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Competitive Bridgehead Substitution in Electrophilic Oxidation Reactions of Protoadamantane. Synthesis of 3-Protoadamantanol. On the Utility of Molecular Mechanics Calculations for Predicting the Bridgehead Reactivity of Hydrocarbons with Electrophiles

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Oxidation of protoadamantane with lead tetraacetate or chromic acid or by dry ozonation on silica gel occurs by competitive attack at the C-3 (minor) and C-6 (major) bridgehead positions. The structure of the minor product was established unequivocally by the synthesis of 3-protoadamantanol in eight steps from 4-protoadamantanone. The reactivities of the bridgehead positions in a series of polycyclic hydrocarbons related to adamantane have now been tested by the oxidation of these compounds with bromine, chromic acid, and lead tetraacetate. The results of these studies are compared to the calculated (molecular mechanics calculations with the Bingham–Schleyer force field) increase in strain energy that would result from the formation of a carbocation at each bridgehead position in these compounds. It is concluded that molecular mechanics calculations provide a means to predict which bridgehead positions in hydrocarbons *cannot* be functionalized by direct electrophilic substitution.

It is now well established that molecular mechanics calculations permit the quantitative determination of the geometries and energies of a wide variety of structurally different hydrocarbons.[1] Schleyer has pioneered the application of these calculations to correlate and predict the relative bridgehead reactivities of various derivatives of bicyclic and polycyclic hydrocarbons in reactions proceeding by heterolytic or homolytic cleavage of the bridgehead to substituent bond (eq 1).[2] In this treatment

$$R{-}X \rightarrow R^+ + X^- \text{ or } R\cdot + X\cdot \tag{1}$$

the logarithm of the rate constant of the reaction is compared to the calculated difference in strain energy between the transition state and the ground state. The ground-state species is approximated by the parent hydrocarbon and the transition-state species by the corresponding carbocation. The power of this approach has been demonstrated by the successful correlation of the calculated changes in strain energies with the experimental rates of solvolysis for 17 bridgehead derivatives of bicyclic and polycyclic hydrocarbons whose reactivities vary by more than 22 powers of ten[2] and with the rates of thermal decomposition of 12 bridgehead peresters whose reactivities range over 10^4.[3]

Bromination has been widely employed as a useful method for the introduction of a substituent onto the skeletal framework of polycyclic hydrocarbons (eq 2).

$$R{-}H \xrightarrow{Br_2} R{-}Br \tag{2}$$

Although no quantitative study has been carried out, Schleyer has noted that the qualitative ease of bromination of some polycyclic hydrocarbons seems to parallel the solvolysis rates of the resulting bromides.[4–6] These observations have led him to suggest that the relative proclivity for bromination at alternative intramolecular sites in these substrates can be related to the calculated change in strain energy (Δ strain) for formation of a carbocation at these positions.[7] Since ionic bromination of hydrocarbons shows a strong preference for attack at tertiary C–H bonds, attention is directed to the bridgehead positions. The calculated increases in strain energy for the generation of carbocations at the various bridgehead sites in a series of polycyclic hydrocarbons related to adamantane (**3**) are summarized in Table I. It must be emphasized that the mechanism for the bromination of hydrocarbons has not been determined. Although at one time this reaction was thought to proceed by an ionic pathway with the formation of intermediate bridgehead carbocations,[8] more recently it has been speculated that pentacoordinate intermediates or transition states or even radical cation pathways may be involved.[6]

Consistent with Schleyer's proposal, bromination of protoadamantane[4] (**2**) or [6]diadamantane[5] (**5**) occurs exclusively at the bridgehead position in each substrate which has the lowest calculated Δ-strain value (see Table I). However, nearly all other reported reactions of **5** with electrophiles give competitive attack at the alternative bridgehead positions.[5,9] Consequently, we were prompted

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[1] For recent reviews, see: (a) Ōsawa, E.; Musso, H. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 1–12. (b) Burkert, U.; Allinger, N. L. "Molecular Mechanics"; American Chemical Society: Washington, DC, 1982. (c) Ōsawa, E.; Musso, H. *Top. Stereochem.* **1982**, *13*, 117–193 and references cited therein.

[2] (a) Gleicher, G. J.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1967**, *89*, 582–593. (b) Bingham, R. C.; Schleyer, P. v. R. *Ibid.* **1971**, *93*, 3189–3199. (c) Parker, W.; Tranter, R. L.; Watt, C. I. F.; Chang, L. W. K.; Schleyer, P. v. R. *Ibid.* **1974**, *96*, 7121–7122.

[3] Rüchardt, C.; Golzke, V.; Range, G. *Chem. Ber.* **1981**, *114*, 2769–2785.

[4] (a) Karim, A.; McKervey, M. A.; Engler, E. M.; Schleyer, P. v. R. *Tetrahedron Lett.* **1971**, 3987–3990. (b) Karim, A.; McKervey, M. A. *J. Chem. Soc., Perkin Trans. 1* **1974**, 2475–2479. In ref 4b it is noted that refluxing protoadamantane with bromine gives 6-bromoprotoadamantane in 95% yield "with traces of two other substances one of which is thought to be 1-bromoadamantane".

