

S0040-4039(96)00198-0

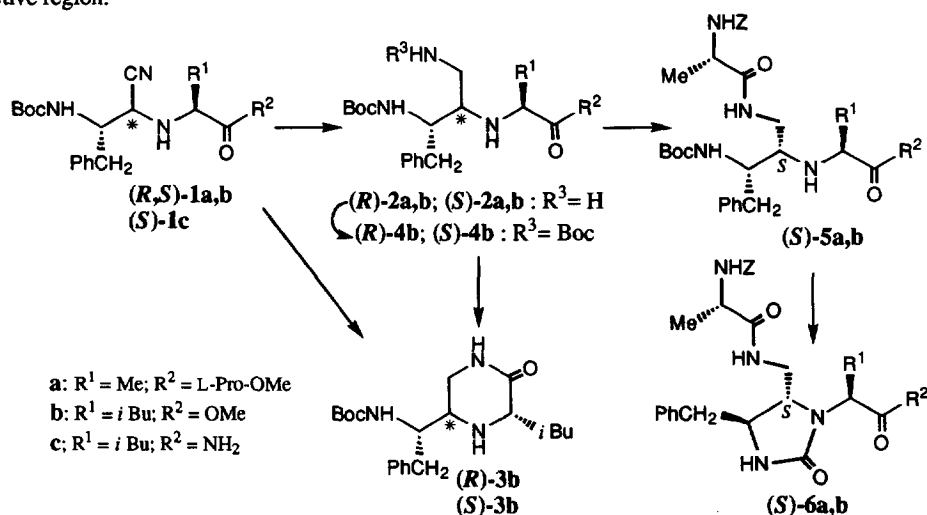
Branched Peptides and Conformationally Constrained Analogues from Cyanomethyleneamino Pseudopeptides

M. Luisa Suárez-Gea, M. Teresa García-López, Rosario González-Muñiz, Susana Herrero
 and Rosario Herranz*

Instituto de Química Médica, C.S.I.C., Juan de la Cierva 3, E-28006 Madrid, Spain

Abstract: Catalytic hydrogenation of cyanomethyleneamino pseudopeptides, followed by peptide coupling and cyclization of the resulting aminomethyleneamino intermediates, gives access to branched and conformationally constrained peptide analogues.

Taking into account that the [CH(CN)NH] group could be a good peptide bond surrogate and a mimic of the tetrahedral transition state involved in peptidase action¹, we have previously reported the synthesis of cyanomethyleneamino pseudopeptides², and the preliminary biological data resulting from the incorporation of this new peptide backbone modification into aminopeptidase inhibitors³ and neurotensin analogues⁴. On the other hand, considering the chemical versatility of the cyano group, Ψ[CH(CN)NH] pseudopeptides were transformed into the corresponding Ψ[CH(CONH₂)NH] analogues⁵. Now, a similar consideration has prompted us to study and to communicate herein the use of these pseudopeptides as precursors of branched and conformationally restricted peptide analogues *via* catalytic hydrogenation, followed by peptide coupling or cyclization. Independently on the constituent amino acids of the pseudopeptide, the amino group generated from the cyano reduction can be used for branching or cyclization reactions, while most classical procedures for these reactions are applicable to those peptides containing reactive side chains, such as those of Asp, Glu, Lys or Cys⁶⁻⁹. If this is not the case, replacement of amino acid residues with appropriately functionalized analogues is required. Such replacements are permissible in the silent region of peptides, but may lead to inactive compounds when applied to their active region.



For this study the epimeric mixtures of Ψ[CH(CN)NH] pseudotri- and pseudodipeptides $(R,S)\text{-1a}^5$ and $(R,S)\text{-1b}^2$, which could not be resolved, and the optically pure amide pseudodipeptide $(S)\text{-1c}^5$ were used as

starting materials. In the first case, as outlined in the scheme, the Pd(C) catalysed hydrogenation, at room temperature and in the presence of AcOH, gave the corresponding epimeric pair of $\Psi[\text{CH}(\text{CH}_2\text{NH}_2)\text{NH}]$ pseudotripeptides (*R*)- and (*S*)-**2a** in good yield¹⁰, which was chromatographically resolved. Similarly, the hydrogenation of (*R,S*)-**1b** led to (*R*)- and (*S*)-**2b**, but these compounds were unstable, and in the hydrogenation medium cyclized partially to the 2-oxopiperazine derivatives (*R*)- and (*S*)-**3b**. The resulting (1:1) mixture of epimeric pairs (*R,S*)-**2b** and (*R,S*)-**3b** was also chromatographically resolved (MeOH-CH₂Cl₂; 0-10%). Each separated epimer (*R*)- and (*S*)-**2b** was transformed at room temperature into the corresponding 2-oxopiperazine **3b**, after 48 h in MeOH solution. This cyclization was avoided when the hydrogenation was carried out in the presence of di-*tert*-butyl-dicarbonate, to give the di(*N*-Boc) derivatives (*R*)- and (*S*)-**4b**, respectively. On the other hand, the open amide pseudodipeptide resulting from the hydrogenation of (*S*)-**1c** was too unstable, obtaining only the cyclic 2-oxopiperazine derivative (*R*)-**3b**¹¹.

