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Tricyclic Scaffolds for the Rapid Assembly of Abiotic Receptors

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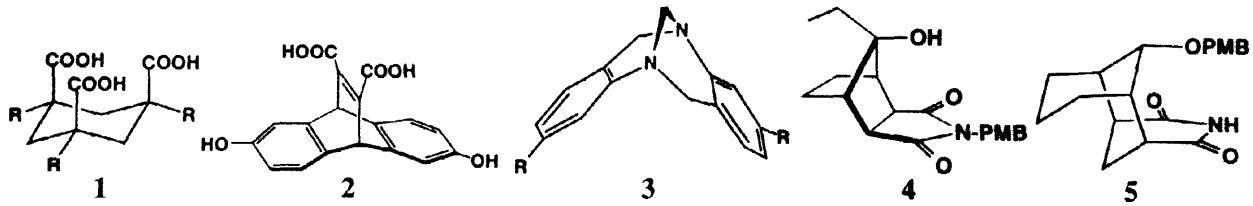
Abstract: The design and synthesis of tricyclic scaffolds for the modular assembly of abiotic receptors soluble in organic solvent is described. Their application to the rapid preparation of simple receptors for 9-alkyladenine guests is also reported.

INTRODUCTION

Over the past few decades, the field of host-guest chemistry has flourished into a highly active branch of supramolecular chemistry. Much of the activity is focused on the design, synthesis and study of abiotic (i.e. non-natural) receptor models capable of selective recognition of organic and inorganic guests in solution or in the solid state.[1] As model systems of molecular recognition, such abiotic receptors provide not only a controlled means of studying the fundamentals of non-covalent interactions, but also build a foundation for the development of novel pharmaceuticals, chemosensors, carriers, catalysts and other molecular devices.

All the aforementioned applications rely on the directed display of functional groups in three-dimensional space and their non-covalent interaction with another molecular entity. To this effect, macrocyclization has been a common strategy for preorganizing functionality in a convergent fashion yielding "endoreceptor" systems.[2] An alternative strategy for spatial preorganization has involved the use of rigid organic structures as scaffolding devices. Many of the more versatile scaffolds can display functional groups in a fixed convergent fashion and permit the rapid assembly of numerous receptor systems and other molecular devices in a modular fashion. For example, scaffolds derived from Kemp's triacid **1** have been widely used for the design of abiotic receptors,[3] catalysts,[4] chiral auxiliaries,[5] chiral proton sources,[6] sensors,[7] transport mediators,[8] replicators,[9] biophysical probes,[10] even combinatorial peptidomimetic libraries.[11] Likewise, functionalized ethenoanthracenes **2**,[12] Troger's base derivatives **3**,[13] even steroids[14] have been shown to be valuable building blocks for other classic abiotic receptor assemblies. In 1996, we reported the synthesis of tricyclic hydroxyimide **4** and its application for the modular assembly of receptor models.[15] In 1997, scaffold **5** was reported as an isosteric analog of our previously reported hydroxyimide **4**.[16]



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We wish to disclose a comprehensive follow-up to our original study, including the development of a second-generation hydroxyimide and its conversion into a series of simple receptors toward the neutral organic guest benchmark, 9-butyladenine (9-BuA).

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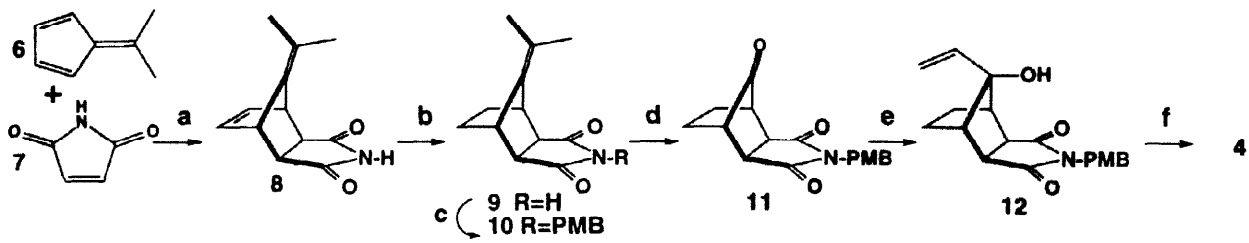
Tricyclic hydroxyimide **4** was designed such that it would *a)* preorganize functional groups in three-dimensional space, *b)* be obtainable by a short synthetic route in multigram quantity and *c)* be readily incorporated into model receptors. The rigid framework enforced a hydroxyl group to be *syn* to a masked imide group. This imide serves as a readily modifiable three-point hydrogen bonding (H-bonding) array for binding to a complementary guest. The hydroxyl group serves as a functional handle for the attachment of the recognition module to other receptor components *via* acylation.

Results And Discussion

Synthesis of first-generation hydroxyimide 4.

As illustrated in Scheme 1, cycloaddition of 6,6-dimethylfulvene **6** and maleimide **7** in refluxing toluene afforded two Diels-Alder adducts in an 8:1 ratio.[15] The major isomer crystallized readily from MeOH/$CHCl_3$ and was shown to be the desired *exo* isomer **8** by X-ray crystallography.[17] Selective catalytic hydrogenation of the disubstituted olefin in **8** afforded the partially saturated derivative **9** which was N-protected with t-BuOK/p-methoxybenzyl chloride in DMF to produce the corresponding PMB-imide **10**. Ozonolysis of the exocyclic olefin group in **10** followed by reductive work-up afforded ketone **11** in quantitative yield. Due to the severe internal angle strain, ketone **11** readily formed the corresponding hydrate or hemiacetal if exposed to trace amounts of water or alcohol, respectively.



Scheme 1. a) toluene, reflux, 71%; b) H_2/Pd-C, EtOH, 98%; c) t-BuOK/p-methoxybenzyl chloride, DMF, 75%; d) O_3/CH_2Cl_2, -78°, then Me_2S, 100%; e) H_2C=CHMgBr, THF, -78°, 70%; f) H_2/Pd-C, 100%.

