Mechanistic Study of Base-Promoted Rearrangement of 1,5-Dibromopentacyclo[5.3.0.0^{2,5}.0^{3,9}.0^{4,8}]decane-6,10-dione to 10-Oxa-9-oxopentacyclo[5.3.0.0^{2,4}.0^{3,6}.0^{5,8}]decane-3-carboxylic Acid

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(Received March 4, 1993)

The conversion of 1,5-dibromopentacyclo[5.3.0.0^{2,5}.0^{3,9}.0^{4,8}]decane-6,10-dione (**1**) to 10-oxa-9-oxopentacyclo [5.3.0.0^{2,4}.0^{3,6}.0^{5,8}]decane-3-carboxylic acid (**6**) on treatment with 5% aqueous potassium hydroxide was shown to proceed through 1, *exo*-7-dibromo-9-oxotetracyclo[4.3.0.0^{2,5}.0^{3,8}]nonane-*endo*-4-carboxylic acid (**2**). Treatment of **1** with the base in heavy water gave rise to 2-*d*-**6** deuterated at the 2-position, but **2** gave the protium analog **6** after the same treatment. These results are discussed in relation to reactions of similar compounds which have been previously described in the literature.

Since the first successful synthesis of the cubane ring skeleton was accomplished by employing the base-promoted "quasi Favorskii" or "semibenzylic acid" rearrangement of α-halo ketones, several synthetic and mechanistic studies involving these interesting cage compounds have appeared.[1—6] Some non-enolizable α-halo ketones undergo ring opening in a type of Haller–Bauer cleavage[7] instead of the normal Favorskii-type ring contraction.

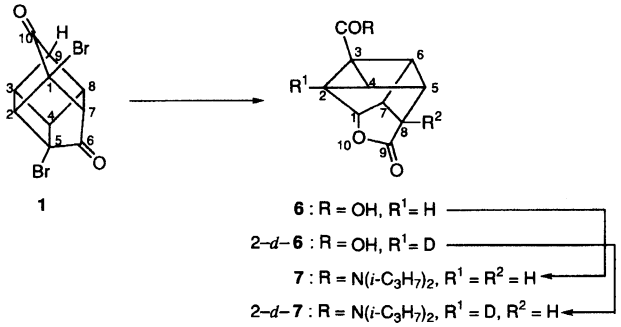
In our previous paper, we described the base-promoted rearrangement of 1,5-dibromopentacyclo-[5.3.0.0^{2,5}.0^{3,9}.0^{4,8}]decane-6,10-dione (**1**) to a new cage compound, 10-oxa-9-oxopentacyclo[5.3.0.0^{2,4}.0^{3,6}.0^{5,8}]-decane-3-carboxylic acid (**6**).[8] This paper describes the nature of this rearrangement.

Results and Discussion

In order to estimate the mechanism of the formation of **6**, 1,5- and 5,9-dibromo-1,3-bishomocubanes (**1** and **3**), 1,*exo*-7-dibromo-9-oxotetracyclo[4.3.0.0^{2,5}.0^{3,8}]-nonane-*endo*-4-carboxylic acid (**2**) and its 4-deuterio analog (4-*d*-**2**), and 1- and 8-bromo-4-homocubanecarboxylic acids (**4** and **5**) were examined under a variety of conditions. Compound **2** was assumed to be an intermediate in the conversion of **1** to **6** on the basis of a mechanistic proposal.

Compounds **1**,[8] **3**,[1,6] **4**,[1,6] and **5**[8] were prepared according to procedures described in the literature. Treatment of **4** with hydrogen bromide (33%) in acetic acid at 70 °C resulted in rapid addition of HBr, producing **2** in a 22% yield. Reaction of **4** with deuterium bromide in AcOD afforded 4-*d*-**2** in an 18% yield. The bromine atom on the 7-position and the carboxyl group on the 4-position were assigned as *exo*- and *endo*-configurations, respectively, based on the ^{1}H NMR spectral data, compared with those described in the literature.[9]

Reaction of non-enolizable α-halo ketones (**1**, **2**, and 4-*d*-**2**) with aqueous potassium hydroxide was studied under a variety of conditions (Table 1 and Schemes 1 and 2). When **1** was treated with 25% aqueous hydroxide solution under reflux, **6** or any other identifiable material could not be obtained. Treatment of **1** with



Scheme 1.

