Reduction of Adamantanone: Face Selection Induced by 4-Halo and 4,9-Dihalo Substitution

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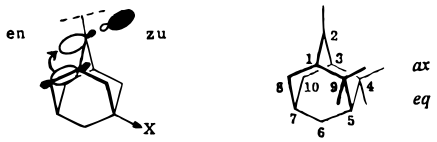
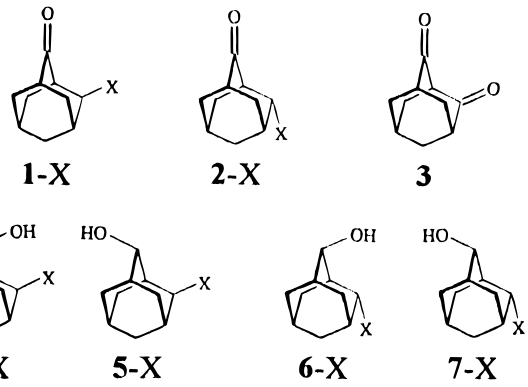
Received January 17, 1996

Our studies[1] of the stereochemistry of addition and elimination as well as those of several other groups[2] have been based largely on the reactions of 2-adamantylidenes bearing substituents in the 5- and/or 7-positions.[3] In these probes, the two faces at C-2 are thereby rendered electronically different while steric equivalence is maintained. We find that attack of all reagents at C-2 occurs at the *zu* face if an electron-withdrawing substituent is located at C-5, while we interpret as an indication that transition state hyperconjugation[4] controls the stereochemistry. Since the product or rate ratios are usually rather modest, the though arose that, perhaps, substantially more robust effects might be expected from substituents located at C-4 and C-9. In the axial positions of these secondary carbons, substituents will clearly influence face selection at C-2 sterically, but in the equatorial ones, they should not.



There are a few scattered data on nucleophilic addition to 4-substituted adamantanones **1**-X, **2**-X, and **3** in the literature. Thus, McKervey[5] reported that the sodium borohydride reduction of **1**-Br gives exclusively **4**-Br—surely a consequence of the size of the bromine atom. The same group also reported[6] that the reduction of **1**-OH with lithium aluminum hydride yields coaxial **4**-OH in a 19:1 excess over isomer **5**-OH; both H-bonding and the size of the 4-hydroxy group may have contributed to this result. More pertinent to our present purpose is the fact that the same reduction of adamantane-2,4-dione (**3**) gave **4**-OH, **5**-OH, and **7**-OH in a ratio of 45:39:16, respectively (note that **5**- and **6**-X are identical when X is OH). From these data, one can readily calculate that in this reduction **3** must initially have given **2**-X and **1**-X in the surprisingly modest ratio of 53:47, respectively, and even more startling, that **2**-OH must give **5**-X in excess over **7**-X by a margin of 70:30. Evidently, an equatorial 4-hydroxy substituent does not direct this nucleophile to the *zu* face at C-2, and even a carbonyl group at C-4 can only barely manage this. Duddeck published one report[7] that **2**-F with zinc borohydride gave **6**-F and **7**-F in a 2:1 ratio and another[8] mentioning a 2:3 ratio (the latter paper also reported a 2:1 ratio for **4**-F and **5**-F from **1**-F). The solvolyses of various sulfonate esters of **4**−**7**-X has been studied by Grob, and his work provided an additional motive for the study reported herein: the effect of equatorial 4-substituents on the solvolysis rate of both *syn*- and *anti*-2-sulfonate esters is even smaller than that of 5-substituents. This finding led Grob to question our interpretation that hyperconjugation is responsible for the effect of 5-substituents.[9]



A weak point in all of these observations and conclusions is that an equatorial 4-substituent affects only one of the four bonds vicinal and periplanar to the trigonal center, whereas a 5-substituent equally influences two of them. Furthermore, while a 5-substituent is well aligned with these two vicinal bonds with a dihedral angle of 180°, a 4-substituent is geminal to one of these (*i.e.*, with an angle of 109°). We felt that it would be difficult to assess the relative weight of these two arguments unless data could be produced with a 2,4,9-trisubstituted system with the 4- and 9-substituents

(1) First observation: le Noble, W. J.; Chiou, D.-M.; Okaya, Y. *Tetrahedron Lett.* **1978**, 1961. Recent examples: (a) Kaselj, M.; Adcock, J. L.; Luo, H.; Zhang, H.; Li.H.; le Noble, W. J. *J. Am. Chem. Soc.* **1995**, *117*, 7088. (b) Lau, J.; Gonikberg, E. M.; Hung, J.-t.; le Noble, W. J. *J. Am. Chem. Soc.* **1995**, *117*, 11421. (c) Gonikberg, E. M.; le Noble, W. J. *J. Org. Chem.* **1995**, *60*, 7751.