[5] Gund, T. M.; Schleyer, P. v. R.; Unruh, G. D.; Gleicher, G. J. *J. Org. Chem.* **1974**, *39*, 2995–3003.

[6] Ōsawa, E.; Engler, E. M.; Godleski, S. A.; Inamoto, Y.; Kent, G. J.; Kausch, M.; Schleyer, P. v. R. *J. Org. Chem.* **1980**, *45*, 984–991.

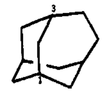
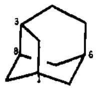
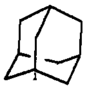
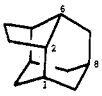
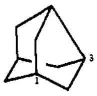
[7] It has been recommended that Δ-strain values should include a correction factor for the hyperconjugative stabilizing effect of β-alkyl branching.[6]

[8] (a) Landa, S.; Kriebel, S.; Knobloch, E. *Chem. Listy* **1954**, *48*, 61–64. (b) Landa, S.; Hala, S. *Collect. Czech. Chem. Commun.* **1959**, *24*, 93–98. (c) Stetter, H.; Schwarz, M.; Hirschhorn, A. *Chem. Ber.* **1959**, *92*, 1629–1635. (d) Stetter, H.; Wulff, C. *Ibid.* **1960**, *93*, 1366–1371. (e) Stetter, H.; Schwarz, M.; Hirschhorn, A. *Angew. Chem.* **1959**, *71*, 429–430. (f) Stetter, H.; Wulff, C. *Ibid.* **1960**, *72*, 351.

[9] (a) Courtney, T.; Johnston, D. E.; McKervey, M. A.; Rooney, J. J. *J. Chem. Soc., Perkin Trans. 1* **1972**, 2691–2696. (b) Jones, S. R.; Mellor, J. M. *Ibid.* **1976**, 2576–2581. (c) Jones, S. R.; Mellor, J. M. *J. Chem. Soc., Perkin Trans. 2* **1977**, 511–517. (d) Leddy, B. P.; McKervey, M. A.; McSweeney, P. *Tetrahedron Lett.* **1980**, *21*, 2261–2264.

0022-3263/85/1950-2759$01.50/0

Table I. Calculated Increases in Strain Energies for Formation of Bridgehead Carbocations and Ratios of Bridgehead Products Resulting from Reactions with Electrophiles

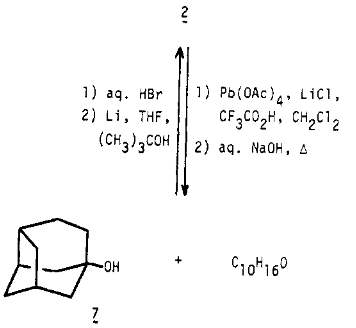
compd	position of cation	Δ strain $(R^+ - RH)$,[a] kcal/mol	Br_2	CrO_3 HOAc[b]	$Pb(OAc)_4$ LiCl, TRA[b]
 1	C-3	5.6[c]	81	97	69
	C-1	6.5[c]	19	3	31
 2	C-6	10.8[d]	100[d]	89	90
	C-3	12.9[d]		11	10
	C-8	17.7[d]			
	C-1	18.3[d]			
 3	C-1	12.3[e]	100[h]	100[j]	100[k]
 4	C-8	12.2[f]		10	11
	C-6	13.0[f]	47[f]	27	27
	C-1	13.6[f]	53[f]	63	62
	C-2	17.4[f]			
 5	C-1	13.0[g]	100[g]		90[k]
	C-4	13.4[g]			10[k]
 6	C-1	18.8[e]	nr[i,l]	nr[l]	nr[l]
	C-3	20.3[e]			

[a] Difference in strain energy of cation (R^+) and the corresponding hydrocarbon (RH) calculated by the Bingham–Schleyer force field.[2b] [b] The initial product residues are hydrolyzed with base to give the isolated alcohols. [c] Bingham, R. C. Ph.D. Thesis, Princeton University, NJ, 1970. [d] Reference 4. [e] Reference 2b. [f] Reference 6. [g] Reference 5. [h] Reference 8. [i] Wishnok, J. S.; Schleyer, P. v. R.; Funke, E.; Pandit, G. D.; Williams, R. O.; Nickon, A. *J. Org. Chem.* **1973**, *38*, 539–542. [j] Reference 22. [k] Reference 9b. [l] No reaction.

