Onset of Anh Hyperconjugation in the Transition State of Carbonyl Addition by Deactivation of Periplanar Vicinal Bonds

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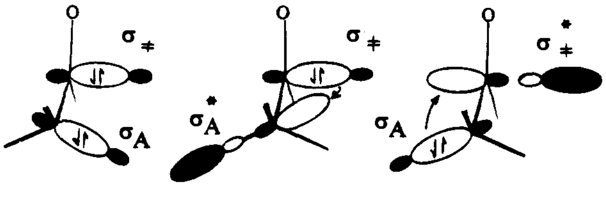
Abstract: The previously observed preferential *syn* delivery of hydride anion in the reduction of the carbonyl group of 5-fluoroadamantan-2-one is inverted if the identities of all hydrogen and fluorine atoms are reversed. A similar and somewhat smaller alteration is observed in the reduction of 5-chloroperfluoroadamantan-2-one. The interpretation is that the periplanar bonds are then no longer capable of stabilizing the transition state by electron donation, and instead do so by accepting electron density from the incipient bond into the σ^* orbitals. The configurations of the reduction products were deduced from their ^{19}F NMR spectra by means of a chemical shift additivity procedure.

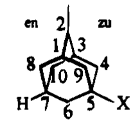
The subject of diastereoselectivity in addition and elimination has attracted much attention in recent years. One of the schools of thought is promulgating the idea that hyperconjugation can lower the energy of the transition state sufficiently to make a significant contribution to the observed product ratios.[1] As we have noted in an earlier discussion,[2] three ideas, advanced by Felkin,[3] Anh,[4] and Cieplak,[5] describe the types of hyperconjugation that can play a role. The first of these is basically the repulsion between the occupied incipient carbon–nucleophile bond and synperiplanar σ orbitals; the others describe the attractive interaction between the newly forming bond and the vacant antiperiplanar σ^* orbitals, and that between the antibonding component of the nascent orbital with the antiperiplanar σ orbitals, respectively (see Figure 1).

In efforts to determine whether one of these interactions is dominant, many experiments have been done, some of which have made use of relatively rigid and symmetrical probe molecules in which the two faces of the trigonal carbon atom are essentially identical from the steric point of view and in which the identities of the periplanar bonds are well defined.[6] Our own studies have been based on 5-substituted adamantane derivatives with the trigonal carbon at C-2. The vicinal bonds are distinguished electronically by the substituent X at C-5 *versus* the unsubstituted function C-7H. For example, it was found that the reduction of 5-fluoroadamantan-2-one (**1-F**) with sodium borohydride produces the (*E*)-alcohol in a 60:40 excess over the (*Z*)-isomer: attack at the *en* face must surmount a higher barrier than that at the *zu* alternative.



(a) (b) (c)

Figure 1. Hyperconjugative interactions in the addition of a nucleophile to a carbonyl trigonal carbon. (a) The Felkin term, involving the occupied σ_A and $\sigma_{\ddagger}$ orbitals, is repulsive and destabilizing. (b) The Anh term, involving $\sigma_A{}^*$ and $\sigma_{\ddagger}$, is attractive and stabilizing. (c) The Cieplak term, involving σ_A and $\sigma_{\ddagger}{}^*$, is also attractive and stabilizing.



We concluded that the Cieplak stabilization to the transition state outweighs the Anh contribution, since the latter predicts the opposite stereochemistry.[7] A long and growing list of addition and elimination reactions has led to the belief that this result is exceedingly general; these processes include both nucleophilic and electrophilic additions, the capture of intermediates such as carbenes, radicals, carbanions, and carbocations, pericyclic reactions, metal complexation, sulfur oxidation, and so on.[8]

