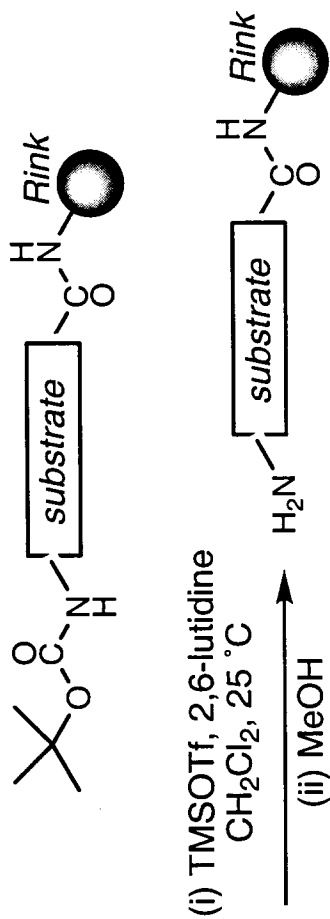
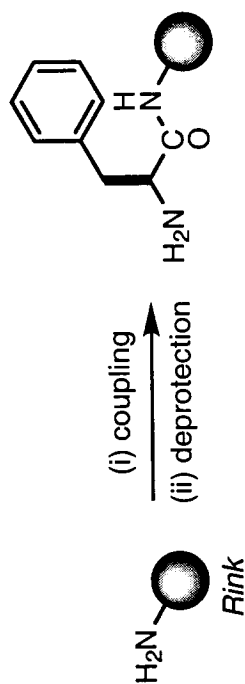


Goal: Removal of BOC Groups from Substrates on Acid Sensitive Resins



Relative Efficiencies of BOC/TMSOTf Removal vs FMOC Piperidine

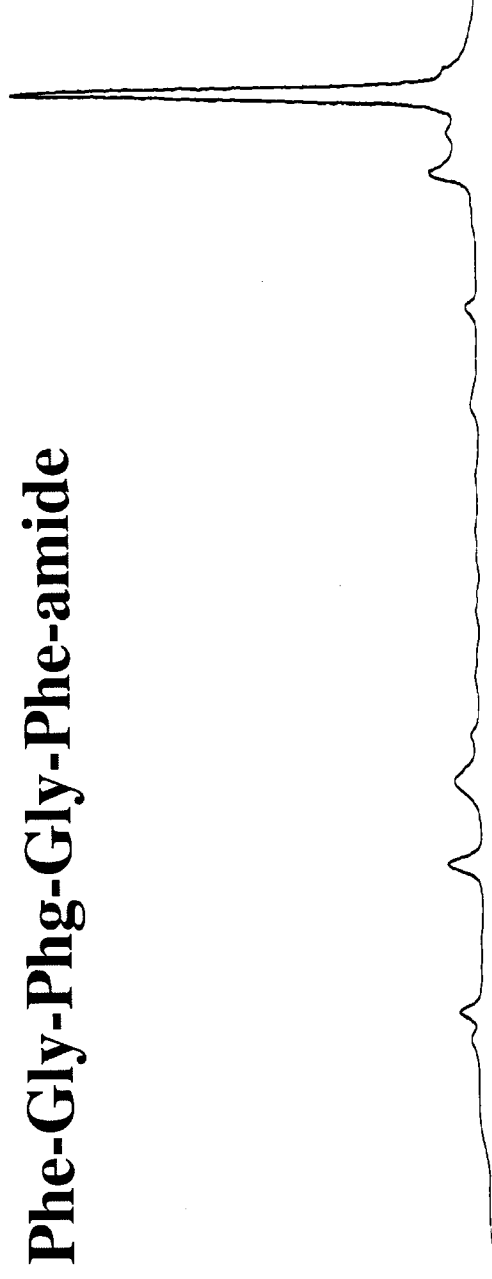


Conditions A: (i) BOC-Phe-OH, TFFH, NEt_3 , 25 °C, 1h;
(ii) 1M TMSOTf, 1.5 M lutidine, CH_2Cl_2 , 1h; (iii) MeOH wash
relative yield 0.93

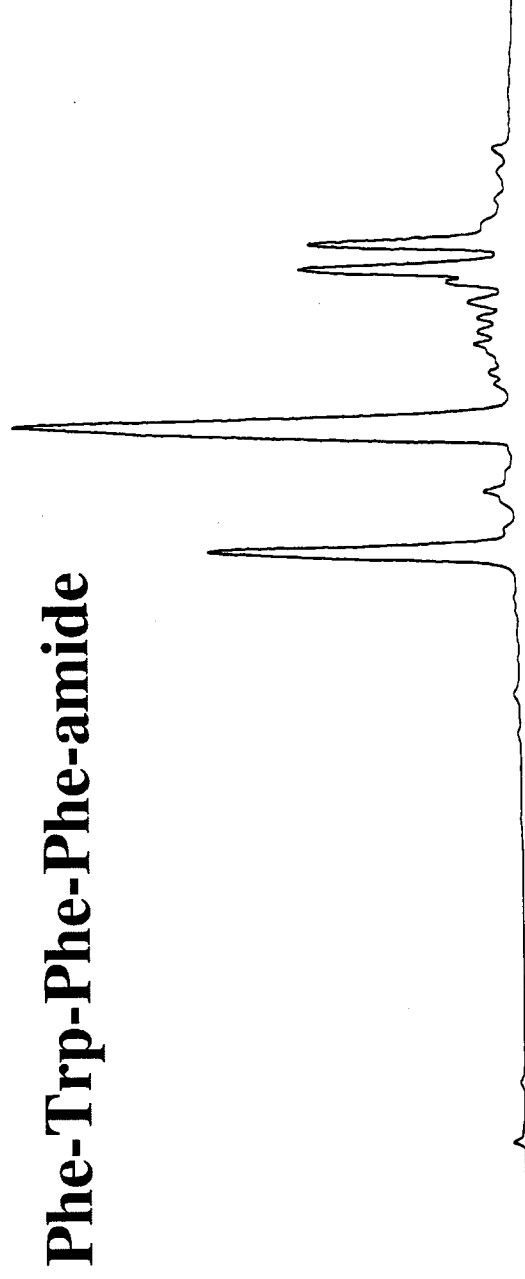
Conditions B: (i) FMOC-Phe-OH, TFFH, NEt_3 , 25 °C, 1h;
(ii) piperidine, CH_2Cl_2 , 1h
relative yield 1.00

Best and Worst Case HPLC Data

Phe-Gly-Phe-Gly-Phe-amide



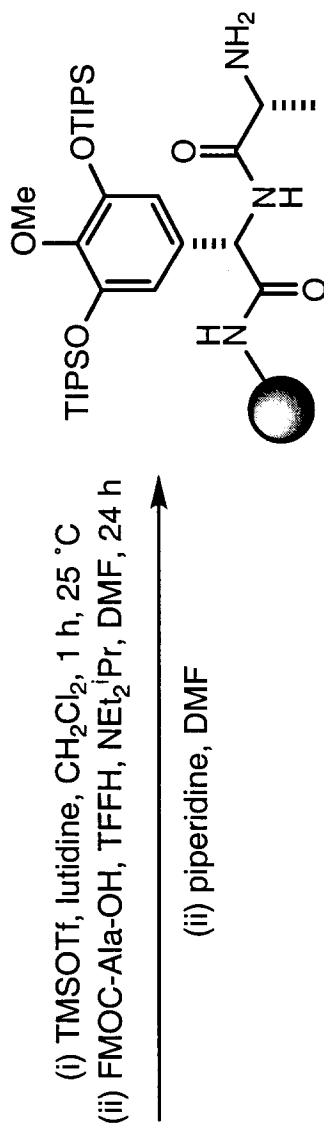
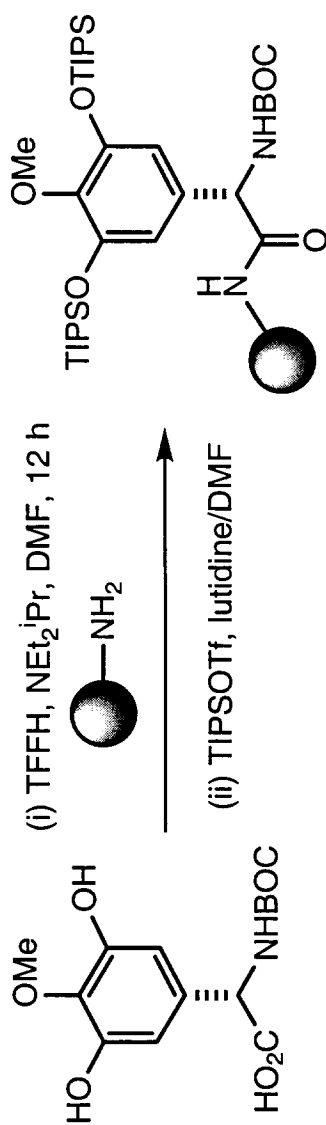
Phe-Trp-Phe-Phe-amide



