Orthocyclophanes. 4.[1-3] Functionalization of [1$_n$]Orthocyclophanes on the Aromatic Rings

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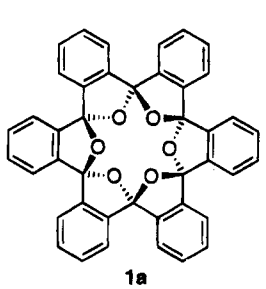
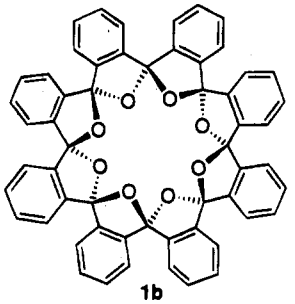
Functionalization of the [1$_n$]orthocyclophanes ([1$_n$]OCPs) has been accomplished by introducing groups on the aromatic rings of the cycles. Dilithiation of dibromoaromatic **10** followed by condensation with various aromatic dialdehydes, such as **14**, **20**, and **30**, gave rise to [1$_n$]OCP cycles bearing methoxy groups on the aromatic rings. Several polymethoxy[1$_n$]OCPs have been prepared that are reasonably soluble in organic solvents, in contrast to their parent hydrocarbons. Since methoxy functions can be converted to phenolic hydroxy groups and then to other functionalities, the methoxy derivatives may have broad applications to the modification of [1$_n$]OCPs for the preparation of a variety of supramolecules.

Introduction

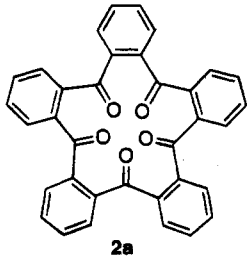
The chemistry of [1$_n$]orthocyclophanes, or [1$_n$]OCPs, is currently an area under active investigation. Since the methylene functions between two aromatic nuclei can readily be converted to other functionalities, the [1$_n$]OCP cycles are expected to be precursors to novel macrocycles having interesting binding properties. In previous investigations, we developed general synthetic routes[1] to [1$_n$]OCP cycles and reported the oxidation of their methylene functions and the resulting new families of crown compounds, starands (**1a**, **1b**)[4] and ketonands (**2a**, **2b**).[3]



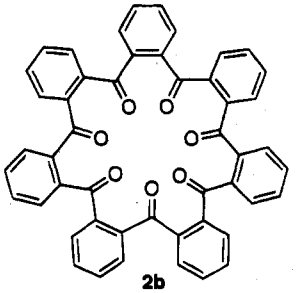
1a



1b



2a



2b

Herein, we report further modification of the [1$_n$]OCP series by introduction of functional groups to their aromatic rings. Previously, we described a convenient synthesis of [1$_3$]OCP (**3a**)[5] by cycloalkylation of 2-(2-benzylbenzyl)benzyl alcohol in AcOH–H_2SO_4 but were unable to prepare the higher homologs of the [1$_n$]OCPs ($n \geq 4$) by this acid-catalyzed intramolecular Friedel–Crafts alkylation of *o*-benzylbenzylic alcohols (*o*-BBAs).[6] Recently, we accomplished the synthesis of [1$_4$]OCP (**4a**) and [1$_5$]OCP (**5a**)[1] by the Pd-catalyzed hydrogenation of the corresponding cyclic diones **4b** and **5b**, respectively. Although [1$_7$]OCP could also be prepared in this manner,[3] we were unable to prepare [1$_6$]OCP (**6a**) by the reduction of either [1$_6$]OCP-1,4-dione (**6b**) or the 1,3-isomer (**6c**).[4] We were also unable to obtain the higher representatives of the even-numbered [1$_n$]OCP series, such as [1$_8$]- and [1$_{10}$]OCPs, by the reduction of the corresponding diketones.

It may be that the even-numbered [1$_n$]OCPs in general are so insoluble that they cannot be extracted from the reaction mixture, even though they are produced. The insolubility of the even-numbered [1$_n$]OCPs may be accounted for by the molecular symmetry; the higher the symmetry of a molecule, the closer is its packing in a crystal. Whereas the odd-numbered [1$_n$]OCPs, such as [1$_5$]- and [1$_7$]OCPs, are rather soluble in conventional organic solvents in spite of their higher molar mass,[3] the lower homolog [1$_4$]OCP (**4a**) is too sparingly soluble to permit a ^{13}C NMR spectrum.[1]

One of our goals of the present research is the preparation of soluble derivatives of the even-numbered [1$_n$]OCP cycles, such as **7a**, **7b**, and the higher analogs, in which functional groups are introduced on the aromatic rings. The present paper provides general synthetic routes leading to the methoxy derivatives of the [1$_n$]OCP series. Since methoxy group(s) can be converted to other functionalities, these derivatives are expected to be the precursors of other new macrocycles.

Results and Discussion

The synthesis of the methoxy derivatives of the [1$_n$]-OCP cycles has been accomplished by dimetalation of an aromatic dibromide, such as **10**, followed by condensation with an appropriate aromatic dialdehyde, such as **14**, to give a cyclocondensation product. Several polymethoxy-

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(3) Lee, W. Y.; Park, C. H.; Kim, H.-J.; Kim, S. Orthocyclophanes. 3. Ketonands, Novel Ketonic Crowns of Polyoxo[1$_n$]orthocyclophane Constitution. *J. Org. Chem.* **1994**, *59*, 878.

(4) Lee, W. Y.; Park, C. H.; Kim, S. *J. Am. Chem. Soc.* **1993**, *15*, 1184.

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(6) Lee, W. Y.; Sim, W.; Kim, H.-J. *J. Chem. Soc., Perkin Trans. 1* **1993**, 719.

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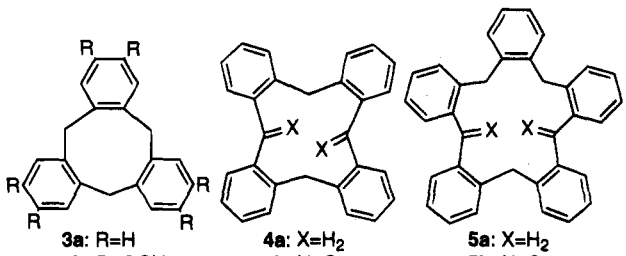
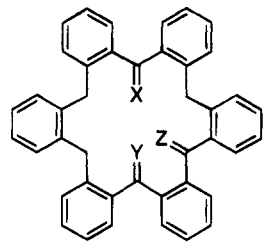


