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Chiral Recognition of Tartaric Acid derivatives with Chromenone-Benzoxazole Receptors and a Spirobifluorene Spacer

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Abstrac: The combination of a spirobifluorene spacer with two chromenone-amino-benzoxazole binding arms affords a chiral cleft type receptor. Due to the strong chiral recognition, resolution of the receptor racemic mixture can be achieved by means of a silica gel TLC plate impregnated with optically pure dibenzoyl tartaric acid. Slow complex formation on the ^{1}H-NMR scale with this host at -10^{o}C allows observation of different signals for free and complex guests in ^{1}H-NMR.

Asymmetric aromatic binding blocks have proved to be useful in chiral recognition.[1] Spirobifluorene has been successfully introduced into crown ethers by Prelog.[2] Hamilton[3] and Diederich[4] have also prepared chiral hydrogen bonding receptors based on this unit. In the latter case, reasonable chiral discrimination with benzyloxycarbonyl aspartic and glutamic acids was reported.

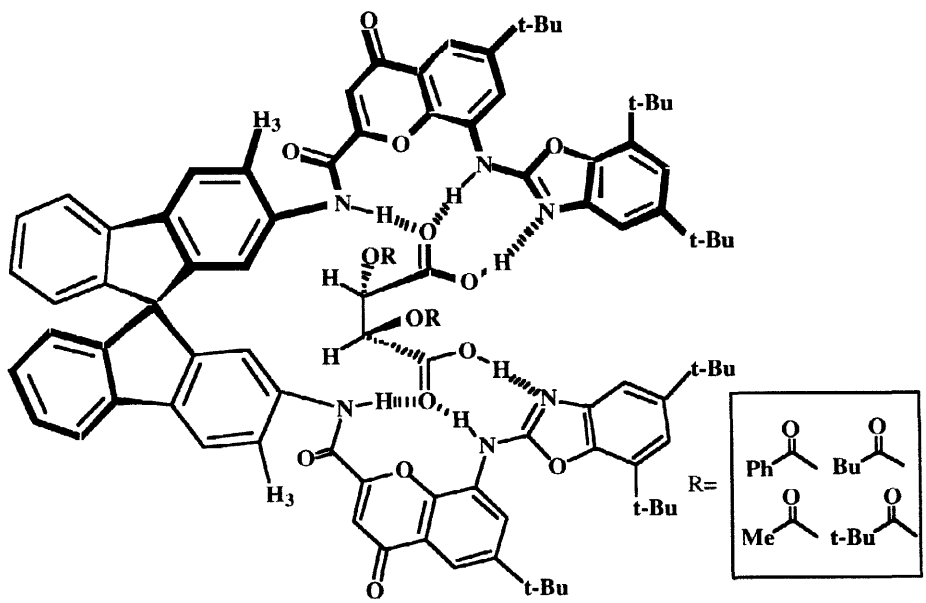

Figure 1: Proposed structure for receptor **1** and its associate with tartaric acid derivatives.

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Combination of a spirobifluorene with two chromenone binding arms provides receptor **1**, which presents a cleft suitable for associating tartaric acid derivatives. In the complex (Figure 1), the asymmetric carbon atoms are placed close to the spirobifluorene unit and hence some chiral discrimination may be expected.

Compound **1**[5] can be easily prepared from 2,2'-diaminospirobifluorene[6] and the chromenone-2-carboxylic acid,[7] as shown in Figure 2.

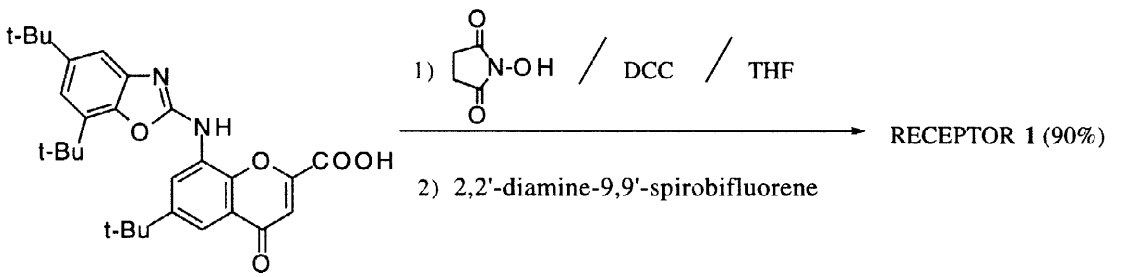

Figure 2: Preparation of receptor **1**.

