Articles

Face Selection in the Capture of Anionic Carbon

Vani R. Bodepudi and William J. le Noble*

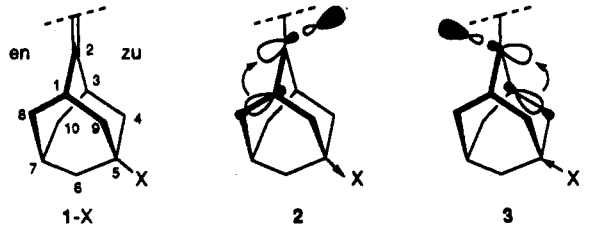
Department of Chemistry, State University of New York, Stony Brook, New York 11794

Received December 29, 1993®

Several reactions of 2-(5-phenyladamantyl) derivatives have been examined with the objective of determining the stereochemistry of addition of electrophiles to a trigonal center C_2 carrying a full or partial negative charge. These reactions included the carbonation and bromination of the 2-lithioadamantane(s); attack at the *zu* face was found to be predominant. Methylation of 5-phenyl-2-adamantanone with either methyllithium or lithium dimethylcuprate gave mixtures of the methyl alcohols in which the *E*-isomer is the main product. Attempts to study the reactions of the enolate anion derived from the (*E*)- and (*Z*)-phenyl 2-(5-phenyladamantyl) ketones **7**-Ph were not successful: bromination could not be forced at all, and methylation and protonation occur at oxygen. The enol ether and enol were studied also; brominations of these neutral species occur at the *zu* face. It is concluded that even the imposition of negative charge upon the trigonal center does not engender the type of hyperconjugation envisioned by Anh in the capture of electrophiles. Protonation of the enol ether led to an equilibrium mixture of ketones **7**-Ph; protonation of the enol itself gave an excess of the *E*-isomer. Possible reasons for this unexpected outcome are discussed.

The stereochemistry of addition reactions and their reverse is subject to several effects, one of which, the electronic factor, has been the focus of our interest for several years. The probe with which we have pursued this interest is a series of adamantane derivatives **1**-X in which the C_5 substituent transmits its effect through the rigid and geometrically well-defined carbon skeleton to the trigonal center at C_2 and thereby differentiates its two faces without being sterically involved. To date, we have found remarkably uniform results in a wide variety of reactions; these findings may be summarized by the statement that all kinetically controlled additions and eliminations occur preferably at the *zu* face if the group X is electron withdrawing (compared to the hydrogen at C_7), and at the *en* face if it is a donor.[1] We have interpreted these results in terms of transition-state hyperconjugation in the Cieplak sense, *i.e.*, the transition states are believed to be stabilized via hyperconjugative acceptance of electron density by the incipient σ^* orbital from the antiperiplanar vicinal bonds.[2] The proposed orbital alignments may be seen in **2** and **3**. Adcock[3] has furthermore suggested that the interactions of group X with the bonds vicinal to itself may also be hyperconjugative.

While the isomer ratios have generally been modest (1.25–3) with neutral probes **1**, much larger values have been observed with carbocations (3–10[3]), and this led us to wonder[4] whether reversed stereochemistry might be encountered in additions of electrophiles to anionic carbon. A model that could account for this possibility was proposed years ago by Anh;[5] it involves hyperconjugative donation by the incipient σ bond into the antiperiplanar σ^* components of the vicinal bonds. Four reactions were considered as possible candidates to provide information on this question: electrophilic capture by 2-lithioadamantane, the dimethylcuprate reaction with adamantanone, electrophilic substitution at enolate carbon, and enolate ester Claisen rearrangements. The last of these four studies is reported in a companion paper;[6] the other three are described here. Initially, we also considered Grignard reagents as a logical candidate for these studies; however, when such reagents are prepared from 2-bromoadamantanes, the yields of addition products are too low.[7]



1-X **2** **3**

Results and Discussion

Solutions of 2-lithioadamantane can be easily prepared and efficiently converted into various derivatives.[8] An important concern in the use of organolithium reagents is the nature of this species which is usually oligomeric,[9] of unknown structure and possibly fluxional in character. It

• Abstract published in *Advance ACS Abstracts*, May 15, 1994.

(1) For an example and references, see: Bodepudi, V.; le Noble, W. J. *J. Org. Chem.* **1991**, *56*, 2001.

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

(3) Adcock, W.; Trout, N. A. *J. Org. Chem.* **1991**, *56*, 3229.

(4) Li, H.; le Noble, W. J. *Recl. Trav. Chim. Pays-Bas* **1992**, *111*, 199. In this paper, an extensive discussion and comparison of the Anh, Cieplak, and Felkin models is presented.

