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Scalable Synthesis of Cryptophane-1.1.1 and its Functionalization

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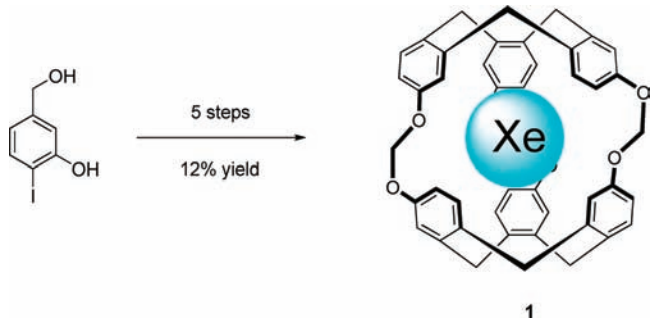
ABSTRACT



Cryptophanes, cage molecules for which xenon exhibits a high affinity, are good candidates for xenon biosensing. Cryptophane-1.1.1 (1) exhibits the highest binding constant for xenon encapsulation in organic solution determined to date. This property suggests that the cryptophane-1.1.1 core (1) is optimal for sensing applications. A high-yielding scalable synthesis of compound 1 is reported as well as an easy way to functionalize it.

Laser-polarized ^{129}Xe NMR spectroscopy can be usefully applied to in vitro and in vivo magnetic resonance imaging (MRI).[1] By using optical pumping to increase the nuclear spin polarization of xenon by several orders of magnitude (10^4 to 10^5), small amounts of gas dissolved in biological tissues (blood, lungs, etc.) can be detected rapidly with an excellent signal-to-noise ratio. Carrier molecules bearing suitable functions can be designed to overcome the nonspecificity of the xenon atom toward biological targets. Good candidates for xenon biosensing are cryptophanes, cage molecules for which xenon has a high affinity. The recently synthesized cryptophane-1.1.1 (Figure 1) exhibits the highest binding constant for xenon encapsulation in organic solution determined to date.[2] This property suggests that the cryptophane-1.1.1 core **1** is optimal for direct sensing applications using xenon.

In their pioneering work, Brotin and Dutasta synthesized this important molecule in 1.5% overall yield from 4-allyloxy 3-methoxybenzyl alcohol, and no further functionalization has been described.[2] Here we report a scalable synthesis of compound **1** from commercially available iodinated phenol **2** with 12% overall yield and an easy way to functionalize it (Scheme 1).

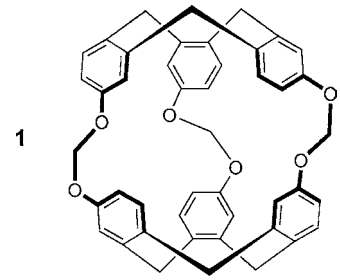


Figure 1. Structure of cryptophane-1.1.1.

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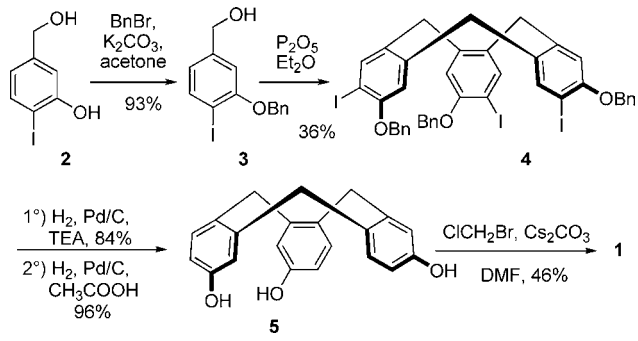
Scheme 1. Synthesis of Cryptophane **1** by Cyclotriphenolene Unit Dimerization



To avoid unwanted electrophilic attacks during the cyclotrimerization step, we chose the iodinated phenol **2** to start the synthesis. Iodine blocks the reactive ortho position. The phenol moiety of compound **2** was protected as benzyl ether to furnish **3** in 93% yield. Several of the numerous methods developed for the cyclotrimerization of benzyl alcohol derivatives were screened using **3** as substrate (Table 1).[3]

