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A Novel Synthetic Pathway for Paracyclophane Receptors

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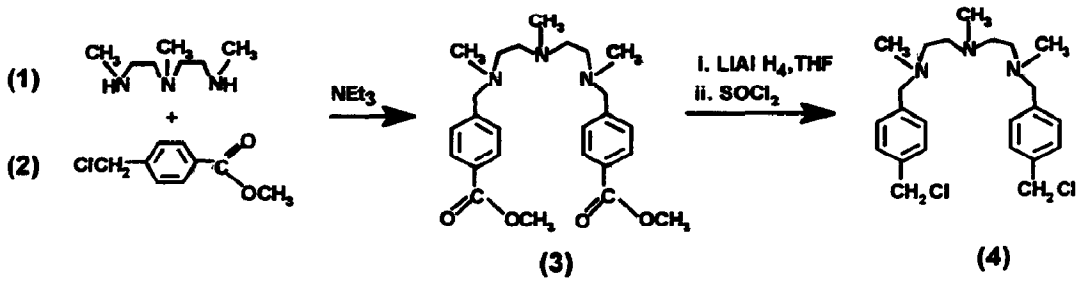
Abstract. The synthesis of 1,4,7-trimethyl-1,7-bis(p-(α-chloromethyl)benzyl)-1,4,7-triazaeptane is reported. This compound behaves as a versatile building block for the assembly of 1,4-dibenzo aza or oxa-aza macrocycles.

The design of polyammonium receptors containing structural features that impart high selectivity in the recognition of different guests has received much attention in the past several years.[1-5] Aromatic subunits are often introduced as integral parts of the receptors. Polyammonium receptors containing two or more 1,4-benzo moieties have been most often used as water-soluble receptors with hydrophobic cavities that can also interact with guests by π-stacking or π-cation interactions. Particularly, great effort has been devoted to design and synthesis of macrocyclic or macropolycyclic receptors containing 1,4-benzo subunits as rigid spacers to link two polyamine chains or two polyaza-crown structures to form ditopic macrocycles or cryptands.[6-12] In most cases, the aromatic spacers bridge two equal aza or oxa-aza binding moieties.

We are interested in design and synthesis of macrocyclic receptors characterized by aromatic spacers that link two binding subunits showing different coordination features. With this aim, we have synthesized the precursor molecule 4, which contains a N_3 moiety. The interest for this subunit is mainly due to its binding ability towards transition metal ions. The resulting complexes are characterized by an unsaturated coordination sphere and behave as receptors for small molecules or anionic species.[13-19]

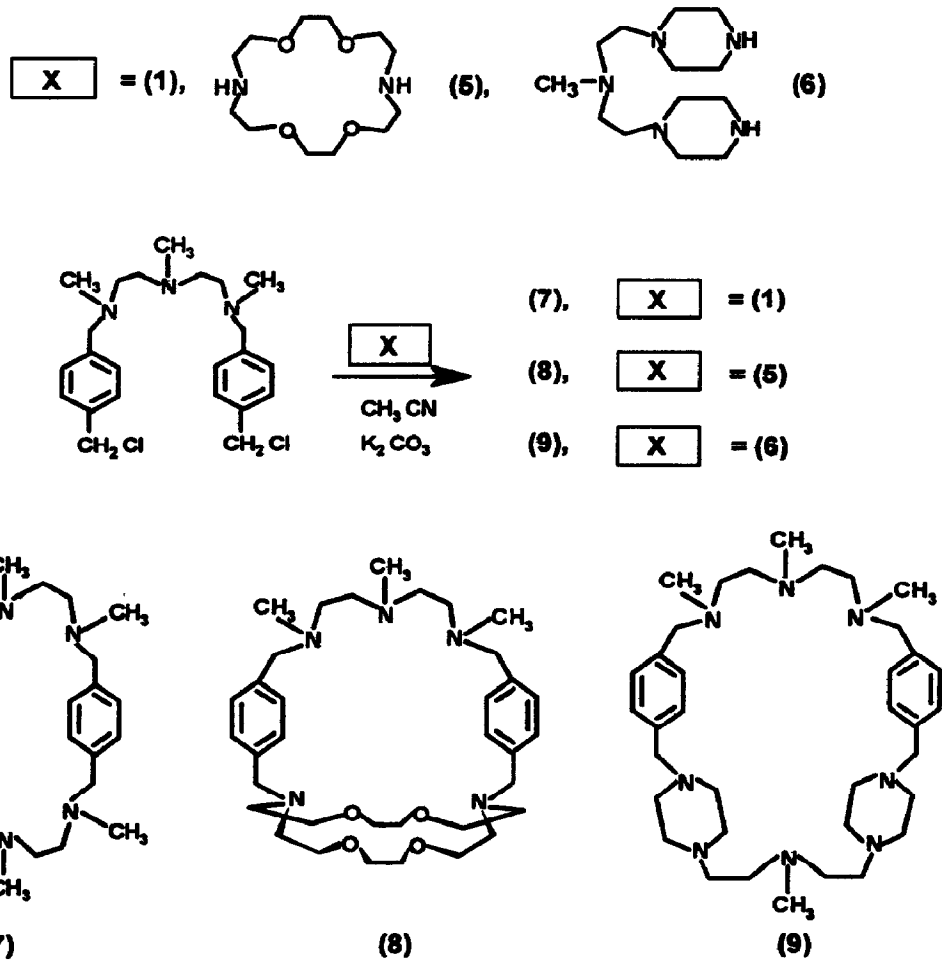


Scheme 1

Such a mode of complexation can lead to an activation of the coordinated molecule. Furthermore, the binding and activation ability of the N_3 moiety is strongly influenced by the remaining macrocyclic framework.