(5) Anh, N. T.; Eisenstein, O. *Tetrahedron Lett.* **1976**, 155. Anh, N. T. *Top. Curr. Chem.* **1980**, *88*, 145.

(6) Mukherjee, A.; Wu, Q.; le Noble, W. J. *J. Org. Chem.*, following paper in this issue.

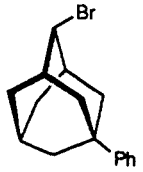
(7) Molle, G.; Bauer, P.; Dubois, J. E. *J. Org. Chem.* **1982**, *47*, 4120.

(8) Wierenga, J. H.; Wynberg, H.; Strating, J. *Synth. Commun.* **1971**, 7.

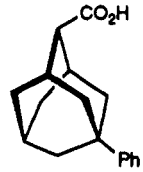
(9) For a recent example, see: Galiano-Roth, A. S.; Kim, Y.-J.; Gilchrist, A. T.; Harrison, D. J.; Fuller, D. J.; Collum, D. B. *J. Am. Chem. Soc.* **1991**, *113*, 5053.

0022-3263/94/1959-3265$04.50/0

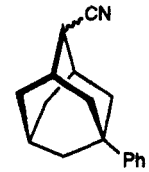
was therefore clear that results could be useful in this connection only if the two epimeric substrates give the same ratio of products. This turned out to be the case. We were able by means of crystallization procedures to obtain small samples of pure (*Z*)-2-bromo-5-phenyladamantane (*Z*-4-Ph) from the 3:1 (*Z*:*E*) mixture produced by reaction of the corresponding alcohols with KBr in polyphosphoric acid. The pure *Z*-isomer and the mixture of the two isomers were both treated with *tert*-butyllithium in ether at −45 °C followed by dry ice, and identical mixtures resulted in which the carboxylic acid *Z*-5-Ph exceeded the *E*-epimer by a margin of 57:43. If bromine was added as the electrophile, the two starting materials were obtained, again in a 57:43 (*Z*:*E*) ratio. Both the bromides and the carboxylic acids had already been identified.[1] These results were the first indication that the Anh type of hyperconjugation is not manifest even when the trigonal carbon carries negative charge. They are consistent with an observation by Eliel[10] that 4-*tert*-butyl-1-lithio-1-phenylcyclohexane is attacked by methyl iodide preferentially at the axial face (70:30).



Z-4-Ph



Z-5-Ph



6-Ph

A second attempt to effect attack at negatively charged carbon was based on a report by Gassman[11] to the effect that *endo*-tricyclo[3.2.1.0^{2,4}]octan-8-one is alkylated with methyllithium or methylmagnesium iodide to give the *E*-alcohol in at least 90% excess, but the *Z*-isomer forms in almost as large an excess when lithium dimethylcuprate is employed. It was suggested that a radical anion is involved in the latter reaction.[11] A similar contrast between two reagents led to a fruitful investigation in an earlier instance.[12] As in that case, we found no decisive difference in the epimeric composition of the tertiary alcohol products when the two reagents were compared vis-a-vis 5-phenyl-2-adamantanone; the *Z*-alcohol exceeded the *E*-isomer in both reactions by about 2:1. Again, a partial negative charge on carbon is evidently not enough to guarantee a reversal of stereochemistry.

The results of addition to anionic trigonal carbon are thus limited in scope to the electrophilic reactions with the lithio derivative of (*E*)- and/or (*Z*)-4, the dimethylcuprate reaction of 5-phenyladamantanone, and the enolate Claisen rearrangement described in the following paper. In view of the preferred formation of products resulting from attack at the *zu* face in these three instances, we conclude that even with anionic carbon, the incipient bond is electron deficient and hyperconjugative assistance by antiperiplanar vicinal bonds characterizes and stabilizes the transition states.

