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SYNTHESIS OF THREE-BRIDGED CYCLOPHANES VIA META- AND ORTHO-CYCLOPHANE¹

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Abstract: Three-bridged cyclophanes 6a-b and 10 were obtained from directly olefinated meta- and ortho-cyclophanes under [2 + 2] photocycloaddition.

Synthesis of multi-bridged cyclophanes linked by cyclobutane rings is a fascinating field in the cyclophane chemistry, because of their attractive structures and reactivities. Styrene derivatives are used as the starting materials for the synthesis of meta- and para-cyclophanes of this sort through the [2 + 2] photocycloaddition.² Using this photochemical method and palladium catalyzed transformations, we have designed a dimethoxy-metacyclophane and a dibromo-orthocyclophane as possible intermediates for the multi-bridged cyclophanes, since palladium catalysts are widely employed to convert leaving groups to olefinic moieties on aromatic rings.³ There are, however, few examples of the transformation on molecules having several leaving groups to appropriate polyfunctional olefins all at once. Moreover, the functional group interconversion on the cyclophane skeleton has unique feature because of plausible retardation or acceleration by steric hindrance and transannular interaction.⁴ On this respect, the palladium-catalyzed reaction leading to pseudo-geminal functional groups upon a cyclophane has not been well-revealed. So, we were prompted to investigate the palladium-catalyzed reaction of a cyclophanyl triflate or halide, in order to investigate the kind of reactions in the vicinity of cyclophane skeletons and also to develop a synthetic method toward multi-bridged



cyclophanes. We would like to report the synthesis and structure of cyclobutanebridged meta- and ortho-cyclophanes and their conversion into three-bridged cyclophanes.

Dimethoxy[2.5]metacyclophane $\underline{2}$ was prepared by the sequence shown in Scheme 1. Diolefin $\underline{1}$ was irradiated with a 400 W high pressure Hg lamp (Pyrex filter) for 16 h at room temperature in dry benzene (10 mM) to afford cyclophane $\underline{2}$ in a 68% yield. After evaporation, crude metacyclophane $\underline{2}$ was purified by column chromatography (SiO₂, hexane-benzene). Physical and analytical data of all new cyclophanes are listed.⁵

The structures were determined by NMR spectroscopic methods including COSY, NOESY, and ¹³C experiments. The syn conformation of <u>2</u> was exhibited by the ¹H-NMR chemical shifts of aromatic protons ($\delta 6.4 - 7.0$). The cyclobutane ring is confirmed to be fused in a cis manner ($\delta 4.52$).^{6,7} Exo orientation of the cyclobutane ring to methoxyl groups was confirmed by NOE interactions between the ethano-bridge and H¹ protons and between the methoxyl groups and H³ protons. Anisole derivative <u>2</u> was treated with boron tribromide in dry benzene under reflux for 1 h to give phenol derivative <u>3</u> in a 85% yield. Triflate <u>4</u> was obtained in a 87% yield by the reaction of trifluoromethanesulfonic anhydride and phenol <u>3</u> in pyridine at room temperature for 24 h. Under the reported reaction conditions,³ however, olefin <u>5</u> was obtained from <u>4</u> in very low yields. Therefore, the conditions were modified to rather severe ones; i.e., triflate <u>4</u> (0.065 mmol) was treated with Pd(PPh₃)₂Cl₂(0.037 mmol), Et₃N (0.39 mL), and a corresponding olefin (ethyl acrylate or styrene, 1.8 mmol) in DMF (1.9 mL) in a sealed ampule at 130 °C for 24 h under N₂. Yields of <u>5a</u> and <u>5b</u> were 68 and 77%, respectively.

