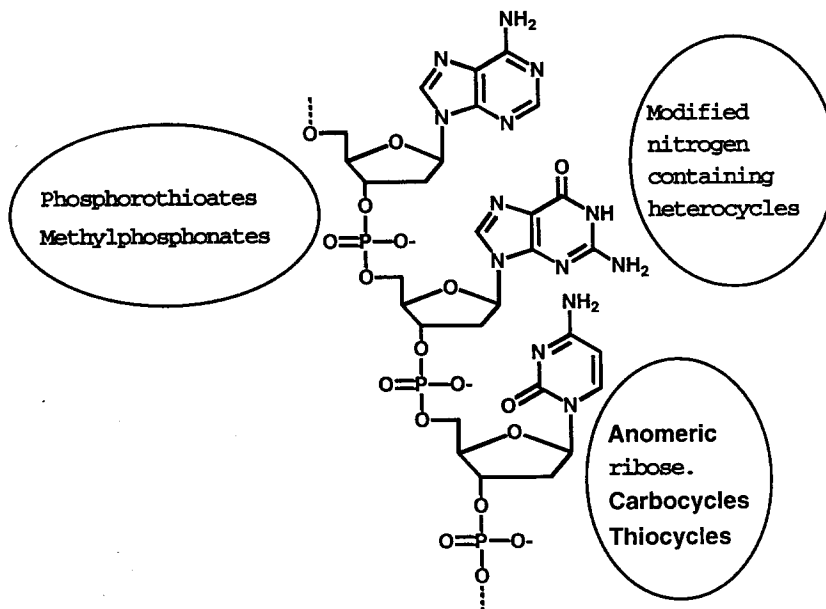
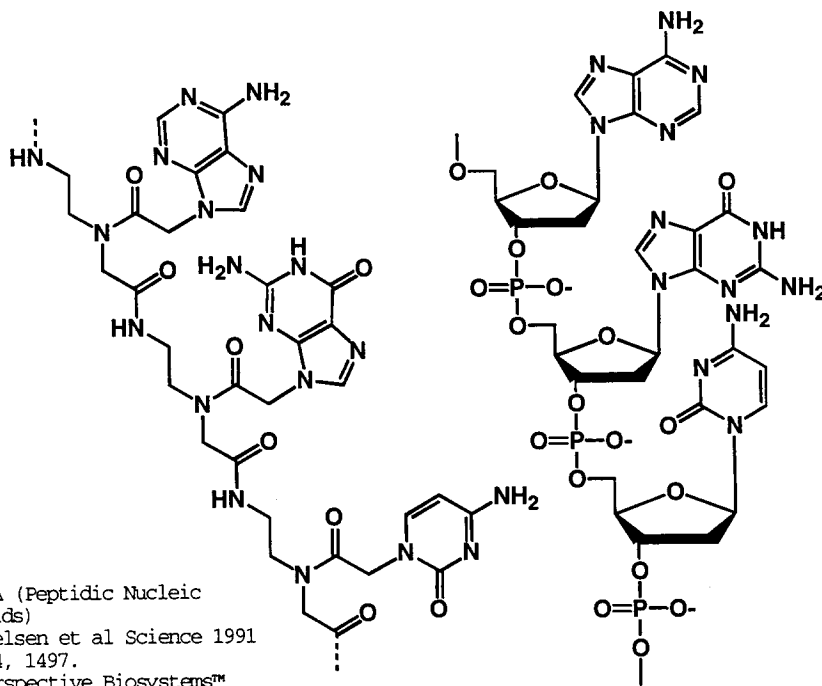


Antisense drugs

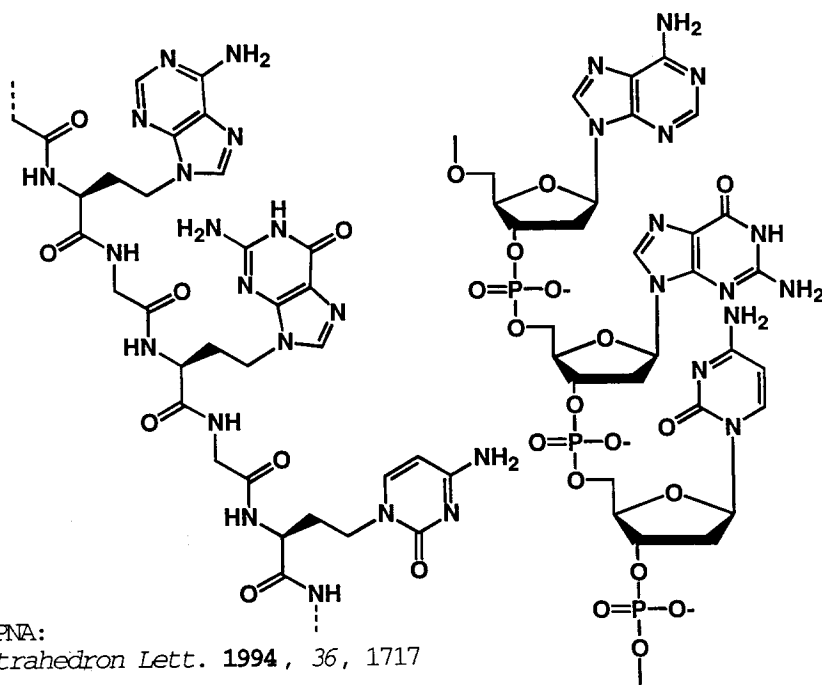
Products	Targets
Antisense Oligonucleotides	Inhibition of t-RNA (translation)
Antigene Oligonucleotides	Inhibition of DNA (transcription)
Antisignature Oligonucleotides	Inhibitor of r-RNA (protein synthesis)

Any oligonucleotide can be designed to target a sequence within the entire genome

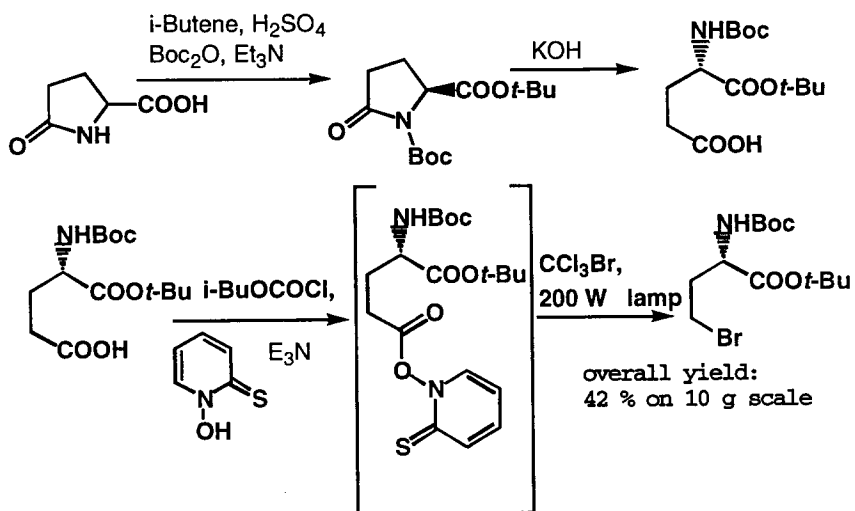




PNA (Peptidic Nucleic
Acids)
Nielsen et al Science 1991
254, 1497.
Perspective Biosystems™