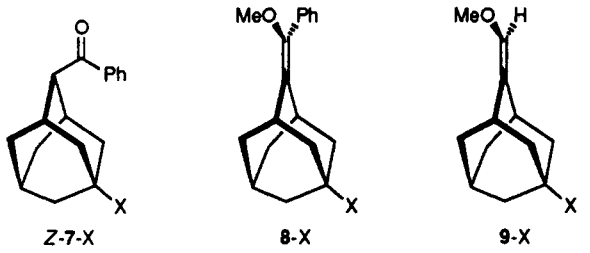
We then turned our attention to the van Leusen TosMIC reaction, in which tosylmethyl isocyanide is allowed to react with carbonyl compounds to give the nitriles with one extra carbon atom.[13] We made this choice for two reasons. First, the nitriles were intended to be used for the preparation of the corresponding 2-adamantyl phenyl ketones as the starting materials for the next study. Second, the configurations of the nitriles themselves were of interest in connection with the present project: the last step in the highly circuitous pathway of this reaction has been presumed[13] to be the protonation of the α-cyano anions, hence (*E*)-6-Ph was expected to be the principal product. However, the opposite turned out to be the case: the major product was (*Z*)-6-Ph, by a margin of 57:43, as determined by means of a proton NMR integration of the α-H signals. The configurations were established by conversion of the products into the corresponding ketones (see below). But rather than conclude that we have uncovered an exception to the findings described above, we believe that a strong reservation is in order regarding the suggested mechanism[13] of the TosMIC reaction. Although it must be at least partially correct (several intermediates have been identified), it is at variance with a study reported by Hünig[14] concerning the analogous 4-*tert*-butyl-1-cyanocyclohexanide anion. This well-authenticated species is protonated preferably at the axial face unless very bulky acids such as mesitol are employed. Since axial attack upon a trigonal carbon incorporated in a cyclohexane ring invariably parallels *syn* addition to C_2 in 2-adamantanones bearing an electronegative 5-substituent, our TosMIC reaction should have produced (*E*)-6-Ph. Proof of this conjecture will depend on a future determination of the complete mechanism of this reaction (see further below).

The stereochemistry of addition to enolates was the subject of our subsequent study. This reaction has obviously attracted much previous attention, and the following literature is pertinent. For exocyclic enolates (both carbon atoms of the enolate group in the ring), explanations of the ratios of products of attack at carbon have favored the steric factor, the sterically less hindered side being approached preferentially in a kinetically controlled step—sometimes to give the thermodynamically disfavored product.[15] An electronic interpretation has been advanced to explain axial attack upon exocyclic enolates (carbonyl carbon is then bound to the ring); the need for continued overlap was held responsible.[16] Both viewpoints have enjoyed considerable support, not necessarily as alternatives to one another.[17] Chelation control was recently advanced as another possibility in a case of endocyclic enolate alkylation.[18] Bredt's rule negates any possibility of studying endocyclic enolates based on adamantanones, but exocyclic enolates based on the adamantane skeleton offer the possibility of studying their product stereochemistry in the absence of any steric difference between the two faces.

2-Cyanoadamantane and the mixture of 2-cyano-5-phenyladamantanes obtained as described above were allowed to react with phenyllithium followed by hydrolysis[19] to prepare both the parent 2-adamantyl phenyl ketone 7-H and a mixture of the two 5-phenyl derivatives 7-Ph;

(10) Keys, B. A.; Eliel, E. L.; Juaristi, E. *Israel J. Chem.* **1989**, *29*, 171.
(11) Gassman, P. G.; Schaffhausen, J. G.; Raynolds, P. W. *J. Am. Chem. Soc.* **1982**, *104*, 6408.
(12) Lin, M.-h.; Silver, J. E.; le Noble, W. J. *J. Org. Chem.* **1988**, *53*, 5155.
(13) Oldenziel, O. H.; van Leusen, D.; van Leusen, A. M. *J. Org. Chem.* **1977**, *42*, 3114.
(14) Gerlach, U.; Hünig, S. *Tetrahedron Lett.* **1987**, *28*, 5805.
(15) Zimmerman, H. E. *J. Org. Chem.* **1955**, *20*, 549.
(16) Corey, E. J.; Sneen, R. A. *J. Am. Chem. Soc.* **1956**, *78*, 6269.
(17) Reviews: Zimmerman, H. E. *Acc. Chem. Res.* **1987**, *20*, 263. Pollack, R. M. *Tetrahedron* **1989**, *45*, 4913.
(18) Durkin, K. A.; Liotta, D. *J. Am. Chem. Soc.* **1990**, *112*, 8162.
(19) van Leusen, A. M.; van Leusen, D. *Synth. Commun.* **1978**, *8*, 397.

a 58:42 mixture was obtained. The effect of small additions of the shift reagent Eu(fod)$_3$ was measured to identify the signals of $C_{4,9}$ and $C_{8,10}$; the chemical shift of the epimers could be confirmed by calculation by means of the additivity procedure.[20] The *Z*-isomer was the predominant one; as noted above, this result is the basis of the analysis of the mixture of nitrile 6-Ph. Fractional crystallization of the mixture gave pure, solid (*E*)-7-Ph and a viscous liquid sample of (*Z*)-7-Ph still containing 10–20% of the *E*-isomer. The two samples gave rise to identical product mixtures in all reactions studied.



