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Design and Synthesis of a Heterocyclic Amine Receptor

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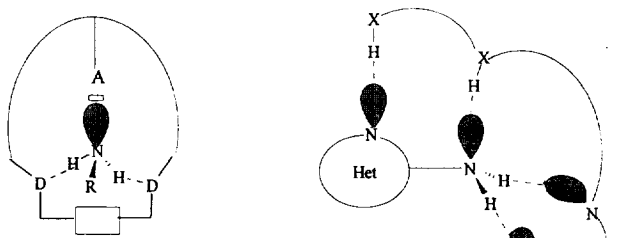
Abstract: After a short review on the amine receptors already published in the literature, the design of a new host **1** is described. This new host possesses two heterocyclic parts (isoquinoline and pyridine) separated by a flexible arm. The synthesis of receptor **1** involves regioselective acylation or halogenoacylation at the C-7 of isoquinoline followed by a Willgerodt-Kindler reaction affording the isoquinoline-7-acetic acid derivatives **4b,c**. Coupling of **4c** with 2-aminopyridine gives the required host **1**. The association constants of this latter compound with some amine guests are determined using the classical NMR titration method.

INTRODUCTION

Molecular recognition has become a very exciting field of investigations for organic chemists. Alot of work has been devoted to the design of synthetic hosts able to receive specific guests possessing various functional groups, for example: carboxylic acids or diacids and their salts, amines, ammonium salts. This field has thoroughly been reviewed.[1] The design of receptors for amine groups is of particular interest since this class of compounds is used for the synthesis of many biologically active molecules. For example, it would be interesting to design an artificial receptor able to bind both a carboxylic acid derivative and an amine with a view to facilitating the reaction leading to an amide. To the best of our knowledge, the only approach of this kind of artificial enzyme has been reported by Tabushi *et al*[2] but no experimental data were given. An approach of this difficult problem involves on one hand the design and the study of structures able to bind amines. On the other hand, it would be of interest to perform the same study on structures able to bind carboxylic acids. The ultimate work would be to combine the obtained information for the design of the above mentioned artificial receptor able to bind both reagents. We were first interested in the synthesis of new amine receptors.

First, several systems have been designed for the binding of amine groups.[3] These amine receptors often combine an electrophilic center for complexation of the lone pair of the amine nitrogen and basic centers for hydrogen bonding with the N-H moieties (Scheme 1, Host-Guest association type A). Efficient molecules were recently reported by Reetz *et al* and Takaya *et al* [4] who obtained a three point binding with a crown ether containing a Lewis acid center. The amine R-NH_2 forms a reversible bond with the boron center and takes on the character of an ammonium salt. A similar approach has been described by Bradshaw *et al*[5] with

triazole or 4-hydroxypyridine containing macrocycles. In these systems, a proton is transferred to the amine and the resulting ammonium salt is attached by the lone pairs of oxygen atoms of the crown and the lone pair of the heterocyclic nitrogen. More recently the same group has reported a new pyridino aza-crown ether containing a p-nitrophenol substituent and having a good affinity for benzylamine.[6] Some calixarenes have also been described by Gutzsche[7] or Kubo.[8]



Amine-Host association type A
(A = Electrophilic center)
(D = Basic center)

Amine-Host association type B
(Het = Heterocyclic part of guest)
(X, X' = Electronegative elements on Host)

Scheme 1

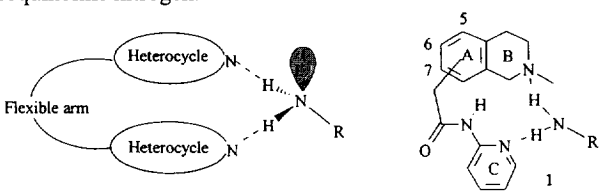
The complexation of aminosubstituted nitrogen containing heterocycles has been reported frequently, a three- or four-point binding being ensured by hydrogen bond interactions of the receptor with the two NH moieties and the lone pairs of the heterocyclic nitrogen atoms [9] or only with heterocyclic nitrogen atoms (Scheme 1, Host-Guest association type B).[10]

As it can be seen, the systems described above may not be used in a synthetic purpose because they are too specific of the amine substituent, too rigid in the case of crowns or they involve an ammonium salt. We have started a program with the goal to develop amine receptors, possessing a scope as large as possible and, if possible, not involving binding with the lone pair of the amine nitrogen in order to preserve the reactivity of this nucleophilic center. In this paper, we present our first results concerning the design, the synthesis of such hosts and their complexation with some amine guests.

RESULTS AND DISCUSSION

1-Design of The Amine Receptor.

If the lone pair of the amine is not involved in the binding with the host, only two binding points remain: The two N-H bonds. So it is necessary to design two hydrogen bonds, for example with the lone pairs of two heterocyclic nitrogen atoms. After a careful study with CPK models and molecular modeling softwares, we selected the host **1** where the binding of the amine group would be ensured by two hydrogen bonds with the pyridine nitrogen and the isoquinoline nitrogen.



The flexible arm may be connected either at C-6 or C-7 of ring A.

Scheme 2

Molecular mechanics and semi-empirical calculations[11] performed on **1** alone clearly showed that in the minimized structure (Figure 1): 1- The oxygen of the carbonyl group is close to the 3 position of the pyridine ring. 2- The pyridine ring and the benzene ring of the isoquinoline are quasi perpendicular, the distance between the two heterocyclic nitrogen atoms (about 6 Å) being compatible with the establishment of two hydrogen bonds with an amine guest. 3- The 2-carboxamidopyridine moiety may be connected either to the 6 or the 7 position of the isoquinoline part of this potential receptor. In the literature, the examples of 6 or 7-substituted isoquinoline systems are rather seldom. However, some 7-acetylisoquinoline compounds have been previously described.[12] For this reason, we chose to connect the carboxamidopyridine group to the 7-position.

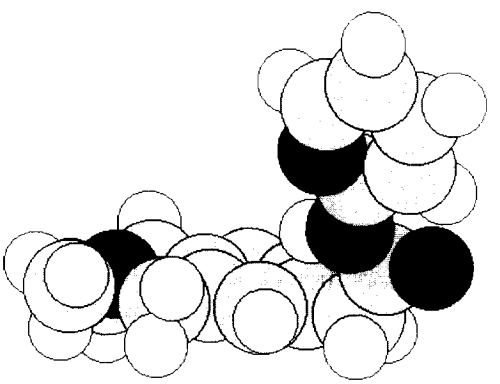
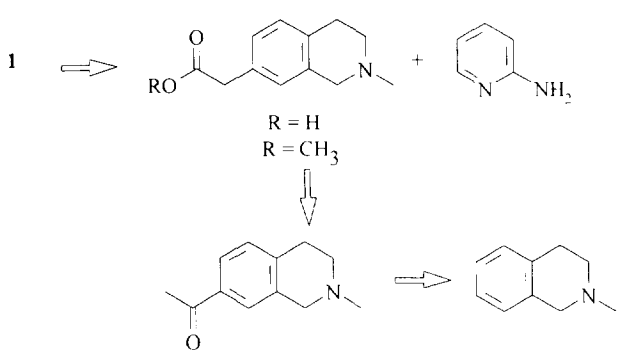