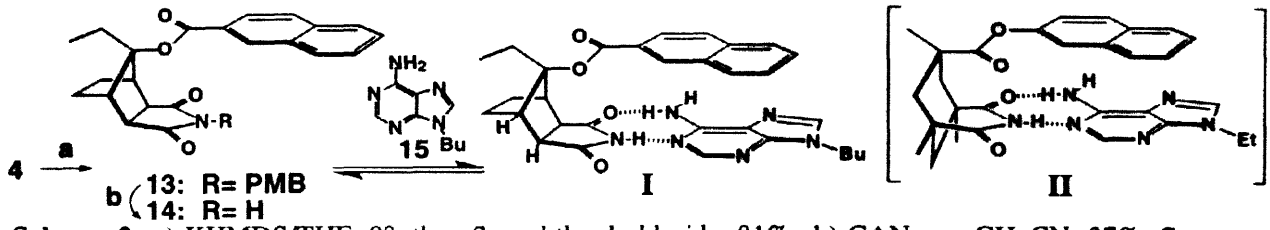
Treatment of ketone **11** with vinylmagnesium bromide in THF solution at -78° afforded the major adduct **12** in 70% yield which resulted from nucleophilic attack from the least hindered carbonyl face. The proper stereochemistry of the tertiary hydroxyl in **12** was initially established by nOe experiments and later confirmed by anisotropic shifts of subsequent derivatives. For example, naphthoylation of **4** caused a 0.98 ppm upfield shift of the methylene signal of the PMB protecting group in **13**. Finally, catalytic hydrogenation of the vinyl group in **12** produced scaffold **4** in quantitative yield.

A simple receptor based on hydroxyimide 4.

As described previously, scaffold **4** was converted into simple adenine receptor **14**[18] (Scheme 2) and titrated with 9-BuA (**15**) in $CDCl_3$. Complexation-induced shifts supported the H-bonded and π-stacked complex **I** in both Watson-Crick and Hoogsteen binding modes (Watson-Crick mode shown in **I**). Quantitative treatment of the titration data with HOSTEST [19] gave an excellent fit to the 1:1 binding isotherm (R^2>99.99) and revealed an association constant $K_a = 184 \pm 9\ M^{-1}$ which is twice as high as the naphthoyl ester-based host derived from Kemp's triacid (Scheme 2, complex **II**, $K_a = 90\ M^{-1}$).[18b]

Considering the electrostatic model proposed by Hunter and Sanders for π-stacking interactions[20], the electron-withdrawing carbonyl of the naphthoyl group in complex **I** should enhance the stacking properties of the aryl ring compared to **II** in which the ether oxygen of the ester is a weak electron donor. The π-polarizing nature of the ester carbonyl in **I** will contribute favorably to the π-stacking interaction between the aryl ring and the purine[21], as it would reduce the π-π replusion between the two surfaces. Moreover, the carbonyl-naphthyl conjugation in **I** favors conformations where the ring is coplanar to the ester plane. The ester carbonyl in **I** would also decrease the dispersive contribution of the naphthyl ring towards π-stacking compared to **II**.

However, in a highly polarizable solvent such as $CHCl_3$, this contribution should be less important.[22]

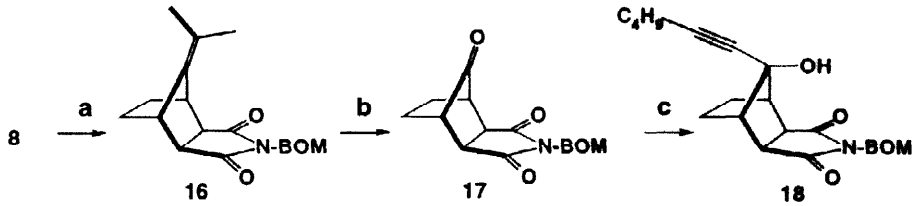


Scheme 2. a) KHMDS/THF, 0°, then 2-naphthoyl chloride, 81%; b) CAN, aq. CH_3CN, 37%. Compare complex **I** with Kemp's triacid derived naphthoyl ester **II** (Watson-Crick mode shown for both complexes).

Synthesis of second-generation hydroxyimide 18.

During this preliminary study, two synthetic limitations were noted: 1) The chain attached to the tertiary carbinol in **4** was an ethyl group. Lengthening this alkyl chain could certainly improve receptor solubility in non-polar media.[23] Having a terminally functionalized chain instead of the ethyl group would also pave a synthetic path toward water-soluble receptor derivatives and polymer-supported variants, the latter being amenable to combinatorial assembly by split synthesis protocols. 2) The oxidative removal of the imide PMB protecting group (aq CAN/CH_3CN), while relatively efficient on simple systems such as **13**, gave varying results on more complex receptors derived from the same tricyclic scaffold. Thus, the second-generation hydroxyimide scaffold **18** was sought (Scheme 3).

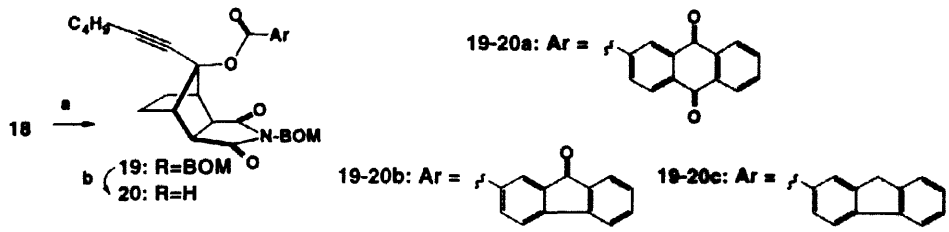
Numerous alternative imide protecting groups were investigated until the benzyloxymethyl (BOM) was found to undergo clean deprotection from a variety of imide derivatives.[24] Treatment of the potassium imide anion of hydrogenated Diels-Alder adduct **8** with chloromethylbenzyl ether (BOMCl) in DMF afforded the N-BOM protected derivative **16** in 84% yield. Ozonolysis under the previously established conditions produced



Scheme 3. a) tBuOK, BOMCl/DMF, 84%; b) O_3/CH_2Cl_2, Me_2S, 99%; c) C_4H_9-C≡CLi/THF, -78°, 70%.

ketone **17** which, when reacted with alkynyllithium nucleophiles, gave chemo- and stereoselective addition in *anti* fashion with respect to the BOM-imide group.[25] For example, 1-hexynyllithium addition to ketone **17** afforded the second-generation hydroxyimide scaffold **18** which crystallized readily from the crude reaction extract in 70% yield.[26] Esterification of various arylcarboxylic acids to hydroxyimide **18**, followed by removal of the imide BOM group, would produce simple receptors **20** (Scheme 4) capable of binding 9-alkyladenines *via* a complement of H-bonding and aryl stacking interactions. Such receptors would allow for an isolated study of the π-stacking interactions to the bound adenine-derived guest which is "base paired" to the imide. Indeed, the aryl linkers in **20a-c** are ester groups and are less likely to interfere with the purine binding event whether through host self-association or orthogonal H-bonding to the guest. Compared to an amide linker, the ester is less "sticky" as it bears no H-bonding donor and its carbonyl is a weaker acceptor. Moreover, bifurcated H-bonding interactions with the guest 6-NH_2 group would be precluded since the ester linkage is inverted compared to the corresponding Kemp's triacid derived homologue (cf. **II**).

