Synthesis of Unusual Aromatic L-Amino Acids by Asymmetric Hydrogenation of Cyclic Dehydrodipeptides

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Synopsis. To prepare L-Tyr(Me) and L-Amp (L-2-amino-5-(*p*-methoxyphenyl)pentanoic acid), their precursors cyclo(-*ΔZ*Tyr(Me)-L-Ala-) and cyclo(-*ΔZ*Amp-L-Ala-) were hydrogenated in *N,N*-dimethylformamide. The content of LL isomers in the hydrogenated products was over 94%. Mild acid hydrolysis of the hydrogenated products and subsequent recrystallization gave pure L-Tyr(Me) and L-Amp.

Unusual aromatic amino acids L-Tyr(Me)[1] and L-Amp were found in puromycin[2] and Cyl-2,[3] and AM-toxin I,[4] respectively. Both amino acids had been synthesized by us and others.[5-7] However, preparation of Ac-DL-Amp and its enzymatic resolution in the synthesis of L-Amp were troublesome and time-consuming.[7] Recently we developed a simple method for preparation of optically pure α-amino acids by asymmetric hydrogenation of cyclo(-*ΔZ*aminoacyl-L-aminoacyl-),[8] and could prepare L-2-amino-5-phenylpentanoic acid which is a constituent of AM-toxin II and its homologs in moderate yields.[9] Therefore, we intended to apply the method for preparation of L-Tyr(Me) and L-Amp. Some modification, however, seemed necessary because the method contained acid hydrolysis in the final step which might cause partial decomposition of the methoxy moiety of the L-Tyr(Me) and L-Amp side chains.[7]

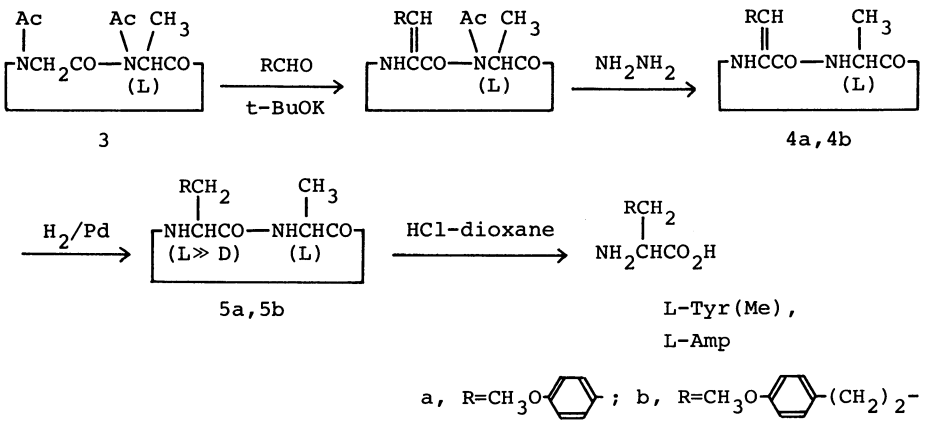
We investigated hydrolytic conditions of cyclo(-L-Tyr(Me)-L-Ala-) (**1**) using the mixture of 1—6 M HCl (1 M=1 mol dm^{-3}) and dioxane[10] as a preliminary experiment. As shown in Table 1, the conditions of 1 M HCl-dioxane (1:1), 110 °C and 72 h were adequate for **1**. Almost complete hydrolysis and negligible demethylation of the Tyr(Me) residue were observed. The conditions selected for cyclo(-L-Amp-L-Ala-) (**2**) were 0.5 M HCl-dioxane (1:1), 110 °C and 96 h.

