

Synthesis and Transannular Reactions of a Polycyclic Compound Containing Three Parallel Face-to-Face Double Bonds

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Rigid polycyclic molecules having two isolated double bonds located in the laticyclic topology¹ and spatially in close proximity have provided suitable frameworks for the study of transannular interactions and reactions.² In the aspect of chemical reactions, face-proximate double bonds in these systems may undergo transannular reactions by three modes (Chart 1). Photochemical [2 + 2] cycloadditions to produce cyclobutane rings (closure, *O*-type) are very facile and well known.³ Stepwise additions to double bonds usually lead to the transannular bridge formation in either cross (*N*-type) or parallel (*U*-type) manner or both.⁴ We recently reported that transannular bromination of *endo*-5,12:*endo*-6,11-dietheno-5,5a,6,11,11a,12-hexahydronaphthacene (**1**) produced both *N*-type and *U*-type adducts.⁵ Our continuous interest in the transannular reactions of rigid polycyclic hydrocarbons containing π -face-proximate double bonds⁶ led us to prepare the tetrahydrofuran-grafted *syn*-sesterbicyclo[2.2.2]octene **2**⁷ which contains three parallel, face-to-face double bonds. Herein, we report the results of the synthesis, transannular photocyclization and bromination of **2**, and the X-ray crystal structure of the resulting bromination product.

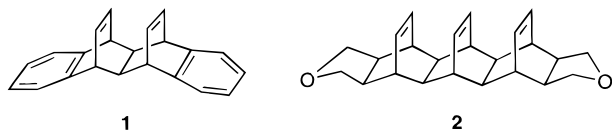
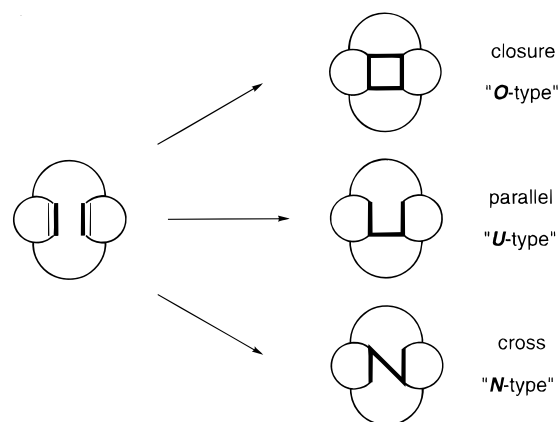


Chart 1



The synthesis of **2** from readily accessible chlorinated tetracyclic diol **3** is outlined in Scheme 1. The underlying synthetic approach is that a dechlorination–deacetalization–decarbonylation process⁶ is employed to unmask the cyclohexadiene moiety in **3** or **7** (e.g. **7** → **8** → **6** → **5**) for connecting another cyclohexadiene moiety by Diels–Alder reaction using *p*-benzoquinone as an equivalent (**5/6** → **9** → **12**), setting up for subsequent construction of the third bicyclo[2.2.2]octene substructure by another Diels–Alder reaction with maleic anhydride. Thus, chlorinated tetracyclic diol **3** was converted by our previously reported procedure^{6d} to keto diol **4** which was then subjected to acid-catalyzed dehydration in toluene in the presence of triethyl orthoformate at 100 °C to produce a mixture of decarbonylated product **5** and dienone **6** in 65% and 25% yields, respectively. Increasing the reaction temperature or elongation of the reaction time did not improve the yield of **5**. Alternatively, dienone **6** was prepared in an overall yield of 70% from **3** by dehydration of tetracyclic diol **3** followed by dechlorination with sodium/*tert*-butyl alcohol in THF and deacetalization with 3 M HClO₄ in CH₂Cl₂. Reaction of dienone **6** with *p*-benzoquinone in refluxing benzene resulted in slow decarbonylation of **6** (formation of **5**), followed by cycloaddition to furnish single cycloadduct **9** in nearly quantitative yield. The *syn* orientation of the cyclohexendione moiety with respect to the bridged C=C double bond is expected based on the Alder rule, and as observed in the Diels–Alder reactions of related 1,3-cyclohexadienes with substituted dienophiles.⁶

Reduction of **9** with sodium borohydride/cerium chloride in methanol at 0 °C gave enediol **10** in 89% yield. Conversion of enediol **10** to the corresponding dimesylate **11** with methanesulfonyl chloride in the presence of triethylamine was a crucial step, due to facile aromatization via elimination of two molecules of methanesulfonic acid, even when the reaction was performed at 0 °C. Thus, the dimesylate **11** was prepared at –45 °C and, without further purification, was subsequently converted to 1,3-cyclohexadiene **12** in 56% yield after chromatographic purification. In order to minimize the decomposition of **12** via retro-[4 + 2] cycloaddition, the Diels–Alder reaction of **12** and maleic anhydride was carried out in benzene at 45 °C in the presence of zinc chloride as catalyst. The reaction furnished the carboxylic anhydride **13** in moderate yield. We anticipated that

