Tetrahedron Letters 49 (2008) 4366–4368

Contents lists available at ScienceDirect

Tetrahedron Letters

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

Synthesis of norleucine-derived phosphonopeptides

Jan Pícha, Miloš Buděšínský, Miloslav Šanda, Jiří Jiráček *

Institute of Organic Chemistry and Biochemistry, v.v.i., Academy of Sciences of the Czech Republic, Flemingovo nám. 2, 166 10 Prague 6, Czech Republic

ARTICLE INFO

Article history:
Received 2 April 2008
Revised 25 April 2008
Accepted 7 May 2008
Available online 10 May 2008

ABSTRACT

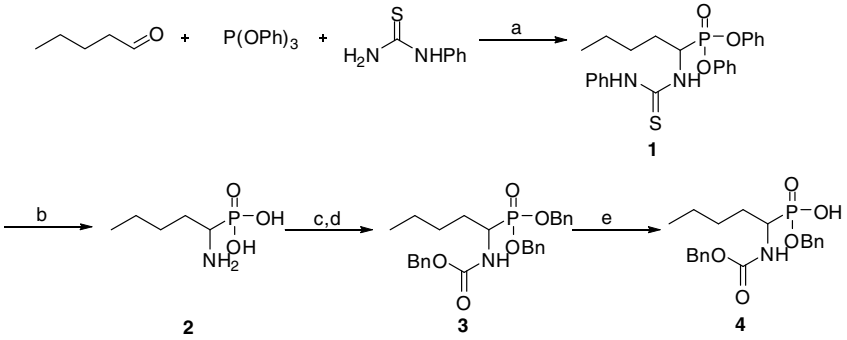
The synthesis of norleucine-derived phosphonopeptides was achieved by BOP-catalyzed coupling of the monobenzyl ester of a *N*-CBz-protected phosphonate derivative of norleucine with hydroxyl moieties of derivatized lactic or glycolic acids. The complete deprotection of the product esters/carbamates was achieved in good yields by one-step Pd-catalyzed hydrogenolysis.

Phosphinopeptides[1,2] and phosphonopeptides[3,4] (also called depsipeptides[5]) have found important applications in biology and medicine primarily as inhibitors of metalloenzymes. The replacement of a hydrolysable peptide bond by non-hydrolysable phosphinate[6] or phosphonate[7,8] moieties mimics the hypothetical transition state of the substrate upon hydrolysis and may result in potent inhibition of the respective peptidases.

We present here an efficient solution synthesis of a novel type of pseudopeptide mimicking the sequences Nle-Ala(Gly) or Nle-Ala(Gly)-Val with all the examples containing the phosphonate analogue of norleucine at the N-terminus. These compounds may represent potential inhibitors of methionine or leucine aminopeptidases. The proposed pseudopeptide sequences should fulfill the structural requirements of methionine aminopeptidases Nle or Met at P_1 and a small aliphatic residue, such as Ala or Gly, in the P'_1 position. The C-terminal Val at the P'_2 position was chosen based on our recent results with statine pseudopeptides as inhibitors of methionine aminopeptidases.[9]

In the present work, we modified the previously published methodology for the preparation of phosphonopeptides described by Campagne et al.[10] The first step of our approach was the synthesis of the protected phosphonate analogue of norleucine **4** (Scheme 1). (*R*,*S*)-Diphenyl 1-(3-phenylthioureido)pentanephosphonate **1** was synthesized from valeraldehyde, triphenyl phosphite, and *N*-phenylthiourea according to the procedure described by Stec et al.[11] This was converted to (*R*,*S*)-1-aminopentanephosphonic acid **2** by refluxing in concentrated hydrochloric acid followed by treatment with propylene oxide. Reaction of **2** with benzyl chloroformate afforded the *Z*-protected phosphonate, and heating this free acid with 2 equiv of *N*,*N*′-diisopropyl-*O*-benzylisourea[12] in a mixture of benzene and DMF (1:5) gave the corresponding dibenzyl ester **3**.[13] The key intermediate **4** was obtained in high yield after base-catalyzed hydrolysis[14] of **3**.

