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# Enzyme Mimics for Michael Additions with Novel Proton Transport Groups

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*Dedicated to Prof. Miguel Yus on the occasion of his 60th birthday*

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Molecular receptors with an enzyme-like behavior in the Michael addition of pyrrolidine to an α,β-unsaturated lactam have been designed. Catalytic activities are discussed and related to the substrate association constants. Chiral assistance of enantiomerically pure receptors was also investigated. One of the receptors shows a 4:1 enantiomeric ratio (60 % *ee*) for the addition of pyrrolidine and 3-pyrroline.



## Introduction

In the course of searching for catalysts that are as effective as natural enzymes, H-bond catalysis has recently received much attention due to the resemblance of many of them to natural enzymes.[1–23] The design of these artificial enzymes could be inspired in knowledge about enzyme catalytic mechanisms. In this regard, enoyl CoA hydratase is an attractive model.[24,25] Its active site shows an oxyanion hole (Figure 1), a well-established feature for many other enzymes, which allows stabilization of the negative charge developed in the Michael acceptor carbonyl group.[26–31] The active site also contains two glutamate residues (Figure 1), which hold the nucleophile in the right position. One of them provides assistance for the proton transfer of the nucleophile to the unsaturated carbonyl α-carbon.

In a recent paper,[23] we have designed and synthesized molecular receptors with excellent catalytic activities in the Michael addition of pyrrolidine to α,β-unsaturated valerolactam **1**. These receptors, and the ones prepared in this work, combine an oxyanion-like structure (a xanthonediamide skeleton) with groups capable of assisting the proton transfer from the nucleophile to the lactam (Figure 2).

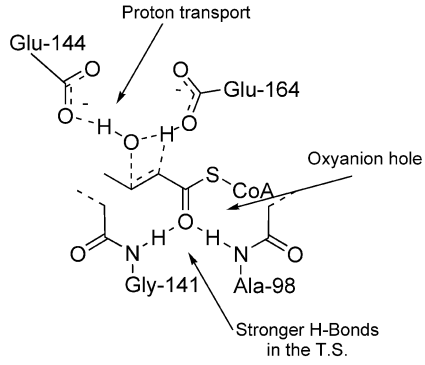


Figure 1. Structure of the oxyanion hole in enoyl-CoA hydratase.

Despite their important role in natural enzymes, glutamates were ruled out because the carboxylate probably blocks the receptor cleft. Instead, basic amino groups were included in the structure (receptors **4** to **6**, Scheme 1), yielding receptors with up to 10000-fold $k_{cat}/k_{uncat}$ values. Molecular-modelling studies showed that amino-group activity in the receptors corresponded to a Bruice proton slide-like mechanism, in which the non-bonding electrons of the good H-bond acceptor (amino group) facilitate proton transfer.[32–35]

Nevertheless, the basic amino group is also able to establish intramolecular H bonds with the xanthoneamide groups, reducing the substrate association constant. As a consequence, the measured half-life time of the reaction does not reflect the actual catalytic activity. As pointed out by Bruice[32,33] it is the ability as an H-bond acceptor and not the basicity that is important for an auxiliary group to carry out the proton transport in a proton-slide mechanism. Therefore, in this paper the catalytic effect of non-basic oxy-

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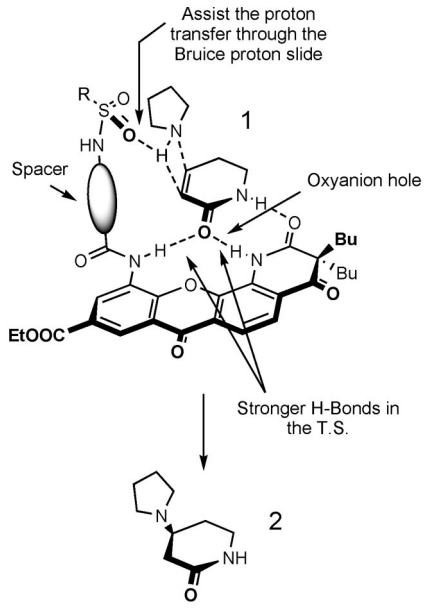
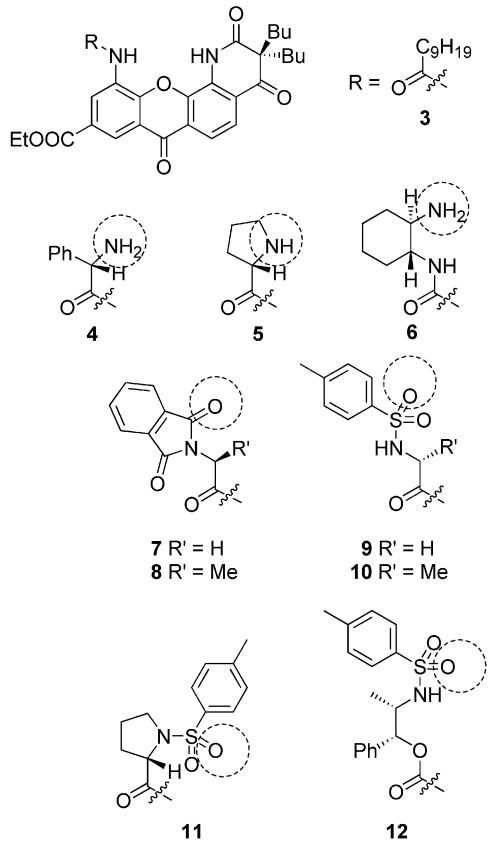



