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Synthesis of a cryptand with tetrahedral connectivity using multiple ring-closing olefin metathesis

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Abstract—By connecting six terminal olefins sequentially in one molecule under metathesis conditions, three macrocycles were formed efficiently in one pot yielding a novel cryptand with tetrahedral connectivity.

Since its emergence in 1967,[1] host–guest chemistry has found wide applications in areas such as molecular recognition, catalysis, separation, transportation, molecular electronics, and drug delivery.[2–5] Of various host molecules developed, the ones that contain a cavity formed by multiple macrocycles have the advantage of more restricted conformation, richer interactions between host and guest, and thus, higher affinity between them. However, compared to the preparation of other host molecules that possess no or only one macrocycle, the synthesis of such hosts is more challenging; usually, the multiple macrocycles are formed in separate steps, high dilution and/or slow addition techniques are required to prevent intermolecular oligomerization, and in some cases, even under these conditions, oligomerization products prevail. Consequently, the discovery of methodologies for efficient preparation of such hosts is highly desired. In recent years, olefin ring-closing metathesis (RCM) has proved to be a reliable tool for the construction of various macrocycles.[6,7] It has not only been used for the synthesis of numerous biologically active natural products, but also been used for the preparation of interesting architectures such as cyclic polymers,[8] catenanes,[9] rotaxanes,[10] and cored dendrimers.[11–13] The application of this reaction in the synthesis of macrocyclic molecules that are useful for host–guest chemistry also has been reported. For example, using olefin metathesis as the macrocyclization reactions, Grubbs' group prepared crown ether analogs[14] and McKervey's group constructed bridged, multifunctional calixarenes.[15] However, to the best of our knowledge, there are no literature reports on the application of multiple RCM in the synthesis of artificial receptors that posses a cavity formed by multiple macrocycles, which are potentially useful for complexation of various ions or small molecules. In this communication, we report the results on the preparation of a bell-shaped cryptand using such a strategy.

As shown in Scheme 1, the synthesis commenced with saponification of the known methyl ester **2**[11–13] with KOH to give **3**. Carboxylic acid **3** was then activated with *i*-butylchloroformate and coupled to **4**,[16,17] and the coupled intermediate treated with trifluoroacetic acid to remove the Boc protecting group to give **5**. The pentaerythritol derivative **6**[18] was oxidized with $NaIO_4$ and a catalytic amount of $RuCl_3{\cdot}3H_2O$ following a reported procedure[19] to give the triacid **7**. Without purification, triacid **7** was transformed to triacid chloride by treating with excess $SOCl_2$ in CH_2Cl_2 at reflux.[20] After removal of excess $SOCl_2$ on a rotary evaporator and drying under vacuum, the residue was allowed to react with amine **5** in CH_2Cl_2 in the presence of pyridine to give the multiple macrocyclization precursor **8**. Multiple olefin RCM of **8** was simply achieved by stirring its solution in CH_2Cl_2 at 40 °C or room temperature at a concentration of 0.001 M catalyzed by 30 mol% Grubbs' catalyst (**9**) under inert atmosphere for 12 h (Scheme 2).

Keywords: Cryptand; Host; Macrocyclization; Receptor; Ring-closing metathesis.
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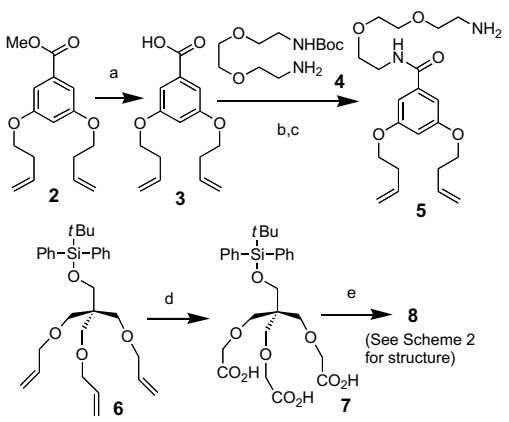


Scheme 1. Synthesis of the olefin RCM precursor **8**. Reagents and conditions: (a) KOH (2.5 equiv), THF/EtOH/H_2O (1:1:1), rt, 5 h, 88%; (b) *i*-BuOC(O)Cl (1.1 equiv), *N*,*N*-diisopropylethylamine (2.0 equiv), DMF, 0 °C, 1 h, then, **4** (1.1 equiv), 0 °C to rt, 2 h, 75%; (c) TFA, rt, 2 h, 93%; (d) $NaIO_4$ (30 equiv), $RuCl_3{\cdot}3H_2O$ (20 mol%), H_2O/MeCN/CCl_4 (3:2:2), rt, 4 h, 52%; (e) $SOCl_2$ (15 equiv), CH_2Cl_2, reflux, 4 h, volatile components removed on rotary evaporator, then, **5** (3.6 equiv), pyridine (10 equiv), CH_2Cl_2, rt, 12 h, 58%.