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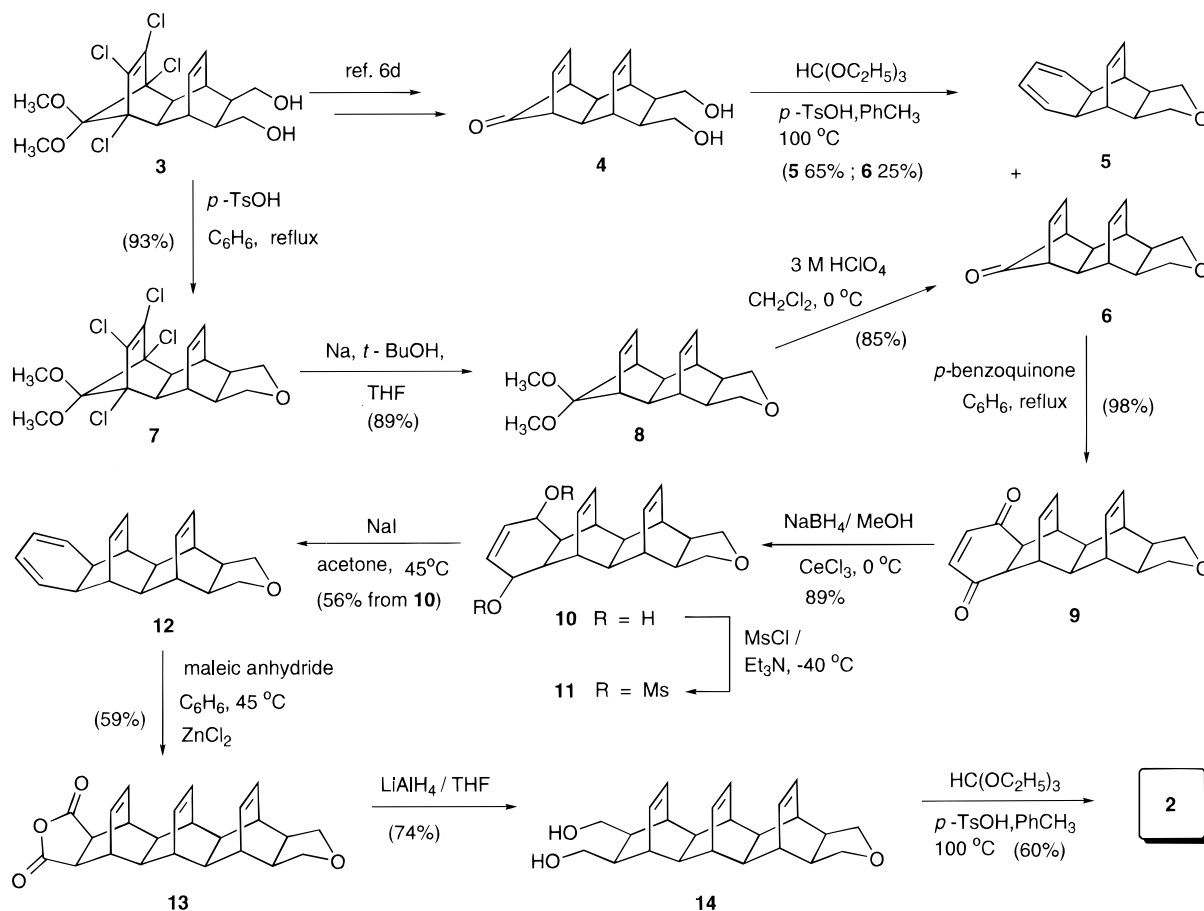
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Scheme 1



maleic anhydride would follow the Alder rule and attacked the cyclohexadiene moiety of **12** from the diene-face *anti* to the etheno-bridge (*exo*-side). Lithium aluminum hydride reduction of carboxylic anhydride **13** in THF gave, in 74% yield, the corresponding 1,4-diol **14** which was transformed to the desired tetrahydrofuran-grafted *syn*-sesterbicyclo[2.2.2]octene **2** in 60% yield following the same procedure used for intramolecular dehydration of **4**. The structural assignment of **2** is consistent with spectroscopic data. The $^1\text{H-NMR}$ spectrum of **2** displays the characteristic signals for the two types of vinyl protons at etheno-bridges at δ 5.28 (dd, 2H) and δ 5.65 (dd, 4H), and signals for the methylene protons of the tetrahydrofuran rings at δ 3.24 (dd, 4H) and δ 3.75 (dd, 4H). The $^{13}\text{C-NMR}$ spectrum of **2** demonstrates the inherent C_{2v} symmetry in the molecule by displaying seven lines for 24 carbon atoms.

As shown in Scheme 2, irradiation of octacyclic triene **2** dissolved in a mixed solvent of acetone/benzene (1:9) with a 450 W medium-pressure Hanovia lamp under nitrogen atmosphere proceeded smoothly with an intramolecular

[2 + 2] cycloaddition to form decacyclic monoene **15** in 80% yield. Reaction of a dilute CHCl_3 solution of triene **2** with bromine at 0 °C produced dibromide **17** as the major product (55%) via transannular 1,6-homoconjugated addition, along with several unidentified minor products. The dibromide **17**, with molecular formula $\text{C}_{24}\text{H}_{28}\text{Br}_2\text{O}_2$, displayed a $^1\text{H NMR}$ spectrum consistent with the assigned structure and a $^{13}\text{C NMR}$ spectrum of 12 lines for 24 carbon atoms, indicating the presence of a C_2 symmetry element in the molecule. To confirm the structural assignment, the single-crystal X-ray structure of **17** was analyzed and is shown in Figure 1,⁸ which clearly shows that two bromine atoms are located to have *endo,endo*-stereochemistry (or *anti,anti* with respect to tetrahydrofuran ring).⁹ The stereochemical outcome of two bromine atoms is rationalized as follows. Similar to the bromination of **1**, transannular carbon-carbon bridge formation by *N*-type (Chart 1) dominates the reaction pathways, yielding the dibromide **16a** which subsequently underwent substitution to form, via **16b**, the more stable *endo,endo*-dibromide **17** (Scheme 2).