Scheme 1 shows the route for preparation of L-Tyr(Me) and L-Amp. Compound **3** was converted into **4a** in 52% and **4b** in 40%, respectively. According to our previous papers,[8,9] Pd black and DMF were used for hydrogenation, and chiral induction (%) in hydrogenation was determined by HPLC. While the chiral induction of cyclo(-*ΔZ*phe-L-Ala-) was previously found to be of temperature dependence,[9] **4a** showed unexpectedly uniform chiral induction of about 95% between 0 °C and 50 °C. The high chiral induction of 97% at 20 °C was observed in the case of **4b**. Acid hydrolysis of the hydrogenated products (**5a** and **5b**) under the conditions found above followed by neutralization of the hydrolysates gave crude products. Pure L-Tyr(Me) and L-Amp were obtained after recrystallization in 66% from **4a** and 56% from **4b**, respectively. The total yield (34%) of L-Tyr(Me)

Table 1. Hydrolysis and Demethylation of Cyclo(-L-Tyr(Me)-L-Ala-)

Solvent	Time	Hydrolysis	Demethylation
	h	%	%
6 M HCl-dioxane[a]	24	99	24
2 M HCl-dioxane[a]	24	90	6
1 M HCl-dioxane[a]	24	69	<1
1 M HCl-dioxane[a]	72	98	2

[a] Ratio of 1—6 M HCl and dioxane is 1:1 (v/v); Temperature, 110 °C.



Scheme 1.

in the present work was lower than the reported one (62%).[6] The higher yield in the latter is due to simple modification of natural L-Tyr. On the other hand, the yield (22%) of L-Amp was comparable to that (24%) described before,[7] indicating that the present method is useful in cases where optically active natural amino acids are not available as starting materials.

Experimental

Optical rotation was measured with a Union high sensitivity polarimeter PM-71. HPLC was carried out with a Hitachi 635A liquid chromatograph and monitered at 210 nm. Amino acid analysis was performed with a Hitachi amino acid analyzer KLA-5. Thin-layer chromatography was carried out on Merck silica gel G with the following solvent systems: R_f^1, $CHCl_3$–MeOH (9:1); R_f^2, $CHCl_3$–MeOH–AcOH (95:5:1).

Cyclo(-L or D-aminoacyl-L-Ala-). Authentic samples were prepared from the corresponding Z-dipeptide-OMe according to the literature.[9] All the compounds afforded satisfactory results of elemental analysis. Cyclo(-L-Tyr(Me)-L-Ala-) (**1**): Yield, 80%; mp 274—276 °C (decomp); $[\alpha]_D^{20}$ −4.8° (*c* 1, DMF); R_f^1=0.35. Cyclo(-D-Tyr(Me)-L-Ala-) (**6**): Yield, 73%; mp 235—237 °C (decomp); $[\alpha]_D^{20}$ −17.2° (*c* 0.5, DMF); R_f^1=0.34, R_f^2=0.65. Cyclo(-L-Amp-L-Ala-) (**2**): Yield, 88%; mp 211—213 °C; $[\alpha]_D^{19}$ −31.0° (*c* 0.5, DMF); R_f^2=0.34. Cyclo(-D-Amp-L-Ala-) (**7**): Yield, 61%; mp 204—206 °C; $[\alpha]_D^{19}$ −3.5° (*c* 0.5, DMF); R_f^2=0.41.

Cyclo(-ΔTyr(Me)-L-Ala-) (4a). Compound **3** was allowed to react with *p*-methoxybenzaldehyde in the presence of *t*-BuOK. Cyclo(-ΔTyr(Me)-*N*-Ac-L-Ala-) obtained was treated with $NH_2NH_2 \cdot H_2O$ to give **4a** using the same procedure in the literature;[8] yield, 52%; mp 254—257 °C (decomp); $[\alpha]_D^{22}$ −17.0° (*c* 1, DMF); R_f^1=0.47. Found: C, 63.11; H, 5.77; N, 11.50%. Calcd for $C_{13}H_{14}N_2O_3$: C, 63.40; H, 5.73; N, 11.38%.