Olefin moieties in <u>5a</u> and <u>5b</u> were assigned to be of <u>trans</u>-configuration by comparison with IR and ¹H-NMR spectra of ethyl <u>trans</u>-cinnamate or <u>trans</u>-stilbene. Olefins <u>5a</u> and <u>5b</u> were irradiated in benzene for 2.5 h to give three-bridged cyclophanes <u>6a</u> and <u>6b</u> in 67 and 65% yields, respectively. The benzylic methine protons attaching to new cyclobutane rings clearly exhibit an NOE interaction with the methine protons of the other cyclobutane rings. Methine protons attaching at the carbons with COOEt or Ph have another NOE interaction with H³ aromatic protons. Accordingly, the directions of two cyclobutane rings are confirmed as shown in Scheme 1.

On the other hand, orthocyclophane <u>8</u> was prepared by the sequence shown in Scheme 2. The photocycloaddition of olefin <u>7</u> was carried out under the same conditions as above. After evaporation, two isomers, cyclophanes <u>8a</u> and <u>8b</u>, were isolated in 62 and 8.4% yields, respectively, by column chromatography (SiO₂, benzene-hexane).

Both isomers <u>8a</u> and <u>8b</u> were confirmed to be of syn conformation by the fact that aromatic protons do not show any large high-field shifts. The cyclobutane moieties of cyclophanes <u>8a</u> and <u>8b</u> are of cis-configuration, according to the chemical shifts of their methine protons.^{6,7} The methine signal of minor isomer <u>8b</u> appears at \$4.38 more deshielded than that of <u>8a</u>. This is ascribed to the anisotropy of the ether oxygen, 6 so that the methines and ether oxygens are located in their vicinity, and this clearly means the structure of isomer <u>8b</u> as depicted in Scheme 2. The NOE interaction between the ethano-bridge and aromatic H^1 protons also supports the structure of <u>8b</u>. The cyclobutane methine signal of major isomer 8a appears at \$3.78. This chemical shift is quite usual for cis-cyclobutane unit,⁷ indicating no significant electronic effect. Therefore, this isomer has endo configuration for the two tethers. Interestingly, both ethano-bridge and methine protons exhibit NOE interactions with aromatic H^{\perp} protons. According to the network examination with the space filling model, the mobility including conformational changes of all segments in 8a is more easier than that of <u>8b</u>, and the ethano-bridge and methine protons of <u>8a</u> can easily approach to the aromatic protons. The flexibility is consistent with the chemical shifts of aromatic protons of <u>8a</u> (\$6.73-7.46) which are less upfielded than those of <u>8b</u> (s6.43-7.17). Hence, the face-to-face conformation of cyclophane <u>8a</u> is holded less tightly than that of <u>8b</u>. The vinylation of bromides <u>8a</u> and <u>8b</u> was carried out with Pd(PPh₃)₂Cl₂ (5 mol%), nBu₃SnCH=CH₂ (1.2 eq), and LiCl (5 eq) at 100 °C for 2 h in DMF.³ Yields were 49 and 43%, respectively. They were irradiated in benzene and, interestingly, only one photoproduct 10 was obtained from <u>9a</u> in a 43% yield, while olefin <u>9b</u> did not give any three-bridged cyclophanes due to low reactivity, which is probably caused by the rigid exo-configuration as mentioned above.

The analysis of cyclophane <u>10</u> by ¹H-NMR spectroscopy gives the following evidences on the structure: 1) NOE interactions are observed between H_b protons of cyclobutane ring and H^2 protons, the ethano-bridges of two cyclobutane rings and H^1 protons, and α -methylene protons of the ether linkage and H^3 protons, respectively. 2) H_a protons of cyclobutane ring appear at \$4.77 because of the deshielding effect of ether oxygens just like for <u>8b</u> (vide supra). Based on these observations, the structure of cyclophane <u>10</u> was concluded as shown in Scheme 2. It is apparent that flexible <u>9a</u> readily reacted at <u>para</u> position and changed the configuration of cyclobutane ring from endo- to exo-one during the photoreaction to avoid to make a the highly strained structure, probably through cycloreversion and cyclization processes. The mechanism is now investigated.

