Tetrahedron Letters 51 (2010) 4121–4124

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

# A reasonably stereospecific multistep conversion of Boc-protected α-amino acids to Phth-protected β$^3$-amino acids

Andrea Temperini [a,*], Antonella Capperucci [b,*], Alessandro Degl'Innocenti [b], Raffaella Terlizzi [a], Marcello Tiecco [a]

[a] Dipartimento di Chimica e tecnologia del Farmaco, Sezione di Chimica Organica, Università di Perugia, via del Liceo 1, 06123 Perugia, Italy
[b] Dipartimento di Chimica, Università di Firenze, via della Lastruccia 3-13, 50019 Sesto Fiorentino, Italy

ARTICLE INFO

*Article history:*
Received 30 March 2010
Revised 28 May 2010
Accepted 28 May 2010
Available online 2 June 2010

Dedicated to Professor Saverio Florio on the occasion of his 70th birthday

*Keywords:*
α-Amino acids
Selenium
Propargylic amines
β-Amino acids

ABSTRACT

A method for the synthesis of β$^3$-amino acids starting from α-amino acids is described. This conversion can be effected by an eight-step procedure which involves the transformation of the carboxylic group into an alkyne followed by a selenium-mediated conversion of the carbon–carbon triple bond to a *Se*-phenyl selenocarboxylate intermediate. The reactive *Se*-phenyl selenocarboxylate intermediates can be trapped with water, alcohols or the amine of an amino acid derivative to give β$^3$-amino acids, β$^3$-amino esters or mixed peptides, respectively. The whole transformations of the carboxylic group into an alkyne and of the alkyne group into β$^3$-amino acids may not require purification of the intermediate products but a work-up and isolation procedure of crude materials.



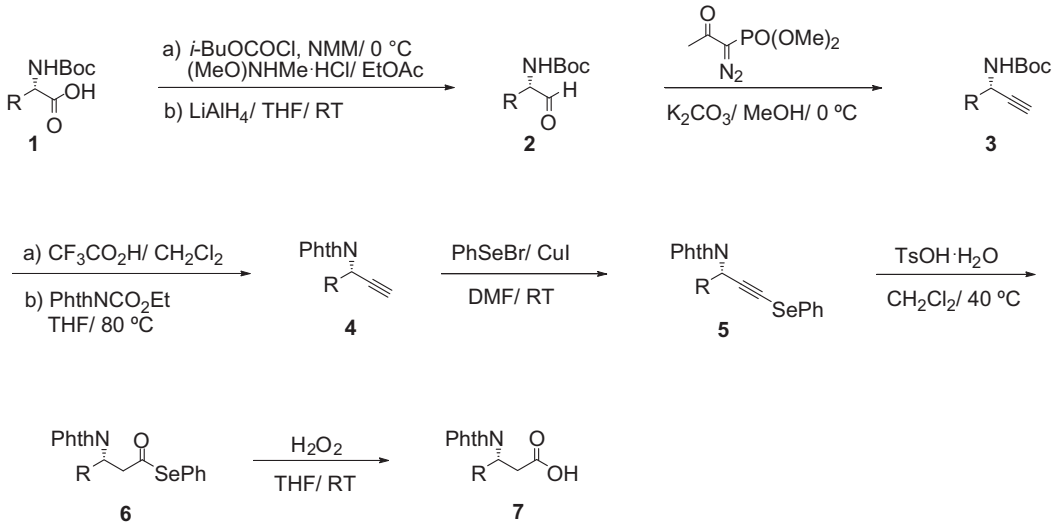
The synthesis of β$^3$-amino acids has attracted considerable attention due to their important role in synthetic chemistry and as key components of a variety of biologically active natural molecules.[1] In medicinal chemistry they represent key components of drugs and β-lactams.[2] β$^3$-Amino acids also have considerable importance in the study of biomimetic polymers which contain both secondary and tertiary structure analogues to those of natural proteins.[3] Different approaches have been developed for the synthesis of β$^3$-amino acids starting from α-amino acids as starting materials because of their ready availability.[4] In this field we have recently introduced a facile synthesis of *Se*-phenyl selenocarboxylates from readily accessible terminal alkynes.[5] These results induced us to devise a new stereospecific conversion of commercially available optically active *N*-Boc α-amino acids **1** into the *N*-phthaloyl β-homologues **7** (Scheme 1).

