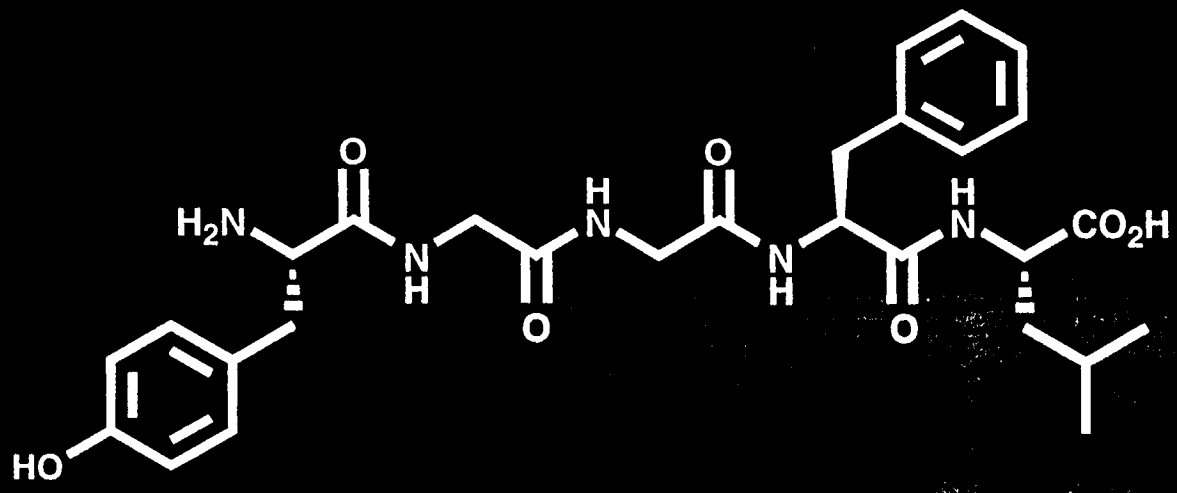
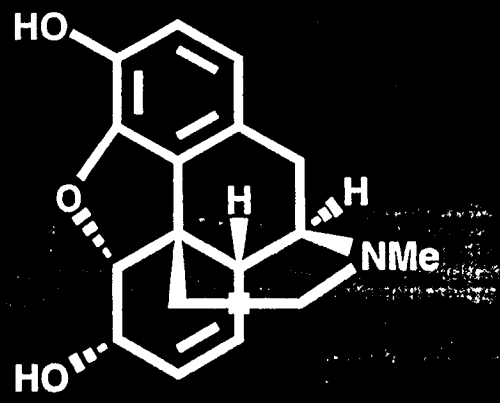
Linear Peptide → Nonpeptide



LEUCINE ENKEPHALIN



MORPHINE

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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

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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 lipophillic membrane

  - **Potential antigenicity**

    recombinant proteins, mAbs

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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

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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

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Conformational Constraints

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

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β–Turn and Molecular Recognition

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

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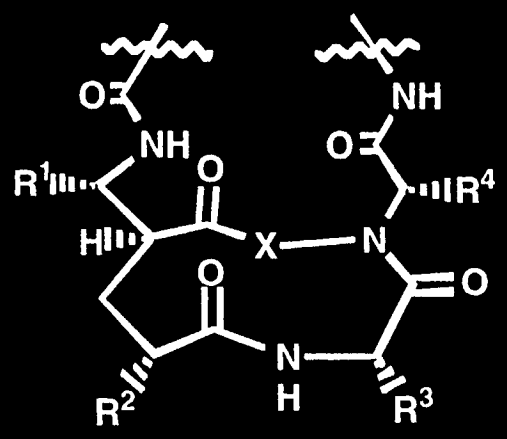
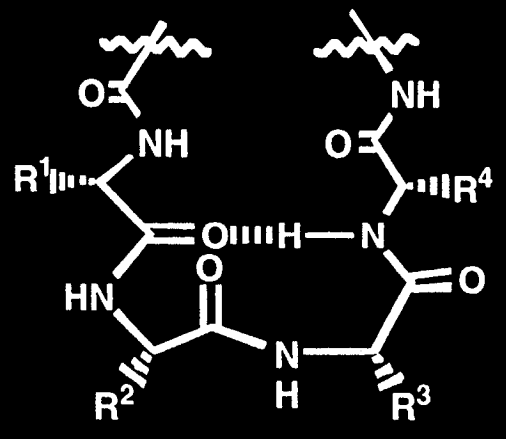
Essential Features of a β-turn Template

