COMMUNICATION

Enantioselective recognition of α-amino acid derivatives with a *cis*-tetrahydrobenzoxanthene receptor †

Ana I. Oliva,[a] Luis Simón,[a] José V. Hernández,[a] Francisco M. Muñiz,[a] Anna Lithgow,[b] Alicia Jiménez[b] and Joaquín R. Morán *[a]

[a] *Departamento de Química Orgánica, Plaza de los Caídos 1-5, Universidad de Salamanca, Salamanca, E-37008, Spain. E-mail: romoran@usal.es; Fax: 0034923294574; Tel: 0034923294481*

[b] *Servicios Generales de la Universidad de Salamanca, Salamanca, Spain*

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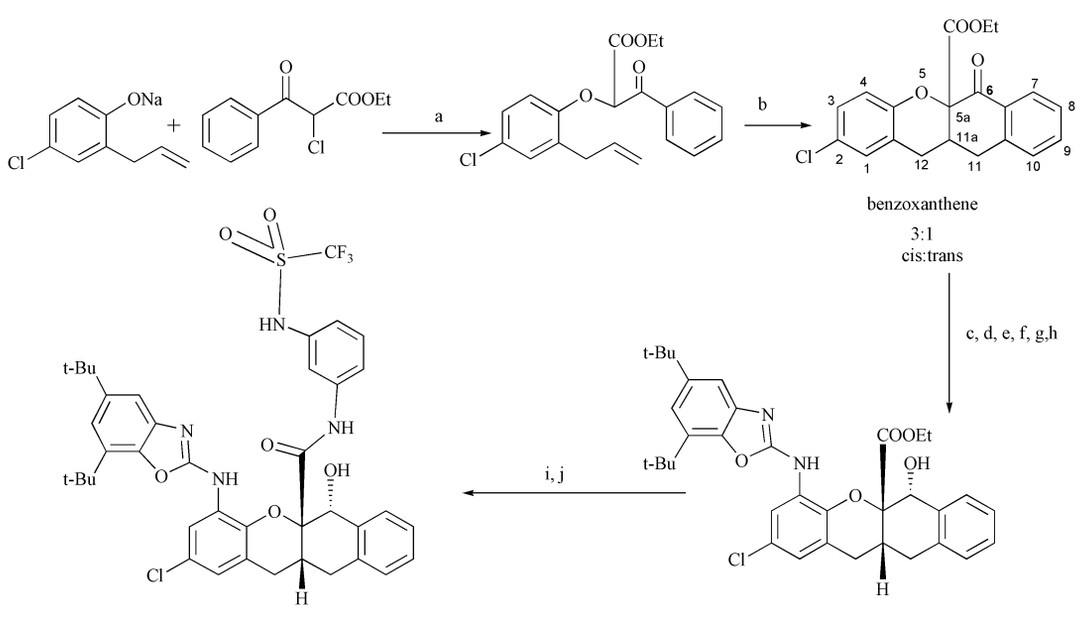
A *cis*-tetrahydrobenzoxanthene receptor has shown good enantioselective association with benzyloxycarbonyl amino acid derivatives.

Large scale amino acid enantioselective synthesis remains a challenge.[1] Nevertheless, the resolution of industrially available racemic mixtures by making use of chiral recognition could be a promising alternative.[2] Enantioselective phase transfer is particularly attractive. Xanthones[3] and chromenones[4] have so far been successfully used to discriminate between hydroxyacid enantiomers. These skeletons themselves, however, show no chiral centers, which is not helpful in the design of asymmetric receptors. Molecular models show that a benzoxanthene, as in receptor **1** (Scheme 1), could offer a good framework for holding two hydrogen bond donors to associate with a carbonyl group in an asymmetric environment. This skeleton has the added advantange that it can be easily prepared from an oxidative intramolecular cyclization[5] of readily available precursors, as shown in Scheme 1, where the numbering of the benzoxanthene base molecule has been included.

