Metacyclophanes and Related Compounds. 26.[1] Tetrahydroxy[2.*n*.2.*n*]metacyclophanes. Preparation, Reactions, and Spectra

Masashi Tashiro,*[,2] Akihiko Tsuge,[2] Tsuyoshi Sawada,[3] Toshihiro Makishima,[3] Seiji Horie,[3] Takashi Arimura,[3] Shuntaro Mataka,[2] and Takehiko Yamato[4]

Institute of Advanced Material Study and Department of Molecular Science and Technology, Graduate School of Engineering Sciences, Kyushu University, 6-1 Kasuga-koh-en, Kasuga-shi, Fukuoka 816, Japan, and Department of Industrial Chemistry, Faculty of Science and Engineering, Saga University, 1, Honjo-machi, Saga 840, Japan

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Tetra-*tert*-butyltetrahydroxy- and tetrahydroxy[2.*n*.2.*n*]metacyclophanes, **1** and **2** (**a**, $n = 1$; **b**, $n = 2$; and **c**, $n = 3$), were prepared from *p*-*tert*-butylanisole by using the *tert*-butyl group as a positional protective function. Acetylation of **1b** and **2b** with Ac_2O gave tetraacetates **9** and **10**. Methylation of **2b** with MeI gave tetramethoxy **11**, while dimethoxy derivatives **12** and **13** were obtained in the reaction of **1b** and **2b**, respectively, with CH_2N_2. Tetrakis(allyloxy)MCPs, **14** and **15** were prepared by the reaction of **1b** and **2b**, respectively, with allyl bromide. When heated in diethylaniline, **14** was deallylated, giving **1b**, while **15** afforded the Claisen rearrangement product **16**. Bromination of **2b** gave tetrabromoMCP **17**. Oxidation of **2b** gave the expected tetrakis quinone **19**, which, on reduction with Zn in the presence of Ac_2O, afforded octaacetate **20**. Of these tetranuclear MCPs, tetrahydroxy[2.2.2.2]MCPs **1b**, **2b**, **16**, and **17** form the strong intramolecular hydrogen bond, while the corresponding [2.1.2.1]MCPs **1a** and **2a** and [2.3.2.3]MCPs **1c** and **2c** do not.

Since the first report[5] of Gutsche on calix[4]arene, calix[*n*]arenes have been attracting attention, especially as potential enzyme mimics in host–guest chemistry.[6] Calixarenes fundamentally consist of phenol rings that are connected to each other by methylene bridges at the two ortho positions of the ring, and, thus, are considered as members of the metacyclophane (MCP) family. In an earlier paper[7] of this series, we reported the preparation, reactions, and ^1H NMR spectral behavior of macrocyclic MCPs such as tetramethyl[2.2.2.2]MCP and trimethyl[2.2.2]MCP. We now describe the preparation, reactions, and spectra of calix[4]arene-analogous macrocyclic MCPs such as tetrahydroxy[2.*n*.2.*n*]MCPs **1** and **2**.

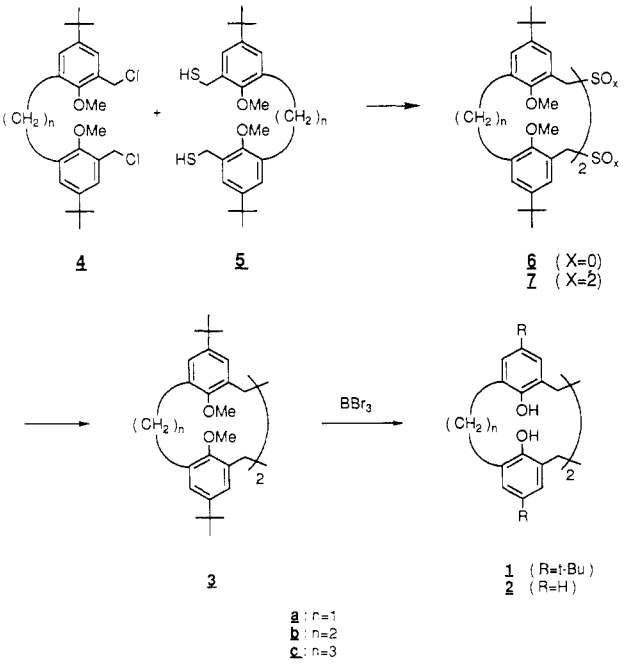
Results and Discussion

Preparation of Tetrahydroxy[2.*n*.2.*n*]metacyclophanes. Preparative routes of **1** and **2** are given in Scheme I.

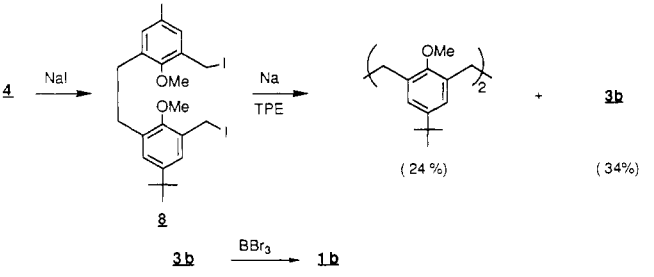
We previously reported convenient preparative routes to a series of [2.*n*]MCPs using the *tert*-butyl group as a positional protective function.[8-12] This strategy was adapted for the preparation of tetramethoxy[2.*n*.2.*n*]MCP **3** (Scheme I).

Bis(chloromethyl) **4** and dithiol **5** were prepared as usual. The cyclization of **4** and **5** was carried out under highly diluted conditions in 10% ethanolic CsOH in the presence of a small amount of $NaBH_4$, giving **6** in 43–55% yield. When either NaOH or KOH was used in place of CsOH, the yield of **6** was very low. Oxidation of **6** with *m*-

Scheme I



Scheme II



(1) For part 25, see: Tashiro, M.; Yamato, T.; Kajiwara, A.; Torii, A. *The Report of the Institute of Advanced Material Study*; Kyushu University, 1989; Vol. 3, p 47.
(2) Institute of Advanced Material Study.
(3) Department of Molecular Science and Technology.
(4) Saga University.
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(12) Yamato, T.; Arimura, T.; Tashiro, M. *J. Chem. Soc., Perkin Trans. 1* **1987**, 1.