The absolute configuration at C-5 in 2-oxopiperazines **3b**, and, therefore, that at the peptide bond surrogate in the open pseudodipeptide precursors **2b**, was assigned on the basis of the coupling constants and NOEs observed in the ¹H NMR spectra of **3b**. These data also suggest that in (CD₃)₂CO solution the 2-oxopiperazine ring of (*S*)-**3b** adopts a preferred half-chair conformation, while in the (*R*)-**3b** epimer a twist-boat conformation is preferred.

The coupling of the (*S*)-epimer of $\Psi[\text{CH}(\text{CH}_2\text{NH}_2)\text{NH}]$ pseudopeptides (*S*)-**2a** and **-2b** with *Z*-L-Ala-OH, by the DCC/HOBt method, gave the branched peptide analogues (*S*)-**5a** and **-5b**, respectively. However, under the same conditions or using bis(2-oxo-3-oxazolidinyl)phosphinic chloride (BOP-Cl) or benzotriazolylloxy tris(dimethylamino)phosphonium hexafluorophosphate (BOP) as coupling agents, it was not possible to obtain their epimers (*R*)-**5a** and **-5b**. This lower reactivity could be due to a higher steric hindrance in these epimers. As in the starting cyanomethyleneamino pseudopeptides **1**, acylation of the secondary NH at the peptide bond surrogate was not observed². Finally, removal of the Boc protecting group in the orthogonally protected branched peptide derivatives (*S*)-**5a,b**, followed by reaction with bis(trichloromethyl)carbonate yielded the restricted derivatives (*S*)-**6a** and **-6b**, respectively, whose ¹H NMR spectra showed a J_{4,5} value of 4Hz consistent with a H₄,H₅ *trans* disposition in the 2-oxoimidazolidine ring².

In conclusion, the latent amino functionality in cyanomethyleneamino pseudopeptides provides ready access to branched peptide analogues and to conformationally restricted scaffolds, such as the 2-oxopiperazines **3** and the 2-oxoimidazolidines **6**, attractive for the synthesis of peptidomimetic libraries.

ACKNOWLEDGEMENTS: We thank the CICYT (SAF 94-0705) and DGICYT (UE 95-0021) for financial support.

REFERENCES AND NOTES

- Herranz, R.; Suárez-Gea, M.L.; Vinuesa, S.; García-López, M.T.; Martínez, A. *Tetrahedron Lett.* **1991**, *32*, 7579-7582.
- Herranz, R.; Suárez-Gea, M.L.; Vinuesa, S.; García-López, M.T. *J. Org. Chem.* **1993**, *58*, 5186-5191. Herranz, R.; Suárez-Gea, M.L.; García-López, M.T.; González-Muñiz, R.; Johansen, N.L.; Madsen, K.; Thøgersen, H.; Suzdak, P. *Tetrahedron Lett.* **1993**, *34*, 8357-8360.
- Suárez-Gea, M.L.; Vinuesa, S.; García-López, M.T.; Pérez, C.; Herranz, R. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 1491-1496.
- González-Muñiz, R.; García-López, M.T.; Gómez-Monterrey, I.; Herranz, R.; Jimeno, M.L.; Suárez-Gea, M.L.; Johansen, N.L.; Madsen, K.; Thøgersen, H.; Suzdak, P. *J. Med. Chem.* **1995**, *38*, 1015-1021.
- Suárez-Gea, M.L.; García-López, M.T.; Herranz, R. *J. Org. Chem.* **1994**, *59*, 3600-3603.
- Picard, I.L.; Wiegandt, D.L.; Spatola, A.F. *Peptides. Chemistry, Structure and Biology*, Hodges, R.S. and Smith, J. eds. ESCOM: Leiden, **1994**; pp 104-106, and references cited therein.
- Tam, J.P. *Proc. Natl. Acad. Sci. USA* **1988**, *85*, 5409-5413.
- Hagiwara, D.; Miyake, H.; Murano, K.; Morimoto, H.; Murai, M.; Fujii, T.; Nakanishi, I.; Matsuo, M. *J. Med. Chem.* **1993**, *36*, 2266-2278.
- Fairlie, D.P.; Abbenante, G.; March, D.R. *Curr. Med. Chem.* **1995**, *2*, 654-686, and references cited therein.
- All new compounds gave satisfactory analytical and spectroscopical data.
- In the specification of chirality at the peptide bond surrogate the ligand preference in the products resulting from the hydrogenation of $\Psi[\text{CH}(\text{CN})\text{NH}]$ pseudopeptides change. Thus, (*S*)-epimers **1** are transformed into (*R*)-aminomethyleneamino derivatives.