Association of receptor **1** with tartaric acid derivatives in $CDCl_3$ afforded strong upfield shifts in the guest CHs (0.5 ppm), in agreement with the proposed geometry (Figure 1). The K_{ass} in $CDCl_3$ was too high to be measured accurately with the ^{1}H-NMR method. However, a competitive experiment, using the method of Whitlock,[8] between racemic receptor **1** and L-(+)-dibenzoyl tartaric acid afforded a chiral recognition of 37. This large discrimination suggested dibenzoyl tartaric acid as the resolving agent to separate both enantiomeric receptors. Indeed, if racemic receptor **1** was eluted with $CHCl_3$/MeOH (98/2) from silica gel TLC previously impregnated using a 1% solution of the enantiomerically pure tartaric acid derivative in ether, two yellow spots were obtained with R_f values of 0.2 and 0.6, corresponding to the two different diastereomeric complexes of host **1** and the tartaric acid derivative.

Probably, as in previous cases,[9,7b] the low polarity of the complex, which cannot form as many hydrogen bonds with the silica gel as the free receptor, offers a way in which the receptor can be easily eluted. Both enantiomeric receptors were recovered from the silica gel as the dibenzoyl tartaric complexes. Treatment with aqueous carbonate afforded the pure compounds.

Evaluation of association constants in chloroform was achieved by means of a competitive scale.[8] Aliphatic tartaric acid derivatives had showed smaller association constants, specially if they show bulky substituents such as the pivaloyl group.

Competitive experiments revealed that D-dipivaloyl tartaric acid had the smallest association constant with host **1** 1.7×10^2 times smaller than L-dibenzoyl tartaric acid. However, even in this case the K_{ass} was too high for the ^{1}H-NMR method. The lack of a strong acid-base hydrogen bond leads amides to show smaller association constants with benzoxazole receptors [7b] and hence dibutyroyl tartaric acid monoamide was prepared.

This compound is readily soluble in $CDCl_3$ and the K_{ass} of its D-enantiomer with the (+)-receptor **1** could be measured from a conventional titration to be 2.3×10^5 M^{-1}. From this value it is possible to deduce all the other association constants in Table 1. Dibutyroyl tartaric acid monoamide showed a smaller chiral discrimination than the previous dibenzoyl derivative in agreement with the hypothesis that smaller K_{ass} provide reduced chiral recognition.[10]

