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A Convergent Hydroxyimide Module for Molecular Recognition

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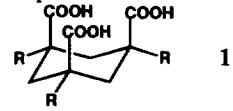
Abstract: The design and synthesis of a new module for the rapid assembly of abiotic receptors soluble in organic solvent is described. The utility of the module is exemplified by its conversion into a simple receptor for 9-butyladenine .Copyright © 1996 Published by Elsevier Science Ltd

The design and synthesis of abiotic receptors (i.e. non-natural) capable of selective recognition of organic guests in solution is, currently, a very active branch of supramolecular chemistry. Such receptors can serve as model systems for the understanding of fundamental molecular recognition phenomena. Furthermore, abiotic receptors can serve as the foundation for the development of novel sensors, carriers and other molecular devices. Different types of receptors have been shown to bind selectively to neutral organic targets in various media, including water, the ubiquitous biological solvent.[2] Basic to all these receptor designs is the presence of an organic scaffold capable of preorganizing functional groups in three-dimensional space.

Some of the more versatile receptors tend to be those that are assembled in a modular fashion from small structurally specialized building blocks. For example, Kemp's triacid derivatives **1** have been used for the design of cleft-like receptors because of the relative disposition of the three carboxylic acid groups.[3] Likewise, functionalized ethenoanthracenes **2** were found to be valuable building blocks for the assembly of water-soluble macrocycles due to the geometry of the two phenolic handles.[2a]



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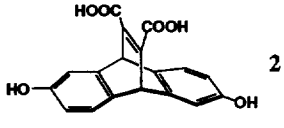

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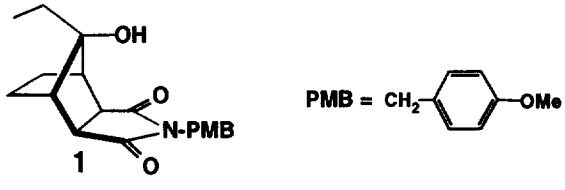
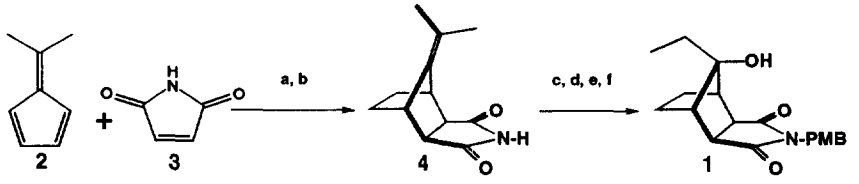
Our research group has been involved in the design of various modules that would *a)* preorganize functional groups in three-dimensional space, *b)* be readily incorporated into model receptors, and *c)* be obtainable by a short synthetic route in multigram quantity. We now wish to report the synthesis of hydroxyimide module **1** (Scheme 1) and to demonstrate its usefulness by synthesizing a simple receptor for adenine derivatives.



Scheme 1.

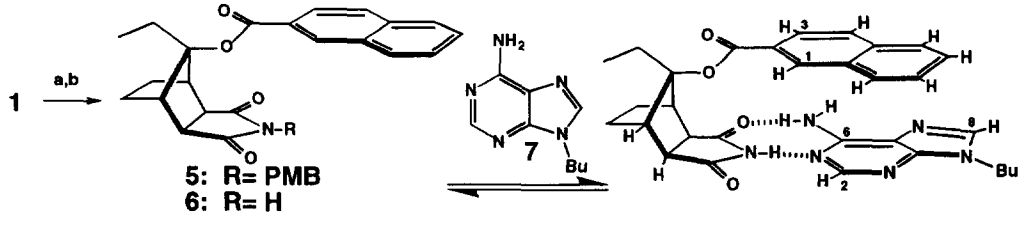
Hydroxyimide **1** was chosen for its structural simplicity and for the ability of the rigid carbobicyclic framework to enforce a hydroxyl group *cis* to a latent imide functional group. The imide offers a readily modifiable three-point hydrogen bonding array for binding to an organic guest. The hydroxyl group serves as a functional handle for the attachment of the module to other receptor components *via* ester, carbamate, or ether linkages. The chain attached to the carbinol, in this case an ethyl group, influences the overall solubility of the receptors. Retrosynthetic analysis revealed that the target could be obtained *via* a simple Diels-Alder strategy starting from 6,6-dimethylfulvene **2** and maleimide **3** (Scheme 2).



Scheme 2. a) toluene, reflux, 89%; b) H_2/Pd-C, 97%; c) KHMDS/p-methoxybenzyl chloride, 75%; d) O_3/CH_2Cl_2, -78°, 100%; e) H_2C=CHMgBr, THF, -78°, 70%; f) H_2/Pd-C, 100%.

The relative stereochemistry of the tertiary hydroxyl in **1** was established by nOe experiments. For instance, irradiation of the CH_2 group of the ethyl chain gave a 6.6% nOe to the two top hydrogens of the ethano bridge.

The convergent nature of the scaffold was put to the test by converting it into a simple adenine receptor based on mimicry of the AT base pair in DNA.[4] Deprotection of the imide in **1** would generate a hydrogen bonding array equivalent to that of thymine, and the appending of an aryl group nearby would mimic the adjacent base pair in duplex DNA. Accordingly, the potassium alkoxide of hydroxyimide **1** was acylated with 2-naphthoyl chloride to give naphthoyl ester **5** in 81% yield (Scheme 3).



