Syntheses of 1-Substituted 12-Oxahexacyclo[7.2.1.$0^{2,8}$.$0^{3,7}$.$0^{4,11}$.$0^{6,10}$]dodecanes and Their Transformation into Pentacyclo[6.3.0.$0^{2,6}$.$0^{3,10}$.$0^{5,9}$]undecane Derivatives

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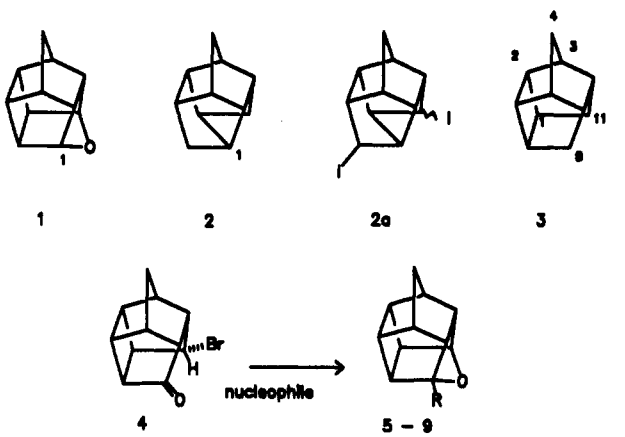
The reaction of nucleophilic reagents (organomagnesium and organosodium compounds containing active methylene groups) with *exo*-11-bromopentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecan-8-one leads to the formation of 1-substituted-12-oxahexacyclo[7.2.1.0^{2,8}.0^{3,7}.0^{4,11}.0^{6,10}]dodecanes which can be used in the synthesis of trishomocubane derivatives. It is shown, using the 1-methyl- and 1-phenyl-substituted 12-oxadodecanes, that iodotrimethylsilane readily cleaves the ether bond at C(1). The resulting carbonium ions rearrange to form 1,7,11-trisubstituted pentacyclo[6.3.0.0^{2,6}.0^{3,10}.0^{5,9}]-undecanes.

The synthesis and chemistry of substituted trishomocubanes have been the subject of several recent reviews.[1,2] The cleavage of the ether bond in 12-oxahexacyclo[7.2.1.0^{2,8}.0^{3,7}.0^{4,11}.0^{6,10}]dodecane (1) by electrophilic reagents leads to the rearrangement of the carbon framework and to the formation of derivatives of pentacyclo[6.3.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane (2).[3] For example, treatment of 1 with iodotrimethylsilane at 90 °C for 150 h gives **2a**.[3] Such reactions offer an entry for the synthesis of 1-substituted trishomocubanes via 1-substituted derivatives of 1. Although no general synthesis of 1-substituted derivatives of 1 has been reported, the extensive investigations of transannular interactions between C(8) and C(11) in derivatives of **3**[2,4] suggest a possible synthetic pathway.



Discussion

We wish to report that *exo*-11-bromopentacyclo-[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecan-8-one,[5] **4**, is a convenient precursor for the preparation of 1-substituted derivatives of **1**. The reactions of methylmagnesium iodide, phenylmagnesium bromide and benzylmagnesium chloride with **1** yield the 1-methyl-, 1-phenyl-, and 1-benzyloxadodecane derivatives **5–7**, respectively. The sodium salts of malonic and cyanoacetic esters react similarly with **1** to give compounds **8** and **9**. Treatment of **4** with sodium methoxide affords **10**. Independent syntheses of **5**[6] and **10**[7] have been reported previously. Ketal **10** appears to arise from an intramolecular S_N2 displacement of bromine via intermediate **11**.[8] The reaction of 11,11-dimethoxypentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecan-8-one (**12**) with phenylmagnesium bromide to yield **13**[9] is consistent with this observation.

When **4** is boiled with methanol a methanolic HBr solution is formed and compound **14** is isolated. The stereochemistry of the methoxy group in **14** follows from the conversion of **14** to the known alcohol **16**. Wolff–Kishner reduction of **14** yields **15** which was demethylated with iodotrimethylsilane to give **16**.[10] The melting point and NMR data for **16** agree with literature values.[10] Unique features in the ^{1}H NMR spectra of derivatives of **3** aid in the assignment of configuration. The *exo*-protons at C(8) and C(11) of **3** exhibit 3–5-Hz couplings with the

