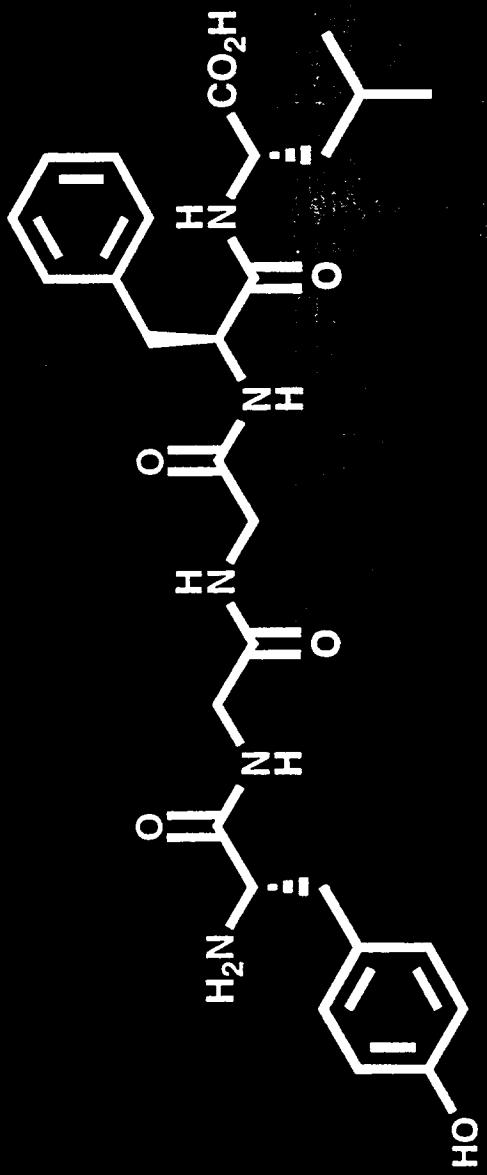
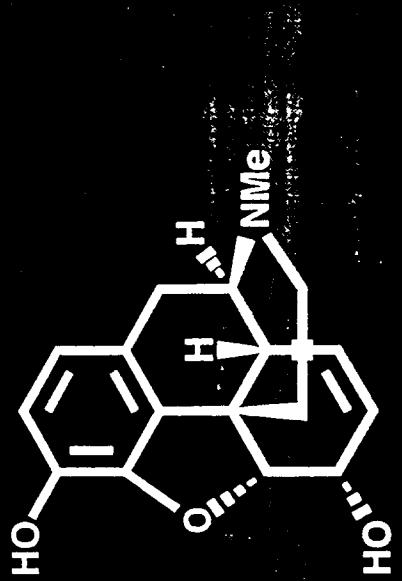


Linear Peptide → Nonpeptide



LEUCINE ENKEPHALIN



MORPHINE

Moleumetics

Peptides Advantages and Disadvantages

- ◆ Availability
 - solid phase synthesis and libraries
 - recombinant DNA and phage display
- ◆ Stability
 - proteolysis
- ◆ Specificity
 - multiple low energy conformations presenting multiple pharmacophoric ensembles

Molecules

Peptides Advantages and Disadvantages

- ◆ Pharmaceutical candidates

- Oral availability

- proteolytic degradation in the gut

- poor absorption from the intestinal track

- Low BBB penetration

- inability to pass lipophilic membrane

- Potential antigenicity

- recombinant proteins, mAbs

Molecules

Designing Nonpeptides From Peptides

The goal is to determine the receptor bound or bioactive conformation; as peptides are characteristically highly flexible molecules whose structure is strongly influenced by their environment, their random conformation in solution complicates their use for this purpose

Molecules

Designing Nonpeptides From Proteins

The goal is to reduce complex multidomain molecules to small functional conformationally restricted components, which are amenable to high resolution structural analysis and rapid modification

Molecules

Conformational Constraints

- ◆ *Deduce biologically active conformation*
- ◆ Improve potency
- ◆ Increase specificity
- ◆ Increase proteolytic stability

