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Tetrahedron 60 (2004) 3755–3762
Tetrahedron

Urea-tetrahydrobenzoxanthene receptors for carboxylic acids

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Received 7 October 2003; revised 22 January 2004; accepted 5 March 2004

Abstract—Hydrogen-bonding receptors for carboxylic acids have been prepared based on a *cis* tetrahydrobenzoxanthene skeleton. X-ray diffraction study of one of these compounds revealed that the cleft is suitable for establishing strong linear hydrogen bonds with the oxygen of a water molecule. Complexes that set only three H-bonds with the guests showed no chiral recognition with amino acid derivatives. However, suitable functionalization of the receptor provided a fourth H-bond with certain amino acid derivatives, leading to significant enantioselective complexation in this case.

1. Introduction

Enantioselective complexation of suitable guests may be of great importance in the resolution of racemic mixtures.[1] Several hydrogen-bonding receptors have been shown to be capable of chiral recognition of carboxylic acids,[2] amino acids and their derivatives.[3]

4-Amino-6-hydroxy-tetrahydrobenzoxanthene has been reported to be a very suitable scaffold for the association of acid guests.[4] This molecule has an appropriate cleft to establish two linear hydrogen bonds with an oxygen atom, as shown in an X-ray diffraction study.[4] The formation of urea function on the 4-amino substituent could provide a third hydrogen bond with a carboxylic acid, as shown in Figure 1.

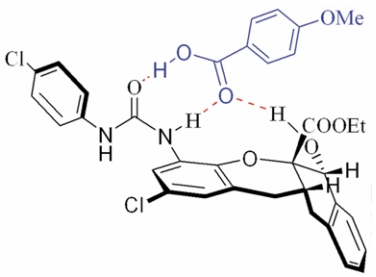

Figure 1. Proposed complex between receptor **1** and a carboxylic acid.

Keywords: Receptor; Amino acids; Chiral recognition; Enantioselectivity; Carboxylic acids; Tetrahydrobenzoxanthene.
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0040–4020/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2004.03.015

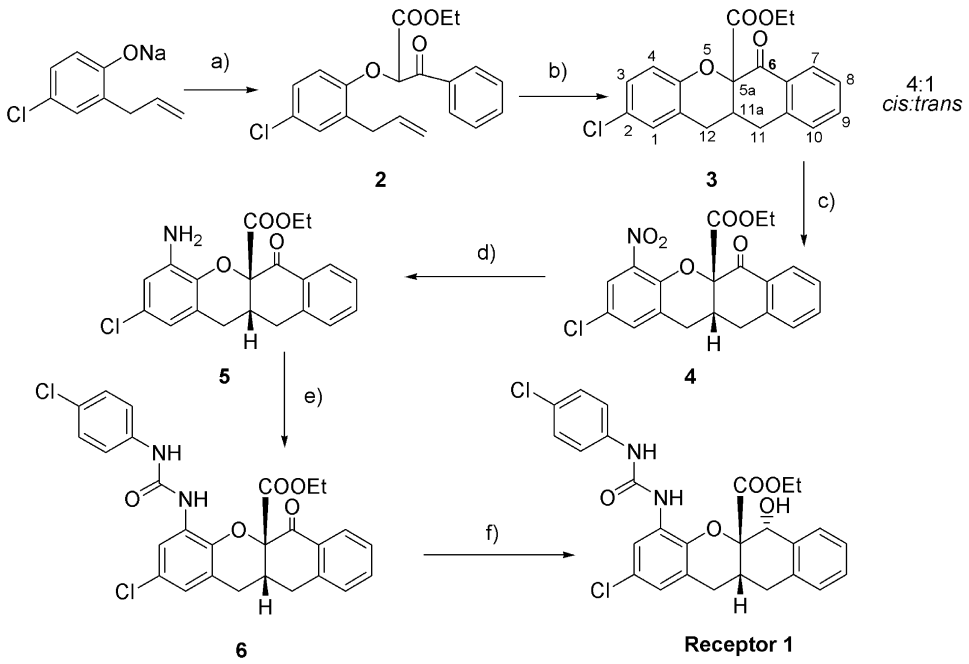
2. Results and discussion

Preparation of receptor **1** was accomplished starting from 2-allyl-4-chlorophenol and ethyl benzoylchloroacetate (Scheme 1). The key step is the oxidative double cyclization of the ketoester **2** in the presence of manganese acetate.[5] So far, this reaction has provided a mixture of both *cis* and *trans* stereoisomers. These compounds are easily separated, because the *trans* compound is highly crystalline.

Since the *cis* compound was the major product, we continued the preparation of the receptors with this isomer. Further conventional synthetic steps provided receptor **1** (Scheme 1).

To confirm the structure of receptor **1**, crystals of the racemic compound were grown from wet MeOH, and an X-ray analysis was carried out. The results are shown in Figure 2 and they not only confirm the proposed *cis* structure but also show that the cleft is suitable for the association of an oxygen atom, since a water molecule was found inside the cleft, establishing H-bonds with the two urea NHs (2.23 and 2.39 Å) and the C-6 hydroxyl group (2.06 Å). The water molecule provides further hydrogen bonds with two neighboring receptor molecules, which show the enantiomeric configuration. In one of them, the carbonyl urea group acts as the H-bond acceptor and, in the other one, this role is played by the C-6 hydroxyl group.

