

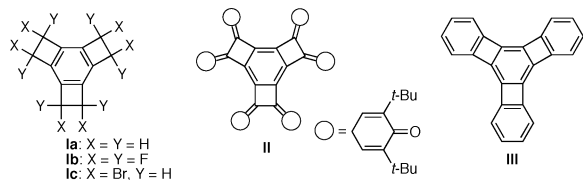
## Dodecamethoxy- and Hexaoxotricyclobutabenzene: Synthesis and Characterization

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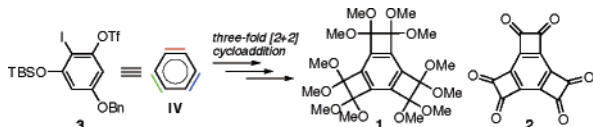
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The idea that annulation of a small ring onto benzene would induce bond-length alternation by trapping out one Kekulé resonance structure is a provocative concept for chemists.<sup>1</sup> Tricyclobutabenzene (TCBB) **1a**<sup>2</sup> serves as a key model compound in this discussion, to which cognates, such as halo-substituted derivatives **1b**, **1c**,<sup>3,4</sup> hexamethylene derivative **II**,<sup>5</sup> and triangular [4]phenylene derivative **III**,<sup>6</sup> are compared.



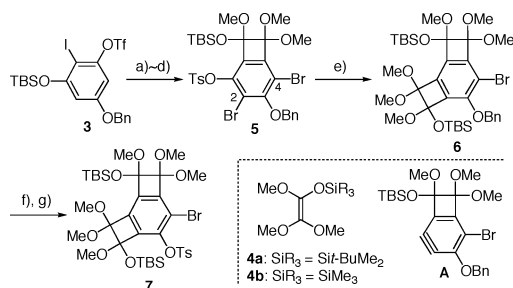
We report the syntheses of two new cognates, dodecamethoxy-TCBB **1** and hexaoxo-TCBB **2**, via 3-fold [2 + 2] cycloadditions of benzyne and ketene silyl acetals (KSAs).<sup>7</sup> The present synthesis overcomes numerous issues in previously reported synthesis of TCBBs<sup>8</sup> and uses the selectively protected 2-iodophloroglucinol derivative **3** as a novel synthetic equivalent of benztriyne **IV**. Intermediate **3** has advantages for the rapid and regioselective annulation of three fully functionalized four-membered rings as in **1** and **2**.



The first cycloaddition occurred by treatment of iodotriflate **3** with *n*-BuLi in the presence of KSA **4a** to give a single cycloadduct, which was converted to bromotosylate **5** by selective hydrolysis of the aryl silyl ether followed by the dibromination and tosylation (Scheme 1). The high regioselectivity of this first [2 + 2] cycloaddition could be rationalized by the directing effect of the silyloxy group as described before.<sup>7</sup>

Benzyne **A**, generated from **5**, cleanly underwent the second [2 + 2] cycloaddition with KSA **4a** to give cycloadduct **6** in 54% yield.<sup>10</sup> Key features of this process include the following: (1) halogen–lithium exchange of **5** exclusively occurred at the bromine atom between the electron-withdrawing toluenesulfonate and the benzyloxy group, generating benzyne **A** selectively without losing the C4 bromide;<sup>11</sup> (2) highly regioselective cycloaddition gave **6** exclusively, which was interesting in its own right, as we recently reported that a four-membered ring also has a powerful directing effect in the benzyne cycloaddition (Figure 1).<sup>12</sup> The regioselectivity issues raised a question of which is the more influential directing

### Scheme 1<sup>a</sup>



<sup>a</sup> Reagents and conditions: (a) **4a**, *n*-BuLi, Et<sub>2</sub>O, –78 °C, 5 min; (b) aq. KF, *n*-Bu<sub>4</sub>NCl, CH<sub>3</sub>CN, 0 → 25 °C, 5 h; (c) NBS, *i*-Pr<sub>2</sub>NEt, CH<sub>2</sub>Cl<sub>2</sub>, –78 °C, 1 h; (d) TsCl, K<sub>2</sub>CO<sub>3</sub>, acetone, 25 °C, 10 h (**5**: 48%, 4 steps); (e) **4a**, *n*-BuLi, Et<sub>2</sub>O, 0 °C (**6**: 54%, syn/anti = 1.5:1); (f) H<sub>2</sub>, Pd/C, EtOAc, 25 °C; (g) TsCl, K<sub>2</sub>CO<sub>3</sub>, acetone, 25 °C, 10 h (**7-syn**: 83%, 2 steps, **7-anti**: 81%, 2 steps).

groups. To address this, the structure of **6** was determined by X-ray analysis after converting to the bromotosylate **7**, confirming that the directing ability of the benzyloxy group overrides that of the four-membered ring.

