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Facile, Rapid, and High-Yield Synthesis of Pillar[5]arene from Commercially Available Reagents and Its X-ray Crystal Structure

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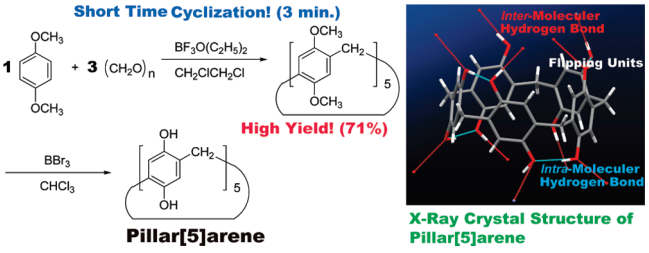

We monitored the progress of formation of dimethoxypillar[5]arene by size-exclusion chromatography. Surprisingly, the cyclization reaction completely finished in just 3 min. By improving the reaction conditions and purification process, we successfully obtained dimethoxypillar[5]arene in a short time and in high yield (71%) from commercially available reagents. By improving the deprotection reaction of the methoxy moieties, pillar[5]arene was isolated quantitatively. Single crystal X-ray analysis confirmed the structure of pillar[5]arene in the solid state.

Cyclodextrins,[1] crown ethers,[2] and *meta*-bridged cyclophane derivatives (calixarenes)[3] are well-known classical macrocycles and have played a major role in host−guest and supramolecular chemistry. Much attention has been paid to the design of new macrocyclic hosts, of which cucurbiturils are one of leading candidates because they have interesting symmetrical pumpkin-shaped architectures.[4] As a result of their highly symmetrical architectures, they form very stable host−guest complexes with organic and inorganic cations, and with neutral organic guests in aqueous media. *Para*-bridged cyclophane derivatives should also be potential candidates because they should form highly symmetrical architectures compared with *ortho*- and *meta*-bridged cyclophane derivatives. However, one of the most serious problems for the synthesis of these high-symmetry macrocyclic hosts is low yields and cumbersome synthetic pathways. For cucurbiturils, even in optimized conditions yields of isolated cucurbit[*n*]urils were 8% ($n = 5$), 46% ($n = 6$), 24% ($n = 7$), and 8% ($n = 8$).[4a] Synthesis of *para*-bridged cyclophane derivatives was more difficult, whereas various *ortho*- and *meta*-bridged cyclophane derivatives have been synthesized. Of *para*-bridged cyclophanes, synthesis of [1.1.1.1.1]cyclophane has been known for more than 20 years. However, its synthesis is laborious, and the overall yields were below 1%.[5] Because connections between *para*-substituted units should afford rigid linear oligomers compared with *ortho*- and *meta*-substituted monomers, intramolecular cyclization should hardly take place. Improvement of yields and development of conventional synthetic procedures for this new class of macrocyclic hosts is necessary for them to become widely accepted and used by many researchers.

Recently, we have discovered a new class of *para*-bridged cyclophane derivatives and named it "pillar[5]arene".[6−8]

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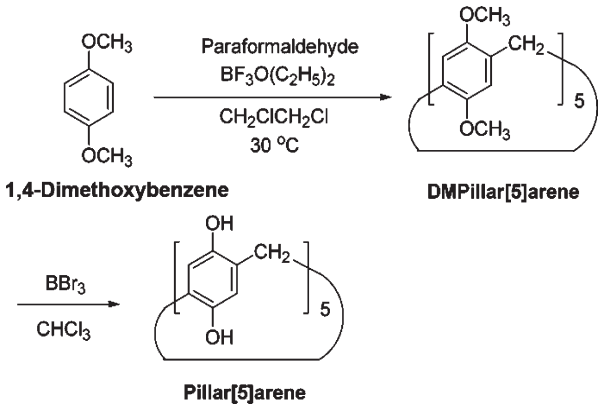
SCHEME 1. Synthesis of Pillar[5]arene



