JOC*Note*

# Tris(arylmethyl) Derivatives of 1,3,5-Trimethoxy- and 1,3,5-Triethylbenzene

Samah Simaan,[†] Jay S. Siegel,[‡] and Silvio E. Biali*,[†]

*Department of Organic Chemistry, The Hebrew University of Jerusalem, Jerusalem 91904, Israel, and Department of Chemistry, University of California—San Diego, La Jolla, California 92093-0358*

*silvio@vms.huji.ac.il*

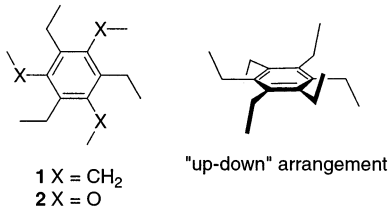
*Received January 7, 2003*

**Abstract:** The hexasubstituted benzenes **7** and **9b** were synthesized starting from **3** and **8b**, respectively. In the crystal, **9b** adopts the fully alternated conformation with all arylmethyl groups oriented syn.

In the lowest energy conformation of hexaethylbenzene (**1**), the ethyl rings are oriented perpendicular to the central ring in a fully alternated up—down disposition.[1,2] In this arrangement, the three ethyl groups at the 1, 3, and 5 positions of the central ring are all pointing to the same face of the aryl ring, while the rest of the ethyls point in the opposite direction (Chart 1). Molecular mechanics calculations have indicated that the fully alternated conformation of **1** is ca. 3.5 kcal mol$^{-1}$ lower in energy than a nonalternated conformation possessing two pairs of *o*-ethyl groups oriented toward the same face (a syn arrangement).[2,3] Hexasubstituted benzene derivatives possessing substituents nearly isosteric to ethyl groups (e.g., bromomethyl groups) adopt a similar conformation.[4] The 1,3,5 vs 2,4,6 facial differentiation of the side chains of **1** can be exploited for the design of ligands in which three substituents (binding groups) are oriented toward the same face of the aromatic group, thus achieving a certain degree of preorganization.[5−7]

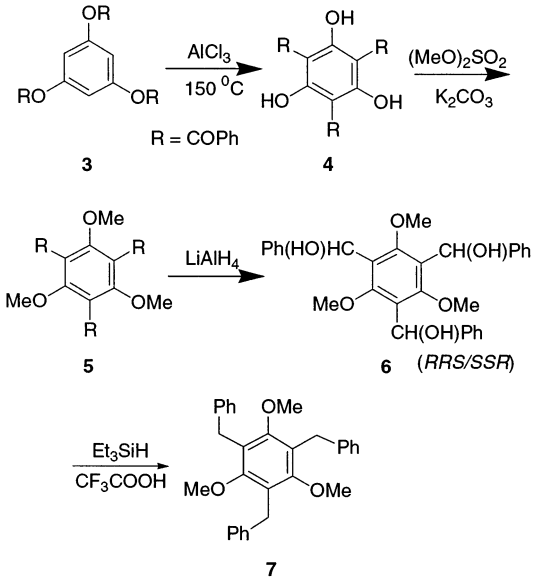
Of synthetic interest are derivatives structurally related to **1** where the 1, 3, and 5 positions of the ring are substituted by arylmethyl groups. These derivatives could be used as scaffolds for the construction of elaborated molecular hosts via electrophilic substitution of the peripheral aromatic rings. If properly oriented, the four aromatic rings could provide four "walls" delimiting a hydrophobic pocket.[8] The hexasubstituted benzene **7** has been prepared by Wittmann and co-workers via trimerization of the ketene derived from benzylmalonyl dichloride, followed by treatment of the resulting product with dimethyl sulfate/methanolic KOH.[9] In this paper, we describe an alternative synthesis of **7** and the preparation and crystal structure of a hexasubstituted benzene structurally related to **1** in which three ethyls have been replaced by arylmethyl groups (**9b**).