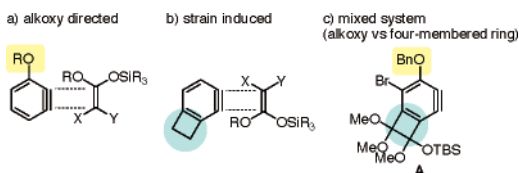
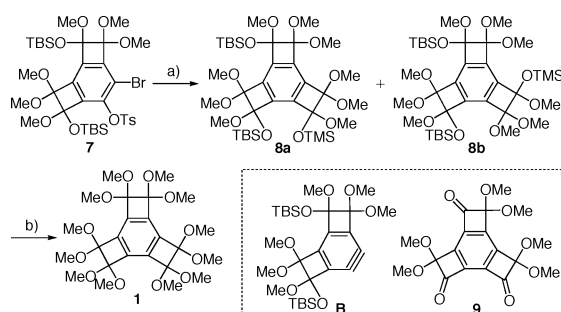


Figure 1. Regioselectivity of substituted benzyne.

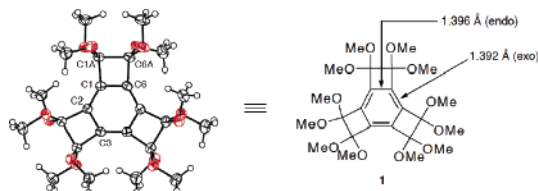
Bromotosylate **7** was subjected to the third [2 + 2] cycloaddition with KSA **4b**, furnishing fully oxygenated tricyclobutabenzene **8** in 51% yield (Scheme 2). Amazingly, the cycloaddition was highly regioselective, giving cycloadduct **8a** as the major regioisomer, along with a small amount of minor regioisomer **8b**. The structure

### Scheme 2<sup>a</sup>

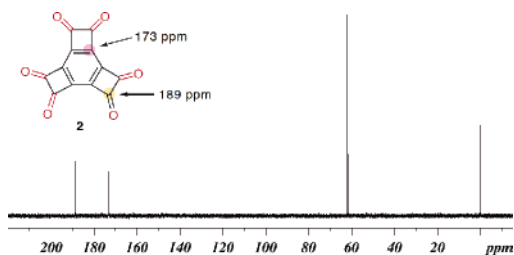


<sup>a</sup> Reagents and conditions: (a) **4b**, *n*-BuLi, Et<sub>2</sub>O, 0 °C (**8**: 51% from **7-syn**, **8a/8b** = 6:1); (b) (MeO)<sub>3</sub>CH, TsOH, MeOH, 60 °C (**1**: 51% from **7-syn**, 56% from **7-anti**, 2 steps).

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**Figure 2.** Molecular structure of **1**. Selected exptl<sup>13</sup> [calcd<sup>14</sup>] distances (Å) and angles (°): C<sub>1</sub>–C<sub>2</sub> 1.389(2) [1.390], C<sub>1</sub>–C<sub>6</sub> 1.396(2) [1.399], C<sub>1</sub>–C<sub>1A</sub> 1.523(2) [1.530], C<sub>6</sub>–C<sub>6A</sub> 1.529(2) [1.530], C<sub>1A</sub>–C<sub>6A</sub> 1.614(2) [1.623]; C<sub>6</sub>–C<sub>1</sub>–C<sub>2</sub> 120.2(1) [120.0], C<sub>1</sub>–C<sub>2</sub>–C<sub>3</sub> 119.8(1) [120.0], C<sub>1</sub>–C<sub>6</sub>–C<sub>6A</sub> 94.0(1) [94.2], C<sub>6</sub>–C<sub>1</sub>–C<sub>1A</sub> 94.1(1) [94.2], C<sub>1</sub>–C<sub>1A</sub>–C<sub>6A</sub> 86.0(1) [85.8], C<sub>6</sub>–C<sub>6A</sub>–C<sub>1A</sub> 85.7(1) [85.8].