Table 1. Formation of **4** from Benzyl Alcohol **3**

entry	catalyst	solvent	temp	time (h)	isolated yield (%)
1	$Sc(OTf)_3$	MeCN	reflux	72	no reaction
2	$HClO_4$ 60%	No solvent	rt	24	no reaction
3	$HClO_4$ 70%	MeOH	0 °C to rt	18	no reaction
4	$HClO_4$ 60% AcOH	MeOH	rt	60	no reaction
5	P_2O_5 1 equiv	Et_2O	reflux	12	10
6	P_2O_5 2 equiv	Et_2O	reflux	12	15
7	P_2O_5 3 equiv	Et_2O	reflux	12	36

The use of scandium triflate as Lewis acid left the starting material unchanged even after refluxing for 3 days (entry 1). The same results were obtained using perchloric acid as dehydrating agent (entries 2−4). Refluxing **3** with 1 equiv of phosphorus pentoxide for 12 h generated the expected cyclotriphenolene derivative **4** in 10% yield (entry 5). By increasing the amount of P_2O_5 (2 equiv), the yield rose to 15% (entry 6). Under the best conditions (entry 7, P_2O_5, 3 equiv, diethyl ether, reflux, 12 h), benzyl alcohol **3** underwent a smooth trimerization affording **4** in 36% yield. Catalytic hydrodeiodination of **4** using molecular hydrogen and Pd/C in the presence of triethylamine,[4] followed by removal of the benzyl protective groups (H_2, Pd/C, CH_3COOH), afforded cyclotriphenolene **5** in 81% yield over the two steps. All these reactions were conducted on 30-g scale or more without the need of chromatographic purification (see the Supporting Information).

We then turned our efforts to the dimerization of the cyclotriphenolene unit **5** to furnish cryptophane **1**. The dimerization proceeded along with polymerization reactions. A careful choice of experimental conditions minimized the unwanted polymer, as shown in Table 2.

Table 2. Formation of Cryptophane **1** from **5**[a]

entry	$ClCH_2Br$ (equiv)	Cs_2CO_3 (equiv)	DMF (mL)	temp (°C)	yield (%)
1	0.5	10	4	60	<10
2	50	10	4	60	15
3	50	10	20	60	15
4	50	10	25	60	10[b]
5	500	5	4	60	30
6	500	10	4	60	35
7	500	10	4	40	20
8	500	10	4	80	45
9	500	10	20	80	44
10	500	10	400	80	46

[a] All reactions were carried out for 13 h on a 100-mg scale, except for entry 9 (500-mg scale) and entry 10 (10-g scale). [b] Addition with a syringe pump over 13 h.

When the dimerization was carried out in the presence of 0.5 equiv of $ClCH_2Br$ (entry 1), cyclotriphenolene **5** was converted to cryptophane **1** in less than 10% yield. The yield was increased to 15% by using 50 equiv of $ClCH_2Br$ (entry 2). Higher dilution and slow addition of cyclotriphenolene **5** had no impact on the reaction outcome (entries 3 and 4). A significant improvement was obtained using 500 equiv of $ClCH_2Br$ (entry 5). The influence of temperature was also investigated (entries 6−8). The use of 10 equiv of Cs_2CO_3 was required to obtain the best result (entry 8). Finally, these

