COMMUNICATION

ChemComm
www.rsc.org/chemcomm

A C_3-symmetric molecular scaffold for the construction of large receptors

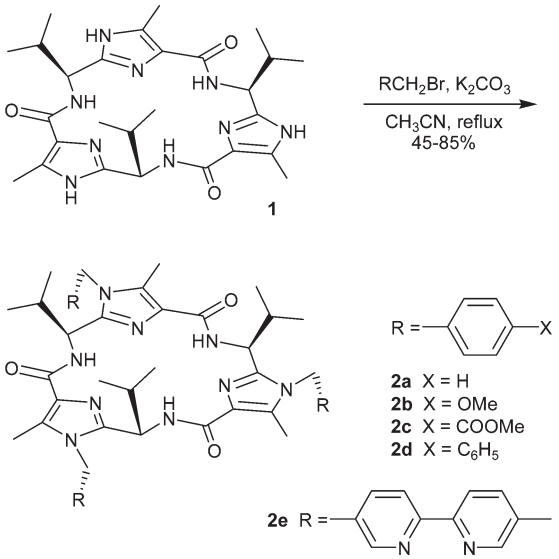
Gebhard Haberhauer,* Thomas Oeser and Frank Rominger
Organisch-Chemisches Institut, Universität Heidelberg, Im Neuenheimer Feld 270, D-69120 Heidelberg, Germany. E-mail: gebhard.haberhauer@urz.uni-heidelberg.de; Fax: +49 (0) 6221 544205

Received (in Cambridge, UK) 28th April 2004, Accepted 29th June 2004
First published as an Advance Article on the web 6th August 2004

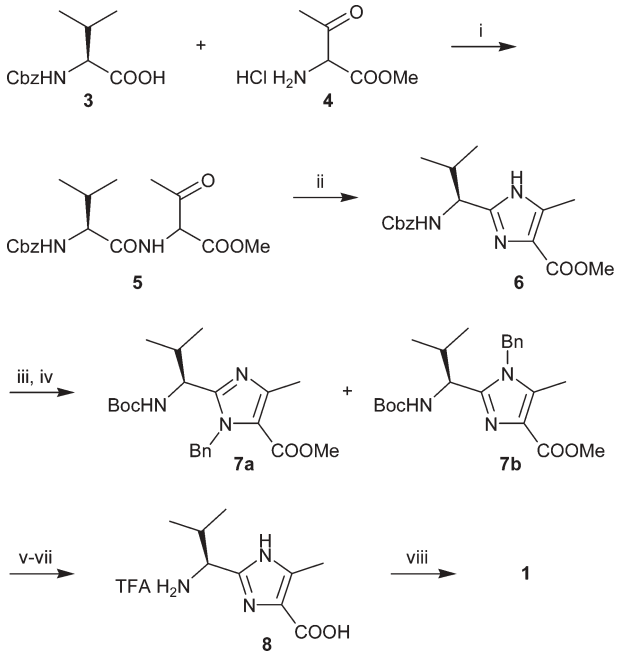
A novel C_3-symmetric scaffold has been efficiently synthesized exhibiting the property that variable receptor arms can be easily attached by simple alkylation reactions; the utility of the scaffold as a skeleton for large receptors has been examined with a corresponding tris(bipyridyl) derivative toward phloroglucinol.

The use of receptor molecules with pre-organized ligands for the effective binding of guest molecules is well documented.[1] A suitable pre-organization of functional groups and conformational constraint can be achieved by controlling the stereochemistry through steric hindrance of the substituents around a rigid platform. For example, the exceptional stereochemical characteristic of hexasubstituted benzene derivatives is leading many chemists to use such persubstituted systems as platforms for the construction of rather small receptor systems.[2]

