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Synthesis and NMR Spectral Analysis of Hexacyclo[6.6.2.$0^{2,7}$.$0^{3,12}$.$0^{6,11}$.$0^{9,14}$]hexadeca-4,15-diene[1]

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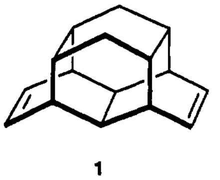
Polycyclic cage compounds that possess novel molecular frameworks have attracted considerable interest among organic chemists for many decades.[2,3] The title compound 1 is a $C_{16}H_{18}$ hydrocarbon in which two six-membered rings in chair conformations are connected in-between by five six-membered rings in nontwist boat conformations. Structurally, 1 embeds the carbon skeleton of seco-hexaprismane (2)[4] and iceane (3)[5] and may serve as synthetic precursor to these two ring systems. Physicochemically, the hexacyclic cage diene 1 is also an attractive substrate for the study of intracyclic group interactions.[6] In a continuation of our interest in the development of metholodogy and design in the synthesis of novel polycyclic cage compounds,[1,7] we herein describe an expedient synthesis of compound 1 based on a retrosynthetic analysis involving the domino Diels–Alder cycloaddition between appropriate synthetic equivalents of *acs*-hexahydroanthracene 4 and acetylene as shown below.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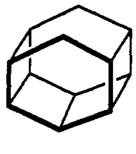
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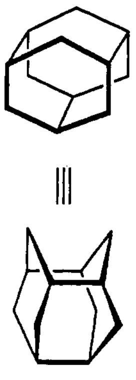
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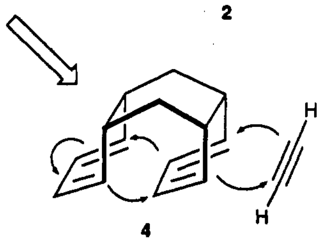

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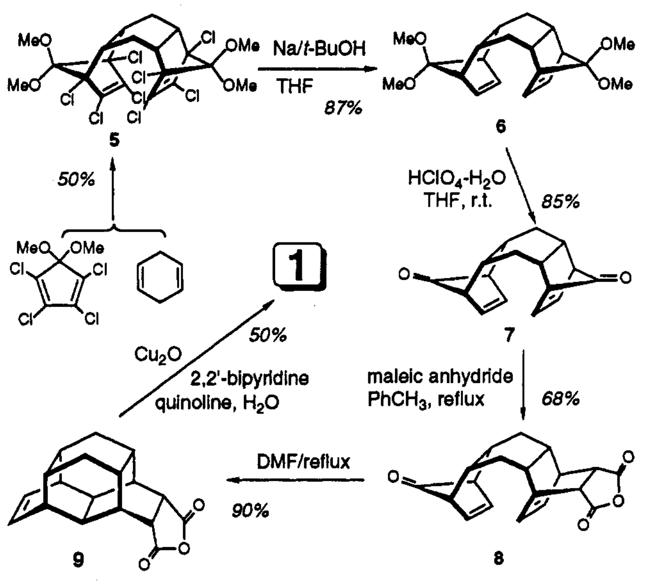
Scheme 1