Z-7-X 8-X 9-X

Reaction of 7-H with lithium diisopropylamide led principally to reduction to the benzyl alcohol, but sodium hydride in DMF gave the desired enolate. Bromination of the enolates derived from 7-H and 7-H could not be forced; only the starting ketones could be recovered, although the expected bromo ketones, when prepared independently, were found to be stable (*e.g.*, in THF; see below). Approach to the secondary carbons of the adamantane skeleton is notoriously hindered; thus, true S_n2 reactions at these sites appear to be unknown. The reaction of C_2 of the enolate anion with bromine may well require just such an approach. The enolates did react with methyl iodide; however, no *C*-alkylation occurred, and enol ethers 8-X were the exclusive products. Although this result was disappointing, enolate *O*-alkylation does appear to be useful as an alternative for the preparation of these ethers.[21]

Protonation likewise begins by neutralization at the oxygen site as shown by the following results. Quenching of the enolate of 7-H with D_2O followed immediately by an aqueous workup procedure afforded the original ketone, without deuterium; C_2 appeared as the normal singlet in the ^{13}C NMR spectrum rather than the expected triplet. The triplet only began to manifest itself if some time was allowed to pass after the quench and before further workup. If a full day was allowed, the deuteration appeared to be complete (Figure 1). We conclude from these results that the enol must be formed initially, that it loses deuterium in the workup, and that acid-catalyzed rearrangement to the ketone is relatively slow, with *C*-protonation as the last step.[22]

With the methyl enol ether 8-Ph and the semistable enol thence available, a study of the electrophilic capture of these species appeared to be worthwhile. We had previously studied electrophilic addition to methyleneadamantanes; the structures now available allowed some extension to olefinic ones in which the trigonal site C_2 has at least partial negative charge by way of resonance. In remarkable contrast to the failed bromination of the

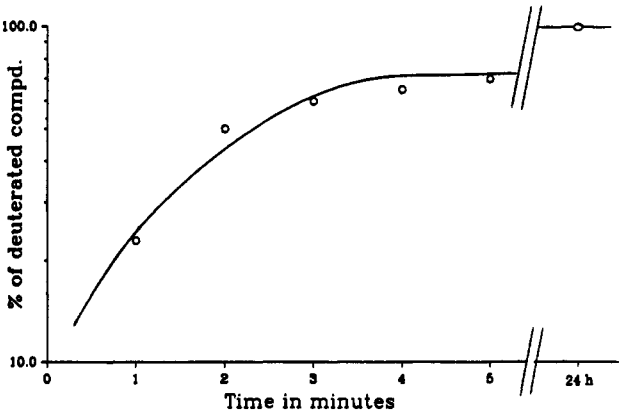


Figure 1. Deuterium uptake by the enolate anion of 7-H from D_2O as a function of delay before aqueous workup.

enolate anion of 7-Ph, the reaction of ethers 8-H and 8-Ph with bromine in carbon tetrachloride proceeded uneventfully to give the corresponding α-bromo ketones. The epimers obtained with 8-Ph were identified in the usual way: the methylene carbons C_4 and C_{8-10} were assigned with the help of Eu(fod)$_3$ additions and their effect on the ^{13}C chemical shifts and independently by means of additivity calculations. The *E*/*Z* ratio was 40:60. The same mixture (41:59) was obtained from the much slower bromination of 7-Ph in acetic acid. Similarly, enol ether 9-Ph—which had been obtained by methylation of the enolate anion derived from 2-formyl-5-phenyladamantane—upon treatment with bromine in carbon tetrachloride gave mostly the *Z*-bromo aldehyde, although the ratio was rather smaller in that case (48:52).

The acid-catalyzed hydrolysis of 8-Ph was examined next. When the configuration of the recovered ketone was examined, we found that the *E*-isomer predominates under these conditions by a margin of 55:45. But this result was found to be uninformative: when either pure *E*-7-Ph or nearly pure *Z*-7-Ph was exposed to 5% HBr in acetic acid, this same identical mixture was formed, which we therefore believe to be the equilibrium mixture. But protonation of the enolate anion under neutral or weakly basic conditions gave a different result. As we have seen, the enol is formed first; if this is given sufficient time to reach the keto stage, the *Z*-isomer of 7-Ph is in excess, by a margin of 56:44. If we were to try to make a correction for the equilibrium position, this ratio would even become a bit larger. The result was the same whether *E*- or *Z*-7-Ph was used to generate the enolate anion and, subsequently, the enol. This reaction seems exceptional, the more so because it is not even an anionic reaction (note that prior protonation of nitrogen in 6 may also be a feature in that reaction).