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(1) For a recent contribution and summary of this view, see: Coxon, J. M.; Houk, K. N.; Luibrand, R. T. *J. Org. Chem.* **1995**, *60*, 418. Perhaps the chief contending idea is that electrostatic effects control diastereoselection. For recent papers supporting this notion, see for example: (a) Paddon-Row, M. N.; Wong, S. S. *J. Chem. Soc., Chem. Commun.* **1991**, 327. (b) Broughton, M. B.; Green, S. M.; Rzepa, H. S. *J. Chem. Soc., Chem. Commun.* **1992**, 998. (c) Paddon-Row, M. N.; Wu, Y.-D.; Houk, K. N. *J. Am. Chem. Soc.* **1992**, *114*, 10638. (d) Fujita, M.; Akimoto, S.; Ogura, K. *Tetrahedron Lett.* **1993**, *34*, 5139. (e) Adcock, W.; Clark, C. A.; Trout, N. A. *Tetrahedron Lett.* **1994**, *35*, 297. (f) Wipf, P.; Kim, Y. *J. Am. Chem. Soc.* **1994**, *116*, 11678. A possible weak spot for this interpretation has been the lack of information concerning solvent effects.

(2) Li, H.; le Noble, W. J. *Recl. Trav. Chim. Pays-Bas* **1992**, *111*, 199.

(3) Cherest, M.; Felkin, H. *Tetrahedron Lett.* **1968**, 2205.

(4) Anh, N. T. *Top. Curr. Chem.* **1980**, *88*, 145.

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

(6) Among the systems fitting this description to varying degrees and their proponents are the following: (a) (*cis*-3,4-disubstituted cyclobutenes) Burdisso, M.; Gandolfi, R.; Rastelli, A. *Tetrahedron Lett.* **1991**, *32*, 2659. (b) (5,5-diphenyl-substituted cyclopent-2-enones) Halterman, R. L.; McCarthy, B. A.; McEvoy, M. A. *J. Org. Chem.* **1992**, *57*, 5585. (c) (5-substituted cyclopentadienes) Macaulay, J. B.; Fallis, A. G. *J. Am. Chem. Soc.* **1990**, *112*, 1136. (d) (*cis*-5,6-disubstituted cyclohexadienes) Gillard, J. R.; Burnell, D. J. *Can. J. Chem.* **1992**, *70*, 1296. (e) (2,3-di-*endo*-substituted 7-norbornanones) Mehta, G.;Khan, F. A. *Tetrahedron Lett.* **1992**, *33*, 3065. (f) (benzonorbornen-7-ones) Paquette, L. A.; Klinger, F. *J. Org. Chem.* **1982**, *47*, 272. One of the problems with the simple monocyclic and bicyclic probes such as cyclohexanones and even 2-norbornyl derivatives has been the softness to distortion of these systems, prompting various assumptions to be made concerning transition state geometry.

(7) Cheung, C. K.; Tseng, L. T.; Lin, M.-h.; Srivastava, S.; le Noble, W. J. *J. Am. Chem. Soc.* **1986**, *108*, 1598. In this and all of our subsequent papers, the numbering used to describe the adamantane probes is one of convenience rather than of IUPAC rigor; it consistently refers to the carbon skeleton of adamantane as it is shown in the text.

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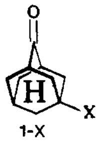
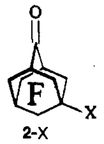
Table 1. ^{19}F NMR Shifts of Compounds **2**−**4** Relative to CCl_3F