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





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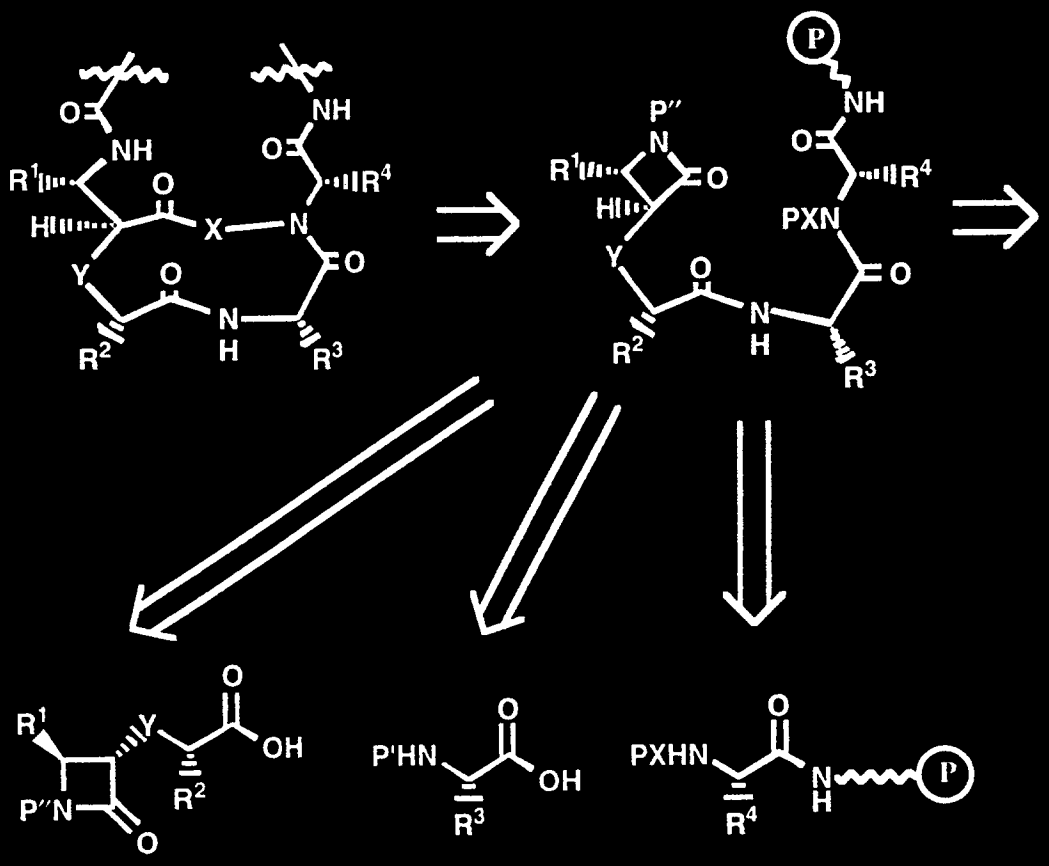
Retrosynthesis



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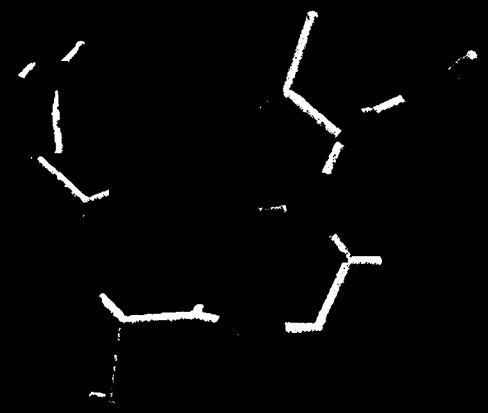
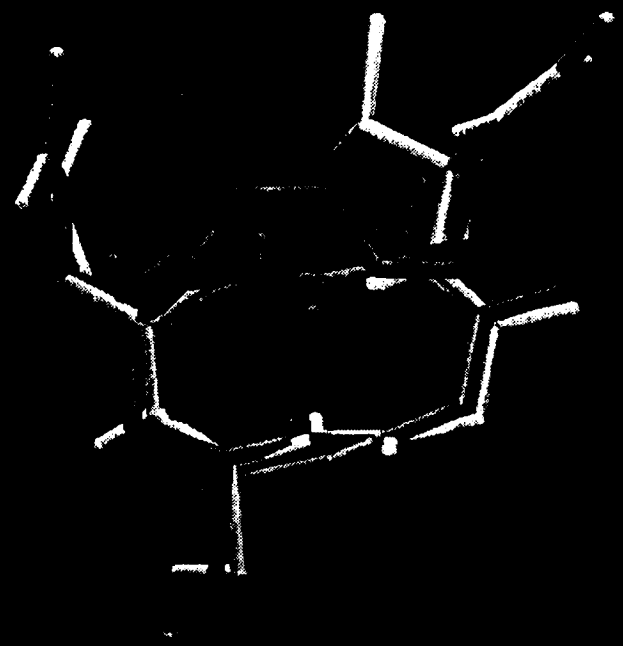
10-, 12- and 14-Membered β-Turn Templates Overlayed on a CDR2