Is it possible that the protonation mechanism is more complex than we realize, and that it is characterized by special features that would leave these results in harmony with our earlier work? It has traditionally been one of the more difficult ones to pin down, with rates varying from diffusion controlled to reaction rate limiting. In one scenario, the ketone would not be formed by direct *C*-protonation of the enol followed by *O*-deprotonation but rather via the *O*-protonated enol. If this species—which is surely present in at least low equilibrium concentration—undergoes an antarafacial [1,3] shift, the stereochemistry might be opposite to that normally

(20) Srivastava, S.; Cheung, C. K.; le Noble, W. J. *Magn. Reson. Chem.* **1985**, *23*, 232.
(21) Curci, R.; Lopez.; Troisi, L. Rashid, S. M. K.; Schaap, A. P. *Tetrahedron Lett.* **1987**, *28*, 5319.
(22) Kresge, A. J.; Yin, Y. *Can. J. Chem.* **1991**, *69*, 84.

observed.[23] Antarafacial shifts do not involve especially large strains in longer conjugated systems, but [1,3] hydrogen shifts of this type do not seem to have been reported. Alternatively, the reaction might be mediated by one or more water molecules, imparting to it the nature of a [3,n] sigmatropic shift. Still another pathway would be a type of conducted tour mechanism, an example of which was discovered by Cram[24] many years ago. Unfortunately, the whereabouts of acidic hydrogen are notoriously difficult to trace, and these possibilities are purely conjectural for now.

Experimental Section

All NMR spectra were measured in $CDCl_3$ at 300 MHz for protons and 75 MHz for ^{13}C.

2-Bromo-5-phenyladamantane (4-Ph). P_2O_5 (0.55 g) was entered under day nitrogen into a three-necked flask fitted with a condenser; phosphoric acid (1.4 mL) was added dropwise, and a viscous liquid formed after a few minutes of stirring. KBr (2.2 g) was added to this liquid, followed by a 55/45 mixture of the (*E*)- and (*Z*)-5-phenyl-2-adamantanols obtained by $LiAlH_4$ reduction of the ketone.[25] An orange color developed as the mixture was stirred and heated to 120 °C for 1.5 h. Aqueous workup gave a 25:75 mixture of the known[1] *E*- and *Z*-bromides. A small sample of the pure *Z*-isomer was obtained by crystallization from methanol; mp 66-69 °C.

Reactions of the 2-Lithio-5-phenyladamantanes. Addition of either the mixture or the pure *Z*-bromide (0.145 g, 0.50 mmol) to 1.4 M *tert*-butyllithium (2.6 mL) in ether (20 mL) at −55 °C followed 1 h later by excess dry ice gave the known[1] (*E*)- and (*Z*)-5-phenyladamantane-2-carboxylic acids 5-Ph in a ratio of 43:57, respectively. Treatment of either solution with excess bromine gave back the *E*- and *Z*-bromides 4-Ph, but now in the *E*:*Z* ratio of 43:57, respectively.

Methylation of 5-Phenyl-2-adamantanone. (a) With Methyllithium. This reaction was done in the standard way,[26] the (*E*)- and (*Z*)-2-methyl-5-phenyladamantan-2-ols were obtained in a 63:37 ratio, respectively, by integration of the C_2 signals. The epimeric mixture was not separated. ^1H NMR: δ 7.5–7.28 (m, 5H), 2.56–1.63 (m, 14H), 1.49 (s, 3H). ^{13}C NMR: δ 150.34, 149.95, 128.01, 125.57, 125.45, 124.73, 73.11, 72.72, 43.92, 43.58, 40.35 (*E*-$C_{4,9}$), 39.55, 39.39, 38.26 (*Z*-$C_{4,9}$), 35.80, 35.16, 34.04 (*Z*-$C_{8,10}$), 31.95 (*E*-$C_{8,10}$), 27.91, 27.38, 26.94. The assignments are based on an additivity calculation.

(b) With Lithium Dimethylcuprate. This reagent, prepared from 1.3 g (6.5 mmol) of cuprous iodide and 11 mL of 1.2 M methyllithium in 40 mL of ether, was treated with a solution of 0.1 g (0.44 mmol) of the same ketone in 10 mL ether for 2 h. After workup, both the tertiary methyl alcohols and the secondary alcohols resulting from reduction were found to be present; the two pairs could be completely separated (silica gel, 2% ethyl acetate–hexane). The tertiary mixture had an *E*/*Z* ratio of 65:35; the (known[26]) secondary alcohols were present in the *E*/*Z* ratio of 55:45, respectively.

2-Cyanoadamantane (6-H). This compound was prepared from adamantanone as described by van Leusen.[13] ^1H NMR: δ 2.90 (s, 1H), 2.17–1.72 (m, 14H). ^{13}C NMR: δ 122.25, 36.99, 36.68, 36.60 ($C_{8,10}$), 33.06 ($C_{4,9}$), 30.35, 26.85, 26.72 ($C_{4,5,9}$ are arbitrarily assigned to be at the *zu* face).