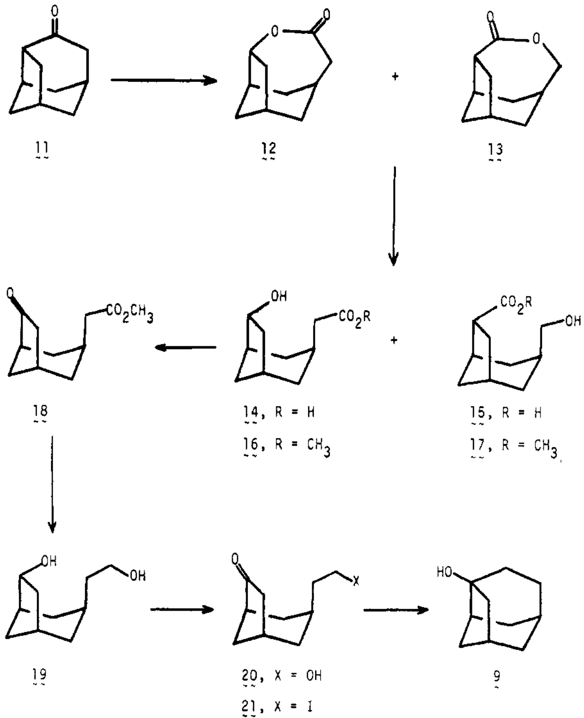
to determine if the regiospecificity observed in the reaction of bromine with protoadamantane would be maintained in the reaction of **2** with other electrophiles.

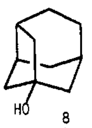
Results and Discussion

Jones and Mellor have reported that bridgehead functionalization of bicyclic and polycyclic hydrocarbons can be achieved by oxidation of these substrates with lead tetraacetate and chloride ion in a solution of trifluoroacetic acid and methylene chloride.[9b] Subsequent hydrolysis of the resulting trifluoroacetates gives the corresponding alcohols. The identity of the oxidizing agent in this reaction has not been established. However, it is clear that oxidation does not occur via a radical cation intermediate.[9c] At present, a mechanism proceeding by electrophilic attack at a carbon–hydrogen bond is favored.[9c] Oxidation of protoadamantane with lead tetraacetate under these conditions provided a mixture of 6-protoadamantanol[4] (**7**) *and* an isomeric tertiary alcohol in a ratio of 89:11, respectively. We were not successful in separating these alcohols by chromatography. However, the skeletal framework of the unknown alcohol follows from the observation that treatment of the mixture of alcohols with concentrated hydrobromic acid, followed by reduction of the resulting mixture of the corresponding bromides with lithium–*tert*-butyl alcohol–tetrahydrofuran, gave only **2**. Thus, in principle, the unknown alcohol could be 1-, 3-, or 8-protoadamantanol (**8**, **9**, and **10**, respectively). However, the molecular mechanics calculations clearly suggest that electrophilic attack at C-3 in **2** should be strongly preferred over attack at C-1 or C-8. Consequently, it appeared that



Scheme I





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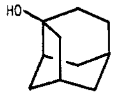

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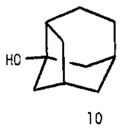
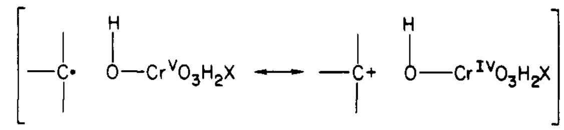


10

9 was the most likely structure for the unknown alcohol, and so we undertook the preparation of **9** by an unequivocal route.

Our synthesis of 3-protoadamantanol is summarized in Scheme I. The starting material for this sequence is commercially available 1-adamantanol, which can be readily transformed into 4-protoadamantanone (**11**) by a straightforward three-step procedure in 85% overall yield.[10] Baeyer–Villager oxidation of **11** with *m*-chloroperbenzoic acid provided a 65:35 mixture of lactones **12** and **13**, respectively, in a combined yield of 93%. In order to prepare **9**, it did not prove to be necessary to separate **12** and **13**. Base hydrolysis of the mixture of lactones gave a mixture of the hydroxy acids **14** and **15**, which was esterified with diazomethane to afford **16** and **17**. Oxidation of this mixture with 2 equiv of sodium metaperiodate in the presence of a catalytic amount of ruthenium dioxide[11] led to the loss of **17** and the isolation of only **18**. By this series of reactions, **18** was obtained in 58% yield from **12**. Reduction of **18** with lithium aluminum hydride afforded diol **19** in 78% yield. Treatment of **19** with ceric ammonium nitrate and sodium bromate in aqueous acetonitrile permitted exclusive oxidation of the secondary alcohol[12] and so provided keto alcohol **20** in 67% yield. The corresponding keto iodide **21**[13] was prepared in 71% yield from **20** by reaction of **20** with trimethylsilyl iodide that was generated in situ.[15] Recently, Molander and Etter have reported that lanthanide reducing agents can be used to affect efficient cyclization of a variety of 2-(haloalkyl)cycloalkanones.[16] Slow addition of **21** to a solution of samarium(II) iodide in tetrahydrofuran in the presence of a catalytic amount of ferric chloride gave 3-protoadamantanol (**9**) in 44% yield. The ^{13}C NMR spectrum of **9** proved to be identical with that of the unknown alcohol obtained in the oxidation of protoadamantane with lead tetraacetate.