Type II β-turn of the CDR2 of Ig 2rhe



10-membered



6 atom rms deviation
10-mem = 0.97 Å
12-mem = 0.41 Å
14-mem = 0.48 Å

12-membered

14-membered

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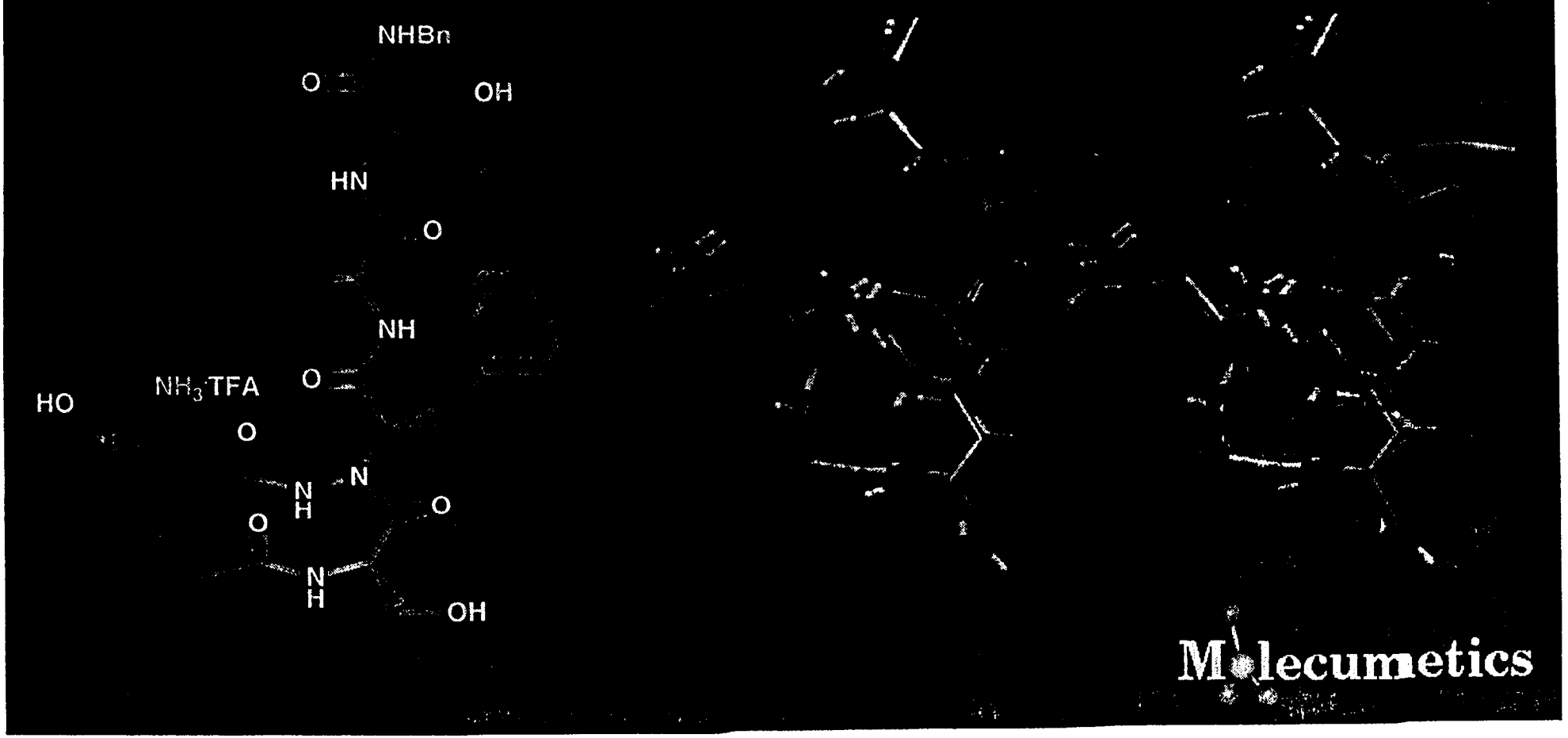
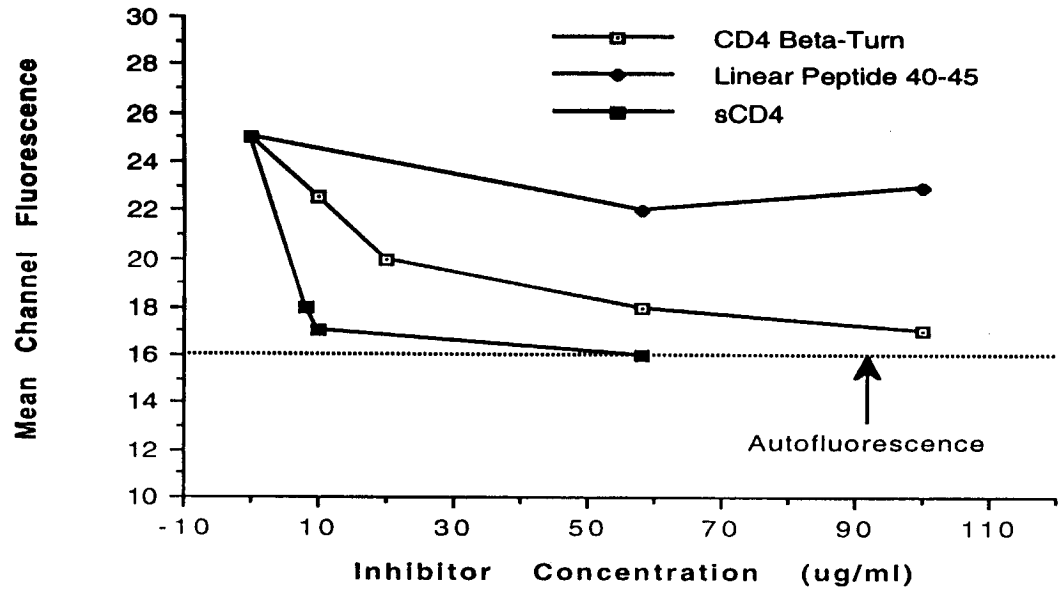
β-turn template (green) of the 2nd CD-like region (Gln^{40}–Thr^{45}) of CD4