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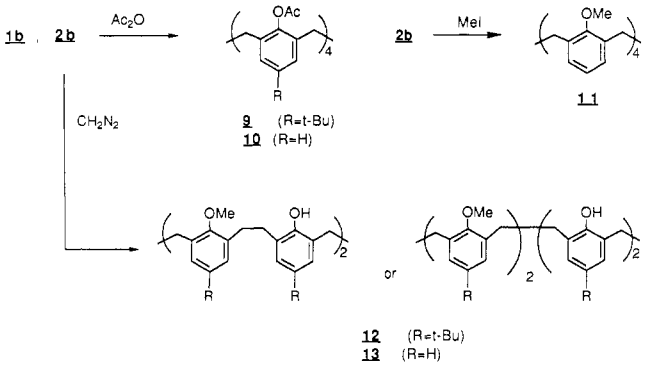
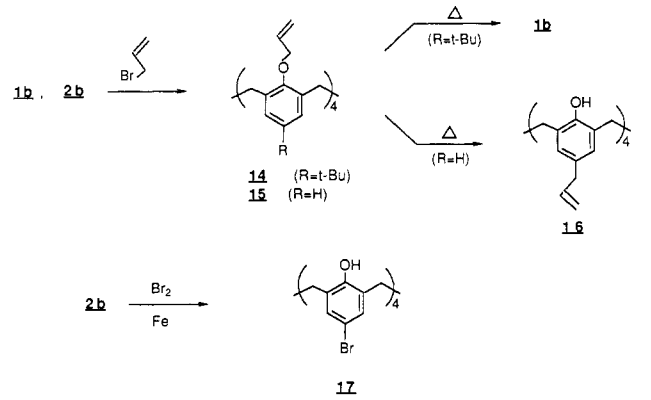
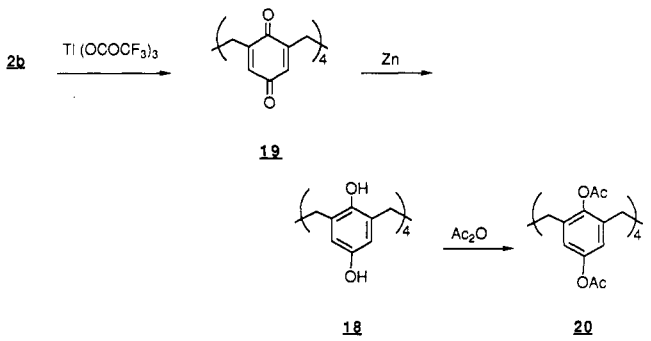
Scheme III



Scheme IV



Scheme V



chloroperoxybenzoic acid afforded the corresponding disulfone **7** in high yield. Pyrolysis of **7** under reduced pressure (0.4 Torr) was carried out according to the reported method,[9] affording the desired cyclophane **3** in 34–40% yield.

Demethylation of **3** with BBr_3 in CH_2Cl_2 gave tetra-*tert*-butyltetrahydroxyMCP **1**. The *tert*-butyl groups of **1** were removed by the trans-*tert*-butylation reaction with toluene in the presence of $AlCl_3$-CH_3NO_2 catalyst to give the expected **2**.

TetrahydroxyMCP **1b** was previously obtained by demethylation of **3b** which was obtained in the cyclization of diiodide **8** with Na in the presence of tetraphenylethene (TPE) as shown in the Scheme II.[9] Although this method affords a shorter route to **3b** than the above-mentioned dithiane method, the procedures in the latter seem more suitable for larger scale preparation than those of the former.

Reactions of Tetrahydroxy[2.2.2.2]MCP. Some reactions of tetrahydroxy[2.2.2.2]MCPs **1b** and **2b** were investigated (Schemes III–V), since **1b** and **2b** form strong intramolecular hydrogen bonds like calix[4]arene as will be described later.

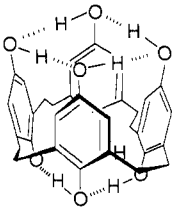


Figure 1. Cylindrical conformation of **18**.

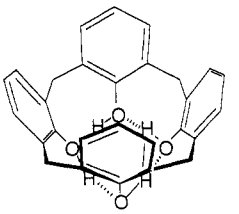


Figure 2. Cone conformation of calix[4]arene.

Acetylation of **1b** and **2b** gave the tetraacetates **9** and **10** in 48% and 37% yields. The reaction of **2b** with MeI afforded tetramethoxy derivative **11**. It is noted that **11** could not be obtained in the trans *tert*-butylation of **3b**. Methylation of **1b** and **2b** with a 20-fold excess of CH_2N_2 afforded dimethoxy derivatives **12** and **13**, respectively, but not tetramethoxy ones. The OH signals for **12** were observed at 5.96 ppm in the ^1H NMR spectrum and at 3450 cm^{-1} in the IR spectrum, suggesting either the absence of an intramolecular hydrogen bond or the presence of a weak one. Unfortunately, it is not clear which structure is correct. It was reported that calix[4]arene gave a monomethoxy derivative in the methylation with CH_2N_2.[6]

When the sodium salts of **1b** and **2b** were treated with allyl bromide in the presence of NaH, the corresponding allylated MCPs **14** and **15** were obtained in 35% and 54% yields, respectively. When refluxed in diethylaniline, **14** afforded the deallylated **1b**, while **15** gave the expected **16** in a quantitative yield.

Bromination of **2b** in the presence of Fe powder gave the tetrabromoMCP **17** in 64% yield.

Due to the double intramolecular hydrogen-bonding system, octahydroxy[2.2.2.2]MCP **18** could be expected to take a "cylindrical" form (Figure 1). Oxidation of **2b** by thallium trifluoroacetate in trifluoroacetic acid gave the expected [2.2.2.2]MCP quinone **19**, albeit in low yield. When the yellow solution of **19** was treated with zinc powder, the reaction mixture became colorless, suggesting the formation of **18**. The tetraacetate **20** was obtained when the reaction mixture was treated with Ac_2O. Unfortunately, at the present time, the isolation of **18** was unsuccessful and resulted in the formation of resinous materials.

Spectral Behavior of [2.*n*.2.*n*]MCP. It was previously reported that in the ^1H NMR spectrum the methyl groups of 7,15,22,30-tetramethyl[2.1.2.1]MCP appear as a single peak at room temperature due to the rapid movement of the [2.1.2.1]MCP ring system.[13]

In the spectra of tetramethoxy[2.*n*.2.*n*]MCP **3**, protons of *tert*-butyl groups, the methoxy groups, and the ethano bridges each appear as a singlet. This indicates the flexible structure of **3**. It is noted that, as the ring size of **3** becomes smaller, the methoxy group comes in close proximity to the aromatic ring and the signal of the methoxy group shifts to a higher field. The methoxy signals of [2.1.2.1]-MCP **3a** and [2.2.2.2]MCP **3b** appear around 2.9 ppm and those of [2.3.2.3]MCP **3c** resonate at 3.20 ppm.

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Table I. Selected ^{1}H NMR and IR Spectral Data for Tetrahydroxy[2.*n*.2.*n*]MCPs 1, 2, 16, and 17

system	MCP	IR (KBr) ν (OH)	^{1}H NMR δ ($CDCl_3$) OH	-$(CH_2)_n$
[2.1.2.1]	**1a**	3418	8.80 (s)	2.84 (8 H, s), 3.90 (4 H, s)
	2a	3362	7.44 (s)	2.87 (8 H, s), 3.86 (4 H, s)
[2.2.2.2]	**1b**	3220	10.40 (br s)	2.94 (16 H, br s)
	2b	3240	10.38 (br s)	2.92 (16 H, s)
	16	3210	10.38 (br s)	2.86 (16 H, br s)
	17	3220		
[2.3.2.3]	**1c**	3354	8.55 (s)	1.90–2.20 (4 H, m) 2.48–2.75 (8 H, m), 2.87 (8 H, s)
	2c	3362	8.65 (s)	2.05–2.20 (4 H, m) 2.66–2.74 (8 H, m), 2.90 (8 H, s)

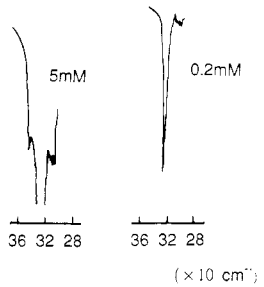

Figure 3. IR spectra of **1b** (in CCl_4).

