Attempted Transformation of 2,3,5,6-Tetrachloro-4,4-dimethoxypentacyclo-[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane-8,11-dione toward Pentaprismane Retaining Chloro Group

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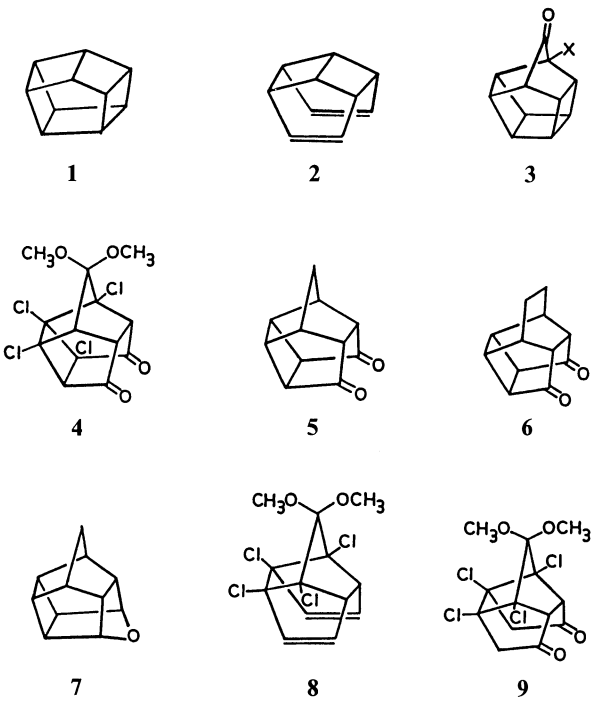
Synopsis. An attempt towards synthesis of homohypostrophene derivative, 1,2,6,8-tetrachloro-7,7-dimethoxytetracyclo[6.3.0.0^{2,6}.0^{5,9}]undeca-3,10-diene from 2,3,5,6-tetrachloro-4,4-dimethoxypentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane-8,11-dione is described.

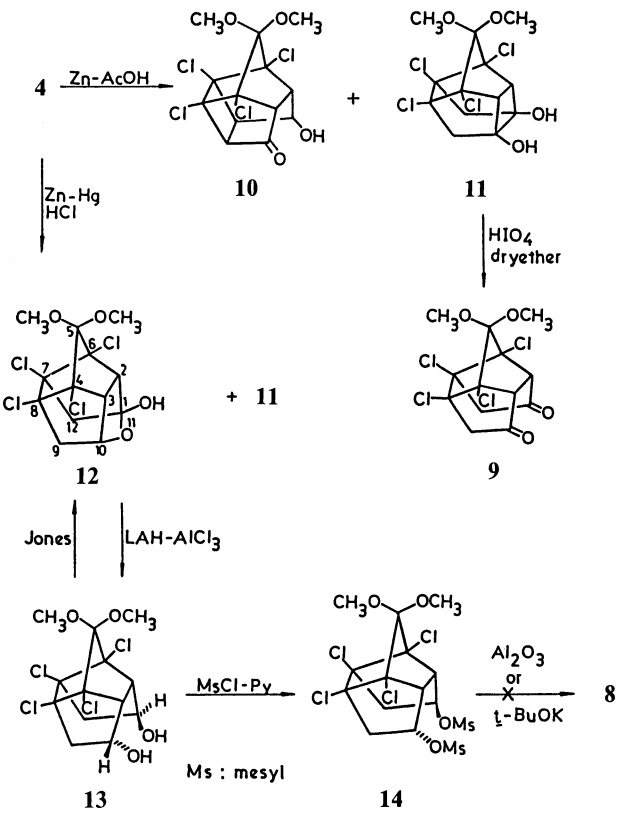
Strained polycyclic systems have fascinated organic chemists since long, and interest in this area appears to be growing since a recent issue of Chemical Reviews is entirely devoted to the chemistry of strained ring systems.[1)]

