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Synthesis and Structural Analysis of Three-bridged [2.2.n](1,2,4)- and [4.4.n](1,2,4)-Cyclophanes[1)]

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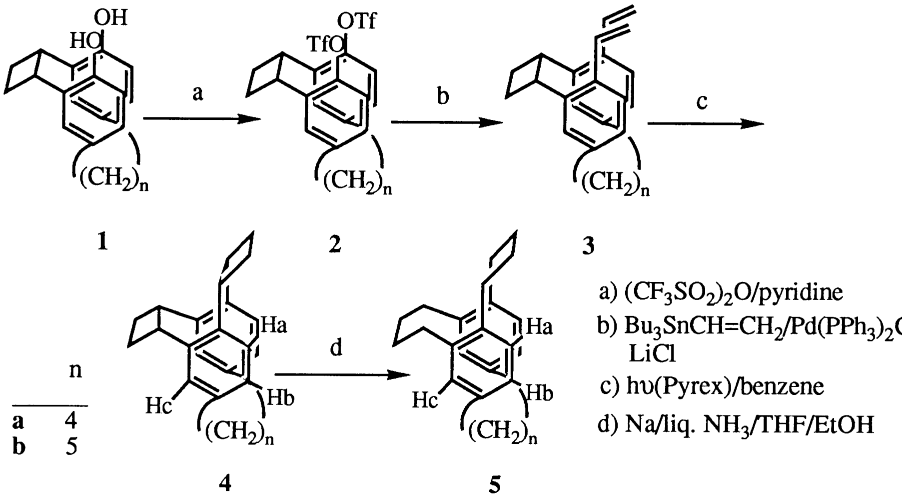
Three-bridged [2.2.n](1,2,4)cyclophanes **4a** and **b** were obtained by [2+2] photocycloaddition of divinylmetacyclophanes in 21 and 86% yields, respectively. Birch reduction of cyclophanes **4a** and **b** gave [4.4.n](1,2,4)-cyclophanes in 45-61% yields.

Intramolecular [2 + 2] photocycloaddition is one of the excellent synthetic methods for three-bridged cyclophanes, whose precursor olefins have two isolated vinyl groups on aromatic rings.[2)] Cyclophanes fused by cyclobutane ring show unique features on their structures concerned with the cyclobutane methine configuration and the aromatic ring conformation.[2)] Multi-bridged cyclophanes have attracted much interest in respects of synthetic method, stereochemistry, strain energy, and aromatic ring interaction.[3)] We previously reported a stepwise synthesis of three-bridged 1,2,4-cyclophanes by using cinnamate or stilbene derivatives derived from [2.5]metacyclophane.[4)] But, we could not introduce the vinyl groups on metacyclophane skeleton at that time. Accordingly, we investigated the synthetic method for direct vinylation in the metacyclophane skeleton and the photochemical reactivity of vinyl groups in order to make [2.2.n](1,2,4)cyclophanes. Few examples have been reported on the reactions in bulky cyclophane skeletons and/or at pseudo-geminal positions, so far.[3)] We would like to report here the syntheses of three-bridged [2.2.n](1,2,4)cyclophanes via photocycloaddition and [4.4.n](1,2,4)cyclophanes via ring-opening.



a) $(CF_3SO_2)_2O$/pyridine
b) $Bu_3SnCH=CH_2/Pd(PPh_3)_2Cl_2$/LiCl
c) hυ(Pyrex)/benzene
d) Na/liq. NH_3/THF/EtOH

Scheme 1.

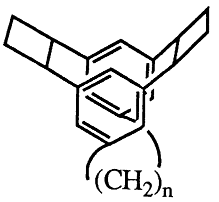
The synthetic route is shown in Scheme 1. Triflates **2a** and **b** were obtained from the reactions of dihydroxymetacyclophanes **1a** and **b** (78 mM) with $(CF_3SO_2)_2O$ (2 equiv.) in dry pyridine at room temperature for 24 h under N_2 in 59 and 87% yields, respectively. The vinylation of triflates **2a** and **b** under the reported conditions gave only the mono-vinyl derivatives.[5] Therefore the conditions were modified to rather severer ones; i.e., triflates **2a** and **b** (0.21 M) were treated with $Pd(PPh_3)_2Cl_2$ (10 mol%), $Bu_3SnCH=CH_2$ (1.2 equiv.), and LiCl (5 equiv.) in dry DMF at 100 °C for 2 h under N_2.[4] Yields of olefins **3a** and **b** were 70 and 72%, respectively. [2 + 2] Photocycloaddition of olefins **3a** and **b** (2-3 mM) was performed with a high pressure Hg lamp (Pyrex filter) in dry benzene at room temperature for 2-5 h under N_2. After column chromatography (SiO_2, benzene/hexane), pure cyclophanes **4a** and **b** were obtained in 21 and 86% yields, respectively.