Figure 1: Minimized structure of **1**

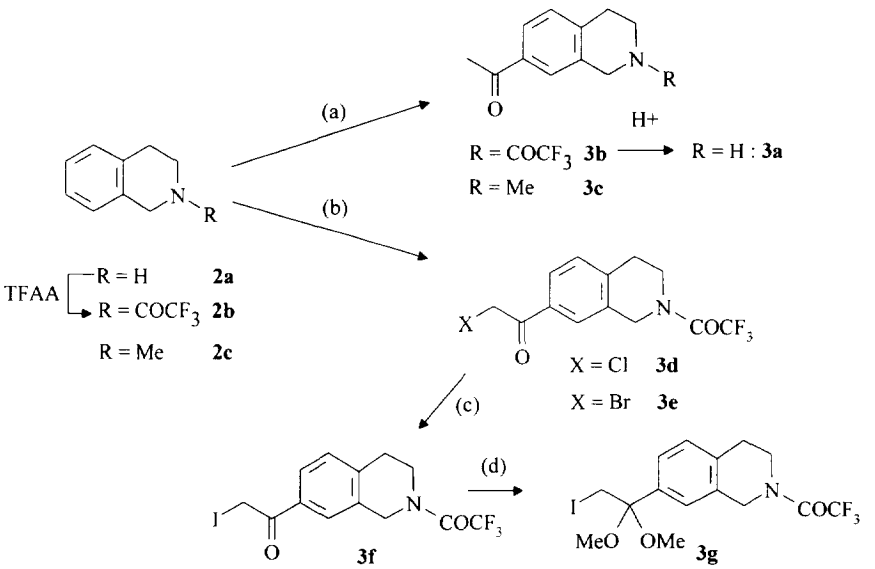
2-Synthesis.



Scheme 3

As it can be seen above on the Scheme 3, the receptor **1** may be obtained by coupling of 2-aminopyridine with a derivative of isoquinoline-7-acetic acid. This latter compound can be obtained by a Willgerodt type reaction from the 7-acetylisoquinoline system mentioned above.

a) Acylation reactions:



a) $MeCOCl/AlCl_3$ in CS_2. b) $Cl\text{-}CH_2\text{-}COCl/ AlCl_3$ in CS_2. c) Na I / Acetone. d) $HC(OMe)_3$ / MeOH

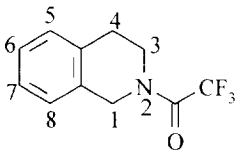
Scheme 4

The commercially available 1,2,3,4-tetrahydroisoquinoline **2a** was first reacted with trifluoroacetic anhydride (TFAA) to afford the N-protected compound **2b** (Scheme 4). Under aluminium trichloride catalysis, compound **2b** underwent clean Friedel-Crafts acylation as described in the literature and afforded compound **3b** as a single isomer in a 86 % yield.[12] We confirmed the formation of a single isomer by ^1H 200 MHz NMR spectroscopy and semi-empirical calculations (table 1, see below for comments) are in good agreement with this regioselectivity. Under acidic conditions, the cleavage of the N-$COCF_3$ bond proceeded smoothly to give **3a**. We performed the same Friedel-Crafts acylation on the N-methyl derivative **2c** (the latter compound was obtained by quaternization of isoquinoline with methyl iodide followed by reduction of the intermediate isoquinolinium salt with sodium borohydride[13]). Under the same conditions used for the conversion of **2b** into **3b**, compound **3c** was isolated with great difficulties in a 35 % yield. After hydrolysis, the reaction mixture is very acidic and it is necessary to add a large amount of sodium hydroxide before extracting the amine **3c**. It is well known that isoquinoline derivatives are not very stable in aqueous basic medium and we think that **3c** may decompose by ring opening. It was possible to improve the yield of the acylation reaction leading to **3c**, on a 1g scale (55 % yield). It must be emphasized that the regioselectivity of this reaction is similar to that obtained with **2b** (confirmed by ^1H 200 MHz NMR spectroscopy). This fact may be explained by the results of MNDO calculations performed on compounds **2b** and on the protonated form of **2c** as a model of the reactive species resulting from complexation of aluminium trichloride with the lone pair of the isoquinoline nitrogen (see Table 1). In Table 1 the net charges and M. O. coefficients in the HOMO's of the

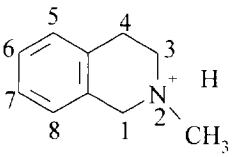
benzene ring of **2b** and protonated **2c** are reported . It can be seen that the 7-position possesses the highest negative charges and the highest value of MO coefficient in the case of **2b**.

Similarly, Friedel-Crafts chloroacylation of **2b** afforded **3d** whereas a mixture of **3d** and **3e** was obtained in the case of bromoacetyl chloride (compound **3e** was alternatively synthesized by bromination of **3b** in a 67 % yield). Subsequent Finkelstein reaction gave **3f** which was converted in a 75 % yield into the iodoketal **3g** with the methanol/ methyl orthoformate system (the utility of this latter compound **3g** will appear below). In the case of the N-methyl derivative **2c**, the halogenoacylation reaction always gave poor yields whatever the conditions and the reagent used.

Table 1 : Net Charges and M.O. coefficients in the HOMO of **2b** and protonated **2c**



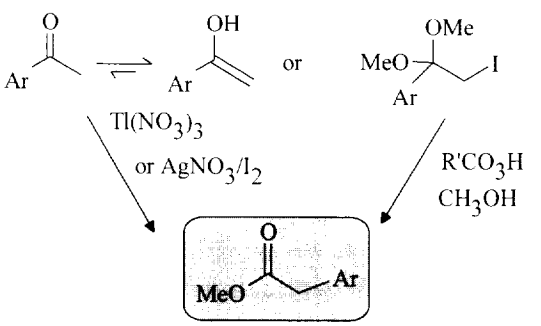
Position	Net charges	M.O. coefficient.
5	- 0.0373	0.075
6	- 0.0489	0.436
7	**- 0.054**	**0.505**
8	- 0.0326	0.060



Position	Net charges	M.O Coefficient
5	-0.019	0.475
6	-0.011	0.010
7	**-0.033**	**0.471**
8	-0.007	0.507

b)Willgerodt reaction:

In order to convert the acetyl group into a 7-acetic acid derivative, we decided to use the Kindler variation of the Willgerodt reaction.[14] In the Kindler modification, various catalysts may be used and the mechanisms have been thoroughly studied.[15] Two systems are often used: Tl (III) nitrate and iodine/silver nitrate. In the first case, the enol form of the ketone reacts with the catalytic system to afford an intermediate species, the final ester being obtained after migration of the aryl group (scheme 5). The second case is less interesting because side deketalisation reactions are frequently observed. Alternatively, an iodoketal may be used and the aryl migration may occur after oxidation with a peracid (often mCPBA, see Scheme 5).[16]

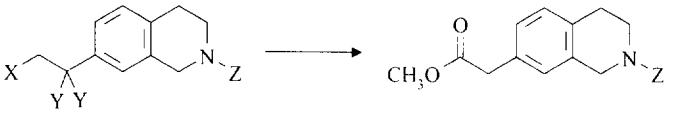


Scheme 5

We did not find any example of Willgerodt reaction involving an acylated compound possessing a secondary amine group like in compound **3c**. The first attempts using published procedures on similar

compounds gave low yields. So, it was decided to reinvestigate the experimental conditions and to use both the acylated products **3b,c** and the iodoketal **3g**. The results are described in Table 2.

