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Asymmetric Synthesis of Two-Residue Modules Designed for Mimicry of Beta Strands

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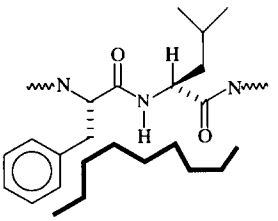
Abstract : A novel design and asymmetric synthesis of two-residue mimics is presented as part of a modular approach to beta strand mimicry.

Our interest in the mimicry of beta strands stems from structural work with CD4, the cellular receptor protein for HIV-1.[1-3] Residues Phe43 and Lys46 are two of the key residues implicated by site-directed mutagenesis[4] in the binding of CD4 to the viral protein gp120. Both residues are part of the C" beta strand as established by x-ray crystal structures of soluble CD4.[5,6] This beta strand lies on the most exposed region of the C'C" ridge of CD4 which protrudes from the rest of the first domain. One can envision that gp120 approaches edge on, i.e. facing the outer edge of this ridge, and interacts with exposed elements of the beta strand. Thus, Phe43, the most important contributor to binding, Lys46 and, by inference, the backbone atoms that connect these residues are implicated in the recognition process. The 43-46 segment Phe-Leu-Thr-Lys is, therefore, an attractive target for CD4 mimicry.

The beta strand is a structural motif for which few small molecule mimics have been reported. In the elegant beta strand mimic recently reported by Smith et al.,[7] backbone constraints in a pyrrolidone framework result in presentation of sidechains on alternating sides of the structure. Our strategy for building a non-peptide mimic was to construct two-residue modules,[8] constrained at a single side of the backbone structure, which could be combined to form four-residue targets. In this communication we report our preliminary work toward the development of a general methodology for the construction of suitable modules that are extendable from carboxyl or amine functionalities.

The initial target segment was Phe43-Leu44, with design focused on its backbone structure and exposed Phe sidechain. The isobutyl sidechain of Leu was considered unimportant since it is not exposed in the CD4 crystal structures and its mutation to methyl (Leu44-->Ala) has no significant effect on binding[4] and therefore was not incorporated into our framework. We chose to replace the natural amide linkage by an electronically similar vinylamide functionality to allow for conformational restriction.[9] Computational assessment of mimicry of Phe43-Leu44 by these vinylamides was based on five criteria: (i) overlay of the Phe α–β bond; (ii) overlay of

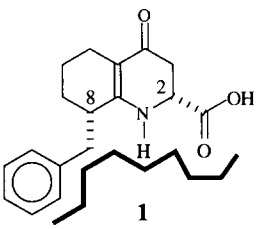
the Phe carbonyl with the carbon-carbon double bond of the vinylamide; (iii) overlay of the Leu Nα-H bond; (iv) overlay of the Leu carbonyl; and (v) degree of encroachment on space not occupied in the protein. These



Segment Phe43-Leu44 of CD4 : The exposed region indicated by the bold line is the targeted surface for mimicry.

criteria account for exposed hydrogen-bonding sites including the acid-base character of these sites, and the overal backbone shape. They also ensure that constraints be made exclusively from an unexposed, and presumably non-interacting, region of this beta strand.

Vinylamide **1** met these structural criteria. Moreover it appeared accessible from readily available cyclic ketones and aspartic acid derivatives. A general synthetic strategy utilizing these starting materials could allow for the synthesis of a large variety of two-residue modules.



