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# Branched Peptides and Conformationally Constrained Analogues from Cyanomethyleneamino Pseudopeptides

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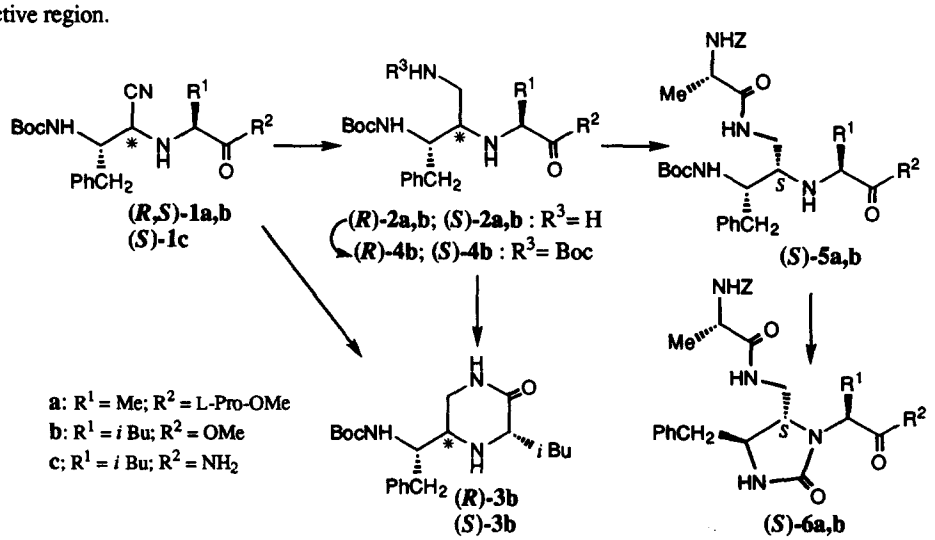
***Abstract***: Catalytic hydrogenation of cyanomethyleneamino pseudopeptides, followed by peptide coupling and cyclization of the resulting aminomethyleneamino intermediates, gives access to branched and conformationally constrained peptide analogues.

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 action[1], we have previously reported the synthesis of cyanomethyleneamino pseudopeptides[2], and the preliminary biological data resulting from the incorporation of this new peptide backbone modification into aminopeptidase inhibitors[3] and neurotensin analogues[4]. On the other hand, considering the chemical versatility of the cyano group, Ψ[CH(CN)NH] pseudopeptides were transformed into the corresponding Ψ[CH($CONH_2$)NH] analogues[5]. 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 Cys[6-9]. 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*)-**1a**[5] and (*R*,*S*)-**1b**[2], which could not be resolved, and the optically pure amide pseudodipeptide (*S*)-**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 Ψ[CH($CH_2NH_2$)NH] pseudotripeptides (*R*)- and (*S*)-**2a** in good yield[10], which was chromatographycally 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 chromatographycally resolved (MeOH-$CH_2Cl_2$; 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 $(CD_3)_2CO$ 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 Ψ[CH($CH_2NH_2$)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 benzotriazolyloxy 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 observed[2]. 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 $H_4$,$H_5$ *trans* disposition in the 2-oxoimidazolidine ring[2].

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.

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10. All new compounds gave satisfactory analytical and spectrocopical data.
11. In the specification of chirality at the peptide bond surrogate the ligand preference in the products resulting from the hydrogenation of Ψ[CH(CN)NH] pseudopeptides change. Thus, (*S*)-epimers **1** are transformed into (*R*)-aminomethyleneamino derivatives.

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