Anisic acid was used to study the complexation properties of receptor **1** in deuterochloroform. NMR experiments were carried out to establish not only the association constant and the discrimination with chiral guests.[6] A standard titration at 20 °C afforded a K_{ass}=190 M^{-1} (Fig. 3). Evaluation of the data has been carried out with a Monte Carlo based curve



Scheme 1. Reagents and conditions: (a) ethyl benzoylacetate, toluene, t=65 °C, yield: 83%; (b) $Mn(OAc)_3{\cdot}4H_2O$, AcOH/Ac_2O, t=20 °C, yield: 66%; (c) HNO_3/H_2SO_4, Ac_2O, t=−10 °C, yield: 95%; (d) $SnCl_2$, rt, yield: 90%; (e) chlorophenylisocyanate, toluene, yield: 80%; (f) K-selectride, THF, yield: 91%.

fitting computer program. From these data a 1/1 stoichiometry can be deduced for the complex[7] (Fig. 4). Since receptor **1** is an asymmetric structure, its possible chiral recognition was tested with enantiomerically pure L-benzyloxycarbonylalanine. However, no discrimination was detected in competitive experiments.[6] The three-point model[8] may explain the lack of enantioselectivity, since the interaction of host and guest through the carboxylic acid corresponds only to a single point. In a search for more attractive forces between host and guest, substrates **7** and **8** were prepared as shown in Scheme 2.

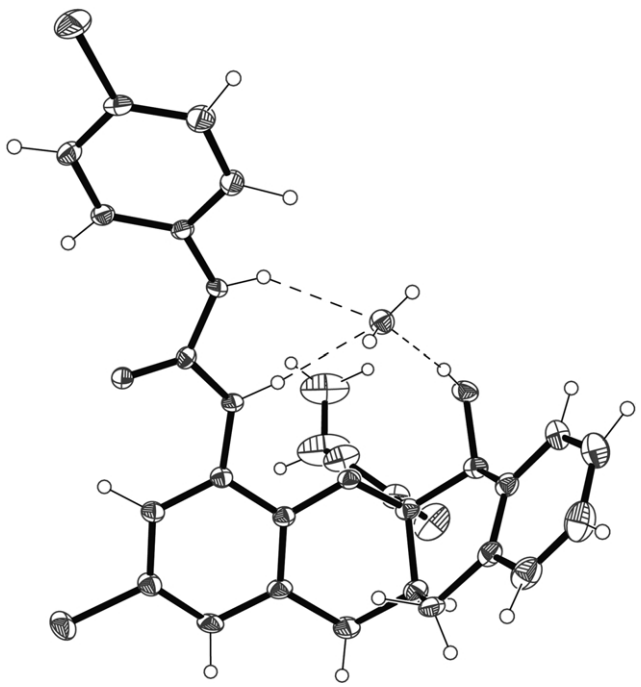


Figure 2. X-ray structure of receptor **1**. The receptor crystallizes with one molecule of water.

CPK models show that these two last guests could establish a fourth hydrogen bond with receptor **1**, as shown in Figure 5.

Competitive titrations in $CDCl_3$ did not reveal any significant discrimination with receptor **1**, but the results were better with a new receptor **9**, in which the ester had been changed into an amide (Scheme 3).

Chiral discrimination with guest **7** was 1.8 while the more acidic H-bond of guest **8** provided 6.0 (Figs. 6 and 7). Competitive experiments were carried out with the racemic receptors and enantiomerically pure amino acid derivatives, adding small portions of the guest to the receptor solution in $CDCl_3$. Formation of the diastereomeric complexes afforded a splitting of the ^1H NMR host **9** signals. Plotting of the chemical shifts of these protons with respect to each other and the use of a home-made curve-fitting program provided the chiral discrimination.

The initially proposed geometry for the complex of receptor **9** and guest **8** is shown in Figure 8. In this structure, in order to establish the strong H-bond with the carboxylic acid, the urea adopts a *syn*/*anti* conformation. Since the most stable geometry in the ureas is usually the *anti*/*anti* conformer, we anticipated strong anisotropic shifts in the H-3 proton during the titrations. The absence of this effect led us to consider an alternative geometry for the complex in which the urea presents the more stable *anti*/*anti* conformation. Figure 9 shows this structure.

To decide between the two possible geometries for this complex, a new guest **10** was prepared (Scheme 2). In this guest, disubstitution of the sulphonamide should prevent the

δ Receptor (ppm)	Acid equivalents	δ Receptor (ppm)	Acid equivalents
5.167	0.0	5.190	1.0
5.170	0.1	5.191	1.1
5.173	0.2	5.193	1.2
5.176	0.3	5.194	1.3
5.178	0.4	5.195	1.4
5.180	0.5	5.196	1.5
5.182	0.6	5.199	1.7
5.184	0.7	5.201	1.9
5.186	0.8	5.205	2.3
5.188	0.9	5.215	4.5

K_{ass} : 190 M^{-1}
Maximum δ : 5.2299.
[receptor **1**]: 4 10^{-3} M

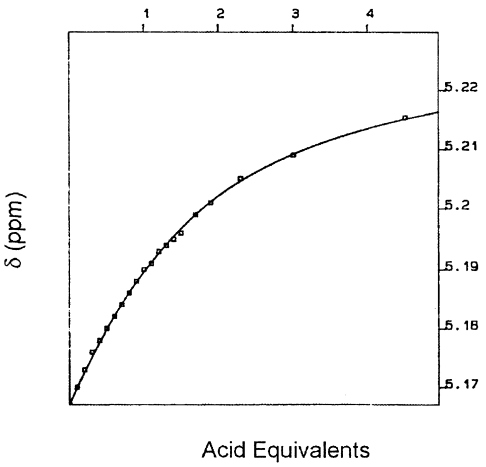


Figure 3. Absolute titration data and graphical representation between receptor **1** and anisic acid.

formation of the fourth H-bond in the initially proposed structure, while no effect was expected for the alternative geometry. A competitive titration between host **9** and guest **10** revealed no chiral recognition, in support of the initially proposed structure.

