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Tetrahedron Letters 44 (2003) 7727–7730

TETRAHEDRON LETTERS

Dynamic kinetic resolution of α-bromo amides for asymmetric syntheses of di- and tripeptide analogues

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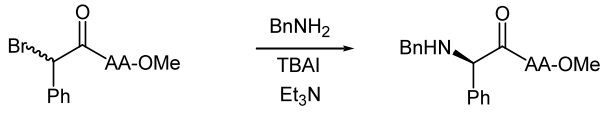
Received 19 July 2003; revised 9 August 2003; accepted 22 August 2003

Abstract—Effective dynamic kinetic resolution in the nucleophilic substitution reactions of α-bromo amides derived from L-leucine and L-proline is described. The methodology is used with dibenzylamine as a nucleophile in the presence of TBAI and Et_3N to provide di- and tripeptide analogues up to 95% yield and >99:1 dr.

Incorporation of unnatural amino acids into peptides to enhance their metabolic stability and activity is an area of major interest in peptidomimetic chemistry. In addition to classical peptide coupling of commercially available or individually prepared unnatural amino acid residue, direct modification of peptide chain is an alternative synthetic approach for this purpose as numerous peptide analogues can be efficiently prepared for the construction of peptide libraries.[1] However, controlling the stereochemical outcome of the direct peptide modification is not a trivial issue and hence the development of a novel asymmetric synthetic method for the incorporation of unnatural amino acids remains a challenging goal. Herein we describe our recent progress toward accomplishing this goal via dynamic resolution of α-bromo acetamides in nucleophilic substitution with an amine nucleophile.[2] The chiral information of an amino acid precursor is efficiently transferred to the C–N bond formation, which can build an unnatural amino acid onto the peptide chain with remarkable stereoselectivity.

We chose to limit our initial focus to six amino acid precursors for the identification of suitable stereocontrolling elements and then the substitution reactions of α-bromo-α-phenyl acetamides **1a**–**6a** derived from the corresponding L-amino acid methyl esters and racemic α-bromo-α-phenyl acetic acid were investigated as shown in Table 1. When the two diastereomeric mixture (1:1) of *N*-(α-bromo-α-phenylacetyl)-(L)-alanine methyl ester **1a** was treated with benzylamine ($BnNH_2$, 3.0 equiv.), TBAI (tetrabutylammonium iodide, 1.0 equiv.) and triethylamine (1.0 equiv.) in CH_3CN for 24 h at room temperature, the dipeptide analogue **7** was obtained in 93% yield with 53:47 dr (diastereomeric ratio). Also, when the diastereomeric mixtures of phenylalanine methyl ester **2a** and phenylglycine methyl ester **3a** were allowed to react with benzylamine under the same condition used for **1a**, no significant stereoselectivity was noted for the substitution reactions to

Table 1. Substitutions with benzylamine



1a-6a **7-12**

Entry[a]	AA[b]	%Yield[c]	Dr[d] (α*R*:α*S*)
1	L-Ala (**1a**)	93 (**7**)	53:47
2	L-Phe (**2a**)	89 (**8**)	57:43
3	L-Phg (**3a**)	92 (**9**)	51:49
4	L-Ile (**4a**)	95 (**10**)	69:31
5	L-Leu (**5a**)	97 (**11**)	71:29
6	L-Pro (**6a**)	81 (**12**)	77:23

[a] All reactions were carried out in CH_3CN for 24 h at rt.
[b] Initial drs of **1**–**6** are approximately 50:50.
[c] Isolated yields.
[d] The drs are determined by ^1H NMR of reaction mixture using the authentic products prepared from racemic phenylglycine as a standard.

Keywords: dynamic kinetic resolution; asymmetric syntheses; peptidomimetics; nucleophilic substitution.
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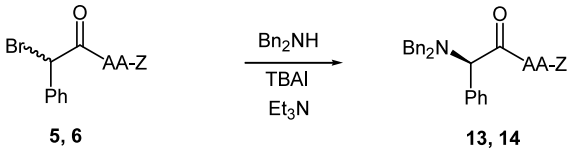
doi:10.1016/j.tetlet.2003.08.091