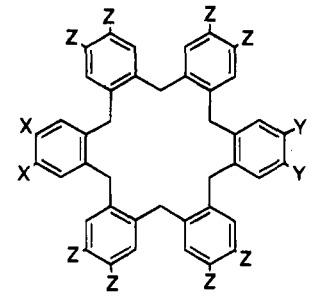
3a: R=H
3b: R=OCH_3

4a: X=H_2
4b: X=O

5a: X=H_2
5b: X=O



6a: X=Y=Z=H_2
6b: X=Y=O, Z=H_2
6c: X=Z=O, Y=H_2



7a: X=OCH_3, Y=Z=H_2
7b: X=Y=OCH_3, Z=H_2
7c: X=Y=Z=OCH_3

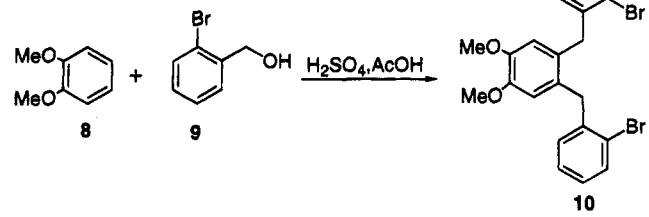
[1_n]OCPs have been prepared. Whereas the parent hydrocarbons of the even-numbered [1_n]OCPs are too insoluble to be extracted into organic solvents, their methoxy derivatives are reasonably soluble and can be extracted without difficulty from the reduction mixture.

Cyclotriveratrylene (CTV, **3b**), the first methoxy derivative of [1_n]OCP reported, was prepared by Robinson in 1915 by treating veratryl alcohol with concd H_2SO_4, though the structure was assigned later.[7] Recently, Keehn *et al.*[8] reported a modification of Robinson's work, which involves the treatment of veratryl alcohol with a dilute solution of trifluoroacetic acid (CF_3CO_2H) in chloroform at or below room temperature (rt) to produce a separable mixture of hexamethoxy[1_3]OCP (**3b**) (19%), octamethoxy[1_4]OCP (42%), decamethoxy[1_5]OCP (13%), and dodecamethoxy[1_6]OCP (**7c**) (5%). This modification, however, is not adequate for the preparation of the methoxy derivatives of the [1_n]OCPs, not only because of the poor selectivity of the reaction but also because of the difficult product separation involved. Moreover, this method is limited in its control of the cycle size and number of methoxy functions introduced.

In this work, we have developed preparative methods for the methoxy derivatives of every size of [1_n]OCP cycle (Schemes 1–3). One of the key materials, dibromide **10**, was prepared in a manner analogous to the literature procedure[9] for synthesis of the dichloro analog. Acid-catalyzed Friedel–Crafts alkylation of veratrole (**8**) with 2-bromobenzyl alcohol (**9**) in AcOH/H_2SO_4 provided crystalline aromatic dibromide **10**, bearing methoxy groups (Scheme 1).

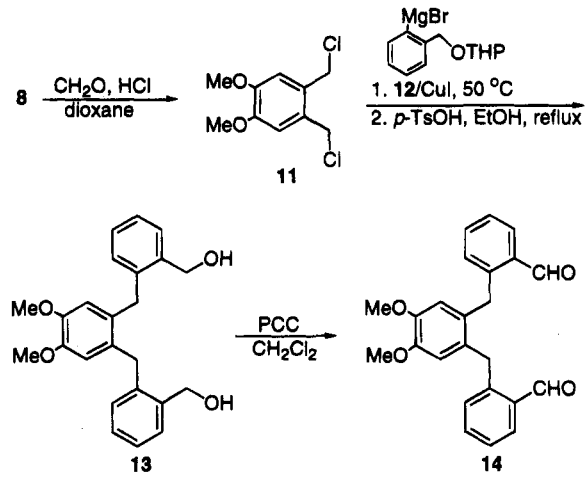
The other key compound, aromatic dialdehyde **14**, was prepared also starting from **8** (Scheme 2). Treatment of **8** in dioxane with CH_2O/HCl at 0 °C afforded crystalline 4,5-dimethoxy-1,2-bis(chloromethyl)benzene (**11**), mp 86–

Scheme 1



8 **9** **10**

Scheme 2



11 **13** **14**

86.5 °C (lit.[10] mp 85.5 °C). Reaction of **11** with Grignard reagent **12** in the presence of CuI, followed by removal of the THP protecting groups from the resultant coupling product gave benzylic diol **13**, which was then oxidized with PCC to the corresponding dialdehyde **14**.

Generation of the [1_6]OCP cycle was accomplished by treatment of **10** in THF with *n*-BuLi at 0 °C to give dilithio reagent **15**, followed by condensation with **14** and successive hydrolytic workup to give cyclic diol **16** (Scheme 3). Because it proved difficult to isolate and purify, crude **16** was oxidized directly with PCC to the corresponding dione **17**, which was then subjected to a Clemmensen reduction in toluene to give tetramethoxy-[1_6]OCP (**18**). In striking contrast to hydrocarbon [1_6]-OCP (**6a**), the tetramethoxy derivative **18** could be extracted without difficulty from the reaction mixture to give pure crystals.

Attempted oxidation of tetramethoxy aromatic **17** by heating with ceric ammonium nitrate (CAN) in AcOH generated none of the expected tetramethoxy[1_6]starand but resulted in a mixture of unidentified products. This is unlike the oxidation of **6b** and/or **6c** with CAN, which gave rise to an isomerization product, [1_6]starand (**1a**),[4] rather than the corresponding hexaone. It can be rationalized that the methoxy aromatics are subject to oxidative demethylation to give quinoid derivatives. It has been reported that the oxidation of 1,4-dimethoxybenzene[11] with CAN in acid results in *p*-benzoquinone and the oxidation of 1,2- and/or 1,4-dimethoxylated aromatics[12] with CAN generates *p*- and/or *o*-benzoquinones.

(7) (*a*) Robinson, G. M. *J. Chem. Soc.* **1915**, 267. (*b*) Lindsey, A. S. *J. Chem. Soc.* **1965**, 1685. (*c*) Erdman, H.; Haglid, F.; Ryhage, R. *Acta Chem. Scand.* **1964**, *18*, 1249. (*d*) Goldup, A.; Morrison, A. B.; Smith, G. W. *J. Chem. Soc.* **1965**, 3864.

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(9) Arcoleo, A.; Natoli, M. C.; Marino, M. L. *Synth. Commun.* **1975**, 207.

