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Dibenz[*c,h*]acridine Receptors for Dibutylmalonic Acid. Decarboxylative Catalytic Activity†

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Abstract: New molecular receptors with dibenz[*c,h*]acridine skeleton bearing functional groups complementary to malonic acids have been developed. Dibutylmalonic acid is bound in chloroform with Kass values between 10^2 and 10^5 M^{-1} via hydrogen-bonding interactions. The catalytic ability of several of these receptors in the decarboxylative reaction of this diacid has been investigated.

The decarboxylation of suitably substituted amidomalonic acids is a well known procedure for preparing racemic α-aminoacids.[1] However, the natural enzyme L-aspartate decarboxylase induces the chiral decarboxylation of these diacids.[2]

Similarly, it would be interesting to synthesize a chiral molecular receptor for complexing malonic acids, with catalytic decarboxylative activity and able to induce chirality in the process. Such a molecule would be an enzyme-like catalyst, which would allow the preparation of chiral amino acids.

As a first step, it is necessary to develop receptors with good recognition of malonic acid derivatives. There are many synthetic receptors that have been reported to complex malonic acids,[3] we are also developing new receptors for dibutylmalonic acid that are derivatives of the rigid 2,12-diamino-5,6,8,9-tetrahydro dibenz[*c,h*] acridine framework show structure **6**, which features convergent hydrogen-bonding sites for malonic acid derivatives.

In this paper we communicate the synthesis and complexation properties of these receptors and the results of the decarboxylative catalytic activity of some of them.

RESULTS AND DISCUSSION

Synthetic strategies

There are several different methods in the literature to prepare 5,6,8,9-tetrahydrodibenz[*c,h*]acridines[4] but none of them are used to prepare 2 and 12 difunctionalized derivatives in which we are interested. On the other hand it is not easy to obtain them from the unfunctionalizated basic structure. Our synthetic strategy is based in the dimerization of easily prepared derivatives of α-tetralone, as shown in Scheme 1. The key steps of the synthesis are the condensation of enamine **2** with the Mannich-base **3** leading to intermediate **4**, and cyclization of the diaminodicarbonyl **5** to compound **6**.

† This paper is dedicated to the memory of the late Prof. Joaquín de Pascual Teresa

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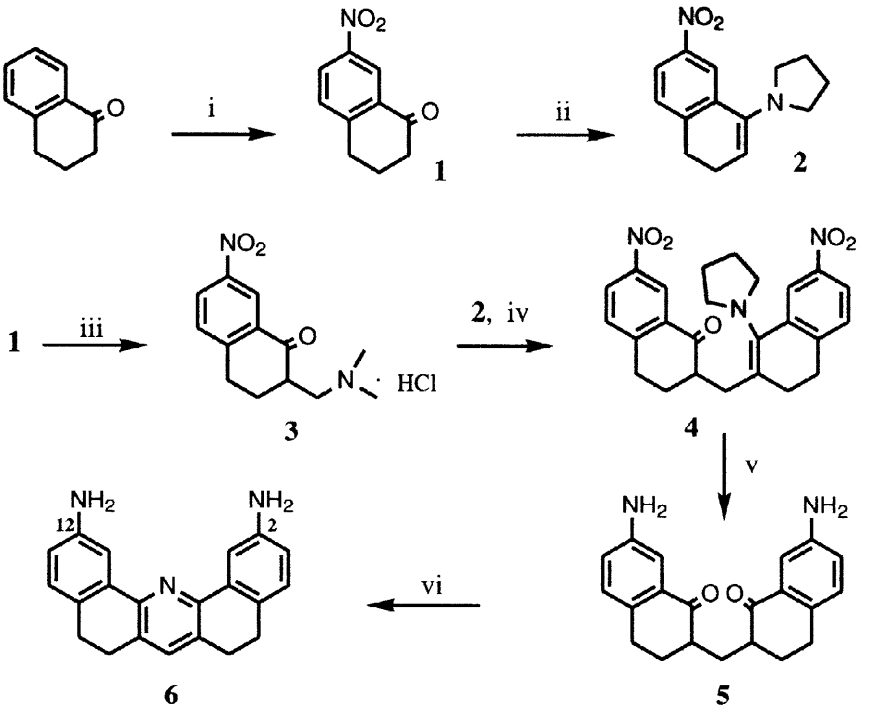
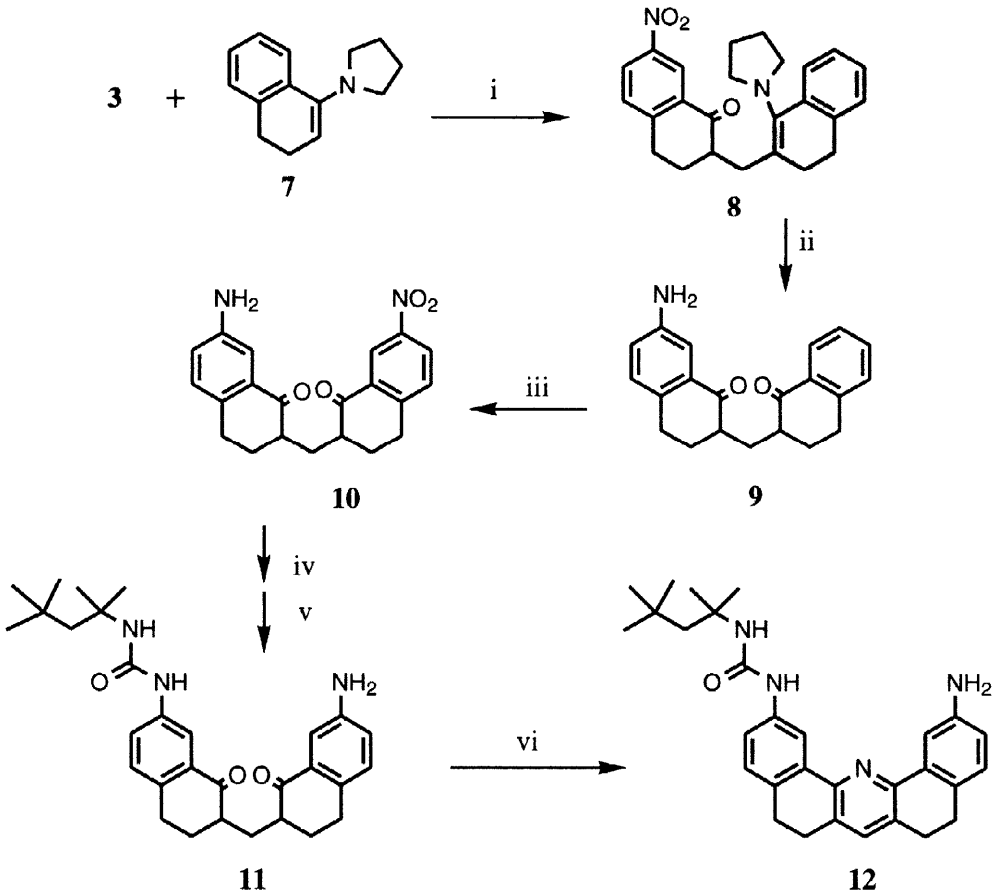


Scheme 1. *Reagents and conditions:* i) HNO_3/H_2SO_4, (63%); ii) $TiCl_4$/pyrrolidine, (90%); iii) $H_2C{=}^{+}N(CH_3)_2Cl^{-}$/AcCl, 12h, r.t., (88%); iv) EtOH, 3h r.t., (76%); v) $SnCl_2$/HCl, 10 min., 60°C, (87%); vi) 1: $AcO^{-}NH_4^{+}$/AcOH, 3h reflux; 2: KOH/EtOH, 4h reflux, (61%).

The preparation of enamine **2** was carried out from ketone **1** by treatment with pyrrolidine and titanium tetrachloride as catalyst.[5] On the other hand, the treatment of **1** with a molar equivalent of Eschenmoser's salt yielded the hydrochloride **3** as a white crystalline solid. The condensation of **2** and **3** in ethanol at room temperature produced diketone **4**, which did not require isolation because upon reduction to **5** hydrolysis of the enamine took place.

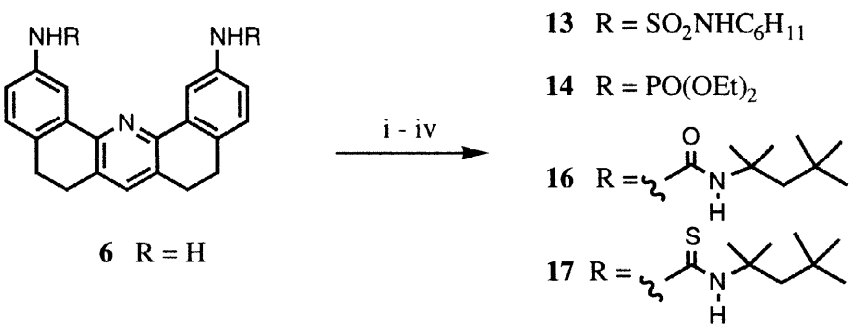
Accordingly, crude dinitroderivative **4** was reduced to the diaminodicarbonyl compound **5** with tin dichloride dihydrate in HCl.[6] The ^1H NMR spectrum of the reaction product showed a diastereomeric mixture which it was unnecessary to resolve because the stereogenic centers are lost in the final step of the synthetic sequence. Cyclization[7] of the reduced compound with ammonium acetate in acetic acid for 3 h under reflux provided a diacetamide, which upon treatment with KOH in ethanol at reflux for 4 h afforded the dibenz[*c*,*h*]acridine **6**.