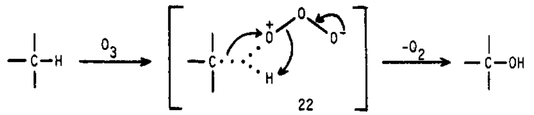
We have also found that oxidation of protoadamantane with chromium trioxide in a mixture of acetic acid and acetic anhydride, followed by hydrolysis of the resulting acetates, proceeds by competitive attack at C-6 and C-3 in **2** to give **7** and **9** in a ratio of 90:10, respectively. Chromic acid oxidations of polycyclic hydrocarbons are known to show a significant preference for substitution at the bridgehead positions.[17] These reactions are believed to proceed by way of a species that is best represented as the resonance hybrid shown below.



$$\left[-\overset{|}{\underset{|}{C}}\cdot \quad \overset{H}{\overset{|}{O}}-Cr^{V}O_3H_2X \longleftrightarrow -\overset{|}{\underset{|}{C}}{+} \quad \overset{H}{\overset{|}{O}}-Cr^{IV}O_3H_2X\right]$$

This intermediate may result from either hydrogen atom or hydride ion transfer from the hydrocarbon to a chromium(VI) complex.[18]

Competitive attack at C-3 and C-6 in protoadamantane also was found to occur in the dry ozonation of **2** adsorbed on silica gel. This method for the introduction of oxygen into unactivated tertiary carbon–hydrogen bonds in cyclic hydrocarbons has been developed by Mazur and his coworkers.[19,20] It involves initial adsorption of the hydrocarbon on silica gel by impregnation with a volatile solvent. A stream of ozone is then passed through this material at −78 °C until the silica gel is apparently saturated with ozone. The silica gel is then allowed to warm slowly to room temperature. Workup simply involves elution of the products from the silica gel with an organic solvent. Mazur has proposed that this reaction proceeds by the formation of an ozone–alkane complex which decomposes electrophilically via transition-state **22** with insertion of an oxygen atom into the C–H bond.[21] When ozone was passed for 2 h through silica gel bearing 0.7% by weight of **2**, the products consisted of alcohols **7** and **9**, obtained in yields of 55% and 11%, respectively, as well as trace amounts of ketone **11** and 5-protoadamantanone.



22

In summary, although the reaction of bromine with protoadamantane leads to regiospecific substitution at C-6 on the hydrocarbon skeleton, oxidation of **2** with lead tetraacetate or chromic acid or by dry ozonation of **2** adsorbed on silica gel occurs by competitive attack at C-6 (major) *and* C-3 (minor). These results parallel our earlier observations with homoadamantane (**1**) and ethanoadamantane (**4**) (see Table I). In the case of **1**, it had been claimed that reaction of **1** with bromine only gives products resulting from attack at C-3.[22] We found this report to be in error and that oxidation of **1** with bromine, chromic acid, or lead tetraacetate occurs by competitive attack at C-3 (major) *and* C-1 (minor).[23] In the case of **4**, it had been reported that bromination only gives substitution at C-1 and C-6.[6] However, we found that oxidation of **4** with lead tetraacetate or chromic acid proceeds by competitive attack at the C-1, C-6, *and* C-8 bridgehead positions.[24] Taken together, the results summarized in Table I clearly show that the oxidation of hydrocarbons with bromine is an inappropriate reaction for gauging the reactivity of bridgehead positions in electrophilic oxidation reactions.

The most striking conclusion from these studies is that substitution does not take place in any of these reactions

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(10) Majerski, Z.; Hammersak, Z. *Org. Synth.* **1979**, *59*, 147–153.

(11) Moriarty, R. M.; Gopal, H.; Adams, T. *Tetrahedron Lett.* **1970**, 4003–4006.

(12) Tomioka, H.; Oshima, K.; Nozaki, H. *Tetrahedron Lett.* **1982**, *23*, 539–542.

(13) The chloride analogue of **21** has been prepared previously by a much less efficient reaction sequence.[14] Reaction of this chloro ketone with base gives 2-protoadamantanone.[14]

(14) Spurlock, L. A.; Clark, K. P. *J. Am. Chem. Soc.* **1972**, *94*, 5349–5360.

(15) Olah, G. A.; Narang, S. C.; Gupta, B. G. B.; Malhotra, R. *J. Org. Chem.* **1979**, *44*, 1247–1251.

(16) Molander, G. A.; Etter, J. B. *Tetrahedron Lett.* **1984**, *25*, 3281–3284.

(17) (a) Wiberg, K. B. In "Oxidation in Organic Chemistry: Part A"; Wiberg, K. B., Ed.; Academic Press: New York, 1965; Chapter 2. (b) Bingham, R. C.; Schleyer, P. v. R. *J. Org. Chem.* **1971**, *36*, 1198–1201. (c) Paquette, L. A.; Meehan, G. V.; Marshall, S. J. *J. Am. Chem. Soc.* **1969**, *91*, 6779–6784.

(18) Rocek, J. *Tetrahedron Lett.* **1962**, 135–138.

(19) (a) Cohen, Z.; Keinan, E.; Mazur, Y.; Varbony, T. H. *J. Org. Chem.* **1975**, *40*, 2141–2142. (b) Cohen, Z.; Varkony, H.; Keinan, E.; Mazur, Y. *Org. Synth.* **1980**, *59*, 176–182.

(20) For a review, see: Bailey, P. S. "Ozonation in Organic Chemistry"; Academic Press: New York, 1982; Vol. 2, pp 312–319.

