Chinese Chemical Letters Vol. 13, No. 8, pp 721 – 724, 2002
http://www.imm.ac.cn/journal/ccl/html

Diastereoselective α–Alkylation of β–Amino Esters: Preparation of Novel α–Substituted β–Amino Esters from α–Amino Acids

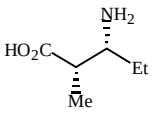
Zhi Hua MA, Cong LIU, Yong Hua ZHAO, Wei LI, Jian Bo WANG*

Key Laboratory of Bioorganic Chemistry and Molecular Engineering of Ministry of Education, Department of Chemical Biology, College of Chemistry, Peking University, Beijing 100871

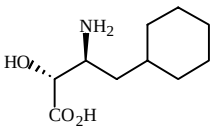
Abstract: Enantiomerically pure α–substituted β–amino esters were prepared from natural *L*-α-amino acids through Arndt-Eistert homologation and diastereoselective α–alkylation.

Keywords: Diastereoselectivity, alkylation, β-amino esters.

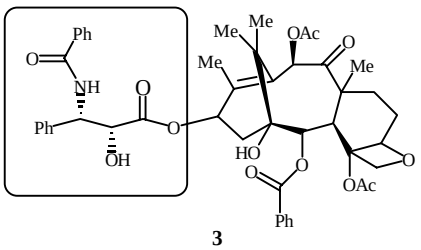
β-Amino acids and their derivatives have attracted considerable attention in recent years due to their occurrence in biologically active natural products, such as dolastatins **1**[1], cyclohexylnorstatine **2**[2] and taxol **3**[3]. β–Amino acids also find application in the synthesis of β–lactams[4], piperidines[5], indolizidines[6]. Moreover, the peptides consisting of β–amino acids, the so called β–peptides, have been extensively studied recently[7]. Consequently, considerable efforts have been directed to the synthesis of β–amino acids and their derivatives[8]. Stereoselective synthesis of α–substituted β–amino acids has been a challenging project, and there are only limited methods available[9]. In this communication, we report our study on the stereoselective synthesis of α–substituted β–amino esters starting from natural amino acids through *Arndt-Eistert homologation*[10] and stereoselective α–alkylation of β–amino esters.



1



2



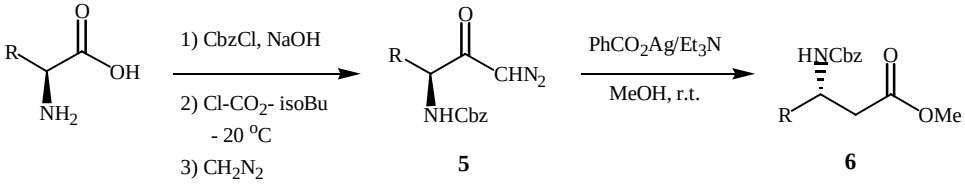
3

The natural amino acids *L*-alanine **4a**, *L*-phenylalanine **4b** and *L*-leucine **4c** were taken as starting material. After the amino group was protected with benzyloxycarbonyl group (Cbz), the acids were converted to their corresponding α–diazo ketones in two steps (**Scheme 1**). The *Wolff rearrangement* of the α–diazo ketones

*E-mail: wangjb@pku.edu.cn

under standard condition give the β–amino methyl ester in good yields. Since it is known that the *Wolff rearrangement* proceeds with the retention of the configuration at the carbon where the migration occurs[11], the β–amino methyl esters thus obtained retain the stereochemistry of the original *L*-α-amino acids. It is worthwhile to mention that this four-step process can be applied to large-scale preparation of β–amino methyl esters, because the diazo ketones can be easily purified by recrystallization from the crude product.

Scheme 1



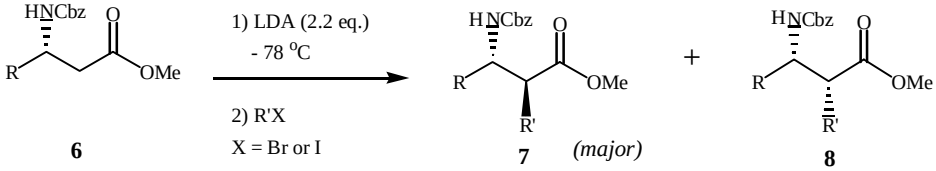
4a R = Me, **4b** R = $PhCH_2$, **4c** R = Me_2CHCH_2

Table 1 The preparation of the β–amino methyl esters from the *L*-α-amino acids.

Entry	*L*-α-amino acids **4**	Diazo ketone **5** (%)[a,b]	β–Amino ester **6** (%)[b]
1	**4a.** R = Me *L*-alanine	82	92
2	**4b.** R = $PhCH_2$ *L*-phenylalanine	78	95
3	**4c.** R = Me_2CHCH_2 *L*-leucine	76	84

[a]Overall yields for three steps. [b]The yields refer to isolated yields.