The characteristic feature of tetrahydroxy[1.1.1.1]MCP (calix[4]arene) is the "cone" shape conformation due to the strong intramolecular hydrogen bond[14,15] (Figure 2); the signal at 10.19 ppm in the ^{1}H NMR spectrum (in $CDCl_3$) and the absorption at 3160 cm^{-1} in the IR spectrum (KBr) are quoted as evidenced for this conformation.

Hydrogen bonding was also expected to fix the conformation of the flexible [2.*n*.2.*n*]MCP system. IR and ^{1}H NMR spectral data for **1** and **2** are summarized in Table I. Of three kinds of tetrahydroxy[2.*n*.2.*n*]MCP systems, [2.2.2.2]MCPs **1b** and **2b** provide evidence for the presence of a calix[4]arene-like intramolecular hydrogen bond; ^{1}H NMR spectra (in $CDCl_3$) show the signals for the hydroxy groups around 10.40 ppm as a broad singlet and IR spectra (in KBr) show the absorption for the OH streching vibration around 3220 cm^{-1}. IR spectra (in CCl_4) also show this peak at 3220 cm^{-1}, which is accompanied by a small peak, ascribable to an intermolecular hydrogen bond, at 3400 cm^{-1} (Figure 3). However, in contrast to calix[4]arene,[14,15] which shows the bridge methylenes as an AB pattern in the ^{1}H NMR spectrum, the ethano bridges of **1b** and **2b** appear as a single peak at room temperature. The *tert*-butyl groups of **1b** are also observed as a single peak. The ^{1}H NMR spectrum of **1b** at −40 °C showed somewhat broadened peaks, but is essentially same in the temperature range of −40 to +60 °C. These observations indicate that **1b** and **2b** are confomationally flexible, though the hydroxy groups are close to each other. TetraallylMCP **16** and tetrabromoMCP **17** similarly form intramolecular hydrogen bonds and are flexible.

It is concluded that the calix[4]arene-like intramolecular hydrogen bonds could not fix the conformation of tetrahydroxy[2.2.2.2]MCPs **1b**, **2b**, **16**, and **17**.

In the ^{1}H NMR spectra of the smaller [2.1.2.1]MCPs, **1a** and **2a**, and the larger [2.3.2.3]MCPs, **1c** and **2c**, the protons of ethylene bridge appear as a singlet. Their hydroxy signals are observed at 2–3-ppm higher field than those of [2.2.2.2]MCP **1b** and **2b**. In the IR spectra, hydroxy signals of **1a**, **1c**, **2a**, and **2c** are observed 100–150 cm^{-1} higher than those of **1b** and **2b**. The hydroxy groups in **1a**, **1c**, **2a**, and **2c** are presumably more remote from each other and, therefore, form weaker intramolecular hydrogen bonds than those in **1b** and **2b**.

The ^{1}H NMR spectra of acetates **8**, **9**, and **20** show the protons of ethano bridges as singlets. The acetyl groups of **8** and **9** (1.40 and 1.30 ppm, respectively) and those (2.28 ppm) on the outer positions of **20** are also observed as singlets, while the acetyl groups on the inner positions of **19** appear as two singlets of equal intensity at 1.30 and 1.70 ppm, respectively. The reason for these differences is not known.

Experimental Section

All melting points are uncorrected. ^{1}H NMR spectra were recorded at 100 MHz in $CDCl_3$ unless otherwise stated. Mass spectra were obtained at 75 eV, using a direct inlet system. Column chromatography was carried out on silica gel (Wako gel, C-300).

Bis(5-*tert*-butyl-2-methoxyphenyl)methane (21). To a stirred mixture of 3.00 g (9.61 mmol) of 5,5′-di-*tert*-butyl-2,2′-dihydroxydiphenylmethane[16] in 14 mL of methanol was added 100 mL of 20% aqueous NaOH. The mixture was warmed (bath temperature 90–100 °C) and 6.00 g (47.6 mmol) of Me_2SO_4 was added dropwise at the temperature. The reaction mixture was then refluxed for 3 h, cooled to room temperature, extracted with CH_2Cl_2, dried over $MgSO_4$, and evaporated in vacuo to leave the residue, which, on recrystallization from ethanol, afforded 2.82 g (86%) of **21** as colorless needles, mp 83–84 °C: ^{1}H NMR δ 1.25 (18 H, s), 3.81 (6 H, s), 3.95 (2 H, s), 6.64–6.84 (2 H, m), 7.04–7.26 (4 H, m); MS *m/z* 340 (M^+). Anal. Calcd for $C_{23}H_{32}O_2$: C, 81.13; H, 9.47. Found: C, 81.09; H, 9.60.

Bis[5-*tert*-butyl-3-(chloromethyl)-2-methoxyphenyl]methane (4a). After a mixture of 3.66 g (10.8 mmol) of **21**, 24.3 g (810 mmol) of paraformaldehyde, 55 mL of 80% phosphoric acid, 65 mL of concentrated hydrochloric acid, and 50 mL of acetic acid was stirred at 90–100 °C for 10 h, it was cooled to room temperature and extracted with benzene. The extract was washed with saturated aqueous Na_2CO_3 and water, dried over $MgSO_4$, and evaporated in vacuo to leave a residue, which, on recrystallization from ethanol, afforded 3.64 g (77%) of **4** as colorless prisms, mp 88–89 °C: ^{1}H NMR δ 1.23 (18 H, s), 3.79 (6 H, s), 4.24 (2 H, s), 4.67 (4 H, s), 6.98 (2 H, d, J = 2.5 Hz), 7.25 (2 H, d, J = 2.5 Hz); MS *m/z* 440, 438, 436 (M^+). Anal. Calcd for $C_{25}H_{34}O_2Cl_2$: C, 68.64; H, 7.83. Found: C, 68.42; H, 8.00.

1,3-Bis[5-*tert*-butyl-3-(chloromethyl)-2-methoxyphenyl]propane (4c). After a mixture of 2.00 g (5.4 mmol) of 1,3-bis(5-*tert*-butyl-2-methoxyphenyl)propane,[17] 1.00 g (35.6 mmol) of paraformaldehyde, 4 mL of 80% phosphoric acid, 7 mL of concentrated hydrochloric acid, and 6 mL of acetic acid was stirred at 85–90 °C for 13 h, it was worked up as described in the preparation of **4a** to afford 1.12 g (44%) of **4c** as colorless prisms (hexane), mp 79.5–81.5 °C: ^{1}H NMR δ 1.29 (18 H, s), 1.84–2.09 (2 H, m), 2.60–2.95 (4 H, m), 3.78 (6 H, s), 4.64 (4 H, s), 7.16 (2 H, d, J = 2.5 Hz), 7.21 (2 H, d, J = 2.5 Hz); MS *m/z* 468, 466, 464 (M^+). Anal. Calcd for $C_{27}H_{38}O_2Cl_2$: C, 69.67; H, 8.23. Found: C, 69.64; H, 8.25.