Pentaprismane **1**, the third member of prismane family[2)] has long defied synthesis until recently.[3)] Several earlier ingenious synthetic routes directed towards **1** were futile,[4)] including the hypostrophene **2** as a key intermediate.[4b)] Favorskii rearrangement of an appropriately substituted homopentaprismanone **3** has been considered the most promising sequence in this context. Along this line, the readily available dimethyl acetal **4** is the most suitable starting material since it incorporates a latent keto group and a leaving group at appropriate centers. However, numerous attempts to form a carbon–carbon bond directly between the two carbonyl groups in **4** and related diones **5** and **6** have failed.[5a,6–8)] One of the most common products observed during such attempts is the oxa bridged derivative like **7**.[6c)] We envisaged that homopentaprismanone skeleton **3** could be obtained by $\pi^{2s}+\pi^{2s}$ cycloaddition of the diene **8**. We therefore planned to convert **4** into the tetracyclic dione **9**, a potential precursor of **8**, and wish to report our results herein.

With the above objective, the dione **4** was treated with zinc in acetic acid to induce cyclobutane cleavage, since the parent dione **5** is known to undergo such cleavage upon treatment with zinc. However, the reduction of **4** gave a product mixture in which the hydroxy ketone **10** was the major product and the vicinal diol **11** as minor product (Scheme 2). The structure of **10** and **11** was clearly revealed from their spectral data. Oxidation of **11** with periodic acid in dry ether gave the desired



Scheme 1.



Scheme 2.

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tetracyclic dione **9**, however, the overall yield of **9** was too low to be of synthetic value. We therefore attempted the reduction of **4** with amalgamated zinc in hydrochloric acid[10a] which yielded **12** as the major product accompanied with a small amount of the diol **11**. The structure of **12** was deduced from its high-field ^{1}H NMR spectrum by use of LAOCN-4A simulation.

The reduction of **12** with lithium aluminium hydride gave only small amounts of isomeric alcohols. However, treatment of **12** with lithium aluminium hydride–aluminium chloride (1 : 4) mixture[11] afforded crystalline diol **13** in 80% yield. It is interesting to note that our attempt to transform the diol **13** into by Jones oxidation was futile and it gave back the hemiacetal **12** from which it was derived. While bismesylation of **13** with mesyl chloride in pyridine proceeded quantitatively to give **14**, attempted elimination of mesyl groups with basic alumina[10b,12] and potassium *t*-butoxide in dimethyl sulfoxide failed. The dimesylate **14** proved inert to substitution of mesyl groups with potassium iodide in acetone (Scheme 2).

While the inertness of **14** towards basic reagents was beyond expectation, several reasons can be conceived. The mesyloxyl groups lack assistance from solvent because they are tightly hidden in the small space between two ethano bridges. Deactivation by four chloro groups in the molecule should also be substantial.[13,14]

Experimental

Melting points are corrected. IR spectra (KBr pellet) were obtained on a JASCO model IR-G spectrometer. ^{1}H NMR spectra were measured on Hitachi R-20B (60 MHz), JEOL JNM PS-100 (100 MHz) and JEOL (400 MHz) spectrometers. Mass spectra were recorded on a JEOL model JMS-D300 mass spectrometer with an ionizing energy of 70 eV, an accelerating voltage of 3 kV, a chamber temperature of 200 °C and a pressure of 10^{-6} Torr (1 Torr=133.322 Pa). Elemental analyses were performed at the Analysis center, Department of Pharmacy, Hokkaido University.

Reduction of 4 with Zinc in Acetic Acid: 2,3,5,6-Tetrachloro-11-hydroxy-4,4-dimethoxypentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]-undecane-8-one (10) and 3,5,9,10-Tetrachloro-4,4-dimethoxypentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane-1,7-diol (11): Diketone **4** (2.0 g, 5 mmol) and activated zinc dust (7 g) were stirred in acetic acid (50 ml) for 8 h at room temperature. Zinc dust was filtered off and washed with dichloromethane. The filtrate was poured onto water (200 ml) and extracted with dichloromethane (3×50 ml). Combined extracts were washed with aqueous sodium hydrogen carbonate, water and brine, and dried over sodium sulfate. Removal of the solvent gave a crude residue (1.7 g), which was found to be a mixture of two products (TLC). Column chromatography through silica gel afforded a fast moving product (0.7 g, 35%) and a slow moving product (0.3 g, 15%).