Molecules

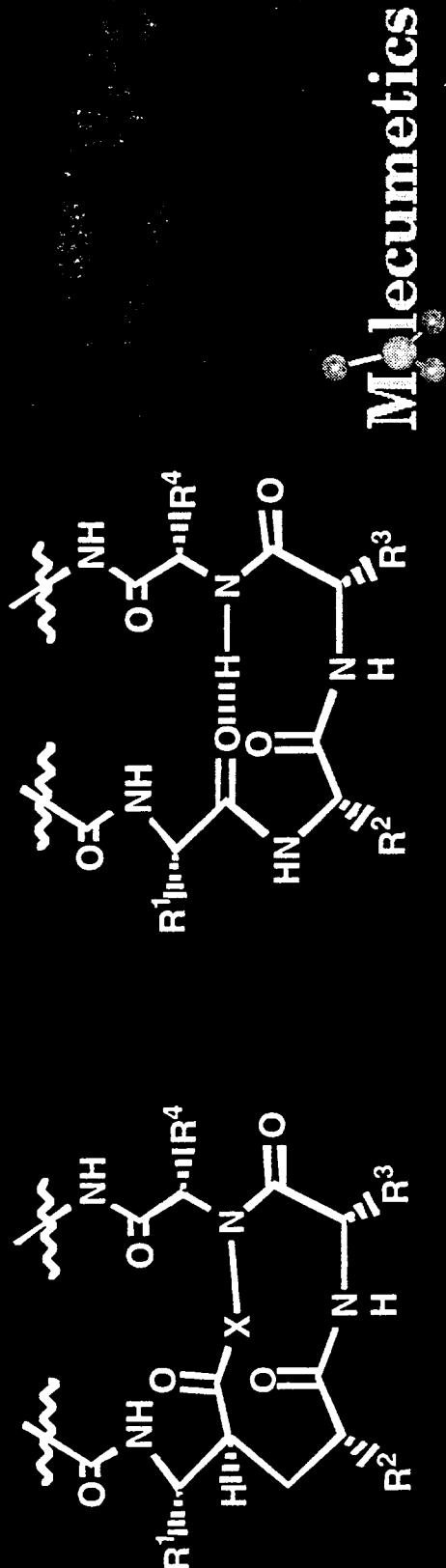
β -Turn and Molecular Recognition

- ◆ Ligand Receptors Interactions
- ◆ Antigen-Antibody Recognition
- ◆ Co- and Post-translational modification
(Proteolytic Processing, Glycosylation,
Phosphorylation)

Molecules

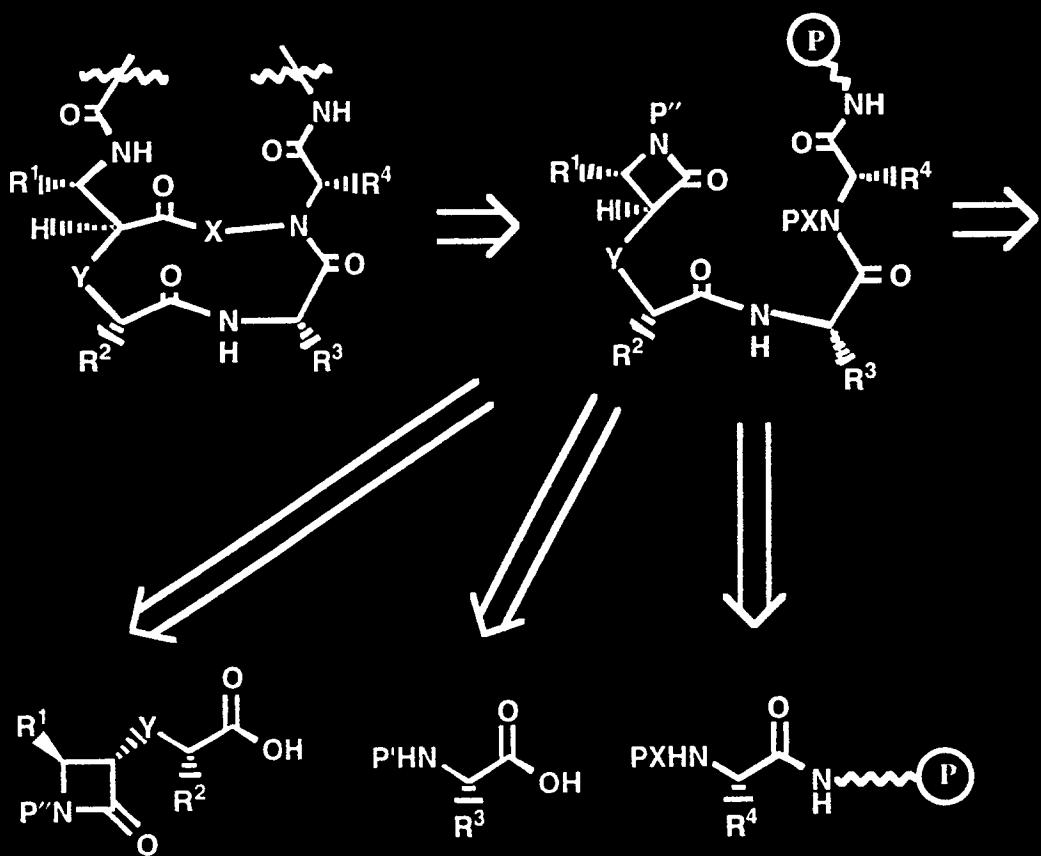
Essential Features of α β -turn Template

