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Scalable Synthesis of Cyclotriphenolene

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Supporting Information

ABSTRACT: Hyperpolarized xenon magnetic resonance imaging (^{129}Xe MRI) is becoming a powerful imaging method that requires cage molecules to encapsulate xenon. Cyclotriphenolene **1** is a key compound for the synthesis of cryptophane cages. A scalable procedure for the synthesis of cyclotriphenolene **1** was developed by which 40 g of **1** can now be synthesized within 3 days, starting from inexpensive benzyl alcohol.

RESULTS AND DISCUSSION

Laser-polarized ^{129}Xe NMR spectroscopy appears to be a promising tool for in vitro and in vivo magnetic resonance imaging (MRI).[1] Indeed, the nuclear spin polarization of xenon can be increased by several orders of magnitude (10^4−10^5) through optical pumping, thus allowing the rapid detection of small amounts of gas dissolved in biological tissues (blood, lungs...) with an excellent signal-to-noise ratio. The nonspecificity of the xenon atom towards biological targets can be overcome by the design of carrier molecules bearing suitable functionalities. Good candidates for xenon biosensing are cryptophanes, cage molecules for which xenon exhibits a high affinity. The recently synthesized cryptophane-111 **2** (Figure 1) exhibits the highest binding constant for xenon encapsulation in organic solution determined to date.[2] This property suggests that the cryptophane-111 core is optimized for sensing applications even though no water-soluble congeners have been synthesized so far.

The synthesis of compound **2** and numerous other cryptophane analogues requires the key compound **1**. Three syntheses of **1** are known. The first one involves seven steps and a 14% overall yield.[2] The second synthesis, recently published by our group, involves four steps and a 27% overall yield, but it uses a rather expensive starting material.[3] Therefore, the price of cyclotriphenolene **1** is higher than $100 per gram. The third synthesis by Brotin and Dutasta (Scheme 1) requires only two steps, but the yield is low (6%), and more importantly it requires a tedious chromatographic purification step which prevents large-scale production.[4]

For NMR and MRI developments, a fast and cheap synthesis of compound **1** with a price of less than $10 per gram is urgently needed. Here we describe an approach that permits the synthesis of 40 g. of compound **1** in only 3 days for a price lower than $10 per gram.

We have revisited the synthesis described in Scheme 1. The very low price of the starting material ($200/kg) renders this approach attractive. We first tried to increase the yield of the cyclotrimerization step. Several of the numerous methods developed for the cyclotrimerization of benzyl alcohol derivatives were screened using **3** as substrate (Table 1).[5] The use of Lewis acids such as $CeCl_3$, $InCl_3$, $(CF_3SO_3)_3Yb$, and $(CF_3SO_3)_3Sc$ left the starting material unchanged even after 12 h (entry 1). Only traces of the expected compound were obtained using $SnCl_4$, $TiCl_4$, $GaCl_3$, or $ZrCl_4$ (entry 2). TiF_4 catalyzed the cyclotrimerization to furnish compound **4** in 5% yield (entry 3). Reacting **3** with 1.5 equiv of phosphorus pentoxide for 2 h generated the expected cyclotriphenolene derivative **4** in 6% yield (entry 4).

All experiments were carried out in dichloromethane solution at room temperature with 1.5 equiv of Lewis acid for 12 h (entries 1−3) or for 2 h (entries 4−7).

Since TiF_4 is rather expensive, we decided to use P_2O_5, the cheaper catalyst. Although the yield was not improved, the synthetic scheme is still attractive because of the low price of the starting material, but this approach needs a purification procedure that avoids use of a chromatographic column. The main impurities were phosphoric acid and polymeric material, as shown by the ^{1}H NMR spectrum (Figure 2, A)

Decreasing the amount of P_2O_5 would facilitate the purification procedure. The yield remained unchanged when the amount of P_2O_5 was decreased from 1.5 to 0.5 equiv (entries 5−7). The quantity of P_2O_5 cannot be further decreased without altering the yield. Next we tried to purify the product by a liquid/liquid extraction procedure. Each attempt to wash the dichloromethane phase with water was unsuccessful and furnished a stable emulsion which needed several hours to settle. Filtration of the dichloromethane solution through a short pad silica gel led to a significant improvement.

The quantity of silica gel as well as the volume of washing solvent (dichloromethane) was tuned in order to use the minimum amount. In addition, we studied the influence of the diameter and the height of the pad silica gel. Reaction of 100 g of **3** and 52 g of P_2O_5 led to a mixture that was filtered through a pad silica gel of 300 g (diameter: 6 cm, height 25 cm, eluted with 500 mL of dichloromethane) to furnish after solvent evaporation

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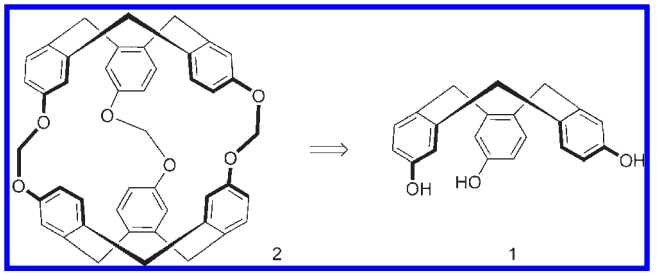

Figure 1. Structures of cryptophane-1.1.1 and cyclotriphenolene.