In this paper, we wish to report the synthesis of the C_3-symmetric molecular scaffold **1** which can be easily transformed into enlarged receptors **2** using standard alkylation conditions (Scheme 1).[3]† The advantage of this concept is that starting from a single scaffold (**1**), a variety of large three-armed receptors (**2**) can be synthesized in a simple manner by attaching three pre-formed receptor arms (RCH_2Br) to platform **1**. Due to steric repulsion between the isopropyl groups and the arms, the preferred conformation of **2** should be the *three-down* conformation, *i.e.* all three arms are oriented opposite to the isopropyl groups of the adjacent α-C-atoms. Furthermore, the isopropyl groups of the α-C-atoms in **1** and **2** guarantee that the azole moieties of the macrocycle do not form a single plane but have a cone-like structure.[4] This deviation from planarity should result in the three arms (*R*) of **2** being substantially equidistant without divergence to each other in the case of the *three-down* conformation, making them more suitable for the inclusion of substrates. The synthetic pathway to platform **1** is shown in Scheme 2. As starting material we used Cbz-protected L-valine (**3**) which was activated as mixed anhydride using isobutyl chloroformate and coupled to the keto ester **4** at −25 °C.[4] The resulting amidoketone **5** was condensed to the imidazole **6** with ammonium trifluoroacetate which was formed *in situ* from methanolic ammonia and trifluoroacetic acid in refluxing xylenes with azeotropic removal of water. Saponification of the methyl ester of imidazole **6** without racemization at the α-C-atom of the L-valine-based moiety failed. To overcome this problem, we replaced the Cbz-group by the Boc-group and protected the NH of the imidazole ring with a benzyl group. The methyl esters of the resulting benzyl imidazoles **7a,b** can be simply saponified by using aqueous NaOH providing the corresponding carbocyclic acids in 95% yield. Subsequent removal of the benzyl group at the imidazole ring by hydrogenolysis followed by amine deprotection using trifluoroacetic acid gave the amino acid **8**. Several methods for a one-pot trimerization of the imidazole **8** were examined. The most advantageous route proved to be the activation of the acid group with pentafluorophenyl diphenylphosphinate (FDPP) in the presence of an excess of Hünig's base in acetonitrile under high dilution conditions (0.05 M) at room temperature. This method provided scaffold **1** in a satisfactory yield (35%).



Scheme 1 Transformation of C_3-symmetric scaffold **1** into the three-armed platforms **2**.



Scheme 2 Synthesis of scaffold **1**. *Reagents and conditions*: (i) ClCOO*i*-Bu, NMM, THF, −25 °C, 80%; (ii) NH_3, TFA, xylenes, reflux, 72%; (iii) Boc_2O, H_2, $Pd(OH)_2$, THF, 95%; (iv) BnBr, K_2CO_3, CH_3CN, reflux 2h, 51% for **7a**, 32% for **7b**; (v) 2 M NaOH, MeOH–dioxane, 95%; (vi) H_2, $Pd(OH)_2$, MeOH; (vii) TFA, DCM, 90% (two steps); (viii) FDPP, *i*-Pr_2NEt, CH_3CN, rt, 35%.

DOI: 10.1039/b406335j

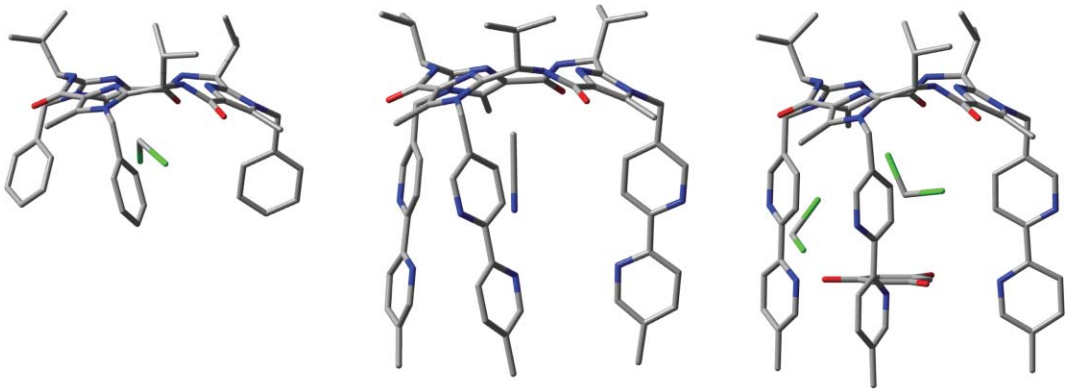


Fig. 1 Crystal structures of (a) the three-armed receptor **2a** with dichloromethane guest, (b) the free receptor **2e** with acetonitrile guest and (c) the complex of receptor **2e** with phloroglucinol and dichloromethane; all hydrogen atoms and some representations of disordered dichloromethane have been omitted for clarity. In the case of (b) a second independent molecule with some disorder is omitted as well as the acetonitrile of solvation. In all cases the receptors show threefold crystallographic symmetry.

