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Synthesis of Asymmetric Septi-(*p*-Phenylene)s

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Abstract In this *Letter*, we describe the synthesis of two amphiphilic septi(*p*-phenylene)s. One terminus of each rigid-rod scaffold is linked through a spacer to a hydrophilic IDA-subunit, the two benzenes at the other terminus carry hydrophobic substituents of different size. These synthetic receptor models are expected to mimic biological processes that occur at cell membranes.

Cell-surface receptors are membrane proteins that bind an external ligand to initiate a response in the cell. For example, the acetylcholine receptor (a transmitter-gated ion channel) and the LDL receptor (a cholesterol endocytosis mediator) are both located in the plasma membrane with the ligand-binding site exposed to the extracellular medium.[1] To understand the molecular mechanism of these complex processes, model studies with synthetic analogs will be essential. Recently, we have introduced a new strategy for the modeling of cell membrane processes that takes advantage of the well-defined organization of rigid-rod molecules in lipid bilayers.[2-4] These highly ordered systems have already been applied for the development of unprecedented, nonpeptide proton channel models which mimic the hydrogen-bonded chain mechanism involved in bioenergetic processes.[3] Here, we use the same strategy for the design of synthetic cell-surface receptor models that allow us, in principle, to study various ligand-dependent signal transduction processes (Figure 1), and report the synthesis of two prototypes, i.e., receptor models **1** (Scheme 1) and **2** (Scheme 2).

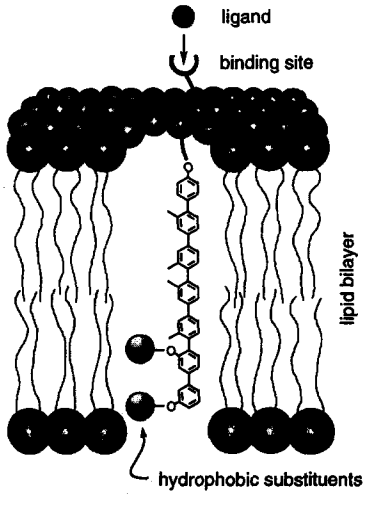

Figure 1

The design of the rigid rod-shaped cell-surface receptor models **1** and **2** is shown in Figure 1. One terminus of asymmetric septi(*p*-phenylene)s was linked through a spacer to iminodiacetate (IDA). Among various possibilities, we selected this synthetic ligand-binding site because IDA chelates Cu(II) ($K_a \approx 10^{11}$ M^{-1}) and other divalent cations, and IDA-Cu(II) complexes selectively bind histidine (His) containing peptides ($K_a \approx 10^{3.5}$ M^{-1}).[5] Recently, these selective interactions have been widely applied, most noteworthily to stabilize secondary structures of peptides[6] and to immobilize proteins on lipid mono- and bilayers. Two years ago, Arnold's group further observed

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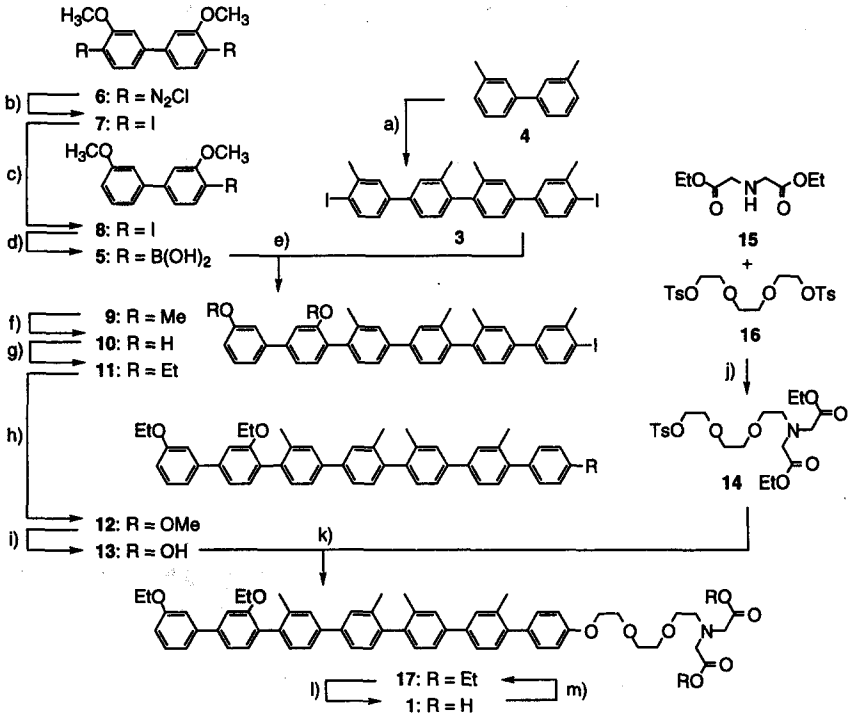
Cu(II)-poly(His)-induced changes in the lateral distribution of IDA-lipid conjugates in lipid bilayers.[5] Thus, Cu(II) and Cu(II)-poly(His) are two possible ligands to control, respectively, the charge and the assembly of our new, potentially multifunctional cell-surface receptor models.