Another explanation for the lack of movement of proton 3 during the titration could be that receptor **9** already shows the urea *syn/anti* form at the beginning of the experiment. This is possible if, under the experimental conditions (10^{-3} M), the receptor is not in the free form but forming a dimer, as shown in Figure 10. Adding 10% deuteromethanol to the deuterochloroform solution in the NMR tube strongly deshielded the H-3 signal from 7.7 to 8.2 ppm. This effect supports the aggregation hypothesis, since a strongly competitive solvent such as MeOD should break the hydrogen bond dimer of receptor **9**.

The stability of the dimer of receptor **1** was established in $CDCl_3$ using the dilution method changing the concentration from 10^{-1} M to 2.3×10^{-4} M. A value of 3.3×10^{3} M^{-1} was determined (Fig. 11). Extrapolation of the chemical shift of proton H-3 at infinite dilution provide δ=8.11 ppm, in good agreement with the chemical shift of this proton in ketone **6**, which lacks the right functionality to form the dimer.

We hope that further developments in this structure will provide a highly selective recognition of amino acid derivatives.

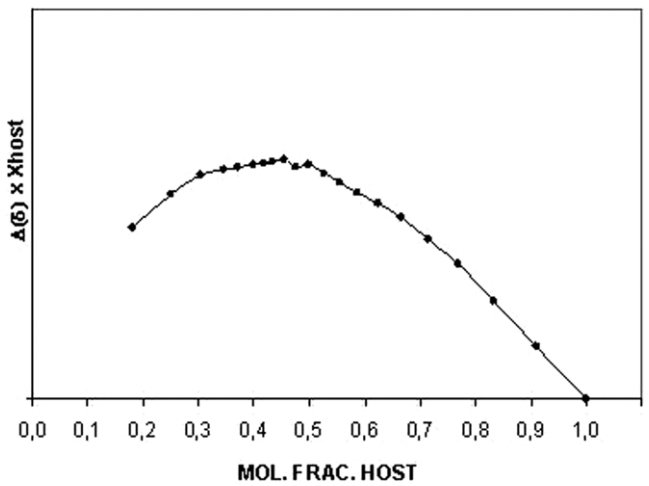


Figure 4. Job plot for the complex between receptor **1** and anisic acid.

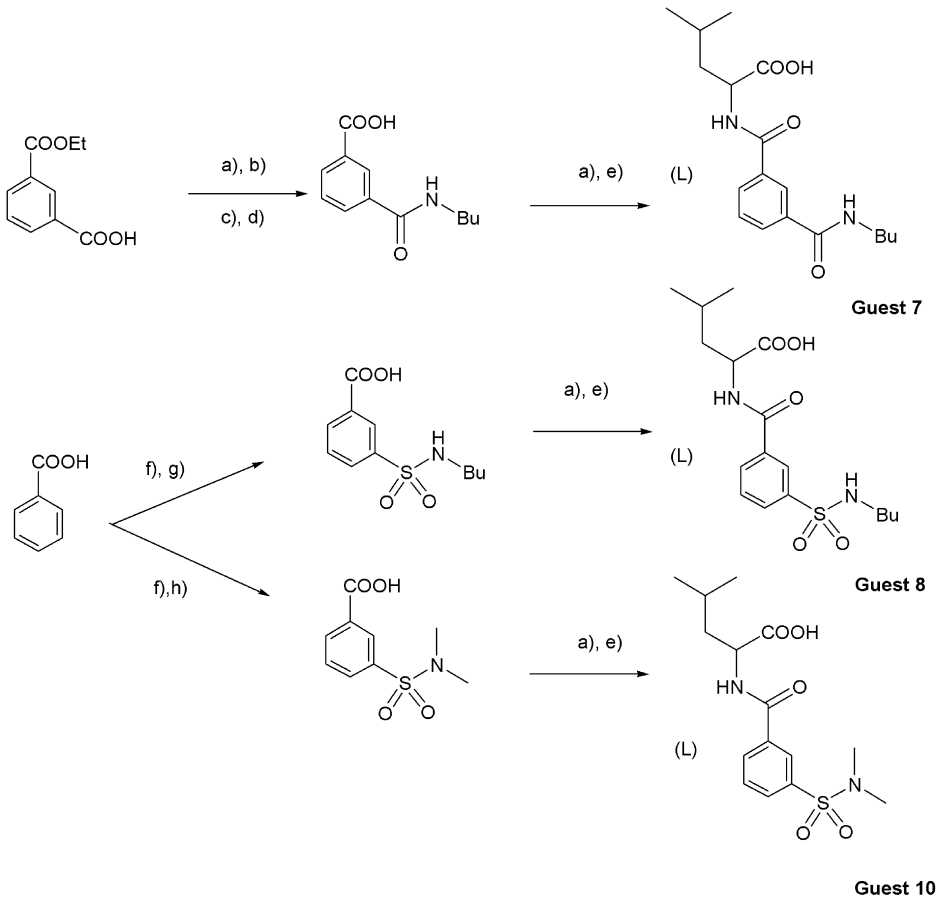
3. Experimental

3.1. General

^{1}H and ^{13}C NMR spectra were acquired on a Bruker Advance DRX 400 MHz and Bruker WP 200 MHz spectrometer. Mass spectrometry data were obtained with a VG. MOD. TS-250, 70 eV. IR spectra were recorded on a BONEN MB-100FT IR spectrometer. Melting points were obtained with a Stuart Scientific SMP3 Apparatus. THF was distilled from sodium/benzophenone.