Table 2. Substitutions with dibenzylamine



5, 6 13, 14

Entry	AA–Z[a]	Solvent	% Yield[b]	Dr[c] (αR:αS)
1	L-Leu-OMe (**5a**)	CH_3CN	83 (**13a**)	89:11
2	L-Leu-O*t*Bu (**5b**)	CH_3CN	63 (**13b**)	93:7
3	L-Leu-O*t*Bu (**5b**)	CH_2Cl_2	68 (**13b**)	96:4
4	L-Leu-OBn (**5c**)	CH_2Cl_2	95 (**13c**)	93:7
5	L-Leu-NHNaph (**5d**)	CH_2Cl_2	81 (**13d**)	89:11
6	L-Pro-OMe (**6a**)	CH_2Cl_2	93 (**14a**)	>99:1
7	L-Pro-O*t*Bu (**6b**)	CH_2Cl_2	91 (**14b**)	>99:1

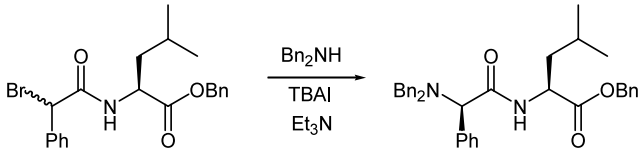
[a] Initial drs of **5** and **6** are approximately 50:50.
[b] Isolated yields.
[c] The drs are determined by ^{1}H NMR of reaction mixture using the authentic products prepared from racemic phenylglycine as a standard.

afford the dipeptide analogues **8** and **9** in 89 and 92% yields, respectively. On the other hand, moderate stereoselectivities were observed in the reactions of **4a**, **5a** and **6a** as shown in entries 4, 5 and 6. The reactions of isoleucine methyl ester **4a**, leucine methyl ester **5a** and proline methyl ester **6a** gave the dipeptide analogues **10**, **11** and **12** in high yields with promising stereoselectivities of 69:31 dr, 71:29 dr and 77:23 dr (αR:αS), respectively.[3] The observed drs and yields of the products **10**, **11** and **12** suggest that the α-bromo stereogenic centers are configurationally labile with respect to the rate of substitution and two diastereomers of **4a**–**6a** are dynamically resolved under the reaction conditions.

In an effort to improve the stereoselectivity of the reaction, we examined the substitutions of **5a** and **6a** with the more sterically demanding secondary amine nucleophile, dibenzylamine (Bn_2NH) as shown in Table 2. The nucleophile showed sufficient reactivity for the nucleophilic substitutions and the stereoselectivity of the reaction was increased remarkably. Treatment of leucine methyl ester **5a** with dibenzylamine (Bn_2NH, 3.0 equiv.), TBAI (1.0 equiv.) and Et_3N (1.0 equiv.) in CH_3CN for 24 h at room temperature gave **13a** in 83% yield with 89:11 dr (αR:αS) (entry 1). As with leucine *t*-butyl ester **5b** and leucine benzyl ester **5c** (entries 2, 3 and 4), better stereoselectivities were noted for these substitution reactions and best results were observed in CH_2Cl_2.[3,4] We also found that the leucine 2-naphthyl amide **5d** provided **13d** with a comparable stereoselectivity of 89:11 dr in 81% yield. It was pleasing to observe that almost complete diastereocontrol was achieved in the reactions of proline methyl ester **6a** and proline *t*-butyl ester **6b**, where the dipeptide analogues **14a** and **14b** were obtained in satisfactory 91–93% yields (entries 6 and 7).

In order to understand the source of asymmetric induction in nucleophilic substitution reactions of α-bromo amides, we carried out a series of reactions as shown in Table 3. The reaction of leucine benzyl ester **5c** (50:50 dr) in the absence of both TBAI and Et_3N for 24 h gave the dipeptide analogues **13c** with slower rate and much lower stereoselectivity (66:34 dr, entry 2) than the results (93:7 dr) in entry 1. The addition of Et_3N did not affect the reaction rate and stereoselectivity significantly to produce **13c** with 71:29 dr in 51% yield (entry 3). In contrast, the dipeptide analogue **13c** was obtained in 90% yield with 89:11 dr in the presence of TBAI (entry 4). The observed results point to the importance of the presence of TBAI for rate acceleration and high stereoselectivity.[5] The lack of stereoselectivity in the absence of TBAI may be explained by the slow epimerization of **5c** with respect to the substitution with the amine nucleophile. When **5c** with 74:26 dr was treated with dibenzylamine in the presence of both TBAI and Et_3N, the reaction gave the product **13c** with 93:7 dr as shown in entry 5. In addition, almost same dr of product **13c** was observed in the reaction of **5c** with reversed diastereomeric enrichment of 34:66 dr (entry