Inhibitor of HIV gp120 Binding



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Essential Features of an α-Helix Mimetic

- Nucleate and stabilize weakly α-helical peptides in H_2O
- Protect against proteolytic degradation
- Amino and carboxy termini
- Incorporation into solid phase peptide synthesis

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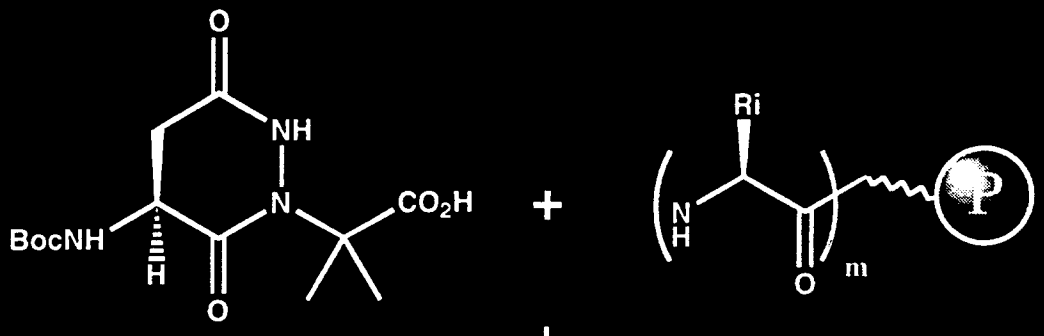
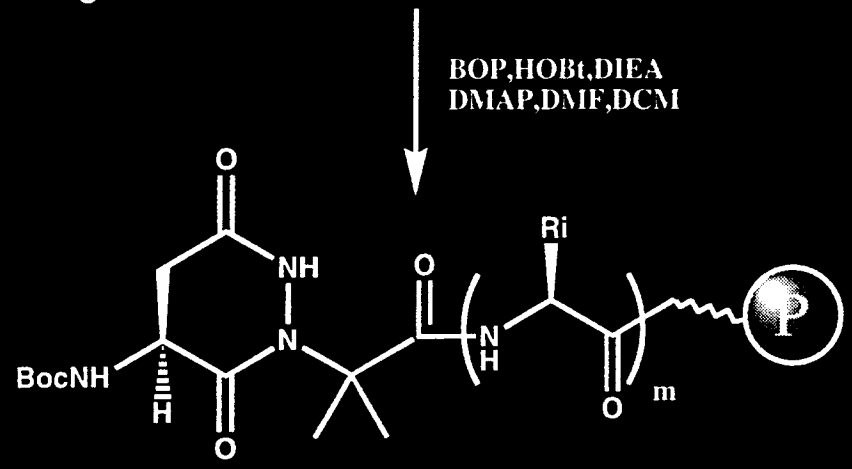
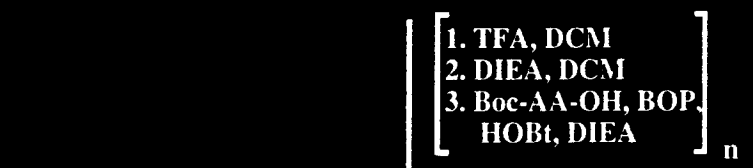
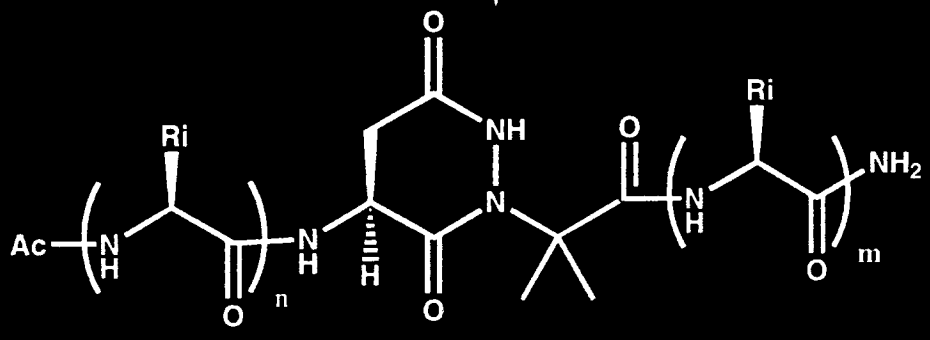
Solid Phase Synthesis
α-Helix Incorporating Mimetics