To determine the preferred stereochemical orientation of the arms of platforms **2**, we performed a conformational search for **2a** by molecular mechanics calculations with Monte Carlo minimization procedures, using the MM2* force field as implemented in the MacroModel program.[5] As was expected, the low-energy conformation of **2a** is the *three-down* conformation. The lowest-energy *two-down–one-up* conformation is calculated to be 4.4 kJ mol^{-1} higher in energy. For further stereochemical investigations, we examined the solid-state structures of **2a** and **2e**. The obtained X-ray structures confirmed in both cases that the *three-down* conformation was preferred and the arms were almost equidistant to each other (Fig. 1).‡ In platform **2a**, which was crystallized from methylene chloride, the shortest distance between two phenyl arms is about 8 Å resulting in the formation of a cavity enclosing a solvent molecule. The distance and the orientation of the bipyridyl arms in **2e**, which was crystallized from acetonitrile, are essentially the same as in **2a**.

In order to prove the utility of the platforms **2** as large receptors, we examined the behaviour of **2e** toward phloroglucinol. Like comparable tris(bipyridyl) cages reported by other groups,[6] **2e** was found to solubilise phloroglucinol in dichloromethane and chloroform. Unfortunately, due to the insolubility of this guest molecule in $CDCl_3$, it was impracticable to determine the stability constant of the formed complex by NMR titration. However, in a $CDCl_3$ solution containing 10% acetonitrile, which is known to lower substantially binding constants for hydroxy-substituted benzenes,[7] the NMR titration resulted in a binding constant of 680 ± 85 M^{-1}. Furthermore, we were able to grow single crystals of this complex from CD_2Cl_2 (Fig. 1).‡ The three bipyridyl arms take hold of the pholoroglucinol by forming three hydrogen bridges. These hydrogen bridges are formed exclusively by the nitrogen atoms of the pyridyl rings remotest from the scaffold. From the X-ray structure it cannot be deduced whether the nitrogen atoms of the pyridyl rings neighbouring the scaffold point into the interior of the receptor or to the exterior. The cavity between the phloroglucinol and the platform is filled with solvent molecules. To the best of our knowledge, receptor **2e** is the first non-cage receptor which is able to encapsulate phloroglucinol. Moreover, this is the first X-ray structure of an encapsulated phloroglucinol.

Finally, the versatility of the present approach to large receptor synthesis should be emphasised. The ready availability of platform **1** will allow us to produce a series of three-armed receptors suitable for binding other selected guests.

We thank the Deutsche Forschungsgemeinschaft for support and Dr Andreea Schuster for assistance.

Notes and references

† Synthesis of platforms **2**: To a solution of **1** (0.20 mmol) in acetonitrile (30 ml) were added K_2CO_3 (1.50 mmol) and RCH_2Br (0.75 mmol) at room temperature and the mixture was stirred at reflux for 8 h. 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 accomplished by chromatography on silica gel (DCM–AcOEt–MeOH, 75 : 25 : 3) to yield **2** (45–85%) as white solids.