(2) (a) Tabushi, I.; Aoyama, Y. *J. Org. Chem.* **1973**, *38*, 3447. (b) Dekkers, A. W. J. D.; Verhoeven, J. W. *Tetrahedron* **1973**, *29*, 1691. (c) Bone, J. A.; Pritt, J. R.; Whiting, M. C. *J. Chem. Soc., Perkin Trans. 2* **1975**, 1447. (d) Grob, C. A.; Bolleter, M.; Kunz, W. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 708. (e) Lantvoev, V. I. *Russ. J. Org. Chem. (Engl. Transl.)* **1980**, *16*, 1409. (f) Hummelen, J. C. Thesis, University of Groningen, 1985, p 86. (g) Nelsen, S. F.; Kapp, D. L.; Akaba, R.; Evans, D. H. *J. Am. Chem. Soc.* **1986**, *108*, 6863. (h) Finne, E. S.; Gunn, J. R.; Sorensen, T. S. *J. Am. Chem. Soc.* **1987**, *109*, 7811. (i) Laube, T.; Stilz, H. U. *J. Am. Chem. Soc.* **1987**, *109*, 5876. (j) Fukunishi, K.; Kohno, A.; Kojo, S. *J. Org. Chem.* **1988**, *53*, 4369. (k) Fernandez, M. J.; Galvez, E.; Lorente, A.; Iriepa, I.; Soler, J. A. *J. Heterocycl. Chem.* **1989**, *26*, 307. (l) Kovalev, V. V.; Rosov, A. K.; Shokova, E. A.; Luzikov, Y. M.; Savel'ev, Y. I. *Bull. Chem. Ser. USSR (Engl. Transl.)* **1988**, 463. (m) Goncharov, A. V.; Panov, V. N.; Maleev, A. A.; Potekhin, K. A.; Kurkutova, E. N.; Struchkov, Y. T.; Palulin, V. A.; Zefirov, N. S. *Doklady (Engl. Transl.)* **1991**, *318*, 148. (n) Burgess, K.; van der Donk, W. A.; Jarstfer, M. B.; Ohlmeyer, M. J. *J. Am. Chem. Soc.* **1991**, *113*, 6139. (o) Johnson, R. A.; Herr, M. E.; Murray, M. C.; Chidester, C. G.; Han, F. *J. Org. Chem.* **1992**, *57*, 7209. (p) Vinkovic, V.; Mlinaric-Majerski, K.; Marinic, Z. *Tetrahedron Lett.* **1992**, *33*, 7441. (q) Huang, X. L.; Dannenberg, J. J. *J. Am. Chem. Soc.* **1993**, *115*, 6017. (r) Adcock, W.; Clark, C. I.; Trout, N. A. *Tetrahedron Lett.* **1994**, *35*, 297. (s) Huang, X.; Bennet, A. J. *J. Chem. Soc., Perkin Trans. 2* **1994**, 1279. (t) Chung, W.-S.; Liu, Y.-D.; Wang, N.-J. *J. Chem. Soc., Perkin Trans. 2* **1995**, 581. (u) Herrman, R.; Kirmse, W. *Liebigs Ann. Chem.* **1995**, 699.

(3) As in our previous papers, we have for the sake of convenience named all compounds except **12** as numbered in the text. The terms axial (*ax*) and equatorial (*eq*) refer to the six-membered ring defined by C-1−5 and C-9.

(4) Cieplak, A. S. *J. Am. Chem. Soc.* **1981**, *103*, 4540.

(5) Cuddy, B. D.; Grant, D.; McKervey, M. A. *J. Chem. Soc. C* **1971**, 3173.

(6) McKervey, M. A.; Faulkner, D.; Hamill, H. *Tetrahedron Lett.* **1970**, 1971.