As it was not possible to achieve the synthesis of non-symmetrically substituted structures by mono functionalization of **6** because the yield of the mono functionalized product was very poor, Scheme 1 was modified to the more general synthetic route showed in Scheme 2. This approach was adequate for the preparation of tetrahydro dibenz[*c*,*h*]acridines carrying different substituents at the 2 and 12 positions. In this work, a urea function was selected for the first monofunctionalization, although other groups could be also introduced.



Scheme 2. *Reagents and conditions:* i) EtOH, r.t. (90%); ii) $SnCl_2$/HCl, 10 min, 60°C (92%); iii) HNO_3 /H_2SO_4, - 30°C (62%); iv) 1: Cl_2CO/THF; 2 : t-octylamine /THF (91%); v) H_2, Pd/C (5%) /EtOH, 2h, r.t. (95%); vi) 1 : $AcO^-NH_4^+$, 2h, reflux; 2: KOH/EtOH, 3h, reflux (78%)

The functional modification of the amino groups in **6** or **12** allowed the preparation of symmetric (receptors **13**, **14**, **16** and **17** Figure 1) or asymmetric 2,12-disubstituted receptors with 5,6,8,9-tetrahydrodibenz [*c,h*] acridine skeleton.



Reagents : i) N-cyclohexylsulfamoyl chloride/pyridine (77%); ii) diethyl chlorophosphate/ pyridine (74%); iii) 1. phosgene; 2.*tert*-octylamine (73%); iv) : 1. thiophosgene; 2. *tert*-octylamine (67%).

Figure 1. Structure of receptors **13**,**14**,**16** and **17**, directly synthesized from diamine **6**.

Binding properties of the Dibutylmalonic Acid Receptors

The establishement of a host-guest complex through four H-bonds with a malonic acid derivative could be achieved by a 1,3 arrangement of hydrogen bond donors and acceptors in the host, well suited for binding the guest.

The geometry of receptor **13** with two sulfurylamide arms, has the required planarity in the cavity for complexing dibutylmalonic acid (DBMA) with four linear hydrogen bonds, withthe advantage of allowing the intramolecular H-bond of the guest to be maintained in the complex (Figure 2). The synthesis of receptor **13**, with symmetric sulfurylamide functionalization (Figure 1), was carried out by treatment of **6** with N-cyclohexylsulfamoyl chloride in pyridine at room temperature, in 77% yield.

The binding properties were followed by ^{1}H NMR spectroscopy in chloroform. The analysis of titration data using a non-linear least squares regression led to the determination of the association constants. Among the malonic acids, dibutylmalonic acid was chosen as guest due to its solubility in this solvent. NMR titrations of afore cited receptors with DBMA were performed at 293K; the calculated association constants are summarized in Table 1.

The signal of the sulfurylamide N*H* linked to the aromatic ring was shifted 0.12 ppm downfield after guest addition. Analysis of the ^{1}H NMR titrations data led to the deduction of an association constant of $7x10^2$ M^{-1}, lower than the expected for a four H-bond complex binding. That could be explained because the receptor shows a self complementary structure which leads to a strong dimerization in this solvent (Figure 2). When a dilution titration was performed over the range of concentrations studied, a value of K_d= $2x10^3$ M^{-1} for the dimerization was measured.

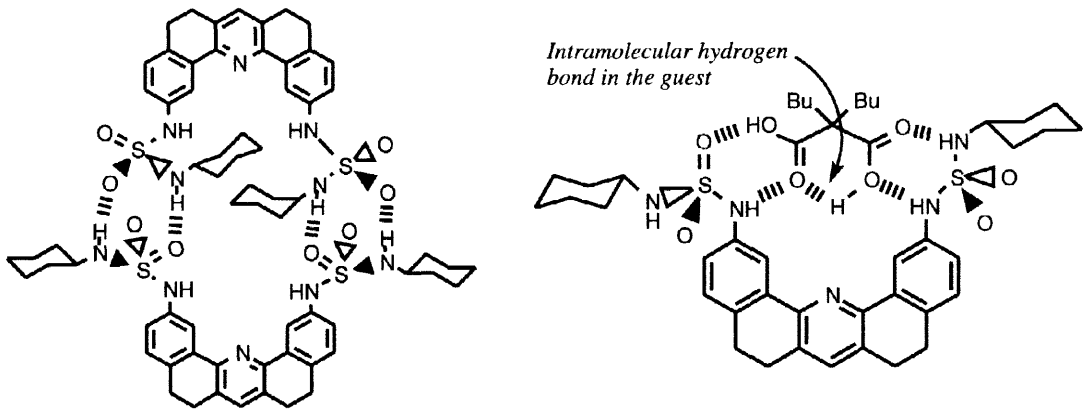


Figure 2. Proposed structures for the dimer of disulfurylamide **13** and the four hydrogen bond complex between the free form of this compound and dibutylmalonic acid, with an intramolecular hydrogen bond.

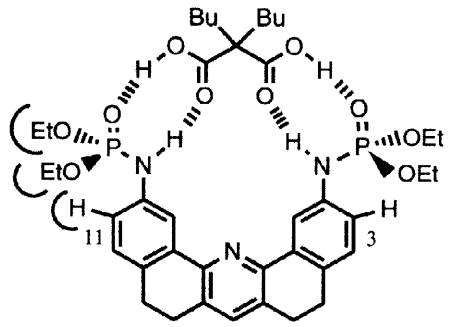


Figure 3. Proposed complex between receptor **14** and DBMA

CPK models show that receptor **14** has a good complementarity with DBMA to establish a complex with four H-bonds (Figure 3). The tetrahedral structure of the phosphorylamide group of **14**, is interesting because it avoids steric repulsions with *ortho* aromatic protons at the 3 and 11 positions of the acridine framework, because these aromatic protons are placed between the ethoxy groups of the phosphorylamide. This receptor, with symmetrical functionalization, was prepared in 74% yield by reaction of **6** with a bimolecular amount of diethyl chlorophosphate in pyridine at room temperature (Figure 1).

Several signals of receptor **14** were shifted after guest addition; among them, the N*H* of the phosphorylamide showed a 2.22 ppm downfield shift, demonstrating that this receptor strongly binds DBMA (Table 1).

The bislactam receptor **15** (Figure 4) has a 1,3-relationship between donor and acceptor hydrogen bonds, as for preceding receptors, and butyl chains for increasing the solubility of the molecule. This receptor was obtained by acylation of the amine groups of **6** with the chloride of dibutylmalonic acid monoethylester, followed by hydrolysis of the ester groups and cyclization with Eaton's reagent (phosphorus pentoxide, 7.5 % wt in methanesulfonic acid)[9] (56 % overall yield).[10]

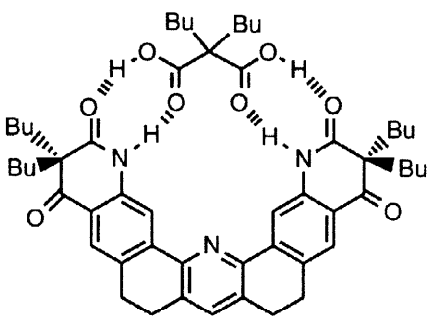


Figure 4. Proposed complex between receptor **15** and DBMA

The addition of DBMA to this receptor led to a progressive downfield shift of the aromatic protons inside the cavity to 8.23 ppm ($\Delta\delta$ = 0.27 ppm), due to the anisotropic effect produced in the complex by the nonbonding electrons of the carbonyl groups of the guest on the spatially close aromatic hydrogens.

The plotting of deshielding measurements gave a very high value for the association constant of this receptor, which is slightly higher than that of the diphosphorylamide receptor **14** (Table 1).

The entropic factors are more favorable for complexing the guest in rigid structure **15** where the H-bonds are more preorganized into the cavity than in **14**. We propose a host-guest complex with four H-bonds, as Figure 4 shows.

Other receptors carrying an urea **16** and a thiourea **17**, well known functional groups for their role in the molecular recognition of carboxylic acids, have been developed.[11] In these receptors *tert*-octyl residues had been introduced because branched alkyl chains could facilitate the solubilization of the molecules.

These receptors were prepared by treatment of **6** with an excess of phosgene or thiophosgene, followed by addition of *tert*-octylamine (yields 73 % for **16** and 67 % for **17**).

N,N'-Disubstituted ureas prefer an *anti-anti* conformation, but the structure of the substituents affects the conformational equilibrium.[12] In this case, a conformational analysis of compound **16** using Macromodel showed only an $\Delta\Delta G < 1$ Kcal/mol between *anti-anti* and *syn-anti* conformations.

Figure 5 shows above cited host conformations and H-bond modes resulting from each in the complex with DBMA. The *anti-anti* host conformation binding the guest in a conformation that shows both hydrogen atoms in the carboxylic groups in the *anti* position which in known to be disfavour due to the lack of anomeric effect.[13]

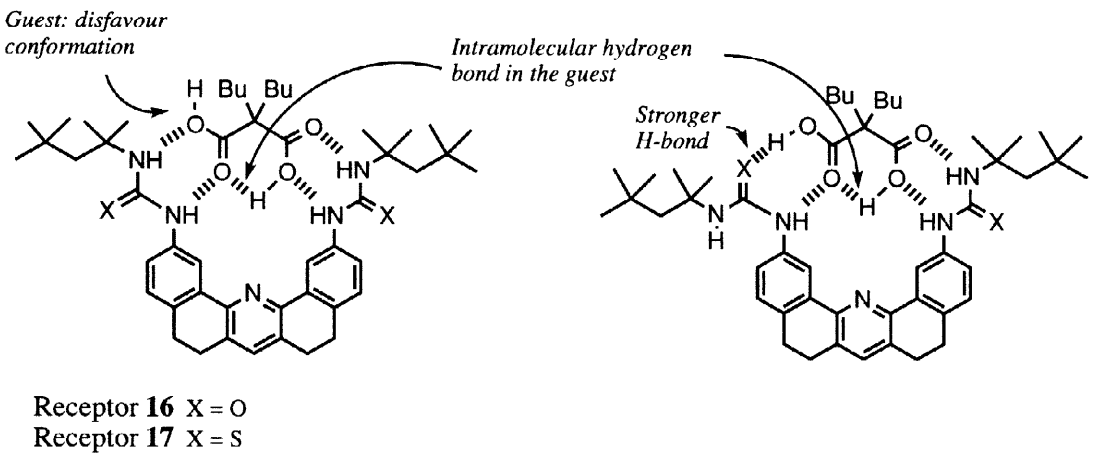


Figure 5. Proposed complexes for *anti-anti* and *syn-anti* conformations of receptors **16** and **17** with DBMA, maintaining the intramolecular hydrogen bond in the guest.