**CHART 1**




**1** X = $CH_2$
**2** X = O

**SCHEME 1**




The synthetic approach utilized for the preparation of **7** is depicted in Scheme 1. The triester **3** was rearranged to **4** according to the literature procedure.[10] After the phenolic OH groups were protected by methylation, the three carbonyl groups were reduced to methylenes in a two-step sequence. Initially, the carbonyl groups of **5** were reduced to alcohol functionalities by treatment with $LiAlH_4$. This step introduces three stereocenters, and two enantiomeric pairs of configurational isomers (*RRR*/*SSS* and *RRS*/*SSR*) are possible for **6**. Under fast rotations of the side chains, the *RRR*/*SSS* and *RRS*/*SSR* isomers

[†] The Hebrew University of Jerusalem.
[‡] University of California—San Diego.

(1) For reviews on the conformation of alkyl groups, see: (a) Berg, U.; Sandström, J. *Adv. Phys. Org. Chem.* **1989**, *25*, 1. (b) Eliel, E. L.; Wilen, S. H.; Mander, L. N. In *Stereochemistry of Organic Compounds*; Wiley: New York, 1994; Chapter 10. (c) See also: Metzger, J. V.; Chanon, M. C.; Roussel, C. M. *Rev. Heteroatom Chem.* **1997**, *16*, 1.

(2) Iverson, D. J.; Hunter, G.; Blount, J. F.; Damewood, J. R., Jr.; Mislow, K. *J. Am. Chem. Soc.* **1981**, *103*, 6073.

(3) See also: Gottlieb, H. E.; Ben-Ari, C.; Hassner, A.; Marks, V. *Tetrahedron* **1999**, *55*, 4003.

(4) Marsau, P. *Acta Crystallogr.* **1965**, *18*, 851.

(5) See, for example: (a) Hou, Z.; Stack, T. D. P.; Sunderland, C. J.; Raymond, K. N. *Inorg. Chim. Acta* **1997**, *263*, 341. (b) Metzger, A.; Lynch, V. M.; Monahan, M. K. C.; Anslyn, E. V. *Angew. Chem., Int. Ed.* **1998**, *37*, 649. (c) Szabo, T.; O'Leary, B. M.; Rebek, J., Jr. *Angew. Chem., Int. Ed.* **1998**, *37*, 3410. (d) Tam-Chang, S.-W.; Stehouwer, J. S.; Hao, J. *J. Org. Chem.* **1999**, *64*, 334. (e) Chin, J.; Oh, J.; Jon, S. Y.; Park, S. H.; Walsdorff, C.; Stranix, B.; Ghossoub, A.; Lee, S. J.; Chung, H. J.; Park, S.-M.; Kim, K. *J. Am. Chem. Soc.* **2002**, *124*, 5374.

(6) For a review of facially segregated host molecules structurally related to **1**, see: Hennrich, G.; Anslyn, E. V. *Chem. Eur. J.* **2002**, *8*, 2219.

(7) Kilway, K. V.; Siegel, J. S. *Tetrahedron* **2001**, *57*, 3615.

(8) See, for example: Choi, H.-J.; Park, Y. S.; Yun, S. H.; Kim, H. S.; Cho, C. S.; Ko, K.; Ahn, K. H. *Org. Lett.* **2002**, *4*, 795.

(9) Wittmann, H.; Illi, V.; Ziegler, E. *Monatsh. Chem.* **1967**, *98*, 1108. See also: Wittmann, H.; Rathmayr, H. *Z. Naturforsh. B* **1972**, *27*, 528.

(10) Rosemund, K. W.; Lohfert, H. *Ber.* **1928**, *61*, 2601.

