Dynamic Resolution of α-Bromo Tertiary Amides for Stereoselective Preparation of Dipeptide Analogues

Hyun Jung Kim, Ji-yeon Chang, Eun-kyoung Shin, and Yong Sun Park*

*Department of Chemistry, Konkuk University, Seoul 143-701, Korea. *E-mail: parkyong@konkuk.ac.kr*
Received November 24, 2004

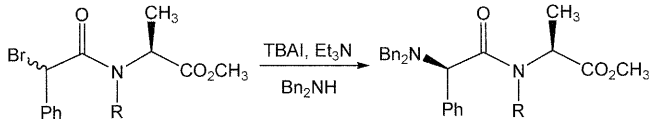
Dynamic resolution of α-bromo tertiary acetamides in asymmetric nucleophilic substitution reaction is described. Intermolecular substitution of α-bromo tertiary acetamides with dibenzylamine in the presence of TBAI and Et_3N gave the dipeptide analogues **7-10** with high stereoselectivities up to 90 : 10 dr. Also, cyclic dipeptide analogues **20-29** were produced by the intramolecular nucleophilic cyclization of α-bromo tertiary acetamides with low stereoselectivities in 84-42% yields.

Key Words : Dynamic resolution, Asymmetric syntheses, Nucleophilic substitution

Introduction

Dynamic resolution of configurationally labile α-halo esters or amides in nucleophilic substitutions with various heteroatom nucleophiles has been recognized as an effective synthetic method for asymmetric syntheses of α-heteroatom substituted carboxylic acids.[1] We have recently reported the dynamic kinetic resolution of α-bromo acetamides in nucleophilic substitution for asymmetric syntheses of di- and tripeptide analogues.[2] The chiral information of an amino acid precursor is efficiently transferred to the new C-N bond formation at α-bromo carbon center, which can build an unnatural amino acid onto the amino acid precursor with remarkable stereoselectivity. Our successful results on dynamic resolution of α-bromo secondary acetamides prompt us to extend the methodology to nucleophilic substitution of α-bromo tertiary acetamides. Numerous modifications of peptides and peptide mimetics are based on the tertiary amide bond due to the higher protease stability and conformational flexibility.[3] Herein we describe our recent results on both intermolecular and intramolecular nucleophilic substitutioins of α-bromo tertiary acetamides for asymmetric syntheses of *N*-alkylated dipeptide analogues.

Table 1. Nucleophilic substitutions of α-bromo tertiary amides



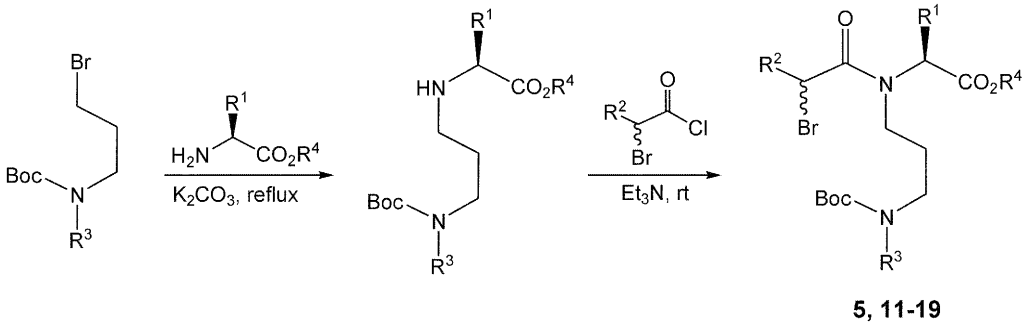
Entry	S.M.[a]	R	Product	Yield (%)[b]	Dr (α*R*:α*S*)[c]
1	**1**	H	**6**	96	90:10
2	**2**	CH_3	**7**	59	77:23
3	**3**	$PhCH_2$	**8**	50	88:12
4	**4**	*p*-MeO-$PhCH_2$	**9**	56	88:12
5	**5**	Bn(Boc)N$(CH_2)_3$	**10**	74	90:10

[a]Initial drs of **1-5** are approximately 50 : 50. [b]Isolated yields. [c]The drs are determined by ^{1}H NMR of reaction mixture using the authentic products prepared from racemic phenylglycine as a standard.

Results and Discussion

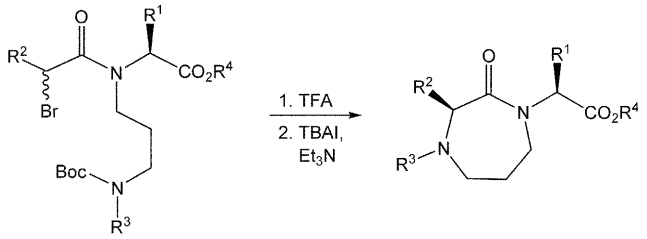
We previously reported that (*S*)-alanine is an efficient precursor for asymmetric syntheses of dipeptide analogues *via* dynamic resolution of α-bromo acetamide **1** as shown in Table 1, entry 1. When the two diastereomeric mixture (*ca.* 50 : 50) of *N*-(α-bromo-α-phenylacetyl)-(*S*)-alanine methyl ester (**1**) was treated with dibenzylamine (Bn_2NH), tetrabutylammonium iodide (TBAI) and triethylamine (Et_3N) in CH_2Cl_2 at room temperature, the dipeptide analogue **6** was obtained in 96% yield with 90 : 10 diastereomeric ratio (dr). The scope of the dynamic resolution has been examined with four different *N*-alkyl-*N*-(α-bromo-α-phenyl acetyl) (*S*)-alanine methyl esters **2-5** derived from the corresponding *N*-alkyl (*S*)-alanine methyl esters and racemic α-bromo-α-phenyl acetic acid. Treatment of *N*-methyl alanine methyl ester **2** with Bn_2NH (1.2 equiv), TBAI (1.0 equiv) and Et_3N (1.0 equiv) in CH_2Cl_2 for 24 h at room temperature gave **7** in 59% yield with 77 : 23 dr (α*R*:α*S*). (entry 2) The absolute configuration of the major product was assigned by comparison to the ^{1}H NMR of authentic epimers individually prepared from the coupling of *N*-alkyl (*S*)-alanine and (*R*)-phenylglycine derivative. Higher level of stereoselectivities (88 : 12 dr, 90 : 10 dr) was observed in the reactions of *N*-benzyl, *N*-*p*-methoxybenzyl and *N*-(3-aminopropyl) substituted (*S*)-alanine methyl esters **3-5**. (entries 3-5)