Table 2: Willgerodt-Kindler reaction of **3b,c** and **3g** under various conditions.

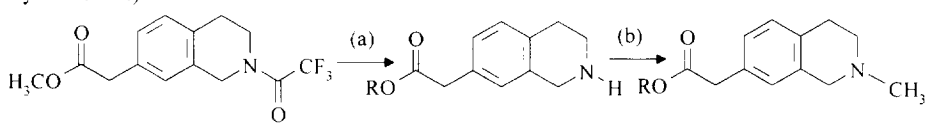


X = H, Y = O, Z = $COCF_3$: **3b**
X= H, Y = O, Z = CH_3 : **3c**
X = I, Y = OCH_3, Z = $COCF_3$: **3g**

Z = $COCF_3$: **4b**
Z = CH_3 : **4c**

Entry	Compound	Conditions	Yield in ester
1	**3b**	Tl(III), CH_3OH, r.t., 5 h	51 %
2	**3c**	Tl(III), CH_3OH, r.t.,5 h	55 %
3	**3g**	Tl(III), CH_3OH, r.t., 4 days	22 % (78 % unchanged **3g**)
4	**3g**	4.3 eq. mCPBA, CH_3OH, r.t., 16 h	60 % (+ unchanged **3g**)

The yields obtained with **3c** and **3b** are similar (entries 1-2). However, starting from **3b** instead of **3c**, required two supplementary steps in order to obtain the N-methyl derivative **4c**: 1-cleavage of the N-trifluoroacetyl group.[17] 2- N-methylation of the resulting secondary amine (Scheme 6). During the first step, with the sodium borohydride/ethyl alcohol system, a side-transesterification reaction was observed leading to a mixture of the methyl ester **5a** and the ethyl ester **5b** (the use of methanol instead of ethanol gave lower yields). The N-methylation under classical conditions[18] afforded the ester mixture **4c-6** in a 58 % yield (overall yield 33 %). These results clearly showed that we had better to use the direct conversion of **3c** into **4c** (overall yield 57 %).



R = $COCF_3$: **4b**

R = CH_3 : **5a**
R = C_2H_5: **5b**

R = CH_3 : **4c**
R = C_2H_5: **6**

a) $NaBH_4/C_2H_5OH$. b) 1) HCHO, 2) $NaBH_4$.

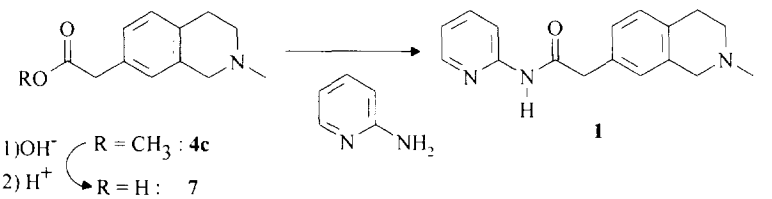
Scheme 6

c) Conversion into receptor 1:

Having at hand the required ester, the final conversion into the carboxamide moiety was more difficult than it could be predicted probably due to the presence in the same molecule of both a carboxylic acid derivative and a tertiary amine. The ester **4c** was hydrolysed with an accurately measured amount of base (1.5 equivalents for instance) and the crude reaction mixture was exactly neutralized with the same amount of 1N aqueous hydrochloric acid (volumetric standard solution). After removal of solvents and careful drying of the solid, a mixture of carboxylic acid and sodium chloride was obtained and used without further purification. A lot of methods known to convert an ester or an acid into a carboxamide moiety were tested. The main results are summarized in Table 3. It must be mentioned that some of these reactions were checked

on phenylacetic acid or methyl phenylacetate. In all the tested cases, phenylacetic acid derivatives gave satisfactory yields.

Table 3: Synthesis of receptor **1** under various conditions.



Entry	Compound	Conditions	% of **1** (c)
1	Acid **7**[a]	DCC, THF[19]	24 % (90 %)[20]
2	Acid **7**[a]	EDC, THF[21]	7 % (-)
3	Acid **7**[a]	CCM[22], CH_3CN	12 % (-)
4	Acid **7**[a]	ETC[23] or BOP[24] or NMPC	-------(-)
5	Acid **7**[a]	ClCOOEt, NMM, CH_2Cl_2[25]	ester **6** (54 %)
6	Ester **4c**	10 % mol NaCN, EtOH, 180 °C[26]	ester **6** (-)
7	Ester **4c**	$NaEt_2AlH_2$, 2-aminopyridine (2 eq.)[27]	-------(50 %)
8	Ester **4c**	$LiAlH_4$, 2-aminopyridine (4 eq.)[28]	60 %[b] (60 %)

(a): The carboxylic acid was obtained with NaCl as mentioned above.

(b) **1** was isolated with 10-20 % of 2-aminopyridine

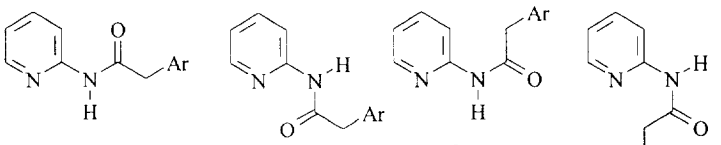
(c) % yield of 2-pyridyl-NH-$COCH_2Ph$ obtained with a phenylacetic acid derivative when tested.

DCC: dicyclohexylcarbodiimide; EDC: 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide

ETC: 1-(3-triethylaminopropyl)-3-ethylcarbodiimide, CCM: *N*-cyclohexyl-*N'*-(2-morpholinoethyl)-carbodiimide methyl-p-toluenesulfonate. NMPC: N-methyl-2-chloropyridinium iodide. NMM: N-methylmorpholine. BOP: Benzotriazol-1-yloxytris(dimethylamino)-phosphonium hexafluorophosphate.

The use of peptide coupling reagents (entries 1-4) always gave poor yields in **1**. The mixed anhydride strategy starting from the acid (entry 5) or the use of sodium cyanide (entry 6) afforded only the ethyl ester. The recently described method of Solladié-Cavallo[28] involving a complex between lithium aluminium hydride and the appropriate amine (4 eq.) gave a 60 % yield of a mixture of amide **1** and 2-aminopyridine. The decreasing of the amount of 2-aminopyridine (2 eq. for example) resulted in poor yields in **1**. The remaining 2-aminopyridine was removed after bulb to bulb distillation followed by HPLC on a C_8 column.

