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Molecular Scaffold for the Construction of Three-Armed and Cage-Like Receptors

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Dedicated to Professor Günther Helmchen on the occasion of his 65th birthday

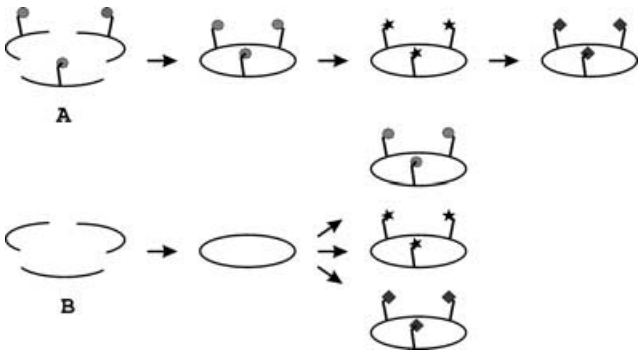
Abstract: An efficient procedure was developed for the synthesis of the C_3-symmetric molecular scaffold **2**. The latter can easily be converted by a single step into either the three-armed receptors **11**–**16** or the cage-like receptor **17**. X-ray structures were obtained for **2**, **11**, and **16**, which are discussed in regard to their aptitude as receptor platforms. The interaction of the three-armed receptors **12**–**16** and the cage-like receptor **17** with phloroglucinol was investigated. In accordance with the conclusions obtained from molecular modeling and X-ray crystallographic studies on the host–guest complexes, the three-armed bipyridine receptor **16** exhibits, due to its induced fit, a larger association constant toward phloroglucinol than the cage **17**. This new receptor system shows all of the positive features characteristic of 2,4,6-trialkylbenzene receptor systems, such as conformational control by steric gearing, ready availability, and versatility in derivatization. These attributes, combined with the advantageous size of the components, allows this system to be readily tailored to provide receptors for larger, biologically important molecules.

Keywords: C_3 symmetry · chirality · molecular recognition · receptors · supramolecular chemistry

Introduction

Recently, an increasing number of molecular receptors consisting of three receptor arms fixed on a rigid platform have been reported.[1,2] Among these, the benzene ring has proved to be a particularly effective scaffold, as it combines two properties that are essential for a useful platform: a good synthetic availability and the preorganization of the receptor arms.[2] By making simple modifications, numerous receptors with different functionalities can be synthesized, thus allowing rapid optimization with respect to a certain substrate. In the case of the benzene platform, the preorganization of the arms is due to the so-called steric gearing.[3] This is based on the fact that certain subunits within the receptor obtain and retain a preorganized geometry by adoption of a thermodynamically favored conformation, in which steric interactions are minimized.

For instance, the preferred conformation of 1,3,5-R-2,4,6-R′-substituted benzene moieties is an alternating *ababab* geometric pattern.[4] It is this conformational control that renders supplementary complex syntheses superfluous, thus making the benzene platform so attractive.[3] In the case of larger platforms, the above two properties—easy modification and preorganization of the receptor arms by steric gearing—have not been combined, yet. In general, larger platforms are synthesized stepwise from three subunits that already carry the recognition sites (Scheme 1, route A). The conformational rigidity, which guarantees the orientation of the receptor arms, is achieved by the incorporation of sup-



Scheme 1.

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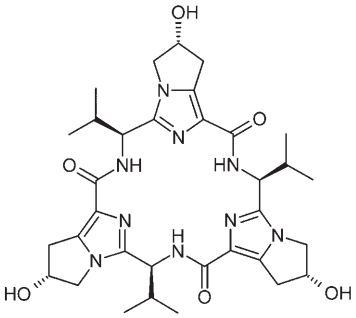
plementary cycles or polycycles.[5] A modification of the recognition sites is only possible by transformation of the functional groups. A representative example of such a system is the platform **1**.[6] The three bicyclic imidazole units linked by *trans* amide bonds form the rigid scaffold, and the preorganization of the three hydroxyl groups is based on the identical configuration of the carbon atoms that carry them. A variation in the recognition sites, that is, the hydroxy groups, is not easy to realize.



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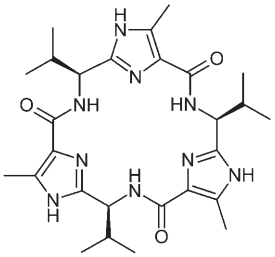

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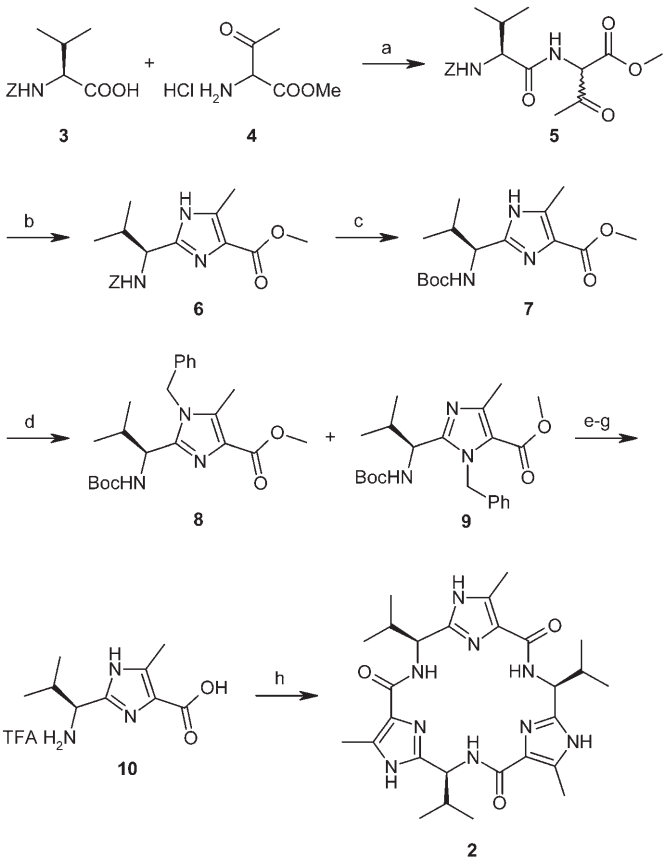
Here, we report on the efficient synthesis of a system that combines the properties of good versatility in derivatization and preorganization of the receptor arms by steric gearing. In contrast to platform **1**, the first requirement is the stepwise construction of scaffold **2** (Scheme 1, route B). Only then are the three arms attached to the scaffold by simple alkylation reactions. This permits the synthesis of numerous receptor systems possessing different recognition sites. As in the benzene systems, the preorganization of the receptor arms is based exclusively upon steric gearing. Some of the results of this work have already been communicated in preliminary form.[7] Here, we report details of the extended study.

Results and Discussion

Synthesis: The first variant in the synthesis of scaffold **2** is shown in Scheme 2. In the first step, the amido ketone **5** is synthesized from readily available **3** and **4**[8] by the mixed anhydride method. Condensation of **5** with ammonia to the desired imidazole **6** needed to be optimized. Application of the conditions reported to be useful for the synthesis of imidazoles, that is, the use of ammonium acetate in acetic acid,[9] gave only moderate yields of **6**, and partial racemization at the α-carbon atom of the L-valine-based moiety was observed (Table 1).

The best results, 72% yield and essentially no racemization, were obtained by using ammonium trifluoroacetate, formed in situ from methanolic ammonia and trifluoroacetic acid, in the refluxing of xylenes with azeotropic removal of



Scheme 2. Synthesis of scaffold **2**: a) ClCOO*i*Bu, NMM, THF, −25 °C, 80%; b) see Table 1; c) Boc_2O, H_2, $Pd(OH)_2$, THF, 95%; d) BnBr, K_2CO_3, CH_3CN, Δ, 32% for **8**, 51% for **9**; e) 2 M NaOH, MeOH/dioxane, 95%; f) H_2, $Pd(OH)_2$, MeOH; g) TFA, DCM, 90% (two steps); h) FDPP, iPr_2NEt, CH_3CN, RT, 35%.

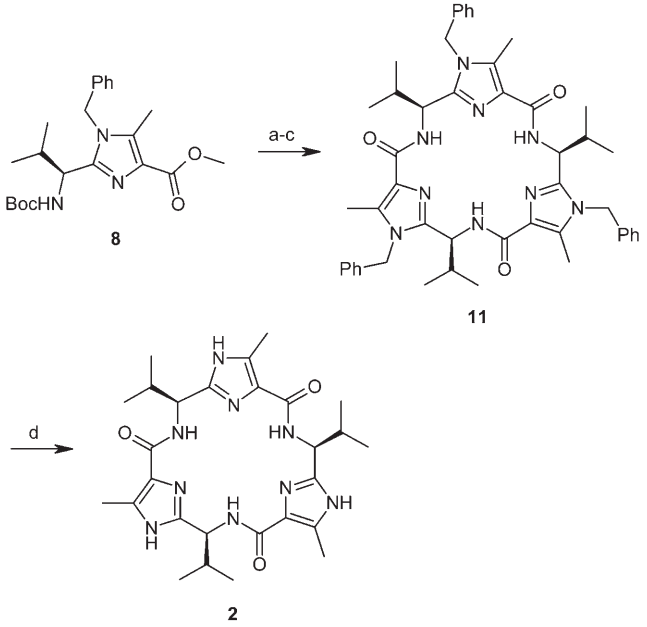
Table 1. Yields and enantiomeric purities for **6**, obtained under various reaction conditions for cyclization.