- Reproduce spatial orientation of amino acid residues
- Varying degrees of conformational flexibility
- Incorporation into solid phase peptide synthesis



Molecules

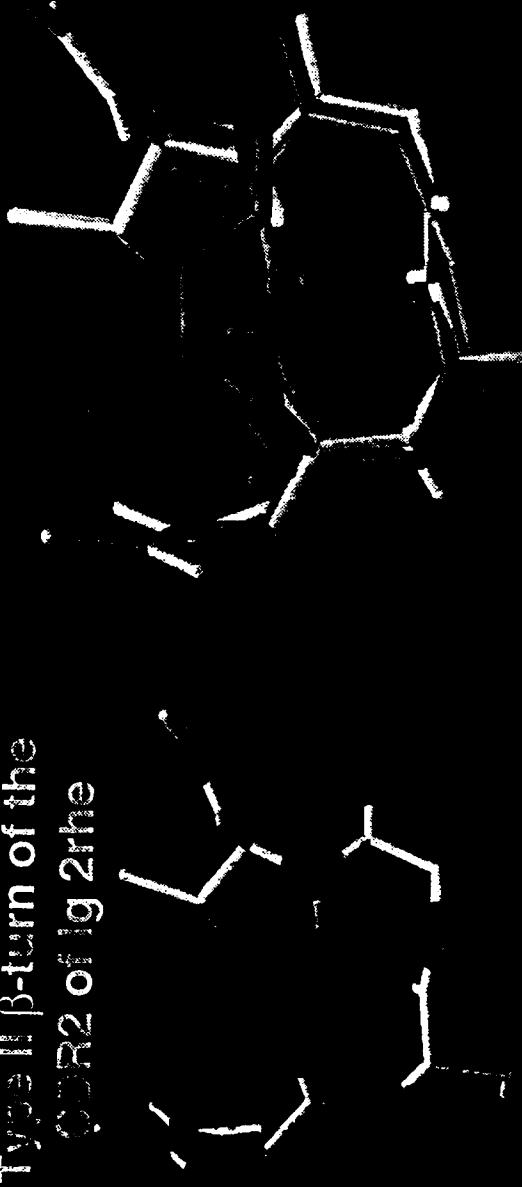
Retrosynthesis



Molecumetics

10-, 12- and 14-Membered β -Turn Complexes Overlayed on a CDR2

Type II β -turn of the
CDR2 of Ig 2rhe



12-membered

14-membered

10-membered

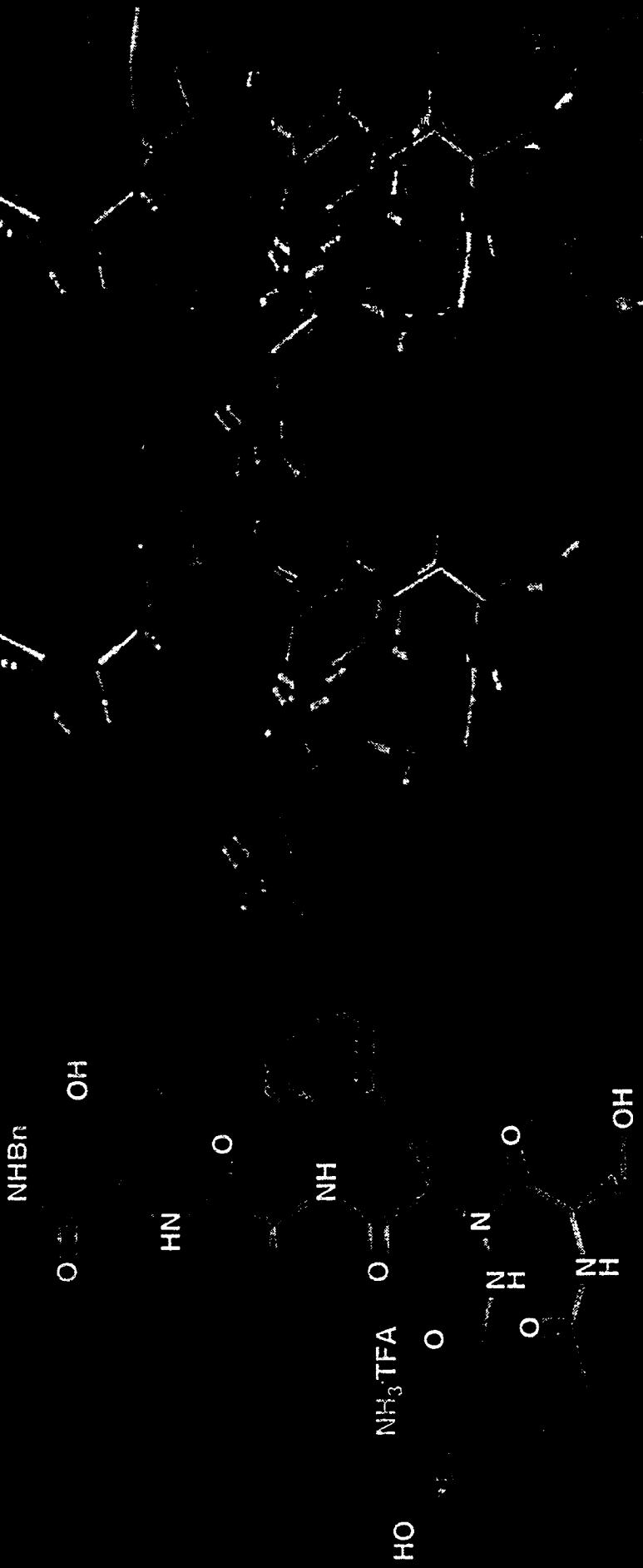
6 atom rms deviation

$$\begin{aligned}10\text{-mem} &= 0.97 \text{ \AA} \\12\text{-mem} &= 0.41 \text{ \AA} \\14\text{-mem} &= 0.48 \text{ \AA}\end{aligned}$$