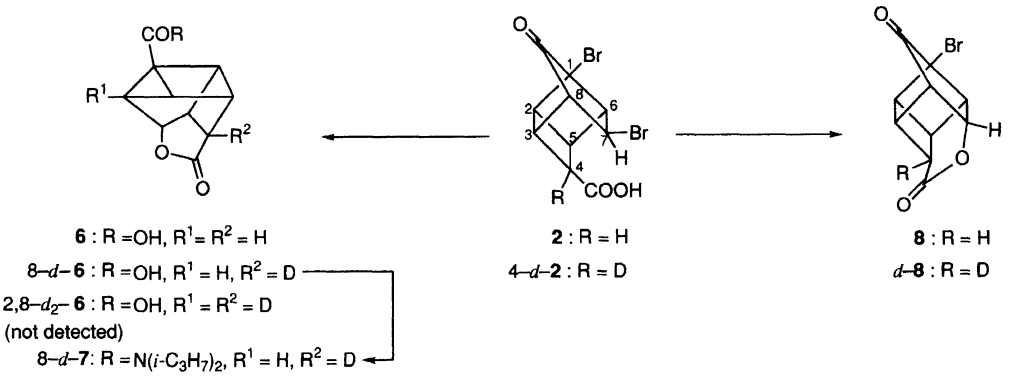
10% aqueous potassium hydroxide in refluxing water yielded **6** in a 25% yield. When **1** was treated with 5% aqueous potassium hydroxide at 60 °C, **6** was produced in a less than 5% yield and unchanged **1** was recovered in a high yield. The optimum conditions for the formation of **6** involved the reaction of **1** with 5% aqueous potassium hydroxide at 80 °C for 15 min. Treatment of **1** in heavy water gave 2-*d*-**6** deuterated at the 2-position. The position of the deuterium was determined on the basis of the ^{1}H NMR spectrum of amide derivative 2-*d*-**7**, compared with that of the protium analog **7**. From the NMR spectra of **7** and 2-*d*-**7**, it was shown that the characteristic double–doublet, J=6 and 3 Hz, at δ=2.58 assigned to the proton on the 2-position of **7** disappeared, and the double–double–doublet, J=8, 4, and 1 Hz, at δ=5.71 assigned to the proton on the 1-position of **7** changed to the double–doublet, J=8 and 1 Hz, at δ=5.72 assigned to the proton on the 1-position of 2-*d*-**7**. These results revealed that deuterium was introduced exclusively at the 2-position.

As proof that **2** is a key intermediate in the conversion of **1** to **6**, **2** was subjected to further treatment with 5% potassium hydroxide in water. Treatment of **2** with the base in water or in heavy water yielded only the protium analog **6** (Scheme 2). When the deuterated analog 4-*d*-**2** was treated under the same conditions, only 8-*d*-**6**, deuterated at the 8-position, was obtained in a good yield without the formation of dideuterio analog 2,8-d_2-**6**, deuterated at the 2- and 8-positions. Interestingly,

Table 1. Reaction of **1**, **2**, and 4-*d*-**2** with Aqueous Potassium Hydroxide

Entry	Substrate	Conditions			Product	(Yield)[a]
		Base	Temp/°C	Time		%
1	**1**	25% KOH	Water/ref[b]	3.5 h	—[c]	
2	**1**	10% KOH	Water/ref[b]	10 min	**6**	(25)
3	**1**	5% KOH	60	6 h	**6**	(less than 5)
4	**1**	5% KOH	80	15 min	**6**	(88)
5	**1**	5% KOD[d]	80	15 min	2-*d*-**6**	(50)
6	**2**	5% KOH	80	15 min	**6**	(88)
7	**2**	5% KOD[d]	80	15 min	**6**	(72)
8	**2**	pH 9[e]	90	30 min	**8**	(88)
9	4-*d*-**2**	5% KOH	80	15 min	8-*d*-**6**	(77)
10	4-*d*-**2**	5% KOD[d]	80	15 min	8-*d*-**6**	(67)
11	4-*d*-**2**	pH 9[e]	90	30 min	*d*-**8**	(53)

a) Isolated yield. b) water/ref: In refluxing water. c) Rearranged product(s) was not detected. d) The reaction was carried out in heavy water. e) KOH was used as the base.



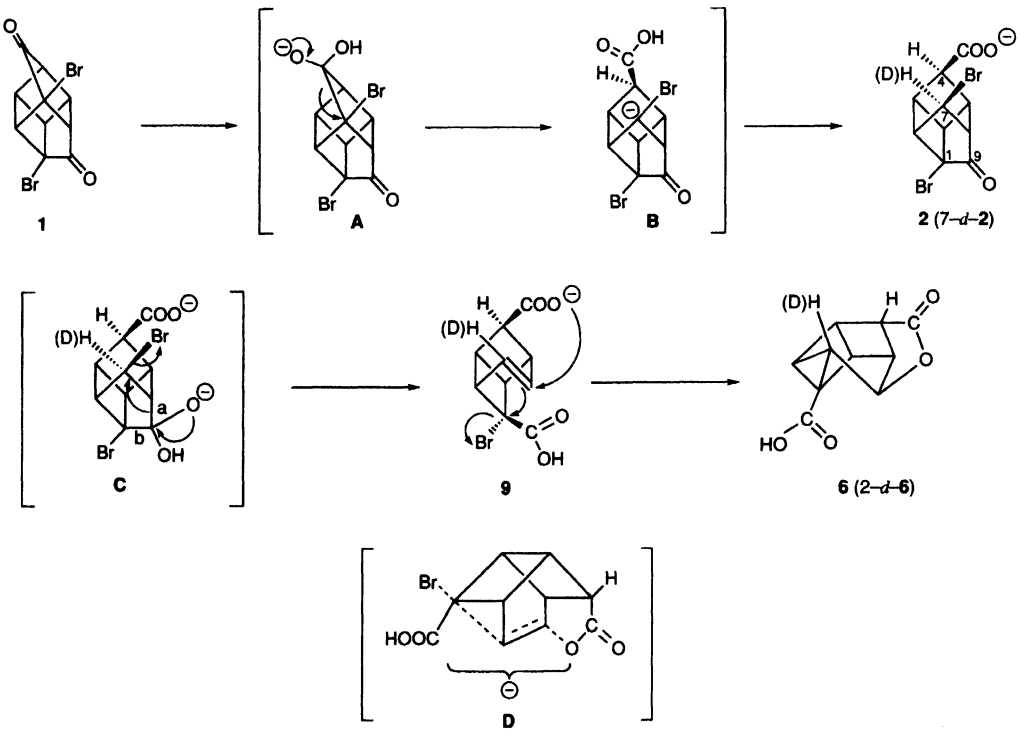
Scheme 2.

