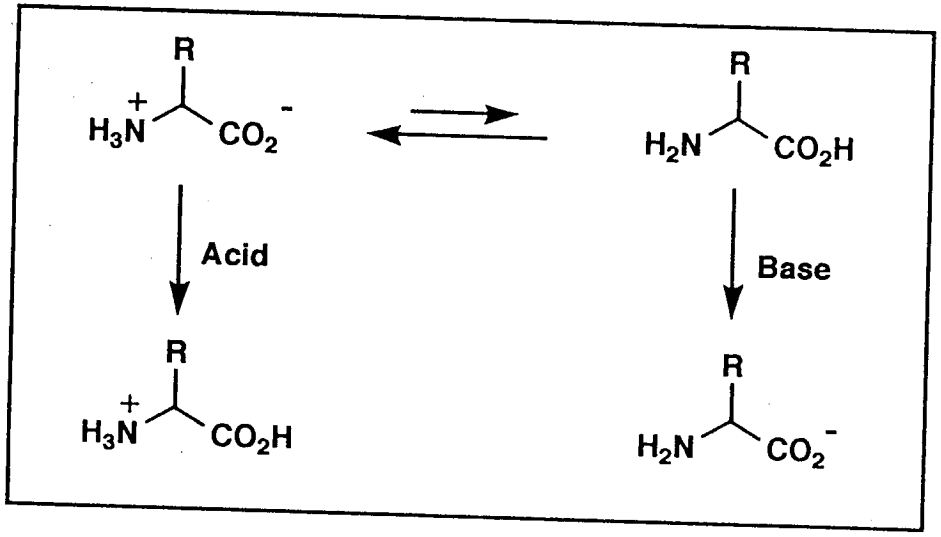
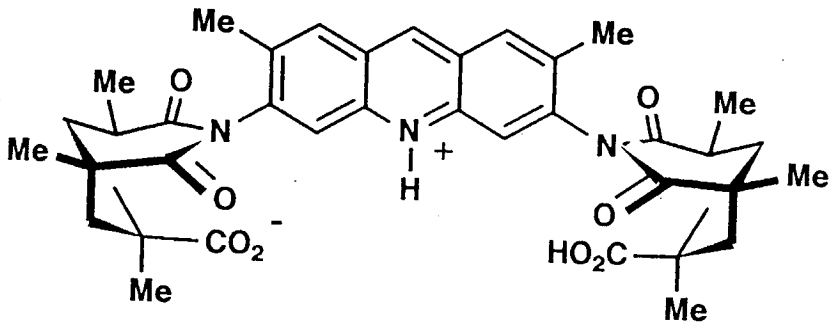
DESIGN FOR MOLECULAR RECOGNITION: Playing around the Target

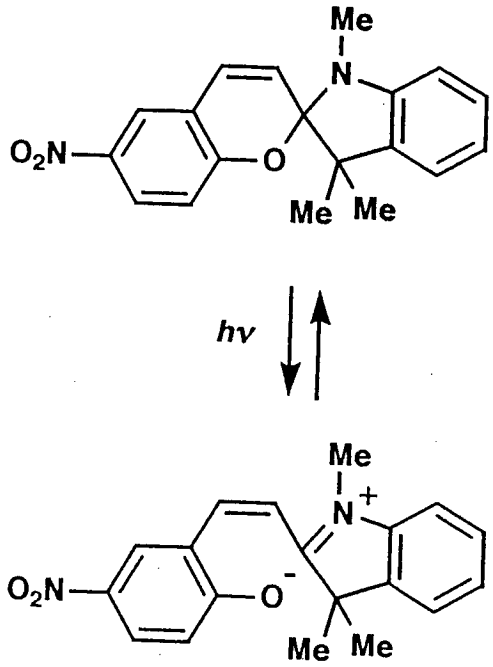
Example: Free Amino Acids (Zwitterion Recognition)



- √ • Binding site for ammonium
- √ • Binding site for carboxylate (non complementary)
- √ • Lateral chain recognition
- √ • Chirality



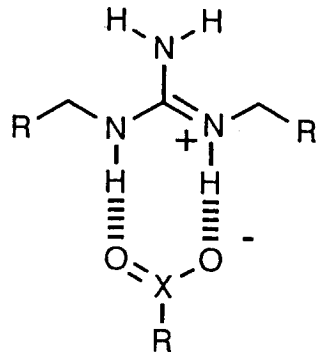
J. Rebek, Jr. *et al., J. Am. Chem. Soc.*. **1985**, *107*, 6738; *ibid.*, **1987**, *109*, 2432.



J. Sunamoto *et al.., J. Am. Chem. Soc.* **1982**, *104 5502.*

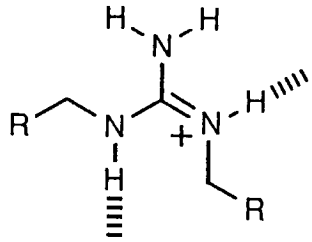
Bicyclic Chiral Guanidinium Anion Receptors

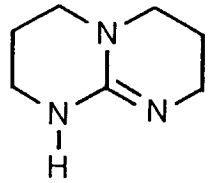
Convergent zwitterionic H-bonds



X = C , P, S ...

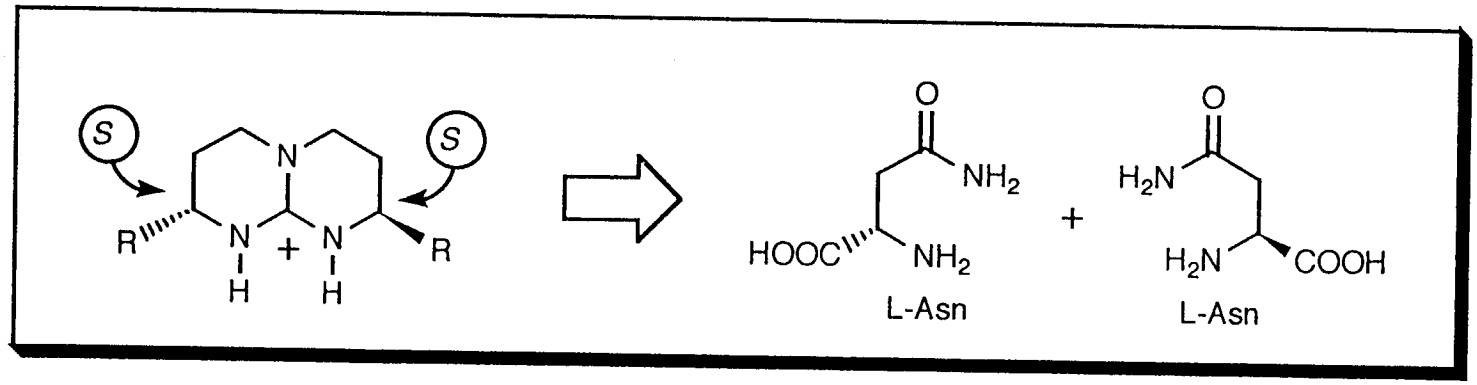
Divergent zwitterionic H-bonds





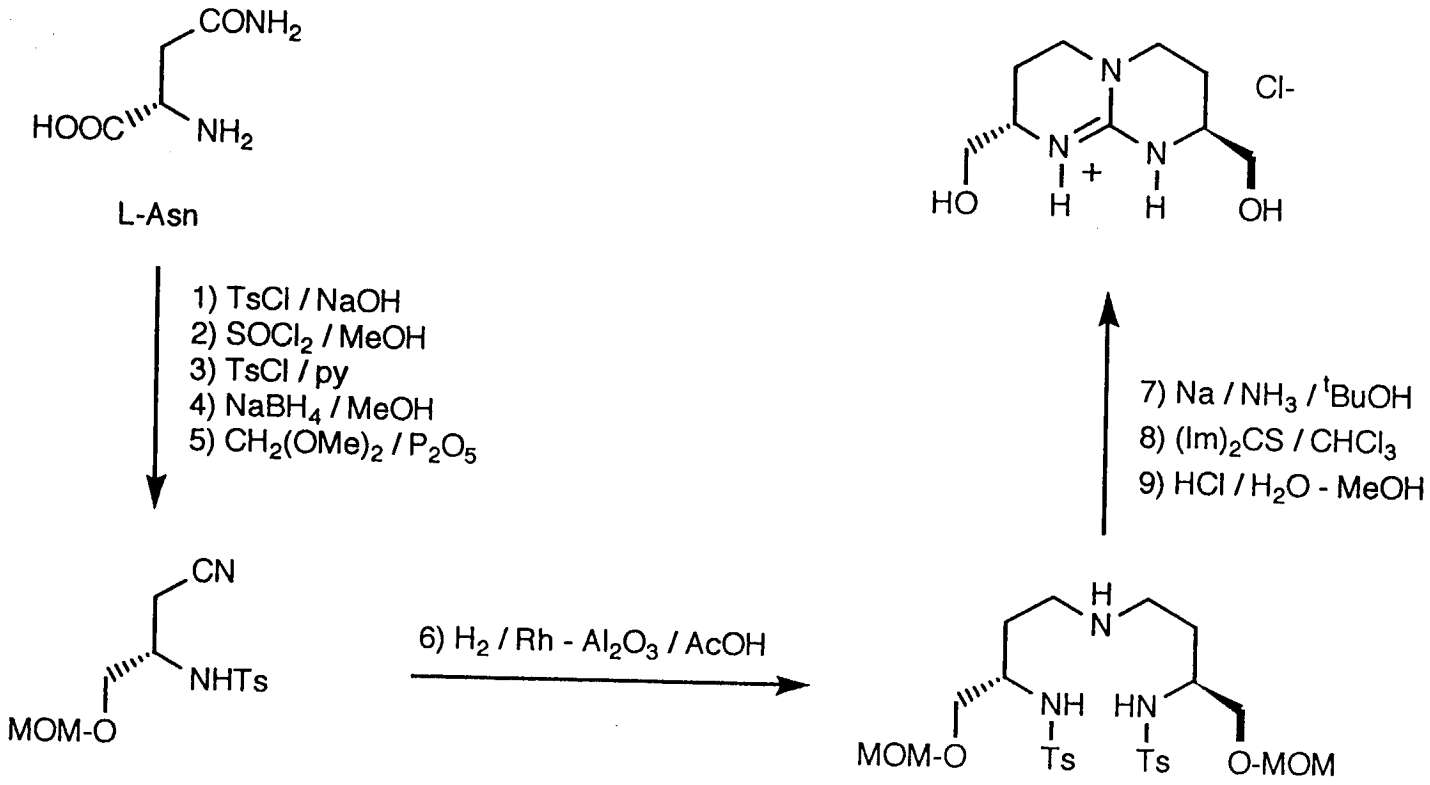
1,5,7-Triazabicyclo[4.4.0]dec-5-ene

($) *Aldrich*



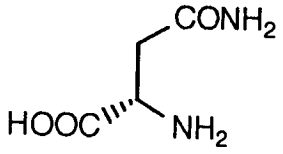
The Triamine Route (1988)