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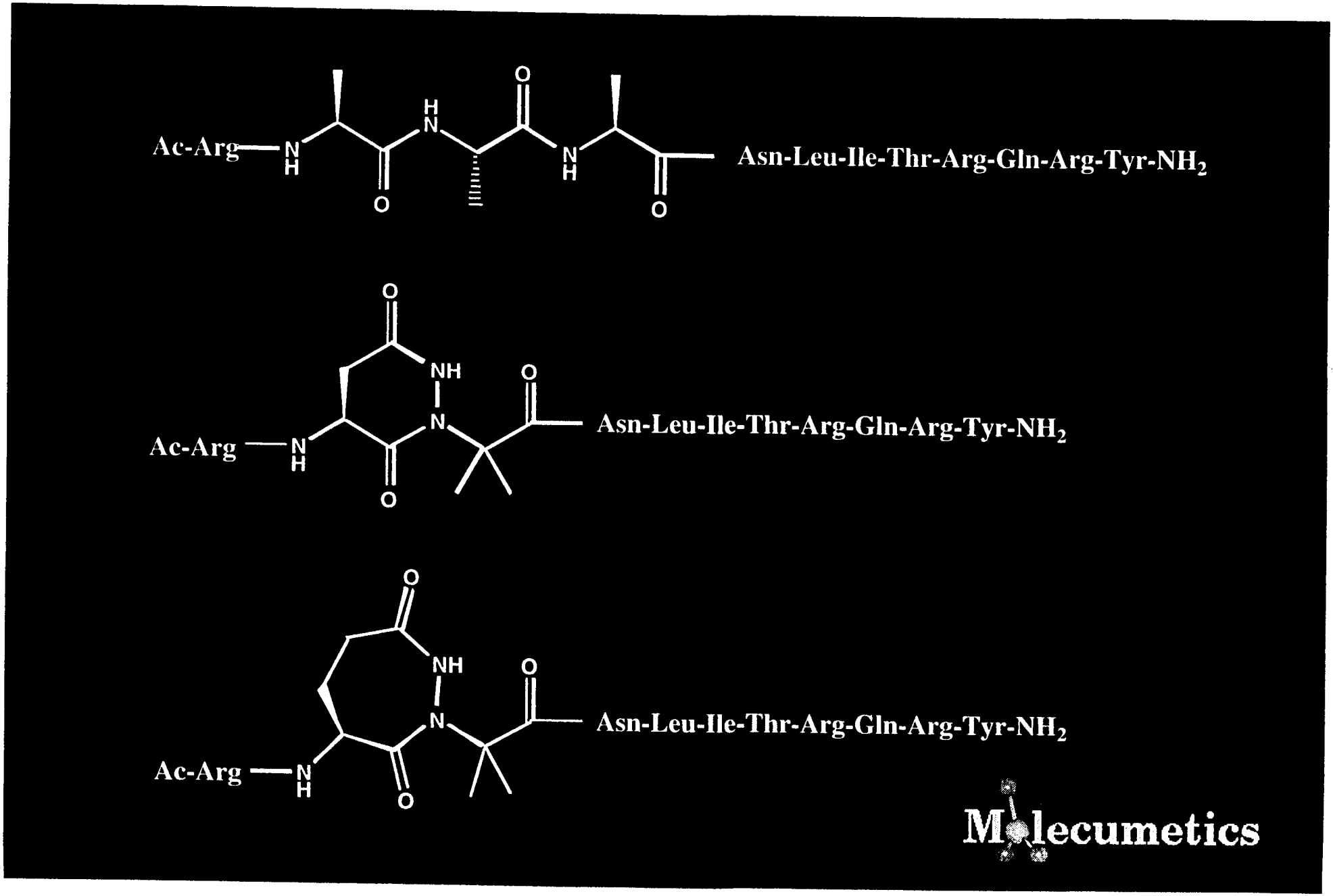