Scheme 1. Synthesis of cyclotriphenolene 1

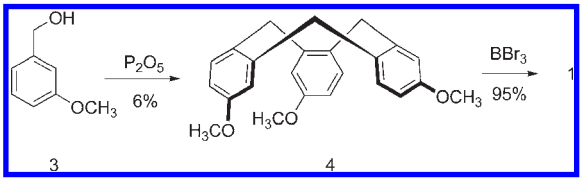

Table 1. Cyclotrimerization of 3

entry	catalyst	yield (%)
1	$CeCl_3$, $InCl_3$, $(CF_3SO_3)_3Yb$, $(CF_3SO_3)_3Sc$	The starting material was recovered unchanged.
2	$SnCl_4$, $TiCl_4$, $GaCl_3$, $ZrCl_4$	Traces of **4**; no starting material was recovered.
3	TiF_4	5
4	P_2O_5 (1.5 equiv)	6
5	P_2O_5 (1 equiv)	6
6	P_2O_5 (0.75 equiv)	6
7	P_2O_5 (0.5 equiv)	6

53 g of a wax. Interestingly, no cyclotriphenolene was held on the pad, as demonstrated by HPLC analysis. This easy purification removed all phosphoric acid and several polymeric materials. We then turned our attention to finding a solvent that can dissolve the impurities without dissolving the cyclotriphenolene compound. Among several solvents tested we found that Et_2O was the most efficient. The 52 g obtained through the silica gel filtration was dissolved in 150 mL of Et_2O and sonicated until a white precipitate appeared. The precipitate was collected by filtration and dried to furnish 5.4 g of compound **4**. The organic phase was concentrated to 50 mL and left overnight. An additional precipitate was formed, collected by filtration and dried to furnish another 1.2 g of **4**. The two fractions of compound **4** were mixed together and analyzed by ^{1}H NMR (Figure 2, B).

In order to improve the purity of compound **4**, this sequence of purification (dissolution in Et_2O, sonication, and precipitation) was repeated and furnished 5.2 g (6%) of perfectly pure cyclotriphenolene **4** (Figure 2, C). This synthesis and purification procedure was repeated starting with 414 g of benzyl alcohol **3** to give, in one working day, 24.8 g of **4**.

Demethylation of **4** by BBr_3 on a 49-g scale followed by a crystallization step in acetonitrile afforded 41 g of pure **1**. Once again, this procedure is easily carried out in one working day.

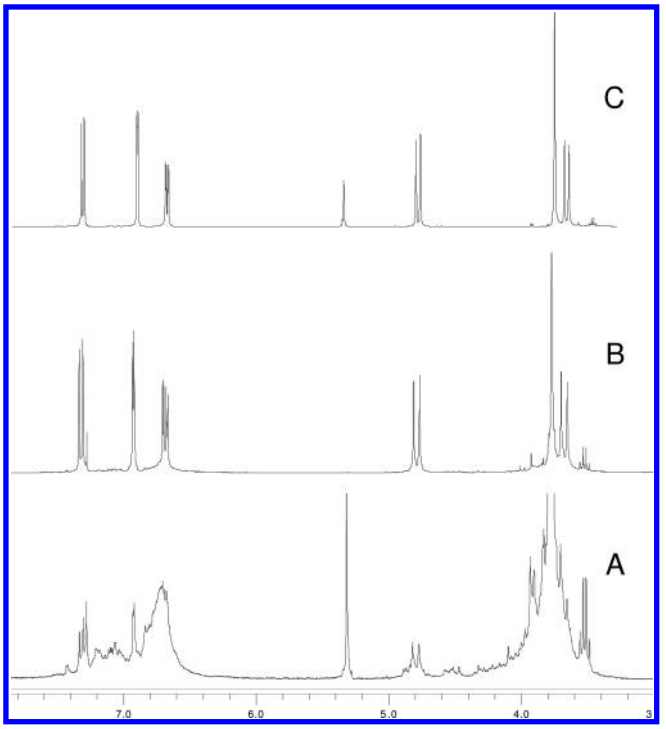

Figure 2. ^{1}H NMR spectrum of compound **4**: A crude product, B after the first ethyl ether precipitation, C final product.