(9 Steps, overall yield 4%)



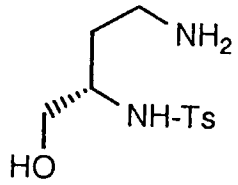
The Thiourea Route (1990)

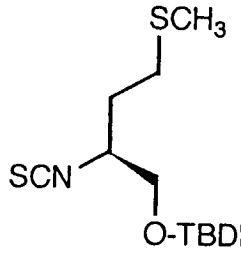
(9 Steps, overall yield 46 %)



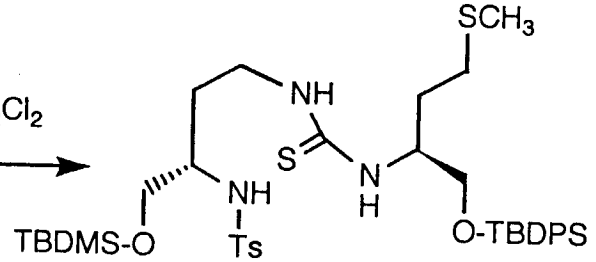
L-Asn

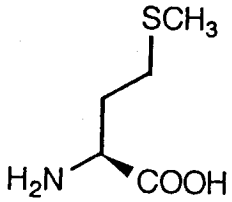
1) $TsCl$ / $NaOH$ / Me_2CO
2) $LiBH_4$ / $TMSCl$





6) a) Δ / CH_3CN
b) $TBDMSCl$ / Im / CH_2Cl_2

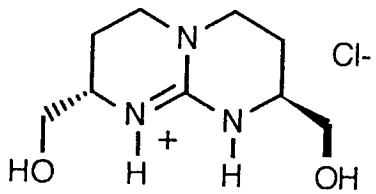




L-Met

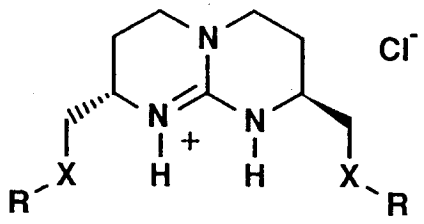
3) $BH_3 . Me_2S$ / THF
4) $TBDPSCl$ / Im / CH_3CN
5) Cl_2CS / Na_2CO_3 / H_2O - CH_2Cl_2

7) $TfOMe$ / Et^iPr_2N / CH_2Cl_2
8) a) $Al(Hg)$ / H_2O / THF
b) NH_4Cl
9) HCl / H_2O - CH_3CN

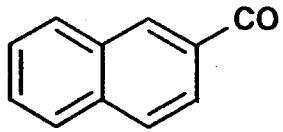


H. Kurzmeier and F.P. Schmidtchen, *J. Org. Chem.* **1990**, *55*, 3749.

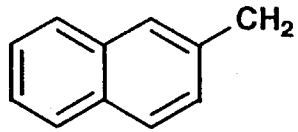
Some Symmetric guanidines



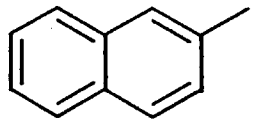
R =



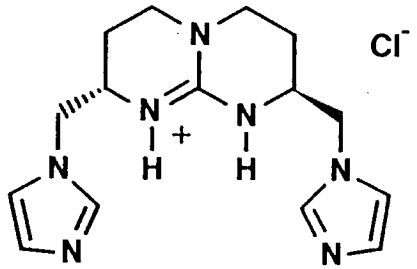
X = O, NH

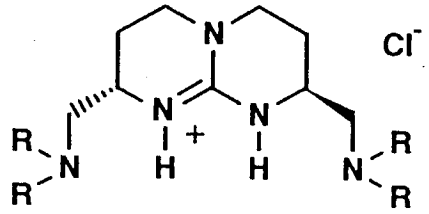


X = S



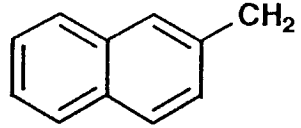
X = O, S



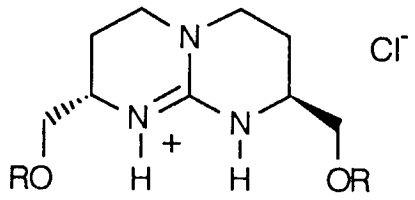


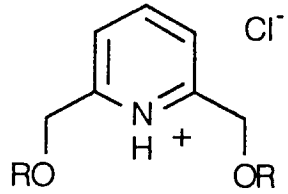
R = H

R =



Relative Influences of Stacking and Salt Bridge on Selectivities





% Extractions

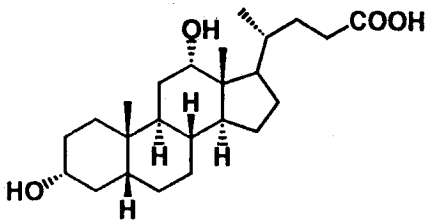
Oxoanion	R = palmitoyl	R = 2-naphthoyl		R = 2-naphthoyl
AcO^-	44	51		<5
N-Ac-L-Val^-	40	46		<5
(p)O_2N-$C_6H_4COO^-$	84	100	(1)	68
(p)CH_3O-$C_6H_4COO^-$	61	100		73
N-Ac-L-Trp^-	54	100	(2)	<5
N-Ac-D-Trp^-	60	99	(3)	<5
N-Ac-L-Phe^-	58	86		<5
N-Ac-D-Phe^-	59	89		<5

Determined by ^{1}H-NMR integration (± 5 % error) of the extraction of equimolar amounts of carboxylate sodium salts (D_2O) by receptors ($CDCl_3$)

K_s (^{1}H-NMR saturation method): (Gu^+Cl^- + Et_3NH^+carboxylate$^-$)

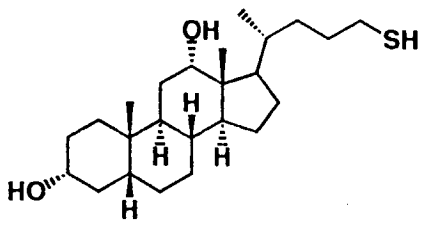
(1) 1609 (± 12 %)
(2) 1051 (± 19.3%)
(3) 534 (± 15.6%)

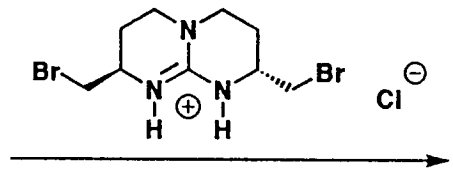
Molecular Recognition of Glucuronic Acid



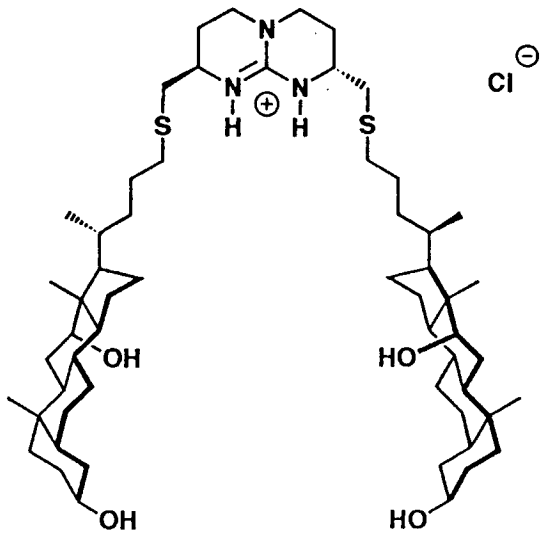
Deoxycholic acid

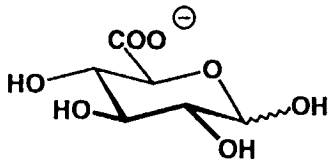
1. Ac_2O , py (76 %)
2. BH_3 . THF (78 %)
3. NBS , Ph_3P (68 %)
4. $(NH_2)_2CS$, NaOH (70 %)



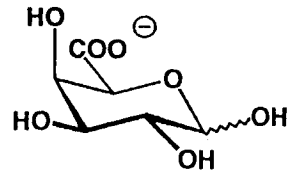


NaOMe , MeOH (41 %)



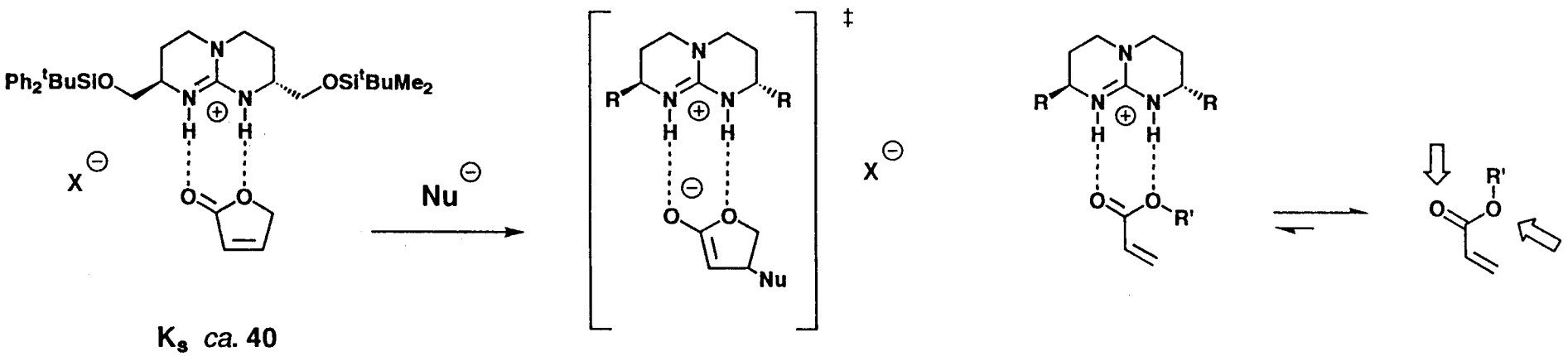


Glucuronate Ks > 10000



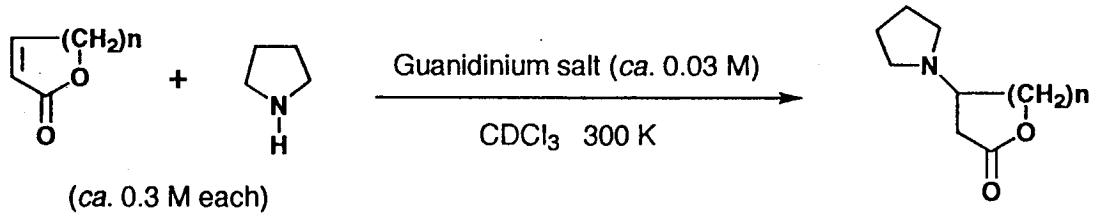
Galacturonate Ks = 210 (± 10%)