As illustrated in Scheme 4, the potassium alkoxide of scaffold **18** was coupled with a series of aroyl chlorides in THF to give the N-protected hosts **19a-c**. Removal of the BOM group in a two-step sequence (BBr_3/CH_2Cl_2 or H_2/Pd-C, followed by ammonolysis of the N-hydroxymethylene intermediates) produced the anthraquinone, fluorenone and fluorene-derived hosts, **20a**, **20b** and **20c**, respectively.



Scheme 4. a) KH, ArCOCl/THF, 25-39%; b) BBr_3/CH_2Cl_2 or H_2/Pd-C, then NH_3/THF, 52-66%.

As for the first-generation scaffold **14**, the convergent nature of the anthraquinone-imide **20a** was verified by NMR titration with 9-BuA.[27] Inspection of the NMR titration spectra data revealed large complexation-induced shifts of both host and guest protons which are in agreement with a binding geometry involving simultaneous H-bonding and π-stacking (Table 1). Of particular interest are the large upfield shifts of the carbon-bound protons of guest **15** (H-2, H-8, N-CH_2) which ranged from -0.3 to -0.46 ppm in the presence of less than 5 equivalents of host **20a**.

Table 1. Complexation-Induced Shifts From the Titration of Host **20a** with 9-BuA **15** in $CDCl_3$.[a]

Hydrogen(s)	CIS[b] (ppm)
Host **20a:**	
imide NH	+ 5.06
H1 (anthraquinone)	– 0.10
H3-H4 (anthraquinone)	– 0.25
H5-H8 (anthraquinone)	– 0.42
9-BuA **15:**	
6-amino	+ 0.61[c]
H2	– 0.46[c]
H8	– 0.32[c]
N-CH_2 (butyl side-chain)	– 0.30[c]

[a] At 84% saturation, from addition of 7 equivalents of 9-BuA. [b] Complexation-Induced Shift. [c] Comparing the chemical shift of pure 9-BuA and the solution containing the highest **20a**:**9-BuA** ratio (4.7:1).

Quantitative treatment of the titration data for **20a** with HOSTEST gave a poor fit to the simple 1:1 binding isotherm. Inspection of the graphed signal residuals revealed severe systematic deviations from the calculated values indicating that the simple 1:1 binding model did not adequately represent the system under study. A simple dilution titration of host **20a** and quantitative treatment of the data with HOSTEST returned a dimerization

Table 2. HOSTEST Treatment of the Titration Data for Hosts **20a-c** with 9-BuA **15**[a].

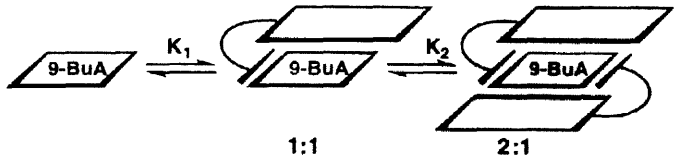
Entry	Host	Binding model[b]	K_{dim}	K_1	K_2 (M^{-1})	Residuals (R^2)[c]
1	**20a**	dim[d] + 1:1	11±1	358±13		99.983
2	**20a**	dim + 1:1 + 2:1	11±1	349±1	1±0	99.998
3	**20b**	1:1		533±12		99.817
4	**20b**	dim + 1:1	11±2	497±40		99.946
5	**20b**	dim + 1:1 + 2:1	11±2	353±38	26±16	99.998
6	**20c**	dim + 1:1 + 2:1	9±1.4	337±1.4	24±2.1	99.996

[a] All titrations were carried out in triplicate. Macroscopic association constants reported with errors representing ±σ. [b] HOSTEST binding model used to treat the titration data. [c] Residuals from the determination of K_1 and/or K_2 as reported by HOSTEST. [d] dim=host dimerization.

constant, K_{dim}, of 11 M^{-1} which is compatible with known imide dimerization data.[28] Including this

dimerization value into the HOSTEST treatment of the **20a**/9-BuA titration data greatly reduced the signal residuals, resulting in a K_a of 358 M^{-1} (Table 2, entry 1) for the binding of **20a** to 9-BuA.

The high K_a for anthraquinone-derived host **20a** was rather surprizing based on literature precedent[29] and, to probe this further, fluorenone and fluorene-derived hosts **20b** and **20c** were also prepared and titrated. Complexation-induced shifts comparable to those obtained for the titration of **20a** were observed for **20b-c**. Dimerization constants for hosts **20b** and **20c** were also determined by dilution titration (K_{dim}= 11 M^{-1} and 9 M^{-1}, respectively) and incorporated into the data treatment. However, HOSTEST analysis of the titration curves for hosts **20b** and **20c** with 9-BuA, as described previously, produced curve fits that still deviated systematically from the expanded host dimerization/1:1 binding model. Only when allowance for 2:1 host:guest association into the HOSTEST calculations were the titration curve fits reconciled, resulting in much smaller signal residuals in an essentially randomized fashion. As a representative example, the analysis of fluorenone-derived **20b** shows clearly the improved fit upon expanding the simple 1:1 binding model to include both host dimerizatrion and 2:1 binding (Table 2, entries 3–5). The 2:1 binding stoichiometry is a likely scenario since 9-BuA offers two imide binding edges (Watson-Crick and Hoogsteen binding modes) and can be boxed in between two host aryl rings (Scheme 5). The titration data for anthraquinone-based **20a** were also re-examined, allowing for 2:1 binding stoichiometry, but the K_2 value was very low and K_a (i.e. K_1) did not change appreciably (Table 2, entry 2).



Scheme 5. 1:1 and 2:1 binding of hosts **20b-c** with 9-BuA **15**.

