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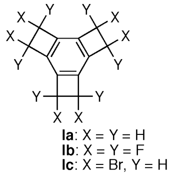
Dodecamethoxy- and Hexaoxotricyclobutabenzene: Synthesis and Characterization

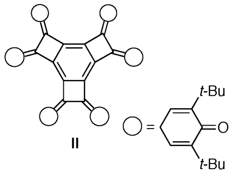
Toshiyuki Hamura, Yousuke Ibusuki, Hidehiro Uekusa, Takashi Matsumoto, Jay S. Siegel,[†]
Kim K. Baldridge, and Keisuke Suzuki*

Interactive Research Center of Science, Department of Chemistry, Tokyo Institute of Technology, SORST, Japan Science and Technology Corporation (JST), O-okayama, Meguro-ku, Tokyo 152-8551, Japan, and the Institute of Organic Chemistry, University of Zürich, Winterthurerstrasse 190, Zürich CH-8057, Switzerland

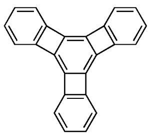
Received June 9, 2006; E-mail: ksuzuki@chem.titech.ac.jp

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.[1] Tricyclobutabenzene (TCBB) **Ia**[2] serves as a key model compound in this discussion, to which cognates, such as halo-substituted derivatives **Ib**, **Ic**,[3,4] hexamethylene derivative **II**,[5] and triangular [4]phenylene derivative **III**,[6] are compared.



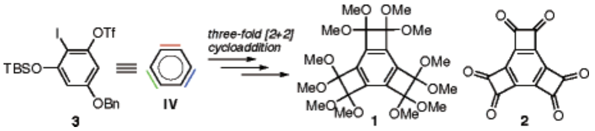


II



III

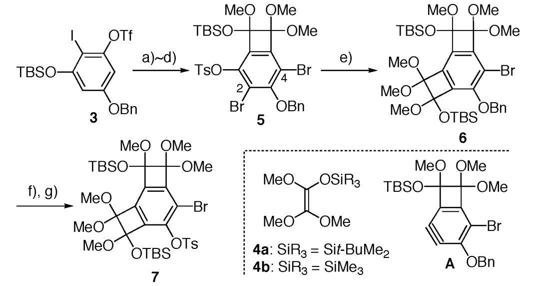
We report the syntheses of two new cognates, dodecamethoxy-TCBB **1** and hexaoxo-TCBB **2**, via 3-fold [2 + 2] cycloadditions of benzyne and ketene silyl acetals (KSAs).[7] The present synthesis overcomes numerous issues in previously reported synthesis of TCBBs[8] and uses the selectively protected 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**[9] 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 siloxy group as described before.[7]

Benzyne **A**, generated from **5**, cleanly underwent the second [2 + 2] cycloaddition with KSA **4a** to give cycloadduct **6** in 54% yield.[10] 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;[11] (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).[12] The regioselectivity issues raised a question of which is the more influential directing 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.

Scheme 1[a]



[a] Reagents and conditions: (a) **4a**, *n*-BuLi, Et_2O, −78 °C, 5 min; (b) aq. KF, *n*-Bu_4NCl, CH_3CN, 0 → 25 °C, 5 h; (c) NBS, *i*-Pr_2NEt, CH_2Cl_2, −78 °C, 1 h; (d) TsCl, K_2CO_3, acetone, 25 °C, 10 h (**5**: 48%, 4 steps); (e) **4a**, *n*-BuLi, Et_2O, 0 °C (**6**: 54%, syn/anti = 1.5:1); (f) H_2, Pd/C, EtOAC, 25 °C; (g) TsCl, K_2CO_3, acetone, 25 °C, 10 h (**7-syn**: 83%, 2 steps, **7-anti**: 81%, 2 steps).

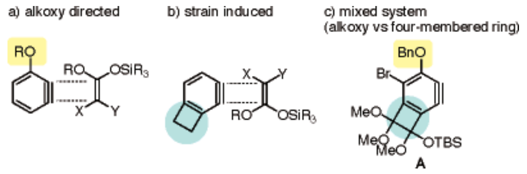
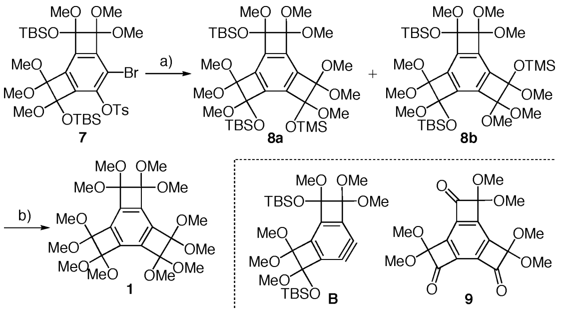


Figure 1. Regioselectivity of substituted benzynes.