The synthetic approach to hexacyclic 1 is outlined in Scheme 1. The known pentacyclic bis-enone 7[8] undergoes thermal decarbonylation to formally generate *acs*-hexahydroanthracene 4 which is trapped by maleic anhydride, an acetylene equivalent, followed by oxidative decarboxylation of the resulting adduct to furnish 1. Thus, the endo, syn, endo 2:1 cycloadduct 5[8,9] obtained from the Diels–Alder reaction of 1,2,3,4-tetrachloro-5,5-dimethoxycyclopentadiene and 1,4-cyclohexadiene was subjected to dechlorination with sodium/*tert*-butyl alcohol in tetrahydrofuran (THF) to afford bis-acetal 6[8] in 87% yield. Deacetalization of 6 with 3 M aqueous perchloric acid in THF gave the pentacyclic bis-enone 7[8] in 85% yield. The structure of 7 was assured by comparison of its IR and ^{1}H NMR spectral data with reported ones[8] and by analysis of its ^{13}C NMR spectrum which showed five lines of expected chemical shifts in accordance with its inherent symmetry. Heating bis-enone 7 with an excess amount of maleic anhydride in toluene under reflux led to thermal decarbonylation of 7 with subsequent formation of cycloadduct 8 as the sole isolated product in 68% yield. Apparently, the insolubility of keto anhydride 8 in the reaction medium (refluxing toluene) forced 8 to precipitate out and prevented it from further decarbonylation. The infrared spectrum of 8 showed absorption bands at 1778 (very strong) and 1850 cm^{-1}, indicating the presence of an anhydride moiety. The appearance of two types of olefinic protons at δ 6.34 (t) and 6.10 (dd) in its ^{1}H NMR spectrum established the presence of 7-norbornenone and bicyclo[2.2.2]oct-2-ene systems, respectively. No determined effort was made to establish the stereochemistry of anhydride moiety in 8. The assignment of syn orientation (as relative to C=C) as depicted was based on expectation of the dienophile to approach decarbonylated 7 from the less-hindered "outside" face and an endo-type addition in accordance with the Alder rule. When a solution of 8 in dimethylformamide (DMF) was heated under reflux for 6 h, thermal decarbonylation occurred with a subsequent intramolecular Diels–Alder reaction to furnish caged hexacyclic ene anhydride 9 in 85% yield. The infrared spectrum of 9 showed absorption bands due to an anhydride moiety at 1766 and 1850 cm^{-1}, and its ^{1}H NMR spectrum displayed an absorption due to vinyl protons of a bicyclo[2.2.2]oct-2-ene substructure at δ 6.27 (dd). Oxidative degradation of 9 to the title hexacyclic diene 1

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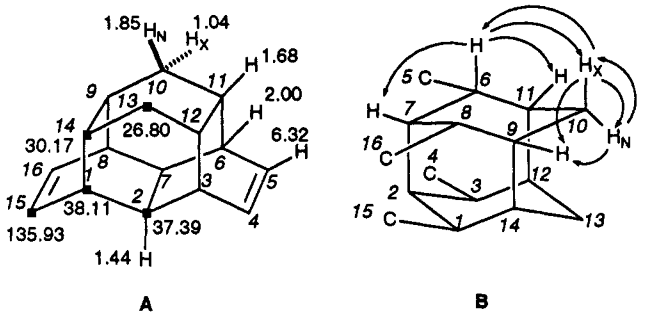

Figure 1. (A) Carbon-13 and proton NMR chemical shifts for 1; (B) Selected NOE results for 1 (C═C bonds omitted for clarity).

was achieved by treatment of 9 with Cu_2O in hot quinoline in the presence of 2,2′-bipyridine and a small amount of water.[10]