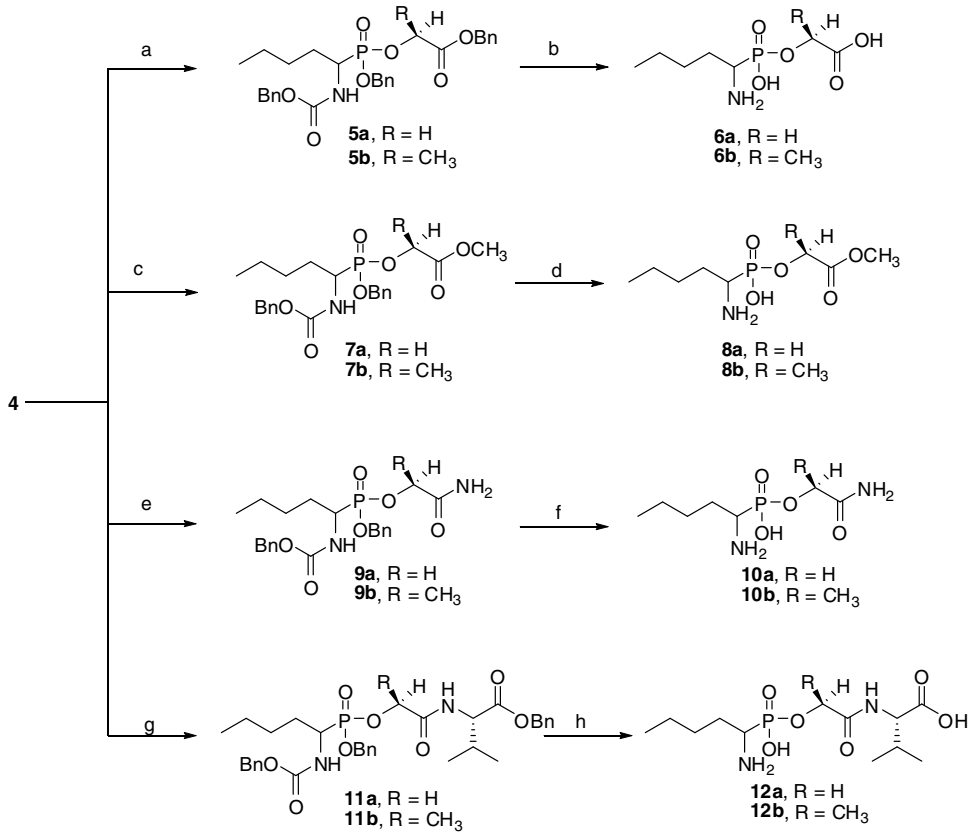
The above-mentioned *N*-CBz-protected phosphonate monoester **4** was used as a starting material for the synthesis of a series of phosphodipeptides and phosphonotripeptides **5**–**12** (Scheme 2).



Scheme 1. Reagents, conditions, and yields: (a) AcOH, 80 °C, 3 h (81%); (b) 35% HCl and AcOH, reflux for 20 h, then 1,2-epoxypropane, ethanol (58%); (c) benzyl chloroformate, Na_2CO_3, water, and dioxane, 0 °C, 2 h then at rt overnight (88%); (d) *N*,*N*′-diisopropyl-*O*-benzylisourea, benzene, and DMF, 80 °C, 8 h (75%); (e) DABCO, toluene, 80 °C, 8 h (92%).

* Corresponding author. Tel.: +420 220183441; fax: +420 220183571.
E-mail address: jiracek@uochb.cas.cz (J. Jiráček).