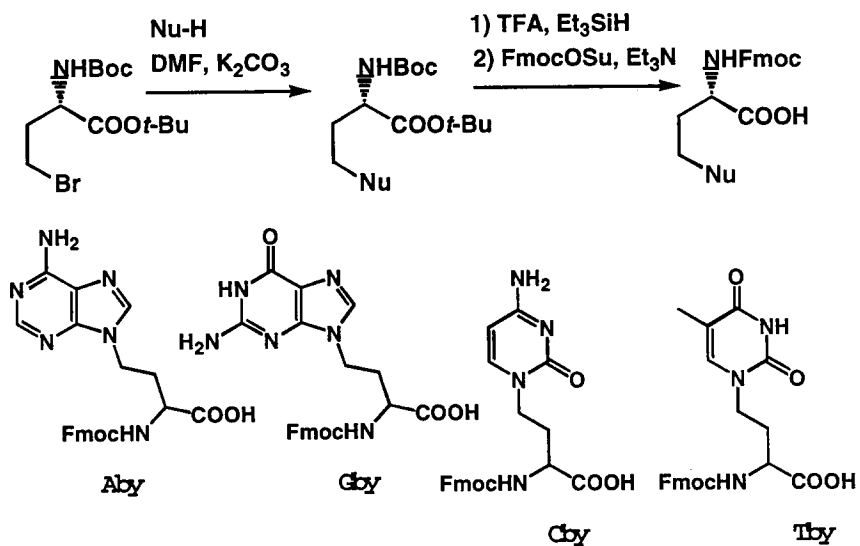


C-PNA:
Tetrahedron Lett. 1994, 36, 1717



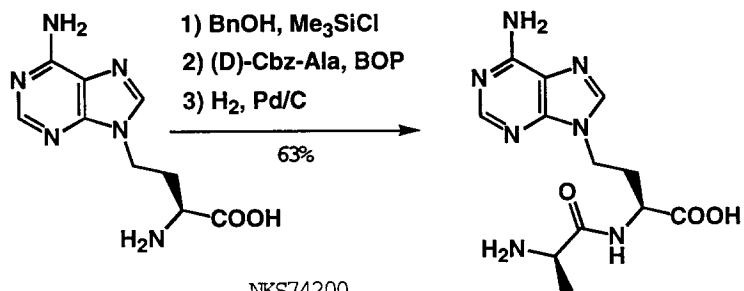
$[\alpha]_D = +10.2$ ($c=1$, CDCl_3)

Molecules Online 1998, 2, 86



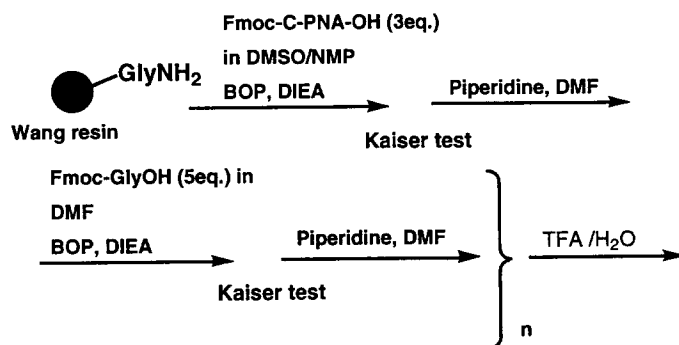
Nucleobase containing amino acids suitable for SPPS

Synthesis of a natural product with antibiotic activity



NKS74200
fungicide metabolite from *Talaromyces* sp.
(Morino et al. *J. Antibiot.* 1995, 48, 1509)

The synthesis of a "real" Peptidic Nucleic Acid



Aby-Gly-Aby-Gly-Tby-Gly-Tby-Gly-Aby-Gly-Aby-Gly

Properties of C-PNA

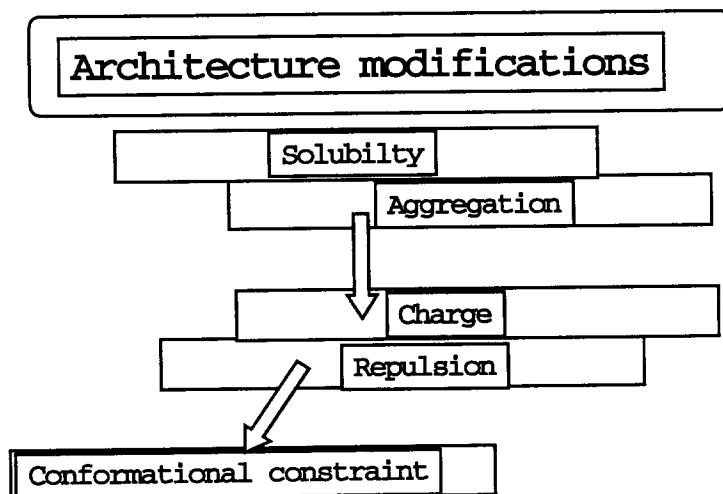
Low solubility in water or buffers

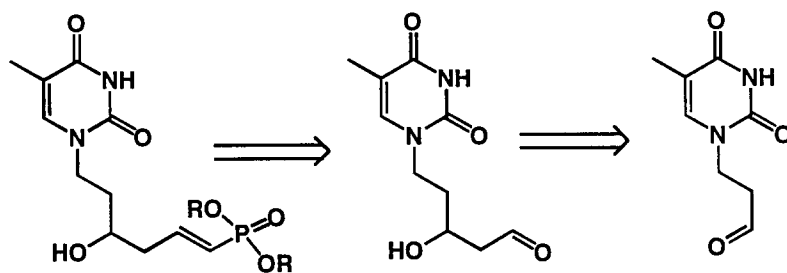
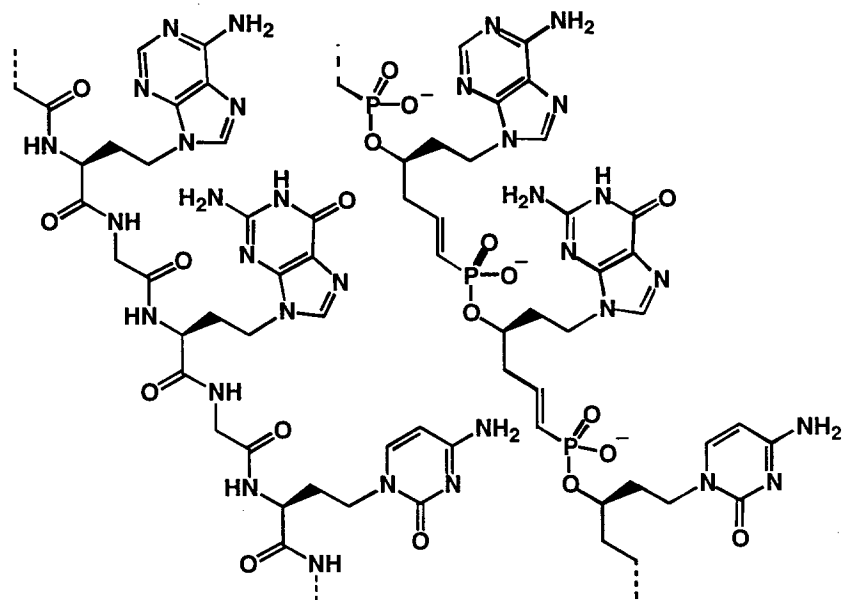
Aggregate in solution in a β -sheet type arrangement

