$\mathrm{ArC}H_2\mathrm{N}$), 3.22 (d, AB system, J = 14.2 Hz, 2 H, $\mathrm{ArC}H_2\mathrm{N}$), 6.95–8.05 (m, 12 H, arom); IR ($\mathrm{CHCl_3}$) 3338 ν(NH), 2817 ν_s($\mathrm{CH_2}$ of $\mathrm{(CH_2)_3N}$) cm^{-1}; FAB MS m/z (relative intensity) 451 (M$^+$ + 1, 48), 365 (64), 281 (100), 279 (94), 266 (99), 252 (26). Anal. Calcd for $\mathrm{C_{30}H_{34}N_4}$: C, 79.96; H, 7.61; N, 12.43. Found: C, 80.05; H, 7.80; N, 12.37.

(*S*,1*S*,2*R*)-2-Azido-2′-[[*N*-(2-hydroxy-1-methyl-2-phenylethyl)-*N*-methylamino]methyl]-1,1′-binaphthyl [(*S*,1*S*,2*R*)-11]. A procedure similar to that described for the preparation of **8b** was followed. Starting from 1 g (1.75 mmol) of quaternary salt[11] (*S*,1*S*,2*R*)-**6** (crystallized with 1 EtOH), 810 mg (95%, oil) of (*S*,1*S*,2*R*)-**11** was separated by flash chromatography (petroleum ether–ether–acetone (90:5:5 and then 85:5:10)): $[\alpha]^{26}{}_\mathrm{D}$ −84° (c 0.50, $\mathrm{CHCl_3}$); ^{1}H NMR ($\mathrm{CDCl_3}$) δ 0.65 (d, J = 7.0 Hz, 3 H, $\mathrm{CCH_3}$), 2.06 (s, 3 H, $\mathrm{NCH_3}$), 2.53–2.69 (m, 1 H, $\mathrm{C}H\mathrm{CH_3}$), 3.29 (d, AB system, J = 14.0 Hz, 1 H, $\mathrm{ArC}H_2\mathrm{N}$), 3.45 (d, AB system, J = 14.0 Hz, 1 H, $\mathrm{ArC}H_2\mathrm{N}$), 4.01 (d, AB system, J = 14.0 Hz, 1 H, $\mathrm{ArC}H_2\mathrm{N_3}$), 4.11 (d, AB system, J = 14.0 Hz, 1 H, $\mathrm{ArC}H_2\mathrm{N_3}$), 4.69 (br s, 1 H, Ph(OH)C*H*), 6.95–8.11 (m, 17 H, arom); IR ($\mathrm{CCl_4}$) 3619 ν(OH), 2791 ν_s($\mathrm{CH_3}$ of $\mathrm{CH_3N}$), 2099 ν_{as}($\mathrm{N_3}$), 1496 ν_{ring}(Ph) cm^{-1}; EI MS m/z (relative intensity) 379 (M$^+$ − $\mathrm{C_7H_7O}$, 52), 351 (48), 294 (100), 266 (69), 252 (22). Anal. Calcd for $\mathrm{C_{32}H_{30}N_4O}$: C, 78.98; H, 6.21; N, 11.51. Found: C, 78.75; H, 6.31; N, 11.45.

(*R*,1*S*,2*R*)-2-Azido-2′-[[*N*-(2-hydroxy-1-methyl-2-phenylethyl)-*N*-methylamino]methyl]-1,1′-binaphthyl [(*R*,1*S*,2*R*)-11]. A procedure similar to that described for the preparation of **8b** was followed except that the reaction mixture was heated for 4 h. With 1 g (1.91 mmol) of quaternary salt[11] (*R*,1*S*,2*R*)-**6** as starting material, 809 mg (87%, oil) of (*R*,1*S*,2*R*)-**11** was obtained by flash chromatography (petroleum ether–ether–acetone (80:10:10)): $[\alpha]^{26}{}_\mathrm{D}$ +72° (c 0.50, $\mathrm{CHCl_3}$); ^{1}H NMR ($\mathrm{CDCl_3}$) δ 0.56 (d, J = 6.8 Hz, 3 H, $\mathrm{CCH_3}$), 2.08 (s, 3 H, $\mathrm{NCH_3}$), 2.63 (dq, J = 6.8, 4.4 Hz, 1 H, $\mathrm{C}H\mathrm{CH_3}$), 3.18 (d, AB system, J = 13.9 Hz, 1 H, $\mathrm{ArC}H_2\mathrm{N}$), 3.44 (d, AB system, J = 13.9 Hz, 1 H, $\mathrm{ArC}H_2\mathrm{N}$), 4.00 (d, AB system, J = 14.0 Hz, 1 H, $\mathrm{ArC}H_2\mathrm{N_3}$), 4.09 (d, AB system, J = 14.0 Hz, 1 H, $\mathrm{ArC}H_2\mathrm{N_3}$), 4.61 (d, J = 4.4 Hz, 1 H, Ph(OH)C*H*), 6.98–8.08 (m, 17 H, arom); IR ($\mathrm{CCl_4}$) 3619 $\nu(\mathrm{OH_{free}})$, 3484 $\nu(\mathrm{OH_{assoc}})$, 2790 ν_s($\mathrm{CH_3}$ of $\mathrm{CH_3N}$), 2099 ν_{as}($\mathrm{N_3}$), 1494 ν_{ring}(Ph) cm^{-1}; EI MS m/z (relative intensity) 379 (M$^+$ − $\mathrm{C_7H_7O}$, 45), 351 (44), 294 (100), 266 (52), 252 (23). Anal. Calcd for $\mathrm{C_{32}H_{30}N_4O}$: C, 78.98; H, 6.21; N, 11.51. Found: C, 79.13; H, 6.08; N, 11.40.