**Figure 3.** <sup>13</sup>C NMR spectra of **2** (125 MHz, D<sub>2</sub>SO<sub>4</sub>, TMS as reference).

of **8a** (syn/anti stereoisomers) was unequivocally assigned through derivatization to the corresponding triketone **9** by two-step hydrolysis [(i) TsOH, CH<sub>2</sub>Cl<sub>2</sub>, MeOH, 25 °C; (ii) BF<sub>3</sub>·Et<sub>2</sub>O, H<sub>2</sub>O, –78 → 25 °C].<sup>9</sup> This high regioselectivity (**8a**/**8b** = 6:1) is striking in view of the pseudo-symmetric oxygenation pattern of benzynes **B** having two four-membered rings with high symmetry, where the difference in both rings appears to be small. Cycloadduct **8** could also be converted to the symmetrical hexakis(dimethyl)acetal **1** under acidic conditions.

Acetal **1** gave single crystals suitable for X-ray analysis (slow crystallization, hexane, EtOAc, –15 °C). The central benzene ring of **1** is planar, and all internal angles are almost 120° (Figure 2).<sup>13</sup> The average C–C bond length in the central benzene ring  $Q$  = 1.394 Å (exptl) [1.395 Å (calcd)], and the endo/exo bond lengths were essentially the same (endo 1.396 Å/exo 1.392 Å exptl) [endo 1.399 Å/exo 1.390 Å (calcd)];  $\delta_{\text{endo-exo}}$  = 0.004 Å [0.009 Å].<sup>14</sup>

Experimental/computational structures show a decrease in  $Q$  and  $\delta$  as a function of the electronegativity of rim atoms in **1a**–**1Ib**:  $Q$  = 1.401, 1.394, 1.389 Å;  $\delta$  = 0.023, 0.004, –0.006 Å. Various explanations exist for this effect.<sup>15</sup> NMR computations for **1** (146.8, 114.6, 56.3 ppm) match well the observed <sup>13</sup>C spectrum (141.0, 111.0, 51.7 ppm). Thus, structures and properties of these compounds are well predicted computationally.

Hexaexo-TCBB **2** was observed for the first time by cleavage of hexaacetal **1** with concentrated sulfuric acid.<sup>16</sup> The <sup>13</sup>C NMR in D<sub>2</sub>SO<sub>4</sub> showed that all acetal functionalities were cleanly removed to give quantitatively the characteristic peaks of the 1,2-dione moiety (189 and 173 ppm) expected for ketone **2** [194.2 and 179.1 (calcd)]<sup>14</sup> (Figure 3). Methanol (62 ppm) was generated during the deprotection of **1**.

The computationally predicted structure of **2** is planar with an average benzene bond length  $Q$  = 1.402 Å and a bond alternation  $\delta$  = 0.002<sub>3</sub> Å (exo = 1.401(4) Å; endo = 1.403(7) Å).<sup>14,17</sup> Although the related **II** with exo methylene groups displays essentially the same average bond length  $Q$  = 1.405 Å, the bond alternation  $\delta$  = 0.045(8) Å (exo = 1.382(1) Å; endo = 1.427(9) Å) is much larger. Notable also is the longer C–C bond length between the carbonyls of **2** (1.592 Å) versus that between the methylenes of **II** (1.513 Å). These trends are already seen in the simple cyclobutenes and will form the basis for a future paper.

**Acknowledgment.** We thank Prof. Yves Rubin, UCLA, for helpful discussions. This research was partially supported by the 21st Century COE program, a Grant-in-Aid for Young Scientists (B), and the Swiss National Fund.