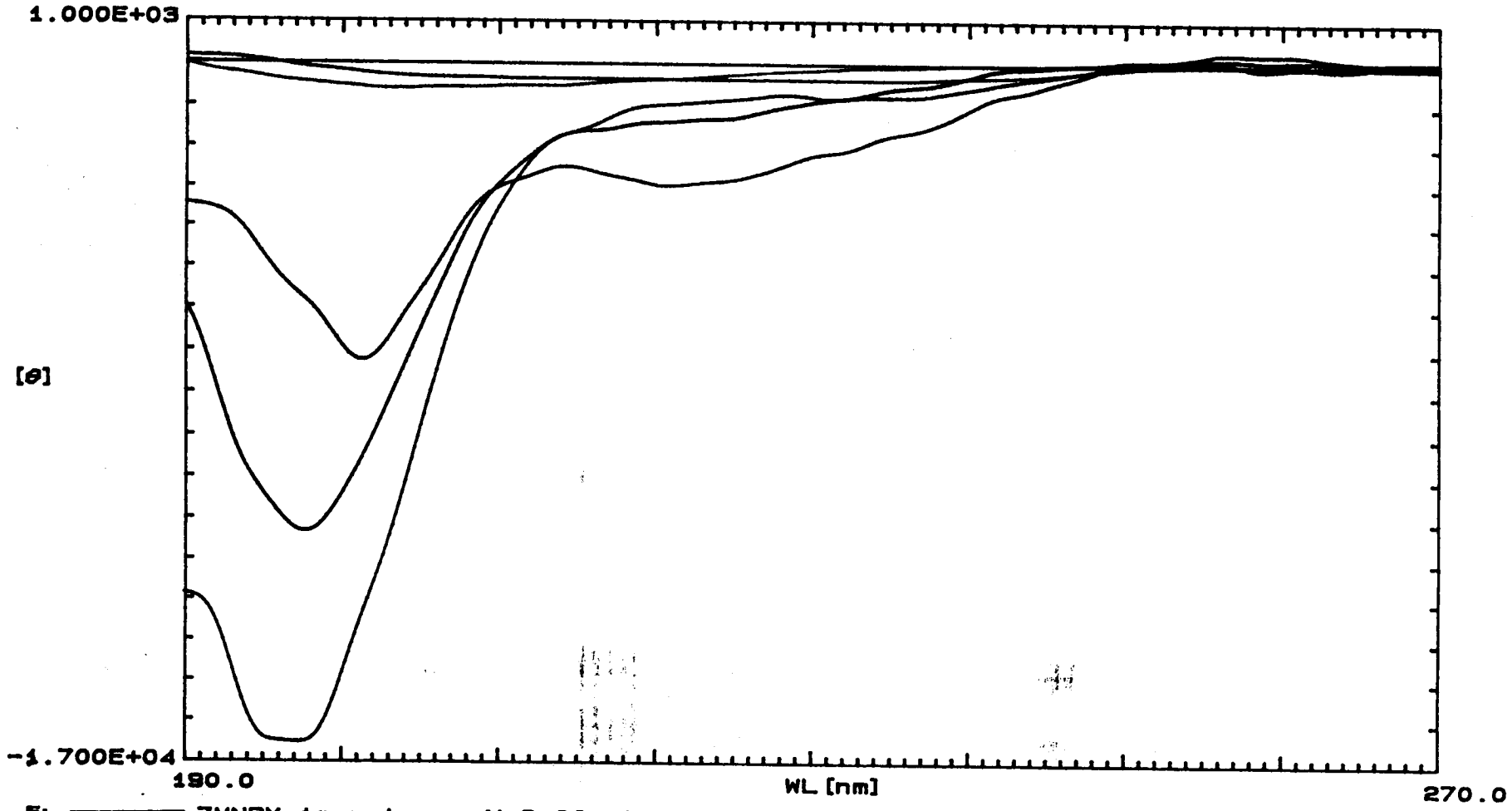
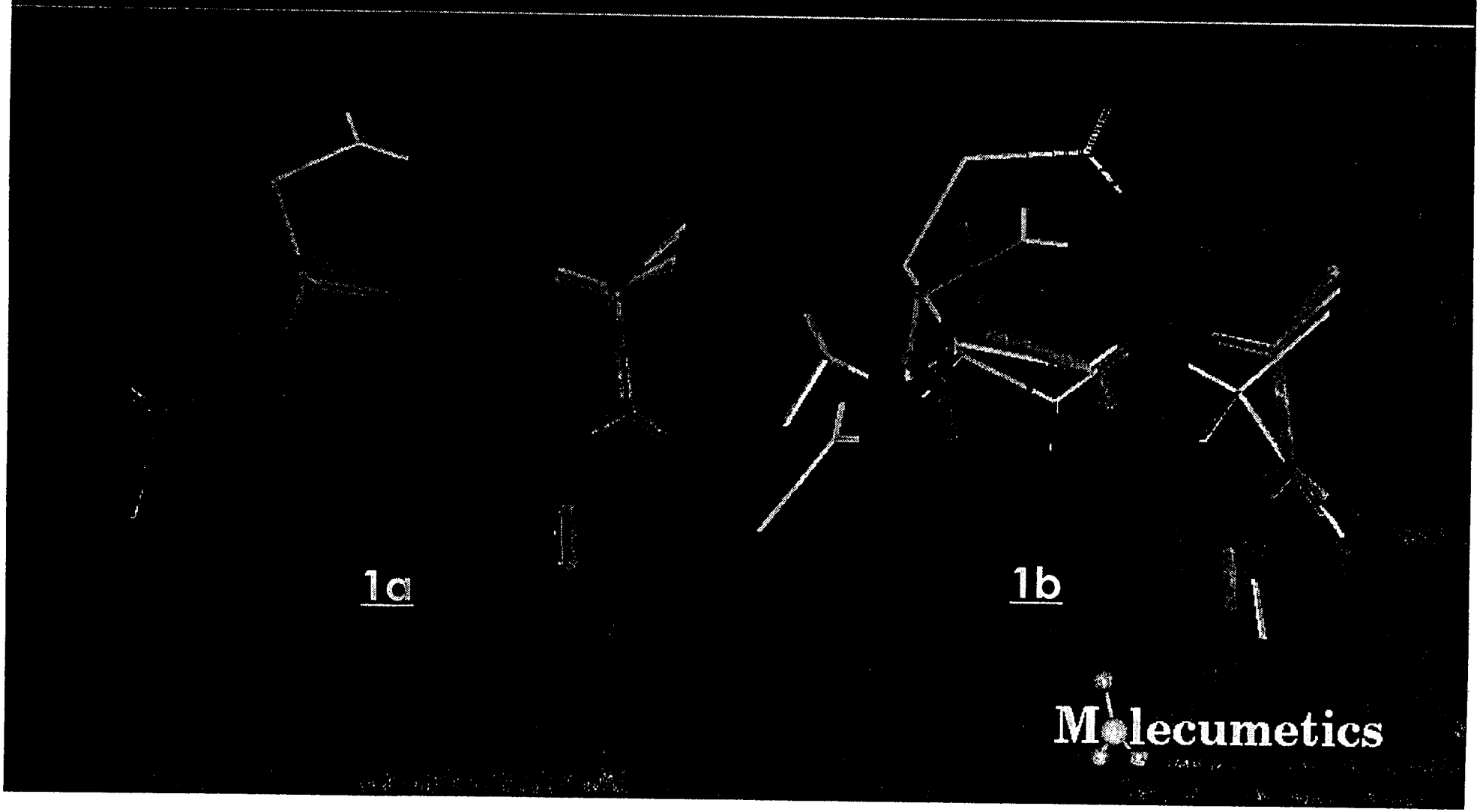