The structure of 1 was established by spectral and elemental analyses. The infrared spectrum of 1 shows absorption bands at 1613 and 669 cm^{-1}, consistent with the *cis*-1,2-disubstituted endocyclic double bonds. The inherent C_{2v} symmetry expected for 1 is obviously demonstrated by a five-line ^{13}C NMR spectrum and a ^1H NMR spectrum containing six groups of absorptions. The resonances for all carbons and protons in 1, except methylene protons, were unequivocally assigned using chemical shift, DEPT, HETCOR, and ^1H-^1H COSY experiments. Assignments are presented in Figure 1A. While the DEPT and HETCOR spectra identified the diastereotopic geminal protons (δ 1.85 and 1.04) attached to C-10/C-13 (δ 26.80), the spatial disposition of these two protons remained ambiguous. The assignment of steric configuration of these two diastereotopic methylene protons, designated as H_N and H_X in Figure 1A, was resolved by analysis of NOE difference spectra. Thus, irradiation of protons of bridgehead carbons at δ 2.00 (br s, H-1/H-3/H-6/H-8) enhances vicinally located methine protons at δ 1.68 (br s, H-9/H-11/H-12/H-14) and δ 1.44 (br s, H-2/H-7), vinyl protons at δ 6.32 (dd, J = 4.5, 3 Hz, H-4/H-5/H-15/H-16), and more importantly the methylene protons at δ 1.04 (double br s, J = 13 Hz). The latter enhancement indicates that the signal at δ 1.04 must be due to H_Xs which have a 1,3-diaxial relationship with H-1/H-3/H-6/H-8. Correspondingly, irradiation of methylene protons, H_Xs, enhances the geminal partners at δ 1.85 (double quintet, J = 13, 2 Hz), the methine protons at δ 1.68, and the protons of bridgehead carbon atoms at δ 2.00. When the other pair of methylene protons H_Ns (at δ 1.85) was irradiated, only enhancements of geminal H_Xs and vicinal H-9/H-11/H-12/H-14 were observed. No correlation is found in the NOE difference spectrum between the signals at δ 1.85 and 2.00, which is consistant with the distance between protons H_Ns and H-1/H-3/H-6/H-8 being too great for mutual spin relaxation to occur. The results of the NOE experiment is shown in Figure 1B.

The rigid hydrocarbon 1 presents a well-defined example to demonstrate steric influences of proximate nuclei on proton NMR chemical shifts.[11] A chemical shift difference of 0.81 ppm for diastereotopic methylene protons, H_Ns and H_Xs, is revealed in the ^1H NMR spectruim of 1 and can be attributed to steric effects. These two pairs of methylene protons (H_N and H_X) are held rigidly in a cyclohexane ring of nontwist boat conformation at a distance less than or near the sum of the van der Walls radii.[12] The steric compression between the endo protons (H_Ns) produces a large downfield shift in H_Ns relative to the chemical shift of the corresponding exo protons (H_Xs) which in turn experience shielding effect.

Experimental Section

Melting points were determined on a Thomas-Hoover apparatus and are not corrected. NMR spectra were obtained on a Varian VXR-300FT or Unity-300 spectrometer. All chemical shifts were expressed in δ (ppm) with reference to $CDCl_3$ (δ 7.27 for ^1H MNR and δ 77.0 for ^{13}C MNR). Infrared (IR) spectra were recorded as KBr pellets on a BIO-RAD FTS-40 spectrophotometer. Mass spectra (MS) were determined by the EI mode. Microanalyses were performed by Analytical Center of Cheng-Kung University.

(1β,3β,4α,7α,8β,10β,11α,14α)-4,5,6,7,11,12,13,14-Octachloro-15,15,16,16-tetramethoxypentacyclo[8.4.0.$1^{4,7}$.$1^{11,14}$.$0^{3,8}$]hexadeca-5,12-diene (5). A stirring mixture of 1,2,3,4-tetrachloro-5,5-dimethoxycyclopentadiene (56.0 g, 0.2 mol) and 1,4-cyclohexadiene (8.5 g, 0.1 mol) was heated at 80 °C for 72 h. During these hours, the reaction mixture gradually became viscous and turbid. The reaction mixture was cooled and the resulting precipitate was collected by filtration and washed with hexane to give 5 (35 g, 50%) as colorless crystals suitable for use in the next reaction: mp 250–252 °C (lit.[9] 258–260 °C); IR (KBr) 2957, 1610, 1462 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.58 (s, 6H), 3.54 (s, 6H), 2.52–2.57 (m, 4H), 1.85–1.95 (m, 2H), 0.45–0.58 (m, 2H); ^{13}C NMR (75.43 MHz, $CDCl_3$) δ 129.48 (s). 112.15 (s), 78 .27 (s), 52.74 (1), 51.59 (q), 45.44 (d), 18.53 (t).