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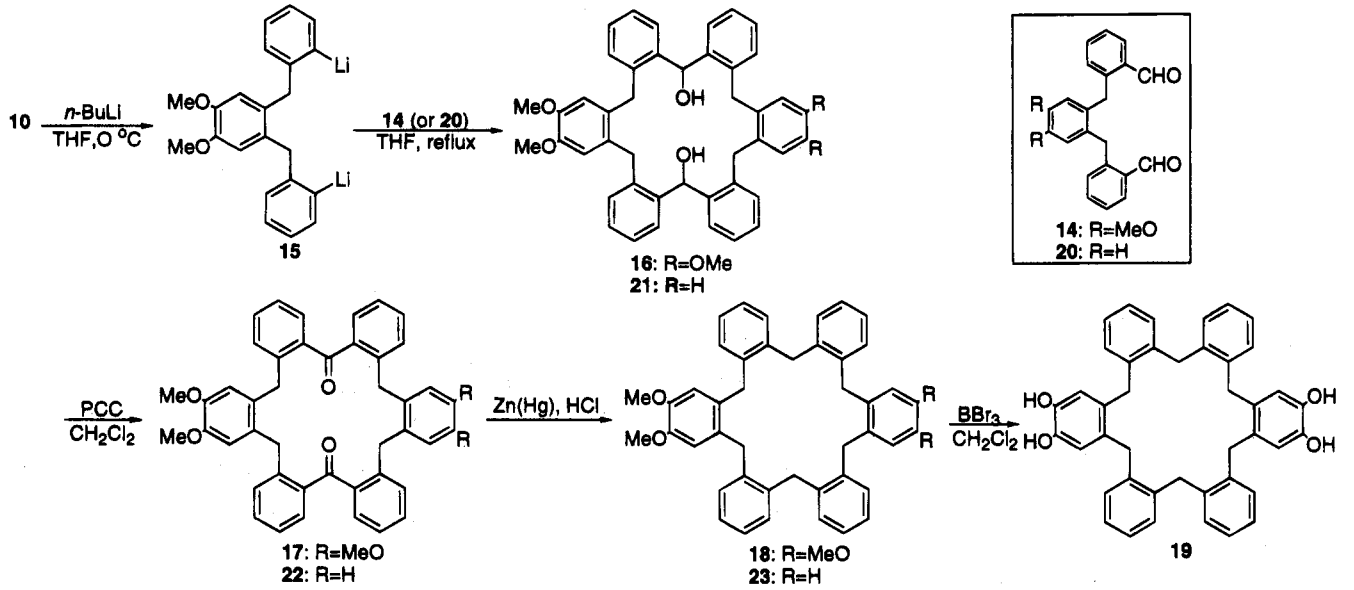
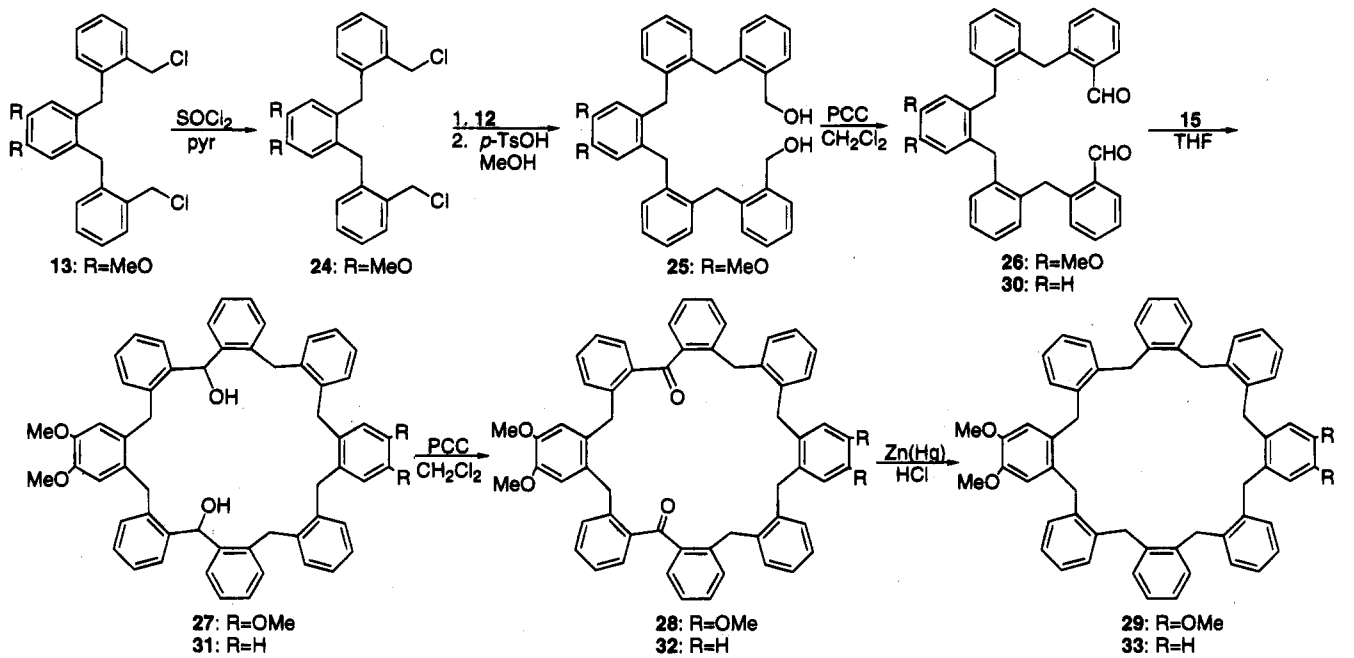
(11) Jacob, P.; Callery, P. S.; Shulgin A. T.; Castagnoli, N. *J. Org. Chem.* **1976**, *41*, 3627.

(12) (*a*) Chorn, T. A.; Giles, R. G. F.; Mitchell, P. R. K.; Green, I. R. *J. Chem. Soc., Chem. Commun.* **1981**, 534. (*b*) Sibi, M. P.; Dankwardt, J. W.; Snieckus, V. *J. Org. Chem.* **1986**, *51*, 271. (*c*) Uno, H. *J. Org. Chem.* **1986**, *51*, 350.

Scheme 3



Scheme 4



Treatment of a solution of **18** in CH_2Cl_2 with BBr_3 at 0 °C, followed by stirring under nitrogen at rt, gave tetraphenolic cyclophane (**19**). Since the phenolic OH functions can be modified by the introduction of side chains, tetrahydroxy[1$_6$]OCP (**19**) could serve as a precursor to other classes of crown compounds.

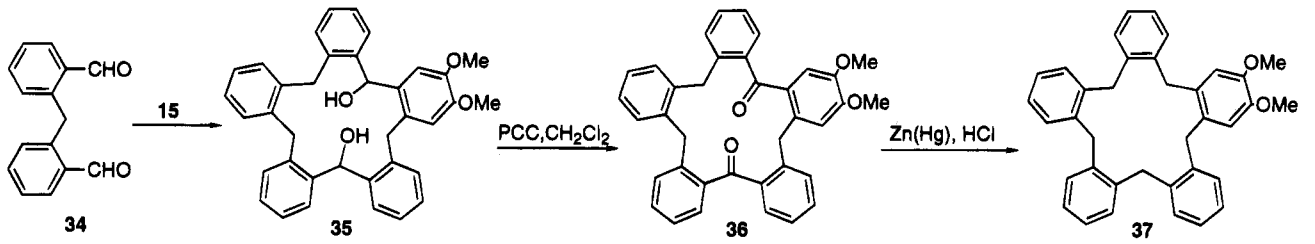
The dimethoxy derivative of the [1$_6$]OCP cycle was also synthesized (Scheme 3). Treatment of dialdehyde **20**[13] in THF with dilithio reagent **15**, followed by oxidation of the resultant cyclic diol **21** with PCC, afforded cyclic dione **22**. Treatment of **22** with Zn(Hg)–HCl in toluene gave crystalline dimethoxy[1$_6$]OCP (**23**), mp 260–262 °C, which was soluble in organic solvents, in contrast to its parent hydrocarbon [1$_6$]OCP, and could be extracted from the reduction mixture.