10.1021/jo034016u CCC: $25.00 
Published on Web 03/28/2003

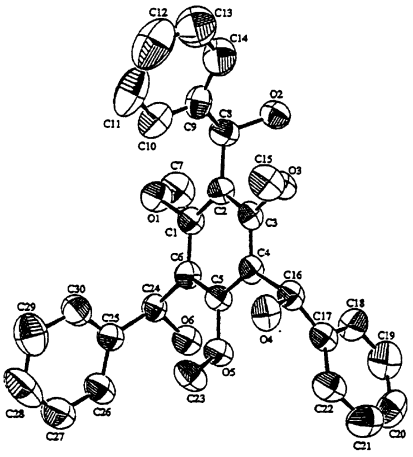


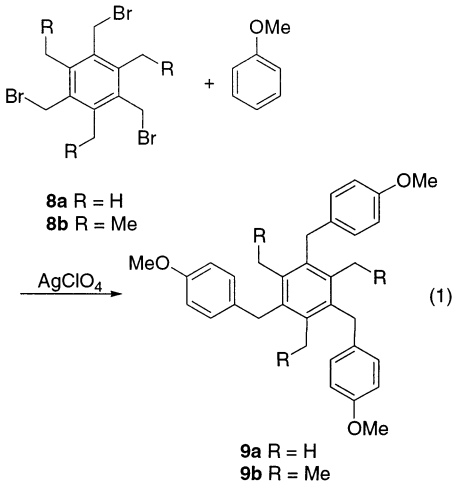
**FIGURE 1.** Crystal structure of **6**.

possess averaged symmetries[11] isomorphous to $C_3$ and $C_2$, respectively. The NMR spectra were consistent with a derivative of bilateral symmetry. For example, two signals each in a 2:1 ratio were observed for the methoxy and the CHOH protons. On this basis, it could be concluded that the compound formed preferentially is the *RRS/SSR* stereoisomer. This structural assignment was corroborated by X-ray crystallography which indicated that the product obtained was indeed the *RRS/SSR* isomer (Figure 1).[12]

Notably, in the crystal conformation a pair of methoxy groups as well as a pair of phenyls of the CH(OH)Ph units are pointing to opposite faces of the central aryl ring. For derivatives of **2**, a lower relative stability of the all-alternated up−down arrangement (cf. Chart 1) over nonalternated ones (as compared to **1**) could be expected since the former conformation should be destabilized by the presence of the three O-Me dipoles oriented in a nearly parallel fashion. This effect together with hydrogen-bonding interactions may contribute to the presence in the crystal of the nonalternated conformation.[13] The reduction of the alcohol functionalities of **6** was achieved by ionic hydrogenation[14] ($Et_3SiH/CF_3COOH$) yielding **7**, the tribenzyl analogue of **2**. The $^1H$ and $^{13}C$ NMR spectra of **7** were fully consistent with the proposed structure.

For the preparation of a tribenzyl analogue of **1,** we attempted first Friedel−Crafts benzylations of 1,3,5-triethylbenzene using $AlCl_3$ as catalyst. However, as indicated by $^1H$ NMR spectroscopy, the ethyl groups migrated under the reaction conditions. Fortunately, a literature search uncovered a promising method for the preparation of the target compound. In 1976, Zavada, Pankova, and Arnold reported that the reaction of 1,3,5-tris(bromomethyl)mesitylene (**8a**) with anisole (the solvent of the reaction) in the presence of $AgClO_4$ as the Lewis acid yields mainly the product resulting from the

**SCHEME 2**




para alkylation of three anisole molecules (**9a**, Scheme 2).[15]

An attractive feature of this reaction is the use of a silver salt as the electrophilic catalyst rather than $AlCl_3$, since it could be expected that no detachment of the ethyl substituents will take place under the reaction conditions. Patterned after this report, the triethyl derivative **8b** (readily available by exhaustive bromomethylation of 1,3,5-triethylbenzene)[7,16] was reacted with anisole under reaction conditions similar to those reported for **8a**. The reaction proceeded readily as evidenced by the nearly immediate precipitation of yellow AgBr. The reaction worked best with anhydrous $AgClO_4$, while other silver salts (such as $AgNO_3$) yielded less satisfactory results. $^1H$ NMR analysis of the crude reaction product indicated that no rearrangement of the ethyls took place and that the product consisted of an isomeric mixture derived from (mono) alkylation at the ortho or para positions of the anisole ring. Crystallization from $CHCl_3$/EtOH afforded the pure tris(*p*-methoxybenzyl) triethyl derivative **9b** in 18% yield. This compound displayed in the $^1H$ NMR spectrum a pair of doublets for the aromatic protons, in agreement with the target compound derived from para alkylation of anisole. The hexasubstituted benzene derivative **9b** is more conformationally rich than the parent **1** due to the presence of two types of substituents (ethyl and anisyl) on the central ring, which increases the number of different up−down orientations. In addition, each of these arrangements may exist in several conformations resulting from the possible orientations of the peripheral aryl and OMe groups around the $CH_2$−anisyl and Ar−OMe bonds, respectively. Four basic arrangements are possible for a given anisyl ring depending on the "perpendicular" or "eclipsed" orientation relative to the methylene group (Figure 2).[17]