Bis[5-*tert*-butyl-3-(mercaptomethyl)-2-methoxyphenyl]methane (5a). After a solution of 3.00 g (6.86 mmol) of **4a** and 1.35 g (17 mmol) of thiourea in 150 mL of DMSO was stirred at room temperature for 14 h under a nitrogen stream, it was poured into 500 mL of cold aquous 10% NaOH. The mixture was stirred at room temperature for 2 h, acidified with 10% hydrochloric acid, and extracted with CH_2Cl_2. The extract was washed with water, dried over $MgSO_4$, and evaporated in vacuo to afford a rersidue, which, on chromtography using hexane as an eluant, gave 1.72 g (58%) of **5a** as a colorless liquid: ^{1}H NMR δ 1.22 (18 H, s), 1.91 (2 H, t, J = 8 Hz), 2.73 (6 H, s), 2.76 (4 H, d, J = 8 Hz), 3.03 (2

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H, s), 6.89 (2 H, d, J = 2.5 Hz), 7.15 (2 H, d, J = 2.5 Hz); MS m/z 432 (M^+). Anal. Calcd for $C_{25}H_{36}O_2S_2$: C, 69.39; H, 8.39. Found: C, 69.24; H, 8.64.

1,2-Bis[5-*tert*-butyl-3-(mercaptomethyl)-2-methoxyphenyl]ethane (5b). After a solution of 13.6 g (30 mmol) of **4b** and 5.3 g (70 mmol) of thiourea in 200 mL of DMSO was stirred at 40–45 °C for 14 h under a nitrogen stream, it was worked up as described in the preparation of **5a** to afford a residue, which, on recrystallization from a mixture of benzene and ethanol, gave 10 g (75%) of **5b** as colorless prisms, mp 148–149 °C: ^{1}H NMR δ 1.28 (18 H, s), 1.90 (2 H, t, J = 8 Hz), 2.93 (4 H, s), 3.72 (4 H, d, J = 8 Hz), 3.80 (6 H, s), 7.04–7.06 (4 H, m); MS m/z 446 (M^+). Anal. Calcd for $C_{26}H_{38}O_2S_2$: C, 69.91; H, 8.57. Found: C, 70.01; H, 8.54.

1,3-Bis[5-*tert*-butyl-3-(mercaptomethyl)-2-methoxyphenyl]propane (5c). After a solution of 3.00 g (6.45 mmol) of **4c** and 1.36 g (17.8 mmol) of thiourea in 150 mL of DMSO was stirred at 55–60 °C for 14 h under a nitrogen stream, it was worked up as described in the preparation of **5a** to afford a residue, which, on chromatography using a 9:1 mixture of hexane and EtOAc as an eluant, gave 1.72 g (58%) of **5c** as a cololess liquid: ^{1}H NMR δ 1.29 (18 H, s), 1.88 (2 H, t, J = 8 Hz), 1.70–2.10 (2 H, m), 2.50–2.80 (4 H, m), 3.76 (4 H, d, J = 8 Hz), 3.77 (6 H, s), 7.07 (2 H, d, J = 2.6 Hz), 7.11 (2 H, d, J = 2.6 Hz); MS m/z 460 (M^+). Anal. Calcd for $C_{27}H_{40}O_2S_2$: C, 70.38; H, 8.75. Found: C, 70.48; H, 9.03.

6,13,22,29-Tetra-*tert*-butyl-9,16,25,32-tetramethoxy-2,18-dithia[3.1.3.1]metacyclophane (6a). A solution of 9.82 g (22.5 mmol) of **4a** and 9.72 g (22.5 mmol) of **5a** in 500 mL of a mixture of ethanol and benzene was added dropwise from a Hershberg funnel with stirring to a refluxing mixture of 15.1 g (purity; 80%; 90 mmol) of CsOH and 1.70 g (45 mmol) of $NaBH_4$ in 4 L of ethanol. When the addition was complete (100 h), the mixture was concentrated and extracted with CH_2Cl_2. The extract was dried over $MgSO_4$ and concentrated. The residue was triturated with hexane to give crude **6a**, which was isolated by filtration. The filtrate was concentrated and chromatographed, using a 17:3 mixture of hexane and ethyl acetate as an eluent, giving additional **6a**. Recrystallization from a mixture of hexane and chloroform gave 9.90 g (55%) of **6a** as colorless prisms, mp 287–290 °C dec: ^{1}H NMR δ 1.20 (36 H, s), 3.18 (12 H, s), 3.65 (8 H, s), 3.82 (4 H, br s), 6.97 (4 H, d, J = 2.5 Hz), 7.09 (4 H, d, J = 2.5 Hz); MS m/z 796 (M^+). Anal. Calcd For $C_{50}H_{68}O_4S_2$: C, 75.33; H, 8.60. Found: C, 75.27; H, 8.67.

6,14,23,31-Tetra-*tert*-butyl-9,17,26,34-tetramethoxy-2,19-dithia[3.2.3.2]metacyclophane (6b). A solution of 9.0 g (20 mmol) of **4b** and 8.9 g (20 mmol) of **5** in 300 mL of benzene was added dropwise from a Hershberg funnel with stirring to a refluxing mixture of 9.84 g (purity; 80%; 50 mmol) of CsOH and 1.5 g (40 mmol) of $NaBH_4$ in 3 L of ethanol. When the addition was complete (40 h), the mixture was concentrated and the residue was extracted with CH_2Cl_2. The extract was dried over $MgSO_4$, concentrated, and chromatographed, using hexane as an eluent, to give 9.06 g (55%) of **6b** as colorless prisms (a 1:1 mixture of hexane and benzene), mp 254 °C: ^{1}H NMR δ 1.20 (36 H, s), 2.92 (8 H, s), 3.30 (12 H, s), 3.52 (8 H, s), 6.90 (4 H, d, J = 3 Hz), 7.10 (4 H, d, J = 3 Hz); MS m/z 824 (M^+). Anal. Calcd for $C_{52}H_{72}O_4S_2$: C, 75.68; H, 8.79. Found: C, 75.61; H, 8.87.