Scheme 2



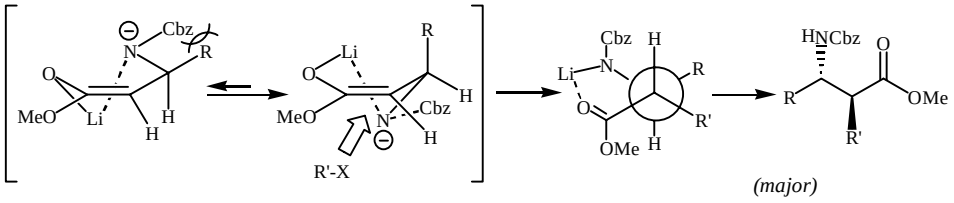
The β–amino methyl esters **6a-c** were treated with 2 equivalents of lithium diisopropylamine (LDA) at –40 - –78°C in anhydrous THF. Halides were then added at –78°C. The crude products were analyzed with ^1H NMR to give the ratio of the two diastereoisomers.

Table 2 Diastereoselective α–alkylation of β–amino ester **6a-c**

Entry	β-Amino Ester **6**	R'X	Yield (%) [a]	de (%)[c]
1	**6a**	$PhCH_2Br$	48	71
2	**6a**	$CH_2=CHCH_2I$	75	>95
3	**6a**	CH_3I	72	63
4	**6b**	$PhCH_2Br$	77	67
5	**6b**	$CH_2=CHCH_2I$	72	>95
6	**6b**	CH_3I	92	>95
7	**6c**	$PhCH_2Br$	42[b]	67
8	**6c**	$CH_2=CHCH_2I$	34[b]	>95
9	**6c**	CH_3I	41[b]	>95

[a]Yields after column chromatography. [b]Considerable amount of starting materials were recovered and yields were not optimized. [c]The diastereoisomer ratios are determined by ^1H NMR (400 MHz).

Scheme 3



9 **10** **11** **7**

The stereochemistry of the newly introduced stereogenic center was determined by converting the major product **7** into *N*-tosyl α–alkyl β–amino methyl esters, which are known compounds[12], and then comparing their spectral data. As expected, the major alkylation products have *anti* configuration. This selectivity is consistent with the previously reported α–alkylation of *N*-tosyl protected β–amino esters[12]. Again, the *anti* selectivity could be rationalized by the following consideration. The dianion will form a chelation structure, in which a lithium ion chelates between enolate oxygen and the deprotonated *N*-Cbz protected amino group. In the chelated enolate, the conformation with the alkyl group in the axial position is more stable, and the attack by the halides from the opposite side of the R group leads to the *anti* selectivity products.

In summary, we have studied the stereoselective α–alkylation of *N*–Cbz protected α–amino esters, and have prepared several unknown *N*-Cbz protected α–substituted β–amino esters from the corresponding naturally occurring *L*-α–amino acids.

Acknowledgment

The project is generously supported by the National Natural Science Foundation of China (Grant No. 29972002, 20172002), the Trans-Century Training Programme Foundation for the Talents by

Ministry of Education, and Bayer Co. Ltd (Germany). We thank Dr. Scherkenbeck for the helpful discussion.

References

1. G. R. Pettit, Y. Kamano, H. Kizu, *et al*., *Heterocycles*, **1989**, *28*, 553.
2. K. Iizuka, T. Kamijo, H. Harada, *et al.*, *J. Chem. Soc., Chem. Commun.* **1989**, 1678.
3. K. C. Nicolaou, W. M. Dai, R. K. Guy, *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 15.
4. For example, S. Kim, P. H. Lee, T. A. Lee, *J. Chem. Soc., Chem. Commun.* **1988**, 1242.
5. C. W. Jefford, J. B. Wang, *Tetrahedron Lett.* **1993**, *34*, 2911.
6. C. W. Jefford, J. B. Wang, *Tetrahedron Lett.* **1993**, *34*, 3119.
7. For a review for β–peptide, see: (a) D. Seebach, J. L. Matthews, *Chem. Comm.* **1997**, 2015. (b) S. H. Gellman, *Acc. Chem. Res.* **1998**, *31*, 173. (c) D. Seebach, S. Abele, K. Gademann, B. Jaun, *Angew. Chem., Int. Ed.* **1999**, *38*, 1596.
8. For reviews, see: (a) E. Juaristi, D. Quintana, J. Escalante, *Aldrichim. Acta* **1994**, *27*, 3. (b) D. C. Cole, *Tetrahedron* **1994**, *50*, 9517. (c) G. Cardillo, C. Tomasini, *Chem. Soc. Rev.* **1996**, 117.
9. (a) E. Fernandez-Megia, M. M. Paz, F. J. Sardina, *J. Org. Chem.* **1994**, *59*, 7643. (b) J. M. Humphery, R. J. Bridges, J. A. Hart, *et al.*, *J. Org. Chem.* **1994**, *59*, 2467. (c) S. Hanessian, R. Margarita, A. Hall, X. Luo, *Tetrahedron Lett.* **1998**, *39*, 5883.
10. For reviews on Wolff rearrangement, see: (a) M. P. Doyle, M. A. McKervey, *J. Chem. Soc., Chem. Commun.* **1997**, 983. (b) H. Meier, K. –P. Zeller, *Angew. Chem., Int. Ed. Engl.* **1975**, *14*, 32.
11. J. Wang, Y. Hou, *J. Chem. Soc., Perkin Trans. 1* **1998**, 1919, and reference cited therein.
12. J. Wang, Y. Hou, P. Wu, *et al*., *Tetrahedron: Asymmetry*, **1999**, *10*, 4553.

Received 27 November, 2001