No antisense activity

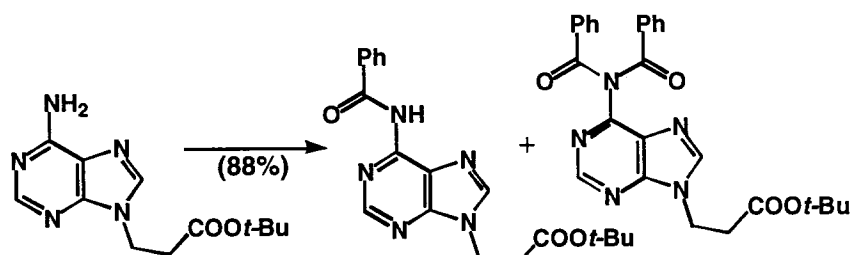
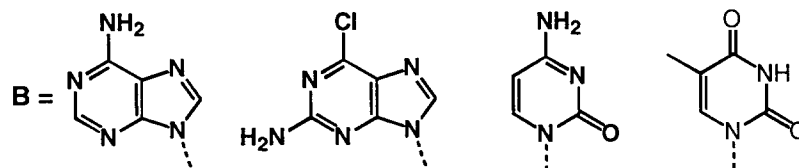
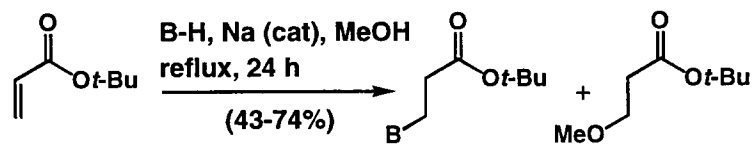
Effective co-ordination activity with Cu(II),
Co(II) and Fe(II).

Inhibition of RNA polymerase and other
nucleoproteines (Zn finger)





Michael-type addition of a nucleobase on

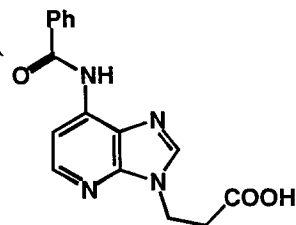


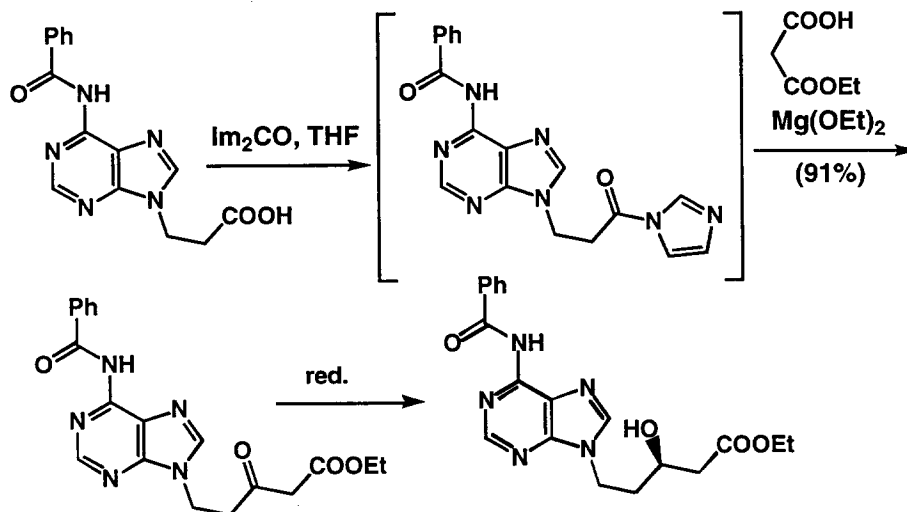
reaction conditions

reaction conditions	ratio
PhCOCl / Py: 2.5 / 10	30 / 70
PhCOCl / Py: 1 / 10	30 / 70
(PhCO) ₂ O / Py: 1.5 / 10	90 / 10
PhCOCl / Py : 1 / 10 in CH ₃ CN	95 / 5

HCl/EtOAc

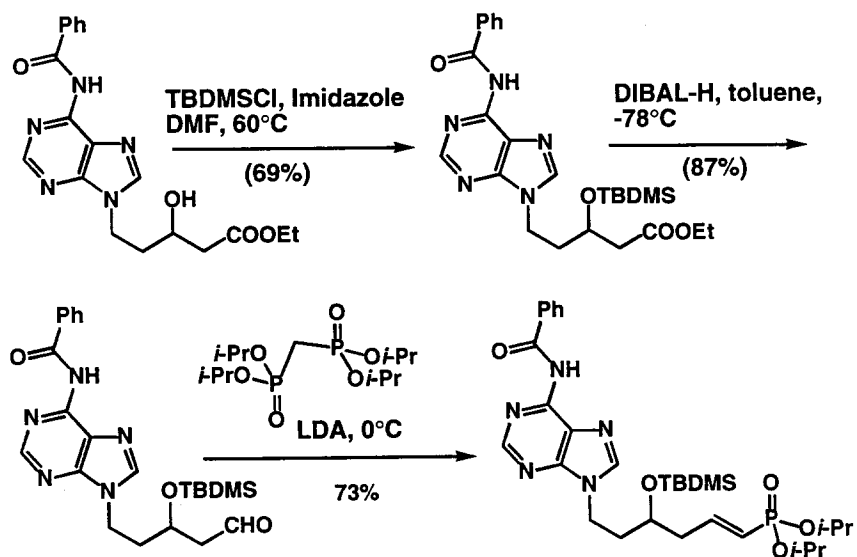
(84%)

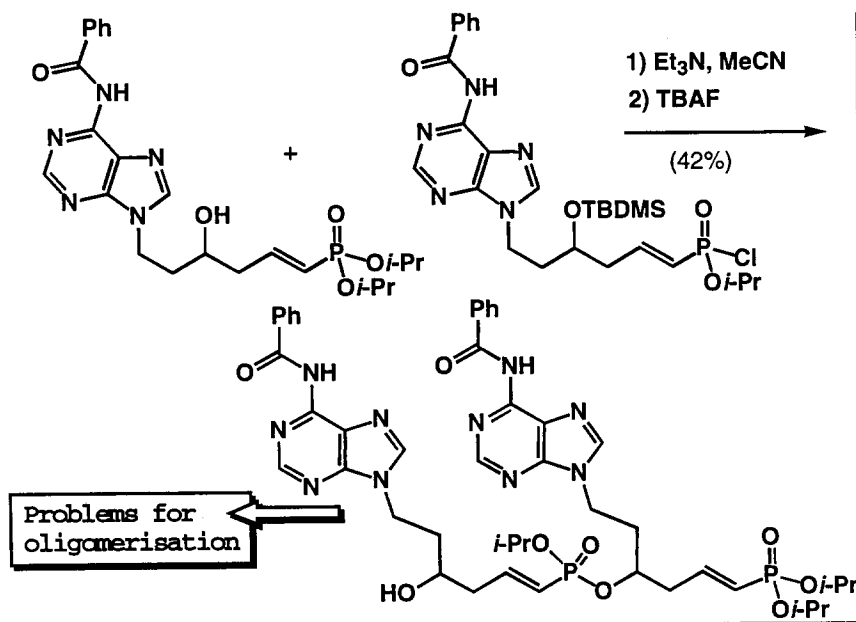
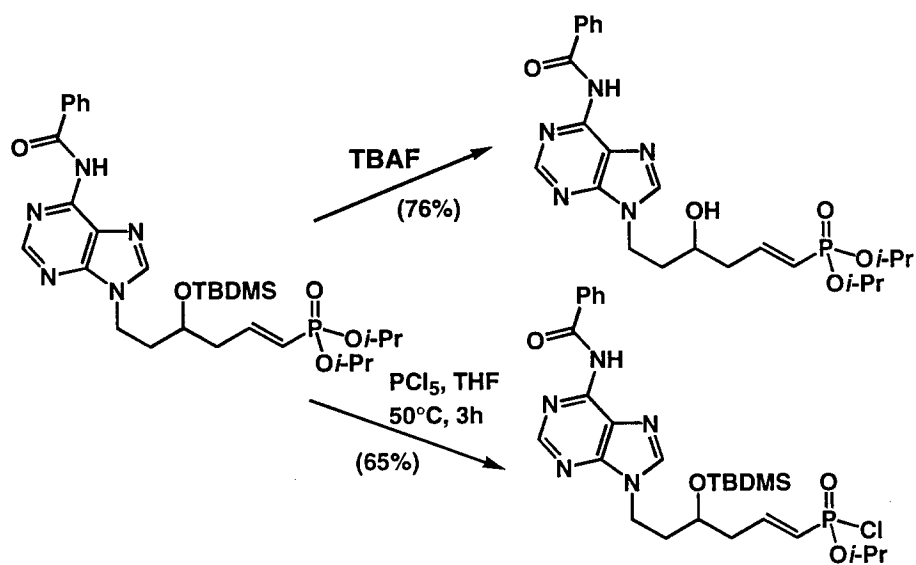


