Synthesis of [1.1.1.1]Metacyclophane Macrocycle

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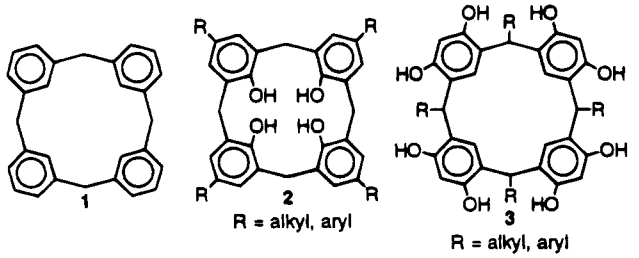
Received July 12, 1994[⊗]

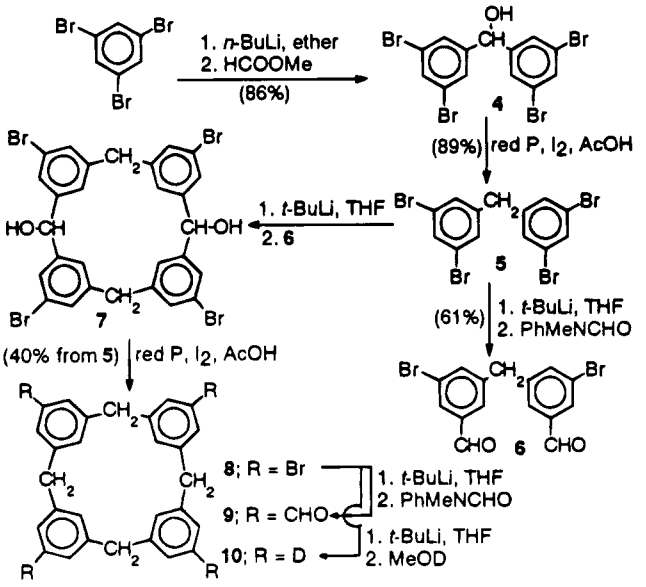
Additions of organodilithium reagents to dialdehydes allow for construction of [1.1.1.1]metacyclophane macrocycle in ~40% yield in the ring forming step, without resort to standard high dilution techniques. The present methodology is complementary to the conventional condensations leading to phenol- and resorcinol-based cyclotetramers.

[1.1.1.1]Metacyclophane **1** macrocycle is a parent structure to calix[4]arenes **2** and calix[4]resorcinarenes **3**, which are widely studied as complex forming agents with relevance to enzymes and receptors.[1,2] Their synthesis relies on the aromatic electrophilic substitution-based ring forming steps, followed by functional group transformations.[3-11]



Now we report a synthesis of a [1.1.1.1]metacyclophane macrocycle, based on addition of organodilithium reagents to dialdehydes. In particular, we describe the synthesis and solid state structure of tetrabromo-substituted [1.1.1.1]metacyclophane **8** (Scheme 1 and Figure 1), which is not readily available using conventional synthetic routes relying on electrophilic aromatic substitution. The synthetic methods leading to **8** should make feasible rational construction of novel cages and two-dimensional networks, relevant to novel approaches to materials.[12]

Scheme 1



Results and Discussion

Addition of methyl formate to 2 equiv of monolithiated 1,3,5-tribromobenzene[13] in ether gives alcohol **4** (Scheme 1). Subsequently, reduction of **4** with red P/iodine in refluxing AcOH provides **5**.[14] Double lithiation of **5** with *tert*-BuLi in THF at −78 °C is followed by addition of *N*-methylformanilide[15] to provide dialdehyde **6**, after hydrolysis. Typically, **6** is purified directly by column chromatography; however, for some reaction mixtures, it is advantageous to improve solubility by converting **6** to its ethylene glycol diacetal and, then, carrying out chromatography.

The macrocyclization step is implemented by fast addition of **6** in THF (0.06 M) to a precooled (−78 °C) solution of double lithiated **5** in THF/pentane (8/1, 0.05 M). After the reaction mixture is allowed to attain ambient temperature overnight, macrocycle **7** is isolated. Typically, a crude mixture of two isomers **7** is carried over to the next step, removal of the OH-groups, which gives macrocycle **8** in ~40% yield from **5** and **6**.[16,17]

Tetralithiation of **8** proceeds in a good yield as evidenced by isolation of the deuteron quenching product

[⊗] Abstract published in *Advance ACS Abstracts,* November 15, 1994.