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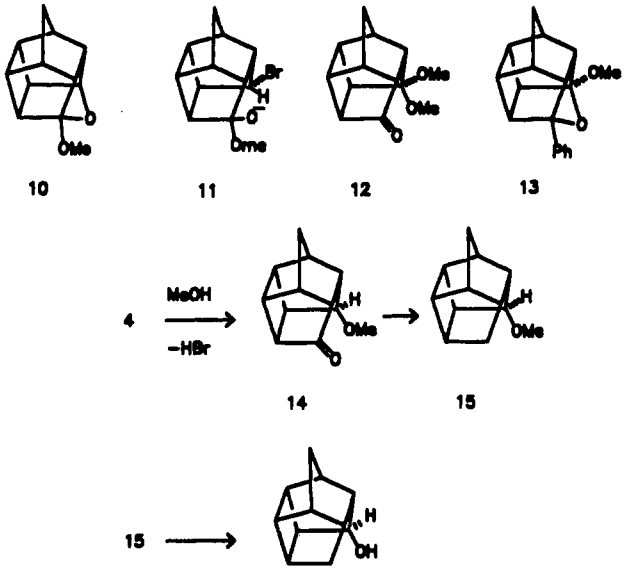
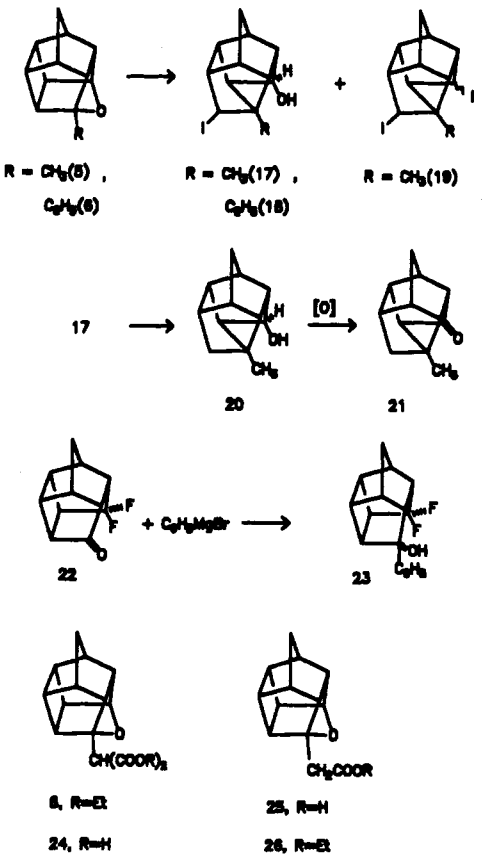


adjacent protons, while the *endo*-protons at C(8) and C(11) of **3** exhibit couplings of less than 1 Hz and frequently appear as singlets.[11] The spectra of several derivatives of **3** are gathered in the supplementary material. The above generalities are observed, e.g. the *endo*-proton at C(11) of **4** is a singlet, while the *exo*-protons at C(11) of **14**, **15**, and **16** are multiplets. In addition, the endo orientation of the electronegative substituent at C(8) in **15** and **16** leads to a strong downfield shift of the C(11) *endo*-proton in these compounds. The endo orientation of the electronegative group has little effect on protons at C(5) and C(6); however, an exo substituent shifts these resonances downfield. Compound **14** is not converted into compound **10** under these conditions. By analogy with the work of Barborak and co-workers,[7] **14** might arise from **10** if **10** is formed by the reaction of methanol with **4**. However, when **10** was boiled in a methanolic HBr solution, no conversion to **14** was observed.

It may appear to be surprising that an S_N2 displacement can take place at C(11) in **4**. However, the cyclohexanone ring of **4** is in a boat conformation with the bromine atom equatorial. Modeling of an S_N2 displacement of the halogen by methoxide indicates that the transition state for **4** → **14** is only 10–15 kcal/mol higher in energy than a similar displacement in *p*-bromocyclohexanone. The approach of methoxide to *p*-bromocyclohexanone leads to an intermediate twist-boat conformation which permits entry of the nucleophile into the face opposite the halogen. Because of the rigidity of **4**, the methoxide initially must enter more obliquely until the hydrogen at C(11) has moved into the plane of the three carbon atoms. In the transition state the O··C··Br angle is calculated to be 160°. If such modeling is meaningful, the S_N2 displacement in this system is energetically allowed. However, the reaction would be expected to be slow due to the geometric constraints upon the trajectory of the attacking group. A carbocation intermediate in **4** → **14** is not likely since the carbocation would rapidly rearrange to the trishomocubane **2**.

