ORGANIC LETTERS

2002
Vol. 4, No. 5
795−798

Novel C_{3V}-Symmetric Tripodal Scaffold, Triethyl *cis,cis,cis*-2,5,8-Tribenzyltrindane-2,5,8-tricarboxylate, for the Construction of Artificial Receptors

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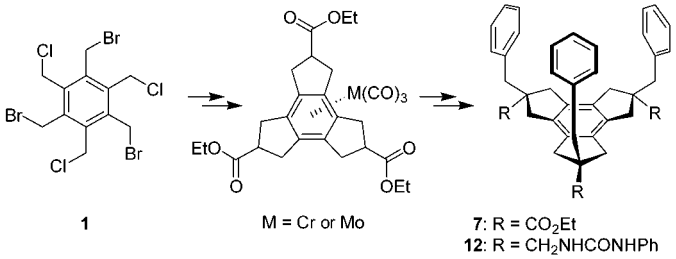
Received December 24, 2001

ABSTRACT



A novel C_{3V}-symmetric scaffold, trindane 7, has been efficiently synthesized from 1,3,5-tris(bromomethyl)-2,4,6-tris(chloromethyl)benzene (1) in six steps with 47% overall yield. The control of all-*syn* stereochemistry in the tribenzylation step has been achieved by blocking one side of the trindane ring as metal carbonyl complexes. The potential utility of trindane 7 as a receptor skeleton has been examined with a urea derivative 12 toward several anionic guests.

Design and synthesis of artificial receptors for selective recognition of bioactive substrates have received considerable interest in recent years.[1] Receptor molecules with preorganized ligands are useful for the effective binding of guest molecules.[2] To achieve this objective, the ligands are usually attached to rigid skeletons such as calixarenes, resorcinarenes, 1,3,5-trialkylbenezenes, Tröger's base, and the steroid nucleus.[3−7]

We were interested in the receptors that have three ligands arranged in a fixed, "all-*syn*" stereochemistry, which would be useful for the recognition of oxoanions such as nitrate, carbonate, chlorate, sulfate, and phosphate ions. Hamilton and Choi have reported notable C_3-symmetric macrocyclic anion receptors with convergent hydrogen bonding functionalities, which bind tetrahedral anions with high selectivity and affinity.[8]

Described here is a development of a novel synthetic route to the C_{3V}-symmetric scaffold that has three potential binding sites fixed on the same side and its urea derivative as an anion receptor.

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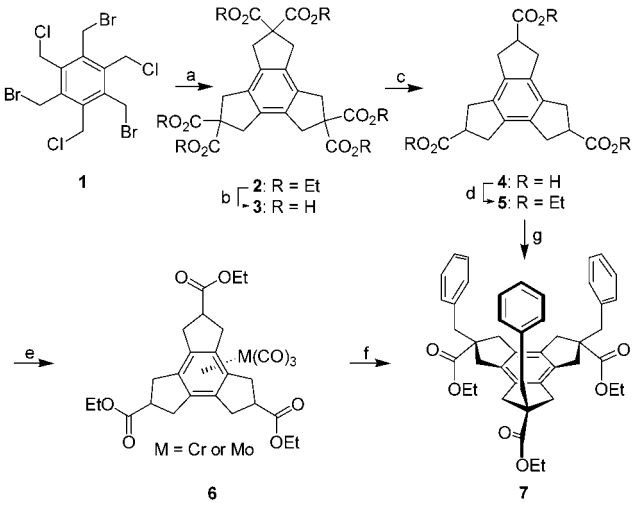
10.1021/ol017294t CCC: $22.00
Published on Web 02/13/2002

Scheme 1[a]



[a] Reagents and conditions: (a) $CH_2(CO_2Et)_2$, EtONa, EtOH, reflux, 80%; (b) KOH, EtOH/H_2O, reflux, 98%; (c) pyridine, reflux, 98%; (d) EtOH, H_2SO_4, reflux, 94%; (e) $Cr(CO)_6$, *n*-Bu_2O/THF, reflux, 95%, or $Mo(CO)_6$, 90%; (f) LDA, BnBr, THF, −30 °C to rt, then I_2, 68%; (g) LDA, BnBr, THF, −30 °C to rt, 21%.

