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

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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 (RCH₂Br) 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 -Catoms. Furthermore, the isopropyl groups 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

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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 2 Synthesis of scaffold 1. *Reagents and conditions*: (i) CICOO*i*-Bu, NMM, THF, -25 °C, 80%; (ii) NH₃, TFA, xylenes, reflux, 72%; (iii) Boc₂O, H₂, Pd(OH)₂, THF, 95%; (iv) BnBr, K₂CO₃, CH₃CN, reflux 2h, 51% for 7a, 32% for 7b; (v) 2 M NaOH, MeOH–dioxane, 95%; (vi) H₂, Pd(OH)₂, MeOH; (vii) TFA, DCM, 90% (two steps); (viii) FDPP, *i*-Pr₂NEt, CH₃CN, rt, 35%.



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 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 CDCl₃, it was impracticable to determine the stability constant of the formed complex by NMR titration. However, in a CDCl₃ 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 CD₂Cl₂ (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.

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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 RCH₂Br (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 MgSO₄ 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 C₄₈H₅₇N₉O₃·CH₂Cl₂ (**2a**): M = 892.95, hexagonal, space group *P*6₃, Z = 2, a = 13.5462(4), b = 13.5462(4), c = 14.8813(9) Å, V = 2364.9(2) Å³, $\rho = 1.254$ g cm⁻³, T = 100(2) K, $\theta_{max} = 25.68^{\circ}$, 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 C₆₃H₆₉N₁₅O₃·2*CH₃CN (**2e**): M = 1166.44, trigonal (rhombohedral axes), space group *R*3, Z = 2, a = 22.2326(1), b = 22.2326(1), c = 22.2326(1) Å, $\alpha = 36.035(1)$, $\beta = 36.035(1)$, $\gamma = 3401.81(3)$ Å³, $\rho = 1.139$ g cm⁻³, T = 200(2) K, $\theta_{max} = 21.93^{\circ}$, 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 C₆₃H₆₉N₁₅O₃·C₆H₆O₃·2*CH₂Cl₂ (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) Å³, $\rho = 1.155$ g cm⁻³, T = 100(2) K, $\theta_{max} = 28.27^{\circ}$, 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.rs.org/suppdata/cc/b4/b406335j/ for crystallographic data in .cif format.

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