Compound **1** was unambigously identified by ^1H and ^{13}C NMR spectroscopies. The secondary amide group of this molecule could have four conformations (**A**,**B**,**C**,**D** on Scheme 7). In the ^1H NMR spectrum of **1**, the chemical shift of the H_3 proton of the pyridine ring is higher than that of H_4. This fact may be attributed to the magnetic anisotropy of the carbonyl goup which is near the H_3 proton when this group adopts a trans conformation with respect to the pyridine nitrogen as it was found above using molecular mechanics calculations (conformer **A** on Scheme 7). So, only conformer **A** could be observed in deuteriochloroform solutions.

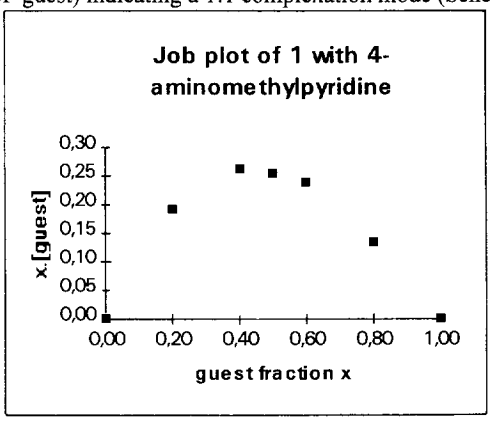


Ar = 7-(1,2,3,4-tetrahydro-2-methylisoquinolin)-yl

Scheme 7

3-Association constants of receptor 1 with various amines.

The receptor **1** was pure enough to undergo the determination of binding constants[29] with various amines. These binding constants (Kass) were calculated from data issued from the classical NMR titration method described in the literature[30] (see experimental section for the description of a typical experiment) assuming a 1:1 complexation mode. When a complexation occured, a shift of the signal corresponding to the NH_2 group of the amine guest was observed. A Job plot[31] for **1** and 4-aminomethylpyridine gave a maximum at about x = 0.5 (mole fraction of guest) indicating a 1:1 complexation mode (Scheme 8).



Scheme 8

Table 4: Association constants of receptor **1** with some amines (py = pyridine):

Amine	Kass (M^{-1})	δo free amine (ppm)	max Δδ (ppm)
tert-$C_4H_9NH_2$	-----	1.53	no shift
n-$C_4H_9NH_2$	220	1.24	0.63
2-py-NH_2	?	dilution effect	-----
Ph-CH_2NH_2	42	1.54	0.5
4-py-CH2NH2	250	1.56	0.36
2-py-CH2NH2	6.5	1.65	0.25

As it can be seen in the table above, no association was observed in the case of the bulky tert-butylamine whereas good values of K_{ass} were observed in the cases of n-butylamine and 4-aminomethylpyridine. On the other hand, 2-substituted pyridine derivatives gave very weak binding with **1**. Despite the fact that the NMR method gave no result with 2-aminopyridine, we think that the binding with **1** could occur in a small extent if we consider the great difficulties encountered in the removal of this amine from the crude reaction mixture.

These first results are promising and the work concerning the association of receptor **1** with other amines is in progress. An NMR study of the binding of n-butylamine or aminomethylpyridines using various methods like NOESY or ROESY is also in progress in order to explain the large difference between 2 and 4-aminomethylpyridines. The results of these studies will be published later.

Acknowledgement. Our work was supported by a research grant from the *Région Haute Normandie*. We thank Dr. J. P. Vigneron and Dr. J. Brienne from the *Collège de France* for helpful discussions.

EXPERIMENTAL

The infra-red spectra were recorded on a Beckman IR 4250 spectrometer. The ^1H and ^{13}C NMR spectra were recorded either on a 200 MHz or a 400 MHz Bruker apparatus. Spectra were recorded in deuteriochloroform or in hexadeuterio dimethyl sulfoxide (DMSO-d_6). Chemicals were purchased from Aldrich Co or Janssen Co and, unless otherwise stated, were used without further purification.

7-acetyl-2-trifluoroacetyl-1,2,3,4-tetrahydroisoquinoline ***3b***.

To a mixture of 2-trifluoroacetyl-1,2,3,4-tetrahydroisoquinoline **2b**[12] (26.09 g, 0.11 mol) and aluminium trichloride (91 g, 0.66 mol) in carbon disulfide (100 ml) was added dropwise freshly distilled acetyl chloride (26.5 g, 0.33 mol). This addition was carried out in order to maintain a gentle reflux. The mixture was then heated to reflux for 1 hour. The excesses of carbon disulfide and acetyl chloride were removed by distillation and the residue cautiously hydrolysed with aqueous hydrochloric acid (3M solution, 100 ml). After extraction with dichloromethane, the organic layers were washed successively with water, 5% aqueous sodium hydrogenocarbonate and water. After drying on magnesium sulfate and removal of solvent the brown residue was triturated in cyclohexane and filtered. The product can be recrystallized from methanol/ water and the yield was 72% of a yellow solid. m.p. = 84-86°C. ^{1}H NMR (200MHz, $CDCl_3$) : 7.80 (m, 2H, H_6 and H_8) ; 7.30 (t, J= 7.5 Hz, 1H, H_5) : 4.83 (s, 2H, CH_2 at 1) : 3.87 (2dd, J=12.8 Hz and 5.4 Hz, 2H, CH_2 at 3) ; 3.00 (t, J= 5.6Hz, 2H, CH_2 at 4) ; 2.60 (s, 3H, CH_3 acetyle). IR : 1693 cm^{-1} ($COCF_3$ and $COCH_3$). Anal. Calcd for $C_{13}H_{12}F_3NO_2$: C, 57.57 ; H, 4.46; N, 5.16. Found : C, 57.6 ; H, 4.46; N, 5.14.

7-acetyl-2-methyl-1,2,3,4-tetrahydroisoquinoline ***3c*** :

To a cooled solution of 2 methyl-1,2,3,4-tetrahydroisoquinoline **2c**[13] (4 g, 27 mmol) in carbon disufilde (40 ml), aluminium trichloride (21.7 g, 0.16 mol) was added. Acetyl chloride (8.52 g, 0.11 mol) was then added at such a rate to maintain a slow reflux of carbon disufilde. The mixture was heated to reflux for 1 hour and then carbon disulfide and acetyl chloride were removed by distillation. The excess of aluminium trichloride was carefully destroyed with cooling by an aqueous solution of 3M hydrochloric acid. The mixture was then neutralized, under cooling, with 15% aqueous sodium hydroxide. The residue was taken with water and extracted with dichloromethane. After drying on magnesium sulfate, removal of the solvent, the remaining oil was purified by flash chromatography on silica (ethyl acetate/cyclohexane 7/3). The yield was 40% of a yellow oil. ^{1}H NMR ($CDCl_3$, 200 MHz) : 7.70 (dd, 1H, H_6) ; 7.63 (s, 1H, H_8) : 7.18 (d, 1H, J=8 Hz, H_5) ; 3.61 (s, 2H, CH_2 at 1) ; 2.96 (t, J= 5.5 Hz, 2H, CH_2 at 4) ; 2.70 (t, 2H, J=5.5Hz, CH_2 at 3) ; 2.55 (s, 3H, CH_3 acetyle) ; 2.46 (s, 3H, N-CH_3). IR (film) = 1680 cm^{-1} (C=O). MS : M^+=188g (EI).