(1β,3β,4α,7α,8β,10β,11α,14α)-15,15,16,16-Tetramethoxypentacyclo[8.4.0.$1^{4,7}$.$1^{11,14}$.$0^{3,8}$]hexadeca-5,12-diene (6). To a solution of 5 (40 g, 0.07 mol) in THF (550 mL) were added *tert*-butyl alcohol (95 g, 1.32 mol) and sodium (90 g, 3.9 mol) chopped into 5-mm cubes. The mixture was vigorously stirred and refluxed under nitrogen atmosphere for 40 h, cooled to room temperature, and filtered to remove unchanges sodium. The filtrate was poured into ice–water (140 mL) and extracted with dichloromethane (150 mL × 2). The organic phase was washed with brine (150 mL × 2), dried, and concentrated. The resulting pale brown residue (20.6 g) was recrystallized from ethyl acetate–hexane (2:1 by vol) to afford pure 6 (19 g, 87%) as colorless crystals: mp 114–115 °C (lit.[8] 237–240 °C); IR (KBr) 3060, 2921, 1600, 1463, 1284, 1249, 1138, 1067 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.03 (t, J = 2.2 Hz, 4H), 3.21 (s, 6H), 3.13 (s, 6H), 2.70 (br s, 4H), 2.10–2.21 (m, 4H), 1.33 (br d, J = 12.3 Hz, 2H), 0.30–0.42 (m, 2H); ^{13}C NMR (75.43 MHz, $CDCl_3$) δ 132.53 (d), 119.22 (s), 51.71 (q), 49.75 (q), 49.05 (d), 36.37 (d), 26.10 (t).

(1β,3β,4α,7α,8β,10β,11α,14α)-Pentacyclo[8.4.0.$1^{4,7}$.$1^{11,14}$.$0^{3,8}$]hexadeca-5,12-diene-15,16-dione (7). A solution of 6 (1 g, 3 mmol) in THF (25 mL) was treated with aqueous perchloric acid (3 M, 10 mL) and the resulting solution was stirred at room temperature for 3 h. The reaction mixture was poured into water (100 mL) and extracted with dichloromethane (70 mL × 3). The organic layers were combined and washed with saturated sodium bicarbonate solution until the aqueous layer was not acidic, and it was further washed with brine, dried, and filtered. Removal of solvent under reduced pressure gave crude 7 which was recrystallized from ethyl acetate to furnish pure 7 (0.6 g, 85%) as colorless crystals: mp 170–171 °C (lit.[8] 178–180 °C); IR (KBr) 3057, 3005, 2919, 1790 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.44 (t, J = 2 Hz, 4H), 2.84 (m, 4H), 2.23–2.35 (m, 4H), 1.50 (double t, J = 13; 4 Hz, 2H), 0.54–0.71 (m, 2H); ^{13}C NMR (75.43 MHz, $CDCl_3$) δ 204.14 (s), 131.70 (d), 51.66 (d), 33.48 (d), 24.17 (t).

(1β,3β,4α,7α,8β,10β,11α,14α,15β,16β)-17-Oxo-pentacyclo[8.4.0.$2^{4,7}$.$1^{11,14}$.$0^{3,8}$]heptadeca-5,12-diene-15,16-dicarboxylic Anhydride (8). A stirred solution of bis-enone 7 (1 g, 4.2 mmol) and maleic anhydride (0.6 g, 6.1 mmol) in dry toluene (4 mL) was

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heated under reflux for 2 days. During this period, precipitate was forming in the reaction mixture, making stirring difficult. The reaction mixture was cooled and the resulting precipitate was collected by filtration and washed with ethyl acetate to give crude 8 (0.9 g, 68%) suitable for use in the next reaction. A pure sample of 8 was obtained as colorless crystals by recrystallization from dichloromethane: mp 206–208 °C; IR (KBr) 3057, 2947, 1850, 1778, 1464, 1241, 1091, 917 cm^{-1}; ^{1}H NMR (300 MHz, pyridine-d_5) δ 6.34 (t, J = 2 Hz, 2H), 6.10 (dd, J = 4; 3 Hz, 2H), 3.46 (s, 2H), 2.90 (br s, 2H), 2.78 (br s, 2H), 2.10 (m, 2H), 1.64 (br d, J = 12.7 Hz, 2H), 1.16 (double t, J = 13; 3 Hz, 2H), 0.46 (dd, J = 13; 10 Hz, 2H); MS (mode: E I) *m/e* (rel inten) 282 (55, M^+–28), 254 (57), 226 (55), 210 (60), 174 (19), 129 (25), 91 (24), 58 (100); HRMS calcd for $C_{19}H_{18}O_4$–CO 282.1251, obsd 282.1259.

