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Synthesis of a heterocyclic receptor for carboxylic acids

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Abstract—The synthesis of a tricyclic receptor having a bowl shape and three binding points for carboxylic acids has been achieved starting from readily available 1-tetralone derivatives. This host possesses a six-membered lactam moiety and a carboxamide at the end of a flexible arm. The association constant with benzoic acid and the stoichiometry of the complex have been determined using ^{1}H NMR dilution experiments.

For several years, we have been interested in the design and synthesis of new receptors for acids and amines. In three previous papers, we described the synthesis of flexible receptors for amines,[1] acids[2] or both acids and amines.[3] These hosts possessed a heterocyclic structure with a flexible arm containing a carboxamide moiety allowing supplementary hydrogen bonding with the guest. The binding interaction between substrate and receptor will be significantly enhanced if the receptor topography is inherently complementary to that of the substrate.[4] Our goal was to design a cleft receptor for carboxylic acids. The concave nature of the cleft also reduces the probability of self complexation.[4]

We selected the design described in Fig. 1. The three binding points are ensured by a five- or a six-membered lactam and a remote carboxamide incorporated on the benzene ring of a heterocyclic structure having a bowl shape. In order to obtain this bowl shape, ring B must be saturated and a *cis*-fusion between rings B and C is required.

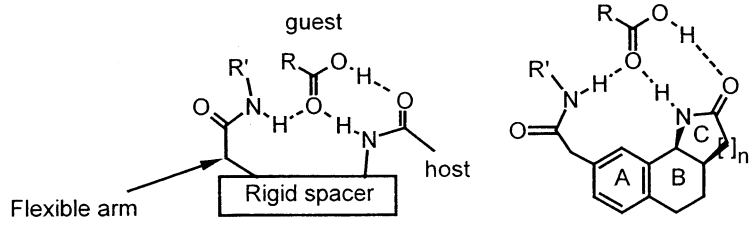
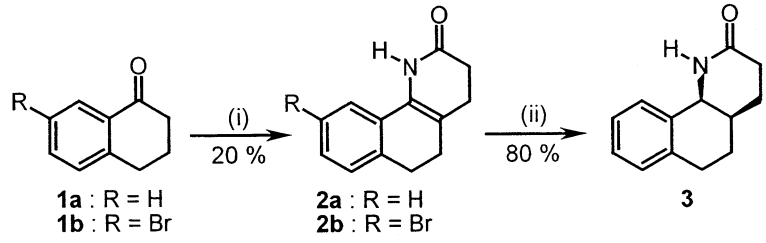


Figure 1. Cleft receptor design (left) and proposed receptor design (right).



Scheme 1. (i) 1) PTSA, pyrrolidine, toluene, reflux, 4 h. 2) Acrylamide, 90–100°C, 38 h; (ii) H_2/Pd-C, EtOH, 3 bar, rt.

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Synthesis of the host

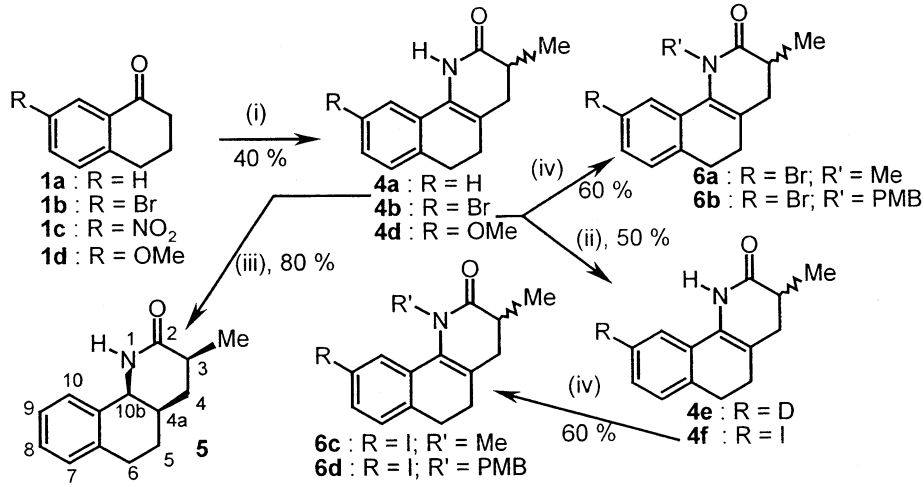
The main problem was to design a synthetic route affording both the tricyclic structures depicted in Fig. 1 with $n = 1$ or 2 and the possibility of functionalising the benzene ring. References concerning the syntheses of these tricyclic lactams are rather scarce.[5] A retrosynthetic analysis showed that 7-substituted α-tetralones would be valuable precursors of the required tricyclic structure. The 7-methoxy- or the 7-nitrotetralones are commercially available and the 7-bromo derivative could be conveniently synthesised.[6] As the synthesis of the five-membered lactam (Fig. 1, $n = 1$) is tedious we decided to add an extra carbon atom. Molecular modelling (MM2 force field implemented in PCMODEL®) showed that the six-membered lactam could also ensure three binding points with a carboxylic acid.

We first tried the Stork enamine reaction on the tetralones **1a**,**b** (Scheme 1). Reaction of acrylamide with the intermediate pyrrolidine enamine led to the benz[*h*]quinolines **2a**,**b** in low yields due to side polymerisation reaction. The replacement of acrylamide by methacrylamide did not improve these yields.