3.2. Preparation of compounds 1–10

3.2.1. *cis* 2-Chloro-4-[3-(4-chloro-phenyl)-ureido]-6-hydroxy-6,11,11a,12-tetrahydrobenzo[*b*] xanthene-5a-carboxylic acid ethyl ester (1). Ketone **6** (3.5 g, 6.7 mmol) was slowly added over a cold (0 °C) K-selectride THF solution (20 ml, 20 mmol, 1 M in THF). After 10 min, the reaction mixture was poured over an aqueous HCl (2 M) solution and filtered to yield the crude alcohol. Crystallization in methanol yielded the pure compound (3.2 g, 91%). Mp: decomposition over 155 °C. ^{1}H NMR (400 MHz, $CDCl_3$+10% CD_3OD) δ (ppm): 8.20 (1H, d, J=2 Hz), 7.63 (1H, d, J=8 Hz), 7.33 (2H, d, J=8 Hz), 7.21 (2H, d, J=8 Hz), 7.3–7.2 (2H, m), 7.05 (1H, d, J=8 Hz), 6.70 (1H, d, J=2 Hz), 5.31 (1H, s), 4.3–4.2 (2H, m), 3.0–2.6 (5H, m), 1.21 (3H, t, J=7 Hz). ^{13}C NMR (400 MHz, DMSO) δ (ppm): 170.4 (1C), 151.9 (1C), 140.2 (1C), 138.0 (1C), 136.1 (1C), 133.9 (1C), 128.9 (1C), 128.6 (2C), 127.3 (1C), 126.5 (1C), 126.3 (1C), 125.7 (1C), 124.3 (1C), 121.8 (1C),



Scheme 2. Reagents and conditions: (a) $SOCl_2$; (b) $BuNH_2$; (c) NaOH; (d) HCl; (e) (L)-leucine sodium salt; (f) $HClSO_3$; (g) $BuNH_2$; (h) Me_2NH.

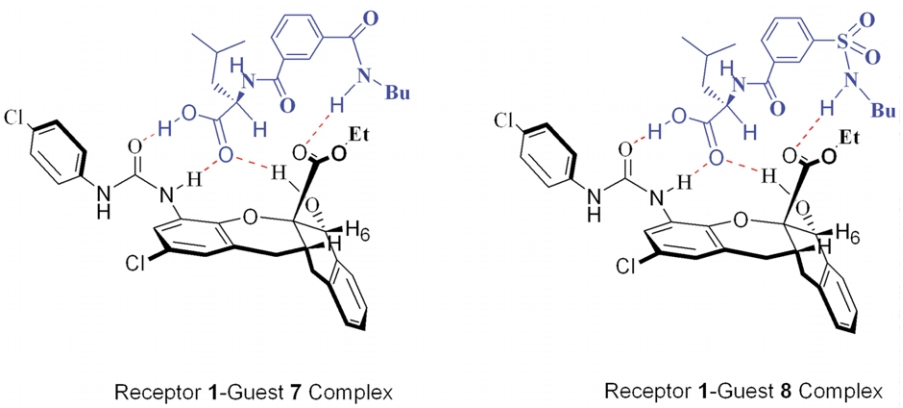
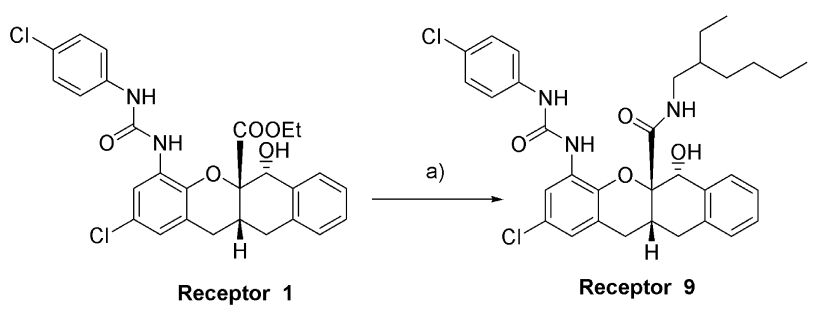


Figure 5. Proposed complex between receptor **1** and guests **7** and **8**.



Scheme 3. Reagents and conditions: (a) 2-ethylhexylamine, BuLi, THF, 50 °C, 75%.

δ Enantiomer **1** (ppm)	δ Enantiomer **2** (ppm)
9.0122	9.0122
9.0500	9.0767
9.0600	9.0928
9.0713	9.1089
9.0750	9.1170
9.0928	9.1385
9.1089	9.1600
9.1358	9.1895
9.1573	9.2083
9.1895	9.2325
9.2110	9.2486
9.2325	9.2567

K_{ass} ratio: 1.8
Maximum δ 1: 9.2407.
Maximum δ 2: 9.2664.

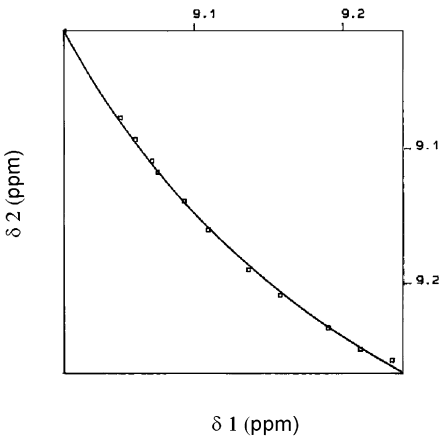


Figure 6. Competitive titration data and graphical representation between receptor **9** and guest **7**.

δ Enantiomer **1** (ppm)	δ Enantiomer **2** (ppm)
5.2689	5.2689
5.2743	5.3039
5.2797	5.3173
5.2851	5.3227
5.2931	5.3281
5.2931	5.3281
5.2958	5.3281

K_{ass} ratio: 6.0
Maximum δ 1: 5.2964.
Maximum δ 2: 5.3290.

