J|A|C|S
COMMUNICATIONS

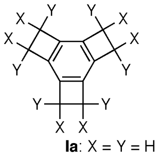
Poly-Oxygenated Tricyclobutabenzenes via Repeated [2 + 2] Cycloaddition of Benzyne and Ketene Silyl Acetal

Toshiyuki Hamura, Yousuke Ibusuki, Hidehiro Uekusa, Takashi Matsumoto, and Keisuke Suzuki*

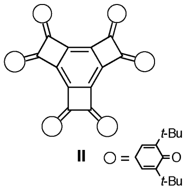
Department of Chemistry, Tokyo Institute of Technology, and SORST, Japan Science and Technology Agency (JST), O-okayama, Meguro-ku, Tokyo 152-8551, Japan

Received January 13, 2006; E-mail: ksuzuki@chem.titech.ac.jp

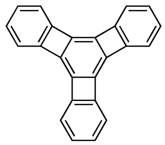
Tricyclobutabenzenes (TCBBs) **I** constitute a class of strained aromatic compounds of interest from theoretical and synthetic points of view.[1] However, the syntheses have been limited to the parent compound **Ia**,[2] halo-substituted derivatives **Ib** and **Ic**,[3,4] hexamethylene derivative **II**,[5] and triangular [4]phenylene derivative **III**.[6]



Ia: X = Y = H
Ib: X = Y = F
Ic: X = Br, Y = H

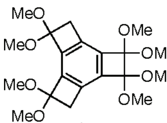


II

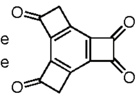


III

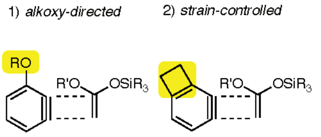
We now report an efficient and flexible route to poly-oxygenated derivatives of **I** (**1** and **2**) by exploiting the [2 + 2] cycloaddition of benzyne and ketene silyl acetal (KSA).[7,8] Two regiocontrolling steps (vide infra) enable a potential and general approach to various structurally elaborate TCBBs with oxygen functionalities selectively installed. Also described is an intriguing structural feature related to the strained four-membered ring annelation of benzene.



1



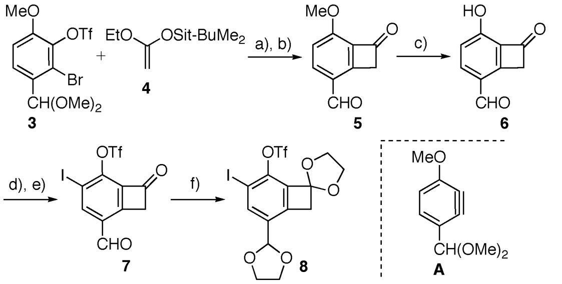
2



Scheme 1 shows the first [2 + 2] cycloaddition. Treatment of bromotriflate **3**[9] with *n*-BuLi in the presence of KSA **4** cleanly gave, after acid hydrolysis, ketoaldehyde **5** as a single product (60%, two steps). The highly regioselective nature of the [2 + 2] cycloaddition can be ascribed to the directing effect of the methoxy group in benzyne **A** as described before.[8] Demethylation of **5** gave phenol **6**, which was converted to iodotriflate **7** by iodination and triflate formation. The carbonyl groups in **7** were masked as ethylene acetals to give bis-acetal **8**, ready for the second [2 + 2] cycloaddition.

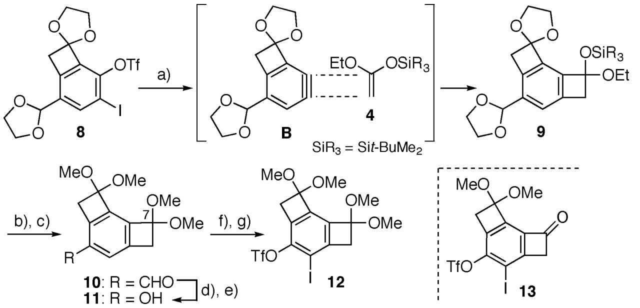
Scheme 2 shows the second cycloaddition of the benzyne generated from **8**, which also proceeded regioselectively by virtue of the ring strain.[10] Treatment of **8** with *n*-BuLi in the presence of KSA **4** cleanly gave cycloadduct **9** as a single product in 70% yield. Conversion of **9** to aldehyde **10** was achieved by exposure to acidic methanol followed by the selective hydrolysis of the exocyclic acetal by careful acid treatment (90%, two steps). Baeyer−Villiger oxidation of **10** and hydrolysis of the resulting formate gave phenol **11** (76%, two steps), which was converted to iodotriflate **12**. For the iodination stage, the presence of *i*-Pr_2NEt was essential for coping with the lability of the C(7) acetal in **11**; otherwise, the product was triflate **13** lacking the C(7) acetal.[11]