(*R*,*R*)-Bis[[2-[(*N*,*N*-dimethylamino)methyl]-1,1′-binaphthyl-2′-yl]methyl] Sulfide [(*R*,*R*)-13]. Treatment of 300 mg (0.741 mmol) of quaternary salt[19] (*R*)-**2** in 3 mL of DMF with 534 mg (2.22 mmol, 3.0 equiv) of $\mathrm{Na_2S{\cdot}9H_2O}$ at 100 °C for 10 min under $\mathrm{N_2}$, followed by pouring into brine, yielded a precipitate which was filtered, washed with brine, and extracted with benzene (2 × 20 mL) under reflux. The benzene solution was filtered, and the solvent was evaporated in vacuo to give 225 mg (89%) of (*R*,*R*)-**13** as an amorphous solid: $[\alpha]^{20}{}_\mathrm{D}$ +91° (c 0.27, benzene); ^{1}H NMR ($\mathrm{CDCl_3}$) δ 1.98 (s, 12 H, $\mathrm{CH_3}$), 2.84 (d, AB system, J = 14.2 Hz, 2 H, $\mathrm{ArC}H_2\mathrm{N}$), 3.13 (d, AB system, J = 13.9 Hz, 2 H, $\mathrm{ArC}H_2\mathrm{S}$), 3.23 (d, AB system, J = 13.9 Hz, 2 H, $\mathrm{ArC}H_2\mathrm{S}$), 3.26 (d, AB system, J = 14.2 Hz, 2 H, $\mathrm{ArC}H_2\mathrm{N}$), 6.80–8.00 (m, 24 H, arom); IR ($\mathrm{CCl_4}$) 2819 and 2771 ν_s($\mathrm{CH_3}$), 676 and 669 ν_s(C–S–C) cm^{-1}; FAB MS m/z (relative intensity) 681 (M$^+$ + 1, 53), 638 (8), 358 (17), 324 (58), 279 (100), 266 (91), 252 (35). Anal. Calcd for $\mathrm{C_{48}H_{44}N_2S}$: C, 84.66; H, 6.51; N, 4.11; S, 4.71. Found: C, 84.54; H, 6.70; N, 3.98; S, 4.58.

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Registry No. (±)-**1**, 64091-25-4; (±)-**2**, 97781-19-6; (*R*)-**2**, 144068-74-6; (±)-**3**, 144068-75-7; (±)-**4**, 143970-96-1; (±)-**5**, 143970-97-2; (*S*,1*S*,2*R*)-**6**, 86593-80-8; (*R*,1*S*,2*R*)-**6**, 86631-57-4; (±)-**7a**, 143970-98-3; (±)-**7b**, 143970-99-4; (±)-**7c**, 143971-00-0; (±)-**8a**, 143971-01-1; (±)-**8b**, 143971-02-2; (±)-**8c**, 143971-03-3; (±)-**9a**, 143971-04-4; (±)-**9b**, 143971-05-5; (±)-**9c**, 143971-06-6; (±)-**10**, 143971-07-7; (*S*,1*S*,2*R*)-**11**, 143971-08-8; (*R*,1*S*,2*R*)-**11**, 144068-76-8; (*R*,*R*)-**13**, 143971-09-9; $\mathrm{HSBu^n}$, 109-79-5; $\mathrm{CH_2(CO_2Et)_2}$, 105-53-3; $\mathrm{Ph_2PH}$, 829-85-6; morpholine, 110-91-8; piperazine, 110-85-0.