Therefore, these ureas can act either a with *syn* or *anti* conformations as a donor-acceptor or double donor of hydrogen bonds respectively in the complexation of DBMA, which allows the intramolecular hydrogen bond of the guest to be maintained in the complex (Figure 5).

A 1.80 ppm downfield shift of the N*H* of the urea group binds to aromatic ring was observed upon titration, also the H-1 signals were shifted about 0.12 ppm. The high association constant value deduced from the titration data confirms the formation of an effective complex, despite the twisted geometry of the receptor due to steric hindrance of the *ortho* hydrogens of the aromatic rings; this torsion prevents the formation of fully linear hydrogen bonds with the guest.

The association constant for dithiourea receptor **17** was four times lower than the one observed for the related diurea probably because thiourea S atom is less good H-bond acceptor that O atom. This result is in agreement with the results published by Wilcox.[14]

Taking into account these association constant results a new receptor **18** was designed (Figure 6) in which both urea and phosphorylamide binding arms are included, as double donor and donor-acceptor of H-bonds respectively. This would allow the complexation of DBMA by **18** maintaining the intramolecular hydrogen bond in the guest.

The synthesis of **18** from diamine **6** was carried out by treatment with one equivalent of 4-chlorophenyl isocyanate. The monourea derivative was isolated from the crude of reaction by column cromatography. Posterior treatment with diethyl chlorophosphate gave the chloroform soluble receptor **18** in a 32% overall yield. The value obtained for the association constant with this receptor and DBMA was 1.3 x 10^5 M^{-1}, which is very close to that obtained for diphosphorylamide receptor **14** (Table 1). In our opinion, this very good result can be better explained if the intramolecular hydrogen bond of malonic acid is maintained in the complex (Figure 6).

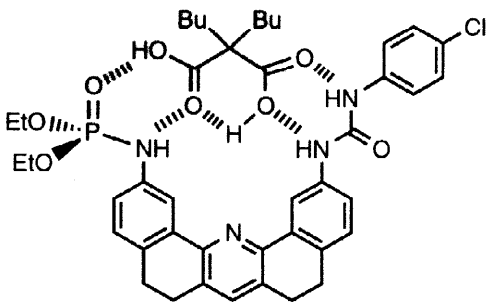


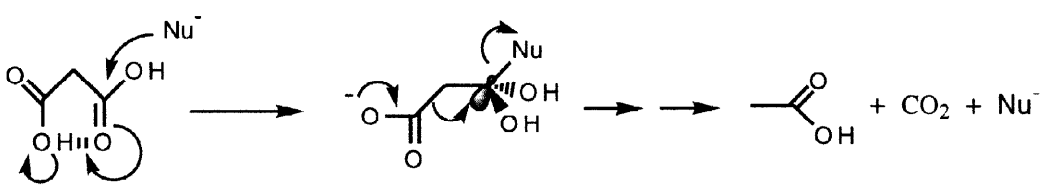
Figure 6. Proposed complex between receptor **18** and DBMA

Table 1. Association constants of receptors **13-18** with dibutylmalonic acid in $CDCl_3$ at 20 °C

Receptor	Kass [M^{-1}]
disulfamoylamide **13**	7 2 x 10^2
diphosphorylamide **14**	1.5 x 10^5
bislactam **15**	2.8 x 10^5
diurea **16**	2.6 x 10^4
dithiourea **17**	7.8 x 10^3
phosphorylamide-urea **18**	1.3 x 10^5

Decarboxylation studies

It is known that weak nucleophiles, such as pyridine or quinoline, strongly catalyze the decarboxylation reaction[15] of substituted malonic acids through a mechanism in which the intramolecular hydrogen bond in the malonic acid[16] favours the nucleophilic addition by intramolecular general acid catalysis. Then, a decarboxylative fragmentation step of a carboxylate with a good β-leaving group takes place[17] (Scheme 3).



Scheme 3 : Proposed mechanism for malonic acid decarboxylation

Therefore, a higher stabilization of this transition state in relation to the ground state will be produced if the hydrogen bonds formed in the complex become stronger.[18] We expected this, because a carboxylate must be generated in the transition state and the hydrogen bonds in the complex will be stronger as the negative charge on the oxygen atom increases. Backing up this decarboxylation mechanism of malonic acid, we carried out

this reaction with the developed receptors that can associate with the guest while maintaining its intramolecular H-bond in the complex.

Catalytic studies were performed using gas volumetry, as described by Corey.[19] The decarboxylative kinetic experiments with DBMA were carried out with no receptors or with addition of 6% of a receptor. With receptors **16** and **17**, a forward decarboxylation reaction resulted with a four-fold reduction of half life (Table 2). Slightly higher than in the preceding cases was the activity of receptor **18**, which could indicate that the high acidity of the N*H* 4-chlorophenyl urea provided a stronger H-bond in the transition state.

Noticing the last result, we reconsidered the receptor **13**, because its more acidic sulfurylamide groups N*H* could establish stronger H-bonds in the transition state. The decarboxylation half-life decreased to 16 min., which is a good result assuming that only the non-dimerized host molecules are participating in the reaction.

Table 2. Half-life decarboxylation of dibutylmalonic acid for receptors with binding scheme of double donor and acceptor-donor H-bonds.[a]

catalyst receptor	approx half-life
none	110 min
15	26 min
16	28 min
18	22 min
13	16 min

[a] In all cases, catalyst concentration is 0.06 M and isoquinoline concentratration is 0.0003 M.

The stabilization of the positive charge developed in the nucleophile in the transition state could contribute to the reduction of the reaction time, as observed in previous work.[3g] CPK models showed that in receptors **19** and **20** there could be interactions of the nonbonding electrons of the ester group and the positively charged isoquinoline nitrogen ring in the transition state (Figure 7).

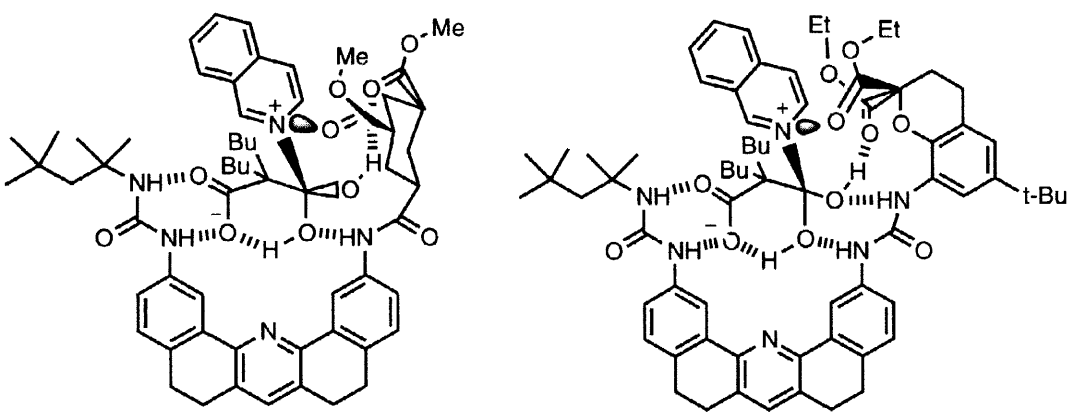


Figure 7. Proposed transition states for decarboxylation of DBMA in the complexes **19**•DBMA and **20**•DBMA

The synthesis of **19** and **20** were carried out following Scheme 2. When **12** was treated with the chloride of *cis*-3,5-methoxycarbonylcyclohexanecarboxylic acid in triethylamine, receptor **19** was obtained in 62% yield. In the treatment of **12** with the isocyanate of 8-amine-6-*tert*-butylchroman-2,2-dicarboxylic acid diethyl ester,[20] receptor **20** was produced in 68% yield.

The binding study with receptor **19** showed a Kass of the same order of diurea **16**, unfortunately it was not possible to measure shifts of the geminal protons to ester groups because they were overlapped, however the constant value seems to be in agrement with the establishement of a complex with four H-bonds.

Receptor **20** showed a value of the association constant of $1.4 \times 10^5\ M^{-1}$, suggesting that a fifth bond should be established between the receptor and guest (Figure 7). This additional hydrogen bond produced a drastic 10-fold increase of the binding constant in comparison with **19**. The lack of protons close to the atoms implicated in the additional H-bond did not allow direct observation by NMR, but the formation of a new bond is implicated bearing in mind that the Kass value is also one order higher that in the case of diurea **16**.

Table 3 . Half-life of decarboxylation[a] of dibutylmalonic acid and association constants for receptors **19** and **20**

catalyst receptor	approx half-life	Kass $[M^{-1}]$
none	110 min	
19	32 min	1.3×10^4
20	24 min	1.4×10^5

[a] In all cases, catalyst concentration is 0.06 M and isoquinoline concentration 0.0003 M.

