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A macrocyclic receptor for the chiral recognition of hydroxycarboxylates†

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Abstract

Good chiral recognition of hydroxycarboxylates such as lactic or mandelic acids has been achieved with a macrocyclic receptor, readily available from a known bis-chromenylurea and a spirobifluorene linker. Resolution of the receptor racemic mixture was carried out taking advantage of its complexing properties with (*R*)-mandelic acid tetramethylammonium salt on a TLC plate.

Keywords: macrocyclic hydrogen bonding receptor; chiral recognition; hydroxyacids; spirobifluorene; chromenone.

Chiral recognition of carboxylates may be of great importance in the resolution of racemic mixtures of technically and biologically relevant compounds.

A bis-chromenyl urea skeleton **1** (Fig. 1) has shown promising properties in the association of carboxylates.[1] Nevertheless, this fragment lacks stereogenic centers and therefore is unable, alone, to discriminate between carboxylate enantiomers.

In order to develop receptors capable of chiral recognition, we have been searching for a suitable spacer able to close a macrocycle by bridging the gap between the two chromenone binding arms. Spirobifluorene has already been very successful in chiral recognition,[2] and in our case a bis-aminomethylspirobifluorene unit seemed to be the right fragment to yield an essentially tension-free macrocycle (Fig. 1).

Preparation of the macrocyclic receptor **2**[3] (Scheme 1) was accomplished by reacting the bis-aminomethylspirobifluorene unit with nitrochromenone 2-carboxylic acid chloride,[4] followed by reduction of the nitro groups, treatment with phosgene, and slow hydrolysis of the intermediate isocyanates. The yield was reasonably high (60%) and the overall yield 35%, in agreement with the lack of angular stress predicted for this macrocycle.

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

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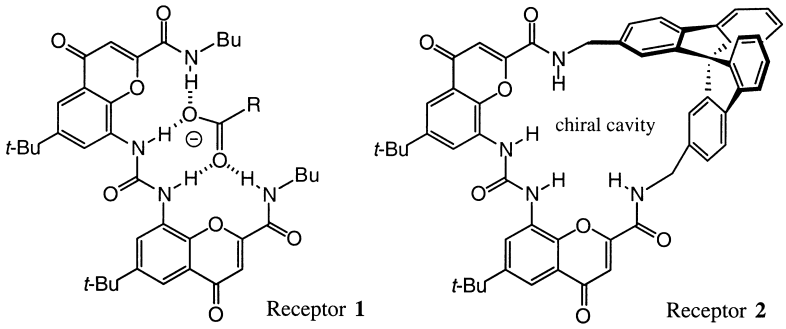
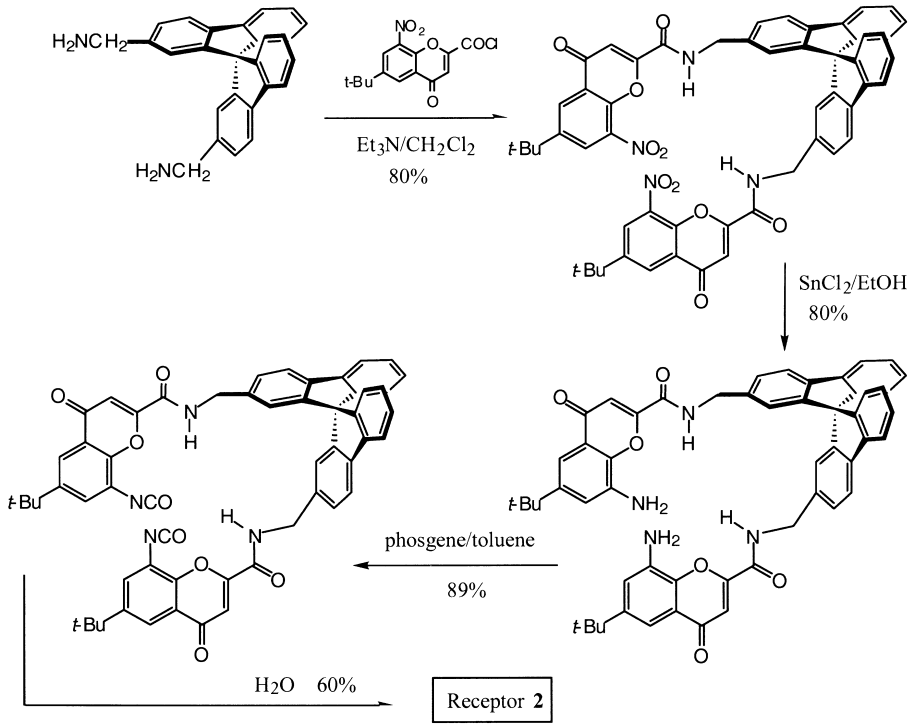