Transition State Stabilization in Michael Additions



K_s *ca.* 40

Model Reaction:

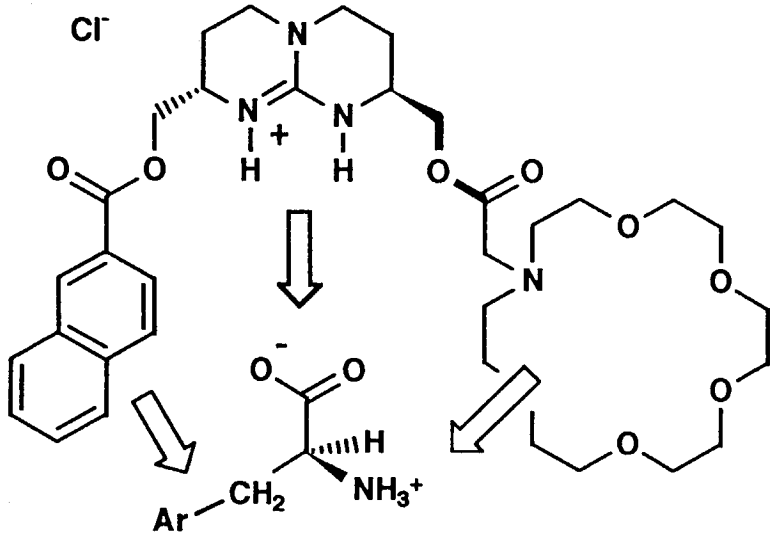


(*ca.* 0.3 M each)

n	$X^{\ominus}$	$t_{1/2}$ (min)
1	blank	267
1	chloride	138
1	tetrafluoroborate	58
2	blank	206
2	tetrafluoroborate	30

i) Catalysis was <u>inhibited</u> by tetrabutylammonium 4-nitrobenzoate
ii) Significant rate enhancements were <u>not</u> observed for methyl acrylate or methyl crotonate

A Molecular Receptor for Amino Acids Under Neutral Conditions



- √ • Non-complementary Binding Sites for Ammonium and Carboxylate
- √ • Side-chain Recognition (Stacking)
- √ • Chirality (C_2 axis; Both Enantiomers Available)
- √ • Lipophilicity (Extraction)

Side Chain Selectivities *(Amino Acid Analysis)*

Mixture of 3 Amino Acids

	Concentration (nm/50µl)	Ratio
Phe	9.4396	100
Trp	9.1257	97
Val	0.6101	6

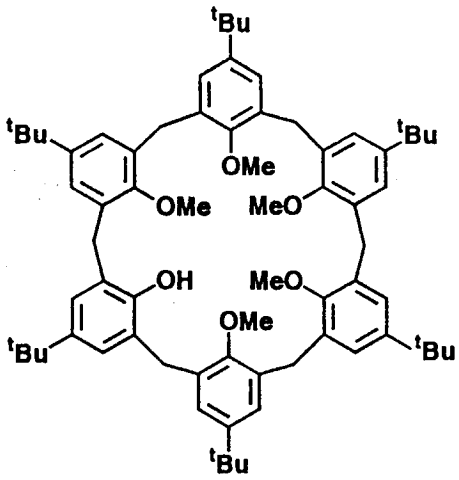
Mixture of 13 Amino Acids

	Total amount (µmol)	Ratio
Phe	2.61	100
Trp	1.20	46
Leu	0.73	28
Tyr	0.45	17
Ile	0.28	11
Gly	0.13	5
Val	0.11	4
Ala	0.09	3
Arg	0.05	2
Asp	0.05	2
Pro	0.05	2
His	0.04	1
Asn	Not determined	

Chiral Recognition *(HPLC Analysis of Diastereomeric L-Leu-?-AA Dipeptides)*

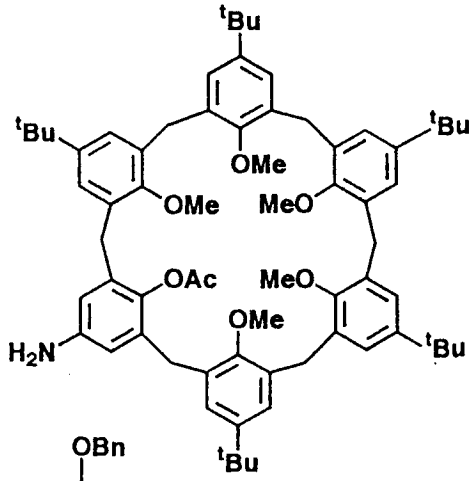
Amount of D-isomer in the problem samples:

D-Trp (determined as L-Leu-D-Trp): < 0.5 %
D-Phe (determined as L-Leu-D-Phe): ≤ 2 %

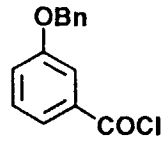


1. 1 equiv 65%HNO_3/H_2SO_4 (1:1)
2. Ac_2O / cat. H_2SO_4 / r.t. 24 hr

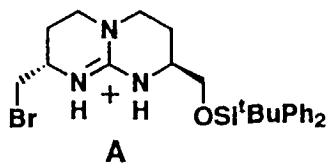
3. H_2 / Pd-C / THF / cat. HCl



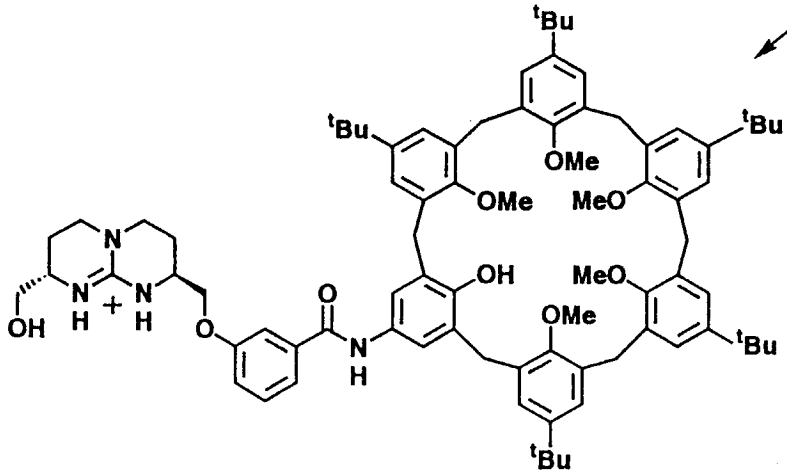
1. Et_3N

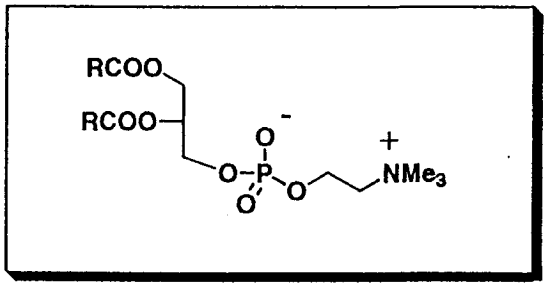


2. H_2 / Pd-C / THF
3. Cs_2CO_3 / CH_3CN / 48 hr
   add **A** and then
   Cs_2CO_3 / H_2O , 70° C, 24 hr



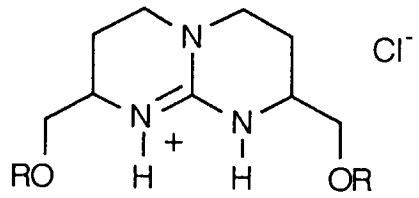
A





A Receptor for Phosphatidylcholine and Phosphorylcholine

Mononucleotide extraction

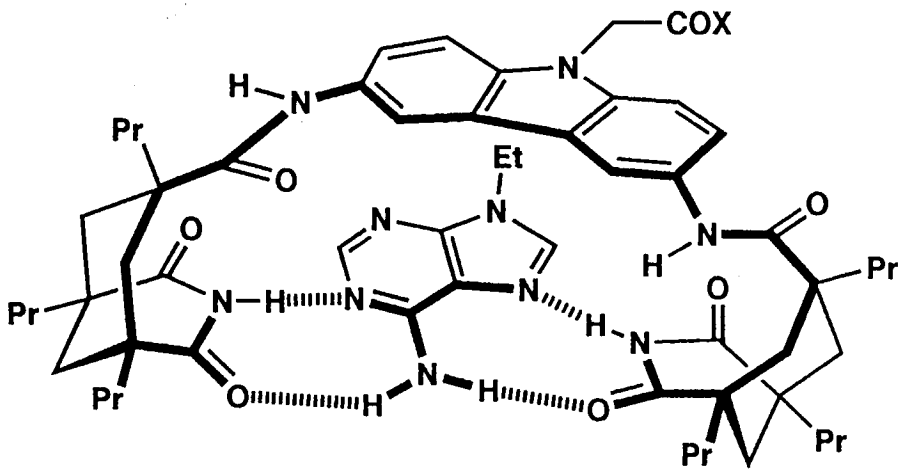


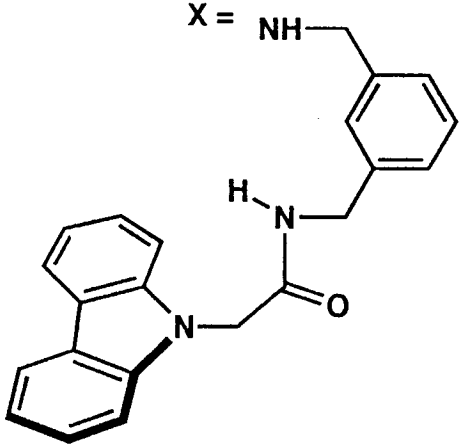
Nucleotide	R = 2-naphthoyl *(S,S)*	R = 2-naphthoyl *(R,R)*	R = palmitoyl *(S,S)*
5'-AMP^{-}	<5	<5	<5
5'-AMP^{2-}	6	5	<5
3'-AMP^{-}	2	2	<5
3'-AMP^{2-}	30	28	10
3',5'-cAMP^{-}	20	17	13
2',3'-cAMP^{-}	50	46	30
3',5'-cGMP^{-}	8	<5	<5
2',3'-cGMP^{-}	<5	<5	<5