when **2** and 4-*d*-**2** were treated with the aqueous base at 90 °C, the pH being maintained at 9 during the reaction, the corresponding **8** and *d*-**8** were obtained without the formation of **6** and deuterated analogs 2-*d*-**6** and 8-*d*-**6**. Neither **6** or any other identifiable material could be obtained from the reaction of **8** with 5% aqueous potassium hydroxide at 80 °C for 15 min.

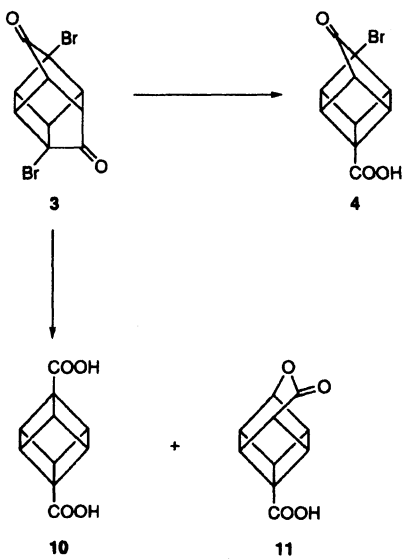
The formation of **6** from **1** involves double Haller–Bauer-type ring cleaved reactions as illustrated in Scheme 3. Compound **1** reacts with hydroxide ion to give an intermediate **A** which is converted via a Haller–Bauer-type reaction into bromocarbanion intermediate **B**. Intermediate **B** reacts with H^+ (or D^+) to give protium analog **2** (or 7-*d*-**2** deuterated at the 7-position; not isolated). The reaction of **2** (or 7-*d*-**2**) with hydroxide ion gives a proposal intermediate **9** via an intermediate **C** indicating that ring cleavage (breakage of bond a) and succeeding elimination of a bromine atom rather than Favorskii rearrangement have occurred. Compound **9** may be converted via an intermediate **D** into the end rearrangement product **6** (or 2-*d*-**6**). In a series of this reaction, the basicity must play a major role in order to bring about the Haller–Bauer-type reaction and complete the cycle of intermediates capable of being converted into the end rearrangement product.

In a related study, we reinvestigated the reactions of **3**, **4**, and **5** with aqueous potassium hydroxide to see whether ring cleavage or Favorskii rearrangement occurred (Schemes 4 and 5). On treatment with 25% aqueous potassium hydroxide under reflux, **3** gave a mixture of cubane-1,4-dicarboxylic acid (**10**) (the normal Favorskii rearrangement product) and lactone **11** (the Haller–Bauer-type reaction product) in a ratio of 10 : 1. Interestingly, **3**, when treated with 10% aqueous potassium hydroxide in refluxing water, was found to give **4** in a 76% yield. Compound **4** was converted to **10** in a 44% yield by treating with 25% aqueous potassium hydroxide in refluxing water. These results show that the Favorskii rearrangement of **3** to the cubane skeleton occurred stepwise giving the homocubane skeleton **4** as an intermediate.

Compound **5**, when treated with 25% aqueous potassium hydroxide for 3.5 h in refluxing water, was found to give a mixture of cubane-1,3-dicarboxylic acid **12**[3] (25% yield), lactone **13**[9] (6% yield), and *endo*-7-hydroxytetracyclo[4.2.0.0^{2,5}.0^{3,8}]octane-1,*exo*-4-dicarboxylic acid (**14**) (23% yield). These compounds were isolated as their methyl esters. The reaction gave two



Scheme 3.



Scheme 4.