A soluble [1$_8$]OCP cycle could also be prepared by introducing methoxy functions on the aromatic ring(s) (Scheme 4). Treatment of diol **13** in CH_2Cl_2 with $SOCl_2$/pyridine gave benzylic dichloride **24**. Reaction of **24** with Grignard **12** in the presence of CuI, followed by removal of the THP protecting groups from the coupling product provided benzylic diol **25**, which was then oxidized with PCC to dialdehyde **26**. Reaction of **26** with dilithio reagent **15** gave cyclic diol **27**, which was then oxidized with PCC to give cyclic dione **28**. Clemmensen reduction of **28** resulted in the corresponding orthocyclophane, tetramethoxy[1$_8$]OCP (**29**). Tetramethoxy derivative **29** is soluble in organic solvents and was easily extracted with CH_2Cl_2 to give crystals after chromatographic purification.

The synthesis of the dimethoxy derivative of the [1$_8$]-OCP cycle was initiated by the cyclocondensation of dilithio reagent **15** with dialdehyde **30**[3] to generate cyclic diol **31** (Scheme 4). Oxidation of **31** with PCC to give cyclic dione **32**, followed by Clemmensen reduction,

(13) Lee, W. Y.; Park, C. H; Lee, J. H.; Choi, K. D.; Sim, W. *Bull. Kor. Chem. Soc.* **1989**, *10*, 397.

Scheme 5



furnished crystalline dimethoxy[1_8]OCP (**33**), which is reasonably soluble in organic solvents.

Methoxy derivatives of the odd-numbered [1_n]OCP could also be prepared (Scheme 5). Cyclocondensation of dilithio reagent **15** with dialdehyde **34**[1] to give cyclic diol **35**, oxidation of **35** with PCC to afford cyclic dione **36**, and successive reduction of **36** with Zn(Hg)–HCl gave dimethoxy[1_5]OCP (**37**).

In summary, synthetic sequences leading to the polymethoxy derivatives of the [1_n]OCP series have been developed. Although the higher homologs of the even-numbered [1_n]OCP could not be obtained due to their insolubility in extraction solvents, their methoxy derivatives are conveniently soluble. The methoxy derivatives of [1_n]OCPs might have broad applications in the modification of the [1_n]OCP series. Since their methoxy functions can be demethylated to prepare the corresponding polyphenolic analogs, various other side chains might be introduced at the phenolic sites. Their methylene functions can also be converted to other functionalities to provide new classes of supramolecular ionophores.

Experimental Section

General. All anhydrous reactions were conducted with precautions for rigorous exclusion of air and moisture. Melting points are uncorrected. Diethyl ether (Et_2O) and tetrahydrofuran (THF) were purified by refluxing with sodium benzophenone ketyl under nitrogen, followed by distilling prior to use. Dichloromethane (CH_2Cl_2) was dried by distilling over calcium hydride. Flash column chromatography was carried out using silica gel 60 (E. M. Merck, 0.040 mm, 230–400 mesh ASTM). ^1H NMR and ^{13}C NMR spectra were recorded using $CDCl_3$ as solvent except where noted, and tetramethylsilane as internal reference. All chemical shifts (δ) are reported in parts per million, and J values are in Hz. Chemicals were purified, when necessary, according to the reported procedure.[14] Routine workup was conducted by extracting the reaction mixture with CH_2Cl_2 except where noted, washing the extract successively with aqueous $NaHCO_3$ and water, and drying ($MgSO_4$), followed by concentration *in vacuo*.

General Procedure A. Biscoupling of Aromatic Grignard and Benzylic Dihalide Followed by Deprotection To Give Benzylic Diol. Grignard reagent **12** was prepared by dropwise addition of a solution of 2-bromobenzyl THP ether (*e.g.*, 50 mmol) in dry THF (20 mL) to Mg-turnings (1.5 g) immersed in dry THF (10 mL) followed by stirring for 3 h under gentle reflux. The Grignard **12** was added at 0 °C to a solution of a benzylic dihalide (*e.g.*, **11**, 10 mmol) in dry THF (30 mL) containing CuI (0.5 g) under nitrogen. After being stirred at rt for 2 h followed by at 50 °C for 5 h, the reaction mixture was quenched with aqueous NH_4Cl and the solvent was evaporated from the mixture *in vacuo*. The residual mixture was extracted with CH_2Cl_2, and the extract was washed with water, dried ($MgSO_4$), and concentrated *in vacuo* to give a crude condensation product, a di-THP ether, which was deprotected without purification. A solution of the crude product and *p*-TsOH (1.5 g) in MeOH (70 mL) was refluxed for 3 h, cooled to rt, and treated with aqueous $NaHCO_3$. After routine workup, the crude product was recrystallized from ether to give a crystalline diol (*e.g.*, **13**).

General Procedure B. Oxidation of Diol with PCC to Dialdehyde. A mixture of a diol (*e.g.*, **13**, 8.0 mmol), Celite (3g), PCC (14 g), and CH_2Cl_2 (60 mL) was stirred for 5 h at rt. The mixture was filtered by suction through silica gel on a Büchner funnel followed by washing the silica gel thoroughly with CH_2Cl_2/Et_2O (1:1, v/v). After concentration of the filtrate *in vacuo*, the crude product was chromatographed (SiO_2/CH_2Cl_2) and recrystallized from n-C_6H_{14}/CH_2Cl_2 (2:1, v/v) to give the corresponding dialdehyde (*e.g.*, **14**).

General Procedure C. Preparation of Dilithio Reagent. To a solution of dibromide (*e.g.*, **10**, 8.0 mmol) in dry THF (200 mL) was added n-BuLi (16 mmol, in n-C_6H_{14}) dropwise at 0 °C under nitrogen, and the mixture was stirred for 30 min, whereupon the solution turned red and then finally to pale yellow to give the corresponding dilithio reagent (*e.g.*, **15**).

General Procedure D. Cyclocondensation of Dilithio Reagent and Aromatic Dialdehyde Followed by Oxidation To Give Cyclic Dione. To a dilithio reagent (*e.g.*, **15**, 7 mmol) was added at 0 °C a solution of an aromatic dialdehyde (*e.g.*, **14**, 7 mmol) in dry THF (100 mL), and the mixture was allowed to warm to rt followed by refluxing for 10 h. After being cooled, the reaction mixture was quenched with aqueous NH_4Cl followed by removal of the solvent *in vacuo*. The mixture was taken up with CH_2Cl_2, and the organic layer was washed successively with aqueous $NaHCO_3$ and water, dried ($MgSO_4$), and concentrated to give a crude cyclic diol (*e.g.*, **16**, sticky oil), which was roughly separated on silica gel and oxidized directly without further purification.