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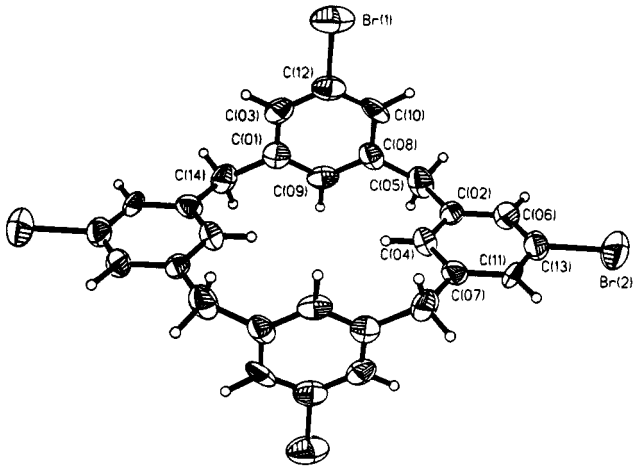

Figure 1. X-ray structure for macrocycle **8**. The bromine and carbon atoms are depicted with ellipsoids representing the 50% probability level; hydrogen atoms are displayed with circles of arbitrary size. In the solid the molecule has ideal inversion symmetry (a crystallographic symmetry operator); only symmetry unique C- and Br-atoms are labeled.

9. Analogously to **6**, tetraaldehyde **10** is obtained from **8** in modest yield (Scheme 1).

Macrocycles **8**–**10** have well-resolved NMR spectra in $CDCl_3$, with no appreciable signal broadening at ambient temperature; in particular, benzylic methylene protons appear as a singlet (300 MHz). This is in agreement with the previous reports on **1**, which suggested either 1,3-alternate conformation and/or a conformationally flexible molecule in solution.[4]

In the solid state, **8** has a chair conformation, similar to **1**.[4]

Conclusion

Calix[4]arene macrocyclic rings are constructed using organolithium methodology. The present procedure is applicable to [1.1.1.1]metacyclophanes, which are difficult to prepare with conventional methods, and it should be readily extendable to synthesis of O-protected calix[4]-arenes.

Experimental Section

Ether and tetrahydrofuran (THF) for use on vacuum line were distilled from sodium/benzophenone in a nitrogen atmosphere. Major chemicals were obtained from Aldrich.

NMR spectra were obtained using Omega spectrometers (^1H, 500 MHz and 300 MHz) in either $CDCl_3$ or Me_2SO-d_6; the chemical shift references were as follows: ^1H, TMS, 0.0 ppm ($CDCl_3$) and Me_2SO-d_5, 2.50 ppm; ^{13}C, $CDCl_3$, 77.0 ppm and Me_2SO-d_6, 40.5 ppm. IR spectra were obtained using the FT instrument Analect RFX-30; standard KBr pellet techniques were employed. In addition to prominent peaks characteristic for aromatics, only stretches relevant to hydroxyl and aldehyde functionalities were reported.

Elemental analyses were carried out by Dr. G. M. Dabkowski, Director-Microlytics, P.O. Box 199, S. Deerfield, MA 01373.

X-ray Crystallography.[18] X-ray diffraction data were collected with a Siemens P4F auto-diffractometer using graphite-monochromatized Mo Kα radiation ($\lambda = 0.71073$ Å) from a 0.28 × 0.15 × 0.11 mm^3 colorless, prismatic crystal using a 2θ–θ scan (scan range $\theta = 1.20° + \alpha_1\alpha_2$ separation, scan speed 3.00–60.00° min^{-1}); background radiation was collected at each scan extreme for half the total scan time (three reference reflections measured periodically displayed neither systematic nor significant change in their respective intensities). Of the 2984 reflections measured (the range of indices: $-1 \le h \le 11$, $-1 \le k \le 9$, $-20 \le l \le 20$), 2161 were diffraction symmetry ($2/m$) unique ($R_{int} = 3.11\%$); of these 836 were classified as observed $\{|F| > 4.0\sigma(F)\}$. Data were corrected for variations in check reflections, for Lorentz and polarization effects and for absorption (empirical). The space group was determined to be $P2_1/n$ with $a = 9.597(1)$, $b = 7.618(1)$, $c = 17.382(1)$ Å, $\beta = 103.61(1)°$, $Z = 2$, $\varrho_{calc} = 1.813$ mg m^{-3}. The initial crystal structure model was determined by Patterson methods, developed by difference Fourier methods and refined by full-matrix least-squares techniques. Hydrogen atom positions were calculated from known geometry ($d_{C-H} = 0.96$ Å); H-atoms were refined with fixed isotropic atomic displacement parameters using a riding atom model. Carbon and bromine atoms were refined with anisotropic atomic displacement parameters. Final cycles of refinement were weighted $\{w^{-1} = \sigma^2(F) + 0.0007F^2\}$. Refinement of 146 variables converged to $R = 0.0511$, $R_w = 0.0522$ and a goodness-of-fit = 1.11. The maximum shift in a variable was 0.020; the maximum shift over error was 0.004; largest difference peak was 0.57 e$^-$ Å^{-3}; the deepest hole was −0.43e$^-$ Å^{-3}. Fractional atomic coordinates, atomic displacement parameters, parameters describing bonding geometry and conformation, and observed and calculated structure factors are available as supplementary material.