Scheme 1 shows the synthetic procedure and chemical structures of dimethoxypillar[5]arene (DMpillar[5]arene) and pillar[5]arene. Cyclization of 1,4-dimethoxybenzene afforded DMpillar[5]arene. DMpillar[5]arene is a cyclic pentamer that is composed of phenolic units and has composition analogous to that of typical calixarenes. However, the repeating units in DMpillar[5]arene are connected by methylene bridges at the *para*-position, which is quite different from the *meta*-bridged calixarenes. X-ray crystal analysis[6a] shows that as a result of the different substitution position, DMpillar[5]arene forms a very beautiful symmetrical pillar architecture, whereas typical calixarenes form a basket structure. The average angle of C−C methylene bridge between the units is 110°, which is closed to stable single C−C bond angle of 109.5°. Therefore, DMpillar[5]arene is conformationally stable. However, as with typical *para*-bridged cyclophane derivatives, the yield of DMpillar[5]arene was not high (22%).[6a] Pillar[5]arene (Scheme 1), which is obtained by deprotection of the methoxy groups of DMpillar[5]arene, is a useful building block for construction of polypseudorotaxane[6e] and polyrotaxane.[6g] Thus a facile, rapid, and high-yield synthesis of pillar[5]arene from cheap and commercially available reagents is desired. To develop a general synthesis procedure of DMpillar[5]arene, in the present study we monitored the formation of DMpillar[5]arene. New findings from the monitoring of the formation of DMpillar[5]arene are as follows: (1) The cyclization reaction was completed in 3 min. (2) Using excess paraformaldehyde (3 equiv of paraformaldehyde per equivalent of 1,4-dimethoxybenzene) gave DMpillar[5]arene. In the previous protocol[6a] we used 1.0 equiv of paraformaldehyde to 1,4-dimethoxybenzene. In those conditions the product obtained after the reaction was a mixture of polymer and DMpillar[5]arene. Therefore, we removed polymer from the mixture to isolate DMpillar[5]arene. However, by using 3 equiv of paraformaldehyde, the product obtained after the reaction was DMpillar[5]arene and little polymer was obtained. Thus, pure DMpillar[5]arene was isolated in high yield (71%). It is also found that the short reaction time (3 min) is enough to form DMpillar[5]arene.

To monitor the cyclization reaction, we determined size-exclusion chromatography (SEC) profiles of the product obtained at various times (Figure 1). Before addition of $BF_3O(C_2H_5)_2$ (0 s), the peak from 1,4-dimethoxybenzene (monomer) was observed with a retention volume of 24.3 mL. After adding $BF_3O(C_2H_5)_2$ (10 s), the peak from 1,4-dimethoxybenzene

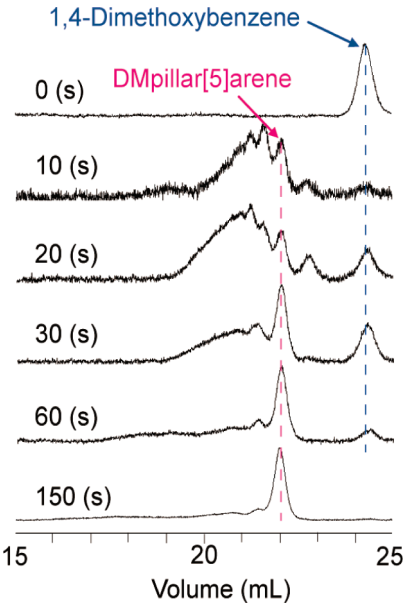


FIGURE 1. SEC traces of the obtained products after quenching of the reaction by addition of methanol. Feed ratio (1,4-dimethoxybenzene/paraformaldehyde) is 1:1.

dramatically decreased and peaks from oligomer (retention volume 20−22 mL) and DMpillar[5]arene (retention volume 22.0 mL) were observed. A decrease in the molecular weight of the oligomer and an increase in the amount of DMpillar[5]arene were subsequently observed as the reaction time was increased. Over 180 s, the SEC traces hardly changed, indicating completion of the cyclization reaction. It is very interesting that the reaction was completed in just 3 min.

We also investigated the effect of the amount of paraformaldehyde on the cyclization reaction (Figure 2). Using 0.2 and 0.33 equiv of paraformaldehyde per equivalent of 1,4-dimethoxybenzene afforded a mixture of oligomers and DMpillar[5]arene. 1,4-Dimethoxybenzene-end oligomers should mainly form. The product using 1.0 equiv of paraformaldehyde contained DMpillar[5]arene and polymer. In the cases using excess paraformaldehyde (3.0 and 5.0 equiv of paraformaldehyde to 1,4-dimethoxybenzene), no peaks from polymer and peak from DMpillar[5]arene were observed. In these cases, because we used excess paraformaldehyde, methylol-end oligomers should be formed. These methylol-end oligomers were reactive and thus converged conformationally stable DMpillar[5]arene. From these results, we concluded that reaction for 30 min using 3 equiv of paraformaldehyde per equivalent of 1,4-dimethoxybenzene was the optimum condition for the synthesis of DMpillar[5]arene. Pure DMpillar[5]arene was isolated from the reaction mixture by the addition of methanol, collecting the precipitate and then removing the insoluble part in chloroform. For further purification, the crude product was recrystallized from chloroform/acetone (1:1 v/v) to yield crystalline DMpillar[5]arene. Our synthesis procedure uses very cheap commercially available reagents [1,4-dimethoxybenzene, paraformaldehyde, and $BF_3O(C_2H_5)_2$], and the reaction time is very short. Thus, we believe that our procedure can form the basis for large scale synthesis of DMpillar[5]arene.