To a solution of the crude diol in CH_2Cl_2 (50 mL) containing Celite (2 g) was added PCC (5.0 g), and the mixture was stirred for 6 h at rt. The reaction mixture was filtered by suction followed by washing the precipitate with CH_2Cl_2/Et_2O (1:1, v/v). After evaporated the solvent *in vacuo*, the crude product was chromatographed on silica gel eluting with CH_2Cl_2, followed by recrystallization from Et_2O to provide a crystalline cyclic dione (*e.g.*, **17**).

General Procedure E. Clemmensen Reduction of Cyclic Dione. A mixture of Zn-powder (9 g), $HgCl_2$ (900 mg), water (15 mL), and concd HCl (3 mL) was stirred for 1 h to give amalgamated zinc. To this mixture was added a solution of a diketone (*e.g.*, **17**, 1.0 mmol) in toluene (20 mL) followed by concd HCl (15 mL), and the mixture was refluxed for 2 days. Four 5-mL portions of concd HCl were added at approximately 8-h intervals during the refluxing period. After routine workup, the crude product was chromatographed (SiO_2, n-C_6H_{14}) to give a crystalline cyclophane (*e.g.*, **18**).

4,5-Dimethoxy-1,2-bis(2-bromobenzyl)benzene (10). 2-Bromobenzyl alcohol (**9**) (18.7 g, 100 mmol) was added to a stirred solution of veratrole **8** (6.9 g, 50 mmol) in AcOH (20 mL) at 0 °C. To this mixture was added concd H_2SO_4 (30 mL) dropwise with stirring in an ice-bath, followed by stirring overnight. The reaction mixture was poured carefully into ice–water (100 mL) and extracted with CH_2Cl_2, and the organic layer was washed successively with aqueous $NaHCO_3$ and water, dried ($MgSO_4$), and evaporated *in vacuo*. The crude product was chromatographed on silica gel eluting with CH_2Cl_2/n-C_6H_{14} (1:2, v/v) to give 11.0 g (46%) of crystalline dibromide **10**: mp 93–95 °C; IR (KBr) 1600, 1585, 1170 cm^{-1}; ^1H NMR (200 MHz) δ 7.51–6.94 (m, 8 H), 6.59 (s, 2 H), 3.96 (s, 4 H), 3.77 (s, 6 H); ^{13}C NMR (50.3 MHz) δ 147.5, 139.7,

(14) Perrin, D. D.; Armarego, W. L. F.; Perrin, D. R. *Purification of Laboratory Chemicals*, 3rd ed.; Pergamon Press: Oxford, 1988.

132.5, 130.2, 129.7, 127.6, 127.2, 124.8, 113.4, 55.71, 38.64; EIMS m/z (rel intens) 478 (M^+, 53), 476 (M^+, 100), 474 (M^+, 51), 239 (27); HRMS (EI) calcd for $C_{22}H_{20}Br_2O_2$ M 473.9830, found M^+ 473.9844.

4,5-Dimethoxy-1,2-bis(chloromethyl)benzene (11). To a solution of veratrole **8** (42 g, 300 mmol) in 1,4-dioxane (250 mL) was added concd HCl (40 mL) with stirring at 0 °C. To this mixture, while HCl gas was introduced through a gas bubbler, was added formalin (35%, 30 mL), followed by a second equal portion of formalin after an interval of 45 min. To this mixture was introduced HCl gas for 2 h at 0 °C, followed by heating at 30–40 °C for 1 h, whereupon the color of the mixture turned to green. After routine workup, the crude product was chromatographed on silica gel eluting with CH_2Cl_2/n-C_6H_{14} (1:1, v/v) to provide 26.0 g (37%) of 4,5-bis(chloromethyl)veratrole **11** as needles: mp 85–86 °C (lit.[10] mp 85.5 °C); IR (KBr) 1600, 1520, 1470, 1100 cm^{-1}; ^{1}H NMR (200 MHz) δ 6.67 (s, 2 H), 4.69 (s, 4 H), 3.89 (s, 6 H); ^{13}C NMR (50.3 MHz) δ 150.0, 129.3, 114.1, 56.64, 43.99; EIMS m/z (rel intens) 238 (M^+, 2), 236 (M^+, 12), 234 (M^+, 19), 199 (100); HRMS (EI) calcd for $C_{10}H_{12}Cl_2$ M 202.032, found M^+ 202.150.

4,5-Dimethoxy-1,2-bis[2-(hydroxymethyl)benzyl]benzene (13). According to general procedure A, Grignard reagent **12** was prepared using 2-bromobenzyl THP ether (8.1 g, 30 mmol), and the reagent was reacted with benzylic dichloride **11** (2.4 g, 12 mmol) followed by removal of the THP protecting groups from the biscoupling product to give 4.0 g (88%) of crystalline diol **13**: mp 145–146 °C; IR (KBr) 3600–3300, 1600, 1110, 1090 cm^{-1}; ^{1}H NMR (200 MHz) δ 7.35–6.95 (m, 8 H), 6.56 (s, 2 H), 4.51 (s, 4 H), 3.93 (s, 6 H), 3.75 (s, 6 H), 2.19 (m, 2 H); ^{13}C NMR (50.3 MHz) δ 147.2, 140.0, 137.7, 130.5, 128.3, 126.8, 125.9, 114.1, 60.76, 55.50, 34.00; EIMS m/z (rel intens) 378 (M^+, 48), 360 ($M^+ - H_2O$, 5), 342 (32), 311 (88), 239 (100); HRMS (EI) calcd for $C_{24}H_{26}O_4$ M 378.1832, found M^+ 378.1804.

1,2-Dimethoxy-4,5-bis(2-formylbenzyl)benzene (14). According to general procedure B, diol **13** (3.0 g, 8.0 mmol) was oxidized with PCC to give 2.41 g (81%) of crystalline dialdehyde **14**: mp 160–162 °C; IR (KBr) 2760, 2720, 1690, 1600, 1100 cm^{-1}; ^{1}H NMR (200 MHz) δ 10.14 (s, 2 H), 7.88–7.77 (m, 2 H), 7.50–7.26 (m, 4 H), 7.10–6.99 (m, 2 H), 6.51 (s, 2 H), 4.36 (s, 4 H), 3.74 (s, 6 H); ^{13}C NMR (50.3 MHz) δ 193.01, 147.5, 143.1, 134.2, 134.1, 132.8, 131.2, 130.9, 127.2, 114.4, 56.16, 35.33; EIMS m/z (rel intens) 374 (M^+, 17), 356 ($M^+ - H_2O$, 35), 255 (100); HRMS (EI) calcd for $C_{24}H_{22}O_4$ M374.1519, found M^+ 374.1543.