‡ *Crystal data*: for $C_{48}H_{57}N_9O_3{\cdot}CH_2Cl_2$ (**2a**): $M = 892.95$, hexagonal, space group $P6_3$, $Z = 2$, $a = 13.5462(4)$, $b = 13.5462(4)$, $c = 14.8813(9)$ Å, $V = 2364.9(2)$ Å^3, $\rho = 1.254$ g cm^{-3}, $T = 100(2)$ K, $\theta_{max} = 25.68°$, radiation Mo Kα, $\lambda = 0.71073$ Å, $\mu = 0.19$ mm^{-1}, 20642 reflections measured, 3014 unique ($R_{int} = 0.042$), 2989 observed ($I > 2\sigma(I)$), $R1(F) = 0.126$, $wR(F^2) = 0.253$.‡ For $C_{63}H_{69}N_{15}O_3{\cdot}2{*}CH_3CN$ (**2e**): $M = 1166.44$, trigonal (rhombohedral axes), space group $R3$, $Z = 2$, $a = 22.2326(1)$, $b = 22.2326(1)$, $c = 22.2326(1)$ Å, $\alpha = 36.035(1)$, $\beta = 36.035(1)$, $\gamma = 36.035(1)°$, $V = 3401.81(3)$ Å^3, $\rho = 1.139$ g cm^{-3}, $T = 200(2)$ K, $\theta_{max} = 21.93°$, radiation Mo Kα, $\lambda = 0.71073$ Å, $\mu = 0.07$ mm^{-1}, 21493 reflections measured, 5458 unique ($R_{int} = 0.0546$), 4296 observed ($I > 2\sigma(I)$), $R1(F) = 0.069$, $wR(F^2) = 0.168$.‡ For $C_{63}H_{69}N_{15}O_3{\cdot}C_6H_6O_3{\cdot}2{*}CH_2Cl_2$ (complex **2e** and phloroglucinol): $M = 1380.29$, trigonal (hexagonal axes), space group $R3$, $Z = 3$, $a = 12.9951(5)$, $b = 12.9951(5)$, $c = 40.694(3)$ Å, $V = 5951.5(6)$ Å^3, $\rho = 1.155$ g cm^{-3}, $T = 100(2)$ K, $\theta_{max} = 28.27°$, radiation Mo Kα, $\lambda = 0.71073$ Å, $\mu = 0.20$ mm^{-1}, 20311 reflections measured, 6464 unique ($R_{int} = 0.0323$), 6003 observed ($I > 2\sigma(I)$), $R1(F) = 0.073$, $wR(F^2) = 0.199$. CCDC 239318–239320. See http://www.rsc.org/suppdata/cc/b4/b406335j/ for crystallographic data in .cif format.

1 J.-M. Lehn, *Supramolecular Chemistry: Concepts and Perspectives*, VCH, Weinheim, 1995.
2 For some recent examples see: B. J. Postnikova and E. V. Anslyn, *Tetrahedron Lett.*, 2004, **45**, 501; S.-G. Kim, K.-H. Kim, Y. K. Kim, S. K. Shin and K. H. Ahn, *J. Am. Chem. Soc.*, 2003, **125**, 13819; G. Hennrich and E. V. Anslyn, *Chem.–Eur. J.*, 2002, **8**, 2218.
3 For recent examples of C_3-symmetric platforms see: S. Kubik, *J. Am. Chem. Soc.*, 1999, **121**, 5846; S. R. Waldvogel, R. Fröhlich and C. A. Schalley, *Angew. Chem., Int. Ed.*, 2000, **39**, 2472.
4 G. Haberhauer and F. Rominger, *Tetrahedron Lett.*, 2002, **43**, 6335.
5 MacroModel: F. Mohamadi, N. G. J. Richards, W. C. Guida, R. Kiskamp, M. Lipton, C. Caufield, G. Chang, T. Hendrickson and W. C. Still, *J. Comput. Chem.*, 1990, **112**, 440; MM2: N. L. Allinger, *J. Am. Chem. Soc.*, 1977, **99**, 8127; Monte Carlo (MCMM): G. Chang, W. C. Guida and W. C. Still, *J. Am. Chem. Soc.*, 1989, **111**, 4379.
6 I. M. Atkinson, A. R. Carroll, R. J. A. Janssen, L. F. Lindoy, O. A. Matthews and G. V. Meehan, *J. Chem. Soc., Perkin Trans. 1*, 1997, 295; F. Ebmeyer and F. Vögtle, *Angew. Chem., Int. Ed. Engl.*, 1989, **28**, 79.
7 C. F. Martens, R. J. M. Klein Gebbink, M. C. Feiters and R. J. M. Nolte, *J. Am. Chem. Soc.*, 1994, **116**, 5667.