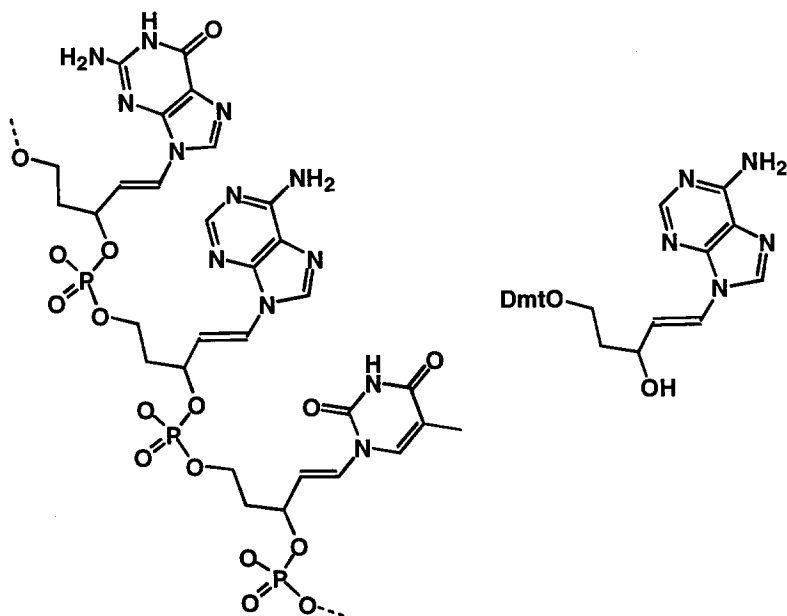
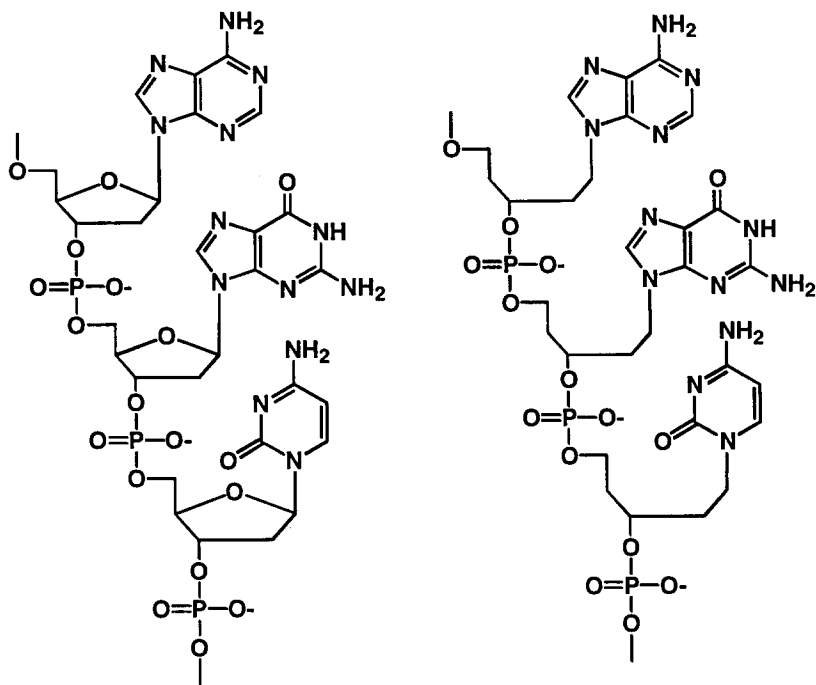


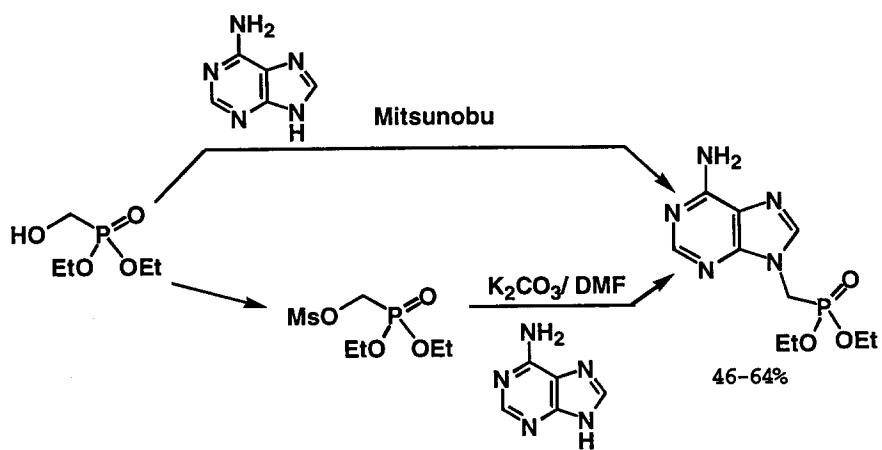
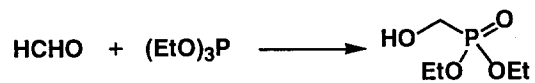
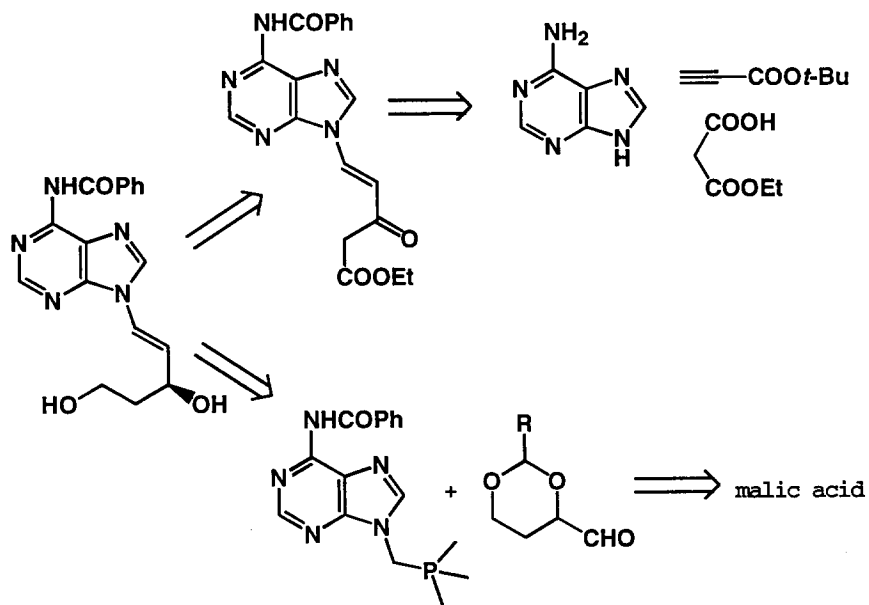
H_2 , (R)-(BINAP)RuBr₂, 80°C,
Parr apparatus, 79% (95% ee HPLC)