Figure 2. Proposed mechanism for the catalytic effect of the receptors with sulfonamide active groups in the addition of amines to the lactam **1**.




Scheme 1. Structure of the catalysts studied in this work. The group responsible for catalysis by the proton slide is highlighted.

gen atoms, which are good H-bond acceptors,[36–38] is reported. Additionally, the asymmetric induction of the chiral receptors was investigated (including the previously reported receptors **4**–**6**[23]).

## Results and Discussion

Kinetic experiments were carried out in benzene at 298 K. The lactam concentration was 0.8 M. A high concentration of pyrrolidine (3.0 M) was used to prevent catalytic activity by the reaction product, which could have complicated the interpretation of the process under study. Under these conditions, the half-life time of the reaction (referred to lactam) was 2385 min in the absence of a catalyst.[23] Receptors were added at 0.04 M concentration and the lactam concentration was deduced from the $^1$H NMR spectra at different times.

Despite the formation of diastereomeric complexes with the amino lactam **2**, the chiral receptors (**8**, **10**, **11** or **12**) did not split the signals of the reaction product. To assess asymmetric induction, we prepared a chiral shift reagent **13** derived from the xanthone-diamine skeleton (Figure 3). Although this receptor shows no improved catalytic activity, it associates the Michael adduct **2**, leading to diastereomeric complexes with different $^1$H NMR spectra. The aromatic rings in the diphenylethylenediamine moiety supply strong anisotropic fields, while the sulfonamide NH provides an additional H bond with the amine nitrogen of lactam **2**, fixing the geometry of the complex and improving the association constant. Addition of 25% of this receptor completely split the signals of the pyrrolidine α-hydrogen atoms (Figure 3). These signals were used in the analysis owing to their large size and because irradiation of the β pyrrolidine protons affords reasonably narrow signals, which after Gaussian deconvolution using the Mestre-C[39] program afforded the enantiomeric ratio. The absolute stereochemistry was determined using the circular dichroism of the product (see Supporting Information).

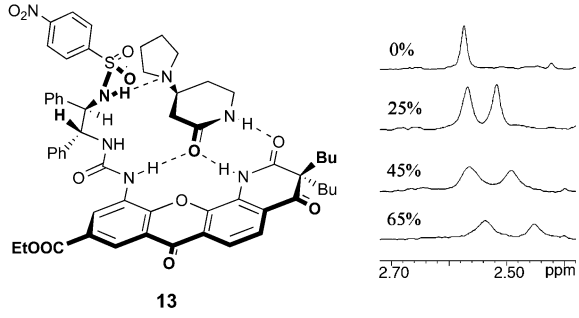



Figure 3. Structure of the complex between the chiral shift reagent **13** and the aminolactam **2** and the induced chemical shifts in the pyrrolidine signals.

The results are summarized in Table 1. The previously reported receptors included here (**4**, **5**, and **6**) showed only small chiral assistances (ratio below 3:1).