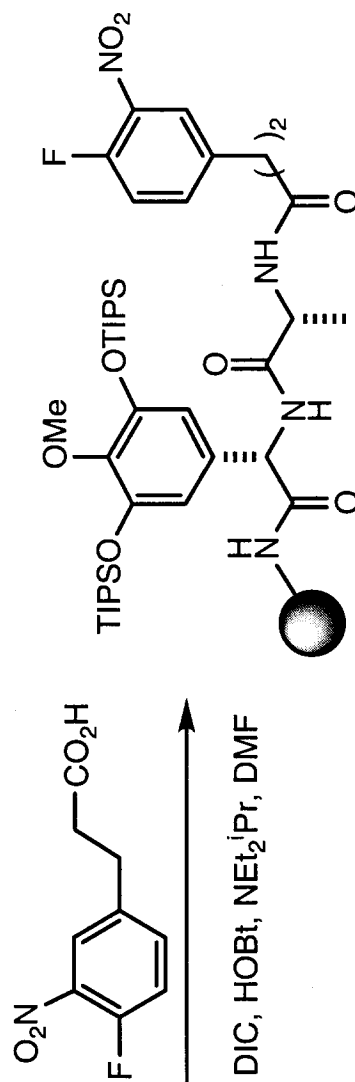
Purity Data for Peptides Prepared via Iterative BOC/TMSOTf Deprotection

sequence	purity (%)	side chain protection
Phe-Gly-Phe-Gly-Phe-amide	85	none
Phe-Phe-Phe-Phe-amide	97	none
Phe-Met-Arg-Phe-amide	93	Arg(Mtr)
Phe-Thr-Ser-Phe-amide	71	Ser(TIPS); Thr(TIPS)
Asp-Glu-Lys-Gln-amide	39	Asp(Fm); Glu(Fm); Lys(FMOC)
Phe-Lys-Phe-Phe	85	Lys(FMOC)
Ile-Asn-Asn-Ser-Val-amide	90	Ser(TIPS)
Tyr-Gly-Gly-Phe-Leu-amide	87	Tyr(TIPS)
Phe-His-Phe-Phe-amide	53	His(DNP)
Phe-Trp-Phe-Phe-amide	54	Trp(FOR)

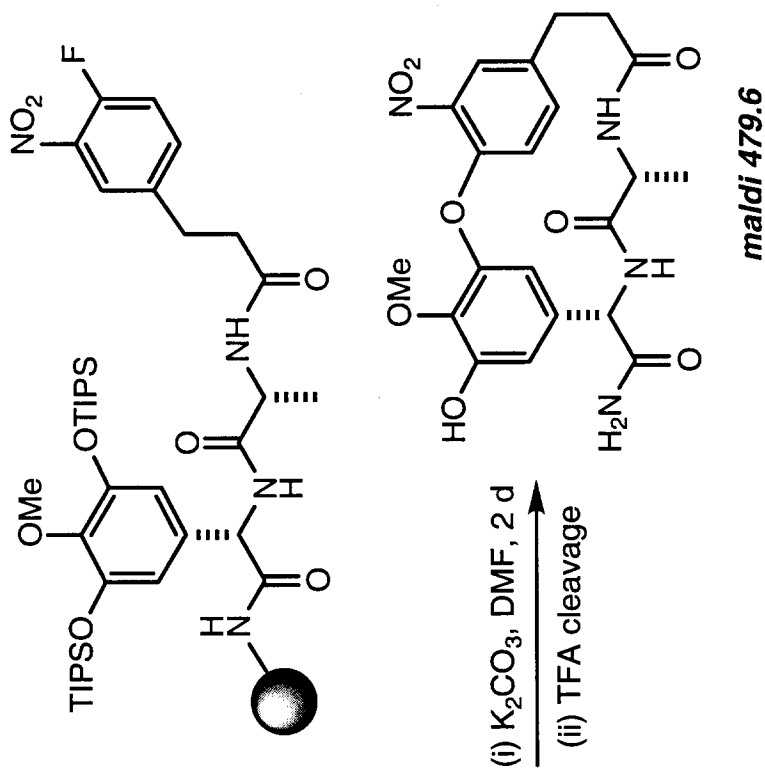
Preparation of the Vancomycin D-O-E Ring Precursor



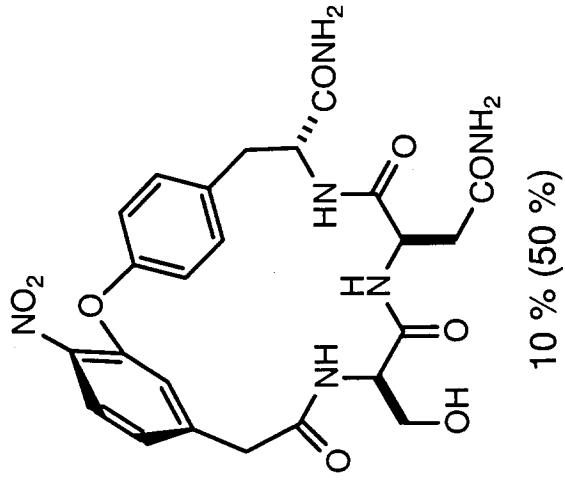
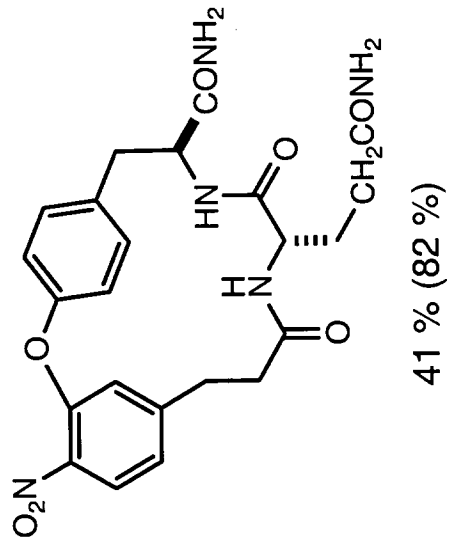
(ii) piperidine, DMF