Reagents	Solvent	*T* [°C]	*t*	Yield [%]	*ee* [%]
CH_3COONH_4	AcOH	115	5 d	50	38
CH_3COONH_4	xylenes	145	6 h	30	90
AcOH, NH_3	xylenes	145	7 h	15	92
CF_3COONH_4	xylenes	145	6 h	37	94
CF_3COONH_4	xylenes, DMSO	145	5 h	25	94
CF_3COONH_4		150	10 min	30	90
CF_3COOH, NH_3	xylenes	145	8 h	72	>96

water. Hydrolysis of the methyl ester of imidazole **6** without racemization at the α-carbon atom of the L-valine-based moiety failed. To overcome this problem, we replaced the benzyloxycarbonyl (Cbz) group by the *tert*-butyloxycarbonyl (Boc) group and protected the NH group of the imidazole ring with a benzyl group. The methyl esters of the resulting benzyl imidazoles **8** and **9** can be simply hydrolyzed by using aqueous NaOH, thus providing the corresponding carbocyclic acids in 95% yield. Subsequent removal of the benzyl group at the imidazole ring by hydrogenolysis followed by amine deprotection with trifluoroacetic acid gave

the amino acid **10**. The most advantageous route for a one-pot trimerization of the imidazole **10** proved to be the activation of the acid group with pentafluorophenyl diphenylphosphinate (FDPP) in the presence of excess Hünig's base in acetonitrile under high dilution conditions at room temperature. This method provided scaffold **2** in a moderate yield (35%).

A significantly better yield of scaffold **2** was achieved by the second synthetic variant (Scheme 3). In this case, the

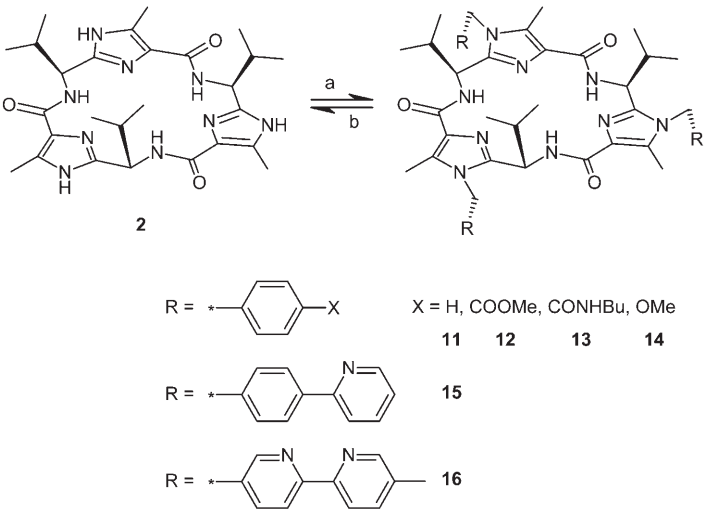


Scheme 3. Improved synthesis of scaffold **2**: a) 2 M NaOH, MeOH/dioxane, 95%; b) TFA, DCM; c) FDPP, iPr$_2$NEt, CH_3CN, RT, 60%; d) H_2, $Pd(OH)_2$, MeOH, 90%.

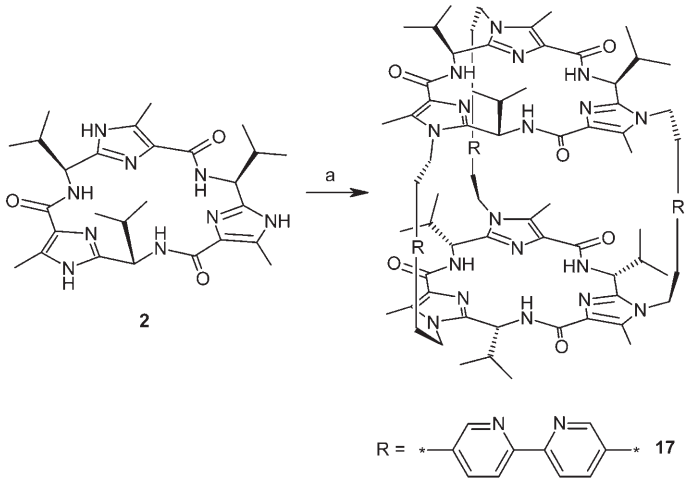
imidazole building block **8** is deprotected at the C terminus and then at the N terminus, thus yielding the free amino acid, which is cyclotrimerized as described above by using FDPP and Hünig's base in acetonitrile. The platform formed can be isolated in 60% yield. The removal of the benzyl groups with palladium hydroxide yields the desired scaffold. By this synthetic route, scaffold **2** is available on a gram scale.

Starting from scaffold **2**, the corresponding receptors can now be obtained by simple fixation of the arms (Scheme 4). The three-armed receptors were formed in good yields (65–77%) if the alkylation was carried out in the presence of K_2CO_3 in acetonitrile. A further advantage of these systems is that benzylic arms can be removed by hydrogenolysis, thus making the scaffold recyclable. The cage-like receptor **17** can also be synthesized in good yields by using the above alkylation protocol (Scheme 5).

Structural investigations: We hypothesized that the steric gearing in the receptors **11–16** is due to repulsive interactions between the isopropyl groups and the receptor arms. Therefore, we expected that the preferred conformation of



Scheme 4. Syntheses of the three-armed receptors **11–16**: a) RCH_2Br, K_2CO_3, CH_3CN, Δ, 65–77%; b) H_2, $Pd(OH)_2$, MeOH, 60–90%.



Scheme 5. Syntheses of the cage-like receptor **17**: a) $BrCH_2RCH_2Br$, K_2CO_3, CH_3CN, Δ, 46%.

11–16 is the *three-down* conformation, that is, all three arms should be oriented opposite to the isopropyl groups of the adjacent α-carbon atoms. To determine the preferred stereochemical orientation of the arms of platform **11** in the gas phase, we applied the Austin Model 1 (AM1) semiempirical quantum chemical method[10,11] to calculate several conformations with different orientations of the benzyl and isopropyl groups. As expected, the low-energy conformation of **11** is the *three-down* conformation. However, the lowest-energy *two-down-one-up* conformation was calculated to be only 1.1 kJ mol^{-1} higher in energy, and the lowest-energy *three-up* conformation was 4.7 kJ mol^{-1} higher in energy. The lowest activation energy required for the changing from *down* to *up* was determined to be 15.2 kJ mol^{-1}. In summary, the calculations predict a slight preference of the *three-down* conformation.

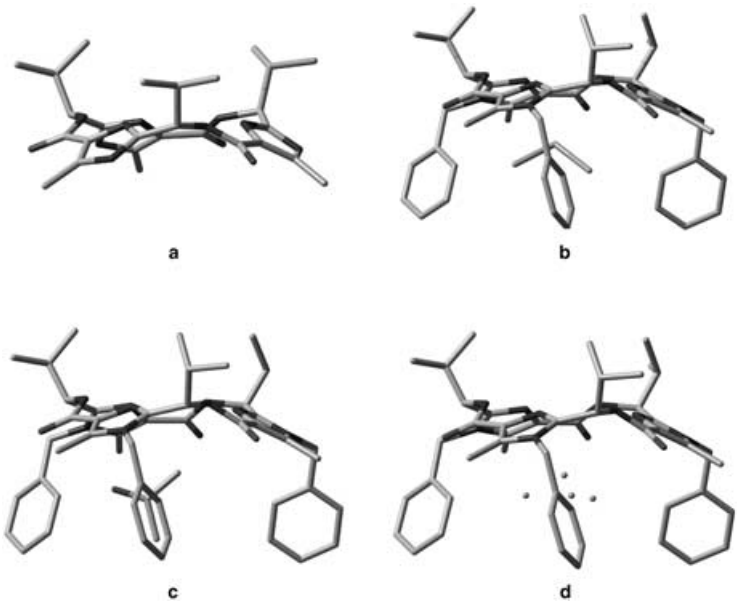


Figure 1. Crystal structures of scaffold **2** (a) and the three-armed receptor **11** crystallized from methylene chloride (b),[7] acetone (c), and methanol (d). All hydrogen atoms, and in (a) some solvent molecules, have been omitted for clarity.