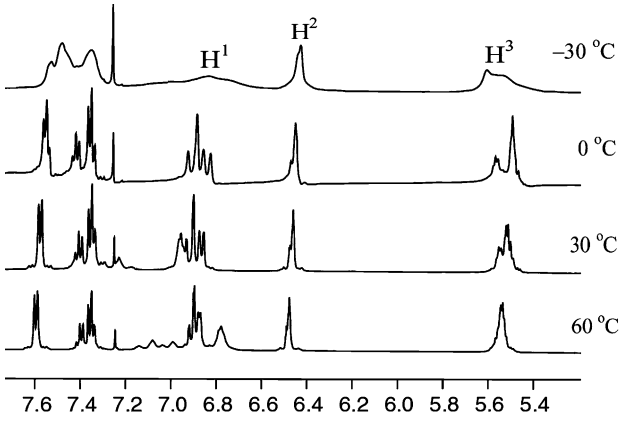
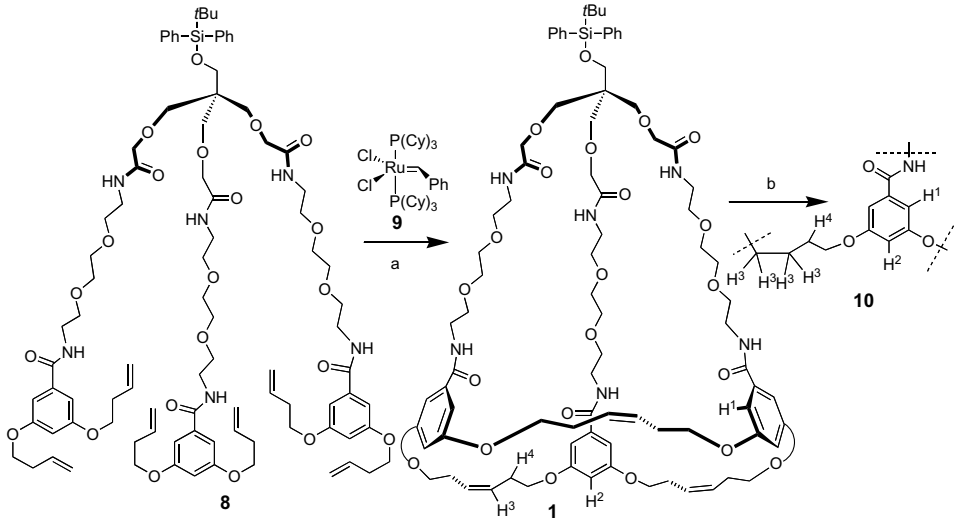


Figure 1. Partial variable temperature ^1H NMR of **1**.

The catalyst was decomposed by bubbling air through the solution, which was then concentrated under reduced pressure. As revealed by TLC (silica gel, CH_2Cl_2/MeOH, 19:1), there were two UV active spots with $R_f = 0.42$ and 0.39, respectively, which were separated by flash chromatography (silica gel, CH_2Cl_2/MeOH, 19:1). The upper spot gave only a very small amount of gray oily material, which was not pure as indicated by NMR and MALDI-MS; its purification and characterization was not further pursued. The more UV intense lower spot, cryptand **1**, was isolated as a white foam in 66% yield irrespective of the temperature under which the reaction was performed. In the ^1H NMR spectra (Fig. 1) at 30 °C, signals of H^1 ($\delta \sim 6.90$, see Scheme 2 for hydrogen denotation), H^2 ($\delta \sim 6.49$), H^3 (δ 5.59–5.47), and H^4 ($\delta \sim 2.40$, not shown) appeared as complex multiplets. In an effort to find out whether this was a result of different conformers or different stereoisomers or both, variable temperature ^1H NMR spectra were obtained. As shown in Figure 1, although the resonances of olefinic hydrogens at δ 5.59–5.48 (H^3) became almost symmetric at 60 °C and had a tendency to merge to a single peak at −30 °C, the signals of H^1 remained unchanged even at 60 °C (note, there was a broad signal due to exchangeable protons moving from $\delta \sim 6.19$ at 30 °C to $\delta \sim 6.78$ at 60 °C). This information was insufficient to draw conclusions about the number and identity of the stereoisomer(s) in the product. In order to see if reduction of the three double bonds could simplify the ^1H NMR spectra, a solution of **1** in ethanol was stirred under a hydrogen atmosphere in the presence of Pd/C to give **10** (Scheme 2). The H^3 resonances moved from δ 5.59–5.47 to δ 1.49 as a broad singlet (not shown), while those of H^1 ($\delta \sim 6.90$) and H^2 ($\delta \sim 6.49$) remained complex below 0 °C, but became simpler at higher temperature. However, this did not prove that **1** contained more than one stereoisomer because reduction of the double bonds could change



Scheme 2. Synthesis of the bell-shaped cryptand **1** and its hydrogenation. Reagents and conditions: (a) **9** (30 mol%), CH_2Cl_2 (0.001 M **8**), 40 °C or rt, 12 h, 66%; (b) Pd/C (10%), H_2 (1 atm), EtOH, rt, 24 h, 86%.

