Synthesis of 2,5-Dehydrohomoadamantane (Tetracyclo[5.3.1.$0^{2,5}$.$0^{3,9}$]undecane) from 2,4-Dehydrohomoadamantane (Tetracyclo[5.3.1.$0^{3,5}$.$0^{4,9}$]undecane)[1,2]

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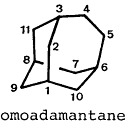
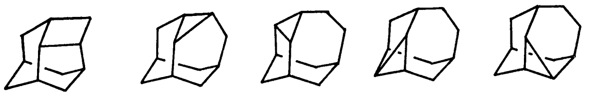
A reaction of 2,4-dehydrohomoadamantane with NBS in AcOH followed by $LiAlH_4$ reduction and subsequent CrO_3–pyridine complex oxidation gave *endo*-2-bromohomoadamantan-4-one (**9**) in good yield. A treatment of **9** with *t*-BuOK in *t*-BuOH followed by Wolff-Kishner reduction furnished 2,5-dehydrohomoadamantane.

Out of five possible "non-bridgehead" monodehydrohomoadamantanes, the strained cage compounds which incorporate a small ring in homoadamantane framework (**1**—**5**),[3—6] 2,5-dehydrohomoadamantane (**1**) is the only compound which contains a cyclobutane ring in its structure. Recently, Sasaki *et al.* reported a synthesis of **1** utilizing an intramolecular ketene cycloaddition.[3] During our search for synthesis and reactions of strained cage systems,[4b,5b,7] we have had an opportunity to investigate **1** and now wish to describe an alternative synthetic route of **1** starting from 2,4-dehydrohomoadamantane (**2**).



Homoadamantane
(Tricyclo[4.3.1.$1^{3,8}$]undecane)



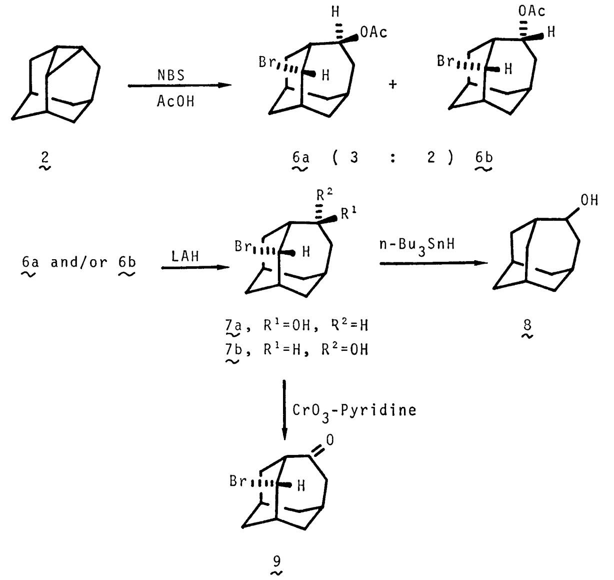
1(2,5) 2(2,4) 3(2,11) 4(2,9) 5(2,10)

Fig. 1. "Non-bridgehead" Monodehydrohomoadamantanes.

Results and Discussion

When **2** was allowed to react with *N*-bromosuccinimide (NBS) in acetic acid, two isomeric bromo acetates, *endo*-2-bromo-*exo*-4-acetoxy- and *endo*-2-bromo-*endo*-4-acetoxyhomoadamantanes (**6a** and **6b**) were obtained in 70% combined yield in a ratio of 3:2 (GLC analysis). The structures of **6a** and **6b** were determined by the following experimental results. Reductions of **6a** and **6b** with lithium aluminum hydride gave bromo alcohols (**7a** and **8b**) in 68 and 81% yields, respectively. When a mixture of **7a** and **7b** was reduced with tributyltin hydride, only homoadamantan-4-ol (**8**)[8] was obtained in 78% yield. No other alcohol could be detected. These chemical transformations clearly indicate that the bromo acetates (**6a** and **6b**) and bromo alcohols (**7a** and **7b**) retain a homoadamantane skeleton and that the acetoxyl and hydroxyl groups are located at C_4-position in the homoadamantane system.