^{1}H-NMR integral of nucleotide $H_{1'}$ *vs.* CH_2OCO receptor signals (± 5 % error)

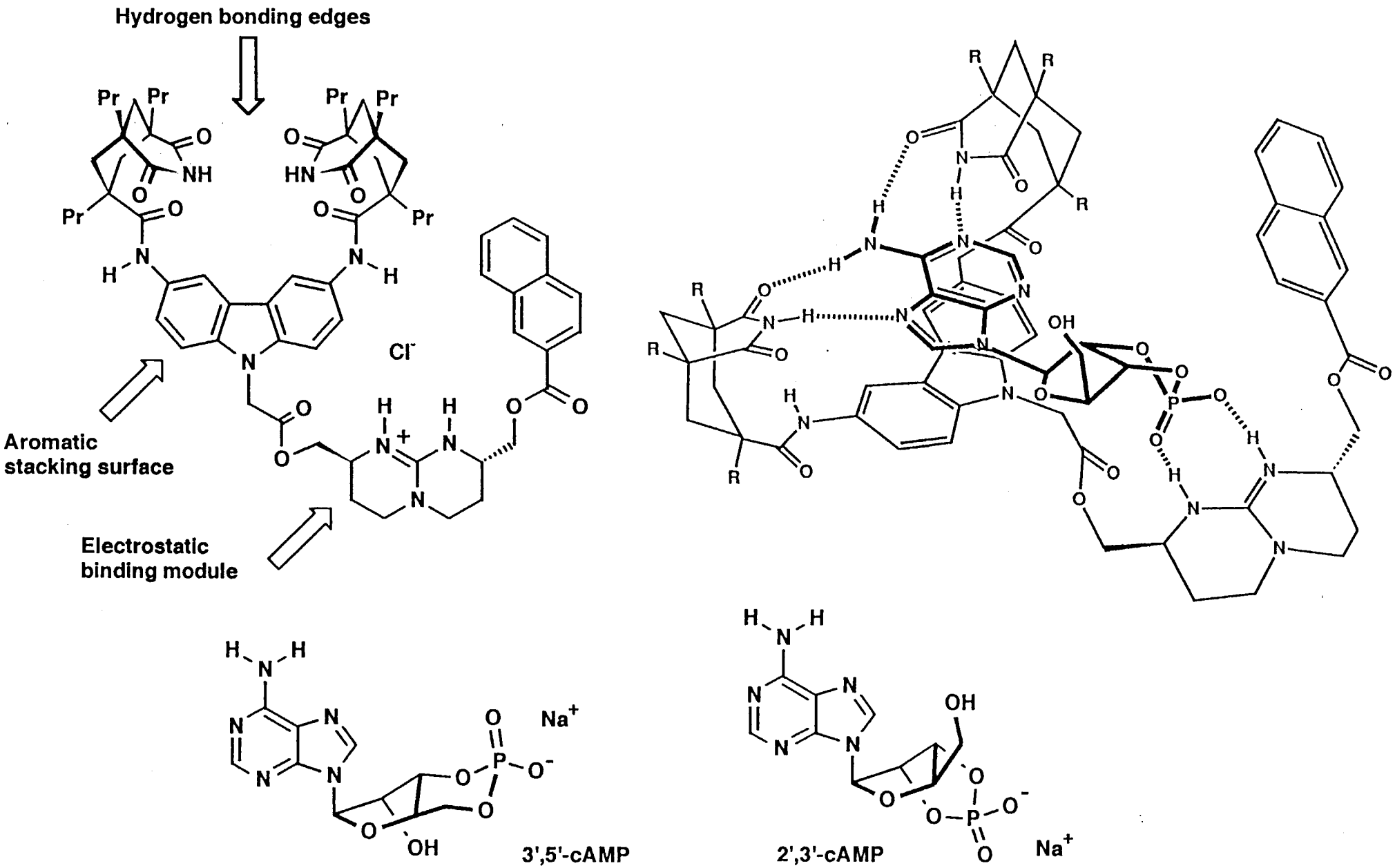
Liquid-liquid extraction: *Receptor:* 5.5×10^{-3} mmol in 2 ml CH_2Cl_2
Nucleotide: 5.5×10^{-2} mmol in 0.5 ml H_2O

The Carbazolyl Cleft (Scorpion Receptors)

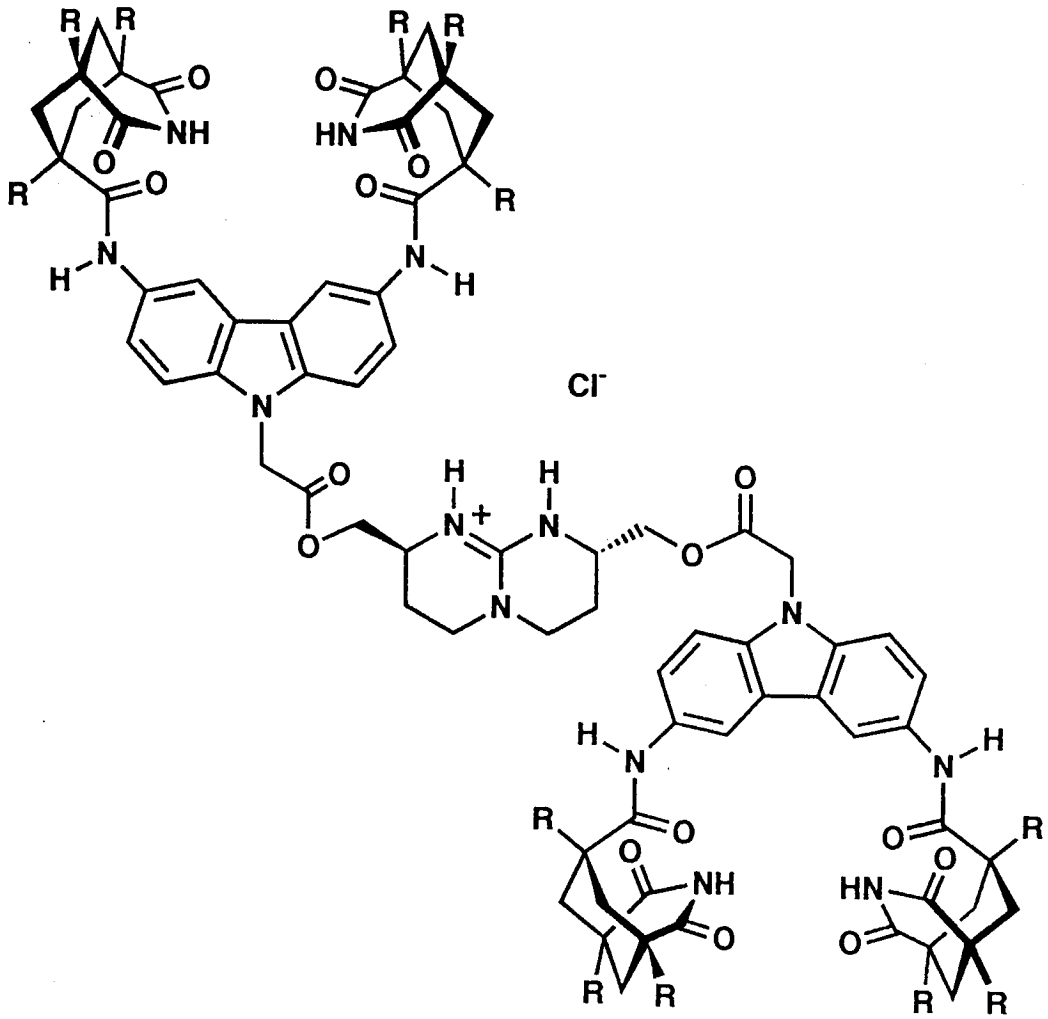


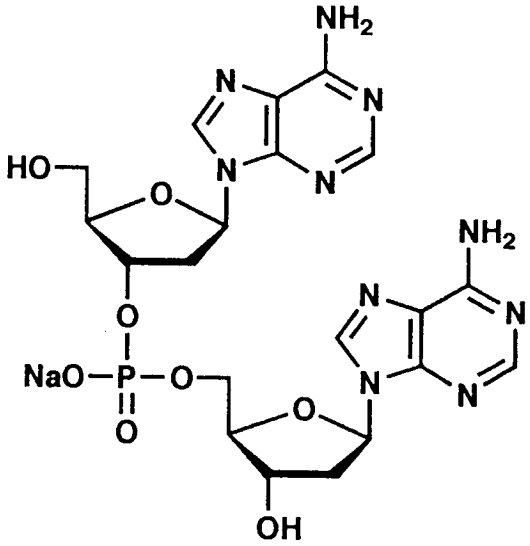
	K_s, 24° C	
	$CDCl_3$	CD_3OD
X = OCH_3	5×10^4	30
X = 	$> 5 \times 10^5$	420

A Molecular Receptor for cyclic-AMP



A Molecular Receptor for Dinucleotide Monophosphates



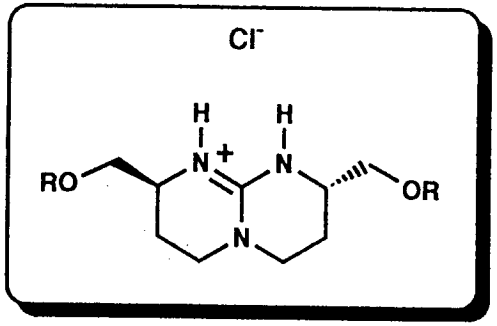


d(AA)