(21) Tal, D.; Keinan, E.; Mazur, Y. *J. Am. Chem. Soc.* **1978**, *101*, 502–503.

(22) "Unpublished observations" of S. H. Liggero and P. v. R. Schleyer reported in: Bingham, R. C.; Schleyer, P. v. R. *J. Org. Chem.* **1971**, *36*, 1198–1201.

(23) Israel, R. J.; Murray, R. K., Jr. *J. Org. Chem.* **1983**, *48*, 4701–4705.

(24) Sosnowski, J. J.; Murray, R. K., Jr. *J. Org. Chem.* **1984**, *49*, 2174–2176.

at any bridgehead position in any of these polycyclic hydrocarbons where the calculated increase in strain energy for carbocation formation is greater than or equal to 17.4 kcal/mol.[25] Particularly noteworthy is the lack of reactivity of the bridghead positions in noradamantane (**6**). In view of the strong preference for a carbocation to adopt a planar geometry, it appears that the increase in strain energy that would result from the formation of a carbocation at any of these positions is sufficiently great that reaction does not occur. Consequently, molecular mechanics calculations seem to provide a means to predict which bridgehead positions of bicyclic and polycyclic hydrocarbons *cannot* be functionalized by direct electrophilic substitution of the parent hydrocarbon.

When the Schleyer–Bingham force field is employed, the greatest increase in strain energy for formation of a cation at a bridgehead position which also is reported to undergo electrophilic bridgehead functionalization[9b,26] is 16.3 kcal/mol for C-1 in bicyclo[2.2.2]octane.[2b,25] Consequently, we also conclude that electrophilic functionalization is *possible* for all bridgehead positions where the increase in strain energy is less than or equal to this value.

Experimental Section

Melting points were obtained in sealed capillary tubes with a Mel-Temp melting point apparatus and are uncorrected. Infrared spectra were obtained on Perkin-Elmer 180 or Unicam SP1100 spectrophotometers. Proton magnetic resonance spectra were recorded with a Bruker AM 250-MHz spectrometer. Apparent splittings are reported in all cases. Carbon magnetic resonance spectra were recorded with the Bruker instrument at 62.9 MHz. Both the ^{1}H and ^{13}C NMR spectra were obtained with $CDCl_3$ as the solvent and are referenced to an internal standard of tetramethylsilane. Electron-impact mass spectra were obtained with a Du Pont 21-492B mass spectrometer at an ionization potential of 70 eV. Elemental analyses were performed by Micro-Analysis, Inc., Wilmington, DE.

Oxidation of Protoadamantane with Lead Tetraacetate. Protoadamantane[4b] (314 mg, 2.31 mmol) and lead tetraacetate (1.33 g, 3.0 mmol, dried over potassium hydroxide under vacuum and stored in the dark in a dessicator over phosphorus pentoxide) were stirred with trifluoroacetic acid (5 mL) that was 0.1 M in lithium chloride and methylene chloride (5 mL) for 24 h in the dark. The reaction mixture was then partitioned between ether (20 mL) and aqueous sodium hydroxide (0.8 g in 20 mL of water). The aqueous layer was extracted with ether (3 × 15 mL). The organic extracts were combined and then washed with saturated aqueous sodium bicarbonate (2 × 20 mL) and water (2 × 20 mL) and dried over anhydrous magnesium sulfate. Evaporation of the solvent at reduced pressure provided a mixture of trifluoroacetates, which were hydrolyzed by refluxing this material with 10% aqueous sodium hydroxide for 16 h. During this time, a considerable amount of white solid sublimed onto the condenser coils. This material was dissolved in ether. The crude reaction mixture was also extracted with ether (3 × 10 mL). The various ether extracts were combined and dried over anhydrous magnesium sulfate. Evaporation of the solvent at reduced pressure provided a white solid residue, which was sublimed [60–80 °C (0.3 mm)] to give 171 mg of a white solid. Analysis of this material by quantitative ^{13}C NMR indicated that the only compounds present were alcohols **7** and **9** and unreacted **2** and that they were obtained in a ratio of 67:8:25, respectively.

The ^{13}C NMR parameters of **2** and **7** are as follows. **2**:[4b] δ 42.0 (t), 40.2 (t), 37.4 (t), 35.3 (d), 34.4 (d), 34.1 (d), 32.3 (t), 28.1 (d), 27.7 (t), 23.3 (t). **7**:[4] δ 71.4 (C-6), 48.1 (t), 41.2 (t), 41.0 (t), 36.6 (t), 36.4 (t), 35.9 (d), 34.9 (d), 33.3 (d), 24.2 (t).

3- and 6-Bromoprotoadamantanes from a Mixture of 3- and 6-Hydroxyprotoadamantanes. A suspension of a 90:10 mixture of alcohols **7** and **9** (48 mg, 0.32 mmol) obtained above in 47% hydrobromic acid (10 mL) was sealed in an aerosol bottle and heated at 100 °C for 2.5 h. After the reaction mixture had cooled, it was poured into water (50 mL) and then extracted with ether (3 × 20 mL). The combined ether extracts were dried over anhydrous magnesium sulfate. Evaporation of the solvent at reduced pressure provided 70 mg (100% yield) of a mixture of the corresponding bromides.