Single crystals of **9b** were grown from chloroform/EtOH and submitted to X-ray diffraction.[18] The multi-

(11) See ref 1b, p 91.

(12) Crystal data for **6**: $C_{30}H_{30}O_6$, space group $C_c$, $a$ = 9.997(4) Å, $b$ = 26.118(5) Å, $c$ = 12.236(8) Å, $\beta$ = 101.78°, $V$ = 3128(2) Å$^3$, $Z$ = 4, $\rho_{calcd}$ = 1.03 g cm$^{-3}$, $\mu$(Cu K$\alpha$) = 5.82 cm$^{-1}$, no. of unique reflections = 2920, no. of reflections with $I \geq 2\,\sigma_I$ = 1920, $R$ = 0.068, $R_w$ = 0.081.

(13) Packing forces may be also responsible for the nonalternation of the groups, as observed in several polyethylarene derivatives. See, for example: Marks, V.; Gottlieb, H. E.; Melman, A.; Byk, G.; Cohen, S.; Biali, S. E. *J. Org. Chem.* **2001**, *66*, 6711.

(14) Carey, F. A.; Tremper, H. S. *J. Org. Chem.* **1971**, *36*, 758.

(15) Zavada, J.; Pankova, M.; Arnold, Z. *Collect. Czech. Chem. Commun.* **1976**, *41*, 1777.

(16) Walsdorff, C.; Saak, W.; Pohl, S. *J. Chem. Res., Synop.* **1996**, 282; *J. Chem. Res., Miniprint* **1996**, 1601. See also: Metzger, A.; Lynch, V. M.; Anslyn, E. V. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 862.

(17) The anisyl ring may be oriented perpendicular or eclipsed to either the *pro-R* and *pro-S* benzylic hydrogens. In each case, these two arrangements may be enantiomeric or diastereomeric depending on the conformation of the other sidearms.

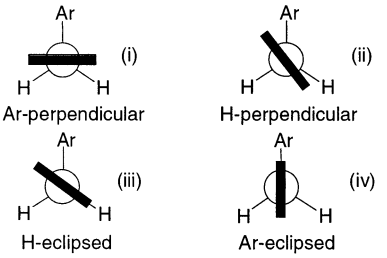



**FIGURE 2.** Four basic arrangements of a given peripheral aryl ring of **9b** viewed along the anisyl−$CH_2$ bond. The black rectangle represents a side view of the anisyl ring while the label "Ar" represents the central ring. Conformations i and ii represent "perpendicular" arrangements. In conformations iii and iv, the anisyl ring is eclipsed with one of the groups attached to the methylene carbon.

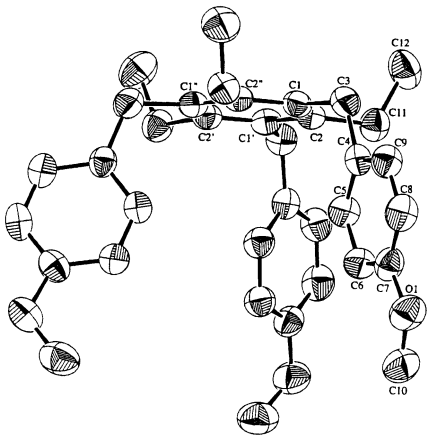



**FIGURE 3.** Crystal structure of **9b** (side view).

armed compound **9b** adopts in the crystal a conformation of crystallographic $C_3$ symmetry with full up−down alternation of the sidearms and therefore with the three *p*-methoxybenzyl groups pointing toward the same face of the central ring (Figure 3). The three peripheral rings are oriented in the H-perpendicular arrangement.[19]

In summary, two hexasubstituted benzene derivatives (**7** and **9b**) have been synthesized starting from **3** and **8b**. X-ray crystallography indicates that **9b** adopts in the crystal a conformation with facial segregation of substituents with the peripheral rings oriented in the H-perpendicular conformation.