The key steps of this conversion are the synthesis of the optically active *N*-Boc propargylic amines **3** from the *a*-amino acids **1** and the formal oxidative-hydration of the C–C triple bond to give **7**. General methods for the stereoselective synthesis of **3** have been already reported in the literature[6] however, on the basis of previous experience,[7] we envisioned that the use of the Bestmann–Ohira[8] modification of the Seyferth–Gilbert reagent might constitute an approach for the synthesis of the essential *N*-Boc propargylic amines **3** from the corresponding α-amino aldehyde intermediates **2**.

Thus the commercially available *N*-Boc α-amino acids **1a–d** were converted, under mild conditions, into the corresponding Weinreb amide intermediates by the mixed anhydride method.[9] These crude amides were directly reduced with 1.2 molar equiv of lithium aluminium hydride[10] to give the *N*-Boc *a*-amino aldehydes intermediates **2a–d**. Because of their chemical and configurational instability,[11] the crude aldehydes **2** were directly used for the reaction with the Bestmann–Ohira reagent, in the presence of anhydrous potassium carbonate. The crude *N*-Boc propargylic amines **3** were thus obtained. An analytical sample of compound **3a**, *ent*-**3a**, **3c** and *ent*-**3c** was used to detect the extent of the racemization at the stereogenic α-carbon by GC–MS on chiral column. Under the reaction conditions employed L- and D-valine **1a** and *ent*-**1a** as well as D-serine *ent*-**1c** derivatives suffered a partial racemization. As evidenced in previous works[12] these losses of enantiopurity very likely occurred during the synthesis of the aldehydes and/or during the work-up procedure, depending on the structure. Since the Boc-amino-protecting group is not stable under the reaction conditions employed for the conversion of the C–C triple bond into the *Se*-phenyl selenocarboxylate group,[5] compounds **3** were treated with trifluoroacetic acid in dichloromethane to give the corresponding propargylic amine salts which

* Corresponding authors. Tel.: +39 075 5855121; fax: +39 075 5855116.
*E-mail address:* tempa@unipg.it (A. Temperini).

0040-4039/$ - see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2010.05.143




**Scheme 1.** Multistep synthesis of *N*-phthloyl-$\beta^3$-amino acids **7** from *N*-Boc-α-amino acids **1**.

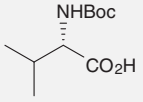
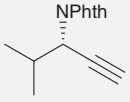
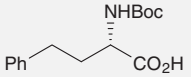
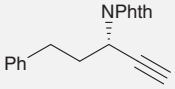
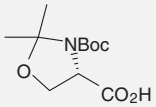
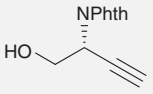
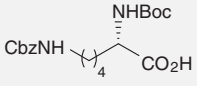
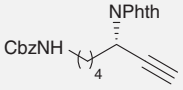
were then protected as *N*-phthaloyl derivatives **4**. The reaction of **3c** and *ent*-**3c** under the conditions reported above led to complete acetonide decomposition to give the free hydroxy derivatives, as already reported in the literature.[13]

Following this protocol the pure *N*-phthaloyl propargylic amines **4** were obtained in good overall yields from **1** (Table 1). HPLC analysis of compound **4b** revealed that a partial racemization of the starting α-amino acid **1b** occurred during the preparation of the corresponding aldehyde. The enantiomeric ratios of compounds **4d** and *ent*-**4d** could not be determined since these compounds did not show any separation on the chiral columns employed.

The propargylic amines **4** were then converted[14] into the corresponding alkynyl phenyl selenide intermediates **5**. These intermediates were obtained sufficiently pure to be directly employed in the following step (Scheme 1). The treatment of **5** with an excess of *p*-toluenesulfonic acid monohydrate in refluxing dichloromethane[5] gave the *Se*-phenyl selenocarboxylates **6**. Compounds **6** were then treated with hydrogen peroxide in tetrahydrofuran to give the corresponding N-protected $\beta^3$-amino acids **7** in good global yields from **4**. The results of these experiments are collected in Table 2. As indicated in Scheme 2, the $\beta^3$-amino acid derivatives of *N*-phthaloyl propargylic amines **4c** and *ent*-**4c** could not be obtained because the treatment of their alkynyl phenyl selenide intermediates with *p*-toluenesulfonic acid monohydrate in refluxing dichloromethane afforded lactones **8** and *ent*-**8**, respectively, in good yields. The formation of these lactones is in agreement with previous observations[15] which indicated that when an alkynyl phenyl selenide holds an oxygen atom in a suitable position the reaction with *p*-toluenesulfonic acid gives rise to a proton-induced ring-closure reaction affording γ-lactones.

