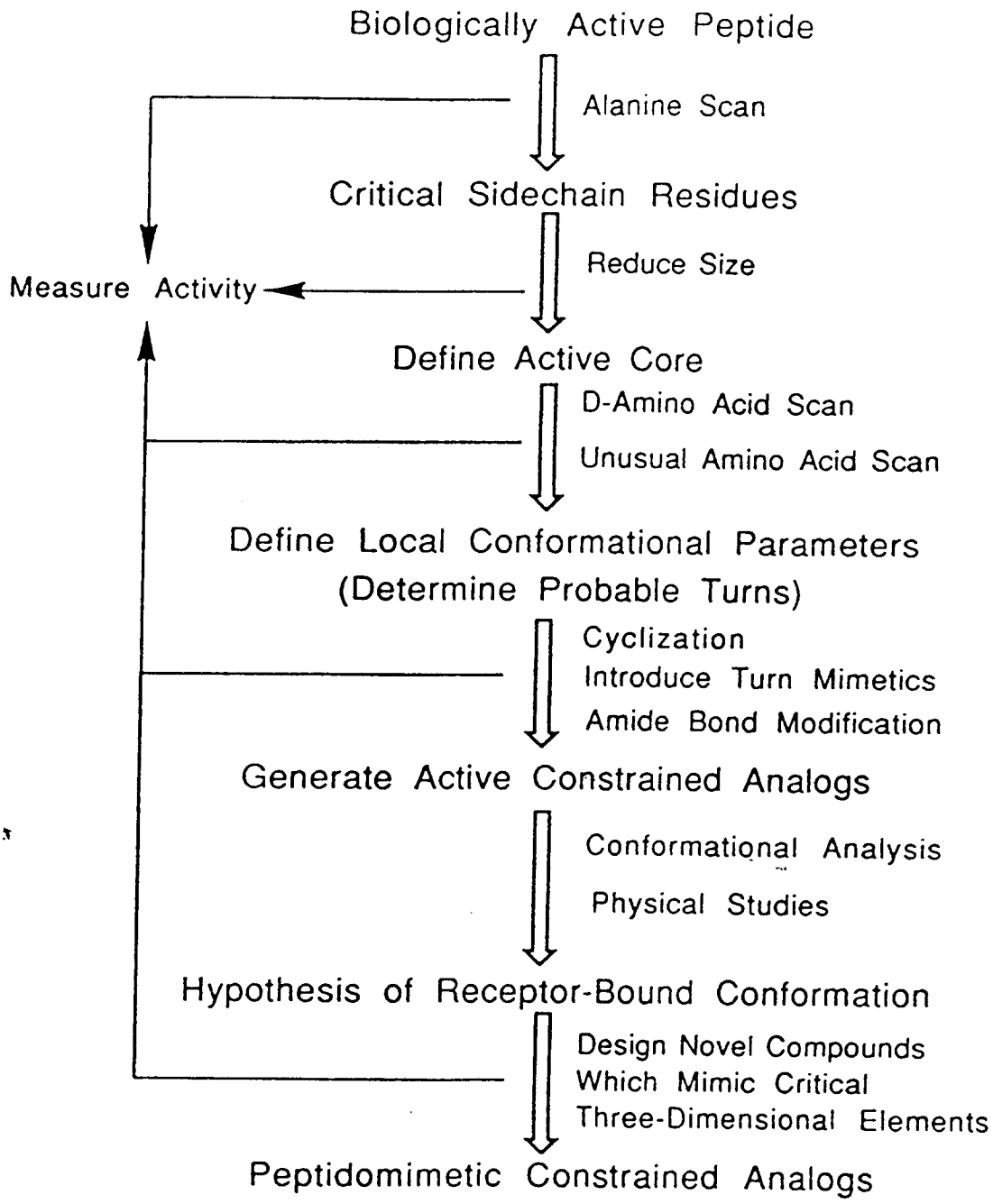


Fig. 1. A hierarchical approach to peptidomimetic design.

Bibliography

Overview:

Marshall, G. R. A Hierarchical Approach to Peptidomimetic Design. *Tetrahedron* 49:3547-3558(1993).

Receptor-bound Conformation of Angiotensin:

Plucinzka, K., T. Kataoka, , W.L. Cody, J.X. He, C. Humblet, G.H. Lu, E. Lunney, T.C. Major, R.L. Panek, P. Schelkun, R. Skeean and G.R. Marshall. Multiple Binding Modes for the Receptor-Bound Conformations of Cyclic AII Agonists. *J. Med. Chem.* 36:1902-1913(1993).

Nikiforovich, G. V. and G. R. Marshall. Three-Dimensional Recognition Requirements for Angiotensin Agonists: A Novel Solution for an Old Problem. *Biochem. Biophys. Res. Comm.* 195:222-228(1993).

Nikiforovich, G.V., J. Kao, K. Plucinska, W.-J. Zhang, and G.R. Marshall. Conformational Analysis of Two Cyclic Analogs of Angiotensin: Implications for the Receptor-Bound Conformation. *Biochemistry* 33:3591-3598(1994).

Electrochemical Ring Annulation:

Cornille, F., Y.M. Fobian, U. Slomczynska, D.D. Beusen, G.R. Marshall and K.D. Moeller. Anodic Amide Oxidations: Conformationally Restricted Peptide Building Blocks from the Direct Oxidation of Dipeptides. *Tetrahedron. Lett.* (in press).

Cornille, F., U. Slomczynska, M.L. Smythe, D.D. Beusen, K.D. Moeller and G.R. Marshall. Electrochemical cyclization of dipeptides to form novel bicyclic, reverse-turn peptidomimetics: Synthesis and conformational analysis of 7,5-bicyclic systems. *J. Am. Chem. Soc.* (in press).

Chimeric Amino Acids:

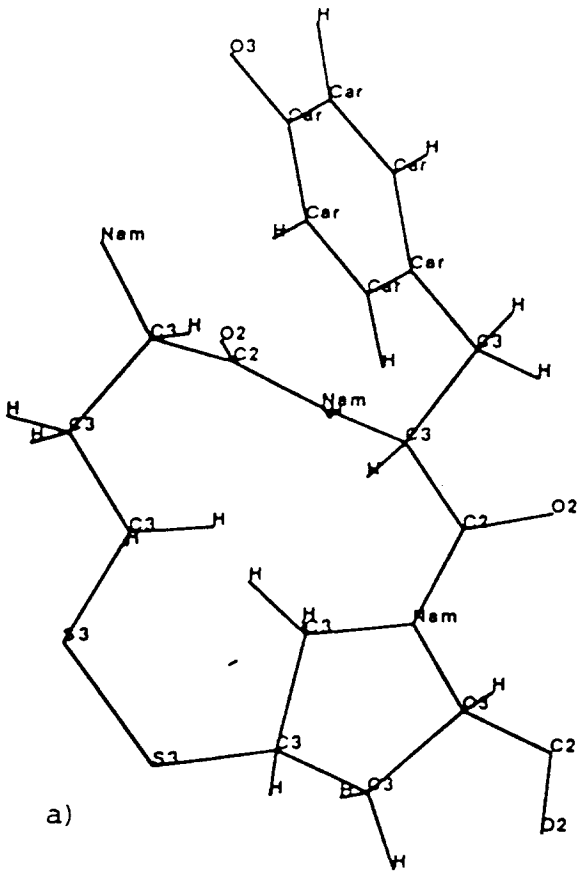
Kolodziej, S.A., G.V. Nikiforovich, R. Skeean, M.-F. Lignon, J. Martinez and G.R. Marshall. Ac-[3- and 4-Alkylthioproline31]-CCK4 Analogs: Synthesis and Implications for the CCK-B Receptor-Bound Conformation. *J. Med. Chem.* (submitted)

Nikiforovich, G.V., S.A. Kolodziej, B. Nock, N. Bernad, J. Martinez and G.R. Marshall. Conformationally Re-addressed CCK-B/δ-Opioid Peptide Ligands. *Biopolymers* (submitted)

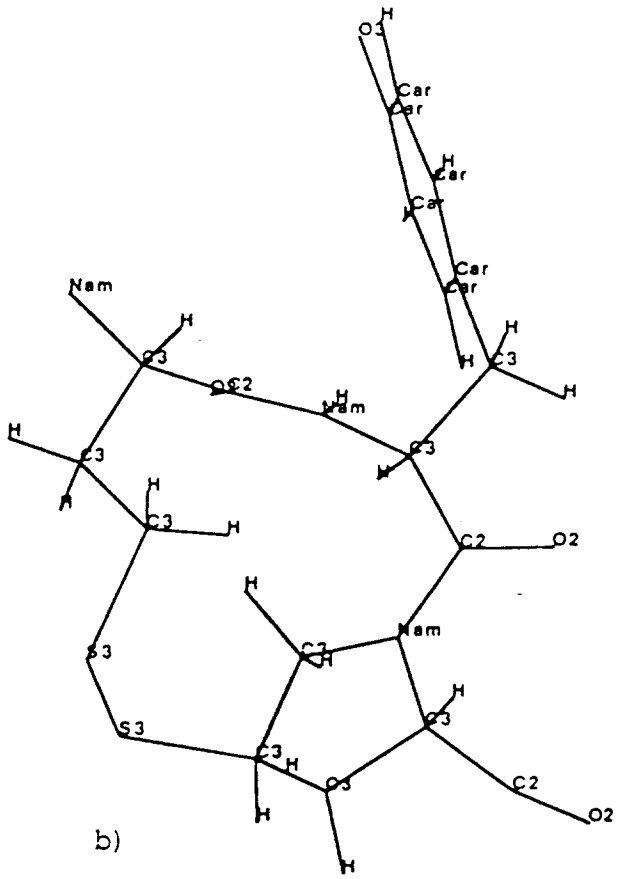
Table 1. c[Sar^1,Cys^3,Mpt^5]-AII ; amide proton NMR parameters in DMSO-d_6 and in H_2O,pH 3 at 25deg.