Deprotection of the methoxy-substituents using BBr_3 was also investigated. With chloroform containing a small amount

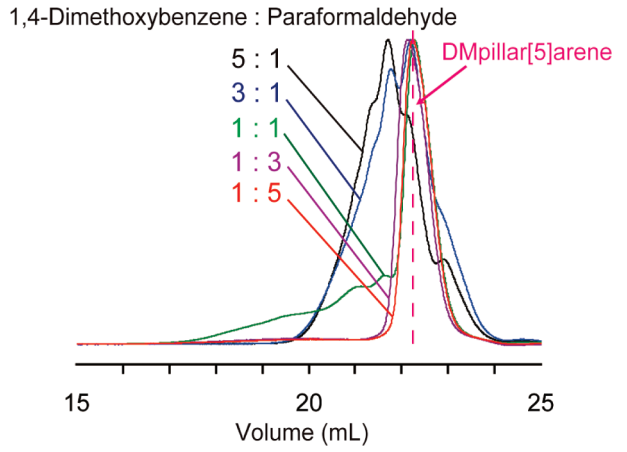


FIGURE 2. SEC traces of the obtained products after quenching of the reaction by addition of methanol. Feed ratios (1,4-dimethoxybenzene/paraformaldehyde) are 5:1 (black line), 3:1 (blue line), 1:1 (green line), 1:3 (purple line), and 1:5 (red line). Reaction time is 30 min.

of water as the reaction medium, the reaction mixture became cloudy during the reaction, indicating precipitation of partially deprotected pillar[5]arene. However, the reaction in anhydrous chloroform was homogeneous and afforded pillar[5]arene quantitatively. It is very important to use anhydrous chloroform solvent for this deprotection reaction.

Pillar[5]arene is susceptible to oxidation, which may be prevented by storing under nitrogen or, in the case of solutions, solvent degassing.

Single crystal X-ray analysis of pillar[5]arene confirmed the formation of pillar[5]arene and the structure of pillar[5]arene in the solid state (Figure 3a). Crystals were grown by slow evaporation of a solution of pillar[5]arene in acetone. As with DMpillar[5]arene, the structure of pillar[5]arene was a cyclic pentamer with the constituent units connected by methylene bridges at the *para*-position. Two acetone molecules were included in the cavity of pillar[5]arene. However, unlike the X-ray crystal structure of DMpillar[5]arene, formation of intramolecular hydrogen bonds between OH groups was observed. Intermolecular hydrogen bonds of OH groups with OH moieties in the other pillar[5]arene molecules and with ketone groups in two acetone molecules were also found. These intra- and intermolecular hydrogen bonds disturbed the pentagonal structure (Figure 3a, top view) and induced flipping of the constituent units (Figure 3a, side view). In the solid state, the flipping of two phenolic units (Figure 3b, 1 and 3 positions) in pillar[5]arene was observed. In contrast, no flipping of units took place in DMpillar[5]arene in the solid state. The flipping was not reported in the X-ray analysis of the other alkyl-substituted pillar[5]arenes,[6h,8a] and thus the flipping of the units in the solid state is a particular property in pillar[5]arene. Observation of flipping of the units in X-ray crystal structure among pillar[5]arene derivatives is a first example. The flipping in the crystalline state is consistent with the conformational characteristics of pillar[5]arene in solution.[6d] In the ^{1}H NMR spectra of pillar[5]arene in acetone-d_6 at low temperatures, splits of the proton signals were observed, indicating that the flipping of the units took place.

In conclusion, we monitored the progress of formation of DMpillar[5]arene by SEC analysis. Surprisingly, the cyclization

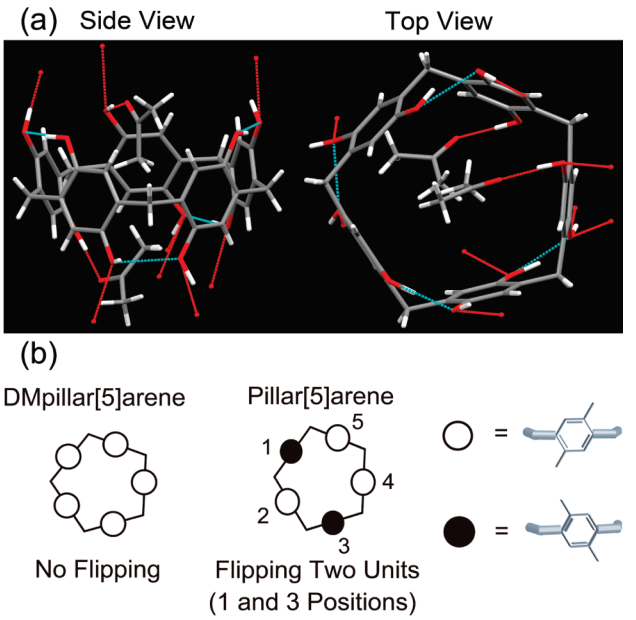


FIGURE 3. (a) Crystal structure of pillar[5]arene. The blue and red lines indicate intra- and intermolecular hydrogen bonds, respectively. (b) Conformations of DMpillar[5]arene and pillar[5]arene in the crystalline state.