Thus far, this synthesis still affords a mixture of *cis* and *trans* ring closures; this drawback can be overcome because the minor *trans* isomer can be almost completely separated from the reaction mixture as a crystalline compound. The *cis* structure can be purified after the nitration stage, in which it also readily crystallizes. A few more conventional synthetic steps provide receptor **1**‡ (Scheme 1), where the benzoxazole ring, due to its basicity, has been included to favour strong carboxylic acid binding. The structure of this compound together with the fact that its geometry is suitable for associating with carboxylic acids was secured through X-ray diffraction analysis (Fig. 1). The outcome of this analysis was highly encouraging because the receptor crystallizes with two methanol molecules, one of them setting two strong linear H-bonds in the cavity designed for the amino acid carbonyl group. Other receptors that bind oxygen atoms have been described.[6]

The binding properties of receptor **1** were studied in deuterochloroform. Conventional ^{1}H-NMR titration[7] with decanoic acid and Cbz-glycine (Cbz = benzyloxycarbonyl) gave K_{ass} = 1.2 × 10^4 M^{-1} and K_{ass} = 1.5 × 10^4 M^{-1}, respectively, similar to the complexes obtained with chromenone receptors, an observation that supports the formation of three H-bonds.[4] Complex formation in both cases can be readily followed due to the strong shielding of the receptor H_3 (Fig. 2) (8.3 to 7.9 ppm in the decanoic complex and 7.8 ppm in the glycine complex). Locking the benzoxazole nitrogen in a conformation distant from H_3 may be responsible for these large shifts.

Titration of a racemic mixture of receptor **1** with amino acid derivatives, such as Cbz-phenylglycine, shows, however, association (K_{ass} = 2.3 × 10^4 M^{-1}) but neither splitting of the host



Scheme 1 Synthesis of receptors **1** and **2**. a) Diglyme, T = 80 °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) $SnCl_2$, r.t., yield: 90%; e) thiophosgene, Na_2CO_3, CH_2Cl_2–H_2O, r.t., yield: 95%; f) 2-amino-4,6-di-*tert*-butylphenol, toluene–CH_2Cl_2, yield: 91%; g) MeI, 2,4,6-trimethylpyridine, EtOH–THF, r.t., yield: 87%; h) K-Selectride, THF, yield: 90%; i) *m*-phenylenediamine lithium salt, THF, −30 °C, yield: 88%; j) trifluoromethanesulfonic anhydride, toluene, −80 °C, yield: 88%.

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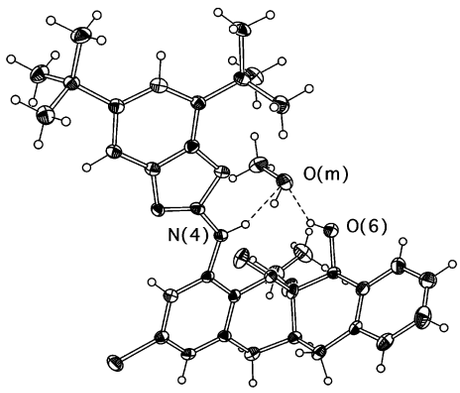

Fig. 1 X-ray crystal structure of receptor **1** showing intermolecular hydrogen bonds, which are indicated by dashed lines: N(4) ··· O(m) = 2.96 Å; O(6) ··· O(m) = 2.67 Å. One of the methanol molecules has been omitted for clarity.