2,23-Dioxo-12,13,33,34-tetramethoxyheptacyclo-[36.4.0.0^{3,8}.0^{10,15}.0^{17,22}.0^{24,29}.0^{31,36}]dotetraconta-1(38),3(8),4,6,-10(15),11,13,7(22),18,20,24(29),25,27,31(36),32,34,39,41-octadecaene, Tetramethoxy[1$_6$]OCP-1,4-dione (17). According to general procedures C and D, dibromide **10** (3.59 g, 7.54 mmol) was dilithiated with n-BuLi, followed by condensation with dialdehyde **14** (2.82 g, 7.54 mmol) to give cyclic diol **16**, which was then oxidized with PCC to afford 1.30 g (25% based on **10**) of crystalline **17**: mp 284–285 °C dec; IR (KBr) 1665, 1600, 1450, 1165 cm^{-1}; ^{1}H NMR (200 MHz) δ 7.35–6.94 (m, 16 H,), 6.44 (s, 4 H), 4.01 (s, 8 H), 3.71 (s, 12 H); ^{13}C NMR (50.3 MHz) δ 200.4, 148.5, 141.8, 131.6, 131.5, 130.8, 126.2, 114.7, 56.46, 27.68; EIMS m/z (rel intens) 688 (M^+, 100), 341 (24), 311 (15); HRMS calcd for $C_{46}H_{40}O_6$ M 688.2827, found M^+ 688.2866.

5,6,26,27-Tetramethoxyheptacyclo[36.4.0.0^{3,8}.0^{10,15}.-0^{17,22}.0^{24,29}.0^{31,36}]dotetraconta-1(38),3(8),4,6,10(15),11,13,17-(22),18,20,24(29),25,27,31(36),32,34,39,41-octadecaene, Tetramethoxy[1$_6$]OCP (18). The cyclic dione **17** (690 mg, 1.0 mmol) was reduced according to general procedure E to give 630 mg (95%) of crystalline **18**: mp 219–220 °C dec; IR (KBr) 3020, 1600, 1450, 750 cm^{-1}; ^{1}H NMR (200 MHz) δ 7.82–7.26 (m, 16 H), 6.47 (s, 4 H), 3.71 (m, 24 H); ^{13}C NMR (50.3 MHz) δ 147.4, 138.9, 138.4, 130.5, 129.6, 129.4, 126.4, 126.9, 113.4, 55.90, 35.98, 35.54; EIMS m/z (rel intens) 660 (M^+, 78), 329 (33), 151 (18); HRMS (EI) calcd for $C_{46}H_{44}O_4$ M 660.3228, found M^+ 660.3253.

5,6,26,27-Tetrahydroxyheptacyclo[36.4.0.0^{3,8}.0^{10,15}.-0^{17,22}.0^{24,29}.0^{31,36}]dotetraconta-1(38),3(8),4,6,10(15),11,13,17-(22),18,20,24(29),25,27,31(36),32,34,39,41-octadecaene, Tetrahydroxy[1$_6$]OCP (19). To a solution of cyclophane **18** (240 mg, 364 μmol) in CH_2Cl_2 (20 mL) at 0 °C was added BBr_3 (600 mg, 2.40 mmol) dropwise under nitrogen, followed by stirring overnight at rt. The mixture was allowed to warm to rt, water (100 mL) was added in portions, and the mixture was stirred for 2 h. The mixture was taken up in CH_2Cl_2, and the organic layer was washed successively with water and aqueous $NaHCO_3$, dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was chromatographed (SiO_2, CH_2Cl_2/Et_2O) and recrystallized from Et_2O to give 41 mg (28%) of crystalline tetraphenol **19**: mp 237–239 °C dec; IR (KBr) 3600–3100 (s), 1600, 1450, 1300 cm^{-1}; ^{1}H NMR (200 MHz) δ 8.59 (s, 4 H), 7.17–6.79 (m, 16 H), 6.33 (s, 4 H), 3.72 (s, 4 H), 3.56 (s, 8 H); ^{13}C NMR (200 MHz, DMSO-d_6/acetone-d_6; 1:1, v/v) δ 143.27, 138.88, 138.11, 129.14, 129.09, 128.38, 126.13, 126.11, 116.96, 34.41, 34.37; EIMS m/z (rel intens) 605 (MH^+, 50), 604 (M^+, 100), 301 (55), 283 (45); HRMS (EI) calcd for $C_{42}H_{36}O_4$ M 604.2614, found M^+ 604.2846.

2,23-Dioxo-12,13-dimethoxyheptacyclo[36.4.0.0^{3,8}.-0^{10,15}.0^{17,22}.0^{24,29}.0^{31,36}]dotetraconta-1(38),3(8),4,6,10(15),11,-13,7(22),18,20,24(29),25,27,31(36),32,34,39,41-octadecaene, Dimethoxy[1$_6$]OCP-1,4-dione (22). According to general procedures C and D, dibromide **10** (4.67 g, 9.81 mmol) was dilithiated, followed by condensation with dialdehyde **20** (3.07 g, 9.77 mmol), to give cyclic diol **21**, which was then oxidized with PCC to give 1.48 g (24%) of crystalline **22**: mp 226–228 °C dec; IR (KBr) 1660, 1600, 1450, 1260, 1100 cm^{-1}; ^{1}H NMR (200 MHz) δ 7.33–6.95 (m, 20 H), 6.46 (s, 2 H), 4.09 (s, 4 H), 4.00 (s, 4 H), 3.72 (s, 6 H); ^{13}C NMR (50.3 MHz) δ 200.7, 147.4, 140.9, 140.5, 138.9, 138.7, 138.7, 131.0, 130.9, 130.8, 130.4, 130.3, 130.1, 129.98, 126.4, 125.6, 125.6, 113.8, 55.90, 36.31, 35.76; EIMS m/z (rel intens) 628 (M^+, 100), 331 (20), 281 (30); HRMS (EI) calcd for $C_{44}H_{36}O_4$ M 628.2614, found M^+ 628.2566.

5,6-Dimethoxyheptacyclo[36.4.0.0^{3,8}.0^{10,15}.0^{17,22}.0^{24,29}.0^{31,36}]-dotetraconta-1(38),3(8),4,6,10(15),11,13,17(22),18,20,24-(29),25,27,31(36),32,34,39,41-octadecaene, Dimethoxy[1$_6$]-OCP (23). Dione **22** (600 mg, 960 μmol) was reduced according to general procedure E to provide 350 mg (61%) of crystalline **23**: mp 260–262 °C dec; IR (KBr) 1600, 1380, 1290 cm^{-1}; ^{1}H NMR (200 MHz) δ 7.17–6.86 (m, 20 H), 6.50 (s, 2 H), 3.77 (s, 4 H), 3.73 (s, 6 H), 3.70 (s, 4 H), 3.67 (s, 4 H); ^{13}C NMR (50.3 MHz) δ 147.4, 138.8, 138.5, 138.4, 138.3, 130.5, 129.9, 129.41, 129.2, 126.5, 126.4, 113.6, 95.41, 55.88, 36.06, 35.99, 35.54; EIMS m/z (rel intens) 600 (M^+, 100), 269 (26), 179 (37); HRMS (EI) calcd for $C_{44}H_{40}O_2$ M 600.3028, found M^+ 600.3245.