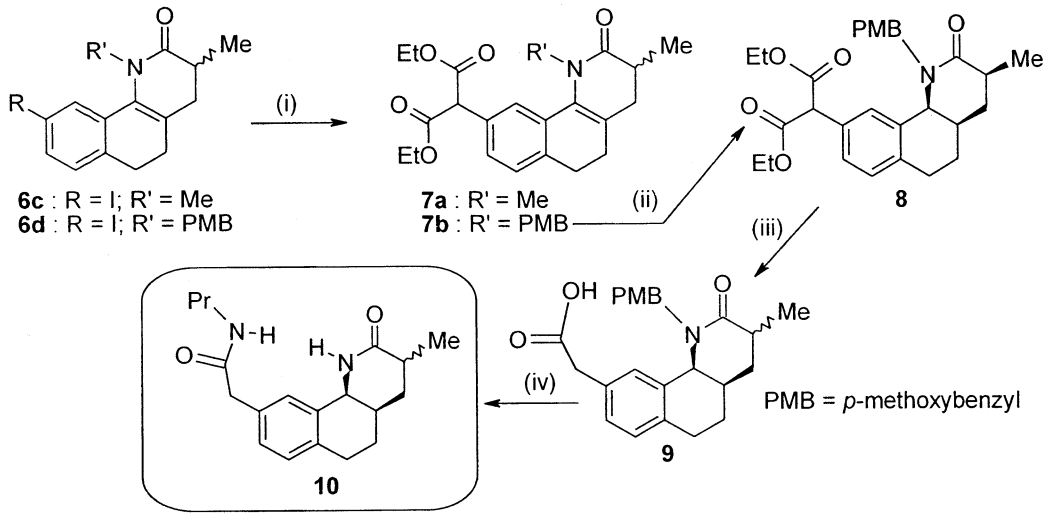
Alternatively (Scheme 2), the tetralones **1a**–**d** were reacted with methacrylamide under conditions published by the Corriu's group.[7] While no reaction occurred with 7-nitrotetralone (**1c**), this method afforded the benzo[*h*]quinolines **4a**,**b**,**d** in medium yields (Scheme 2). The unsubstituted compound **4a** was reduced with hydrogen under palladium catalysis. The 4a–10b ring junction of the resulting product **5** was shown to be *cis* since a small coupling constant was observed between the corresponding hydrogen atoms ($J = 4.0$ Hz). In order to introduce the side chain we tried various cross-coupling reactions between the 7-bromo derivative **4b** and diethyl malonate, acetylacetone, or ethyl cyanoacetate.[8] Whatever the conditions,[9] no conversion was achieved with either the lactam **4b** or with its *N*-methyl derivative **6a** obtained via methylation with KOH/DMSO/MeI. It is well known that iodine is more reactive in this kind of reaction. The bromine lithium exchange reaction was carried out on **4b** and subsequent quenching with methanol-*d* or iodine afforded compounds **4e**,**f**. While no coupling reaction could be achieved with the free iodolactam **4f**, the *N*-methylated lactam **6c** afforded the diester **7a** via reaction with diethyl malonate under cuprous iodide catalysis (Scheme 3). This sequence of reactions clearly showed that the N–H lactam must be protected in order to achieve the cross coupling. We had no success with the *Z* group ($COOCH_2Ph$) so we selected the *p*-methoxybenzyl moiety (PMB) as a protecting group, since it is stable under the reductive conditions leading to a *cis*-ring junction and could be conveniently removed under mild oxidative conditions. After conversion of the iodolactam **4f** into its PMB derivative **6d**, this latter compound afforded the diester **7b**. Reduction of the carbon–carbon double bond yielded **8** as a single diastereoisomer ($J = 4.0$ Hz as in **5**). Alkaline hydrolysis of **8** and subsequent decarboxylation[10] led to the acid **9**, which was converted into the carboxamide under classical pepditic coupling conditions (EDCI, HOBT, n-$PrNH_2$).[11] Oxidative cleavage of the PMB group with CAN[12] yielded the targeted host **10**.[13]

Complexation studies

Having at hand the two hosts **5** and **10**, we carried out the complexation studies of carboxylic acids using NMR experiments. We studied first the self association of **5** and **10**. On dilution of a host solution, an upfield chemical shift of the amide protons was observed. The chemical shift values were noted as a function of the concentration and Horman–Dreux[14] analysis of these data gave no dimerisation constant (K_d) for **5** and $K_d = 20$ M^{-1} for **10**. On addition of the guest to the host solutions, a downfield chemical shift of the amide protons of the host was observed. The stoichiometry of the complexes was 1/1 as shown by the continuous variation method of Job.[15] With benzoic acid, the association constant (K_a) was 80 M^{-1} for **5** and 200 M^{-1} for **10**. This binding study clearly shows that the presence of the supplementary carboxamide moiety in com-



Scheme 2. (i) Methacrylamide, $Si(OMe)_4$, CsF, 80°C, neat; (ii) 1) 2.2 equiv. *n*-BuLi. 2) 3.3 equiv. *tert*-BuLi. 3) 5 equiv. MeOD or I_2; (iii) H_2/Pd-C, EtOH, 1 bar, rt; (iv) 1) KOH, DMSO. 2) MeI or PMBCl.



Scheme 3. (i) NaH, EtOOC-CH_2-COOEt, CuI, dioxane; (ii) H_2/Pd-C, EtOH, 1 bar, rt; (iii) 1) 3% NaOH. 2) CuI, MeCN; (iv) 1) *n*-propylamine, HOBT, EDCI, DMSO. 2) CAN, H_2O, MeCN, rt.

pound **10** led to a significant increasing of the association constant.

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