Cyclo(-ΔAmp-L-Ala-) (4b). This compound was prepared from **3** and 3-(*p*-methoxyphenyl)propionaldehyde; yield, 40%; mp 231–233 °C; $[\alpha]_D^{20}$ −17.5° (*c* 0.5, DMF); R_f^1=0.40. Found: C, 65.42; H, 6.66; N, 10.26%. Calcd for $C_{15}H_{18}N_2O_3$: C, 65.67; H, 6.61; N, 10.21%.

Acid Hydrolysis of Authentic Samples. A mixture of **1** and Lys·HCl (5 μmol each) was heated in a sealed tube with 1—6 M HCl-dioxane (1:1) at 110 °C for certain intervals. Lys·HCl was used as a standard for determination of hydrolysis percentage by comparison with Ala formed in hydrolysis. Amino acid analysis and calculation of demethylation were carried out as described before.[7] The results are shown in Table 1. A similar procedure was applied for **2**.

HPLC of Authentic Samples. The separation of DL and LL isomers of cyclo(-Tyr(Me)-Ala-) was performed under the following conditions: column, LiChrosorb RP-8 (4×250 mm); eluent, H_2O–CH_3CN (95:5); flow rate, 1.0 ml/min. Elution volume and relative intensity were determined as 44 ml and 99% for **6**, and 51 ml and 100% for **1**. The conditions on the separation of DL and LL isomers of cyclo(-Amp-Ala-) were as follows: column, LiChrosorb RP-18 (4×150 mm); eluent, H_2O–CH_3CN–*i*-PrOH (14:1:1); flow rate, 1.0 ml/min. Eluent volume and intensity were 22.5 ml and 94% for **7**, and 31.2 ml and 100% for **2**.

Determination of Chiral Induction in Hydrogenation of Cyclic Dehydrodipeptides. Compound **4a** (7.4 mg, 30 μmol) in absolube DMF (8 ml) was hydrogenated in the presence of Pd black (ca. 10 mg) at 0 °C for 10 h, and an aliquot was applied to HPLC. The ratio of the DL and LL isomers in cyclo(-Tyr(Me)-Ala-) was 2.5:97.5 after correction of the apparent ratio by relative intensity. Therefore, the chiral induction (%) was calculated as 95%, and those at 25 °C and 50 °C were 97% and 94%, respectively. The chiral induction of **4b** was 97% at 20 °C.

Preparation of L-Amino Acids. **L-Tyr(Me)**: Hydrogenated product of **4a** (1.23 g, 5 mmol) was hydrolyzed with 1 M HCl-dioxane (1:1, 150 ml) at 110 °C for 3 d and evaporated in vacuo. The residue was dissolved in water (10 ml) and the solution was neutralized with Et_3N. The resulting solid was collected and washed with cold water. Dissolution of the crude product in 6 M HCl and neutralization with Et_3N gave pure L-Tyr(Me); yield, 0.65 g (66%); $[\alpha]_D^{25}$ −6.2° (*c* 1, 1 M HCl) (lit,[5] $[\alpha]_D^{29}$ −5.9° (*c* 2, 1 M HCl)). Found: C, 61.49; H, 6.71; N, 7.27%. Calcd for $C_{10}H_{13}NO_3$: C, 61.52; H, 6.71; N, 7.18%.

L-Amp: This was prepared from **4b** as described above except for hydrolysis with 0.5 M HCl-dioxane (1:1) for 4 d; yield, 56%; $[\alpha]_D^{22}$ +30.8° (*c* 1, 5 M HCl–DMF (1:1)) (lit,[7] $[\alpha]_D^{21}$ +31.8° (*c* 2, 5 M HCl–DMF). Found: C, 64.71; H, 7.61; N, 6.08%. Calcd for $C_{12}H_{17}NO_3$: C, 64.55; H, 7.68; N, 6.27%.

References

1) Abbreviations: Amp, 2-amino-5-(*p*-methoxyphenyl)-pentanoic acid; Δ, α,β-dehydro; DMF, *N*,*N*-dimethylformamide; Et_3N, triethylamine; HPLC, high-performance liquid chromatography; Tyr(Me), *O*-methyltyrosine.

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