CONCLUSION

In conclusion, we have demonstrated that within 3 days more than 40 g of cyclotriphenolene **1** can be synthesized and purified using a very simple and scalable procedure. Moreover, since this synthesis uses very cheap chemicals, the price of **1** is lower than $10/g. We believe this rapid and inexpensive access to compound **1** will greatly improve the synthesis of new cryptophanes for MRI applications.

EXPERIMENTAL SECTION

Organic solvents (Aldrich) were used without further purification. Filtrations through silica gel were carried out using Merck silica gel (40−63 μm). ^{1}H NMR (400 MHz), ^{13}C NMR (100 MHz) spectra were recorded on a Bruker Avance 400 MHz spectrometer. Chemical shifts are reported in parts per million (ppm, δ) downfield from residual solvent peaks, and coupling constants are reported in Hertz (Hz). Splitting patterns are designated as singlet (s), broad singlet (bs), doublet (d), triplet (t). Splitting patterns that could not be interpreted or easily visualized are designated as multiplet (m). Unless otherwise noted, all other commercially available reagents and solvents were used without further purification.

2,7,12-Trimethoxy-10,15-dihydro-5H-tribenzo[*a*,*d*,*g*]cyclononene: 4. 3-Methoxy benzyl alcohol (414 g, 3 mol) was added to a stirred mixture of P_2O_5 (213 g, 1.5 mol) in dichloromethane (1.67 L) in 5 min. A weak reflux was observed while a solid phase appeared. The mixture was heated to 40 °C for 1 h, and the reactor was cooled to 5 °C. The organic phase was drawn off (1.5 L). The solid phase was washed with CH_2Cl_2 (2 × 500 mL), and the solvent was evaporated. The residue was dissolved using the organic phase which was first drawn off (1.5 L). This solution was filtered through a pad silica gel of 1.2 kg (diameter: 12 cm, height 25 cm, eluted with 3.6 L of dichloromethane). The solvent was removed under reduced pressure to provide a pale yellow

wax (210 g). The residue was dissolved in 600 mL of Et_2O and sonicated until a white precipitate appeared. The precipitate was collected by filtration and dried to furnish 21.4 g of compound **4**. The organic phase was concentrated to 150 mL and left for several hours. An additional precipitate was formed, collected by filtration and dried to furnish another 4.5 g of **4**. The two fractions of compound **4** (25.9 g.) were mixed together and dissolved in 60 mL of Et_2O, sonicated, and left at 0 °C overnight. The precipitate was collected by filtration and dried to furnish a white powder (24.8 g. 6% yield). ^{1}H NMR (400 MHz, CD_2Cl_2, 20 °C) δ 7.31 (d, J(H,H) = 8.4 Hz, 3 H, Ar), 6.90 (d, ^4J(H,H) = 2.8 Hz, 3 H, Ar), 6.67 (dd, ^3J(H,H) = 8.4 Hz, ^4J(H,H) = 2.8 Hz, 3 H, Ar), 4.78 (d, ^2J(H,H) = 13.6 Hz, 3 H, H_a), 3.74 (s, 9 H; OCH_3), 3.65 (d, ^2J(H,H) = 13.6 Hz, 3 H, H_e).

10,15-Dihydro-5*H*-tribenzo[*a*,*d*,*g*]cyclononene-2,7,12-triol: 1. Boron tribromide (980 mL of a 1 M solution of BBr_3 in CH_2Cl_2) was added dropwise to a suspension of compound **4** (49 g, 136 mmol) in dry CH_2Cl_2 (200 mL) at 0 °C. The solution was warmed to room temperature and stirred overnight. The solution was poured onto an ice and H_2O slurry. The aqueous solution was neutralized to pH 6 and filtered. The solid residue was washed with 600 mL of hot water and dried to provide a slightly colored powder. The powder was poured into 150 mL of acetonitrile and sonicated for 20 min. The precipitate was filtered, washed with 220 mL of acetonitrile and dried to furnish 41 g. (95% yield) of pure **1**. ^{1}H NMR (400 MHz, acetone-d6, 20 °C) δ 7.99 (s, 3 H) 7.21 (d, 3 H, ^{3}J(H,H) = 8.0 Hz, Ar), 6.88 (d, 3 H, ^4J(H,H) = 2.6 Hz, Ar), 6.55 (dd, 3 H, ^3J(H,H) = 8.0 Hz, ^4J(H,H) = 2.6 Hz, Ar), 4.78 (d, 3 H, ^2J(H,H) = 13.4 Hz, H_a), 3.55 (d, 3 H, ^2J(H,H) = 13.4 Hz, H_e).

■ ASSOCIATED CONTENT

Supporting Information. NMR spectral data (^{1}H, ^{13}C and HSQC) for **1** and **4**. Mass spectra (HRMS) for compound **4**. This material is available free of charge via the Internet at http://pubs.acs.org.

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