Each bromo alcohol (**7a** or **7b**) was further subjected to the oxidation with chromium trioxide–pyridine complex to afford the same product, *endo*-2-bromohomoadamantan-4-one (**9**) in 91 or 95% yield; these results show that **6a** and **6b**, and **7a** and **7b** also, are isomeric in relation to C_4-position and that the bromine substituents have the same configurations. The ^{1}H-NMR (PMR) spectrum of **9** showed a singlet peak at 4.55 ppm due to the C_2 carbinyl proton. Previous studies[7a,9] showed that *exo*-C_2-proton does not couple with the adjacent protons, whereas *endo*-C_2-proton does couple, giving a triplet with a coupling constant of *ca.* 4 Hz. The configuration of the bromine substituent of **9** was thus determined to be *endo*. The configurations of substituents at C_4-positions of **6a**, **6b**, **7a**, and **7b** were deduced by comparison of their ^{13}C-NMR (CMR) and PMR spectra with each other. In a cage system such as adamantane, a γ_{syn}-carbon to a substituent has 4—7 ppm higher chemical shift than a γ_{anti}-carbon does because of a stronger interaction between the former and the substituent.[10] On the other hand, a γ_{syn}-hydrogen is reported to appear at 0.4—0.6 ppm lower field than its counterpart, a γ_{anti}-hydrogen.[11] Our results are summarized in Table 1. The chemical shifts of the carbons at the 2-positions of **6a** and **7a** are higher than those of **6b** and **7b** and the chemical shifts of the C_2-hydrogens of the former are lower than those of the latter. These facts lead to our conclusion that **6a** and **7a** are *endo*-2-bromo-*exo*-4-acetoxyhomoadamantane and *endo*-2-bromo-*exo*-homoadamantan-4-ol and that **6b** and **7b** are *endo*-2-bromo-*endo*-4-acetoxyhomoadamantane and *endo*-2-bromo-*endo*-homoadamantan-4-ol.

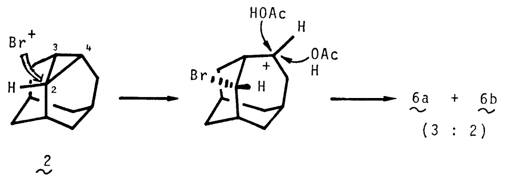


Scheme 1.

Table 1. Chemical shifts[a] of $\underline{C}_2$ and C_2-$\underline{H}$

	6a	6b	7a	7b
$\underline{C}$-Br	56.2	59.1	56.7	60.8
C$\underline{H}$-Br	4.75	4.40	4.87	4.38

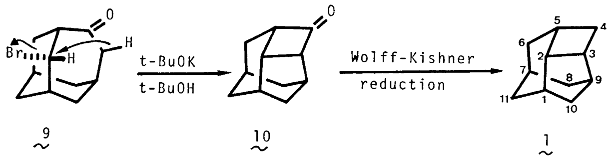
a) ppm relative to TMS.



Scheme 2.

On the basis of the structures of **6a** and **6b**, we constructed the following reaction scheme with respect to the cleavage of the cyclopropane by bromonium ion (Scheme 2). An initial attack of the strained C_2–C_4 bond by bromonium ion must occur exclusively at C_2-position with inversion of configuration giving a carbocation intermediate.[12)] The subsequent nucleophilic attack by the solvent from both sides will give **6a** and **6b** almost non-selectively. The remarkable regioselectivity observed in the initial bromination stage may be attributed not only to steric but also to electronic reasons, because ^{13}C–H coupling constants of C_2 and C_4 (or C_3) ($J_{C_2\text{-H}}=163$ Hz and $J_{C_4(3)\text{-H}}=158$ Hz) indicate that C_2-carbon with more s-character in C_2–H bond should have more p-electron density than $C_{4(3)}$-carbon.[13)]

A treatment of **9** with potassium *t*-butoxide in *t*-butyl alcohol at room temperature induced an efficient cyclization to give 2,5-dehydrohomoadamantan-4-one (**10**) in 86% yield. The ketone (**10**) showed a characteristic absorption band at 1775 cm^{-1} due to cyclobutanone in its IR spectrum; the PMR spectrum was identical with that reported.[14)] The final Wolff-Kishner reduction was nicely conducted to afford 2,5-dehydrohomoadamantane (**1**) in 71% yield.