compd		F-1,3	F-2	F-5	F-6	F-7	F-4,9^b ax	F-4,9^b eq	F-8,10^b ax	F-8,10^b eq
2-H	obsd	−211.43			−108.38	−220.16	−112.00	−108.44	−123.30	−120.03
2-H	calcd	−211.63			−108.59	−220.07	−111.87	−107.90	−124.22	−120.25
2-F	lit.[9]	−215.82		−224.26	−121.16	−224.26	−124.44	−120.47	−124.44	−120.47
3-F	lit.[10]	−223.89	−121.27	−223.89	−121.27	−223.89	−121.27		−121.27	
2-Cl	obsd	−211.12			−114.34	−219.70	−117.21	−114.01	−124.13	−120.28
2-Cl	calcd	−211.37			−114.21	−219.71	−117.49	−113.52	−124.15	−120.18
3-Cl	lit.[11]	−219.34	−120.98		−114.32	−219.34	−114.32		−120.98	
3-H	lit.[11]	−219.70	−121.05		−108.70	−219.70	−108.70		−121.05	
4-F	obsd^a	−214.27		−223.38	−121.70	−224.73	−124.37	−120.72	−117.76	−120.49
(*E*)-**4**-H	obsd	−210.35			−109.04	−220.55	−111.65	−108.76	−117.19	−120.57
(*E*)-**4**-H	calcd	−210.08			−109.13	−220.54	−111.80	−108.15	−117.54	−120.27
(*Z*)-**4**-H	obsd	−209.63			−109.04	−219.22	−104.23	−107.99	−123.63	−120.93
(*Z*)-**4**-H	calcd	−210.08			−109.13	−219.19	−105.19	−107.92	−124.15	−120.50
(*E*)-**4**-Cl	obsd	−209.27			−115.00	−218.88	−110.47	−113.82	−124.06	−120.76
(*E*)-**4**-Cl	calcd	−209.72			−114.75	−218.83	−110.81	−113.54	−124.08	−120.43
(*Z*)-**4**-Cl	obsd	−209.57			−115.00	−220.23	−117.18	−114.55	−117.44	−120.55
(*Z*)-**4**-Cl	calcd	−209.72			−114.75	−220.18	−117.42	−113.77	−117.47	−120.20

^{a} Assume C-4,9 to be syn to OH. ^{b} ax = axial, eq = equatorial.

We wondered whether this order of relative contributions to the transition state stabilization could be reversed in a predictable way. This might be achieved, for example, by lowering the donor capacity of the periplanar bonds, and thereby simultaneously raising their accepting ability. Thus, substitution of all hydrogen atoms in **1**-F except H-7 by fluorine atoms might lead to such reversal: the periplanar bonds are then as incapable of functioning as donors as they can be made while their accepting ability should be optimal. The Cieplak contribution should now be minimized and any Anh tendency promoted to a maximum. The comparison is therefore between the behaviors of ketones **1**-F and **2**-H.


1-X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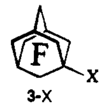
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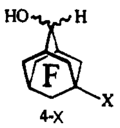
4-X

Recent work in one of our laboratories has shown that it is possible to fluorinate adamantanone as well as partially halogenated adamantanes completely.[9] The chemical shifts and the relative intensities of the ^{19}F NMR signals of "F-adamantanone" (**2**-F) together with the known spectrum of perfluoroadamantane (**3**-F)[10] (two signals in a 1:3 ratio) readily allow the five signals to be assigned (see Table 1). The axial and equatorial fluorines (in the cyclohexanone rings) are coupled with $J \approx 260$ Hz; the chemical shifts are all readily understandable in terms of the dipolar effect of the carbonyl group. Perfluorination of 5-chloroadamantanone gave the 5-chloro analog **2**-Cl, which could be reduced with zinc in acetic acid to furnish the desired starting material **2**-H. Both ketones were completely characterized as detailed in the Experimental Section; the NMR data which form the basis for both analysis and assignment are discussed in some detail here.