However, catalytic activity was not improved. Kinetic measurements (Table 3) of decarboxylative activity were similar to previous results. The lack of rigidity of these molecules probably does not favour the expected geometry of the transition state.

In summary, we have developed new hosts featuring several functionalizations in a semirigid structure with a dibenz[c,h]acridine skeleton that undergo strong and selective complexation with malonic acids in chloroform. The results obtained in the decarboxylative catalytic activity assays with receptors that complexed the guest with maintenence of its intramolecular hydrogen-bond showed a significant reduction in the reaction half life in the presence of 6% of receptor. We consider that these results can be improved by incorporation into the **6** and **12** structures of more elaborate moieties, as could be phosphorinane rings similarly at we have made in benzophenone receptors,[3g] which could allow better catalytic results to be obtained.

Acknowledgments
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Experimental

General. M.p.'s were determined on a Kofler hot-stage apparatus and are uncorrected. Column chromatography was performed on silica gel Merck 60, 230-400 mesh, and TLC on silica gel Merck 60, F_{254}. Infrared spectra were recorded on Bomem MB-100FT spectrophotometer as liquid films unless otherwise stated. The ^1H NMR and ^{13}C NMR spectra were recorded on a Bruker WP-200-SY spectrometer

operating at 200 MHz and 50.3 MHz respectively. Chemical shifts (δ) are reported in ppm with TMS as internal standard; *J* values are recorded in Hz. Mass spectra were measured on a VG-TS-250 spectrometer (electronic impact 70 eV). Elemental analyses were carried out using a Perkin-Elmer 240 B Analyser.

1-(7-Nitro-3,4-dihydro-1-naphthyl)pyrrolidine (2): 7-nitro-α-tetralone (15 g, 0.078 mol) in diethyl ether (200 ml) was mixed with pyrrolidine (40 ml, 0.47 mol) in diethyl ether (80 ml). A suspension of $TiCl_4$ (4.3 ml, 0.039 mol) in hexane (60 ml) was added dropwise to the former solution under argon atmosphere at 0 °C. The precipitate which appeared was filtered off and the solvent was evaporated from the filtrate to give the enamine **2** as an oil (17.2 g, 90%); ν_{max}/cm^{-1} 3084, 3046, 2957, 2893, 2839, 1617, 1522, 1343, 1254 and 849; $\delta_H(CDCl_3)$ 8.22 (1H, d, *J*=2.4 Hz, H-8), 7.99 (1H, dd, *J*=8.2, 2.4 Hz, H-6), 7.28 (1H, d, *J*=8.2 Hz, H-5), 5.29 (1H, t, *J*=4.6 Hz, H-2), 2.95 (4H, m, $2CH_2$), 2.74 (2H, t, *J*=7.0 Hz, H-4), 2.27 (2H, m, H-3) and 1.94 (4H, m, $2CH_2$); $\delta_C(CDCl_3)$ 146.8 (s), 145 (s), 144.1 (s), 134.4 (s), 127.7 (d), 121.1 (d), 118.6 (d), 106.3 (d), 2 x 50.6 (t), 28.9 (t), 2 x 23.9 (t) and 22.0 (t).

2-Dimethylaminomethyl-7-nitro-3,4-dihydro-1(2H)-naphthalenone hydrochloride (3): To a solution of N,N,N',N'-tetramethyldiaminomethane (57 ml, 0.42 mol) in dry diethyl ether (500 ml) at 0 °C was added dropwise acetylchloride (30 ml, 0.42 mol) in diethyl ether (350 ml). Once finish the addition, the reaction was stirred for 30 min. at room temperature under Ar to give a white solid, which was quickly filtered and added to acetylchloride (30 ml). Then 7-nitro-α-tetralone **1** (30 g, 0.16 mol) was added to this mixture and the reaction was stirred for 12 h at room temperature. The resulting precipitate was collected to give the hydrochloride **3** (40 g, 88%) as a white solid, mp 161 °C; ν_{max}(Nujol)/cm^{-1} 3025, 2562, 2475, 1682, 1609, 1534, 1425, 1233 and 1092; δ_H (CD_3OD) 8.69 (1H, d, *J*=2.2 Hz, H-8), 8.34 (1H, dd, *J*=8.3, 2.2 Hz, H-6), 7.61 (1H, d, *J*=8.3 Hz, H-5), 3.68 (1H, dd, *J*=8.9, 3.7 Hz, CH_2N, H-3), 3.45-3.10 (4H, m, CH_2N, H-2, H-4), 3.01 (3H, s, NCH_3), 2.97 (3H, s, NCH_3), 2.40-2.25 (1H, m, H-3) and 2.15-1.90 (1H, cd, *J*=12.0, 4.0 Hz, H-3); $\delta_C(CD_3OD)$ 198.8 (s), 152.6 (s), 148.5 (s), 133.7 (s), 132.1 (d), 128.9 (d), 123.0 (d), 59.9 (t), 45.6 (q), 43.9 (d), 43.5 (q), 29.7 (t) and 28.1 (t); *m/z* 249 (M^++1, 4%), 248 (M^+, 14%), 203 (60), 191 (8), 175 (64), 163 (15), 145 (10), 128 (100), 115 (83), 102 (25), 89 (55).

7-Nitro-2-(7-nitro-1-pyrrolidin-1-yl-3,4-dihydro-2-naphthylmethyl)-3,4-dihydro-1(2H)-naphthalenone (4): Compound **3** (18.5 g, 0.065 mol) was added slowly to a solution of enamine **2** (19 g, 0.079 mol) in absolute ethanol (35 ml) under Ar. After stirring for 2 h, the reaction was cooled to 0 °C and filtered to give **4** (21.5 g, 76%) as a yellow solid, mp 154 °C, (Found: C, 67.02; H, 5.72; N, 9.38. $C_{25}H_{25}N_3O_5$ requires: C, 67.10; H, 5.63; N, 9.39%); $\nu_{max}(CHCl_3)/cm^{-1}$ 3030, 1667, 1613, 1600, 1520, 1343, 1148 and 1078; $\delta_H(CDCl_3)$ 8.44 (1H, d, *J*=2.4 Hz, H-8), 8.14 (1H, d, *J*=2.4 Hz, H-8'), 8.03 (2H, dd, *J*=8.2, 2.4 Hz, H-6, H-6'), 7.28 (1H, d, *J*=8.2 Hz, H-5), 7.21 (1H, d, *J*=8.2 Hz, H-5') and 3.3-1.5 (19H); $\delta_C(CDCl_3)$ 203.0 (s), 147.3 (s), 145.9 (s), 145.4 (s), 143.3 (s), 141.7 (s), 139.7 (s), 133.0 (s), 129.9 (d), 127.7 (d), 122.4 (d), 121.7 (d), 121.1(d), 115.0 (d), 109.8 (s), 45.2 (t), 33.1 (d), 30.8 (t), 27.8 (t), 26.1 (t), 24.6 (t), 24.4 (t) and 22.3 (t); *m/z* 447 (M^+, 6%), 406 (10), 257 (100), 244 (24), 203 (23), 175(12), 141 (10), 128 (29), 115 (18) and 89 (12).

7-Nitro-2-(7-nitro-1-oxo-1,2,3,4-tetrahydro-2-naphthylmethyl)-3,4-dihydro-1(2H)-naphthalenone: Compound **4** (21 g, 0.047 mol) was dissolved in a mixture of HCl (5 ml) and ethanol (100 ml). The reaction was heated to 60 °C and stirred for 10 min. The dinitro dicarbonyl compound obtained was a white solid (17.5 g, 95%), mp 183°C; ν_{max}(Nujol)/cm^{-1} 3086, 1688, 1611, 1520, 1422, 1348, 1080 and 940; δ_H($CDCl_3$) 8.82 (2H, d, *J*=2.4 Hz, H-8), 8.30 (2H, dd, *J*=8.4, 2.4 Hz, H-6), 7.45 (2H, d, *J*=8.4 Hz, H-5), 3.18 (4H, t, *J*=5.4 Hz, H-4), 3.09-2.65 (2H, m), 2.55-2.30 (2H, m), 2.07-1.90 (3H, m) and 1.75-1.55 (1H, m); δ_C($CDCl_3$) 197.9 (s), 150.4 (s), 147.3 (s), 133.3 (s), 130.3 (d), 127.2 (d), 122.8 (d), 45.9 (d), 44.8 (d), 29.9 (t), 29.2 (t), 29.0 (t), 28.7 (t) and 28.6 (t); *m/z* 394 (M^+, 11%), 204 (28), 191 (100), 174 (19), 145 (18), 115 (28) and 89 (23).