Medium-Sized Cyclophanes. 24.[1] Bromination of 8-Substituted [2.2]Metaparacyclophanes

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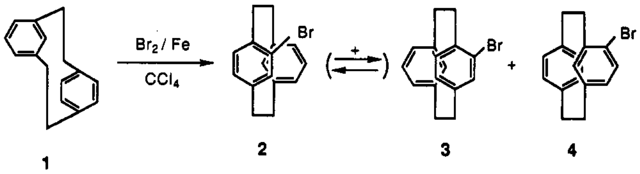
Introduction

The meta-bridged benzene ring of [2.2]metaparacyclophane (MPCP = metaparacyclophane) (**1**) has been shown to undergo conformational flipping[2-7] with a substantial energy barrier (ca. 20 kcal mol^{-1}). According to X-ray crystallographic studies of **1**,[8] the deformations of benzene rings are similar to those of the corresponding rings in [2.2]para- and -metacyclophanes, with para- and meta-bridged rings bent in a boat- and a chairlike form, respectively. The angle between the two aromatic planes defined by the carbon atoms 3, 4, 6, and 7 on one hand and 12, 13, 15, and 16, on the other, is about 13°. It should be noted that the angle between the 11,12,16-plane and 10,11-bond vector (or between 13,14,15-plane and 1,14-bond vector) is even larger than the analogous angle in [2.2]paracyclophane. The para-bridged moiety of **1** is thus more strongly tilted than those of the isomeric compound. Introduction of the substituents at the 8-position increases the strain in the molecule in comparison with the unsubstituted [2.2]MPCP (**1**); the deformation of the para-bridged benzene ring of 8-methyl[2.2]MPCP was estimated to be 15° by our recent X-ray crystallography.[9]

Cram et al. reported[10] the bromination of [2.2]MPCP with bromine in the presence of ferric bromide to afford three kinds of monobromides. However, since **2** and **3** equilibrate by ring rotation at room temperature, the orientation of bromination to the para-bridged benzene ring of **1** has not yet been established.



Thus there is substantial interest in investigating the bromination of 8-substituted [2.2]MPCPs, which might afford single monobromides because the ring rotation of the meta-bridged benzene ring is impossible at room temperature. And also in order to study the orientation of bromination of the para-bridged benzene ring in detail, we have attempted to protect the 5-position of [2.2]MPCPs by the bulky *tert*-butyl group. We report here on the bromination of 5-*tert*-butyl-8-substituted-[2.2]MPCPs (**5**).

Results and Discussion

Bromination of 5-*tert*-butyl-8-methyl[2.2]MPCP (**5a**) with 1.1 equiv of bromine in a carbon tetrachloride solution in the presence of iron powder afforded 15-bromo substitution product **6a** in 61% yield along with starting compound. No bromo substitution at the 12-position was observed. In contrast, 8-methoxy derivative **5b** exclusively afforded 12-bromo substitution product **7b** in 85% yield.

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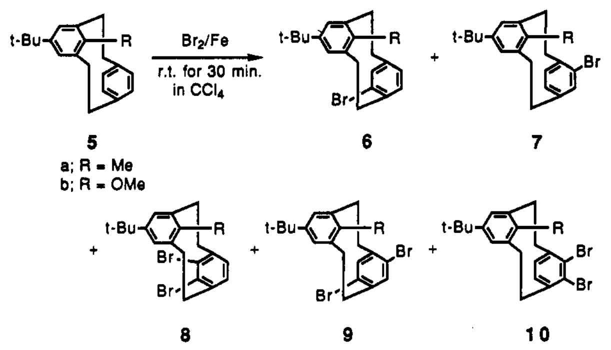
Table I. Bromination of [2.2]MPCP 5 with Bromine in CCl_4



run	substrate	bromine/5 (mol/mol)	products[a] (yield, %)
1	**5a**	1.1	**5a** (39), **6a** (61)
2	**5a**	2.2	**6a** (19), **8a** (79)
3	**5b**	1.1	**5b** (15), **7b** (85)
4	**5b**	2.2	**7b** (5), **9b** (60), **10b** (35)

[a] Yields determined by GLC analyses.

It was also found that the same tendency was observed in the dibromo substitution in **5a** with 2.2 equiv of bromine to give 15,16-dibromo derivative **8a**. However, 8-methoxy derivative **5b** gave a mixture of 12,15- and 12,13-dibromo derivatives **9b** and **10b** in 60 and 35% yield, respectively (Table I).