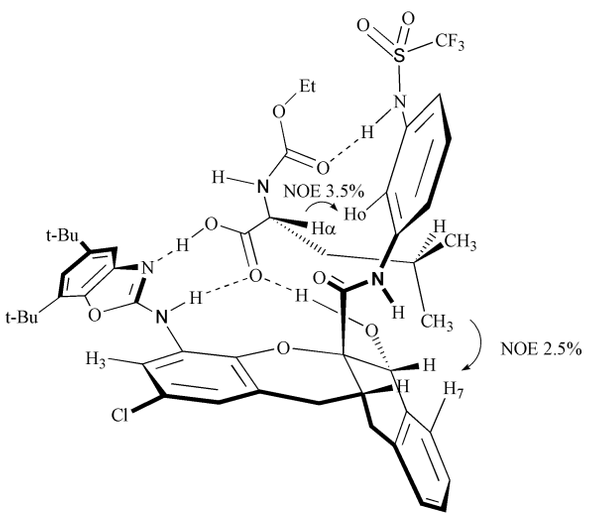

Fig. 2 Proposed structure for the complex formed by receptor **2** (6*S*, 5a*R*, 11a*S*) and ethoxycarbonyl-L-leucine.

receptor nor chiral discrimination; the presence alone of a chiral environment does not seem to be sufficient to achieve discrimination between the guest enantiomers; further interactions between the amino acid α carbon substituents and the receptor are necessary to secure reasonable stability differences between both diastereomeric complexes. CPK models show that, in receptor **2**, a new H-bond between the phenylenediamine NH in the receptor and the carbonyl group of a carbamoyl amino acid derivative could fix the free rotation of the guest, increasing the difference in association constants of both enantiomeric guests (Fig. 2). Several groups were tested to activate the phenylenediamine NH (acetate, mesylate and triflate), triflamide showing the best results, probably due to the high acidity of its NH.

Transformation of receptor **1** into receptor **2**§ (Scheme 1) can be accomplished in high yield by treating **1** with the lithium salt of *m*-phenylenediamine in THF, followed by reaction with trifluoromethanesulfonic anhydride. Competitive titrations[7] were carried out by adding small amounts of the enantiomeric pure guests (amino acid derivatives, Table 1) to a deuterochloroform solution of the racemic host, yielding splitting of the ^{1}H-NMR host **2** signals. Graphic representation of the chemical shifts of these protons against each other, and the use of a home made curve fitting program, provide the chiral discrimination, and disclosed significant enantioselectivity for receptor **2**.

These promising results suggested that it might be possible to resolve a racemic mixture of host **2**, using its supramolecular properties.[3] Ethoxycarbonyl-L-leucine was selected as the guest due to its lack of UV absorption at 250 nm. Preparative TLCs were impregnated with a 2% amino acid solution in chloroform, dried and loaded with host **2** (50 mg); elution with CH_2Cl_2

Table 1 Enantioselective discrimination for receptor **2** with different guests in $CDCl_3$ at 20 °C.

Guest	K_{rel} [a]
Ethoxycarbonyl-L-proline	57.0
Cbz-L-phenylglycine	16.0
Cbz-L-phenylalanine	15.0
Ethoxycarbonyl-L-alanine	8.4
Ethoxycarbonyl-L-leucine	7.6
Boc-L-leucine	4.0

[a] K_{rel} refers to the relative association constants between the guest and the two enantiomers of receptor **2**.

resulted in two different bands (R_f = 0.72, R_f = 0.23) for each of host **2** enantiomers. From these bands, receptors were obtained as complexes. The free hosts were released by washing an ethyl acetate solution with 4% aqueous sodium carbonate.

Since association constants for receptor **2** were too large for an accurate direct measurement, we used a competitive method.[7] A relative association constant of 5.8 was established against a known receptor[4] with K_{ass} = 1.4 × 10^4 M^{-1} when ethoxycarbonyl-L-leucine was the guest. Therefore the weak receptor **2** complex should show K_{ass} = 8.4 × 10^4 M^{-1} while K_{ass} = 6.4 × 10^5 M^{-1} can be calculated for the strong one with the previous guest.

NOE experiments on the strong complex were specially revealing since they supported a possible geometry for this associate. Crossed effects between host and guest place the phenylenediamine H_o proton close to the α carbon CH in the guest (3.5%) and the H_7 aromatic proton in the host in the proximity of the methyl of the leucine isobutyl group (2.5%) (Fig. 2). From these data, we propose the configuration shown in Fig. 2 for the strong complex (host **2**–L-leucine derivative) as (6*S*, 5a*R*, 11a*S*/L). The proximity between the leucine CH α carbon and the phenylenediamine group in the host provides an explanation for the chiral recognition, since in the weak complex the leucine α proton exchanges position with the amino acid side chain, and the bulky isobutyl group then collides with the host phenylenediamine unit.