Scheme 3.

Experimental

All the temperatures were uncorrected. Melting points were measured in sealed capillaries. The IR spectra were recorded on a Shimadzu IR-27 spectrometer. The MS spectra were taken by using a Hitachi RMS-4 mass spectrometer. The PMR and CMR spectra were obtained on Varian EM-390 and CFT-20 spectrometers, tetramethylsilane being chosen as an internal standard. Micro analyses were performed in Kyoto University Elemental Analysis Center.

Reaction of Tetracyclo[5.3.1.0^{3,5}.0^{4,9}]undecane (2) with N-*Bromosuccinimide (NBS).* A solution of **2** (998 mg; 6.74 mmol) and NBS (1521 mg; 8.54 mmol) in AcOH (25 ml) was stirred at 60 °C under argon for 28 h. The reaction mixture was poured onto water and extracted with CH_2Cl_2. The organic solution was washed successively with brine, aqueous $NaHCO_3$, and brine, and dried (Na_2SO_4). After filtration, the solvent was evaporated and the residue (2.16 g) was chromatographed on silica gel (100 g). Elution by hexane gave the unreacted starting material (41 mg). Subsequent elution by hexane and CH_2Cl_2 (4:1) gave **6a** (480 mg), a mixture of **6a** and **6b** (324 mg), and **6b** (250 mg). The combined yield of **6a** and **6b** (1054 mg) was 55% and the ratio of **6a** and **6b** was determined to be 3:2 by GLC analysis (PEG 20 M, 220 °C) of the crude products. Similarly, the reaction of **2** (207 mg; 1.40 mmol) and NBS (282 mg; 1.58 mmol) in AcOH (5 ml) at 45—50 °C for 6 d gave a mixture of **6a** and **6b** (282 mg, 70%). *endo*-2-Bromo-*exo*-4-acetoxytricyclo[4.3.1.1^{3,8}]undecane (**6a**): bp 70 °C (bath temp)/133 Pa. MS *m/e* (rel intensity): 228, 226 (M^+—AcOH, 47, 48), 165 (17), 147 (100). IR (neat): 2825, 1740, 1445, 1365, 1240, 1015, 960, 715 cm^{-1}. PMR δ (CCl_4): 4.90 (1H, d.d.d, J=10.0, 5.4, 3.6 Hz), 4.65 (1H, s), 2.02 (3H, s), 2.75—1.20 (14H, br. complex m). CMR δ ($CDCl_3$); 169.9 (C), 76.0 (CH), 56.2 (CH), 46.9 (CH), 41.3 (CH_2), 37.7 (CH_2), 36.0 (CH, CH_2), 30.4 (CH_2), 30.2 (CH_2), 28.6 (CH), 26.7 (CH), 21.3 (CH_3). Found: C, 54.25; H, 6.58%. Calcd for $C_{13}H_{19}BrO_2$: C, 54.36; H, 6.67%. *endo*-2-Bromo-*endo*-4-acetoxytricyclo[4.3.1.1^{3,8}]undecane (**6b**): bp 70 °C (bath temp)/133 Pa. MS *m/e* (rel intensity): 228, 226 (M^+—AcOH, 49, 48), 165 (26), 147 (100). IR (neat): 2925, 1740, 1450, 1365, 1245, 1020, 965, 720, 710 cm^{-1}. PMR δ (CCl_4): 5.02 (1H, d.d.d, J=9.0, 6.0, 3.0 Hz), 4.40 (1H, s), 1.98 (3H, s), 2.70—1.20 (14H, br. complex m). CMR δ ($CDCl_3$): 169.9 (C), 74.8 (CH), 59.1 (CH), 46.4 (CH), 40.9 (CH_2), 40.0 (CH_2), 35.5 (CH), 34.7 (CH_2), 30.2 (CH_2), 28.7 (CH), 26.5 (CH), 25.6 (CH_2), 21.3 (CH_3). Found: C, 54.53; H, 6.76%. Calcd for $C_{13}H_{19}BrO_2$: C, 54.36; H, 6.67%.