Scheme 3. a) KHMDS/THF 0°, then 2-naphthoyl chloride, 81% b) CAN/aq. acetonitrile, 46%.

Large anisotropic shifts in the NMR spectrum of the naphthoylated adduct **5** provided further evidence for the desired stereochemistry. Indeed, naphthoylation of **1** caused a 0.98 ppm upfield shift of the methylene signal of the PMB protecting group in **5**. Removal of the imide protecting group under mild oxidative conditions (CAN/aq. CH_3CN) provided model receptor **6**. Dilution of a $CDCl_3$ solution of **6** indicated no tendency for host self-association. As illustrated in Scheme 3, compound **6** should bind to 9-butyladenine in organic solvent *via* complementary hydrogen bonding and aryl stacking interactions in either Watson-Crick or Hoogsteen binding modes (Watson-Crick mode shown in Scheme 3).

^{1}H-NMR titration of a $CDCl_3$ solution of receptor **6** with 9-butyladenine **7** resulted in sizeable complexation-induced shifts of both host and guest protons[5] (Table 1). After the addition of 10 equivalents of guest, saturation had reached 86% and the imide NH in **6** had shifted downfield from 7.10 to 12.05 ppm[6], a clear indication of hydrogen bonding to the guest. This was corroborated by downfield shifts of the 6-amino hydrogens of **7**. In addition, large upfield shifts of the naphthoyl protons were indicative of stacking interactions between the host and the purine nucleus of the guest. Corresponding upfield shifts of the carbon-bound protons of 9-butyladenine were also observed.

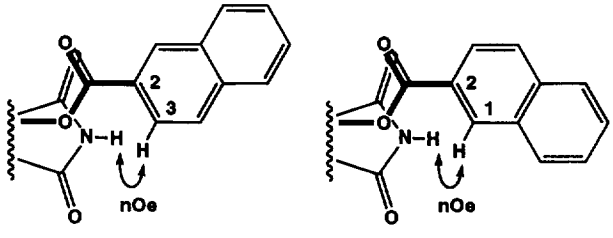
Table 1. Complexation-Induced Shifts From the Titration of Host **6** with Guest **7**.[a]

Hydrogen(s)	CIS[b] (ppm)
Host **6**:	
imide NH	+ 4.95
H1 (naphthoyl)	– 0.11
H3-H4 (naphthoyl)	– 0.25
H5-H8 (naphthoyl)	– 0.42
Guest **7**:	
6-amino	+ 0.89[c]
H2	– 0.17[c]
H8	– 0.24[c]
N-CH_2 (butyl side-chain)	– 0.19[c]

[a] At 86% saturation, from addition of 10 equivalents of guest. [b] Complexation-Induced Shift. [c] Comparing the chemical shift of pure **7** and the solution containing the highest **6**:**7** ratio (5:1).

Quantitative treatment of the titration data with Hostest [7] gave an excellent fit to the 1:1 binding isotherm (R^2>99.99) and revealed an association constant[8] K_a = 184 M^{-1} which is twice as high as an earlier naphthol ester-based AT base pair mimic.[4d] The carbonyl of the naphthoyl group in **6** can presumably enhance the electron acceptor character of the aromatic ring as well as favor the ester conformations where the ring is quasi-parallel to the imide plane.

The geometry of the complex was probed by carrying out homonuclear nOe experiments on a 1:10 mixture of **6**:**7**. Irradiation of the imide NH revealed a close intramolecular contact with both H1 (1.8%) and H3 (0.7%) naphthoyl protons, suggesting that the naphthoyl group exists in both possible conformations about the ester CO—$C2_{naph}$ single bond (Scheme 4).



Scheme 4. Top view of **6** showing the two possible conformers about the ester CO—$C2_{naph}$ bond. Guest omitted for clarity.

Important intermolecular nOe's were observed in addition to the anticipated intramolecular contacts.

Irradiation of the imide NH gave nOe's to both H2 (1.9%) and H8 (2.0%) protons of the purine, suggesting that the complex exists as a rapidly equilibrating mixture of both Watson-Crick and Hoogsteen binding modes. No nOe was observed between the guest's carbon-bound protons and the naphthoyl protons even though the CIS and the magnitude of the association constant clearly indicate aryl stacking. This perhaps is not surprising due to the various conformations of the complex, which are all "productive" for multi-point binding.

Thus, a short synthetic route to hydroxyimide **1** has been developed and its utility as a module for the preparation of abiotic receptors has been established. The solubility of the module can be easily altered at the Grignard addition step (Scheme 2, step e) by using a properly functionalized reagent (i.e. longer alkyl chain, latent water-solubilizing group, etc...). Work on the binding properties of other hydroxyimide-based receptors, including water-soluble variants are currently in progress. We are also investigating the use of chiral esters based on **1** for the desymmetrization of prochiral enolates and will report on these developments in due course.

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5. A 5 mM $CDCl_3$ solution of **6** was titrated by incremental addition of a 10 mM $CDCl_3$ solution of **7** until 10 equivalents of **7** were added.
6. Limiting shift = 12.85 ppm from subsequent analysis of the titration data.
7. Hostest 5.0, Craig S. Wilcox, Department of Chemistry, University of Pittsburgh, Pittsburgh, PA.
8. Average of three titrations, $\sigma = 8.9\ M^{-1}$.

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