2-Adamantyl Phenyl Ketone (7-H). This compound was prepared from the nitrile and phenyllithium as described.[19] Recrystallization from acetone–water: mp 97 °C, lit.[19] mp 92–94 °C, ^1H NMR: δ 7.81 (m, 2H), 7.42–7.51 (m, 3H), 3.45 (s, 1H), 2.31 (bs, 2H), 2.10–1.55 (m, 12H). ^{13}C NMR: δ 204.05, 137.13, 132.09, 128.37, 128.01, 52.06, 38.76 ($C_{8,10}$), 37.36, 32.72 ($C_{4,9}$), 30.26, 27.90, 27.46. The ^{13}C assignments (in part, see supplementary material) are based on attached proton tests and on shifts caused by the addition of small known amounts of Eu(fod)$_3$; the relative slopes in arbitrary units are C_2, 10.65; $C_{1,3}$, 8.9; $C_{4,9}$, 6.43; C_5, 3.86; $C_{8,10}$, 2.92; C_7, 2.11; C_6, 2.07.

Reaction of 7-H with LDA. A solution of lithium diisopropylamide was prepared from the amine (2 mmol) and *n*-butyllithium (1 mL, 2 M) in ether at −78 °C and treated with 7-H (0.24 g, 1 mmol), also in ether. The mixture was stirred at −78 °C for 45 min, the reaction was quenched with D_2O, and the solution was diluted with dilute aqueous ammonium chloride and extracted with methylene chloride. The residue obtained after routine workup was chromatographed (silica gel, 5% ethyl acetate–hexane) to give 10% of α-(2-adamantyl)benzyl alcohol, mp 95–97 °C. ^1H NMR: δ 7.34–7.24 (m, 5H), 4.85 (d, 1H, J = 12 Hz), 2.32 (bs, 1H), 2.10–1.20 (m, 15H). ^{13}C NMR: δ 143.97, 128.37, 127.60, 126.65, 74.61, 51.35, 38.96, 38.75, 38.18, 32.16, 31.58, 28.81, 27.93, 27.76. Most of compound 7-H (82%) was recovered.

2-(2-Deuterioadamantyl) Phenyl Ketone (7-H-*d*). A suspension of sodium hydride (30 mg, 1.25 mmol, 50% in mineral oil, washed three times with pentane) in dimethylformamide (4.5 mL, dried over potassium hydroxide, vacuum-distilled, and stored over 4-Å molecular sieves) was treated with 7-H (100 mg, 0.41 mmol) at room temperature, and the mixture was stirred for 6 h. A pale yellow enolate anion solution resulted, the reaction was quenched with D_2O (0.2 mL), and the solution was stirred overnight, diluted with cold water, and extracted with methylene chloride (4 × 15 mL). After washing with brine, drying over magnesium sulfate, and reduction to small volume by rotary evaporation, chromatography (silica gel, 2% ethyl acetate–hexane) gave 83 mg of 7-H-*d*. The δ 3.45 signal was absent from the ^1H NMR spectrum; the ^{13}C NMR was identical with that of the protio analog except that the δ 52.06 signal had been replaced by a 1:1:1 triplet centered at s 51.55 with J_{CD} = 18.5 Hz. If only 1 min was allowed to elapse before the dilution with water was done, the final product contained only 23% deuterium at C_2 (see Figure 1).

2-(Methoxyphenylmethylene)adamantane (8-H). A solution of the parent enolate ion, prepared as described above, was treated with methyl iodide (0.20 mL, 3.2 mmol) at 45–50 °C for 40 h, with stirring. After aqueous workup and chromatography (silica gel, 2% ethyl acetate–hexane), 56 mg (53%) of 9-H was obtained; mp 92 °C (lit.[21] mp 94–95 °C). ^1H NMR: δ 7.36–7.24 (m, 5H), 3.29 (s, 3H), 3.27 (bs, 1H), 2.62 (bs, 1H), 1.97–1.78 (m, 12H). ^{13}C NMR: δ 143.53, 135.42, 131.49, 129.33, 127.94, 127.33, 57.65, 39.19 ($C_{8,9}$), 39.05 ($C_{4,10}$), 37.19, 32.19, 30.17, 28.32. The assignments are based on attached proton tests, a shift reagent study, and the polarization of C–H bonds by nearby electronegative atoms.