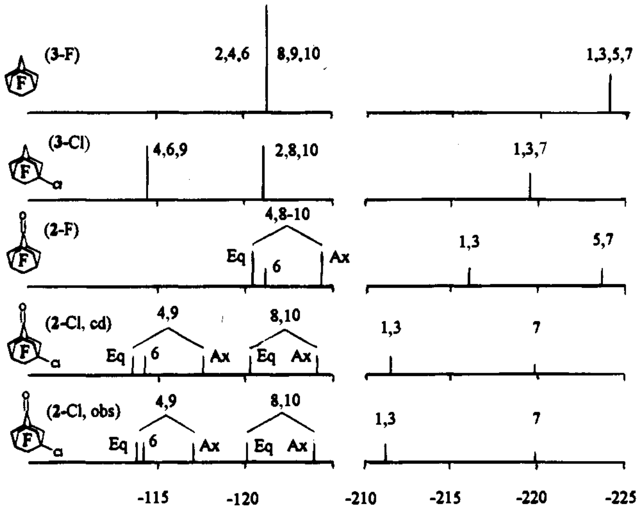

Figure 2. ^{19}F NMR stick spectra of **3**-F, **3**-Cl, and **2**-F, and those of **2**-Cl as calculated from them and as observed.

We noted with interest that the ^{19}F NMR spectra of **2**-Cl and **2**-H could with good precision be calculated from those of 5-chloro-F-adamantane (**3**-Cl),[11] 5-hydryl-F-adamantane (**3**-H),[11] and compounds **2**-F[9] and **3**-F,[10] on the basis of additivity; for example, for ketone **2**-Cl, δ(**2**-Cl) = δ(**2**-F) + δ(**3**-Cl) − δ(**3**-F). The procedure is illustrated in Figure 2, and observed and calculated values are given in Table 1; the average deviation is about 0.2−0.3 ppm. The ^{1}H NMR spectrum of **2**-H is also interesting: it consists of a single octet at δ 4.086, its symmetry indicating splitting by an *odd* number of equivalent fluorines. The ratio is approximately 1:4:9:14:14:9:4:1. The explanation is that the signal is actually a decet, the interacting fluorines being those bound to carbons 1, 3, and 7 and 4, 6, and 9. The former three are one bond further removed from the proton, but they are at the far end of favorable W-conformations; the latter six are closer but suffer from 60° dihedral angles. The two outer wings of the signal cannot be seen among the noise.

Reduction of **2**-F with a slight excess of $LiBH_4$ is dry ether at 0 °C gave pure secondary alcohol **4**-F. The parent peak in the mass spectrum was not observable, but the fragmentation pattern, beginning with the loss of HF, left no doubt about the identity of the product. The IR spectrum showed a broad OH peak at 3300−3700 and a weak CH peak at 2941 cm^{-1}. The proton NMR spectrum consists of two peaks in a 1:1 ratio, one being a broad singlet at δ 4.3 and the other a symmetrical quintet in a ratio which suggests that it is really a heptet with the outer

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(8) For a recent example and a reference to earlier papers, see: Bodepudi, V. R.; le Noble, W. J. *J. Org. Chem.* **1994**, *59*, 3265.

(9) Adcock, J. L.; Luo, H. *J. Org. Chem.* **1992**, *57*, 4297.

(10) Adcock, J. L.; Luo, H.; Dai, S. *Magn. Res. Chem.* **1993**, *31*, 969.

(11) Adcock, J. L.; Luo, H.; Zuberi, S. S. *J. Org. Chem.* **1992**, *57*, 4749. Note that the assignments for fluorines d and f in 2-hydryl-F-adamantanone should be reversed in that paper. We were able to find only one instance of the use of additivity or ^{19}F NMR chemical shifts in the literature, namely, that of perfluoro-*n*-alkanes (see: Pretsch, E.; Clerc, T.; Seibl, J.; Simon, W. *Tables of Spectral Data for Structure Determination of Organic Compounds*, 2nd ed.; Springer-Verlag: New York, 1989).