Introduction of conformational constraints into peptides, so that particular backbone conformations are enforced, is one of most promising avenues for probing peptide-receptor interactions. Cyclization can impose significant conformational restrictions on the peptide backbone and hence the location of attached side chains.[4] Encouraged by the results on dynamic resolution of α-bromo tertiary acetamides **3-5** as shown in Table 1, we have designed *N*-(3-aminopropyl) α-bromo tertiary amides **11-19** as substrates for asymmetric syntheses of cyclic peptide analogues by intramolecular nucleophilic cyclization. The substrates were readily prepared from *L*-amino acid ester through the *N*-alkylation with *N*-Boc *N*-(3-bromopropyl)benzylamine followed by the *N*-acylation with racemic α-bromo-α-methyl (or phenyl) acyl



Scheme 1. Preparation of *N*-(3-aminopropyl) α-bromo acetamides

Table 2. Intramolecular nucleophilic substitutions of α-bromo tertiary amides



Entry	S.M	R^1	R^2	R^3	R^4	% Yield[a]	Dr[b] (αS:αR)
1	**5**	CH_3	Ph	CH_2Ph	CH_3	64 (**20**)	56:44
2	**11**	CH_3	CH_3	CH_2Ph	CH_3	84 (**21**)	55:45
2	**12**	CH_3	CH_3	CH_2Ph	CH_2Ph	73 (**22**)	57:43
3	**13**	CH_2Ph	CH_3	CH_2Ph	CH_3	55 (**23**)	54:46
4	**14**	$CH(CH_3)_2$	CH_3	CH_2Ph	CH_3	76 (**24**)	57:43
5	**15**	$CH(CH_3)_2$	Ph	H	CH_3	83 (**25**)	53:47
6	**16**	$CH(CH_3)CH_2CH_3$	CH_3	CH_2Ph	CH_3	66 (**26**)	52:48
7	**17**	$CH(CH_3)CH_2CH_3$	Ph	CH_2Ph	CH_3	81 (**27**)	54:46
8	**18**	$CH_2CH(CH_3)_2$	CH_3	CH_2Ph	CH_2Ph	42 (**28**)	57:43
9	**19**	$CH_2CH(CH_3)_2$	Ph	CH_2Ph	CH_2Ph	51 (**29**)	52:48

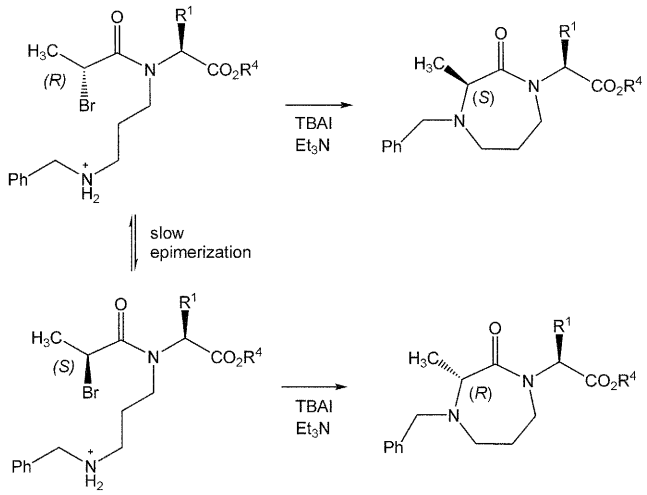
[a]Isolated yields. [b]Drs are determined by ^{1}H NMR.

chloride in 33-21% overall yields as shown in Scheme 1.