Protoadamantane from a Mixture of 3- and 6-Bromoprotoadamantanes. Lithium metal (220 mg, 31 mmol) was added to a solution of the mixture of the bromides (70 mg, 0.32 mmol) obtained above in anhydrous *tert*-butyl alcohol (4 mL) and anhydrous tetrahydrofuran (15 mL), and the mixture was stirred at room temperature for 5 h. At this point water (10 mL) was added, and stirring was continued for 0.5 h. The resulting solution was extracted with ether (2 × 20 mL), and the combined ether extracts were dried over anhydrous magnesium sulfate. Evaporation of the solvent at reduced pressure gave 4 mg of a white solid. The ^{13}C NMR spectrum of this material was identical with that of an authentic sample of **2**.

Dry Ozonation of Protoadamantane Adsorbed on Silica Gel. A solution of **2** (290 mg, 2.13 mmol) in pentane (100 mL) was mixed with silica gel (42 g of Merck silica gel 60), and the solvent was evaporated at reduced pressure and room temperature with a rotary evaporator. The resulting dry powder was allowed to rotate for an additional 2 h. The protoadamantane–silica gel dispersion was then poured into a tightly closed gas-washing bottle. The remaining space in the vessel was packed loosely with glass wool, and the vessel was immersed in a cooling bath that was maintained at −78 °C. A flow of oxygen was passed through the vessel for 2 h, and then an ozone–oxygen mixture was passed through the vessel for 2 h. At this point the cooling bath was removed, and the reaction vessel was allowed to slowly warm to room temperature. The silica gel was then transferred to a chromatography column, and it was eluted sequentially with heptane and ethyl acetate until no more material eluted from the column. Distillation of the solvent from the heptane eluent at atmospheric pressure provided no residue. Evaporation of the solvent from the ethyl acetate eluent gave 332 mg of a white solid. Analysis of this material by quantitative GLC (10 ft × 0.25 in. DC-550 column, 175 °C) and quantitative ^{13}C NMR showed that ozonation provided a mixture of alcohols **7** and **9** and 4- and 5-protoadamantanones in yields of 55%, 11%, <1%, and <1%, respectively. The ketones were identified by comparison of their spectral parameters with those of authentic samples.

Chromic Acid Oxidation of Protoadamantane. Chromium trioxide (755 mg, 7.35 mmol) was added in small portions to a stirred solution of **2** (1.0 g, 7.35 mmol) in acetic acid (15 mL) and acetic anhydride (15 mL) at room temperature. After the addition was complete, the reaction mixture was stirred for 6 h at room temperature. At this point the reaction mixture was diluted with ice water (50 mL), and it was then extracted with ether (3 × 30 mL). The combined ether extracts were washed with 10% aqueous sodium carbonate (3 × 40 mL) and water (2 × 40 mL), and then dried over anhydrous magnesium sulfate. Evaporation of the solvent at reduced pressure provided an oil, which was hydrolyzed by refluxing this material with 10% aqueous potassium hydroxide (50 mL) for 16 h. During this time, a white solid sublimed onto the condenser coils. This material was dissolved in ether. The crude reaction mixture was also extracted with ether (3 × 20 mL). The various ether extracts were combined and dried over anhydrous magnesium sulfate. Evaporation of the solvent at reduced pressure provided 731 mg of a white solid, which was column chromatographed on silica gel. Elution with pentane gave 319 mg of unreacted **2**. Further elution with 4:1 pentane/ether afforded 80 mg of a mixture of overoxidation products. Finally, elution with 1:1 pentane/ether provided 190 mg (25% yield based on consumed **2**) of a mixture of **7** and **9**. Analysis of this material by quantitative ^{13}C NMR showed that **7** and **9** were obtained in a ratio of 89:11, respectively.

Baeyer–Villager Oxidation of 4-Protoadamantanone. *m*-Chloroperbenzoic acid (12.0 g, 70 mmol) was added in small portions to a solution of **11**[10] (8.4 g, 56 mmol) in methylene chloride (330 mL), which was stirred at room temperature. The progress of the reaction was monitored by GLC (10 ft × 0.25 in. OV-101 column, 170 °C). Additional oxidant (500 mg, 3.0 mmol) was

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[25] Of course, the absolute value of this number depends upon the particular force field that is being utilized for the molecular mechanics calculations.

[26] Ōsawa, E. *Tetrahedron Lett.* **1974**, 115–117.

added to the reaction mixture each day until all of the starting material had been consumed (3 days). The reaction mixture was then diluted with methylene chloride (200 mL), washed successively with 2% aqueous sodium thiosulfate (200 mL), saturated aqueous sodium bicarbonate (2 × 200 mL), and brine (200 mL), and finally dried over anhydrous magnesium sulfate. Evaporation of the solvent at reduced pressure afforded 8.65 g (93% yield) of a white solid. The more intense signals in the ^{13}C NMR spectrum of this material are assigned to lactone **12**: δ 173.8 (s), 80.3 (d), 43.4 (t), 39.1 (t), 37.8 (d), 37.3 (t), 35. 3 (t), 33.3 (d), 32.0 (t), 23.5 (d). The less intense signals in the ^{13}C NMR spectrum of this material are assigned to lactone **13**: δ 174.9 (s), 72.4 (t), 45.6 (d), 39.3 (t), 38.5 (t), 36.1 (d), 34.7 (d), 29.9 (t), 29.5 (t), 27.9 (d). Analysis of this material by quantitative ^{13}C NMR showed that **12** and **13** were obtained in a ratio of 65:35, respectively.