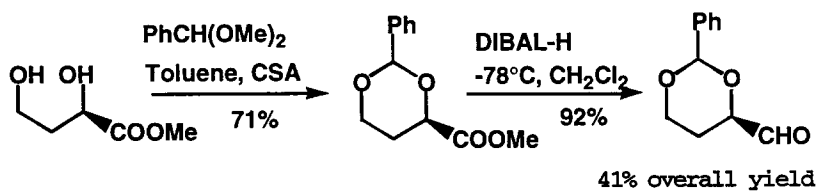
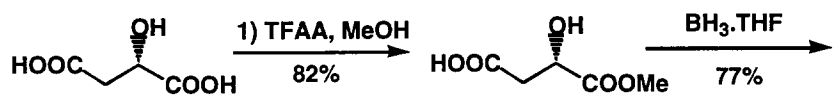
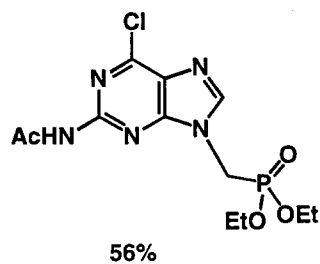
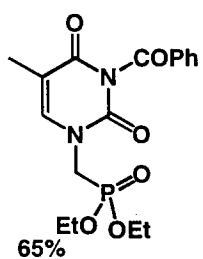
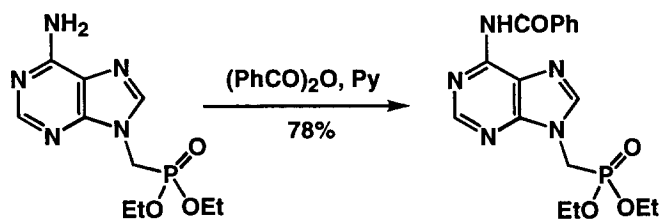
J.P.Genet et al *Tetrahedron Lett.* 1995, 36, 4801

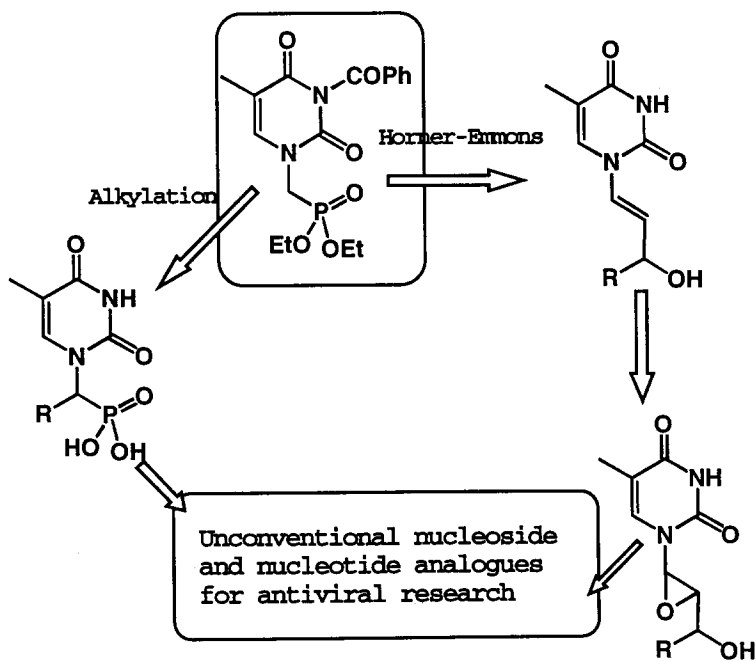
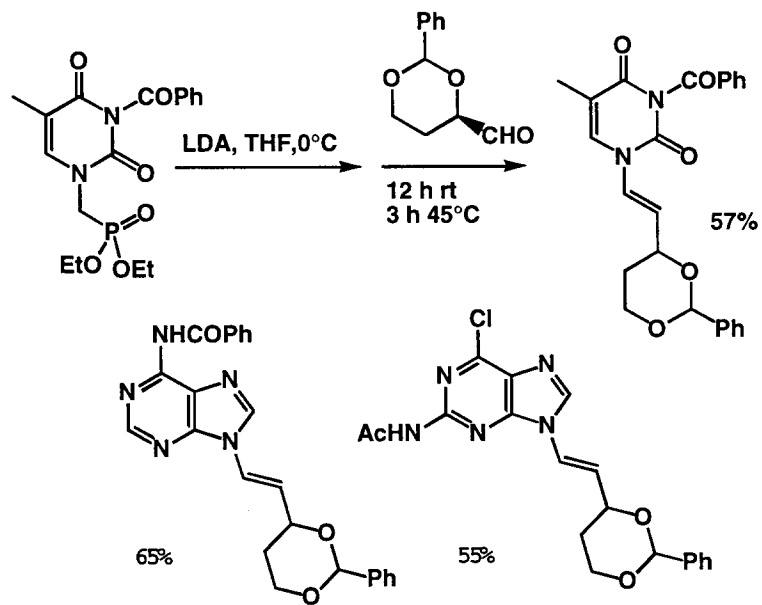


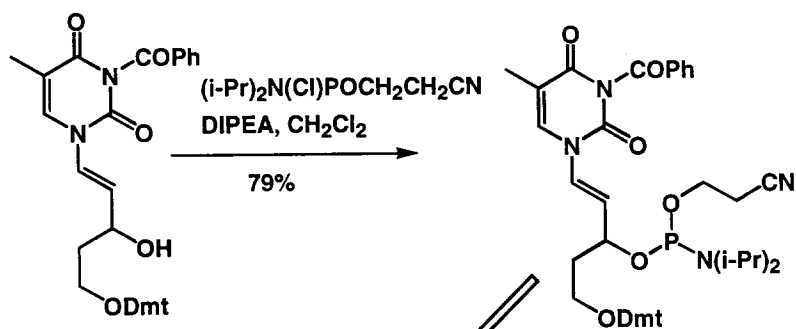
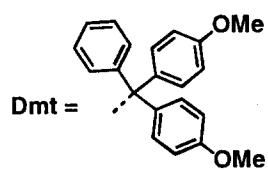
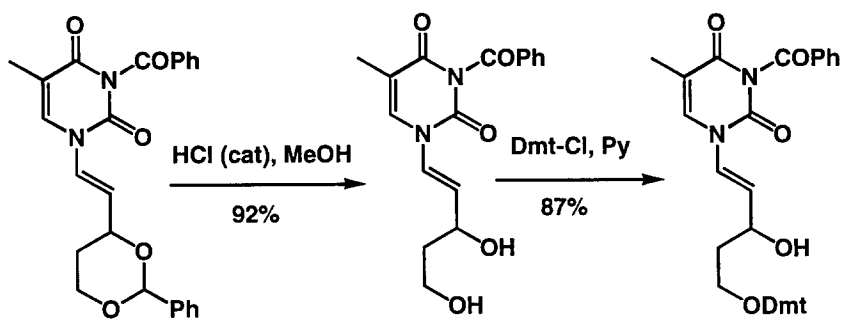