The structures of the products obtained in the present work were determined from their elemental analyses and spectral data. The ^1H NMR spectrum of **6a** in $CDCl_3$ shows a doublet ($J = 1.0$ Hz) at δ 5.99 for one aromatic C-16 proton which is in a strongly shielding region opposite the meta-bridged benzene ring and δ 6.91 and 6.96 for external aromatic C-12 and C-13 protons, respectively. On the other hand, the signals of two aromatic protons for C-12 and C-13 of **7b** were observed at an upper field of δ 5.72 and 5.76. These data strongly support the assignment of structures 15-bromo[2.2]MPCP (**6a**) and 12-bromo-[2.2]MPCP (**7b**).

Scheme I

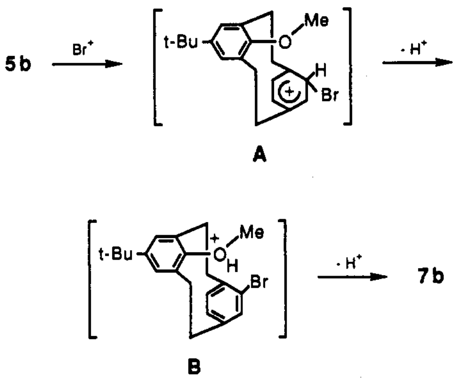
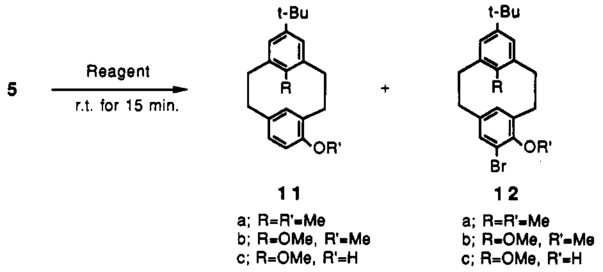


Table II. Bromination of [2.2]MPCP 5 in MeOH and CH_2Cl_2–H_2O



run	substrate	reagent	reagent/5 (mol/mol)	products[a] (yield, %)
1	**5a**	Br_2	1	**5a** (30), **11a** (60), **12a** (2)
2	**5a**	BTMA·Br_3	1	**5a** (57), **11a** (23), **12a** (1)
3	**5b**	Br_2	1	**5b** (20), **11b** (63), **12b** (2)
4	**5b**	BTMA·Br_3	1	**5b** (27), **11b** (47), **12b** (6)
5	**5b**	BTMA·Br_3	3	**5b** (0), **11b** (0), **12b** (85)
6[b]	**5b**	BTMA·Br_3	3	**5b** (16), **11c** (27), **12c** (56)

[a] Yields determined by GLC analyses. [b] Solvent: CH_2Cl_2 containing a small amount water.

The different directive effects of the 8-substituent to the para-bridged benzene ring on the position of electrophilic substitution were first observed with these compounds. According to X-ray crystallographic studies of 8-methyl-[2.2]MPCP,[9] the 8-methyl group is located opposite the para-bridged benzene ring which apparently sterically blocks electrophilic attack at 12,13-position. Therefore, internal attack of the electrophile on the para-bridged benzene ring of **5a** exclusively proceeds to give 15-bromo derivatives **6a**. On the other hand, with a methoxy group at this position, bromination occurs predominantly in the pseudogeminal position in spite of the above steric hindrence. This pseudogeminal directing effect of the methoxy group might be attributed to the basicity and geometric availability of the oxygen of the methoxy group. The oxygen is probably the strongest base in the medium. In the rate- and product-controlling step, the oxygen accepts a proton from the pseudogeminal σ-complex A to form intermediate B, thus producing a pseudogeminal substituted product (**7b**) as shown in Scheme I. This result is consistent with Cram's report[10,11] that acetyl and nitro groups in the position of the [2.2]paracyclophane nucleous directed bromine substitution to occur nearly exclusively in the 13-position to give the pseudogeminal disubstituted hydrocarbon.

On the other hand, the bromination of **5a** and **5b** with 1 equiv of bromine in a methanol solution at rt for 15 min led to isomerization to strainless metacyclophane (MCP = metacyclophane) and substitution of a methoxy group on an aromatic ring to afford the unexpected products **11a** and **11b** in 60 and 63% yield along with a small amount of their brominated derivatives **12a** and **12b** (Table II). This novel reaction also occurred upon bromination of **5** with benzyltrimethylammonium tribromide (BTMA·Br_3) in dichloromethane, which was recently found to be a convenient solid brominating reagent.[12,13] When **5b** was treated with 3 equiv of BTMA·Br_3 in dichloromethane containing a small amount of water, 12-hydroxy-substituted [2.2]MCPs **11c** and **12c** were obtained in 27 and 56% yields, respectively. The reaction of **11** with 1.1 equiv of

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(1) Medium-Sized Cyclophanes. Part 23. Yamato, T.; Matsumoto, J.; Tokuhisa, K.; Suehiro, K.; Tashiro, M. *J. Chem. Res., Synop.*, in press.

