Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron Letters 47 (2006) 8757–8760
Tetrahedron Letters

One-pot synthesis of β-amino acid derivatives from α-amino acids

Carlos J. Saavedra,[a] Rosendo Hernández,[a,*] Alicia Boto[a,*] and Eleuterio Álvarez[b]

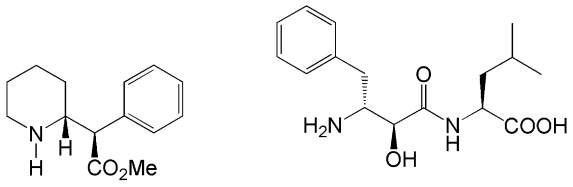
[a]*Instituto de Productos Naturales y Agrobiología del CSIC, Avda. Astrofísico Francisco Sánchez, 3, 38206-La Laguna, Spain*
[b]*Instituto de Investigaciones Químicas CSIC, Avda. Américo Vespucio, 49, Isla de la Cartuja, 41092 Sevilla, Spain*

Received 24 August 2006; revised 29 September 2006; accepted 2 October 2006
Available online 20 October 2006

Abstract—The one-pot transformation of α-amino acid into β-amino acid derivatives is described. The application of this method to the synthesis of modified dipeptides was also illustrated.

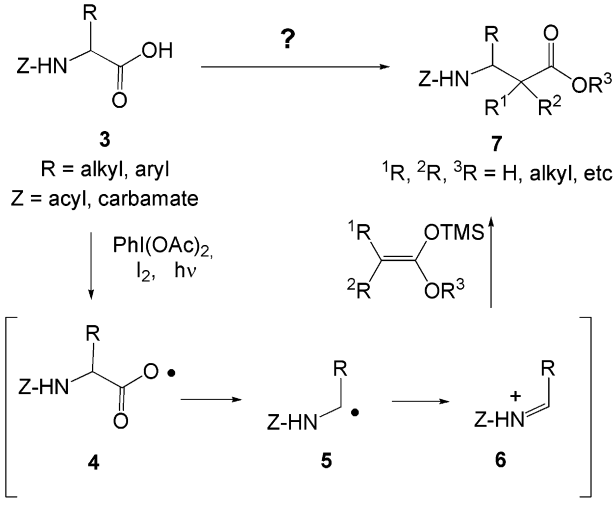
The synthesis of β-amino acids[1] and peptides containing them[2] has arisen great interest, due to the promising biological activities shown by many of these compounds. For instance, β-amino acid **1** (methylphenidate or Ritalin®, Fig. 1) is clinically used as a treatment for the attention deficit disorder in children,[3] and dipeptide **2** (bestatine or Ubenimex®) is an immunological response modifier.[4]

In previous articles, we have reported the syntheses of alkaloids and α-amino phosphonates from α-amino acids **3** (Scheme 1) using a tandem radical fragmentation–addition of nucleophiles reaction.[5] When substrates **3** were treated with (diacetoxyiodo)benzene (DIB) and iodine, under irradiation with visible light, an O-radical **4** was generated, which underwent β-scission,[6] generating a C-radical **5**. This intermediate was oxidized in the reaction mixture to an acyliminium ion



1 2

Figure 1. Bioactive β-amino acid derivatives.