The CPK models suggested that the receptors **7** and **8** can place the carbonyl oxygen atoms of the phthalimide group close to the valerolactam α carbon in the complex. Therefore, they could be active in transporting the pyrrolidine proton. Both phthalimide derivative receptors showed improved half-life times, in agreement with a proton-slide mechanism. The alanine derivative **8** had a smaller half-life

Table 1. Relative association constants and kinetic activities of receptors.[a]

| Receptor | $t_{1/2}$ [min] | $K_{rel}$ | Enantiomeric ratio *S*/*R* (pyrrolidine) | Enantiomeric ratio *S*/*R* (3-pyrroline) |
|---|---|---|---|---|
| **3** | 85 | 1.00 | | |
| **4** | 48 | 0.064 | 1.6:1 (23% *ee*) | 1.2:1 (9% *ee*) |
| **5** | 85 | 0.007 | 2.6:1 (44% *ee*) | 1.4:1 (16% *ee*) |
| **6** | 33 | 0.071 | 0.4:1 (42% *ee*) | 0.4:1 (42% *ee*) |
| **7** | 68 | 0.588 | | |
| **8** | 42 | 0.053 | 3.8:1(58% *ee*) | 1.9:1 (31% *ee*) |
| **9** | 24 | 0.280 | | |
| **10** | 96 | 0.599 | 1:1 | |
| **11** | 102 | | 1:1 | |
| **12** | 51 | 0.240 | 4.0:1 (60% *ee*) | 4.3:1 (62% *ee*) |

[a] Kinetic experiments in benzene at 298 K. [pyrrolidine] = 3.0 M; [lactam] = 0.8 M; [receptor] = 0.04 M. For chiral assistance experiments, [nucleophile] = 0.80 M. The enantiomeric ratio was measured in the reaction half-life. $K_{rel}$ relative to receptor **3**, measured in benzene solution.

time than the glycine derivative **7**, even though the association constant was 10 times smaller. The methyl group in the alanine fragment probably favours a suitable conformation for catalysis. This receptor also shows a noticeable chiral assistance (3.8 ratio, 58% *ee*). Asymmetric induction was also checked using 3-pyrroline as the nucleophile. In this case, integration of the $^1$H NMR signals was easier, but the enantiomeric excess was smaller, showing only a ratio of 2.0 (33% *ee*) between the integrals of the enantiomeric lactams.

Sulfonamides have been shown to be hydrogen-bond acceptors similar to amines.[36] Therefore, the receptors **9** to **12** were prepared. The best catalytic activity was obtained for the tosylglycine derivative **9** (half-life time 24 min). The presence of the methyl group in the tosylalanine receptor **10** strongly reduced the catalytic activity despite a stronger association constant. Unlike in the phthalimide derivative receptors, the methyl group handicaps the productive conformation in the receptor. Since the half-lives and association constants were similar to those of the decanoyl receptor **3**, the sulfonamide is probably not active in the proton-transport step. This can also explain the lack of asymmetric induction. The same features were observed for the receptor **11**, with long half-life times (102 min) and no asymmetric induction.

The most interesting results were obtained with the tosyl norephedrine derivative **12**. The complex of this receptor and lactam **1** was four times weaker than for the decanoyl receptor **3**, probably due to intramolecular H-bond formation. Although the catalytic activity was slightly smaller than for the receptors **8** and **9** ($t_{1/2}$ = 51 min), analysis of the chiral assistance afforded a 4.0:1 ratio (60% *ee*). A different experiment with 3-pyrroline revealed a similar result, with a 4.3:1 ratio (62% *ee*).

Although half-life times of the catalyzed reaction might be useful in characterizing the catalytic activity of the receptors, this magnitude might conceal other phenomena as association of the substrate or inhibition. For the receptors **4**, **5** and **6** these effects have been shown to be very relevant in determining the real catalytic activity. Therefore, for the receptors **8**, **9**, and **12**, we performed a similar analysis to that described already for these receptors.[23]

We first noticed that the equation that describes Michael–Menten kinetics in the presence of a competing product, can be further simplified if one assumes that the association constant of the product and the substrate is similar; see Equation (1).

$$\frac{d[\text{lactam}]}{dt} = \frac{k_{cat}[\text{lactam}][\text{receptor}]_0}{K_M(1+\frac{[\text{product}]}{K_i})+[\text{lactam}]}[\text{pyrr}]^n$$

$$K_I \approx K_I \Rightarrow \frac{d[\text{lactam}]}{dt} = \frac{k_{cat}[\text{receptor}]_0}{K_M+[\text{lactam}]_0}[\text{lactam}][\text{pyrr}]^n \quad (1)$$