For further stereochemical investigations, we examined the solid-state structures of scaffold **2** and the receptors **11** and **16** (Figure 1a–d and Figure 2a). As can be seen, the solid structures obtained supported the assumption that, in the case of the receptors **11**–**16**, the *three-down* conformation is preferred. This conformation also leads to the formation of a cavity under the platform, which is filled out by (disordered) solvent molecules. For **11**, we could show that the *three-down* conformation is formed irrespective of the solvent from which the crystals were isolated. A superposition of the structures of **11** (Figure 1b–d) shows that, although different solvent molecules are incorporated, there are scarcely any conformational differences. In addition, the distance between and orientation of the bipyridyl arms in **16** are essentially the same as for the benzyl arms in **11**. The shortest distance between two phenyl arms or two bipyridyl arms is about 8 Å, which means that these receptors should definitely be able to include larger molecules. As in similar imidazole platforms, the azole moieties of the macrocycles do not form a single plane, but have a cone-like structure.[12] This deviation from planarity results in the three arms of **11** and **16** being largely equidistant and without divergence from each other, which should make them more suitable for the inclusion of substrates.

Indirect evidence for preorganization of the arms in solution is, in our opinion, the successful synthesis of the cage molecule **17**. Generally, the yields of such five-component cyclizations are very poor. The known difficulties in the syn-

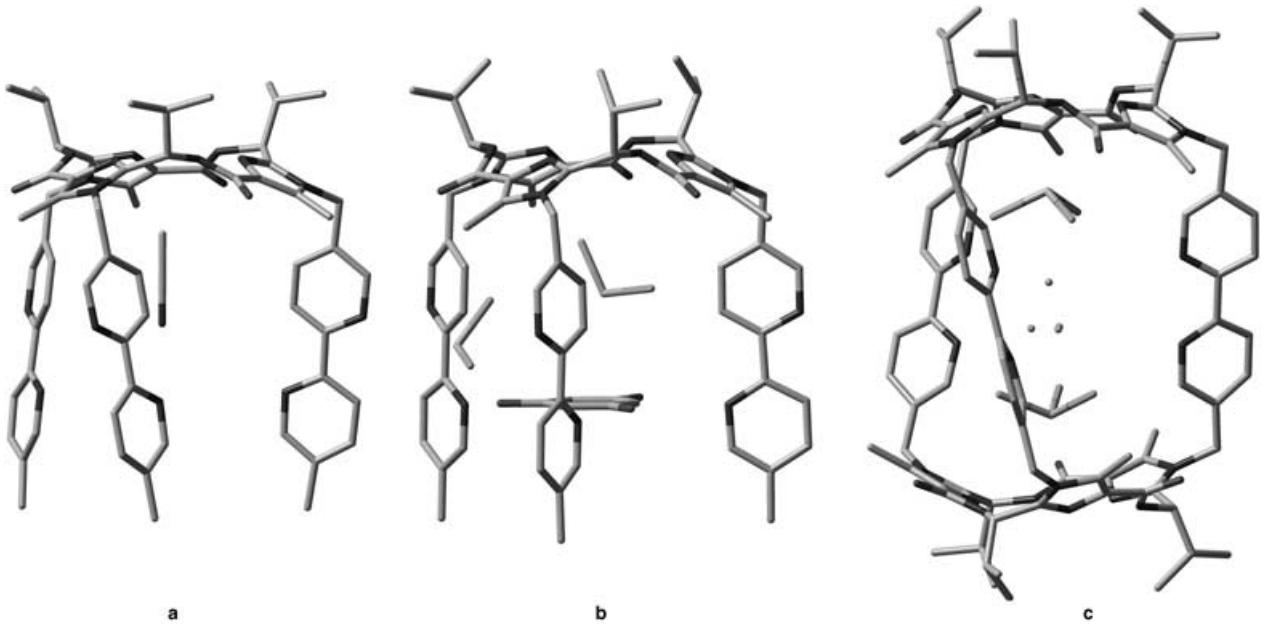


Figure 2. Crystal structures of the free receptor **16** with acetonitrile guest (a),[7] the complex of receptor **16** with phloroglucinol and dichloromethane (b),[7] and the cage-like receptor **17** with chloroform guests (c). All hydrogen atoms have been omitted for clarity. In (a), a second independent molecule with some disorder has been omitted, as well as some acetonitrile of solvation. In (c), all solvent molecules outside the cage and the phloroglucinol molecules outside the cage have been omitted.

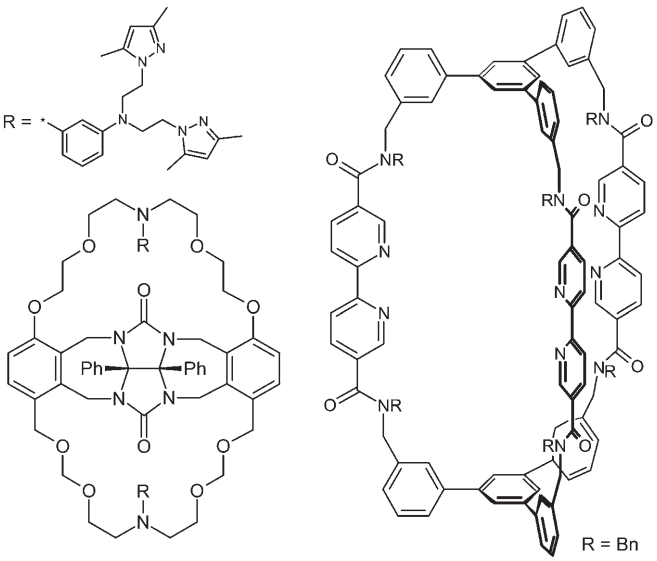
theses of such cage-like compounds can be overcome only by arranging the reactive centers in a way that forces the closure of the desired ring system.[13] For example, if 1,3,5-R-2,4,6-R′-substituted benzene moieties are used as building blocks, the corresponding cage molecules are obtained in a single-step reaction under mild conditions in 40% yield.[14] Because **17** can be obtained in a single-step reaction and in a similar yield, we conclude that the arms in this case, too, are well preorganized in solution.

Binding studies: To test the concept described, the behavior of the receptors **12–17** toward phloroglucinol was investigated.[15] These receptors possess three recognition sites that should be able to accept hydrogen bridges. Because phloroglucinol is not soluble in pure $CDCl_3$, the association constants of the complexes were determined by performing NMR titrations in $CDCl_3$ containing 10% acetonitrile. The results are summarized in Table 2. Receptor **16**, which has three bipyridine arms, shows the highest association constant by far ($680 \pm 85\,M^{-1}$). Comparison with the known receptors **18**[15b] and **19**[15c] is difficult, as their association constants were determined by using pure $CDCl_3$ and, therefore, have higher values. However, Nolte et al. showed that the binding constants drop by a factor of twenty upon progression from pure $CDCl_3$ to a mixture of $CDCl_3/CD_3CN$ (10%) (entries 3 and 4 in Table 2).[15b] If this factor is considered, the association constant of **16** is of the same order as those of **18** and **19**.

The receptors **12–14**, with an ester, amide, or ether as hydrogen-acceptor groups, exhibit lower stability constants, as expected. Interestingly, the platform **15**, which possesses only one pyridine ring per arm, has a value significantly lower ($50 \pm 10\,M^{-1}$) than **16**. Very surprisingly, the cage-like compound **17**, which, like **16**, has three bipyridine groups as recognition sites and which, due to its cage-like structure, is much better preorganized, shows an association constant four times lower than that of **16**.

Table 2. Association constants of complexes formed between receptors **12–19** and polyhydroxybenzene moieties.

Receptor	Substrate	Solvent	K_a [M^{-1}]
19	1,3,5-trihydroxybenzene	$CDCl_3$	11000 ± 2000[15c]
18	1,3,5-trihydroxybenzene	$CDCl_3$	3500 ± 400[15b]
18	1,3-dihydroxybenzene	$CDCl_3$	2000 ± 300[15b]
18	1,3-dihydroxybenzene	$CDCl_3/CD_3CN$ (10%)	109 ± 15[15b]
12	1,3,5-trihydroxybenzene	$CDCl_3/CD_3CN$ (10%)	15 ± 5
13	1,3,5-trihydroxybenzene	$CDCl_3/CD_3CN$ (10%)	130 ± 15
14	1,3,5-trihydroxybenzene	$CDCl_3/CD_3CN$ (10%)	65 ± 10
15	1,3,5-trihydroxybenzene	$CDCl_3/CD_3CN$ (10%)	50 ± 10
16	1,3,5-trihydroxybenzene	$CDCl_3/CD_3CN$ (10%)	680 ± 85
16	trihydroxyacetophenone	$CDCl_3/CD_3CN$ (10%)	120 ± 15
16	1,2,3-trihydroxybenzene	$CDCl_3/CD_3CN$ (10%)	85 ± 10
16	1,2-dihydroxybenzene	$CDCl_3/CD_3CN$ (10%)	40 ± 8
16	1,3-dihydroxybenzene	$CDCl_3/CD_3CN$ (10%)	50 ± 10
16	1,4-dihydroxybenzene	$CDCl_3/CD_3CN$ (10%)	30 ± 5
17	1,3,5-trihydroxybenzene	$CDCl_3/CD_3CN$ (10%)	150 ± 15



18 **19**

To obtain insights into the binding mode, we tried to obtain single crystals of both of the latter receptor–phloroglucinol complexes. In case of the platform **16**, we were able to grow single crystals of this complex from CD_2Cl_2 (Figure 2b).[7] The three bipyridyl arms take hold of the phloroglucinol molecule by forming three hydrogen bridges. These hydrogen bridges are formed exclusively by the nitrogen atoms of the pyridyl rings remote from the scaffold. From the X-ray structure, it is unclear whether the nitrogen atoms of the pyridine rings neighboring the scaffold face into the interior or towards the exterior of the receptor. The cavity between the phloroglucinol and the platform is filled with disordered solvent molecules (CD_2Cl_2).