	DMSO				H_2O			
Amide	δ [ppm]	$\Delta\delta/\Delta T$ [ppb/°K]	$^3J_{N\alpha}$ [Hz]	$\phi^{a)}$ [deg]	δ [ppm]	$\Delta\delta/\Delta T$ [ppb/°K]	$^3J_{N\alpha}$ [Hz]	$\phi^{a)}$ [deg]
Arg	8.84	2.3	6.5	-165,-80 +50, +75	8.59	4.5	5.5	-170, -72 +30, +90
Cys	8.20	4.4	5.0	-170, -70 +60, +85	8.19	5.8	6.0	-168, -75 +35, +80
Tyr	9.21	2.2	8.5	-140, -95	8.90	5.8	8.0	-150, -85
His	8.60	4.2	6.0	-168, -75 +35, +80	8.44	6.1	6.0	-168, -75 +35, +80
Phe	8.50	4.2	6.0	-168, -75 +35, +80	8.15	6.7	6.5	-165, -80 +50, +75

a) read from the spectra; the angles are listed according to Bystro v's equation.

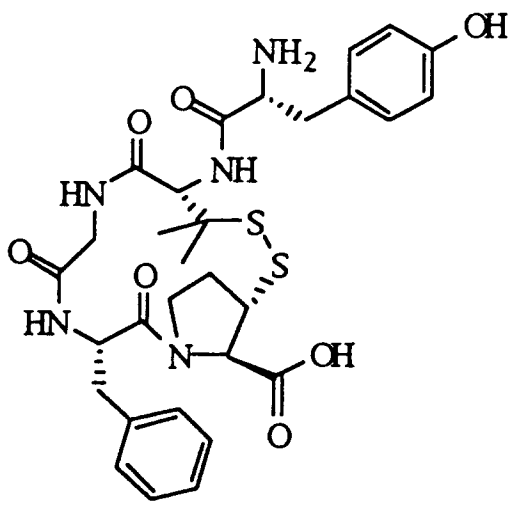

O3
Car
Car
Car
Car
Car
Car
Nam
C3
O2
C2
Nam
C3
C2
O2
C3
S3
C3
Nam
S3
C3
O3
C2
O3
O2

a)


O3
Car
Car
Car
Car
Car
Car
Nam
C3
O2
C2
Nam
C3
C2
O2
C3
S3
C3
Nam
S3
C3
O3
C2
O2

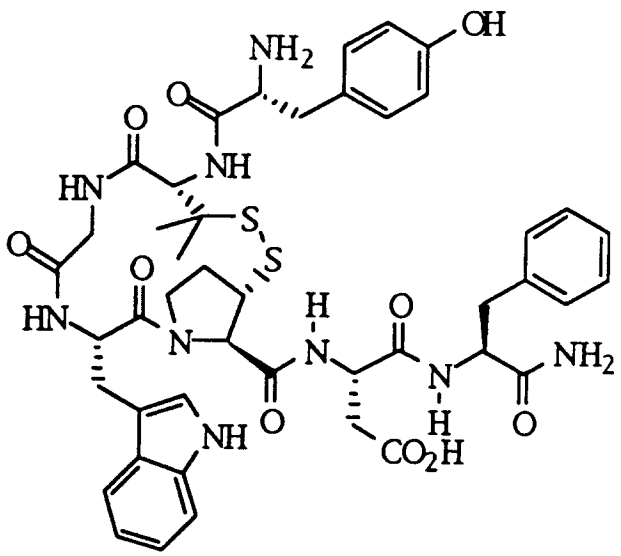
b)

Cyclic Disulfide Enkephalin Analogs with 3-Mpt



cyclo-(Tyr-D-Pen-Gly-Phe-D,L-3-Mpt)

SK-I-273-A/B



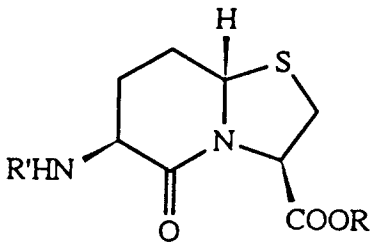
cyclo-(Tyr-D-Pen-Gly-Phe-D,L-3-Mpt)-Asp-Phe-NH_2

SK-I-275-A/B

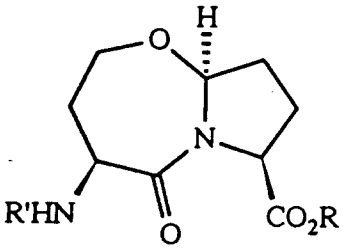
K_I's for 3-Mpt-Containing Opioid Analogs

	Opioid Receptor Binding (nM)		
	δ	μ	κ
273A	104	>5,000	>5,000
273B	3.5	63	>5,000
275A	19	226	>5,000
275B	4.5	>2,500	>5,000