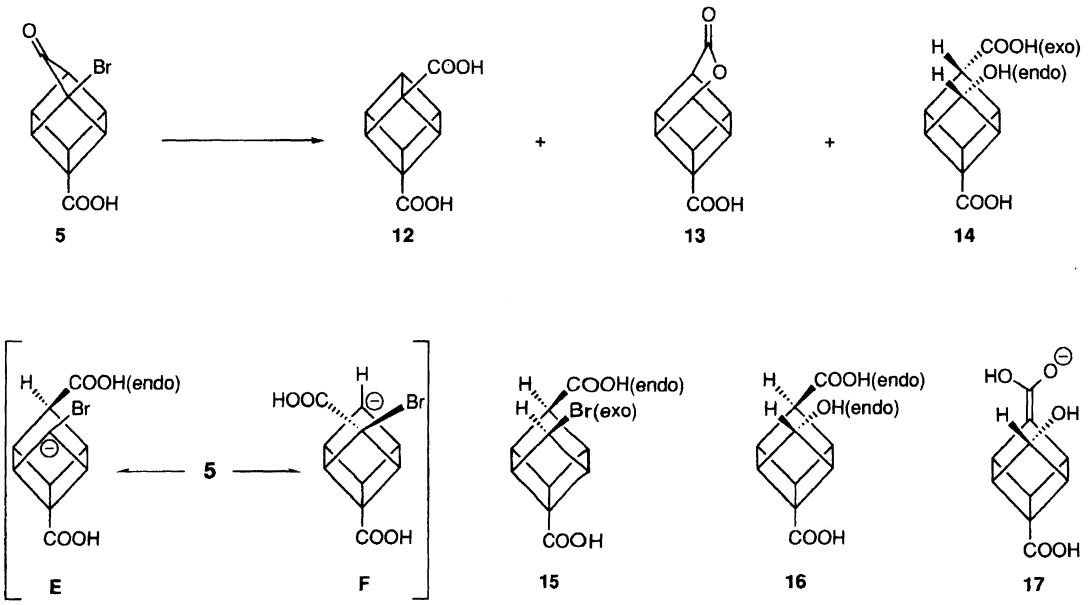
products, **12** and **13**, indicating that both reactions of ring cleavage and Favorskii rearrangement had occurred. As shown in Scheme 5, reaction of **5** with hydroxide ion forms two bromocarbanions (**E** and **F**). Bromocarbanion **E** gives **15** which is converted to lactone **13**. Compound **13** is then hydrolyzed to **16**. These reactions appear to be completely regio- and stereospecific. Compound **16** isomerizes to **14** via **17** as a final product which is not able to cyclize to lactone **13**. On the other hand, bromocarbanion **F** gives cubane-1,3-dicarboxylic acid (**12**) via Favorskii rearrangement.

The stereochemistry of **14**, **15**, and **16** was determined on the basis of their ^{1}H NMR spectra, compared with those of compounds which have been described in the literature.[10]

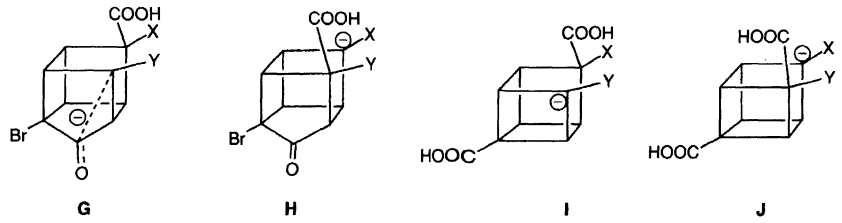
The formation of **6** from α-halo ketone **2** represents a new example of a Haller–Bauer-type reaction in the bishomocubane system. In the reaction of a series of bishomocubanes **1** and **3** with alkali, exclusive cleavage of the C_1–C_{10} bond takes place without cleavage of the C_9–C_{10} bond to give carbanion **G**, which may be stabilized by homo-conjugation between the carbanion and the carbonyl group. Thus, this carbanion **G**, which is more stable than carbanion **H**, is always formed in the initial stage of the reaction (Scheme 6). Carbanion **G**, which has no leaving group on the carbon atom to which the carboxyl group is attached, gives ring cleaved product **2** (or 7-*d*-**2**) taking a proton (or deuterium) from the solvent. The presence of a leaving group on the carbon atom brings about the ring-contracted product.

In the homocubane system (**4** and **5**), two important differences are to be noted. First, the reaction of **4** with aqueous base gives **10** indicating that the reaction is controlled by a factor arising from the stability of the end ring-contracted product rather than from the ring strain or from the stability of the bromocarbanion. Secondly, the reaction of **5** with aqueous base gives the end products via the two carbanions (**I** and **J**).

The formation of the ring-cleaved product and the normal Favorskii-type contraction product can be attributed to a combination of factors due to ring strain, the stability of the carbanion intermediates and to the



Scheme 5.



Scheme 6.

added stability of the end product(s). These factors may play a major role in determining what reaction pathways are open to the molecule.

Experimental

Melting points were measured in a Gallenkamp melting point apparatus and are uncorrected. Infrared (IR) spectra were recorded on a Hitachi 260-30 infrared spectrophotometer and proton nuclear magnetic resonance (^{1}H NMR) and carbon 13 nuclear magnetic resonance (^{13}C NMR) spectra were measured on Hitachi R-90 (90 MHz) and Bruker AM 360 (360 MHz) spectrometers with tetramethylsilane as an internal standard. Chemical shifts are reported in ppm (δ) and signals are described as s (singlet), d (doublet), t (triplet), m (multiplet), q (quartet), quin (quintet) or br (broad). All spectra were consistent with the assigned structures. Mass spectra (MS) and high-resolution mass spectra (HRMS) were obtained on a JMS-DX 300 spectrometer operating at an ionization potential of 70 eV. Combustion analyses were performed on a Perkin-Elmer Model 240C elemental analyzer.