In summary, we have demonstrated the feasibility of constructing *syn*-sesterbicyclo[2.2.2]octene **2** in which three double bonds are disposed in parallel proximity by tandem [4 + 2] cycloadditions. Electrophilic addition to **2** occurs transannularly, resulting in the sequential

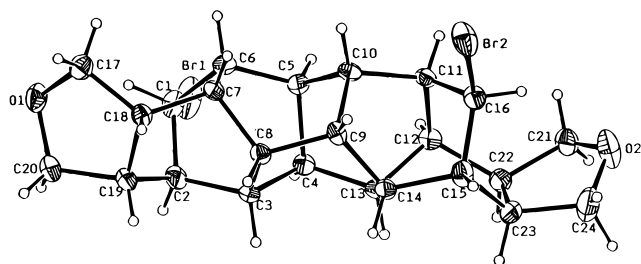
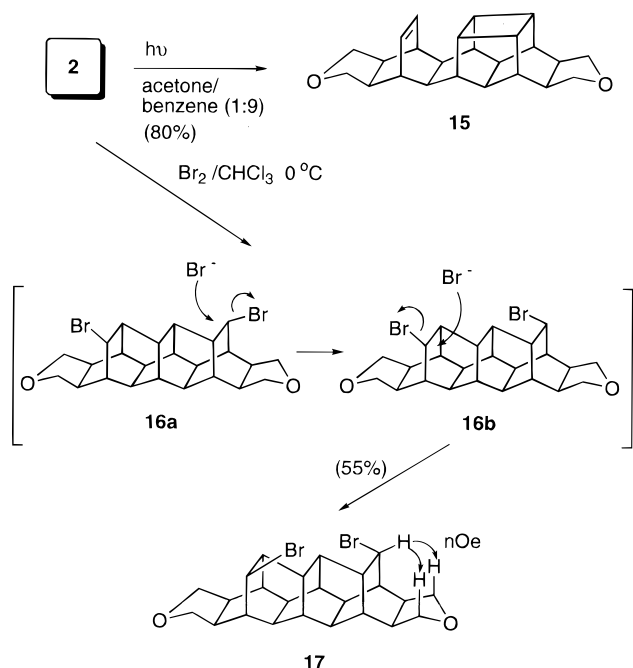


Figure 1. ORTEP diagram of *endo,endo*-dibromide **17**.

(8) The authors have deposited X-ray data with the Cambridge Crystallographic Data Center. The coordinates can be obtained, on request, from the Director, Crystallographic Data Center, 12 Union Road, Cambridge, CB2 1EZ, UK.

(9) A nuclear Overhauser enhancement study was undertaken to determine the relative stereochemistry of two bromine atoms. Irradiation of the proton at 5.08 ppm (CHBr) produced 6.3% and 4.0% enhancement of the protons at the carbons next to oxygen atoms.

Scheme 2



construction of bridges across the double bonds in *N*-type manner to form dibromo adduct 17.

Experimental Section

Melting points were determined in open capillaries (Thomas Hoover) and are uncorrected. Analytical thin-layer chromatography (TLC) was performed on E. Merck silica gel 60F₂₅₄ plate (0.25 mm). Flash chromatography was performed on E. Merck silica gel (230–400 mesh). ¹H-NMR spectra were measured at 300 MHz and ¹³C-NMR at 75.4 MHz, respectively. Chemical shifts referred to TMS or to the residual H in perdeuterated solvents (7.26 ppm for CDCl₃). ¹³C-NMR multiplicities were determined using DEPT pulse sequences. 2D COSY (homo and hetero) experiments were performed with compounds 2 and 9, and MS spectra were determined at 70 eV in the EI mode unless otherwise stated. IR spectra in KBr were determined by FT-IR. Microanalyses were performed by Analytical Centers of National Cheng Kung and Taiwan Universities, Taiwan.

Acid-Catalyzed Dehydration of Ketodiol 4. A mixture of ketodiol 4 (20.2 g, 81.3 mmol), TsOH·H₂O (1.5 g, 7.9 mmol), and triethyl orthoformate (20.0 g, 135.1 mmol) in dry toluene (150 mL) was heated at 100 °C for 36 h under N₂ to the completion of the reaction. After cooling, toluene was removed under reduced pressure. The resulting brown residue was chromatographed on silica gel using gradient 10–40% CH₂Cl₂ in hexane as eluent to give 5 and 6.

(1α,2α,7α,8α,9α,13α)-11-Oxatetracyclo[6.5.2.0^{2,7}.0^{9,13}]-pentadeca-3,5,14-triene (5): white solid (10.5 g, 65%); mp 97–98 °C (hexane); *R*_f 0.65 (CH₂Cl₂); IR (KBr) 3057, 2923, 2861, 1599, 1376, 1106, 926, 740, 693 cm⁻¹; ¹H-NMR (CDCl₃) δ 2.56 (m, 4H), 2.89 (s, 2H), 3.35 (dd, 2H, *J* = 5.4, 8.4 Hz), 3.85 (dd, 2H, *J* = 7.8, 8.1 Hz), 5.35 (m, 2H), 5.50 (m, 2H), 6.34 (dd, 2H, *J* = 3.9, 3.9 Hz); ¹³C-NMR (CDCl₃) δ 39.05(d), 39.85(d), 45.46(d), 72.80(t), 121.06(d), 129.25(d), 134.26(d); HRMS *m/z* calcd for C₁₄H₁₆O: (M⁺) 200.1202, obsd 200.1209. Anal. Calcd for C₁₄H₁₆O: C, 83.96; H, 8.05. Found: C, 83.83; H, 8.05.