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[a]



[a] Reagents and conditions: (a) **4b**, *n*-BuLi, Et_2O, 0 °C (**8**: 51% from **7-syn**, **8a**/**8b** = 6:1); (b) $(MeO)_3CH$, TsOH, MeOH, 60 °C (**1**: 51% from **7-syn**, 56% from **7-anti**, 2 steps).

[†] Visiting professor (Jan. 1−Mar. 31, 2005) on leave from University of Zürich.

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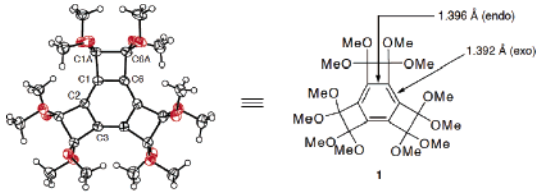

Figure 2. Molecular structure of **1**. Selected exptl[13] [calcd[14]] distances (Å) and angles (°): C_1-C_2 1.389(2) [1.390], C_1-C_6 1.396(2) [1.399], C_1-C_{1A} 1.523(2) [1.530], C_6-C_{6A} 1.529(2) [1.530], $C_{1A}-C_{6A}$ 1.614(2) [1.623]; $C_6-C_1-C_2$ 120.2(1) [120.0], $C_1-C_2-C_3$ 119.8(1) [120.0], $C_1-C_6-C_{6A}$ 94.0(1) [94.2], $C_6-C_1-C_{1A}$ 94.1(1) [94.2], $C_1-C_{1A}-C_{6A}$ 86.0(1) [85.8], $C_6-C_{6A}-C_{1A}$ 85.7(1) [85.8].

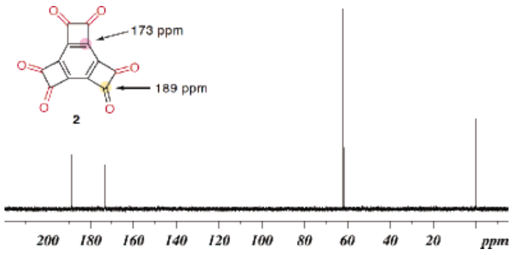

Figure 3. ^{13}C NMR spectra of **2** (125 MHz, D_2SO_4, TMS as reference).

of **8a** (syn/anti stereoisomers) was unequivocally assigned through derivatization to the corresponding triketone **9** by two-step hydrolysis [(i) TsOH, CH_2Cl_2, MeOH, 25 °C; (ii) $BF_3{\cdot}Et_2O$, H_2O, $-78 \rightarrow 25$ °C].[9] This high regioselectivity (**8a**/**8b** = 6:1) is striking in view of the pseudo-symmetric oxygenation pattern of benzyne **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 the all internal angles are almost 120° (Figure 2).[13] 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)]; $\delta_{\text{endo}-\text{exo}} = 0.004$ Å [0.009 Å].[14]

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

Hexaoxo-TCBB **2** was observed for the first time by cleavage of hexaacetal **1** with concentrated sulfuric acid.[16] The ^{13}C NMR in D_2SO_4 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)][14] (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 $\delta = 0.002_3$ Å (exo = 1.401(4) Å; endo = 1.403(7) Å).[14,17] Although the related **II** with exo methylene groups displays essentially the same average bond length Q = 1.405 Å, the bond alternation δ = 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.

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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_2O. 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**: $C_{24}H_{36}O_{12}$, MW = 516.53, colorless crystal, 0.38 × 0.20 × 0.08 mm, monoclinic, space group $P2_1/c$, $Z = 4$, 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^3, λ(Mo Kα) = 0.71073 Å, μ = 0.107 mm^{-1}. 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^2 (SHELXL97). A total of 45 417 reflections were measured and 5897 were independent. Final $R1 = 0.0472$, $wR2 = 0.1170$ (4999 refs; $I > 2\sigma(I)$), and GOF = 1.055 (for all data, $R1 = 0.0570$, $wR2 = 0.1218$).

(14) Computations: B3LYP[14a] DFT and MP2[14b] methods were employed, using GAMESS[14c] and GAUSSIAN.[14d] As substantiated, previously optimized geometries were obtained with B3LYP/cc-pVDZ.[14e] Subsequent single point GIAO chemical shielding computations[14f] relative to TMS were performed using the DZ(2d,p) basis set.[14g] 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.; Baldridge, 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**: $C-C_{\text{endo}}$ 1.403(7) Å, $C-C_{\text{exo}}$ 1.401(4) Å, $C_{\text{ar}}-C_{\text{CO}}$ 1.519(3) Å, $C_{\text{CO}}-C_{\text{CO}}$ 1.592(9) Å, C=O 1.188(5) Å; $C_{\text{ar}}-C_{\text{ar}}-C_{\text{ar}}$ 120.0°, $C_{\text{ar}}-C_{\text{ar}}-C_{\text{co}}$ 93.57°, $C_{\text{ar}}-C_{\text{CO}}-C_{\text{CO}}$ 86.43°, $C_{\text{CO}}-C_{\text{CO}}-O_{\text{CO}}$ 136.69°.

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