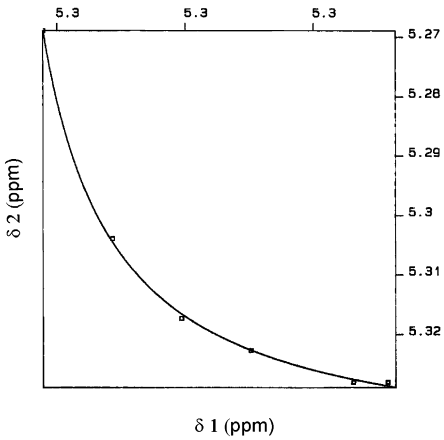


Figure 7. Competitive titration data and graphical representation between receptor **9** and guest **8**.

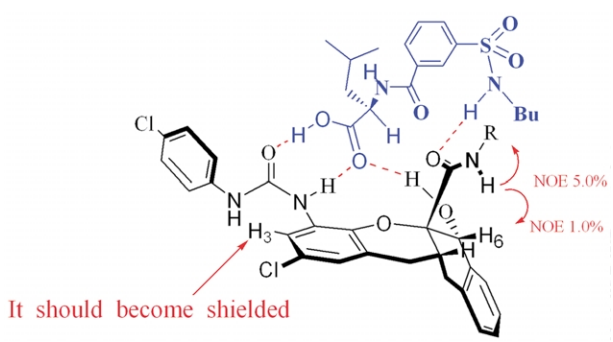


Figure 8. Proposed complex between receptor **9** and guest **8**.

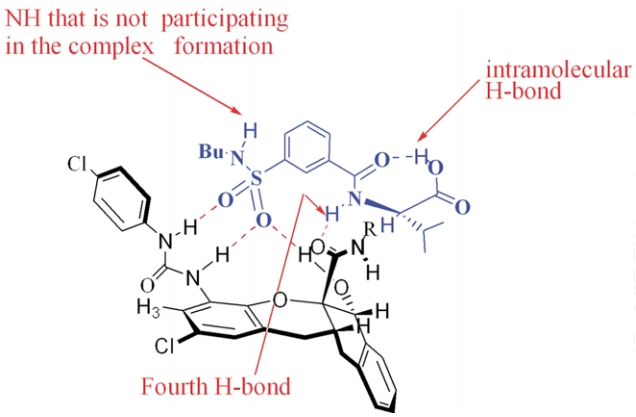


Figure 9. Alternative geometry for the complex between receptor **9** and guest **8**.

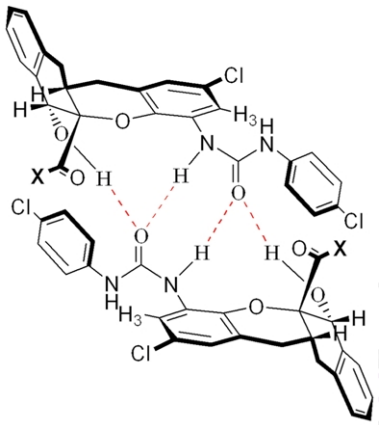


Figure 10. Proposed dimer for receptors **1** and **9**.

δ Receptor **1** (ppm)	Concentration (x10^{-1}M)
7.7140	1.1696
7.7187	0.5848
7.7200	0.2924
7.7290	0.1462
7.7496	0.0731
7.7679	0.0365
7.7942	0.0183
7.8288	0.0091
7.8792	0.0046
7.9206	0.0002

Dimerization Constant: 3.3x10^{3}M^{-1}
Maximum δ free receptor: 8.1096.
Maximum δ dimer: 7.6938.

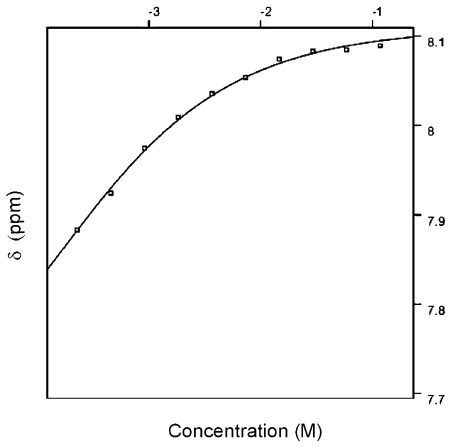


Figure 11. Dimerization titration data of receptor **1** and graphical representation.

120.9 (1C), 120.0 (2C), 115.8 (1C), 82.4 (1C), 71.6 (1C), 61.4 (1C), 30.2 (1C), 30.0 (1C), 28.4 (1C), 13.9 (1C). IR ν (cm^{-1}): 3219, 2924, 1730, 1680, 1603, 1539, 1493, 1194, 1088, 1045, 813, 753, 726. MS (FAB): 77, 30%; 527 (M^{+}+1), 15%. HRMS (FAB): calcd for $C_{27}H_{25}Cl_2N_2O_5$: 527.1140, found: 527.1173. Calcd analysis for $C_{27}H_{24}Cl_2N_2O_5$: C, 61.49; H, 4.59; N, 5.31. Found: C, 61.23; H, 4.83; N, 5.21.