Scheme 1. Synthesis of Iodotriflate **8** via First [2 + 2] Cycloaddition[a]



[a] Reagents and conditions: (a) **4**, *n*-BuLi, THF, −78 °C, 5 min; (b) aq HF, CH_3CN, 25 °C, 15 h (**5**; 60% in 2 steps); (c) $AlCl_3$, $ClCH_2CH_2Cl$, 60 °C, 13 h; (d) $BnMe_3N^+ICl_2^-$, $NaHCO_3$, CH_2Cl_2, rt, 20 h; (e) Tf_2O, pyr, CH_2Cl_2, 0 °C, 5 min; (f) ethylene glycol, TsOH, benzene, reflux, 28 h (**8**; 60% in 4 steps).

Scheme 2. Synthesis of Iodotriflate **12** via Second [2 + 2] Cycloaddition[a]



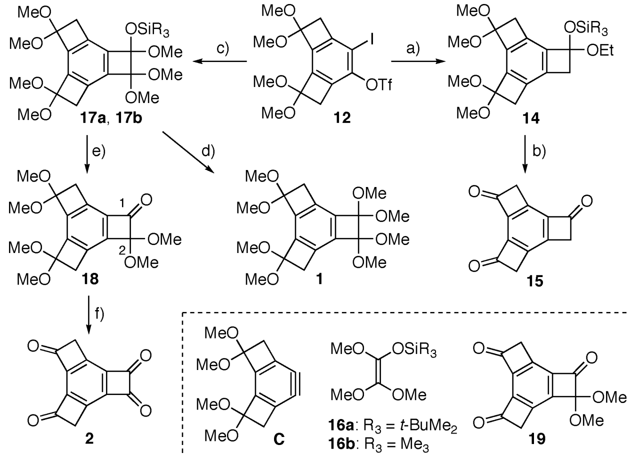
[a] Reagents and conditions: (a) **4**, *n*-BuLi, THF, −78 °C, 5 min (**9**; 70%); (b) TsOH, MeOH, rt, 10 h; (c) 0.12 M H_2SO_4, THF, rt, 5 h (**10**; 90% in 2 steps); (d) mCPBA, CH_2Cl_2, 40 °C, 14 h; (e) 0.1 M NaOH, 1,4-dioxane, 0 °C → rt, 42 h (**11**, 76% in 2 steps); (f) $BnMe_3N^+ICl_2^-$, *i*-Pr_2NEt, CH_2Cl_2, −78 → −50 °C, 7 h; (g) Tf_2O, pyr, CH_2Cl_2, 0 °C, 5 min (**12**; 75% in 2 steps).

Scheme 3 shows the third cycloaddition en route to several TCBBs. The benzyne precursor **12** served as an efficient branching point to several highly oxygenated TCBBs via dicyclobutabenzyne **C**. Treatment of **12** with *n*-BuLi in the presence of KSA **4** (THF, −78 °C) gave 79% yield of cycloadduct **14**. Acid treatment of **14** furnished triketone **15** in 92% yield as colorless crystals, which in itself was notable in view of the high strain with three sp^2-carbon atoms in the four-membered rings.

The corresponding reaction of **C** with fully oxygenated KSA **16a** cleanly gave cycloadduct **17a**, which was converted to octamethoxy TCBB **1** by treatment with acidic methanol. The cycloaddition with KSA **16b** gave cycloadduct **17b**, which was selectively transformed to monoketone **18** by acid hydrolysis of the C(1) silyl acetal (58%, two steps). However, attempts at the full deprotection of ketone **18** to tetra-oxo compound **2** by using

10.1021/ja0602647 CCC: $33.50 © 2006 American Chemical Society

Scheme 3. Third [2 + 2] Cycloaddition[a]



[a] Reagents and conditions: (a) **4**, *n*-BuLi, THF, −78 °C, 5 min (**14**; 79%); (b) aq HF, CH_3CN, −10 °C → rt, 2 h (**15**; 92%); (c) **16a** or **16b**, *n*-BuLi, Et_2O, −78 °C, 5 min; (d) TsOH, MeOH, rt, 50 h (**1**; 55% in 2 steps); (e) aq HF, CH_3CN, −16 °C, 20 min (**18**; 58% in 2 steps); (f) $BF_3{\cdot}Et_2O$, H_2O, THF, −20 °C → rt, 2 h (**2**; 84%).

