H-4′), 6.72—6.86 (br, 1H, N–H), 7.39—7.43 (m, 1H, H-5′). FD–MS m/z: 209 (M^+). *Anal.* Calcd for $C_{10}H_{11}NO_4$: C, 57.41; H, 5.30; N, 6.70. Found: C, 57.39; H, 5.24; N, 6.72. **11**, mp 138—139 °C. $[\alpha]_D^{24}$ −133.7° ($c=1.00$, $CHCl_3$). IR (KBr): 3360, 1720, 1710, 880 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 90 MHz) δ: 1.85 (s, 3H, CH_3COO), 2.96 (d, $J=7.0$ Hz, 2H, H-4), 5.08 (d, $J=7.0$ Hz, 1H, H-2), 5.57 (dt, $J=7.0$, 7.0 Hz, 1H, H-3), 6.25—6.40 (m, 2H, H-3′, H-4′), 6.36—6.51 (br, 1H, N–H), 7.38—7.43 (m, 1H, H-5′). MS m/z: 209 (M^+). *Anal.* Calcd for $C_{10}H_{11}NO_4$: C, 57.41; H, 5.30; N, 6.70. Found: C, 57.47; H, 5.46; N, 6.57.

Methyl (2*S*,3*S*)-3-Acetoxypyroglutamate (2) The furan (**10**, 1.98 g, 9.4 mmol) was dissolved in methanol (60 ml) and cooled to −78°C. A stream of ozonized oxygen was bubbled for 2 h at the same temperature. After being flushed with nitrogen, the solution was warmed to room temperature over 30 min, concentrated to about a half of the initial volume and treated with diazomethane at 0 °C. The solvent was evaporated *in vacuo* and the resulting residue was purified by silica gel chromatography. Elution with a mixture of *n*-hexane and ethyl acetate (2:3, v/v) gave the methyl ester (**2**, 1.66 g, 87%) as a crystalline solid, which on recrystallization from *n*-hexane and ethyl acetate afforded colorless needles, mp 130—131 °C. $[\alpha]_D^{23}$ +60.4° ($c=1.00$, $CHCl_3$). IR ($CHCl_3$): 3420, 1740, 1710 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 500 MHz) δ: 2.11 (s, 3H, CH_3COO), 2.36 (dd, $J=17.9$, 2.6 Hz, 1H, H-4$_\alpha$), 2.82 (dd, $J=17.9$, 6.8 Hz, 1H, H-4$_\beta$), 3.80 (s, 3H, $COOCH_3$), 4.26 (d, $J=0.9$ Hz, 1H, H-2), 5.46 (ddd, $J=6.8$, 2.6, 0.9 Hz, 1H, H-3), 7.33 (br, 1H, N–H). MS m/z: 202 ($M^+ +1$). *Anal.* Calcd for $C_8H_{11}NO_5$: C, 47.76; H, 5.51; N, 6.96. Found: C, 47.91; H, 5.44; N, 6.74.

(2*S*,3*S*)-3-Hydroxyglutamic Acid (1) Hydrochloride A solution of the ester (**2**, 150 mg, 0.75 mmol) in 6 N hydrochloric acid (2 ml) was refluxed for 12 h and evaporated *in vacuo*. The residue was dissolved in a small amount of concentrated hydrochloric acid, then acetonitrile was added dropwise to give colorless needles of the salt (**1**·HCl, 138 mg, 92%), mp 172—174 °C (dec.). $[\alpha]_D^{22}$ +19.8° ($c=1.01$, H_2O). IR (KBr): 3400, 3150, 1740, 1730 cm^{-1}. ^{1}H-NMR (D_2O, 500 MHz, external TMS) δ: 2.62 (d, $J=6.4$ Hz, 2H, H-4), 3.99 (d, $J=3.0$ Hz, 1H, H-2), 4.32 (dt, $J=6.4$, 3.0 Hz, 1H, H-3). FAB–MS m/z: 164 ($M^+ -$Cl). *Anal.* Calcd for $C_5H_9NO_5$·HCl: C, 30.09; H, 5.05; N, 7.02. Found: C, 29.86; H, 5.04; N, 7.17.

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