In conclusion, <u>syn</u>-meta- and ortho-cyclophanes were easily obtained by means of photocycloaddition. And also after olefinated, the cyclophanes gave the threebridged phanes under photoirradiation. Thus, the photocycloaddition combined with



a) hv(Pyrex)/benzene. b) nBu₃SnCH=CH₂/PdCl₂(PPh₃)₂/LiCl/DMF. c) hv(Pyrex)/benzene.

palladium-catalyzed transformations at the olefin preparation is developed as a reasonable route toward a multi-bridged cyclophane. Further investigation is now in progress and will be reported elsewhere.

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 Intramolecular [2 + 2] photocycloaddition. part 12.
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Press, New York (1983). 5) Physical and analytical data of cyclophanes 2, 3, 4, 5, 6, 8, 9, and 10. Compd; Mp; Anal. calcd (found); $MS(M^+)$; $IR(v) cm^{-1}$; 1H-NMR in CDC13 & (intensity, multiplicity, J in Hz). 2; $110-113 \, {}^\circ\text{C}$; For C23H28O2: C, 82.10 (81.93), H, 8.39 (8.31); m/z 336; 2952, 1510, 1265, 1142, 1046, 814; 0.18 (1H, m), 0.90 (1H, m), 1.52 (2H, m), 1.71 (2H, m), 2.30-2.74 (8H, m), 3.62 (6H, s), 4.52 (2H, m), 6.43 (2H, d, 8.2), 6.62 (2H, dd, 8.2 & 2.1), 7.04 (2H, d, 2.1). 3; 212-214 ${}^\circ\text{C}$; For C21H24O2.0.1H20: C, 81.31 (81.19), H, 7.86 (7.87); m/z 308; 3352, 2932, 1497, 1251, 1212, 807; 0.12 (1H, m), 0.89 (1H, m), 1.60 (4H, m), 2.40 (2H, m), 2.60 (6H, m), 4.43 (2H, m), 5.03 (2H, bs), 6.46 (2H, d, 8.1), 6.58 (2H, dd, 8.1 & 2.1), 6.95 (2H, d, 2.1). 4; 78-82 \, {}^\circ\text{C}; For C23H22F606S2: C, 48.25 (48.09), H, 3.87 (4.01); m/z 572; 2952, 1439, 1220, 1154, 900; 0.12 (1H, m), 1.01 (1H, m), 1.67 (4H, m), 2.54 (6H, m), 2.72 (2H, m), 4.51 (2H, m), 6.79 (2H, dd, 8.3 & 2.0), 6.88 (2H, d, 8.3), 7.21 (2H, d, 2.0). 5a; 145-150 \, {}^\circ\text{C}; For C31H36O4: C, 78.78 (78.55), H, 7.68 8.3), 7.21 (2H, d, 2.0). 5a; 145-150 °C; For C₃₁H₃₆O4: C, 78.78 (78.55), H, 7.68 (7.69); m/z 472; 2926, 1724, 1312, 1164, 972; 0.15 (1H, m), 1.01 (1H, m), 1.34 (6H, t, 7.2), 1.62 (2H, m), 1.77 (2H, m), 2.51 (2H, m), 2.61 (4H, m), 2.75 (2H, m), 4.24 (4H, q, 7.2), 4.57 (2H, m), 6.03 (2H, d, 15.8), 6.72 (2H, dd, 7.8 & 1.5), 7.14 (2H, d, 7.8), 7.19 (2H, d, 1.5), 7.86 (2H, d, 