Cyclization of the Vancomycin D-O-E Ring Precursor

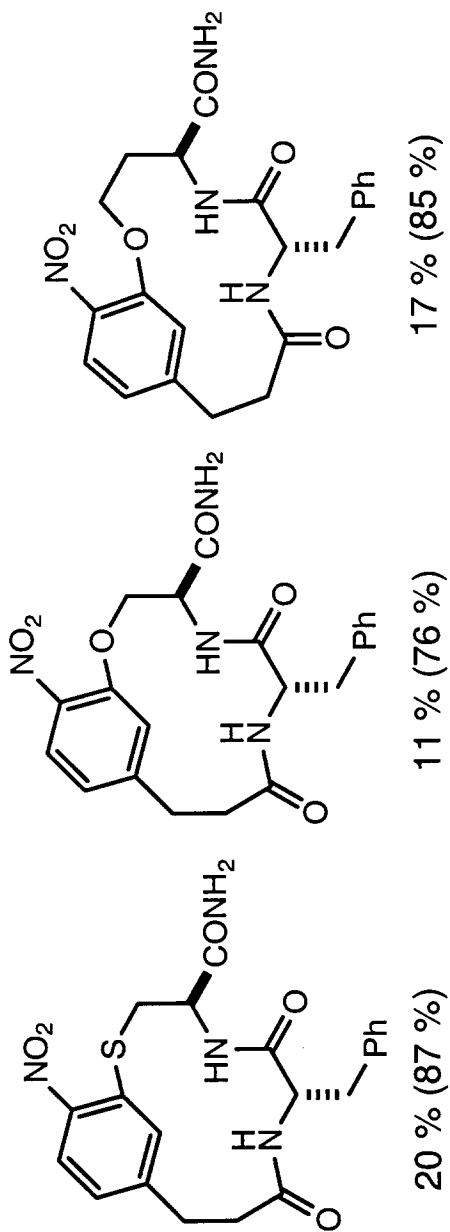


On-Resin Cyclization Product Featuring Tyrosine

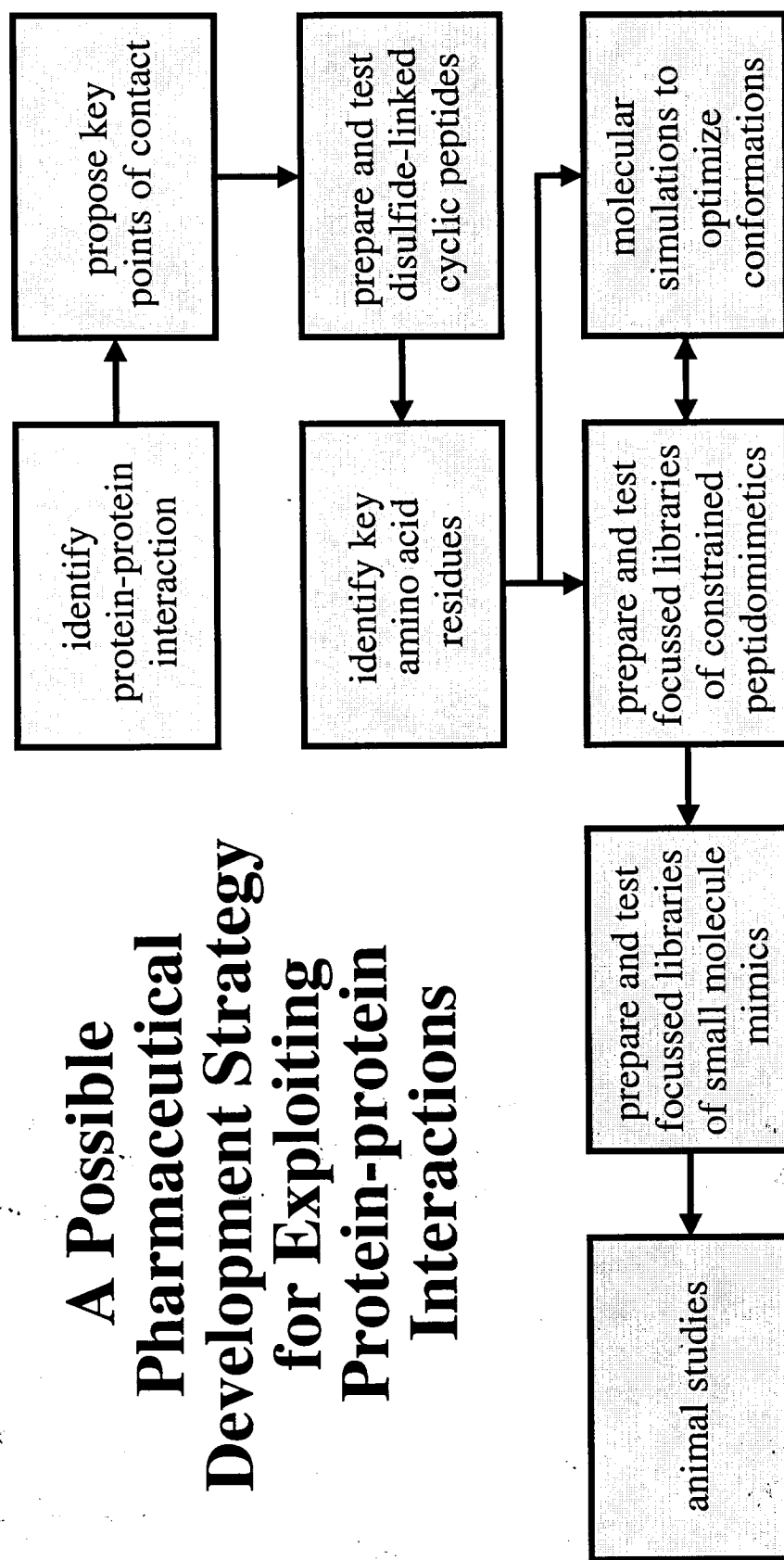


On-Resin Cyclization Product

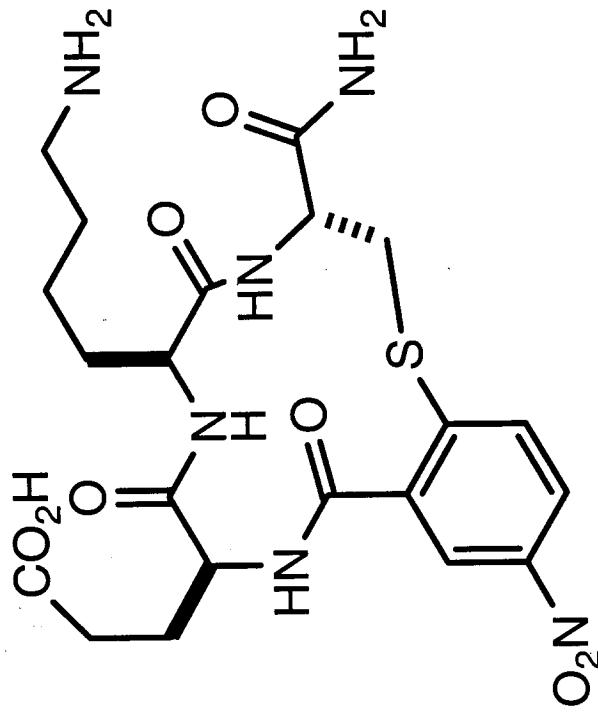
Featuring Cysteine, Serine, and Homoserine



A Possible Pharmaceutical Development Strategy for Exploiting Protein-protein Interactions



Choice of HPLC Detection Wavelength



detection method monomer:dimer

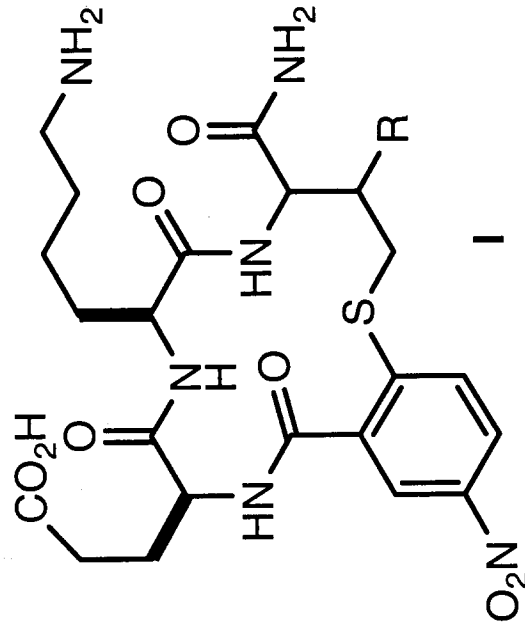
UV @280 nm	75	22
UV @254 nm	63	33
UV @215 nm	49	46
254/215 nm ave.	56	40
product ratios	56	39

macrocyclization conditions:

(i) 5.0 K₂CO₃, DMF, 25 °C, 35 h

(ii) TFA cleavage

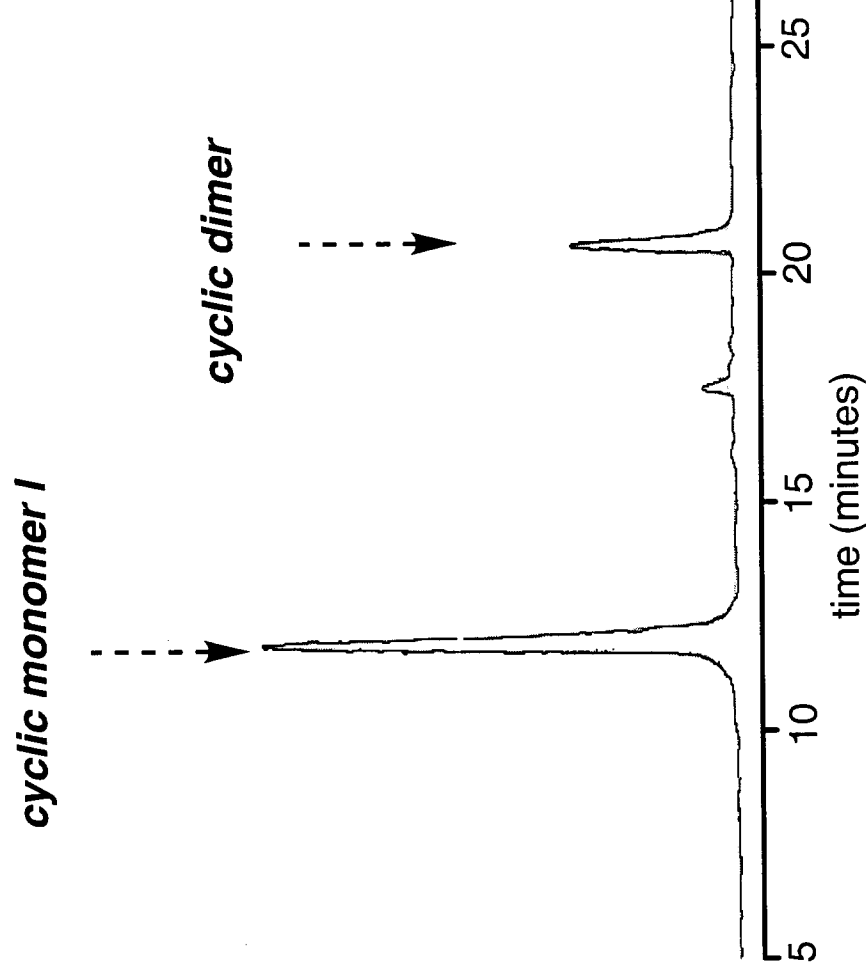
Unexpected Formation of Cyclic Dimers



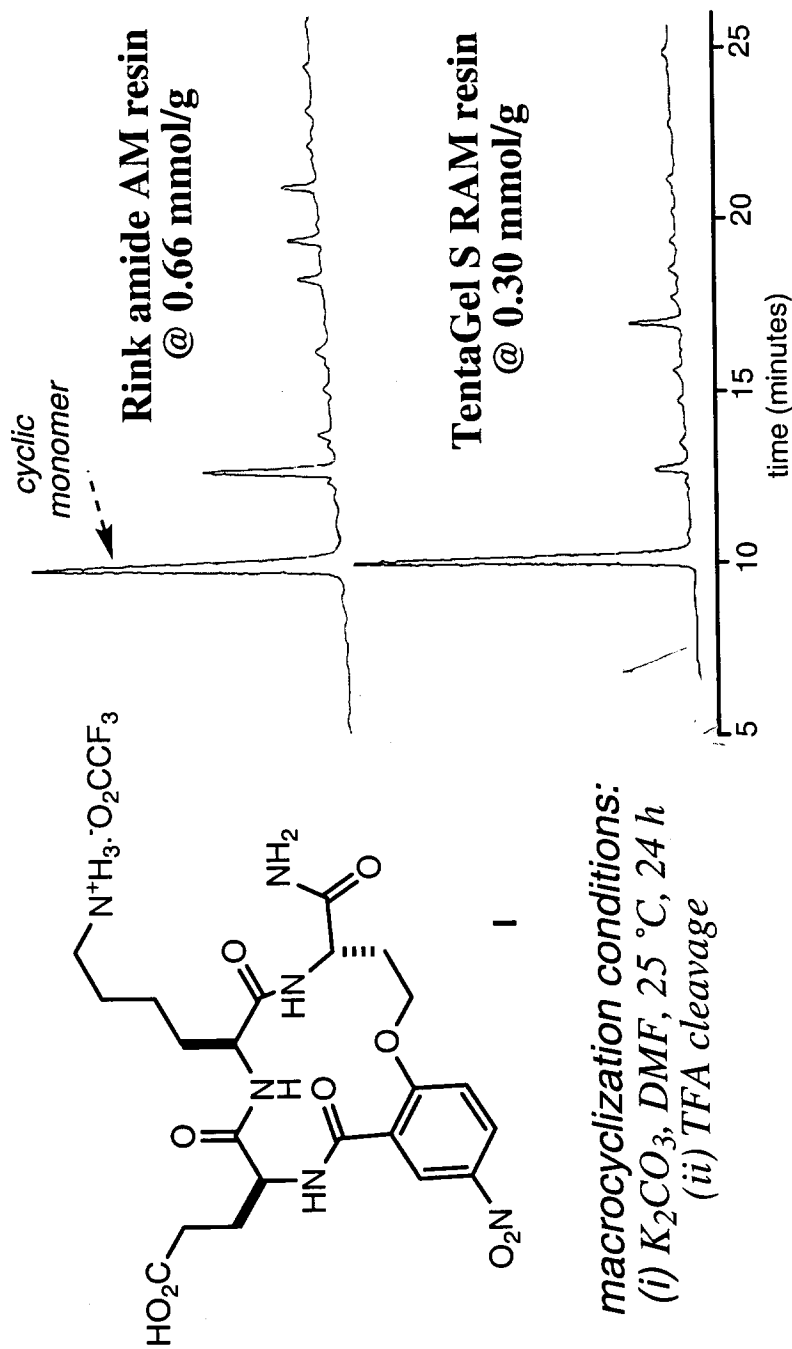
macrocyclization conditions:

- (i) $5.0 \text{ K}_2\text{CO}_3$, DMF, 25°C , 35 h
- (ii) TFA cleavage

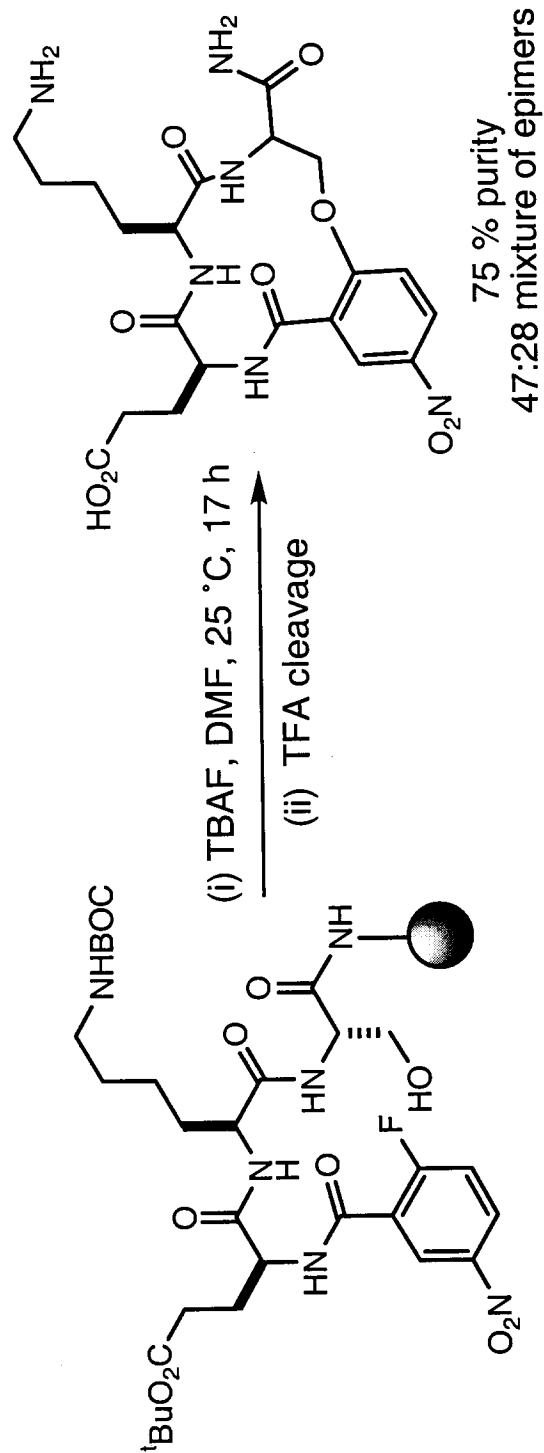
resin: Rink AM 0.66 mmol/g



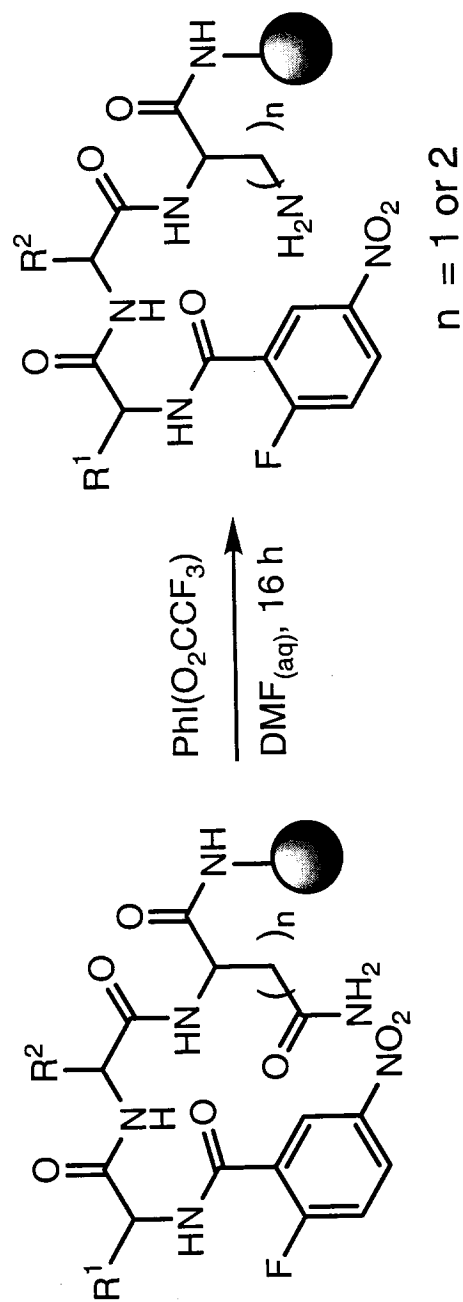
Suppression of Cyclic Dimer Formation at Low Resin Loadings