4,5-Dimethoxy-1,2-bis[2-(chloromethyl)benzyl]benzene (24). To a solution of diol **13** (4.00 g, 10.6 mmol) in CH_2Cl_2 (100 mL) containing pyridine (2.10 g, 26.5 mmol) was added dropwise with stirring a solution of $SOCl_2$ (3.78 g, 31.8 mmol) followed by refluxing overnight. After routine workup, the crude product was chromatographed (SiO_2, CH_2Cl_2) to give 4.0 g (91%) of crystalline dichloride **24**: mp 101–102 °C; IR (KBr) 1600, 1450, 1170 cm^{-1}; ^{1}H NMR (200 MHz) δ 7.37–6.92 (m, 8 H), 6.57 (s, 4 H), 4.51 (s, 4 H), 4.02 (s, 4 H,), 3.76 (s, 6 H); ^{13}C NMR (50.3 MHz) δ 147.7, 139.3, 135.5, 130.2, 130.1, 129.7, 129.1, 126.8, 113.8, 55.95, 44.49, 35.06; EIMS m/z (rel intens) 419 (M^+, 3), 418 (M^+, 13), 417 (M^+, 17), 416 (M^+, 68), 415 (M^+, 26), 414 (M^+, 100), 276 (54), 239 (41); HRMS (EI) calcd for $C_{24}H_{24}O_2Cl_2$ M 414.1153, found M^+ 414.1154.

4,5-Dimethoxy-1,2-bis[2-[2-(hydroxymethyl)benzyl]benzyl]benzene (25). According to general procedure A, dichloride **24** (3.50 g, 8.43 mmol) was reacted with Grignard **12** (21 mmol) followed by removal of the protecting groups in the biscondensation product. After workup, the crude product was chromatographed (SiO_2, CH_2Cl_2) to afford 3.23 g (68.7%) of crystalline diol **25**: mp 146–148 °C; IR (KBr) 3600–3100 (s), 1600, 1450 cm^{-1}; ^{1}H NMR (200 MHz) δ 7.37–6.88 (m, 16 H), 6.48 (s, 2 H), 4.44 (s, 4 H), 3.86 (s, 4 H), 3.73 (s, 10 H), 1.81 (s, 2 H); ^{13}C NMR (50.3 MHz) δ 147.5, 138.7, 138.5, 138.0, 130.5, 129.8, 129.5, 129.5, 128.2, 127.9, 126.6, 113.5, 63.16, 55.93, 35.84, 35.35; EIMS m/z (rel intens) 559 (MH^+, 18), 558 (M^+, 44), 192 (86), 179 (100); HRMS (EI) calcd for $C_{38}H_{38}O_4$ M 558.2770, found M^+ 558.2778.

4,5-Dimethoxy-1,2-bis[2-(2-formylbenzyl)benzyl]benzene (26). According to general procedure B, diol **25** (3.00 g, 5.38 mmol) was oxidized with PCC (3.50 g) to give 2.72 g (91%) of crystalline **26**: mp 116–118 °C; IR (KBr) 1700, 1600, 1450, 1100 cm^{-1}; ^1H NMR (200 MHz) δ 10.05 (s, 2 H), 7.84–6.83 (m, 16 H), 6.47 (s, 2 H), 4.27 (s, 4 H), 3.75 (s, 4 H), 3.73 (s, 6 H); ^{13}C NMR (50.3 MHz) δ 192.3, 147.5, 142.4, 138.5, 138.3, 134.0, 133.8, 132.15, 130.9, 130.3, 129.7, 129.6, 129.5, 126.8, 126.7, 126.6, 113.4, 82.64, 55.85, 35.81, 35.23; EIMS *m/z* (rel intens) 554 (M^+, 100), 239 (12), 179 (41); HRMS (EI) calcd for $C_{38}H_{34}O_4$ M 554.2457, found M^+ 554.2460.

2,23-Dioxo-12,13,40,41-tetramethoxynonacyclo[50.4.0.0^{3,8}.0^{10,15}.0^{17,22}.0^{24,29}.0^{31,36}.0^{38,43}.0^{45,50}]hexapentaconta-1(52),3(8),4,6,10(15),11,13,17(22),18,20,24(29),25,27,31(36),32,34,38(43),39,41,45(50),46,48,53,55-tetracosaene, Tetramethoxy[1$_8$]OCP-1,4-dione (28). According to general procedure D, dialdehyde **26** (1.80 g, 3.25 mmol) and dilithio reagent **15** (3.26 mmol) was reacted followed by oxidation of the resultant cyclic diol **27** to provide 665 mg (23.5%) of dione **28**: mp 136–138 °C; IR (KBr) 1665, 1600, 1450, 1250, 1100 cm^{-1}; ^1H NMR (200 MHz) δ 7.28–6.66 (m, 24 H), 6.33 (s, 2 H), 6.30 (s, 2 H), 4.14 (s, 4 H), 3.67 (s, 16 H), 3.41 (s, 4 H); ^{13}C NMR (50.3 MHz) δ 200.45, 147.29, 147.17, 140.81, 139.80, 139.51, 138.98, 138.74, 138.53, 131.23, 130.87, 130.57, 130.48, 130.39, 130.23, 130.06, 129.73, 129.28, 126.41, 126.15, 125.79, 113.73, 113.30, 55.85, 36.25, 35.55, 35.19; FABMS *m/z* (rel intens) 869 (MH^+, 93), 868 (M^+, 100), 433 (17), 315 (28), 297 (57), 265 (65), 239 (89); HRMS (FAB) calcd for $C_{60}H_{52}O_6$ M 868.3764, found M^+ 868.9810

5,6,33,34-Tetramethoxynonacyclo[50.4.0.0^{3,8}.0^{10,15}.0^{17,22}.0^{24,29}.0^{31,36}.0^{38,43}.0^{45,50}]hexapentaconta-1(52),3(8),4,6,10(15),11,13,17(22),18,20,24(29),25,27,31(36),32,34,38(43),39,41,45(50),46,48,53,55-tetracosaene, Tetramethoxy[1$_8$]OCP (29). According to general procedure E, Clemmensen reduction of **28** (500 mg, 575 μmol) gave 210 mg (43.4%) of crystalline **29**: mp 232–234 °C; IR (KBr) 1600, 1450, 1220 cm^{-1}; ^1H NMR (200 MHz) δ 7.13–6.81 (m, 24 H), 6.47 (s, 4 H), 3.73 (s, 12 H), 3.62 (s, 8 H), 3.51 (s, 8 H); ^{13}C NMR (50.3 MHz) δ 147.46, 138.53, 138.27, 137.93, 130.41, 129.34, 128.90, 126.56, 126.50, 126.43, 113.52, 55.85, 35.86, 35.41; FABMS *m/z* (rel intens) 841 (MH^+, 97), 307 (83), 289 (70), 239 (100); HRMS (FAB) calcd for $C_{60}H_{56}O_4$ M 840.4179, found (MH^+) 841.0303.