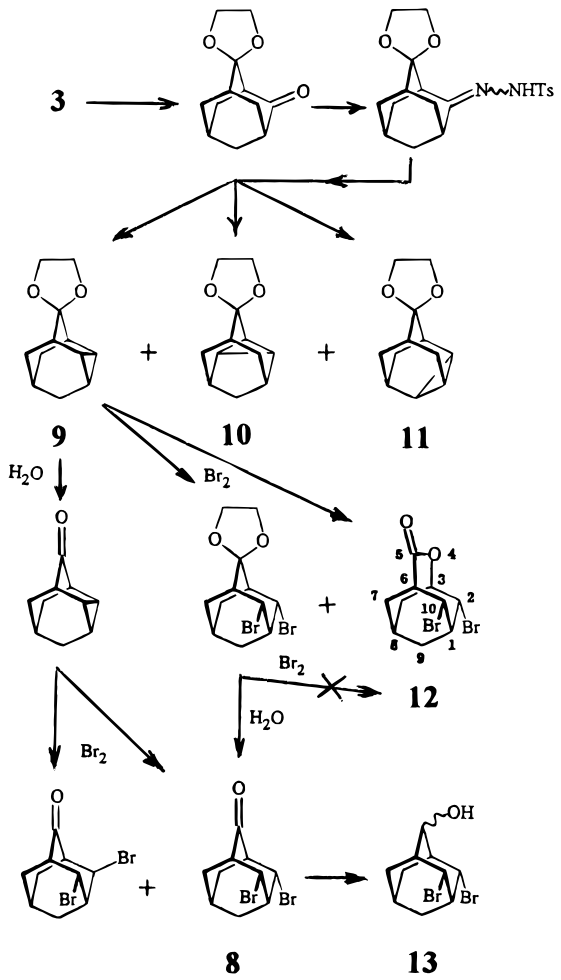
(7) Duddeck, H.; Islam, M. R. *Tetrahedron* **1981**, *37*, 1193.

(8) Duddeck, H.; Islam, M. R. *J. Fluorine Chem.* **1984**, *25*, 371. Professor Duddeck has now privately informed us that the information contained in ref 7 is correct, according to his original spectra and in agreement with our own experiments.

(9) Grob, C. A.; Wang, G.; Yang, C. *Tetrahedron Lett.* **1987**, *28*, 1247. See also: Yang, C.; Grob, C. A. 206th National Meeting of the American Chemical Society, Chicago, IL, Fall 1993; Abstract ORGN 399.

S0022-3263(96)00106-5 CCC: $12.00

Scheme 1



equatorial. No such substituted adamantanes were known, however.[10]

We were able to obtain at least modest samples of **8** by means of a route employing a 2-fold application of the Wynberg method of substituting a second proximal secondary center in adamantanone.[11] For purposes of comparison, we also prepared samples of **1**- and **2**-Br and of **1**- and **2**-F. The synthesis is outlined in Scheme 1 (the attempted conversion of the *unprotected* dione **3** into the corresponding monotosylhydrazone was not successful). Three insertion products **9**−**11** are possible; all three were obtained, and in the ratio of 1:1.5:1.8, respectively. They were separated by means of column chromatography. The assignment by means of ^{13}C NMR was straightforward since the numbers of resonances are 9, 8, and 12, respectively. We note here in passing that **10** has been described in its unprotected ketone form by Baldwin.[12] We also note that the bromination of **9** gave a fair yield of dibromo lactone **12** via oxidative cleavage of one of the ether linkages (a known process[13]); all four of the possible monobromo lactones had been reported by Duddeck.[14] Lactone **12** does not form by bromination of **9**: the ether cleavage occurs first. The structure and configuration of **12** were proven by means of an X-ray diffraction experiment (see Figure 1).[22] This byproduct can be avoided by doing the hydrolysis first, but bromination of the 4,9-didehydroadamantanone so obtained then also gives a substantial amount of the *ax*,*eq* isomer of **8**. The steric requirements of the ketal moiety are apparently such that only the *eq*,*eq* isomer can form when the bromination is done first.