6,15,24,33-Tetra-*tert*-butyl-9,18,27,36-tetramethoxy-2,20-dithia[3.3.3.3]metacyclophane (6c). A solution of 3.57 g (7.67 mmol) of **4c** and 3.53 g (7.67 mmol) of **5c** in 500 mL of a 1:1 mixture of ethanol and benzene was added dropwise from a Hershberg funnel with stirring to a refluxing mixture of 5.15 g (purity; 80% 30.7 mmol) of CsOH and 0.58 g (15 mmol) of $NaBH_4$ in 4 L of ethanol for 200 h. The mixture was worked up as described in the preparation of **6a** to give 2.78 g (43%) of **6c** as colorless prisms (a mixture of hexane and benzene), mp 209–211 °C: ^{1}H NMR δ 1.20 (36 H, s), 3.18 (12 H, s), 3.65 (8 H, s), 3.82 (4 H, br s), 6.97 (4 H, d, J = 2.5 Hz), 7.09 (4 H, d, J = 2.5 Hz); MS m/z 852 (M^+). Anal. Calcd for $C_{54}H_{76}O_4S_2$: C, 75.77; H, 9.27. Found: C, 76.01; H, 8.98.

6,13,22,29-Tetra-*tert*-butyl-9,16,25,32-tetramethoxy-2,18-dithia[3.1.3.1]metacyclophane 2,2,18,18-Tetraoxide (7a). After a mixture of 2.92 g (3.67 mmol) of **6a** and 3.27 g (purity 80%; 15.2 mmol) of *m*-chloroperbenzoic acid in 100 mL of CH_2Cl_2 was stirred at room temperature for 12 h, it was washed with 10% aqueous K_2CO_3 and water, dried over $MgSO_4$, and evaporated in vacuo to leave a residue, which was washed with hexane and methanol, giving 2.70 g (86%) of **7a** as colorless crystalline powder, mp 361 °C dec: MS m/z 860 (M^+). Anal. Calcd for $C_{50}H_{68}O_8S_2$: C, 69.73; H, 7.96. Found: C, 69.78; H, 8.12.

6,14,23,31-Tetra-*tert*-butyl-9,17,26,34-tetramethoxy-2,19-dithia[3.2.3.2]metacyclophane 2,2,19,19-Tetraoxide (7b). After mixture of 10.0 g (12.1 mmol) of **6b** and 15.7 g (purity 80%; 72.8 mmol) of *m*-chloroperoxybenzoic acid in 600 mL of CH_2Cl_2 was stirred at room temperature for 12 h, it was washed with 10% aqueous K_2CO_3 and water, dried over $MgSO_4$, and evaporated in vacuo to give 10.8 g (100%) of **7b** as a colorless crystalline powder, mp 348–350 °C: ^{1}H NMR δ 1.23 (36 H, s), 3.52 (8 H, s), 3.56 (12 H, s), 3.71 (8 H, s), 7.06 (4 H, d, J = 2.5 Hz), 7.15 (4 H, d, J = 2.5 Hz); MS m/z 888 (M^+). Anal. Calcd for $C_{52}H_{72}O_8S_2$: C, 70.24; H, 8.16. Found: C, 70.00; H, 8.23.

6,15,24,33-Tetra-*tert*-butyl-9,18,27,36-tetramethoxy-2,20-dithia[3.3.3.3]metacyclophane 2,2,20,20-Tetraoxide (7c). After a mixture of 0.80 g (0.94 mmol) **6c** and 1.10 g (purity 80%; 5.2 mmol) of *m*-chloroperoxybenzoic acid in 100 mL of CH_2Cl_2 was stirred at room temperature for 5 h, it was poured into water and extracted with CH_2Cl_2. The extract was washed with 10% aqueous K_2CO_3 and saturated NaCl solution, dried over $MgSO_4$, and evaporated in vacuo to leave a residue, which, on recrystallization from a mixture of hexane and chloroform, gave 0.73 g (84%) of **7c** as colorless prisms, mp 410 °C dec: ^{1}H NMR δ 1.26 (36 H, s), 1.60–1.84 (4 H, m), 2.24–2.53 (8 H, m), 2.93 (8 H, s), 6.84 (4 H, d, J = 2.2 Hz), 6.87 (4 H, d, J = 2.2 Hz); MS m/z 788 ($M^+ - 2SO_2$). Anal. Calcd For $C_{54}H_{76}O_8S_2$: C, 70.58; H, 8.63. Found: C, 70.71; H, 8.35.

5,12,20,27-Tetra-*tert*-butyl-8,15,23,30-tetramethoxy-[2.1.2.1]metacyclophane (3a). After 900 mg (1.05 mmol) of **7a** was pyrolyzed at 470 °C under reduced pressure (0.6 Torr) according to the reported method,[7] the crude product was dissolved in CH_2Cl_2 and chromatographed with benzene as an eluant, giving **3a**. Recrystallization from a mixture of hexane and benzene afforded 261 mg of **3a** as colorless needles, mp 230–231 °C: ^{1}H NMR δ 1.24 (36 H, s), 2.91 (12 H, s), 2.98 (8 H, br s), 3.60 (4 H, br s), 7.00 (4 H, d, J = 2.5 Hz), 7.04 (4 H, d, J = 2.5 Hz); MS m/z 732. Anal. Calcd for $C_{50}H_{68}O_4$: C, 81.92; H, 9.35. Found: C, 82.07; H, 9.37.

5,13,21,29-Tetra-*tert*-butyl-8,16,24,32-tetramethoxy-[2.2.2.2]metacyclophane (3b). One gram (0.89 mmol) of **7b** was pyrolyzed (470 °C, 0.4 Torr) and worked up as descibed in the preparation of **3a**, giving 0.31 g (40%) of **3b**.[9]

5,14,22,31-Tetra-*tert*-butyl-8,17,25,34-tetramethoxy-[2.3.2.3]metacyclophane (3c). Similarly, 0.55 g (0.60 mmol) of **7c** was pyrolyzed (460 °C, 0.6 Torr) and worked up as descibed in the preparation of **3a**, giving 0.17 g (37%) of **3c** as colorless prisms (a mixture of hexane and benzene), mp 220–223 °C: ^{1}H NMR δ 1.20 (36 H, s), 1.60–1.84 (4 H, m), 2.24–2.53 (8 H, m), 2.93 (8 H, s), 3.20 (12 H, s), 6.84 (4 H, d, J = 2.2 Hz), 6.87 (4 H, d, J = 2.2 Hz); MS m/z 788 (M^+). Anal. Calcd for $C_{54}H_{76}O_4$: C, 82.18; H, 9.71. Found: C, 81.99; H, 9.91.

5,12,20,27-Tetra-*tert*-butyl-8,15,23,30-tetrahydroxy-[2.1.2.1]metacyclophane (1a). To a solution of 109 mg (0.15 mmol) of **3a** in 5 mL of dry CH_2Cl_2 in an ice bath was added dropwise a solution of 432 mg (1.73 mmol) of BBr_3 in 10 mL of dry CH_2Cl_2, and the reaction mixture was stirred at room temperature for 12 h. It was poured into ice–water (50 mL) and extracted with CH_2Cl_2. The extract was washed with water, dried over $MgSO_4$, and evaporated in vacuo to give a residue, which, on recrystallization from light petroleum ether, gave 71 mg (70%) of **1a** as colorless needles, mp 222–225 °C: IR (KBr) ν 3418 cm^{-1}; ^{1}H NMR δ 1.14 (36 H, s), 2.84 (8 H, br s), 3.90 (4 H, s), 6.92 (4 H, d, J = 2.5 Hz), 7.06 (4 H, d, J = 2.5 Hz), 8.80 (4 H, br s, exchanged with D_2O); MS m/z 676 (M^+). Anal. Calcd for $C_{46}H_{60}O_4$: C, 81.61; H, 8.93. Found: C, 81.65; H, 8.81.