Numerical integration of the kinetic equations was performed using the fourth-order Runge–Kutta method.[40] In this analysis it is assumed that the mechanism is first order in pyrrolidine ($n$ = 1) and that the contribution from a bimolecular mechanism is negligible. Although it would be desirable to confirm this point, determination of this order is difficult in the presence of the catalyst: it will require kinetic experiments at different pyrrolidine concentrations, but pyrrolidine concentration may also affect the association constant with the catalyst, making interpretation of the results difficult. Therefore, we simply used $n$ = 1 in the integration and checked that the $k_{cat}/k_{uncat}$ ratio obtained was at least 10 times larger than the same value obtained for the receptor **3**. Because the receptor **3** lacks any group that might assist the proton-transport step, this 10-fold increment in catalytic activity is probably a consequence of the auxiliary group replacing the second pyrrolidine molecule (kinetic order in pyrrolidine has been found to be 2 in the absence of catalyst).[23] If there is a contribution of a possible second-order mechanism, it will be small for the accuracy that is sought in these experiments. A similar estimation of $k_{cat}$ for the receptors **7**, **10** and **11** shown in this work was not valid because, from the values obtained for $k_{cat}$ for these receptors, it was not possible to rule out a relevant contribution for the bimolecular mechanism.

In order to calculate $k_{cat}$ it is necessary to measure $K_M$. The measurement of small association constants with receptors using 3.0 M pyrrolidine is problematic, so indirect measurement of $K_M$ was employed. Relative association constants with respect to the receptor **3** have been found by means of competitive titration in deuterated chloroform. These relative constants were used to approximate real association constants, assuming that the same ratio would be obtained under the reaction conditions. With these values, and the association constant for receptor **3** measured in the reaction conditions (between 11 $M^{-1}$ and 40 $M^{-1}$),[23] $K_M$ values were estimated.

The results are shown in Table 2. In this Table, values for the receptors **3**, **4**, **5** and **6** are also included to facilitate comparison. As can be seen, carbonyl and sulfonamide oxygen lone pairs are almost as effective as amine lone pairs in assisting the proton transfer for the reaction. Besides, these receptors do not show the association problems of the amine receptors.

Table 2. Catalytic activities of receptors.

| Receptor | $k_{cat}/k_{uncat}$ | Receptor | $k_{cat}/k_{uncat}$ |
|---|---|---|---|
| **3** | $10^{2.7\pm0.1}$ [a] | | |
| **4** | $10^{3.4\pm0.1}$ [b] | **8** | $10^{3.8\pm0.2}$ [b] |
| **5** | $10^{4.2\pm0.2}$ [b] | **9** | $10^{3.8\pm0.1}$ [b] |
| **6** | $10^{3.9\pm0.2}$ [b] | **12** | $10^{3.5\pm0.1}$ [b] |

[a] Calculated considering second-order kinetics in pyrrolidine (adimensional). [b] mol $L^{-1}$.

The low enantioselectivity of these receptors (compared with the high catalytic activity) cannot be ascribed to a competing no enantioselective process in which auxiliary groups acts only as spectators. It is reasonable to think that these receptors will be as effective as receptor **3** in catalyzing this non selective process, but comparison of the catalytic activities allows us to deduce that product generated by this process will not exceed 10% of the total product, so enantiomeric ratios around 20:1 will be expected. Instead, it is very likely that, due to their structure flexibility, receptors can adopt different conformations to catalyze the formation of both enantiomers.

Modelling studies were performed for the receptor **9** using the GAUSSIAN 98W[41] program. Transition-state structures were optimized using ONIOM[42–44] method. Those atoms directly involved in the reaction were treated with a B3LYP[45]/3-21G**[46–49] level of theory. The rest of atoms were studied using the semiempirical AM1[50] method. The resulting structures are shown in Figure 4, where atoms included in the high-level layer are drawn as a "ball and stick" model, whereas those in the low-level layer are drawn as wires. Single-point energies were calculated on optimized structures using B3LYP/6-31G**[51–53] level of theory, and PCM[54–57] solvation model was employed to account for the benzene solvent. This energy was added to the thermal corrections to Gibbs free energy calculated with the same level of theory used in the optimization.

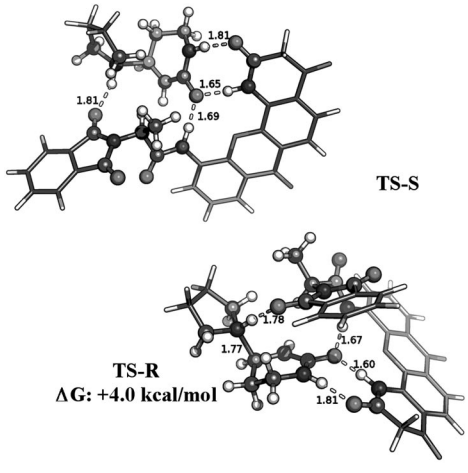



Figure 4. Structure of the transition states obtained from modelling studies for receptor **8**.