7-chloroacetyl-2-trifluoroacetyl-1,2,3,4-tetrahydroisoquinoline ***3d***

As described above, a mixture of 2-trifluoroacetyl-1,2,3,4-tetrahydroisoquinoline **2b** (2 g, 8.7 mmol), aluminium trichloride (11 g, 82 mmol) in carbon disufilde (20 ml) was treated with chloroacetyl chloride (2.95 g, 26 mmol) and then heated to reflux for 1 hour. After removal of the excess of reagent and destruction of excess of aluminium trichloride with 3M aqueous hydrochloric acid, the product was extracted with

dichloromethane. After drying on magnesium sulfate and removal of the solvent, the crude product was purified by flash chromatography on silica (ethyl acetate, cyclohexane 55/45). A 88% yield of a yellow solid was obtained. m.p. = 114°C. ^{1}H NMR (200 MHz, $CDCl_3$) : 7.80 (m, 2H, H_6, H_8) ; 7.30 (d, 1H, J = 7.5 Hz, H_5) ; 4.84 (d, 2H, CH_2 at 1) ; 4.70 (s, 2H, CH_2Cl) ; 3.9 (2dd, 2H, CH_2 at 3, J = 6.2 and 14.0 Hz) ; 3.0 (t, 2H, CH_2 at 4, J = 3.8 Hz). Anal. Calcd for $C_{13}H_{11}ClF_3NO_2$: C, 50.08 ; H, 3.63 ; N, 4.58. Found : C, 50.7 ; H, 3.53 ; N, 4.32

7-bromoacetyl-2-trifluoroacetyl-1,2,3,4-tetrahydroisoquinoline ***3e***

A small amount of aluminium trichloride was added to a solution of 7-acetyl-2-trifluoroacetyl-1,2,3,4-tetrahydroisoquinoline **3b** (0.14 g, 0.53 mmol) in methanol (10 ml). Bromine (93 mg, 0.6 mmol) was then added and the resulting mixture was stirred for 1 hour at room temperature, under an argon atmosphere. The product was extracted with dichloromethane and was purified, after drying and removal of solvents, by flash chromatography on silica (diethyl ether) to afford 67% of a colorless oil. ^{1}H NMR (200 MHz, $CDCl_3$) : 7.80 (m, 2H, H_6, H_8) ; 7.30 (d, 1H, J= 7.8 Hz, H_5) ; 4.85 (d, 2H, CH_2 at 1) ; 4.42 (s, 2H, CH_2Br) ; 3.88 (2dd, 2H, J = 6.4 Hz and 12.7 Hz, CH_2 at 3) ; 3.03 (t, 2H, J = 6 Hz, CH_2 at 4). ^{13}C NMR (200 MHz, $CDCl_3$) ; 169(C=O) ; 159(C_7) ; 135 (C_{1a}) ; 128 (C_{4a}) ; 123.3 (Ph) ; 115 (CF_3) ; 41.1 (CH_2 at 1) ; 38.7 (CH_2 at 3) ; 37 (CH_2Br); 26.4 (CH_2 at 4).

7-iodoacetyl-2-trifluoroacetyl-1,2,3,4-tetrahydroisoquinoline ***3f***

A solution of 7-chloroacetyl-2-trifluoroacetyl-1,2,3,4-tetrahydroisoquinoline **3d** (0.340 g, 1.11 mmol) or the bromoacetylderivative **3e** (0.389 g, 1.11 mmol) and anhydrous sodium iodide (0.732 g, 5mmol) in dry acetone (10 ml) was stirred for 24 h at room temperature. The insoluble material was filtered and the filtrate extracted with dichloromethane. The organic layer was washed with a saturated aqueous solution of sodium thiosulfate and then dried on magnesium sulfate. An orange solid was obtained. The yield was 95% with **4a** and 90% with **4b**. mp = 91 °C. ^{1}H NMR (200 MHz, $CDCl_3$) : 7.80 (m, 2H, H_6 and H_8) ; 7.30 (d, 1H, J = 7.7 Hz, H_5) ; 4.85 (2s, 2H, CH_2 at 1) ; 4.34 (s, 2H, CH_2I) ; 3.90 (2dd, J = 5.7 Hz and 13.8 Hz, 2H, CH_2 at 3) ; 3.00 (t, J = 5.7 Hz, 2H, CH_2 at 4). IR (KBr) : 1690cm^{-1}

7-iodoacetyl-2-trifluoroacetyl-1,2,3,4-tetrahydroisoquinoline dimethyl ketal ***3g***

A solution containing iodoketone **3f** (2. 34 g, 5.8 mmol), methyl orthoformate (2.8 g, 26 mmol) and p-toluene sulfonic acid (0.5 g) in methanol (10 ml) was heated to reflux for 90 min. After cooling to room temperature, the solution was neutralized with sodium carbonate (5 % solution) and extracted with dichloromethane. After washing with a saturated aqueous solution of sodium thiosulfate, drying on magnesium sulfate and removal of the solvents, a pale yellow oil was obtained in a 75 % yield. ^{1}H NMR (200 MHz, $CDCl_3$) : 7.30 (m, 2H, H_6 and H_8); 7.20 (d, 1H, J = 7.3 Hz, H_5); 4.80 (2s, 2H, CH_2 at 1); 3.90 (2dd, 2H, J = 5.5 and 12.8 Hz, CH_2 at 3); 3,50 (s, 2H, CH_2-I); 3.21 (s, 6H, 2xCH_3O); 3.00 (t, 2H, J = 5.5 Hz, CH_2 at 4). IR (film): 1694 ($COCF_3$). Anal. calcd for $C_{15}H_{17}F_3INO_3$: C, 40.65; H, 3.87; N, 3.16. Found: C, 40.8; H, 3.9; N, 2.99.

methyl 2-[7-(2-trifluoroacetyl-1,2,3,4-tetrahydroisoquinolein)-yl]ethanoate ***4b***

a) with MCPBA. A solution of iodoketal **3g** (0.302 g, 0.7 mmol) and MCPBA (0.528 g, 2.9 mmol) in methanol or dichloromethane (10 ml) was stirred at room temperature for 16 h. Aqueous sodium carbonate (10 % solution) was then added. After extraction with dichloromethane and washing with an aqueous solution of sodium thiosulfate, the solvents were dried and removed under reduced pressure to afford an oil (Yield 60 %). The product was purified by flash chromatography (silica, cyclohexane/ethylacetate 70/30). ^{1}H NMR (200 MHz, $CDCl_3$) : 7.10 (d, 2x1H, J = 4.6 Hz, H_5 and H_6) ; 7.04 (s, 1H, H_8) ; 4.73 (d, 2H, CH_2 at 1) ; 3.8 (2dd,

2H, CH_2 at 3, J = 6.1 Hz and 10.7 Hz) ; 3.65 (s, 3H, CH_3O) ; 3.56 (s, 1H, CH_2 CO) ; 2.9 (t, 2H, CH_2 at 4 ; J = 6 Hz). IR (film) : 1737 ($COOCH_3$) and 1692 ($COCF_3$).