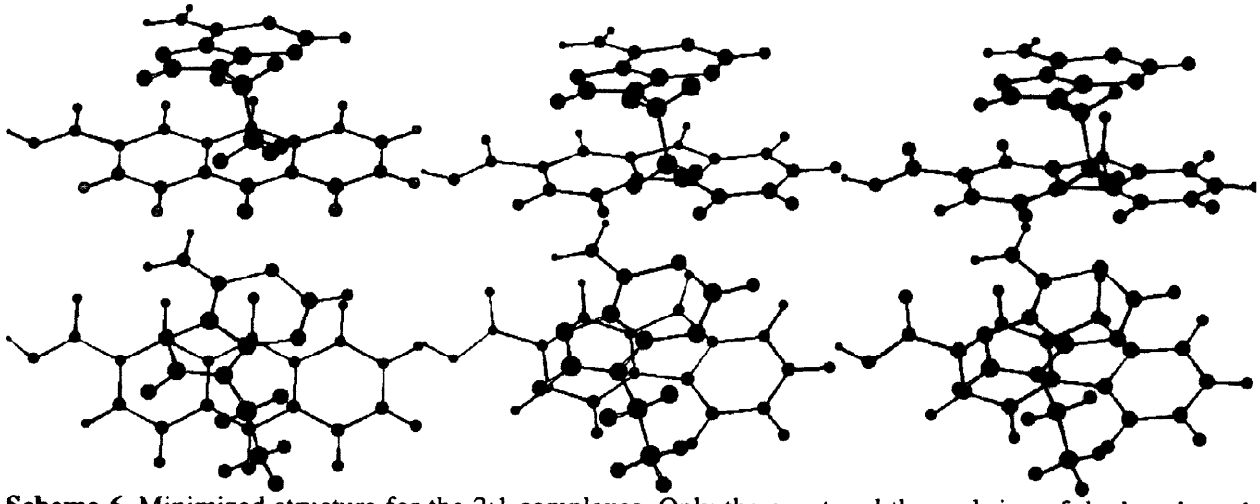
As indicated in Table 2, the K_a for 1:1 association to 9-BuA was found to be very similar for all three hosts bearing a tricyclic aryl surface, thus one must guard against deriving definite conclusions on the influence of aryl ring structure on binding affinity. The van der Waals term for the binding of receptors **20a-c** to 9-BuA should be similar since it is proportional to the area of π-overlap.[30] However, one cannot avoid noticing that the least electron-withdrawn ring (i.e. in host **20c**) produced the lowest K_a while **20a** gave the highest K_a, which is in line with the Hunter/Sanders electrostatic model for π-stacking interactions. Indeed, the π-polarizing nature of the ring carbonyls in **20a** and **20b** should contribute to the favorable electrostatic interaction between the aryl ring and the purine by reducing π-π replusion between the two surfaces.

Analysis of 2:1 complexes based on 20a-c.

The titration results suggest considerable ternary 2:1 complex formation for fluorene-derived hosts **20b** and **21c**, and little or no such behavior for **20a**. The formation of 2:1 complex must be weighted in appropriately since the K_1 and K_2 values reported by HOSTEST are macroscopic constants. After statistical correction, the values for K_2 should be ≈4 times greater for comparison with the macroscopic K_1 ($K_{2\,corr.}$ ≈ 4, 104, and 96 M^{-1}, for **20a**, **20b**, and **20c**, respectively).[31] The magnitude of the larger K_2 values can only be rationalized if H-bonding as well as stacking interactions are invoked in the binding of the second host molecule. Stoichiometry analyses support the titration results since the break in the Job plots[32] for **20a**/9-BuA and **20c**/9-BuA appear at 0.55 and 0.65 mole fractions of 9-BuA, respectively.

Molecular modeling calculations[33] were carried out to gain insight on why, under the same conditions, host **20a** is much less likely to "box in" 9-BuA in a 2:1 complex whereas **20b** and **20c** readily do so. In a typical 2:1 complex, one of the hosts must associate to 9-BuA in the Watson-Crick mode whereas the other must bind to that same 9-BuA in the Hoogsteen geometry, thereby stacking an aryl ring to both faces of the bound 9-BuA (Scheme 5). The 9-butyl group of 9-BuA should be quasi-perpendicular to the adenine ring to minimize $A^{1,3}$-strain with purine carbons 4 and 8. Energy minimized structures for the three 2:1 complexes suggest that the 9-butyl group encounters severe steric hindrance if rotated towards the stacked aryl surface of the Watson-Crick bound host. Hence, the 2:1 complexes with the N-Bu group oriented toward the aryl ring on the

Hoogsteen side were retained for examination. For the 2:1 complexes based on **20b** and **20c**, the N-butyl chain fits into the "bay-region" of the fluorene ring (i.e.spanning fluorene positions 4 thru 5) allowing for unhampered stacking of the guest between both aryl surfaces (Scheme 6). For the **20a/9-BuA** 2:1 complex, however, the N-Bu group encounters the C-4 carbonyl of the anthraquinone ring which interferes with the π-stacking of the surfaces on the Hoogsteen side. Thus, in this 2:1 complex, the anthraquinone ring on the the Watson-Crick side is well stacked to the adenine, whereas the anthraquinone ring on the other side cannot stack properly with the guest. Host **14** did not show any 2:1 complexation presumably due to the smaller π-stacking surface of its naphthyl ring.



Scheme 6. Minimized structure for the 2:1 complexes. Only the guest and the aryl ring of the host bound in Hoogsteen mode are shown. 9-BuA is colored in black and the N-Bu was trunctated to an ethyl group for clarity. Left: **20a/9-BuA**, centre: **20b/9-BuA** , right: **20c/9-BuA**. Above: side views, below: top views.

Thus, a two-generation synthetic route leading to tricyclic hydroxyimide **18** has been developed and its utility as a scaffold for the modular assembly of abiotic receptors has been established. The nature and orientation of the aryl ester linker improves aryl stacking interactions to the H-bonded guest, which is in agreement with the Sanders/Hunter electrostatic model. Ternary complexes of 2:1 type were observed with receptors that can "box in" 9-BuA while minimizing steric contacts with the 9-alkyl group of the purine guest. 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 these scaffolds for the design of novel combinatorial libraries of peptidomimetics, chiral auxiliaries and catalysts, and will report on our findings in due course.