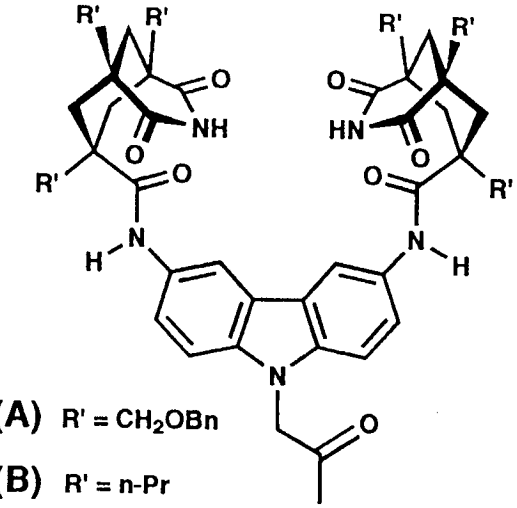
R
n-Propyl
CH_2O-Benzyl
CH_2OH

Extraction of Oligonucleotides by the ApA Receptor

Sequence	Length	MW	% Extracted	% Released	Receptor / NA	Nucleic Acid [ ] μM
AA	2	660	35	43	1/1	50
d(AAA)	3	990	29	60	1/1	50
d(AAA AA)	5	1650	21	34	1/1	25
d(TAT ATA)	6	1980	11	26	1/1	12
d(AAA AAA A)	7	2310	14	16	1/1	12
d(TTT TTA A)	7	2310	10	30	1/1	12
d(GCA TTA A)	7	2310	6	40	1/1	12
d(TTT GGA A)	7	2310	13	23	1/1	12
$d(A_8)$	8	2640	12	30	1/1	12
$d(T_8)$	8	2640	<5	--	1/1	12
CCC UCU AAA AA	11	3630	37	28	1/1	10
$(AG)_8$-dT	17	5610	23	8	1/1	6
HH Ribozyme ...d(GC)	19	6270	17	12	2/1	6
HH Ribozyme ...GC	19	6270	27	10	2/1	6
A_{20}	20	6600	68	10	1/1	6
RNA PCR Primer ....GG	20	6600	20	17	2/1	6
HH Substrate ...GC	24	7920	24	4	4/1	6
RNA PCR Primer ...CC	24	7920	24	--	4/1	6
HH Ribozyme ...GU	35	11550	10	2	4/1	6
HH Ribozyme ...d(GT)	35	11550	13	6	4/1	6
Sun Y Ribozyme ...UC	36	11880	12	6	4/1	6
tRNA Alanine ...CCA	76	25080	6	6	8/1	1.5

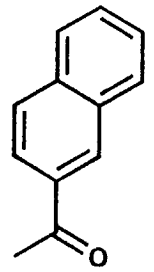


R =

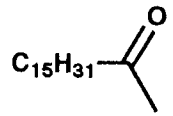


(A) R' = CH_2OBn

(B) R' = n-Pr



(C)

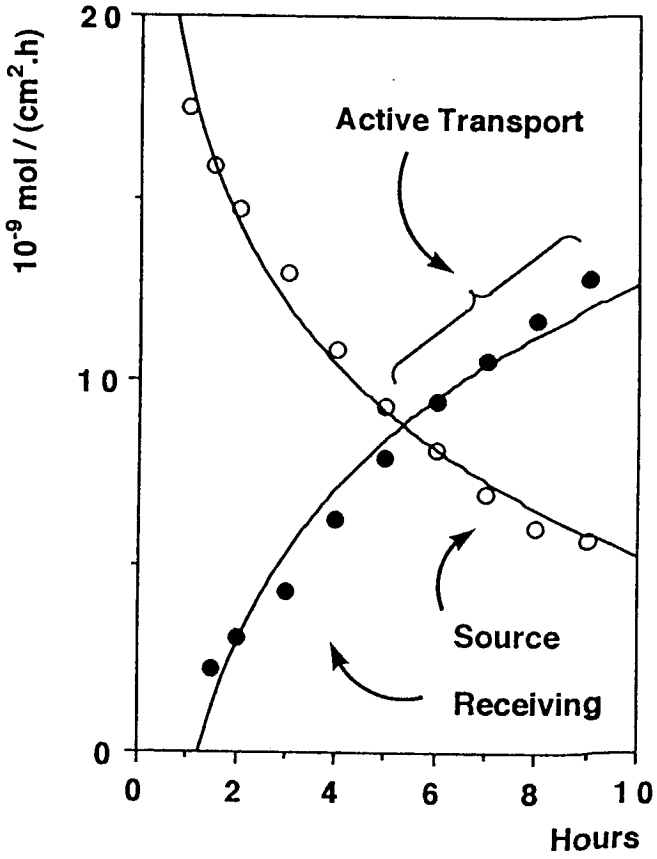


(D)

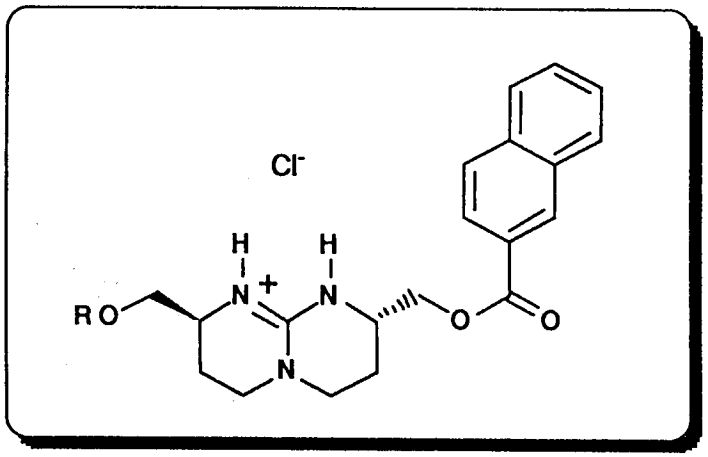
Nuc	Carrier	Conc. (μM)	Initial Transport Rate (10^{-9} mol/cm².h)	Active Transport Rate (10^{-9} mol/cm².h)
d(AA)	(A)	5	1.027 ± 0.0041	0.755 ± 0.048
	(B)	5	1.221 ± 0.019	0.787 ± 0.035
	Blank		No (in 9 h)	
	(C)	20	No (in 24 h)	
	(D)	20	No (in 9 h)	
dApT	(A)	12	1.058 ± 0.053	0.792 ± 0.041
TpdA	(A)	12	0.910 ± 0.001	0.484 ± 0.041
d(AG)	(A)	20	0.360 ± 0.004	

No transport was observed for d(AC), d(CA), d(CG), d(GG)
[Nuc] in source phase = 10 μM
[NaCl] in receiving phase = 10 mM
Contact surface = 1.568 cm²

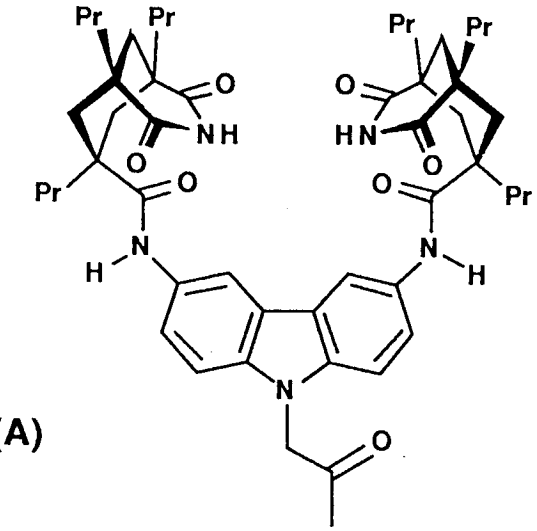
Transport of d(AA)



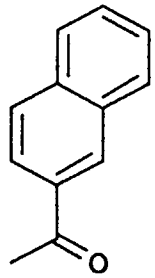
Dinucleotide Transport



R =



(A)

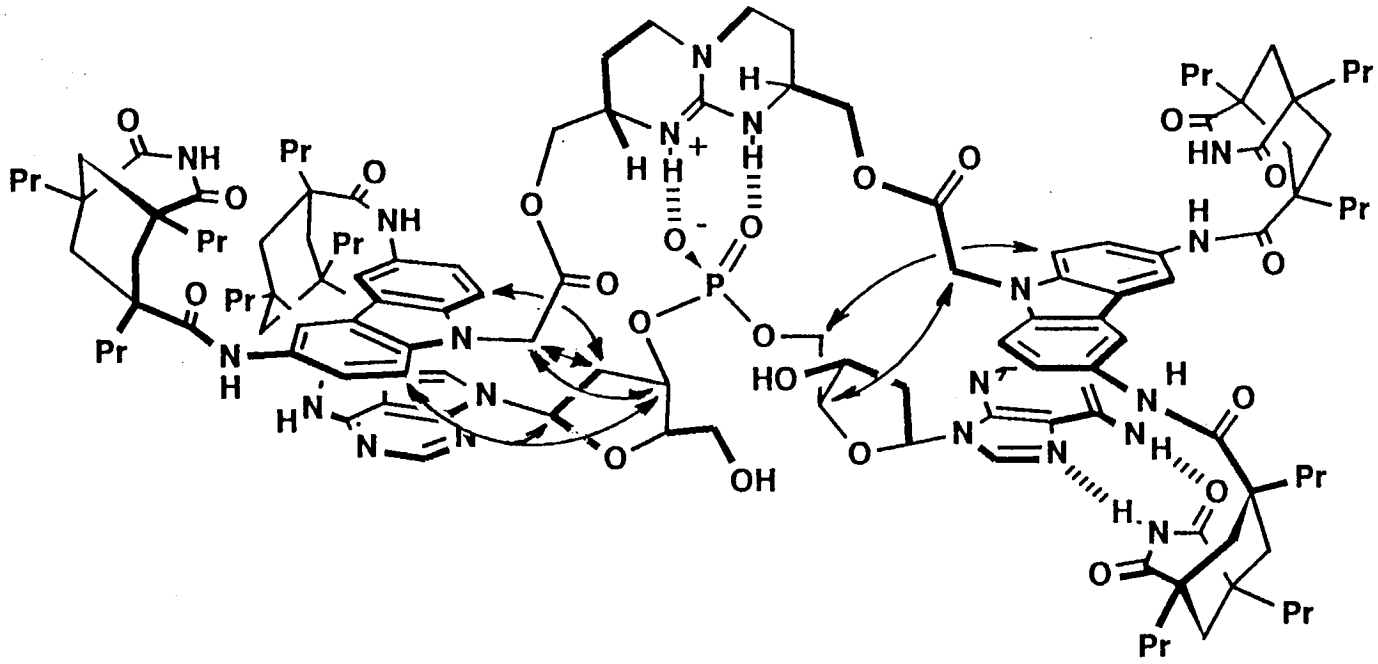


(B)