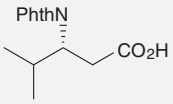
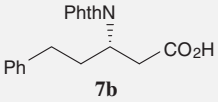
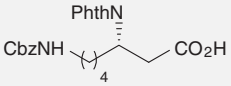
HPLC analysis of products **8** and *ent*-**8** indicates that no racemization occurred during the conversion of **3c** and *ent*-**3c** into lactones **8** and *ent*-**8**, respectively. Moreover, analytical samples of the crude *Se*-phenyl selenocarboxylate intermediates **6a**, *ent*-**6a** and **6b** were converted[5] into the corresponding N-protected

**Table 1**
Multistep conversion of *N*-Boc-α-amino acids **1** into the corresponding N-protected propargylic amines **4**

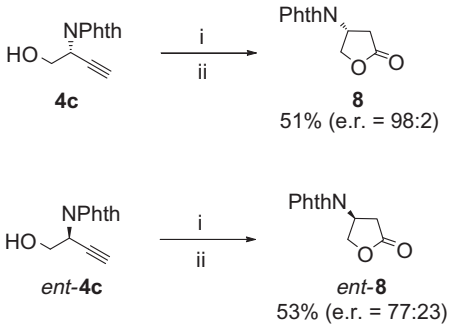
| α-Amino acids **1** | | N-Protected propargylic amines **4** | | er[a] | Yield[b] (%) |
|---|---|---|---|---|---|
|  | **1a** |  | **4a** | 86:14 | 30 |
| | *ent*-**1a** | | *ent*-**4a** | 85:15 | 27 |
|  | **1b** |  | **4b** | 77:23[c] | 35 |
|  | **1c** |  | **4c** | 99:1 | 56 |
| | *ent*-**1c** | | *ent*-**4c** | 77:23 | 60 |
|  | **1d** |  | **4d** | —[d] | 32 |
| | *ent*-**1d** | | *ent*-**4d** | —[d] | 27 |

[a] Enantiomeric ratio determined by chiral GC–MS on a purified analytical sample of the corresponding intermediate **3**.
[b] Total yield calculated from **1**.
[c] Enantiomeric ratio of **4b** determined by chiral HPLC.
[d] Compounds **4d** and *ent*-**4d** did not show any HPLC separation.

**Table 2**
Multistep preparation of enantiomerically enriched N-protected $\beta^3$-aminoacids **7** from N-protected propargylic amines **4**

| N-Protected propargylic amines **4** | N-Protected $\beta^3$-amino acids **7** | Yield[a] (%) | er[b] |
|---|---|---|---|
| **4a** |  | 63 | 87:13 |
| *ent*-**4a** | *ent*-**7a** | 65 | 83:17 |
| **4b** |  **7b** | 76 | 77:23 |
| **4d** |  | 50 | —[c] |
| *ent*-**4d** | *ent*-**7d** | 56 | —[c] |

[a] Total yield calculated from **4**.
[b] Determined by chiral HPLC on the corresponding methyl ester derivatives.
[c] Enantiomeric ratio was determined by proton magnetic resonance analysis of the corresponding mixed αβ-dipeptide.

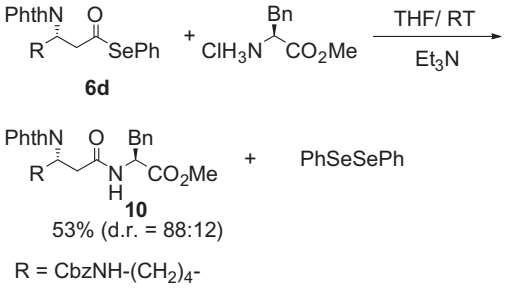



**Scheme 2.** Formation of lactone **8** from **4c** and lactone *ent*-**8** from *ent*-**4c**. Reagents and conditions: (i) PhSeBr (1.1 equiv), CuI (2 equiv), DMF, rt, 48 h; (ii) *p*-TsOH (2 equiv), $CH_2Cl_2$, 70 °C, 4 h.