Problems with 13-Membered Rings and *O*-Nucleophiles

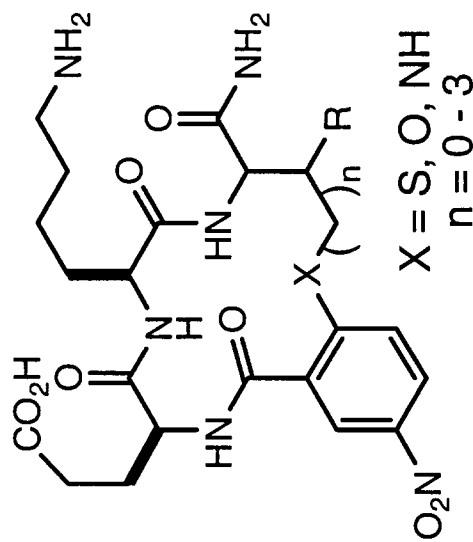


On-Resin Hofmann Rearrangements to Produce Lower Homologs of Orn and Lys



Influence of Nucleophile and Ring Size on Macrocyclization Efficiency

ring size	X	n	purity (%)		
			linear mono'r	cyclic mono'r	cyclic dimer
13	S	0	-	56	40
13	NH	0	-	30	-
13	O	0	55	<2	38
13	O	0	90	<2	2
14	NH	1	-	90	-
14	O	1	-	61	-
15	NH	2	-	93	-
16	NH	3	-	82	-

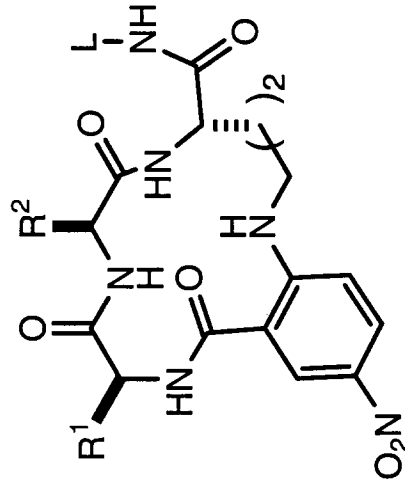


macrocyclization conditions:
(i) 5.0 K₂CO₃, DMF, 25 °C, 35 h
(ii) TFA cleavage

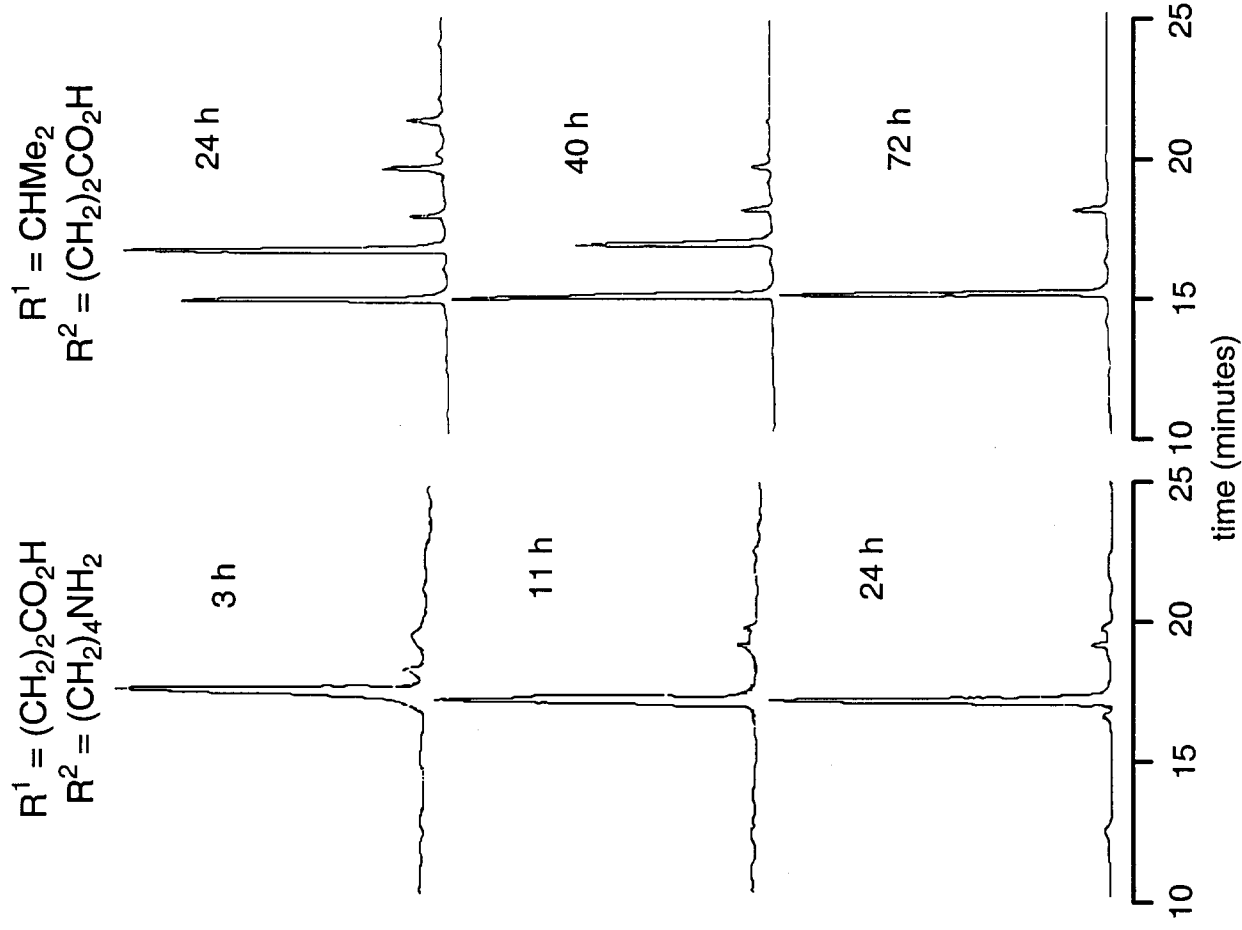
resin: Rink AM 0.66 mmol/g

R = H except for entry 4
where R = Me

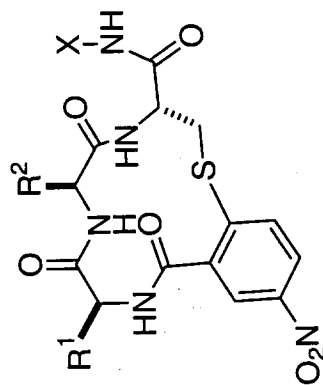
Substituent Effects On Cyclization Rates



conditions:
 K_2CO_3 , DMF, 25 °C
 then TFA cleavage



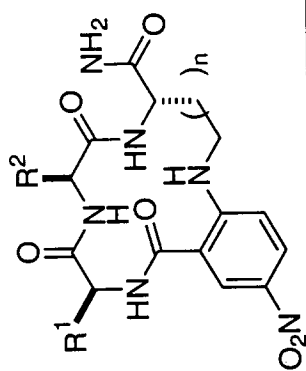
S-Compounds Prepared and Isolated



macrocyclization conditions:
(i) 5.0 K₂CO₃, DMF, 25 °C, 24 h
(ii) TFA cleavage

resin: TentaGel S RAM 0.66 mmol/g

R ¹	R ²	X	purity (%)	isol'd yield (%)
(CH ₂) ₄ NH ₂	(CH ₂) ₂ COOH	H	55	24
MeEtCH	(CH ₂) ₄ NH ₂	H	67	23
(CH ₂) ₂ COOH	(CH ₂) ₄ NH ₂	H	75	33
(CH ₂) ₂ COOH	(CH ₂) ₄ NH ₂	CH ₂ CONH ₂	70	31
(CH ₂) ₂ COOH	(CH ₂) ₄ NH ₂	(CH ₂) ₂ CONH ₂	66	32
(CH ₂) ₂ COOH	(CH ₂) ₄ NH ₂	(CH ₂) ₅ CONH ₂	63	32
(CH ₂) ₄ NH ₂	H	H	85	38
(CH ₂) ₄ NH ₂	H	CH ₂ CONH ₂	87	27
CH ₃	H	H	93	39
(CH ₂) ₂ COOH	(CH ₂) ₄ NH ₂	CH ₂ COOH	40	23