(1α,2α,3β,6β,7α,8α,9α,13α)-11-Oxapentacyclo[6.5.2.1^{3,6}.0^{2,7}.0^{9,13}]-hexadeca-4,14-dien-16-one (6): a colorless crystalline solid (4.6 g, 25%); mp 109–111 °C (Et₂O/hexane); *R*_f 0.45 (CH₂Cl₂); IR (KBr) 2931, 2836, 1767, 1344, 1105, 1048, 921, 740, 721, 693 cm⁻¹; ¹H-NMR (CDCl₃) δ 2.51–2.55 (m, 4H), 2.72 (m, 2H), 3.00 (m, 2H), 3.31 (dd, 2H, *J* = 5.7, 8.7 Hz), 3.80 (dd, 2H, *J* = 8.1, 8.4 Hz), 5.72 (dd, 2H, *J* = 4.7, 3.3 Hz), 5.91 (dd, 2H, *J* = 2.4, 2.7 Hz); ¹³C-NMR (CDCl₃) δ 35.12(d), 36.88(d), 47.14(d), 51.51(d), 71.68(t), 128.38(d), 132.35(d), 199.91(s); MS *m/z* (relative intensity) 228 (M⁺, 38), 122 (83), 92 (100), 91 (75), 78 (29);

HRMS *m/z* calcd for C₁₅H₁₆O₂ (M⁺) 228.1151, obsd 228.1154. Anal. Calcd for C₁₅H₁₆O₂: C, 78.92; H, 7.06. Found: C, 78.79; H, 7.09.

(1α,2α,3β,6β,7α,8α,9α,13α)-3,4,5,6-Tetrachloro-16,16-dimethoxy-11-oxapentacyclo[6.5.2.1^{3,6}.0^{2,7}.0^{9,13}]-hexadeca-4,14-diene (7): 3,4,5,6-Tetrachloro-9,10-bis(hydroxymethyl)-13,13-dimethoxytetracyclo[6.2.2.1^{3,6}.0^{2,7}]-trideca-4,11-diene (3) (5.02 g, 11.8 mmol) was mixed with TsOH·H₂O (0.19 g, 1.0 mmol) in dry benzene solution and heated at 80 °C under nitrogen for 18 h using a Dean–Stark trap to remove the water. The reaction was monitored by TLC analysis until 3 disappeared. Solvent was removed under reduced pressure. Aqueous sodium carbonate (10%, 10 mL) was added, and the mixture was extracted with dichloromethane (2 × 30 mL). The dichloromethane extracts were washed with water (30 mL) and brine (20 mL), dried, and evaporated to leave 7 (4.62 g). Flash chromatography on silica gel (EtOAc/hexane, 1:10) furnished 7 (4.46 g, 93%) as a colorless crystalline solid: mp 127–128 °C (EtOAc/hexane); *R*_f 0.74 (1:1, EtOAc/hexane); IR (KBr) 3045, 2930, 1608, 1186, 1121, 927, 760, 741 cm⁻¹; ¹H-NMR (CDCl₃) δ 2.48–2.52 (m, 2H), 2.73 (s, 2H), 2.80 (m, 2H), 3.63 (dd, 2H, *J* = 5.7, 8.7 Hz), 3.50 (s, 3H), 3.50 (s, 3H), 3.84 (dd, 2H, *J* = 8.4, 8.4 Hz), 6.01 (dd, 2H, *J* = 3.6, 4.5 Hz); ¹³C-NMR (CDCl₃) δ 31.89(d), 46.77(d), 50.92(d), 51.52(q), 52.70(q), 71.72(t), 77.28(s), 113.94(s), 127.89(s), 128.69(d); MS *m/z* (relative intensity) 412 (M⁺ + 2, 1.2), 410 (M⁺, 0.95), 379 (9.3), 377 (25), 375 (26), 257 (61), 255 (99), 253 (100), 211 (6.3), 209 (18), 207 (19), 122 (15); HRMS *m/z* calcd for C₁₇H₁₈O₃Cl₄ (M⁺) 410.0012, obsd 410.0022. Anal. Calcd for C₁₇H₁₈O₃Cl₄: C, 49.55; H, 4.40. Found: C, 49.52; H, 4.50.