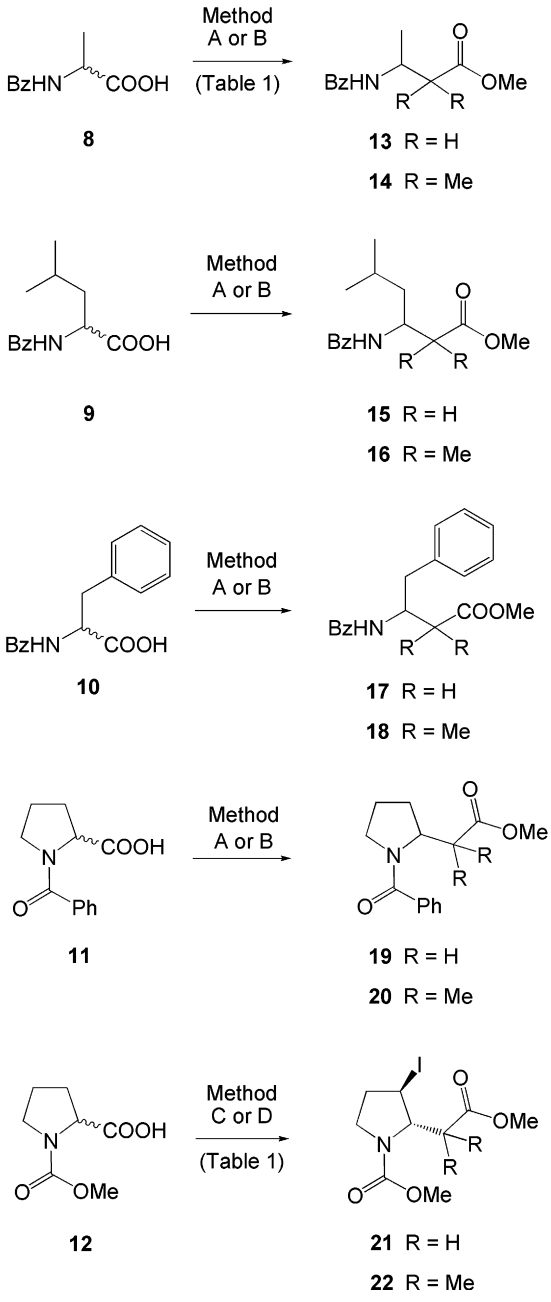
Scheme 1. β-Scission in amino acid derivatives.

6,[7,8] which was trapped by oxygen, nitrogen, phosphorous or carbon nucleophiles. We reasoned that the addition of enolsilylethers to the acyliminium ion could generate β-amino acid derivatives **7** or modified peptides (when $Z = [aa]_n$). The feasibility of this strategy is discussed herein.

In order to study the fragmentation–addition reaction, different amino acid derivatives **8**–**12** (Scheme 2) were prepared, in good yields, by the acylation or carbamoylation of commercial precursors. Substrates **8**–**11** were treated with DIB and iodine at room temperature and under irradiation with visible light (Table 1, entries 1–8). The reaction mixture was then cooled to 0 °C and the enolsilylether and $BF_3{\cdot}OEt_2$ were added,

Keywords: Radicals; β-Amino acids; Dipeptides; Fragmentation; Acyliminium ions; Nucleophilic addition.
* Corresponding authors. Tel.: +34 922 251004; fax: +34 922 260135; e-mail addresses: rhernandez@ipna.csic.es; alicia@ipna.csic.es

0040-4039/$ - see front matter © 2006 Published by Elsevier Ltd.
doi:10.1016/j.tetlet.2006.10.007



Scheme 2. One-pot transformation of α-amino acid into β-amino acid derivatives.

affording β-amino acid derivatives **13**–**20**. In spite of their different volume, both nucleophiles gave similar product yields. In this way, α-amino acids were transformed in one step into the corresponding β-analogues.

The biological activities of amino acids **13**–**20** are under study. Thus, the derivatives of β-homophenylalanine (related to compounds **17** and **18**) have been reported as a new treatment for type II diabetes.[9] Moreover, their insertion into more complex structures could also be of interest. For example, related β-amino acids are units of aminopeptidase inhibitors such as bestatine **2** or amastatine,[2d] and several β-amino acids with lipophilic side chains (such as compounds **13**, **15** and **17**) have been used as components of glycine reuptake inhibitors in the CNS.[10]

Table 1. One-pot β-fragmentation–alkylation reaction

Entry	Substrate	Conditions[a,b,c,d]	Products[e] (%)
1	**8**	A[a]	**13** (50)
2	**8**	B[b]	**14** (41)
3	**9**	A	**15** (55)
4	**9**	B	**16** (67)
5	**10**	A	**17** (50)
6	**10**	B	**18** (55)
7	**11**	A	**19** (85)
8	**11**	B	**20** (77)
9	**12**	C[c]	**21** (69)
10	**12**	D[d]	**22** (56)