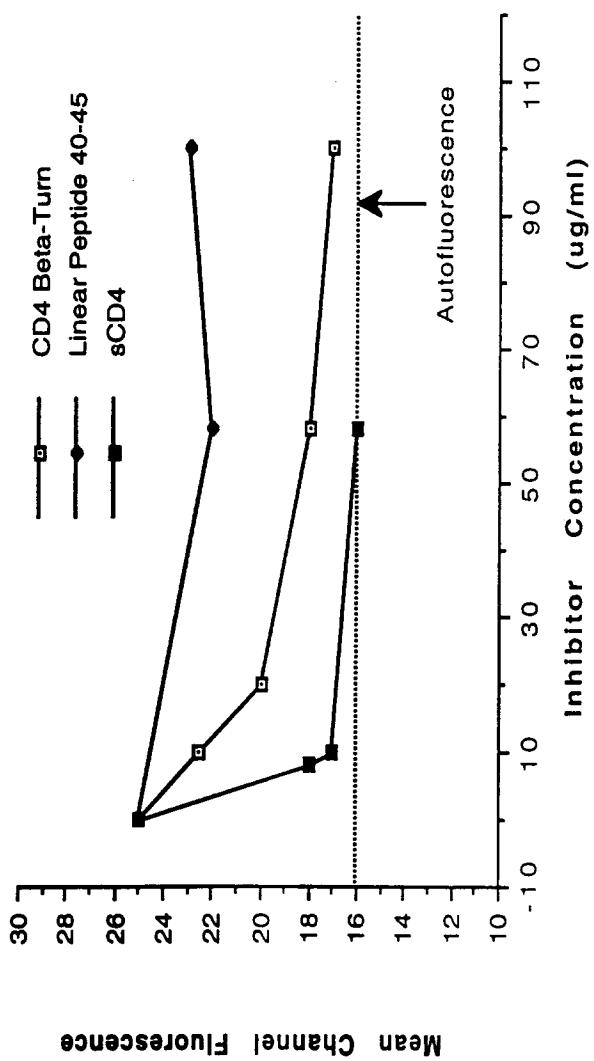
Molecumetics

Moleumetics

CD40-Ligand (green) of the 2nd
IgD-like Region (Gln⁴⁰-Thr⁴⁵) of CD4



Inhibitor of HIV gp120 Binding



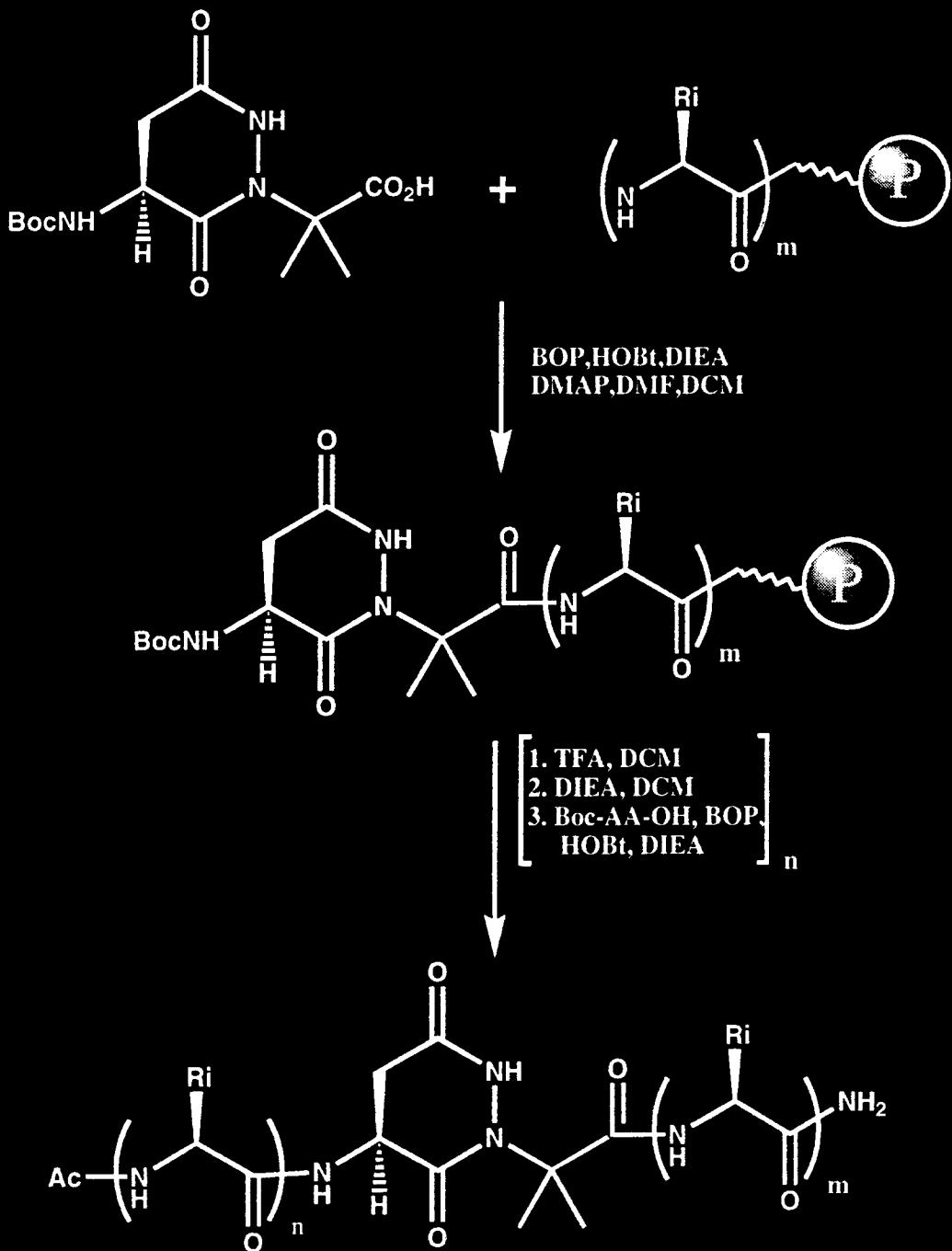
Molecules

Essential Features of an α -Helix Mimetic

- Nucleate and stabilize weakly α -helical peptides in H₂O
- Protect against proteolytic degradation
- Amino and carboxy termini
- Incorporation into solid phase peptide synthesis