Figure 1. Complex of receptor **1** and a carboxylate, showing four linear hydrogen bonds, and the chiral cavity of receptor **2**



Scheme 1. Preparation of receptor **2**

^{1}H NMR competitive experiments[5] were undertaken to assess the chiral recognition properties of receptor **2**. Treatment of a DMSO solution of the racemic receptor with increasing amounts of the salts of enantiomerically pure acids, such as naproxen, leucine-CBZ and mandelic acid, always afforded splitting of the receptor signals. Plotting these signals against each other gave straight lines in the first two cases (no chiral discrimination) and only in the hydroxyacid was the line curved, corresponding to a constants ratio of 14. A similar experiment in acetone-d_6 with mandelic acid afforded a similar value $K_{rel.} = 15$.

As in other cases, the supramolecular properties of receptor **2** were the key for the resolution of its racemic mixture.[6] When this mixture was eluted ($CHCl_3$/ethyl acetate, 8/2) on silica gel previously

impregnated with a 1% methanolic solution of the (*R*)-mandelic acid tetramethylammonium salt, splitting of the two yellow enantiomers was easily observed, with $R_f = 0.07$ and $R_f = 0.16$ (lactic acid tetramethylammonium salt gave similar results). A blank experiment showed a larger $R_f = 0.49$, indicating that the effect of the mandelic salt is to delay elution of the receptor **2**. Probably, complexation of the mandelic acid carboxylate transforms the neutral guest into a very polar charged complex, which is preferentially adsorbed on the silica gel. This effect means that elution becomes more difficult as the dissociation constant of the complex increases, providing a mechanism for the separation as a function of the association constant of each receptor enantiomer with the guest. After preparative TLC both receptors were obtained as the corresponding complexes. Washing the associates with 4% aqueous sodium carbonate afforded the pure enantiomers, the one corresponding to the most polar spot showing $[\alpha]_D^{20} = +187$ ($c = 0.23$, acetone) and $[\alpha]_D^{20} = -188$ ($c = 0.24$, acetone) the less polar one.

Conventional titrations in DMSO-d_6, confirmed that the more polar complex was the strongest, with $K_{ass} = 2.8 \times 10^4$ M^{-1}, while the weak one had $K_{ass} = 1.7 \times 10^3$ M^{-1}. Taking into account a 20% experimental error, this ratio 16:1 is in agreement with the previous value.

A possible steric source for the chiral recognition of receptor **2** is shown in Fig. 2. Assuming that the large mandelic acid phenyl group points outwards from the receptor cavity, the α-hydrogen must be placed close to the spirobifluorene upper aromatic group, in the most sterically congested zone, while the hydroxyl must lie over the spirobifluorene lower aromatic rings. In the diastereomeric complex, in which hydrogen and hydroxyl group exchange positions, the hydroxyl group, due to its larger size, collides with the spirobifluorene upper aromatic rings, reducing the stability of the complex. An explanation for the chiral recognition based on steric effects is consistent with the fact that smaller guests show larger K_{ass} in DMSO-d_6; for example, tetramethylammonium salts of (*S*)-lactic acid show $K_{ass} = 3.5 \times 10^3$ M^{-1}, (*R*)-lactic acid $K_{ass} = 3.5 \times 10^4$ M^{-1}, propionic acid $K_{ass} = 9.5 \times 10^4$ M^{-1} and formic acid $K_{ass} = 2 \times 10^5$ M^{-1}.