The structural elucidation was performed with ^1H NMR, including COSY, NOESY, and ^{13}C NMR. ^1H NMR data of all cyclophanes are listed in Table 1.[6] The cis configuration of two cyclobutane rings of cyclophanes **4a** and **b** was assigned from the typical chemical shifts of cyclobutane methine protons which appear at δ 4.07 to 4.11.[7] The exo direction[4] of cyclobutane rings of **4a** and **b** was decided by NOESY experiments; i.e., the methylene bridges of two

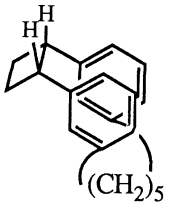
Table 1. ^1H NMR Data of Cyclophanes **1**, **2**, **3**, **4**, and **5**

Compd	^1H NMR δ (intensity, multiplicity, J in Hz)[a]
1a	1.44 (2H, m), 1.87 (2H, m), 2.28 (2H, m), 2.42-2.73 (6H, m), 4.46 (2H, m), 5.03 (2H, bs), 6.36 (2H, d, 8.0), 6.50 (2H, dd, 2.0 & 8.0), 6.95 (2H, d, 2.0).
2a	1.51 (2H, m), 1.98 (2H, m), 2.43 (2H, bt-like), 2.50-2.80 (6H, m), 4.57 (2H, m), 6.71 (2H, dd, 2.1 & 8.3), 6.80 (2H, d, 8.3), 7.18 (2H, d, 2.1).
3a	1.67 (2H, m), 2.03 (2H, m), 2.40 (2H, m), 2.62 (6H, m), 4.50 (2H, m), 5.14 (2H, dd, 1.6 & 12), 5.35 (2H, dd, 1.6 & 16), 6.64 (2H, dd, 1.4 & 7.9), 6.86 (2H, dd, 12 & 16), 7.02 (2H, d, 7.9), 7.22 (2H, d, 1.4).
3b	0.18 (1H, m), 0.95 (1H, m), 1.56 (2H, m), 1.80 (2H, m), 2.39-2.61 (6H, m), 2.74 (2H, m), 4.40 (2H, m), 5.13 (2H, dd, 1.5 & 13), 5.34 (2H, dd, 1.5 & 17), 6.70 (2H, dd, 1.8 & 8.0), 6.88 (2H, dd, 13 & 17), 7.06 (2H, d, 8.0), 7.16 (2H, d, 1.8).
4a	1.35 (2H, m), 1.68 (2H, m), 2.43 (12H, m), 4.11 (4H, m), 6.55 (2H, dd, 1.5 & 8.2), 6.68 (2H, d, 8.2), 6.71 (2H, d, 1.5).
4b	0.33 (2H, m), 1.13 (2H, m), 1.59 (2H, m), 2.27-2.70 (12H, m), 4.07 (4H, m), 6.65 (2H, dd, 1.6 & 8.1), 6.76 (2H, d, 1.6), 6.82 (2H, d, 8.1).
5a	1.73 (4H, m), 1.86-2.20 (8H, m), 2.32 (4H, m), 2.42 (4H, m), 2.65 (4H, m), 6.50 (2H, dd, 2.0 & 8.2), 6.51 (2H, d, 2.0), 6.64 (2H, d, 8.2).
5b	0.68 (2H, m), 1.35 (2H, m), 1.50-1.85 (4H, m), 2.02 (6H, m), 2.50 (8H, m), 2.75 (4H, m), 6.57 (2H, dd, 1.6 & 8.2), 6.63 (2H, d, 1.6), 6.71 (2H, d, 8.2).

a) A Varian Gemini-200 FT NMR spectometer. In $CDCl_3$, using TMS as an internal standard.



n=3, 4
6



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cyclobutane rings had the NOE interaction with aromatic Ha and Hc protons. Obviously this fact showed that the obtained [2.2.n](1,2,4)cyclophanes **4a** and **b** were only one isomer from possible four isomers in contrast with the isomer mixtures of [2.2.n](1,3,5)cyclophanes **6**[2a] and also showed that the ring rotation of cyclophanes **3a** and **b** could not occur under photoirradiation. The exclusive formation of cyclophanes **4a** and **b** was explained by the MM2 calculation; i.e., the strain energies (ΔSE) for **4a** and **b** are ca. 15 kcal/mol less than their isomers whose cyclobutane rings face to each other. Accordingly the obtained cyclophanes **4a** and **b** are the products formed from the most stable conformer of olefins under photoirradiation.[2]