In the case of the cage-like compound **17**, we were able to grow single crystals of a mixture of **17** and phloroglucinol from $CDCl_3$ and acetonitrile. Interestingly, in the solid structure, phloroglucinol is not incorporated into the cage, but remains outside, together with further solvent molecules. Inside the cage, there are three places for chloroform molecules, and two of the vacancies are completely occupied (Figure 2c). The reason why phloroglucinol is not included in the cage in the solid state and why **16** is a better receptor than **17** by a factor of four can be recognized by taking the distances between the bipyridine arms into consideration: In the free receptor **16**, the distance between the centers of the lower pyridine units is 9.46 Å, whereas in the corresponding receptor–substrate complex with phloroglucinol, it is 10.05 Å. This means that, for optimal binding, the distance between the arms must increase. This is easily feasible for

16, as receptor **16** permits an induced fit. In the case of the cage-like compound **17**, the distances between the pyridine ring centers are 9.31 Å and 9.36 Å, which are too low to permit optimal binding. Because of its rigid structure, an adjustment is not possible.

This hypothesis was proved by the results of AM1 calculations in the gas phase: The complex of **16** and phloroglucinol demonstrated an energetic stabilization of $\Delta H = 18.6\ kJ\,mol^{-1}$, whereas the value calculated for the complex of **17** and phloroglucinol was only $\Delta H = 6.2\ kJ\,mol^{-1}$. In the latter case, the phloroglucinol molecule is not bound perpendicularly to the bipyridine arms, because the distance between the arms is too short. Rather, it is placed diagonally inside the cage.

To investigate the selectivity of **16** toward phloroglucinol, comparative experiments using di- and triphenol derivatives were conducted (Table 2). As expected, the association constants were drastically reduced once the symmetry of the substrates no longer corresponded to C_3 symmetry and/or the number of binding sites of the substrates decreased. Thus, the data obtained are in good agreement with expectations based on host–guest complementarity.

Conclusion

We have developed an efficient procedure for the synthesis of a C_3-symmetric molecular scaffold that can easily be converted by a single step into either three-armed receptors or cage-like receptors. Because of the versatility in derivatization of this scaffold, optimization with respect to different substrates is feasible. The preorganization by steric gearing in the three-armed receptors is good and conforms to the desired receptor properties; however, improving the preorganization by the formation of cage-like structures can even be counterproductive, as the possibility of an induced fit is abolished.

The new receptor system described exhibits all of the positive features characteristic of 2,4,6-trialkylbenzene receptor systems, such as conformational control by steric gearing, ready availability, and versatility in derivatization. These attributes, combined with the advantageous size of the components, allows this system to be readily tailored to provide receptors for larger, biologically important molecules.

Experimental Section

General remarks: Aminoketone **4**,[8] 4-(2-pyridyl)benzylbromide,[16] 5-(bromomethyl)-5′-methyl-2,2′-bipyridyl,[17] and 5,5′-bis(bromomethyl)-2,2′-bipyridyl[17] were prepared according to reported procedures. All chemicals were of reagent grade and were used as purchased. All moisture-sensitive reactions were performed under an inert atmosphere of argon using distilled dry solvents. Reactions were monitored by performing TLC analysis with silica gel 60 F_{254} thin-layer plates. Flash chromatography was performed by using silica gel 60 (230–400 mesh). Melting points were determined in capillary tubes and are uncorrected. ^1H and ^{13}C NMR spectra were measured by using Bruker WH 300, Avance 300, and Avance 500 instruments. All chemical shifts (δ) are given in ppm relative to TMS. The spectra were referenced to deuterated solvents, indicated in brackets in the analytical data. HRMS spectra were recorded by using a JEOL JMS-700 instrument. IR spectra were measured by using a Bruker Vector 22 FTIR spectrometer. Elemental microanalyses were performed at the microanalytical laboratory of the University of Heidelberg.

General procedure for the cleavage of the methyl ester group: The protected compound (1 equiv) was dissolved in methanol/dioxane (10:7, 0.08 M), then 2 M NaOH (10 equiv) was added slowly at 0 °C. Stirring was continued until TLC analysis revealed the consumption of all starting material, then brine, 1 M HCl, and dichloromethane (DCM) were added. The aqueous phase was extracted repeatedly with DCM; the organic layers were combined, dried over $MgSO_4$, and concentrated in vacuo to give the acid compound, which was used in the next step without further purification.

General procedure for the cleavage of the Boc group: The Boc-protected compound (1 equiv) was dissolved in DCM (20 mL mmol^{-1} starting material) and the solution was cooled to 0 °C. TFA (1.5 mL/10 mL DCM) was added at this temperature. The ice bath was removed after 30 min and stirring was continued at room temperature for 3 h. The mixture was concentrated in vacuo to yield quantitatively the TFA salt, which was used in the next step without further purification.

General procedure for the cleavage of the benzyl group: The benzyl (Bn)-protected compound (1 equiv) was dissolved in MeOH (20 mL mmol^{-1} starting material) at room temperature. $Pd(OH)_2$ (50 mg mmol^{-1} starting material) was added and the solution was stirred under an H_2 atmosphere at room temperature for 1 d. The solution was filtered and the solvent was removed in vacuo to give the free imidazole, which was used in the next step without further purification.

Amidoketone 5: Compound (*S*)-Z-Val-OH (**3**; 16.33 g, 65.0 mmol, Z = benzyloxycarbonyl) was dissolved in tetrahydrofuran (THF) (400 mL), *N*-methylmorpholine (NMM) (6.574 g, 65.0 mmol) was added, and the solution was cooled to −25 °C. Isobutyl chloroformate (8.877 g, 65.0 mmol) was added, during which the reaction mixture was maintained at −25 °C. After 35 min, aminoketone **4** (10.89 g, 65.0 mmol), followed by a second equivalent of NMM (6.574 g, 65.0 mmol), were added at −25 °C. Stirring was continued for 20 h as the mixture was allowed to warm to room temperature. The solvent was evaporated and the residue was dissolved in AcOEt, and then washed with water and brine. The organic layer was dried over $MgSO_4$ and concentrated in vacuo. Purification was achieved by performing chromatography with silica gel (petroleum ether/ethyl acetate: 1:1) to yield **3** (19.00 g, 52.33 mmol, 80 %) as a white solid. M.p. 132 °C; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.38–7.27 (m, 10H; $C_{Ar}H$), 7.13–7.03 (m, 2H; CONH), 5.42–5.31 (m, 2H; $NHCO_2$), 5.23 (m, 2H; $CHCO_2Me$), 5.12 (m, 4H; $C_{Ar}CH_2$), 4.22–4.12 (m, 2H; CHCONH), 3.80 (s, 6H; CO_2Me), 2.38 (s, 3H; COMe), 2.37 (s, 3H; COMe), 2.26–2.10 (m, 2H; $CHMe_2$), 1.02–0.90 ppm (m, 12H; $CHMe_2$); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 197.9, 197.8, 171.1, 166.21, 166.18, 156.3, 136.2, 128.52, 128.51, 128.2, 128.1, 128.04, 128.03, 67.2, 67.1, 63.0, 62.8, 59.9, 53.32, 53.27, 31.2, 31.0, 28.0, 27.9, 19.1, 19.0, 17.5, 17.4 ppm; IR (KBr): $\tilde{\nu}$ = 3415, 3297, 3064, 3036, 2962, 2874, 1754, 1725, 1689, 1651, 1536, 1454, 1438, 1366, 1289, 1249, 1160, 1042, 700 cm^{-1}; HRMS (FAB+): *m*/*z* calcd for $C_{18}H_{25}N_2O_6$ $[M+H]^+$: 365.1713; found: 365.1739; elemental analysis calcd (%) for $C_{18}H_{24}N_2O_6$: C 59.33, H 6.64, N 7.69; found: C 59.10, H 6.66, N 7.72.