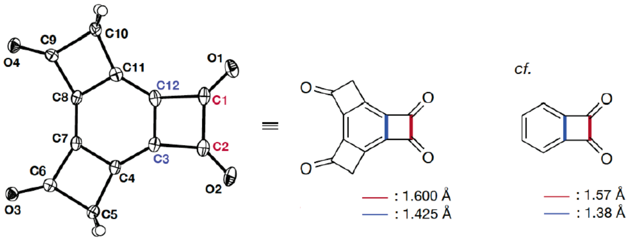


Figure 1. Molecular structure of **2**. Selected distances (Å) and angles (deg): C_3-C_4 1.408(3), C_4-C_7 1.406(3), C_7-C_8 1.403(3), $C_{12}-C_3$ 1.425(3), C_3-C_2 1.518(3), C_1-C_2 1.600(3), C_4-C_5 1.531(3), C_5-C_6 1.566(3), C_6-C_7 1.522(3); $C_3-C_4-C_7$ 118.4(2), $C_4-C_7-C_8$ 121.2(2), $C_{12}-C_3-C_4$ 120.4(2), $C_{12}-C_3-C_2$ 93.2(2), $C_3-C_2-C_1$ 86.5(2), $C_3-C_2-O_2$ 137.6(2), $C_1-C_2-O_2$ 135.9(2), $C_4-C_5-C_6$ 83.8(2), $C_5-C_6-C_7$ 90.2(2), $C_6-C_7-C_4$ 89.8(2), $C_7-C_4-C_5$ 96.1(2), $C_5-C_6-O_3$ 134.4(2), $C_7-C_6-O_3$ 135.3(2).

aqueous HF in CH_3CN were unsuccessful and gave only a small amount of partially deprotected product **19**. Several common conditions for acetal hydrolysis also failed, affording a low yield of monoacetal **19** and/or complex mixtures of products, presumably due to the increased strain by the poly-oxo substitutions. Fortunately, a good solution was provided by the use of $BF_3{\bullet}OEt_2$ containing a small amount of H_2O, giving tetraketone **2** in 84% yield.

Ketone **2**, thus obtained, has a π-conjugated structure with one or two carbonyl groups on each four-membered ring. Such a system has never been synthesized nor theoretically studied.[12] Fortunately, careful crystallization of **2** (hexanes−EtOAc, −10 °C) gave single crystals suitable for X-ray analysis (Figure 1).

Notably, the C−C bond lengths in the central benzene ring were essentially the same (ca. 1.40 Å), except for the slightly longer length of the annelated C_3-C_{12} bond (1.425 Å).[13] This slight elongation could be related to *the extreme elongation (1.600 Å) of the C_1-C_2 bond* that connects the two carbonyl groups. This is far longer than the 1.48 Å expected for a normal $C(sp^2)-C(sp^2)$ single bond,[14] and exceeds the length of the cisoid dicarbonyl C−C bond in isatin (1.54 Å).[15] Nonbonded lone pair repulsion[15] and/or negative hyperconjugative interaction between the oxygen lone pairs and the adjacent C−C bond σ^*-orbital[16] may be invoked; however, more detailed theoretical and experimental studies are necessary to understand the origin of the long dicarbonyl C−C bond length in **2**, which is *even longer* than the corresponding *unusually long* bond of the simple benzocyclobutenedione (1.57 Å).[17]

In summary, we have developed a synthetic route to highly oxygenated TCBBs, which relied on the repeated regioselective [2 + 2] cycloaddition of benzyne and ketene silyl acetals. Further work is in progress for the syntheses of other theoretically interesting derivatives, including fully conjugated π-systems.

Acknowledgment. We thank Prof. Jay S. Siegel, Zürich, for helpful discussions. Partial financial support was provided by the 21st Century COE Program.