1

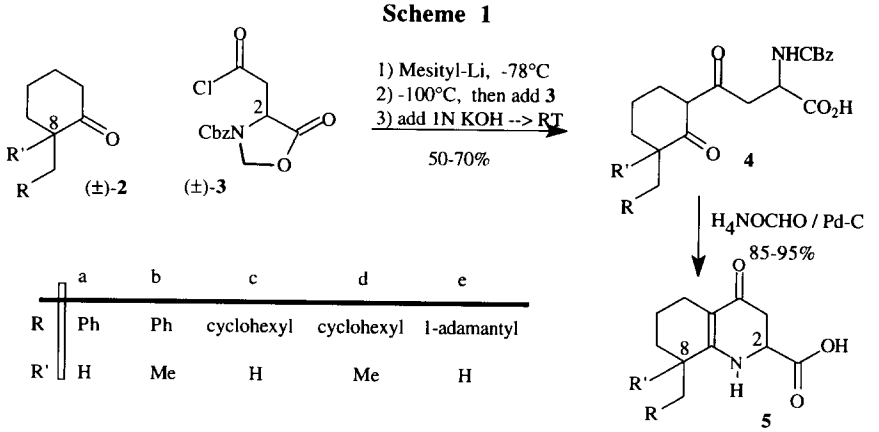
A cyclic vinylamide module designed to mimic segment Phe43-Leu44 of CD4 with constraints made from a single side. The bold line indicates region of mimicry.

The required 1-azo-4-oxo-9,10-dehydro-[4.4.0]-decane nucleus of **1** had been previously constructed by the condensation of cyclic secondary β-aminoesters with six- and five-membered ring ketones.[10-12] Although we originally planned to apply this literature procedure to our particular target molecules, we discovered that the aminoester component is largely restricted to cyclic, secondary β–aminoesters while our starting materials would have to be acyclic, primary aminoesters.

An alternative tactic, in which the carbon-carbon bond is created first, proved successful. Selective C-acylation of the lithium enolate of ketone (±)**2a** with aspartic acid derivative (±)-**3**[13] was the key step (Scheme 1). This conversion was accomplished in THF at -100°C[14] and afforded carboxylic acid **4a** after saponification with 1N KOH (aq).[15] The sterically more congested (±)-**2b-2e** were also subjected to this one-pot process, and **4b-4e** were obtained in good overall yield. Hydrogenolysis led directly to the desired two-residue modules **5a-5e** in 85-95% yield as 1:1 mixtures (by nmr) of the (±)-cis and (±)-trans isomers (at C2 relative to C8).

A single-enantiomer synthesis was also possible through this chemistry. The 1:1 cis/trans ratio of **5a-5c** suggested (but did not establish) that epimerization at C2 or C8 had not occurred at any point throughout the synthetic route. The synthesis of module **1** [cis-(2R,8S)-**5a**], in which epimerization could occur at either C2 or C8, served well to confirm our suspicion that epimerization is not a problem in this method. In the ^{1}HNMR spectrum of **5a**, the cis/trans mixture may be clearly observed; there are two N-H resonances (5.83 and 5.61

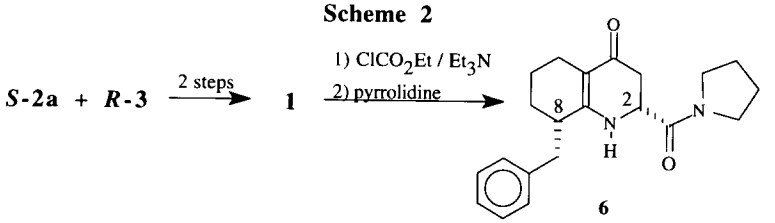
Scheme 1



ppm) and two C8-H resonances (3.34 and 3.25 ppm) which are base-line resolved. When readily prepared S-**2a**[16] and R-**3**[13] were taken through our established route (Scheme 2), only the resonances at 5.83 and 3.34 ppm were observed. The unambiguous conclusion is that the stereochemistry of the starting materials is maintained and the product is module **1**.

Module **1** is poised to be part of a four-residue (two-module) beta strand mimic as illustrated by the straightforward conversion of **1** to amide **6**. These results establish a synthetic methodology that allows for the rapid synthesis of a series of two-residue mimics (**5a-5e** represent 20 compounds). We have also established that the asymmetric syntheses of any of these diastereomers should be straightforward and our efforts therefore continue with respect to the synthesis of complementary modules with free amine functionality.

Scheme 2



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