***N*-Z-imidazole methyl ester 6 (Z = benzyloxycarbonyl)**: Both TFA (3.88 g, 34.0 mmol) and NH_3 in MeOH (7 M, 4.86 mL, 34.0 mmol) were added to a solution of **5** (6.19 g, 17.0 mmol) in xylenes (200 mL) at room temperature. The solution was stirred at 150 °C with azeotropic removal of water for 8 h and then cooled to room temperature. The solvent was concentrated, and the residue was dissolved in AcOEt, and then washed with saturated $NaHCO_3$ solution and brine. The organic layer was dried over $MgSO_4$ and concentrated in vacuo. Purification was achieved by performing chromatography with silica gel (petroleum ether/ethyl acetate: 2:3) to provide 4.24 g of **6** (12.3 mmol, 72 %) as a white solid. M.p. 133–134 °C; ^1H NMR (500 MHz, [D$_4$]methanol): δ = 7.42–7.27 (m, 5H; $C_{Ar}H$), 5.18–5.04 (m, 2H; $C_{Ar}CH_2$), 4.51 (d, J = 7.6 Hz, 2H; CHC_{Imi}), 3.88 (s, 3H; COOMe), 2.49 (s, 3H; $C_{Imi}Me$), 2.21–2.10 (m, 1H; $CHMe_2$), 1.00 (d, J =

6.5 Hz, 3H; CHMe_2), 0.87 ppm (d, J=6.6 Hz, 3H; CHMe_2); ^{13}C NMR (125 MHz, [D$_4$]methanol): δ=158.4, 138.2, 129.5, 129.0, 128.9, 67.8, 56.8, 51.7, 33.9, 19.6, 19.1 ppm; IR (KBr): $\tilde{\nu}$=3205, 3065, 3033, 2963, 2875, 1715, 1581, 1532, 1443, 1405, 1341, 1284, 1242, 1210, 1111, 1026, 735, 697 cm^{-1}; HRMS (FAB+): m/z calcd for $C_{18}H_{24}N_3O_4$ [M+H]$^+$: 346.1767; found: 346.1813; elemental analysis calcd (%) for $C_{18}H_{23}N_3O_4$: C 62.59, H 6.71, N 12.17; found: C 62.34, H 6.66, N 11.99.

***N*-Boc-imidazole methyl ester 7**: Di-*tert*-butyldicarbonate (Boc_2O) (5.76 g, 26.0 mmol) and $Pd(OH)_2$ (0.80 g) were added to a solution of **6** (8.12 g, 23.5 mmol) in THF (200 mL) at room temperature. The solution was stirred under an H_2 atmosphere at room temperature for 1 d, then filtered, and the solvent was removed in vacuo. Flash chromatography with silica gel (petroleum ether/ethyl acetate: 2:3) gave 6.96 g of **7** (22.4 mmol, 95%) as a white solid. M.p. 161–162 °C; ^{1}H NMR (300 MHz, [D$_4$]methanol): δ=4.36 (d, J=7.6 Hz, 1H; CHC_{Imi}), 3.79 (s, 3H; COOMe), 2.40 (s, 3H; C_{Imi}Me), 2.07–1.92 (m, 1H; CHMe$_2$), 1.37 (s, 9H; $CCMe_3$), 0.89 (d, J=6.6 Hz, 3H; CHMe_2), 0.76 ppm (d, J=6.8 Hz, 3H; CHMe_2); ^{13}C NMR (75 MHz, [D$_4$]methanol): δ=157.7, 80.6, 56.1, 51.7, 34.2, 28.7, 19.6, 19.0 ppm; IR (KBr): $\tilde{\nu}$=3335, 3071, 2971, 2934, 2875, 1715, 1594, 1525, 1441, 1394, 1368, 1324, 1285, 1247, 1206, 1172, 1113, 1040, 1013 cm^{-1}; HRMS (FAB+): m/z calcd for $C_{15}H_{26}N_3O_4$ [M+H]$^+$: 312.1923; found: 312.1944; elemental analysis calcd (%) for $C_{15}H_{25}N_3O_4$: C 57.86, H 8.09, N 13.49; found: C 57.72, H 7.99, N 13.32.

***N*-Boc-benzyl-imidazole methyl esters 8 and 9**: Both K_2CO_3 (9.54 g, 69.0 mmol) and BnBr (5.99 g, 35.0 mmol) were added to a solution of **7** (7.16 g, 23.0 mmol) in acetonitrile (400 mL) at room temperature and the mixture was stirred at reflux for 4 h. The solvent was evaporated and the residue was dissolved in AcOEt, extracted with water and brine, dried over $MgSO_4$, and concentrated in vacuo. Purification was achieved by performing chromatography with silica gel (petroleum ether/ethyl acetate: 3:1 to 1:1) to yield **9** (4.73 g, 11.8 mmol, 51%) and **8** (2.98 g, 7.42 mmol, 32%) as white solids.

Data for **8**: M.p. 148–149 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.36–6.94 (m, 5H; C_{Ar}H), 5.33 (d, J=16.9 Hz, 1H; $C_{Ar}CH_2$), 5.20–5.09 (m, 2H; $C_{Ar}CH_2$, $NHCO_2$), 4.45 (m, 1H; CHC_{Imi}), 3.89 (s, 3H; COOMe), 2.48 (s, 3H; C_{Imi}Me), 2.31–2.17 (m, 1H; CHMe$_2$), 1.35 (s, 9H; CMe_3), 0.93 (d, J=6.7 Hz, 3H; CHMe_2), 0.58 ppm (d, J=6.6 Hz, 3H; CHMe_2); ^{13}C NMR (75 MHz, $CDCl_3$): δ=164.3, 155.4, 148.9, 136.1, 135.6, 128.9, 128.1, 127.9, 126.1, 79.4, 52.1, 51.5, 46.8, 32.5, 28.2, 19.9, 18.5, 10.3 ppm; IR (KBr): $\tilde{\nu}$=3353, 2968, 2931, 1699, 1574, 1520, 1454, 1441, 1390, 1364, 1335, 1307, 1246, 1221, 1171, 1084, 1015, 730 cm^{-1}; HRMS (FAB+): m/z calcd for $C_{22}H_{32}N_3O_4$ [M+H]$^+$: 402.2393; found: 402.2394; elemental analysis calcd (%) for $C_{22}H_{31}N_3O_4$: C 65.81, H 7.78, N 10.47; found: C 65.68, H 7.81, N 10.41.

Data for **9**: M.p. 91–93 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.32–7.02 (m, 5H; C_{Ar}H), 5.81 (d, J=16.1 Hz, 1H; $C_{Ar}CH_2$), 5.52 (d, J=16.1 Hz, 1H; $C_{Ar}CH_2$), 5.08 (d, J=9.6 Hz, 1H; $NHCO_2$), 4.53 (m, 1H; CHC_{Imi}), 3.79 (s, 3H; COOMe), 2.49 (s, 3H; C_{Imi}Me), 2.15–2.00 (m, 1H; CHMe$_2$), 1.39 (s, 9H; CMe_3), 0.92 (d, J=6.7 Hz, 3H; CHMe_2), 0.53 ppm (d, J=6.6 Hz, 3H; CHMe_2); ^{13}C NMR (75 MHz, $CDCl_3$): δ=161.6, 155.4, 152.4, 147.5, 137.4, 128.6, 127.4, 126.5, 118.3, 79.5, 51.8, 51.2, 48.1, 32.9, 28.3, 19.4, 18.4, 16.0 ppm; IR (KBr): $\tilde{\nu}$=3430, 3361, 2971, 2933, 1709, 1517, 1472, 1451, 1392, 1368, 1314, 1282, 1247, 1170, 1134, 1011, 733 cm^{-1}; HRMS (FAB+): m/z calcd for $C_{22}H_{32}N_3O_4$ [M+H]$^+$: 402.2393; found: 402.2374; elemental analysis calcd (%) for $C_{22}H_{31}N_3O_4$: C 65.81, H 7.78, N 10.47; found: C 65.59, H 7.79, N 10.31.

TFA aminoimidazole carboxylic acid 10: Imidazole **8** (2.01 g, 5.00 mmol) was converted into the free acid as described above in the general procedure for the cleavage of the methyl ester group. Yield 1.84 g (4.75 mmol, 95%). M.p. 86–88 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.64–7.43 (m, 1H; $NHCO_2$), 7.39–7.05 (m, 5H; C_{Ar}H), 5.23 (d, J=16.9 Hz, 1H; $C_{Ar}CH_2$), 5.14 (d, J=16.9 Hz, 1H; $C_{Ar}CH_2$), 4.44 (m, 1H; CHC_{Imi}), 2.54 (s, 3H; C_{Imi}Me), 2.53–2.39 (m, 1H; CHMe$_2$), 1.39 (s, 9H; CMe_3), 0.97 (d, J=6.6 Hz, 3H; CHMe_2), 0.46 ppm (d, J=6.6 Hz, 3H; CHMe_2); ^{13}C NMR (75 MHz, $CDCl_3$): δ=165.6, 156.2, 149.2, 135.9, 135.6, 134.1, 128.9, 127.9, 126.4, 78.8, 52.3, 47.0, 32.1, 28.3, 20.0, 19.2, 10.0 ppm; IR (KBr): $\tilde{\nu}$=3409, 3258, 2972, 2932, 2876, 1709, 1631, 1503, 1455, 1390, 1368, 1281, 1252, 1169, 1119, 1013, 873, 731 cm^{-1}; HRMS (FAB+): m/z calcd for $C_{21}H_{30}N_3O_4$ [M+H]$^+$: 388.2236; found: 388.2234; elemental analysis calcd (%) for $C_{21}H_{29}N_3O_4 \cdot 0.5\,H_2O$: C 63.62, H 7.63, N 10.60; found: C 63.34, H 7.43, N 10.48.