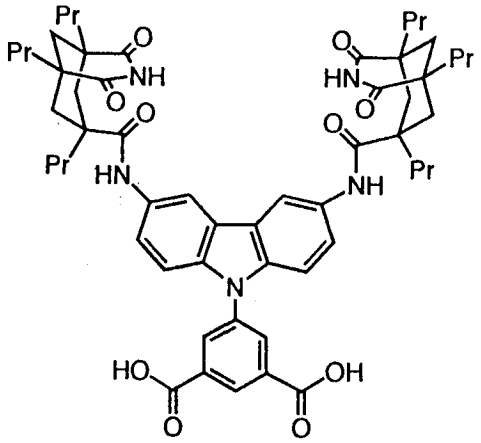
Nucleotide	Carrier	Conc. (μM)	Initial Transport Rate (10^{-9} mol/cm^2.h)	Active Transport Rate (10^{-9} mol/cm^2.h)
2',3'-cAMP	(A)	7.5	2.194 ± 0.016	1.216 ± 0.004
	Blank		No (in 9 h)	
	(B)	7.5	No (in 9 h)	
	(B)	20	No (in 9 h)	
3',5'-cAMP	(A)	7.5	1.820 ± 0.040	0.964 ± 0.013
2',3'-cGMP	(A)	7.5	No (in 9 h)	
3',5'-cGMP	(A)	7.5	No (in 9 h)	
3'-AMP	(A)	25	1.383 ± 0.037	0.685 ± 0.023
	(B)	20	No (in 9 h)	
5'-AMP	(A)	25	No (in 9 h)	

No leakage of (A) (25 μM) was observed in a blank experiment
[Nuc] in source phase = 15 μM
[NaCl] in receiving phase = 10 mM
Contact surface = 1.568 cm^2

AMP Transport

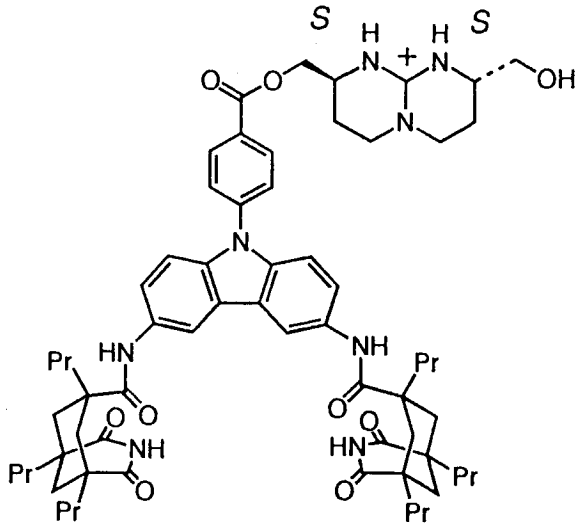


A Receptor for ApApA



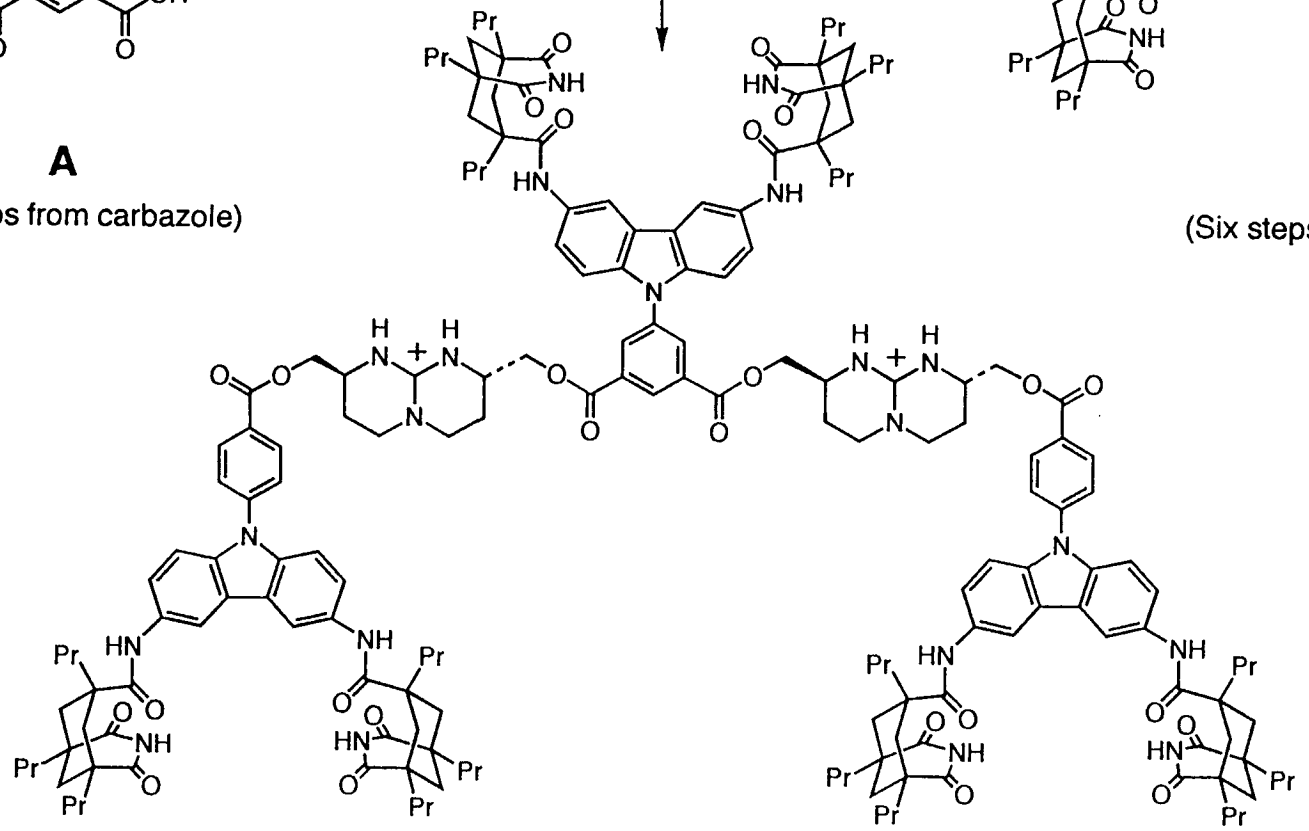
A

(Five steps from carbazole)

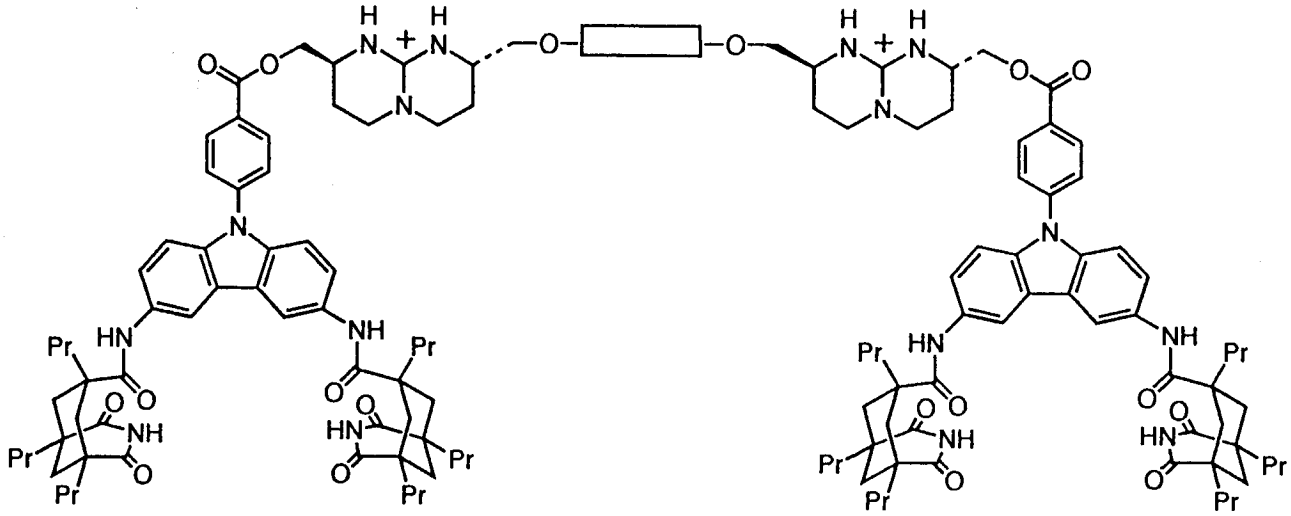


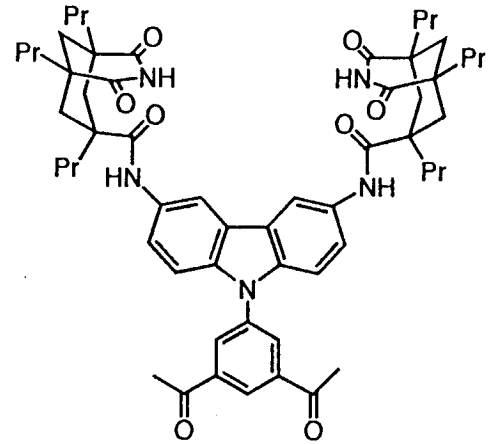
B

(Six steps from carbazole)

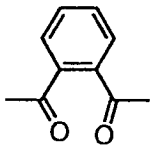


(AAA) Transport





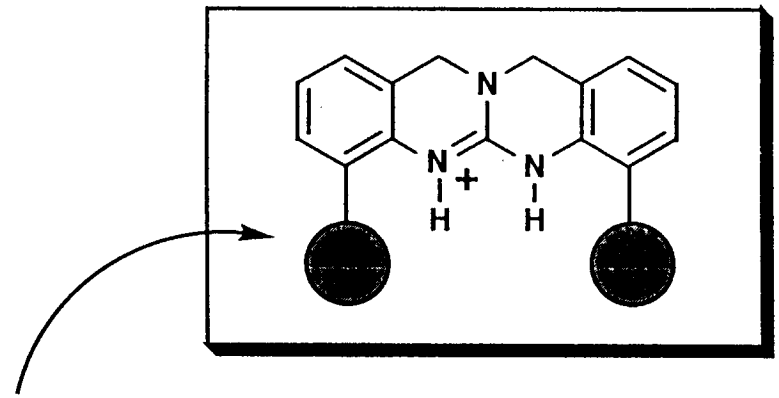
(A)



(B)