Intramolecular cyclizations by nucleophilic substitution were achieved by the treatment of **5** and **11-19** (1 : 1 diastereomeric mixture) with trifluoroacetic acid for the deprotection of *N*-Boc group followed by the addition of tetra *n*-butyl ammonium iodide (TBAI, 1.0 equiv) and Et_3N (2.2 equiv) in CH_2Cl_2 at room temperature. The substitution was completed after 30 min and the diazepinones **20-29** were obtained in 84-42% yield with diastereomeric ratios (drs) ranging from 57 : 43 to 52 : 48 as shown in Table 2. In the reaction of (*S*)-alanine derivative **5**, dipeptide analogue **20** was obtained in 64% yield with 56 : 44 dr as shown in entry 1. Similar stereoselectivities were observed in the reactions of (*S*)-phenylalanine derivative (**13**), (*S*)-valine derivatives (**14**, **15**), (*S*)-isoleucine derivatives (**16**, **17**) and (*S*)-leucine derivatives (**18**, **19**) in moderate yields. The absolute configurations of **21**, **23** and **24** were assigned by comparison to the ^{1}H-NMR of the products from the cyclization reaction of authentic epimers, (αS)-**11**, (αS)-**13** and (αS)-**14** on the basis of inversion mechanism. The absolute configurations of other products are provisionally assigned by analogy to the formation of **21**, **23** and **24**. In an effort to improve the stereoselectivity of the intramolecular nucleophilic substitution of α-bromo tertiary acetamides, various reaction conditions have been examined with alanine derivative **11**. Of the solvents explored, CH_2Cl_2 consistently gave the best drs and yields. The dipeptide analogue **21** was obtained with 55 : 45 dr in CH_3CN, 51 : 49 dr in THF, 51 : 49 dr in ether, and 54 : 46 dr in DMF. Also, the reaction in the presence of diisopropylethylamine (DIEA) as a base provided **21** with 55 : 45 dr. When we examined the substitutions both at 0 °C and 50 °C, temperature appeared to have little influence on the selectivity.

In order to understand the reason for low stereoselectivities in intramolecular nucleophilic substitution reactions of α-bromo tertiary amides, the rate of epimerization with respect to the substitution was examined in the reactions of **13** as shown in Table 3, entries 1 and 2. If the epimerization is fast with respect to the rate of substitution, the drs of products are not dependent on the initial drs of **13**, since the stereoselectivity is determined by the difference in transition states energies. When **13** with 99 : 1 dr (αR:αS) was treated in the presence of both TBAI and DIEA, the reaction gave the product **23** with 99 : 1 dr (αS:αR) as shown in entry 1. In addition, the reaction of **13** with reversed diastereomeric enrichment of 1 : 99 dr (αR:αS) gave **23** of 1 : 99 dr (αS:αR). (entry 2) Thus, the dr of **23** is dependent on the starting ratio of two epimers of **13**. These preliminary results indicate that the epimerization promoted by TBAI and Et_3N are considerably slow with respect to the intramolecular substitution.[5] A key element for efficient dynamic resolution is that the epimerization between (αS)-epimer and (αR)-epimer should be much faster than the substitution. Thus, decrease in rate of intramolecular substitution would allow for a more efficient epimerization process and improve the stereoselectivity. To explore this possibility, a syringe pump addition of Et_3N for neutralization and substitution was performed to simulate the low concentration of the nucleophile. In this experiment, substrate **11** was dissolved in dry CH_2Cl_2 with TBAI and the solution of Et_3N was added *via* syringe pump over 2.5 h. Consistent with our hypotheses, the experiment furnished the desired product **21** with improved diastereomeric ratio of 61 : 39 in 67% yield. (entry 3) The reaction of **18** with slow addition of the base also

Table 3. Epimerization-substitution reactions



Entry	S.M.	Dr of S.M. (αR:αS)	Product	%Yield	Dr (αS:αR)
1	**13**	99 : 1[a]	**23**	88	99 : 1
2	**13**	1 : 99[a]	**23**	44	1 : 99
3[b]	**11**	50 : 50	**21**	67	61 : 39
4[b]	**18**	50 : 50	**28**	54	63 : 37

[a]The highly enantioenriched (α*R*)-**13** and (α*S*)-**13** were obtained by column chromatography separation. [b]Et_3N was added for 2.5 h by syringe pump.

gave the improved selectivity (63 : 37 dr) as shown in entry 4. The longer addition time, however, did not give the higher selectivity.

In summary, we have described dynamic resolution of α-bromo tertiary acetamides in asymmetric nucleophilic substitution reactions. Intermolecular substitution of α-bromo tertiary acetamides with dibenzylamine gave the dipeptide analogues **7-10** with high stereoselectivities up to 90 : 10 dr. Intramolecular nucleophilic substitution, however, gave diazepinones **20-29** with low stereoselectivities, probably due to fast substitution with respect to the epimerization process. Current work is aimed at understanding mechanistic details of these processes.

Experimental Section

General procedure for the preparation of 2, 3 and 4. *N*-Alkyl (*S*)-alanine methyl ester (1.0 equiv), racemic α-bromo α-phenyl acyl chloride (1.0 equiv) and Et_3N (1.1 equiv) were dissolved in CH_2Cl_2 and stirred at room temperature. After the resulting reaction mixture was stirred at room temperature for 3 h, the mixture was treated with extractive work up and the organic phase was dried over $MgSO_4$. Filtration and concentration provided the crude product that was purified by column chromatography on silica gel. A colorless oil was obtained in 53-41% yields and the purity (>95%) was estimated by NMR. No further attempts were made to optimize the yields.

***N*-Methyl-*N*-(α-bromo-α-phenyl acetyl) (*S*)-alanine methyl ester (2).** ^{1}H NMR ($CDCl_3$, 400 MHz, two diastereomers) 7.54-7.27 (m, 5H), 5.72 (s, 1H), 5.22, 5.14 (m, 1H), 3.73, 3.66 (s, 3H), 2.90, 2.89 (s, 3H), 1.42, 1.38 (d, *J* = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) 172.1, 168.0, 136.1, 129.3, 129.1, 128.4, 59.2, 53.7, 47.8, 32.9, 14.7.