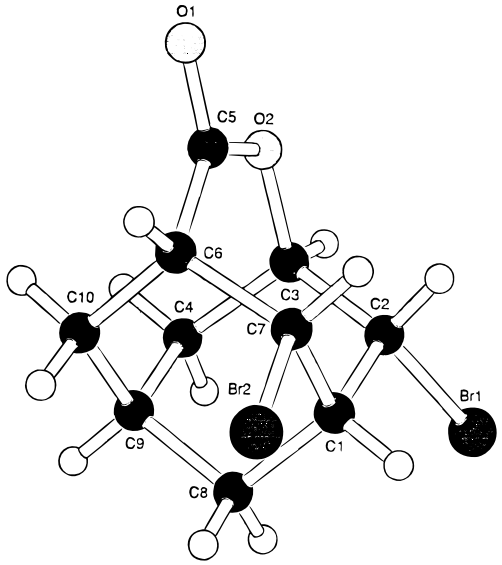


Figure 1. ORTEP diagram showing the structure and configuration of compound **12**. The numbering refers to the tables in the supporting information.

Table 1. Product Distribution in the Reduction of 1, 2, 3, and 8

compd	reducing agent[a]	% product						ref
		4-X	**5**-X	**6**-X	**7**-X	*Z*-**13**	*E*-**13**	
3	$LiAlH_4$[b]	45	39		16			6
1-OH	$LiAlH_4$[b]	95	5					6
2-OH	$LiAlH_4$[b]		30		70			c
1-F	$Zn(BH_4)_2$	33	67					8
1-F	$NaBH_4$	100	0					this work
2-F	$Zn(BH_4)_2$			33	67			7
2-F	$Zn(BH_4)_2$			60	40			8
2-F	$NaBH_4$			33	67			this work
1-Br	$NaBH_4$[d]	99						6
1-Br	$NaBH_4$	100	0					this work
2-Br	$NaBH_4$			24	76			this work
8	$NaBH_4$					14	86	this work

[a] All reactions are done in methanol at 0 °C unless otherwise noted. [b] In refluxing ether. [c] Calculated from data in ref 6. [d] At room temperature.

The reductions were done with sodium borohydride in methanol at 0 °C (Table 1). The product ratios were determined by means of ^{1}H NMR; the published ^{1}H and ^{13}C NMR spectra are in agreement with ours for both the ketones **1**−**2**-F and -Br[6,7,15] and alcohols **4**−**7**-F and -Br.[7,8,16−18] The assignments of (*E*)- and (*Z*)-**13** were made by means of the unseparated mixture; the addition of $Eu(fod)_3$ clearly resulted in a downfield shift of the CHBr

(10) The only 4,9-substituted adamantanone known is the 4-*ax*,9-*eq*-dibromoadamantan-2-one obtained in 4% yield in the reaction of hydrobromic acid with 7-*ax*-bromo-4-oxohomoadamantan-5-one: Duddeck, H.; Brosch, D. *J. Org. Chem.* **1985**, *50*, 5401.

(11) Udding, A. C.; Strating, J.; Wynberg, H. *Tetrahedron Lett.* **1968**, 1345.

(12) Baldwin, J. E.; Fogelsong, W. D. *J. Am. Chem. Soc.* **1968**, *90*, 4303. See also: (b) Murray, R. K.; Morgan, T. K.; Babiak, K. A. *J. Org. Chem.* **1975**, *40*, 1079. (c) Murray, R. K.; Morgan, T. K. *J. Org. Chem.* **1993**, *58*, 5548.

(13) Deno, N. C.; Potter, N. H. *J. Am. Chem. Soc.* **1967**, *89*, 3550, 3555.

(14) Duddeck, H.; Kaiser, M. *Z. Naturforsch.* **1982**, *37B*, 1672.

(15) Snatzke, G.; Eckhardt, G. *Chem. Ber. Bunsen Ges.* **1968**, *101*, 2010.

(16) Duddeck, H.; Wolff, P. *Org. Magn. Reson.* **1977**, *9*, 528.

(17) Duddeck, H. *Tetrahedron* **1978**, *34*, 247.

(18) Farcasiu, D.; von R. Schleyer, P. *Tetrahedron Lett.* **1973**, 3835.

protons in the latter compound much larger than those in the *E*-isomer.