0040-4039/$ - see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2008.05.028



Scheme 2. Reagents, conditions, and yields: (a) benzyl glycolate or benzyl (*S*)-lactate, BOP, TEA, DMF, rt, overnight, R = H (88%), R = CH_3 (86%); (b) 10% Pd/H_2, methanol, rt, overnight, R = H (70%), R = CH_3 (69%); (c) methyl glycolate or methyl (*S*)-lactate, BOP, TEA, DMF, rt, overnight, R = H (85%), R = CH_3 (82%); (d) 10% Pd/H_2, methanol, rt, overnight, R = H (78%), R = CH_3 (73%); (e) glycolamide or (*S*)-lactamide, BOP, TEA, DMF, rt, overnight, R = H (74%), R = CH_3 (70%); (f) 10% Pd/H_2, methanol, rt, overnight, R = H (77%), R = CH_3 (64%); (g) $HOCH_2CONHCH(S\text{-}iPr)COOBn$ or $HOCH(S\text{–}CH_3)CONHCH(S\text{-}iPr)COOBn$, BOP, TEA, DMF, rt, overnight, R = H (70%), R = CH_3 (72%); (h) 10% Pd/H_2, methanol, rt, overnight, R = H (65%), R = CH_3 (56%).

Compound **4** was esterified easily with the benzyl ester, methyl ester or amide forms of glycolic or L-lactic acids using the activating agent BOP[10] to give the mixed diesters **5a**, **5b**, **7a**, **7b**, **9a**, and **9b** as outlined in Scheme 2. To obtain compounds **11a** and **11b**, precursor **4** was reacted with the previously prepared[15] dipeptides composed of benzyl L-valine and glycolic or L-lactic acid. All the mixed diester precursors were fully deprotected by hydrogenolysis. After HPLC purifications, we obtained target compounds **6a**, **6b**, **8a**, **8b**, **10a**, **10b**, **12a**, and **12b**. All the intermediates and final products gave correct spectra. As examples, the NMR spectra for compounds **12a** and **12b** are given.[16]

The synthetic route presented for phosphonate pseudopeptides is convenient, mainly for masking the amino and hydroxy groups with a non-polar protecting group, which permits easy work-up of the intermediates. Condensation of **4** with esters or amides of glycolic and lactic acid proceeds without sensitivity to steric hindrance, and the final step of the synthesis enables the complete removal of the protecting groups under mild conditions. At present, we are investigating the application of the *N*-Fmoc-protected derivatives of **6a** and **6b** as building blocks for solid-phase peptide synthesis, providing a tool for the development of phosphonic peptide libraries.

Acknowledgments

This project was supported by Grant 203/06/1405 (to J.J.) of the Grant Agency of the Czech Republic, by Chemical Genetics Consortium No. LC060777 of the Ministry of Education, Youth and Sports of the Czech Republic (to J.J.) and by Research Project Z4 055 0506 of the Academy of Sciences of the Czech Republic.