EXPERIMENTAL

^{1}H-NMR spectra were obtained in $CDCl_3$ using a Varian XL-200 or a Varian Unity-400 spectrometer. All ^{13}C-NMR spectra were obtained in $CDCl_3$ on a Varian Unity-400 spectrometer. Chemical shifts are reported in parts per million (δ) relative to tetramethylsilane or to residual solvent peak. Infrared spectra were recorded on a Bruker IFS 25 IR spectrophotometer (KBr tablets) or a Perkin-Elmer 598 IR spectrophotometer ($CHCl_3$ solutions in 0.5mm NaCl cells). High-resolution mass spectra (HRMS) were obtained on a Kratos MS50 TC mass spectrometer in EI mode unless otherwise indicated. Melting points were measured on a Gallenkamp capillary melting point apparatus and are uncorrected. THF, ether, and benzene were distilled from Na-benzophenone ketyl; dichloromethane, acetonitrile, and triethylamine were distilled from CaH_2. All reactions were carried out in flame-dried glassware, under argon atmosphere, unless specified otherwise.

NMR titrations.

In a typical procedure, a 5 mM $CDCl_3$ solution of host was titrated with aliquots of a 10 mM $CDCl_3$

solution of 9-BuA until near-saturation of the imide NH signal. At least 20 data points were recorded for each titration. Each titration was carried out in triplicate. Dilution experiments were carried out in a similar fashion adding aliquots of $CDCl_3$ to host solutions. Titration data were treated with HOSTEST according to the various binding equilibria described in the text. Job plots were obtained by recording NMR spectra of various host-guest mixtures maintaining the total concentration of the solutes constant. The observed imide chemical shifts were graphed as a function of guest mole fraction, and the point of maximum chemical shift was intrapolated.

Preparation of exo-Diels-Alder adduct 8.

A solution of 6,6-dimethylfulvene **6** (2.76 g, 26.0 mmol) and maleimide **7** (2.43 g, 25.0 mmol) in anhydrous toluene (120 ml) was refluxed for 24 h. Evaporation of solvent *in vacuo* followed by recrystallization (10% MeOH/$CHCl_3$) afforded pure *exo*-dimethyl imide **8** (3.63 g, 71%), m.p. 202.6-204.6 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.93 (s, 1H), 6.38 (m, 2H), 3.72 (m, 2H), 2.75 (s, 2H), 1.54 (s, 6H). ^{13}C NMR ($CDCl_3$): δ 177.6, 140.3, 137.3, 134.9, 49.2, 45.6, 19.6. IR (NaCl, $CDCl_3$): 3400, 3300, 2900, 2880, 1770, 1720. HRMS: calcd. for $C_{12}H_{13}NO_2$ (M+) 203.0946, found *m/z* 203.0946.

Hydrogenation of Diels-Alder adduct 8.

A mixture of diolefin **8** (11.73 g, 0.0577 mmol) and 10% Pd/C (10% w/w, 1.11 g) in 95% ethanol (150 ml) was stirred overnight under hydrogen atmosphere. Filtration through Celite and evaporation of solvents *in vacuo* afforded saturated adduct **9** (11.63 g, 98%) as a white solid, m.p. 200.7-204.7 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.78 (s, 1H), 3.07 (m, 2H), 2.70 (s, 2H), 1.68 (m, 2H), 1.61 (s, 6H), 1.46 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 179.4, 134.4, 121.9, 49.5, 39.8, 27.3, 20.7. IR (NaCl, $CDCl_3$): 3400, 2920, 1770, 1670. HRMS: calcd. for $C_{12}H_{15}NO_2$ (M+) 205.1103, found *m/z* 205.1114.

Protection of imide 9.

To a solution of imide **9** (1.52 g, 7.41 mmol) in anhydrous DMF (20 ml) was added t-BuOK (1.66 g, 14.8 mmol) and p-methoxybenzyl chloride (2.32 g, 14.8 mmol). The mixture was stirred overnight under Ar, poured into water and extracted with Et_2O (3×). The combined organic layers were washed with brine, dried over $MgSO_4$, and the solvents were evaporated *in vacuo* to afford PMB-imide **10** (1.82 g, 75%) as colorless crystals, m.p. 105.6-107 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.25 (d, 2H, J = 8.7 Hz), 6,77 (d, 2H, J = 8.9 Hz), 4.44 (s, 2H), 3.74 (s, 3H), 2.61 (s, 2H), 2.22 (m, 2H), 1.60 (m, 2H), 1.38 (m, 2H), 1.23 (s, 6H). ^{13}C NMR ($CDCl_3$): δ 178.5, 159.0, 134.1, 130.5, 128.5, 121.7, 113.8, 55.3, 49.5, 41.6, 39.8, 27.4, 20.3. IR (NaCl, $CDCl_3$): 2960, 2860, 1770, 1610, 1600. HRMS: calcd. for $C_{20}H_{23}NO_3$ (M+) 325.1678, found *m/z* 325.1651.

Ozonolysis of PMB-imde 10.

A solution of PMB-imide **10** (3.45 g, 10.6 mmol) in anhydrous CH_2Cl_2 (75 ml) was saturated with ozone at -78°C until bluish. The reaction was quenched with dimethyl sulfide (1.16 ml, 15.9 mmol) and stirred overnight under Ar. The solvents were evaporated *in vacuo* to afford ketone **11** (3.17 g, 100%) as a beige solid which was used as is for the subsequent Grignard reaction. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.22 (d, 2H, J = 8.9 Hz), 6.80 (d, 2H, J = 8.8 Hz), 4.52 (s, 2H), 3.75 (s, 3H), 2.94 (s, 2H), 2.40 (m, 2H), 2.03 (m, 2H), 1.71 (m, 2H). IR (NaCl, $CDCl_3$): 2980, 2880, 1780, 1710, 1600. HRMS: calcd. for $C_{17}H_{17}O_4N$ (M+) 299.1157, found *m/z* 299.1157.

Vinyl Grignard addition to ketone 11.

To a solution of ketone **11** (2.76 g, 9.22 mmol) in anhydrous THF (30 ml) stirred at 0°C was syringed in vinylmagnesium bromide (14.7 ml, 14.7 mmol, 1.0M in THF) dropwise under Ar. After 1 hr, the reaction mixture was carefully acidified with 1N HCl, and extracted with Et_2O (2×). The combined organic layers were washed with brine, dried over $MgSO_4$, and the solvents were evaporated *in vacuo* . Crystallization with EtOAc/hexane afforded N-protected hydroxyimide **12** (1.50 g, 50%) as a brown solid, m.p. 120.7-122.2 °C.