Table 3. Dynamic kinetic resolution of **5c** promoted by TBAI



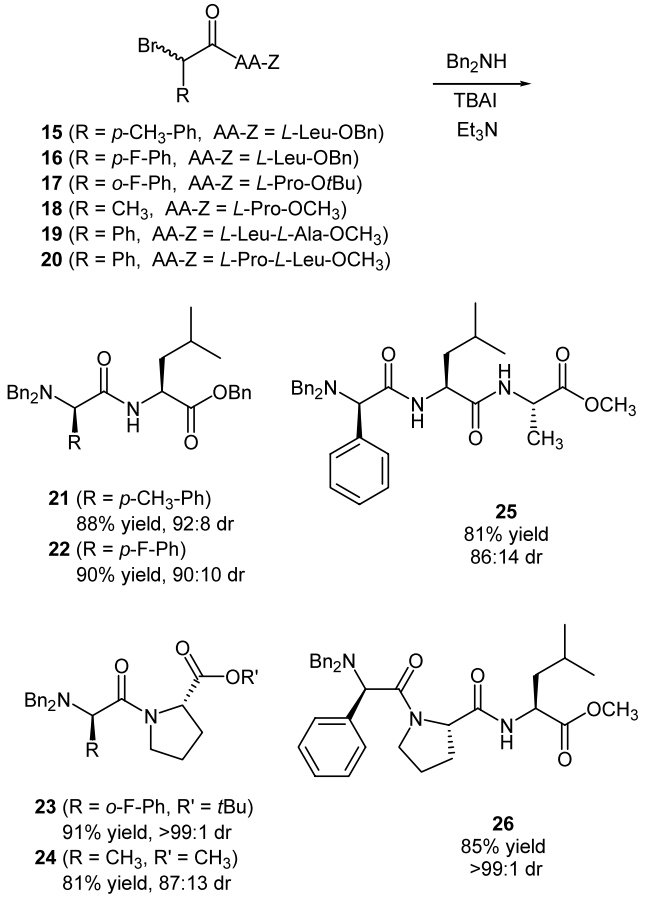
5c 13c

Entry[a]	Dr of **5c**	TBAI (equiv.)	Et_3N (equiv.)	% Yield[b]	Dr (αR:αS)
1	50:50	1.0	1.0	92	93:7
2	50:50	None	None	43	66:34
3	50:50	None	1.0	51	71:29
4	50:50	1.0	None	90	89:11
5	74:26	1.0	1.0	93	93:7
6	34:66	1.0	1.0	95	94:6

[a] All reactions were carried out in CH_2Cl_2 for 24 h at rt.
[b] Isolated yields.

6). Thus, the dr of product **13c** is not dependent on the starting ratio of two epimers of **5c** (entries 1, 5 and 6). We have also found that the dr of the product **13c** does not change in the course of the reaction by monitoring the reaction using ^{1}H NMR. These preliminary results indicate that the epimerization promoted by TBAI and Et_3N is sufficiently fast with respect to the rate of substitution and the primary pathway of the asymmetric induction is a dynamic kinetic resolution in which the product ratio is determined by the difference in the diastereomeric transition state energies for the substitution reaction with dibenzylamine nucleophile.[6,7]

With the identification of leucine and proline as appropriate stereocontrolling elements for dynamic kinetic resolution of α-bromo-α-phenyl acetamides, we set out to examine the scope of this methodology with α-bromo acetamides **15**–**20** as shown in Scheme 1. Treatment of α-(*p*-methylphenyl)acetyl leucine benzyl ester **15** (50:50 dr) with dibenzylamine (Bn_2NH, 3.0 equiv.), TBAI (1.0 equiv.) and Et_3N (1.0 equiv.) gave the dipeptide analogue **21** in 88% yield with 92:8 dr. This methodology is also practical for the asymmetric preparation of the dipeptide analogues **22** and **23** with fluorine substituted α-aryl substituents. We were pleased to observe that the reaction of α-methyl α-bromoacetyl proline ester **18** also took place with high stereoselectivity, affording the dipeptide analogue **24** in 81% yield with 87:13 dr. For asymmetric syntheses of tripeptide analogues, we further examined the stereoselective dynamic kinetic resolution of the L-Leu-L-Ala dipeptide derivative **19**. The reaction afforded the tripeptide analogue **25** with slightly lower stereoselectivity (86:14 dr). The first adjacent amino acid and second amino acid probably interact with each other in such a way that the overall effect is decreased. As with **20** derived from L-Pro-L-Leu dipeptide, the reaction successfully took place with almost complete stereoselectivity to afford the tripeptide analogue **26** in 85% yield. It is noteworthy that the efficiency of the transfer of stereochemical information was not affected by the introduction of second chiral amino acid residue.