The major product was recrystallized from ethyl acetate–hexane to give pure hydroxy ketone **10**, mp 222 °C; MS, *m/z* 374 (M$^+$); IR 3325, 2950, 1775 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=4.98 (1H, m, H-C-O), 4.15 (1H, s, OH), 3.60 (3H, s, OCH_3), 3.55 (3H, s, OCH_3), 3.35—3.32 (2H, m), 3.05—1.88 (2H, m). Found: C, 41.59; H, 3.04; Cl, 37.57%. Calcd for $C_{13}H_{12}O_4Cl_4$: C, 41.73; H, 3.23; Cl, 37.91%.

The minor product was likewise recrystallized to give pure **11**, mp 193 °C; MS, *m/z* 376 (M$^+$); IR 3330 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ=5.75 (2H, br s, OH), 3.49 (3H, s, OCH_3), 3.43 (3H, s, OCH_3), 2.79 (2H, s, CH), 2.45 (4H, AB, $\Delta\delta$=0.06, J=12 Hz, CH_2). Found: C, 41.54; H, 3.67; Cl, 37.28%. Calcd for $C_{13}H_{14}O_4Cl_4$: C, 41.52; H, 3.67; Cl, 37.71%.

Oxidation of 11 with Anhydrous Periodic Acid: 5,6,8,9-Tetrachloro-7,7-dimethoxytetracyclo[6.3.0.0^{2,6}.0^{5,9}]undecane-3,11-dione (9). To a solution of diol **11** (0.15 g, 0.38 mmol) in dry ether (10 ml) was added an ethereal solution of periodic acid (prepared by stirring 1 g of the acid in dry ether (20 ml)) and the mixture was stirred for 5 h at room temperature. The solution was washed with aqueous sodium hydrogen carbonate and dried over sodium sulfate. Removal of the solvent gave a residue which was crystallized from ethyl acetate–hexane to give 0.05 g (33%) of pure tetracyclic diketone **9**, mp 177—178 °C; IR 775 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=3.65 (3H, s, OCH_3), 3.55 (3H, s, OCH_3), 3.33 (2H, s, CH), 3.27 (2H, d, J_{AB}=ca. 14 Hz), 3.01 (2H, d, J_{AB}=ca. 14 Hz). Found: C, 41.15; H, 3.35; Cl, 37.43%. Calcd for $C_{13}H_{12}O_4Cl_4$: C, 41.73; H, 3.23; Cl, 37.91%.

Reduction of 4 with Zinc Amalgam: 11-Oxa-4,6,7,8-tetrachloro-5,5-dimethoxypentacyclo[5.4.1.0^{2,6}.0^{3,10}.0^{4,8}]dodecane-1-ol (12). To amalgamated zinc (80 g) in dil HCl (400 ml) was added **4** (4.0 g, 10.6 mmol) and the mixture was stirred at 70—80 °C for 7 h. The solution was decanted into water (200 ml) and extracted with dichloromethane (2×80 ml). Combined organic extracts were thoroughly washed with sodium hydrogen carbonate solution, water and brine, and dried over sodium sulfate. Evaporation of the solvent left a residue (3.7 g) which was subjected to column chromatography through silica gel. The first eluate amounted to 1.4 g (37%) of pure **12**, mp 228—229 °C; MS, *m/z* 376 (M$^+$); IR 3425 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=4.71 (1H, ddd, H_{10}, $J_{3,10}$=6.84 Hz, $J_{9exo,10}$=5.86 Hz, $J_{9endo,10}$=2.44 Hz), 3.69 (3H, s, OCH_3), 3.65 (3H, s, OCH_3), 3.42 (1H, d, H_3, $J_{2,3}$=11.71 Hz, $J_{3,10}$=6.84 Hz), 3.13 (1H, s, OH), 2.90 (1H, d, H_2, $J_{2,3}$=11.71 Hz), 2.90 (2H, AB system, $\Delta\delta$=0.08, H_{12endo}, H_{12exo}, J=14.65 Hz), 2.67 (1H, dd, H_{9exo}, $J_{9exo,10}$=5.86 Hz, $J_{9endo,9exo}$=ca. 15 Hz), 2.66 (1H, dd, H_{9endo}, $J_{9endo,10}$=2.44 Hz, $J_{9endo,9exo}$=ca. 15 Hz). Found: C, 41.27; H, 3.69; Cl, 37.30%. Calcd for $C_{13}H_{14}O_4Cl_4$: C, 41.52; H, 3.75; Cl, 37.71%.