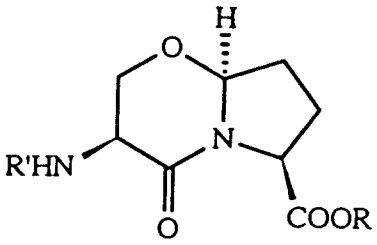
β-Turn Constraints



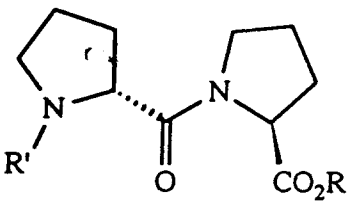
BTD



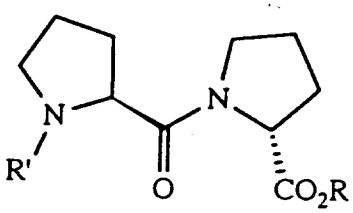
HsecPro



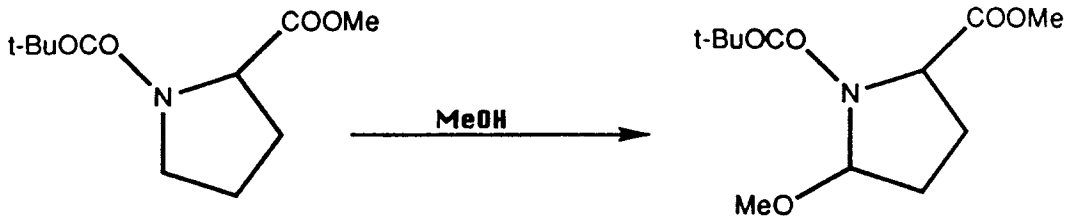
SercPro



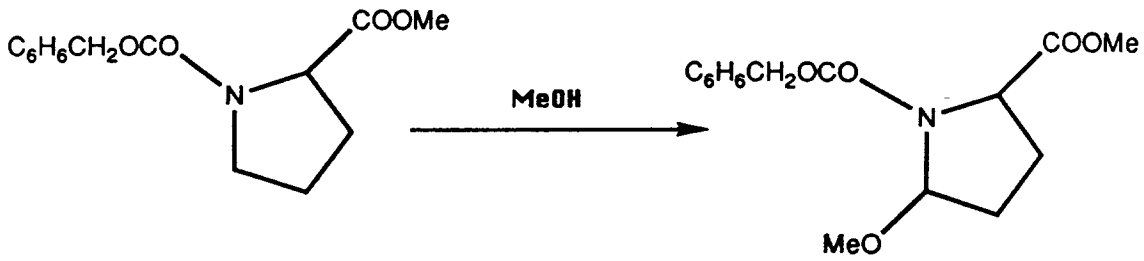
DProLPro



LProDPro



yield 78%



yield 75%

Conditions: MeOH; Et_4N^+ Tos^-; charcoal anode, platinum cathode

H^1 NMR: **1δH of Pro diappeard**

1δ H of Pro shifted from 3.65 ppm to 5.4 ppm

8 lines at 3,2-3,8 ppm correponds to COOMe and OMe ; 4 isomers

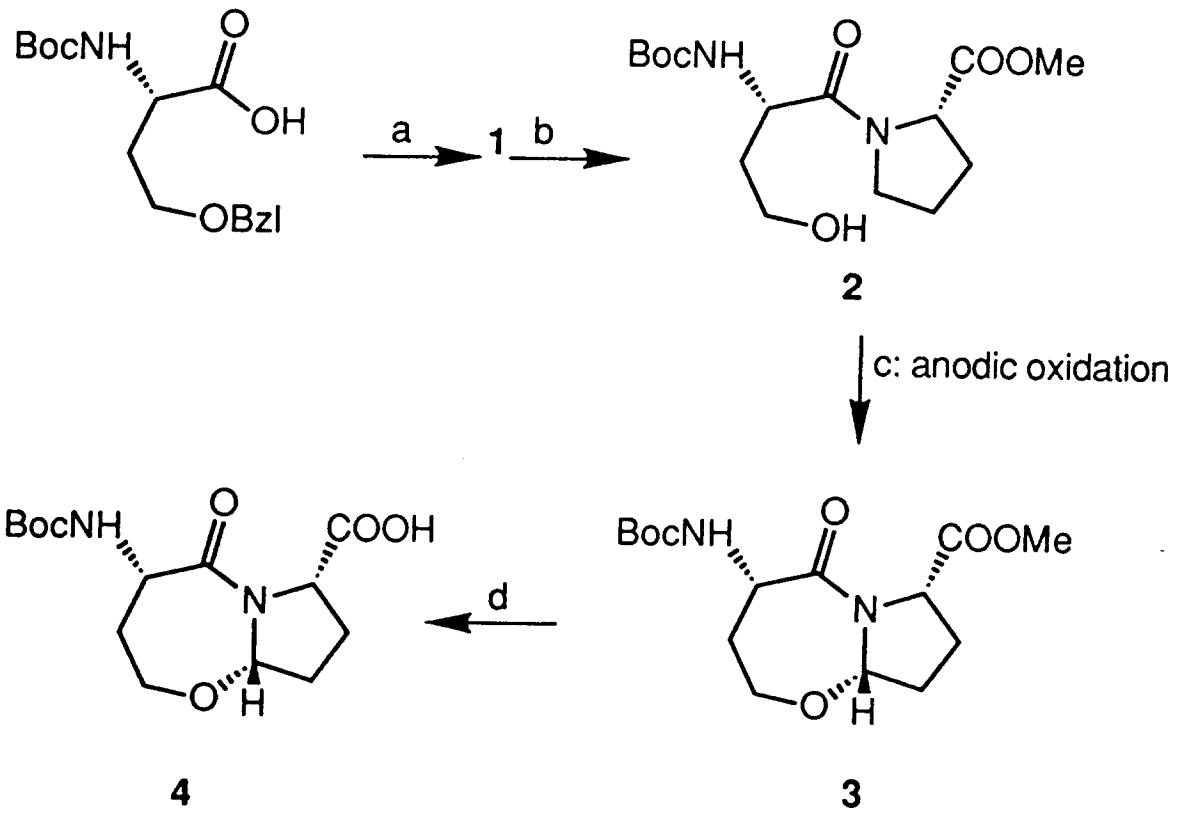


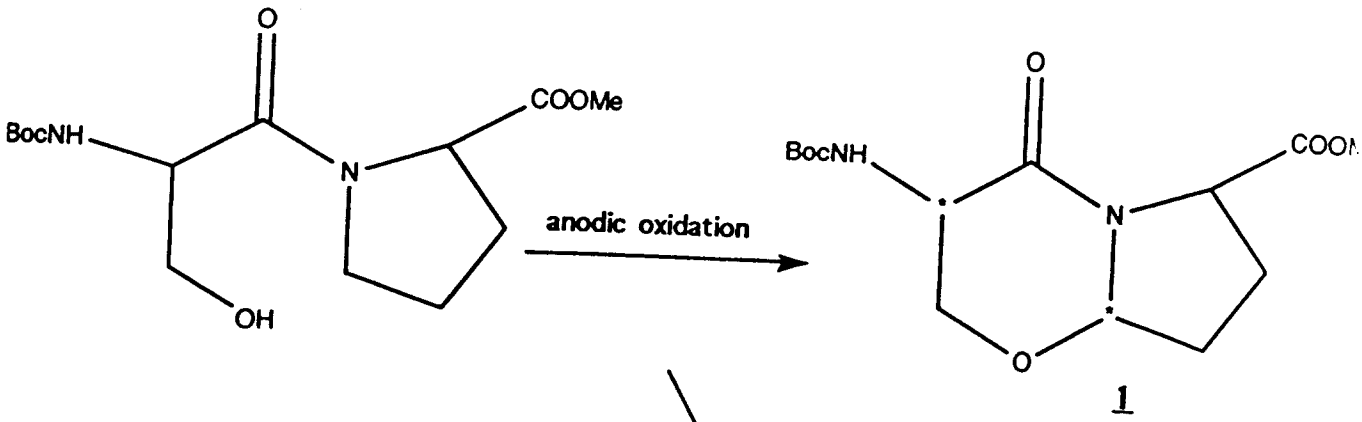
Figure 2 : (a) H-Pro-OMe, TBTU, diisopropyethylamine, overnight, RT, 81%

(b) H_2 45psi, Pd/C, 48 h, RT, 77%

(c) platinum electrodes, 1M Bu_4NBF_4 in$CH_3CN/(CH_3)_2CHOH$ 95/5 constant current 138mA(density 6.9 mA/cm^2), 3.8 F, 48%

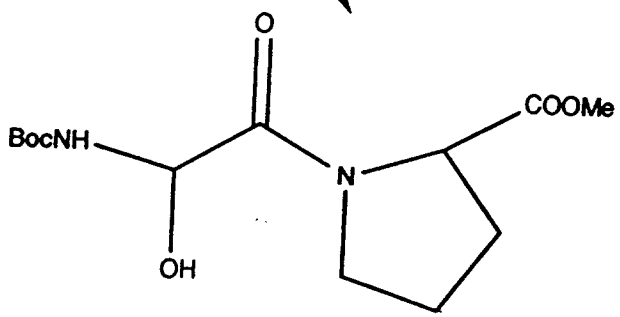
(d) [i] NaOH 1N, MeOH,1H, RT [ii] $KHSO_4$ 1M; 84%

Anodic oxidation of Boc-Ser-Pro-OMe



1

yield 20- 30 %



2

yield 20-30%

Conditions

substrate concentration: 0.2M

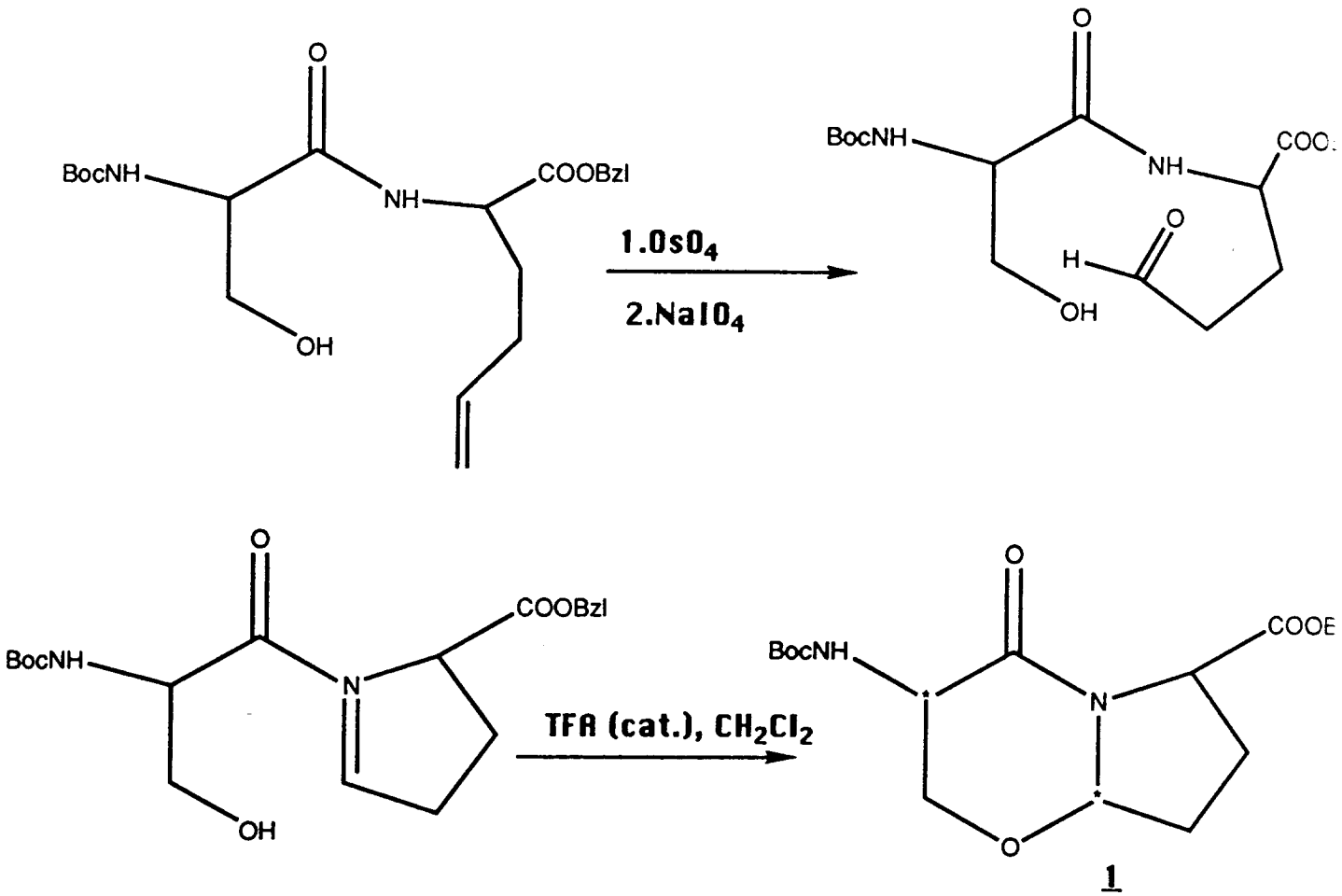
acetonitrile, platinum electrodes

electrolyte: $Bu_4N^+ BF_4^-$ (0.5 - 1M)

constant current: 14mA:

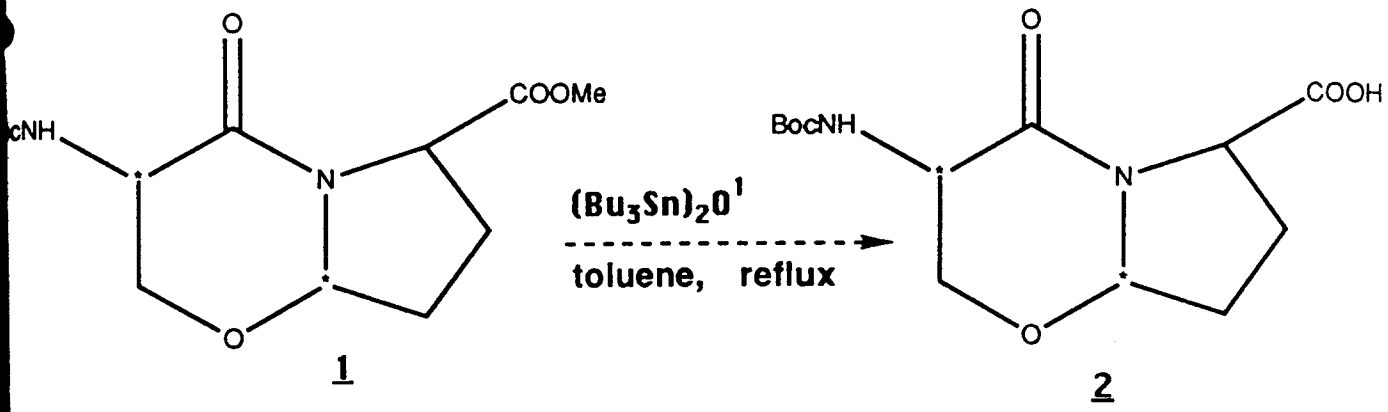
Difficult separation; two systems ethyl acetate/ hexane 50:50

hexane/ isopropanol 85:15



1

J. E. Baldwin, C. Hulme, C. J. Schofield and A. J. Edwards
J. Chem. Soc., Chem. Commun., 935 (1993)



1 2

configuration at the fused ring
(kinetically controled)