Methyl p-(α-chloromethyl)benzoate **2** was prepared by following the procedure reported by Codington et al. for the analogous bromo derivative.[20]

Reactions of **1**[21] with methyl p-(α-chloromethyl)benzoate **2** or methyl p-(α-bromomethyl)benzoate carried out in usual mild conditions (CH_3CN in the presence of a base) leads to the diesther **3** in very poor yields. Better yields are gained by using more drastic conditions (NEt_3 as solvent, 100 °C, 7h). After removing the solvent, the resulting yellowish oil was chromatographated on neutral alumina (eluent $CHCl_3$) to yield **3** as a colorless oil (70%).



Scheme 2

The bischloromethyl derivative **4** is obtained from **3** with standard methods (Scheme 1).

Reduction of the diesther **3** was carried out with $LiAlH_4$ in THF (at reflux, 15 h). After cooling at room temperature, 15% NaOH aqueous solution was added dropwise. The suspension was filtered and the resulting solution was evaporated to dryness to yield the corresponding dialcohol (90 %). This compound can be purified as trihydrochloride salt (m. p. > 250 °C). Compound **4** is obtained by treating the dialcohol with $SOCl_2$ in $CHCl_3$. The resulting suspension was heated at 60 °C for 4h. After cooling at room temperature, the suspension was filtered to give **4**·3HCl as a white solid (93 %, m.p. 220-230 °C, with decomposition) (Scheme 1).

4, as unprotonated amine, is not stable at air exposure and immediately hydrolyzes in water or in not anhydrous solvents. On the other hand, its salts are much more stable and can be easily manipulated. For this reason, it has been used in the following cyclization reactions as trihydrochloride salt.

Compound **4** is a versatile building block for the assembly of macrocyclic or macropolycyclic structures.

Reaction of **4** with compounds **1**, **5** and **6**[22] in CH_3CN in the presence of K_2CO_3, a modification of the method of Richman and Atkins,[23] affords the macrocycles **7**, **8** and **9**, respectively (Scheme 2). In a typical cyclization reaction, a suspension of **4**·3HCl (1 mmol) in anhydrous CH_3CN (50 cm^3) was added dropwise over a period of 7 h to a refluxing suspension of the compounds **1**, **5** or **6** (1 mmol) in anhydrous CH_3CN (50 cm^3) in the presence of potassium carbonate as base (10 mmol). Refluxing was continued for 7 h and after a purification by chromatography (alumina att. II/III, eluent $CHCl_3$/MeOH 100:1.5) the cyclophanes **7-9** were obtained in satisfactory yields (**7**: 35%; **8**: 18%; **9**: 26%). All compounds showed the expected spectroscopic properties and satisfactory elemental analyses and mass spectra.[24]

In conclusion, **4** results a versatile precursor for macrocyclic or macropolycyclic receptors. The same synthetic procedure can produce other *p*-cyclophane receptors by substitution of the **X** fragment with other reagents in the cyclization reaction, originating macrocyclic molecules characterized by two 1,4-benzo units that link two different binding moieties.

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(24) (7): ^{1}H NMR δ ($CDCl_3$) 2.16 (s, 12 H), 2.22 (s, 6 H), 2.41 (m, 16 H), 3.30 (s, 8 H), 7.25 ppm (s, 8 H); ^{13}C NMR 42.8, 43.7, 52.4, 52.7, 61.5, 130.9, 137.4 ppm. MS (FAB): 496 ($M + H^+$). Anal. Calcd for $C_{30}H_{50}N_6$: C, 72.83; H, 10.18; N, 16.99. Found: C, 72,5; H, 10.3; N, 16.7.
(8): ^{1}H NMR δ ($CDCl_3$) 2.15 (s, 3 H), 2.17 (s, 6 H), 2.44 (m, 8 H), 2.88 (t, 8 H), 3.43 (s, 4 H), 3.56 (s, 8 H), 3.60 (t, 8 H) 3.64 (s, 4 H), 7.17 (d, 4 H) 7.27 ppm (d, 4 H); ^{13}C NMR 43.0, 43.3, 54.5, 54.7, 55.3, 59.8, 62.4, 70.0, 70.9, 128.6, 128.9, 137.4, 138.6 ppm. MS (FAB): 613 ($M + H^+$). Anal. Calcd for $C_{35}H_{57}N_5O_4$: C, 68.70; H, 9.39; N, 11.44, Found: C, 68 6; H, 9.5; N, 11.4.
(9): ^{1}H NMR δ ($CDCl_3$) 2.19 (s, 3 H), 2.20 (s, 6 H), 2.23 (s, 3 H), 2.47 (m, 32 H), 3.44 (s, 4 H), 3.47 (s, 4 H), 7.21 (m, 8 H); ^{13}C NMR 42.8, 43.0, 43.1, 52.9, 53.3, 54.4, 54.7, 55.7, 56.1, 62.5, 62.9, 128.9, 129.3, 136.5, 137.8 ppm. MS (FAB): 606 ($M + H^+$). Anal. Calcd for $C_{36}H_{60}N_8$: C, 71.48; H, 10.00; N, 18.52. Found: C, 71.5; H, 10 1; N, 18.4

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