The reaction of the oxa-derivatives **5** and **6** with iodotrimethylsilane proceeded smoothly with **17** and **19** isolated from the reaction of **5** and **18** isolated from the reaction of **6**. The C–O bond cleavage in **5** and **6** gives the more stable tertiary carbonium ion which rearranges to the trishomocubane skeleton. X-ray crystal structure analyses of **18** and **19** establish these assignments. The ^{1}H NMR spectra of **17**, **18**, and **19** each contain two signals in the 4 ppm region assigned to CHX resonances, while the starting materials **5** and **6** have only one such CHX signal. The C*H*OH proton and the OH proton are doublets with coupling constants of 8.4 Hz which disappear in the presence of CD_3OD. Reduction of **17** with zinc in acetic acid yields the alcohol **20**, which upon oxidation with Jones



reagent gives **21**, an isomer of the previously isolated 1-methylpentacyclo[6.3.0.0^{2,6}.0^{3,10}.0^{5,9}]undecan-11-one.[12]

In contrast to the reaction of bromoketone **4**, difluoro ketone **22**[13] reacts with phenylmagnesium bromide to give alcohol **23** without subsequent S_N2 displacement of fluoride. The hydroxy proton resonance of **23** is a doublet of doublets due to coupling with the fluorine atoms; J_{HF}(endo) = 31.2 Hz and J_{HF}(exo) = 2 Hz. The addition of CD_3OD to **23** eliminates the couplings in the ^{19}F spectrum.

The substituted malonic ester derivative **8** can be used to prepare a variety of other 1-substituted derivatives of **1**. Hydrolysis of **8** with alcoholic KOH gives the malonic acid derivative **24**, which upon thermal decarboxylation yields **25**. Reaction of **25** with thionyl chloride provides the acid chloride which upon treatment with ethanol yields the ester **26**.[14]

Reaction of either **24** or **25** with iodotrimethylsilane does not lead to isolable iodo derivatives of trishomocubane. Each reaction mixture contains silated starting material and several diiodides that are not easily separated. When alcohol **27**, obtained from the $LiAlH_4$ reduction of **26**, is

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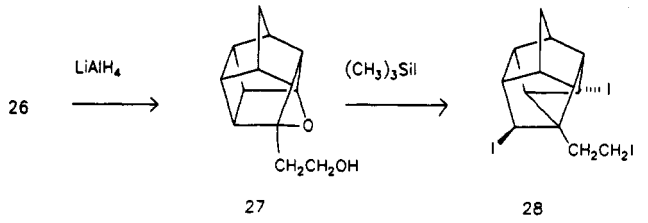

26 27 28

reacted with iodotrimethylsilane, the triiodo derivative 28 of trishomocubane is obtained. The stereochemistries of the iodo substituents in 28 are assumed to be that of 19.

It has been demonstrated that 1-substituted oxadecane derivatives of 1 can be prepared conveniently from bromo ketone 4. Reaction of some of these 1-substituted oxadecanes with iodotrimethylsilane lead to 1,7,11-trisubstituted trishomocubanes in good yields.

Experimental Section

General. All ^1H NMR and ^{13}C NMR spectra were recorded at 200 MHz using hexamethyldisiloxane as reference in $CDCl_3$ or at 500 MHz with TMS as reference. Column chromatography was performed on silica gel. All X-ray data were collected by standard techniques and the structures solved by direct methods.[15]

General Procedure for Grignard Reactions with *exo*-11-Bromopentacyclo[5.4.9.0^{2,6}.0^{3,10}.0^{5,9}]undecan-8-one (4)[5]. To 2 mol of alkyl- or arylmagnesium reagent[16] in ether was added dropwise with stirring a solution of 1 mol bromo ketone 4 in THF. After 2 h the reaction mixture containing excess organomagnesium reagent was treated with water followed by a saturated solution of NH_4Cl. The ether layer was separated and the water layer extracted with additional ether, and the combined ether layers were washed with sodium bisulfite, 10% NaOH, and then water. The ether was removed and the reaction product purified by either distillation or silica gel chromatography.

1-Methyl-12-oxahexacyclo[7.2.1.0^{2,8}.0^{3,7}.0^{4,11}.0^{6,10}]-dodecane (5). CH_3MgI (11.0 g, 66 mmol) in dry ether was reacted with 7.15 g (30 mmol) of 4 in dry THF. After isolation of the crude product, 4.6 g of pure 5 were obtained by distillation: yield 88%, bp 119 °C (28 mm), lit.[6] 60 °C (1 mm).