3.2.2. 2-(2-Allyl-4-chloro-phenoxy)-3-oxo-3-phenyl-propionic acid ethyl ester (2). Methanolic sodium hydroxide (12.6 g in 80 ml methanol, 0.32 mmol) was added to a methanol (80 ml) solution of 2-allyl-4-chlorophenol (53.2 g, 0.32 mmol). The solvent was eliminated and the solid residue was dissolved in diethyleneglycol dimethyl ether (100 ml) and toluene (15 ml). 25 ml of the solvent was evaporated to eliminate traces of water and methanol and ethyl benzoylchloroacetate (71.5 g, 0.32 mmol) were added under argon atmosphere. The reaction mixture was warmed to 80 °C (20 min). Neutral pH was obtained adding acetic acid and the reaction mixture was purified with steam and crystallization in EtOH/H_2O to afford 94.0 g of the pure product (83%). Mp: 43–45 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm): 8.07 (2H, d, *J*=8 Hz), 7.62 (1H, t, *J*=8 Hz), 7.47 (2H, t, *J*=8 Hz), 7.13 (1H, s), 7.12 (1H, dd, *J*=2, 8 Hz), 6.7 (1H, d, *J*=8 Hz), 5.90 (1H, m), 5.66 (1H, s), 5.12 (1H, dd, *J*=2, 10 Hz), 5.0 (1H, dd, *J*=2, 18 Hz), 4.29 (2H, c, *J*=7 Hz), 4.22 (2H, d, *J*=5 Hz), 1.23 (3H, t, *J*=7 Hz). IR ν (cm^{-1}): 2924, 1759, 1744, 1688, 1642, 1597, 1489, 1208, 1132, 1072, 934, 814. MS (EI): 105, 100%; 77, 42%; 167, 18%; 254, 15%; 358 (M^{+}), 2%. HRMS (EI): calcd for $C_{20}H_{19}ClO_4$: 358.0972, found: 358.0953. Calcd analysis for $C_{20}H_{19}ClO_4$: C, 66.95; H, 5.34. Found: C, 66.67; H, 5.06.

3.2.3. *cis* 2-Chloro-6-oxo-6,11,11a,12-tetrahydro-benzo-[*b*]xanthene-5a-carboxylic acid ethyl ester (3). Compound **2** (40.0 g, 0.11 mol) in propionic acid (1000 ml) was slowly added (48 h) at room temperature and under argon atmosphere to an acetic acid (800 ml) solution of manganese (III) acetate (60.0 g, 0.22 mol) and acetic anhydride (200 ml). Workup with steam and extraction of the ethyl acetate solution with aqueous sodium carbonate (4%) yielded a crude mixture of the *cis* and *trans* stereoisomers. Crystallization in ether/hexane provided the pure *trans* isomer (5.0 g) while silica gel chromatography, eluting with hexane/ethyl acetate, yielded an oily product: the pure *cis* compound (22.0 g, 54%). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.09 (1H, dd, *J*=2, 8 Hz), 7.55 (1H, dt, *J*=2, 8 Hz), 7.37 (1H, t, *J*=8 Hz), 7.23 (1H, d, *J*=8 Hz), 7.10 (1H, dd, *J*=2, 9 Hz), 7.03 (1H, d, *J*=2 Hz), 6.92 (1H, d, *J*=9 Hz), 4.27 (2H, q, *J*=7 Hz), 3.29 (1H, m), 3.06–2.90 (3H, m), 2.65 (1H, dd, *J*=3, 17 Hz), 1.23 (3H, t, *J*=7 Hz). IR ν (cm^{-1}): 2982, 2932, 1755, 1692, 1603, 1479, 1292, 1233, 1188, 1119, 1044, 909, 814, 731. MS (FAB): 307, 100%; 289, 50%; 217, 25%; 357 (M^{+}+1), 20%; 359, 10%. HRMS (EI): calcd for $C_{20}H_{17}ClO_4$: 356.0815, found: 356.0841. Calcd analysis for $C_{20}H_{17}ClO_4$: C, 67.32; H, 4.80. Found: C, 67.15; H, 4.98.

3.2.4. *cis* 2-Chloro-4-nitro-6-oxo-6,11,11a,12-tetrahydro-benzo[*b*]xanthene-5a-carboxylic acid ethyl ester (4). Acetic anhydride (20 ml) and sulfuric acid (2 ml) were

added to a cold (−10 °C) solution of compound **3** (30.0 g, 84.1 mmol) in acetic anhydride (100 ml). Fuming nitric acid (3 ml) in acetic anhydride (60 ml) was then added dropwise, keeping the reaction mixture below −5 °C. Once nitration is finished, the reaction mixture was poured over ice water (1000 ml). After stirring for 2 h, the crude product was filtered. Crystallization in methanol yielded the pure compound (32.0 g, 95%). Mp: 147–149 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.08 (1H, d, J=8 Hz), 7.72 (1H, d, J=2 Hz), 7.56 (1H, t, J=8 Hz), 7.39 (1H, t, J=8 Hz), 7.26 (1H, d, J=8 Hz), 7.26 (1H, d, J=2 Hz), 4.28 (2H, q, J=7 Hz), 3.33 (1H, m), 3.1–3.0 (3H, m), 2.76 (1H, dd, J=4, 17 Hz), 1.22 (3H, t, J=7 Hz). IR ν (cm^{-1}): 2953, 2866, 1750, 1684, 1601, 1528, 1296, 1252, 1204, 1132, 1045, 756, 723. MS (EI): 118, 100%; 105, 55%; 77, 25%; 216, 40%; 170, 38%; 401 (M^+), 25%; 355, 15%; 403, 10%. HRMS (EI): calcd for $C_{20}H_{16}ClNO_6$: 401.0666, found: 401.0623. Calcd analysis for $C_{20}H_{16}ClNO_6$: C, 59.78; H, 4.01; N, 3.49. Found: C, 59.69; H, 3.93; N, 3.64.