endo-*2-Bromo*-exo-*tricyclo[4.3.1.1^{3,8}]undecan-4-ol (7a).* To a suspension of $LiAlH_4$ (60 mg) in dry Et_2O (5 ml) was added dropwise a solution of **6a** (105 mg; 0.37 mmol) in dry Et_2O (5 ml). The mixture was stirred under reflux for 10 min. Aqueous Na_2SO_4 was added to the cooled reaction mixture. The organic layer was collected and dried (Na_2SO_4). After filtration, the solvent was evaporated and the residue was chromatographed on silica gel. Elution by hexane and CH_2Cl_2 (3:2) gave **7a** (61 mg, 68%): mp 147—149 °C. MS *m/e* (rel intensity): 228, 226 (M^+—H_2O, 30, 31), 147 (100). IR (KBr): 3325, 2950, 1445, 1015, 715 cm^{-1}. PMR δ ($CDCl_3$): 4.87 (1H, s) ,4.00 (1H, d.d.d, J=10.0, 5.0, 3.0 Hz), 2.70—1.20 (15H, br. complex m). CMR δ ($CDCl_3$): 74.3 (CH), 56.7 (CH), 51.0 (CH), 43.9 (CH_2), 38.1 (CH_2), 36.2 (CH, CH_2), 30.8 (CH_2), 30.6 (CH_2), 28.7 (CH), 26.9 (CH). Found: C, 54.08; H, 7.25%. Calcd for $C_{11}H_{17}BrO$: C, 53.89; H, 6.99%.

endo-*2-Bromo*-endo-*tricyclo[4.3.1.1^{3,8}]undecan-4-ol (7b).* Reduction of **6b** (111 mg; 0.39 mmol) with $LiAlH_4$ (52 mg) in a similar manner to the above gave a crude product which was chromatographed on silica gel. Elution by hexane and CH_2Cl_2 (3:2) gave **7b** (77 mg, 81%): mp 134—136 °C. MS *m/e* (rel intensity): 246, 244 (M^+, 2, 2), 228, 226 (M^+—H_2O, 8, 8), 165 (66), 147 (100). IR (KBr): 3360, 2925, 1450, 1045, 1010, 715, 680 cm^{-1}. PMR δ ($CDCl_3$); 4.38 (1H, s), 4.08 (1H, d.d.d, J=9.0, 6.0, 3.0 Hz), 2.80—1.00 (15H, br. complex m). CMR δ ($CDCl_3$): 72.9 (CH), 60.8 (CH), 50.1 (CH), 43.5 (CH_2), 40.5 (CH_2), 35.6 (CH), 34.4 (CH_2), 30.4 (CH_2), 28.6 (CH), 26.5 (CH), 24.6 (CH_2). Found: C, 54.01; H, 7.10%. Calcd for $C_{11}H_{17}BrO$: C, 53.89; H, 6.99%.

*Reduction of **7a** and **7b** with* n-*Bu$_3$SnH.* A solution of a mixture of **7a** and **7b** (435 mg; 1.78 mmol) and *n*-Bu$_3$SnH (2.0 g, 6.9 mmol) in benzene (50 ml) was refluxed under nitrogen for 20 h. The solvent was evaporated and the residue was chromatographed on silica gel. Elution by hexane and CH$_2$Cl$_2$ (9:1) gave tricyclo[4.3.1.1^{3,8}]undecan-4-ol (**8**) (229 mg, 78%).

endo-*2-Bromotricyclo[4.3.1.1^{3,8}]undecan-4-one (**9**).* To a mixture of pyridine (1.6 ml) and CH$_2$Cl$_2$ (5 ml) was added CrO$_3$ (160 mg; 1.6 mmol) and then a solution of **7a** (83 mg; 0.34 mmol) in CH$_2$Cl$_2$ (5 ml). The reaction mixture was stirred at room temperature for 30 min and washed with aqueous 5% NaOH, aqueous 5% HCl, and brine, and dried (Na$_2$SO$_4$). After filtration, the solution was passed through a short silica-gel column and the solvent was evaporated to give **9** (76 mg, 91%): mp 124—126 °C. MS *m/e* (rel intensity): 244, 242 (M$^+$, 6, 6), 163 (100). IR (KBr): 2925, 1690, 1460, 1445, 1365, 1200, 1150, 1070, 950, 930, 800 cm^{-1}. PMR δ (CDCl$_3$): 4.55 (1H, s), 3.15 (1H, d, J=6 Hz), 2.90—1.20 (13H, br. complex m). CMR δ (CDCl$_3$): 212.5 (C), 58.8 (CH), 54.4 (CH), 49.9 (CH$_2$), 37.3 (CH$_2$), 36.8 (CH$_2$), 36.0 (CH), 29.3 (CH$_2$), 27.9 (CH$_2$), 26.7 (CH), 25.6 (CH). Found: C, 54.63; H, 6.19%. Calcd for C$_{11}$H$_{15}$BrO: C, 54.33; H, 6.22%.