(1α,2α,3β,6β,7α,8α,9α,13α)-16,16-Dimethoxy-11-oxapentacyclo[6.5.2.1^{3,6}.0^{2,7}.0^{9,13}]-hexadeca-4,14-diene (8): To a solution of 7 (4.40 g, 10.7 mmol) and *tert*-butyl alcohol (14.5 g, 196 mmol) in dry THF (100 mL) was added sodium (11.3 g, 490 mmol) in small pieces over a period of 30 min under nitrogen. The mixture was vigorously stirred under reflux for 48 h. The solution turned to a purple color. The reaction mixture was cooled to room temperature and filtered to remove unchanged sodium. The filtrate was poured into ice–water (30 mL) and extracted with dichloromethane (2 × 60 mL). The combined extracts were washed with brine (30 mL), dried, and concentrated. The resulting residue was subjected to chromatography on silica gel (gradient elution with 0–10% ethyl acetate in hexane) to afford 8 (2.62 g, 89%) as a white solid: mp 130–131 °C (EtOAc/hexane); *R*_f 0.66 (1:1, EtOAc/hexane); IR (KBr) 3062, 2930, 1346, 1262, 1116, 1051, 923, 716 cm⁻¹; ¹H-NMR (CDCl₃) δ 2.47–2.51 (m, 6H), 2.80 (s, 2H), 3.07 (s, 3H), 3.22 (s, 3H), 3.30 (dd, 2H, *J* = 5.4, 8.7 Hz), 3.78 (m, 2H), 5.52 (dd, 2H, *J* = 2.1, 2.1 Hz), 5.64 (m, 2H); ¹³C-NMR (CDCl₃) δ 35.57(d), 39.56(d), 48.03(d), 48.61(d), 49.69(q), 51.84(q), 71.90(t), 120.1(s), 130.58(d), 131.77(d); MS *m/z* (relative intensity) 274 (M⁺, 31), 243 (24), 151 (100), 121 (35); HRMS *m/z* calcd for C₁₇H₂₂O₃ (M⁺) 274.1569, obsd 274.1573. Anal. Calcd for C₁₇H₂₂O₃: C, 74.43; H, 8.08. Found: C, 74.49; H, 8.03.

(1α,2α,3β,6β,7α,8α,9α,13α)-11-Oxapentacyclo[6.5.2.1^{3,6}.0^{2,7}.0^{9,13}]-hexadeca-4,14-dien-16-one (6): To a solution of 8 (100 mg, 0.37 mmol) in dichloromethane (20 mL) was added 3 M perchloric acid (5 mL) at 0 °C over 5 min. After stirring for 6 h, the mixture was poured into 30 mL of cold water, and the organic layer was separated. The aqueous layer was extracted with water (3 × 10 mL), saturated sodium bicarbonate, and brine and dried over anhydrous MgSO₄. Concentration under reduced pressure and chromatography on silica gel using gradient 0–20% EtOAc in hexane as eluent afforded 6 (72 mg, 85%).

(1α,2α,3α,4α,8α,9α,10α,11α,12α,17α)-6-Oxahexacyclo[9.6.2.2^{3,9}.0^{2,10}.0^{4,8}.0^{12,17}]-heneicos-14,18,20-triene-13,16-dione (9): Freshly sublimed *p*-benzoquinone (1.78 g, 16.5 mmol), ketone 6 (3.77 g, 16.5 mmol), and distilled benzene (60 mL) were placed in a round-bottom flask. The reaction mixture was then refluxed under N₂ atmosphere for 18 h. After being cooled, half of the benzene was removed *in vacuo*, and hexane (15 mL) was added for crystallization to yield 9 (5.01 g, 98%). An analytical sample was obtained by recrystallization from CH₂Cl₂/hexane (2:1) as a light-yellowish solid: mp 215–217 °C dec; *R*_f 0.53 (2:1, EtOAc/hexane); IR (KBr) 3048, 2935, 1667, 1377, 1278, 1115, 919, 695 cm⁻¹; ¹H-NMR (CDCl₃) δ 2.19 (s, 2H), 2.47–2.54 (m, 4H), 3.00 (s, 2H), 3.15 (m, 2H), 3.28 (dd, 2H, *J* = 5.4, 8.7 Hz), 3.79 (m, 2H), 5.77 (m, 4H), 6.62 (s, 2H); ¹³C-NMR (CDCl₃) δ 37.71(d), 40.68(d), 42.15(d), 46.90(d), 50.75(d), 71.92(t), 131.93-

(d, two peaks), 142.25(d), 198.84(s); MS m/z (relative intensity) 308 (M^+ , 100), 280 (39), 160 (57), 92 (57), 91 (58); HRMS m/z calcd for $C_{20}H_{20}O_3$ (M^+) 308.1413, obsd 308.1422. Anal. Calcd for $C_{20}H_{20}O_3$: C, 77.90; H, 6.54. Found: C, 77.61; H, 6.43.

(1 α ,2 α ,3 α ,4 α ,8 α ,9 α ,10 α ,11 α ,12 α ,17 α)-6-Oxahexacyclo[9.6.2.2^{3,9}.0^{2,10}.0^{4,8}.0^{12,17}]heneicosane-14,18,20-triene-13,16-diol (10). A solution of cerium(III) chloride heptahydrate (7.69 g, 20.6 mmol) and dione **9** (6.40 g, 20.6 mmol) in methanol (60 mL) was stirred at room temperature for 10 min. Sodium borohydride (0.78 g, 20.6 mmol) was then added in portions at 0 °C and vigorous stirring was continued for 1 h. The cooled reaction mixture was poured into ice-water, and the white solids were filtered off. The filtrate was extracted with dichloromethane (50 mL). The extracts were washed with brine, dried, and concentrated *in vacuo*. The combined solids were recrystallized from 2:1 dichloromethane/hexane to afford diol **10** (5.72 g, 89%) as a white solid: mp 230–232 °C (CH_2Cl_2 /hexane); R_f 0.28 (2:1, EtOAc/hexane); IR (KBr) 3395, 3039, 2924, 1669, 1380, 1032, 912, 712 cm^{-1} ; 1H -NMR ($CDCl_3$) δ 2.10 (m, 4H), 2.30 (br, 2H), 2.46–2.57 (m, 6H), 3.29 (dd, 2H, $J = 5.7, 8.7$ Hz), 3.77 (m, 2H), 4.17 (m, 2H), 5.80 (dd, 2H, $J = 3.3, 4.5$ Hz), 5.87 (dd, 2H, $J = 3.0, 4.7$ Hz), 6.39 (dd, 2H, $J = 2.4, 4.4$ Hz); ^{13}C -NMR ($CDCl_3$) δ 38.11(d), 39.36(d), 44.26(d), 47.39(d), 47.53(d), 65.42(d), 72.02(t), 131.09(d), 132.15(d), 136.46(d); MS m/z (relative intensity) 312 (M^+ , 5), 294(25), 227(27), 129(31), 86(100), 57(61); HRMS m/z calcd for $C_{20}H_{24}O_3$ (M^+) 312.1726, obsd 312.1725. Anal. Calcd for $C_{20}H_{24}O_3$: C, 76.89; H, 7.74. Found: C, 76.65; H, 7.80.