$\beta^3$-amino acid methyl esters **9a**, *ent*-**9a** and **9b**. The enantiomeric ratios of these esters (HPLC analysis) were identical with those of the corresponding propargylic amine precursors (Table 1) indicating that no racemization occurred during the multistep conversion of **4** into **6**. The enantiomeric purity of the acids **7d** and *ent*-**7d** was measured on the corresponding amides because the corresponding methyl esters could not be separated by HPLC. Thus *Se*-phenyl selenocarboxylate **6d** and *ent*-**6d** were reacted with enantiomerically pure L-phenylalanine methyl ester hydrochloride in tetrahydrofuran and in the presence of triethylamine.

The corresponding mixed αβ-dipeptides **10** and **11** (Scheme 3) were obtained in 53% and 67% good global yields from **6d** and *ent*-**6d**, respectively. Due to the nature of the transformations involved, no racemization occurred during the conversion of **3d** into **4d** and of **5d** into **6d** as demonstrated above. Thus, the diastereoisomeric ratios of dipeptides **10** and **11**, determined by proton NMR, represented the enantiomeric composition of **6d** and *ent*-**6d** as well as those of the *N*-Boc propargylic amine **3d** and *ent*-**3d**, respectively. Finally, the *N*-phthaloyl $\beta^3$-amino acids **7** can be deprotected[16] by reaction with hydrazine hydrate to give the corresponding $\beta^3$-amino acid hydrochlorides.

In conclusion, the present methodology represents a new procedure for the homologation of natural and unnatural α-amino acids.




**Scheme 3.** Formation of mixed α/β-dipeptide **10** from intermediate **6d**. Global yield calculated from **4d**. The diastereoisomeric mixed α/β-dipeptide **11** was obtained in 67% global yield from *ent*-**6d** by the same procedure.

The whole transformations of **1** into **4** and of **4** into **7** may not require purification of the intermediate products but a work-up and isolation procedure of crude materials: there are solvent changes from EtOAc to THF to MeOH to $CH_2Cl_2$ to THF on the way from **1** to **4** and from DMF to $CH_2Cl_2$ to THF on the way from **4** to **7**. It is worth noting that the entire synthetic procedure is of general application since different functionalities present in the substrates such as phenyl, hydroxy, phthaloyl and benzyloxycarbonyl groups are tolerated under the reaction conditions employed. Modifications of the above strategy to minimize the loss of enantiomeric purity of the starting α-amino acids are currently under investigation in our laboratory.

## Acknowledgements

Financial support from MIUR, National Projects PRIN 2007, Consorzio CINMPIS, Bari and University of Perugia is gratefully acknowledged.

## Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.05.143.