Scheme 1.

We have presented a novel and practical approach for the asymmetric syntheses of di- and tripeptide analogues via dynamic kinetic resolution of α-bromo amides. This can provide a general procedure not only for the incorporation of optically pure unnatural amino acids into peptides but also for the highly stereoselective N-terminal functionalization of peptides. Further applications of this methodology to various α-alkyl substituents and other peptide precursors are under investigation.

Acknowledgements

This paper was supported by a grant from the Ministry of Science and Technology, Korea, and the Korea Science and Engineering Foundation through the Research Center for Proteineous Materials. Y.S.P. also thanks Molecular and Cellular BioDiscovery Research Program (M1-0311-13-0003 from the Ministry of Science and Technology for the support of this work.

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3. The absolute configurations at α-positions of **11**, **12**, **13b**, **13c** and **14b** were assigned by comparison to the ^{1}H NMR of authentic epimers prepared from commercially available (*R*)-phenylglycine. Those of **21**–**26** were assigned by anal-

ogy to the formation of **13c** and **14b**. The absolute configurations of two isomers of **13c** were confirmed by comparison of Chiral-HPLC retention time with authentic material individually prepared from the coupling of L-leucine derivative and (*S*)- or (*R*)-phenylglycine derivative using racemic material as a standard. [Chiralcel OD column; 5% 2-propanol in hexane; 0.5 mL/min; major diastereomer had a retention time of 14.8 min, minor diastereomer had a retention time of 14.1 min.]

4. In the reaction of **5c**, the dipeptide analogue **13c** was obtained with 91:9 dr in CH_3CN, 89:11 dr in DMF, 88:12 dr in ether, 88:12 dr in $CHCl_3$, 84:16 dr in MeOH, 83:17 in CCl_4 and 82:18 dr in ionic liquid, 1-butyl-3-methylimidazolium tetrafluoroborate ([bmim][BF_4]).
5. It has been proposed by several examples that the epimerization promoted by TBAI via nucleophilic displacement of the iodide ion and/or Et_3N via keto-enol tautomerization.[6a–f]
6. Two limiting pathways can be envisaged for dynamic resolution in nucleophilic substitution of α-bromo carboxylic acid derivatives. In one pathway, α-bromo stereogenic center undergoes rapid epimerization and one of the two diastereomers reacts preferentially under the reaction condition. This is a case of dynamic kinetic resolution, in which the stereoselectivity is determined by the difference in the diastereomeric transition state energies for the reaction with the nucleophiles. In a different pathway, the stereoselectivity of the reaction is determined by the ratio of the diastereomers that is established before the substitution. This is termed dynamic thermodynamic resolution because the ratio of diastereomer is thermodynamically controlled and the stereoselectivity of the reaction is not determined by the difference in the rates of substitutions. For reviews on dynamic kinetic resolution in nucleophilic substitution of α-bromo carboxylic acid derivatives, see: (a) 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; (b) Ben, R. N.; Durst, T. *J. Org. Chem.* **1999**, *64*, 7700; (c) Kubo, A.; Kubota, H.; Takahashi, M.; Nunami, K. *J. Org. Chem.* **1997**, *62*, 5830. For reviews on dynamic thermodynamic resolution in nucleophilc substitution of α-bromo carboxylic acid derivatives, see: (d) Nam, J.; Lee, S.-k.; Park, Y. S. *Tetrahedron* **2003**, *59*, 2397; (e) Nam, J.; Lee, S.-k.; Kim, K. Y.; Park, Y. S. *Tetrahedron Lett.* **2002**, *43*, 8253; (f) Lee, S.-k.; Nam, J.; Park, Y. S. *Synlett* **2002**, 790.
7. The configurational stability of **13c** was examined by the treatment with Bn_2NH (3.0 equiv.), TBAI (1.0 equiv.) and Et_3N (1.0 equiv.) in CH_2Cl_2 for 48 h. No epimerization was detected by ^1H NMR and Chiral-HPLC, which can rule out the possibility of epimerization after the replacement of Br with dibenzylamine in the stereoselective nucleophilic substitution reaction.