(*E*)- and (*Z*)-2-Cyano-5-phenyladamantane (6). The procedure was identical to that used for the parent compound 6-H, but with 5-phenyl-2-adamantanone as the starting material. The yield of the solid mixture was 72%. The *E*/*Z* ratio was 43:57 on the basis of integration of the α-protons after chromatography (silica gel, 2% ethyl acetate–hexane) and on the determination of configuration of the derived ketones (see next section). ^1H NMR: δ 7.38–7.22 (m, 5H), 2.930 and 2.926 (2 s, 1H), 2.38–1.74 (m, 13H). ^{13}C NMR: δ 149.27, 149.19, 128.32, 126.09, 126.04, 124.68, 124.56, 121.86, 121.74, 42.52, 42.23, 42.15 (*E*-$C_{4,9}$) 38.73 (*Z*-$C_{4,9}$), 36.58, 36.34, 35.86 (*Z*-$C_{8,10}$), 35.40, 32.35 (*E*-C_{8-10}), 31.24, 31.30, 27.72 and 27.56.

(*E*)- and (*Z*)-2-(5-Phenyladamantyl) Phenyl Ketone (7-H). The preparation from 6-Ph was identical to that used for the parent compound 7-H. The yield was 85% and the *E*/*Z* ratio was 42/58, by integration of the α-proton. The same ratio was found by means of capillary GC. Crystallization from water–acetone (1:4) gave samples of the minor *E*-isomer in pure form; mp 112 °C. ^{H} NMR: δ 7.84–7.81 (m, 2H), 7.47–7.12 (m, 8H), 3.48 (s, 1H), 2.51 (s, 2H), 2.08–1.92 (m, 9H), 1.57 and 1.55 (2 s, 2H). ^{13}C NMR: δ 203.55, 150.12, 137.08, 132.15, 128.39, 128.11, 127.93, 125.67, 124.73, 51.33, 44.12 ($C_{4,9}$), 42.96, 36.08, 31.82 ($C_{8,10}$), 30.86, 28.12. The assignments rest on attached proton tests, additivity calculations, and a shift reagent study; the relative slopes in arbitrary units are C_2, 12.4; $C_{1,3}$, 10.8; $C_{8,10}$, 7.84; C_7, 4.56; $C_{4,9}$, 3.7; C_5, 3.22; C_6, 2.56. The residue upon evaporation of the mother liquor was a viscous liquid enriched in the Z-isomer; the *E*/*Z*

(23) Lin, M.-h.; Boyd, M. K.; le Noble, W. J. *J. Am. Chem. Soc.* **1989**, *111*, 8746.
(24) Cram, D. J.; Ford, W. T.; Gosser, L. *J. Am. Chem. Soc.* **1968**, *90*, 2598.
(25) Geluk, H. W. *Synthesis* **1972**, 374.
(26) Cheung, C. K.; Tseng, L. T.; Lin, M.-h.; Srivastava, S.; le Noble, W. J. *J. Am. Chem. Soc.* **1986**, *108*, 1598.

ratio was 0.25. *Z*-7-Ph: ^{1}H NMR δ 7.84–7.81 (m, 2H), 7.47–7.12 (m, 8H), 3.43 (s, 1H), 2.51 (bs, 2H), 2.26–.186 (m, 9H), 1.72 and 1.68 (2 s, 2H); ^{13}C NMR δ 203.62, 150.43, 137.03, 132.01, 128.39, 128.11, 127.93, 125.48, 124.68, 51.07, 42.92, 38.20 ($C_{4,9}$), 37.86 ($C_{8,10}$), 35.64, 31.09, 28.69.

2-(2-Deuterio-5-phenyladamantyl) Phenyl Ketone (7-Ph-*d*). The experiment was carried out as for the parent deuterio ketone. The epimers were not separated. The δ 3.48 signal was absent from the ^{1}H NMR spectrum; in the ^{13}C NMR, the C_2 signals at 51.33 and 51.07 ppm were replaced by a pair of 1:1:1 triplets with J_{CD} = 18.7 Hz. The *E*/*Z* ratio was 42:58.

Reactions of 7-Ph Enolate Ion. This anion was generated from 7-Ph and sodium hydride as described for 7-H. It proved to be necessary to use a nitrogen atmosphere since otherwise some oxidation to 5-phenyl-2-adamantanone occurs.[27] Hydrolysis regenerated 7-Ph with an *E*/*Z* ratio of 43:57; it was shown that the isomers do not epimerize under the conditions of their formation. No reaction occurred between the enolate and bromine in 24 h; the ketone was recovered unchanged. The reaction with methyl iodide was carried out as described for the enolate anion of 7-H; a 70% yield of 2-(methoxyphenylmethylene)-5-phenyladamantane (8-Ph) was obtained as a colorless oil. ^{1}H NMR: δ 7.37–7.10 (m, 10H), 3.47 (bs, 1H), 3.34 (s, 3H), 2.81 (bs, 1H), 2.23 (bs, 7H), 2.09–1.82 (m, 10H). ^{13}C NMR: δ 150.37, 144.12, 135.45, 129.91, 129.41, 128.13, 128.05, 127.12, 125.64, 124.86, 57.63, 44.69, 44.40, 42.74, 38.42, 38.24, 36.52, 32.78, 30.64, 29.16.