***N*-Benzyl-*N*-(α-bromo-α-phenyl acetyl) (*S*)-alanine methyl ester (3).** ^{1}H NMR ($CDCl_3$, 400 MHz, two diastereomers) 7.42-7.24 (m, 10H), 5.56, 5.43 (s, 1H), 4.84-4.47 (m, 3H), 3.71, 3.66 (s, 3H), 1.43, 1.37 (d, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) 171.9, 168.6, 136.2, 129.6, 129.5, 129.4, 129.0, 128.9, 128.4, 126.6, 59.2, 55.4, 51.0, 48.0, 15.0.

***N*-*p*-Methoxybenzyl-*N*-(α-bromo-α-phenyl acetyl) (*S*)-alanine methyl ester (4).** ^{1}H NMR ($CDCl_3$, 400 MHz, two diastereomers) 7.43-6.79 (m, 9H), 5.58, 5.45 (s, 1H), 4.81-4.49 (m, 3H), 3.79, 3.75 (s, 3H), 3.71, 3.67 (s, 3H), 1.43, 1.39 (d, *J* = 7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) 172.0, 168.6, 160.7, 138.6, 136.3, 130.6, 129.5, 129.1, 118.7, 114.0, 55.7, 52.7, 50.9, 48.0, 45.8, 15.0.

General procedure for the preparation of 7, 8, 9 and 10. To a solution of (α*RS*)-α-bromo acetamides in dry CH_2Cl_2 (*ca.* 0.1 M) at room temperature was added dibenzylamine (1.2 equiv), TBAI (1.0 equiv) and Et_3N (1.2 equiv). After the resulting reaction mixture was stirred at room temperature for 24 h, the solvent in mixture was evaporated and the crude product was purified by column chromatography on silica gel. The purity (>95%) of products was estimated by NMR.

***N*-Methyl-*N*-[(*R*)-α-phenyl-*N*,*N*-(dibenzyl)glycinyl] (*S*)-alanine methyl ester (7).** A colorless oil was obtained in 59% yield. ^{1}H NMR ($CDCl_3$, 400 MHz, major diastereomer) 7.40-7.23 (m, 15H), 5.32 (m, 1H), 4.74 (s, 1H), 3.98-3.70 (m, 4H), 3.84 (s, 3H), 2.40 (s, 3H), 1.40 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) 173.3, 172.7, 141.0, 137.3, 129.7, 129.6, 129.4, 129.2, 129.0, 128.8, 128.7, 128.6, 128.3, 127.4, 127.3, 63.1, 65.0, 53.6, 52.7, 52.6, 31.8, 15.0.

***N*-Benzyl-*N*-[(*R*)-α-phenyl-*N*,*N*-(dibenzyl)glycinyl] (*S*)-alanine methyl ester (8).** A colorless oil was obtained in 50% yield. ^{1}H NMR ($CDCl_3$, 400 MHz, major diastereomer) 7.39-7.24 (m, 20H), 5.10 (s, 1H), 4.84-4.46 (m, 3H), 3.82-3.53 (m, 4H), 3.71 (s, 3H), 1.46-1.41 (d, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) 173.6, 172.4, 156.4, 141.1, 137.4, 136.5, 130.1, 129.9, 129.5, 129.3, 129.1, 129.0, 128.2, 127.9, 127.6, 127.4, 127.2, 63.8, 55.0, 52.5, 51.2, 49.7, 28.9, 14.6.

***N*-*p*-Methoxybenzyl-*N*-[(*R*)-α-phenyl-*N*,*N*-(dibenzyl)-glycinyl] (*S*)-alanine methyl ester (9).** A colorless oil was obtained in 56% yield. ^{1}H NMR ($CDCl_3$, 400 MHz, major diastereomer) 7.40-6.40 (m, 19H), 4.78 (s, 1H), 4.19 (m, 1H), 4.14-3.78 (m, 6H), 3.81 (s, 3H), 3.65 (s, 3H), 1.42 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) 173.8, 172.4, 160.1, 138.1, 137.4, 130.0, 129.9, 129.0, 128.6, 128.5, 127.2, 119.6, 113.5, 112.9, 63.6, 55.5, 55.3, 54.9, 52.6, 51.4, 14.7.

***N*-(*N*-Boc-*N*-benzyl-3-aminopropyl)-*N*-[(*R*)-α-phenyl-*N*,*N*-(dibenzyl)glycinyl] (*S*)-alanine methyl ester (10).** A colorless oil was obtained in 74% yield. ^{1}H NMR ($CDCl_3$, 400 MHz, major diastereomer) 7.37-7.18 (m, 20H), 4.68 (s, 1H), 4.06-3.65 (m, 7H), 3.80 (s, 3H), 2.91-2.45 (m, 4H), 1.74 (m, 2H), 1.29 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) 172.9, 172.7, 172.7, 155.8, 141.2, 140.6, 138.6, 137.6,

129.9, 129.6, 129.2, 129.1, 128.9, 128.8, 128.6, 128.5, 127.6, 127.4, 127.3, 127.1, 80.2, 63.7, 54.7, 52.6, 45.7, 45.1, 43.9, 31.3, 28.7, 27.6, 15.7.