[a] Method A. The substrate (1 mmol) in dry dichloromethane (15 mL) was treated with DIB (2.5 mmol) and iodine (1 mmol) and irradiated with visible light (100 W tungsten-filament lamp). The reaction mixture was stirred at room temperature under nitrogen until no starting material was observed by TLC analysis (about 3 h). It was then cooled to 0 °C and $BF_3{\cdot}OEt_2$ (2 equiv) and $CH_2{=}C(OTBS)OMe$ (5 equiv) were added. The reaction mixture was allowed to reach rt and stirred for 4 h, and afterwards it was poured into aqueous $NaHCO_3$–10% $Na_2S_2O_3$ and extracted with CH_2Cl_2.

[b] Method B. As Method A, but using $Me_2C{=}C(OTMS)OMe$ as the nucleophile.

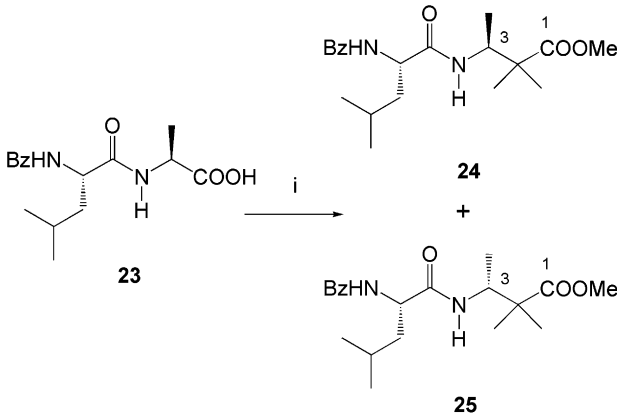
[c] Method C. The substrate (1 mmol) in dry acetonitrile (15 mL) was treated with DIB (2.5 mmol) and iodine (2 mmol) and irradiated with visible light (100 W tungsten-filament lamp). The reaction mixture was stirred at room temperature under nitrogen until no starting material was observed by TLC analysis (about 3 h). Dry methanol was then added and the mixture was poured into aqueous 10% $Na_2S_2O_3$ and extracted with CH_2Cl_2. The organic layer was dried and evaporated, and the crude product was solved in dry acetonitrile, cooled to 0 °C, and treated with $BF_3{\cdot}OEt_2$ (2 equiv) and $CH_2{=}C(OTBS)OMe$ (5 equiv). The reaction mixture was allowed to reach rt and stirred for 4 h, and afterwards it was poured into aqueous $NaHCO_3$ and extracted with CH_2Cl_2.

[d] Method D. As Method C, but using $Me_2C{=}C(OTMS)OMe$ as nucleophile.

[e] Yields are given for products purified by chromatography on silica gel.

The fragmentation–alkylation of methyl carbamate **12** using methods A or B gave a complex mixture of products, so different conditions were tried (methods C or D, entries 9 and 10).[11] In the first step, a tandem fragmentation–β-iodination–addition of methanol reaction took place. The crude product was then treated with the Lewis acid and the nucleophile to give the iodinated β-amino acid derivatives (±)-**21** or (±)-**22** in good yields. The introduction of iodine in a previously non-functionalized position is specially interesting, since these iodinated pyrrolidines could be valuable intermediates in the synthesis of alkaloids and bactericidal iminoglyco acids.[12]

Another interesting application of the scission–alkylation reaction would be the preparation of modified peptides, which is a rapidly growing field in medicinal chemistry.[2] Starting from bioactive peptides, the modification of the C-terminal residue could afford derivatives with different biological activity, potency or selectivity.[13] Since the modified residue would be attached to chiral amino acid units, the reaction was expected to be stereoselective.



Scheme 3. Reagents and conditions: (i) DIB, I_2, hν, CH_2Cl_2, then 0 °C, $BF_3{\cdot}OEt_2$, $Me_2C{=}C(OTMS)OMe$, 58%, **24**:**25** 5:2.