We find that both **1**-F and **1**-Br direct the reagent completely to the remote face of the ketone, so that the steric factor evidently dominates the electronic one—even in the case of the small fluorine atom (we include electrostatic repulsion between nucleophile and halogen unshared electrons in this factor). While this is not greatly surprising, the results with an equatorial substituent are unexpected. Thus, the effect of an equatorial 4-fluoro substituent on the face selectivity is only barely larger than that of a 5-substituent (60:40[19]). It is also curious that the effect of an equatorial 4-fluoro substituent is less than that of a bromine atom in that position. Such a bromine atom does have a somewhat greater effect than one at C-5, but the increase is not impressive. Even with a second bromine at C-9, the *Z*-alcohol is still a substantial portion of the product.

These results cannot be reconciled with the single idea that 4-substituents deactivate only one vicinal bond rather than two as a 5-substituent does. While that fact may play a role, it cannot be the lone or even principal one, since if that were the case, a very much larger effect would have been expected from the second equatorial bromine at C-9. The observed product ratio is not even twice that of a single bromine ($86/14 < (76/24)^2$). The best explanation of these data as well as of Grob's is that alignment is the more critical factor: pure anti-periplanarity—with a dihedral angle between the interacting bonds close to 180°—is needed for the maximum transmission of a substituent effect to a remote site through single bonds (extended hyperconjugation). A similar notion ("double hyperconjugation") has been advanced by Adcock[20] to account for certain features in the NMR spectra of 2,5-disubstituted adamantanes. Paddon-Row *et al.*[21] have found that the presence of even a single *s-cis* "kink" severely retards electron transfer in otherwise completely *s-trans* carbon frameworks. We are presently searching for evidence of chemical effects of even more remote substituents in rigid systems.

Experimental Section

IR spectra were measured in KBr pellets; absorptions are given in cm^{-1}. All NMR spectra were recorded in $CDCl_3$ at 250 MHz (^1H) or at 63 MHz (^{13}C). High-resolution mass spectra were recorded in the Mass Spectrometry Laboratory at the University of Illinois. The signals are assigned below only where the identities of the nuclei are obvious; the ^{13}C signals are grouped according to the outcome of DEPT experiments. The preparations of 4-hydroxyadamantan-2-one and adamantan-2,4-one have been described.[6] A mixture of the known bromoadamantanes **1**- and **2**-Br was obtained by heating a solution of a mixture of the two epimeric 4-hydroxyadamantan-2-ones in 62% hydrobromic acid to reflux and separated by means of column chromatography (silica, 200−400 mesh; petroleum ether:acetone = 10:1); the products were identified by ^1H and ^{13}C NMR.[6,15] Reflux of a cyclohexane solution of a mixture of **1**- and **2**-Br with silver fluoride gave a mixture of **1**- and **2**-F, which was likewise separated by column chromatography, with the products again being identified by means of their known NMR spectra.[7,8,16−18]

Preparation of the Ethylene Ketals of 4,9-, 4,10-, and 4,6-Didehydroadamantan-2-one (8−10). A solution of **3** (1.0 g, 6.5 mmol), *p*-toluenesulfonic acid monohydrate (20 mg), and ethylene glycol (0.37 mL, 6.5 mmol) in benzene (45 mL) was heated to reflux in a Dean−Stark dehydration apparatus for 7 h. The solution was allowed to cool, washed with 40 mL of 10% sodium chloride solution, and dried over magnesium sulfate. After removal of the solvent, 1.2 g of the monoketal was obtained (88%). Recrystallization from chloroform/hexane at −80 °C gave white crystals: mp 35 °C; IR 2922 (s), 2856 (m), 1720 (s), 1123 (m), 1083 (m), 1030 (m); ^1H NMR δ 3.72 (m, 4H), 2.28 (d, 2H, J = 15.8 Hz), 2.10 (td, 1H, J = 2.9, 10.3 Hz), 1.94 (d, 1H, J = 12.3 Hz), 1.82−1.60 (m, 8H); ^{13}C NMR δ 213.01 (CO), 111.24 (COO), 64.21 and 63.97 (CH_2O), 55.59, 44.89, 35.68 and 25.71 (CH), 38.29, 36.85, 33.14 and 31.43 (CH_2); MS m/z 208 (M^+), 190 ($M^+ - H_2O$); HRMS fd 208.1100, calcd 208.1099.

