

A Novel Scaffold for the Modular Assembly of Receptor Models

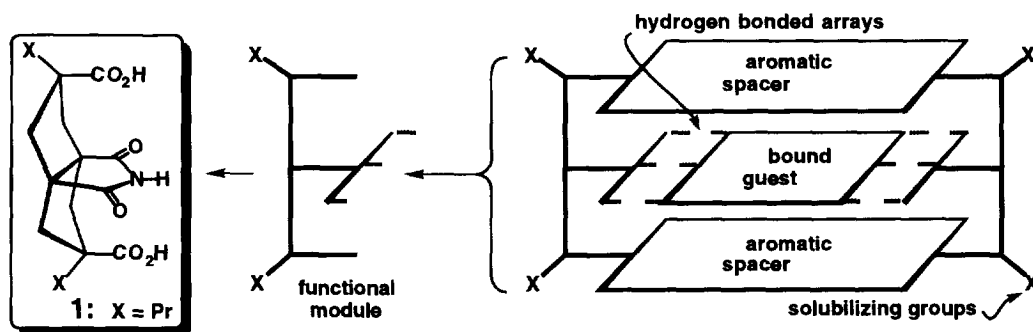
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Abstract: The design and synthesis of a novel tricyclic scaffold for the modular assembly of receptor models and other molecular devices is described. Its structural features are exemplified by the preparation of a simple molecular tweezer for 9-ethyladenine. Copyright © 1996 Elsevier Science Ltd

The design of abiotic structures capable of non-covalent recognition of organic targets in solution is a very active component of supramolecular chemistry. Not only can these structures serve as receptor models for molecular recognition, but they also constitute key elements for the creation of novel chemosensors, carriers and other molecular devices. Abiotic receptors rely generally on a non-peptidic framework for displaying binding groups in three-dimensional space, in a predetermined fashion. The framework can also be used to dictate the overall dimensions of the receptor, its solubility, as well as its conformational mobility.

As part of our continuing effort to develop highly functionalized modules for the rapid assembly of model receptors and other devices, we wish to report the design of tricyclic module **1** (Scheme 1). Held in place by the fused carbobicyclic framework, the two carboxylic acid handles in **1** can position two aromatic surfaces (*via* acylation) at a suitable distance for the intercalation of a largely aromatic guest ($\approx 7\text{-}7.5\text{\AA}$). Condensing **1** with arylamines or alcohols can generate tweezer-like receptors¹ while difunctionalized aromatic spacers could produce macrocyclic variants² (shown in Scheme 1). More importantly, the framework of module **1** can enforce a hydrogen bonding array to converge inside the receptor cavity. In non-competing solvents

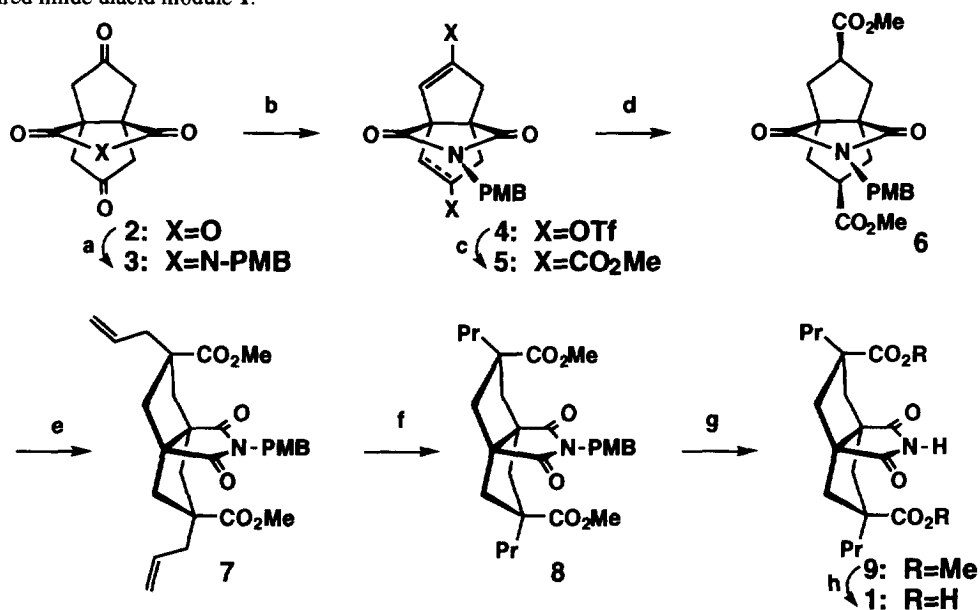


Scheme 1. Receptors based on module **1** (macrocyclic variant shown).