The free acid (1.84 g, 4.75 mmol) was converted into the *N*-benzyl-deprotected free acid as described above in the general procedure for the cleavage of the benzyl group. Yield 1.27 g (4.27 mmol, 90%). M.p. 92–94 °C; ^{1}H NMR (300 MHz, [D$_4$]methanol): δ=4.41 (d, J=7.4 Hz, 1H; CHC_{Imi}), 2.45 (s, 3H; C_{Imi}Me), 2.12–1.97 (m, 1H; CHMe$_2$), 1.30 (s, 9H; CMe_3), 0.92 (d, J=6.7 Hz, 3H; CHMe_2), 0.77 ppm (d, J=6.8 Hz, 3H; CHMe_2); ^{13}C NMR (75 MHz, [D$_4$]methanol): δ=161.6, 157.7, 150.0, 137.3, 122.6, 81.5, 55.8, 33.1, 28.6, 19.3, 19.1, 10.9 ppm; IR (KBr): $\tilde{\nu}$=3387, 2973, 2935, 2879, 1718, 1645, 1517, 1475, 1391, 1370, 1348, 1285, 1252, 1164, 1132, 1013, 874 cm^{-1}; HRMS (FAB+): m/z calcd for $C_{14}H_{24}N_3O_4$ [M+H]$^+$: 298.1767; found: 298.1743.

The *N*-benzyl-deprotected free acid was subjected to Boc deprotection to give the free amino acid **10**. M.p. 50–52 °C; ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ=9.75–8.09 (br s, 5H; NH_3, COOH, N_{Imi}H), 4.07 (d, J=6.7 Hz, 1H; CHC_{Imi}), 2.41 (s, 3H; C_{Imi}Me), 2.26–2.14 (m, 1H; CHMe$_2$), 0.93 (d, J=6.8 Hz, 3H; CHMe_2), 0.82 ppm (d, J=6.8 Hz, 3H; CHMe_2); ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ=162.9, 159.0, 158.6, 158.1, 157.6, 143.5, 139.5, 123.5, 122.0, 118.1, 114.2, 110.3, 53.1, 31.1, 18.3, 17.9, 12.4 ppm; IR (KBr): $\tilde{\nu}$=3433, 2977, 2943, 1672, 1558, 1504, 1558, 1504, 1439, 1397, 1385, 1318, 1260, 1202, 1142, 839, 799, 723 cm^{-1}; HRMS (FAB+): m/z calcd for $C_{11}H_{17}F_3N_3O_4$ [M+H]$^+$: 198.1243; found: 198.1241.

Scaffold 2: Both iPr$_2$NEt (1.24 g, 9.60 mmol) and FDPP (1.61 g, 4.20 mmol) were added to a solution of **10** (1.00 g, 3.20 mmol) in acetonitrile (70 mL) at room temperature, and the mixture was stirred at this temperature for five days. The solvent was evaporated and the residue was dissolved in AcOEt, then extracted with water and brine, dried over $MgSO_4$, and concentrated in vacuo. Flash chromatography with silica gel (DCM/AcOEt/MeOH: 75/25/10) gave 200 mg of **2** (0.37 mmol, 35%) as a white solid. M.p. >250 °C; ^{1}H NMR (300 MHz, [D$_4$]methanol): δ=4.87 (d, J=5.5 Hz, 3H; CHC_{Imi}), 2.49 (s, 9H; C_{Imi}Me), 2.21–2.07 (m, 3H; CHMe$_2$), 0.98 (d, J=6.8 Hz, 9H; CHMe_2), 0.95 ppm (d, J=6.8 Hz, 9H; CHMe_2); ^{13}C NMR (75 MHz, [D$_4$]methanol): δ=165.3, 146.6, 133.1, 130.2, 53.4, 35.8, 19.0, 18.8, 10.7 ppm; IR (KBr): $\tilde{\nu}$=3378, 3225, 2965, 2931, 2875, 1646, 1603, 1546, 1516, 1466, 1439, 1405, 1389, 1370, 1336, 1286, 1224, 1155, 1038, 1023, 909, 880, 806, 783, 775, 643 cm^{-1}; HRMS (FAB+): m/z calcd for $C_{27}H_{40}N_9O_3$ [M+H]$^+$: 538.3254; found: 538.3243; elemental analysis calcd (%) for $C_{27}H_{39}N_9O_3 \cdot {}^1/_3CH_2Cl_2 \cdot {}^1/_3CH_3OH$: C 57.63, H 7.17, N 21.86; found: C 57.39, H 7.45, N 21.89.

Receptor 11: Imidazole **8** (2.01 g, 5.00 mmol) was subjected to methyl and Boc deprotection successively to give the corresponding free amino acid. Yield 1.91 g (4.76 mmol, 95%). M.p. 72 °C; ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ=8.48 (s, 3H; NH_3), 7.43–7.04 (m, 5H; C_{Ar}H), 5.45–5.24 (m, 2H; $C_{Ar}CH_2$), 4.35 (s, 1H; CHC_{Imi}), 2.36 (s, 3H; C_{Imi}Me), 2.20–2.06 (m, 1H; CHMe$_2$), 0.91 (d, J=6.7 Hz, 3H; CHMe_2), 0.72 ppm (d, J=6.8 Hz, 3H; CHMe_2); ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ=164.3, 158.7, 158.3, 157.9, 157.4, 143.9, 136.4, 136.0, 128.7, 128.5, 127.6, 126.2, 122.3, 118.4, 114.4, 110.5, 51.0, 46.4, 31.8, 18.4, 17.6, 10.1 ppm; IR (KBr): $\tilde{\nu}$=3433, 3035, 2973, 2940, 1679, 1547, 1514, 1506, 1435, 1354, 1328, 1202, 1141, 800, 725 cm^{-1}; HRMS (FAB+): m/z calcd for $C_{18}H_{23}F_3N_3O_4$ [M+H]$^+$: 288.1712; found: 288.1717; elemental analysis calcd (%) for $C_{18}H_{22}F_3N_3O_4 \cdot 0.5\,CF_3COOH$: C 49.78, H 4.95, N 9.17; found: C 49.71, H 5.12, N 9.15.

Both iPr$_2$NEt (1.24 g, 9.60 mmol) and FDPP (1.61 g, 4.20 mmol) were added to a solution of the free amino acid (1.28 g, 3.20 mmol) in acetonitrile (70 mL) at room temperature, and the mixture was stirred at room temperature for 5 d. The solvent was evaporated and the residue was dissolved in AcOEt, then extracted with water and brine, dried over $MgSO_4$, and concentrated in vacuo. Purification was achieved by performing chromatography with silica gel (petroleum ether/ethyl acetate: 1:2) to yield 520 mg (0.64 mmol, 60%) of **11** as a white solid. M.p. 246 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ=8.51 (d, J=9.1 Hz, 3H; CONH), 7.31–6.96 (m, 15H; C_{Ar}H), 5.22–5.15 (m, 6H; $C_{Ar}CH_2$, CHC_{Imi}), 5.08 (d, J=16.9 Hz, 3H; $C_{Ar}CH_2$), 2.41 (s, 9H; C_{Imi}Me), 2.00–1.92 (m, 3H; CHMe$_2$), 0.99 (d, J=6.7 Hz, 9H; CHMe_2), 0.96 ppm (d, J=6.9 Hz, 9H;

$CHMe_2$); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 163.2$, 147.2, 135.3, 132.3, 130.1, 129.0, 127.9, 126.0, 49.6, 46.9, 34.5, 19.8, 17.2, 9.9 ppm; IR (KBr): $\tilde{\nu} = 3387$, 3064, 3032, 2963, 2930, 2873, 1662, 1595, 1508, 1456, 1427, 1388, 1369, 1355, 1261, 1223, 1141, 1092, 1029, 933, 877, 810, 783, 770, 730, 696, 632, 510 cm^{-1}; HRMS (FAB+): m/z calcd for $C_{48}H_{58}N_9O_3$ $[M+H]^+$: 808.4663; found: 808.4661; elemental analysis calcd (%) for $C_{48}H_{57}N_9O_3 \cdot {}^2/_3CH_2Cl_2$: C 67.60, H 6.80, N 14.58; found: C 67.55, H 6.88, N 14.53.