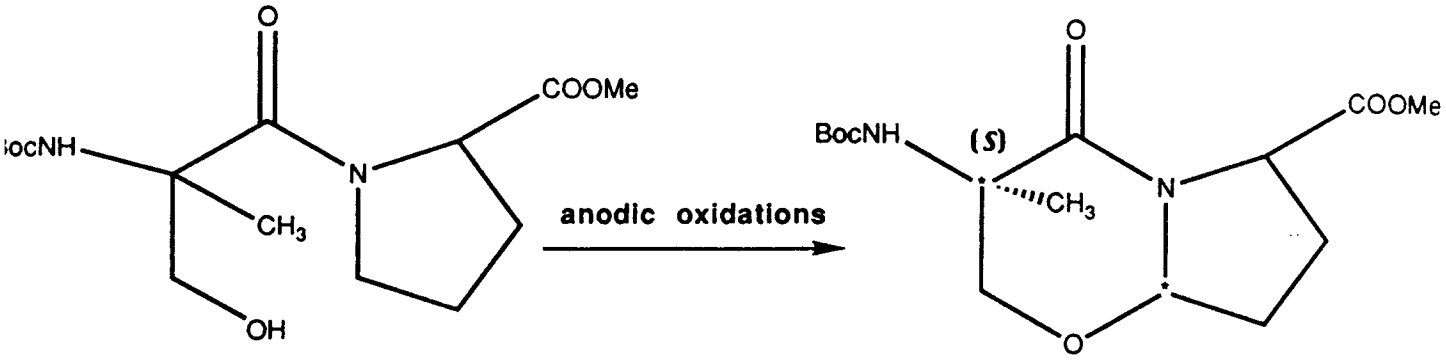
Prolonged treatmnet
with TFA[2]

Conversion to *R* configuration at the fused ring (70%)
Thermodynamically controlled

. Tetrahedron Lett., 1985, 26, 647

. J.Chem. Soc., Chem. Commun., 1993, 935

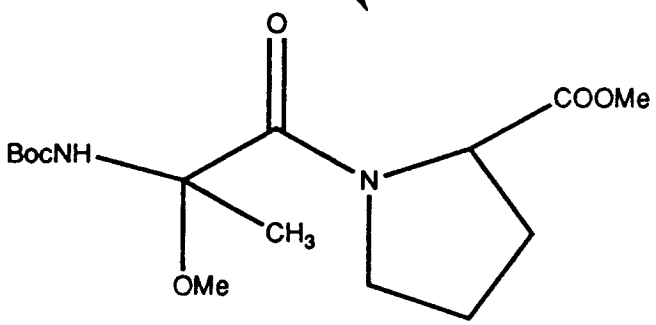
Anodic oxidation of Boc-MeS-Pro-OMe



R,S-isomers

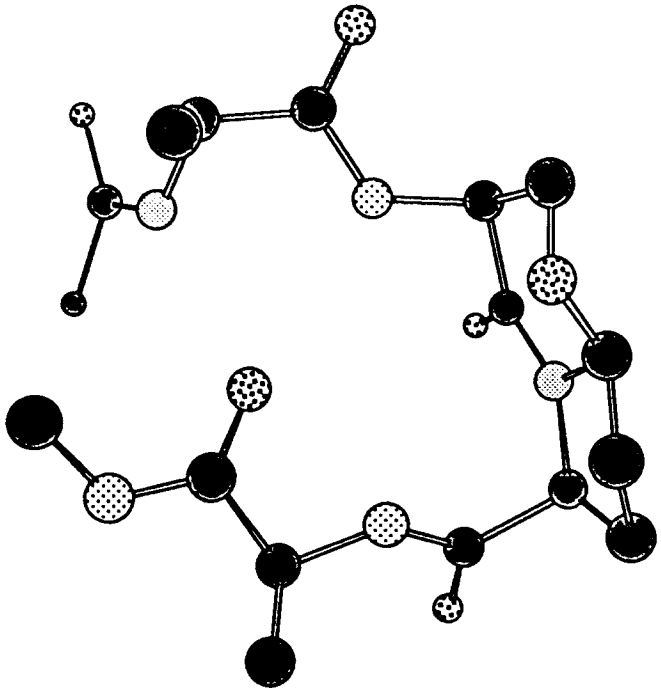
Boc-*S*-MeScPro-OMe (2)