reaction was completed in 3 min. By using 3 equiv of paraformaldehyde to 1,4-dimethoxybenzene, pure DMpillar[5]arene was successfully isolated in high yield (71%). By using anhydrous chloroform for deprotection of the methoxy moieties in DMpillar[5]arene, pillar[5]arene was isolated in quantitative yield, and the overall yield was 71%. The rapid high yield synthesis of pillar[5]arene is convenient and astounding compared with the other *para*-bridged cyclophane derivatives. Compared with the other synthetic macrocycles such as crown ethers, calixarenes, and cucurbiturils, the yield of pillar[5]arene is extremely high. This is because the pentagonal cyclic structure of DMpillar[5]arene should be the conformationally stable architecture. Single crystal X-ray analysis of pillar[5]arene clearly confirmed the formation of pillar[5]arene and the structure of pillar[5]arene in the solid state. With their unique symmetric pillar architectures and facile and rapid high yield synthesis, pillar[5]arenes will be widely used in molecular recognition for various guests and material chemistry to construct novel supramolecular architectures.

Experimental Section

DMpillar[5]arene. DMpillar[5]arene was synthesized by modification of the procedure previously reported[6a] as follows. To a solution of 1,4-dimethoxybenzene (1.38 g, 10 mmol) in 1,2-dichloroethane (20 mL) was added paraformaldehyde (0.93 g, 30 mmol). Then, boron trifluoride diethyl etherate [$BF_3O(C_2H_5)_2$, 1.25 mL, 10 mmol] was added to the solution, and the mixture was stirred at 30 °C for 30 min. The solution was poured into methanol, and the resulting precipitate was collected by filtration. The obtained solid was recrystallized from chloroform/acetone (1:1 v/v) to yield 0.83 g of DMpillar[5]arene as a while solid (Yield: 71%). ^{1}H NMR ($CDCl_3$, 270 MHz, ppm): δ 6.84 (s, 10H, phenyl), 3.76 (s, 10H, methylene), 3.71 (s, 30H, methoxy). ^{13}C NMR ($CDCl_3$, 67.5 MHz, ppm): δ 150.4, 128.0, 133.6 (C of phenyl), 55.5 (C of methoxy group), 29.5 (C of methylene bridge). Anal. Calcd for $C_{45}H_{50}O_{10}C_2H_4Cl_2$: C, 66.43; H, 6.40. Found: C, 66.39; H, 6.34. FAB mass m/z = 750 (M^+). FT-IR (KBr): 1250 cm^{-1} (s, C−O−C,

antisymmetric stretching), 1040 cm^{-1} (s, C−O−C, symmetric stretching). Melting point (T_m): 248.5−249.0 °C.

Pillar[5]arene. Pillar[5]arene was synthesized by modification of the procedure previously reported[6a] as follows. To a solution of DMpillar[5]arene (2.00 g, 2.67 mmol) in anhydrous chloroform (150 mL) was added boron tribromide (13.6 g, 54.3 mmol). The mixture was stirred at 25 °C for 72 h. Then, water was added into the mixture. The resulting precipitate was collected and washed with 0.5 M aqueous hydrochloric acid and chloroform to give 1.61 g (2.64 mmol) of pillar[5]arene quantitatively. For further purification, the solid was recrystallized from acetone. ^{1}H NMR (acetone-d_6, 270 MHz, ppm): δ 7.96 (s, 10H, hydroxyl group), 6.66 (s, 10H, phenyl), 3.59 (s, 10H, methylene). ^{13}C NMR (acetone-d_6, 67.5 MHz, ppm): δ 147.4, 128.2, 117.9 (C of phenyl), 30.6 (C of methylene bridge). FAB mass m/z = 610 (M^+). Anal. Calcd for $C_{35}H_{30}O_{10}2.20(CH_3COCH_3)$: C, 66.47; H, 6.12. Found: C, 66.13; H, 5.81. FT-IR (KBr) 3268 cm^{-1} (br, −OH).

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Supporting Information Available: NMR spectra and X-ray crystallographic data of pillar[5]arene in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.