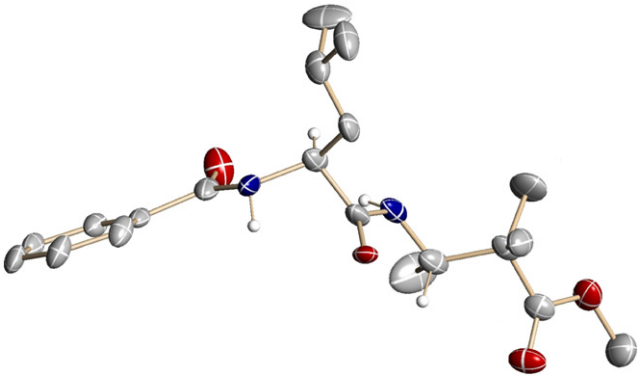


Figure 2. X-ray analysis of dipeptide **24**.

The reaction was studied with the Leu-Ala derivative **23**, using $Me_2C{=}C(OTMS)OMe$ as the nucleophile. The scission–alkylation afforded modified dipeptides **24**[14] and **25** (Scheme 3), which could be separated by chromatography and crystallization. The configuration of **24** was determined by X-ray analysis (Fig. 2).[15] As expected, the reaction was diastereoselective (**24**:**25**, 5:2). However, the isolation of the two possible diastereomers is also interesting, in order to determine the influence of the configuration into the biological activity.

In summary, the one-pot fragmentation–alkylation reaction is a versatile and efficient pathway to obtain many different β-amino acid derivatives from readily available precursors. The synthesis of modified peptides is another interesting application of this reaction.

Acknowledgements

This work was supported by the Research Programme PPQ2003-01379 of the Plan Nacional de Investigación Científica, Desarrollo e Innovación Tecnológica, Ministerios de Ciencia y Tecnología y de Educación y Ciencia, Spain. We also acknowledge financial support from FEDER funds. C.J.S. thanks the CSIC for an I3P fellowship.