Solvents were dried over molecular sieves 4A overnight. Reagents employed in this study were commercially available. 33% HBr in AcOH was purchased from Merck Co., Ltd.

The deuterium content in each of the compounds studied in this series was monitored by ^{1}H NMR and/or mass spectrometry both of which indicated retention of isotope purity throughout the synthesis. Compounds 2-*d*-**6**, 8-*d*-**6**, 2-*d*-**7**, and *d*-**8** via ^{1}H NMR and mass spectral analyses showed >95% deuterium content at the labelled positions.

Reaction of 1,2, and 4-*d*-2 with Aqueous Potassium Hydroxide. A typical example is given to illustrate the general procedure. A solution of **1** (100 mg, 0.314 mmol) in 5% KOH (8 ml) was stirred for 15 min at 80 °C. The resulting mixture was treated according to the procedure used for the preparation of **6**. Results are given in Table 1.

Reaction of 8 with 5% KOH. A solution of **8** (120 mg, 0.47 mmol) in 5% KOH (1.5 ml) was stirred for 15 min at 80 °C. The resulting mixture was treated according to the procedure used in the preparation of **6**. No identifiable material could be obtained.

1,5-Dibromopentacyclo[5.3.0.0^{2,5}.0^{3,9}.0^{4,8}]decane-6,10-dione (1) A solution of 1,5-dibromopentacyclo-[5.3.0.0^{2,5}.0^{3,9}.0^{4,8}]decane-6,10-dione 10-ethylene acetal[8] (500 mg, 1.38 mmol) in concd H_2SO_4 (5 ml) was stirred for 24 h at room temperature and then poured into ice–water (100 ml). The aqueous layer was saturated with $(NH_4)_2SO_4$ and extracted with AcOEt. The AcOEt layer was dried over $MgSO_4$ and evaporated to give colorless crystals. The crystals were purified by column chromatography on silica gel

with a (5 : 1) mixture of hexane and AcOEt to give the pure monohydrate of **1** which was recrystallized from a mixture of AcOEt and hexane to give the analytically pure monohydrate of **1** as colorless plates. Yield 441 mg (95%); mp 155.7—156.4 °C; ^{1}H NMR (360 MHz, DMSO-d_6) δ=2.76 (1H, t, J=5 Hz), 2.80 (1H, dd, J=6 and 2 Hz), 3.06 (1H, dt, J=7 and 5 Hz), 3.21—3.25 (1H, m), and 3.33—3.45 (2H, m); ^{13}C NMR (360 MHz, DMSO-d_6) δ=38.5, 40.3, 41.9, 44.1, 51.3, 55.8, 56.6, 68.6, 107.5, and 204.9. IR (KBr) 3440, 3330, and 1770 cm^{-1}; MS m/z 334 (M$^+$). Found: C, 35.64; H, 2.25; Br, 47.35%. Calcd for $C_{10}H_8Br_2O_3$: C, 35.75; H, 2.40; Br, 47.57%. A mixture of the monohydrate of **1** (201 mg, 0.598 mmol) and molecular sieves 4A (1 g) in C_6H_6 (20 ml) was stirred for 2 h in refluxing C_6H_6. After removal of the solvent, the residue was recrystallized from $CHCl_3$ to give pure **1** as colorless crystals. Yield 190 mg (100%); mp 161.1—162.5 °C. (lit,[8] 161.1—162.5 °C).

1,*exo*-7-Dibromo-9-oxotetracyclo[4.3.0.0^{2,5}.0^{3,8}]nonane-*endo*-4-carboxylic Acid (2). A solution of **4** (2.87 g, 9.58 mmol) in 33% HBr in AcOH (100 ml) was stirred for 19 h at 70 °C. After removal of the solvent, the residue obtained was purified by column chromatography on silica gel with $CHCl_3$ as an eluent to give crystals, which were recrystallized from a mixture of $CHCl_3$ and hexane to give pure **2** as colorless plates. Yield 708 mg (22%), mp 182—189 °C; ^{1}H NMR (360 MHz, $CDCl_3$) δ=3.13 (1H, dt, J=6 and 4 Hz), 3.16 (1H, dt, J=6 and 1 Hz), 3.37 (1H, dd, J=6 and 5 Hz), 3.43 (1H, t, J=6 Hz), 3.42—3.46 (1H, m), 3.65 (1H, tt, J=6 and 4 Hz), 4.73 (1H, q, J=1 Hz), and 4.8—5.8 (1H, b); ^{13}C NMR (360 MHz, $CDCl_3$) δ=37.3, 41.8, 42.0, 42.9, 45.7, 47.8, 53.4, 54.1, 175.9, and 200.5; IR (KBr) 3000, 1810, 1795, and 1705 cm^{-1}; MS m/z 334 (M$^+$). Found: C, 35.59; H, 2.29; Br, 47.49%. Calcd for $C_{10}H_8Br_2O_3$: C, 35.75; H, 2.40; Br, 47.57%.