(1) (a) Schröder, L.; Lowery, T. J.; Hilty, C.; Wemmer, D. E.; Pines, A. *Science* **2006**, *314*, 446. (b) Berthault, P.; Bogaert-Buchmann, A.; Desvaux, H.; Huber, G.; Boulard, Y. *J. Am. Chem. Soc.* **2008**, *130*, 16456. (c) Huber, G.; Brotin, T.; Dubois, L.; Desvaux, H.; Dutasta, J.-P.; Berthault, P. *J. Am. Chem. Soc.* **2006**, *128*, 6239. (d) Spence, M. M.; Ruiz, E. J.; Rubin, S. M.; Lowery, T. J.; Winssinger, N.; Schultz, P. G.; Wemmer, D. E.; Pines, A. *J. Am. Chem. Soc.* **2004**, *126*, 15287. (e) Mynar, J. L.; Lowery, T. J.; Wemmer, D. E.; Pines, A.; Fréchet, J. M. J. *J. Am. Chem. Soc.* **2006**, *128*, 6334. (f) Schröder, L.; Chavez, L.; Meldrum, T.; Smith, M.; Lowery, T. J.; Wemmer, D. E.; Pines, A. *Angew. Chem., Int. Ed.* **2008**, *47*, 4316. (g) Hilty, C.; Lowery, T. J.; Wemmer, D. E.; Pines, A. *Angew. Chem., Int. Ed.* **2005**, *45*, 70. (h) Schlundt, A.; Kilian, W.; Beyermann, M.; Sticht, J.; Günther, S.; Höpner, S.; Falk, K.; Roetzschke, O.; Mitschang, L.; Freund, C. *Angew. Chem., Int. Ed.* **2009**, *48*, 4142. (i) Driehuys, B.; Cofer, G. P.; Pollaro, J.; Boslego Mackel, J.; Hedlund, L. W.; Johnson, G. A. *Proc. Natl. Acad. Sci. U.S.A.* **2006**, *103*, 18278. (j) Spence, M. M.; Rubin, S. M.; Dimitrov, I. E.; Ruiz, E. J.; Wemmer, D. E.; Pines, A.; Qin Yao, S.; Tian, F.; Schultz, P. G. *Proc. Natl. Acad. Sci. U.S.A.* **2001**, *98*, 10654. (k) Hill, P. A.; Wei, Q.; Troxler, T.; Dmochowski, I. J. *J. Am. Chem. Soc.* **2009**, *131*, 3069. (l) Hill, P. A.; Wei, Q.; Eckenhoff, R. G.; Dmochowski, I. J. *J. Am. Chem. Soc.* **2007**, *129*, 11662. (m) Hill, P. A.; Wei, Q.; Eckenhoff, R. G. J.; Dmochowski, I. J. *J. Am. Chem. Soc.* **2007**, *129*, 9262. (n) Chambers, J. M.; Hill, P. A.; Aaron, J. A.; Han, Z.; Christianson, D. W.; Kuzma, N. N.; Dmochowski, I. J. *J. Am. Chem. Soc.* **2009**, *131*, 563. (o) Brotin, T.; Dutasta, J.-P. *Chem. Rev.* **2009**, *109*, 88.

(2) Fogarty, H. A.; Berthault, P.; Brotin, T.; Huber, G.; Desvaux, H.; Dutasta, J.-P. *J. Am. Chem. Soc.* **2007**, *129*, 10332.

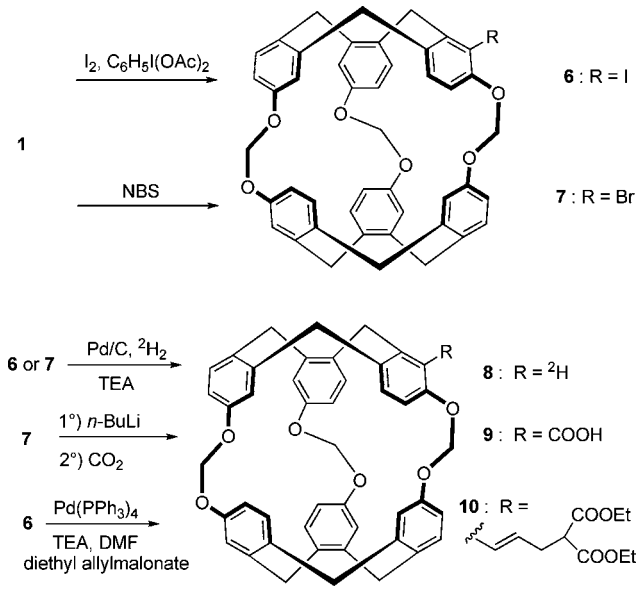
(3) (a) Collet, A.; Jacques, J. *Tetrahedron Lett.* **1978**, 1265. (b) Cram, D. J.; Tanner, M. E.; Keipert, S. J.; Knobler, C. B. *J. Am. Chem. Soc.* **1991**, *113*, 8909. (c) Lindsey, A. S. *J. Chem. Soc.* **1965**, 1685. (d) Carré, M.M. P.; Libermann, D. *Bull. Soc. Chim. Fr.* **1935**, 291. (e) Atwood, J. L.; Orr, G. W.; Means, N. C.; Hamada, F.; Zhang, H.; Bott, S. G.; Robinson, K. D. *Inorg. Chem.* **1992**, *31*, 603. (f) Brotin, T.; Roy, V.; Dutasta, J. P. *J. Org. Chem.* **2005**, *70*, 6187.