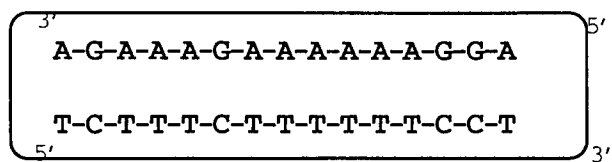








Phosphoramidate suitable
for standard
oligonucleotide synthesis



$T_m = 49^\circ\text{C}$

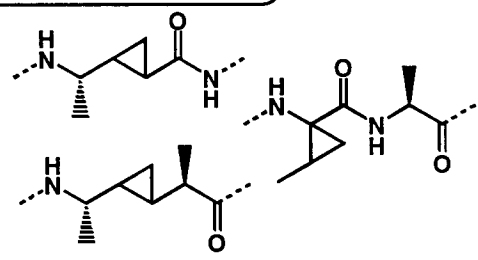
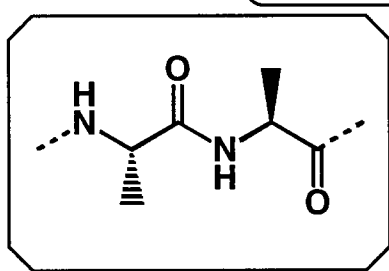
$T_m(1), T_m(15) = 48^\circ\text{C}$

$T_m(8), T_m(9) = 50^\circ\text{C}$

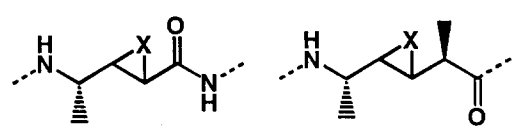
$T_m(8-10) = 44^\circ\text{C}$

The introduction of the new oligonucleotides confers to the strand a binding capacity comparable with conventional ODN

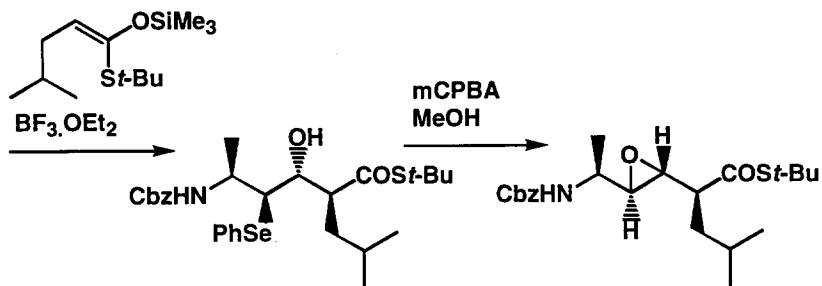
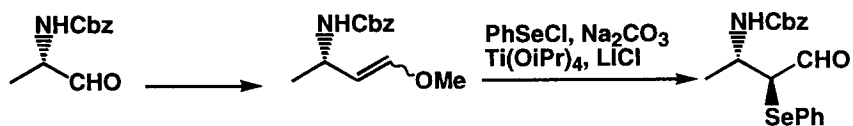
Peptidomimetics



Small ring containing peptidomimetics

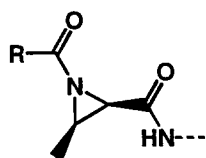


Constrained heterocyclic peptidomimetics

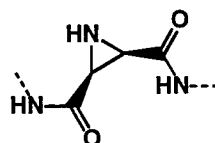


Tetrahedron Lett. 1996, 37, 2651.

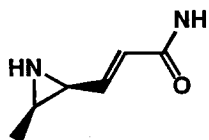
Aziridine peptidomimetics



Goodman, M. et al.
Chem. Biol. 1994, 1, 231

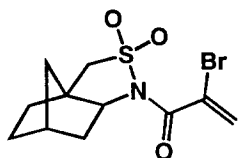
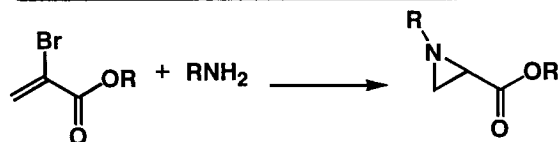


Jones, B.J. et al.
J. Med. Chem. 1995, 38, 3078
Prati, F. Moretti, I et al.
J. Org. Chem. 1997, 62, 8784