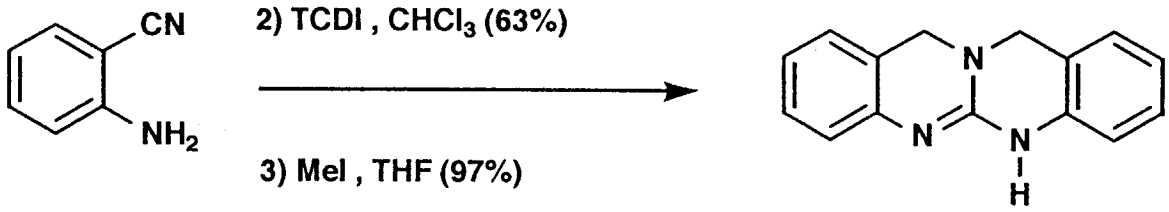
Carrier conc. (μM)	[NaCl] (mM)	k (mol/hcm^2) (x10^{-9})	k (mol/hcm^2) (x10^{-9})
(A) 5	500	1.018 ± 0.006	0.834 ± 0.02
(B) 20	10	1.075 ± 0.00	0.781 ± 0.038

DIBENZOGUANIDINES

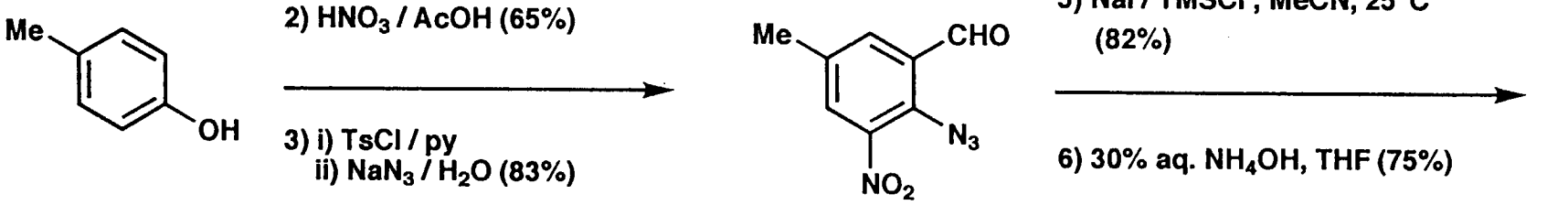


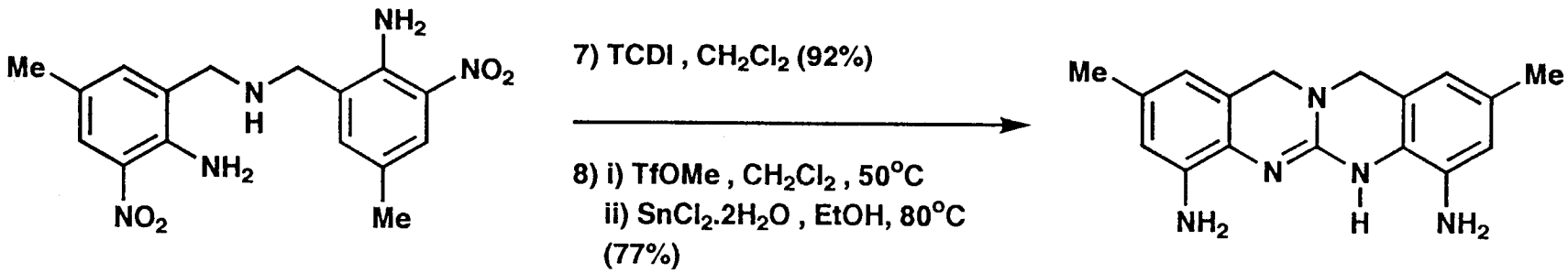
- ✓ Chiral barrier
- ✓ Additional binding sites

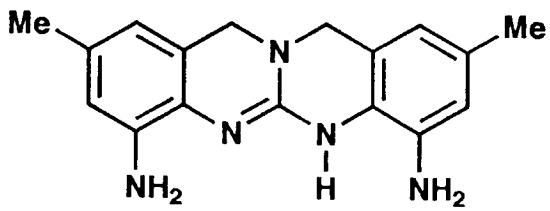
Parent System:



DIBENZOGUANIDINES: Functionalized Derivatives

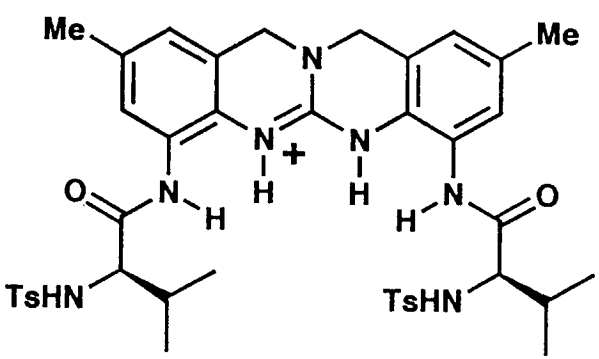




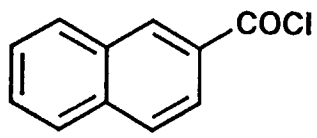


1) (*D*)-Ts-Val-OH , $(COCl)_2$,
THF-Et_3N (93%)

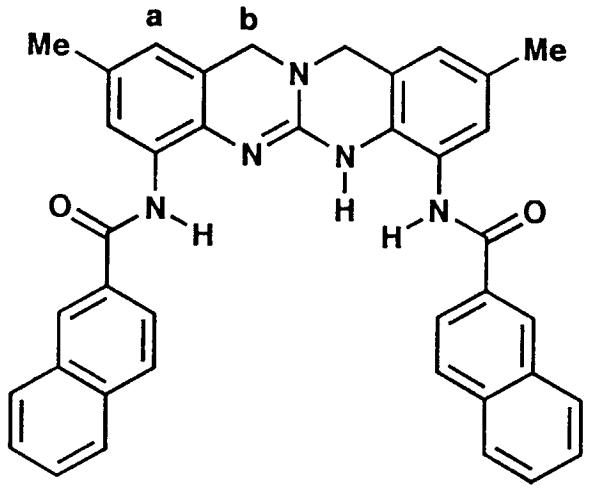
2) HCl



Other aa's: Trp, Val, Pro

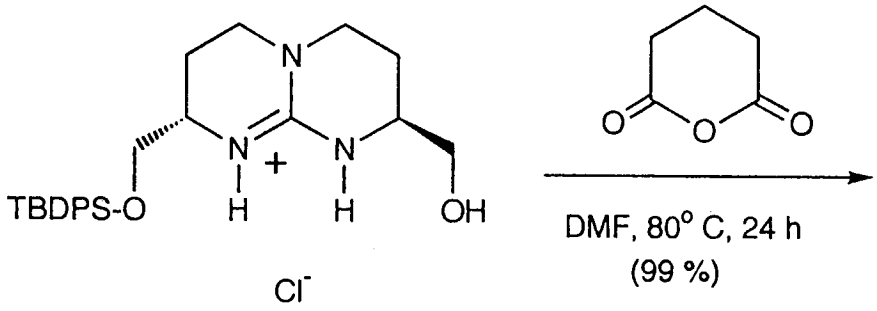


CH_2Cl_2 (40%)

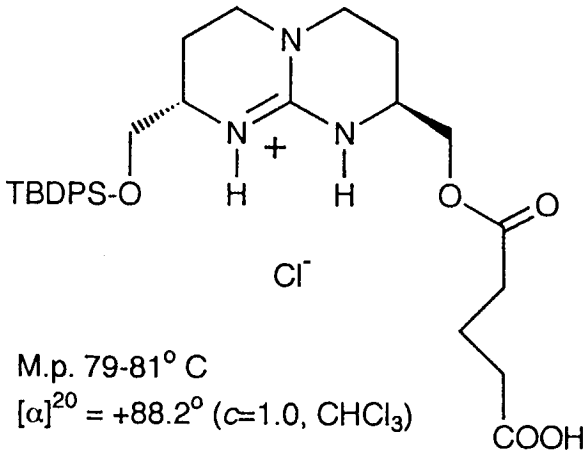


		a	b	
^{1}H-NMR	$CDCl_3$	7.53	2.29	DIMER
	$CDCl_3/CD_3OD$ (5:1)	7.29	4.06	

Molecular Recognition of Tetrahedral Oxoanions

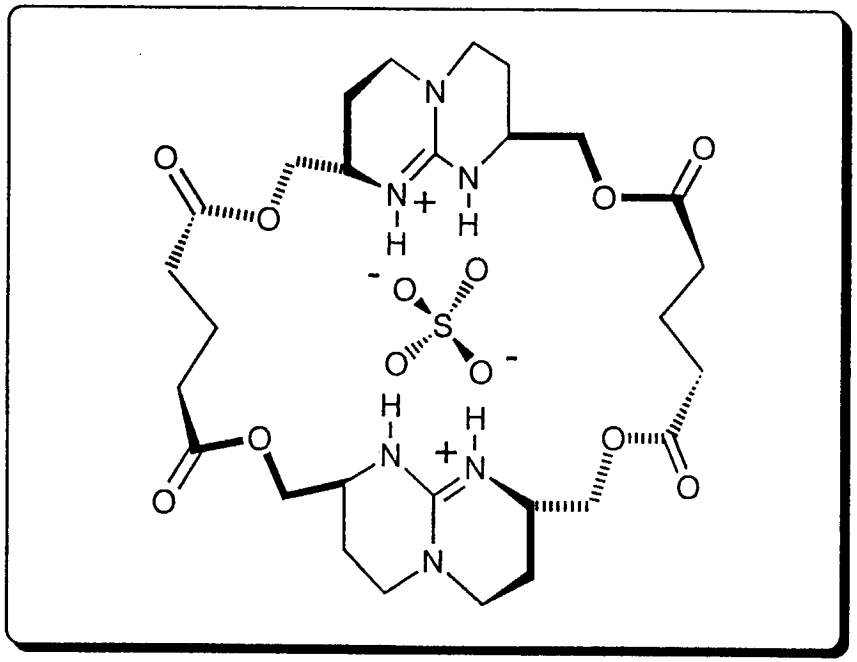


DMF, 80° C, 24 h
(99 %)