Bis(3,5-dibromophenyl)methanol (4). n-BuLi (36.0 mL of a 2.5 M solution in hexane, 90.0 mmol) was added to a suspension of 1,3,5-tribromobenzene (28.3 g, 90.0 mmol) in ether (600 mL) at −78 °C. After 90 min at −78 °C, methyl formate (2.7 mL, 44 mmol) was added. Subsequently, the temperature of the cooling bath was allowed to rise to ambient temperature over 16 h. Addition of water, followed by extraction with ether in conjunction with usual aqeuous workup gave 22.4 g of crude mixture. Boiling in hexane gave 19.3 g (86%) of colorless crystals (mp 169.5–170.5 °C); ^1H NMR ($CDCl_3$): 7.606 (t, J = 2, 2 H), 7.430 (d, J = 2, 4 H), 5.676 (d, J = variable, 1 H), 2.351 (d, J = variable, 1 H). $\{^1H\}$ ^{13}C NMR ($CDCl_3$): 146.12, 133.81, 128.25, 123.36, 73.86. IR (KBr pellet, cm^{-1}): 3330 (OH), 1580 (aryl), 1560 (aryl).

Bis(3,5-dibromophenyl)methane (5). A mixture of **4** (72.8 g, 0.146 mmol), red phosphorus (15.3 g, 0.492 mol), and iodine (7.41 g, 29.2 mmol) in AcOH (1800 mL) was refluxed for 42 h. Addition of water, filtration, washing of the solid residue with water and MeOH and soxhlet extraction with chloroform gave 63.0 g (89%) of white crystals (mp 192–193 °C) in two crops. EIMS, cluster: m/z (peak height) at M$^+$, 479.7 (1.5), 480.7 (<0.5), 481.7 (6.5), 482.7 (1), 483.7 (10), 484.7 (1.5), 485.7 (6), 486.7 (1), 487.7 (1.5); (M − Br)$^+$, 402.5 (2.5), 404.5 (2.5). High resolution EIMS: M$^+$, 483.7306 (−3.1 ppm dev. for $^{12}C_{13}{}^1H_8{}^{79}Br_2{}^{81}Br_2$), (M − Br)$^+$, 402.8145 (−2.9 ppm dev for $^{12}C_{13}{}^1H_8{}^{79}Br_2{}^{81}Br_1$). ^1H NMR ($CDCl_3$): 7.554 (s, 2 H), 7.231 (s, 4 H), 3.839 (2 H). $\{^1H\}$ ^{13}C NMR ($CDCl_3$): 143.13, 132.60, 130.72, 123.29, 40.40. IR (KBr pellet, cm^{-1}): 1580 (aryl), 1550 (aryl).

Calixarenes 7 and 8. t-BuLi (6.15 mL of a 1.7 M solution in pentane, 10.5 mmol) was added to a suspension of bis(3,5-dibromophenyl)methane (**5**) (1.27 g, 2.62 mmol) in THF (50 mL) at −78 °C. After 1 h at −78 °C, dialdehyde **6** (1.00 g, 2.62 mmol) in THF (50 mL) was transferred with cannula within 5 min to the stirred red homogeneous reaction mixture. Subsequently, the temperature of the cooling bath was allowed to raise to ambient temperature overnight; after an additional 1 day at ambient temperature, water (5 mL) was added and, then, the THF layer was washed with brine and dried over $MgSO_4$. Removal of solvent gave a light yellow solid (2.05 g), which is used without further purification in the next step, removal of the HO-groups. A small sample for a spectroscopic characterization is obtained by treatment with boiling chloroform and recrystallization from THF/chloroform (1/10); white

(17) A low yield (~5%) macrocyclization, based upon addition of dilithium reagent to ketone/aldehyde, has been reported for tetrathiaquaterenes (thiophene analogs of [1.1.1.1]metacyclophane); see: Ahmed, M.; Meth-Cohn, O. *J. Chem. Soc., C* **1971**, 2104. Ahmed, M.; Meth-Cohn, O. *Tetrahedron Lett.* **1969**, 1493.