The product (1.2 g) was converted into the corresponding tosylhydrazones by treatment with tosylhydrazine (1.4 g, 6.0 mmol) in methanol (10 mL) at room temperature for 4 h. A mixture of the *cis*- and *trans*-tosylhydrazones precipitated; it was isolated by filtration and drying (1.9 g, 92%): IR 3221 (s), 2925 (s), 1328 (s), 1164 (s), 1034 (s); ^1H NMR δ 7.78 (d, 4H, J = 8 Hz), 7.25 (d, 4H, J = 8 Hz), 3.94−3.65 (m, 8H), 2.95 (s, 2H), 2.49 (s, 2H), 2.38 (s, 6H), 2.10−1.92 (m, 4H), 1.80−1.50 (m, 16H); ^{13}C NMR, δ 167.75 and 166.15 (C=N), 143.64 and 143.60 (CNH), 135.52 and 135.40 (CMe), 129.43, 129.40, 127.92 and 127.78 (aryl CH), 111.06 and 110.99 (COO), 64.88, 64.58 and 64.05 (CH_2O), 47.54, 41.08, 38.03, 36.74, 36.30, 30.47, 26.21 and 26.17 (CH), 37.84, 37.08, 36.56, 35.23, 34.09, 33.66, 33.61 and 32.49 (CH_2), 21.61 (CH_3). Treatment of small quantities of this mixture (200 mg, 0.57 mmol) with 50% sodium hydride (30 mg, 0.63 mmol) in dry tetrahydrofuran (1.5 mL) at room temperature for 2 h afforded the tosylhydrazone sodium salts. After drying, pyrolysis at 170 °C yielded 25 mg (23%) of a 1:1.5:1.8 mixture of **9**, **10**, and **11**. Column chromatography on basic alumina with ligroin (60−80 °C):ether (0−20%) gave pure samples of all three compounds.

Ethylene ketal of 4,9-didehydroadamantan-2-one (9): mp 30−31 °C; IR 3035 (w), 2928 (s), 2855 (m), 1116 (s), 1033 (s); ^1H NMR δ 3.89 (m, 4H), 2.03 (s, 2H), 1.76 (s, 1H), 1.70 (s, 4H), 1.39−1.30 (m, 4H), 1.15 (t, 1H, J = 7.4 Hz); ^{13}C NMR, δ 122.46 (COO), 65.05 and 63.35 (CH_2O), 36.91 (C-1,3), 28.96 (C-8,10), 27.95 (C-6), 24.16 (C-7), 17.96 (C-4,9), 17.64 (C-5); MS m/z 192 (M^+), 125, 99; HRMS fd 192.1150, calcd 192.1149.

Ethylene ketal of 4,10-didehydroadamantan-2-one (10): mp 36−37 °C; IR 3015 (w), 2920 (s), 2860 (m), 1410 (m), 1110 (s); ^1H NMR δ 4.05−3.85 (m, 4H), 2.20 (s, 2H), 2.12−2.02 (m, 1H), 1.92−1.67 (m, 5H), 1.50−1.37 (m, 3H), 1.28 (tt, 1H, J = 1.7, 7.8 Hz); ^{13}C NMR, δ 108.94 (COO), 64.43 (CH_2O), 52.64 (C-6), 35.58 (C-1), 31.88 (C-8,9), 30.57 (C-5,7), 27.64 (C-4,10), 26.80 (C-3); MS m/z 192 (M^+), 163, 149, 137, 112, 99; HRMS fd 192.1150, calcd 192.1149.

Ethylene ketal of 4,6-didehydroadamantan-2-one (11): IR 3020 (w), 2932 (s), 2863 (m), 1120 (s), 1037 (m); ^1H NMR, δ 3.93−3.75 (m, 4H), 2.29 (d, 1H, J = 12.4 Hz), 2.19 (bs, 2H), 2.12−2.00 (m, 1H), 1.87 (d, 1H, J = 11.7 Hz), 1.80 (td, 1H, J = 2.5, 12.5 Hz), 1.67 (s, 1H), 1.58−1.32 (m, 4H), 1.20 (t, 1H, J = 7.5 Hz); ^{13}C NMR, δ 109.73 (COO), 64.20 and 64.06 (CH_2O), 49.34, 31.54 and 27.37 (CH_2), 40.27, 35.33, 30.69, 23.76, 22.34 and 20.55 (CH); MS m/z 192 (M^+), 125, 99; HRMS fd 192.1150, calcd 192.1149.