Titration of guests revealed the importance of the amino acid side chain and the carbamoyl substituent. Benzyloxycarbonyl derivatives provide the best substrates, with chiral recognitions of up to 15 (with Cbz-phenylglycine), while steric hindrance from the *tert*-butyl group probably yields Boc derivatives with small association constants and poor enantioselectivities. The combination of the ethoxycarbonyl group with the rigidity of the proline afforded specially good discrimination up to 57.

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Notes and references

† Electronic supplementary information (ESI) available: binding data. See http://www.rsc.org/suppdata/p2/b2/b203054c/

‡ Selected physical data for receptor **1**: FABMS: 57 (M^+), 100%; 603, 60%; 385, 45%; 129, 45%; 483, 40%; 605, 30%; 91, 20%. ^{1}H NMR (400 MHz, $CDCl_3$): 8.47 (d, *J* = 2 Hz, 1H), 7.72 (d, *J* = 8 Hz, 1H), 7.33 (d, *J* = 2 Hz, 1H), 7.26 (t, *J* = 8 Hz, 1H), 7.18 (t, *J* = 8 Hz, 1H), 7.10 (d, *J* = 2 Hz, 1H), 7.03 (d, *J* = 8 Hz, 1H), 6.79 (d, *J* = 2 Hz, 1H), 5.33 (d, *J* = 9 Hz, 1H), 4.28–4.20 (m, 2H), 3.05–2.65 (m, 4H), 2.60 (dd, *J* = 3 Hz, *J* = 18 Hz, 1H), 1.45 (s, 9H), 1.34 (s, 9H), 1.20 (t, *J* = 7 Hz, 3H). mp 136–138 °C.

Crystal data for receptor **1**: $C_{35}H_{39}ClN_2O_5 \times 2CH_3OH$, *M* = 666.25, monoclinic, space group $P2_1/n$ (n° 14), *a* = 16.012(1) Å, *b* = 12.401(1) Å, *c* = 19.494(1) Å, α = λ = 90°, β = 111.98(1)°, *V* = 3589.5(4) Å^3, *Z* = 4, D_c = 1.235 Mg m^{-3}, μ(Cu-Kα) = 1.345 mm^{-1}, *F*(000) = 1424. Data (6113 total reflections and 2091 observed reflections [$I > 2\sigma(I)$]) were measured on a Seifert 3003 SC rotating anode diffractometer with (Cu-Kα) radiation (graphite monochromator) using 2θ–ω scans at 293 K. The crystallographic data for the structure reported in this paper are deposited at the Cambridge Crystallographic Data Centre as

supplementary material. CCDC reference number 182407. See http://www.rsc.org/suppdata/p2/b2/b203054c/ for crystallographic files in .cif or other electronic format.

§ Selected physical data for receptor **2**: FABMS: 57 (M^+), 100%; 155, 30%; 385, 20%; 513, 20%; 797, 10%; 861, 10%. ^{1}H NMR (400 MHz, $CDCl_3$): 7.86 (d, J = 2 Hz, 1H), 7.56 (m, 2H), 7.3–6.9 (m, 8H), 6.94 (d, J = 2 Hz, 1H), 5.29 (s, 1H), 3.32–3.22 (m, 2H), 2.89 (dd, J = 3 Hz, J = 18 Hz, 1H), 2.68–2.55 (m, 2H), 1.44 (s, 9H), 1.22 (s, 9H). mp 168–170 °C; $[a]_D^{20}$ = −181.6 (c = 0.10% $CDCl_3$); $[a]_D^{20}$ = +180.8 (c = 0.10% $CDCl_3$).

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