(18) The authors have deposited atomic coordinates for **8** with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, U.K.

solid (mp > 290 °C dec). NMR analyses indicate 1/1 diastereomeric mixture. EIMS, cluster: *m/z* (peak height) at M^+, 703.8 (3.5), 704.8 (1.5), 705.8 (7.5), 706.8 (3), 707.8 (10), 708.7 (3.5), 709.8 (4.5), 710.8 (2), 711.8 (1.5), 712.8 (0.5); calcd for $C_{28}H_{20}O_2Br_4$, 703.8 (2), 704.8 (0.5), 705.8 (7), 706.8 (2), 707.8 (10), 708.8 (3.5), 709.8 (7), 710.8 (2), 711.8 (2), 712.8 (0.5). High resolution EIMS: M^+, 707.8159 (−0.5 ppm dev for $^{12}C_{28}{}^1H_{20}{}^{16}O_2{}^{79}Br_2{}^{81}Br_2$), $(M - OH)^+$, 690.8124 (0.7 ppm dev for $^{12}C_{28}{}^1H_{19}{}^{16}O_1{}^{79}Br_2{}^{81}Br_2$). ^1H NMR (Me_2SO-d_6): 7.50, 7.47 (s, 8 H), 7.20, 7.14 (s, 4 H), 6.13 (bs, 2 H, exchangeable with D_2O), 5.62 (bs, 2 H), 3.84 (s, 4 H). $\{^1H\}$ ^{13}C NMR/DEPT (Me_2SO-d_6): 149.4 (q), 149.3 (q), 144.7 (q), 130.9 (CH), 127.5 (CH), 127.4 (CH), 125.7 (CH), 122.6 (q), 73.8 (CH), 41.2 (CH_2, overlapped with solvent peaks). IR (KBr pellet, cm^{-1}): 3330 (OH), 1600 (aryl), 1570 (aryl).

The crude **7** (2.04 g), red phosphorus (4.45 g, ~0.15 mol), and iodine (1.08 g, 4.2 mmol) in AcOH (100 mL) was refluxed for 48 h. Subsequently, AcOH and iodine were distilled off; the remaining solid residue was washed with water and MeOH and, then, extracted with chloroform in a soxhlet apparatus. Removal of chloroform gave 1.45 g of crude product. Recrystallization from benzene gave in two crops 0.83 g (40+ %) of **8** as a white crystalline solid (mp > 290 °C dec). Anal. Calcd for $C_{28}H_{20}Br_4$: C, 49.74; H, 2.98. Found: C, 49.91; H, 3.17. EIMS, cluster: *m/z* (peak height) at M^+, 671.9 (2), 672.9 (1), 673.9 (4.5), 674.9 (3), 675.9 (10), 676.9 (3.5), 677.9 (4.5), 678.9 (2), 679.9 (2); calcd for $C_{28}H_{20}Br_4$, 671.9 (2), 672.9 (<1), 673.9 (7), 674.9 (2.5), 675.9 (10), 676.9 (3), 677.9 (6.5), 678.9 (2), 679.9 (2); $(M - Br)^+$, 594.9 (4.5), 593.9 (3.5), 596.9 (5), 597.9 (3.5), 596.9 (2). ^1H NMR ($CDCl_3$): 7.231 (s, 8 H), 6.543 (s, 4 H), 3.762 (s, 8 H). $\{^1H\}$ ^{13}C NMR/DEPT ($CDCl_3$): 142.81 (q), 130.03 (CH), 127.54 (CH), 122.61 (q), 41.01 (CH_2). IR (KBr pellet, cm^{-1}): 1600 (aryl), 1570 (aryl).