(1 α ,2 α ,3 α ,4 α ,8 α ,9 α ,10 α ,11 α ,12 α ,17 α)-6-Oxahexacyclo[9.6.2.2^{3,9}.0^{2,10}.0^{4,8}.0^{12,17}]heneicosane-13,15,18,20-tetraene (12). To a stirred solution of diol **10** (0.98 g, 3.14 mmol) in dichloromethane (30 mL) at –40 °C was added triethylamine (0.95 g, 9.41 mmol), followed by a solution of methanesulfonyl chloride (0.98 g, 8.56 mmol) in dichloromethane (20 mL). The reaction mixture was stirred for 2 h, allowed to warm to 0 °C over 10 min, diluted with dichloromethane (30 mL), and washed with ice-water (15 mL). The aqueous layer was extracted with dichloromethane (2 \times 10 mL), and the combined organic layers were dried and evaporated to afford the crude dimesylate **11**. The resulting **11** was dried at 0.1 Torr for 1 h (1.39 g, 95%) and used in the next reaction without further purification.

To a solution of sodium iodide (0.92 g, 6.28 mmol) in dry acetone (60 mL) was slowly added a solution of the prepared dimesylate **11** in acetone (60 mL) over 5 min. The stirred reaction mixture was heated at 45 °C for 15 h and then cooled to room temperature. This brown slurry was diluted with dichloromethane (40 mL) and washed with a solution of sodium thiosulfate (1.56 g, 8.28 mmol) in water (50 mL). The aqueous layer was extracted with dichloromethane (3 \times 10 mL), and the combined organic layers were washed with brine (20 mL), dried, and evaporated. The residue was chromatographed (silica gel, eluted with hexane) to afford tetraene **12** (0.48 g, 56% yield from **10**) as a white solid: mp 162–163 °C (Et_2O /hexane); R_f 0.65 (2:1 hexane/ CH_2Cl_2); IR (KBr) 3045, 2924, 2855, 1377, 1109, 923, 718 cm^{-1} ; 1H -NMR ($CDCl_3$) δ 2.13 (s, 2H), 2.37 (m, 2H), 2.43 (m, 4H), 2.89 (s, 2H), 3.26 (dd, 2H, $J = 5.4, 8.3$ Hz), 3.77 (m, 2H), 5.29 (m, 2H), 5.41 (m, 2H), 5.75 (dd, 2H, $J = 3.3, 4.4$ Hz), 5.91 (dd, 2H, $J = 3.0, 4.8$ Hz); ^{13}C -NMR ($CDCl_3$) δ 38.01(d), 41.44(d), 42.35(d), 43.54(d), 47.03(d), 72.11(t), 120.98(d), 129.42(d), 132.03(d), 133.04(d); MS m/z (relative intensity) 278 (M^+ , 1.9), 122 (98), 92 (100), 91 (83), 78 (55); HRMS m/z calcd for $C_{20}H_{22}O$ (M^+) 278.1672, obsd 278.1672. Anal. Calcd for $C_{20}H_{22}O$: C, 86.28; H, 7.97. Found: C, 86.13; H, 8.04.

(1 α ,2 α ,3 α ,4 α ,8 α ,9 α ,10 α ,11 α ,12 α ,13 α ,14 α ,15 α ,16 α ,17 α)-6-Oxaheptacyclo[9.6.2.2^{3,9}.2^{13,16}.0^{2,10}.0^{4,8}.0^{12,17}]tricosane-18,20,22-triene-14,15-dicarboxylic Anhydride (13). A solution of tetraene **12** (0.40 g, 1.44 mmol) and maleic anhydride (0.15 g, 1.53 mmol) in benzene (10 mL, dried over $LiAlH_4$) was stirred under N_2 , and freshly prepared zinc chloride (20 mg, 0.14 mmol, dried with Bunsen burner under vacuum) was added. The reaction mixture was stirred for 18 h at 45 °C and then was diluted with dichloromethane (30 mL) and washed with water (20 mL). The organic layer was dried over $MgSO_4$ and evaporated. Purification of the crude product by silica gel chromatography using 1:1 dichloromethane/hexane as eluent afforded the carboxylic anhydride **13** (0.32 g, 59%) as a white solid: mp 273–274.5 °C (CH_2Cl_2 /hexane); R_f 0.30 (CH_2Cl_2); IR (KBr) 3042, 2922, 1862, 1774, 1232, 1076, 931, 915, 709, 683 cm^{-1} ; 1H -NMR ($CDCl_3$) δ 2.00 (s, 2H), 2.07 (s, 2H), 2.41 (m, 6H), 3.04 (br s, 2H),

3.12 (m, 2H), 3.23 (dd, 2H, $J = 5.1, 8.3$ Hz), 3.75 (m, 2H), 5.31 (dd, 2H, $J = 3.0, 4.5$ Hz), 5.66 (m, 2H), 5.79 (dd, 2H, $J = 3.0, 4.4$ Hz); ^{13}C -NMR ($CDCl_3$) δ 36.90(d), 37.67(d), 40.05(d), 43.10(d), 44.92(d), 46.32(d), 47.29(d), 71.93(t), 130.88(d, two peaks), 131.26(d), 132.09(d), 172.37(s); MS m/z (relative intensity) 376 (M^+ , 81), 347 (5), 306 (7), 304 (7), 122 (72), 92 (100), 78 (61); HRMS m/z calcd for $C_{24}H_{24}O_4$ (M^+) 376.1675, obsd 376.1673. Anal. Calcd for $C_{24}H_{24}O_4$: C, 76.57; H, 6.43. Found: C, 76.54; H, 6.43.