7-Amino-2-(7-amino-1-oxo-1,2,3,4-tetrahydro-2-naphthylmethyl)-3,4-dihydro-1(2H)-naphthalenone (5): The dinitro compound **4** (17 g, 0.043 mol) was added to a solution of $Cl_2Sn{\cdot}2H_2O$ (58 g, 0.258 mol) in ethanol (150 ml) and HCl (5 ml). The mixture was heated for 10 min. Then the ethanol was evaporated and the residue was treated with water, Na_2CO_3 and ethyl acetate. Evaporation of the organic layer gave **5** (12.6 g, 87%) as a white solid, mp 139 °C (Found: C, 75.26; H, 6.50; N, 8.31. $C_{21}H_{22}N_2O_2$ requires: C, 75.42; H, 6.63; N, 8.38%); ν_{max}(Nujol)/cm^{-1} 3432, 3345, 1672, 1611, 1501, 1314 and 1192; δ_H($CDCl_3$) 7.29 (2H, d, *J*=2.3 Hz, H-8), 7.03 (2H, d, *J*=8.1 Hz, H-5), 6.82 (2H, dd, *J*=8.1, 2.3 Hz, H-6), 3.68 (4H, N*H*), 2.90 (4H, t, *J*=4.9 Hz, H-4), 2.70 (2H, m), 2.35-2.15 (2H, m), 2.00 (2H, t, *J*=6.7 Hz) and 1.95-1.85 (2H, m); δ_C($CDCl_3$) 200.9 (s), 145.0 (s), 134.3 (s), 133.2 (s), 129.6 (d), 120.8 (d), 112.5 (d), 45.9 (d), 45.0 (d), 30.7 (t), 29.5 (t) and 27.6 (t); *m/z* 335 (M^++1, 15%), 334 (M^+, 33%), 316 (8), 173 (48), 161 (100), 145 (52), 130 (42), 105 (59) and 91 (12).

2,12-Diamine-5,6,8,9-tetrahydrodibenz[c,h]acridine (6): Ammonium acetate (14 g) was added to a solution of compound **5** (12 g, 0.036 mol) in acetic acid (100 ml) and heated at reflux for 3 h. After that, water was added and the resulting precipitate was filtered off to give the diacetamide (10.7 g, 75%). This compound was added to a solution of KOH (40 g) in ethanol (100 ml) and the resulting mixture was heated at 80 °C for 4 h. The solvent was removed under reduced pressure and the residue was taken up in water. The precipitate was filtered to give **6** (8 g, 61%); white crystralls whit mp 224 °C (from methanol-dichloromethane) (Found: C, 80.39; H, 6.20; N, 13.22. $C_{21}H_{19}N_3$ requires: C, 80.48; H, 6.11; N, 13.41%); ν_{max}(Nujol)/cm^{-1} 3430, 3400, 3341, 3221, 1615, 1553, 1499, 1410, 1306, 1271, 1246 and 820; δ_H($CDCl_3$) 7.87 (2H, d, *J*=2.4 Hz, H-1, H-13), 7.29 (1H, s, H-7), 7.03 (2H, d, *J*=8.0 Hz, H-4, H-10), 6.66 (2H, dd, *J*=8.0, 2.4 Hz, H-3, H-11) and 2.87 (8H, m, H-5, H-6, H-8, H-9); δ_H[$(CD_3)_2SO$)] 7.63 (2H, d, *J*=2.4 Hz, H-1, H-13), 7.37 (1H, s, H-7), 6.92 (2H, d, *J*=8.0 Hz, H-4, H-10), 6.56 (2H, dd, *J*=8.0, 2.4 Hz, H-3, H-11) and 2.9-2.6 (8H, m, H-5, H-6, H-8, H-9); δ_C[$(CD_3)_2SO$)] 149.7 (s), 146.9 (s), 134.9 (d), 134.6 (s), 130.1 (s), 127.9 (d), 125.4 (s), 114.8 (d), 109.9 (d), 27.6 (t) and 26.5 (t); *m/z* 314 (M^++1, 32%), 313 (M^+, 100%), 297 (8), 282 (7), 157 (9) and 98 (6).

1-(3,4-Dihydro-1-naphthyl)pyrrolidine (7) : Following the same procedure used to prepare **2**, the enamine **7** was obtained from α-tetralone (90 %). ν_{max}($CHCl_3$)/cm^{-1} 3059, 2930, 2879, 2825, 1685, 1617, 1565, 1486, 1457, 1371, 1286, 1186, 1136, 1101 and 1038; δ_H($CDCl_3$) 7.48 (1H, d, *J*=7.2 Hz, H-8), 7.35-7.15 (3H, m, H-5, H-6, H-7), 5.23 (1H, t, *J*=4.6 Hz, H-2), 3.02 (4H, m, 2CH_2), 2.72 (2H, t, *J*=7.0 Hz, H-4), 2.27 (2H, m, H-3) and 1.96 (4H, m, 2CH_2).

7-Nitro-2-(1-pyrrolidin-1-yl-3,4-dihydro-2-naphthylmethyl)-3,4-dihydro-1(2H)-naphthalenone (8) : Hydrochloride **3** (18.5 g, 0.065 mol) was added to a solution of enamine **7** (16 g, 0.080 mol) in absolute ethanol (35 ml); a yellow solid was appearing and then filtered off to give **8** (23.5 g, 90%), mp 129 °C; ν_{max}(Nujol)/cm^{-1} 3030, 1669, 1524, 1343, 1146, 1090, 1011, 951 and 918; δ_H($CDCl_3$) 8.42 (1H, d, *J*=2.4 Hz, H-8), 7.99 (1H, dd, *J*=8.2, 2.4 Hz, H-6), 7.32 (1H, d, *J*=7.4 Hz, H-8'), 7.23-7.06 (3H, m, H-5, H-5', H-7'), 7.02 (1H, dt, *J*=6.8, 1.8 Hz, H-6') and 3.2-1.6 (19 H).

7-Amino-2-(1-oxo-1,2,3,4-tetrahydro-2-naphthylmethyl)-3,4-dihydro-1(2H)-naphthalenone (9) : A solution of **8** (24 g, 0.060 mol) in ethanol (125 ml) with conc. HCl (5 ml), was added to a solution of $SnCl_2 \cdot 2H_2O$ (81 g, 0.359 mol) in ethanol (200 ml) and conc. HCl (5 ml). The reaction mixture was worked up as described for compound **5**, giving **9** (17.6 g, 92%) as a courless crystalls, mp 113 °C (from ethyl acetate-hexane) (Found: C, 78.97; H, 6.59; N, 4.37. $C_{21}H_{21}NO_2$ requires: C, 78.97; H, 6.63; N, 4.39%); ν_{max}(Nujol)/cm^{-1} 3426, 3341, 3040, 1682, 1678, 1599, 1495, 1454, 1306, 1225, 1194, 897 and 828; δ_H($CDCl_3$) 7.97 (1H, dd, *J*=7.6, 1.4 Hz, H-8'), 7.41 (1H, td, *J*=7.6, 1.4 Hz, H-7'), 7.25 (1H, d, *J*=2.6 Hz, H-8), 7.24 (1H, t, *J*=7.6 Hz, H-6'), 7.18 (1H, d, *J*=7.6 Hz, H-5'), 6.97 (1H, d, *J*=8.0 Hz, H-5), 6.77 (1H, dd, *J*=8.0, 2.6 Hz, H-6) and 3.72 (2H, N*H*) 3.1-1.7 (12H); δ_C($CDCl_3$) 200.8 (s), 200.5 (s), 145.1 (s), 143.9 (s), 134.0 (s), 133.2 (s), 133.1 (d), 132.7 (s), 129.5 (d), 128.7 (d), 127.4 (d), 126.5 (d), 120.8 (d), 112.3 (d), 45.9 (d), 45.0 (d), 30.7 (t), 29.6 (t), 29.2 (t), 28.5 (t) and 27.6 (t).

7-Amino-2-(7-nitro-1-oxo-1,2,3,4-tetrahydro-2-naphthylmethyl)-3,4-dihydro-1(2H)-naphthalenone (10) : Amine **9** (17 g, 0.053 mol) and conc. H_2SO_4 (60 ml) were cooled to -30 °C. A solution of fuming HNO_3 (2.2 ml, 0.053 mol) and conc. H_2SO_4 (18 ml) were added dropwise to this solution. After the addition was complete the solution was kept at the same temperature for 15 min. The solution was neutralized with aqueous NaOH (30%) and K_2CO_3. The resulting precipitate was filtered and purified by column chromatography (silica /dichloromethane-ether, 9:1) (Found: C, 69.20; H, 5.45; N, 7.62. $C_{21}H_{20}N_2O_4$ requires: C, 69.22; H, 5.53; N, 7.69%). The fractions were collected and concentrated and the residue was purified by crystallization from chloroform to give **10** as a yellow solid (12 g, 62%), mp 205 °C; ν_{max}(Nujol)/cm^{-1} 3461, 3374, 1692, 1670, 1607, 1512, 1501, 1344, 1323, 1198, 1086 and 841; δ_H($CDCl_3$) 8.83 (1H, d, *J*=2.4 Hz, H-8'), 8.29 (1H, dd, *J*=8.4, 2.4 Hz, H-6'), 7.44 (1H, d, *J*=8.4 Hz, H-5'), 7.28 (1H, d, *J*=2.6 Hz, H-8), 7.05 (1H, d, *J*=8.0 Hz, H-5), 6.83 (1H, dd, *J*=8.0, 2.6 Hz, H-6), 3.16 (2H, t, *J*=5.2 Hz), 3.0-2.9 (2H, m), 2.89-2.55 (2H, m), 2.50-2.20 (2H, m) and 2.10-1.80 (4H, m).