2,23-Dioxo-12,13-dimethoxynonacyclo[50.4.0.0^{3,8}.0^{10,15}.0^{17,22}.0^{24,29}.0^{31,36}.0^{38,43}.0^{45,50}]hexapentaconta-1(52),3(8),4,6,10(15),11,13,17(22),18,20,24(29),25,27,31(36),32,34,38(43),39,41,45(50),46,48,53,55-tetracosaene, Dimethoxy[1$_8$]OCP-1,4-dione (32). According to general procedure D, dialdehyde **30** (2.75 g, 5.57 mmol) and dilithio reagent **15** (5.57 mmol) were reacted followed by oxidation of the resultant cyclic diol **31** with PCC to give 1.20 g (26.8%) of crystalline **32**: mp 195–196 °C; IR (KBr) 1665, 1600, 1450, 1100 cm^{-1}; ^1H NMR (200 MHz) δ 7.30–6.65 (m, 28 H), 6.35 (s, 4 H), 4.12 (s, 4 H), 3.69 (s, 6 H), 3.65 (s, 4 H), 3.46 (s, 4 H); ^{13}C NMR (50.3 MHz) δ 200.5, 147.2, 140.8, 139.8, 139.7, 139.5, 138.7, 138.6, 138.5, 138.4, 131.3, 130.9, 130.7, 130.3, 130.0, 129.7, 129.5, 129.4, 126.6, 126.5, 126.2, 125.8, 113.6, 108.4, 55.83, 36.26, 35.66, 35.41; FABMS *m/z* (rel intens) 809 (MH^+, 100), 808 (M^+, 85), 369 (14), 307 (54), 265 (74), 252 (52); HRMS (FAB) calcd for $C_{58}H_{48}O_4$ M 808.3553, found (MH^+) 809.9036.

5,6-Dimethoxynonacyclo[50.4.0.0^{3,8}.0^{10,15}.0^{17,22}.0^{24,29}.0^{31,36}.0^{38,43}.0^{45,50}]hexapentaconta-1(52),3(8),4,6,10(15),11,13,17(22),18,20,24(29),25,27,31(36),32,34,38(43),39,41,45(50),46,48,53,55-tetracosaene, Dimethoxy[1$_8$]OCP (33). According to general procedure E, dione **32** (500 mg, 618 μmol) was reduced with Zn(Hg)/HCl to give 220 mg (45.6%) of crystalline **33**: mp 265–267 °C dec; IR (KBr) 1600, 1455, 1110 cm^{-1}; ^1H NMR (200 MHz) δ 7.24–6.85 (m, 28 H), 6.40 (s, 2 H), 3.69 (s, 6 H), 3.58 (s, 4 H), 3.56 (s, 8 H), 3.48 (s, 4 H); ^{13}C NMR (50.3 MHz) δ 147.37, 138.56, 138.18, 138.02, 130.29, 129.35, 129.14, 126.55, 113.07, 55.78, 35.92, 35.41; FABMS *m/z* (rel intens) 780 (M^+, 28), 307 (100), 289 (89), 239 (72); HRMS (FAB) calcd for $C_{58}H_{52}O_2$ M 780.3967, found M^+ 780.8678.

2,16-Dioxo-26,27-dimethoxyhexacyclo[29.4.0.0^{3,8}.0^{10,15}.0^{17,22}.0^{24,29}]pentatriaconta-1(31),3(8),4,6,10(15),11,13,17(22),18,20,24(29),25,27,32,34-pentadecaene, Dimethoxy[1$_5$]OCP-1,3-dione (36). According to general procedure D, dialdehyde **34** (2.00 g, 8.93 mmol) and dilithio reagent **15** (8.93 mmol) was condensed, followed by oxidation of the resultant cyclic diol **35** to give 550 mg (11.4%) of crystalline **36**: mp 209–211 °C; IR (KBr) 1660, 1595, 1440 cm^{-1}; ^1H NMR (200 MHz) δ 7.51–6.74 (m, 16 H), 6.69 (s, 2 H), 3.85 (s, 6 H), 3.65 (s, 6 H); ^{13}C NMR (50.3 MHz) δ 201.4, 147.8, 141.0, 139.1, 139.1, 136.6, 131.4, 131.0, 130.5, 130.0, 129.9, 129.5, 128.7, 126.8, 126.1, 115.0, 55.06, 36.83; EIMS *m/z* (rel intens) 538 (M^+, 100), 520 ($M^+ - H_2O$, 5), 281 (14), 165 (9); HRMS (EI) calcd for $C_{37}H_{30}O_4$ M 538.2144, found M^+ 538.2140.

5,6-Dimethoxyhexacyclo[29.4.0.0^{3,8}.0^{10,15}.0^{17,22}.0^{24,29}]pentatriaconta-1(31),3(8),4,6,10(15),11,13,17(22),18,20,24(29),25,27,32,34-pentadecaene, Dimethoxy[1$_5$]OCP (37). Clemmensen reduction of dione **36** (451 mg, 838 μmol), according to general procedure E, furnished 110 mg (25.8%) of crystalline **37**: mp 164–166 °C; IR (KBr) 1600, 1440, 1170, 1100 cm^{-1}; ^1H NMR (200 MHz) δ 7.23–6.87 (m, 16 H), 6.54 (s, 2 H), 3.79 (s, 4 H), 3.74 (s, 6 H), 3.70 (s, 2 H), 3.67 (s, 4 H); ^{13}C NMR (50.3 MHz) δ 147.2, 138.5, 138.4, 138.2, 138.1, 130.4, 130.3, 130.2, 130.0, 129.8, 126.4, 126.2, 114.1, 55.90, 37.88, 37.77, 36.92; EIMS *m/z* (rel intens) 510 (M^+, 43), 269 (27), 179 (30), 74 (100); HRMS (EI) calcd for $C_{37}H_{34}O_2$ M 510.2259, found M^+ 510.2553.

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Supplementary Material Available: Additional experimental data and copies of ^1H and ^{13}C NMR spectra of **10**, **11**, **13**, **14**, **17**, **18**, **22-26**, **28**, **29**, **32**, **33**, **36**, and **37** (22 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.