low stereoselectivity at ring fusion
two diastereoisomers in ratio 6:4

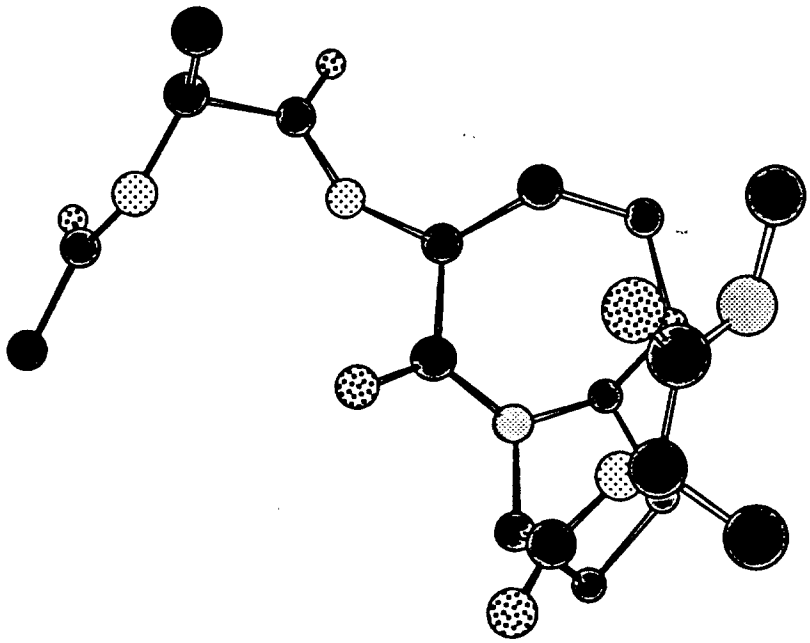


2

Boc-*R*,*S*-α-methoxyalanyl-Pro-OMe

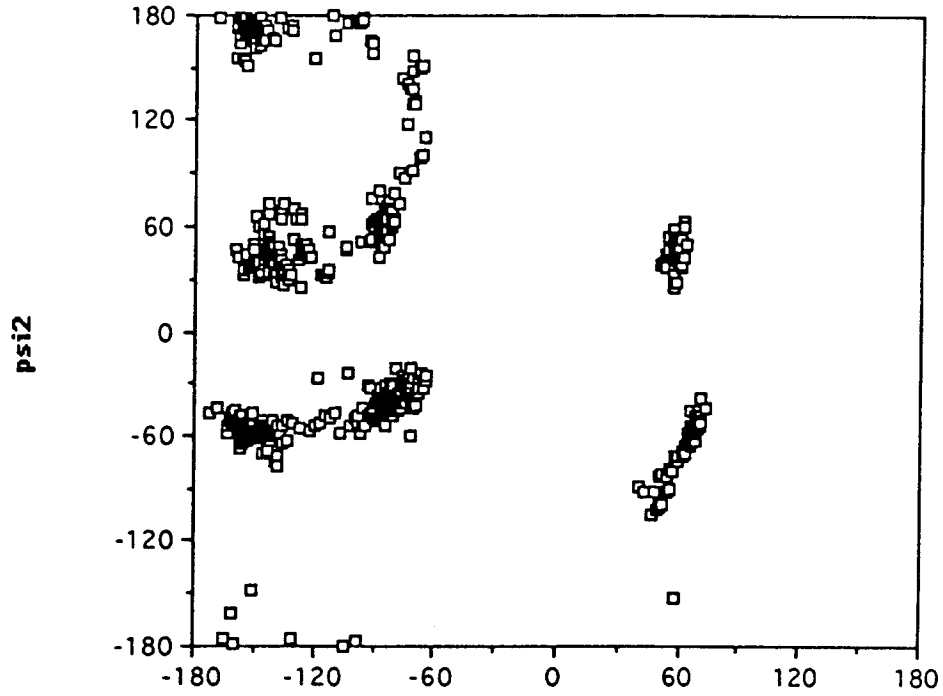


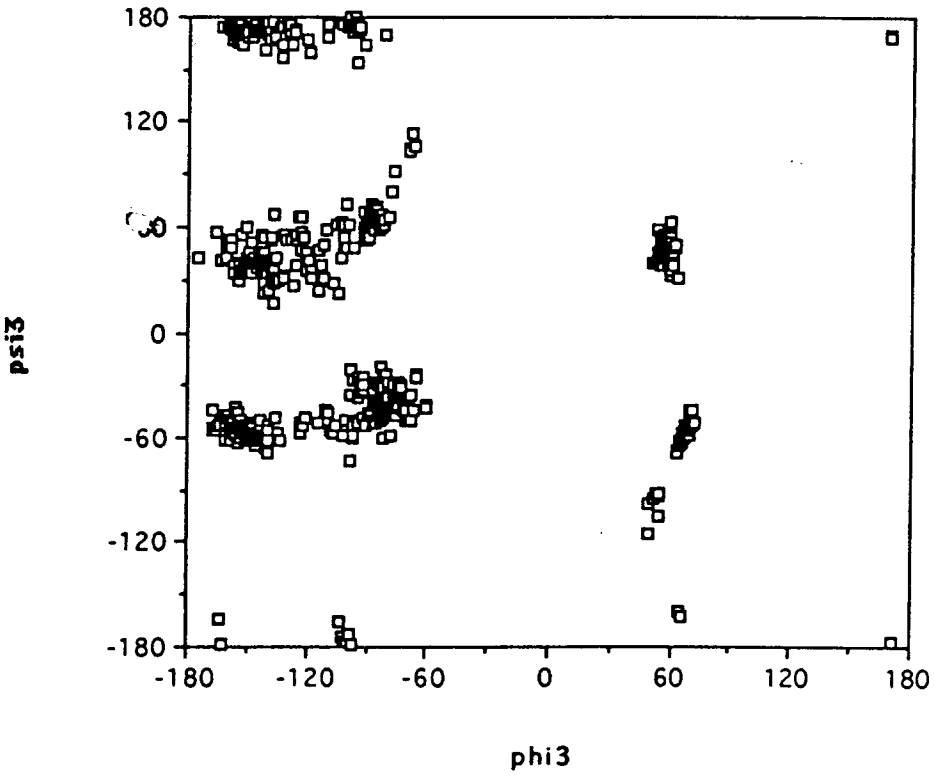
Ac-Ala-SercPro-Ala-NMe global minimum



Ac-Ala-HsecPro-Ala-NMe global minimum

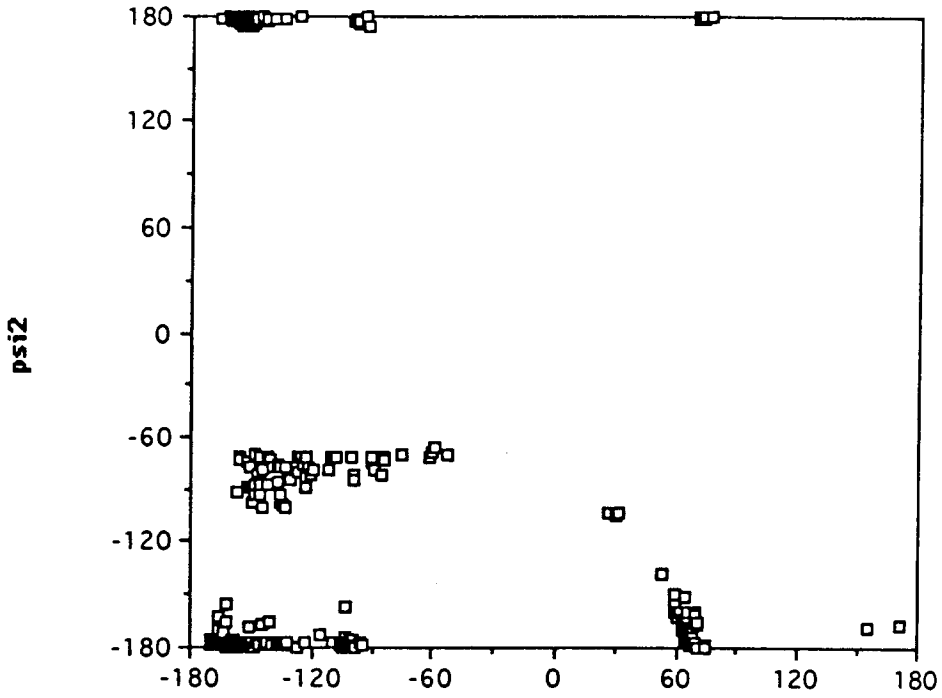
Ac-Ala-Ala-Ala-Ala-NHMe

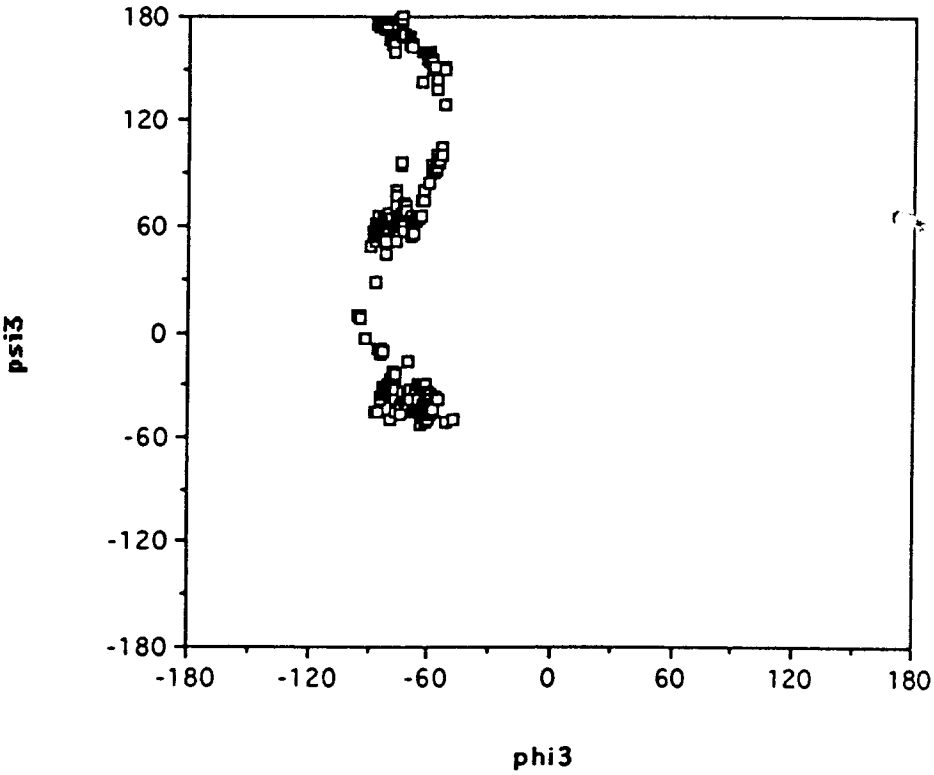




Conformational search using Amber-OPLS extended atom

