ENANTIOSELECTIVE SYNTHESIS OF β–AMINO ACID *VIA* ASYMMETRIC BROMOLACTAMIZATION

Sang-sup Jew,* Kyung-hoi Cha, Sang-deog Kang, Yun-hee Woo,
Hyung-ook Kim, and Hyeung-geun Park

College of Pharmacy, Seoul National University,
San 56-1, Sinllim-Dong, Kwanak-Gu, Seoul, Korea 151-742

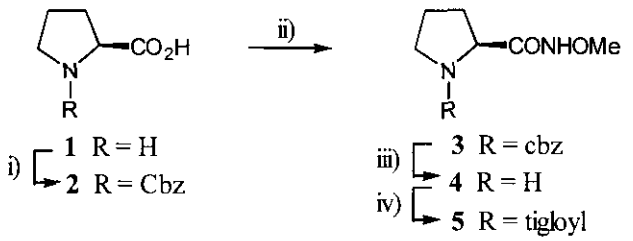
Abstract-Asymmetric bromolactamization using (*S*)-(-)-*N*-methoxy-2-pyrrolidine carboxamide (**4**) as a chiral auxiliary was performed successfully. The seven membered bromolactam obtained by asymmetric bromolactamization was converted to enantiomerically pure 3(*S*)-amino-2(*R*)-methylbutanoic acid (**10**).

An asymmetric bromolactonization procedure using (*S*)-proline as a chiral auxiliary affords highly optically active α–hydroxy acids and the procedure was successfully applied to the synthesis of optically active anthracycline antibiotics.[1] In connection with the asymmetric synthesis of biologically active β–amino acids, we designed a new electrophilic cyclization, bromolactamization in which nitrogen nucleophile participates intramolecularly in a different way from the bromolactonization. Although halolactonization and related electrophilic cyclization of olefins are well known,[2] early attempts to form lactams from olefinic amides by similar procedures produced the lactones from the corresponding intermediate cyclic iminoether instead.[3] In this paper, we wish to report a new asymmetric bromolactamization using (*S*)-(-)-*N*-methoxy-2-pyrrolidinecarboxamide (**4**) as a chiral auxiliary.

The chiral auxiliary (**4**) was prepared from (*S*)-(-)-proline (**1**) as shown in Scheme 1. *N*-Protected proline (**2**)[4] prepared from **1** was coupled to methoxylamine by using diethyl cyanophosphonate[5] followed by deprotection to give **4** *via* **3**. *N*-Acylation of **4** with tiglic acid and DCC gave **5**, mp 81-82 °C, $[\alpha]_D^{25}$

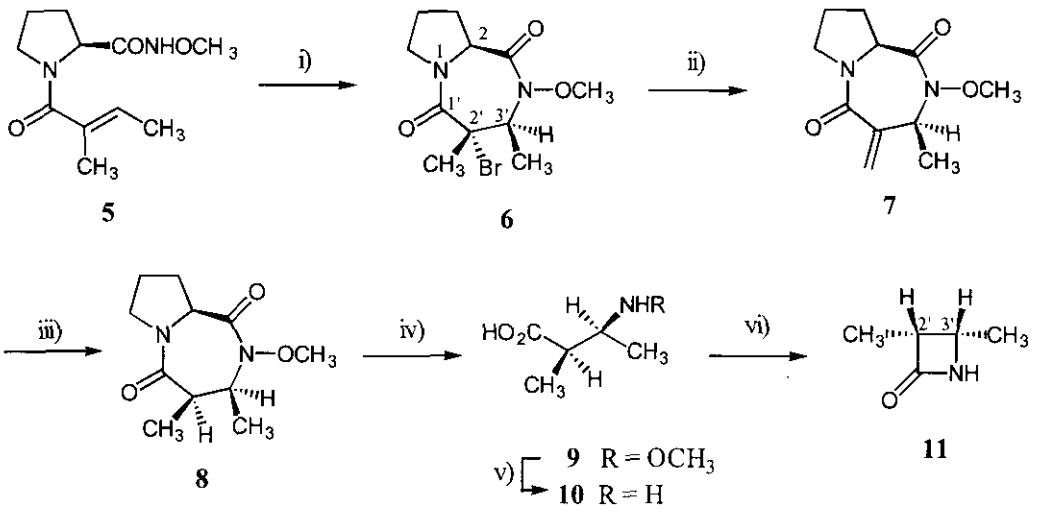
$-152.5°$ (c 0.92, $CHCl_3$) in 84% yield.