References and notes

1. For recent reviews on the synthesis or uses of β-amino acids, see: (a) Liljeblad, A.; Kanerva, L. T. *Tetrahedron* **2006**, *62*, 5831–5854; (b) *Enantioselective Synthesis of β-amino Acids*; Juaristi, E., Soloshonok, V. A., Eds.; Wiley-VCH: New York, 2005; (c) Viso, A.; Fernández de la Pradilla, R.; García, A.; Flores, A. *Chem. Rev.* **2005**, *105*, 3167–3196; (d) Xu, L.-W.; Xia, C.-G. *Eur. J. Org. Chem.* **2005**, 633–639; (e) Cordova, A. *Acc. Chem. Res.* **2004**, *37*, 102–112; (f) Davies, S. G.; Smith, A. D.; Price, P. D. *Tetrahedron: Asymmetry* **2005**, *16*, 2833–2891; (g) France, S.; Weatherwax, A.; Taggi, A. E.; Lectka, T. *Acc. Chem. Res.* **2004**, *37*, 592–600; (h) Ma, J.-A. *Angew. Chem., Int. Ed.* **2003**, *42*, 4290–4299; (i) Taggi, A. E.; Hafez, A. M.; Lectka, T. *Acc. Chem. Res.* **2003**, *36*, 10–19; (j) Sewald, N. *Angew. Chem., Int. Ed.* **2003**, *42*, 5794–5795; (k) Liu, M.; Sibi, M. P. *Tetrahedron* **2002**, *58*, 7991–8035; (l) Ellman, J. A.; Owens, T. D.; Tang, T. P. *Acc. Chem. Res.* **2002**, *35*, 984–995; (m) Park, K.-H.; Kurth, M. J. *Tetrahedron* **2002**, *58*, 8629–8659; (n) Fülop, F. *Chem. Rev.* **2001**, *101*, 2181–2204.
2. (a) Gellman, S. H. *Acc. Chem. Res.* **1998**, *31*, 173–180; (b) Abele, S.; Seebach, D. *Eur. J. Org. Chem.* **2000**, 1–15; (c) Cheng, R. P.; Gellman, S. H.; DeGrado, W. F. *Chem. Rev.* **2001**, *101*, 3219–3232; (d) Bauvois, B.; Dauzonne, D. *Med. Res. Rev.* **2006**, *26*, 88–130.
3. Matsumura, Y.; Kanda, Y.; Shirai, K.; Onomura, O.; Maki, T. *Tetrahedron* **2000**, *56*, 7411–7422, and references cited therein.
4. (a) Pearson, W. H.; Hines, J. V. *J. Org. Chem.* **1989**, *54*, 4235–4237; (b) Suda, H.; Takita, T.; Aoyagi, T.; Umezawa, H. *J. Antibiot.* **1976**, *29*, 600–601.
5. For examples on the decarboxylation of amino acids, see: (a) Boto, A.; Gallardo, J. A.; Hernández, R.; Saavedra, C. J. *Tetrahedron Lett.* **2005**, *46*, 7807–7811; (b) Boto, A.; de León, Y.; Gallardo, J. A.; Hernández, R. *Eur. J. Org. Chem.* **2005**, 3461–3468; (c) Boto, A.; Hernández, R.; Suárez, E. *J. Org. Chem.* **2000**, *64*, 4930–4937.
6. For reviews on β-scission, see: (a) Hartung, J.; Gottwald, T.; Spehar, K. *Synthesis* **2002**, 1469–1498; (b) Zhdankin, V.; Stang, P. J. *Chem. Rev.* **2002**, *102*, 2523–2584; (c) Togo, H.; Katohgi, M. *Synlett* **2001**, 565–581; (d) Suárez, E.; Rodríguez, M. S. In *Radicals in Organic Synthesis*; Renaud, P., Sibi, M. P., Eds.; Wiley-VCH: Weinheim, 2001; Vol. 2, pp 440–454; For recent references on the β-fragmentation reaction, see: (e) Boto, A.; Hernández, D.; Hernández, R.; Suárez, E. *J. Org. Chem.* **2003**, *68*, 5310–5319.
7. For a discussion on the mechanism of the oxidation step, see: Boto, A.; Hernández, R.; León, Y.; Murguía, J. R.; Rodríguez-Afonso, A. *Eur. J. Org. Chem.* **2005**, 673–682.
8. For recent reviews on acyliminium ions, see: (a) Maryanoff, B. E.; Zhang, H.-C.; Cohen, J. H.; Turchi, I. J.; Maryanoff, C. A. *Chem. Rev.* **2004**, *104*, 1431–1628; (b) Royer, J.; Bonin, M.; Micouin, L. *Chem. Rev.* **2004**, *104*, 2311–2352.
9. (a) Kubryk, M.; Hansen, K.-B. *Tetrahedron: Asymmetry* **2006**, *17*, 205–209; (b) Weber, A. *J. Med. Chem.* **2004**, *48*, 4135–4141.
10. Wolin, R. L.; Santillán, A., Jr.; Barclay, T.; Tang, L.; Venkatesan, H.; Wilson, S.; Lee, D. H.; Lovenberg, T. W. *Bioorg. Med. Chem.* **2004**, *12*, 4493–4509.
11. Boto, A.; Hernández, R.; León, Y.; Suárez, E. *J. Org. Chem.* **2001**, *66*, 7796–7803.
12. (a) La Ferla, B.; Bugada, P.; Cipolla, L.; Peri, F.; Nicotra, F. *Eur. J. Org. Chem.* **2004**, 2451–2470; (b) Schweizer, F. *Angew. Chem., Int. Ed.* **2002**, *41*, 230–253.