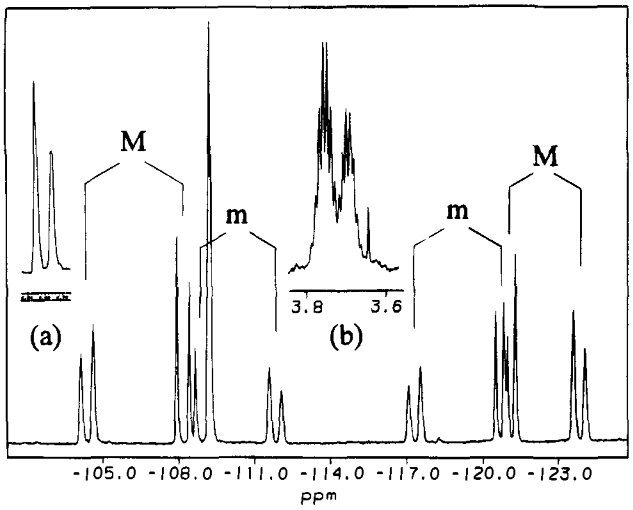
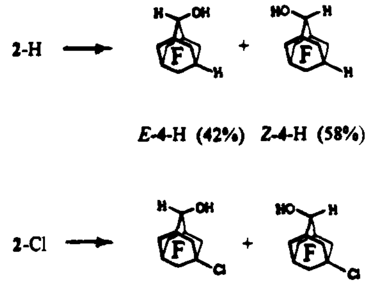


Figure 3. CF_2 region in the ^{19}F NMR spectrum of **4**-H. The spectrum did not change if the delay time between pulses was changed from 1 to 50 s. The assignment of which peaks belong to one isomer and which belong to the other was based on ^{19}F COSY experiments. Additivity calculations were then used to assign the major isomer (M) as (*Z*)-**4**-H and the minor isomer (m) as (*E*)-**4**-H as described in the text. Inset b shows the proton signals of C-5H (the spike at δ 3.639 is an unidentified impurity). The integrations of the ^{19}F and ^{1}H signals agreed to within experimental error with one another and with those of the GC peaks shown in inset a.

wings invisible in the noise ($J \approx 6$ Hz). The fluorine resonances are shown in Table 1; the assignments were straightforward on the basis of comparisons with the known chemical shifts in the parent compounds, and of coupling patterns ($J_{5,7} = 11.7$ Hz, $J_{Ax,Eq} \approx 270$ Hz).

The reduction of **2**-H was carried out in an identical way to give a product proved by means of GC to consist of two components with similar retention times; the ratio was 58:42. Both components had weak parent peaks at $m/z = 386$, and the fragmentation patterns were fully consistent with the structures of secondary alcohol **4**-H. The IR spectrum was similar to that of **4**-F. ^{1}H NMR at 600 MHz revealed two broad OH peaks at δ 3.20 and 1.74 and two multiplets at δ 3.9 and 4.9. The higher field multiplet (Figure 3) consists of a pair of almost completely separated decets with outer wings missing in the noise; $J_{HF} = 5.75$ Hz. The ratio was determined to be 58:42. The lower field multiplet consists of a pair of overlapping septets, also in the ratio of 58:42. The H-2 peaks of the minor isomer showed weak splitting into doublets with $J_{HF} = 1.00 \pm 0.15$ Hz; this was the first hint that this isomer might have the (*E*)-configuration.[12] When the reduction of **2**-Cl was carried out with an excess of zinc, at a somewhat higher temperature and for a longer time than needed for reduction, it was converted into a mixture of the same two components but in a somewhat different ratio (60:40); a comparison of the two ^{19}F NMR spectra helped us decide how to divide the peaks into two sets (Figure 3). The observed fluorine resonances are given in Table 1 together with the values calculated on the basis of additivity. Since we do not have independent evidence that the F-4,9 and F-8,10 signals were assigned correctly in **4**-F, it is important to note that the deviation of the calculated from the observed axial fluorine resonances is almost 20 times larger if the opposite assumption is made. We believe that this convincingly demonstrates that the major isomer indeed has the (*Z*)-configuration. As Figure 3 furthermore shows, the minor isomer has the longer retention time in GC, as might be expected of the more polar isomer. The borohydride reduction of **2**-Cl similarly gave rise to a quantitative yield of a solid mixture of two alcohols, (*Z*)-**4**-Cl and (*E*)-**4**-Cl. Both GC and ^{19}F NMR intergrations gave the ratio at 55:45, and ^{19}F chemical shift analysis showed the major isomer to have the (*E*)-configuration. The ratio is somewhat closer to unity in this case, as expected, but the stereochemistry is the same (note that changing H-5 to Cl-5 interchanges the (*E*)- and (*Z*)-designations). The data are once again displayed in Table 1. Our results may be summarized by