1-[7-(7-Nitro-1-oxo-1,2,3,4-tetrahydro-2-naphthylmethyl)-8-oxo-5,6,7,8-tetrahydro-2-naphthyl]-3-(1,1,3,3-tetramethylbutyl)urea : Compound **10** (11 g, 0.030 mol) in THF (150 ml) was added to a solution of an excess of phosgene (20% in toluene, 20 ml) in THF (150 ml). The reaction mixture was concentrated and the residue obtained dissolved in THF (100 ml) and *tert*-octylamine was added (4.5 g, 0.035 mol). After 10 min the reaction was concentrated under reduced pressure to give a viscous oil which was treated with HCl (2M) and extracted with ethyl acetate. When the solvent was dried over Na_2SO_4 and evaporated, the expected urea nitro compound was obtained (14.8 g, 91%) as a yellow solid mp 110 °C; ν_{max}($CHCl_3$)/cm^{-1} 3370, 1686, 1655, 1611, 1589, 1528, 1499, 1346, 1263, 1219, 1096 and 909; δ_H($CDCl_3$) 8.77 (1H, d, *J*=2.4 Hz, H-8'), 8.26 (1H, dd, *J*=8.4, 2.4 Hz, H-6'), 7.73 (1H, dt, *J*=8.2, 2.4

Hz, H-6), 7.54 (1H, d, *J*=2.4 Hz, H-8), 7.42 (1H, d, *J*=8.4 Hz, H-5'), 7.12 (1H, d, *J*=8.2 Hz, H-5), 6.97 (1H, s, N*H*), 4.98 (1H, s, N*H*), 3.13 (2H, t, *J*=6.0 Hz, H-4'), 2.94 (2H, t, *J*=6.0 Hz, H-4), 2.90-2.60 (2H, m), 2.45-2.16 (2H, m), 1.99 (2H, t, *J*=6.8 Hz), 1.95-1.82 (2H, m), 1.75 (2H, s, $(CH_3)_3CCH_2C(CH_3)_2$), 1.38 (6H, s, $C(CH_3)_2$) and 0.97 (9H, s, $(CH_3)_3C$); $\delta_C(CDCl_3)$ 200.0 (s), 198.4 (s), 154.6 (s), 150.4 (s), 147.4 (s), 138.7 (s), 138.2 (s), 133.6 (s), 132.8 (s), 130.2 (d), 129.6 (d), 127.0 (d), 126.5 (d), 122.8 (d), 118.3 (d), 2 x 54.9 (s), 52.2 (t), 45.8 (d), 45.1, 44.9 (d), 3 x 31.6 (q), 30.9 (t), 2 2 x 29.9 (q), 29.7 (t), 29.5 (t), 28.8 (t) and 27.9 (t).

1-[7-(7-Amino-1-oxo-1,2,3,4-tetrahydro-2-naphthylmethyl)-8-oxo-5,6,7,8-tetrahydro-2-naphthyl]-3-(1,1,3,3-tetramethylbutyl)urea (11): To a solution of the nitro compound (14 g, 0.027 mol) in ethanol (100 ml) was added 5% Pd/C (2.7 g), the reaction was stirred at room temperature under argon for 2 h. The mixture was filtered, and the organic layer was distilled at reduce pressure giving **11** (12.5 g, 95%) as a white solid, mp 105 °C; (Found: C, 73.77; H, 8.14; N, 8.46. $C_{30}H_{39}N_3O_3$ requires: C, 73.59; H, 8.03; N, 8.58%); ν_{max}(Nujol)/cm^{-1} 3366, 1670, 1613, 1541, 1499, 1458, 1364, 1310, 1254, 1217, 898 and 824; $\delta_H(CDCl_3)$ 7.79 (1H, ddd, *J*=8.4, 6.2, 2.4 Hz, H-6), 7.52 (1H, t, *J*=2.4 Hz, H-8), 7.28 (1H, d, *J*=2.2 Hz, H-8'), 7.18 (1H, d, *J*=7.2 Hz, N*H*), 7.10 (1H, d, *J*=8.4 Hz, H-5), 7.01 (1H, d, *J*=8.2 Hz, H-5'), 6.80 (1H, td, *J*=8.2, 2.2 Hz, H-6'), 5.12 (1H, d, *J*=4.0 Hz, N*H*), 2.98 -2.52 (6H, m), 2.36-2.10 (2H, m), 2.02 (2H, t, *J*=7.4 Hz), 1.98-1.81 (2H, m), 1.75 (2H, s, $(CH_3)_3CCH_2C(CH_3)_2$), 1.38 (6H, s, $C(CH_3)_2$) and 0.96 (9H, s, $(CH_3)_3C$); $\delta_C(CDCl_3)$ 201.0 (s), 200.3 (s), 154.9 (s), 145.2 (s), 138.4 (s), 134.2 (s), 133.2 (s), 132.8 (s), 129.6 (d), 129.4 (d), 126.2 (d), 120.9 (d), 118.1 (d), 112.5 (d), 54.7 (s), 52.0 (t), 45.7 (d), 45.1 (d), 31.6 (q), 30.0 (q), 30.6 (t), 29.2 (t) and 27.6 (t).

1-(12-Amino-5,6,8,9-tetrahydrodibenz[c,h]acridin-2-yl)-3-(1,1,3,3-tetramethylbutyl) urea (12): To a stirred solution of the diketone **11** (12 g, 0.024 mol) in glacial acetic acid, was added ammonium acetate and the solution was heated at reflux for 2 h. The reaction was quenched by the addition of water. The resulting precipitate was filtered, two products were obtained, the desired amine **12** and the N-acetyl derivative. Purification by chromatography gave **12** (6 g, 52%) (silica /hexane-ethyl acetate 7:3). The acetyl derivative (hexane-ethyl acetate 6:3) was heated at reflux for 3 h with a solution of KOH (10g, 0.18 mol) in ethanol (25 ml) to give the amine. The total yield in the formation of **12** was 78%, white solid whit mp 188 °C (Found: C, 76.91; H, 7.80; N, 11.90. $C_{30}H_{36}N_4O$ requires: C, 76.89; H, 7.74; N, 11.95%); ν_{max}(Nujol)/cm^{-1} 3422, 3370, 3316, 3237, 1634, 1553, 1507, 1437, 1400, 1364, 1290, 1258 and 1223; $\delta_H(CDCl_3)$ 8.14 (1H, d, *J*=2.4 Hz, H-1), 7.83 (1H, d, *J*=2.4 Hz, H-13), 7.48 (1H, dd, *J*=8.1, 2.4 Hz, H-3), 7.29 (1H, s, H-7), 7.16 (1H, d, *J*=8.1 Hz, H-4), 7.01 (1H, d, *J*=8.0 Hz, H-10), 6.63 (1H, dd, *J*=8.0, 2.4 Hz, H-11), 6.49 (1H, s, N*H*), 4.74 (1H, s, N*H*), 2.88-2.80 (8H, m, H-5, H-6, H-8, H-9), 1.73 (2H, s, $(CH_3)_3CCH_2C(CH_3)_2$), 1.38 (6H, s, $C(CH_3)_2$) and 0.95 (9H, s, $(CH_3)_3C$); $\delta_C(CDCl_3)$ 155.2 s), 150.7 (s), 149.8 (s), 145.6 (s), 138.0 (s), 136.0 (s), 135.7 (s), 133.8 (s), 131.3 (s), 130.6 (s), 135.3 (d), 128.7 (d), 128.6 (d), 122.7 (d), 118.5 (d), 116.1 (d), 111.8 (d), 2 x 54.8 (s), 52.5 (t), 3 x 31.6 (q), 2 x 29.9 (q), 28.5 (t), 28.1 (t), 27.7 (t) and 27.5 (t).

2,12-Cyclohexylsulfamoylamine-5,6,8,9-tetrahydrodibenz[c,h]acridine (13): To a solution of diamine **6** (500 mg, 1.60 mmol) in pyridine (10 ml), cyclohexylsulfamic acid chloride (530 mg, 3.20 mmol) was added in batches, under a stream of argon. The last compound was prepared from

cyclohexylsulfamic acid sodium salt, by treatment with HCl (2M) and PCl_5. The reaction mixture was stirred at room temperature for 1 h. Then the solvent was removed and the residue was extracted with ethyl acetate, dried over Na_2SO_4, and concentrated under reduced pressure. Crystallization from chloroform afforded **13** (782 mg, 77%), pale yellow solid mp 156 °C. (Found: C, 62.03; H, 6.25; N, 10.75. $C_{33}H_{41}N_5O_4S_2$ requires: C, 62.34; H, 6.49; N, 11.01%); ν_{max}(KBr)/cm^{-1} 3290, 2950, 2850, 1616, 1555, 1439, 1319, 1155 and 949; δ_H($CDCl_3$) 8.57 (2H, d, *J*=2.5 Hz, H-1, H-13), 7.32 (1H, s, H-7), 7.14 (2H, d, *J*=8.0 Hz, H-4, H-10), 6.87 (2H, s, N*H*-Ph), 6.79 (2H, dd, *J*=8.0, 2.5 Hz, H-3, H-11), 6.34 (2H, d, *J*=7.6 Hz, N*H*-cyclohex.), 3.25 (2H, m, C*H*NH), 2.91 (8H, m, H-5, H-6, H-8, H-9) and 1.95-1.10 (20H, cyclohex.); δ_C($CDCl_3$) 136.9 (s), 136.1 (d), 135.9 (s), 135.4 (s), 132.5 (s), 130.8 (s), 128.5 (d), 117.7 (d), 113.8 (d), 53.1 (d), 33.5 (t), 27.7 (t), 27.4 (t), 25.3, 24.8 (t); *m/z* 635 (M^+, 1%), 475 (4), 313 (24), 311 (13), 260 (81), 231 (11) and 217 (100).