Flash chromatography of the mother liquor (33% EtOAc/hexane) afforded a second crop of **12** (602 mg, 20%). ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.30 (d, 2H, *J* = 6.6 Hz), 6.78 (d, 2H, *J* = 6.6 Hz), 6.13-5.99 (m, 1H), 5.36-5.18 (m, 2H), 4.467 (s, 2H), 3.74 (s, 3H), 2.75 (s, 2H), 2.52 (m, 2H), 1.81-1.74 (m, 2H), 1.36-1.23 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 179.7, 158.9, 136.9, 130.5, 128.0, 117.3, 113.6, 85.5, 55.2, 48.6, 47.0, 42.0, 26.1. IR (NaCl, $CDCl_3$): 3600, 3050, 2975, 2890, 1770, 1700, 1500, 1390. HRMS: calcd. for $C_{19}H_{21}O_4N$ (M+) 327.1470, found *m/z* 327.1476.

Hydrogenation of hydroxyimide 12.

A mixture of hydroxyimide **12** (2.00 g, 6.11 mmol) and 10% Pd/C (10% w/w, 200 mg) in 95% ethanol (150 ml) was stirred overnight under hydrogen atmosphere. Filtration through Celite and evaporation of solvent *in vacuo* afforded pure hydroxyimide scaffold **4** (2.01 g, 100%) as a white solid, m.p. 121-123 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.31 (d, 2H, *J* = 8.57 Hz), 6.78 (d, 2H, *J* = 8.61 Hz), 4.46 (s, 2H), 3.75 (s, 3H), 2.70 (s, 2H), 2.40 (m, 2H), 1.75 (m, 2H), 1.54 (q, 2H, *J* = 7.44 Hz), 1.31-1.23 (m, 2H), 0.88 (t, 3H, *J* = 7.46 Hz). ^{13}C NMR ($CDCl_3$): δ 180.1, 158.9, 130.3, 128.3, 113.7, 86.7, 55.2, 49.1, 45.5, 41.8, 26.5, 26.0, 8.5. IR (NaCl, $CDCl_3$): 3440, 2960, 2880, 1690, 1605, 1460. HRMS: calcd. for $C_{19}H_{23}NO_4$ (M+) 329.1627, found *m/z* 329.1629.

Preparation of naphthoyl ester 13.

KHMDS (5.83 ml, 2.92 mmol, 0.5 M solution in toluene) was added to a stirred solution of hydroxyimide **4** (800 mg, 2.43 mmol) in THF (15 ml) at 0°C. After 5 min, 2-naphthoyl chloride (555 mg, 2.92 mmol) was added and stirring was continued for 20 min at 0°C. The reaction mixture was acidified with 1N HCl and extracted twice with Et_2O (2×). The combined organic layers were washed with brine, dried over $MgSO_4$, and the solvents were evaporated *in vacuo*. Crystallization from Et_2O afforded naphthoyl ester **13** (953 mg, 81%) as a pale brown solid, m.p. 190-193 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.46 (s, 1H), 8.03~7.99 (m, 1H), 7.93~7.85 (m, 3H), 7.61~7.55 (m, 2H), 6.96 (d, 2H, *J*=8.64 Hz), 6.7 (d, 2H, *J*=7.82 Hz), 3.66 (s, 3H), 3.48 (s, 2H), 3.28 (s, 2H), 2.79 (s, 2H), 2.09~2.06 (m, 2H),1.91~1.87 (m, 2H), 1.41~1.37 (m, 2H), 0.92 (t, 3H, *J*=7.55 Hz). ^{13}C NMR ($CDCl_3$): δ 178.1, 164.9, 159.0, 135.7, 132.4, 131.4, 130.0, 128.5, 128.4, 127.8, 127.0, 126.9, 125.2, 124.8, 113.7, 94.5, 55.2, 49.1, 43.6, 40.8, 25.9, 21.0, 8.7. IR (NaCl, $CHCl_3$): 2980, 2840, 1740, 1700, 1395. HRMS: calcd. for $C_{30}H_{29}NO_5$ (M+) 483.2045;,found, *m/z* 483.2030.

Deprotection of naphthoyl ester 13.

A solution of naphthoyl ester **13** (75 mg, 0.16 mmol) and ceric ammonium nitrate (389 mg, 0.710 mmol) in CH_3CN (3 ml) and water (1 ml) was stirred at rt for 4 hrs. The solution was poured into 1N HCl and extracted twice with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$ and solvents were evaporated *in vacuo* to afford pure naphthoylated host **14** as a colorless solid (21 mg, 37%), m.p. 204-205.4 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.42 (s, 1H), 7.92-7.83 (m, 4H), 7.58-7.51 (m, 2H), 7.27 (s, 1H), 3.20 (s, 2H), 2.70 (s, 2H), 2.11-2.07 (m, 2H), 1.90 (m, 2H), 1.39-1.23 (m, 3H), 0.87 (t, 3H, *J* = 7.38 Hz). ^{13}C NMR ($CDCl_3$): δ 178.8, 164.8, 135.6, 132.5, 131.2, 129.7, 128.5, 128.4, 127.8, 127.2, 126.6, 125.0, 94.5, 50.1, 43.8, 40.8, 25.7, 20.9, 8.6. IR (NaCl, $CHCl_3$): 2980, 2885, 1785, 1730, 1635, 1460. HRMS: calcd. for $C_{22}H_{21}NO_4$ (M+) 363.1470, found, *m/z* 363.1461.

Preparation of BOM-imide 16.

To a solution of imide **8** (1.40 g, 6.82 mmol) in anhydrous DMF (15 ml) was added t-BuOK (1.21 g, 10.2 mmol) and chloromethylbenzyl ether (BOMCl, 1.54 ml, 10.2 mmol) and the reaction mixture was stirred overnight under Ar. The solution was poured into water and extracted with Et_2O (3×). The combined organic layers were washed with brine, dried over $MgSO_4$ and solvents were evaporated *in vacuo* to afford BOM-imide **16** (1.87 g, 84%) as colorless crystals, m.p. 97.7-98.3 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.30 (m, 5H), 4.87 (s, 2H), 4.47 (s, 2H), 3.09 (m, 2H), 2.66 (s, 2H), 1.68 (m, 2H), 1.527 (s, 6H), 1.43 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 178.5, 137.4, 134.5, 128.3, 127.9, 127.5, 121.7, 71.3, 67.2, 48.1, 40.0, 27.4, 20.6. IR

(NaCl, $CHCl_3$): 2940, 2890, 1780, 1705, 1445, 1350. HRMS: calcd. for $C_{20}H_{23}NO_3$ (M+) 325.1678, found *m/z* 325.1663.