The second eluate (0.4 g, 10%) was identical with **11** in every respect.

Reduction of 12 with Lithium Alminium Hydride–Aluminium Chloride: 5,6,8,9-Tetrachloro-7,7-dimethoxytetracyclo-[6.3.0.0^{2,6}.0^{5,9}]undecane-3-*endo*, 11-*endo*-diol (13). To a slurry of lithium aluminium hydride (0.5 g) in anhydrous ether (50 ml) was slowly added an ethereal solution (60 ml) of aluminium chloride (6.5 g) with stirring at 0 °C. To this mixture was slowly added a solution of **12** (0.5 g, 1.31 mmol) in ether (10 ml) within half an hour. The reaction mixture was stirred at 0 °C for one hour and then under reflux for five hours. After this period, the reaction flask was again cooled with ice and the inorganic reagents were carefully destroyed by adding HCl (30%, 50 ml) under the stream of nitrogen. The resulting mixture was extracted with ether (50 ml×3), and the combined extracts were washed with water. Removal of ether left a crude product (0.5 g) which was recrystallized from ethyl acetate–hexane to furnish 0.49 g (80%) of pure **13**, mp 209 °C; MS, *m/z* 378 (M$^+$); IR 3100, 2900 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=4.75 (2H, brs, H-C-O), 3.65 (3H, s, OCH_3), 3.61 (3H, s, OCH_3), 3.0—2.5 (6H, m). Found: C, 42.03; H, 4.25; Cl, 36.25%. Calcd for $C_{13}H_{16}O_4Cl_4$: C, 41.29; H, 4.26; Cl, 37.5%.

Jones Oxidation of 13. To a solution of **13** (0.5 g) in acetone (20 ml) was added dropwise freshly prepared Jones reagent until pale yellow color persisted after the addition of the reagent. The resulting solution was stirred at room temperature for half an hour. Usual work up gave crystalline solid (0.4 g, 80%) mp 228 °C, which was identical with **12** in every respect.

5,6,8,9-Tetrachloro-7,7-dimethoxytetracyclo[6.3.0.0^{2,6}.0^{5,9}]-undecane-3-*endo*, 11-*endo*-diyl Bis(methanesulfonate) (14). To a solution of diol **13** (0.55 g, 1.45 mmol) in pyridine (30 ml) was added methanesulfonyl chloride (1 ml) at 0 °C under stirring. After stirring for 2 h at 0 °C, the reaction mixture was diluted with ice water and extracted with dichloromethane (50 ml×2). The combined extracts were washed with dil HCl, water and brine, and dried over sodium sulfate. Solvent was stripped off and the residue was recrystallized from hexane to give **14**, (0.7 g, 90%) mp 137 °C; MS, *m/z* 534 (M^+); IR 1360, 1180 cm^{-1}; ^1H NMR ($CDCl_3$) δ=5.4 (2H, br s, H-C-OMs), 3.70 (3H, s, OCH_3), 3.65 (3H, s, OCH_3), 3.2—2.9 (12H, m). Found: C, 34.00; H, 4.00; S, 12.22%. Calcd for $C_{15}H_{20}O_8Cl_4S_2$: C, 33.71, H, 3.77; S, 12.00%.

Attempted Reactions of Bis(methanesulfonate) (14). To a slurry of basic alumina (10 g) in dry dichloromethane (50 ml) was added a solution of dimesylate **14** (0.1 g) in dichloromethane (10 ml) and the mixture was stirred for 24 h at room temperature and heated for further 30 h under reflux. No change was noticed by TLC. Unreacted mesylate was quantitatively recovered after filtration and evaporation of solvent.

Similarly, no reaction could be effected either with an excess of potassium *t*-butoxide in dimethyl sulfoxide in cold and at room temperature, or with potassium iodide in acetone under reflux.

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