The scaffold **7** has an extended feature of recently reported, C_3-symmetric tripodal receptors based on 1,3,5-tris(halomethyl)-2,4,6-trialkylbenzene frames.[5] A notable difference between the two types is in the preorganization of the ligand groups: In the first case the ligands are fixed in the same side (all-*syn* form), whereas in the latter case a similar conformation of the ligands (the so-called *ababab* conformation) can be obtained through a conformational equilibrium.

The first type of receptor has attracted synthetic interest in view of its apparent advantage in constructing container molecules.[9] We have devised an efficient approach to control the all-*syn* stereochemistry using metal carbonyl complexation. Our approach to trindane **7** is illustrated in Scheme 1. The known hexacarboxylate **2** can be synthesized in high yield, starting from 1,3,5-tris(bromomethyl)-2,4,6-tris(chloromethyl)benzene (**1**), which was in turn synthesized from mesitylene through chloromethylation followed by radical bromination. Thus, treatment of **1** with sodium enolate of diethyl malonate in ethanol gave hexaester **2** in 80% yield, a significantly improved yield from the procedure of Holý and co-workers (64% yield)[10] in which hexakis(bromomethyl)benzene was used as the starting material. Polymeric side products were readily removed by column chromatography on silica gel. The improved yield may result from a more selective alkylation of the enolate, reducing side products. Saponification of hexaester **2**, followed by decarboxylation of the resultant hexacarboxylic acid (**3**), and subsequent Fischer esterification of **3** in ethanol gave a mixture of *cis,cis,cis*- and *cis,trans,trans*-trindane-2,5,8-tricarboxylic ester **5** in 90% overall yield.

Next, direct benzylation of the ester enolate of **5**, formed by treatment with LDA in THF, gave 21% of the desired *cis,cis,cis*-2,5,8-tribenzyltridane **7** and 75% of the *cis,trans,-trans*-isomer after column chromatography. The yield of all-*syn* isomer **7** is close to a statistical value of 25%, obtained by assuming independent alkylations. One way to improve the stereoselectivity of the alkylation step is to block one face of the trindane skeleton by metal complexation. This idea was realized in the following experiments. Treatment of triester **5** with $Cr(CO)_6$ or $Mo(CO)_6$ gave the corresponding benzene-coordinated metal tricarbonyl complexes **6**, from which all-*syn* isomer **7** was prepared in a greatly improved yield (68%) by treatment with LDA followed by benzyl bromide. Thus, the metal carbonyl moiety in the trindane system can afford a steric barrier toward the approaching electrophile to the π-face of the ester enolate in the same side. Therefore, the electrophile approaches from the opposite side, providing the product with all-*syn* stereochemistry. Both metal complexes gave similar results.[11] The metal carbonyl group in complex **6** was decomplexed prior to isolation by addition of iodine; otherwise, a complex mixture resulted from partial decomposition of the metal carbonyl during the chromatographic separation.

The *cis,cis,cis*-stereochemistry of triester **7** was confirmed by NMR analyses: Two sets of doublets (δ 2.88 and 3.22 ppm, ^2J = 15.9 Hz) from the two diastereotopic trindane benzylic protons, a singlet (δ 3.04 ppm) from the benzylic protons, and 11 carbon peaks were observed, as expected from its C_{3V} symmetry. The conformational freedom of triester **7** is expected to be relatively limited, except for the free rotations of the three benzyl groups and three ester groups. A low-energy conformation was deduced by molecular mechanics calculations and is presented in Figure 1.[12]

Each of the phenyl groups is located *anti* to the ester group and is nearly perpendicular to the trindane molecular plane,

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(12) The low-energy conformation was determined by molecular mechanics calculations with Monte Carlo minimization procedures, using MMFF94 force field as implemented in the Spartan program. The equilibrium geometry for the low energy conformations was calculated at AM1 level.

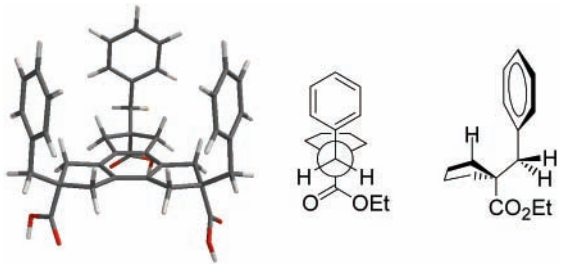


Figure 1. An energy-minimized structure of triethyl *cis,cis,cis*-2,5,8-tribenzyltrindane-2,5,8-tricarboxylate **7** and conformational representations of its partial structure.