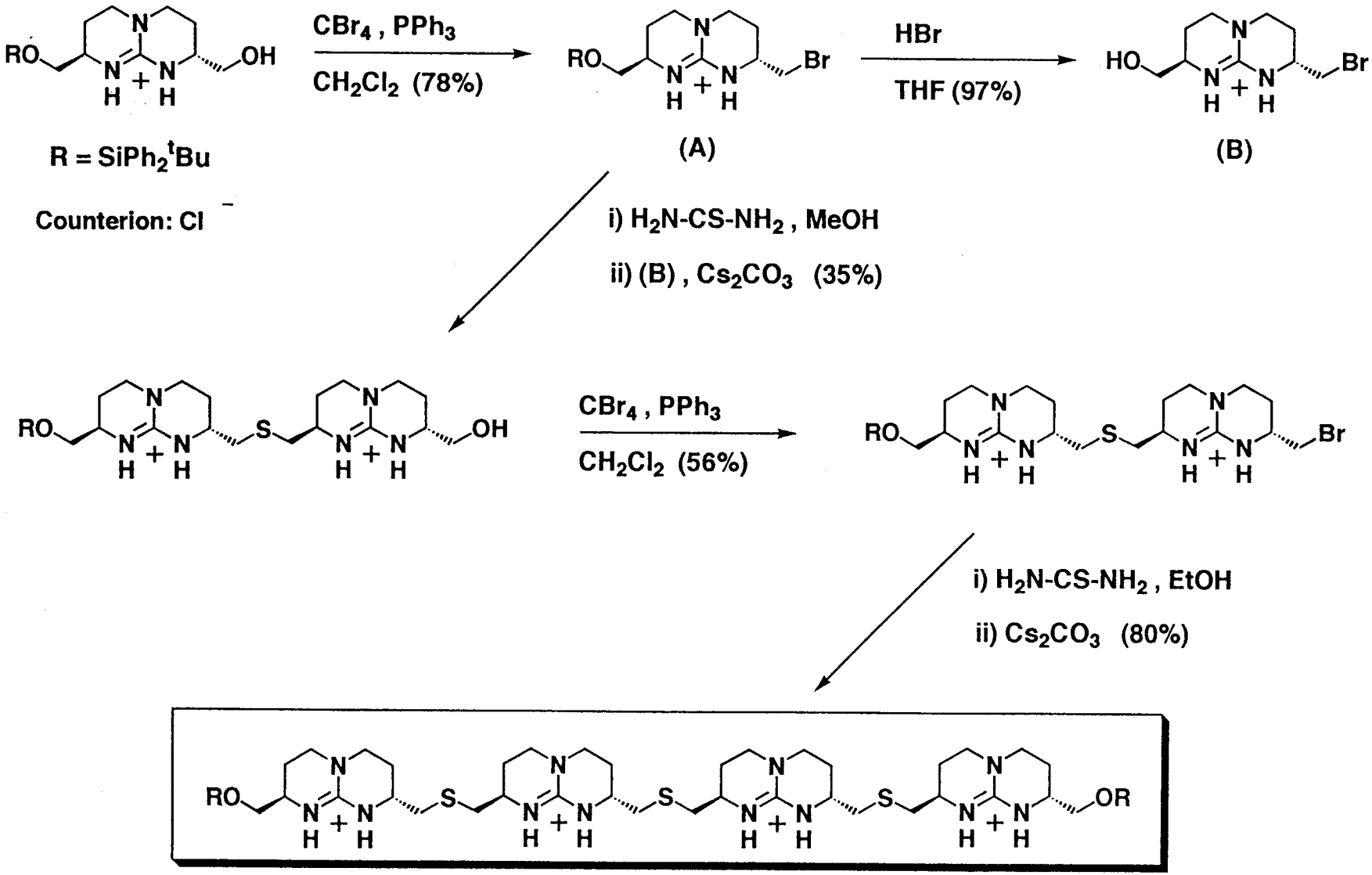
M.p. 79-81° C
$[\alpha]^{20}$ = +88.2° (*c*=1.0, $CHCl_3$)

1) Py (HF)x (92 %)
2) Ag_2SO_4
3) CDI / DMF, 100° C, 7 days (7 %)



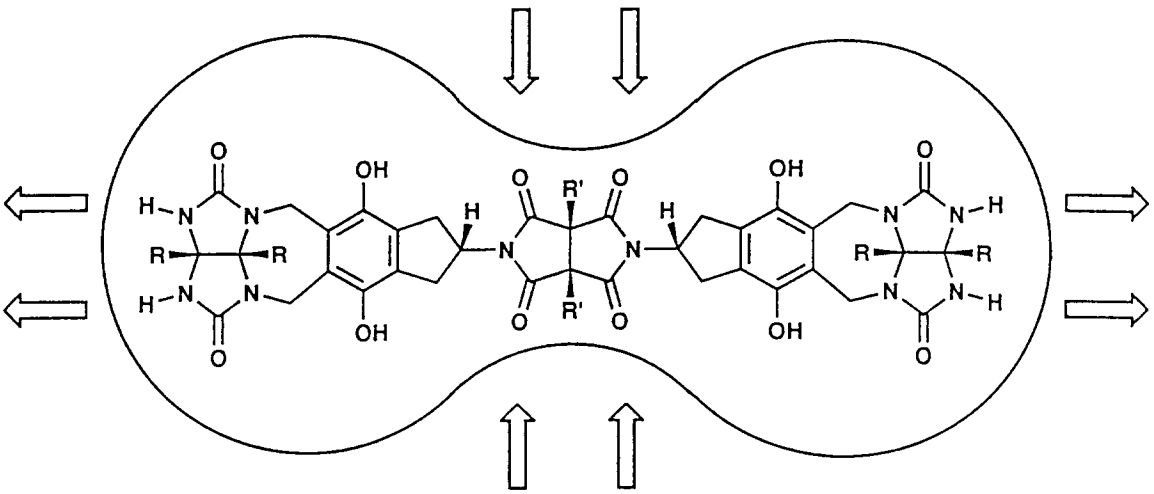
$[\alpha]^{20}$ = +99.8° (*c*=0.6, $CHCl_3$)

A Polyguanidinium chain for DNA binding



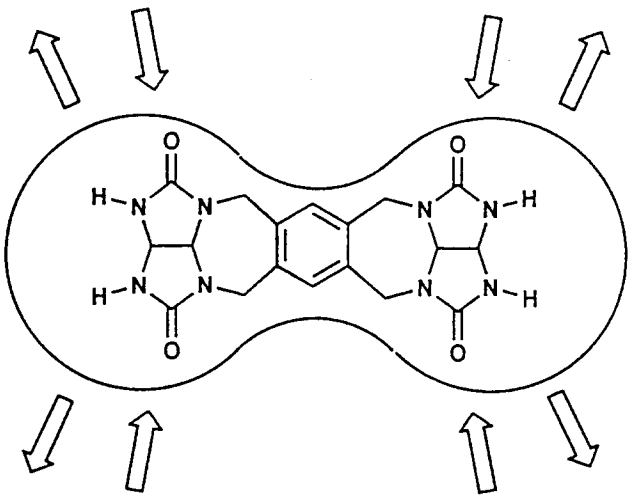
The Bigger Tennis Ball (Softball)

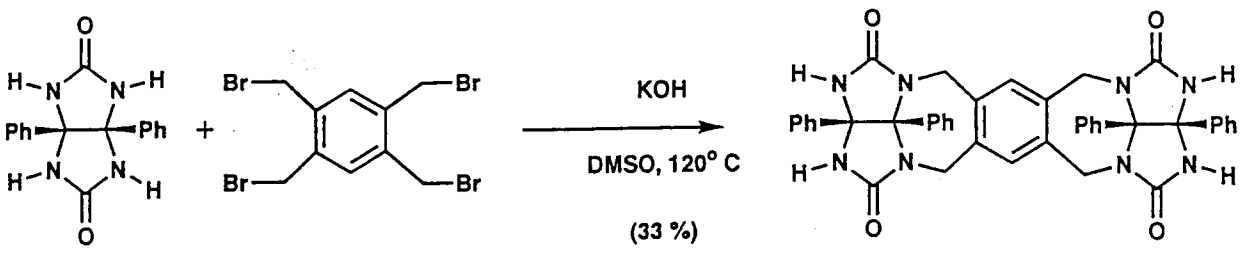
AA-DD H-bonds



A Simplified Prototype

AD-DA H-bonds

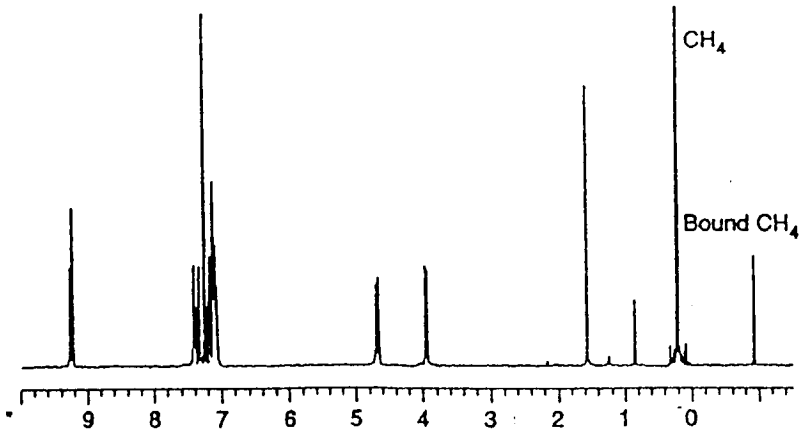


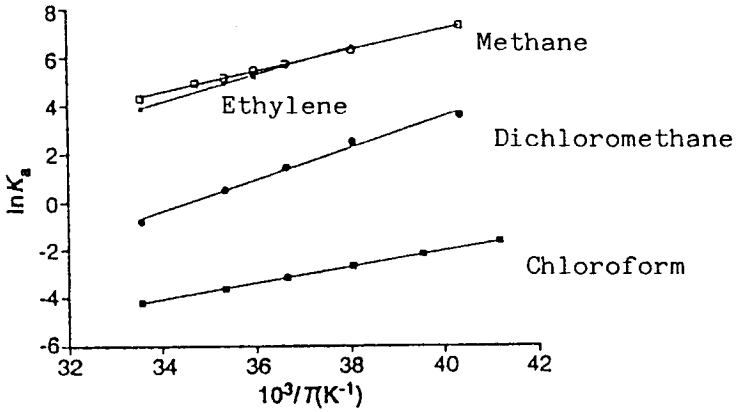


FAB-MS = 1429

500MHz NMR Signals (ppm) for Guest Resonances with Tball ($CDCl_3$, 25° C)

Guest	δ (free guest)	δ (bound guest)	Δδ
Methane	0.22	-0.91	1.13
Ethane	0.86	-0.41	1.27
Ethylene	5.42	4.04	1.38





Inclusion of Guest Species in Tball Cavity

Guest	K_{inc} (M^{-1}) at 273 K	T range (K)	Δ*H* (kcal/mol)	Δ*S* (e.u.)	Guest Volume (A^3)
Chloroform	0.04	243-298	-7	-31	73
Dichloromethane	4	248-298	-13	-45	58
Ethylene	280	263-298	-11	-30	40
Methane	300	248-298	-9	-20	28