5,13,21,29-Tetra-*tert*-butyl-8,16,24,32-tetrahydroxy-[2.2.2.2]metacyclophane (1b). To a solution of 2.00 g (2.6 mmol) of **3b** in 200 mL of dry CH_2Cl_2 was added dropwise a solution of 14.0 g (56 mmol) of BBr_3 in 50 mL of dry CH_2Cl_2. The reaction mixture was treated and worked up as previously reported,[9] giving 1.85 g (100%) of **1b**. The ^{1}H NMR data reported earlier[9] are now corrected as follows: ^{1}H NMR δ 1.32 (36 H, s), 2.94 (16 H, br s), 7.10 (8 H, m), 10.40 (4 H, br s, exchanged with D_2O). Anal. Calcd

for $C_{48}H_{64}O_4$: C, 81.77; H, 9.15. Found: C, 81.46; H, 9.16.

5,14,22,31-Tetra-*tert*-butyl-8,17,25,34-tetrahydroxy-[2.3.2.3]metacyclophane (1c). To a solution of 436 mg (0.55 mmol) of **3c** in 10 mL of dry CH_2Cl_2 in an ice bath was added dropwise a solution of 1.07 g (4.26 mmol) of BBr_3 in 5 mL of dry CH_2Cl_2, and the reaction mixture was stirred at room temperature for 14 h. It was worked up as described in the preparation of **1a**, giving 334 mg (82%) of **1c** as a colorless crystalline powder, mp 281 °C dec: IR (KBr) ν 3354 cm^{-1}; ^1H NMR δ 1.31 (36 H, s), 1.90–2.20 (4 H, m), 2.48–2.75 (8 H, m), 2.87 (8 H, br s), 7.04 (8 H, s), 8.55 (4 H, br s, exchanged with D_2O); MS m/z 732 (M^+). Anal. Calcd for $C_{50}H_{68}O_4$: C, 81.92; H, 9.34. Found: C, 81.61; H, 9.35.

8,15,23,30-Tetrahydroxy[2.1.2.1]metacyclophane (2a). To a solution of 100 mg (0.14 mmol) of **1a** in 20 mL of toluene was added a solution of 1.00 g (7.4 mmol) of $AlCl_3$ in 2 mL of nitromethane. After the reaction mixture was stirred at room temperature for 3.5 h, it was poured into ice–water (60 mL) and extracted with CH_2Cl_2. The extract was washed with water, dried over $MgSO_4$, and evaporated in vacuo to leave a residue, which, on recrystallization from a mixture of ethanol and light petroleum ether, gave 56 mg (84%) of **2a** as colorless needles, mp 290 °C: IR (KBr) ν(OH) 3362 cm^{-1}; ^1H NMR δ 2.87 (8 H, s), 3.86 (4 H, s), 6.60–7.00 (12 H, m), 7.44 (4 H, s); MS m/z 452 (M^+). Anal. Calcd for $C_{30}H_{28}O_4$: C, 79.62; H, 6.28. Found: C, 79.92; H, 6.45.

8,16,24,32-Tetrahydroxy[2.2.2.2]metacyclophane (2b). To a solution of 500 mg (0.71 mmol) of **1b** in 80 mL of toluene and 20 mL of CS_2 was added a solution of 1.90 g (14 mmol) of $AlCl_3$ in 3 mL of nitromethane. After the reaction mixture was stirred at room temperature for 6 h, it was poured into ice–water and extracted with $CHCl_3$. The extract was washed with water, dried over $MgSO_4$, and evaporated in vacuo. The residue was chromatographed, using $CHCl_3$ as an eluent, to give 290 mg (85%) of **2b** as colorless prisms (toluene), mp 290 °C dec: IR (KBr) ν(OH) 3240 cm^{-1}; ^1H NMR δ 2.92 (16 H, br s), 6.70–7.38 (12 H, m), 10.38 (4 H, br s, exchanged with D_2O); MS m/z 480 (M^+). Anal. Calcd for $C_{32}H_{32}O_4$: C, 80.00; H, 6.71. Found: C, 79.74; H, 6.80.

8,17,25,34-Tetrahydroxy[2.3.2.3]metacyclophane (2c). A solution of 2.00 g of $AlCl_3$ in 3 mL of nitromethane was added to a solution of 200 mg (0.27 mmol) of **1c** in 100 mL of toluene, and the reaction mixture was stirred at 65 °C for 3.5 h. It was poured into ice–water (100 mL) and extracted with CH_2Cl_2. The extract was washed with water, dried over $MgSO_4$, and evaporated in vacuo. The residue was chromatographed, using benzene as an eluant, to give 111 mg (80%) of **2c** as colorless plates (ether), mp 229–232 °C: IR (KBr) ν 3362 cm^{-1}; ^1H NMR δ 2.05–2.20 (4 H, m), 2.66–2.74 (8 H, m), 2.90 (8 H s), 6.85–7.11 (12 H, m), 8.65 (4 H, br s, exchanged with D_2O); MS m/z 508 (M^+). Anal. Calcd for $C_{34}H_{36}O_4$: C, 80.29; H, 7.13. Found: C, 80.11; H, 7.16.

5,13,21,29-Tetra-*tert*-butyl-8,16,24,32-tetraacetoxy-[2.2.2.2]metacyclophane (9). After a mixture of 100 mg (0.14 mmol) of **1b** and a few drops of concentrated sulfuric acid in 30 mL of acetic anhydride was refluxed for 6 h, it was poured into water and extracted with $CHCl_3$. The extract was washed with water, dried over $MgSO_4$, and evaporated in vacuo to leave the residue, which was chromatographed using $CHCl_3$ as an eluant, affording 50 mg (48%) of **9**·0.5H_2O, colorless prisms (a mixture of hexane and benzene), mp 380–381 °C: IR (KBr) ν 1750 cm^{-1}; ^1H NMR δ 1.31 (36 H, s), 1.40 (12 H, s), 2.70 (16 H, br s), 7.15 (8 H, s); MS m/z 872 (M^+). Anal. Calcd for $C_{56}H_{72}O_8$·0.5H_2O: C, 76.28; H, 8.29. Found: C, 76.18; H, 8.36.

8,16,24,32-Tetraacetoxy[2.2.2.2]metacyclophane (10). After a mixture of 70 mg (0.15 mmol) of **2b** and a few drops of concentrated hydrochloric acid in a mixture of 10 mL of Ac_2O and 10 mL of AcOH was refluxed for 6 h, it was worked up as described in the preparation of **8** to afford a residue, which was chromatographed using a 1:1 mixture of hexane and EtOAc as an eluant, affording 35 mg (37%) of **10**, colorless prisms (a mixture of hexane and EtOAc), mp >300 °C: IR (KBr) ν 1750 cm^{-1}; ^1H NMR δ 1.30 (12 H, s), 2.70 (16 H, br s), 7.13 (8 H, s); MS m/z 648 (M^+). Anal. Calcd for $C_{40}H_{40}O_8$: C, 74.06; H, 6.21. Found: C, 73.64; H, 6.35.