Methyl 2-(6-Oxobicyclo[3.2.1]oct-3-*endo*-yl)ethanoate (18). A 65:35 mixture of lactones **12** and **13**, respectively (2.0 g, 12.0 mmol), was added to a stirred solution of sodium hydroxide (481 mg, 12.0 mmol) in water (50 mL). The reaction mixture was stirred at reflux for 3 h, then cooled to room temperature, and acidified with 10% aqueous hydrochloric acid. The resulting solution was extracted with ethyl acetate (5 × 25 mL), and the combined extracts were dried over anhydrous magnesium sulfate. Evaporation of the solvent at reduced pressure provided a mixture of **14** and **15**, which crystallized upon standing. This mixture of **14** and **15** was esterified with a solution of diazomethane in ether (prepared from Diazald) to afford a mixture of **16** and **17**.

Ruthenium dioxide (20 mg, 0.1 mmol) was added at room temperature to a stirred suspension of the mixture of **16** and **17** obtained above in water (20 mL). A solution of sodium metaperiodate (2.7 g, 8.0 mmol) in water (10 mL) was then added slowly to the stirred reaction mixture. This procedure was repeated twice so that a total of 60 mg of ruthenium dioxide and 5.1 g of sodium metaperiodate in 30 mL of water were added finally to the reaction mixture. The resulting solution was stirred then for 2 h at room temperature. At this point, the reaction mixture was filtered, and the filter cake was washed with ether (2 × 20 mL). The filtrate was also extracted with ether (3 × 30 mL). The ether extracts and washings were combined and dried over anhydrous magnesium sulfate. Evaporation of the solvent at reduced pressure provided a pale yellow oil, which was Kugelrohr distilled [140–145 °C (1.0 mm)] to give 941 mg (58% yield based on **12**) of **18** as a colorless oil: ^{1}H NMR δ 3.65 (s, 3 H, CH_3), 2.65 (br s, 1 H), 2.5–1.36 (m, 12 H); ^{13}C NMR δ 222.9 (C-6), 173.1 (CO_2CH_3), 51.5 (OCH_3), 45.8 (C-7), 44.5 (C-5), 42.1 ($CH_2CO_2CH_3$), 34.9 (t), 34.4 (t), 34.1 (t), 31.5 (C-1), 26.4 (C-3); IR ν ($CHCl_3$) 3020, 1730, 1510, 1410, 1210, 1035 cm^{-1}.

Anal. Calcd for $C_{11}H_{16}O_3$: C, 67.35; H, 8.16. Found: C, 67.58; H, 8.18.

3-*endo*-(2-Hydroxyethyl)bicyclo[3.2.1]octan-6-ol (19). A solution of **18** (1.49 g, 7.6 mmol) in anhydrous ether (40 mL) was added dropwise at room temperature to a stirred suspension of lithium aluminum hydride (2.66 g, 70 mmol) in anhydrous ether (300 mL). After the addition was complete, the reaction mixture was stirred for 15 h at room temperature. The solution was then cooled to 0 °C, and the excess lithium aluminum hydride that was present was destroyed by the successive dropwise addition of water (2.6 mL), 3 M aqueous sodium hydroxide (2.6 mL), and water (5 mL). The resulting inorganic salts were filtered and washed with ether (3 × 25 mL). The filtrate and the ether washings were combined and dried over anhydrous magnesium sulfate. Evaporation of the solvent at reduced pressure provided a viscous colorless oil, which was Kugelrohr distilled [115–125 °C (0.5 mm)] to provide 1.006 g (78% yield) of **19**: ^{1}H NMR δ 4.18 (dt, J = 10 and 5 Hz, 1 H, $CHOH$), 3.66 (t, J = 6.6 Hz, 2 H, CH_2OH), 2.35–1.98 (m, 4 H), 1.89–1.44 (m, 8 H), 1.23–1.0 (m, 3 H); ^{13}C NMR δ 74.0 (C-6), 60.8 (CH_2OH), 40.9 (t), 40.3 (t), 40.1 (t), 37.4 (C-5), 31.8 (C-1), 30.0 (t), 26.6 (t), 24.0 (C-3).

Anal. Calcd for $C_{10}H_{18}O_2$: C, 70.55; H, 10.66. Found: C, 70.79; H, 10.57.