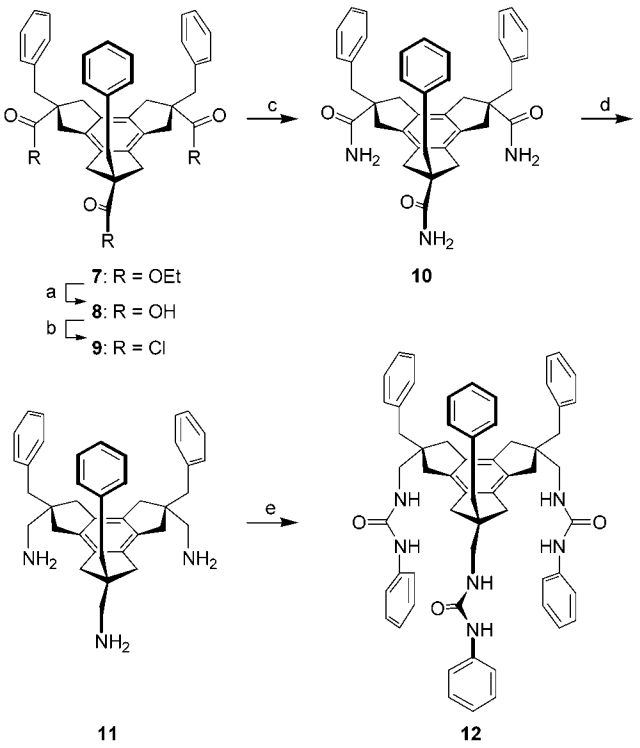
in which the five-membered rings adapt an envelope conformation and the wing tips of the envelops point toward one side. Thus, the molecule has the C_{3V} symmetry. This molecular geometry places the trindane benzylic protons and the ester group in a *trans*-diaxial relationship. It is known that in ethylbenzene the angle between the methyl group and the benzene plane is 70°.[13] As shown in Figure 1, each ring plane of the phenyl groups parallels the principal molecular axis such that the molecule has a vase-like shape, which is a promising aspect for constructing container molecules.[14]

From the scaffold **7** the tripodal urea receptor **12** has been synthesized, in which the urea groups can serve as hydrogen bonding donors and may bind anionic guests such as $H_2PO_4^-$, HSO_4^-, NO_3^-, and CO_3^{2-} ions (Scheme 2). Saponification of triester **7** with KOH in THF/water gave tricarboxylic acid **8** in a quantitative yield after acidification. Treatment of tricarboxylic acid **8** with oxalyl chloride and a catalytic amount of DMF gave triacid chloride **9** in a quantitative yield. Ammonia gas was bubbled into a THF solution of acid chloride **9** to yield tricarboxamide **10** in 72% yield. The tricarboxamide **10**, which is relatively insoluble in toluene, was treated with Red-Al under a reflux condition to afford triamine **11** in 85% yield. Finally, the target tris(phenylurea) **12** was synthesized from triamine **11** by treatment with phenyl isocyanate in THF in the presence of triethylamine in 85% yield.

Interestingly, the tripodal urea **12** did not show a symmetrical structure in $CDCl_3$ by ^1H NMR analysis even at a highly dilute concentration (10^{-3} M). It is likely that an intramolecular hydrogen bonding operates between the urea groups in a nonsymmetrical fashion in nonpolar solvents such as $CDCl_3$. The unsymmetrical structure, however, turned to a symmetrical one in polar solvents such as DMSO-d_6. In this solvent, tripodal urea **12** exhibited an expected symmetrical structure belonging to a C_{3V} point group. Solvation of the urea groups by polar DMSO may disrupt the intramolecular hydrogen bonding observed in $CDCl_3$.

To evaluate the anion binding ability of tripodal urea **12**, NMR titration experiments were performed in DMSO-d_6.

Scheme 2[a]



[a] Reagents and conditions: (a) KOH, THF/H_2O, reflux, 98%; (b) $(COCl)_2$, THF, 0 °C, 98%; (c) NH_3 (g), THF, rt, 72%; (d) Red-Al, toluene, reflux, 85%; (e) PhNCO, NEt_3, THF, rt, 85%.