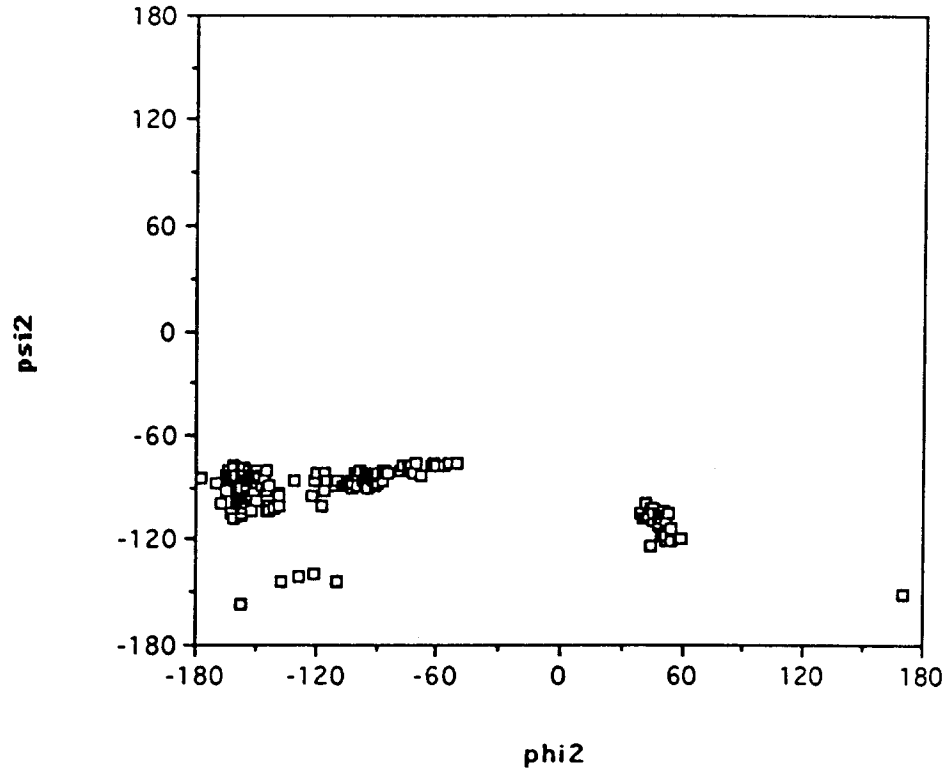
Ac-Ala-HsecPro-Ala-NMe

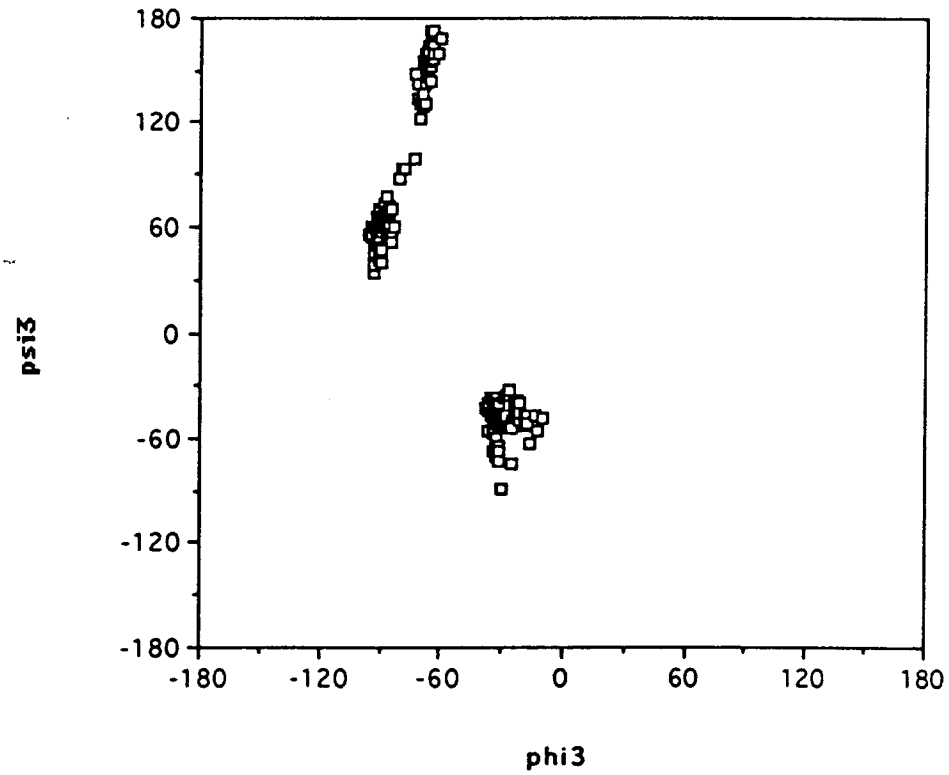




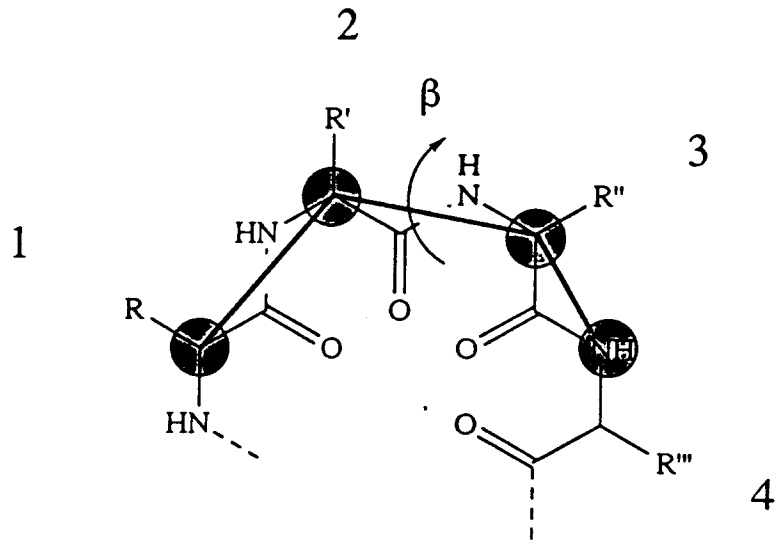
Conformational search using Amber-OPLS

Ac-Ala-SercPro-Ala-NHMe



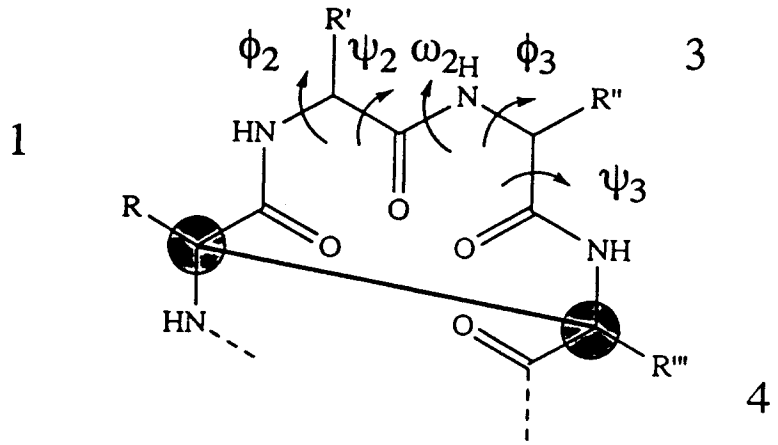


Conformational search using Amber-OPLS extended atom



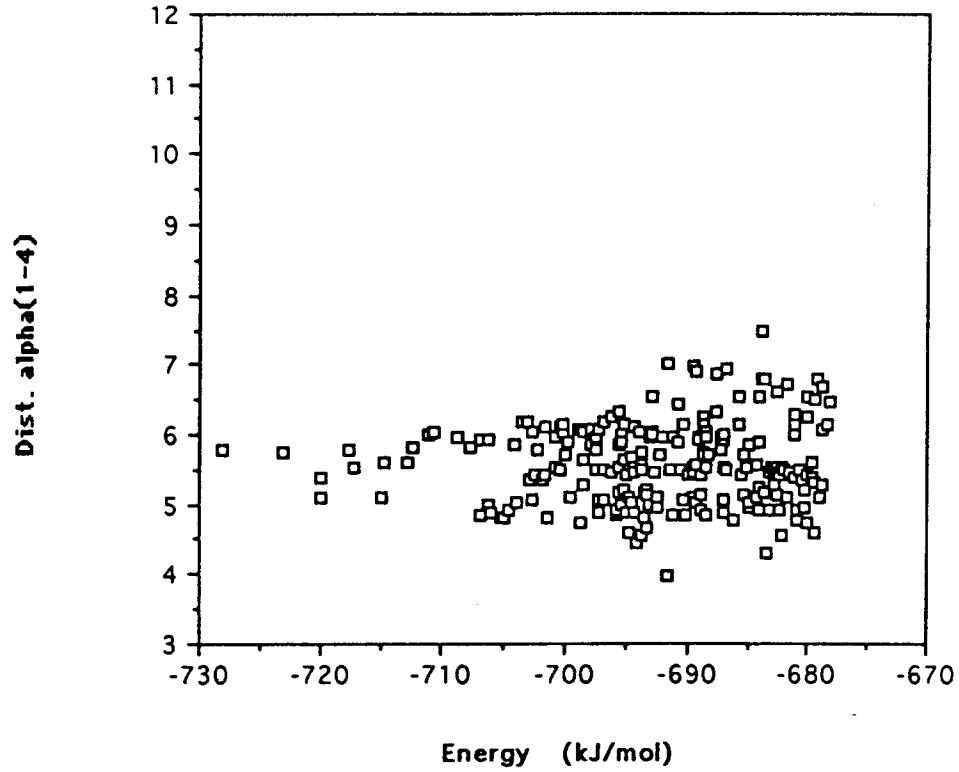
Angle β

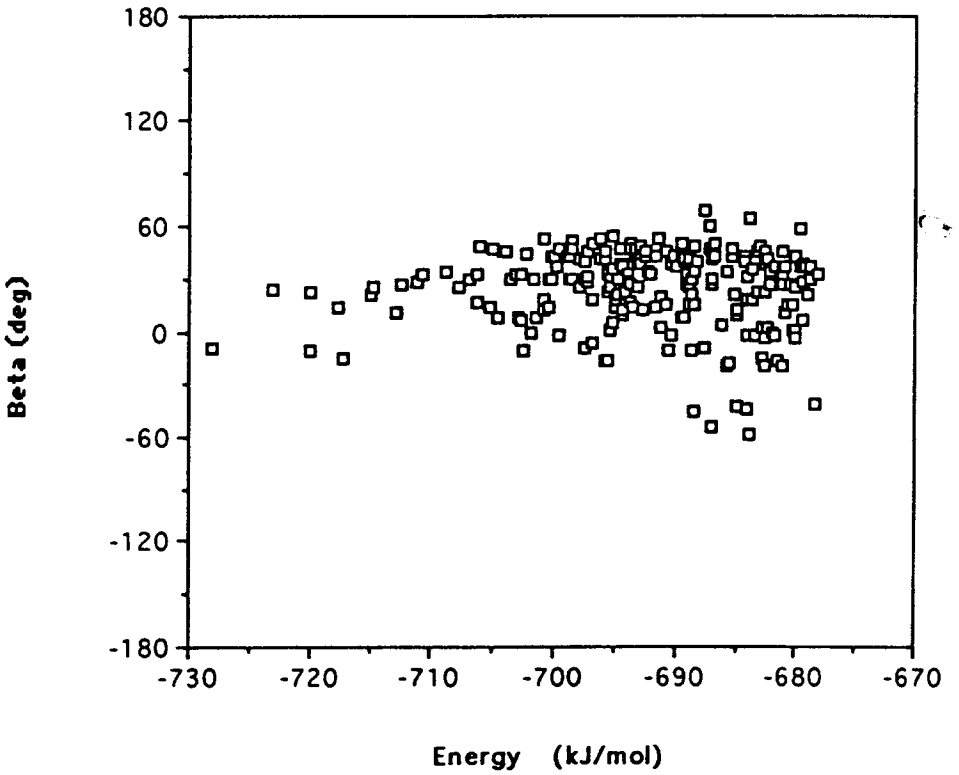
J. B. Ball et al. FEBS Letters, 237, 15-18.