3-*endo*-(2-Hydroxyethyl)bicyclo[3.2.1]octan-6-one (20). Ceric ammonium nitrate (548 mg, 1.0 mmol) was added to a stirred suspension of **19** (1.70 g, 10 mmol) and sodium bromate (1.51 g, 10 mmol) in aqueous acetonitrile (50 mL of 7:3 CH_3CN/H_2O v/v). The reaction mixture was heated at 85 °C for 30 min. After cooling, the reaction mixture was diluted with ether (50 mL), and the layers were separated. The organic layer was then washed successively with saturated aqueous sodium bicarbonate (25 mL) and brine (25 mL) and dried over anhydrous magnesium sulfate. Evaporation of the solvent at reduced pressure afforded a colorless oil, which was Kugelrohr distilled [125–135 °C (0.5 mm)] to provide 1.13 g (67% yield) of **20**: ^{1}H NMR δ 3.58 (t, J = 6.5 Hz, 2 H, CH_2OH), 2.64 (br s, 1 H), 2.35–1.4 (m, 13 H); ^{13}C NMR δ 213.2 (C-6), 61.0 (CH_2OH), 45.9 (C-7), 44.9 (C-5), 41.0 (CH_2CH_2OH), 35.6 (t), 34.6 (t), 34.4 (t), 31.7 (C-1), 26.1 (C-3); IR ν ($CHCl_3$) 3635, 3475, 3025, 2950, 1735, 1225, 1205 cm^{-1}; exact mass calcd for $C_{10}H_{16}O_2$ 168.115, found 168.115.

Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.40; H, 9.59. Found: C, 71.47; H, 9.66.

3-*endo*-(2-Iodoethyl)bicyclo[3.2.1]octan-6-one (21). Chlorotrimethylsilane (1.40 g, 13.0 mmol) was added slowly to a solution of **20** (1.13 g, 6.7 mmol) and sodium iodide (2.05 g, 13.7 mmol) in anhydrous acetonitrile (30 mL), and the reaction mixture was stirred for 48 h at room temperature under nitrogen. The reaction mixture was then diluted with ether (75 mL), washed successively with 10% aqueous sodium thiosulfate (25 mL) and brine (25 mL), and dried over anhydrous magnesium sulfate. Evaporation of the solvent at reduced pressure provided 1.32 g (71% yield) of **21** as an oil: ^{1}H NMR δ 3.25–3.08 (m, 2 H, CH_2I), 2.76–2.59 (br s, 2 H, $CH_2C{=}O$), 2.40–1.33 (m, 11 H); ^{13}C NMR δ 212.5 (C-6), 45.9 (C-7), 44.5 (C-5), 41.0 (CH_2CH_2I), 34.8 (t), 34.0 (t), 33.4 (t), 31.4 (d), 30.3 (d), 5.0 (CH_2I); IR ν ($CHCl_3$) 2960, 1735, 1255 cm^{-1}.

3-Protoadamantanol (9). Samarium metal (651 mg of 40 mesh powder, 4.3 mmol) was transferred in a glovebag under nitrogen to a round-bottomed flask which was equipped with a septum inlet, a nitrogen inlet, and a Teflon-coated magnetic stirring bar. The metal was stirred and flame-dried under a flow of nitrogen. Upon cooling, anhydrous tetrahydrofuran (2.0 mL, which was purified by distillation from lithium aluminum hydride followed by distillation from sodium benzophenone ketyl and then purged with anhydrous nitrogen) was added to the samarium to make a slurry. Meanwhile, 1,2-diiodoethane (1.01 g, 3.6 mmol, purified according to the procedure of Kagan[27]) was placed in a separate flask, flushed with nitrogen for 10 min, and then dissolved in anhydrous tetrahydrofuran (6 mL). The resulting solution was added slowly by syringe to the slurry of samarium in tetrahydrofuran. After a short induction period, samarium(II) iodide began to form, and the reaction mixture was stirred at room temperature for 1 h. At this point a solution of **21** (500 mg, 1.80 mmol) in anhydrous tetrahydrofuran (4 mL) was added dropwise via syringe. Anhydrous ferric chloride (10 mg) was then added, and the reaction mixture was stirred for 15 h at room temperature. The reaction was quenched with saturated aqueous potassium carbonate (8 mL) and transferred to a separatory funnel. Ether (50 mL) was then added, and the layers were separated. The aqueous phase was extracted with ether (3 × 25 mL). The organic phase was combined with the ether extracts, and these were washed with brine (50 mL) and then dried over a mixture of anhydrous magnesium sulfate and potassium carbonate. Evaporation of the solvent at reduced pressure provided an oily solid, which was sublimed [100–105 °C (0.7 mm)] to give 120 mg (44% yield) of **9** as a white solid: ^{1}H NMR δ 2.24–2.15 (m, 2 H), 2.07–1.27 (m, 14 H); ^{13}C NMR δ 79.6 (s), 48.0 (t), 44.4 (d), 39.8 (t), 39.2 (t), 36.2 (d), 33.2 (t), 32.1 (t), 27.6 (d), 27.5 (t). Exact mass calcd for $C_{10}H_{16}O$ 152.120, found 152.121.

Anal. Calcd for $C_{10}H_{16}O$: C, 78.89; H, 10.59. Found: C, 78.99; H, 10.57.

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[27] Girard, P.; Namy, J. L.; Kagan, H. B. *J. Am. Chem. Soc.* **1980**, *102*, 2693–2698.