Dialdehyde 6 and Tetraaldehyde 9. *t*-BuLi (4 or 8 equiv of 1.7 M solution in pentane) was added to a suspension of **5** or **8** (1 equiv) in THF (0.05 or 0.008 M) at −78 °C. After 1 h or 2 h at −78 °C, followed by intermittent (30 min) use of an ice/water bath in the case of **8**, *N*-methylformanilide (2 or 4 equiv) in THF (1.6 or 0.2 M) was added at −78 °C to the reaction mixture. Subsequently, the temperature of the cooling bath was allowed to raise to 0 °C over 16 or 20 h. Addition of water (5 or 2 mL), followed by extraction with chloroform (300 mL) or ethyl acetate (2 × 25 mL) in conjunction with usual aqueous workup, gave crude product. Both products when pure, especially the tetraaldehyde, have little solubility in common organic solvents. Thus, although crystallization from chloroform/hexane and column chromatography in chloroform for **6** and **9**, respectively, give almost pure products, analytically pure compounds are better obtained via intermediate acetals, as shown below.

Dialdehyde 6. From 4.01 g (8.29 mmol) of **5**, 2.8 g of a yellow solid was obtained, which, after crystallization from chloroform/hexane (1/1), gave 1.95 g (5.10 mmol, 61%) of crystalline solid (mp >200 °C dec). Anal. Calcd for $C_{15}H_{10}O_2Br_2$: C, 47.16; H, 2.64. Found: C, 47.48; H, 2.85. EIMS, cluster: *m/z* (peak height) at M^+, 379.9 (24), 380.9 (17), 381.9 (46), 382.9 (14), 383.9 (24); $(M - CO)^+$, 351.9 (10), 353.9 (20), 355.9 (10). High resolution EIMS: M^+, 379.9025 (5.8 ppm dev for $^{12}C_{15}{}^1H_{10}{}^{16}O_2{}^{79}Br_2$), 381.9010 (−4.8 ppm dev for $^{12}C_{15}{}^1H_{10}{}^{16}O_2{}^{79}Br_1{}^{81}Br_1$), 383.8998 (−2.8 ppm dev. for $^{12}C_{15}{}^1H_{10}{}^{16}O_2{}^{81}Br_2$); $(M - CO)^+$, 353.9086 (1.8 ppm dev for $^{12}C_{14}{}^1H_{10}{}^{16}O_1{}^{79}Br_1{}^{81}Br_1$). ^1H NMR ($CDCl_3$): 9.933 (s, 2 H), 7.901 (s, 2 H), 7.619 (s, 2 H), 7.580 (s, 2 H), 4.084 (s, 2 H). $\{^1H\}$ ^{13}C NMR ($CDCl_3$): 190.48, 142.54, 138.29, 137.55, 131.29, 128.33, 123.76, 40.53. IR (KBr pellet, cm^{-1}): 2730 (C-H), 1710 (C=O), 1590 (aryl), 1570 (aryl).

Purification of the dialdehyde was also carried out via the corresponding diacetal. Reflux of crude dialdehyde **6** (2.4 g) with ethylene glycol (2.0 mL) and TsOH (25 mg) in benzene (100 mL) in a Dean−Stark assembly for 10 h was followed by usual aqueous workup and column chromatography (TLC grade silica, hexane/EtOAc, from 5/1 to 3/1). Diacetal of **6** was isolated as white solid (1.0 g, mp 64−66 °C). ^1H NMR ($CDCl_3$): 7.50 (s, 2 H), 7.28 (s, 2 H), 7.20 (s, 2 H), 5.73 (s, 2 H), 4.12−4.00 (m, 8 H), 3.92 (s, 2 H).

Hydrolysis of the diacetal to dialdehyde was affected by HCl_{aq} (1 M, 8.5 mL) in THF (55 mL) for 48 h at ambient temperature. From 1.37 g of the diacetal, 1.05 g (94%) of dialdehyde as white powder was obtained (mp >200 °C dec).