1-Phenyl-12-oxahexacyclo[7.2.1.0^{2,8}.0^{3,7}.0^{4,11}.0^{6,10}]dodecane (6). PhMgBr (11.96 g, 66 mmol) in dry ether was reacted with 7.15 g (30 mmol) of 4 in dry THF. After isolation of the crude product, 6.02 g of pure 6 were obtained by column chromatography, eluent (hexane–ethyl acetate 10:1): yield 85%, mp 54–55 °C; ^1H NMR ($CDCl_3$) δ 1.92 and 1.56 (AB dd, J_{AB} = 10.6 Hz, CH_2), 2.43 (m, 1 H), 2.60 (m, 4 H), 2.85 (m, 3 H), 4.85 (t, 1 H), 7.12–7.36 (m, 5 H). Anal. Calcd for $C_{17}H_{16}O$: C, 86.40; H, 6.83. Found: C, 86.48; H, 6.85.

1-Benzyl-12-oxahexacyclo[7.2.1.0^{2,8}.0^{3,7}.0^{4,11}.0^{6,10}]dodecane (7). $C_6H_5CH_2MgCl$ (9.95 g, 66 mmol) in dry ether was reacted with 7.15 g (30 mmol) of 4 in dry THF. After isolation of the crude product, 5.4 g of pure 7 were obtained by distillation: yield 72%, bp 142–143 °C (0.15 mm), mp 61–62 °C; ^1H NMR ($CDCl_3$) δ 1.75 and 1.36 (AB dd, J_{AB} = 10.4 Hz, CH_2), 1.86 (m, 1 H), 2.25–2.50 (m, 5 H), 2.70 (m, 2 H), 3.06 (m, 2 H, CH_2Ph), 4.67 (t, 1 H), 7.19 (5 H, C_6H_5). Anal. Calcd for $C_{18}H_{18}O$: C, 86.36; H, 7.25. Found: C, 86.25; H, 7.13.

Diethyl 12-Oxahexacyclo[7.2.1.0^{2,8}.0^{3,7}.0^{4,11}.0^{6,10}]dodecane-1-malonate (8). To a precooled (ice bath) solution of sodium malonic ester in alcohol (0.6 g of sodium, 50 mL of ethanol, 4.2 g of diethyl malonate) was added dropwise a solution of 6.27 g (26 mmol) of bromo ketone 4 in 120 mL of ethanol (dissolved without heating). After standing for 12 h at 20 °C, the reaction mixture was poured into water and extracted with ether. The ether solution was dried (Na_2SO_4), and the solvent was removed. Purification by distillation gave 5.9 g (71%) of 8, bp 157–159 °C (0.15 mm). The analytical specimen was purified additionally by chromatography over silica gel (hexane–ethyl acetate 6:1): ^1H NMR ($CDCl_3$) δ 1.21 (t, 6 H, $2CH_3$), 1.84 and 1.46 (AB dd, J_{AB} = 10.6 Hz, CH_2), 2.29–2.91 (m, 8 H), 3.93 (s, 1 H), 4.15 (m, 4 H, $-OCH_2-$), 4.71 (m, 1 H). Anal. Calcd for $C_{18}H_{22}O_5$: C, 67.90; H, 6.97. Found: C, 67.91; H, 6.96.

Ethyl α-cyano-12-oxahexacyclo[7.2.1.0^{2,8}.0^{3,7}.0^{4,11}.0^{6,10}]dodecane-1-acetate (9) was prepared as described above by reacting 0.6 g of Na and 2.96 g of ethyl cyanoacetate (26.2 mmol) with 6.27 g (26.2 mmol) of 4. After isolation of the crude product, 4.76 g of pure 9 were obtained by chromatography over silica gel (hexane–ethyl acetate 5:1): yield 67%, bp 153–154 °C (0.15 mm); ^1H NMR ($CDCl_3$) δ, 1.27 (t, CH_3), 1.90 and 1.52 (AB dd, J_{AB} = 10.8 Hz, CH_2), 2.40–2.85 (m, 8 H), 3.95 (s, 1 H), 4.20 (q, OCH_2, 2 H), 4.78 (t, 1 H). Anal. Calcd for $C_{16}H_{17}NO_3$: C, 70.83; H, 6.32. Found: C, 70.82; H, 6.44.