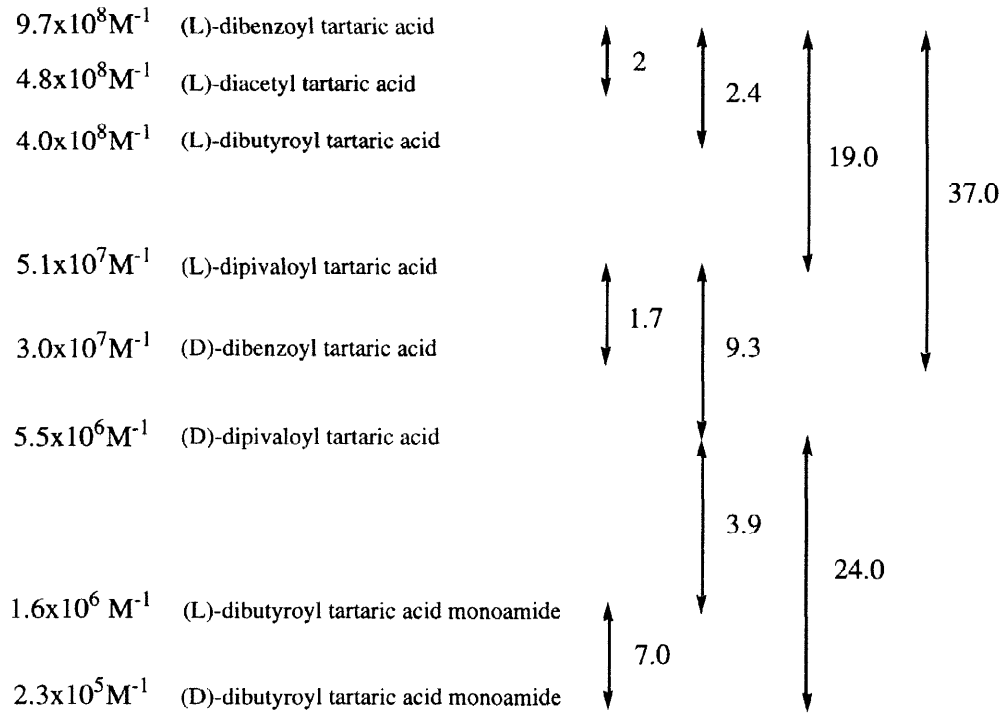

Table 1

Table 1: K_{ass} for (+) receptor **1** and tartaric acid derivatives in $CDCl_3$ at 20 °C.

CPK models reveal that only the R-(+)-receptor **1** adapts to L-tartaric acid in a conformation essentially free of tension, with the guest CHs pointing inside the cleft (these hydrogens are shielded around 0.5 ppm due to the proximity of the spirobifluorene aromatic groups) (Figure 1). If host **1** conserves this conformation, D-tartaric acid fits with its two acyloxy substituents placed in the position previously occupied by the small hydrogen atoms. However, the similar strong upfield shift shown by the tartaric acid CHs in both diastereomeric complexes indicates that this may not be the case, owing to the lack of space inside the cleft. Again, the D-tartaric acid CHs are placed close to the spirobifluorene unit, inside the cleft. To adapt this geometry, host **1** adopts a twisted conformation on the chromenone binding arms, which leads to tensions and a reduced association constant. COSY and ROESY experiments were done with the free host and both complexes in benzene-d_6 (receptor signals are sharper in benzene) to test the previous hypothesis. The most interesting findings were a strong anisotropic effect in the spirobifluorene H_3 (0.71 ppm), due to the proximity of the non-bonding electrons of the carbonyl groups of the benzoate in the weak (R,SS) complex, and a negative 5% NOE effect between the ortho benzoate protons and the spirobifluorene H_3 in the strong (R,RR) associate. Finally, the correct configuration of the (+) receptor was established through correlation with the known R-(+)-9,9'-spirobifluorene-2,2'-carboxylic acid.[4] Curtius degradation of this latter compound yielded (+)-2,2'-diaminospirobifluorene from which (+)-host **1** could be synthesised. Large broadening of the tartaric acid CHs were observed in the titration of the tartaric acid benzoyl derivatives with receptor **1**. This effect seemed to be related with a slow complex formation under the titration conditions because lowering the temperature to -10 °C yielded two different singlets in the ^{1}H-NMR spectrum at 5.88 and 5.39 ppm

corresponding to the free and complex forms of dibenzoyl tartaric acid.

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(5) Host **1:** m.p. 262 ^{o}C. $[\alpha]_D$= +17.5 (c = 0.95 in $CHCl_3$). ^{1}H NMR (Benzene-d6; 400 MHz) δ: 8.34 (2H; d; J= 8 Hz); 8.12 (2H; d; J= 8 Hz); 8.07 (2H; d; J= 8 Hz); 7.98 (2H; d; J= 2 Hz); 7.75 (2H; d; J= 2 Hz); 7.57 (2H; s); 7.55 (2H; d; J= 8 Hz); 7.08 (2H; t; J= 8 Hz); 7.02 (2H; d; J= 8 Hz); 6.97 (2H; d; J= 2 Hz); 6.83 (2H; t; J= 8 Hz); 6.68 (2H; d; J= 8 Hz); 1.32 (18H; s); 1.25 (18H; s); 1.10 (18H; s).

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