Supporting Information Available: General procedures and spectral data for compounds **1**, **2**, **5**−**15**, and **17**, **18**. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) (a) Siegel, J. S. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1721−1723. (b) Frank, N. L.; Siegel, J. S. In *Advances in Theoretically Interesting Molecules*; Thummel, R. P., Ed.; JAI Press: Stamford, CT, 1995; Vol. 3, pp 209−260.
(2) (a) Nutakul, W.; Thummel, R. P.; Taggart, A. D. *J. Am. Chem. Soc.* **1979**, *101*, 770−771. (b) Doecke, C. W.; Garratt, P. J.; Shahriari-Zavareh, H.; Zahler, R. *J. Org. Chem*. **1984**, *49*, 1412−1417. (c) Boese, R.; Bläser, D.; Billups, W. E.; Haley, M. M.; Maulitz, A. H.; Mohler, D. L.; Vollhardt, K. P. C. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 313−317.
(3) (a) Camaggi, G. *J. Chem. Soc. C* **1971**, 2382−2388. (b) Thummel, R. P.; Korp, J. D.; Bernal, I.; Harlow, R. L.; Soulen, R. L. *J. Am. Chem. Soc*. **1977**, *99*, 6916−6918.
(4) Stanger, A.; Ashkenazi, N.; Boese, R.; Bläser, D.; Stellberg, P. *Chem.*−*Eur. J.* **1997**, *3*, 208−211.
(5) Kawase, T.; Minami, Y.; Nishigaki, N.; Okano, S.; Kurata, H.; Oda, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 316−319.
(6) (a) Diercks, R.; Vollhardt, K. P. C. *J. Am. Chem. Soc.* **1986**, *108*, 3150−3152. (b) Mohler, D. L.; Vollhardt, K. P. C.; Wolff, S. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 1151−1153. (c) Boese, R.; Matzger, A. J.; Mohler, D. L.; Vollhardt, K. P. C. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1478−1481.
(7) For reviews on arynes, see: (a) Hoffmann, R. W. *Dehydrobenzene and Cycloalkynes*; Academic: New York, 1967. (b) Kessar, S. V. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon: Oxford, U.K., 1991; Vol. 4, pp 483−515.
(8) (a) Matsumoto, T.; Hosoya, T.; Katsuki, M.; Suzuki, K. *Tetrahedron Lett.* **1991**, *32*, 6735−6736. (b) Hosoya, T.; Hasegawa, T.; Kuriyama, Y.; Matsumoto, T.; Suzuki, K. *Synlett* **1995**, 177−179. (c) Hosoya, T.; Hasegawa, T.; Kuriyama, Y.; Suzuki, K. *Tetrahedron Lett.* **1995**, *62*, 3377−3380. (d) Hosoya, T.; Hamura, T.; Kuriyama, Y.; Matsumoto, M.; Suzuki, K. *Synlett* **2000**, 520−522. (e) Hamura, T.; Hosoya, T.; Yamaguchi, H.; Kuriyama, Y.; Tanabe, M.; Miyamoto, M.; Yasui, Y.; Matsumoto, T.; Suzuki, K. *Helv. Chim. Acta* **2002**, *85*, 3589−3604.
(9) Compound **3** was prepared from isobromovanillin via selective bromination, triflation, and acetalization.
(10) Hamura, T.; Ibusuki, Y.; Sato, K.; Matsumoto, M.; Osamura, Y.; Suzuki, K. *Org. Lett.* **2003**, *5*, 3551−3554.
(11) Use of $NaHCO_3$ was not effective as an acid scavenger. Iodotriflate **13** was obtained in 35% yield; see: Kajigaeshi, S.; Kakinami, T.; Yamasaki, H.; Fujisaki, S.; Kondo, M.; Okamoto, T. *Chem. Lett.* **1987**, 2109−2112.
(12) (a) Faust, R.; Glendening, E. D.; Streitwieser, A.; Vollhardt, K. P. C. *J. Am. Chem. Soc.* **1992**, *114*, 8263−8268. (b) Baldridge, K. K.; Siegel, J. S. *J. Am. Chem. Soc.* **1992**, *114*, 9583−9587. (c) Stanger, A.; Tkachenko, E. *J. Comput. Chem.* **2001**, *22*, 1377−1386.
(13) Crystallographic data for **2**: $C_{12}H_4O_4$, MW = 212.15, yellow crystal, 0.20 × 0.05 × 0.01 mm, orthorhombic, space group $P2_12_12_1$, $Z = 4$, $T = 93$ K, $a = 10.0583(3)$, $b = 5.8983(2)$, $c = 15.2143(4)$ Å, $V = 902.62(5)$ Å^3, $\lambda(\text{Mo K}\alpha) = 0.71073$ Å, $\mu = 0.120$ 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 11883 reflections were measured and 1216 were independent. Final $R1 = 0.0403$, $wR2 = 0.0976$ (1085 refs; $I > 2\sigma(I)$), and GOF = 1.038 (for all data, $R1 = 0.0487$, $wR2 = 0.1004$).
(14) Allen, F. H.; Kennard, O.; Watson, D. G.; Brammer, L.; Orpen, A. G.; Taylor, R. *J. Chem. Soc., Perkin Trans. 2* **1987**, *S1*.
(15) Palenik, G. J.; Koziol, A. E.; Katritzky, A. R.; Fan, W.-Q. *J. Chem. Soc., Chem. Commun.* **1990**, 715−716.
(16) (a) Rathna, A.; Chandrasekhar, J. *J. Chem. Soc., Perkin Trans. 2* **1991**, 1661−1666. (b) Cerioni, G.; Janoschek, R.; Rappoport, Z.; Tidwell, T. T. *J. Org. Chem.* **1996**, *61*, 6212−6217.
(17) Allen, F. H.; Trotter, J. *J. Chem. Soc. B* **1970**, 916−920.

JA0602647