8,16,24,32-Tetramethoxy[2.2.2.2]metacyclophane (11). To a suspension of 90 mg (2 mmol) of NaH (50% dispersion in mineral oil) in 5 mL of dry DMF was added a suspension of 100 mg (0.2 mmol) of **2b** under a nitrogen atomosphere in 25 mL of dry THF and 20 mL of dry DMF. After the mixture was stirred for 1 h, 280 mg (0.4 mmol) of MeI was added and the mixture was stirred at room temperature for 12 h. It was poured into ice–water and extracted with $CHCl_3$. The extract was washed with water, dried over $MgSO_4$, and evaporated in vacuo to leave a residue, which was chromatographed using EtOAc as an eluant to give 90 mg (85%) of **11**, colorless prisms (hexane), mp 153–155 °C: ^1H NMR δ 2.92 (16 H, s), 3.12 (12 H, s), 6.74 (12 H, s); MS m/z 538 (M^+). Anal. Calcd for $C_{36}H_{40}O_4$: C, 80.56; H, 7.51. Found: C, 80.57; H, 7.57.

5,13,21,29-Tetra-*tert*-butyl-8,16-dihydroxy-24,32-dimethoxy- or 5,13,21,29-Tetra-*tert*-butyl-8,24-dihydroxy-16,32-dimethoxy[2.2.2.2]metacyclophane (12). To a solution of 200 mg (0.2 mmol) of **1b** in 100 mL of THF was added 100 mL of a 0.33 M ethereal solution of CH_2N_2. After the reaction mixture was stirred at room temperature for 3 h, a small amount of AcOH was added. The mixture was washed with water, dried over $MgSO_4$, and evaporated in vacuo. The residue was chromatographed, using $CHCl_3$ as an eluant, to give 125 mg (61%) of **12**, colorless prisms (a 1:1 mixture of hexane and benzene), mp 212–213 °C: IR (KBr) ν 3450 cm^{-1}; ^1H NMR δ 1.04 (18 H, s), 1.24 (18 H, s), 2.80 (16 H, s), 3.72 (6 H, s), 5.96 (2 H, s, exchanged with D_2O), 6.70 (4 H, s), 6.90 (4 H, s); MS m/z 732 (M^+). Anal. Calcd for $C_{50}H_{68}O_4$: C, 81.92; H, 9.35. Found: C, 82.12; H, 9.42.

8,16-Dihydroxy-24,32-dimethoxy- or 8,24-Dihydroxy-16,32-dimethoxy[2.2.2.2]metacyclophane (13). To a solution of 100 mg (0.2 mmol) of **2b** in 100 mL of THF was added 20 mL of a 0.33 M ether solution of CH_2N_2. The reaction mixture was treated and worked up as described in the preparation of **11** to give 90 mg (85%) of **13**, colorless prisms (CCl_4), mp 205–207 °C: IR (KBr) ν 3550, 3370 cm^{-1}; ^1H NMR δ 2.84 (16 H, s), 3.68 (6 H, s), 5.82 (2 H, s, exchanged with D_2O), 6.50–6.93 (12 H, m); MS m/z 508 (M^+). Anal. Calcd for $C_{34}H_{36}O_4$·0.5H_2O: C, 78.89; H, 7.20. Found: C, 79.22; H, 7.19.

5,13,21,29-Tetra-*tert*-butyl-8,16,24,32-tetrakis(allyloxy)-[2.2.2.2]metacyclophane (14). To a suspension of 70 mg (1.5 mmol) of NaH (50% dispersion in a mineral oil) in 10 mL of dry DMF was added dropwise a suspension of 100 mg (0.14 mmol) of **1b** in a mixture of 5 mL of dry DMF and 15 mL of dry THF under nitrogen. After the mixture was stirred for 1 h, 180 mg (1.5 mmol) of allyl bromide was added and the reaction mixture was stirred for 12 h at room temperature. It was poured into water and extracted with $CHCl_3$. The extract was washed with water, dried over $MgSO_4$, and evaporated in vacuo. The residue was triturated with CH_3CN to give 42 mg (35%) of **14**, colorless prisms (CH_3CN), mp 182–183 °C: ^1H NMR δ 1.26 (36 H, s), 2.67 (16 H, br s), 3.73–3.92 (8 H, m), 4.78–5.04 (8 H, m), 5.40–5.80 (4 H, m), 6.94 (8 H, s); MS m/z 864 (M^+). Anal. Calcd for $C_{60}H_{80}O_4$·0.5H_2O: C, 82.42; H, 9.33. Found: C, 82.72; H, 9.32.

8,16,24,32-Tetrakis(allyloxy)[2.2.2.2]metacyclophane (15). To a suspension of 240 mg (5 mmol) of NaH (50% dispersion in a mineral oil) in 20 mL of dry DMF was added dropwise a suspension of 200 mg (0.56 mmol) of **2b** in a mixture of 10 mL of dry DMF and 30 mL of dry THF under nitrogen. After the mixture was stirred for 1 h, 540 mg (4.5 mmol) of allyl bromide was added and the reaction mixture was stirred for 12 h at room temperature. It was worked up as described in the preparation of **14** to give 190 mg (71%) of **15**, colorless prisms (CH_3CN), mp 89–92 °C: ^1H NMR δ 2.83 (16 H, br s), 3.90 (8 H, br s), 4.80–5.48 (8 H, m), 5.80 (4 H, br s), 6.76 (12 H, br s); MS m/z 640 (M^+). Anal. Calcd for $C_{44}H_{48}O_4$: C, 82.46; H, 7.55. Found: C, 82.52; H, 7.78.

Compound 1b. A solution of 20 mg (0.02 mmol) of **14** in 5 mL of *N*,*N*-diethylaniline was heated at 200 °C for 4 h. After the reaction mixture was cooled to room temperature, the formed precipiate was collected and washed with hexane to give 11 mg (67%) of **1b**.[9]

5,13,21,29-Tetraallyl-8,16,24,32-tetrahydroxy[2.2.2.2]metacyclophane (16). A solution of 100 mg (0.16 mmol) of **15** in 10 mL of *N*,*N*-diethylaniline was heated at 200 °C for 4 h. After the reaction mixture was cooled to room temperature, the formed precipiate was collected and washed with hexane to give 75 mg (75%) of **16**, colorless needles, mp 304 °C dec: IR (KBr) ν 3210 cm^{-1}; ^1H NMR δ 2.86 (16 H, br s), 3.30 (8 H, d, J = 6 Hz), 4.82–5.22 (8 H, m), 5.72–6.20 (4 H, m), 6.88 (8 H), 10.38 (4 H, br s, exchanged with D_2O); MS m/z 640 (M^+). Anal. Calcd for $C_{44}H_{48}O_4$: C, 82.46; H, 7.55. Found: C, 82.71; H, 7.56.

