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Synthesis of Aib- and Phe(2Me)-Containing Cyclopentapeptides

Arnhold, Franziska S ; Linden, Anthony ; Heimgartner, Heinz

Abstract: Some recently described pentapeptides containing the alpha,alpha-disubstituted alpha-amino acids Aib and Phe(2Me) have been cyclized in DMF solution using diphenyl phosphorazidate (DPPA), O-(1H-benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium tetrafluoroborate/1-hydroxybenzotriazole (TBTU/HOBt), and diethyl phosphorocyanidate (DEPC), respectively, to give the corresponding cyclopentapeptides in fair-to-good yields. In the case of peptides with L-amino acids, and (R)- and (S)-Phe(2Me), the yields differed significantly in favor of the L/(R) combination. The conformations in the crystals of cyclo(Gly-Aib-(R,S)-Phe(2Me)-Aib-Gly) and cyclo(Gly-(R)-Phe(2Me)-Pro-Aib-Gly) have been determined by X-ray crystallography, leading to quite different results. In the latter case, the conformation in solution has been elucidated by NMR studies.

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Synthesis of Aib- and Phe(2Me)-Containing Cyclopentapeptides

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Scheme 1

Scheme 2

Scheme 3

Scheme 4

Graphical Abstract

Figure 1

Molecule A

Molecule B

Figure 2

Molecule A

Molecule B

(R)-5f A **(R)-5f B**

Figure 3

Figure 4

a)

b)