***exo*-4-*Deuterio*-1,*exo*-7-dibromo-9-oxotetracyclo[4.3.0.0^{2,5}.0^{3,8}]nonane-*endo*-4-carboxylic Acid.** (4-*d*-**2**) was prepared as described for **2** using DBr in AcOD instead of HBr in AcOH. Yield 18.0%; mp 183.5—184.2 °C (sublimation); ^{1}H NMR (360 MHz, $CDCl_3$) δ=3.06 (1H, m), 3.14 (1H, m), 3.35—3.43 (2H, m), 3.60 (1H, m), 4.85 (1H, bs), and 6.50 (1H, bs); IR ($CHCl_3$) 3000, 2900, 2800, 2700, 1800, 1780, and 1705 cm^{-1}; MS m/z 335 (M$^+$). Found: C, 35.59; H, 2.40; Br, 47.21%. Calcd for $C_{10}H_7DBr_2O_3$: C, 35.64; H, 2.69; Br, 47.21%.

5,9-Dibromopentacyclo[5.3.0.0^{2,5}.0^{3,9}.0^{4,8}]decane-6,10-dione (3). This compound was prepared according to the procedure described in the literature. Yield 95%; mp 234.6—235.5 °C (lit,[6] 230—232 °C).

1-Bromo-9-oxopentacyclo[4.3.0.0^{2,5}.0^{3,8}.0^{4,7}]nonane-4-carboxylic Acid (4). Method 1. This compound was prepared by the procedure described in the literature. Yield 76%; mp 221.5—222.5 °C (lit,[6] 219—220 °C).

Method 2. Reaction of 3 with 10% KOH A solution of **3** (100 mg, 0.315 mmol) in 10% KOH (1 ml) was stirred for 3.5 h in refluxing water. The reaction mixture was treated according to Method 1 to give **4**. Yield 61 mg (76%); mp 221.5—222.5 °C (lit,[6] 219—220 °C).

8-Bromo-9-oxopentacyclo[4.3.0.0^{2,5}.0^{3,8}.0^{4,7}]nonane-4-carboxylic Acid (5). A solution of 8-bromo-9-ethylenedioxypentacyclo[4.3.0.0^{2,5}.0^{3,8}.0^{4,7}]nonane-4-carboxylic acid[8] (500 mg, 1.67 mmol) in 75% H_2SO_4 (15 ml) was stirred for 24 h at room temperature and then poured into ice–water (200 ml). The aqueous layer was saturated with $(NH_4)_2SO_4$ and extracted with AcOEt. After removal of the solvent, the residue was dissolved in saturated aqueous $NaHCO_3$ solution. The aqueous layer was washed with CH_2Cl_2, acidified with concd HCl, and then washed with CH_2Cl_2. The resulting aqueous layer was saturated with $(NH_4)_2SO_4$ and extracted with AcOEt. The AcOEt layer was dried over $MgSO_4$ and evaporated to give **5** as colorless crystals. Yield 383 mg (90%); mp 236.7—239 °C; ^{1}H NMR (360 MHz, DMSO-d_6) δ=3.18 (1H, t, J=5 Hz), 3.74 (2H, m), 3.80 (1H, m), 3.90 (2H, m), and 12.59 (1H, bs, COOH); ^{13}C NMR (90 MHz, DMSO-d_6) δ=37.2, 38.8, 45.6, 48.8, 54.3, 57.4, 170.6, and 204.4; IR (KBr) 1770 and 1690 cm^{-1}; MS m/z 254 (M$^+$). Found: C, 47.34; H, 2.89; Br, 18.62%. Calcd for $C_{10}H_7BrO_3$: C, 47.09; H, 2.77; Br, 18.82%.

10-Oxa-9-oxopentacyclo[5.3.0.0^{2,4}.0^{3,6}.0^{5,8}]decane-3-carboxylic Acid (6). A solution of **2** (200 mg, 0.595 mmol) in 5% KOH (12 ml) was stirred for 15 min at 80 °C. The resulting solution was cooled to below 10 °C, acidified with concd HCl to pH 1, saturated with NaCl, and extracted with AcOEt. The AcOEt layer was dried over $MgSO_4$ and evaporated to give crystals. The crystals were purified by column chromatography on silica gel with $CHCl_3$ as an eluent to give **6**. Recrystallization from AcOEt gave analytically pure **6**. Yield 102 mg (89%); mp 121.1—122.2 °C (lit,[8] 121.1—122.2 °C).

2-*Deuterio*-10-oxa-9-oxopentacyclo[5.3.0.0^{2,4}.0^{3,6}.0^{5,8}]decane-3-carboxylic Acid (2-*d*-6). Compound **1** (190 mg, 0.595 mmol) in 5% KOD (7.1 ml) was allowed to react under conditions as described for **6** to give 2-*d*-**6**. Yield 57 mg (50%); mp 195.2—197.0 °C (AcOEt); ^{1}H NMR (360 MHz, $CDCl_3$) δ=2.80 (1H, t, J=7 Hz), 3.03 (1H, t, J=4 Hz), 3.33 (1H, tt, J=7 and 5 Hz), 3.40 (1H, ddd, J=7, 5, and 3 Hz), 3.58 (1H, ddt, J=8, 7, and 5 Hz), 5.72 (1H, dd, J=8 and 1 Hz), and 9.5—10.5 (1H, bs); ^{13}C NMR (90 MHz, $CDCl_3$) δ=32.7, 33.3, 37.3, 38.3 (t, J_{C-D}=26 Hz), 39.4, 40.6, 47.5, 85.6, 175.6, and 176.0; IR (KBr) 2980, 1775, and 1690 cm^{-1}; MS m/z 193 (M$^+$).