Scheme 1



Reagents and conditions: i) benzyl chloroformate (1.2 eq), 1N-NaOH, 0 °C, 10 min (97%), ii) $MeONH_2 \cdot HCl$ (1.0 eq), diethyl cyanophosphonate (1.1 eq), Et_3N (2.2 eq), DMF, 0 °C, 0.5 h; then rt, 13 h (91%), iii) 10% Pd/C (cat), H_2, MeOH, rt, 14 h (94%), iv) tiglic acid (1.0 eq), DCC (1.2 eq), DMAP (cat), CH_2Cl_2, 0 °C, 10 min; then rt, 12 h (84%)

Scheme 2



Reagents and conditions: i) NBS (2.0 eq), EtOH free $CHCl_3$, rt, 48 h (50% after recrystalized), ii) DBU (4.0 eq), C_6H_6, refl, 14 h (84%), iii) 5% Pd/C (cat), H_2, MeOH, rt, 1 h (100%), iv) 6N-HCl, refl, 6 h (94%), v) PtO_2 (cat), H_2, MeOH, rt, 1 h (100%), vi) 2-chloro-1-methylpyridinium iodide (1.1 eq), Et_3N (2.2 eq), MeCN, refl, 3 h (60%)

The bromolactamization of **5** with *N*-bromosuccinimide (NBS) in EtOH-free chloroform provided seven membered bromolactam (**6**), mp 106-109 °C, $[\alpha]_D^{25}$ $-118.7°$ (c 1.08, $CHCl_3$), in 55% yield instead of imino ether as illustrated in Scheme 2.[6] The extensive investigation of solvent effect let us choose

$CHCl_3$ as the reaction solvent. By the X-Ray crystallographic analysis of the recrystalized (**6**),[7] the absolute configurations of C(2') and C(3') were identified as (*S*) and (*S*), respectively. As we expected, the diastereomerically pure **6**[8] obtained by recrystalization was debrominated by n-Bu_3SnH to give a mixture of **8** and its diastereomer (2:1) which was determined by ^1H NMR. However, by the hydrogenation of exomethylene lactam (**7**) (mp 114-115 °C, $[\alpha]_D^{22}$ –187.8° (c 0.68, MeOH)) which was obtained by the dehydrobromination of pure **6**, the diastereomeric pure lactam (**8**)[8] (mp 168-170 °C, $[\alpha]_D^{24}$ –212.7° (c 0.72, MeOH)) was prepared. To complete the asymmetric bromolactamization, the chiral auxiliary of **8** was removed to give the enantimerically pure **9**, $[\alpha]_D^{26}$ –33.8° (c 2.02, MeOH). In order to determine the absolute configuration of C(2') of **8** prepared from **7**, **9** was transformed to **10** by hydrogenolysis followed by cyclization to afford β–lactam (**11**), $[\alpha]_D^{26}$ +16.8° (c 1.06, $CHCl_3$). A large coupling constants (J = 5.5 Hz) between the vicinal protons at C(2') and C(3') of **11** clearly demonstrates the *cis* relationship which means the absolute configuration of C(2') of **10** is (*R*) (Scheme 2).

In conclusion, we have developed a novel asymmetric bromolactamization using (*S*)-(-)-*N*-methoxy-2-pyrrolidine carboxamide (**4**). 3(*S*)-amino-2(*R*)-methylbutanoic acid (**10**) could be prepared from tiglic acid in 33% overall yield over 5 steps. This procedure can be applied as an excellent synthetic method for the optically active β–amino acid bearing vicinal two chiral centers.

ACKNOWLEDGEMENT

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6 By careful analysis, we found that the six membered bromolactam was formed in 27% yield in this reaction.

7 The pure **6** was obtained by recrystalization with Et_2O. X-Ray analysis data of **6**: empirical formular $C_{11}H_{17}N_2O_3Br$ 305.16; orthorhombic; space group $P2_12_12_1$; a = 6.0096 (0.1664) Å, b = 12.5852 (0.0795) Å, c = 17.0938 (0.0585) Å; R = 0.059.

8 By HPLC analysis and ^1H NMR, it was diastereomerically pure.

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