Ozonolysis of BOM-imide 16.

A solution of BOM-imide **16** (1.88 g, 5.78 mmol) in anhydrous CH_2Cl_2 (30 ml) was saturated with ozone at -78°C until bluish. The reaction was quenched with dimethyl sulfide (0.63 ml, 8.7 mmol) and stirred overnight under Ar. The solvents were evaporated *in vacuo* to afford ketone **17** (1.72 g, 99%) as a beige solid which was used as is for the subsequent Grignard addition. ^1H NMR (400 MHz, MeOD-d4): δ 7.30 (m, 5H), 4.94 (s, 2H), 4.49 (s, 2H), 2.90 (s, 2H), 2.42 (m, 2H), 2.06 (m, 2H), 1.72 (m, 2H). IR (NaCl, $CHCl_3$): 2980, 2880, 1780, 1710, 1600, HRMS: calcd. for $C_{17}H_{17}NO_4$ 299.1157, found 193.0739 ([M-BnO]+).

Preparation of hydroxyimide 18.

To a solution of 1-hexyne (0.458 ml, 3.99 mmol) in anhydrous THF (3ml) was syringed in n-butyllithium (2.30 ml, 3.68 mmol, 1.6 M in hexane) dropwise under Ar at -78°. After stirring for 5 min, a solution of BOM-imide **17** (920 mg, 3.07 mmol) in THF (10 ml) was syringed in dropwise and the mixture stirred for 30 min. The reaction was quenched with 1N HCl, poured into water and extracted with Et_2O (3×). The combined organic layers were washed with brine, dried over $MgSO_4$ and solvents were evaporated *in vacuo*. Crystallization from Et_2O afforded the second-genereation hydroxy-imide **18** (817 mg, 70%) as white crystals, m.p. 122.1-123.7 °C. ^1H NMR (200 MHz, $CDCl_3$): δ 7.32 (m, 5H), 4.89 (s, 2H), 4.56 (s, 2H), 2.72 (s, 2H), 2.66 (m, 2H), 2.15 (t, 2H, *J*=6.7 Hz)), 2.04 (m, 2H), 1.41 (m, 4H), 1.30 (m, 2H), 0.90 (t, 3H, *J*=6.98 Hz). ^{13}C NMR ($CDCl_3$): δ 179.4, 137.8, 128.3, 127.7, 127.6, 87.3, 79.4, 78.2, 71.9, 67.8, 49.4, 48.0, 30.5, 26.4, 21.9, 18.3, 13.5. IR (NaCl, $CHCl_3$): 3320, 2920, 2880, 1780, 1710, 1460. HRMS: calcd. for $C_{23}H_{27}NO_4$ (M+) 381.1940, found m^+/z 381.1945.

Preparation of anthraquinone-derived BOM-imide 19a.

KHMDS (1.55 ml, 0.77 mmol, 0.5 M in toluene) was added to a stirred solution of hydroxyimide **18** (243 mg, 0.637 mmol) in anhydrous THF (15 ml) at 0°C. After 5 min, 2-anthraquinoyl chloride (209 mg, 0.772 mmol) was added and stirring was continued for 20 min. The reaction mixture was poured into water and extracted with Et_2O (2×). The combined organic layers were washed with brine, dried over $MgSO_4$ and the solvents were evaporated *in vacuo*. Flash chromatography (100% $CHCl_3$) afforded anthraquinoyl-BOM-imide **19a** (120 mg, 31%) as a pale yellow solid, m.p. 186-189.1 °C. ^1H NMR (200 MHz, $CDCl_3$): δ 8.77 (s, 2H), 8.30-8.23 (m, 4H), 7.80 (d, 2H), 7.62 (s, 1H), 4.31 (s, 2H), 4.17 (s, 2H), 3.34 (m, 2H), 2.94 (s, 2H), 2.21 (t, 4H, *J*=5 Hz), 1.48-1.32 (m, 6H), 0.86 (t, 3H, *J*=7.1 Hz). ^{13}C NMR ($CDCl_3$): δ 182.3, 181.7, 177.4, 162.4, 137.3, 136.3, 134.6, 134.4, 133.4, 133.3, 129.7, 128.7, 128.2, 127.6, 127.4, 127.2, 89.2, 84.6, 74.3, 72.0, 67.1, 47.9, 47.0, 30.3, 25.9, 21.9, 18.4, 13.5. IR (NaCl, $CHCl_3$): 2980, 2880, 1785, 1740. HRMS: calcd. for $C_{38}H_{33}O_7N$ (M+) 615.6833 found m^+/z 615.6834.

Deprotection of anthraquinone-derived BOM-imide 19a.

To a stirred solution of anthraquinoyl-BOM-imide **19a** (75 mg, 0.12 mmol) in CH_2Cl_2 (20 ml) was added BBr_3 (0.24 ml, 0.24 mmol, 1.0 M in hexane) under Ar at rt. After stirring for 5 min. the mixture was quenched with 1N HCl, poured into water and extracted with Et_2O (2×). The combined organic layers were washed with brine, dried over $MgSO_4$, and solvents were evaporated *in vacuo* . This crude N-hydroxymethylene imide was redissolved in THF (5 ml) and NH_3 was bubbled until saturation (15 min) at 0°C. The reaction mixture was stirred overnight then concentrated *in vacuo*. Preparative thin layer chromatography (100% $CHCl_3$) yielded anthraquinone-derived host **20a** (40 mg, 66%) as a yellow solid, m.p. 150-153.2 °C. ^1H NMR (200 MHz, $CDCl_3$): δ 8.71 (s, 1H), 8.20-8.15 (m, 4H), 8.09 (s, 1H), 7.79-7.74 (m, 2H), 3.34 (s, 1H), 2.97 (s, 2H), 2.20 (t, 3H, *J* =6.82 Hz), 1.46-1.32 (m, 6H), 0.85 (t, 3H, *J* =7.02 Hz). ^{13}C NMR ($CDCl_3$): δ 182.2, 181.6, 178.4, 162.4, 135.8, 134.7, 134.5, 133.5, 133.1, 132.8, 128.8, 127.7, 127.4, 127.2, 89.2, 84.6, 74.4, 49.3, 47.2, 30.3, 25.9, 21.9, 18.5, 13.5. IR (NaCl, $CHCl_3$): 3400, 2980, 2885, 2240, 1780, 1725, 1680, 1600,