Tetraaldehyde 9. From 0.310 g (0.456 mmol) of **8**, 0.162 g of yellow solid was obtained, which gave 82.0 mg (0.174 mmol, 38%) of colorless solid after column chromatography (TLC grade silica gel, 18 psi, chloroform). Anal. Calcd for $C_{32}H_{24}O_4$: C, 81.34; H, 5.12; $C_{32}H_{24}O_4 \cdot (H_2O)_{0.33}$: C, 80.32; H, 5.20. Found: C, 80.24; H, 5.19. EIMS: *m/z* (peak height) at M^+, 472.2 (4); $(M - CO)^+$, 444.2 (10); $(M - CO - CO)^+$, 416.2 (9); $(M - CO - CO - CO)^+$, 388.2 (4); $(M - CO - CO - CO - CO)^+$, 360.2 (3). High resolution EIMS: M^+, 472.1685 (2.3 ppm dev for $^{12}C_{32}{}^1H_{24}{}^{16}O_4$), 473.1728 (4.1 ppm dev for $^{12}C_{31}{}^{13}C_1{}^1H_{24}{}^{16}O_4$); $(M - CO - CO)^+$, 416.1784 (1.9 ppm dev for $^{12}C_{30}{}^1H_{24}{}^{16}O_2$), 417.1830 (4.7 ppm dev for $^{12}C_{29}{}^{13}C_1{}^1H_{24}{}^{16}O_2$). ^1H NMR ($CDCl_3$): 9.997 (s, 4 H), 7.647 (s, 8 H), 6.868 (s, 4 H), 4.018 (s, 8 H). $\{^1H\}$ ^{13}C NMR ($CDCl_3$): 191.95, 141.94, 137.20, 134.63, 128.45, 41.18. IR (KBr pellet, cm^{-1}): 2740 (C-H), 1690 (C=O), 1600 (aryl).

A convenient way to purify the tetraaldehyde relies on the corresponding tetraacetal. Crude tetraaldehyde **9** (0.486 g) was obtained from **8** (0.608 g), as described above. Boiling crude **9** with ethylene glycol (2.0 mL) and TsOH hydrate (25 mg) in benzene (100 mL) in a Dean−Stark assembly for 17 h was followed by usual aqueous workup and column chromatography (flash silica, chloroform). Tetraacetal of **9** was isolated as white solid in two fractions, 0.168 g (95+% pure) and 0.070 g (~90% pure). ^1H NMR ($CDCl_3$): 7.18 (s, 8 H), 6.66 (s, 4 H), 5.76 (s, 4 H), 4.14−4.00 (m, 16 H), 3.85 (s, 8 H).

The tetraacetal (0.153 g, 0.236 mmol) in chloroform (2.0 mL) was diluted with THF (10 mL), followed by HCl_{aq} (1 M, 1.0 mL). After 48 h of vigorous stirring, the white precipitate was collected and washed with MeOH (3 × 2 mL), followed by chloroform (2 × 2 mL); the resultant white powder was tetraaldehyde **9** (0.106 g, mp >250 °C dec).

Tetradeuteriocalixarene 10. THF (ca. 5 mL) was vacuum transferred to **8** (20 mg, 0.030 mmol) in a Schlenk flask. Following sonication, the cloudy suspension of **8** was cooled to −78 °C, and *t*-BuLi (0.14 mL of 1.7 M solution in pentane, 0.24 mmol) was added under stream of nitrogen. After 2 h, the reaction mixture was warmed up to ambient temperature for 2 h and, then, quenched with MeOD (0.4 mL). Concentration in vacuo and recrystallization from chloroform (by slow evaporation) gave 8.6 mg (81%) of white crystalline solid (mp 184−186 °C). FABMS (3-NBA), *m/z* at M^+, 364. EIMS: *m/z* (peak height) at M^+, 363 (1.5), 364 (10), 365 (3), 366 (0.5). High resolution EIMS: M^+, 364.2135 (1.5 ppm dev for $^{12}C_{28}{}^1H_{20}{}^2H_4$), 365.2164 (0.3 ppm dev for $^{12}C_{27}{}^{13}C_1{}^1H_{20}{}^2H_4$), 366.2196 (−0.2 ppm dev for $^{12}C_{26}{}^{13}C_2{}^1H_{20}{}^2H_4$). ^1H NMR ($CDCl_3$): 7.065 (s, 8 H), 6.679 (s, 4 H), 3.835 (s, 8 H). $\{^1H\}$ ^{13}C NMR ($CDCl_3$): 141.51, 128.5 (1:1:1, weak), 128.94, 126.61, 41.92.

Acknowledgment. We gratefully acknowledge the National Science Foundation, Chemistry Division for the support of this research (CHE-9203918 to A.R. and CHE-9214428 to J.J.S.). Mass spectral determinations were performed by the Midwest Center for Mass Spectrometry with partial support by the National Science Foundation, Biology Division (DIR-9017262).

Supplementary Material Available: Copies of ^1H NMR spectra for all new compounds (9 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.