b) under Willgerodt-Kindler conditions and starting from ***3b***. To a solution of **3b** (4.1 g, 15 mmol) in methanol (28 ml) containing perchloric acid (70 % aqueous solution, 8 ml) thallium (III) nitrate (trihydrate, 10 g, 22 mmol) was added and the mixture stirred for 5 hours at room temperature. After filtration of the insoluble material, methanol was removed and the residue taken up with water. Extraction with dichloromethane followed by drying with magnesium sulfate and removal of solvent afforded an oil which can be purified by flash chromatography on silica (eluent cyclohexane/ethyl acetate 75/25) Yield : 51%. the spectral characteristics are the same as described above.

c) with Iodoketal ***3g*** *and Tl-(III) nitrate.* A solution of iodoketal **3g** (0.2 g, 0.4 mmol) and thallium-(III) nitrate (trihydrate, 0.278 g, 0.6 mmol) in methanol (5 ml) was stirred for 4 days at room temperature. The work up described above afforded **4b** in a 22 % yield.

methyl 2-[7-(2-methyl-1,2,3,4-tetrahydroisoquinolein)-yl]ethanoate ***4c***

To a solution of **3c** (5 g, 26 mmol) in methanol (30 ml) containing perchloric acid (70 % aqueous solution, 20 ml) thallium (III) nitrate (trihydrate, 13 g, 29 mmol) was added and the mixture stirred for 5 hours at room temperature. After filtration of the insoluble material, methanol was removed and the residue taken up with water. Extraction with dichloromethane and removal of solvent afforded an oil which was neutralized with potassium carbonate (5 % aqueous solution). After extraction with dichloromethane followed by drying with magnesium sulfate and removal of the solvent, the product was purified by flash chromatography on silica (eluent cyclohexane/ethyl acetate 75/25 + a few drops of triethylamine). Yield : 55% of a pale yellow oil. ^1H NMR (200 MHz, $CDCl_3$) : 7.05 (s, 2H, H_5 and H_6) ; 6.93 (s, 1H, H_8) ; 3.68 (s, 3H, CH_3-0) ; 3.56 (s, 2 x 2H, CH_2 at 1 and CH_2 at 7) ; 2.90 (t, 2H, J = 5.3 Hz, CH_2 at 4) ; 2.70 (t, 2H, J = 5.3 Hz, CH_2 at 3) ; 2.45 (s, 3H, CH_3N). ^{13}C NMR (200 MHz, DMSO-d_6) : 171 (C=O), 135 (C_7), 133 (C_{4a}), 132 (C_{1a}) , 128.5 (C_5), 127.5 (C_6 + C_8), 57.6 (C_1), 52.7 (C_3), 51.9 ($CH_3$0), 46 (N-CH_3), 44 (CH_2-CO), 28.7 (C_4). IR (film): 1737 (ester). MS ($C_{13}H_{17}NO_2$; M=219.2 g.mol^{-1}): M^+ = 218 (EI)

mixture of methyl and ethyl 2-[7-(1,2,3,4-tetrahydroisquinoline)-yl] acetates ***5a,b***

To a solution of methyl 2-[7-(2-trifluoroacetyl-1,2,3,4-tetrahydroisoquinoline)-yl] acetate **4b** (5.77 g, 19 mmol) in ethanol (100 ml), sodium borohydride (2.87 g, 76 mmol) was added with cooling. The mixture was stirred for 6 h at room temperature. The solvent was removed, the residue taken with water and then extracted twice with dichloromethane. An orange oil was obtained after drying with magnesium sulfate and removal of solvent. Yield : 57%. ^1H NMR (200 MHz, $CDCl_3$) : 7.05 (d, J = 8.9 Hz, 2H, H_5 and H_6) ; 6.92 (s, 1H, H_8) ; 4.14 (q, J = 7.1 Hz, 1.5H, O-CH_2 ester) ; 3.98 (s, 2H, CH_2 at 1) ; 3.68 (s, 0.75H, CH_3O) ; 3.56 (s, 2H, CH_2-COOCH3) ; 3.54 (s, 2H, CH_2-COOEt) ; 3.12 (t, 2H, J = 5.9 Hz, CH_2 at 4) ; 2.77 (t, 2H, J = 5.9 Hz, CH_2 at 3) ; 2.69 (s, 1H, NH) ; 1.25 (t, 2.25H, J = 7.1 Hz, CH_3 ethyl ester). IR (film) : 1731 cm^{-1} (C=O ester).

Mixture of methyl and ethyl 2-[7-(2-methyl-1,2,3,4-tetrahydroisoquinoline)-yl]acetates ***4c-6***

A solution of the preceeding mixture of **5a,b** (2.8 g) and formaldehyde (35% aqueous solution, 4 ml, 0.14 mol) in methanol (50 ml) was heated to reflux for 6 h. The reaction can be monotired by TLC (Alumina plates, ethylacetate/cyclohexane 25/75 ; R_f = 0.8). After cooling sodium borohydride (1.7 g, 45 mmol) was added and the mixture stirred for 12 h at room temperature. After removal of solvent, the product was extracted with dichloromethane. Drying on magnesium sulfate and subsequent removal of solvent afforded the ester mixture **4c-6** in a 55% yield after purification by flash chromatography on neutral alumina (ethyl acetate/cyclohexane 25/75 + a few drops of triethylamine). Orange oil ^1H NMR (200 MHz, $CDCl_3$) : 7.05 (s, 2H, H_5 and H_6) ; 6.93 (s, 1H, H_8) ; 4.15 (q, 1.5H, J = 7.5 Hz, O-CH_2-CH_3) ; 3.66 (s, 0.75H, CH_3-0) ; 3.60 (s,

2H, CH_2 at 7) ; 3.55 (s, 2H, CH_2 at 1) ; 2.90 (t, 2H, J = 5.3 Hz, CH_2 at 4) ; 2.72 (t, 2H, J = 5.3 Hz, CH_2 at 3) ; 2.47 (s, 3H, CH_3N) ; 1.24 (t, 2.25H, CH_3-CH_2O, J = 7.5 Hz)

Synthesis of receptor 1

Preparation of the carboxyclic acid 7. A solution of ester **4c** (0.512 g, 2.3 mmol) ; sodium hydroxide (pellets, 0.189 g, 4.4 mmol) ; in ethanol (95 %, 45 ml) was heated to reflux for 4h. After removal of solvent, aqueous hydrochloric acid (1M volumetric standard solution, 4.4 ml) was cautiously added under cooling. Water was removed by azeotropic distillation with toluene (three times) and the remaining solid was obtained and used without further purification. ^1H NMR (200 MHz, DMSO-d6) : 6.90 (s, 2H, H_5 and H_6) ; 6.83 (s, 1H, H_8) ; 3.44 (s, 2H, CH_2-COOH) ; 3.28 (s, 2H, CH_2 at 1) ; 2.73 (m, 2H, CH_2 at 4) ; 2.50 (m, 2H, CH_2 at 3) ; 2.30 (s, 3H, CH_3-N). IR (KBr) ; 3440 cm^{-1} (carboxylate) and 1576 cm^{-1} (C=O)