On the other terminus of the septi(*p*-phenylene)s we attached hydrophobic substituents of different size. Transmembrane orientation of the rigid-rod molecule should place this hydrophobic "bulk" in the inner leaflet of the lipid bilayer. We anticipate that variation of the size of these substituents will be crucial in manipulating membrane curvature and thus differentiating between membrane processes such as ligand-gated pore formation,[7] ligand-dependent membrane fusion,[8] and receptor-mediated endocytosis *via* the clathrin-coated pit-inhibited pathway.[9] Here, we focused on the synthesis of two extreme cases, receptor **1** with small terminal substituents and **2** with large adamantaneethyloxy groups.

Scheme 1

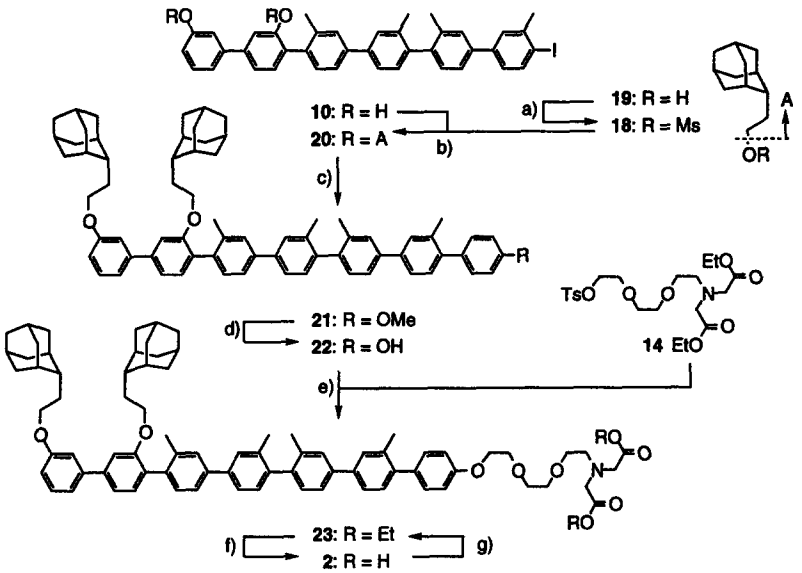


a) see ref. 10, 3 steps, 26%; b) KI, H_2O, 0°, 14 h, 68%; c) *n*-BuLi, THF, 0°, 30 min, then H_2O, 67%; d) see ref. 2, 75%; e) $Pd(PPh_3)_4$, Na_2CO_3, toluene, 8 h, 80-100°, 50%; f) BBr_3, CH_2Cl_2, 14 h, -78° → rt, 93%; g) EtBr, Cs_2CO_3, DMF, 14 h, 80-100°, 93%; h) 4-methoxyphenylboronic acid, $Pd(PPh_3)_4$, Na_2CO_3, toluene, 8 h, 80-100°, 86%; i) $LiPPh_2$, THF, 24 h, rt, 72%; j) NEt_3, MeCN, THF, 24 h, 80°, 69%; k) Cs_2CO_3, DMF, 14 h, 55°, 63%; l) aq. NaOH, THF/MeOH, 1 h, rt, quant.; m) EtOH, EDC, CH_2Cl_2, 0° → rt, 4 h, 75%.

Both receptor models were synthesized from bisiodotetratoluene **3**, which was prepared from bitoluene **4** in three steps following the pioneering Mainzer-protocols (Scheme 1).[10] The second starting material, boronic acid **5**, was found to be more easily accessible from the diazonium salt **6** than from bianisole.[2] Iodo-de-

diazoniation of "fast blue B salt" **6** with KI readily gave diiodide **7**, which was partially dehalogenated with *n*-BuLi to afford iodide **8** in an overall yield of 46% (compared to 26% for direct iodination of bianisole). The replacement of the aromatic iodide in **8** by the boronic acid in **5** was done as before.[2] Suzuki-coupling[11] of boronic acid **5** and diiodide **3** gave monoiodide **9** in 50% yield. At this stage, the methyl ethers were cleaved with BBr_3. For receptor model **1**, alkylation of diphenol **10** with ethyl bromide afforded the aryl ethyl ether **11**, which was elongated with 4-methoxyphenylboronic acid to give heptamer **12** in 86% yield. Selective cleavage of the aryl methyl ether in **12** with $LiPPh_2$ yielded aryl ethyl ether **13**.[12] The tosyl-activated, ester-protected spacer-binding site conjugate **14** was prepared in one step from amine **15** and ditosylate **16**. Alkylation of the rigid-rod molecule **13** with diester **16** yielded conjugate **17**. Base-catalyzed deprotection of **17** gave receptor model **1** in overall 14 steps.