2,12-(Diethoxyphosphoramide)-5,6,8,9-tetrahydrodibenz[c,h]acridine (14): To a solution of diamine **6** (500 mg, 1.60 mmol) in pyridine (5 ml) was added diethyl chlorophosphate (552 mg, 3.20 mmol) with stirring at room temperature, under Ar. After 5 h the solvent was evaporated. Then, water (25 ml) was added and the resulting precipitate was collected to give **14** as a white solid (690 mg, 74%), mp 207 °C (from hexane-dichloromethane) (Found: C, 59.69; H, 6.16; N, 6.92. $C_{29}H_{37}N_3O_6P_2$ requires: C, 59.48; H, 6.37; N, 7.18%); ν_{max}(KBr)/cm^{-1} 3200, 3000, 1615, 1553, 1491, 1441, 1235, 1219, 1020 and 988; δ_H($CDCl_3$) 8.11 (2H, s, H-1, H-13), 7.30 (1H, s, H-7), 7.13 (2H, d, *J*=8.0 Hz, H-4, H-10), 7.09 (2H, d, *J*=8.0 Hz, H-3, H-11), 6.13 (2H, d, *J*=9.0 Hz, N*H*), 4.19 (8H, m, CH_3CH_2O), 2.87 (8H, m, H-5, H-6, H-8, H-9) and 1.32 (12H, t, *J*=7.0 Hz, CH_3CH_2O); δ_C($CDCl_3$) 2 x 150.1 (s), 2 x 138.9 (s), 2 x 135.9 (s), 135.4 (d), 2 x 131.4 (s), 2 x 131.0 (s), 2 x 128.6 (d), 2 x 117.7 (d), 114.6 (d), 114.4 (d), 2 x 62.9 (t), 2 x 62.8 (t), 2 x 28.2 (t), 2 x 27.5 (t), 2 x 18.3 (q) and 2 x 18.1 (q); *m/z* 587 (M^++2, 6%), 585 (M^+, 50%), 477 (10), 449 (27), 373 (9), 313 (33), 283 (5), 236 (13), 197 (22) and 156 (10).

3,3,13,13-Dibutyl-6,7,9,10-tetrahydro-2,4,12,14(1H,3H,13H,15H)-diquin[6,7-c][7,6-h]acridinetetraone (15): The treatment of diamine **6** (1 g, 3.19 mmol) in ethyl acetate with the chloride of dibutylmalonic acid monoethyl ester (1.7 g, 6.38 mmol) and triethylamine (2 ml), gave the diester (2.1 g), which was treated with ethanolic NaOH (10%) and kept at reflux for 30 min. The ethanol was removed *in vacuo* and the crude product taken up in ethyl acetate and washed with HCl (2M). The organic layer was dried (Na_2SO_4) to give, after evaporation of the solvent, a brown solid (1.93 g), which was treated with Eaton's reagent (phosphorus pentoxide, 7.5 wt % in methanesulfonic acid). The mixture was heated at 90 °C for 1 h. Addition of aqueous sodium bicarbonate and extraction with ethyl acetate gave a residue that was purified by crystallization in methanol affording the bislactam **15** (1.76 g, 83%)as white crystals mp 311 °C (Found: C, 76.44; H, 7.79; N, 5.99. $C_{43}H_{51}N_3O_4$ requires: C, 76.64; H, 7.63; N, 6.23%); ν_{max}(KBr)/cm^{-1} 2925, 1690, 1655, 1618, 1489, 1439, 1397, 1312, 1246; δ_H($CDCl_3$) 9.39 (2H, s, N*H*), 8.18 (2H, s, H-16, H-18), 7.85 (2H, s, H-5, H-11), 7.45 (1H, s, H-8), 2.99 (8H, m, H-6, H-7, H-9, H-10), 2.02 (8H, m, $CH_3(CH_2)_2CH_2$), 1.12 (16H, m, $CH_3(CH_2)_2CH_2$), 0.67 (12H, t, *J*=6.7 Hz, $CH_3(CH_2)_3$); δ_C($CDCl_3$) 198.1 (s), 175.2 (s), 149.1 (s), 2 x 141.9 (s), 2 x 140.3 (s), 136.2 (d), 2 x 133.7 (s), 2 x 132.9 (s), 2 x 126.5 (d), 2 x 119.8 (s), 2 x 112.3 (d), 2 x 61.8 (s), 40.2 (t), 27.8 (t), 27.3 (t), 27.2 (t), 22.9 (t), 4 x 13.7 (q); *m/z* 674 (M^++1, 9%), 673 (M^+, 28%), 617 (87), 575 (80), 519 (28), 477 (57), 420 (10), 238 (100), 183 (19), 149 (20).

1-(1,1,3,3-Tetramethylbutyl)-3-{12-[3-(1,1,3,3-tetramethylbutyl)ureido]-5,6,8,9-tetrahydrodibenz[c,h]acridin-2-yl}urea (16): To a solution of phosgene in 20% toluene (2.5 ml) in THF (5 ml) was added diamine **6** (500 mg, 1.60 mmol) in THF (5 ml), under argon atmosphere. After the addition, the solvent was removed and a yellow solid obtained (750 mg), which was identified as the isocyanate and disolved in THF (10 ml). *tert*-Octylamine (584 mg, 4.53 mmol) was added and the mixture and was stirred at room temperature for 15 min. After that the solvent was removed *in vacuo* and the residue treated with aqueous HCl (2M) was obtained a yellow solid which was identified as the corresponding hydrochloride. Treatment with aqueous K_2CO_3 provided pure compound **16** (930 g, 73%) as a white solid, mp 142 °C (from ethanol) (Found: C, 74.80; H, 8.37; N, 11.03. $C_{39}H_{53}N_5O_2$ requires: C, 75.08; H, 8.56; N, 11.22%); ν_{max}(Nujol)/cm^{-1} 3661, 3366, 3198, 1669, 1611, 1555, 1456, 1395, 1287 and 1219; δ_H($CDCl_3$) 8.07 (2H, d, *J*=2.4 Hz, H-1, H-13), 7.46 (2H, dd, *J*=8.0, 2.4 Hz, H-3, H-11), 7.27 (1H, s, H-7), 7.11 (2H, d, *J*=8.0 Hz, H-4, H-10), 6.68 (2H, s, N*H*), 4.87 (2H, s, N*H*), 2.84 (8H, m, H-5, H-6, H-8, H-9), 1.78 (4H, s, $(CH_3)_3CCH_2C(CH_3)_2$), 1.42 (12H, s, $C(CH_3)_2$) and 0.98 (18H, s, $(CH_3)_3C$); δ_C($CDCl_3$) 2 x 155.6 (s), 2 x 150.0 (s), 2 x 138.1 (s), 135.6 (d), 2 x 134.2 (s), 2 x 133.1 (s), 2 x 130.8 (s), 2 x 128.4 (d), 2 x 122.2 (d), 2 x 117.9 (d), 4 x 54.7 (s), 2 x 52.3 (t), 6 x 31.6 (q), 4 x 30.1 (q), 2 x 28.0 (t) and 2 x 27.5 (t).

1-(1,1,3,3-Tetramethylbutyl)-3-{12-[3-(1,1,3,3-tetramethylbutyl)ureido]-5,6,8,9-tetrahydrodibenz[c,h]acridin-2-yl}thiourea (17): To a solution of thiophosgene (1 ml) in THF (5 ml) was added diamine **6** (500 mg, 1.60 mmol) in THF (5 ml), under Ar. After the addition, the solvent was removed *in vacuo*, and the residue was disolved in THF (10 ml). An excess of *tert*-octylamine was added and the mixture was stirred up at room temperature for 15 min. After evaporation of the solvent, the resulting residue was washed with HCl (2M). The yellow solid obtained was treated with K_2CO_3 (4%) to precipitate **17** (700 mg, 67%) as a white solid, mp 201 °C (Found: C, 71.59; H, 8.10; N, 10.52. $C_{39}H_{53}N_5S_2$ requires: C, 71.41; H, 8.14; N, 10.68%); ν_{max}(Nujol)/cm^{-1} 3372, 3194, 3144, 1547, 1512, 1452, 1373, 1256, 1227, 1150, 1007, 920 and 903; δ_H($CDCl_3$) 8.24 (2H, d, *J*=2.2 Hz, H-1, H-13), 7.49 (2H, s, N*H*), 7.38 (1H, s, H-7), 7.29 (2H, d, *J*=8.0 Hz, H-4, H-10), 7.16 (2H, dd, *J*=8.0, 2.2 Hz, H-3, H-11), 6.16 (2H, s, N*H*), 2.96 (8H, m, H-5, H-6, H-8, H-9), 2.00 (4H, s, $(CH_3)_3CCH_2C(CH_3)_2$), 1.60 (12H, s, $C(CH_3)_2$) and 0.94 (18H, s, $(CH_3)_3C$); δ_H[$(CD_3)_2SO$] 9.32 (2H, s, N*H*), 8.10 (2H, d, *J*=2.0 Hz, H-1, H-13), 7.54 (2H,s, N*H*), 7.49 (2H, dd, *J*=8.2, 2.0 Hz, H-3, H-11), 7.22 (2H, d, *J*=8.2 Hz, H-4, H-10), 7.21 (1H, s, H-7), 2.87 (8H, m, H-5, H-6, H-8, H-9), 2.07 (4H, s, $(CH_3)_3CCH_2C(CH_3)_2$), 1.49 (12H, s, $C(CH_3)_2$) and 0.97 (18H, s, $(CH_3)_3C$); δ_C[$(CD_3)_2SO$] 2 x 179.6 (s), 2 x 149.1 (s), 2 x 138.1 (s), 135.5 (d), 2 x 134.4 (s), 2 x 133.8 (s), 2 x 130.7 (s), 2 x 127.7 (d), 2 x 124.9 (d), 2 x 119.4 (d), 4 x 56.4 (s), 2 x 49.1 (t), 6 x 30.9 (q), 4 x 29.4 (q), 2 x 26.9 (t) and 2 x 26.7 (t).