1-Methoxy-12-oxahexacyclo[7.2.0.0^{2,8}.0^{3,7}.0^{4,11}.0^{6,10}]dodecane (10). To a sodium methoxide solution (0.92 g, 40 mmol) of Na in 120 mL of MeOH was added a solution of the bromo ketone 4 (4.8 g, 20 mmol, dissolved in 150 mL of MeOH without heating). After 3 h at rt the solution was diluted with water and extracted with ether. The ether layer was dried over Na_2SO_4, and the solvent was removed. Distillation gave 3.47 g (91%) of 10: bp 87–88 °C (0.15 mm); ^{13}C NMR ($CDCl_3$) δ 39.79(d), 39.87-(d), 39.96(d), 40.89(d), 41.66 (t, CH_2), 42.71(d), 43.32(d), 51.14-(d), 51.43 (q, OCH_3), 52.98(d), 79.61(d), 120.95(s). The ^1H NMR spectrum is similar to that reported by Barborak et. al.[7]

***endo*-11-Methoxypentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecan-8-one (14).** A solution of 4.8 g (20 mmol) of bromo ketone 4 in 100 mL of methanol was boiled for 4 h. The excess methanol was removed under reduced pressure, and the residue was purified by chromatography over silica gel (hexane–ethyl acetate 6:1) and by distillation: yield, 2.94 g (77%); bp 118 °C (0.1 mm), 182 °C (28 mm); ^1H NMR ($CDCl_3$) δ, 1.09 and 1.46 (AB dd, J_{AB} = 11 Hz, CH_2), 1.91 (m, 1 H), 2.02–2.66 (m, 7 H), 3.27 (H11, $J_{1,11}$ = 4.8 Hz, $J_{10,11}$ = 3.8 Hz); ^{13}C NMR ($CDCl_3$) δ 36.2(6), 37.5(4), 39.3(1), 39.5-(7), 40.2(2), 41.0(5), 43.6(3), 48.9(9), 50.1(10), 79.4(11), 215.0(8). Anal. Calcd for $C_{12}H_{14}O_2$: C, 75.76; H, 7.42. Found: C, 75.63; H, 7.50.

***endo*-8-Methoxypentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane (15).** The reduction of 6.9 g (36 mmol) of 14 by 11 mL (98%) of hydrazine hydrate in diethylene glycol was carried out using the procedure of Dekker and Oliver:[10] yield 5.3 g (83%); bp 123–124 °C (30 mm); ^1H NMR ($CDCl_3$) δ 1.01 and 2.29 (AB dd, J_{AB} = 11.4 Hz, C(11)H_2), 1.20 and 1.71 (AB dd, J_{AB} = 10.2 Hz, C(4)H_2), 2.20–2.69 (m, 8 H), 3.44 (1 H, J ambiguous); ^{13}C NMR ($CDCl_3$) δ 28.3(11), 35.0(4), 35.8(1), 35.9(7), 39.2(6), 42.0(10), 42.1(2), 42.5-(5), 42.6(9), 46.9(3), 82.6(8). Anal. Calcd for $C_{12}H_{16}O$: C, 81.77; H, 9.15. Found: C, 81.65; H, 9.05.

***endo*-Pentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecan-8-ol (16).** A mixture of 0.92 g (5.2 mmol) of methoxyundecane (15) in 2 mL (2.8 g, 14 mmol) of iodotrimethylsilane was allowed to stand for 3 h at 20 °C. The excess of iodotrimethylsilane was removed under reduced pressure (20 mm), and the residue was decomposed carefully with water and then extracted with ether and washed with a 5% $NaHSO_3$ solution. The ether solution was dried with Na_2SO_4, and the solvent was removed by distillation. The reaction products were separated by chromatography on silica gel (hexane–ethyl acetate 5:1). Yield, 0.17 g of 16 (59% yield based on reacted methoxyundecane 15) and 0.6 g of starting material. A mixed melting point (mp 231 °C, lit.[10] 231–232 °C) with an authentic sample of 16 (by synthesis) gave no depression: ^1H NMR ($CDCl_3$) δ 1.08 and 2.32 (AB dd, C(11)H_2), 1.17 and 1.71 (AB dd, C(4)H_2), 2.21–2.73 (m, 8 H), 3.95 (H(8), $J_{7,8}$ = 4.5 Hz, $J_{8,9}$ = 3.5 Hz); ^{13}C NMR ($CDCl_3$) δ 28.7(11), 35.0(4), 35.9(1), 38.7(7), 39.8-(6), 41.9(2,10), 43.0(5), 45.6(9), 46.9(3), 74.0(8).