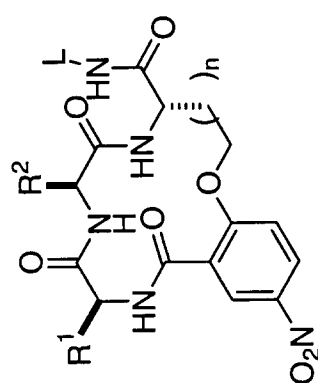


N- Analog Isolated

macrocyclization conditions:
(i) 5.0 K₂CO₃, DMF, 25 °C, 35 h
(ii) TFA cleavage

resin: Rink AM 0.66 mmol/g

entry	n	ring size	time (h)	R ¹	R ²	purity (%)	isolated yield (%)
1	0	13	35	(CH ₂) ₂ COOH	(CH ₂) ₄ NH ₂	30	9
2	1	14	24	(CH ₂) ₂ COOH	(CH ₂) ₄ NH ₂	90	30
3	1	14	20	EtMeCH	(CH ₂) ₄ NH ₂	86	48
4	1	14	16	(CH ₂) ₃	CH(CH ₃) ₂	78	43
5	1	14	30	CH ₂ OH	(CH ₂) ₄ NH ₂	82	40
6	1	14	40	CH ₂ Ph	CH ₂ CH ₂ SCH ₃	93	37
7	2	15	60	(CH ₂) ₂ COOH	(CH ₂) ₄ NH ₂	93	56
8	2	15	70	ⁱ Pr	(CH ₂) ₂ COOH	91	74
9	2	15	35	CH ₂ ⁱ Pr	CH ₂ (CH ₃)OH	90	89
10	2	15	40	CH ₂ Ph	CH ₂ C ₃ H ₃ N ₂	96	73
11	2	15	40	(CH ₂) ₃	CH ₂ SCH ₂ NH-COCH ₃	91	67
12	3	16	23	(CH ₂) ₂ COOH	(CH ₂) ₄ NH ₂	83	52
13	3	16	17	EtMeCH	(CH ₂) ₄ NH ₂	89	52



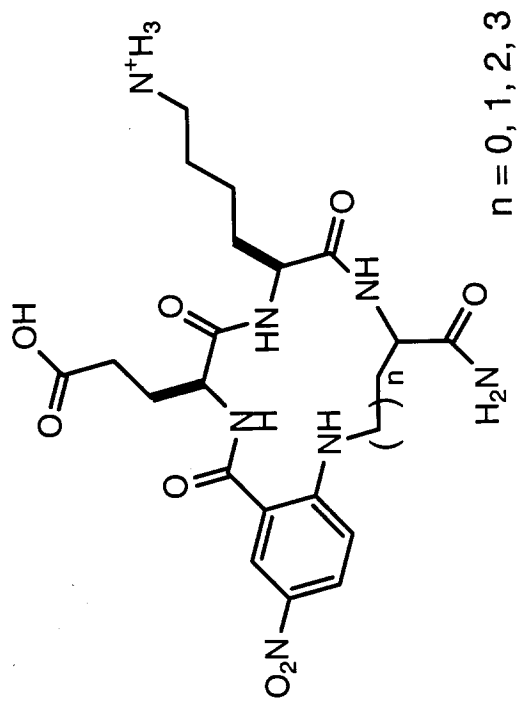
O- Analog Isolated

macrocyclization conditions:
(i) 5.0 K₂CO₃, DMF, 25 °C, 20 - 70 h
(ii) TFA cleavage

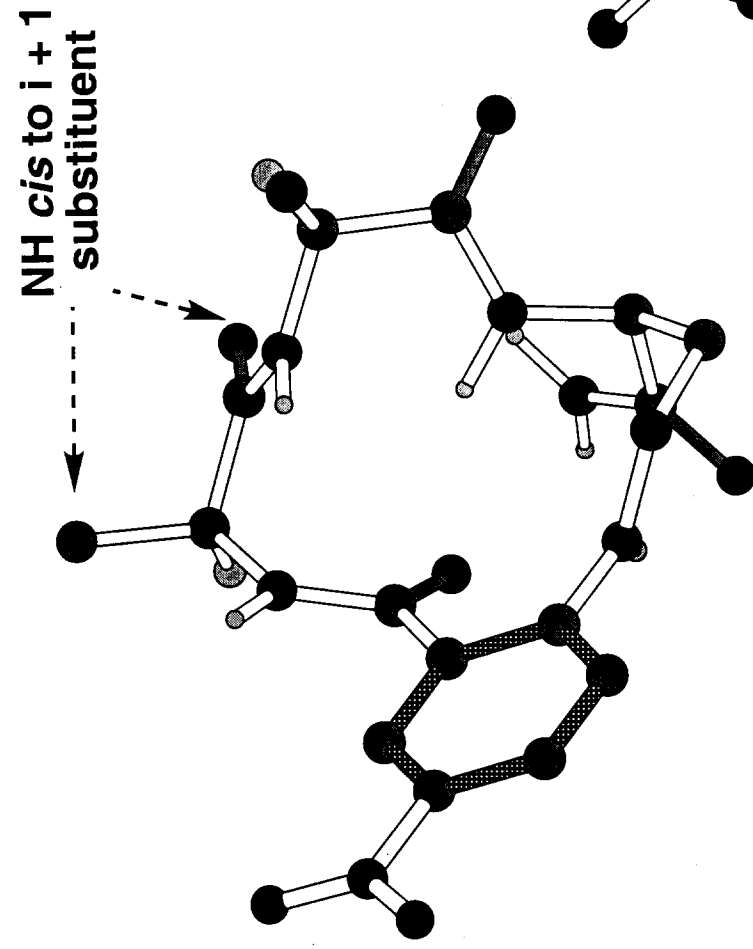
resin: TentaGel S RAM 0.30 mmol/g

n	ring size	time (h)	R ¹	R ²	L	purity (%)	isol'd yield (%)
1	14	30	MeEtCH	CH ₂ CONH ₂	H	61	23
1	14	17	MeEtCH	CH ₂ CONH ₂	CH ₂ CONH ₂	56	20
1	14	24	CH ₂ CONH ₂	(CH ₂) ₃ (from Pro)	H	51	18
1	14	16	MeEtCH	(CH ₂) ₄ NH ₂	H	80	37
1	14	24	CH ₂ CONH ₂	CH ₂ OH	H	49	11
1	14	60	CH ₂ OH	CH ₂ ⁱ Pr	H	94	65
1	14	70	ⁱ Pr	(CH ₂) ₂ COOH	H	77	43
1	14	24	CH ₂ COOH	MeEtCH	H	70	25
1	14	24	(CH ₂) ₂ COOH	(CH ₂) ₄ NH ₂	H	89	43
1	14	16	(CH ₂) ₂ COOH	(CH ₂) ₄ NH ₂	CH ₂ CONH ₂	63	32
1 ^a	14	24	(CH ₂) ₂ COOH	(CH ₂) ₄ NH ₂	CH ₂ CO ₂ H	71	33
1	14	24	D-(CH ₂) ₂ COOH	(CH ₂) ₄ NH ₂	H	60	48
1	14	24	(CH ₂) ₂ COOH	D-(CH ₂) ₄ NH ₂	H	59	38
0 ^b	13	35	(CH ₂) ₂ COOH	(CH ₂) ₄ NH ₂	H	30	14

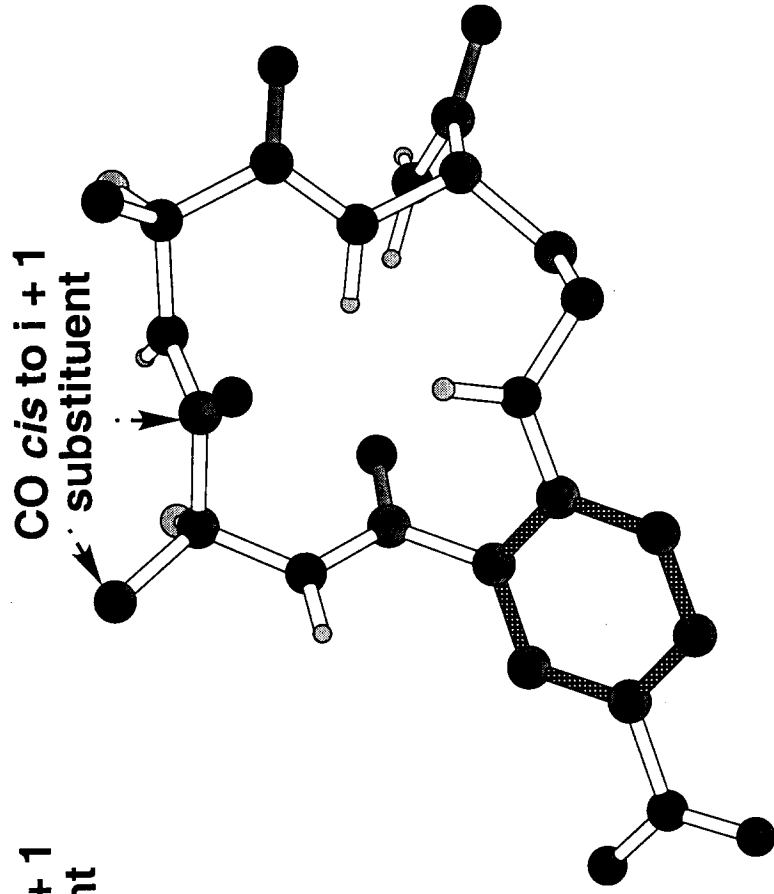
Comparison of the Conformations of 13 - 16 Membered Ring Structures