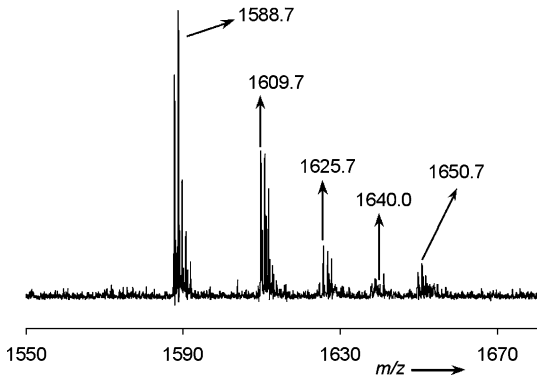


Figure 2. MALDI-MS of cryptand **1**. The peaks at *m*/*z* 1588.7, 1609.7, 1625.7 correspond to $[M + H]^+$ (calcd 1588.9), $[M + Na]^+$ (1610.9), $[M + K]^+$ (1626.9), respectively.

the flexibility of the molecule. Despite its complex NMR spectra, the structure irrespective of the geometry of the three double bonds of cryptand **1** was clearly supported by the MALDI-MS spectrum. As illustrated in Figure 2, the peaks at *m*/*z* 1588.7, 1609.7, 1625.7 corresponded to $[M + H]^+$ (calcd 1588.9), $[M + Na]^+$ (1610.9), $[M + K]^+$ (1626.9), respectively. The less intense peaks at *m*/*z* 1640.0 and 1650.7 could be due to complexation of other metal ions to **1**; no other peaks with comparable intensity were observed. The lack of peaks in the region *m*/*z* 3100–3400 (Supplementary material) supports the absence of products formed through dimerization of compound **8**. Other possible RCM cyclizations (Scheme 3) could lead to 11- and 22-membered ring products. Only two examples (**11** and **12**) are shown in the figure, but the absence of these and other products containing 11- and 22-membered rings is supported by ^{1}H NMR. The formation of the 11-membered ring as shown in structure **11** has been demonstrated to be improbable.[11–13] If such a product were formed, the resulting NMR spectrum would contain easily distinguishable features that are not present in the NMR spectrum of compound **1**. In particular, as has been shown for an 11-membered ring metacyclophane, the two methylene protons at the β positions show significant chemical shift differences (>1 ppm) because of the relative placement of the hydrogen atoms with respect to the plane of the benzene ring.[21] The shift differences for the γ and δ positions are of similar magnitude. Formation of a 22-membered ring would either leave an unreacted terminal alkene in the third arm (easily distinguishable by NMR) or higher order products formed through oligomerization. Such products if formed would have been lost in the purification of compound **1**, whose purity was established by the presence of a single spot on thin layer chromatography.

In conclusion, using an unprecedented multiple olefin RCM strategy, we successfully synthesized and characterized a novel cryptand with tetrahedral connectivity. Potentially, by using other molecules, instead of the pentaerythritol derivative, as platforms, other linkers between the platform and the olefins, and other RCM olefin units, a novel class of host molecules may be accessible through this approach. Because the olefin RCM is tolerant of a broad range of functional groups, the linkers could potentially include peptides and other oligomers capable of presenting a rich molecular landscape. Research toward this end and investigation of the ability of cryptand **1** to complex guest molecules and ions are under investigation.

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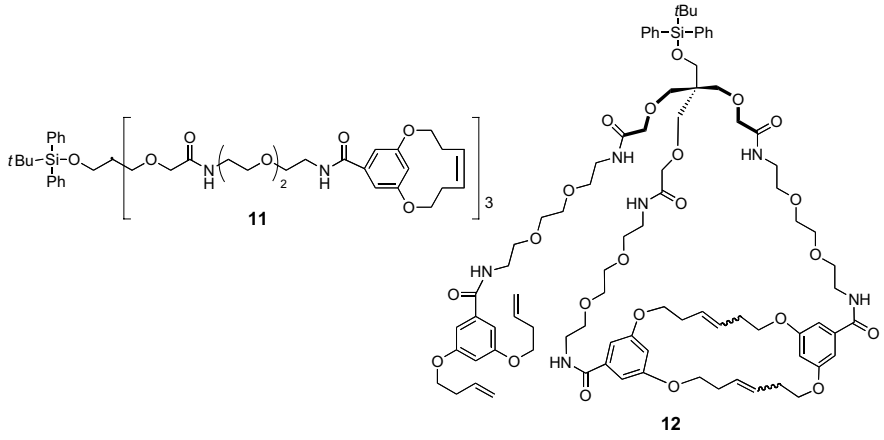
Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2004.09.090. Experimental procedures for the preparation of intermediates **3**, **5**, **7**, **8**, and **14**, cryptand **1** and its hydrogenation product **10** are available as supplementary data. The ^{1}H NMR, ^{13}C NMR, and MALDI spectra of **1** are also included.



Scheme 3. Conceptional examples of 11- and 22-membered ring products.

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