2-Benzoyl-2-bromoadamantane. A solution of bromine in carbon tetrachloride was used to titrate a solution of 8-H in the same solvent until the yellow color persisted. After removal of the solvent, the residue was essentially the pure bromo ketone. ^{1}H NMR: δ 8.05–7.37 (m, 5H), 2.67 (bs, 2H), 2.53–1.68 (m, 12H). ^{13}C NMR: δ 136.21, 131.67, 129.68, 128.03, 78.22, 37.79, 36.65, 35.74 ($C_{4,9}$), 34.02 ($C_{8,10}$), 26.78, 26.67.

(*E*)- and (*Z*)-2-Benzoyl-2-bromo-5-phenyladamantane. When the same procedure was applied to 8-Ph, the product mixture was obtained and analyzed without separation; the *E*/*Z* ratio was 41:59. ^{1}H NMR: δ 8.05–7.12 (m, 12H), 2.89 (bs, 2H), 2.58–2.79 (2 d, 2H), 2.11–1.73 (m, 9H). ^{13}C NMR: δ 149.29, 148.79, 131.78, 129.70, 129.67, 128.37, 128.33, 128.12, 126.02, 126.01, 124.85, 124.57, 77.21, 42.88 and 43.48, 40.94 (*Z*-$C_{4,9}$), 39.68 (*E*-$C_{4,9}$), 37.69, 37.24, 35.39, 35.34, 35.03 (*E*-$C_{8,10}$), 33.34 (*Z*-$C_{8,10}$), 27.58. The assignments rest on attached proton tests and a shift reagent study.

Bromination of the Ketones in Acetic Acid. Ketone 7-H was brominated only very slowly at room temperature in acetic acid, but the α-bromo ketone could be isolated after 24 h. Similarly, 7-Ph under these conditions gave a mixture of the same epimers as described above, and in the same ratio.

2-(Morpholinomethylene)adamatane. The method of Adam[28] was used. ^{1}H NMR: δ 5.27 (s, 1H), 3.70 (t, 4H), 3.0 (bs, 1H), 2.55 (t, 4H), 2.25 (bs, 1H), 1.95–1.7 (m, 12H). ^{13}C NMR: δ 139.20, 128.05, 66.65, 53.66, 39.83 ($C_{8,9}$), 38.62 ($C_{4,10}$), 37.20, 36.83, 31.25, 28.61.

2-(Morpholinomethylene)-5-phenyladamantane. The same method was used, with a mixture of (*E*)- and (*Z*)-2-formyl-5-phenyladamantanes as the starting material. ^{1}H NMR: δ 7.31–7.14 (m, 5H), 5.33 (s, 1H), 3.70 (t, 4H), 3.18 (bs, 1H), 2.56 (t, 4H), 2.42 bs, 1H), 2.17 (bs, 1H), 1.99–1.77 (m, 10H). ^{13}C NMR: δ 150.13, 137.69, 128.53, 127.99, 125.49, 124.65, 66.68, 53.66, 45.17 (C_9), 44.03 (C_4), 42.67, 38.99 (C_8), 37.79 (C_{10}), 37.20, 36.69, 31.60, 29.28. This enamine regenerated the aldehydes upon protonation, with an *E*/*Z* ratio of 50:50.

Acknowledgment. This work was supported by the National Science Foundation (Grant No. Che 8903149). W. le Noble thanks Prof. Paul Wender for a stimulating discussion.

Supplementary Material Available: ^{1}H and ^{13}C NMR spectra for all the new compounds mentioned in this paper as well as an Experimental Section with more extensive NMR assignments (25 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.

(27) See: Doering, W. E.; Haines, R. M. *J. Am. Chem. Soc.* **1954**, *76*, 482. Russell, G. A.; Bemis, A. G.; Ceets, E. J. Janzen, E. G.; Moye, A. T. *Adv. Chem. Ser.* **1968**, *75*, 174. Bordwell, F. G.; Knipe, A. C. *J. Am. Chem. Soc.* **1971**, *93*, 3416.

(28) Adam, W.; Encarnation, L. A. A. *Chem. Ber.* **1982**, *115*, 2592.