E-4-H (42%) Z-4-H (58%)

Z-4-Cl (45%) E-4-Cl (55%)

The conclusion is that, under these unusual circumstances, the electron demand by the vicinal bonds is greater than that of the incipient bond, and that Anh hyperconjugation accordingly becomes dominant.[13] One interesting corollary is that this same reversal may be the reason for an observation published by Meyers,[14] who found that the stereochemistry of cyclopropanation of a bicyclic allyl ether (*syn* to oxygen) did not change upon the introduction of a pentafluoroethyl group in the α position. He interpreted this response as evidence that Cieplak hyperconjugation could not be relied upon as a predictor of stereochemistry. It now appears that the substitution may have had the unintended effect of reversing the hyperconjugative electron flow in the transition state.

Experimental Section

5-Chloroperfluoroadamantan-2-one (2-Cl, "5-Chloro-F-adamantanone"). This compound was prepared from 5-chloroadamantan-2-one[15] as follows. The perfluorination was carried out by means of the aerosol direct technique described elsewhere.[16] The operating conditions are described in the supporting information (p S-11). The fluorinated material was handled by vacuum line and characterized by its vapor phase IR spectrum recorded on a Bio-Rad Spc 3200 spectrometer. The negative chemical ionization (electron attachment) mass spectrum was recorded on a VG.ZAB-EQ mass spectrometer. Samples were introduced into the source via the reference inlet to a pressure of 10^{-6} Torr, diluted with nitrogen to $10^{-5}-10^{-4}$ Torr, and bombarded with 70 eV electrons. Elemental analyses were performed by E&R Microanalytical Laboratory, Inc., Corona, NY. The ketone (1.65 g; 8.97 mM) was fluorinated in 1,2,3-trichloropropane (7.04 g; 42.4 mM) solution over a period of 4.5 h; **2**-Cl (2.19 g; 5.25 mM; 58.5%) was collected in a −22 °C trap and 1,2,3-trichloroperfluoropropane (8.0 g; 33.7 mM; 79.3%) condensed in the −79 °C trap. The vapor phase IR spectrum had absorption bands at 1814 (2), 1313 (w),

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(12) (a) Takahashi, M.; Davis, D. R.; Roberts, J. D. *J. Am. Chem. Soc.* **1962**, *84*, 2935. (b) Cross, A. D.; Landis, P. W. *J. Am. Chem. Soc.* **1962**, *84*, 1736.

(13) One difficulty with the Felkin model (implied but not explicitly stated in our 1986 paper[7]) is the common nature of the carbonyl and carbocation stereochemistries. In all of the extensive literature on σ delocalization in carbocations, no proposals have ever been made to attribute observed selectivities to the Felkin model, *i.e.*, to repulsion between the leaving group (or capturing nucleophile) and the synperiplanar bonds (see also: le Noble, W. J. *Croat. Chem. Acta (Special Issue)* **1992**, *11*, 5).

(14) Meyers, A. I.; Wallace, R. H. *J. Org. Chem.* **1989**, *54*, 2509. An alternative interpretation has also been offered: Durkin, K. A.; Liotta, D. *J. Am. Chem. Soc.* **1990**, *112*, 8162.

(15) Geluk, H. W. *Synthesis* **1972**, 374.