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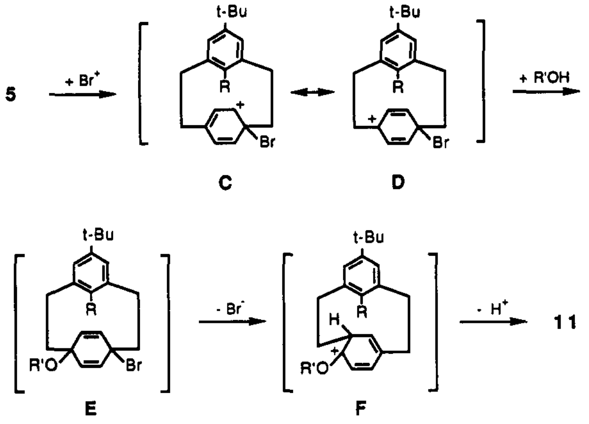
Scheme II



bromine or BTMA·Br$_3$ afforded compound 12 in quantitative yield. This result strongly suggests that compound 11 was an intermediate in the formation of 12.

The structures of the products 11 and 12 were determined from their elemental analyses and spectral data. The ^{1}H NMR spectrum of **11a** in CDCl$_3$ shows an upfield shift of the internal methyl protons at δ 0.57 and an internal C-16 aromatic proton at δ 3.63 due to the ring current effect[14,15] of the opposite aromatic ring compared to those of original MPCP (**5a**). These data strongly support the [2.2]MCP structure **11a**.

Cram et al. reported[16] the AlCl$_3$-catalyzed isomerization of [2.2]paracyclophane to the less strained [2.2]MPCP along with transannular isomerization product 1,2,3,3a,4,5-hexahydropyrene and [2.2]MCP.

In the case of bromination of 8-substituted [2.2]MPCP (**5**), the bromination of the ipso position of the ethylene bridge on the para-bridged benzene ring afforded the cation intermediate C to generate cyclohexadienyl cation intermediate D. The resultant cyclohexadienyl cation then might be trapped by the reaction with methanol or water to form E, which isomerized to the strainless MCP skeleton intermediate F to afford 8-substituted [2.2]MCP (**11**) (Scheme II).

This novel isomerization reaction might be attributed to the substituent at 8-position, which increases the strain in the molecule in comparison with the unsubstituted [2.2]MPCP (**1**). This fact is also supported by the increased deformation of the para-bridged benzene ring as mentioned above.

In conclusion, the different directive effects of 8-substituents on the para-bridged benzene ring on the position of electrophilic substitution were first observed with 8-substituted [2.2]MPCP derivatives and the present isomerization reaction of 8-substituted [2.2]MPCP **5** to form [2.2]MCPs **11** and **12** is strongly affected by the bulkiness of the substituents in 8-position which increases the strain in the molecule. These results will open up new mechanistic aspects for cyclophane chemistry. Further studies on the electrophilic substitution of [2.2]MPCPs (**5**) are now in progress.

Experimental Section

All melting and boiling points are uncorrected. ^{1}H NMR spectra were recorded at 270 MHz with Me$_4$Si as an internal reference. IR spectra were measured as KBr pellets. Mass spectra were obtained at 75 eV using a direct inlet system.

Bromination of 5-*tert*-Butyl-8-substituted-[2.2]metaparacyclophanes (5) with Bromine in Carbon Tetrachloride. Typical Procedure. To a solution of 50 mg (0.17 mmol) of 5-*tert*-butyl-8-methoxy[2.2]metaparacyclophane (**5b**) and 10 mg of Fe powder in 10 mL of CCl$_4$ was added a solution of 30 mg (0.19 mmol) of Br$_2$ in 10 mL of CCl$_4$ at rt. After the reaction mixture was stirred for 30 min, it was poured into water (10 mL). The organic layer was extracted with CH$_2$Cl$_2$ (10 mL). The extract was washed with 10% aqueous sodium thiosulfate (5 mL) and water (5 mL), dried (Na$_2$SO$_4$), and concentrated. The residue was column chromatographed over silica gel with hexane as an eluent to give 54 mg (85%) of **5-*tert*-butyl-8-methoxy-12-bromo[2.2]metaparacyclophane (7b)**: colorless prisms (hexane); mp 103–104 °C; ^{1}H NMR (CDCl$_3$) δ 1.30 (9 H, s), 2.30–3.48 (8 H, m), 3.23 (3 H, s), 5.72 (1 H, dd, J = 8.1, 1.5 Hz), 5.76 (1 H, d, J = 8.1 Hz), 6.75 (1 H, d, J = 2.4 Hz), 6.78 (1 H, J = 2.4 Hz), 7.23 (1 H, d, J = 1.5 Hz); MS m/e 372, 374 (M$^+$). Anal. Calcd for C$_{21}$H$_{25}$BrO: C, 67.56; H, 6.75. Found: C, 67.40; H, 6.70.