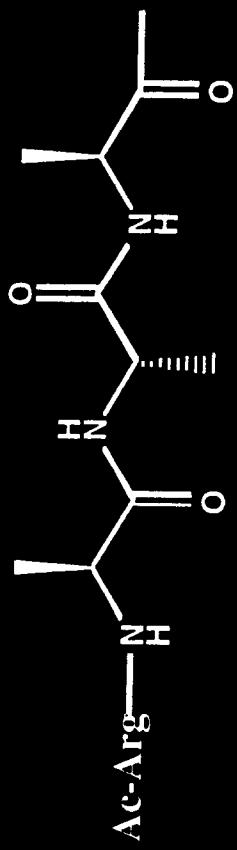


Solid Phase Synthesis α -Helix Incorporating Mimetics

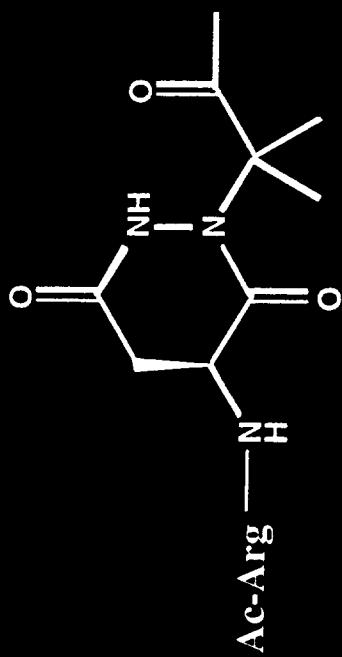


Molecumetics

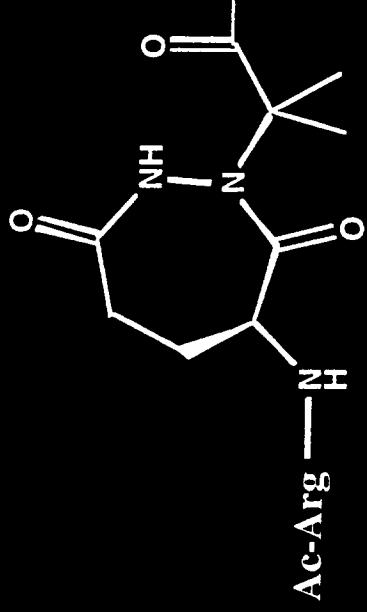
Moleculometrics



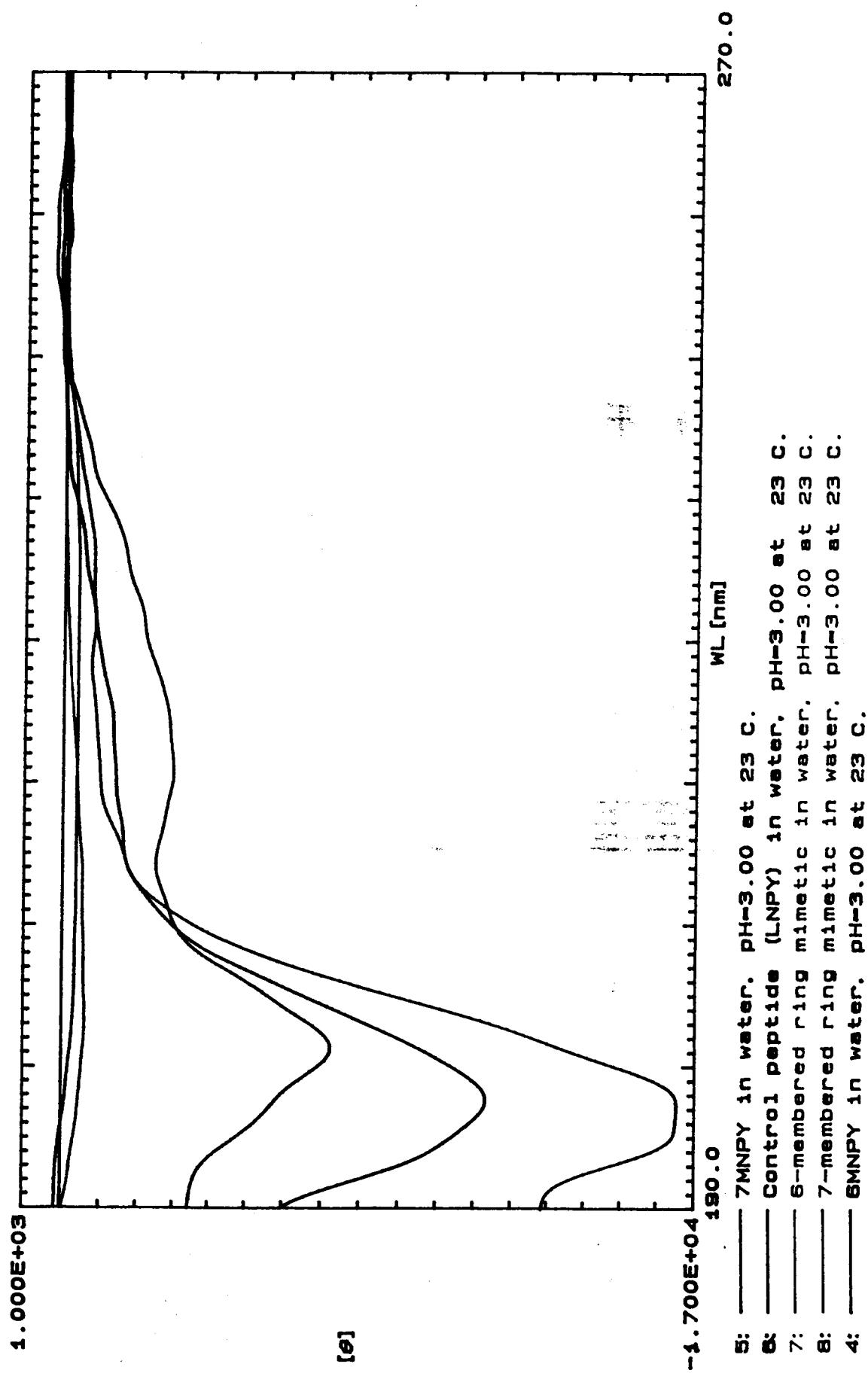
Asn-Leu-Ile-Thr-Arg-Gln-Arg-Tyr-NH₂



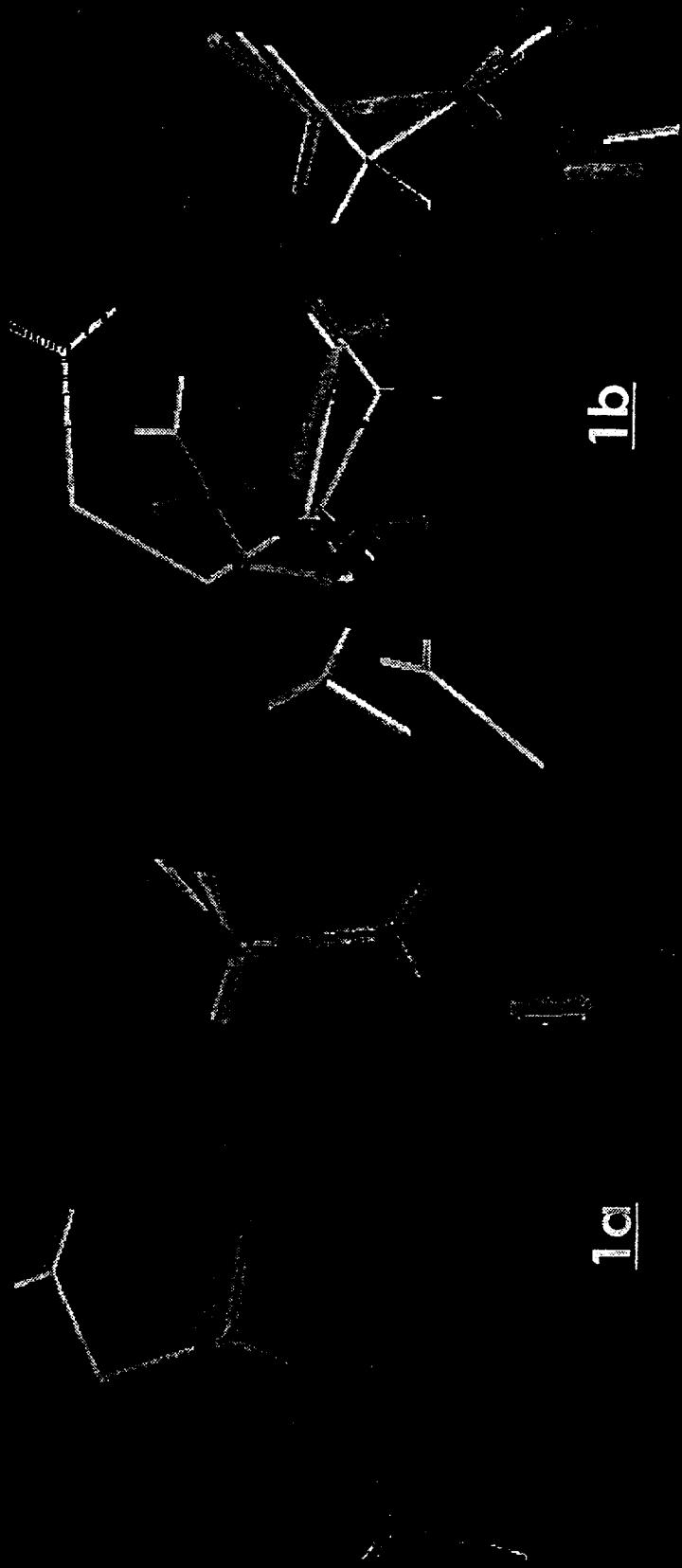