General procedure for the preparation of 5 and 11-19. *N*-Boc *N*-(3-bromopropyl)benzylamine was prepared by known procedure[6] and treated with (*S*)-amino acid methyl ester (or benzyl ester) and K_2CO_3 in DMF at reflux for *N*-alkylation. The obtained *N*-alkyl amino acid ester (1.0 equiv), racemic α-bromo α-phenyl (or α-methyl) acyl chloride (1.0 equiv) and Et_3N (1.1 equiv) were dissolved in CH_2Cl_2 and stirred at room temperature for 3 h. The mixture was treated with extractive work up and the organic phase was dried over $MgSO_4$. Filtration and concentration provided the crude product that was purified by column chromatography on silica gel. A colorless oil was obtained in 33-21% yields and the purity (>95%) was estimated by NMR. No further attempts were made to optimize the yields.

***N*-(*N*-Boc-*N*-benzyl-3-aminopropyl)-*N*-(α-bromo-α-phenyl acetyl) (*S*)-alanine methyl ester (5).** ^{1}H NMR ($CDCl_3$, 400 MHz, two diastereomers) 7.50-7.21 (m, 10H), 5.80, 5.66 (s, 1H), 4.38 (m, 2H), 4.20, 4.00 (m, 1H), 3.66, 3.64 (s, 3H), 3.17 (m, 4H), 1.49 (s, 9H), 1.41, 1.36 (d, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) 171.6, 167.3, 156.1, 138.6, 136.7, 129.5, 129.2, 129.1, 128.9, 127.9, 127.5, 80.7, 60.7, 56.3, 52.6, 51.3, 46.7, 44.7, 29.1, 15.0.

***N*-(*N*-Boc–*N*-benzyl-3-aminopropyl)-*N*-(α-bromopropionyl) (*S*)-alanine methyl ester (11).** ^{1}H NMR ($CDCl_3$, 400 MHz, two diastereomers) 7.35-7.24 (m, 5H), 4.64, 4.52 (m, 1H), 4.50 (m, 2H), 4.12, 4.06 (m, 1H), 3.72, 3.68 (s, 3H), 3.49-2.90 (m, 4H), 1.81 (m, 2H), 1.74 (d, J = 6.7 Hz, 3H), 1.50 (s, 9H), 1.39 (d, J = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) 171.9, 169.5, 156.1, 138.8, 129.1, 128.9, 127.9, 80.2, 55.7, 52.6, 49.7, 46.2, 45.0, 39.0, 28.8, 22.1, 21.4, 15.7.

***N*-(*N*-Boc–*N*-benzyl-3-aminopropyl)-*N*-(α-bromopropionyl) (*S*)-alanine benzyl ester (12).** ^{1}H NMR ($CDCl_3$, 400 MHz, two diastereomers) 7.36-7.23 (m, 10H), 5.15, 5.11 (m, 2H), 4.41-3.95 (m, 2H), 4.40 (m, 2H), 3.50-2.90 (m, 4H), 1.81 (m, 2H), 1.75, 1.69 (d, J = 6.5 Hz, 3H), 1.48 (s, 9H), 1.42 (d, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) 171.2, 169.3, 156.1, 138.8, 136.1, 129.1, 129.0, 128.9, 128.7, 128.6, 128.5, 80.7, 67.2, 56.2, 53.9, 45.0, 46.5, 38.6, 28.8, 21.8, 21.2, 14.5.

***N*-(*N*-Boc–*N*-benzyl-3-aminopropyl)-*N*-(α-bromopropionyl) (*S*)-phenylalanine methyl ester (13).** ^{1}H NMR ($CDCl_3$, 400 MHz, two diastereomers) 7.32-7.10 (m, 10H), 4.41-4.10 (m, 3H), 4.03 (m, 1H), 3.70 (s, 3H), 3.33-3.07 (m, 6H), 1.81 (m, 2H), 1.78, 1.72 (d, J = 6.5 Hz, 3H), 1.46, 1.44 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) 172.4, 170.7, 156.0, 138.3, 136.2, 130.0, 129.9, 129.6, 128.1, 127.8, 127.6, 80.4, 63.4, 60.8, 55.1, 52.8, 51.3, 44.6, 38.7, 28.8, 22.0, 21.4.

***N*-(*N*-Boc–*N*-benzyl-3-aminopropyl)-*N*-(α-bromopropionyl) (*S*)-valine methyl ester (14).** ^{1}H NMR ($CDCl_3$, 400 MHz, two diastereomers) 7.36-7.24 (m, 5H), 4.70-4.10 (m, 4H), 3.69, 3.65 (s, 3H), 3.50-3.00 (m, 4H), 2.40, 2.27 (m, 1H), 1.90 (m, 1H), 1.70 (d, 3H), 1.50 (s, 9H), 1.04-0.83 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) 171.8, 170.5, 156.2, 138.8, 128.9, 127.8, 127.5, 80.6, 66.0, 52.3, 47.2, 45.1, 43.4, 38.7, 28.8, 28.2, 22.1, 20.6, 19.5.

***N*-(*N*-Boc-3-aminopropyl)-*N*-(α-bromo-α-phenyl acetyl) (*S*)-valine methyl ester (15).** ^{1}H NMR ($CDCl_3$, 400 MHz, two diastereomers) 7.63-7.28 (m, 5H), 5.84, 5.64 (s, 1H), 5.00, 4.70 (brs, 1H), 4.20, 3.90 (d, 1H), 3.67, 3.66 (s, 3H), 3.50-3.00 (m, 4H), 2.35 (m, 1H), 1.95-1.55 (m, 2H) 1.47 (s, 9H), 1.03-0.73 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) 171.7, 168.1, 156.5, 136.5, 129.5, 129.3, 129.0, 79.4, 63.6, 52.4, 45.3, 38.4, 31.3, 28.8, 28.4, 21.1, 19.2.