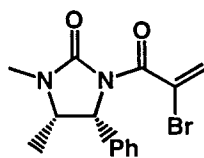


Wipf, P. et al.
J. Org. Chem. 1997, 62, 1586

The Gabriel-Cromwell reaction

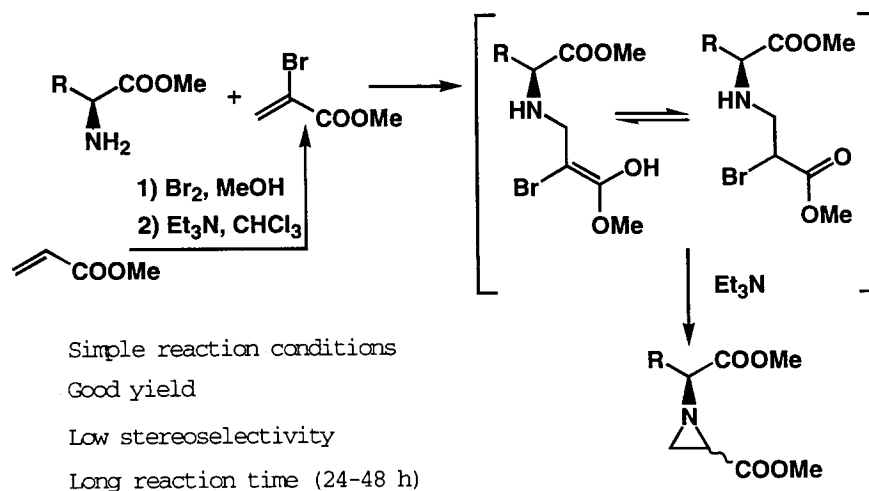


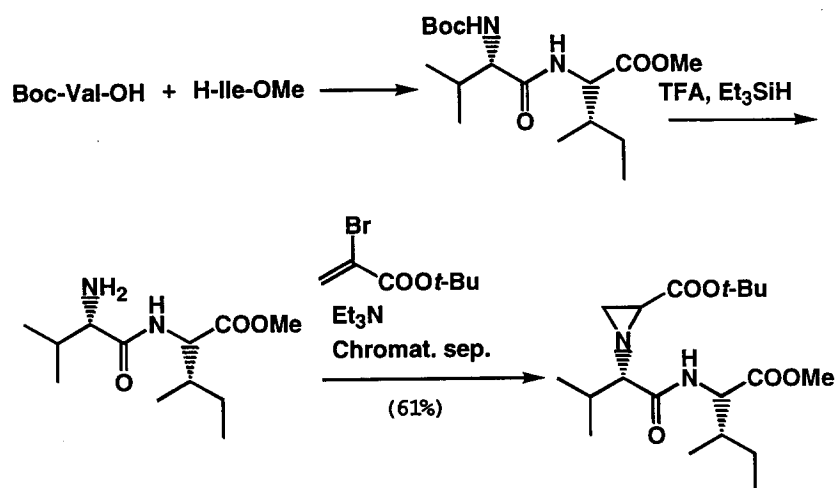
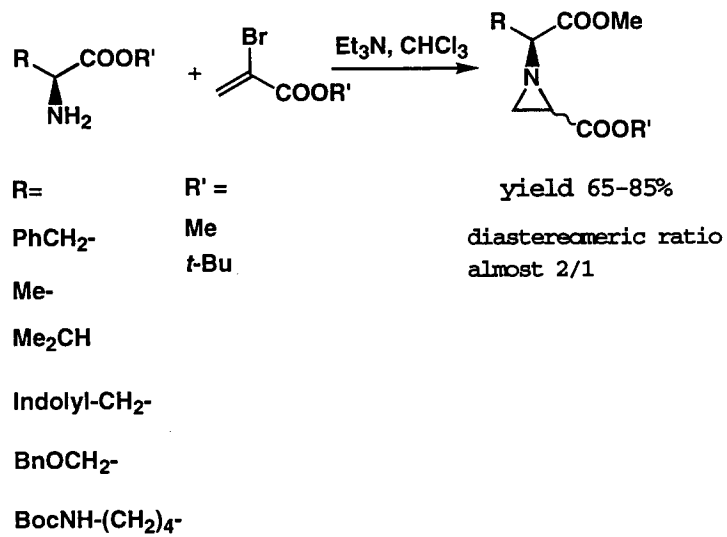
Garner P. et al.
Tetrahedron Lett. 1994, 35, 1653

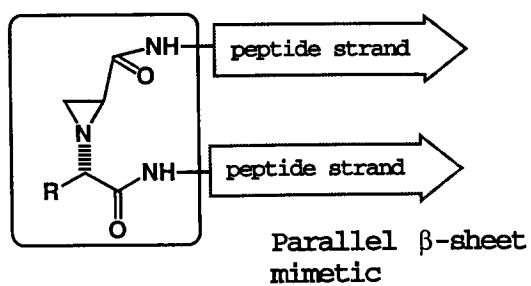
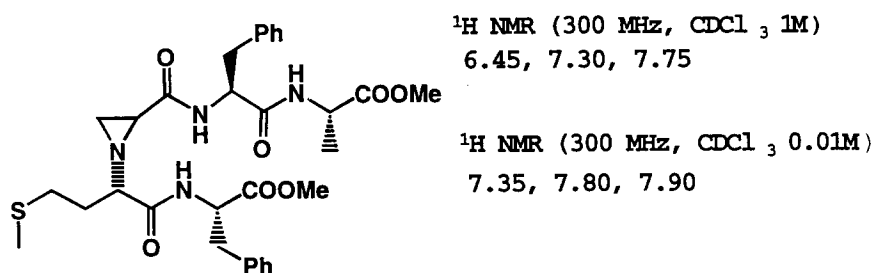
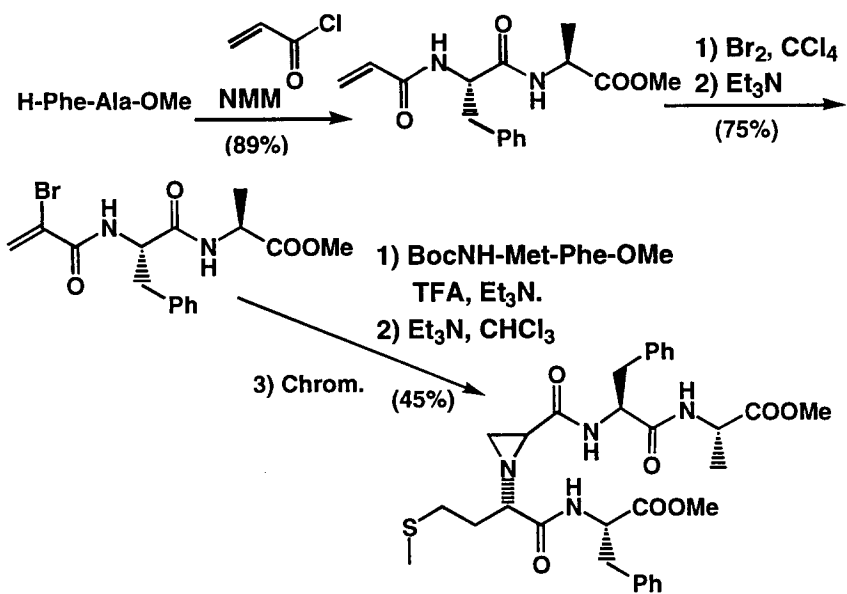


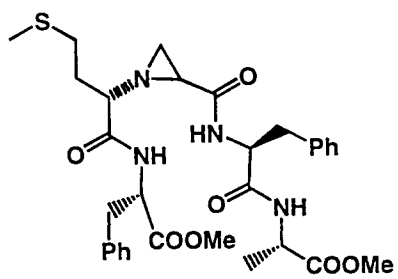
Cardillo, G. et al.
Tetrahedron Asymmetry, 1996, 7, 755

The Gabriel-Cromwell reaction for the synthesis of aziridine containing peptidomimetics

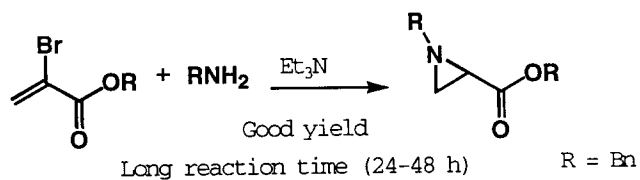




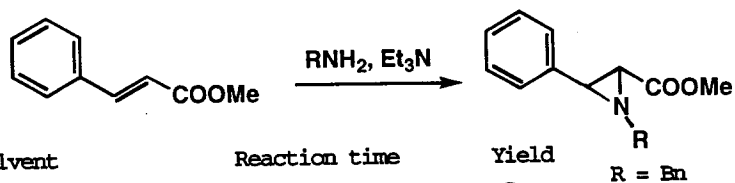




Local minimum energy
conformation

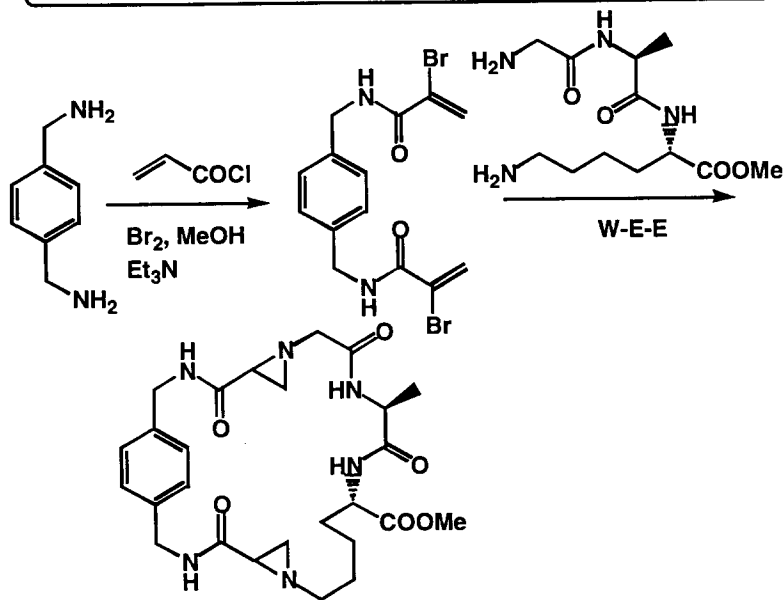


Solvent	Reaction time	Yield
CDCl ₃	24 h	76%
Acetone	24 h	50%
DMF	8 h	61%
DMSO	4 h	76%
EtOH	4 h	60%
H ₂ O	4 h	89%