The found transition-state structures show a hydrogen bond between the pyrrolidine nucleophile and the phthalimide oxygen, in agreement with a proton-slide mechanism. Due to the flexibility of the receptor, two diastereomeric transition states have been found, each driving to different enantiomers. Although the calculations were able to predict correctly the major enantiomer of the reaction, the energy difference between both transition states (4.0 kcal/mol) is too high for the enentioselectivity obtained. Single-point calculations on structures derived from these transition states revealed that in the one leading to *S* product the phthalimide amino acid adopts a 1.8 kcal/mol more stable conformation (see details in the Supporting Information). Additionally, the pyrrolidine-lactam reacting complex shows a 0.9 kcal/mol more stable arrangement in this transition state. In conclusion, despite the energy difference calculated for both transition states, it is clear that both enantiomers are generated in a catalytic reaction, explaining the low enantioselectivity of the receptor.

## Conclusions

The catalytic activities and chiral assistances of some receptors included in this study support the notion that no basic, good H-bond acceptor groups (such as neutral imide and sulfonamide oxygen atoms) can assist the proton-transfer mechanism. To the best of our knowledge, this is the only example in the literature in which these groups have been proposed to play this role. These unprecedented results broaden the possibilities in the design of new artificial enzymes. Nevertheless, the catalytic and stereochemical results obtained with these xanthone receptors are still far from those obtained with natural enzymes. A more careful design of the receptor auxiliary groups, and the employment of more rigid receptors, should in the future lead to enzyme mimics with enhanced synthetic possibilities.

## Experimental Section

Synthesis of the receptors **3**, **4**, **5**, and **6** has been described previously.[21,23]

**Synthesis of the Receptors 7 to 11:** See Figure 5. An excess (3 to 5 equiv.) of acyl chlorides obtained from phthaloyl amino acid derivatives and tosyl amino acid derivatives was added to a solution of xanthoneamine derivative (1 g, 2.1 mmol) in THF (10 mL). After 20 min at room temperature, water (1 mL) was added dropwise and the reaction mixture was heated to 50 °C for 10 min. The solvent was evaporated off at reduced pressure and the solid residue was dissolved in ethyl acetate. This solution was washed several times with a $Na_2CO_3$ solution (4%) and the organic layer was dried with anhydrous $Na_sSO_4$. Recrystallization of receptors was performed in methanol/water mixtures. Yields of receptors, **7**: 89% (1.24 g), **8**: 92% (1.31 g), **9**: 92% (1.58 g), **10**: 90% (1.33 g), **11**: 87% (1.33 g).

**Synthesis of Receptor 12:** See Figure 6. Xanthoneamine derivative (1 g, 2.1 mmol) was dissolved in $CH_2Cl_2$ (10 mL) and an excess of 0.6 M phosgene solution in toluene was added (2 mL). The mixture was refluxed for 30 min. The solvent and reagent excess were evaporated off at reduced pressure and the solid residue was dissolved in toluene (40 mL). This solvent was again evaporated off under vacuum, and chlorobenzene (10 mL) was used to dissolve the solid

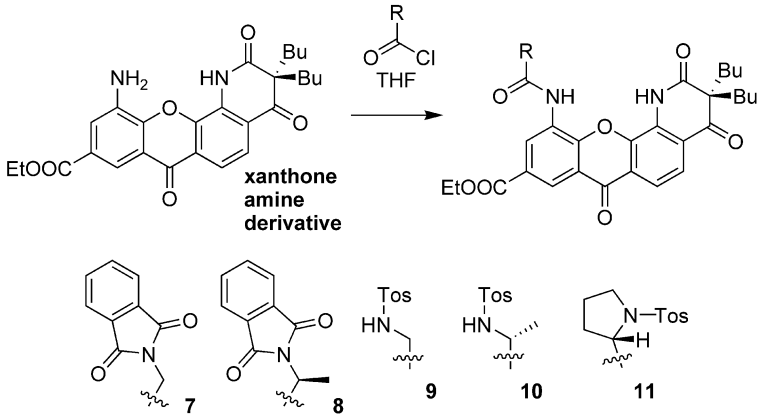



Figure 5. Synthesis of the receptors **7** to **11**.