(4) Faucher, N.; Ambroise, Y.; Cintrat, J. C.; Doris, E.; Pillon, F.; Rousseau, B. *J. Org. Chem.* **2002**, *67*, 932–934.

optimized conditions were applied to a larger quantity of cyclotriphenolene **5** (500 mg, entry 9) and allowed the synthesis of cryptophane **1** in 44% yield. A slightly better yield of 46% was obtained on a 10-g scale (entry 10). The purification was performed without the need of any chromatographic column (liquid/liquid extraction and filtration through a short pad silica gel led to pure **1**). The reaction led almost exclusively to the chiral D_3-symmetry (anti) form, as observed by chiral HPLC.

We then turned our attention to the functionalization of the cryptophane-1.1.1 (**1**), which has never been reported before. Since cryptophane **1** is composed of phenoxy moieties, it can, in principle, be iodinated or brominated. When it was submitted to iodination (I_2, $C_6H_5I(OAc)_2$),[5] the reaction afforded compound **6** (Scheme 2). The yield based on recovered starting material was 55%.

Scheme 2. Functionalization of the Cryptophane Core



As the iodine atom broke down the symmetry of compound **1**, the ^{1}H NMR spectrum of iodine compound **6** was difficult to interpret. In order to determine the iodination position, we replaced the iodine atom by a deuterium using a catalytic hydrodeiodination reaction with deuterium gas.[4] The ^{1}H NMR spectrum of the deuterated cryptophane **8** unambiguously showed that the iodination had occurred at the *ortho* position of the phenoxy ring, as represented in Scheme 2. The aromatic region of the ^{1}H NMR spectrum of **8** was composed of three broad peaks of relative intensity 6/6/5. Each broad peak was attributed using COSY correlations. (See the Supporting Information.) Alternatively, compound **1** could easily be brominated using *N*-bromosuccinimide in $CHCl_3$ to furnish **7** in 64% yield based on recovered starting material. Once again, the bromination position was determined by deuteration and ^{1}H NMR analysis of the deuterated cryptophane **8**.

Starting from these halogenated compounds, a large number of chemical functions can be introduced using either organolithium or palladium chemistry. We performed one of each reaction type. The lithiation of bromine **7** by *n*-BuLi followed by carboxylation with CO_2 afforded the carboxylic acid **9** in a modest but nonoptimized yield of 27%. In addition, the palladium-catalyzed Heck vinylation of iodide **6** by diethyl allylmalonate ($Pd(PPh_3)_4$, TEA, DMF) provided **10** in 52% yield.[6] Compound **10** is a very versatile compound as one carboxylate group can be used to introduce a water-soluble moiety while the other can be used to introduce a protein ligand. To the best of our knowledge, this is the first time that a Heck reaction has been used to functionalize any cryptophane.

In conclusion, we describe a short, high-yielding, and scalable synthetic route to cryptophane-1.1.1 (**1**). Previously, compound **1** was synthesized in 1.5% overall yield and can now be obtained in 12% overall yield. Moreover, we demonstrate for the first time that functionalization of **1** can be realized by means of iodination or bromination and can afford a large variety of substituted xenon containers. We are using this approach for the development of new water-soluble containers for Xe imaging.

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Supporting Information Available: Detailed experimental procedures, full characterization, and copies of ^{1}H, ^{13}C NMR, and IR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(5) Togo, H.; Nogami, G.; Yokoyama, M. *Synlett* **1998**, 534.

(6) (a) Lemhadri, M.; Battace, A.; Zair, T.; Doucet, H.; Santelli, M. *J. Organomet. Chem.* **2007**, *692*, 2270. (b) Gao, X.; Yu, W.; Mei, Y.; Jin, Z. *Tetrahedron. Lett.* **2004**, 8169.