Distance $C\alpha_1$-$C\alpha_4$

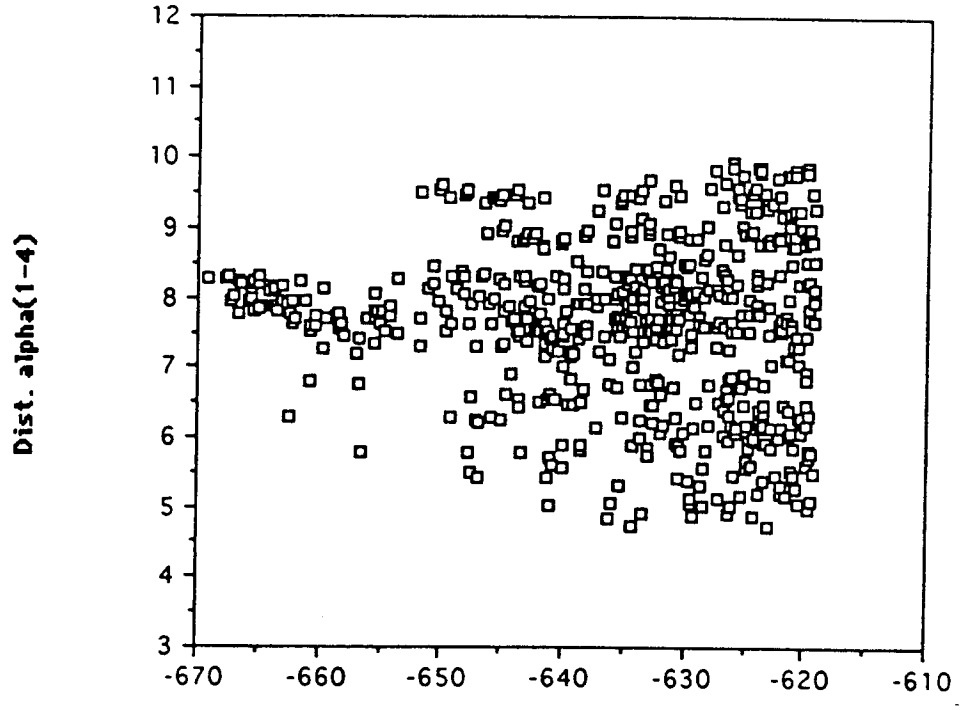
Ac-Ala-Ser*c*Pro-Ala-NMe

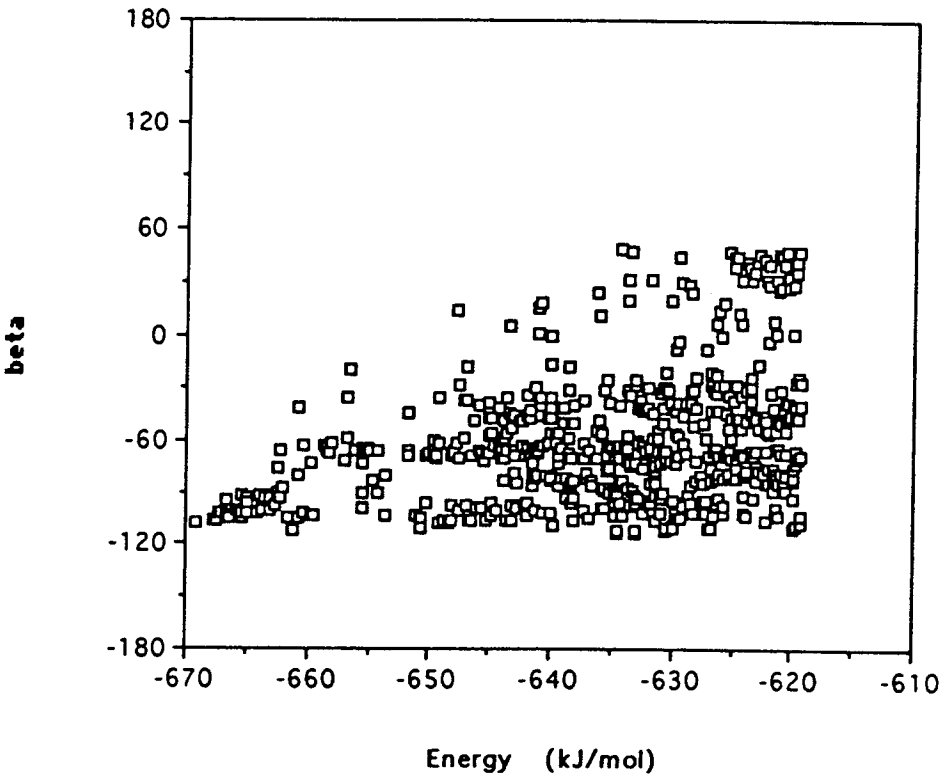




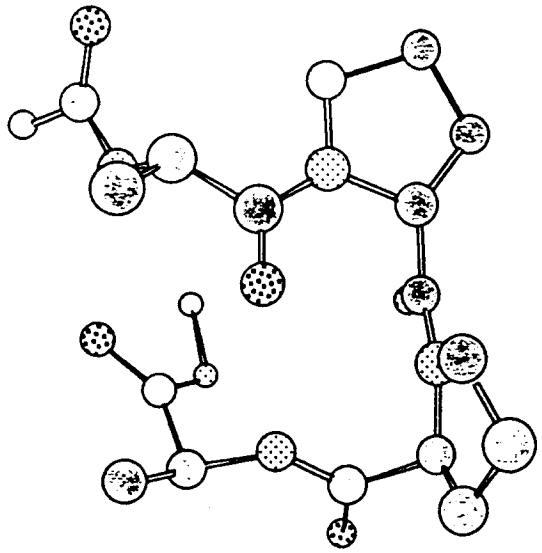
Conformational search using Amber-OPLS

Ac-Ala-HsecPro-Ala-NMe

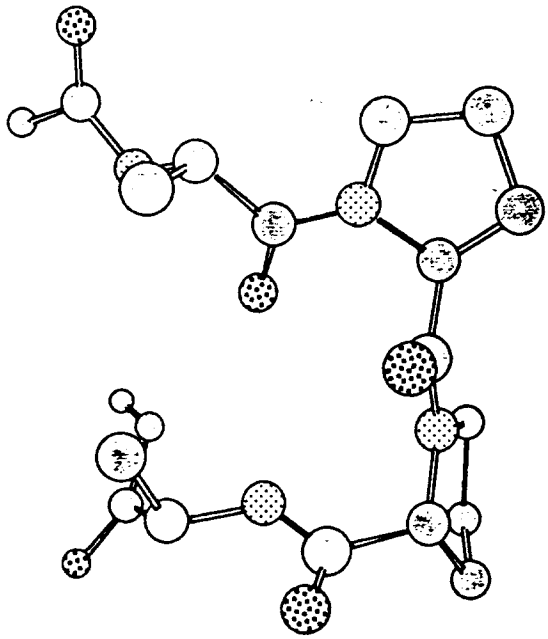




Conformational search using Amber-OPLS

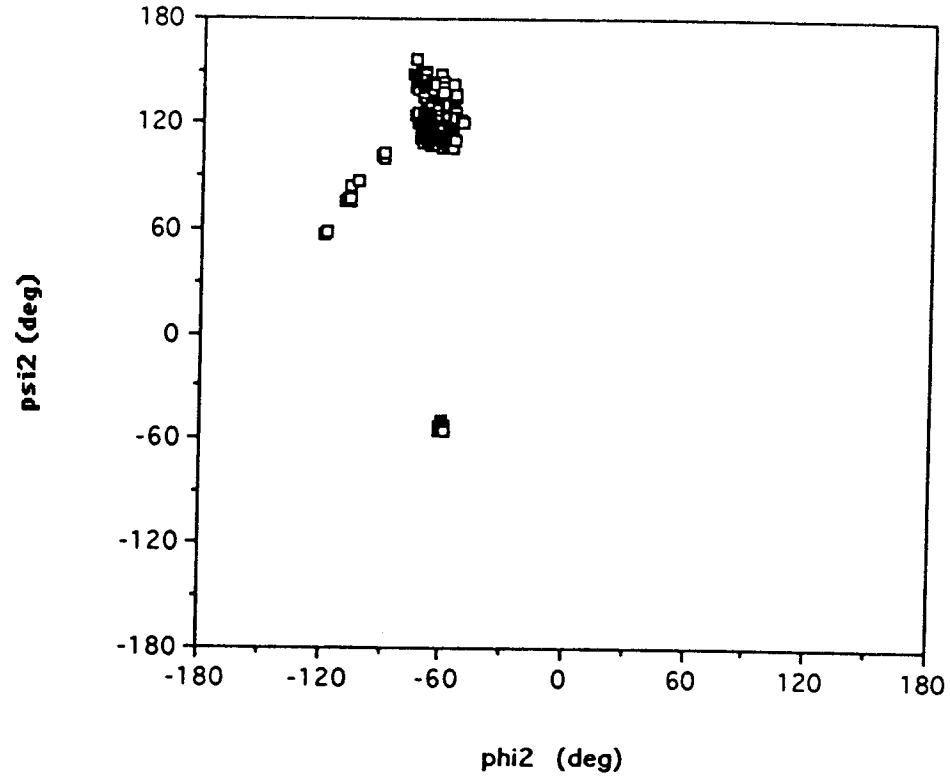


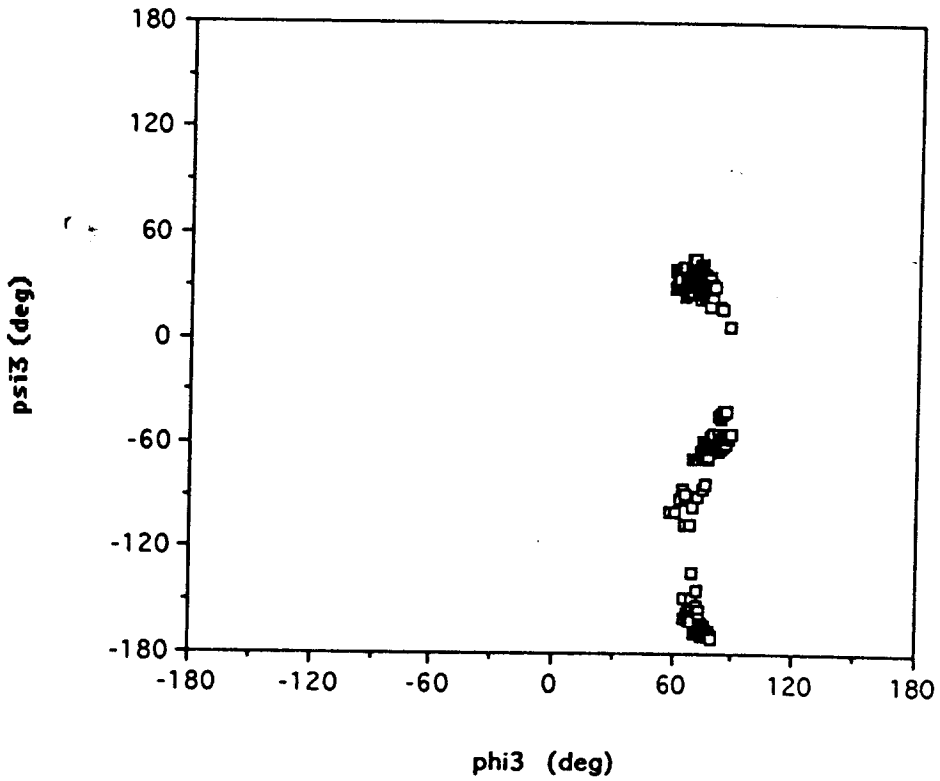
Ac-Ala-DPro-LPro-Ala-NMe Global minimum



Ac-Ala-LPro-DPro-Ala-NMe Global minimum

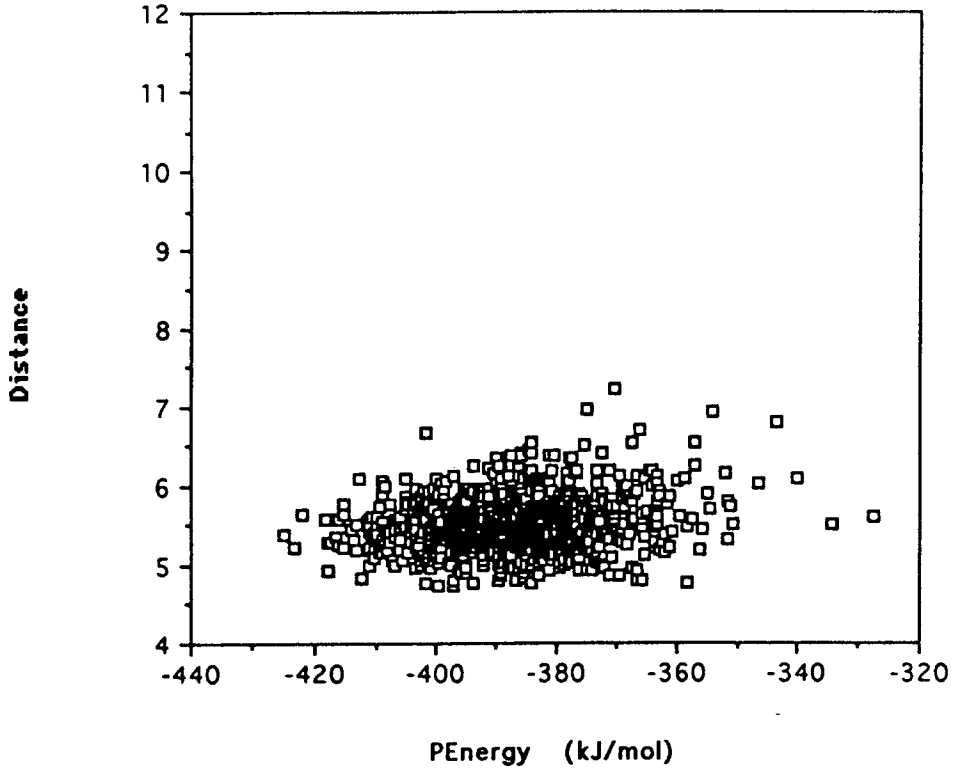
Ac-Ala-LPro-DPro-Ala-NMe

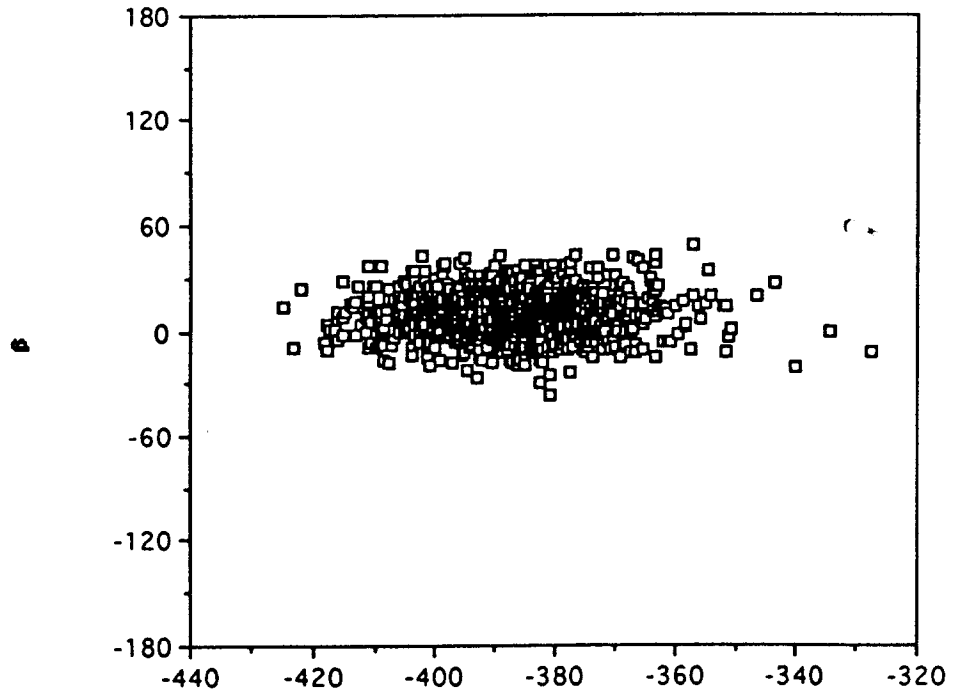




Conformational search using Amber-OPLS

Ac-Ala-LPro-DPro-Ala-NMe

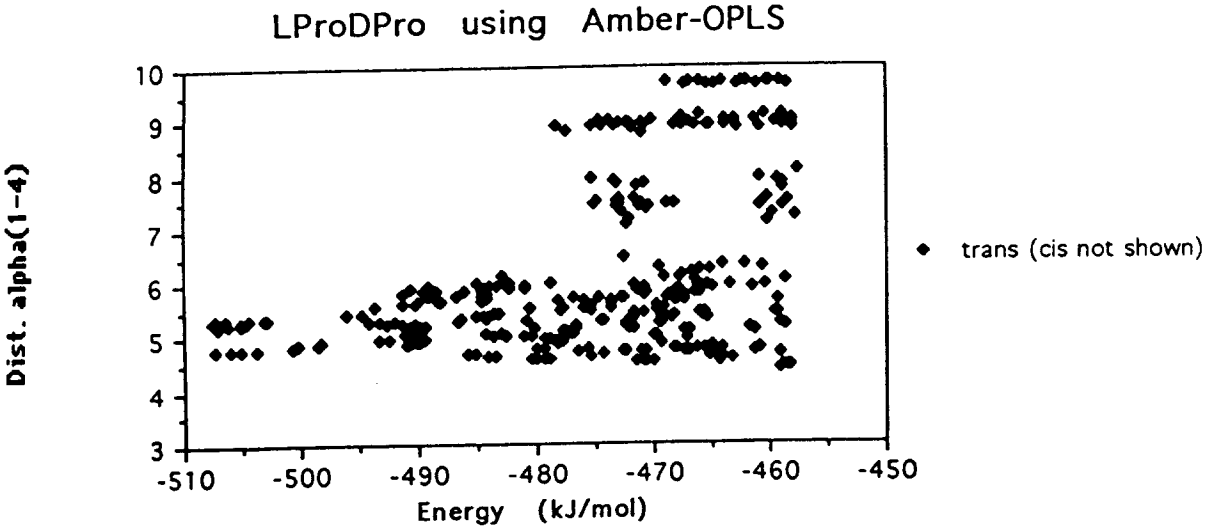


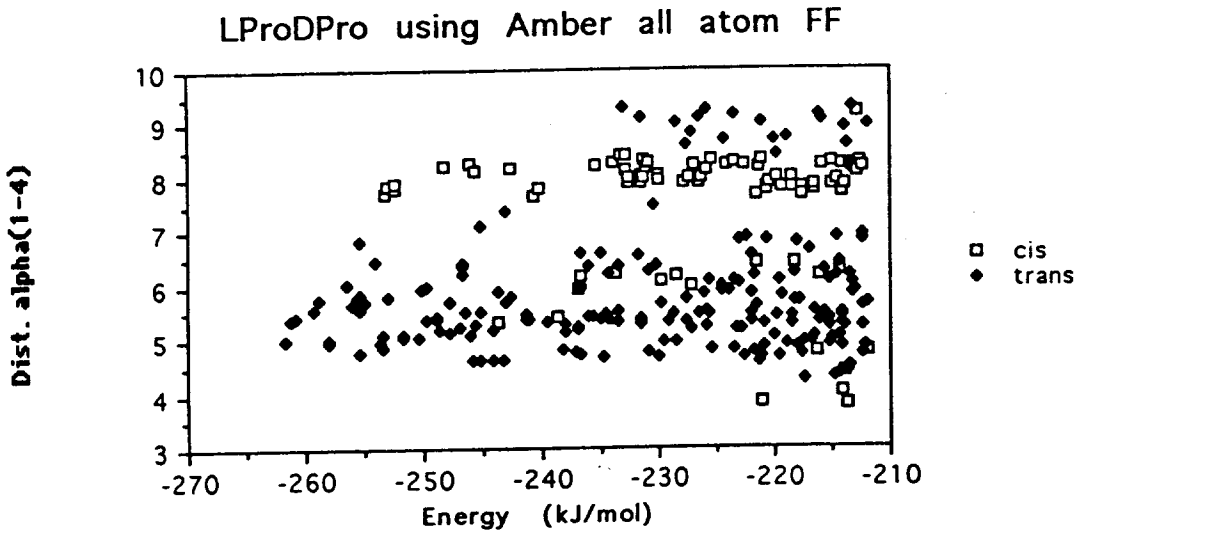


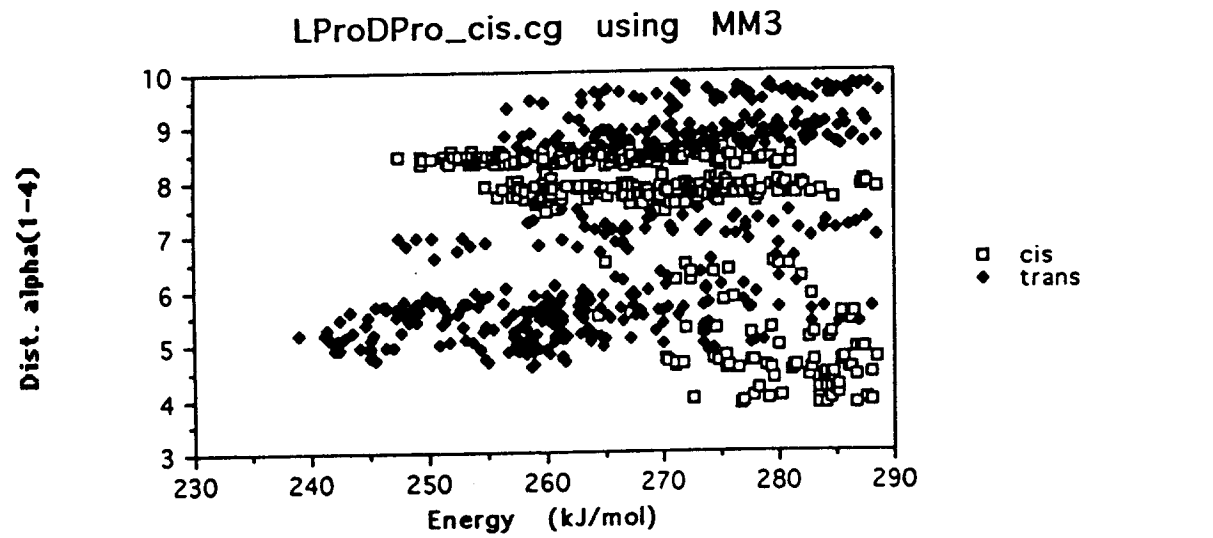
1000 ps MD at 300 K using Amber-OPLS

Energies of ω_2 Cis and Trans Minima

Compound	ΔE cis/trans (kJ/mol)		
	Amber-OPLS	Amber all atom	MM3
LPro-DPro	25.3	8.1	9.0
DPro-LPro	24.5	13.0	14.5


LProDPro using Amber-OPLS