1-[12-(Dietoxiphosphoramide)-5,6,8,9-tetrahydrodibenz[c,h]acridin-2-yl)-3-(4-chlorophenyl)urea (18) : To a stirred solution of diamino acridine **6** (500 mg, 1.60 mmol) in ethyl acetate (25 ml) was added 4-chlorophenyl isocyanate (245 mg, 1.60 mmol). The mixture was stirred at room temperature for 10 min. A solid precipitated from the solution and was filtered off and identified as the diurea (150 mg, 15%), mp > 350 °C. When the solvent was removed from the filtrate, the monourea derivative (390 mg, 52%) was obtained as a white solid, mp > 350 °C. To a solution of the monourea (200 mg, 0.43 mmol)

in pyridine (2 ml) was added an excess of diethyl chlorophosphate. After that it was diluted with water and extracted with ethyl acetate. The organic layer was dried (Na_2SO_4) and evaporated to give a residue which was purified by crystallization from dichloromethane-hexane to afford **18** (158 mg, 61%) as white crystals, mp 135 °C (from dichloromethane-hexane) (Found: C, 67.26; H, 5.48; N, 9.73. $C_{32}H_{32}N_4O_4Cl$ requires: C, 67.18; H, 5.64; N, 9.79%); ν_{max}(Nujol)/cm^{-1} 3480-3160, 1703, 1649, 1597, 1551, 1493, 1306, 1225, 1013, 982 and 828; δ_H($CDCl_3$) 8.31 (1H, s, H-1), 8.16 (1H, s, H-13), 7.88 (1H, d, *J*=7.8 Hz, H-3), 7.64 (1H, d, *J*=7.8 Hz, H-4), 7.32 (2H, d, *J*=8.6 Hz, C_6H_4), 7.24 (1H, s, H-7), 7.14 (1H, d, *J*=8.4 Hz, H-10), 7.07 (1H, d, *J*=8.4 Hz, H-11), 6.95 (2H, d, *J*=8.6 Hz, C_6H_4), 4.31 (4H, m, CH_3CH_2O), 2.84 (4H, s, H-5, H-6), 2.79 (4H, s, H-8, H-9) and 1.35 (6H, t, *J*=7.0 Hz, CH_3CH_2O); δ_C[$(CD_3)_2SO$)] 152.5 (s), 2 x 149.5 (s), 139.5 (s), 138.7 (s), 137.8 (s), 135.3 (d), 134.7 (d), 134.6 (d), 132.1 (d), 130.7 (d), 130.6 (d), 130.3 (s), 128.3 (d), 128.0 (d), 127.9 (d), 125.2 (s), 120.1 (d), 119.6 (d), 118.1 (d), 115.7 (d), 114.1 (d), 61.9 (t), 61.8 (t), 2 x 27.2 (t), 26.7 (t), 26.5 (t), 15.8 (q) and 15.7 (q).

5-{12-[3-(1,1,3,3 -Tetramethylbutyl)ureido] -5,6,8,9- tetrahydrodibenz [c,h]acridin-2-yl carbamoyl} cyclohexane-1,3-dicarboxylic acid dimethyl ester (19): To a stirred solution of monoamine **12** (500 mg, 1.07 mmol) in ethyl acetate (50 ml) with triethylamine (0.5 ml), was added an excess of 5-chlorocarbonylcyclohexane-1,3-dicarboxylic acid dimethyl ester, which was prepared by the reaction of cyclohexane-1,3,5-tricarboxylic acid and H_2SO_4 in methanol. The mixture was stirred up at reflux for 15 min under Ar. The reaction was poured into water and extracted with ethyl acetate, the organic layer dried over Na_2SO_4, and the solution evaporated to dryness. The residue was purified by column chromatography (silica /hexane-ethyl acetate, 6:4) affording **19** (478 mg, 62%) as a no crystalline white powder. (Found: C, 70.77; H, 7.20; N, 8.20. $C_{41}H_{50}N_4O_6$ requires: C, 70.87; H, 7.25; N, 8.06%), ν_{max}($CHCl_3$)/cm^{-1} 3362, 3310, 2953, 1734, 1684, 1603, 1547, 1435, 1395, 1256 and 1026; δ_H($CDCl_3$) 8.18 (1H, d, *J*=2.2 Hz, H-1), 8.14 (1H, d, *J*=2.4 Hz, H-13), 7.92 (1H, dd, *J*=8.0, 2.4 Hz, H-11), 7.60 (1H, dd, *J*=8.2, 2.2 Hz, H-3), 7.36 (1H, s, N*H*), 7.33 (1H, s, H-7), 7.21 (1H, d, *J*=8.0 Hz, H-10), 7.17 (1H, d, *J*=8.2 Hz, H-4), 6.42 (1H, s, N*H*), 4.80 (1H, s, N*H*), 3.68 (6H, s, CH_3O), 2.91 (8H, s, H-5, H-6, H-8, H-9), 2.5-2.2 (3H, m, C*H*CO), 1.74 (2H, s, $(CH_3)_3CCH_2C(CH_3)_2$), 1.7-1.2 (6H, m, cyclohex.), 1.40 (6H, s, $C(CH_3)_2$) and 0.96 (9H, s, $(CH_3)_3C$); δ_C($CDCl_3$) 2 x 174.6 (s), 164.8 (s), 155.6 (s), 2 x 150.1 (s), 138.1 (s), 137.2 (s), 135.8 (s), 135.4 (d), 134.1 (s), 133.7 (s), 131.1 (s), 128.6 (d), 128.5 (2C, d), 122.8 (d), 121.4 (d), 118.6 (d), 116.6 (d), 2 x 54.7 (s), 52.4 (t), 2 x 51.8 (q), 44.6 (d), 42.0 (d), 31.6 (q), 31.3 (t), 30.5 (t), 2 x 29.8 (q), 28.1 (t), and 27.7 (t).

6-tert-Butyl-8-(3-{12-[3-(1,1,3,3-tetramethylbutyl)ureido]-5,6,8,9-tetrahydrodibenz[c,h] acridin-2-yl}ureido)chroman-2,2-dicarboxylic acid diethyl ester (20): To a solution of monoamine **12** (500 mg, 1.07 mmol) in chloroform (10 ml) was added the isocyanate of 8-amine-6-*tert*-butylchroman-2,2-dicarboxylic acid diethyl ester in chloroform (10 ml). After the reaction was complete, the solvent was removed and the residue was purified by column chromatography (silica /chloroform-ethyl acetate, 9:1) to afford **20** (615 mg, 68%) as a white powder (Found: C, 71.26; H, 7.20; N, 8.22. $C_{50}H_{61}N_5O_7$ requires: C, 71.15; H, 7.28; N, 8.30%); ν_{max}($CHCl_3$)/cm^{-1} 3372, 2961, 1744, 1667, 1615, 1549, 1505, 1431, 1393, 1308, 1213, 1121 and 1017; δ_H($CDCl_3$) 8.11 (1H, d, *J*=2.4 Hz, H-13), 7.86 (1H, dd, *J*=8.2, 2.2 Hz, H-3), 7.73 (1H, d, *J*=2.2 Hz, H-1), 7.59 (1H, dd, *J*=8.2, 2.4 Hz, H-11), 7.55 (1H, d, *J*=2.2 Hz, C*H*-crom.), 7.13 (1H, s, H-7), 7.06 (1H, d, *J*=8.2 Hz, H-10), 6.96 (1H, d, *J*=8.2

Hz, H-4), 6.78 (1H, d, *J*=2.2 Hz, C*H*-crom.), 5.30 (1H, s, N*H*), 4.20 (4H, c, *J*=7.0 Hz, CH_3CH_2O), 2.80 (8H, m, H5, H-6, H-8, H-9), 2.7-2.5 (4H, CH_2-crom.), 1.77 (2H, s, $(CH_3)_3CCH_2C(CH_3)_2$), 1.29 (6H, s, $C(CH_3)_2$), 1.23 (9H, s, t-Bu), 1.10 (6H, t, *J*=7.0 Hz, CH_3CH_2O) and 0.97 (9H, s, $(CH_3)_3C$); $\delta_C(CDCl_3)$ 2 x 168.1 (s), 155.5 (s), 154.0 (s), 149.9 (s), 149.8 (s), 144.7 (s), 141.7 (s), 138.9 (s), 137.4 (s), 135.4 (s), 134.9 (s), 134.8 (d), 133.0 (s), 131.5 (s), 130.3 (s), 130.2 (s), 128.2 (d), 128.0 (d), 126.6 (s), 121.6 (d), 121.1 (d), 120.5 (d), 120.2 (s), 118.7 (d), 117.8 (d), 116.2 (d), 82.2 (s), 2 x 63.1 (t), 2 x 54.2 (s), 51.7 (t), 34.3 (s), 3 x 31.6 (q), 3 x 31.5 (q), 2 x 30.1 (q), 28.2 (t), 27.9 (t), 27.5 (t), 26.9 (t), 22.2 (t); 14.1 (q) and 13.8 (q).

Association constant measurements

Titrations were carried out in $CDCl_3$ solutions at a constant 10^{-3} M host concentration which a guest was added until saturation was reached. The changes in the chemical shifts of host were monitored making use of a MonteCarlo nonlinear curve-fitting program.

Catalytic activity measurements

Isoquinoline (0.1168 g, 0.9 mmol), nitrobenzene (3.2032 g, 26 mmol) and dibutylmalonic acid (4.5450 g, 21 mmol) were dissolved in ether (50 ml). A part of the solution (2 ml) was added to 0.06 mmol of the different receptors. The ether was vacuum-distilled and the remaining oil was heated to 125 °C in a thermostatted oil bath. The formation of CO_2 was followed using a gas-burette until gas formation ceased. The $t_{1/2}$ was evaluated by interpolation in the kinetic plot of $v_{(CO_2)}$ / t.

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