5,13,21,29-Tetrabromo-8,16,24,32-tetrahydroxy[2.2.2.2]metacyclophane (17). To a mixture of 160 mg (0.33 mmol) of **2b** and 200 mg of Fe powder in 50 mL of $CHCl_3$ was added a solution of 422 mg (2.6 mmol) of Br_2 in 20 mL of $CHCl_3$. After the reaction mixture was stirred at room temperature for 12 h, it was poured into ice–water and extracted with $CHCl_3$. The extract was washed with water, dried over $MgSO_4$, and evaporated in vacuo to give 230 mg (87%) of **17**·C_6H_6, colorless needles (benzene), mp >350 °C: IR (KBr) ν(OH) 3220 cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.71 (16 H, br s), 6.93 (8 H, s), 7.74 (4 H, br s, exchanged with D_2O); MS m/z 792, 794, 796, 798, 800 (M^+). Anal. Calcd for $C_{32}H_{28}O_4Br_4 \cdot C_6H_6$: C, 52.20; H, 3.92. Found: C, 51.90; H, 3.97.

[2.2.2.2]Metacyclo-1,4-benzoquinonophane (19). After a mixture of 100 mg (0.26 mmol) of **2b** and 4 mL of 0.88 M solution of $Tl(OCOCF_3)_3$ in CF_3CO_2H was stirred at room temperature for 13 h in the dark, it was poured into ice–water and extracted with $CHCl_3$. The extract was washed with water, dried over $MgSO_4$, and concentrated in vacuo to leave a residue, which was subjected to preparative TLC (precoated plates with concentrating zone, 20 × 20 cm, kiesel gel 60F_{254}S) using ether as an eluant. The fraction of R_f = 0.45 afforded 8 mg (5%) of **19**·$3H_2O$ as orange prisms (CCl_4), mp 129–132 °C: IR (KBr) ν 1650 cm^{-1}; ^1H NMR δ 2.62 (16 H, s), 6.48 (8 H, s); MS m/z 536 (M^+). Anal. Calcd for $C_{32}H_{24}O_8 \cdot 3H_2O$: C, 65.08; H, 5.08. Found: C, 65.57; H, 5.17.

5,8,13,16,21,24,28,32-Octaacetoxy[2.2.2.2]metacyclophane (20). A mixture of 10 mg (0.017 mmol) of **19**·$3H_2O$, 500 mg of zinc powder, and a few drops of concentrated hydrochloric acid in 10 mL of acetic acid and 10 mL of acetic anhydride was refluxed for 10 min, poured into water, and extracted with $CHCl_3$. The extract was washed with water, dried over $MgSO_4$, and evaporated in vacuo to give 9 mg (59%) of **20** as colorless needles (CCl_4), mp 350 °C: IR (KBr) ν 1750 cm^{-1}; ^1H NMR δ 1.30 (6 H, s), 1.69 (6 H, s), 2.17 (12 H, s), 2.65 (16 H, br s), 6.85 (8 H, s); MS m/z 880 (M^+). Anal. Calcd for $C_{48}H_{48}O_{16} \cdot 0.5H_2O$: C, 64.79; H, 5.54. Found: C, 65.03; H, 5.62.

Registry No. **1a**, 125685-43-0; **1b**, 76447-59-1; **1c**, 125666-21-9; **2a**, 125666-22-0; **2b**, 125666-23-1; **2c**, 125666-24-2; **3a**, 125666-19-5; **3b**, 76447-58-0; **3c**, 125666-20-8; **4a**, 125665-97-6; **4b**, 76447-56-8; **4c**, 125665-98-7; **5a**, 125665-99-8; **5b**, 125666-00-4; **5c**, 125666-01-5; **6a**, 125666-02-6; **6b**, 125666-03-7; **6c**, 125666-04-8; **7a**, 125666-14-0; **7b**, 125666-17-3; **7c**, 125666-18-4; **9**, 125666-05-9; **10**, 125666-06-0; **11**, 125666-07-1; **12**, 125666-08-2; **13**, 125666-09-3; **14**, 125666-10-6; **15**, 125666-11-7; **16**, 125666-12-8; **17**, 125666-13-9; **19**, 125666-15-1; **20**, 125666-16-2; **21**, 98085-84-8; 5,5′-di-*tert*-butyl-2,2′-dihydroxydiphenylmethane, 799-13-3; 1,3-bis(5-*tert*-butyl-2-methoxyphenyl)propane, 108656-63-9.

Approaches to Avermectin Assembly: A Concise Stereospecific Synthesis of the Hexahydrobenzofuran Entity

Anthony G. M. Barrett,* Thomas E. Barta, John A. Flygare, Michal Sabat, and Christopher D. Spilling*

Department of Chemistry, Northwestern University, 2145 Sheridan Road, Evanston, Illinois 60208

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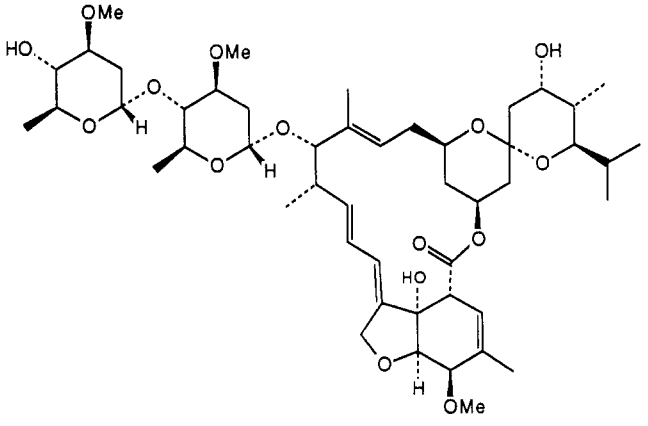
Epoxy ketone **18** was prepared in racemic form via the Diels–Alder reaction of 1-acetoxy-1,3-pentadiene with acrylic acid, subsequent iodolactonization, ortho ester protection, and oxidation. Reaction of **18** with 4-[(*tert*-butyldiphenylsilyl)oxy]-2-lithio-1-(lithiooxy)-(*Z*)-2-butene, which was prepared from stannane **19** and butyllithium, gave the bicyclic avermectin fragment **21**.

Introduction

The avermectins[1] and milbemycins[2] are potent parasiticidal and anthelmintic agents isolated from *Streptomyces avermitilis* and *S. hygroscopicus* subsp. *aureolacrimosus*, respectively. These molecules, for example, avermectin A_{2b} (**1**), are attractive synthetic targets on account of their significant biological activities and challenging molecular architecture. Several total syntheses of milbemycin β_3,[3] milbemycin β_1 and E,[4] and avermectin A_{1a}[5] have recently been published. In addition, many synthetic studies of spiroketals and of the "southern" hexahydrobenzofuran ring system have been described.[6] In spite of all these



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