Procedure for the Reaction of Compounds 5 and 6 with Iodotrimethylsilane. Compound 5 or 6 was mixed with iodotrimethylsilane in a 1:3 molar ratio at 20 °C. After 1 h the excess iodotrimethylsilane was removed under reduced pressure (20 mm). On cooling, the residue was decomposed carefully with water, extracted with ether, and washed with a 5% $NaHSO_3$ solution and then water. After removal of the ether, the reaction products were separated by chromatography. In the case of

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compound 6 only product 18 was characterized; the mixture of diiodides was tar-like, dense, highly colored, and difficult to separate.

11-*exo*-Iodo-1-methylpentacyclo[6.3.0.0^{2,6}.0^{3,10}.0^{5,9}]undecan-7-*endo*-ol (17). 6.97 g (40 mmol) of 5 was reacted with 24 g (17 mL, 120 mmol) of $(CH_3)_3SiI$ to give 3.75 g (31% yield) of chromatographically recovered 17 [mp 103–104 °C; IR ν 3610 cm^{-1}; ^{1}H NMR δ 1.29 (s, 2 H, CH_2), 1.42 (s, CH_3), 1.58 (s, 1 H, OH), 1.67 (m, 1 H), 1.87 (m, 1 H), 2.1 (m, 2 H), 2.21 (m, 1 H), 2.34 (m, 1 H), 2.97 (m, 1 H), 3.92 (s, 1 H), 4.18 (s, 1 H). Anal. Calcd for $C_{12}H_{15}OI$: C, 47.70; H, 5.00; I, 42.00. Found: C, 47.80; H, 4.96; I, 42.08] and 3.04 g (18.5%) of **7-*exo*,11-*exo*-Diiodo-1-methylpentacyclo[6.3.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane (19)** [mp 113–114 °C; ^{1}H NMR 1.09 (S,CH_3), 1.36 (br s, 2 H, CH_2), 1.60 (t, 1 H), 2.05 (m, 1 H), 2.28 (m, 3 H), 3.15 (m, 1 H), 3.21 (m, 1 H), 3.91 (s, 1 H), 4.13 (s, 1 H). Anal. Calcd for $C_{12}H_{14}I_2$: C, 34.98; H, 3.43;, I, 61.63. Found: C, 35.12; H, 3.34; I, 61.83].

11-*exo*-Iodo-1-phenylpentacyclo[6.3.0.0^{2,6}.0^{3,10}.0^{5,9}]undecan-7-*endo*-ol (18). Ether 6 (2.36 g, 10 mmol) was reacted with 6 g (4.3 mL, 30 mmol) of $(CH_3)_3SiI$ to yield 1.64 g of chromatographically recovered 18: yield 45%, mp 141–142 °C; IR ν 3610 cm^{-1}; ^{1}H NMR 1.00 (d, 1 H, OH), 1.43 (s, CH_2), 2.16 (m, 1 H), 2.30 (m, 1 H), 2.47 (m, 3 H), 2.79 (t, 1 H), 3.11 (m, 1 H), 4.04 (d, C*H*OH), 4.16 (1 H, CHI), 7.34 (m, 5 H, C_6H_5). Anal. Calcd for $C_{17}H_{17}OI$: C, 56.06; H, 4.70; I, 34.84. Found: C, 56.13; H, 4.54; I, 34.42.

1-Methylpentacyclo[6.3.0.0^{2,6}.0^{3,10}.0^{5,9}]undecan-7-*endo*-ol (20). Iodo derivative 17 (6.0 g, 20 mmol) was reduced by an excess of zinc dust in acetic acid.[17] The alcohol 20 and its acetate were boiled in a solution of KOH in methanol for 3 h. The yield was 3.17 g (90%) of 20; mp 108–109 °C (eluted from silica gel with hexane–ethyl acetate 5:1); IR ν 3610 cm^{-1} (OH); ^{1}H NMR δ 1.23 (br s, 2 H, CH_2), 1.27 (m, 2 H, CH_2), 1.36 (s, CH_3), 1.48 (br s, OH), 1.63 (br s, 1 H), 1.83 (m, 2 H), 1.97 (m, 3 H), 2.22 (m, 1 H), 4.10 (br s, C*H*OH). Anal. Calcd for $C_{12}H_{16}O$: C, 81.77; H, 9.15. Found: C, 81.60; H, 9.06.