Compounds **6a**, **8a**, **9b**, and **10b** were obtained by the bromination of **5** with bromine in the same manner described above. The yields are compiled in Table I.

5-*tert*-Butyl-8-methyl-15-bromo[2.2]metaparacyclophane (6a): colorless prisms (hexane); mp 82–84 °C; ^{1}H NMR (CDCl$_3$) δ 1.27 (9 H, s), 1.71 (3 H, s), 2.30–3.27 (8 H, m), 5.99 (1 H, d, J = 1.0 Hz), 6.67 (1 H, d, J = 2.0 Hz), 6.78 (1 H, d, J = 2.0 Hz), 6.91 (1 H, dd, J = 8.0, 1.0 Hz), 6.96 (1 H, d, J = 8.0 Hz); MS m/e 356, 358 (M$^+$). Anal. Calcd for C$_{21}$H$_{25}$Br: C, 70.59; H, 7.05. Found: C, 70.40; H, 7.10.

5-*tert*-Butyl-8-methyl-15,16-dibromo[2.2]metaparacyclophane (8a): colorless prisms (hexane); mp 183–184 °C; ^{1}H NMR (CDCl$_3$) δ 1.35 (9 H, s), 1.86 (3 H, s), 2.61–3.39 (8 H, m), 6.82 (2 H, s), 7.08 (2 H, s); MS m/e 434, 436, 438 (M$^+$). Anal. Calcd for C$_{21}$H$_{24}$Br$_2$: C, 57.82; H, 5.55. Found: C, 57.70; H, 5.40.

5-*tert*-Butyl-8-methoxy-12,15-dibromo[2.2]metaparacyclophane (9b): colorless prisms (hexane); mp 134–136 °C; ^{1}H NMR (CDCl$_3$) δ 1.33 (9 H, s), 2.22–3.40 (8 H, m), 3.27 (3 H, s), 6.08 (1 H, s), 6.82 (1 H, d, J = 2.4 Hz), 6.89 (1 H, d, J = 2.4 Hz), 7.26 (1 H, s); MS m/e 450, 452, 454 (M$^+$). Anal. Calcd for C$_{21}$H$_{24}$Br$_2$O: C, 55.78; H, 5.35. Found: C, 55.61; H, 5.36.

5-*tert*-Butyl-8-methoxy-12,13-dibromo[2.2]metaparacyclophane (10b): colorless oil; ^{1}H NMR (CDCl$_3$) δ 1.30 (9 H, s), 2.29–3.49 (8 H, m), 3.28 (3 H, s), 5.77 (2 H, s), 6.78 (2 H, s); MS m/e 450, 452, 454 (M$^+$). Anal. Calcd for C$_{21}$H$_{24}$Br$_2$O: C, 55.78; H, 5.35. Found: C, 55.81; H, 5.30.

Bromination of 5-*tert*-Butyl-8-substituted-[2.2]metaparacyclophanes (5) with Bromine in Methanol. Typical Procedure. To a solution of 50 mg (0.17 mmol) of **5b** in 10 mL of methanol was added a solution of 30 mg (0.19 mmol) of Br$_2$ in 10 mL of methanol at rt. After the reaction mixture was stirred for 15 min, it was poured into water (10 mL). The organic layer was extracted with CH$_2$Cl$_2$ (10 mL). The extract was washed with 10% aqueous sodium thiosulfate (5 mL) and water (5 mL), dried (Na$_2$SO$_4$), and concentrated. The residue was column chromatographed over silica gel with a 1:1 benzene–hexane mixture as an eluent to give 22 mg (40%) of **11b** and a small amount of **12b**.

5-*tert*-Butyl-8,12-dimethoxy[2.2]metacyclophane (11b): colorless oil; ^{1}H NMR (CDCl$_3$) δ 1.30 (9 H, s), 1.52–3.60 (8 H, m), 3.00 (3 H, s), 3.78 (3 H, s), 3.91 (1 H, d J = 2.5 Hz), 6.61 (1 H, d, J = 8.0 Hz), 6.98 (1 H, dd, J = 8.0, 2.5 Hz), 7.03 (2 H, s); MS m/e 324 (M$^+$). Anal. Calcd for C$_{22}$H$_{28}$O$_2$: C, 81.44; H, 8.70. Found: C, 81.59; H, 8.51.