1460. HRMS: calcd. for $C_{30}H_{25}NO_6$ (M+) 495.1681, found *m/z* 495.1709.

*Preparation of fluorenone-derived BOM-imide **19b**.*

Same procedure as for the preparation of **19a** using KHMDS (1.56 ml, 0.78 mmol), hydroxyimide **18** (200 mg, 0.52 mmol), and 9-fluorenone-2-carbonyl chloride (189 mg, 0.779 mmol) in THF (15 ml). Flash chromatography (100% $CHCl_3$) afforded fluorenononone-derived BOM-imide **19b** (120 mg, 39%) as a pale yellow solid, m.p. 198.3-201.1 °C. ^1H NMR (200 MHz, $CDCl_3$): δ 8.04 (s, 1H), 7.89 (d, 2H, *J* =7.8 Hz), 7.72 (d, 2H, *J* =7 Hz), 7.54 (m, 3H), 7.40 (m, 1H), 7.15 (m, 5H), 4.35 (s, 2H), 4.22 (s, 2H), 3.27 (s, 2H), 2.69 (s, 2H), 2.17 (m, 4H), 1.39 (m, 6H), 0.84 (t, 3H, *J* =6.8 Hz). ^{13}C NMR ($CDCl_3$): δ 177.5, 148.8, 143.0, 137.5, 136.2, 134.9, 134.7, 134.2, 130.4, 129.7, 128.2, 127.6, 127.3, 125.4, 124.7, 121.3, 120.1, 88.9, 84.0, 77.2, 76.6, 76.3, 74.5, 72.0, 67.2, 47.9, 47.1, 30.3, 25.9, 21.9, 21.9, 18.4, 13.5. IR (NaCl, $CHCl_3$): 2970, 2880, 2240, 1780, 1730, 1720, 1610, 1450. HRMS: calcd. for $C_{37}H_{33}O_6N$ (M+) 587.2307, found *m/z* 587.2322.

*Deprotection of fluorenone-derived BOM-imide **19b**.*

Same procedure as for the deprotection of **19a** using BOM-imide **19b** (150 mg, 0.255 mmol) and BBr_3 (0.51 ml, 0.51 mmol, 1.0M solution in hexane) in CH_2Cl_2 (20 ml). Preparative thin layer chromatography (1% MeOH/$CHCl_3$) afforded host **20b** (65 mg, 55%) as a light green solid, m.p. 261.4-263.0 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 8.16 (s, 1H), 8.00 (d, 1H, *J* =3.7 Hz), 7.69 (d, 1H, *J* =1.9 Hz), 7.69-7.54 (m, 3H), 7.52 (s, 1H), 7.39 (t, 1H, *J* =5.7 Hz)), 3.29 (s, 2H), 2.87 (s, 2H) 2.21-2.16 (m, 4H), 1.47-1.23 (m, 6H), 0.86 (t, 3H, *J* =6.95 Hz). ^{13}C NMR ($CDCl_3$): δ 192.3, 178.7, 162.9, 148.5, 143.0, 136.4, 135.0, 134.5, 134.1, 130.3, 125.5, 124.6, 121.2, 120.4, 88.8, 84.0, 74.6, 49.2, 47.2, 30.4, 25.9, 21.9, 18.5, 13.5. IR (NaCl, $CHCl_3$): 3400, 2960, 2880, 1780, 1730, 1610, 1450. HRMS: calcd. for $C_{29}H_{25}O_5N$ (M+) 467.1732, found *m/z* 467.1761.

*Preparation of fluorene-derived BOM-imide **19c**.*

Same procedure as for the preparation of **19a** using KHMDS (5.17 ml, 2.58 mmol) hydroxymide **18** (663 mg, 1.74 mmol), and fluorene-2-carbonyl chloride (593 mg, 2.59 mmol) in THF (15 ml). Flash chromatography (100% $CHCl_3$) afforded fluorene-derived BOM-imide **19c** (254 mg, 25%) as a pale yellow solid, m.p. 184.1-187.8 °C. ^1H NMR (200 MHz, $CDCl_3$): δ 7.94 (s, 1H), 7.85-7.76 (m, 3H) 7.59-7.55 (m, 1H) 7.43-7.34 (m, 2H), 7.38-7.03 (m, 3H), 4.30 (s, 2H), 4.07 (s, 2H), 3.86 (s, 2H), 3.29 (s, 2H), 2.71 (s, 2H), 2.18 (t, 2H, *J* = 6.92 Hz), 1.48-1.20 (m, 12H), 0.84 (t, 3H, *J* =7.0 Hz). IR (NaCl, $CHCl_3$): 2970, 2880, 2240, 1780, 1730, 1710, 1620, 1350. HRMS: calcd. for $C_{37}H_{35}O_5N$ (M+) 573.2515, found m^+/z 573.2530.

*Deprotection of fluorene-derived BOM-imide **19c**.*

A solution of BOM-imide **19c** (127 mg, 0.221 mmol) in 95% ethanol (20 ml) was stirred with Pearlman's catalyst ($Pd(OH)_2$, 100 mg) under H_2 atmosphere for 24 hrs. The solution was filtered through Celite and the solvent was evaporated *in vacuo*. This crude N-hydroxymethylene imide was redissolved in THF (5 ml) and NH_3 was bubbled until saturation (15 min) at 0°C. The reaction mixture was stirred overnight then concentrated *in vacuo*. Preparative thin layer chromatography ($CHCl_3$) yielded fluorene-derived host **20c** (52 mg, 52%) as a light green solid, m.p. 251.9-253.5°C. ^1H NMR (200 MHz, $CDCl_3$): δ 8.22 (s, 1H), 7.91 (s, 1H), 7.80-7.71 (m, 3H), 7.56 (s, 1H, *J* =3.42 Hz), 3.81 (s, 2H), 3.00 (s, 2H), 2.25 (s, 2H), 1.74-1.72 (m, 2H), 1.23-1.15 (m, 10H), 1.08-1.06 (m, 2H), 0.75 (m, 3H). ^{13}C NMR ($CDCl_3$): δ 178.7, 162.1, 144.5, 143.4, 128.1, 127.1, 126.3, 125.3, 120.8, 119.8, 93.9, 50.1, 44.2, 36.8, 31.6, 29.4, 27.9, 25.7, 24.4, 22.5, 12.5. IR (NaCl, $CHCl_3$): 3400, 2980 , 2830, 1780, 1730 1610. HRMS: calcd. for $C_{29}H_{31}O_4N$ (M+) 457.2253, found m^+/z 457.2268.

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