***N*-(*N*-Boc–*N*-benzyl-3-aminopropyl)-*N*-(α-bromopropionyl) (*S*)-isoleucine methyl ester (16).** ^{1}H NMR ($CDCl_3$, 400 MHz, two diastereomers) 7.36-7.24 (m, 5H), 4.71-4.06 (m, 4H), 3.71, 3.66 (s, 3H), 3.47-3.18 (m, 4H), 2.04-1.30 (m, 8H), 1.50 (s, 9H), 0.98-0.83 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) 172.1, 170.6, 156.2, 138.7, 129.1, 128.9, 127.8, 80.7, 60.5, 52.7, 52.3, 46.0, 45.1, 42.9, 34.6, 28.8, 25.5, 24.5, 22.1, 16.4, 11.1.

***N*-(*N*-Boc-*N*-benzyl-3-aminopropyl)-*N*-(α-bromo-α-phenyl acetyl) (*S*)-isoleucine methyl ester (17).** ^{1}H NMR ($CDCl_3$, 400 MHz, two diastereomers) 7.55-7.23 (m, 10H), 5.92, 5.81 (s, 1H), 4.62 (m, 3H), 3.71, 3.65 (s, 3H), 3.50-3.00 (m, 4H), 2.60-1.30 (m, 5H) 1.49 (s, 9H), 0.96-0.74 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) 171.6, 168.5, 156.2, 138.5, 136.9, 129.5, 129.2, 129.0, 128.6, 127.9, 127.5, 80.7, 66.7, 52.5, 52.3, 46.4, 44.9, 38.6, 34.5, 28.9, 26.1, 25.0, 16.6, 11.2.

***N*-(*N*-Boc–*N*-benzyl-3-aminopropyl)-*N*-(α-bromopropionyl) (*S*)-leucine benzyl ester (18).** ^{1}H NMR ($CDCl_3$, 400 MHz, two diastereomers) 7.33-7.22 (m, 10H), 5.11 (m, 2H), 4.75-4.00 (m, 4H), 3.55-2.95 (m, 4H), 1.85-1.35 (m, 8H), 1.48 (s, 9H), 0.91 (d, J = 6.4 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) 171.6, 170.2, 156.1, 138.7, 135.5, 129.0, 128.9, 128.8, 128.6, 127.8, 127.6, 80.6, 67.4, 58.9, 53.0, 49.5, 44.5, 42.1, 38.7, 28.8, 25.1, 23.2, 22.3, 14.6.

***N*-(*N*-Boc-*N*-benzyl-3-aminopropyl)-*N*-(α-bromo-α-phenyl acetyl) (*S*)-leucine benzyl ester (19).** ^{1}H NMR ($CDCl_3$, 400 MHz, two diastereomers) 7.50-7.18(m, 15H), 5.50, 5.27 (s, 1H), 5.08 (m, 2H), 4.62-3.95 (m, 3H), 3.50-3.00 (m, 4H), 1.90-1.60 (m, 5H) 1.47 (s, 9H), 0.91 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) 173.4, 171.3, 168.0, 156.1, 138.5, 135.8, 129.4, 129.2, 128.9, 128.8, 128.6, 128.4, 128.1, 127.9, 127.6, 80.7, 67.4, 63.5, 58.1, 52.9, 46.0, 42.1, 38.2, 28.8, 25.3, 23.4, 22.4.

General procedure for the preparation of 20-29. After removal of Boc group with 20% TFA in methylene chloride, the cyclization was mediated by Et_3N. To a solution of (αRS)-α-bromo acetamide (1.0 equiv) and TBAI (1.0 equiv) in dry CH_2Cl_2 (*ca.* 0.01 M) at room temperature was added Et_3N (2.2 equiv) slowly. After the resulting reaction mixture was stirred at room temperature for 1 h, the solvent in mixture was evaporated and the crude product was purified by column chromatography on silica gel. The purity (>95%) of products was estimated by NMR.

4-Benzyl-2-oxo-3-phenyl-α-(*S*)-methyl hexahydro-1*H*-1,4-diazepine-1-acetic acid methyl ester (20). A colorless oil was obtained in 64% yield. ^{1}H NMR ($CDCl_3$, 400 MHz, two diastereomers) 7.56-7.25 (m, 10H), 5.43, 5.33 (m, 1H), 5.18, 5.17 (s, 2H), 4.97 (s, 1H), 3.93 (m, 2H), 3.77, 3.75 (s, 3H), 3.55-2.85 (m, 4H), 2.02-1.76 (m, 1H), 1.49, 1.47 (d, J =

7.2 Hz, 3H), 1.45 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) 174.4, 172.9, 139.4, 137.2, 129.0, 128.8, 127.8, 127.7, 127.6, 127.5, 73.6, 57.1, 54.5, 52.6, 47.7, 44.9, 25.5, 15.5.