4-*eq*,9-*eq*-Dibromoadamantan-2-one (8). Bromine (0.016 mL, 0.31 mmol) was added to a solution of **9** (60 mg, 0.31 mmol) in CCl_4 (1.5 mL) at −20 °C. After 2 h, the solvent was evaporated, and recrystallization of the residue from chloroform/hexane gave 45 mg (45%) of white crystals that were identified as 2-*ax*,10-*ax*-dibromo-4-oxahomoadamantan-5-one (**12**, *ax* with respect to the six-membered rings), mp 147 °C. The mother liquor yielded a residual oil which was purified by passing through a column of neutral alumina. Elution with ligroin (60−80 °C):ether (8:2) gave the pure ketal of **8** (12 mg, 11%): mp 101−102 °C (an additional experiment showed that there was

(19) Cheung, C. K.; Tseng, L. T.; Lin, M.-h.; Srivastava, S.; le Noble, W. J. *J. Am. Chem. Soc.* **1986**, *108*, 1598.

(20) (a) Adcock, W.; Iyer, V. S. *J. Org. Chem.* **1988**, *53*, 5259. (b) Adcock, W.; Krstic, A. R.; Duggan, P. J.; Shiner, V. J.; Coope, J.; Ensinger, M. W. *J. Am. Chem. Soc.* **1990**, *112*, 3140. (c) Adcock, W.; Coope, J.; Shiner, V. J.; Trout, N. A. *J. Org. Chem.* **1990**, *55*, 1411. (d) Adcock, W.; Trout, N. A. *J. Org. Chem.* **1991**, *56*, 3229. See also: (e) Hrovat, D. A.; Borden, W. T. *J. Org. Chem.* **1992**, *57*, 2519. (f) Vinkovic, V.; Mlinaric-Majerski, K.; Marinic, Z. *Tetrahedron Lett.* **1992**, *33*, 7441. (b) McKinley, A. J.; Ibrahim, P. N.; Balaji, V.; Michl, J. *J. Am. Chem. Soc.* **1992**, *114*, 10631.

(21) Kroon, J.; Oliver, A. M.; Paddon-Row, M. N.; Verhoeven, J. W. *Rec. Trav. Chim. Pays-Bas* **1988**, *107*, 509.

(22) The author has deposited atomic coordinates for **12** with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

no reaction of this ketal with bromine, indicating that bromination occurs first); IR 2944 (s), 2860 (m), 1223 (m), 1115 (s), 1034 (s); ^{1}H NMR, δ 4.60 (s, 2H), 3.95 (s, 4H), 2.29 (bs, 2H), 2.24 (s, 1H), 2.13 (s, 2H), 2.04 (s, 2H), 1.88 (d, 2H, J = 13.1 Hz), 1.75 (s, 1H); ^{13}C NMR, δ 110.10 (COO), 64.73 and 64.64 (CH_2O), 53.42 and 43.99 (C-1,3,4,9), 42.04 (C-5), 29.51 (C-8,10), 25.62 (C-7), 25.53 (C-6); MS m/z 354, 352, 350 (1:2:1, M^+), 273, 271 (1:1, $M^+ - Br$), 229, 227 (1:1, $M^+ - C_2H_4BrO$), 191 ($M^+ - HBr_2$). **12**: IR 2936 (m), 2865 (m), 1735 (s), 1168 (s), 1077 (s); ^{1}H NMR δ 4.58 (bs, 2H), 4.41 (s, 1H), 3.39 (d, 1H, J = 5.5 Hz), 2.65−2.50 (m, 2H), 2.44−2.25 (m, 3H), 2.17 (s, 1H), 1.95−1.74 (m, 2H); ^{13}C NMR δ 172.48 (C-5), 75.70 (C-3), 49.58, 48.55, 47.41 and 41.62 (CH), 30.10, 26.19 and 22.91 (CH_2), 25.05 (C-8); MS m/z 201, 199 (1:1, $M^+ - CBrOO$), 119. The X-ray diffraction experiment was done with Mo Kα radiation, and 1039 reflections were collected. The full set of data and results are shown in the supporting information.