**Supporting Information Available:** General procedures, spectral data for compounds **1**, **3**, and **5–9**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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- (9) For details, see Supporting Information.
- (10) The reaction was performed in dilute solution because of the poor solubility of bromotosylate **5** in Et<sub>2</sub>O. Choice of the leaving group was also important. For example, the reaction of the corresponding bromotriflate gave low yield of the cycloadduct **6**. The same situation was observed for the third [2 + 2] cycloaddition of **7**.
- (11) Recently, related chemoselective generation of polyfunctionalized arynes by I/Mg exchange of 2-iodophenyl sulfonates was reported. See: Sapountzis, I.; Lin, W.; Fisher, M.; Knochel, P. *Angew. Chem., Int. Ed.* **2004**, *43*, 4364–4366.
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- (13) Crystallographic data for **1**: C<sub>24</sub>H<sub>36</sub>O<sub>12</sub>, MW = 516.53, colorless crystal, 0.38 × 0.20 × 0.08 mm, monoclinic, space group P2<sub>1</sub>/c, Z = 4, T = 93(2) K, a = 12.3650(13), b = 10.4112(7), c = 22.0747(16) Å, β = 115.171(6)°, V = 2571.9(4) Å<sup>3</sup>, λ(Mo Kα) = 0.71073 Å, μ = 0.107 mm<sup>–1</sup>. Intensity data were collected on a Bruker SMART 1000 diffractometer. The structure was solved by direct methods and refined by the full-matrix least-squares on F<sup>2</sup> (SHELXL97). A total of 45 417 reflections were measured and 5897 were independent. Final R1 = 0.0472, wR2 = 0.1170 (4999 refs; I > 2σ(I)), and GOF = 1.055 (for all data, R1 = 0.0570, wR2 = 0.1218).
- (14) Computations: B3LYP<sup>14a</sup> DFT and MP2<sup>14b</sup> methods were employed, using GAMESS<sup>14c</sup> and GAUSSIAN.<sup>14d</sup> As substantiated, previously optimized geometries were obtained with B3LYP/cc-pVDZ.<sup>14e</sup> Subsequent single point GIAO chemical shielding computations<sup>14f</sup> relative to TMS were performed using the DZ(2d,p) basis set.<sup>14g</sup> Since B3LYP is known to overestimate the deshielding contributions to the chemical shielding tensor in cases when electron correlation is important, MP2 was also used. (a) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev.* **1988**, *B37*, 785–789. (b) Moller, C.; Plesset, M. S. *Phys. Rev.* **1934**, *46*, 618. (c) Schmidt, M. W.; Baldrige, K. K.; Boatz, J. A.; Elbert, S. T.; Gordon, M. S.; Jensen, J. H.; Koseki, S.; Matsunaga, N.; Nguyen, K. A.; Su, S.; Windus, T. L.; Elbert, S. T. *J. Comput. Chem.* **1993**, *14*, 1347. (d) Frisch, M. J.; et al. *GAUSSIAN 03*; Gaussian, Inc.: Pittsburgh, PA, 2003. (e) Dunning, T. H., Jr.; Hay, P. J. In *Modern Theoretical Chemistry*; Schaefer, H. F., III, Ed.; Plenum: New York, 1976; Vol. 3, p 1. (f) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648–5652. (g) Gauss, J. *Chem. Phys.* **1993**, *99*, 3629.
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- (16) Rubin, Y.; Knobler, C. B.; Diederich, F. *J. Am. Chem. Soc.* **1990**, *112*, 1607–1617. Protonation of **2** has little effect on the chemical shift, compared to the previously reported tetraketone derivative; see ref 8.
- (17) Selected geometries for **2**: C–C<sub>endo</sub> 1.403(7) Å, C–C<sub>exo</sub> 1.401(4) Å, C<sub>ar</sub>–C<sub>co</sub> 1.519(3) Å, C<sub>co</sub>–C<sub>co</sub> 1.592(9) Å, C=O 1.188(5) Å; C<sub>ar</sub>–C<sub>ar</sub>–C<sub>ar</sub> 120.0°, C<sub>ar</sub>–C<sub>ar</sub>–C<sub>co</sub> 93.57°, C<sub>ar</sub>–C<sub>co</sub>–C<sub>co</sub> 86.43°, C<sub>co</sub>–C<sub>co</sub>–O<sub>co</sub> 136.69°.

JA064063E