(16) Adcock, J. L.; Cherry, M. L *Ind. Eng. Chem. Res.* **1987**, *26*, 208.

1284 (s), 1276 (s), 1252 (m), 1221 (w), 1025 (w), 1007 (w), 965 (m), 948 (m), and 856 (w) cm^{-1}. The carbonyl absorption at 1814 cm^{-1} may be compared with that of F-adamantanone (**2**-F) (1815 cm^{-1}); see pp S-11−14 in the supporting information. After purification by means of gas chromatography, a white solid was obtained, mp 153−4 °C. The mass spectrum showed the parent peaks at *m/z* = 418 and 420 in the expected 3:1 ratio. The fragmentation pattern is shown in the supporting information. HRMS: found 417.9430, calcd 417.9430. Anal. Calcd for $C_{10}F_{13}OCl$: C, 28.70, F, 59.00. Found: C, 28.61, F, 63.46.

5-Hydryl-F-adamantanone (2-H). A solution of **2**-Cl (50 mg) in glacial acetic acid was treated at 0 °C with zinc dust (12 mg) for 3 h. After the addition of saturated sodium chloride (40 mL), the resulting mixture, upon standing overnight at 0 °C, gave rise to a white deposit from which the supernatant liquid portion was decanted. Addition of chloroform (2 mL) caused the deposit to dissolve. Filtration through a cotton plug removed unreacted zinc and produced a colorless solution which was dried over molecular sieves. The solvent was removed by bulb-to-bulb distillation at 10 °C which gave a white solid that was pure by the GC standard, mp 121−4 °C. The parent peak in the MS spectrum was observed at *m/z* = 384. HRMS: found 383.9816, calcd 383.9819. The IR spectrum showed the carbonyl peak at 1807 cm^{-1}; the CH stretch was too weak to observe. ^{1}H NMR: δ 4.09 (octet, 1H, J = 5.5 Hz); see pp S-3−10 in the supporting information.

2-Hydryl-F-adamantan-2-ol (4-F). F-adamantanone (**2**-F) (8 mg) was dissolved in dry ether at 0 °C, and lithium borohydride (2 mg) was added. Aqueous workup provided **4**-F as a white solid, mp 135−7 °C. HRMS: found 383.9820, calcd 383.9819. ^{1}H NMR: δ 4.84 (quintet, 1H, H-2, J = 6 Hz), 4.22 (br s, 1H, OH). The spectra are discussed in the main text; see pp S-15−21 in the supporting information.

(*E*)- and (*Z*)-2,5-Dihydryl-F-adamantan-2-ol (4-H). This reduction was carried out in the same way as that of **2**-F. A white solid was obtained of melting range 142−6 °C. HRMS: found for the two isomers 365.9898 and 365.9895, calcd for M$^+$ − HF 365.9913. ^{1}H NMR (600 MHz): δ 4.87 (m, (*Z*)-H-2), 4.86 (m, (*E*)-H-2), 3.74 (octet, (*Z*)-H-5, J = 5.7 Hz), 3.68 (octet, (*E*)-H-5, J = 5.5 Hz); see pp S-22−36 in the supporting information.

(*E*)- and (*Z*)-5-Chloro-2-hydryl-F-adamantan-2-ol (4-Cl). This reduction was also carried out in the same way as that of **2**-F. Again, a white solid resulted; it had a melting range of 155−7 °C. HRMS: found for the two isomers 399.9527, calcd for M$^+$ − HF 399.9524. ^{1}H NMR: δ 4.82 (m, 1H, H-2 (*E* + *Z*)), 4.09 (br s, 1H, OH (*E* + *Z*)). The spectra are shown on pp S-37−46 in the supporting information.

Acknowledgment. The Mass Spectrometer Facility at the University of Illinois produced the high-resolution mass spectra. The National Science Foundation provided financial support for which we express our thanks.

Supporting Information Available: GC−MS, HRMS, IR, and NMR spectra of all new compounds (46 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

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