8-*Deuterio*-10-oxa-9-oxopentacyclo[5.3.0.0^{2,4}.0^{3,6}.0^{5,8}]decane-3-carboxylic Acid (8-*d*-6). Reaction of 4-*d*-**2** (200 mg, 0.594 mmol) with 5% KOH (8 ml) gave 8-*d*-**6**. Yield 88 mg (77%); mp 187.6—188.3 °C; ^{1}H NMR (270 MHz, $CDCl_3$) δ=3.03 (2H, m), 3.38 (1H, m), 3.41 (1H, m), 3.58 (1H, m), and 5.72 (1H, dt, J=8 and 2 Hz); MS m/z 193 (M$^+$).

***N*,*N*-Diisopropyl-10-oxa-9-oxopentacyclo[5.3.0.0^{2,4}.0^{3,6}.0^{5,8}]decane-3-carboxamide (7).** Acyl chloride, which was prepared from **6** (54 mg, 0.279 mmol) and $SOCl_2$ (0.3 ml), was allowed to react with diisopropylamine (0.3 ml) at room temperature for 30 min. The resulting mixture was diluted with AcOEt (150 ml) and washed with brine and 10% HCl, successively. The AcOEt layer was dried over $MgSO_4$ and evaporated to give colorless crystals, which were recrystallized from a mixture of AcOEt and hexane to give pure **7** as colorless scales. Yield 63 mg (80%); mp 117.0—118.9 °C; ^{1}H NMR (360 MHz, $CDCl_3$) δ=1.1—1.5 (12H, m), 2.58 (1H, dd, J=6 and 3 Hz), 2.75 (1H, t, J=7 Hz), 2.74—2.79 (1H, m), 3.22 (1H, ddd, J=7, 4, and 3 Hz), 3.32 (1H, tt, J=7 and 5 Hz), 3.59 (1H, m), 3.3—3.6 (2H, m), and 5.71 (1H, ddd, J=8, 4, and 1 Hz); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ=20.8, 26.0, 32.5, 36.4, 39.0, 41.0, 44.4, 46.0, 47.5, 49.0, 86.7, 167.2, and 176.2; MS m/z 275 (M$^+$).

***N,N*-Diisopropyl-2-*deuterio*-10-oxa-9-oxopentacyclo[5.3.0.0^{2,4}.0^{3,6}.0^{5,8}]decane-3-carboxamide (2-*d*-7).** This compound was prepared from 2-*d*-**6** (18 mg, 0.093 mmol) as described for **7**. Yield 18 mg (70%); ^{1}H NMR (360 MHz, $CDCl_3$) δ=1.1—1.5 (12H, m), 2.75 (1H, t, J=7 Hz), 2.76—2.78 (1H, m), 3.22 (1H, ddd, J=7, 4, and 3 Hz), 3.32 (1H, tt, J=7 and 5 Hz), 3.59 (1H, ddt, J=8, 7, and 4 Hz), 3.2—3.6 (2H, m), and 5.72 (1H, dd, J=8 and 1 Hz); MS m/z 276 (M^+).

***N,N*-Diisopropyl-8-*deuterio*-10-oxa-9-oxopentacyclo[5.3.0.0^{2,4}.0^{3,6}.0^{5,8}]decane-3-carboxamide (8-*d*-7).** This compound was prepared from 4-*d*-**2** (18 mg, 0.093 mmol) as described for **7**. Yield 20 mg (80%); ^{1}H NMR (360 MHz, $CDCl_3$) δ=1.1—1.5 (12H, m), 2.58 (1H, m), 2.77 (1H, m), 3.21 (1H, m), 3.31 (1H, m), 3.3—3.7 (2H, b), 3.58 (1H, m), and 5.72 (1H, dd, J=8 and 3 Hz); MS m/z 276 (M^+).

5-Bromo-9-oxapentacyclo[5.4.0.0^{2,5}.0^{3,11}.0^{4,8}]undecane-6,10-dione (8). Five percent aqueous KOH was added to a suspension of **2** (179 mg, 0.532 mmol) in H_2O (10 ml) to give a clean solution. The solution was adjusted to pH 9 with 5% HCl or 5% KOH and stirred for 30 min at 90 °C. The pH of the solution was kept at 9 using 5% KOH until the reaction was complete. The resulting solution was saturated with NaCl and extracted with AcOEt. The AcOEt layer was dried over $MgSO_4$ and evaporated to give **8** as an oil, which was triturated with a mixture of hexane and AcOEt to give crystals. Recrystallization from a mixture of AcOEt and hexane gave **8** as colorless needles. Yield 119 mg (88%); mp 196.0—197.2 °C; ^{1}H NMR (360 MHz, $CDCl_3$) δ=2.80 (1H, quin, J=3 Hz), 3.05—3.15 (2H, m), 3.21 (1H, ddd, J=10, 7, and 5 Hz), 3.37 (1H, dd, J=7 and 5 Hz), 3.40 (1H, dt, J=7 and 4 Hz), and 5.45 (1H, quin, J=3 Hz); MS m/z 254 (M^+).