General procedure for the syntheses of three-armed platforms 12–16: Both K_2CO_3 (207 mg, 1.50 mmol) and RCH_2Br (0.75 mmol) were added to a solution of **2** (108 mg, 0.20 mmol) in acetonitrile (30 mL) at room temperature and the mixture was stirred at reflux for 8 h. The solvent was evaporated and the residue was dissolved in AcOEt, extracted with water and brine, dried over $MgSO_4$, and concentrated in vacuo. Purification was achieved by performing chromatography with silica gel (DCM/AcOEt/MeOH: 75:25:5) to yield the three-armed platforms **12–16** (65–77%) as white solids.

Data for receptor **12**: Yield 70%. M.p. 183°C; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 8.49$ (d, $J = 9.2$ Hz, 3H; NHCO), 7.98 (d, $J = 8.4$ Hz, 6H; $C_{Ar}H$), 7.05 (d, $J = 8.4$ Hz, 6H; $C_{Ar}H$), 5.29–5.09 (m, 9H; $C_{Ar}CH_2$, CHC_{Imi}), 3.90 (s, 9H; COOMe), 2.39 (s, 9H; $C_{Imi}Me$), 2.05–1.91 (m, 3H; $CHMe_2$), 1.00 (d, $J = 6.8$ Hz, 9H; $CHMe_2$), 0.97 ppm (d, $J = 6.8$ Hz, 9H; $CHMe_2$); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 166.4$, 163.0, 147.3, 140.3, 132.2, 130.4, 130.0, 126.0, 52.2, 49.6, 46.7, 34.6, 19.8, 17.3, 9.8 ppm; IR (KBr): $\tilde{\nu} = 3388$, 2961, 2874, 1725, 1664, 1614, 1595, 1558, 1509, 1460, 1434, 1417, 1388, 1372, 1314, 1283, 1224, 1192, 1111, 1019, 964, 930, 839, 771, 751, 627 cm^{-1}; HRMS (FAB+): m/z calcd for $C_{54}H_{64}N_9O_9$ $[M+H]^+$: 982.4827; found: 982.4878.

Data for receptor **13**: Yield 65%. M.p. 191°C; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 8.51$ (d, $J = 9.1$ Hz, 3H; CONH), 7.67 (d, $J = 8.3$ Hz, 6H; $C_{Ar}H$), 6.98 (d, $J = 8.3$ Hz, 6H; $C_{Ar}H$), 6.33 (t, $J = 5.7$ Hz, 3H; $CONHCH_2$), 5.24–5.05 (m, 9H; $C_{Ar}CH_2$, CHC_{Imi}), 3.47–3.35 (m, 6H; $CONHCH_2$), 2.35 (s, 9H; $C_{Imi}Me$), 2.07–1.93 (m, 3H; $CHMe_2$), 1.62–1.49 (m, 6H; CH_2), 1.44–1.31 (m, 6H; CH_2), 1.03–0.89 ppm (m, 27H; CH_2CH_3, $CHMe_2$); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 166.8$, 163.0, 147.2, 138.5, 134.7, 132.2, 130.3, 127.7, 126.0, 49.6, 46.6, 39.8, 34.7, 31.7, 20.1, 19.8, 17.3, 13.8, 9.8 ppm; IR (KBr): $\tilde{\nu} = 3382$, 3068, 2960, 2930, 2872, 1649, 1595, 1573, 1508, 1463, 1432, 1388, 1372, 1350, 1310, 1225, 1192, 1146, 1111, 1019, 963, 929, 839, 814, 783, 771, 747, 636, 539 cm^{-1}; HRMS (FAB+): m/z calcd for $C_{63}H_{85}N_{12}O_6$ $[M+H]^+$: 1105.6715; found: 1105.6704.

Data for receptor **14**: Yield 70%. M.p. 159°C; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 8.48$ (d, $J = 9.1$ Hz, 3H; NHCO), 6.91 (d, $J = 8.7$ Hz, 6H; $C_{Ar}H$), 6.79 (d, $J = 8.8$ Hz, 6H; $C_{Ar}H$), 5.21–4.93 (m, 9H; $C_{Ar}CH_2$, CHC_{Imi}), 3.75 (s, 9H; $C_{Ar}OMe$), 2.40 (m, 9H; $C_{Imi}Me$), 2.02–1.88 (m, 3H; $CHMe_2$), 1.01–0.92 ppm (m, 18H; $CHMe_2$); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 163.2$, 159.2, 147.1, 132.2, 130.1, 127.4, 114.3, 55.3, 49.5, 46.5, 34.5, 19.9, 17.2, 9.9 ppm; IR (KBr): $\tilde{\nu} = 3386$, 2962, 2932, 2873, 2836, 1662, 1613, 1594, 1515, 1463, 1420, 1388, 1370, 1354, 1331, 1294, 1251, 1177, 1142, 1111, 1090, 1033, 916, 878, 821, 783, 730, 635, 554, 515 cm^{-1}; HRMS (FAB+): m/z calcd for $C_{51}H_{64}N_9O_6$ $[M+H]^+$: 898.4980; found: 898.4958.

Data for receptor **15**: Yield 77%. M.p. 198°C; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 8.66$ (d, $J = 4.5$ Hz, 3H; $C_{Ar}H$), 8.54 (d, $J = 9.2$ Hz, 3H; NHCO), 7.93 (d, $J = 8.3$ Hz, 6H; $C_{Ar}H$), 7.75–7.66 (m, 6H; $C_{Ar}H$), 7.21 (m, 3H; $C_{Ar}H$), 7.10 (d, $J = 8.2$ Hz, 6H; $C_{Ar}H$), 5.27–5.13 (m, 9H; $C_{Ar}CH_2$, CHC_{Imi}), 2.43 (s, 9H; $C_{Imi}Me$), 2.05–1.97 (m, 3H; $CHMe_2$), 1.02 (d, $J = 6.7$ Hz, 9H; $CHMe_2$), 0.99 ppm (d, $J = 6.8$ Hz, 9H; $CHMe_2$); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 163.2$, 156.6, 149.5, 147.3, 138.9, 136.9, 136.2, 132.3, 130.3, 127.6, 126.4, 122.3, 120.6, 49.6, 46.8, 34.6, 19.9, 17.3, 9.9 ppm; IR (KBr): $\tilde{\nu} = 3387$, 3051, 2962, 2928, 2872, 1661, 1593, 1563, 1508, 1467, 1436, 1410, 1388, 1371, 1348, 1294, 1224, 1195, 1153, 1110, 1094, 1060, 1015, 989, 926, 828, 776, 738, 623, 551 cm^{-1}; HRMS (FAB+): m/z calcd for $C_{63}H_{67}N_{12}O_3$ $[M+H]^+$: 1039.5459; found: 1039.5436.

Data for receptor **16**: Yield 65%. M.p. 178°C; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 8.45$ (m, 9H; NHCO, $C_{Ar}H$), 8.30 (d, $J = 8.3$ Hz, 3H; $C_{Ar}H$), 8.24 (d, $J = 8.1$ Hz, 3H; $C_{Ar}H$), 7.59 (m, 3H; $C_{Ar}H$), 7.38 (m, 3H; $C_{Ar}H$), 5.30–5.13 (m, 9H; $C_{Ar}CH_2$, CHC_{Imi}), 2.44 (s, 9H; $C_{Imi}Me$), 2.37 (s, 9H; $C_{Ar}Me$), 2.11–1.95 (m, 3H; $CHMe_2$), 1.04 (d, $J = 6.7$ Hz, 9H; $CHMe_2$), 0.98 ppm (d, $J = 6.7$ Hz, 9H; $CHMe_2$); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 163.1$, 156.3, 152.9, 149.7, 147.3, 147.2, 137.4, 134.7, 133.7, 132.0, 130.6, 130.5, 121.0, 120.7, 49.6, 44.7, 34.6, 19.9, 18.4, 17.5, 9.9 ppm; IR (KBr): $\tilde{\nu} = 3388$, 2962, 2927, 2873, 1662, 1596, 1556, 1508, 1468, 1426, 1403, 1387, 1373, 1337, 1221, 1132, 1109, 1058, 1029, 934, 829, 784, 759, 739, 650, 634 cm^{-1}; HRMS (FAB+): m/z calcd for $C_{63}H_{70}N_{15}O_3$ $[M+H]^+$: 1084.5786; found: 1084.5774.