4-Benzyl-3-methyl-2-oxo-α-(*S*)-methyl hexahydro-1*H*-1,4-diazepine-1-acetic acid methyl ester (21). A colorless oil was obtained in 84 % yield. ^{1}H NMR ($CDCl_3$, 400 MHz, two diastereomers) 7.32-7.22 (m, 5H), 5.40, 5.35 (q, *J* = 7.2 Hz, 1H), 3.98, 3.89 (q, *J* = 6.8 Hz, 1H), 3.78, 3.72 (s, 3H), 3.82-3.25 (m, 4H), 3.06-2.84 (m, 2H), 2.10-1.34 (m, 2H), 1.49-1.33 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) 174.9, 172.9, 139.9, 129.1, 128.7, 127.4, 60.2, 53.4, 52.5, 50.0, 45.8, 23.7, 16.7, 15.9, 15.3.

4-Benzyl-3-methyl-2-oxo-α-(*S*)-methyl hexahydro-1*H*-1,4-diazepine-1-acetic acid benzyl ester (22). A colorless oil was obtained in 73% yield. ^{1}H NMR ($CDCl_3$, 400 MHz, two diastereomers) 7.32-7.22 (m, 10H), 5.45, 5.41 (q, *J* = 7.2 Hz, 1H), 5.20, 5.16 (s, 2H), 3.94, 3.85 (q, *J* = 6.8 Hz, 1H), 3.79-3.28 (m, 4H), 3.00-2.81 (m, 2H), 3.06-2.84 (m, 2H), 2.15-1.26 (m, 2H), 1.51-1.37 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) 175.1, 172.6, 140.0, 136.1, 129.1, 128.9, 128.7, 128.6, 127.3, 127.2, 67.5, 60.3, 53.7, 52.2, 49.6, 45.9, 23.7, 16.7, 15.9.

4-Benzyl-3-methyl-2-oxo-α-(*S*)-benzyl hexahydro-1*H*-1,4-diazepine-1-acetic acid methyl ester (23). A colorless oil was obtained in 55% yield. ^{1}H NMR ($CDCl_3$, 400 MHz, two diastereomers) 7.36-7.05 (m, 10H), 5.67, 5.57 (dd, *J* = 6.0, 10.2 Hz, 1H), 3.84-2.71 (m, 9H), 3.79, 3.76 (s, 3H), 1.80-1.20 (m, 2H), 1.31, 1.27 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) 176.5, 172.2, 140.0, 137.6, 129.4, 129.1, 128.9, 128.7, 128.5, 127.2, 60.1, 59.3, 52.7, 52.2, 46.8, 46.2, 35.7, 23.2, 16.8.

4-Benzyl-3-methyl-2-oxo-α-(*S*)-isopropyl hexahydro-1*H*-1,4-diazepine-1-acetic acid methyl ester (24). A colorless oil was obtained in 76% yield. ^{1}H NMR ($CDCl_3$, 400 MHz, two diastereomers) 7.32-7.22 (m, 5H), 5.08, 4.87 (d, *J* = 10.6 Hz, 1H), 3.93 (m, 1H), 3.79, 3.72 (s, 3H), 3.82-3.34 (m, 4H), 3.02-2.84 (m, 2H), 2.20 (m, 1H), 1.95-1.34 (m, 2H), 1.40, 1.05 (d, *J* = 6.8 Hz, 6H), 1.01, 0.86 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) 176.2, 172.4, 139.9, 128.9, 128.7, 127.4, 63.7, 61.6, 59.7, 52.2, 45.9, 44.0, 28.4, 24.1, 20.4, 19.1.

2-Oxo-3-phenyl-α-(*S*)-isopropyl hexahydro-1*H*-1,4-diazepine-1-acetic acid methyl ester (25). A colorless oil was obtained in 83% yield. ^{1}H NMR ($CDCl_3$, 400 MHz, two diastereomers) 7.40-7.26 (m, 5H), 4.98, 4.92 (d, *J* = 9.7 Hz, 1H), 4.78, 4.66 (s, 1H), 3.73, 3.70 (s, 3H), 3.55 (m, 2H), 3.28 (m, 1H), 3.01 (m, 1H), 2.23 (m, 1H), 1.76 (m, 2H), 1.05-0.89 (d, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) 175.2, 172.2, 139.7, 128.8, 128.7, 128.2, 128.0, 67.8, 63.1, 52.2, 49.5, 44.1, 30.5, 28.5, 20.0.

4-Benzyl-3-methyl-2-oxo-α-(*S*)-s-butyl hexahydro-1*H*-1,4-diazepine-1-acetic acid methyl ester (26). A colorless oil was obtained in 66% yield. ^{1}H NMR ($CDCl_3$, 400 MHz, two diastereomers) 7.32-7.22 (m, 5H), 5.15, 5.03 (d, *J* = 10.8 Hz, 1H), 3.93 (m, 1H), 3.79, 3.71 (s, 3H), 3.82-3.29 (m, 4H), 3.02-2.80 (m, 2H), 2.05 (m, 1H), 1.85 (m, 1H), 1.62-1.10 (m, 2H), 1.40 (d, *J* = 6.9 Hz, 4H), 1.01-0.87 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) 176.2, 172.5, 139.9, 128.9, 128.7, 127.3, 61.9, 60.5, 52.2, 45.4, 34.8, 26.4, 25.3, 24.1, 22.5, 16.9, 16.4, 16.1, 11.2.