1-Methylpentacyclo[6.3.0.0^{2,6}.0^{3,10}.0^{5,9}]undecan-7-one (21). Alcohol 20 (1.76 g, 10 mmol) was oxidized through use of the Jones reagent,[18] and 1.65 g (95% yield) of product was purified by sublimation at 100 °C (20 mm): mp 88–89 °C; ^{1}H NMR δ 1.15 (s, CH_3), 1.38–1.47 (m, 2 H), 1.55–1.70 (m, 3 H), 1.84 (m, 1 H), 2.02 (m, 1 H), 2.31 (m, 1 H), 2.47 (m, 3 H). Anal. Calcd for $C_{12}H_{14}O$: C, 82.72; H, 8.10. Found: C, 82.69; H, 8.09.

11,11-Difluoro-8-phenylpentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecan-8-*endo*-ol (23). To a precooled (ice bath) solution of phenylmagnesium bromide (0.50 g, 20 mol, Mg, and 3.15 g, 20 mmol, bromobenzene in 100 mL of ether) was added dropwise a solution of 1.96 g of difluoro ketone 22[13] in 70 mL of ether. After stirring for 3 h at 20 °C, the excess phenylmagnesium bromide was decomposed with water and a saturated solution of NH_4Cl. The ether layer was separated and dried (Na_2SO_4). The ether was removed, and the reaction mixture separated by chromatography over silica gel (hexane–ethyl acetate 5:1): yield 2.16 g (79%), mp 114–115 °C; ^{1}H NMR δ 1.54 and 1.11 (AB dd, J_{AB} = 11 Hz, CH_2), 1.85 (br s, 1 H), 2.68 (m, 5 H), 2.9 (m, 1 H), 3.23 (m, 1 H), 3.62 (dd, OH, J_{HF} = 31.2 Hz, 2 Hz), 7.18–7.30 (5 H, C_6H_5); ^{19}F NMR 101.35 and 104.15 (F_A and F_B of AB system, J_{AB} = 237 Hz, J_{HF} = 31.2 Hz). Anal. Calcd for $C_{17}H_{16}F_2O$: C, 74.43; H, 5.88; F, 13.85. Found: C, 74.57; H, 5.79; F, 13.76.

12-Oxahexacyclo[7.2.1.0^{2,8}.0^{3,7}.0^{4,11}.0^{6,11}]dodecane-1-malonic Acid (24). To 5 g (15.7 mmol) of diester 8 dissolved in 25 mL of anhydrous ethanol was added a solution of 4 g of KOH in 80 mL of anhydrous methanol, and the mixture allowed to stand for 48 h at 20 °C. Water (100 mL) was added and the alcohol was distilled off under reduced pressure (20 mm) at 50–60 °C. After cooling in an ice bath, the solution was carefully acidified with 20% HCl. The precipitated diacid was filtered, washed with cold water, and crystallized from aqueous methanol. Water of crystallization was removed at 60 °C (0.1 mm) over P_2O_5: yield 2.85 g (69%), mp 125 °C (with decomposition); ^{1}H NMR: δ 1.86 and 1.49 (AB dd, J_{AB} = 10.6 Hz, CH_2), 2.39 (m, 2 H), 2.50–3.00 (m, 6 H), 3.86 (s, 1 H), 4.70 (m, 1 H); ^{13}C NMR δ 39.72(d), 40.79-(d), 41.73 (t, CH_2), 42.95(d), 43.18(d), 43.44(d), 44.95(d), 53.13-(d), 53.25(d), 55.44(d), 84.06(d), 93.19(s), 167.89(s), 168.02(s). Anal. Calcd for $C_{14}H_{14}O_5$: C, 64.11; H, 5.38. Found: C, 63.99; H, 5.27.

12-Oxahexacyclo[7.2.1.0^{2,8}.0^{3,7}.0^{4,11}.0^{6,10}]dodecane-1-acetic Acid (25). The diacid 24 (10.5 g, 45 mmol) was heated at 125–150 °C in an oil bath until CO_2 elimination ceased. The residue was crystallized from hexane–ethyl acetate 3:1: yield 5.35 g (61%), mp 87–88 °C; ^{1}H NMR δ 1.86 and 1.49 (AB dd, J_{AB} = 10.6 Hz, CH_2), 2.38 (m, 2 H), 2.59 (m, 4 H), 2.76 (m, 2 H), 2.83 (s, CH_2CO), 4.75 (t, 1 H), 8.60 (br s, OH). Anal. Calcd for $C_{13}H_{14}O_3$: C, 71.54; H, 6.47. Found: C, 71.43; H, 6.46.