Ac-Arg
Asn-Leu-Ile-Thr-Arg-Gln-Arg-Tyr-NH2
Ac-Arg
Asn-Leu-Ile-Thr-Arg-Gln-Arg-Tyr-NH2
Ac-Arg
Asn-Leu-Ile-Thr-Arg-Gln-Arg-Tyr-NH2
Molecumetics

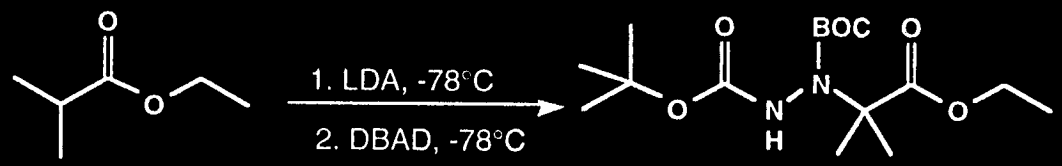


5: ——— 7MNPY in water, pH=3.00 at 23 C.
6: ——— Control peptide (LNPY) in water, pH=3.00 at 23 C.
7: ——— 6-membered ring mimetic in water, pH=3.00 at 23 C.
8: ——— 7-membered ring mimetic in water, pH=3.00 at 23 C.
4: ——— 6MNPY in water, pH=3.00 at 23 C.

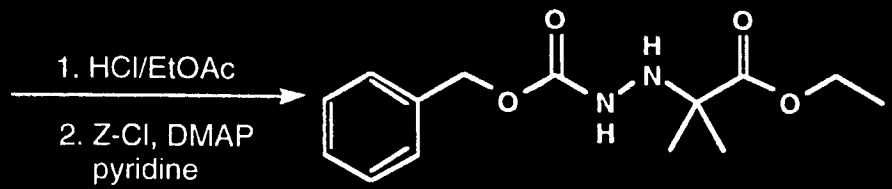
NMR Structures of 6M and 7M α-Helix Templates in Chloroform