The chemical shifts induced on complexation were analyzed by WinEQNMR, a nonlinear least squares regression program that calculates association constants.[15] Titrations of tripodal urea **12** were carried out with spherical halide anions such as F^-, Cl^-, Br^-, and I^- and also with oxoanions such as $H_2PO_4^-$, HSO_4^-, NO_3^-, ClO_3^-, ClO_4^-, and CO_3^{2-} as their tetrabutylammonium salts. The addition of anionic guests caused substantial downfield shifts of the urea protons, indicating the formation of host−guest complexes. For example, the NH proton attached to the phenyl ring showed a downfield shift of 1.5 ppm upon saturation of the host with $H_2PO_4^-$. In the case of I^-, ClO_4^-, and ClO_3^-, very small complexation-induced chemical shifts were observed. The titration data for other anions are shown in Figure 2. Except for F^-, all titration isotherms with the anions fitted well to a 1:1 binding model. In the case of F^- a complex binding equilibrium was suspected. The receptor showed a significant binding affinity toward $H_2PO_4^-$ ($K_a = 521$ M^{-1}). For other anions such as NO_3^-, HSO_4^-, Cl^-, Br^-, and CO_3^{2-}, however, the receptor exhibited weak binding affinities ($K_a < 60$ M^{-1}). The observed affinity toward $H_2PO_4^-$ seems to exceed that of calix[4]arene-based bis(phenylurea) receptor, with which a comparable value was obtained in $CDCl_3$.[3c]

Usually weaker binding affinities are observed in polar solvents than in nonpolar solvents,[16] but the observed affinity

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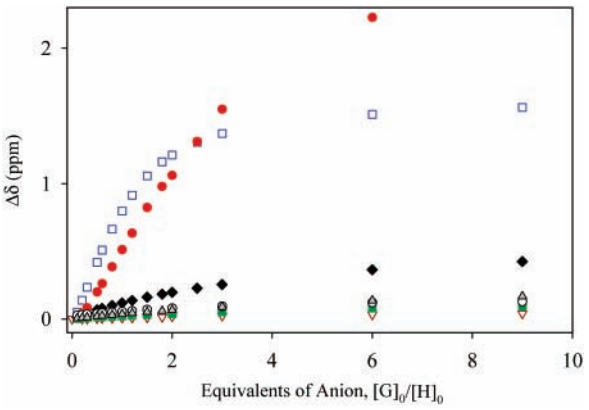

Figure 2. NMR titration curves of urea **12** with tetrabutylammonium salts of anionic guests in DMSO-d_6 at 25 °C ($[H]_0$ = 4.0 mM, $[G]_0$ = 40 mM; axis: complexation-induced chemical shifts of the PhNH urea proton). (●, F^-; □, $H_2PO_4^-$; ♦, Cl^-; ▲, CO_3^{2-}; ○ NO_3^-; ■, Br^-; ▽, HSO_4^-).

toward $H_2PO_4^-$ is about 20 times lower than that observed with a tris(2-aminoethyl)amine-based tripodal urea receptor.[17] The lower affinity suggests that three urea ligands of **12** may not provide an ideal cooperative binding mode toward the $H_2PO_4^-$ ion. A further study on the structural optimization of the receptor system would result in more efficient receptors toward given anionic guests.

In conclusion, we have developed an efficient synthetic route to the novel C_{3V}-symmetric scaffold, which can be manipulated into artificial receptors with tripodal ligand functionalities. As a demonstration, we derivatized the tripodal system into a urea type receptor, which showed a moderate binding affinity toward an anionic guest $H_2PO_4^-$ in DMSO. We are currently developing other types of receptors and novel container molecules for selective recognition of small molecules and anions based on the preorganized tripodal scaffold.

Acknowledgment. This work was supported by grant 2001-1-12300-005-3 from the Basic Research Program of the Korea Science & Engineering Foundation. H.-J.C. thanks M. J. Hynes (NUI, Galway Ireland) for giving us the computer program WinEQNMR and helpful discussion.

Supporting Information Available: Detailed synthetic procedures for synthetic Schemes 1 and 2 and selected NMR titration data. This material is available free of charge via the Internet at http://pubs.acs.org.

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