5-*tert*-Butyl-8,12-dimethoxy-13-bromo[2.2]metacyclophane (12b): colorless oil; ^{1}H NMR (CDCl$_3$) δ 1.27 (9 H, s), 1.72–3.39 (8 H, m), 2.98 (3 H, s), 3.79 (3 H, s), 3.82 (1 H, d, J = 2.0 Hz), 6.97 (1 H, d, J = 2.4 Hz), 6.99 (1 H, d, J = 2.4 Hz), 7.16 (1 H, d, J = 2.0 Hz); MS m/e 402, 404 (M$^+$). Anal. Calcd for C$_{22}$H$_{27}$BrO$_2$: C, 65.51; H, 6.75. Found: C, 65.70; H, 6.51.

Bromination of 5-*tert*-Butyl-8-substituted-[2.2]metaparacyclophanes (5) with BTMA·Br$_3$ in Methanol. Typical Procedure. To a solution of 50 mg (0.17 mmol) of **5b** in 10 mL of methanol was added 71 mg (0.17 mmol) of BTMA·Br$_3$ at rt. After the reaction mixture was stirred for 15 min, it was treated as described above to give a mixture of **11b** and **12b**.

Compounds **11a**, **12a**, **11c**, and **12c** were obtained by the bromination of **5** with bromine or BTMA·Br$_3$ in the same manner described above. The yields are compiled in Table II.

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5-*tert*-Butyl-8-methyl-12-methoxy[2.2]metacyclophane (11a): colorless oil; ^{1}H NMR ($CDCl_3$) δ 0.57 (3 H, s), 1.35 (9 H, s), 1.69–1.80 (1 H, m), 2.11–2.20 (1 H, m), 2.53–2.64 (2 H, m), 2.85–2.98 (3 H, m), 3.51–3.58 (1 H, m), 3.63 (1 H, d, J = 2.0 Hz), 3.81 (3 H, s), 6.58 (1 H, d, J = 8.3 Hz), 7.02–7.06 (3 H, m); MS *m/e* 308 (M^+). Anal. Calcd for $C_{22}H_{28}O$: C, 85.66; H, 9.15. Found: C, 85.59; H, 9.21.

5-*tert*-Butyl-8-methyl-12-methoxy-13-bromo[2.2]metacyclophane (12a): colorless prisms (hexane); mp 104–106 °C; ^{1}H NMR ($CDCl_3$) δ 0.62 (3 H, s), 1.33 (9 H, s), 1.80–3.47 (8 H, m), 3.57 (1 H, d, J = 2.0 Hz), 3.82 (3 H, s), 7.03 (1 H, d, J = 2.4 Hz), 7.04 (1 H, d, J = 2.4 Hz), 7.24 (1 H, d, J = 2.0 Hz); MS *m/e* 386 388 (M^+). Anal. Calcd for $C_{22}H_{27}BrO$: C, 68.22; H, 7.03. Found: C, 68.59; H, 7.21.

5-*tert*-Butyl-8-methoxy-12-hydroxy[2.2]metacyclophane (11c): colorless oil; IR (KBr) 3350 (OH) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.35 (9 H, s), 1.72–3.48 (8 H, m), 3.05 (3 H, s), 3.90 (1 H, d, J = 2.0 Hz), 5.29 (1 H, s), 6.55 (1 H, d, J = 8.3 Hz), 6.91 (1 H, dd, J = 8.3, 2.0 Hz), 7.05 (1 H, d, J = 2.4 Hz), 7.07 (1 H, d, J = 2.4 Hz); MS *m/e* 310 (M^+). Anal. Calcd for $C_{21}H_{26}O_2$: C, 81.25; H, 8.44. Found: C, 81.20; H, 8.62.

5-*tert*-Butyl-8-methoxy-12-hydroxy-13-bromo[2.2]metacyclophane (12c): pale yellow oil; IR (KBr) 3450 (OH) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.34 (9 H, s), 1.71–3.54 (8 H, m), 3.06 (3 H, s), 3.88 (1 H, d, J = 2.0 Hz), 5.39 (1 H, s), 7.03 (1 H, d, J = 2.4 Hz), 7.07 (1 H, d, J = 2.4 Hz), 7.14 (1 H, d, J = 2.4 Hz); MS *m/e* 388, 390 (M^+). Anal. Calcd for $C_{21}H_{25}O_2$: C, 64.79; H, 6.47. Found: C, 64.50; H, 6.62.