4-Benzyl-2-oxo-3-phenyl-α-(*S*)-s-butyl hexahydro-1*H*-1,4-diazepine-1-acetic acid methyl ester (27). A colorless oil was obtained in 81% yield. ^{1}H NMR ($CDCl_3$, 400 MHz, two diastereomers) 7.58-7.26 (m, 10H), 5.17, 5.10 (d, *J* = 10.0 Hz, 1H), 5.00, 4.94 (s, 1H), 3.92-3.25 (m, 4H), 3.76, 3.74 (s, 3H), 3.03 (m, 1H), 2.80 (m, 1H), 2.03 (m, 1H), 1.85-1.15 (m, 4H), 1.03-0.77 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) 173.9, 172.3, 139.3, 137.4, 129.0, 128.8, 127.9, 127.8, 127.7, 127.6, 60.8, 58.0, 52.2, 47.3, 44.1, 42.1, 34.2, 26.1, 25.1, 16.3, 11.5.

4-Benzyl-3-methyl-2-oxo-α-(*S*)-iso-butyl hexahydro-1*H*-1,4-diazepine-1-acetic acid benzyl ester (28). A colorless oil was obtained in 42% yield. ^{1}H NMR ($CDCl_3$, 400 MHz, two diastereomers) 7.38-7.17 (m, 10H), 5.52, 5.41 (m, 1H), 5.19, 5.15 (s, 2H), 3.90-2.70 (m, 7H), 2.10-1.50 (m, 5H), 1.39 (m, 3H), 1.02 (d, *J* = 6.2 Hz, 3H), 0.95, 0.93 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) 176.0, 172.6, 139.9, 136.1, 129.0, 128.9, 128.8, 128.7, 128.6, 127.3, 67.4, 61.0, 56.6, 45.8, 44.7, 38.6, 25.8, 23.9, 23.6, 22.2.

4-Benzyl-2-oxo-3-phenyl-α-(*S*)-iso-butyl hexahydro-1*H*-1,4-diazepine-1-acetic acid benzyl ester (29). A colorless oil was obtained in 51% yield. ^{1}H NMR ($CDCl_3$, 400 MHz, two diastereomers) 7.49-7.20 (m, 15H), 5.55, 5.44 (m, 1H), 5.18, 5.17 (s, 2H), 4.96, 4.93 (s, 1H), 3.84 (m, 2H), 3.50-2.77 (m, 4H), 1.90-1.30 (m, 5H), 1.06, 1.03 (d, *J* = 6.3 Hz, 3H), 0.94, 0.92 (d, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) 182.0, 172.4, 142.0, 139.4, 135.0, 129.1, 128.9, 128.8, 128.7, 127.9, 127.7, 127.6, 127.5, 127.4, 67.5, 57.0, 56.8, 47.0, 44.6, 38.6, 25.7, 25.5, 23.8, 22.1.

Acknowledgement. This paper was supported by Konkuk University in 2003.

References and Notes

1. (a) Valenrod, Y.; Myung, J.; Ben, R. N. *Tetrahedron Lett.* **2004**, *45*, 2545. (b) Nam, J.; Lee, S.-k.; Park, Y. S. *Tetrahedron* **2003**, *59*, 2397. (c) Nam, J.; Lee, S.-k.; Kim, K. Y.; Park, Y. S. *Tetrahedron Lett.* **2002**, *43*, 8253. (d) Lee, S.-k.; Nam, J.; Park, Y. S. *Synlett* **2002**, 790. (e) Caddick, S.; Afonso, C. A. M.; Candeias, S. X.; Hitchcock, P. B.; Jenkins, K.; Murtagh, L.; Pardoe, D.; Santos, A. G.; Treweeke, N. R.; Weaving, R. *Tetrahedron* **2001**, *57*, 6589. (f) Lee, S.-k.; Lee, S. Y.; Park, Y. S. *Synlett* **2001**, 1941. (g) Ben, R. N.; Durst, T. *J. Org. Chem.* **1999**, *64*, 7700. (h) Kubo, A.; Kubota, H.; Takahashi, M.; Nunami, K. *J. Org. Chem.* **1997**, *62*, 5830. (i) Ward, R. S.; Pelter, A.; Goubet, D.; Pritchard, M. C. *Tetrahedron: Asymmetry* **1995**, *6*, 469.
2. (a) Nam, J.; Chang, J.-y.; Shin, E.-k.; Kim, H. J.; Kim, Y.; Jang, S.; Park, Y. S. *Tetrahedron* **2004**, *60*, 6311. (b) Nam, J.; Chang, J.-y.; Hahm, K.-S.; Park, Y. S. *Tetrahedron Lett.* **2003**, *44*, 7727.
3. (a) Dugave C.; Demange L. *Chem. Rev.* **2003**, *103*, 2475. (b) Patch, J. A.; Barron, A. E. *J. Am. Chem Soc.* **2003**, *125*, 12092. (c) Rückle, T.; Lavallaz, P.; Keller, M.; Dumy, P.; Mutter, M. *Tetrahedron* **1999**, *55*, 11281.
4. (a) Ha, J. D.; Shin, E. Y.; Chung, Y.; Choi, J.-K. *Bull. Korean Chem. Soc.* **2003**, *24*, 1567. (b) Kang, S. H.; Park, C. M.; Lee, S. B. *Bull. Korean Chem. Soc.* **2004**, *25*, 1615.
5. It has been proposed by several examples that the epimerization of α-bromo amides and α-bromo ester can be readily induced by a halide ion *via* nucleophilic displacement of bromide ion and/or by a base *via* keto-enol tautomerism.[1]
6. Wu, S.; Lee, S.; Beak, P. *J. Am. Chem. Soc.* **1996**, *118*, 715.