Cage-like receptor 17: Both K_2CO_3 (166 mg, 1.20 mmol) and $BrCH_2(C_5H_3N)_2CH_2Br$ (103 mg, 0.30 mmol) were added to a solution of **2** (108 mg, 0.20 mmol) in acetonitrile (200 mL) at room temperature and the mixture was stirred at reflux for 8 h. The solvent was evaporated and the residue was dissolved in AcOEt, extracted with water and brine, dried over $MgSO_4$, and concentrated in vacuo. Purification was achieved by performing chromatography with silica gel (DCM/AcOEt/MeOH: 75:25:7) to yield 74 mg of **17** (0.046 mmol, 46%) as a white solid. M.p. >250°C; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 8.70$ (d, $J = 8.6$ Hz, 6H; $C_{Ar}H$), 8.24 (d, $J = 8.3$ Hz, 6H; NHCO), 8.11 (m, 6H; $C_{Ar}H$), 7.21–7.15 (m, 6H; $C_{Ar}H$), 5.39 (d, $J = 17.6$ Hz, 6H; $C_{Ar}CH_2$), 5.15 (m, 6H; CHC_{Imi}), 5.05 (d, $J = 17.6$ Hz, 6H; $C_{Ar}CH_2$), 2.33 (s, 18H; $C_{Imi}Me$), 2.22–2.09 (m, 6H; $CHMe_2$), 1.11 (d, $J = 6.8$ Hz, 18H; $CHMe_2$), 1.06 ppm (d, $J = 6.7$ Hz, 18H; $CHMe_2$); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 162.6$, 155.3, 146.7, 146.2, 134.2, 132.1, 130.9, 130.7, 121.2, 49.6, 44.6, 35.7, 19.6, 17.8, 9.6 ppm; IR (KBr): $\tilde{\nu} = 3389$, 2962, 2931, 2872, 1660, 1596, 1555, 1508, 1469, 1428, 1388, 1372, 1329, 1223, 913, 824, 781, 763, 733, 638 cm^{-1}; HRMS (FAB+): m/z calcd for $C_{90}H_{103}N_{24}O_6$ $[M+H]^+$: 1615.8492; found: 1615.8499.

Host–guest titrations: Stock solutions of the guest (1 μmol/100 μL) in CD_3CN and the receptor (1 μmol/100 μL) in $CDCl_3$ were prepared. In total, 10 NMR tubes were set up by adding increasing amounts of the host solution (0–500 μL) to 100 μL of the guest solution. All samples were made up to a volume of 1 mL with $CDCl_3$ and the respective ^1H NMR spectra were recorded. The chemical shifts of prominent guest protons were plotted against the host concentration. From the resulting saturation curves, K_a and δ_{max} were calculated by using the SIGMA Plot 8.0 software package.

X-ray crystal structure analysis: For $C_{27}H_{39}N_9O_3 \cdot 2CH_3OH$ (**2**); $M_r = 601.76$, colorless crystal (irregular), dimensions $0.27 \times 0.23 \times 0.11$ mm^3, crystal system orthorhombic, space group $P2_12_12_1$, $Z = 4$, $a = 9.1365(6)$, $b = 9.3066(6)$, $c = 40.850(3)$ Å, $V = 3473.5(4)$ $Å^3$, $\rho_{calcd} = 1.151$ $g\,cm^{-3}$, $T = 100(2)$ K, $\theta_{max} = 24.75°$, radiation $Mo_{K\alpha}$, $\lambda = 0.71073$ Å, 0.3° omega scans with CCD area detector, covering a whole sphere in reciprocal space, 27209 reflections measured, 5906 unique (R(int) = 0.0392), 5496 observed [$I > 2\sigma(I)$], intensities were corrected for Lorentz and polarization effects, an empirical absorption correction was applied by using SADABS[18] based on the Laue symmetry of the reciprocal space, $\mu = 0.08$ mm^{-1}, min/max transmission = 0.98/0.99, structure was solved by using direct methods and refined against F^2 with a full-matrix least-squares algorithm by using the SHELXTL (6.12) software package,[19] 578 parameters refined, hydrogen atoms were treated by using appropriate riding models, except for 31, which were refined isotropically, Flack absolute structure parameter −0.3(13), goodness of fit 1.13 for observed reflections, final residual values $R1(F) = 0.049$, $wR(F^2) = 0.115$ for observed reflections, residual electron density −0.19 to 0.35 $eÅ^{-3}$.

For $C_{48}H_{57}N_9O_3 \cdot C_3H_6O \cdot H_2O$ (**11**) (crystallization from acetone); $M_r = 882.10$, colorless crystal (polyhedron), dimensions $0.25 \times 0.22 \times 0.14$ mm^3, crystal system hexagonal, space group $P6_3$, $Z = 2$, $a = 13.4888(4)$, $b = 13.4888(4)$, $c = 14.9241(9)$ Å, $V = 2351.61(17)$ $Å^3$, $\rho_{calcd} = 1.246$ $g\,cm^{-3}$, $T = 100(2)$ K, $2\theta_{max} = 28.39°$, radiation $Mo_{K\alpha}$, $\lambda = 0.71073$ Å, 0.3° omega scans with CCD area detector, covering a whole sphere in reciprocal space, 25065 reflections measured, 3917 unique (R(int) = 0.0447), 3861 observed [$I > 2\sigma(I)$], intensities were corrected for Lorentz and polarization effects, an empirical absorption correction was applied by using SADABS[18] based on the Laue symmetry of the reciprocal space, $\mu = 0.08$ mm^{-1}, min/max transmission = 0.98/0.99, structure was solved by direct methods and refined against F^2 with a full-matrix least-squares algorithm by using the SHELXTL-PLUS (5.10) software package,[19] 227 parameters refined, hydrogen atoms were treated by using appropriate riding models, except for H9 at N9, which was refined isotropically, Flack absolute structure parameter −1(2), goodness of fit 1.26 for observed reflections, final resid-

ual values $R1(F)=0.068$, $wR(F^2)=0.151$ for observed reflections, residual electron density -0.31 to $0.62\ e\text{Å}^{-3}$.

For $C_{48}H_{57}N_9O_3$·disordered solvent (**11**) (crystallization from methanol); $M_r=808.03$, colorless crystal (polyhedron), dimensions $0.22\times0.06\times0.05\ mm^3$, crystal system hexagonal, space group $P6_3$, $Z=2$, $a=13.535(2)$, $b=13.535(2)$, $c=14.845(4)$ Å, $V=2355.3(8)$ Å^3, $\rho_{calcd}=1.139\ g\,cm^{-3}$, $T=100(2)$ K, $\theta_{max}=24.14°$, radiation $Mo_{K\alpha}$, $\lambda=0.71073$ Å, 0.3° omega scans with CCD area detector, covering a whole sphere in reciprocal space, 17654 reflections measured, 2517 unique (R(int) = 0.1251), 2210 observed [$I>2\sigma(I)$], intensities were corrected for Lorentz and polarization effects, an empirical absorption correction was applied by using SADABS[18] based on the Laue symmetry of the reciprocal space, $\mu=0.07\ mm^{-1}$, min/max transmission = 0.98/1.00, structure was solved by direct methods and refined against F^2 with a full-matrix least-squares algorithm by using the SHELXTL-PLUS (5.10) software package,[19] 214 parameters refined, hydrogen atoms were treated by using appropriate riding models, except for the amide hydrogen atom H9 at N9, which was refined isotropically, Flack absolute structure parameter $-1(4)$, goodness of fit 1.18 for observed reflections, final residual values $R1(F)=0.087$, $wR(F^2)=0.206$ for observed reflections, residual electron density -0.49 to $0.46\ e\text{Å}^{-3}$.

For $C_{90}H_{102}N_{24}O_6\cdot2\,C_6H_6O_3$·disordered solvent (**17**); $M_r=2832.09$, colorless crystal (polyhedron), dimensions $0.40\times0.30\times0.28\ mm^3$, crystal system hexagonal, space group $P6_3$, $Z=2$, $a=15.119(2)$, $b=15.119(2)$, $c=34.458(5)$ Å, $V=6821.7(17)$ Å^3, $\rho_{calcd}=1.379\ g\,cm^{-3}$, $T=100(2)$ K, $\theta_{max}=21.96°$, radiation $Mo_{K\alpha}$, $\lambda=0.71073$ Å, 0.3° omega scans with CCD area detector, covering a whole sphere in reciprocal space, 40674 reflections measured, 5530 unique (R(int) = 0.0456), 5179 observed [$I>2\sigma(I)$], intensities were corrected for Lorentz and polarization effects, an empirical absorption correction was applied by using SADABS[18] based on the Laue symmetry of the reciprocal space, $\mu=0.54\ mm^{-1}$, min/max transmission = 0.81/0.86, structure was solved by direct methods and refined against F^2 with a full-matrix least-squares algorithm by using the SHELXTL (6.12) software package,[19] 565 parameters refined, hydrogen atoms were treated by using appropriate riding models, Flack absolute structure parameter 0.27(14), goodness of fit 1.30 for observed reflections, final residual values $R1(F)=0.100$, $wR(F^2)=0.264$ for observed reflections, residual electron density -0.45 to $0.93\ e\text{Å}^{-3}$.

CCDC 264694–264697 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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