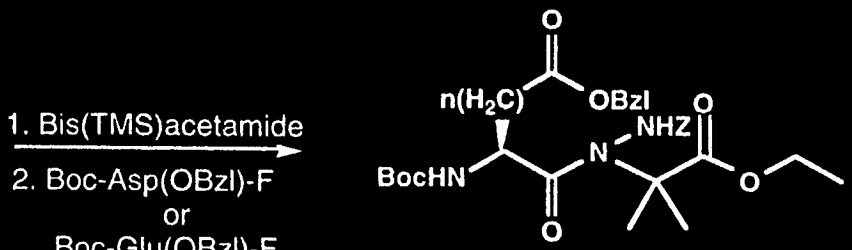
Scheme 1



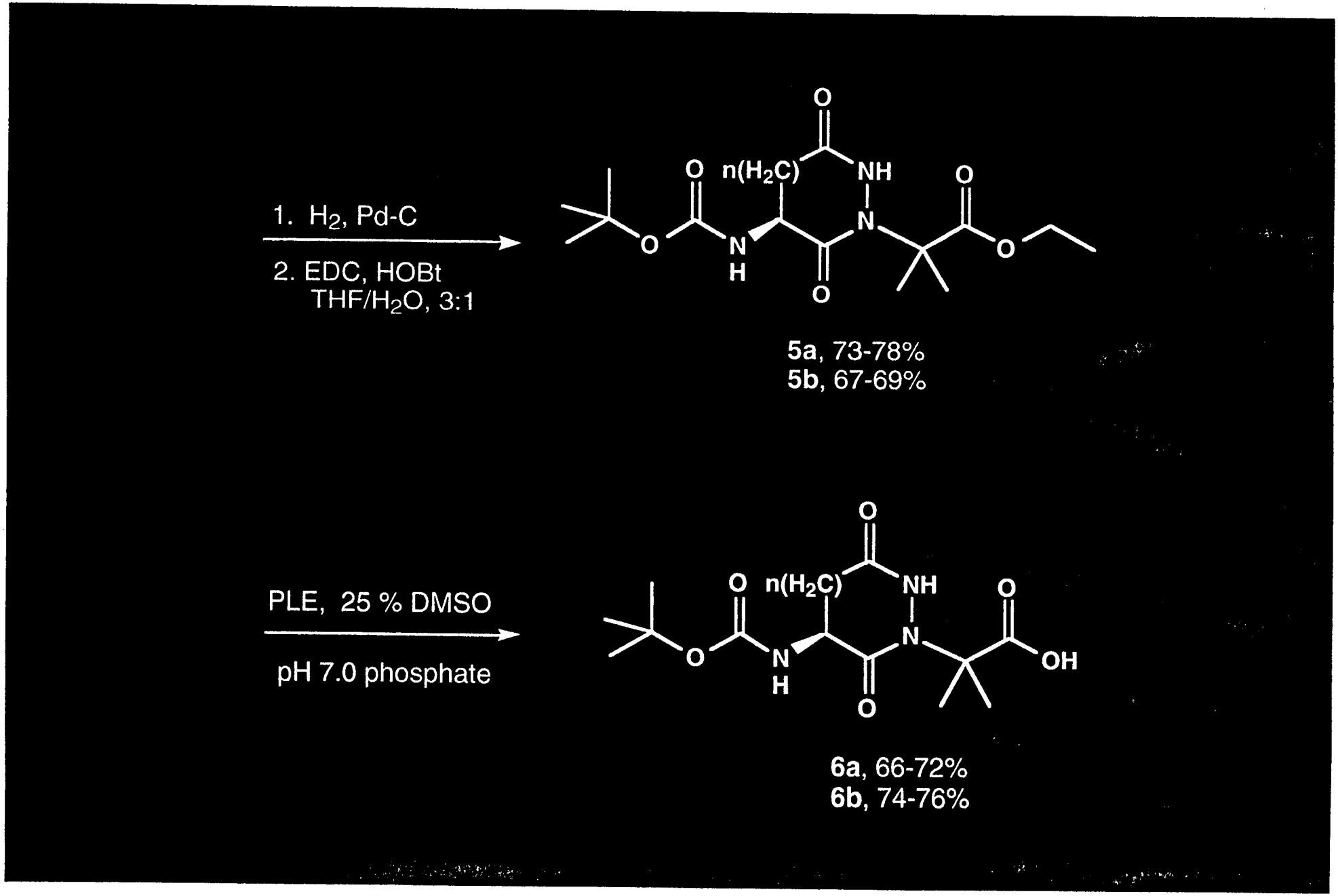
2, 75-79%



3, 68-70%



4a, 35-48%
4b, 44-55%


1. H_2, Pd-C
2. EDC, HOBt
THF/H_2O, 3:1
n(H_2C)
NH
N
H
O
5a, 73-78%
5b, 67-69%
PLE, 25 % DMSO
pH 7.0 phosphate
OH
6a, 66-72%
6b, 74-76%

Hydrogen Bond Occurrence during 500 ps Molecular Dynamics Simulation

Hydrogen bond	$(Ala)_8$	1a (6m)	1b (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%

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JOE	MEARA	Ph.D.	
RICHARD	SHEN		ANALYTICAL
ELIZA	YEUNG		SYNTHESIS