Comparison of Type I and Type II β -turns

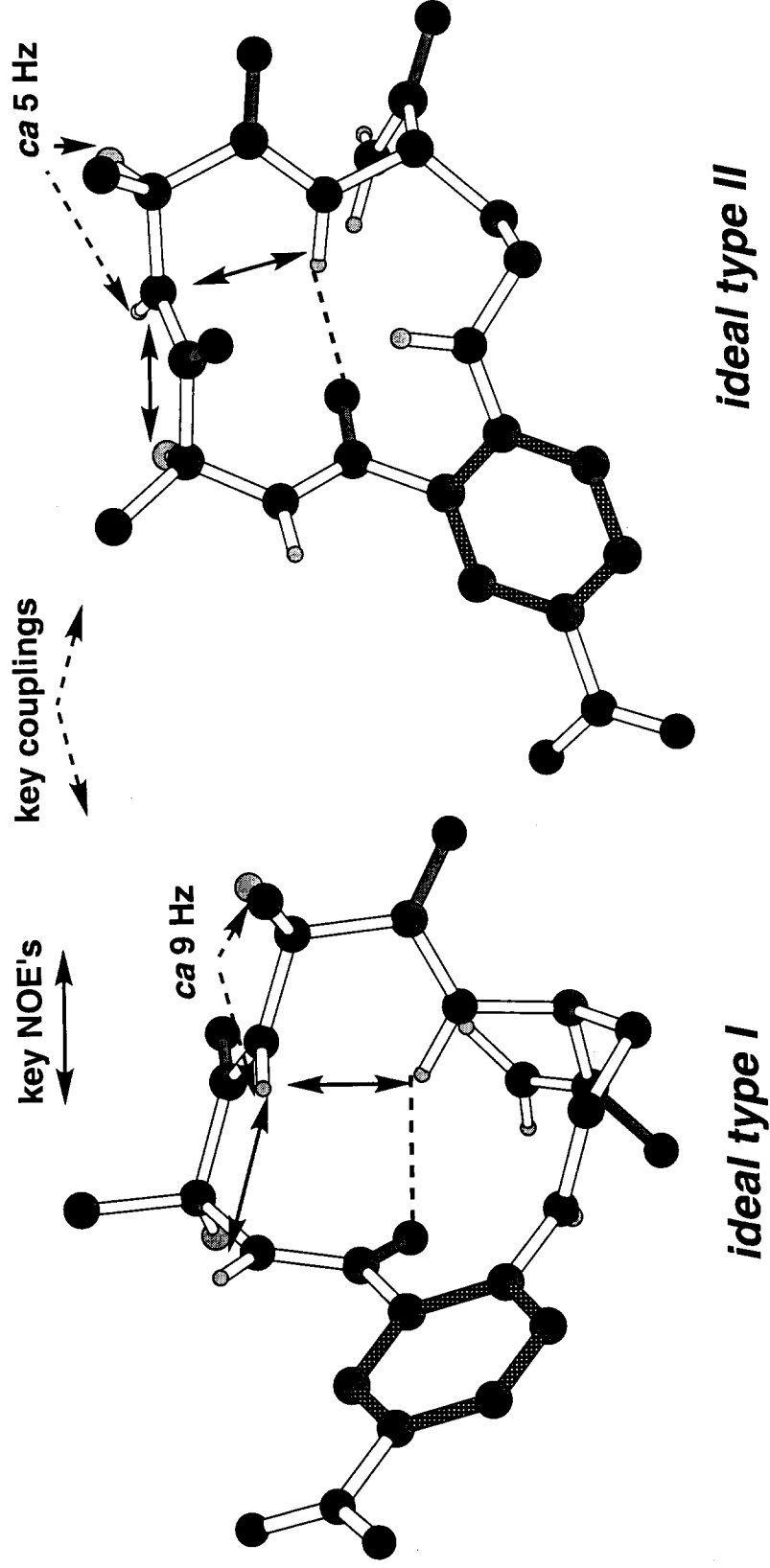


ideal type I

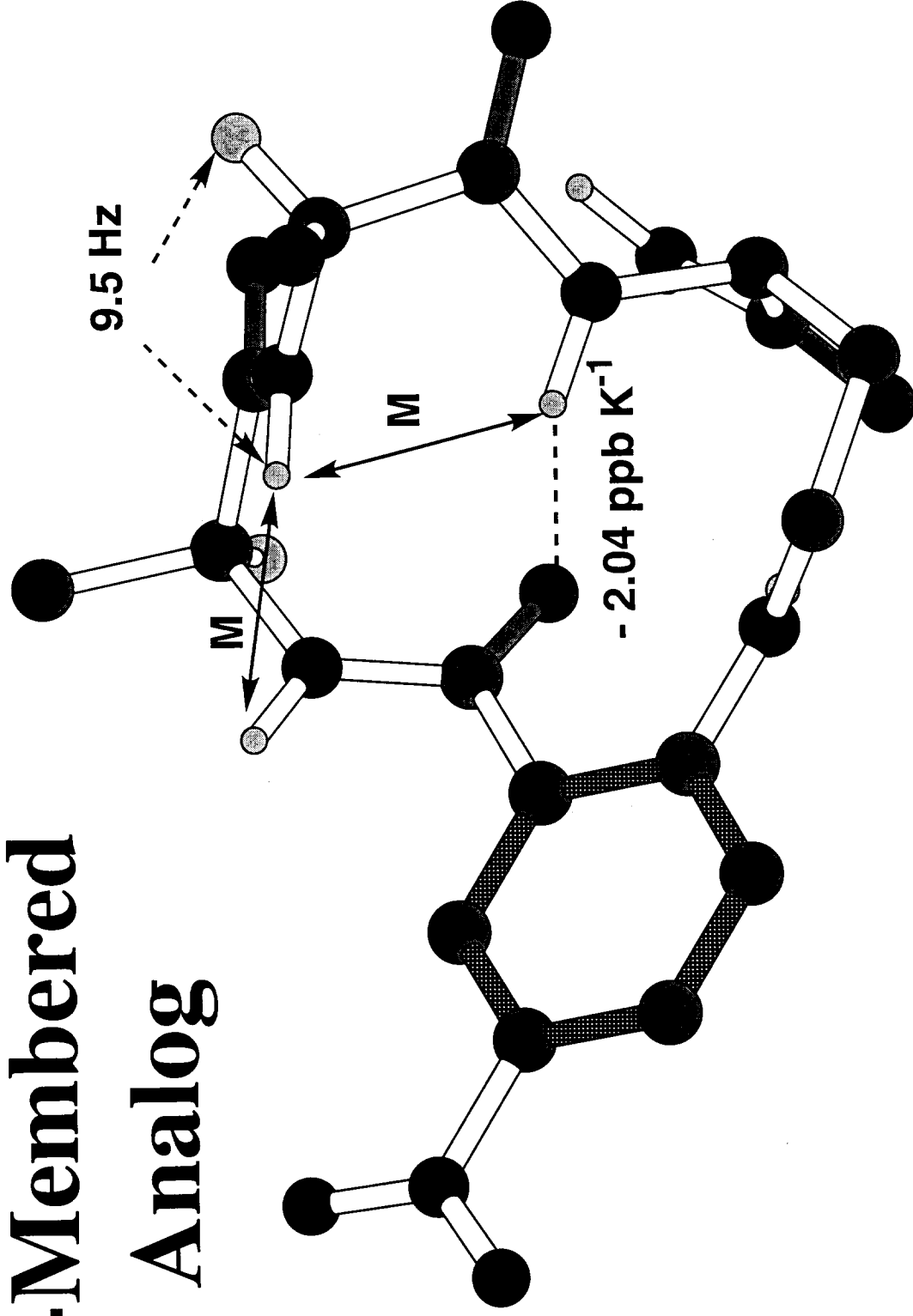


ideal type II

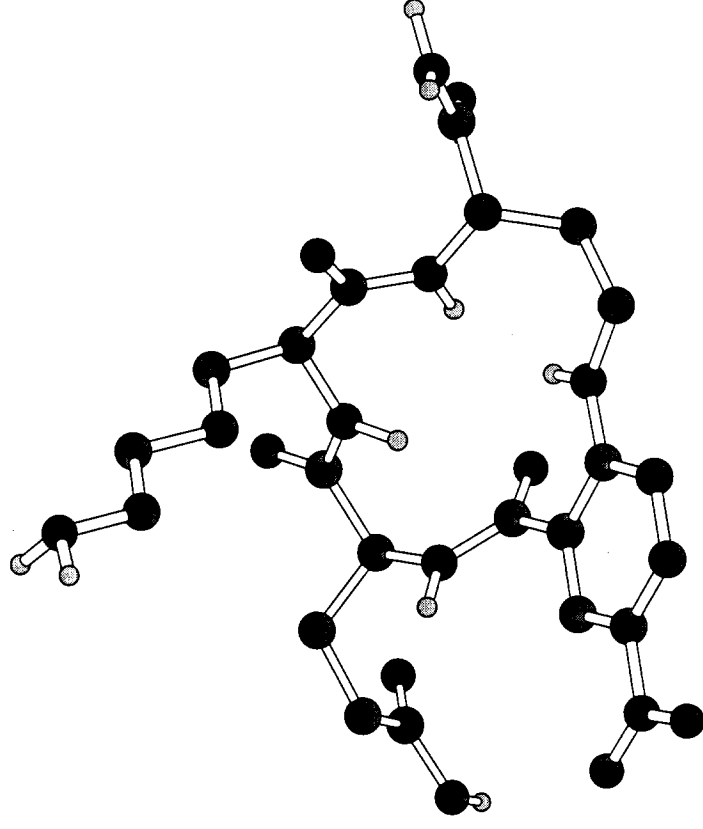
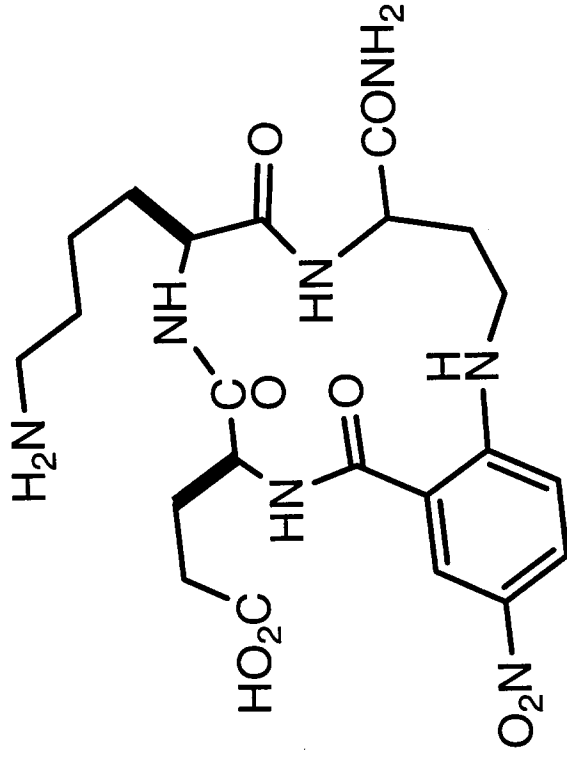
Critical Data for Type I and Type II β -turns

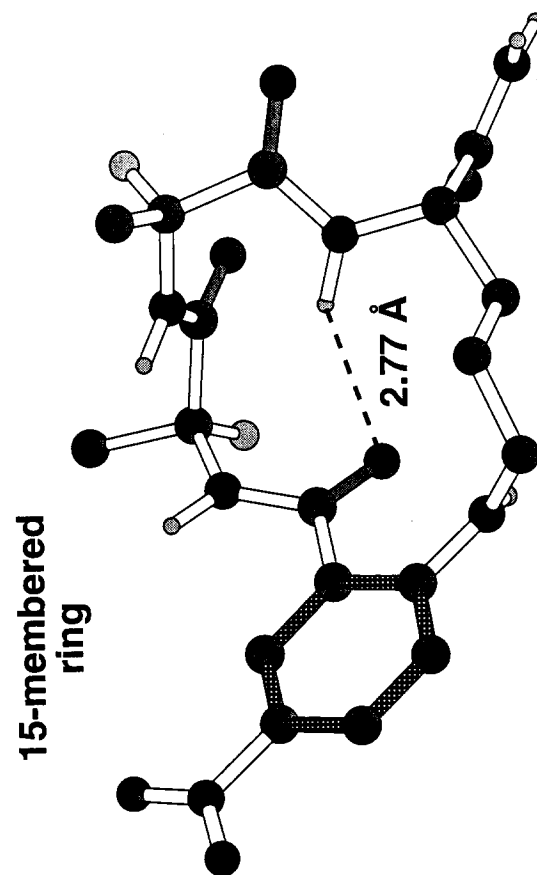
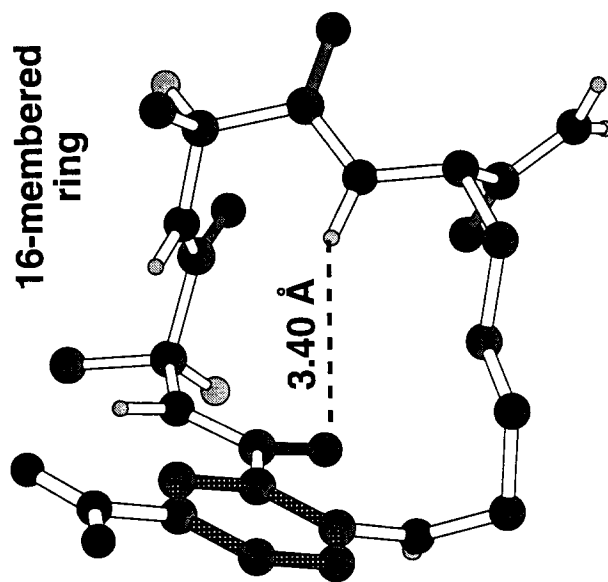
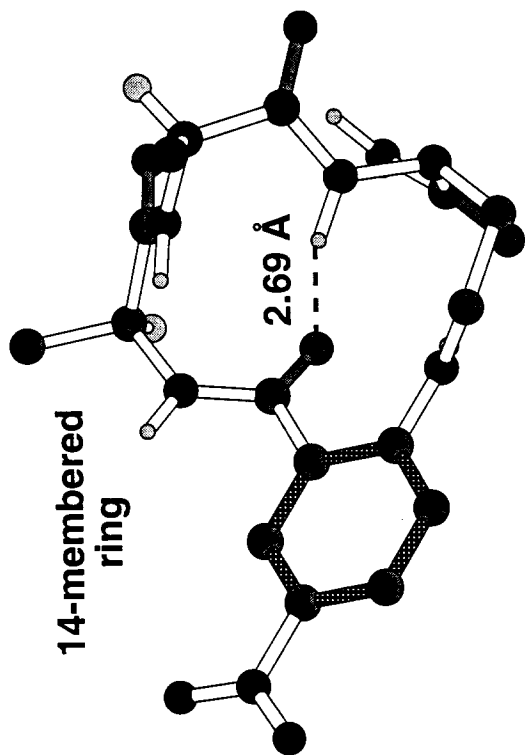
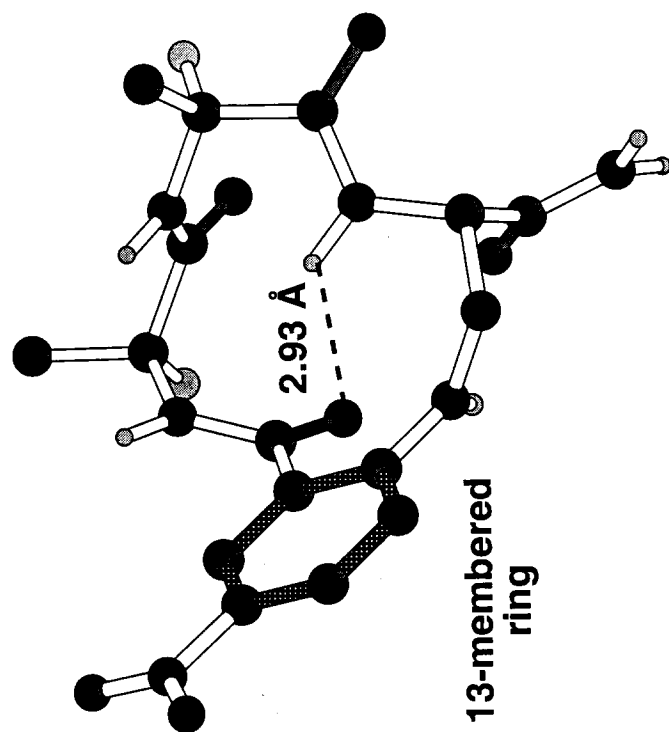


Key Data for 14-Membered Analog



Minimized Conformation of a Turn Analog





Conclusions from Conformational Comparison of 13 - 16 Membered Rings

- data for all the ring sizes was more consistent with type I β -turn than type II;
- the most perfect fit of the data for a type I β -turn was for the 14-membered ring case;
- the 14-membered ring was expected to give the best fit because it has the correct ring size for a turn-extended-turn conformation