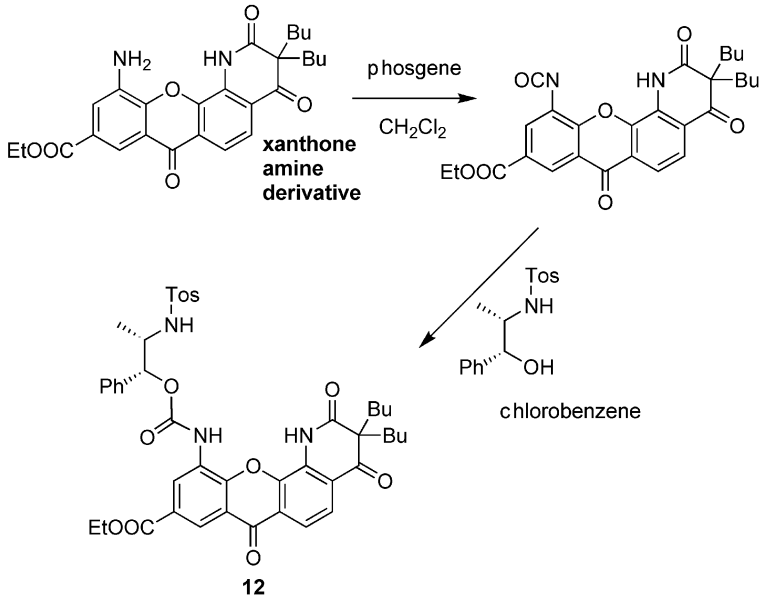



Figure 6. Synthesis of the receptor **12**.

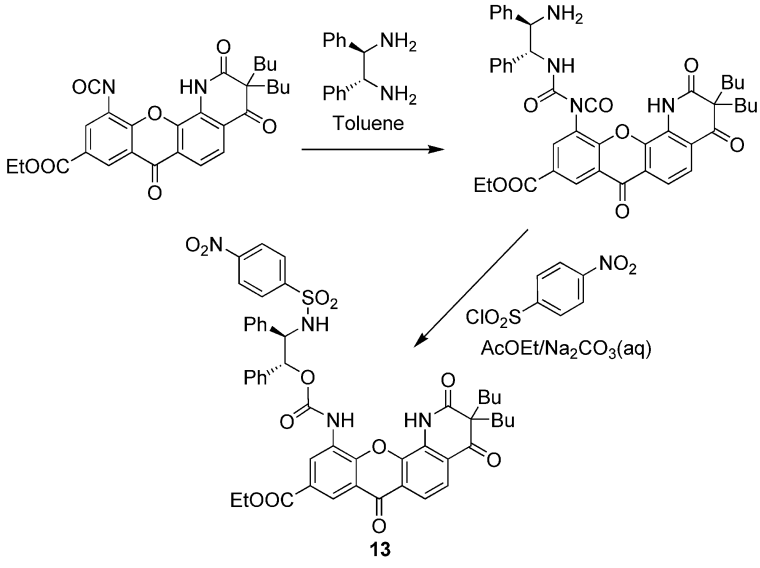



Figure 7. Synthesis of the receptor **13**.

residue. To this solution, an excess (3.2 g, 10.5 mmol) of *N*-tosylnorephedrine was added and the mixture was heated to 130 °C for one week. The solvent was evaporated and receptor **12** was purified by column chromatography on silica gel. Yield 43% (0.73 g).

**Synthesis of Receptor 13:** See Figure 7. The isocyanate of the xanthone amine derivative **2**, obtained as described for receptor **12** (1 g, 2.0 mmol), was dissolved in toluene (40 mL). A solution of diphenylethylenediamine (2 g, 9.4 mmol) in toluene (40 mL) was added dropwise for 15 min. The reaction mixture was washed first with a dilute solution of HCl and then with a 4% $Na_2CO_3$ solution. The organic layer was dried with anhydrous $Na_2SO_4$ and the amino intermediate was obtained after evaporation of the solvent. Yield 93% (1.32 g). The amino intermediate (1 g, 1.4 mmol) was dissolved in dry ethyl acetate (30 mL), and stirred at room temperature with a 4% $Na_2CO_3$ solution. An excess (3 equiv.) of *p*-nitrobenzenesulfonyl chloride was then added. After 1 h, when the reaction was completed, the organic layer was separated and dried with anhydrous sodium sulfate. The desired compound was recovered after evaporation at reduced pressure of the solvent. Yield 86% (1.08 g).

**Supporting Information** (see also the footnote on the first page of this article): Physical data for receptors. Competitive titration experiments. Graphical plots of lactam concentration vs. time. Deconvolution of spectra for chiral assistance determination. Circular dichroism of product. Cartesian coordinates of transition state structures.

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