15.8). <u>5b</u>; 74-76 °C; For C₃₇H₃₆: m/z 480; 2932, 1495, 960, 890, 720, 692; 0.25 (1H, m), 0.98 (1H, m), 1.63 (2H, m), 1.84 (2H, m), 2.58 (6H, m), 2.80 (2H, m), 4.56 (2H, m), 6.64-6.80 (6H, m), 2.80 (2H, m), 4.56 (2H, m), 6.64-6.80 (6H, m), 2.51 (2H, m), 4.56 (2H, m), 7.21 (104, m), 5.50 (2H, m), 4.56 (2H, m), 5.50 (2H(2H, m), 1.84 (2H, m), 2.58 (6H, m), 2.80 (2H, m), 4.56 (2H, m), 6.64-6.80 (6H, m), 7.15 (4H, m), 7.31(10H, m). <u>6a</u>; 42-43 °C; For C₃₁H₃₆O₄: C, 78.78 (78.86), H, 7.68 (7.70); m/z 472; 2925, 1736, 1196, 790; 0.34 (2H, m), 1.10 (2H, m), 1.28 (6H, t, 7.0), 1.58 (2H, m), 2.30-2.65 (8H, m), 3.77 (2H, d, 6.5), 4.12 (2H, m), 4.21 (4H, q, 7.0), 4.34 (2H, d, 6.5), 6.61 (2H, dd, 8.5 & 2.0), 6.68 (2H, d, 8.5), 6.74 (2H, d, 2.0). <u>6b</u>; 157-160 °C; For C₃₇H₃₆: C, 92.44 (92.21), H, 7.56 (7.70); m/z 480; 2940, 1496, 700; 0.42 (2H, m), 1.13 (2H, m), 1.58 (2H, m), 2.40-2.68 (8H, m), 4.22 (2H, m), 4.42 (4H, m), 6.68 (2H, dd, 8.0 & 1.5), 6.80 (2H, d, 1.5), 6.96 (2H, d, 8.0), 7.05-7.26 (10H, m). <u>8a</u>; 69-72 °C; For C₁₉H₁₈Br₂O₂: C, 52.08 (52.10), H, (2H, m), 6.73 (2H, d, 8.7), 7.23 (2H, dd, 8.7 & 2.5), 7.46 (2H, d, 2.5). <u>8b</u>; $170-171 \circ C$; For C19H18Br2O2: C, 52.08 (52.08), H, 4.14 (4.17); m/z 438; 2960, 5.15 (2H, dd, 11 & 1.6), 5.66 (2H, dd, 18 & 1.6), 6.72 (2H, dd, 11 & 18), 6.84 (2H, d, 8.4), 7.22 (2H, dd, 2.1 & 8.4), 7.46 (2H, d, 2.1). <u>9b</u>; liq.; For C_{23H24}O₂: m/z 332; 1.98 (2H, m), 2.50 (4H, m), 4.12 (2H, m), 4.28 (2H, m), 4.42 (2H, m), 5.01 (2H, dd, 12 & 1.1), 5.45 (2H, dd, 18 & 1.1), 6.50 (2H, dd, 12 & 18), (2H, M), 5.01 (2H, dd, 12 & 1.17, 5.43 (2H, dd, 18 & 1.17, 5.30 (2H, dd, 12 & 187, 5.50 (2H, d, 8.5), 6.95 (2H, dd, 2.2 & 8.5), 7.13 (2H, d, 2.2). <u>10</u>; 173-176 °C;For C₂₃H₂₄O₂: C, 83.10 (82.87), H, 7.28 (7.15); m/z 332; 2950, 1510, 1250, 1130, 1070, 820; 2.60 (10H, m), 4.05 (2H, t-like), 4.19 (2H, m), 4.30 (2H, m), 4.77 (2H, t-like), 6.11 (2H, d, 8.3), 6.28 (2H, dd, 8.3 & 2.3), 6.93 (2H, d, 2.3).**6**) Y. Okada, K. Sugiyama, Y. Wada, and J. Nishimura, <u>Tetrahedron Lett</u>.,**31**, 107 (1900)107 (1990). 7) J. Nishimura, A. Ohbayashi, H. Doi, K. Nishimura, and A. Oku, Chem. Ber.,

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