(i.e. CDCl_3), complementary hydrogen bonding between host and guest can translate into high binding selectivities. Furthermore, receptors based on **1** have the potential for guest-selective binding in water, since the contact points could be maintained in a relatively desolvated micro-environment.³ The receptor solubility would be adjusted through appropriate "X" groups at the back of the modules.

The tricyclic anhydride **2**, assembled through a Weiss-Cook condensation⁴, provided a suitably functionalized framework for the assembly of module **1** (Scheme 2). Treatment of **2** with *p*-methoxybenzylamine in refluxing acetic acid generated a latent hydrogen bonding array as the PMB-protected imide in **3**. The ketones in **3** were chemoselectively homologated *via* their corresponding enol triflate **4** followed by palladium-mediated carbonylation using the procedure developed by Ortar⁵ to yield α,β -unsaturated esters **5** in 83% overall from **2**. Catalytic hydrogenation of **5** produced diester **6** as a single stereoisomer, as proven by $^1\text{H-NMR}$ nOe experiments.⁶

The bis potassium enolate of **6** was prepared from KHMDS in THF at -0° and alkylated with excess allyl bromide. Of the three possible stereoisomeric products, the desired diester **7** was isolated by flash chromatography in 35% yield from an intractable mixture of the other two possible isomers. The *endo-endo* stereochemistry⁷ of **7** was confirmed by nOe experiments and by the upfield shift of the $^1\text{H-NMR}$ methyl ester singlet upon alkylation (3.17 ppm for **7** vs 3.51 ppm for **6**)⁸ resulting from closer contact to the neighboring PMB group. Hydrogenation of the allyl groups, followed by deprotection of the imide in **8** under mild oxidative conditions (CAN/aq. CH_3CN) afforded diester **9** in 75% yield overall from **7**. Basic hydrolysis generated the desired imide diacid module **1**.

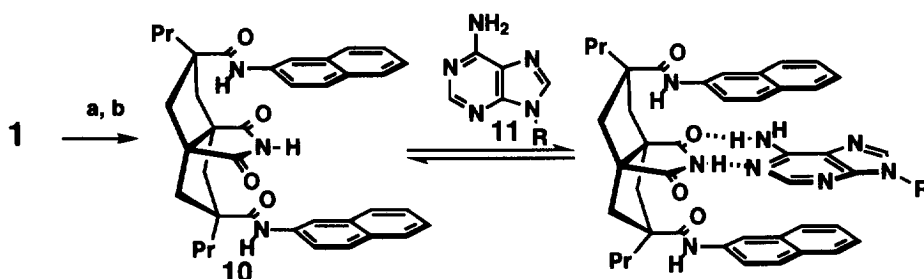


Scheme 2. a) *p*-Methoxybenzylamine, AcOH reflux, 89%; b) KHMDS, PhNTf₂, THF, 0° quantitative; c) Pd(OAc)₂, Ph₃P, Et₃N, MeOH, DMF, CO atmosphere, 93%; d) H₂/Pd-C, EtOH-THF, 99%; e) KHMDS, THF, 0° , allyl bromide quench, 35%; f) H₂/Pd-C, EtOH, quantitative; g) CAN, CH₃CN-H₂O, 78%; h) 3N NaOH, MeOH reflux, 96%.

Although the fused bicyclo[3.3.0]octane framework of **1** is conformationally flexible⁹, the two propyl groups should impose a steric bias favoring the *endo-endo* conformation in which the two cyclopentane rings are flipped toward the imide, maintaining the desired relative disposition of the functional groups. Monte Carlo calculations suggest that the *endo-endo* conformers are more stable than the lowest energy *exo-endo* conformer by at least 2.17 kcal/mol in chloroform solution.¹⁰