5-Bromo-11-*deuterio*-9-oxapentacyclo[5.4.0.0^{2,5}.0^{3,11}.0^{4,8}]undecane-6,10-dione (*d*-8). Compound *d*-**2** (179 mg, 0.532 mmol) was treated under the same conditions employed for the preparation of **8** to give *d*-**8** as an oil. Yield 71.5 mg (53%); ^{1}H NMR (270 MHz, $CDCl_3$–CD_3OD) δ=2.76 (1H, quin, J=3 Hz), 3.18 (2H, m), 3.21 (1H, m), 3.39 (1H, m), and 5.45 (1H, quin, J=3 Hz); MS m/z 255 (M^+).

1,4-Bis(methoxycarbonyl)pentacyclo[4.2.0.0^{2,5}.0^{3,8}.0^{4,7}]octane(the Dimethyl Ester of 10) and 4-Methoxycarbonyl-10-oxapentacyclo[4.4.0.0^{2,5}.0^{3,8}.0^{4,7}]decan-9-one (the Methyl Ester of 11). Reaction of 3 with 25% KOH. A solution of **3** (4.18 g, 13.1 mmol) in 25% KOH (40 ml) was stirred for 3.5 h in refluxing water. The reaction mixture was cooled and acidified with concd HCl to below pH 1. The resulting solution was saturated with $(NH_4)_2SO_4$ and extracted with AcOEt. The AcOEt layer was dried over $MgSO_4$ and evaporated. The residue was dissolved in MeOH and treated with diazomethane overnight. After removal of the solvent, the residue was purified by column chromatography on silica gel with $CHCl_3$ as an eluent. The first elution contained the dimethyl ester of **10**. Yield 1.26 g (44%); mp 162.3—164.1 °C (lit,[6] 161—162 °C). The second elution gave the methyl ester of **11**. Yield 121 mg (4.4%); mp 212.0—214.0 °C; ^{1}H NMR (360 MHz, $CDCl_3$) δ=3.41 (1H, tt, J=5 and 1 Hz), 3.51 (2H, m), 3.68 (2H, bt, J=6 Hz), 3.73 (3H, s), 3.78 (1H, t, J=6 Hz), and 5.31 (1H, t, J=6 Hz); ^{13}C NMR (90 MHz, $CDCl_3$) δ=36.3, 37.6, 38.1, 41.6, 51.9, 52.1, 71.2, 169.7, and 169.9; IR (KBr) 3050, 3030, 2960, 1755, and 1730 cm^{-1}; MS (FAB) 207 (M+1). Found: C, 64.16; H, 4.78%. Calcd for $C_{11}H_{10}O_4$: C, 64.07; H, 4.89%.

1,3-Bis(methoxycarbonyl)pentacyclo[4.2.0.0^{2,5}.0^{3,8}.0^{4,7}]octane (the Dimethyl Ester of 12), 4-Methoxycarbonyl-9-oxapentacyclo[4.4.0.0^{2,5}.0^{3,8}.0^{4,7}]decan-10-one (the Methyl Ester of 13), and *endo*-7-Hydroxy-1,*exo*-4-Bis(methoxycarbonyl)tetracyclo[4.2.0.0^{2,5}.0^{3,8}]octane (the Dimethyl Ester of 14). Reaction of 5 with 25% KOH. A solution of **5** (284 mg, 1.11 mmol) in 25% KOH (3 ml) was stirred for 3.5 h in refluxing water. The resulting mixture was treated according to the procedure as described for **10** and **11** to give three methyl esters; the dimethyl ester of **12**: Yield 61 mg (25%); mp 56.2—58.6 °C (from pentane). (This ester was hydrolyzed in 10% NaOH to **12**; mp 170—171 °C (from hexane) (lit,[3] 171 °C (decomp))), the methyl ester of **13**: Yield 16 mg (6%); mp 212.6—213.6 °C (from a mixture of CH_2Cl_2 and hexane) (lit,[9] 208.5—210 °C), and the dimethyl ester of **14**: Yield 62 mg (23%); mp 116.0—117.0 °C (from a mixture of CH_2Cl_2 and hexane); ^{1}H NMR (360 MHz, $CDCl_3$) δ=2.65 (1H, bs), 3.43 (2H, m), 3.66 (3H, s), 3.70 (3H, m), 3.82—3.85 (3H, m), 4.35 (1H, s), and 4.69 (1H, bs); ^{13}C NMR (90 MHz, $CDCl_3$) δ=40.7, 42.5, 44.5, 46.8, 50.8, 51.6, 51.7, 66.1, 171.5, and 175.1; IR (KBr) 3440, 3020, 2990, 2955, 2920, 1735, and 1710 cm^{-1}; MS (FAB) 239 (M+1). Found: C, 60.46; H, 5.66%. Calcd for $C_{12}H_{14}O_5$: C, 60.50; H, 5.92%.

We would like to express our thanks to the Material Analytical Center of the ISIR, Osaka University for spectral measurements and microanalyses.

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