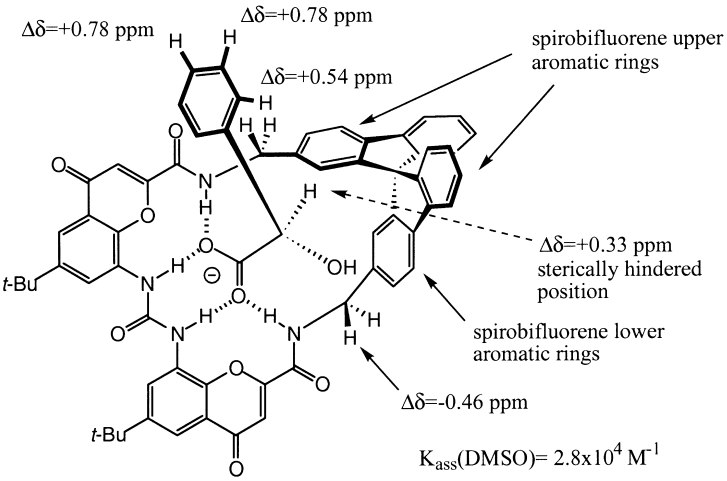


Figure 2. Strong complex of receptor **2** and mandelic acid tetramethylammonium salt, showing the most representative chemical shifts

Anisotropic effects support the above geometry since the mandelic acid hydrogen is shielded in the strong complex (0.33 ppm) because it lies on the face of an aromatic ring, while the same hydrogen is deshielded in the weak complex, in which it is placed over the edge of the lower

benzene ring, moving from 4.33 ppm to 4.64 ppm (Fig. 2). The most striking anisotropic effects, however, are observed in the mandelic aromatic protons in the strong (*R*/*R*) complex. These protons are strongly shielded, probably by the chromenone rings and/or by an upper spirobifluorene ring. Only very small shifts are observed for the same aromatic ring in the weak (*R*/*S*) complex.

The circular dichroism of the strong complex [λ ($\Delta\ \varepsilon$ nm): 300 (–1.66), 250 (–2.21), 230 (+5.20), <200 (>-6) in ethanol] also confirms the above geometry. The positive Cotton effect of the short wavelength absorption band ($B\perp$ transition, 230 nm) is in agreement with the *R* configuration for this complex, according to the Wagnière C_2 rule and the similarity with the CD spectra of Prelog's spirobifluorenes.[7]

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3. Physical data of receptor **2**: mp = 305°C; HRMS (FAB, MH^+), 887.334 ($C_{56}H_{47}O_7N_4$, 887.344); ^{1}H NMR (400 MHz, acetone d_6): 8.73 (d, 2H, $J=2$ Hz), 7.98 (d, 2H, $J=7.5$ Hz), 7.95 (d, 2H, $J=7.95$ Hz), 7.75 (d, 2H, $J=2$ Hz), 7.50 (d, 2H, $J=7.5$ Hz), 7.40 (t, 2H, $J=7.5$ Hz), 7.14 (t, 2H, $J=7.5$ Hz), 7.01 (s, 2H), 6.72 (s, 2H), 6.64 (d, 2H, $J=7.5$ Hz), 4.66 (dd, 2H, $J=13.3$ and 5 Hz), 4.39 (dd, 2H, $J=13.3$ and 5 Hz), 1.39 (s, 18H); ^{13}C NMR (50.3 MHz, $CDCl_3$–MeOD): 178.9 (2C), 160.4 (2C), 154.0 (2C), 152.0 (1C), 149.9 (2C), 148.8 (2C), 148.6 (2C), 143.7 (2C), 141.3 (2C), 141.1 (2C), 137.5 (2C), 128.0 (2C), 127.9 (2C), 127.8 (2C), 127.7 (2C), 126.9 (2C), 123.9 (2C), 123.2 (2C), 123.1 (2C), 120.3 (2C), 120.0 (2C), 114.4 (2C), 111.7 (2C), 65.7 (1C), 44.2 (2C), 35.2 (2C), 31.1 (6C).
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