The aromatic proton peaks of **4a** and **b** shift to up-field region and gather around the limited region (δ 6.55-6.71 for **4a** and δ 6.65-6.82 for **4b**) due to the face-to-face arrangement of benzene rings. Apparently the strain energies for aromatic ring moiety of three-bridged cyclophanes **4a** and **b** increase more than syn-metacyclophane **7**. In fact, three-bridged cyclophanes **4a** and **b** have ΔSE=24.4-29.3 kcal/mol higher strain energies than metacyclophane **7**[8] according to the MM2 calculation (see Table 2).

Birch reduction is a useful procedure for cyclobutane ring opening.[9] We had previously reported the synthesis of [4.n]- and [4.4.n](1,3,5)cyclophanes by this reduction.[2a,8] In this investigation, the conversion from [2.2.n](1,2,4)cyclophanes **4a** and **b** to [4.4.n](1,2,4)cyclophanes **5a** and **b** was attempted by this method. Birch reduction was performed with cyclophanes **4a** and **b** (3.3 mM), Na (19 mM), liq. NH_3/THF (1/1), and EtOH (22 mM) at -60 °C for 1 h under N_2 (Scheme 1). After column chromatography, cyclophanes **5a** and **b** were obtained in 61 and 45% yields, respectively.

Table 2. Strain Energy (ΔSE) of Cyclophanes **4**, **5**, and **7**[a)]

Compd	SE/kcal mol^{-1}	ΔSE/kcal mol^{-1}
4a	93.4	36.0
4b	88.5	31.1
5a	25.4	
5b	27.2	
7[b),c)]	35.4	6.7

a) Strain energy was calculated by MM2 program. Strain energy difference (ΔSE) is based on *cis*-diphenylcyclobutane (SE=28.7 kcal/mol) as a standard. b) See Ref. 8. c) syn-Conformer.

The structures of cyclophanes **5a** and **b** were determined with ^{1}H NMR spectroscopy. The cyclobutane ring opening was confirmed with the disappearance of cyclobutane methine protons for **4a** and **b** at δ 4.11 and δ 4.07, respectively. Interestingly the aromatic protons of **5a** (δ 6.50-6.64) and **5b** (δ 6.57-6.71) exhibited only a small difference from those of **4a** (δ 6.55-6.71) and **4b** (δ 6.65-6.82). And also, the methylene bridges could not move freely even after cyclobutane rings opening, which was judged from unsymmetrical resonance peaks for benzylic or phenethylic protons (see Table 1). These results showed that the conformation of **5** resembles that of **4** due to the similar three-bridged structure.

The MM2 calculation exhibited that the strain energies of **5a** and **5b** are SE=25.4 and 27.2 kcal/mol, respectively (Table 2). These strain energies of **5** are 3.9-10.6 kcal/mol smaller than those of **4** compensated with the strain energy of cyclobutane ring. This small difference of strain energy between cyclophanes **4** and **5** would be caused by three-bridged cyclophane structure, although the bridged chains were reduced from C_2- to C_4-bridges.

In conclusion, we successfully developed a synthetic route of three-bridged [2.2.n](1,2,4)-cyclophanes and [4.4.n](1,2,4)cyclophanes. Further investigation is now in progress and will be reported elsewhere.

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6) Mp (°C); Anal. Calcd (Found); MS (M$^+$); IR (υ); **4a**; 152-154; For $C_{24}H_{26}$, C, 91.66 (91.46), H, 8.34 (8.25); 314; 2930, 2852, 1488, 1443, 1242, 820; **4b**; 169-172; For $C_{25}H_{28}$, C, 91.41 (91.11), H, 8.59 (8.76); 328; 2930, 2850, 1491, 1442, 1240, 812; **5a**; 121-123; For $C_{24}H_{30}\cdot 0.5H_2O$, C, 88.00 (88.02), H, 9.56 (9.31); 2948, 2860, 1510, 1456, 820; **5b**; 37-38; For $C_{25}H_{32}\cdot 0.2H_2O$, C, 89.33 (89.29), H, 9.71 (9.57); 2920, 2856, 1500, 1454, 804.
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