13. For an electrochemical decarboxylation of peptides, see: Renaud, P.; Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 843–844.
14. All the compounds were completely characterized by ^{1}H and ^{13}C NMR, MS, HRMS, IR and elemental analysis. 2D-COSY, HSQC and NOESY experiments were also carried out. *Selected data for compound* **24**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.97 (6H, d, $J = 5.8$ Hz), 1.04 (3H, d, $J = 6.8$ Hz), 1.20 (6H, s), 1.67–1.98 (3H, m), 3.67 (3H, s), 4.08 (1H, dddd, $J = 7.1, 7.1, 7.1, 10.2$ Hz), 4.67 (1H, ddd, $J = 6.0, 8.3, 8.3$ Hz), 6.87 (2H, br b, $2 \times$ NH), 7.40 (2H, dd, $J = 7.2, 7.9$ Hz), 7.48 (1H, dd, $J = 7.0, 7.8$ Hz), 7.79 (2H, d, $J = 7.5$ Hz); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 16.7 (CH_3), 22.3 (CH_3), 22.7 (CH_3), 22.8 (CH_3), 23.2 (CH_3), 25.0 (CH), 41.8 (CH_2), 46.0 (C), 51.3 (CH), 51.9 (CH_3), 52.5 (CH), 127.1 ($2 \times$ CH), 128.5 ($2 \times$ CH), 131.7 (CH), 134.0 (C), 167.3 (C), 171.6 (C), 176.9 (C). Anal. Calcd for $C_{20}H_{30}N_2O_4$: C, 66.27; H, 8.34; N, 7.73. Found: C, 66.13; H, 8.26; N, 7.76. *Selected data for compound* **25**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.98 (3H, d, $J = 6.3$ Hz), 0.99 (3H, d, $J = 6.3$ Hz), 1.12 (3H, d, $J = 6.6$ Hz), 1.17 (6H, s), 1.65–1.81 (3H, m), 3.67 (3H, s), 4.09 (1H, dddd, $J = 6.8, 6.8, 6.9, 9.7$ Hz), 4.65 (1H, ddd, $J = 6.0, 8.3, 8.3$ Hz), 6.70 (1H, d, $J = 8.2$ Hz, NH), 6.85 (1H, d, $J = 9.6$ Hz, NH), 7.43 (2H, dd, $J = 7.2, 7.8$ Hz), 7.50 (1H, dd, $J = 7.3, 7.5$ Hz), 7.79 (2H, d, $J = 7.0$ Hz); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 16.9 (CH_3), 22.3 (CH_3), 22.9 ($2 \times CH_3$), 23.2 (CH_3), 25.0 (CH), 41.4 (CH_2), 46.0 (C), 51.3 (CH), 51.9 (CH_3), 52.3 (CH), 127.0 ($2 \times$ CH), 128.6 ($2 \times$ CH), 131.7 (CH), 134.0 (C), 167.3 (C), 171.2 (C), 177.0 (C). Anal. Calcd for $C_{20}H_{30}N_2O_4$: C, 66.27; H, 8.34; N, 7.73. Found: C, 66.25; H, 8.47; N, 7.92.
15. *Crystal data for* **24**: $C_{20}H_{30}N_2O_4$, $M_r = 362.46$, colourless needle ($0.55 \times 0.11 \times 0.10$ mm^3) from CH_2Cl_2/*n*-hexane, trigonal, space group $P6_5$ (no. 170), $a = b = 11.7280(10)$ Å, $c = 26.998(5)$ Å, $\alpha = \beta = 90°$, $\gamma = 120°$, $V = 3216.0(7)$ Å^3, $Z = 6$. $\rho_{calcd} = 1.123$ g cm^{-3}, λ (Mo Kα) = 0.71073 Å, $F(000) = 1176$, $\mu = 0.078$ mm^{-1}, $T =$ 100(2) K. 26186 reflections measured for the range $3.45° < \theta < 26.37°$. Final refinement with 2240 [$R_{int} = 0.0802$] unique reflections and 317 parameters gave, $R_1 = 0.0774$, $wR_2 = 0.1858$ [for 1336 reflections with $I > 2\sigma(I)$], $R_1 = 0.1434$, $wR_2 = 0.2375$ (all data) ($S = 1.092$). The X-ray crystallographic file, in CIF format, has been deposited with the Cambridge Crystallographic Data Centre, CCDC No. 618736 for **24**. Copy of this information may be obtained free of charge from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk or http://www.ccdc.cam.ac.uk/conts/retrieving.html.