(1 α ,2 α ,3 α ,4 α ,8 α ,9 α ,10 α ,11 α ,12 α ,13 α ,14 α ,15 α ,16 α ,17 α)-14,15-Bis(hydroxymethyl)-6-oxaheptacyclo[9.6.2.2^{3,9}.2^{13,16}.0^{2,10}.0^{4,8}.0^{12,17}]tricosane-18,20,22-triene (14). A solution of anhydride **13** (0.25 g, 0.66 mmol) in anhydrous THF (40 mL) was carefully added dropwise to a stirred mixture of $LiAlH_4$ (0.062 g, 1.63 mmol) in THF (10 mL). After the addition was completed, the mixture was stirred for 6 h and then heated at 60 °C for another 1 h. After cooling to rt, the solution was quenched with water (0.06 mL), 15% $NaOH_{(aq)}$ (0.06 mL), and then water (0.18 mL). The suspension was stirred overnight and then filtered. The residue was acidified with 15% HCl and extracted with dichloromethane. The combined organic solution was dried and evaporated to dryness. The crude product was recrystallized from chloroform/hexane to give **14** (0.18 g, 74%): mp 258–261 °C; R_f 0.55 (EtOAc); IR (KBr) 3293, 3043, 2909, 1646, 1379, 1270, 1180, 1107, 1041, 925, 698 cm^{-1} ; 1H -NMR ($CDCl_3$) δ 2.02 (s, 2H), 2.08 (s, 2H), 2.21 (m, 2H), 2.37–2.45 (m, 8H), 2.84 (br, 2H, -OH), 3.23 (dd, 2H, $J = 5.7, 8.7$ Hz), 3.43–3.58 (m, 4H), 3.75 (m, 2H), 5.25 (dd, 2H, $J = 3.3, 4.7$ Hz), 5.58 (dd, 2H, $J = 3.3, 4.7$ Hz), 5.64 (dd, 2H, $J = 3.0, 4.4$ Hz); ^{13}C -NMR ($CDCl_3$) δ 37.90(d), 40.05(d), 40.64(d), 45.16(d), 45.52(d), 47.40(d), 47.60(d), 64.67(t), 72.05(t), 131.19(d), 131.40(d), 132.11(d); MS m/z (relative intensity) 366 (M^+ , 13), 348 (44), 320 (21), 278 (12), 167 (35), 155 (24), 117 (32), 92 (100), 91 (97), 79 (51); HRMS m/z calcd for $C_{24}H_{30}O_3$ (M^+) 366.2196, obsd 366.2202. Anal. Calcd for $C_{24}H_{30}O_3$: C, 78.65; H, 8.25. Found: C, 78.36; H, 8.33.

(1 α ,2 α ,3 α ,4 α ,8 α ,9 α ,10 α ,11 α ,12 α ,13 α ,14 α ,18 α ,19 β ,20 α)-6,16-Dioxaocacyclo[9.9.2.2^{3,9}.2^{13,19}.0^{2,10}.0^{4,8}.0^{12,20}.0^{14,18}]hexacosane-21,23,25-triene (2). A solution of **14** (0.10 g, 0.27 mmol) in toluene (5 mL) was treated with triethyl orthoformate (1.12 g, 7.56 mmol) and $TsOH \cdot H_2O$ (65 mg, 0.34 mmol). The reaction mixture was then heated under reflux for 24 h using Dean-Stark trap to remove the water. Solvent was evaporated under reduced pressure, and the residue was subjected to chromatography using 10% ethyl ether in hexane as eluent to afford **2** (0.056 g, 60%) as a white solid: mp > 280 °C dec turn brown; R_f 0.21 (20% Et_2O /hexane); IR (KBr) 3044, 2914, 1379, 1033, 927, 688 cm^{-1} ; 1H -NMR ($CDCl_3$) δ 2.01 (s, 4H), 2.32 (m, 2H), 2.38–2.45 (m, 8H), 3.24 (dd, 4H, $J = 8.7, 5.4$ Hz), 3.75 (dd, 4H, $J = 8.1, 8.0$ Hz), 5.28 (dd, 2H, $J = 4.7, 3.0$ Hz), 5.65 (dd, 4H, $J = 4.0, 3.6$ Hz); ^{13}C -NMR ($CDCl_3$) δ 37.92(d), 40.72(d), 45.36(d), 47.42(d), 72.03(t), 131.18(d), 132.10(d); MS m/z (relative intensity) 348 (M^+ , 58), 320 (13), 278 (8), 227 (19), 155 (15), 141 (12), 122 (53), 92 (100), 91 (97), 79 (71); HRMS m/z Calcd for $C_{24}H_{28}O_2$ (M^+) 348.2090, obsd 348.2094. Anal. Calcd for $C_{24}H_{28}O_2$: C, 82.72; H, 8.10. Found: C, 82.69; H, 8.02.