## Experimental Section

**Preparation of 4.** The compound was prepared according to the literature procedure.[10] Phloroglucin tribenzoate (**3**, 1.0 g, 2.3 mmol) and 1 g of $AlCl_3$ were mixed together in a three-necked flask under an inert atmosphere until a homogeneous mixture was obtained, which was heated at 150−160 °C for 3 h. After cooling, a dilute solution of aq HCl (50 mL) was carefully added to the mixture. The solid that formed was filtered and dissolved in a dilute solution of aq KOH. After removal of the solid impurities by filtration, the filtrate was acidified with dilute HCl. The solid which separated was recrystallized from EtOH/water yielding 0.27 g (27%) of **4** (lit: 30%): mp 176 °C (lit. mp 185 °C); $^1$H NMR (400 MHz, DMSO-$d_6$, rt) $\delta$ 14.56 (s, 3H), 7.65 (d, $J$ = 7.3 Hz, 6H), 7.55 (t, $J$ = 7.2 Hz, 3H), 7.45 (t, $J$ = 7.1 Hz, 6H).

**Preparation of 5.** To a solution of 0.5 g of **4** (1.14 mmol) in 30 mL of acetonitrile was added $K_2CO_3$ (1.57 g, 11.4 mmol). After 90 min reflux, dimethyl sulfate was added (0.18 mL, 1.90 mmol), and the reflux was continued with stirring for an additional 17 h. After evaporation of the solvent, 20 mL of ammonium hydroxide was added to the residue, and the solution was extracted three times with $CH_2Cl_2$. After evaporation of the organic solvent, the residue was recrystallized from EtOH, yielding brown needles of **5** (0.15 g, 27%): mp 180−185 °C; $^1$H NMR (400 MHz, $CDCl_3$, rt) $\delta$ 7.92 (d, $J$ = 7.3 Hz, 6H,), 7.59 (t, $J$ = 7.4 Hz, 3H), 7.48 (t, $J$ = 7.6 Hz, 6H,), 3.52 (s, 9H).

**Reduction of 5 with $LiAlH_4$.** A 480 mg (1 mmol) portion of **5** was dissolved in 70 mL of dry THF, and to the solution was slowly added $LiAlH_4$ (0.76 g, 20 mmol). After being stirred for 3 h under an inert atmosphere, the mixture was quenched with a few drops of water and the stirring continued for an additional 90 min. The mixture was filtered and the filtrate evaporated. The residue was purified by recrystallization from $CHCl_3$, yielding 310 mg (64%) **6**: mp 120 °C; $^1$H NMR (400 MHz, $C_6D_6$, rt) $\delta$ 7.49 (d, $J$ = 8.1 Hz, 2H), 7.40 (d, $J$ = 8.2 Hz, 4H), 7.13−7.08 (m, 6H), 7.02−6.99 (m, 3H), 6.23 (d, $J$ = 11.4 Hz, 1H), 6.16 (d, $J$ = 10.0 Hz, 2H), 4.02 (d, $J$ = 11.6 Hz, 1H), 3.51 (d, $J$ = 10.5 Hz, 2H), 2.96 (s, 6H), 2.93 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$, rt) $\delta$ 157.6, 157.5, 144.8, 144.7,129.0, 128.5, 128.3, 128.2, 127.0, 127.0, 125.5, 125.1, 68.7, 68.6, 63.2, 63.1; CI MS (+DCI) $m/z$ 469 ($MH^+ - H_2O$).