A solution of the ketal (12 mg, 0.03 mmol) in 88% formic acid (1.2 mL) was heated to 65 °C for 20 min, diluted with water, and extracted with pentane:ether = 8:2. The combined extracts were dried over magnesium sulfate. Removal of the solvent gave **8** as a white solid (8.5 mg, 81%): mp 131−132 °C; IR 2928 (s), 2861 (m), 1735 (s), 1712 (s), 898 (m); ^{1}H NMR δ 4.35 (s, 2H), 2.82 (s, 2H), 2.65 (d, 2H, J = 11 Hz), 2.48 (s, 1H), 2.37 (s, 2H), 1.95−1.83 (m, 3H); ^{13}C NMR δ 208.81 (C-2), 53.44 and 50.88 (C-1,3,4.9), 41.85 (C-5), 34.76 (C-8,10), 26.34 (C-7), 25.08 (C-6); MS m/z 310, 308, 306 (1:2:1, M^+), 229, 227 ($M^+ - Br$), 201, 199 (1:1, $M^+ - CBrO$), 119; HRMS fd 305.9255, calcd 305.9255.

Alternatively, **9** could be hydrolyzed first, as described above, to give the 4,9-didehydroadamantanone as a white solid melting above 130 °C: IR 3050 (w), 2916 (s), 1728 (s); ^{1}H NMR δ 2.53 (s, 2H), 1.90−1.72 (m, 7H), 1.53−1.37 (m, 3H); ^{13}C NMR δ 215.91 (C-2), 41.19 (C-1,3), 33.71 (C-8,10), 26.52 (C-6), 24.87 (C-7), 14.90 (C-5), 12.75 (C-4,9); MS m/z 148 (M^+), 120 ($M^+ - CO$), 105, 91, 79. Bromination of this compound as described above gave two 4,9-dibromoadamantanones in the ratio of 70:30. The main product was identified by its mass spectrum and GC retention time as **8**; the minor product is assumed to be the *eq,ax* isomer from the similarity of its GC retention time and almost identical mass spectrum; the main difference is that the minor isomer has a much larger 227/199 peak ratio.

Reduction Experiments. Sodium borohydride (1.5 mg) was added to a stirred solution of **8** (10 mg, 0.03 mmol) in methanol (1 mL) at 0 °C. After 3 h, the mixture was poured into an ammonium chloride solution and extracted with chloroform. The combined extracts were dried over magnesium sulfate. Evaporation left a solid mixture of (*E*)- and (*Z*)-**13**: IR 3520−3100 (m), 2923 (s), 2865 (m), 1108 (s); ^{1}H NMR δ 4.89 (s, H-4,9(*Z*)), 4.32 (s, H-4,9(*E*)), 4.25 (s, H-2(*Z*)), 3.91 (s, H-2(*E*)), 2.48−1.50 (m, 22H); ^{13}C NMR δ (*E*) 72.26 (C-2), 53.22 (C-4,9), 41.99, 41.36 and 26.21 (C-1,3,5,7), 31.13 and 26.15 (C-6,8,10), (*Z*) 75.89 (C-2), 53.69 (C-4,9), 43.08, 41.68 and 25.71 (C-1,3,5,7), 29.69 and 26.01 (C-8,10); MS m/z 312, 310, 308 (1:2:1, M^+), 294, 292, 290 ($M^+ - H_2O$), 231, 229 (1:1, $M^+ - Br$), 213, 211 (1:1, $M^+ - BrH_2O$). Integration of the well-separated H-4,9 peaks showed that the ratio of isomers was $E:Z$ = 86:14. A duplicate experiment gave the identical result. The assignment of configuration rests on the effect of $Eu(fod)_3$ on the ^{1}H NMR spectrum of the mixture: plots of the chemical shifts against the amounts of $Eu(fod)_3$ added were linear (r = 0.997), and the slopes (in arbitrary units) were as follows: (*E*) H-4,9, 3.25; H-2, 4.38; (*Z*) H-4,9, 1.63; H-2, 8.25. The reductions of **1**- and **2**-Br and of **1**- and **2**-F were carried out in the same way but on a somewhat larger scale (0.24 mmol). The isomer ratios were determined by integration of the H-4 signals in the ^{1}H NMR spectra; the spectral data were in agreement with those published.[7,8,16−18]

Acknowledgment. The National Science Foundation supported this work. We are indebted to Professor Joseph Lauher for the X-ray diffraction study.

Supporting Information Available: IR, ^{1}H and ^{13}C NMR, and mass spectral data for all compounds mentioned in the Experimental Section (61 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.

JO9601066