Registry No. **5a**, 144182-39-8; **5b**, 144182-48-9; **6a**, 144182-40-1; **7b**, 144182-41-2; **8a**, 144182-42-3; **9b**, 144182-43-4; **10b**, 144182-44-5; **11a**, 144182-45-6; **11b**, 118249-24-4; **11c**, 144182-49-0; **12a**, 144182-46-7; **12b**, 144182-47-8; **12c**, 144182-50-3.

Palladium-Catalyzed, Carbonylative, Intramolecular Coupling of Hydroxy Vinyl Triflates. Synthesis of Substituted α,β-Butenolides

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The α,β-butenolide substructure is found in a wide variety of natural products including many flavor components and insect pheromones.[1a] In addition, compounds incorporating functionalized α,β-butenolides, or their derivatives, have been shown to be biologically active and some display antitumor activity.[1b] Although approaches to the synthesis of α,β-butenolides have been diverse they can be classified as either elaboration of an existing five-membered ring or cyclization of an appropriate acyclic precursor.[1a,b] Our approach to the synthesis of α,β-butenolides relies on a palladium-catalyzed, carbonylative, intramolecular coupling of a hydroxy vinyl trifluoromethanesulfonate (triflate) to effect the desired ring closure. Palladium-catalyzed methodologies have been reported previously for the synthesis of α,β-butenolides and these have included (a) the hydroarylation of alkyl 4-hydroxy-2-alkynoates,[2] and (b) the carbonylative cyclization of hydroxy vinyl iodides.[3a,b] The advantages offered by the use of vinyl triflates is their ease of formation from ketones using standard enolate chemistry and their ability to undergo palladium-catalyzed couplings readily.[4a,b] We wish to report that vinyl triflates can be used efficaciously for the synthesis of α,β-butenolides.

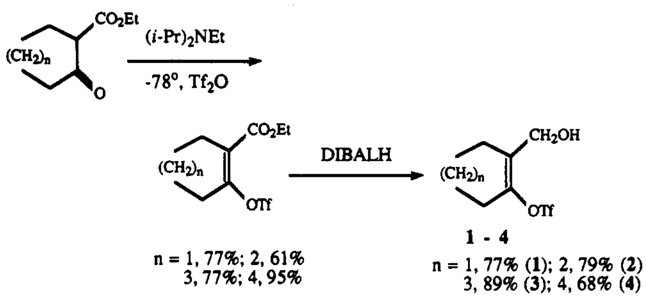

Figure 1.

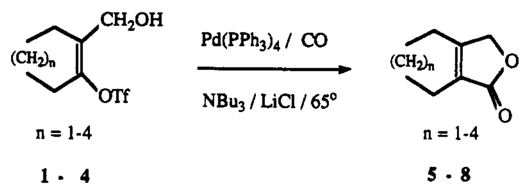

Figure 2.

Results and Discussion

Cyclic vinyl triflates were readily prepared from the corresponding β-keto esters by a two-step process as indicated in Figure 1. Addition of *N,N*-diisopropylethylamine to the β-keto ester at low temperature, followed by the addition of triflic anhydride (Tf_2O) gave the corresponding ethoxycarbonyl-substituted vinyl triflate[5] in good yield for the ring sizes five through eight. The addition of 2 equiv of DIBALH to the ethoxycarbonyl-substituted vinyl triflates resulted in a clean reduction of the ester to the expected hydroxymethylene with no reduction of the triflate group. The same procedure was used on ethyl salicylate to give 2-[[(trifluoromethyl)sulfonyl]oxy]benzyl alcohol. The initial conditions used for the carbonylative coupling of the hydroxy vinyl triflates were similar to those reported for the reaction of hydroxy vinyl iodides.[3b] Thus addition of hydroxy vinyl triflate **2** to an acetonitrile solution of $Pd(PPh_3)_4$ (10 mol %), potassium carbonate and lithium chloride under 1 atmosphere of carbon monoxide gave the expected 4,5,6,7-tetrahydro-1(3*H*)-isobenzofuranone (**6**) in 43% yield. The observed yields for the carbonylative couplings of the other hydroxy vinyl triflates described in Figure 1 were also in the range of 40–50% under these conditions. Improved yields of products (75–95%) were obtained by performing the intramolecular cyclizations with tri-*n*-butylamine in place of potassium carbonate as described in Figure 2. The size of the ring appears to have negligible influence on the yield of the α,β-butenolide (entires 1–4, Table I). The hydroxyaryl triflate 2-[[(trifluoromethyl)sulfonyl]oxy]benzyl alcohol also underwent the intramolecular coupling in moderate yield (entry 5, Table I). The reaction mixtures changed from a initial yellow color through orange to black as the reaction proceeded. The black color is presumably caused by the precipitation of palladium and usually indicated that the reaction was complete. The course of the reaction was conveniently monitored by TLC analysis of the mix-

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