Scheme 2



a) MsCl, CH_2Cl_2, NEt_3, 5 min, 0°, 93%; b) Cs_2CO_3, DMF, 14 h, 80-100°, 55%; c) 4-methoxyphenylboronic acid, $Pd(PPh_3)_4$, Na_2CO_3, toluene, 8 h, 80-100°, 81%; d) $LiPPh_2$, THF, 24 h, rt, 43%; e) Cs_2CO_3, DMF, 14 h, 55°, 70%; f) aq. NaOH, THF/MeOH, 1 h, rt, quant.; g) EtOH, EDC, CH_2Cl_2, 0° → rt, 4 h, 77%.

The synthesis of receptor model **2** (Scheme 2) diverged from that for **1** at the stage of hexamer **10**. Alkylation of **10** with mesylate **18**, prepared from the adamantane derivative **19** in 93% yield, gave hexamer **20**. Application of the three step procedure developed for **1**, namely Suzuki-coupling (to yield **21**), selective aryl methyl ether cleavage (to give **22**), and coupling with tosylate **14** gave diester **23**, which was deprotected to give **2** in overall 15 steps.

Not surprisingly, we were so far unable to get satisfactory spectroscopic data for RP-HPLC purified amphiphiles **1** and **2**. The ^1H NMR spectra in benzene-d_6, pyridine-d_5, and various CD_3OD-$CDCl_3$ mixtures gave qualitatively correct, but broad signals. MALDI- and FAB-MS measurements failed as well. Only the

fluorescence properties of both models (excitation: 307 nm, emission: 380 nm) were as expected. To prove the structure of **1** and **2**, both diacids were re-esterified with ethanol. The obtained products were identical with diesters **17** and **23**, respectively.[13] Extensive studies on the activity of the synthetic receptor models **1** and **2** are ongoing and will be reported elsewhere.

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13. All products except **1** and **2** (see text) gave satisfactory spectroscopic data. For example: **17:** ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60 - 7.49 (m, 7H), 7.40 - 7.18 (m, 13H), 6.99 (d, 2H, J = 8.5 Hz), 6.91 (br. dd, 1H, ^3J = 8.1 Hz, ^4J = 2.1 Hz), 4.18 (t, 2H, J = 4.8 Hz), 4.16 (q, 4H, J = 7.0 Hz), 4.13 (q, 2H, J = 6.9 Hz), 4.10 (q, 2H, J = 6.9 Hz), 3.89 (t, 2H, J = 4.9 Hz), 3.73 (t, 2H, J = 3.0 Hz), 3.66 - 3.56 (m, 8H); 3.00 (t, 2H, J = 5.7 Hz), 2.37 (s, 3H), 2.30 (s, 3H), 2.20 (s, 6H), 1.47 (t, 3H, J = 6.9 Hz), 1.32 (t, 3H, J = 6.9 Hz), 1.26 (t, 6H, J = 7.0 Hz). FAB-HRMS: calc. for $C_{64}H_{72}NO_9$: 998.52069. Found: 998.51483. **23:** ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.59 - 7.49 (m, 7H), 7.40 - 7.16 (m, 13H), 6.99 (d, 2H, J = 8.5 Hz), 6.91 (br. dd, 1H, ^3J = 8.1 Hz, ^4J = 2.1 Hz), 4.19 (t, 2H, J = 4.8 Hz), 4.16 (q, 4H, J = 7.0 Hz), 4.12 (t, 2H, J = 7.4 Hz), 4.07 (t, 2H, J = 7.0 Hz), 3.89 (t, 2H, J = 4.8 Hz), 3.73 (t, 2H, J = 3.0 Hz), 3.67 - 3.57 (m, 8H); 3.00 (t, 2H, J = 5.6 Hz), 2.37 (s, 3H), 2.28 (s, 3H), 2.20 (s, 6H), 2.05 - 1.95 (m, 3H), 1.90 - 1.84 (m, 3H), 1.77 - 1.41 (m, 28H), 1.26 (t, 6H, J = 7.0 Hz). FAB-HRMS: calc. for $C_{84}H_{100}NO_9$: 1266.73987. Found: 1266.74525.