3.2.5. *cis* 4-Amino-2-chloro-6-oxo-6,11,11a,12-tetrahydro-benzo[*b*]xanthene-5a-carboxylic acid ethyl ester (5). Compound **4** (17.0 g, 0.04 mol) was slowly added to a warm solution of $SnCl_2$–$2H_2O$ (29.0 g, 0.13 mol) in methanol (35 ml). Aqueous saturated Na_2CO_3 was added and the suspension was stirred for 30 min. Extraction with hot ethyl acetate yielded 14.1 g of an oily product (90%). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.08 (1H, d, J=8 Hz), 7.54 (1H, t, J=8 Hz), 7.36 (1H, t, J=8 Hz), 7.23 (1H, d, J=8 Hz), 6.53 (1H, d, J=2 Hz), 6.41 (1H, d, J=2 Hz), 4.26 (2H, q, J=7 Hz), 3.28 (1H, m), 3.10–2.80 (3H, m), 2.59 (1H, dd, J=2, 17 Hz), 1.23 (3H, t, J=7 Hz). IR ν (cm^{-1}): 2924, 2855, 1751, 1688, 1601, 1487, 1456, 1292, 1196, 1026, 756. MS (EI): 77, 100%; 89, 65%; 106, 36%; 371 (M^+), 8%. HRMS (EI): calcd for $C_{20}H_{18}ClNO_4$: 371.0956, found: 371.0958. Calcd analysis for $C_{20}H_{18}ClNO_4$: C, 64.61; H, 4.88; N, 3.77. Found: C, 64.38; H, 4.61; N, 3.57.

3.2.6. *cis* 2-Chloro-4-[3-(4-chloro-phenyl)-ureido]-6-oxo-6,11,11a,12-tetrahydrobenzo[*b*]xanthene-5a-carboxylic acid ethyl ester (6). One third of a toluene (80 ml) solution of the amine **5** (15.5 g, 41.7 mmol) was distilled to eliminate traces of water. *p*-Chlorophenylisocyanate (6.4 g, 41.7 mmol) was added at room temperature. When the reaction was completed, toluene was evaporated under vacuum and the crude product was crystallized in methanol to yield the expected urea (17.5 g, 80%). Mp: decomposition over 127 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.12 (1H, d, J=2 Hz), 8.10 (1H, d, J=8 Hz), 7.60 (1H, t, J=8 Hz), 7.54 (1H, s), 7.40 (1H, t, J=8 Hz), 7.33 (2H, d, J=8 Hz), 7.29 (1H, d, J=8 Hz), 7.24 (2H, d, J=8 Hz), 6.74 (1H, d, J=2 Hz), 4.29 (2H, q, J=7 Hz), 3.35–3.31 (1H, m), 3.10–2.94 (3H, m), 2.69 (1H, dd, J=3, 18 Hz), 1.25 (3H, t, J=7 Hz). IR ν (cm^{-1}): 3374, 2959, 1746, 1715, 1676, 1601, 1539, 1294, 1188, 1088, 1045, 949, 835, 723. MS (FAB): 217, 75%; 105, 45%; 77, 37%; 525 (M^++1), 25%; 371, 15%. HRMS (FAB): calcd for $C_{27}H_{23}Cl_2N_2O_5$: 525.0984, found: 525.1021. Calcd analysis for $C_{27}H_{22}Cl_2N_2O_5$: C, 61.72; H, 4.22; N, 5.33. Found: C, 61.48; H, 4.29; N, 5.42.

3.2.7. 2-(3-Butylcarbamoyl-benzoylamino)-4-methyl-pentanoic acid (7). Isophthalic acid monobutyl amide (5.0 g, 22.6 mmol) was refluxed in thionyl chloride (25 ml) for 20 min until no more gases evolved. Thionyl chloride was eliminated under reduced pressure and the crude acid chloride was reacted with an aqueous solution (40 ml) of (L)-leucine sodium salt (11.6 g, 75.7 mmol). After stirring for 30 min, the reaction was filtered and the aqueous solution was acidified with 2 M HCl. Filtration provided 5.6 g of the product (74%). Mp: 72–74 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm): 8.42 (1H, s), 8.02 (1H, d, J=8 Hz), 7.80 (1H, d, J=8 Hz), 7.68 (1H, d, J=8 Hz), 7.42 (1H, t, J=8 Hz), 6.62 (1H, s), 5.0–4.9 (1H, s), 3.46 (2H, q, J=6 Hz), 1.9–1.3 (7H, m), 1.0–0.84 (9H, m). IR ν (cm^{-1}): 3329, 2926, 1721, 1638, 1541, 1466, 1302, 1152, 926, 729, 665. MS (FAB): 204, 100%; 335 (M^++1), 70%; 86, 30%; 289, 20%. HRMS (FAB): calcd for $C_{18}H_{27}N_2O_4$: 335.1971, found: 335.1942. Calcd analysis for $C_{18}H_{26}N_2O_4$: C, 64.65; H, 7.84; N, 8.38. Found: C, 64.49; H, 7.57; N, 8.45.

3.2.8. 2-(3-Butylsulfamoyl-benzoylamino)-4-methyl-pentanoic acid (8). *m*-Butylaminosulfonyl-benzoic acid (19.6 g, 76.2 mmol) was refluxed in thionyl chloride until gas evolution ceased. Thionyl chloride was evaporated and the acid chloride was added over an aqueous solution (40 ml) of (L)-leucine sodium salt (11.6 g, 75.7 mmol). The reaction product was precipitated from the clear solution by adding 2 M HCl. Filtration afforded the expected guest (16.1 g, 57%). Mp: 90–92 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm): 8.34 (1H, s), 8.06 (1H, d, J=8 Hz), 7.97 (1H, d, J=8 Hz), 7.57 (1H, t, J=8 Hz), 7.46 (1H, d, J=8 Hz), 5.30 (1H, s), 4.67 (1H, s), 2.92 (2H, q, J=6 Hz), 1.8–1.1 (7H, m), 0.93 (6H, d, J=5 Hz), 0.62 (3H, t, J=7 Hz). IR ν (cm^{-1}): 3266, 2945, 1724, 1647, 1541, 1462, 1328, 1159, 1088, 759. MS (FAB): 240, 100%; 371 (M^++1), 55%; 86, 52%; 137, 50%. HRMS (FAB): calcd for $C_{17}H_{27}N_2O_5S$: 371.1641, found: 371.1622. Calcd analysis for $C_{17}H_{26}N_2O_5S$: C, 55.12; H, 7.07; N, 7.56; S, 8.66. Found: C, 54.96; H, 7.23; N, 7.58; S, 8.46.