(3 α ,4 α ,5 α ,9 α ,10 α ,11 α ,12 α ,13 α ,14 α ,15 α ,16 α ,20 α ,21 α ,22 α ,23 α)-7,18-Dioxadecacyclo[11.10.1.2^{15,21}.0^{2,10}.0^{3,24}.0^{4,12}.0^{5,9}.0^{11,23}.0^{14,22}.0^{16,20}]-25-hexacosene (15). A solution of octacyclic triene **2** (50 mg, 0.14 mmol) and acetone (2 mL) in benzene (18 mL) was placed in a quartz tube (10 mm o.d. \times 200 mm length). A stream of nitrogen was bubbled through the solution. The solution was irradiated with a 450-W Hanovia medium pressure mercury lamp in a quartz immersion well for 7 h. The solvent was then evaporated *in vacuo* to leave pale yellow solid residue. Purification was accomplished by column chromatography on silica gel (0–25% EtOAc/hexane) and recrystallization (dichloromethane/hexane), furnishing intramolecular cycloadduct **15** (40 mg, 80%): mp > 303 °C dec; R_f 0.51 (1:2 EtOAc/hexane); IR (KBr) 3041, 2919, 1639, 1470, 1384, 1247, 1180, 1105, 1068, 1023, 925, 745 cm^{-1} ; 1H -NMR ($CDCl_3$) δ 1.33 (d, 2H, $J = 0.6$ Hz), 1.45 (d, 2H, $J = 0.6$ Hz), 2.06 (s, 2H), 2.12 (s, 2H), 2.29 (d, 2H, $J = 0.6$ Hz), 2.40 (d, 2H, $J = 0.6$ Hz), 2.46–2.52 (m, 6H), 3.35 (dd, 2H, $J = 6, 8.4$ Hz), 3.57 (dd, 2H, $J = 3, 8.3$ Hz), 3.71 (m, 2H), 3.84 (m, 2H), 6.02 (dd, 2H, $J = 3.6, 4.1$ Hz); ^{13}C -NMR ($CDCl_3$) δ 34.17(d), 35.38(d), 37.45(d), 37.58(d), 37.68(d), 38.67(d), 39.58(d), 42.55(d), 46.69(d), 72.77(t), 73.28(t), 131.07(d); MS m/z (relative intensity) 348 (100), 318 (10), 227 (27), 155 (13), 122 (58), 92 (75), 91(55); HRMS m/z Calcd for

$C_{24}H_{28}O_2$: (M^+) 348.2090, obsd 348.2082. Anal. Calcd for $C_{24}H_{28}O_2$: C, 82.72; H, 8.10. Found: C, 82.62; H, 8.19.

(1 α ,8 α ,9 α ,13 α ,14 α ,15 α ,16 α ,17 α ,18 α ,19 α ,20 α ,24 α ,25 α ,26 α)-endo-2,endo-7-Dibromo-11,22-dioxadecacyclo[13.9.2.0^{3,19}.0^{4,25}.0^{5,17}.0^{6,14}.0^{8,16}.0^{9,13}.0^{18,26}.0^{20,24}]hexaicosane (17). To a stirred solution of octacyclic triene **2** (0.10 g, 0.28 mmol) in dry chloroform (15 mL) at 0 °C was added dropwise over 15 min a solution of bromine (0.051 g, 0.28 mmol) in chloroform (2 mL). The reaction mixture was stirred for 6 h, and the solvent was removed under reduced pressure. The orange-colored oily residue was subjected to chromatography on silica gel using gradient dichloromethane/hexane as eluent to afford dibromide **17** (0.080 g, 55%) as a white solid: mp 213–214 °C (EtOAc/hexane); R_f 0.58 (1:2 CH_2Cl_2 /hexane); IR (KBr) 2927, 2860, 1332, 1285, 1077, 998, 902, 715 cm^{-1} ; 1H -NMR ($CDCl_3$) δ 1.49 (dd, 2H, $J = 6.3, 6.3$ Hz), 1.84 (dd, 2H, $J = 6.3, 6.3$ Hz), 2.08 (m, 4H), 2.21 (d, 2H, $J = 5.4$ Hz), 2.29 (m, 2H), 2.48 (m, 4H), 2.69 (m, 2H), 3.73 (dd, 2H, $J = 6.3, 9.2$ Hz), 3.89 (d, 2H, $J = 9.3$ Hz), 3.95 (m, 4H) 5.08 (d, 2H, $J = 5.7$ Hz); ^{13}C -NMR ($CDCl_3$) δ 31.90-(d), 32.13(d), 32.77(d), 34.97(d), 36.13(d), 36.18(d), 42.32(d), 43.13(d), 43.34(d), 52.34(d), 70.42(t), 72.46(d); MS m/z (relative

intensity) 510 ($M^+ + 4, 9$), 508 ($M^+ + 2, 16$), 506 ($M^+, 8$), 429 (100), 427 (99), 383 (10), 347 (10), 319 (8), 193 (5), 129 (17), 91 (35); HRMS m/z Calcd for $C_{24}H_{28}O_2Br_2$ (M^+) 506.0456, obsd 506.0463. Anal. Calcd for $C_{24}H_{28}O_2Br_2$: C, 56.71; H, 5.55. Found: C, 56.69; H, 5.48.

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Supporting Information Available: 1H - and ^{13}C -NMR spectra for all new compounds (43 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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