Asn-Ile-Thr-Arg-Gln-Arg-Tyr-NH₂



Asn-Leu-Ile-Thr-Arg-Gln-Arg-Tyr-NH₂

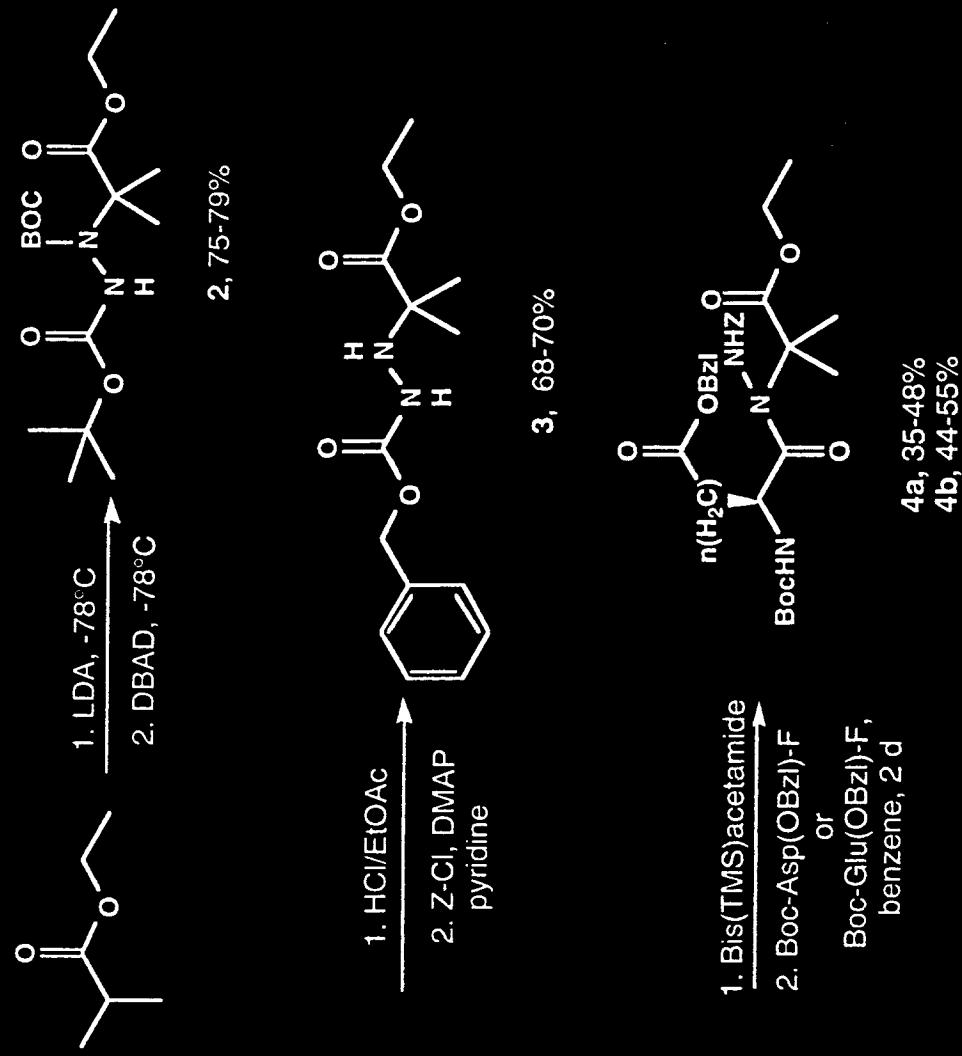


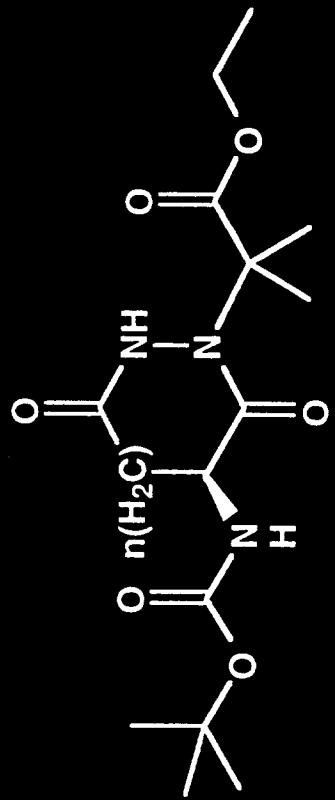
NMR Structures of 6M and 7M α -Helix Templates in Chloroform



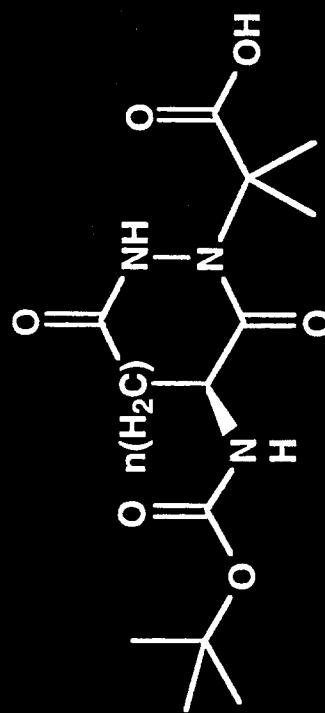
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Scheme 1





5a, 73-78%
5b, 67-69%



6a, 66-72%
6b, 74-76%

1. H_2 , Pd-C
2. EDC, HOBT
 $\text{THF}/\text{H}_2\text{O}, 3:1$

PLE, 25 % DMSO
pH 7.0 phosphate

Hydrogen Bond Occurrence during 500 ps Molecular Dynamics Simulation

Hydrogen bond	(Ala) ₈	<u>1a</u> (6m)	<u>1b</u> (7m)
HB1(A4 → Ac)	49%	81%	1%
HB2(A5 → A1)	59%	21%	0%
HB3(A6 → A2)	42%	84%	1%
HB4(A7 → A3)	47%	85%	95%
HB5(A8 → A4)	51%	97%	99%
HB6(NHMe → A5)	26%	88%	13%

Moleumetics

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MIN LEE	Ph.D.	NMR
JAN URBAN	Ph.D.	SYNTHESIS
MAHER QABAR	Ph.D.	
BEN GARDNER	Ph.D.	
JOE HEARA	Ph.D.	ANALYTICAL
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