The chiral sequence of a natural peptide inhibitor of HIV-1 integrase elucidated

Integramide A, an efficient inhibitor of the coupled reaction of HIV-1 integrase, is a 16-mer linear peptide characterized by nine Cα-methylated α-amino acids (five Iva, isovaline, and four Aib, α-aminoisobutyric acid, residues) that was isolated from fungal extracts of Dendrodochium sp. The amino acid sequence was fully elucidated by the Merck groups a few years ago (Fig. 1). On the other hand, the chiral sequence was only partially determined. In particular, the precise stereochemistry of the Iva14-Iva15 dipeptide (known to contain one D- and one L-residue) near the C-terminus was not reported.

To solve this unsettled stereochemical issue and to assess integramide A primary structure-bioactivity relationship we performed by solution methods the total chemical independent syntheses of both L-D and D-L 16-mer diastereomers and compared their properties with those of the natural inhibitor. For an unambiguous, complete stereochemical assignment of integramide A we relied heavily on HPLC (Fig. 2) and NMR (Fig. 3) techniques.

Figure 1. Amino acid sequence of integramide A and chemical structures of Aib, Iva, and Hyp.

Figure 2. HPLC profiles for artificial mixtures of the natural integramide A (A), and the two synthetic diastereomers L-Iva14-D-Iva15 (L-D) and D-Iva14-L-Iva15 (D-L): mixture of L-D and A (I); mixture of L-D, D-L, and A (II); mixture of D-L and A (III).
Our results clearly indicate that the chirality sequence of the Iva14-Iva15 dipeptide of the natural product is L-D. The stereochemical inversion in the two integramide A diastereomers, evaluated as inhibitors of HIV-1 integrase in the coupled reaction of proviral DNA into the host cell DNA, is in general not detrimental, but it is even slightly beneficial against the strand transfer reaction.

References