Dist. alpha(1-4)
10
9
8
7
6
5
4
3
-510
-500
-490
-480
-470
-460
-450
Energy (kJ/mol)
trans (cis not shown)


LProDPro using Amber all atom FF
Dist. alpha(1-4)
10
9
8
7
6
5
4
3
-270
-260
-250
-240
-230
-220
-210
Energy (kJ/mol)
cis
trans


LProDPro_cis.cg using MM3
Dist. alpha(1-4)
10
9
8
7
6
5
4
3
230
240
250
260
270
280
290
Energy (kJ/mol)
cis
trans

ACKNOWLEDGEMENTS:

A.) Electrochemistry (Kevin Moeller, Chem.-W.U.)
Fabrice Comeille, CNRS/Paris
Ursula Slomczynska, Polytechnika,Lodz
David Chalmers, Monash U./Melbourne

B.) Chimeric Amino Acids
Steve Kolodziej, UMSL/St. Louis
Rick Skeean, Parke-Davis/Ann Arbor

C.) Angiotensin
Krystina Plucinzka, Gdansk
Wei-Jun Zhang, Shanghai

D.) Molecular Modeling
Gregory Nikiforovich, CMD-W.U.
Takahiro Kataoka, Shionogi/Osaka
Mitsuaki Yodo, Shionogi/Osaka
Mark Smythe, Brisbane
David Chalmers, Monash U./Melbourne

E.) NMR
Denise Beusen, CMD-W.U.
Jeff Kao, Chem.-W.U.

Garland R. Marshall
Center for Molecular Design
Washington University
Sept. 28, 1994