2-[7-(2-methyl-1,2,3,4-tetrahydroisoquinoline)-yl]-N-(2-pyridyl)acetamide ***1***. A slurry of lithium aluminium hydride (0.388 g, 5.7 mmol) in dry tetrahydrofuran (10 ml) was heated to reflux for 90 min. After cooling at room temperature, a solution of 2-aminopyridine (2.4 g, 25 mmol) in tetrahydrofuran (10 ml) was slowly added and the resulting mixture stirred for 24 h. A solution of ester **4c** (1.12 g, 5.1 mmol) in tetrahydrofurane (5 ml) was then added and the mixture stirred again for 24 h at room temperature. After carefuly hydrolysis with water (0.2 ml), 10% aqueous sodium hydroxide (0.2 ml) and water (0.6 ml) and 24 h stirring at room temperature, the insoluble material was filtered and washed with dichloromethane. After drying on magnesium sulfate, the solvents were removed under reduced pressure. The excess of 2-aminopyridine was removed by bulb to bulb distillation and the product purified by HPCL on a C_8 Columm : Columm Zorbax (5 µm), 9.4mm x 250mm. Detection wavelength : 290 nm. Injected volume : 0.2 ml. Eluent : phosphate buffer pH = 6/ acetonitrile (60/40) + triethylamine (10 $mmol.l^{-1}$). Flow rate : 3ml min^{-1}. Stick orange oil. HRMS : 281.1523 g. ^1H NMR (200 MHz, $CDCl_3$) : 8.56 (s, 1H, NH) ; 8.20 (2xd, 2H, J = 8 Hz, H_3 and H_6 pyridine ring) ; 7.68 (t, 1H, J = 8 Hz, H_4 pyridine ring) ; 7.00 (m, 4H, H_5 pyridine and H_5, H_6, H_8 isoquinoline) 3.88 (s, 2H, CH_2CO) ; 3.58 (s, 2H, CH_2 at 1) ; 2.90 (t, 2H, J = 5.6 Hz, CH_2 at 4) ; 269 (t, 2H, J = 5.6Hz, CH_2 at 3) ; 2.45 (s, 3H, CH_3N). IR : (film) 1688 (C=O amide).

Determination of binding constants of 1 with various amines : NMR titration method.

The following solutions were prepared : - Receptor **1** was accurately weighed and diluted in $CDCl_3$ (0.5 ml) in order to obtain a concentration exactly known of about 0.02 M into an NMR tube. The NMR spectra of host **1** alone was then recorded. - The amine guest was accurately weighed and diluted in $CDCl_3$ (5 ml) in order to obtain a concentration exactly known of about 0.3 M. Aliquotes of the amine stock solution were successively added and the corresponding NMR spectra recorded : aliquots of 10 µl until having host/guest ~1, then 20 µl aliquots until a total added volume of 100 µl, 40µl aliquots until a total added volume of 300 µl, 100µl aliquots until a total added volume of 1000 µl and finally 200 µl aliquots until a total volume of 2 ml. Typically 18 NMR spectra were recorded with concentrations ranging from 0.019 to 0.006 M in receptor **1**. The chemical shifts of selected protons were measured (normally those were the NH_2 protons of the amine guest since their chemical shifts were most sensitive to the degree of binding). Dilution experiments were also performed in order to be sure that the observed shifts were only due to complexation of guest. A typical experiment is reported below.

Complexation study of 4-aminomethylpyridine. Initial concentration of receptor : 0.0188 M. Concentration of the amine stock solution: 0.282 M. Chemical shift of the NH_2 protons δo = 1.559. Are successively given for each experimental point : Point number, cumulated volume of guest solution (µl), host concentration ($mol.l^{-1}$), guest concentration ($mol.l^{-1}$), chemical shift (δ ppm). Point 1: 10, 0.0184, 0.00553, 1.926. Point 2: 20, 0.0181, 0.01084, 1.884. Point 3: 30, 0.0177, 0.016, 1.840. Point 4: 50, 0.0171, 0.0256, 1.756. Point 5: 70, 0.0165, 0.0346, 1.717. Point 6: 90, 0.0159, 0.0430, 1.693. Point 7: 110, 0.0154, 0.0508,

1.678. Point 8: 150, 0.0144, 0.0651, 1.652. Point 9: 190, 0.0136, 0.0776, 1.639. Point 10: 230, 0.0129, 0.0888, 1.624. Point 11: 270, 0.0122, 0.0989, 1.616. Point 12: 310, 0.0116, 0.108, 1.611. Point 13: 410, 0.0103, 0.127, 1.595. Point 14: 610, 0.0084, 0.155, 1.578. Point 15: 810, 0.0072, 0.0174, 1.567. Point 16: 1010, 0.0062, 0.1886, 1.563. Point 17: 1410, 0.049, 0.0208, 1.561. The association constant was computed with a turbopascal program based on the mole fraction method described by Horman and Dreux.[30]

Job plot showing a 1:1 complexation mode between ***1*** *and 4-aminomethylpyridine.* Equimolar solutions (0.0124 $mol.l^{-1}$) of host **1** and 4-aminomethylpyridine were prepared and mixed in various amounts in order to obtain a constant value for the sum [Host]+ [Guest]. ^1H NMR spectra of the mixtures were recorded, and the chemical shifts were analyzed by the classical method. [31b,c] Are successively given for each experimental point : Point number, host concentration ($mol.l^{-1}$), guest concentration ($mol.l^{-1}$), chemical shift (δ Hz) of the NH_2 protons. Point 1: 0.00, 0.0124, 306.2. Point 2: 0.0025, 0.0099, 319.6. Point 3: 0.005, 0.0074, 338.1. Point 4: 0.0062, 0.0062, 348.1. Point 5: 0.0074, 0.005, 358.7. Point 6: 0.0099, 0.0025, 382.7.