Ethyl 12-Oxahexacyclo[7.2.1.0^{2,8}.0^{3,7}.0^{4,11}.0^{6,11}]dodecane-1-acetate (26). The decomposition product from 10.5 g (45 mmol) of diacid 24, as described above, was treated without purification with 12 mL of $SOCl_2$ at 90 °C until the cessation of HCl elimination. The excess $SOCl_2$ was removed under reduced pressure (20 mm), and 50 mL of anhydrous ethanol was added to the residue. After 2 h the reaction mixture was distilled: yield 8.3 g (84%), bp 133–134 °C (0.15 mm). The spectral characteristics were identical to those in the literature.[14]

12-Oxahexacyclo[7.2.1.0^{2,8}.0^{3,7}.0^{4,11}.0^{6,10}]dodecane-1-ethanol (27). To 0.92 g (24.2 mmol) of $LiAlH_4$ in ether (15 mL) was added with stirring a solution of 6.0 g (24.4 mmol) of 26 in ether (25 mL). After stirring for 2 h at 20 °C, a solution of water (10 mL) and THF (15 mL) was added. The ether layer was separated and solvent removed giving 4.28 g (86% yield) of 27, bp 141–142 °C (0.15 mm): ^{1}H NMR δ 1.5 and 1.93 (H_A and H_B of AB system, J_{AB} = 11 Hz), 2.07 (m, 2 H, CH_2), 2.30–2.90 (m, 9 H), 3.78 (t, 2 H, J = 6 Hz), 4.74 (t, 1 H, J = 4 Hz). Anal. Calcd for $C_{13}H_{16}O_2$: C, 76.46; H, 7.90. Found: C, 76.23; H, 7.69.

1-(7,11-Diiodopentacyclo[6.3.0.0^{2,6}.0^{3,10}.0^{5,9}]undecyl-1)2-iodoethane (28). A solution of 3.2 g (15.6 mmol) of 27 and iodotrimethylsilane (20 mL) was allowed to stand for 1 h at 20 °C. The excess iodotrimethylsilane was removed under reduced pressure (20 mm), the residue dissolved in ether (60 mL), washed with 5% $NaHSO_3$ (50 mL), and then 50 mL of water. The ether layer was dried over Na_2SO_4. The oily residue was redissolved in ether yielding a solid which was recrystallized from ethyl acetate yielding 2.6 g (30%) of 28: mp 144–145 °C dec; ^{1}H NMR δ 1.43 (br s, CH_2, 2 H), 1.66 (m, 1 H), 1.99–2.37 (m, CH_2, 2 H), 2.37(br s, 4 H), 3.05 (m, CH_2, 2 H), 3.23 (m, 1 H), 4.13 (s, 1 H). Anal. Calcd for $C_{13}H_{15}I_3$: C, 28.28; H, 2.74, I, 68.98. Found: C, 28.23; H, 2.51; I, 68.75.

X-ray Data. Compound 18. Monoclinic, space group $P2_1/c$, a = 8.664(2), b = 20.407(8), c = 7.928(1) Å, β = 101.46(2)°, V = 1373.8(6) Å^3, Z = 4, D_x = 1.760 g cm^{-3}, R = .0378, R_w = 0.0368 for 2684 reflections, 241 parameters, absorption correction, S = 1.737, $(\Delta/\sigma)_{max}$ = 0.002, Mo Kα radiation. Compound 19. Triclinic, $P\bar{1}$, a = 6.452(2), b = 8.883(2), c = 10.972(3) Å, α = 97.35(2), β = 102.67(2), γ = 98.10(2)°, V = 599.1(3) Å^3, Z = 2, D_x = 2.280 g cm^{-3}, R = 0.0474, R_w = 0.0781 for 2552 reflections, 151 parameters, absorption correction, S = 2.925, $(\Delta/\sigma)_{max}$ = 0.018.

Theoretical Calculations. Energies and transitions state pathways were modeled using AMPAC,[19] MOPAC,[20] and MM3.[21]

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Supplementary Material Available: NMR data for 3, 8-oxo-3, 4, 14, 15, and 16 and X-ray data for compounds 18 and 19 (13 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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