The oxidation of **7b** (70 mg; 0.29 mmol) in a similar manner to the above gave **9** (67 mg, 95%) also.

*Tetracyclo[5.3.1.0^{2,5}.0^{3,9}]undecan-4-one (**10**).* A solution of **9** (242 mg; 1.00 mmol) and potassium *t*-butoxide (179 mg; 1.59 mmol) in *t*-butyl alcohol (15 ml) was stirred at room temperature for 1.5 h. The reaction mixture was poured onto water and extracted with hexane. The organic layer was washed with brine and dried (Na$_2$SO$_4$). After filtration, the solvent was evaporated and the residue (156 mg) was chromatographed on silica gel. Elution by hexane and CH$_2$Cl$_2$ (4:1) gave **10** (139 mg, 86%): mp 223—225 °C (lit,$^{3)}$ mp 224—227 °C). MS *m/e* (rel intensity): 162(M$^+$, 3), 134 (97), 92 (100). IR (KBr): 2930, 1775, 1445, 1190, 1165, 1120, 1100, 1050 cm^{-1}. PMR δ (CCl$_4$): 3.53 (1H, q, J=6.8 Hz), 3.10 (1H, m), 2.76 (1H, q, J=7.5 Hz), 2.60—1.00 (11H, br. complex m). CMR δ (CDCl$_3$): 211.3 (C), 70.9 (CH), 54.5 (CH), 46.3 (CH$_2$), 35.2 (CH$_2$), 33.8 (CH, CH$_2$), 33.7 (CH), 31.9 (CH), 31.0 (CH$_2$), 28.1 (CH). Found: C, 81.15; H, 8.56%. Calcd for C$_{11}$H$_{14}$O: C, 81.44; H, 8.70%.

*Tetracyclo[5.3.1.0^{2,5}.0^{3,9}]undecane (**1**).* A mixture of **10** (206 mg: 1.21 mmol), KOH (675 mg), and 100% hydrazine hydrate (1 ml) in diethylene glycol (8 ml) was stirred at 110 °C for 30 min and then at 180 °C for 3 h under nitrogen. The sublimed product on the condenser was dissolved in pentane and washed with brine, and dried (Na$_2$SO$_4$). After filtration, the solvent was evaporated and the residue was resublimed at 110 °C/1729 Pa to give **1** (134 mg, 71%): mp 171—172 °C (lit,$^{3)}$ 177—179 °C). MS *m/e* (rel intensity): 148 (M$^+$, 95), 106 (100). IR (KBr): 2925, 2860, 1445 cm^{-1}. PMR δ (CDCl$_3$): 2.90—1.00 (br. complex m). CMR δ (CDCl$_3$): 44.0 (CH, CH$_2$), 38.4 (CH), 37.9 (CH$_2$), 36.8 (CH), 35.6 (CH$_2$), 33.5 (CH), 33.2 (CH$_2$), 31.6 (CH), 29.6 (CH), 28.2 (CH$_2$). Found: C, 88.92; H, 11.02%. Calcd for C$_{11}$H$_{16}$: C, 89.12; H, 10.88%.

References

1) Part of this work was presented at the 37th National Meeting of the Chemical Society of Japan, Yokohama, April 1978, Abstr. 3C14.

2) In cases where there is no ambiguity, we have used trivial nomenclatures for simplicity. The IUPAC names are described in the Experimental section.

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12) We have already observed that a radical type cleavage of **2** also shows the same regioselectivity.$^{7a)}$

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14) We thank Professors T. Sasaki and S. Eguchi for sending the specimen of **10** to us.