REFERENCES AND NOTES

1. For reviews see a) Hoss, R.; Vögtle, F. *Angew. Chem. Int. Ed. Engl.*, **1994**, *33*, 375-384. b) Anderson, S.; Anderson, H. L.; Sanders, J. K. M. *Acc. Chem. Res.* **1993**, *26*, 469-476. c) Lehn, J. M.; *Angew. Chem. Int. Ed. Engl.*, **1988**, *27*, 89-112. d) Cram, D. J. *Angew. Chem. Int. Ed. Engl.* **1988**, *27*, 1009-1020. e) Pedersen, C. J. *Angew. Chem. Int. Ed. Engl.* **1988**, *27*, 1021-1027.
2. Tabushi, I. *Tetrahedron*, **1984**, *40*, 269-292
3. a) Cram, D.J. ; Cram, J.M. *Acc. Chem. Research*, **1978**, *11*, 8-14. b) Graf, E. ; Kintzinger, J.P. ; Lehn, J.M. ; Lemoigne, J. *J. Am. Chem. Soc.*, **1982**, *104*, 1672-1678. c) Behr, J.P. ; Lehn, J.M. *Helv. Chim. Acta*, **1980**, *63*, 2112-2118. d) Behr, J.P.; Lehn, J.M. ; Vierling, P. *Helv. Chim. Acta*, **1982**. *65*, 1853-1864. e) Canceill, J. ; Collet A. ; Gabard, J. ; Kotzyba-Hibert, F. ; Lehn, J.M. *Helv. Chim. Acta*, **1982**, *65*, 1894-1897. f) Webb, T. H.; Wilcox, C. S. *Chem. Soc. Rev.*, **1993**, 383-395.
4. a) Reetz, M-T. ; Niemeyer, C.M. ; Hermès, M. ; Goddard, R. *Angew. Chem. Int. Ed. Engl.*, **1992**, 31, 1017-1019. b) Nozaki, K.; Tsutsumi, T.; Takaya, H. *J. Org. Chem.*, **1995**, *60*, 6668-6669.
5. Wang, T. ; Bradshaw, J-S. ; Izatt, R.M., *J. Heterocyclic Chem.*, **1994**, *31*, 1097-1114 and references cited therein.
6. Bordunov, A. V.; Hellier, P. C.; Bradshaw, J. S.; Kent Dalley, N.; Kau, X.; Xian Xin Zhang; Izatt, R. M. *J. Org. Chem.*, **1995**, 6097-6112.
7. Bauer, L.J. ; Gutsche, C.D. *J. Am. Chem. Soc.*, **1985**, *107*, 6063-6069 and references cited therein for a comprehensive study of conformational properties of calixarenes.
8. Kubo, Y. ; Maruyama, S. ; Ohhara, N. ; Nakamura, M. ; Tokita, S. *J. Chem. Soc. Chem. Commun.*, ,**1995**, 1727-1728.
9. Pieters, R.J. ; Rebek Jr. J. *Rec. Trav. Chim., Pays-Bas*, **1993**, *112*, 330-334.
10. a) Kelly, T.R. ; Bridger, G-J. ; Zhao, C. *J. Am. Chem. Soc.*, **1990**, *112*, 8024-8034. b) Papadopoulou, M. V.; Goswami, S.; Hamilton, A. D. *J. Heterocyclic Chem.*, **1995**, *32*, 675-681.
11. Molecular mechanics and semi-empirical calculations were performed either with HYPERCHEM and PCMODEL, MOPAC6. Structures were first minimized with the MM2 force field and semi-empirical calculations were there done at the MNDO level. In the case of receptor **1**, the AMBER force field was also used with the parameters published. See for example: a) Weiner, S. J.;

Kollman, P. A.; Nguyen, D. T.; Case, D. A. *J. Comput Chem.*, **1986**, *7*, 230-252. b) Clark, M.; Cramer, R. D.; Van Opdenbosch, N. *J. Comput. Chem.*, **1989**, *10*, 982-1012.

12. El-Fehail Ali, F.; Gleason, J. G.; Hill, D. T.; Krell, R. D.; Kruse, C. H., Lavanchy, P. G.; Volpe, B. W. *J. Med. Chem.*, **1982**, *25*, 1235-1240.

13. Blagg, J.; Coote, S. J.; Davies, S. G.; Mobbs, B. E. *J. Chem. Soc. Perkin Trans. I*, **1986**, 2257-2261.

14. Brown, E. V. *Synthesis*, **1975**, 358-375.

15. a) Mac Killop, A.; Swann, B. P.; Taylor, E. C. *J. Am. Chem. Soc.*, **1971**, *93*, 4919-4920. b) a) Mac Killop, A.; Swann, B. P.; Taylor, E. C. *J. Am. Chem. Soc.*, **1973**, *95*, 3340-3343. c) Higgins, S. D.; Thomas, C. B. *J. Chem. Soc. Perkin Trans. I*, **1982**, 235-242. d) Higgins, S. D.; Thomas, C. B. *J. Chem. Soc. Perkin Trans. I*, **1983**, 1483-1488.

16. Cambie, R. C.; Chambers, D.; Lindsay, B. G.; Rutledge, P. S.; Woodgate, P. D. *J. Chem. Soc. Perkin Trans. I*, **1980**, 822-827.

17. Weygand, F.; Frauendorfer, E. *Chem. Ber.*, **1970**, *103*, 2437-2449.

18. a) Sondengam, B. L.; Hentchoya Hémo, J.; Charles, G. *Tetrahedron Letters*, **1973**, 261-263. b) Kapnang, H.; Charles, G.; Sondengam, B. L.; Hentchoya Hémo, J. *Tetrahedron Letters*, **1977**, 3469-3472.

19. Mikolajczyk, M.; Kielbasinski, P. *Tetrahedron*, **1981**, *37*, 233-284.

20. Buzas, A.; Canac, F.; Egnell, C.; Fréon, P. *C. R. Acad. Sci. Ser. C*, **1966**, *262*, 658-661.

21. Sheehan, J. C.; Preston, J.; Cruickshank, P. A. *J. Am. Chem. Soc.*, **1965**, *87*, 2492-2493.

22. a) Sheehan, J. C.; Hllavka, J. J. *J. Org. Chem.*, **1956**, *12*, 439-441 b) Raposo, C.; Martin, M.; Mussons, H. L.; Crego, M.; Anaya, J.; Caballero, M. C.; Moran, J. R. *J. Chem. Soc. Perkin Trans. I*, **1994**, 2113-2116.

23. a) Sheehan, J. C.; Cruickshank, P. A.; Boshart, G. L. *J. Org. Chem.*, **1961**, *26*, 2525-2528. b) Taha, T. S. M.; Ferguson-Miller, S. *Biochemistry*, 1992, 31, 9090-9097.

24. a) Nguyen, D. L.; Seyer, R.; Heitz, A.; Castro, B. *J. Chem. Soc. Perkin Trans. I*, **1985**, 1025-1031. b) Hudson, D. *J. Org. Chem.*, **1988**, *53*, 617-624.

25. Cossu, S.; Conti, S.; Giocomelli, G.; Falormi, M. *Synthesis*, **1994**, 1429-1432.

26. Högberg, T.; Ström, P.; Ebner, M.; Rämsby, S. *J. Org. Chem.*, **1987**, *52*, 2033-2036.

27. Sim, T. B.; Yoon, N. M. *Syn. Lett.*, **1994**, 827-828.

28. Solladié-Cavallo, A.; Bencheqroun, M. *J. Org. Chem.*, **1992**, *57*, 5831-5834.

29. Connors, K. A. *Binding Constants*; Wiley: New York, 1989; p. 26.

30. a) Horman, I.; Dreux, B. *Anal. Chem.* **1983**, *55*, 1219-1221. b) Horman, I.; Dreux, B. *Helvetica Chim. Acta*. **1984**, *67*, 754-764. c) Kelly, T. R.; Kim, M. H. *J. Am. Chem. Soc.* **1994**, *116*, 7072-7080.

31 a) Job, A. *Ann. Chim. (10 th series)* **1928**, *9*, 113-204. For recent and comprehensive examples of Job plots see: b) Blanda, M. T.; Horner, J. H.; Newcomb, M. *J. Org. Chem.* **1989**, *54*, 4626-4636. c) Coteron, J. M.; Hacket, F.; Schneider, H. J. *J. Org. Chem.* **1996**, *61*, 1429-1435.

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