## References and notes

1. (a) Liu, M.; Sibi, M. *Tetrahedron* **2002**, *58*, 7991–8035; (b)*Enantioselective Synthesis of β-Amino Acids*; Juaristi, E., Soloshonok, V. A., Eds.; Wiley-VCH: New York, 2005; (c) Seebach, D.; Overhand, M.; Kuhnle, F. N. M.; Martinoni, B.; Oberer, L.; Hommel, U.; Widmer, H. *Helv. Chim. Acta* **1996**, *79*, 913–941; (d) Appella, D. H.; Christianson, L. A.; Karle, I. L.; Powell, D. R.; Gellman, S. H. *J. Am. Chem. Soc.* **1996**, *118*, 13071–13072.
2. Ma, J. S. *Chemistry Today* **2003**, *4*, 65–68.
3. (a) Seebach, D.; Schreiber, J. V.; Abele, S.; Daura, X.; van Gunsteren, W. F. *Helv. Chim. Acta* **2000**, *83*, 34–57; (b) Cheng, R. P.; Gellman, S. H.; DeGrado, W. F. *Chem. Rev.* **2001**, *101*, 3219–3232; (c) Steer, D. L.; Lew, A.; Perlmutter, P.; Smith, A. I.; Aguilar, M. I. *Curr. Med. Chem.* **2002**, *9*, 811–822; (d) Seebach, D.; Beck, A. K.; Bierbaum, D. J. *Chem. Biodivers.* **2004**, *1*, 1111–1239; (e) Cardillo, G.; Gentilucci, L.; Tolomelli, A. *Mini-Rev. Med. Chem.* **2006**, *6*, 293–304.
4. (a) Balenovic, K.; Bregant, N.; Cerar, D.; Tkalcic, M. *J. Org. Chem.* **1951**, *16*, 1308–1310; (b) Penke, B.; Czombos, J.; Balaspiri, L.; Petres, J.; Kocas, K. *Helv. Chim. Acta* **1970**, *53*, 1057–1061; (c) Gmeimer, P. *Tetrahedron Lett.* **1990**, *31*, 5717–5720; (d) Seki, M.; Matsumoto, K. *Tetrahedron Lett.* **1996**, *37*, 3165–3168; (e) Caputo, R.; Cassano, E.; Longobardo, L.; Palumbo, G. *Tetrahedron* **1995**, *51*, 12337–12350; (f) Dexter, C. S.; Jackson, R. F. W. *Chem. Commun.* **1998**, 75–76; (g) Farras, J.; Ginesta, X.; Sutton, P. W.; Taltavull, J.; Egeler, F.; Romea, P.; Urpi, F.; Vilarrasa, J. *Tetrahedron* **2001**, *57*, 7665–7674; (h) Gray, D.; Concellon, C.; Gallagher, T. *J. Org. Chem.* **2004**, *69*, 4849–4850; (i) Saavedra, C. J.; Hernandez, R.; Boto, A.; Alvarez, E. *Tetrahedron Lett.* **2006**, *47*, 8757–8760; (l) Katritzky, A. R.; Tao, H.; Jiang, R.; Suzuki, K.; Kirichenko, K. *J. Org. Chem.* **2007**, *72*, 407–414; (m) Byrne, C. M.; Church, T. L.; Kramer, J. W.; Coates, G. W. *Angew. Chem., Int. Ed.* **2008**, *47*, 3979–3983.
5. Tiecco, M.; Testaferri, L.; Temperini, A.; Bagnoli, L.; Marini, F.; Santi, C.; Terlizzi, R. *Eur. J. Org. Chem.* **2004**, 3447–3458.
6. Zani, L.; Bolm, C. *Chem. Commun.* **2006**, 4263–4275.
7. Reginato, G.; Mordini, A.; Messina, F.; Degl'Innocenti, A.; Poli, G. *Tetrahedron* **1996**, *52*, 10985–10996.

8. (a) Ohira, S. *Synth. Commun.* **1989**, *19*, 561–564; (b) Muller, S.; Liepold, B.; Roth, G. J.; Bestmann, H. J. *Synlett* **1996**, 521–522.
9. Moyer, M. P.; Shiruba, J. F.; Rapoport, H. *J. Org. Chem.* **1986**, *51*, 5106–5110.
10. Fehrentz, J.-A.; Castro, B. *Synthesis* **1983**, 676–678.
11. (a) Jurczak, J.; Golebiowski, A. *Chem. Rev.* **1989**, *89*, 149–164; (b) Hili, R.; Baktharaman, S.; Yudin, A. K. *Eur. J. Org. Chem.* **2004**, 5201–5213.
12. (a) Myers, A. G.; Zhong, B.; Movassaghi, M.; Kung, D. W.; Lanman, B. A.; Kwon, S. *Tetrahedron Lett.* **2000**, *41*, 1359–1362; (b) Soto-Caitoli, B.; Justo de pomar, J.; Soderquist, J. A. *Org. Lett.* **2008**, *10*, 333–336.
13. Meffre, P.; Gauzy, L.; Branquet, E.; Durand, P.; Le Goffic, F. *Tetrahedron* **1996**, *52*, 11215–11238.
14. Braga, A. L.; Silveira, C. C.; Reckziegel, A.; Menezes, P. H. *Tetrahedron Lett.* **1993**, *34*, 8041–8042.
15. Tiecco, M.; Testaferri, L.; Temperini, A.; Terlizzi, R.; Bagnoli, L.; Marini, F.; Santi, C. *Synlett* **2006**, 587–590.
16. Tiecco, M.; Testaferri, L.; Temperini, A.; Terlizzi, R.; Bagnoli, L.; Marini, F.; Santi, C. *Tetrahedron Lett.* **2007**, *48*, 4343–4345.