References and notes

1. Dive, V.; Georgiadis, D.; Matziari, M.; Makaritis, A.; Beau, F.; Cuniasse, P.; Yiotakis, A. *Cell. Mol. Life Sci.* **2004**, *61*, 2010.
2. Yiotakis, A.; Georgiadis, D.; Matziari, M.; Makaritis, A.; Dive, V. *Curr. Org. Chem.* **2004**, *8*, 1135–1158.
3. Kafarski, P.; Lejczak, B. In *Aminophosphinic and Aminophosphonic Acids. Chemistry and Biological Activity*; Kukhar, V. P., Hudson, H. R., Eds.; Synthesis of Phosphono- and Phosphinopeptides; John Wiley & Sons Ltd: Chichester, 2000; pp 173–203.
4. Kafarski, P.; Lejczak, B. In *Aminophosphinic and Aminophosphonic Acids, Chemistry and Biological Activity*; Kukhar, V. P., Hudson, H. R., Eds.; The Biological Activity of Phosphono- and Phosphinopeptides; John Wiley & Sons Ltd: Chichester, 2000; pp 407–442.
5. Isomura, S.; Ashley, J. A.; Wirsching, P.; Janda, K. D. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 861.
6. Collinsova, M.; Jiracek, J. *Curr. Med. Chem.* **2000**, *7*, 629.
7. Hanson, J. E.; Kaplan, A. P.; Bartlett, P. A. *Biochemistry* **1989**, *28*, 6294.
8. Phillips, M. A.; Kaplan, A. P.; Rutter, W. J.; Bartlett, P. A. *Biochemistry* **1992**, *31*, 959.
9. Mitra, S.; Dygas-Holz, A. M.; Jiracek, J.; Zertova, M.; Zakova, L.; Holz, R. C. *Anal. Biochem.* **2006**, *357*, 43.
10. Campagne, J. M.; Coste, J.; Jouin, P. *Tetrahedron Lett.* **1995**, *36*, 2079.
11. Kudzin, Z. H.; Stec, W. J. *Synthesis* **1978**, 469.
12. Davies, J. S.; Howe, J.; Lebreton, M. *J. Chem. Soc., Perkin Trans. 2* **1995**, 2335.
13. Hoffmann, M. *J. Prakt. Chem.* **1988**, *330*, 820.
14. Hoffmann, M. *Phosphorus Sulfur Silicon Relat. Elem.* **1998**, *134*, 109.
15. Toth, I.; Anderson, G. J.; Hussain, R.; Wood, I. P.; Fernandez, E. D.; Ward, P.; Gibbons, W. A. *Tetrahedron* **1992**, *48*, 923.
16. Compound **12a**: mixture of diastereoisomers ~2:1; only signals of the major isomer are given: ^1H NMR (600 MHz, DMSO): 0.86 (3H, t, J = 7.3, CH_3); 0.89 (6H, d, J = 6.8, 2 × CH_3); 1.26 (2H, m, CH_2); 1.40 (2H, m, CH_2); 1.57 and 1.76 (2H, m, CH_2); 2.08 (1H, m, CH); 2.96 (1H, m, N–CH–P); 4.18 (1H, dd, J = 8.2

and 5.3, N–CH–CO); 4.37 (2H, m, O–CH_2–CO); 7.98 (2H, b, NH_2); 8.32 (1H, d, J = 8.2, NH); ^{13}C NMR (150.9 MHz, DMSO): 13.98 (CH_3); 18.01 and 19.29 (2 × CH_3); 22.20 (CH_2); 28.02 (d, J(C, P) = 7.8, CH_2); 28.66 (CH_2); 30.15 (CH); 48.02 (d, J(C, P) = 143.5, N–CH–P); 57.30 (N–CH); 62.88 (d, J(C, P) = 6.0, O–CH_2); 170.91 (CO–N); 172.79 (COOH). HRMS (ESI) calcd for $C_{12}H_{26}O_6N_2P_1$ [M+H]+ 325.1523; found: 325.1525. Compound **12b**: ^{1}H NMR (600 MHz, DMSO): 0.85 (3H, t, J = 7.4, CH_3); 0.89 (6H, d, J = 6.8, 2 × CH_3); 1.26 (2H, m, CH_2); 1.36 and 1.42 (2H, m, CH_2); 1.38 (3H, d, J = 6.8, CH_3); 1.61 and 1.77 (2H, m, CH_2); 2.09 (1H, m, CH); 3.08 (1H, m, N–CH–P); 4.14 (1H, dd, J = 8.4 and 5.6, N–CH–CO); 4.84 (1H, dq, J = 6.8 and 7.6, O–CH–CO); 8.08 (2H, b, NH_2); 8.18 (1H, d, J = 8.4, NH); ^{13}C NMR (150.9 MHz, DMSO): 13.91 (CH_3); 18.19 and 19.32 (2 × CH_3); 20.46 (d, J(C, P) = 5.1, CH_3); 22.08 (CH_2); 27.77 (d, J(C, P) = 7.8, CH_2); 28.38 (CH_2); 30.10 (CH); 47.70 (d, J(C, P) = 147.2, N–CH–P); 57.46 (N–CH); 70.89 (d, J(C, P) = 6.0, O–CH); 172.29 (d, J(C, P) = 3.2, CO–N); 172.83 (COOH). HRMS (ESI) calcd for $C_{13}H_{28}O_6N_2P_1$ [M+H]+ 339.1680; found: 339.1678.