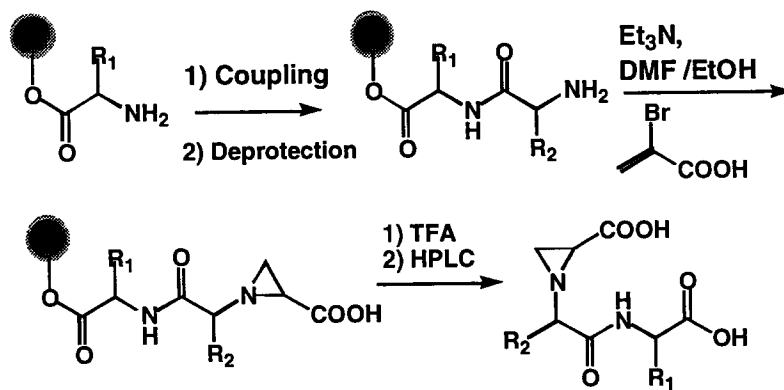


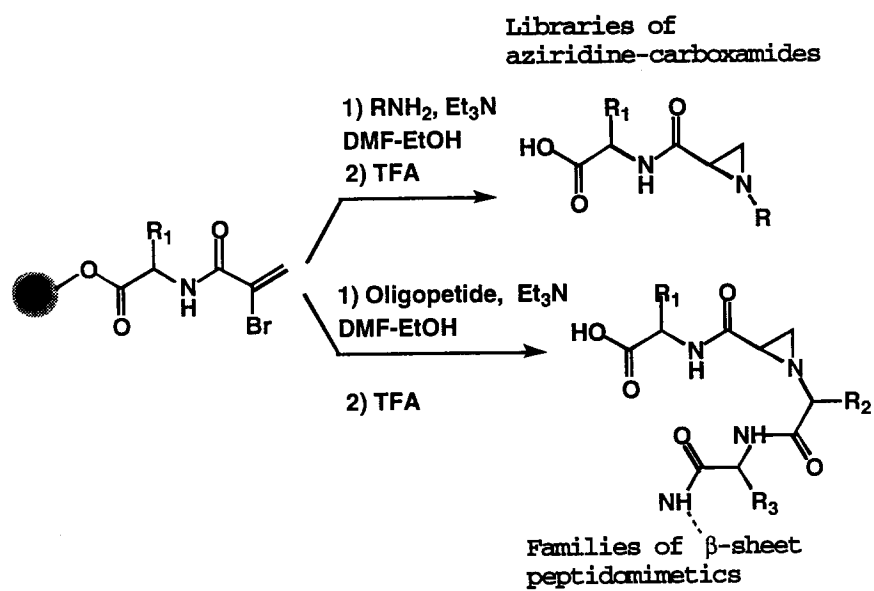
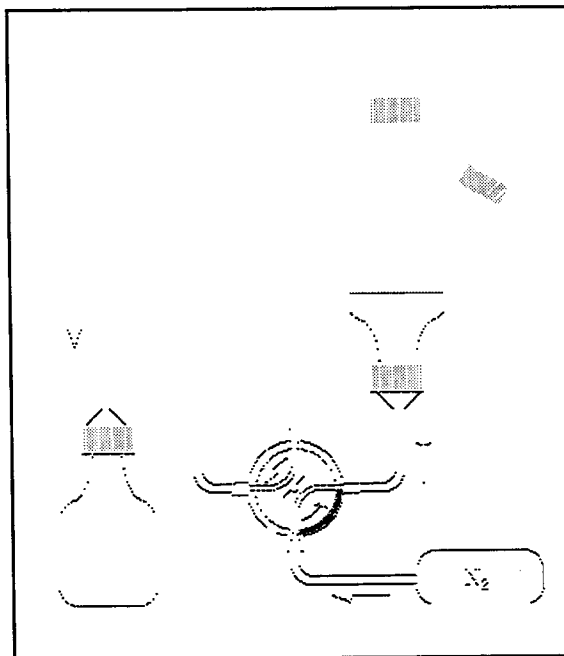
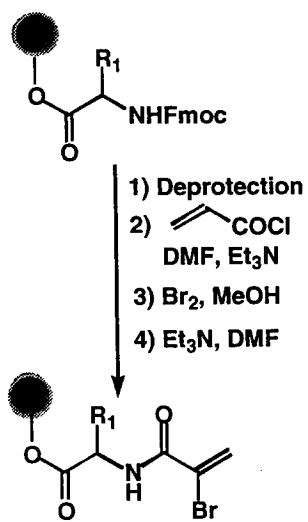
Solvent	Reaction time	Yield	
CDCl ₃	106 h	6%	
DMF	106 h	0%	
DMSO	14 h	46%	
EtOH	14 h	13%	
H ₂ O	14 h	39%	
H ₂ O - EtOH 2/1 1M 60°C		6 h	75%

The Water-Ethanol-Ether system

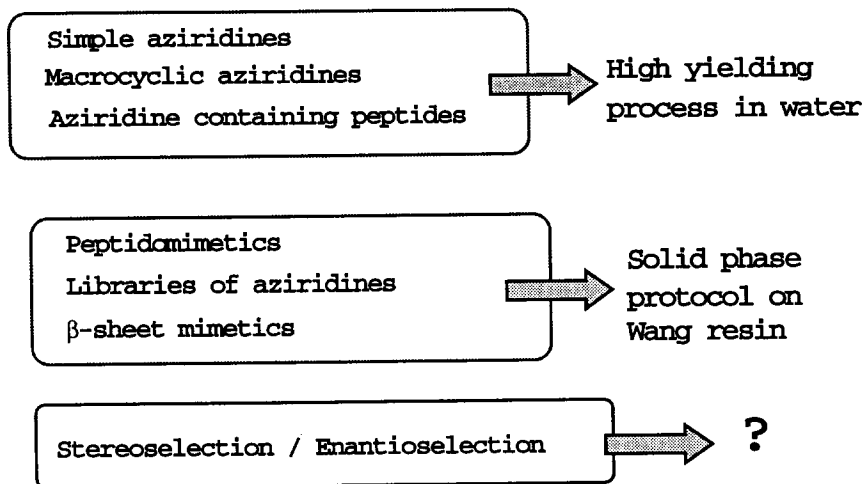


The Gabriel-Cromwell reaction on solid phase





Gabriel-Cromwell reaction



University of Sassari
Professor Giampaolo Giacomelli
Simo Falorni
Alghero
Pepetti
Grazia Esposito
Grazia Perino
Filigheddu
Grazia Masala
Ledda
Andro Falchi
Luisella Ruiu
Mariangela Demarcus

Dr. Mario Pirastu
Dr. Carla Rozzo
Institute of Molecular
Genetics, CNR, Alghero

Dr. André Mann
Dr. Elisabeth Trifilieff
CNRS, Strasbourg

M.U.R.S.T
C.N.R.
Regional Council of
Sardinia
Consorzio
Porto Conte Ricerche