Hexacyclo[6.6.2.0^{2,7}.0^{3,12}.0^{6,11}.0^{9,14}]hexadeca-15-ene-4,5-dicarboxylic Anhydride (9). A solution of keto anhydride 8 (0.13 g, 0.42 mmol) in DMF (2.5 mL) was heated to reflux for 6 h. The solvent was removed under reduced pressure and the residue was chromatographed over a short column packed with silica gel using ethyl acetate as eluant to give crude **9** which was recrystallized from ethyl acetate–benzene to finish pure 9 (0.1 g, 85%) as colorless crystals: mp 174–176 °C; IR (KBr) 2890, 1850, 1766, 1610, 1445, 1230, 1085, 1060, 950, 915 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.27 (dd, J = 3; 5 Hz, 2H), 3.14 (s, 2H), 2.11 (br s, 2H), 1.99 (d, J = 13 Hz, 2H), 1.96 (br s, 2H), 1.89 (s, 2H), 1.71 (s, 2H), 1.53 (s, 2H), 1.12 (d, J = 13 Hz, 2H); ^{13}C NMR (75.43 MHz, $CDCl_3$) δ 173.75 (s), 134.76 (d), 45.01 (d), 37.67 (d), 35.30 (d), 32.07 (d), 29.92 (d), 29.78 (d), 27.61 (t); MS, *m/e* (rel inten) 282 (M^+, 22), 254 (5), 226 (6), 210 (6), 129 (6), 78 (100), 51 (13). Anal. Calcd for $C_{18}H_{18}O_3$: C, 76.57; H, 6.43. Found: C, 76.32; H, 6.38.

Hexacyclo[6.6.2.0^{2,7}.0^{3,12}.0^{6,11}.0^{9,14}]hexadeca-4,15-diene (1). A mixture of anhydride **9** (1.00 g, 3.54 mmol), copper(I) oxide (1.10 g, 7.66 mmol), 2,2′-bipyridine (0.60 g, 3.83 mmol), quinoline (10 mL), and water (0.3 mL) was stirred vigorously and heated to reflux over 4 h. Heating at this temperature was continued for 12 h during which excess water was allowed to distill off. After a further 24 h at reflux, the dark mixture was cooled, diluted with ether–hexane (1:1, 50 mL), and filtered through a pad of Celite. The yellow filtrate was washed with hydrochloric acid (10%), saturated sodium bicarbonate solution, and dried. The solvent was removed under reduced pressure and the residue (0.55 g) was chromatographed over a short column packed with silica gel using hexane as eluant to give pare yellow viscous liquid which was recrystallized from methanol-water at 5 °C to afford pure 1 (0.5 g, 60%) as colorless crystals: mp 29–30 °C; IR (KBr) 3041, 2912, 2856, 1613, 1370, 792, 669 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) and ^{13}C NMR (75.43 MHz, $CDCl_3$) see text and Figure 1: MS, *m/e* (rel inten) 210 (M^+, 100), 132 (22), 129 (14), 128 (13), 117 (14), 115 (12), 91 (21), 79 (10), 78 (49), 77 (10), 54 (29). Anal. Calcd for $C_{16}H_{18}$: C, 91.37; H, 8.63. Found: C, 91.07; H, 8.60.

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Supplementary Material Available: Copies of ^{1}H, ^{13}C, and 2-D NMR spectra of 1 (10 pages). This material is contained in libraries on microfiche, immediately follows this article in microfilm version of the journal, and can be ordered from ACS; see any current masthead page for ordering information.