3.2.9. *cis* 2-Chloro-4-[3-(4-chloro-phenyl)-ureido]-6-hydroxy-6,11,11a,12-tetrahydro-benzo[*b*] xanthene-5a-carboxylic acid (2-ethyl-hexyl)-amide (9). BuLi (1.2 ml, 1.92 mmol, 1.6 M in hexane) was added to a solution of 2-ethylhexylamine (0.24 g, 1.93 mmol) in THF (5 ml) with stirring at −30 °C under an argon atmosphere. After drying by azeotropic distillation, a solution of receptor **1** (0.10 g, 0.19 mmol) in toluene (3 ml) was added to the reaction mixture. The reaction mixture was stirred for 1 h at −30 °C and was then extracted with ethyl acetate and washed with HCl, Na_2CO_3 and water several times. Purification of the product was accomplished by crystallization from a CH_2Cl_2/hexane mixture to give 0.09.g (75%) of a white solid. Mp: 90–92 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.75 (1H, s), 7.6–6.8 (1H, s), 7.54 (1H, d, J=8 Hz), 7.26–6.96 (7H, m), 6.81 (1H, d, J=2 Hz), 5.27 (1H, s), 3.4–2.4 (5H, m), 1.4–0.7 (14H, m), 0.67 (3H, t, J=7 Hz). ^{13}C NMR (400 MHz, DMSO) δ (ppm): 170.5 (1C), 152.2 (1C), 140.9 (1C), 138.2 (1C), 137.3 (1C), 134.1 (1C), 135.1 (1C), 128.6 (2C), 127.8 (1C), 127.1 (1C), 126.2 (1C), 125.7 (1C), 125.3 (2C), 124.6 (1C), 122.2 (1C), 120.0 (2C), 1167.0 (1C), 83.0 (1C), 71.1 (1C), 56.0 (1C), 38.8 (1C), 30.6 (1C), 30.2 (1C), 29.7 (1C), 29.4 (1C), 28.3 (1C), 23.5 (1C), 22.5 (1C), 13.9 (1C), 10.8 (1C). IR ν (cm^{-1}): 3314, 2924, 1643, 1599, 1537, 1464, 1306, 1209, 1127, 1094, 828, 752. MS (FAB): 300, 50%; 437, 28%; 610 (M^++1), 15%. HRMS (FAB): calcd

for $C_{33}H_{38}Cl_2N_3O_4$: 610.2239, found: 610.2216. Calcd analysis for $C_{33}H_{37}Cl_2N_3O_4$: C, 64.92; H, 6.11; N, 6.88. Found: C, 64.75; H, 6.02; N, 6.54.

3.2.10. 2-(3-Dimethylsulfamoyl-benzoylamino)-4-methyl-pentanoic acid (10). *m*-Dimethylamino-sulfonyl-benzoic acid (18.5 g, 80.7 mmol) was refluxed in thionyl chloride until gas evolution ceased. Thionyl chloride was evaporated and the acid chloride was added over an aqueous solution (40 ml) of (L)-leucine sodium salt (11.6 g, 75.7 mmol). The reaction product was precipitated from the clear solution by adding 2 M HCl. Filtration afforded the expected guest (12.3 g, 45%). Mp: 52–54 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm): 8.21 (1H, s), 8.11 (1H, d, J=8 Hz), 7.91 (1H, d, J=8 Hz), 7.64 (1H, t, J=8 Hz), 7.05 (1H, d, J=8 Hz), 4.75 (1H, s), 2.73 (6H, s), 1.9–1.6 (3H, m), 0.99 (6H, d, J=5 Hz). IR ν (cm^{-1}): 3329, 2938, 1724, 1643, 1537, 1343, 11571, 1086, 955, 748, 704. Calcd analysis for $C_{15}H_{22}N_2O_5S$: C, 52.62; H, 6.48; N, 8.18; S, 9.36. Found: C, 52.89; H, 6.22; N, 8.43; S, 9.47.

3.3. X-ray structure analysis summary of receptor 1

A single crystal of compound **1** was subjected to X-ray diffraction studies on a Seifert 3003 SC four-circle diffractometer (Cu K_α radiation, graphite monochromator) at 293(2) K. Crystal data for **1**: $C_{27}H_{24}N_2O_5Cl_2{\cdot}H_2O$, M=545.40, monoclinic, space group Cc(no. 9), a=14.329(3) Å, b=20.999(4) Å, c=9.680(2) Å, $\alpha=\gamma=90°$, β=118.46(3), V=2560.6(9) Å^3, Z=4, D_c=1.415 Mg/m^3, m(Cu K_α)=2.670 mm^{-1}, F(000)=1136. 1953 reflections were collected, of which 1775 were considered to be observed with $I>2\sigma(I)$. The structure was determined by direct methods using the SHELXTL™ suite of programs. Full-matrix least squares refinement based on F^2 with anisotropic thermal parameters for the non-hydrogen atoms led to agreement factors of R_1=0.0416 and ωR_2=0.1020.

The crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited at the Cambridge Crystallographic Data Centre as supplementary material no. CCDC 220049.

Acknowledgements

We thank Anna Lithgow for the 400 MHz NMR spectra and César Raposo for the mass spectra. We also thank the "Dirección General de Investigación Científica y Técnica" (DGICYT Grant BQU-2002-00676) and JCL (SA 053/03) for their support of this work. The MEC is acknowledged for three fellowships (F.M.M., L.S., A.I.O.).

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