**Preparation of 1,3,5-Tribenzyl-2,4,6-trimethoxybenzene (7).** Compound **6** (200 mg 0.41 mmol) was dissolved in 20 mL of dry $CH_2Cl_2$, and to the solution was added 0.38 mL (4.9 mmol) of trifluoroacetic acid followed by 1.56 mL of triethylsilane (9.8 mmol), and the mixture was stirred at rt for 70 h. After neutralization with a saturated solution of $NaHCO_3$, the phases were separated and the organic phase was dried ($MgSO_4$) and evaporated. The residue was recrystallized from $CHCl_3$/ether to yield 146 mg (81%) **7**: mp 115 °C (lit.[9] mp 101 °C); $^1$H NMR (400 MHz, $CDCl_3$, rt) $\delta$ 7.35 (d, $J$ = 7.0 Hz, 6H), 7.18 (t, $J$ = 7.2 Hz, 6H), 7.06 (t, $J$ = 7.2 Hz, 3H), 4.15 (s, 6H), 3.27 (s, 9H); $^{13}$C NMR (100 MHz, $CDCl_3$, rt) $\delta$ 157.8, 142.0, 128.61, 128.57, 126.1, 124.4, 62.0, 30.8; CI MS $m/z$ 439.2 ($MH^+$).

**Preparation of 9b.** To 2 mL of dry anisole were added $CaCO_3$ (1.5 g) and anhydrous $AgClO_4$ (1.3 g) (CAUTION, anhydrous $AgClO_4$ can explode when struck.) The mixture (protected from light) was stirred under an inert atmosphere for 15 min. 1,3,5-Tris(bromomethyl)-2,4,6-triethylbenzene (0.73 g, 1.65 mmol) was then added to the mixture, which resulted in the immediate precipitation of yellow AgBr. The mixture was stirred at rt for 4 h. After the mixture was poured into 20 mL of water, the solid that precipitated was filtered and the filtrate was extracted twice with dichloromethane and once with ether. The organic phase was dried ($MgSO_4$) and the solvent evaporated. Recrystallization of the residue from $CHCl_3$/EtOH yielded 0.16 g (18%) of **9b**: mp 170 °C; $^1$H NMR (400 MHz, $CDCl_3$, rt) 6.92 (d, $J$ = 8.4 Hz, 6H), 6.80 (d, $J$ = 8.5 Hz, 6H), 4.07 (s, 6H), 3.77 (s, 9H), 2.45 (q, $J$ = 7.4 Hz, 6H), 1.08 (t, $J$ = 7.4 Hz, 9H); $^{13}$C NMR (100 MHz, $CDCl_3$, rt) $\delta$ 157.6, 141.1, 134.2, 133.4, 128.6, 113.7, 55.2, 33.7, 23.6, 15.2; CI MS $m/z$ 1057.3 ($MH^+$).

**Acknowledgment.** We thank Dr. Shmuel Cohen for the crystal structure determinations and the USA−Israel Binational Science Foundation for support of this work.

**Supporting Information Available:** NMR spectra for **4**−**7** and **9b** and crystal data for **6** and **9b**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO034016U

(18) Crystal data for **9b**: $C_{36}H_{42}O_3$, space group $R\bar{3}$, $a$ = 18.555(1) Å, $c$ = 15.113(1) Å, $V$ = 4506.0(3) Å$^3$, $Z$ = 6, $\rho_{calcd}$ = 1.11 g cm$^{-3}$, $\mu$(Mo K$\alpha$) = 0.72 cm$^{-1}$, no. of unique reflections = 1696, no. of reflections with $I \geq 3\sigma_I$ = 1128, $R$ = 0.048, $R_w$ = 0.068.

(19) According to MM3 calculations (Alchemy 2000 program), the conformation with all rings oriented in the Ar-perpendicular arrangement is a local maximum (with three negative eigenvalues in the vibrational matrix) lying 12.3 kcal mol$^{-1}$ above the H-perpendicular conformation. Inspection of the calculated Ar-perpendicular form indicates that close contacts are present between the aromatic protons and the methylene protons of the ethyl group.