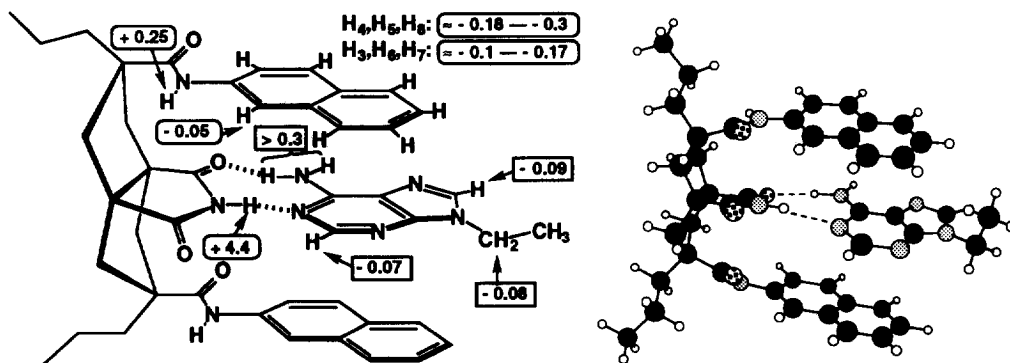
The convergent nature of the scaffold was demonstrated by converting **1** into a simple molecular tweezer for adenine derivatives based on mimicry of the AT base pair in DNA.¹¹ Accordingly, the diacid chloride derived from module **1** was refluxed with 2-aminonaphthalene in a pyridine/CH₂Cl₂ solution to give compound **10** (Scheme 3). Dilution of a CDCl₃ solution of **10** indicated no tendency for host self-association.

As illustrated in Scheme 3, compound **10** should bind to 9-ethyladenine *via* aryl stacking and complementary hydrogen bonding interactions in either Watson-Crick or Hoogsteen binding modes (Watson-Crick mode shown in Scheme 3).



Scheme 3. a) SOCl₂ reflux; b) 2-aminonaphthalene, 2:5 pyridine:CH₂Cl₂ reflux, 33% overall. Watson-Crick binding mode illustrated on the right.

Addition of 9-ethyladenine **11** to a CDCl₃ solution of receptor **10** resulted in predictable complexation-induced shifts (CIS) for both host and guest protons¹² (Scheme 4). The large downfield shift of the imide NH



Scheme 4. Left: Complexation-induced shifts (ppm) determined by saturation of tweezer **10** (<1mM) with 9-ethyladenine **11** (≈30 eq), rounded boxes represent CIS for **10**, square boxes represent CIS for **11**, Watson-Crick binding mode shown. Right: Minimized structure (MM2*)¹⁰ of Watson-Crick complex.

coupled with smaller shifts of the amide NH in **10** and the 6-amino hydrogens of **11** are consistent with the base-pairing hydrogen bonding motif.^{11c} Furthermore, important upfield shifts of the naphthyl protons support aryl stacking between the host and the purine nucleus of the guest. Corresponding upfield shifts of the carbon-bound protons of 9-ethyladenine were also observed. Scheme 4 illustrates the minimized structure of the Watson-Crick complex but both Watson-Crick and Hoogsteen complexation modes can be reasonably expected to exist in solution.^{11c} In addition, other stable tweezer conformers can be generated based on rotation about the C—CO_{amide} and N_{amide}—C_{aryl} bonds where aryl stacking to the guest is less optimal. The latter issue can be simply resolved by the use of larger symmetric arylamines such as 9-aminoacridine or 2-aminopyrene.

Thus, a short synthetic route to the imide diacid module **1** has been developed and its structural features were demonstrated by subsequent conversion to a simple molecular tweezer. The solubility of the module can be readily adjusted at the alkylation step (Scheme 2, step e) using a properly functionalized electrophile (i.e. longer alkyl chain,¹³ latent water-solubilizing group, etc...). Work on the macrocyclic receptors based on **1** and on a water-soluble version of **1** for the design of chemosensors and novel DNA-binding agents is in progress. We will report on these developments in due course.

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- For example, irradiation of the methylene and aryl signals of the PMB protecting group gave enhancements to the methyl ester singlet in **6**.
- For this discussion, "endo" refers to the conformation of the individual cyclopentane units where the ester is quasi-axial and closest to the imide while "exo" refers to the other envelope conformation where the ester is quasi-equatorial, pointing away from the imide.
- This is also consistent with the observed chemical shift for the methyl esters in the other two alkylation isomers: *exo-exo* (3.65 ppm), *exo-endo* (3.33 and 3.68 ppm).
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